EIGHTH EDITION

Rook's Textbook of Dermatology



EDITED BY
Tony Burns
Stephen Breathnach
Neil Cox
Christopher Griffiths

WILEY-BLACKWELL

Rook's Textbook of Dermatology



The Editors
From l to r, Tony Burns, Stephen Breathnach, Christopher Griffiths and Neil Cox standing in front of a portrait of Arthur Rook, the father of the *Textbook of Dermatology*.

We dedicate this edition to Neil Cox, who died shortly before the book went to press. Neil was a hugely talented dermatologist whose contribution to the specialty has been outstanding. In addition to a multitude of other publications, he has contributed to and edited two editions of *Rook's Textbook*. Enormously hard-working, his input has been of inestimable value. He will be sorely missed.

Tony Burns
Stephen Breathnach
Christopher Griffiths

Rook's Textbook of Dermatology

EDITED BY

Tony Burns
MB, BS, FRCP, FRCP(Edin)
Emeritus Consultant Dermatologist, Leicester Royal Infirmary, Leicester

Stephen Breathnach
MA, MB, BChir, MD, PhD, FRCP
Consultant Dermatologist, St John's Institute of Dermatology, Guy's and St Thomas' NHS Foundation Trust, St Thomas' Hospital, London, and Consultant Dermatologist, Epsom & St Helier University Hospitals NHS Trust, Epsom, Surrey

Neil Cox
BSc, MB, ChB, FRCP(Lond & Edin)
Consultant Dermatologist, Department of Dermatology, Cumberland Infirmary, and Visiting Professor, University of Cumbria, Carlisle

Christopher Griffiths
BSc, MD, FRCP, FRCPath
Professor of Dermatology and Consultant Dermatologist, The Dermatology Centre, University of Manchester, Salford Royal Hospital, Salford, Manchester

IN FOUR VOLUMES

VOLUME 1

EIGHTH EDITION

WILEY-BLACKWELL
A John Wiley & Sons, Ltd., Publication

This edition first published 2010, © 1968, 1972, 1979, 1986, 1992, 1998, 2004, 2010 by Blackwell Publishing Ltd

Blackwell Publishing was acquired by John Wiley & Sons in February 2007. Blackwell's publishing program has been merged with Wiley's global Scientific, Technical and Medical business to form Wiley-Blackwell.

Registered office: John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

Editorial offices: 9600 Garsington Road, Oxford, OX4 2DQ, UK
The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK
111 River Street, Hoboken, NJ 07030-5774, USA

For details of our global editorial offices, for customer services and for information about how to apply for permission to reuse the copyright material in this book please see our website at www.wiley.com/wiley-blackwell

The right of the author to be identified as the author of this work has been asserted in accordance with the Copyright, Designs and Patents Act 1988.

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, except as permitted by the UK Copyright, Designs and Patents Act 1988, without the prior permission of the publisher.

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic books.

Designations used by companies to distinguish their products are often claimed as trademarks. All brand names and product names used in this book are trade names, service marks, trademarks or registered trademarks of their respective owners. The publisher is not associated with any product or vendor mentioned in this book. This publication is designed to provide accurate and authoritative information in regard to the subject matter covered. It is sold on the understanding that the publisher is not engaged in rendering professional services. If professional advice or other expert assistance is required, the services of a competent professional should be sought.

The contents of this work are intended to further general scientific research, understanding, and discussion only and are not intended and should not be relied upon as recommending or promoting a specific method, diagnosis, or treatment by physicians for any particular patient. The publisher and the author make no representations or warranties with respect to the accuracy or completeness of the contents of this work and specifically disclaim all warranties, including without limitation any implied warranties of fitness for a particular purpose. In view of ongoing research, equipment modifications, changes in governmental regulations, and the constant flow of information relating to the use of medicines, equipment, and devices, the reader is urged to review and evaluate the information provided in the package insert or instructions for each medicine, equipment, or device for, among other things, any changes in the instructions or indication of usage and for added warnings and precautions. Readers should consult with a specialist where appropriate. The fact that an organization or Website is referred to in this work as a citation and/or a potential source of further information does not mean that the author or the publisher endorses the information the organization or Website may provide or recommendations it may make. Further, readers should be aware that Internet Websites listed in this work may have changed or disappeared between when this work was written and when it is read. No warranty may be created or extended by any promotional statements for this work. Neither the publisher nor the author shall be liable for any damages arising herefrom.

ISBN: 978-1-4051-6169-5

Catalogue records for this book are available from the British Library and Library of Congress.

Set in 9.5/12pt Palatino by Toppan Best-set Premedia Limited
Printed and bound in Singapore by Fabulous Printers Pte Ltd

1 2010

Contents

Contributors, ix

Preface to Eighth Edition, xv

Preface to First Edition, xvi

VOLUME 1

1 Introduction and Historical Bibliography, 1.1
D.A. Burns & N.H. Cox

2 Comparative Dermatology, 2.1
D.A. Burns, N.H. Cox & P.B. Hill

3 Anatomy and Organization of Human Skin, 3.1
J.A. McGrath & J. Uitto

4 Functions of the Skin, 4.1
C.B. Archer

5 Diagnosis of Skin Disease, 5.1
N.H. Cox & I.H. Coulson

6 Epidemiology of Skin Disease, 6.1
H.C. Williams

7 Evidence-Based Dermatology, 7.1
M. Bigby & H.C. Williams

8 Skin and Skin Disease Throughout Life, 8.1
G.W.M. Millington & R.A.C. Graham-Brown

9 Racial Influences on Skin Disease, 9.1
L.C. Fuller & E.M. Higgins

10 Histopathology of the Skin: General Principles, 10.1
E. Calonje

11 Molecular Biology, 11.1
E.A. O'Toole

12 Inflammation, 12.1
M. Steinhoff, R.W. Groves, P.E. LeBoit & T.A. Luger

13 Clinical Immunology, Allergy and Photoimmunology, 13.1
G.P. Spickett & T. Schwarz

14 Wound Healing, 14.1
E.A. O'Toole & J.E. Mellerio

15 Genetics and Genodermatoses, 15.1
A.D. Irvine and J.E. Mellerio

16 Prenatal Diagnosis of Genetic Skin Disease, 16.1
J.A. McGrath

17 The Neonate, 17.1
D.G. Paige, A.R. Gennery & A.J. Cant

18 Naevi and other Developmental Defects, 18.1
C. Moss & H. Shahidullah

19 Disorders of Keratinization, 19.1
M.R. Judge, W.H.I. McLean & C.S. Munro

20 Psoriasis, 20.1
C.E.M. Griffiths & J.N.W.N. Barker

21 Pruritus, 21.1
M.W. Greaves

22 Urticaria and Mastocytosis, 22.1
C.E.H. Grattan & A. Kobza Black

23 Eczema, Lichenification, Prurigo and Erythroderma, 23.1
J. Berth-Jones

24 Atopic Dermatitis, 24.1
P.S. Friedmann, M.R. Ardern-Jones & C.A. Holden

VOLUME 2

25 Contact Dermatitis: Irritant, 25.1
S.M. Wilkinson & M.H. Beck

26 Contact Dermatitis: Allergic, 26.1
M.H. Beck & S.M. Wilkinson

27 Occupational Dermatoses, 27.1
J.S.C. English

28 Mechanical and Thermal Injury, 28.1
C.T.C. Kennedy, D.A.R. Burd & D. Creamer

29 Cutaneous Photobiology, 29.1
J.L.M. Hawk, A.R. Young & J. Ferguson

30 Bacterial Infections, 30.1
R.J. Hay & B.M. Adriaans

31 Mycobacterial Infections, 31.1
V.M. Yates

32 Leprosy, 32.1
D.N.J. Lockwood

33 Virus Infections, 33.1
J.C. Sterling

34 Syphilis and Bacterial Sexually Transmitted Infections, 34.1
G.R. Kinghorn

35 HIV and the Skin, 35.1
C.B. Bunker & F. Gotch

36 Mycology, 36.1
R.J. Hay & H.R. Ashbee

37 Parasitic Worms and Protozoa, 37.1
F. Vega-López & R.J. Hay

38 Diseases Caused by Arthropods and Other Noxious Animals, 38.1
D.A. Burns

39 Genetic Blistering Diseases, 39.1
J.-D. Fine & S.M. Burge

40 Immunobullous Diseases, 40.1
F. Wojnarowska & V.A. Venning

41 Lichen Planus and Lichenoid Disorders, 41.1
S.M. Breathnach

42 Disorders of the Sebaceous Glands, 42.1
A.M. Layton

43 Rosacea, Perioral Dermatitis and Similar Dermatoses, Flushing and Flushing Syndromes, 43.1
J. Berth-Jones

44 Disorders of Sweat Glands, 44.1
I.H. Coulson

VOLUME 3

45 Disorders of Connective Tissue, 45.1
N.P. Burrows & C.R. Lovell

46 Subcutaneous Fat, 46.1
D.H. McGibbon

47 Diseases of the Veins and Arteries: Leg Ulcers, 47.1
P.S. Mortimer, K.G. Burnand & H.A.M. Neumann

48 Disorders of Lymphatic Vessels, 48.1
P.S. Mortimer

49 Purpura and Microvascular Occlusion, 49.1
N.H. Cox & W.W. Piette

50 Vasculitis, Neutrophilic Dermatoses and Related Disorders, 50.1
N.H. Cox, J.L. Jorizzo, J.F. Bourke & C.O.S. Savage

51 The 'Connective Tissue Diseases', 51.1
M.J.D. Goodfield, S.K. Jones & D.J. Veale

52 Non-Melanoma Skin Cancer and Other Epidermal Skin Tumours, 52.1
A.G. Quinn & W. Perkins

53 Tumours of the Skin Appendages, 53.1
E. Calonje

54 Lentigos, Melanocytic Naevi and Melanoma, 54.1
J.A. Newton Bishop

55 Histiocytoses, 55.1
A.C. Chu

56 Soft-Tissue Tumours and Tumour-like Conditions, 56.1
E. Calonje

57 Cutaneous Lymphomas and Lymphocytic Infiltrates, 57.1
S.J. Whittaker

58 Disorders of Skin Colour, 58.1
A.V. Anstey

59 Metabolic and Nutritional Disorders, 59.1
R.P.E. Sarkany, S.M. Breathnach, A.A.M. Morris, K. Weismann & P.D. Flynn

60 Necrobiotic Disorders, 60.1
D.A. Burns

61 Sarcoidosis, 61.1
D.J. Gawkrodger

62 Systemic Disease and the Skin, 62.1
N.H. Cox & I.H. Coulson

VOLUME 4

63 The Skin and the Nervous System, 63.1
C.B. Archer & D.J. Eedy

64 Psychocutaneous Disorders, 64.1
L.G. Millard & J. Millard

65 Disorders of Nails, 65.1
D.A.R. de Berker & R. Baran

66 Disorders of Hair, 66.1
A.G. Messenger, D.A.R. de Berker & R.D. Sinclair

67 The Skin and the Eyes, 67.1
J.N. Leonard & J.K.G. Dart

68 The External Ear, 68.1
C.T.C. Kennedy

69 The Oral Cavity and Lips, 69.1
C. Scully & A. Hegarty

70 The Breast, 70.1
D.A. Burns

71 The Genital, Perianal and Umbilical Regions, 71.1
C.B. Bunker & S.M. Neill

72 General Aspects of Treatment, 72.1
A.Y. Finlay and C.H. Smith

73 Topical Therapy, 73.1
J. Berth-Jones

74 Systemic Therapy, 74.1
S.M. Breathnach, C.H. Smith, R.J.G. Chalmers & R.J. Hay

75 Drug Reactions, 75.1
S.M. Breathnach

76 Erythema Multiforme, Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis, 76.1
S.M. Breathnach

77 Dermatological Surgery, 77.1
C.M. Lawrence & N.R. Telfer

78 Lasers and Flashlamps in the Treatment of Skin Disorders, 78.1
R.J. Barlow

79 Radiotherapy and Reactions to Ionizing Radiation, 79.1
C.G. Kelly & I. Peat

80 Minimally Invasive Treatments and Procedures for Ageing Skin, 80.1
N.J. Lowe

Index

The index to all four volumes can be found at the end of Volume 4

Contributors

Adriaans, Beverley M.

MD, FRCP
Consultant Dermatologist, Department of Dermatology, Gloucestershire Royal Hospital, Gloucester GL1 3NN
Co-author of
Chapter 30: Bacterial Infections

Anstey, Alexander V.

MD, FRCP
Consultant Dermatologist, Department of Dermatology, Royal Gwent Hospital, Newport NP20 2UB
Author of
Chapter 58: Disorders of Skin Colour

Archer, Clive B.

BSc, MD, PhD, MSc Med Ed(Lond), FRCP (Edin, Lond)
Consultant Dermatologist, Honary Clinical Senior Lecturer, Bristol Dermatology Centre, Bristol Royal Infirmary, Bristol BS2 8HW
Author of
Chapter 4: Functions of the Skin
Co-author of
Chapter 63: The Skin and the Nervous System

Ardern-Jones, Michael R.

BSc, MRCP, DPhil
Senior Lecturer and Honorary Consultant in Dermatology, Division of Infection, Inflammation and Immunity, School of Medicine, University of Southampton, Southampton General Hospital, Southampton SO16 6YD
Co-author of
Chapter 24: Atopic Dermatitis

Ashbee, H. Ruth

BSc, PhD
Principal Clinical Scientist, Mycology Reference Centre, Department of Microbiology, Leeds General Infirmary, Leeds LS1 3EX
Co-author of
Chapter 36: Mycology

Baran, Robert

MD
Head of Nail Disease Centre, Le Grand Palais, 42 Rue des Serbes, 06400 Cannes, and Consultant Dermatologist, Gustave Roussy Cancer Institute, 94805 Villejuif, France
Co-author of
Chapter 65: Disorders of Nails

Barker, Jonathan N.W.N.

BSc, MD, FRCP, FRCPath
Professor of Clinical Dermatology, St John's Institute of Dermatology, King's College London, Guy's Hospital, London SE1 9RT
Co-author of
Chapter 20: Psoriasis

Barlow, Richard J.

MD, FRCP
Consultant Dermatologist, St John's Institute of Dermatology, St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH
Author of
Chapter 78: Lasers and Flashlamps in the Treatment of Skin Disorders

Beck, Michael H.

FRCP, MBchB
Honorary Clinical Lecturer Occupational and Environmental Health Group, University of Manchester and Retired Consultant Dermatologist and Director of Contact Dermatitis Investigation Unit, Department of Dermatology, Salford Royal Hospital, Stott Lane, Salford M6 8HD
Co-author of
Chapter 25: Contact Dermatitis: Irritant
Chapter 26: Contact Dermatitis: Allergic

Berth-Jones, John

FRCP
Consultant Dermatologist, Department of Dermatology, University Hospitals Coventry and Warwickshire, Walsgrave, Coventry CV2 2DX
Author of
Chapter 23: Eczema, Lichenification, Prurigo and Erythroderma
Chapter 43: Rosacea, Perioral Dermatitis and Similar Dermatoses, Flushing and Flushing Syndromes
Chapter 73: Topical Therapy

Bigby, Michael

MD
Associate Professor of Dermatology, Harvard Medical School and Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Boston MA 02215, USA
Co-author of
Chapter 7: Evidence-Based Dermatology

Bourke, John F.

MD, FRCP(Ire)
Consultant Dermatologist, Department of Dermatology, South Infirmary-Victoria Hospital, Old Blackrock Road, Cork, Ireland
Co-author of
Chapter 50: Vasculitis, Neutrophilic Dermatoses and Related Disorders

Breathnach, Stephen M.

MA, MD, PhD, FRCP
Consultant Dermatologist, St John's Institute of Dermatology, Guy's and St Thomas' NHS Foundation Trust, St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH
Editor
Author of
Chapter 41: Lichen Planus and Lichenoid Disorders
Chapter 75: Drug Reactions
Chapter 76: Erythema Multiforme, Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis
Co-author of
Chapter 59: Metabolic and Nutritional Disorders
Chapter 74: Systemic Therapy

Bunker, Christopher B.

MA, MD, FRCP
Consultant Dermatologist, Chelsea and Westminster and Royal Marsden Hospitals, Professor of Dermatology, Division and Faculty of Medicine, Imperial College London, Department of Dermatology, 369 Fulham Road, London SW10 9NH
Co-author of
Chapter 35: HIV and the Skin
Chapter 71: The Genital, Perianal and Umbilical Regions

Burd, D. Andrew R.

MBChB, FRCS, MD
Professor, The Chinese University of Hong Kong, Department of Surgery, 4/F Clinical Science Building, Prince of Wales Hospital, Shatin, New Territories, Hong Kong
Co-author of
Chapter 28: Mechanical and Thermal Injury

Burge, Susan M.

DM, FRCP
Consultant Dermatologist, Churchill Hospital, Old Road, Headington, Oxford OX3 7LJ
Co-author of
Chapter 39: Genetic Blistering Diseases

Burnand, Kevin G.

MBBS, FRCS, MS
Professor of Surgery, Academic Department of Surgery, St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH
Co-author of
Chapter 47: Diseases of the Veins and Arteries: Leg Ulcers

Burns, David Anthony

MB BS FRCP
Emeritus Consultant Dermatologist, Leicester Royal Infirmary, Infirmary Square, Leicester LE1 5WW
Editor
Author of
Chapter 38: Diseases Caused by Arthropods and Other Noxious Animals
Chapter 60: Necrobiotic Disorders
Chapter 70: The Breast
Co-author of
Chapter 1: Introduction and Historical Bibliography
Chapter 2: Comparative Dermatology

Burrows, Nigel P.

MD, FRCP
Consultant Dermatologist and Associate Lecturer, Department of Dermatology, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ
Co-author of
Chapter 45: Disorders of Connective Tissue

Calonje, Eduardo

MD DipRCPath
Consultant Dermatologist, Department of Histopathology, St John's Institute of Dermatology, St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH
Author of
Chapter 10: Histopathology of the Skin: General Principles
Chapter 53: Tumours of the Skin Appendages
Chapter 56: Soft-Tissue Tumours and Tumour-like Conditions

Cant, Andrew J.

BSc, MD, FRCP, FRCPCH
Consultant in Paediatric Immunology & Infectious Diseases, Children's BMT Unit, Newcastle General Hospital, Westgate Road, Newcastle upon Tyne NE4 6BE
Co-author of
Chapter 17: The Neonate

Chalmers, Robert J.G.

MB, FRCP
Consultant Dermatologist, Dermatology Centre, University of Manchester, Salford Royal Hospital, Stott Lane, Manchester M6 8HD
Co-author of
Chapter 74: Systemic Therapy

Chu, Anthony C.

FRCP
Professor of Dermatologic Oncology, Buckingham University and Consultant Dermatologist, Hammersmith Hospital, Du Cane Road, London W12 0HS
Author of
Chapter 55: Histiocytoses

Coulson, Ian H.

BSc, MB, BS, FRCP
Consultant Dermatologist, Dermatology Unit, Burnley General Hospital, Casterton Avenue, Burnley BB10 2PQ
Author of
Chapter 44: Disorders of Sweat Glands
Co-author of
Chapter 5: Diagnosis of Skin Disease
Chapter 62: Systemic Disease and the Skin

Cox, Neil H.

BSc, MB, ChB, FRCP
Consultant Dermatologist, Department of Dermatology, Cumberland Infirmary, Carlisle CA2 7HY and Visiting Professor, University of Cumbria, Carlisle CA1 2HH
Editor
Co-author of
Chapter 1: Introduction and Historical Bibliography
Chapter 2: Comparative Dermatology
Chapter 5: Diagnosis of Skin Disease
Chapter 49: Purpura and Microvascular Occlusion
Chapter 50: Vasculitis, Neutrophilic Dermatoses and Related Disorders
Chapter 62: Systemic Disease and the Skin

Creamer, Daniel

BSc, MD, FRCP
Consultant Dermatologist, Department of Dermatology, King's College Hospital, Denmark Hill, London SE5 9RS
Co-author of
Chapter 28: Mechanical and Thermal Injury

Dart, John K.G.

MA DM FRCS FRCOphth
Consultant Ophthalmologist, Moorfields Eye Hospital NHS Foundation Trust, 162 City Road, London EC1 2PD and Honorary Reader in Ophthalmology, University College London
Co-author of
Chapter 67: The Skin and the Eyes

de Berker, David A.R.

BA, MBBS, MRCP
Consultant Dermatologist, Bristol Dermatology Centre, Bristol Royal Infirmary, Marlborough Street, Bristol BS2 8HW
Co-author of
Chapter 65: Disorders of Nails
Chapter 66: Disorders of Hair

Eedy, David J.

MD, FRCP
Consultant Dermatologist, Department of Dermatology, Craigavon Area Hospital, 68 Lurgan Road, Portadown, Co Armagh BT63 5QQ
Co-author of
Chapter 63: The Skin and the Nervous System

English, John S.C.

FRCP
Consultant Dermatologist, Department of Dermatology, Queen's Medical Centre, Clifton Boulevard, Nottingham NG7 2UH
Author of
Chapter 27: Occupational Dermatoses

Ferguson, James

MD, FRCP
Professor and Consultant Dermatologist, Photobiology Unit, Department of Dermatology, Ninewells Hospital and Medical School, Dundee, Tayside DD1 9SY
Co-author of
Chapter 29: Cutaneous Photobiology

Fine, Jo-David

MD, MPH
Professor of Medicine (Dermatology) and Pediatrics, Vanderbilt University, School of Medicine, 1900 Patterson Street, Nashville, TN 37203, USA
Co-author of
Chapter 39: Genetic Blistering Diseases

Finlay, Andrew Y.

MBBS, FRCP (London & Glasgow)
Professor of Dermatology, Department of Dermatology, Cardiff University School of Medicine, Heath Park, Cardiff CF14 4XN
Co-author of
Chapter 72: General Aspects of Treatment

Flynn, Paul D.
PhD, FRCP, MRCPI
Consultant Physician, Acute and Metabolic Medicine, Addenbrooke's Hospital, Cambridge CB2 2QQ and Fellow and Director of Studies in Medical Science, Sidney Sussex College, Cambridge
Co-author of
Chapter 59: Metabolic and Nutritional Disorders

Friedmann, Peter S.
MD, FRCP, FMedSci
Professor of Dermatology, Dermatopharmacology Unit, Southampton General Hospital, Tremona Road, Southampton SO16 6YD
Co-author of
Chapter 24: Atopic Dermatitis

Fuller, L. Claire
MA, FRCP
Consultant Dermatologist, Department of Dermatology, Kent and Canterbury Hospital, Ethelbert Road, Canterbury, Kent CT1 3NG
Co-author of
Chapter 9: Racial Influences on Skin Disease

Gawkrodger, David J.
MD, FRCP, FRCPE
Consultant Dermatologist and Honorary Professor of Dermatology, Department of Dermatology, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF
Author of
Chapter 61: Sarcoidosis

Gennery, Andrew R.
MD, MRCP, MRCPCH, DCH, DipMedSci
Reader, Paediatric Immunology, Children's BMT Unit, Newcastle General Hospital, Westgate Road, Newcastle upon Tyne NE4 6BE
Co-author of
Chapter 17: The Neonate

Goodfield, Mark J.D.
MD, FRCP
Consultant Dermatologist, Department of Dermatology, Leeds General Infirmary, Great George Street, Leeds LS1 3EX
Co-author of
Chapter 51: The 'Connective Tissue Diseases'

Gotch, Frances
PhD, FRCPath
Professor of Immunology, Department of Immunology, Imperial College School of Medicine, Chelsea and Westminster Hospital, 369 Fulham Road, London SW10 9NH
Co-author of
Chapter 35: HIV and the Skin

Graham-Brown, Robin A.C.
BSc, MB, BS, FRCP, FRCPCH
Consultant Dermatologist and Honorary Senior Lecturer, University Hospitals of Leicester, Leicester LE1 5WW
Co-author of
Chapter 8: Skin and Skin Disease Throughout Life

Grattan, Clive E.H.
MA MD FRCP
Consultant Dermatologist, Department of Dermatology, Norfolk and Norwich University Hospital, Colney Lane, Norwich NR4 7UY
Co-author of
Chapter 22: Urticaria and Mastocytosis

Greaves, Malcolm W.
MD, PhD, FRCP, FAMS
Emeritus Professor of Dermatology, Cutaneous Allergy Clinic, St John's Institute of Dermatology, St Thomas' Hospital, Lambeth Palace Road, London SEI 7EH
Author of
Chapter 21: Pruritus

Griffiths, Christopher E.M.
BSc, MD, FRCP, FRCPath
Professor of Dermatology and Consultant Dermatologist, The Dermatology Centre, University of Manchester, Salford Royal Hospital, Salford, Manchester M6 8HD
Editor
Co-author of
Chapter 20: Psoriasis

Groves, Richard W.
MBBS, FRCP
Head, Clinical Immunodermatology, St John's Institute of Dermatology, Guy's Hospital, Great Maze Pond, London SE1 9RT
Co-author of
Chapter 12: Inflammation

Hawk, John L.M.
BSc, MD, FRACP, FRCP
Emeritus Professor of Dermatological Photobiology and Honorary Consultant Dermatologist, St John's Institute of Dermatology, St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH
Co-author of
Chapter 29: Cutaneous Photobiology

Hay, Roderick J.
DM, FRCP, FRCPath, FMedSci
Professor of Cutaneous Infection, Dermatology Department, King's College Hospital, Denmark Hill, Camberwell, London SE5 9RS
Co-author of
Chapter 30: Bacterial Infections
Chapter 36: Mycology
Chapter 37: Parasitic Worms and Protozoa
Chapter 74: Systemic Therapy

Hegarty, Anne
BA BDentSC, MSc, MFDRCSI, MBBS
Consultant in Oral Medicine, The Charles Clifford Dental Hospital, Wellesley Road, Sheffield S10 2SZ
Co-author of
Chapter 69: The Oral Cavity and Lips

Higgins, Elisabeth M.
MA, FRCP
Consultant Dermatologist, Department of Dermatology, King's College Hospital, Denmark Hill, Camberwell, London SE5 9RS
Co-author of
Chapter 9: Racial Influences on Skin Disease

Hill, Peter B.
BVsc, PhD, DVD, DipACVD, DipECVD, MRCVS
Specialist in Veterinary Dermatology, Veterinary Specialist Centre, North Ryde, Sydney, NSW 2113, Australia
Co-author of
Chapter 2: Comparative Dermatology

Holden, Colin A.
BSc, MD, FRCP
Consultant Dermatologist, Department of Dermatology, Epsom and St Helier NHS Trust, Wrythe Lane, Carshalton, Surrey SM5 1AA
Co-author of
Chapter 24: Atopic Dermatitis

Irvine, Alan D.
MD, FRCPI, MRCP
Consultant Paediatric Dermatologist, Our Lady's Hospital for Sick Children, Crumlin, Dublin 12, Ireland
Co-author of
Chapter 15: Genetics and Genodermatoses

Jones, Stephen K.
BMedSci, BM, BS, FRCP (London & Edinburgh)
Consultant Dermatologist, Department of Dermatology, Clatterbridge Hospital, Bebington, Wirral CH63 4JY
Co-author of
Chapter 51: The 'Connective Tissue Diseases'

Jorizzo, Joseph L.
MD
Professor, Former and Founding Chair, Department of Dermatology, Wake Forest University School of Medicine, Winston-Salem, NC, USA
Co-author of
Chapter 50: Vasculitis, Neutrophilic Dermatoses and Related Disorders

Judge, Mary R.
MD, FRCP, DCH
Consultant Dermatologist, Department of Dermatology, Salford Royal Hospital, Greater Manchester M6 8HD
Co-author of
Chapter 19: Disorders of Keratinization

Kelly, Charles G.
MSc, FRCP, FRCR
Consultant Clinical Oncologist, Northern Centre for Cancer Treatment, Newcastle General Hospital, Westgate Road, Newcastle upon Tyne NE4 6BE
Co-author of
Chapter 79: Radiotherapy and Reactions to Ionizing Radiation

Kennedy, Cameron T.C.
MA, MB, BChir, FRCP
Consultant Dermatologist and Clinical Senior Lecturer, Bristol Dermatology Centre, Bristol Royal Infirmary, Marlborough Street, Bristol BS2 8HW
Author of
Chapter 68: The External Ear
Co-author of
Chapter 28: Mechanical and Thermal Injury

Kinghorn, George R.
MD, FRCP (London & Glasgow)
Consultant and Honorary Professor of Genitourinary Medicine, Department of Genitourinary Medicine, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF
Author of
Chapter 34: Syphilis and Bacterial Sexually Transmitted Infections

Kobza Black, Anne
MD, FRCP
Honorary Senior Lecturer, St John's Institute of Dermatology, St Thomas' Hospital, London SE1 7EH
Co-author of
Chapter 22: Urticaria and Mastocytosis

Lawrence, Clifford M.
MD, FRCP
Consultant Dermatologist, Department of Dermatology, Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne, Tyne and Wear NE1 4LP
Co-author of
Chapter 77: Dermatological Surgery

Layton, Alison M.
MB, ChB, FRCP
Consultant Dermatologist, Harrogate and District Hospital, Lancaster Park Road, Harrogate, North Yorkshire HG2 2SX
Author of
Chapter 42: Disorders of the Sebaceous Glands

LeBoit, Philip E.
MD
Professor of Pathology and Dermatology, Division Chief, Dermatopathology, University of California San Francisco, 1701 Divisadero Street, San Francisco CA94115, USA
Co-author of
Chapter 12: Inflammation

Leonard, Jonathan N.
BSc, MD, FRCP
Consultant Dermatologist, Department of Dermatology, St Mary's Hospital, Praed Street, London W2 1NY
Co-author of
Chapter 67: The Skin and the Eyes

Lockwood, Diana N.J.
MD, FRCP
Consultant Physician and Leprologist, Hospital for Tropical Diseases, Mortimer Market, Capper Street, London WC1E 6AU
Author of
Chapter 32: Leprosy

Lovell, Christopher R.
MD, FRCP
Consultant Dermatologist, Kinghorn Dermatology Unit, Royal United Hospital, Combe Park, Bath, Avon BA1 3NG
Co-author of
Chapter 45: Disorders of Connective Tissue

Lowe, Nicholas James
MD, FRCP, FACP
Consultant Dermatologist and Clinical Professor, UCLA School of Medicine, Los Angeles, CA, USA and The Cranley Clinic, Harcourt House, 19A Cavendish Square, London W19 OPN
Author of
Chapter 80: Minimally Invasive Treatments and Procedures for Ageing Skin

Luger, Thomas A.
MD
Professor and Chairman, Department of Dermatology, University of Münster, Von Esmarchstrasse 58, D-48149 Münster, Germany
Co-author of
Chapter 12: Inflammation

McGibbon, David H.
MB, ChB, FRCP
Consultant Dermatologist, St John's Institute of Dermatology, St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH
Author of
Chapter 46: Subcutaneous Fat

McGrath, John A.
MD, FRCP
Professor of Molecular Dermatology, St. John's Institute of Dermatology, King's College London, London SE1 9RT
Author of
Chapter 16: Prenatal Diagnosis of Genetic Skin Disease
Co-author of
Chapter 3: Anatomy and Organization of Human Skin

McLean, W.H. Irwin
BSc (Hons), PhD, DSc, FRSE
Professor of Human Genetics, Human Genetics Unit, Division of Pathology and Neuroscience, University of Dundee, Ninewells Hospital and Medical School, Dundee, Tayside DD1 9SY
Co-author of
Chapter 19: Disorders of Keratinization

Mellerio, Jemima E.
BSc, MD, FRCP
Consultant Dermatologist, St John's Institute of Dermatology, St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH
Co-author of
Chapter 14: Wound Healing
Chapter 15: Genetics and Genodermatoses

Messenger, Andrew G.
MD, FRCP
Consultant Dermatologist, Department of Dermatology, Royal Hallamshire Hospital, Sheffield, UK
Co-author of
Chapter 66: Disorders of Hair

Millard Jonathan
MRCPsych
Consultant, The Becklin Centre, Alma Street, Leeds LS9 7BE
Co-author of
Chapter 64: Psychocutaneous Disorders

Millard, Leslie G.
MD, FRCP
Consultant Dermatologist, Rotherham District Hospitals Trust, Moorgate Road, Rotherham S60 2UD
Co-author of
Chapter 64: Psychocutaneous Disorders

Millington George W.M.
BSc, MB, PhD, MRCP
Consultant Dermatologist, Norfolk and Norwich University Hospital, Norwich NR4 7UY
Co-author of
Chapter 8: Skin and Skin Disease Throughout Life

Morris, Andrew A.M.
BM, BCh, PhD, FRCPCH
Consultant Paediatrician with Special Interest in Metabolic Diseases, Willink Biochemical Genetics Unit, Department of Genetic Medicine, Royal Manchester Children's Hospital, Oxford Road, Manchester M13 9WL
Co-author of
Chapter 59: Metabolic and Nutritional Disorders

Mortimer, Peter S.
MD, FRCP
Professor of Dermatological Medicine, St George's, University of London, Cranmer Terrace, London SW17 ORE and Consultant Skin Physician, St George's Hospital London and the Royal Marsden Hospital, London SW3 6JJ
Author of
Chapter 48: Disorders of Lymphatic Vessels
Co-author of
Chapter 47: Diseases of the Veins and Arteries: Leg Ulcers

Moss, Celia
DM, FRCP, MRCPCH
Consultant Dermatologist and Honorary Professor of Paediatric Dermatology, Birmingham Children's Hospital, Steelhouse Lane, Birmingham B4 6NL
Co-author of
Chapter 18: Naevi and other Developmental Defects

Munro, Colin S.
MA, MD, FRCP
Professor of Dermatology, Alan Lyell Centre for Dermatology, Southern General Hospital, Glasgow G51 4TF
Co-author of
Chapter 19: Disorders of Keratinization

Neill, Sallie M.
FRCP
Consultant Dermatologist, St John's Institute of Dermatology, St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH
Co-author of
Chapter 71: The Genital, Perianal and Umbilical Regions

Neumann, H.A. Martino
MD, PhD
Head of the Department of Dermatology and Venereology, Erasmus Medical Center, Rotterdam, The Netherlands
Co-author of
Chapter 47: Diseases of the Veins and Arteries: Leg Ulcers

Newton Bishop, Julia A.
MD, FRCP
Professor of Dermatology, Section of Epidemiology and Biostatistics, Leeds Institute of Molecular Medicine, St James's University Hospital, Leeds LS9 7TF
Author of
Chapter 54: Lentigos, Melanocytic Naevi and Melanoma

O'Toole, Edel A.
MB, BCh, PhD, FRCP(Ire), FRCP
Professor of Molecular Dermatology and Honorary Consultant Dermatologist, Centre for Cutaneous Research, Barts and The London School of Medicine & Dentistry, Queen Mary, University of London, 4 Newark Street, London E1 2AT
Author of
Chapter 11: Molecular Biology
Co-author of
Chapter 14: Wound Healing

Paige, David G.
MBBS, MA, FRCP
Consultant Dermatologist, Barts and the Royal London NHS Trust, Whitechapel, London E1 1BB
Co-author of
Chapter 17: The Neonate

Peat, Irene
FRCR, FRCP
Consultant Clinical Oncologist, Oncology Unit, Leicester Royal Infirmary, Leicester LE1 5WW
Co-author of
Chapter 79: Radiotherapy and Reactions to Ionizing Radiation

Perkins, William
MBBS, FRCP
Consultant Dermatologist, Nottingham University Hospital Queen's Medical Centre, Clifton Boulevard, Nottingham NG7 2UH
Co-author of
Chapter 52: Non-Melanoma Skin Cancer and Other Epidermal Skin Tumours

Piette, Warren W.
MD
Chair and Program Director of the Dermatology Training Program, John H Stroger Jr Hospital of Cook County, Division of Dermatology, 1900 W Polk St, Admin Bldg Rm 519, Chicago, Illinois 60612, USA
Co-author of
Chapter 49: Purpura and Microvascular Occlusion

Quinn, Anthony G.
BMSc, MBChB, PhD, FRCP
Senior Vice President and Chief Medical Officer, Synageva BioPharma Corporation, 60 Hickory Drive, Waltham, Massachusetts 02451, USA
Co-author of
Chapter 52: Non-Melanoma Skin Cancer and Other Epidermal Skin Tumours

Sarkany, Robert P.E.
FRCP, MD
Director of Photobiology, St John's Institute of Dermatology, St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH
Co-author of
Chapter 59: Metabolic and Nutritional Disorders

Savage, Caroline O.S.
PhD, FRCP, FMedSci
Professor of Nephrology, Renal Immunobiology, School of Immunity and Infection, The College of Medical and Dental Sciences, University of Birmingham, Edgbaston, Birmingham B15 2TT
Co-author of
Chapter 50: Vasculitis, Neutrophilic Dermatoses and Related Disorders

Schwarz, Thomas
MD
Professor and Chairman, Department of Dermatology, Venereology and Allergology, University Hospital Schleswig-Holstein Campus, Kiel, Germany
Co-author of
Chapter 13: Clinical Immunology, Allergy and Photoimmunology

Scully, Crispian
CBE, MD, PhD, MDS, MRCS, BSc, FDSRCS, FDSRCPS, FFDRCSI, FDSRCSE, FRCPath, FMedSci, FHEA, FUCL, DSc, DChD, DMed(HC), Drh.c.
Director (Special Projects) and Professor UCL-EDI, 256 Gray's Inn Road, London WC1X 8LD
Co-author of
Chapter 69: The Oral Cavity and Lips

Shahidullah, Hossain
BMedSci, MD, FRCP Edin
Consultant Dermatologist, Department of Dermatology, Derbyshire Royal Infirmary, London Road, Derby DE1 2QY
Co-author of
Chapter 18: Naevi and other Developmental Defects

Sinclair, Rodney D.
MBBS, MD, FACD
Professor and Director of Dermatology, Department of Dermatology, St Vincent's Hospital, Fitzroy, Melbourne, Victoria 3065, Australia
Co-author of
Chapter 66: Disorders of Hair

Smith, Catherine H.
MD, FRCP
Consultant Dermatologist and Senior Lecturer, St John's Institute of Dermatology, St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH
Co-author of
Chapter 72: General Aspects of Treatment
Chapter 74: Systemic Therapy

Spickett, Gavin P.
MA, DPhil, FRCPath. FRCP, FRCPE
Consultant Clinical Immunologist, Regional Department of Immunology, Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP
Co-author of
Chapter 13: Clinical Immunology, Allergy and Photoimmunology

Steinhoff, Martin
MD, PhD
Department of Dermatology, University of Münster, Von-Esmarch-Strasse 58D-48149, Münster, Germany
Co-author of
Chapter 12: Inflammation

Sterling, Jane C.

MB, BChir, MA, FRCP, PhD
Senior Lecturer, Department of Dermatology, University of Cambridge, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ
Author of
Chapter 33: Virus Infections

Telfer, Nicholas R.

FRCP
Consultant Dermatological Surgeon, Department of Dermatology, Salford Royal Hospital, Stott Lane, Salford, Lancs M6 8HD
Co-author of
Chapter 77: Dermatological Surgery

Uitto, Jouni

MD, PhD
Professor and Chair, Department of Dermatology and Cutaneous Biology, Jefferson Institute of Molecular Medicine, Thomas Jefferson University, 233 South 10th Street, Philadelphia PA19107, USA
Co-author of
Chapter 3: Anatomy and Organization of Human Skin

Veale, Douglas J.

MD, FRCFI, FRCP (Lon)
Consultant Rheumatologist, Department of Rheumatology, Bone and Joint Unit, St Vincent's University Hospital, Elm Park, Dublin 4, Republic of Ireland
Co-author of
Chapter 51: The 'Connective Tissue Diseases'

Vega-López, Francisco

MD, MSc, PhD, MFTM, RCPSG, FRCP
Consultant Dermatologist, University College London Hospitals NHS Foundation Trust and Honorary Professor, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT
Co-author of
Chapter 37: Parasitic Worms and Protozoa

Venning, Vanessa A.

DM, FRCP
Consultant Dermatologist, Department of Dermatology, Churchill Hospital, Old Road, Headington, Oxford OX3 7LJ
Co-author of
Chapter 40: Immunobullous Diseases

Weismann, Kaare

MD, PhD
Professor of Dermatology, Consultant Dermatologist, The Skin Clinic, Privatehospital Hamlet, DK-2860 Søborg, Denmark
Co-author of
Chapter 59: Metabolic and Nutritional Disorders

Whittaker, Sean J.

MD, FRCP
Head of Clinical Services, St John's Institute of Dermatology, St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH
Author of
Chapter 57: Cutaneous Lymphomas and Lymphocytic Infiltrates

Wilkinson, S. Mark

MD, FRCP
Department of Dermatology, Leeds General Infirmary, Great George Street, Leeds LS1 3EX
Co-author of
Chapter 25: Contact Dermatitis: Irritant
Chapter 26: Contact Dermatitis: Allergic

Williams, Hywel C.

FRCP, MSc, PhD
Professor of Dermato-Epidemiology, Centre of Evidence-Based Dermatology, Nottingham University Hospitals NHS Trust, Derby Road, Nottingham NG7 2UH
Author of
Chapter 6: Epidemiology of Skin Disease
Co-author of
Chapter 7: Evidence-Based Dermatology

Wojnarowska, Fenella

BM, BCh, DM(Oxon), FRCP
Professor of Dermatology, Department of Dermatology, Churchill Hospital, Old Road, Headington, Oxford OX3 7LJ
Co-author of
Chapter 40: Immunobullous Diseases

Yates, Victoria M.

MBChB, FRCP
Honorary Consultant Dermatologist, The Dermatology Centre, Salford Royal NHS Foundation Trust, Greater Manchester and Department of Dermatology, Royal Bolton NHS Trust, Minerva Road, Bolton BL4 0JR
Author of
Chapter 31: Mycobacterial Infections

Young, Antony R.

PhD
Professor of Experimental Photobiology, St John's Institute of Dermatology, Division of Genetics and Molecular Medicine, King's College School of Medicine, King's College London, Guy's Hospital, London SE1 9RT
Co-author of
Chapter 29: Cutaneous Photobiology

Preface to the Eighth Edition

Just over forty years ago, the first edition of *Textbook of Dermatology* was published under the leadership of Arthur Rook, Darrell Wilkinson and John Ebling. Now designated *Rook's Textbook of Dermatology*, but known to many dermatologists as 'The Rook book', or simply 'Rook', it is in its eighth edition.

The editorial team that supervised compilation of the seventh edition has also been involved in preparation of the current edition. As always, we would like to express our gratitude to previous editors and contributors whose efforts have provided the framework upon which this book has expanded and continued to evolve over the years. We are also indebted to contributors to earlier editions who have generously allowed some of their material to be retained for the present edition, and to those colleagues who have donated colour photographs. The origin of these is given in the legend to each figure, and where no acknowledgement is given the figures have been provided by the authors of that chapter.

Our aim is to continue to provide an updated reference guide to dermatological diseases, and to encourage understanding of scientific aspects of dermatology, although the book is not intended to provide extensive details of research in the basic sciences. Nowadays there is electronic access to vast amounts of information, but we believe that a reference textbook, which can be readily accessed in the clinic or consulting room, or perused at leisure in an armchair, continues to be a valuable resource.

For this edition, every chapter has been updated, and several have been extensively modified and expanded, including the chapters on comparative dermatology and radiotherapy and reactions to ionizing radiation. There is also a separate chapter on the sexually transmitted diseases. Changes to chapters dealing with lasers and dermatological surgery reflect developments in recent years, and a new chapter describing skin rejuvenation procedures is indicative of the interest in this aspect of dermatology.

We thank our long-suffering wives and families for their tolerance and support over many years.

We should also like to thank the production team of Wiley-Blackwell for their efforts throughout the preparation of this edition, in particular Julie Elliott, Martin Sugden, Anne Bassett, the indexer Caroline Sheard, and the copy editor and proof reader.

D.A. Burns
S.M. Breathnach
N.H. Cox
C.E.M. Griffiths

Preface to the First Edition

No comprehensive reference book on dermatology has been published in the English language for ten years and none in England for over a quarter of a century. The recent literature of dermatology is rich in shorter texts and in specialist monographs but the English-speaking dermatologist has long felt the need for a substantial text for regular reference and as a guide to the immense monographic and periodical literature. The editors have therefore planned the present volume primarily for the dermatologist in practice or in training, but have also considered the requirements of the specialist in other fields of medicine and of the many research workers interested in the skin in relation to toxicology or cosmetic science.

An attempt has been made throughout the book to integrate our growing knowledge of the biology of skin and of fundamental pathological processes with practical clinical problems. Often the gap is still very wide but the trends of basic research at least indicate how it may eventually be bridged. In a clinical textbook the space devoted to the basic sciences must necessarily be restricted but a special effort has been made to ensure that the short accounts which open many chapters are easily understood by the physician whose interests and experience are exclusively clinical.

For the benefit of the student we have encouraged our contributors to make each chapter readable as an independent entity, and have accepted that this must involve the repetition of some material.

The classification employed is conventional and pragmatic. Until our knowledge of the mechanisms of disease is more profound no truly scientific classification is possible. In so many clinical syndromes multiple aetiological factors are implicated. To emphasize one at the expense of others is often misleading. Most diseases are to some extent influenced by genetic factors and a large proportion of common skin reactions are modified by the emotional state of the patient. Our knowledge is in no way advanced by classifying hundreds of diseases as genodermatoses and dozens as psychosomatic.

The true prevalence of a disease may throw light on its aetiology but reported incidence figures are often unreliable and incorrectly interpreted. The scientific approach to the evaluation of racial and environmental factors has therefore been considered in some detail.

The effectiveness of any physician in practice must ultimately depend on his ability to make an accurate clinical diagnosis. Clinical descriptions are detailed and differential diagnosis is fully discussed. Histopathology is here considered mainly as an aid to diagnosis but references to fuller accounts are provided.

The approach to treatment is critical but practical. Many empirical measures are of proven value and should not be abandoned merely because their efficacy cannot yet be scientifically explained. However, many familiar remedies old and new have been omitted either because properly controlled clinical trials have shown them to be of no value or because they have been supplanted by more effective and safer preparations.

There are over nine hundred photographs but no attempt has been made to provide an illustration of every disease. To have done so would have increased the bulk and price of the book without increasing proportionately its practical value. The conditions selected for illustrations are those in which a photograph significantly enhances the verbal description. There are a few conditions we wished to illustrate, but of which we could not obtain unpublished photographs of satisfactory quality.

The lists of references have been selected to provide a guide to the literature. Important articles now of largely historical interest have usually been omitted, except where a knowledge of the history of a disease simplifies the understanding of present concepts and terminology. Books and articles provided with a substantial bibliography are marked with an asterisk.

Many of the chapters have been read and criticized by several members of the team and by other colleagues. Professor Wilson Jones, Dr R.S. Wells and Dr W.E. Parish have given valuable assistance with histopathological, genetic and immunological problems respectively. Many advisers, whose services are acknowledged in the following pages, have helped us with individual chapters. Any errors which have not been eliminated are, however, the responsibility of the editors and authors.

The editors hope that this book will prove of value to all those who are interested in the skin either as physicians or as research workers. They will welcome readers' criticisms and suggestions which may help them to make the second edition the book they hope to produce.

CHAPTER 1
Introduction and Historical Bibliography

D.A. Burns[1] *& N.H. Cox*[2]

[1]Leicester Royal Infirmary, Leicester, UK
[2]Department of Dermatology, Cumberland Infirmary, Carlisle, UK

What is dermatology?, 1.1
The evolution of dermatology, 1.1
The dermatologist's work, 1.5
Selected historical bibliography, 1.8

What is dermatology?

Dermatology is defined in The New Oxford Dictionary of English as 'The branch of medicine concerned with the diagnosis and treatment of skin disorders' [1]. However, dermatologists do not confine themselves merely to a study of intrinsic disorders of the skin, but must also study internal medicine and the many environmental and occupational factors that so frequently cause skin problems.

A plethora of external factors, including numerous chemicals, can adversely affect the skin in some circumstances. The clinical dermatologist must be knowledgeable about these potential hazards, and this will often require a detailed study of the multiplicity of chemicals, plants, animals, parasites, microorganisms, radiation, climatic conditions, etc. to which the skin is exposed. In many cases, the dermatologist will need to obtain exact details of what is involved in the patient's occupation and hobbies, and many dermatologists build up a considerable knowledge of the different jobs involved in their local industries.

The dermatologist must also have a good knowledge of internal medicine, as most systemic diseases can occasionally affect the skin, either directly or as a result of a complication of the disease or its treatment. Drugs taken by the patient have to be considered by the dermatologist, because the unwanted effects of many drugs include provocation of rashes. This applies not only to prescribed medication, but also to over-the-counter and complementary/alternative remedies. The use of complementary medicine is increasing in the Western world, and many individuals with dermatological problems use such remedies [2–4], their availability having been made easier by the advent of the Internet [5].

A dermatologist must also pay attention to the psyche, as psychological factors play an important part in dermatology. The skin is of major importance in our 'body image', and the fact that skin diseases are often regarded with revulsion by the general population adds to the distress they cause, so that the psychological disturbance induced by skin problems may be out of all proportion to their 'medical' significance. Sometimes, these psychological problems are exacerbated by the reactions of the patient's relatives, friends or colleagues, and in other cases they are partly accounted for by feelings of guilt or despondency, induced by the belief that skin diseases are due to 'uncleanliness' of some kind (with or without sexual overtones). In recent years there has been increasing awareness of the impact of skin diseases on social and leisure activities, work and sexual relationships, and questionnaires such as the Dermatology Life Quality Index (DLQI) have been employed to measure the impairment of quality of life (see Chapter 72). Not only may skin diseases cause stress or depression, but also psychological stress from another cause can exacerbate, or even be involved in causation of, some skin diseases.

Whatever the complexity of these psychological nuances, the dermatologist must be aware of their existence and try to deal with them accordingly. As described later (Chapter 64), some patients have 'skin problems' that are imagined or self-inflicted, and the presentation to the dermatologist seems to be a 'cry for help' with marital or other social problems. In other cases, the dermatological consultation may be a manifestation of an underlying psychological disorder such as depression or schizophrenia.

References

1 Pearsall J, ed. *The New Oxford Dictionary of English*. Oxford: Oxford University Press, 1998.
2 Baron SE, Goodwin RG, Nicolau N *et al*. Use of complementary medicine among outpatients with dermatologic conditions within Yorkshire and South Wales, United Kingdom. *J Am Acad Dermatol* 2005; **52**: 589–94.
3 Berk DR, Kanzler MH. Prevalence of alternative medicine use for skin conditions in a primary care population. *Arch Dermatol* 2004; **140**: 892.
4 Elston DM. Escharotic agents, Fred Mohs and Harry Hoxsey. *J Am Acad Dermatol* 2005; **53**: 523–5.
5 Affleck A, Varma S. A case of DIY Mohs surgery using bloodroot obtained from the internet. *Br J Dermatol* 2007; **157** (Suppl. 1): 111–2.

The evolution of dermatology

Skin diseases predate written records, and many of the earliest medical writings deal with dermatological subjects. The history of dermatology is too large a subject to be covered in this book, although a selected historical bibliography is given at the end of this chapter. The development of modern dermatology is briefly outlined below.

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

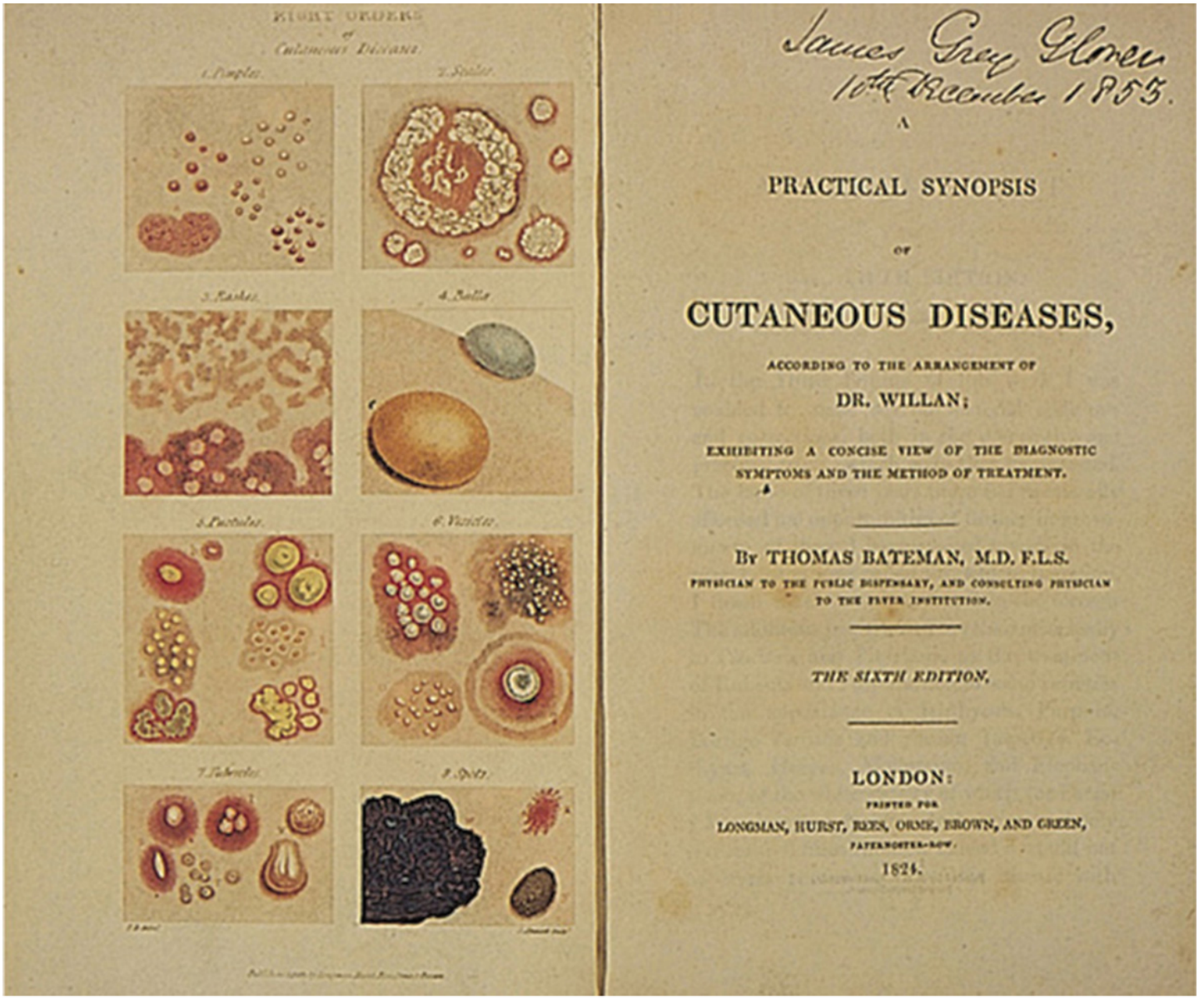


Fig. 1.1 The title page and facing plate from the 6th edition (1824) of Thomas Bateman's *A Practical Synopsis of Cutaneous Diseases, According to the Arrangement of Dr Willan*. The plate shows the eight orders of cutaneous eruption in Willan's classification.

Dermatology evolved as a branch of internal medicine during the 19th century. Previously, many diseases of the skin had fallen within the province of the quack or the surgeon, and indeed many of the older surgical textbooks devote much attention to the treatment of skin disease. The physicians of that time were little concerned with the skin, apart from the eruptions of the acute infectious fevers. In the early 18th century, individuals such as Daniel Turner advocated use of preparations applied to the skin as treatment for internal diseases. During the last decades of the 18th century, however, many of the great physicians began to record their observations on the diseases of the skin, and this continued throughout the 19th century. Towards the end of that century, skin diseases, particularly the chronic infections such as syphilis and tuberculosis, formed a significant part of the general physician's practice, and by the early 20th century some physicians were beginning to specialize in dermatology. This trend towards increasing specialization has continued ever since.

In the first half of the 20th century, dermatology was slow to develop along scientific lines. The emphasis was very much on the clinical description, naming and classification of the numerous skin disorders, and this led to a profusion of synonyms which are daunting to those attempting to get to grips with dermatological nomenclature. Only empirical treatment was available, and it was often ineffective, messy and malodorous. Dermatology certainly lagged behind some of the other medical specialties in its understanding of basic disease processes. In retrospect, this seems to

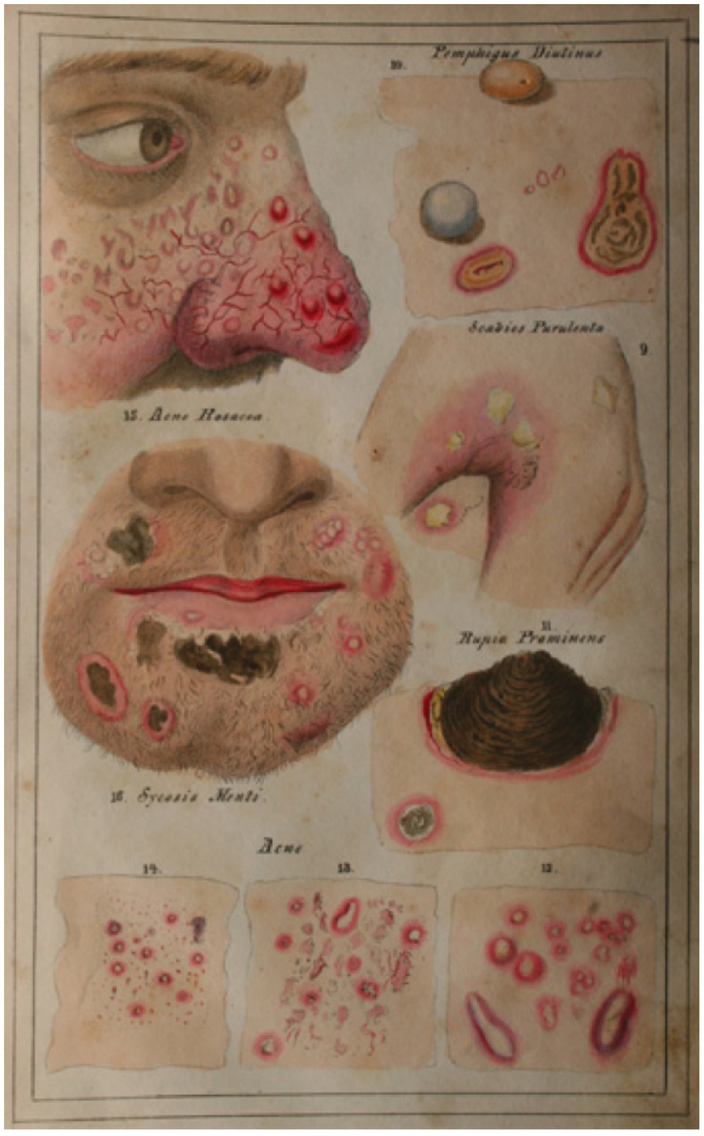


Fig. 1.2 A variety of mainly pustular disorders, from N Worcester, *A Synopsis of the Symptoms, Diagnosis and Treatment of the More Common and Important Diseases of the Skin* (1845).

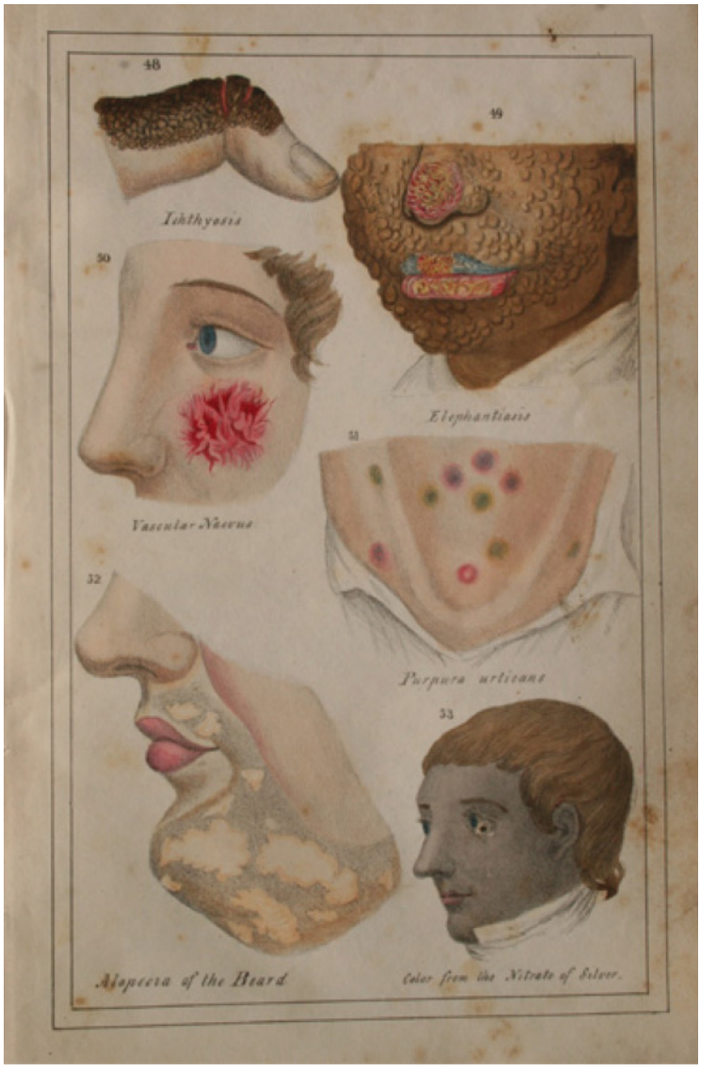
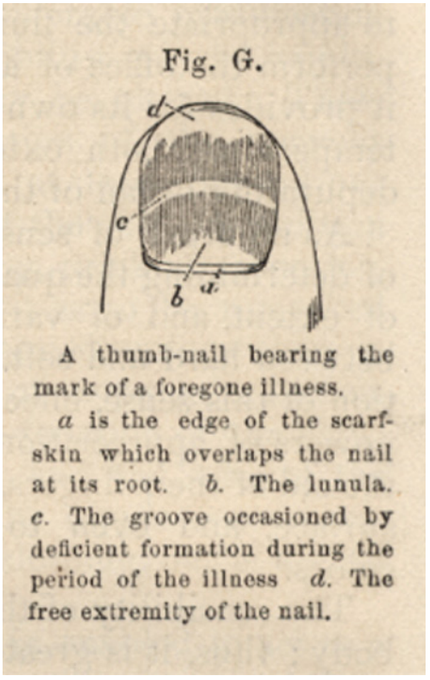


Fig. 1.3 Illustrations from N Worcester, *A Synopsis of the Symptoms, Diagnosis and Treatment of the More Common and Important Diseases of the Skin* (1845), including a dramatic illustration of argyria (made more startling by the shift in position of the blue colouring of the pupil of the eye).

have been due to two main factors. The first was that most skin diseases could be identified by external examination alone, and therefore seemed to need no further investigation. The second, and perhaps more important factor, was that most skin diseases could not be investigated by the relatively crude tests that were available at that time. It was only when skin biopsy became a standard technique, with the plethora of pathological knowledge that followed, that an understanding of the pathogenesis of many skin diseases began to emerge.

In the second half of the 20th century, there was an explosion of dermatological knowledge, mainly as a result of the introduction of sophisticated research techniques which not only led to a better knowledge of the pathogenesis and treatment of skin disorders, but also facilitated the development of more targeted treatments. The need for measurement and a more scientific approach in dermatology was made over 40 years ago [1], and research, at least during training, became the norm for generations of dermatologists. Advances in pathology techniques, especially immunopathology, helped the understanding of skin disease. More recently, the techniques of molecular biology have also been applied (Chapter 11), leading to, amongst other things, important developments in genetics and the understanding of mechanisms underlying cancer. As a result, increasing numbers of non-medical scientists are studying the skin, and its accessibility, which paradoxically inhibited investigation in the first half of the 20th century, is now of course very helpful to the research worker.

Dermatological treatment patterns have changed over the last 50 years, and will no doubt continue to do so. Recent advances in treatment include topical immunosuppressants, immune response modifiers, enzyme replacement treatments (e.g. for


Fig. G.

A thumb-nail bearing the mark of a foregone illness.

a is the edge of the scarf-skin which overlaps the nail at its root. *b*. The lunula. *c*. The groove occasioned by deficient formation during the period of the illness *d*. The free extremity of the nail.

Fig. 1.4 An early picture of a Beau's line, from the section on nail growth in Erasmus Wilson's *Diseases of the Skin; a System of Cutaneous Medicine*. This is from the 1868 revised 6th edition. Erasmus Wilson also published major works on anatomy.



Fig. 1.6 Infantile eczema. From: JV Shoemaker, *A Practical Treatise on Diseases of the Skin* (1890).



Fig. 1.5 Cutaneous horns. From: JV Shoemaker, *A Practical Treatise on Diseases of the Skin* (1890).

Fabry's disease) and biological therapies for psoriasis and other dermatoses. Further sophistication in treatment should parallel increasing knowledge of the roles of inflammatory mediators in disease, and gene therapy is on the horizon. Some older treatment modalities, such as radiotherapy, are used much less, but are still of considerable value in selected cases (Chapter 79) and have even increased in use for some conditions such as lentigo maligna.

Dermatology is thus changing at an ever-accelerating pace, both in the amount of scientific knowledge and treatments available, and with regard to disease patterns and patients' expectations. Increasing specialization within dermatology is becoming more common, with the expansion of expertise in dermatological surgery, laser therapy, photobiology, contact allergy, histopathology, and other areas; some dermatologists now only work in subspecialty areas such as paediatric dermatology, skin surgery, etc. Certainly, dermatologists can no longer be regarded only as general physicians with an interest in the skin, although some training in internal medicine is still regarded as desirable in most countries. In the UK, trainee dermatologists are expected to have completed a minimum of 2 years of general professional training and to have passed a postgraduate examination in general medicine (Membership of the Royal College of Physicians, MRCP) before they can start their specialist training in dermatology. The specialist training entails 4 years in an approved training post, with an annual assessment of progress, on satisfactory completion of which the trainee is awarded a Certificate of Completion of Training (CCT).

It seems possible that the days of the generalist dermatologist are numbered. Future dermatologists will perhaps regard themselves as dermatological physicians, surgeons or researchers and train accordingly. The future cannot be predicted, but it seems certain that with the increasing sophistication of populations throughout the world, the demand for dermatological expertise is likely to increase.



Fig. 1.7 Discoid lupus erythematosus, from Henry Radcliffe Crocker's *Atlas of Diseases of the Skin* (1896). Radcliffe Crocker made many contributions to dermatology; this atlas was available in an unbound form, apparently so that the colour plates could be used for teaching.

Reference

1 Shuster S. Trends in dermatology (Dowling Oration). *Trans St John's Hosp Dermatol Soc* 1966; **52**: 163–75.

The dermatologist's work

There are probably at least 2000 different skin conditions that might present to the dermatologist, and the conditions seen vary enormously in severity. They range from cosmetic problems, such as dry skin or wrinkles, through a huge variety of acute or chronic diseases, which may be disfiguring, itchy or painful, but are rarely fatal, to life-threatening conditions, which, if untreated, may prove fatal within days (e.g. toxic epidermal necrolysis), weeks (e.g. pemphigus), months (e.g. malignant melanoma) or years (e.g. mycosis fungoides). In the UK, about 70% of consultations for dermatological problems are related to skin cancer, acne, psoriasis, viral warts and other infections, benign tumours, leg ulcers, and various forms of dermatitis [1]. In an audit of dermatology services in Edinburgh, UK, in November 2005, management of patients with eczema and psoriasis accounted for one-third of outpatient clinic visits. It was notable that, compared with data from 1980, attendances for both benign and malignant skin tumours had increased six-fold [2].

Obviously, the pattern of disease varies from one country to another, and even in the same city the work of dermatologists will differ, depending on their particular interests and expertise and on the social mix of their patients. Involvement with cosmetic procedures, in particular, varies according to the constraints of the health-care system in which the dermatologist works.



Fig. 1.8 Sarcoma cutis, from Radcliffe Crocker, *Atlas of Diseases of the Skin* (1896). The reasons behind wide excision of melanoma are readily apparent.

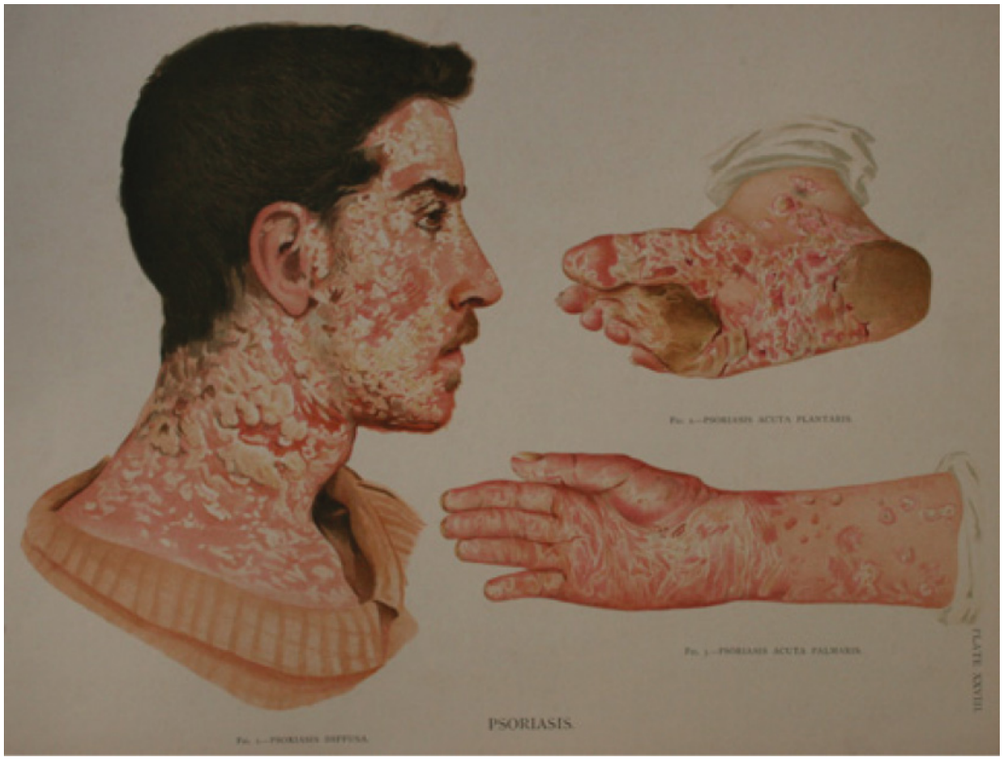


Fig. 1.9 Psoriasis, from Radcliffe Crocker, *Atlas of Diseases of the Skin* (1896); the illustration is as valid now as it was then.

Space precludes any detailed consideration of the work of dermatologists throughout the world, but in the British system patients are normally first seen by a primary-care physician (general practitioner [GP]) who refers the patient to the hospital consultant if he or she thinks it necessary or advisable (secondary care). It has been estimated that around one in seven primary care consultations relates to a dermatological problem [3,4]. Hospital dermatology services are provided by consultant dermatologists and their supporting staff. The British Association of Dermatologists provides guidelines for provision of services in secondary care [5], and the current working target with regard to consultant dermatologists is 1/100 000 population (assuming that there is provision of some supporting medical staff and nursing expertise), although in parts of the UK this is not achieved. There is government pressure in the UK for some dermatology services to be provided in smaller community settings [6], rather than in secondary-care hospitals. A more seamless 'Integrated service' has been proposed, with dermatologists having a greater role in teaching, care of complex patients, and administration of this new model of care [7]. This system would involve more non-medical practitioners such as expert nurses and pharmacists, but the mainstay of the intermediate level of care is likely to be provided by GPs, who have undertaken additional training in dermatology and work as a team, performing some independent clinics and some clinics with consultant staff. Subsequent research has shown potential advantages of this intermediate grade (termed GP with a Special Interest, GPwSI) in provision of local services for patients, but there is also some unease about the relatively small amount of training that some such individuals undertake and some aspects of care have been documented as less safe or more expensive [8,9].

In the USA, the dermatologist-to-population ratio increased from 1.9 per 100 000 in 1970 to 3.5 per 100 000 in 2002 [10], although there is considerable interstate and intrastate variation in this ratio [11]. There are, of course, some countries from which dermatologists are conspicuously absent.

There is continuing concern about provision of an adequate number of trained dermatologists to satisfy increasing demand, and that an increase in the number of dermatologists specializing in surgical and cosmetic procedures might lead to a shortage of those dealing with 'medical' dermatology patients [10–16]. It is also important that planning should take account of factors such as age [17], the high proportion of women in dermatology and the changing roles of nursing staff [18].

Many skin diseases, for example warts, acne vulgaris or psoriasis, can be quickly diagnosed by their clinical features, and need little or no further investigation. At the other extreme, there are some patients, for example those with lymphoma, who need detailed and time-consuming investigations both to confirm the diagnosis and as a basis for treatment.

The most common investigations performed in a dermatology clinic, other than simple blood tests or swabs for microbiology, are skin biopsies. Other investigations include the extraction and identification of scabies mites, the microscopic examination of hairs, microscopy for fungal mycelia or spores, patch testing and photopatch testing. In occasional cases, special procedures may be needed, such as the examination of pets for animal parasites, or a visit to the patient's workplace or home to search for possible allergens.



Fig. 1.10 Structure of the skin, from WS Gottheil, *Skin Diseases* (1897).



Fig. 1.11 Scabies, from RW Taylor, *A Clinical Atlas of Venereal and Skin Diseases* (1889).



Fig. 1.12 Impetigo contagiosa, from the *Portfolio of Dermochromes* by Professor Jacobi (1903). The English adaptation of the text was performed by JJ Pringle of the Middlesex Hospital. The majority of the illustrations were of models in the Breslau Clinic.

The management of this infinite variety of skin disorders ranges from simple reassurance and explanation through the gamut of topical and systemic remedies, to the performance or supervision of numerous physical procedures such as UV irradiation, photochemotherapy, curettage and cautery, surgical excision and laser treatment. Some dermatologists will also undertake complicated and specialized techniques such as prenatal investigation and Mohs micrographic surgery, which may require close collaboration with other specialists, and newer techniques such as photodynamic therapy are finding a niche in the dermatologist's armamentarium.

Greater patient expectations and a generally more litigious attitude in society have combined in recent years to fuel physicians' concern about being sued, and the increasing complexity of dermatological practice and involvement in cosmetic procedures may heighten the risk. Thankfully, however, litigation is still relatively infrequent in dermatology compared with other specialties [19–21]. Evidence-based guidelines have been produced for many dermatological conditions, both in the UK [22] and in many other countries [23,24], and are probably helpful in encouraging good practice (although evidence that they fundamentally alter practice is lacking); manufacturers of some drugs used in dermatology produce quite rigid guidance (for example, for administration of isotretinoin in females), and dermatologists in the UK are also subject to various government directives, such as those from the National Patient Safety Agency and the National Institute of Health and Clinical Excellence. These may apply to uses of certain medications (e.g. prescribing of methotrexate, or of specific biological agents,

for psoriasis) or may cover a broader remit, such as guidelines for management of skin cancer [25].

References

1 Williams HC. *Dermatology. Health Care Needs Assessment*. Second Series. Oxford: Radcliffe Medical Press, 1997.
2 Benton EC, Kerr OA, Fisher A *et al*. Dermatology workload: twenty-five years on. *Br J Dermatol* 2007; **157** (Suppl. 1): 57.
3 Fry J. *General Practice: The Facts*. Oxford: Radcliffe Medical Press, 1993.
4 Kerr OA, Benton EC, Walker JJ *et al*. Dermatological workload: primary versus secondary care. *Br J Dermatol* 2007; **157** (Suppl. 1): 1–2.
5 British Association of Dermatologists. *Service Provision Guidelines*. http://www.bad.org.uk/guidelines/service
6 Department of Health. *Implementing Care Closer to Home: convenient quality care for patients*. http://www.pcc.nhs.uk/173.php
7 Dermatology Workforce Group, 2007. *Models of Integrated Service Delivery in Dermatology*. http://www.bad.org.uk/healthcare/service/Service_Models_Final_(February_2007).pdf
8 National Coordinating Centre for NHS Service Delivery and Organization, 2005. *Evaluation of a Primary Care Dermatology Service: final report*. http://www.sdo.nihr.ac.uk/files/project/34-final-report.pdf
9 National Coordinating Centre for NHS Service Delivery and Organization. Can primary care reform reduce demand on hospital outpatient departments? http://www.sdo.nihr.ac.uk/files/adhoc/82-research-summary.pdf
10 Resneck J Jr, Kimball AB. The dermatology workforce shortage. *J Am Acad Dermatol* 2004; **50**: 50–4.
11 Resneck J Jr. Too few or too many dermatologists? *Arch Dermatol* 2001; **137**: 1295–301.
12 Suneja T, Smith ED, Chen GJ *et al*. Waiting times to see a dermatologist are perceived as too long by dermatologists. Implications for the dermatology workforce. *Arch Dermatol* 2001; **137**: 1303–7.
13 Williams HC. Increasing demand for dermatological services: how much is needed? *J Roy Coll Phys Lond* 1997; **31**: 261–2.
14 Werth VP, Voorhees J, Freedberg IM, Sontheimer RD. Preserving medical dermatology. A colleague lost, a call to arms, and a plan for battle. *Dermatol Clin* 2001; **19**: 583–92.
15 Resneck JS Jr, Tierney EP, Kimball AB. Challenges facing academic dermatology: survey data on the faculty workforce. *J Am Acad Dermatol* 2006; **54**: 211–6.
16 Loo DS, Liu C, Geller AC *et al*. Academic dermatology manpower. *Arch Dermatol* 2007; **143**: 341–7.
17 Jacobson CC, Resneck JS Jr, Kimball AB. Generational differences in practice patterns of dermatologists in the United States: implications for workforce planning. *Arch Dermatol* 2004; **140**: 1477–82.
18 Cox NH. The expanding role of nurses in surgery and prescribing in British departments of dermatology. *Br J Dermatol* 1999; **140**: 681–4.
19 Drummond A, Kane D, Bilsland D. Legal claims in Scottish National Health Service dermatology departments 1989–2001. *Br J Dermatol* 2003; **149**: 111–4.
20 Read S, Hill HF 3rd. Dermatology's malpractice experience: clinical settings for risk management. *J Am Acad Dermatol* 2005; **53**: 134–7.
21 Resneck JS Jr. Trends in malpractice premiums for dermatologists. Results of a national survey. *Arch Dermatol* 2006; **142**: 337–40.
22 British Association of Dermatologists. *Clinical Guidelines*. http://www.bad.org.uk/healthcare/guidelines
23 American Academy of Dermatology. *Clinical Research and Guidelines*. http://www. aad.org/research/guidelines.html
24 New Zealand Dermatological Society. http://www.dermnetnz.org/doctors
25 National Institute for Clinical Excellence (NICE). *Improving Outcomes for People with Skin Tumours Including Melanoma: The Manual, 2006*. http://www.nice.org.uk/nicemedia/pdf/CSG_Skin_Manual.pdf

Selected historical bibliography

Books on the history of dermatology

1 Ainsworth GC. *Introduction to the History of Mycology*. Cambridge: University Press, 1976.
2 Crissey JT, Parish LC. *The Dermatology and Syphilology of the Nineteenth Century*. New York: Praeger, 1981.
3 Crissey JT, Parish LC, Holubar K. *Historical Atlas of Dermatology and Dermatologists*. Boca Raton: Parthenon, 2002.
4 Dyall-Smith D, O'Brien T, eds. Dermatological discoveries of the 20th century: a record of selected dermatological discoveries throughout the century. A supplement to the 19th World Congress of Dermatology: Sydney, 1997.
5 Friedman R. *A History of Dermatology in Philadelphia*. Florida: Froben, 1955.
6 Friedman R. *The Story of Scabies*. New York: Froben, 1967.
7 Gold S. *A Biographical History of British Dermatology*. London: British Association of Dermatologists, 1995/96 (now available at http://www.bad.org.uk/public/history).
8 Klasen JH. *History of Free Skin Grafting—Knowledge or Empiricism*? Berlin: Springer-Verlag, 1981.
9 Malacrida LM, Panconesi E. *Vincenzo Chiarugi, his Times, and his Book on Sordid Cutaneous Diseases*. Florence: Edizioni Riviste Scientifiche, 1989.
10 Mettler CC, Mettler FA. *History of Medicine*. Philadelphia: Blakiston, 1947: 660–89.
11 Parish LC, Louis A. *Duhring MD; Pathfinder for Dermatology*. Springfield: Thomas, 1967.
12 Pusey WA. *The History of Dermatology*. Springfield: Thomas, 1979.
13 Russell B. *St John's Hospital*. Edinburgh: Livingstone, 1963.
14 Russo GG, Parish JL. *The History of Dermatology*. New York: Parthenon, 2001.
15 Schönfeld W. *Kurze Geschichte der Dermatologie und Venerologie*. Hanover: Oppermann, 1954.
16 Shelley WB, Crissey JT. *Classics in Clinical Dermatology: with Biographical Sketches*, 2nd edn. Boca Raton: Parthenon, 2003.
17 Shelley WB, Shelley ED. *A Century of International Dermatological Congresses*. Parthenon, 1992.
18 Sutton RL. *The Sixteenth Century Physician and his Methods: Mercurialis on Diseases of the Skin*. Kansas City: Lowell Press, 1986.
19 Tilles G. *La Naissance de la Dermatologie (1776–1880)*. Paris: R. da Costa, 1989. (This book contains short biographies of Alibert, Cazenave, Hebra, Hutchinson, Kaposi, Lorry, Plenck, Willan, Wilson, Unna and others, with 90 colour plates reproduced from their books.)
20 Wasserman HP. *Ethnic Pigmentation: Historical, Physiological and Clinical Aspects*. Amsterdam: Excerpta Medica; New York: American Elsevier, 1974.
21 Wilson PK. *Surgery, Skin and Syphilis. Daniel Turner's London (1667–1741)*. Amsterdam: Editions Rodopi BV, 1999.

General articles

Ancient and medieval dermatology

1 Cotterill JA. Choosing a dermatological hero for the Millennium. William Shakespeare (1564–1616). *Clin Exp Dermatol* 2000; **25**: 93–5.
2 Dirckx JH. Ovid's dermatologic formulary. *Am J Dermatopathol* 1980; **2**: 327–32.
3 Dirckx JH. Dermatologic terms in the De Medicina of Celsus. *Am J Dermatopathol* 1983; **5**: 363–9.
4 Huckbody E. Dermatology throughout the dark ages. The interchange of experience. *Int J Dermatol* 1980; **19**: 344–7.
5 Lascaratos J, Tsiamis C, Lascaratos G, Stavrianeas NG. The roots of cosmetic medicine: hair cosmetics in Byzantine times (AD 324–1453). *Int J Dermatol* 2004; **43**: 397–401.
6 Laur WE. Shave and a haircut—two sesterces: a brief account of men and their hair in Imperial Rome. *Int J Dermatol* 1981; **20**: 504–5.
7 Liddell K. Choosing a dermatological hero for the Millennium. Hippocrates of Cos (460–377 BC). *Clin Exp Dermatol* 2000; **25**: 86–8.
8 Liddell K. Skin disease in antiquity. *Clin Med* 2006; **6**: 81–6.
9 Lieber E. Skin diseases: contagion and sin in the Old Testament. *Int J Dermatol* 1994; **33**: 593–5.
10 Marmelzat WL. History of dermatologic surgery. From the beginnings to late antiquity. *Clin Dermatol* 1987; **5**: 1–10.
11 Marmelzat WL. Medicine and history. The contributions to dermatologic surgery of Aulus Cornelius Celsus (circa 30 B.C.–A.D. 50). *J Dermatol Surg Oncol* 1977; **3**: 161–2, 166.
12 Menon IA, Haberman HF. Dermatological writings of ancient India. *Med Hist* 1969; **13**: 387–92.

13 Obermayer ME. Mexican dermatology of the pre-Columbian period. *Int J Dermatol* 1974; **13**: 293–9.
14 Pastinszky I. Die Dermatologie in lateinischen Sprichwörtern, Zitaten und Redewendungen. *Dermatol Monatsschr* 1973; **159**: 45–55.
15 Radbill SX. Pediatric dermatology in antiquity: Part I. *Int J Dermatol* 1975; **14**: 363–8.
16 Radbill SX. Pediatric dermatology in antiquity: Part II. Roman Empire. *Int J Dermatol* 1976; **15**: 303–7.
17 Radbill SX. Pediatric dermatology in antiquity: Part III. *Int J Dermatol* 1978; **17**: 427–34.
18 Simon I. La dermatologie hébraique dans l'Antiquité et au Moyen Age. (Périodes Biblique, Talmudique et Rabbinique.) *Rev Hist Med Heb* 1974; **110**: 149–54.
19 Solomons B. Disorders of the hair and their treatment before the 18th century. *Br J Dermatol* 1966; **78**: 113–20.
20 Steudel J. Bau und Funktion der Haut in der Antike. *Stud Generale* 1964; **17**: 583–8.
21 Sutton RL. Diseases of the skin. Mercurialis, 1572. *Arch Dermatol* 1966; **94**: 763–72.
22 Verbov J. Celsus and his contributions to dermatology. *Int J Dermatol* 1978; **17**: 521–3.
23 Zanca A, Zanca A. Ancient observations of 'uncombable hair syndrome'. *Int J Dermatol* 1993; **32**: 707.

More recent history

1 Albert MR. Nineteenth-century patent medicines for the skin and hair. *J Am Acad Dermatol* 2000; **43**: 519–26.
2 Albert MR, Mackool BT. A dermatology ward at the beginning of the 20th century. *J Am Acad Dermatol* 2000; **42**: 113–23.
3 Baer RL. Historical overview of the evolution of investigative dermatology (1775–1993). *J Invest Dermatol* 1994; **103**: 3–6.
4 Beerman H. Cutaneous pathology—a historical view. *J Cutan Pathol* 1974; **1**: 3–9.
5 Booth CC. Choosing a dermatologist for the Millennium. Robert Willan (1757–1812). *Clin Exp Dermatol* 2000; **25**: 85–6.
6 Booth CC. Robert Willan MD FRS (1757–1812): dermatologist of the Millennium. *J R Soc Med* 1999; **92**: 313–8.
7 Branford WA. Hutchinson and Nettleship, nettlerash and albinism. *Br J Dermatol* 2000; **143**: 16–22.
8 Burton JL. Diet and dermatology in 1888: the influence of H. Radcliffe Crocker. *Br J Dermatol* 1988; **119**: 471–7.
9 Caplan RM. Osler's legacies to dermatologists. *Int J Dermatol* 1998; **37**: 72–5.
10 Copeman PWM. Choosing a dermatological hero for the Millennium. Erasmus Wilson (1809–1884). *Clin Exp Dermatol* 2000; **25**: 82–4.
11 Cossidente A. History and fundamentals of psychosomatic dermatology. *Clin Dermatol* 1984; **2**: 1–16.
12 Crissey JT, Parish LC. Two hundred years of dermatology. *J Am Acad Dermatol* 1998; **39**: 1002–6.
13 Everett MA. Jean Louis Alibert. The father of French dermatology. *Int J Dermatol* 1984; **23**: 351–6.
14 Goldsmith LA. Mendelism in early 20th-century American dermatology. *Arch Dermatol* 1993; **129**: 1405–8.
15 Holubar K, Schmidt C. Art in dermatology versus dermatology in art. Anton Elfinger (1821–1864) and Carl Heitzmann (1836–1896) Hebra's forgotten painter-physicians. *Int J Dermatol* 1994; **33**: 385–7.
16 Hunter JAA. Turning points in dermatology during the 20th century. *Br J Dermatol* 2000; **143**: 30–40.
17 Jackson R. Historical outline of attempts to classify skin diseases. *Can Med Assoc J* 1977; **116**: 1165–8.
18 Leach D, Beckwith J. The founders of dermatology: Robert Willan and Thomas Bateman. *J R Coll Physicians Lond* 1999; **33**: 580–2.
19 Levell NJ. Thomas Bateman MD FLS 1778–1821. *Br J Dermatol* 2000; **143**: 9–15.
20 Muller GH. History of veterinary dermatology. *Int J Dermatol* 1977; **16**: 57–65.
21 Noojin RO. Brief history of industrial dermatology. *Arch Dermatol Syphilol* 1954; **70**: 723–31.
22 Ormsby OS. History of dermatology, 1847–1947. *Arch Dermatol Syphilol* 1949; **59**: 374–95.
23 Potter BS. Bibliographic landmarks in the history of dermatology? *J Am Acad Dermatol* 2003; **48**: 919–32.
24 Rees JL. Genetics, past and present, and the rise of systems dermatology. *Br J Dermatol* 2000; **143**: 41–6.
25 Roelandts R. The history of phototherapy: something new under the sun? *J Am Acad Dermatol* 2002; **46**: 926–30.
26 Rook A. Dermatology in Britain in the late 19th century. *Br J Dermatol* 1979; **100**: 3–11.
27 Rosser EJ Jr, Ongley RC. Comparative dermatology: a historical overview. *Clin Dermatol* 1994; **12**: 487–9.
28 Savin JA. Osler and the skin. *Br J Dermatol* 2000; **143**: 1–8.
29 Schnalke T. A brief history of the dermatologic moulage in Europe. *Int J Dermatol* 1988; **27**: 134–9.
30 Schnalke T. A brief history of the dermatologic moulage in Europe. Part II Breakthrough and rise. *Int J Dermatol* 1992; **31**: 134–41.
31 Schnalke T. A brief history of the dermatologic moulage in Europe. Part III Prosperity and decline. *Int J Dermatol* 1993; **32**: 453–63.
32 Siddiqui AH, Cormane RH. Dermatologic origins and developments down to the early twentieth century. *J Invest Dermatol* 1976; **66**: 122–5.
33 Tilles G, Wallach D. Robert Willan and the French Willanists. *Br J Dermatol* 1999; **140**: 1122–6.
34 Wallach D. Choosing a dermatological hero for the Millennium. Jean-Louis Alibert (1768–1837). *Clin Exp Dermatol* 2000; **25**: 90–3.
35 Wheeland RG. History of lasers in dermatology. *Clin Dermatol* 1995; **13**: 3–10.
36 Wilson PK. Choosing a dermatological hero for the Millennium. Daniel Turner (1667–1741). *Clin Exp Dermatol* 2000; **25**: 88–9.
37 Wright RC, Goldman L. Contact dermatitis: a historical perspective. *Int J Dermatol* 1979; **18**: 665–8.

History of various diseases

Blisters

1 Doubleday CW. Who is Nikolsky and what does his sign mean? *J Am Acad Dermatol* 1987; **16**: 1054–5.
2 Holubar K. Pemphigus. A disease of man and animal. (Historical and other aspects.) The 3rd Frank Kral Lecture. Philadelphia, 15 Oct 1987. *Int J Dermatol* 1988; **27**: 516–20.
3 Holubar K. Autoimmune skin disease since 1963. The rise of immunodermatology. *Dermatology* 1994; **189** (Suppl.): 3–5.
4 Holubar K. Historical background. In: Wojnarowska F, Briggaman R, eds. *Management of Blistering Diseases*. London: Chapman and Hall, 1990.
5 Lever WF. Savary's 1814 article on the history of pemphigus related to contemporary views. *Int J Dermatol* 1979; **18**: 584–5.
6 Panconesi E. Historical aspects of blistering eruptions. *Clin Dermatol* 1993; **11**: 437–9.

Pigmentation, moles and melanoma

1 Bennett JP, Hall P. Moles and melanoma: a history. *Ann R Coll Surg Engl* 1994; **76**: 373–80.
2 Garnis-Jones S, Jackson R. Origin of the nevus cell: a retrospective. *Int J Dermatol* 1992; **31**: 291–4.
3 McLeod GR, Davis NC. Historical overview of melanoma. *Clin Dermatol* 1992; **10**: 5–7.
4 Millington GWM, Levell NJ. From genesis to gene sequencing: historical progress in the understanding of skin color. *Int J Dermatol* 2007; **46**: 103–5.
5 Nordlund JJ. Pigment cell biology: an historical review. *J Invest Dermatol* 1989; **92** (Suppl. 4): 535–605.

Mycology

1 Ainsworth GC. A century of medical and veterinary mycology in Britain. *Trans Br Mycol Soc* 1951; **34**: 1.
2 Ditonzo EM. Milestones and protagonists in the history of human mycology. *Eur Acad Dermatol Venereol Bull* 1990; **1**: 11–12.
3 Keddie FM. Medical mycology 1841–1870. In: Poynter FN, ed. *Medicine and Science in the 1860s*, new series, vol. 16. London: Wellcome Institute of the History of Medicine Publications, 1968: 137–49.

4 Rook A. Early concepts of the host–parasite relationship in mycology. The discovery of the dermatophytes. *Int J Dermatol* 1978; **17**: 666.
5 Zakon SJ, Benedek T. David Gruby and the centenary of medical mycology. *Bull Hist Med* 1944; **16**: 155–68.

Psoriasis

1 Behçet PE. Psoriasis. *Arch Dermatol Syphilol* 1936; **33**: 327–34.
2 Farber EM. The language of psoriasis. *Int J Dermatol* 1991; **30**: 295–302.
3 Farber EM. History of the treatment of psoriasis. *J Am Acad Dermatol* 1992; **27**: 640–5.
4 Fry L. Psoriasis. *Br J Dermatol* 1988; **119**: 445–61.
5 Holubar K. History of psoriasis and parapsoriasis. *Gesnerus* 1989; **46**: 257–61.
6 Holubar K. Psoriasis—one hundred years ago. IVth Int Symposium on Psoriasis (Arthritis), Jerusalem, 1989. *Dermatologica* 1990; **180**: 1–4.
7 Rook A. Edward Beck's treatise on lepra vulgaris. *Med Hist* 1957; **1**: 160.
8 Russell B. Lepra, psoriasis, or the Willan–Plumbe syndrome. *Br J Dermatol* 1950; **62**: 358–61.
9 Waisman M. Historical note: Koebner on the isomorphic phenomenon. *Arch Dermatol* 1981; **117**: 415.
10 Zampieri A. Notes on history of psoriasis. *Acta Derm Venereol* 1994; **186** (Suppl): 58–9.

Syphilis

1 Cole HN. Antiquity of syphilis with some observations on its treatment through the ages. *Arch Dermatol Syphilol* 1951; **64**: 12–22.
2 Hudson EH. Christopher Columbus and the history of syphilis. *Acta Trop* 1968; **25**: 1–16.
3 Pappas PG. Syphilis 100 years ago: parallels with the AIDS pandemic. *Int J Dermatol* 1993; **32**: 708–9.
4 Pusey WA. *The History and Antiquity of Syphilis*. Springfield: Thomas, 1933.
5 Quétel C. *The History of Syphilis*. Cambridge: Polity Press, 1998.
6 Temkin O. Therapeutic trends and the treatment of syphilis before 1900. *Bull Hist Med* 1955; **29**: 309–16.

Tattoos

1 Blackburn M. *Tattoos from Paradise. Traditional Polynesian Patterns*. Atglen: Schiffer, 1999.
2 Goldstein N, Sewell M. III. Tattoos in different cultures. *J Dermatol Surg Oncol* 1979; **5**: 857–64.
3 Levy J, Sewell M, Goldstein N. II. A short history of tattooing. *J Dermatol Surg Oncol* 1979; **5**: 851–6.
4 Scutt RWB, Gotch C. *Art, Sex and Symbol. The Mystery of Tattooing*. New York: Cornwall Books, 1986.
5 Terwiel BJ. Tattooing in Thailand's history. *JR Asiatic Soc GB Irel* 1979; 156–66.

Ulcers

1 Anning ST. The history of varicosis. In: Dodd H, Cockett FB, eds. *The Pathology and Surgery of the Veins of the Lower Limb*. Edinburgh: Livingstone, 1956: 3.
2 Levine JM. Historical notes on pressure ulcers: the cure of Ambrose Pare. *Decubitus* 1992; **5**: 23–4, 26.
3 Levine JM. Historical perspective: the neurotrophic theory of skin ulceration. *J Am Geriatr Soc* 1992; **40**: 1281–3.

Virology

1 Beswick TSL. The origin and the use of the word herpes. *Med Hist* 1962; **6**: 214–32.
2 Hutfield DC. History of herpes genitalis. *Br J Vener Dis* 1966; **42**: 263–8.

Other diseases

1 Bondeson J. Pachyonychia congenita. A historical note. *Am J Dermatopathol* 1993; **15**: 594–9.
2 Branford WA. Edward Nettleship (1845–1913) and the description of urticaria pigmentosa. *Int J Dermatol* 1994; **33**: 214–6.
3 Burns DA. 'Warts and all'—the history and folklore of warts: a review. *J R Soc Med* 1992; **85**: 37–40.
4 Champion RH. Urticaria: then and now. *Br J Dermatol* 1988; **119**: 427–36.
5 Crissey JT, Parish LC. The red face: historical considerations. *Clin Dermatol* 1993; **11**: 197–201.
6 Ehring F. Leprosy illustration in medical literature. *Int J Dermatol* 1994; **33**: 872–83.
7 Frain-Bell W. The effect of light on the skin. *Br J Dermatol* 1988; **119**: 479–85.
8 Giacometti L. Facts, legends, and myths about the scalp throughout history. *Arch Dermatol* 1967; **95**: 629–31.
9 Griffiths WA. Pityriasis rubra pilaris—an historical approach. *Trans St John's Hosp Dermatol Soc* 1975; **61**: 58–69.
10 Hay RJ. The control of infective skin diseases—the lessons of leprosy research. *Br J Dermatol* 1988; **119**: 495–502.
11 Higgins E, Pembroke A, du Vivier A. Radon dermatitis: a historical perspective. *Int J Dermatol* 1992; **31**: 214–7.
12 Holubar K. The man behind the eponym. Hyperkeratosis follicularis et parafollicularis in cutem penetrans; Josef Kyrle and 'his' disease. *Am J Dermatopathol* 1985; **7**: 261–3.
13 Jadassohn W. Kosmetik und Dermatologie einst und Heute. *Cosmetologica* 1970; **19**: 227–30.
14 James DG. Historical aspects of sarcoidosis. *Clin Med* 1968; **3**: 265.
15 Jansen T, Plewig G. An historical note on pyoderma faciale. *Br J Dermatol* 1993; **129**: 594–6.
16 Jensen J. The story of xanthomatosis in England prior to the First World War. *Clin Med* 1967; **2**: 289.
17 Kikuchi I. Hansen's disease in Japan: a brief history. *Int J Dermatol* 1997; **36**: 629–33.
18 Linares HA, Larson DL, Willis-Galstaun BA. Historical notes on the use of pressure in the treatment of hypertrophic scars or keloids. *Burns* 1993; **19**: 17–21.
19 MacFadyen EE, Ferguson MM. Pitcairne's disease: an historical presentation of orofacial granulomatosis. *J R Soc Med* 1996; **89**: 77–8.
20 Masouye I, Saurat JH. Keratosis lichenoides chronica: the centenary of another Kaposi's disease. *Dermatology* 1995; **191**: 188–92.
21 Michelson HE. The history of lupus vulgaris. *J Invest Dermatol* 1946; **7**: 261–7.
22 Montgomery DW. The naming of alopecia areata. *Ann Med Hist* 1931; **3**: 540.
23 Parish WE. Atopy: one hundred years of antibodies, mast cells and lymphocytes. *Br J Dermatol* 1988; **119**: 437–43.
24 Potter B. The history of the disease called lupus. *J Hist Med Allied Sci* 1993; **48**: 80–90.
25 Ramos-e-Silva M. Giovan Cosimo Bonomo (1663–1696) discoverer of the etiology of scabies. *Int J Dermatol* 1998; **37**: 625–30.
26 Renbourn ET. The history of sweat and prickly heat. 19th–20th century. *J Invest Dermatol* 1958; **30**: 249–59.
27 Richards P. Leprosy in Scandinavia. *Centaurus* 1960; **7**: 101.
28 Ronchese F. Les dartres. *Centaurus* 1954; **3**: 236.
29 Rook A. The historical background. In: Warin RP, Champion RH. *Urticaria*. London, Philadelphia: Saunders, 1974.
30 Routh HB, Bhowmik KR. History of elephantiasis. *Int J Dermatol* 1993; **32**: 913–6.
31 Sehgal VN, Wagh SA. The history of cutaneous tuberculosis. *Int J Dermatol* 1990; **29**: 666–8.
32 de Silva U, Parish LC. Historical approach to scleroderma. *Clin Dermatol* 1994; **12**: 201–5.
33 Smith NP. From mushrooms to molecular biology. 100 years of skin tumours with particular reference to cutaneous lymphoma. *Br J Dermatol* 1988; **119**: 487–94.
34 Solomons B. Disorders of the hair and their treatment before the 18th century. *Br J Dermatol* 1966; **78**: 113–20.

CHAPTER 2
Comparative Dermatology

D.A. Burns[1], N.H. Cox[2] & P.B. Hill[3]

[1]Leicester Royal Infirmary, Leicester, UK
[2]Department of Dermatology, Cumberland Infirmary, Carlisle, UK
[3]Veterinary Specialist Centre, North Ryde, Sydney, Australia

The evolutionary sources of the skin components, 2.1
The epidermis and the dermis and their derivatives, 2.1
Invertebrates, 2.1
Vertebrates, 2.2
Glands, 2.4
Glands of vertebrates, 2.4
Pigment cells, 2.5
Animal colours, 2.5
Chromatophores and melanocytes, 2.5
Colours, patterns, genetics and pigment biology, 2.6
Animal models and human disease, 2.7
Comparative clinical dermatology, 2.8
Introduction, 2.8
Parasitic disease, 2.9
Bacterial disease, 2.11
Fungal disease, 2.12
Atopic and other dermatitis, 2.13
Psoriasis, 2.14
Immune-mediated disease, 2.14
Mechanobullous disorders, 2.17
Drug eruptions, 2.17
Cutaneous manifestations of systemic disease, 2.17
Alopecia, 2.18
Neoplastic skin disease, 2.19
Selected disorders that appear to differ from human disease, 2.20

An appreciation of the evolutionary history of skin structure and biochemistry, and knowledge of skin diseases in animals [1], gives perspective to the human condition but also may provide clues to understanding human skin disease, models for its investigation and targets for development of gene therapy for genodermatoses [2]. Useful historical overviews of comparative dermatology are provided by Beerman [3] and Rosser & Ongley [4].

References

1 Chan LS, ed. *Animal Models of Human Inflammatory Skin Diseases*. Boca Raton: CRC Press, 2004.
2 Jiang Q-J, Uitto J. Animal models of epidermolysis bullosa—targets for gene therapy. *J Invest Dermatol* 2005; **124**: xi–xiii.
3 Beerman H. Perspectives in comparative dermatology. *Arch Dermatol* 1968; **98**: 400–5.
4 Rosser EJ Jr, Ongley RC. Comparative dermatology: a historical overview. *Clin Dermatol* 1994; **12**: 487–9.

The evolutionary sources of the skin components [1–5]

Although the anatomy of skin differs greatly between animal classes and shows considerable variety in relation to the exigencies of lifestyle even within groups, it is nevertheless possible to recognize various long-standing elements. Structural materials, such as cross-linked proteins similar to collagen, are found in the most primitive animals. For example, supporting structures of aromatically cross-linked proteins associated with polysaccharides are found in coelenterate polyps, and the cuticles of parasitic worms such as *Ascaris*, are composed of collagen proteins linked by disulphide bonds. Among the vertebrates, keratin first seems to have occurred in the lips and in the breeding tubercles of some fish, but similar materials are found in invertebrates.

Glands and pigment cells have an equally long history. The simplest glands are the unicellular goblet cells, which secrete mucus in coelenterates and fish alike. Multicellular glands of various degrees of complexity are ubiquitous.

Melanins, which are pigments produced by the oxidation of tyrosine, are equally widespread and are found, for example, in worms, molluscs, arthropods and echinoderms, as well as throughout the vertebrates.

References

1 Bereiter-Hahn J, Matoltsy AG, Richards KS, eds. *Biology of the Integument*, Vol. 1. *Invertebrates*. Berlin: Springer-Verlag, 1984.
2 Bereiter-Hahn J, Matoltsy AG, Richards KS, eds. *Biology of the Integument*, Vol. 2. *Vertebrates*. Berlin: Springer-Verlag, 1986.
3 Sengel P. *Morphogenesis of Skin*. Cambridge: Cambridge University Press, 1976.
4 Spearman RIC. *The Integument. A Textbook of Skin Biology*. Cambridge: Cambridge University Press, 1973.
5 Spearman RIC, ed. *Comparative Biology of Skin*. Symposium of the Zoological Society, London, No. 39. London: Academic Press, 1977.

The epidermis and the dermis and their derivatives

Invertebrates

Life began in the sea, just as the human fetus develops bathed in the amniotic fluid. Among the simplest and most archaic animals are the coelenterates, namely the corals, jellyfish and their allies.

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

Such forms have only two layers of cells: an ectoderm in contact with the aquatic environment, and an endoderm lining the gut cavity. The ectoderm may, nevertheless, contain gland cells, stinging cells, pigment cells and sensory cells, and its outer surface may bear microvilli, suggesting an absorptive function [1]. Microvilli are similarly found on the outside of the integument of flukes and tapeworms, which are internal parasites [2,3], and on the amniotic border of periderm of the human embryo.

Marine worms and their relatives in fresh water and on land have a thick cuticle outside their epidermis [4,5]. Arthropods, animals with jointed limbs, of which crustacea and insects are examples, have a tough exoskeleton, which has helped some of their forms to colonize land. In crabs and lobsters this cuticle is hardened by the inclusion of calcareous material. Insect cuticle is composed of chitin, a polysaccharide containing amino groups, assembled into microfibrils and embedded in a protein matrix [6,7]. A critical function of the cuticle is restriction of water loss. An obvious disadvantage of the exoskeleton is that growth can only occur if it is periodically shed, a procedure that leaves its owner vulnerable to predation or other damage [8].

One interesting feature of annelid worms is that they bear stiff bristles or chaetae, made of a keratin-like material with properties similar to that of human hair. Although of epidermal origin, chaetae are not composed of aggregated cells produced by an active matrix. Lateral cells may add substance or provide tanning agents, but the bulk of each chaeta is secreted by only a single basal cell [9].

Vertebrates

In all vertebrates, animals with a backbone, the skin is characterized by an outer stratified epidermis and an underlying dermis, also known as the corium or cutis. The epidermis consists of closely packed cells, which are renewed from the basal layer and which constitute a barrier. The dermis is a connective tissue of mesodermal origin and is made up mainly of extracellular ground substance and collagen fibres manufactured by scattered cells.

The evolution of the vertebrates and their successful colonization of land is associated with a variety of structures, such as glands, scales, feathers and hair, as well as horns, claws and nails. Some of these, notably the scales of fish, are derived from the dermis or have substantial dermal components. Most, however, are epidermal, although their formation is orchestrated by interactions with the dermis.

Fish [10–12]

With few exceptions, such as eels and some catfish, fish have scales of one type or another. Sharks have placoid scales (dermal denticles), which project from the skin. It is their presence that gives shark leather, or shagreen, its characteristic rough feel. In essence, the placoid scale has the same structure as a mammalian tooth, of which it is regarded as a forerunner (Fig. 2.1). Its bulk is formed by a cone of dentine, of dermal origin, which during its formation becomes capped with enamel deposited by an epidermal enamel organ [13].

Bony fish have elasmoid scales, consisting of plates of collagen with superficial mineralization, covered by a thin layer of dermis and epidermis. The skin of catfish has been investigated as a model of membranes, having permeation characteristics similar to mucous membranes [14] and a collagen matrix structure resembling sclera. Fish scales can be hydrolysed and made into 'fish scale collagen (FSC)' sheets that have been investigated as a wound dressing material [15], which has significantly advantageous cost issues in under-developed countries where fish scale is otherwise a waste product.

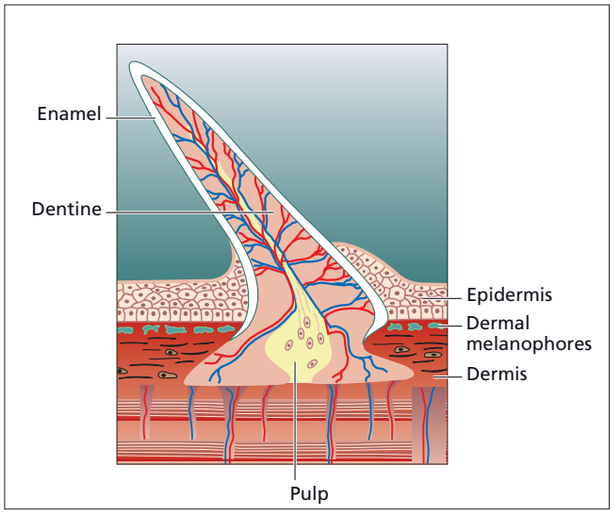


Fig. 2.1 Placoid scale of a shark.

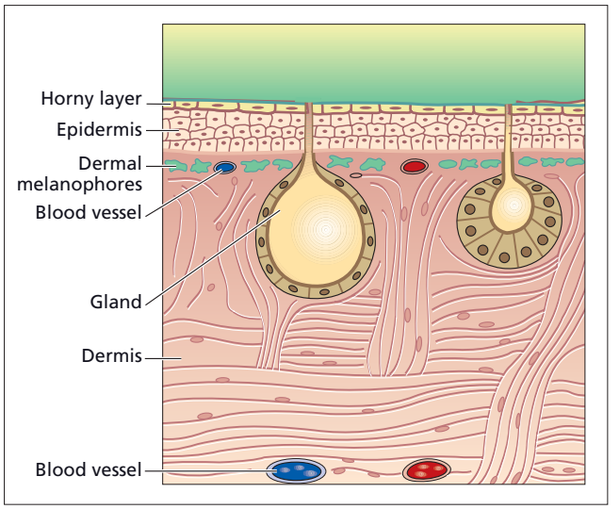


Fig. 2.2 Section of frog skin. Note the flattened superficial horny layer, only one cell deep, which is periodically sloughed as the 'scarf skin', the dermal chromatophores and the multicellular glands.

Amphibia [16,17]

Amphibians were the first vertebrates to emerge from the water, although they still depend on it for reproduction. Their epidermis has several layers of cells, which are formed by a basal stratum germinativum and ultimately become keratinized to form a very thin horny layer, only one cell deep in most species, which is intermittently sloughed (Fig. 2.2). Although the amphibia have lungs, they also respire through their moist skin.

Reptiles [18]

Reptiles are truly terrestrial, in that they do not need an aqueous environment for the development of their larvae. Their chief problem, prevention of desiccation, is solved by possession of scales, which in essence are overlapping folds of skin. An additional property of scales is that they allow the passage of infrared radiation from the sun. The cold-blooded reptiles are dependent on this external source of heat to achieve and maintain a constant body temperature similar to that of mammals.

Reptile scales contain a thick stratum corneum in which waxes are sandwiched between keratinized cells. Snakes and lizards do not, like mammals, renew their epidermis by continuous proliferation and exfoliation of cells. The vertically stratified epidermis is periodically shed as a whole, subsequent to the formation of a complete new generation of epidermal cells below it. In crocodiles and turtles, total shedding does not occur, but regional sheets of stratum corneum are periodically desquamated.

Birds [19]

The most obvious integumental feature of birds is the possession of feathers, which are considered to have evolved from reptile scales and, like scales, they are periodically moulted and replaced.

The legs and feet of birds bear scales, and some other areas, such as the comb and wattles of the domestic cockerel, are naked. The epidermis of birds, as distinct from its derivatives, is thin, and so is the dermis in most species, although ostrich skin is thick enough to be processable into leather.

Mammals [20–22]

Mammals, in general, are characterized by hair, but not all possess it. The epidermis also produces a range of other derivatives such as quills, claws, nails, hooves and horns. Antlers are made of bone, but they are covered with epidermis, the velvet, when newly grown; other horns, such as those of sheep, have a heavily keratinized epidermal sheath over underlying bone. The horn of the rhino is an exception, consisting of tubules and cortex growing from a papillary epidermis over the frontal bones [23]. The bony plates of the armadillo are similarly of dermal origin.

Hair, wool and quill are all produced by follicles that are ingrowths of epidermis enclosing a papilla of mesodermal cells in their bases. The hair is not considered to be the homologue of the scale and the feather. It is more likely that the first hairs to arise in evolution were part of sensory structures between the scales of some ancestral reptile [24]. Spines of animals such as the hedgehog and porcupine are protective, but have also led to interesting evolutionary issues; the hedgehog flea (*Archaeopsylla erinacei*) appears to be quite species-specific, although it will transiently infest other animals such as dogs. The converse is also true—one author collected 2000 fleas from hedgehogs and only one (a mole flea) was not the highly adapted *A. erinacei* species [25]. A feature of human hair that is occasionally important is its facility to retain heavy metals and other chemicals. This facility can be used for example to prove arsenic poisoning; spines of the hedgehog have been similarly used to assess pollution by silver, copper, lead, arsenic and other elements [26].

Seasonal change in hair growth is characteristic of mammals, the hair becoming more dense in colder parts of the year followed by hair fall (moulting) in warmer months. In many species there is a softer warm underfur, and a harsher guard hair coat for protection against the elements. In humans, moulting as such is not readily apparent but hair fall and regrowth is not completely random; in March, 90% of scalp hair is in anagen in temperate climates, but hair fall doubles by about August or September [27]. Nail growth shows no seasonal variation.

Mammalian epidermis is of several types. Most furry species, from rodents to sheep, have a thin epidermis, which is only two or three cells deep. Human epidermis lacks a protective pelt and, perhaps in compensation, is somewhat thicker. The epidermis of the palms and soles has a much thicker stratum corneum than skin that bears hair follicles.

The elephant, rhinoceros and hippopotamus all have skins with very thick hyperkeratotic horny layers. Whales, which lack hair, also have a very thick epidermis, although the cells remain parakeratotic, that is they retain their nuclei. Whale skin has a highly indented dermoepidermal junction, which suggests a very high rate of epidermal cell production. The whole epidermis bears a remarkable and striking similarity to that of psoriatic human epidermis.

References

1 Hündgen M. Cnidaria: cell types. In: Bereiter-Hahn J, Matoltsy AG, Richards KS, eds. *Biology of the Integument*, Vol. 1. *Invertebrates*. Berlin: Springer-Verlag, 1984: 47–56.

2 Lyons KM. Epidermal adaptations of parasitic platyhelminths. In: Spearman RIC, ed. *Comparative Biology of Skin*. Symposium of the Zoological Society, London, No. 39. London: Academic Press, 1977: 97–144.

3 Threadgold LT. Parasitic platyhelminths. In: Bereiter-Hahn J, Matoltsy AG, Richards KS, eds. *Biology of the Integument*, Vol. 1. *Invertebrates*. Berlin: Springer-Verlag, 1984: 132–91.

4 Richards KS. Annelida: cuticle. In: Bereiter-Hahn J, Matoltsy AG, Richards KS, eds. *Biology of the Integument*, Vol. 1. *Invertebrates*. Berlin: Springer-Verlag, 1984: 310–22.

5 Welsch U, Storch V, Richards KS. Annelida: epidermal cells. In: Bereiter-Hahn J, Matoltsy AG, Richards KS, eds. *Biology of the Integument*, Vol. 1. *Invertebrates*. Berlin: Springer-Verlag, 1984: 269–96.

6 Brusca RC, Brusca GJ. *Invertebrates*, 2nd edn. Sunderland, Mass: Sinauer Associates; 2002: 478–9, 485–8.

7 Gullan PJ, Cranston PS. *The Insects. An Outline of Entomology*. Oxford: Blackwell Science, 2000: 16–21.

8 Gnatzy W, Romer F. Arthropoda: cuticle: formation, moulting and control. In: Bereiter-Hahn J, Matoltsy AG, Richards KS, eds. *Biology of the Integument*, Vol. 1. *Invertebrates*. Berlin: Springer-Verlag, 1984: 638–84.

9 Schroeder PC. Annelida: chaetae. In: Bereiter-Hahn J, Matoltsy AG, Richards KS, eds. *Biology of the Integument*, Vol. 1. *Invertebrates*. Berlin: Springer-Verlag, 1984: 297–309.

10 Spearman RIC. *The Integument. A Textbook of Skin Biology*. Cambridge: Cambridge University Press, 1973.

11 Whitear M. The skin of fishes including cyclostomes: epidermis. In: Bereiter-Hahn J, Matoltsy AG, Richards KS, eds. *Biology of the Integument*, Vol. 2. *Vertebrates*. Berlin: Springer-Verlag, 1986: 8–38.

12 Whitear M. The skin of fishes including cyclostomes: dermis. In: Bereiter-Hahn J, Matoltsy AG, Richards KS, eds. *Biology of the Integument*, Vol. 2. *Vertebrates*. Berlin: Springer-Verlag, 1986: 39–64.

13 Raschi W, Tabit C. Functional aspects of placoid scales: a review and update. *Aust J Mar Freshwater Res* 1992; **43**: 123–47.

14 Konrádsdóttir F, Loftsson T, Sigfússon SD. Fish skin as a model membrane: structure and characteristics. *J Pharm Pharmacol* 2009; **61**: 121–4.

15 Sankar S, Sekar S, Mohan R *et al*. Preparation and partial characterization of collagen sheet from fish (*Lates calcarifer*) scales. *Int J Biol Macromol* 2008; **42**: 6–9.
16 Fox H. The skin of amphibia: epidermis. In: Bereiter-Hahn J, Matoltsy AG, Richards KS, eds. *Biology of the Integument*, Vol. 2. *Vertebrates*. Berlin: Springer-Verlag, 1986: 78–110.
17 Fox H. The skin of amphibia: dermis. In: Bereiter-Hahn J, Matoltsy AG, Richards KS, eds. *Biology of the Integument*, Vol. 2. *Vertebrates*. Berlin: Springer-Verlag, 1986: 111–5.
18 Landmann L. The skin of reptiles: epidermis and dermis. In: Bereiter-Hahn J, Matoltsy AG, Richards KS, eds. *Biology of the Integument*, Vol. 2. *Vertebrates*. Berlin: Springer-Verlag, 1986: 150–87.
19 Sawyer RH, Knapp LW, O'Guin WM. The skin of birds: epidermis, dermis and appendages. In: Bereiter-Hahn J, Matoltsy AG, Richards KS, ed. *Biology of the Integument*, Vol. 2. *Vertebrates*. Berlin: Springer-Verlag, 1986: 194–238.
20 Chapman RE. The skin of mammals: hair, wool, quill, nail, claw, hoof, and horn. In: Bereiter-Hahn J, Matoltsy AG, Richards KS, eds. *Biology of the Integument*, Vol. 2. *Vertebrates*. Berlin: Springer-Verlag, 1986: 293–317.
21 Matoltsy AG. The skin of mammals: structure and function of the mammalian epidermis. In: Bereiter-Hahn J, Matoltsy AG, Richards KS, eds. *Biology of the Integument*, Vol. 2. *Vertebrates*. Berlin: Springer-Verlag, 1986: 255–71.
22 Matoltsy AG. The skin of mammals, dermis. In: Bereiter-Hahn J, Matoltsy AG, Richards KS, eds. *Biology of the Integument*, Vol. 2. *Vertebrates*. Berlin: Springer-Verlag, 1986: 272–7.
23 Hieronymus TL, Witmer LM, Ridgely RC. Structure of white rhinocerus *Ceratotherium simum* horn investigated by X-ray computed tomography and squamoproliferative processes. *J Cutan Pathol* 2003; **30**: 358–62.
24 Maderson PFA. Some speculation on the evolution of the vertebrate integument. *Am Zool* 1972; **12**: 159–71.
25 Morris P. *Hedgehogs*. Weybridge, UK: Whittet Books, 1983: 32.
26 D'Havé H, Scheirs J, Mubiana VK *et al*. Non-destructive pollution exposure assessment in the European hedgehog (*Erinaceus europaeus*): II. Hair and spines as indicators of endogenous metal and As concentrations. *Environ Pollut* 2006; **142**: 438–48.
27 Randall VA, Ebling FJ. Seasonal changes in human hair growth. *Br J Dermatol* 1991; **124**: 146–51.

Glands

Glands are organs that manufacture and discharge their products either by extrusion (*merocrine*) or by complete disintegration (*holocrine*) of their cells.

Glands of vertebrates

Amphibia [1]

Amphibian glands are of a number of types and have various functions, including the production of mucus, poison and even courtship stimulants.

Reptiles [2]

Multicellular glands, both holocrine and merocrine, are found in reptiles. So-called 'generation glands' in lizards and snakes are connected with the shedding and sloughing cycle. Odour-producing glands, used in both courtship and aggression, are present in most reptiles, including turtles and crocodiles as well as lizards and snakes.

Birds

In birds, the only conspicuous glands are the large uropygial or preen glands, although there are also some small tubular glands in the vent region [3]. The uropygial gland is holocrine and secretes an oily material by way of ducts which open on a papilla. Histologically, it closely resembles both the mammalian sebaceous glands and the holocrine glands of reptiles. The product of the uropygial gland is transferred by the beak of the bird to the feathers, and is important for their maintenance.

Mammals

Nearly all mammals have both holocrine and merocrine glands. Whales alone lack sebaceous glands. Only whales, elephants, sea cows and scaly anteaters have no tubular glands in their skin.

Merocrine glands occur in many different sites and serve several functions. The tubular glands associated with hair follicles were designated by Schiefferdecker [4] as 'apocrine', on the grounds that secretion involved decapitation of at least some of the cells, as distinguished from 'eccrine' glands in which the cells remain intact. Although electron microscopy has cast doubt on these criteria, the terms remain useful. Alternative designations of 'epitrichial' and 'atrichial' have been proposed, but apocrine glands do not invariably open into hair ducts. In primates, most tubular glands can, in fact, be clearly assigned to one type or the other on histochemical grounds.

A major function of sebaceous and apocrine glands is the production of scent for intraspecific communication. Although sebaceous units occur throughout hairy skin and so, in some species, do apocrine units, they also occur in batteries to form discrete scent organs [5,6]. Such structures are found in most mammalian orders and can occur in almost any area of the body.

Eccrine glands are found in two sites. On footpads, including human soles and palms, they occur in many different mammals, and their main function appears to be to increase surface friction by moistening the keratin. On hairy skin, however, where they function to cool the body by sweating, they occur only in primates and are most abundant in humans.

An interesting phenomenon in the hippopotamus is the function of 'sweat' produced by subdermal glands. At first colourless, then red, and finally brown as the pigment polymerizes, this fluid contains red and orange pigments that have anti-UV and antibacterial properties. The protective action of this 'sunscreen' may explain why albino hippos seem to have healthy skin [7].

References

1 Fox H. The skin of amphibia: dermal glands. In: Bereiter-Hahn J, Matoltsy AG, Richards KS, eds. *Biology of the Integument*, Vol. 2. *Vertebrates*. Berlin: Springer-Verlag, 1986: 116–35.
2 Quay WB. The skin of reptiles: glands. In: Bereiter-Hahn J, Matoltsy AG, Richards KS, eds. *Biology of the Integument*, Vol. 2. *Vertebrates*. Berlin: Springer-Verlag, 1986: 188–93.
3 Quay WB. The skin of birds: uropygial gland. In: Bereiter-Hahn J, Matoltsy AG, Richards KS, eds. *Biology of the Integument*, Vol. 2. *Vertebrates*. Berlin: Springer-Verlag, 1986: 248–54.
4 Schiefferdecker P. Die Hautdrüsen des Menschen und der Säugetiere, ihre biologische und ressenanatomische Bedeutung, sowie die Muscularis sexualis. *Zoologica* 1922; **27**: 1–154.
5 Ebling FJ. Hormonal control of mammalian skin glands. In: Müller-Schwarze D, Mozell MM, eds. *Chemical Signals in Vertebrates*. New York: Plenum Press, 1977: 17–33.
6 Quay WB. The skin of mammals: scent glands. In: Bereiter-Hahn J, Matoltsy AG, Richards KS, eds. *Biology of the Integument*, Vol. 2. *Vertebrates*. Berlin: Springer-Verlag, 1986: 357–73.

7 Saikawa Y, Hashimoto K, Nakata M *et al*. The red sweat of the hippopotamus. *Nature* 2004; **429**: 363.

Pigment cells

Animal colours [1–5]

Colours abound throughout the animal kingdom. Some, such as the metallic sheen of beetles and the gleam of the feathers in the peacock's tail, are produced by *interference*, that is by the reflection of light from both the outer and inner surfaces of a film. So-called structural colours can also be produced by *diffraction*, or by *scattering* of the shorter waves of white light by very small particles, a phenomenon that produces the pale blue of the clear sky or the bright blue on the mandrill's face. The blue colour of the human Mongolian spot is a similar optical effect.

Most colours are, however, due to pigments. The most widespread and the most important in man is *melanin*, which also gives colour to the feathers of blackbirds, black beetles and slugs, and fills the ink sacs of the octopus and the squid. Melanin exists in two forms: black or dark-brown *eumelanin* and reddish or yellow *phaeomelanin*. Both are oxidation products of tyrosine.

Not all brown or black pigments are melanin. Insects and crustacea have *ommochromes*, synthesized from the amino acid tryptophan. Another group are the white, yellow and orange *pterins*, which give colour to the wings of butterflies and to spotted salamanders. There are the widespread *carotenoids*, imparting colour to red sponges, goldfish and pink flamingos, for example, as well as to human skin. None can be synthesized by animals; all are acquired by eating plants. Of particular importance in human skin coloration is the oxygen-carrying pigment of the blood, *haemoglobin*, which is responsible for the pink tint of white people and the bright red of human lips and baboons' buttocks.

Chromatophores and melanocytes

In many animals, pigment is formed in specialized cells. Pigment cells start their evolutionary history in coelenterates and appear to reach the peak of their variety in each of two unrelated groups: the molluscs and the vertebrates.

Molluscs

Molluscs contain not only melanins and ommochromes but also porphyrins and bilichromes. The squid, cuttlefish and octopus have assemblages of differently coloured pigment cells, or chromatophores, containing yellow, orange, red, red–brown, blue, violet–black or black ommochromes. Underlying these are so-called iridiophores and leukophores, which absorb, reflect and scatter light [4,6,7]. The chromatophores can be expanded rapidly or contracted by smooth-muscle fibres that are attached to the periphery of each cell [8]. Contraction of the muscle pulls out the cell and its pigment into a flat plate, and relaxation causes the cell and pigment to concentrate into a small dot. The animals are thus able to change colour and pattern to match their backgrounds extremely rapidly. The information about background is obtained through the eye and mediated through colour centres in the brain [9].



Fig. 2.3 Brindle coat colour in a dog.

Vertebrates in general

The pigment cells of vertebrates differ from those of molluscs in that their size is not controlled by muscle fibres. There are two mechanisms of colour change, each involving a distinctive cell. Short-term *physiological* colour change is brought about by active redistribution of pigment-containing organelles within the boundaries of relatively large cells, which are collectively known as *chromatophores*. Long-term *morphological* colour change results from alterations in the numbers of smaller pigment cells known as *melanocytes*, or in the amount of pigment each produces. The dendritic pigment cell of the human epidermis is an example. Genetic control of switching between synthesis of red–yellow phaeomelanin versus black–brown eumelanin is under the control of two genes, *Agouti* and *Melanocortin-1*, in all vertebrates except domestic dogs in which a more complicated system has been demonstrated. A genome-wide linkage scan of Labrador–greyhound cross dogs segregated for black, yellow and brindle coat colours (Fig. 2.3) showed that a different gene, the K locus on chromosome 16, is additionally involved in colour switching in the dog [10].

Fish

Fish contain chromatophores in both the dermis and the epidermis, but in most species the dermal chromatophores are the more important [11]. Several types can be distinguished, namely black or brown melanophores, red erythrophores and yellow xanthophores. In each, the pigments, namely melanins, carotenoids and pteridines, are contained within organelles. In addition, there are leukophores and iridiophores containing colourless pigments, mainly guanine. Iridiophores cannot translocate the pigment-containing organelles; the guanine is deposited in crystalline platelets. Their function is to produce physical colours by reflection, scattering or diffraction.

There are two modes of regulation: hormonal and nervous. Hormones, in particular the melanocyte-stimulating hormone (MSH) of the pituitary, appear to provide the more primitive mechanism. It is the only one present in lampreys, the prevailing

means of control in sharks, and it is retained in the evolution of amphibia, reptiles and mammals. Only in some bony fish does nervous control take over, making it possible, for example, for the flounder, a flat fish, to mimic a chequerboard on which it is placed.

Amphibia and reptiles

Amphibia also have both dermal chromatophores, of similar types to those found in fish, and dendritic epidermal melanocytes [12].

The pattern is continued in reptiles [13]. Lizards have a layer of melanophores in the dermis, with two to four layers of iridiophores above them and, more superficially, xanthophores and erythrophores [14,15]. In addition, melanocytes occur in the basal layer of the epidermis and transfer melanosomes into the keratinocytes.

Birds

In birds [16], melanocytes are responsible for transferring eumelanin and phaeomelanin into the feather germ to produce black, grey, brown and related tints, and also to form the dark background for structural blue and interference colours. Carotenoids, also, may be responsible for yellow and red, and sometimes even for green, violet and blue. It is of interest that the pelican can produce cosmetic coloration of the plumage by a rose-coloured secretion from the preen gland.

The striking white colour of many aquatic birds, for example, the albatross, seagull and swan, is entirely structural. Pigment-free feathers contain irregularly distributed air-filled cavities, which equally reflect all wavelengths of light. Some blue, green and violet coloration, for example that of kingfishers and parrots, is produced by scattering or interference.

Mammals [5]

In comparison with their vertebrate relatives—fish, amphibia, reptiles and birds—and, indeed, many invertebrates, mammals are drab animals. Even the power to perceive colours has been lost in most mammalian orders. Animals as diverse as crabs, octopuses, insects, fish and birds all have colour vision, but dogs are colour blind, and the bull remains indifferent to the redness of the rag even if enraged by the antics of the matador. One evolutionary explanation is that for many millions of years our ancestors were small, insect-eating, nocturnal mammals for which colour vision had no adaptive advantage. An alternative explanation is that hairs were initially mechanoreceptors that allowed more precise information about objects in contact with the skin; however, increasingly dense hair coats meant that the colour changes related to dermal chromatophores in reptiles became less important in hair-bearing mammals.

All was not lost forever. Something was retained and something was regained. All mammals retain epidermal melanocytes, and monkeys, apes and humans share with some species of squirrel the power to appreciate colours. The return of colour as an item of social commerce is symbolized, for example, by the rump of the sexually receptive female macaque or the bright-blue scrotum of the vervet monkey.

However, drab coat colours in young mammals (typically paler than in the adult) may elicit protective behaviour by adults at times of danger, and often have important camouflage function. Adult coat colours may help to camouflage predators, such as tigers, or their prey; in some instances, extrinsic pigments also provide camouflage (for example, algae that grow on the fur of the sloth).

Colours, patterns, genetics and pigment biology

Experiments in thousands of species, investigation of spontaneous mutations such as albino animals, and some of the techniques used in animal models (discussed earlier) have contributed to understanding of the genetics and molecular mechanisms in pigmentation, as well as providing models for some human diseases. Some aspects are discussed in Chapter 58; recent reviews and an extensive text are also available [17,18]. Some examples are briefly outlined here.

Amongst fish, the common aquarium zebra fish (zebra danio, *Danio rerio*) has been extensively investigated. The wild type has horizontal dark blue and silver stripes, but many mutant types are found. Some, such as the *leopard* pattern, which has spots instead of stripes caused by a *connexin-40* mutation, and more recently described with *connexin-41.8* mutations [19], are sold for tropical aquaria as a specific colour pattern (leopard danio) distinct from the zebra danio. The *sparse* mutant (due to a *kit* mutation that influences melanocyte migration and survival) has much paler and less well defined stripes but with normal fins and tail; the *panther* mutant is due to mutation in a *kit*-related gene *colony stimulating factor-1 receptor* (*csf1r*) that affects xanthophore migration. Other mutants include *touchstone*, in which defects in *trpm7* cause apoptosis of melanoblasts and melanophores after migration; *choker* (defects in *stromal-derived factor 1a*, *sdf1a*, that codes for a chemokine that attracts melanophores), *obelix* (*jaguar*) in which a defect in *kir7.1* affects potassium channels and leads to fewer wider stripes compared with the wild type, *colourless* (*sox10* defects), *nacre* (a variant lacking melanophores, due to mutations in *microphthalmia-a*, *mitfa*), *lockjaw* and *mont blanc* (defects in *transcription factor activating protein-2a*, *tfap2a*), *picasso* (a blotchy-patterned zebrafish due to mutations in *erbb3*, coding for a tyrosine kinase receptor) and *rose* (mutation in the *endothelin receptor b1*, *ednrb1*).

In mammals, colours and patterning of the hair coat of mice have been extensively investigated, in part due to the large amount of background knowledge of mouse biology and the massive range of mutations, and also because of the short breeding time and ease of husbandry of these animals. Coat lengths, colours and patterns in different breeds of domestic animals are additionally of commercial importance for breeding and showing. An important aspect of hair colouring and patterns that has been described in many mammals is that of 'pigment type switching'. This determines the production of eumelanin versus phaeomelanin and is described in detail in [20]. Key genes are *Melanocortin 1 receptor* (*Mc1r*) and *Agouti* (*A*); the Agouti protein, in conjunction with the proteins Attractin (Atrn) and Mahoganoid (Mgrn1), inhibits Mc1r function and causes phaeomelanin production. Additional genes play a part in some specific colour variations. These include the *K* gene (*Dominant black*) described above in dogs, which has a dominance pattern favouring black over brindle colouring, and brindle over yellow [10]. The *Tortoiseshell*

(or *Orange*) gene on the X chromosome is well known, causing a characteristic coat pattern in domestic cats and Syrian hamsters with this gene. Brindle colouring in dogs (Fig. 2.3) has not been demonstrated to have a specific causative mutation, but black mask (melanistic mask), in which a black muzzle occurs and may extend up to the ears, appears to be related to a specific (M264V) mutation in *Mc1r* [21].

The merle pattern (or 'blue merle') in dogs is characterized by areas of diluted pigment, associated with auditory and ophthalmological abnormalities. It is inherited as an autosomal dominant trait with incomplete penetrance. It is caused by retrotranspondon insertion in *SILV* [22], leading to the suggestion that this may be a candidate gene for the phenotypically similar Waardenburg's syndrome (WS) in humans. However, several mouse models of this syndrome have been described [23], including *Splotch* (*Sp*) mice, in which a mutation in *PAX3* has elucidated the molecular basis of WS types I and III; *microphthalmia* mice, which have a mutation in *mi* (equivalent to the human *MITF*, mutations which may explain some cases of WS type II), and a chemically induced mutation in *endothelin 3* (*Edn3*) in mice [24], a mutation which had also been documented in some cases of human WS IV. This is not unexpected, as several types of Waardenburg's syndrome have been documented; indeed, the WS type IV phenotype is also caused by mutations in the *endothelin-B receptor* gene (*EDNRB*) and in a transcription factor *SOX-10*. However, it suggests that numerous inherited or induced mutations in animals may provide useful information about human disease, as investigation of large pedigrees is much simpler than in many human diseases.

References

1 Ebling FJG. The role of colour in cosmetics. In: Counsell JN, ed. *Natural Colours for Food and Other Uses*. London: Applied Science Publishers, 1981: 55–81.

2 Fogden P, Fogden M. *Animals and their Colours*. London: Peter Lowe, 1974.

3 Fox HM, Vevers G. *The Nature of Animal Colours*. London: Sidgwick and Jackson, 1960.

4 Bagnara JT, Matsumoto J. Comparative anatomy and physiology of pigment cells in nonmammalian tissues. In: Nordlund JJ, Boissy RE, Hearing VJ *et al.*, eds. *The Pigmentary System*, 2nd edn. Oxford: Blackwell Publishing, 2006: 11–59.

5 Quedevo WC Jr, Holstein TJ. General biology of mammalian pigmentation. In: Nordlund JJ, Boissy RE, Hearing VJ *et al.*, eds. *The Pigmentary System*, 2nd edn. Oxford: Blackwell Publishing, 2006: 63–90.

6 Bubel A. Mollusca: epidermal cells. In: Bereiter-Hahn J, Matoltsy AG, Richards KS, eds. *Biology of the Integument*, Vol. 1. *Invertebrates*. Berlin: Springer-Verlag, 1984: 400–47.

7 Messenger JB. Reflecting elements in cephalopod skin and their importance for camouflage. *J Zool* 1974; **174**: 387–95.

8 Bagnara JT, Hadley ME. *Chromatophores and Color Change*. Englewood Cliffs: Prentice Hall, 1973.

9 Wells MJ. The brain and behaviour of cephalopods. In: Wilbur KM, Yonge CM, eds. *The Physiology of Mollusca*, Vol. II. London: Academic Press, 1966: 547.

10 Kerns JA, Cargill EJ, Clark LA *et al*. Linkage and segregation analysis of black and brindle coat color in domestic dogs. *Genetics* 2007; **176**: 1679–89.

11 Schliwa M. The skin of fishes including cyclostomes: pigment cells. In: Bereiter-Hahn J, Matoltsy AG, Richards KS, eds. *Biology of the Integument*, Vol. 2. *Vertebrates*. Berlin: Springer-Verlag, 1986: 65–77.

12 Bagnara JT. The skin of amphibia: pigment cells. In: Bereiter-Hahn J, Matoltsy AG, Richards KS, eds. *Biology of the Integument*, Vol. 2. *Vertebrates*. Berlin: Springer-Verlag, 1986: 136–49.

13 Landmann L. The skin of reptiles: epidermis and dermis. In: Bereiter-Hahn J, Matoltsy AG, Richards KS, eds. *Biology of the Integument*, Vol. 2. *Vertebrates*. Berlin: Springer-Verlag, 1986: 150–87.

14 Bagnara JT. Developmental aspects of vertebrate chromatophores. *Am Zool* 1983; **23**: 465–78.

15 Taylor JD, Bagnara JT. Dermal chromatophores. *Am Zool* 1972; **12**: 43–62.

16 Durrer H. The skin of birds: coloration. In: Bereiter-Hahn J, Matoltsy AG, Richards KS, eds. *Biology of the Integument*, Vol. 2. *Vertebrates*. Berlin: Springer-Verlag, 1986: 239–47.

17 Nordlund JJ, Boissy RE, Hearing VJ *et al.*, eds. *The Pigmentary System*, 2nd edn. Oxford: Blackwell Publishing, 2006.

18 Silver DL, Hou L, Pavan WJ. The genetic regulation of pigment cell development. *Adv Exp Med Biol* 2006; **589**: 155–69.

19 Watanabe M, Iwashita M, Ishii M *et al*. Spot pattern of leopard Danio is caused by mutuation in the zebrafish connexin 41.8 gene. *EMBO Rep* 2006; **7**: 893–7.

20 Barsh GS. Regulation of pigment type switching by agouti, melanocortin signaling, attractin, and mahoganoid. In: Nordlund JJ, Boissy RE, Hearing VJ *et al.*, eds. *The Pigmentary System*, 2nd edn. Oxford: Blackwell Publishing, 2006: 395–409.

21 Schmutz SM, Berryere TG, Ellinwood NM *et al*. MC1R studies in dogs with melanistic mask or brindle patterns. *J Hered* 2003; **94**: 69–73.

22 Clark LA, Wahl JM, Rees CA, Murphy KE. Retrotranspondon insertion in SILV is responsible for merle patterning of the domestic dog. *Proc Natl Acad Sci USA* 2006; **103**: 1157–8.

23 Spritz RA. Melanoblast development and associated disorders. In: Nordlund JJ, Boissy RE, Hearing VJ *et al.*, eds. *The Pigmentary System*, 2nd edn. Oxford: Blackwell Publishing, 2006: 140–54.

24 Matera I, Cockroft JL, Moran JL *et al*. A mouse model of Waardenburg syndrome type IV resulting from an ENU-induced mutation in endothelin 3. *Pigment Cell Res* 2007; **20**: 210–5.

Animal models and human disease

Animal models and animal equivalents of human disease are discussed in several chapters throughout this book, and only a brief discussion is provided here. Clearly, animal research extends to all areas of medicine, not just dermatology, and includes testing of drugs; a view has been expressed that medical progress depends on animal models, although the extent to which this is true has been debated [1]. Caution has been advocated in extrapolating from animal research to humans [2]. There is also a significant public objection to animal research and pressure to use different methods; some drugs, for example, can be tested on cell cultures or on cultured human skin equivalents.

There are several different ways in which animals may have a role in human dermatology research, other than pharmaceutical studies. Some diseases that appear to be identical or very similar in humans and animals may give clues about epidemiology, pathogenesis or genetic aspects. Those diseases due to identifiable mutations may be especially useful, but some multifactorial diseases also have considerable similarity between humans and animals. For example, the similarity between human and canine atopic dermatitis and allergic reactions has led to detailed studies comparing human and canine mast cells [3] (note, however, canine mast cell tumours are a very different entity from human mast cell proliferations, see p. 2.22).

Experiments involving immunodeficient mice such as the 'nude' mouse have been widely used in dermatology, typically transplanting human skin affected by a dermatosis; much work on psoriasis was performed using such models [4–6]. An alternative use of such models is by transplanting normal human skin in order to study skin constituents or for attempts to provoke dermatoses; for example, injecting normal human skin grafted to

severe combined immunodeficient mice with adenovirus-linked complementary DNA to provoke interleukin-8 (IL-8) synthesis caused development of pyoderma gangrenosum-like skin lesions. This observation supported the view that IL-8, a potent neutrophil chemoattractant, might be involved in the aetiology of pyoderma gangrenosum [7].

Rapid advances in genetic knowledge and DNA technology allowed generation of chimeric animals (by injection of stem cells into blastocysts), transgenic animals (for example, by injection of a specific gene and its regulatory sequences into a fertilized oocyte, to create an animal that expresses the desired protein) and of 'knockout' mice in which a specific gene has been deleted (achieved by injecting cultured stem cells with a 'knockout vector', a DNA construct containing an altered or inactive gene flanked by long sequences homologous to those around the gene of interest, such that the active gene is replaced during DNA replication in a process termed homologous replication). Such methodologies [8,9] allow the effects of abnormally present, absent or altered genes to be studied. Multiple knockouts may be combined, sometimes with effects that may not be fully predicted; for example, it is not surprising that mice with triple knockout of involucrin, envoplakin and periplakin have a defective epidermal barrier, but they also have defective filaggrin processing due to upregulation of a protease inhibitor (serpina1b), delayed degradation of some desmosomal proteins, and a $CD4^+$ T-cell infiltrate with reduction in γδ T cells, similar to the situation in atopic dermatitis [10].

A potential difficulty of this technology is that there may be several different models for human diseases. This is additionally complicated when genetic techniques of inbreeding, backcrossing, positional cloning and congenic substitution mapping are also considered. For example, in addition to the multiple knockout of cornified envelope proteins described above, other mouse models of atopic dermatitis include the Naruto Research Institute Otsuka Atrichia (NOA) mouse, the NC/Nga mouse (NC) and the APOC1 mouse (in which there is transgenic overexpression of human apolipoprotein C1 [11]). Mouse models of atopic dermatitis are discussed in more detail in [12].

Similarly, although there is no accepted animal equivalent of psoriasis, there are several animal models of this condition [13–18]. Hundreds of other models exist for a wide range of human diseases (such as systemic sclerosis [19]), physiological functions, and aspects of carcinogenesis (such as tumour angiogenesis with fluorescent imaging, using the AngioMouse model [20], and tumour inflammation [21]).

References

1 Matthews RAJ. Medical progress depends on animal research—doesn't it? *J Roy Soc Med* 2008; **101**: 95–8.

2 Hackam DG. Translating animal research into clinical benefit. *BMJ* 2007; **334**: 163–4.

3 de Mora F, Puigdemont A, Torres R. The role of mast cells in atopy: what can we learn from canine models? A thorough review of the biology of mast cells in canine and human systems. *Br J Dermatol* 2006; **155**: 1109–23.

4 Gilhar A, Etzioni A. The nude mouse model for the study of human skin disorders. *Dermatology* 1994; **189**: 5–8.

5 Ueda K, Yanagihara M, Nakagawa S, Fujita T. Functional morphology of lesions of psoriasis vulgaris transplanted into nude mice at an early stage. *J Dermatol* 1994; **21**: 940–6.

6 Sugai J, Katakai Y, Iizuka M *et al*. Interaction of cultured keratinocytes and fibroblasts from human psoriatic and normal skin in immunodeficient mice. *J Dermatol Sci* 1998; **17**: 190–7.

7 Oka M, Berking C, Nesbit M *et al*. Interleukin-8 overexpression is present in pyoderma gangrenosum ulcers and leads to ulcer formation in human xenografts. *Lab Invest* 2000; **80**: 595–604.

8 Schuldiner AR. Molecular medicine. Transgenic animals. *N Engl J Med* 1996; **334**: 653–5.

9 Mazjoub JA, Muglia LJ. Molecular medicine. Knockout mice. *N Engl J Med* 1996; **334**: 904–7.

10 Sevilla LM, Nachat R, Groot KR *et al*. Mice deficient in involucrin, envoplakin, and periplakin have a defective epidermal barrier. *J Cell Biol* 2007; **179**: 1599–612.

11 Oranje AP, Verbeek R, Verzaal P *et al*. Wet-wrap treatment using dilutions of tacrolimus ointment and fluticasone propionate cream in human APOC1 (+/+) mice with atopic dermatitis. *Br J Dermatol* 2009; **160**: 54–61.

12 Jin H, He R, Oyoshi M, Geha RS. Animal models of atopic dermatitis. *J Invest Dermatol* 2009; **129**: 31–40.

13 Chen CL, Yull FE, Cardwell N *et al*. RAG2−/−, I kappa B-alpha−/− chimeras display a psoriasiform skin disease. *J Invest Dermatol* 2000; **115**: 1124–33.

14 Danilenko DM. Review paper: preclinical models of psoriasis. *Vet Pathol* 2008; **45**: 563–75.

15 Schön MP. Animal models of psoriasis: a critical appraisal. *Exp Dermatol* 2008; **17**: 703–12.

16 Hvid H, Teige I, Kvist PH *et al*. TPA induction leads to a Th17-like response in transgenic K14/VEGF mice: a novel in vivo screening model of psoriasis. *Int Immunol* 2008; **20**: 1097–106.

17 Leon F, Contractor N, Fuss I *et al*. Antibodies to complement receptor 3 treat established inflammation in murine models of colitis and a novel model of psoriasiform dermatitis. *J Immunol* 2006; **177**: 6974–82.

18 Zenz R, Eferl R, Kenner L *et al*. Psoriasis-like skin disease and arthritis caused by inducible epidermal deletion of Jun proteins. *Nature* 2005; **437**: 369–75.

19 Akhmetshina A, Venalis P, Dees C *et al*. Treatment with imatinib prevents fibrosis in different preclinical models of systemic sclerosis and induces regression of established fibrosis. *Arthritis Rheum* 2008; **60**: 219–24.

20 Amoh Y, Katsuoka K, Hoffman RM. Color-coded fluorescent protein imaging of angiogenesis: the AngioMouse models. *Curr Pharm Des* 2008; **14**: 3810–9.

21 Cataisson C, Ohman R, Patel G *et al*. Inducible cutaneous inflammation reveals a protumorigenic role for keratinocyte CXCR2 in skin carcinogenesis. *Cancer Res* 2009; **69**: 319–28.

Comparative clinical dermatology

Introduction

Diseases of the skin represent one of the most common manifestations of illness seen in animals. A survey of small animal practitioners in 1985 revealed that skin disorders were the most common reason for visits to veterinary practitioners—a situation similar to that with humans. Throughout evolutionary history, the skin, in its capacity as a protective barrier, has been subjected to continuous attack by biting insects, pathogenic microorganisms and environmental insults. The skin immune system has evolved responses to try to deal with such assaults, but in doing so has generated mechanisms that can harm the skin, resulting in allergic inflammation and autoimmune reactions. Genetic mutation over time has also resulted in non-fatal variations in skin structure and function, leading to genodermatoses that have not been eliminated by natural selection.

This wide variety of disease pathomechanisms occurs throughout the animal kingdom and, in domesticated species, the

resulting dermatoses have been studied extensively. Our knowledge of veterinary dermatology has risen exponentially in recent decades and, in companion animal species such as dogs and cats, has reached a high level of sophistication. In dogs, over 300 different skin diseases have been characterized both clinically and histopathologically and, in most, the precise aetiology or underlying pathogenesis is known. Skin conditions in less common species are also well documented, including such diverse aetiologies as squamous cell carcinoma of the ventral scent gland in gerbils, epitheliotropic lymphoma in hamsters and dysecdysis (failure of skin shedding) in snakes.

A knowledge of comparative dermatology provides a fascinating insight into the similarities and differences between human skin diseases and those seen in other animals. Some conditions, such as atopic dermatitis and pemphigus, are seen in multiple species. Others, such as psoriasis, are only seen in humans. Many show species or breed dispositions, such as the tendency for dogs to suffer from massive proliferation of their *Demodex* mite populations. These similarities or differences are not only interesting in their own right, they can also provide animal models to study human diseases, as briefly described above.

There are also some important differences between animal and human dermatology. Some disorders that are similarly named have very different characteristics and behaviour, such as mast cell tumours in dogs and equine sarcoids; *Trichophyton verrucosum* causes little reaction, and is a self-limiting infection in cattle, but is highly inflammatory in humans. A selection of such conditions will be briefly discussed later in the chapter. Some of the apparently similar disorders are listed in Table 2.1.

At a practical level, there are also significant differences in therapeutics (other than economic viability). The presence of fur in mammals precludes use of many topical preparations, especially as animals groom and potentially may ingest topical therapy. Dermatoses or wounds often tend to be licked frequently, producing secondary eroded areas (pyotraumatic dermatitis, hot spot or acute moist dermatitis). Similar localized lesions are termed lick granuloma or acral lick dermatitis. Local treatments, and attempts to retain dressings or bandages on licked areas, have limited success. Thus, especially for more widespread dermatoses, there is greater use of treatments that can be used as a bath, there are many interesting treatments for ectoparasites (including spot treatments applied to an area the animal cannot lick, such as the nape of the neck), and there is significant use of systemic therapies. The last-mentioned issue itself carries problems that may not apply in humans, such as different metabolism and reactions between species; cats, for example, notoriously have adverse reactions to medicines that are generally widely used in other animals. Any form of tumour removal, and diagnostic biopsies from some sites, are likely to require general rather than local anaesthesia, and novel methods to assist safe handling of some animals may have to be employed (such as putting aggressive snakes in a refrigerator for a few hours). Diagnosis and treatment in fish and reptiles can pose problems that differ from those in mammals, due to the presence of scales and (in the case of fish) the aquatic environment.

A brief bibliography of relevant texts is provided below, mainly relating to small animal veterinary dermatology [1–9].

Table 2.1 Some animal disorders that are similar to human diseases.

Type of disorder	Examples
Genetic	Epidermolysis bullosa (many animals)
	Hyperelastosis cutis (probably equivalent to Ehlers–Danlos syndrome; occurs in dogs, cats, horses)
	Some congenital hair shaft abnormalities
	Canine Darier's disease
Dermatitis and inflammatory	Atopic dermatitis (more similar in dogs than in cats)
	Contact dermatitis
	Sweet's syndrome (dogs)
Infections	Impetigo and pyodermas (but usually due to *Staphylococcus pseudintermedius* in small animals)
	Lyme disease (dogs)
	Rickettsial infection (dogs)
	Leishmaniasis
Parasitic diseases	Scabies (canine)
Drug eruptions	Erythema multiforme, exfoliative dermatitis, vasculitis, fixed drug eruption (some species), urticaria, toxic epidermal necrolysis (some species)
Hair disorders	Alopecia areata
	Androgenetic alopecia (some primates)
Metabolic and endocrine disorders	Thyrotoxicosis (common in cats), hypothyroidism
	Zinc deficiency
	Amyloidosis
	Phaeochromocytoma
Autoimmune diseases	Bullous pemphigoid, pemphigus foliaceus, linear IgA disease, cicatricial pemphigoid, epidermolysis bullosa acquisita
	Lupus erythematosus
Neoplasia	Squamous cell carcinoma
	Many other benign and malignant tumours

References

1 Scott DW, Miller WH, Griffin CE. *Muller and Kirk's Small Animal Dermatology*, 6th edn. Philadelphia: WB Saunders, 2001.
2 Hill PB. *Small Animal Dermatology*. London: Elsevier Science, 2002.
3 Gross TL, Ihrke PJ, Walder EJ, Affolter VK. *Skin Diseases of the Dog and Cat. Clinical and Histopathologic Diagnosis*, 2nd edn. Oxford: Blackwell Science, 2005.
4 Moriello KA. *Small Animal Dermatology*. London: Manson Publishing, 2005.
5 Foster AP, Foil CS, eds. *BSAVA Manual of Small Animal Dermatology*, 2nd edn. Gloucester: British Small Animal Veterinary Association, 2003.
6 Ettinger SJ, Feldman EC, eds. *Textbook of Veterinary Internal Medicine*, 6th edn. St Louis, Missouri: Elsevier Saunders, 2000.
7 Mueller RS, ed. *Dermatology for the Small Animal Practitioner*. Jackson, USA: Teton New Media, 2006.
8 Scott DW, Miller WH Jr. *Equine Dermatology*. Philadelphia: WB Saunders, 2003.
9 White SD, ed. Skin diseases. In: Robinson NE, ed. *Current Therapy in Equine Medicine*, 5th edn. St Louis, Missouri: Saunders, 2003: 174–225.

Parasitic disease (see also Chapter 38) [1–6]

Infestation of the skin with ectoparasites is far more common in animals than in humans. In mammals and birds the skin is covered in hair or feathers, providing a larger area in which parasites can dwell. Animals also have lower hygiene standards than humans, and may live or be kept in large groups allowing effective contagion. Some parasites, such as fleas, *Sarcoptes* and *Cheyletiella*, can be zoonotic.

Infestation with fleas commonly results in skin disease in dogs and cats, causing a pruritic dermatosis over the dorsum (back). In

areas with cold winters, there is a seasonal effect, with more cases in summer and autumn. The skin reacts to salivary antigens that elicit immediate (type I), delayed (type IV) and late-phase IgE-mediated hypersensitivity reactions, termed flea bite dermatitis or canine flea allergy dermatitis (FAD). Chronic cases may develop self-induced alopecia with lichenification and hyperpigmentation, and occasionally nodular lesions. Lesions affect predominantly the caudal part of the body, especially the lumbosacral region and base of the tail, perineum and thighs. This is an extremely common disorder and difficult to manage fully as fleas are ubiquitous; a study of 2653 dogs and 1508 cats demonstrated flea infestation in 21% of cats and almost 7% of dogs, with features of FAD in 8% of cats and 3.3% of dogs [7]. Secondary damage to the skin as well as secondary pyoderma are common complications. It should be noted that systemic flea control agents, that rely on the flea ingesting blood from the dog, may give some long-term control by reducing the flea population but are slow to work as the affected animal is still getting antigenic stimulation from bites; external flea control chemicals, or combination treatments, have been felt to be more effective. However, this conclusion has been questioned lately, as studies have shown that fleas may feed for a shorter period of time in dogs treated with systemic ectoparasiticides than with topically acting agents.

The human flea, *Pulex irritans,* which no longer infests humans in developed countries, can be found on pigs (whose skin is similar to that of humans) but, again, not in developed countries.

Lice are occasionally found on dogs and cats, but are common on horses, cattle, pigs and poultry. Unlike fleas, lice are totally host-specific, and do not spread from one species to another or cause zoonoses. Infested animals usually have low-grade pruritus and mild scaling over the trunk, neck and head. In primates, the gorilla carries *Pthirus gorillae*, the ancestor of the human crab louse (*Pthirus pubis*), chimpanzees carry *Pediculus* species (*P. schaeffi*) but not *Pthirus*, and orang-utans do not have any lice.

Sarcoptic mange is seen commonly in dogs, foxes and pigs, but rarely in horses and cattle. In dogs (canine sarcoptic acariasis) it is one of the most pruritic skin diseases, causing papular dermatitis and erythema, especially on the margins of the ears, over the elbows and on the hocks. Alopecia and areas of crusting, secondary to scratching, may be profound. In some situations it may behave in an enzootic fashion; for example, dogs kennelled together, such as hounds for fox-hunting, may all be affected (Fig. 2.4). The pathogenetic mechanisms of pruritus appear to be similar to the situation in humans, and a canine equivalent of crusted (Norwegian) scabies may also occur. The causative mite, *Sarcoptes scabiei* var. *canis* is relatively species-specific, but can be transmitted to cats and to humans; although it cannot reproduce on human skin, it can cause a transient papular eruption.

In cats, feline scabies is due to the mite *Notoedres cati*, causing feline notoedric acariasis or 'head mange' [6]. It is particularly common where there are large populations of feral cats. Like canine scabies, the ears are commonly affected but the rash may spread to affect the whole facial area and front legs, gradually involving the whole body. Greasy scaling and crusting, alopecia, lichenification and obvious pruritus are apparent; generalized dermatopathic lymphadenopathy occurs. Although also fairly species-specific, transient transfer to dogs and humans may occur.



Fig. 2.4 Sarcoptic mange in a dog, transmitted in an enzootic fashion.

The main differential diagnoses of the pruritic infestations in cats and dogs include atopic dermatitis, food allergies, *Malassezia* overgrowth and pyodermas. Allergic contact dermatitis may also need to be considered. Otodectic acariasis and pemphigus foliaceus are also in the differential diagnosis of head mange in cats. The specific body distribution, demonstration of mites, microbiology samples from pyodermas and response to treatment all help in making these diagnoses; histology is not usually required but, if performed, eosinophils are usually more prominent in infestation than in atopic dermatitis.

Infestation with *Cheyletiella* mites is relatively common in dogs, cats and pet rabbits, causing a diffuse scaling dermatosis over the dorsal trunk, and cheyletiellosis may be enzootic in catteries. The condition may be only mildly pruritic in pets but can lead to a pruritic papular dermatitis in their owners.

Demodicosis is a skin condition seen commonly in dogs but very rarely in other species. It is a follicular disorder caused by massive proliferation of commensal *Demodex* mites (including *D. canis, D. injai* and possibly a third species), which can lead to localized or generalized skin disease (demodectic mange). The localized form is usually seen in juvenile dogs and appears as focal patches of non-inflammatory alopecia, usually on the head or limbs, which can resolve spontaneously. The generalized form is more severe and can result in widespread areas of alopecia, scaling and comedones (Figs 2.5 & 2.6). This form of the disease does not self-cure and requires prolonged treatment with acaricidal agents. The tendency to develop demodicosis appears to be hereditary (data suggest an autosomal recessive mode of inheritance), and certain breeds seem to be predisposed to the generalized form. The pathogenesis has not been established, although some studies have demonstrated immunosuppression, and a hereditary *D. canis*-specific, T-lymphocyte defect may be involved.

In cats, other *Demodex* species are implicated, including *D. cati* and *D. gatoi*, leading to feline superficial demodicosis. Localized and generalized follicular forms occur, and a superficial contagious form due to *D. gatoi* which inhabits the epidermis and behaves rather more like sarcoptic than demodectic mange.

Mange in sheep (*Psoroptes ovis*) or cattle (*Chorioptes bovis*) is a common skin condition causing severe pruritus and damage to

the fleece or hide. In sheep, it is known colloquially as 'scab', and control of the parasite is a major economic burden on the sheep industry. The similar-appearing mites *Otodectes cynotis* (dogs and cats) and *Psoroptes cuniculi* (rabbits) are a common cause of otitis externa, especially in young animals, and there are reports of the former causing problems in humans [8,9].

In horses and farm animals, significant pruritic skin disease can be caused by biting flies such as *Culicoides* midges (the cause of a disease affecting the mane and tail known as 'sweet itch', and responsible for much distress in human visitors to the West coast of Scotland during the summer months), *Simulium* blackflies, *Tabanid* horse flies, stable flies and mosquitoes.

Ivermectin, which is used to treat filarial disease, scabies and lice in humans, but whose use is restricted, is employed to treat a variety of parasitic diseases in veterinary medicine. Adverse effects are uncommon in humans, but it must not be given to certain breeds of dog—collies, old English sheepdog, Australian shepherd, Shetland sheepdog, or crosses thereof—as it affects the central nervous system and may cause death.

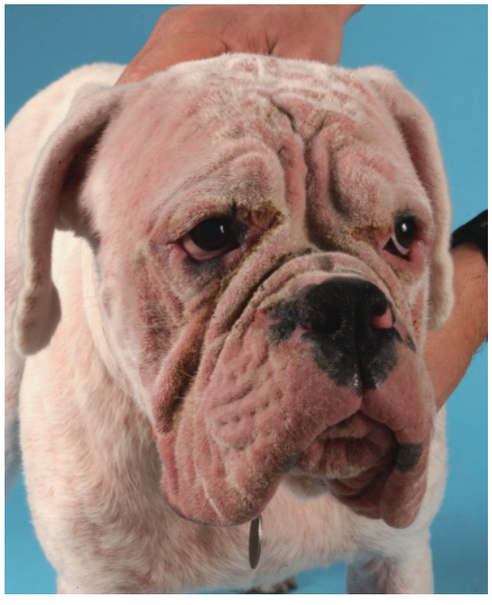


Fig. 2.5 A boxer dog with generalized demodicosis (demodectic mange).

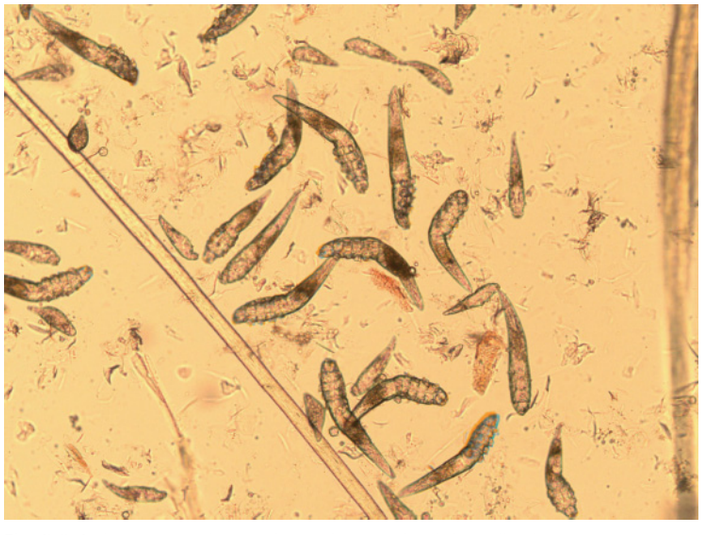


Fig. 2.6 A skin scraping from a dog with generalized demodicosis.

References

1 Wall R, Shearer D. *Veterinary Ectoparasites: Biology, Pathology and Control*, 2nd edn. Oxford: Blackwell Science, 2001.
2 Curtis C, Paradis M. Sarcoptic mange, cheyletiellosis and trombiculosis. In: Foster AP, Foil CS, eds. *BSAVA Manual of Small Animal Dermatology*, 2nd edn. Gloucester: British Small Animal Veterinary Association, 2003: 146–52.
3 Craig M. Demodicosis. In: Foster AP, Foil CS, eds. *BSAVA Manual of Small Animal Dermatology*, 2nd edn. Gloucester: British Small Animal Veterinary Association, 2003: 153–8.
4 Scott DW, Miller MH, Griffin CE. Parasitic skin disease. In: *Muller and Kirk's Small Animal Dermatology*, 6th edn. Philadelphia: WB Saunders, 2001: 457–76.
5 Angarano DW, Parish LC. Comparative dermatology: parasitic disorders. *Clin Dermatol* 1994; **12**: 543–50.
6 Gross TL, Ihrke PJ, Walder EJ, Affolter VK. *Skin Diseases of the Dog and Cat. Clinical and Histopathologic Diagnosis*, 2nd edn. Oxford: Blackwell Science, 2005: 200–37.
7 Bond R, Riddle A, Mottram L *et al*. Survey of flea infestation in dogs and cats in the United Kingdom during 2005. *Vet Record* 2007; **160**: 503–6.
8 Van de Heyning J, Thienpoint D. Otitis externa caused by the mite *Otodectes cynotis*. *Laryngoscope* 1977; **87**: 1938–41.
9 Herwick RP. Lesions caused by canine ear mites. *Arch Dermatol* 1978; **114**: 130.

Bacterial disease [1–3]

Bacterial skin infections are common in dogs, cats, horses, cattle, sheep and pigs. Interestingly, staphylococcal skin infections can be caused by three different organisms, depending on the species affected. In dogs, the most common type of superficial pyoderma is caused by *Staphylococcus pseudintermedius*. In horses, cattle and sheep, *S. aureus* would be the most likely isolate, whereas in pigs, *S. hyicus* is typically involved. Staphylococcal pyoderma in the dog is one of the commonest skin diseases seen in this species; the most frequent presentation is a papular or pustular eruption often affecting the ventral abdomen. A virtually pathognomonic lesion is the so-called 'staphylococcal ring', a circular patch of alopecia with a peripheral ring of erythema, surrounded by an epidermal collarette (Fig. 2.7). Although most canine impetigo is due to



Fig. 2.7 Typical lesions of staphylococcal folliculitis in a dog, comprising annular areas of erythema surrounded by epidermal collarettes.

S. pseudintermedius, *Pseudomonas* spp., *Enterobacter* spp. and *Escherichia coli* have been implicated. Impetigo is commonest in young animals; in older dogs it may be a clue to underlying Cushing's syndrome, hypothroidism or immunosuppression. Staphylococcal toxins [2] and superantigens [3] explain some of the pathogenicity. Deeper staphylococcal infections are also seen in the dog, characterized by furunculosis, nodules and draining tracts, and deeper *Pseudomonas* infection also occurs [4]. In most cases staphylococcal disease in the dog is secondary to an underlying cause, often atopic dermatitis, but is highly pruritic whether primary or secondary to atopic disease. There are species-specific differences in binding of staphylococci to corneocytes, and differences between atopic and non-atopic dogs [5]. Pemphigus foliaceus can resemble these superficial pyodermas, due to the bullous or pustular component.

Cats rarely suffer from staphylococcal skin infections, possibly because this group of pathogens is relatively poorly adherent to cat corneocytes [6]. However, the tendency of cats to fight makes them very susceptible to cutaneous abscesses caused by the oral cavity organism *Pasteurella multocida*—which can be problematic in animal bites of humans. The rump and face are common sites for cat bite abscesses. Abscesses are also common in farm animal species, and in horses are often caused by corynebacteria, clostridia and β-haemolytic streptococci.

Bacterial skin diseases are common in captive reptiles, amphibians and fish, usually as a result of poor husbandry. Typically, Gram-negative organisms are involved such as *Pseudomonas* or *Aeromonas* (an organism also present in the leech gut and complicating the use of medicinal leeches), resulting in ulcerative skin disease. Snakes and lizards lack lysosomal enzymes so tend to get pyogranulomas instead of frank abscesses. Tortoises and turtles can suffer from ulcerative diseases of the shell caused by the organisms *Citrobacter freundii* and *Beneckea chitinivora*.

Infections in horses that leave scarring may be very important in terms of the value of the horse. Staphylococcal infection may be due to *S. aureus, S. intermedius* or, less often, *S. hyicus* and has various names in common usage including summer itch, summer scab, saddle scab, acne and sweating eczema. An important infective differential diagnosis is dermatophilosis ('rain scald'), a disorder characterized by moist, raw, alopecic patches, caused by *Dermatophilus congolensis*. The spores may be found on fomites (such as gates) and thus transfer to other animals; wetting of the coat precipitates the disease. Other differential diagnoses include dermatophytosis (see below), other bacterial infections, demodicosis and pemphigus foliaceus.

As in humans, staphylococcal resistance to antibiotics is an increasing problem [7].

References

1 Noli C. Staphylococcal pyoderma. In: Foster A, Foil C. *BSAVA Manual of Small Animal Dermatology*. Gloucester: British Small Animal Veterinary Association, 2003: 159–68.

2 Terauchi R, Sato H, Hasegawa T *et al*. Isolation of exfoliative toxin from *Staphylococcus intermedius* and its local toxicity in dogs. *Vet Microbiol* 2003; **94**: 19–29.

3 Hendricks A, Schuberth HJ, Schueler K *et al*. Frequency of superantigen-producing *Staphylococcus intermedius* isolates from canine pyoderma and proliferation-inducing potential of superantigens in dogs. *Res Vet Sci* 2002; **73**: 273–7.

4 Baxter CG, Vogelnest LJ. Multifocal papular deep bacterial pyoderma in a Boxer dog caused by *Pseudomonas aeruginosa*. *Aust Vet J* 2008; **86**: 435–9.

5 Woolley KL, Kelly RF, Fazakerley J *et al*. Reduced in vitro adherence of *Staphylococcus* species to feline corneocytes compared to canine and human corneocytes. *Vet Dermatol* 2008; **19**: 1–6.

6 Simou C, Thoday KL, Forsythe PJ, Hill PB. Adherence of *Staphylococcus intermedius* to corneocytes of healthy and atopic dogs: effect of pyoderma, pruritus score, treatment and gender. *Vet Dermatol* 2005; **16**: 385–91.

7 Kania SA, Williamson NL, Frank LA *et al*. Methicillin resistance of staphylococci isolated from the skin of dogs with pyoderma. *Am J Vet Res* 2004; **65**: 1265–8.

Fungal disease

Trichophyton verrucosum, the organism responsible for cattle ringworm (Fig. 2.8), is the usual cause of kerion in children, the severity of the inflammatory response being a manifestation of the reaction usually provoked when a zoophilic fungus infects a human. In cattle, the infection produces areas of scaling alopecia that are usually more evident when the animals are under cover during the winter months, but tend to clear in spring when they are put out to pasture.

Trichophyton mentagrophytes, from small rodents, and *T. erinacei*, from hedgehogs, tend to produce inflammatory lesions on exposed areas of human skin, and the latter has caused kerion [1]. The patient shown in Fig. 2.9 acquired infection with *T. erinacei* as a result of working at a hedgehog rescue centre.

Trichophyton equinum causes equine dermatophytosis and is readily transmitted from horse to horse, both by direct contact and on articles of tack [2,3]. Its transmission to humans, however, appears to be unusual, which is perhaps surprising in view of the popularity of equestrian pursuits, and there are only a few reports in the dermatological literature. In a survey of superficial fungal diseases carried out in the USA in 1994, there was no *T. equinum* strain among 1222 specimens [4], and in a Spanish survey, over a 36-year period, there was only one *T. equinum* strain in 3351 dermatophytoses [5]. Human onychomycosis caused by *T. equinum* is rare. Huovinen *et al*. [6] reported a case successfully treated with terbinafine.

Most cases of canine and feline dermatophytosis are caused by *Microsporum canis*, *Trichophyton mentagrophytes* (from rodent contact) and *M. gypseum* (from contaminated soil) [7,8]. In cats, up to 98% of infections are caused by *M. canis*. In cats and dogs, as in humans, *M. canis* infection usually produces patches of scaling



Fig. 2.8 Dermatophytosis in a cow.



Fig. 2.9 Severe reaction to hedgehog ringworm affecting the base of the palm in a human.



Fig. 2.10 Generalized dermatophytosis in a terrier cross.

alopecia, and affected areas may fluoresce apple green under Wood's light. In animals, infection may be generalized (Fig. 2.10). Infections in dogs and cats with geophilic and unusual species of dermatophytes frequently cause highly inflamed lesions, and kerion in dogs and cats is often caused by *Microsporum gypseum*.

References

1 Jury CS, Lucke TW, Bilsland D. *Trichophyton erinacei*: an unusual cause of kerion. *Br J Dermatol* 1999; **141**: 606–7.

2 Lloyd DH, Littlewood JD, Craig JM, Thomsett LR. *Practical Equine Dermatology*. Oxford: Blackwell Science, 2003: 27–30.

3 Pascoe RR. The epidemiology of ringworm in racehorses caused by *Trichophyton equinum* var. *autotrophicum*. *Aust Vet J* 1979; **55**: 403–7.



Fig. 2.11 Severe atopic dermatitis in a West Highland white terrier, a genetically predisposed breed.

4 Kemna EG, Elewski BE. A U.S. epidemiologic survey of superficial fungal diseases. *J Am Acad Dermatol* 1996; **35**: 539–42.

5 Pereiro-Miguens M, Pereiro M, Pereiro M Jr. Review of dermatophytoses in Galicia from 1951 to 1987 and comparison with other areas of Spain. *Mycopathologia* 1991; **113**: 65–78.

6 Huovinen S, Tunnela E, Huovinen P *et al*. Human onychomycosis caused by *Trichophyton equinum* transmitted from a racehorse. *Br J Dermatol* 1998; **138**: 1082–4.

7 Foil C. Dermatophytosis. In: Foster AP, Foil CS, eds. *BSAVA Manual of Small Animal Dermatology*, 2nd edn. Gloucester: British Small Animal Veterinary Association, 2003: 169–74.

8 Foil CS. Fungal diseases. *Clin Dermatol* 1994; **12**: 529–42.

Atopic and other dermatitis

Atopic dermatitis (AD) has been most extensively studied in the dog [1–3], but is also recognized in cats, sheep and horses. In veterinary medicine it is considered that canine AD is a cutaneous manifestation of an allergic disease, and there are many pathogenetic and immunological similarities between AD in humans and dogs. Any breed of dog may be affected, but a hereditary basis is supported by a predisposition to develop AD in some, particularly terriers (Fig. 2.11), boxers, German shepherd dogs, Lhasa Apsos, Dalmatians, Irish setters, golden retrievers and Labrador retrievers.

As in humans, the usual presenting problem is pruritus (which is manifest as rubbing, scratching and licking in dogs), and secondary pyoderma is common. Lichenification occurs commonly, as in humans, and flea allergy may complicate the clinical picture. Clinical signs of AD appear between 1 and 3 years of age, and (unlike humans) rarely before 6 months of age. The disease tends to affect the face, ears, feet and ventrum. In addition to corticosteroids, and treatment of secondary pyoderma, ciclosporin is also a licensed treatment, but the mainstay of treatment in dogs is allergen-specific immunotherapy.

Feline AD is less well defined and less similar to human AD; cats can get both asthma and AD, but the two conditions do not usually occur together. Feline AD usually presents as pruritus with alopecia and excoriations around the head and neck, or as a 'miliary dermatitis', but some eosinophilic disorders (feline



Fig. 2.12 *Malassezia pachydermatis* overgrowth in a Basset hound resulting in widespread erythroderma. This condition responds well to antifungal therapy.

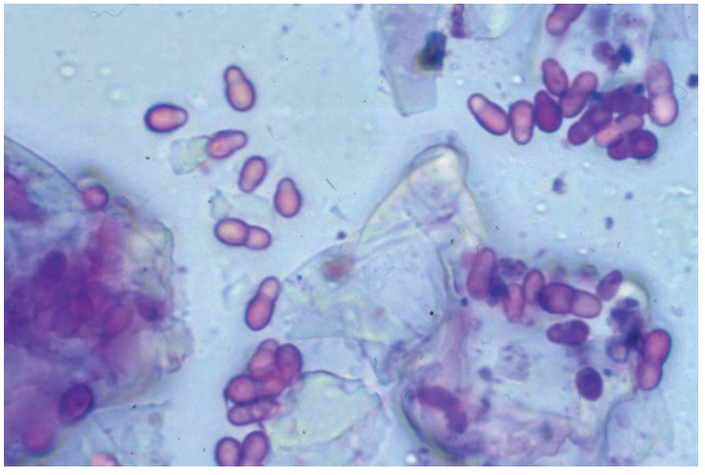


Fig. 2.13 Microscopic appearance of a skin sample from a dog with cutaneous *Malassezia* overgrowth.

eosinophilic plaque, feline eosinophilic granuloma and feline indolent ulcer) have also been suggested as manifestations.

There is also a spontaneous mouse model of AD in NC/Nga mice, and there are experimental mouse models of AD.

Various patterns of *Malassezia* dermatitis occur, the implicated organism being *Malassezia pachydermatis* in dogs (Figs 2.12 & 2.13), and either *M. pachydermatitis* or other *Malassezia* spp. in cats. In some instances, the infection may be secondary to other dermatitis (e.g. atopic), and it has also been described in cats with thymoma-associated exfoliative dermatitis and other forms of pre-existing skin damage. In dogs there is a breed predisposition, mainly Basset hounds, Westies and Cocker spaniels. In some respects this entity resembles human seborrhoeic dermatitis, with erythema and greasy scaling that may affect flexures, facial folds and ears. Other cases in which the abdomen, feet and forelegs are involved are less reminiscent of the human form; additionally, pruritus, which is sometimes significant (and may be due to an underlying dermatosis), is not typical in humans. In cats, *Malassezia* dermatitis may be related to immune deficiency (feline immunodeficiency virus, FIV, or feline leukaemia virus, FeLV).

References

1 Frank LA. Atopic dermatitis. *Clin Dermatol* 1994; **12**: 565–71.

2 Hill PB, Olivry T. The ACVD task force on canine atopic dermatitis (V): biology and role of inflammatory cells in cutaneous allergic reactions. *Vet Immunol Imunopathol* 2001; **81**: 187–98.

3 Hillier A, Olivry T. Spontaneous canine model of atopic dermatitis. In: Chan LS, ed. *Animal Models of Human Inflammatory Skin Diseases*. Boca Raton: CRC Press, 2004: 353–69.

Psoriasis

There is no natural animal model for psoriasis; a disorder found especially in Springer spaniels, and termed psoriasiform-lichenoid dermatosis, does not behave similarly or appear similar—it has psoriasiform epidermal hyperplasia but a lichenoid pattern of mixed inflammatory cell infiltrate [1]. This condition is usually antibiotic-responsive and is thought to be an aberrant response of the epidermis to staphylococcal antigens. A disorder termed 'psoriasiform dermatitis of the pawpads' has also been described, but histologically has subtle spongiosis and a mixed inflammatory infiltrate often including significant numbers of eosinophils [1]; it is probably an allergic or atopic phenomenon, but clinically may resemble the early stages of canine zinc-responsive dermatitis.

The SCID (severe combined immunodeficiency) mouse/human skin xenotransplantation model is a useful experimental model, and there are several transgenic animal models (see previously). For example, induced loss of Jun proteins in mice causes not only morphological and histological features resembling cutaneous psoriasis, but also arthritis; further support that these proteins may be involved in the pathogenesis of psoriasis includes the fact that the gene *JunB* is underexpressed in psoriasis lesions, and also that it is located in the *PSOR6* psoriasis susceptibility gene region [2].

References

1 Gross TL, Ihrke PJ, Walder EJ, Affolter VK. *Skin Diseases of the Dog and Cat. Clinical and Histopathologic Diagnosis*, 2nd edn. Oxford: Blackwell Science, 2005: 111–2; 152–4.

2 Zenz R, Eferl R, Kenner L *et al*. Psoriasis-like skin disease and arthritis caused by inducible epidermal deletion of Jun proteins. *Nature* 2005; **437**: 369–75.

Immune-mediated disease [1,2]

Many of the immune-mediated disorders identified in humans have been described in animals, including several immunobullous diseases, lupus erythematosus (LE), erythema multiforme (EM) and toxic epidermal necrolysis (TEN). Canine dermatomyositis is also described but has several differences from the human disease. Vitiligo also occurs, again with some differences from human patterns.

Bullous disorders

Bullous pemphigoid [3–5]. Canine, feline, equine and porcine (Yucatan minipigs) homologues of bullous pemphigoid (BP) in humans have been identified, but it is rare in animals. Whereas human BP is a disease of the elderly, there is much variation in the age of onset in animals—pigs around the time of puberty, dogs



Fig. 2.14 Pemphigus foliaceus in a cross breed dog. The nasal distribution is common.

during middle age and horses during senescence. The clinical phenotype of canine, feline and porcine BP is similar to that seen in humans, whereas that seen in horses differs considerably, with severe oral involvement, systemic signs and a poor prognosis.

In canine and porcine BP there is subepidermal inflammation consisting of neutrophils and eosinophils, and bullae are often haemorrhagic. In cats and horses there are few or no inflammatory cells in either the bullae or the superficial dermis. In all these species, IgG autoantibodies bind to a 180-kDa protein in the basement membrane zone.

Cicatricial pemphigoid (mucous membrane pemphigoid) [2,3]. This occurs in cats and dogs, but is very rare in the former. It is the most common autoimmune subepidermal blistering disease of dogs, whereas it is rare in humans. It is very similar to its human counterpart.

Pemphigus [2,3,5–9]. It was not until 1975 that the first description of a canine disease analogous to human pemphigus vulgaris (PV) was described in the veterinary literature. Since then, pemphigus foliaceus (PF) and pemphigus erythematosus have also been reported in the dog, and forms of pemphigus have been recognized in cats, horses, goats and llamas.

In contrast with humans, in whom PV is the most common form of pemphigus, in domestic animals it is PF (Fig. 2.14). The clinical features comprise a primary pustular eruption that can affect the face, nose, pinnae, trunk and footpads. The fragile nature of the pustules often leads to widespread crusting. There may be breed predilection for PF in dogs, as several breeds appear to be predisposed, but there is no breed predilection in cats. It is a relatively common immune-mediated skin disease in the horse, and the Appaloosa breed may be predisposed.

Canine PV is the least common of the pemphigus variants in the dog. There is no defined breed predilection. The disease occurs primarily in mature dogs. Lesions usually arise first in the oral cavity, on other mucosal sites or at mucocutaneous junctions. Other clinical features, histopathology and immunopathology are similar to human disease. Canine PV can be considered a natural model for the human disease.

In humans, Ashkenazi Jews in particular have an increased susceptibility to pemphigus vulgaris, and in South Africa, PV is more common in Indians than in black or white races.

Paraneoplastic pemphigus has been recorded in dogs [2,5].

There are mouse and hamster models of BP, and experimental mouse models of mucous membrane pemphigoid, PV and PF.

Epidermolysis bullosa acquisita [2–4,10]. Although a rare disease, epidermolysis bullosa acquisita (EBA) is recognized as one of the most common autoimmune subepidermal blistering dermatoses identified in dogs, and accounts for 25% of dogs with blistering diseases associated with antibasement membrane autoantibodies—ten times higher than in humans. Affected animals belong to several breeds, but a high proportion are Great Danes, suggesting genetic predisposition.

It is clinically, histopathologically and immunologically similar to its human counterpart.

Dermatomyositis [1,2,11]

In dogs, this occurs in several forms, all designated as variants of ischaemic dermatopathy/canine dermatomyositis. The causes and associations (listed below) are different from those in humans, and the crusting, alopecia and ulceration that may occur are not particularly reminiscent of human dermatomyositis. Additionally, the muscle disease is usually subtle.

Canine variants include:

1. A hereditary condition affecting particularly rough collies, Shetland sheepdogs and Beauceron shepherd dogs. Skin lesions first appear in dogs under 6 months old, and consist of erythema, scaling alopecia and crusting on the face, ears, carpal and tarsal areas, digits and tail tip. Pawpads may be affected, and pressure areas. Poor collateral blood flow of extremities and pressure areas has been implicated. Myositis, if present, occurs after the skin lesions, but can be severe and may affect mastication. Sunlight, oestrus and trauma can aggravate the disease.
2. Juvenile onset ischaemic dermatopathy, sometimes linked with (non-rabies) vaccination.
3. Two forms specifically occurring after rabies vaccination, one causing localized panniculitis and the other a generalized disease (generalized vaccine-induced ischaemic dermatopathy, GVIID).
4. Generalized idiopathic ischaemic dermatopathy (GIID), which has no major breed predilection but may be slightly more common in adult long-haired toy or miniature breeds.

Only the first of these would usually be classed as dermatomyositis, with the others being classified as ischaemic dermatoses.



Fig. 2.15 Cutaneous lupus erythematosus affecting the nasal planum of a dog, a typical predilection site.

There is no association with malignancy in the canine forms of this disease, although this underlies about 30% of human dermatomyositis.

Lupus erythematosus (LE) [2,5]

LE occurs in a number of animals, including dogs, cats and horses. Cutaneous LE is one of the most common autoimmune skin conditions in the dog and particularly affects long-nosed breeds including rough collies and the German shepherd dog. Lesions have some morphological similarity to those of humans, consisting of erythema, scaling, depigmentation and ulceration. The condition typically affects the nasal planum first (Fig. 2.15), and then the junction with hair-bearing skin, and then haired skin of the dorsal aspect of the muzzle; many cases are restricted to the planum. Lesions may also occur in the mouth and on the ears and genitalia.

Systemic lupus erythematosus (SLE) is rare in the dog and cat, but the features are similar to the disease in humans, and the suggested criteria for diagnosis are adapted from those of the American Rheumatism Association.

Less common variants include exfoliative cutaneous LE of the German short-haired pointer, which usually affects the head and back but may be generalized, and vesicular cutaneous LE of the Shetland sheepdog and collie, in which there is extensive ulcerative disease.

Cutaneous LE and systemic LE are rare in cats, and very rare in horses. The equine version tends to differ from that seen in small animals, in that the skin lesions in horses with systemic features are most commonly of discoid LE type, presenting as sharply defined areas of depigmentation around mucocutaneous junctions (skin around the eyes, nostrils, mouth and perianal region). The systemic features in horses include polyarthritis, fever, weight loss and various ocular features including uveitis and hypopyon.

Vasculitis and panniculitis

These both occur in other species. Vasculitis is probably most commonly drug-induced or part of hypersensitivity reactions; it can occur in some situations that would be unusual in humans, for example post-vaccination (especially for rabies) and in canine dermatomyositis. It can occur as a paraneoplastic phenomenon. Vasculitis tends to affect the paw pads, edges of the pinnae or the tip and margins of the pinna.

Panniculitis, as in humans, has many causes; it is, for example, documented in pancreatitis or associated with pancreatic tumours (see Chapter 62 for discussion of this association in humans).

Erythema multiforme (EM) and toxic epidermal necrolysis (TEN) [2,5,12–14]

Equine erythema multiforme is said to be secondary to a number of factors, including drugs, infections and malignancy, and the basic lesions are either macular or vesicular.

EM is an uncommon disease in dogs. Many cases appear to be idiopathic, but some are associated with drug administration. Lesions are vesiculobullous and/or ulcerative in most cases, and involve the axillae, groins, mucocutaneous junctions, oral cavity and footpads. EM is very rare in the cat, and is usually associated with drug administration. The diagnosis is confirmed by skin biopsy.

TEN is rare in animals, and is usually triggered by drugs. There is a generalized vesiculobullous eruption and stomatitis, usually followed by a fatal outcome. As with human disease, there is debate about the value of systemic steroids in treatment.

References

1 Scott DW, Miller WH, Griffin CE. Immune-mediated disorders. In: Scott DW, Miller WH, Griffin CE. *Muller and Kirk's Small Animal Dermatology*, 6th edn. Philadelphia: WB Saunders, 2001: 742–56.

2 Gross TL, Ihrke PJ, Walder EJ, Affolter VK. *Skin Diseases of the Dog and Cat. Clinical and Histopathologic Diagnosis*, 2nd edn. Oxford: Blackwell Science, 2005: 27–84.

3 Olivry T, Chan LS. Autoimmune blistering dermatoses in domestic animals. *Clin Dermatol* 2001; **19**: 750–60.

4 Olivry T. Natural bullous pemphigoid in companion animals. In: Chan LS, ed. *Animal Models of Human Inflammatory Skin Diseases*. Boca Raton: CRC Press, 2004: 201–11.

5 Foster AP. Blistering and erosive immune-mediated skin disease. In: Foster AP, Foil CS, eds. *BSAVA Manual of Small Animal Dermatology*, 2nd edn. Gloucester: British Small Animal Veterinary Association, 2003: 197–205.

6 Iwasaki T, Olivry T. Spontaneous canine model of pemphigus foliaceus. In: Chan LS, ed. *Animal Models of Human Inflammatory Skin Diseases*. Boca Raton: CRC Press, 2004: 309–19.

7 Lloyd DH, Littlewood JD, Craig JM, Thomsett LR. *Practical Equine Dermatology*. Oxford: Blackwell Science, 2003: 35–8.

8 Olivry T. Spontaneous canine model of pemphigus vulgaris. In: Chan LS, ed. *Animal Models of Human Inflammatory Skin Diseases*. Boca Raton: CRC Press, 2004: 263–73.

9 Wurm S, Mattise AW, Dunstan RW. Comparative pathology of pemphigus in dogs and humans. *Clin Dermatol* 1994; **12**: 515–24.

10 Olivry T. Spontaneous canine model of epidermolysis bullosa acquisita. In: Chan LS, ed. *Animal Models of Human Inflammatory Skin Diseases*. Boca Raton: CRC Press, 2004: 227–37.

11 Foster AP, Foil CS. *BSAVA Manual of Small Animal Dermatology*, 2nd edn. Gloucester: British Small Animal Veterinary Association, 2003: 78.

12 Lloyd DH, Littlewood JD, Craig JM, Thomsett LR. *Practical Equine Dermatology*. Oxford: Blackwell Science, 2003: 51.

13 Hinn AC, Olivry T, Luther PB *et al*. Erythema multiforme, Stevens–Johnson syndrome, and toxic epidermal necrolysis in the dog. *J Vet Allergy Clin Immunol* 1998; **6**: 13–20.

14 Scott DW, Miller WH. Erythema multiforme in dogs and cats: literature review and case material from the Cornell University College of Veterinary Medicine (1988–1996). *Vet Dermatol* 1999; **10**: 297–309.

Mechanobullous disorders

Mechanobullous disorders in animals are rare. Epidermolysis bullosa (EB) has been described in a variety of animals, including sheep, cattle, horses, cats and dogs. In dogs, reports of EB include lethal junctional epidermolysis bullosa (JEB) in a toy poodle [1], a non-lethal subtype of JEB in a mongrel [2], and a disorder corresponding to mild JEB in humans that occurs in a breed of German short-haired pointers [3]. Dystrophic EB has been reported in an Akita Inu [4]. Reported cases of EB in sheep include recessive dystrophic EB [5]. These animals provide useful models in the investigation of mechanobullous disorders in humans, and targets for development of gene therapy [6].

References

1 Dunstan RW, Stills RC, Wilkinson RW *et al*. A disease resembling junctional epidermolysis bullosa in a toy poodle. *Am J Dermatopathol* 1988; **10**: 442–7.

2 Nagata M, Iwasaki T, Masuda H, Shimizu H. Non-lethal junctional epidermolysis bullosa in a dog. *Br J Dermatol* 1997; **137**: 445–9.

3 Capt A, Spirito F, Guaguere E *et al*. Inherited junctional epidermolysis bullosa in the German Pointer: establishment of a large animal model. *J Invest Dermatol* 2005; **124**: 530–5.

4 Nagata M, Shimizu H, Masunaga T *et al*. Dystrophic form of inherited epidermolysis bullosa in a dog (Akita Inu). *Br J Dermatol* 1995; **133**: 1000–3.

5 Bruckner-Tuderman L, Guscetti F, Herensperger F. Animal model for dermolytic mechanobullous disease: sheep with recessive dystrophic epidermolysis bullosa lack collagen VII. *J Invest Dermatol* 1991; **96**: 452–8.

6 Jiang Q-J, Uitto J. Animal models of epidermolysis bullosa—targets for gene therapy. *J Invest Dermatol* 2005; **124**: xi–xiii.

Drug eruptions

In addition to erythema multiforme and toxic epidermal necrolysis (TEN), discussed above, Stevens–Johnson syndrome (SJS), urticaria, exfoliative dermatitis, vasculitis, lupus erythematosus (LE)-like reactions, drug-induced pemphigus foliaceus and fixed drug eruptions (FDE) occur in several species. In many of these, as in humans, other triggers such as infections are possible alternative causes. The distinction between autoimmune pemphigus foliaceus, drug-induced pemphigus foliaceus and pemphigus foliaceus-like drug reactions may be difficult but drug-induced cases usually resolve after the causative drug is discontinued. In contrast, LE-like reactions may persist.

In horses, FDE and TEN may not occur, or have not been reported as such.

Cutaneous manifestations of systemic disease

As in humans, animals exhibit cutaneous manifestations of systemic diseases, such as infections, endocrinopathies and metabolic disorders, and the reader is referred to veterinary texts for further information. Only a few with human counterparts will be mentioned here.

Acrodermatitis enteropathica [1]

'Zinc-responsive dermatosis' occurs as two syndromes. Syndrome I is an uncommon condition, which is inherited as an autosomal recessive trait, and affects zinc absorption and metabolism (i.e. similar to acrodermatitis enteropathica). It is most consistent in white northern-bred dogs such as Siberian huskies, Alaskan malamutes and sometimes in Samoyeds. Affected dogs have erythema, crusting and alopecia around orifices, eyes, genitalia and pressure points. Syndrome II may represent acquired zinc deficiency. The clinical features are similar but usually more severe, and may affect any breed.

A disorder that has some similarities, but in which affected dogs do not thrive and eventually die, occurs in white bull terriers; it has been suggested that it may be a heterozygous form of the disease but due to the different clinical course is currently best viewed as a separate entity, known as lethal acrodermatitis.

Acanthosis nigricans [2]

Canine acanthosis nigricans (AN), in which there is hyperpigmentation and hyperkeratosis in the axillary and inguinal regions, occurs as a result of obesity, endocrinopathy (e.g. hypothyroidism, sex hormone imbalances) or pruritus associated with canine atopy or food allergy.

Superficial necrolytic dermatitis (SND; canine metabolic necrolytic dermatitis; hepatocutaneous syndrome) [2–5]

This is the canine equivalent of necrolytic migratory erythema (NME) in humans. NME usually occurs as a paraneoplastic process in the glucagonoma syndrome, but there are other associations, including liver disease. In canine SND the majority of affected animals have a concurrent hepatopathy (hepatocutaneous syndrome (HS)) and relatively few have glucagonoma syndrome (GS).

Clinical features of SND include erythematous crusting and hyperkeratosis on the paw pads, around the eyes and mouth and on the external genitalia. In some affected animals there has been a toxic insult to the liver, but the majority have hepatic changes that may represent a form of cirrhosis. Hypoalbuminaemia and diabetes mellitus are common accompanying features.

The precise pathomechanism of HS is unknown but it may be due to a hepatic metabolic abnormality causing amino acid catabolism; profound hypoaminoacidaemia is documented, and the liver may have a characteristic vacuolar hepatopathy with parenchymal collapse, visible as a honeycomb pattern on ultrasound. As in humans, GS is associated with a malignant tumour of the alpha islet cells of the pancreas.

SND occurs in cats, but is rare; it may be associated with pancreatic glucagonomas, hepatopathy, thymic amyloidosis or intestinal lymphoma.

Nodular dermatofibrosis [2,6–9]

Another paraneoplastic syndrome seen in dogs is nodular dermatofibrosis, in which cutaneous lesions which are composed of a dense proliferation of dermal collagen and develop mainly on the head, back and distal parts of the legs, are associated with renal cystadenocarcinomas and uterine leiomyomas. It is a syndrome that occurs in German shepherd dogs, and it resembles hereditary leiomyomatosis and renal cell cancer (HLRCC) (OMIM 605839) in humans.

In dogs with nodular dermatofibrosis, skin lesions precede clinical evidence of renal disease by months to years, and the renal tumours are bilateral. Multiple uterine leiomyomas are found in the majority of female dogs with this syndrome.

The HLRCC syndrome in humans is caused by mutations in the *fumarate hydratase* (*FH*) gene, which encodes one of the

tricarboxylic acid cycle's enzymes. It is thought that *FH* functions as a tumour suppressor. HLRCC-associated renal cancers are usually solitary, unilateral and aggressive.

References

1 Freiman HS, Grubelich LS. Diseases of the foot and nails: humans, cats and dogs. *Clin Dermatol* 1994; **12**: 573–7.
2 Angarano DW, Brewer WG. Comparative dermatology: veterinary cutaneous paraneoplastic syndromes. *Clin Dermatol* 1993; **11**: 15–9.
3 Mullans EA, Cohen PR. Iatrogenic necrolytic migratory erythema: a case report and review of nonglucagonoma-associated necrolytic migratory erythema. *J Am Acad Dermatol* 1998; **38**: 866–73.
4 Byrne KP. Metabolic dermatoses. In: Foster AP, Foil CS. *BSAVA Manual of Small Animal Dermatology*, 2nd edn. Gloucester: British Small Animal Veterinary Association, 2003: 206–12.
5 White SD. An approach to pododermatitis. In: Foster AP, Foil CS, eds. *BSAVA Manual of Small Animal Dermatology*, 2nd edn. Gloucester: British Small Animal Veterinary Association, 2003: 113.
6 Badeloe S, van Geel M, van Steensel MAM *et al*. Diffuse and segmental variants of cutaneous leiomyomatosis: novel mutations in the *fumarate hydratase* gene and review of the literature. *Exp Dermatol* 2006; **15**: 735–41.
7 Lehtonen HJ, Blanco I, Piulats JM *et al*. Conventional renal cancer in a patient with *fumarate hydratase* mutation. *Human Pathol* 2007; **38**: 793–6.
8 Varol A, Stapleton K, Roscioli T. The syndrome of hereditary leiomyomatosis and renal cell cancer (HLRCC): the clinical features of an individual with a fumarate hydratase gene mutation. *Australas J Dermatol* 2006; **47**: 274–6.
9 Grubb RL 3rd, Franks ME, Toro J *et al*. Hereditary leiomyomatosis and renal cell cancer: a syndrome associated with an aggressive form of inherited renal cancer. *J Urol* 2007; **177**: 2079–80.

Alopecia [1–6]

Alopecia is a common sign of disease in animals. It may be congenital or acquired. Congenital alopecia universalis occurs in some breeds of cat including Sphinx cats and Canadian hairless cats, some breeds may have hereditary hypotrichosis (Burmese, Birman, Devon Rex, Siamese), and hair shaft disorders include trichorrhexis nodosa, pili torti and hair shaft dysplasia of Abyssinian cats; congenital hair abnormalities in dogs are represented by the Mexican hairless dog, the Abyssinian dog, Chinese crested dog and the Xoloitzcuintli. Hypohidrotic ectodermal dysplasia in dogs causes sparse hair and, exactly as in humans, abnormal dentition including absent, pointed and malaligned incisors (Fig. 2.16).

Causes of focal acquired alopecia in animals include dermatophytosis, demodicosis, sarcoptic mange, dermatomyositis, flea allergy and alopecia areata (AA). Any pruritic skin disease can lead to focal patches of alopecia in animals. Spontaneous alopecia may be caused by folliculitis (demodicosis, dermatophytosis, staphylococcal infection, alopecia areata, pseudopelade, drug eruption), telogenization (endocrine disease, hair cycling abnormalities, excessive steroid use), follicular infiltration (cutaneous lymphoma), follicular destruction (scarring) or follicular dysplasias. More extensive and symmetrical alopecia occurs particularly in association with endocrine disorders such as hypothyroidism (Fig. 2.17), Cushing's syndrome and sex hormone-related problems. Cushing's syndrome in dogs causes alopecia, mainly of the trunk. It is rare in cats, but also causes alopecia or a dry coat, mainly apparent on the abdomen. In contrast, Cushing's syndrome is moderately common in older horses and the coat tends to become longer and denser (Fig. 2.18). In dogs, alopecia may occur after rabies vaccination.



(a)



(b)

Fig. 2.16 Congenital, X-linked ectodermal dysplasia, the canine analogue of anhidrotic ectodermal dysplasia. (a) Alopecia in a Springer spaniel puppy. (b) Pointed and malaligned incisor teeth in a collie cross.

Progress in research into alopecia areata in humans has been aided by the development of two animal models for human AA—the inbred rodent models of the C3H/HeJ mouse and the Dundee Experimental Bald Rat (DEBR) [7,8], and both of these have provided important data on the genetics and immunological abnormalities of AA. AA-like hair loss has been reported in dogs [9], cats, horses [5,10], cattle and non-human primates. However, an unexplained 'linear alopecia' in horses, although apparently idiopathic and not explained by dermatomal or vascular structures, is quite distinct, having a granulomatous folliculitis pathologically [11].



Fig. 2.17 Symmetrical, non-pruritic alopecia in a Dachshund suffering from hypothyroidism.



Fig. 2.18 Hypertrichosis in a pony suffering from Cushing's syndrome.

In primates, uacaris and stump-tailed macaques undergo progressive balding of the scalp analogous to androgenetic alopecia in humans (Fig. 2.19). The follicles become progressively smaller, with a change from terminal to vellus hair.

Paraneoplastic alopecia has been described in cats, either non-inflammatory or associated with paraneoplastic exfoliative dermatitis.

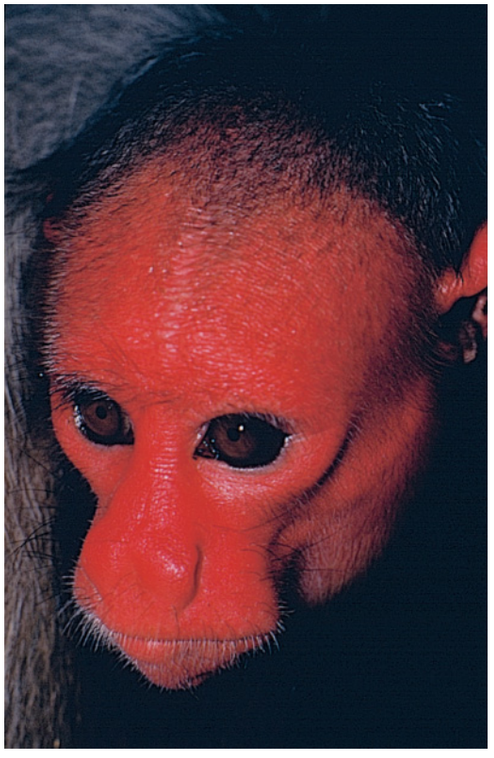


Fig. 2.19 *Cacajao calvus*, the white uacari. Uacaris are notable because both sexes undergo progressive balding of the scalp in which the follicles produce only vellus hairs. (Courtesy of E. Parker, Oxford Scientific Films Ltd.)

References

1 Roosje P, Henfrey J. An approach to alopecia in the cat. In: Foster AP, Foil CS, eds. *BSAVA Manual of Small Animal Dermatology*, 2nd edn. Gloucester: British Small Animal Veterinary Association, 2003: 71–6.

2 Paterson S. An approach to focal alopecia in the dog. In: Foster AP, Foil CS, eds. *BSAVA Manual of Small Animal Dermatology*, 2nd edn. Gloucester: British Small Animal Veterinary Association, 2003: 77–82.

3 Paradis M, Cerundolo R. An approach to symmetrical alopecia in the dog. In: Foster AP, Foil CS, eds. *BSAVA Manual of Small Animal Dermatology*, 2nd edn. Gloucester: British Small Animal Veterinary Association, 2003: 83–93.

4 Frank LA. Comparative dermatology—canine endocrine dermatoses. *Clin Dermatol* 2006; **24**: 317–25.

5 Lloyd DH, Littlewood JD, Craig JM, Thomsett LR, eds. *Practical Equine Dermatology*. Oxford: Blackwell Science, 2003: 100–8.

6 Heripret D. Alopecia. In: Ettinger SJ, Feldman EC, eds. *Textbook of Veterinary Internal Medicine*, 6th edn. St Louis, Missouri: Elsevier Saunders, 2000: 34–7.

7 McElwee KJ. Spontaneous rat model of alopecia areata in the Dundee Experimental Bald Rat. In: Chan LS, ed. *Animal Models of Human Inflammatory Skin Diseases*. Boca Raton: CRC Press, 2004: 451–67.

8 McElwee KJ, Yu M, Park SW *et al*. What can we learn from animal models of alopecia areata? *Dermatology* 2005; **211**: 47–53.

9 Tobin DJ, Olivry T. Spontaneous canine model of alopecia areata. In: Chan LS, ed. *Animal Models of Human Inflammatory Skin Diseases*. Boca Raton: CRC Press, 2004: 469–81.

10 Scott DW. Alopecia areata. In: Robinson NE, ed. *Current Therapy in Equine Medicine*, 5th edn. St Louis, Missouri: Saunders, 2003: 215–6.

11 Scott DW. Linear alopecia and linear keratosis. In: Robinson NE, ed. *Current Therapy in Equine Medicine*, 5th edn. St Louis, Missouri: Saunders, 2003: 216–7.

Neoplastic skin disease

Skin neoplasms are the most frequently diagnosed tumours of domesticated animals and tend to occur in older animals—feline squamous cell carcinoma (SCC) occurs at an average age of 11 years and canine SCC at an average age of 9 years. Actinic damage and solar-induced neoplasia occur in dogs and cats, and affect lightly-pigmented or unpigmented, sparsely-haired areas [1,2] (Fig. 2.20).

As with humans, the animals that lack pigment protection are particularly vulnerable in hot climates. The most commonly affected dog breeds are white English bull terriers, fox terriers, whippets, beagles, white boxers, American Staffordshire bull terriers and American bulldogs. White cats are most susceptible to solar damage, which particularly affects the ears.



Fig. 2.20 Squamous cell carcinoma on the white nose of a cat; this was excised and repaired with a flap from the nasal dorsum and glabella. (Courtesy of Mrs F.H. Cox, Carlisle, UK.)

As in humans, actinic damage leads to solar keratoses and subsequently SCC—in dogs and cats, SCCs occur more frequently than basal cell carcinomas, whereas the reverse is the case in humans. Papillomavirus structural antigens have been demonstrated in some SCCs, suggesting a viral aetiological role in at least some cases. White cats have SCC about 13 times as frequently as other cats [3]. There is an association of feline immunodeficiency virus infection with certain types of neoplasia, including SCC [4].

Selected other neoplasms with behaviour that differs from human 'equivalents' are discussed below.

References

1 Shearer D, Dobson J. An approach to nodules and draining sinuses. In: Foster AP, Foil CS, eds. *BSAVA Manual of Small Animal Dermatology*, 2nd edn. Gloucester: British Small Animal Veterinary Association, 2003: 55–65.

2 Burrows M. Actinic (solar) dermatoses. In: Foster AP, Foil CS, eds. *BSAVA Manual of Small Animal Dermatology*, 2nd edn. Gloucester: British Small Animal Veterinary Association, 2003: 213–9.

3 Scott DW, Miller MH, Griffin CE. *Muller and Kirk's Small Animal Dermatology*, 6th edn. Philadelphia: WB Saunders, 2001: 1252.

4 Hutson CA, Rideout BA, Pedersen NC. Neoplasia associated with feline immunodeficiency virus infection in cats of Southern California. *J Am Vet Med Assoc* 1991; **199**: 1357–62.

Selected disorders that appear to differ from human disease

Although there are many similarities between human and animal diseases, some diseases differ. In some instances this represents similar nomenclature being used for fundamentally different disorders. There are inevitably some disorders that are distinct because of species differences, especially in animals that have diverged longer ago in evolutionary terms—there are also some breed-specific diseases, some of which have been discussed already. Clearly animals that have a scaly reptilian skin, or that have hooves, will have some diseases that differ from anything that occurs in humans. A few examples of disorders without human equivalents are listed in Table 2.2.

Of perhaps greater interest from a comparative point of view are diseases that have human equivalents (or similar names) but that behave differently or appear to have a different cause from that in humans. Some of these have been discussed above, such as superficial necrolytic dermatitis and canine dermatomyositis. Hypohidrotic ectodermal dysplasia, discussed above as a cause of sparse hair and abnormal dentition, does not have overt hypohidrosis (and the risk of hyperthermia, as seen in humans), because dogs only sweat from paw pads and their temperature control is by panting. Some other examples are listed in Table 2.3; a few disorders with specifically different behaviour compared with human counterparts, or similarly named diseases that are distinct between species, are discussed below.

Equine and other animal melanomas [1–6]

Equine melanomas occur most commonly in grey horses, and usually develop in older animals. It is estimated that up to 80% of grey horses older than 15 years develop melanoma, and the anus, vulva and tail are commonly involved. In a study of 296 grey horses of Lipizzaner breed (the greys used by the Spanish Riding School in Vienna) cutaneous melanomas were present in 148 horses (50%), and in 75% of cases lesions occurred underneath the tail [3]. Grey horses are born with dark hair-coats, but with age the hair becomes progressively white. Pigment is retained in the perianal area. However, in contrast with malignant melanoma in humans and in solid-coloured horses, pigment cell tumours frequently display almost benign clinical features in ageing grey horses.

An immunohistopathological study comparing human and equine melanotic tumours [4] revealed that grey horse melanomas have features in common with human blue naevi and desmoplastic malignant melanomas, whereas their resemblance to other types of human cutaneous malignant melanoma is less pronounced. In contrast with human malignant melanoma, melanomas in grey horses are encapsulated, and metastasis is retarded or inhibited by as yet unknown factors. It has been proposed that grey horse-specific genetic factors that inhibit metastatic processes may be responsible for this phenomenon. The authors of this study suggested that further investigation aimed at identifying the factors responsible for retarding metastasis might be of value in developing therapeutic strategies for the treatment of human melanoma.

Animal-type melanoma in humans is a deep, nodular, densely pigmented tumour with relatively good prognosis. It has recently been demonstrated to exhibit low nuclear expression of the π isoform of glutathione S-transferase (GST-π), one of a family of molecules involved in tumour progression, possibly explaining the better than expected prognosis [5].

Canine and feline melanomas [6] are also different from those in humans, as there does not appear to be a role of ultraviolet triggering, malignant transformation from preceding benign naevi appears to be rare, and *in situ* melanomas are also rare (although this may in part be because they are not noticed). Melanomas are rare anyhow, accounting for only 1–2% of skin tumours in cats

Table 2.2 Some animal diseases that do not have an obvious human counterpart.

Type of disease	Examples	Comment
Papulosquamous	Psoriasiform-lichenoid dermatosis	Epidermal morphology is the only resemblance to psoriasis
Infections and parasitic	Cheyletiellosis, parasitic mange	Crusted scabies is the nearest equivalent to mange, but in animals many other ectoparasites are important
	Scabies (cats)	Tends to affect the face ('head mange')
	Habronemiasis (summer sores) in horses	Seasonal nodular lesions due to hypersensitivity to larvae of *Habronema* spp. (stomach worm) that are excreted in faeces and then inoculated into the wound sites by flies
	Dermatophilosis (rain scald) in horses	Exudative lesions due to an actinomycete *Dermatophilus congolensis*
	Distemper (dogs)	Causes hyperkeratosis of the nasal planum and foot pad ('hard pad disease') ± impetigo
	Calcivirus infection (cats)	Ulceration of foot pads and perianal skin
	Feline rhinotracheitis	Can cause multiple oral and skin ulcers, sometimes with necrotizing facial rash on the nose and periocular area
Hypersensitivity reactions	Flea allergy dermatitis (FAD)	Common in dogs and cats
	Eosinophilic disorders in horses (hypersensitivity reactions are suspected but not proven)	Collagenolytic granuloma, axillary nodular necrosis, unilateral papular dermatosis
Hair disorders	Linear alopecia (and linear keratosis) of horses	Vertically orientated lesions, one or more stripes
	Black hair follicle dystrophy (occurs in horses and dogs)	Selective poor growth of black hairs associated with distorted follicles and melanophages
Neoplasia	Equine melanoma	See text
	Melanocytoma–acanthoma	See text
	Canine Sertoli cell tumour-associated skin disease	Causes feminization with gynaecomastia, typically also ventral and caudal alopecia and focal depigmentation
Species-specific diseases	Idiopathic ulceration of collies (rough collies and Shetland sheepdogs)	Represents a vesicular form of cutaneous lupus erythematosus; affects abdomen and groin, usually difficult to treat
	Hyperplastic dermatosis of the West Highland terrier ('armadillo Westie syndrome')	Resembles very severe seborrhoeic dermatitis, and may represent hypersensitivity to *Malassezia pachydermatis* but with a heritable component
	Facial dermatitis of Persian and Himalayan cats	Reminiscent of human seborrhoeic dermatitis but presumed to be hereditary, and differs from other seborrhoeic disease in cats as it is site-specific
	Schnauzer comedo syndrome (miniature Schnauzers)	Relatively common, dorsally situated comedones, may be crusted
Miscellaneous	Canine ear margin seborrhoea	Especially Dachshund breed. Very rare; although greasy scales of the edge of the pinnae resemble those of human seborrhoeic dermatitis it is felt to be a disorder of cornification; sometimes associated with hypothyroidism
	Feline acquired skin fragility syndrome	Fragile skin, that tears easily; has been associated with Cushing's syndrome, diabetes and liver disease
	Lupoid onychitis (symmetrical lupoid onychodystrophy)	Progressive nail destruction; may be multifactorial, some have lichenoid histology

and dogs; most studies suggest that they are less common in cats than in dogs. Cutaneous melanomas include spindle cell, desmoplastic, balloon cell (clear cell) and feline giant epithelioid melanoma. A disorder termed melanocytoma–acanthoma also occurs in dogs, but not in cats—this is rare, has follicular elements histologically, and is cured by excision. There appears to be no human equivalent of this neoplasm.

References

1 Lloyd DH, Littlewood JD, Craig JM, Thomsett LR. *Practical Equine Dermatology*. Oxford: Blackwell Science, 2003: 83–5.

2 Goldschmidt MH. Pigmented lesions of the skin. *Clin Dermatol* 1994; **12**: 507–14.

3 Seltenhammer MH, Simhofer H, Scherzer S *et al*. Equine melanoma in a population of 296 grey Lipizzaner horses. *Equine Vet J* 2003; **35**: 153–7.

4 Seltenhammer MH, Heere-Ress E, Brandt S *et al*. Comparative histopathology of grey-horse-melanoma and human malignant melanoma. *Pigment Cell Res* 2004; **17**: 674–81.

5 Orlandi A, Costantini S, Campione E *et al*. Relation between animal-type melanoma and reduced nuclear expression of glutathione S-transferase π. *Arch Dermatol* 2009; **145**: 55–62.

6 Gross TL, Ihrke PJ, Walder EJ, Affolter VK. *Skin Diseases of the Dog and Cat. Clinical and Histopathologic Diagnosis*, 2nd edn. Oxford: Blackwell Science, 2005: 813–36.

Sarcoid

Equine 'sarcoids' are the most common skin tumour in horses (also in donkeys and mules), and bear no relationship to human sarcoidosis. They vary from alopecic macules or warty plaques to subcutaneous nodules (fibroblastic tumours, Fig. 2.21) which may ulcerate, and even 'malevolent' sarcoids, which spread along fascia and around vessels [1]. In over 90% of cases, bovine papillomavirus types 1 (BPV-1) or 2 (BPV-2) are found. The presence of a BPV-transforming gene, *E5*, has also been implicated. BPV can be latent in the skin (as in humans) and may be reactivated at areas of trauma, a phenomenon noted in some cases of equine sarcoid. Contact with affected animals increases the risk of these lesions, and it has been suggested that some may spread after bites from flying insects. There is a high recurrence rate after surgical excision, but cryotherapy, hyperthermic therapies, intralesional

Table 2.3 Some animal disorders that share some features with, or have similar nomenclature to, human diseases, but that behave differently.

Type of disease	Examples	Comment
Bacterial	'Pyoderma'	Covers various infections, usually due to staphylococcal spp. but mainly *S. pseudintermedius*, often secondary to excoriation and underlying pruritus
	Abscesses	Usually caused by bites or foreign bodies (thorns etc); organisms therefore differ from those likely in humans
Viral	Equine sarcoid, feline sarcoid	Equine variant may behave in a neoplastic fashion; unrelated to human sarcoidosis
Infestations	Demodicosis	Canine form and feline follicular form, see text
Inflammatory	Dermatomyositis (ischaemic dermatopathy)	May be hereditary; not associated with malignancy; see text for more detail
	Metabolic necrolytic dermatitis	Equivalent to necrolytic migratory erythema, but mainly caused by a hepatopathy causing severe hypoaminoacidaemia, the human form being mainly caused by glucagonomas
	Photosensitivity	May be similar, but occurs especially in cattle and horses due to ingestion of plant alkaloids (see text)
	Interdigital furunculosis (interdigital pyoderma)	Inflammation and crusting between paw pads The features are somewhat similar to a mixture of pilonidal sinus and lichenification, probably caused by a mixture of penetration by hairs, trauma and secondary bacterial and *Malassezia* infection Stocky breeds with short coarse hair are predisposed, e.g. mastiffs, boxers and bulldogs
	Paronychia	Similar to humans in having the potential to be acute or chronic, but different organisms Acute paronychia may be staphylococcal but *E. coli* also occurs; chronic changes often involve *Malassezia* spp. Immune-mediated diseases, especially pemphigus, may present with claw disease, and immune deficiency (feline leukaemia virus, feline immunodeficiency virus) infection should be considered
	Feline acne	Clinical resemblance to human acne (comedones, pustules) but usually confined to the chin, and sometimes around the lips; possibly related to poor grooming, and has been described behaving in a contagious fashion within households
Colour disorders	Vitiligo	May behave as in humans but strongly heritable in some breeds, no strong association with other autoimmune diseases, and may be limited distribution (nasal planum, 'snow nose')
Neoplasia	Melanoma	Rare; equine melanoma in particular has a different course



Fig. 2.21 Equine sarcoid, nodular form (the hair has been shaved prior to topical cytotoxic treatment). (Courtesy of Mrs F.H. Cox, Carlisle, UK.)

cytotoxics and radiotherapy have all been used. The lesions shown in Fig 2.21 were treated with a topical mixture of heavy metals and cytotoxic chemotherapy that has been advocated in the UK.

Feline sarcoids (fibropapillomas) have also been described, especially in cats living outdoors in rural areas ('barn cats'). These also contain papillomavirus that has high sequence homology with bovine, ovine, deer and European elk papillomavirus. Lesions are single or multiple, firm, sometimes ulcerated, and tend to occur around the muzzle area, on extremities or the tip of the tail, and occasionally intraorally.

Reference

1 Carr EA. Equine sarcoid. In: Robinson NE, ed. *Current Therapy in Equine Medicine*, 5th edn. St Louis, Missouri: Saunders, 2003: 203–5.

Mast cell tumour [1–3]

In humans, mast cell proliferations (Chapter 22) usually occur as solitary (or few) localized mastocytomas, typically occurring in children and involuting over time, or as urticaria pigmentosa, which may be of childhood (usually self-resolving) or adult (more persistent) onset. Malignant mast cell proliferations are systemic and rare.

In contrast, in dogs, urticaria pigmentosa is rare but mast cell tumours are common (about 10–15% of all skin tumours, and multiple in 10–15% of cases) and typically aggressive. Most are in dogs aged 6–8 years, but onset may be earlier (especially in Chinese shar peis). There are some breeds that have a predilection for mast cell tumours, and some body site differences between breeds. The lesions are erythematous nodules that may be several centimetres in diameter, often with alopecia, and ulceration in larger lesions. Eosinophils are commonly present histologically along with cords and sheets of neoplastic mast cells. Similar to humans, mutations in *c-kit* can be demonstrated; increased expression of KIT and high proliferation assessed by Ki-67 are both linked with poorer prognosis. The more aggressive stage III tumours have a 2-year survival of less than 10%.

Feline mastocytomas generally occur in older animals, around 10 years of age, and have a much more benign behaviour, although those in young animals may be more aggressive.

References

1 Hill PB, Martin RJ. A review of mast cell biology. *Vet Dermatol* 1998; **9**: 145–66.
2 Hill PB. Mast cells: a review of their biology and role in cutaneous inflammation. In: Thoday KL, Foil C, Bond R, eds. *Advances in Veterinary Dermatology*, Vol. 4. Oxford: Blackwell Publishing, 2002: 161–77.
3 Gross TL, Ihrke PJ, Walder EJ, Affolter VK. *Skin Diseases of the Dog and Cat. Clinical and Histopathologic Diagnosis*, 2nd edn. Oxford: Blackwell Science, 2005: 853–65.

Vitiligo [1]

Vitiligo with features very similar to the human disorder occurs in animals, the main difference being that leucotrichia is the norm; some confusion arises because other causes of loss of pigmentation have been given the same term. A degree of heritable tendency occurs, as in humans, although the strength of this varies between breeds—the Belgian Tervuren has a relatively high frequency, and Rottweilers, German shepherd dog, old English sheepdog and dachshund all have some predisposition. Vitiligo in dogs is much less common than in humans, and does not appear to be specifically linked with other organ-specific autoimmune diseases, although it has been reported with diabetes in a dachshund. It is even rarer in cats, although it may occur in Siamese cats (always female). In dogs, vitiligo is usually facial, especially the muzzle, and acral (acrofacial variant) or periorificial (this being similar to vitiligo in some humans). Depigmentation of claws and buccal mucosa occurs in some animals.

Another feature of vitiligo that is unusual is a site-limited variant that affects only the nasal planum (the non-hair-bearing area of the nose), which is called 'Dudley nose' or 'snow nose'; it is most common in some retrievers and in the Siberian husky and the Alaskan malamute.

Reference

1 Gross TL, Ihrke PJ, Walder EJ, Affolter VK. *Skin Diseases of the Dog and Cat. Clinical and Histopathologic Diagnosis*, 2nd edn. Oxford: Blackwell Science, 2005: 853–65.

Photosensitivity

In humans, the commonest causes of photosensitivity are idiopathic eruptions such as polymorphic light eruption, drug-induced photosensitivity and photosensitivity related to exogenous topical agents. Some photosensitivity disorders such as porphyrias combine genetic factors and toxins (such as alcohol in porphyria cutanea tarda).



Fig. 2.22 Photosensitivity in a cow; this is usually caused by ingestion of hepatotoxic plants.

In cattle and horses, ingested plant alkaloids, topical plant-derived photosensitizers and agents causing hepatic damage are much more important (Fig. 2.22). External chemicals implicated in equine contact photoallergy include sunscreens (sometimes applied to the muzzle of grey horses), antiseptics (such as triclosan or chlorhexidine used as treatments, for example for rain scald), antihistamines (for bites) and plants that contain psoralens, hypericins or phytoallexins (e.g. St John's wort, spring parsley, Bishop's weed and others) [1]. Ingestion of plants containing pyrrolizidine alkaloid, such as ragwort and common groundsel may cause severe photosensitivity; in the UK, it is an offence to allow ragwort to grow in fields where horses graze, or in adjacent fields. Elevated blood levels of phylloerythrins occur due to such alkaloid exposure, but also because of hepatic damage following infections (especially leptospirosis), biliary calculi, cholestasis and cholangiohepatitis, mycotoxins, chemical toxins (copper, phosphorus, others) and (limited to Corriedale lambs) as a genetic defect.

Reference

1 Boord M. Photosensitivity. In: Robinson NE, ed. *Current Therapy in Equine Medicine*, 5th edn. St Louis, Missouri: Saunders, 2003: 174–6.

CHAPTER 3

Anatomy and Organization of Human Skin

J.A. McGrath[1] *& J. Uitto*[2]

[1]St John's Institute of Dermatology, King's College London (Guy's campus), London, UK
[2]Department of Dermatology and Cutaneous Biology, Thomas Jefferson University, Philadelphia, USA

Components of normal human skin, 3.1
Functions of skin, 3.2
Regional skin variation, 3.3
Skin development, 3.3
Skin maintenance, 3.5
Epidermal and adnexal structures, 3.7
Keratinocytes, 3.9
Skin barrier, 3.10
Eccrine and apocrine glands, 3.12
Pilosebaceous unit, 3.13
Nails, 3.14
Merkel cells, 3.15
Skin as an immune system, 3.16
Innate immunity, 3.16
Langerhans' cells, 3.17
Immune surveillance, 3.18
Mast cells, 3.19
Melanocytes, 3.20
Epidermal attachment complexes, 3.21
Desmosomes, 3.21
Adherens junctions, 3.23
Gap junctions, 3.24
Tight junctions, 3.24
Dermal–epidermal basement membrane, 3.25
Type IV collagen, 3.27
The laminin family, 3.28
The hemidesmosome–anchoring filament complex, 3.30
Anchoring fibrils, 3.32
Extracellular matrix of connective tissue, 3.33
The collagen family of proteins, 3.34
Elastic fibres, 3.42
Proteoglycan/glycosaminoglycan macromolecules, 3.45
Fibroblasts, 3.49
Blood vessels and lymphatics, 3.50
Subcutaneous fat, 3.52

Components of normal human skin

Skin is the largest organ in the body. In a 70-kg individual, the skin weighs over 5 kg and covers a surface area approaching 2 m^2. Human skin consists of a stratified, cellular epidermis and an underlying dermis of connective tissue (Fig. 3.1). Beneath the dermis is a layer of subcutaneous fat, which is separated from the rest of the body by a vestigial layer of striated muscle.

The epidermis is mainly composed of keratinocytes and is typically 0.05–0.1 mm in thickness. It is formed by division of cells in the basal layer which give rise to the spinous layer. This layer contains cells that move outwards and progressively differentiate, forming the granular layer and the stratum corneum. The cellular progression from the basal layer to the skin surface takes about 30 days but is accelerated in diseases such as psoriasis. The 'brick-like' shape of keratinocytes is provided by a cytoskeleton made of keratin intermediate filaments. As the epidermis differentiates, the keratinocytes become flattened. This process involves the filament aggregating protein, filaggrin, a protein component of keratohyalin granules. Indeed, keratin and filaggrin comprise 80–90% of the mass of the epidermis. The outermost layer of the epidermis is the stratum corneum, where cells (now called corneocytes) have lost nuclei and cytoplasmic organelles. The corneocyte has a highly insoluble, cornified envelope within the plasma membrane, formed by cross-linking of soluble protein precursors, including involucrin and loricrin, the latter contributing 70–85% to the mass of the cornified cell envelope; it also contains several lipids (fatty acids, sterols and ceramides) released from lamellar bodies within the upper, living epidermis. Other cells in the epidermis are the melanocytes, Langerhans' cells and Merkel cells. Melanocytes are dendritic cells that distribute packages of melanin pigment in melanosomes to surrounding keratinocytes to give skin its colour. The number of melanocytes does not differ much between white and black skin. Rather it is the nature of the melanin and the size of the melanosomes that account for the different appearances. The Langerhans' cells are also dendritic in nature, although these are of mesenchymal origin and originate from bone marrow. Langerhans' cells are antigen-presenting cells and process antigens encountered by the skin to local lymph nodes and thus have a key role in adaptive immune responses in the skin. Merkel cells are probably derived from keratinocytes. They have a role as mechanosensory receptors in response to touch.

Human skin contains pilosebaceous follicles and sweat glands. The hair follicles comprise pockets of epithelium that are continuous with the superficial epidermis but which also envelop a small papilla of dermis at their base. A bundle of smooth muscle, the arrector pili, extends at an angle between the surface of the dermis and a point in the follicle wall. Above the insertion, there are holocrine sebaceous glands which open into the pilary canal. In some sites, such as the axillae, the follicles may be associated with apocrine glands. Also derived from the epidermis and opening directly to the skin surface are the eccrine sweat glands.

The epidermis is attached to the dermis via a complex network of proteins and glycoproteins that extend from inside basal

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

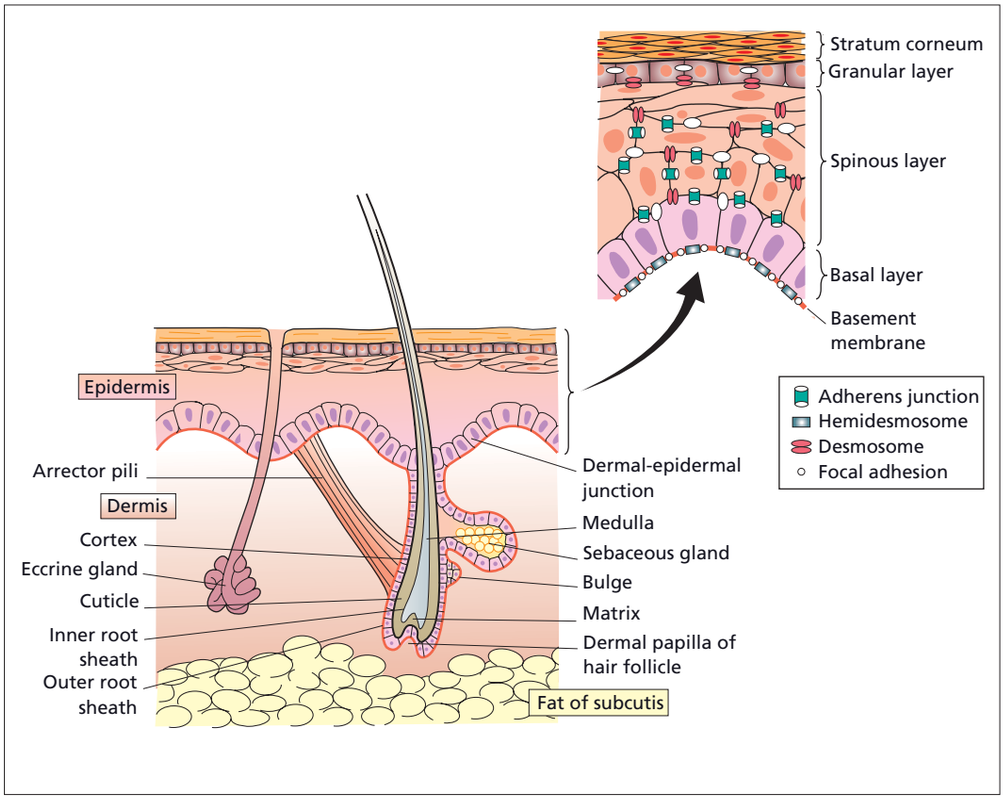


Fig. 3.1 The skin and its appendages.

keratinocytes into the superficial dermis. Besides adhesion, the dermal–epidermal junction components also contribute to cell migration (for example during wound healing) as well as epithelial–mesenchymal signalling events. Over 30 different macromolecules (collagens, laminins, integrins) interact within a basement membrane zone that is less than 200 µm across.

The dermis is a supporting matrix or ground substance in which polysaccharides and proteins are linked to produce macromolecules that have a remarkable capacity for retaining water. The thickness of the dermis varies from less than 0.5 mm to more than 5 mm. There are two principal types of protein fibre: collagen and elastic tissue. Collagen is the major extracellular matrix protein comprising 80–85% of the dry weight of the dermis. Twenty-nine different collagens have been identified in vertebrate tissue (depicted by Roman numerals in the order of their discovery, from I to XXIX), of which at least 12 are expressed in skin. The main interstitial dermal collagens are types I and III whereas the principal basement membrane collagen (at the dermal–epidermal junction and around dermal blood vessels, nerves and appendages) is type IV collagen. Triple-helical collagen monomers polymerize into fibrils and fibres, which then become stabilized by the complex formation of both intra- and intermolecular crosslinks. Collagen fibres are extremely tough and provide skin with its tensile strength. Elastic fibres account for no more than 2–4% of the extracellular matrix in the dermis and consist of two components, elastin and elastin-associated microfibrils, which together give skin its elasticity and resilience. Elastic microfibrils are composed of several proteins, including fibrillin, which surround the elastin and which can extend throughout the dermis in a web-like configuration to the junction between the dermis and the epidermis. The dermis also contains a number of non-collagenous glycoproteins including fibronectins, fibulins and integrins. These extracellular matrix components facilitate cell adhesion and cell motility. Between the dermal collagen and elastic tissue is the ground substance made up of glycosaminoglycan/proteoglycan macromolecules. These contribute only 0.1–0.3% of the total dry weight of the dermis but provide a vital role by maintaining hydration, mostly due to the high water-binding capacity of hyaluronic acid. About 60% of the total weight of the dermis is water.

The dermis has a very rich blood supply, although no vessels pass through the dermal–epidermal junction. There is a superficial and a deep vascular plexus. The motor innervation of the skin is autonomic, and includes a cholinergic component to the eccrine sweat glands and adrenergic components to both the eccrine and apocrine glands, to the smooth muscle and the arterioles and to the arrector pili muscle. The sensory nerve endings are of several kinds; some are free, some terminate in hair follicles and others have expanded tips.

Functions of skin

A key role of skin is to provide a mechanical barrier against the external environment. The cornified cell envelope and the stratum corneum restrict water loss from the skin while keratinocyte-derived endogenous antibiotics (defensins and cathelicidins)

provide an innate immune defence against bacteria, viruses and fungi. The epidermis also contains a network of about 2×10^9 Langerhans' cells, which serve as sentinel cells whose prime function is to survey the epidermal environment and to initiate an immune response against microbial threats, although they may also contribute to immune tolerance in the skin. Melanin, which is mostly found in basal keratinocytes, also provides some protection against DNA damage from ultraviolet radiation.

An important function of skin is thermoregulation. Vasodilatation or vasoconstriction of the blood vessels in the deep or superficial plexuses helps regulate heat loss. Eccrine sweat glands are found at all skin sites and are present in densities of 100–600/cm^2; they play a role in heat control and produce approximately 1 litre of sweat per hour during moderate exercise. Secretions from apocrine sweat glands contribute to body odour (pheromones). Skin lubrication and waterproofing is provided by sebum secreted from sebaceous glands.

Subcutaneous fat has important roles in cushioning trauma as well as providing insulation and a calorie reserve. In non-obese subjects, about 80% of the body's total fat is found in subcutaneous tissue. Fat also has an endocrine function, releasing the hormone leptin, which acts on the hypothalamus to regulate hunger and energy metabolism. Other functions of fat cells include tissue remodelling and phagocytosis.

Nails provide protection to the ends of the fingers and toes as well as being important in pinching and prising objects. Hair may have important social and psychological value, reflecting the notion that the appearances of human skin and its associated structures have a major impact on interpersonal relationships and personal well-being. Skin also has a key function in synthesizing various metabolic products, such as vitamin D.

Regional skin variation

There are two main kinds of human skin: glabrous skin (non-hairy skin) and hair-bearing skin. Glabrous skin is found on the palms and soles and has a grooved surface with alternating ridges and sulci giving rise to the dermatoglyphics (fingerprints). Glabrous skin has a compact stratum corneum which may be up to 10 times thicker compared to other body sites such as the flexures, where the epidermis is at its thinnest. Glabrous skin also contains encapsulated sense organs within the dermis, as well as a lack of hair follicles and sebaceous glands. In contrast, hair-bearing skin has both hair follicles and sebaceous glands but lacks encapsulated sense organs. Hair follicle size, structure and density can vary between different body sites; the scalp has large hair follicles that may extend into subcutaneous fat whereas the forehead has only small, vellus hair-producing follicles although sebaceous glands are large. The number of hair follicles remains unchanged until middle life but there is a changing balance between vellus and terminal hairs throughout life. In hair-bearing sites, such as the axilla, there are apocrine glands in addition to the eccrine sweat glands. Sebaceous glands are actively functioning in the newborn, and from puberty onwards, and the relative activity modifies the composition of the skin surface lipids. The structure of the dermal–epidermal junction also shows regional variations in the number of hemidesmosomal-anchoring filament complexes (more in the leg than the arm). In the dermis, the arrangement and size of elastic fibres varies from very large fibres in perianal skin to almost no fibres in the scrotum. Marked variation in the cutaneous blood supply is found between areas of distensible skin such as the eyelid and more rigid areas such as the fingertips. There may also be regional differences in biomechanical properties which can affect percutaneous absorption of creams and ointments.

Skin development

The skin arises by the juxtaposition of two major embryological elements: the prospective epidermis that originates from a surface area of the early gastrula, and the prospective mesoderm that comes into contact with the inner surface of the epidermis during gastrulation. The mesoderm not only provides the dermis, but is essential for inducing differentiation of the epidermal structures, such as the hair follicle. The melanocytes are derived from the neural crest.

After gastrulation, there is a single layer of neuroectoderm on the embryo surface; this layer will go on to form the nervous system or the skin epithelium depending on the molecular signals it receives (Fig. 3.2). Activation of Wnt signalling will block the ability of the ectoderm to respond to fibroblast growth factors (FGFs). Without FGFs the cells express bone morphogenic proteins (BMPs) and progress to an epidermal lineage. Conversely, lack of Wnt signalling promotes a neural fate [1].

The embryonic epidermis consists of a single layer of multipotent epithelial cells, which is covered by a special layer known as periderm that is unique to mammals (Figs 3.3 & 3.4). Periderm provides some protection to the newly forming skin as well as exchange of material with the amniotic fluid. The embryonic dermis is at first very cellular and at 6–14 weeks three types of cell are present: stellate cells, phagocytic macrophages and granule-secretory cells, either melanoblasts or mast cells. From weeks 14 to 21, fibroblasts are numerous and active, and perineural cells, pericytes, melanoblasts, Merkel cells and mast cells can be individually identified. The various structural components of the skin that can be recognized postnatally start to appear at different embryonic time-points, for example, hair follicles and nails (9 weeks), sweat glands (9 weeks for the palms and soles, 15 weeks for other sites) and sebaceous glands (15 weeks). Touch pads become recognizable on the fingers and toes by week 6 and reach their greatest development at week 15. After this, they flatten and become indistinct. It is these areas that determine the pattern of dermatoglyphics that take their place.

The mesoderm not only provides the dermis but is essential for inducing differentiation of the epidermal structures, such as the hair follicle in mammals [2]. The earliest development of the hair rudiments occurs at about 9 weeks in the regions of the eyebrow, upper lip and chin (Fig. 3.5).

Mesenchymal cells, derived from the dermomyotome, populate the skin and interact with the overlying epidermis to induce formation of hair placodes [3]. Key components of the mesenchymal signals to produce hair follicles include FGFs and BMP-inhibitory factors such as Noggin; excessive BMP stimulation can reduce hair

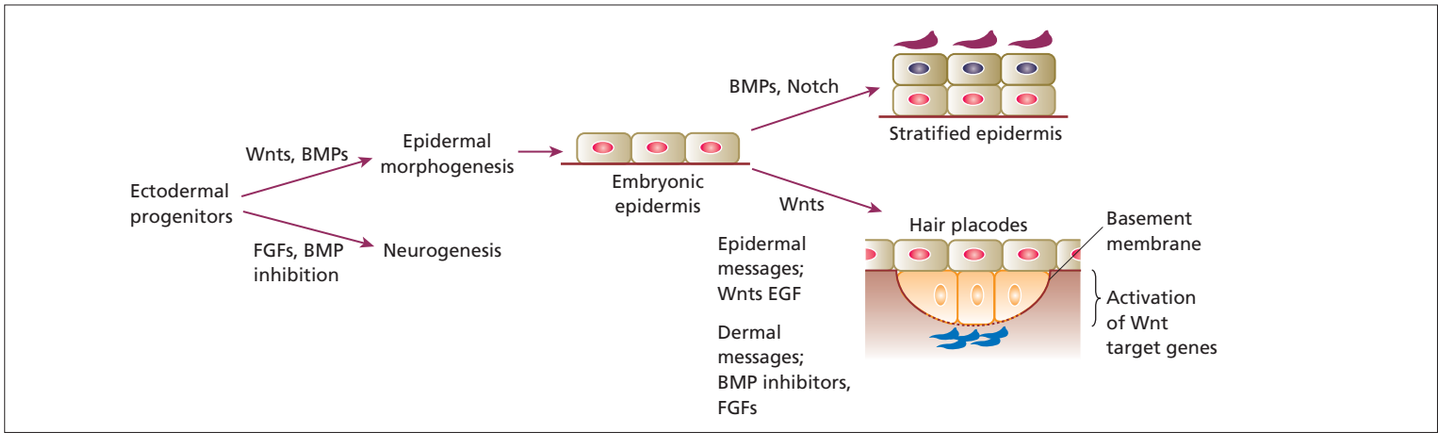


Fig. 3.2 Embryonic development of the skin depends on specific signalling molecules. Relative stimulation or inhibition by these signalling molecules also determines whether embryonic epidermis progresses to a stratified epidermis or whether formation of skin appendages is induced. BMP, bone morphogenic protein; FGF, fibroblast growth factor; EGF, epidermal growth factor.

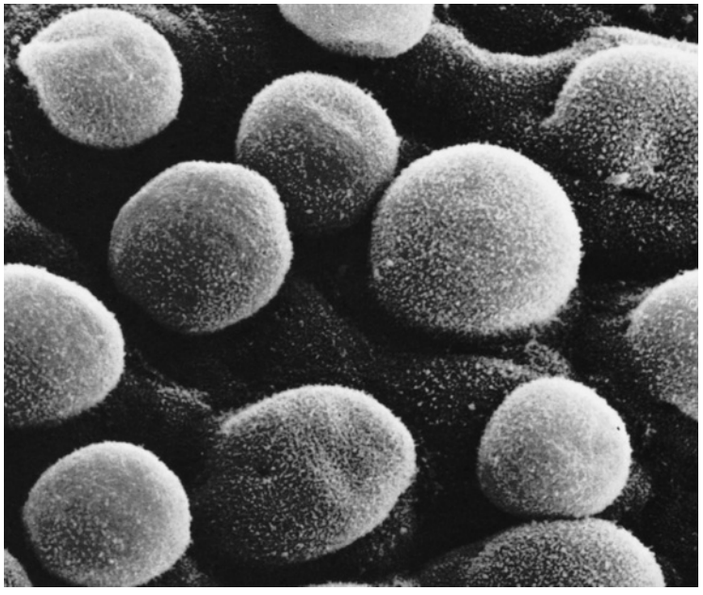


Fig. 3.3 Scanning electron micrograph of an 85–110 day (estimated gestation age) human embryo. Single globular blebs project from the periderm cells. (Courtesy of Professor K.A. Holbrook.)

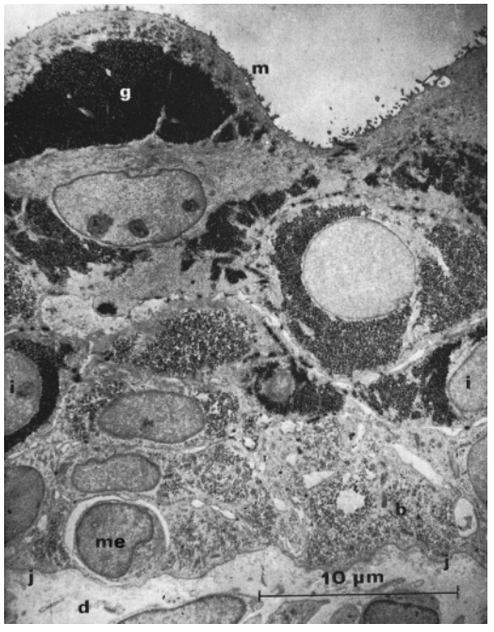


Fig. 3.4 Electron micrograph of the full-thickness epidermis from the back of a 14-week human fetus. Osmium fixation and lead staining. The periderm cells are full of glycogen (g) and have microvilli (m) at their amniotic border. Cells of the intermediate layer (i) also contain glycogen. Basal-layer cells (b) have lost glycogen by this stage. Just above the dermal–epidermal junction (j) there is a melanocyte (me); the surrounding space indicates that it is a recent immigrant from the dermis (d). (Courtesy of Professor A.S. Breathnach, St John's Institute of Dermatology, King's College London,UK.)

follicle density. The epidermal response to form the hair placode is generated by Wnt signals such as Wnt10b and sonic hedgehog (Shh) which also has a key role in the formation of the dermal papilla. After it is formed, the dermal papilla sends further signals to transform the placode into a hair follicle. At the centre of the signalling crosstalk is the bipartite transcription factor composed of LEF1 and stabilized β-catenin, which is essential for hair follicle formation. Hair follicle development is also influenced by Smads, a group of signalling mediators and antagonists of the transforming growth factor-β (TGF-β) superfamily: Smad-4 affects hair follicle differentiation by mediating BMP signalling; Smad-7 affects hair follicle development and differentiation by blocking TGF-β/Activin/BMP pathways [4].

Signalling responses differ between follicular and interfollicular epidermis: BMP signalling is active in the interfollicular epidermis and is both an epidermis-promoting signal as well as a follicle-inhibiting signal; epidermal growth factor receptor (EGFR) signalling may have a similar role in governing follicle density. As hair follicles mature to form inner and outer root sheaths, several signalling pathways are involved, including Wnt, Notch and BMP receptors. There are also marked changes in certain cell adhesion

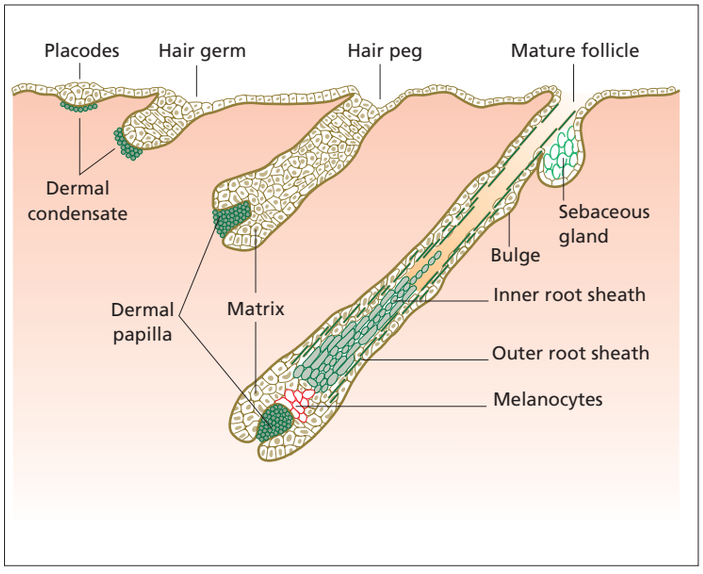


Fig. 3.5 Embryonic stages of hair follicle morphogenesis.

proteins, notably E-cadherin and P-cadherin. The hair follicles are arranged in patterns, usually in groups of three. It appears that the first follicles develop over the surface at fixed intervals of between 274 and 350 μm. As the skin grows, these first hair germs become separated, and new rudiments develop between them when a critical distance, dependent on the region of the body, has been reached. There is no large-scale destruction of follicles during postnatal development, only a decrease in actual density as the body surface increases; nor do any new follicles develop in adult skin. In interfollicular epidermis, the undersurface of the epidermis is smooth, but during the fourth month, at the same time as the hair follicle starts to develop, it becomes irregular.

Sebaceous glands first appear as hemispherical protuberances on the posterior surfaces of the hair pegs. The cells contain moderate amounts of glycogen, but soon the cells in the centre lose this, and become larger and foamy as they accumulate droplets of lipid. The sebaceous glands become differentiated at 13–15 weeks, and are then large and functional. The sebum forms part of the vernix caseosa. At the end of fetal life, sebaceous glands are well developed and generally large. After birth, the size is rapidly reduced, and they enlarge to become functional again only after puberty. The molecular signals that induce sebaceous gland differentiation involve the c-Myc transcription factor as well as the adipogenic transcription factor peroxisome proliferator-activated receptor γ (PPAR-γ) [5].

Eccrine glands start to develop on the palms and soles at about 3 months, but not over the rest of the body until the fifth month [6]. In embryos of 12 weeks, the rudiments of eccrine sweat glands are first identifiable as regularly spaced undulations of the developing epidermis. Cells that go on to form the eccrine sweat glands are oblong, palisading and lie closely together, but otherwise they do not differ from the rest of the developing basal epidermis. By 14–15 weeks, the tips of the eccrine sweat gland rudiments have penetrated deeply into the dermis, and have begun to form the coils. In the overlying epidermis, columns of cells that are destined to form the intraepidermal sweat ducts are recognizable. Each column is composed of two distinct cylindrical layers, comprising two inner cells that are elongated and curved so that they embrace the inner cylinder. The intraepidermal duct appears to form by the coalescence of groups of intracytoplasmic cavities formed within two adjacent inner cells. In the intradermal segment, the lumen forms by dissolution of the desmosomal attachment plaques between the cells that compose the inner core of the eccrine duct germ.

Nails begin to develop in the third month. Key signalling events in nail development involve the R-spondin family of transcription factors [7]. In fetuses at 16–18 weeks (crown to rump length 120–150 mm), keratinizing cells from both dorsal and ventral matrices can be distinguished. Melanocytes take their origin from the neural crest. This can be identified in early human embryos, but the elements arising from it soon lose themselves in the mesenchyme, and pigmented melanocytes cannot be identified, even in black skin fetuses, before 4–6 months of gestation. However, dopa-positive melanocytes can be demonstrated earlier. Langerhans' cells are derived from the monocyte–macrophage–histiocyte lineage and enter the epidermis at about 12 weeks. Merkel cells appear in the glabrous skin of the fingertips, lip, gingiva and nail bed, and in several other regions, around 16 weeks.

Although some cells of the dermis may migrate from the dermatome (ventrolateral part of the somite) and take part in the formation of the skin, most of the dermis is formed by mesenchymal cells that migrate from other mesodermal areas [8]. These mesenchymal cells give rise to the whole range of blood and connective tissue cells, including the fibroblasts and mast cells of the dermis and the fat cells of the subcutis. In the second month, the dermis and subcutis are not distinguishable from each other but distinct collagen fibres are evident in the dermis by the end of the third month. Later, the papillary and reticular layers become distinct and, at the fifth month, the connective tissue sheaths are formed around the hair follicles. Elastic fibres are first detectable at 22 weeks.

References

1 Fuchs E. Scratching the surface of skin development. *Nature* 2007; **445**: 834–42.
2 Schmidt-Ullrich R, Paus R. Molecular principles of hair follicle induction and morphogenesis. *BioEssays* 2005; **27**: 247–61.
3 Rendl M, Lewis L, Fuchs E. Molecular dissection of mesenchymal-epithelial interactions in the hair follicle. *PLoS Biol* 2005; **3**: e331.
4 Owens P, Han G, Li AG, Wang XJ. The role of Smads in skin development. *J Invest Dermatol* 2008; **128**: 783–90.
5 Honeycutt KA, Roop DR. c-Myc and epithelial stem cell fate determination. *J Dermatol* 2004; **31**: 368–75.
6 Loomis CA. Development and morphogenesis of the skin. *Adv Dermatol* 2001; **17**: 183–210.
7 Bergmann C, Senderek J, Anhuf D *et al.* Mutations in the gene encoding Wnt-signaling component R-spondin 4 (RSPO4) cause autosomal recessive anonychia. *Am J Hum Genet* 2006; **79**: 1105–9.
8 Olivera-Martinez I, Thelu J, Dhouailly D. Molecular mechanisms controlling dorsal dermis generation from the somite dermomyotome. *Int J Dev Biol* 2004; **48**: 93–101.

Skin maintenance

To maintain skin homeostasis, regenerate skin appendages and repair itself after injury, the skin contains stem cells which reside

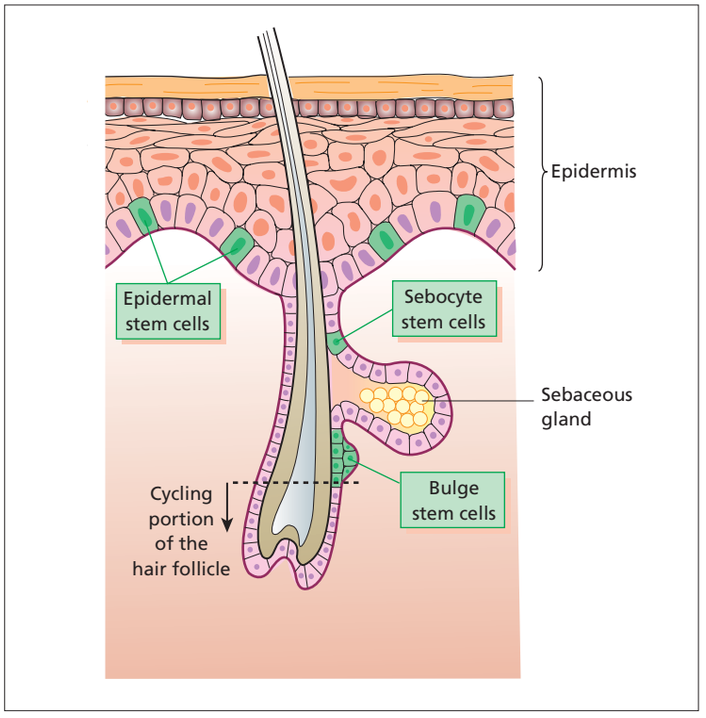


Fig. 3.6 Epithelial stem cells are found within the interfollicular epidermis, the base of sebaceous glands and in the bulge area of hair follicles.

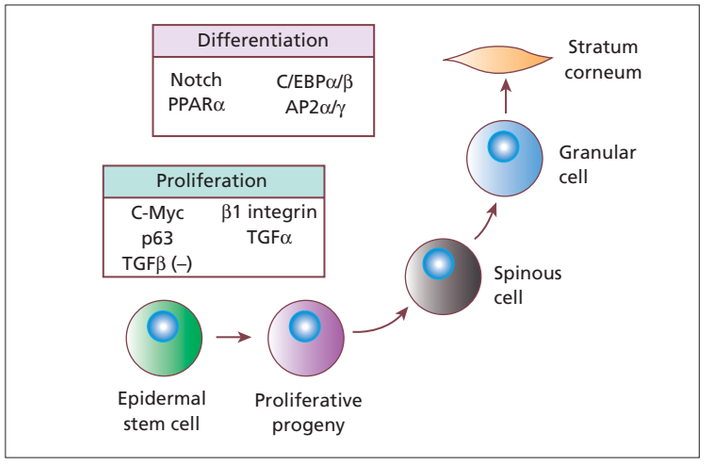


Fig. 3.7 Epidermal stem cell proliferation regulated positively by β1 integrin and TGF-α, and negatively (–) by TGF-β signalling; the transcription factors c-Myc and p63 also promote epidermal proliferation. Notch signalling and the transcription factors PPARα, AP2α/γ, and C/EBPα/β control the differentiation of epidermal cells.

in the bulge area of hair follicles, the basal layer of interfollicular epidermis and the base of sebaceous glands [1] (Fig. 3.6). These stem cells generate a proliferative progeny that can undergo differentiation. The molecular signals involved in regulating epidermal stem cell proliferation and differentiation are illustrated in Fig. 3.7.

Stem cells are able to self-renew as well as give rise to the differentiating cells [2]. In the epidermis, some basal cells can periodically withdraw from the cell cycle and commit to terminal differentiation. It is still not clear, however, whether every cell or only a proportion of cells in the basal layer is a stem cell. One long-established theory divides basal keratinocytes into epidermal proliferation units, which comprise one self-renewing stem cell and about 10 tightly packed, transient, amplifying cells (each capable of dividing several times and then exiting the basal layer to undergo terminal differentiation) [3]. This unit gives rise to a column of larger and flatter cells that culminates in a single hexagonal surface. Stem cells within epidermal proliferation units are associated with a profile of particular chemical, molecular and biological characteristics [4]. For example, stem cells retain labelling with injected ^{3}H-thymidine or Brdu after repeated cell division. In culture, actively growing clones present after serial passaging are considered to indicate an origin from stem cells. Potential markers of interfollicular epidermal stem cells are α6 and β1 integrin as well as p63, whereas sebocyte stem cells express Blimp1. Markers of hair follicle bulge stem cells include CD34, NFATc1, vitamin D receptor, TCF3, Sox9 and Lhx2.

In the epidermal proliferation unit concept of stem cell behaviour, the division of basal cells has been viewed as a symmetrical process in which equal daughter cells are generated; the basal cells progressively reduce their adhesiveness to the underlying epidermal basement membrane, delaminate and commit to terminal differentiation (Fig. 3.8).

However, recent data suggest that basal cells can also undergo asymmetrical cell division, shifting their spindle orientation from lateral to perpendicular [5]. Asymmetrical cell divisions provide a natural means of maintaining a proliferative daughter cell that retains the cell markers associated with stem cells, while the other daughter cell has reduced markers such as β1 integrin, increased expression of Notch signals, and is committed to terminal differentiation. Asymmetrical cell divisions, therefore, can bypass the need for transient amplifying cells.

The structural and biological composition of the dermal–epidermal junction also influences the proliferative properties of basal keratinocytes. Laminin-332 promotes anchorage as a ligand via α6β4 integrins in hemidesmosomes and signalling/migration via its association with α3β1 in focal adhesions. Signalling via α3β1 integrin stimulates the MAP-kinase pathway, turnover of focal adhesions and epidermal migration. The basement membrane is also a reservoir for growth factors that can promote epidermal proliferation (e.g. TGF-α, EGFs and insulin growth factors) or restrict it (e.g. TGF-β). EGFR signalling also enhances proliferation and migration in the epidermis, possibly by phosphorylating β4 integrin and promoting hemidesmosome disassembly. Thus the control of basal keratinocyte stem cell activity in maintaining homeostasis and responding to injury is through the regulation of at least two opposing tyrosine kinase pathways and two integrin structures.

A key transcription factor in regulating the self-renewal and long-term proliferative capacity of the stem cell is p63, a member of the p53 family of proto-oncogenes. However, the precise role of p63 is not clear; it may have a direct effect on stem-cell renewal, or lineage commitment, and/or an effect on switching from proliferation to terminal differentiation [6]. Notch signalling also appears to have an important gatekeeper function in the transition

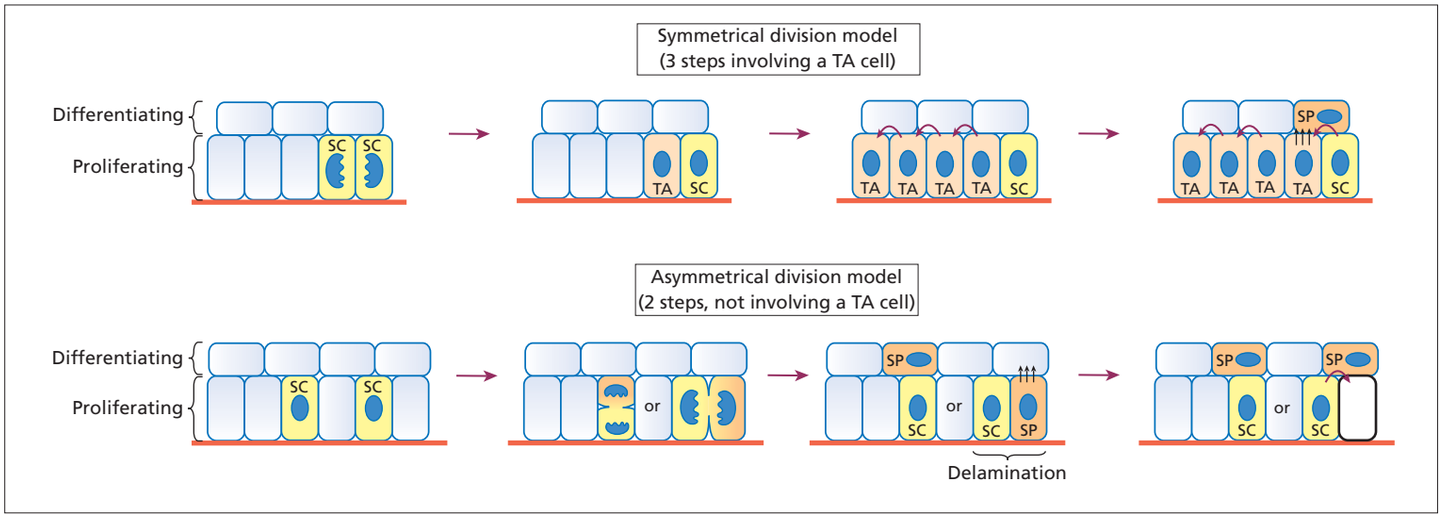


Fig. 3.8 Possible mechanisms for the proliferative potential of stem cells (SC) in the basal keratinocyte layer. In the symmetrical division model, two stem cells are produced. Some of these cells in contact with the epidermal basement membrane are transit-amplifying cells (TA). These cells are capable of dividing four to five times before leaving the basal layer (delamination, black arrows) to become a spinous layer cell (SP) and entering terminal differentiation. In the asymmetrical division model, there is preferential partitioning of proliferation-associated factors into the stem cell daughter cell and, conversely, preferential partitioning of differentiation-inducing components into the daughter cell that is destined to become a spinous layer cell. Depending on the orientation of the cell spindle, the daughter cell destined for differentiation can either become a spinous layer cell directly or delaminate from the basal layer to enter terminal differentiation. *In vivo*, both mechanisms may exist.

from basal to suprabasal cells; there is basal expression of Notch ligands such as Delta1 and suprabasal expression of Notch receptors and Notch downstream targets such as Hes1 [7].

Stem cells in hair follicles are located in the lowest permanent part of the follicle, within the outer root sheath. These cells cycle more slowly than other cells and have the capacity to migrate (e.g. to the base of the hair follicle in follicular regeneration), as well as to differentiate into diverse lineages (e.g. outer root sheath, inner root sheath, hair shaft, sebocytes and interfollicular epidermis). Despite this multipotency, however, the follicle stem cells only function in pilosebaceous unit homeostasis and do not contribute to interfolliclular epidermis unless the skin is wounded [8].

Hair follicles undergo cycles of degeneration and regeneration throughout life. During the growth phase (anagen), which requires activation of hair follicle stem cells, matrix cells proliferate rapidly but then undergo sudden apoptosis (catagen). The hair bulb and root shrivel to form an epithelial strand which forces the dermal papilla to rest at the base of the non-cycling part of the hair follicle [9]. The hairs then enter a resting phase (telogen). At a molecular level, inhibition of BMP signalling and activation of Wnt signalling converge to regulate stem cell activation. From microarray studies, *Sox9*, *Tcf3* and *Lhx2* appear to be markers of follicular stem cells whether they are quiescent or proliferative.

Apart from stem cells in the hair follicles and interfollicular epidermis, other cells in the dermis and subcutis may have stem cell properties. These include cells that have been termed skin-derived precursors (SKPs), which can differentiate into both neural and mesodermal progeny [10]. In addition, a subset of dermal fibroblasts can have adipogenic, osteogenic, chondrogenic, neurogenic and hepatogenic differentiation potential [11]. Moreover, dermal fibroblasts can be reprogrammed into cells bearing an embryonic stem cell (pluripotent) phenotype by the insertion of just four key transcription factors, *Oct4*, *Sox2*, *Klf4* and *Myc* [12].

References

1 Braun KM, Prowse DM. Distinct epidermal stem cell compartments are maintained by independent niche microenvironments. *Stem Cell Rev* 2006; **2**: 221–31.
2 Fuchs E. Skin stem cells: rising to the surface. *J Cell Biol* 2008; **180**: 273–84.
3 Potten CS. The epidermal proliferative unit: the possible role of the central basal cell. *Cell Tissue Kinet* 1974; **7**: 77–88.
4 Watt FM, Hogan BL. Out of Eden: stem cells and their niches. *Science* 2000; **287**: 1427–30.
5 Lechler T, Fuchs E. Asymmetric cell divisions promote stratification and differentiation of mammalian skin. *Nature* 2005; **437**: 275–80.
6 Truong AB, Khavari PA. Control of keratinocyte proliferation and differentiation by p63. *Cell Cycle* 2007; **6**: 295–9.
7 Blanpain C, Lowry WE, Pasolli HA, Fuchs E. Canonical notch signaling functions as commitment switch in the epidermal lineage. *Gene Dev* 2006; **20**: 3022–35.
8 Ito M, Yang Z, Andl T *et al*. Wnt-dependent *de novo* hair follicle regeneration in adult mouse skin after wounding. *Nature* 2007; **447**: 316–20.
9 Cotsarelis G. Epithelial stem cells: a folliculocentric view. *J Invest Dermatol* 2006; **126**: 1459–68.
10 Toma JG, McKenzie IA, Bagli D, Miller FD. Isolation and characterization of multipotent skin derived precursors from human skin. *Stem Cells* 2005; **23**: 727–37.
11 Chen FG, Zhang WJ, Bi D *et al*. Clonal analysis of nestin (–) vimentin (+) multipotent fibroblasts isolated from human dermis. *J Cell Sci* 2007; **120**: 2875–83.
12 Park IH, Zhao R, West JA *et al*. Reprogramming of human somatic cells to pluripotancy with defined factors. *Nature* 2008; **451**: 141–6.

Epidermal and adnexal structures

The normal epidermis is a terminally differentiated, stratified, squamous epithelium. The major cell, making up 95% of the total,

is the *keratinocyte*, which moves progressively from attachment to the epidermal basement membrane towards the skin surface, forming several well-defined layers during its transit [1]. Thus, on simple morphological grounds, the epidermis can be divided into four distinct layers: *stratum basale* or *stratum germinativum*, *stratum spinosum*, *stratum granulosum* and *stratum corneum*. The term *Malpighian* layer includes both the basal and spinous cells. Other cells within the epidermis include melanocytes, Langerhans' cells and Merkel cells (Fig. 3.9).

The stratum basale is a continuous layer that is generally only one cell thick but it may be two to three cells thick in glabrous skin and in hyperproliferative epidermis. The basal cells are small and cuboidal (10–14 nm in diameter) and have large, dark-staining nuclei, and dense cytoplasm which contains many ribosomes and dense tonofilament bundles. Immediately above the basal cell layer, the epibasal keratinocytes enlarge to form the spinous/prickle-cell layer or *stratum spinosum* (Fig. 3.10).



Fig. 3.9 Photomicrograph of a 1-μm-thick plastic section of normal human skin. The tissue was fixed with half-strength Karnovsky's medium and embedded in Epon. This technique allows the cellular components of the epidermis, including keratinocytes, melanocytes (straight arrows) and probable Langerhans' cells (curved arrows) to be clearly resolved. × 400. Basic fuchsin and methylene blue.

The stratum spinosum is succeeded by the *stratum granulosum* or granular layer, which contains intracellular granules of keratohyalin. At high magnification, the dense mass of keratohyalin granules from human epidermis has a particulate substructure, with particles of irregular shape, on average 2 nm in length, and occurring randomly in rows or lattices. The cytoplasm of cells of the upper, spinous layer and granular cell layer also contains smaller lamellated granules averaging 100–300 nm in size, which are known as lamellar granules or bodies, membrane-coating granules or Odland bodies. These are numerous within the uppermost cells of the spinous layer and migrate towards the periphery of the cells as they enter the granular cell layer (Fig. 3.11). They discharge their lipid components into the intercellular space, playing important roles in barrier function and intercellular cohesion within the stratum corneum [2].

The outermost layer of epidermis is the stratum corneum where cells (now corneocytes) have lost nuclei and cytoplasmic organelles. The cells become flattened and the keratin filaments align into disulphide cross-linked macrofibres, under the influence of *filaggrin*, the protein component of the keratohyalin granule, responsible for keratin filament aggregation. The key role of filaggrin in skin biology has been demonstrated by the discovery of very common loss-of-function mutations in the filaggrin gene as the cause of the genetic disorder ichthyosis vulgaris and as a major risk factor for the development of atopic dermatitis, atopic asthma and systemic allergies [3]. The corneocyte has a highly insoluble, cornified envelope within the plasma membrane, formed by cross-linking of the soluble protein precursor, *involucrin*, following the action of a specific epidermal transglutaminase also synthesized in the high stratum spinosum (Fig. 3.12).

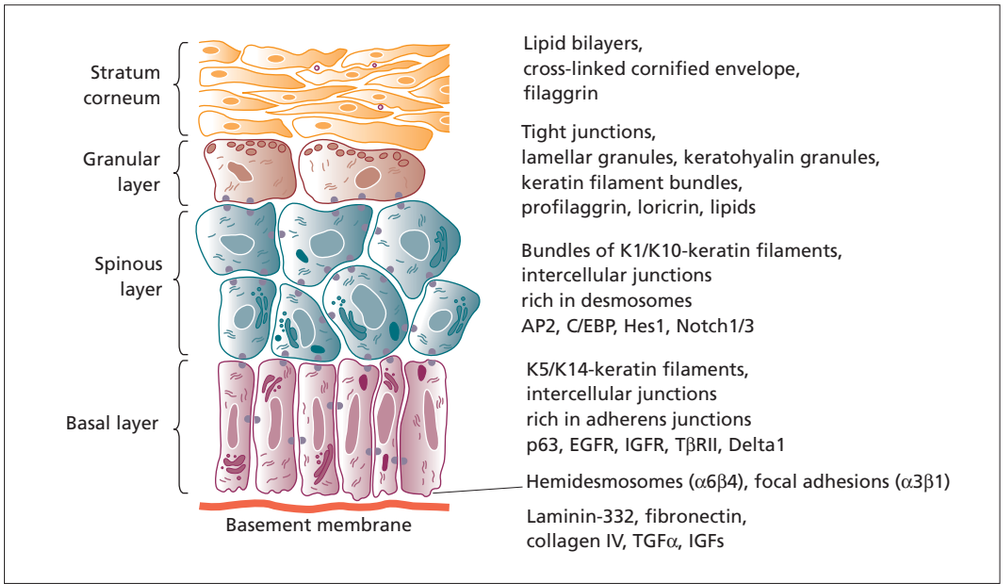


Fig. 3.10 The process of epidermal differentiation is associated with expression of different structures, macromolecules, transcription factors and other signalling molecules and their receptors in the different keratinocyte layers.

The process of desquamation involves degradation of the lamellated lipid in the intercellular spaces and loss of the residual intercellular desmosomal interconnections [4]. In palmoplantar skin there is an additional zone, also electron-lucent, the *stratum lucidum*, between the granulosum and corneum. These cells are still nucleated, and may be referred to as 'transitional' cells.

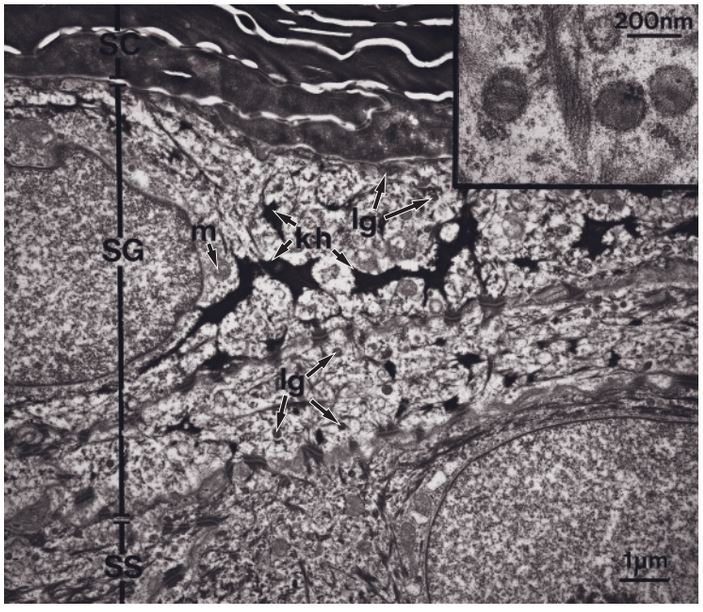


Fig. 3.11 Electron micrograph showing details of upper part of epidermis including stratum corneum (SC), stratum granulosum (SG) and the most superficial cell layer of stratum spinosum (SS). Note the irregularly shaped keratohyalin granules (kh) and the small, round lamellar granules (lg). The latter are present in both SS and SG and are smaller than mitochondria (m). Inset shows details of lamellar granules. Scale bar = 1 μm.

References

1 Houben E, De Paepe K, Rogiers V. A keratinocyte's course of life. *Skin Pharmacol Physiol* 2007; **20**: 122–32.

2 Feingold KR. Thematic review series: skin lipids. The role of epidermal lipids in cutaneous permeability barrier homeostasis. *J Lipid Res* 2007; **48**: 2531–46.

3 Sandilands A, O'Regan GM, Liao J *et al*. Prevalent and rare mutations within the filaggrin gene cause ichthyosis vulgaris and predispose individuals to atopic dermatitis. *J Invest Dermatol* 2006; **126**: 1770–5.

4 Milstone LM. Epidermal desquamation. *J Dermatol Sci* 2004; **36**: 131–40.

Keratinocytes

The filamentous cytoskeleton of all mammalian cells, including epidermal keratinocytes, comprises: actin, containing microfilaments approximately 7 nm in diameter; tubulin, containing microtubules 20–25 nm in diameter; and filaments of intermediate size, 7–10 nm in diameter, known as intermediate filaments. There are six types of intermediate filaments: keratins in epithelial cells; vimentin within mesenchymal cells; glial filament acidic protein (GFAP) in glial cells; neurofilaments in neurones; desmin in muscle cells; and peripherin in peripheral nerves. The nuclear matrix proteins, nuclear lamins A, B and C, are also intermediate filaments. The polypeptide building blocks of all intermediate filaments have a similar backbone structure of a classical α-helical region with heptad repeats, having four separate helical zones with interhelical linker sequences, and non-helical carboxy- and amino-terminals. There are 70 intermediate filament genes (including those encoding keratins, desmins, and lamins), which are now known to be associated with at least 72 distinct human diseases, including skin blistering, muscular dystrophy, cardiomyopathy, premature ageing syndromes, neurodegenerative disorders and cataract [1].

The human genome possesses 54 functional keratin genes located in two compact gene clusters, as well as many non-functional pseudogenes, scattered around the genome [2]. Keratin genes are very specific in their expression patterns. Each one of the many highly specialized epithelial tissues has its own profile

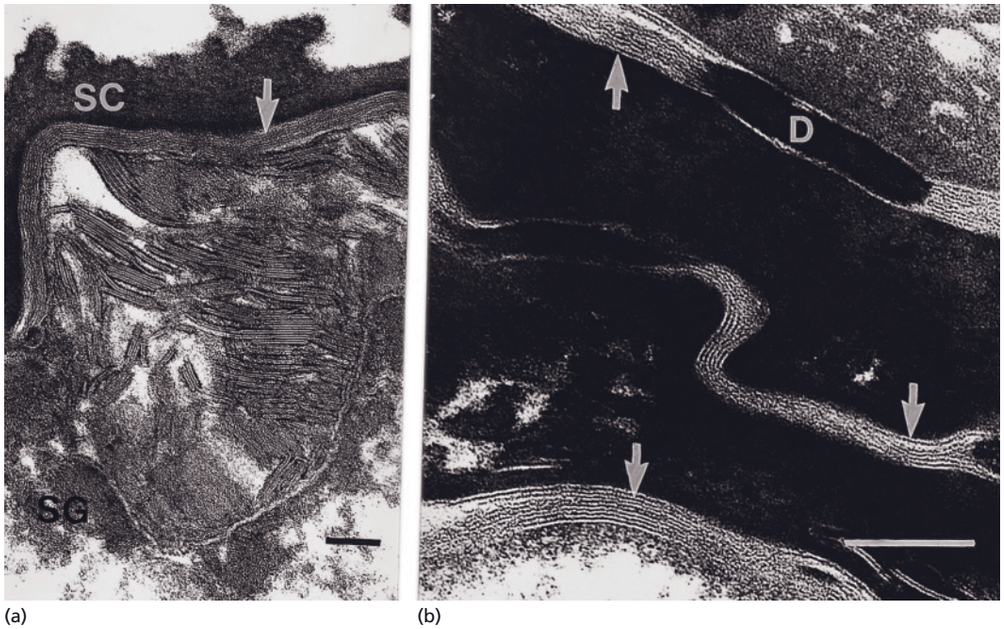


Fig. 3.12 Electron micrograph showing location of epidermal lipids by ruthenium oxide staining. (a) Extrusion of lamellar body lipids or sheets can be seen at the interface between the stratum granulosum (SG) and stratum corneum (SC). Scale bar = 0.1 μm. (b) Sheets of lipid bilayers (arrowed) are present in the intercellular spaces of the stratum corneum. Some regions show a repetitive pattern of staining. D, desmosome. Scale bar = 0.1 μm. (Courtesy of Dr M. Fartasch, Department of Dermatology, University of Erlangen, Germany.)

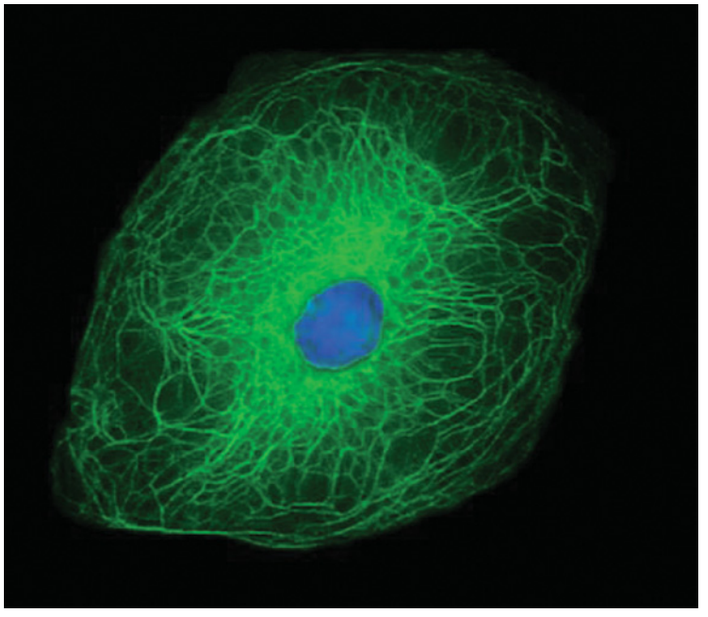


Fig. 3.13 The structural organization of the keratin filament network within a keratinocyte. (Courtesy of Prof. W.H.I. McLean, University of Dundee, Scotland.)

of keratin gene expression. Hair and nails express modified keratins, containing large amounts of the amino acid cysteine which forms numerous chemical cross-links to further strengthen the cytoskeleton. The genes encoding individual keratins fall into two gene families: type I (basic) and type II (acidic). Mapping the tissue distribution of keratins shows coexpression of particular acidic–basic pairs in a cell- and tissue-specific manner. Heterodimers are assembled into higher-order protofibrils and protofilaments by an antiparallel stagger of some complexity.

Simple epithelia are characterized by the keratin pair K8/K18, and the stratified squamous epithelia by K5/K14 (Fig. 3.13). In addition, stratified squamous epithelia express up to four other keratin pairs during epithelial differentiation. In skin, suprabasal keratins K1/K10 are characteristic of epidermal differentiation. In the stratum granulosum, release of filaggrin from the keratohyalin granules forms macrofibres. Retinoid levels, growth factors and hormones may regulate keratin gene expression. Mesenchymal signals may also direct or permit intrinsic patterns of keratinocyte differentiation. K15 is expressed in basal keratinocytes of the hair-follicle bulge region at the site of pluripotential stem cells. K9 and K2e expression is site restricted in skin: K9 to palmoplantar epidermis and K2e to superficial interfollicular epidermis. Apart from their structural properties, keratins may also have direct roles in cell signalling, the stress response and apoptosis [3]. In epidermal hyperproliferation, as in wound healing and psoriasis, expression of suprabasal keratins K6/K16/K17 is rapidly induced.

Currently, 21 of the 54 known keratin genes have been linked to monogenic genetic disorders, and some have been implicated in more complex traits, such as idiopathic liver disease or inflammatory bowel disease [4]. The first genetic disorder of keratin to be described was epidermolysis bullosa simplex, which involves mutations in the genes encoding K5 or K14. About half of the keratin genes are expressed in the hair follicle, and mutations in these genes may underlie cases of monilethrix as well as hair and nail ectodermal dysplasias [5].

References

1 Szeverenyi I, Cassidy AJ, Chung CW *et al*. The human intermediate filament database: comprehensive information on a gene family involved in many human diseases. *Hum Mutat* 2008; **29**: 351–60.

2 Schweizer J, Bowden PE, Coulombe PA *et al*. New consensus nomenclature for mammalian keratins. *J Cell Biol* 2006; **174**: 169–74.

3 Magin TM, Vijayaraj P, Leube RE. Structural and regulatory functions of keratins. *Exp Cell Res* 2007; **313**: 2031–2.

4 Uitto J, Richard G, McGrath JA. Diseases of epidermal keratins and their linker proteins. *Exp Cell Res* 2007; **313**: 1995–2009.

5 McLean WH, Irvine AD. Disorders of keratinisation: from rare to common genetic diseases of skin and other epithelial tissues. *Ulster Med J* 2007; **76**: 72–82.

Skin barrier

One of the key functions of the epidermis is to form a barrier against the external environment. To that end, terminal differentiation of keratinocytes leads to formation of the cornified cell envelope. The cornified envelope is rendered highly insoluble by the formation of glutamyl-lysyl isodipeptide bonds between envelope proteins, catalysed by transglutaminases [1]. There are at least three distinct transglutaminases, but TG1 (keratinocyte transglutaminase) can cross-link envelope proteins in the absence of other enzymes. Mutations in TG1 underlie some cases of lamellar ichthyosis or non-bullous congenital ichthyosiform erthroderma; mutations in TG5 result in autosomal recessive skin peeling syndrome [2,3]. Several different proteins contribute to the cornified envelope (Fig. 3.14).

Involucrin is the best-established envelope precursor although it is also a marker of differentiation in epithelia such as cornea. Other cytosolic envelope precursors include the family of small proline-rich proteins (SPR1) including *cornifin* or SPR1 and *pancornulins*. Other envelope proteins include *SKALP/elafin* and *keratolinin/cystatin*, a 36-kDa protein cross-linked by transglutaminase into a 150-kDa multimer.

Some precursors of the cornified envelope are delivered by granules. Small, smooth, sulphur-rich L granules contain the cysteine-rich protein *loricrin*, and accumulate in the stratum granulosum [4]. Loricrin is the major component of the cornified envelope. Expression of loricrin depends on a high calcium concentration and is down-regulated by retinoids. Profilaggrin in F granules may make a minor contribution to the envelope. Membrane-associated proteins that contribute to the cornified envelope include the plakin family members, periplakin, envoplakin, epiplakin, desmoplakin as well as plectin.

Formation of the cornified cell envelope is triggered by a rise in intracellular calcium levels [5]. This leads to cross-link formation between plakins and involucrin catalysed by transglutaminase. Other desmosomal proteins are then also cross-linked, forming a scaffold along the entire inner surface of the plasma membrane. Ceramides from the secreted contents of lamellar bodies are then esterified onto glutamine residues of the scaffold proteins. The cornified cell envelope is reinforced by the addition of a variable amount of SPRs, repetin, trichohyalin, cystostatin α, elafin and LEP/XP-5 (skin-specific protein). Although most desmosomal components are degraded, keratin intermediate filaments (mostly

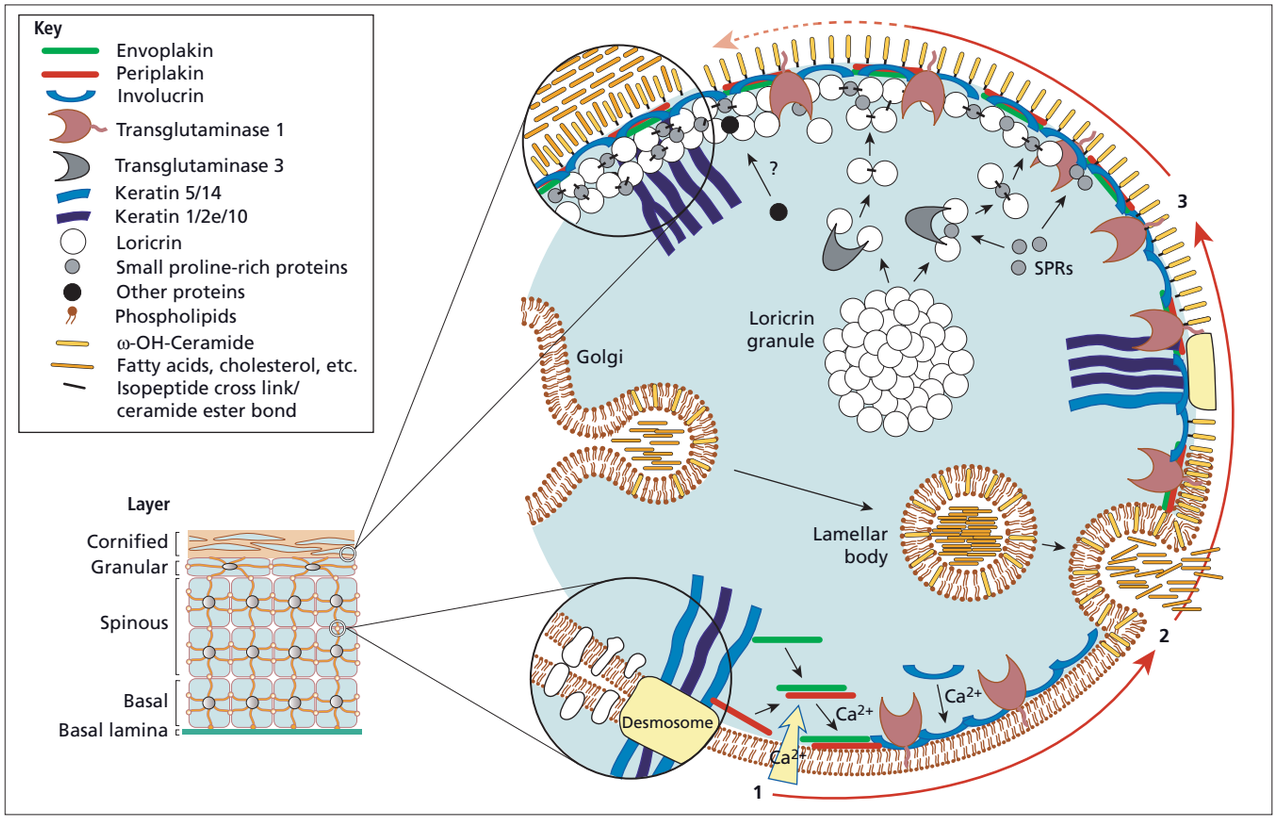


Fig. 3.14 Assembly of the epidermal cornified cell envelope. In response to increasing intracellular calcium, an internal scaffold of desmosomal proteins is made along the plasma membrane. The contents of lamellar bodies (ceramides and other fatty acids, cholesterol and cholesterol esters) are released into the extracellular milieu to form a lipid membrane. The developing envelope is then added to and reinforced by recruitment of various proteins, including loricrin, small proline-rich proteins (SPR1), other desmosomal remnants and attached keratin filaments. The resulting cornified cell envelope is durable and flexible and provides important mechanical and barrier functions.

K1, K10 and K2e) may be cross-linked to desmoplakin and envoplakin remnants. Together these assembly and degradation events result in durable, flexible but dead cells that have vital mechanical and water-permeability barrier functions.

During epidermal differentiation, there are profound changes in the composition of lipids; in the viable layers phospholipids, cholesterol and triglycerides predominate, but in the upper stratum spinosum and stratum granulosum lipid is synthesized and packaged into lamellated, membrane-bound organelles known as *membrane-coating granules*, lamellar granules or Odland bodies [6]. They are found adjacent to the cell membrane with alternating thick and thin dense lines separated by lighter lamellae of equal width, consistent with packing of flattened discs within a membrane boundary. Immunochemistry has confirmed the presence of phospholipids, glycolipids and free sterols. The organelles move towards the plasma membrane as the cells move through the granular layer and cluster at the cell membrane. They fuse with the plasma membrane, dispersing their contents into the intercellular space. Polar lipids from the lamellar granules are remodelled into neutral lipids in the intercellular space between corneocytes, forming an important barrier to permeability. The lamellar granules also contain hydrolytic enzymes, lipases and glycosidases, which are responsible for this remodelling. Thus, the stratum corneum is rich in ceramides, free sterols and free fatty acids. Linoleate appears to be essential for proper barrier function as an ester-linked residue in acyl ceramides; thus, in essential fatty acid deficiency, substitution of this linoleate by oleate causes a defect in barrier function. The skin is an active lipid-synthesizing tissue, with a daily production rate of 100 mg/day.

In human epidermis, nearly all sterol is present as cholesterol. In many cells, cholesterol biosynthesis may be modulated by uptake of exogenous cholesterol, mediated by low-density lipoprotein (LDL) receptors, but these are only present on the plasma membrane of basal keratinocytes, and are rapidly down-regulated on epidermal differentiation. Sterol synthesis is higher in the stratum granulosum, and is thus relatively autonomous and uninfluenced by dietary or circulating sterol levels. Cholesterol sulphate is highest in the stratum granulosum and corneum, where it is thought to play a role in cell cohesion. In X-linked recessive ichthyosis due to steroid sulphatase deficiency, scales contain high levels of cholesterol sulphate giving increased intercellular adhesion.

References

1 Candi E, Schmidt R, Melino G. The cornified envelope: a model of cell death in the skin. *Nat Rev Mol Cell Biol* 2005; **6**: 328–40.

2 Schmuth M, Gruber R, Elias PM, Williams ML. Ichthyosis update: towards a function-driven model of pathogenesis of the disorders of cornification and the role of corneocyte proteins in these disorders. *Adv Dermatol* 2007; **23**: 231–56.

3 Cassidy AJ, van Steensel MA, Steijlen PM *et al*. A homozygous missense mutation in TGM5 abolishes epidermal transglutaminase 5 activity and causes acral peeling skin syndrome. *Am J Hum Genet* 2005; **77**: 909–17.
4 Ishida-Yamamoto A, Tanaka H, Nakane H *et al*. Programmed cell death in normal epidermis and loricrin keratoderma. Multiple functions of profilaggrin in keratinization. *J Investig Dermatol Symp Proc* 1999; **4**: 145–9.
5 Bikle DD, Oda Y, Xie Z. Calcium and 1,25(OH)2D: interacting drivers of epidermal differentiation. *J Steroid Biochem Mol Biol* 2004; **89–90**: 355–60.
6 Elias PM, Williams ML, Holleran WM *et al*. Thematic review series: skin lipids. Pathogenesis of permeability barrier abnormalities in the ichthyoses: inherited disorders of lipid metabolism. *J Lipid Res* 2008; **49**: 697–714.

Eccrine and apocrine glands

Human sweat glands are generally divided into two types: apocrine and eccrine [1]. The eccrine gland is the primary gland responsible for thermoregulatory sweating in humans. Eccrine sweat glands are distributed over nearly the entire body surface. Sweat glands become identifiable in the palms and soles in the 16th fetal week, and in the rest of the body from the 22nd week onwards. The number of sweat glands in humans varies greatly, ranging from 1.6 to 4.0 million. The structure of the eccrine sweat gland consists of a bulbous secretory coil leading to a duct. The secretory coil is located in the lower dermis, and the duct extends through the dermis and opens directly onto the skin surface. The active sweat glands are present most densely on the sole, forehead and palm, somewhat less on the back of the hand, still less on the lumbar region, and the lateral and extensor surfaces of the extremities, and least on the trunk and the flexor and medial surfaces of the extremities. The uncoiled dimension of the secretory portion of the gland is approximately 30–50 μm in diameter and 2–5 mm in length. The size of the adult secretory coil ranges from 1 to 8×10^{-3} mm^3.

Human perspiration is classified into two types: insensible perspiration and active sweating. Insensible perspiration involves water loss from the respiratory passages, the skin and gaseous exchanges in the lungs. In the skin, the epidermis is supplied with water originating from blood in the skin microcirculation and interstitial spaces so that water can evaporate from its dry surface. Thus, the evaporation of water from the skin may depend on several environmental factors, such as ambient temperature and ambient humidity. Heat, mental stimuli, muscular exercise and carbon dioxide can all induce active sweating in human beings. Active sweating may be classified into two types: thermal and mental/emotional. Thermal sweating plays an important role in keeping the body's temperature constant and involves the whole body surface [2]. Mental or emotional sweating usually appears on the palms and soles. The physiological features of mental sweating differ considerably from those of thermal sweating. Mental sweating has a shorter latent period for its onset and immediately attains a certain rate of secretion that corresponds to the intensity of stimulation, remaining for the duration of the stimulation and subsiding quickly after it ends. Eccrine glands contribute to both types of sweating.

The secretory nerve fibres innervated in human sweat glands are sympathetic, which seem to be cholinergic in character as sweating is produced by pilocarpine and stopped by atropine [3]. Vasoactive intestinal peptide (VIP) coexisting in the cholinergic nerve fibres has been suggested as a candidate neurotransmitter that may control the blood circulation of the sweat glands. The sudorific nervous system is also separated into parts for thermal and emotional sweating, each being controlled by its own regulatory centre in the brain which is associated with the sweat glands in its respective region of the skin. The exact neurological pathways responsible for sweating are not entirely understood. Evidence from animal studies suggests that efferent signals from the preoptic hypothalamus travel via the tegmentum of the pons and the medullary raphe regions to the intermediolateral cell column of the spinal cord. From here, neurones emerge via the ventral horn, pass through the white ramus communicans, and then synapse in the sympathetic ganglia. Postganglionic nonmyelinated C fibres pass through the grey ramus communicans, combine with peripheral nerves and travel to sweat glands. Sympathetic nerve terminals cluster mainly around the secretory coil of the sweat gland, but a few projections extend to the sweat duct. Acetylcholine is the primary neurotransmitter released from cholinergic sudomotor nerves and binds to muscarinic receptors on the eccrine sweat gland, although sweating can also occur via exogenous administration of α- or β-adrenergic agonists. Released acetylcholine is rapidly hydrolysed by acetylcholinesterase, and this response may be one of a number of mechanisms by which the rate of sweating rate is regulated.

When acetylcholine binds to muscarinic receptors on the sweat gland, intracellular Ca^{2+} concentrations increase. This results in an increase in the permeability of K^+ and Cl^- channels, which initiates the release of an isotonic precursor fluid from the secretory cells [4]. This precursor fluid is similar to plasma but is devoid of proteins. As the fluid travels up the duct toward the surface of the skin, sodium and chloride are reabsorbed, resulting in sweat on the surface being hypotonic relative to plasma. When the rate of sweat production increases, however, for example during exercise or heat stress, ion reabsorption mechanisms can be overwhelmed due to the large quantity of sweat secreted into the duct, resulting in higher ion losses. The sodium content in sweat on the skin's surface, therefore, is greatly influenced by sweat rate.

Apart from eccrine glands, the skin also contains apocrine sweat glands [5]. Eccrine glands do not show cytological changes during secretion whereas apocrine glands are characterized by decapitation secretion, in which part of the cell is pinched off and released into the lumen. Apocrine glands are located only in genital, axillary and mammary areas, where they are always connected to a hair follicle. Apocrine glands have a low secretory output, and hence no significant role in thermoregulation. They are composed of a coiled secretory portion and an excretory duct. The inner layer of the secretory portion contains a single columnar secretory cell type containing numerous, large dense granules located at the apical aspect, which contribute to the lipid-rich secretion produced. The inner layer is also surrounded by a fenestrated layer of myoepithelial cells but the lumen is generally larger in diameter than that present in eccrine tissue. The apocrine excretory duct does not have any known reabsorptive function and consists of a double layer of cuboidal cells that merge distally with the epithelium of the hair follicle, resulting in emptying of the secretion into the hair follicle. The exact role of apocrine glands in humans is unknown. A third type of intermediate sweat glands, the apoeccrine glands, has also been described in axillary skin but their existence is not universally accepted.

References

1 Wollina U, Abdel-Naser MB, Ganceviciene R, Zouboulis CC. Receptors of eccrine, apocrine, and holocrine skin glands. *Dermatol Clin* 2007; **25**: 577–88.
2 Morimoto T, Itoh T. Thermoregulation and body fluid osmolality. *J Basic Clin Physiol Pharmacol* 1998; **9**: 51–72.
3 Shibasaki M, Wilson TE, Crandall CG. Neural control and mechanisms of eccrine sweating during heat stress and exercise. *J Appl Physiol* 2006; **100**: 1692–701.
4 Quinton PM. Cystic fibrosis: lessons from the sweat gland. *Physiology (Bethesda)* 2007; **22**: 212–25.
5 Lonsdale-Eccles A, Leonard N, Lawrence C. Axillary hyperhidrosis: eccrine or apocrine. *Clin Exp Dermatol* 2003; **28**: 2–7.

Pilosebaceous unit

The pilosebaceous units develop from epidermal downgrowths under the influence of specific mesenchymal cell condensations between the 10th and 14th week estimated gestational age. They have complex groups of specialized cell layers with distinctive pathways of differentiation. There are four classes of pilosebaceous unit: terminal on the scalp and beard; apopilosebaceous in axilla and groin; vellus on the majority of skin; and sebaceous on the chest, back and face. The dermal papilla is located at the base of the hair follicle with a rich extracellular matrix. Around the papilla are germinative (matrix) cells that have a very high rate of division, and give rise to spindle-shaped central cortex cells of the hair fibre, and the single outer layer of flattened, overlapping cuticle cells. A central medulla is seen in some hairs, with regularly stacked, condensed cells interspersed with air spaces or low-density cores. The cortical cells are filled with keratin intermediate filaments orientated along the long axis of the cell, interspersed with a dense interfilamentous protein matrix. Terminal differentiation of cortical cells is associated with the appearance of a contiguous, laminated, intercellular layer, which appears critical for filament integrity. The cuticular cells are morphologically distinct; these are flattened, outward-facing cells, with three layers inside the cuticle of condensed, flattened protein granules: endocuticle, exocuticle and 'a' layer [1].

Around the cuticle is the inner root sheath (IRS), which is composed of three distinct layers of cells that undergo keratinization: the IRS cuticle, the Huxley layer and the outermost Henle layer [2]. Differentiation in the IRS involves the development of trichohyalin granules, with 8 to 10-nm filaments orientated in the direction of hair growth. The IRS moves up the follicle, forming a support for the hair fibre, and degenerates above the sebaceous gland. The outermost layer is the outer root sheath (ORS), which is continuous with the epidermis and expresses epithelial keratins, K5/K14, K1/K10 and K6/K16 in the upper ORS and K5/K14/K17 in the deeper ORS.

Normal growth of the hair fibre is 300–400 µm/day, generated by the high rate of proliferation of progenitor cells in the follicle bulb. Compartmentalization within the bulb gives rise to the different layers within the follicle, with the majority of bulb cells forming the IRS. There are three phases of cyclical hair growth: anagen, when growth occurs; catagen, a regressing phase; and telogen, a resting phase (Fig. 3.15). The follicle re-enters anagen, and the old hair is replaced by a new one.

Immediately above the basal layer in the hair bulb, cells undergo a secondary pathway of 'trichocyte' or hair differentiation, and express a further complex group of keratins, the hard keratins [3]. Two families of hair keratins, types I and II, are present in mammals, which have distinctive amino- and carboxyterminals with high levels of cysteine residues, and lack the extended glycine

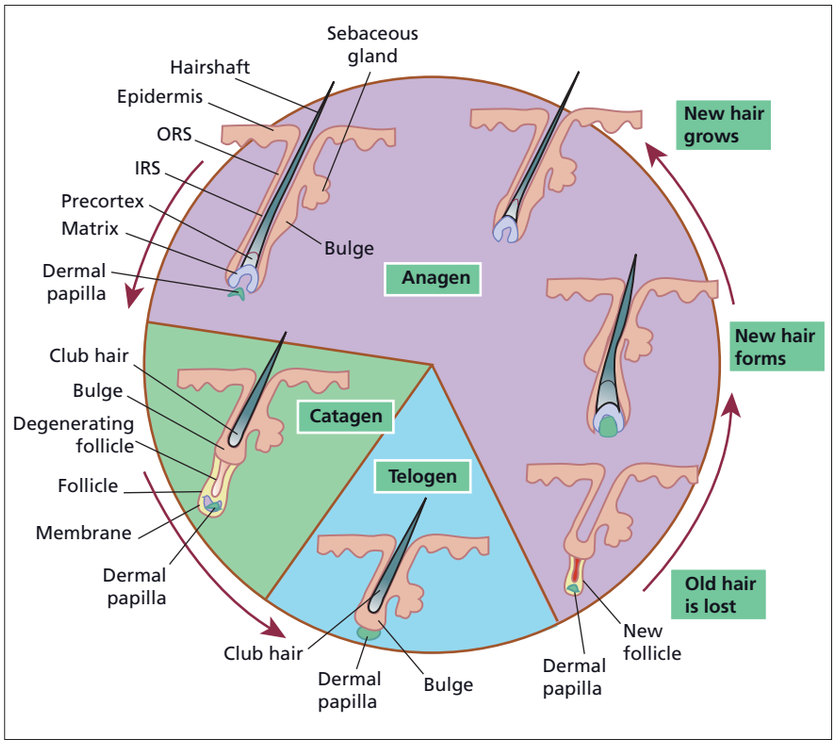


Fig. 3.15 The hair cycle. There are three components to the hair cycle: anagen (where new hair forms and grows), followed by catagen (regressing phase) and telogen (resting phase), and then loss of old hair. The hair cycle is associated with discrete changes in hair follicle anatomy, both in the shape of the follicle and in the subjacent dermal papilla. IRS, inner root sheath; ORS, outer root sheath.

residues of epidermal keratins. The proteins differ from epithelial keratins in their positions on two-dimensional gels but they can be grouped into acidic and basic families; there are four major proteins in each of these families and several minor proteins, Ha 1–4 and Hb 1–4. Recent cloning of the hair keratin genes, which cluster on chromosomes 12 and 17, has shown a greater number of hair keratin genes, *HaKRT1–6* (including 3.1 and 3.2) and *HbKRT1–6*. Mutations in hair keratin genes have been found to be causative for autosomal dominant forms of the human disease monilethrix. In addition, keratin 17 null mice also demonstrate varying degrees of alopecia, depending on the age and strain of the mice.

Over the last decade, several naturally occurring, human inherited disorders of hair have provided fascinating insight into hair development and growth. These include key signalling molecules such as ectodysplasin, as well as transcription factors, including hairless and the vitamin D receptor, structural hair keratins, desmosomal proteins, a G protein-coupled receptor, a serine protease and a copper transporter [4]. More common hair variants, such as curly hair, may be explained by dynamic changes during hair growth [5]. Curvature of curly hair is programmed from the very basal area of the follicle and the bending process is linked to a lack of axial symmetry in the lower part of the bulb, affecting the connective tissue sheath, ORS, IRS and the hair shaft cuticle.

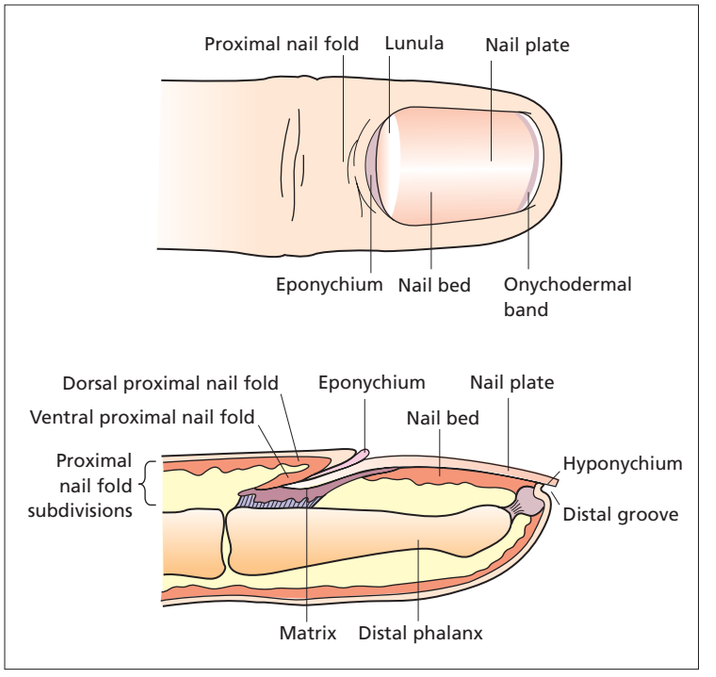


Fig. 3.16 Anatomy and structure of the human nail.

References

1 Schlake T. Determination of hair structure and shape. *Semin Cell Dev Biol* 2007; **18**: 267–73.
2 Fuchs E. Scratching the surface of skin development. *Nature* 2007; **445**: 834–42.
3 Schweizer J, Langbein L, Rogers MA, Winter H. Hair follicle-specific keratins and their diseases. *Exp Cell Res* 2007; **313**: 2010–20.
4 Bazzi H, Christiano AM. Broken hearts, woolly hair, and tattered skin: when desmosomal adhesion goes awry. *Curr Opin Cell Biol* 2007; **19**: 515–20.
5 Thibaut S, Barbarat P, Leroy F, Bernard BA. Human hair keratin network and curvature. *Int J Dermatol* 2007; **46** (Suppl. 1): 7–10.

Nails

The main purpose of the nail apparatus is to provide protection to the digit tips, enhance sensory discrimination, help increase dexterity, facilitate scratching or grooming, and, in some individuals, to function as a cosmetic accessory [1]. The earliest signs of finer nail development occur at 8–9 weeks' gestation: there is an invagination of the primitive epidermis to form an uninterrupted groove delineating a flattened surface at the end of each digit, known as the nail field. A key transcription factor in nail initiation is R-spondin 4, mutations in which underlie congenital anonychia [2]. A group of cells from the proximal part of the nail fold then grows proximally into the digit, stopping approximately 1 mm from the phalanx and giving rise to the matrix primordium. This site will eventually contribute to the epithelium of the proximal nail fold as well as the distal and intermediate matrix epithelium. From the distal part of the nail fold, a visible mound of cells emerges on the dorsum of the distal tip of each digit, which is known as the distal ridge [3]. At 13 weeks' gestation, the proximal nail fold is formed and the first signs of nail plate growth are observed from the lunula. At this stage, the stratum corneum and the stratum granulosum start to materialize from the nail field epithelium, beginning distally and advancing toward the proximal nail fold. At 18 weeks' gestation, the granular layer recedes, and the nail bed epithelium takes on a postnatal appearance. Likewise, at 20 weeks' gestation, the process of cellular differentiation and maturation within the matrix is similar to that seen in adult nails. By 32 weeks' gestation, virtually all the components of the nail can be recognized. Toe nail development is similar to that of finger nails but the stages occur about 4 weeks later.

The nail unit is comprised of the nail plate and four epithelial structures: the proximal nail fold, the matrix, the nail bed and the hyponychium [4] (Fig. 3.16). The nail plate is a rectangular, translucent and relatively inflexible structure, and contains calcium, phosphate, iron, zinc, manganese and copper, but it is mainly sulphur within the nail matrix that is responsible for the nail plate's physical qualities. The nail plate arises from beneath the proximal nail fold and is bordered on both sides by the lateral nail folds. The proximal aspect may contain white semicircular areas called lunulae, which are the visible portions of the distal matrix [5]. The dorsal surface of the nail unit appears pink in colour because of the enhanced vasculature of the underlying nail bed. The proximal nail fold has a dorsal and a ventral epithelial surface. It is a continuation of the skin of each digit (the dorsal surface) that folds underneath itself, resting above the nail matrix (the ventral surface). The dorsal proximal nail fold is devoid of hair follicles, sebaceous glands and dermatoglyphic markings and the ventral proximal nail fold also lacks rete ridges. At the junction between the dorsal and ventral surfaces is the eponychium (cuticle) which protects the matrix from damage. The lateral nail folds are extensions of the skin surface of the sides of the digits and join the nail bed medially.

The nail matrix forms the nail plate and is divided into three regions: the dorsal section of the matrix contributes to the most

superficial layers of the nail plate whereas the intermediate region of the matrix forms the deeper layers. The ventral subdivision is the most distal part of the nail matrix. The nail bed is the area underneath the nail plate (between the lunula and the hyponychium). It has a role in forming the deeper layers of the nail plate, as its thin epidermal layer represents the ventral portion of the nail matrix. The hyponychium is located underneath the free edge of the nail plate and denotes the transition of the nail bed to the normal epidermis of the fingers and toes. There is also part of the hyponychium, known as the onychodermal band, that reflects on to the ventral surface of the nail plate to protect the nail parenchyma from trauma.

The epithelium of the matrix is composed of at least two to three actively dividing, basal keratinocyte layers. These cuboidal cells have their vertical axes aligned in a diagonal manner, which allows the nail plate to develop in an upward and outward direction. As these cells differentiate and migrate they become flatter, losing their nuclei and becoming integrated into the developing nail plate as onychocytes, or nail plate cells. This process of cellular maturation is similar to stratum corneum formation within the epidermis but does not require keratohyalin. The matrix also contains melanocytes, which pigment surrounding keratinocytes and manifest as longitudinal bands across the nail plate; this may be a common racial variant in darker-skinned individuals. The nail bed is composed of a thin epidermal layer and a dermal layer, but there is no subcutaneous fat. As the epidermis is thin, the differentiation of keratinocytes to onychocytes occurs within one to two cell layers. The epidermis of the nail bed also contains parallel longitudinal ridges from the lunula to the hyponychium. These ridges interlock to provide strong binding between the nail bed and the nail plate. The dermal layer of the nail bed contains blood vessels to supply the nail unit, as well as lymphatics. Trauma to these vessels results in splinter haemorrhages.

References

1 Jiraravuthisan MM, Sasseville D, Vender RB *et al*. Psoriasis of the nail: anatomy, pathology, clinical presentation, and a review of the literature on therapy. *J Am Acad Dermatol* 2007; **57**: 1–27.

2 Blaydon DC, Ishii Y, O'Toole EA *et al*. The gene encoding R-spondin 4 (RSPO4), a secreted protein implicated in Wnt signaling, is mutated in inherited anonychia. *Nat Genet* 2006; **38**: 1245–7.

3 McCarthy DJ. Anatomic considerations of the human nail. *Clin Podiatr Med Surg* 1995; **12**: 163–81.

4 Achten G, Parent D. The normal and pathologic nail. *Int J Dermatol* 1983; **22**: 556–65.

5 Cohen PR. The lunula. *J Am Acad Dermatol* 1996; **34**: 943–53.

Merkel cells

Merkel first gave the name *tastzellen* to certain cells that he found near the base of the rete-peg in the snout skin of the mole. As there were intraepidermal neurites with expanded tips (Merkel discs) adjacent to them, he believed them to be transducers of physical stimuli. Merkel cells are post-mitotic cells scattered throughout the epidermis of vertebrates and constitute 0.2–5% of epidermal cells [1]. They are located amongst basal keratinocytes and are mainly found in hairy skin, tactile areas of glabrous skin, taste buds, the anal canal, labial epithelium and eccrine sweat glands (Fig. 3.17).

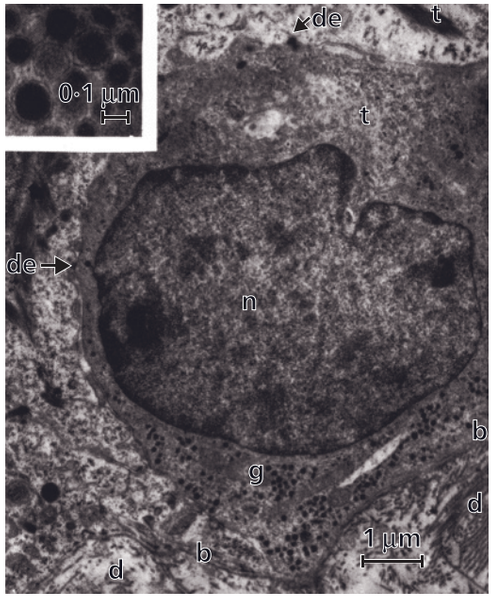


Fig. 3.17 Merkel cell in human epidermis. The dermis (d) with collagen fibres is seen in the lower part of the picture; b, basement membrane; de, desmosomes making connections with adjacent basal keratinocyte; g, spherical granules (see inset); n, nucleus of Merkel cell; t, tonofilaments. (Courtesy of Professor A.S. Breathnach, St John's Institute of Dermatology, King's College London,UK.)

Sun-exposed skin may contain twice as many Merkel cells as non-sun-exposed skin. They form close connections with sensory nerve endings and secrete or express a number of peptides. Human Merkel cells express immunoreactivity for various neuropeptides including *Met*-enkephalin and vasoactive intestinal polypeptide, in addition to neurone-specific enolase and synaptophysin-like and pancreastatin-like material. They also contain chromogranin A [2].

Merkel cells are easily identifiable on transmission electron microscopy. They are oval with a long axis of approximately 15 µm, orientated parallel to the basement membrane. They also have a large bilobed nucleus and clear cytoplasm, which reflects a relative scarcity of intracellular organelles. Merkel cells contain numerous neurosecretory granules, each 50–160 nm across; these are found opposing the junctions with the sensory nerve endings. The close contact between Merkel cells and nerve fibres represents a Merkel cell–neurite complex, but there is no clear evidence of synaptic transmission, although numerous vesicles can be identified in neurones apposed to Merkel cells [3].

Human skin contains an extensive neural network that consists of cholinergic and adrenergic nerves and myelinated and unmyelinated sensory fibres. The skin also contains several transducers involved in the perception of touch, pressure and vibration, including Ruffini organs surrounding hair follicles, Meissner's corpuscles, Vater–Pacini corpuscles located in the deep layer of the dermis, and nerve endings which pass through the epidermal basement membrane. Some of these contain Merkel cells, which form the Merkel cell–neurite complex, while others are free nerve endings. The cell bodies for all these neurones reside in the dorsal root ganglion. The Merkel cell–neurite complexes are thought to

serve as mechanoreceptors and to be responsible for the sensation of touch.

In glabrous skin, the density of Merkel cells is approximately 50 per mm^2. They are clustered near unmyelinated sensory nerve endings, where they group and form 'touch spots' at the bottom of rete ridges. These complexes are also known as hair discs, touch domes, touch corpuscles or Iggo discs. The complex is innervated by a single, slowly adapting type 1 nerve fibre. In hairy skin, Merkel cells also cluster in the rete ridges and in the outer root sheath of the hair follicle where the arrector pili muscles attach. The function of Merkel cells in hair follicles is unclear, although they may be involved in the induction of new anagen cycles.

There are two hypotheses for the origin of Merkel cells: one possibility is that they differentiate from epidermal keratinocyte-like cells and the other is that they arise from stem cells of neural crest origin that migrated during embryogenesis, in similar fashion to melanocytes [4]. A unifying view, however, could be that there is very early migration of the Merkel cells from the neural crest and population of the epidermis during the sixth or seventh embryonic week in humans and that these cells subsequently only undergo further differentiation once in the epidermis.

Circulating autoantibodies against Merkel cells have been described in pemphigus and graft-versus-host disease. Merkel cells are absent in vitiligo lesions, in keeping with an autoimmune destruction or neural involvement. Merkel cell hyperplasia is a common histological finding and may accompany keratinocyte hyperproliferation as well as being frequently seen in adnexal tumours such as naevus sebaceus, trichoblastomas, trichoepitheliomas and nodular hidradenomas [5]. Merkel cell hyperplasia is associated with hyperplasia of nerve endings that occurs in neurofibromas, neurilemmomas, nodular prurigo or neurodermatitis. It is not clear whether Merkel cell carcinoma originates from Merkel cell or their precursors but the latter may be more likely given that many dermal Merkel cell carcinomas do not connect with the epidermis.

References

1 Boulais N, Misery L. Merkel cells. *J Am Acad Dermatol* 2007; **57**: 147–65.
2 Moll I, Roessler M, Brandner JM *et al.* Human Merkel cells—aspects of cell biology, distribution and functions. *Eur J Cell Biol* 2005; **84**: 259–71.
3 Lucarz A, Brand G. Current considerations about Merkel cells. *Eur J Cell Biol* 2007; **86**: 243–51.
4 Szrder V, Grim M, Halata Z, Sieber-Blum M. Neural crest origin of mammalian Merkel cells. *Dev Biol* 2003; **253**: 258–63.
5 Sidhu GS, Chandra P, Cassai ND. Merkel cells, normal and neoplastic. *Ultrastruct Pathol* 2005; **29**: 287–94.

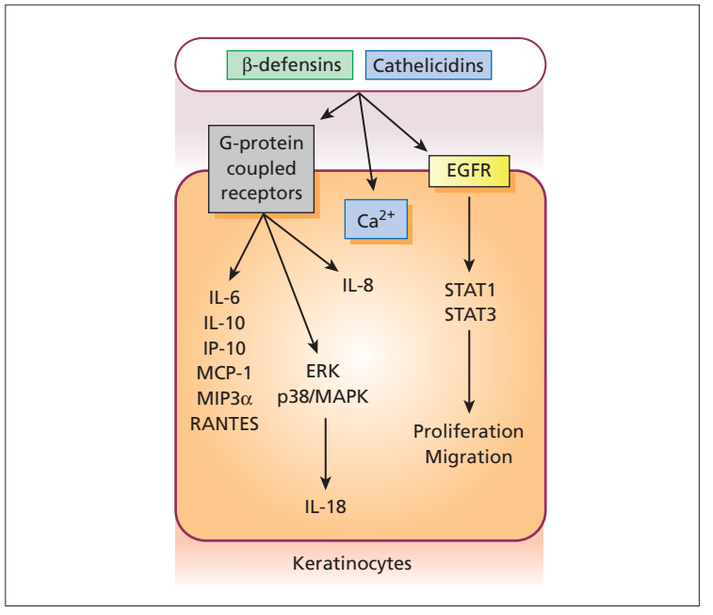


Fig. 3.18 As part of the innate immune defence system, antimicrobial peptides can stimulate G-protein coupled receptors to induce cytokine and chemokine release from keratinocytes as well as epidermal growth factor receptor (EGFR) signalling to influence cell proliferation and migration.

Skin as an immune system

Innate immunity

The skin continuously encounters microbial pathogens and to defend against this cells within the epidermis and dermis have evolved several innate strategies to prevent infection. One of the primary mechanisms used by the skin in the early stages of immune defence is the synthesis, expression and release of antimicrobial peptides [1]. There are more than 20 antimicrobial peptides in the skin, including cathelicidins, β-defensins, substance P, RANTES, RNase 2,3,7 and S100A7 (Fig. 3.18).

Many peptides have antimicrobial action against bacteria, viruses and fungi. The antimicrobial activity of most peptides occurs as a result of unique structural characteristics that enable them to disrupt the microbial membrane while leaving human cell membranes intact. Some may play a specific role against certain microbes in normal skin, whereas others act only when the skin is injured and the physical barrier disrupted [2]. Other peptides may play a larger role, signalling host responses through chemotactic, angiogenic, growth factor and immunosuppressive activity; these peptides are known as alarmins [3]. For example, some alarmins not only kill bacteria but also stimulate expression of syndecan-1 and -4 in dermal fibroblasts, which is critical to the process of wound healing. Alarmins may also stimulate elements of the host defence system, such as barrier repair and recruitment of inflammatory cells [4].

The production by human skin of antimicrobial peptides such as defensins and cathelicidins occurs constitutively but also greatly increases after infection, inflammation or injury. Some skin diseases, including atopic dermatitis or rosacea, show altered expression of antimicrobial peptides, partially explaining the pathophysiology of these diseases [5]. In atopic dermatitis there is decreased expression of multiple antimicrobial peptides, which contributes to an increased susceptibility to infections, and in rosacea there are excessive and abnormally processed cathelicidin peptides, which can reproduce elements of the disease in mice. Certain antimicrobial peptides can influence host-cell responses in specific ways. For example, the human cathelicidin peptide LL-37 can activate mitogen-activated protein kinase (MAPK) and

extracellular signal-related kinase in epithelial cells, and blocking antibodies to LL-37 hinder wound repair in human skin equivalents. Defensins and cathelicidins have immunostimulatory and immunomodulatory capacities as catalysts for secondary host defence mechanisms. At nanomolar concentrations they are chemotactic for distinct subpopulations of leukocytes as well as some non-leukocytes. Human β-defensins (hBDs) 1–3 are chemotactic for memory T cells and immature dendritic cells. hBD2 attracts mast cells and activated neutrophils, whereas hBD3–4 is also chemotactic for monocytes/macrophages. Cathelicidins are chemotactic for neutrophils, monocytes/macrophages and CD4 T lymphocytes. Epidermal keratinocytes stimulated with either β-defensins or cathelicidins release an array of cytokines through stimulation of G protein-coupled receptors. In addition, antimicrobial peptides induce keratinocyte proliferation and migration, which involves EGFR signalling and STAT activation.

References

1 Goodarzi H, Trowbridge J, Gallo RL. Innate immunity: a cutaneous perspective. *Clin Rev Allergy Immunol* 2007; **33**: 15–26.
2 Niyonsaba F, Nagoka I, Ogawa H. Human defensins and cathelicidins in the skin: beyond direct antimicrobial properties. *Crit Rev Immunol* 2006; **26**: 545–76.
3 Gallo RL. Sounding the alarm: multiple functions of host defense peptides. *J Invest Dermatol* 2008; **128**: 5–6.
4 Radek K, Gallo RL. Antimicrobial peptides: natural effectors of the innate immune system. *Semin Immunopathol* 2007; **29**: 27–43.
5 Wollenberg A, Klein E. Current aspects of innate and adaptive immunity in atopic dermatitis. *Clin Rev Allergy Immunol* 2007; **33**: 35–44.

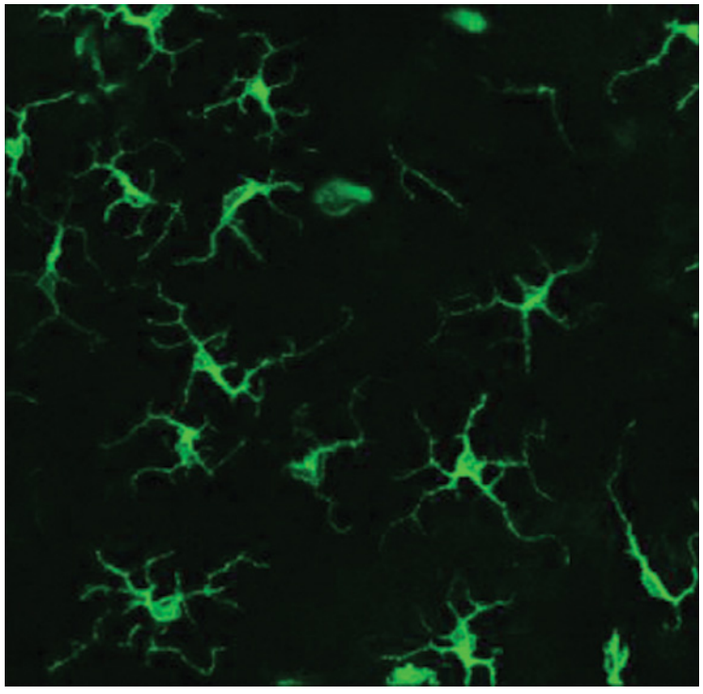


Fig. 3.19 Dendritic appearance of epidermal Langerhans' cells. Exposure to antigen provokes increased movement of Langerhans' cells as well as direct cell–cell contact between Langerhans' cells. (Courtesy of Dr R. Mohr, University of Toledo, Ohio, USA.)

Langerhans' cells

Dendritic cells of a form similar to melanocytes, but free from pigment and dopa negative, were first described by Langerhans, who demonstrated their existence in human epidermis by staining with gold chloride. More recently, the dynamic behaviour of epidermal Langerhans' cells has been investigated by combining time-lapse, intravital, confocal imaging technology and I-Aβ–enhanced green fluorescent protein (EGFP) knock-in mice in which Langerhans' cells can be identified by EGFP-associated fluorescence. Without stimulation, some Langerhans' cells exhibit a unique motion, which has been termed *dendrite surveillance extension and retraction cycling habitude* (dSEARCH), and which is characterized by rhythmic extension and retraction of dendritic processes between intercellular spaces. Topical application of an antigen such as dinitrofluorobenzene leads to greater dSEARCH motion and also triggers direct cell-to-cell contact formation between adjacent Langerhans' cells. It appears that, *in vivo*, dSEARCH motion allows for a more efficient antigen sampling through scanning of a wider area and it is also evident that, under pathological stimulation, adjacent Langerhans' cells may exchange antigens between cells [1] (Fig. 3.19).

Langerhans' cells, in combination with macrophages and dermal dendrocytes, represent the skin's mononuclear phagocyte system [2]. Langerhans' cells are capable of phagocytosis, antigen processing, antigen presentation and interactions with lymphocytes (Fig. 3.20).

They can also release cytokines, such as interleukin-1, to promote lymphocyte chemotaxis and activation [3]. Langerhans' cells are intraepidermal macrophages whose dendrites trap antigens among keratinocytes. The cells then leave the epidermis and migrate via lymphatics to a regional lymph node. In the paracortical region of lymph nodes, the Langerhans' cell (or 'interdigitating reticulum cell' as it is then known) expresses protein on its surface to present to a T lymphocyte that can then undergo clonal proliferation. There may be some selectivity in whether certain antigens are presented to lymph nodes by Langerhans' cells or by dermal dendrocytes. The timing of antigen presentation may also vary, with the possibility that sequential presentation of skin-acquired antigens may regulate cell-mediated immunity.

Langerhans' cells may contribute to several skin pathologies including infections, inflammation and cancer and they play a pivotal role in regulating the balance between immunity and peripheral tolerance [4]. Langerhans' cells appear, however, to have characteristics distinct from other dendritic cells in that they are more likely to induce Th2 responses than the Th1 responses that are usually necessary for cellular immune responses against pathogens. It has also been shown that Langerhans' cells are dispensable for contact hypersensitivity and that dermal dendrocytes can serve as antigen presenting cells in the absence of Langerhans' cells. Indeed, Langerhans' cells-deficient mice appear to have enhanced contact hypersensitivity. With regard to a specific function, Langerhans' cells, or a subset thereof, may have regulatory properties that counteract the proinflammatory activity of surrounding keratinocytes. It is plausible that under non-inflammatory steady-state conditions, Langerhans' cells carry skin-specific components to draining lymph nodes to prevent immunization and to induce peripheral tolerance against

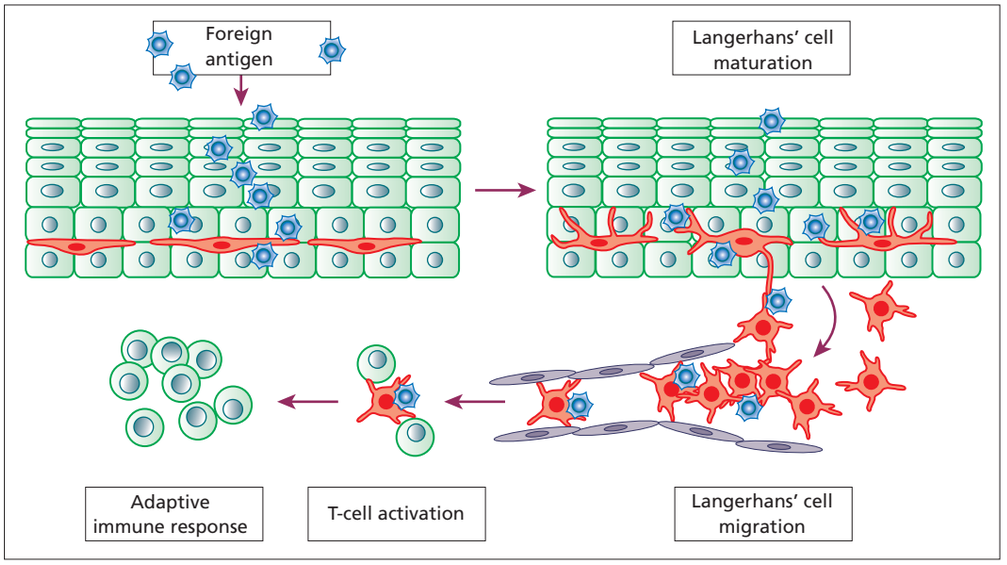


Fig. 3.20 When exposed to foreign antigen the activity of resting Langerhans' cells increases and the cells mature. Antigen is then processed and transported to the lymph nodes. T cells are then activated and an immune response is triggered.

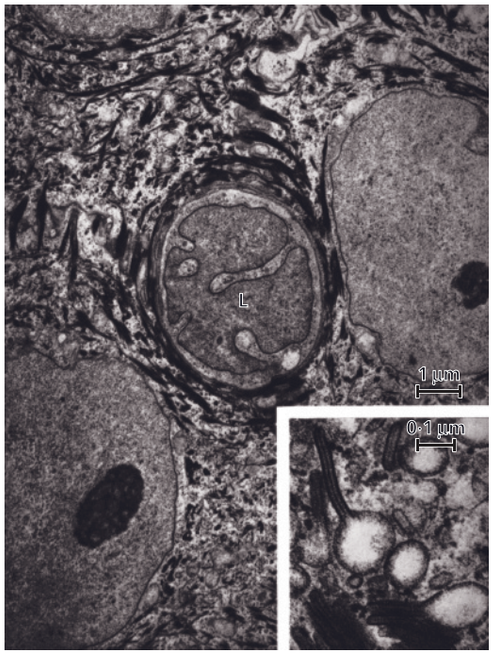


Fig. 3.21 Langerhans' cell (L) with its characteristically indented nucleus, situated between keratinocytes. Inset: Langerhans' cell granules showing racquet-shaped profiles. (Courtesy of Professor A.S. Breathnach, St John's Institute of Dermatology, King's College London, UK.)

epidermal self-determinants [5]. It also appears that Langerhans' cells may indeed consist of distinct subsets, since Langerhans' cells that repopulate the skin after inflammation have been shown to derive from monocyte precursors. Under the electron microscope, Langerhans' cells share with melanocytes a lobulated nucleus, a relatively clear cytoplasm and well-developed endoplasmic reticulum, Golgi complex and lysosomes (Fig. 3.21).

They differ in lacking melanosomes or premelanosomes, and in possessing a characteristic granule which is rod- or racquet-shaped. These 'Birbeck' granules have been shown to represent subdomains of the endosomal recycling compartment and form at sites where the protein Langerin accumulates.

Using ultrastructural evidence of the presence of the characteristic granules, Langerhans' cells have been identified in the outer root sheath of the human hair and the secretory duct of the sebaceous gland and in the epithelium of the crypts of the human tonsil. The discovery of similar granules in cells in the dermis in histiocytosis X resulted in the renaming of this condition as Langerhans' cell histiocytosis.

References

1 Mohr RE, Takashima A. Epidermal Langerhans' cell movement *in situ*: a model for understanding immunologic function in the skin. *Arch Dermatol* 2007; **143**: 1438.
2 Leon B, Lopez-Bravo M, Ardavin C. Monocyte-derived dendritic cells. *Semin Immunol* 2005; **17**: 313–8.
3 Bennett CL, Noordegraaf M, Martina CA, Clausen BE. Langerhans' cells are required for efficient presentation of topically applied hapten to cells. *J Immunol* 2007; **179**: 6830–5.
4 Mathers AR, Larregina AT. Professional antigen presenting cells of the skin. *Immunol Res* 2006; **36**: 127–36.
5 Asahina A, Tamaki K. Role of Langerhans' cells in cutaneous protective immunity: is the reappraisal necessary? *J Dermatol Sci* 2006; **44**: 1–9.

Immune surveillance

Besides the antigen detection and processing role of epidermal Langerhans' cells, cutaneous immune surveillance is also carried out in the dermis by an array of tissue-resident T cells, macrophages, and dendritic cells [1] (Fig. 3.22).

These immune sentinel and effector cells are able to provide rapid and efficient immunological backup to restore tissue homeostasis should the epidermis be breached. The dermis contains a very large number of resident T cells; remarkably, there are approximately 2×10^{10} skin-resident T cells, which is twice the total number of T cells in the circulating blood [2]. There are

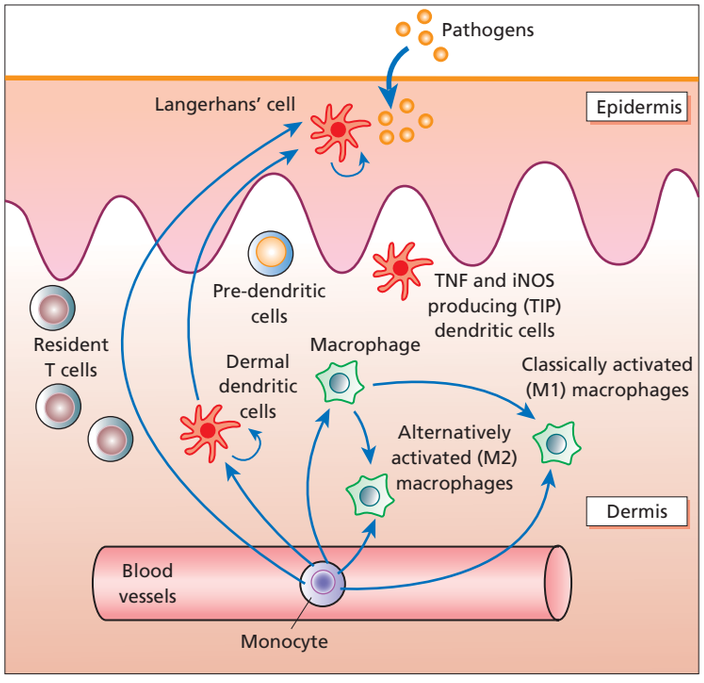


Fig. 3.22 Immune surveillance in normal skin is carried out by an array of skin-based dendritic cells, macrophages and resident T cells.

several distinct populations of dermal dendritic cells; some have potent antigen-presenting capacities, others have low antigen-presenting capacity but the potential to develop into $CD1a^+$ and Langerin-positive Langerhans' cells, while some are proinflammatory. Another recent addition to the family of skin immune sentinels is type I interferon-producing plasmacytoid predendritic cells, which are rare in normal skin but which can accumulate in inflamed skin [3]. A further component of the dermal immune system is the dermal macrophage. This cellular diversity of dermal immune sentinels is reflected in some flexibility or plasticity in function. For example, immature dendritic cells, including dermal dendritic cells, can be phagocytic, which is a cellular function usually attributed to macrophages [4]. Alternatively, macrophages, which normally are phagocytic cells, can also be potent antigen-presenting cells for $CD8^+$ T cells. This means that tissue-resident mononuclear sentinels of the dermis are likely to exist in a pluripotent state. Depending on microenvironmental factors and cues, they may acquire an antigen-presenting mode, a migratory mode or a tissue-resident phagocytic mode.

References

1 Nestle FO, Nickoloff BJ. Deepening our understanding of immune sentinels in the skin. *J Clin Invest* 2007; **117**: 2382–5.
2 Loser K, Beissert S. Dendritic cells and T cells in the regulation of cutaneous immunity. *Adv Dermatol* 2007; **23**: 307–33.
3 Magyarics Z, Csillag A, Pazmandi K *et al*. Identification of plasmacytoid predendritic cells by one-color flow cytometry for phenotype screening. *Cytometry A* 2008; **73**: 254–8.
4 Savina A, Amigorena S. Phagocytosis and antigen presentation in dendritic cells. *Immunol Rev* 2007; **219**: 143–56.

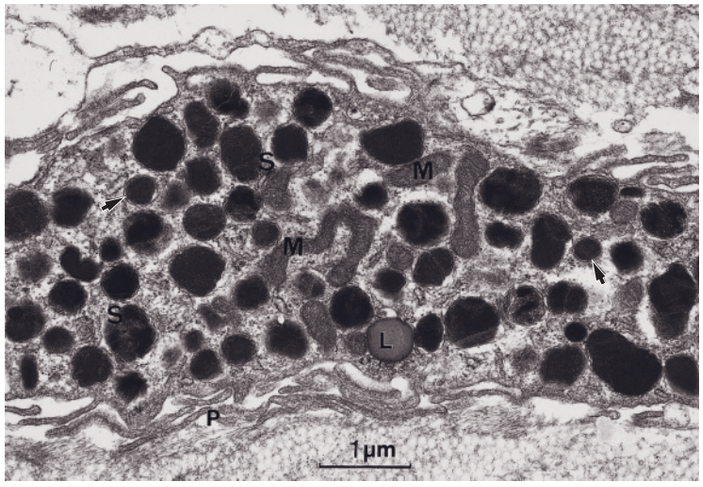


Fig. 3.23 Part of a human skin mast cell showing characteristic granules, some with scroll-like profiles (S). Arrows indicate perigranular membrane; L, lipid droplet; M, mitochondria; P, peripheral processes.

Mast cells

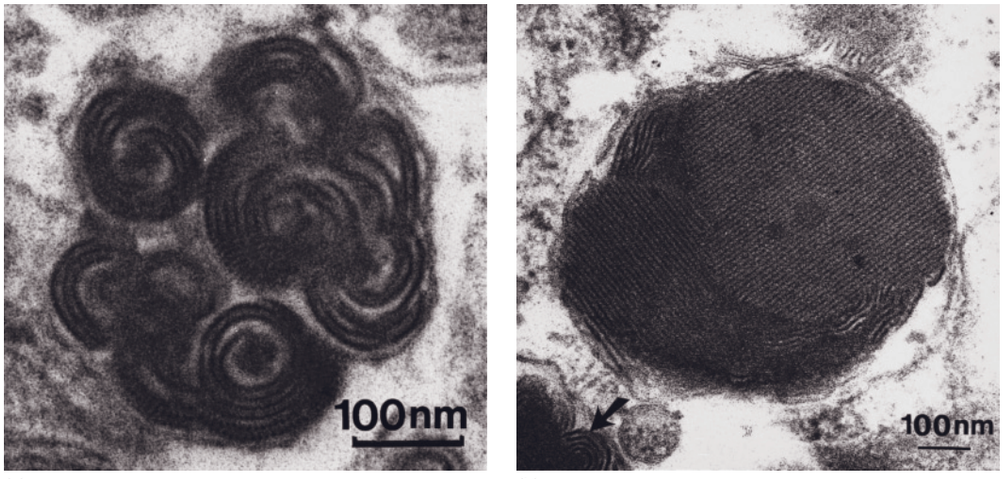
Mast cells were first described by Ehrlich in 1877, who distinguished them from other connective tissue cells by their ability to stain metachromatically with basic aniline dyes. Mast cells are larger than eosinophils and basophils. They occur in most tissues, but are particularly numerous in skin, bronchus, nasal mucosa and gut. In the skin, mast cells are distributed close to blood vessels, nerves and appendages, and are most numerous in the subpapillary dermis, in the region of the superficial dermal vascular plexus. There are about 7000 mast cells per mm^3 in normal skin.

Dermal mast cells are ovoid or spindle-shaped, mononuclear or occasionally binuclear, and only rarely show signs of mitosis in normal skin. Their major distinguishing feature is the presence of numerous, round cytoplasmic granules (Figs 3.23 and 3.24).

Mast cells are heterogeneous and fall into two main types—connective tissue and mucosal—which can be differentiated by their morphology, tissue distribution, histochemical characteristics and responses to degranulating agents. Solubility of the granules in formaldehyde and content of neutral proteinase, namely tryptase and chymase (chymotryptic proteinase) will vary according to the type of cell. For example, human foreskin mast cells contain both proteinases, whereas mast cells in intestinal mucosa and lung contain mainly tryptase [1].

Human mast cells arise from $CD34^+$ pluripotent stem cells in the bone marrow. They then circulate in the blood as precursors and home to tissues where they mature under the influence of stem cell factor (SCF) and local cytokines and other factors. Mast cell growth and differentiation are also influenced by several other cytokines, including IL-3, IL-4, IL-6, IL-9, IL-10 and nerve growth factor (NGF). Mast cells are long lived and may proliferate in association with IgE-dependent activation and in the presence of IL-4 [2].

Kit (CD117), expressed on haematopoietic stem cells and progenitor cells, is the tyrosine kinase transmembrane receptor for



(a) (b)

Fig. 3.24 High-magnification views of dermal mast cell granules. (a) Typical scroll-like configuration of lamellae, some of which show a cross-banding of regular periodicity. (b) The substructure of this granule is a highly organized lattice.

SCF which is involved in differentiation of both myeloid and lymphoid lineages. While Kit is down-regulated on other bone marrow-derived cells during their differentiation, Kit remains highly expressed on mast cells and is critical for many mast cell functions such as survival, differentiation, chemotaxis and enhancement of signalling events during mast cell activation. The importance of Kit is shown by the finding of activating mutations in the *KIT* gene in patients with urticaria pigmentosa [3].

Upon activation of mast cells via crosslinking of the high affinity IgE receptor (FcεRI) or non-IgE-mediated activation through complement receptors or toll-like receptor (TLR) activation, mast cells can release histamine, serotonin and proteases as well as newly synthesized leukotrienes, prostaglandins, cytokines and chemokines. In addition to IgE-mediated activation, human mast cells exposed to IFN-γ can be activated following IgG-mediated aggregation of FcγRI to release similar mediators. Additional IgE-independent mast cell triggers have been described, including SCF, complement (C3a and C5a), neuropeptides (substance P), adenosine, TLR and scavenger receptors.

Mast cell products may both induce an immediate reaction and contribute to a late-phase reaction. The immediate phase reaction occurs within minutes of FcεRI crosslinking and its consequences are referred to as an immediate hypersensitivity reaction. Late-phase reactions peak 6–12 h following antigen challenge and are associated with cytokine and chemokines from eosinophils, neutrophils and basophils that have been secondarily recruited. Mast cell activation results in increased vascular permeability and smooth muscle contraction, as well as fibroblast deposition of collagen, induction of B cells to class switch to synthesize IgE, basophil histamine release, recruitment of neutrophils and eosinophils, and promotion of T cells to a T helper 2 (Th2) phenotype.

Mast cells play an important role in both adaptive and innate immunity, and contribute to the skin pathology seen in contact dermatitis, atopic dermatitis (AD), immunobullous disease, scleroderma and chronic graft-versus-host disease [4]. In AD, there is an increase in mast cell numbers in lesional skin. Mast cells reside in the papillary dermis and undergo migration through the basal lamina into the epidermis. Although overall levels of histamine are not increased in AD, tryptase and activation of proteinase-activated receptor-2 (PAR-2) may contribute to the pruritus seen in AD, as tryptase is reported to be increased up to fourfold in AD patients and PAR-2 expression is markedly enhanced on primary afferent nerve fibres in skin biopsies from patients with AD. Chymase may play a role in eliciting and maintaining chronic inflammation in AD by increasing spongiosis and compromising the skin barrier. Mast cell–nerve interactions may also play a role in promoting inflammation in AD [5]. There is an increased number of contacts between mast cells and nerves in both lesional and non-lesional skin which may lead to inflammation mediated by neuropeptides such as substance P, calcitonin gene-related peptide, vasoactive intestinal peptide and NGF.

References

1 Hide M, Yanase Y, Greaves MW. Cutaneous mast cell receptors. *Dermatol Clin* 2007; **25**: 563–75.
2 Galli SJ, Tsai M. Mast cells: versatile regulators of inflammation, tissue remodeling, host defense and homeostasis. *J Dermatol Sci* 2008; **49**: 7–19.
3 Hungness SI, Akin C. *Curr Allergy Asthma Rep* 2007; **7**: 248–54.
4 Navi D, Saegusa J, Liu FT. Mast cells and immunological diseases. *Clin Rev Allerg Immunol* 2007; **33**: 144–55.
5 Theoharides TC, Kalogeromitros D. The critical role of mast cells in allergy and inflammation. *Ann N Y Acad Sci* 2006; **1088**: 78–99.

Melanocytes

Melanocytes are pigment-producing cells located in the skin, inner ear, choroid and iris of the eye. In skin and hair, two forms of melanin pigment are produced; brown/black eumelanin and yellow/red phaeomelanin (Fig. 3.25).

The melanin is subsequently transferred in melanosomes to neighbouring keratinocytes in the epidermis and into the growing shaft in hair follicles. Variations in the types of melanin pigment produced and their distribution within skin and hair contribute to the vast diversity in colour. A key protein involved in melanosome assembly is NCKX5, encoded by the gene *SLC24A5* [1]. Loss of expression of this gene in mice results in marked changes in

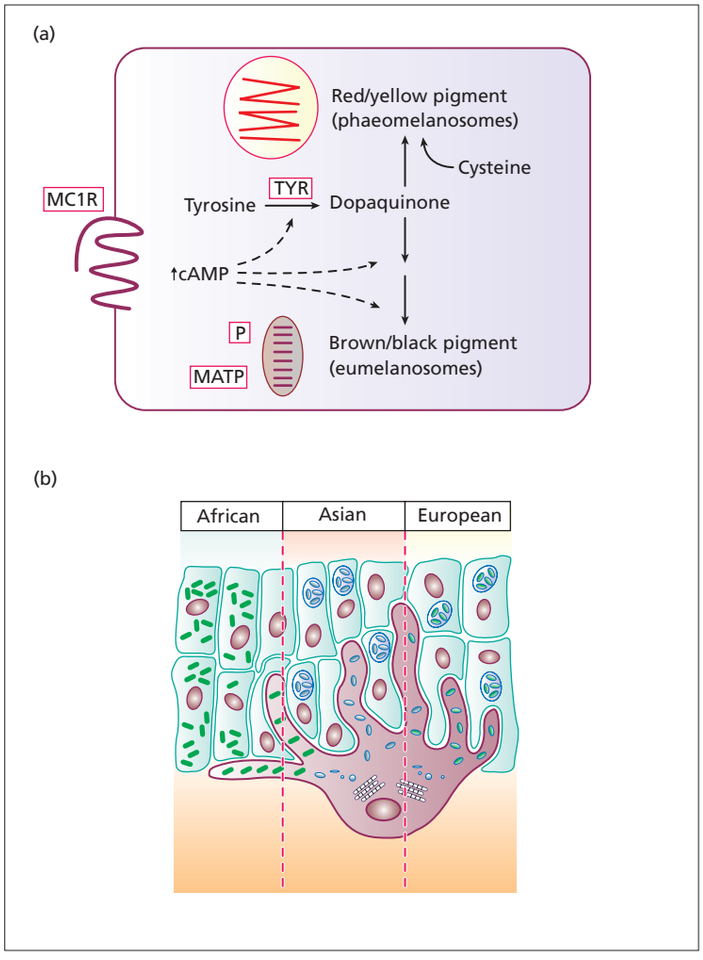


Fig. 3.25 (a) Activation of the melanocortin 1 receptor (MC1R) promotes the synthesis of eumelanin at the expense of phaeomelanin. Oxidation of tyrosine by tyrosinase (TYR), however, is required for synthesis of both pigment types. Melanosomal membrane components, including the membrane-associated transport protein (MATP) and the pink-eyed dilution protein (P), play a role in determining the amount of pigment synthesis within melanosomes. (b) In African, Asian and European skin there is a gradient of melanosome size and number; in addition, melanosomes in African skin are more widely dispersed.

skin colour with loss of pigment. Melanin production also provides skin protection by reducing damage from harmful ultraviolet radiation. In humans, alterations in melanocyte development and function can lead to various pigmentary disorders. These include disorders with reduced melanocytes in skin, such as Piebaldism and Waardenburg syndrome, and disorders with defective pigment production or processing, such as albinism, Hermansky–Pudlak and Chediak–Higashi syndromes.

The melanin-producing melanocytes in adult skin and hair develop from embryonically derived melanocyte precursors called melanoblasts. During development, melanoblasts emerge from a subset of neural crest cells and migrate to the skin and developing hair follicles. In the hair follicle, melanocytes are divided into two distinct populations: differentiated melanocytes, located in the hair matrix region, and melanocyte stem cells, located at the lower permanent portion of the hair follicle. The life cycles of the follicular melanocytes and melanocyte stem cells are closely related to the cyclical nature of the hair follicle and during anagen new melanocytes are generated from the pool of slow-proliferating melanocyte stem cells [2]. Differentiated melanocytes express *Sox10, Kit, Mitf, Pax3* and *Dct* but melanocyte stem cells only express *Pax3* and *Dct* [3]. Whether a subpopulation of melanocyte stem cells exists that may be relevant to the pathogenesis of melanoma is not yet known, although some of the melanocyte stem cells do express markers such as CD166, CD133 or Nestin which are found in stem cells from other lineages and may be multipotent in culture, capable of differentiating into various cell types (e.g. adipocytes, chondrocytes).

Alterations in melanocyte signalling pathways also contribute to common hair abnormalities such as hair greying. One particular pathway involves Notch signalling [4]. The Notch signalling pathway is an essential cell–cell interaction mechanism, which regulates processes such as cell proliferation, cell fate decisions, differentiation or stem cell maintenance. Notch signalling in melanocytes is essential for the maintenance of proper hair pigmentation, including regeneration of the melanocyte population during hair follicle cycling. Deletion of Notch1 and Notch2 or RBP-Jkappa in melanocyte lineages results in a gene dosage-dependent, precocious hair greying, due to the elimination of melanoblasts and melanocyte stem cells. Aberrant Notch signalling may also be relevant in the development or progression of melanoma.

Melanocytes possess melanocyte-specific receptors including melanocortin-1 (MC1R) and melatonin receptors [5]. The activation or the inhibition of melanocyte-specific receptors can augment normal melanocyte function, skin colour and photoprotection. Moreover, receptor polymorphisms are known to underlie red hair phenotypes. Receptor targeting may also be relevant to the treatment of melanoma. Notably, melanocytes also possess G-protein-couple receptors, such as Frizzled5, and receptor tyrosine kinases, including c-Kit and hepatocyte growth factor (HGF) receptor. These receptors activate two crucial cell-signalling pathways, RAS/RAF/MEK/ERK and PI3K/AKT, integral to melanoma cell survival, and could serve as targets for future therapies of disseminated melanoma.

References

1 Ginger RS, Askew SE, Ogborne RM *et al.* SLC24A5 encodes a trans-Golgi network protein with potassium-dependent sodium-calcium exchange activity that regulates human epidermal melanogenesis. *J Biol Chem* 2008; **283**: 5486–95.
2 Buac K, Pavan WJ. Stem cells of the melanocyte lineage. *Cancer Biomark* 2007; **3**: 203–9.
3 Murisier F, Beermann F. Genetics of pigment cells: lessons from the tyrosinase gene family. *Histol Histopathol* 2006; **21**: 567–78.
4 Schouwey K, Beermann F. The Notch pathway: hair graying and pigment cell homeostasis. *Histol Histopathol* 2008; **23**: 609–19.
5 Carlson JA, Linette GP, Aplin A, Ng B, Slominski A. Melanocyte receptors: clinical implications and therapeutic relevance. *Dermatol Clin* 2007; **25**: 541–57.

Epidermal attachment complexes

Desmosomes

Desmosomes are the major adhesion complex in epidermis, anchoring keratin intermediate filaments to the cell membrane

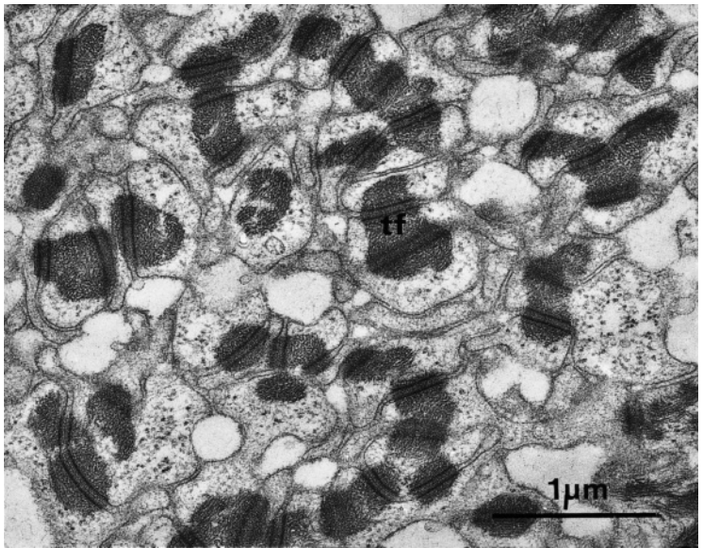


Fig. 3.26 Electron micrograph of desmosomes in the spinous layer. These intercellular junctions are closely associated with tonofilaments (tf), many of which, in this view, are cross-sectioned.

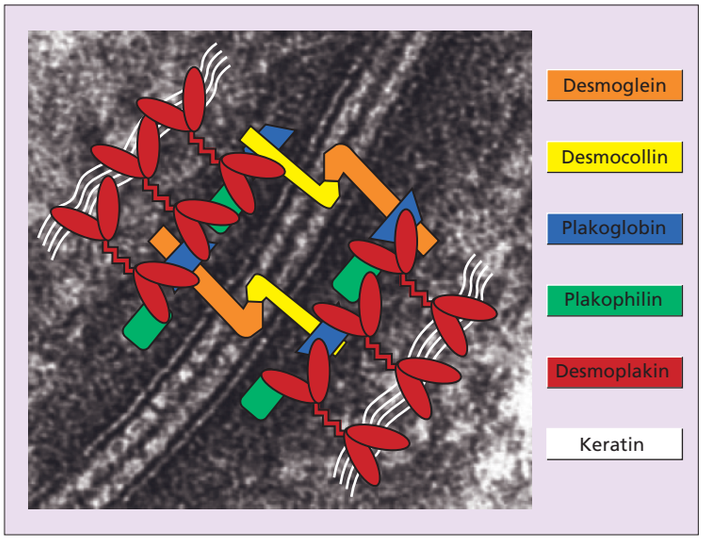


Fig. 3.27 Macromolecular composition of desmosomes linking adjacent keratinocytes. Cells are connected via transmembranous cadherin glycoproteins (desmogleins and desmocollins). Attachment of these molecules to the keratin filament cytoskeleton occurs via a network of desmosomal plaque proteins (desmoplakin, plakoglobin and plakophilin). The background to this figure is a transmission electron micrograph of a desmosome to highlight how the molecules function as an adhesive complex.

and bridging adjacent keratinocytes, and allowing cells to withstand trauma. Desmosomes are also found in the myocardium, meninges and cortex of lymph nodes. The desmosome has a characteristic ultrastructural appearance, in which the cell membrane of two adjacent cells forms a symmetrical junction with a central intercellular space of 30 nm containing a dense line (Fig. 3.26). Plaques of electron-dense material run along the cytoplasm parallel to the junctional region, in which three ultrastructural bands can be distinguished: an electron-dense band next to the plasma membrane, a less dense band and then a fibrillar area [1].

The main components of desmosomes in the epidermis consist of the products of three gene superfamilies: the desmosomal cadherins, the armadillo family of nuclear and junctional proteins and the plakins [2]. The transmembranous cadherins comprise mostly heterophilic associations of desmogleins and desmocollins. There are four main epidermis-specific desmogleins (Dsg1–4) and three desmocollins (Dsc1–3), all of which show differentiation-specific expression. For example, Dsg1 and Dsc1 are preferentially expressed in the superficial layers of the epidermis whereas Dsg3 and Dsc3 show greater expression in basal keratinocytes. The intracellular parts of these glycoproteins are attached to the keratin filament network via desmoplakin, plakoglobin and other macromolecules, including the armadillo protein, plakophilin 1, an important stabilizer of keratinocyte adhesion in differentiated keratinocytes, as well as other site-specific plakin cell envelope proteins, such as envoplakin and periplakin [3]. The network of the major interactive desmosomal proteins is depicted in Fig. 3.27.

Further clues to the biological function and *in vivo* contribution to keratinocyte adhesion of these desmosomal components have arisen from various mouse models and human diseases, both inherited and acquired [4,5]. Naturally occurring human mutations have been reported in nine different desmosome genes; these result in a spectrum of dominant and recessive diseases with variable skin, hair and heart abnormalities. A summary of recent gene mutation findings is represented in Fig. 3.28.

The desmosome proteins may also serve as autoantigens in several immunobullous blistering skin diseases [6]. The specific diseases linked to particular desmosomal target antigens are shown in Fig. 3.29.

Antibodies to multiple desmosomal proteins may develop in diseases such as paraneoplastic pemphigus, possibly through the phenomenon of epitope spreading [7]. Disruption of the extracellular domain of Dsg1 has also been demonstrated as the basis of staphylococcal scalded skin syndrome and bullous impetigo in which this desmosomal cadherin is cleaved by the bacterial toxin [8].

References

1 Holthofer B, Windoffer R, Troyanovsky S, Leube RE. Structure and function of desmosomes. *Int Rev Cytol* 2007; **264**: 65–163.
2 Green KJ, Simpson CL. Desmosomes: new perspectives on a classic. *J Invest Dermatol* 2007; **127**: 2499–515.
3 North AJ, Bardsley WG, Hyam J *et al*. Molecular map of the desmosomal plaque. *J Cell Sci* 1999; **112**: 4325–36.
4 Lai-Cheong J, Arita K, McGrath JA. Genetic diseases of junctions. *J Invest Dermatol* 2007; **127**: 2713–25.
5 Bazzi H, Christiano AM. Broken hearts, woolly hair, and tattered skin: when desmosomal adhesion goes awry. *Curr Opin Cell Biol* 2007; **19**: 515–20.
6 Fassihi H, Wong T, Wessagowit V, McGrath JA, Mellerio JM. Target proteins in inherited and acquired blistering skin diseases. *Clin Exp Dermatol* 2006; **31**: 252–9.
7 Chan LS. Epitope spreading in paraneoplastic pemphigus: autoimmune induction in antibody-mediated blistering diseases. *Arch Dermatol* 2000; **136**: 663–4.
8 Stanley JR, Amagai M. Pemphigus, bullous impetigo and the staphylococcal scalded-skin syndrome. *N Eng J Med* 2006; **355**: 1800–10.

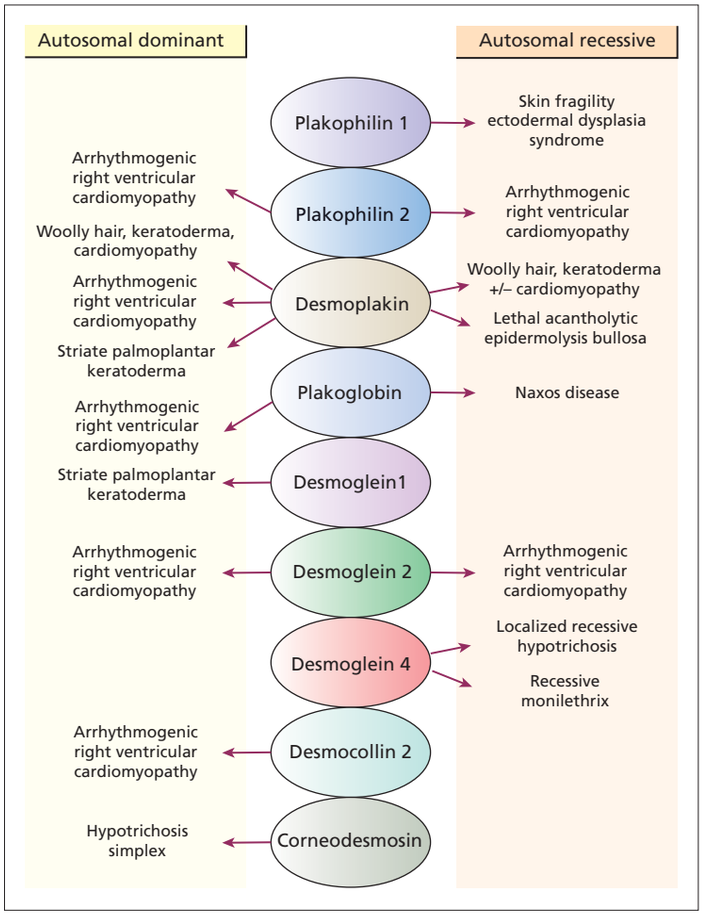


Fig. 3.28 Autosomal dominant and autosomal recessive mutations in human desmosome genes result in skin, hair and cardiac abnormalities.

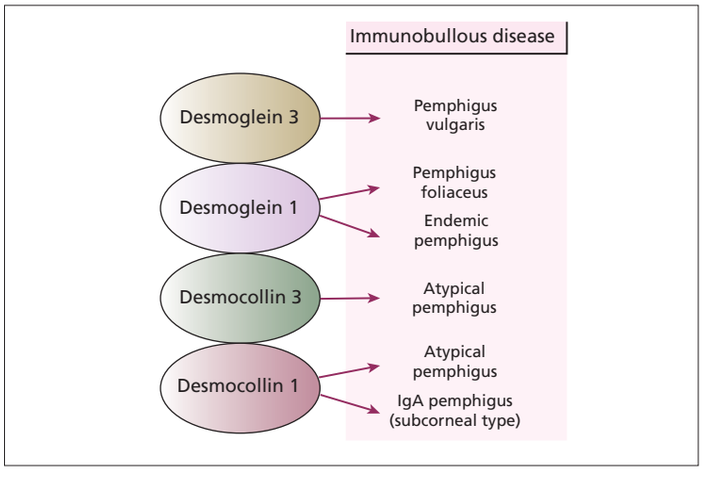


Fig. 3.29 Desmosomal components as targets for immunobullous diseases. Antibodies to these proteins may directly lead to blistering skin and mucous membrane disorders.

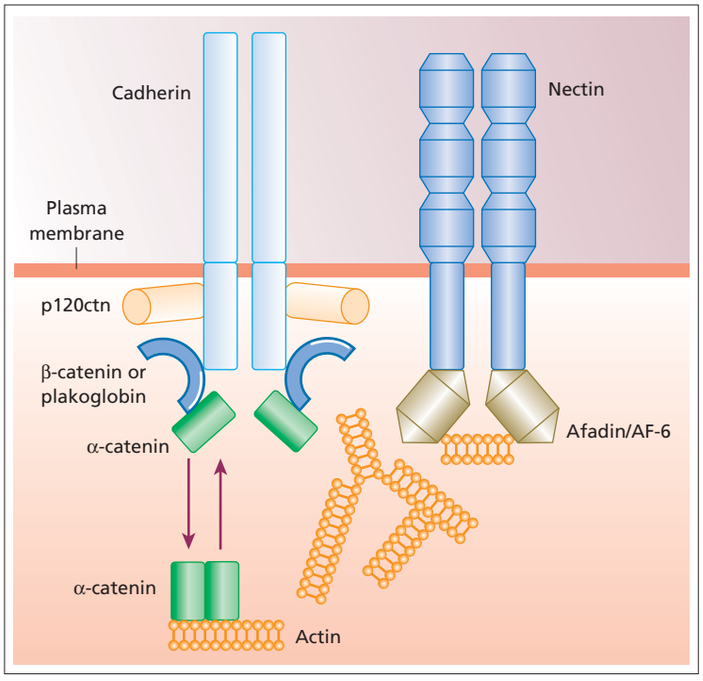


Fig. 3.30 Macromolecular composition of an adherens junction in keratinocytes. There are two main components, nectin–afadin and the classical cadherin–catenin complex, which can both attach to the actin cytoskeleton.

Adherens junctions

Adherens junctions are electron dense, transmembrane structures that engage with the actin skeleton [1]. They can associate with tight junctions and desmosomes or exist separately from these junction complexes. Adherens junctions contribute to epithelial assembly, adhesion, barrier formation, cell motility and changes in cell shape. They are characterized by two opposing membranes separated by approximately 20 nm and are 0.2–0.5 μm in diameter. Adherens junctions may also spatially coordinate signalling molecules and polarity cues as well as serving as docking sites for vesicle release. They comprise two basic adhesive units: the nectin–afadin complex and the classical cadherin complex [2,3] (Fig. 3.30).

There are several different nectins and cadherins and these may be variably incorporated into adherens junctions; the precise composition will impact on the adhesive specificity and other functions of the junction. The nectins form a structural link to the actin cytoskeleton via afadin (also known as AF-6) and may be important in the initial formation of adherens junctions. The cadherins form a complex with the catenins (α-, β-, and p120 catenin) and help mediate adhesion and signalling. Cell signalling via β-catenin can activate several Wnt pathways, which implicates adherens junctions in co-ordinating morphogenetic movements with cell fate determination. Adherens junctions are also associated with a variety of actin-binding molecules, suggesting multiple dynamic interactions with the cytoskeleton.

The first human gene mutation reported in a component of adherens junctions was in plakoglobin (also a component of desmosomes, see Fig. 3.10) in individuals with Naxos disease [4].

However, mutations have subsequently been reported in the *CDH3* gene, which encodes P-cadherin; these mutations result in autosomal recessive hypotrichosis with juvenile macular dystrophy [5]. P-cadherin mutations are also found in a different disorder, ectodermal dysplasia–ectrodactyly–macular dystrophy (EEM) syndrome, in which there is hypotrichosis, macular degeneration, hypodontia and limb defects, including ectrodactyly, syndactyly and camptodactyly [6].

References

1 Niessen CM. Tight/adherens junctions: basic structure and function. *J Invest Dermatol* 2007; **127**: 2525–32.
2 Irie K, Shimizu K, Sasikawa T, Ikeda W, Takai Y. Roles and modes of action of nectins in cell–cell adhesion. *Semin Cell Dev Biol* 2004; **15**: 643–56.
3 Niessen CM, Gumbiner BM. Cadherin-mediated cell sorting not determined by binding or adhesion specificity. *J Cell Biol* 2002; **156**: 389–99.
4 Lai-Cheong J, Arita K, McGrath JA. Genetic diseases of junctions. *J Invest Dermatol* 2007; **127**: 2713–25.
5 Sprecher E, Bergman R, Richard G *et al*. Hypotrichosis with juvenile macular dystrophy is caused by a mutation in *CDH3*, encoding P-cadherin. *Nat Genet* 2001; **29**: 134–6.
6 Kjaer KW, Hansen L, Schwabe GC *et al*. Distinct CDH3 mutations cause ectodermal dysplasia, ectrodacytly, macular dystrophy (EEM) syndrome. *J Med Genet* 2005; **42**: 292–8.

Gap junctions

Gap junctions comprise clusters of intercellular channels, known as connexons, that directly form connections between the cytoplasm of adjacent keratinocytes (and other cells) [1]. Thirteen different human connexins have been described. Connexons originate following assembly of six connexin subunits within the Golgi network that are then transported to the plasma membrane. The connexins are divided into three groups (α, β and γ) according to their gene structure, overall gene homology and specific sequence motifs [2]. At the plasma membrane, connexons associate with other connexons to form a gap junction (Fig. 3.31).

Homotypic or heterotypic connexins (formed from one or more than one type of connexin, respectively) are possible and the formation and stability of gap junctions can be regulated by protein kinase C, Src kinase, calcium concentration, calmodulin, adenosine 3′,5′-cyclic monophosphate (cAMP) and local pH [3]. Apart from the connexins, vertebrates also contain another class of gap junction proteins, the pannexins, which are related to the innexins found in non-chordate animals. To date, however, no human abnormalities of pannexins have been reported. The function of gap junctions is to permit sharing of low-molecular-mass metabolites (<1000 Da) and ion exchange between neighbouring cells, thus allowing intercellular coordination and uniformity to maintain tissue/organ homeostasis in multicellular organisms [3]. Gap junction communication is essential for cell synchronization, differentiation, cell growth and metabolic coordination of avascular organs, including epidermis.

Inherited abnormalities in genes encoding four different connexins (Cx26, 30, 30.3 and 31) have been detected in several forms of keratoderma and/or hearing loss but non-dermatological disorders can also arise from mutations in the higher molecular weight connexins (Cx32, 40, 43, 46 and 50). The spectrum of diseases associated with connexin gene pathology is illustrated in Fig. 3.32.

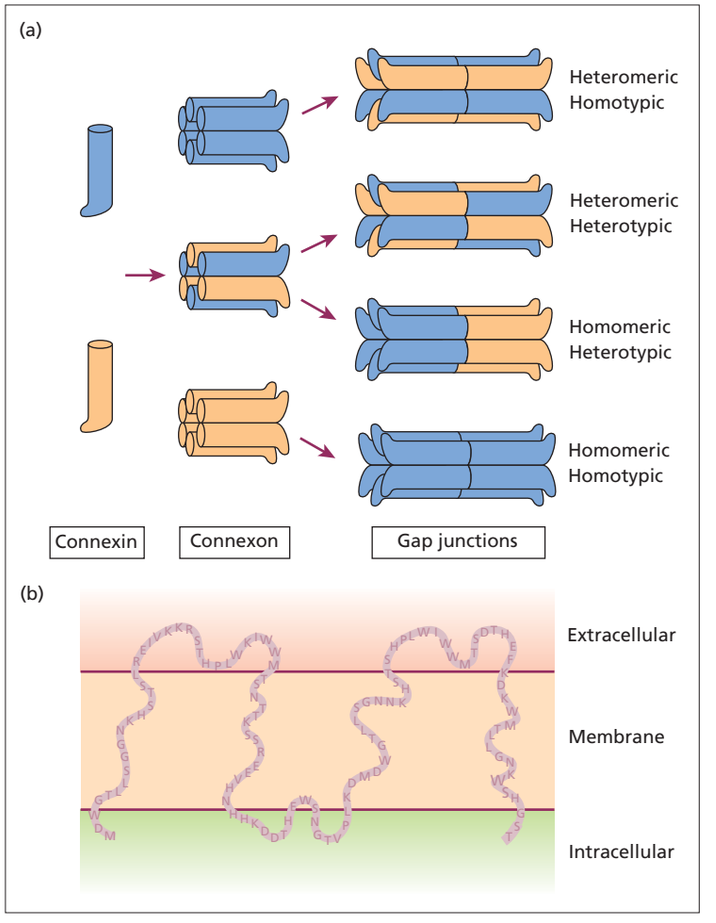


Fig. 3.31 Formation and structure of gap junctions in human skin. (a) In the Golgi network six connexin subunits assemble to form a connexon. The connexon is then transported to the plasma membrane. Other connexons then coaggregate to form homotypic or heterotypic gap junctions. (b) The gap junction protein is a transmembranous molecule with intracellular, transmembranous and extracellular domains (here illustrated for Cx26).

References

1 Mese G, Richard G, White TW. Gap junctions: basic structure and function. *J Invest Dermatol* 2007; **127**: 2516–24.
2 Richard G. Connexin disorders of the skin. *Clin Dermatol* 2005; **23**: 23–32.
3 Kelsell DP, Dunlop J, Hodgkins MB. Human diseases: clues to cracking the connexin code? *Trends Cell Biol* 2001; **11**: 2–6.

Tight junctions

Tight junctions are the major regulators of permeability in simple epithelia, but they are also present in skin, with a key role in skin barrier integrity and maintaining cell polarity [1]. Tight junctions regulate the paracellular flux of water-soluble molecules between adjacent cells [2]. The principal structural proteins of tight junctions are the claudins, of which there are approximately 24 subtypes. The other component transmembranous proteins are the IgG-like family of junctional adhesion molecules (JAMs) and the occludin group of proteins. The main claudins in the epidermis are claudin 1 and 4. These transmembranous proteins do not bind to one another but the claudins and occludins can bind to the intracellular zonula occudens proteins ZO-1, ZO-2, ZO-3; these proteins can also interact with actin thus providing a direct link

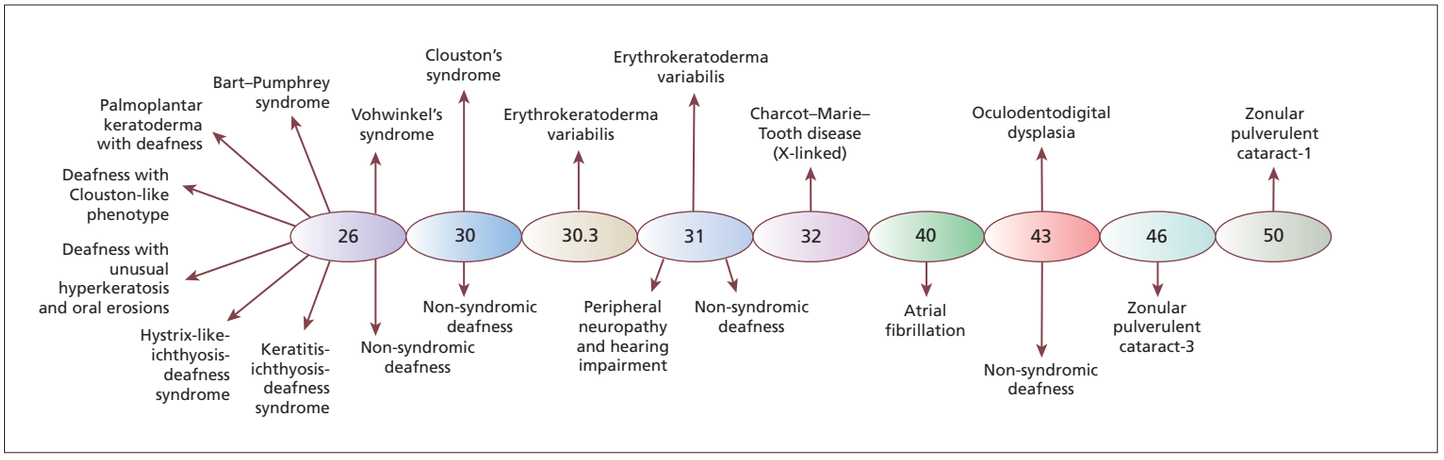


Fig. 3.32 Disease associations arising from gene mutations in the different molecular weight connexins.

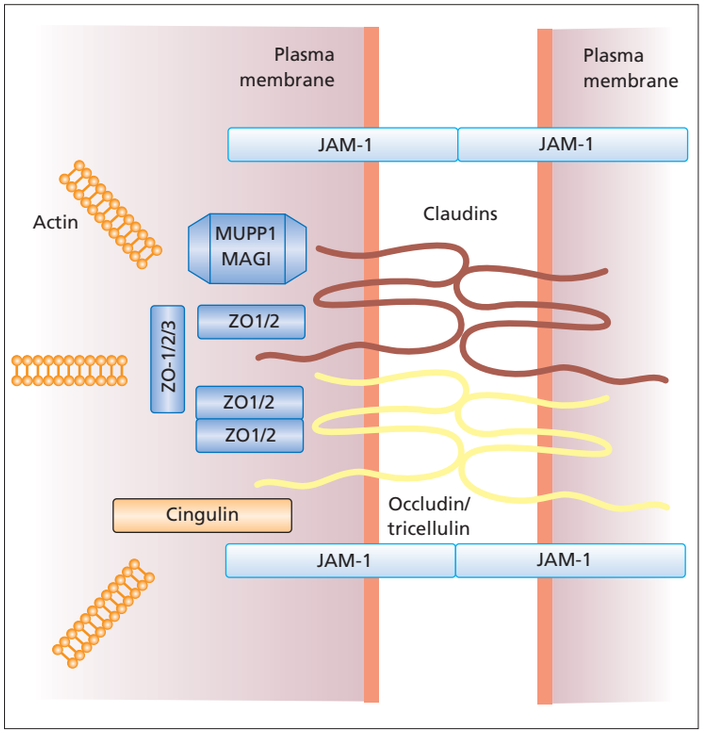


Fig. 3.33 Structural composition of a tight junction in human skin. There are three transmembranous families of proteins, the junctional adhesion molecules (JAMs), the claudins and the occludins, of which the latter two bind to zonula occludens proteins (ZO) and then directly to actin. MUPP1, multiple PDZ domain protein; MAGI, membrane-associated guanyl kinase inverted protein.

with the cytoskeleton [1,3]. The structural organization of a tight junction is shown in Fig. 3.33.

Mutations in claudin 16 (also known as paracellin-1) result in familial hypomagnesaemia with hypercalciuria and nephrocalcinosis; mutations in claudin 14 underlie the autosomal recessive deafness disorder DFNB29 leading to cochlear hair cell degeneration; mutations in the gene encoding the ZO-2 protein have been found in some cases of familial hypercholanaemia. With respect to skin, mutations in claudin 1 have been demonstrated in one autosomal recessive pedigree with clinical features of diffuse ichthyosis with large scales, hypotrichosis, scarring alopecia and sclerosing cholangitis [4]. Collectively, these human disorders demonstrate the key role tight junctions play in the skin, kidney, ear and liver.

References

1 Niessen CM. Tight/adherens junctions: basic structure and function. *J Invest Dermatol* 2007; **127**: 2525–32.
2 Morita K, Miyachi Y. Tight junctions in the skin. *J Dermatol Sci* 2003; **31**: 81–9.
3 Brander JM, Kief S, Wladykowski E, Houdek P, Moll I. Tight junction proteins in the skin. *Skin Pharmacol Physiol* 2006; **19**: 71–7.
4 Hadj-Rabia S, Baala L, Vabres P *et al*. Claudin-1 mutations in neonatal sclerosing cholangitis associated with ichthyosis: a tight junction disease. *Gastroenterology* 2004; **127**: 1386–90.

Dermal–epidermal basement membrane

The interface between the lower part of the epidermis and the top layer of the dermis comprises the dermal–epidermal basement membrane zone (BMZ), which consists of a number of extracellular matrix macromolecules [1,2] (Fig. 3.34 & Table 3.1).

Many of these components are glycoproteins, and the BMZ can be recognized histologically by positive labelling with PAS stain. Ultrastructural examination of the BMZ by transmission electron microscopy shows the presence of two distinct layers with different optical densities (Fig. 3.35).

The upper layer, the lamina lucida, is a less electron dense region which directly abuts the plasma membranes of the basal keratinocytes. Below the lamina lucida is the lamina densa, an electron-dense region which at the lower part interacts with the mesenchymal matrix of the upper dermis. The major biochemical components of the BMZ are type IV collagen and a number of collagenous glycoproteins, including laminin 322 [3]. Associated with the cutaneous BMZ are ultrastructurally recognizable attachment structures which form a contiguous network extending from the intracellular milieu of basal keratinocytes through the plasma membrane of the basal cells, traversing the dermal–epidermal basement membrane and extending to the upper papillary dermis (Fig. 3.34). The components of this network are the hemidesmo-

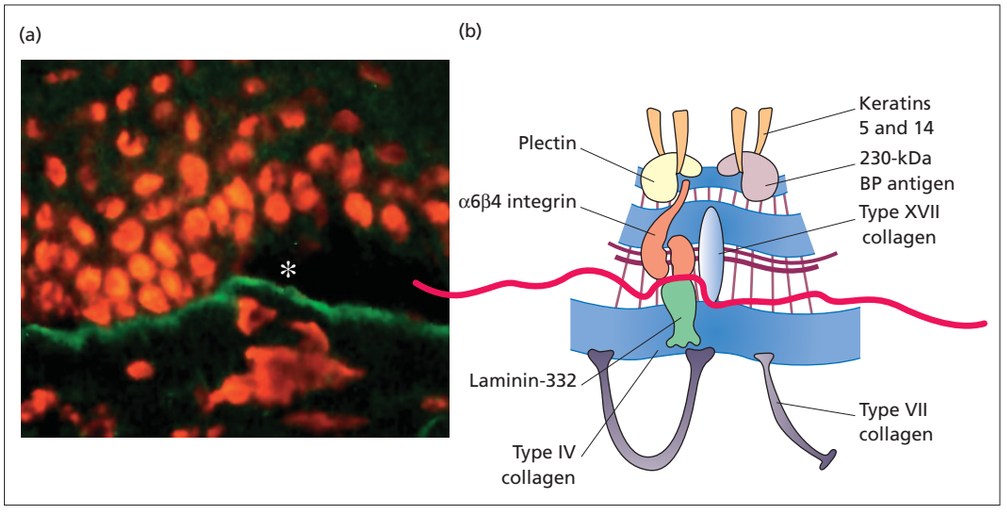


Fig. 3.34 NaCl-induced separation between the epidermis and dermis and antigen mapping within the cutaneous basement membrane. (a) The dermal–epidermal basement membrane visualized by immunofluorescence staining with antibodies to type VII collagen. This maps to the base of the split because cleavage occurs through the lamina lucida and type VII collagen is located below the lamina densa. (b) Schematic showing the molecular complexity at the dermal–epidermal junction and how various proteins map above or below the NaCl-induced split (red line and asterisk). BP, bullous pemphigoid.

Table 3.1 Molecular components of the epidermal basement membrane zone.

Intermediate filament (IF) components
Keratin 5
Keratin 14
Hemidesmosomal plaque components
230-kDa bullous pemphigoid antigen (BP230/BPAG1)
Plectin
Transmembrane components
α6β4 integrin
Type XVII collagen (180-kDa bullous pemphigoid antigen/BPAG2)
α3β1 integrin
Type XIII collagen
Syndecans 1 and 4
Lamina lucida/lamina densa components
Laminin 332 (laminin 5)
Laminin 311 (laminin 6)
Laminin 511 (laminin 10)
Lamina densa components
Type IV collagen
Laminin 111 (laminin 1)
Nidogen
BM-40/SPARC
Perlecan
Anchoring fibril components
Type VII collagen
GDA-J/F3 antigen

somes, anchoring filaments and anchoring fibrils. The biochemical components of the BMZ are synthesized by basal keratinocytes and dermal fibroblasts, which both contribute to the development and repair of the basement membrane [4]. The critical importance of this network structure in securing the adherence of the epidermis to the underlying dermis is reflected in the group of diseases, epidermolysis bullosa, in which components of the hemidesmosomes, anchoring filaments or anchoring fibrils are genetically altered or missing, and, as a result, fragility at the dermal–

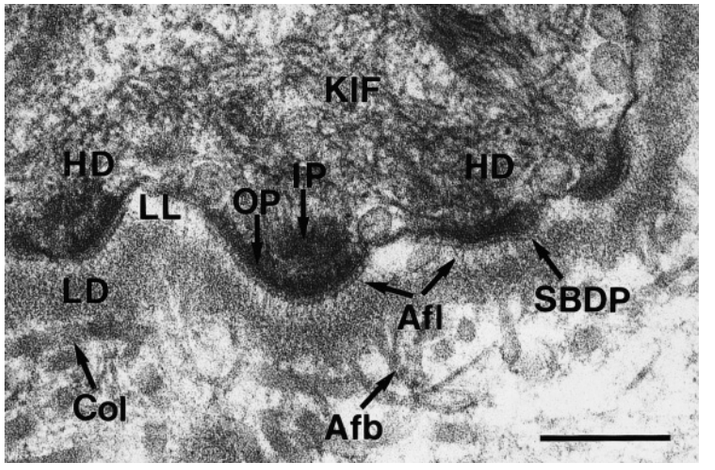


Fig. 3.35 Transmission electron microscopy of the dermal–epidermal junction in human skin recognizing hemidesmosomes (HD), anchoring filaments (Afl), and anchoring fibrils (Afb). The HD consists of an intracellular inner plaque (IP) and outer plaque (OP) as well as sub-basal dense plate (SBDP) in the upper lamina lucida (LL). The anchoring filaments traverse the lamina lucida appearing as thread-like structures which concentrate under the hemidesmosomes and merge with the lamina densa (LD). Anchoring fibrils extend from the lower part of the LD to the upper papillary dermis where they closely associate with interstitial collagen fibres (Col). Keratin intermediate filaments (KIFs) associate with intracellular components of HDs. Scale bar, 0.25 μm.

epidermal junction ensues, clinically manifesting as erosions and blisters following minor trauma [5] (Fig. 3.36).

References

1 Fine JD. Structure and antigenicity of the skin basement membrane zone. *J Cutan Pathol* 1991; **18**: 401–9.
2 Uitto J, Pulkkinen L. Molecular complexity of the cutaneous basement membrane zone. *Mol Biol Rep* 1996; **23**: 35–46.
3 Ghohestani RF, Li K, Rousselle P *et al*. Molecular organization of the cutaneous basement membrane zone. *Clin Dermatol* 2001; **5**: 551–62.
4 El Ghalbzouri A, Jonkman MF, Dijkman R *et al*. Basement membrane reconstruction in human skin equivalents is regulated by fibroblasts and/or exogenously activated keratinocytes. *J Invest Dermatol* 2005; **124**: 79–86.
5 Uitto J, Richard G. Progress in epidermolysis bullosa: from eponyms to molecular genetic classification. *Clin Dermatol* 2005; **23**: 33–40.

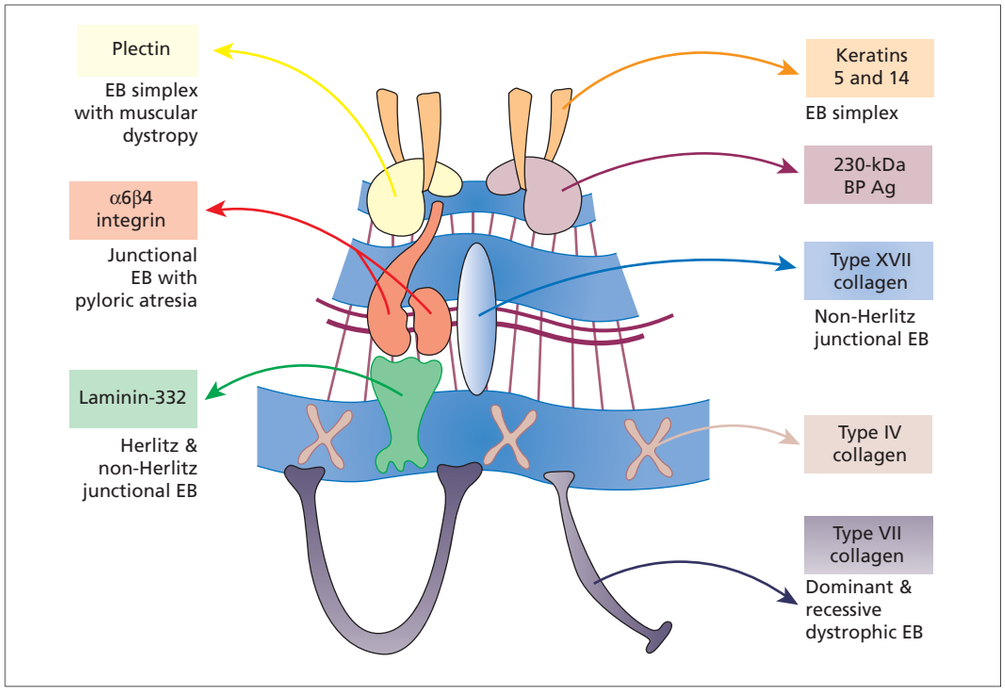


Fig. 3.36 Schematic representation of the gene/protein systems within the cutaneous basement membrane zone that can harbour mutations and result in blistering of the skin in different forms of epidermolysis bullosa (EB). BP, bullous pemphigoid.

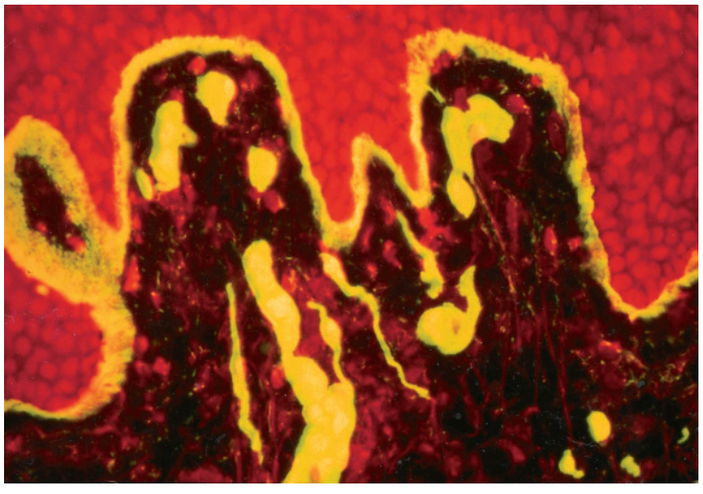


Fig. 3.37 Immunofluorescence staining of the dermis and the cutaneous basement membrane zone with an antibody for type IV collagen. Note positive staining at the dermal–epidermal basement membrane and around the dermal blood vessels. Original magnification, ×250.

Type IV collagen

The major component of the dermal–epidermal basement membrane is type IV collagen, a heterogeneous group of macromolecules which are present in diverse combinations in various basement membranes [1] (Fig. 3.37).

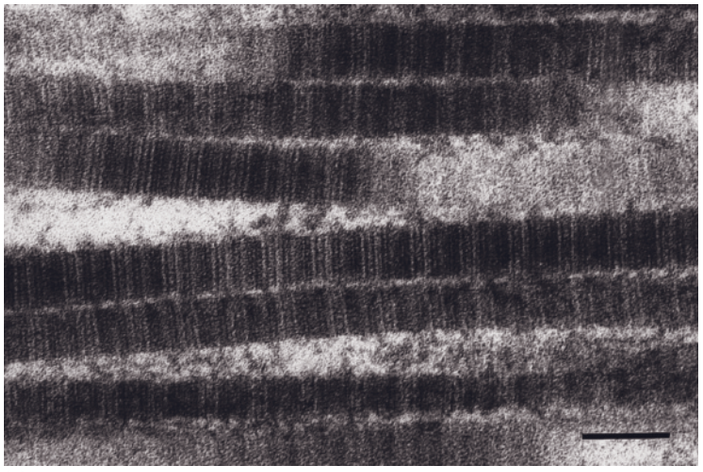
Like all collagens, each type IV collagen molecule consists of three polypeptide subunits, known as α-chains. Some collagen molecules are homopolymers, that is the three α-chains are genetically identical, as in the case of type II, III and VII collagens, while others are heteropolymers so that there are two or even three different kinds of polypeptides, as for example in type I and type VI collagens. For type IV collagen, there are six genetically distinct but structurally related α-chains, and the precise composition of the α-chains varies with the tissue location of the basement membranes. In the case of the cutaneous basement membrane zone, the major type IV collagen consists of α1 and α2 chains, with the chain composition $[\alpha1(IV)]_2\alpha2(IV)$, although other type IV collagen subunit polypeptides are also present in lower quantities. The α3 chain of type IV collagen has been shown to be the antigen recognized by circulating autoantibodies characteristic of Goodpasture's syndrome, while structural aberrations in the α5 chain of type IV collagen are associated with Alport syndrome [2]. Autoantibodies against α5 and α6 chain epitopes have also been reported in patients with glomerulonephritis and subepidermal blistering [3].

The characteristic fibre structure of interstitial collagens results from the lateral aggregation of individual molecules in a quarter stagger array; this gives rise to a 64-nm cross-striation pattern, when examined by transmission electron microscopy (Fig. 3.38).

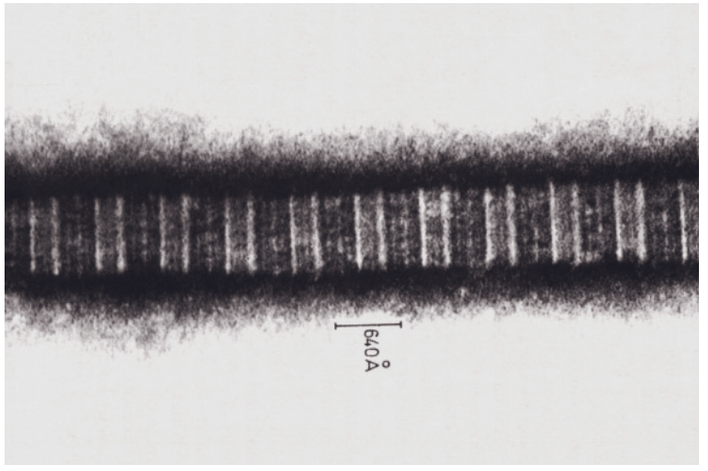
In the case of type IV collagen, the non-collagenous globular domains both at the amino- and carboxyl-ends of the individual collagen molecules interact to form dimers and tetramers which then assemble into lattice-like structures and associate laterally in a complex hexagonal arrangement (Fig. 3.39). This arrangement allows high flexibility to the basement membrane structure and makes interactions with other collagenous and non-collagenous basement membrane components possible [1].

References

1 Khoshnoodi J, Pedchenko V, Hudson BG. Mammalian collagen IV. *Microsc Res Tech* 2008; **71**: 357–70.
2 Hudson BG, Tryggvason K, Sundaramoorthy M *et al*. Alport's syndrome, Goodpasture's syndrome, and type IV collagen. *N Eng J Med* 2003; **25**: 2543–56.
3 Ghohestani RF, Rotunda SL, Hudson B *et al*. Crescentic glomerulonephritis and subepidermal blisters with autoantibodies to α5 and α6 chains of type IV collagen. *Lab Invest* 2003; **83**: 605–11.



(a)



(b)

Fig. 3.38 Demonstration of periodicity in collagen fibres of 640A. (a) Collagen fibrils in the reticular dermis show a characteristic banding pattern after standard processing and staining with uranyl acetate and lead citrate for transmission electron microscopy. Scale bar, 0.1 μm. (b) Transmission electron micrograph of a shadowed replica of unfixed, freeze-frozen and surface-sublimated rat-tail tendon collagen showing the step-like banding of the fibres. Original magnification, × 40 500. ((b) Courtesy of G.A. Meek.)

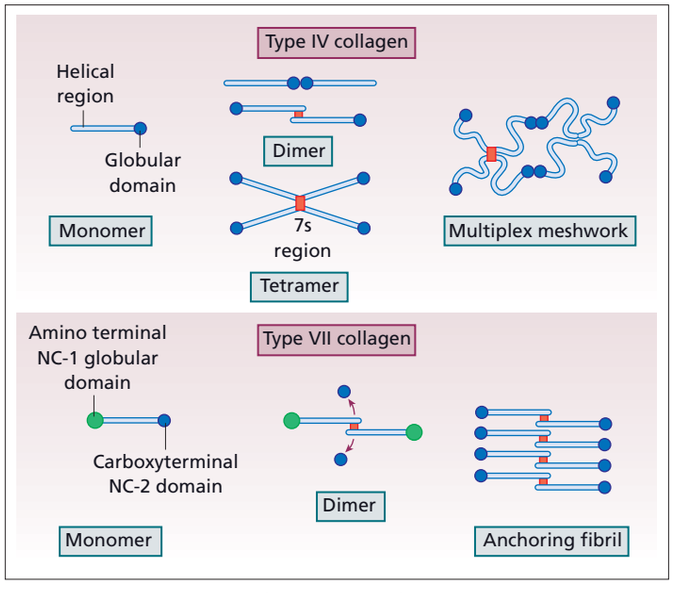


Fig. 3.39 Schematic illustration of the assembly of type IV and type VII collagen molecules into supramolecular structures. The red boxes represent intermolecular disulphide bonds.

Table 3.2 Chain composition of major laminins in the skin.

Type*	Chain composition	Old designation	Distribution in basement membranes
111	α1β1γ1	1	Blood vessels, LD
332	α3β3γ2	5	LL/LD
311	α3β1γ1	6	LL/LD
511	α5β1γ1	10	LL/LD

* For the latest nomenclature, see [4].
LD, lamina densa; LL, lamina lucida.

The laminin family

Other components that contribute to the cutaneous basement membrane zone include members of the laminin family of multidomain proteins [1,2]. As many as 16 different laminins have been identified thus far and at least four of them are physiologically present in the skin in significant quantities (Table 3.2) [3]. Each laminin molecule consists of three polypeptide subunits, α, β and γ chains, which form a cruciform structure with three short arms and one long arm when visualized by rotary shadowing electron microscopy (Fig. 3.40).

The short arms represent the N-terminal segments of the α, β and γ chains. The long arm consists of an extended rod-like structure of the triple-stranded, coiled-coil domain of all three chains. This domain serves as the site of chain assembly of the three subunit polypeptides. The α-chain contains an additional C-terminal segment which contains five globular segments located at the tip of the long arm, known as the G domain. The major laminin within the cutaneous basement membrane zone is laminin 332, previously known as laminin 5 (for the most recent nomenclature see [4,5]) (Fig. 3.41). In addition, laminin 311 and laminin 511 are also integral components of the cutaneous basement membrane zone, while laminin 111 is present in basement membranes of the blood vessels in human dermis.

The cell binding of laminins is mediated by integrins, a family of cellular receptors, each consisting of two subunit polypeptides (Fig. 3.42). Integrins also mediate outside-in signal transduction elicited by laminins and regulate cell migration, proliferation, differentiation and adhesion [6]. The principal integrin in the cutaneous BMZ is the α6β4 integrin, which is critical for the adhesion of basal cells to the underlying BMZ.

The cruciform structure of laminins contains both globular and rod-like segments which have been individually implicated in various functions, including interactions with other extracellular matrix molecules, such as the hemidesmosomal components and type VII collagen, as well as in cell attachment and spreading, neurite outgrowth and cellular differentiation. Collectively, the laminins play vital roles in the development and maintenance of the supramolecular organization of basement membrane. The

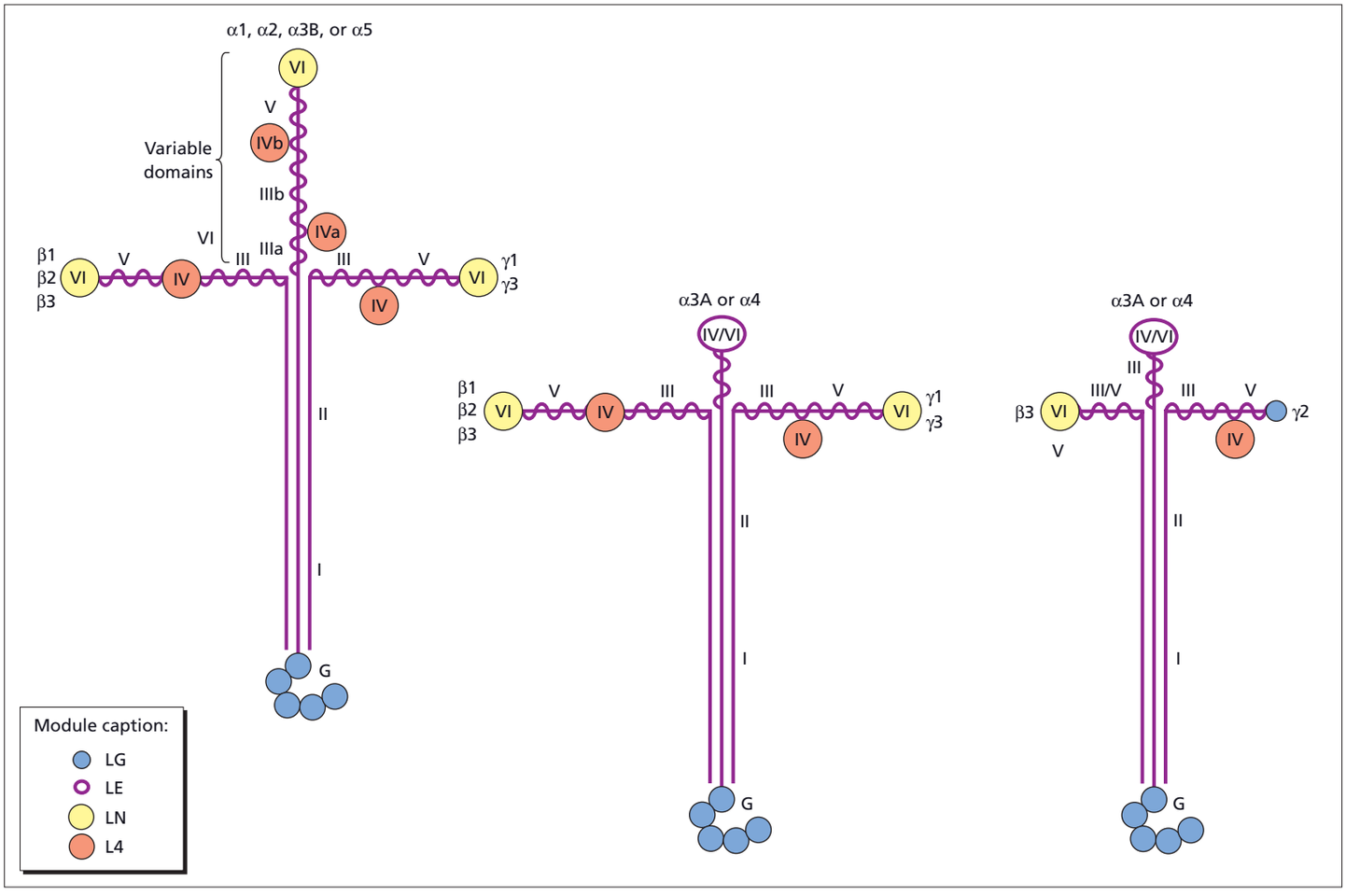


Fig. 3.40 Schematic representation of the different isoforms and the domain organizations of laminin, each consisting of three distinct subunit polypeptides, α, β, and γ chains. The LE modules are formed by approximately 60 residues each and have homology to epidermal growth factor. The LN and L4 modules are folded into globular structures located between LE modules (domain IV) or at the amino-terminus of each chain (domain VI). The coiled-coil central region, comprising all three polypeptides, is represented as vertical straight lines. Note the presence of a G domain consisting of five globular segments (LG) at the carboxy-terminus of the α chains. (Adapted from [10].)

critical role of laminin 332 in providing integrity to the cutaneous basement membrane zone is evident by observations that genetic mutations in any of the three polypeptide subunits, that is the *LAMA3*, *LAMB3* or *LAMC2* genes which encode the α3, β3, and γ2 chains, respectively, can result in junctional forms of epidermolysis bullosa (EB) with profound fragility of the skin (Fig. 3.42). Furthermore, mutations in the *ITGA6* and *ITGB4* genes (encoding the α6 and β4 subunit polypeptides of integrin, respectively) cause a form of junctional EB frequently associated with pyloric atresia [7].

Other basement membrane zone components at the dermal–epidermal junction include a glycoprotein known as nidogen (previously called entactin) which interacts with type IV collagen either alone or as a laminin–nidogen complex (Fig. 3.41) [8]. Nidogens are a family of highly conserved, sulphated glycoproteins within a spectrum of binding proteins. Although nidogens are an abundant component of various basement membranes, genetic analyses have shown that they are not required for the overall architecture of the basement membrane. Instead, nidogens appear to play a critical role in the development of basement membranes in tissues undergoing rapid growth or turnover [9].

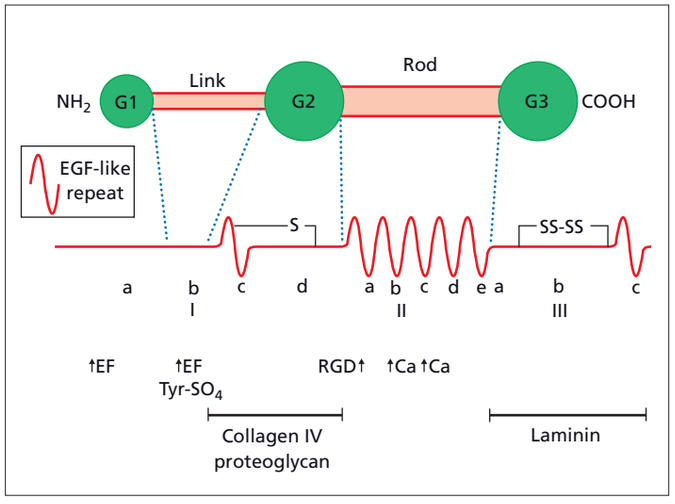


Fig. 3.41 Model of nidogen containing subdomains with predicted binding activities to type IV collagen, proteoglycans, and laminin 1. EF and Ca refer to putative calcium binding sites; RGD is a putative cell-binding sequence. EGF, epidermal growth factor. (Adapted from [11].)

Another class of integral basement membrane constituents is the heparan sulphate proteoglycans (HSPGs). These molecules consist of a core protein with different numbers of covalently associated heparan and sulphate chains which make these molecules highly negatively charged and hydrophilic. These proteoglycans are capable of interacting with a number of basement membrane components and they are likely to contribute to the overall architecture of the basement membrane. Specific cell surface HSPGs are found also on the surface of epithelial cells and possibly mediate cell-matrix interactions.

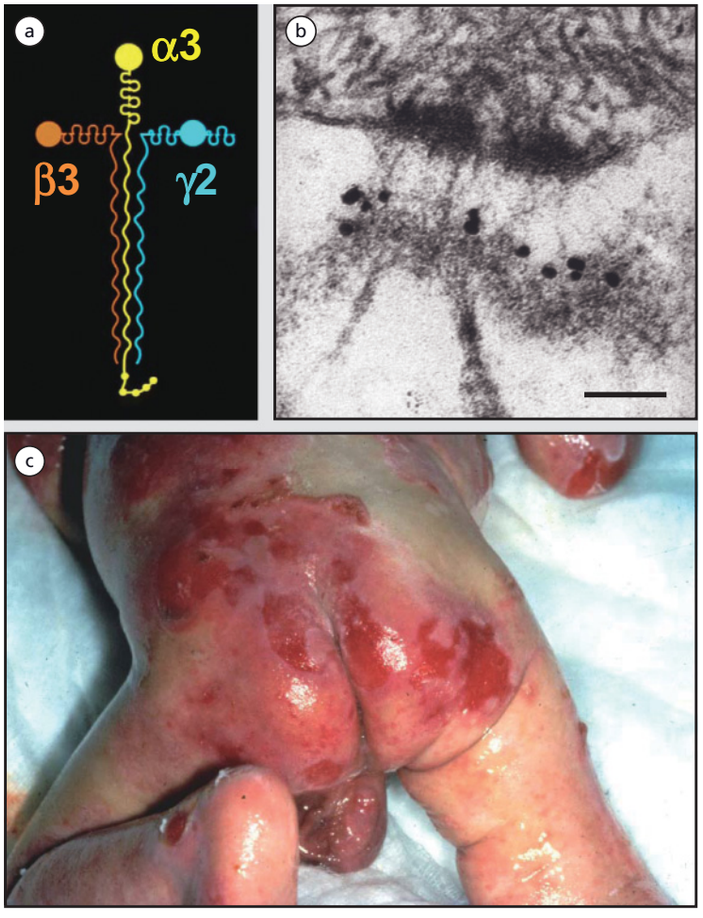


Fig. 3.42 Laminin 332 in inherited skin disease. (a) Schematic representation of laminin 332 expressed in the cutaneous basement membrane zone. (b) Immunogold electron microscopy using an antibody to the γ2 chain of laminin 332 shows labelling at the lamina lucida–lamina densa interface below a hemidesmosome. (c) In the absence of laminin 332, affected individuals develop erosions and blisters at the level of lamina lucida, manifesting with the Herlitz form of junctional EB.

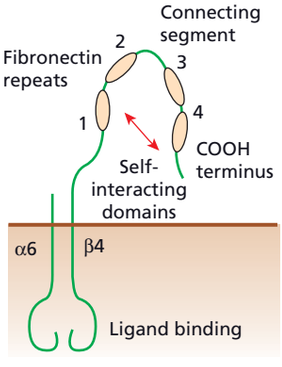
References

1 Engel J. Laminins and other strange proteins. *Biochemistry* 1992; **31**: 10643–51.
2 Miner JH. Laminins and their roles in mammals. *Microsc Res Tech* 2008; **71**: 349–56.
3 Tzu J, Marinkovich MP. Bridging structure with function: structural, regulatory, and developmental role of laminins. *Int J Biochem Cell Biol* 2008; **40**: 199–214.
4 Aumailley M, Bruckner-Tuderman L, Carter WG *et al*. A simplified laminin nomenclature. *Matrix Biol* 2005; **24**: 326–32.
5 Sugawara K, Tsuruta D, Ishii M *et al*. Laminin-332 and -511 in skin. *Exp Dermatol* 2008; **17**: 473–80.
6 Belkin AM, Stepp MA. Integrins as receptors for laminins. *Microsc Res Tech* 2000; **51**: 280–301.
7 Varki R, Sadowski S, Pfendner E *et al*. Epidermolysis bullosa. I. Molecular genetics of the junctional and hemidesmosomal variants. *J Med Genet* 2006; **43**: 641–52.
8 Ho MS, Böse K, Mokkapati S *et al*. Nidogens—extracellular matrix linker molecules. *Microsc Res Tech* 2008; **71**: 387–96.
9 Mokkapati S, Baranowky A, Mirancea N *et al*. Basement membranes in skin are differently affected by lack of nidogen 1 and 2. *J Invest Dermatol* 2008; **128**: 2259–67.
10 Aumailley M, Rouselle P. Laminins of the dermo–epidermal junction. International Society of Matrix Biology, Elsevier Science, 1999.
11 Niessen CM, Hogervorst F, Jaspars LH *et al*. The α6β4 integrin is a receptor for both laminin and kalinin. *Exp Cell Res* 1994; **211**: 360–7.

The hemidesmosome–anchoring filament complex

The dermal–epidermal junction of skin is characterized by the presence of specific structures that are critical for the functional integrity of the skin. These ultrastructurally recognizable components include hemidesmosomes, anchoring filaments and anchoring fibrils. The molecular composition and the specific domain organizations of the component macromolecules have been largely characterized (Fig. 3.44).

The hemidesmosomes are seen ultrastructurally as electron dense attachment complexes, which extend from the intracellular compartment of the basal keratinocytes to the lamina lucida in the upper portion of the dermal–epidermal basement membrane (Fig.



α6β4 integrin	Domain	Function
	β4 integrin	
	COOH terminus	Plectin binding
	COOH terminus	Proximal endodomain binding
	Connecting segment	Hemidesmosome assembly
	Connecting segment	Plectin binding
	Connecting segment	Tyrosine activation motif
	Connecting segment and 3rd FN repeat	Collagen XVII binding
	NH_2 half, endodomain	COOH terminus binding
	Exodomain	Extracellular ligand binding
	α6 integrin	
	Proximal exodomain	Collagen XVII binding
	Exodomain	Extracellular ligand binding

Fig. 3.43 The molecular composition, domain organization, and functions of the α6β4 integrin, the main keratinocyte integrin in hemidesmosomes. This integrin is important in hemidesmosome assembly and protein–protein interactions [11].

3.45). The intracellular component of a hemidesmosome within the basal keratinocytes attaches to the keratin intermediate filament network, while in the extracellular space within the lamina lucida the hemidesmosomes are contiguous with anchoring filaments, thread-like structures which traverse the lamina lucida and tend to concentrate below the hemidesmosomes; this unit is termed the hemidesmosome–anchoring filament complex.

Early biochemical studies identified at least five major components of hemidesmosomes, originally designated as HD1–HD5 with molecular masses of approximately 500, 230, 200, 180 and 120 kD, respectively. Various molecular and immunological approaches have subsequently identified HD2 and HD4 as the 230-kDa and 180-kDa bullous pemphigoid antigens (BPAG1 and BPAG2), respectively [1–3]; HD3 and HD5 correspond to the β4 and α6 integrin subunit polypeptides, respectively; and HD1 corresponds to plectin, a large intracytoplasmic adhesion molecule. The intracellular hemidesmosomal plaque contains the 230-kDa bullous pemphigoid antigen, a non-collagenous protein of the plakin family that serves as an autoantigen in bullous pemphigoid. The 180-kDa bullous pemphigoid antigen, a transmembrane collagenous protein, also known as type XVII collagen, interacts with α6β4 integrin and extends from the intracellular compartment of basal cells to the extracellular space, thus stabilizing the association of basal keratinocytes to the underlying basement membrane (Fig. 3.34 and 3.43).

Attesting to the critical importance of the hemidesmosomes in providing stability to the association of basal keratinocytes with the underlying BMZ is the finding that mutations in the genes encoding hemidesmosomal proteins (with the exception of *BPAG1*) have been shown to result in different forms of EB [4,5] (Fig. 3.36). For example, mutations in the *BPAG2* gene result in a relatively mild, non-Herlitz type of junctional EB; mutations in the α6β4 integrin genes (*ITGA6*, *ITGB4*) cause skin fragility associated with congenital pyloric atresia; mutations in the plectin gene (*PLEC1*) result in skin blistering disorder frequently associated with late-onset muscular dystrophy. The finding of skin and muscle manifestations as a result of mutations in the plectin gene can be explained by the fact that plectin is expressed not only in the hemidesmosomes in the epidermis but also in the sarcolemma and the Z-lines of muscle [6,7]. The causative nature of the mutations in these hemidesmosomal genes has been verified by development of targeted mutant ('knockout') mouse models, which

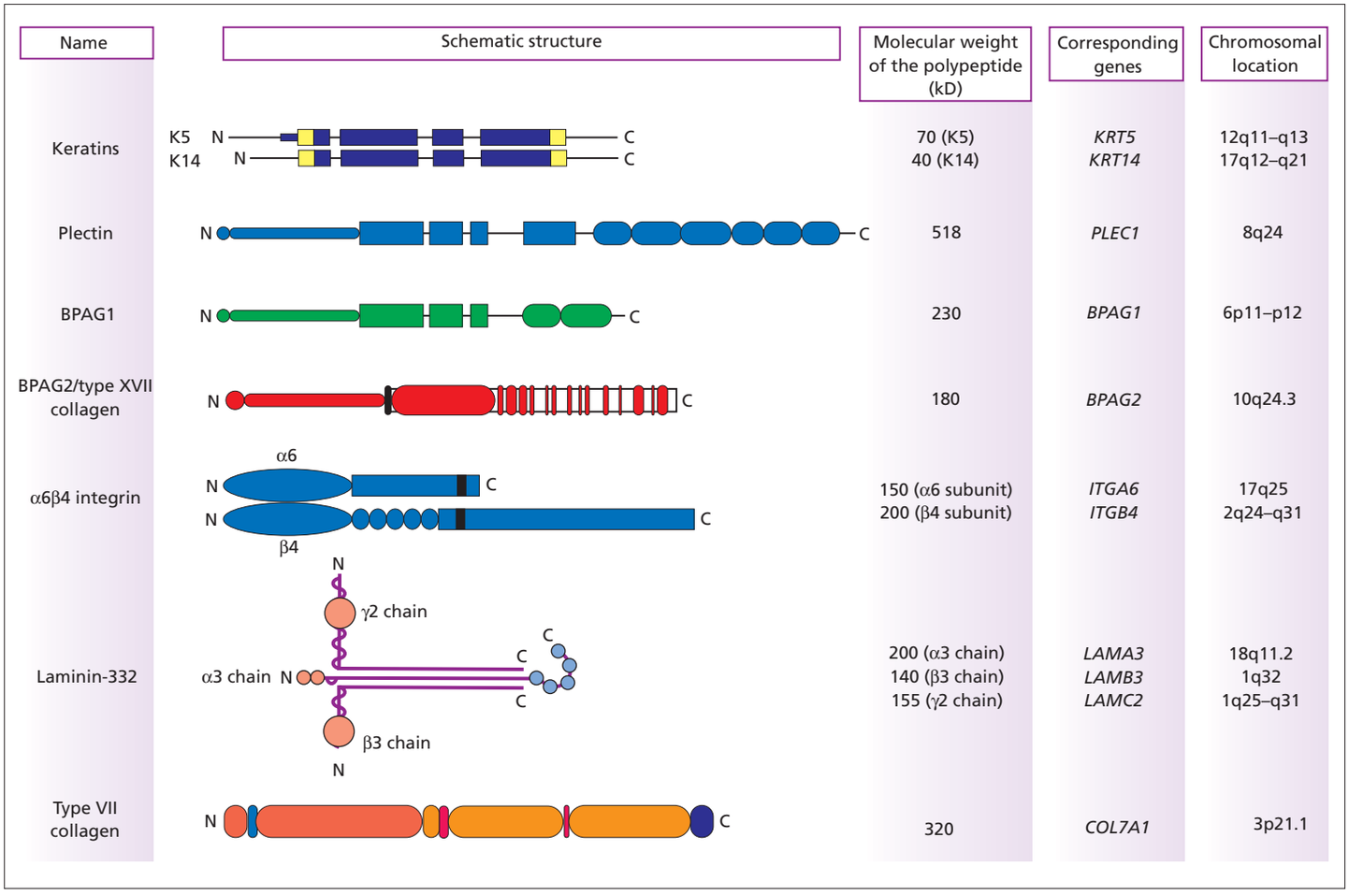


Fig. 3.44 Schematic representation of the structure and domain organization of the major protein components at the cutaneous basement membrane zone, with their molecular weights and chromosomal locations of the corresponding genes. BPAG, bullous pemphigoid antigen. (Adapted from [1].)

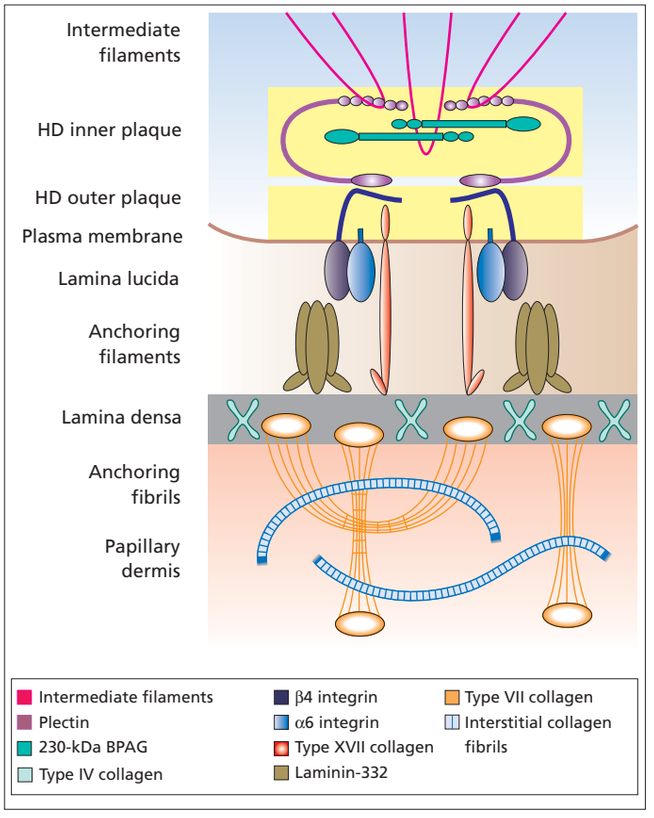


Fig. 3.45 Schematic representation of the molecular interactions of the major components of the cutaneous basement membrane zone. The individual components are identified in the colour key and their domain organizations are given in Fig. 3.44. HD, hemidesmosomes; BPAG, bullous pemphigoid antigens; IFAP, intermediate filament-associated protein. (Adapted from [1].)

frequently recapitulate the clinical, genetic, histological and ultrastructural features encountered in patients with EB [8,9].

The hemidesmosomes are complexed with anchoring filaments, which are thread-like structures that tend to coalesce below hemidesmosomal outer plaques (Figs 3.34 and 3.45). Electron microscopy and immunohistochemical analyses have suggested that laminin 332 may be the major component of the anchoring filaments, although the presence of additional molecules has also been suggested, including ladinin, a recently characterized protein with currently unknown function. As indicated above, laminin 332 is a disulphide-bonded complex of α3, β3, and γ2 chains which associate into a trimeric, cruciform structure. After the initial assembly, the α3 and γ2 chains are proteolytically processed, and many of the conformational epitopes are recognized by specific antibodies. Complete absence of any of the three subunit polypeptides of laminin 332, due to loss-of-function mutations in both alleles of the corresponding gene, results in Herlitz junctional EB (Fig. 3.42) [5]. Since laminin 332 binds to α6β4 integrin in the hemidesmosomes and to type VII collagen in the anchoring fibrils, the severity of skin fragility in this form of EB apparently reflects the loss of its ability to bridge the hemidesmosomes and the anchoring fibrils, resulting in separation of the epidermis from dermis within the lamina lucida.

References

1 Pulkkinen L, Uitto J. Hemidesmosomal variants of epidermolysis bullosa. Mutations in the α6β4 integrin and the 180-kD bullous pemphigoid antigen/type XVII collagen genes. *Exp Dermatol* 1998; **7**: 46–64.

2 McGrath JA, Gatalica B, Christiano AM *et al*. Mutations in the 180-kD bullous pemphigoid antigen (BPAG2), a hemidesmosomal transmembrane collagen (COL17A1), in generalized atrophic benign epidermolysis bullosa. *Nat Genet* 1995; **11**: 83–6.

3 Koster J, Geerts D, Favre B *et al*. Analysis of the interactions between BP180, BP230, plectin and the integrin α6β4 important for hemidesmosome assembly. *J Cell Sci* 2003; **116**: 387–99.

4 Pulkkinen L, Uitto J. Mutation analysis and molecular genetics of epidermolysis bullosa. *Matrix Biol* 1999; **18**: 29.

5 Varki R, Sadowski S, Pfendner E *et al*. Epidermolysis bullosa. I. Molecular genetics of the junctional and hemidesmosomal variants. *J Med Genet* 2006; **43**: 641–52.

6 Uitto J, Richard G, McGrath JA. Diseases of epidermal keratins and their linker proteins. *Exp Cell Res* 2007; **313**: 1995–2009.

7 Sonnenberg A, Liem RK. Plakins in development and diseases. *Exp Cell Res* 2007; **313**: 2189–203.

8 Jiang QJ, Uitto J. Animal models of epidermolysis bullosa—targets for gene therapy. *J Invest Dermatol* 2005; **124**: xi–xiii.

9 Fritsch A, Loeckermann S, Kern JS *et al*. A hypomorphic mouse model of dystrophic epidermolysis bullosa reveals mechanisms of disease and response to fibroblast therapy. *J Clin Invest* 2008; **118**: 1669–79.

Anchoring fibrils

Anchoring fibrils are ultrastructurally recognizable, U-shaped structures which extend from the lower part of lamina densa to the upper reticular dermis [1] (Fig. 3.46).

Type VII collagen is the major, if not the exclusive, component of anchoring fibrils [2]. Individual collagen molecules are approximately 450 nm long, consisting of a central triple helical segment flanked by non-helical globular domains at each end of the triple helix: NC1 at the amino terminus and NC2 at the carboxy terminus of the molecule (Fig. 3.39). In addition, the triple helical segment of type VII collagen contains imperfections in the triple helix, including a central 39-amino acid non-collagenous segment. These interruptions in the glycine-X-Y sequence are thought to provide flexibility to the type VII collagen molecules [3].

The gene encoding type VII collagen (*COL7A1*) is extremely complex, consisting of 118 exons on the short arm of human chromosome 3 [4]. Type VII collagen is synthesized by both dermal fibroblasts and epidermal keratinocytes, although the basal cell appears to be the major source of type VII collagen during early prenatal development of skin. Upon secretion, two type VII collagen molecules align into an antiparallel dimer with overlapping NC2 domains, and after partial proteolysis of the NC2 domain, the dimer is stabilized by intermolecular disulphide bonds (Fig. 3.39). Subsequently, a large number of type VII molecules laterally aggregate to form anchoring fibrils in which the NC1 domains at both ends attach to the basement membrane. The U-shaped loops then entrap, and possibly interact with large interstitial collagen fibres consisting of type I, III, and V collagens [2,5] (Fig. 3.34).

The critical importance of the anchoring fibrils in securing the adhesion of the dermal–epidermal basement membrane to the underlying dermis is illustrated by the dystrophic forms of EB. Specifically, complete absence of type VII collagen results in severe, generalized, recessive dystrophic EB with fragility of the

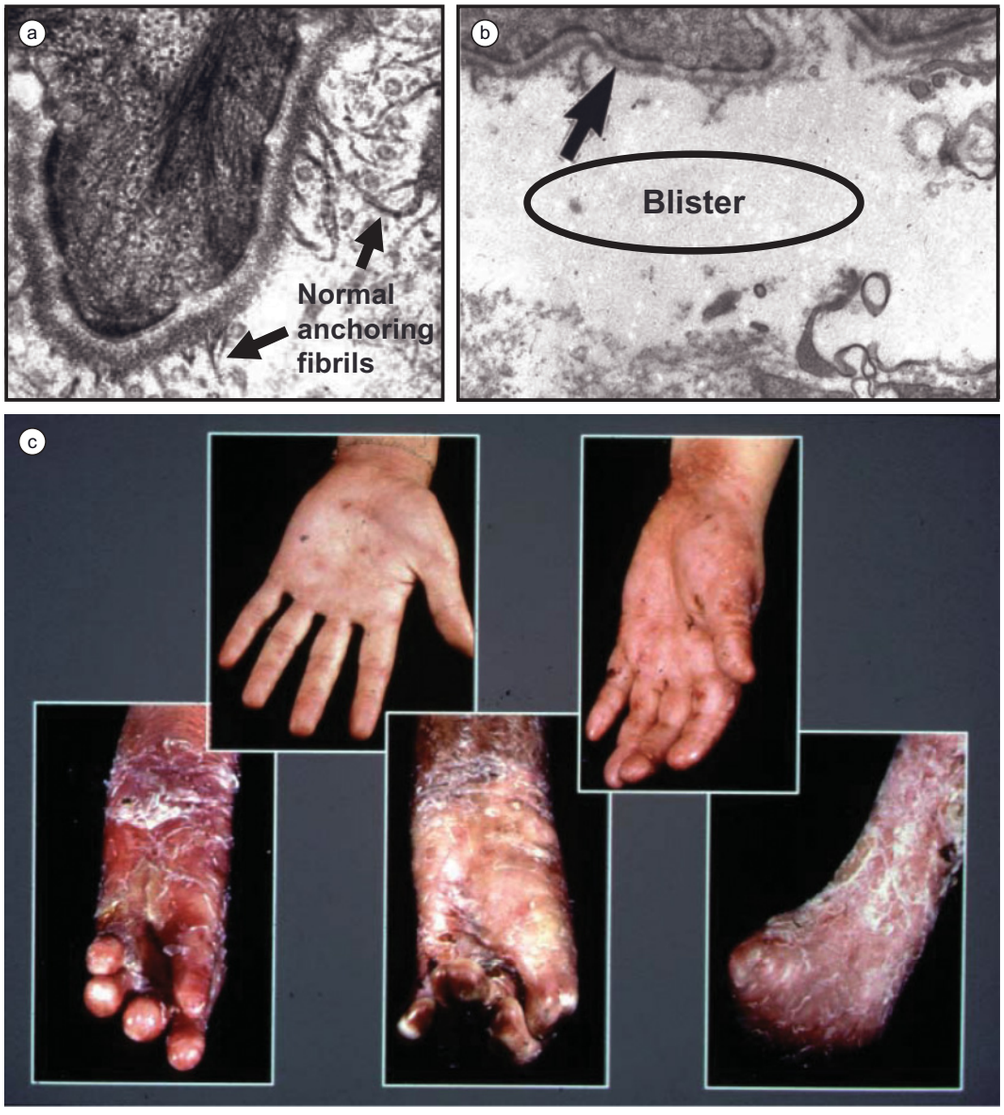


Fig. 3.46 (a) Anchoring fibrils extend from the lower part of lamina densa to the underlying upper dermis forming U-shaped loops which entrap and interact with the large collagen fibres consisting of type I, III, and V collagens. (b) In the absence of type VII collagen, the lamina densa detaches as a result of minor trauma from the underlying dermis and leads to blisters. (c) Chronic blistering and erosions result in variable scarring of the hands in recessive dystrophic EB.

skin and mucous membranes leading to mutilating scarring of the hands and feet (Fig. 3.46). Missense mutations, particularly glycine substitution mutations, can result in somewhat milder, dominantly inherited dystrophic EB [6].

References

1 Shimizu H, Ishiko A, Masunaga T *et al*. Most anchoring fibrils in human skin originate and terminate in the lamina densa. *Lab Invest* 1997; **76**: 753–63.
2 Burgeson RE. Type VII collagen, anchoring fibrils, and epidermolysis bullosa. *J Invest Dermatol* 1993; **101**: 252–5.
3 Christiano AM, Greenspan DS, Lee S *et al*. Cloning of human type VII collagen. Complete primary sequence of the α1(VII) chain and identification of intragenic polymorphisms. *J Biol Chem* 1994; **269**: 20256–62.
4 Christiano AM, Hoffman GG, Chung-Honet LC *et al*. Structural organization of the human type VII collagen gene (COL7A1), composed of more exons than any previously characterized gene. *Genomics* 1994; **21**: 169–79.
5 Villone D, Fritsch A, Koch M. Supramolecular interactions in the dermo-epidermal junction zone: Anchoring fibril-collagen VII tightly binds to banded collagen fibrils. *J Biol Chem* 2008; **238**: 24506–13.
6 Varki R, Sadowski S, Uitto J *et al*. Epidermolysis bullosa. II. Type VII collagen mutations and phenotype-genotype correlations in the dystrophic subtypes. *J Med Genet* 2007; **44**: 181–92.

Extracellular matrix of connective tissue

The major component of human skin is the dermis demarcated on the top by the lower border of the dermal–epidermal basement membrane interface and at the bottom by the subcutis. In contrast to the epidermis, the dermis is largely acellular and consists primarily of the extracellular matrix of connective tissues, a complex meshwork of various macromolecules. There are four major classes of extracellular matrix components: (a) collagen fibres, which provide tensile strength to allow skin to serve as a protective organ against external trauma; (b) elastic structures, which provide elasticity and resilience to normal human skin;

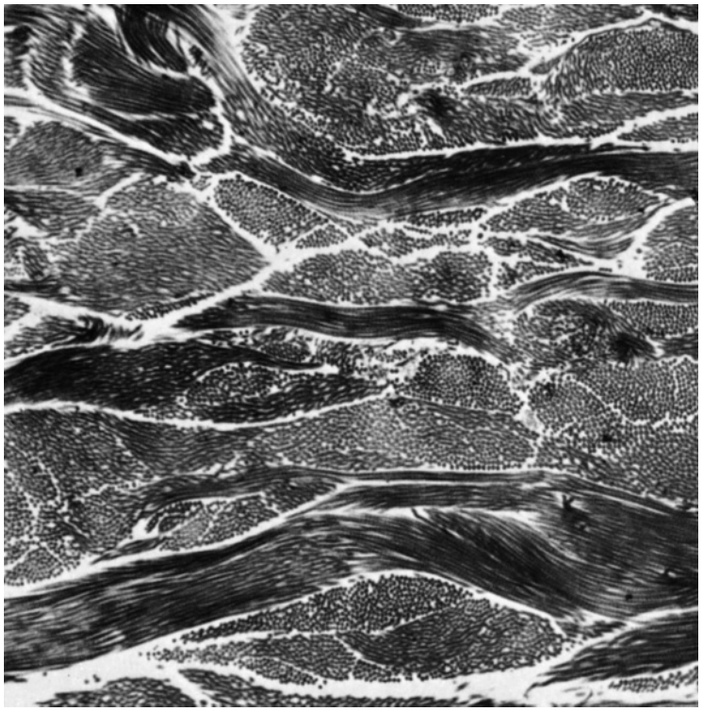


Fig. 3.47 Transmission electron micrograph of a section of dermis from the human forearm shows bundles of collagen fibres, both in transverse and longitudinal sections. Original magnification, ×4900. (Courtesy of Professor A.S. Breathnach, St. John's Institute of Dermatology, King's College London, UK.)

Table 3.3 Genetic heterogeneity of collagens.

Collagen type	Chain composition	Supramolecular assembly	Tissue distribution†
I	$[\alpha1(I)]_2\alpha2(I)$	Fibrillar	Dermis, bone, tendons
III	$[\alpha1(III)]_3$	Fibrillar	Fetal dermis, blood vessels, GI tract
IV	$[\alpha1(IV)]_2\alpha2(IV)$*	Basement membrane	Ubiquitous
V	$[\alpha1(V)]_2\alpha2(V)$*	Fibrillar	Ubiquitous
VI	$[\alpha1(VI)\ \alpha2(VI)\ \alpha3(VI)]$*	Microfibrils	Ubiquitous
VII	$[\alpha1(VII)]_3$	Epithelial basement membranes	Epithelial basement membranes
VIII	$[\alpha1(VIII)]_3$	Network forming	Endothelia
XIII	$[\alpha1(XIII)]_3$	Transmembrane	Ubiquitous, including epidermis
XIV	$[\alpha1(XIV)]_3$	FACIT	Skin, cornea
XV	$[\alpha1(XV)]_3$	Basement membrane	Ubiquitous
XVII	$[\alpha1(XVII)]_3$	Transmembrane	Hemidesmosomes
XXIX	Unknown	Unknown	Epidermis

* Additional α-chains have been identified.

† Distribution in the skin and other major tissues is indicated; lesser amounts may be present in other tissues.

FACIT, fibril-associated collagens with interrupted triple helices.

(c) non-collagenous glycoproteins, such as fibrillins, fibulins and integrins, which often serve as organizers of the matrix and facilitate cell-matrix interactions; and (d) proteoglycan/glycosaminoglycan macromolecules, which provide hydration to the skin. Maintenance of proper quantities and appropriate interactions between the extracellular matrix components is a prerequisite for the physiological homeostasis of the dermis.

The collagen family of proteins

The major extracellular matrix component in the dermis is collagen, which comprises a family of closely related yet genetically distinct proteins [1–4]. The major collagen fibres in the dermis provide tensile strength to the skin to serve as a protective organ against external trauma (Fig. 3.47).

A characteristic feature of all collagens is the presence of the triple-helical conformation, which is predicated upon the primary amino acid sequence of the subunit polypeptides, α-chains, depicting a repeating glycine-X-Y sequence. The collagens also demonstrate non-collagenous flanking segments at the ends of the individual molecules. Currently, 29 distinct collagens have been identified in vertebrate tissues, and have been characterized to the extent that they are referred to by Roman numeral designation (I–XXIX) in the order of their discovery, many of them being present in the skin (Table 3.3).

All collagen molecules consist of three subunit polypeptides which can either be identical as homotrimers or can consist of two or even three genetically different polypeptides in heterotrimeric molecules. Since the different subunits are all distinct gene products, there are over 40 different genes in the human genome that encode the different subunit polypeptides, the α-chains, of these distinct collagens [5].

References

1 Myllyharju J, Kivirikko KI. Collagens, modifying enzymes and their mutations in humans, flies and worms. *Trends Genet* 2004; **20**: 33–43.

2 Shaw LM, Olsen BR. FACIT collagens: diverse molecular bridges in extracellular matrices. *Trends Biochem Sci* 1991; **16**: 191.

3 Franzke CW, Bruckner P, Bruckner-Tuderman L. Collagenous transmembrane proteins: recent insights into biology and pathology. *J Biol Chem* 2005; **280**: 4005–8.

4 Kuivaniemi H, Tromp G, Prockop DJ *et al*. Mutations in fibrillar collagens (types I, II, III, and XI), fibril-associated collagen (type IX), and network-forming collagen (type X) cause a spectrum of diseases of bone, cartilage, and blood vessels. *Hum Mutat* 1997; **9**: 300–15.

5 Chu M-L, Prockop DJ. Collagen: gene structure. In: Royce PM, Steinmann B, eds. *Connective Tissue and its Heritable Disorders: Molecular, Genetic and Medical Aspects*, 2nd edn. New York: Wiley-Liss, 2002: 223–43.

Collagens in the skin

On the basis of their fibre architecture in tissues, the genetically distinct collagens can be divided into different classes [1,2]. Types I, II, III, V and IX align into large fibrils and are designated as fibril-forming collagens. Type IV is arranged in an interlacing network within the basement membranes, while type VI is a distinct microfibril-forming collagen, and type VII collagen forms anchoring fibrils. FACIT collagens (fibril-associated collagens with interrupted triple-helices) include types IX, XII, XIV, XIX, XX and XXI. Many of the latter collagens associate with larger collagen fibres and serve as molecular bridges, stabilizing the

Table 3.4 Molecular defects in the Ehlers–Danlos syndrome.

Current type	Old designation	Mode of inheritance	Mutated gene(s)	Pathophysiology
Classic	I, II	AD, AR	*COL5A1, COL5A2, TNX**	Defective collagen fibril assembly
Hypermobile	III	AD	*TNX*	Unknown
Vascular	IV	AD	*COL3A1*	Fragility of tissues rich in type III collagen
Kyphoscoliosis	VI	AR	*PLOD1*	Defective collagen cross-linking due to reduced lysyl hydroxylase activity
Arthrochalasia	VII a,b	AD	*COL1A1, COL1A2*	Defective conversion of type I procollagen to collagen (structural defect)
Dermatosparaxis	VII c	AR	pN(I) peptidase	Defective conversion of type I procollagen intermediate to collagen (enzyme defect)

* Heterozygous type V collagen gene defects are dominant while loss-of-function mutations in the tenascin-X gene (*TNX*) are recessive.
AD, autosomal dominant; AR, autosomal recessive.

organization of the extracellular matrices. The major collagens significantly contributing to skin physiology and pathology are presented in Table 3.3. Other collagen types, including types II, IX, X, XI, XIX, XX and XXI, are not discussed in detail because they are not present in the skin to a significant extent or their participation in maintaining skin physiology is unclear.

Type I collagen, the most abundant form, is the predominant collagen in human dermis, accounting for approximately 80% of the total collagen. Type I collagen contains two different kinds of α-chain with an $[\alpha(I)]_2\alpha2(I)$ stoichiometry. A collagen consisting of three identical α1(I) chains has also been identified (so-called α1(I)-trimer), but it appears to be only a minor component of connective tissue in the skin. Type I collagen associates with type III collagen to form broad, extracellular fibres in the human dermis. Mutations in type I and III collagens, or in their processing enzymes, can result in connective tissue abnormalities in the different forms of Ehlers–Danlos syndrome (Table 3.4), and mutations in the type I collagen gene are responsible for the fragility of bones in osteogenesis imperfecta.

Type III collagen accounts for about 10% of the total bulk of collagen found in adult human dermis. It was originally shown to predominate in human skin during embryonic development, but during the early postnatal period, type I collagen synthesis accelerates, resulting in the ratio of type I to type III collagen in the adult human skin being approximately 8:1. Type III collagen is most prominent in vascular connective tissues, the gastrointestinal tract and the uterus. It consists of three identical α-chains, α1(III), and mutations in the type III collagen gene can cause the vascular type of the Ehlers–Danlos syndrome [3,4].

Type IV collagen is a basement membrane collagen present within the dermal–epidermal junction as well as in the vascular basement membranes (Fig. 3.37). The predominant form of type IV collagen in human skin is a heterotrimer of $[\alpha1[IV)]_2\alpha2(IV)$, although occasional homopolymers from these two chains may be assembled. The type IV collagen molecule is characterized by the presence of non-collagenous interruptions within the triple-helical domains, thus conferring flexibility to the molecule. In addition to α1 and α2 chains, four other polypeptides of type IV collagen have been identified [5]. Type IV collagen molecules containing these polypeptides are present primarily in the glomerular basement membranes, and their importance for renal physiology is attested by the fact that mutations in the gene encoding the α5(IV) polypeptide results in Alport syndrome. The α3(IV) chain harbours the epitopes recognized by antibodies in Goodpasture's syndrome, and the α5 chain of type IV collagen has been shown to be a target of circulating autoantibodies in a novel autoimmune disease with subepidermal blisters and renal insufficiency.

Type V collagen consists of interrelated collagens containing four different types of α-chains. Type V collagen is present in most connective tissues, including dermis, where it represents less than 5% of the total collagen. Type V collagen is located on the surface of large collagen fibres in the dermis, and its function is to regulate the lateral growth of these fibres. Thus, in the absence of type V collagen, the collagen fibre diameter is variable and the contour of the individual fibres can appear irregular, some of them having 'flower-like' morphology in cross-section. The importance of type V collagen in contributing to connective tissue stability is attested by the fact that mutations in the type V collagen gene underlie most patients with classic, autosomal dominant forms of Ehlers–Danlos syndrome [6].

Type VI collagen, as originally discovered, consists of three distinct α-chains, α1(VI), α2(VI) and α3(VI), which fold into a relatively short triple-helical domain and contain large globular domains at both ends. More recently, three additional α-chains have been suggested to belong to the type VI family of collagens [7]. Type VI collagen is a relatively minor collagen in human dermis where it assembles into thin microfibrils independent of the broad collagen fibres, which consist primarily of type I and type III collagens. The microfibrillar network has an anchoring function, stabilizing the assembly of collagen fibres as well as basement membranes. Mutations in the three type VI collagen genes can lead to different forms of muscular dystrophy with little effect on the physiology of skin [8].

Type VII collagen, the major if not the exclusive component of anchoring fibrils, consists only of one type of α1 chain, α1(VII). This polypeptide has a characteristic modular structure, with the central collagenous domain being flanked by amino-terminal (NC1) and carboxy-terminal (NC2) collagenous domains with homology to known protein sequences (Fig. 3.48). A large number of genetic mutations have been identified in the *COL7A1* gene, as shown in Fig. 3.48. The mutations above the type VII collagen polypeptide are associated with recessively inherited forms of dystrophic epidermolysis bullosa and are primarily premature termination-causing ones resulting in the synthesis of truncated,

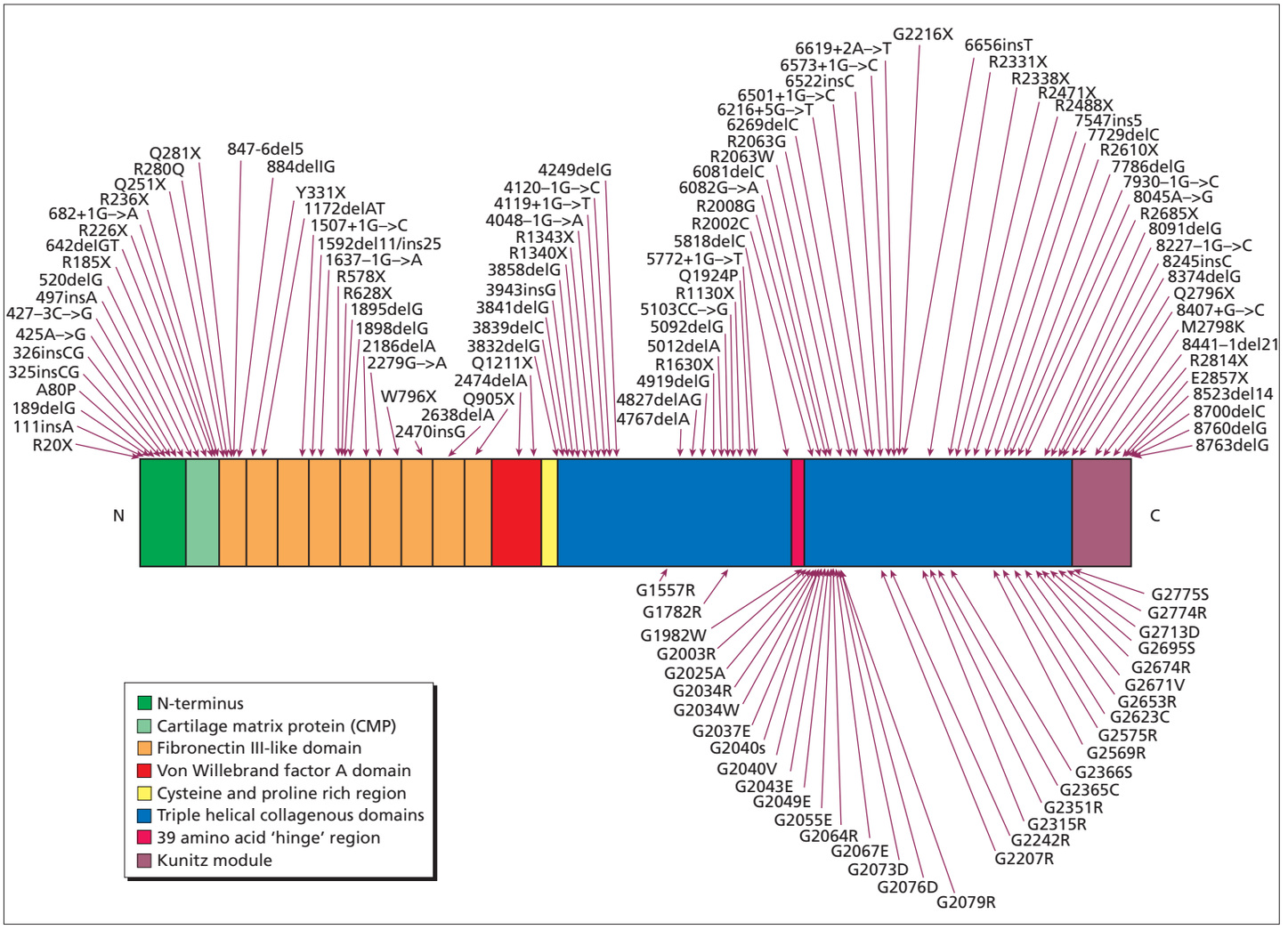


Fig. 3.48 Schematic representation of a type VII collagen monomer with its domain organization and illustration of mutations underlying the dystrophic forms of epidermolysis bullosa. (Adapted from [14].)

and therefore non-functional, polypeptides. The mutations depicted below the polypeptide are missense mutations causing substitutions of critical glycine residues in the triple-helical collagenous domain of the protein and are associated with dominantly inherited forms of epidermolysis bullosa [9].

Type VII collagen molecules become organized into anchoring fibrils through the formation of antiparallel dimers linked through their carboxy-terminal ends (Fig. 3.39). The large amino-terminal, non-collagenous NC1 domains interact with type IV collagen and laminin 332 at the dermal–epidermal basement membrane, forming U-shaped loops that entrap larger fibres in a manner that stabilizes the association of the lower part of the lamina densa to the upper papillary dermis (Fig. 3.46). Consequently, altered expression or changes in the molecular interactions of type VII collagen with other basement membrane components can result in skin fragility as exemplified by the dystrophic forms of epidermolysis bullosa [9]. In addition to the heritable forms of EB, type VII collagen serves as an autoantigen in the autoimmune blistering skin disease EB acquisita, the majority of antigenic epitopes residing within the NC1 domain [10].

Type XVII collagen was initially identified as the 180-kDa bullous pemphigoid antigen (BPAG2) recognized by circulating autoantibodies in the sera of patients with bullous pemphigoid or herpes gestationis. Subsequent characterization of the protein and the corresponding gene has indicated that BPAG2 is, in fact, a collagenous molecule consisting of 15 collagenous domains with characteristic Gly-X-Y repeat sequences which form triple-helices [11] (Fig. 3.49).

Type XVII collagen is a transmembrane protein in type 2 topography, that is the amino-terminal segment of the molecule is intracellular while the carboxy-terminal ectodomain, containing the collagenous segments, is in the extracellular space. The importance of type XVII collagen to the stability of the dermal–epidermal junction is attested to by the fact that mutations in the corresponding gene (*COL17A1*) result in a non-Herlitz variant of junctional EB, originally designated as generalized atrophic benign

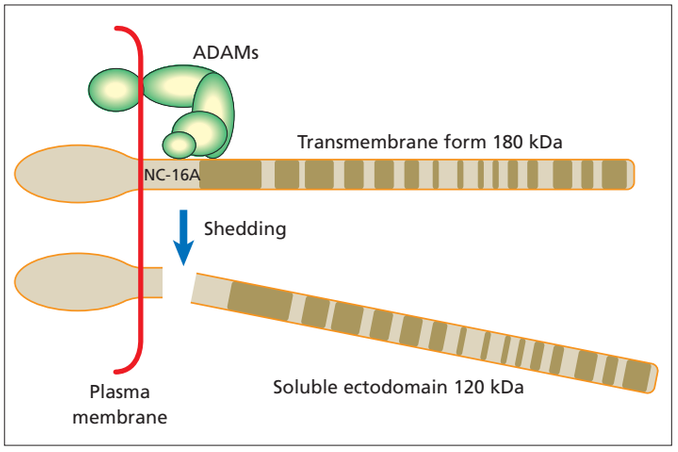


Fig. 3.49 Schematic representation of type XVII collagen, a transmembrane protein in type 2 orientation. Note that the ectodomain traversing the lamina lucida contains 15 distinct triple-helical collagenous segments (COL1–15). The non-collagenous segment between COL15 and the transmembrane domain, NC-16A, harbours the major epitopes recognized by autoantibodies in bullous pemphigoid. ADAMs, a disintegrin and metalloproteinase with thrombospondin motifs cleaves the protein at a sequence in the NC-16A, resulting in release of the ectodomain. (Adapted from [15].)

epidermolysis bullosa (GABEB), and circulating autoantibodies to type XVII collagen (BPAG2) are associated with bullous pemphigoid [12].

Type XXIX collagen is a putative epidermal collagen with a specific gene expression pattern; the highest level of expression is in the skin, lung and the gastrointestinal tract [13]. In the skin, expression is restricted to the epidermis with the highest level in suprabasal layers. This collagen was initially identified through genetic linkage of patients with atopic dermatitis to a locus on the short arm of chromosome 3q21. The locus contained a single gene encoding a collagenous segment flanked by multiple von Willebrand factor-A like domains, with a high degree of homology with the α3 chain of type VI collagen. Immunofluorescence staining of skin from patients with atopic dermatitis demonstrated a striking lack of collagen XXIX in the viable, outermost spinous and granular layers, suggesting a role in atopic dermatitis.

References

1 Myllyharju J, Kivirikko KI. Collagens, modifying enzymes and their mutations in humans, flies and worms. *Trends Genet* 2004; **20**: 33–43.

2 Kuivaniemi H, Tromp G, Prockop DJ *et al*. Mutations in fibrillar collagens (types I, II, III, and XI), fibril-associated collagen (type IX), and network-forming collagen (type X) cause a spectrum of diseases of bone, cartilage, and blood vessels. *Hum Mutat* 1997; **9**: 300–15.

3 Schwarze U, Schievink WI, Petty E *et al*. Haploinsufficiency for one COL3A1 allele of type III procollagen results in a phenotype similar to the vascular form of Ehlers–Danlos syndrome, Ehlers–Danlos syndrome type IV. *Am J Hum Genet* 2001; **69**: 989–1001.

4 Pepin M, Schwarze U, Superti-Furga A *et al*. Clinical and genetic features of Ehlers–Danlos syndrome type IV, the vascular type. *N Engl J Med* 2000; **342**: 673–80.

5 Khoshnoodi J, Pedchenko V, Hudson BG. Mammalian collagen IV. *Microsc Res Tech* 2008; **71**: 357–70.

6 Schwarze U, Atkinson M, Hoffman GG *et al*. Null alleles of the COL5A1 gene of type V collagen are a cause of the classical forms of Ehlers-Danlos syndrome (types I and II). *Am J Hum Genet* 2000; **66**: 1757–65.

7 Fitzgerald J, Rich C, Zhou FH *et al*. Three novel collagen VI chains, α4(VI), α5(VI) and α6(VI). *J Biol Chem* 2008; **283**: 20170–80.

8 Lampe AK, Zou Y, Sudano D *et al*. Exon skipping mutations in collagen VI are common and are predictive for severity and inheritance. *Hum Mutat* 2008; **29**: 809–22.

9 Varki R, Sadowski S, Uitto J *et al*. Epidermolysis bullosa. II. Type VII collagen mutations and phenotype-genotype correlations in the dystrophic subtypes. *J Med Genet* 2007; **44**: 181–92.

10 Remington J, Chen M, Burnett J *et al*. Autoimmunity to type VII collagen: epidermolysis bullosa acquisita. *Curr Dir Autoimmun* 2008; **10**: 195–205.

11 Gatalica B, Pulkkinen L, Li K *et al*. Cloning of the human type XVII collagen gene (COL17A1), and detection of novel mutations in generalized atrophic benign epidermolysis bullosa. *Am J Hum Genet* 1997; **60**: 352–65.

12 Van den Bergh F, Giudice GJ. BP180 (type XVII collagen) and its role in cutaneous biology and disease. *Adv Dermatol* 2003; **19**: 37–71.

13 Söderhäll C, Marenholz I, Kerscher T *et al*. Variants in a novel epidermal collagen gene (COL29A1) are associated with atopic dermatitis. *PLoS Biol* 2007; **5**: e242.

14 Uitto J, Pulkkinen L. The genodermatoses: candidate diseases for gene therapy. *Hum Gene Ther* 2000; **11**: 2267–75.

15 Powell AM, Sakuma-Oyama Y, Oyama M *et al*. Collagen XVII/BP180: a collagenous transmembrane protein and component of the dermoepidermal anchoring complex. *Clin Exp Derm* 2005; **30**: 682–7.

Collagen biosynthesis

The genetically distinct collagens demonstrate considerable tissue specificity, and, accordingly, they are synthesized by a number of different cell types, including dermal fibroblasts, epidermal keratinocytes, vascular endothelial cells and smooth muscle cells. The individual α-chains are initially synthesized as precursor molecules, pro-α-chains, with non-collagenous extensions at the ends of the collagenous domain (Fig. 3.50).

While in the rough endoplasmic reticulum, three individual pro-α-chains assemble into a trimeric molecule through their interactions of the non-collagenous sequences at the carboxy-terminal end. Upon completion of the prolyl hydroxylation reactions, the collagenous domains of the α-chains fold into triple-helical conformations, and the collagen molecules are then secreted through Golgi vesicles into the extracellular milieu. In the extracellular space, parts of the non-collagenous peptide extensions are cleaved by specific proteases, and the collagen molecules then assemble into their tissue-specific supramolecular organization. For example, the fibrillar collagens align into a characteristic quarter-stagger arrangement and form fibres, the growth occurring at the tip of the growing fibre. The coarse collagen fibres in the mid-dermis consist primarily of type I and type III collagens, and type V collagen associates with them on the surface of the fibre so as to regulate the diameter of the growing fibre (Fig. 3.38). Type VII collagen assembles into centrosymmetric anchoring fibrils within the dermal–epidermal basement membrane zone, and type XVII collagen assumes a transmembrane type 2 orientation as a component of the hemidesmosomes (Figs 3.36 and 3.40).

A characteristic feature of collagen is the presence of hydroxyproline and hydroxylysine residues, two amino acids that are post-translationally synthesized by hydroxylation of proline and lysine residues, respectively [1] (Fig. 3.51).

These hydroxylation reactions are catalysed in the rough endoplasmic reticulum by prolyl and lysyl hydroxylases, respectively, enzymes that require ascorbic acid, molecular oxygen and ferrous iron as cofactors. The hydroxylation of prolyl residues is necessary for the stabilization of the triple-helical conformation at physiological temperatures, and hydroxylysyl residues are required for formation of stable covalent crosslinks. Thus, for example, as a

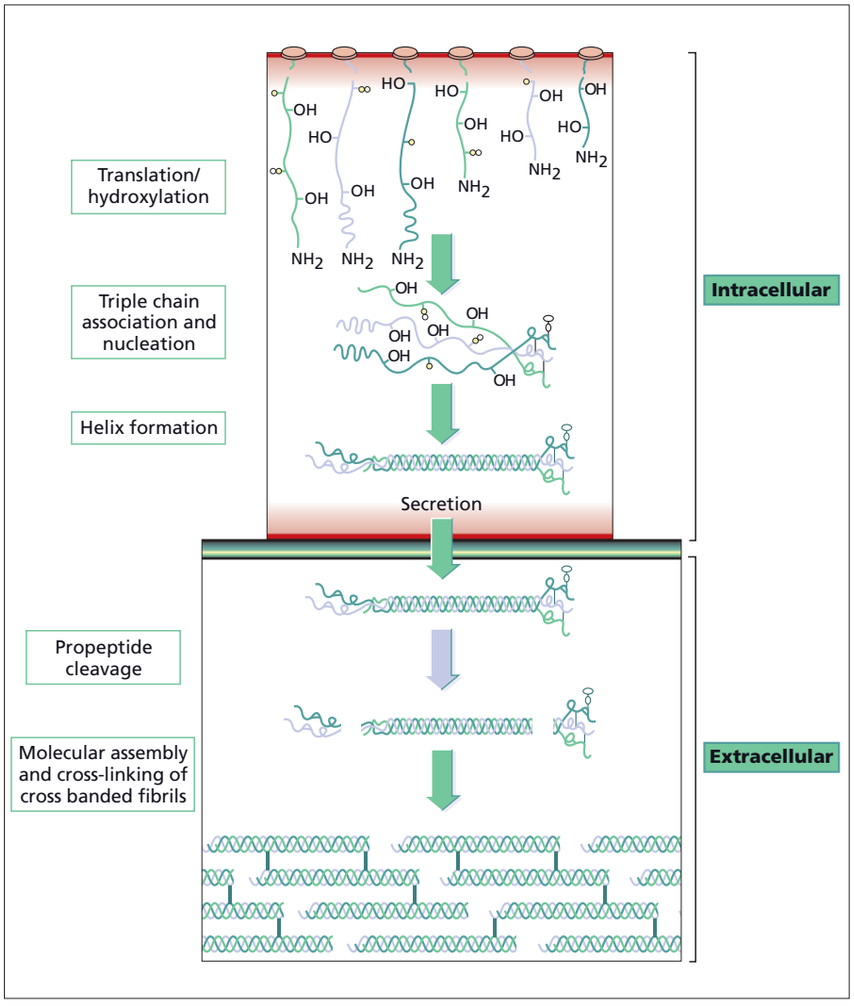


Fig. 3.50 Steps in the intracellular biosynthesis of triple-helical type I procollagen, its secretion into the extracellular space, and assembly and cross-linking of mature collagen fibres in the extracellular space.

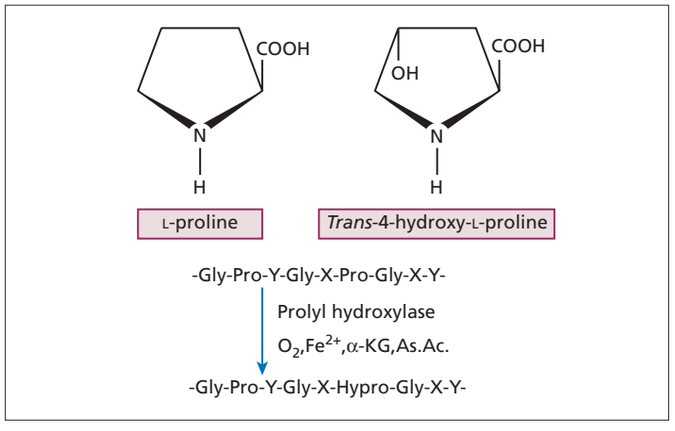


Fig. 3.51 Schematic representation of the enzymatic hydroxylation of prolyl residues in the Y-position of the repeating Gly-X-Y amino acid sequence to form hydroxyproline, an amino acid characteristic of collagen. Note that the reaction requires molecular oxygen, ferrous iron, α-ketoglutarate (α-KG) and ascorbic acid (As.Ac.) as co-factors.

result of ascorbic acid deficiency in scurvy, the hydroxylation reactions are suboptimal, the newly synthesized collagen is poorly functional, and clinically scurvy manifests with connective tissue weakness. Similarly, low oxygen tension in chronic ulcers and wounds due to poor circulation may impair collagen production, resulting in poor healing.

Hydroxylation of the lysyl residues is followed by *O*-glycosylation, catalysed first by galactosyltransferase, which adds a galactosyl residue to the hydroxyl group of hydroxylysine, followed by glucosyltransferase reaction to form glucosyl-galactosyl-hydroxylysine in *O*-glycosidic linkage. Additional glycosylation in *N*-glycosidic linkage will take place on the non-collagenous extensions at the end of the triple-helical molecule, but the functional significance of these glycosylation reactions is currently unclear.

Reference

1 Myllyharju J. Prolyl 4-hydroxylases, key enzymes in the synthesis of collagens and regulation of the response to hypoxia, and their roles as treatment targets. *Ann Med* 2008; **23**: 1–16.

Regulation of collagen gene expression

The regulation of collagen gene expression has to be tightly controlled in order to maintain normal amounts and ratios of genetically distinct collagens under physiological conditions. At the same time, regulatory mechanisms have to be responsive to the needs of rapid collagen synthesis in repair processes, such as wound healing. On the other hand, uncontrolled collagen synthesis can lead to excessive accumulation of collagen in fibrotic diseases, as exemplified by systemic sclerosis, keloids and hypertrophic scars [1,2].

An important control mechanism is at the level of collagen mRNA formation through regulation of the transcriptional activity of the corresponding genes. In general, there is a good correlation between the rate of collagen biosynthesis and the corresponding procollagen mRNA levels, as demonstrated in several *in vitro* models, including cultured fibroblasts. The transcriptional regulation of collagen gene expression involves a number of both *cis*-acting elements and *trans*-acting factors. The *cis*-acting elements, nucleotide sequences within the regulatory regions of the gene that serve as binding sites for *trans*-acting regulatory proteins, have been identified in most collagen gene regulatory regions [2]. Such factors can either up-regulate or suppress the transcriptional promoter activity. An example of such *trans*-acting factors are the retinoic acid nuclear receptors (RAR and RXR) that form a complex with the ligand (a retinoid) which then binds to the retinoic acid-responsive elements (RARE) in the target gene [3]. Retinoids, such as all-*trans*-retinoic acid, have been shown to modulate collagen gene expression both *in vitro* and *in vivo*, and quiescent non-proliferating cells can be stimulated by retinoic acid to activate type I collagen synthesis. These observations may have relevance to the elevated rate of collagen synthesis observed in photodamaged dermis treated by topical application of retinoids [4]. All-*trans*-retinoic acid has also been demonstrated to increase the density of anchoring fibrils along the cutaneous basement membrane zone in adult human skin, suggesting that retinoids are capable of up-regulating type VII collagen gene expression.

Collagen gene expression can also be modulated by a number of cytokines and growth factors, and one of the most powerful modulators of connective tissue gene expression is transforming growth factor-β (TGF-β) [1,5]. In general, TGF-β is pro-fibrotic and it has been shown to up-regulate the expression of a number of extracellular matrix protein genes, including those encoding collagen types I, III, IV, VI and VII. Elevated levels of TGF-β have also been demonstrated in various fibrotic lesions, including the skin in systemic sclerosis and keloids. The up-regulatory activity of TGF-β can be counteracted by other cytokines, including tumour necrosis factor-α and interferon-γ, which antagonize the TGF-β action [1]. These cytokines have been tested for their efficacy for the treatment of keloids and other fibrotic diseases, with variable results.

A number of hormones clearly regulate collagen gene expression, as certain endocrine disorders dramatically change the amount of collagen found in connective tissues, including the skin. Glucocorticosteroids also affect collagen biosynthesis; inhibition is much more pronounced with fluorinated steroids compared to hydrocortisone. The glucocorticosteroid inhibition of collagen biosynthesis occurs in lower concentrations at the transcriptional level through inhibition of the promoter activity. In higher concentrations and with more potent glucocorticosteroids, inhibition of prolyl hydroxylase activity also is evident, leading to deficient hydroxylation of collagen polypeptides and subsequently to reduced amounts of newly synthesized collagen. These mechanisms would explain the connective tissue side effects, such as dermal atrophy, associated with intralesional or prolonged topical application of fluorinated glucocorticosteroids.

References

1 Uitto J, Kouba DJ. Cytokine modulation of extracellular matrix gene expression: relevance to fibrotic skin diseases. *J Dermatol Sci* 2000; **24**: S60.

2 Karsenty G, Park RW. Regulation of type I collagen gene expression. *Int Rev Immunol* 1995; **12**: 177.

3 de Thé H, Vivanco-Ruiz MM, Tiollais P *et al.* Identification of a retinoic acid responsive element in the retinoic acid receptor β gene. *Nature* 1990; **343**: 177–80.

4 Griffiths CE, Russman AN, Majmudar G *et al.* Restoration of collagen formation in photodamaged human skin by tretinoin (retinoic acid). *N Engl J Med* 1993; **329**: 530–5.

5 Roberts AB. The ever-increasing complexity of TGF-β signaling. *Cytokine Growth Factor Rev* 2002; **13**: 3–5.

Collagen cross-linking

The alignment of collagen molecules into their specific supramolecular organization occurs spontaneously, but these fibre structures do not attain the necessary tensile strength until the molecules have been covalently linked together by specific intra- and intermolecular cross-links [1,2]. The most common forms of cross-link in type I collagen are derived from lysine and hydroxylysine residues, and in some collagens there are also cysteine-derived disulphide bonds. The first step in the cross-linking process is enzymatic synthesis of aldehyde residues from lysyl and hydroxylysyl residues by removal of the ε-amino group of these amino acids (Fig. 3.52).

This oxidative deamination reaction is catalysed by lysyl oxidases (LOX), a group of enzymes that require copper as a co-factor. These enzymes act primarily upon native collagen fibrils and poorly, if at all, on denatured collagen (gelatin) or isolated α-chains. Similar deamination reaction catalysed by lysyl oxidase occurs also in elastin.

In addition to the classic human lysyl oxidase, four additional lysyl oxidase-like (LOXL1–4) genes/proteins have been identified. These lysyl oxidase-like enzymes have been postulated to play a role in a number of disease processes. For example, *LOXL1* gene sequence variants confer susceptibility to exfoliation glaucoma and elastin was found to be the major component of the ocular lesions in this disease [3,4]. The expression of lysyl oxidase-like 2 is increased in a number of cancers, and LOXL2 has been shown to be a marker for poor prognosis with decreased overall and disease-free survival in squamous cell carcinomas [5]. LOXL3 and 4 demonstrate structural features similar to LOX and have wide tissue distribution [6,7]. Alterations in lysyl oxidase activities have also been described in a number of experimental systems involving age-related changes in the cardiovascular system [8].

References

1 Rucker RB, Murray J. Cross-linking amino acids in collagen and elastin. *Am J Clin Nutr* 1978; **31**: 1221–36.

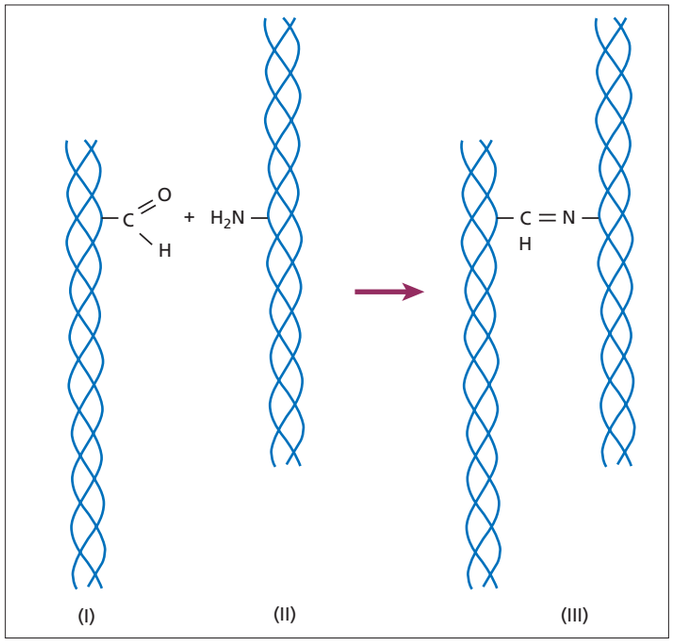


Fig. 3.52 Schematic representation of the formation of intermolecular cross-links between individual collagen molecules. The cross-linking is initiated by conversion of lysine or a hydroxylysine residue that contains an ε-amino group to a corresponding aldehyde (I). The aldehyde then reacts with an unmodified ε-amino group in an adjacent collagen molecule (II) to form a Schiff base-type covalent crosslink (III).

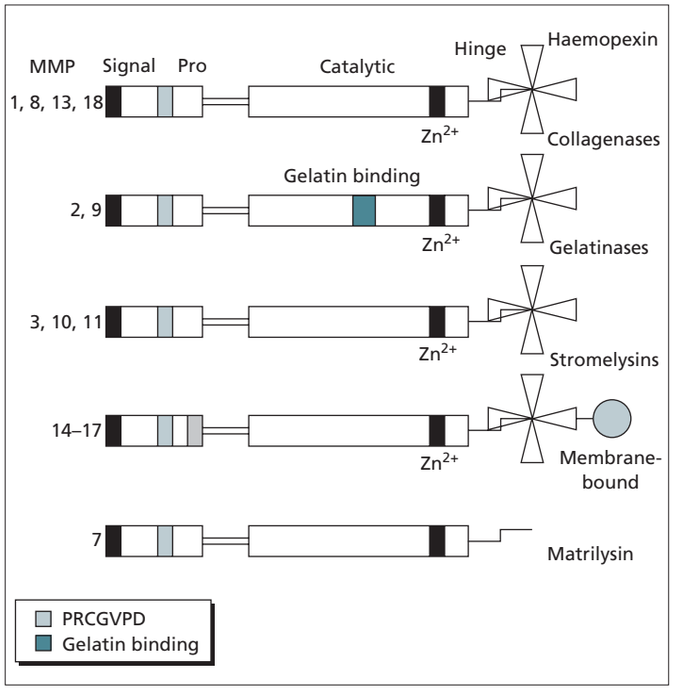


Fig. 3.53 Schematic representation of the structural organization of various matrix metalloproteinases, divided into different subclasses. The signal, propeptide, active catalytic hinge and haemopexin regions are highlighted. Note that MMP-7 lacks the haemopexin region, while MMPs 14–17 harbour membrane-binding sequences at the carboxy-terminal end.

2 Yamauchi M, Shiiba M. Lysine hydroxylation and cross-linking of collagen. *Methods Mol Biol* 2008; **446**: 95–108.
3 Thorleifsson G, Magnusson KP, Sulem P *et al*. Common sequence variants in the LOXL1 gene confer susceptibility to exfoliation glaucoma. *Science* 2007; **317**: 1397–400.
4 Challa P, Schmidt S, Liu Y *et al*. Analysis of LOXL1 polymorphisms in a United States population with pseudoexfoliation glaucoma. *Mol Vis* 2008; **14**: 146–9.
5 Peinado H, Moreno-Bueno G, Haridsson D *et al*. Lysyl oxidase-like 2 as a new poor prognosis marker of squamous cell carcinomas. *Cancer Res* 2008; **68**: 4541–50.
6 Mäki JM, Tikkanen H, Kivirikko KI. Cloning and characterization of a fifth human lysyl oxidase isoenzyme: the third member of the lysyl oxidase-related subfamily with four scavenger receptor cysteine-rich domains. *Matrix Biol* 2001; **20**: 493–6.
7 Kim DJ, Lee DC, Yang SJ *et al*. Lysyl oxidase like 4, a novel target gene of TGF-β1 signaling, can negatively regulate TGF-β1 induced cell motility in PLC/PRF/5 hepatoma cells. *Biochem Biophys Res Commun* 2008; **373**: 521–7.
8 Pascual G, Mendieta C, Mecham RP *et al*. Down-regulation of lysyl oxidase-like in aging and venous insufficiency. *Histol Histopathol* 2008; **23**: 179–86.

Collagen degradation

Collagen fibres, once fully matured by the cross-linking processes, are relatively stable and can exist in tissues under normal physiological conditions for long periods. However, there is continuous, yet slow, degradation and turnover of collagen in normal situations, as attested by continuous urinary excretion of hydroxyproline as a marker of collagen degradation. In addition, in certain physiological situations, as exemplified by reabsorption of the postpartum uterus, and in pathological conditions, such as tissue invasion and tumour metastases, degradation of connective tissues and particularly collagen is accelerated. There are a number of enzymes that comprise the family of matrix metalloproteinases (MMP), enzymes capable of degrading the extracellular matrix components. These proteinase families include the collagenases, gelatinases, stromelysins, matrilysins and the membrane-type MMPs [1–3] (Fig. 3.53).

Native collagen is resistant to nonspecific proteolytic degradation in physiological situations due to the fact that the triple-helical conformation is not readily degradable by general proteases. However, collagenases have the ability to degrade collagen triple-helix at physiological pH and temperature. The vertebrate collagenase was initially isolated from tadpole tails which, when cultured upon reconstituted type I native collagen substrate, exercise proteolytic activity, and similar techniques were subsequently employed to demonstrate the presence of collagenase in human skin. Interstitial collagenase (MMP1) was initially shown to be synthesized as a proenzyme by cultured fibroblasts, and later on, different cell types, including epidermal keratinocytes, were shown to express a similar or identical enzyme. The ability of interstitial collagenase to digest the type I collagen triple helix is based on its ability to specifically cleave the α1(I) chain at a particular glycine-isoleucine, or α2(I) chain at a glycine-leucine peptide bond. This initial cleavage results in two degradation products, three-quarters and one-quarter of the size of the original collagen molecule. These shortened triple-helical fragments have a lower helix-to-coil transition temperature (Tm) than the full-length molecule, and subsequently at temperatures below 37°C the triple-helix unravels, rendering the individual polypeptides susceptible to general proteolytic degradation. It should be noted that type I collagen has several additional glycine-isoleucine and glycine-leucine sequences, but these are not susceptible to

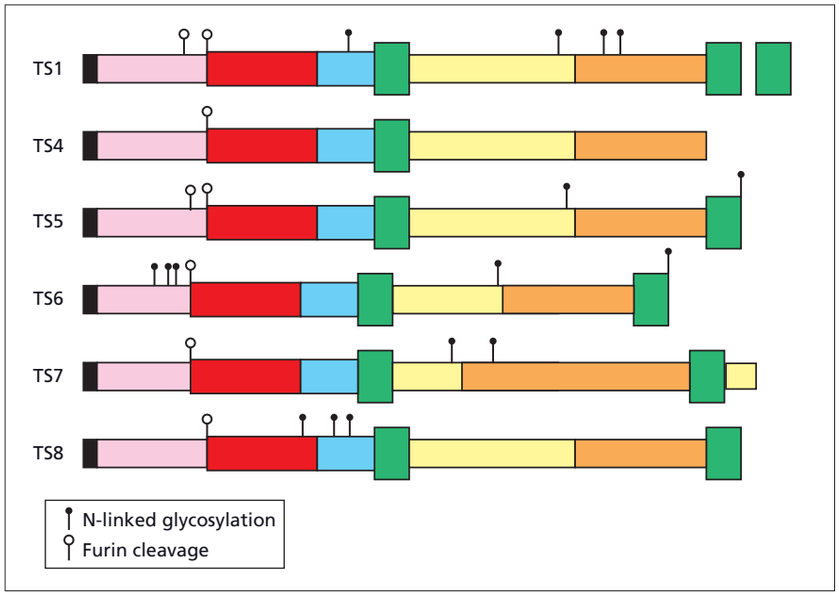


Fig. 3.54 Schematic representation of the main organization of various ADAMTS family metalloproteinases. The catalytic domain is shown in red, while other domains include the thrombospondin type I repeat sequences (green), disintegrin-like domain (blue), and cysteine domain (yellow). The signal peptidase is shown in black, the propeptide sequence is coloured pink, and the spacer domain is in orange.

collagenase degradation in this collagen when in the native triple-helical conformation. A similar enzyme (MMP8) has been identified in human neutrophils with comparable degrading characteristics. The neutrophil collagenase is stored in neutrophil granules and released upon stimulation. MMP1 and MMP8 can, in addition to type I collagen, degrade a number of other collagens, including types III and VII.

Another group of extracellular proteolytic enzymes is the gelatinases, which are able to degrade denatured collagen (gelatin) but can also cleave certain native collagens, such as types IV, V and VII, with certain interruptions or imperfections in their collagenous triple helices, thus allowing the proteolytic cleavage at these sites. The basement membrane collagen IV can also be degraded by MMP3 (stromelysin-1) and MMP10 (stromelysin-2).

In general, MMPs are synthesized and secreted as inactive proenzymes, which become activated proteolytically by removal of the propeptide. The MMPs are zinc metalloenzymes and require calcium for their activity. Consequently, the enzymes can be inhibited by chelators of divalent cations, and, pharmacologically, tetracyclines have been suggested to inhibit MMP proteolytic activity due to their ability to bind calcium. The MMPs also have specific, small molecular weight peptide inhibitors, so-called tissue inhibitors of metalloproteinases (TIMPs). These proteins stoichiometrically complex with MMPs preventing the degradative events.

In normal human skin, a number of MMPs are synthesized and secreted by fibroblasts and keratinocytes. The expression of these enzymes is activated in various pathological situations, including invasion and metastasis of cutaneous malignancies, as well as during dermal wound healing and epidermal regeneration [2,4]. Finally, proteolytic enzymes play a pathophysiological role in tissue separation in a number of blistering diseases, such as bullous pemphigoid, dermatitis herpetiformis and epidermolysis bullosa acquisita [5].

Another metalloproteinase family has been designated as ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs). The prototype, *ADAMTS-1* gene can be induced by interleukin-1 *in vitro* or by lipopolysaccharide injection in mice, and, thus, this metalloproteinase was initially associated with inflammatory processes [6]. Subsequently, a number of ADAMTS genes have been identified with similar domain organizations, consisting of a signal sequence, a propeptide, a metalloproteinase domain, a disintegrin-like domain, a cysteine-rich region and a variable number of thrombospondin type-1 molecules [7] (Fig. 3.54). These molecules are zinc-dependent proteases with a high level of expression in fetal tissues. ADAMTS proteases also have high levels of expression in tumour cells and tissues, including melanoma and colon carcinoma. Of particular interest in the context of collagen processing is ADAMTS-2, which serves as procollagen I/II amino-propeptide processing enzyme.

Regulation of extracellular matrix turnover and collagen degradation during postpartum involution of the uterus has been attributed to relaxin, a hormone initially implicated in pregnancy-related conditions. More recently, it has become clear that a number of tissues, including skin, can serve as targets of relaxin. These tissues contain a relaxin family peptide receptor-1 (RFPR1) which mediates the relaxin effects on connective tissue metabolism, contributing to the maintenance of tissue homeostasis. The critical role of relaxin and its receptor has been illustrated by targeted mutant mice in which the absence of relaxin leads to collagen accumulation in a number of tissues, similar to systemic sclerosis [8,9].

References

1 Nagase H, Woessner JF Jr. Matrix metalloproteinases. *J Biol Chem* 1999; **274**: 21491–4.

2 Lemaitre V, D'Armiento J. Matrix metalloproteinases in development and disease. *Birth Defects Res C Embryo Today* 2006; **78**: 1–10.

3 Flannery CR. MMPs and ADAMTSs: functional studies. *Front Biosci* 2006; **11**: 544–69.

4 Pirilä E, Korpi JT, Korkiamäki T *et al*. Collagenase-2 (MMP-8) and matrilysin-2 (MMP-26) expression in human wounds of different etiologies. *Wound Repair Regen* 2007; **15**: 47–57.

5 Shimanovich I, Mihai S, Oostingh GJ *et al*. Granulocyte-derived elastase and gelatinase B are required for dermal-epidermal separation induced by autoantibodies from patients with epidermolysis bullosa acquisita and bullous pemphigoid. *J Pathol* 2004; **204**: 519–27.
6 Kuno K, Kanada N, Nakashima E *et al*. Molecular cloning of a gene encoding a new type of metalloproteinase-disintegrin family protein with thrombospondin motifs as an inflammation associated gene. *J Biol Chem* 1997; **272**: 556–62.
7 Cal S, Obaya AJ, Lamazares M *et al*. Cloning, expression analysis, and structural characterization of seven novel human ADAMTSs, a family of metalloproteinases with disintegrin and thrombospondin-1 domain. *Gene* 2002; **283**: 49–62.
8 Samuel CS, Lekgabe ED, Mookerjee I. The effects of relaxin on extracellular matrix remodeling in health and fibrotic diseases. *Adv Exp Med Biol* 2007; **612**: 88–103.
9 Samuel CS, Zhao C, Bathgate RA *et al*. The relaxin gene-knockout mouse: a model of progressive fibrosis. *Ann NY Acad Sci* 2005; **1041**: 173–81.

Elastic fibres

An integral component of the dermal connective tissue is the elastic fibre network which provides resilience and elasticity to the skin. Elastic fibres are a relatively minor component in normal sun-protected adult skin, being less than 2–4% of the total dry weight of the dermis. The elastic fibre system in the reticular dermis consists of horizontally oriented fibres which interconnect to provide a network structure. Extending from these horizontal fibres is a network of vertical extensions of relatively fine fibrils, which consist either of bundles of microfibrils (oxytalan fibers) or of small amounts of cross-linked elastin (elaunin fibres) (Fig. 3.55).

Elastic fibres have two principal components: (a) elastin, a well-characterized connective tissue protein which forms the core of the mature fibres; and (b) the elastin-associated microfibrils which consist of a family of proteins, some of them less defined [1–3]. Examination of mature elastic fibres by transmission electron microscopy reveals an electron-lucent core which consists of elastin (Fig. 3.56). Surrounding the elastin core are distinct microfibrillar structures, which appear electron-dense under routine electron microscopy staining. While elastin is the major component and the microfibrils are less conspicuous in fully mature elastic fibres, the relative proportion of these two components varies during the embryonic development of elastic fibres and/or connective tissue repair. The first elements of elastic fibres that form consist of bundles of microfibrils, which can be visualized by electron microscopy during the first trimester of gestation. These microfibrils form a scaffold, allowing alignment of the elastin molecules in parallel array so as to guide the growth of fibres with relatively uniform diameters [4]. During the second trimester of fetal development the elastic fibres remain immature, but with increasing fetal age maturation of the fibres occurs and the elastin component becomes more prominent. In fully developed elastic fibres, well over 90% of the total content is elastin with relatively few microfibrillar components, mostly confined to the outer surface of the fibres.

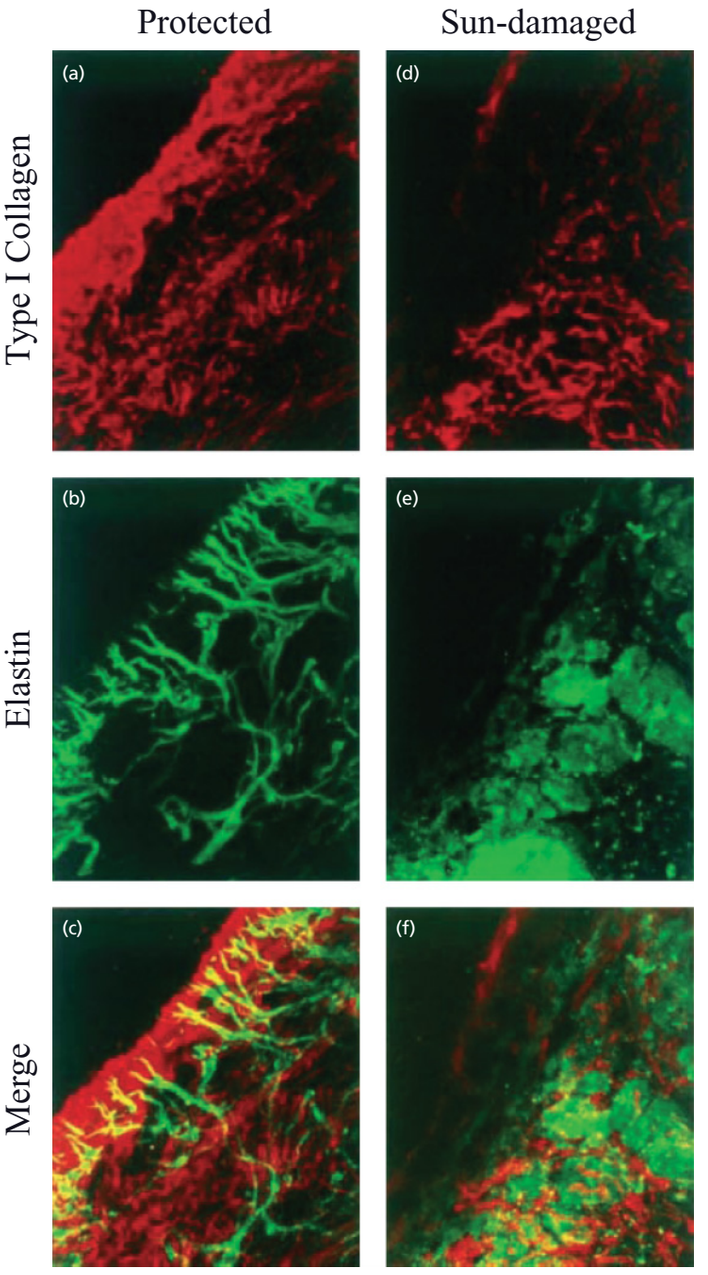


Fig. 3.55 Immunofluorescence staining of type I collagen (a,d) and the elastic fibre network (b,e) in the dermis of human skin visualized by confocal laser scanning microscopy. Merging of the images (c,f) reveals that the elastic fibres assume a horizontal orientation in the mid-dermis while vertical extensions (oxytalan and elaunin fibres) reach the upper dermis, terminating just below the dermal–epidermal junction. Note that in sun-damaged skin there is a dramatic decrease and disorganization of both collagen and elastic fibres in comparison with sun-protected skin. (Adapted from [5].)

References

1 Midwood KS, Schwarzbauer JE. Elastic fibers: building bridges between cells and their matrix. *Curr Biol* 2002; **12**: R279.
2 Kielty CM. Elastic fibres in health and disease. *Expert Rev Mol Med* 2006; **8**: 1–23.
3 Rosenbloom J, Abrams WR. Elastin and the microfibrillar apparatus. In: Boyce RM, Steinmann B, eds. *Connective Tissue and its Heritable Disorders*, 2nd edn. New York: Wiley-Liss, 2002: 249–69.
4 Kozel BA, Ciliberto CH, Mecham RP. Deposition of tropoelastin into the extracellular matrix requires a competent elastic fiber scaffold but not live cells. *Matrix Biol* 2004; **23**: 23–34.
5 Uitto J, Bernstein EF. Molecular mechanisms of cutaneous aging: connective tissue alterations in the dermis. *J Invest Dermatol Symp Prog* 1998; **1**: 41–4.

Elastin

Elastin is initially synthesized as a precursor polypeptide, 'tropoelastin', which consists of approximately 700 amino acids with a molecular mass of approximately 70 kDa [1]. The amino acid composition of tropoelastin is similar to collagen, in that about one-third of the total amino residues consist of glycine. However, glycine is not evenly distributed in elastin in every third position as it is in a typical collagenous sequence. Instead, the tropoelastin primary sequence shows domains rich in glycine, valine and proline, alternating with lysine and alanine-rich sequences. A characteristic sequence motif in the latter setting is the presence of two lysine residues separated by two or three alanine residues (Fig. 3.57).

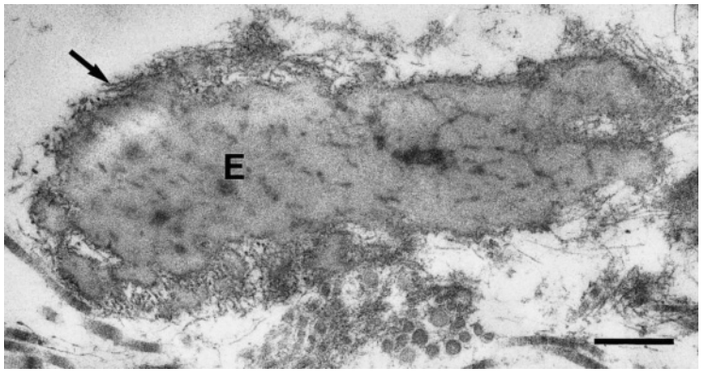


Fig. 3.56 Transmission electron microscopy of an elastic fibre in the reticular dermis. The central electron-pale core consists of elastin (E), while the electron dense areas represent the elastin-associated microfibrillar proteins which are particularly evident at the periphery of the fibre (arrow). Scale bar, 0.5 µm.

The lysine residues in tropoelastin are critical for formation of covalent cross-links, desmosine and its isomer, isodesmosine, that are unique to elastin. The first step in formation of these elastin-specific cross-links is oxidative deamination of three lysine residues to form corresponding aldehydes, so-called allysines. Three of these resulting aldehydes, together with a fourth lysine residue containing the intact unmodified ε-amino group, spontaneously fuse to form a stable desmosine compound which covalently links two of the tropoelastin polypeptides. Addition of desmosines to other parts of the molecule progressively converts tropoelastin molecules into an insoluble fibrous structure which can be stretched, but upon release the fibres recoil providing resilience and elasticity to the skin (Fig. 3.58). The content of desmosine in various elastin preparations is fairly constant, with approximately 1.5 residues per 1000 amino acids, and desmosine or isodesmosine

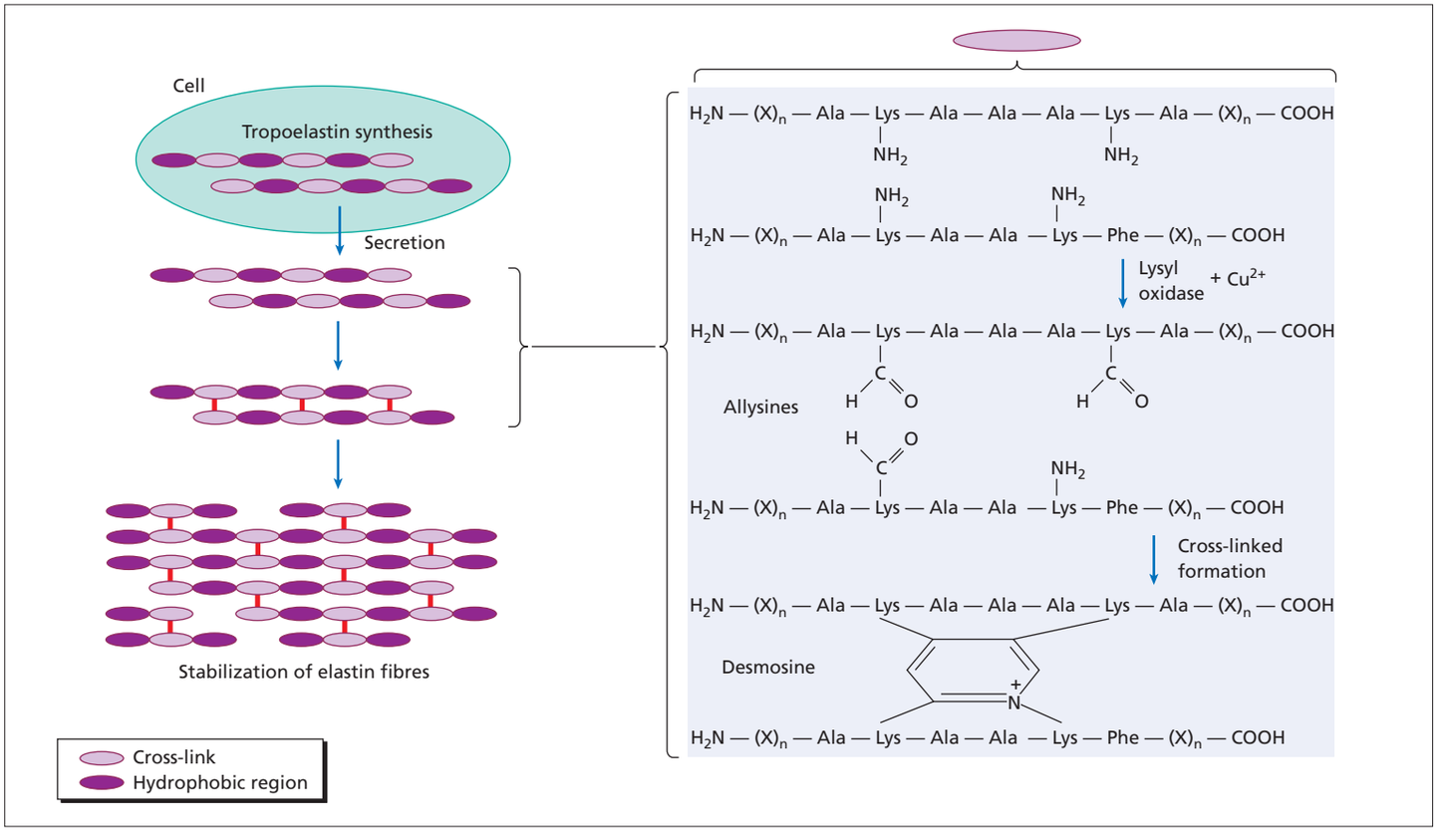


Fig. 3.57 Assembly and cross-linking of elastic fibres. Newly-synthesized elastin precursor polypeptides, tropoelastins, with alternating hydrophobic and cross-link regions are secreted into the extracellular milieu. Lysine residues in characteristic lys-ala-ala-lys or lys-ala-ala-ala-lys sequences in the cross-link region undergo oxidative deamination of the ε-amino groups catalysed by lysyl oxidase, an enzyme requiring copper as co-factor. Three resulting allysine residues fuse with an unmodified lysine residue to form desmosines, elastin-specific cross-link molecules. (Modified from [6].)

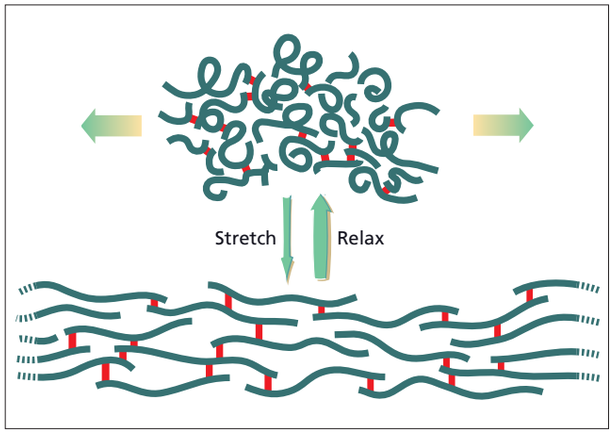


Fig. 3.58 Schematic representation of elastic fibres cross-linked by desmosines (red). In relaxed state, the fibres assume coiled-coil conformations. When the fibres are stretched and then released, they return to relaxed state, the contraction providing elasticity and resilience to the skin.

can therefore provide a quantitative measure of the insoluble elastin content in tissues.

The human elastin gene spans approximately 45 kb of genomic DNA on chromosome 7 and consists of 34 exons corresponding to 3.5 kb of human elastin mRNA sequences. Examination of the gene structure reveals that the alternating cross-link domains, characterized by presence of lysyl residues separated by two or three alanines, and the hydrophobic domains, are encoded by individual exons. The elastin mRNAs are synthesized in a number of cell types present in elastin-rich tissues, as for example, the vascular smooth muscle cells in arterial connective tissues. In the skin, the primary cell type responsible for elastin production appears to be the fibroblast which, under tissue culture conditions, expresses the elastin gene. Keratinocytes have also been suggested to express the elastin gene, but the level of expression is very low in comparison to dermal fibroblasts and the potential significance of elastin in the epidermis remains unclear.

Primary mutations in the elastin gene have been demonstrated in cutis laxa, a group of diseases that manifest with loss or fragmentation of elastic fibres [2]. It should be noted, however, that this group of heritable diseases is highly heterogeneous, and mutations in the fibulin-4 and fibulin-5 genes have also been observed. Williams syndrome is a contiguous gene deletion syndrome that also involves the elastin gene, with clinical manifestations predominantly in the cardiovascular system [3]. Finally, cutis laxa can develop as a post-inflammatory condition, probably mediated by proteolytic enzymes released from the inflammatory cells [4].

An interesting observation during the processing of elastin mRNA precursor molecules is that they undergo extensive alternative splicing, leading to formation of elastin molecules of varying primary sequences. In fact, at least six exons in the human elastin gene have been reported to be subject to alternative splicing, and this mechanism can provide significant variation in the primary sequence composition of elastin polypeptides, leading to different types of elastic fibres in different tissues. However, the physiological significance of the alternative splicing has not been established.

The oxidative deamination of lysyl residues to corresponding aldehydes is catalysed by a group of enzymes, lysyl oxidases, which require copper for their activity. Thus, copper deficiency can lead to reduced lysyl oxidase activity and synthesis of elastic fibres that are not stabilized by sufficient amounts of desmosines. In such a situation, the individual tropoelastin polypeptides remain soluble and susceptible to non-specific proteolysis, and the elastin-rich tissues are fragile. Clinical manifestations of copper deficiency can vary depending on the level of copper and its circulating transport protein, caeruloplasmin, as manifested by Menkes' syndrome and the occipital horn syndrome, two conditions allelic due to mutations in the copper transporter protein gene, *ATP7A* [5]. Copper deficiency can also occur in patients undergoing long-term treatment with high doses of D-penicillamine, a copper chelating agent, which can result in abnormalities in the elastic structures in the skin and other tissues.

The metabolic turnover of elastin is slow, but a portion of elastin in the body is continuously degraded as reflected by the continuous presence of desmosines in the urine. Thus, there may be an ongoing turnover and repair of elastic fibres in normal tissues. In addition, there are a number of pathological conditions in which degradation of elastin is the histopathologic hallmark, such as some forms of cutis laxa and cutaneous ageing. Elastic fibres are degraded by elastases, a group of elastolytic enzymes in different tissues and with different cleavage specificities [4]. The classic elastases, such as those originally isolated from the pancreas, are serine-proteases, and their activity can be inhibited by serum factors, such as α1-antitrypsin and α2-macroglobulin. In addition to these classic serine-elastases, there are a number of metalloenzymes that are capable of degrading elastic structures, particularly the microfibrillar components. These metalloelastases are present in the skin and originate from fibroblasts and monocyte-macrophages.

References

1 Wise SG, Weiss AS. Tropoelastin. *Int J Biochem Cell Biol* 2009; **41**: 494–7.
2 Kielty CM. Elastic fibres in health and disease. *Expert Rev Mol Med* 2006; **8**: 1–23.
3 Pober BR, Johnson M, Urban Z. Mechanisms and treatment of cardiovascular disease in Williams–Beuren syndrome. *J Clin Invest* 2008; **118**: 1606–15.
4 Antonicellil F, Bellon G, Debelle L *et al*. Elastin-elastases and inflamm-aging. *Curr Top Dev Biol* 2007; **79**: 99–155.
5 Kaler SG, Holmes CS, Goldstein DS *et al*. Neonatal diagnosis and treatment of Menkes disease. *N Eng J Med* 2008; **358**: 605–14.
6 Mahoney MG, Brennan D, Starcher B *et al*. Extracellular matrix in cutaneous aging: the effects of 0.1% copper-zinc malonate-containing cream on elastin biosynthesis. *Exp Dermatol* 2009; **18**: 205–11.

Elastin-associated microfibrils

The elastin-associated microfibrils consist of tubular structures of approximately 10–12 nm in diameter. Both ultrastructural evidence and biochemical analyses have confirmed that the microfibrils differ from elastin, and they may also be found in a number of tissues as individual microfibrillar structures without direct association with elastin. It is now known that the elastin-associated microfibrils consist of a number of proteins, which can be divided into several different categories based on their molecu-

lar characteristics [1]. Many of them form gene families with closely related structure and function, but clearly different from other groups in their structural features.

One of the microfibrillar protein families is the fibrillins, which are a critical part of the microfibrillar structure [2]. Two distinct, yet closely homologous, human genes encode fibrillin 1 (FBN1) and fibrillin-2 (FBN2), proteins characterized by multiple repeats of sequence motifs previously observed in the epidermal growth factor (EGF) precursor molecule, with each motif having six conserved cysteine residues. Electron microscopy has established that monomeric fibrillin molecules synthesized by fibroblasts show an extended flexible molecule, which is approximately 148 nm long and 2.2 nm wide. Multiple fibrillin molecules can then align in a parallel, head-to-tail fashion to form microfibrils associated with elastin in tissues, such as skin and the arterial connective tissues. It should be noted that fibrillin is also a major component of microfibrils in tissues such as the ocular ciliary zonule and the periodontal ligament, without microscopic or immunoreactive evidence of elastin. The importance of fibrillin 1 is illustrated by the fact that the mutations in the corresponding gene (*FBN1*) underlie Marfan's syndrome, manifesting with skeletal abnormalities, aortic dilatations, subluxation of the lens and cutaneous laxity [3]. Fibrillin 2 (*FBN2*) mutations cause congenital contractural arachnodactyly with some similarities, but also differences, to Marfan's syndrome.

The latent transforming growth factor-β binding family of proteins (LTBP) has some structural similarities with the fibrillins, including repeating EGF-like domains [4]. Transforming growth factor-β, a pro-fibrotic cytokine, is secreted as a latent complex bound to LTBP. There are at least four distinct proteins in the family, with a molecular weight ranging from 125 to 310 kD. One of the putative functions of LTBPs is to facilitate the secretion of TGF-β or binding of the inactive complex to the cell surface where activation takes place. However, LTBPs have also been found as free proteins associated with components of the extracellular matrix. LTBP1, a prototype of this subfamily of elastin-associated microfibrillar proteins, is clearly a component of the elastic fibres in human skin, and its levels are altered in solar elastosis.

Another family of the elastin-associated microfibrillar proteins consists of fibulins, extracellular matrix glycoproteins with characteristic calcium binding EGF-like domains. Five distinct fibulins have been characterized (fibulins 1–5; FBLN1–5), and at least four of them have been located within the elastic fibres in different tissues [5]. In addition, FBLN-5 has been shown to bind both muscle cells and elastin, thus apparently facilitating cell-matrix interactions. The importance of FBLN-4 and FBLN-5 in skin physiology is attested by demonstration of mutations in the corresponding genes in patients with cutis laxa, manifesting with loose and sagging skin and loss of recoil [6–8].

In addition to fibrillins, LTBPs and fibulins, a number of other proteins have been shown to be associated with elastic fibres in the microfibrillar network. Several of these proteins belong to the families of microfibril-associated glycoproteins (MAGP) or microfibril-associated proteins (MFAP), highly acidic, relatively small molecules, some of which have been characterized in detail [1]. In addition, interface proteins, so called emilins, as well as lysyl oxidases critical for the crosslinking and stabilization of elastic fibre structures, have been shown to be associated with elastic fibres [9,10].

References

1 Rosenbloom J, Abrams WR. Elastin and the microfibrillar apparatus. In: Boyce RM, Steinmann B, eds. *Connective Tissue and its Heritable Disorders*, 2nd edn. New York: Wiley-Liss, 2002: 249–69.

2 Ramirez F, Sakai LY, Dietz HC, Rifkin DB. Fibrillin microfibrils: multipurpose extracellular networks in organismal physiology. *Physiol Genomics* 2004; **19**: 151–4.

3 Robinson PN, Arteaga-Solis E, Baldock C *et al*. The molecular genetics of Marfan syndrome and related disorders. *J Med Genet* 2006; **43**: 769–87.

4 Hirai M, Horiguchi M, Ohbayashi T *et al*. Latent TGF-β-binding protein 2 binds to DANCE/fibulin-5 and regulates elastic fiber assembly. *EMBO J* 2007; **26**: 3283–95.

5 Chu ML, Tsuda T. Fibulins in development and heritable disease. *Birth Defects Res C Embryo Today* 2004; **72**: 25–36.

6 Hucthagowder V, Sausgruber N, Kim KH *et al*. Fibulin-4: a novel gene for an autosomal recessive cutis laxa syndrome. *Am J Hum Genet* 2006; **78**: 1075–80.

7 Markova D, Zou Y, Ringpfeil F *et al*. Genetic heterogeneity of cutis laxa: a heterozygous tandem duplication within the fibulin-5 (FBLN5) gene. *Am J Human Genet* 2003; **72**: 998–1004.

8 Hu Q, Loeys BL, Coucke PJ *et al*. Fibulin-5 mutations: mechanisms of impaired elastic fiber formation in recessive cutis laxa. *Hum Mol Genet* 2006; **15**: 3379–86.

9 Bressan GM, Daga-Gordini D, Colombatti A *et al*. Emilin, a component of elastic fibers preferentially located at the elastin-microfibrils interface. *J Cell Biol* 1993; **121**: 201–12.

10 Verdone G, Doliana R, Corazza A *et al*. The solution structure of EMILIN1 globular C1q domain reveals a disordered insertion necessary for interaction with the α4β1 integrin. *J Biol Chem* 2008; **283**: 18947–56.

Proteoglycan/glycosaminoglycan macromolecules

Proteoglycans form a number of subfamilies defined by a core protein to which polymers of unbranched disaccharide units, glycosaminoglycans (GAG), are linked by an O-linkage to serine residues (Fig. 3.59). There are a number of distinct core proteins, the number of attached disaccharides varies, and the molecular mass of GAGs is highly variable. Commensurate with variability in structure, different proteoglycans are of different functional importance as critical components of cell membranes and the extracellular matrix of the skin during development, homeostasis and disease [1].

GAGs are highly charged polyanionic molecules which attach to the core protein. The characteristic feature of GAGs is their primary structure, consisting of alternating pairs of different monosaccharides, glucose or galactose, joined in 1-3 or 1-4 linkage (Fig. 3.60). After the initial synthesis of GAGs, the polymers undergo complex post-assembly modifications catalysed by specific enzymes. Sulphatases catalyse replacement of *N*-acetyl by *N*-sulphate and epimerases convert D-glucuronic to L-iduronic acid. The linear GAG chains, consisting of linked disaccharide units, are highly variable in size, ranging from just a few to several thousands and, consequently, the molecular mass of naturally occurring GAGs can range from 5×10^3 to 5×10^7 Daltons.

The degree of post-assembly modifications is highly variable, and the control of this reaction depends on the specific characteristics of the GAGs, the associated core protein as well as the cell type and tissue environment (Fig. 3.61). The simplest GAG, hyaluronic acid, is not sulphated, while other GAGs show sulphation of varying degrees. Within the individual GAG chains, there are regions that show either low or high degree of sulphation, a

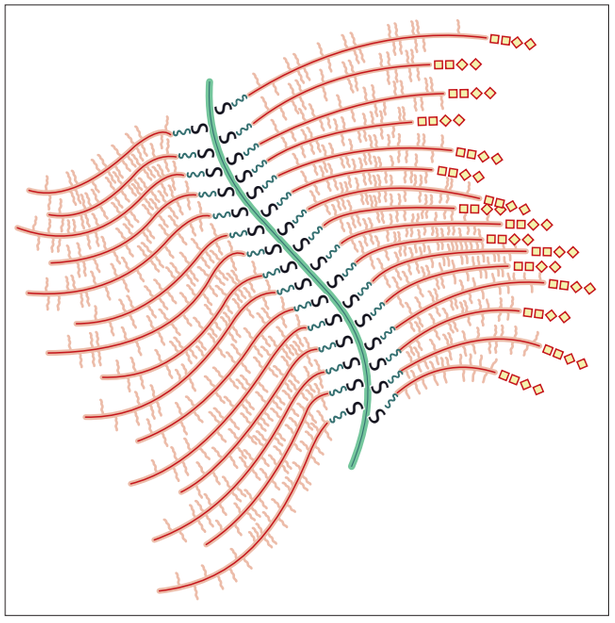


Fig. 3.59 Representation of a prototypic proteoglycan in which the central core (green) is hyaluronic and the link proteins are represented by S-shapes, joining the protein side-chains and carbohydrate polymers. (Adapted from [9].)

feature that may facilitate interactions of proteoglycans and GAGs with their numerous binding partners.

The core proteins of proteoglycans have been increasingly characterized through cloning and sequencing of the corresponding genes. These genes are expressed in a number of different types of cells, including dermal fibroblasts which are the principal cell type for proteoglycan synthesis in the dermis. Newly synthesized core protein polypeptides are transferred to Golgi vesicles where the attachment of GAG chains occurs. The final product, consisting of a core protein with attached GAG chains, allows classification of the proteoglycans. It should be noted that hyaluronic acid is a GAG produced without synthesis of a core protein; instead, this macromolecule is synthesized by a complex of enzymes at the plasma membrane, with subsequent extrusion into the extracellular space.

Known core proteins with their predominant tissue distribution and associated GAG components are listed in Table 3.5. The core proteins can be intracellular, reside on the cell surface or be part of the extracellular matrix. For example, serglycin shows an intracellular core protein present in secretory granules of haematopoietic cells, such as mast cells and eosinophils, associated with either heparan sulphate or chondroitin sulphate GAGs. This proteoglycan is found in the skin in areas infiltrated by mast cells or eosinophils, and, on subsequent release, serglycin is a major form of highly sulphated heparan sulphate GAG in the skin.

There are a number of cell-surface proteoglycans which function at the interface between the plasma membranes and the extracellular matrix. The mode of attachment to the cell surface is variable. For example, the glypican family of proteoglycans is attached to the cell surface by a phospholipid anchor, while the syndecans have membrane-spanning core proteins. Syndecans and glypicans are present in a number of cells and tissues, including abundant expression in the skin. Syndecan expression varies during development and maturation of tissues, and, for example, syndecan-1 is particularly abundant in keratinocytes. The nature of the attached GAG chains, however, changes as keratinocytes differentiate. Syndecans-1 and 4 are also induced in the dermis and granulation tissue, and it has been shown that deletion of syndecan-4 from mice greatly decreases the rate of wound repair. Furthermore, there are alterations in syndecan-1 expression as a result of malignant transformation [2–4].

The extracellular matrix contains a number of different proteoglycans as an integral component of the connective tissue meshwork. In the dermis, fibroblasts produce large proteoglycans, as exemplified by versican, consisting of a core protein with attachment sites for 12 to 15 GAG side chains (Fig. 3.62). The GAGs in versican are primarily chondroitin sulphate or dermatan sulphate, but versican can also bind hyaluronic acid, resulting in formation of large aggregates. In the skin, versican has been identified in the dermis and epidermis as a product of fibroblasts and keratinocytes, respectively.

Extracellular matrix contains a number of small proteoglycans, exemplified by the family of leucine-rich repeat motifs. The prototype of this family is decorin, abundantly present in the skin. The decorin core protein is relatively small in size and has a single dermatan sulphate side chain covalently bound to a serine residue at the amino acid position 4 of the core protein. This proteoglycan was designated 'decorin' due to the observation that it associates with collagen and 'decorates' the fibres *in vivo*. This binding is attributed to the availability of decorin core protein to bind type I collagen, but the single GAG chain of decorin also binds to tenascin-X, another extracellular component with affinity for collagen fibrils. Consequently, these interactions contribute to the connective tissue organization and architecture with functional consequences for normal skin physiology [4,5].

Proteoglycan/GAG complexes have a multitude of functions. For example, the proteoglycans containing heparan sulphate and dermatan sulphate have the ability to bind extracellular matrix components, including various collagens. In addition, these proteoglycans bind several growth factors, cytokines, cell adhesion molecules and growth factor binding proteins and they can serve as antiproteases. In addition to binding to a number of extracellular molecules, proteoglycans also play a role in the adhesion of cells to the extracellular matrix. For example, syndecan-4, which is selectively enriched in dermal fibroblasts, facilitates the adherence of the cells in conjunction with other extracellular matrix binding molecules, such as the integrins. Furthermore, the formation of focal adhesions requires heparan sulphate and subsequent activation of protein kinase C by a domain in the syndecan-4 core protein cytoplasmic tail [6].

Proteoglycans also interact with other extracellular matrix molecules besides collagen. In addition to decorin, which is known to associate primarily with type I collagen, chondroitin sulphate and dermatan sulphate bind fibronectin and laminin. The largest extracellular GAG, hyaluronic acid, plays an important role in providing physicochemical properties to the skin, mediated at least in part by its hydrophilicity and viscosity in dilute solutions.

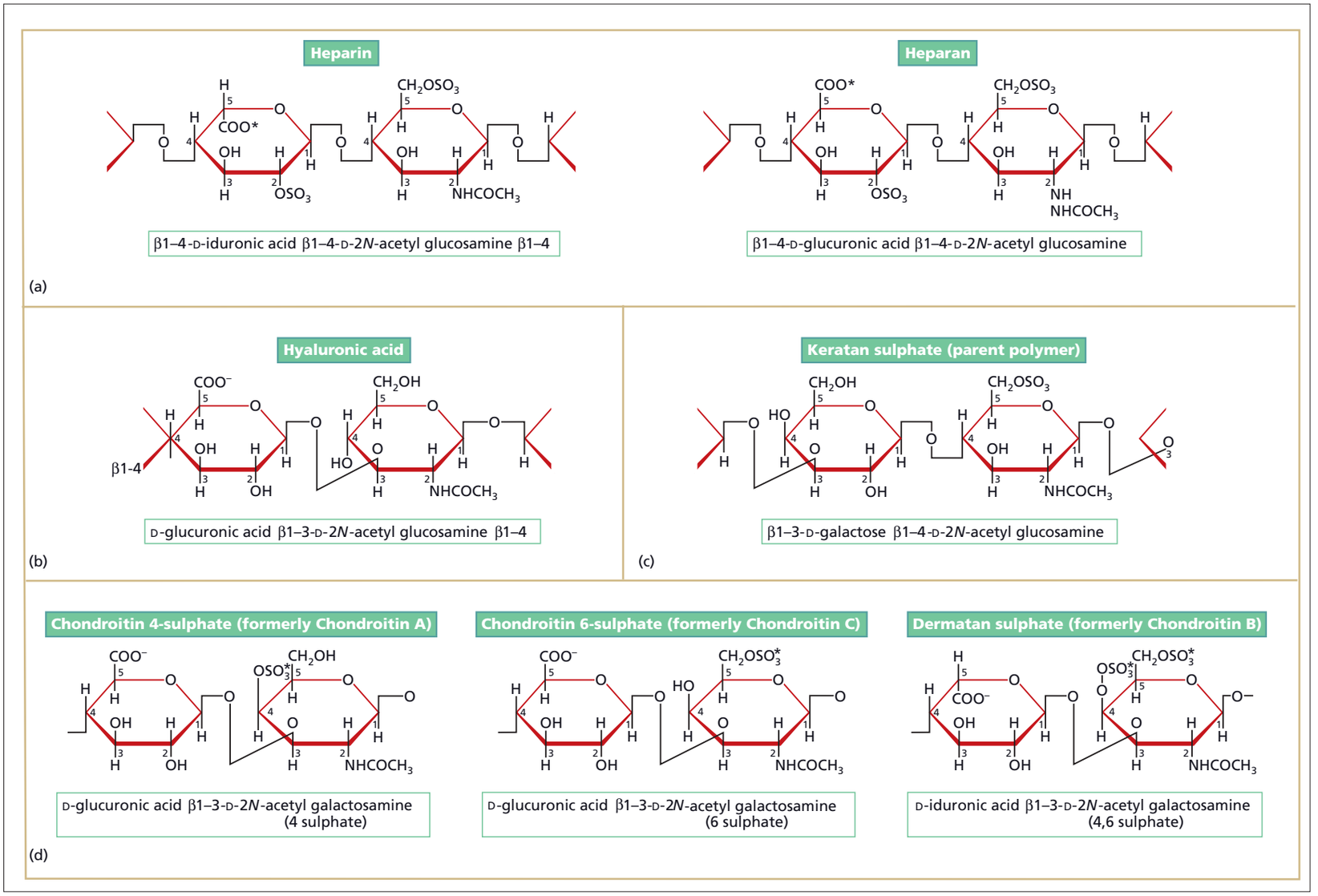


Fig. 3.60 Schematic representation of the glycosaminoglycan molecules which comprise the carbohydrate polymer side-chains of proteoglycan molecules, including (a) heparin and heparan, (b) hyaluronic acid, (c) keratan sulphate, and (d) various chrondroitin sulphates. Note the variants that include O-sulphation at the 6 position of both glucosamine and galactose.

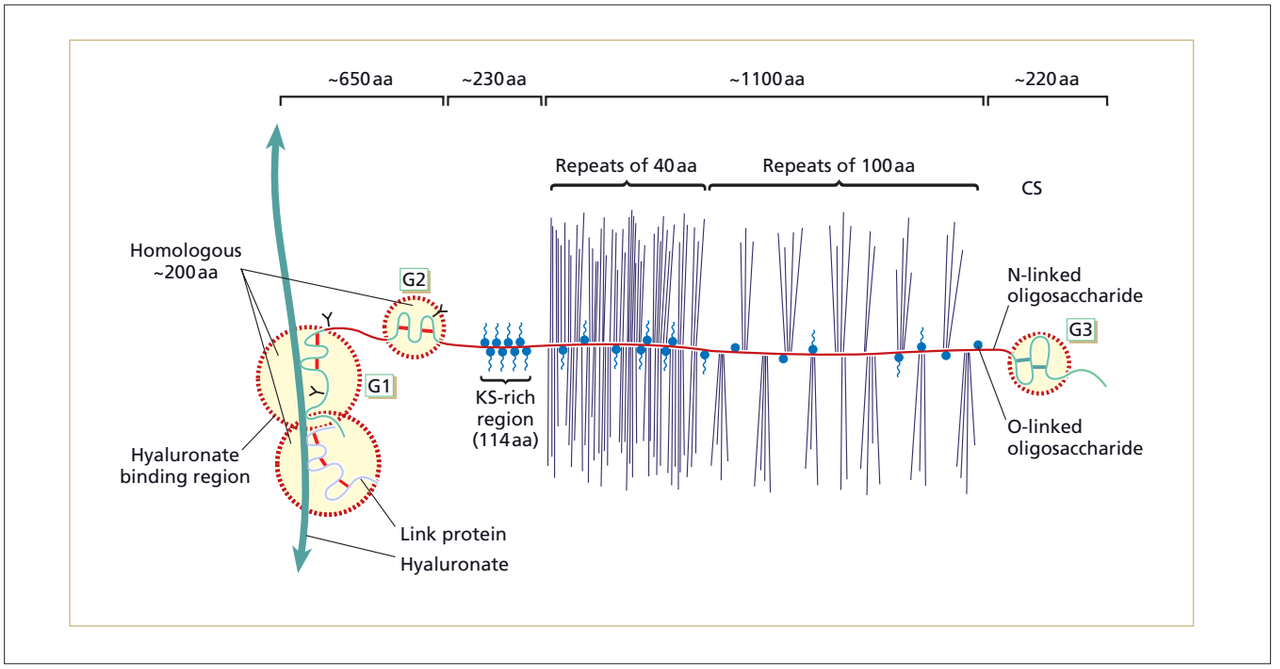


Fig. 3.61 Schematic representation of the core protein aggrecan joined by link proteins to hyluronate, with keratan sulphate (KS, blue) and chondroitin sulphate (CS, purple) side-chains. aa, amino acids (Adapted from [10].)

Table 3.5 Molecular characteristics and tissue distribution of selected proteoglycans.

PG	Protein (kDa)	Glycosaminoglycan(s)	Gene location	Tissue distribution
Decorin	36	CS/DS	12q21–23	Connective tissue
Biglycan	38	CS/DS	Xq28	Cell surface
Fibromodulin	42	KS	1q32	Collagen matrix
Lumican	38	KS	12q21–22	Cornea, bowel, cartilage, muscle
Epiglycan	36	CS/DS		Epiphyseal cartilage
Versican	260–370	CS/DS (10–30)	5q13	Skin, blood vessel, cartilage, brain
Aggrecan	220	CS (100)	15q26	Cartilage, blood vessel, brain
Perlecan	400–470	HS/CS	1p36	Cartilage, bone marrow
Agrin	210	HS (3–6)	1q32	Cell membranes, kidneys, neuromuscular
Neurican	136	CS (3–7)		Brain
Brevican	100	CS (1–3)		Brain
Testican	44	HS/CS	21	Testis

CS, chondroitin sulphate; DS, dermatan sulphate; KS, keratan sulphate; HS, heparan sulphate.

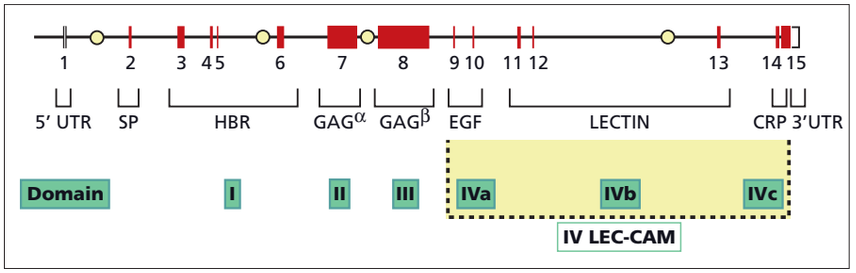


Fig. 3.62 The human versican gene: intron–exon organization (top) and deduced functional domains of the encoded protein. UTR, untranslated region; SP, signal peptide; HBR, hyaluronan-binding region; GAG, glycosaminoglycan; EGF, epidermal growth factor; CRP, complement regulatory protein. (Adapted from [11].)

Most notably, hyaluronic acid has an expansive water-binding capacity, providing hydration to normal skin. The expression of hyaluronan is developmentally regulated in the skin, and the gene required for its synthesis, hyaluronan synthase, has been characterized. During wound healing, the physicochemical properties of hyaluronan may serve to expand the matrix and thus aid cell movement. The relatively high content of hyaluronan may also explain the finding that wounds in fetal skin heal without scarring. Finally, other properties attributed to large proteoglycans complexes, such as those formed with versican or basement membrane proteoglycans, include their ability to serve as ionic filters, regulate salt and water balance and provide an elastic cushion [7].

Quantitative changes in the deposition of tissue proteoglycans have been encountered in a number of pathological processes. These include elevated hyaluronic acid synthesis in keloids and other fibrotic processes, as well as in pretibial myxoedema. In other skin conditions, including lichen myxoedematosus, systemic scleroderma and pseudoxanthoma elasticum, the lesional areas of skin have been reported to display abnormal amounts of proteoglycans. In most of these cases, the changes in proteoglycan/GAG content are secondary to an unrelated primary event. Finally, during innate cutaneous ageing in sunprotected areas of skin, the content of hyaluronic acid diminishes, possibly explaining the reduced turgor in aged skin [8].

References

1 Iozzo RV. Basement membrane proteoglycans: from cellar to ceiling. *Nat Rev Mol Cell Biol* 2005; **6**: 646–56.
2 Gallo R, Kim C, Kokenyese R *et al*. Syndecans-1 and -4 are induced during wound repair of neonatal but not fetal skin. *J Invest Dermatol* 1996; **107**: 667–83.
3 Echtermeyer F, Streit M, Wilcox-Adelman S *et al*. Delayed wound repair and impaired angiogenesis in mice lacking syndecan-4. *J Clin Invest* 2001; **107**: R9–14.
4 Danielson KG, Baribault H, Holmes DF *et al*. Targeted disruption of decorin leads to abnormal collagen fibril morphology and skin fragility. *J Cell Biol* 1997; **136**: 729–43.
5 Keene DR, San Antonio JD, Mayne R *et al*. Decorin binds near the C terminus of type I collagen. *J Biol Chem* 2000; **275**: 21801–4.
6 Esko JD, Lindahl U. Molecular diversity of heparan sulfate. *J Clin Invest* 2001; **108**: 169–74.
7 Agren UM, Tammi M, Ryynänen M, Tammi R. Developmentally programmed expression of hyaluronan in human skin and its appendages. *J Invest Dermatol* 1997; **109**: 219–24.
8 Ghersetich I, Lotti T, Campanile G *et al*. Hyaluronic acid in cutaneous intrinsic aging. *Int J Dermatol* 1994; **33**: 119–22.
9 Stryer L. Carbohydrates. In: *Biochemistry*, 4th edn. New York: WH Freeman, 1995: 461–82.
10 Heinegard D, Oldberg A. Glycosylated matrix proteins. In: Royce PM, Steinmann B, eds. *Connective Tissue and its Heritable Diseases*. New York: Wiley Liss, 1993: 189–209.
11 Dours-Zimmerman MT, Zimmerman DR. A novel glycosaminoglycan attachment domain, identified in two alternative splice variant of versican. *J Biol Chem* 1994; **269**: 32992–8.

Fibroblasts

The principal cell type responsible for the synthesis of connective tissue in the dermis is the fibroblast, which is of mesenchymal origin. The term fibroblast refers to a fully differentiated, biosynthetically active cell, while the term fibrocyte refers to an inactive cell. Biosynthetically active fibroblasts, as detected in developing or regenerating tissues, have an abundant cytoplasm, well-developed rough endoplasmic reticulum, and prominent ribosomes attached to the membrane surfaces, features characteristic of cells engaged in active synthesis and secretion of extracellular matrix macromolecules (Fig. 3.63). As indicated in the case of collagen, the polypeptides are first assembled in the cisternae of the rough endoplasmic reticulum, and the precursor polypeptides subsequently undergo extensive post-translational modifications. The newly-synthesized polypeptides are then transferred to the Golgi vesicles and secreted to the extracellular milieu.

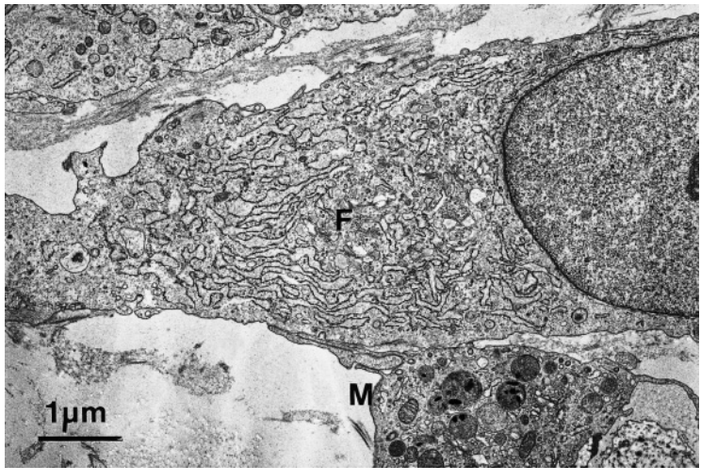


Fig. 3.63 Transmission electron microscopy of an activated dermal fibroblast (F) in a healing wound. Note the prominent rough endoplasmic reticulum in the cytoplasm of this cell. There is an adjacent macrophage (M) with characteristic phagolysosomes, some of which contain ingested melanosomes.

Human skin fibroblasts are the principal cell synthesizing collagen in the dermis. While the source of elastic fibres in the skin is less obvious, fibroblasts clearly have the capacity to synthesize elastic tissues *in vitro*, and they probably are the primary source of elastin within the dermis as well. Finally, fibroblasts are the primary, if not the exclusive, cellular source of proteoglycan/glycosaminoglycan macromolecules. There is, however, considerable heterogeneity within fibroblast populations, and it has been demonstrated that the ratio of type I/III collagen synthesis or fibronectin expression in any given fibroblast population can be variable. For example, fibroblasts isolated from the papillary versus reticular dermis of skin have higher rate of synthesis of type III collagen, and there can be as many as 30-fold differences in the level of fibronectin expression within individual cells [1].

The multiple functions of the stroma of vertebrate animals is dependent on the architecture of the extracellular matrix, which contains mesenchymal cells and provides a structural scaffold for blood and lymphatic vessels and nerves. Reciprocal interactions between the mesenchymal and epithelial cells are known to play a critical role in the development and morphogenesis of tissues, such as skin. More recently, the specific gene expression patterns in cultured fibroblasts derived from fetal and adult human skin at different anatomical sites have been explored [2,3]. Fibroblasts from different sites were shown to display distinct and characteristic transcriptional patterns, and groups of differentially expressed

genes include some involved in extracellular matrix synthesis, lipid metabolism and cell signalling pathways that control proliferation, cell migration and fate determination. Large differences in the gene expression programmes were also related to anterior–posterior, proximal–distal and dermal versus non-dermal anatomic divisions.

Remarkably, adult fibroblasts maintain key features of *HOX* gene expression patterns established during embryogenesis, suggesting that the *HOX* genes direct topographic differentiation and retain the detailed positional memory in fibroblasts. In that sense, fibroblasts from different parts of the skin should be considered distinct, differentiated cell types. Collectively, these findings suggest that site-specific variations in fibroblast gene expression programmes are systematically related to their positional identities relative to the major anatomical axes [2,3].

While fibroblasts demonstrate certain variability in their gene expression profile, they are considered fully differentiated cells with relatively little plasticity. Recent, remarkable observations suggest, however, that fibroblasts can be induced to become pluripotent stem cells (iPS), essentially indistinguishable from embryonic stem cells (ES) [4,5]. Specifically, transduction of cultured fibroblasts with four transcription factors, *Oct4*, *Sox2*, *Klf4* and *cMyc*, generated pluripotent stem cells, and similar protocols have been developed without the participation of the *Myc* retrovirus [6]. Furthermore, transduction of human skin cancer cell lines with mir-302, a member of the microRNA family, which is highly expressed in slow-growing human embryonic cells and which quickly decreases after differentiation and proliferation, rapidly converted the cancer cells into a pluripotent state with the expression of key embryonic cell markers [7]. Collectively, development of these technologies holds promise for the reprogramming of fibroblasts in a manner that allows development of patient- and disease-specific pluripotent stem cells for the treatment of diseases without a significant risk of immune rejection.

MicroRNAs (miRNAs) are short non-coding RNAs involved in post-transcriptional regulation of gene expression, and over 500 miRNAs have been identified so far in humans [8]. Their biological importance was initially demonstrated for a role in cancer and, subsequently, they have been suggested to play a role in a number of clinical conditions. Certain miRNAs have also been suggested to contribute to skin development, for example by invoking differentiation through suppression of 'stemness' of the stem cells [9,10]. Recent results have also suggested that miRNA deregulation may be involved in the pathogenesis of psoriasis by contributing to the dysfunction of the cross-talk between resident and infiltrating cells [11].

References

1 Sorrell JM, Baber MA, Caplan AI. Clonal characterization of fibroblasts in the superficial layer of the adult human dermis. *Cell Tissue Res* 2007; **327**: 499–510.

2 Chang HY, Chi JT, Dudoit S *et al*. Diversity, topographic differentiation, and positional memory in human fibroblasts. *Proc Natl Acad Sci* USA 2002; **99**: 12877–82.

3 Rinn JL, Bondre C, Gladstone HB *et al*. Anatomic demarcation by positional variation in fibroblast gene expression programs. *PLoS Genet* 2006; **2**: e119.

4 Takahashi K, Tanabe K, Ohnuki M *et al*. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell* 2007; **131**: 861–72.

5 Park IH, Zhao R, West JA *et al*. Reprogramming of human somatic cells to pluripotency with defined factors. *Nature* 2008; **451**: 141–6.

6 Nakagawa M, Koyanagi M, Tanabe K *et al*. Generation of induced pluripotent stem cells without Myc from mouse and human fibroblasts. *Nat Biotechnol* 2008; **26**: 101–6.

7 Lin SL, Chang DC, Chang-Lin S *et al*. Mir-302 reprograms human skin cancer cells into a pluripotent ES-cell-like state. *RNA* 2008; **14**: 2115–24.

8 Fabbri M, Croce CM, Calin GA. MicroRNAs. *Cancer J* 2008; **14**: 1–6.

9 Yi R, O'Carroll D, Pasolli HA *et al*. Morphogenesis in skin is governed by discrete sets of differentially expressed microRNAs. *Nat Genet* 2006; **38**: 356–62.

10 Yi R, Poy MN, Stoffel M *et al*. A skin MicroRNA promotes differentiation by repressing 'stemness.' *Nature* 2008; **452**: 225–9.

11 Sonkoly E, Wei T, Janson PC. MicroRNAs: novel regulators involved in the pathogenesis of psoriasis? *PLoS ONE* 2007; **2**: e610.

Fibroblasts in disease

Certain types of fibroblast may be associated with disease processes resulting from altered extracellular matrix production. For example, the fibroblastic cells in keloids, connective tissue tumours characterized by excessive deposition of collagen, depict large rough endoplasmic reticulum and have the characteristics of myofibroblasts with a well-developed intermediate filament network [1,2]. The keloid fibroblasts also appear to be less responsive to signals that normally regulate the homeostatic level of collagen gene expression and are necessary to maintain the regulated growth of normal collagen fibres. Another example of morphologically abnormal fibroblasts is those noted in the skin of patients with lipoid proteinosis. Transmission electron microscopy of the skin shows fibroblastic cells with peculiar cytoplasmic inclusions with characteristic duplication of basal lamina at the dermal–epidermal junction and surrounding the blood vessel walls [3]. This autosomal recessive disorder with protean cutaneous and neurological manifestations is now known to result from mutations in the extracellular matrix protein 1 gene (*ECM1*) [4].

References

1 Lee YS, Vijayasingam S. Mast cells and myofibroblasts in keloids: a light microscopic, immunohistochemical and ultrastructural study. *Ann Acad Med Singapore* 1995; **24**: 902–5.

2 Matsuoka LY, Uitto J, Wortsman J *et al*. Ultrastructural characteristics of keloid fibroblasts. *Am J Dermatopathol* 1998; **10**: 505–8.

3 Moy LS, Moy RL, Matsuoka LY *et al*. Lipoid proteinosis: ultrastructural and biochemical studies. *J Am Acad Dermatol* 1987; **16**: 1193–201.

4 Chan I, Liu L, Hamada T *et al*. The molecular basis of lipoid proteinosis: mutations in extracellular matrix protein 1. *Exp Dermatol* 2007; **16**: 881–90.

Blood vessels and lymphatics

The arteries entering the skin form a deep plexus, the 'fascial' network, from which individual vessels rise to the border between the subcutaneous adipose tissue and the dermis to form a 'cutaneous' vessel network. These vessels then branch out towards various cutaneous appendages and provide ascending arterioles to generate a subpapillary plexus, which forms capillary loops entering the papillary dermis between the rete ridges. From these capillaries the blood is drained by venules which form intermediate plexuses. Thus, the cutaneous vasculature is rather elaborate and limited to the dermis, while the epidermis has no blood vessels [1–3] (Fig. 3.64).

In addition to providing nutrients and oxygen to the skin, the vasculature plays a major role in regulating the body temperature.

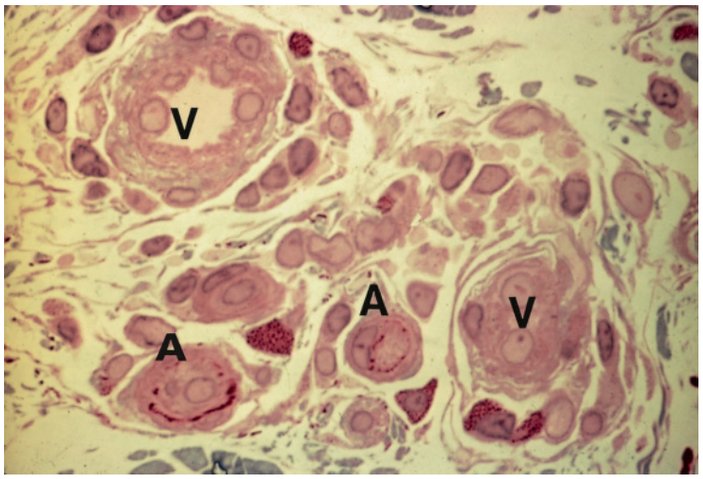


Fig. 3.64 Histology of microvessels in reticular dermis. Arterioles (A) can be distinguished from venules (V) by the presence of elastic lamina which stains red. Surrounding mast cells can be distinguished by their prominent red/blue cytoplasmic granules. (Basic fuchsin and methylene blue stain; original magnification, ×400.)

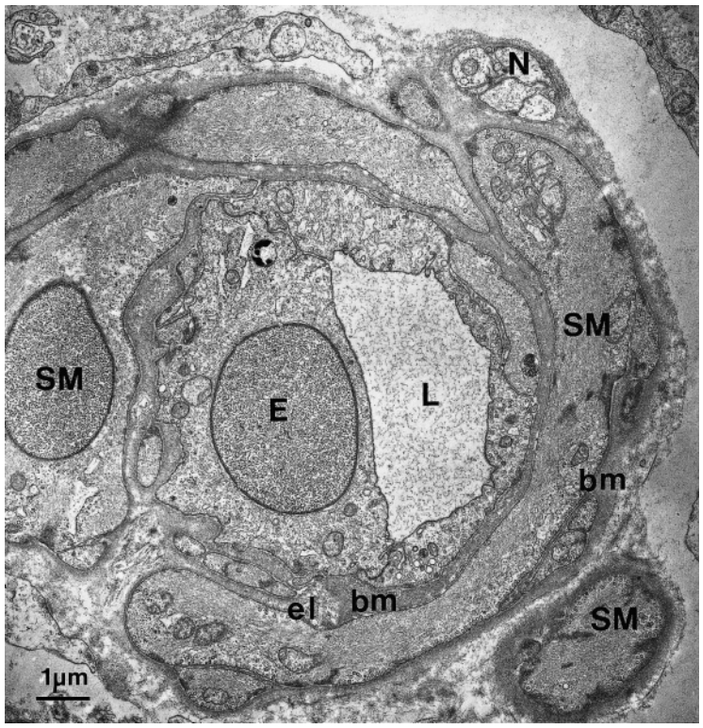


Fig. 3.65 Transmission electron microscopy of cross-section through a small arteriole in the skin. Note the relatively smooth surface of the endothelial cell (E) surrounding the lumen (L) and the presence of smooth muscle (SM) with an associated nerve (N). There is a small amount of elastic tissue (el) adjacent to the endothelial basement membrane (bm).

This is accomplished by controlling the blood flow through the capillaries in the upper dermis so that opening allows dissipation of excess heat while constriction of the blood vessels slows the blood flow to the skin and conserves the core energy. The amount of blood flowing through the superficial layers of the dermis can also be controlled by arterial–venous anastomoses, which act as shunts to short-circuit the flow.

The innermost component of the blood vessels is the endothelium, consisting of adjoining endothelial cells that surround the lumen. Arterioles are characterized by a subendothelial layer of elastic tissue, while venules generally do not have elastic tissue in their walls (Figs 3.65 & 3.66). The endothelium of capillaries and the small arterioles and venules is surrounded by pericytes, which appear to share certain characteristics with both endothelial and smooth muscle cells. Capillaries contain a single, discontinuous layer of pericytes, whereas venules may include more than one pericyte layer in their periendothelial investment. Smooth muscle cells are found chiefly in the walls of ascending arterioles but also within the arterioles of the superficial and deep plexus and in collecting venules. Smooth muscle cells and pericytes are surrounded by a basement membrane, which also encompasses the outer surface of endothelial cells. Veil cells are long, thin cells with an attenuated cytoplasm, and they more closely resemble fibroblasts than pericytes. They do not have a basement membrane investment and are located outside the vessel wall [4].

At the ultrastructural level, endothelial cells possess many of the common cellular organelles, including the rough and smooth endoplasmic reticulum, mitochondria and lysosomes, and micropinocytotic vesicles are also evident. Intermediate filaments containing vimentin are present and have been reported to be more abundant on the venous than on the arterial site. Dense bodies associated with actin-like filaments of 5–6 nm diameter are found in the endothelial cells of the larger arterioles, and they may have a role in endothelial contraction.

Weibel–Palade bodies are endothelium-specific inclusions that occur more frequently in the venous side of the microvasculature



Fig. 3.66 Transmission electron microscopy of a transverse section through a venule in the skin. The surface of the endothelial cells (E) in the lumen (L) is more convoluted than in its arteriolar counterpart (see Fig. 3.65). The endothelial cells are surrounded by pericytes (P), and not smooth muscle cells, and the basement membrane (bm) contains dense strands (arrows). The arrowheads indicate Weibel–Palade bodies.

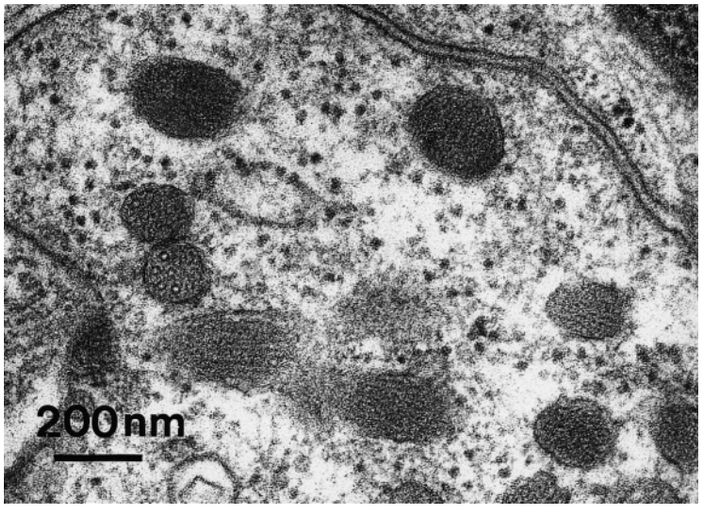


Fig. 3.67 High-magnification view of Weibel–Palade bodies revealing tubular profiles in cross-section.

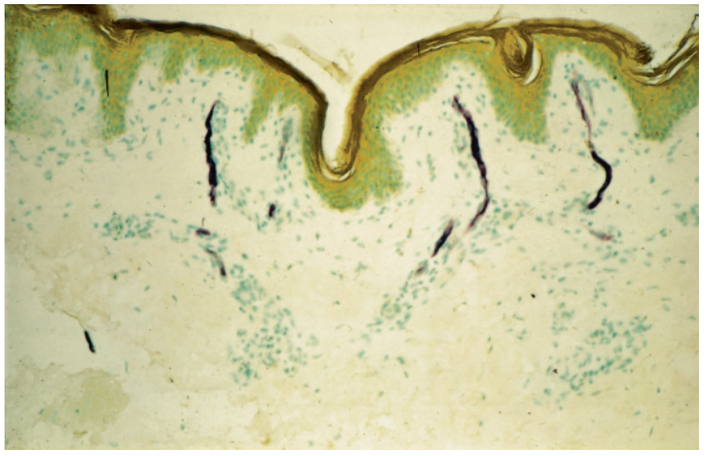


Fig. 3.68 Histochemical detection of alkaline phosphatase activity indicates the presence of arterial microvessels in the superficial dermis. Original magnification, ×160.

(Fig. 3.67). They are not found in dermal lymphatics but have been reported in larger lymph vessels. Weibel-Palade bodies contain factor XIII-related antigen, von Willebrand factor and GMP-140, a protein that was first described in platelet α-granules.

Fenestrations, which allow rapid passage of water and solutes between the circulation and the extravascular space, have been observed in capillaries, mainly in the vicinity of epidermal appendages but also in papillary dermis, facing the epidermis [5].

A major feature distinguishing arterial from venous microvessels is the ultrastructural appearance of the basement membrane. Venules and venous capillaries have a multilaminated basement membrane, whereas arterioles possess a more homogeneous matrix, lacking the electron-dense strands. Vascular basement membrane contains laminin 111, type IV collagen, fibronectin and heparan sulphate proteoglycans. It does not contain, however, bullous pemphigoid antigens, type VII collagen or laminin 332, components of the epidermal basement membrane zone.

A number of endothelium-specific antigens have been recognized, and they may have a special value in studies of cutaneous pathology. Endothelial cells are the major source of angiotensin-converting enzyme as well as various cytokines and adhesion molecules. The microvasculature is also a rich source of enzymes that may be involved in cellular processes, such as endocytosis and vesicular transport. Acid phosphatase has been localized to lysosome-like structures in the endothelium, and alkaline phosphatase reactivity has been used extensively to map the distribution and arborization of the arterial network in the upper dermis (Fig. 3.68).

The lymphatic network in the skin serves to transport particulate and liquid materials, such as proteins, from the extravascular compartment of the dermis. Interconnecting lymphatic spaces arise from terminal bulbs in the papillary layer and ultimately form the system that drains into the lymph nodes. The vessels have a broad lumen surrounded by a single endothelial layer, which is discontinuous in the terminal components and rests on an often discontinuous basal lamina. These processes are critical for the normal function of skin, as altered function and development of lymphatics can lead to diseases, including primary and secondary lymphoedemas [6–8].

References

1 Ryan TJ. Cutaneous circulation. In: Goldsmith LA, ed. *Biochemistry and Physiology of the Skin*. New York: Oxford University Press, 1983: 817–77.

2 Braverman IM, Yen A. Ultrastructure of the human dermal microcirculation. II. The capillary loops of the dermal papillae. *J Invest Dermatol* 1977; **68**: 44–52.

3 Braverman IM, Yen A. Ultrastructure of the human dermal microcirculation. III. The vessels in the mid- and lower dermis and subcutaneous fat. *J Invest Dermatol* 1982; **78**: 297–304.

4 Pober JS. Cytokine-mediated activation of vascular endothelium: physiology and pathology. *Am J Pathol* 1988; **133**: 426–33.

5 Nicosia RF, Madri JA. The microvascular extracellular matrix. Developmental changes during angiogenesis in the aortic ring-plasma clot model. *Am J Pathol* 1987; **128**: 78–90.

6 Ylitalo K, Tammela T, Petrova TV. Lymphangiogenesis in development and human disease. *Nature* 2005; **438**: 946–53.

7 Hosking B, Mäkinen T. Lymphatic vasculature: a molecular perspective. *Bioessays* 2007; **29**: 1192–202.

8 Jurisic G, Detmar M. Lymphatic endothelium in health and disease. *Cell Tissue Res* 2009; **335**: 97–108.

Subcutaneous fat

Fat is a major component of the human body and approximately 80% of fat is in the subcutis; the rest surrounds internal organs. In non-obese males, 10–12% of body weight is fat, while in females the figure is 15–20%. Fat comprises white and brown adipose tissue. Brown fat is more common in infants and children and is characterized by different mitochondrial properties and increased heat production [1]. The function of fat is to provide insulation, mechanical cushioning and an energy store. In addition, fat may have an endocrine function, communicating with the hypothalamus via secreted molecules such as leptin to alter energy turnover in the body and to regulate appetite [2]. Adipocytes also have important signalling roles in osteogenesis and angiogenesis, and additional physical functions such as phagocytosis. Multipotent

stem cells have been identified in human fat, which are capable of developing into adipocytes, osteoblasts, myoblasts and chondroblasts. Molecular biological insight into genes, proteins, hormones and other molecules that influence fat deposition and distribution are gradually being realized, both from research on rare inherited disorders (such as the lipodystrophies or obesity syndromes) as well as population studies on more common forms of obesity [3].

References

1 Wehrli NE, Bural G, Houseni M *et al*. Determination of age-related changes in structure and function of skin, adipose tissue, and skeletal muscle with computed tomography, magnetic resonance imaging, and positron emission tomography. *Semin Nucl Med* 2007; **37**: 195–205.

2 Farooqi IS, O'Rahilly S. Mutations in ligands and receptors of the leptin-melanocortin pathway that lead to obesity. *Nat Clin Pract Endocrinol Metab* 2008; **4**: 569–77.

3 Bessesen DH. Update on obesity. *J Clin Endocrinol Metab* 2008; **93**: 2027–34.

CHAPTER 4
Functions of the Skin

C.B. Archer
Bristol Dermatology Centre, Bristol Royal Infirmary, Bristol, UK

Barrier functions, 4.2
The epidermis and stratum corneum as a physical barrier, 4.2
Percutaneous absorption, 4.4
Microorganisms: antimicrobial peptides (AMPs) as a chemical barrier, 4.5
Ultraviolet radiation, 4.6
Temperature regulation, 4.7
Skin failure, 4.7
Mechanical functions, 4.7
Immunological functions, 4.8
Sensory and autonomic functions, 4.9
Bioengineering and the skin, 4.10
Sociosexual communication, 4.11

Introduction

The skin is arguably the largest immunologically active organ in the body, and its relative accessibility for basic scientific research has allowed much progress in our understanding of its multiplicity of functions. The most obvious functions of the skin are to provide a protective physical barrier between the body and the environment, preventing the inward and outward passage of water and electrolytes, reducing penetration by destructive chemicals, arresting the penetration of microorganisms and external antigens, and absorbing radiation from the sun. The skin is important in the regulation of body temperature and is designed, to an extent, to respond to mechanical forces; the epidermis has a degree of mechanical strength to withstand damage and the ability to repair itself if damaged, and the dermis provides elasticity in response to mechanical insults.

The immunological functions of the skin depend both on cells in the epidermis and on dermal cellular constituents. Antimicrobial peptides (AMPs) are a diverse group of proteins that are involved as a first line of immune defence by many living things, including plants, insects, bacteria and vertebrates [1,2]. In human skin, AMPs provide a chemical barrier to potentially pathogenic microorganisms. The skin also contains sensory and autonomic nerves and several types of sensory receptor, which detect the incoming stimuli of touch, vibration, pressure, change in temperature (warmth and cold), pain (including heat pain) and itch. As in other animals, human skin has a role in sociosexual communication.

The aim of this chapter is to consider the functions of the skin in relation to its structure. It is important to understand physiological functions of the skin, so that one can plan a logical approach to the management of skin diseases. For example, if a patient has extensive areas of denuded skin, as seen following severe burns or in toxic epidermal necrolysis, the skin is unable to play its usual part in the maintenance of fluid balance and temperature regulation, a clinical situation referred to as 'skin failure' [3]. In addition, a knowledge of the skin as a barrier is important from the point of view of the delivery of topical treatments for skin diseases, and ceramide-dominant barrier-repair lipids have been reported to improve atopic dermatitis [4]. The contribution of bioengineering to present knowledge is also discussed.

It is beyond the scope of this chapter to provide a detailed account of skin biochemistry, and some biochemical functions of the skin are discussed in chapters referring to specific skin diseases. For example, androgen biochemistry is discussed in relation to disorders of the sebaceous glands in Chapter 42, altered cyclic nucleotide metabolism in atopic dermatitis [5] in Chapter 24, and phosphoinositide cell-regulatory abnormalities in psoriasis [6] in Chapter 20. Under the influence of sunlight, the skin is the site of vitamin D synthesis (see Chapter 59). In addition to its effects on calcium and bone metabolism, vitamin D_3 has antiproliferative and immunomodulatory effects, both of which are likely to be relevant to the treatment of psoriasis with vitamin D analogues (see Chapter 20).

Nails and hair are discussed elsewhere (see Chapters 65 and 66, respectively). Briefly, the scalp hair has a role in heat regulation and in display. Nails are mainly protective, aid in performing delicate tasks and are of cosmetic importance, a more noticeable feature when the nails are either absent or disfigured.

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

References

1 Gallo RL, Murakami M, Ohtake T *et al.* Biology and clinical relevance of naturally occurring antimicrobial peptides. *J Allergy Clin Immunol* 2002; **110**: 823–31.
2 Zasloff M. Antimicrobial peptides in health and disease. *N Engl J Med* 2002; **347**: 1199–200.
3 Irvine C. 'Skin failure'—a real entity: discussion paper. *J R Soc Med* 1991; **84**: 412–3.
4 Chamlin SL, Frieden IJ, Fowler A *et al.* Ceramide-dominant, barrier-repair lipids improve childhood atopic dermatitis. *Arch Dermatol* 2001; **137**: 1110–2.
5 Archer CB. Cyclic nucleotide metabolism in atopic dermatitis. *Clin Exp Dermatol* 1987; **12**: 424–31.
6 Horn F, Marks F, Fisher GJ *et al.* Decreased protein kinase C activity in psoriatic versus normal epidermis. *J Invest Dermatol* 1987; **88**: 220–2.

Barrier functions

The epidermis and stratum corneum as a physical barrier

The skin acts as a two-way barrier to prevent the inward or outward passage of water and electrolytes. The physical barrier is largely situated in the epidermis, isolated epidermis being as impermeable as whole skin, whereas once the epidermis is removed the residual dermis is almost completely permeable. The epidermal barrier is localized to the stratum corneum.

On routine histology, the stratum corneum shows a basket-weave structure, and early investigators therefore believed it to be porous, and considered the barrier must lie below it [1]. In 1953, Blank [2] found that the water permeability of excised full-thickness skin remained unchanged by successive stripping with adhesive tape until the lowest part of the stratum corneum was removed, and proposed that the barrier lay within a thin layer of the innermost region. Subsequently, these observations were considered to be consistent with the belief that there is a uniformly good diffusion barrier throughout all or most of the horny layer [3–5].

The barrier depends on both the cornified material of the keratinocytes and the intercellular material, particularly lipids, regional differences in permeability being related to lipid content and not to thickness of the stratum corneum. A two-compartment model of the stratum corneum as a barrier is currently accepted, in which protein-rich cells, the corneocytes, are embedded within a continuous lipid-rich matrix.

Within the keratinocytes are synthesized both the fibrous proteins of keratin and a histidine-rich protein known as keratohyalin, currently usually referred to as filaggrin (filament-aggregating protein, see below) [6,7]. Around each corneocyte is an envelope, formed by cross-linking of the precursors involucrin and keratohyalin, which forms an insoluble exoskeleton and acts as a rigid scaffold for the internal keratin filaments [8,9]. There is evidence that lipids are chemically bound to its surface [10].

The intercellular cement is the product of ovoid organelles, 0.2–0.3 μm in diameter, known as membrane-coating granules, Odland bodies or lamellar bodies [11]. They become identifiable in cells of the spinous layer, and migrate to the cell periphery and fuse with the plasma membrane in the granular layer. They then discharge their contents into the intercellular spaces, which expand to form 10–40% of the total volume of the tissue.

The lamellar bodies originally contain neutral sugars linked to lipids and proteins, hydrolytic enzymes and free sterols, but the composition of the secretion changes greatly as they migrate outwards. Phospholipids, present in the stratum basale, diminish in the stratum spinosum, and virtually disappear at the level of the stratum corneum. However, neutral lipids and sphingolipids, in particular ceramides, are increased in the stratum corneum [12–17]. Cholesterol sulphate increases from the spinous to the granular layer, but is decreased in the stratum corneum.

In parallel with these biochemical events, changes can be observed in the ultrastructure of the intercellular material (Fig. 4.1) [18]. Within the granules, bilayers become arranged to form discs, which represent flattened, unilamellar liposomes. The formation of such flattened liposomes has been demonstrated *in vitro* by exposing a mixture of ceramides, cholesterol, palmitic acid and cholesterol sulphate to a hypertonic medium [19,20]. After extrusion into the intercellular space, the discs become arranged parallel to the cell membranes and then fuse to form uninterrupted sheets [21].

In consequence of their origin by fusion of flattened vesicles, the intercellular lamellae of the stratum corneum consist of two lipid bilayers in close apposition [22]. The stratum compactum has been considered to form the principal diffusion barrier. It has also been proposed that in the stratum dysjunctum, the vesicular bodies maintain the patency of the intercellular space, and thus facilitate the absorption of applied substances by a form of shunt mechanism, as well as functioning as a reservoir. Vickers [23] first showed that the horny layer can retain topically applied corticosteroids, and such reservoir effects were later confirmed for hydrocortisone [24] and established for hexachlorophene [25].

In atopic dermatitis, the xerosis and permeability barrier abnormality seem to have a role in driving disease activity [26]. Both involved and clinically uninvolved skin in atopic dermatitis have impaired barrier function [27], which correlates with a reduction in the stratum corneum ceramide fraction [28]. Emollients do not usually correct the underlying stratum corneum lipid abnormality, but ceramide-dominant barrier-repair lipids have been shown to improve atopic dermatitis in children [29].

The function of filaggrin in the formation of the stratum corneum has been reviewed by Smith *et al*. [30] following exciting genetic findings in ichthyosis vulgaris and atopic dermatitis. Keratohyalin granules in the granular layer of interfollicular epidermis are predominantly composed of the 400-kD protein profilaggrin. Following a short, unique N-terminal domain, most of the profilaggrin molecule consists of 10 to 12 repeats of the 324-residue filaggrin sequence [31]. Upon terminal differentiation of granular cells, profilaggrin is proteolytically cleaved into filaggrin peptides of approximately 37 kD and the N-terminal domain contains an S100-like calcium-binding domain. Filaggrin rapidly aggregates the keratin cytoskeleton, causing collapse of the granular cells into flattened, anuclear squames. This condensed cytoskeleton is cross-linked by transglutaminases during formation of the cornified cell envelope.

Smith *et al*. [30] identified homozygous or compound heterozygous mutations in the filaggrin gene in individuals with moderate or severe ichthyosis vulgaris, loss or reduction of this major structural protein leading to varying degrees of impaired keratinization. Palmer *et al*. from the same group [32] showed that two independent loss-of-function genetic variants in the filaggrin gene are very strong predisposing factors for the development of atopic dermatitis.

References

1 Calvery HD, Draize JH, Laug EP. The metabolism and permeability of normal skin. *Physiol Rev* 1946; **26**: 495–540.

2 Blank IH. Further observations on factors which influence the water content of the stratum corneum. *J Invest Dermatol* 1953; **21**: 259–69.

3 Blank IH. Cutaneous barriers. *J Invest Dermatol* 1965; **45**: 249–56.

4 Kligman AM. The biology of the stratum corneum. In: Montagna W, Lobitz WC, eds. *The Epidermis*. New York: Academic Press, 1964: 387–433.

5 Scheuplein RJ, Bronaugh RI. Percutaneous absorption. In: Goldsmith LA, ed. *Biochemistry and Physiology of the Skin*, Vol. II. New York: Oxford University Press, 1983: 1255–95.

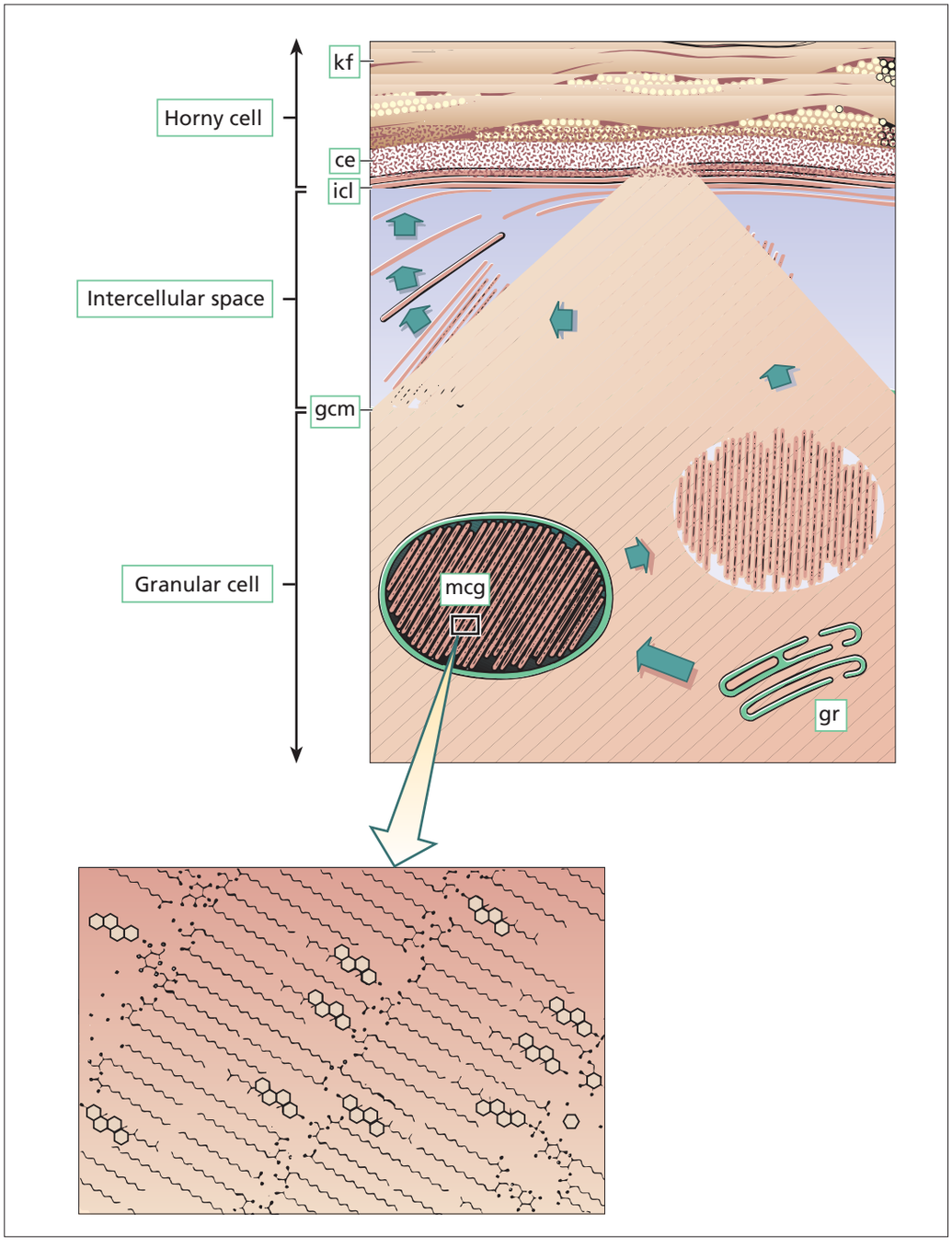


Fig. 4.1 A diagrammatic representation of events in the formation of the epidermal water barrier as seen in electron micrographs. The process includes assembly of a membrane-coating granule or lamellar body (mcg) from the Golgi region (gr) in an epidermal granular cell bounded by a granular cell membrane (gcm); subsequent expulsion of the granule into the intercellular space; and its rearrangement into the intercellular lamellae (icl) that lie parallel with the cell envelope (ce) and the keratin filaments (kf) of the horny cell. The expanded insert shows the proposed arrangement of the acylglucosylceramide molecules (bold) within multiple bimolecular lipid leaflets formed from lipids known to be present in the epidermal granular cells. Hydrogen atoms are omitted from the lipid structures [18]. (Courtesy of P.W. Wertz.)

6 Baden HP, Lee LD. Fibrous proteins of human epidermis. *J Invest Dermatol* 1978; **71**: 148–51.

7 Bernstein IA. The proteins of keratohyalin. In: Goldsmith LA, ed. *Biochemistry and Physiology of the Skin*. New York: Oxford University Press, 1983: 170–83.

8 Goldsmith LA. The epidermal cell periphery. In: Goldsmith LA, ed. *Biochemistry and Physiology of the Skin*. New York: Oxford University Press, 1983: 184–96.

9 Rice RH, Green H. The cornified envelope of terminally differentiated human epidermal keratinocytes consists of cross-linked protein. *Cell* 1977; **11**: 417–22.

10 Swartzendruber DC, Wertz PW, Madison KC *et al.* Evidence that the corneocyte has a chemically bound lipid envelope. *J Invest Dermatol* 1987; **88**: 709–13.

11 Odland GF, Holbrook KA. The lamellar granules of epidermis. In: Mali JWH, ed. *Current Problems in Dermatology*. Basel: Karger, 1981: 29–49.

12 Gray GM, White RJ. Glycolipids and ceramides in human and pig epidermis. *J Invest Dermatol* 1978; **70**: 336–41.

13 Gray GM, Yardley HJ. Different populations of pig epidermal cells: isolation and lipid composition. *J Lipids Res* 1975; **16**: 441–7.

14 Wertz PW. Lipids of keratinizing tissues. In: Bereiter-Hahn J, Matoltsy AG, Richards KS, eds. *Biology of the Integument*, Vol. 2. *Vertebrates*. Berlin: Springer-Verlag, 1986: 815–23.

15 Wertz PW, Miethke MC, Long SA *et al.* The composition of the ceramides from human stratum corneum and from comedones. *J Invest Dermatol* 1985; **84**: 410–2.

16 Yardley HJ. Epidermal lipids. In: Goldsmith LA, ed. *Biochemistry and Physiology of the Skin*. New York: Oxford University Press, 1983: 363–81.

17 Yardley HJ, Summerley R. Lipid composition and metabolism in normal and diseased epidermis. *Pharmacol Ther* 1981; **13**: 357–83.
18 Wertz PW, Downing DT. Glycolipids in mammalian epidermis: structure and function in the water barrier. *Science* 1982; **217**: 1261–2.
19 Abraham W, Downing DT. Preparation of model membranes for skin permeability studies using stratum corneum lipids. *J Invest Dermatol* 1989; **93**: 809–13.
20 Abraham W, Wertz PW, Downing DT. Fusion patterns of liposomes formed from the stratum corneum lipids. *J Invest Dermatol* 1988; **90**: 259–62.
21 Landmann L. Epidermal permeability barrier: transformation of lamellar granule disks into intercellular sheets by a membrane-fusion process, a freeze-fracture study. *J Invest Dermatol* 1986; **87**: 202–9.
22 Swartzendruber DC, Wertz PW, Kitko DJ *et al.* Molecular models of the intercellular lipid lamellae in mammalian stratum corneum. *J Invest Dermatol* 1989; **92**: 251–7.
23 Vickers CFH. Existence of a reservoir in the stratum corneum. *Arch Dermatol* 1963; **88**: 20–3.
24 Stoughton RB. Induction of a steroid reservoir in human skin. *Arch Dermatol* 1965; **91**: 657–60.
25 Stoughton RB. Hexachlorophene deposition in human stratum corneum. *Arch Dermatol* 1966; **94**: 646–8.
26 Elias PM, Wood LC, Feingold KR. Epidermal pathogenesis of inflammatory dermatoses. *Am J Contact Dermatol* 1999; **10**: 119–26.
27 Seidenari S, Giusti G. Objective assessment of the skin of children affected by atopic dermatitis: a study of pH, capacitance, and TEWL in eczematous and clinically uninvolved skin. *Acta Derm Venereol (Stockh)* 1995; **75**: 429–33.
28 Imokawa G, Abe A, Jin K *et al.* Decreased level of ceramides in stratum corneum of atopic dermatitis: an etiologic factor in atopic dry skin. *J Invest Dermatol* 1991; **96**: 523–6.
29 Chamlin S, Frieden IJ, Fowler A *et al.* Ceramide-dominant, barrier-repair lipids improve childhood atopic dermatitis. *Arch Dermatol* 2001; **137**: 1110–2.
30 Smith FJD, Irvine AD, Terron-Kwiatkowski A *et al.* Loss-of-function mutations in the gene encoding filaggrin cause ichthyosis vulgaris. *Nature Genet* 2006; **38**: 337–42.
31 Gan S-Q, McBride OW, Idler WW *et al.* Organization, structure and polymorphisms of the human profilaggrin gene. *Biochemistry* 1990; **29**: 9432–40.
32 Palmer CNA, Irvine AD, Terron-Kwiatkowski A *et al.* Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nature Genet* 2006; **38**: 441–6.

Percutaneous absorption

The skin is considered to be a composite membrane, with three anatomically distinct layers [1]: the stratum corneum (10 μm), the viable epidermis (100 μm) and the uppermost papillary layer of the dermis (100–200 μm), each having a different diffusion constant. Even healthy adult human skin allows some permeation of almost every substance, and rates of penetration of different materials may differ by 10 000-fold.

Percutaneous absorption has been studied both *in vivo* and *in vitro*. The penetration *in vivo* of topically applied substances can be assessed by physiological or pharmacological means, or analysed by chemical or histological techniques. Thus, vasoconstriction has been utilized for corticosteroids, vasodilatation for nicotinates, wealing for histamine, sweating for pilocarpine and anaesthesia for local anaesthetics. The application of compounds labelled with radioisotopes and their location through time in layers of stratum corneum, successively stripped by adhesive tape, has been particularly useful. Body fluids, such as blood and urine, can similarly be analysed for substances that have traversed the skin.

In vitro methods usually utilize sheets of whole epidermis or stratum corneum rather than whole skin. Epidermal sheets can be prepared from skin removed surgically, or obtained from cadavers within 48 h of death. The epidermis can be separated by mild heat [2], ammonia vapour [3] or even distilled water. For removal of the Malpighian layer, digestion in 0.2% trypsin [2] or in dispase, a bacterial neutral protease, has been used [4]. The prepared skin material is mounted as a membrane in a diffusion cell between an upper compartment containing a substance, the penetration of which is under study, and a lower compartment containing a buffer solution, which is replenished as samples are removed for analysis at known time intervals, to determine the content of the test substance.

The properties of the skin barrier have a purely physicochemical basis, and do not depend upon the energy-requiring activities of living cells. They are essentially the same *in vitro* as *in vivo*, are unaffected by reversal of the membrane and are maintained long after the skin is removed from the body [5]. Penetrants in weak solutions (although not those at very high concentrations) obey Fick's first law of diffusion, which states that the rate of flow, or flux, is the product of the average concentration of the molecules and their average velocity. In simple terms, the permeability of the barrier for any given penetrant can be completely characterized by the ratio of the flux to the concentration applied, which is known as the permeability constant, and is expressed in length per unit time. The principles of skin permeability and percutaneous absorption have been reviewed in detail elsewhere [1,6–8].

Permeability constants of human and animal skins have been published for a large number of different molecules [6,8]. They vary considerably between species. For example, human skin, which is slightly permeable to water, is relatively impermeable to sodium, potassium and other ions in aqueous solution. In contrast, penetration of various ions through many animal skins is comparatively rapid. Most covalent substances in aqueous solution, such as glucose, urea and the macromolecular human serum albumin, have very low permeability constants in both human and rabbit skin. Others, such as certain aliphatic alcohols, have high constants. Solutes in organic liquids generally show a permeability similar to the solvents themselves. The presence of a solvent is not necessary, for solids dried on the skin continue to penetrate long after a volatile vehicle has evaporated [9]. Thus, for example, application to the scalp of corticosteroids in alcohol may be an effective therapy. In addition, vapours and permanent gases can penetrate skin [10].

The efficiency of the barrier differs between body sites. The scrotum is particularly permeable [11] and the face, forehead and dorsa of the hands may be more permeable to water than the trunk, arms and legs. The palms are particularly impermeable to nearly all molecules except water.

The barrier is affected by many other factors, such as age, environmental conditions and physical trauma, and permeability can be enhanced by various agents, permitting increased access of topically applied drugs.

By virtue of the stratum corneum being adapted to prevent excessive water loss from the body, there is an excellent barrier to the influx of polar molecules, such as water itself. However, many potentially destructive chemicals are non-polar, and the barrier function of the skin slows down penetration of such compounds rather than impeding penetration completely.

References

1 Scheuplein RJ, Bronaugh RL. Percutaneous absorption. In: Goldsmith LA, ed. *Biochemistry and Physiology of the Skin*, Vol. 2. New York: Oxford University Press, 1983: 1255–95.
2 Foreman MI, Clanachan I, Kelly IP. Diffusion barriers in skin: a new method of comparison. *Br J Dermatol* 1983; **108**: 549–53.
3 Humphries WT, Wildnauer RH. Thermomechanical analysis of the stratum corneum. I. Technique. *J Invest Dermatol* 1971; **57**: 32–7.
4 Kitano Y, Okada N. Separation of the epidermal sheet by dispase. *Br J Dermatol* 1983; **108**: 555–60.
5 Swarbrick J, Lee G, Brom J. Drug permeation through human skin. I. Effect of storage conditions of skin. *J Invest Dermatol* 1982; **78**: 63–6.
6 Schaefer H. *Skin Permeability*. Berlin: Springer-Verlag, 1982.
7 Scheuplein RJ. Percutaneous absorption after 25 years: or 'old wine in new wineskins'. *J Invest Dermatol* 1976; **67**: 31–8.
8 Tregear RT. *Theoretical and Experimental Biology*, Vol. 5. *Physical Functions of Skin*. London: Academic Press, 1966.
9 Scheuplein RJ, Ross LW. Mechanism of percutaneous absorption. V. Percutaneous absorption of solvent deposited solids. *J Invest Dermatol* 1974; **62**: 353–60.
10 Fitzgerald LR. Cutaneous respiration in man. *Physiol Rev* 1957; **37**: 325–6.
11 Smith JG Jr, Fischer RW, Blank H. The epidermal barrier: a comparison between scrotal and abdominal skin. *J Invest Dermatol* 1961; **36**: 337–41.

Microorganisms: antimicrobial peptides (AMPs) as a chemical barrier

An intact stratum corneum prevents invasion of the skin by normal skin flora or pathogenic microorganisms. However, both minor injury to the skin, as well as skin diseases, can provide portals of entry to microorganisms, particularly streptococci or staphylococci. The same organisms give rise to different patterns of infection depending, in part, on the nature of the injury. Cellulitis, a dermal and subcutaneous process, may follow a minor abrasion to the skin or tinea pedis affecting the toe webs. Larger abrasions of the skin, as one sees with the lesions of atopic dermatitis (atopic eczema), tend to be associated with superficial infections, such as the crusted lesions of impetigo. In addition, the appendages of the skin can provide a route for infection by some organisms, such as *Staphylococcus aureus* (as seen in folliculitis or a boil) or fungal infections. Colonization with microorganisms occurs more readily in moist areas (flexural sites), and the dryness of the skin surface and continuous shedding of corneal cells help prevent sustained growth of pathogenic organisms.

Sebaceous lipids have been reported to possess antibacterial properties [1], and glycophospholipids and free fatty acids of the stratum corneum have bacteriostatic effects [2], selective for pathogenic microorganisms.

AMPs are a diverse group of peptides that are present on epithelial surfaces, such as the epidermis and its appendages, as a first line of immune defence by many living things [3,4]. AMPs directly kill a broad spectrum of microbes, including Gram-positive and Gram-negative bacteria, fungi and certain viruses. In addition, these peptides interact with the host itself, targeting events that complement their role as naturally occurring antibiotics.

AMPs can be divided into several categories on the basis of their structures, and most of them include a cationic charge and the ability to interact with bacterial membranes through hydrophobic amino acids. Two major families of AMPs have been characterized in mammals: defensins and cathelicidins.

Defensins are a broadly dispersed family of gene-encoded antibiotics that are subdivided predominantly into the α-defensins and the β-defensins, according to the alignment of the disulphide bridges and their molecular structure [5]. Human neutrophils express a number of distinct defensins, six α-defensins having been identified [6]. Four of these are known as α-defensins 1, 2, 3 and 4 (also referred to as human neutrophil peptides (HNPs) 1–4). The other two α-defensins, known as human defensins 5 and 6 (HD-5 and HD-6), are abundantly expressed in Paneth's cells of the small intestinal crypts and in epithelial cells of the female urogenital tract [3].

In humans, four types of β-defensins have been identified, referred to as human β-defensins (HBDs) 1–4, but it seems that many β-defensins have yet to be discovered [7]. β-defensins have a broad spectrum of antimicrobial activity and act indirectly, being chemotactic for immature dendritic and memory T cells [8], promoting histamine release and prostaglandin D_2 production in mast cells [9,10], and acting as an adjuvant in enhancing antibody production [11]. Human neutrophil α-defensins (HNPs 1–3) also increase the expression of tumour necrosis factor-α (TNF-α) and interleukin-1 (IL-1) in human monocytes that have been activated by bacteria (*Staphylococcus aureus*) [12].

Cathelicidins have been found only in mammals, being limited to a single gene in humans. The human cathelicidin LL-37/hCAP18 was cloned from cDNA isolated from human bone marrow as FALL-39 [13]. The mature AMP is referred to as LL-37 because it begins with two leucine residues and is 37 amino acids long. The term hCAP18 was independently used, because the peptide is a cationic AMP whose mass before proteolytic processing is approximately 18 kDa [14]. The bactericidal activity of human cathelicidin peptide requires proteolytic activation from its precursor by enzymes including neutrophil elastase and proteinase [15]. LL-37 has a broad spectrum of antimicrobial activity and is a chemoattractant for various inflammatory cell types [16,17]. As with the defensins, LL-37 has the potential to participate in the innate immune response both by killing bacteria and by recruiting a cellular immune response.

HBD-2 is present in psoriatic scale [18] and HBD-2 and HBD-3 are increased in keratinocytes from patients with psoriasis [19]. Dermcidin and LL-37 have been found constitutively in sweat gland secretions [20] and HBD-1 and HBD-2 have been demonstrated in ductal epithelia of sweat glands and in normal hair follicles [21]. Other proteins with antibacterial activity in the skin include adrenomedullin [22], cystatin [23] and secretory protease inhibitor [24]. Impaired production of AMPs has been observed in the epidermis in atopic dermatitis, and Th2 cytokines inhibit the expression of HBD-2, one of the AMPs deficient in atopic skin [25].

In normal skin, potential sites of entry of bacteria such as hair follicles and sweat glands produce small amounts of AMPs that provide a chemical barrier to infection where a physical barrier is absent or limited. After injury, the skin responds rapidly with increased production of AMPs from the epidermis and recruited neutrophils (Fig. 4.2) [3]. Cutaneous defence mechanisms by antimicrobial peptides have been reviewed [26,27].

References

1 Kligman AM. The use of sebum. In: Montagna W, Ellis RA, Silver AF, eds. *Advances in Biology of Skin*, Vol. 4. *The Sebaceous Glands*. New York: Pergamon, 1963: 110.

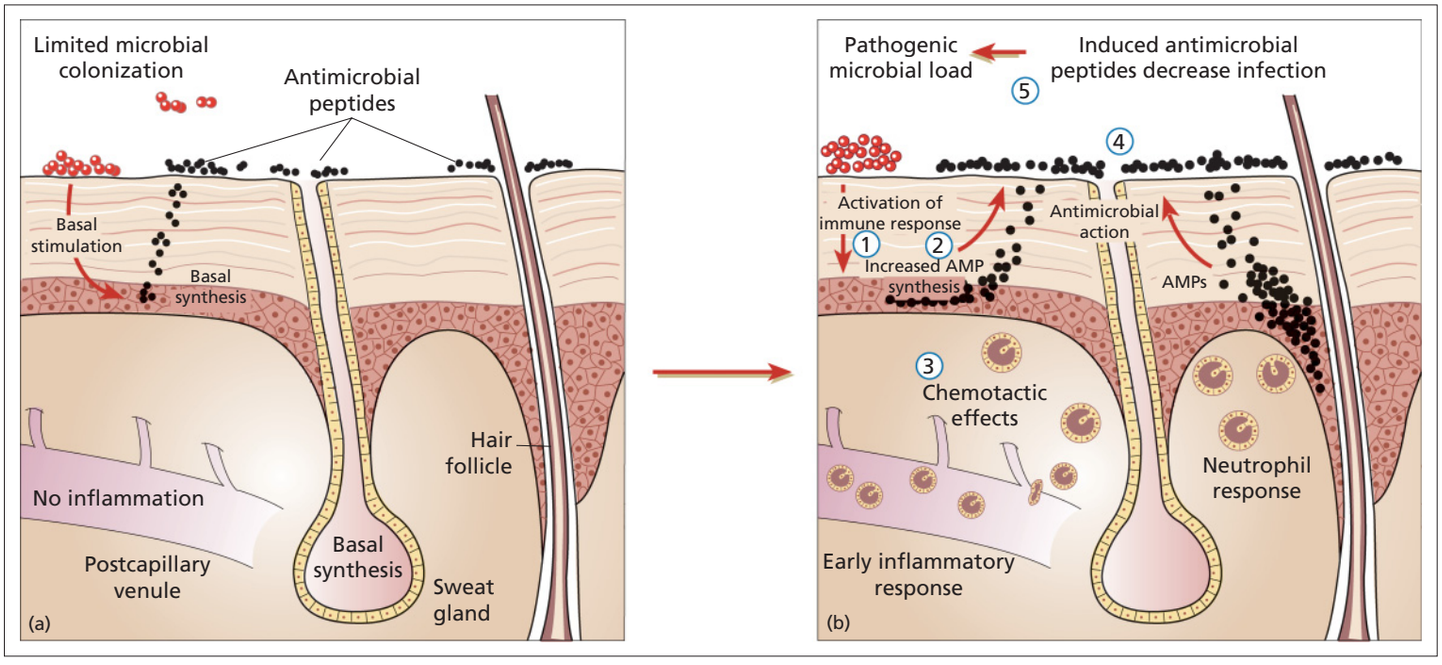


Fig. 4.2 Antimicrobial peptide (AMP) defence. (a) In normal skin, small amounts of AMPs are produced by the epidermis and are concentrated around hair follicles and in sweat. (b) After injury or infection, keratinocytes increase synthesis of AMPs and further AMPs are produced by neutrophils that are recruited as part of the acute inflammatory response. (Modified from Gallo *et al.* [3].)

2 Miller SJ, Aly R, Shinefield HR, Elvis PM. *In vitro* and *in vivo* antistaphylococcal activity of human stratum corneum lipids. *Arch Dermatol* 1988; **124**: 209–15.
3 Gallo RL, Murakami M, Ohtake T *et al.* Biology and clinical relevance of naturally occurring antimicrobial peptides. *J Allergy Clin Immunol* 2002; **110**: 823–31.
4 Zasloff M. Antimicrobial peptides in health and disease. *N Engl J Med* 2002; **347**: 1199–200.
5 Raj PA, Dentino AR. Current status of defensins and their role in innate and adaptive immunity. *FEMS Microbiol Lett* 2002; **206**: 9–18.
6 Harwig SS, Ganz T, Lehrer RI. Neutrophil defensins: purification, characterization, and antimicrobial testing. *Methods Enzymol* 1994; **236**: 160–72.
7 Schutte BC, Mitros JP, Bartlett JA *et al.* Discovery of five conserved β-defensin gene clusters using a computational search strategy. *Proc Natl Acad Sci USA* 2002; **99**: 2129–33.
8 Yang D, Chertov O, Bykovskaia SN *et al.* β-Defensins: linking innate and adaptive immunity through dendritic and T cell CCR6. *Science* 1999; **286**: 525–8.
9 Befus AD, Mowat C, Gilchrist M *et al.* Neurophil defensins induce histamine secretion from mast cells: mechanisms of action. *J Immunol* 1999; **163**: 947–53.
10 Niyonsaba F, Someya A, Hirata M *et al.* Evaluation of the effects of peptide antibiotics human β-defensins-1/-2 and LL-37 on histamine release and prostaglandin D_2 production from mast cells. *Eur J Immunol* 2001; **31**: 1066–75.
11 Tani K, Murphy WJ, Chertov O *et al.* Defensins act as potent adjuvants that promote cellular and humoral immune responses in mice to a lymphoma idiotype and carrier antigens. *Int Immunol* 2000; **12**: 691–700.
12 Chaly YV, Paleolog EM, Kolesnikova TS *et al.* Neutrophil α-defensin human neutrophil peptide modulates cytokine production in human monocytes and adhesion molecule expression in endothelial cells. *Eur Cytokine Netw* 2000; **11**: 257–66.
13 Agerberth B, Gunne H, Odeberg J *et al.* FALL-39, a putative human antibiotic, is cysteine-free and expressed in bone marrow and testis. *Proc Natl Acad Sci USA* 1995; **92**: 195–9.
14 Cowland JB, Johnsen AH, Borregaard N. hCAP-18, a cathelin/probactenecin-like protein of human neutrophil specific granules. *FEBS Lett* 1995; **368**: 173–6.
15 Sorense OE, Follin P, Johnsen AH *et al.* Human cathelicidin, hCAP-18, is processed to the antimicrobial peptide LL-37 by extracellular cleavage with proteinase 3. *Blood* 2001; **97**: 3951–9.
16 De Y, Chen Q, Schmidt AP *et al.* LL-37, the neutrophil granule- and epithelial cell-derived cathelicidin, utilizes formyl peptide receptor-like 1 (FPRL-1) as a receptor to chemoattract human peripheral blood neutrophils, monocytes, and T cells. *J Exp Med* 2000; **192**: 1069–74.
17 Niyonsaba F, Iwabuchi K, Someya A *et al.* A cathelicidin family of human antibacterial peptide LL-37 induces mast cell chemotaxis. *Immunology* 2002; **106**: 20–6.
18 Harder J, Bartels J, Christophers E *et al.* A peptide antibiotic from human skin. *Nature* 1997; **387**: 861.
19 Harder J, Bartels J, Christophers E *et al.* Isolation and characterization of human β-defensin-3, a novel human inducible peptide antibiotic. *J Biol Chem* 2001; **276**: 5707–13.
20 Schittek B, Hipfel R, Sauer B *et al.* Dermcidin: a novel human antibiotic peptide secreted by sweat glands. *Nat Immunol* 2001; **2**: 1133–7.
21 Fulton C, Anderson GM, Zasloff M *et al.* Expression of natural peptide antibiotics in human skin. *Lancet* 1997; **350**: 1750–1.
22 Martinez A, Elsasser TH, Muro-Cacho C *et al.* Expression of adrenomedullin and its receptor in normal and malignant human skin: a potential pluripotent role in the integument. *Endocrinology* 1997; **138**: 5597–604.
23 Zeeuwen PL, Van Vlijmen-Willems IM, Jansen BJ *et al.* Cystatin M/E expression is restricted to differentiated epidermal keratinocytes and sweat glands: a new skin-specific proteinase inhibitor that is a target for cross-linking by transglutaminase. *J Invest Dermatol* 2001; **116**: 693–701.
24 Ashcroft GS, Lei K, Jin W *et al.* Secretory leukocyte protease inhibitor mediates non-redundant functions necessary for normal wound healing. *Nat Med* 2000; **6**: 1147–53.
25 Ong PY, Ohtake T, Brandt C *et al.* Endogenous antimicrobial peptides and skin infections in atopic dermatitis. *N Engl J Med* 2002; **347**: 1151–60.
26 Braff MH, Bardan A, Nizet V, Gallo RL. Cutaneous defense mechanisms by antimicrobial peptides. *J Invest Dermatol* 2005; **125**: 9–13.
27 Niyonsaba F, Nagaoka I, Ogawa H. Human defensins and cathelicidins in the skin: beyond direct antimicrobial properties. *Crit Rev Immunol* 2006; **26**: 545–76.

Ultraviolet radiation

The sun's radiation is made up of infrared, visible and ultraviolet (UV) light (see Chapter 29), and it is the UV rays that affect the skin. The shorter wavelength UVB rays penetrate the epidermis

and are the cause of sunburn and, in the long term, contribute to premature ageing of the skin and the pathogenesis of skin cancer. UVA rays penetrate the skin more deeply and are considered to have an important role in chronic sun damage, particularly skin ageing but also skin cancer development.

The skin has two barriers to UV radiation: a melanin barrier in the epidermis; and a protein barrier, concentrated in the stratum corneum. Both function by absorbing radiation, thereby minimizing absorption by DNA and other cellular constituents. Melanin is synthesized by melanocytes in the basal layer of the epidermis and transferred to surrounding keratinocytes in melanosomes. The partially protective mechanism of delayed tanning [1] is associated with an increase in the number of functional melanocytes, an increase in the number of melanosomes synthesized, and an increased rate of transfer of melanosomes to the keratinocytes. In the long term, there is thickening of the epidermis in response to chronic sun exposure.

Absorption of radiation by epidermal lipids may contribute to protection from UV radiation, in a similar way to that suggested for some low-molecular-weight degradation products of epidermal proteins, including urocanic acid [2]. The role of UV-induced cytokines in the regulation of melanin production is not yet clear [3,4].

References

1 Ortonne J-P. The effects of ultraviolet exposure on skin melanin pigmentation. *J Int Med Res* 1990; **18** (Suppl. 3): 8C–17C.

2 Baden HP, Pathak MA. The metabolism and function of urocanic acid in skin. *J Invest Dermatol* 1967; **48**: 11–7.

3 Kupper TS, Chua AO, Flood P *et al.* Interleukin 1 gene expression in cultured keratinocytes is augmented by ultraviolet irradiation. *J Clin Invest* 1987; **80**: 430–6.

4 Swope VB, Abdel-Malek Z, Kassem LW *et al.* Interleukin 1α and IL-6 and tumor necrosis factor-α are paracrine inhibitors of human melanocyte proliferation and melanogenesis. *J Invest Dermatol* 1991; **96**: 180–5.

Temperature regulation

The advantage of maintaining a constant body temperature is that the metabolic processes are not directly dependent on changes in the environmental temperature. However, at extremes of ambient temperature, heat may need to be lost or retained. The skin provides a sensory input to thermoregulation and functions to allow heat loss or conservation.

The thermoreceptor cells of the skin are distributed irregularly over the skin, there being warm- and cold-sensitive thermoreceptors. Information on changes in their stimulation in response to changes in temperature is sent to the hypothalamus, leading to either inhibition of sweating or stimulation of shivering [1]. However, the skin thermoreceptors have a relatively minor role in modifying core temperature, and skin temperature has a greater role in mediating behaviour, for example by turning on the heating or putting on extra clothing. At high temperatures, heat pain via nociceptors is perceived rather than warmth.

From an effector point of view, the skin has a major role in thermoregulation of the human body [2]. Heat can be lost through the skin surface by radiation, convection, conduction and evaporation. Of importance in these mechanisms is the rich blood supply of the dermis, which is much greater than that needed for nutrition. The cutaneous circulation is described elsewhere (see Chapters 3 and 47). The essential point about its function, however, is that a system of arteriovenous shunts, which are plentiful in the feet, hands, lips, nose and ears, enables the blood flow to an extensive and more superficial venous plexus to be considerably varied.

In high environmental temperatures, the process of evaporation is considerably enhanced by eccrine sweating.

References

1 Kobayashi S. Temperature-sensitive neurons in the hypothalamus: a new hypothesis that they act as thermostats, not as transducers. *Prog Neurobiol* 1989; **32**: 103–7.

2 Hammel HT. Regulation of internal body temperature. *Annu Rev Physiol* 1968; **30**: 641–710.

Skin failure

Skin failure has been defined by Irvine [1] as 'a loss of normal temperature control with inability to maintain the core temperature, failure to prevent percutaneous loss of fluid, electrolytes and protein with resulting imbalance and failure of the mechanical barrier to penetration of foreign materials'. The term was initially used to bring to the attention of non-dermatologists the need for specialist care in this dermatological emergency. Apart from in thermal burns, skin failure can occur as a consequence of a number of dermatological diseases, including Stevens–Johnson syndrome, toxic epidermal necrolysis, pustular psoriasis and erythroderma of various causes. Depending on the extent of the disease, pemphigus vulgaris, graft-versus-host disease and epidermolysis bullosa are other potential examples.

Used in this specific sense, skin failure is an interesting concept that has not gained common usage. The term is sometimes used in a more general sense to reflect disability in dermatology [2].

Hence, Ryan [2] has included a wide range of skin diseases as examples of 'skin failure', such as hand dermatitis, the development of sunburn and skin cancer in the albino African, and failure of display because of disfigurement. He has emphasized the need for dermatologists and allied health professionals to use a language that can be understood by everyone, particularly patients, when referring to the consequences of skin disease [3].

Both authors [1,2] have drawn attention to the fact that skin failure represents severe loss of function as occurs in other organ systems, for example heart failure, liver failure, renal failure and respiratory failure.

References

1 Irvine C. 'Skin failure'—a real entity: discussion paper. *J R Soc Med* 1991; **84**: 412–3.

2 Ryan TJ. Disability in dermatology. *Br J Hosp Med* 1991; **46**: 33–6.

3 Ryan TJ. A paper that changed clinical practice. *Clin Exp Dermatol* 2003; **28**: 113–4.

Mechanical functions

Although the epidermis and subcutaneous fat each have a role in the protective function of the skin, the mechanical properties of the skin related to hard blows with blunt objects depend mainly

on the dermis. Skin is elastic to a degree and can, for a few seconds at a time, be stretched reversibly by 10–50%. Skin pulls easily at first. The initial response appears to involve a reorientation of collagen fibres towards the load axis and a decrease in their convolution [1]. The tonus of skin is probably maintained by the elastic fibres, and it seems likely that these fibres provide the small forces that restore the extensibility of slack skin.

Once the initial slack has been taken up, the skin becomes much more difficult to extend. It gradually stretches if it is maintained taut for a long time, as, for example, when using tissue-expanding techniques in skin surgery. This further extension under continued stress is referred to as 'viscous extension', 'viscous slip' or 'creep', and is irreversible. This slip depends on the collagen fibrils. It is unlikely that slipping occurs within the fibril itself; either the individual fibrils slip relative to each other, or whole fibrils do so within the related ground substance. The most probable hypothesis to explain the relative lack of slip is that slip is interfibrillar, that the collagen fibrils are very long and that the interfibrillar substance is highly viscous. It appears that dermatan sulphate is more closely connected to the collagen than hyaluronic acid, and it is probable that this material is the one responsible for restraining the viscous slip.

From these considerations it is clear that disorders in which the skin is hyperelastic, such as Ehlers–Danlos syndrome (see Chapters 3 and 45), must involve a breakdown of the collagen mechanism. The striae seen in adolescence, pregnancy and in situations of excessive systemic corticosteroids, whether administered or as part of Cushing's syndrome, are thought to involve a breakdown of the fibril overlap, so that there is no viscous force to limit further slip.

A further property of skin is that it can be compressed. If a small object is pressed into the skin, a depression is formed that remains after the object is removed; thus, skin becomes moulded round the object exerting the force, and the pressure on any one point is reduced. This compression is primarily because of a flow of ground substance through the dermis between the collagen fibres.

The epidermis itself is relatively strong and holds together under the pressure from blister fluids. On the other hand, the dermal–epidermal junction in human skin is relatively weak. The superficial collagen in the papillary layer appears to be particularly easy to weaken, and many blistering agents appear to act at this level.

By virtue of its protein and lipid constituents, the stratum corneum is a relatively strong elastic tissue. The network of structural proteins allows exogenous forces to spread throughout the tissue. The elasticity of the stratum corneum is also influenced by the degree of hydration of the corneal cell proteins, which in turn depends on the water content of the tissue, and by the humidity of the surrounding environment [2]. Stratum corneum proteins, lipids [3,4] and low-molecular-weight by-products of keratohyalin breakdown, referred to as natural moisturizing factors [5], bind and retain water in the stratum corneum, thus maintaining its elasticity.

References

1 Brown IA. A scanning electron microscope study of the effects of uniaxial tension on human skin. *Br J Dermatol* 1973; **89**: 383–93.

2 Blank IH. Factors which influence the water content of the stratum corneum. *J Invest Dermatol* 1952; **18**: 433–40.

3 Imokawa G, Akasaki S, Kuno O *et al.* Water-retaining function in the stratum corneum and its recovery properties by synthetic pseudo-ceramides. *J Soc Cosmet Chem* 1989; **40**: 273–85.

4 Imokawa G, Kuno H, Kawai M *et al.* Stratum corneum lipids serve as a bound-water modulator. *J Invest Dermatol* 1991; **96**: 845–51.

5 Scott IR, Richard S, Harding G *et al.* Does catabolism of stratum corneum proteins yield functionally active molecules? *Ann NY Acad Sci* 1988; **548**: 125–36.

Immunological functions

The immunological functions of the skin have been the subject of intense research in recent years, and it is clear that the skin has an important role in immunological host defence, particularly involving those cells residing in (keratinocytes, Langerhans' cells) or passing through (T lymphocytes) the epidermis (see Chapters 12 and 13). The role of AMPs as a first line of defence against microorganisms has been discussed above (see p. 4.5).

Antigens are from either the external environment (exogenous antigens) or are newly formed in the cell itself (endogenous antigens). T lymphocytes are able to recognize antigen only when it has been presented by specialized cells, termed antigen-presenting cells (APCs) or accessory cells [1–3]. The T cell recognizes the antigen in association with products of the major histocompatibility complex (MHC) gene region of the APC. In helper T cell (Th cell) activation, the antigen moiety is usually presented in the context of MHC class II molecules, whereas most cytotoxic T cells recognize the antigen in association with MHC class I molecules.

Any cell expressing the respective MHC gene product can act as an APC [4] and the predominant APC populations in the MHC class II-dependent antigen-presenting pathway are mononuclear phagocytes [3,4], Langerhans' cells [5–7], B cells [8] and lymphoid dendritic cells [9]. T-cell activation is preceded by interaction of surface molecules, including T-cell antigen receptor (TCR) occupancy by the antigen–MHC complex.

In human skin, most T cells are found in the dermis, usually grouped around postcapillary venules and the appendages. Intraepidermal T cells account for less than 10% of T cells in human skin. Langerhans' cells involved in antigen presentation in damaged epidermis undergo phenotypic and functional changes prior to leaving the epidermis, entering the dermal lymphatics and migrating to the paracortical areas of the draining lymph nodes. At this stage, they present the antigen–MHC complex on their surface to the TCR on either $CD4/CD8^-$ or $CD4^-/CD8$ naïve resting T cells, and elicit an antigen-specific T-cell response. The T-cell blasts thus generated then seem to preferentially return to the skin sites bearing the antigen.

It will be seen from this brief outline that epidermal cells are intimately involved in the afferent and effector limbs of the immune response. The broader principles of immunology, the mechanisms of immune responses and the implications for clinical dermatology are fully explored in Chapters 12 and 13. As discussed elsewhere, immunological dysfunction probably has a pathogenetic role in a wide range of skin diseases, including the immunobullous disorders, allergic contact dermatitis, atopic dermatitis, psoriasis and cutaneous T-cell lymphoma (mycosis fungoides).

References

1 Stingl G, Katz SI, Shevach EM *et al.* Detection of Ia antigens on Langerhans' cells on guinea pig skin. *J Immunol* 1978; **120**: 570–8.
2 Rosenthal AS, Lipsky PE, Shevach EM. Macrophage–lymphocyte interaction and antigen recognition. *Fed Proc* 1975; **34**: 1743–8.
3 Unanue ER. Antigen-presenting function of the macrophage. *Annu Rev Immunol* 1984; **2**: 395–428.
4 Germain RN. The ins and outs of antigen processing and presentation. *Nature* 1986; **322**: 687–9.
5 Stingl G, Katz SI, Clement L *et al.* Immunologic functions of Ia-bearing epidermal Langerhans' cells. *J Immunol* 1978; **121**: 2005–13.
6 Stingl G, Gazze-Stingl LA, Aberer W *et al.* Antigen presentation by murine epidermal Langerhans' cells and its alteration by ultraviolet B light. *J Immunol* 1981; **127**: 1707–13.
7 Braathen LR, Thorsby E. Studies on human epidermal Langerhans' cells. I. Allo-activating and antigen-presenting capacity. *Scand J Immunol* 1980; **11**: 401–8.
8 Chesnut RW, Grey RM. Antigen presentation by B cells and its significance in T–B interactions. *Adv Immunol* 1986; **39**: 51–94.
9 Steinman RM. The dendritic cell system and its role in immunogenicity. *Annu Rev Immunol* 1991; **9**: 271–96.

Sensory and autonomic functions

The skin is innervated by a dense, three-dimensional network of highly specialized afferent sensory and efferent autonomic nerve branches. The sensory nervous system detects the sensations of touch, vibration, pressure, change in temperature (warmth and cold), pain (including heat pain) and itch [1,2]. The autonomic nervous system is innervated by postganglionic cholinergic parasympathetic nerves and adrenergic and cholinergic sympathetic nerves. The autonomic system has an important role in maintaining cutaneous homeostasis by regulating vasomotor functions, pilomotor activity and eccrine sweat gland secretion, and is discussed further in Chapter 63.

The sensory nerves are either myelinated A fibres or unmyelinated C fibres, the latter containing sensory and autonomic fibres. The rate of transmission of a nerve impulse is proportional to the diameter of the nerve, and the various types of A fibres are thicker (1–20 μm) than the slow-conducting unmyelinated C fibres (0.2–1.5 μm). The myelinated human cutaneous nerves have been divided into Aβ and Aδ types on the basis of their conduction velocities, corresponding to 35–75 m/s and 5–20 m/s, respectively [2]. In the upper dermis, small myelinated nerves lose their nerve sheaths, and together with the unmyelinated nerves end in either free nerve endings or as specialized sensory receptors, such as Meissner's corpuscles or Merkel's receptors [2].

Much of the research into the sensory functions of the skin was carried out from the 1950s to the 1970s but, since the discovery of neuropeptides with implications for potential pharmacological modulation, there has been renewed interest in this field. Electrophysiological studies showed the existence of functionally specific afferent units [3]. Two major categories of afferent unit have been clearly established: mechanoreceptors and thermoreceptors [4,5]. A third group of pain receptors (nociceptors) respond only to high-threshold stimulation, including mechanical, thermal (heat pain) or chemical stimulation. Within each of these categories some of the afferent units determined functionally can be clearly identified with morphologically distinct structures.

Touch is mediated by mechanoreceptors in the skin, there being two main functional groups [5] according to the way they respond to constant or persistent stimuli. *Slowly adapting* mechanoreceptors respond continuously to a persistent stimulus, whereas *rapidly adapting* mechanoreceptors respond at the onset and frequently at the end of the stimulus, but not throughout the duration of the stimulus.

Glabrous and hairy skins have different types of mechanoreceptor (Fig. 4.3). The predominant mechanoreceptor in hairy skin is the hair-follicle receptor. Glabrous skin (e.g. the hairless skin of the palmar surface of the hands) has two main types of superficial mechanoreceptor: a rapidly adapting receptor, the Meissner's corpuscle; and a slowly adapting receptor, the Merkel's receptor.

Subcutaneous tissue and the deeper dermis beneath both hairy and glabrous skin contain two types of mechanoreceptors: the Pacinian corpuscle, a rapidly adapting receptor; and Ruffini's corpuscle, a slowly adapting receptor. In contrast to the small receptive-field size of Meissner's corpuscles and Merkel's receptors in the upper dermis, the receptive fields of Pacinian and Ruffini's corpuscles are large. When Pacinian corpuscles are tested with uniform or constant-velocity displacement, no impulses result, but sinusoidal displacement (vibration) generates a regular stream of impulses.

The sensations of warmth and cold are mediated by thermal receptors. Two distinct kinds of thermoreceptor [3,6] have been identified in tongue, hairy and glabrous skin of a number of mammals, including humans. Such fibres show a steady discharge dependent on temperature, but no response to non-painful intensities of mechanical stimulation. Temperature sensitivity is punctate, each afferent fibre being connected with a few receptive spots with a diameter in hairy skin of less than 1 mm.

Cold and warmth spots correspond to discrete zones of innervation by cold and warmth receptors. Cold receptors show a frequency rise on sudden cooling, the frequency of firing being proportional to the rate and degree at which the temperature is lowered. Cutaneous cold receptors are activated from approximately 1–20°C below the normal skin temperature of 34°C. Warmth receptors show a steady discharge at constant temperatures in the range 32–45°C, an acceleration of the discharge on warming the skin, small receptive fields and a high sensitivity to temperature change. At temperatures greater than approximately 45°C, heat pain via nociceptors is perceived rather than warmth.

Pain is mediated by *nociceptors*, receptors that respond selectively to stimuli that can damage tissue. Three types of nociceptor can be distinguished. Mechanical nociceptors are activated by strong mechanical stimulation, such as sharp objects. Pricking of the skin gives rise to two kinds of sensation. The initially felt 'pricking' or 'fast' pain is punctate, superficial and local, and this is followed by a more diffuse 'burning' or 'slow' pain [5]. Thermal nociceptors respond to heat or cold. In humans, heat nociceptors respond when the temperature of their receptive field exceeds 45°C, the heat pain threshold. Cold nociceptors respond to cold noxious stimuli. In addition, there are polymodal nociceptors that respond to several different kinds of noxious stimuli, including mechanical, heat and chemical [5].

Itching [7–10] is closely related to pain and is discussed in detail in Chapter 21.

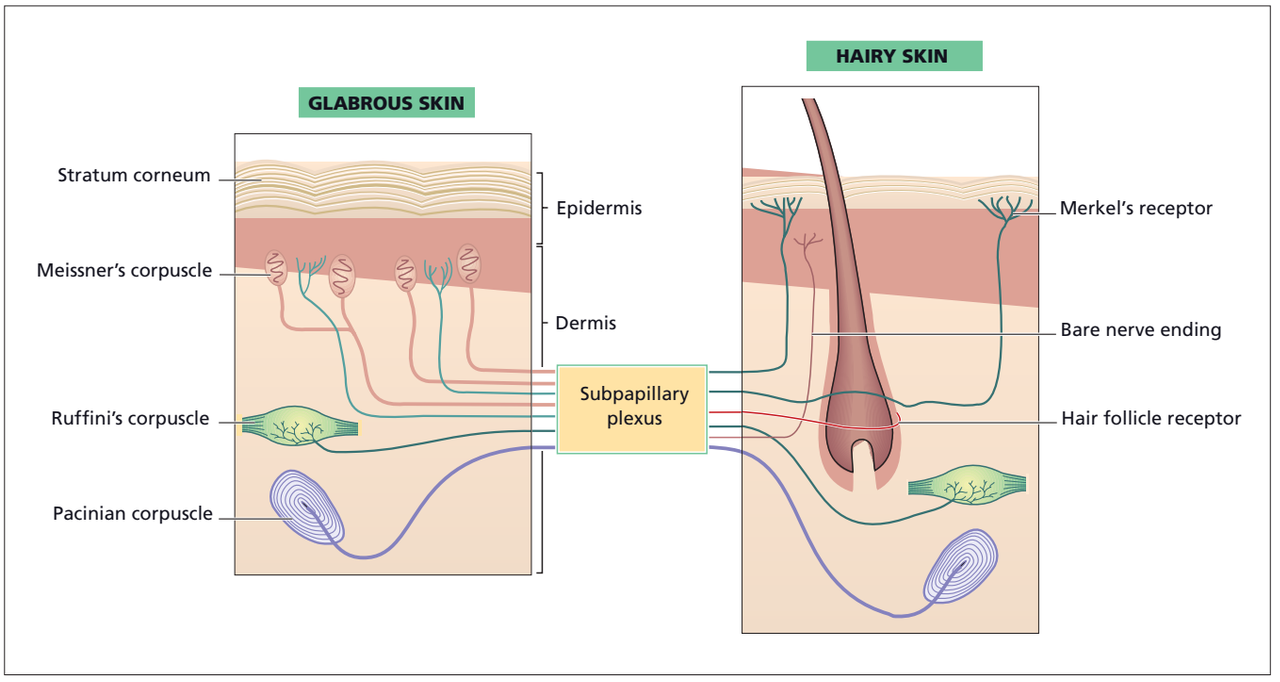


Fig. 4.3 Diagram to show the location of sensory receptors in hairless (glabrous) and hairy skin. The receptors of glabrous skin are Meissner's corpuscles and Merkel's receptors in the dermal papillae, and bare nerve endings. The receptors of hairy skin are hair-follicle receptors, Merkel's receptors, and bare nerve endings. Pacinian corpuscles and Ruffini's corpuscles are situated in the subcutaneous fat and deeper dermis in both glabrous and hairy skin.

In addition to classical neurotransmitters such as noradrenaline (norepinephrine) and acetyl choline, peripheral nerves contain neuropeptides. Neuropeptides are released from nerve terminals following depolarization, and have a role in regulating synaptic transmission. A number of neuropeptides have been demonstrated in human skin, including substance P, vasoactive intestinal peptide (VIP), somatostatin, calcitonin gene-related peptide (CGRP), neuropeptide Y and bombesin [11–13]. In addition to acting as neurotransmitters, neuropeptides have a role in the mediation of inflammation in the skin, and are discussed more fully in Chapters 12 and 63.

References

1 Metz D, Luger T. Nervous system in the skin. In: Freinkel RK, Woodley DT, eds. *The Biology of the Skin*. New York: Parthenon, 2000: 153–76.

2 Lynn B. Cutaneous sensation. In: Goldsmith LA, ed. *Physiology, Biochemistry and Molecular Biology of the Skin*. New York: Oxford University Press, 1991: 779–815.

3 Iggo A, Young DW. Cutaneous thermoreceptors and thermal nociceptors. In: Kornhuber H, ed. *The Somatosensory System*. Stuttgart: Thieme, 1975: 5–22.

4 Iggo A, ed. *Handbook of Sensory Physiology, Somatosensory System*. Berlin: Springer-Verlag, 1973.

5 Iggo A. Cutaneous receptors. In: Hubbard JI, ed. *The Peripheral Nervous System*. New York: Plenum, 1974: 347–404.

6 Iggo A. Cutaneous thermoreceptors in primates and subprimates. *J Physiol* 1969; **200**: 403–30.

7 Chapman L, Goodell H, Wolff HG. Structures and processes involved in the sensation of itch. In: Montagna W, ed. *Advances in Biology of Skin*, Vol. 1. *Cutaneous Innervation*. Oxford: Pergamon, 1960: 161–88.

8 Rothman S. Pathophysiology of itch sensation. In: Montagna W, ed. *Advances in Biology of Skin*, Vol. 1. *Cutaneous Innervation*. Oxford: Pergamon, 1960: 189–200.

9 Sinclair DC. Psychophysiology of cutaneous sensation. In: Jarrett A, ed. *The Physiology and Pathophysiology of the Skin*, Vol. 2. *The Nerves and Blood Vessels*. London: Academic Press, 1973: 429–573.

10 Bernhard JD. Pathophysiology of itching. *Lancet* 1996; **348**: 1513.

11 Brain SD, Williams TJ. Neuropharmacology of peptides in skin. *Semin Dermatol* 1988; **7**: 278–83.

12 Johansson O. Evidence for PHI-immunoreactive nerve fibres in the human skin: coexistence with VIP? *Med Biol* 1986; **64**: 67–73.

13 Eipper BA, Staffers DA, Mainn RE *et al*. The biosynthesis of neuropeptides: peptide α-amidation. *Annu Rev Neurosci* 1992; **15**: 57–85.

Bioengineering and the skin

In recent years, there has been much emphasis on the importance of objective measurement in dermatology and, driven in part by the cosmetics industry, there have been a number of advances in bioengineering technology. Relatively non-invasive bioengineering techniques can be used to assess the functions of the skin either in the resting state or in test conditions (e.g. the use of transepidermal water loss [TEWL] measurement in irritancy testing), or to quantify the response of clinical disorders to treatment (e.g. the use of ultrasound to assess therapeutic responses in chronic dermatoses). Selected aspects of bioengineering and the skin are discussed here. The importance of validation of and comparison between the plethora of similar techniques has been emphasized [1].

TEWL measurement is used to assess the barrier function of the stratum corneum, usually to predict irritancy of substances or to contribute to the assessment of clinical disorders. Various methods

have been used, but an open-chamber gradient-estimation method in the form of the *evaporimeter* is preferred, because it allows continuous measurement in ambient air, with little alteration of the microclimate overlying the skin surface [2].

In the past, TEWL was taken to indicate the water vapour passing through the stratum corneum by passive diffusion [3], but currently TEWL refers to the total amount of water loss through the skin, which includes sweating [2]. Many irritants, such as detergents and solvents, damage the skin by impairing the barrier function of the stratum corneum, and TEWL measurement has been reported to be more sensitive in assessing such irritancy effects than visual scoring [4,5], laser Doppler flowmetry, colorimetry and skin thickness by ultrasound A scan [5]. A higher TEWL has been demonstrated in lesional skin of various types of dermatitis [6,7], in psoriatic plaques [8] and in non-lesional skin of patients with atopic dermatitis [9,10].

Cutaneous gaseous exchange, a term preferable to cutaneous respiration, is the absorption of oxygen and the elimination of carbon dioxide through the skin surface [11]. In clinical medicine, transcutaneous oxygen tension (tcPo_2) measurement is used to quantify the adequacy of skin circulation, and to estimate the severity of leg ulceration, because tcPo_2 reflects the degree of oxygen supply by tissue perfusion.

The mechanical properties have been assessed by a number of techniques, designed either to induce a skin deformation and record the resisting force, or to place a load on the skin and measure the resulting deformation. The assessment of vertical forces to the skin is often avoided because this, in part, measures the contribution of the subcutaneous fat, which varies considerably between different subjects and different sites of the body in the same subject [12]. Non-invasive methods include twistometry [12], suction techniques [13], indentometry [14] and ballistometry [15].

TEWL decreases during the ageing process, becoming obvious after the fifth decade [16]. The decrease in TEWL with age is considered to be partly caused by an increased size of corneocytes and increased thickness of the stratum corneum, related to an elevated accumulation of corneocytes resulting from impaired desquamation [17]. Stratum corneum hydration is also decreased in elderly subjects [18,19], the 'dryness' of the skin in the elderly differing from pathologically dry skin, in which there is impaired barrier function.

References

1 Kligman AM. Perspectives on bioengineering of the skin. In: Serup J, James GBE, eds. *Handbook of Non-Invasive Methods and the Skin*. Boca Raton, FL: CRC Press, 1995: 3–8.

2 Pinnagoda J, Tupker RA. Measurement of transepidermal water loss. In: Serup J, James GBE, eds. *Handbook of Non-Invasive Methods and the Skin*. Boca Raton, FL: CRC Press, 1995: 173–8.

3 Wilson DR, Maibach H. Transepidermal water loss: a review. In: Leveque JL, ed. *Cutaneous Investigation in Health and Disease: Noninvasive Methods and Instrumentation*. New York: Dekker, 1989.

4 Tupker RA, Pinnagoda J, Coenraads PJ, Nater JP. The influence of repeated exposure to surfactants on the human skin as determined by transepidermal water loss and visual scoring. *Contact Dermatitis* 1989; **20**: 108–14.

5 Agner T, Serup J. Sodium lauryl sulphate for irritant patch testing: a dose–response study using bioengineering methods for determination of skin irritation. *J Invest Dermatol* 1990; **95**: 543–7.

6 Shahidullah M, Raffle EJ, Rimmer AR, Frain-Bell W. Transepidermal water loss in patients with dermatitis. *Br J Dermatol* 1969; **81**: 722–30.

7 Bichman C, Serup J. Hydration studies on scaly hand eczemas. *Contact Dermatitis* 1987; **16**: 155–9.

8 Rajka G, Thune P. The relationship between the course of psoriasis and transepidermal water loss, photoelectric plethysmography and reflex photometry. *Br J Dermatol* 1976; **94**: 253–61.

9 Van der Valk PGM, Nater JP, Bleumink E. Vulnerability of the skin to surfactants in different groups of eczema patients and controls as measured by water vapour loss. *Clin Exp Dermatol* 1985; **10**: 98–103.

10 Tupker RA, Pinnagoda J, Coenraads PJ, Nater JP. Susceptibility to irritants: role of barrier function, skin dryness and history of atopic dermatitis. *Br J Dermatol* 1990; **123**: 199–205.

11 Takiwaki H. Measurement of transcutaneous oxygen tension. In: Serup J, Jamec GBE, eds. *Handbook of Non-Invasive Methods and the Skin*. Boca Raton, FL: CRC Press, 1995: 185–95.

12 Agache PG. Twistometry measurement of skin elasticity. In: Serup J, Jamec GBE, eds. *Handbook of Non-Invasive Methods and the Skin*. Boca Raton, FL: CRC Press, 1995: 319–28.

13 Gniadecka M, Serup J. Suction chamber method for measurement of skin mechanical properties: the Dermaflex. In: Serup J, Jamec GBE, eds. *Handbook of Non-Invasive Methods and the Skin*. Boca Raton, FL: CRC Press, 1995: 329–34.

14 Manny-Aframian V, Dikstein S. Indentometry. In: Serup J, Jamec GBE, eds. *Handbook of Non-Invasive Methods and the Skin*. Boca Raton, FL: CRC Press, 1995: 349–52.

15 Hargens CW. Ballistometry. In: Serup J, Jamec GBE, eds. *Handbook of Non-Invasive Methods and the Skin*. Boca Raton, FL: CRC Press, 1995: 359–64.

16 Leveque JL, Corcuff P, de Rigal J, Agache P. *In vivo* studies of the evolution of physical properties of the human skin with age. *Int J Dermatol* 1984; **23**: 322–9.

17 Farinelli N, Beradesca E. The skin integument: variation relative to sex, age, race, and body region. In: Serup J, Jamec GBE, eds. *Handbook of Non-Invasive Methods and the Skin*. Boca Raton, FL: CRC Press, 1995: 23–6.

18 Berardesca E, Maibach HI. Bioengineering and the patch test. *Contact Dermatitis* 1988; **18**: 3–9.

19 Borroni G, Berardesca E, Bellosta M *et al*. Evidence for regional variations in water content of the stratum corneum in senile skin: an electrophysiologic assessment. *Ital General Rev Dermatol* 1982; **19**: 91.

Sociosexual communication

The skin, by virtue of its visual appeal, smell and feel, has an important role in social and sexual communication in humans, as it does in other animals. Cosmetics and clothes are used to enhance the appearance and sometimes (but not always) sexual attraction. There are many interesting parallels between humans and other animals, particularly primates, in terms of both visual communication and body odour. The reader is referred to Ebling's fascinating account for further information [1].

Reference

1 Ebling FJG. Functions of the skin. In: Rook A, Wilkinson DS, Ebling FJG, Champion RH, Burton JL, eds. *Textbook of Dermatology*, 5th edn. Oxford: Blackwell Scientific Publications, 1992: 125–55. (Section on sociosexual communication, pp. 133–8.)

CHAPTER 5
Diagnosis of Skin Disease

N.H. Cox[1] *& I.H. Coulson*[2]

[1]Department of Dermatology, Cumberland Infirmary, Carlisle, UK
[2]Dermatology Unit, Burnley General Hospital, Burnley, UK

Fundamentals of diagnosis, 5.1
Disease definition, 5.1
The history, 5.3
The presenting complaint, 5.4
General history, 5.5
Examination of the skin, 5.6
Individual lesions—nomenclature, 5.6
Shape of lesions, linear and annular lesions, 5.8
Pattern of lesions, 5.9
Distribution of lesions, 5.15
Colour of skin and of lesions, 5.15
Palpation of the skin, 5.17
Additional simple clinical examination, 5.18
Additional clinical investigations, 5.19
Diascopy, 5.19
Wood's light, 5.19
Clinical microscopy, dermoscopy, and other imaging systems, 5.20
Fine-needle aspiration of lymph nodes (FNA), 5.21
Commonly used laboratory tests, 5.21
Radiological and imaging examinations, 5.22
Skin testing, 5.22
Oral provocation tests, 5.25
Telemedicine, 5.25

Fundamentals of diagnosis

As for any other organ system, diagnosis of skin disease involves a history, examination and sometimes additional tests. The visibility of skin allows an instant diagnosis in some cases, or at least a 'diagnostic label' for the type of disease process being considered, using a variety of visual clues which include not only the individual lesional morphology but other factors such as the body site distribution, colour, scaling and arrangement of lesions. Such apparently effortless pattern recognition is actually quite complex when the individual components are analysed separately [1]. Further history, histopathology examination of skin biopsies, and other investigations, may be needed to refine the diagnosis or, in some instances, to identify a cause. The concept often held by non-dermatologists, that dermatology just involves having a 'quick look' at a patient, ignores issues around investigation and successful management (Fig. 5.1).

Whilst visual aspects are of great importance in dermatology diagnosis, other sensory modalities are also used in examination; for example, palpation may help in determining induration, quality of scaling and temperature changes [2], and even smell may be diagnostic in some instances. Some conditions may lack objective signs or may just have secondary changes (for example, due to scratching); in several eruptions, a knowledge of internal disease is required in order to make a diagnosis. This chapter briefly introduces aspects of the history, examination and other diagnostic manoeuvres.

References

1 Lawrence CM, Cox NH. *Physical Signs in Dermatology*, 2nd edn. London: Mosby, 2002.
2 Cox NH. Palpation of the skin—an important issue. *J Roy Soc Med* 2006; **99**: 598–600.

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

Disease definition

Most skin diseases do not have a cause which is both identified and unique to that disorder. Conversely, many known causes of skin disease may play a part in several different types of disorder (for example, ultraviolet light may cause or contribute to sunburn, skin cancers, skin ageing and various patterns of photosensitivity; chromate may cause irritant contact dermatitis, caustic burns or allergic contact dermatitis at various body sites). Current definitions of most skin diseases therefore rely on the presence of a constellation of clinical, histopathological and sometimes immunopathological or genetic features. Even common and important diseases such as psoriasis have no strict and unique diagnostic criteria; indeed, some feel (and genetic studies are perhaps starting to support the thesis) that what has been accepted as 'psoriasis' should actually be more tightly classified morphologically [1] in order to help understand phenotypic heterogeneity [2]; it may be that this common dermatosis is several different diseases or is expressed according to different pathomechanisms.

The diagnostic stringency required for day-to-day clinical management may differ from that required in epidemiological and therapeutic research, in which it is clearly important to be sure that all studies are actually describing the same entity [3]. In some disorders which remain difficult to classify, such as parapsoriasis [4], numerous names may have been applied over the years and it may be difficult to know exactly what was meant in a previous publication. This problem applies even in atopic eczema/dermatitis, a very common disorder and generally considered a fairly straightforward diagnosis, and has significant implications for epidemiological research. Similarly, treatments and prognosis may vary between different types of cutaneous T-cell lymphoma (CTCL), but it is impossible to be certain about the types of CTCL that have been assessed in some studies.

Scientific advances are resolving some of these diagnostic and terminology issues, but many disease definitions in dermatology are still based on a constellation of clinically determined,



Fig. 5.1 The distribution of eczema in this patient strongly suggests that a reaction to footwear is the prime culprit. Despite this immediately apparent clue, appropriate investigation, management and resolving schooling issues were time consuming.

morphological cutaneous features. Some of these have distinct anatomical correlates (e.g. myxoid cyst), a specific external cause (e.g. scabies), or have a known genetic or biochemical defect (e.g. many genodermatoses). Many will have characteristic histological features, although—particularly in the case of inflammatory dermatoses—there are often areas of overlap between disease entities.

In other cases, there may be a number of different cutaneous features or multiorgan involvement which are associated together as a syndrome, as in systemic lupus erythematosus (SLE) or Behçet's disease. A syndrome is usually defined by the simultaneous presence of a fixed combination of disease indicants, but these may not all be present in an individual case and may not require to be present concurrently; additionally, 'overlap' syndromes can occur where features of two or more related syndromes are present in the same patient. In such instances, making a diagnosis may rely on fulfilling a certain number of criteria—for example, the American Rheumatism Association (ARA) criteria for diagnosis of SLE [5]. This can be further refined by having major and minor criteria in order to achieve a given sensitivity and specificity. In some instances, such as the International Study Group diagnostic criteria for Behçet's disease, a single diagnostic criterion must be fulfilled (recurrent oral aphthae) together with a given number of minor criteria [6]. In other instances, the number of criteria in each category which need to be fulfilled may vary—for example, in the diagnostic criteria for streptococcal toxic shock, the number of minor criteria that need to be fulfilled depends on the strength of the major criteria that are achieved [7]. All such diagnostic criteria may need to be updated to take into account new diagnostic techniques. However, it should be noted that many such criteria have been derived for confirmation of diagnosis for epidemiological or research reasons, rather than being a prerequisite for clinical diagnosis and management of individual patients. Thus, even for the same disorder, different diagnostic criteria may exist, with different purposes, complexity, levels of sensitivity and specificity, and validity; in atopic dermatitis, the criteria of Hanifin and Rajka are fulfilled by having three (of four) major criteria and three (of 22) minor criteria [8], whilst those of Williams and Pembroke proposed a single obligatory criterion (itchy skin) together with three (of five) additional features [9]. Clearly, some of the 22 minor criteria will have greater discriminatory value than others. Validation of such diagnostic criteria has been discussed in more detail elsewhere, using these examples [10].

Observer experience may also influence how well diagnostic criteria work in practice; the UK 'seven-point' checklist for suggesting melanoma as a diagnosis in pigmented lesions, whilst a useful tool to generate suspicion by patients and non-specialists [11,12], does not have sufficient sensitivity or specificity to allow risk to be assessed from the score criteria when they are used in the clinical situation of a primary care physician deciding that urgent dermatological opinion is required [13]. However, it is only by recording, challenging and refining such diagnostic criteria that advances will occur. This is particularly important for trainees and non-experts; for example, a diagnostic algorithm designed for use by rural health workers in under-developed countries was tested and had about 80% accuracy [14], a major benefit for care providers with essentially no access to ongoing education. At the other end of the scale, more sophisticated computer-assisted diagnostic algorithms can be constructed from detailed morphological and body site descriptions [15].

It is also important not to view such diagnostic criteria as static; for example, in Sweet's syndrome (Chapter 50), proposed diagnostic criteria have been modified over a period of years, and criteria for drug-induced Sweet's disease have been added. In other areas, proof of genetic mutations is redefining disease diagnosis—for example, in the classification of different types of epidermolysis bullosa [16–18]. Careful correlation of genotype and phenotype enables large diagnostic systems to be constructed, which aid diagnosis for subsequent patients [19,20] as well as assisting epidemiological research [21].

Having an accurate diagnosis is obviously important for patients, for prognosis, and may become important for more precisely targeted treatment [22,23]. It also enables construction of diagnostic coding systems, which are widely used in determining the cost of skin disease (largely relating to reimbursements for periods of care in insurance-led health-care systems, termed 'diagnosis-related groups' (DRGs [24,25]) or 'health-related groups'), but which also aid epidemiological and therapeutic research. There is, however, concern about accuracy of coding, costing and case mix issues in such systems.

Diagnosis, and thus construction of valid databases, is influenced by many issues. Specifically, drug reaction surveillance generally relies on voluntary reporting [26,27], which may vary according to perceived severity, 'newness' or other unusual aspects. For example, searching the UK Committee on Safety of Medicines data for reports of toxic epidermal necrolysis (searched as TEN), most reports relate to lamotrigine [28] although historically this would not be the commonest cause of TEN—reporting may reflect increased use of a drug, 'newness' of the drug or severity of the reaction, active encouragement not to report well-known reactions, etc. Cutaneous reactions typically account for most adverse drug reaction reports, for example they comprise almost 30% in the French Pharmacovigilance database [27], but accurate

diagnosis of different types of drug eruption will often vary according to whether the reporting physician has dermatological experience or not. Similarly, in occupational reporting, the cases and situations encountered by occupational health physicians (mainly irritant dermatitis in larger industrial settings) will differ from those seen by dermatologists (more allergic contact dermatitis, including a greater emphasis on occupations such as hairdressing) [29–31]. Generally, systems that are designed to include other disciplines, such as the World Health Organization's International Classification of Diseases (ICD) system, have been felt to be dermatologist 'non-friendly', and unhelpful for clinical and epidemiological dermatology [32], so some national bodies have created their own diagnostic indexing systems (such as the British Association of Dermatologists Dermatological Diagnostic Index System, DDIS.)

References

1 Griffiths CEM, Christophers E, Barker JNWN *et al*. A classification of psoriasis vulgaris according to phenotype. *Br J Dermatol* 2007; **156**: 258–62.
2 Christophers E. Explaining phenotype heterogeneity in patients with psoriasis. *Br J Dermatol* 2008; **158**: 437–41.
3 Burton JL. The logic of dermatological diagnosis. *Clin Exp Dermatol* 1981; **6**: 1–21.
4 Lambert WC, Everett MA. The nosology of parapsoriasis. *J Am Acad Dermatol* 1981; **5**: 373–95.
5 Tan EM, Cohen AS, Fries JF *et al.* The. revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982; **25**: 1271–7.
6 International Study Group for Behçet's disease. Criteria for diagnosis of Behçet's disease. *Lancet* 1990; **335**: 1078–80.
7 Wiesenthal AM, Ressman M, Caston SA, Todd JK. Toxic shock syndrome, 1: clinical exclusion of other syndromes by strict and screening definitions. *Am J Epidemiol* 1985; **122**: 847–56.
8 Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Dermatol Venereol* (Stockh) 1980; **92**: 44–7.
9 Williams HC, Pembroke AC. *Br J Dermatol* 1994; **131**: 406–16.
10 Remitz A, Reitamo S. The clinical manifestations of atopic dermatitis. In: Reitamo S, Luger TA, Steinhof M, eds. *Textbook of Atopic Dermatitis*. London: Informa Healthcare, 2008: 1–12.
11 MacKie RM, Doherty VR. Seven-point checklist for melanoma. *Clin Exp Dermatol* 1991; **16**: 151–3.
12 Keefe M, Dick DC, Wakeel RA. A study of the value of the seven-point checklist in distinguishing benign pigmented lesions from melanoma. *Clin Exp Dermatol* 1990; **15**: 167–71.
13 Cox NH, Madan V, Sanders T. The U.K. skin cancer 'two-week' proforma: assessment of potential modifications to improve referral accuracy. *Br J Dermatol* 2008; **158**: 1293–8.
14 Mahé A, Faye O, N Diaye HT *et al*. Definition of an algorithm for the management of common skin diseases at primary health care level in sub-Saharan Africa. *Trans R Soc Trop Med Hyg* 2005; **99**: 39–47.
15 Ahn HH, Kang KY, Kang MK *et al*. A novel computer-assisted algorithmic method for differential diagnosis of dermatological diseases. *J Dermatol* 2005; **32**: 956–62.
16 Nakamura H, Sawamura D, Goto M *et al*. Epidermolysis bullosa simplex associated with pyloric atresia is a novel clinical subtype caused by mutations in the plectin gene (PLEC1). *J Mol Diagn* 2005; **7**: 28–35.
17 Fine J-D, Eady RAJ, Bauer EA *et al.* The classification of inherited epidermolysis bullosa (EB): Report of the Third International Consensus Meeting on Diagnosis and Classification of EB. *J Am Acad Dermatol* 2008; **58**: 931–50.
18 Wessagowit V, Kim SC, Woong OS, McGrath JA. Genotype-phenotype correlation in recessive dystrophic epidermolysis bullosa: when missense doesn't make sense. *J Invest Dermatol* 2005; **124**: 863–6.
19 *Online Mendelian Inheritance in Man* http://www.ncbi.nlm.nih.gov/sites/entrez?db=OMIM
20 Leech SN, Moss C. A current and online genodermatosis database. *Br J Dermatol* 2007; **156**: 1115–8.
21 Gwin M, Khoury MJ. Dermatology and the human genome: an epidemiologic approach. *Arch Dermatol* 2007; **143**: 1194–6.
22 Harr T, Itin PH. Pharmacogenomics in dermatology. *J Dtsch Dermatol Ges* 2005; **3**: 214–21.
23 Nickoloff BJ, Nestle FO. Recent insights into the imunopathogenesis of psoriasis provide new therapeutic opportunities. *J Clin Invest* 2004; **113**: 1664–75.
24 Hensen P, Fürstenberg T, Luger TA *et al*. Case mix measures and diagnosis-related groups: opportunities and threats for inpatient dermatology. *J Eur Acad Dermatol Venereol* 2005; **19**: 582–8.
25 Roeder N. DRGs in dermatology: quality of coding and effects of case mix. *J Dtsch Dermatol Ges* 2003; **1**: 36–45.
26 Medicines and Healthcare Products Regulatory Agency. Committee on Safety of Medicines. http://www.mhra.gov.uk/Committees/Medicinesadvisorybodies/CommitteeonSafetyofMedicines/index.htm
27 Thiessard F, Roux E, Miremont-Salamé G *et al*. Trends in spontaneous adverse reaction reports to the French Pharmacovigilance system (1986–2001). *Drug Safety* 2005; **28**: 731–40.
28 Medicines and Healthcare Products Regulatory Agency. http://www.mhra.gov.uk/SearchHelp/Search/Searchresults/index.htm?within=Yes&keywords=TEN
29 Cherry N, Meyer JD, Adisesh A *et al*. Surveillance of occupational skin disease: EPIDERM and OPRA. *Br J Dermatol* 2000; **142**: 1128–34.
30 Shum KW, Meyer JD, Chen Y *et al*. Occupational contact dermatitis to nickel: experience of the British dermatologists (EPIDERM) and occupational physicians (OPRA) surveillance schemes. *Occup Environ Med* 2003; **60**: 954–7.
31 Cox NH, Gawkrodger DJ, Spiro J *et al*. Hand dermatitis: fit to work? *Expert Rev Dermatol* 2006; **1**: 497–502.
32 Shenefelt PD. Limits of ICD-9-CM code usefulness in epidemiological studies of contact and other types of dermatitis. *Am J Contact Dermatitis* 1998; **9**: 176–8.

The history

Clinical diagnosis is paramount in dermatology, a discipline where histopathological and other techniques are often not routinely used, and which may only support a clinical diagnosis rather than being specific in their own right. However, whilst not necessarily required for rashes, histopathology for confirmation of the diagnosis, and for assessment of adequacy of excision, is important in the case of skin neoplasms—an increasing part of the work of dermatologists. Histopathological support for a diagnosis is often appropriate for some rashes (especially if systemic therapy is being considered).

In most cases, a carefully directed history is important for refining the diagnosis, for identifying further investigations (both to confirm a diagnosis and to determine the investigations that might help to identify a cause) and to address issues that may be important for optimal management. The amount of history required, and the sequence of history-taking and examination, may vary depending on the condition and on the referral information already provided to the dermatologist from a primary care provider. For example, a patient with hand dermatitis, especially if it is of possible occupational causation (Chapter 27), may need a detailed history about agents handled, hand washing and protective gloves that are used (Fig. 5.2).

Several national committees, consensus conferences, workshops and therapeutic guidelines have suggested minimum data sets for the medical history and morphological findings in skin diseases [1,2] as well as the information and investigations that are suitable for (especially systemic) therapies [3–5]; these are likely to become an important part of the clinical history along with the more fundamental issues pertaining to diagnosis, that are discussed below.



Fig. 5.2 A selection of glove materials; knowledge of types of protective gloves is potentially of high importance in preventing industrial hand dermatitis.



Fig. 5.3 Herpes simplex. Itch typically precedes the visible cutaneous signs, and is often described as having a burning quality (note also the typical 'herpetiform' clustering and also that these lesions are pustules, implying a duration of a few days).

References

1 McHenry PM, Williams HC, Bingham EA. Management of atopic eczema. Joint Workshop of the British Association of Dermatologists and the Research Unit of the Royal College of Physicians of London. *BMJ* 1995; **310**: 843–7.

2 Cox NH. Dermatological aspects of the NHS National Cancer Data Project. *Br J Dermatol* 2003; **149**: 1089–91.

3 Roberts DLL, Anstey AV, Barlow RJ *et al*. UK guidelines for the management of cutaneous melanoma. *Br J Dermatol* 2002; **146**: 7–17.

4 Grattan CEH, Humphreys FY. Guidelines for evaluation and management of urticaria in adults and children. *Br J Dermatol* 2007; **157**: 1116–23.

5 Smith CH, Anstey AV, Barker JN *et al*. British Association of Dermatologists guidelines for use of biological interventions in psoriasis 2005. *Br J Dermatol* 2005; **153**: 486–97.

The presenting complaint

The following issues are likely to form part of the dermatological history, especially for dermatoses, in most consultations, although the emphasis on each will vary according to the diagnostic area.

Symptoms. Itch is the prime dermatological symptom, but may be variously described by different patients; there are individual differences in threshold and perception. Intense itch is typical in scabies, atopic dermatitis and lichen planus, whereas psoriasis and pityriasis versicolor usually cause less severe itch for the same degree of body surface involvement. Indeed, the degree of itch (as judged by the amount of scratching, and the general affect, and even without any other history), is potentially useful in distinguishing between atopic versus seborrhoeic dermatitis in infants.

Other symptoms include various qualities of pain, such as sharp pain (e.g. chondrodermatitis of the ear), burning (e.g. chilblains) or tenderness (e.g. erythema nodosum). The site may influence symptoms; for example, urticaria causes itch, but the same pathology affecting the palms often causes pain (because the oedema is deeper and the firmer tissues of the palm cannot distend easily). Both the quality and intensity of symptoms should therefore be recorded.

Symptoms usually parallel overt development of an eruption, but discordance can be diagnostically useful—for example, localized itch preceding herpetic vesicles (Fig. 5.3), or fever and malaise preceding erythema and swelling in cellulitis of the leg or erysipelas.

Duration, evolution, periodicity and previous episodes. The overall duration of a rash or localized lesion is usually apparent to the patient, although there are exceptions; basal cell carcinoma, for example, is often noticed only when it ulcerates, and the patient will therefore underestimate the duration of the lesion. Whether the onset of a rash was sudden or gradual may be diagnostically useful. The overall duration is also of diagnostic help for localized lesions. For example, a presumed keratoacanthoma that is still enlarging after a few months is probably a squamous cell carcinoma; lesions that turn black overnight do so due to intralesional bleeding, not as a result of becoming a melanoma.

More precise details may require carefully phrased questions. In urticaria, the diagnostic feature is that individual lesions change from day to day (usually over a few hours), but the overall duration of the process may be years. Asking the patient about the duration of the eruption needs to distinguish between these two aspects. Similarly, if lesions are not present, then diagnosis may depend on the patient's description, but there are pitfalls; weals are often described as 'blisters', a term which should not be taken at face value, and distinguishing between eruptions triggered by heat or sunlight often causes confusion. It is helpful to ask the patient whether any particular factors (e.g. dietary items, cosmetics, work chemicals, sunlight) appear to provoke (or alleviate) the condition.

Some dermatoses have a characteristic evolutionary sequence (e.g. pityriasis rosea, in which a solitary larger 'herald patch' precedes the widespread eruption by a few days, or 'pre-pemphigoid' eczematous lesions). Other disorders may demonstrate periodicity; for example, occupational contact dermatitis may improve at

weekends or holiday periods, and both photosensitivity and airborne contact allergy to plants may be seasonal.

Previous episodes of a similar type are likely to be relevant, but other skin problems may be important even if they do not appear to be the same process. For example, patients with type IV hypersensitivity to fragrance materials might at different times have eyelid rash due to cosmetics, axillary rash due to deodorants, widespread eczema due to soaps or clothing detergents or diffuse facial rash due to airborne perfume agents. In such cases the body site distribution may be confusing, but the sequence of sites affected should be determined, especially the site of initial involvement in the case of rashes.

Previous episodes are also potentially relevant for localized lesions (e.g. patients with two or three previous basal cell carcinomas have a high risk of another, so the level of suspicion may be greater in those with a positive previous history of these lesions).

Previous therapy. Previous treatment and response should be documented to guide future therapy, and to exclude the possibility of the diagnosis being obscured (for example, tinea incognito due to use of topical corticosteroids).

General history

Medical history, medications and dietary history. General medical conditions may have cutaneous features, and should be noted, especially in patients with rashes or generalized skin symptoms (see Chapter 62). Recent illnesses, even if apparently resolved, deserve special attention, as conditions such as urticaria, vasculitis, guttate psoriasis and erythema multiforme can be triggered by viral or bacterial infections in the weeks preceding the onset of the rash. Any recent or current systemic medication should be noted, including regular or intermittent self-medication or that received from relatives or friends, both as a possible cause of drug eruptions and to avoid interactions with treatment prescribed for the skin complaint. Topical therapies should also be considered, both in terms of their efficacy (or lack of), as well as because they may conceal or even cause a dermatosis. Allergies to medicaments or other agents may be important, as are drugs that might interact with anaesthetics or cause surgical bleeding.

Dietary history may be important in some individuals, especially those with intermittent urticaria or anaphylaxis. However, diet is often erroneously blamed for skin eruptions.

Family history. This may be important if a genodermatosis is suspected, in disorders with more complex inheritance (e.g. atopic dermatitis, psoriasis), and in some non-inherited disorders in which family contact is important (e.g. scabies, chickenpox).

Occupation and leisure activities. An occupational history may be of importance, both current and previous, particularly in individuals with eczema; a detailed account of processes and chemicals may be required, together with additional testing (Chapters 25–27). Hands are the most commonly affected site in occupational dermatitis, and it is useful to record details of hand protection (e.g. gloves, barrier creams) as well as the agents to which the patient is exposed. Hobbies less commonly cause problems, but may involve exposure to a variety of common allergens. Outdoor work or hobbies may also involve exposure to sun, cold or to plant allergens. An overview of some of these aspects is given in Table 5.1.

Ethnicity and cultural aspects (Chapter 9). Several disorders have a predilection to occur in specific racial groups—for example, the high frequency of sarcoidosis in black patients [1], or prurigo pigmentosa in the Japanese [2]. The morphology of common diseases may be altered by racial pigmentation, and normal pigmentary variations may be apparent. The severity of diseases may appear to be different between races or cultural groups; atopic eczema has been noted to be more frequent in children born in England of Asian or Caribbean origin [3,4]. Cultural differences may be diagnostically important, such as use of hair pomades and skin depigmenting agents, or may influence acceptance and understanding.

Geographical factors. Foreign travel, especially if recent, is a potentially important cause of dermatological disease. The place(s) visited may lead to specific likely diagnoses, and documentation should include any brief stopping-off countries. A long visit increases the risk of significant exposure to environmental agents, but dust-borne spores and insect vectors may be carried in aircraft and potentially alter the natural history of a disorder by allowing exposure outside the anticipated geographical distribution.

Social and psychological factors. The living conditions, economic status and standard of nutrition of the patient may be relevant both as a guide to diagnosis and to ensure compliance with the treatment advised. Specific examples of important social factors include the strong association between cigarette smoking and palmoplantar pustulosis, and the multiple influences of excessive alcohol intake on the severity and therapeutic options in psoriasis. A sexual history is also required in some instances. The effects of skin problems on lifestyle, relationships, costs to the patient and costs to the community from work days lost are important, and it is helpful to know the patient's main concerns. This applies particularly to chronic skin eruptions, but many patients with discrete lesions primarily want reassurance that they are not malignant. It is unlikely that many skin eruptions are due to 'nerves', but psychological factors can clearly be of importance in aggravating or perpetuating symptoms, and may be the primary abnormality in some instances (Chapter 64).

References

1 Sartwell PE. Racial differences in sarcoidosis. *Ann NY Acad Sci* 1976; **278**: 368–70.

2 Nagashima M. Prurigo pigmentosa: clinical observations in 14 cases. *J Dermatol* 1978; **5**: 61–7.

3 Sladden MJ, Dure-Smith B, Berth-Jones J, Graham-Brown RAC. Ethnic differences in the pattern of skin disease seen in a dermatology department: atopic dermatitis is more common in Asian referrals in Leicestershire. *Clin Exp Dermatol* 1991; **16**: 348–9.

4 Williams HC, Pembroke AC, Forsdyke H *et al.* London born black Caribbean children are at increased risk of atopic dermatitis. *J Am Acad Dermatol* 1995; **32**: 212–7.

Table 5.1 Some occupations and hobbies and their dermatological problems. (Adapted from GM White and NH Cox, *Diseases of the Skin*, 2nd edn. London: Mosby, 2000: 12. See also 'Occupational Dermatoses', Chapter 27.)

Activity	Examples of dermatological implications that may occur
Agricultural	Irritant dermatitis (e.g. to disinfectants, physical 'wear and tear') (Chapter 25) Contact allergy (e.g. rubber chemicals in gloves or footwear) (Chapter 26) Hazards from animals (e.g. tinea; Chapter 36) Hazards from plants (e.g. lichen allergy in forestry)
Gardening	Irritant or contact allergic dermatitis related to many plants Contact allergy to gloves Bites and stings; harvest mites etc. (Chapter 38)
Building trade and 'do-it-yourself'	Irritant dermatitis from cement (also causes chemical burns), plaster, solvents, preservatives, fibreglass Contact allergic dermatitis, especially from chromate in cement, epoxy resin, formaldehyde resins, colophony in soldering flux Mechanical—frictional palmar dermatitis from tools; vibration white finger related to use of some tools
Cars (trade or home)	Irritant dermatitis from solvents, paints, hand cleansers Contact allergic dermatitis from paints, resins, metals, rubber (gloves, tyres, tubing) Chemical leukoderma from rubber chemicals in tyre manufacture
Cooking (work or home)	Irritant dermatitis (detergents/hand washing, juices of meat, fruit and vegetables) Contact allergic dermatitis (or urticaria in some cases) from fruits, garlic, spices, meat, fish, gloves Physical—cuts, burns
Cleaning (work or home)	Irritant dermatitis from detergents Contact allergic dermatitis to fragrances or antimicrobials in detergents, polishes etc., or to gloves
Health workers	Irritant dermatitis from cleaning agents/hand washing Contact allergies—latex allergy (urticaria or dermatitis), medicament allergies (dentists—allergy to balsam flavourings, mercury, resins) Infections and infestations, e.g. scabies, especially nursing homes
Hairdressers	Irritant dermatitis from shampoos, bleaches etc. Contact allergic dermatitis from perfumes, dyes, bleaches, lanolin, antimicrobials; contact urticaria due to henna
Textiles (work or hobby)	Irritant dermatitis from solvents, bleaches, detergents/hand washing Contact allergic dermatitis—dyes, formaldehyde resins (finishes), mordants
Travel	Physical—photodermatoses, prickly heat Animals—bites, stings, seabather's eruption, swimmer's eruption, other marine invertebrate hazards Infections—cutaneous larva migrans, tungiasis, leishmaniasis, tropical viral exanthems Contact allergy—exotic plants, phytophotodermatitis

Examination of the skin

Most patients referred to the dermatologist have objective changes in the appearance or consistency of the skin. Even those who describe itch without rash often have dry skin or other features that can be elicited, such as dermographism. Most lesions and eruptions can either be diagnosed fully, or at least assigned to a diagnostic category, by clinical examination; indeed, clinical diagnosis is more precise than laboratory tests in many disorders. The ability to elicit and interpret cutaneous physical signs is therefore of fundamental importance in dermatological training.

The patient should always be examined in a good light, preferably daylight, and with magnification of lesions if necessary. Ideally, the entire skin should be examined in every patient, and particularly if the diagnosis is in doubt, as this may reveal lesions that are more easily identifiable and have not been modified by secondary changes. Adolescents and elderly people will often deny the existence of lesions other than those presented for examination, the former because they are unwilling to undress and the latter because they have not seen them.

In the examination of the skin, it is helpful to consider the morphology of individual lesions, their overall pattern and spatial relationship to each other, and their body site distribution. Each of these aspects is discussed more fully below. Specific attention to hair, nails and the mucous membranes is required. Careful description and use of nomenclature aids the monitoring of changes during follow-up, and any discussion with colleagues.

Touching the skin is important in most instances, and is discussed in more detail below. Gloves should be worn for examination of the mouth, genital/perineal region, or in the case of infective or infected dermatoses.

Additional, simple aids to clinical examination include use of Wood's light, diascopy, dermoscopy, starch iodine testing to identify sweat duct orifices and hair microscopy.

Individual lesions—nomenclature

The commoner descriptive terms applied to cutaneous lesions are listed below. These definitions are broadly in agreement with those recommended by the Nomenclature Committee of the International League of Dermatological Societies [1]. However, it is important to note that some of these definitions have been challenged subsequently [2–5]. A particular problem that many authors have glossed over is the dynamic aspects of skin disease. For example, some papules (less than 0.5 or 1 cm, depending on the source of the definition) are destined to grow larger and become nodules, whereas others (such as syringomas) rarely do so. Additionally, some eruptions may have essentially similar lesions but whose size may include both papules and nodules. Recording of actual size of lesions, or the range of sizes, is often a more useful clinical record [6].

References

1 Winkelmann RK. Glossary of basic dermatology lesions: the International League of Dermatological Societies Committee on Nomenclature. *Acta Derm Venereol Suppl (Stockh)* 1987; **130**: 1–16.

2 Lewis EJ, Dahl MV, Lewis CA. On standard definitions: 33 years hence. *Arch Dermatol* 1997; **133**: 1169.

3 Resnik KS, Ackermann AB. On standard definitions of individual skin lesions. *Arch Dermatol* 1998; **134**: 636–7.
4 Ashton RE. Standard definitions in dermatology: the need for further discussion. *Arch Dermatol* 1998; **134**: 637.
5 Malak JA, Kibbi AG. Revised terminology in dermatology: a call for the new millennium. *Arch Dermatol* 2001; **137**: 93–4.
6 Lawrence CM, Cox NH. *Physical Signs in Dermatology*, 2nd edn. London: Mosby, 2002: 1–12.

Glossary

alopecia—absence of hair from a normally hairy area.
aphtha—a small ulcer of the mucosa.
atrophy—a loss of tissue from one or more of the epidermis, dermis or subcutaneous tissues. There may be fine wrinkling and increased translucency if the process is superficial.
burrow—a small tunnel in the skin that houses a parasite, such as the scabies acarus.
callus—a localized hyperplasia of the stratum corneum.
cellulitis—an inflammation of cellular tissue, particularly purulent inflammation of the deep dermis and subcutaneous tissue.
comedo (pl. comedones)—a plug of keratin and sebum in a dilated pilosebaceous orifice.
crusts (scabs)—crusts consist of dried serum and other exudates.
cyst—any closed cavity or sac (normal or abnormal) with an epithelial, endothelial or membranous lining and containing fluid or semisolid material.
ecchymosis (bruise)—a macular area of haemorrhage more than 2 mm in diameter.
en cocarde (or 'cockade')—a rosette pattern of concentric rings, usually applied to naevi.
erosion—a loss of epidermis, which heals without scarring. It commonly follows a blister.
erythema—redness of the skin produced by vascular congestion or increased perfusion.
excoriation—loss of skin substance, specifically produced by scratching.
exfoliation—the splitting off of the epidermal keratin in scales or sheets.
fibrosis—the formation of excessive fibrous tissue.
fissure—any linear gap or slit in the skin surface.
fistula—an abnormal passage from a deep structure, such as a hollow viscus, to the skin surface or between two structures. It is often lined with squamous epithelium.
gangrene—death of tissue, usually due to loss of blood supply.
guttate lesions—small round or oval lesions distributed as a 'shower' of droplets. Usually applied to a form of psoriasis.
haematoma—a localized tumour-like collection of blood.
keratoderma—a horny thickening of the skin.
lichenification—thickening of the epidermis (and to some extent also of the dermis) in response to prolonged rubbing.
macule—a circumscribed alteration in the colour of the skin. Authorities vary on the issue of scaling causing texture change within the definition.
maculopapular—rash consisting of both macules and papules.
milium—a tiny white cyst containing lamellated keratin.
nodule—a solid mass in the skin, which can be observed as an elevation or can be palpated. It is more than 0.5 cm in diameter. It may involve epidermis and dermis, dermis and subcutis, or subcutis alone. It may consist of fluid, other extracellular material (e.g. amyloid), inflammatory or neoplastic cells.
papilloma—a nipple-like mass projecting from the surface of the skin.
papule—a circumscribed palpable elevation, less than 0.5 cm in diameter. By careful examination it is often possible to determine whether the thickening involves predominantly the epidermis or the dermis and what type of pathological process is concerned. The only distinction between a papule and a nodule is the size, and this is artificial; some lesions characteristically occur at the smaller size of a papule, whereas others typically enlarge from a papule to become a nodule. Recording a finite size is more useful.
petechia (pl. petechiae)—a punctate haemorrhagic spot, approximately 1–2 mm in diameter.
plaque—an elevated area of skin, usually defined as 2 cm or more in diameter. It may be formed by the extension or coalescence of either papules or nodules as in psoriasis and granuloma annulare, respectively. Small plaque is sometimes used for such lesions 0.5–2 cm in diameter.
poikiloderma—the association of cutaneous pigmentation, atrophy and telangiectasia.
pustule—a visible accumulation of free pus. It may occur within a pilosebaceous follicle or a sweat duct or, less often, on glabrous skin. Most commonly due to infections (Fig. 5.3), but some eruptions typically cause sterile pustules.
pyoderma—any purulent skin disease.
scale—a flat plate or flake of stratum corneum. A *collarette* scale is a fine, peripherally attached and centrally detached scale at the edge of an inflammatory lesion. Annular scaling is also seen in porokeratosis (Fig. 5.4). *Furfuraceous or pityriasiform* scales are fine and loose. *Ichthyotic* scales are large and polygonal. Scaling may accompany or follow many inflammatory disorders. Silvery scales are characteristic of processes involving parakeratosis, especially psoriasis. The silvery colour is due to reflection of light at the many air–keratin interfaces and can be altered by wetting the skin.



Fig. 5.4 Annular scaling in porokeratosis; subtle atrophy is also visible centrally.

scar—replacement by fibrous tissue of another tissue that has been destroyed by injury or disease. An *atrophic* scar is thin and wrinkled. A *hypertrophic* scar is elevated, with excessive growth of fibrous tissue. A *cribriform* scar is perforated with multiple small pits.

sclerosis—diffuse or circumscribed induration of the subcutaneous tissues. It may also involve the dermis, when the overlying epidermis may be atrophic. It is characteristically seen in scleroderma, but may occur as a sequel to or in association with many different processes.

sinus—a cavity or track with a blind ending.

target lesions—these are less than 3 cm in diameter and have three or more zones, usually a central area of dusky erythema or purpura, a middle paler zone of oedema, and an outer ring of erythema with a well-defined edge.

tumour—literally a swelling. The term is used to imply enlargement of the tissues by normal or pathological material, or cells that form a mass. It may be inflammatory or non-inflammatory, benign or malignant. The term should be used with care, as many patients believe it implies a malignancy with a poor prognosis.

ulcer (of skin)—a loss of dermis and epidermis, often with loss of the underlying tissues.

vegetation—a growth of pathological tissue consisting of multiple, closely set, papillary masses.

vesicles and bullae—visible accumulations of fluid within or beneath the epidermis. Vesicles are small (less than 0.5 cm in diameter) and often grouped. Bullae, which may be of any size over 0.5 cm, should be subdivided as multilocular (due to coalesced vesicles, typically in eczema) or unilocular.

weal—a transient area of dermal or dermal and hypodermal oedema, white, compressible and usually evanescent. It is the characteristic lesion of urticaria. It is often surrounded by a red, axon-mediated flare.

Shape of lesions, linear and annular lesions

The shape of each lesion and the pattern in which neighbouring lesions are arranged in relation to each other is often of great significance and may provide an easily recognizable clue to a rapid visual diagnosis. The main shapes, with examples, are listed in Table 5.2 and illustrated in Figs. 5.5–5.10. The mechanism or anatomical factor dictating the shape can sometimes be inferred, as in the case of many linear lesions (Table 5.3) or the vascular patterning leading to livedo (Fig. 5.5); in other instances, such as many annular lesions (Table 5.4) and reticulate lesions (Fig. 5.6), the explanation for the pattern is less clear.

A specific cause of a linear lesion is the Koebner or isomorphic phenomenon [1]. This term is applied when localized, non-specific trauma locally provokes lesions of a dermatosis which is usually spontaneously present elsewhere, and usually in a relatively 'active' or eruptive phase. It is particularly characteristic of psoriasis (Fig. 5.9, see also Chapter 20) and lichen planus, but occurs in several other dermatoses (Table 5.3). Less common dermatoses in which this may occur include erythema multiforme [2], Sweet's disease and scleromyxoedema [3]. The trauma may be mild, and is usually a scratch or similar, although light or heat may do the same. Occasionally, one disease may be responsible for the localization of another, such as granuloma annulare developing at sites of herpes zoster, or psoriasis developing at sites of contact dermatitis; this has been termed the isotopic response [4]. Development of lesions of pyoderma gangrenosum or Behçet's disease at sites of injection of serum or saline (or even just pinprick or venepuncture) is known as pathergy.

Table 5.2 Main shapes of skin lesions. (Adapted from GM White and NH Cox, *Diseases of the Skin*, 2nd edn. London: Mosby, 2000: 6.)

Shape	Description	Examples
Discoid (nummular)	A filled circle	Discoid eczema, psoriasis
Petaloid	Discoid lesions which have merged together	Seborrhoeic dermatitis on the trunk
Arcuate	Incomplete circles	Urticaria
Annular	Open circles with different central skin compared with the rim	Tinea corporis, granuloma annulare
Polycyclic	Circles which have merged together	Psoriasis
Livedo	Chicken-wire criss-cross pattern	Erythema ab igne, polyarteritis nodosa, microvascular occlusion disorders
Reticulate	Fine lace-like pattern	Oral lichen planus
Target	Multiple concentric rings	Erythema multiforme
Stellate	Star-shaped	Lesions of meningococcal septicaemia
Digitate	Finger-shaped	Chronic superficial dermatosis
Linear	Straight line	Koebner reaction to a scratch in lichen planus or psoriasis (see also Table 5.3)
Serpiginous	Snake-like	Cutaneous larva migrans
Whorled	Swirling pattern	Epidermal naevi, late-stage incontinentia pigmenti

Some annular shapes result from centrifugal extension of an infection from the point of inoculation (e.g. tinea corporis with dermatophyte fungi or erythema chronicum migrans in *Borrelia burgdorferi* infection). In others, a spreading neoplastic or inflammatory process leaves central scarring or ulceration, for example superficial basal cell carcinoma and discoid lupus erythematosus. In eruptions in which an allergic process is probably involved, the annular configuration is attributed to the refractory state of the central area. In some conditions, annular shapes can be related to the vascular network (see livedo, Chapter 49, and Fig. 5.5). Some involve an iatrogenic component, for example warts recurring at the margin of a blistered cryotherapy site. However, in many diseases, such as lichen planus, sarcoidosis or psoriasis, there is no satisfactory explanation for the occurrence of annular lesions. In clinical evaluation of annular lesions, it is particularly helpful to consider surface features such as scaling as an aid to identifying epidermal involvement and thus narrowing the differential diagnosis.

References

1 Boyd AS, Neldner KH. The isomorphic response of Koebner. *Br J Dermatol* 1990; **29**: 401–10.

2 Huff JC, Weston WL. Isomorphic phenomenon in erythema multiforme. *Clin Exp Dermatol* 1983; **8**: 409–13.

3 Durani BK, Kurzen H, Hartschuh W, Naeher H. Koebner phenomenon due to scratch test in scleromyxoedema. *Br J Dermatol* 2001; **145**: 306–8.

4 Wolf R, Brenner S, Ruocco V, Filioli FG. Isotopic response. *Int J Dermatol* 1995; **34**: 341–8.

Table 5.3 Anatomical and causative factors in linear lesions (Figs 5.7–5.9). (Adapted from C.M. Lawrence and N.H. Cox, *Physical Signs in Dermatology*, 2nd edn. London: Mosby, 2002: 21.)

Determinant of pattern	Examples
Blood vessels	Thrombophlebitis, Mondor's disease (linear thrombophlebitis on the trunk) Eczema related to varicose veins Temporal arteritis
Lymphatics	Lymphangitis Sporotrichosis, fish tank granulomas
Dermatome	Herpes zoster, zosteriform naevus, zosteriform Darier's disease, zosteriform metastases
Nerve trunks	Leprosy (thickened cutaneous nerves)
Developmental, Blaschko lines	Pigmentary demarcation line, linea nigra Epidermal naevi, incontinentia pigmenti, hypomelanosis of Ito Linear psoriasis, linear lichen planus, lichen striatus
Skin stretching	Striae due to growth spurt (on lower back)
Infestation	Scabies, larva migrans (both usually serpiginous)
External factors	
Plants	Phytophotodermatitis
Allergens	Elastoplast, nail varnish (neck), necklace, waistbands, etc.
Chemical	Caustics, e.g. phenol
Thermal	Burns
Physical	*Trauma to previously normal skin* Keloid scar, bruising, dermatitis artefacta, amniotic constriction bands *Trauma to skin with a pre-existing dermatosis* Purpura (cryoglobulinaemia, amyloid, vasculitis) Blisters (epidermolysis bullosa, porphyrias) *Koebner phenomenon* Psoriasis, lichen planus, lichen nitidus, vitiligo, lichen sclerosus, pityriasis rubra pilaris *Inoculation* Warts, molluscum contagiosum *Other mechanism* Scar sarcoid
Other determinants	Linear scleroderma (limb, central forehead) Senear–Caro ridge (on hands in psoriasis) Dermatomyositis (dorsum of fingers; Gottron sign) Interstitial granulomatous dermatitis (rope or cord sign) Flagellate pigmentation due to cytotoxic drugs (e.g. bleomycin)

Table 5.4 Examples of lesions that are characteristically annular or often include annular morphology (Fig. 5.10).

Infections
'Ringworm' dermatophyte infections
Impetigo
Erythema chronicum migrans
Syphilis (secondary, tertiary)
Leprosy
Inflammatory
Psoriasis
Seborrhoeic dermatitis
Atopic dermatitis (some)
Halo eczema (Meyerson's phenomenon)
Subacute cutaneous lupus erythematosus
Lichen planus
Sarcoidosis
Granuloma annulare
Actinic granuloma
Erythema multiforme
Urticaria
Serum sickness and serum sickness-like eruption
Linear IgA disease/chronic bullous dermatosis of childhood
Bullous pemphigoid
Subcorneal pustular dermatosis
Erythema annulare centrifugum
Jessner's lymphocytic infiltrate
Erythema marginatum rheumaticum
Pityriasis rosea (herald patch)
Vascular
Purpura annularis telangiectoides
Neoplastic
Superficial basal cell carcinoma
Mycosis fungoides
Other cutaneous lymphomas
Keratinization disorders
Porokeratosis

Pattern of lesions

The arrangement of individual lesions may create a characteristic pattern, such as the grouping of vesicles in herpes simplex—this pattern is so striking that it is applied to other lesions which do not share the same aetiology (herpetiform mouth ulcers).

Useful terminology to describe patterns includes:

Agminate—clustered; used to describe lesions such as acne agminata, where granulomatous lesions cluster around the lids (Fig. 5.11), or agminate naevi, an unusual clustering of melanocytic naevi.

Grouped or clustered—characteristic of some infections (herpetic vesicles, molluscum contagiosum, plane warts), flea bites, as well as of endogenous lesions such as lichen planus, leiomyomata, lymphangioma circumscriptum (Fig. 5.12).

Satellite—a cluster of lesions around a larger central lesion. May occur due to local lymphatic spread of neoplasm such as melanoma (Fig. 5.13); may occur in chronic bullous disease of childhood/linear IgA disease.

Confluent—lesions merging together, locally or widespread, e.g. pityriasis versicolor.

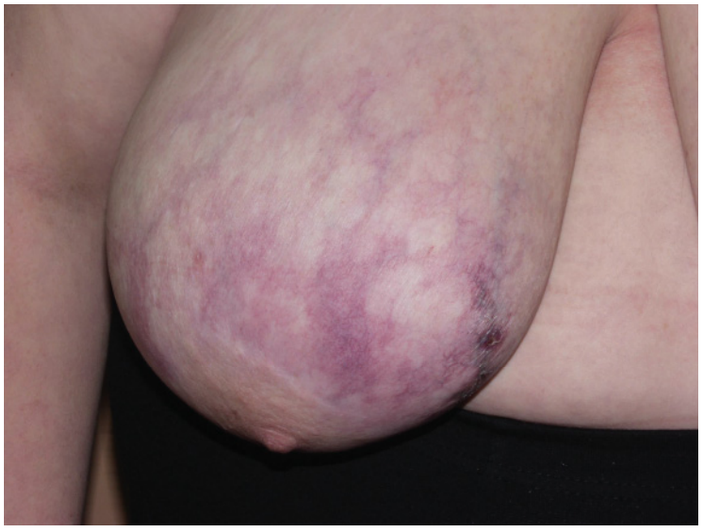
Scattered, disseminated and exanthematous—for example, many drug eruptions, viral exanthemata, as well as some extrinsic causes (Fig. 5.14).

Spared—patterns of sparing may also be diagnostically important, e.g. islands of sparing occur within the otherwise often confluent orange–red erythema of pityriasis rubra pilaris, sparing within skin folds in papuloerythroderma of Ofuji, or areas shielded by clothing or a wristwatch may be overtly spared in photosensitivity (Fig. 5.15).

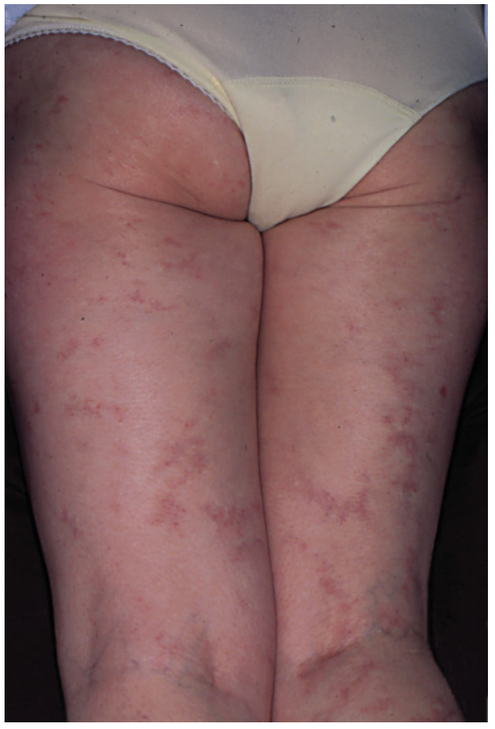
Symmetrical—often endogenous (e.g. psoriasis) and *asymmetrical*, often of exogenous cause (e.g. tinea).



(a)

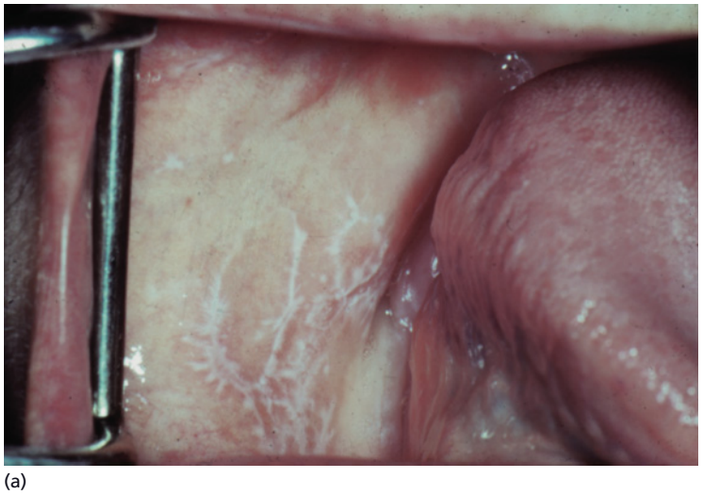


(b)



(c)

Fig. 5.5 Livedo. This is a 'chickenwire' patterning that is determined by the arrangement of the skin vasculature. (a) Resolving erythema infectiosum (fifth disease). (b) Diffuse dermal angiomatosis of the breast. (c) Cutaneous polyarteritis nodosa—a 'broken' livedo is typical in this disorder and in some disorders of microvascular occlusion.



(a)



(b)

Fig. 5.6 Examples of reticulate lesions. (a) In some cases this may be confined to specific localized lesions, as in buccal lichen planus. (b) In other cases it may describe an overall morphology of an eruption such as confluent and reticulate papillomatosis.



(a)



(b)



(c)



(d)



(e)

Fig. 5.7 Some examples of linear lesions. (a) Growth striae. (b) Lichen striatus. (c) Dermographism. (d) Linear epidermal naevus. (e) Linear excoriations in dermatitis artefacta.



Fig. 5.8 Lymphangitis. Inflammation in distal superficial lymphatic vessels is reticulate, but becomes more linear as it spreads up a limb in deeper, larger lymphatic channels.



Fig. 5.9 Koebner phenomenon in psoriasis.



(a)



(b)

Fig. 5.10 Annular lesions. (a) Annular granuloma annulare. (b) Erythema annulare centrifugum, a superficial lesion with scaling. (c) Annular scale in porokeratosis. (d) Annular lesion of tinea corporis. (e) Annular lichen planus. (f) Characteristic annular arrangement of blisters in chronic bullous disease of childhood. (g) Subacute cutaneous lupus erythematosus; annular lesions on the trunk are common.



(c)



(e)



(f)



(d)

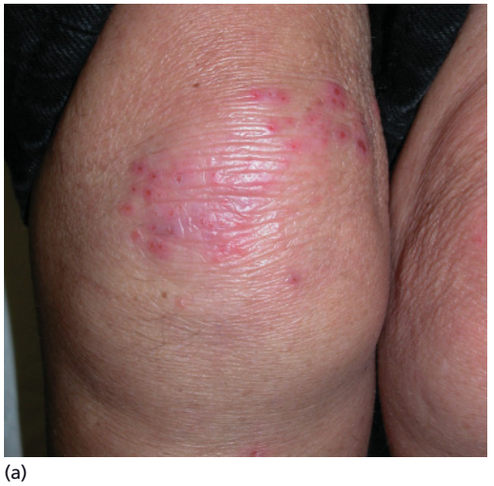


(g)

Fig. 5.10 *Continued*



Fig. 5.11 Acne agminata; this is merely a historical term for grouped lesions.



(a)



(b)



(c)



(d)

Fig. 5.12 Grouped lesions. (a) Dermatitis herpetiformis, a cluster of lesions on the knee. (b) Grouped pigmented areas in a speckled lentiginous naevus. (c) Grouped vesicles in herpes simplex. (d) Grouped lesions within a mosaic plantar wart.

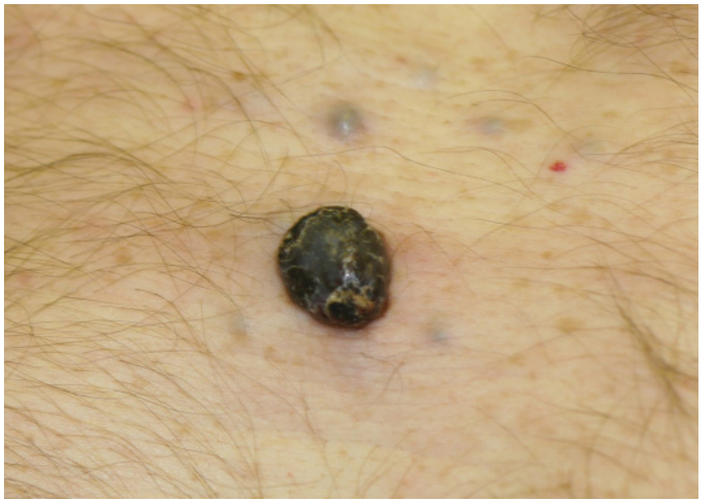


Fig. 5.13 Satellite lesions—in this case, local metastases around a primary nodular melanoma.



Fig. 5.14 Scattered lesions. The predominantly 'buckshot' pattern here is typical of 'strimmer' or 'weedwacker' dermatitis, in which photosensitizing plant products have been spattered onto the skin and produced localized photosensitivity. A useful clue to diagnosis is that, in addition, some of the individual lesions have a linear morphology (seen here as is a poorly defined linear band crossing the elbow joint) representing direct contact with a causative plant stem.



Fig. 5.15 A drug-induced phototoxic eruption. There is a striking pattern of sparing of skin covered by a sandal.

Distribution of lesions

The overall distribution of lesions in many common dermatoses may be so characteristic that it is of great assistance in clinical diagnosis, even though the mechanism in most instances is not understood. Examples of body site predilection of dermatoses are provided in Table 5.5. Some of these are explained by anatomy, sites of contact, etc. (see below), but even some demarcations that presumably have an anatomical basis are not fully understood, for example Wallace's line on the foot or the equivalent on the hand (Fig. 5.16). Some, for example those at flexural sites (Table 5.6), are often modified in appearance by moist occlusion. Important factors in determining the distribution of dermatoses include the following:

Anatomical factors

- blood supply, e.g. venous eczema
- skin appendages, e.g. acne, hidradenitis
- type of skin, e.g. eruptions may be localized to the glabrous skin of palms and soles
- neural, e.g. herpes zoster
- developmental, e.g. disorders which follow lines of Blaschko (Chapter 15)
- regional variation in the skin surface microenvironment, e.g. erythrasma is usually localized to flexures
- others, e.g. polychondritis is restricted to sites where there is cartilage, affecting ears, nose, joints (and trachea)

External factors

- solar exposure, e.g. photosensitivity disorders, squamous cell carcinoma
- chemical exposure, e.g. contact dermatitis
- infective, e.g. orf

Colour of skin and of lesions

Normal skin colour is due to melanin, phaeomelanin, haemoglobin, oxyhaemoglobin and carotenoids (Chapter 58). The colour of the skin is greatly modified by the scatter of light, which is responsible, for example, for the whiteness of scale and the blueness of any melanin deep in the dermis, although colour contrast with surrounding skin also alters perception of the colour of skin and subcutaneous structures [1]. The range of colours that may be seen

Table 5.5 Some examples of disorders that have predilection for specific body sites.

Body site	Type of disorder	Examples
Scalp	Hair disorders/alopecia	Alopecia areata, androgenetic alopecia
	Inflammatory dermatoses	Psoriasis, seborrhoeic dermatitis, lichen simplex
	Localized lesions	Pilar cysts, organoid naevus, squamous cell carcinoma, atypical fibroxanthoma, cutaneous metastases
Eyelids	Inflammatory dermatoses	Atopic dermatitis, contact allergy (cosmetics, nickel), seborrhoeic blepharitis, angiooedema, dermatomyositis
	Localized lesions	Basal cell carcinoma, xanthelasma
Ears	Inflammatory dermatoses	Seborrhoeic dermatitis, psoriasis, atopic dermatitis, relapsing polychondritis
	Infection	Pseudomonas ('malignant') otitis externa
	Localized lesions	Actinic keratosis, squamous cell carcinoma, chondrodermatitis nodularis, atypical fibroxanthoma, angiolymphoid hyperplasia with eosinophilia, gouty tophi
Face	Inflammatory dermatoses	Acne, atopic dermatitis, seborrhoeic dermatitis, rosacea, lupus erythematosus, lupus pernio, photosensitivity
	Infections	Herpes zoster, erysipelas, impetigo
	Localized lesions	Naevi and freckles, actinic keratoses, basal and squamous cell carcinomas, keratoacanthoma, lentigo maligna
Lips	Inflammatory dermatoses	Dermatitis (atopic, contact), cheilitis (angular, actinic), angiooedema, contact urticaria, erythema multiforme
	Infections	Herpes simplex, viral warts
	Localized lesions	Vascular lesions (venous lake, pyogenic granuloma), squamous cell carcinoma
Hands	Inflammatory and other dermatoses	Dermatitis (dyshidrotic, pompholyx, contact), psoriasis and palmoplantar pustulosis, keratodermas, erythema multiforme, photosensitivity (dorsal hand), collagen vascular disorders and vasculitis, granuloma annulare
	Infections	Paronychias, onychomycosis, scabies (especially fingerwebs), viral warts
	Localized lesions	Actinic keratoses, squamous cell carcinoma, subungual melanoma
	Nail disorders	Koilonychia, pachyonychia congenita, many others
Limbs	Inflammatory and other dermatoses	Psoriasis (elbows, knees), atopic dermatitis (limb flexures), discoid eczema, venous eczema and ulceration (lower leg), asteatotic eczema (lower leg), lichen simplex (lower leg), lichen planus (flexor forearms, shins), dermatitis herpetiformis (knee, elbow), granuloma annulare (elbows), erythema nodosum (legs), vasculitis (legs), papular urticaria/flea bites (lower leg)
	Localized lesions	Bowen's disease (lower leg), dermatofibroma
Feet	Inflammatory and other dermatoses	Dermatitis (pompholyx, contact, juvenile plantar), psoriasis and palmoplantar pustulosis, vasculitis and arterial disease, callosities/corns
	Infections	Dermatophyte fungal infection (skin and nails), pitted keratolysis, verrucae
	Localized lesions	Eccrine poroma, subungual exostosis
Axillae (see also Table 5.6)	Inflammatory dermatoses	Psoriasis, contact dermatitis, hidradenitis suppurativa, acanthosis nigricans, fibroepithelial polyps, freckles in neurofibromatosis (Crowe's sign)
	Infections	Staphylococcal boils, erythrasma
	Localized lesions	Apocrine hidrocystoma
Genital	Inflammatory and other dermatoses	Psoriasis/Reiter's syndrome, lichen planus and lichen nitidus (penis), lichen sclerosus (penis, vulva), lichen simplex (scrotum, vulva), fixed drug eruption (penis), Zoon's balanitis (glans penis), plasma cell vulvitis, other vulval dermatoses
	Infections	Sexually transmitted diseases, genital warts, molluscum contagiosum
	Localized lesions	Epidermoid cysts (scrotal), squamous cell carcinoma (penis, vulva)



Fig. 5.16 A keratoderma showing abrupt discontinuation at Wallace's line.

in individual skin lesions is enormous (Table 5.7). Although many red, scaly rashes tend to resemble each other, many dermatoses have their own distinctive colour which aids recognition—for example, the orange and yellow–orange palms of pityriasis rubra pilaris and carotenaemia, respectively. Some colours can be logically explained—for example, the purple of lichen planus is due to the redness of inflammation combined with the blue–brown of melanin within the dermis.

Examination of pigmented skin requires a degree of practice, as the physical signs may be modified. Erythema is seen as a dark area, macular or diffuse. Dermal oedema lightens the skin and weals appear pale. Papules may be pale or dark according to the degree of oedema or the presence of acanthosis or hyperkeratosis, which mask pigment. Purpura may be difficult to detect, but may appear jet-black in lighter-pigmented skin. Post-inflammatory depigmentation and hyperpigmentation are exaggerated

Table 5.6 Some disorders that have a predilection for flexural sites. (Adapted from GM White and NH Cox, *Diseases of the Skin*, 2nd edn. London: Mosby, 2000: 24. See also Chapter 71.)

Type of Disorder	Disorder	Comment (all refer to major flexures unless specified)
Inflammatory dermatoses	Psoriasis	Common in flexures, typically red and shiny rather than the usual white scale (Chapter 20); may be termed the 'inverse pattern' if mainly flexural distribution
	Seborrhoeic dermatitis	Usually with lesions elsewhere also; central face, scalp etc.
	Contact dermatitis	Irritant or allergic; may affect the vault of the axilla (e.g. deodorants) or axillary folds (e.g. clothing dermatitis) (Chapters 25 and 26)
	Intertrigo	Especially inframammary; may be due to simple maceration, but also secondary infection may occur (staphylococcal, streptococcal, candidal)
	Napkin rash	Many causes, the commonest are irritant and candidal (see Chapter 17)
	Lichen planus	Not often mainly flexural, but may cause confusion as flexural and genital lesions are often brown in colour and/or annular in morphology, rather than the usual purplish plaques, and may lack the anticipated pruritus
	Hidradenitis suppurativa	Affects axillae, groin, inframammary area (Chapters 30 and 42)
	Crohn's disease	Cutaneous lesions affect especially the perineum (Chapter 71)
	Atopic dermatitis	Affects elbow and knee flexures, uncommonly the major flexures other than in infants when the process may be generalized (Chapter 24)
Bullous diseases	Pemphigus vegetans	Rare, mainly flexural (Chapter 40)
	Hailey–Hailey disease	Inherited, variable (Chapter 39)
Infections	Dermatophytes	Especially male groin; usually associated with tinea pedis (Chapter 36)
	Erythrasma	Brownish colour, fluoresces under Wood's light (Chapter 30)
	Trichomycosis axillaris	Coated hair shafts (Chapter 66)
	Candidosis	Especially in napkin rash or bedbound elderly adults, commoner in diabetes; satellite pustules are characteristic (Chapter 36)
	Bacterial	Various types—follicular infections (furuncles), perianal abscesses, secondary infection of intertrigo, Gram-negative toe-web infections etc. (Chapter 30)
	Scabies	Multiple itchy flexural nodules are highly suggestive of the relatively chronic nodular variant—penile lesions are also common in this pattern (Chapter 38)
	Parvovirus B19	Often acral, but the laterothoracic type may include axillary involvement, and a bathing trunk pattern involves groin flexures; often purpuric
Localized lesions	Fibroepithelial polyps (skin tags)	A common normal variant
	Neurofibromatosis	Axillary freckling is seen (Crowe's sign) (Chapter 15)
	Fox–Fordyce disease	An apocrine occlusion dermatosis (Chapter 44)
	Pseudoxanthoma elasticum	Inherited defect of elastic tissue, most apparent on the neck and axillae (Chapter 45)
Miscellaneous	Hyperhidrosis and other sweat apparatus disorders	Mainly axillae (Chapter 44)
	Acanthosis nigricans	May be endocrine-related or paraneoplastic (Chapters 19 and 62)
	Acrodermatitis enterpathica/zinc deficiency	Severe napkin rash and perioral rash in an infant (Chapter 17); acquired version in adults; necrolytic migratory erythema of glucagonoma syndrome may have the same pattern (Chapter 62)
	Langerhans cell histiocytosis	May present as severe napkin rash (Chapter 17)
	Mycosis fungoides	Often affects shielded sites, may be limited to main flexures ± buttocks
	Granular parakeratosis	Rare—hyperkeratotic, mainly adult female axilla
	'Inverse' pattern of drug eruption	See Chapter 75

compared to paler skin—for example, after herpes zoster, syphilis, leprosy, lichen simplex and many other conditions. Normal pigmentary variation between body sites is also more apparent in darker skin, and may cause confusion (for example, dark crease lines on the relatively pale palms); pigmentary demarcation lines may also be visible (Futcher's and Voigt's lines) [2].

References

1 Reisfeld PL. Blue in the skin. *J Am Acad Dermatol* 2000; **42**: 597–605.
2 Futcher PHA. Peculiarity of pigmentation of the upper arms in negroes. *Science* 1938; **88**: 570–1.

Palpation of the skin

Palpation of rashes or localized lesions imparts additional information about texture, consistency, thickness, tenderness and temperature [1]. It has been shown, using a trained 'blinded' observer, that the scaling of psorasis and eczema can be distinguished by palpation alone [2]. Gentle scratching or rubbing alters visibility of scaling and may elicit dermographism. The main 'touch' modalities in examining the skin are:

Simple palpation—to determine texture, etc., as above.

Blunt pressure—e.g. to detect oedema, assess capillary refill, identify the dermal defect that occurs in anetoderma.

Linear or shearing pressure—to elicit dermographism, or Nikolsky's sign in pemphigus (Chapter 40).

Squeezing or pinching—to determine localization and consistency of lesions, e.g. a pinch of skin can be lifted up over a subcutaneous nodule, whereas squeezing a tethered intradermal process such as a dermatofibroma produces dimpling (Fig. 5.17).

Table 5.7 Colours of skin lesions. (Adapted from CM Lawrence and NH Cox, *Physical Signs in Dermatology*, 2nd edn. London: Mosby, 2002: 21.)

Colour	Examples
Black	Melanin, e.g. some naevi, melanoma Exogenous pigments, e.g. tattoos, pencil/ink Exogenous chemicals, e.g. silver nitrate, gold salts Deeply situated blood or melanin, e.g. angiomas, blue naevus
Blue-grey	Inflammatory diseases, e.g. orf Drug-induced pigmentation, e.g. phenothiazines, minocycline
Dark brown	Melanin near the skin surface, e.g. most melanocytic naevi Exogenous pigments, e.g. dithranol (anthralin) staining
Pale brown	Melanin near the skin surface, e.g. lentigo, freckles
Muddy brown	Melanin in the superficial dermis, e.g. post-inflammatory pigmentation
Purple	Vascular lesions, e.g. angiomas Other disorders where telangiectasia is a prominent feature, e.g. lupus pernio (chronic sarcoidosis), dermatomyositis
Dusky blue	Reduced amounts of oxygenated haemoglobin, e.g. poor arterial supply, central causes of cyanosis, methaemoglobinaemia
Violaceous and lilac	Lichen planus, edge of plaques of morphoea, connective tissue disorders, e.g. dermatomyositis
Pink-red	Many exanthemata and common disorders, such as psoriasis
Red-brown	Inflammatory dermatoses, e.g. seborrhoeic eczema, secondary syphilis Haemosiderin, e.g. pigmented purpuric dermatoses
Scarlet-red	Lesions with a strong arterial supply, e.g. pyogenic granuloma, spider naevus Altered haemoglobin, e.g. carbon monoxide poisoning
Orange	Haemosiderin, e.g. lichen aureus Inflammatory disorders, e.g. pityriasis rubra pilaris
Yellow-white/ yellow-pink	Xanthomatous disorders
Yellow-orange	Carotenaemia (ingested carotene, myxoedema)
Yellow-green	Jaundice
Green	Exogenous pigment, e.g. copper salts
White-ivory	Lichen sclerosus et atrophicus, morphoea
White (or pale pink, depending on vascularity)	Vitiligo, naevus anaemicus, arterial insufficiency, chemical depigmentation on vascularity

Stretching—may produce blanching of vascular lesions, and helps in visualizing lesions such as 'submarine' comedones, the elastomas of Buschke–Ollendorf syndrome and the glassy edge of a superficial basal cell carcinoma.

Rubbing—may cause release of chemicals, e.g. rubbing a mastocytoma causes urtication and a flare due to histamine release (Darier's sign), rubbing a neuroblastoma causes surrounding pallor due to catecholamine release.

Scratching and picking—scratching scale in psoriasis makes the scale appear more silver in colour by introducing air–keratin interfaces; more vigorous scratching or picking off the scale produces small bleeding points (Auspitz's sign). Neither of these is specific to psoriasis. Removal of crusts overlying nodules may demonstrate the extent of the lesion, and additional diagnostic features, more accurately.



Fig. 5.17 Squeezing the skin adjacent to a dermatofibroma causes a dimpled appearance, also termed a positive 'pinch sign'.

References

1 Cox NH. Palpation of the skin—an important issue. *J Roy Soc Med* 2006; **99**: 598–600.

2 Cox NH. A literally blinded trial of palpation in dermatologic diagnosis. *J Am Acad Dermatol* 2007; **56**: 949–51.

Additional simple clinical examination

Wetting the skin with water or mineral oil (which lasts longer) fills air spaces in scale and allows underlying features to become more visible. In some instances, this just enhances underlying redness—for example, in psoriasis. In other instances, diagnostic features may become apparent to the naked eye (such as Wickham's striae in lichen planus) or with the aid of additional magnification (e.g. use of a dermatoscope to examine pigmented lesions). Soaking of the skin may make the lesions of pitted keratolysis more apparent.

Application of heat or cold may identify specific physical urticarias. Whole-body warming may confirm cholinergic urticaria. Even whole-body cooling has been used, to identify dysarthria as being due to Raynaud's phenomenon of the tongue.

Pinprick sensation may be lost in leprosy, and decreased *light touch sensation* (using specific graded monofilaments) can predict diabetes-related neuropathic ulceration.

Paring the skin allows distinction between a wart and a corn, or may confirm the presence of old blood in talon noir or a haematoma.

Smell may be useful—for example, in suspecting anaerobic wound infection, or in diagnosis of rarities such as trimethylaminuria.

Simple microscopy may be diagnostic for hair shaft abnormalities and for distinguishing between hair casts and head lice egg cases (nits), and is used to detect cutaneous fungal disease. Dermoscopy, an *in vivo* form of magnification, is discussed on p. 5.20.

Table 5.8 Uses of Wood's light.

Fungal infection	Tinea capitis—green fluorescence associated with *Microspora* species and favus (see also Chapter 36) Pityriasis versicolor—yellow
Bacterial infections	Erythrasma, acne—coral pink (porphyrins) *Pseudomonas pyocyanea*—yellowish green (pyocyanin)
Infestations	Scabies—fluorescein solution fills the burrows and can be viewed with Wood's light
Porphyrias (see also Chapter 59)	Urine, faeces and occasionally blister fluid fluoresce in porphyria cutanea tarda; teeth in erythropoietic porphyria; blood in protoporphyria
Pigmentary disorders	Vitiligo is accentuated (see text), dermal pigment becomes less apparent Detection of ash leaf macules in tuberous sclerosis
Drugs and chemicals	Detection in tissues, e.g. staining of teeth or sebum from tetracyclines and of the nails from mepacrine Detection of fluorescent contact or photosensitizers on the skin, or in cosmetics and industrial agents, e.g. ballpoint-pen ink, eosin, furocoumarins, halogenated salicylanilides, pitch ingredients Fluorescein can be added to topical medications to investigate sites of application or of manipulation (e.g. in the investigation of dermatitis artefacta)
Tumours	Red fluorescence can occur in some malignant tumours and other lesions of the skin, especially squamous cell carcinomas Conversion of aminolaevulinic acid to protoporphyrin IX occurs within tumours as the first step in photodynamic therapy and can be detected with Wood's light
Miscellaneous	Lipofuscins in sweat from patients with chromhidrosis can be identified by Wood's light examination of stained clothing Research use of fluorescent 'markers' for the investigation of cutaneous penetration and epidermal turnover Detection of mineral oil on the skin in the assessment of barrier creams

Additional clinical investigations

Diascopy

Pressing a glass slide or (more safely) a stiff, clear, colourless piece of plastic onto the skin compresses blood out of small vessels, to allow evaluation of other colours. Diascopy is of particular value in detecting granulomatous nodules, which have a translucent brownish colour known as 'apple jelly' nodules (e.g. in lupus vulgaris). In naevus anaemicus, a localized area of vasoconstriction, other pigments are unaltered—diascopy of adjacent skin therefore reveals an identical colour to that of the 'depigmented' area. By contrast, diascopy of skin adjacent to vitiligo, in which there is loss of melanin, demonstrates that the vitiligo remains paler. Application of medium pressure to a spider naevus can compress radiating arterioles and allow visualization of pulsatile flow in the feeding vessel.

Wood's light

This is a source of ultraviolet light from which virtually all visible rays have been excluded by a Wood's (nickel oxide) filter. Applications of Wood's light are listed in Table 5.8 [1,2].

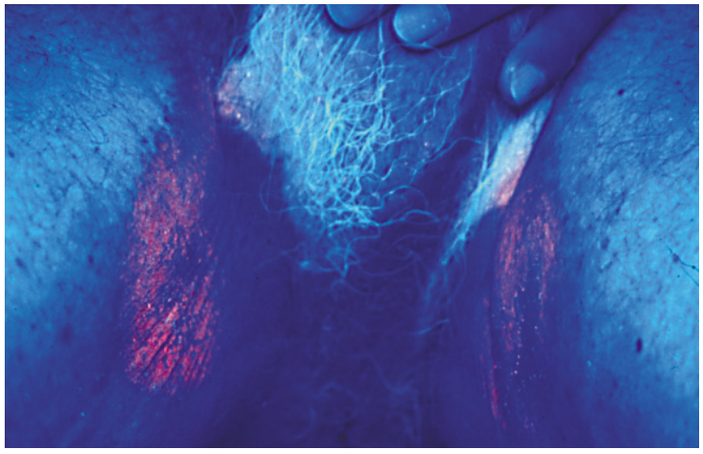


Fig. 5.18 Coral pink fluorescence of erythrasma in the groin creases, viewed with Wood's light.

Variations in epidermal pigmentation are more apparent under Wood's lamp than under visible light, whereas variations in dermal pigment are less apparent [3]. Thus, for example, it can be used to distinguish vitiligo from naevus anaemicus. Vitiligo is due to loss of epidermal melanin, and the depigmented areas are greatly exaggerated under Wood's light; naevus anaemicus is due to localized dermal vasoconstriction with normal overlying epidermal pigmentation, and the pallor completely disappears under Wood's light. The ash-leaf macules of tuberous sclerosis are much more prominent under Wood's lamp [3].

Many organisms produce chemicals that fluoresce under Wood's light [4,5] including *Propionibacterium acnes* [6], and *Corynebacterium minutissimum*, the bacterium responsible for erythrasma (Fig. 5.18), and conversion of aminolaevulinic acid to protoporphyrin occurs in several tumours and other skin lesions, leading to the technique of photodynamic diagnosis [7] as well as photodynamic therapy (Chapter 78). Fluorescein can be added to topical agents in studies of their use—for example, to detect areas that are missed during sunscreen application [8]. Wood's light can also be used to view *ex vivo* specimens, such as blood or urine in porphyrias [9], or even inanimate objects, such as clothing from patients with chromhidrosis [10].

There are pitfalls of using Wood's light:

- It is useful to diagnose tinea capitis acquired from cats or dogs, but most fungi do not fluoresce, so a negative test does not exclude the diagnosis.
- There is some reflection of light from any scaly dermatosis, which may be confused with the relatively subtle colour change of pityriasis versicolor.
- Optical brighteners in detergents fluoresce strongly—white shirts and coats may be a considerable distraction.
- Erythrasma fluoresces pink due to porphyrins—it is a reasonably frequent finding that the expected fluorescence is negative if the affected skin has been washed prior to a clinic appointment.

References

1 Caplan RM. Medical uses of Wood's lamp. *JAMA* 1967; **202**: 123–5.
2 Asawanonda P, Taylor CR. Wood's light in dermatology. *Int J Dermatol* 1999; **38**: 801–7.

3 Gilchrest BA, Fitzpatrick TB, Anderson RR, Parrish JA. Localization of melanin pigment in the skin with Wood's lamp. *Br J Dermatol* 1977; **96**: 245–8.
4 Halprin KM. Diagnosis with Wood's light: tinea capitis and erythrasma. *JAMA* 1967; **199**: 841.
5 Polk HC Jr, Ward CG, Clarkson JG, Taplin D. Early detection of *Pseudomonas* burn infection: clinical experience with Wood's light fluorescence. *Arch Surg* 1969; **98**: 292–5.
6 Johnsson A, Kjeldstad B, Melo TB. Fluorescence from pilosebaceous follicles. *Arch Dermatol Res* 1987; **279**: 190–3.
7 Fritsch C, Lang K, Neuse W *et al*. Photodynamic diagnosis and therapy in dermatology. *Skin Pharmacol Appl Skin Physiol* 1998; **11**: 358.
8 Halprin KM. Diagnosis with Wood's light, 2: the porphyrias. *JAMA* 1967; **200**: 460.
9 Gaughan MD, Padilla RS. Use of a topical fluorescent dye to evaluate effectiveness of sunscreen application. *Arch Dermatol* 1998; **134**: 515–7.
10 Cox NH, Popple AW, Large DM. Autofluorescence of clothing as an adjunct in diagnosis of apocrine chromhidrosis. *Arch Dermatol* 1992; **128**: 275–6.

Clinical microscopy, dermoscopy and other imaging systems

Microscopy is an important laboratory technique, discussed briefly later. However, microscopy in a clinical setting also has several uses.

Dermoscopy

This technique, also known as dermatoscopy or epiluminescence microscopy, is an extension of the use of simple magnification. Dermoscopes have built-in illumination, and are applied to the skin surface with a film of oil on the lesion to enhance visibility of subcorneal structures. The technique is mainly used in the diagnosis of doubtful pigmented lesions (Chapter 54). The images may be viewed directly, photographed or recorded digitally for subsequent or sequential analysis. A structured system of analysing the colours and appearances of the structural elements (pigment network, globules and dots, horn cysts and pseudofollicular openings and the vascular patterns visualized) may increase the accuracy of diagnosing malignant melanoma [1]. Scoring systems such as the ABCD dermatoscopy score (assessing *a*symmetry, *b*order *c*olour and *d*ermatoscopic structures) [2] and a 'seven-point check list' [3] have been devised. Computerized image analysis is being developed to aid in distinguishing benign melanocytic lesions from melanoma [4]. Dermoscopes can also be useful in distinguishing haemangiomas, angiokeratomas, pigmented basal cell carcinomas and seborrhoeic keratoses from melanocytic lesions. More novel uses include the identification of scabies burrows and mites, diagnosis of tungiasis and other parasitic infections.

References

1 Stolz W, Braun-Falco O, Bilek P *et al. Colour Atlas of Dermatoscopy.* Boston: Blackwell Scientific Publications, 1994.
2 Binder M, Schwarz M, Winkler A *et al.* Epiluminescence microscopy: a useful tool for the diagnosis of pigmented skin lesions for formally trained dermatologists. *Arch Dermatol* 1995; **131**: 286–91.
3 Argenziano G, Fabbrocini G, Carli P *et al*. Epiluminescence microscopy for the diagnosis of doubtful melanocytic skin lesions: comparison of the ABCD rule of dermatoscopy and a new 7-point checklist based on pattern analysis. *Arch Dermatol* 1998; **134**: 1563–70.
4 Binder M, Kittler H, Seeber A *et al*. Epiluminescence microscopy-based classification of pigmented skin lesions using computerized image analysis and an artificial neural network. *Melanoma Res* 1998; **8**: 261–6.

Other imaging systems for localized lesions

Spectrophotometric image analysis of pigmented lesions (SIAoscopy) allows the assessment of eight narrow-band spectrally filtered images of the skin over an area of 24 × 24 mm with radiation ranging from 400 to 1000 nm. The value of this technique as an adjunct to clinical examination and dermoscopy has produced differing opinions [1–3]; it has also been used in diagnosis of non-melanoma skin cancers [4], and used with an algorithmic approach to diagnosis [5].

In vivo confocal laser scanning microscopy (CLSM) represents a novel imaging tool that allows the non-invasive examination of skin cancer morphology in real time at a 'quasi-histopathological' resolution, viewing microanatomical structures and individual cells. It may show promise in the assessment of suspected melanoma [6].

References

1 Moncrieff M, Cotton S, Claridge E, Hall P. Spectrophotometric intracutaneous analysis: a new technique for imaging pigmented skin lesions. *Br J Dermatol* 2002; **146**: 448–57.
2 Haniffa MA, Lloyd JJ, Lawrence CM. The use of a spectrophotometric intracutaneous analysis device in the real-time diagnosis of melanoma in the setting of a melanoma screening clinic. *Br J Dermatol* 2007; **156**: 1350–2.
3 Govindan K, Smith J, Knowles L *et al*. Assessment of nurse-led screening of pigmented lesions using SIAscope. *J Plast Reconstr Aesthet Surg* 2007; **60**: 639–45.
4 Tehrani H, Walls J, Price G *et al*. A novel imaging technique as an adjunct to the *in vivo* diagnosis of nonmelanoma skin cancer. *Br J Dermatol* 2006; **155**: 1177–83.
5 Wood A, Morris H, Emery J *et al*. Evaluation of the MoleMate training program for assessment of suspicious pigmented lesions in primary care. *Inform Prim Care* 2008; **16**: 41–50.
6 Gerger A, Koller S, Kern T *et al.* Diagnostic applicability of *in vivo* confocal laser scanning microscopy in melanocytic skin tumors. *J Invest Dermatol* 2005; **124**: 493–8.

Identification of scabies mites

Scabies mites can be extracted from the end of a burrow using a needle, with microscopy to confirm the diagnosis. The technique can be useful to convince sceptical sufferers of their infestation. Alternatively, application of mineral oil [1] or 5% potassium hydroxide to an affected interdigital space, followed by light scalpel scraping, reveals the acarus or its eggs. The faecal pellets (scybala) of the mite are also diagnostic, but are dissolved by potassium hydroxide; they remain intact in oil. Burrows can also be removed by a very superficial shave technique, and can be made more apparent by application to the skin of either black ink, or fluorescein with Wood's light visualization. Dermatoscopy (see above) can also be used—the mite appears as a dark triangle shape—or higher-resolution microscopy with a standard light microscope [2]. Outwith the scope of this section, scabies can also be identified using polymerase chain reaction (PCR) to detect mite antigens [3].

References

1 Austin VH. Mineral oil versus KOH for Sarcoptes. *J Am Acad Dermatol* 1982; **7**: 555.
2 Haas N. Sterry W. The use of ELM to monitor the success of antiscabetic therapy. *Arch Dermatol* 2001; **137**: 1656–7.
3 Bezold G, Lange M, Schiener R *et al.* Hidden scabies: diagnosis by polymerase chain reaction. *Br J Dermatol* 2001; **144**: 614–8.

Other simple microscopy procedures

Simple light microscopy is helpful in evaluating hair shaft abnormalities (this, and more complex electron microscopy, are discussed in Chapter 66).

Microscopy of skin scrapings for fungi is discussed in Chapter 36. Scraping the base of a herpetic vesicle with simple Giemsa staining may reveal giant cells (Tzanck smear); molluscum contagiosum can be identified in a similar fashion. Examination of skin pustule smears after fixation and haematoxylin and eosin staining may be useful in the rapid diagnosis confirmation of infantile eosinophilic folliculitis and incontinentia pigmenti; in both conditions, the pustules are filled with eosinophils.

Skin surface biopsies using tape-stripping or adhesive microscope slides pressed onto the skin allow observation of cells of the stratum corneum and of bacteria, fungi such as *Pityrosporon* species, and *Demodex* mites [1–3]. Plastic polymer (Silflo) skin surface impressions may be useful for the study of eccrine gland pore size and numbers.

References

1 Goldschmidt H, Kligman AM. Exfoliative cytology of human horny layer: methods of cell removal and microscopic techniques. *Arch Dermatol* 1967; **96**: 572–6.

2 Marks R, Dawber RPR. Skin surface biopsy: an improved technique for the examination of the horny layer. *Br J Dermatol* 1971; **84**: 117–23.

3 Barton SP, King CS, Marks R *et al*. A technique for studying the structural detail of isolated human corneocytes. *Br J Dermatol* 1980; **102**: 63–73.

Fine-needle aspiration of lymph nodes (FNA)

Aspiration of lymph node tissue using a 25- or 27-gauge needle allows cytological assessment of lymph nodes and is useful in the staging of metastatic malignant melanoma and squamous cell carcinoma of the skin, as well as the assessment of lymph nodes in suspected lymphoma. In patients with palpable lymph nodes and melanoma, the technique has been shown to have high specificity and sensitivity [1] (Fig. 5.19). Combining the technique with flow cytometry can help in the differentiation of lymphoma from reactive and dermatopathic lymphadenopathy [2].

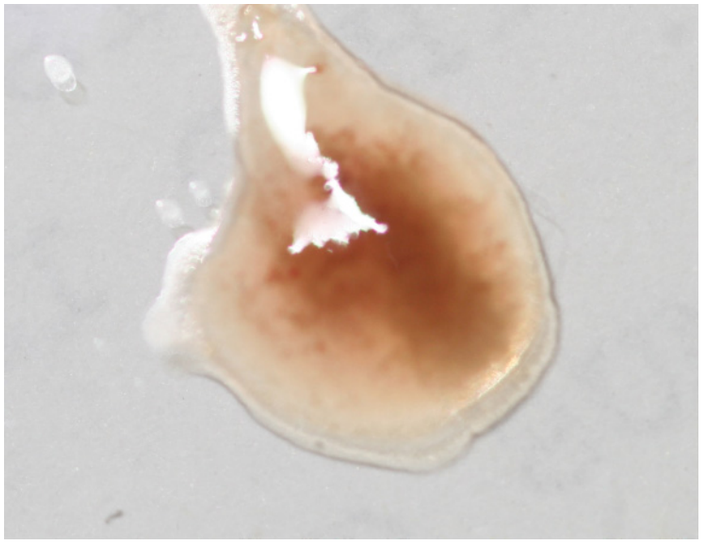


Fig. 5.19 Fine-needle aspiration. In this case, the fluid obtained on aspiration of a 5-cm lymph node in a patient with melanoma had a readily apparent black colour.

References

1 Cangiarella J, Symmans WF, Shapiro RL *et al*. Aspiration biopsy and the clinical management of patients with malignant melanoma and palpable regional lymph nodes. *Cancer* 2000; **25**: 62–6.

2 Nasuti JF, Yu G, Boudousquie A, Gupta P. Diagnostic value of lymph node fine needle aspiration cytology: an institutional experience of 387 cases observed over a 5-year period. *Cytopathology* 2000; **11**: 18–31.

Commonly used laboratory tests

Numerous special investigations are used to refine a dermatological diagnosis, or for disease or therapy monitoring. Many of these are discussed specifically in relevant chapters—for example, testing for photosensitivity (Chapter 29) or for contact allergy (Chapter 26). The commonest tests which involve additional laboratory processing of samples are as follows:

- Blood tests for haematology or biochemistry. These are used in numerous situations, both diagnostically and for assessing the impact of a skin disease or for monitoring systemic therapy. Many infective disorders or acute inflammatory conditions are associated with neutrophilia or with abnormal results of inflammatory markers such as erythrocyte sedimentation rate or C-reactive protein; eosinophilia is also a feature of several dermatological conditions (briefly listed in Table 5.9, and discussed in more detail in Chapter 62).
- Blood tests for immunological studies. For example, in the diagnosis of connective tissue diseases (Chapter 51), IgE and radioallergosorbent test (RAST) in atopic and allergic diseases (Chapters 13 and 24).
- Histology of skin biopsy (Chapter 10). This may include special staining methods, direct immunofluorescence studies and immunocytochemistry. 'Rush' frozen sections may be necessary—for example, during micrographic surgery or in the urgent diagnosis of some blistering conditions [1].

Table 5.9 Some 'dermatological' causes of eosinophilia (more than 0.44×10^9/L eosinophils).

Atopic disorders, especially asthma and eczema
Parasitic infestations
Worms (intestinal or systemic)
Scabies
Allergy to food or drugs
Tryptophan myalgia syndrome
Collagen vascular disease (especially polyarteritis nodosa and variants), dermatomyositis and eosinophilic fasciitis
Malignancy, especially Hodgkin's disease and eosinophilic leukaemia
Bullous disorders
Dermatitis herpetiformis
Pemphigus
Pemphigoid
Erythema neonatorum
Hypereosinophilic syndrome

- Other immunological and microscopy studies for bullous diseases, e.g. immunoblotting (Chapter 40) and electron microscopy (Chapters 16 and 39).
- Bacteriology and mycology samples (Chapters 30–37). May include samples for microscopy and culture, serological tests, PCR tests (e.g. for mycobacteria).
- Cytological examination. Usually in the context of FNA from lymph nodes, discussed above.

Reference

1 Amon RB, Dimond RL. Toxic epidermal necrolysis: rapid differentiation between staphylococcal and drug induced disease. *Arch Derm* 1975; **111**: 1437.

Radiological and imaging examinations

These have an important role in dermatology, but less than in many other specialties, because the skin can so readily be seen and felt. Ultrasound [1,2], magnetic resonance imaging (MRI) [3–5], radio-isotope scans and even positron emission tomography (PET) [6,7], are all used in clinical dermatological practice, mainly in relation to detection of lymphadenopathy or other metastatic skin cancer. High resolution ultrasound is increasingly important in documentation of nodal enlargement and tumour infiltration, and can be used to guide biopsies. Other uses of radiological procedures in dermatology include, for example, for the accurate assessment of the thickness of lesions in scleroderma, the extent of infection in severe forms of cellulitis (and distinction, using MRI, from necrotizing fasciitis), and assessment of local invasion of tumours. Various imaging techniques are also important in the management of diseases such as neurofibromatosis, where there may be central nervous system involvement, or in the assessment of muscle change in dermatomyositis. Lymphoscintigraphy may be a useful functional assessment of the lymphatic system of the swollen lower limb (Chapter 48). Doppler assessment of the peripheral lower limb arteries is an essential bedside technique prior to the use of high-compression bandaging in the management of venous leg ulcers (see Chapter 47); use of standard electronic sphygmomanometer systolic pressure measurements is not accurate in measurement of peripheral arterial pressures [8].

References

1 Stiller MJ, Driller J, Shupack JL *et al.* Three dimensional imaging for diagnostic ultrasound in dermatology. *J Am Acad Dermatol* 1993; **29**: 171–5.
2 Harland CC, Bamber JC, Gusterson BA, Mortimer PS. High frequency, high resolution B-scan ultrasound in the assessment of skin tumours. *Br J Dermatol* 1993; **128**: 525–32.
3 Zemtsov A, Dixon L. Magnetic resonance in dermatology. *Arch Dermatol* 1993; **129**: 215–8.
4 Sanig P, Le Breton C, Pavlovic M *et al.* Magnetic resonance imaging in adults presenting with severe acute infectious cellulitis. *Arch Dermatol* 1994; **130**: 1150–8.
5 Franck JM, MacFarlane D, Silvers DN *et al.* Atrophoderma of Pasini and Pierini: atrophy of dermis or subcutis? *J Am Acad Dermatol* 1995; **32**: 122–3.
6 Wong WL, Chevretton E, McGurk M, Croft D. Pet-FDG imaging in the clinical evaluation of head and neck cancer. *J R Soc Med* 1995; **88**: 469–72.
7 Böni R, Huch-Böni RA, Steinert H *et al.* Staging of metastatic melanoma by whole-body positron emission tomography using 2-fluorine-18-fluor-2-deoxy-D-glucose. *Br J Dermatol* 1995; **132**: 556–62.
8 Aboyans V, Lacroix P, Doucet S *et al.* Diagnosis of peripheral arterial disease in general practice: can the ankle-brachial index be measured either by pulse palpation or an automatic blood pressure device? *Int J Clin Pract* 2008; **62**: 1001–7

Skin testing

Substances may be introduced into the skin by a variety of techniques to study pharmacological and immunological [1] reactions under controlled conditions. Such tests are extremely valuable, but details of the type of test and the time at which it is read must correspond to the pathological process under consideration. Interpretation of the relevance of tests, either positive or negative, must always be correlated with the clinical picture. All too often, evidence adduced from tests is either meaningless or misleading.

Absorption of many substances through the intact skin is poor and variable, but direct application to the surface of the skin is used for patch testing. The epidermal barrier may be overcome either by removing it or by introducing the material directly into the dermis. The following techniques for skin testing are most commonly used.

Techniques for skin testing

Epicutaneous tests—patch tests

Patch tests are usually used to detect contact allergy of the delayed hypersensitivity type. They are usually read at 48–72 h and again up to 1 week, but can also be read at 15–30 min to detect contact urticaria. At times, patch testing may usefully be combined with scratch testing. Details of these techniques are discussed in Chapter 26.

Intradermal injection

The injection is made into the superficial layer of the dermis through a fine-bore (26- or 27-gauge) needle with its bevel pointing upwards. The quantity that may conveniently be injected varies from 0.01 to 0.1 mL. Precise measurement of smaller quantities is difficult and requires syringes with especially well-fitting plungers and a micrometer screw gauge. For routine clinical purposes, an approximation is sufficient—either 0.05 mL or the amount that just causes a visible weal (0.01–0.02 mL).

The optimal time for reading the reaction naturally varies with the pharmacological agent or the type of immunological reaction. Most such tests are read at either 15–20 min or at 48 h, but it may be important to read the tests at other times, for example at 4–12 h or after 4 days. The response to be observed at 15 min—for example, after an injection of histamine or after immediate-weal allergy tests—is a weal with a surrounding flare (Fig. 5.20). The weal is a more accurate measure than the flare. When the test is read at 48 h—for example, in the tuberculin reaction—the sizes of the indurated papule and of the erythematous reaction should be observed.

The site of the test is of some importance [2,3]. In general, the whole skin surface is capable of responding to skin tests, but there are regional variations. The back and the flexor aspects of the forearms are most conveniently used. The skin on the ulnar aspect of the forearm is more sensitive than the radial, and the proximal



Fig. 5.20 A positive prick test reaction to latex allergen.

more sensitive than the distal. These differences are not of sufficient magnitude to affect routine testing, but must be taken into account by using symmetrical areas for controls in any accurate quantitative testing.

A test solution must always be compared with a control solution injected in a comparable site at the same time. A positive test may be taken as one that is significantly different from the control. Assessment of what is significant is difficult, and varies with the enthusiasm of the tester. If a difference of less than 5 mm is accepted, reproducible results may not be obtained on retesting [4].

The measurement of a weal is usually made by diameter, although more sophisticated methods, such as volume measurements and Doppler flow, have been used [5]. If the weal is not circular, an approximation may be made by averaging maximum/minimum diameters, or more accurately the area may be calculated by the formula $D_1 \times D_2 \times \pi/4$, where D_1 and D_2 are the maximum and minimum diameters [6]. For irregular weals, a tracing may be made on squared paper. Pseudopodia should be noted, but for measurement of diameter they are ignored. Attempts to assess the volume of a weal are less satisfactory for routine use.

The size of the weal is not directly proportional to the dose of the active agent, but varies also with the total volume of fluid injected. An approximation of a linear relationship may best be achieved, often only over a narrow range, by plotting the response against the log dose. For accurate quantitative observations, weal diameters below 4 mm or above 15 mm cannot be relied upon.

Antihistamines may greatly inhibit the immediate weal tests. In the case of very long-acting agents, this effect may last as long as 3 weeks. They have no appreciable effect on delayed hypersensitivity patch tests. Moderate to large doses of corticosteroids, in contrast, may somewhat inhibit patch tests, although smaller doses—for example, prednisone 10 mg daily—are not necessarily a contraindication to testing. Steroids do not greatly inhibit the immediate weal tests. When a patient feels faint, any immediate weal test may be completely inhibited.

Prick test

This is a modification of the intradermal injection. A small quantity of the test solution is placed on the skin and a prick is made through it with a sharp needle. This should be superficial and not sufficient to draw blood. The quantity has been estimated as 3×10^{-6} mL [3]. The size of the weal and flare are measured after 15 min (Fig. 5.20). This test gives reproducible results and is convenient for much routine allergy testing. Because of the discrepancy in quantities injected, the testing solutions are made up at different strengths for prick testing and intradermal testing. The intradermal injection of prick-test solutions may be dangerous.

Scratch test

The scratch test resembles the prick test. A linear scratch about 1 cm long, but not sufficient to draw blood, is made through the epidermis. This test gives less reproducible results than the prick test.

Modified prick test

Here, a drop of the test solution is placed on the skin. A needle is then inserted very superficially and almost horizontally into the skin and lifted to raise a tiny tent of epidermis. This test is slightly more sensitive than the ordinary prick test, but gives no more reproducible results.

Skin-window technique [7,8]

The surface of the skin over an area a few millimetres square is scratched off with a scalpel, the test solution applied and the area covered with a coverslip. This is removed at various intervals—for example, 3 h, 6 h, 12 h, 24 h and 48 h—and immediately replaced by another coverslip. The cells on the coverslip are stained with ordinary haematological stains. The cellular response at varying time intervals can be assessed.

References

1 Pepys J. Skin tests. *Br J Hosp Med* 1984; **32**: 120–4.
2 Rappaport BZ, Becker EL. Quantitative studies in skin testing, 4: the volume–response relationship. *J Allergy* 1949; **20**: 358–63.
3 Squire JR. The relationship between horse dandruff and horse serum antigens in asthma. *Science* 1950; **9**: 127–50.
4 Gottlieb PM, Stupniker S, Askovitz J. The reproducibility of intradermal skin tests: a controlled study. *Ann Allergy* 1960; **18**: 949–60.
5 Serup J. Quantification of weal reactions with laser Doppler flowmetry. *Allergy* 1985; **40**: 233–7.
6 Herxheimer A. The action of drugs on the skin. *Ann Rev Pharmacol* 1961; **1**: 351–68.
7 Hu F, Fosnaugh RP, Bryan HG *et al*. Human skin window: a cytologic method for the study of allergic inflammation. *J Invest Dermatol* 1961; **37**: 409–19.
8 Rebuck JW, Crowley JH. A method of studying leukocytic functions in vivo. *Ann NY Acad Sci* 1955; **59**: 757–805.

Immediate weal tests

These tests are used for detecting IgE antibodies. The passive transfer test may be used to detect circulating IgE, but is not recommended because of the risk of serum hepatitis or human immunodeficiency virus (HIV). These antibodies play a role in hay fever, asthma, atopic dermatitis and anaphylactic reactions. They occur especially, but not exclusively, in patients with a personal or family background of atopy. Positive skin tests to a wide variety

of antigens are extremely frequent in these patients and must always be correlated with the history. They are principally used in the assessment of hay fever and asthma and have a limited place in the management of atopic dermatitis (Chapter 24). They are disappointing in the diagnosis of urticaria. False-positive and false-negative reactions are common.

Severe systemic reactions and, very rarely, fatalities may occur after correct use of standard testing solutions, and epinephrine (adrenaline) and hydrocortisone injections should always be at hand when skin tests are performed [1,2].

Alternative methods of detecting and measuring circulating antibodies are the RAST and the enzyme-linked immunosorbent assay (ELISA). RAST correlates well with skin testing [3,4]. It is particularly useful (i) in testing very young children; and (ii) with allergens associated with risk on prick testing (e.g. drugs).

The autologous serum test is a technique used in the investigation of chronic idiopathic urticaria whereby the patient's own serum is injected intradermally. It is regarded as being positive if at 30 min there is a weal 1.5 mm larger than at the saline control injection site. Positive reactions are indicative of functional autoantibodies against the high-affinity IgE receptor FcεRI, or against IgE [5] (Chapter 22).

Delayed (4–8 h) tests

The clinical interpretation of tests that are positive at 4–8 h can be difficult. Sometimes, these represent an Arthus reaction, but ideally this should be confirmed histologically. Other such tests represent a delayed variant of the immediate weal (15-min) test.

Intradermal tests for the detection of delayed sensitivity to bacterial, fungal and viral antigens

The tuberculin test. Testing for evidence of tuberculosis has achieved new importance in dermatology, in part because of an increasing incidence of tuberculosis associated with HIV infection, and also because screening is a necessary part of the work-up before use of antitumour necrosis factor biological drugs (for example, in psoriasis). A positive result to the standard strength (10 tuberculin units, TU) is an indication of previous mycobacterial infection, but not necessarily by *Mycobacterium tuberculosis* (especially if the reaction is weak or doubtful). Reactions to 1 TU (1/100 dilution of purified protein derivative (PPD)) are, however, significant. In sarcoidosis, reactions may be wholly negative, or only positive to 100 TU. The minimum size of a positive reaction is taken as 5 mm. An intermediate (24-h) reaction sometimes occurs.

Comparable doses of PPD may vary according to their source. Misleading negative reactions may occur in anergic patients. Tuberculin tests are discussed further in Chapter 31.

The Heaf test. Used in mass testing and in children. It is roughly equivalent to, or perhaps slightly more sensitive than, a dilution of 1:100 old tuberculin [6].

Candida antigen is used in a similar manner to the tuberculin test. Depressed reactivity occurs in sarcoidosis and other immunosuppressed conditions. Negative reactions in normal subjects are, however, not uncommon and depend on age and locality.

Trichophytin detects past infection by *Trichophyton* species. Its value is limited.

The lepromin test. This is discussed in Chapter 32.

Histoplasmin, coccidioidin and similar antigenic tests are of most value in areas where these diseases are not endemic. The Frei test and cat scratch fever antigen are of some value in the UK, where the relevant diseases are comparatively rare. A positive reaction is then significant. Conversely, Brucella antigen and toxoplasmin are of limited use in dermatological practice.

Delayed-type bacterial antigen tests [7–9]. These are not widely used, partly because their specificity and interpretation are difficult to assess. They consist of standard preparations of bacterial extracts, each probably containing a mixture of antigenic components, which may produce an immediate, or delayed 48-h reaction or an even later reaction. The normal 48-h response is a papule showing, histologically, a tuberculin-type reaction of lymphocytic type. Occasionally, however, especially in cases of vasculitis, an acute leukocytoclastic reaction occurs within 6–8 h [8] and is fully established at 24–48 h. Sometimes, the reaction is severe enough to produce a sterile abscess. It is tempting to believe that these reactions may be of some significance in conditions such as erythema multiforme, erythema nodosum (streptococcal), allergic vasculitis and, perhaps, pustular psoriasis. However, the antigens at present in use are relatively impure and the reactions may be non-specific. Further careful immunological studies are required.

Long-delayed (6-week) intradermal reactions. These comprise the Kveim test and the Mitsuda test. They are read at 6 weeks, but biopsy is essential with the Kveim test. Kveim test antigen is no longer available in the UK.

References

1 Lockey RF, Benedict LM, Turkeltaub PC, Bukantz SC. Fatalities from immunotherapy (IT) and skin testing (ST). *J Allergy Clin Immunol* 1987; **79**: 660–77.

2 Reid MJ, Lockey RF, Turkeltaub PC, Platts Mills TE. Survey of fatalities from skin testing and immunotherapy, 1985–89. *J Allergy Clin Immunol* 1993; **92**: 6–15.

3 Ahlstedt S, Eriksson N, Lindgren S *et al.* Specific IgE determination by RAST compared with skin and provocation tests in allergy diagnosis with birch pollen, Timothy pollen and dog epithelium allergens. *Clin Allergy* 1974; **4**: 131–40.

4 Seltzer JM. Correlation of allergy test results obtained by IgE RAST and prick-puncture methods. *Ann Allergy* 1985; **54**: 25–30.

5 Sabroe RA, Grattan CE, Francis DM *et al.* The autologous serum skin test: a screening test for autoantibodies in chronic idiopathic urticaria. *Br J Dermatol* 1999; **140**: 446–52.

6 Report to Research Committee of British Tuberculosis Association. *Tubercle* 1959; **40**: 317–35.

7 Shelley WB. Bacterial endotoxin (lipopolysaccharide) as a cause of erythema multiforme. *JAMA* 1980; **243**: 58–60.

8 Shelley WB, Wood MG, Beerman H. Pustular psoriasis elicited by streptococcal antigen and localized to the sweat pore. *J Invest Dermatol* 1975; **65**: 466–71.

9 Wilkinson DS. Some clinical manifestations of allergic vasculitis. *Br J Dermatol* 1965; **77**: 186–92.

Oral provocation tests

The administration of a drug, food or chemical by mouth may sometimes be called for to confirm the diagnosis of an eruption or to establish its exact cause. Such tests are used in the following situations.

1 To determine the cause of a drug eruption or to isolate one from a number of drugs or ingredients of a compound drug. It is applicable only when the drug given and the dose chosen are unlikely to provoke a severe reaction in the patient. It may be a valuable method of proving the cause of a fixed drug eruption but should rarely, if ever, be used if the reaction has been of a generalized or acute nature. The subject is discussed in more detail in Chapter 75.

2 In the course of the investigation of food allergens [1–3]. The reintroduction of specific foods, one at a time, is an established part of exclusion, elimination and challenge diets. It is important that the role of the suspect food is subsequently confirmed by reintroducing it in a disguised form to avoid identification by the patient. The procedure is applicable to patients with atopic eczema (Chapter 24), chronic or recurrent urticaria (Chapter 22) and possibly to some other dermatological conditions that have an allergic basis. However, it must be carried out with care and is only valuable if the tests are properly controlled and the patient is cooperative and well motivated.

3 In establishing the role of additives in chronic urticaria or angio-oedema (Chapter 22). Tartrazine, benzoates and antioxidants have been especially implicated [4–6]. Although oral provocation with increasing test doses of these substances is theoretically simple, the same reservations apply, and the administration of the diets and the 'blind' challenge require time, patience and motivation. Audit has shown that these tests appear to benefit the patient at low cost, but their scientific validity remains uncertain [7].

The role of oral nickel and chromate in the behaviour of endogenous hand eczema has been studied [8,9]. Some authors have produced flares of vesicular hand eczema after oral administration of nickel, but others have been unable to reproduce these results when interspersing test doses with placebo capsules.

Oral provocation with balsam of Peru was used in a series of 221 patients [10]. Flares of an existing dermatitis occurred in 45 patients, only 17 of whom had shown positive patch-test reactions to this substance. Subsequent dietary restriction of flavourings was said to clear or 'markedly improve' the dermatitis in half the patients.

Sublingual food tests are unreliable [11].

References

1 Committee on Provocative Food Testing. Identification of food allergens. *Ann Allergy* 1973; **31**: 375–92.

2 Joint Report of the Royal College of Physicians and the British Nutrition Foundation: food intolerance and food aversion. *J R Coll Physicians Lond* 1984; **18**: 83–123.

3 Lessof MH, ed. *Clinical Reaction to Foods*. Chichester: Wiley, 1983: 103–33.

4 Juhlin L. Incidence of intolerance and food additives. *Int J Dermatol* 1980; **19**: 548–51.

5 Juhlin L. Recurrent urticaria: clinical investigation of 330 patients. *Br J Dermatol* 1981; **104**: 369–81.

6 Michäelsson G, Juhlin L. Urticaria induced by preservatives and dye additives in food and drugs. *Br J Dermatol* 1973; **88**: 525–32.

7 Smith R, Burton JL. Oral challenge tests for urticaria: an ethical dilemma. *Br J Dermatol* 1994; **131**: 583–4.

8 Burrows D, Creswell S, Merrett JD. Nickel, hands and hip prostheses. *Br J Dermatol* 1981; **105**: 437–44.

9 Kaaber K, Veien NK, Tjell JC. Low nickel diet in the treatment of patients with chronic nickel dermatitis. *Br J Dermatol* 1978; **98**: 197–201.

10 Veien NK, Hattel T, Justesen O *et al*. Oral challenge with balsam of Peru. *Contact Dermatitis* 1985; **12**: 104–7.

11 Lehman CW. A double blind study of sublingual provocative food testing: a study of its efficacy. *Ann Allergy* 1980; **45**: 144–9.

Telemedicine

Considerable clinical experience is needed in order to make correct dermatological diagnoses, and since trained dermatologists are in relatively short supply even in many developed countries, telemedicine—remote consultation via an electronic link—may become an attractive option. It is particularly useful in remote or rural areas where there are no specialists.

Dermatologists have for many years conducted long-range consultations by telephone or by mailing histology slides or clinical photographs, but the unique feature of telemedicine is the two-way electronic network that now allows immediate interactive communication between the patient, the primary care physician and the specialist (so-called real-time teleconsultation). Different parts of the patient can be viewed at various magnifications, and the specialist can ask supplementary questions and advise on the most suitable biopsy sites if necessary. Such teleconsultations may be extremely valuable for obtaining international specialist opinion. A less satisfactory, but relatively time-efficient approach is the 'store and forward' system, whereby history details and images taken remotely are reviewed later by a distant specialist. Both for the primary care physician and specialist, teleconsultation time exceeds the duration of face to face consultation [1]. This does not allow simultaneous supplementary history and directed image choice, which may hamper appropriate management.

Several trials have shown that telemedicine can be effective, with high levels of satisfaction reported by patients, GPs and hospital specialists [2–4] though good photographic technique and lighting are essential for optimal results. It may be useful for tumour triage as well as assessing inflammatory dermatoses [5]. A personal encounter between specialist and patient may offer additional advantages, such as enhanced information about the patient's personality, with more patient participation in decisions and a placebo effect, which can lead to greater compliance [6]. The ability to palpate and smell can also give valuable diagnostic information (p. 5.17) but telemedicine clearly has considerable potential for dermatological diagnosis. With the ubiquity of high resolution mobile phone cameras, an increasing number of patients bring images of themselves, and this may be valuable in assessing evanescent eruptions. Mobile phone teledermatology may help in triage [7,8].

References

1 Berghout RM, Eminović N, de Keizer NF, Birnie E. Evaluation of general practitioner's time investment during a store-and-forward teledermatology consultation. *Int J Med Inform* 2007; **76** (Suppl. 3): S384–91.

2 Mallett RB. Teledermatology in practice. *Clin Exp Dermatol* 2003; **28**: 356–9.
3 Mofid M, Nesbitt T, Knuttel R. The other side of teledermatology: patient preferences. *J Telemed Telecare* 2007; **13**: 246–50.
4 Eedy DJ, Wootton R. Teledermatology: a review. *Br J Dermatol* 2001; **144**: 696–707.
5 Moreno-Ramirez D, Ferrandiz L, Nieto-Garcia A *et al*. Store-and-forward teledermatology in skin cancer triage: experience and evaluation of 2009 teleconsultations. *Arch Dermatol* 2007; **143**: 479–84.
6 Editorial. Telemedicine: fad or future? *Lancet* 1995; **345**: 73–4.
7 Chung P, Yu T, Scheinfeld N. Using cellphones for teledermatology, a preliminary study. *Dermatol Online J* 2007; **13**: 2.
8 Ebner C, Wurm EM, Binder B *et al*. Mobile teledermatology: a feasibility study of 58 subjects using mobile phones. *J Telemed Telecare* 2008; **14**: 2–7.

CHAPTER 6
Epidemiology of Skin Disease

H.C. Williams
Centre of Evidence-Based Dermatology, Nottingham University Hospitals NHS Trust, UK

What is epidemiology and why is it relevant to dermatology?, 6.1
Thinking in terms of populations rather than individuals, 6.2
The community diagnosis, 6.2
Skin diseases as 'entities' in the population, 6.2
Making comparisons and drawing inferences, 6.2
The prevention paradox, 6.3
How much of a public health problem is skin disease?, 6.4
The need for a clear disease definition in epidemiological studies, 6.4
Burden, impairment, disability and handicap caused by skin disease, 6.5
Routine data that describe the burden of dermatological disease, 6.5
Special prevalence studies of skin disease in general, 6.6
The burden of skin disease in developing countries, 6.8
What determines the frequency of skin disease in populations?, 6.11
Risk factors, association and causation, 6.11
Describing the natural history and associations of specific skin diseases, 6.13
Health-services research in dermatology, 6.14
Needs assessments in dermatology, 6.14
Services available for people with skin diseases, 6.14
The relationship between need, supply and demand for dermatological care, 6.15
Systematic reviews and the Cochrane Collaboration, 6.16
Conclusions, 6.17
Glossary of epidemiological terms, 6.18
Checklist for reading 'epidemiological studies' in dermatology, 6.19
Recommended further reading and useful dermatoepidemiology resources, 6.19

What is epidemiology and why is it relevant to dermatology?

> *Epidemiology is the simplest and most direct method of studying the causes of diseases in humans and many contributions have been made by studies that have demanded nothing more than an ability to count, to think logically and to have an imaginative idea.*
>
> (Sir Richard Doll, 1987 [1])

Many dermatologists still think of epidemiology in terms of describing the prevalence and the age, sex and geographical characteristics of a particular skin disease. Whilst it is true that epidemiology is often used in this fashion to describe the *burden* of disease in human populations, as Sir Richard Doll points out above, epidemiology also offers one of the most powerful and direct methods of evaluating the *causes* of skin diseases in human populations. One definition of epidemiology is therefore 'the study of the distribution and causes of diseases in human populations'. In addition to describing the burden and causes of skin diseases in populations, *clinical epidemiology* is concerned with describing the natural history and prognosis of diseases and with evaluating interventions which seek to prevent or treat diseases [2]. The term *dermatoepidemiology* refers to the study of the epidemiology of dermatological disorders [3]. Because epidemiological studies are often concerned with making observations about highly complex natural experiments, methods for minimizing bias or adjusting for confounding factors (see glossary) have had to be developed. These new methods, along with the high scientific rigour necessary for designing and interpreting epidemiological studies, are aspects from which all dermatological research can benefit. Epidemiology is therefore relevant to dermatology for the six reasons shown in Table 6.1.

Although epidemiology is still sometimes perceived as a novel aspect of dermatology, the first epidemiological discoveries in dermatology can be traced back to 1746, when James Lind [4] concluded that scurvy in sailors was related to dietary factors. He then showed, by means of a controlled study, that the disease readily responded to the addition of fresh oranges and lemons in the sailors' diet (the principles developed by Lind have resulted in the establishment of a library documenting the development of fair tests in treatments in health care [5]). In 1914, Joseph Goldberger [6] observed that 8% of 418 patients admitted to the Georgia State Sanatorium developed pellagra, compared with none of the 293 Sanatorium employees. He suggested that pellagra was due to an absence of 'essential vitamins', today recognized as nicotinic acid, and proceeded to test his suggestion in a community trial. Thus, dermatoepidemiology is not such a new subject, and with over 2000 skin disease reaction patterns described, the scope of the topic is vast. This chapter will therefore not deal with the epidemiology of specific skin diseases, which will be described where possible under the relevant disease sections. It will instead attempt to illustrate the relevance of modern epidemiology to dermatology by using specific examples. The principles of evidence-based dermatology, which relies heavily on methods developed from

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

Table 6.1 The relevance of epidemiology to dermatology.

To quantify the burden of skin disease in the community
To identify the causes or risk factors for skin diseases
To describe the natural history, prognosis and disease associations of skin diseases
To evaluate the effectiveness of dermatological treatments and organization of health care
To provide a methodological framework for underpinning evidence-based practice in dermatology
To provide appropriate methods for designing and interpreting clinical dermatological research

clinical epidemiology, are discussed in more detail in Chapter 7 by Bigby and Williams. A glossary of commonly used epidemiological terms and further reading sources are to be found at the end of this chapter.

References

1 Doll R. Foreword. In: Hennekens CH, Buring JE, Mayrent SL, eds. *Epidemiology in Medicine*. Toronto: Little, Brown, 1987: xi–xii.

2 Sackett DL, Haynes RB, Guyatt GH, Tugwell P. *Clinical Epidemiology*. Toronto: Little, Brown, 1985.

3 Chuang T-Y, Reizner GT. Dermatoepidemiology. Part 1: Epidemiologic methods. *Int J Dermatol* 1993; **32**: 251–6.

4 Lind J. *A Treatise of the Scurvy in Three Parts, Containing an Inquiry into the Nature, Causes and Cure of That Disease, together with a Critical and Chronological View of What Has Been Published on the Subject*. Edinburgh: Sands, Murray and Cochran, 1753.

5 Chalmers I. The James Lind Library. Illustrating the development of fair tests of treatments in health care. Royal College of Physicians of Edinburgh http://www.jameslindlibrary.org/ (Accessed 1st December 2007.)

6 Goldberger J. The etiology of pellagra. *Public Health Rep* 1914; **29**: 1683–6.

Thinking in terms of populations rather than individuals

The community diagnosis

One of the first hurdles to overcome when considering the epidemiology of a skin disease is to think in terms of *populations* rather than *individuals*. Many physicians find this conceptual jump quite difficult, as they are used to dealing with *individual* patients on a daily basis, whereas epidemiological studies refer to *groups* of individuals. Just as molecules, genes and individuals exhibit various aggregate characteristics, entire groups or populations exhibit their own unique characteristics and problems that enable a *community diagnosis* to be achieved [1].

Interesting patterns can occur when one explores the potential implications of treating an entire community (the public health approach) rather than sick individuals who present themselves to doctors (the high-risk approach). Rose [2], for example, showed that a 10-mm lowering of blood pressure distribution as a whole (e.g. from reducing salt intake) would correspond to about a 30% reduction in the total attributable mortality, simply because of the shape of the change conferred on the distribution curve in relation to specific 'disease' cut-off points. In other words, a little bit of benefit spread across the entire population distribution may result in large population benefits in absolute terms.

Table 6.2 Prevalence of scabies among 756 Kuna Indians on the island of Ticantiki, Panama [3].

Date	Community treatment status	Prevalence of scabies (%)
July 1986	Conventional treatment	33.0
October 1986	Community control and surveillance instituted	0.7
July 1987	Breakdown due to supply problem	3.6
December 1988	Programme running again	1.5
March 1990	US invasion of Panama	12.0

During the scabies epidemics that occurred on the islands near Panama in the 1980s [3], it was found that even the best topical treatments when administered properly had no sustainable impact on the overall prevalence of scabies (which was very high in this population and which was associated with considerable morbidity from secondary pyoderma). When a *population* approach was adopted, that is treating all individuals with a programme of continuing surveillance, the prevalence of scabies fell dramatically to less than 2%, as shown in Table 6.2, and was sustained at that level until the US invasion of Panama interrupted these efforts. Thus, just as individuals become 'diseased', entire populations can become sick [2]. In these situations, whether it be an infestation such as scabies or a disease of modern society such as obesity, tackling the problem based on a population diagnosis is usually beneficial, cost-effective and appropriate [4].

Skin diseases as 'entities' in the population

The concept of considering the health of entire populations also applies to the classification of skin diseases. Typically, dermatologists are preoccupied with deviants who present themselves to secondary and tertiary care because of disease severity and/or chronicity and who are at the extreme end of the normal distribution curve of variations in skin health and disease. Such individuals usually have well-defined physical signs which prompt those studying them to declare them as discrete 'entities' [5,6]. Such distinctions often become blurred when community surveys are undertaken. In a community survey of atopic eczema, for instance [7], it was noticed that indeterminate or borderline cases who had limited areas of dry skin or a single patch of eczematous inflammation were quite common. In these circumstances, perhaps the more relevant question is not 'Has the person got eczema?' but 'How much eczema does the person have?'

The concept of a distribution of disease severity at a population level may also be helpful in evaluating different treatment policies. For example, it has been estimated that a small change in the treatment threshold of isotretinoin from severe to moderate cases of acne could result in a 15-fold increase in prescriptions in absolute terms, simply because moderate cases outnumber severe cases by so much [8].

Making comparisons and drawing inferences

Epidemiological reasoning usually progresses in an ordered fashion, starting with a hypothesis that has been suggested by

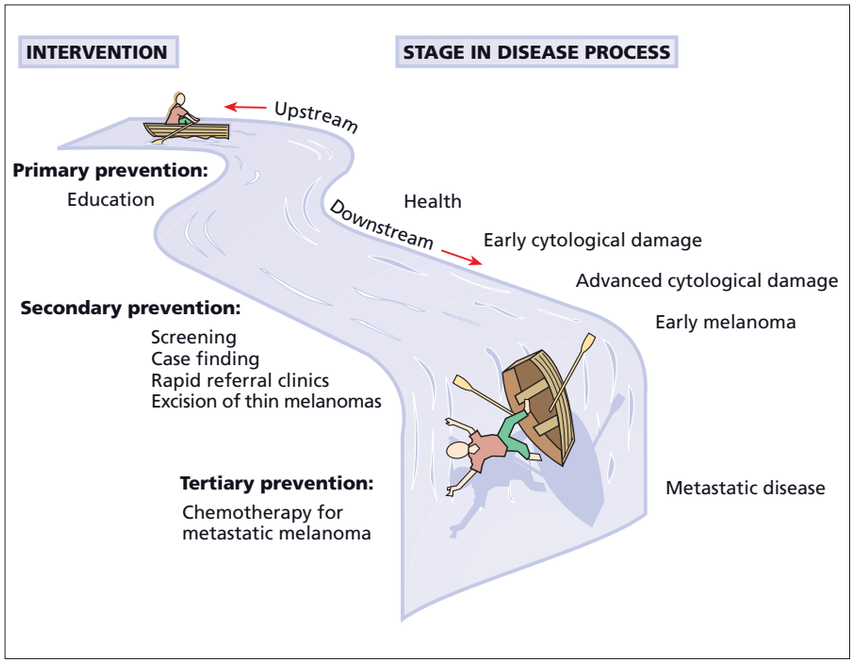


Fig. 6.1 Disease prevention in a serious condition such as melanoma is much more sensible than treating sick individuals with expensive drugs at the end of a long chain of irreversible pathological events.

good clinical observations (e.g. palmoplantar psoriasis seems to be commoner in smokers) or descriptive studies of populations. The hypothesis (that smoking is a risk factor for palmoplantar psoriasis) is then tested in an epidemiological study, which gathers and analyses data in a systematic fashion in relation to an appropriate comparison group to see if a statistical association exists. *Analytical epidemiology* is therefore concerned with making comparisons. These comparisons rely upon the uneven distribution of disease and risk factors within and between populations to shed light on possible causes of ill health. Thus, previous case–control studies [9] showed that smoking was far more common in patients with lung cancer—a finding which led to more sophisticated studies to establish disease causality [10]. If everyone had smoked, it is unlikely that smoking would have been identified as a cause of lung cancer.

In the simplest form of epidemiological study, a count is made of the number of cases with a particular skin disease (the numerator) within a catchment population (the denominator). The probability or frequency of disease occurrence may then be compared in two or more populations—for example, one exposed to a putative causative agent compared with another which is not. Inferences are then drawn based on the magnitude of the differences of disease frequency between the populations in light of possible alternative explanations such as chance, bias and confounding (see glossary). If such associations are genuine, further evidence is usually needed to determine whether they are causal in nature [11]. The whole process brings us one step nearer to the dermatoepidemiologist's ultimate goal—that of preventing skin disease, providing such causes are amenable to individual/public health manipulation. Prevention of skin disease is clearly more desirable than treating diseased individuals (Fig. 6.1).

When referring to an epidemiological study, it is important to make a distinction between the study population chosen for a particular study (e.g. those attending a hospital outpatient clinic) and the base population about whom one wishes to make inferences, as shown in Fig. 6.2. [12]

The prevention paradox

Interventions that confer large population health gains may not confer much benefit to individuals. Thus, in the example of scabies in Panama above [3], although the population's health as a whole benefited greatly, many apparently healthy individuals may have not appreciated being treated for scabies, as it was not known who would have developed scabies in the absence of the prevention programme. Similarly, it is difficult to say which child will benefit from being immunized for tuberculosis in a BCG immunization programme, because events have not yet occurred. This conflict between large gains in the health of entire populations versus small gains in individuals has been termed the 'prevention paradox' [4]. In the field of contact dermatitis, for example, eradication of a rare but potent contact sensitizer may have a great impact on affected individuals but little impact on the overall total burden of contact dermatitis in the general population. On the other hand, reduction in the amount of contact with formaldehyde, a less potent but far more common sensitizer in the general population, will result in a much larger reduction in the burden of contact dermatitis in that population, simply because far more people are exposed to formaldehyde [13]. As Table 6.3 illustrates, a little bit of harm affecting a lot of people can therefore add up to more than a lot of harm affecting a few people, in *population terms.* The first step when considering the epidemiology of skin disease is therefore to think about *populations* rather than *individuals*.

References

1 Barker DJP, Rose G. *Epidemiology in Medical Practice*, 2nd edn. Edinburgh: Churchill Livingstone, 1979.

2 Rose G. Sick individuals and sick populations. In: Buck C, Llopis A, Nájera E, Terris M, eds. *The Challenge of Epidemiology*. Washington: Pan American Health Organization, 1988: 829–37.
3 Taplin D, Porcelain SL, Meinking TL *et al*. Community control of scabies: a model based on the use of permethrin cream. *Lancet* 1991; **337**: 1016–8.
4 Rose G. Strategy of prevention: lessons from cardiovascular disease. *BMJ* 1978; **40**: 1069–118.
5 Kendell RE. *The Role of Diagnosis in Psychiatry*. Oxford: Blackwell Scientific Publications, 1975.
6 Burton JL. The logic of dermatological diagnosis. *Clin Exp Dermatol* 1981; **6**: 1–21.
7 Williams HC, Pembroke AC, Forsdyke H *et al*. London-born black Caribbean children are at increased risk of atopic dermatitis. *J Am Acad Dermatol* 1995; **32**: 212–7.
8 Williams HC. Dermatology. In: Stevens A, Raftery J, eds. *Health Care Needs Assessment*, Series II. Oxford: Radcliffe Medical Press, 1997: 261–348.
9 Wynder EL, Graham EA. Tobacco smoking as a possible etiologic factor in bronchogenic carcinoma: a study of six hundred and eighty-four proved cases. *JAMA* 1950; **143**: 329–36.
10 Doll R, Bradford-Hill A. Mortality in relation to smoking: ten years' observations of British doctors. *BMJ* 1964; **i**: 1460–7.
11 Bradford-Hill A. The environment and disease: association or causation? *J R Soc Med* 1965; **58**: 295–300.
12 Miettinen OS. Commentary on the paper by Zhang *et al*. Lack of evolution of epidemiologic methods and concepts. In: Morabia A, ed. *A History of Epidemiological Methods and Concepts*. Basel: Birkhäser Verlag, 2004, 365–6.
13 Williams HC. Relative and attributable risk and its relevance to the prevention of contact dermatitis. In: Elsner P, Lachapelle JM, Wahlberg J, Maibach HI, eds. *Current Problems in Dermatology*, Vol. 25. Basle: Karger, 1996: 10–7.

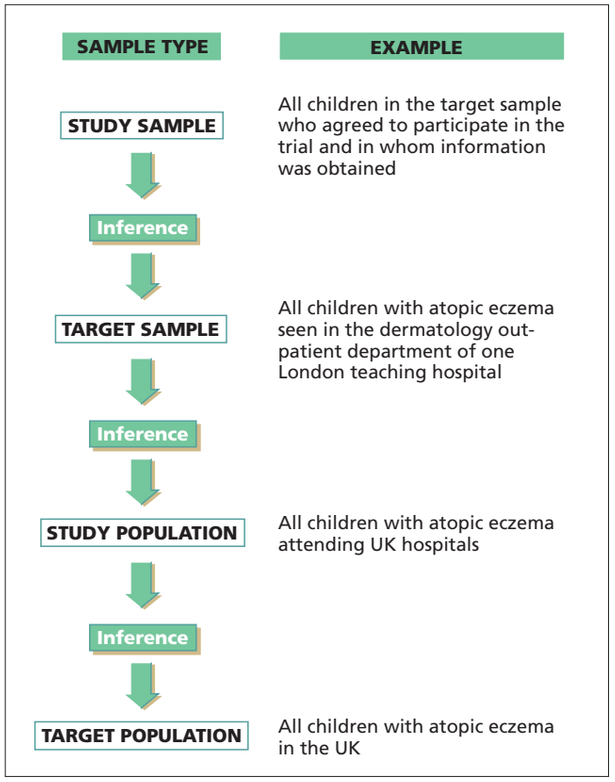


Fig. 6.2 Generalizing the results of a clinical trial of a new treatment for atopic eczema from a study of children attending one hospital department to all children with atopic eczema in the UK requires several jumps of inference.

Table 6.3 The prevention paradox: a little bit of harm affecting a lot of people can add up to more than a lot of harm affecting a few people. From Williams [13] with kind permission from Karger, Basle.

	Eradication of exposure in:	
	The population	**The individual**
Rare—Exposure with high relative risk (e.g. contact sensitization to diphencyprone)	Small benefit	Large benefit
Common—Exposure with low relative risk (e.g. smoking and psoriasis)	Large benefit	Small benefit

How much of a public health problem is skin disease?

The need for a clear disease definition in epidemiological studies

A glance at the dermatological journals makes it clear that the subject matter of most current research is defined—wholly or in part—by diagnostic criteria. But if these criteria are not explicitly stated, are prone to vary from one patient to the next in unpredictable ways, and vary systematically from place to place and time to time, the usefulness of such research is gravely impaired. Although phrases such as 'diagnosed by dermatologists' or 'diagnosed independently by two experienced physicians' and 'all with typical symptoms' may be adequate for dealing with individual patients, they are hopelessly inadequate when describing groups of individuals in epidemiological studies [1]. For instance, it has been shown that even experienced physicians are perfectly capable of disagreeing with each other over the classical signs of atopic dermatitis [2], and when two agree, a third is capable of disagreeing. What is regarded as 'typical' in London may be nothing of the sort in Lourdes, Lima, Lhasa or Lusaka.

Diagnostic criteria that work well in hospital studies may perform poorly in community studies because of the effect of low disease prevalence on positive predictive value (see glossary) and an increase in borderline cases. The properties of good diagnostic criteria for use in epidemiological studies are summarized in Table 6.4.

Not only is it important to use diagnostic criteria of known validity and repeatability in epidemiological studies, but it is

Table 6.4 The attributes of a good disease definition for use in epidemiological studies. From Williams [3], with permission.

Validity: it measures what it purports to measure by including cases and excluding non-cases
Repeatability: good replication of the definition between and within observers
Acceptability: to the study population in order to ensure high response rates
Coherence: with prevailing clinical concepts
Easy to administer by field workers
Reflects some degree of morbidity
Comprehensiveness: applicable to a range of ages, ethnic groups and disease severities
Comparability: they should contain elements which allow some comparison with previous studies

sometimes important to qualify cases identified by such criteria by some measure of disease severity. For example, prevalence surveys of acne in the absence of severity measures are not very helpful in quantifying the disease problem, since physiological acne (non-inflammatory lesions) affects over 90% of adolescents [4]. Again, severity grading systems used in a hospital setting (which are usually non-linear and tend to favour severe and currently active disease) may not be so helpful in separating disease severity in milder community cases, where intermittent disease may be more common.

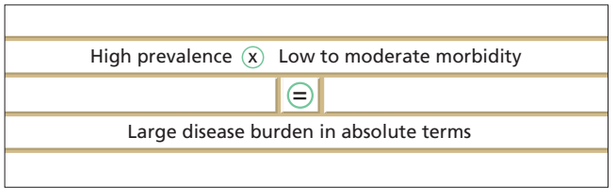


Fig. 6.3 Skin disease is a major public health problem: in public health terms, a little bit of misery affecting a lot of people can add up to more than serious illnesses which affect only a few people.

Burden, impairment, disability and handicap caused by skin disease

The burden of skin disease can refer to disease occurrence using terms such as prevalence or incidence (epidemiological burden), the effects of skin disease on a person's well-being (quality of life burden) or the direct and indirect costs associated with skin disease (economic burden). A working group affiliated to the US National Institute of Arthritis and Musculoskeletal Diseases (NIAMS) examined such conceptual frameworks in more detail, supplemented by thorough reviews of current data [5]. They concluded that further research is needed to reach consensus on how skin diseases and their associated burden should be defined. Burden of skin disease was also the theme of the 2008 International Dermato-Epidemiology Association Congress in Nottingham (http://www.nature.com/jid/journal/v128/n10/pdf/jid2008267a.pdf, accessed 28th July 2009), the findings of which will be summarized in a forthcoming publication.

In addition to the concept of burden, consideration of the three concepts of impairment, disability and handicap may be helpful in separating those effects which result from disordered function from those which are conferred on individuals by society. Impairment refers to the organic lesion produced by a disease, for example a broken limb; disability is the dysfunction that results from that impairment, for example not being able to walk; and handicap is the disadvantage that society confers upon the individual as a result of the impairment, for example unemployment. Handicap in skin disease may not be as explicit as that associated with a broken limb, but the psychological consequences of skin disease, which include 'failure of display' [6,7], may be just as important. It has been shown that relatively minor skin complaints often cause more anguish to people than other more serious medical problems [6]. Also, because skin disease is so common, a little bit of morbidity affecting a lot of people can add up to far more than a lot of morbidity affecting only a few people. It is this product of high prevalence times moderate morbidity that makes skin disease very important from the public health point of view (Fig. 6.3). Small changes in health policy can have large financial implications, simply because they affect so many people.

One population-based, cross-sectional study conducted in the USA on a random sample of 20 479 people examined by dermatologists in 1971 to 1974 [8] has pointed to the magnitude of disability and handicap from skin diseases; skin conditions were reported to limit activity in 10.5 per 1000 of the population aged 1–74 years, or 9% of those persons with such skin conditions. About 10% of those with skin complaints considered the condition to be a handicap to their employment or housework, and 1% considered themselves to be severely handicapped. About one-third of those persons with skin conditions indicated that the condition(s) were a handicap in their social relations. The dermatological examiners rated more than two-thirds of those with skin complaints as disfigured to some extent from the condition, and about one-fifth of those were rated moderately or severely disfigured. More than half of those with skin complaints reported some overall discomfort from the condition such as itching or burning. An estimated 62.8 per 1000 US civilians (or 56% of those with skin complaints) indicated that the conditions were recurrent, with 49% active in the preceding 7–12 months.

The 1989 UK General Household Survey estimated that 16 per 1000 persons were affected by a long-standing skin disorder sufficiently severe to limit their activities [9]. Another survey of disability, amongst 14 000 adults conducted in the mid-1980s, found that 1% of complaints causing disability in private households and 2% in communal establishments were due to skin disease [10]. A survey of self-reported skin problems in 8000 adults in Uppland, Sweden, found that 20.5% reported skin problems [11]. Those reporting skin problems scored lower on all eight dimensions of the SF-36, a generic quality-of-life instrument.

In addition to disability and handicap, some chronic skin diseases such as atopic eczema also incur considerable additional direct costs to families, such as that needed to purchase moisturizers, special soaps, extra laundry expenses, cotton clothing and bedding. The Lothian Atopic Dermatitis Study estimated that the mean cost to the patient was £25.90 per 2 months, while the mean cost to the Health Service was £16.20 in 1994 [12]. A systematic review of cost studies of atopic dermatitis in the US found very wide ranging costs estimates of 364 million to 3.8 billion US dollars per year, with very little information on indirect costs [13]. Another study estimated the direct cost of care for patients with psoriasis and psoriatic arthritis in the United States [14]. An ambitious project in the United States tried to estimate the direct and indirect costs of people with 22 of the commonest skin disease categories in 2004 and found that they accounted for around $29 billion in direct costs (medical care and products), $10 billion in lost productivity costs and a further $56 billion for loss of quality of life [15].

Routine data that describe the burden of dermatological disease

Generally speaking, routinely published medical statistics on skin disorders are sparse and, when available, are of limited use to the dermatologist in describing the burden of skin disease in the community. Special surveys are usually required to determine the

prevalence and morbidity of skin diseases in general or specific skin diseases.

Some routinely published data on skin disease morbidity have limited uses.

1 **Mortality**. Overall mortality is relatively low for skin diseases, accounting for at least 2578 deaths in 1992 in the UK [16] (or 0.46% of deaths from all causes and all ages). Melanoma alone accounted for a total of 1142 deaths in England and Wales in 1992, with 48% of deaths occurring in economically active adults [16]. Mortality statistics of melanoma and non-melanoma skin cancer may be useful in discerning trends over time, which may be related to the biology or treatment of these diseases.
2 **Morbidity**. Most routinely published morbidity data refer to those who seek medical help in the primary-care setting. With the exception of a few conditions, such as cellulitis, where incidence and demand are closely related, the extent to which routine morbidity data reflect the burden of dermatological need in the community is unclear. Despite these limitations, routine statistics, such as the UK morbidity surveys from general practice [17], are useful in that they provide an estimate of the magnitude and demographic determinants of those who seek medical care. Several important findings have already emerged from careful analysis of dermatological data from general practice databases [18–21].
3 **Skin cancer registration data** (i.e. cases presenting to physicians for the first time who are also reported) are of variable completeness and accuracy [22], but they have contributed some knowledge to understanding secular trends in reported cancer incidence and variations by sex, age and latitude. Special skin cancer registers, such as the Scottish Melanoma Group Database [23] and the German Central Malignant Melanoma Registry [24], are examples of more complete databases with stringent controls on data quality.
4 **Other special registers** maintained by groups of enthusiastic individuals exist and may be useful for certain types of epidemiological studies, for example the UK Epi-Derm surveillance system for monitoring occupationally acquired skin diseases, the US National Epidermolysis Bullosa Registry [25], the German *Dokumentationszentrum schwerer Hautreaktionen* for severe cutaneous drug reactions [26] and national registers of sexually transmitted diseases. The US PUVA cohort study has produced many useful findings related to subsequent skin cancer risks which have informed clinical practice [27]. Other sources of data, such as in-patient and outpatient statistics and prescription data, tell us something about those who present themselves to tertiary medical care. Record-linkage studies may provide useful insights into the determinants of in-patient versus outpatient care [28].

Special prevalence studies of skin disease in general

Self-reported skin disease

In 1986, the Proprietary Association of Great Britain commissioned a detailed, nationwide survey of 1217 adults and the parents of 342 children to determine how British people manage minor ailments and some chronic, recurring illnesses [29]. Skin complaints were the commonest ailment reported in the previous 2 weeks, comprising 25% of 6009 adult 'ailments' and 36% of 806 child 'ailments'. In addition to estimating the age- and sex-specific incidence of skin complaints over a 2-week period, the study provides a useful estimate of the proportion of skin complaints that are not considered by the public to be sufficiently severe to seek medical care, and the potential service implication should that threshold change. For example, of the 291 people complaining of acne/spots/greasy skin, 47% took no action, 34% used or bought an over-the-counter preparation, and 12% used medicines prescribed by a doctor, the remaining 7% using home remedies.

Similar proportions of self-reported 'skin disease in the last 2 weeks' have been recorded in two earlier studies [30,31]. A survey of 20 000 randomly chosen residents aged 20–65 years in Gothenburg, Sweden, found that 27% of females and 25% of males reported symptoms of skin disease in the previous 12 months [32]. Another survey of 8000 people aged 20–84 years in Sweden found that 20.5% reported a skin disease and/or use of topical dermatological drugs, with a higher frequency in women (23.3%) than men (17.3%) [11]. A survey of a representative sample of 18 137 people in France found that 86.8% reported some kind of skin problem since birth, and that in 28.7% of these it impaired their quality of life [33].

Examined skin disease

The Lambeth Study

Only one study in the UK has ever estimated the prevalence of skin diseases in the general population according to some form of physical examination. This study, conducted by Rea *et al*. in 1975 [34], was based on a questionnaire on skin symptoms which was sent to a stratified sample of 2180 adults in Lambeth, London. All positive respondents and one-fifth of those responding negatively were then interviewed and examined at home by a team of seven doctors and 11 nurses trained in the recognition of common skin disorders. Only exposed skin (face, scalp, neck, forearms, hands, knees and lower legs) was examined, and the overall response rate was 90.5%. Because of difficulties in agreeing on objective criteria for skin disease severity, skin disease was classified into trivial (not justifying medical attention), moderate (justifying medical attention) and severe (needing early medical attention because of severe symptoms or risk of progression), based upon the judgment of the examiner. The key findings of this study were as follows.

1 The overall proportion of the population found to have any form of skin disease was 55% (95% confidence intervals 49.6–61.3%).
2 The overall proportion considered to have skin disease worthy of medical care (i.e. moderate or severe) was 22.5% (95% confidence intervals 17.8–27.2%).

As shown in Table 6.5, the group containing tumours and naevi had the highest overall prevalence (20.5%), but 90% were considered as trivial by the examiners. In the eczema group, on the other hand, with an overall prevalence of 9%, more than two-thirds were graded as moderate/severe, so that the highest prevalence of conditions justifying medical care fell into this group (6.1%). Clear age trends emerged for specific disease groupings, for example acne and warts in younger age groups, although age, sex

Table 6.5 Prevalence of examined skin disease expressed as rates per 1000 in a survey of 2180 adults in Lambeth [34]. Prevalence rates have been rounded to the nearest whole number, and 95% confidence intervals for the main findings are shown in parentheses.

Skin condition	Both sexes		Male		Female	
	All grades	Moderate and severe	All grades	Moderate and severe	All grades	Moderate and severe
Tumours and vascular lesions	205	14	142	1	264	27
Eczema	90	61	100	80	81	43
Acne	86	35	109	35	64	35
Scaly dermatoses	85	29	118	39	53	19
Scalp and hair disorders	82	14	79	8	95	18.9
Prurigo and allied conditions	82	39	61	17	95	60
Erythematous and other dermatoses	75	21	31	21	117	22
Infective and parasitic conditions	46	7	48	11	44	3
Warts	34	2	36	–	33	3
Nail disorders	33	19	24	13	42	25
Psoriasis	16	6	24	4	8	8
Mouth and tongue disorders	9	1	15	–	3	1
Chronic ulcer	2	–	4	–	–	–
Any skin condition	555 (496–614)	225 (178–272)	479 (400–559)	213 (147–280)	607 (520–693)	236 (170–302)

and social class trends were not found when all forms of skin disease were considered together, since several conditions had trends in opposite directions.

HANES-1

Another detailed, cross-sectional study of skin diseases was conducted within the first US Health and Nutrition Examination Survey (HANES-1) [8]. This study, conducted on a representative population sample of 20749 persons aged 1–74 years from 65 primary sampling units throughout the USA during 1971 to 1974, included a detailed, structured skin examination by 101 dermatologists. Clinical findings were backed up by laboratory investigations, such as mycology culture and skin biopsy where possible. Key points emerging from this study were as follows.

1. Nearly one-third (312 per 1000 population) had one or more significant skin conditions which were considered by the dermatologist to be worthy of evaluation by a physician at least once.
2. The prevalence of significant skin pathology increased rapidly with age from 142 per 1000 children aged 1–5 years to 362 per 1000 youths aged 12–17 years and to 365 per 1000 young adults aged 18–24 years, due primarily to the increase in acne at puberty.
3. After a slight decline at age 25–34 years, the prevalence of skin pathology again increased steadily, reflecting the increase in chronic diseases such as psoriasis, vitiligo, malignant and benign tumours, actinic and seborrhoeic keratoses.
4. In this study, significant skin pathology was slightly commoner in males.
5. An additional 12.5% of the population was deemed to have a skin condition that was clinically inactive at the time of examination.

Both of these studies therefore suggest that significant skin disease is extremely common. Even though dermatology is characterized by an enormous range of disease-reaction patterns, prevalence surveys suggest that the bulk of the skin disease problem is made up of less than 10 disease groups [35]. The prevalence of skin disease documented in these two large population studies [8,34] also suggests that most individuals with skin disease do not seek medical help. Knowledge of this submerged section of the dermatological iceberg is important, as small changes in the population's perception of the need for medical help can have large effects on the delivery of health care.

Caution should be applied to prevalence studies with low response rates, as it cannot be assumed that respondents share the same characteristics as non-respondents. Indeed, a survey of non-respondents to a prevalence survey for skin disease in Australia found that people who did not respond to the initial survey were more likely to have skin cancers than respondents [36]. This important finding emphasizes the need to sample non-respondents in general prevalence surveys of skin diseases.

Surveys limited to children

A large, comprehensive survey of examined skin disease in 2491 schoolchildren was conducted in the state of Victoria, Australia, with specific reports published pertaining to warts, atopic dermatitis, acne and tinea pedis [37–40]. Another survey of 1006 primary and secondary schoolchildren in Hong Kong found that 31.3% had one or more skin disorders, 70% of whom did not seek medical attention [41]. A study of 2788 children from eight randomly selected schools in Amman, Jordan, found a similar prevalence of 19.23% [42], and a study that involved a dermatologist examining 1114 children aged 6–12 years in Bucharest, Romania, found a point prevalence of one or more skin diseases of 22.8% [43].

Collectively, these surveys suggest that, like adults, around one-fifth to one-quarter of schoolchildren in urban centres have one or more skin diseases. Skin examination surveys conducted

at one point in time (point prevalence surveys) are likely to underestimate the true burden of skin disease in children, since they will miss many children with infectious skin diseases of short duration, such as impetigo.

The burden of skin disease in developing countries

Table 6.6 summarizes studies of skin disease prevalence that have been conducted in developing countries compared with data from some developed countries [8,34,44–54]. Making comparisons between countries is difficult, as survey methods have differed in terms of population ages, method of sample selection and classification of diseases. The distinction between any form of skin disease and that which would benefit from medical care is particularly prone to vary according to the views of the dermatologist examiner and the availability of local services. Use of traditional healers is common in developing countries, especially amongst older community members [55]. Some general points can be made regarding the prevalence surveys in these countries: (i) skin diseases are very common; (ii) infections and infestations predominate; (iii) skin diseases are most common among the younger age groups; and (iv) most are easily treated and (v) knowledge of diagnosis and management and resources for treatment are usually very scarce in the public sector. Making such generalizations is always hazardous, as even within 'developing' countries, urban pockets may occur with a disease spectrum very similar to developed countries. A comprehensive review of skin diseases in developing countries covering prevalence and patterns at the community level, effective therapies, economic assessments and current status of community control measures is to be found in an excellent World Bank publication [56]. Scabies, bacterial and fungal infections including tinea capitis and tinea imbricata, tropical ulcer and HIV-related skin diseases and pigmentary disorders are covered in some detail.

References

1 Williams HC. *The Derivation and Validation of Diagnostic Criteria for Atopic Dermatitis for Use in Epidemiological Studies* [doctoral dissertation]. London: University of London, 1994.

2 Williams HC, Burney PGJ, Strachan D, Hay RJ. The UK Working Party's diagnostic criteria for atopic dermatitis, 2: observer variation of clinical diagnosis and signs of atopic dermatitis. *Br J Dermatol* 1994; **131**: 397–405.

3 Williams HC. Defining cases. In: Williams HC, Strachan DP, eds. *The Challenge of Dermato-Epidemiology*. Boca Raton: CRC Press, 1997: 13–23.

4 Rademaker M, Garioch JJ, Simpson NB. Acne in schoolchildren: no longer a concern for dermatologist. *BMJ* 1989; **298**: 1217–20.

5 VanBeek M, Beach S, Braslow L *et al*. Highlights from the report of the working group on 'Core measures of the burden of skin diseases'. *J Invest Dermatol* 2007; **127**: 2701–6.

6 Ryan TJ. Disability in dermatology. *Br J Hosp Med* 1991; **46**: 33–6.

7 Ryan TJ. Healthy skin for all. *Int J Dermatol* 1994; **33**: 829–35.

8 Johnson MLT. *Skin Conditions and Related Need for Medical Care Among Persons 1–74 years, United States, 1971–4.* Washington, DC: US Department of Health, Education and Welfare/National Center for Health Statistics, 1978: 1–72. (Vital and Health Statistics, Series 11, No. 212; Department of Health, Education and Welfare Publication No. (PHS) 79–1660.)

9 Breeze E, Trevor G, Wilmot A. *The 1989 General Household Survey*. London: HMSO, 1991.

10 Martin J, Meltzer H, Elliot D. *The Prevalence of Disability Among Adults*. London: HMSO, 1988.

11 Bibgefors K, Lindberg M, Isacson D. Self-reported dermatological problems and use of prescribed topical drugs correlate with decreased quality of life: an epidemiological survey. *Br J Dermatol* 2002; **147**: 285–90.

12 Herd RM, Tidman MJ, Prescott RJ, Hunter JAA. The cost of atopic eczema. *Br J Dermatol* 1996; **135**: 20–3.

13 Mancini AJ, Kaulback K, Chamlin SL. The socioeconomic impact of atopic dermatitis in the United States: a systematic review. *Pediatr Dermatol* 2008; **25**: 1–6.

14 Javitz HS, Ward MM, Farber E *et al*. The direct cost of care for psoriasis and psoriatic arthritis in the United States. *J Am Acad Dermatol* 2002; **46**: 850–60.

15 Bickers DR, Lim HW, Margolis D *et al*; American Academy of Dermatology Association; Society for Investigative Dermatology. The burden of skin diseases: 2004. A joint project of the American Academy of Dermatology Association and the Society for Investigative Dermatology. *J Am Acad Dermatol* 2006; **55**: 490–500.

16 Office of Population Censuses and Surveys. *1992 Mortality Statistics.* London: HMSO, 1994.

17 Royal College of General Practitioners. *Morbidity Statistics from General Practice: Fourth National Study, 1991–92.* London: HMSO, 1995.

18 Gelfand JM, Weinstein R, Porter SB *et al*. Prevalence and treatment of psoriasis in the United Kingdom: a population-based study. *Arch Dermatol* 2005; **141**: 1537–41.

19 Gelfand JM, Neimann AL, Shin DB *et al*. Risk of myocardial infarction in patients with psoriasis. *JAMA* 2006; **296**: 1735–41.

20 Langan SM, Smeeth L, Hubbard R *et al*. Bullous pemphigoid and pemphigus vulgaris–incidence and mortality in the UK: population based cohort study. *BMJ* 2008; **337**: a180.

21 Meal A, Leonardi-Bee J, Smith C *et al*. Validation of THIN data for non-melanoma skin cancer. *Qual Prim Care* 2008; **16**: 49–52.

22 Richards C, Richards H, Pheby D. Skin cancer: how accurate are local data? *BMJ* 1995; **310**: 503.

23 MacKie RM, Aitchison TC, Sirel JM, Watt DC. Prognostic models for subgroups of melanoma patients from the Scottish Melanoma Group Database 1979–1986, and their subsequent validation. *Br J Cancer* 1995; **71**: 173–6.

24 Garbe C. Risk factors for the development of malignant melanoma and identification of risk groups in German-speaking regions. *Hautarzt* 1995; **46**: 306–14.

25 Fine JD, Johnson LB, Suchindram CM. The National Epidermolysis Bullosa Registry. *J Invest Dermatol* 1994; **102;** 54S–56S.

26 Mockenhaupt M, Schröder W, Höchstetter R *et al*. Drug attributability in HIV-infected patients with Stevens–Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN). *Br J Dermatol* 1995; **133**: 1005.

27 Malanos D, Stern RS. Psoralen plus ultraviolet A does not increase the risk of cataracts: a 25-year prospective study. *J Am Acad Dermatol* 2007; **57**: 231–7.

28 Ferguson JA, Goldacre MJ, Newton JN, Dawber RPR. An epidemiological profile of in-patient workload in dermatology. *Clin Exp Dermatol* 1992; **17**: 407–12.

29 Everyday Health Care. *A Consumer Study of Self-Medication in Great Britain*. London: British Market Research Bureau Ltd, 1987.

30 Wadsworth MEJ, Butterfield WJH, Blaney R. *Without Prescription*. London: Office of Health Economics, 1968.

31 Dunnell K, Cartwright A. *Medicine Takers, Prescribers and Hoarders*: *Report of the Institute of Social Studies in Medical Care.* London: Routledge and Kegan Paul, 1972.

32 Meding B. Normal standards for dermatological health screening at places of work. *Contact Dermatitis* 1992; **27**: 269–70.

33 Wolkenstein P, Grob JJ, Bastuji-Garin S *et al*.; Société Française de Dermotologie. French people and skin diseases: results of a survey using a representative sample. *Arch Dermatol* 2003; **139**: 1614–9.

34 Rea JN, Newhouse ML, Halil T. Skin disease in Lambeth: a community study of prevalence and use of medical care. *Br J Prev Soc Med* 1976; **30**: 107–14.

35 Williams HC. Dermatology. In: Stevens A, Raftery J, eds. *Health Care Needs Assessment*, Series II. Oxford: Radcliffe Medical Press, 1997: 261–348.

36 Gill D, Merlin K, Plunkett A *et al*. Population-based surveys on the frequency of common skin diseases in adults: is there a risk of response bias? *Clin Exp Dermatol* 2000; **25**: 62–6.

37 Kilkenny M, Merlin K, Young R, Marks R. The prevalence of common skin conditions in Australian school students, 1: common, plane and plantar viral warts. *Br J Dermatol* 1998; **138**: 840–5.

Table 6.6 Overall prevalence of skin disease in population-based studies conducted throughout the world.

Country	Author	Date of survey	Sample size	Study population	Definitions	Overall prevalence of skin disease	Commonest diagnoses	Comment
UK	Rea [34]	1975	2180	Stratified sample of adults	Examination by team of 7 dermatologists and 11 nurses	23%*	Eczema Acne Scaly dermatoses Prurigo Erythematous and other disorders	Only 21% had sought medical advice
USA	Johnson [8]	1971–4	28043	65 primary sampling units throughout the USA, population aged 1–74 years	Examination by 101 dermatologists	31%†	Diseases of sebaceous glands Fungal diseases Malignant and benign tumours Atopic dermatitis Other eczemas	Detailed survey of usage of health care
Sweden	Larsson [44]	1976	8298	School pupils 12–16 years old in AC county, North Sweden	Examination by dermatologists	Not stated	Acne Verrucae Atopic dermatitis Striae Pigmented lesions	Many children had more than one diagnosis
Faroe Islands	Lomholt [45]	1948	10984	Survey of 7 islands between Norway and Iceland	Examination by dermatologists	5%‡	Eczema Seborrhoeic dermatitis Neurodermatitis Acne Leg ulcer	Part of detailed psoriasis survey
Mexico	Estrada-Castañón [46]	1990	50000	41 representative communities in Guerrero state (all ages)	Examination by team of dermatologists and nurses	50% of all households included someone with a skin problem	Pityriasis alba Scabies Pyoderma Acne Melasma	60% of skin conditions could be classified into 10 diagnoses
Brazil	Bechelli [47]	1981	9995	School children of 6–16 years in four urban and three rural communities in north-west Brazil	Examination by 4 dermatologists	26%	Pediculosis capitis Pityriasis versicolor Pyoderma Pityriasis alba Dermatophytosis	Tropical region with 85% relative humidity
Brazil	Romiti [48]	1976	9414	School children aged 5–15 years in Santos municipality	Examination by dermatologist	37%	Infestations Superficial mycoses Viral infections Eczemas Acne	Different disease spectra seen at local dermatology service

(Continued p. 6.10)

Table 6.6 *Continued*

Country	Author	Date of survey	Sample size	Study population	Definitions	Overall prevalence of skin disease	Commonest diagnoses	Comment
Tanzania	Henderson [49]	1991	958	Complete survey of 2 administrative units at Mvumi village	Examination by dermatologist	49%§	Pyoderma Scabies Pediculosis capitis Dermatophytosis Leg sores	Dry, central plateau
Tanzania	Gibbs [50]	1994	1114	254 randomly selected households from 2 villages	Examination by dermatologist	27%	Prurigo Scabies Viral warts Pyoderma Papular urticaria	Infectious dermatoses increased in the young Overcrowding linked with increased skin disease prevalence
Mali	Mahé [51]	1994	1817	Random sample of 30 clusters of children aged less than 13	Examination by dermatologist	34%	Pyoderma Tinea capitis Pediculosis capitis Scabies Mollusca	Pyoderma and scabies significant health problem
Ethiopia	Figueroa [52]	1994	3979	House to house survey in 3 rural communities	Examination by dermatologist	14%	Ectoparasites Onchodermatitis Dermatophytosis Pyoderma	Only those who considered themselves to have a skin problem were examined
Pakistan	Porter [53]	1980	444	All children aged less than 5 years in 3 villages in Punjab	Examination by research assistants trained by a dermatologist	36%	Pyoderma (54% of skin disease) Atopic eczema Scabies Warts Other eczemas	Marked variation in prevalence of pyoderma between villages, possibly due to differences in malathion control of insect population
Ethiopia	Figueroa [52]	1996	112	Children in schools in Shebe	Examination by dermatologists	80%	Infestations and fungal	Over 98% of the skin diseases was considered treatable
Sumatra	Saw [54]	1999	917	All residing in 3 rural villages	Examination by trained doctors	28.2%	Fungal and bacterial infections Dermatitis	High response rate

* Thought to justify medical care.
† Significant skin pathology.
‡ Only those who presented themselves spontaneously with a skin disease.
§ Some of those examined might have more than one diagnosis.

38 Marks R, Kilkenny M, Plunket A, Marks R. The prevalence of common skin conditions in Australian school students, 2: atopic dermatitis. *Br J Dermatol* 1999; **140**: 468–73.
39 Kilkenny M, Merlin K, Plunkett A, Marks R. The prevalence of common skin conditions in Australian school students, 3: acne vulgaris. *Br J Dermatol* 1998; **139**: 840–5.
40 Merlin K, Kilkenny M, Plunkett A, Marks R. The prevalence of common skin conditions in Australian school students, 4: tinea pedis. *Br J Dermatol* 1999; **140**: 897–901.
41 Fung WK, Lo KK. Prevalence of skin disease among school children and adolescents in a student health service center in Hong Kong. *Pediatr Dermatol* 2000; **17**: 440–6.
42 Shakkoury WA, Abu-Wandy E. Prevalence of skin disorders among male schoolchildren in Amman, Jordan. *East Med Health J* 1999; **5**: 955–9.
43 Popescu CM, Williams HC, Forsea D. The prevalence of skin conditions in Romanian school children. *Br J Dermatol* 1999; **140**: 891–6.
44 Larsson P-Å, Leiden S. Prevalence of skin diseases among adolescents, 12–16 years of age. *Acta Derm Venereol (Stockh)* 1980; **60**: 415–23.
45 Lomholt G. Prevalence of skin diseases in a population. *Dan Med Bull* 1964; **11**: 1–7.
46 Estrada-Castañón R, Torres-Bibiano B, Alarcón-Hernández H *et al.* Epidemiología cutánea en dos sectores de atención médica en Guerrero, México. *Dermatol Rev Mex* 1992; **36**: 29–34.
47 Bechelli LM, Haddad N, Pimenta WP *et al.* Epidemiological survey of skin diseases in school children living in the Porus valley (Acre state, Amazonia, Brazil). *Dermatologica* 1981; **163**: 78–93.
48 Romiti N, Almeida JRP, Dinato SLM. Recenseamento dermiatrico no municipio de Santos. *Ann Brazil Dermatol* 1978; **53**: 385–406.
49 Henderson CA. Skin disease in rural Tanzania. *Int J Dermatol* 1996; **35**: 640–2.
50 Gibbs S. Skin disease and socio-economic conditions in rural Africa: Tanzania. *Int J Dermatol* 1996; **35**: 633–9.
51 Mahé A, Prual A, Konate M, Bobin P. Skin disease of children in Mali; a public health problem. *Trans R Soc Trop Med Hyg* 1995; **89**: 467–70.
52 Figueroa JI, Fuller LC, Abraha A, Hay RJ. The prevalence of skin disease among school children in rural Ethiopia—a preliminary assessment of dermatologic needs. *Pediatr Dermatol* 1996; **13**: 378–81.
53 Porter MJ, Mack RW, Chaudhary MA. Paediatric skin disease in Pakistan: a study of 3 Punjab villages. *Int J Dermatol* 1984; **23**: 613–6.
54 Saw SM, Koh D, Adjani MR *et al*. A population-based prevalence survey of skin diseases in adolescents and adults in rural Sumatra, Indonesia, 1999. *Trans R Soc Trop Med Hyg* 2001; **95**: 384–8.
55 Satimia FT, McBride SR, Leppard B. Prevalence of skin disease in rural Tanzania and factors influencing the choice of health care, modern or traditional. *Arch Dermatol* 1998; **134**: 1363–6.
56 Hay R, Bendeck SE, Chen S *et al*. Skin diseases. In: Jamison DT, Breman JG, Measham AR *et al*. *Disease Control Priorities in Developing Countries*, 2nd edn. New York: Oxford University Press, 2006: 707–22.

What determines the frequency of skin disease in populations?

Risk factors, association and causation

In the first instance, epidemiological studies seek to establish *risk factors* for diseases, that is factors which are associated with an increased frequency of disease. When *associations* between skin diseases and risk factors are discovered (e.g. by demonstrating an increased risk of palmoplantar psoriasis in smokers [1]), it should be understood that such *associations* do not necessarily imply *causation*. The association between smoking and psoriasis may simply be a *chance* finding (around one in 20 studies with a *P* value of less than 0.05 in favour of rejecting the null hypothesis of no association will be wrong due to chance alone), or it could be due to *confounding* (i.e. a third factor such as alcohol, which is independently associated with both smoking and psoriasis [2]). The association could be due to a *bias*—for example, people with psoriasis in hospital may be more likely to recall antecedent events or seek reasons for explaining their illness in comparison with healthy controls [3]. Further analyses or new studies are usually needed to establish whether risk factors are *causative*—for example, by evaluating the strength of the association, biological gradient, relationship in time, the consistency between different studies, biological plausibility, coherence of evidence with external sources, experimental evidence, and specificity of findings as suggested by the Bradford-Hill criteria of causality [4].

The causes of some skin diseases are already established—for example, the herpes simplex virus causes cold sores—but for most dermatological conditions, the causes are unknown. Nevertheless, epidemiological research has already established many *risk factors* for skin diseases which maybe help to serve as pointers to specific causes. Direct manipulation of these risk factors may help in preventing or reducing disease even before the specific cause is found. For example, in the London cholera epidemics of the 1850s, John Snow [5] postulated that the disease was spread by some 'morbid matter' in the water supply and proceeded to intervene by removing the pump handle in Broad Street. This resulted in a dramatic fall in incident cholera cases. All of this occurred some 20 years before germ theory had become established in Europe. Snow's work illustrates one of the beauties of epidemiological research, which is that knowledge of pathophysiology is not a prerequisite for determining aetiology.

Even when a causative agent is discovered, for example *Vibrio cholerae*, exposure to this agent does not necessarily imply disease. Of those exposed to cholera during an outbreak, some will die from the disease, some will be very ill, some will be slightly unwell, some will be apparently healthy (but still carry the organism) and some will not be affected at all. The absence of disease in some individuals following exposure is probably due to a whole range of factors such as chance, infecting dose, genetic heterogeneity, and other constitutional and environmental factors which interact together to produce the final clinical picture. This phenomenon of apparent health in the presence of an established harmful exposure has been exploited by individuals in order to avoid modifying their behaviour. One often hears statements such as 'my grandfather smoked 40 cigarettes a day all his life and he did not get lung cancer'. In order to explain such phenomena, we return to the epidemiological concept of *groups* of people or *populations* and *probability* of disease [6]. On average, groups of people who smoke cigarettes are 10 times more likely to develop lung cancer when compared with those who do not smoke.

It is also important to separate risk factors associated with disease *incidence*, that is number of new cases in a given population occurring over a defined period, from those which determine disease *chronicity*, that is the determinants of how long a particular disease will last once an individual has it, as the risk factors for each of these aspects may be different. Many dermatoepidemiology surveys have measured the *prevalence* of skin disease when examining risk factors [7], but because prevalence is a function of incidence times chronicity, it is often difficult to say whether these risk factors are important in people developing a disease for the first time, or whether they maintain the disease once established.

Risk factors for skin disease may operate at many different levels. Some may predispose to disease (e.g. a mother with atopic eczema genetically predisposes her child to atopic eczema), some may precipitate disease (e.g. exposure to high levels of house-dust mite may precipitate atopic eczema for the first time), and some may be important in perpetuating that disease (e.g. failure to use prescribed treatments may worsen the course of atopic eczema).

Some of the commonest risk factors for skin disease are discussed below.

Genetics

In addition to a few rare diseases such as epidermolysis bullosa, where specific chromosomal mutations have been closely correlated with different disease phenotypes, several genes may be important in many of the major inflammatory skin diseases. Thus in atopic dermatitis, genes such as filaggrin mutations which play a key role in skin barrier function, as well as several other genes that code for inflammatory responses, may be important in explaining the variation in disease phenotype [8]. Genes such as those that predispose for melanoma may only express their beneficial or deleterious effects when individuals who carry them are additionally exposed to key environmental risk factors such as ultraviolet light [9]. Some genes may be responsible for disease predisposition and some may be responsible for disease severity and chronicity, as exemplified by molecular subsets in the gene expression signatures in the skin in scleroderma [10].

The early environment

There is evidence to suggest that the experience of the fetus *in utero* (e.g. in terms of nutrition) is critical in 'programming' adult diseases such as hypertension and diabetes [11], and *in utero* programming may well operate for many skin diseases such as atopic eczema [12].

The later environment

Age and sex are often included in the descriptive epidemiology of many skin diseases and may point to further risk factors. The marked female preponderance of lichen sclerosus, for example, suggests that hormonal factors may be important in this disease.

Ethnic group may account for some variations in disease rates. Thus, it has been shown that atopic eczema is twice as common in black Caribbean children in comparison with similar white children [13] and, conversely, that mortality from most cancers is less common in black ethnic groups in the UK [14]. Ethnic group, which refers to a way of life encompassing a whole range of dietary and cultural factors, must be distinguished from racial factors [15], which are often more difficult to define because of the considerable mixing of modern populations. Care also has to be taken in lumping many distinct ethnic groups together—for example, combining the diverse cultures of black Africans and black Caribbeans into 'blacks' may be totally inappropriate, both in terms of respecting the identity of the separate cultures and because such lumping together may obscure important epidemiological associations [16]. The term 'race' should not be used in epidemiological studies, as it has no scientific meaning [17]. Migration itself may be an important factor in determining skin diseases; for example, individuals who migrated from China (where atopic eczema is not very common) developed much higher rates of disease (similar to the rates in the local population) after migration to Hawaii [18]. Migrants may not be totally representative of their indigenous peoples, but they may nevertheless show the effect of the environment in determining the frequency of skin disease.

Secular factors may reflect changes in the natural history of skin disease or of transient environmental exposures. Thus, the epidemic of melanoma skin cancer has been attributed by some to increased exposure to sunlight over the last 40 years [19]. There is reasonable evidence to suggest that the prevalence of atopic eczema has increased two- to threefold over the last 30 years, but the reasons for this change are less clear [20].

Socioeconomic factors may also be crucial in accounting for the distribution of skin disease. In many poorer countries where overcrowding and poor sanitation may occur, infectious or ectoparasitic skin diseases such as secondarily infected scabies or pediculosis are commoner [21,22]. In wealthier countries where such infectious dermatoses are less common, new 'diseases' such as concern regarding the cosmetic appearance of sun-damaged skin or thread veins may preoccupy the population in their quest for a perfect skin. Some skin diseases, such as atopic eczema, also demonstrate a genuine positive social class trend, that is higher prevalences in more wealthy groups [7]. Some of this increase in reported eczema may have been due to differences in reporting between socioeconomic groups, but other genuine environmental factors such as hygiene, carpets, central heating, family size, or differences in treatment also probably play a part.

Geography and climate are important considerations in describing the frequency of skin disease. Thus, consideration of the marked latitude gradient of melanoma in white-skinned peoples has supported the concept that exposure to sunlight is an important risk factor for this disease [23]. Paul [24] has drawn attention to the concepts of *macroclimate*, which in the ordinary geographical sense refers to temperature, rainfall and humidity, and *microclimate*, which refers to the immediate domestic and occupational environment a given individual finds himself or herself in. These are discussed further by Marshall [25] and Canizares [26]. The combination of temperature, rainfall and humidity may be crucial to sustain certain infectious disease vectors such as the *Simulium* fly in onchocerciasis, and may for example account for seasonal fluctuations in pyoderma secondary to scabies during the wet season in Lilongwe in Malawi [27].

Occupational factors are occasionally a very important factor for skin disease. Thus, exposure to irritants and contact sensitizers in light and heavy industry accounts for a very large burden of hand dermatitis and lost revenue for both individuals and the state. Certain occupations, for example mining, where workers are constantly exposed to damp conditions, may predispose to fungal infections. Some diseases may occasionally occur in outbreaks from work-related substances, for example chloracne due to dioxins, vinyl chloride disease, and hydroquinone-induced leukomelanoderma. The reader is referred to standard texts of occupational dermatoses and to Chapter 27 for further reading [28,29].

Infective agents may directly cause or be suspected to cause many skin diseases. Thus, for a long time, it was suspected that fifth disease was caused by an infectious agent, but it was not until 1983 that human parvovirus B19 was identified as the causative

organism [30]. Similarly, there is reasonable circumstantial evidence to suggest that diseases such as pityriasis rosea are caused by infectious agents, even though no specific agents have yet been consistently isolated [31].

Dietary factors may be crucial in some skin diseases. As the examples of Lind and Goldberger in the opening section showed, vitamin deficiency states may directly cause skin diseases. Other deficiency diseases with skin manifestations, such as acrodermatitis enteropathica, are completely reversible with administration of the appropriate agent, in this case zinc. Some diseases, such as phenylketonuria and dermatitis herpetiformis, may be transformed by restricting substances that affected individuals cannot handle—for example, phenylalanine and gluten, respectively. Some skin diseases, such as atopic eczema and acute urticaria, may be modified by avoidance of dietary allergens in a proportion of cases. Leisure activities such as gardening or habits such as smoking cigarettes and drinking alcohol may be important risk factors for many skin diseases including contact dermatitis, psoriasis and porphyria cutanea tarda. Medicines, although intended to alleviate human disease, are a very common cause of cutaneous eruptions, some of which (e.g. toxic epidermal necrolysis) can be fatal.

References

1 O'Doherty CJ, MacIntyre C. Palmoplantar pustulosis and smoking. *BMJ* 1985; **291**: 861–4.
2 Williams HC. Smoking and psoriasis. *BMJ* 1994; **308**: 428–9.
3 Naldi L, Parazzini F, Peserico A *et al.* Family history, smoking habits, alcohol consumption and risk of psoriasis. *Br J Dermatol* 1992; **127**: 212–7.
4 Bradford-Hill A. The environment and disease: association or causation? *J R Soc Med* 1965; **58**: 295–300.
5 Snow J. *On the Mode of Communication of Cholera*, 2nd edn. London: Churchill Livingstone, 1854.
6 Rose G. Sick individuals and sick populations. In: Buck C, Llopis A, Nájera E, Terris M, eds. *The Challenge of Epidemiology*. Washington: Pan American Health Organization, 1988: 829–37.
7 Williams HC, Strachan DP, Hay RJ. Childhood eczema: disease of the advantaged? *BMJ* 1994; **308**: 1132–5.
8 Bieber T. Atopic dermatitis. *N Engl J Med* 2008; **358**: 1483–94.
9 Stratigos AJ, Dimisianos G, Nikolaou V *et al*. Melanocortin receptor-1 gene polymorphisms and the risk of cutaneous melanoma in a low-risk southern European population. *J Invest Dermatol* 2006; **126**: 1842–9.
10 Milano A, Pendergrass SA, Sargent JL *et al*. Molecular subsets in the gene expression signatures of scleroderma skin. *PLoS ONE* 2008; **3**: e2696.
11 Barker DJP. *Fetal and Infant Origins of Adult Disease*. London: British Medical Journal Publishing Group, 1992.
12 Godfrey KM, Barker DJP, Osmond C. Disproportionate fetal growth and raised IgE concentration in adult life. *Clin Exp Allergy* 1994; **24**: 641–8.
13 Williams HC, Pembroke AC, Forsdyke H *et al.* London-born black Caribbean children are at increased risk of atopic dermatitis. *J Am Acad Dermatol* 1995; **32**: 212–7.
14 Marmot MG, Adelstein AM, Bulusu L. *Immigrant Mortality in England and Wales 1978.* London: HMSO, 1984.
15 Silver SE. Melanocytic nevus density in Asian, Indo-Pakistani, and white children. *J Am Acad Dermatol* 1992; **27**: 277–88.
16 Bhopal R. Needs of black and ethnic minorities. *BMJ* 1992; **305**: 1156–7.
17 Williams HC. Have you ever seen an Asian/Pacific Islander? *Arch Dermatol* 2002; **138**: 673–4.
18 Worth RM. Atopic dermatitis among Chinese infants in Honolulu and San Francisco. *Hawaiian Med J* 1962; **22**: 31–6.
19 Polednak AP. Trends in cancer incidence in Connecticut, 1935–91. *Cancer* 1994; **74**: 2863–72.
20 Williams HC. Is the prevalence of atopic dermatitis increasing? *Clin Exp Dermatol* 1992; **17**: 385–91.
21 Gbakima AA, Lebbie AR. The head louse in Sierra Leone: an epidemiological study among school children, in the Njala area. *West Afr J Med* 1992; **11**: 165–71.
22 Harris MD, Nako T, Hopkins DM *et al.* Skin infections in Tanna, Vanuatu in 1989. *Papua New Guinea Med J* 1992; **35**: 906–7.
23 Weinstock MA. Melanoma and nevi. In: Williams HC, Strachan DP, eds. *The Challenge of Dermato-Epidemiology*. Boca Raton, FL: CRC Press, 1997: 191–207.
24 Paul JR. *Clinical Epidemiology*. Chicago: University of Chicago Press, 1958.
25 Marshall J. Epidemiology of skin diseases. In: Simons RDG, Marshall J, eds. *Essays on Tropical Dermatology.* Amsterdam: Excerpta Medica Foundation, 1969: 17–23.
26 Canizares O. Epidemiology and ecology of skin diseases in the tropics and subtropics. In: Canizares O, ed. *A Manual of Dermatology for Developing Countries*, 2nd edn. Oxford: Oxford University Press, 1993: 22–35.
27 Kristensen JK. Scabies and pyoderma in Lilongwe, Malawi: prevalence and seasonal fluctuation. *Int J Dermatol* 1991; **30**: 699–702.
28 Adams RM. *Occupational Skin Disease*, 2nd edn. London: Saunders, 1990.
29 Rycroft RJG, Menné T, Frosch PJ. *Textbook of Contact Dermatitis*, 2nd edn. Berlin: Springer, 1995.
30 Anderson LJ. Human parvovirus B19. *Pediatr Ann* 1990; **19**: 509–16.
31 Chuang T-Y, Perry HO, Ilstrup DM, Kurkland LT. Recent upper respiratory tract infection and pityriasis rosea: a case–control study of 249 matched pairs. *Br J Dermatol* 1983; **108**: 587–91.

Describing the natural history and associations of specific skin diseases

Questions commonly asked by patients with a skin disease are 'How long will it last?' and 'Will it come back again?' Special studies are required to answer these questions, which ideally involve following, over many years, individuals with typical and well-defined disease in terms of morphology and severity [1]. Such prospective studies are rare in dermatology. Another approach is to identify cases with a specific skin disease from old hospital records and then to trace them in order to find out what has happened to them since they were seen [2]. Studies on the natural history of disease are often difficult to interpret because of incomplete follow-up, the intermittent nature of many skin diseases (leading to the need to distinguish between 'real' and 'apparent' clearance rates) [3] and because the treatment of many diseases has improved with time. Guidelines regarding the attributes of what makes a good follow-up study are summarized elsewhere [4].

Disease associations of specific skin diseases may also give insight into possible causative factors. Thus, the high incidence of laryngeal carcinoma in psoriasis patients might be evidence for the possible role of cigarette smoking in psoriasis [5]. Many publications have emerged over the last 7 years linking psoriasis with the metabolic syndrome, suggesting that it is a systemic disease and that patients with psoriasis should be screened for cardiovascular risk factors [6]. Establishing disease co-occurrence, for example atopic eczema and psoriasis, may also shed light on shared or opposed immunopathological mechanisms [7,8]. Great care has to be exercised in interpreting disease associations generated from hospital sources because, in the absence of an appropriate denominator, many types of bias may occur [9,10].

References

1 Sackett DL, Haynes RB, Guyatt GH, Tugwell P. *Clinical Epidemiology.* Toronto: Little, Brown, 1985: 173–85.

2 Rystedt I. Long term follow-up in atopic dermatitis. *Acta Derm Venereol (Stockh)* 1985; **114** (Suppl.): 117–21.
3 Williams HC, Strachan DP, Hay RJ. The natural history of childhood eczema. *Br J Dermatol* 1993; **129** (Suppl. 42): 26.
4 Williams HC, Wuthrich B. The natural history of atopic dermatitis. In: Williams HC, ed. *Atopic Dermatitis: the Epidemiology, Causes and Prevention of Eczema*. Cambridge: Cambridge University Press, 2000: 41–59.
5 Jorgen HO, Moller H, Frentz G. Malignant tumors in patients with psoriasis. *J Am Acad Dermatol* 1992; **27**: 716–22.
6 Azfar RS, Gelfand JM. Psoriasis and metabolic disease: epidemiology and pathophysiology. *Curr Opin Rheumatol* 2008; **20**: 416–22.
7 Henseler T, Ye B, Christophers E. Coincidence of psoriasis and other diseases. *Arch Dermatol* 1992; **284**: 19.
8 Beer WE, Smith AE, Kassab JY *et al*. Concomitance of psoriasis and atopic dermatitis. *Dermatology* 1992; **184**: 265–70.
9 Williams HC, Strachan DP. Psoriasis and eczema are not mutually exclusive diseases. *Dermatology* 1994; **189**: 238–40.
10 Gerber LM, Wolf AM, Braham RL, Alderman MH. Effects of sample selection on the coincidence of hypertension and diabetes. *JAMA* 1982; **247**: 43–6.

Table 6.7 A guide to the number of persons per 100 000 per year using dermatology services. From Williams [4] with permission.

Number with a skin complaint	25 000 (at least 25% of total population) [5]
Number who will self-treat	7500 (30% of those with skin complaint) [6]
Number who will seek advice from GP	14 550* (15% of total population or 19% of all GP consultations) [7]
Number referred to dermatologist	1162 (8% of those attending their GP for skin problems, or 1.2% of the total population) [8]
Number admitted to hospital	24–31 (2–3% of all new dermatology referrals) [9]
Number of deaths due to skin disease	5† (0.4% of all new dermatology referrals) [10]

* Excludes skin neoplasms, viral warts, herpes simplex and scabies.
† Includes people dying from cellulitis, chronic ulcer of the skin and severe drug reactions who might not have been admitted under a dermatologist's care.

Health-services research in dermatology

Broadly defined, dermatological health-services research is concerned with studying how dermatological health care is delivered with the ultimate aim of benefiting patients. Dermatological health services research thus covers a wide variety of service aspects, such as determinants of referrals to hospital departments, evaluation of cost-effectiveness of alternative treatment strategies, quantifying the dermatological needs of the community, evaluating the role of dermatological nurses and exploring economic aspects of screening and other prevention strategies. These diverse studies require a range of quantitative and qualitative research methods, such as focus groups, comparative studies, randomized controlled trials and health economic modelling. Research establishes which treatments or services should be used, whereas audit seeks to establish whether health-care providers perform these services to a required standard [1]. As in any other branch of epidemiology, health-services research requires meticulous attention to be given to aspects of study design. A useful introduction to health-services research in dermatology is given elsewhere [2].

Needs assessments in dermatology

When evaluating dermatological health services, certain steps need to be followed [3].

1 Establish the size and nature of the dermatological need based on epidemiological data
2 Summarize currently available supply of services for that problem
3 Appraise the evidence for effectiveness of those services
4 Propose models of care which best fit the epidemiological data and evidence of effectiveness of care within current resources
5 Propose outcome measures and targets which can be monitored after implementation.

Such an assessment has been attempted for UK dermatological health services by the author [4], and a comprehensive update of the assessment will be available on the Centre of Evidence-Based Dermatology website in 2009 (see Resources at the end of this chapter).

Services available for people with skin diseases

People with skin problems obtain help from various sources, including self-help, advice from pharmacists, advice and treatment from the primary-care team and specialist services. Little research has been conducted to clarify the relative health gain and appropriateness of the various health-care settings for different subgroups of skin disease. The estimated number of people using current dermatology health services in the UK at various entry points, for a population of 100 000 over a 1-year period, is summarized in Table 6.7 [5–10].

Self-help

Although self-help/medication is not traditionally regarded as a health service, the range and availability of over-the-counter skin products is an important element in the equation of balancing need, supply and demand. Around 30% of those with a skin complaint decide to self-medicate, and this proportion is similar for trivial and for moderate to severe disease [6]. Many effective skin treatments are available over the counter in the UK, such as 1% hydrocortisone for mild eczema, topical aciclovir cream for cold sores, topical benzoyl peroxide for acne, and numerous antifungal preparations and wart removers. Pharmacists occupy a key role in advising the public on the use of these products, but whether this advice is beneficial or whether it simply delays appropriate medical consultation has not been studied adequately in the UK [11]. Self-help groups are often a useful source of advice to those with chronic skin diseases [12].

Primary care

The majority of those with a skin complaint who seek medical help are treated by their general practitioner (GP). In the UK, around 6–8% of all GP diagnoses involve the skin [13,14]. Morbidity statistics from General Practice in the UK from 1995 [7] suggest that 1455 people per 10 000 person-years at risk (approximately 15% per year) consult their GP because of a skin condition (excluding benign and malignant skin neoplasms and some skin infections). In the USA, it has been estimated that around 36.5% of patients attending their family practitioner over a 2-year period had a skin complaint [15].

Table 6.8 The nine categories of skin disease which account for over 70% of dermatological diagnoses in primary and secondary care. From Williams [4].

Skin cancer (including melanoma)
Acne
Atopic eczema
Psoriasis
Viral warts
Other infective skin conditions
Benign tumours and vascular lesions
Leg ulceration
Contact dermatitis and other eczemas

The range of skin disorders seen in general practice is similar to that in the general population, with relatively few subcategories accounting for the majority of consultations [13,16]. As one would anticipate, proportionally more incident diseases such as skin infections (e.g. impetigo, herpes simplex and viral exanthems) are seen in general practice than in secondary care [7,16].

Secondary care

Although dermatology covers around 2000 disease-reaction patterns, over 70% of specialist activity is concerned with fewer than 10 main disease categories, as shown in Table 6.8 [4]. Age-specific attendance rates are more common in female patients and also increase with increasing age. Around 12% of referrals were considered inappropriate by dermatologists in one UK study [17]. Another UK study showed that even a relatively junior physician with 3 months' dermatology training considered that 26% of 490 consecutive referrals were probably unnecessary [18], and that 75% of these unnecessary referrals belonged to just seven disease categories (warts, eczema, naevi, basal cell carcinoma, acne, psoriasis and seborrhoeic warts). There is considerable variation in referral rates to specialist care within the UK and there is some evidence to suggest that much of the regional variation in referral rates may be governed by established patterns of care and the number of available consultants, rather than by any objective dermatological need [4]. Roland and Morris [19] showed no relationship between referral rates for dermatology services and medical need as suggested by standardized mortality ratios or mean number of prescriptions issued by GPs (standardized regression coefficient of 0.1). It should be emphasized, though, that mortality ratios are not a suitable surrogate measure for dermatological need. A strong relationship between dermatology referral rates and the number of dermatology consultants per 100 000 population was present, however, in their study (standardized regression coefficient of 0.82, $P < 0.001$).

Traditional boundaries between what might be considered as primary and secondary care have become blurred over the last 5 years, and the relationship between the two in terms of cost-effectiveness is far from straightforward. Thus, specialists from secondary care might conduct work in a primary-care setting and general practitioners might develop an interest in skin diseases and work partly in a secondary-care setting. Specialist dermatology nurses might work across both settings. Thus it is more appropriate to separate skill mix and practice setting when considering the pyramid of dermatological care from generalist to specialist services in the UK and elsewhere. A recent report found that transfer of some activities and professional behaviour change strategies targeted at primary care are generally effective in reducing demand on secondary care, whereas relocation of specialists into a community setting and better liaison strategies do not, although they may improve quality of care [20]. Another randomized, controlled study has shown that, despite widespread adoption of minor surgery for skin problems in primary care, minor surgery is more cost-effective in the secondary care sector [21]. Another report found that the general practitioner with a special interest service for dermatology is more costly than hospital outpatient care, but this additional cost needs to be weighed against improved access and broadly similar health outcomes [22].

The relationship between need, supply and demand for dermatological care

Unlike commerce, which aims to balance supply with demand, caring for sick human beings requires consideration of a third factor—that of medical need. Medical need may be defined as the ability to benefit from medical care, demand as that which people ask for, and supply as what the service does or could provide [3,4]. Not all dermatological need is demanded (e.g. a person may be unaware that he or she has an early melanoma), not all that is demanded is needed (e.g. cosmetic removal of all moles), although all that is supplied is usually needed or demanded. The division between what constitutes reasonable need (e.g. somebody worried that a mole may be cancerous) and demand (e.g. somebody requesting removal of an 'ugly' mole) is especially blurred in dermatology. Defining 'need' in dermatology is therefore quite difficult, and is a process which requires participation of society so that appropriate policies can be set in the light of finite resources.

Two population surveys conducted in the 1970s have produced useful data on the relationship between the need, supply and demand for dermatological care. In a study of 2180 adults in Lambeth who were examined for skin disease [6], it was shown that for those with moderate/severe skin disease, only 24% had made use of any medical service in the previous 6 months. A further 30% had used self-medication. Medical usage was still considerable for those with trivial skin disease, with 10% using medical services and 33% self-medicating.

In the US HANES-1 study [23], there was a considerable mismatch between what the dermatologists considered to represent medical need and what the population were concerned about. Only one-third (31%) of persons with significant skin pathology diagnosed by the dermatologists expressed concern about these specific skin conditions, whereas nearly 18% of those who complained about their skin conditions were not considered to have serious conditions by the dermatologists.

Thus, both of these population studies suggest that, at any one time, around one-quarter to one-third of the population have a skin problem which could benefit from medical care, yet around 80% do not seek medical help. As Savin points out [24], with increased public and professional awareness of effective treatment, this submerged sector of the population is likely to surface and place heavy demands on the current system.

The relationship between need, supply and demand for dermatology services in developing countries may be very different from those in developed countries. Many surveys have shown a high prevalence of need, mainly due to infectious dermatoses [25,26]. There is marked maldistribution of care for people with skin diseases throughout the world, with meagre to absent dermatological services in many countries [27]. Leprosy, onchocerciasis and leishmaniasis are probably the commonest skin diseases worldwide, but the epidemiological research afforded to these diseases is usually scanty. Groups such as the International Foundation for Dermatology work to remedy such inequalities, with the ultimate aim of a healthy skin for all [24]. Getting the right people to the right services is a major challenge. In the state of Guerrero in Mexico, for instance, skin complaints represent the second commonest reason for referral to rural clinics, resulting in a detrimental effect on other important activities such as immunization programmes and antenatal care [28]. In addition to such opportunity costs, this study also showed how much family income is wasted on ineffective treatments for skin infections and scabies. An excellent report on skin diseases in developing countries has been commissioned by the World Bank [29]. This report points out that, although few die from skin diseases, the population needs for effective services must be met because: (i) skin diseases are extremely common, with the result that patients present in such large numbers in community settings that ignoring them is not a viable option; (ii) disfigurement from diseases such as filariasis leading to lymphoedema, or hypopigmentation from leprosy, often lead to significant morbidity and social isolation; (iii) the costs of treating even minor skin diseases can be high; and (iv) screening for skin diseases such as leprosy is an important strategy, yet a basic knowledge of diagnosis and management of such diseases is often missing at a primary-care level.

Systematic reviews and the Cochrane Collaboration

Reviewing the effectiveness of services in the light of an epidemiologically based needs assessment helps health-service planners to distinguish those interventions which confer maximum health gain (e.g. establishment of community leg-ulcer clinics) from those where services are ill-deployed (e.g. specialists involved in the routine treatment of viral warts) [4]. Using published evidence to inform everyday clinical decisions on disease treatment is something that most physicians aspire to, yet with over 240 specialist journals in dermatology alone [30], keeping abreast of important therapeutic developments in dermatology is difficult. Even enthusiastic teachers place their median reading time at about 2 h per week [31]. Most physicians therefore rely on reviews of the primary research in order to help them make therapeutic decisions in their daily practice. Unfortunately, the quality of traditional expert reviews is often suspect, because reviewers have not conducted their review in a systematic fashion with regard to the scientific principles of considering bias and sampling error [32]. Expert therapy reviews, published in the top medical journals, have been shown to miss important studies and to be far more biased in their conclusions when compared with systematic reviews [33]. Lessons from general medicine have suggested that deficiencies in reviews have meant that advice on some highly effective forms of care have been delayed for many years and other forms of care have continued to be used long after research has shown them to be ineffective or even harmful [34].

Over 30 years ago, the late Professor Archie Cochrane drew attention to our great collective ignorance on the effects of health care and explained how collated evidence from randomized, controlled trials could help the use of resources more rationally, and proceeded to criticize the medical profession for not producing a critical summary, by speciality, of all relevant trials, which is periodically updated [35]. The worldwide Cochrane Collaboration—groups of individuals dedicated to preparing and maintaining systematic reviews of health care—has evolved in response to this challenge [36]. Unlike traditional reviews, systematic reviews employ a structured methodology, which includes: (i) defining the primary objective of the review; (ii) predefining the clinically important outcome measures; (iii) the systematic retrieval of all (published and unpublished) relevant material; (iv) abstracting the quantitative information; (v) summarizing and quality appraisal of the retrieved evidence; and (vi) interpreting the results. In addition to the benefits of reducing bias by inclusion of unpublished data and by giving more weight to high-quality studies according to predefined criteria, the increased statistical power afforded by the quantitative pooling of many small studies (meta-analysis) can often provide a clear answer to many small studies that appear at first to be 'conflicting' in their recommendations [37].

Summarizing the effectiveness of various dermatological interventions (be these aimed at preventing new disease, treating established disease or preventing disability) is a time-consuming process. Like any scientific methods, techniques such as meta-analysis have their limitations [38,39]. Many systematic reviews of dermatological intervention have already been conducted, although the poor quality of dermatology trials in terms of unclear entry criteria [40], diversity of outcome measures [41] and inadequate details [42] have served as an obstacle for some reviews. The quality of reporting clinical trials in dermatological journals is generally poor [43,44]. The adoption of the CONSORT guidelines for better clinical trial reporting by several of the top dermatology journals should help to improve the situation [45–47]. An international Cochrane Skin Group formed in 1997 in response to the challenge of providing an up-to-date summary of dermatological health-care interventions [48,49]. Reviews produced by the Cochrane Skin Group have been shown to be more methodologically rigorous than non-Cochrane reviews [50]. The editorial base of the Cochrane Skin Group coordinates a worldwide, voluntary effort in preparing, maintaining and disseminating systematic reviews of health-care interventions in relation to skin diseases and maintains its own specialized register of dermatological clinical trials. Further information about the Cochrane Skin Group is available on the website indicated at the end of this chapter. Epidemiological principles that underpin the theory and practice of evidence-based medicine are discussed more fully in Chapter 7.

References

1 Smith R. Audit and research. *BMJ* 1992; **305**: 905–9.

2 Chren MM. Dermatologic health services research. *Dermatol Clin* 1995; **13**: 689–95.

3 Stevens A, Raftery J. Introduction. In: Stevens A, Raftery J, eds. *Health Care Needs Assessment, Series I.* Oxford: Radcliffe Medical Press, 1994: 11–30.
4 Williams HC. Dermatology. In: Stevens A, Raftery J, eds. *Health Care Needs Assessment, Series II.* Oxford: Radcliffe Medical Press, 1997: 261–348.
5 British Market Research Bureau Ltd. *Everyday Health Care. A Consumer Study of Self-Medication in Great Britain*. London: Proprietary Association of Great Britain, 1987.
6 Rea JN, Newhouse ML, Halil T. Skin disease in Lambeth: a community study of prevalence and use of medical care. *Br J Prev Soc Med* 1976; **30**: 107–14.
7 Royal College of General Practitioners. *Morbidity Statistics from General Practice: Fourth National Study, 1991–2.* London: HMSO, 1995.
8 Carmichael AJ. Achieving an accessible dermatology service. *Dermatol Pract* 1995; **3**: 13–6.
9 Ferguson JA, Goldacre MJ, Newton JN, Dawber RPR. An epidemiological profile of inpatient workload in dermatology. *Clin Exp Dermatol* 1992; **17**: 407–12.
10 Office of Population Censuses and Surveys. *1992 Mortality Statistics*. London: HMSO, 1994.
11 Williams HC. Extended role of pharmacists in dermatology [editorial]. *J Clin Pharm Ther* 1996; **20**: 310–2.
12 Funnell C. Importance of patient self-help groups—a British perspective. *Retinoids Today Tomorrow* 1995; **41**: 6–8.
13 Horn R. The pattern of skin disease in general practice. *Dermatol Pract* 1986; **4**: 14–9.
14 Steele K. Primary dermatological care in general practice. *J R Coll Gen Pract* 1984; **34**: 22–4.
15 Lowell BA, Froelich CW, Federman DG, Kirsner RS. Dermatology in primary care: prevalence and patient disposition. *J Am Acad Dermatol* 2001; **45**: 250–5.
16 Royal College of General Practitioners. *Morbidity Statistics from General Practice: Third National Study, 1981–82*. London: HMSO, 1986.
17 Stevenson C, Horne G, Charles-Holmes S, Shrank A. Dermatology outpatients in the West Midlands: their nature and management. *Health Trends* 1991; **23**: 162–5.
18 Sladden MJ, Graham-Brown RAC. How many referrals to dermatology outpatients are really necessary? *J R Soc Med* 1989; **82**: 437–8.
19 Roland M, Morris R. Are referrals by general practitioners influenced by the availability of consultants? *BMJ* 1988; **297**: 599–600.
20 Roland M, McDonald R, Sibbald B. *Can Primary Care Reform Reduce Demand on Hospital Outpatient Departments?* Report for the NHS Service Delivery and Organisation R&D Programme. London, 2007. (Summary available at http://www.sdo.nihr.ac.uk/files/adhoc/82-research-summary.pdf)
21 George S, Pockney P, Primrose J *et al.* A prospective randomised comparison of minor surgery in primary and secondary care. The MiSTIC trial. *Health Technol Assess* 2008; **12** (23): iii–iv, ix–38.
22 Coast J, Noble S, Noble A *et al*. Economic evaluation of a general practitioner with special interest led dermatology service in primary care. *BMJ* 2005; **331**: 1444–8.
23 Johnson MLT. *Skin Conditions and Related Need for Medical Care Among Persons 1–74 years, United States, 1971–4.* Washington, DC: US Department of Health, Education and Welfare/National Center for Health Statistics: 1978: 1–72. (Vital and Health Statistics, Series 11, No. 212; Department of Health, Education and Welfare Publication No. (PHS) 79–1660.)
24 Savin J. The hidden face of dermatology. *Clin Exp Dermatol* 1993; **18**: 393–5.
25 Kottenhahn RK, Heck JE. Prevalence of pediatric skin diseases in rural Honduras. *Trop Doct* 1994; **24**: 87–8.
26 Romiti N, Almeida JRP, Dinato SLM. Recenseamento dermiatrico no municipio de Santos. *Ann Brazil Dermatol* 1978; **53**: 385–406.
27 Ryan TJ. Healthy skin for all. *Int J Dermatol* 1994; **33**: 829–35.
28 Hay RJ, Hernandez HA, Lopez GC *et al.* Wastage of family income on skin disease in Mexico. *BMJ* 1994; **309**: 848.
29 Hay R, Bendeck SE, Chen S *et al.* Skin diseases. In: Jamison DT, Breman JG, Measham AR *et al*., eds. *Disease Control Priorities in Developing Countries*, 2nd edn. New York: Oxford University Press, 2006: 707–22.
30 Delamere FM, Williams HC. How can hand searching the dermatological literature benefit people with skin problems? *Arch Dermatol* 2001; **137**: 332–5.
31 Davidoff F, Haynes B, Sackett D, Smith R. Evidence based medicine: a new journal to help doctors identify the information they need. *BMJ* 1995; **310**: 1085–6.
32 Sackett DL, Haynes RB. On the need for evidence-based medicine. *Evid Based Med* 1995; **1**: 5–6.
33 Ladhani S, Williams HC. The management of established postherpetic neuralgia: a comparison of the quality and content of traditional vs. systematic reviews. *Br J Dermatol* 1998; **139**: 66–72.
34 Antman EM, Lau J, Kupelnick B *et al.* A comparison of results of metaanalyses of randomized control trials and recommendations of clinical experts. *JAMA* 1992; **268**: 240–8.
35 Cochrane AL. *Effectiveness and Efficiency: Random Reflections on Health Services.* London: Nuffield Provincial Hospitals Trust, 1972. [Reprinted London: British Medical Journal/Nuffield Provincial Hospitals Trust, 1989.]
36 Bero L, Rennie D. The Cochrane Collaboration. *JAMA* 1995; **274**: 1935–8.
37 Williams HC, Seed P. Inadequate size of 'negative' clinical trials in dermatology. *Br J Dermatol* 1993; **128**: 317–26.
38 Mulrow CD. Rationale for systematic reviews. In: Chalmers I, Altman D, eds. *Systematic Reviews*. London: British Medical Journal Publishing Group, 1995: 1–8.
39 Eysenck HJ. Problems with meta-analysis. In: Chalmers I, Altman D, eds. *Systematic Reviews*. London: British Medical Journal Publishing Group, 1995: 64–74.
40 Petersen LJ, Kristensen JK. Selection of patients for psoriasis clinical trials: a survey of the recent dermatological literature. *J Dermatol Treat* 1992; **3**: 171–6.
41 Eady EA, Cove JH, Joanes DN, Cunliffe WJ. Topical antibiotics for the treatment of acne vulgaris: a critical evaluation of the literature on their clinical benefit and comparative efficacy. *J Dermatol Treat* 1990; **1**: 215–26.
42 Naldi L, Carrel C-F, Parazzini F *et al.* Development of anthralin shortcontact therapy in psoriasis: survey of published clinical trials. *Int J Dermatol* 1992; **31**: 126–30.
43 Bigby M, Stern RS, Bigby JA. An evaluation of method reporting and use in clinical trials in dermatology. *Arch Dermatol* 1985; **121**: 1394–9.
44 Adetugbo K, Williams H. How well are randomized controlled trials reported in the dermatology literature? *Arch Dermatol* 2000; **136**: 381–5.
45 Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet* 2001; **357**: 1191–4.
46 Cox NH, Williams HC. Can you COPE with CONSORT? *Br J Dermatol* 2000; **142**: 1–3.
47 Weinstock MA. The JAAD adopts the CONSORT statement. *J Am Acad Dermatol* 1999; **41**: 1045–7.
48 Williams H, Adetugbo K, Po AL *et al*. Preparing, maintaining, and disseminating systematic reviews of clinical interventions in dermatology. The Cochrane Skin Group. *Arch Dermatol* 1998; **134**: 1620–6.
49 Collier A, Johnson CR, Delamere F *et al*. The Cochrane Skin Group: promoting the best evidence. *J Cutan Med Surg* 2005; **9**: 324–31.
50 Collier A, Heilig L, Schilling L *et al*. Cochrane Skin Group systematic reviews are more methodologically rigorous than other systematic reviews in dermatology. *Br J Dermatol* 2006; **155**: 1230–5.

Conclusions

This chapter has demonstrated the fundamental importance that the discipline of epidemiology plays in understanding skin diseases in context, from the clinic to the population. Not only is epidemiology concerned with issues such as describing the incidence, prevalence and human and financial cost of skin disease, but it is also one of the most direct ways of finding out the causes of skin diseases. Finding out causes is important because it may lead to prevention of skin disease on a massive scale. For example, it has been found through a number of epidemiological studies that atopic eczema is less common in large, less economically advantaged families [1,2]. This observation gave rise to the hygiene hypothesis, which postulated that increased exposure to microbes and infections in early life might protect against atopy [1,3]. The

hygiene hypothesis led to a full-scale, randomized, controlled trial of lactobacilli cultures given to pregnant mothers and infants, a study which suggested that around 50% of atopic eczema could be prevented by such a measure in infants [4]. Even though this particular study had some potential flaws [5], it nevertheless demonstrates the power of prevention.

Epidemiological principles have been key to developing the principles of evidence-based medicine and of health services research in relation to dermatology. Although traditional epidemiology may be superseded by genetic epidemiology and other new hybrids as biomedical knowledge develops, there will always be a need for a thorough understanding of the principles of assessing risk and the roles that the 'big three' factors of chance, bias and confounding may play in any study. Similarly, the principles of critically appraising published literature using a framework derived from epidemiology are as basic to dermatological clinical practice as diagnosing skin rashes [6,7].

References

1 Strachan DP. Hay fever, hygiene, and household size. *BMJ* 1989; **299**: 1259–60.

2 Williams HC, Strachan DP, Hay RJ. Childhood eczema: disease of the advantaged? *BMJ* 1994; **308**: 1132–5.

3 Sherriff A, Golding J. Hygiene levels in a contemporary population cohort are associated with wheezing and atopic eczema in preschool infants. *Arch Dis Child* 2002; **87**: 26–9.

4 Kalliomaki M, Salminen S, Arvilommi H *et al*. Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. *Lancet* 2001; **357**: 1076–9.

5 Williams HC. Prevention of atopic eczema: a dream not so far away? *Arch Dermatol* 2002; **138**: 391–2.

6 Williams HC. Beyond the year 2000: how may epidemiology influence future clinical practice in dermatology? *Clin Dermatol* 2001; **19**: 55–8.

7 Williams HC. How to critically appraise a study reporting effectiveness of an intervention. In: Williams HC, Bigby M, Diepgen T *et al*., eds. *Evidence-Based Dermatology,* 2nd edn. London: BMJ Books; Oxford: Blackwell Publishing, 2008: 44–51.

Glossary of epidemiological terms

Measures of disease frequency

Prevalence. The proportion of people with a disease at any one time. *Point* prevalence refers to prevalence at one point in time. *Period* prevalence refers to proportion with a disease (existing and new cases) over a longer period, for example 1 year.

Incidence. The rate of new cases developing over a specified time period, for example the incidence of melanoma in the USA in men in 1983–1987 was 6.9 per 100 000 per year [1].

Measures of disease associations

Risk factor. A factor that increases the risk of disease. This could be a specific exposure, for example asbestos giving rise to mesothelioma, or an attribute such as gender or social class which is indirectly associated with an increased frequency of disease.

Relative risk. This is the *ratio* of the risk of disease occurring in those exposed to the agent under investigation divided by the risk of those not exposed. It is a measure of the strength of the risk factor.

Attributable risk. This is the *difference* between the incidence rate in those exposed to a factor and the incidence rate in those unexposed. It is a measure of the absolute effect of the exposure.

Odds ratio. An approximation of relative risk used in case–control studies. It is the ratio of the odds of exposure in cases to the odds of exposure in controls.

Hazard ratio. This a special form of relative risk that is used in studies that examine survival to express the relative risk of an endpoint or 'hazard' occurring at any given time.

Interpreting results

Sampling error. This refers to the variation in values that a given sample could be expected to show by chance alone.

P-value. When referring to the association of a disease with a particular exposure, a *P*-value of <0.05 means that a value as extreme as that obtained by the study would be expected to be observed by chance in less than one in 20 such studies (or <5% of the time). It is convention at this level of significance to reject the null hypothesis of no difference between the compared groups.

*Confidence interval*s. This refers to the range of plausible values for a main study finding. It is based on the size of the sample and the size of the difference between compared groups. For example, the 95% bounds of a relative risk of 2.0 for smoking in a sample of psoriasis sufferers was 1.5–2.5. If the association is a genuine one, this means that the reader can be 95% confident that the true population relative risk resides between the values of 1.5 and 2.5.

Bias. Bias is a systematic error resulting in an incorrect conclusion about the association between an exposure and an outcome. Over 30 types of bias have been described [2], but they fall into two main groups: (i) *selection*, that is the two groups to be compared are not comparable in terms of factors in addition to the exposure of interest; and (ii) *information*, that is collection of information about the disease and exposure in a fashion that could bias response—for example, those evaluating a new drug were aware of the treatment allocation when assessing patients' response to treatment. An excellent description of the main forms of bias in epidemiological research is to be found elsewhere [3].

Confounding. This is where the association between an exposure and disease is mixed up with a third factor which is independently associated with both the exposure and the disease, for example the protective effect of prolonged breastfeeding (the exposure) on the development of atopic eczema (the disease) may be due to confounding by parental atopy. The risk of atopic eczema is increased in children born to atopic parents, and atopic parents are more likely to practise prolonged breastfeeding in their infants because they may be more aware of a possible protective effect of breastfeeding.

Association and causation. Association between an exposure and disease does not necessarily imply causation. Other factors such as chance, bias and confounding may explain that association.

Validity and repeatability

Internal validity, for example of a diagnostic test, refers to the extent to which the test measures what it is meant to measure. This is normally measured in terms of sensitivity (proportion of

true cases correctly identified) and specificity (proportion of non-cases correctly identified).

External validity refers to the extent to which findings from one particular study (the study population) can be generalized to the target population—for example, to what extent are the favourable results of a clinical trial to test a new oral agent for children with severe atopic eczema attending hospital applicable to children with milder eczema in the community?

Predictive value. When comparing the performance of a test or diagnostic criterion to a gold standard (e.g. clinical diagnosis of melanoma against histological diagnosis), the positive predictive value refers to the probability that someone is a genuine case given a positive test result. Negative predictive value refers to the probability that a person does not have that disease given a negative test result. In addition to sensitivity and specificity, predictive value is dependent on the overall prevalence of the disease being studied [4].

Repeatability. This refers to the extent to which two observations agree with each other. This may be between two observers (inter-observer agreement) or between replicate measurements in one observer (within-observer agreement). Repeatability is measured by chance-corrected agreement measures such as the κ statistic [5], or by differences between two observers plotted against corresponding means of observations and *not* correlation coefficients [6].

Types of epidemiological study

Observational or descriptive studies. These are studies where the frequency of a disorder is described in terms of its association with various background attributes such as age, sex and ethnicity.

Analytical studies. These set out to test specific hypotheses on the relationship between a potential exposure and disease. These may be *cross-sectional*—for example 'Is atopic eczema more common in black Caribbean children in London compared with white children?'; *case–control*—for example 'Is a history of preceding infection more common in people with pityriasis rosea than in controls?'; or *cohort*—for example 'Are people who are exposed to diesel fumes more likely to develop asthma than those who are not?'

Intervention studies. These are studies in which groups of individuals are allocated to an experimental treatment prospectively. Clinical trials are the commonest examples. Occasionally, such trials are conducted at a community level—for example, vaccine trials.

Screening. This refers to the examination of healthy people who would not otherwise have sought medical help for the presence or absence of disease. Principles for evaluating the usefulness of screening are described elsewhere [7].

References

1 Parkin DM, Muir CS, Whelan SL *et al.*, eds. *Cancer Incidence in Five Continents*, Vol. 6. Lyon: International Agency for Research on Cancer, 1992.

2 Sackett DL. Bias in analytical research. *J Chron Dis* 1979; **32**: 51–63.

3 Delgado-Rodríguez M, Llorca J. Bias. *J Epidemiol Community Health* 2004; **58**: 635–41.

4 Armitage P, Berry G. *Statistical Methods in Medical Research*, 2nd edn. Oxford: Blackwell Scientific Publications, 1991.

5 Williams HC, Burney PGJ, Strachan D, Hay RJ. The UK Working Party's diagnostic criteria for atopic dermatitis, 2: observer variation of clinical diagnosis and signs of atopic dermatitis. *Br J Dermatol* 1994; **131**: 397–405.

6 Brennan P, Silman A. Statistical methods for assessing observer variability in clinical measures. *BMJ* 1992; **304**: 1491–4.

7 Barker DJP, Rose G. *Epidemiology in Medical Practice*, 2nd edn. Edinburgh: Churchill Livingstone, 1979: 116–24.

Checklist for reading 'epidemiological studies' in dermatology

This checklist represents a general approach to exploring key elements that should have been included in an epidemiological study. For recommendations on what to include when reporting case–control, cohort and prevalence studies, please refer to the STROBE checklist (STrengthening the Reporting of OBservational studies in Epidemiology) at http://www.strobe-statement.org/Checklist.html (accessed 15th December 2008).

1 Is there a clear objective(s)?
2 Is the study design appropriate and efficient for the question posed?
3 Have cases (numerators) been clearly defined?
4 Is there a population denominator?
5 Have the main hypotheses and outcome measures been stated *a priori*?
6 Is there a rationale for the study's sample size?
7 Have potential confounders been considered and measured?
8 Has the study attempted to minimize selection and information biases?
9 Have the data been analysed appropriately?
10 Are the main results clearly presented with confidence intervals?
11 Have subgroups or *post hoc* findings been treated appropriately?
12 Have the authors discussed alternative explanations such as chance, bias and confounding?
13 Are the study's conclusions supported by the main results?
14 Who sponsored the study? Could sponsorship have affected the choice of data and the way they were presented?

Recommended further reading and useful dermatoepidemiology resources

General epidemiology

Schlesselman JJ. *Case Control Studies: Design, Conduct, Analysis.* Oxford: Oxford University Press, 1982.

Hennekens CH, Buring JE. *Epidemiology in Medicine*. Boston: Little, Brown, 1987.

Sackett DL, Haynes RB, Guyatt GH, Tugwell P. *Clinical Epidemiology: a Basic Science for Clinical Medicine*, 2nd edn. Boston: Little, Brown, 1991.

Rothman KJ, Greenland S, Lash TL. *Modern Epidemiology*, 3rd edn. London: Lippincott, Williams and Wilkins, 2008.

Gordis L. *Epidemiology*, 3rd edn. Philadelphia: Elsevier Saunders, 2004.

Biostatistics

Kirkwood BR. *Essentials of Medical Statistics*. Oxford: Blackwell Scientific Publications, 1988.

Kahn HA. *Statistical Methods in Epidemiology*. Oxford: Oxford University Press, 1989.

Gore SM, Altman DG. *Statistics in Practice*. London: British Medical Association, 1991.

Altman DG. *Practical Statistics for Medical Research*. London: Chapman and Hall, 1992.

Gilmore SJ. Evaluating statistics in clinical trials: making the unintelligible intelligible. *Aust J Dermatol* 2008; **49**: 177–84; quiz 185–6.

Systematic reviews

Chalmers I, Altman D. *Systematic Reviews*. London: British Medical Journal Publishing Group, 1995.

The Cochrane Library. London: British Medical Journal Publishing Group, 1997.

Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.1 [updated September 2008]. The Cochrane Collaboration, 2008. Available from http://www.cochrane-handbook.org.

Dermatoepidemiology reports

Chuang TY. Dermatoepidemiology, 1: epidemiologic methods. *Int J Dermatol* 1993; **32**: 251–6.

Weinstock MA. Dermatoepidemiology. *Dermatol Clin* 1995; **13**: 505–716.

Grobb JJ, MacKie RM, Stern R, Weinstock MA. *Epidemiology, Causes and Prevention of Skin Diseases*. Oxford: Blackwell Science, 1997.

Marks R. Dermatoepidemiology: wherefore art thou in this perilous time of need? *Int J Dermatol* 2001; **40**: 167–8.

Barzilai DA, Mikkilineni R, Davis BR, Stevens SR, Mostow EN. Implementation of dermato-epidemiology curriculum at Case Western Reserve University dermatology program. *Dermatol Online J* 2004; **10**: 1.

Williams H, Svensson A, Diepgen T *et al.*; European Dermato-Epidemiology Network (EDEN). Epidemiology of skin diseases in Europe. *Eur J Dermatol* 2006; **16**: 212–8.

Langan SM, Bouwes Bavinck JN *et al.*; European Dermato-Epidemiology Network. Update on the activities of the European Dermato-Epidemiology Network (EDEN). *Dermatology* 2006; **213**: 1–2.

VanBeek M, Beach S, Braslow L *et al*. Highlights from the report of the working group on 'Core measures of the burden of skin diseases'. *J Invest Dermatol* 2007; **127**: 2701–6.

Dermatoepidemiology textbooks

Williams HC, Strachan DP. *The Challenge of Dermato-epidemiology*. Boca Raton: CRC Press, 1997. [This contains a comprehensive 'toolbox' section at the start of the book, followed by a summary of the epidemiology of specific skin diseases.]

Williams HC. *Atopic Dermatitis*. Cambridge: Cambridge University Press, 2000. [A textbook dedicated to the epidemiology of atopic eczema].

Epidemiology computer software

Gardner MJ, Gardner SB, Winter PD. *Confidence Interval Analysis (CIA) Version 1.2*. London: British Medical Journal Publishing Group, 1991.

Dean AD, Dean JA, Burton JH, Dicker RC. *Epi Info, Version 3.5.1: a Word Processing, Database and Statistics Programme for Epidemiology on Microcomputers*. Atlanta, GA: Centers for Disease Control, 2008. Available as a free download from http://www.cdc.gov/epiinfo/.

Evidence-based dermatology

Bigby M. Evidence-based medicine in a nutshell: a guide to finding and using the best evidence in caring for patients. *Arch Dermatol* 1998; **134**: 1609–18.

Bigby M. Snake oil for the 21st century. *Arch Dermatol* 1998; **134**: 1512–4.

Rees J. Evidence-based medicine: the epistemology that isn't. *J Am Acad Dermatol* 2000; **43**: 727–9.

Williams H. Dowling Oration 2001. Evidence-based dermatology—a bridge too far? *Clin Exp Dermatol* 2001; **26**: 714–24.

Williams HC, Bigby M, Diepgen T *et al*. *Evidence-Based Dermatology*, 2nd edn. London: BMJ Books, Blackwell Publishing, 2008.

See also the 'Evidence-Based Dermatology' section published each quarter in the *Archives of Dermatology* (http://archderm.ama-assn.org/).

Interest groups/societies

The British Epidermo-Epidemiology Society (BEES) runs an annual meeting, annual 3-day course on understanding epidemiological principles in evidence-based dermatology and a summer school: http://www.bees.org.uk/about/

The European Dermato-Epidemiology Network (EDEN). Website containing details of current epidemiological projects and meetings: http://eden.dermis.net/content/e02eden/e01aims/e01programm/index_ger.html

International Dermatoepidemiology Association (IDEA). Normally accessed via EDEN or ADEN. For details of the last IDEA Congress in 2008, go to http://www.nature.com/jid/journal/v128/n10/pdf/jid2008267a.pdf

Useful websites and online resources

ebderm.org: Ebderm.org is a web-based tool designed to help dermatology residents, dermatologists, and other allied health professionals learn and practise evidence-based dermatology. http://ebderm.org

Centre of Evidence-Based Dermatology: http://www.nottingham.ac.uk/dermatology/. The author's team which includes the Cochrane Skin Group, the UK Dermatology Clinical Trials Network, and the National Library for Health Skin Disorders Specialist Library. It also contains a listing of departmental research, tutorials, online resources such as the UK Diagnostic Criteria for Atopic Dermatitis manual and useful links.

UK Centre of Evidence-Based Medicine based at Oxford: http://www.cebm.net/. Contains a list of useful teaching resources for EBM, along with a glossary of terms and Palm resources.

Cochrane Library: http://www.thecochranelibrary.com. Widely acknowledged as the most reliable source of evidence, it con-

tains the largest collection of systematic reviews and clinical trials in the world. It is free to any user in the UK with an IP address, and also in many other countries such as India, Finland, Ireland and Norway.

National Library For Health Skin Disorders Specialist Library: http://www.library.nhs.uk/skin/. The largest and most complete collection of quality appraised Internet resources for dermatology health professionals. Includes annual evidence updates.

Trainees' curriculum for dermatoepidemiology: http://www.nottingham.ac.uk/~muzidea/aadcurric.htm. A list of guided reading and questions developed by dermatoepidemiologists from IDEA in conjunction with the American Academy of Dermatology.

Guidelines on reporting various study designs such as epidemiological studies, randomized controlled clinical trials, diagnostic test studies etc. are all to be found at the EQUATOR website (Enhancing the QUAlity and Transparency Of health Research) at http://www.equator-network.org/ (accessed 22nd December 2008).

ProQolid: Patient-reported outcome and quality of life instruments database http://www.qolid.org/

CHAPTER 7

Evidence-Based Dermatology

M. Bigby[1] *& H.C. Williams*[2]

[1]Beth Israel Deaconess Medical Center, Boston, MA, USA
[2]Centre of Evidence-Based Dermatology, Nottingham University Hospitals NHS Trust, UK

The need for evidence-based medicine, 7.1
Distinguishing effective treatments from those that are ineffective or harmful, 7.1
Keeping up with the literature, 7.2
Practising evidence-based medicine, 7.2
Formulating questions and finding evidence, 7.2
Formulating well-built clinical questions, 7.2
What is 'the best evidence?', 7.3
Finding the best evidence, 7.5
Critically appraising evidence and applying it to individual patients, 7.7
Critically appraising the evidence, 7.7
Critically appraising systematic reviews, 7.7
Critically appraising individual clinical trials, 7.10
Critical appraisal of a study about a diagnostic test, 7.13
Critically appraising a study about adverse events (case–control and cohort studies), 7.14
Conclusions, 7.15
Shortcut method and evaluating the data in clinical research papers, 7.16
Shortcut method for appraising clinical research papers, 7.16
Evaluating the data in clinical research papers, 7.17
Statistical methods, 7.19

The need for evidence-based medicine

Distinguishing effective treatments from those that are ineffective or harmful [1]

Distinguishing effective treatments from those that are ineffective or harmful has been a problem facing medical practitioners since medicine has been practised. Prior to the 1940s, determination of treatment efficacy was based on expert opinion, trial and error, uncontrolled observation and small case series. The only treatments that could be distinguished as effective were those that produced dramatic increases in survival, such as streptomycin for tuberculosis meningitis [1]. The publication of the randomized, controlled clinical trial (RCT) that demonstrated that streptomycin was effective in the treatment of pulmonary tuberculosis was a landmark event in determining treatment efficacy [2]. Since then, the RCT has become the gold standard for determining the efficacy of therapeutic interventions. Hundreds of RCTs were conducted between 1950 and the 1970s. However, their results were not catalogued or used systematically to inform medical decision-making.

Evidence-based medicine is a framework designed to help practitioners distinguishing interventions that are effective from those that are ineffective or harmful. The origin of evidence-based medicine is most often traced to Pierre Charles Alexander Louis who introduced the teaching of statistical methods into the study of medicine in post-revolutionary France. However, a strong case can be made that its modern originator was Archie Cochrane, a British epidemiologist and physician who, in 1971, published his response to being asked to evaluate the effectiveness of the British National Health Service in delivering health care to the population of the UK. In his analysis he concluded that medical science was poor at distinguishing interventions that were effective from those that were not and that physicians were not using available evidence from clinical research to inform their decision-making [1,3].

Like-minded epidemiologists and physicians responded to Archie Cochrane's challenge by examining the methods by which medical decisions and conclusions were reached, and proposed an alternative method of summarizing evidence based on finding, appraising and utilizing available data from clinical research performed on patients. In 1985, Sackett and colleagues published a landmark book entitled *Clinical Epidemiology: A Basic Science for Clinical Medicine* that detailed the rationale and techniques of this evidence-based approach [4]. These authors and others reduced the rules of evidence to a small subset of principles that were easier to teach and to understand, and reintroduced the concept in 1992. They named this technique 'evidence-based medicine' (EBM). It was defined as the conscientious, explicit and judicious use of the best current evidence in making decisions about the care of individual patients [5]. The definition was expanded to include the integration of independent, clinical expertise, the best available external clinical evidence from systematic research, and patients' values and expectations [6]. Others, such as Ian Chalmers, were instrumental in setting up the Cochrane Collaboration, a global network of individuals, mainly volunteers, who were tasked with preparing and maintaining unbiased systematic reviews of all randomized controlled trials, organized according to specialty [7]. Whereas making decisions about therapy has been the primary focus of EBM, its principles have been extended to diagnosis, prognosis, harmful effects of interventions and economic analyses [1].

It has been estimated that physicians need evidence (e.g. about the accuracy of diagnostic tests, the power of prognostic markers,

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

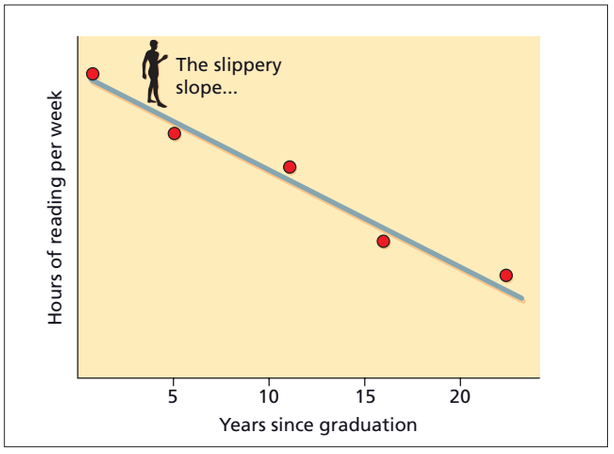


Fig. 7.1 Relationship between reading and years from graduation from medical school. Based on Sackett [11].

the comparative efficacy and safety of interventions) about twice for every three outpatients seen (and five times for every inpatient). In reality, we get less than a third of this evidence [1,8,9].

Keeping up with the literature

The best external evidence that informs patient care comes from clinical research involving patients. It has a short doubling time (10 years) and replaces currently accepted diagnostic tests and treatments with new ones that are more powerful, more accurate, more efficacious and safer [1].

In the field of medicine the amount of data published far exceeds our ability to read it. Keeping up by reading the literature is an impossible task for most practising physicians. It would require reading around 19 articles a day, 365 days a year. The average practising physician spends one half hour per week reading the medical literature related to the patients whom he or she sees (Fig. 7.1) [1,6,8]. The burden of literature for dermatologists is no less daunting, since there are now more than 200 journals devoted to dermatology worldwide [10]. This expansion in the biomedical literature has been one of the main reasons for developing secondary research synthesis summaries (systematic reviews) of all available evidence, so that the busy physician can go to just one place for an up-to-date summary.

Even if he or she had the time, the best clinical evidence published in journals is often inaccessible to the average practising physician. Most are not adequately trained in clinical decision-making, clinical research, epidemiology or statistics to adequately read and critically evaluate many articles published in the primary medical literature. Commonly used techniques and concepts, such as odds-ratio, confidence interval, utility, Yates' correction or fixed-effects model, as examples, are often poorly understood. Evidence-based medicine provides a systematic method to evaluate the medical literature that allows the average practising physician not only to understand the medical literature but also to apply it to the care of individual patients.

Table 7.1 The five steps of practising evidence-based dermatology.

1. Formulating a well-built clinical question generated from a patient encounter
2. Searching for valid external evidence
3. Critically appraising that evidence for relevance and validity
4. Applying the results of that appraisal of evidence back to the patient
5. Recording the information for future use

Practising evidence-based medicine

What then is evidence-based medicine? Practising EBM consists of five steps (Table 7.1). Once learned, the techniques of EBM can be performed rapidly and efficiently to use available external evidence from the medical literature combined with clinical experience and patient preferences in order to make clinical decisions.

References

1 Bigby M, Corona R, Szklo M. Evidence-based medicine. In: Freedberg IM, Eisen AZ, Wolf K, Austen, KF, Goldsmith LA, Katz SI, eds. *Fitzpatrick's Dermatology in General Medicine*, 7th edn. New York: McGraw-Hill, 2008: 8–18.
2 Anonymous. Medical Research Council Streptomycin In Tuberculosis Trials Committee. Streptomycin treatment of pulmonary tuberculosis. *BMJ* 1948; **ii**: 769–82.
3 Cochrane A. *Effectiveness and Efficiency. Random Reflections on Health Services*. London: Nuffield Provincial Hospital Trust, 1972.
4 Sackett DL, Haynes RB, Guyatt GH, Tugwell P. *Clinical Epidemiology: A Basic Science for Clinical Medicine*. Boston: Little, Brown & Company, 1991.
5 Evidence-Based Medicine Working Group. Evidence-based medicine: a new approach to teaching the practice of medicine. *JAMA* 1992; **268**: 2420–5.
6 Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. *BMJ* 1996; **312**: 71–2.
7 Chalmers I, Dickersin K, Chalmers TC. Getting to grips with Archie Cochrane's agenda. *BMJ* 1992; **305**: 786–8.
8 Strauss SR, Sackett DL. Bringing evidence to the clinic. *Arch Dermatol* 1998; **134**: 1519–20.
9 Covell DG, Uman GC, Manning PR. Information needs in office practice: are they being met? *Ann Intern Med* 1985; **103**: 596–9.
10 Arndt K. Information excess in medicine. Overview, relevance to dermatology, and strategies for coping. *Arch Dermatol* 1992; **128**: 1249–56.
11 Sackett DL. Surveys of self-reported reading times of consultants in Oxford, Birmingham, Milton-Keynes, Bristol, Leicester, and Glasgow. In: Rosenberg WMC, Richardson WS, Haynes RB, Sackett DL, eds. *Evidence-Based Medicine*. London: Churchill Livingstone, 1997: 1–20.

Formulating questions and finding evidence

Formulating well-built clinical questions [1]

A central issue in practising EBM is that of trying to find answers to clinically relevant questions that arise in caring for individual patients. Asking *well-built clinical questions* may be the most important step in practising EBM. A well-built clinical question has four elements: a patient or problem, an intervention, a comparison intervention (if necessary) and an outcome. These are encompassed in the acronym PICO (patient, intervention, comparator and outcome). Well-built clinical questions about individual patients can be grouped into several categories, relating to issues such as aetiology, diagnosis, therapy, prevention, prognosis and harm.

A well-built clinical question has two strong advantages. One major benefit of careful and thoughtful question forming is that it

makes it easier to search for, and critically appraise, the available evidence. The well-built question makes it relatively straightforward to determine and combine the appropriate search terms needed to obtain relevant information from whichever database(s) you choose (e.g. Medline, EMBASE or the Cochrane Library). Second, having to formulate well-built clinical questions will also train you to clearly define your patient, to be specific about the interventions used and to choose carefully described outcomes that are important to your patient and to yourself.

What is 'the best evidence?' [2]

Practising evidence-based medicine is dependent on finding and utilizing the best evidence. Potential sources of evidence include having an understanding of the aetiology and pathophysiology of disease, application of logic and personal experience, views of colleagues or experts, and information from textbooks, articles published in journals and systematic reviews. An important principle of EBM is that the quality (strength) of evidence is based on a *hierarchy of evidence* (Fig. 7.2). The order of the hierarchy of evidence is dependent on the type of question being asked (Table 7.2). The hierarchy of evidence consists of results of well-designed experimental studies such as RCTs (especially if the studies have results of similar magnitude and direction, and if there is homogeneity among studies), results of observational studies such as case series, expert opinion and personal experience, in descending order. The hierarchy was created to encourage the use of the evidence that is most likely to be true and useful in clinical decision-making. The ordering of this hierarchy has been widely discussed, actively debated and sometimes hotly contested [3]. It is important to consider study quality when referring to the evidence hierarchy. For example, a well-designed cohort study may provide more

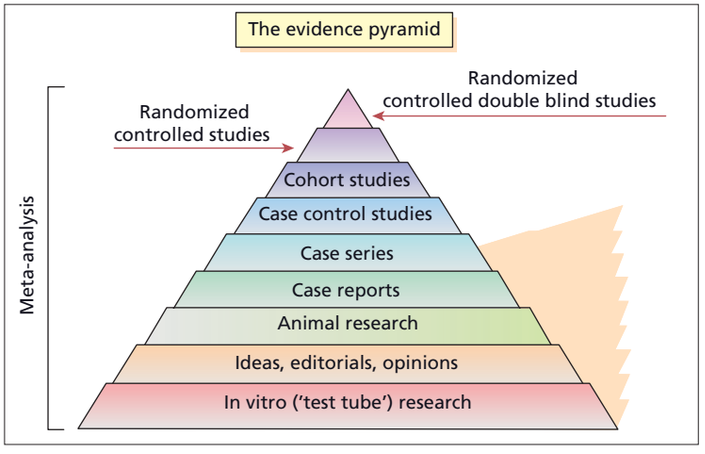


Fig. 7.2 The hierarchy of evidence. Permission to reprint granted by SUNY Downstate Medical Center, Medical Research Library of Brooklyn Guide to Research Methods, The Evidence Pyramid. SUNY Health Sciences, Evidence Based Medicine Course. http://servers.medlib.hscbklyn.edu/ebm/2100.htm.

Table 7.2 Levels of evidence.

Level of evidence	Type of study	Other studies reaching this evidence level
1a	Multiple RCTs* with homogeneity†	Multiple level 1b (see immediately below) diagnostic studies with homogeneity; or CDR‡ with 1b studies from different clinical centres
1b	Individual RCT (with narrow confidence intervals)	Independent blind comparison of an appropriate spectrum of consecutive patients, all of whom have undergone both the diagnostic test and the reference standard
1c	All or none§	Very high sensitivity or specificity¶
2a	Cohort studies with homogeneity	Multiple level ≥2 (see below) diagnostic studies with homogeneity
2b	Individual cohort study (including low-quality RCT, e.g. <80% follow-up)	Independent blind comparison but either in non-consecutive patients or confined to a narrow spectrum of study individuals (or both), all of whom have undergone both the diagnostic test and the reference standard; or a diagnostic CPG not validated in a test set
2c	'Outcomes' research**	
3a	Case–control studies with homogeneity	Multiple 3b and better studies (see below) with homogeneity
3b	Individual case–control study	Independent blind comparison of an appropriate spectrum, but the reference standard was not applied to all study patients
4	Case series (and poor quality cohort and case–control studies)	Reference standard was not applied independently or not applied blindly
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or logical deduction	

Modified from: Ball C, Sackett D, Phillips B, Haynes B, Straus S. NHS R&D Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=1025 (last accessed 30 October 2007).

* RCT, randomized controlled trial.

† Homogeneity, lacking variation in the direction and magnitude of results of individual studies.

‡ CDR, clinical decision rule. These are algorithms or scoring systems that lead to a prognostic estimation or a diagnostic category.

§ All or none, interventions that produced dramatic increases in survival or outcome such as streptomycin for tuberculosis meningitis.

¶ A diagnostic finding with a specificity so high that a positive result rules in the diagnosis or a diagnostic finding with sensitivity so high that a negative result rules out the diagnosis.

** Outcomes research includes cost–benefit, cost–effectiveness and cost–utility analyses.

reliable evidence than a small, poorly conducted RCT (even though the RCT theoretically provides a stronger design for minimizing bias).

A systematic review is an overview of available evidence that answers a specific clinical question, contains a thorough, unbiased search of the relevant literature, explicit criteria for assessing studies and structured presentation of the results. When there are similar studies in a systematic review (e.g. RCTs using the same interventions and outcomes), the authors of a systematic review may use a statistical technique, called meta-analysis, to combine quantitative data from several studies in order to provide a more precise and informative overall estimate of treatment effects.

Meta-analysis is credited with allowing recognition of important treatment effects by combining the results of small trials that individually lacked the power to demonstrate differences among treatments. For example, the benefits of intravenous streptokinase in acute myocardial infarction was recognized by the results of a cumulative meta-analysis of smaller trials at least a decade before it was recommended by experts and before it was demonstrated to be efficacious in large clinical trials [4]. Meta-analysis has been criticized for the discrepancies between the results of meta-analysis and those from large clinical trials [5]. For example, results of a meta-analysis of 14 small studies of calcium to treat pre-eclampsia showed benefit of treatment, whereas a large trial failed to show a treatment effect [6]. The frequency of such discrepancies ranges from 10% to 23% [6]. Discrepancies can often be explained by differences in treatment protocols, heterogeneity of study populations or changes that occur over time [6].

The type of question being asked determines the type of clinical study that is likely to provide the best evidence. Questions about therapy and interventions for disease prevention are best addressed by RCTs. Questions about diagnosis are best addressed by cohort studies. RCTs are usually a good source of evidence for the harmful effects of interventions for adverse events that occur frequently, but are not always reliable for identifying rare but potentially important adverse events. For adverse effects that occur infrequently, cohort studies, case–control studies, or post-marketing surveillance studies are best. Case reports are often the first line of evidence for rare adverse events and sometimes they are the only evidence.

Over half a million RCTs have been conducted in medicine. Studies have demonstrated that failure to use randomization or adequate concealment of allocation results in larger estimates of treatment effects, predominantly caused by a poorer prognosis in non-randomly selected control groups compared with randomly selected control groups [7]. However, some studies comparing randomized and non-randomized clinical trials of the same interventions have reached disparate and conflicting results [8,9]. In some instances, observational studies find stronger treatment effects than RCTs [7]. Other studies have demonstrated that the results of well-designed observational studies (with either a cohort or a case–control design) do not systematically overestimate the magnitude of the effects of treatment as compared with RCTs on the same topic [8,9]. Sifting through the controversy leads to the following limited conclusions: (i) trials using historical controls result in larger estimates of treatment effects compared with randomized controlled trials; and (ii) large, inclusive, fully masked RCTs are likely to provide the best possible evidence about effectiveness [3].

Whereas personal experience is an invaluable part of becoming a competent physician, the pitfalls of relying too heavily on personal experience have been widely documented. Nisbett and Ross extensively reviewed people's ability to draw inferences from personal experience and document several pitfalls [10]. They include:

1. over-emphasis on vivid, anecdotal occurrences and under-emphasis on significant statistically strong evidence
2. bias in recognizing, remembering and recalling evidence that supports pre-existing knowledge structures (e.g. ideas about disease aetiology and pathogenesis) and parallel failure to recognize, remember and recall evidence that is more valid
3. failure to accurately characterize population data because of ignorance of statistical principles including sample size, sample selection bias and regression to the mean
4. inability to detect and distinguish statistical association and causality, and
5. persistence of beliefs in spite of overwhelming contrary evidence.

Nisbett and Ross provide numerous examples of problems associated with recall from controlled clinical research. Physicians may remember patients who improved, often assume that patients who did not return for follow-up improved, and conveniently forget the patients who did not improve. A patient treated with a given medication may develop a severe life-threatening reaction; on the basis of this single undesirable experience, the physician may avoid using that medication for many future patients, even though, *on average,* it may be more efficacious and less toxic than the alternative treatments that the physician chooses. Few physicians keep adequate, easily retrievable records to codify results of treatments with a particular agent or of a particular disease; and even fewer actually carry out analyses. Few physicians make provisions for tracking those patients who are lost to follow-up. Therefore statements made about a physician's 'clinical experience' may be biased. Finally, for many conditions, a single physician sees far too few patients to enable reasonably firm conclusions to be drawn about the response to treatments. For example, suppose a physician has treated 20 patients with lichen planus with tretinoin and found that 12 (60%) had an excellent response. The confidence interval for this response rate (i.e. the true response rate for this treatment in the larger population from which this physician's sample was obtained) ranges from 36% to 81%. Thus the true overall response rate might well be substantially less (or more) than the physician concludes from personal experience.

Expert opinion can be valuable, particularly for rare conditions in which the expert has the most experience or when other forms of evidence are not available. However, several studies have demonstrated that expert opinion often lags significantly behind conclusive evidence. Experts may rely too heavily on bench research, pathophysiology and treatments based on logical deduction from pathophysiology and from the same pitfalls noted regarding reliance on personal experience.

It is widely believed that clinical decisions can be made on the basis of understanding the aetiology and pathophysiology of disease and logic [11]. This paradigm is problematic since the

accepted hypothesis for the aetiology and pathogenesis of disease changes over time. For example, in the last 20 years, hypotheses about the aetiology of psoriasis have shifted from a disorder of keratinocyte proliferation and homeostasis, to abnormal signalling of adenosine cyclic monophosphate, to aberrant arachidonic acid metabolism, to aberrant vitamin D metabolism, to the current favourite: a T-cell-mediated autoimmune disease. Each of these hypotheses spawned logically-deduced treatments. The efficacy of many of these treatments has been substantiated by rigorous, controlled clinical trials, whereas others are used even in the absence of systematically collected observations. Therefore, many options are available for treating patients with severe psoriasis (e.g. UVB, narrow-band UVB, the Goeckerman regimen, psoralen–UVA, methotrexate, ciclosporin and biological agents) and others for mild-to-moderate psoriasis (e.g. dithranol, topical corticosteroids, calcipotriol and tazarotene). However, we lack a clear sense of which is best, in what order they should be used or in what combinations.

Treatments based on logical deduction from pathophysiology may have unexpected consequences. For example, the observation that antiarrhythmic drugs could prevent abnormal ventricular depolarization after myocardial infarction logically lead to their use to prevent sudden death after myocardial infarction. However, an RCT showed increased mortality of patients treated with antiarrhythmic drugs compared with placebo [12].

In the field of dermatology, it was postulated that thalidomide might be a useful treatment for toxic epidermal necrolysis based on the observation that thalidomide showed antitumour necrosis factor-alpha properties, yet an RCT of thalidomide was stopped early because it was found that mortality was significantly higher in the thalidomide group than in the placebo group [13].

Textbooks can be valuable, particularly for rare conditions and for conditions for which the evidence does not change rapidly over time. However, textbooks have several well-documented shortcomings. They tend to reflect the biases and shortcomings of the experts who write them. By virtue of how they are written, produced and distributed, most are at least 2 years out of date at the time of publication. Most textbook chapters are narrative reviews that do not consider the quality of the evidence reported.

Finding the best evidence [2]

The ability to find the best evidence to answer clinical questions is crucial for practising EBM. Finding evidence requires access to electronic searching, searching skills and available resources. Evidence about therapy is the easiest to find. The best sources for finding the best evidence about treatment include:

1. the Cochrane Library
2. searching the Medline and EMBASE databases
3. primary journals
4. secondary journals
5. evidence-based dermatology and evidence-based medicine books
6. the National Guideline Clearinghouse (http://www.jcaai.org)
7. the National Institute for Health and Clinical Excellence (NICE) (www.nice.org.uk)

The Cochrane Collaboration developed in response to Archie Cochrane's challenge to organize a critical summary, by specialty or subspecialty, adapted periodically, of all relevant RCTs. The Cochrane Library contains the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effectiveness (DARE), the Cochrane Central Register of Controlled Trials (Central) and the Health Technology Assessment Database (HTA). It is the most complete and best index database of systematic reviews of therapy, RCTs and controlled clinical trials, and is the best and most efficient place to find evidence about therapy.

The Cochrane Database of Systematic Reviews is the most comprehensive collection of high-quality, systematic reviews available. Volunteers, according to strict guidelines developed by the Cochrane Collaboration, write the systematic reviews in the Cochrane library. Systematic reviews conducted within the Cochrane Collaboration are rated among the best [14]. The last issue of the Cochrane Library (2008, issue 1, accessed 31 March 2008) contained 5171 completed systematic reviews. The number of reviews relevant to dermatology is around 200 and is steadily increasing.

Central is a database of over 527 885 controlled clinical trials. It is compiled by searching the Medline and EMBASE databases, and additionally by hand searching many journals. Hand searching of journals to identify controlled clinical trials and RCTs was undertaken because members of the Cochrane Collaboration noticed that many trials were incorrectly classified in the Medline database. As an example, Adetugbo and William hand searched the *Archives of Dermatology* from 1990 to 1998 and identified 99 controlled clinical trials; 19 of the trials were not classified as controlled clinical trials on Medline and 11 trials that were not controlled clinical trials were misclassified as controlled clinical trials on Medline [15].

DARE is a database of abstracts of systematic reviews published in the medical literature. It contained abstracts and bibliographic details on over 7048 published systematic reviews. DARE is the only database to contain abstracts of systematic reviews that have been quality assessed. Each abstract includes a summary of the review together with a critical commentary about the overall quality.

HTA consists of completed and ongoing Health Technology Assessments (studies of the medical, social, ethical and economic implications of health-care interventions) from around the world. The aim of the database is to improve the quality and cost-effectiveness of health care.

The Cochrane library can be easily searched using simple Boolean combinations of search terms as well as by more sophisticated search strategies. The Cochrane Database of Systematic Reviews, DARE, Central and HTA can be searched simultaneously. The Cochrane Library is available on a personal or institutional subscription basis on CD, and on the world wide web from Wiley InterScience (http://www3.interscience.wiley.com). Subscriptions to the Cochrane Library are updated quarterly. The Cochrane Library is offered free of charge in many countries by national provision and to faculty and students by many medical schools in the USA.

The second best method for finding evidence about treatment, and the best source for finding most other types of best evidence,

in dermatology is by searching the Medline or EMBASE databases. Medline is the National Library of Medicine's (NLM) bibliographic database covering the fields of medicine, nursing, dentistry, veterinary medicine, the health-care system and the preclinical sciences. The Medline file contains bibliographic citations and author abstracts from approximately 5000 current biomedical journals published in the USA and 80 other countries. The file contains approximately 15 million records dating back to the 1950s.

Medline searches have inherent limitations that make their reliability less than ideal [2]. For example, Spuls *et al*. conducted a systematic review of systemic treatments of psoriasis [16]. Treatments analysed included UVB, PUVA, methotrexate, ciclosporin and oral retinoids. The authors used an exhaustive strategy to find relevant references including Medline searches, contacting pharmaceutical companies, polling leading authorities, reviewing abstract books of symposia and congresses, and reviewing textbooks, reviews, editorials, guideline articles and the reference lists of all papers identified. Of 665 studies found, 356 (54%) were identified by Medline search (range 30% to 70% for different treatment modalities). The 17 of 23 authorities who responded provided no references beyond those identified by Medline searching.

Specific search strategies, known as 'filters', have been developed to help find relevant references and to exclude irrelevant references for systematic reviews and for evidence about aetiology, diagnosis, therapy and prevention, prognosis, and clinical prediction guides (http://www.ncbi.nlm.nih.gov/entrez/query/static/clinicaltable.html#ClinicalQueries). These filters have been incorporated into the PubMed Clinical Queries search engine of the NLM and are available at http://www.ncbi.nlm.nih.gov/entrez/query/static/clinical.shtml. PubMed Clinical Queries is the preferred method for searching the Medline database for the best clinically relevant evidence. It can be freely used by anyone with Internet access.

EMBASE (http://www.embase.com/) is Excerpta Medica's database covering drugs, pharmacology and biomedical specialties. EMBASE has better coverage of European and non-English language sources, and may be more up to date than Medline. The overlap in journals covered by Medline and EMBASE is about 34% (range 10% to 75% depending on the subject) [17]. EMBASE contains over 11 million records from 1974 to the present. EMBASE.com performs simultaneous searches of EMBASE and Medline databases and eliminates duplicate records. Personal and institutional subscriptions are available.

Structured abstracts of articles are published in secondary journals (e.g. the Evidence-based Dermatology section of the *Archives of Dermatology*). The articles are strictly selected on the basis of methodological quality and are accompanied by commentary putting the information in clinical perspective. The Evidence-based Dermatology section is published quarterly in the *Archives of Dermatology*. *Clinical Evidence* is a 6-monthly-updated compendium of evidence on the effects of common clinical interventions. Twenty-four skin-related diseases were included in the latest issue (last accessed 30 October 2007). It is available through the American College of Physicians and the British Medical Association (http://clinicalevidence.org/ceweb/index.jsp).

Full text versions of many primary journals are now available on the Internet. Available vendors include DataStar, DIALOG, DIMDI, Ovid Online and STN, among others. The National Guideline Clearinghouse maintains a database of guidelines for the treatment of disease written by panels of experts following strict guidelines of evidence. The database is accessible through the Internet (http://www.guideline.gov). However, current coverage of dermatological topics is limited.

The UK National Institute for Health and Clinical Excellence (NICE; www.nice.org.uk) produces guidance on public health, health technologies and clinical practice based on the best available evidence. It includes guidance for treating atopic eczema, a final appraisal determination on the use of calcineurin inhibitors for atopic dermatitis and on the use of biologics for psoriasis, and a full set of guidelines for skin cancer, including melanoma. The Skin Disorders Specialist Library provides a 'one-stop shop' of reliable Internet resources on skin diseases including guidelines, patient information resources, evidence sources and updates of systematic reviews; part of the UK National Library for Health, and directed at UK health professionals, it is freely available anywhere in the world (http://www.library.nhs.uk/skin/) [18].

References

1 Rzany B, Bigby M. Formulating well built clinical questions. In: Williams HC, Bigby M, Diepgen T, Herxheimer A, Naldi L, Rzany B, eds. *Evidence-Based Dermatology*, 2nd edn. London: Blackwell Publishing, 2008.

2 Bigby M, Corona R, Szklo M. Evidence-based medicine. In: Freedberg IM, Eisen AZ, Wolf K, Austen, KF, Goldsmith LA, Katz SI, eds. *Fitzpatrick's Dermatology in General Medicine*, 7th edn. New York: McGraw-Hill, 2008: 8–18.

3 Bigby M. Challenges to the hierarchy of evidence: does the emperor have no clothes? *Arch Dermatol* 2001; **137**: 345–6.

4 Lau J, Antman EM, Jimenez-Silva J, Kupelnick B, Mosteller F, Chalmers TC. Cumulative meta-analysis of therapeutic trials for myocardial infarction. *N Engl J Med* 1992; **327**: 248–54.

5 LeLorier J, Gregoire G, Benhaddad A, Lapierre J, Derderian F. Discrepancies between meta-analyses and subsequent large randomized, controlled trials. *N Engl J Med* 1997; **337**: 536–42.

6 Lau J, Ionnidis JPA, Schmid CH. Summing up evidence: one answer is not always enough. *Lancet* 1998; **351**: 123–27.

7 Kunz R, Oxman AD. The unpredictability paradox: review of empirical comparisons of randomised and non-randomised clinical trials. *BMJ* 1998; **317**: 1185–90.

8 Benson K, Hartz AJ. A comparison of observational studies and randomized, controlled trials. *N Engl J Med* 2000; **342**: 1878–86.

9 Concato J, Shah N, Horwitz R. Randomized, controlled trials, observational studies, and the hierarchy of research design. *N Engl J Med* 2000; **342**: 1887–92.

10 Nisbett R, Ross L. *Human Inference: strategies and shortcomings of social judgment*. Englewood Cliffs, NJ: Prentice-Hall Inc, 1980.

11 Bigby M. Paradigm lost. *Arch Dermatol* 2000; **136**: 26–7.

12 Echt DS, Liebson PR, Mitchell LB *et al*. Mortality and morbidity in patients receiving encainide, flecanide, or placebo: the cardiac arrythmia suppression trial. *N Engl J Med* 1991; **324**: 781–8.

13 Wolkenstein P, Latarjet J, Roujeau JC *et al*. Randomised comparison of thalidomide versus placebo in toxic epidermal necrolysis. *Lancet* 1998; **352**: 1586–9.

14 Collier A, Heilig L, Schilling L, Williams H, Dellavalle RP. Cochrane Skin Group systematic reviews are more methodologically rigorous than other systematic reviews in dermatology. *Br J Dermatol* 2006; **155**: 1230–5.

15 Adetugbo K, Williams H. How well are randomized controlled trials reported in the dermatology literature? *Arch Dermatol* 2000; **136**: 381–5.

16 Spuls PI, Witkamp L, Bossuyt PM, Bos JD. A systematic review of five systemic treatments for severe psoriasis. *Br J Dermatol* 1997; **137**: 943–9.

17 Greenhalgh T. Searching the literature. In: *How to Read a Paper: the Basics of Evidence Based Medicine*. London: BMJ Publishing Group, 2001: 15–26.

18 Grindlay D, Kamel Boulos MN, Williams HC. Introducing the National Library for Health Skin Conditions Specialist Library. *BMC Dermatology* 2005; **5**: 4.

Critically appraising evidence and applying it to individual patients

Critically appraising the evidence [1]

After finding evidence, the next step in practising EBM involves *critically appraising the evidence*. The criteria to critically appraise systematic reviews are listed in Table 7.3 (other lists for appraisal of other types of study are provided later in Tables 7.5–7.7). Papers that meet defined appraisal are more likely to provide information that is true and useful in the care of patients. Detailed explanation of each criterion and examples using a patient with a dermatological complaint are available [2].

Critically appraising evidence consists of three steps, determining whether the results are:

1 valid (i.e. as unbiased as possible)
2 clinically important and
3 applicable to the specific patient being seen.

Determining the validity of evidence centres on ascertaining whether the evidence was produced in a manner most likely to eliminate and avoid bias. Clinical importance is determined by looking at the magnitude of the effect of the intervention (e.g. treatment effect for systematic reviews, meta-analyses and RCTs; likelihood ratio for diagnostic studies; and relative risk or odds ratios for studies of harm) and its corresponding precision (usually expressed as the 95% confidence interval). To determine whether the evidence is applicable to a specific patient requires physician expertise, knowledge of the patient's preferences, and an evaluation of the availability, risks and benefits of the intervention.

Critically appraising systematic reviews [3]

Are the results of the systematic review valid?

Not all systematic reviews and meta-analyses are equal. A systematic review should be conducted in a manner that will include all of the relevant trials, minimize the introduction of bias, and synthesize the results to be as truthful and useful to clinicians as possible. Systematic reviews should be reported fully according to the Quality of Reporting of Meta-Analyses (QUOROM) guidance [4].

In general, the criteria to critically appraise systematic reviews and meta-analyses are similar to the criteria used to appraise the individual studies that make up the systematic review. Like the well-built clinical question for individual studies, a focused clinical question for a systematic review should contain four elements:

1 a patient, group of patients or problem
2 an intervention
3 comparison intervention(s) and
4 specific outcomes.

The patient populations should be similar to the majority of patients likely to be seen in the population to which one wishes to apply the results of the systematic review. The interventions studied should be those commonly available in practice. Outcomes reported should be those that are most relevant to physicians and patients.

The overwhelming majority of systematic reviews involve therapy. Therefore, RCTs should be used for systematic reviews of therapy if they are available. The quality of included trials is assessed using the criteria that are used to evaluate individual RCTs. The quality criteria commonly used include concealed random allocation, groups similar in terms of known prognostic factors, equal treatment of groups, masked (also known as blinded) evaluation of treatment outcomes and accounting for all patients entered into the trial in analysing results (intent-to-treat design).

Systematic reviews of treatment efficacy should always include a thorough assessment of common and serious adverse events, as well as of efficacy, in order to come to an informed and balanced decision about the utility of a treatment. A thorough assessment of adverse events should include data from RCTs, case–control studies, post-marketing surveillance studies and some of the other sources shown in Table 7.4.

Publication bias (i.e. the tendency that studies that are easy to locate are more likely to show 'positive' effects) is an important concern for systematic reviews; Sterne *et al*. have written a useful review of this subject [5]. It results from allowing factors other than the quality of the study to influence its acceptability for publication. Several studies have shown that factors such as sample size, direction and statistical significance of findings, or investigators' perception of whether the findings are 'interesting', are related to the likelihood of publication [6].

Language bias may also be a problem, i.e. the tendency for studies that are 'positive' to be published in an English language journal, and additionally may be published more quickly than inconclusive or negative studies (a factor that applies to any journal, whatever the language). A thorough, systematic review should therefore include a search for high-quality, unpublished trials, and should not restrict itself to journals written in English.

Studies with small samples are less likely to be published, especially if they have negative results. By emphasizing only those

Table 7.3 Critical appraisal of a systematic review.

Are the results of this systematic review valid?
Did the review address a focused clinical question?*
Were the criteria used to select articles for inclusion appropriate?*
Is it unlikely that important, relevant studies were missed?†
Was the validity of the included studies appraised?†
Were assessments of studies reproducible?†
Were the results similar from study to study?†
Are the valid results of this systematic review important?
What are the overall results of the review?
How precise were the results?
Can you apply this valid, important evidence in caring for your patient?
Can the results be applied to my patient's care?
Were all clinically important outcomes considered?
Are the benefits worth the harms and costs?

From http://www.cebm.net/index.aspx?o=1157 (last accessed 31 October 2007).

* Primary guides.

† Secondary guides.

Table 7.4 Other sources for data on adverse reactions to drugs.

Resource	Source	Comments
Meyler's Side Effects of Drugs	http://www.elsevier.com	Data 1–2 years old
Side Effects of Drugs Annuals	http://www.elsevier.com	Data 1–2 years old
Reactions Weekly and Reactions Database	ADIS Press: http://www.ovid.com	Requires registration and fee
Current Problems in Pharmacovigilance	http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=368	Drug safety bulletin of the MHRA and the Commission on Human Medicines (CHM); issues freely searchable
Australian Adverse Drug Reactions Bulletin	http://www.tga.gov.au/adr/aadrb.htm	Back issues and free email subscription available
European Public Assessment Reports	http://www.emea.europa.eu/index/indexh1.htm	Free, searchable database of reports
MedWatch	http://www.fda.gov/medwatch/	Searchable, database of spontaneous reports of adverse reactions to drugs maintained by the US Food and Drug Administration

studies that are positive, this type of publication bias jeopardizes one of the main goals of meta-analysis (that of achieving an increase in power when pooling results of small studies). Chan and colleagues have also documented selective reporting of outcomes with positive results, a feat that is easily accomplished since most RCTs use multiple outcomes that are not prespecified in the public domain [7]. Creation of study registers (e.g. see http://clinicaltrials.gov/) and advance publication of research designs have been proposed as ways to prevent publication bias (see http://prsinfo.clinicaltrials.gov/icmje.html).

Publication bias can be detected by several methods, such as using a simple graphic test (funnel plot), by calculating the 'fail-safe' N, using Begg's rank correlation method or the Egger regression method, and others [8]. These techniques are of limited value when fewer than 10 RCTs are included. Testing for publication bias is almost never possible in systematic reviews of skin diseases, because of the limited number and sizes of trials.

For many diseases, the studies published are dominated by drug company-sponsored trials of new, expensive treatments. This bias in publication can result in data-driven systematic reviews that draw more attention to those medicines. This problem underlines the need to develop a protocol for a systematic review before the data are explored, as is the current practice with Cochrane reviews. Question-driven systematic reviews answer the clinical questions of most concern to practitioners. In many cases, studies that are of most relevance to doctors and patients have not been done in the field of dermatology due to inadequate sources of independent funding. Systematic reviews that have been sponsored directly or indirectly by industry are also prone to bias by over-inclusion of unpublished 'positive' studies that are kept 'on file' by that company [9]. Until it becomes mandatory to register all clinical trials conducted on human beings in a central register, and to make all of the results available in the public domain, distortions may occur due to selective withholding or release of data.

Generally, reviews that have been conducted by volunteers in the Cochrane Collaboration are of better quality than non-Cochrane reviews [10]. However, potentially serious errors have even been noted in up to a third of such reviews [11]. In general, the studies included in systematic reviews are reviewed by at least two reviewers. Data such as numbers of people entered into studies, numbers lost to follow-up, effect sizes and quality criteria are recorded on predesigned data abstraction forms by at least two reviewers. Differences between reviewers are usually settled by consensus or by a third arbitrator. A systematic review in which there are large areas of disagreement among reviewers should lead the reader to question the validity of the review.

Are the results of the systematic review important?

Results in the individual clinical trials that make up a systematic review may be similar in magnitude and direction (e.g. they may all indicate that treatment A is superior to treatment B by a similar magnitude). In this situation, assuming that publication bias can be excluded, the systematic review should provide results that are most likely to be true and useful. However, it may be impossible to draw firm conclusions from systematic reviews in which studies have results of widely different magnitude and direction.

The magnitude of the difference between the treatment groups in achieving meaningful outcomes is the most useful summary result of a systematic review. The most easily understood measures of the magnitude of the treatment effect are the difference in response rate and its reciprocal, the number needed to treat (NNT) [1,12]. The NNT represents the number of patients that one would need to treat, on average, to achieve one additional cure. Whilst the interpretation of NNT may be straightforward within an individual trial, interpretation of NNT requires some caution within a systematic review, as this statistic is highly sensitive to baseline event rates. For example, if a treatment 'A' is 30% more effective than treatment 'B' for clearing psoriasis, and 50% of people on treatment B are cleared with therapy, then 65% will clear with treatment A. These results correspond to a rate difference of 15% (65 – 50) and an NNT of 7 (1/0.15). This difference sounds quite worthwhile clinically. But if the baseline clearance rate for treatment B in another trial or setting is only 30%, the rate difference will be only 9% and the NNT now becomes 11 and, if the baseline

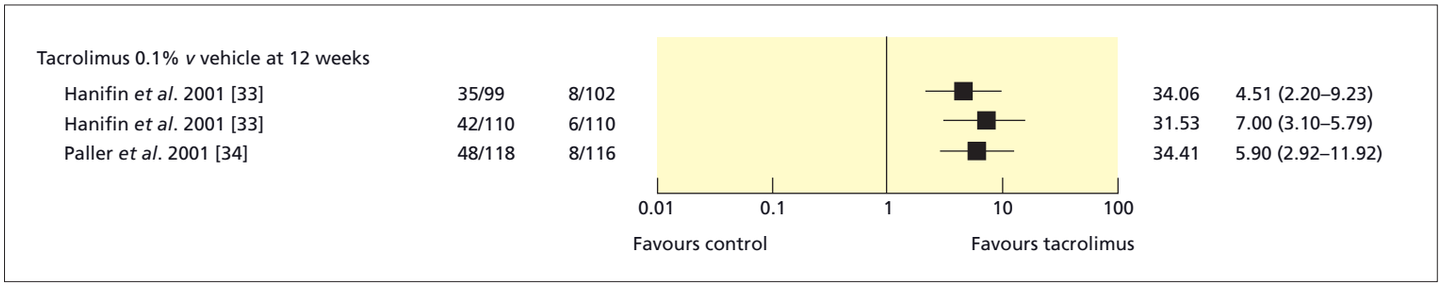


Fig. 7.3 Typical Forest Plot showing the results of a meta-analysis of trials of tacrolimus 0.1% ointment versus vehicle in the management of moderate to severe atopic dermatitis. The X-axis represents the rate ratio of the investigator global assessment of response. From Ashcroft *et al.* [32].

clearance rate is 10%, then the NNT for treatment A will be 33, which is perhaps less worthwhile. In other words, it does not make sense to provide one NNT summary measure within a systematic review if 'control' or baseline event rates differ considerably between studies. Instead, a range of NNTs for a range of plausible control event rates that occur in different clinical settings should be given, along with their 95% confidence intervals.

The precision of the estimate of the differences among treatments presented within a systematic review should always be estimated. The confidence interval provides a useful measure of the precision of the treatment effect [1,13]. The calculation and interpretation of confidence intervals are described below.

The point estimates and confidence intervals of the individual trials and the synthesis of all trials when a meta-analysis is performed are typically displayed graphically in a Forest Plot, an example of which is shown in Fig. 7.3. Results are most commonly expressed as the odds ratio of the treatment effect (that is, the odds of achieving a good outcome in the treated group divided by the odds of achieving a good result in the control group). An odds ratio of 1 (null) indicates no difference between treatment and control and is usually represented by a vertical line passing through 1 on the x-axis. An odds ratio of greater or less than 1 implies that the treatment is superior or inferior to the control respectively. The point estimate of individual trials is indicated by a square whose size is proportional to the size of the trial (i.e. number of patients analysed). The precision of the trial is represented by the 95% confidence interval that appears in Forest Plots as the brackets surrounding the point estimate. If the 95% confidence interval (represented by the brackets) does not cross null (the vertical line representing an odds ratio of 1), then the individual trial is statistically significant at the $P = 0.05$ level. The summary value for all trials is shown graphically as a parallelogram whose size is proportional to the total number of patients analyed from all trials. The lateral tips of the parallelogram represent the 95% confidence interval and if they do not cross null (odds ratio of 1), then the summary value of the meta-analysis is statistically significant at the $P = 0.05$ level. See the section below on Critically Appraising a Study about Adverse Events (Case Control and Cohort Studies) for a discussion of the relationship between odds ratio, relative risk, risk difference and NNT.

Certain conditions must be met when meta-analysis is performed to synthesize results from different trials. The trials should have conceptual homogeneity (i.e. they must involve similar patient populations, have used similar treatments and have measured results in a similar fashion at a similar point in time). There are two main statistical methods by which results are combined: using random effects models or fixed effects models. Random effects models assume that the different studies' results may come from different populations with varying responses to treatment. Fixed effects models assume that each trial represents a random sample of a single population with a single response to treatment. In general, random effects model are more conservative (i.e. they are less likely to show statistically significant results than fixed effects models). When the combined studies have statistical homogeneity (i.e. when the studies are reasonably similar in direction, magnitude and variability), the random effects and fixed effects models give similar results.

The key principle when considering combining results from several studies is that conceptual homogeneity precedes statistical homogeneity. In other words, results of several different studies should not be combined if it does not make sense to combine them; for example, if the patient groups or interventions studied are not sufficiently similar to each other. Although what constitutes 'sufficiently similar' is a matter of judgement, the important thing is to be explicit about one's decision to combine or to not combine different studies. Tests for statistical heterogeneity are typically of very low power, so that failure to detect statistically significant heterogeneity does not 'prove' homogeneity. When there is evidence of heterogeneity between studies, the reasons for the heterogeneity (such as different disease subgroups, intervention dosage or study quality) should be sought.

Sometimes, the robustness of an overall meta-analysis is tested further by means of a sensitivity analysis. In a sensitivity analysis the data are re-analysed but exclude those studies that are suspect because of quality or patient factors, in order to see whether their exclusion makes a substantial difference to the direction or magnitude of the main, original results. In some systematic reviews in which a large number of trials have been performed, it is possible to evaluate whether certain subgroups (e.g. children versus adults) are more likely to benefit than others. Subgroup analysis is rarely possible in dermatology because few trials are available.

The conclusions in the discussion section of a systematic review should closely reflect the data that have been presented within that review. The authors should make it clear which of the treatment recommendations are based on the review data and which reflect their own judgements. In addition to making clinical recommendations of therapies when evidence exists, many reviews in dermatology find little evidence to address the questions posed.

This lack of conclusive evidence does not mean that the review is a waste of time, especially if the question addressed appears to be an important one. For example, a systematic review of antistreptococcal therapy for guttate psoriasis provided the authors with an opportunity to call for primary research in this area, and to make recommendations on study design and outcomes that might help future researchers [14].

Can the results of the systematic review be applied to your specific patient?

Applying evidence summarized in a systematic review to specific patients requires the same processes used to apply the results of individual controlled clinical trials to patients (see below).

Critically appraising individual clinical trials [1,2,15,16]

Are the results of the trial valid?

To determine whether an individual clinical trial is valid, pay particular attention to the features that strengthen clinical trials and that help to validate their conclusions (Table 7.5). The 'big three' that should always be assessed are:

Table 7.5 Critical appraisal of a paper about therapy.

Are the results of this single preventive or therapeutic trial valid?
Was the assignment of patients to treatments randomized?
—and was the randomization list concealed?
Were all patients who entered the trial accounted for at its conclusion?
—and were they analysed in the groups to which they were randomized?
Were patients and clinicians kept 'blind' to which treatment was being received?
Aside from the experimental treatment, were the groups treated equally?
Were the groups similar at the start of the trial?
Are the valid results of this trial important?
Calculations:
Intervention Response Rate (IRR)
Comparison (Intervention) Response Rate (CRR)
Difference in Response Rates (DRR (IRR – CRR))
Number Needed to Treat (NNT (1/DRR))
What is the 95% confidence interval of the difference in response rates (DRR)?*
What is the 95% confidence interval of the NNT?**
Can you apply this valid, important evidence in caring for your patient?
Do these results apply to your patient?
Is your patient so different from those in the trial that its results can't help you?
How great would the potential benefit of therapy actually be for your individual patient?
Do the regimen and its consequences satisfy your patient's values and preferences?
Do your patient and you have a clear assessment of your values and preferences?
Do this regimen and its consequences meet them?

From http://www.cebm.net/index.aspx?o=1157.

* The 95% confidence interval of the difference in response rates (DRR) is from:

$$\text{DRR} - 1.96x\text{SE to DRR} + 1.96x\text{SE where SE} = \sqrt{\frac{IRR(1-IRR)}{\#\,\text{Intervention Patients}} + \frac{CRR(1-CRR)}{\#\,\text{Comparison Patients}}}$$

** The 95% confidence interval of the NNT = 1/limits on the confidence interval of its DRR.

1 Is the method of generating the randomization sequence and subsequent concealment of allocation of participants clearly described and appropriate?
2 Were participants and study assessors masked to the intervention?
3 Were all those who originally entered the study accounted for in the results and analysis (i.e. was an intention-to-treat analysis performed)?

Ideally, patients should be randomly assigned to treatment groups to avoid the introduction of biases and to distribute intrinsic prognostic factors equally among treatment groups. Randomization controls patient selection and evaluation bias by physicians and study personnel. Non-randomized studies have limited value in distinguishing useful from useless or even harmful therapy. When compared with RCTs, studies in which patients are not allocated randomly more commonly show larger effects, many of which are false positive. For example, the belief that use of azathioprine reduced the dose of corticosteroids necessary to treat bullous pemphigoid was suggested by several uncontrolled or non-randomized studies. However, a randomized trial of the effects of azathioprine on corticosteroid dose in patients with bullous pemphigoid indicated that azathioprine had no or negligible effects on remission or corticosteroid doses [17].

Randomization has the disadvantage of depending on chance for an equal statistical distribution of prognostic factors among groups. Therefore, it is always important to identify known prognostic factors such as disease severity, and to compare their distribution among treatment groups at baseline. The common practice of assigning *P* values to differences in characteristics at baseline is inappropriate. Although demographic and known prognostic factors may not be equally distributed among treatment groups when patients are randomly assigned to them, the impact of the unequal distribution of prognostic factors on treatment results should be assessed. Inequality of groups in randomized trials is a more significant problem in studies with few patients but can usually be adjusted for in appropriate analyses.

When patients are assigned randomly, the method used to randomize should be reported. The most widely accepted and unbiased methods are using sealed random numbers obtained from tables, or random numbers generated by computers. In this method, patients are assigned a random number after they are admitted to a trial. That number has been previously assigned to a treatment group and the assignment is unknown to the patient and the investigator. Correct randomization or concealment of assignment is often not done in published studies, and the methods of randomization are rarely reported. Many commonly encountered methods of randomization (for example, on the basis of admitting team, alternative assignment, odd or even days of entry, birth dates, social security numbers, or day of the week), can lead to significant introduction of selection bias. For example, a physician who would like a new treatment to be superior in efficacy to an older treatment may be able to enter patients most likely to respond to treatment on even days and patients least likely to respond on odd days if he or she knows that the new treatment is assigned on even days and the older treatment is assigned on odd days.

Concealment of treatment allocation refers to the steps taken by the trialists to conceal the allocation of participants to the intervention groups from those recruiting the trial participants. Concealing the allocation of interventions from those recruiting participants is a crucial step in the progress of an RCT. Concealing the sequence from recruiters is adequate if investigators and patients cannot foresee the assignment to intervention groups (e.g. using numbered and coded identical sealed boxes prepared by central pharmacy, or sealed opaque envelopes); conversely, it is inadequate if the allocation schedule is open for the recruiting physician to view beforehand (e.g. using unsealed envelopes).

The randomization list should be kept away from enrolment sites (for example by a central clinical trials office or pharmacy). Internet randomization by a third party, whereby details of a new potentially eligible trial participant are entered irrevocably onto a trial database before an allocation code is offered, is another very secure way of concealing allocation.

It is important to make the evaluation of the outcome of a trial as masked as possible to avoid the introduction of bias. Masking can refer to at least four groups of people: those recruiting patients, the study participants themselves, those assessing the outcomes in study participants and those analysing the results. Masking of physicians and patients is especially important when subjective outcomes such as pain are being measured. Masking of patients and evaluators also ensures that ancillary therapies and outcome evaluations are applied equally, thus minimizing performance bias. A patient who is known to be receiving a new treatment may be observed more closely, may receive better ancillary care and may have different expectations compared with a control patient. Changes in disease status may receive greater (or lesser) emphasis, and adverse events may similarly receive more (or less) attention. Masking is less of an issue for some studies that use very objective outcomes such as death.

However, masking is often not possible. In dermatology, many treatments produce skin changes that make it apparent what treatment is being used. For example, the drying effects of topical and systemic retinoids and the tanning effects of UVB therapy make the recipients of those therapies readily apparent. An unmasked study may still be valid but the designers of an unmasked study must make allowances for the possibility that bias may have been introduced and should increase the statistical rigor for demonstrating differences.

The whole purpose of randomization is to create two or more groups that are as similar to each other in as many respects as possible, the only difference between them being the intervention under study. In this way the additional effects of the intervention can be assessed. A potentially serious violation of this principle is the failure to take into account all those who were randomized when conducting the final main analysis, for example participants who deviate from the study protocol, those who do not adhere to the interventions and those who subsequently drop out for other reasons. People who drop out of trials tend to differ from those who remain in them in several ways; for example, they may drop out because they encounter adverse events, get worse (or no better), or simply because the proposed regimen is too complicated for them to follow. They may also drop out because the treatment is working so well. Ignoring participants who have dropped out in the analysis is not acceptable, as their very reason for dropping out is likely to be related in some direct or indirect way to the study interventions. Excluding participants who drop out at any stage after randomization potentially biases the results. One way to reduce such bias is to perform an intention-to-treat (ITT) analysis, in which all those initially randomized are included in the final analysis.

Unless one has detailed information on why participants dropped out of a study, it cannot be assumed that an analysis of those remaining in the study to the end is representative of those randomized to the groups at the beginning. Failure to perform an ITT analysis may inflate or deflate estimates of treatment effect. Performing an ITT analysis is often regarded as a major criterion by which the quality of an RCT is assessed.

It may be entirely appropriate to conduct an analysis of all those who remained at the end of a study (a 'per protocol' analysis) alongside the ITT analysis. Discrepancies between results of ITT and per protocol analyses may indicate the potential benefit of the intervention under ideal compliance conditions, and identifies a need to explore ways of reformulating the intervention so that fewer participants drop out of the trial. Discrepancies may also indicate serious flaws in the study design. A good discussion of when and where it might be appropriate to exclude trial participants from the main analysis may be found in [18].

Other features that strengthen the validity of trials [1,2,15,16]

In evaluating a clinical trial in dermatology, look for clinical outcome measures that are clear cut and clinically meaningful to you and your patients. For example, in a study of a systemic treatment for warts, complete disappearance of warts is a meaningful outcome, whereas a decrease in the volume of warts is not. Historically, three principal methods are used to determine patient outcomes in dermatological clinical trials. The first involves examining patients before, during and at the conclusion of treatment, and reporting how the patients appear at the various time points. The second involves determining the degree of improvement during treatment [19]. A third method, determining the impact of therapy on the quality of the patient's life, is being increasingly used in dermatological trials.

An example of the first method is commonly encountered in therapeutic trials of psoriasis. A common practice is to assign numerical values to the amount of erythema, scaling and degree of infiltration, to determine the area of the body surface involved, and to formulate an 'index' by calculating a derivative of some product of these four numbers. The overall condition of the patient can then be represented by this index. A common example is the psoriasis area and severity index (PASI) that ranges from 0 to 72 [20]. The major problem with such indices is that they presume that area of involvement corresponds with severity of disease. For example, a patient with thick plaque-type psoriasis of the knees, elbows and scalp may have the same index (score) as a patient with diffuse but minimal psoriasis of the trunk and arms. Whereas the former patient is notoriously difficult to treat, the latter will generally respond rapidly and easily to many forms of therapy.

The second problem with indices is that they lend an air of accuracy to the analysis and presentation of data that are not warranted. For example, Tiling-Grosse and Rees demonstrated that physicians and medical students were poor at estimating the area of skin disease and, therefore, some of the components that make up indices may be inaccurate [21]; this potential inaccuracy is magnified in severity indices such as PASI, where scores for surface are multiplied with scores for erythema and scaling. Finally, calculating the means, differences in means and percentages of change in indices in response to treatment often do not convey an accurate clinical picture of the changes that have occurred.

The second method of assessment groups patients according to their degree of improvement. Treatments are then compared by their ability to move patients to higher degrees of improvement. There are two major problems with this form of assessment. The first is that the categories of improvement are often not well defined. The second problem is that the categories are not additive. That is, 60–80% improvement is often assumed to be twice as good as 20–40%, although no such numerical relationship exists between these subjectively defined categories.

To be most useful, the outcome variables to measure must be clearly defined, as objective as possible and should have clinical and biological significance. The best indices and scales are the ones that accurately reflect the state of the disease and the ones with validity and reliability that have been verified by previous work. The development of scales and indices for cutaneous diseases, and testing their validity, reproducibility and responsiveness, has been inadequate. Therefore a lack of clearly defined and useful outcome variables remains a major problem in interpreting dermatological clinical trials.

Until better scales are developed, trials with the simplest and most objective outcome variables are the best. They lead to the least amount of confusion and have the strongest conclusions. Thus, trials in which a comparison is made between death and survival, patients with recurrence of disease and those without recurrence, or patients who are cured and those who are not cured, are studies with outcome variables that are easily understood and verified. For trials in which the outcomes are less clear-cut and more subjective in nature, a simple ordinal scale is probably the best choice. The best ordinal scales involve a minimum of human judgement, have a precision that is much smaller than the differences being sought and are sufficiently standardized that they can be used by others and will produce similar results.

In addition to being clearly defined, outcome variables should have clinical and biological significance. For example, in a therapeutic trial of patients with severe acne, treatment was associated with a decrease in lesion count from a mean of 400 to a mean of 350. This numerical difference may be of statistical significance, but it does not convey what the clinical significance of the change in lesion number represents. This result may mean that some patients with severe acne cleared completely whereas other patients remained the same or got worse. It could also mean that most patients got slightly better. Furthermore, does an individual patient look better when their lesion number has been reduced from 400 to 350? Are scarring and complications less?

To strengthen clinical trials and to help validation of their conclusions, the outcome variables should be few in number and should be chosen before initiation of the study. All trial protocols should be registered in clinical trial registries in the public domain. Having many outcome variables increases the likelihood that spurious, chance differences will be detected. An ineffective treatment may be claimed to be efficacious when tested using poorly designed outcome assessment tools. Conversely, an effective therapy may be found ineffective by an insensitive scale.

Special precautions are recommended when dealing with 'substitute or surrogate endpoints', especially when no differences are detected in clinically important outcomes. Examples of such endpoints include CD4:CD8 ratios instead of survival in studies of treatments of AIDS, ANA levels or sedimentation rates instead of clinical measures of disease activity in lupus erythematosus, and volume of warts instead of proportion of patients cleared of warts. Carefully chosen and validated surrogate endpoints often allow studies to provide answers to questions that would typically require much larger or longer trials if the targeted clinical endpoint were utilized. For example, a well-designed, short clinical trial may be sufficient to demonstrate that a new drug effectively lowers serum cholesterol or that another drug is effective in controlling hypertension. In both cases much longer and larger studies would be required to demonstrate that the cholesterol-lowering drug and the antihypertensive drug reduced morbidity and mortality from atherosclerotic and hypertensive cardiovascular diseases, respectively. Surrogate endpoints must, however, correlate with clinical outcomes, and their validity must be demonstrable in earlier studies.

Are the results of the clinical trial important? [1,2,15,16]

Once sound, clinically relevant outcome measures are chosen, the magnitude of the difference between the treatment groups in achieving these meaningful outcomes, the NNT and the precision of these estimates should be determined.

A trial comparing placebo, aciclovir, prednisone and aciclovir–prednisone in the treatment of herpes zoster [22] provides good examples of the application of the concepts of NNT and confidence intervals. At day 30 of the trial, 48 of 52 patents treated with aciclovir were totally healed compared with 22 of 52 patients who received placebo. The response rates for aciclovir and placebo were 0.92 and 0.42 respectively, and the difference in response rates was 0.5. The NNT was therefore 2.0 (1/0.5). This result means that, for every two patients treated with aciclovir instead of placebo, one additional patient would be totally healed by day 30. The 95% confidence interval for the difference in response rates is from 0.35 to 0.65, and the 95% confidence interval for the NNT is 2 to 3.

Misinterpreting trials that fail to show statistically significant differences among treatments is a common error of interpretation in dermatology clinical trials. It is important to remember that 'not statistically significant' means that a difference has a reasonably high probability of having been due to chance; it does not mean that there is no difference or that treatment is necessarily ineffective. Significant differences in treatment effects in comparison trials may be missed if the number of subjects tested is small. For example, in a 1978 survey of 71 published trials with negative

results, Freiman *et al*. found that a 25% or 50% improvement in outcome might have been missed in 57 (80%) and 34 (48%) of the studies respectively [23]. A follow-up study conducted by Moher *et al*. in 1994 indicated that 25% or 50% improvements in outcome might have been missed in 84% and 64% of 102 negative studies, respectively [24]. The sample sizes of many dermatological trials are often inadequate to detect clinically important differences. For example, 58 clinical trials with negative conclusions, published in three British dermatological journals over 4 years, were reviewed to determine the risk of their having missed an effective treatment. All but one of the 44 evaluable trials had a greater than 1 in 10 risk of having missed a 25% relative treatment difference (median risk 81%), and 31 of the trials (70%) were so small that they had a greater than 1 in 10 risk of having missed a 50% relative treatment difference (median risk 42%) [25].

Can the results of the trial be applied to your specific patient?

Applying external evidence to the patient in front of you is one of the most difficult steps of EBM. Having identified some relevant and valid information from clinical trials in relation to a clinical question generated by a patient encounter, four questions now need to be asked in order to guide the application of such information to that patient. They are listed in Table 7.4.

When faced with the task of determining whether the results of a particular study are applicable to a specific patient, physicians should ask themselves whether there are any compelling reasons that the results should not be applied to the patient, rather than expecting a perfect match of the study participants and patient. Only if the answer is 'yes' should the study's results be considered not applicable to the patient. Whilst participants in clinical trials may be different from the patient who originally prompted you to ask an evidence-based question in obvious biological ways, such as age, sex and clinical disease type, in most circumstances these differences do not prevent you from making some useful generalizations from the literature. Perhaps one of the most frequent problems encountered is that of having to generalize trials of adult therapy to children, in whom RCTs are rarely performed. Yet, children can suffer almost all of the 'adult' skin diseases, and practitioners frequently have no choice but to use adult-based data as a means of informing treatment decisions.

Critical appraisal of a study about a diagnostic test [1,2]

Are the results valid?

To be valid, studies about diagnostic tests should include masked comparison with a criterion ('gold') standard, evaluation in an appropriate spectrum of patients and consistent application of the criterion standard (Table 7.6). Few studies in dermatology meet this standard.

Are the results important?

Important terms and concepts that must be understood to determine whether the results of a paper about a diagnostic test are clinically important include the likelihood ratio, the pre-test probability, the post-test probability, and the threshold for action. The likelihood ratio is the percentage of people with the disease who have a positive test divided by the percentage of people who do not have the disease but who have a positive test. The likelihood ratio is traditionally taught as the (sensitivity/[1 – the specificity]); it provides an estimation of how much higher the likelihood of the disease is, given a positive test (post-test probability), compared with the probability before the test is done (pre-test probability). An ideal test is one that will almost always be positive when the disease is present and negative when the disease is absent. Thus, it is one with a high sensitivity and specificity. Such a test would have a very high likelihood ratio.

In order for the likelihood ratio to be useful, one has to have an idea of how likely the disease is to be present before the test is done (i.e. the pre-test probability) and a sense of how certain one needs to be to conclude that the patient has the disease and to act on it (i.e. the threshold for action) [26]. The pre-test probability is determined from available published data or is based on physician experience and judgment. Once the pre-test probability is known or estimated and the likelihood ratio determined, a nomogram can be used to estimate the post-test probability (Fig. 7.4).

If the nomogram is not available, the calculations can be done manually, but require conversion of probabilities to odds. The

Table 7.6 Critical appraisal of a paper about a diagnostic test.

Are the results of this diagnostic study valid?

- Was there an independent, blind comparison with a reference ('gold') standard of diagnosis?
- Was the diagnostic test evaluated in an appropriate spectrum of patients (like those in whom it would be used in practice)?
- Was the reference standard applied regardless of the diagnostic test result?

Are the valid results of this diagnostic study important?

Calculations:

		Target disorder	
		Present	Absent
Diagnostic test result	Positive	a	b
	Negative	c	d

Sensitivity = a/(a + c) Specificity = d/(b + d)

Likelihood ratio for a positive test result = [a/(a + c)]/[b/(b + d)] = sensitivity/(1 – specificity)

Likelihood ratio for a negative test result = [c/(a + c)]/[d/(b + d)] = (1 – sensitivity)/specificity

Can you apply this valid, important evidence about a diagnostic test in caring for your patient?

- Is the diagnostic test available, affordable, accurate and precise in your setting?
- Can you generate a clinically sensible estimate of your patient's pre-test probability (from practice data, from personal experience, from the report itself or from clinical speculation)?
- Will the resulting post-test probabilities affect your management and help your patient? (Could it move you across a test-treatment threshold? Would your patient be a willing partner in carrying it out?
- Would the consequences of the test help your patient?

From http://www.cebm.net/index.aspx?o=1157.

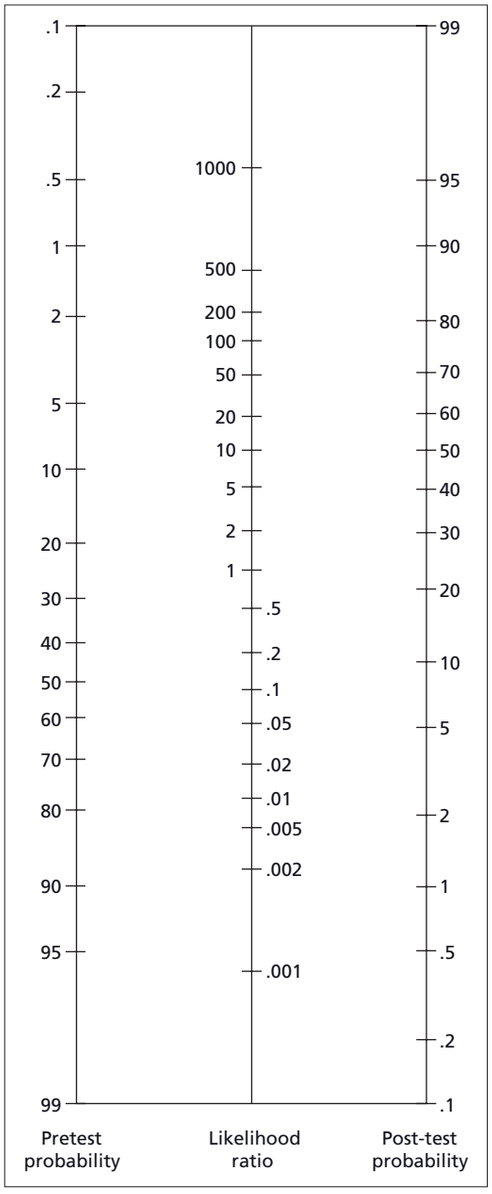


Fig. 7.4 Nomogram for determining the post-test probability. To determine the post-test probability, draw a straight line through the pre-test probability and the likelihood ratio and read the post-test probability on the right.

odds of disease is defined as the probability of disease divided by one minus the probability (odds = probability/[1 − probability]). For a defined group of individuals or patients, it can be also calculated as the ratio of the number of those with disease to those without disease. Thus, if the probability (proportion) of a disease is 0.20 (20%), the odds of that disease are 0.20/(1 − 0.20) = 0.20/0.80, that is 1 : 4. This result means that for every person with the disease, there are four people without the disease. The post-test odds are equal to the pre-test odds times the likelihood ratio (post-test odds = pre-test odds × LR). The formula (probability = odds/[odds +1]) is used to convert odds back to probability.

For example, suppose that based on clinical judgement the estimated probability that a patient with a cluster of vesicles on his cheek has herpes zoster is 0.6 (60%), then his odds of having herpes zoster are 1.5 : 1 (calculated from 0.6/[1 − 0.6]). Assume, for this example, that the sensitivity and specificity of a direct fluorescent antibody (DFA) test for herpes zoster are 80% and 96% respectively. Therefore, the likelihood ratio for a positive DFA is 0.80/[1 − 0.96] = 20. If this patient's DFA test is positive, his post-test odds are 30 (calculated from 1.5 × 20) and the post-test probability of herpes zoster is 0.97 (97%) (calculated from 30/[30 + 1]). This probability is certainly high enough to act upon.

Whether formally or informally, physicians develop thresholds of certainty at or above which they are comfortable with establishing a diagnosis and acting on the diagnoses. Action may take the form of communicating the diagnosis or prognosis to the patient, prescribing treatment or referring the patient. When history and physical evidence lead a clinician to suspect a diagnosis, but the degree of certainty does not exceed the threshold for establishing a diagnosis, a test is done to increase the probability that the disease is present above the clinician's threshold for action [26]. Studies reporting diagnostic tests in dermatology should adhere to established, international reporting standards [27].

Can the results of the diagnostic study be applied to your specific patient?

The key questions to ask to determine whether the results of a diagnostic study can be applied to a specific patent are shown in Table 7.5.

Critically appraising a study about adverse events (case–control and cohort studies) [1,2]

Are the results valid?

To be valid, studies about the harmful effects of exposures should include cohorts with comparable groups of exposed and unexposed individuals (or cases and controls), objective outcome measures and adequate follow-up. In addition, the results should make clinical and biological sense (Table 7.7). Few dermatological studies meet these criteria.

Are the results important? [1,2,28]

Important terms and concepts that must be understood to determine whether the results of a paper about harmful effects of exposures are clinically important include case–control and cohort studies, risk ratios and odds ratios. In a cohort study, a group of individuals who are exposed to an agent is compared with an appropriately selected unexposed control group, and both groups are followed either until an event of interest occurs or for a prespecified length of time. The association of exposure to the harmful outcome is expressed as the relative risk (Table 7.6). A relative risk of 1 implies that there is no association. If the relative risk is greater than unity, then the result implies a positive association between exposure and the harmful outcome. If it is less than unity, then the implication is of an inverse association. However, in order to infer a causal association reflected by either an increase in risk (relative risk of more than 1), or a protective effect (relative risk less than 1), it is important to evaluate the validity and precision of the relative risk estimate. The precision can be readily assessed by means of the 95% confidence interval. A confidence interval that does not include 1.0 denotes a statistically significant association. Because

Table 7.7 Critical appraisal of a paper about harm.

Are the results of this harm study valid?

- Were there clearly defined groups of patients, similar in all-important ways other than exposure to the treatment or other cause?
- Were treatment exposures and clinical outcomes measured in the same ways in both groups (e.g. was the assessment of outcomes either objective (e.g. death) or blinded to exposure)?
- Was the follow-up of study patients complete and long enough?
- Do the results satisfy some 'diagnostic tests for causation'?
  - Is it clear that the exposure preceded the onset of the outcome?
  - Is there a dose–response gradient?
  - Is there positive evidence from a 'de-challenge–re-challenge' study?
  - Is the association consistent from study to study?
  - Does the association make biological sense?

Are the valid results from this harm study important?

Calculations:

		Adverse outcome	
		Present (case)	Absent (control)
Exposed to the Treatment	Yes (Cohort)	a	b
	No (Cohort)	c	d

In a randomized trial or cohort study: relative risk = [a/(a + b)]/[c/(c + d)]

In a case–control study: odds ratio (or relative odds) = ad/bc

Should these valid, potentially important results of a critical appraisal about a harmful treatment change the treatment of your patient?

- Can the study results be extrapolated to your patient?
- What are your patient's risks of the adverse outcome?
- What are your patient's preferences, concerns and expectations from this treatment?
- What alternative treatments are available?

From Sackett *et al.* [31].

the most likely result of a study is the point estimate (i.e. the reported result), the observed association (expressed by the point estimate) may be causal, even if the confidence interval includes 1.0 due to a small sample size. Other criteria, such as dose–response effect, consistency, biological plausibility and specificity, need to be considered when inferring causality from observational data [29].

Case–control studies can be used when the undesirable outcome (e.g. lymphoma) is recognized but the causative agent has not yet been discovered. Case–control studies are also used when there is a very long time period between exposure and outcome, or when the frequency of adverse events is very small. In a case–control study, patients with a disease of interest are compared with appropriately selected controls. The odds of exposure to suspected causative agents are ascertained in cases and controls (Table 7.6). The odds of an event are the ratio of the number of events to the number of non-events. Events are exposures to potentially harmful risk factors in case–control studies. The odds of exposure of the cases are divided by the odds of exposure among the controls to derive the 'odds ratio', which is a good estimate of the relative risk when the outcome (e.g. disease or death) is relatively rare (i.e. when it occurs in less than 5% of the exposed subjects). The association between exposure and outcome is expressed as the odds ratio in case–control studies. An odds ratio of 1 implies no association. If the odds ratio is greater than 1, then the result implies a positive association between exposure and the harmful outcome. If the odds ratio is less than 1, then the result implies a protective effect of the exposure. As noted above, it is important to evaluate the validity and precision of the odds ratio estimate by examining the 95% confidence interval.

For example, suppose a case–control study was performed to study the relationship between limb deformity and exposure to thalidomide. The results of the study indicated that patients with limb deformities were more likely than controls to have been exposed to thalidomide *in utero*. The odds ratio for thalidomide exposure was 3.5 and the confidence interval was from 1.8 to 6.6. Thus the odds that patients with limb deformities were exposed to thalidomide *in utero* were 3.5 times the odds of thalidomide exposure in controls. Since the odds ratio is greater than 1, and its 95% confidence interval does not include 1, the result implies that the positive association between thalidomide use and limb deformities was not likely to have been due to chance. These results (an odds ratio of 3.5 and confidence interval of 1.8 to 6.6) were actually the results of a study by Wolf *et al.* who studied the relationship between sunscreen use and melanoma in a case–control study in Austria [30]. Their results indicated that patients with melanoma were more likely than controls to have used sunscreen often. In order to infer causality it is important to assess whether the results could have resulted from confounding (i.e. the association between exposure and outcome could have been explained by other factors, such as age or sex), whether there might have been any bias (for example, people with melanoma may have been more likely to recall sun protective behaviour), and whether the results are biologically plausible.

To add confusion to an already difficult area, clinical researchers will often report results of meta-analyses, cohort studies and RCTs using odds ratios. Odds ratios are used because they have stronger statistical properties than other measures [28]. For example, odds ratios can take any value between zero and infinity, are symmetrical in a log scale and can be used to make adjustments for confounding factors (using multiple regression analysis). Unfortunately, they are the least intuitively understood measure of association. If a meta-analysis, controlled trial or cohort study is reported using odds ratios, the relative risk, the difference in response rates or the NNT can often be calculated if the primary data are provided. Alternatively, these more readily understandable measures can be derived if the number of subjects in each group, odds ratio and overall event rate are provided (http://www.cebm.net/index.aspx?o=1044).

Can the results be applied to your specific patient?

The key questions to ask to determine whether the results of a case–control or cohort study can be applied to a specific patent are shown in Table 7.6.

Conclusions

EBM is the use of the best current evidence in making decisions about the care of individual patients. It relies on asking clinical

questions, finding the best evidence to answer the questions, critically appraising the evidence, applying the evidence to specific patients and saving the critically appraised evidence. The EBM approach is most appropriate for common, frequently encountered conditions.

Results from well-designed clinical studies on patients are at the pinnacle of the hierarchy of evidence used to practise evidence-based medicine. Recommendations about treatment, diagnosis and harm made in this textbook and in other sources should take into account the validity, magnitude, precision and applicability of the evidence upon which it is based.

References

1 Bigby M, Corona R, Szklo M. Evidence-based medicine. In: Freedberg IM, Eisen AZ, Wolf K, Austen, KF, Goldsmith LA, Katz SI, eds. *Fitzpatrick's Dermatology in General Medicine*, 7th edn. New York: McGraw-Hill, 2008: 8–18.

2 Bigby M. Evidence-based medicine in a nutshell. A guide to finding and using the best evidence in caring for patients. *Arch Dermatol* 1998; **134**: 1609–18.

3 Bigby M, Williams HC. Appraising systematic reviews and meta-analyses. In: Williams HC, Bigby M, Diepgen T, Herxheimer A, Naldi L, Rzany B, eds. *Evidence-Based Dermatology*, 2nd edn. London: BMJ Books, 2008: 38–43.

4 Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of reporting of meta-analyses. *Lancet* 1999; **354**: 1896–900.

5 Sterne JA, Egger M, Smith GD. Systematic reviews in health care: Investigating and dealing with publication and other biases in meta-analysis. *BMJ* 2001; **323**: 101–5.

6 Dickersin K, Min YI, Meinert CL. Factors influencing publication of research results. Follow-up of applications submitted to two institutional review boards. *JAMA* 1992; **267**: 374–8.

7 Chan AW, Altman DG. Identifying outcome reporting bias in randomised trials on PubMed: review of publications and survey of authors. *BMJ* 2005; **330**: 753–9.

8 Macaskill P, Walter SD, Irwig L. A comparison of methods to detect publication bias in meta-analysis. *Stat Med* 2001; **20**: 641–54.

9 Jorgensen AW, Hilden J, Gotzsche PC. Cochrane reviews compared with industry supported meta-analyses and other meta-analyses of the same drugs: systematic review. *BMJ* 2006; **333**: 782.

10 Collier A, Heilig L, Schilling L, Williams H, Dellavalle RP. Cochrane Skin Group systematic reviews are more methodologically rigorous than other systematic reviews in dermatology. *Br J Dermatol* 2006; **155**: 1230–5.

11 Olsen O, Middleton P, Ezzo J, Gøtzsche PC *et al*. Quality of Cochrane reviews: assessment of sample from 1998. *BMJ* 2001; **323**: 829–32.

12 Manriquez JJ, Villouta MF, Williams HC. Evidence-based dermatology: Number needed to treat and its relation to other risk measures. *J Am Acad Dermatol* 2007; **56**: 664–71.

13 Bigby M. Confidence intervals. *Arch Dermatol* 2000; **136**: 386–7.

14 Owen CM, Chalmers RJ, O'Sullivan T, Griffiths CE. Antistreptococcal interventions for guttate and chronic plaque psoriasis. *Cochrane Database Syst Rev* 2000; **2**: 1.

15 Bigby M, Gadenne A-S. Understanding and evaluating clinical trials. *J Am Acad Dermatol* 1996; **34**: 555–90.

16 Williams HC. How to critically appraise a randomized controlled trial. In: Williams HC, Bigby M, Diepgen T, Herxheimer A, Naldi L, Rzany B, eds. *Evidence-Based Dermatology*, 2nd edn. London: BMJ Books, Blackwell Publishing, 2008: 44–51.

17 Guillaume J-C, Vaillant L, Bernard P *et al*. Controlled trial of azathioprine and plasma exchange in addition to prednisolone in the treatment of bullous pemphigoid. *Arch Dermatol* 1993; **129**: 49–53.

18 Fergusson D, Aaron SD, Guyatt G, Hebert P. Post-randomisation exclusions: the intention to treat principle and excluding patients from analysis. *BMJ* 2002; **325**: 652–4.

19 Allen AM. Clinical trials in dermatology, Part 3: Measuring responses to treatment. *Int J Dermatol* 1980; **19**: 1–6.

20 Fredriksson T, Pettersson U. Severe psoriasis-oral therapy with a new retinoid. *Dermatologica* 1978; **157**: 238–44.

21 Tiling-Grosse S, Rees J. Assessment of area of involvement in skin disease: a study using schematic figure outlines. *Br J Dermatol* 1992; **128**: 69–74.

22 Whitley R, Weiss H, Gann J *et al*. Acyclovir with and without prednisone for the treatment of herpes zoster. *Ann Intern Med* 1996; **125**: 376–83.

23 Freiman JA, Chalmers TC, Smith JH, Kuebler RR. The importance of beta, the type ii error and sample size in the design and interpretation of the randomized control trial. *N Engl J Med* 1978; **299**: 690–4.

24 Moher D, Dulberg CS, Wells GA. Statistical power, sample size, and their reporting in randomized controlled trials. *JAMA* 1994; **272**: 122–4.

25 Williams HC, Seed P. Inadequate size of 'negative' clinical trials in dermatology. *Br J Dermatol* 1993; **128**: 317–26.

26 Bigby M. Ruling out the diagnosis. *Arch Dermatol* 1996; **132**: 697–8.

27 Bossuyt PM, Reitsma JB, Bruns DE *et al*. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. *BMJ* 2003; **326**: 41–4.

28 Bigby M. Odds ratios and relative risks. *Arch Dermatol* 2000; **136**: 770–1.

29 Thygesen LC, Andersen GS, Andersen H. A philosophical analysis of the Hill criteria. *J Epidemiol Community Health* 2005; **59**: 512–6.

30 Wolf P, Quehenberger F, Mullegger R, Stranz B, Kerl H. Phenotypic markers, sunlight-related factors and sunscreen use in patients with cutaneous melanoma: an Austrian case–control study. *Melanoma Res* 1998; **8**: 370–8.

31 Sackett D, Richardson W, Rosenberg W, Haynes R. *Evidence-Based Medicine*: *How to Practice and Teach EBM*. Edinburgh: Churchill Livingstone, 1996.

32 Ashcroft DM, Dimmock P, Garside R, Stein K, Williams HC. Efficacy and tolerability of topical pimecrolimus and tacrolimus in the treatment of atopic dermatitis: meta-analysis of randomised controlled trials. *BMJ* 2005; **330**: 516–25.

33 Hanifin JM, Ling MR, Langley R, Breneman D, Rafal E. Tacrolimus ointment for the treatment of atopic dermatitis in adult patients: part I, efficacy. *J Am Acad Dermatol* 2001; **44**: S28–38.

34 Paller A, Eichenfield LF, Leung DYM, Stewart D, Appell M. A 12-week study of tacrolimus ointment for the treatment of atopic dermatitis in pediatric patients. *J Am Acad Dermatol* 2001; **44**: S47–57.

Shortcut method and evaluating the data in clinical research papers

Shortcut method for appraising clinical research papers [1]

The EBM criteria for appraising evidence represent subsets of other schemes for appraising the quality of clinical research. These method include QUOROM (Quality of Reporting of Meta-Analyses), AMSTAR (Assessment of Multiple Systematic Reviews), CONSORT (Consolidated Standards of Reporting Trials), STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) and the methods of DerSimonian, Evans and Pollock, Poynard, Nyberg and many others [1–5]. What is common to all of these methods is that they require reading the entire paper, especially the methods section. Doing so is often not possible for busy clinicians trying to find answers to specific problems. Nor is it the most efficient use of his or her time. Instead, a shortcut method for evaluating the literature is available (Table 7.8). A shortcut method to evaluate clinical trials will enable you to use your time efficiently. It allows you to decide not to read the majority of poorly conceived, designed, executed or reported trials, or those trials with insignificant results. After each step you should re-ask the questions, 'Am I still interested in this trial?' and 'Is it worth spending my valuable time on it?'.

First read the title. If the title holds interest for you, read the abstract. If after reading the abstract you still feel that the article

Table 7.8 Shortcut method.

Step	Comments
Read title	If interesting, continue.
Read abstract	If still worthy of your time, continue.
Look at figures and tables	Find most important data. Are the data adequately reported? Is there a control group? Are outcomes clinically important? Are data subjected to statistical testing and are tests used correctly? If still worthy of your time, continue.
Read results	Are complications reported? Are compliance and lost patients considered? Ask yourself 'If everything the authors say is true, is it important for my patients, my practice or for the field of dermatology?' If 'no,' stop reading; if 'yes' or 'possibly,' continue.
Read methods	How were patients chosen and allocated? Are outcomes clearly defined and assessed blindly? Are the conclusions valid? If yes, continue.
Record citation	Note authors, citation and conclusions of the study for easy retrieval later.
Read discussion	
Read introduction	

is worthy of your time, look at the figures and tables. Authors generally display their best or most convincing data in figures and tables [6]. In a well-written study, you should be able see the important results in summary figures and tables. Try to pick out the one or two figures or tables that hold the most important data. Look at the data to see whether they are summarized and displayed correctly (see section Evaluating the data in clinical research papers, below). Determine whether there is an appropriate control group, whether the outcomes are clinically and biologically important, whether the data are subjected to statistical analysis and whether the correct statistical methods were used. *It is important that you examine and assess the data yourself.* If you are still convinced that the article is worthy of your time, then read the results. Determine whether complications are reported, and whether compliance and lost patients were considered. After reading the results ask yourself the question, 'If everything the authors say is true, is it important for my patients, for my practice or for dermatology as a whole.' If the answer is an emphatic 'no', stop reading; if 'yes or possibly', continue to the methods.

While reading the methods pay particular attention to the features that strengthen clinical trials and that help in validating their conclusions. In particular, determine the eligibility criteria, whether patients were randomly allocated, and whether the outcome is clearly defined and assessed masked. Make an effort to find out who paid for the study and whether all possible conflicts of interest were declared [7]. If your conclusion is that the trial was conducted in a reasonable manner and the conclusions are valid, then make some notation of whom the authors are and the conclusions of the study. Several software packages for cataloguing and managing references are available for most computer platforms (e.g. EndNote and Reference Manager). Finally, if you still have time and interest, read the discussion and introduction, in that order.

Evaluating the data in clinical research papers [1]

Are the data adequately reported?

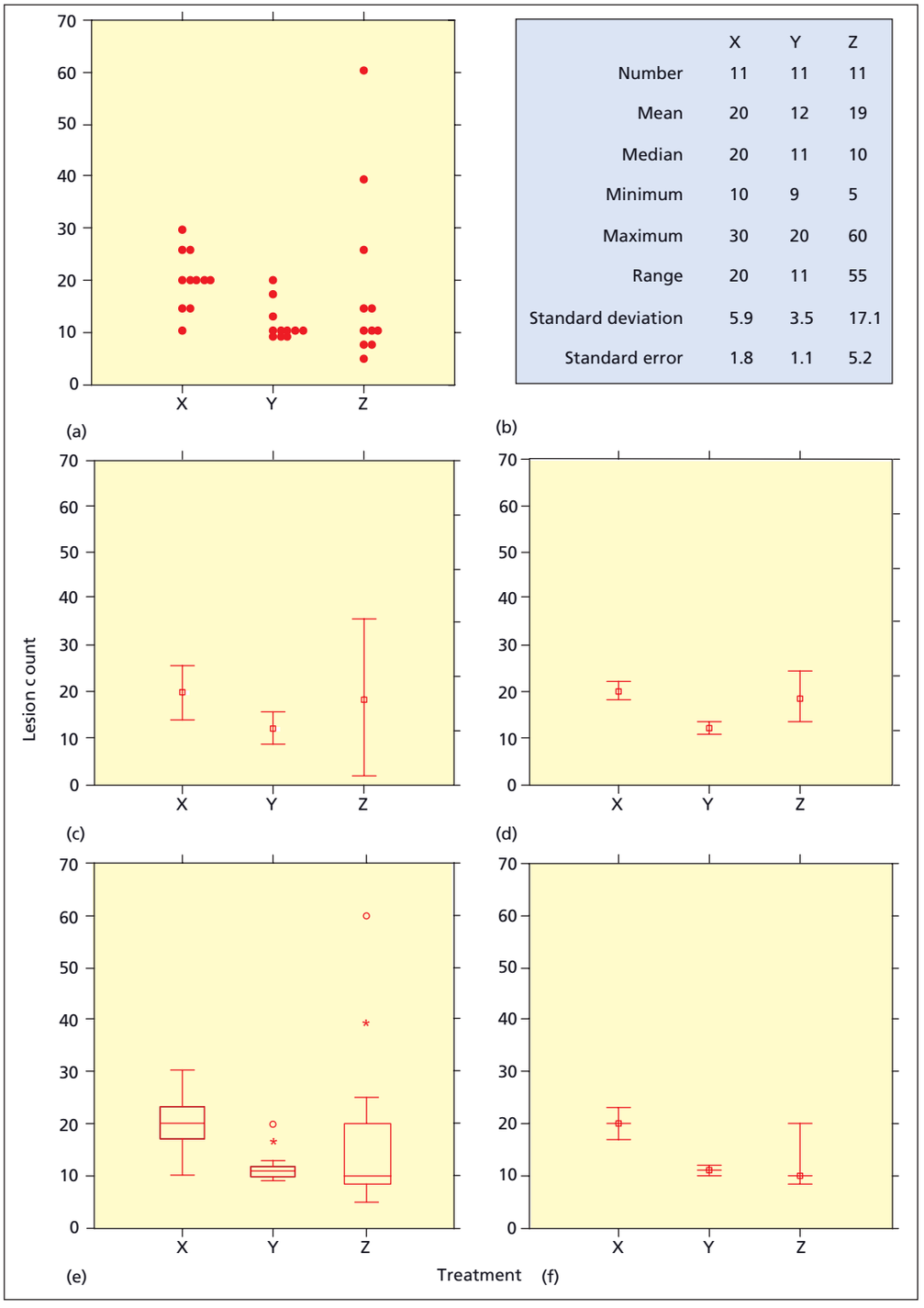
The authors of a study should present their results in sufficient detail to allow the reader to perform his or her own preferred analysis of the data. At a minimum, the presentation of interval data (i.e. discrete or continuous data such as lesion counts or area of involvement) should include a summary measure of the centre of the data for each group (usually the mean and/or median) and a measure of the variability of the data.

The mean is simply calculated as the sum of the data points divided by the total number of data points. The mean is the most appropriate choice for normally distributed data (i.e. data that are distributed in the shape of the bell curve). The median is a better choice for data that are skewed or that contain outliers (Fig. 7.5a,b). The median for an odd number of data points is the value in the middle when the data are ordered from lowest to highest. The median for an even number of data points is determined by taking the mean of the two numbers in the middle when the data points are ordered from lowest to highest. Thus, half of the data points fall above and half fall below the median. The magnitude of the difference between the mean and the median is a crude indicator of the degree of skewing. If the difference is none or small the data are or approach normal (i.e. are symmetrically distributed); if the difference is large the data are skewed.

The standard deviation, range, inter-quartile range, and 95% confidence intervals are commonly used to indicate the variability or spread of the data (Fig. 7.5b,f). The standard deviation (SD) is the square root of the average squared deviation of values from the mean. That is:

$$\mathrm{SD} = \sqrt{\sum \left(X - \bar{X}\right)^2 / (n-1)}$$

The SD is an important summary statistic for normally distributed data only. For normally distributed data, approximately 68% of the data points will lie within the range from the mean minus one SD to the mean plus one SD (mean ± 1 SD); and 95% of the data points will lie within the range from the mean minus two times the SD to the mean plus two times the SD (mean ± 2 SD). These relationships do not apply to skewed data or to small data sets that contain outliers. Note in Fig. 7.5c that the mean and SD do not adequately describe the centre of the data or its distribution for skewed data, or for data with outliers (treatments Y and Z). The range is the interval from the highest to the lowest data points. The range may be a good indicator for variability for data that are tightly arranged around the mean and for small data sets. The range is greatly influenced by outliers and may not give adequate indication of skewed data. Therefore the range is not a good descriptive statistic for skewed data sets or for data with outliers (Fig. 7.5a,b). The inter-quartile range is the interval that contains the middle 50% of the data points. It excludes the highest 25% of the data points and the lowest 25%. The inter-quartile range is a reasonable descriptive statistic to describe skewed data and data with outliers (Fig. 7.5e). Confidence intervals are the best way to present the degree of uncertainty of normally distributed data as well as skewed data or data with outliers (see discussion of confidence intervals below). The 95% confidence interval around the mean can be calculated for normally distributed data using the



	X	Y	Z
Number	11	11	11
Mean	20	12	19
Median	20	11	10
Minimum	10	9	5
Maximum	30	20	60
Range	20	11	55
Standard deviation	5.9	3.5	17.1
Standard error	1.8	1.1	5.2

Fig. 7.5 Hypothetical final lesion counts in a clinical trial of treatments X, Y and Z. The same data are displayed or summarized in each panel. A graphical display of all of the data points (a) gives an accurate description of the magnitude and distribution of the results. Commonly used summary statistics are given in (b). The mean with error bars consisting of one standard deviation (c) or one standard error (d) provide little useful information even for the normally distributed response to treatment X, and are totally misleading for treatment Y and for treatment Z which has outliers. A box plot of the data (e) shows the median (line within the box), the interquartile range (top and bottom of the box), and adequately represents skewed data (note asymmetry of median within the box in the Y plot) and the presence of outliers (note asymmetry of median within the box in the Z plot and the outliers indicated by asterisk and open circle). The 95% confidence interval about the median (f) adequately represents skewed data and the presence of outliers. If the 95% confidence intervals around two means or medians do not overlap, you can be confident at about the 95% level that the two population means or medians are different.

sample mean, standard error and the *t* distribution. For skewed data, the confidence interval around the median should be used (Fig. 7.5f). The confidence interval provides a range of values in which the 'population' or true response to treatment lies. For example, the population or true mean has only a 1 in 20 (5%) chance of lying outside the 95% confidence interval. If the 95% confidence intervals around two means or medians do not overlap, you can be confident at the 95% level that the two population means or medians, from which the samples were drawn, are different.

The standard error (SE) is the standard deviation divided by the square root of the number of data points ($SE = SD/\sqrt{n}$). Unfortunately, the SE is commonly, but incorrectly, used to summarize the variability of data. This choice is made partly because of tradition

and partly because the SE is always smaller than the SD and 95% confidence interval and, therefore, looks better (Fig. 7.5c,f). The SE is correctly used to analyse normally distributed data in inferential statistics (see discussion of the *t*-test below). The common practice of reporting the mean ± SE is firmly ingrained in the medical and scientific literature but is often misleading and inappropriate, and should be discouraged. The SE is an important and useful statistic only for normally distributed data sets. It is used to make predications or inferences about the population from which the sample is chosen. That is, for large, normally distributed data sets, the chance that the true or population mean (from which the sample was drawn) will lie outside the range [mean ± 2SE] is only 5%. The relationship between the sample mean, the population mean and the SE does not apply to skewed data or to small data sets that contain outliers.

Descriptive statistics are at best incomplete summaries of the data; considerably more information may be conveyed by graphic displays (see Fig. 7.5). The production and interpretation of graphic displays is well reviewed by O'Brien and Shampo [8]. Figures that show individual observations are an excellent tool for presenting small datasets, and for data that are skewed or have outliers (Fig. 7.5a). Unfortunately, such diagrams are under-utilized in the scientific and medical literature. Graphic displays of data using 'error bars' showing 1 SD or 1 SE depict at best 68% of the sample or 68% confidence intervals respectively and, therefore, are misleading and should be avoided or approached with scepticism (Fig. 7.5c,d).

Categorical data are preferably presented in tables in which treatments and outcome are represented in rows and columns. Examples of categorical outcomes include cured and not cured, survived and died, and minimal, moderate and marked improvement. Categorical outcomes should be clearly defined, limited in number, clinically important and declared before the trial is begun.

Are data subjected to statistical testing and are tests used correctly?

Observed differences in outcome in clinical trials may be due to chance alone. It is therefore imperative that statistical analyses be performed to verify that the results are from treatment and not from chance. This admonition is especially true for trials containing few patients, which includes many published dermatological trials.

Statistical methods

Understanding P

Understanding the meaning of *P* is fundamental to understanding and interpreting statistical testing. In the simplest terms, all clinical trials begin with the null hypothesis that the treatments are the same. If the results of the trial indicate that the outcomes of treatment are different, then a statistical test is performed to determine whether the difference can be from chance or from sampling variation alone. If chance is not a likely explanation of the difference, the null hypothesis that the treatments are the same is rejected. '*P*' represents the probability that a difference as large as the observed difference might arise by chance if the treatments are the same. The error of believing that a difference in treatments exist, when in fact there is no difference in treatments and the observed differences were from chance or sampling variation alone, is referred to as a Type I (or Type α) error. The statement that 'the difference was statistically significant ($P = 0.05$)' means that the probability that a difference as large as the observed difference might have arisen by chance is 1 in 20, and that the author will accept this degree of chance as being sufficiently unlikely that the null hypothesis that the treatments are the same can be rejected. Conversely, the statement that 'the difference was not statistically significant ($P = 0.10$)' means that the probability that a difference as large as the observed difference might have arisen by chance was 1 in 10, and that the author will not accept this degree of chance as being sufficiently unlikely that the null hypothesis that the treatments are the same can be rejected. It is important to remember that 'not significant' means that a difference is not proven; it does not mean that there is no difference.

The acceptance of a significance level of 0.05 as the cut-off for rejecting the null hypothesis is a tradition based on quality control standards and is not an absolute truth. At times, more stringent standards are required and, paradoxically, tests that do not meet the $P = 0.05$ standard may sometimes be significant. For example, in a trial of a new chemotherapeutic agent involving 30 randomized patients with metastatic melanoma, 7 of 15 patients treated with the new agent survived 5 years compared with 3 out of 15 control patients treated with conventional surgery, chemotherapy and radiation. Whereas the result does not achieve statistical significance when compared by chi-squared testing (see below) (Yates corrected chi-squared = 1.35; $P = 0.25$), the result is, nonetheless, potentially significant. If the therapy is beneficial and the estimated difference in response rates is the true difference in response rates, it might result in the saving of 2072 lives annually (based on 7770 deaths from melanoma annually and the degree of survival advantage in this hypothetical example). Because of the biological and clinical importance of the results suggested by the study, the treatment should be subjected to study in a larger patient population with more power to detect a difference if one exists (see discussion of power below). Others might argue that the adherence to the 95% standard ($P = 0.05$) should be relaxed in cases such as this. The potential benefit of the treatment may be revealed by the use of confidence intervals (see discussion of confidence intervals below).

Investigators should indicate what statistical procedures were utilized to compare results. Simply stating that the difference was statistically significant ($P < 0.05$) does not constitute an adequate description of the statistics used. The exact procedure used (e.g. *t*-test or chi-squared test), and the results obtained, must be specified. The *t*-test and the analysis of contingency tables (e.g. chi-squared and Fisher's exact test) are the most commonly employed procedures, and should be understood by all physicians.

The t*-test*

The *t*-test is the most commonly used statistical test in the biomedical literature. The *t*-test is used to determine whether the difference in the means of two samples is from chance (sampling

variation) alone. It should be emphasized that the *t*-test at a significance level of 0.05 is designed to compare the difference in the means of only two samples or populations. The *t*-test has additional important restrictions. It should only be used to compare the means of interval data that are normally distributed. Additionally, the data analysed by the *t*-test should be sufficiently large, should not contain outliers, should be statistically independent and the variability of the two treatment groups should be similar. In most instances a two-sided *t*-test is appropriate. When a one-sided *t*-test is performed the reasons should be specified. The unpaired *t*-test should be used to analyse two different groups (e.g. patients receiving alternative treatments). The paired *t*-test should be used to analyse the effects of two different treatments on the same patients (e.g. in a cross-over or left–right comparison study).

Statistical analysis using the *t*-test will be illustrated using data from a study comparing calcipotriol and betamethasone ointments in the treatment of stable plaque type psoriasis [9]. In this multicentre RCT, 201 and 200 patients were randomized to treatment with calcipotriol and betamethasone respectively. Outcomes were measured by changes in PASI scores. At the end of 6 weeks of treatment the improvement (decrease) in PASI scores were 5.50 and 5.32 for calcipotriol and betamethasone respectively. The statistical significance of the small difference in the change in PASI scores was evaluated using an unpaired *t*-test. The *t* value and corresponding significance level can be determined using computer programs or calculated using a *t*-distribution table and the formula. Not surprisingly, the result indicated that the difference was not statistically significant ($P = 0.76$). Thus, the trial failed to demonstrate a difference between the two treatments.

Misuse of the *t*-test was one of the most commonly encountered errors in the use of statistics found by Gore *et al*. in his review of the use of statistical methods in the *British Medical Journal* [10]. They found that 52% (32/62) of analytical reports that utilized statistical analyses contained at least one error in the use of statistics. Eleven of the errors were misuse of the *t*-test. The errors included using the *t*-test to analyse data that were not normally distributed (non-parametric), had different variability or had used an unpaired *t*-test to analyse paired data. Another commonly encountered error in the use of the *t*-test is its use to compare the means of more than two samples. This error in the use of the *t*-test occurred in 61% and 44% respectively of articles that used statistical analyses published in *Circulation Research* and *Circulation* in 1977 [11].

The *t*-test should not be used to analyse data that are skewed, or data in which the variability (SD) are very different between treatment groups. Nor should it be used to analyse small data sets, because it is impossible to verify that small data sets are normally distributed. In these situations, the Mann–Whitney U test, the distribution-free equivalent of the *t*-test, may be used for unpaired data and the Wilcoxon test can be used for paired data. The *t*-test should also not be used to compare more than two groups because it ignores possible associations among groups and thus increases the likelihood that spurious results will be obtained. Comparison of means of more than two groups can be performed with different forms of analysis of variance.

Table 7.9 Format of a fourfold contingency table.

	Good response	No or poor response	Total
Treatment A	a	b	H1
Treatment B	c	d	H2
Total	V1	V2	N

The chi-squared for unpaired data is calculated using the formulas:

$$\text{chi-squared (uncorrected)} = \frac{|a \times d - b \times c|^2 N}{H1 \times H2 \times V1 \times V2}$$

$$\text{chi-squared (Yates' corrected)} = \frac{|a \times d - b \times c| - 0.5 \times N|^2 N}{H1 \times H2 \times V1 \times V2}$$

in which $|a \times d - b \times c|$ indicates the absolute value of $a \times d - b \times c$.

Contingency tables

Chi-squared is the most commonly used test to determine whether the categorical data in contingency tables differ because of chance alone. The format of a typical fourfold (2×2) contingency table is shown in Table 7.9. The numbers in the table (indicated by a, b, c and d) are the numbers of patients in each treatment group that fall into each outcome category. The assumption made to formulate the null hypothesis that the treatments are the same is that the overall response rate (i.e. the total number of patients with good responses divided by the total number of patients; V1/N in Table 7.9) is the same for both treatments. Chi-squared is then used to determine how likely it is that the actual numbers observed could be obtained by chance or sampling variation if the response rate for the two treatments were the same. A continuity correction in the chi-squared is recommended to analyse smaller data sets (20 to 40 patients). This correction is used to account for the use of continuous curves to approximate the discrete frequencies in contingency tables. The Yates correction is most commonly used (Table 7.9). Chi-squared should not be used to analyse small trials (trials with less than 20 patients) or when the predicted number of patients in any cell (positions a, b, c or d in Table 7.9) is less than five. In such circumstances, the Fisher exact test should be performed. Chi-squared is used to analyse unpaired data and McNemar's test is used to analyse paired contingency table data. Contingency table analyses can be easily modified and used to compare more than two treatments and more than two outcomes.

Like the *t*-test, the chi-squared test is frequently used incorrectly in published clinical trials. In their analysis of the use of statistics in medical papers published in the *British Medical Journal*, Gore *et al.* found that chi-squared was used incorrectly in 12 of 62 published papers [10]. The errors included omission of the continuity correction for studies with few patients, omission of a clearly stated hypothesis to be tested, lack of consideration of degrees of freedom and misuse of the test to study paired data.

Confidence intervals

Standard statistical hypothesis testing generally results in a determination of a *P* value that represents the probability that a differ-

ence as large as the observed difference might arise by chance. If this probability is equal to or less than a predetermined 'critical value' (usually 0.05), then the null hypothesis is rejected and the difference is considered statistically significant. If the *P* value exceeds the predetermined value, the null hypothesis is not rejected and the difference is considered not statistically significant. This dichotomous treatment of the results of clinical trials as being significant or not significant may sometimes be misleading and may hide meaningful estimates in the differences between the treatments. What matters most in a therapeutic trial is whether investigators have been able to detect a medically significant difference in treatments and how large the difference is likely to be, as described above in the hypothetical study of treatment for melanoma. The conventional significance levels are useful guides to the interpretation of trial results but they should not be considered strict rules. The absurdity of the dichotomous significance testing approach is best appreciated by considering two trials, one of which has a *P* value of 0.05 and the other a *P* value of 0.06. The difference in the level of significance is very small, yet the former is considered statistically significant and the latter is not.

Reporting results with confidence intervals is an alternative or complementary way to present the results of clinical trials. Many believe that it is far preferable. In simple terms, the reported result provides the best estimate of the treatment effect and the confidence interval provides a range of values in which the 'population' or true response to treatment lies. For example, the population or true mean has only a 1 in 20 chance of falling outside the 95% confidence interval. Alternatively if the trial is repeated many times, 95% of the confidence intervals produced will contain the true or population mean response to treatment. The true response rate will most likely lie near the middle of the confidence interval and will rarely be found at or near the ends of the interval.

The confidence interval provides a direct, numerical measurement of the imprecision of the estimate of the response to treatment that is due to sampling variability. The width of the confidence interval is determined by the sample size (the larger the sample the narrower the interval), the variability of the response being measured (the larger the variability the wider the interval) and the degree of confidence desired (the higher the confidence desired the wider the interval) (Fig. 7.6). Confidence intervals can be determined for means and their differences, and for proportions and their differences, by looking them up in tables, by calculating them with formulas or by using computer software. It is important that, in comparative studies, confidence intervals should be reported for the differences between groups, not for the results of each group separately.

There is a close relationship between the results of a test of a hypothesis and the associated confidence interval; if the difference between treatments is significant at the 5% level, then the associated 95% confidence interval excludes the zero difference. The advantage of using confidence intervals instead of, or in addition to, *P* values is that confidence intervals provide an indication of size of the differences in treatments and give numerical measurements of the inexactness in our knowledge of the real differences in treatments.

Confidence intervals can be valuable in interpreting data from trials in which the difference is not statistically significant (i.e. the

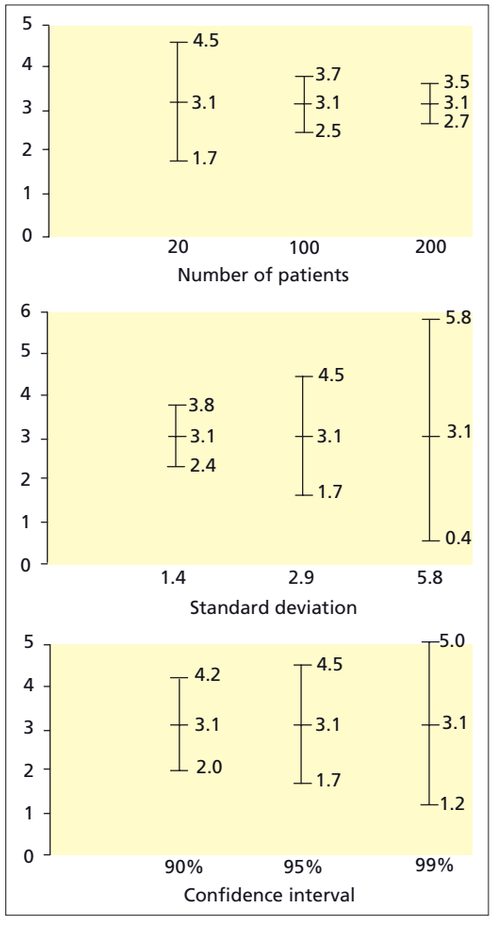


Fig. 7.6 The confidence interval is dependent on the sample size, sample variability and confidence level desired. In the top panel, the mean change in PASI score was 3.1 with a standard deviation of 2.9. The 95% confidence interval is shown and narrows as the number of patients studied increases from 20 to 200. In the middle panel, the mean change in PASI score of 20 patients was 3.1. The 95% confidence interval is shown and widens as the sample variability (standard deviation) increases. In the lower panel, the mean change in PASI score of 20 patients was 3.1 with a standard deviation of 2.9. The confidence interval widens as the degree of confidence desired increases from 90% to 99%.

P value is greater than 0.05). To determine whether a treatment effect may have been missed in a study reporting negative results, one should look at the upper boundary of the 95% confidence interval. If this value would be clinically important if it were the true response, then an important treatment effect may have been missed in the study. In the calcipotriol and betametasone trial as an example, the upper boundary of the difference in PASI scores was 0.78. As the range of possible PASI scores is 0–72, this small degree of difference in PASI scores would be unlikely to have much clinical significance and therefore it is unlikely that a significant treatment advantage for calcipotriol was missed in this study.

In contrast, consider our hypothetical new treatment for metastatic melanoma that had a 5-year survival rate of 7/15 versus 3/15 for conventional treatment. The cure rates for the new treatment and for conventional treatment were 47% and 20% respectively, and the difference between them was 27%. The 95% interval

for the difference in proportions was –10% to 51%. The upper boundary of the difference in cure rates was 51%. This difference would clearly have a significant impact on the treatment of patients with metastatic melanoma and, therefore, a significant treatment advance may have been missed in this study. Also note that the 95% confidence interval of the difference in proportions does not exclude the zero difference; therefore, we cannot be 95% certain that the response rates of the two treatments are different.

Confidence intervals also may be useful in interpreting the response to a single treatment. Ninety-five per cent confidence intervals for the response rate of a single treatment can be determined using formulas, tables, nomograms and computer programs. An important point can be made from determining the confidence interval of a single proportion. There is a degree of uncertainty in reported response rates that can be expressed in exact numerical terms by determining the confidence interval.

Confidence intervals also may be useful in interpreting the rate of side-effects observed in a clinical trial. For example, in the calcipotriol study 40 out of 201 patients (20%) treated with calcipotriol developed lesional or perilesional irritation. The 95% confidence interval for this adverse reaction would be 14% to 26%. Thus a high rate of local irritation can be anticipated with calcipotriol and the rate may be as high as 26%. If no untoward reactions occur in a study, it is still possible to determine the 95% confidence interval of adverse reactions. Accurate upper limits of the reaction rate can be obtained by referring to available tables. A reasonable approximation of the rate of adverse reactions in this situation can be obtained by dividing 3 by the number of patients who were exposed to the studied treatment.

Power

Significant differences in treatment effects in comparison trials may be missed if the number of subjects tested is small. For example, in a 1978 survey of 71 published trials with negative results, Freiman *et al.* found that a 25% or 50% improvement in outcome might have been missed in 57 (80%) and 34 (48%) of the studies respectively [12]. The importance of this observation, and the importance of determining the power of studies to detect clinically significant differences in treatments, is illustrated by the fact that this study has been cited more than 700 times. Despite the recognition of the importance of power, a follow-up study conducted by Moher *et al.* in 1994 indicated that 25% or 50% improvements in outcome might have been missed in 84% and 64% of 102 negative studies respectively [13].

Power is an expression of the ability of a trial to detect a difference in treatments, if one exists. The investigators in a well-designed clinical trial should have an estimate or prediction of the anticipated differences among treatments and knowledge of the magnitude of differences that would be clinically important. The trial should then be designed to enrol sufficient patients to ensure, with reasonable certainty, that a statistically significant difference would be obtained if the anticipated or clinically important differences between the treatments existed. The error of believing that there are no differences between treatments, when in fact there are differences, is a Type II (Type β) error.

The power of a trial to detect a significant difference is determined by the response rates of the treatments, the significance level desired by the investigators and the number of patients treated. The power of a trial to detect differences between treatments can be calculated using formulas, nomograms, programmable calculators or computer software. Conventionally, a power of 80% with a significance level of 0.05 is considered adequate. The choice of a power of 80% means that, if the anticipated or clinically important difference in treatments really exists, four of five trials with the specified number of patients in the treatment groups will show a statistically significant difference. However, higher power sometimes may be desirable. For example, increasing the power to 90% means that 9 of 10 trials would detect a statistically significant difference between treatments if the difference really exists. The power of a study design to detect clinically significant differences in treatments is best considered before the trial is initiated. However, studies that fail to demonstrate statistically significant differences among treatments should always include a discussion of power.

The sample size needed to detect a difference is small when the difference in treatments is large. Conversely, the sample size needed to detect differences is large when the difference in treatments is small or when the response rate of the comparison treatment is high.

As noted by Moher *et al.* [13], 'If a trial with negative results has a sufficient sample size to detect a clinically important effect, then the negative results are interpretable—the treatment did not have an effect at least as large as the effect considered to be clinically relevant. If a trial with negative results has insufficient power, a clinically important but statistically insignificant effect is usually ignored or worse, is taken to mean that the treatment under study made no difference. Thus, there are important scientific reasons to report sample size and/or power calculations.'

The importance of statistical analyses must be kept in proper perspective. Statistics are a tool for trying to ensure that results of clinical trials are not due to chance or sampling variation alone. The combination of hypothesis testing and the use of confidence intervals give a measure of the likelihood that results of a trial are due to chance, and the precision of the estimated difference in treatments, respectively. Statistical analyses cannot tell you the medical significance of differences in treatments. In other words, statistically significant should not and cannot be equated with medically significant. Conversely, a trial the results of which indicate that the difference in treatments was not statistically significant does not necessarily mean that there is not a medically important difference between treatments. It may simply mean that too few patients were used to detect the difference that does exist.

References

1 Bigby M, Gadenne A-S. Understanding and evaluating clinical trials. *J Am Acad Dermatol* 1996; **34**: 555–90.

2 Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. *Lancet* 1999; **354**: 1896–900.

3 Tugwell P, Moher D, Bouter LM. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol* 2007; **7**: 10–7.

4 Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet*; **357**: 1191–4.
5 von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ* 2007; **335**: 806–8.
6 Murray GD. Statistical guidelines for the *British Journal of Surgery. Br J Surg* 1991; **78**: 782–4.
7 Williams HC, Naldi L, Paul C, Vahlquist A, Schroter S, Jobling R. Conflicts of interest in dermatology. *Acta Derm Venereol* 2006; **86**: 485–97.
8 O'Brien PC, Shampo MA. *Statistics for Clinicians*. Rochester, MN: Mayo Foundation, 1981.
9 Cunliffe WJ, Berth-Jones J, Claudy A *et al*. Comparative study of calcipotriol (MC 903) ointment and betamethasone 17-valerate ointment in patients with psoriasis vulgaris. *J Am Acad Dermatol* 1992; **26**: 736–43.
10 Gore SM. Statistics in question. *Statistics in Medicine*. London: British Medical Journal, 1984: 27–97.
11 Glantz SA. Current topics biostatistics: how to detect, correct and prevent errors in the medical literature. *Circulation* 1980; **61**: 1–7.
12 Freiman JA, Chalmers TC, Smith JH *et al*. The importance of beta, the type ii error and sample size in the design and interpretation of the randomized control trial. *N Engl J Med* 1978; **299**: 690–4.
13 Moher D, Dulberg CS, Wells GA. Statistical power, sample size, and their reporting in randomized controlled trials. *JAMA* 1994; **272**: 122–4.

CHAPTER 8
Skin and Skin Disease Throughout Life

G.W.M. Millington[1] *& R.A.C. Graham-Brown*[2]

[1]Department of Dermatology, Norfolk and Norwich University Hospital, Norwich, UK
[2]University Hospitals of Leicester, Leicester, UK

Birth to puberty, 8.1
Somatic growth, 8.1
Sexual development, 8.2
The skin in childhood, 8.3
Syndromes of short stature, 8.3
Puberty and adolescence, 8.4
Hormonal events and cutaneous changes, 8.4
Premature and delayed puberty and hypogonadism, 8.5
Dermatoses of puberty and adolescence, 8.6
The menstrual cycle, 8.8
Hormonal influences, 8.8
Cutaneous changes, 8.8
Pregnancy, childbirth and the puerperium, 8.9
Endocrine background, 8.9
Physiological skin changes related to pregnancy, 8.10
Vascular changes, 8.10
Dermatoses modified by pregnancy, 8.11
AIDS and pregnancy, 8.13
The dermatoses of pregnancy, 8.13
Mid-life, obesity and the skin, 8.16
Introduction to obesity, 8.16
Physiological function of adipose tissue, 8.16
Cutaneous pathophysiology in the obese, 8.17
Cutaneous disorders in the obese, 8.17
Syndromes of obesity with cutaneous features, 8.18
The menopause, 8.19
Hormonal and physiological changes, 8.19
Skin disorders of the menopause, 8.20
Old age, 8.21
Biology of ageing, 8.21
The ageing skin, 8.22
Skin disease in old age, 8.25
Specific skin problems in old age, 8.27

Introduction

Human life is a continuum, but within which are several identifiable phases. Life passes through a period of development to 'maturity', which is then followed by a process of intrinsic ageing leading inexorably to senescence. Throughout life, alterations take place in the structure and function of the skin and there are important differences in the range, presentation, prognosis and treatment of skin disorders at various ages. Indeed, some of the physiological events that accompany puberty, pregnancy, the menopause and old age can, of themselves, be sufficient reason for a patient to seek specialist dermatological advice.

This chapter provides an overview of the skin during these stages in life. The dermatological problems of the neonatal period and infancy have been dealt with elsewhere (see Chapter 17). This chapter deals principally with the skin and its disorders during puberty, the menstrual cycle, pregnancy, childbirth and the puerperium, mid-life, the menopause and old age.

Birth to puberty

Somatic growth

Growth, defined as an increase in size, occurs in most tissues, including the reproductive system. In particular, the changes in the skeleton, which can be monitored radiologically, and in the visible teeth, have traditionally been used as indices of maturity [1]. However, there is increasing evidence that there is no connection between skeletal maturity and onset of puberty [2].

Between birth and maturity the skeleton and body keep in step with increases in weight of 20- to 25-fold, whereas the somatic muscles increase by 30- to 40-fold and the nervous system by less than fivefold. The surface area of the skin increases sevenfold. In the first year after birth the body length increases by approximately 50% to around 75 cm and another 12–13 cm are added in the second year. Subsequently, growth remains steady at 6 cm/year until the spurt associated with puberty. Weight follows a similar pattern [1].

Five highly related genes encode human growth hormone (GH). One of these is expressed solely in the anterior pituitary somatotrophs and the rest in placental villous syncytiotrophoblasts. The initiation of *GH* expression during development depends upon epigenetic modifications at the *GH* locus under the control of its distal locus control region [3]. The expression of certain other developmental genes, such as *Pit1,* is necessary to produce GH [4].

Postnatal growth is dependent on GH, secreted by the anterior pituitary gland, although other hormonal interactions may also be necessary. GH is a protein with 191 amino acids, which exerts an effect on a number of tissues, including the viscera and bone. In particular, it affects stature by stimulating proliferation of cartilage cells at the epiphyseal plates until the point when the epiphyses of the long bones have fused. GH also antagonizes the actions of insulin, possibly by reducing its binding at target sites, or by interacting with a second-messenger system. Some of the effects of GH are indirect, in the sense that they are mediated through the production of polypeptide growth factors in the target

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

tissue. The most important of these are insulin-like growth factor 1 (IGF-1) and IGF-2 [5].

The secretion of GH from the pituitary is mediated primarily by the interaction between hypothalamic GH-releasing hormone and somatostatin, a 14-amino acid polypeptide that has numerous regulatory and neuromodulatory effects. Negative feedback both by IGF-1 and GH itself may also be involved, as may cell–cell interactions, between somatotrophs and between somatotrophs and folliculostellate cells respectively in the anterior pituitary [4]. The basal concentration of GH in the plasma is below 1 mIU/L, but it can reach peaks of up to 60 times this amount in adolescence. Bursts of GH secretion occur every 1–2 h during sleep, but can also be provoked by physiological and psychological stresses.

Excessive GH secretion before puberty gives rise to gigantism, but once the epiphyses of the long bones have fused it results in thickening of the bones and enlargement of the hands and feet, known as acromegaly. Acromegalics also have, on average, abnormally high sebum secretion, mediated by the increased activity of GH and IGF-1 [6]. The range of skin manifestations in acromegaly is discussed in Chapter 62.

Deficiency of GH, either in isolation or as a component of general hypopituitarism, is one cause of short stature [7].

References

1 Sinclair D. *Human Growth After Birth*, 5th edn. Oxford: Oxford University Press, 1989.

2 Flor-Cisneros A, Roemmich JN, Rogol AD *et al.* Bone age and onset of puberty in normal boys. *Mol Cell Endocrinol* 2006; **254–255**: 202–6.

3 Ho Y, Liebhaber SA, Cooke NE. Activation of the human GH gene cluster: roles for targeted chromatin modification. *Trends Endocrinol Metab* 2004; **15**: 40–5.

4 Asa SL, Tannenbaum GS. Cell–cell communication in the pituitary: orchestrator of pulsatile growth hormone secretion? *Trends Endocrinol Metab* 2006; **17**: 299–300.

5 Edmonson SR, Thumiger SP, Werther GA *et al.* Epidermal homeostasis: the role of the growth hormone and insulin-like growth factor systems. *Endocr Rev* 2003; **24**: 737–64.

6 Deplewski D, Rosenfield RL. Role of hormones in pilosebaceous unit development. *Endocr Rev* 2000; **21**: 363–92.

7 Saenger P, Czernichow P, Hughes I *et al.* Small for gestational age: short stature and beyond. *Endocr Rev* 2007; **28**: 219–51.

Sexual development

The period between infancy and puberty that we call childhood is, in relation to sexual development, a hiatus in hormonally controlled events that have already been initiated in the fetus. While the dermatological problems of the neonatal period are so distinctive and of such practical importance as to merit a separate chapter, an understanding of the hormonal status of the fetus and the neonate and of the cutaneous implications, is an essential starting point in this journey.

Sex determination as a mechanism equates to a binary switch that locks the embryonic gonads, at a molecular level, into either future testes or ovaries. The initial event in both sexes is the formation of a bipotential primordium. Several genes are involved in this initial stage including *LIM1* (*LHX1*), *SF1* (*ZPF162*), *WT1*, *EMX2* and *LHX9* [1]. Males become differentiated from females by their possession of a Y chromosome, which causes the undifferentiated gonads to become testes. A number of genes are involved in this process, including *SRY*, *SOX9*, *DAX1 (NROB1)*, *SF1* and *ATRX* [1,2]. Anti-Müllerian duct hormone (AMH) is a 560-amino acid glycoprotein secreted from the Sertoli cells of the testis [3]. AMH causes the degeneration of the Müllerian duct between the seventh and eighth weeks of gestation [3]. When fragments of fetal testes or isolated Sertoli cells are placed adjacent to cultured tissue segments containing portions of the Wolffian and Müllerian ducts, the Müllerian duct atrophies even though no change occurs in the Wolffian duct. AMH is thought to bind to the mesenchyme cells surrounding the Müllerian duct and to cause them to secrete a paracrine factor that induces apoptosis in the Müllerian duct epithelium [3]. Oestrogen is needed for the complete development of both the Müllerian and the Wolffian ducts. In females, oestrogen secreted from the fetal ovaries appears sufficient to induce the differentiation of the Müllerian duct into its various components: the uterus, oviducts and cervix [3]. Testosterone, which causes virilization of the Wolffian duct, is needed to form most of the male system. Conversion of testosterone to 5α-dihydrotestosterone is necessary for the development of the prostate from the urogenital sinus and of the external genitalia. In the latter trimesters of intrauterine life, the testicles descend to their position in the scrotum in response to gonadotrophin from the fetal pituitary, as well as testosterone.

The fetal testis continues to secrete testosterone even after birth [4]. At 50 days of age the level of plasma testosterone (250 ng/100 mL) is more than seven times that in umbilical cord blood (35 ng/100 mL) and is unlikely to be of maternal origin. By about the age of 6 months the plasma level of testosterone falls, and is maintained at a low concentration for the rest of childhood.

In males, the production of testosterone appears at first sight to correlate with activity of the sebaceous glands, which become functional by 17 weeks of gestation. The glands are large at birth and the skin surface lipid is high, approximately 400 g/cm^2, remaining so for approximately 3 months [5]. The level throughout the rest of childhood is maintained at approximately 100 g/cm^2. Neonatal skin-surface lipid is, however, as high in females as in males, although the hormonal pattern is quite different; the maximum plasma testosterone occurs immediately after birth and falls very rapidly [4]. The pattern of dehydroepiandrosterone, however, very closely follows that of sebum levels in both sexes [6]. For these reasons, it seems possible that the production of sebum in the neonatal period and the occurrence of acne in prepubertal children may be related to adrenal activity.

Sebaceous activity starts to increase again towards the end of childhood, in advance of other signs of approaching puberty [7]. Dramatic changes take place between the ages of 8 and 9 years, in both males and females and it seems possible that these are related to an increase in output of adrenal androgens. Comedones may develop around this period [7].

References

1 Harley VR, Clarkson MJ. Sex with two sox on: SRY and SOX9 in testis development. *Trends Endocrinol Metab* 2002; **13**: 106–11.

2 Tang P, Park DJ, Marshall-Graves JA *et al.* ATRX and sex differentiation. *Trends Endocrinol Metab* 2004; **15**: 339–44.

3 Klattig J, Englert C. The Müllerian duct: recent insights into its development and regression. *Sex Dev* 2007; **1**: 271–8.

4 Forest MG, Cathiard AM, Bertrand JA. Evidence of testicular activity in early infancy. *J Clin Endocrinol Metab* 1973; **37**: 148–51.
5 Agache P, Blanc D, Barrand C *et al*. Sebum levels during the first year of life. *Br J Dermatol* 1980; **103**: 643–9.
6 Zouboulis CC, Chen WC, Thornton MJ *et al*. Sexual hormones in human skin. *Horm Metab Res* 2007; **39**: 85–95.
7 Zouboulis CC, Boschnakow A. Chronological ageing and photoageing of the human sebaceous gland. *Clin Exp Dermatol* 2001; **26**: 600–7.

The skin in childhood

The skin, along with other organ systems, undergoes some degree of maturation during the hiatus of childhood, before the resumption of sexual development at puberty and the transition to adulthood. The skin disorders seen in children in part reflect these physiological changes, but many of the most troublesome cutaneous problems encountered result from intrinsic genetic abnormalities conditioned by environmental influences. Perhaps the best example is atopic eczema (see Chapter 24), which has now reached very high levels of prevalence in some societies [1–3]. The ways in which the environment affects the child changes, as he or she becomes more mobile and travels further afield, thus becoming exposed to potential antigens.

School years bring exposure to a wide variety of infections and contagions, such as measles, chickenpox, impetigo, warts, molluscum contagiosum, scabies and head lice. There is also a gradual increase in contact with potential irritants: at school during lessons, in sporting activities such as swimming and team games and in hobbies. The wearing of jewellery and cosmetics and exposure to sensitizers such as rubber chemicals in footwear and preservatives in medicaments, bring a further range of dermatological problems in the form of allergic contact dermatitis, which is not as rare before puberty as is often suggested [4]. One disorder that appears to have a definite predilection for the prepubertal period in girls is lichen sclerosus [5], which may, but does not always, improve and disappear as puberty approaches [6]. In boys, the same pathological changes are frequently found in prepuces removed to relieve phimosis.

There is an increasing awareness in recent years that both girls and boys may present to the dermatologist with symptoms and signs that indicate sexual abuse [7]. Vulval or perianal soreness and inflammation for which no other cause can be found should be considered suspicious, as should the presence of anogenital warts [8], although these may be acquired innocently. Proof of sexual abuse is always difficult unless there has been disclosure or confession from within the family unit. Furthermore, the social and legal implications of formal investigations for the child and his or her family are enormous. Inquiries must therefore be undertaken with care, although there is a well-established framework in many countries to deal with the problem, generally involving paediatricians, social workers and the police [7]. It is important to note that the changes associated with lichen sclerosus and Crohn's disease in childhood can be mistaken, by non-dermatologists, for evidence of sexual abuse [7], although their presence does not exclude it.

Syndromes of short stature

There is no uniformly agreed definition of short stature, although a reasonable cut-off would seem to be below the third centile for the child's community [9]. There are several disorders in which abnormal or delayed growth and development are accompanied by cutaneous changes. Some lead to short stature (a term preferred to 'dwarfism'), which is a common feature of chromosomal abnormalities. In others, delayed sexual development (infantilism) is also present and this will be discussed briefly in relation to premature and delayed puberty. It is important to note that due allowance must be made for parental height in assessing possible delayed growth in a child [10]. Some of the more important of the disorders in which skin changes accompany short stature are listed in Table 8.1.

Table 8.1 Disorders in which short stature may occur with cutaneous changes.

Often severe	Moderate
Rothmund–Thomson syndrome	Turner's syndrome
Bloom's syndrome	Hypohidrotic ectodermal dysplasia
Cockayne's syndrome	Marinesco–Sjögren syndrome
Bird-headed dwarfism	Xeroderma pigmentosum
Progeria	Trichorhinophalangeal syndrome
Cornelia de Lange syndrome	Focal dermal hypoplasia
Cartilage–hair hypoplasia	Werner's syndrome
Conradi's disease	Darier's disease
Polydysplastic epidermolysis bullosa	Atopic dermatitis
Ataxia–telangiectasia	
Leprechaunism	
Growth retardation, alopecia, pseudo-anodontia, optic atrophy (GAPO)	
Short stature, alopecia and macular degeneration	

Furthermore, it is well known that severe skin disease of any kind in childhood can have a considerable impact on general physical development. Atopic eczema is a good example, short stature being very common in severely affected individuals, at least until puberty [11], although the assessment of this may be complicated by systemic or topical steroid therapy.

References

1 Bleiker TO, Shahidullah H, Dutton E *et al*. The prevalence and incidence of atopic dermatitis in a birth cohort: the importance of a family history. *Arch Dermatol* 2000; **136**: 274.
2 Graham-Brown RAC. Measuring the impact of childhood atopic dermatitis. *Int J Clin Pract* 2006; **60**: 895.
3 Lewis-Jones S. Quality of life and childhood atopic dermatitis: the misery of living with childhood eczema. *Int J Clin Pract* 2006; **60**: 984–92.
4 Militello G, Jacob SE, Crawford GH. Allergic contact dermatitis in children. *Curr Opin Pediatr* 2006; **18**: 385–90.
5 McLelland J. Lichen sclerosus in children. *J Obstet Gynaecol* 2004; **24**: 733–5.
6 Holder JE, Berth-Jones J, Graham-Brown RAC. Lichen sclerosus et atrophicus presenting in childhood: a follow-up study. *Br J Dermatol* 1994; **131** (Suppl. 44): 50.
7 Berth-Jones J, Graham-Brown RAC. Childhood sexual abuse: a dermatological perspective. *Clin Exp Dermatol* 1990; **15**: 321–30.
8 Hanson RM, Glasson M, McCrossin I *et al*. Anogenital warts in childhood. *Child Abuse Neglect* 1989; **13**: 225–33.
9 Saenger P, Czernichow P, Hughes I *et al*. Small for gestational age: short stature and beyond. *Endocr Rev* 2007; **28**: 219–51.
10 Tanner JM, Goldstein H, Whitehouse RH. Standards for children's height at ages 2–9 years allowing for height of parents. *Arch Dis Child* 1970; **45**: 755–62.

11 Baum WF, Schneyer U, Lantzsch AM *et al.* Delay of growth and development in children with bronchial asthma, atopic dermatitis and allergic rhinitis. *Exp Clin Endocrinol Diabetes* 2002; **110**: 53–9.

Puberty and adolescence

Hormonal events and cutaneous changes

Puberty is the attainment of the ability to reproduce. The term adolescence embraces these events, but is also used in a wider sense to include the phase of psychological and social adjustment to the physical changes. Thus, depending on the society, adolescence may be prolonged well beyond the completion of puberty [1].

Puberty occurs physiologically because the hypothalamus begins to secrete one key decapeptide, gonadotrophin-releasing hormone (GnRH). The release of GnRH is under the permissive control of the kisspeptin neuropeptide, acting on its GPR54 receptor on the GnRH neurones [2,3]. Glutaminergic input from glial cells may also be important in triggering the increased pulsatility of GnRH secretion [4]. Activated transiently during the first months of postnatal life, the GnRH system remains dormant until its reactivation signals the onset of puberty [5]. Its pulsatile release into the hypothalamohypophyseal portal system then stimulates the production and release of the pituitary gonadotrophin hormones follicle-stimulating hormone (FSH) and luteinizing hormone (LH). These gonadotrophins induce the maturation of the testis and the ovary, which then produce sex steroid hormones and mature sperm and eggs. It should be noted that production of oestrogens at puberty is important for sexual development in both girls and boys. GnRH release is inhibited by negative feedback of the gonadotrophins, neuropeptide Y, opiate peptides, gamma amino butyric acid and, prior to the pubertal surge, steroid hormones and a peptide called inhibin, which is produced by the gonads [4–6].

In the male, initiation of spermatogenesis requires both LH and FSH, but secretion of testosterone by the Leydig cells needs only LH. Levels of serum FSH and LH rise between the ages of 6 and 17 years in both sexes [6]. As puberty develops, LH is released in pulses, at first only at night but later also during the day [6]. The onset of puberty in the male is heralded by an increase in testicular volume resulting from the appearance of a lumen in each seminiferous tubule and an increase in the size and number of the testosterone-producing Leydig cells [1]. Testosterone is responsible for most of the secondary changes such as enlargement of the penis and larynx, growth of pubic, axillary and beard hair and also for a rise in sebum excretion and increased axillary sweating. Slight growth of pubic hair, at around 8 or 9 years and probably provoked by adrenal androgens, may precede other secondary characteristics [1]. Facial hair usually only starts to appear about 2 years later. A full account of the patterns of hair development is given in Chapter 66.

The age at which these changes occur is highly variable but Tanner's data on white British boys give some guidance [7–9]. In 95% of boys, the genitalia started to enlarge at between 9.5 and 13.5 years (mean 11.6 ± 0.9 years of age) and functional maturity, indicated by the ability to ejaculate, was achieved between the ages of 13 and 17 (mean 14.9 ± 1.1) years. The adolescent growth spurt, when the average gain in height reached a peak of 10 cm/year, a velocity of growth similar to that at the age of 2 years, usually occurred between 12.5 and 15 (mean 14.1 ± 0.9) years, approximately 3 years after the first signs of genital enlargement.

In girls, one of the first signs of puberty is the onset of breast development (thelarche), indicated by the elevation of the breast and papilla to form a small mound known as the breast bud [8,10]. The average age in white North American girls is 9.96 ± 1.82 years and 8.87 ± 1.93 years in their African American compatriots [11], but the breasts continue to enlarge for approximately 2 more years. The secretion of ovarian oestrogens promotes breast growth, with the further development of the secretory alveoli during pregnancy requiring the action of progesterone as well. Pubic hair also starts to develop at about age 9, probably as a result of stimulation by androgens from the adrenal cortex, the so-called adrenarche, and is thus dependent on an output of pituitary adrenocorticotrophic hormone (ACTH) [6,12] (see Chapter 66). The most obvious feature of puberty, namely first menstruation or menarche, occurs at an average age of 13 years, but within an age range of 10–16.5 years. The early menstrual cycles do not usually involve ovulation, so full reproductive function is generally delayed for a further year or two. The growth spurt, with a peak height gain of 8 cm/year, occurs between 10.5 and 13 years of age in white British girls [10]; approximately 2 years earlier than in boys. It is also noteworthy that rapid somatic growth precedes the major events of sexual maturation in girls but accompanies or succeeds them in boys.

Both the age at which puberty begins in childhood and the duration of the process vary enormously between individuals, irrespective of gender. The pubertal growth spurt appears, in both sexes, to be dependent on androgenic steroids as well as on growth hormone. Boys with growth hormone deficiency respond less well to testosterone than do normal subjects, not only in relation to acceleration of growth but also for development of the secondary sexual characteristics [13]. In recent decades, the age at which puberty begins has decreased in many countries [1,14,15]. Puberty starts when adequate growth and energy storage has occurred, so the earlier age of puberty may reflect recent trends in increasing adolescent obesity [14,15]. One important signal is the hormone leptin, produced by adipocytes. If fat reserves are low, circulating leptin levels are low and reproductive activity is stopped. Puberty will not begin unless adequate metabolic fuels are available, so leptin levels may act as a 'gate' for puberty [16]. As modern lifestyles are becoming increasingly sedentary, it is little surprise that the prevalence of obesity is increasing in children. Perhaps this increased availability of metabolic fuels and fat reserves, with consequent hyperleptinaemia and hyperinsulinaemia, is opening the puberty 'gate' earlier? In children born small for gestational age, puberty is significantly advanced in girls, but not boys, suggesting that nutritional influences on the onset of puberty are complex [17].

References

1 Patton GC, Viner R. Adolescent health 1. Pubertal transitions in health. *Lancet* 2007; **369**: 1130–9.

2 Seminara SB, Messager S, Chatzidaki EE *et al.* The GPR54 gene as a regulator of puberty. *N Engl J Med* 2003; **349**: 1614–27.

3 Messager S, Chatzidaki EE, Ma D *et al*. Kisspeptin directly stimulates gonadotropin-releasing hormone release via G protein-coupled receptor 54. *Proc Natl Acad Sci USA* 2005; **102**: 1761–6.
4 Ojeda SR, Lomniczi A, Mastronardi C *et al*. Minireview: the neuroendocrine regulation of puberty: is the time ripe for a systems biology approach? *Endocrinology* 2006; **147**: 1166–74.
5 Colledge WH. GPR54 and puberty. *Trends Endocrinol Metab* 2004; **15**: 448–53.
6 Brook CGD, Marshall NJ. *Essential Endocrinology*. Oxford: Blackwell Scientific Publications, 2001.
7 Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. *Arch Dis Child* 1970; **45**: 13–23.
8 Tanner JM. *Growth at Adolescence*. Oxford: Blackwell Scientific Publications, 1962.
9 Tanner JM, Whitehouse RH. Clinical longitudinal standards for height, weight, height velocity, weight velocity and stages of puberty. *Arch Dis Child* 1976; **51**: 170–9.
10 Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. *Arch Dis Child* 1969; **44**: 291–303.
11 Gilli D, Schenker J. The evolving story of female puberty. *Gynecol Endocrinol* 2002; **16**: 163–71.
12 Yeste D, González-Niño C, Pérez de Nanclares G *et al*. ACTH-dependent precocious pseudopuberty in an infant with DAX1 gene mutation. *Eur J Pediatr* 2009; **168**: 65–9.
13 Meinhardt UJ, Ho KKY. Modulation of growth hormone action by sex steroids. *Clin Endocrinol* 2006; **65**: 413–22.
14 Ong KK, Ahmed ML, Dunger DB. Lessons from large population studies on timing and tempo of puberty (secular trends and relation to body size): the European trend. *Mol Cell Endocrinol* 2006; **254–255**: 8–12.
15 Himes JH. Examining the evidence for recent secular changes in the timing of puberty in US children in light of increases in the prevalence of obesity. *Mol Cell Endocrinol* 2006; **254–255**: 13–21.
16 Gamba M, Pralong FP. Control of GnRH neuronal activity by metabolic factors: the role of leptin and insulin. *Mol Cell Endocrinol* 2006; **254–255**: 133–9.
17 Ibanez L, de Zegher F. Puberty and prenatal growth. *Mol Cell Endocrinol* 2006; **254–255**: 22–5.

Premature and delayed puberty and hypogonadism

Although it must be acknowledged that the measurement of the onset and progress of puberty remains somewhat controversial [1], the dermatologist will occasionally see patients with what is clearly an abnormally early or delayed puberty, or with various hypogonadal syndromes. The appearance or non-appearance of sexual hair, or the onset of acne lesions in late childhood are the usual reasons for such referrals. Premature and delayed puberty are matters for endocrinological investigation, but the dermatologist should at least be aware of the range of diagnostic possibilities.

Premature puberty

Signs of puberty before the age of 10 years are generally held to be abnormal. This may result from an early onset of complete (or true) puberty, in which the changes are triggered by early activation of the normal hypothalamo–pituitary–gonadal axis. In some instances, early signs of puberty are caused by false (or pseudo-) puberty, in which sex hormone secretion is independent of normal control mechanisms. Partial or incomplete puberty is also recognized and there are two forms: thelarche (isolated breast development) and pubarche (isolated development of pubic and axillary hair). The former may be unilateral and be confused with tumours.

Table 8.2 Classification of premature puberty. (From Rayner [4].)

Complete (true)	False (pseudopuberty)
Constitutional	Adrenal lesions
Sporadic	Congenital adrenal hyperplasia
Familial	Tumours
Cerebral/neurogenic	Cushing's syndrome/hyperplasia
Tumours	Ovarian tumours
Development defects	Testicular tumours
CNS infections	Iatrogenic (sex hormones)
CNS trauma	Extrapituitary gonadotrophin secreting tumours
McCune–Albright syndrome	Teratoma
Neurofibromatosis	Chorionepithelioma
Tuberous sclerosis	Hepatoblastoma
Silver's syndrome	
Hypothyroidism	
Pineal lesions	
Incomplete	
Premature thelarche, pubarche	

CNS, central nervous system.

It is not clear what causes isolated breast enlargement, although tissue hypersensitivity to oestrogen has been suggested (see Chapter 70). Pubarche is often associated with adrenal androgen secretion and this may be a priming phenomenon in the early phases of normal pubertal development [2]. Indeed, the very early, isolated appearance of sexual hair may presage a true early puberty and the distinction can be a very fine one. Table 8.2 gives a clinical classification of early puberty.

Most instances of premature, complete puberty are constitutional. Although this may be sporadic, there is often a strong family history. Indeed, it seems likely that many families never present at all, accepting that it is quite normal for them. This is particularly true for girls, in whom approximately 80% of premature puberty is thought to be constitutional [3]. There is no difference in the order of events, but mental and emotional development may lag behind the physical changes. In boys, where the event is rarer, there is more often an underlying pathological condition [3].

The investigation of complete premature puberty is obviously a complex process, especially if a neurogenic origin is suspected, but the dermatologist should always look for other features of the specific syndromes listed in Table 8.2: McCune–Albright syndrome, neurofibromatosis, tuberous sclerosis and Silver–Russell syndrome (short stature, craniofacial disproportion and clinodactyly), as well as hypothyroidism [3].

References

1 Coleman L, Coleman J. The measurement of puberty: a review. *J Adolesc* 2002; **25**: 535–50.
2 Auchus RJ, Rainey WE. Adrenarche—physiology, biochemistry and human disease. *Clin Endocrinol (Oxf)* 2004; **60**: 288–96.
3 Traggiai C, Stanhope R. Disorders of pubertal development. *Best Pract Res Clin Obstet Gynaecol* 2003; **17**: 41–56.
4 Rayner PHW. Early puberty. In: Brook CGD, ed. *Clinical Paediatric Endocrinology*. Oxford: Blackwell Scientific Publications, 1981: 224–39.

Table 8.3 Causes of delayed puberty. (From Chaussain [4], Kulin [5] and Santen & Kulin [6].)

Constitutional delay
Hypogonadotrophism
Isolated gonadotrophin deficiency
Hypogonadotrophic hypogonadism (Kallmann's syndrome)
Multiple hormonal deficiency states
Idiopathic
Tumours
Langerhans' cell histiocytosis
Tuberculosis
Sarcoidosis
Vascular disease
Haemochromatosis
Hyperprolactinaemia
Specific syndromes with hypogonadotrophism
Prader–Willi
Laurence–Moon–Biedl
Multiple lentigines
Rud's
Cerebellar ataxia
Systemic disease
Chronic renal failure
Congenital heart disease
Cystic fibrosis
Thalassaemia major
Diabetes mellitus
Hypothyroidism
Gluten intolerance
Anorexia nervosa
Excessive exercise
Hypergonadotrophic hypogonadism
Klinefelter's syndrome
Ullrich–Turner syndrome
Dystrophia myotonica
Trisomy 21 (Down's syndrome)
17β-Hydroxylase deficiency
Androgen insensitivity (testicular feminization syndrome)
Surgical accidents (e.g. during herniorraphy)
Testicular torsion
Anorchia and bilateral cryptorchidism
Irradiation and cytotoxic drugs
Orchitis (e.g. mumps)
Polycystic ovarian disease

Delayed puberty and hypogonadism

Puberty can be considered delayed if there is no sign of sexual development by the age of 15 years in boys and 14 years in girls [1]. There are a number of important causes, listed in Table 8.3. Constitutional delay accounts for at least 50% of male cases and is much more common than in girls [1].

As with premature puberty, pubertal delay requires endocrinological investigation. However, a dermatologist can make a useful contribution if the patient presents first in the skin clinic. Examination can reveal the obesity, short stature and mental retardation of the Prader–Willi syndrome, the polydactyly of the Laurence–Moon–Biedl syndrome, or the increased height and gynaecomastia of Klinefelter's syndrome.

Many extraneous factors can also affect the onset of puberty. Malnutrition and extreme forms of exercise, such as long-distance running and ballet training, may markedly delay onset of puberty, probably by interfering with hypothalamic triggering mechanisms [2,3].

References

1 Traggiai C, Stanhope R. Disorders of pubertal development. *Best Pract Res Clin Obstet Gynaecol* 2003; **17**: 41–56.

2 MacConnie SE, Barkan A, Lampman RM *et al*. Decreased hypothalamic gonadotrophin releasing hormone secretion in male marathon runners. *N Engl J Med* 1986; **315**: 411–7.

3 Warren PW. Effects of undernutrition on reproductive function in the human. *Endocrinol Rev* 1983; **4**: 363–77.

4 Chaussain J-L. Late puberty. In: Brook CGD, ed. *Clinical Paediatric Endocrinology*. Oxford: Blackwell Scientific Publications, 1981: 240–7.

5 Kulin HE. Disorders of sexual maturation: delayed adolescence and precocious puberty. In: De Groot LJ, ed. *Endocrinology*, 2nd edn. Philadelphia: Saunders, 1989: 1873–99.

6 Santen RJ, Kulin HE. Evaluation of delayed puberty and hypogonadism. In: Santen RJ, Swerdloff RS, eds. *Male Reproductive Dysfunction*. New York: Dekker, 1986: 145–89.

Dermatoses of puberty and adolescence

Adolescence is a difficult period for most people. It is a time when the whole emphasis of relationships is supposed to change from the herd bond of the 'gang' to the pair bond of courtship and sexual involvement, but this does not happen all at once or completely. Most of us retain a need for the approbation of our peers throughout life, as well as a desire to develop a close one-to-one relationship. The tensions involved in this are at their most acute during adolescence and, for this reason, many skin diseases, which first presented during childhood, only begin to exert their most damaging influences after the onset of puberty. Adolescence is a bad time to have skin disease, especially on the face or on the extremities.

The physiological changes that occur in the skin during puberty and adolescence also have several effects and may result in sufficient distress to cause the individual to seek medical advice. There are several examples of this: the increase in sebum production frequently results in unacceptably greasy hair, on which many hours and much money is expended; teenagers often present with secondary sexual hair that they perceive to be abnormal, largely as a result of the pressure exerted by the media; young men become anguished when androgenetic, male-pattern balding begins in the teenage years; members of both sexes become disturbed by the onset of 'body odour'.

It has been pointed out that the pressures of coping with a maturing skin are particularly acute for a girl who is persuaded by advertisers that she should have plenty of hair on her head, but none on her face, under her arms or on her legs. Her skin should be free from grease, acne and, moreover, should be odourless [1]. Puberty makes this ideal image virtually impossible to achieve. Several disorders cause special problems or make their first appearance in adolescence. The classic example is acne vulgaris but there are several others (Table 8.4).

Table 8.4 Disorders that present in or cause particular problems during adolescence.

Acne vulgaris
Acne excoriée and neurotic excoriation
Self-mutilation and dermatitis artefacta
Seborrhoeic dermatitis
Pityriasis versicolor
Hyperhidrosis
Axillary bromhidrosis (body odour)
Hidradenitis suppurativa
Fox–Fordyce disease
Polymorphic light eruption
Epidermolysis bullosa simplex (Weber–Cockayne syndrome)
Psoriasis
Atopic dermatitis



Fig. 8.1 Self-inflicted lesions on the cheek of a teenager.

Teenagers may present with a variety of skin disorders in which self-inflicted injury is an important component (Fig. 8.1), varying from mild excoriated acne to severe habitual mutilation. The mental state of these individuals ranges from simple mild anxiety to gross personality disorder, psychotic disturbance and instability. Extreme forms of deliberate self-harm almost invariably begin in adolescence, but most continue for many years [2].

Seborrhoeic dermatitis is generally seen only from adolescence onwards, as is pityriasis versicolor in temperate climates. An explanation for this may lie in the alterations in sebum that appear to occur at puberty [3], especially if it is accepted that yeast organisms have a role in seborrhoeic dermatitis (see Chapter 23). This alteration in sebum is also said to be responsible for the virtual disappearance of scalp ringworm after puberty.

Teenagers may seek help for a number of different axillary problems. Severe eccrine hyperhidrosis can be a very distressing complaint, but usually responds well to treatment (see Chapter 44) [4], as does axillary odour (bromhidrosis). More difficult to deal with are abnormalities of the apocrine glands (hidradenitis and Fox–Fordyce disease).

Polymorphic light eruption often presents for the first time in adolescence [5] and can ruin summer holidays. So does psoriasis [6]; 25% of 5600 patients with psoriasis dated the onset of their disease to between the ages of 10 and 20 years [7]. The impact of the appearance of psoriasis on a teenager should not be underestimated. The patient will be told that psoriasis is probably genetic, that it is likely to continue to be a lifelong problem and that there is no satisfactory cure. All this has to be assimilated during a period of increasing awareness of the importance of being attractive.

Atopic eczema can also be a major problem for the teenager and his or her family. It may present for the first time in adolescence, but this is rare. More commonly, children do not grow out of it as they have been led to believe, or atopic eczema may disappear during childhood only to reappear in adolescence. In this situation, the skin changes and pruritus are often severe and usually have already affected the enjoyment of childhood. The adolescent is then quite abruptly faced with the prospect of the skin problem continuing for an apparently indefinite period into adult life. Many, if not all, affected teenagers become increasingly depressed and frustrated and a sense of hopelessness can descend on the whole family. Many patients completely lose faith in orthodox medicine and seek advice from homeopaths, herbalists, naturopaths and others. A truly sympathetic and holistic approach is therefore required if the dermatologist is to retain the confidence of his or her young patient and their relatives through this difficult period. Good communication needs to be cultivated and maintained. Professional counselling facilities can be very helpful, but are often either neglected or are unavailable.

Another troublesome aspect of atopic eczema in adolescence is that there is a greater tendency to develop involvement of the hands (and feet) as the years go by. This can lead to difficulties in choosing a suitable occupation (see below). Furthermore, treatment parameters usually differ in adolescents and adults from those in childhood atopic eczema [8]. In particular, the information and support needs differ and, in practical therapeutic terms, steroid-sparing strategies may become more important.

Some congenital and genetic diseases, such as tuberous sclerosis and neurofibromatosis, may progress during the teenage years, causing increasing physical and cosmetic disability. Others (e.g. ichthyotic disorders, pigmentary anomalies and port-wine stains), even though largely static, may exert a greater effect because of the social and psychological tensions of adolescence.

However, some disorders improve at puberty. For example, atopic eczema clears in many individuals and autosomal dominant ichthyosis tends to improve.

Skin disease and career

Young people with skin disease are often not aware that they may be at a major disadvantage in pursuing some occupations.

The armed forces medically examine all recruits and are unlikely to accept anyone with either psoriasis, significant atopic eczema or severe acne. It is therefore preferable for acne to be eradicated before rather than after application.

Psoriasis and dermatitis of the hands can be troublesome for those hoping to work in catering. Although they may be accepted by colleges to study, such individuals often find it difficult to obtain subsequent employment.

Hand dermatitis among hairdressers is a far greater problem in those with active or inactive atopic eczema than in those who are unaffected [9]. A teenager with atopic eczema may work in a hair salon for months or even years suffering with hand dermatitis before eventually giving up. The same applies to nursing, where many committed individuals are rejected at the occupational health screen because of dermatitis. Any teenager with a chronic skin disease, especially of the hands, should therefore be made aware of the potential difficulties that he or she may face in the choice of occupation.

References

1 Cotterill JA. Infantile cutaneous ideas. *Br J Dermatol* 1987; **117** (Suppl. 32): 22–3.
2 Shah KN, Fried RG. Factitial dermatoses in children. *Curr Opin Pediatr* 2006; **18**: 403–9.
3 Stewart ME, Steele WA, Downing DT. Changes in the relative amounts of endogenous and exogenous fatty acids in sebaceous lipids during early adolescence. *J Invest Dermatol* 1989; **92**: 371–8.
4 Halford J, Hunt L, Millington GWM. Hyperhidrosis. *BMJ* 2009; **338**: b1166.
5 Mastalier U, Kerl H, Wolf P. Clinical, laboratory, phototest and phototherapy findings in polymorphic light eruptions: a retrospective study of 133 patients. *Eur J Dermatol* 1998; **8**: 554–9.
6 Sanfilippo AM, Barrio V, Kulp-Shorten C *et al*. Common pediatric and adolescent skin conditions. *J Pediatr Adolesc Gynecol* 2003; **16**: 269–83.
7 Farber EM, Nall LM. The natural history of psoriasis in 5600 patients. *Dermatologica* 1974; **148**: 1–18.
8 Graham-Brown RAC. Managing adults with atopic dermatitis. *Dermatol Clin* 1996; **124**: 531–7.
9 Khumalo NP, Jessop S, Ehrlich R. Prevalence of cutaneous adverse effects of hairdressing: a systematic review. *Arch Dermatol* 2006; **142**: 377–83.

The menstrual cycle

Hormonal influences

The menstrual cycle involves changes in the genital tract, which are brought about by two hormones from the ovary. At the start of each cycle, after menstruation is completed, the rising secretion of oestradiol induces the repair and proliferation of the endometrium and the synthesis of receptors for progesterone and oestradiol within its cells. Following ovulation and the formation of the corpus luteum, the rise in progesterone causes the endometrium to double in thickness and the tubular glands to become tortuous and sacculated. The maintenance of this secretory phase is dependent on both oestradiol and progesterone and the breakdown of the endometrium that causes menstrual bleeding is a consequence of the withdrawal of these hormones. The cyclic hormonal changes also affect the vaginal epithelium, which can be monitored through desquamated cells in vaginal smears, the consistency and pH of the cervical mucus and several features of the skin [1].

Synthesis of oestrogens in the ovary first involves the production of the androgens androstenedione and testosterone, in the theca interna cells of the follicle and then their conversion to oestrone and oestradiol in the granulosa cells. Luteinizing hormone (LH) derived from the pituitary gland stimulates these processes. However, the increased production of oestradiol between the eighth and tenth days of the cycle is also dependent on FSH in the sense that this is responsible for the development of numbers of primary follicles in the early follicular phase, which increases the number of granulosa cells [1].

Ovulation in the middle of the cycle is associated with surges in both LH and, to a lesser extent, FSH. The surge in LH lasts for approximately 36 h and is affected by pulsatile output of GnRH from the hypothalamus. It appears that feedback by oestradiol is responsible; in the early follicular phase, oestradiol acts to inhibit secretion of gonadotrophin but, as the follicle ripens, a threshold is exceeded which switches the feedback from negative to positive [1].

Reference

1 Farage MA, Neill S, MacLean AB. Physiological changes associated with the menstrual cycle: a review. *Obstet Gynecol Surv* 2009; **64**: 58–72.

Cutaneous changes

Many women notice changes in their skin and hair during the course of the monthly cycle. For example, 70% of Scottish women reported a few acne papules during the premenstrual phase of their cycle and a significant number of others experienced textural variations. Some found the skin and hair greasier (35%), others drier (16%) [1], despite the fact that sebum production has not reliably been shown to alter significantly. Pre-existing skin disorders, other than acne, may also undergo premenstrual exacerbation; examples are psoriasis, rosacea, atopic eczema, lupus erythematosus, anogenital pruritus, recurrent aphthae and herpes simplex [2,3].

Some women experience premenstrual flushing identical in quality to that associated with the menopause. In one study of 120 women with classical features of the so-called premenstrual syndrome, 72% were observed to have such flushing episodes [4]. This phenomenon may be related in part to the general increase in cutaneous vascularity during the second half of the menstrual cycle [5], but detailed investigation of one of these women revealed that each flush (recorded using skin resistance and finger temperature) coincided with a measurable pulse of LH. Identical findings are reported in menopausal flushes (see p. 8.20), suggesting a common pathogenesis.

Other cutaneous disturbances described in the 'premenstrual syndrome' include minor non-specific abnormalities and recurrent boils. Premenstrual oedema has also been described, most commonly of the feet and ankles, but occasionally involving the hands and even the face. In rare individuals this may be very marked.

It is not at all clear what causes most of the symptoms associated with the 'premenstrual syndrome', but there have been many suggestions, including hormonal influences, abnormalities of fluid balance, nutritional changes (including essential fatty acid deple-



Fig. 8.2 Autoimmune progesterone dermatitis. (Courtesy of Dr J.D. Wilkinson, Amersham Hospital, Amersham, UK.)

tion), neurotransmitters and psychological factors. It seems most probable that the syndrome is a complex of interrelated problems, each with a different basic cause or causes [6].

Autoimmune progesterone dermatitis (Fig. 8.2)

There are also patients in whom the regular appearance of skin changes in the premenstrual period is associated with evidence of hypersensitivity to progesterone. This has generally been established by skin testing, deliberate challenge with progesterone or the presence of antibodies and the term autoimmune progesterone dermatitis has been coined for this syndrome [7]. The cutaneous lesions that have been described are very variable, resembling eczema, particularly the pompholyx type, urticaria, erythema multiforme, dermatitis herpetiformis or anaphylaxis [7]. Many patients develop the eruption after receiving exogenous synthetic progesterone preparations.

Treatment of autoimmune progesterone dermatitis can be difficult. Most patients are unresponsive to topical steroids and antihistamines, but some respond to oestrogen or tamoxifen therapy [7]. One resistant patient required bilateral oophorectomy [7].

References

1 Sutherland H, Stewart I. A critical analysis of the premenstrual syndrome. *Lancet* 1965; **i**: 1180–3.

2 Anderson RH. Autoimmune progesterone dermatitis. *Cutis* 1984; **33**: 490–1.

3 Dalton K. Premenstrual tension: an overview. In: Friedmann RC, ed. *Behavior and the Menstrual Cycle*. New York: Dekker, 1982: 217–42.

4 Casper RF, Graves GR, Reid RL. Objective measurement of hot flushes associated with the premenstrual syndrome. *Fertil Steril* 1987; **47**: 341–4.

5 Edwards EA, Duntley SQ. Cutaneous vascular changes in women in reference to the menstrual cycle and ovariectomy. *Am J Obstet Gynecol* 1949; **57**: 501–9.

6 Campagne DM, Campagne G. The premenstrual syndrome revisited. *Eur J Obstet Gynecol Reprod Biol* 2007; **130**: 4–17.

7 Snyder JL, Krishnaswamy G. Autoimmune progesterone dermatitis and its manifestation as anaphylaxis: a case report and literature review. *Ann Allergy Asthma Immunol* 2003; **90**: 469–77.

Pregnancy, childbirth and the puerperium

Pregnancy, childbirth and the puerperium are associated with profound physiological endocrine upheavals. Many of the consequent cutaneous changes should be considered normal, although not every woman is happy to accept them in this light. The physiological events of pregnancy and its resolution can also modify a number of cutaneous disorders and there are also some pathological skin conditions that are virtually pregnancy-specific.

Endocrine background

Pregnancy is characterized by the advent of a new and unique endocrine organ, the placenta. The hormonal changes of pregnancy start soon after the fertilized ovum becomes implanted in the endometrium, when the developing trophoblast begins to secrete chorionic gonadotrophin. This, in turn, stimulates production of oestrogen and progesterone by the corpus luteum. The increase in the concentration of these steroids suppresses pituitary FSH production and thus prevents further ovulation. At about the ninth week of pregnancy the fetoplacental unit begins to synthesize pregnenolone and progesterone. Pregnenolone crosses to the fetus and is converted to dehydroepiandrosterone by the developing fetal adrenal. This, in turn, returns to the placenta to be aromatized to oestriol. From about the 12th week there are increasing amounts of oestriol and progesterone and the corpus luteum of pregnancy regresses.

The placenta also produces lactogen (hPL) in quantities as great as 1 g/day by late pregnancy. This hormone has some somatotrophic as well as lactogenic properties. A human chorionic thyrotrophin (hCT), structurally different from pituitary thyroid-stimulating hormone (TSH), has also been isolated.

Placental hormones partly facilitate the physiological adaptations that occur in pregnancy including, for example, a considerable increase in blood volume. The thyroid enlarges and takes up more iodine. The pituitary also enlarges and increases its output of ACTH, prolactin and gonadotrophins. Circulating cortisol rises, caused mainly by a decrease in its clearance rate combined with increased cortisol-binding globulin.

The breasts enlarge during pregnancy, most noticeably towards term. In the early phases of a first pregnancy there is a rapid growth and branching of the terminal portions of glandular tissue, together with an increase in the vascularity of the breast as a whole. Later, true acini appear for the first time and alveolar secretion begins during the second trimester. In the last weeks there is considerable parenchymal cell enlargement and the alveoli become distended with colostrum [1].

The state of pregnancy is ended, at least in part, by an alteration in the balance of the antagonistic actions of oestrogen and progesterone. This is probably fine-tuned by the fetal pituitary–adrenal axis and its effect on oestrogen production [1]. Thus, abnormalities of the fetal brain, such as anencephaly, may lead to abnormally early or late onset of parturition. The tendency of labour to be delayed in mothers bearing children with X-linked ichthyosis is caused by a reduction in the processing of hormones by the placental enzyme steroid sulphatase (see Chapter 19).

After birth, the mother's hormonal status changes yet again. Levels of prolactin rise steadily towards the end of pregnancy and at childbirth the apparently inhibitory effect of the fetoplacental steroid hormones is suddenly lost, leaving prolactin acting unopposed. This initiates lactation [1].

Reference

1 Tulchinsky D, Little AB, eds. *Maternal-Fetal Endocrinology*, 2nd edn. Philadelphia: Saunders, 1994.

Physiological skin changes related to pregnancy

Pigmentation (see Chapter 58)

Most women notice a generalized increase in skin pigmentation during pregnancy and the change is more marked in dark-haired than in fair-haired women. Areas that are already pigmented become darker, in particular the nipples, areolae, genital areas and the midline of the abdominal wall. In consequence, the 'linea alba' ('white line') may become brown. The pigmentation usually fades after delivery, but seldom to its previous level. Many women also notice an increase in the size, activity and number of melanocytic naevi [1].

In approximately 70% of women, especially those of dark complexion, chloasmal pigmentation also develops during the second half of pregnancy. Its intensity is not necessarily proportional to that of the general melanosis. Irregular, sharply marginated areas of pigmentation develop in a roughly symmetrical pattern either on the forehead and temples, or on the central part of the face, or both. It usually fades completely after parturition, but may persist [1].

The extent to which human pigmentary changes are brought about by oestrogen and progesterone, or by melanocyte-stimulating hormones derived from pro-opiomelanocortin and other factors (see Chapter 58), is uncertain [2,3].

Hair and nail changes

Many women maintain that hair growth on the scalp is more vigorous during pregnancy. In the latter part, the proportion of follicles retained in anagen rises, but a compensatory decrease after parturition associated with shedding of hairs may result in noticeable postpartum, telogen alopecia [1]. Spontaneous recovery is usual. Mild frontoparietal recession may also occur [4].

Minor degrees of hypertrichosis are not uncommon. Hirsutism, accompanied by acne and, in severe cases, by other evidence of virilization, occurs rarely, usually during the second half of pregnancy. It may result from an androgen-secreting tumour, luteoma, lutein cysts or polycystic ovary disease [1,5,6]. All cases should be thoroughly investigated. A female fetus may be masculinized. In the absence of a tumour that can be eradicated, the problem tends to recur in subsequent pregnancies. Hirsutism may regress between pregnancies, but this is not always complete.

Pregnant women often report brittleness of the nail plate and some develop distal onycholysis, similar to that seen occasionally in thyrotoxicosis [4].

Eccrine, apocrine and sebaceous gland activity

Eccrine activity may be noticeably increased during pregnancy [4], although palmar sweating diminishes [1,4]. This may be responsible for the recognized increased frequency of miliaria. It is often said that apocrine gland activity is reduced during pregnancy, but the evidence is conflicting. There is no increase in apocrine sweating immediately postpartum, but Fox–Fordyce disease usually improves in pregnancy, which suggests that apocrine activity has been reduced [1].

Although there is considerable individual variation, the rate of sebum excretion tends to increase during pregnancy and return to normal after delivery [7].

The rise in sebum excretion during the last trimester of pregnancy, at a time when oestrogens, which suppress sebum secretion, are being produced in large quantities, suggests that a powerful sebotrophic stimulus is released. The sebum excretion rate in women with twins or triplets is no greater than the rate in women with a single fetus, suggesting that the sebotrophic factor comes from the pituitary rather than the placenta [3,8]. Sebum excretion does not fall in women who are lactating [9] and suckling presumably promotes secretion of pituitary factors, such as prolactin, which either stimulate sebaceous glands directly or enhance their response to androgens.

References

1 Nussbaum R, Benedetto AV. Cosmetic aspects of pregnancy. *Clin Dermatol* 2006; **24**: 133–41.

2 Millington GWM. Pro-opiomelanocortin (POMC): the cutaneous roles of its melanocortin products and receptors. *Clin Exp Dermatol* 2006; **31**: 407–12.

3 Millington GWM, Levell NJ. From genesis to gene sequencing: historical progress in the understanding of skin color. *Int J Dermatol* 2007; **46**: 103–5.

4 Muallem MM, Rubeiz NG. Physiological and biological skin changes in pregnancy. *Clin Dermatol* 2006; **24**: 80–3.

5 Rosenfield RL. What every physician should know about polycystic ovary syndrome. *Dermatol Ther* 2008; **21**: 354–61.

6 Judd HL, Benirschke K, De Vane G *et al*. Maternal virilization developing during a twin pregnancy. *N Engl J Med* 1973; **288**: 118–22.

7 Burton JL, Cunliffe WJ, Millar DG *et al*. Effect of pregnancy on sebum excretion. *BMJ* 1970; **ii**: 769–71.

8 Burton JL, Shuster S, Cartlidge M. The sebotrophic effect of pregnancy. *Acta Derm Venereol (Stockh)* 1975; **55**: 11–3.

9 Burton JL, Shuster S, Cartlidge M *et al*. Lactation, sebum excretion and melanocyte-stimulating hormone. *Nature* 1973; **243**: 349–50.

Vascular changes

The vascular changes of pregnancy do not differ qualitatively from those in hyperthyroidism or cirrhosis. All are thought to be due to sustained high levels of circulating oestrogen. Vascular 'spiders' are very common in white women but are said to be less so in black women [1]. They usually disappear postpartum. Palmar erythema is also common, affecting at least 70% of white women and 30% of black women [1]. In some, it takes the form of a diffuse pink mottling of the whole palm, whereas in others the changes are confined to the thenar and hypothenar eminences [1]. Palmar erythema and vascular spiders commonly occur together.

Less commonly, pregnant women develop small haemangiomas [1]. These usually affect the head and neck (Fig. 8.3) and occur in approximately 5% of pregnancies [1].

Varicose veins of the legs and haemorrhoids are frequent complications of pregnancy. A rarer but more serious event is the



Fig. 8.3 Pyogenic granuloma in a port-wine stain during pregnancy. This woman had similar lesions in three successive pregnancies.

development of deep-vein thrombosis, which can lead to permanent damage to the veins of the legs and, occasionally, death from pulmonary embolism. Many pregnant women (possibly 50%) also develop non-pitting oedema of the face, eyelids, feet and hands [2]. The swelling is usually most pronounced in the early morning and disappears during the course of the day. There is no known treatment, but it is important to recognize and differentiate the condition from cardiac, renal or pre-eclamptic oedema.

Gingivitis and pregnancy 'epulis'

Eighty per cent or more of pregnant women develop some gingival oedema and redness [2,3]. This can become painful and ulcerative, especially if oral hygiene is poor. In approximately 2%, the gingival changes are associated with the appearance of a small vascular lesion similar to a pyogenic granuloma, known as a pregnancy epulis or granuloma gravidarum [1]. This may bleed profusely on contact. These phenomena, like palmar erythema and vascular spiders, are probably brought about by the general increase in vascularity associated with high oestrogen levels.

In most women, gum changes resolve after parturition. Vitamin C has been used to try to improve the symptomatology [3].

References

1 Nussbaum R, Benedetto AV. Cosmetic aspects of pregnancy. *Clin Dermatol* 2006; **24**: 133–41.

2 Torgerson RR, Marnach ML, Bruce AJ, Rogers RS. Oral and vulvar changes in pregnancy. *Clin Dermatol* 2006; **24**: 122–32.

3 Hilming F. Gingivitis gravidarum: studies on clinic and on etiology with special reference to the influence of vitamin C. *Oral Surg Oral Med Oral Pathol* 1952; **5**: 734–51.

Table 8.5 Dermatoses and tumours modified by pregnancy.

Infections	*Disorders of connective tissue*
Candidiasis	Ehlers–Danlos syndrome
Trichomoniasis	Pseudoxanthoma elasticum
Condylomata acuminata	
Pityrosporum folliculitis	*Tumours*
Herpes simplex	Bowenoid papulosis
Herpes varicella/zoster	Langerhans' cell histiocytosis
Leprosy	Mycosis fungoides
	Malignant melanoma
Autoimmune disorders	Neurofibromatosis
Lupus erythematosus	
Dermatomyositis/polymyositis	*Miscellaneous*
Pemphigus	Atopic dermatitis
Systemic sclerosis	Erythema multiforme
	Erythrokeratoderma variabilis
Metabolic disorders	Psoriasis (and 'impetigo herpetiformis')
Porphyria cutanea tarda	Acne
Acrodermatitis enteropathica	Hidradenitis suppurativa
	Fox–Fordyce disease

Dermatoses modified by pregnancy

Some dermatoses worsen during pregnancy, some improve and many are unpredictable. Table 8.5 lists those dermatoses and tumours that are commonly modified by pregnancy and the puerperium. The details of most of these are discussed elsewhere in this book; however, some specific points should be noted here.

Infections and immunity in pregnancy

Cell-mediated immunity is depressed during normal pregnancy [1], which probably accounts for the increased frequency and severity of certain infections such as candidiasis. Condylomata acuminata too can be exacerbated, growing very rapidly and occasionally obstructing the birth canal. *Candida*, genital warts and herpes simplex can be transmitted to the baby during childbirth. In babies of very low birth weight, candidiasis and herpes simplex can be life-threatening [2,3]. In view of the known oncogenic potential of some strains, there is a debate about whether mothers infected with human papillomavirus should routinely be offered caesarean section, as generally practised for active herpes simplex infection. However, there is doubt whether this practice prevents neonatal infection [3] either by herpes virus or by genital warts [4]. Bowenoid papulosis (see Chapter 71), a condition closely linked with wart virus infection, may appear for the first time or deteriorate during pregnancy [5].

Podophyllin should never be used in the treatment of warts during pregnancy because of potential maternal and fetal toxicity; physical treatments are preferable [6].

The immune alterations of pregnancy, childbirth and the puerperium have an adverse effect on leprosy in more than one-third of patients [7]. Leprosy reactional states are more common and the decline in immune reactivity may also lead to an increase in drug resistance [7]. Furthermore, there are specific problems with some antileprosy drugs: thalidomide cannot be used because of its teratogenicity and clofazimine has been associated with unexplained fetal deaths [8].

Autoimmune disorders

The outcome of most pregnancies in women with systemic lupus erythematosus is undoubtedly better than was once thought, although a few develop renal damage and disease exacerbation may be severe enough to cause death [9]. Lupus in the mother may affect the baby (neonatal lupus; see Chapter 17). Cutaneous lupus does not appear to be affected by pregnancy [9].

Most women with scleroderma do not experience major problems and some appear to improve [10]. Occasionally, however, there is severe progressive deterioration of renal function, with hypertension and pre-eclampsia. This may lead to fetal loss or even maternal death [10].

Dermatomyositis and polymyositis are generally unaffected by pregnancy, but some patients may deteriorate and it can be associated with a poor fetal outcome [11].

Metabolic disease

There is no consensus about the effects of pregnancy on porphyria cutanea tarda. Some women experience few problems. However, some cases do show clinical and biochemical deterioration and on one occasion this may have been parallel to the physiological rise in oestrogen [12]. Acrodermatitis enteropathica is said always to deteriorate in pregnancy [13].

Disorders of connective tissue

Women with Ehlers–Danlos syndrome types I and IV often have major problems, including bleeding, wound dehiscence and uterine lacerations (see Chapter 45) [14]. They should probably be counselled to avoid pregnancy altogether. Some patients with pseudoxanthoma elasticum have suffered major gastrointestinal bleeds necessitating blood transfusion [14].

Tumours

The relationship between malignant melanoma and pregnancy (and, indeed, exogenous oestrogens) has been discussed for many years [1]. One large series suggests that melanoma developing during pregnancy carries a slightly worse prognosis, but that pregnancy following excision of a tumour does not affect prognosis [15]. Epidemiological studies from the USA have failed to show significant associations between melanoma and reproductive and other hormonal factors in women [16]. Neurofibromata may grow during pregnancy, or appear for the first time. Rupture of major blood vessels in neurofibromatosis has also been reported [17,18] and hypertension is a common complication. Pregnancy may exacerbate mycosis fungoides [19] and the eosinophilic granuloma form of Langerhans' cell histiocytosis [20].

Miscellaneous dermatoses

Atopic eczema often improves in pregnancy, but this is unpredictable; in some patients it is exacerbated. Breastfeeding is often a problem for those suffering from atopic eczema because of nipple eczema and the puerperium may herald deterioration in hand eczema because of exposure to irritants.

Pregnancy may trigger erythema multiforme and vaginal stenosis has been described in severe Stevens–Johnson syndrome occurring in pregnancy [21].

Marked deterioration in erythrokeratoderma variabilis occurred during pregnancy in two related women [22].

The effects of pregnancy on psoriasis are variable, although often consistent in the same individual. On balance psoriasis is more likely to improve during pregnancy with relapse postpartum [23]. A rare occurrence is the sudden eruption of acute pustular psoriasis. This used to be considered as a distinct entity called *impetigo herpetiformis*, but this term is probably best discarded.

References

1 Yip L, McCluskey J, Sinclair R. Immunological aspects of pregnancy. *Clin Dermatol* 2006; **24**: 84–7.

2 Darmstadt GL, Dinulos JG, Miller Z. Congenital cutaneous candidiasis: clinical presentation, pathogenesis, and management guidelines. *Pediatrics* 2000; **105**: 438–44.

3 Prober CG, Sullender WM, Yasukawa LL *et al*. Low risk of herpes simplex virus infections in neonates exposed to the virus at the time of vaginal delivery to mothers with recurrent genital herpes simplex virus infections. *N Engl J Med* 1989; **314**: 240–4.

4 Chuang TY. Condylomata acuminata (genital warts). *J Am Acad Dermatol* 1987; **16**: 376–84.

5 Patterson JW, Kao GF, Graham JH *et al*. Bowenoid papulosis: a clinicopathologic study with ultrastructural observations. *Cancer* 1986; **57**: 823–36.

6 Bargman H. Podophyllin and pregnancy. *Int J Dermatol* 1993; **32**: 691.

7 Duncan ME, Pearson JMH, Ridley DS *et al*. Pregnancy and leprosy: the consequences of alterations of cell-mediated and humoral immunity during pregnancy and lactation. *Lepr Rev* 1982; **55**: 129–42.

8 Farb H, West DP, Pedvis-Leftick A. Clofazimine in pregnancy complicated by leprosy. *Obstet Gynecol* 1982; **59**: 122–3.

9 Clowse ME. Lupus activity in pregnancy. *Rheum Dis Clin North Am* 2007; **33**: 237–52.

10 Steen VD. Pregnancy in scleroderma. *Rheum Dis Clin North Am* 2007; **33**: 345–58.

11 Williams L, Chang PY, Park E *et al*. Successful treatment of dermatomyositis during pregnancy with intravenous immunoglobulin monotherapy. *Obstet Gynecol* 2007; **109**: 561–3.

12 Loret de Mola JR, Muise KL, Duchon MA. Porphyria cutanea tarda and pregnancy. *Obstet Gynecol Surv* 1996; **51**: 493–7.

13 Perez-Maldonado A, Kurban AK. Metabolic diseases and pregnancy. *Clin Dermatol* 2006; **24**: 88–90.

14 Ramos-E-Silva M, Libia Cardozo Pereira A, Bastos Oliveira G *et al*. Connective tissue diseases: pseudoxanthoma elasticum, anetoderma, and Ehlers–Danlos syndrome in pregnancy. *Clin Dermatol* 2006; **24**: 91–6.

15 MacKie RM, Bufalino R, Sutherland C. The effect of pregnancy on melanoma prognosis. *Br J Dermatol* 1990; **123** (Suppl. 37): 40.

16 Holly EA, Cress RD, Ahn DK. Cutaneous melanoma in women. III. Reproductive factors and oral contraceptive use. *Am J Epidemiol* 1995; **141**: 943–50.

17 Brade DB, Bolan JC. Neurofibromatosis and spontaneous hemothorax in pregnancy: two case reports. *Obstet Gynecol* 1984; **63** (Suppl.): 35–8.

18 Tapp E, Hickling RS. Renal artery rupture in a pregnant woman with neurofibromatosis. *J Pathol* 1969; **97**: 398–402.

19 Vonderheid EC, Dellatore DL, van Scott EJ. Prolonged remission of tumor-stage mycosis fungoides by topical immunotherapy. *Arch Dermatol* 1981; **117**: 586–9.

20 Growdon WA, Cline M, Tesler A *et al*. Adverse effects of pregnancy on multifocal eosinophilic granuloma. *Obstet Gynecol* 1986; **67** (Suppl.): 2–6.

21 Graham-Brown RAC, Cochrane GW, Swinhoe JR *et al*. Vaginal stenosis due to bullous erythema multiforme (Stevens–Johnson syndrome). *Br J Obstet Gynaecol* 1981; **88**: 1156–7.

22 Gewirtzman GB, Winkler NW, Dobson RL. Erythrokeratoderma variabilis: a family study. *Arch Dermatol* 1978; **114**: 112–4.

23 Weatherhead S, Robson SC, Reynolds NJ. Management of psoriasis in pregnancy. *BMJ* 2007; **334**: 1218–20.

AIDS and pregnancy

AIDS is a worldwide problem and there have now been many pregnancies in women infected by human immunodeficiency virus (HIV). The infection has often only become apparent after birth when the children developed AIDS. Although it appears that pregnancy may subsequently accelerate the development of AIDS symptoms [1,2], there does not seem to be a tendency for HIV disease to progress during pregnancy itself [3]. If opportunistic infections, such as *Pneumocystis* pneumonia or listeriosis, develop in a pregnant woman with AIDS, the outcome is generally fatal [4,5]. This contrasts with the more usual 70% recovery rate in non-pregnant AIDS patients and suggests that the immune suppression of pregnancy may be additive to that of HIV infection. Kaposi's sarcoma has also been reported in AIDS in pregnancy [6]. The effects of maternal HIV infection on the child can be devastating [7].

References

1 Minkoff H, Nanda D, Menez R *et al*. Pregnancies resulting in infants with acquired immunodeficiency syndrome or AIDS-related complex. *Obstet Gynecol* 1987; **69**: 285–7.

2 Minkoff H, Nanda D, Menez R *et al*. Pregnancies resulting in infants with acquired immunodeficiency syndrome or AIDS-related complex: follow-up of mothers, children and subsequently born siblings. *Obstet Gynecol* 1987; **69**: 288–91.

3 Weisser M, Rudin C, Battegay M *et al*. Does pregnancy influence the course of HIV infection? Evidence from two large Swiss cohort studies. *J AIDS* 1998; **17**: 404–10.

4 Minkoff H, de Regt RH, Landesman S *et al*. *Pneumocystis carinii* pneumonia associated with acquired immunodeficiency syndrome in pregnancy: a report of three maternal deaths. *Obstet Gynecol* 1986; **67**: 284–7.

5 Wetli CV, Roldan ED, Fujaco RM. Listeriosis as a cause of maternal death: an obstetric complication of acquired immunodeficiency syndrome (AIDS). *Am J Obstet Gynecol* 1983; **147**: 7–9.

6 Rawlinson KF, Zubrow AB, Harris MA *et al*. Disseminated Kaposi's sarcoma in pregnancy: a manifestation of acquired immune deficiency syndrome. *Obstet Gynecol* 1984; **63** (Suppl.): 2–6.

7 Winton GB. Skin disease aggravated by pregnancy. *J Am Acad Dermatol* 1989; **20**: 1–13.

The dermatoses of pregnancy

Irritation, rashes and other skin changes are common in pregnancy [1]. The possibility that the patient has an unrelated skin condition such as scabies must not be overlooked. However, there are several skin changes that appear to be specifically related to pregnancy and the puerperium, distinct from physiological events and not caused by exacerbation of a pre-existing condition [2].

Pruritus gravidarum

Itching in pregnancy is dealt with here because it is uncertain whether it is an extension of the physiological changes or a specific dermatosis. As many as one-fifth of pregnant women experience itching [3]. In most, this can be attributed to some identifiable skin disorder such as scabies, eczema, urticaria, a drug eruption or one of the specific pregnancy-related inflammatory dermatoses discussed below. However, there is also a small group of women who experience intense pruritus without evident primary cutaneous changes and it is to these patients that the term pruritus gravidarum is applied.

It is generally considered that pruritus gravidarum is a mild variant of recurrent cholestasis of pregnancy and occurs in 0.02–2.4% of pregnancies [4]. The itching begins in the second or third trimester and is often localized to the abdomen, or the palms and soles, although it may also be very widespread. The patient may be mildly icteric. Liver function tests are occasionally abnormal, with a raised alkaline phosphatase [5].

The cause is thought to be multifactorial [2,6], although it is probable that the irritation itself results from abnormal hepatic excretion of bile acids induced by metabolites of both oestrogen and progesterone, both of which have been shown to affect the handling of bile acids [2,6]. The condition also occurs more commonly in mothers of patients with rare inborn cholestatic syndromes [6].

The itching usually subsides rapidly after childbirth, but may persist for some weeks into the puerperium. It may also recur with subsequent pregnancies and the use of oral contraceptive pills. Recurrent attacks increase the liability to cholelithiasis [3]. Treatment with ursodeoxycholic acid is effective in reducing itch and abnormal liver function tests [6].

Striae

Striae distensae (striae gravidarum) are a common and striking feature of most pregnancies. They are dealt with fully in Chapter 45 [7].

Skin tags

Synonym

- Molluscum fibrosum gravidarum

Multiple tags often appear in the second half of pregnancy. These are most common on the face, the side of the neck, in the axillae and under the breasts. The histological features are those of ordinary skin tags. They are usually small, but may reach 5 mm in size. They generally regress in the puerperium and it has been suggested that they are probably a result of hormonal factors [8].

'Cracked' and sore nipples

Many women experience discomfort, irritation and fissuring of the nipples, especially early in the puerperium as they are trying to establish breastfeeding. Anatomical features, such as relatively flat nipples, contribute to the development of this problem. Mastitis and deep abscesses may occur because of penetration of the broken skin by pyogenic bacteria. The problem is, in essence, one of friction and irritation and can be eased considerably by the judicious use of gentle cleansing and emollients [5].

Inflammatory dermatoses specific to pregnancy

Classification. The older literature is confusing. Dermatoses considered distinct by some authors are lumped together by others. Holmes and Black [9] have suggested a rationalization of the terminology and have proposed a classification that seems the most logical for practical use (Table 8.6), even though alternatives are still employed. Ackerman *et al*. [10] argue that there really are only two dermatoses in this category: pruritic urticarial papules and plaques of pregnancy (PUPPP) and pemphigoid gestationis.

Table 8.6 Specific dermatoses of pregnancy. (From Shornick [11].)

Pemphigoid (herpes) gestationis
Polymorphic eruption of pregnancy
Prurigo of pregnancy
Pruritic folliculitis of pregnancy

However, some of the other dermatoses that have been reported as being pregnancy-associated are discussed here, drawing attention to those descriptions that appear to be at least clinically distinct from PUPPP or pemphigoid gestationis and reviewing whether others are really distinct entities or not.

Pemphigoid (herpes) gestationis

This rare and highly characteristic disorder affects approximately 1 in 10 000 to 1 in 150 000 pregnancies and is considered in detail in Chapter 40. The disease usually appears in the second or third trimester and presents with an intensely itchy urticarial or vesiculobullous eruption. Immunofluorescence reveals a linear band of immunoglobulin G (IgG) at the basement-membrane zone, identical to that seen in bullous pemphigoid. The histopathological features resemble bullous pemphigoid too [12]. Recent studies involving tissue typing have supported earlier suggestions of a genetic predisposition [13]. The disease is often associated with other organ-specific autoimmune diseases and tends to recur in subsequent pregnancies, although this is not always the case [14].

Polymorphic eruption of pregnancy

Synonym
- Pruritic urticarial papules and plaques of pregnancy

In addition to the above designations, these skin changes have been known as toxaemic rash of pregnancy, toxic erythema of pregnancy and 'late-onset' prurigo of pregnancy. It is probable also that some patients with this condition have been recorded in the literature as prurigo gestationis (see below), erythema multiforme and pemphigoid (herpes) gestationis [15,16].

If there is agreement that all these disorders are one and the same, there is still no consensus on which name to use. In the UK, as proposed by Holmes and Black [9], the term polymorphic eruption of pregnancy is favoured. Elsewhere, the lengthy descriptive phrase 'pruritic urticarial papules and plaques of pregnancy' or 'PUPPP', still finds favour, especially in the USA [15,16].

Incidence. Polymorphic eruption of pregnancy occurs in approximately 1 in 160 pregnancies [16]. The eruption begins in the third trimester, usually of a first pregnancy, but is occasionally delayed until a few days postpartum. It rarely recurs in subsequent pregnancies, but when it does it is often less severe [15,16].

Aetiology. The cause remains obscure, although the condition has been related to abnormal weight gains in the mother and to twin pregnancy [16]. Although this study found no link with high fetal birth weight [16], this has previously been thought to be an association [17]. As the disorder occurs predominantly in primigravidae in the third trimester, it has been postulated that excessive abdominal distension may act as a trigger for the skin changes. The typical distribution (see below) may lend some credence to this view. It has also been shown that serum cortisol levels are low in patients with polymorphic eruption of pregnancy, while human chorionic gonadotrophin (hCG) and oestradiol are normal [18]. Unlike pemphigoid gestationis, there is no HLA-association [15].

Pathology. The histology of this condition is non-specific and there are many similarities with the early prebullous phase of pemphigoid gestationis. Most biopsies show epidermal and upper dermal oedema, with a perivascular infiltrate of lymphocytes and histiocytes. There may be a striking number of eosinophils (as there may be in pemphigoid gestationis). Spongiotic vesicles are also seen, as is patchy parakeratosis [15].

Immunofluorescence is generally negative, even by immunoelectron microscopy, and this provides the best means of distinguishing this disorder from pemphigoid gestationis, should there be any diagnostic doubt [19]. There are occasional reports of equivocal immunofluorescence findings with polymorphic eruption of pregnancy, such as minimal C3 deposition along the basement membrane, perivascularly in the dermis or in the epidermis [15]. In these rare situations of equivocal immunofluoresence, a BP180 NC16a enzyme-linked immunosorbent assay has been shown to be highly sensitive and specific in distinguishing pemphigoid gestationis from polymorphic eruption of pregnancy [20].

Clinical features. The patient usually complains of intense itching. The skin lesions closely resemble the very early stage of pemphigoid gestationis. The eruption consists predominantly of urticated papules and plaques. Less commonly, vesicles, target lesions and polycyclic erythematous areas are seen. The most striking feature, however, is the distribution of the lesions. They usually begin and predominate on the abdomen, often closely following the lines of the striae, where present (Fig. 8.4). The umbilicus is frequently spared. Lesions often also appear on the upper arms and thighs.

Despite the outdated term toxaemic rash of pregnancy, there is no suggestion that polymorphic eruption has any adverse effect on the outcome of the pregnancy [15,16].

Treatment. Some patients improve with topical emollients or steroids. Most women are relieved to learn that the condition is not serious, that all should be well with them and their baby and that the rash will disappear at or soon after childbirth [15,16].

Prurigo of pregnancy

Synonyms
- Early-onset prurigo of pregnancy
- Prurigo gestationis of Besnier

The main differences between this disorder and polymorphic eruption of pregnancy are that it begins earlier (usually between 25 and 30 weeks' gestation) and that there are no urticated lesions. It occurs in 1 in 50 to 1 in 200 pregnancies. Clinically, there are



(a)



(b)

Fig. 8.4 Typical lesions of polymorphic eruption of pregnancy: (a) on the arm and (b) on the abdomen. (Courtesy of Dr D.A. Burns, Leicester Royal Infirmary, Leicester, UK.)

multiple excoriated papules over the abdomen and on the extensor surfaces of the limbs. Histology reveals acanthosis and parakeratosis, with perivascular lymphocytic infiltration around upper dermal vessels. Immunofluorescence is negative. The lesions tend to persist throughout pregnancy and may continue well into the puerperium, although the pruritic element often settles shortly after delivery. As with polymorphic eruption of pregnancy, the mother and fetus are unaffected, but prurigo of pregnancy may recur in successive pregnancies, which can cause significant distress to the pregnant woman. It has been suggested that cases labelled 'prurigo of pregnancy' may, in fact, have been eczema.

Only symptomatic treatment is available and this is often rather unsatisfactory [1,2,21].

Pruritic folliculitis of pregnancy

This disorder begins in the second or third trimester and usually resolves within 2 weeks of delivery. The eruption consists of masses of itchy red follicular papules. It strongly resembles steroid-induced acne. Histology reveals a non-specific folliculitis. Immunofluorescence is negative. There is no adverse effect on mother or baby [1,2,21].

Less well-defined dermatoses

Papular dermatitis of pregnancy

Considerable controversy surrounds this entity. It was first described by Spangler *et al*. [22] in 1962, who reported a widespread papular eruption, which they estimated to occur only once in every 2400 pregnancies. In the original description, the rash consisted of widespread, 3–5 mm, intensely itchy papules with a smaller central crust. There were several laboratory abnormalities, including markedly raised urinary chorionic gonadotrophin levels and low urinary oestriol. Of most significance was the observation that there appeared to be a 30% fetal mortality with this eruption. However, there have been no other convincing reports and a recent review of 85 patients found no evidence of increased fetal loss [23]. The confusion may have arisen because Spangler *et al*. [22] included fetal deaths in pregnancies unaffected by a rash and spontaneous abortions, without qualifying these by gestational age [2].

It is now generally accepted that the changes reported as papular dermatitis of pregnancy are probably those of pregnancy prurigo and that the fetal loss in Spangler *et al*.'s series was overestimated.

Autoimmune progesterone dermatitis of pregnancy

There is a single case report of a patient who developed an odd acneiform rash on the extremities and buttocks in two successive pregnancies [24]. There was an associated arthritis and a positive skin test reaction to progesterone. The author used the term autoimmune progesterone dermatitis to describe this phenomenon, thereby leading to confusion with the condition of the same name that is not pregnancy-associated. However, the clinical features of the two disorders are quite distinct.

Prurigo annularis

Two reported cases [25] had annular scaly lesions that persisted for years postpartum. Whether it really had anything to do with the pregnancy must be in doubt.

References

1 Vaughan Jones SA, Black MM. Pregnancy dermatoses. *J Am Acad Dermatol* 1999; **40**: 233–41.

2 Ambros-Rudolph CM, Mullegger RR, Vaughan-Jones SA *et al.* The specific dermatoses of pregnancy revisited and reclassified: results of a retrospective two-center study on 505 pregnant patients. *J Am Acad Dermatol* 2006; **54**: 395–404.

3 Furhoff WR. Itching in pregnancy: a 15-year follow-up study. *Acta Med Scand* 1974; **196**: 403–10.

4 Alcalay J, Wolf JE. Pruritic urticarial papules and plaques of pregnancy: the enigma and the confusion. *J Am Acad Dermatol* 1988; **19**: 1115–6.

5 Black MM, Mayou SC. Skin diseases in pregnancy. In: de Swiet M, ed. *Medical Disorders in Obstetric Practice*, 2nd edn. Oxford: Blackwell Scientific Publications, 1989: 808–29.

6 Milkiewicz P, Elias E, Williamson C *et al*. Obstetric cholestasis. *BMJ* 2002; **324**: 123–4.
7 Salter SA, Kimball AB. Striae gravidarum. *Clin Dermatol* 2006; **24**: 97–100.
8 Muallem MM, Rubeiz NG. Physiological and biological skin changes in pregnancy. *Clin Dermatol* 2006; **24**: 80–3.
9 Holmes RC, Black MM. The specific dermatoses of pregnancy. *J Am Acad Dermatol* 1983; **8**: 405–12.
10 Ackerman AB, Cavegn BM, Robinson MJ *et al*. *Ackerman's Resolving Quandaries in Dermatology, Pathology and Dermatopathology*. Baltimore: Williams & Wilkins, 1995: 219–21.
11 Shornick JK. Herpes gestationis. *J Am Acad Dermatol* 1987; **17**: 539–56.
12 Al-Fouzan AW, Galadari I, Oumeish I *et al*. Herpes gestationis (pemphigoid gestationis). *Clin Dermatol* 2006; **24**: 80–3.
13 Shornick JK, Jenkins RD, Artlett CM *et al*. Class II MHC typing in pemphigoid gestationis. *Clin Exp Dermatol* 1995; **20**: 123–6.
14 Black MM, Najem NM. Remarkable follow-up experiences of a severe persistent case of pemphigoid gestationis. *Clin Exp Dermatol* 2005; **30**: 593–4.
15 Matiz H, Orion E, Wolf R. Pruritic urticarial papules and plaques of pregnancy: polymorphic eruption of pregnancy (PUPPP). *Clin Dermatol* 2006; **24**: 105–8.
16 Rudolph CM, Al-Fares S, Vaughan-Jones SA *et al*. Polymorphic eruption of pregnancy: clinicopathology and potential trigger factors in 181 patients. *Br J Dermatol* 2006; **154**: 54–60.
17 Cohen LM, Capeless EL, Krusinski PA *et al*. Pruritic urticarial papules and plaques of pregnancy and its relationship to maternal–fetal weight gain and twin pregnancy. *Arch Dermatol* 1989; **125**: 1534–6.
18 Vaughan Jones SA, Hern S, Nelson-Piercy C *et al*. A prospective study of 200 women with dermatoses of pregnancy correlating clinical findings with hormonal and immunopathological profiles. *Br J Dermatol* 1999; **141**: 71–81.
19 Jurecka W, Holmes RC, Black MM *et al*. An immunoelectron microscopy study of the relationship between herpes gestationis and polymorphic eruption of pregnancy. *Br J Dermatol* 1983; **108**: 147–51.
20 Powell AM, Sakuma-Oyama Y, Oyama N *et al*. Usefulness of BP180 NC16a enzyme-linked immunosorbent assay in the serodiagnosis of pemphigoid gestationis and in differentiating between pemphigoid gestationis and pruritic urticarial papules and plaques of pregnancy. *Arch Dermatol* 2005; **141**: 705–10.
21 Dahdah MJ, Kibbi AG. Less well defined dermatoses of pregnancy. *Clin Dermatol* 2006; **24**: 118–21.
22 Spangler AS, Reddy W, Bardiwal WA *et al*. Papular dermatitis of pregnancy. *JAMA* 1962; **181**: 577–81.
23 Vaughan Jones SA, Bhogal BS, Black MM. A prospective study of the specific dermatoses of pregnancy in 85 pregnant women including hormone profiles and effects on pregnancy outcome. *Br J Dermatol* 1996; **135** (Suppl. 47): 18.
24 Bierman SM. Autoimmune progesterone dermatitis. *Arch Dermatol* 1973; **107**: 896–901.
25 Sasseville D, Wilkinson RD, Schnader JY. Dermatoses of pregnancy. *Int J Dermatol* 1981; **20**: 223–41.

Mid-life, obesity and the skin

Introduction to obesity

Where energy intake exceeds expenditure, the storage of excess energy in adipocytes leads to obesity. This may present at any age from early childhood onwards, but tends to develop most commonly in mid-life. Obesity can be measured by population means, waist circumference, percentage body fat or body mass index (BMI = weight kg/height m^2). BMI, the most commonly used measure, was first used nearly 150 years ago [1], but one criticism is that it neglects differences in density between muscle and fat, so bodybuilders and children are arbitrarily defined as obese [2]. In 1980, 8% of women and 6% of men in England were obese, with BMIs more than 30 kg/m^2. By 1998, 21% of women and 17% of men were obese [3]. What might be the reasons for this increase?

Individual psychological factors are clearly important [4] and may have a genetic basis, such as the extreme food-seeking behaviour of leptin-deficient humans [5]. Both in developing and developed economies alike, spending on food advertising is increasing greatly. Within a few years of their introduction, 65% of the Chinese population recognized the Coca Cola brand, 42% recognized Pepsi and 40% recognized Nestlé, whilst in North America, fat and sugar form more than half the daily intake of calories, as available food is now both more processed and more energy dense [6]. Fast food consumption, in particular, positively correlates with weight gain and insulin resistance [7]. Watching television, the third major activity after work and sleep in the USA [8], is associated with frequency of meals, obesity and diabetes [9,10]. This modern, obesity-prone living environment may thus be a result of dietary and activity changes induced by strong commercial pressures. A consequence of this is that obesity increases the risk of many systemic illnesses, such as diabetes, hypertension, coronary heart disease, sleep apnoea and osteoarthritis [11], and cancer of breast, endometrium, prostate and bowel [12].

References

1 Quetelet LAJ. *Physique Sociale*. Brussels: C. Muquardt, 1869: 92.
2 Eto C, Komiya S, Nakao T *et al*. Validity of the body mass index and fat mass index as an indicator of obesity in children aged 3–5 year. *J Physiol Anthropol Appl Human Sci* 2004; **23**: 25–30.
3 National Audit Office. *Tackling Obesity in England*. London: Stationery Office, 2001: 11–2.
4 Thayer RE. *Calm Energy, How People Regulate Mood with Food and Exercise*. Oxford: Oxford University Press, 2001.
5 Farooqi IS, O'Rahilly S. Monogenic human obesity syndromes. *Recent Prog Horm Res* 2004; **59**: 409–24.
6 Chopra M, Darnton-Hill I. Tobacco and obesity epidemics: not so different after all? *BMJ* 2004; **328**: 1558–60.
7 Pereira MA, Kartashov AI, Ebbeling CB *et al*. Fast-food habits, weight gain, and insulin resistance (the CARDIA study): 15-year prospective analysis. *Lancet* 2005; **365**: 36–42.
8 Dietz WH. You are what you eat—what you eat is what you are. *J Adolesc Health Care* 1990; **11**: 76–81.
9 Hu FB, Li TY, Colditz GA *et al*. Television watching and other sedentary behaviors in relation to risk of obesity and type 2 diabetes mellitus in women. *JAMA* 2003; **289**: 1785–91.
10 Stroebele N, De Castro JM. Television viewing is associated with an increase in meal frequency in humans. *Appetite* 2004; **42**: 111–3.
11 Kopelman PG. Obesity as a medical problem. *Nature* 2000; **404**: 635–43.
12 Daling JR, Malone KE, Doody DR *et al*. Relation of body mass index to tumor markers and survival among young women with invasive ductal breast carcinoma. *Cancer* 2001; **92**: 720–9.

Physiological function of adipose tissue

In adults, subcutaneous fat consists almost entirely of white adipose tissue. This provides insulation and acts as an energy source. Additionally, white adipose tissue produces many peptide hormones, cytokines and paracrine transmitters. These include leptin, tumour necrosis factor α, transforming growth-factor β, interleukins 1 and 6, acylation stimulating protein, adiponectin, resistin, visfatin, plasminogen activator inhibitor and non-esterified fatty acids among others [1–3]. In contrast, brown fat is most prominent in the newborn where it is likely to have a different metabolic role [4].

References
1 Mohamed-Ali V, Pinkney JH, Coppack SW. Adipose tissue as an endocrine and paracrine organ. *Int J Obes* 1998; **22**: 1145–58.
2 Ahima RS, Flier JS. Adipose tissue as an endocrine organ. *Trends Endocrinol Metab* 2000; **11**: 327–32.
3 Guzik TJ, Mangalat D, Korbut R. Adipocytokines—novel link between inflammation and vascular function? *J Physiol Pharmacol* 2006; **57**: 505–28.
4 Cinti S. The role of brown adipose tissue in human obesity. *Nutr Metab Cardiovasc Dis* 2006; **16**: 569–74.

Cutaneous pathophysiology in the obese

Obesity alters the natural physiology of the skin. Obese individuals have increased transepidermal water loss, dry skin and erythema compared with controls, suggesting a fundamental alteration in the epidermal barrier. Obesity correlates with increased cutaneous blood flow, which may explain the erythema. The obese have larger skin folds and tend to sweat more profusely when overheated than controls. Obesity impairs lymphatic flow, and alters both collagen formation and wound healing [1]. Delayed-type hypersensitivity, to a range of antigens injected intradermally, was reduced in obese women following weight reduction [2]. Conceivably, this could relate to an alteration in the balance of cytokine production by the adipocytes [3]. It is interesting that there is no data so far with regard to potential differences in the activity of sebaceous, apocrine or eccrine glands in the obese compared with the non-obese [1].

Obesity changes the shape of the foot, for example obese children have a lower footprint angle. Obese individuals have a wider forefoot width and also higher plantar pressures during standing and walking. These pressure effects may be the cause of plantar hyperkeratosis, which is thought to be a cutaneous sign of severe obesity [4].

References
1 Yosipovitch G, DeVore A, Dawn A. Obesity and the skin: skin physiology and skin manifestations of obesity. *J Am Acad Dermatol* 2007; **56**: 901–16.
2 Stallone DD, Stunkard AJ, Zweiman B *et al.* Decline in delayed-type hypersensitivity response in obese women following weight reduction. *Clin Diag Lab Immunol* 1994; **1**: 1202–5.
3 Guzik TJ, Mangalat D, Korbut R. Adipocytokines—novel link between inflammation and vascular function? *J Physiol Pharmacol* 2006; **57**: 505–28.
4 Scheinfeld NS. Obesity and dermatology. *Clin Dermatol* 2004; **22**: 303–9.

Cutaneous disorders in the obese

Many skin disorders are associated with obesity. Obesity is associated with insulin resistance and type 2 diabetes mellitus. Therefore, there will be a secondary association with all the cutaneous associations of that disorder. These are detailed elsewhere. Specific dermatological associations with diabetes and obesity include fibroepithelial polyps and acanthosis nigricans [1,2]. Many infections are found with increased frequency in the obese, including candidiasis, candida folliculitis, intertrigo, tinea cruris, erythrasma, cellulitis, furunculosis and folliculitis. Less common infections include necrotizing fasciitis and gas gangrene [1,2].

Occasionally, severe obesity is associated with the development of massive necrosis of both subcutaneous fat and the overlying skin. This may lead to secondary infection and ulcer formation [3]. The obese have increased intra-abdominal pressure, which in women may predispose to urinary incontinence, exacerbating any tendency to infection and ulceration in the groins and genital area [4]. Obesity may result in a range of respiratory complications. This may necessitate a tracheostomy being performed. Cutaneous complications of this procedure include bleeding, erosions, ulceration and infection [4].

Excess adiposity affects sensitivity to pressure and pain. Obese persons have a higher pain threshold than the non-obese. This decreased pain sensitivity might be the reason for the development of distal venous and pressure ulcers in obese individuals. Lymphoedema presents as a soft, pitting swelling most commonly over the shins and results from poor lymphatic return. It is often associated with obesity [1,2].

As stated earlier, obesity is associated with a number of non-cutaneous cancers [5]. Also, a number of epidemiological studies have found a link between excess adiposity and malignant melanoma [6–10]. Others have found no significant association with melanoma [11,12].

Other conditions that may be associated with or aggravated by obesity include varicose eczema, hidradenitis suppurativa, acne, hirsutism, androgenetic alopecia, psoriasis, keratosis pilaris, striae, seborrhoeic dermatitis, scleroedema, livedo reticularis, cutis verticis gyrata, lichen myxoedematosus, lipodermatosclerosis and lichen sclerosus [1,2,13–18].

Obesity is linked with a number of rarer conditions. Keratosis follicularis squamosa is a condition consisting of scaly patches, symmetrically scattered over the trunk, buttocks and thighs. Histopathological examination shows a dilated hair follicle with a follicular plug, surrounded by lamellar orthohyperkeratosis. There may be an association with obesity [19]. Granular parakeratosis is a recently recognized disorder of keratinization that is confined to intertriginous body sites, which may explain the connection with obesity. The histological features are distinctive, a parakeratotic stratum corneum, with the presence of keratohyalin granules. These granules are normally confined to the stratum granulosum. The underlying pathophysiological defect is thought to be a failure in the normal degradation of profilaggrin and is responsive to topical corticosteroids [20]. Pretibial mucin deposition on the shins, associated with autoimmune thyroid disease, is known as pretibial myxoedema. A recent report found a similar condition (both clinically and histologically) in three morbidly obese patients, without thyroid disease. This paper proposed a new entity ‘chronic obesity lymphoedematous mucinosis’ as a subtype of pretibial myxoedema [21]. Dercum’s disease (adiposis dolorosa) is a rare disease characterized by multiple, painful, subcutaneous lipomata that usually occurs in obese, postmenopausal women. It may have a familial basis [22].

Treatments for obesity can have cutaneous complications too. Jejunoileal bypass surgery is no longer performed regularly for weight loss, as there are newer, less invasive techniques (e.g. gastric banding) and also because a considerable proportion of patients suffer side effects such as polyarthritis, tenosynovitis, myalgia, fever, anaemia and renal failure. This condition often responds to antibiotic therapy [23–26]. Cutaneous features are found too with post-jejunoileal bypass surgery, including a pustular erythematous macular eruption, with a neutrophilic infiltrate similar to Sweet’s syndrome [23,25], a non-pruritic papular eruption, with IgG and C3 deposition [24] and erythema nodosum

Table 8.7 Genetic disorders in which obesity may occur with cutaneous changes.

Disorder	Cutaneous features	Accompanying other features
Prader–Willi syndrome [3]	Hypopigmentation	Learning difficulties
Fragile X syndrome [4]	Regional hyperpigmentation	Learning difficulties, prominent mandible, macro-orchidism, large ears
Proopiomelanocortin deficiency [5]	Red hair, fair (type 1) skin	Tall stature, hypoadrenalism
MOMES syndrome [6]	Atopic eczema	Learning difficulties, ocular abnormalities, maxillary hypoplasia, prognathism
Hyperostosis frontalis interna [7]	Hypertrichosis	Thickening of the frontal bone
Ulnar-mammary syndrome [8]	Hypohidrosis, nipple hypoplasia to absent breasts, absent axillary hair, nail duplication	Malformed digits, hypogonadism, delayed growth
McCune–Albright syndrome [3]	Atypical café-au-lait patches, linear epidermal naevi, Cushing's syndrome, acromegaly	Polyostotic fibrous dysplasia, gigantism, thyrotoxicosis, precocious puberty
Carney complex [9]	Lentigines, oral pigmentation, Cushing's syndrome, schwannomata	Cardiac myxoma, multiple endocrine tumours, precocious puberty

MOMES, mental retardation, obesity, mandibular prognathism with eye and skin anomalies.

[23,26]. Pharmacological therapies for obesity can also have cutaneous side effects. For example, orlistat, lipoprotein lipase inhibitor, therapy may be linked with the development of a lichenoid drug eruption [27].

References

1 Yosipovitch G, DeVore A, Dawn A. Obesity and the skin: skin physiology and skin manifestations of obesity. *J Am Acad Dermatol* 2007; **56**: 901–16.
2 Scheinfeld NS. Obesity and dermatology. *Clin Dermatol* 2004; **22**: 303–9.
3 Janigan DT, Prokopetz RD, Chawla S *et al.* Massive necrosis of fat and skin as complication of obesity. *Can Med Assoc J* 1989; **140**: 665–8.
4 Garciá-Hidalgo L. Dermatological complications of obesity. *Am J Clin Dermatol* 2002; **3**: 497–506.
5 Daling JR, Malone KE, Doody DR *et al.* Relation of body mass index to tumor markers and survival among young women with invasive ductal breast carcinoma. *Cancer* 2001; **92**: 720–9.
6 Gallus S, Naldi L, Martin L *et al.* Anthropometric measures and risk of cutaneous malignant melanoma: a case-control study from Italy. *Melanoma Res* 2006; **16**: 83–7.
7 Kirkpatrick CS, White E, Lee J. Case-control study of malignant melanoma in Washington State II. Diet, alcohol, and obesity. *Am J Epidemiol* 1994; **139**: 869–80.
8 Oh SW, Yoon YS, Shin S. Effects of excess weight on cancer incidences depending on cancer sites and histologic findings among men: Korea National Health Insurance Corporation study. *J Clin Oncol* 2005; **23**: 4742–54.
9 Samanic C, Gridley G, Chow WH *et al.* Obesity and cancer risk among white and black United States veterans. *Cancer Causes Control* 2004; **15**: 35–43.
10 Samanic C, Chow WH, Gridley G *et al.* Relation of body mass index to cancer risk in 362,552 Swedish men. *Cancer Causes Control* 2006; **17**: 901–9.
11 Dubin N, Moseson M, Pasternack BS. Epidemiology of malignant melanoma: pigmentary traits, ultraviolet radiation, and the identification of high-risk populations. *Recent Results Cancer Res* 1986; **102**: 56–75.
12 Veierod MB, Thelle DS, Laake P. Diet and risk of cutaneous malignant melanoma: a prospective study of 50,757 Norwegian men and women. *Int J Cancer* 1997; **71**: 600–4.
13 Garciá-Hidalgo L, Orozco-Topete R, Gonzalez-Barranco J *et al.* Dermatoses in 156 obese adults. *Obesity Res* 1999; **7**: 299–302.
14 Chapman DM, Boskey AL, Tesch M *et al.* Subcutaneous microvascular (capillary) calcification. Another basis for livedo-like skin changes? *Clin Exp Dermatol* 1995; **20**: 213–7.
15 McNaughton F, Keczkes K. Scleredema adultorum and diabetes mellitus (scleroedema diutinum). *Clin Exp Dermatol* 1983; **8**: 41–5.
16 Monk BE, Pembroke AC, Vollum DI. Scleroedema of Bushke and diabetes mellitus: a report of two cases. *Clin Exp Dermatol* 1983; **8**: 389–91.
17 Parker SC, Fenton DA, Black MM. Scleredema. *Clin Exp Dermatol* 1989; **14**: 385–6.
18 Woollons A, Darley CR, Lee PJ *et al.* Cutis verticis gyrata of the scalp in a patient with autosomal dominant insulin resistance syndrome. *Clin Exp Dermatol* 2000; **25**: 125–8.
19 Tamiya H, Tsuruta D, Umeda R *et al.* Keratosis follicularis squamosa (Dohi) associated with pseudoacanthosis nigricans. *Br J Dermatol* 2004; **150**: 603–5.
20 Chamberlain AJ, Tam MM. Intertriginous granular parakeratosis responsive to potent topical corticosteroids. *Clin Exp Dermatol* 2003; **28**: 50–2.
21 Tokuda Y, Kawachi S, Murata H *et al.* Chronic obesity lymphoedematous mucinosis: three cases of pretibial mucinosis in obese patients with pitting oedema. *Br J Dermatol* 2006; **154**: 157–61.
22 Campen R, Mankin H, Louis DN *et al.* Familial occurrence of adiposis dolorosa. *J Am Acad Dermatol* 2001; **44**: 132–6.
23 Kennedy C. The spectrum of inflammatory skin disease following jejuno-ileal bypass for morbid obesity. *Br J Dermatol* 1981; **105**: 425–35.
24 Ahmed AR, Drenick E. Cutaneous immunofluorescence studies in bowel bypass syndrome. *Clin Exp Dermatol* 1982; **7**: 477–83.
25 Slater GH, Kerlin P, Georghiou PR *et al.* Bowel-associated dermatosis-arthritis syndrome after biliopancreatic diversion. *Obes Surg* 2004; **14**: 133–5.
26 Katugampola RP, Patel GK, Farrell AM. Intestinal bypass syndrome presenting as erythema nodosum. *Clin Exp Dermatol* 2004; **29**: 261–4.
27 Sergeant A, Milne G, Shaffrali F. Lichenoid eruption associated with orlistat. *Br J Dermatol* 2006; **154**: 1020–1.

Syndromes of obesity with cutaneous features

Obesity presents in children as well as adults [1]. A tiny percentage of these cases will be the result of single gene mutations resulting in a severe obesity phenotype [2]. Some of these genetic syndromes also have a cutaneous phenotype and they are summarized in Table 8.7. A few may have the typical central obesity and other features of Cushing's syndrome.

References

1 Rudolf MCJ, Greenwood DC, Cole TJ *et al.* Rising obesity and expanding waistlines in schoolchildren: a cohort study. *Arch Dis Child* 2004; **89**: 235–7.
2 Farooqi IS, O'Rahilly S. Monogenic human obesity syndromes. *Recent Prog Horm Res* 2004; **59**: 409–24.
3 Millington GWM. Genomic imprinting and dermatological disease. *Clin Exp Dermatol* 2006; **31**: 681–8.
4 de Vries BBA, Fryns JP, Butler MG *et al.* Clinical and molecular studies in fragile X patients with a Prader–Willi-like phenotype. *J Med Genet* 1993; **30**: 761–6.

5 Millington GWM. Pro-opiomelanocortin (POMC): the cutaneous roles of its melanocortin products and receptors. *Clin Exp Dermatol* 2006; **31**: 407–12.
6 Kantaputra PN, Kunachaichote J, Patikulsila P. Mental retardation, obesity, mandibular prognathism with eye and skin anomalies (MOMES syndrome): a newly recognized autosomal recessive syndrome. *Am J Med Genet* 2001; **103**: 283–8.
7 She R, Szakacs J. Hyperostosis frontalis interna: case report and review of literature. *Ann Clin Lab Sci* 2004; **34**: 206–8.
8 Bamshad M, Lin RC, Law DJ *et al*. Mutations in human TBX3 alter limb, apocrine and genital development in ulnar-mammary syndrome. *Nature Genet* 1997; **16**: 311–5.
9 Boikos SA, Stratakis CA. Carney complex: the first 20 years. *Curr Opin Oncol* 2007; **19**: 24–9.

The menopause

Hormonal and physiological changes

Strictly speaking, the term *menopause* defines the fixed single point in a woman's life characterized by her last menstrual period [1,2]. This is established formally after 12 months of amenorrhoea in the middle years of life [2]. The surrounding years, or climacteric, are a time of change and readjustment to the new phase heralded by the menopause and its loss of fertility; literally, *climacteric* means a step up the ladder. It is a crucial phase for a woman, preparing her for the years to come which, in modern societies at least, may now represent at least 30 years, or one-third of her life [2]. It has been estimated that by 2030, there will be 1.2 billion postmenopausal women worldwide [3].

The age of onset of menopause has been the subject of much study. Some of the data have been criticized because of flaws in their collection and interpretation [4,5]. However, the menopause occurs between the ages of 45 and 55 years in 65–70% of women and the median age in most Western populations is around 50 years. Factors that may influence menopausal age include heredity (age of mother's menopause is highly predictive), smoking, parity, socioeconomic factors, exposure to toxins and nutrition [4]. The onset appears to occur a little earlier in developing countries than in Western societies [5].

True premature menopause before the age of 40 years occurs in less than 1% of women [6], but can follow surgery, irradiation, viral infections (especially mumps), accompany various enzymatic and hormonal defects, or be associated with a number of systemic disorders such as Addison's disease, rheumatoid arthritis, diabetes or myasthenia gravis [1].

During the reproductive years, oestrogen is produced mainly by ovarian follicles, but at the menopause there are major changes. There are very few follicles left, the ovaries become atrophic and the level of ovary-derived oestrogen falls. The endocrinology of this period of a woman's life results from the interrelationship of reduced ovarian function and resultant changes in gonadotrophins. Although there may be intermittent bursts of oestrogen in the immediate postmenopausal period because of residual follicular activity, the level of plasma oestradiol ultimately falls to less than 20 pg/L and remains there for the rest of the woman's life [5]. The ratio of oestradiol to oestrone changes, with oestrone becoming the more abundant hormone [2] and most oestrogens being derived from the direct peripheral conversion to oestrone of androstenedione, which has been produced by the adrenals. Some oestrone may arise through the alternative pathway via testosterone and oestradiol [7]. The pituitary–gonadal feedback loop is virtually absent and levels of gonadotrophins are elevated in consequence. In addition, a number of granulosa cell-derived peptide hormones influence FSH levels [8].

These hormonal changes are reflected in a number of physiological alterations [1]. In the breast, glandular tissue decreases and fibrous tissue increases. The body of the uterus becomes smaller and its muscle is partly replaced by fibrous tissue and the endometrium regresses and becomes atrophic. However, it still retains the capacity to respond to exogenous hormones. The vagina becomes shorter and narrower and the vaginal epithelium atrophies. The pH of the vagina rises and infections become more frequent. The external genitalia atrophy, with a loss of vulval subcutaneous fat and thinning of the vulval epithelium. Pubic hair diminishes.

The epithelium of the lower urinary tract also atrophies and this, together with the increased tendency to prolapse, increases the frequency of urinary tract infections. There is a loss of elasticity in the pelvic supporting ligaments, contributing to prolapse and urinary incontinence [9].

There are no structural cutaneous changes that are specifically associated with the menopause, but there are oestrogen receptors in the skin, suggesting that the skin is a target organ for oestrogen and that its withdrawal may be important [2]. It is interesting that there is a far greater concentration of oestrogen receptors in facial skin than in skin on the breasts or thigh. Some of the changes seen after the menopause, such as dryness, epidermal thinning and loss of dermal elasticity, may result, in part, from lower circulating oestrogen levels. Certainly, administration of oestrogen to castrated animals leads to thickening of the dermis and decreased breakdown of collagen. Oestrogen given to postmenopausal women also increases dermal thickness and has been shown to improve skin elasticity and deformability [2]. The application of topical oestrogens to the face in menopausal women has also been reported to improve various parameters, including reduction in the depth of wrinkles [10]. However, the picture is not as clear-cut with regard to the epidermis. Hormone replacement therapy (HRT) may increase the skin's water-holding capacity [11].

References

1 Barbo DM. The physiology of the menopause. *Med Clin North Am* 1987; **71**: 11–22.
2 Wines N, Willsteed E. Menopause and the skin. *Austral J Dermatol* 2001; **42**: 149–60.
3 Hill K. The epidemiology of the menopause. *Maturitas* 1996; **23**: 113–27.
4 Houmard BS, Seifer DB. Predicting the onset of menopause. In: Seifer DB, Kennard EA, eds. *Menopause: Endocrinology and Management*. NJ: Humana, 1999: 1–19.
5 Gosden RG. *Biology of Menopause*. London: Academic Press, 1985: 1–15.
6 Beck-Peccoz P, Persani L. Premature ovarian failure. *Orphanet J Rare Dis* 2006; **1**: 9.
7 Khaw KT. Epidemiology of the menopause. *Br Med Bull* 1992; **48**: 249–61.
8 Bilezikjian LM, Blount AL, Leal AM *et al*. Autocrine/paracrine regulation of pituitary function by activin, inhibin and follistatin. *Mol Cell Endocrinol* 2004; **225**: 29–36.
9 Robinson D, Cardozo LD. The role of estrogens in female lower urinary tract dysfunction. *Urology* 2003; **62** (Suppl.1): 45–51.
10 Schmidt JB, Binder M, Macheiner W *et al*. Treatment of skin ageing symptoms in perimenopausal females with estrogen compounds: a pilot study. *Maturitas* 1994; **20**: 25–30.

11 Hall G, Phillips TJ. Estrogen and skin: the effects of estrogen, menopause, and hormone replacement therapy on the skin. *J Am Acad Dermatol* 2005; **53**: 555–68.

Skin disorders of the menopause

Atrophic vulvovaginitis

It has been known for many years that the atrophic changes in the female external genitalia described above respond, at least partially, to topical oestrogens [1].

Menopausal flushing

The most consistent and distressing complaint associated with the menopause is flushing [2]. This is usually described as a sudden feeling of intense heat in the face, neck and chest, often accompanied by discomfort and sweating. Although the intensity and duration vary, it typically lasts 3–5 min. Visible changes occur in approximately 50% of women and generally consist of a blotchy erythema on the face, neck, upper chest and breasts. Some women also develop palpitations, throbbing in the head and neck, headaches, waves of nausea and anxiety attacks. Sleep disturbance is not uncommon [2]. Physiological changes occurring during hot flushes include increased temperature, pulse rate and respiratory rate [3,4], which are body functions regulated centrally by the hypothalamus.

Neurokinin B (*NKB*) gene expression is elevated in the hypothalamus in postmenopausal women. Oestrogen replacement decreases both the number of *NKB* mRNA-expressing neurones and the level of expression within individual cells. Similarly, *NKB* gene expression is elevated in ovariectomized rats and reduced after oestrogen treatment [5]. NKB is involved in GnRH release from the median eminence [6], which ultimately controls LH release from the pituitary. Flushes are associated with pulsatile release of LH [7], presumably because of failure of the normal feedback mechanisms. However, flushing can occur after hypophysectomy [8] and so LH itself cannot be responsible for the observed vasomotor instability. One suggested mechanism involves alteration of hypothalamic catecholamine levels and a failure of normal central thermoregulatory centres through a GnRH-dependent mechanism. Flushes similar to those seen in the menopause can be induced by an enkephalin analogue and blocked by naloxone infusions [9], indicating that menopausal hot flushes may also be mediated by an opiate-dependent mechanism [10].

The consensus is that oestrogen therapy is the most effective treatment for symptomatic hot flushes [2], although not all authorities have always agreed [4]. Alternatives that can be considered when oestrogens are contraindicated include various progestins [11], clonidine, paroxetine, venlafaxine, gabapentin and the phytooestrogen, black cohosh [12]. Other therapies have been considered ineffective in a systematic review [12].

Keratoderma climactericum

This term has been used to describe the appearance of hard skin on the palms and soles, especially around the heels. Although originally reported as a specific association with the menopause [13], the same changes are seen in men and women at other ages, many of whom are obese [14]. It may therefore be a non-specific effect. There has been a report of a therapeutic response to systemic retinoids [15].

Lichen sclerosus

This disorder is considered in detail in Chapters 51 and 71 but is mentioned here because of its frequent presentation at or around the menopause and because of the significant symptomatology it may cause.

Complications of HRT

The increasing use of HRT, largely to prevent osteoporosis and cardiovascular disease, has revealed a number of problems associated with this treatment. Apart from the ongoing debate regarding the relationship between HRT and cancers of the breast and genital tract, HRT may be responsible for a number of cutaneous problems. Oestrogen therapy may trigger or exacerbate, amongst others, increased skin sensitivity, chloasma (melasma), spider angiomas, darkening of naevi, the skin changes of porphyria cutanea tarda or lupus erythematosus, photosensitivity, pompholyx, erythema multiforme, urticaria and acanthosis nigricans [2,16]. Allergic reactions have been reported to the transdermal patches frequently used as delivery systems for HRT. These may be to the adhesives or to the oestrogens themselves [17].

References

1 Wines N, Willsteed E. Menopause and the skin. *Austral J Dermatol* 2001; **42**: 149–60.
2 Utian WH. Psychosocial and socioeconomic burden of vasomotor symptoms in menopause: a comprehensive review. *Health Qual Life Outcomes* 2005; **3**: 47.
3 Freedman RR, Norton D, Woodward S *et al*. Core body temperature and circadian rhythm of hot flashes in menopausal women. *J Clin Endocrinol Metab* 1995; **80**: 2354–8.
4 Mulley G, Mitchell JRA. Menopausal flushing: does oestrogen therapy make sense? *Lancet* 1976; **i**: 1397–8.
5 Dellovade TL, Merchenthaler I. Estrogen regulation of neurokinin B gene expression in the mouse arcuate nucleus is mediated by estrogen receptor alpha. *Endocrinology* 2004; **145**: 736–42.
6 Krajewski SJ, Anderson MJ, Iles-Shih L *et al*. Morphologic evidence that neurokinin B modulates gonadotropin-releasing hormone secretion via neurokinin 3 receptors in the rat median eminence. *J Comp Neurol* 2005; **489**: 372–86.
7 Ravnikar V, Elkind-Hirsch K, Schiff I *et al*. Vasomotor flushes and the release of peripheral immunoreactive luteinizing hormone releasing hormone in postmenopausal women. *Fertil Steril* 1985; **41**: 881–7.
8 Mulley G, Mitchell JRA, Tattersall RB. Hot flushes after hypophysectomy. *BMJ* 1977; **2**: 1062.
9 Stubbs WA, Delitala G, Jones A *et al*. Hormonal and metabolic responses to an enkephalin analogue in normal man. *Lancet* 1978; **ii**: 1225–7.
10 Casper RF, Yen SSC. Neuroendocrinology of 3 menopausal flushes: an hypothesis of flush mechanism. *Clin Endocrinol* 1985; **22**: 293–312.
11 Loprinzi CL, Michalak JC, Quella SK *et al*. Megestrol acetate for the prevention of hot flashes. *N Engl J Med* 1994; **331**: 347–52.
12 Cheema D, Coomarasamy A, El-Toukhy T. Non-hormonal therapy of postmenopausal vasomotor symptoms: a structured evidence-based review. *Arch Gynecol Obstet* 2007; **276**: 463–9.
13 Haxthausen H. Keratoderma climactericum. *Br J Dermatol* 1934; **46**: 161–7.
14 Scheinfeld NS. Obesity and dermatology. *Clin Dermatol* 2004; **22**: 303–9.
15 Deschamps P, Leory D, Pedailles S *et al*. Keratoderma climactericum (Haxthausen's disease): clinical signs, laboratory findings and response to etretinate in 10 patients. *Dermatologica* 1986; **172**: 259–62.
16 Graham-Brown RAC. Dermatologic problems of the menopause. *Clin Dermatol* 1997; **15**: 143–5.

17 Angelini G. Topical drugs. In: Rycroft RJG, Menné T, Frosch PJ, eds. *Textbook of Contact Dermatitis*, 2nd edn. Berlin: Springer-Verlag, 1995: 493.

Old age

Introduction

Senescence in the skin is a gradual process that ultimately results in the appearances and functional differences that we associate with old age. However, by no means all of these changes are purely intrinsic. The skin is particularly vulnerable to the ageing effects of a number of environmental insults, especially UV radiation [1]. In women there are additional hormonal changes at the menopause (see p. 8.19). These factors are superimposed on the background changes of intrinsic ageing and care needs to be exercised in interpreting which are most important in determining any particular aspect of the appearance and function of the skin in an elderly person. There have been increasing efforts to disengage the roles of these intertwined and contemporaneous processes.

Biology of ageing

Ageing is a complex process that has been defined as the accumulation of molecular damage over time [2]. It is controlled by both genetic and environmental factors [1,3]. Intrinsic factors that may be under genetic control include skin colour [4], antioxidant mechanisms to prevent free-radical damage, telomere shortening, mutations in the mitochondrial genome [5], hormone systems [6] and the absolute length of the continuous cell cycle [1,7].

Clearly, not all age-related change is due to genetic factors alone. For example both excess calories and lack of micronutrients may accelerate the physical changes associated with senescence [8].

In the skin, gravitational forces or traction can activate phospholipase A2, an enzyme involved in the generation of prostaglandins and leukotrienes. These can lead to cytokine release, neutrophil recruitment and free-radical generation [2]. Intercellular adhesion molecule-1 (ICAM-1) is a ligand for lymphocyte function-associated antigens. Anoxia induces ICAM-1 synthesis, which facilitates cell movement out of blood vessels, and thus macrophage migration [2]. Electromagnetic radiation from computers and mobile phones induces histamine, interleukin (IL) 1 and IL-6 release [1]. Cutaneous neuropeptides regulate the expression of cell-surface adhesion molecules on immune cells and endothelial cells in response to neurogenic inflammation [2]. The non-enzymatic glycosylation of blood vessels, a normal feature of ageing and accelerated in diabetes mellitus, also induces ICAM-1 expression [2]. All of these triggers can lead to a self-sustaining inflammatory and ageing process, involving the cyclical synthesis and expression of ICAM-1, with immune cells invading the dermis [2].

Photoageing

If the ageing of most of the bodily organs has, however reluctantly, to be accepted, the ageing of the facial skin appears to be a matter of widespread concern. The reason is that the skin plays a major part in our social and sexual interactions; the concern is not so much to do with physiological functions, which may remain adequate in old age, but about continuing effectiveness, particularly of the facial skin, in communication. To display sexuality or assert social status it is necessary to have skin and hair that look, feel and smell attractive.

The most obvious signs of an ageing skin are atrophy, laxity, wrinkling, sagging, dryness, yellowness, a multiplicity of pigmented and other blemishes and sparse grey hair. Some of these stigmata clearly have genetic components, as some are mimicked by heritable disorders. The abnormal skin in cutis laxa makes young children look old; in progeria, on the other hand, the connective tissue remains evenly dense, although the epidermis shows mottled pigmentation [9]. Of particular relevance to the skin, it is thought that more than 90% of age-associated cosmetic problems are caused by ultraviolet (UV) radiation on exposed skin, which damages telomeres, generates free-radicals and whose effects are largely proportionate to skin type [10].

Ultraviolet (UV) radiation has several direct and indirect effects on the skin. About 50% of UV induced damage is from the generation of free radicals, with direct cellular injury and other mechanisms accounting for the rest [9]. DNA damage induced by UV radiation has been studied extensively in relation to skin cancer (see Chapter 29). These UV-related DNA mutations may be of relevance to specific signs of photoageing such as wrinkling and increased elastin and collagen damage. However, it is not known specifically how DNA photoproducts lead to the photoaged phenotype [10]. Ultraviolet A, and to a lesser extent UVB, may damage DNA indirectly through the generation of free-radicals, which damage cellular DNA as well as lipids and proteins [1,10].

A 4977 base-pair deletion in mitochondrial DNA is found in dermal fibroblasts of photoaged skin. This may be a marker for UVA damage. The mitochondrion has the highest turnover of free-radicals in the cell and is responsible for cellular energy production. Many of the genes involved in this process are encoded in mitochondrial DNA, so mutations in its genome could be associated with the changes seen with photoageing [11].

The transcription factor nuclear factor NF-κB is activated by UV radiation and this leads to elevated levels of the proinflammatory cytokines IL-1, IL-6, vascular endothelial growth factor (VEGF) and tumor necrosis factor (TNF)-α [10]. This attracts neutrophils which increase oxidative damage through their production of free-radicals.

Increased VEGF levels favour angiogenesis, aided by reductions in thrombospondin-1, an angiogenesis inhibitor, and increases in platelet-derived endothelial cell growth factor, an angiogenesis activator. These UV-induced changes in gene expression may contribute to the telangiectases seen in sun-exposed areas, as well as contributing to photocarcinogenesis in elderly people [10].

Within 15 min after UV exposure epidermal growth factor, IL-1 and TNF-α receptors are activated in keratinocytes and fibroblasts. This ultimately leads to the expression and activation of the nuclear transcription factor activator protein 1 (AP-1). AP-1 regulates transcription of matrix metalloproteinases (MMPs), enzymes responsible for degradation of the extracellular matrix [9]. MMPs are found in both epidermal keratinocytes and dermal fibroblasts. Iron is required for the activation of MMP-1, the major metalloproteinase responsible for collagen degradation [10]. The

transcription factor NF-κB is also activated by UV radiation via an iron-dependent mechanism. It amplifies the UV response by stimulating the transcription of inflammatory cytokines and attracting neutrophils that contain preformed neutrophil collagenase (MMP-8). NF-κB is also able to increase expression of MMPs [9].

Up-regulation of MMP can occur after only a minimal dose of UV, well below that required to produce erythema and there is a dose–response relationship between UV exposure and MMP induction. Minimal repetitive exposures to UV radiation at a dose equivalent to 5 to 15 min of exposure to midday sun every other day is enough to maintain these elevated levels of MMP. Exposure to UV radiation insufficient to cause sunburn can lead to the degradation of skin collagen and eventual photoageing [10].

UV irradiation may produce both local and systemic immunosuppression. This is partly mediated by DNA damage and also by altered cytokine expression. UV-induced immunosuppression may have arisen evolutionarily to prevent autoimmunity resulting from UV-mediated DNA damage. It also predisposes the individual to photocarcinogenesis [9]. This subject is covered in greater detail in Chapter 29.

References

1 Millington GWM. Epigenetics and dermatological disease. *Pharmacogenomics* 2008; **9**: 1835–50.
2 Giacomoni PU, Rein G. A mechanistic model for the aging of human skin. *Micron* 2004; **35**: 179–84.
3 Osiewacz HD. Genetic regulation of aging. *J Mol Med* 1997; **75**: 715–27.
4 Millington GWM, Levell NJ. From genesis to gene-sequencing: historical progress in the understanding of skin color. *Intl J Dermatol* 2007; **46**: 103–5.
5 Jansen-Durr, Osiewacz HD. Healthy ageing: a question of stress, damage and repair. *EMBO Reports* 2002; **3**: 1127–32.
6 Laron Z. Do deficiencies in growth hormone and insulin-like growth factor-1 (IGF-1) shorten or prolong longevity? *Mech Ageing Dev* 2005; **126**: 305–7.
7 Vaziri H, Benchimol S. From telomere loss to p53 induction and activation of a DNA-damage pathway at senescence: the telomere loss/DNA damage model of cell aging. *Exp Gerontol* 1996; **31**: 295–301.
8 Simpson SJ, Raubenheimer D. Caloric restriction and aging revisited: the need for a geometric analysis of the nutritional bases of aging. *J Gerontol A Biol Sci Med Sci* 2007; **62**: 707–13.
9 Lapiere CM. The ageing dermis: the main cause of the appearance of old skin. *Br J Dermatol* 1990; **122** (Suppl. 35): 5–11.
10 Rabe JH, Mamelak AJ, McElgunn PJ *et al*. Photoaging: mechanisms and repair. *J Am Acad Dermatol* 2006; **55**: 1–19.
11 Birch-Machin MA. The role of mitochondria in ageing and carcinogenesis. *Clin Exp Dermatol* 2006; **31**: 548–52.

The ageing skin

Dermis

Wrinkling of ageing skin is almost entirely the result of changes in the dermis. The debatable questions concern the nature of these changes and to what extent they are intrinsic or environmentally caused [1].

The dermis diminishes in bulk and in absolute terms the collagen per unit area of unexposed skin decreases with age. This is exaggerated in exposed skin, as after UV irradiation, the procollagen pool is markedly decreased and may be absent by 24 h after exposure *in vivo*. AP-1 and transforming growth factor (TGF)-β are involved in this UV-mediated down-regulation of collagen synthesis. Also, damaged collagen itself may down-regulate new collagen synthesis [1].

Mechanical effects also contribute to decreased collagen synthesis in the photoaged dermis. Cells produce collagen most effectively under high mechanical tension. Impaired distribution and attachment of fibroblasts onto degraded collagen may contribute to inhibition of collagen synthesis. A cycle forms whereby decreased new collagen production due to poor adhesion of fibroblasts to damaged collagen, leads to worsening photoageing [1].

There also appears to be a steady increase in the number of mast cells, mononuclear cells and neutrophils. The fibroblasts show a stellate phenotype and, ultrastructurally, a highly activated endoplasmic reticulum, reflecting increased biosynthetic activity [2]. Although it is often assumed that the lax skin of the aged results from lack of water, there is evidence that water content increases in photoaged skin. Intrinsically aged skin has a similar water content to non-aged skin [3].

Gross morphological changes, especially in the collagen and elastin fibres, have been revealed by electron and light microscopy. Their relationship to molecular changes as determined by physical and chemical methods requires interpretation. Moreover, it has long been clear that such changes are largely the result of exposure to solar radiation, photoageing [1].

Accumulating evidence indicates that intrinsically aged skin shares a number of features with photoaged skin. Commercial interests have dictated a more detailed interrogation of the mechanisms underlying photoageing. However, the same research techniques are now being applied to intrinsically aged skin. There is an age-related loss of fibroblast frequency and size, coupled with a decrease in their synthetic ability [1]. Over the age of 70 years, there is loss of collagens I and III in the papillary dermis with an associated increase in MMPs [1]. Reactive oxygen species and free radicals are key drivers of the degeneration that is so characteristic of aged skin. This oxidative damage is produced in part by the action of mitogen-activated protein (MAP) kinases. In aged skin, stress-activated MAP kinase activity is elevated [4].

In the dermis of young adults, the collagen bundles are well organized. They form a rhomboid network with the individual bundles lying at angles to one another. Intertwined among the collagen bundles lie single branching elastic fibres, apparently aligned haphazardly, in planes parallel with the surface at all levels beneath the dermal–epidermal junction. The network of collagen bundles, although composed of inextensible fibres, is itself extensible as the bundles rotate relative to one another to form parallel alignments. It seems likely that the return of the network to its unstretched state is brought about by the interwoven elastic fibres [1]. Thus, in cutis laxa, an uncommon disorder in which the skin hangs in folds, the elastic fibres appear to be reduced in number and are degenerate (see Chapter 45).

The various descriptions of changes in ageing based on histological staining techniques are often confusing. In general, it appears that the collagen bundles become fragmented and disorientated and elastin fibres become progressively reduced [5]. However, in senile skin from exposed areas there may, paradoxically, be a striking increase in fibres that take up elastin stains in actinic elastosis [1].

Elastic fibres gradually disintegrate with age, even in protected skin and after the age of 70 years most fibres appear abnormal [5,6]. These changes are most probably a combination of reduced synthesis and elastolysis. Similar changes can be produced in protected buttock skin within hours by incubating it with pancreatic elastase and bovine chymotrypsin [6].

Epidermis

Many differences between a senile and young epidermis have been described, but a consistent interpretation of the ageing process has proved difficult. In part, this is because the epidermis varies from site to site. Young skin from the back, like that from the scalp and axilla, has deep and complex rete ridges, whereas that of the face [7] has a fairly flat dermal–epidermal junction. It is widely agreed that in areas where the junction is corrugated in youth, it becomes flattened in the aged [8].

Similarly, there are differences in epidermal thickness, even in young skin. On the face or on the dorsum of the hand, for example, it is considerably greater than on the arms, legs or trunk [8]. In many areas, the whole epidermis becomes thinner with age and the cells become less evenly aligned on the basement membrane and less regular in size, shape and staining properties [8]. There is now some consensus that the cell turnover rate is halved between the third and seventh decades of life [9]. The evidence that the rate of epidermal repair and wound healing declines with age [10] is consistent with the view that the rate of epidermal turnover is decreased.

The permeability of the skin also changes with age. The capacity of the isolated horny layer *in vitro* to restrict water loss does not differ between young adults and persons over 70 years of age, but the aged skin is decidedly more permeable to chemical substances [11]. However, percutaneous absorption of testosterone appears *in vivo* to be reduced in old age. A possible explanation is that, although substances enter aged skin more easily than young skin, they are removed more slowly into the circulation because of changes in the dermal matrix and reduction in the vasculature [11,12]. The response to blistering agents, such as 50% ammonium hydroxide, is initially quicker in elderly than in young subjects, but the formation of the full blister takes longer [13]. These physiological differences must be largely related to changes in the stratum corneum [14]. However, the surface area of individual corneocytes from unexposed areas of the arms, thighs and lower abdomen increases with age, which may reflect an increased transit time [15]. A change in the nature of the corneocytes is also indicated by the tendency of the ageing epidermal surface, especially that of the lower legs, to become dry, flaky and sometimes itchy. Apart from reduced function of the skin glands, the water-binding capacity of the stratum corneum appears to be reduced [14], coupled with an increase in renewal time if damaged [1].

Pigmentation

The most obvious senile changes in white skin are pigmentation irregularities. Yellow or brown macules, known as 'liver spots' or 'age spots' (lentigos), develop on the backs of the hands and exposed parts of the face in more than 50% of persons over 45 years of age. They consist of a localized proliferation of melanocytes at the dermal–epidermal junction. Very rarely, such lentigos appear to develop into *lentigo maligna*, which is a precancerous condition, although it progresses very slowly [16]. Even heavily pigmented skin darkens. A study of 578 adult natives of New Guinea revealed that pigmentation increased with age in skin exposed to the sun, but not in axillary skin and that males darkened more than females [17].

Greying of hair

Greying of the hair in a white population, starts at an average age of 34 and half the population will have 50% grey coverage by age 50. It should be noted that these statistics may not hold for all populations [18]. Interestingly, there is an association between premature greying with both cigarette smoking and osteoporosis [18,19]. It is interesting that sudden onset of white hair seems to be a separate phenomenon to greying and is associated with alopecia areata and vitiligo [20].

The bulbs of grey or white hairs show various abnormalities, but it is uncertain which are critical. In general, the bulbs appear to lack or be deficient in tyrosinase, the enzyme necessary for the first stages of melanin synthesis [21]. Structurally, the follicles of grey hairs still have melanocytes placed normally over the dermal papilla, but the cytoplasm may contain large vacuoles and the melanosomes may be only lightly melanized [21]. The follicles of fully white hairs may completely lack melanocytes. However, among grey or white hairs, there may be a few normal bulbs producing dark hairs. An unexplained fact is that at all ages from their appearance on the chest in males and probably elsewhere, grey hairs tend to be thicker and longer than pigmented ones.

Hair follicles

Scalp hair also becomes finer with age, especially in those with alopecia. Androgenetic alopecia is an extremely common disorder affecting both sexes, with a greater incidence in males than females. The density of hair follicles in the scalp steadily decreases with age, more rapidly in bald than in non-bald persons. This disorder results from the progressive conversion of terminal hairs into indeterminate hairs and then finally into vellus hairs. Patients therefore have a reduction in the terminal-to-vellus hair ratio. Fibrous tracts remain, following miniaturization of the follicles. Patients with this disorder usually have a typical distribution of alopecia, with hair becoming sparse on the vertex while it is still luxuriant on the occiput [22,23]. Genetic variation in the androgen receptor gene is thought to be the principal pathogenic factor in early-onset androgenetic alopecia. The androgen receptor gene is located on the X-chromosome, stressing the importance of the maternal line in the inheritance of androgenetic alopecia. It is not known whether this gene mutation is of significance in women or in men with minimal baldness [24]. Although baldness is mainly a cosmetic issue, some epidemiological studies have linked it with important conditions of old age, such as hypertension [25] and prostate cancer [26].

The weight of beard grown per day reaches a peak in the fourth decade and starts to decrease slightly in the seventh decade [27]. As the density of the hairs remains constant, the decrease in weight must be accounted for by a reduction in the rate of growth, in diameter, or in both. Evidence that the linear growth of beard hair is correlated solely with levels of 5α-dihydrotestosterone (DHT) in

the plasma, not with testosterone, whereas hair density is significantly correlated solely with testosterone, not with DHT [28], suggests that the age changes may result not so much from reduced production of testosterone as by lessened peripheral metabolism.

Chest hairs, which are also androgen-dependent, reach a maximum in number, breadth and length around the fifth decade and then start to diminish markedly [29].

Axillary hair reaches a peak in mass and in rate of production towards the end of the third decade in males and females alike and this is followed by a rapid decline, somewhat more severe in females [30]. Pubic hair appears to follow a similar pattern.

If most of the changes with ageing involve reductions in the amount of hair, this is not true of all sites. In the male, the eyebrows may become bushier and visible hairs develop around the external auditory meati. In the female, hirsutism may occur as a result of endocrine changes associated with the menopause.

Sebaceous and apocrine glands

Sebum production is at its greatest in early adulthood and lessens in old age, remaining unchanged until past the age of 70 years in men, but falling after the menopause in women [31].

Measurements of the sustainable rate of wax ester secretion after depletion of the sebum reservoir by absorption with bentonite clay suggest that sebum secretion declines steadily through each decade by approximately 23% in men and 32% in women [32]. The fatty acid composition also changes [33].

The predominant belief is that, in spite of their decreased output, the sebaceous glands increase in size because turnover of cells is slower in senility [34,35]. However, in one study in 14 women the glands appeared to become smaller and the sebocytes flatter with age [36].

The axillary apocrine glands also regress with age and produce less odour [8].

Eccrine glands

Spontaneous sweating on the fingertips declines in old age, as a result of a combination of a reduction in the number of glands [37] and of the output per gland [38]. The response of the forearm sweat glands to adrenaline declines with age equally in men and women, suggesting an intrinsic deterioration of the glands. This interpretation is supported by histological evidence. In contrast, the effect of age on the response to acetylcholine is much greater in the male than in the female, suggesting that ageing affects cholinergic sweating indirectly through the hormonal balance in the blood [38]. Such a hypothesis is borne out by the evidence that the maximum rate of cholinergic sweating is much greater in adult males than in females or in juveniles and is thus probably androgen-dependent [39].

Nail growth

The rate of linear nail growth increases until well into the third decade. From about the age of 25 years it starts to decrease. Until the age of 70 years, nail growth is greater in men than in women, but thereafter the situation appears to be reversed [40]. Nails are more brittle in the elderly and are characterized by beaded ridging, sometimes called 'sausage links'. Brittleness may be caused by a reduction in the nail content of lipophilic sterols and free fatty acids [41].

Nerves and sensation

Age often decreases sensory perception and increases the threshold for pain [42]. There is evidence for progressive disorganization or loss of some sense organs; for example, the density of Meissner corpuscles in the little finger falls from over 30/mm^2 in young adults to approximately 12/mm^2 by the age of 70 years [43].

Langerhans' cells and immune functions

Langerhans' cells become considerably reduced in number in elderly people, even in light-protected areas [44]. There is a reduction in number of epidermal Langerhans' cells with age, coupled with a reduced ability to migrate from the epidermis in response to TNF-α [45]. Exogenous IL-1β improves the impaired Langerhans' cell migration in aged skin [46].

Peripheral immune function is altered in the elderly. The responses of both T and B cells to specific mitogens are altered in the over 80s, despite the fact that the absolute numbers of T and B cells remain within normal limits [47]. The decreased intensity of delayed hypersensitivity reactions [1,47], the increased risk of photocarcinogenesis and the greater susceptibility to chronic skin infections are some of the consequences of the ageing of the immune system [1,47].

References

1 Rabe JH, Mamelak AJ, McElgunn PJ *et al*. Photoaging: mechanisms and repair. *J Am Acad Dermatol* 2006; **55**: 1–19.

2 Ma W, Wlaschek M, Tantcheva-Poor I *et al*. Chronological ageing and photoageing of the fibroblasts and the dermal connective tissue. *Clin Exp Dermatol* 2001; **26**: 592–9.

3 Waller JM, Maibach HI. Age and skin structure and function, a quantitative approach (II): protein, glycosaminoglycan, water, and lipid content and structure. *Skin Res Technol* 2006; **12**: 145–54.

4 Chung JH, Kang S, Varani J *et al*. Decreased extracellular-signal-regulated kinase and increased stress-activated MAP kinase activities in aged human skin *in vivo*. *J Invest Dermatol* 2000; **115**: 177–82.

5 Antonicelli F, Bellon G, Debelle L *et al*. Elastin-elastases and inflamm-aging. *Curr Top Dev Biol* 2007; **79**: 99–155.

6 Braverman IM, Fonferko E. Studies in cutaneous aging: I. The elastic fibre network. *J Invest Dermatol* 1982; **78**: 434–43.

7 Friedman O. Changes associated with the aging face. *Facial Plast Surg Clin North Am* 2005; **13**: 371–80.

8 Montagna W. Morphology of the aging skin: the cutaneous appendages. In: Montagna W, ed. *Advances in Biology of Skin*, Vol. 6. *Aging*. Oxford: Pergamon, 1965: 1–16.

9 Cerimele D, Celleno L, Serri F. Physiological changes in ageing skin. *Br J Dermatol* 1990; **122** (Suppl. 35): 13–20.

10 Ashcroft GS, Horan MA, Ferguson MWJ. The effects of ageing on cutaneous wound healing in mammals. *J Anat* 1995; **187**: 1–26.

11 Harvell JD, Maibach HI. Percutaneous absorption and inflammation in aged skin: a review. *J Am Acad Dermatol* 1994; **31**: 1015–21.

12 Kelly RI, Pease R, Bull RH *et al*. The effects of aging on the cutaneous microvasculature. *J Am Acad Dermatol* 1995; **33**: 749–56.

13 Grove GL, Duncan S, Kligman AM. Effect of ageing on the blistering of human skin with ammonium hydroxide. *Br J Dermatol* 1982; **107**: 393–400.

14 Raab WP. The skin surface and stratum corneum. *Br J Dermatol* 1990; **122** (Suppl. 35): 37–41.

15 Marks R. Measurement of biological ageing in human epidermis. *Br J Dermatol* 1981; **104**: 627–33.

16 McKenna JK, Florell SR, Goldman GD *et al*. Lentigo maligna/lentigo maligna melanoma: current state of diagnosis and treatment. *Dermatol Surg* 2006; **32**: 493–504.
17 Walsh RJ. Variation in the melanin content of the skin of New Guinea natives at different ages. *J Invest Dermatol* 1964; **42**: 261–5.
18 Stamp T. Grey hairs, false teeth and bad bones. *Lancet* 1995; **345**: 876.
19 Mosley JG, Gibbs ACC. Premature grey hair and hair loss among smokers: a new opportunity for health education? *BMJ* 1996; **313**: 1616.
20 Skellett AM, Millington GWM, Levell NJ. Sudden whitening of the hair: an historical fiction? *J R Soc Med* 2008; **101**: 574–6.
21 Commo S, Gaillard O, Bernard BA. Human hair greying is linked to a specific depletion of hair follicle melanocytes affecting both the bulb and the outer root sheath. *Br J Dermatol* 2004; **150**: 435–43.
22 Olsen EA, Messenger AG, Shapiro J *et al.* Evaluation and treatment of male and female pattern hair loss. *J Am Acad Dermatol* 2005; **52**: 301–11.
23 Otberg N, Finner AM, Shapiro J. Androgenetic alopecia. *Endocrinol Metab Clin North Am* 2007; **36**: 379–98.
24 Hillmer AM, Hanneken S, Ritzmann S *et al.* Genetic variation in the human androgen receptor gene is the major determinant of common early-onset androgenetic alopecia. *Am J Hum Genet* 2005; **77**: 140–8.
25 Ahouansou S, Le Toumelin P, Crickx B *et al.* Association of androgenetic alopecia and hypertension. *Eur J Dermatol* 2007; **17**: 220–2.
26 Hawk E, Breslow RA, Graubard BI. Male pattern baldness and clinical prostate cancer in the epidemiologic follow-up of the first National Health and Nutrition Examination Survey. *Cancer Epidemiol Biomarkers Prev* 2000; **9**: 523–7.
27 Hamilton JB. Age, sex and genetic factors in the regulation of hair growth in man: a comparison of Caucasian and Japanese populations. In: Montagna W, Ellis RA, eds. *The Biology of Hair Growth*. New York: Academic Press, 1958: 399–433.
28 Farthing MJG, Mattei AM, Edwards CRW *et al*. Relationship between plasma testosterone and dihydrotestosterone concentrations and male facial hair growth. *Br J Dermatol* 1982; **107**: 559–67.
29 Hamilton JB, Terada H, Mestler GE *et al*. I. Coarse sternal hairs, a male secondary sex character that can be measured quantitatively: the influence of sex, age and genetic factors. II. Other sex-differing characters: relationship to age, to one another and to values for coarse sternal hairs. In: Montagna W, Dobson RL, eds. *Advances in Biology of Skin*, Vol. 9. *Hair Growth*. Oxford: Pergamon, 1969: 129–51.
30 Pecoraro V, Astore I, Barman JM. Growth rate and hair density of the human axilla: a comparative study of normal males and females and pregnant and postpartum females. *J Invest Dermatol* 1971; **56**: 362–5.
31 Zouboulis CC, Boschnakow A. Chronological ageing and photoageing of the human sebaceous gland. *Clin Exp Dermatol* 2001; **26**: 600–7.
32 Jacobsen E, Billings JK, Frantz RA *et al*. Age-related changes in sebaceous wax ester secretion rates in men and women. *J Invest Dermatol* 1985; **85**: 483–5.
33 Yamamoto A, Serizawa S, Ito M *et al*. Effect of aging on sebaceous gland activity and on the fatty acid composition of wax esters. *J Invest Dermatol* 1987; **89**: 507–12.
34 Kumar P, Barton SP, Marks R. Tissue measurements in senile sebaceous gland hyperplasia. *Br J Dermatol* 1988; **118**: 397–402.
35 Plewig G, Kligman AM. Proliferative activity of the sebaceous glands of the aged. *J Invest Dermatol* 1978; **70**: 314–7.
36 Ito N, Mashiko T, Sato Y. Morphological changes of sebaceous glands with ageing in human females: computer graphic analysis and ultrastructural study. *J Invest Dermatol* 1988; **90**: 570.
37 Oberste-Lehn H. Effects of aging on the papillary body of the hair follicles and on the eccrine sweat glands. In: Montagna W, ed. *Advances in Biology of Skin*, Vol. 6. *Aging*. Oxford: Pergamon, 1965: 17–34.
38 Silver AF, Montagna W, Karacan I. The effect of age on human eccrine sweating. In: Montagna W, ed. *Advances in Biology of Skin*, Vol. 6. *Aging*. Oxford: Pergamon, 1965: 129–50.
39 Rees J, Shuster S. Pubertal induction of sweat gland activity. *Clin Sci (Lond)* 1980; **60**: 689–92.
40 Orentreich N, Markofsky J, Vogelman JH. The effect of aging on the rate of linear nail growth. *J Invest Dermatol* 1979; **73**: 126–30.
41 Helmdach M, Thielitz A, Röpke E-V *et al*. Age and sex variation in lipid composition of human fingernail plates. *Skin Pharmacol Appl Skin Physiol* 2000; **13**: 111–9.
42 Schludermann E, Zubeck JP. Effect of age on pain sensibility. *Percept Mot Skills* 1962; **14**: 295–301.
43 Winkelmann RK. Nerve changes in aging skin. In: Montagna W, ed. *Advances in Biology of Skin*, Vol. 6. *Aging*. Oxford: Pergamon, 1965: 51–61.
44 Grewe M. Chronological ageing and photoageing of dendritic cells. *Clin Exp Dermatol* 2001; **26**: 608–12.
45 Bhushan M, Cumberbatch M, Dearman RJ *et al*. Tumour necrosis factor-α induced migration of human Langerhans' cells: the influence of ageing. *Br J Dermatol* 2002; **146**: 32–40.
46 Bhushan M, Cumberbatch M, Dearman RJ *et al*. Exogenous interleukin-1β restores impaired Langerhans cell migration in aged skin. *Br J Dermatol* 2004; **150**: 1217–8.
47 Thivolet J, Nicolas JF. Skin ageing and immune competence. *Br J Dermatol* 1990; **122** (Suppl. 35): 77–81.

Skin disease in old age

The demography of most nations is changing. Higher standards of housing, hygiene and nutrition, together with improvements in health-care services, have meant that the average lifespan has increased considerably over the last century. Added to this, many couples are now limiting their families to two or three children at most. Virtually every Western society is therefore experiencing an increase in the average age of its population. The provision of health care for elderly people is consequently becoming more and more important. Disease of the skin is no exception to this [1]. Elderly patients present to dermatologists with a wide variety of skin problems; a few are more or less specific to old age, but most are familiar skin disorders whose clinical expression, physical and emotional consequences and management may be altered by the age of the patient and the problems that increasing age bring with it.

The reasons an individual seeks advice for skin changes in old age may be as much influenced by personality and social conditioning as by the absolute severity of the problem. Although some societies are still said to view the outward signs of age, such as wrinkles and grey hair, as marks of distinction, it is clear that in much of the world 'Westernization' is resulting in an increasing degree of social stigmatization associated with looking old. Furthermore, it is recognized that, contrary to the popular belief of the young, elderly people are often anxious to look attractive [2].

Thus, particularly in rich and highly developed societies, there is an increasing reluctance to accept the physiological consequences of old age and the effects of environmental exposure. Some may consider these ageing changes to be abnormal and many older people with plentiful spare time and financial resources have become obsessed with the pursuit of an eternally youthful appearance (Fig. 8.5). One reason for this is that the pharmaceutical and cosmetic industries have invested heavily in the promotion of the concept that 'young is beautiful'. A great deal of money is being, and will continue to be, devoted to the study of compounds that may arrest or reverse the visible effects of ageing. Some are claiming success, most notably with all-*trans* retinoic acid and other retinoids for wrinkles [3]. Such research is also increasingly gaining credence in mainstream medical circles and dermatologists are becoming more involved in this area of practice (see Chapter 80).

However, most people accept (albeit increasingly reluctantly) that ageing is a natural process and only seek medical advice when skin changes are particularly troublesome or severe, or

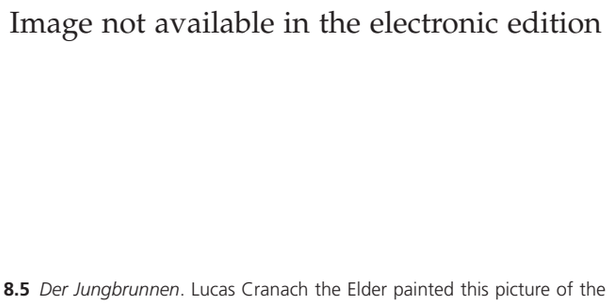


Fig. 8.5 *Der Jungbrunnen*. Lucas Cranach the Elder painted this picture of the Fountain of Youth in 1546, when he was 72 years of age. On the left, a succession of aged and decrepit women are brought to the fountain by an interesting variety of primitive transport. As they move through the basin they are transformed into lovely young maidens. The eternal desire for and, indeed, the possible advantages of rejuvenation are wonderfully expressed. (Courtesy of Staatliche Museen zu Berlin, Gemäldegalerie, Berlin, Germany.)

develop earlier than might otherwise have been expected. Skin changes of sufficient severity to warrant medical attention in elderly patients may result from the interplay of several factors:

1. Alterations in structure and function of the ageing skin
2. Cumulative effects of exposure to a variety of environmental insults, especially UV radiation
3. Cutaneous consequences of ageing or age-related disease in other organ systems
4. Changes in the environment—decreasing occupational exposure, increasing leisure exposure to potential irritants and sensitizers
5. Social circumstances, with poor nutrition, home care and mobility often contributing to the expression, perpetuation of and failure to resolve skin problems
6. Physiological problems, such as dementia, increasing rigidity of attitude and refusal to accept advice
7. Increasing physical frailty, resulting in a relative incapacity to carry out tasks correctly.

Of particular practical importance are the latter three problems, which are frequently ignored. An elderly patient may be too proud to point out that physical incapacity prevents the twice-daily application of a cream, or may deliberately refuse or forget to relate relevant facts about the home situation. The onus is very much on the dermatologist to consider these factors when dealing with skin disease in the elderly patient.

Incidence of skin problems in old age

It is hard to estimate the true frequency of skin disease in the population as a whole, let alone specifically in older age groups. One problem is that the line between that which is physiological and that which is 'truly' pathological, becomes increasingly difficult to draw with advancing years. Another is that studies of skin problems in the elderly have used different types of population and diagnostic groupings that are not directly comparable (Table 8.8). It is probably better therefore to think of skin problems rather than just skin disease in this age group.

Table 8.8 Studies on the incidence of skin disease in elderly people.

Reference	No. of patients	Population studied
Droller [6]	476	Random; at home
Young [9]	330	Ambulatory outpatients from skin clinic; chosen 'at random'
Epstein [10]	687	US private practice
Tindall & Smith [7]	163	Volunteers; at home; black and white people
Verbov [13]	170	Mainly outpatients; some in-patients
Weisman *et al*. [8]	584	Residents of old people's homes
Beauregard & Gilchrest [5]	68	Volunteers: housing projects, geriatric home visits, medical centre employees
McFadden & Hande [11]	257	Dermatology outpatients

However, the vast majority of people over 70 in the USA have at least one troublesome skin condition. Approximately 10% of the over 70s have three or four significant skin conditions [1]. Many studies on elderly individuals selected randomly and not from skin clinics give much the same impression [4–8]. For example, of 68 volunteers aged between 50 and 91 years, living in Boston, USA, two-thirds of the entire group and 83% of those aged over 80 years complained of skin problems of some kind [5]. In a European study, 77.4% of a population of 584 elderly residents of a municipal old people's home in Denmark were found to have a skin problem [8].

Many of the skin problems that are found most commonly on random examination of elderly people are not those for which elderly patients necessarily seek attention from specialist or non-specialist doctors. Although eczemas, pruritus, easy bruising and dryness (under various headings) are certainly seen in skin clinics, tumours, both benign and malignant, tend to figure more prominently than inflammatory problems [9–13].

References

1 Norman RA, Henderson JN. Aging: an overview. *Dermatol Ther* 2003; **16**: 181–5.
2 Gupta M, Gilchrest BA. Psychosocial aspects of aging skin. *Dermatol Clin* 2005; **23**: 643–8.
3 Singh M, Griffiths CEM. The use of retinoids in the treatment of photoaging. *Dermatol Ther* 2006; **19**: 297–305.
4 Johnson M-LT. *Skin Conditions and Related Need for Medical Care Among Persons 1–74 Years, United States 1971–74. Vital Health Statistics*. Series 11, Data from the National Health Survey; no. 212, DHEW Publication no. (PHS) 79–1660. Hyattsville, ML: US Department of Health, Education and Welfare, 1978.
5 Beauregard S, Gilchrest BA. A survey of skin problems and skin care regimens in the elderly. *Arch Dermatol* 1987; **123**: 1638–43.
6 Droller H. Dermatologic findings in a random sample of old persons. *Geriatrics* 1955; **10**: 421–4.
7 Tindall JP, Smith JG. Skin lesions of the aged and their association with internal changes. *JAMA* 1963; **186**: 1039–42.
8 Weisman K, Krakauer R, Wanscher B. Prevalence of skin disease in old age. *Acta Derm Venereol (Stockh)* 1980; **60**: 352–3.

9 Young AW. Dermatologic complaints presented by 330 geriatric patients. *Geriatrics* 1958; **13**: 428–34.
10 Epstein NN. The aging skin. I. Some problems of the aging skin with particular reference to environmental factors. In: Rees RB, ed. *Dermatoses due to Environmental and Physical Factors*. Springfield: Thomas, 1962: 28–38.
11 McFadden N, Hande K-H. A survey of elderly new patients at a dermatology outpatient clinic. *Acta Derm Venereol (Stockh)* 1987; **69**: 260–2.
12 Stern RS, Johnson M-L, DeLozier J. Utilization of physician services for dermatologic complaints. *Arch Dermatol* 1977; **113**: 1062–6.
13 Verbov J. Skin problems in the older patient. *Practitioner* 1975; **215**: 612–22.

Specific skin problems in old age

Most of the skin disorders that are particularly troublesome in the elderly patient are described elsewhere in this book. However, one or two points should be emphasized about certain specific disorders.

Wrinkles and elastosis

These changes, together with greying of the hair, are most readily associated with an aged appearance. The different clinical forms of wrinkles and the clinical syndromes associated with elastosis, are described in Chapter 45 and the histological changes of the ageing dermis are discussed above. Plastic surgeons and dermatologists are becoming increasingly involved in their management. Topical retinoids, botulinum toxin injections, chemical peels, dermabrasion, ablative or non-ablative laser techniques, collagen implants and facelift operations are in widespread use in the treatment and prevention of wrinkling [1,2], described in detail in Chapter 80.

Pruritus

Itching in old age can be so severe that it ruins quality of life [3]. The itch may be localized or generalized and may or may not be accompanied by skin changes. It is crucial to examine an itching elderly person carefully for primary cutaneous disease. In one study, 142 of 162 elderly patients had an identifiable cause for their itching (including xerosis), leaving only 20 to whom the term senile pruritus was applicable [4]. Diagnoses that are particularly easy to miss are scabies [5] (often caused by the inadequate examination facilities in residential homes for the elderly) and bullous pemphigoid, which often begins with a non-specific or even no rash [6]. Non-specific skin changes in anogenital itch may also conceal important diagnoses: candidiasis in undiagnosed diabetes, lichen sclerosus, the classical signs of which may easily be obscured by secondary excoriation and inflammation.

If a primary skin disorder has been ruled out, it is important to investigate any elderly patient with generalized itching for systemic causes: renal disease, cholestasis (especially chronic liver disease), thyroid disease, anaemia or cancer. The relationship between carcinomas and pruritus in the elderly patient is controversial, but there is no doubt that lymphomas, leukaemias and other myelodysplastic disorders may present in this way [7]. The frequency with which a systemic cause is found varies, but is high enough to justify a routine search [7].

When all these causes have been excluded, there remains a small core of elderly patients with intractable pruritus. In some, the itching is accompanied by xeroderma, but in others the skin feels relatively normal to the touch. The management of such patients is extremely difficult and is often totally unsatisfactory for all concerned. The topical use of emollients, soothing preparations such as menthol in calamine and potent topical steroids may be helpful. However, many of those with the worst pruritus are quite unable to manage topical therapy by themselves and it is necessary to resort to relatively sedative systemic drugs, such as phenothiazine-type antihistamines. These, too, have their drawbacks, not the least of which is the development of confusion and disorientation [7].

Senile xerosis and asteatotic eczema

Synonym
- Eczéma craquelé

Ageing skin often feels 'dry' to the touch, although the reason for this is not clear. Water loss is not increased in aged skin [8], but the water content of the epidermis appears to be somewhat reduced [9]. Dryness is often worse in the winter, a fact that has given rise to many of the alternative names used for these changes: winter eczema, prurigo or pruritus hiemalis. The changes are often most pronounced on the legs. In some patients, the surface texture of the skin assumes a cracked appearance resembling crazy paving. This is known as asteatotic eczema or eczéma craquelé (Fig. 8.6). Frequent washing is certainly a causative factor in susceptible individuals [10] and central heating may also play a part by reducing atmospheric humidity. Perhaps it is not surprising that this problem is commonly seen in geriatric in-patients.

The use of emollients to reduce requirements for soaps and detergents will improve xerosis in most patients and, because high water temperature appears to increase the tendency to irritant reactions [11], so will reducing the bath temperature. Moisturizing preparations in the bath are generally held to be effective [3], but bath oils can make the bath very slippery, which has its risks in the elderly and frail patient.

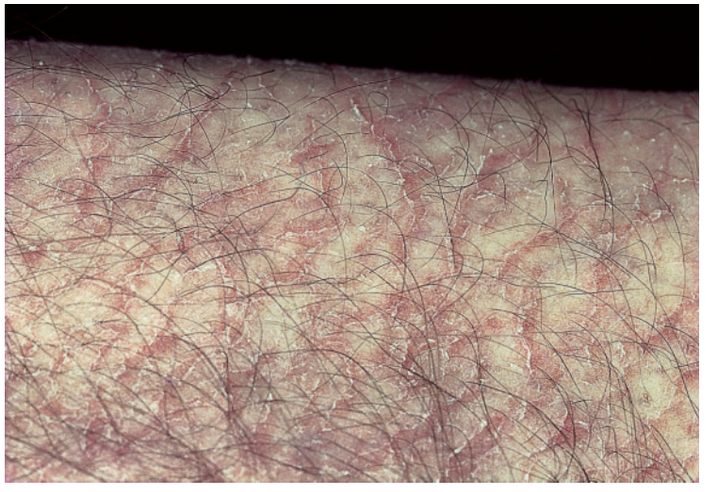


Fig. 8.6 Asteatotic eczema.

Eczema

The aged may suffer from any of the clinical types of eczema. Atopic eczema, for example, occasionally continues into old age or even appears for the first time. However, certain patterns such as asteatotic eczema are more common and more troublesome in elderly subjects.

Seborrhoeic dermatitis may be more common in the elderly infirm and in those confined to bed [12]. In the aged patient, especially the obese, a flexural pattern is often encountered, which may mimic intertrigo and flexural psoriasis.

Some elderly patients present for the first time with a discoid or nummular eczema and gravitational eczema is much more common in the elderly patient (see Chapter 23) and may be complicated by contact sensitivity.

Contact dermatitis of irritant or allergic origin is generally considered to be less common in elderly people, partly because of decreased occupational exposure [13]. This may also reflect the decline in immune reactivity that occurs with age [14] and the fact that irritant responses to some substances are reduced in intensity [15]. However, patch-test positivity remains quite common, presumably from exposure earlier in life. Allergic contact dermatitis remains a significant problem in elderly people, especially resulting from local medicaments, such as aminoglycosides, lanolin, parabens, antihistamines and anaesthetics. Other sensitizers that continue to cause trouble in old age include rubber in gloves and shoes, plastics in hearing aids and spectacle frames, plants and hair dyes [13].

Marked secondary lichenification and chronic lichen simplex are also often seen in older patients.

Bullous disorders

Pemphigoid (see Chapter 40) is much more frequent in the elderly than in other age groups. Old age modifies the management of all blistering diseases because of unwanted effects of drugs, or because of physical and social circumstances. Steroids precipitate glucose intolerance more often in the elderly and sulfapyridine or sulfamethoxypyridazine may be better first-line drugs than dapsone for dermatitis herpetiformis because of the tendency for dapsone to cause haemolysis [16]. Drug regimens should be kept simple and written down where necessary.

Psoriasis

There is a distinct peak of onset of psoriasis in later life, between the ages of 55 and 60 years, that is not as clearly associated with a family history as in patients whose disease begins earlier. This is reflected in different human leukocyte antigen (HLA) associations [17].

Psoriasis causes increased problems in the elderly patient. Disease of lesser extent and severity may be relatively more disabling in old age than in youth and the systemic effects of widespread or acute pustular psoriasis are less well tolerated than in younger individuals. Flexural psoriasis is a particular problem in the elderly patient [17], but other patterns are also seen. Eruptive guttate disease, however, is rare in old age.

Treatment can be difficult. The patient may be unable to apply topical therapies and there may be problems in travelling to and from the hospital for outpatient dithranol treatment, or in standing for psoralen and UVA (PUVA) therapy. One solution is the use of systemic therapy, especially methotrexate. There is less reason for concern over long-term methotrexate toxicity in the elderly patient, relatively small doses may keep the patient comfortable (perhaps because of diminished renal clearance) and the drug is generally well tolerated. The use of etanercept has been found to be well tolerated by the over 65s, with equal clearance rates, when compared with younger patients [18].

Leg ulcers (see Chapter 47)

Leg ulcers are a major problem. Most are caused by venous hypertension, but arterial disease becomes increasingly important with advancing years. Poor wound healing in elderly people, perhaps associated with other illnesses and poor nutrition, may also have a role in the perpetuation of some ulcers [19].

In managing chronic leg ulcers in the elderly patient it is important to take an overview of the whole situation. Strenuous efforts to heal a stable ulcer in someone who is coping independently at home may be inappropriate in some cases if long-stay in-patient treatment will be required [20].

Decubitus ulcers [21]

See Chapter 28.

Varicella zoster and post-herpetic neuralgia

Shingles is much more common in old age, the relative incidence in those over 60 is 11.2 per 1000 patient years. Post-herpetic neuralgia is also much more common in elderly people [22]. Recently, a vaccine has been developed for varicella zoster, which should reduce the population frequency of post-herpetic neuralgia [22].

Skin tumours

Most skin tumours are more common in elderly people: benign, such as seborrhoeic keratoses, senile lentigines and skin tags; dysplastic, such as actinic keratoses; and cancers, especially basal and squamous cell carcinomas. Lentigo maligna is seen predominantly in the elderly [23] and the highest age-specific incidence rates for invasive malignant melanoma are also in those over 60 years.



Fig. 8.7 A large, neglected basal cell carcinoma on the back of an elderly lady.

There is also an association between increasing age and decreasing 5-year survival in malignant melanoma [24]. It is not clear why this should be, but elderly patients seem to present with thicker lesions [24,25] and recent evidence suggests that the proportion of nodular melanomas may rise with increasing age [25]. The tendency to wait longer before presenting for treatment also extends to other tumours and lesions such as that shown in Fig. 8.7 are essentially restricted to elderly people.

Infections with ectoparasites

Outbreaks of scabies in residential homes for the elderly are not uncommon and are usually attributable to one individual with a heavy infection, perhaps with crusted scabies. Clothing lice (see Chapter 38) are, in the UK, almost exclusively seen in elderly vagrants.

References

1 Rabe JH, Mamelak AJ, McElgunn PJ *et al*. Photoaging: mechanisms and repair. *J Am Acad Dermatol* 2006; **55**: 1–19.

2 Wang TD. Patient selection for aging face surgery. *Facial Plast Surg Clin North Am* 2005; **13**: 381–2.

3 Graham-Brown RAC, Monk BE. Pruritus and xerosis. In: Monk BE, Graham-Brown RAC, Sarkany I, eds. *Skin Disorders in the Elderly*. Oxford: Blackwell Scientific Publications, 1988: 133–46.

4 Young AW. The diagnosis of pruritus in the elderly. *J Am Geriatr Soc* 1967; **15**: 750–8.

5 Norman RA. Xerosis and pruritis in the elderly: recognition and management. *Dermatol Ther* 2003; **16**: 254–9.

6 Sami N, Yeh SW, Ahmed AR. Blistering diseases in the elderly: diagnosis and treatment. *Dermatol Clin* 2004; **22**: 73–86.

7 Twycross R, Greaves MW, Handwerker H *et al*. Itch: scratching more than the surface. *QJM* 2003; **96**: 7–26.

8 Waller JM, Maibach HI. Age and skin structure and function, a quantitative approach (II): protein, glycosaminoglycan, water, and lipid content and structure. *Skin Res Technol* 2006; **12**: 145–54.

9 Potts RO, Buras EM, Chrisman DA. Changes with age in the moisture content of human skin. *J Invest Dermatol* 1984; **82**: 97–100.

10 Graham-Brown RAC. Soaps and detergents in the elderly. *Clin Dermatol* 1996; **14**: 85–7.

11 Lazar AP, Lazar P. Dry skin, water and lubrication. *Dermatol Clin* 1991; **9**: 45–51.

12 Mastrolonardo M, Diaferio A, Vendemiale G *et al*. Seborrhoeic dermatitis in the elderly: inferences on the possible role of disability and loss of self-sufficiency. *Acta Derm Venereol* 2004; **84**: 285–7.

13 Monk BE, Graham-Brown RAC. Eczema. In: Monk BE, Graham-Brown RAC, Sarkany I, eds. *Skin Disorders in the Elderly*. Oxford: Blackwell Scientific Publications, 1988: 147–57.

14 Thivolet J, Nicolas JF. Skin ageing and immune competence. *Br J Dermatol* 1990; **122** (Suppl. 35): 77–81.

15 Bettley FR, Donoghue E. The irritant effect of soap on normal skin. *Br J Dermatol* 1960; **72**: 67–76.

16 Leonard JN. Dermatitis herpetiformis, bullous pemphigoid, cicatricial pemphigoid and linear IgA disease. In: Fry L, ed. *Skin Problems in the Elderly*. Edinburgh: Churchill Livingstone, 1985: 182–201.

17 Norman RA, Blanco PM. Papulosquamous diseases in the elderly. *Dermatol Ther* 2003; **16**: 231–42.

18 Militello G, Xia A, Stevens SR *et al*. Etanercept for the treatment of psoriasis in the elderly. *J Am Acad Dermatol* 2006; **55**: 517–9.

19 Moloney MC, Grace P. Understanding the underlying causes of chronic leg ulceration. *J Wound Care* 2004; **13**: 215–8.

20 Herber OR, Schnepp W, Rieger MA. A systematic review on the impact of leg ulceration on patients' quality of life. *Health Qual Life Outcomes* 2007; **5**: 44.

21 Ho CH, Bogie K. The prevention and treatment of pressure ulcers. *Phys Med Rehabil Clin N Am* 2007; **18**: 235–53.

22 Kimberlin DW, Whitley RJ. Varicella-zoster vaccine for the prevention of herpes zoster. *N Engl J Med* 2007; **356**: 1338–43.

23 McKenna JK, Florell SR, Goldman GD *et al*. Lentigo maligna/lentigo maligna melanoma: current state of diagnosis and treatment. *Dermatol Surg* 2006; **32**: 493–504.

24 Morris BT, Sober AJ. Cutaneous malignant melanoma in the older patient. *Dermatol Clin* 1986; **4**: 473–80.

25 Keefe M, White JE, Perkins P. Nodular melanomas in the over-50 age group: the next target for health education. *Br J Dermatol* 1990; **123** (Suppl. 37): 59.

CHAPTER 9
Racial Influences on Skin Disease

L.C. Fuller[1] *& E.M. Higgins*[2]

[1]Kent and Canterbury Hospital, Canterbury, UK
[2]King's College Hospital, London, UK

Introduction, 9.1
What is race?, 9.1
Racial variants in the structure and function of the skin, 9.2
Melanosomes, 9.2
The epidermis, 9.2
Racial differences in hair, 9.2
Normal variants, 9.2
Common diseases that show racially dependent variations, 9.4
Inflammatory and lichenoid conditions, 9.4
Infections, 9.6
Pigmentary disorders, 9.6
Neoplastic disorders, 9.7
Diseases with a distinct racial or ethnic predisposition related to cultural practices/lifestyle, 9.7
Hair and scalp, 9.7
Other applications to the skin, 9.8
Miscellaneous, 9.8
Diseases with a distinct racial or ethnic predisposition, 9.9
Diseases characteristic of specific racial groups, 9.9
Hair and scalp disorders, 9.9
Keratodermas and ichthyoses, 9.10
Pigmentary disorders, 9.11
Childhood and inherited disorders, 9.11
Infections, 9.12
Miscellaneous, 9.12
Diseases with varied racial prevalence, 9.13
Dermatitis, 9.13
Other inflammatory dermatoses, 9.14
Keratinization and fibrotic disorders, 9.15
Pigmentary disorders, 9.16
Infections, 9.18
Neoplasia, 9.18
Miscellaneous, 9.19

Introduction

This chapter aims to describe the normal variants of different 'racial' groups as well as to consider the impact of biological racial variation and cultural racial influences on the expression of skin disease. Specific tropical infections are not covered. Instead, this chapter focuses on racial susceptibility/variation in disease rather than the influence of geographic location, although inevitably the two are sometimes linked.

What is race?

In biology, 'race' refers to a subpopulation or variety of a species that differs in gene frequencies from other members of the classification group.

Many anthropologists do not think 'race' can be usefully applied to humans, because humans do not fall into geographic populations that can readily be distinguished in terms of different sets of biological or physical traits. Thus, classifications of 'race' in humans (Table 9.1) only represent a variation in DNA of 0.1% [1]. Emerging views of 'race' recognize the role of biological or anthropological definitions of the term, but also assert that 'race' reflects a social construct [2], that is a product of historical relationships amongst groups rather than just an inherited trait. Whilst this might be overlapping, 'culture' or 'ethnicity' (distinctive customs, achievements, products, outlooks, etc. of a society or group; the way of life), describing this broader construct and including the social landscape that influences a population group makes sense when considering the skin. Study of dermatological patterns in health and disease should include focusing on the cultural aspects of race, as well as the biological.

References

1 Jorde LB, Wooding SP. Genetic variation, classification and 'race'. *Nat Gen* 2004; **36** (Suppl. 11): S28–33.
2 Haney Lopez IF. The social construction of race: some observations on illusion, fabrication, and choice. *Harvard Civil Rights–Civil Liberties Law Review* 1994; **29**: 1–62, 6–7, 11–17.
3 Garn SM. *Human Races*. Springfield, IL: Charles Thomas, 1965.

Table 9.1 Two suggested classifications of race in humans [3].

Linnaeus 1758	Garn 1965	
Europeans	Amerindian	Mongoloid
Asian	Polynesian	Mongoloid
African	Micronesian	Mongoloid
Amerindian	Melanesian	Mongoloid
	Australoid	
	Indian	
	European	
	African	

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

Racial variants in the structure and function of the skin

The degree of pigmentation is one of the most obvious and immediate factors in distinguishing the main races. Other differences in the structure and function of the skin are less obvious and not so well studied but have some relevance [1] and are discussed below. Where there is little evidence of difference between the races, no further comment is made.

Reference

1 Taylor SC. Skin of color: biology, structure, function and implications for dermatologic disease. *J Am Acad Dermatol* 2002; **46**: S41–62.

Melanosomes (see Chapter 3)

The density of melanocytes is known to be identical amongst different racial groups, although it varies across body sites. It is variability in the amount and type of melanin that accounts for the intrinsic complexion. There is also variation in melanosome size with race—Africans having the largest melanosomes and European Caucasians having the smallest [1]. Furthermore, the patterns of melanosome distribution in keratinocytes of human skin vary. In Caucasian skin the melanosomes are predominantly clustered (84.5%) and membrane-limited, whereas in African skin they are individually distributed (88.8%) over the nucleus of the keratinocyte. In Asian skin the melanosomes are distributed as a combination, some being individually placed and others in clusters [2].

The epidermis

Although the stratum corneum is of equal thickness between races, there are more layers in black skin, and more extensive tape stripping is required to remove it, compared to Caucasian skin [3]. Desquamation in black skin is reported to be 2.5 times greater than in Caucasians and Mongoloids [4]. Additionally, black skin shows higher transepidermal water loss than Caucasian skin [5].

References

1 Alaluf S, Atkins D, Barret K *et al*. Ethnic variation in melanin content and composition in photo exposed and photo protected human skin. *Pigment Cell Res* 2002; **15**: 112–8.

2 Thong HY. The patterns of melanosome distribution in keratinocytes of human skin as one determining factor of skin colour. *Br J Dermatol* 2003; **149**: 498–505.

3 Weigand DA, Haywood C, Gaylor JR. Cell layers and density of Negro and Caucasian stratum corneum. *J Invest Dermatol* 1974; **62**: 563–8.

4 Corcuff P, Lotte C, Rougier A, Maibach HI. Racial differences in corneocytes. *Acta Derm Venereol (Stockh)* 1991; **71**: 146–8.

5 Wilson D, Beradesca E, Maibach HI. *In vitro* transepidermal water loss; differences between black and white human skin. *Br J Dermatol* 1988; **119**: 647–52.

Racial differences in hair (see also Chapter 66)

Human scalp hair is categorized into three distinct forms: African, Asian and Caucasian. However, there are limited data on the influence of racial origin on hair characteristics.

Diameter. Asian hair is thicker in diameter and generally circular in cross section, whereas African hair tends to be more elliptical in cross section with a variable diameter along its shaft. The Caucasian hair-shaft seems to lie somewhere between the two.

Fibre shape. Caucasian and Asian hair shafts are generally cylindrical whereas the African hair shaft resembles a twisted, oval rod [1].

Telogen counts tend to be higher in Afro-Caribbeans than in Caucasians, whereas hair density is lower; mean ± SD: 190 ± 40; 227 ± 55 hairs/cm^2, respectively [2].

Male Caucasoids show more androgenic balding over the vertex with age than Afro-Caribbeans [3]. Black hair colour predominates amongst Asian, African and Amerindian races; however, hair can also be red in these races. European or Caucasoid hair colour varies widely from black in southern Europe to blond in northern countries [4].

Amerindian, Polynesian, Micronesian and Melanesian (collectively known sometimes as Mongoloid) races have less body, beard and axillary hair than Caucasoids [5].

References

1 Franbourg A, Hallegot P, Baltenneck F *et al*. Current research on ethnic hair. *J Am Acad Dermatol* 2003; **48**: S115–9.

2 Loussouarn G. African hair growth parameters. *Br J Dermatol* 2001; **145**: 294–7.

3 Hardy D, Baden HP. Biochemical variations of hair keratins in man and non-human primates. *Am J Phys Anthropol* 1973; **39**: 19–24.

4 Sunderland E. Hair colour variation in United Kingdom. *Ann Hum Genet* 1955; **20**: 312–3.

5 Hamilton JB. Age, sex and genetic factors in the regulation of hair growth in man: a comparison of Caucasian and Japanese populations. In: Montagna W, Ellis RA, eds. *The Biology of Hair Growth*. New York: Academic Press, 1958: 399–433.

Normal variants

Voight's lines

Synonym

- Futcher's lines

These are sharply demarcated borders between areas of darker pigmentation on the dorso-lateral and ventral aspects of the limbs [1]. They are bilateral and most obvious on the proximal part of the limb, especially on the upper arms (Fig. 9.1). The line of demarcation corresponds to innervation within a dermatome; however, histologically, there is no alteration in the distribution or amount of melanin [2]. Occasionally a second such line may be seen postero-medially on the lower part of the limb [2]. Although infrequently seen in other racial groups [3], they are very prevalent in black races. Estimates of their frequency vary, being reported in up to 30% of black individuals [1,3,4]; their occurrence is proportional to the degree of pigmentation. More rarely, a line of hypopigmentation may occur in the midline of the anterior chest wall [1]. It is most prominent in children. Although entirely benign, reassurance may sometimes be required as such lines can be thought to be pathological or may be a source of cosmetic concern.

Hyperpigmentation of the palms and soles

Patchy and rather mottled pigmentation on the palms and soles (Fig. 9.2) is a common finding in black individuals [1]. The lesions are usually multiple, vary in size and have rather indistinct borders but should be easily distinguished from solitary melanocytic naevi, malignant melanoma or lesions of secondary syphilis [4].



Fig. 9.1 Voight's lines. (Courtesy of the late Dr R.R.M. Harman, Bristol Royal Infirmary, Bristol, UK.)

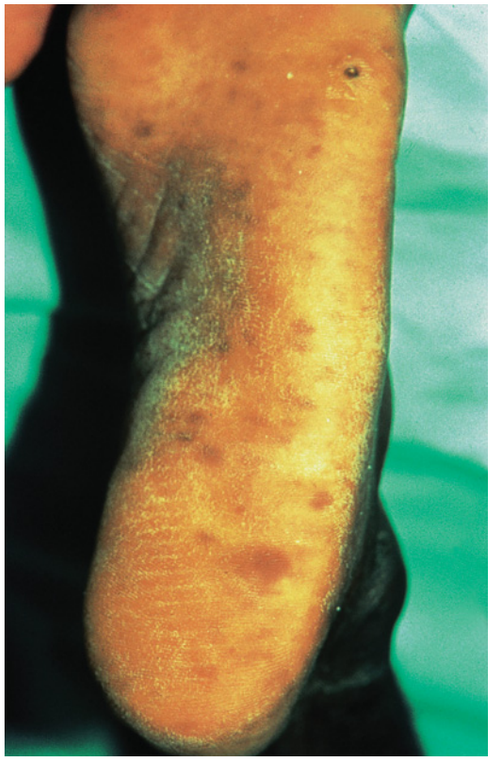


Fig. 9.2 Mottled hyperpigmentation of the soles. (Courtesy of Dr D.J. Barker, Bradford Royal Infirmary, Bradford, UK.)

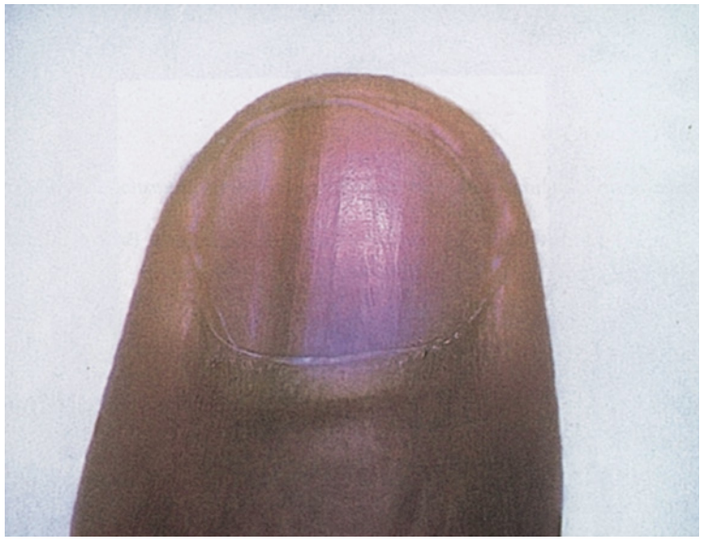


Fig. 9.3 Melanonychia: nail pigmentation.

Melanonychia

Nail pigmentation is quite variable in people with skin types 5 and 6. While some individuals have quite pink nails, in others diffuse pigmentation may occur and there is quite wide inter-family variation. Discrete, longitudinal bands of hyperpigmentation are common, particularly on the first and second digits [4]. Such changes are found in at least 50% of all black Africans, but more so in those with darker skin. They may be noted in childhood, but appear to increase in frequency with age. They are due to increased melanin deposition in the nail plate and matrix [5]. Trauma has been implicated in their development [6]. In children, benign melanocytic hyperplasia is the most common cause [7]. Concern regarding the possibility of malignant melanoma may arise [8], but the pigmented bands of longitudinal melanonychia are static, usually multiple or bilateral, and are not associated with pigmentation extending onto the surrounding skin (Fig. 9.3).

References

1 Grimes PE, Stockton T. Pigmentary disorders in blacks. *Dermatol Clinics* 1988; **6**: 271–81.

2 Volum D. Skin markings in Negro children from the West Indies. *Br J Dermatol* 1972; **85**: 260.

3 James WD, Carter JM, Rodman OG. Pigmentary demarcation lines: a population survey. *J Am Acad Dermatol* 1987; **16**: 584–90.

4 Henderson A. Skin variations in Blacks. *Cutis* 1983; **32**: 376–7.

5 White G. Normal skin changes in the black patient. In: Johnson B, Ronald M, White G, eds. *Ethnic Skin: Medical and Surgical*. St Louis: Mosby, 1998: 32–40.

6 Leyden JJ, Spot DA, Goldschmidt H. Diffuse and banded melanin pigmentation in nails. *Arch Dermatol* 1972; **105**: 548–50.

7 Goettmann-Bonvallot S, André J, Belaich S. Longitudinal melanonychia in children: a clinical and histopathological study of 40 cases. *J Am Acad Dermatol* 1999; **41**: 17–22.

8 André J, Lateur N. Pigmented nail disorders. *Dermatol Clin* 2006; **24**: 329–39.

Oral pigmentation

Oral pigmentation is common in darker races [1]. It most frequently affects the gingivae, but may involve the hard palate, buccal mucosae and tongue [2].

Table 9.2 Some causes of hypopigmentation.

Division	Disorders
Congenital or genetic	Albinism, piebaldism, achromic naevus
Infections	Leprosy, onchocerciasis, pinta, pityriasis versicolor, herpes zoster
Papulosquamous disorders	Pityriasis alba, pityriasis rosea, pityriasis lichenoides chronica, psoriasis, seborrhoeic dermatitis, lichen striatus
Other inflammatory disorders	Discoid lupus erythematosus, systemic sclerosis, sarcoidosis, some eczematous eruptions
Physical or chemical agents	Burns, cryotherapy, ammoniated mercury, hydroquinone products, fluorinated corticosteroids
Miscellaneous	Vitiligo, idiopathic guttate hypomelanosis

Table 9.3 Some causes of hyperpigmentation.

Division	Disorders
Congenital or genetic	Voight's lines, congenital melanocytic naevus, epidermal naevus, Becker's naevus, neurofibromatosis, McCune–Albright disease
Infections	Tinea corporis, herpes simplex, chickenpox, herpes zoster
Papulosquamous disorders	Eczema, lichen simplex, lichen planus, pityriasis rosea
Post-inflammatory	Fixed drug eruption, erythema multiforme, trauma
Physical or chemical agents	Thermal burn, contact dermatitis, ochronosis
Miscellaneous	Melasma, idiopathic macular hyperpigmentation, ashy dermatosis

References

1 Dummett CO, Sakumura JS, Barens G. The relationship of facial skin complexion to oral pigmentation and tooth color. *J Prosthet Dent* 1980; **4**: 392–6.

2 Halder RM, Roberts CI, Nootheti PK. Cutaneous diseases in Black races. *Dermatol Clin* 2003; **21**: 679–87.

Follicular prominence

Follicular accentuation is a frequent finding in black skin, especially in young children. While slightly more common in those with an atopic diathesis, it is not in itself pathological, although it may be mistakenly thought to represent a skin disease. The term 'disseminate and recurrent infundibulofolliculitis' [1] may simply describe accentuation of such a normal variant, or may represent a low-grade eczematous reaction. Follicular reaction patterns are generally more prevalent in black skin [2]. Emollients may be helpful in making the appearance less pronounced, but over-treatment of what is essentially a normal variant should be avoided.

References

1 Brauner GJ. Cutaneous diseases in the black races. In: Demis DJ, Dobson RL, McGuire J, eds. *Dermatology*. Philadelphia: WB Saunders, 1975: 1704–33.

2 McLaurin CI. Cutaneous reaction patterns in Blacks. *Dermatol Clin* 1988; **6**: 353–62.

Common diseases that show racially dependent variations

Studies show that the spectrum of common inflammatory skin disease is not dissimilar in black and white populations living in Western communities, with acne and eczema predominating [1–4]. However, common dermatoses may appear different in black skin and may pose diagnostic difficulty for clinicians unfamiliar with cutaneous reaction patterns in black skin [5]. Erythema is harder to discern, follicular and annular reaction patterns are more common and altered pigmentation, as a post-inflammatory phenomenon (Tables 9.2 & 9.3), may dominate the clinical picture (Fig. 9.4).

References

1 Child FJ, Fuller LC, Higgins EM, du Vivier AWP. A study of the spectrum of skin disease occurring in a black population in SE London. *Br J Dermatol* 1999; **141**: 512–7.



Fig. 9.4 Post-inflammatory pigmentation occuring in association with follicular eczema.

2 Hartshorne ST. Dermatological disorders in Johannesburg, South Africa. *Clin Exper Dermatol* 2003; **28**: 661–5.

3 Taylor SC. Epidemiology of skin diseases in ethnic populations. *Dermatol Clin* 2003; **21**: 601–7.

4 Halder RM, Nootheri PK. Ethnic skin disorders overview. *J Am Acad Dermatol* 2003; **48**: S143–8.

5 McLaurin CI. Cutaneous reaction patterns in Blacks. *Dermatol Clin* 1988; **6**: 353–62.

Inflammatory and lichenoid conditions

Acne (see also Chapter 44)

Although the prevalence of acne may be similar across most races, apart from in the Japanese where it has been reported to be less

common [1], there is evidence that it is more severe in white skin [2]. However, the traditional measures of severity do not give weighting to pigmentary changes. Post-inflammatory hyperpigmentation following acne in a deeply pigmented skin can be devastating and may persist for months, if not years. Thus, earlier and more aggressive intervention in acne in pigmented skins often is justified. Secondary acne, induced by the use of hair oils (pomade acne), has been reported to occur commonly on the forehead of Afro-Caribbeans [3]. Skin lightening products can lead to steroid-induced acne (Fig. 9.5) (see p. 9.8).

References

1 Hamilton JB, Terada H, Mestler GE. Greater tendency to acne in white American than in Japanese populations. *J Clin Endocrinol Metab* 1964; **24**: 267–72.

2 Wilkins JW Jr, Voorhees JJ. Prevalence of nodulocystic acne in white and negro males. *Arch Dermatol* 1970; **102**: 631–4.

3 Arfan-ul-Bari, Khan MB. Dermatological disorders related to cultural practices in black Africans of Sierra Leone. *J Coll Physicians Surg Pak* 2007; **17**: 249–52.



Fig. 9.5 Acne exacerbated by the use of 'skin lighteners' containing topical steroids.

Lichen planus and lichen nitidus (Chapter 41)

The typical violaceous colour of lichen planus is not so easily identifiable in a deeply pigmented skin. Instead a dark purple colour may be appreciated (Fig. 9.6a). As with any disorder disrupting the dermo-epidermal junction in skin types 5 and 6, intense post-inflammatory hyperpigmentation is particularly striking following lichen planus and is often very persistent (Fig. 9.6b). Hypertrophic variants of lichen planus appear more common in Afro-Caribbeans (Fig. 9.6a), whereas oral lesions may be less so [1]. Lichen nitidus, in which minute, pale papular foci of lichenoid inflammation occur, particularly around the umbilicus, is much more common in black skin [2].

Lichen striatus

This linear eruption, more common in children, is often more obvious in black patients [3]. The disorder is characterized by small papules clustered in a linear configuration, following Blaschko's lines and predominantly affecting the limbs. In white patients the papules are pinkish, but in black individuals the lesions are usually hypopigmented, with no discernible erythema. The condition is often asymptomatic and usually self-limiting, resolving over 18 months.

Pityriasis lichenoides chronica (Chapter 57)

This chronic papulo-squamous eruption may begin insidiously, but often becomes extensive. Crops of lesions occur in a relapsing and remitting manner, and the disease course can be very prolonged. Although the characteristic distribution on the inner aspect of the limbs is the norm, facial involvement is not infrequent in black patients [4]. The subsequent post-inflammatory



(a)



(b)

Fig. 9.6 (a) Hypertrophic lichen planus. (b) Post-inflammatory hyperpigmentation following lichen planus may be very striking and persistent.



Fig. 9.7 Pityriasis rosea: small urticated papules occur in the characteristic distribution.

hypopigmentation is usually pronounced and can be devastating [3]. Long-term antibiotics and phototherapy are the mainstay of treatment, but low-dose methotrexate has been shown to be very helpful in recalcitrant disease [5].

References

1 Rosen T, Martin S. Common skin disorders appearing different in blacks. In: *Atlas of Black Dermatology.* Boston: Little, Brown and Co., 1981: 26–8.
2 Child FJ, Fuller LC, Higgins EM, du Vivier AWP. A study of the spectrum of skin disease occurring in a black population in SE London. *Br J Dermatol* 1999; **141**: 512–7.
3 McLaurin CI. Pediatric dermatology in Black patients. *Dermatol Clin* 1988; **6**: 457–73.
4 McLaurin CI. Unusual patterns of common dermatoses in Blacks. *Cutis* 1983; **32**: 352–60.
5 Romani J, Puig L, Fernandéz-Figueras MT, de Moragas JM. Pityriasis lichenoides in children: clinicopathologic review of 22 patients. *Pediatr Dermatol* 1988; **15**: 1–6.

Pityriasis rosea (Chapter 33)

Although pityriasis rosea is twice as common in black individuals as white, occurring with a frequency of 6% [1], the same seasonal peaks and preceding herald patch occur [2]. However, in black skin, individual lesions are smaller and more papular (micropapular), often urticated (Fig. 9.7) and may even be vesicular [3].

An inverse distribution of pityriasis rosea is more frequent in black skin [3] and involvement of the face is seen in 30%, especially in children [2]. The scalp is also more often affected [2]. Lesions in black patients tend to be quite pruritic and more persistent [3], and are known as the 'eczematide' reaction. Post-inflammatory hyperpigmentation occurs in almost half of black patients, but hypopigmentation may also occur [2]. Symptomatic treatment with antihistamines and topical steroids is often required and in severe cases UVB has sometimes been used [3].

References

1 McLaurin CI. Unusual patterns of common dermatoses in Blacks. *Cutis* 1983; **32**: 352–60.
2 Amer A, Fischer H, Li X. The natural history of pityriasis rosea in black American children: how correct is the 'classic' description? *Arch Pediatr Adolesc Med* 2007; **161**: 503–6.
3 Halder RM, Roberts CI, Noothethi PK. Cutaneous disease in black races. *Dermatol Clin* 2003; **21**: 679–87.

Seborrhoeic dermatitis (Chapter 23)

The erythema of seborrhoeic dermatitis is often masked in black skin, especially on the face, and the scale may be very fine. The dominant feature is usually the post-inflammatory hypopigmentation, which may be very sharply demarcated and in an annular configuration [1,2]. Hypopigmentation can be very pronounced in infants with seborrhoeic dermatitis, although it recovers quickly [3].

References

1 Halder RM, Roberts CI, Noothethi PK. Cutaneous disease in black races. *Dermatol Clin* 2003; **21**: 679–87.
2 McLaurin CI. Annular facial dermatoses in Blacks. *Cutis* 1983; **32**: 369–70.
3 McLaurin CI. Pediatric dermatology in Black patients. *Dermatol Clin* 1988; **6**: 457–73.

Infections

Pityriasis versicolor (Chapter 36)

This disorder is more prevalent in tropical climates. The hypopigmentation associated with this pityrosporum-related dermatosis is often more obvious in black skin [1], but the disorder itself does not occur with any increased frequency in different ethnic groups living in the same country [2]. However, extension onto the neck and face is more common in black patients [2].

Syphilis (Chapter 34)

Primary disease is similar in all races, but the manifestations of secondary syphilis vary. Macular lesions are common in Caucasians, but follicular, papular and annular forms are more frequent in black Africans [3,4]. Lesions are often hyperpigmented, and corymbose forms (a cluster of satellites around a central lesion) may occur in black patients [3]. Palmoplantar lesions may be keratotic in black Africans.

References

1 Aljabre SH, Alzayir AA, Abdulghani M, Osman OO. Pigmentary changes of tinea versicolor in dark skinned patients. *Int J Dermatol* 2001; **40**: 273–5.
2 Halder RM, Nandedkar MA, Neal KW. Pigmentary disorders in ethnic skin. *Dermatol Clin* 2003; **21**: 617–28.
3 Rosen T, Martin S. Common skin disorders appearing different in Blacks. In: *Atlas of Black Dermatology*. Boston: Little, Brown and Co., 1981: 46–51.
4 McLaurin CI. Annular facial dermatoses in blacks. *Cutis* 1983; **32**: 369–70.

Pigmentary disorders

Vitiligo (Chapter 58)

Although vitiligo occurs in all ages and races, the clinical effects of the disease are more obvious in a dark skin (Fig. 9.8) and are



Fig. 9.8 Vitiligo.

generally associated with a higher impact on quality of life. Furthermore, in areas where infectious diseases associated with pigment loss occur, cultural stigmatization of leucoderma can be a problem. This is especially problematic in India [1].

Reference

1 Parsad D, Dogra S, Kanwar A. Quality of life in patients with vitiligo. *Health and Quality of Life Outcomes* 2003; **1**: 58 (http://www.hqlo.com/content/1/1/58).

Neoplastic disorders

Mycosis fungoides (Chapter 57)

Hypopigmented mycosis fungoides (MF) is more frequently associated with skin types 5 and 6 than with types 1–4 [1], and appears to occur at a younger age than classical MF [2]. Differentiation from pityriasis versicolor, vitiligo or post-inflammation hypopigmentation is important. In MF, the skin involvement tends to be more centripetal and pruritus is frequent [3].

Histologically, immunohistochemistry of hypopigmented MF shows loss of $CD7^+$ cells [2]. Hypopigmented patch stage MF responds well to phototherapy, and usually follows an indolent course, but in tumour stage MF, black patients often present late, with more aggressive disease and consequently a poorer prognosis [3].

References

1 Stone ML, Styles AR, Cockerell CJ, Pandya AG. Hypopigmented mycosis fungoides: a report of 7 cases and review of the literature. *Cutis* 2001; **67**: 133–8.

2 Whitmore SE, Simmons-O'Brien E, Rotter FS. Hypopigmented mycosis fungoides. *Arch Dermatol* 1994; **130**: 476–80.



Fig. 9.9 Traction alopecia.

3 Halder RM, Bang KM. Skin cancer in African-Americans in the US. *Dermatol Clin* 1988; **6**: 397–407.

Diseases with a distinct racial or ethnic predisposition related to cultural practices/lifestyle

Diseases that have a greater clinical impact due to variation in cultural practices or beliefs are also considered in this section.

Hair and scalp

Hairstyling practices

It has not been established definitively what role hair styling practices have in the various hair complaints suffered by patients of Afro-Caribbean origin. The problems include easy breakage, itching, flaking, and hair loss over the crown and also of the temporal areas.

Follicular degeneration syndrome (FDS) or central centrifugal scarring alopecia, describing hair loss associated with scarring over the crown in Afro-Caribbean women, was initially attributed to the use of hot combing [1]. However, causality has never been established and the term FDS was coined in 1992 [2] to suggest that pathogenesis is multifactorial and not just attributable to hair styling practices, whether chemical (relaxers) or physical (tight mechanical braiding). However, raising awareness of the possible risks of excess use of cosmetic hair products is advocated, as a smaller series correlates misuse with the onset of scarring alopecia [3]. Frontotemporal scarring alopecia is seen commonly in women of Afro-Caribbean extraction and has been attributed to traction from tight braiding practices, but is probably also multifactorial (Fig. 9.9).

Mudi-chood

This is an unusual lichenoid dermatosis of the nape of the neck and upper back seen almost exclusively in young women from the Kerala province of India [1]. The disorder is characterized by small pruritic pustules, which evolve to form pigmented macules and plaques with a hyperkeratotic rim (Fig. 9.10). It is thought to be related to the occlusive effect of plant oils used in the traditional

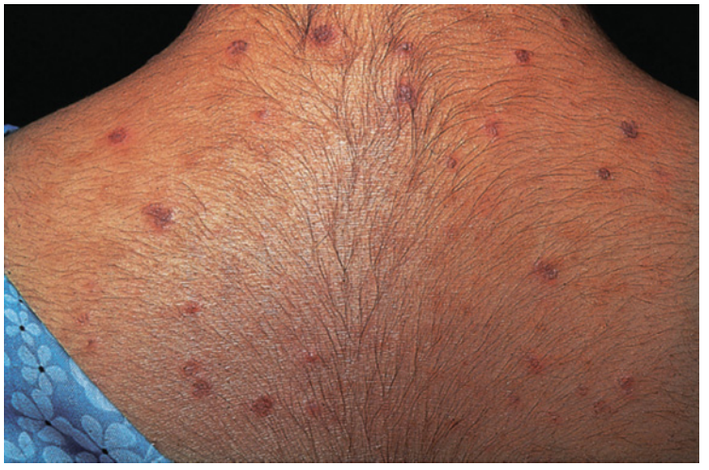


Fig. 9.10 Mudi-chood. (Courtesy of Dr P. Sugathan, Baby Memorial Hospital, Calicut, India.)

grooming of hair, compounded by the heat and humidity of the climate [4,5]. Reducing the use of oils, or cutting the hair shorter, are curative.

Tinea capitis (Chapter 36)

Scalp ringworm (tinea capitis) is an infection caused predominantly by the dermatophyte group of fungi affecting scalp hair follicles and the surrounding scalp skin. Tinea capitis in the UK and France is currently most frequent in urban areas and appears to be more common in children of Afro-Caribbean extraction than in Caucasians and other races [6,7]. This is thought to be due to hair styling practices which render the hair more vulnerable to infection; these include close-cropped styles, tight plaits and sharing clippers, which facilitate transmission of anthropophilic spores [6].

References

1 Lo Presti P, Papp CM, Kligman AM. Hot comb alopecia. *Arch Dermatol* 1968; **98**: 234–8.
2 Sperling LC. The follicular degeneration syndrome in black patients. *Arch Dermatol* 1992; **128**: 68–74.
3 Nicholson AG, Harland CC, Bull RH *et al*. Chemically induced cosmetic alopecia. *Br J Dermatol* 1993; **128**: 537–41.
4 Sugathan P. Mudi-chood. *Dermatol Online J* 1999; **5**: 5.
5 Gharpuray MB, Kulkarin V, Tolat S. Mudi-chood: an unusual tropical dermatosis *Int J Dermatol* 1992; **31**: 396–7.
6 Fuller LC, Child FC, Midgley G, Higgins EM. Scalp ringworm in south-east London and an analysis of a cohort of patients from a paediatric dermatology department. *Br J Dermatol* 2003; **148**: 985–8.
7 Cremer G, Bousseloua N, Roudot-Thoraval F *et al*. Tinea capitis in Creteil. Trends over ten years. *Ann Dermatol Venereol* 1998; **125**: 171–3.

Other applications to the skin

Effects of skin bleaching

In certain parts of the world, it is common practice for individuals with dark skin tones to use agents to lighten the skin; 52.7% of women attending a skin clinic in Senegal had used skin lightening products [1]. The reasons for doing so are complex. The agents used are wide ranging and include hydroquinone, steroids, mercury iodide and caustic agents, but often the ingredients are unknown. Skin lighteners have other less desirable effects on the skin, including steroid-induced acne, tinea facei, striae, macular hyperchromias and telangiectasia. Treatment involves cessation of use of the skin lightening product, but this can be difficult to achieve when admission to its use in the first place is often not forthcoming.

When treating acne related to the use of bleaching products, not only withdrawal of the skin lightener, but also aggressive concomitant treatment of the acne, is required to minimize permanent scarring (Fig. 9.5).

Traditional therapies

Traditional medicinal practices such as cupping, coin rubbing or moxibustion are popular in Eastern cultures, and may result in eccymoses, purpura, circular areas of post-inflammatory hyperpigmentation or, occasionally, true burns [2].

References

1 Mahe A, Ly F, Aymard G, Dangou JM. Skin diseases associated with cosmetic use of bleaching products in women from Dakar, Senegal. *Br J Dermatol* 2003; **148**: 493–500.
2 Halder RM, Nootheri PK. Ethnic skin disorders overview. *J Am Acad Dermatol* 2003; **48**: S143–8.

Miscellaneous

Podoconiosis (Chapter 48)

Synonyms
- Mossy foot
- Big foot disease
- Non-filarial elephantiasis

Podoconiosis is a non-communicable disease first described by Price [1], which produces lymphoedema of the legs. It is caused by exposure of bare feet to irritant, alkalic clay soils. It is thus a geochemical dermatosis confined to communities of bare-foot subsistence farmers. It has been found recently in at least 10 countries in tropical Africa, central America and north-west India where the culprit soils prevail together with low income, high rainfall and high altitude. The disease becomes apparent in susceptible individuals by the third decade. Colloid-sized silicate particles penetrate the skin and are taken up by macrophages in the leg lymphatics, leading to endolymphangitis and obliteration of the lymphatic vessels. Susceptibility is highly inheritable [2], and the economic impact can be catastrophic in affected areas, where communities are dependent on subsistence farming.

With relatively simple measures, such as vulnerable individuals wearing shoes at all times when in contact with irritant soils, this non-communicable disease is entirely preventable. Early stages are reversible with good foot hygiene and the wearing of shoes, but later stages lead to significant economic and social difficulties, and may require interventions such as prolonged episodes of leg elevation and even surgical nodulectomies.

References

1 Price EW. Non filarial elephantiasis—confirmed as a geochemical disease and renamed podoconiosis. *Ethiop Med J* 1988; **26**: 151–3.
2 Davey G, Gebre Hanna E, Adeyamo A *et al*. Podoconiosis; a tropical model for gene–environment interactions. *Trans Roy Soc Trop Med Hygiene* 2007; **101**: 91–6.

Diseases with a distinct racial or ethnic predisposition

Some dermatoses are almost exclusive to certain races. Others may occur more widely, but have varied prevalence in different racial groups.

Diseases characteristic of specific racial groups

Hair and scalp disorders

Pseudofolliculitis barbae

Shaving tightly curled hair creates a sharp residual point, which either retracts under the skin and embeds, or curls over and ingrows, to produce a foreign body inflammatory reaction with papule and pustule formation. Mild cases may be transient, but severe cases are very destructive with subsequent scarring. Initial inflammation is sterile, but secondary infection is not uncommon. Estimates of prevalence vary between 45 and 85% of African Americans [1]. The problem may occur on any part of the body that is repeatedly shaved [2]. It is most common in men, but may be seen in women, related to repeated plucking or shaving of hairs on the chin and neck [3]. The treatment is to allow the hair to grow, reduce inflammation with topical steroids and then use specialized shaving techniques and avoid close shaving [3].

Acne nuchae keloidalis

Synonyms
- Folliculitis keloidalis
- Lichen keloidalis nuchae

This is a scarring process related to ingrown hairs producing a folliculitis, which becomes chronic and scars, in a hypertrophic manner, with associated alopecia. Initially papular, the lesions may coalesce to form large plaques (Fig. 9.11), usually confined to the central occipital area, which are both tender and unsightly. It is one of the most common reasons for black patients to attend dermatology clinics [4]. It is a post-pubertal phenomenon, but onset is rare after age 50 years [2].

The pathogenesis is believed to be multifactorial and exacerbated by secondary infection [2]. Although close-cropped hair styles appear to be the main pathogenetic factor, friction from shirt collars and helmets [5] has also been implicated. The condition is much commoner in black men than in other races, but a similar process occurs in Caucasians. In particular, it has recently been described in transplant recipients taking ciclosporin [6], presumably related to the combined effects of the pro-fibrotic state and concurrent infection and therefore giving further clues about the pathogenesis.

Treatment of early disease has the most impact [7,8], and centres on reducing the inflammatory response with topical steroids, and treating any secondary infection. Late disease presents a treatment challenge, involving intra-lesional steroids, surgery, cryotherapy and laser ablation.



Fig. 9.11 Nuchal acne keloidalis.



Fig. 9.12 Dissecting cellulitis of the scalp.

Dissecting cellulitis

Synonym
- Perifolliculitis capitis abscediens et suffudiens

This is an uncommon, chronic inflammatory condition of the scalp, and may form part of the follicular occlusion tetrad. It occurs in both men and women, but is most common in black men [1]. It tends to begin at the vertex and spread posteriorly, but severe cases may involve the whole scalp. Large, tender fluctuant swellings develop, which progress to produce extensive destruction of hair follicles and permanent scarring alopecia (Fig. 9.12).

Swabs from the affected areas are usually sterile [9]. Treatment involves long-term antibiotics (for their anti-inflammatory effect), oral steroids and retinoids, but disease control is often difficult [1].

References

1 McMichael AJ. Hair and scalp disorders in ethnic populations. *Dermatol Clin* 2003; **21**: 629–44.
2 Kelly AP. Pseudofolliculitis barbae and acne keloidalis nuchae. *Dermatol Clin* 2003; **21**: 645–53.
3 Perry P, Cook-Bolden FE, Rahman Z *et al*. Defining pseudofolliculitis barbae in 2001: a review of the literature and current trends. *J Am Acad Dermatol* 2002; **46** (2 Suppl.): S113–9.
4 Child FJ, Fuller LC, Higgins EM, du Vivier AWP. A study of the spectrum of skin disease occurring in a black population in SE London. *Br J Dermatol* 1999; **141**: 512–7.
5 Knable AL Jr, Hanke CW, Gonin R. Prevalence of acne keloidalis nuchae in football players. *J Am Acad Dermatol* 1997; **37**: 570–4.
6 Azurdia RM, Graham RM, Weismann K *et al*. Acne keloidalis in Caucasian patients on cyclosporine following organ transplantation. *Br J Dermatol* 2000; **143**: 465–7.
7 George AO, Akanji AO, Nduka EU *et al*. Clinical, biochemical and morphological features of acne keloidalis in a black population. *Int J Dermatol* 1993; **32**: 714–6.
8 Adegbidi H, Atadokpede F, do Ango-Padonou F, Yedomon H. Keloid acne of the neck: epidemiological studies over 10 years. *Int J Dermatol* 2005; **44** (Suppl. 1): 49–50.
9 Williams CN, Cohen M, Ronan SG, Lewandowski CA. Dissecting cellulitis of the scalp. *Plast Reconstr Surg* 1986; **77**: 378–82.

Keratodermas and ichthyoses

Keratodermas and focal acral hyperkeratosis (Chapter 19)

Synonyms
- Marginal papular acrokeratoderma
- Acrokeratoelastoidosis

Keratodermas are often very pronounced in black skin, particularly on the dorsum of the distal hands and feet [1,2]. The cutaneous changes become more pronounced with time and may be of great cosmetic concern, but rarely require any intervention other than emollients and avoiding excess friction.

Crateriform keratotic papules along the border of the hands and feet are a frequent finding in black patients [3]. They represent a genodermatosis, and are thought to be related to the breakdown and extrusion of dermal elastic material by fibroblasts [4], but the nosology of this and related conditions has become confused. Over time, a wide variety of names have been applied to this process [4]. Histologically, when elastorrhexis is present, the term acrokeratoelastoidosis of Costa has been used, but when absent, the lesions have been classified as focal acral hyperkeratosis [5].

However, it has now been suggested that they should all be considered variants of the same process [3]; the collective term marginal papular acrokeratodermas has been proposed [6], although no consensus on nomenclature has been agreed.

Keratosis punctata (keratotic pits) of the palmar creases

Small conical pits, confined to the creases of the palms (Fig. 9.13) and volar aspects of the fingers, occur exclusively in black races [7], particularly in men, with a prevalence of about 3% [8]. The aetiology is unknown, but the condition is familial, with apparent autosomal dominant inheritance [9]. Trauma seems to play a part, and the disorder is more frequent in those with manual occupations [8]. It may occur in association with punctuate keratoses of the palms and soles, but there is debate about whether this should be considered a variant of keratosis punctata [9] or a distinct entity [8].



Fig. 9.13 Keratosis punctata of the palmar creases. (Courtesy of Dr D.J. Barker, Bradford Royal Infirmary, Bradford, UK.)

Pityriasis rotunda

This relatively rare disorder, seen in individuals with skin type 6, is a form of acquired ichthyosis in which large, discrete circular patches appear, mainly on the trunk [10,11]. Some lesions coalesce to produce a petaloid appearance. Patches are usually lighter in colour than the surrounding skin, but may be darker. It is usually idiopathic, and is sometimes observed in newly arrived immigrants (possibly due to the effect of change in climate), but has also been reported in association with serious illness or as a paraneoplastic phenomenon [12]. Rare reports in Europeans [10] have described occurrence at a younger age, and are typically familial, so they probably represent a separate, distinct disorder.

References

1 Patel S, Zirwas M, English JC. Acquired palmoplantar keratoderma. *Am J Clin Dermatol* 2007; **8**: 1–11.
2 Shrank AB, Harman RHH. The incidence of skin disease in a Nigerian teaching hospital dermatological clinic. *Br J Dermatol* 1996; **78**: 235–41.
3 Bourrat E. Keratosis palmoplantaris in black skin. *Ann Dermatol Venereol* 2006; **133**: 917–23.
4 Bogle MA, Hwang LY, Tschen JA. Acrokeratoelastoidosis. *J Am Acad Dermatol* 2002; **47**: 448–5.
5 Erkek E, Kocak M, Bozdogan O *et al*. Focal acral hyperkeratosis: a rare cutaneous disorder within the spectrum of Costa acokeratoelastoidosis. *Pediatr Dermatol* 2004; **21**: 128–30.
6 Rongioletti F, Betti R, Crosti C, Rebora A. Marginal papular acrokeratodermas: a unified nosography for focal acral hyperkeratosis, acrokeratoelastoidosis and related disorders. *Dermatology* 1994; **188**: 28–31.
7 Dilaimy MS, Owen WR, Sina B. Keratosis punctata of the palmar creases. *Cutis* 1984; **33**: 394–6.
8 Rustad OJ, Vance JC. Punctate keratoses of the palms and soles and keratotic pits of the palmar creases. *J Am Acad Dermatol* 1990; **22**: 468–76.
9 Fond L, Perrot JL, Gentil-Perret A *et al*. Focal familial palmoplantar keratoderma with punctate hyperkeratosis of the palmar creases. *Ann Dermatol Venereol* 1998; **125**: 898–901.



Fig. 9.14 Dermatosis papulosa nigra.



Fig. 9.15 Mongolian blue spot. (Courtesy of Professor S.S. Bleehan, Royal Hallamshire Hospital, Sheffield, UK.)

10 Ena P, Cerimele D. Pityriasis rotunda in childhood. *Pediatr Dermatol* 2002; **19**: 200–3.
11 Rubin MG, Mathes B. Pityriasis rotunda: two cases in black Americans. *J Am Acad Dermatol* 1986; **14**: 74–8.
12 McLaurin CI. Cutaneous reaction patterns in Blacks. *Dermatol Clin* 1988; **6**: 353–62.

Pigmentary disorders

Dermatosis papulosa nigra

This is a very common condition with a familial basis. Small, deeply pigmented, papules appear on the face (Fig. 9.14), neck and upper torso from the early twenties. The condition is estimated to affect up to 77% of black individuals, and is progressive with more lesions appearing over time [1]. It is more frequent in women than men, and women tend to have more lesions than men [1]. Lesions vary from pin-point to several millimetres in diameter. Histologically, they are identical to seborrhoeic keratoses, and should be considered a variant of such [2]. The main concern is usually cosmetic, but occasionally larger lesions may become inflamed by trauma. Light cautery or hyfrecation may be effective [2], but it is important to acknowledge the potential risk of scarring related to surgical intervention and it is often impractical to remove numerous lesions.

References

1 Grimes PE, Arora S, Minus HR, Kenney JA Jr. Dermatosis papulosa nigra. *Cutis* 1983; **32**: 385–6.
2 Lupo MP. Dermatosis papulosa nigra: treatment options. *J Drugs Dermatol* 2007; **6**: 29–30.

Idiopathic guttate hypomelanosis (Chapter 58)

Myriads of small, pale macules, 1–2 mm in diameter, appear on the distal limbs, particularly the legs and gradually extend over time. Although mild forms may occasionally be seen in other racial groups, it is characteristic of skin types 5 and 6 [1]. Lesions appear later in life and are progressive with age, being most prevalent after the seventh decade [2]. They are often a cause of great cosmetic concern, and patients may be worried that they are developing vitiligo, but histologically the two conditions are quite distinct, and hairs within the affected areas are not depigmented [3]. Histology shows epidermal atrophy with flattening of the dermo-epidermal junction and reduction in the number of melanin granules within the basal layer [1]. There may be a familial basis to the disorder, but actinic factors and ageing are also implicated [2]. The condition is much more prevalent in women [1]. It is benign and asymptomatic, but there is no effective treatment [4].

References

1 Falabella R. Idiopathic guttate hypomelanosis. *Dermatol Clin* 1988; **6**: 241–7.
2 Falabella R, Escobar C, Giraldo N *et al*. On the pathogenesis of idiopathic guttate hypomelanosis. *J Am Acad Dermatol* 1987; **16**: 35–44.
3 Bologna J, Pawalek J. Biology of hypopigmentation. *J Am Acad Dermatol* 1988; **19**: 217–55.
4 Halder RM, Nandedkar MA, Neal KW. Pigmentary disorders in ethnic skin. *Dermatol Clin* 2003; **21**: 617–28.

Childhood and inherited disorders

Mongolian blue spot (Chapters 17 and 54)

Synonym
- Congenital dermal melanocytosis

Mongolian spots are macular areas of bluish-grey pigmentation, occurring over the lower back and present at birth (Fig. 9.15). They are observed in 100% of Mongoloid babies, up to 96% of black African infants but only 10% of Caucasians [1]. The pigmentation is most common in the sacral region, but may extend to cover a large area from the buttocks to upper trunk. They vary considerably in size from a few centimetres diameter to involving the majority of the back. The pigmentation tends to increase initially, reaching a peak by the age of 2 years, and then gradually fades through childhood [2]. Rarely, it may persist into adulthood [2].

References

1 Leung AK. Mongolian spots in Chinese children. *Int J Dermatol* 1988; **27**: 106–8.
2 Lee CS, Lim HW. Cutaneous diseases in Asians. *Dermatol Clin* 2003; **21**: 669–77.



Fig. 9.16 Facial Afro-Caribbean childhood eruption. (Courtesy of Professor H.C. Williams, Queen's Medical Centre, Nottingham, UK.)

Transient neonatal pustular melanosis (Chapter 17)

A transient eruption of sterile vesico-pustules is seen during the neonatal period in 4.4.% of black infants [1]. Individual pustules have a rim of surrounding erythema and, as the lesions progress, the pustules rupture to leave pigmented macules, which gradually fade over a few weeks. Pustules are sterile, but a skin smear shows a mixed inflammatory infiltrate with neutrophils. The most common sites are the face and shins [2]. It probably represents a variant of erythema toxicum neonatorum, but is associated with fewer eosinophils in lesions. No treatment is required as the condition resolves spontaneously, but it can persist for up to 3 months [2].

References

1 Ramamurthy RS, Reveri M, Esterley NB *et al*. Transient neonatal pustular melanosis. *J Pediatr* 1976; **88**: 831–5.
2 McLaurin CI. Pediatric dermatology in Black patients. *Dermatol Clin* 1988; **6**: 457–73.

Facial Afro-Caribbean childhood eruption (FACE)

First recognized by Marten in the early 1960s, the acronym FACE was coined two decades later [1,2]. Multiple, small, pale, flesh-coloured papules appear on the face of children, especially boys. The eruption tends to be concentrated centrally and is often most prominent periorally, but may extend onto the whole face (Fig. 9.16). The condition is pre-pubertal, with an onset around 8 years, and it tends to resolve spontaneously after 3–5 years. The histology is rather non-specific, but appears quite distinct from acne. Topical antibiotics are often given in response to demand for treatment, but have limited effect. The cause is unknown, but it is the authors' impression that the condition may be becoming less frequent.

References

1 Marten RH, Presbury DGC, Adamson JE *et al*. An unusual and acneiform facial eruption in the negro child. *Br J Dermatol* 1976; **91**: 435–8.
2 Williams HC, Ashworth J, Pembroke AC *et al*. FACE—facial Afro-Caribbean childhood eruption. *Clin Exper Dermatol* 1990; **15**: 163–6.

Sickle cell disease

This haemoglobinopathy is unique to those of African or Caribbean heritage, and the cutaneous complications, particularly ulceration [1], are therefore only seen in black patients. Sickle cell ulcers, secondary to cutaneous ischaemia compounded by trauma and secondary infection, are the most common complication, and are often seen in young patients, but rarely before the teenage years [1]. They are very painful and recalcitrant, and present a difficult therapeutic challenge. Hand–foot syndrome, in which painful, non-pitting acral oedema develops as a consequence of infarctions of the small bones of the hands and feet, may be the initial manifestation of the disease in children [2].

References

1 Serjeant GR, Serjeant BE, Mohan JS, Clare A. Leg ulceration in sickle cell disease: medieval medicine in a modern world. *Hematol Oncol Clin North Am* 2005; **19**: 943–56.
2 Rosner F. Hand–foot syndrome in sickle cell disease. *J Clin Oncol* 1998; **16**: 808–9.

Infections

Mould infections (Scytalidosis) (Chapter 36)

Cutaneous mould infections, for example with *Scytaldium* or *Hendersonula* spp., are endemic in parts of West Africa and the Caribbean. Such infections are being seen more commonly in temperate climates, but, apart from rare cases, only occur in immigrants born in the tropics [1]. A fine, white, powdery scale is seen on the palms and soles, most prominently within the skin creases [2]. Nail involvement is common, but the disease is resistant to most standard antifungal agents.

1 Lacroix C, Kac G, Dubertret L *et al*. Scytalidiosis in Paris, France. *J Am Acad Dermatol* 2003; **48**: 852–6.
2 Hay RJ, Moore MK. Clinical features of superficial fungal infections caused by *Hendersonula toruloidea* and *Scytalidium hyalinium*. *Br J Dermatol* 1984; **110**: 677–83.

HTLV-1 associated infective dermatitis

This variant of eczema is common in the Caribbean [1] as well as in South America [2]. It comprises recurrent infective eczema, especially in children and adolescents, which is usually infected/colonized with either *Staphylococcus* or *Streptococcus* species, as a manifestation of underlying infection with HTLV-1. Other sequelae of HTLV infection are likely [2].

References

1 LaGrenade L, Hanchard B, Fletcher V *et al*. Infective dermatitis of Jamaican children: a marker for HTLV-I infection. *Lancet* 1990; **336**: 1345–7.
2 Primo JR, Brites C, Oliveira M de F *et al*. Infective dermatitis and human T cell lymphotropic virus type 1-associated myelopathy/tropical spastic paraparesis in childhood and adolescence. *Clin Infect Dis* 2005; **41**: 535–41.

Miscellaneous

Ainhum

Ainhum describes the development of a fibrotic band around a digit, usually the fifth toe, which causes severe constriction and may progress to spontaneous amputation of the affected digit [1]. It is generally observed in the indigenous black population of

tropical countries. Trauma and infection related to walking barefoot are thought to stimulate the fibrotic reaction.

Dermatosis pustulosa cruris et atrophicans

A condition usually seen in African women, due to the occlusive effect of certain moisturizers, in which large superficial lakes of pus develop on a background of taut shiny skin, on the thighs and lower legs [2]. Lesions are always centred on a follicle, which can be seen as a dark spot within the lake of pus. Although relatively rare in the West [3], milder folliculitis as a pomade effect of excess emollient use is common, especially in adolescent girls. Short courses of antibiotics may be required, but the condition clears on stopping the causal emollient.

Adult T-cell leukaemia lymphoma (ATLL) (Chapter 57)

Cutaneous involvement, with small pale papules resembling sarcoid or large tumid nodules, may be the presenting sign in patients with ATLL [4].

Papuloerythroderma of Ofuji

An unusual eruption, of unknown aetiology, characterized by firm papules, which coalesce into erythroderma, with characteristic sparing of the folds of the body. First described in elderly Japanese men [5], it has now been reported in other races.

References

1 Browne S. Ainhum: a clinical and etiological study of 83 cases. *Ann Trop Med Parasitol* 1961; **55**: 314–20.

2 Harman RMM. Dermatitis cruris pustulosa et atrophicans: The Nigerian shin disease. *Br J Dermatol* 1968; **80**: 97–107.

3 Kpea NT, McDonald CJ. Cutaneous infections in Blacks. *Dermatol Clin* 1988; **6**: 475–88.

4 Yamaguchi T, Ohshima K, Karube K *et al*. Clinicopathological features of cutaneous lesions of adult T-cell leukaemia/lymphoma. *Br J Dermatol* 2005; **152**: 76–81.

5 Nazzari G, Croverto F, Nigro A. Papuloerythroderma (Ofuji): two additional cases and a review of the literature. *J Am Acad Dermatol* 1992; **26**: 499–501.

Diseases with varied racial prevalence

Dermatitis

Atopic dermatitis (Chapter 24)

Atopic dermatitis (eczema) is commoner in London-born black Caribbean children compared to their white counterparts [1]. Furthermore, black children with atopic dermatitis have a sixfold increased risk of having severe disease. It can be difficult to appreciate erythema in a dark skin (Fig. 9.17), so there may be failure to recognize the severity of the eczema [2].

Follicular accentuation is recognized to be more common in Afro-Caribbean dermatoses, and can occur as a finding in normal skin [3]. Follicular eczema is not uncommon in Afro-Caribbeans. It is managed in the usual way; however, it is the authors' observation that excessive use of greasy emollients in such cases can lead to an occlusive folliculitis.

Contact dermatitis (Chapters 25 and 26)

Several reports suggest that black skin may be more resistant to skin irritants than white skin. Tape stripping eradicates this difference, suggesting that this might be due in part to the qualities of the stratum corneum, which it is thought possesses an increased intercellular cohesiveness in black skin. Measurement of early inflammatory reactions to application of irritants, using confocal microscopy, showed that white subjects had more severe inflammatory reactions and also higher transepidermal water loss after application of 4% sodium lauryl sulphate than black skin, in contrast to the situation in non-irritated skin where black skins lose more water [4].



Fig. 9.17 Lichenified eczema.

Capsaicin dermatitis, caused by handling chilli peppers, is a particular problem in the Hispanic population because of their frequent use of this spice in cooking. Symptoms can be quite severe, with burning pain and erythema, requiring topical anaesthetics and topical corticosteroids for symptomatic relief [5].

Allergic contact dermatitis is generally thought to occur less frequently in the black population [6]. Fragrance sensitivity, in particular, is most prevalent in Caucasians [7]. The exception may be hair dye allergy [8], which appears more prevalent in black and Asian populations, probably reflecting increased usage. Cultural variations in exposure probably account for reported differences in prevalence of allergic contact dermatitis. There is some evidence that the incidence of contact dermatitis in Africans is increasing in relation to improved socio-economic conditions and urbanization [9]. Traditional pigments, for example bindi, applied for religious and social reasons, may produce an allergic contact dermatitis in Indian women [10].

Lichen simplex chronicus (Chapter 23)

Hyperpigmented lichen simplex is a common disorder in darkly pigmented skins. It can be associated with repetitive trauma of

any kind. Prayer nodules of the devoutly religious represent an example. Lichen simplex of the scrotum is especially common in African males [9].

References

1 Williams HC, Pembroke AC, Forsdyke H *et al*. London-born black Caribbean children are at increased risk of atopic dermatitis. *J Am Acad Dermatol* 1995; **32**: 212–17.
2 Ben-Gashir MA, Hay RJ. Reliance on erythema scores may mask severe atopic dermatitis in black children compared with their white counterparts. *Br J Dermatol* 2002; **147**: 920–5.
3 Brauner GJ. Cutaneous diseases in the black races. In: Demis DJ, Dobson RL, McGuire J, eds. *Dermatology.* Philadelphia: WB Saunders, 1975: 1704–33.
4 Hicks SP, Swindells KJ, Middelkamp-Hup MA *et al*. Confocal histopathology of irritant contact dermatitis *in vivo* and the impact of skin color (black vs white). *J Am Acad Dermatol* 2003; **48**: 727–34.
5 Halder RM, Nootheri PK. Ethnic skin disorders overview. *J Am Acad Dermatol* 2003; **48**: S143–8.
6 Anderson KE, Maibach HI. Black and white human skin differences. *J Am Acad Dermatol* 1979; **1**: 276–82.
7 Larsen W, Nakayama H, Lindberg M *et al*. Fragrance contact dermatitis: a worldwide muticentre investigation (Part 1). *Am J Contact Dermatitis* 1996; **7**: 77–83.
8 DeLeo VA, Taylor SC, Belsito DV *et al*. The effect of race and ethnicity on patch test results. *J Am Acad Dermatol* 2002; **46**: 107–12.
9 Yahya H. Change in pattern of skin disease in Kaduna, north-central Nigeria. *Int J Dermatol* 2007; **46**: 936–43.
10 Kumar AS, Pandhi RK, Bhutani LK. Bindi dermatoses. *Int J Dermatol* 1986; **25**: 434–5.

Other inflammatory dermatoses

Psoriasis (Chapter 20)

The prevalence of psoriasis is quoted as about 2% in Northern Europeans, but is much less frequent in the black population, probably reflecting genetic/HLA differences. It is more prevalent in East Africans [1] and rare in West Africans [2]. However, when psoriasis does occur in patients with pigmented skin, it is often extensive, quite resistant to therapy and therefore more likely to require systemic treatment.

References

1 Verhagen AR, Koten JW. Psoriasis in Kenya. *Arch Dermatol* 1967; **96**: 39–41.
2 Obasi OE. Psoriasis vulgaris in the Guinea Savannah region of Nigeria. *Int J Dermatol* 1986; **25**: 181–3.

Rosacea (Chapter 43)

Rosacea is rare in black individuals but may be under-reported [1], as the diagnosis may be masked by natural skin pigmentation [2]. However, steroid-induced acne and rosacea are frequent, due to the wide availability of unlicensed skin products containing potent steroids, which are often used as cosmetics [3].

References

1 Rosen T, Stone MS. Acne rosacea in blacks. *J Am Acad Dermatol* 1987; **17**: 70–3.
2 Browning DJ, Rosenwater G, Lugo M. Ocular rosacea in blacks. *Am J Ophthalmol* 1986; **101**: 441–4.
3 Mahé A, Ly F, Aymard G, Dangou JM. Skin diseases associated with cosmetic use of bleaching products in women from Dakar, Senegal. *Br J Dermatol* 2003; **14**: 493–500.

Morphoea and systemic sclerosis (Chapter 51)

Morphoea is less common in black than in white individuals [1]. Systemic sclerosis is also less prevalent in black patients [2] but when it does occur, inflammatory complications (e.g. pericarditis) are more frequent and occur earlier in the disease process [2]. In contrast, digital infarcts are less common in black patients [2]. Overall, the disease in black patients tends to be more aggressive, with a worse overall prognosis than in white patients [2].

References

1 White G. Common diseases in the darker skinned adult. In: Johnson B, Ronald M, White G, eds. *Ethnic Skin: Medical and Surgical*. St Louis: Mosby, 1998: 43–120.
2 Laing TJ, Gillespie BW, Toth MB *et al*. Racial differences in scleroderma among women in Michegan. *Arthritis Rheum* 1997; **40**: 734–42.

Sarcoidosis (Chapter 61)

This chronic, granulomatous disease occurs three to four times more commonly in the black population in the United States compared to the white population, with a prevalence reaching 64 per 100 000 [1]. The highest incidence of all is in black women in the fourth decade of life [1]. Although the disease may present in many ways, cutaneous involvement occurs in 25% [2]. Papular sarcoid is the most frequent form in blacks, but hypopigmented and annular forms are also often seen [2]. Although nasal involvement is common, the violaceous plaques of classical lupus pernio are rare in black individuals [2]. Instead, reddish brown translucent nodules around the nares are common. Erythema nodosum as a presenting feature of sarcoidosis is also less frequently seen in black patients [3].

References

1 English JC 3rd, Patel PJ, Greer KE. Sarcoidosis. *J Am Acad Dermatol* 2001; **44**: 725–6.
2 Minus HR, Grimes PE. Cutaneous manifestations of sarcoidosis in Blacks. *Cutis* 1983; **32**: 361–72.
3 Caruthers B, Day TB, Minus HR *et al*. Sarcoidosis: a comparison of cutaneous manifestations with chest radiographic changes. *J Natl Med Assoc* 1975; **67**: 364–7.

Pemphigus (Chapter 40)

Pemphigus vulgaris is more common in the Indian subcontinent than in the West [1] and tends to occur at a younger age [1]. In contrast, pemphigus foliaceus is rare in Asians [1,2], but is seen more commonly amongst black Africans [2]. An endemic form of pemphigus foliaceus, fogo selvagem, is seen in parts of Brazil [3]. Environmental factors are thought to precipitate disease in immunogenetically susceptible individuals [3].

References

1 Kanwar AJ, Ajith AC, Narang T. Pemphigus in North India. *J Cutan Med Surg* 2006; **10**: 21–5.
2 Aboobaker J, Morar N, Ramdial PK, Hammond MG. Pemphigus in South Africa. *Int J Dermatol* 2001; **40**: 115–9.
3 Friedman H, Campbell I, Rocha-Alvarez R *et al*. Endemic pemphigus foliaceus (fogo selvagem) in native Americans from Brazil. *J Am Acad Dermatol* 1995; **32**: 949–56.

Lupus erythematosus (Chapter 51)

Lupus erythematosus (LE) is increasingly being recognized as an autoimmune disorder whose incidence is closely associated with certain genetic markers. A study of African American families has



Fig. 9.18 Large spontaneous keloids in an African.

shown significant evidence of linkage at chromosomal location 11p13 [1].

Both depigmentation and hyperpigmentation are seen following lesions of discoid lupus erythematosus (DLE). It is the observation of the authors that depigmented scarring is more common in East Africa, whereas hyperpigmentation is more prominent following DLE in Afro-Caribbeans living in London.

Reference

1 Nath SK, Namjou B, Kilpatrick J *et al.* A candidate region on 11p13 for systemic lupus erythematosus: a linkage identified in African-American families. *J Investig Dermatol* Symp *Proc* 2004; **9**: 64–7.

Keratinization and fibrotic disorders

Keloid scarring (Chapter 14)

Keloid scarring represents a pathological response to cutaneous injury, and creates disfiguring results (Fig. 9.18). Medical literature suggests a greater frequency of keloid scar formation in Afro-Caribbean, Malaysian and Indian skin compared with Caucasians; however, many of these references are observational statements, published over 30 years ago, and address spontaneous keloids rather than post-procedural scars. The reported incidence ratios for Afro-Caribbeans : Caucasians have ranged from Brenizer's 2 : 1 [1] to Fox's 19 : 1 [2]. This literature has contributed to the practice of adopting a cautious approach to biopsying Afro-Caribbean skin, because of the perceived increased risk of keloid scar formation. Management continues to be challenging and a recent meta-analysis review demonstrates no statistically significant treatment option likely to guarantee a superior outcome [3].



Fig. 9.19 Prayer nodule.

Knuckle pads

These well circumscribed thickenings of the skin over the proximal interphalangeal joints, and occasionally the metacarpophalangeal joints, are much more frequently, but not exclusively, seen in black individuals. Most cases appear to be idiopathic [4], although there is often a familial basis. Some cases are associated with Dupuytren's contracture [1] and repeated trauma has been implicated in the aetiology [5,6].

Prayer nodules

Thickening of the skin with hyperpigmentation, or the formation of true callosities, may be seen in deeply religious individuals as a result of sustained and repetitive kneeling during prayer. Prayer nodules are most frequently seen in Moslem men [7], and may occur on the knees or forehead (Fig. 9.19), but have also been reported in devout Catholic women from central America [8], in whom they are confined to the knees because of the different posture adopted in prayer.

Acanthosis nigricans (Chapter 19)

Although this is a relatively common disorder across all races, it has been considered to be particularly prevalent in Asians. Some authors report a higher incidence in Afro-Caribbean youths, compared with their Caucasian counterparts. It is associated with insulin resistance [9].

References

1 Brenizer AG. Keloid formation in the negro. *Ann Surg* 1915; **61**: 83–7.
2 Fox H. Observations on skin diseases in the American Negro. *J Cutan Dis* 1908; **26**: 67–79.
3 Leventhal D, Furr M, Reiter D. Treatment of keloids and hypertrophic scars: a meta-analysis and review of the literature. *Arch Facial Plasc Surg* 2006; **8**: 362–8.
4 Mackey SL, Cobb MW. Knuckle pads. *Cutis* 1994; **54**: 159–60.
5 Peterson CM, Barnes CJ, Davis LS. Knuckle pads: does knuckle cracking play an aetiological role? *Pediatr Dermatol* 2000; **17**: 450–2.
6 Rushing ME, Sheehan DJ, Davis LS. Video game-induced knuckle pad. *Pediatr Dermatol* 2006; **23**: 455–7.
7 Kahana M, Cohen M, Ronne M *et al.* Prayer nodules in Moslem men. *Cutis* 1986; **38**: 281–2.
8 Sanchez MR. Cutaneous disease in Latinos. *Dermatol Clin* 2003; **21**: 689–97.

9 Arslanian SA. Metabolic differences between Caucasian and African-American children and the relationship to type 2 diabetes mellitus. *J Pediatr Endocrinol* 2002; **15** (Suppl. 1): 509–17.

Pigmentary disorders

Albinism (Chapter 58)

Oculocutaneous albinism is a worldwide hereditary disease. Although prevalence is globally reported to be 1:20 000 [1], data is emerging to suggest that it is more common in parts of Africa [2] with figures as high as 1/1000 in the Tonga tribe in Zimbabwe [3]. Not only is it more common but the adverse impacts on health can be devastating. These can be divided into actinic, ocular and social. Long hours of sunshine and the high intensity of ultraviolet radiation (UVR) in equatorial regions expose the albino person to large amounts of UVR, and actinic keratoses can develop in children as young as 8 years of age. People affected with albinism living in the tropics are sunburned most of the time and also suffer from actinic cheilitis, premature solar elastosis and numerous solar lentigines. In one survey of 164 albino patients in Tanzania, 19% of <21 year olds and 91% >21 year olds had solar keratoses, whereas 25% of 20 year olds and 34% of the over 30s were found to have overt skin cancers [4].

Ocular problems limit the educational opportunities for the albino child in the Third World. This, coupled with poor resources, lack of employment opportunities and social prejudice, result in severe economic hardship and social isolation for affected individuals. Although more than 50% of albino persons will have an affected relative, the majority of native Africans do not understand the inherited nature of the disease. The Albino Outreach programme in Moshi, Tanzania, attempts to address these issues through education and by providing practical help for sufferers [5].

The Hermansky–Pudlak syndrome, a triad of albinism, platelets lacking dense bodies and storage of ceroid-like material in tissues, occurs with a population frequency of approximately one in 2000 in north-western Puerto Rico [6].

References

1 Witkop CJ. Albinism. *Clin Dermatol* 1989; **7**: 80–91.
2 Hong ES, Zeeb H, Repacholi MH. Albinism in Africa as a public health issue. *BMC Public Health* 2006; **6**; 212.
3 Lund PM, Puri N, Durham-Pierre D *et al*. Oculocutaneous albinism in an isolated Tonga community in Zimbabwe. *J Med Gen* 1997; **34**: 733–5.
4 Lookingbill DP, Lookingbill GL, Leppard B. Actinic damage and skin cancer in albinos in northern Tanzania: findings in 164 patients enrolled in an outreach skin care program. *J Am Acad Dermatol* 1995; **32**: 653–8.
5 Simona B. Albinos in Black Africa: problems and solutions. *Int J Dermatol* 2004; **43**: 618–21.
6 Hermansky F, Pudlak P. Albinism associated with hemorrhagic diathesis and unusual pigmented reticular cells in the bone marrow: report of two cases with histochemical studies. *Blood* 1959; **14**: 162–9.

Progressive macular hypomelanosis (Chapter 58)

Synonyms
- Creole dyschromia
- Idiopathic macular hypomelanosis of the melanodermic halfcast of Guillet–Helenon

This disorder has been noted to be especially common in the Caribbean [1] but has also been found in Asians [2]. It presents with extensive round areas of macular hypopigmentation on the back, especially in young women; individual lesions may coalesce. One study suggests a role for *Propionibacterium acnes* [3], a theory supported by the observation that clearance is faster following antimicrobial regimens than with application of topical steroids [4]. It is mostly unresponsive to therapy, but tends to regress spontaneously over 3–4 years.

References

1 Guillet G, Helenon R, Gauthier Y *et al*. Progressive macular hypomelanosis of the trunk: primary acquired hypopigmentation. *J Cutan Pathol* 1988; **15**: 286–9.
2 Kumarasinghe SP, Tan SH, Thng S *et al*. Progressive macular hypomelanosis in Singapore: a clinico-pathological study. *Int J Dermatol* 2006; **45**: 737–42.
3 Westerhof W, Relyveld GN, Kingswijk MM *et al*. Propionibacterium acnes and the pathogenesis of progressive macular hypomelanosis. *Arch Dermatol* 2004; **140**: 210–4.
4 Relyveld GN, Kingswijk MM, Reitsma JB *et al*. Benzoyl peroxide/clindamycin/UVA is more effective than fluticasone/UVA in progressive macular hypomelanosis: a randomized study. *J Am Acad Dermatol* 2006; **55**: 836–43.

Melasma (Chapter 58)

There is an absence of detailed epidemiological data regarding the prevalence of melasma, but general observation suggests that the condition is more prevalent in Asian populations [1] and in those of Central and South American origin [2]. Indeed, the frequency of melasma in Thai women has been reported to be as high as 40% [1], and at least 50% of Mexican women are thought to develop melasma during pregnancy [2]. Estimates of the general prevalence in Hispanic populations range from 4.1 to 8.2% [2]. The distribution is usually centro-facial or malar [2], but in older patients it tends to be mandibular. Although there is a strong female preponderance, 10–20% of cases of melasma occur in men [1,2]. There is usually histological evidence of significant solar damage in affected individuals [3]. Treatment with combination topical regimes can be very effective, provided they are used in conjunction with rigorous sun protection [3].

Erythema dyschromicum perstans (ashy dermatosis) (Chapter 58)

Originally described in El Salvador, this acquired cutaneous disease is also well recognized in the Asian population. It is characterized by asymptomatic, irregularly shaped, macular areas of greyish pigmentation, particularly on the trunk. It is the distinctive colour [4] that gives rise to the term ashy dermatosis. However, it is true pigmentation and not just the ashy hue seen in black skin in winter, secondary to xerosis [5]. The cause is unknown, but there is strong genetic susceptibility and the condition is thought to have an immunological basis [6]. Recent studies in Mexican Mestizo Indians show that the disease is strongly associated with HLA-DR4 [5]. Reactions to chemical ingestion [2,7] and an association with intestinal parasites have also been postulated [2]. Some cases have been attributed to lichen planus, but there is no consensus view on whether lichen planus and ashy dermatosis represent a spectrum or are distinct. The borders of individual patches may be erythematous. Histologically, there is increased pigmentation of the basal layer of the epidermis, with a mild

perivascular lymphohistiocytic infiltrate and pigmentary incontinence in the papillary dermis. The differential diagnosis includes lichen planus pigmentosus, idiopathic macular hyperpigmentation, macular amyloidosis and fixed drug eruption, although in the latter the preceding inflammatory component is usually obvious and the subsequent post-inflammatory pigmentation much darker. The disease tends to be chronic, but may resolve over time. Improvement with clofazamine has been reported [8].

References

1 Sivayathorn A. Melasma in Orientals. *Clin Drug Invest* 1995; **10**: 34–63.
2 Sanchez MR. Cutaneous disease in Latinos. *Dermatol Clin* 2003; **21**: 689–97.
3 Kauh YC, Zachain TF. Melasma. *Adv Exp Med Biol* 1999; **455**: 491–9.
4 Fernandez-Flores A, Montero MG. Ashy dermatosis, or 'Tyndall-effect dermatosis'. *Dermatol Online J* 2006; **12**: 14.
5 Uhoda E, Piérard-Franchimont C, Petit L, Piérard G. Skin weathering and ashiness in black Africans. *Eur J Dermatol* 2003; **13**: 574–8.
6 Correa MC, Memije EV, Vargas-Alarcón G *et al*. HLA-DR association with the genetic susceptibility to develop ashy dermatosis in Mexican Mestizo patients. *J Am Acad Dermatol* 2007; **56**: 617–20.
7 Penagos H, Jimenez V, Fallas V *et al*. Chlorothalonil: a possible cause of erythema dyschronicum perstans (ashy dermatosis). *Contact Dermatitis* 1996; **35**: 214–8.
8 Barabda L, Torres-Alvarez B, Cortes-Franco R *et al*. Involvement of cell adhesion and activation molecules in the pathogenesis of erythema dyschronicum perstans (ashy dermatosis): the effect of clofazamine therapy. *Arch Dermatol* 1997; **133**: 325–9.

Primary cutaneous amyloidosis (Chapter 59)

Primary cutaneous amyloidosis is rare in Western populations, but has a high incidence in South-east Asia and some South American populations [1,2]. Two main forms, macular amyloidosis and lichen amyloidosis, are seen, but other rare variants exist [2]. Histologically, both of the main types appear similar; deposition of amyloid protein is seen in the papillary dermis, although meticulous sectioning and special stains may be required to confirm the diagnosis if the changes are subtle [2,3]. Clinically, macular amyloidosis is characterized by areas of rippled pigmentation, particularly on the upper back. In lichen amyloidosis, the pigmented lesions are smaller and more papular, and are localized on the shins and lower limb. There is no involvement of internal organs. Macular amyloidosis seems to be more prevalent in Indians [4], but is less common in Chinese individuals, in whom lichen amyloidosis predominates [2]. Macular amyloidosis is more common in females, and has an earlier onset in those with paler skin [3]. Both conditions tend to be pruritic and features of both types may co-exist [2]. Most cases of primary cutaneous amyloidosis are sporadic [2], but familial cases account for about 9% [4]. Friction, particularly from vigorous towelling, is thought to be contributory in some cases [5]. A rare form, ano-sacral cutaneous amyloidosis, has been reported in Oriental patients, particularly men; this may be difficult to distinguish clinically from lichen simplex [6], and indeed there may be an aetiological link, secondary to scratching [7].

References

1 Wong C. Cutaneous amyloidosis. *Int J Dermatol* 1987; **36**: 273–7.
2 Wang WJ, Chang YT, Huang CY, Lee DD. Clinical and histopathological characteristics of primary cutaneous amyloidosis in 794 Chinese patients. *Zhonghua Yi Xue Za Zhi* (Taipei) 2001; **64**: 101–7.
3 al-Ratrout JT, Satti MB. Primary localised cutaneous amyloidosis: a clinicopathological study from Saudi Arabia. *Int J Dermatol* 1997; **36**: 428–34.



Fig. 9.20 Naevus of Ota.

4 Eswaramoorthy V, Kaur I, Das A, Kumar B. Macular amyloidosis: aetiological factors. *J Dermatol* 1999; **26**: 305–10.
5 Mysore V, Bhushnurmath SR, Muirhead DE, Al-Suwaid AR. Frictional amyloidosis in Oman—a study of ten cases. *Indian J Dermatol Venereol Leprol* 2002; **68**: 28–32.
6 Wang W, Huang C, Chang Y *et al*. Ano-sacral cutaneous amyloidosis: a study of 10 Chinese cases. *Br J Dermatol* 2000; **143**: 1266–9.
7 Weyers W, Weyers I, Bonczkowitz M *et al*. Lichen amyloidosis: a consequence of scratching. *J Am Acad Dermatol* 1997; **37**: 923–8.

Naevus of Ota and naevus of Ito (Chapters 18 and 54)

Naevus of Ota is a form of dermal melanosis [1], producing macular pigmentation on the side of the cheek, adjacent to the eye and involving the sclera, within the distribution of the first two branches of the trigeminal nerve [2] (Fig. 9.20). It is most common in Oriental populations, but can occur in other races. It is five times more common in women than in men [1], and accounts for 0.8% of all dermatological consultations in Japan. Naevus of Ota is congenital in 50% of cases; the acquired form usually develops in the second decade [1]. Although usually unilateral, it is bilateral in 5%.

A similar pigmented naevus, naevus of Ito, occurs around the neck and shoulder region, within the distribution of the posterior supraclavicular and lateral brachial nerves. Histologically the two lesions are identical and may co-exist. Treatment with the Q-switched laser can be very effective [2].

Melanocytic naevi (Chapter 54)

Caucasians have more melanocytic naevi than other races. The number of naevi is inversely proportional to the degree of pigmentation of the skin, and increases with age [3]. The median number of melanocytic naevi in white children is 17 compared with 2.5 in those with skin type 5 and 6 [3]; for young adults, the median number of naevi rises to 61 and 16 respectively [3].

References

1 Chan HH, Kono T. Naevus of Ota: clinical aspects and management. *Skin Med* 2003; **2**: 89–96.
2 Wang HW, Liu YH, Zhang GK *et al*. Analysis of 602 Chinese cases of Naevus of Ota and the treatment results treated by Q-switched alexandrite laser. *Dermatol Surg* 2007; **33**: 455–60.

3 Rampen FH, de Wit PE. Racial differences in mole proneness. *Acta Derm Venereol* (*Stockh*) 1989; **69**: 234–6.

Infections

Cellulitis

In Africa, infections are much the commonest skin disease [1]. As populations urbanize or migrate to developing countries, patterns of skin disease begin to change and to mirror those of Western populations, with eczema and acne predominating and the frequency of cutaneous infections becoming lower [2]. Cellulitis, in particular, appears relatively less frequent in black adults [3], possibly due to immunity acquired in childhood.

Candida paronychia (Chapter 36)

Although this chronic fungal infection is well recognized in association with diabetes and occupations in which the hands are repeatedly immersed in water, it also appears to be more common in black individuals [4].

Viral warts (Chapter 33)

Far fewer black than white patients present to UK dermatology departments with viral warts (12% vs. 75% respectively) [4]. Other studies corroborate the relatively low incidence in black clinic attendees [5], but the true prevalence in the community is unknown. Whether this reflects socio-economic factors for attendance at hospital or a genuine difference in disease susceptibility is unclear.

Lyme disease (Chapter 38)

Reported incidence rates for Lyme disease in the Eastern United States are higher for white subjects than for African Americans [6]. However, black patients are more likely to present late, less likely to have erythema chronicum migrans, but more likely to have an associated arthritis [6].

References

1 Onayemi O, Isezuo SA, Njoku CH. Prevalence of different skin conditions in an out-patient setting in NW Nigeria. *Int J Dermatol* 2005; **44**: 7–11.
2 Nnoruka EN. Skin disease in SE Nigeria: a current perspective. *Int J Dermatol* 2005; **44**: 29–33.
3 Allen AM, Taplin D, Twigg L. Cutaneous streptococcal infections in Vietnam. *Arch Dermatol* 1971; **104**: 271–80.
4 Child FJ, Fuller LC, Higgins EM, du Vivier AWP. A study of the spectrum of skin disease occurring in a black population in SE London. *Br J Dermatol* 1999; **141**: 512–7.
5 Halder RM, Nootheri PK. Ethnic skin disorders overview. *J Am Acad Dermatol* 2003; **48**: S143–8.
6 Fix AD, Peña CA, Strickland GT. Racial differences in reported Lyme disease incidence. *Am J Epidemiol* 2000; **152**: 756–9.

Neoplasia

Skin cancer (Chapters 52 and 54)

Not surprisingly, both photoageing [1] in general, and UV-related skin cancer, are far more common in skin types 1–4, particularly those living in the Southern hemisphere [2], than in those with darker skin [3]. In particular, squamous cell carcinoma (SCC) is rare in skin types 5–6, although it can be seen as a complication of scars in discoid lupus erythematosus [4] and it presents a particular problem in patients with albinism living in the tropics. However, in contrast to white populations, there is no increase in the incidence of immunosuppression-related, non-melanoma skin cancer in non-white renal allograft recipients [5]. Additionally, there does not appear to be an increased risk of PUVA-associated SCC in black patients [6].

Basal cell carcinomas are generally less frequent in patients of skin type 4–6 than in fair skinned individuals, but when they do occur, they are more common in women, particularly those from the Orient and Asia, and are often the pigmented variant [7].

Bowen's disease is also relatively rare in non-Caucasians but, when it does occur, it tends to be pigmented, is often on non-sun-exposed skin and may be clinically atypical [3].

Melanoma is predominantly a disease of fair skin [8]. Non-white patients tend to present later, with more advanced tumours [9]. This discrepancy accounts for the poor outcomes reported in ethnic minorities. However, stage for stage, outcomes are similar for all racial groups [9].

References

1 Halder RM, Nootheri PK. Ethnic skin disorders overview. *J Am Acad Dermatol* 2003; **48**: S143–8.
2 Staples MP, Elwood M, Burton RC *et al*. Non-melanoma skin cancer in Australia: the 2002 national survey and trends since 1985. *Med J Aust* 2006; **184**: 6–10.
3 Halder RM, Bang KM. Skin cancer in African-Americans in the US. *Dermatol Clin* 1988; **6**: 397–407.
4 Mulwafu WK, Fagan JJ, Jessop S. Squamous cell carcinoma in black patients with discoid lupus erythematosis. *S Afr J Surg* 2006; **44**: 144–6.
5 Moosa MR, Gralla J. Skin cancer in renal allograft recipients—experience in different ethnic groups residing in the same geographical region. *Clin Transplant* 2005; **19**: 735–41.
6 Murase JE, Lee EE, Koo J. Effect of ethnicity on the risk of developing non-melanoma skin cancer following long-term PUVA therapy. *Int J Dermatol* 2005; **44**: 1016–21.
7 Kikuchi A, Shimizu H, Nishikawa T. Clinical histopathological characteristics of basal cell carcinoma in Japanese patients. *Arch Dermatol* 1996; **132**: 320–4.
8 Katsambas A, Nicolaidou E. Cutaneous malignant melanoma and sun exposure. Recent developments in epidemiology. *Arch Dermatol* 1996; **132**: 444–50.
9 Hemmings DE, Johnson DS, Tominaga GT, Wong JH. Cutaneous melanoma in a multiethnic population: is this a different disease? *Arch Surg* 2004; **139**: 972–3.

Kaposi's sarcoma (Chapter 56)

Kaposi's sarcoma (KS) is a tumour of uncertain aetiology but probable endothelial origin [1]. It can be classified into four distinct types depending on the population affected: classical in those of Ashkenazi Jewish or Mediterranean origin; endemic in Africans; epidemic in association with AIDS; and iatrogenic in those treated with immunosuppressive regimens. All types are more frequent in men and all have been shown to have an association with human herpes virus 8 [1,2].

The annual incidence of classical KS in Greece is 0.47/100 000 population [3]. Classic KS tends to affect the legs and run a chronic indolent course in the elderly. In contrast, endemic KS may affect children. African Bantu have the highest incidence of endemic KS [4]. Iron exposure from volcanic soils has been linked to the development of classical and endemic KS [1]. The disease tends to be more aggressive in African children with endemic KS and in

those with epidemic KS, in whom multiple lesions, internal organ involvement and secondary lymphoedema occur.

References

1 Szajerka T, Jabieki J. Kaposi's sarcoma revisited. *AIDS Rev* 2007; **9**: 230–6.
2 Smith KJ, Nelson A, Angritt P, Morz A. Skelton HG. Kaposi's sarcoma in women: A clinicopathologic study. *J Cutan Med Surg* 1999; **3**: 132–9.
3 Stratigos JD, Katoulis AC, Stavrianeas NG. An overview of classic Kaposi's sarcoma in Greece. *Adv Exper Med Biol* 1999; **455**: 503–6.
4 Wahman A, Melnick SL, Rhame FS, Potter JD. The epidemiology of classic, African, and immunosuppressed Kaposi's sarcoma. *Epidemiol Rev* 1991; **13**: 178–9.

Miscellaneous

Photodermatoses (Chapter 29)

Racial pigmentation has a photoprotective effect. However, even a pigmented skin may become sunburnt, although the erythema may be masked [1]. Conditions such as polymorphic light eruption and chronic actinic dermatitis occur in all races [2]. However, in black skin polymorphic light eruption may be atypical and pin-point in morphology [3].

One condition with a strong racial predilection is actinic prurigo, seen in Native Indian and Mestizo populations of Central and South America, particularly those who live at higher altitudes [4]. Intensely pruritic, polymorphic lesions, with papules, plaques and vesicles, appear on sun-exposed skin. Lesions become excoriated and may heal with scarring. Conjunctival and labial involvement is common [4]. Unexposed skin may be affected and symptoms tend to be chronic, and can persist through the winter months [4].

References

1 Willis I. Photosensitivity reactions in black skin. *Dermatol Clin* 1988; **6**: 369–75.
2 Kerr HA, Lim HW. Photodermatoses in African Americans: A retrospective analysis of 135 patients over a 7-year period. *J Am Acad Dermatol* 2007; **57**: 638–43.
3 Kontos AP, Cusack CA, Chaffins M, Lim HW. Polymorphous light eruption in African Americans: pinpoint papular variant. *Photodermatol Photoimmunol Photomed* 2002; **18**: 303–6.
4 Lane PR, Hogan DJ, Martel MJ *et al*. Actinic prurigo: clinical features and prognosis. *J Am Acad Dermatol* 1992; **26**: 683–92.

Vulvodynia (Chapter 71)

Vulval dysaesthesia appears to be a predominantly Caucasian disorder [1], although data from a wide ethnic mix is sparse and this finding may simply reflect cultural mores and ease of accessing health care.

Reference

1 Hengge UR, Runnebaum IB. Vulvodynia. *Hautarzt* 2005; **56**: 556–9.

Vascular naevi (Chapter 18)

All forms of vascular naevi, including naevus flammeus and port-wine stains, appear to be more common in Caucasoids than black Africans or other racial groups [1].

Reference

1 Osburn K, Schosser RH, Everett MA. Congenital pigmented and vascular lesions in newborn infants. *J Am Acad Dermatol* 1987; **16**: 788–92.

CHAPTER 10
Histopathology of the Skin: General Principles

E. Calonje
St. John's Institute of Dermatology, St Thomas' Hospital, London, UK

Biopsy of the skin, 10.1
Techniques of skin biopsy, 10.3
Information to be provided with the specimen, 10.4
Care of the specimen, 10.4
Laboratory methods, 10.6
Specimen preparation, 10.6
Routine tissue processing, 10.7
Routine staining techniques, including histochemistry, 10.8
Immunopathology, 10.11
Electron microscopy, 10.29
Viral diseases, 10.30
Immunogenotyping, 10.30
Artefacts, 10.30
The approach to microscopic examination of tissue sections, 10.31
Preparing for microscopy, 10.32
Microscopic interpretation, 10.32
How to produce a histopathology skin report, 10.36
Commonly used descriptive terms in dermatopathology, and their diagnostic significance, 10.36
Special problems that may be encountered in skin biopsies, 10.42

Introduction

As well as clinical examination, microscopic examination of skin tissue is probably the single most important diagnostic ancillary technique used by dermatologists in the management of patients with skin disorders. The correlation of clinical appearances with the dermatopathological findings is not only of direct benefit to individual patients, but has also led to the recognition of many new skin disorders and increased our understanding of the mechanisms of skin disease. The science and art of dermatopathology had its beginnings in early 19th-century Europe with the writings of pioneers such as Simon, von Baerensprung, Unna and Gans. It is interesting that these individuals were dermatologists, and this tradition of dermatologists writing about histopathological aspects of skin disease was carried on by researchers such as F. Pinkus, A. Civatte, J. Darier, H. Montgomery, H. Pinkus, W. Lever, and in the last half of the 20th century by R.K. Winkelmann, E. Wilson-Jones and A.B. Ackermann. During the last 20 years, the definition of numerous new disease entities and great advances in histopathological and related techniques have led to a wealth of publications on the histopathology of skin disease. Many major reference texts are now available [1–4].

Close cooperation between the clinician and the diagnostic dermatopathologist is not only desirable, but also essential. The spectrum of skin disease, including rare genetic disorders, infectious diseases, neoplasms and a wide range of inflammatory disorders, is huge, and although in many conditions the histological features are relatively distinctive of a particular skin disorder, in others the changes may be fairly non-specific. Only by close liaison between the disciplines of clinical dermatology and histopathology can the usefulness and limitations of skin biopsy examination be appreciated. The clinician who reviews the histology of his or her own biopsies appreciates the problems of interpretation of an inadequate biopsy, a biopsy from an inappropriate or unrepresentative lesion, and the effects of artefact caused by undue trauma at the time of biopsy. The pathologist in turn can learn, for instance, that epidermal spongiosis, exocytosis of lymphocytes and mild dermal inflammatory changes are the hallmark of a spongiotic process and that a wide variety of clinical entities may show a similar histological picture. Using the term 'chronic non-specific dermatitis' to denote this picture is unhelpful and misleading. What the pathologist should do is to closely correlate the clinical picture with the histological findings and try to reach a more specific diagnosis. Even if this is not possible, the clinical often finds it very useful if a number of differential diagnoses are ruled out.

Dermatopathology as a medical specialty is a rapidly expanding discipline, as witnessed by the plethora of recent publications, the development of many national societies for dermatopathology and the many international meetings currently taking place. In the UK for more than a decade, the Diploma in Dermatopathology of the Royal College of Pathologists has assessed proficiency in dermatopathology for both pathologists and dermatologists. In Europe, a similar exam has been set in recent years by the European Union of Medical Specialists/Sections of Dermatovenereology and of Pathology [5]. This initiative has been received enthusiastically by physicians in both specialties not only throughout Europe but also worldwide. The exam has been so successful that it now also takes place in Latin America under the auspices of the Ibero-Latin American Society of Dermatopathology.

Biopsy of the skin

A thorough understanding of both the indications for skin biopsy and the various biopsy techniques and their limitations is essential if the histopathologist is to provide the maximum useful

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

Table 10.1 Indications for skin biopsy.

Excision of epidermal or dermal neoplasm, whether benign or malignant. Clear margins are required in a malignant neoplasm.
An incisional biopsy (shave or punch biopsy) for confirmation of diagnosis of a lesion too big for removal, which will be treated by alternative methods, e.g. more complex surgery (Mohs), radiotherapy or cryotherapy. Most useful for basal cell carcinoma or *in situ* squamous cell carcinoma (Bowen's disease); avoid in melanocytic lesions, particularly lesions suspected of malignant melanoma.
An incisional biopsy of a hard-to-categorize skin eruption. Most will be inflammatory and a punch biopsy is often performed; sometimes cutaneous T-cell lymphoma is suspected and more than one biopsy may be necessary.
Fresh-tissue incisional skin biopsies for immunopathological study, especially immunofluorescence, in suspected autoimmune dermatoses, e.g. blistering disorders (perilesional skin) or lupus erythematosus (lesional skin).
Simultaneous processing of contiguous incisional biopsies for pathology and for culture of fresh, unfixed tissue when infection is suspected. The tissue can be cultured for various organisms including mycobacteria, deep fungi or examined for protozoa or filarial worms.

information from the study of biopsy sections [6–8]. In addition to light-microscopic examination of paraffin-embedded tissue, material obtained from skin biopsy may be used for a variety of investigative procedures. These include ultrastructural examination (only very seldom used nowadays), immunofluorescence studies, antigen mapping in congenital bullous disorders, immunohistochemistry, microbiological studies, tissue culture and molecular biological methods such as *in situ* hybridization (including FISH: fluorescent i*n situ* hybridization) and polymerase chain reaction, mainly for immunoglobulin and T-cell-receptor gene rearrangement studies. These various investigative techniques often require specific specimens and transport conditions. The individual undertaking skin biopsy should have a clear idea, before carrying out the procedure, of the studies that are to be performed on the specimen obtained. It should be borne in mind that division of the specimen into many small portions for various techniques such as culture, direct immunofluorescence studies and light microscopy may lead to specimens too small, too unrepresentative or too traumatized to provide useful results. It is often better to perform two biopsies or more to guarantee enough tissue to maximize the amount of information from the samples obtained.

Of the various indications for skin biopsy (Table 10.1), a diagnostic skin biopsy is frequently used to confirm a clinical diagnosis or to aid in the establishment of a diagnosis where a clinical diagnosis is not apparent. An excisional biopsy is the method of choice in treatment of skin lesions, particularly malignant neoplasms. It is less often used to remove lesions for cosmetic reasons.

The type of biopsy, the selection of the site to be biopsied and the type of lesion to be biopsied, where there is a widespread eruption, are of utmost importance. Ideally, the lesion biopsied should be an early and untreated lesion and representative of the skin disorder as a whole. Avoiding secondary changes is crucial to obtain adequate information. Excoriated lesions and areas where secondary changes may obscure the primary features should be avoided. If lesions are present at all stages of evolution, such as may be seen in pityriasis lichenoides, it may be appropriate to biopsy more than one lesion. Multiple biopsies are also often helpful in conditions such as early cutaneous T-cell lymphoma, where definite histopathological diagnosis is often difficult. Normal skin should be included with a diagnostic biopsy wherever possible, and the inclusion of perilesional skin is essential when submitting biopsies for direct immunofluorescence studies. In certain conditions, such as connective tissue naevi, the changes may be very subtle and comparison with normal neighbouring skin may be very helpful. When this is done the clinician should mark the area of normal skin with a stitch to facilitate comparison. It is equally important to ensure that the biopsy is deep enough. It is frustrating for the pathologist and clinician alike to receive a specimen with a request form suggesting a diagnosis of panniculitis where sections from the biopsy show only a portion of epidermis and superficial dermis. The general tendency in cases suspected of panniculitis is to perform a punch biopsy. However, not infrequently, the information obtained from this type of biopsy in the setting of panniculitis is minimal and, ideally, a large deep incisional biopsy should be performed to obtain maximum yield. If lesions are widespread and there is a choice of biopsy sites, it is sensible to avoid areas liable to heal badly, such as areas over bony prominences and the lower limbs, and to avoid cosmetically important areas. Secondary changes in some areas of the body, such as changes of venous stasis in biopsies from the lower legs of older people, may be confusing to the inexperienced diagnostic dermatopathologist, and such sites are also best avoided.

Prior to skin biopsy, written informed consent is normally obtained from the patient, and in all but the smallest biopsies, local anaesthetic—usually 1% or 2% lidocaine (lignocaine) with or without epinephrine (adrenaline)—is injected around the biopsy site. Superficial blebs resulting from injecting local anaesthetic into the skin itself should be avoided. Injection of too much local anaesthetic into one area of the skin can cause a prominent distortion artefact in sections that are prepared from biopsy tissue. The effect of epinephrine on dermal blood vessels and mast cells has probably been overemphasized in the past. However, when biopsying conditions such as urticaria pigmentosa, it may be prudent either to avoid the biopsy site itself and inject the anaesthetic in a circle around it or to use an anaesthetic not containing epinephrine. Epinephrine and other vasoconstrictors should not be used in biopsies taken from the fingers or toes, as occasional intense vasospasm can result in tissue necrosis. Recently, topical anaesthetic gels have been developed as an alternative to injections for removal of superficial skin lesions. These topical anaesthetics are particularly helpful with biopsies performed in children. The main topical anaesthetic used is a combination of lignocaine and prilocaine (EMLA). Although this topical preparation is extremely useful, it is important to know that it may cause secondary histological changes that may alter the interpretation of the biopsy. This is probably due to an irritant contact dermatitis and seems to be associated with the time of exposure to the medication and is more common in samples taken from patients with inflammatory dermatoses [9,10]. The histological changes consist of vacuolar change of keratinocytes in the upper layers of the epidermis and clefting at the dermoepidermal junction.

There are circumstances when skin biopsy is best avoided unless absolutely essential (Table 10.2).

Table 10.2 Relative contraindications to skin biopsy.

Infants	Although local anaesthetic creams/gels make this easier
Upper trunk	In order to avoid keloid formation
Lower legs in elderly patients	Poor healing may occur
Cardiac patients	Valvular disease means there is a potential risk of subacute bacterial endocarditis Aspirin/anticoagulants can produce extensive bleeding
Melanoma (incisional) biopsy	Primary excision is preferable to allow proper evaluation and an accurate diagnosis In large lesions on acral sites and face, incisional biopsies are sometimes performed to confirm the diagnosis and plan definitive treatment

Table 10.3 Skin biopsy techniques.

Excision	For removal of a single lesion; an elliptical or fusiform-shaped area of skin is removed
Incision biopsy ('wedge')	Similar to excision, but narrower; to include fat in suspected panniculitis; some normal perilesional skin is included for comparison
Punch biopsy (3–6 mm)	Useful if tissue available is limited, but accurate sampling is essential; a rapid procedure sometimes useful in children
Curettage	For hyperkeratotic lesions, e.g. seborrhoeic keratoses, viral warts, basal cell carcinomas; usually accompanied by cautery
Shave biopsy	For facial protuberant lesions, e.g. benign intradermal naevi
Snip	For skin tags; skin snips also for onchocerciasis

Techniques of skin biopsy (Table 10.3) [6–8]

Elliptical surgical biopsy [8]

This is one of the most commonly used diagnostic skin biopsy techniques. Equipment required includes scalpel, fine-toothed forceps, needle holder, scissors and eyeless needle with suture (Fig. 10.1). The use of a skin hook greatly facilitates manipulation of the biopsy specimen and avoids undue trauma. A reasonable size for an elliptical biopsy is about 5 mm, but smaller specimens may be adequate where indicated for cosmetic reasons. Small lesions may be totally excised, but a biopsy of a larger lesion should be at right angles through the margin to include adjacent normal skin. The long axis of the wound should, where possible, follow the natural crease lines of the skin. For suspicious melanocytic lesions, a simple excision with narrow margins is performed and this is followed by a wider excision on confirmation of the diagnosis. A full discussion of surgical techniques and suture materials is beyond the scope of this chapter, but there are several excellent reviews [7,8] and aspects of cosmetic dermatological surgery are discussed in Chapter 80.

Punch biopsy [11]

The biopsy punch is a metal cylinder of variable diameter with a sharp cutting edge at one end, usually attached to a plastic handle (Fig. 10.2). The punch is pushed into the skin with a downward twisting movement, and then removed. The tissue specimen is lifted and separated from the underlying tissue, and removed from the biopsy punch. The wound may be left to heal without suturing, the base of the wound being cauterized by electrocautery or some other haemostatic agent. Many operators, however, prefer to insert one or two sutures to secure haemostasis.

Punch biopsies are convenient and quick to use, but it is preferable to use at least a 3-mm punch to obtain a satisfactory specimen. Biopsy punches blunt easily, and therefore disposable punches are recommended. Another problem with small punch biopsies is that the specimen is often difficult to orientate, and most pathologists greatly prefer elliptical excision biopsies for diagnostic interpretation. In general, a punch biopsy should not be used for the diagnosis of cutaneous tumours, and this is particularly true for



Fig. 10.1 Instruments for skin biopsy, including scalpel, scissors, needle holder and skin hooks.

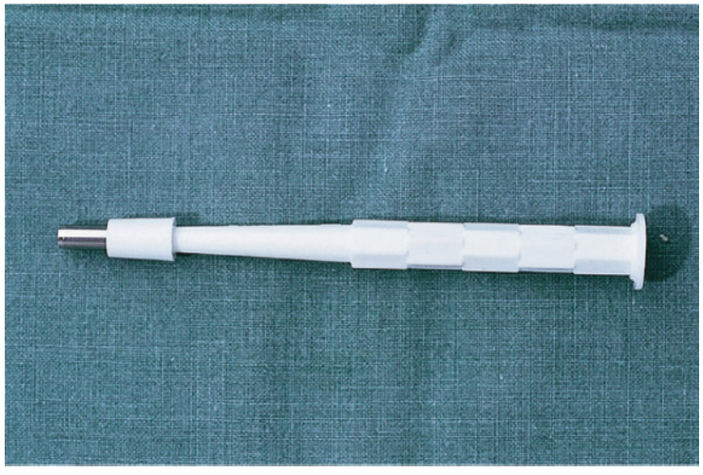


Fig. 10.2 Disposable punch for cutaneous biopsy.

melanocytic lesions. Nevertheless, punch biopsies do have a place in busy outpatient departments and office practices, particularly for diagnosis and management of small cutaneous lesions.

Curettage [12,13]

The technique of curettage with a sharp-edged Volkmann's spoon or disposable curette followed by cautery is often used for the treatment of small benign and malignant skin lesions, such as viral warts, solar and seborrhoeic keratoses, and basal cell carcinomas. The resulting specimen is often badly fragmented, and it is often impossible to comment on adequacy of removal. A combination of curettage and shave excision has been proposed to overcome this problem. Curettage alone is more useful as a therapeutic procedure than as a technique for providing ideal specimens for histopathological diagnosis. It must be emphasized that all specimens should be submitted for histopathological examination. Haemostasis may be achieved by electrocautery, alginate dressings or using aluminium chloride hexahydrate solution on a cotton bud rolled over the wound. It is important to mention a further haemostatic agent, Monsel's solution (ferric subsulphate) that is no longer widely used but may cause problems in the histological interpretation of re-excision specimens. The pigment coats the collagen bundles and induces a histiocytic reaction with numerous siderophages [14]. This may make the interpretation of biopsies very difficult, particularly in the setting of melanocytic lesions.

Shave biopsy

Certain superficial, benign papular or nodular lesions may be treated by shaving off the lesion flush with the surface of the surrounding skin. Many sorts of superficial skin lesion may be treated in this way, in particular melanocytic naevi. Although often a useful cosmetic result may be obtained, this technique has several drawbacks. The whole lesion is rarely removed, and recurrence of the lesion is sometimes a problem. In the case of melanocytic naevi, it is known that lesions that recur following partial excision may often demonstrate atypical histopathological features, sometimes leading to an erroneous diagnosis of a malignant lesion [15]. As with the techniques of curettage and punch biopsy, the wounds resulting from the procedure of shave biopsy normally require some form of cauterization or use of aluminium chloride hexahydrate to achieve haemostasis.

Other biopsy techniques

Various other ways of obtaining portions of skin tissue for diagnostic purposes have been described, including needle biopsy, similar to that used for tissue diagnosis of liver disease and lymph-node pathology (see section on cytodiagnosis). The results from such a technique are generally unsatisfactory for skin lesions, and in no way compare with those achieved using more conventional surgical procedures. Techniques for slit-skin smears for leprosy and skin snips for oncho-cerchiasis are discussed in Chapters 32 and 37, respectively.

Information to be provided with the specimen

For the clinician to obtain the optimum help from the pathologist, it is essential that full clinical details be provided. A fully completed histopathology request form should include the following details for each specimen. The patient should be identified by name, sex, age and usually a hospital reference number, or some other identification record number. It is useful to know the patient's racial group, as prominent epidermal basal layer melanin pigmentation may be pathological in some situations, and represents normal skin for other individuals. A brief clinical history of the duration of the skin condition should be provided, together with details of any treatment including topical and systemic therapy. The site of each biopsy taken should be clearly identified on the request form, and accompanied by specimens in separate, individually labelled containers. Unfortunately, it is not uncommon to receive several biopsies from what are thought to be trivial lesions from the same patient in one container. Sometimes it turns out that one of these lesions is histologically malignant and the others are benign, and in these circumstances it may be impossible to determine the site of the malignant tumour.

Details of previous biopsies, and where possible the histopathology report reference numbers, should always be included on a request form, and finally a suggested clinical diagnosis or list of differential diagnoses is helpful. Where possible, abbreviations should be avoided. It may be that many pathologists will recognize the letters PLC as standing for pityriasis lichenoides chronica, but perhaps there would be fewer who would immediately recognize the letters TMEP as representing a form of urticaria pigmentosa.

Finally, but most importantly, the dermatologist or surgeon sending the biopsy material to the pathologist should give some clear indication on the request form from whom the biopsy is being sent, or to whom the report should be forwarded. If some of the simple advice above were more often heeded by clinicians performing biopsies, it would make the life of a dermatopathologist very much easier.

Care of the specimen

Care is required throughout the biopsy procedure, to avoid trauma to the specimen with forceps or any of the other instruments used during biopsy. The use of skin hooks in manipulating the specimen during biopsy is helpful in this respect [16] and, in order to avoid trauma artefact, division of small specimens into multiple smaller portions of tissue for different diagnostic purposes should be avoided. If a specimen is needed for four separate studies—such as paraffin embedding, direct immunofluorescence studies, electron microscopy and microbiological culture—it is often better to take two separate specimens and divide each of these into two portions than to attempt to divide one specimen into quarters. Biopsies taken for ultrastructural studies should be small (of the order of 1–2-mm cubes) to allow for adequate fixation. Once the biopsy specimen has been taken, it should be placed epidermal side uppermost on a small portion of filter paper, to prevent curling, and transferred promptly to the appropriate transport medium.

For routine diagnostic microscopy of paraffin-embedded material, 10% neutral buffered formalin is still the most widely used fixative and is satisfactory for most purposes [17]. Many other fixatives [17] and transport media such as Michel's [18] (Table 10.4) are available, and these are indicated for either the

study of specific diseases or tissue components, or for the application of specific diagnostic techniques such as immunofluorescence [19]. The use of Michel's medium allows the preservation of antigens for immunofluorescence studies for up to 6 months [20]. By using Michel's medium, specimens may be sent safely without the need for immediate freezing. This medium is also useful for fixation of samples used in immunoelectron microscopy studies [21] and also seems to preserve the antigens relevant for investigation of genetic blistering skin diseases [22]. The specimen has to be washed thoroughly on receipt before freezing it to avoid artefacts. Sodium chloride 0.9% has been proposed as an alternative transport medium to Michel's medium [23]. However, preservation of antigens only lasts for 24 hours and frequent artefacts, including hydropic degeneration of keratinocytes and splitting of the dermoepidermal junction, are seen. Furthermore, this method is not suitable for samples obtained for immunoelectron microscopy or antigen mapping. Table 10.5 gives some details of the more important fixatives and transport media.

Table 10.4 Michel's transport medium for fresh cutaneous tissue.

Ammonium sulphate	55 g in 100 mL buffer
Buffer	1 mol/L potassium citrate (pH 7), 2.5 mL 0.1 mol/L magnesium sulphate, 5 mL 0.1 mol/L ethyl maleimide, 5 mL Distilled water, 87.5 mL Mix 1 : 2 with 1 mol/L potassium hydroxide to pH 7.0

References

1 McKee PH, Calonje E, Granter SR. *Pathology of the Skin with Clinical Correlations*, 3rd edn. Edinburgh: Elsevier Mosby, 2005.
2 Weedon D. *Skin Pathology*, 2nd edn. Edinburgh: Churchill Livingstone, 2002.
3 Ackerman AB, Boer A, Bennin B, Gottlieb GG. *Histologic Diagnosis of Inflammatory Skin Diseases*, 3rd edn. New York: Ardor Scribendi, 2004.
4 Elder D, Elenitsas R, Bernett LJ Jr, Murphy GF, eds. *Lever's Histopathology of the Skin*, 9th edn. Philadelphia: Lippincott, 2005.
5 Kerl H, Cerroni L, Burg G, *et al*. International Board Certification in Dermatopathology: a worldwide effort to raise standards in dermatopathology. *J Cutan Pathol* 2006; **33**: 156–9.
6 Lawrence C. *An Introduction to Dermatological Surgery*, 2nd edn. Edinburgh: Churchill Livingstone, 2002.
7 An KP, Ratner D. Surgical management of cutaneous malignancies. *Clin Dermatol* 2001; **19**: 305–20.
8 Edlich RF, Becker DG, Long WB *et al*. Excisional biopsy of skin tumors. *J Long Term Eff Med Implants* 2004; **14**: 201–14.
9 Cazes A, Prost Squarcioni C, Bodemer C *et al*. Histopathologic cutaneous modifications after the use of EMLA cream, a diagnostic pitfall: review of 13 cases. *Arch Dermatol* 2007; **143**: 1074–6.
10 Hoss DM, Gross EG, Grant-Kels JM. Histopathology of an adverse reaction to a eutectic mixture of the local anesthetic lidocaine and prilocaine. *J Cutan Pathol* 1999; **26**: 100–4.
11 Zuber TJ. Punch biopsy of the skin. *Am Fam Physician* 2002; **65**: 1155–8, 1161–2, 1164.
12 Sheridan AT, Dawber RP. Curettage, electrosurgery and skin cancer. *Australas J Dermatol* 2000; **41**: 19–30.
13 Goldman G. The current status of curettage and electrodesiccation. *Dermatol Clin* 2002; **20**: 569–78.
14 Kuwahara RT, Craig SR, Amonette R. More on Monsel's solution. *Dermatol Surg* 2000; **26**: 979–80.
15 Park HK, Leonard DD, Arrington JH *et al*. Recurrent melanocytic nevi: clinical and histologic review of 175 cases. *J Am Acad Dermatol* 1987; **17**: 285–92.
16 Popkin GL, Gibbs RC. Surgical gems: another look at the skin hook. *J Dermatol Surg Oncol* 1978; **4**: 366–8.
17 Bancroft JD, Gamble M, eds. *Theory and Practice of Histological Techniques*, 5th edn. Edinburgh: Churchill Livingstone, 2001.

Table 10.5 Fixatives and transport media for skin biopsy specimens. (Details of most methods are given in Bancroft and Gamble [17].)

Investigative technique	Fixative/transport medium	Comments
Most routine diagnostic studies on paraffin-processed material	10% neutral buffered formalin solution (pH 7) 10% aqueous formalin (unbuffered)	Most useful fixative for general use H&E staining generally better than with buffered preparation Formalin pigment a nuisance
	Carnoy's solution (pH 2.8)	Good preservation of nuclear chromatin Haemolyses red blood cells; use small specimens
Where rapid fixation required	Place specimen in the oven in alcohol	Microwave fixation
When good preservation of mucopolysaccharides is required	Formal saline solution (pH 3.8)	Nuclei badly distorted Not satisfactory for routine purposes
Demonstration of leprosy bacilli	FMA fixative or Zenker's fluid	Good results for acid-fast bacilli with Wade–Fite stain Mercury deposits must be removed
Transmission electron microscopy and some electron immunocytochemistry	Karnofsky's solution or 2.5% buffered glutaraldehyde solution Post fixation with osmium tetroxide	Small specimens required, normally no more than 1-mm cube
Immunofluorescence and immunoenzyme techniques	Various; periodate lysine paraformaldehyde fixation and cold processing useful for some endothelial cell markers	Various fixatives suitable depending on technique and antigen/substance to be identified Frozen tissue may be required
Transport of specimens for immunofluorescence studies	Michel's medium	Specimen must be thoroughly washed in phosphate-buffered saline before immersion in Michel's medium
Microbiological studies, studies on fat tissue and some immunohistological investigations	Fresh or frozen tissue	Specimens for microbiological examination should be placed in sterile containers and transported to the laboratory as soon as possible

18 Michel B, Milner Y, David K. Preservation of tissue fixed immunoglobulins in skin biopsies of patients with lupus erythematosus and bullous diseases: preliminary report. *J Invest Dermatol* 1973; **59**: 449–52.
19 Skeete MVH, Black MM. Evaluation of special liquid fixative for direct immunofluorescence. *Clin Exp Dermatol* 1977; **2**: 49–56.
20 Vaughan Jones SA, Salas J, McGrath JA *et al*. A retrospective analysis of tissue-fixed immunoreactants from skin biopsies maintained in Michel's medium. *Dermatology* 1994; **189** (Suppl. 1): 131–2.
21 Vaughan Jones SA, Palmer I *et al*. The use of Michel's transport medium for immunofluorescence and immunoelectron microscopy in autoimmune bullous diseases. *J Cutan Pathol* 1995; **22**: 365–70.
22 Woollons A, Holmes GJ, Gratian MJ *et al*. Michel's medium: a potential alternative to cryoprotection for tissue transport in the investigation of genetic skin diseases. *Clin Exp Dermatol* 1999; **24**: 487–9.
23 Vodegel RM, de Jong MC, Meijer HJ *et al*. Enhanced diagnostic immunofluorescence using biopsies transported in saline. *BMC Dermatol* 2004; **4**: 10.

Laboratory methods

Specimen preparation

Frozen sections are not used routinely in dermatopathology, except for Mohs micrographic surgery (described in Chapter 77) and immunofluorescence. Most antibodies used in diagnostic dermatopathology work adequately in samples fixed in formalin, and except in the context of research, frozen sections are therefore not used on a regular basis for immunohistochemical studies. Frozen sections are used for the diagnosis of autoimmune blistering disorders and also for the diagnosis of blistering genetic skin diseases (antigen mapping, see Chapter 39). Although it has been advocated that autoimmune blistering disorders may be diagnosed with immunohistochemistry performed on samples fixed in formalin, the results are often of inferior quality and interpretation is difficult, leading to false-negative and false-positive results. This method is therefore not recommended.

Careful identification and preparation of tissue specimens prior to processing is most important. The first requirement is that the biopsy specimen be placed immediately into a fixative solution. Various routine fixatives are employed; most contain 10% formalin. Because a stock solution of formalin consists of 40% formaldehyde, 10% formalin is really 4% formaldehyde. A minimum of 12 h fixation is recommended for most specimens, but small specimens may only need 6 h, and larger specimens a longer period of fixation, to produce optimal results. After fixation, the biopsy tissue is removed from its container, double-checking that the specimen corresponds with details given on the request form, and the pathologist produces a macroscopic description together with details of 'the cut up'.

Special care should be taken where multiple fragments of tissue are present, for example, in specimens obtained by curettage. It may be necessary to pass the contents of the biopsy container through a filter paper to ensure that all relevant portions of tissue are processed and examined. After orientating the specimen, a description should be made of the size and shape of the specimen, and a note made of whether subcutaneous or other tissue is included. A careful description of surface changes is then made, with particular reference to changes of colour and surface texture, such as erosion or ulceration. Any obvious clinical lesion present on the gross specimen should be described. In some surgical specimens, an identification label, such as a skin suture, is left in place in the biopsy specimen by the surgeon, to enable precise orientation of the specimen. This is particularly important when dealing with neoplastic lesions, where clearance of tumour in the margins of the biopsy specimen needs to be assessed.

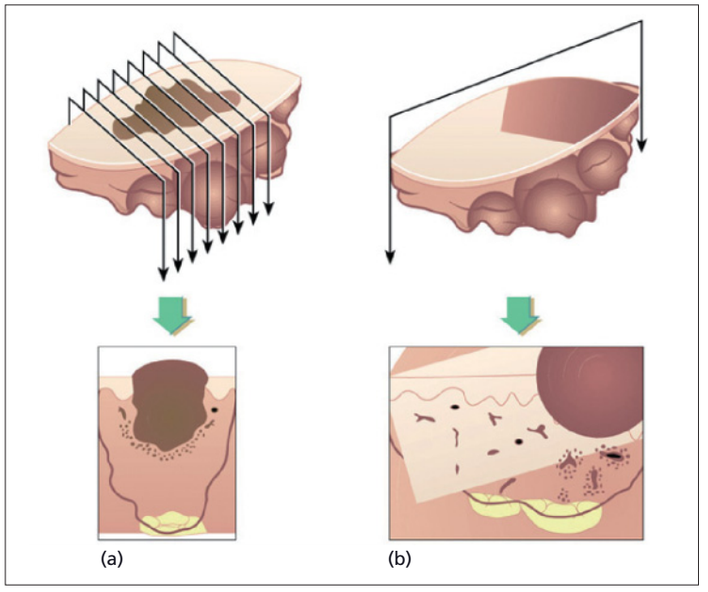
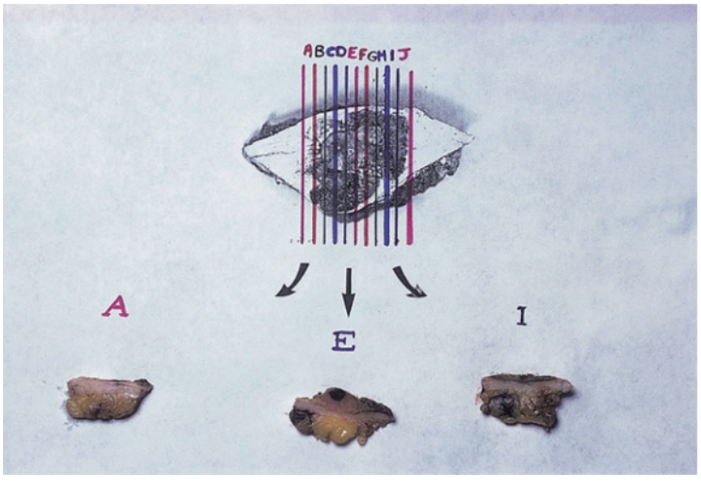


Fig. 10.3 Blocking of elliptical skin biopsy specimens. (a) Neoplastic lesions. Multiple transverse blocks through the whole lesion allow for histopathological examination of the tumour at all levels, and assessment of the narrowest excision margins. (b) Incisional biopsy of inflammatory lesion. Longitudinal blocking is recommended. This allows optimal visualization of the affected and adjacent normal skin.

Prior to sectioning of a gross specimen, especially excised tumours, it is good practice to paint the margins of the biopsy specimen with coloured dyes that are resistant to tissue processing. Various commercial preparations are available, and one or several colours may be used. If the dye is visible on the final tissue section examined by the pathologist, this implies that no tissue has been lost in processing, and that the edge of the section corresponds to the genuine margin of the biopsy. After painting of the biopsy margins, the gross specimen is then sectioned prior to the preparation of histological blocks. There are various techniques for cutting up a standard elliptical skin biopsy. The ideal method depends to some extent on the nature of the suspected diagnosis. A specimen from an excision biopsy of a benign or malignant skin tumour is better handled by taking transverse blocks through the specimen, so that the narrowest excision margins may be examined. For malignant lesions, particularly for suspected malignant melanoma, ideally transverse blocks should be taken at 2-mm intervals throughout the whole length of the lesion (Fig. 10.3a) [1]. An elliptical biopsy, taken, for instance, from the margin of a patch of an inflammatory dermatosis, is best sectioned longitudinally, so that both normal and abnormal skin can be visualized (Fig. 10.3b). With larger specimens, examination of a selection of transverse blocks made from various portions of the tumour may be adequate for diagnostic purposes. Any biopsy tissue not processed should be labelled, and returned to the fixative in the container and stored. Laboratories have different



(a)



(b)

Fig. 10.4 Photocopy procedure for recording the preparation of blocks. (a) The appearance of a macroscopic specimen of malignant melanoma. (b) Transverse blocks are taken from the specimen, and their exact position is recorded on a photocopy made from the surface of the gross specimen.

policies regarding the retention of fixed tissue specimens. Ideally, all specimens should be retained, but limitations of space often mean that most routine specimens can be discarded after a period of a few weeks after the histopathological report has been approved and signed.

In addition to a written description of the gross specimen, and how it has been prepared for blocking, a rough diagram of the specimen is very useful, particularly with larger specimens. This enables clear identification of the portion of the specimen from which various blocks have been taken. An alternative approach for larger specimens, especially when dealing with neoplastic lesions, is either to photograph the specimen or to wrap the specimen in clear cling-wrap film and take a photocopy of the surface. This produces an image the same size as the gross specimen, and details of the blocks taken can be recorded directly on the photocopy image (Fig. 10.4).

Very small specimens may be blocked in their entirety after trimming. Other blocking techniques may be used for specific purposes. An example is the blocking of transverse sections of cylindrical punch biopsies (at least 4 mm in diameter) of scalp disorders [2–5]. This technique is particularly useful in the assessment of various forms of inflammatory alopecia, and facilitates the quantitative morphometric analysis of pilosebaceous follicles and the hair itself. The technique also provides a useful method of studying the morphological details of the normal transverse anatomy of follicular structure, including the various phases of the normal hair cycle. Ideally, when investigating a condition presenting with alopecia, two biopsies should be provided: one for vertical sectioning and one for horizontal sectioning. It has been shown that the interpretation of both horizontal and vertical sections in scalp biopsies is better than each method on its own to obtain a high diagnostic yield [4]. If immunofluorescence studies are required, the specimen for vertical sectioning can be divided into two portions.

Routine tissue processing

Although the skin biopsy specimen may be examined with various techniques, at least a portion of most skin biopsies is routinely processed for light microscopic evaluation of sections from paraffin-embedded tissue. In most modern histopathology departments, the tissue processing is carried out by the use of automated machines. Although it is maintained that superior results may be possible by manual means, this often involves the changing of processing fluids at inconvenient times, and is a time-consuming and labour-intensive procedure. Two main types of automated tissue-processing machine are in use: the traditional carousel type and the enclosed pumped fluid type. Both types of machine have the facility for multiple separate stages in processing. Whether tissue processing is carried out by machine or by hand, after completion of fixation the same basic steps of dehydration, clearing and embedding are involved. The process of dehydration removes aqueous fixative and any tissue water. Clearing refers to the use of a substance such as xylene, which is totally miscible with both the dehydrating agent that precedes it, and the embedding agent that follows it.

For embedding, paraffin wax at 56°C remains by far the most popular material; it is cheap, large numbers of tissue blocks may be processed in comparatively short times, and later sectioning and staining are straightforward. The use of vacuum impregnation in modern and automated tissue-processing machines considerably reduces the overall processing time. At the end of the embedding procedure, paraffin blocks are cut and stained and are then ready for microscopic examination. The dermatopathologist should be aware of relatively common potential artefacts that can cause confusion and misinterpretation (Table 10.6) [6]. When urgent preparation of tissue specimens is required, various processing steps can be shortened. The use of very thin portions of tissue, increasing the temperature of the fixative, microwave-fixation techniques [7,8] and shortening the time used for clearing, can all facilitate rapid processing. Alternatively, cryostat sections can be examined.

Table 10.6 Potential dermatopathological artefacts.

Poor orientation: cross-sectioning making it difficult to evaluate the epidermis and dermis
Sometimes this results in complete loss of the epidermis
Formaldehyde fixation: vacuolation of epidermis
Fixation in non-buffered formaldehyde: pigment deposition
Freezing artefact: prominent intracytoplasmic vacuoles in keratinocytes
Scratch marks across tissue due to nick in microtome knife
Tissue carry-over from microtome knife
Foreign bodies, e.g. formaldehyde pigments, suture, *Alternaria*, spores, starch
Polarization of cell nuclear material by electric current in curetted specimens
Clumped mitoses in podophyllin-treated warts
Pyknotic prickle cells from methotrexate- or hydroxyurea-treated patients

Table 10.7 Some tinctorial stains used in dermatology.

Special stains	Tissue constituent	Appearance
Periodic acid–Schiff (PAS)	Glycogen	Magenta red (diastase sensitive)
	Mucopolysaccharides	Red (fungal wall red)
Van Gieson	Collagen	Red
	Muscle, nerve	Yellow
Congo red	Amyloid	Red with green birefringence
Acid orcein–Giemsa	Elastic fibre	Dark brown
	Collagen	Pink
	Melanin	Black
	Haemosiderin	Green/yellow
	Amyloid	Light blue
	Mast cell granules	Purple
Masson's trichrome	Collagen	Green
	Muscle + fibrin	Red
Aldehyde fuchsin	Elastic fibre	Purple
Gomori's	Reticulin	Black
Alcian blue (pH 4.5, 0.5)	Acid mucopolysaccharides	Blue
Toluidine blue	Acid mucopolysaccharides	Metachromatic purple including mast cells
Perls' Prussian blue	Iron (haemosiderin)	Blue
Masson's Fontana	Melanin	Black
Von Kossa	Calcium salts	Brown/black
Grocott's	Fungus wall	Black
Methenamine silver	Bacteria	
	Gram+	Blue/violet
	Gram–	Red/pink
Ziehl–Neelsen/Wade–Fite	Acid-fast bacilli	Red

Routine staining techniques, including histochemistry (Table 10.7)

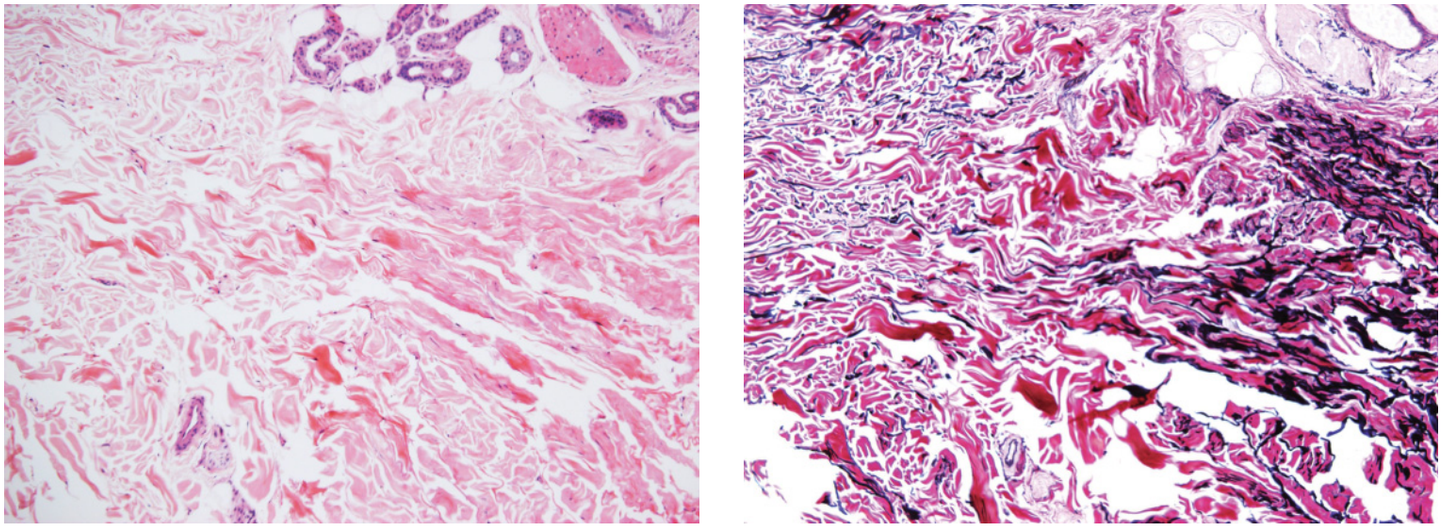
By far the most widely used stain for section from skin biopsies used in histopathology laboratories is haematoxylin and eosin (H&E). This staining technique gives good definition of many cellular and tissue structures in the skin, and is sufficient for the diagnosis of most skin diseases. This stain, however, does not clearly demonstrate certain tissue components, such as elastic fibres (Fig. 10.5a & b), and does not allow differentiation between melanin, haemosiderin and other skin pigments. Special stains are required for these purposes, and also for confirming the nature of abnormal dermal deposits, such as calcium, mucin and amyloid. Another important indication for special staining techniques is the demonstration of microorganisms. Full details of the techniques and applications of special stains used in diagnostic dermatopathology are given in standard reference texts [9–11]. Examples of commonly used staining techniques that are useful in the diagnosis of specific conditions are given below.

The periodic acid–Schiff (PAS) stain demonstrates the presence of carbohydrates, particularly some polysaccharides such as glycogen, and mucoproteins containing neutral mucopolysaccharides. These substances are stained reddish purple by the PAS reaction. Because the cell walls of fungi and yeasts contain neutral polysaccharides, they also stain positively with the PAS reaction (Fig. 10.6). This is a cheap and reliable diagnostic method and it has been advocated that a PAS stain should be routinely used in all biopsies of inflammatory dermatoses [12]. The reasoning for this proposal is based on the fact that the clinical and histological appearances of tinea may be fairly non-specific. The technique is also useful in demonstrating blood-vessel walls, basement membrane (Fig. 10.7), fibrin deposition and the presence of glycogen deposits, for instance in certain sweat gland tumours, such as clear cell hidradenoma, trichilemmoma and some epithelial lesions of uncertain histogenesis, such as the clear cell acanthoma of Degos. The identification of glycogen can be further confirmed by removal by enzyme digestion with diastase in 1% aqueous solution at 37°C for 30 min. Positive staining after the use of diastase indicates the presence of neutral mucopolysaccharides.

The Alcian blue reaction produces a blue coloration in the presence of acid mucopolysaccharides. In addition to demonstrating the presence of mucin in cutaneous mucinoses, the technique is also of value in some cases of extramammary Paget's disease, and occasionally in the demonstration of goblet cells in metastatic carcinoma of the gut. There are small amounts of acid mucopolysaccharide present in the ground substance of normal dermis, and the Alcian blue reaction is very pH-dependent. Care should therefore be exercised in the interpretation of a positive result.

Acid orcein and Giemsa stain was popularized by Pinkus and Mehregan, who recommend its use as a second routine stain [13]. It is a valuable technique which demonstrates, in addition to structures normally visible with H&E stain, the presence of mast cells, eosinophils, metachromatic substances and elastic fibres. The routine use of the orcein–Giemsa stain often avoids recutting of blocks for other special stains. Orcein itself is a constituent in other staining methods, particularly those used to demonstrate elastic fibres.

Special staining techniques are often essential to differentiate between epidermal and dermal deposits of melanin, haemosiderin and other substances. Masson's ammoniacal silver nitrate technique produces a densely black reaction product with melanin. Melanin deposits appear greenish black with the acid orcein–



(a) (b)

Fig. 10.5 (a) Connective tissue naevus. The section stained with H&E only shows focal condensation of the collagen. (b) An elastic van Gieson stain shows marked focal increase in the number of elastic fibres.

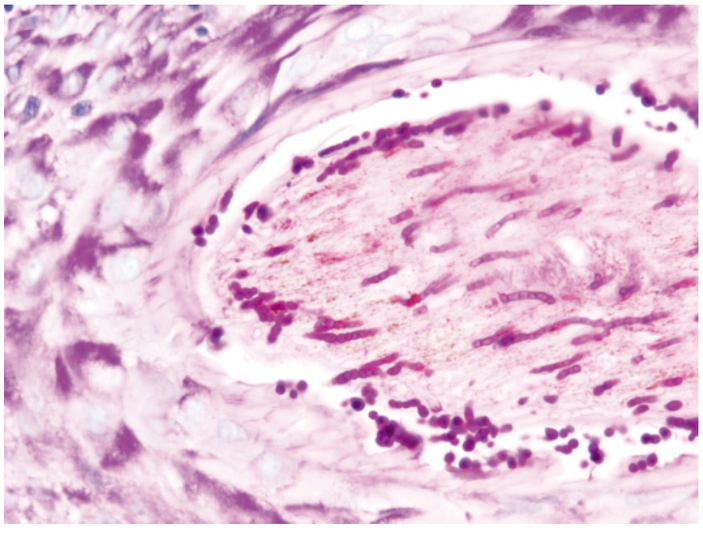


Fig. 10.6 Periodic acid–Schiff (PAS) stain, showing numerous hyphae within the hair shaft in an endothrix infection.

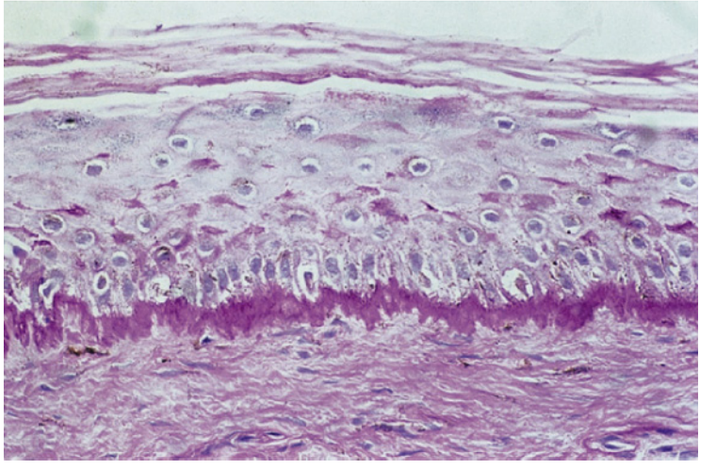


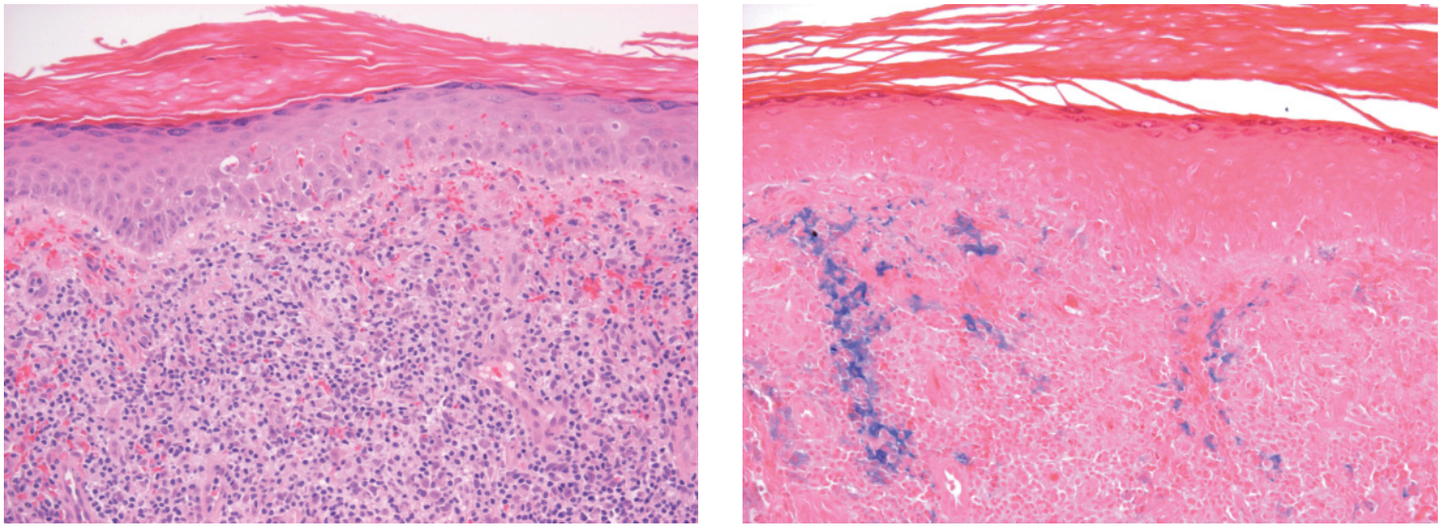
Fig. 10.7 Periodic acid–Schiff (PAS) stain, showing thickening of the basement membrane zone in cutaneous lupus erythematosus.

Giemsa stain referred to above. Iron, which in the context of skin biopsy material normally means haemosiderin pigment, is demonstrated by Perls' Prussian blue reaction, which yields a deep-blue reaction product in the presence of ferric and ferrous iron (Fig. 10.8a & b).

Trichrome stains can demonstrate various elements of connective tissue. Common examples are the van Gieson stain, in which collagen appears red and muscle and nerves yellow, and Masson's trichrome stain, in which collagen is green and muscle red. The latter stain is seldom used nowadays.

Reticulin fibres are demonstrated by Gomori's silver impregnation technique. This technique is particularly useful in the study of certain cutaneous tumours, including vascular tumours and malignant melanoma. The application of this method to melanocytic lesions may reveal foci of expansile growth undetectable in normal H&E-stained preparations.

Certain types of cell present within the skin may be difficult to recognize on conventional H&E-stained material. Mast cells are best demonstrated either by the use of a metachromatic staining technique, such as toluidine blue, or with one of the few enzyme histochemical methods that may be carried out on paraffin-embedded tissue, such as the chloroacetate esterase reaction. The use of this technique applied to formalin-fixed paraffin sections was described by Leder [14], and mast cells and myeloid white cells are easily identified by their bright pinkish red staining (Fig. 10.9). Other histiocytic and dendritic cells that are difficult to visualize on routinely stained material are best visualized with immunohistochemical methods.



(a) (b)

Fig. 10.8 (a) A prominent lymphocytic infiltrate which is focally lichenoid and is associated with extravasation of red blood cells in a case of lichen aureus (H&E). (b) Perls' stain highlighting numerous haemosiderin-containing macrophages, a useful technique to confirm the diagnosis of lichen aureus.

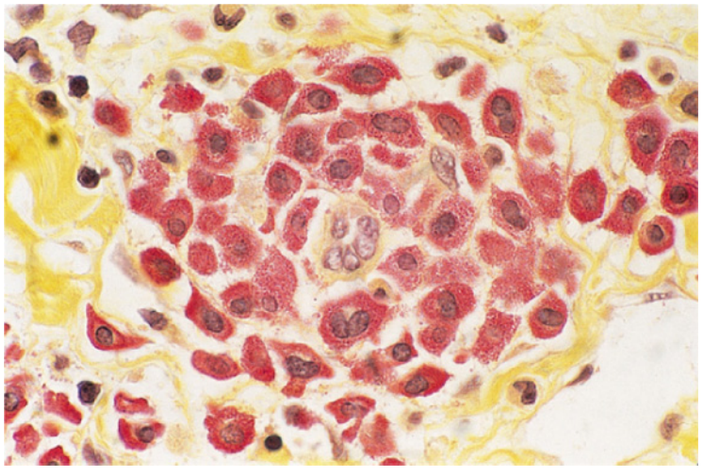


Fig. 10.9 The chloroacetate esterase stain. Mast cells appear red with this technique.

Cutaneous deposits of various naturally occurring and foreign substances often require special staining techniques for their demonstration. The von Kossa method produces a black coloration in the presence of calcium salts, and amyloid deposits may be demonstrated using crystal violet or Congo red. With this latter technique, amyloid deposits stain pinkish red, and under polariscopic examination there is a green birefringence. Another technique useful for the demonstration of amyloid deposits is the thioflavine T method, yielding green fluorescence on examination with a fluorescence microscope. Unfortunately, several of the staining techniques recommended for the demonstration of amyloid are technically unreliable, and none is absolutely specific for amyloidosis. Some cotton dyes other than Congo red, such as pagoda red, have been claimed to be as sensitive as Congo red while being more specific [15]. It is recommended that more than one special stain be used if amyloid is suspected. Occasionally, even with the use of several special stains, amyloid cannot be demonstrated and electron microscopy is necessary for this purpose.

A wide range of techniques is employed for the demonstration of microorganisms in the skin. Reference has already been made to the usefulness of the PAS stain in the demonstration of yeasts and fungi. The silver staining technique of Grocott is also very helpful in the identification of fungal hyphae and yeast bodies. These structures stain black on a pale-green background. Other silver techniques, including the Warthin–Starry technique, are useful in demonstrating spirochaetes, *Bartonella henselae* (the organism that causes bacillary angiomatosis) and *Borrelia* in tissue sections. *Bartonella* may also be demonstrated by the use of a Giemsa stain. The traditional Gram stain demonstrates coccal and bacillary organisms in the skin. Several techniques are available for the demonstration of acid-fast bacilli. The Ziehl–Neelsen method is widely used for the demonstration of mycobacteria, particularly *Mycobacterium tuberculosis.* It is based on the capacity of the lipid-rich cell wall of mycobacteria to take up strong phenol-dye solutions. This dye is retained after differentiation in acid or alcohol. Mycobacteria stain magenta and the background is blue. Auramine–rhodamine is also a sensitive method for demonstrating mycobacteria in tissue sections. Its main drawback is that it requires the use of a fluorescence microscope for interpretation [16]. The Ziehl–Neelsen method should not be used for the demonstration of leprosy bacilli. The use of this technique often leads to a false-negative result. The reason for this is that the leprosy bacilli are less acid- and alcohol-fast. The Wade–Fite stain, or a modification of this technique, is more appropriate for identification of leprosy bacilli and atypical mycobacteria because it uses minimal treatment with alcohol and acid. In fact, in cases with very few organisms, if Ziehl–Neelsen is used instead of Wade–Fite, the diagnosis may be missed.

Even with the above techniques, demonstration of small numbers of microorganisms in the skin may be very difficult, and may require the examination of very many sections. Thankfully, since the last decade of the last century, increasing numbers of newer tests for the detection of microorganisms in paraffin embedded tissue have become available, simplifying the task of pathologists and dermatopathologists. These techniques include *in situ* hybridization, polymerase chain reaction (PCR) and immunohistochemistry and are used for the detection of a wide variety of microorganisms, including bacteria, mycobacteria, viruses and leishmania [17–29]. PCR is a very valuable tool for confirming the diagnosis in these infections, but very stringent conditions are required to avoid false-positive results, especially in the setting of mycobacterial infections. PCR is particularly useful in cases with suspicious histology in which special stains and cultures have been negative. It is important to highlight that mycobacterial DNA has been found in cutaneous lesions of nodular vasculitis and papulonecrotic tuberculid [30,31]. While this confirms the relationship between these two entities and tuberculosis, it does not necessarily mean that the finding may be interpreted as evidence of tuberculous infection in the affected sites. A polyclonal antibody for BCG is very useful as a screening technique for the presence of fungi and bacteria in tissues and this is based on the presence of wide cross-reactivity of this antibody between different species [32,33,34]. The antibody is, however, not useful to detect viruses, leishmania or spirochaetes.

References

1 Mondragon G, Nygaard F. Routine and special procedures for processing biopsy specimens of lesions suspected to be malignant melanomas. *Am J Dermatopathol* 1981; **3**: 265–72.
2 Templeton SF, Santa Cruz DJ, Salomon AR. Alopecia: histologic diagnosis by transverse sections. *Semin Diagn Pathol* 1996; **13**: 2–18.
3 Sperling LC. Scarring alopecia and the dermatopathologist. *J Cutan Pathol* 2001; **28**: 333–42.
4 Elston DM, Ferringer T, Dalton S *et al*. A comparison of vertical versus transverse sections in the evaluation of alopecia biopsy specimens. *J Am Acad Dermatol* 2005; **53**: 267–72.
5 Madani S, Shapiro J. The scalp biopsy: making it more efficient. *Dermatol Surg* 1999; **25**: 537–8.
6 Del Rosario RN, Barr RJ, Graham BS *et al*. Exogenous and endogenous cutaneous anomalies and curiosities. *Am J Dermatopathol* 2005; **27**: 259–67.
7 Bezahler GH. Microwave fixation of biopsy specimens. *Am J Dermatopathol* 1989; **11**: 295.
8 Boon ME, Kok LP. *Microwave Cookbook of Pathology*. Leiden: Coulomb Press, 1987.
9 Bancroft JD, Gamble M, eds. *Theory and Practice of Histological Techniques*, 5th edn. Edinburgh: Churchill Livingstone, 2001.
10 Luna LG. *Histological Procedures and Special Stains: a Practical Guide*. Gaithersburg, MD: Center for Histotechnology Training, 1988.
11 Pearse AGE. *Histochemistry, Theoretical and Applied*, 3rd edn. Boston: Little, Brown & Co., 1972.
12 Al-Amari A, Chatrath V, Bhawan J *et al*. The periodic acid-Schiff stain in diagnosing tinea: should it be used routinely in inflammatory skin diseases? *J Cutan Pathol* 2003; **30**: 611–5.
13 Pinkus H, Hunter R. Simplified acid orcein and Giemsa technique for routine staining of skin sections. *Arch Dermatol* 1960; **82**: 699–700.
14 Leder LD. The chloracetate esterase reaction. *Am J Dermatopathol* 1979; **1**: 39–42.
15 Yanagihara M, Mehregan AM, Mehregan DR. Staining of amyloid with cotton dyes. *Arch Dermatol* 1984; **120**: 1184–5.
16 Tang YW, Procop GW, Zheng X *et al*. Histologic parameters predictive of mycobacterial infection. *Am J Clin Pathol* 1998; **109**: 331–4.
17 Beard J, Benson P, Skillman L. Rapid diagnosis of coccidioidomycosis with a DNA probe to ribosomal RNA. *Arch Dermatol* 1993; **129**: 1589–93.
18 Nagao K, Ota T, Tanikawa A *et al*. Genetic identification and detection of human pathogenic Rhizopus species, a major mucormycosis agent, by multiplex PCR based on internal transcribed spacer region of rRNA gene. *J Dermatol Sci* 2005; **39**: 23–31.
19 Behorf W, Springer E, Bräuninger W *et al*. PCR-testing for *Treponema pallidum* in paraffin-embedded skin biopsies: test design and impact on the diagnosis of syphilis. *J Clin Pathol* 2008; **61**: 390–5.
20 Buffet M, Grange PA, Gerhardt P *et al*. Diagnosing *Treponema pallidum* in secondary syphilis by PCR and immunohistochemistry. *J Invest Dermatol* 2007; **127**: 2345–50.
21 Eisendle K, Grabner T, Zelger B. Focus floating microscopy: 'gold standard' for cutaneous borreliosis? *Am J Clin Pathol* 2007; **127**: 213–22.
22 Wienecke R, Neubert U, Volkenandt M. Molecular detection of *Borrelia burgdorferi* in formalin-fixed paraffin-embedded lesions of Lyme disease. *J Cutan Pathol* 1993; **20**: 385–8.
23 Mouritsen CL, Litwin CM, Maiese RL *et al*. Rapid polymerase chain reaction-based detection of the causative agent of cat-scratch disease (*Bartonella henselae*) in formalin-fixed paraffin-embedded samples. *Hum Pathol* 1997; **28**: 820–6.
24 Reithinger R, Dujardin JC. Molecular diagnosis of leishmaniasis: current status and future applications. *J Clin Microbiol* 2007; **45**: 21–5.
25 Safaei A, Motazedian MH, Vasei M. Polymerase chain reaction for diagnosis of cutaneous leishmaniasis in histologically positive, suspicious and negative skin biopsies. *Dermatology* 2002; **205**: 18–24.
26 Pagliusi SR, Garland SM. International standard reagents for HPV infection. *Dis Markers* 2007; **23**: 283–96.
27 Nashass G, Goldstein B, Zhu W *et al*. Comparison of Tzanck smear, viral cultures and DNA diagnostic methods in detection of herpes simplex and varicella-zoster infection. *JAMA* 1992; **268**: 2541–4.
28 Tan SH, Tan BH, Goh CL *et al*. Detection of *Mycobacterium tuberculosis* DNA using polymerase chain reaction in cutaneous tuberculosis and tuberculids. *Int J Dermatol* 1999; **38**: 122–7.
29 Quiros E, Maroto MC, Bettinardi A *et al*. Diagnosis of cutaneous tuberculosis in biopsy specimens by PCR and Southern blotting. *J Clin Pathol* 1996; **49**: 889–91.
30 Li JY, Lo ST, Ng CS. Molecular detection of *Mycobacterium tuberculosis* in tissues showing granulomatous inflammation without demonstrable acid-fast bacilli. *Diagn Mol Pathol* 2000; **9**: 67–74.
31 Baselga E, Margall N, Barnadas MA *et al*. Detection of *Mycobacterium tuberculosis* DNA in lobular granulomatous panniculitis. *Arch Dermatol* 1997; **133**: 457–62.
32 Wiley EL, Beck B, Freeman RG. Reactivity of fungal organisms in tissue sections using antimycobacterial antibodies. *J Cutan Pathol* 1991; **18**: 204–9.
33 Kutzner H, Argenyi ZB, Requena L *et al*. A new application of BCG antibody for rapid screening of various tissue organisms. *J Am Acad Dermatol* 1998; **38**: 56–60.
34 Byrd J, Mehregan DR, Mehregan DA. Utility of antibacillus Calmette-Guerin antibodies as a screen for organisms in sporotrichoid infections. *J Am Acad Dermatol* 2001; **44**: 261–4.

Immunopathology

There are some situations where even after careful biopsy of an appropriate lesion, expert tissue processing and sectioning, and the use of several special staining techniques, a specific histological diagnosis is still not possible. The use of immunological methods permits the identification of antigens, antibodies and various other cell and tissue components, and has greatly facilitated our ability to achieve a specific diagnosis. Hybridoma monoclonal antibody technology paved the way for the development of numerous antibodies to cell and tissue structures. Further refinement and experimentation with immunohistological techniques has brought this powerful new diagnostic tool within the reach of most histopathology laboratories, particularly with increasing commercial availability of diagnostic cell markers that label routine paraffin sections (Table 10.8).

Table 10.8 Immunocytochemistry panels of cell markers.

1 *Undifferentiated malignancy panel*
MNF 116 (keratin)
AE1/AE3 (keratin)
CAM 5.2 (low-molecular-weight keratin)
Epithelial membrane antigen (EMA)
Leukocyte common antigen (LCA)
S-100
CD31

2 *Spindle cell panel*
As in 1 above plus:
Desmin
H-caldesmon
Calponin
Smooth muscle actin
Q bend 10 (CD34)

3 *Melanocyte panel*
S-100
HMB45
Mart-1 (Melan-A)
MIFT-1
Tyrosinase
Melanoma cocktail

4 *Small blue cell panel*
Chromogranin
Synaptophysin
NSE (neurone-specific enolase)
Cam 5.2
EMA
CEA
S-100
Cytokeratin 20
CD99
FLI-1
Desmin
Myogenin
Muscle-specific actin
Smooth muscle actin

5 *Lymphoma panel*
LCA (CD45)
CD20 (pan-B-cell marker)
CD79a (pan-B-cell marker)
CD2, CD5, CD7 (pan-T-cell markers)
CD3 (pan-T-cell marker)
CD4 (T-helper/inducer lymphocytes)
CD8 (T-cytotoxic/suppressor lymphocytes)
UCHL (CD45Ro) (pan-T-cell marker)
Ber-H2 (CD30)
κ light chain λ light chain
ALK-1
Bcl-2
CD10 (marker of follicle-centre cells)
Bcl-6 (marker of follicle-centre cells)
Ki-67 (proliferation marker)
CD43 (pan-T-cell marker)
CD56 (natural killer cell marker)
TIA-1 (marker of cytotoxic granules)
Granzyme (marker of cytotoxic granules)
Perforin (marker of cytotoxic granules)
MUM 1
FPOX-1

6 *Leukaemia panel*
LCA (leukocyte common antigen)
Lysozyme
Myeloperoxidase
HLA-DR
MT1 (CD43)
KP1
PGM1

7 *Langerhans' cell panel*
S-100
CD1a
Langerin (CD207)

8 *Vascular panel*
CD31
Factor VIII-related antigen
Q bend 10 (CD34)
FLI-1
LYVE-1
Podoplanin (D2–40)

9 *Mast cell markers*
CD117
Tryptase
Microphthalmia transcription factor

10 *Immunofluorescence labelling*
IgG, IgM, IgA, C3, fibrin (much better results with frozen sections)

All cell markers react on paraffin-embedded sections unless otherwise stated.

Immunofluorescence methods

Immunofluorescence is a technique for detecting the presence and position of antigens, antibodies, other cell secretions and cell components in cells or tissue sections. The principle of the technique is that certain fluorochrome dyes exposed to ultraviolet (UV) light emit fluorescent radiation, the colour of which depends upon the particular fluorochrome. When these dyes are conjugated to proteins that are subsequently added to tissue sections, or injected into an animal, the position of the proteins can be traced microscopically by the fluorescence they emit under illumination with UV light with suitable filters.

Two fluorochromes are generally available. Fluorescein is most commonly used. It is best conjugated to protein in the form of fluorescein isothiocyanate, which emits an apple green fluorescence. The second dye is rhodamine RB200, which is conjugated to protein as rhodamine isothiocyanate or sulphonyl chloride; it emits an orange fluorescence.

Preparation of tissues

Tissues to be examined are usually snap frozen in liquid nitrogen, cut in a cryostat at about –20°C, dried and stained without fixation. Sections can be fixed, before staining, in cold acetone or

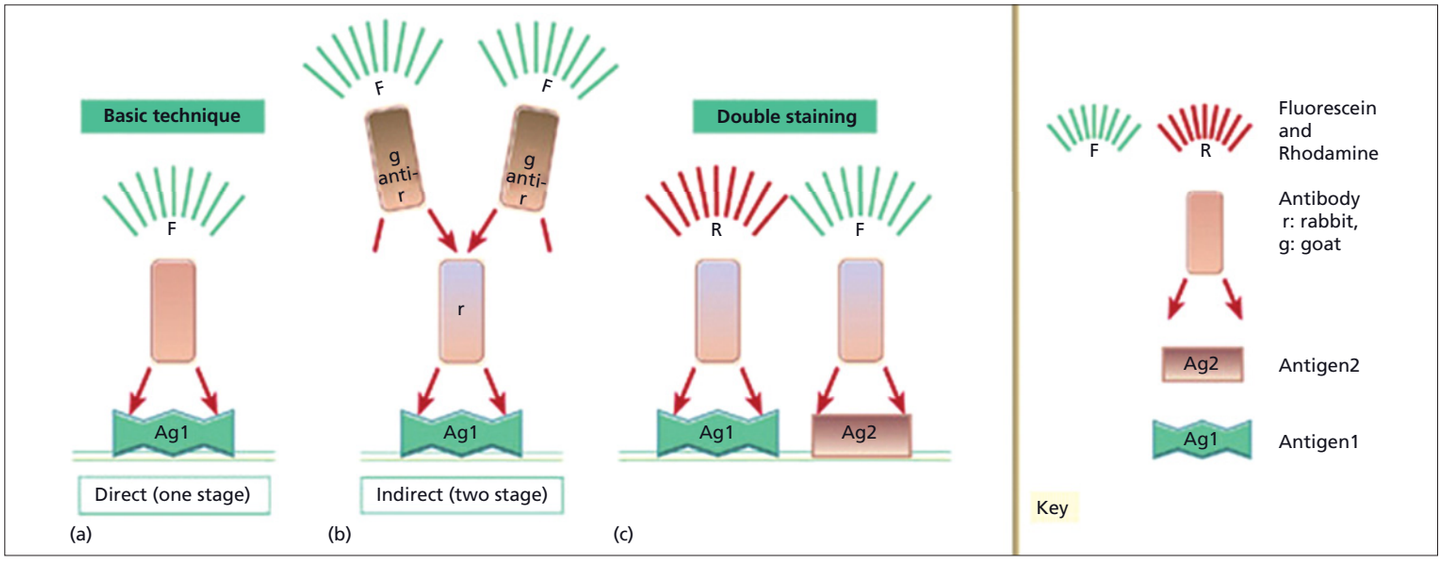


Fig. 10.10 Diagrammatic representation of immunofluorescence techniques.

methanol, provided that these agents do not alter the antigenicity of, or dissolve, the substances to be detected [1]. This provision also applies to the technique of cold formaldehyde [2] or alcohol fixation of tissues, and embedding in paraffin for cutting on a microtome at room temperature. The use of acetone, ethanol and methanol enhances tissue preservation, but sometimes increases non-specific staining.

Many antigens can be detected in routine paraffin tissues; others are masked after fixation in formalin, para-formaldehyde or glutaraldehyde and paraffin embedding. Such antigens can be 'retrieved' or revealed, and detection improved, by heat in strictly controlled conditions [3–8]. Heat treatment is by pressure cooker or by microwave. The heat retrieval solution is citrate buffer, 10 mmol/L sodium citrate made pH 6.0 by HCl. When heated in a pressure cooker, the slides in open metal racks, well spaced, are placed in hot buffer in the pressure cooker and as quickly as possible heated to 15 lb pressure for 1 min only. Then the pressure cooker is plunged into a sink of cold water. In the more often used microwave method, the slides are placed in Coplin jars containing the same buffer; the jars are placed in an open dish. The dish may contain water but this is not essential. The tissues are heated for variable periods; 15 min is usually adequate. Antigens in skin should not require more than 10 min. After the first and every 5 min after, the fluid in the Coplin jar is replenished with water to replace that lost by evaporation. Unfortunately, the dermis is susceptible to disintegration if heating is excessive, though eccrine and sebaceous glands and larger blood vessels remain. The treated sections are stained by standard methods of immunofluorescence or by immunoenzyme techniques.

Some antigens require protease treatment instead of heat; this is usually indicated on the leaflets accompanying vials of commercial antibodies.

Labelling procedures

Tissue sections must be wetted and treated with protein to block or reduce non-specific binding for at least 30 min. The diluent is phosphate-buffered saline (PBS) +0.1% Triton X100 and protein, which may be 0.5% chick albumin, or 0.5–2.0% bovine serum albumin or, rarely, 2–5% of the serum of the same species as the primary antibody. The diluent for the antibody is PBS with 0.1% Triton X100 and 0.5% chick or bovine albumin.

The two principal labelling techniques are direct staining (Fig. 10.10a), in which sections are incubated with fluorochrome-labelled antibody to detect substances (i.e. the corresponding antigen) in tissues, and indirect staining (Fig. 10.10b), in which unconjugated antibody is incubated with the section, and any bound antibody is detected by the subsequent addition of fluorochrome-conjugated antiglobulin sera. These simple techniques may be modified for more sophisticated investigations by using double staining (Fig. 10.10c) on the same section, one with a fluorescein-labelled antibody, the other labelled with rhodamine or some other fluorochrome-conjugated antibody. Thus, it is possible to detect antigen and antibody in an immune complex (Fig. 10.10c) or a secreting cell and its secretions. Usually, the two labelled antibodies are derived from different species.

Direct labelling. Direct staining is used to detect substances, including antibody immunoglobulins in tissues (e.g. *in vivo* bound immunoreactants as in pemphigus and pemphigoid), by the addition of fluorochrome-conjugated antibodies (Fig. 10.10a) with subsequent washing to remove from the preparation all the conjugated antibody except that fixed to the particular substance. The details of the method are as follows.

1 For critical examination to detect small amounts of antigen, sections treated with the conjugated antibody are maintained in humid conditions overnight at 4°C. For more routine procedures, antibody treatment is for 2–4 h at room temperature in a humid container. The containers must be light-proof.
2 Wash tissue in PBS pH 7 with three changes for a total of 20 min.
3 Mount in commercial antifade mountant fluids.

Indirect labelling. The unconjugated antibody, or primary antibody, is incubated with the specimen to bind to the test antigen; the uncombined surplus is removed by washing, and the preparation stained by a fluorochrome-conjugated antiglobulin serum, i.e. this is the secondary antibody which binds to the primary antibody (Fig. 10.10b). The details of the indirect staining method are as follows.

1 Incubate the tissue with the antibody to the test antigen. This is the primary antibody.
2 Wash in PBS with three changes for at least 20 min.
3 In a light-proof humid container, incubate the sections for 30–45 min at room temperature with the conjugated antiglobulin antibody; this is the secondary antibody, to bind to and label the primary antibody.
4 Wash in PBS for 20 min (three changes) with the least exposure to light.
5 Mount.

Indirect staining with conjugated antiglobulin sera is more sensitive than direct staining with conjugated antibodies, because more conjugated antiglobulin molecules are fixed to antibody in the second stage than are antibody molecules fixed to antigen in the first stage. The method has, however, the disadvantage that it increases the likelihood of non-specific staining.

Results are dependent upon the quality of the antibodies. Monoclonal antibodies, which bind to a small sequence of antigen determinants (epitopes), may have weak affinity and be eluted during washing. False-negative results also occur when the particular epitopes are not exposed; thus monoclonal antibodies to different epitopes of the same antigen vary in their ability to detect the antigen.

Technical limitations

All that glows is not specific fluorescence. The two major sources of error are autofluorescence and non-specific binding.

Control tests. In routine use, the specificity of the conjugated antisera and optimal washing dilution is established and blocking tests are not required, except perhaps in sites of severe inflammation. For critical or experimental studies, blocking tests may be required to prove antibody specificity. Before addition of the conjugated antibody, sections may be treated with normal serum of the same species, or unconjugated specific antibody of the same subclass but against an irrelevant antigen, or unconjugated specific antibody, although this is usually expensive. If the selected pretreatment does not block the binding of the subsequent addition of the test-conjugated antibody, the staining is considered to be antigen-specific. Labelled antisera should be centrifuged before use, to remove any particulate matter, and the glass slides, sections and washing solutions should be free of dust, which readily adsorbs conjugates.

Autofluorescence. Tissues exposed to UV light emit their own fluorescence. In skin, this is not quenched by fixation, and is best controlled by appropriate filters.

Antigen non-specific staining. Non-specific staining refers to fluorescent staining of a section by a labelled antibody, not resulting from a specific antigen–antibody reaction. The causes of non-specific staining and the methods available for removing it are described in detail by Nairn [9].

Appropriate blocking before antibody treatment is essential (see above). The use of optimal dilutions of labelled antibody avoids excess fluorochrome application to the tissue, thus reducing potential non-specific staining. Neutrophils, eosinophils and histiocytes are particularly prone to absorb globulins non-specifically, which accounts for much of the apparently specific fluorescence of inflammatory lesions.

The antigen non-specific binding of fluorescein conjugates by eosinophils can be inhibited by prior treatment of the sections with diaminobenzidine in hydrogen peroxide [10,11].

Another source of confusion is the presence of 'natural' antibodies in the labelled antiserum that combine with sites other than those containing the antigen under examination. This does not apply to monoclonal antibodies and rarely to commercial polyclonal antibody, but they may be present in laboratory-prepared polyclonal antibodies. Natural antibodies are removable by absorbing the antisera with tissue powder from the same species as the tissue under test. Aggregated IgG in the conjugate will also bind non-specifically. Aggregation will occur in conjugates frozen and thawed repeatedly; therefore, conjugates should be stored as small samples and discarded after use. It is advisable to centrifuge the antibody before use.

A peculiarity of immunofluorescence tests on skin is the affinity of the stratum granulosum for antibody–fluorescein conjugates. The nature of this antigen non-specific binding has not been ascertained. Tests on the basic protein or filaggrin peculiar to stratum granulosum cells have not shown this to be the binding substance. However, careful preparation of the conjugates provides reagents with little or no affinity for the stratum granulosum.

Counterstaining. Identification of the particular cells or structures binding labelled antibody may be difficult if there is poor contrast with the background, if there is much autofluorescence and if the specific fluorescent binding is weak. Procedures to identify sites of specific binding are combined phase contrast and immunofluorescence, counterstaining for all the background tissue, or selective stains for nuclei. Counterstains have been used successfully but no one technique is applicable to all preparations. The emission from the counterstain may swamp the specific immunofluorescence if the preparation is thick or the charge affinity is strong, as may occur following the addition of Evans blue or brilliant cresyl violet [9] or of unconjugated rhodamine isothiocyanate to provide contrast to the green specific immunofluorescence. Instead of staining all the structures in a tissue, another counterstain procedure is to use dyes that selectively bind to nuclei to identify cells, for example propidium iodide [12,13], ethidium bromide [14] or *p*-phenylenediamine [15], the latter having the additional advantage of reducing fading of the immunofluorescence.

Photobleaching. Fading or photobleaching is a technical limitation of immunofluorescence. Prolonged or repeated examination reduces the intensity of emission, which also decays if prepara-

tions are exposed to sunlight. This fading can be reduced by the addition of *p*-phenylenediamine to the buffered glycerol mounting fluid [16]. This dye was subsequently found to be a useful nuclear counterstain.

References

1 Cerio R, Belter S, MacDonald DM. The effect of fixation on monoclonal antibody labelling of cell surface antigens. *Clin Exp Dermatol* 1987; **12**: 79–82.
2 Cerio R, Dupuy PF, Allen MH *et al*. Monoclonal antibody labelling of mononuclear cell surface antigens in formaldehyde-fixed paraffin-embedded cutaneous tissue. *J Invest Dermatol* 1986; **87**: 499–503.
3 Shi SR, Key ME, Kalra KI. Antigen retrieval in formalin-fixed, paraffin embedded tissues: an enhancement method for immunohistochemical staining based on microwave oven heating of tissue sections. *J Histochem Cytochem* 1991; **39**: 741–8.
4 Munakata S, Hendricks JB. Effect of fixation time and microwave oven heating time on retrieval of the Ki-67 antigen from paraffin-embedded tissue. *J Histochem Cytochem* 1993; **41**: 1241–6.
5 MacIntyre N. Unmasking antigens for immunohistochemistry. *Br J Biomed Sci* 2001; **58**: 190–6.
6 Momose H, Mehta P, Battifora H. Antigen retrieval by microwave irradiation in lead thiocyanate. Comparison with protease-digestion retrieval. *Appl Immunohistochem* 1993; **1**: 77–82.
7 Leong AS, Lee ES, Yin H *et al*. Superheating antigen retrieval. *Appl Immunohistochem Mol Morphol* 2002; **10**: 263–8.
8 Mighell AJ, Robinson PA, Hume WJ. Patterns of immunoreactivity to an anti-fibronectin polyclonal antibody in formalin-fixed, paraffin-embedded oral tissues are dependent on methods of antigen retrieval. *J Histochem Cytochem* 1995; **43**: 1107–14.
9 Nairn RC. *Fluorescent Protein Tracing*, 4th edn. Edinburgh: Churchill Livingstone, 1976.
10 Kingston D, Pearson JR. The use of the peroxidase reaction to obliterate staining of eosinophils by fluorescent-labelled conjugates. *J Immunol Methods* 1981; **44**: 191–8.
11 Valnes K, Brandtzaeg P. Selective inhibition of non-specific eosinophil staining or identification of eosinophilic granulocytes by paired counterstaining in immunofluorescence studies. *J Histochem Cytochem* 1981; **29**: 595–600.
12 Ockleford CD, Hsi BL, Wakely J *et al*. Propidium iodide as a nuclear marker in immunofluorescence, 1: use with tissue cytoskeleton studies. *J Immunol Methods* 1981; **43**: 261–7.
13 Jones KH, Kniss DA. Propidium iodide as a nuclear counterstain for immunofluorescence studies on cells in culture. *J Histochem Cytochem* 1987; **35**: 123–5.
14 van Rood JJ, van Leewen A, Ploem SS. Simultaneous detection of two cell populations by two-colour fluorescence and application to the recognition of B-cell determinants. *Nature* 1976; **262**: 795–7.
15 Oriel R, Mancilla-Jiménez R. Fluorescent staining of nuclear and compound substances: two useful properties of *p*-phenylenediamine. *J Immunol Methods* 1983; **62**: 185–92.
16 Johnson GD, Nogueira Araujo GM de C. A simple method of reducing the fading in immunofluorescence during microscopy. *J Immunol Methods* 1981; **43**: 349–50.

Immunoenzyme methods [1,2]

The immunoenzyme (immunoperoxidase) methods have several advantages over immunofluorescence:

1 Standard microscopes and illumination are used.
2 The preparations are permanent, and the reaction products do not usually fade on repeated examination.
3 Counterstains enable cells containing antigen to be identified with more certainty than using immunofluorescence with dark-ground illumination.
4 Examination is less tiring for the microscopist.
5 The preparations may be examined by electron microscopy.

Technical limitations

Inflammatory lesions may contain endogenous peroxidase activity, and such sections have to be pretreated to remove it [3]. Furthermore, it is possible for the antigen to be modified by the pretreatment, with the result that it is more difficult to detect. This mainly applies to examination of lesions. Normal tissues, for example those used as a substrate to detect antibodies in a patient's serum, rarely require pretreatment. The problem with endogenous peroxidase is analogous to the disadvantage of autofluorescence in the immunofluorescence preparations.

There is less contrast with immunoperoxidase methods than in slides treated by the immunofluorescence technique, and fine stippling or cytoskeletal structures seen by immunofluorescence are not quite so easily detected by immunoperoxidase. Although immunofluorescence may be more discriminating in detecting small amounts of antigen in cryostat-cut sections, the immunoperoxidase methods, used on paraffin-embedded tissues for antigens that are stable during preparation, provide more definite resolution of the tissue and sites of antigen.

Immunoperoxidase methods have another advantage in being the preferred method to re-examine tissues stored in paraffin blocks after routine histology, provided that the antigens are stable in the fixative and dehydrating agents.

Recent improvements in immunoenzyme techniques have resulted in their application to many investigations. The reagent antibody is conjugated with an enzyme, usually horseradish peroxidase, and the antibody conjugate combines with the antigen in the test preparation. The site of binding is detected by adding a substrate for the enzyme: the degradation of many molecules of substrate leaves a deposit confined to the site of binding. Sites of peroxidase activity appear as dark-brown granular deposits that are seen distinctly in contrast to suitable counterstains, for example methyl green or Mayer's haemalum.

Although the application described is the detection of antigen in tissue sections and cell suspensions or monolayers, the principle of the method is the same as that of the enzyme-linked immunosorbent assay (ELISA).

Chemical conjugation of peroxidase to antibody

Antiglobulins conjugated with peroxidase, and peroxidase–antiperoxidase (PAP) complexes, described below, are available commercially.

Use of conjugates

The horseradish peroxidase, conjugated to antibody or to globulin, may be applied to sections to detect antigen by procedures similar to those used for immunofluorescence. There are, however, modifications that increase the sensitivity of the method so that it is equal to, or possibly more sensitive than, indirect immunofluorescence.

The diagrammatic representation of the procedures seen in Fig. 10.11 shows the different forms of conjugate. Antibody against the antigen to be detected may be conjugated directly with the enzyme (Fig. 10.11a). This is not a very discriminating procedure. The indirect or two-stage procedure, whereby the unlabelled antibody bound to the antigen is detected by antiglobulin conjugated to enzyme (Fig. 10.11b), increases sensitivity by increasing the

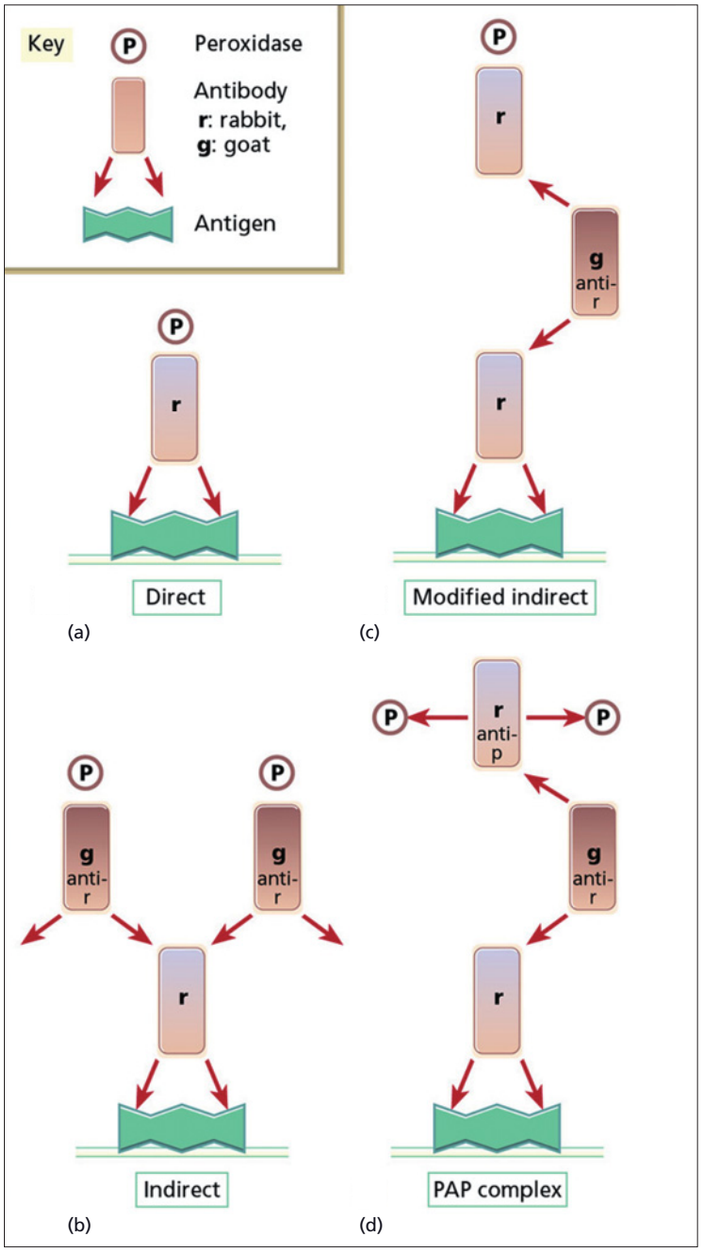


Fig. 10.11 Diagrammatic representation of immunoperoxidase techniques.

number of conjugated antibodies binding to the site, and is more versatile, because one conjugated antiglobulin can detect any antibody of that species.

Two other procedures increase the sensitivity of the technique. The antibody bound to the antigen is treated with unconjugated antiglobulin, which in turn is treated with normal globulin of the same species as the first antibody (Fig. 10.11c), for example, a sequence of rabbit antibody, goat anti-rabbit globulin and then rabbit normal globulin conjugated with peroxidase.

In the second modification, instead of using globulin conjugated chemically with enzyme in the third stage, a PAP complex is added (Fig. 10.11d), for example, rabbit antibody to peroxidase, which gives a more discrete, intense reaction product than chemically prepared conjugates of normal globulin–peroxidase, possibly because chemical treatment tends to alter the antigenic determinants of the normal globulin, and to polymerize the peroxidase.

The enzyme most frequently used is horseradish peroxidase, which forms a dark-brown product from its substrate. Alkaline phosphatase may also be used, and the reaction product with its substrate is red. The two enzymes may be used with appropriate antibodies on the same tissue or cells to detect different antigens, and the relationship of one antigen to another (i.e. double staining). A further enzyme may be used to obtain a more permanent red product that is preferable in cases where interpretation of the results may be hampered by the presence of pigment (haemosiderin and particularly, melanin). This is 3-amino-9-ethylcarbazole [4].

Examination of fixed frozen sections

There are three stages in the procedure:

1 The preparation of the tissue sections.
2 Treatment of the sections with the peroxidase-labelled antibody.
3 Chemical reaction to detect the peroxidase in the tissue.

Preparation and fixation of sections. Sections may be prepared from routine cryostat-cut samples or paraffin-embedded material, and may be treated for antigen-retrieval as described above. Some improvement in cryostat-prepared sections may be achieved by short-term fixation in dilute formalin, as follows.

1 Fix thin slices (2 mm thickness) with 1% formaldehyde in 0.1 mol/L phosphate buffer pH 7.2–7.4 for 30 min.
2 Wash in three changes of 15% sucrose in 0.1 mol/L phosphate buffer pH 7.2–7.4 for 18–24 h at 4°C.
3 Snap freeze in isopentane at the temperature of liquid nitrogen.
4 Cut sections 4–6 µm in a cryostat. Mount on slides, and dry under a fan at room temperature.

Treatment of the sections with antibody. Control for antibody specificity is as described for immunofluorescence. Sections may be treated by the methods described above (Fig. 10.11). The indirect method is probably the most suitable for general use, applying unlabelled antibody, followed by labelled antiglobulin.

1 Moisten section in PBS.
2 Treat with suitable dilution of specific antibody in PBS in a moist chamber at room temperature for 30 min–2 h.
3 Rinse well in PBS: then in two washes of PBS, each for 5 min with gentle agitation. (As the tissues are fixed they are less likely to be washed off the slides than unfixed tissues in the immunofluorescence technique.)
4 Treat with peroxidase-conjugated antiglobulin specific for the antibody applied in Step 2. Use at optimum dilution in PBS for 30 min.
5 Rinse well: wash in PBS for 15 min.

Detection of the peroxidase reaction product by staining. The substrate is a carcinogen and should be handled in small quantities with appropriate precautions. It is made up as follows:

- 3′,3′–diaminobenzidine tetra-HCl (DAB), 25 mg
- 0.05 mol/L pH 7.6 Tris–HCl buffer, 50 mL
- 3% hydrogen peroxide (H_2O_2), 0.15 mL

Dissolve the DAB in the buffer and add the H_2O_2 immediately before staining.

1 Slides treated with conjugated antibody or antiglobulin and washed are incubated with the substrate solution for 5–15 min (the longer period is not always an advantage).
2 Wash in tap water for 5 min. (If required, the reaction products may be intensified by 2% osmium tetroxide for 1 h, and the slides then washed.)
3 If required, the slides may be counterstained with methyl green, or Mayer's haemalum.
4 Treat for about 1 min each with 70%, 90% and twice with 100% industrial spirit, followed by two treatments with xylol.
5 Mount with DPX or Permamount.

Controls

It is necessary to confirm that the reaction observed reflects antibody-conjugated peroxidase and not endogenous peroxidase, and that the antibody binding is specific for antigen.

One section should be stained with DAB only; another section with DAB–methanol–H_2O_2, to confirm the absence of endogenous peroxidase.

Paraffin sections

If the antigens to be detected are stable in the fixatives and dehydrating agents, the immunoperoxidase methods may be applied to sections from paraffin-embedded tissue. The paraffin is removed from the sections with xylol and alcohols; sections are subsequently treated as for frozen sections.

The identity of the cells and tissues containing the antigen is much more easily determined by this method than by cryostat-cut sections, or by immunofluorescence. Immunoglobulins and hormones may be readily detected, but some antigens, such as those of bacteria in vasculitic lesions, tend to be extracted during processing.

Conjugates involving avidin–biotin coupling of antibody and enzyme

Instead of chemical covalent binding of antibody to enzyme to prepare conjugates, the two reagents may be linked non-covalently by the very strong affinity between biotin (a vitamin widely distributed in mammalian tissues) and avidin (a glycoprotein of egg white). Biotin is coupled to the reagent antibody through formation of an intermediate biotin derivative, and the avidin is coupled to the selected enzyme by glutaraldehyde [5]. Each biotin molecule has one combining site for avidin, and avidin has four sites for biotin, although not all of these would combine in a test system. Guesdon *et al*. [5] described two procedures.

1 The antibody–biotin conjugate is incubated with and combines with antigen in the test section or cell. This is followed by addition of peroxidase conjugated with avidin. The avidin binds the peroxidase to any biotin, and subsequent treatment with the substrate for the enzyme reveals the antigen sites (Fig. 10.12a).
2 The antibody–biotin conjugate is used as above to bind to any antigen. Avidin is then added, which becomes strongly linked to the biotin. Then biotin-labelled enzyme is added and the avidin bridges the biotin molecules. As the avidin has a potential four valencies for biotin, there is an enhancement or amplification of the enzyme binding, and therefore greater discrimination of the sites of antigen (Fig. 10.12b).

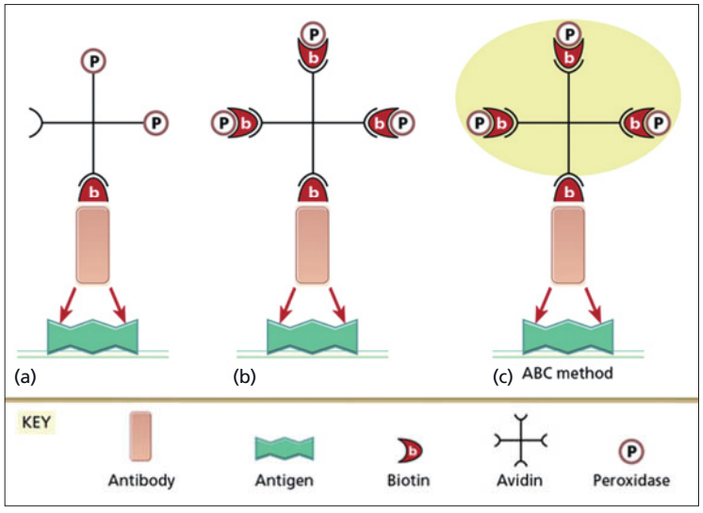


Fig. 10.12 Avidin–biotin staining methods. (a) Antibody coupled with biotin binds with the antigen in tissue. Avidin coupled with peroxidase binds to the biotin on the antibody. Treatment with enzyme substrate reveals the bound peroxidase, and therefore site of antigen. (b) Antibody coupled with biotin binds with the antigen in tissue. Avidin will bind the biotin–antibody complex. Biotin coupled with peroxidase will then bind to the free avidin-combining sites. Finally, treatment with enzyme substrate reveals the bound peroxidase. (c) Complexes (shown within yellow circle) are formed of biotin, coupled with peroxidase, incubated with moderate excess of avidin (ensuring some free avidin combining sites). Antibody coupled with biotin binds to antigen in tissue. The complexes are added to the tissue and the free avidin sites bind to the biotin on the antibody. Finally, treatment with enzyme substrate reveals the bound peroxidase.

A further modification is the avidin–biotin–peroxidase complex (ABC) method (Fig. 10.12c), similar to the PAP method already described. A prepared ABC follows the use of biotin-labelled antiglobulin (to detect unlabelled reagent antibody, or tissue-bound antibody in the tissue). The complex binds through the avidin bridge to biotin on the antiglobulin; the method results in greater intensity of staining.

As in the other immunodetection techniques, it is necessary to ensure that there is no autologous tissue background activity that will cause confusion when interpreting results. In the avidin–biotin methods, it is necessary to eliminate the possibility of endogenous peroxidase activity as in any peroxidase method. It is also necessary to inactivate endogenous biotin present in tissues that would bind the avidin-labelled reagents. However, overcoming any endogenous activity is a complex multistep activity and is not necessary if the appropriate controls (e.g. tissue treated with the avidin conjugates) show no binding.

References

1 Hudson AR, Smoller BR. Immunohistochemistry in diagnostic dermatopathology. *Dermatol Clin* 1999; **17**: 667–89.
2 Schach CP, Smoller BR, Hudson AR *et al*. Immunohistochemical stains in dermatopathology. *J Am Acad Dermatol* 2000; **43**: 1094–100.

Table 10.9 Direct immunofluorescence findings in autoimmune blistering disease.

Disease	Pattern and nature of immunoreactants
Pemphigus	Epidermal cell-surface deposits of IgG and C3
Bullous pemphigoid	Linear, homogeneous deposits of IgG (epidermal side on salt-split skin) and C3 at the dermal–epidermal junction
Linear IgA dermatosis	Linear homogeneous deposits of IgA at the dermal–epidermal junction
Herpes gestationis	Linear homogeneous deposits of C3 at the dermal–epidermal junction. IgG found only rarely
Epidermolysis bullosa acquisita	Linear homogeneous deposits of IgG (dermal side on salt-split skin) and C3 at the dermal–epidermal junction
Mucous membrane pemphigoid	Linear homogeneous deposits of IgG and C3 at the dermal–epidermal junction
Dermatitis herpetiformis	Focal granular deposits of IgA at the papillary tips
Bullous eruption of lupus erythematosus	Linear homogeneous, or non-homogeneous, deposits of multiple immunoglobulins, C3 and fibrin at the dermal–epidermal junction

3 DeLellis RA, Sternberger LA, Mann RB *et al*. Immunoperoxidase techniques in diagnostic pathology. *Am J Clin Pathol* 1979; **71**: 483–8.
4 Krieg R, Haldhuber KJ, Oehring H. Novel chromogenic substrates with metal chelating properties for the histochemical detection of peroxidase activity, derived from 3-amino-9-ethyl carbazole (AEC) and 3,6-diamino-9-ethylcarbazole. *Cell Mol Biol* 2000; **46**: 1191–212.
5 Guesdon JL, Ternynck T, Avrameas S. The use of avidin–biotin interaction in immunoenzymatic techniques. *J Histochem Cytochem* 1979; **27**: 1131–9.

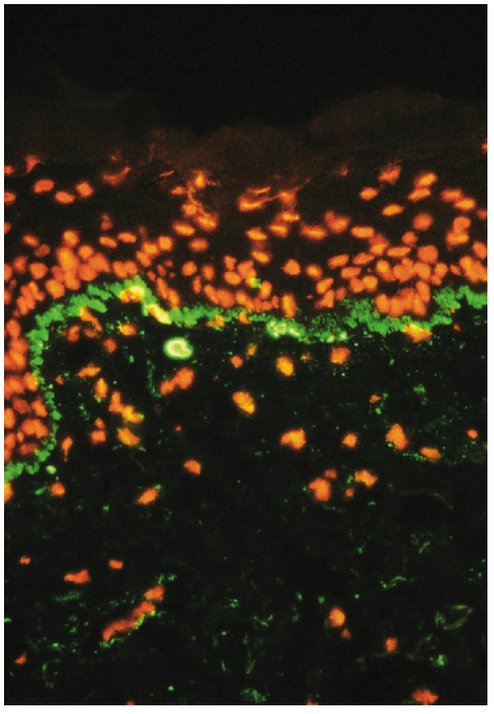


Fig. 10.13 Direct immunofluorescence of lupus erythematosus, showing speckled basement membrane zone deposition of IgM (green); ethidium bromide counterstain (orange). (Courtesy of Mr B.S. Bhogal, St John's Institute of Dermatology, London, UK.)

Applications of immunopathology techniques [1–3]

The immunopathological methods described above have revolutionized diagnostic histopathology, and have helped us to recognize, classify and understand the pathogenesis of a wide variety of cutaneous disorders. Although there are many antigens of diagnostic value that are not stable following formalin fixation and paraffin-embedding of tissue, there is still a wide range of antigens that are stable. A few of the more important areas of diagnostic dermatopathology that highlight the usefulness of immunopathological techniques are described below (Table 10.9).

Immunopathological techniques for the diagnosis of connective tissue diseases and autoimmune blistering diseases mainly rely on the use of immunofluorescence methods. Although some have suggested that immunoperoxidase methods are equally reliable in this setting, formalin fixation results in poor preservation of the antigens of interest and false-negative results are frequent. In the last decade, immunofluorescence studies (antigen mapping) have been increasingly used with success in the diagnosis of genetic blistering diseases, particularly epidermolysis bullosa (see Chapter 39). Samples are fixed in Michel's medium and frozen sections are processed in the same way as samples submitted for the diagnosis of autoimmune blistering disorders.

Lupus erythematosus

The deposition of immunoglobulins and complement at the dermal–epidermal junction is of diagnostic value in patients with lupus erythematosus (Fig. 10.13) and is known as the lupus band test. The presence of immunoglobulins, particularly those other than IgM, at the dermal–epidermal junction in normal non-sun-exposed skin correlates to some extent with the presence of systemic lupus erythematosus and renal involvement [4]. Sequential biopsies may demonstrate the disappearance of a positive lupus band during periods of disease inactivity, and may aid the clinician in the management of the disease. However, this approach is hardly ever used, as it implies repeated invasive procedures and disease activity may be monitored in a simpler way with blood tests. A positive lupus band is usually seen in involved skin in cutaneous lupus erythematosus [5], but false-positive results may be seen in sun-exposed skin from patients who do not have lupus. Immunofluorescence studies, in conjunction with other serological investigations, have led to the recognition of various important subsets of lupus erythematosus. Examples of this include the high incidence of anti-Ro/SSA and anti-La/SSB antibodies in the sera of patients with subacute lupus erythematosus and neonatal systemic lupus erythematosus.

Bullous disorders (see also Chapter 40)

The histological diagnosis of the various cutaneous autoimmune blistering diseases should always be confirmed with immunofluorescence studies. Although in many non-autoimmune blistering diseases a diagnosis can be made on the basis of light microscopic features in biopsies from formalin-fixed tissue, in immunological diseases a specific diagnosis is often not possible. In these circumstances, immunofluorescence studies are essential. Other techniques including immunoelectron microscopy and immunoblotting are extremely helpful. The classification and understanding of the

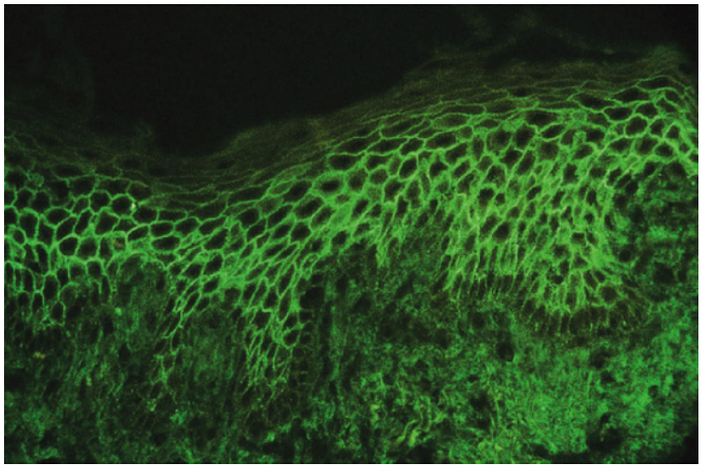


Fig. 10.14 Direct immunofluorescence of pemphigus, showing deposition of intercellular IgG in the epidermis. (Courtesy of Mr B.S. Bhogal, St John's Institute of Dermatology, London, UK.)

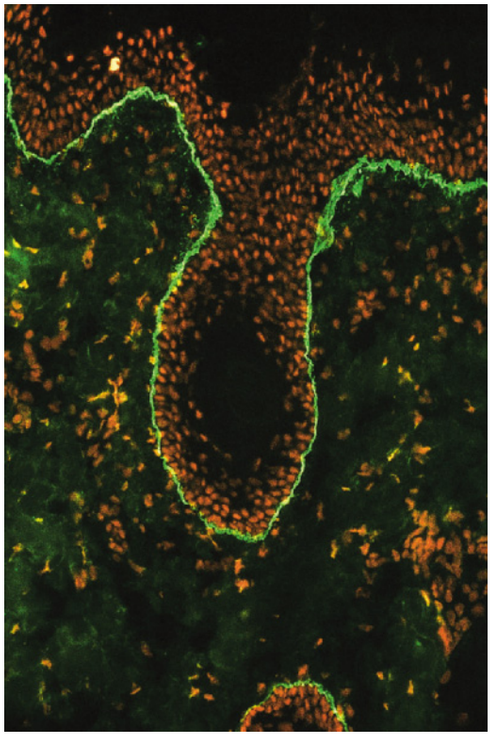


Fig. 10.15 Direct immunofluorescence of bullous pemphigoid, showing linear basement membrane zone deposition of IgG (green); ethidium bromide counterstain (orange). (Courtesy of Mr B.S. Bhogal, St John's Institute of Dermatology, London, UK.)

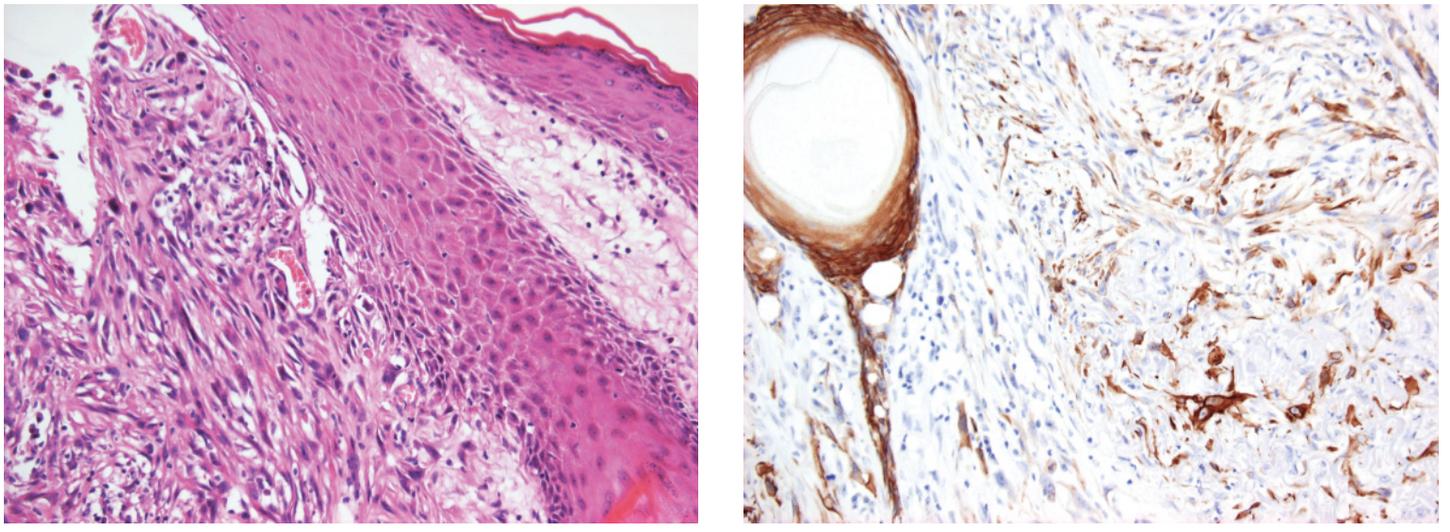
pathogenesis of numerous bullous disorders has been greatly facilitated by advances with these techniques. Ideally, tissue for immunopathological examination and serum for indirect immunofluorescence studies should always be taken at the time of a skin biopsy in a patient with an acquired blistering disorder. The biopsy submitted for immunofluorescence should be from perilesional or clinically normal skin. If lesional skin is submitted for immunofluorescence studies, a false-negative result is often obtained. The results of direct immunofluorescence studies on skin biopsies vary considerably depending on the disease being investigated, and the site of the biopsy. Intercellular epidermal deposition of IgG is present in almost all cases of pemphigus (Fig. 10.14). Complement is also frequently present, and IgA and/or IgM may be seen in a smaller percentage of cases. The additional presence of basement-membrane-zone IgG, or the C3 component of complement, points to a diagnosis of pemphigus erythematosus. Linear basement-membrane-zone IgG and complement deposition, and less commonly IgA or IgM, is associated with bullous pemphigoid (Fig. 10.15). Identical results are usually obtained in epidermolysis bullosa acquisita. The differential diagnosis is greatly aided by the use of the split-skin technique. In this technique, the exposure of the specimen to 1 mol/L NaCl induces a subepidermal blister [6]. In epidermolysis bullosa acquisita, the immunoreactants line the floor of the blister, and in bullous pemphigoid, the immunoreactants line the roof of the blister. With the indirect immunofluorescence technique using patient serum, the detection of linear basement-membrane-zone immunoglobulin antibodies is much more common in the classical form of bullous pemphigoid than in the cicatricial form of the condition, where positive results are obtained in approximately only 10% of cases. The diagnosis of other blistering diseases such as herpes gestationis (pemphigoid gestationis) and dermatitis herpetiformis is also greatly facilitated by immunopathological studies. In addition to direct immunofluorescence examination of skin biopsy material, and indirect immunofluorescence studies carried out on patient serum, the split-skin technique is valuable in the study of most of the subepidermal blistering disorders, enabling localization of the antibody-binding sites to be visualized [6]. Data obtained from such research has shed considerable light on the pathogenesis of many blistering diseases [7,8]. Since the advent of immunopathological techniques, several blistering diseases have been categorized and known entities have been further refined. Immunoblotting and related techniques enable specific antigens to be categorized more precisely.

Cutaneous neoplasms [1–3,9]

One of the most useful applications of immunopathology is in helping to determine the line of differentiation of poorly differentiated benign and malignant neoplasms that may arise from the various cellular components within skin and related tissues. The development within the last few years of increasing numbers of antibodies and other labels that can be utilized on formalin-fixed paraffin-embedded material has increased the usefulness of this application. All the antibodies discussed below work well in formalin fixed paraffin-embedded material.

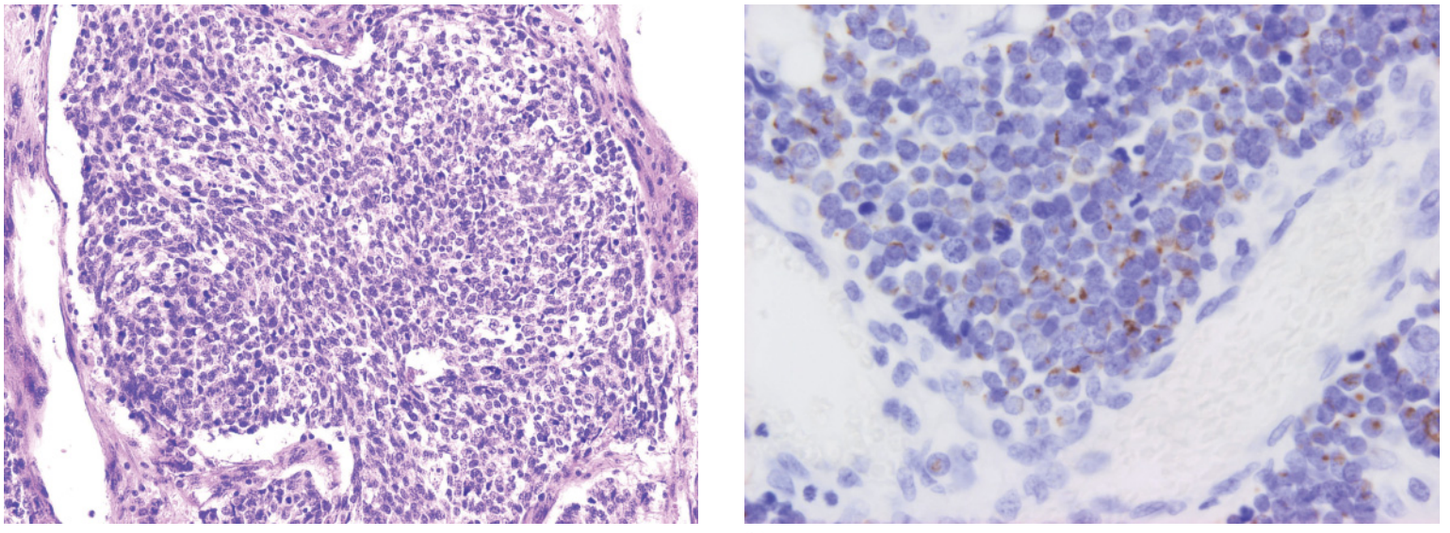
Keratins and other epithelial markers

Cytokeratins represent a group of intermediate filaments, known as tonofilaments, of variable molecular weight that may be demonstrated in keratinizing and non-keratinizing epithelia [10,11]. They represent the main structural component of the cytoskeleton of epithelial cells. About 30 different keratins have been demonstrated in humans by the use of double-diffusion gel electrophoresis. Their molecular weight ranges from 40 to 68 kDa. Keratins are divided according to molecular weight and their charge



(a) (b)

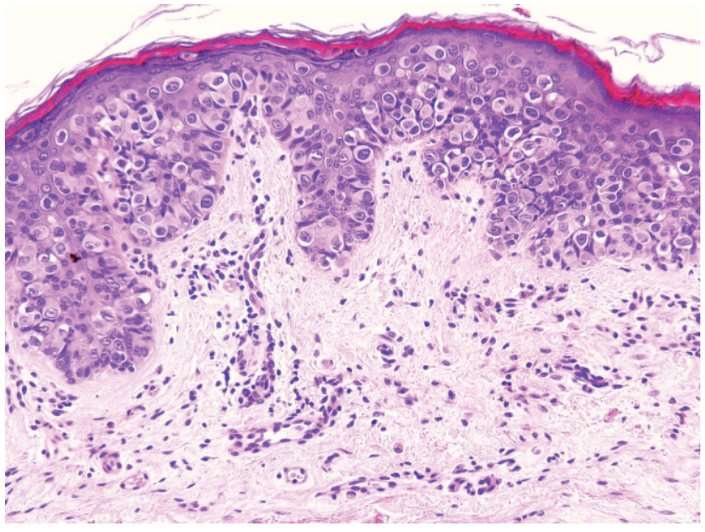
Fig. 10.16 (a) Poorly differentiated tumour composed of pleomorphic spindle-shaped cells in the dermis (H&E). (b) Diffuse positivity of tumour cells for the pan-keratin marker MNF116, confirming that the tumour is a sarcomatoid squamous cell carcinoma.



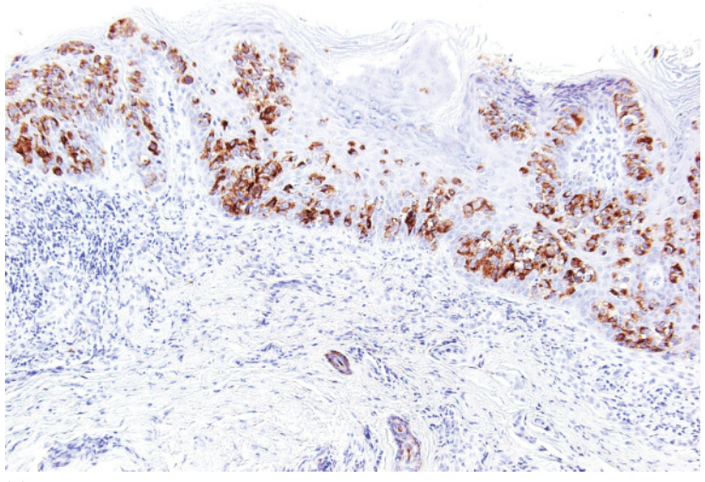
(a) (b)

Fig. 10.17 (a) Typical example of a Merkel cell carcinoma consisting of hyperchromatic cells with scanty cytoplasm. (b) Immunostaining with cytokeratin 20 highlighting the typical perinuclear dot-like positivity of tumour cells.

properties into acidic (type I) and neutral-basic (type II) [10,11]. They associate as pairs of one acidic and one basic keratin polypeptide molecule with each epithelial cell containing at least one keratin pair. The antibodies against keratins most commonly used in dermatopathology include AE1/AE3, MNF116 (Fig. 10.16a & b) and CAM 5.2. They are all cocktails containing several monoclonal antibodies of different molecular weight. CAM 5.2 is a low-molecular-weight keratin antibody, which labels most epithelia, with the exception of stratified squamous epithelia [12]. CAM 5.2 is usually negative in squamous cell carcinoma. It should therefore not be used in the diagnosis of poorly differentiated squamous cell carcinoma, as a negative result is the norm. Positive staining however may be seen in sebaceous carcinoma, and this is an aid in the distinction between this tumour and squamous cell carcinoma. The main use of CAM 5.2 in dermatopathology is in the diagnosis of Merkel cell carcinoma (primary cutaneous neuroendocrine carcinoma), as tumour cells in this lesion display a typical perinuclear dot-like positivity for this antibody. Cytokeratin 20 (CK-20), a low-molecular-weight cytokeratin, expressed usually only in urothelium, gastrointestinal epithelium and Merkel cells, is also very useful in the diagnosis of Merkel cell carcinoma [13,14]. The staining pattern is identical to that of CAM 5.2 (perinuclear dot-like, Fig. 10.17a & b), and a positive result strongly suggests a primary cutaneous origin rather than a metastatic neuroendocrine carcinoma originating in another organ. Only Merkel cell carcinoma and salivary gland small cell carcinoma tend to be



(a)



(b)

Fig. 10.18 (a) Extramammary Paget's disease showing prominent colonization of the epidermis by numerous, atypical, rounded cells with pink cytoplasm. (b) Tumour cells stain diffusely for cytokeratin 7.

positive for this marker, while neuroendocrine tumours from other organs are consistently negative.

Cytokeratin 7 (CK-7) is a very useful antibody for confirmation of the diagnosis of mammary and extramammary Paget's disease [15] (Fig. 10.18a & b). Tumour cells in the latter stain consistently for this antibody while the surrounding epidermis is negative. However, staining for keratin 7 is not specific for mammary and extramammary Paget's disease as positivity has been described in pagetoid Bowen's disease and in rare cases of actinic keratoses [16,17].

It is important to remember that keratin and also EMA expression (see below) is commonly seen in various sarcomas, including epithelioid sarcoma, synovial sarcoma, epithelioid angiosarcoma, and more rarely in other tumours such as leiomyosarcoma and rhabdomyosarcoma [18–21].

Epithelial membrane antigens (EMA) [22] are derived from human milk fat globulin membrane, and consist of high-molecular-weight glycoproteins. Antibodies to EMA and related labels react with a range of normal and neoplastic epithelia, and positivity may be found in squamous and ductal epithelia as well as eccrine, apocrine and sebaceous glands. EMA tends to be at least focally positive in squamous cell carcinoma, sebaceous carcinoma, perineuroma and a wide variety of adnexal carcinomas. It is also positive in plasma cells, in epithelioid sarcoma, synovial sarcoma, epithelioid angiosarcoma and in systemic and much less commonly, primary cutaneous $CD30^+$ large-cell anaplastic lymphoma [23].

Carcinoembryonic antigen is a protein that is normally found in the goblet cells of the small and large intestine. It is found in many adnexal carcinomas, particularly tumours displaying ductal differentiation [24]. It is also expressed in many glandular carcinomas arising in other organs. Its main use in dermatopathology is to highlight ductal differentiation in adnexal tumours.

Neuroendocrine markers

Besides CK-20, whose use in the diagnosis of Merkel cell carcinoma has been described above, markers of neuroendocrine differentiation include neurone-specific enolase, chromogranin and synaptophysin. Neurone-specific enolase is an enzyme described in the brain but also found in neuroendocrine cells [25]. Its use in diagnostic pathology is very limited because of the lack of specificity. Chromogranin A is part of a family of calcium-binding proteins present in the secretory granules of neuroendocrine cells. This protein is very specific but poorly sensitive for neuroendocrine differentiation [26]. Synaptophysin is a transmembrane glycoprotein with a molecular weight of 38 kDa and is a specific marker of neuroendocrine differentiation [27]. CD56 (neural cell adhesion molecule, NCAM) is expressed in neural tissues, natural killer cells and a subset of T cells, among other tissues [28]. This protein is often expressed in tumours with neuroendocrine differentiation and is sometimes included in the immunohistochemical panel used to diagnose Merkel cell carcinoma. However, it is important to highlight its relative lack of specificity.

Melanocytic markers

Over the years, a wide array of markers for melanocytes have been described including S-100, HMB45, Melan-A, Mel-5, tyrosinase and MIFT-1 (microphthalmia transcription factor-1).

It is important to emphasize that no marker allows distinction between benign and malignant melanocytes and that the sensitivity and specificity of different markers is variable. S-100 protein is very sensitive but much less specific than other markers including HMB45, MelanA and MIFT-1. Melanocytic markers are particularly useful as part of a panel in the differential diagnosis of poorly differentiated malignant tumours. Desmoplastic melanomas are usually positive for S-100 but negative for melanocytic markers such as Melan-A, HMB45 and MIFT-1.

S-100 protein is an acidic protein, originally derived from ox brain, and named because of its solubility in 100% ammonium sulphate. It is a sensitive marker of melanocytes [29–31]. Antibodies to S-100 protein, however, also react with Schwann cells, glial cells, adipocytes, chondrocytes, Langerhans' cells and cells of the eccrine sweat coil, and therefore tumours and hamartomas derived from these cells. S-100 also stains the cells in Rosai–Dorfman

disease. S-100 protein is particularly useful in the study of suspected malignant melanoma, as the great majority of, but by no means all, melanomas are positive for this marker [32]. In this context, the technique is particularly valuable in the differentiation of melanoma from other spindle cell neoplasms, and in identifying small deposits of melanoma that may be present in deep dermal tissues, as in determination of accurate Breslow thickness and/or intravascular spread, or the evaluation of spread to sentinel lymph nodes. S-100 is less reliable when used to delineate the epidermal component of a melanocytic lesion. The reason for this is that it also stains Langerhans' cells. More specific markers of melanocytes such as Melan-A should be used for this purpose (see below). S-100 is also often focally positive in a number of soft-tissue tumours and should therefore be used as part of a panel of markers in the diagnosis of poorly differentiated tumours.

HMB-45 (gp100) [33–35] recognizes a 10-kDa antigen localized in premelanosomal vesicles. The antibody was developed from an extract of a lymph-node metastasis of melanoma. This antibody does not stain normal adult melanocytes or intradermal naevi. It is a very specific antibody, which is usually negative in desmoplastic melanoma. Around 90% of primary and metastatic melanomas are positive for this marker.

Melan-A (MART-1) [36,37] is a melanocyte marker that recognizes an antigen present in melanoma cells and recognized by $CD8^+$ cytotoxic T lymphocytes. It is a fairly specific marker of melanocytes. Melan-A stains naevi and melanomas, but it tends to be negative in desmoplastic melanoma, spindle cell melanoma and neurotized naevi. Although Melan-A is a useful melanocytic marker, its usefulness in distinction between *in-situ* melanoma arising in sun-exposed skin and pigmented actinic keratosis has been challenged [38]. The reason for this is that Melan-A may also occasionally stain melanocytes probably as a result of transference of the protein from melanocytes to keratinocytes.

Mel-5 is a monoclonal antibody developed against a 75-kDa glycoprotein present in melanocytes, naevus cells and melanoma cells [39]. As for Melan-A, it does not tend to be expressed in desmoplastic melanoma, spindle cell melanoma and neurotized naevi.

MIFT-1 is the latest addition to the armamentarium of melanocytic markers [40]. This is a nuclear protein involved in the development of melanocytes and in the regulation of melanin synthesis. It stains naevi and melanoma but is usually negative in desmoplastic melanomas. Although it was initially regarded as fairly specific, it has been found to be expressed in macrophages, mast cells, fibroblasts, lymphocytes, Schwann cells and even smooth muscle cells [41]. Its utility as part of a panel for the diagnosis of difficult tumours has proven to be limited.

Cocktails consisting of a mixture of different monoclonal antibodies against melanocytes have been developed and advocated as being effective particularly in the detection of low volume melanoma cells in sentinel lymph node biopsies. One of the main cocktails used consists of a mixture of Mart-1, Melan-A and tyrosine (MCW) [42].

Mesenchymal markers

There are many markers of mesenchymal differentiation that are useful in the differential diagnosis of neoplasms, particularly those that are poorly differentiated. As with many of the other antibodies discussed so far, the specificity and sensitivity of each of these markers is very variable. What this means is that they should always be used as part of a wider panel of markers. Commonly used markers include vimentin, desmin, smooth muscle actin, muscle-specific actin, calponin, h-caldesmon, S-100, CD34, CD31, factor VIII-related antigen and Fli-1.

Vimentin has a molecular weight of 57 kDa and it is found in all mesenchymal cells and their tumours. It has a very low specificity and can be found in melanomas, lymphomas and even carcinomas. Its value is therefore very limited [43].

S-100 has already been described above. It is a very useful marker for neurofibroma and Schwannoma. While the latter tumour tends to be uniformly positive for S-100, the percentage of tumour cells positive for this marker varies in neurofibroma.

Desmin is a polypeptide with a molecular weight of 53 kDa, and is characteristic of smooth, skeletal and cardiac muscle [44]. In skeletal muscle desmin filaments are found in association with the Z-discs of the sarcomeres and the sarcolemmal attachment plaques. In smooth muscle cells, desmin filaments interconnect the fusiform dense bodies with the plasmalemmal dense bodies. Desmin is very specific for muscular differentiation and it is a useful marker only occasionally reported in other tumours such as Schwannoma and epithelioid sarcoma [45,46].

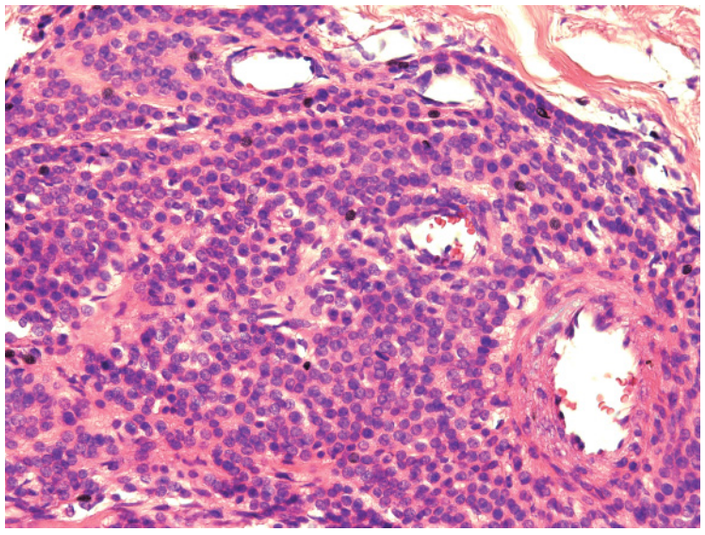
Actin represents a family of intermediate filaments present in the cytoskeleton of eukaryotic cells. They are contractile proteins involved in the control of motility of muscle cells and non-muscle cells. Actin proteins are classified according to their amino acid sequences, and six major isoforms have been described. Of the monoclonal antibodies used in diagnostic pathology the most useful ones are HHF35 (muscle-specific actin) and 1A4 (alpha-smooth-muscle actin) [47–49]. The former reacts with skeletal and smooth muscle and the latter only reacts with smooth muscle. Both types of antibody stain myofibroblasts, pericytes, glomus cells (Fig. 10.19a & b) and myoepithelial cells [48].

Calponin is a basic troponin-T like protein that modulates the interaction between actin and myosin and it is a good marker of smooth muscle and myofibroblastic differentiation [50].

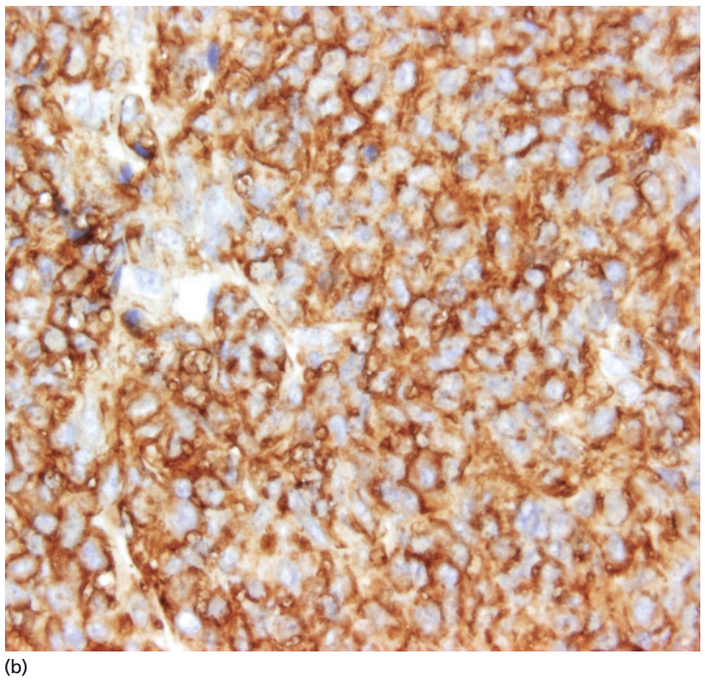
H-caldesmon is a protein combined with actin and tropomyosin that regulates cell contraction. It is fairly specific for smooth-muscle differentiation and less often stains myofibroblasts [51,52].

CD34 is a glycosylated transmembrane protein with a molecular weight of 110 kDa. It is normally present on haematopoietic progenitor cells and vascular endothelial cells [53,54]. This marker, however, is fairly non-specific and it is expressed in a wide number of soft-tissue tumours including dermatofibrosarcoma protuberans (DFSP) (Fig. 10.20a & b), neurofibroma and spindle cell lipoma. Its main use in dermatopathology is as an endothelial cell marker and in the differential diagnosis between DFSP and fibrous histiocytoma and its variants, particularly cellular fibrous histiocytoma. CD34 tends to be diffusely positive in the former and negative or only focally positive, mainly in the periphery of the tumour, in the latter [55,56].

One large group of soft-tissue tumours where useful markers are badly needed is the group of fibrohistiocytic tumours. So-called markers of histiocytic cells, including α-1-antitrypsin and α-1-antichymotripsin, are very non-specific and have no role in the diagnosis of these tumours. Besides, it appears clear that

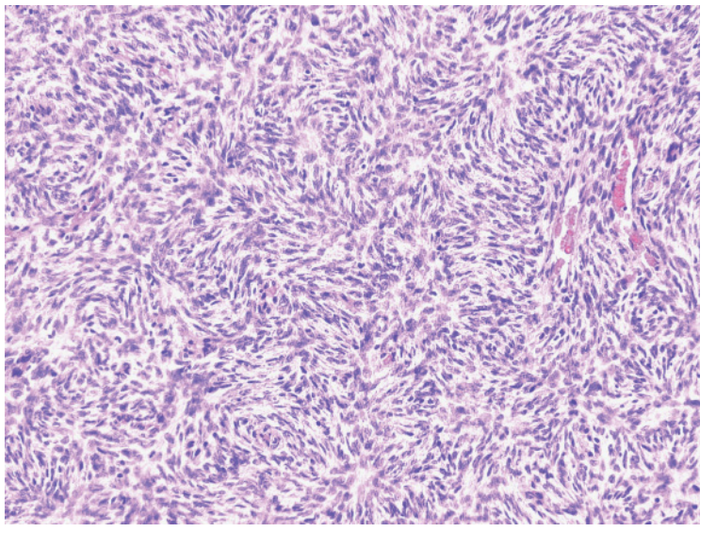


(a)

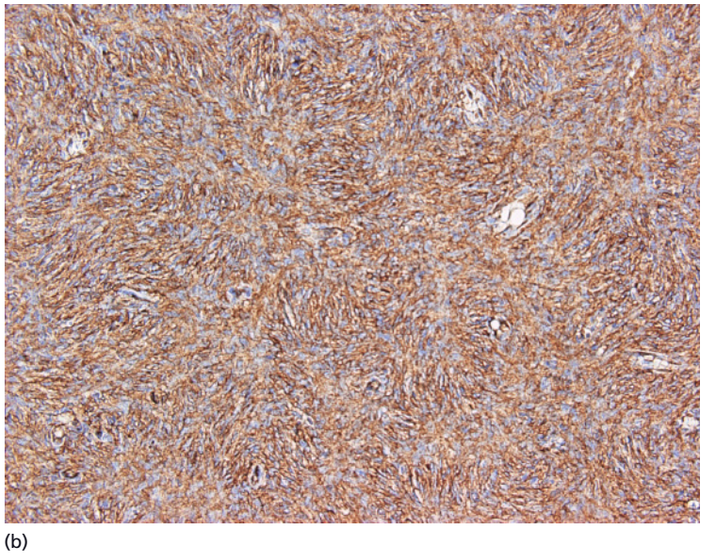


(b)

Fig. 10.19 (a) Glomus tumour composed of uniform, round cells with pale cytoplasm and well-defined cytoplasmic membrane. (b) Strong cytoplasmic staining for smooth-muscle actin in a case of glomus tumour.



(a)



(b)

Fig 10.20 (a) Typical dermatofibrosarcoma protuberans composed of monotonous, spindle-shaped cells with hyperchromatic nuclei arranged in a prominent storiform pattern (H&E). (b) Diffuse staining of tumour cells for CD34.

the so-called fibrohistiocytic tumours usually do not show true histiocytic differentiation. Another interesting polyclonal antibody produced against the blood coagulation transglutaminase, factor XIIIa, seems to be a cell marker for a particular subpopulation of dermal dendritic mononuclear macrophage cells termed dermal dendrocytes [57]. A number of positive cells may be identified in very many different types of soft-tissue tumours. However, combined with other markers, FXIIIa is useful in the differential diagnosis between benign fibrous histiocytoma and DFSP. The former is normally rich in factor XIIIa positive cells particularly at the periphery, in contrast to DFSP which is negative.

A wide range of endothelial markers now available are useful in the histological diagnosis of vascular tumours. The most useful of these markers are CD31, CD34, FVIII-related antigen and Fli-1. There is also an expanding range of markers of lymphatic endothelium, some of which are quite specific (see below).

CD31 refers to a glycoprotein that belongs to the immunoglobulin supergene family and has a molecular weight of 130 kDa. It is also known as platelet-endothelial cell adhesion molecule type I (PECAM-1) and it stains endothelial cells and some haematopoietic cells. CD31 is the most sensitive marker of endothelial cells [58–60]. However, interpretation should be cautious as CD31 also stains macrophages [61].

Antibodies to factor VIII-related antigen label normal and neoplastic endothelium in routine paraffin sections [62]. This marker, however, may be negative in lymphatic capillaries, and because of the presence of factor VIII-related antigen in plasma and tissue exudates, false positive labelling may be encountered.

Fli-1 (friend leukaemia virus integration 1) is a DNA binding transcription factor member of the ETS gene family. Most cases of Ewing's sarcoma (90%) show a translocation t(11;22)(q24;q12) indicating fusion of EWS with Fli-1. Fli-1 is also expressed in endothelial cells and is a useful and fairly specific marker of endothelial cell differentiation [63]. The positive product displays nuclear staining.

None of the previously described endothelial cell markers allows distinction between lymphatic and vascular endothelium. In recent years, a number of antibodies have been described with claims as to their specificity for lymphatic endothelium. These antibodies include vascular endothelial growth factor receptor-3 (VEGFR-3), podoplanin, LYVE-1 (lymphatic vessel endothelial hyaluronan receptor) and Prox-1 (a nuclear transcription factor important in lymphangiogenesis) [64–70]. Some of these markers are not very specific of lymphatic differentiation, particularly VEGFR-3 [64].

Metastatic cutaneous tumours

It is important to remember that all tumours that are present in the skin are not necessarily of cutaneous origin. Reference has already been made to several epithelial markers, many of which may be useful in diagnosing metastatic adenocarcinoma. Immunohistochemistry, however, does not usually allow determination of the site of the primary tumour except in a few instances. The latter include prostate-specific antigen in prostatic carcinoma and thyroglobulin in thyroid carcinoma. Markers for oestrogen and progesterone receptors are not useful in the diagnosis of metastatic breast carcinoma, because adnexal carcinomas may also be positive for one or both markers. Combination of a number of markers may often be useful, however, in determining whether a tumour is primary or metastatic. Thyroid transcription factor-1 (TTF-1) is a 38-kDa nuclear protein expressed in epithelial cells of lung and thyroid. TTF-1 is therefore a useful marker in the diagnosis of cutaneous metastatic tumours [71]. p63, a homologue of the p53 gene, has been demonstrated to be useful in the differential diagnosis between primary and metastatic adenocarcinomas in the skin. Metastatic adenocarcinomas to the skin are usually negative for p63 while primary adnexal adenocarcinomas tend to be positive for this marker [72,73]. Similar findings are obtained in adnexal carcinomas metastatic to other organs. The same finding has been recently reported with podoplanin as metastatic adenocarcinomas to the skin tend to be negative in tumour cells while tumour cells in primary adnexal carcinomas are positive for this marker [74].

Histiocytic markers

CD68 (KP1) is the main marker used to demonstrate histiocytic differentiation in paraffin-embedded material [75,76]. It is an antibody raised against a 110-kDa glycoprotein present in pulmonary macrophages. This antibody stains normal histiocytes, granulocyte precursors, tumour cells in myelomonocytic neoplasms and true histiocytic lymphomas. KP1, however, is not specific for histiocytic differentiation, and expression may be seen in many tumours, including carcinoma, melanoma, granular cell tumours and a variety of sarcomas [77–79]. A more specific marker of histiocytic differentiation is PG-M1, a member of the CD68 group of proteins, which is present only in macrophages and not in myeloid cells [80,81]. Further markers of histiocytic differentiation that are poorly specific are lysozyme and Mac387.

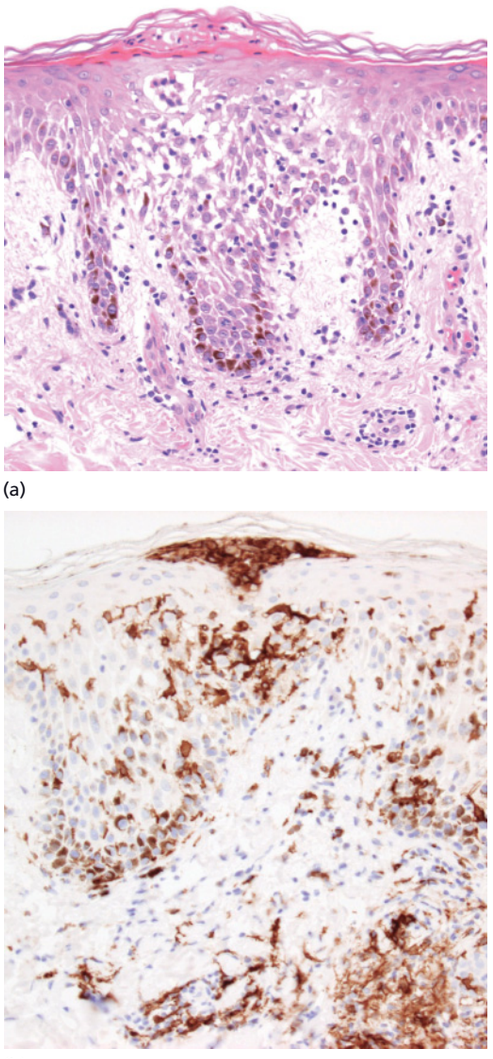
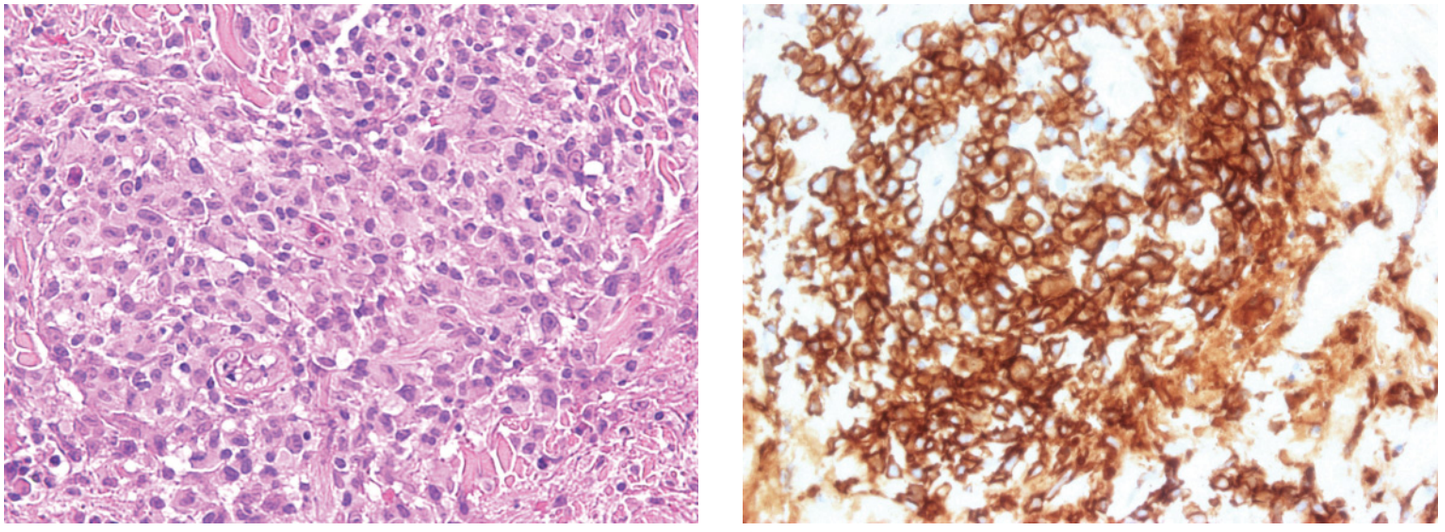


Fig. 10.21 (a) Subacute spongiotic process (eczema) with hyperplasia of Langerhans' cells presenting in a large nest within the epidermis mimicking a Pautrier microabscess (H&E). (b) Staining for CD1a highlighting the nature of the nested cells within the epidermis.

Langerhans' cell markers

The main markers of Langerhans' cells are S-100 and CD1a. More recently, langerin (CD207, a Langerhans' cell specific lectin) has been introduced as a sensitive and specific marker of Langerhans' cells as is CD1a [82,83]. S-100 is very sensitive but poorly specific, particularly as it stains melanocytes. Both the latter and Langerhans' cells are present in healthy and abnormal epidermis. Often, in inflammatory conditions, there is hyperplasia of Langerhans' cells within the epidermis and they are often arranged in nests. This may lead to the erroneous diagnosis of mycosis fungoides as the nests of cells are confused with Pautrier microabscesses. In this setting, immunohistochemistry for Langerhans' cells (Fig. 10.21a



(a) (b)

Fig. 10.22 (a) Sheets of large, atypical lymphoid cells with pleomorphic nuclei and pink cytoplasm. (b) Positive staining of atypical cells in a case of CD30-positive, anaplastic, large T-cell lymphoma. Note the typical strong cytoplasmic membrane positivity and dot-like perinuclear staining.

& b) and other histological parameters, are useful to make the distinction.

Lymphoid markers

One of the most difficult areas in diagnostic dermatopathology is the interpretation of heavy lymphoid infiltrates in cutaneous biopsies. The wide range of conditions that may produce a histological picture simulating lymphoma ranges from insect bites and viral infections through syphilis, to reactive lymphoid hyperplasia where an aetiological factor cannot be demonstrated. Furthermore, recognition of the number of different varieties of malignant lymphoproliferative disorders that may be encountered in the skin continues to increase. Very many different markers for lymphocytes and their subsets are now available, and are particularly useful when used as a battery. It should be remembered that histological and antibody-labelling patterns of cutaneous lymphomas do not necessarily mirror their nodal counterparts, and that very few markers are absolutely specific for cells of one lineage. Furthermore, it has to be realized that in the course of a disease process, many lymphoid cell types may lose their antigenic determinants and label in an anomalous fashion. This is particularly common in some forms of advanced cutaneous lymphoma. Nevertheless, with careful interpretation and the use of antibody panels, considerable information can be derived from the use of monoclonal antibodies [3].

The rationalization of nomenclature in relation to human leukocyte antigens, the CD (or cluster of differentiation) nomenclature, has been a great advance, enabling useful comparison of numerous different monoclonal antibodies developed in different laboratories, and facilitating their classification [3,84,85]. As in other areas of immunopathology, a further bonus for the diagnostic dermatopathologist is the possibility of using many of these leukocyte antigen markers in paraffin processed tissue [85–87]. A full discussion of the applications of immunopathology to the recognition of subsets of lymphocytes in skin biopsies is beyond the scope of this chapter. Useful antibodies available for use on routinely processed material include CD45 (leukocyte common antigen), pan-B-cell markers such as CD20 (L26) and CD79a, and pan-T-cell markers such as CD3, CD2, CD5 and CD7 [88,89]. Determination of the subset of T cells in paraffin-embedded skin biopsies is also possible, as there are commercially available antibodies to CD4 (helper T cells) and CD8 (cytotoxic T cells) T cells [3,90,91]. Immunohistochemistry is also very useful in the determination of clonality, particularly in B-cell infiltrates. Antibodies against kappa and lambda light chains can be used in paraffin-embedded material to demonstrate clonality [3,92,93]. Monotypic Ig light chain expression is very suggestive of a B-cell lymphoma.

Other markers of interest include determinants closely associated with T-cell activation, such as the CD30 antigen. An example of an antibody to the CD30 epitope is Ber-H2, which identifies activated T cells, B cells and Reed–Sternberg cells. In cutaneous biopsies, it is commonly present in examples of CD30-positive lymphoproliferative disorders, including lymphomatoid papulosis types A and C, and CD30-positive anaplastic large cell lymphoma [94–96] (Fig. 10.22a & b).

Anaplastic lymphoma kinase (ALK) is a marker of the protein that results from translocation 2;5 between the ALK and nucleophosmin. Its usefulness resides in the fact that this protein is expressed in systemic large-cell anaplastic lymphoma, but it is usually not expressed in primary cutaneous large-cell anaplastic CD30-positive lymphomas [97,98].

CD56 (neural cell adhesion molecule) is expressed in the central and peripheral nervous system, and it is also a marker of natural killer (NK) cells. Its main use in dermatopathology is in the diagnosis of cutaneous NK/T-cell lymphoma [99,100]. Some subcutaneous panniculitis-like T-cell lymphomas may also express this marker [101].

TIA-1, granzyme and perforin are cytotoxic proteins present in the cytoplasmic granules of NK and cytotoxic T cells. Expression of these proteins can be demonstrated in paraffin-embedded material and this is useful in the diagnosis of NK or cytotoxic lymphomas [102,103].

Markers of B follicle-centre cells such as CD10 and bcl-6, although not entirely specific, are useful in demonstrating the presence of these cells in the skin. Positive staining does not indicate that the cells are neoplastic but that they are of follicle-centre origin [104–106]. Reactive cutaneous germinal centres are positive for these markers. On the other hand, an infiltrate with follicle-centre cells which are positive for bcl-2 is very suggestive of a follicle-centre cell lymphoma, and usually indicates the presence of a 14;18 chromosomal translocation [5,107]. Many primary cutaneous follicle-centre cell lymphomas, however, do not stain for this marker and the t(14;18) chromosomal translocation is often absent [108]. It is worth remembering that normal reactive T lymphocytes are usually bcl-2 positive and these tend to be prominent in B-cell infiltrates. Normal mantle B cells are also bcl-2 positive.

More recently, further markers of B-cell differentiation have been described including MUM-1/ITRF4 (multiple myeloma 1/interferon regulatory factor 4) and FOXP-1. MUM-1 is a protein expressed by late centrocytes and post-germinal germinal centres and FOXP-1 is an essential transcriptional regulator of B-cell development [109]. Cutaneous follicle centre cell lymphomas do not tend to express either MUM-1 or FOXP-1 while diffuse large B-cell lymphoma leg-type tends to be diffusely positive for both markers [109]. In cutaneous marginal zone lymphoma, MUM-1 is only expressed by the neoplastic plasma cells. This pattern of staining, coupled with the other commonly used immunohistochemical markers, is helpful in differential diagnosis [110].

The field of immunopathology in general, and in relation to the study of lymphoid proliferations in particular, continues to grow apace. In addition to the techniques discussed above, it is likely that within the next few years further information of use to the diagnostic pathologist will be gained from studies of cytokines, adhesion molecules and similar substances. The correlation of immunophenotypic studies with immunogenotyping using the latest molecular biological techniques is likely to contribute further to our understanding of cutaneous and systemic lymphomas.

References

1 Hudson AR, Smoller BR. Immunohistochemistry in diagnostic dermatopathology. *Dermatol Clin* 1999; **17**: 667–89.

2 Schach CP, Smoller BR, Hudson AR *et al*. Immunohistochemical stains in dermatopathology. *J Am Acad Dermatol* 2000; **43**: 1094–100.

3 His ED, Yegappan S. Lymphoma immunophenotyping: a new era in paraffin-section immunohistochemistry. *Adv Anat Pathol* 2001; **8**: 218–39.

4 George R, Kurian S, Jacob M *et al*. Diagnostic evaluation of the lupus band test in discoid and systemic lupus erythematosus. *Int J Dermatol* 1995; **35**: 170–3.

5 Zecevic RD, Paulovic MD, Stefanovic D. Lupus band test and disease activity in systemic lupus erythematosus: does it matter? *Clin Exp Dermatol* 2006; **31**: 358–60.

6 Kelly SE, Wojnarowska F. The use of chemically split tissue in the detection of circulating anti-basement zone antibodies in bullous pemphigoid and cicatricial pemphigoid. *Br J Dermatol* 1988; **118**: 31–40.

7 Kottke MD, Delva E, Kowalczyk AP. The desmosome: cell science lessons from human disease. *J Cell Sci* 2006; **119**: 797–806.

8 Sitaru C, Zilliken D. Mechanisms of blister induction by autoantibodies. *Exp Dermatol* 2005; **14**: 861–75.

9 Ordonez NG. Application of immunocytochemistry in the diagnosis of soft tissue sarcomas: a review and update. *Adv Anat Pathol* 1998; **5**: 67–85.

10 Moll R, Franke WW, Schulter DL *et al*. The catalog of human cytokeratins: patterns of expression in normal epithelia, tumors and cultured cells. *Cell* 1982; **31**: 11–24.

11 Cooper D, Schermer A, Sun TT. Classification of human epithelia and their neoplasms using monoclonal antibodies to keratins: strategies, applications and limitations. *Lab Invest* 1985; **52**: 243–56.

12 Leder M, Patel J, Makin C *et al*. An analysis of the sensitivity and specificity of the cytokeratin marker CAM 5.2 for epithelial tumors: results of a study of 203 sarcomas, 40 carcinomas and 28 malignant melanomas. *Histopathology* 1996; **10**: 1315–24.

13 Moll I, Kuhn C, Moll R. Cytokeratin 20 is a general marker of cutaneous Merkel cells, while certain neuronal proteins are absent. *J Invest Dermatol* 1995; **104**: 910–5.

14 Chan JK, Suster S, Wenig BM *et al*. Cytokeratin 20 immunoreactivity distinguishes Merkel cell (primary cutaneous neuroendocrine) carcinomas and salivary gland small cell carcinomas from small cell carcinomas of various sites. *Am J Surg Pathol* 1997; **21**: 226–34.

15 Smith KJ, Tuur S, Corvette D *et al*. Cytokeratin 7 staining in mammary and extramammary Paget's disease. *Mod Pathol* 1996; **10**: 1069–74.

16 Williamson JD, Colome MI, Sahin A *et al*. Pagetoid bowen disease: a report of 2 cases that express cytokeratin 7. *Arch Pathol Lab Med* 2000; **124**: 427–30.

17 Mai KT, Alhalouly T, Landry D *et al*. Pagetoid variant of actinic keratosis with or without squamous cell carcinoma of sun-exposed skin: a lesion simulating extramamary Paget's disease. *Histopathology* 2002; **41**: 331–6.

18 Al-Abbadi MA, Almasri NM, Al-Quran S *et al*. Cytokeratin and epithelial membrane expression in angiosarcoma: an immunohistochemical study of 33 cases. *Arch Pathol Lab Med* 2007; **131**: 288–92.

19 Srivastava A, Rosenberg AE, Selig M *et al*. Keratin-positive Ewing's sarcoma: an ultrastructural study of 12 cases. *Int J Surg Pathol* 2005; **13**: 43–50.

20 Humble SD, Prieto VG, Horenstein MG. Cytokeratin 7 and 20 expression in epithelioid sarcoma. *J Cutan Pathol* 2003; **30**: 242–6.

21 Iwata J, Fletcher CD. Immunohistochemical detection of cytokeratin and epithelial membrane antigen in leiomyosarcoma: a systematic study of 100 cases. *Pathol Int* 2000; **50**: 7–14.

22 Heyderman E, Steele K, Ormerod MG. A new antigen on the epithelial membrane: its immunoperoxidase localisation on normal and neoplastic tissue. *J Clin Pathol* 1979; **32**: 35–9.

23 Chittal SM, Al Saati T, Delsol G. Epithelial membrane antigen in hematolymphoid neoplasms: a review. *Appl Immunohistochem* 1997; **5**: 203–15.

24 Metze D, Grunert F, Neumaier M *et al*. Neoplasms with sweat gland differentiation expressed various glycoproteins of the carcinoembryonic antigen (CEA) family. *J Cutan Pathol* 1996; **23**: 1–11.

25 Vinores SA, Bonnin JM, Rubinstein LJ *et al*. Immunohistochemical demonstration of neuron-specific enolase in neoplasms of the CNS and other tumors. *Arch Pathol Lab Med* 1984; **108**: 536–40.

26 Llombart B, Monteagudo C, López-Guerrero JA *et al*. Clinicopathological and immunohistochemical analysis of 20 cases of Merkel cell carcinoma in search of prognostic markers. *Histopathology* 2005; **46**: 622–34.

27 Wiedenmann B, Franke WW, Kuhn C *et al*. Synaptophysin: a marker protein for neuroendocrine cells and neoplasms. *Proc Natl Acad Sci USA* 1986; **83**: 3500–4.

28 Dunphy CH, DeMello DE, Gale GB. Pediatric CD56+ anaplastic large cell lymphoma: a review of the literature. *Arch Pathol Lab Med* 2006; **130**: 1859–64.

29 Kahn HJ, Baumal R, Marks A. The value of immunohistochemical studies using antibody to S100 protein in dermatopathology. *Int J Dermatol* 1984; **23**: 38–44.

30 Loeffel SC, Gillespie GY, Mirmiran SA *et al*. Cellular immunolocalization of S100 protein within fixed tissue sections by monoclonal antibodies. *Arch Pathol Lab Med* 1985; **109**: 117–22.

31 Nakajima T, Watanabe S, Sato Y *et al*. An immunoperoxidase study of S-100 protein distribution in normal and neoplastic tissues. *Am J Surg Pathol* 1982; **6**: 715–27.

32 Argenyi ZB, Cain C, Bromley C *et al*. S-100 protein negative malignant melanoma: fact or fiction? A light microscopic and immunohistochemical study. *Am J Dermatopathol* 1994; **16**: 233–40.

33 Smoller BR, McNutt NS, Hsu A. HMB-45 recognizes stimulated melanocytes. *J Cutan Pathol* 1989; **16**: 49–53.

34 Wick MR, Swanson PE, Rocamora A. Recognition of malignant melanoma by monoclonal antibody HMB-45: an immunohistochemical study of 200 paraffin-embedded cutaneous tumours. *J Cutan Pathol* 1988; **15**: 201–7.

35 Ordonez NG, Ji XL, Hickey RC. A comparison of HMB-45 monoclonal antibody and S-100 protein in the immunohistochemical diagnosis of melanoma. *Am J Clin Pathol* 1998; **90**: 385–90.

36 Jungbluth AA, Busam KJ, Gerald WL *et al*. A103, an anti Melan-A monoclonal antibody for the detection of malignant melanoma in paraffin-embedded tissues. *Am J Surg Pathol* 1998; **22**: 595–602.

37 Busam KJ, Jungbluth AA. Melan-A, a new melanocytic differentiation marker. *Adv Anat Pathol* 1999; **6**: 12–8.

38 El Shabrawi-Caelen L, Kerl H, Cerroni L. Melan-A: not a helpful marker in distinction between melanoma *in situ* on sun-damaged skin and pigmented actinic keratosis. *Am J Dermatopathol* 2004; **26**: 364–6.

39 Bhawan J. Mel-5: a novel antibody for differential diagnosis of epidermal pigmented lesions of the skin in paraffin-embedded sections. *Melanoma Res* 1997; **7**: 43–8.

40 King R, Googe PB, Weilbaecher KN *et al*. Microphthalmia transcription factor expression in cutaneous benign, malignant melanocytic and nonmelanocytic tumors. *Am J Surg Pathol* 2001; **25**: 51–7.

41 Busam KJ, Iversen K, Coplan KC *et al*. Analysis of microphthalmia transcription factor expression in normal tissues and tumors, and comparison of its expression with S-100 protein, gp100, and tyrosinase in desmoplastic malignant melanoma. *Am J Surg Pathol* 2001; **25**: 197–204.

42 Shidham VB, Oi D, Rao RN *et al*. Improved immunohistochemical evaluation of micrometastasis in sentinel lymph nodes with 'MCW melanoma cocktail'—a mixture of monoclonal antibodies to Mart-1, Melan-A and tyrosinase. *BMC Cancer* 2003; **3**: 15.

43 Azumi N, Battifora H. The distribution of vimentin and keratin in epithelial and nonepithelial neoplasms: a comparative immunohistochemical study on formalin- and alcohol-fixed tumors. *Am J Clin Pathol* 1987; **88**: 286–96.

44 Ngai J, Capetanari YG, Lazarides E. Expression of the genes coding for the intermediate filament proteins vimentin and desmin. *Ann NY Acad Sci* 1985; **455**: 144–57.

45 Truong LD, Rangdaeng S, Cagle P *et al*. The diagnostic utility of desmin: a study of 584 cases and review of the literature. *Am J Clin Pathol* 1990; **93**: 305–14.

46 Ordonez NG. Antidesmin antibodies: their use in diagnostic pathology. *Am J Clin Pathol* 1990; **93**: 430–1.

47 Gown AM, Vogel AM, Gordon D. A smooth muscle specific monoclonal antibody recognizes smooth muscle actin isoenzymes. *J Cell Biol* 1985; **100**: 807–13.

48 Tsukada T, McNutt MA, Ross R *et al*. HHF35, a muscle specific monoclonal antibody, 2: reactivity in normal, reactive, and neoplastic human tissues. *Am J Pathol* 1987; **127**: 389–402.

49 Azumi N, Ben Ezra J, Battifora H. Immunophenotypic diagnosis of leiomyosarcomas and rhabdomyosarcomas with monoclonal antibodies to muscle specific actin (MSA) and desmin in formalin fixed tissue. *Mod Pathol* 1998; **1**: 469–74.

50 Pérez-Montiel MD, Plaza JA, Domínguez-Malagón H *et al*. Differential expression of smooth muscle myosin, smooth muscle actin, h-caldesmon, and calponin in the diagnosis of myofibroblastic and smooth muscle lesions of skin and soft tissue. *Am J Dermatopathol* 2006; **28**: 105–11.

51 Ceballos KM, Nielsen GP, Selig MK *et al*. Is anti h-caldesmon useful for distinguishing smooth muscle and myofibroblastic tumors? An immunohistochemical study. *Am J Clin Pathol* 2000; **114**: 746–53.

52 Watanabe K, Kusakabe T, Hoshi N *et al*. h-Caldesmon in leiomyosarcoma and tumors with smooth muscle cell-like differentiation: its specific expression in the smooth muscle cell tumor. *Hum Pathol* 1999; **30**: 392–6.

53 van de Rijn Rouse RV. CD34: a review. *Appl Immunohistochem* 1994; **2**: 71–80.

54 Ramani P, Bradley NJ, Fletcher CDM. QBEND/10, a new monoclonal antibody to endothelium: assessment of its diagnostic utility in paraffin sections. *Histopathology* 1990; **17**: 237–42.

55 Abenoza P, Lillemoe T. CD34 and Factor XIIIa in differential diagnosis of dermatofibroma and dermatofibrosarcoma protuberans. *Am J Dermatopathol* 1993; **15**: 429–34.

56 Aiba S, Tabata N, Ishii H *et al*. Dermatofibrosarcoma protuberans is a unique fibrohistiocytic tumour expressing CD34. *Br J Dermatol* 1992; **127**: 79–84.

57 Cerio R, Griffiths CEM, Cooper KD *et al*. Characterisation of factor XIIIa positive dermal dendritic cells in normal and inflamed skin. *Br J Dermatol* 1989; **121**: 421–31.

58 Newman PJ, Berndt MC, Gorski J *et al*. PECAM-1 (CD31) cloning and relation to adhesion molecules in the immunoglobulin gene superfamily. *Science* 1990; **247**: 1219–22.

59 Parums DV, Cordell JL, Micklem K *et al*. JC70: a new monoclonal antibody that detects vascular endothelium associated antigen on routinely processed tissue sections. *J Clin Pathol* 1990; **43**: 752–7.

60 De Young BR, Wick MR, Fitzgibbon JF *et al*. CD31: an immunospecific marker for endothelial differentiation in human neoplasms. *Appl Immunohistochem* 1993; **1**: 97–100.

61 McKenney JK, Weiss SW, Folpe AL. CD31 expression in intratumoral macrophages: a potential diagnostic pitfall. *Am J Surg Pathol* 2001; **25**: 1167–73.

62 Leader M, Collins M, Patel J *et al*. Staining for Factor VIII-related antigen and *Ulex europaeus* agglutinin I (UEA-I) in 230 tumors: an assessment of their specificity for angiosarcoma and Kaposi's sarcoma. *Histopathology* 1986; **10**: 1153–62.

63 Folpe AL, Veikkola T, Valtola R *et al*. Vascular endothelial growth factor receptor-3 (VEGFR-3): a marker of vascular tumors with presumed lymphatic differentiation, including Kaposi's sarcoma, kaposiform and Dabska-type hemangioendotheliomas, and a subset of angiosarcomas. *Mod Pathol* 2000; **13**: 180–5.

64 Partanen TA, Alitalo K, Miettinen M. Lack of lymphatic vascular specificity of vascular endothelial growth factor receptor 3 in 185 vascular tumors. *Cancer* 1999; **86**: 2406–12.

65 Sleeman JP, Krishnan J, Kirkin V *et al*. Markers for the lymphatic endothelium: in search of the holy grail? *Microsc Res Tech* 2001; **55**: 61–9.

66 Jackson DG. The lymphatic revisited: new perspectives from the hyaluronan receptor LYVE-1. *Trends Cardiovasc Med* 2003; **13**: 1–7.

67 Xu H, Edwards JR, Espinosa O *et al*. Expression of a lymphatic endothelial cell marker in benign and malignant vascular tumors. *Hum Pathol* 2004; **35**: 857–61.

68 Kahn HJ, Bailey D, Marks A. Monoclonal antibody D2–40, a new marker of lymphatic endothelium, reacts with Kaposi's sarcoma and a subset of angiosarcomas. *Mod Pathol* 2002; **15**: 434–40.

69 Ordonez NG. Podoplanin: a novel diagnostic immunohistochemical marker. *Adv Anat Pathol* 2006; **13**: 83–8.

70 Reis RM, Reis-Filho JS, Longatto Filho A *et al*. Differential Prox-1 and CD31 expression in mucosae, cutaneous and soft tissue vascular lesions and tumors. *Pathol Res Pract* 2005; **201**: 771–6.

71 Ordonez NG. Thyroid transcription factor-1 is a marker of lung and thyroid carcinomas. *Adv Anat Pathol* 2000; **7**: 123–7.

72 Ivan D, Hafeez Diwan A, Prieto VG. Expression of p63 in primary adnexal neoplasms and adenocarcinoma metastatic to the skin. *Mod Pathol* 2005; **18**: 137–42.

73 Ivan D, Nash JW, Prieto VG. Use of p63 expression in distinguishing primary and metastatic cutaneous adnexal neoplasms from metastatic adenocarcinoma to skin. *J Cutan Pathol* 2007; **34**: 474–80.

74 Liang H, Wu H, Giorgadze TA *et al*. Podoplanin is a highly sensitive and specific marker to distinguish primary skin adnexal carcinomas from adenocarcinomas metastatic to skin. *Am J Surg Pathol* 2007; **31**: 304–10.

75 Pulford KA, Rigney EM, Micklem KJ *et al*. KP1: a new monoclonal antibody that detects monocyte/macrophage associated antigen in routinely processed tissue sections. *J Clin Pathol* 1989; **42**: 414–21.

76 Weiss LM, Arber DA, Chang KL. CD68: a review. *Appl Immunohistochem* 1994; **2**: 2–8.

77 McHugh M, Miettinen M. KP1 (CD68): its limited specificity for histiocytic tumors. *Appl Immunohistochem* 1994; **2**: 186–90.

78 Tsang WY, Chan JK. KP1 (CD68) staining of granular cell neoplasms: is K1 a marker for lysosomes rather than histiocytic lineage? *Histopathology* 1992; **21**: 84–6.

79 Facchetti F, Bertalot G, Grigolato PG. KP-1 (CD68) staining of malignant melanomas. *Histopathology* 1991; **19**: 141–5.

80 Falini B, Flenghi L, Pileri S *et al*. PG-M1 a new monoclonal antibody directed against a fixative-resistant epitope on the macrophage-restricted form of the CD68 molecule. *Am J Pathol* 1993; **142**: 1359–72.

81 Groisman GM, Amar M, Schäfer I. The histiocytic marker PG-M1 is helpful in differentiating histiocytes and histiocytic tumors from melanoma. *Appl Immunohistochem Mol Morphol* 2002; **10**: 205–9.

82 Sholl LM, Hornick JL, Pinkus JL *et al*. Immunohistochemical analysis of langerin in Langerhan's cell histiocytosis and pulmonary inflammatory and infectious diseases. *Am J Surg Pathol* 2007; **31**: 947–52.

83 Dzigiel P, Dolilńska-Krajewska B, Dumańska M *et al*. Coexpression of CD1a, langerin and Birbeck's granules in Langerhans cell histiocytoses (LCH) in children: ultrastructural and immunohistochemical studies. *Folia Histochem Cytobiol* 2007; **45**: 21–5.

84 Boyd AW. Human leukocyte antigens: an update on structure, function and nomenclature. *Pathology* 1987; **19**: 329–37.

85 Linder J. Monoclonal antibodies marking paraffin-embedded lymphocytes. In: DeLellis RA, ed. *Advances in Immunohistochemistry*. New York: Raven Press, 1988: 277–300.

86 Zola H, Swart B, Banham A *et al*. CD molecules 2006—human cell differentiation molecules. *J Immunol Methods* 2007; **319**: 1–5.

87 Norton AJ. Immunophenotyping malignant lymphoma using antibodies effective in routinely processed tissue. *Biotest Bull* 1987; **3**: 121–9.

88 Chadburn A, Knowles DM. Paraffin-resistant antigens detectable by antibodies L26 and polyclonal CD3 predict the B- or T-cell lineage in 95% of diffuse aggressive non-Hodgkin's lymphomas. *Am J Clin Pathol* 1994; **102**: 284–91.

89 Segal GH, Stoler MH, Fishleder AJ *et al*. Reliable and cost-effective paraffin section immunohistology of lymphoproliferative disorders. *Am J Surg Pathol* 1991; **15**: 1034–41.

90 Macon WR, Salhany KE. T-cell subset analysis of peripheral T-cell lymphomas by paraffin section immunohistology and correlation of CD4/CD8 results with flow cytometry. *Am J Clin Pathol* 1998; **109**: 610–7.

91 Williamson SL, Steward M, Milton I *et al*. New monoclonal antibodies to the T cell antigens CD4 and CD8: production and characterization in formalin-fixed paraffin embedded tissue. *Am J Pathol* 1998; **152**: 1421–6.

92 Merz H, Rickers O, Schrimel S *et al*. Constant detection of surface and cytoplasmic immunoglobulin heavy and light chain expression in formalin-fixed and paraffin-embedded material. *J Pathol* 1993; **170**: 257–64.

93 Ashton-Key M, Jessup E, Issacson PG. Immunoglobulin light chain staining in paraffin-embedded tissue using a heat mediated epitope retrieval method. *Histopathology* 1996; **29**: 525–31.

94 Kaudewitz P, Stein H, Burg G *et al*. Atypical cells in lymphomatoid papulosis express the Hodgkin cell-associated antigen Ki-1. *J Invest Dermatol* 1986; **86**: 350–4.

95 Lindholm JS, Barron DR, Williams ME *et al*. Ki-1-positive cutaneous large cell lymphoma of T cell type: report of an indolent subtype. *J Am Acad Dermatol* 1989; **20**: 342–8.

96 Ralfkiaer E, Bosq J, Gatter K *et al*. Expression of Hodgkin and Reed–Sternberg cell associated antigen (Ki-1) in cutaneous lymphoid infiltrates. *Arch Dermatol Res* 1987; **279**: 285–92.

97 Su LD, Schnitzer B, Ross CW *et al*. The t(2;5)-associated p80 NPM/ALK fusion protein in nodal and cutaneous CD30$^+$ lymphoproliferative disorders. *J Cutan Pathol* 1997; **24**: 597–603.

98 DeCoteau JF, Butmarc JR, Kinney MC *et al*. The t(2;5) chromosomal translocation is not a common feature of primary cutaneous CD30$^+$ lymphoproliferative disorders: comparison with anaplastic large-cell lymphoma of nodal origin. *Blood* 1996; **87**: 3437–41.

99 Tsang WY, Chan JK, Ng CS *et al*. Utility of a paraffin section-reactive CD56 antibody (123C3) for characterization and diagnosis of lymphomas. *Am J Surg Pathol* 1996; **20**: 202–10.

100 Chan JK. Peripheral T-cell and NK-cell neoplasms: an integrated approach to diagnosis. *Mod Pathol* 1999; **12**: 177–99.

101 Salhany KE, Macon WR, Choi JK *et al*. Subcutaneous panniculitis-like T-cell lymphoma: clinicopathologic, immunophenotypic, and genotypic analysis of alpha/beta and gamma/delta subtypes. *Am J Surg Pathol* 1998; **22**: 881–93.

102 Kumar S, Krenacs L, Medeiros J *et al*. Subcutaneous panniculitic T-cell lymphoma is a tumor of cytotoxic T lymphocytes. *Hum Pathol* 1998; **29**: 397–403.

103 Felgar RE, Macon WR, Kinney MC *et al*. TIA-1 expression in lymphoid neoplasms. Identification of subsets with cytotoxic T lymphocytes or natural killer cell differentiation. *Am J Pathol* 1997; **150**: 1893–900.

104 Arber DA, Weiss LM. CD10: a review. *Appl Immunohistochem* 1997; **5**: 125–40.

105 McIntosh GG, Lodge AJ, Watson P *et al*. NCL-CD10–270: a new monoclonal antibody recognizing CD10 in paraffin embedded-tissue. *Am J Pathol* 1999; **154**: 77–82.

106 Cattoretti G, Chang CC, Cechova K *et al*. BCL-6 protein is expressed in germinal-center B cells. *Blood* 1995; **86**: 45–53.

107 Weiss LM, Warnke RA, Sklar J *et al*. Molecular analysis of the t(14;18) chromosomal translocation in malignant lymphomas. *N Engl J Med* 1987; **317**: 1185–9.

108 Child FJ, Russell-Jones R, Woolford AJ *et al*. Absence of the t(14;18) chromosomal translocation in primary cutaneous B-cell lymphoma. *Br J Dermatol* 2001; **144**: 735–44.

109 Hu H, Wang B, Borde M *et al*. Foxp 1 is an essential transciption regulator of B cell development. *Nat Immunol* 2006; **7**: 819–26.

110 Hoefragel JJ, Mulder MM, Dreef E *et al*. Expression of B-cell transcription factors in primary cutaneous B cell lymphoma. *Mod Pathol* 2006; **19**: 1270–6.

Other special laboratory techniques

Cytodiagnosis and Tzanck smears [1] (Fig. 10.23)

Cytodiagnosis in dermatopathology should not be regarded as a substitute for formal biopsy. The technique has been used as an aid to rapid diagnosis of numerous skin conditions, including epithelial tumours, Paget's disease, malignant melanoma, cutaneous lymphomas and skin metastases. In most of these conditions, a diagnostic surgical biopsy rather than fine needle biopsy, is always preferable. Examination of cytological specimens from skin lesions is of most value in bullous disorders, vesicular virus eruptions and basal cell epithelioma.

In blistering disorders, a small, early, uninfected lesion should ideally be selected. The roof of the blister is removed with scissors, and the base of the blister gently scraped with a blunt scalpel so as not to produce bleeding. The material obtained is spread thinly on a glass slide. This is called a Tzanck smear. However, herpes simplex infections cannot be differentiated from herpes zoster using such a simple technique. For cytodiagnosis of suspected basal cell epitheliomas, any surface crust should be removed from ulcerated tumours, and non-ulcerated tumours should be incised with a sharp, pointed scalpel. The incision should be superficial enough to avoid undue bleeding. A sample of tumour is then obtained with either a blunt scalpel or a small curette, and the tissue obtained is pressed between two glass slides. Smears from blisters and basal cell epitheliomas should be fixed immediately for 2 min in absolute alcohol, and stained with H&E. Following rinsing and drying, the smears are cover slipped for microscopic examination.

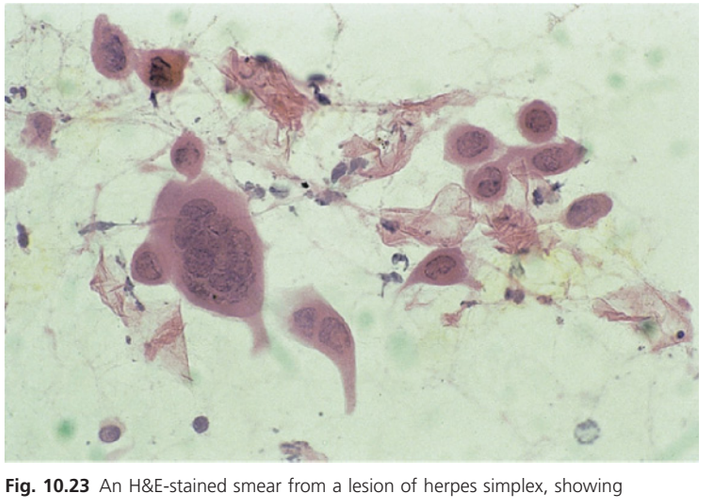


Fig. 10.23 An H&E-stained smear from a lesion of herpes simplex, showing multinucleate giant cells and degenerative nuclear changes.

Microscopic appearances

Bullous disorders. Cytodiagnosis is of most value in pemphigus in its various forms, and in Hailey–Hailey disease, because of the presence of numerous acantholytic keratinocytes. In pemphigus vulgaris, pemphigus vegetans and Hailey–Hailey disease, the cells obtained in the skin smear are usually rounded, and more or less uniform in size, with a relatively large nuclear cytoplasmic ratio. There may be a perinuclear pale halo, with the peripheral part of the cell staining more darkly. In the more superficial forms of pemphigus, including pemphigus foliaceus and Senear–Usher pemphigus, the keratinocytes tend to be more cuboidal in shape, with a small nucleus and more prominent cytoplasm. The cells may contain keratohyalin granules and show evidence of keratinization. Occasional giant cells may be seen, but are quite unlike virus giant cells, which show ballooning degeneration. In addition to the acantholytic disorders mentioned above, occasional acantholytic cells may be obtained in Darier's disease, where dyskeratosis may also be present, and in bullous impetigo. In this latter condition, normally in addition to acantholytic cells there are numerous neutrophil polymorphs and bacteria. The usefulness of cytodiagnosis in subepidermal bullous eruptions is limited, the smear in most instances containing only inflammatory cells. Eosinophils are commonly found in bullous pemphigoid, but may also occur in dermatitis herpetiformis.

Viral disorders. The cytology of herpes simplex, herpes zoster and varicella is often diagnostic because of the presence of characteristic multinucleated giant cells. Keratinocytes of varying size are seen, and as the cell enlarges the nucleus shows some blurring of chromatin pattern and loss of staining. Some of the cells may show condensation of chromatin of the nuclear membrane. The multinucleate giant cells often contain eight or more nuclei, and these nuclei show great variation in size and shape (Fig. 10.23).

Eosinophilic inclusion bodies are very occasionally identified in the herpes virus group of disorders, but commonly examination of many smears may fail to reveal any evidence of this change. Typical ballooning degeneration and giant cell formation as described above does not normally occur in vaccinia or cowpox, but occasionally somewhat enlarged acantholytic cells may be found, and sometimes eosinophilic intracytoplasmic inclusion bodies may be detected. In molluscum contagiosum, characteristic molluscum bodies are easily identified. These are large, rounded, eosinophilic bodies, and may be identified without H&E stain in a potassium hydroxide preparation.

Basal cell carcinoma. In smears obtained from basal cell carcinoma, clumps of closely set, oval or round, deeply basophilic cells are found. The cytoplasm is usually very scanty and in some cases may not be detectable. The nuclei are finely granular with poorly defined nucleoli, and the cells in the smear are very regular in size and shape. In the presence of significant cytological atypia, an alternative diagnosis, such as squamous cell carcinoma or Bowen's disease, should be considered.

Reference

1 Barr RJ. Cutaneous cytology. *J Am Acad Dermatol* 1984; **10**: 163–80.

Electron microscopy

Electron-microscopic examination of cutaneous tissues is performed much less often than light microscopy, and is nowadays rarely used in diagnostic dermatopathology. Electron microscopy has been replaced by antigen mapping by immunohistochemistry in the diagnosis of many genetic disorders, particularly those in the epidermolysis bullosa group. This technique and its applications are described in Chapter 39. Transmission and scanning electron microscopy have greatly increased our understanding not only of the microanatomy of normal skin, but also of many disease processes. The use of newer embedding material has enabled ultrastructural examination to be carried out on single blocks of tissue prepared primarily for light microscopy. With care, even routinely fixed and paraffin-embedded material may produce electron micrographs that provide useful diagnostic information. In recent years, the combination of electron microscopy with immunopathological techniques, autoradiography and cytochemical methods, has greatly enhanced our knowledge of tissue and cell pathophysiology. The contribution of ultrastructural studies to our understanding of normal microanatomy of skin structures and their variants has been referred to in Chapter 3. Below are listed some of the cutaneous disorders where electron microscopy may be of diagnostic help.

Bullous disorders. The classification and subdivision of bullous disorders has been dramatically advanced by electron microscopy and immunoelectron microscopy. With the electron microscope, it is much easier to separate the varieties of epidermolysis bullosa. In epidermolysis bullosa simplex, the plane of cleavage is within the basal cells. Additionally, tonofilament clumping may be seen. Junctional epidermolysis bullosa has various clinical forms, and, although with the electron microscope there is separation in the lamina lucida zone, junctional epidermolysis bullosa is probably a heterogeneous group of disorders. In some forms of this condition, hemidesmosomes are reduced in number, and this may represent a primary defect. In other forms of junctional epidermolysis bullosa, however, hemidesmosomes may be apparently normal. In dystrophic epidermolysis bullosa, again, various abnormalities are observed, but in this case the split is below the lamina densa. Immunoelectron microscopic techniques provide further information in epidermolysis bullosa, and also in some of the other idiopathic blistering disorders. In cicatricial pemphigoid, for instance, immunoreactants may be identified at a lower level in the lamina lucida than in classical bullous pemphigoid. In linear IgA disease, immunoreactants may be found either in the lamina lucida or below it. Sublamina densa deposits of immunoreactants are also seen in epidermolysis bullosa acquisita.

Pigmentary disorders. The quantitative and qualitative evaluation of melanocytes and melanosomes at ultrastructural level can be of great value in the examination of disorders of hyper- and hypopigmentation. In albinism, normal numbers of melanocytes are present, although melanosomes are immature. In vitiligo, a biopsy from affected skin shows either a complete absence or greatly diminished population of melanocytes. In early stages of

vitiligo, some vacuolar degeneration of epidermal melanocytes may be identified.

Cellular identification. In addition to the demonstration of melanocytes, various other cells, both in inflammatory and neoplastic disorders, can be identified clearly with the aid of the electron microscope. The shape of the convoluted nucleus in the peripheral blood from patients with Sézary syndrome is diagnostic. Annulate lamellae, large, dense granules and decapitation secretion are all found ultrastructurally in apocrine secretory cells. Other cellular substructures that may be of diagnostic value are the identification of desmosomes in various epithelia, myofilaments in tumours of muscular origin, the Birbeck granule characteristic of Langerhans' cells, and the Weibel–Palade body found in the endothelial cells of blood vessels.

Identification of dermal deposits. Ultrastructural examination of various forms of amyloidosis shows characteristic deposits of straight, non-branching, non-anastomosing filaments of approximately 6–7 nm in diameter. The apparent increased electron density at their periphery produces a superficial appearance of hollow cylinders. Colloid milia of both the adult and juvenile type may on occasions be confused with amyloid deposition at the light-microscopic level. Ultrastructurally, however, the fibres of colloid milia are of a different thickness to those seen in amyloidosis, and are wavy rather than straight. Other conditions where amorphous hyaline deposits may be seen with the light microscope, such as forms of porphyria and lipoid proteinosis, also have characteristic electron-microscopic appearances.

Viral diseases

Many of the conventional techniques for confirmation of a diagnosis of virus infection, such as virus isolation and culture and the various serological tests, are slow, and the patient has often recovered by the time the diagnosis is established with certainty. Conventional histology either from biopsy or from the scraping of the base of blisters, for instance in herpes simplex or zoster infections, can be useful in experienced hands, but there is quite a high rate of false-negative results. Molecular biological techniques including PCR are more specific, especially for identification of human papillomavirus (HPV) infection, but are not widely available. Direct visualization of virus particles with the electron microscope, using a negative staining technique, can give a positive result within half an hour of a lesion being sampled. This technique has become invaluable for confirmation of diagnosis in disorders caused by many of the main families of viruses, particularly lesions such as herpes simplex and zoster, and hand, foot and mouth disease. Immunohistochemical stains are widely available for various viruses including herpesvirus 1 and 2 and also for cytomegalovirus, and are quite useful in establishing a diagnosis in paraffin embedded sections. Human herpesvirus 8 is a novel type of herpes virus that can be detected in all tumours in patients with Kaposi's sarcoma [1]. A monoclonal antibody raised against the nuclear latent antigen of the virus is very sensitive and specific.

Reference

1 Robin YM, Guillou L, Michel JJ *et al*. Human herpesvirus 8 immunostaining: sensitive and specific method for diagnosis of Kaposi's sarcoma in paraffin-embedded sections. *Am J Clin Pathol* 2004; **121**: 330–4.

Immunogenotyping

In most inflammatory disorders, the lymphocyte population in skin tissue is normally polyclonal, containing progeny of many different parent lymphocytes. In contrast, most lymphomas are monoclonal, with cells being derived from the same parent cell. With the development of DNA probes to detect rearrangements of genes encoding for immunoglobulin and T-cell receptor molecules, it is now a routine technique to assess clonality of T- and B-cell populations by immunogenotyping [1–4]. Refinements in technique mean that significant results can now be obtained from relatively small portions of tissue. The PCR technique is now widely used for the study of clonality in cutaneous lymphoid infiltrates. This subject is discussed in detail in Chapter 57.

References

1 LeBoit PE, Parslow TG. Gene rearrangements in lymphoma. *Am J Dermatopathol* 1987; **9**: 212–8.

2 Weiss LM, Woods GS, Hu E *et al*. Detection of clonal T-cell receptor gene rearrangements in the peripheral blood of patients with mycosis fungoides/Sézary syndrome. *J Invest Dermatol* 1989; **92**: 601–4.

3 Weiss LM, Wood GS, Nickoloff BJ *et al*. Gene rearrangement studies in lymphoproliferative disorders of skin. In: Callen JP, Dahl MV, Golitz LE *et al*., eds. *Advances in Dermatology*, Vol. 3. Chicago: Year Book Medical, 1988: 141–60.

4 Wood GS. T-cell receptor and immunoglobulin gene rearrangements in diagnosing skin disease. *Arch Dermatol* 2001; **137**: 1503–6.

Artefacts (Table 10.6)

The microscopic appearance of the end product produced by processing a tissue specimen is in many ways an artificial representation of what is going on in a complex organ at one point in time. The procedures of biopsy fixation and tissue processing produce significant alterations in size, shape and structure of tissue constituents. We tend to think of fat cells as large, round, empty cells with peripheral nuclei, because this is how we are used to visualizing them microscopically. Cysts that normally contain lipid-rich substances, such as those of steatocystoma multiplex, appear relatively empty when sections from paraffin-embedded material are viewed. The clear halo often seen around melanocytes in the lower layers of the epidermis is at least in part an artefactual change. Some routinely observed tissue artefacts are useful for diagnostic purposes. The so-called separation artefact, where dermal connective tissue separates away from islands of basal cell carcinoma, aids us, for instance, in differentiating a basal cell carcinoma from a trichoepithelioma. In addition to these everyday artefacts, there are a wide range of other changes that may be induced accidentally or by poor processing technique. These changes may in some instances mislead the diagnostic pathologist.

Artefacts due to poor biopsy technique

Undue squeezing of the specimen with forceps can produce a marked artefact, causing the connective tissue to become amorphous and basophilic. Considerable distortion of cellular

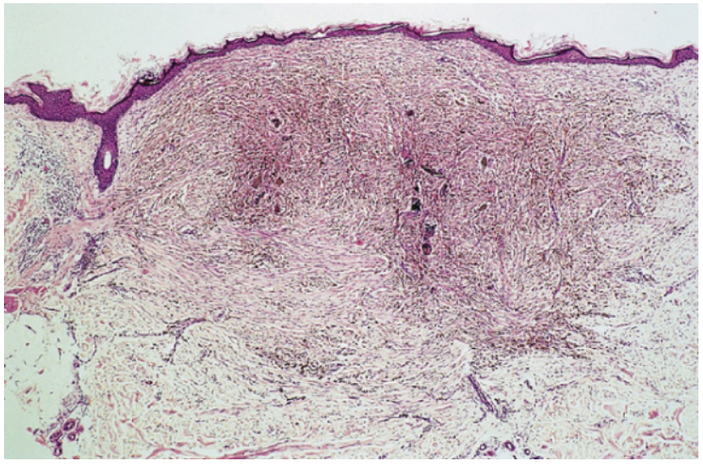


Fig. 10.24 Extensive dermal pigmentation as a result of the application of Monsel's solution.

infiltrates is also seen. Toothed forceps can produce a hole within the tissue specimen, which, although rarely causing diagnostic confusion, is aesthetically unpleasing. When a small tissue specimen is cut up into even smaller pieces, the pressure produced by the knife at the edge of the smaller biopsy portions may lead to connective tissue and cell distortion. It is far better to carry out several small separate biopsies, perhaps with a punch, from the same area than to try and divide a single specimen after it has been removed from the patient. Various techniques of cautery used to secure haemostasis following either a shave biopsy or curettage can lead to unusual histological appearances. Diathermy produces a bizarre alteration of cellular and nuclear morphology, as well as producing a stringy eosinophilic and homogenized appearance to connective tissue. The haemostatic agent, Monsel's solution (20% aqueous ferric subsulphate), can occasionally produce extensive ferrugination of fibrin, dermal collagen and even striated muscle in skin biopsies [1]. The iron pigment deposition can be very confusing and simulate melanin (Fig. 10.24). Particular problems are encountered where this technique is used following shave biopsy of melanocytic naevi. The deposition of this pigment could lead to an erroneous diagnosis of a malignant melanoma [2]. Artefacts may occasionally be induced by local anaesthetic. The epinephrine contained in some local anaesthetics may result in some degranulation of mast cells, and have minor effects on dermal blood vessels, but these are not normally important problems. A large quantity of local anaesthetic, particularly when injected directly into a lesion or superficially in the dermis, can cause appearances simulating marked tissue oedema, or in the case of a cellular naevus, disruption of the normal architecture of the tumour.

Artefacts related to fixation media

It has already been stressed that adequate fixation of skin-biopsy tissue specimens is needed for optimum histological interpretation. Specimens that have been fixed for an insufficient time show poor definition of cell structure and connective tissue. Cells may appear swollen, and staining of such poorly fixed specimens often produces a rather smudged appearance. Similar results may be seen when the specimen has not been placed in the correct fixative, but rather in some inappropriate solution such as normal saline. Formalin pigment may be precipitated out into the tissues in some skin biopsies, particularly where the biopsies have been fixed in a formalin-containing fixative with an acid pH. Formalin pigment artefact is particularly common in biopsies from tissue containing large amounts of haemorrhage, or tissues heavily congested with blood. Even in neutral buffered formal saline, a long fixation may increase the tendency to formalin pigment production. There are some fixatives, such as Zenker's fluid and Heidenhain's Susa, that contain mercuric chloride. Tissues fixed in these media may develop a granular, brownish black deposit. This deposit can be removed, normally by treatment in Lugol's iodine followed by sodium thiosulphate.

Artefacts due to blocking and sectioning

One of the most commonly encountered problems is with the orientation of the specimen. Oblique blocking can give a very misleading picture—for example, suggesting that there is pseudoepitheliomatous hyperplasia of the epidermis or psoriasis, when one is in fact dealing with normal skin. Correct and accurate vertical sectioning and blocking is particularly important where measurements are to be made, such as in the assessment of Breslow thickness and Clark's level of malignant melanoma. Occasionally, fragments of a biopsy adhere to the microtome blade and 'knife carry' may occur, with the result that, for instance, a fragment of basal cell carcinoma may be seen just above the epidermis in a section from a histiocytoma. Normally this artefact is easy to spot, but occasionally it can give rise to confusion. Partial blunting of the microtome knife causes uneven thickness of the histological section. This can give a false impression, both of the density of cellular infiltrates and of the qualities of the connective tissue. Irregularities in the microtome knife edge can cause an unaesthetic artefact known as shatter marks. In the presence of very hard or dense foreign material in the tissues, such as calcium, the foreign material may be drawn through the tissue, forming a tear in the resulting sections.

Artefacts due to staining techniques

It should be remembered that the various staining solutions have a very short shelf-life once made up, and that staining solutions that are old produce a very unsatisfactory end-result. It is also quite common for staining solutions to be contaminated with various foreign materials, such as plant hairs [3] or microorganisms, which may appear to be present within the tissue biopsied, when viewed in the finished mounted preparation.

References

1 Wood C, Severin GL. Unusual histiocytic reaction to Monsel's solution. *Am J Dermatopathol* 1980; **2**: 261–4.

2 Olmstead PM, Lund HZ, Leonard DD. Monsel's solution: a histologic nuisance. *J Am Acad Dermatol* 1980; **3**: 492–8.

3 Pinkus H. Stellate plant hair contaminant in the laboratory. *Arch Dermatol* 1969; **100**: 96–8.

The approach to microscopic examination of tissue sections

Some understanding of the basic principles of microscopy and careful microscope maintenance are essential for optimal visual-

ization of tissue sections, and ultimately therefore for achieving a correct histopathological diagnosis. Knowledge of the techniques and applications of fluorescence microscopy, interference microscopy and polarized light microscopy is also recommended.

Preparing for microscopy

Before using the microscope, some attention should be given to various practical points. Are all the optical surfaces clean? Greasy fingerprints and dust may seriously impair the quality of the image, and before using the microscope all lens surfaces should be cleaned. This may be done with an optical lens tissue. Petroleum spirit is recommended by some manufacturers. Cleaning of objectives with a concave shape can be difficult. A recommended method is to use a small, freshly broken-up piece of expanded polystyrene. It is important that there is no trace of xylene or other organic solvent on an objective treated in this way, or there is a risk of a film of dissolved plastic being left behind.

The microscope light source should be centred, and on most modern microscopes this is easily achieved by a pair of centring screws acting against a spring, or by loosening a screw column and orientating the lamp holder.

The condenser is then adjusted. The aperture diaphragm in the base of the microscope should be closed, and the condenser height adjusted, until the image of the field diaphragm is in focus. The diaphragm should then be centred with adjusting screws. After centring, the field diaphragm should be opened until it just disappears from view. The aperture (substage iris diaphragm) is then adjusted. With experience, this can be done while viewing the image on the slide. Alternatively, an eyepiece can be removed, and while looking down the eyepiece tube the diaphragm is opened until it occupies approximately one-third of the field of view. In this position, the numerical aperture of the condenser is approximately that of the objective in use, and optimum resolution is achieved.

The slide to be examined should then be viewed with the naked eye. Is the specimen a section of solid tissue, or uniformly spread across the slide, like a tissue or cell smear? The size and shape of sections on the slide should be noted, and it may be possible with naked eye examination to identify several tissues. It is important to note the number of sections mounted on one slide, and whether these are likely to represent sections from the same block, or different blocks mounted together. Finally, before putting the slide on the microscope stage, the name or identification number carried by the slide should be correlated with the details on the clinical request form. When inserting the slide into the microscope, make sure that it is the right way up, otherwise it may be impossible to focus the image with higher power objectives.

Microscopic interpretation

Examination of sections

The normal and recommended procedure is to start with lower power examination of the sections and gradually move up to higher power, detailed examination. Low-power scanning examination with a ×2.5 or ×4 objective provides a wealth of information. Identification of tissues is made, orientation of the specimen is possible, and the main site of any pathological changes is often identified. The basic nature of the pathological changes may also be recognized—for example, whether the main pathology represents a neoplastic or inflammatory process. Low-power scanning of all the material on the slide makes it clear whether all sections are from the same block, or whether they represent different portions of tissue. Low-power examination of biopsy material is the first step in the problem-solving exercise, and is the key to good diagnostic dermatopathology. During low-power examination, the site of biopsy and whether this correlates with the clinical information should be evaluated and, secondly, some attempt at pattern diagnosis should be made.

When a foreign body is suspected it is very useful to examine the section under polarized light. This is a quick method of confirming the presence of foreign material within the tissue. However, it is important to emphasize that some endogenous substances polarize and that not all external particles polarize.

Site of biopsy and normal histological variation

Without a working knowledge of the differences in skin microanatomy in the different regions of the body, it is very easy to come to a wrong diagnostic conclusion. For instance, the prominent sebaceous glands seen on facial skin, particularly the nose, may lead to a diagnosis of sebaceous hyperplasia, and the normally thick stratum corneum present on the palms and soles may be interpreted as hyperkeratosis. The following notes describe some of the more typical features seen in skin biopsies from specific sites.

Skin from the palms and soles. In biopsies from these sites, there is a fairly thick Malpighian layer with a thickened basket-weave stratum corneum, and a very prominent epidermal rete ridge pattern. Occasionally, specialized nerve endings (Meissner's corpuscles) may be seen in the dermal papillae. Eccrine sweat glands are fairly numerous, but no pilosebaceous follicles are identified. Vater–Pacini corpuscles are characteristically found in the subcutis. They are large, specialized nerve endings and have an ovoid or round shape with a typical onion ring appearance.

Skin from the areola of the nipple and the scrotum. In these sites, papillomatosis is a common finding, and in the upper dermis there are often numerous small fascicles and fibres of smooth muscle. In biopsies from the areola and nipple, occasional lactiferous ducts may be identified.

Mucous membranes. Histology of mucosal surfaces often shows fairly thick epithelium lacking well-defined keratinization. Focal mild parakeratosis is often seen. The rete ridge pattern normally associated with glabrous skin is not marked, and the cells of the Malpighian layer are large, pale and typically vacuolated.

Axillary skin. In skin from the axillae, papillomatosis of the skin surface is often marked. Abundant hair follicles are present, as are numerous apocrine glands, which are seen in addition to eccrine glands commonly present in other sites.

Scalp skin. Biopsies from the scalp are normally readily identified by the presence of numerous, large hairs (terminal hair follicles) with the hair bulbs frequently in the subcutaneous fat.

Facial skin. Facial skin is characterized by the presence of smaller hair follicles than in the scalp and, particularly in the central facial area, large numbers of mature sebaceous glands. The epidermis is very thin and melanocytes are numerous. The rete ridge pattern at the epidermodermal junction is often very poorly developed, which makes a distinction between papillary and reticular dermis often difficult to assess. *Demodex* organisms may be seen in the ostia of hair follicles and deeper within the sebaceous glands. Muscle may be identified relatively close to the epidermis in certain areas of the face, such as round the eyes or mouth.

Truncal skin. Skin from the trunk shows no very specific histological hallmarks. However, it is normally quite thick, with the distance between the epidermis and the subcutaneous fat being much greater than in biopsies from other sites. Eccrine sweat glands are normally identified at the junction between the dermis and the subcutaneous fat, and may, in skin from the trunk, appear within the reticular dermis itself. The skin from the back contains a very thick dermis with thick collagen bundles in which the ground substance is minimal. This normal pattern is often confused with evidence of a sclerosing dermal process such as morphoea.

Low-power histological pattern diagnosis

Having attempted to recognize the site of the biopsy, and having correlated this with the clinical information, the next task is to interpret any abnormal findings and attempt to come to some diagnostic conclusions. Sometimes, the site of the abnormality in the section is immediately obvious on scanning magnification. This then leads one to examine the appropriate area in more detail. When there is no obvious pathology in the section, a useful approach is to examine each identifiable cutaneous structure in turn. For instance, starting outwards with the stratum corneum and working inwards. Is it increased or decreased in thickness? Is parakeratosis present? Is the pattern of keratinization normal producing a basket-weave pattern, or is the stratum corneum compacted? Examination of the epidermis may reveal atrophy or acanthosis, spongiosis or cell atypicality, and may also reveal colonization of the epidermis by inflammatory or other abnormal cells. Various forms of epidermal degeneration may be noted. Some variants of these are described below. A vesicle or bulla may be present within the epidermis or below it.

Moving on to the dermis, is the arrangement of connective tissue fibres in the papillary and reticular dermis normal, or are the collagen fibres thickened and hyalinized? Is there an increase in interstitial oedema fluid, or is there evidence of increased amounts of mucin separating the collagen bundles? Is the elastic pattern normal? Careful examination of all adnexal structures should be made, and then, finally, any dermal infiltrate should be assessed. The density of the infiltrate, the pattern of the infiltrate (diffuse and interstitial and/or focal and localized) and the composition of the infiltrate are important. The position of the infiltrate in the dermis, whether it is predominantly deep or predominantly involves the epidermis, is also worth noting, as is the relationship of the infiltrate to adnexal structures and blood vessels. The blood vessels themselves should also be examined carefully for evidence, for example, of any vasculitic change or dilatation, increased tortuosity or thickening. A search should be made for any abnormal deposits or pigments such as amyloid, calcium or tattoo pigment. When one has some experience in assessing the different structures in a skin biopsy, one soon learns to recognize certain patterns of neoplastic change and inflammation. Ackerman has described a method of pattern diagnosis appropriate for the study of inflammatory diseases [1]. He suggests recognition of nine major patterns of inflammatory change in the skin, ranging from superficial perivascular dermatitis to panniculitis. Having classified the appearances in the section according to one of these patterns, closer examination enables one to come to a more precise diagnosis. Other authors have described similar schemes of microscopy. The system of pattern analysis can be recommended to those new to dermatopathology. More experienced pathologists have almost always developed their own pattern analysis system.

High-power microscopical examination

By the time one has examined a histological section with a ×2.5 objective, a ×4 to ×8 objective depending on personal preference, and a ×10 objective, one should have some idea in most cases of a differential diagnosis. High-power examination with ×25, ×40 or ×50 and sometimes with a ×100 oil-immersion lens provides an opportunity to confirm one's initial impressions.

Under high-power examination, one examines carefully cells and other structures in the skin in various specific ways. When dealing with neoplastic disorders, the cytology of individual tumour cells, with particular reference to nuclear detail and the variation in size and shape between cells of the same population should be studied. The number of mitotic figures and the number of abnormal mitoses are noted. The pattern of relationship of tumour cells to each other is also an important feature. Loss of polarity of keratinocytes in squamous epithelium is a characteristic feature associated with premalignant epithelial dysplasias, such as Bowen's disease and actinic keratoses, although it can of course also occur in invasive epithelial tumours. The relationship of tumour cells to neurovascular bundles is also important, and the pattern of neoplastic cells in relation to dermal connective tissue should also be evaluated. The so-called Indian-filing pattern of tumour cells lining up one behind another, sandwiched between collagen bundles, is in some contexts suggestive of malignant disease.

In inflammatory conditions under high-power examination, there is an opportunity to try and categorize the different types of cells in the infiltrate. It is important to look over the whole section, as in some areas the infiltrate may be composed of one cell type and in other areas another cell type may predominate. Some infiltrates are composed of almost pure populations of, for example, lymphocytes, and are described as monomorphic, whereas other infiltrates are composed of plasma cells, histiocytes, lymphocytes and eosinophils, and are described as polymorphic. It is only with experience that one becomes confident in recognizing the cytology of cutaneous infiltrates, and one must remember that in some biopsy material, cells may be seen that are impossible to classify by conventional criteria. The following notes describe the more typical appearances of commonly seen inflammatory and related cells, and describe some of the situations where they may be encountered.

Lymphocytes

Lymphocytes originate in the bone marrow and mature through a series of stages both in the bone marrow and the thymus gland, before being released into the peripheral blood and body tissues. The family of lymphocytes is a very heterogeneous one, with many subtypes of lymphocytes. T lymphocytes and B lymphocytes are indistinguishable by normal light microscopy, although on scanning electron microscopy *in vitro* B lymphocytes appear to have rather rougher surfaces than T lymphocytes, and show villous projections. On light-microscopic examination of sections stained with H&E, lymphocytes are roughly 7–12 µm in diameter, and possess small, round, deeply basophilic nuclei, surrounded by a thin rim of cytoplasm, which is usually very difficult to visualize. Numerous immunohistochemical methods are available that readily distinguish T and B lymphocytes, and most of these methods can be carried out using paraffin-embedded sections. In the majority of inflammatory conditions affecting the skin where a significant dermal infiltrate is seen, T cells outnumber B cells. Mature T and B cells are, of course, not the only lymphoid cells that may be found in the skin. In addition to plasma cells (see below), various follicular centre cells and T and B immunoblasts may be seen under certain conditions.

Plasma cells

Plasma cells are responsible for immunoglobulin production. They are a variety of B lymphocyte, approximately 10 µm in diameter, that have a distinct appearance in H&E-stained sections. They have abundant basophilic cytoplasm with a round, eccentrically placed nucleus. The nuclear chromatin is scattered in coarse clumps at the periphery of the nucleus giving it a 'clock face' appearance. Closely adjacent to the nucleus there is a zone of pallor in the cytoplasm, sometimes called the perinuclear hof. This area corresponds to the site where the Golgi apparatus is located. Older plasma cells often contain homogeneous eosinophilic globules of varying size within their cytoplasm, known as Russell bodies. Plasma cells are seen in many situations in the skin, particularly in inflammatory conditions affecting hairy areas, near mucous membranes and in the late stages of some granulomas.

Neutrophils

Neutrophils are the most numerous of the circulating white blood cells, comprising in normal individuals 50–70% of the blood leukocytes. They have a multilobed nucleus (three to four), with the lobes connected by narrow bridges of nucleoplasm. The slightly basophilic cytoplasm contains many smallish granules, many of which ultrastructurally correspond to membrane-bound lysosomes. Neutrophils function primarily as phagocytes, and are directed by chemotactic factors, including the complement cascade to noxious materials present in tissue. Such foreign materials include bacteria, fungi and tissues that have been injured. Collections of neutrophils may be seen in the skin in various infectious conditions, such as impetigo and staphylococcal folliculitis, in various inflammatory disorders of unknown cause, such as pyoderma gangrenosum and Sweet's syndrome, and in various vasculitic disorders, including leukocytoclastic vasculitis, granuloma faciale and erythema elevatum diutinum.

Eosinophils

Eosinophils, like neutrophils, originate in the bone marrow, but are rather larger than neutrophils, being 12–17 µm across. The nucleus of the eosinophil is usually bilobed, and the cytoplasm is filled with eosinophilic granules that are larger than the granules found in neutrophil leukocytes. Eosinophils are highly phagocytic, capable of ingesting various bacteria, fungi, immune complexes and inert particles and, like neutrophils, eosinophils contain hydrolytic and proteolytic enzymes contained in membrane-bound granules. Eosinophils are seen in skin biopsies in certain infections, in reactions to insect bites and other foreign bodies, in some drug reactions, and in bullous eruptions such as bullous pemphigoid, and some forms of pemphigus. They are of major importance in the condition known as eosinophilic cellulitis, and may also occur in association with proliferations of cells of the lymphoid series in certain cutaneous T-cell lymphomas.

Histiocytes/monocytes/tissue macrophages

The term histiocyte is used by different authors to mean different things, and is an unsatisfactory term. Monocytes circulating in the blood may be attracted into the skin for the purposes of phagocytosis. They are then called histiocytes or tissue macrophages. However, many other mesenchymal cells and cells of the granulocyte series are also capable of phagocytosis. The appearances of a histiocyte vary considerably. Many of the cells are fairly large with a lightly staining, sometimes vesicular, elongated nucleus. The cytoplasm is usually pale and cell margins may be indistinct. The cells may be dendritic, spindle-shaped or epithelioid, taking on the latter form particularly in epithelioid cell granulomas. The size of histiocytes is also very variable, ranging from 15 to 25 µm. Compared with some of the cells described above, they are less easy to identify, particularly for the novice, in skin biopsies, and immunohistological methods are often necessary to demonstrate histiocyte subsets. Several factor XIIIa-positive, dendritic phagocytes (dermal dendrocytes) are seen in close proximity to the superficial microvascular plexus. These cells, together with other immune cells, mast cells and endothelial cells, probably collaborate to coordinate antigen presentation, induction of cellular inflammation, wound healing and haemostasis in this microenvironment. Various histiocytes are found in a wide range of inflammatory and neoplastic disorders, but are particularly important in the production of granulomatous inflammation, both in conditions such as granuloma annulare, and in response to cutaneous infection such as mycobacteria.

Giant cells

Many types of giant cell may be recognized in skin tissues. The three best known are the Langhans' giant cell, the foreign-body giant cell and the Touton giant cell. All these giant cells are derived from tissue macrophages, and forms intermediate between the different characteristic types are sometimes seen. The size of these cells varies greatly, but is usually of the order of between 40 and 120 µm. Langhans' giant cells show a characteristic horse-shoe distribution of the nuclei arranged at the cell periphery. They are most characteristically seen in sarcoidosis and tuberculosis.

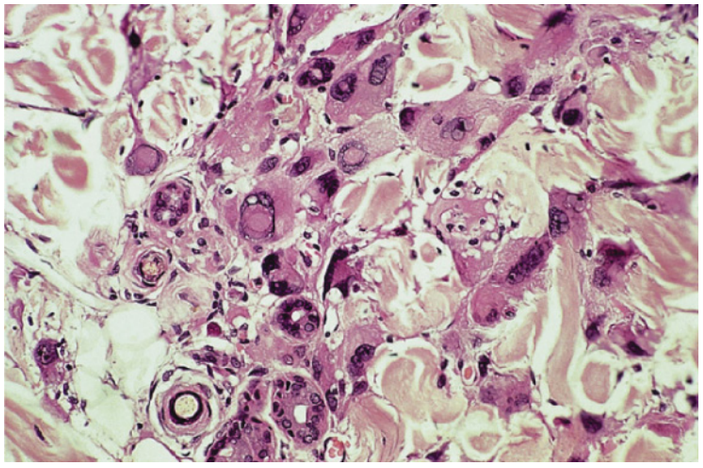


Fig. 10.25 Bizarre multinucleated giant cells from a Spitz naevus.

Foreign-body giant cells contain a haphazard arrangement of nuclei scattered throughout the cell cytoplasm, and may also contain foreign material. Although typically seen in foreign-body granulomas, they are common in other forms of granulomatous inflammation and in situations where there is disruption of pilosebaceous follicular structures with keratin release into the dermal connective tissue. Touton giant cells have a central ring of nuclei enclosing a layer of ground-glass cytoplasm, with a peripheral zone of clearer cytoplasm. They are typically seen in some xanthomas and juvenile xanthogranuloma.

It should be noted that many other forms of giant cell are seen, such as the fairly typical giant cell with scattered nuclei, prominent nucleoli and PAS-positive cytoplasm in multicentric reticulohistiocytosis. Not all giant cells are derived from cells of the macrophage series. Multinucleate cells derived from infected keratinocytes may be seen in various virus infections such as herpes and poxvirus infections, and multinucleate cells derived from melanocytes are quite typical of epithelioid and spindle cell (Spitz) naevi (Fig. 10.25).

Mast cells

Mast cells, unlike the white blood cells and some histiocytes, all of which probably originate from the bone marrow, are likely to arise from undifferentiated mesenchymal cells. In normal skin, they are present around small blood vessels in the dermis. They are approximately 9–16 μm in diameter, and they possess a central round to ovoid, dark-staining nucleus. The cytoplasm contains small granules that stain metachromatically with such stains as toluidine blue. The granules contain vasoactive substances such as heparin, histamine, and eosinophilic and neutrophilic chemotactic factors of anaphylaxis. Mast cell activation may be triggered by neuropeptides derived from unmyelinated axons that surround perivascular mast cells. This in turn triggers adhesive events between leukocytes and endothelial cells, resulting in angiocentric inflammation.

Although in normal skin the cells tend to have a dendritic morphology, in various pathological conditions, including some forms of urticaria pigmentosa, the cells are larger and polygonal with a central, rounded nucleus. In addition to being found in increased numbers in the mastocytoses, they are also commonly seen in various benign and malignant nerve tumours, and in association with some melanocytic naevi.

Fibroblasts

Fibroblasts are often difficult to identify on routine light microscopy. Their nuclei tend to be oval or spindle-shaped, and with moderately basophilic staining. They are usually found between collagen bundles, and may be prominent in conditions where there is an increase in the production of dermal connective tissue or ground substance, such as morphoea and scleromyxoedema. They may also contribute to the histogenesis of the wide range of so-called fibrocytic tumours that may occur in the skin.

Myofibroblasts

These cells are mainly defined by their electron microscopic appearances and display features intermediate between those of fibroblasts and smooth muscle cells. They are mainly seen in reactive reparative processes and in neoplasms. Histologically, they have indistinct cytoplasmic margin, pink pale cytoplasm and vesicular tapering nuclei with a single inconspicuous nucleolus. Myofibroblasts can only be identified with certainty by electron microscopy.

Smooth muscle cells

Smooth muscle cells occur normally in the skin in the arrector pili muscles, in the tunica dartos of the external genitalia, in the areola of the nipple and in the walls of blood vessels. They are easy to identify by recognizing the normal structures in which they occur and also by their cytomorphology, which consists of abundant bright eosinophilic cytoplasm and vesicular nuclei with a single inconspicuous nucleolus.

Rhabdomyocyte (striated muscle cell)

Skeletal muscle occurs in the skin of the neck and of the face. The constituent cells are arranged in bundles and have characteristic cross striations and abundant, bright pink cytoplasm.

Schwann cells

Schwann cells are the main constituent cells of nerves. They envelop the neuroaxons and are characterized by a slender hyperchromatic thin nucleus and inconspicuous cytoplasm.

Endothelial cells

A single layer of endothelial cells lines all types of vascular channels in the skin. These cells usually appear flat with inconspicuous cytoplasm and small histiocyte-like vesicular nuclei. However, in most pathological processes, they become more prominent and may appear somewhat hyperchromatic. This, coupled with an increase in mitotic activity, may lead to confusion with malignant cells, particularly in cross-sections, where the normal architecture of the vascular channel is often not apparent.

Pericytes

Pericytes occur as a single layer of indistinct cells around small dermal blood vessels. They are recognized by their location and by positive staining for actin.

Miscellaneous

In addition to closely examining cytology under the high-power objective, the opportunity should also be taken to look carefully for organisms, foreign bodies or deposits of foreign material such as amyloid. Special staining techniques will often be needed to confirm suspicions, and with these stains bacterial, fungal and protozoal organisms may be identified as well as various forms of parasite. The presence of viral organisms can also be inferred by the presence of characteristic cytopathic changes, such as occur for instance with herpesvirus infections and infections with cytomegalovirus. Close examination of nerves and blood vessels should be carried out, particularly in relation to the presence of any organisms or tumour deposits. After examining adnexal structures and the subcutaneous tissues, it is useful to return to low-power examination and attempt to be certain one has not missed any pathology. It is not uncommon to discover more than one abnormality in a tissue section. Patients who develop solar keratoses may also have seborrhoeic warts, naevi and basal cell epitheliomas. Biopsies from patients with acquired immune deficiency syndrome (AIDS) often have multiple pathologies, and one may, for example, see a biopsy of perianal tissue in which there is evidence of cytomegalovirus infection in the endothelial cells, HPV infection of the overlying epithelium and the presence of Kaposi's sarcoma.

The importance of carefully assessing both the low-power pattern of changes in a skin section, as well as a more detailed examination of the cytology of the pathological changes, cannot be too strongly emphasized.

How to produce a histopathology skin report

After carefully carrying out the recommended procedure for low scanning power and high-power examination of a skin biopsy slide, the pathologist will either need more information, or will be in a position to provide a microscopic histopathological report to supplement the report on the gross pathological appearance of the biopsy specimen before processing. If there is very little obvious abnormality, it may be appropriate to cut deeper levels from the tissue block, or even consider blocking any remaining wet tissue that is in storage. If the specimen has been blocked obliquely or, for instance, the epidermis is missing, reblocking will be necessary. Serial sections may be required to determine pathological features that are only focal, such as changes affecting pilosebaceous follicles in a biopsy from the scalp. Special stains may be required for the evaluation of abnormal dermal deposits, to detect the presence of organisms, or to elucidate the nature of various pigments in the biopsy material. Immunohistochemical studies may also be requested in, for example, cases of cutaneous lymphoma or malignant spindle cell tumours. If there is going to be undue delay in these various extra investigations, a preliminary report should always be issued.

Although reporting of histopathology is to some extent a subjective art, and every pathologist will have his or her own idea of what is an appropriate report, a description of the objective histological changes, and either a suggested diagnosis or a differential diagnosis, are always desirable. In a description of the pathology, it is important never to describe features that are not present, even though they may be consistent with the correct diagnosis. The differential diagnosis suggested by the pathologist should fully take into account the clinical information supplied by the clinician. If the clinician suggests on the request form chronic superficial scaly dermatitis, it would be churlish to sign out the report as subacute eczema without further qualification. In addition to a description of the objective pathological changes and a diagnostic suggestion, it is quite legitimate to add a further comment in certain situations. If the clinician suggests a tumour has been excised, then a comment on the adequacy of excision is obviously useful. Conversely, if the clinician states that this is a diagnostic/incisional or superficial biopsy, it is irritating for the clinician to receive a report stating that tumour extends to one margin of excision.

In some situations where the various histopathological parameters need to be recorded repeatedly in biopsies from specific skin disorders, for example malignant melanoma, specially designed forms facilitate both the recording of information and subsequent computer analysis.

There is some degree of disagreement as to whether it is the role of the histopathologist under any circumstances to make recommendations for treatment, and no general rule can be given on this. If one knows one's clinical colleagues well, it is quite appropriate under certain circumstances to recommend a modest re-excision of the biopsy site, for instance in early superficial spreading melanoma. Some pathologists prefer to make such comments in a separate covering note. With some rarer conditions, particularly if they have serious implications for the patient, a telephone call to the clinician, or again a covering note, may be a reasonable approach. An offer from the pathologist to discuss any interesting case in more detail is often a good idea, and is usually taken up. It is always in the best interests of the patient for there to be a close working relationship between the histopathologist and the clinician.

Finally, it is most important always to appreciate one's own limits of ability. One should never be afraid of asking for a second opinion from a colleague. It has been said that sections from skin biopsies fall into three groups. Firstly, there are those sections where the histological appearances are easy for anyone to interpret and diagnose. Secondly, sections from biopsies, for instance of a very poorly differentiated spindle cell tumour, where one does not know what the diagnosis is, but knows that it is likely that no one else will either. Thirdly, sections where one does not know how to interpret the histological appearances oneself, but does know it is likely that someone else will! Once one is able to divide histological material into one of these three groups, one is already on the way to becoming an accomplished diagnostic dermatopathologist.

Commonly used descriptive terms in dermatopathology, and their diagnostic significance

Acantholysis

Acantholysis is the term used to describe loss of cohesion between keratinocytes, due to breakdown of intercellular bridges. It results in the formation of intraepidermal clefts, vesicles and bullae. It appears to be the primary pathological change in a group of diseases including pemphigus and its variants, Darier's disease, transient and persistent acantholytic dermatosis and warty

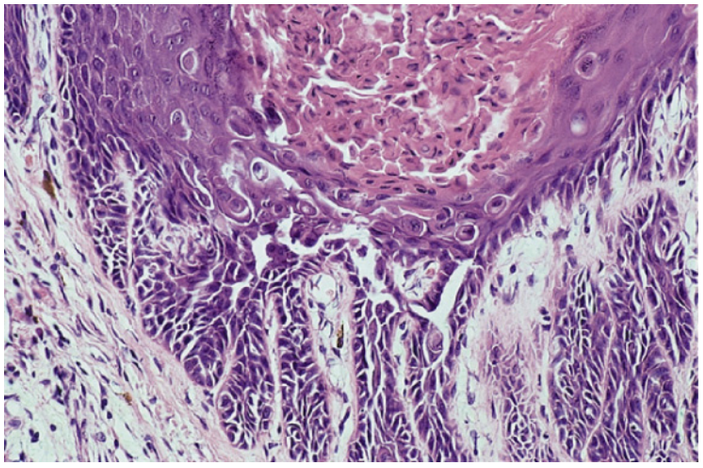


Fig. 10.26 A biopsy from a case of Darier's disease, showing the histological features of parakeratosis, dyskeratosis, acantholysis and formation of villi.

dyskeratoma. The site of acantholysis in these disorders is important. In pemphigus foliaceus and pemphigus erythematosus, acantholysis is usually confined to the upper portion of the epidermis, whereas in pemphigus vulgaris the split is formed at a lower level in the epidermis. In benign familial pemphigus (Hailey–Hailey disease), although acantholysis is often focal or incomplete, where it does occur it tends to affect the full thickness of the epidermis.

Acantholysis may also be seen secondary to some other pathological change, where there is alteration or damage to epidermal cells. It may occur, for example, in bullous impetigo, viral disorders, solar keratoses and some forms of squamous cell carcinoma. When acantholysis occurs in these disorders, the term secondary acantholysis is often used to distinguish the process from primary acantholysis, which occurs in pemphigus and related diseases (Fig. 10.26).

Acanthosis

This term is used to describe an increase in number of cells in the Malpighian or prickle cell layer of the epidermis (from the Greek for prickle or thorn). Sometimes, a distinction is made between increased thickness of the epidermis due to enlarged keratinocytes (pseudoacanthosis) and true acanthosis due to increased numbers of keratinocytes. In practice, acanthosis is commonly used to cover both senses. Increased thickness of the epidermis may result from increased length of rete ridges, as in a psoriasiform tissue reaction, or may affect the whole epidermis, such as in lichenification. Acanthosis is commonly accompanied by other histological changes such as hypergranulosis, hyperkeratosis and papillomatosis.

When reactive epidermal proliferation is marked, the process may simulate an epithelial carcinoma, and in this situation is referred to as pseudoepitheliomatous hyperplasia. Acanthosis may be seen in a wide variety of inflammatory and neoplastic disorders. Some of the common situations where this feature may be seen include the following:

1 Naevoid conditions and localized benign epidermal tumours—for example, keratodermas, epidermal naevi and seborrhoeic keratosis.
2 Virally induced papillomas—for example, viral wart, molluscum contagiosum.
3 Secondary to inflammatory conditions affecting the epidermis, particularly where chronic—for example, persistent friction, lichenification, prurigo and chronic eczema, psoriasis and lichen planus.
4 Secondary to conditions associated with loss of keratinocyte adhesion—for example, the pemphigus group of disorders and Darier's disease.
5 Secondary to conditions associated with the presence of foreign cells within the epidermis, such as malignant melanoma, Paget's disease, mycosis fungoides and Langerhans' cell histiocytosis.
6 Acanthosis is commonly seen overlying a variety of abnormalities in the dermis:
   (a) dermal tumours such as fibrous histiocytoma and granular cell tumour;
   (b) certain forms of cutaneous infection such as lupus vulgaris and blastomycosis;
   (c) overlying dermal deposits of substances such as amyloid, abnormal elastic tissue or in association with foreign bodies; and
   (d) in association with chronic oedema, such as chronic lymphoedema of the lower limb and myxoedema.

Anaplasia

This is a term used to describe variations in nuclear size, dense and clumped heterochromatin, and nuclear contour angulation typical of malignant cells, as in metastatic melanoma.

Apoptosis

This is a morphologically distinct type of cell degeneration and death, usually applied to keratinocytes that become homogeneous and eosinophilic and are extruded into the underlying upper dermis. These eosinophilic bodies (known as Civatte or colloid bodies), and the process of apoptosis, occur characteristically in lichenoid tissue reactions. A similar process may be observed in many other processes, for example, following UV light exposure, in graft-versus-host disease and in cutaneous lupus erythematosus.

Basal lamina (Chapter 3)

This structure, also known as the basement membrane, is a submicroscopic structure approximately 40 nm in thickness, which extends along the undersurface of the epidermal basal cells. It is not visible with light microscopy. The term basement-membrane zone is sometimes applied to the area that may be visualized with the PAS-staining technique (see Fig. 10.7). The basement membrane is a very complex structure composed of large numbers of proteins with important functions in maintaining the structure of the skin. Many of these proteins are of great importance in genetic (epidermolysis bullosa) and acquired diseases (autoimmune blistering diseases).

Bullae

Bullae represent fluid-containing cavities occurring within or below the epidermis. Small bullae are known as vesicles. Determination of the site of bulla formation is most important in

histological assessment of skin biopsies. Intraepidermal bullae may arise as the result of spongiosis, as in acute eczema, from reticular and ballooning degeneration seen in association with viral disorders, or from acantholysis or epidermal cell necrosis. Subepidermal blisters usually result either from a defect in the basement membrane region, such as occurs in some forms of epidermolysis bullosa and porphyria, from a disruption of the basement membrane from intense liquefaction degeneration or necrosis of the basal cell layer, such as may occur in bullous lichen planus or bullous lupus erythematosus, or as a result of dermal inflammatory processes involving the upper dermal connective tissue and basement membrane region. In some conditions, such as erythema multiforme, both subepidermal and intraepidermal factors seem to be involved in bulla formation.

Colloid body

This term, usually regarded as synonymous with Civatte body, describes the homogeneous eosinophilic rounded body resulting from degeneration and death of keratinocytes, particularly in the lower layers of the epidermis. This structure is found in various lichenoid tissue reactions and is involved in the process of apoptosis.

Crust

This term is used to describe collections of inflammatory cells, red blood cells, plasma and fibrin in the superficial portion of the epidermis. A crust may also contain microorganisms, and often replaces a partial or total loss of the epidermis itself.

Curlicue (storiform) pattern

This descriptive term refers to the twisting and curving of dermal fibrohistiocytic cells around collagen bundles, often at the margins of a dermal tumour. The pattern is mainly observed in dermatofibrosarcoma protuberans. The pattern described by this term is the same as that referred to by the term storiform (Fig 10.20a).

Degenerations

Dermal

Colloid degeneration. Colloid degeneration refers to the deposition of extracellular homogeneous gelatinous material of variable composition. It is typically seen in colloid milium, but may also be found in certain epithelial tumours.

Elastotic degeneration. This describes the degenerative changes that develop with increasing age, particularly in the upper part of the dermis in sun-exposed skin. Early changes include an increase in the number and size of connective tissue fibres staining with elastic stains. In advanced stages of the condition, there are masses of disorganized elastotic fibres occurring particularly in the upper third of the dermis, and appearing to replace the normal collagen. This elastotic degeneration is normally separated from the epidermis by a narrow band of normal-staining connective tissue. In sections stained with H&E, the elastotic material is basophilic.

Fibrinoid degeneration. This term describes the deposition in tissue of eosinophilic, granular or fibrillary material resembling fibrin. The composition of the eosinophilic amorphous material may vary in different situations, but fibrinogen, plasma proteins, immunoglobulins and dermal ground substance may be components of the material. It is most typically seen in forms of necrotizing vasculitis, and is also found in disorders such as lupus erythematosus and the collagen diseases.

Hyaline degeneration. This term refers to the presence of homogeneous eosinophilic degenerative material in dermal connective tissue, or in relation to blood vessels. The material has a glassy and refractile appearance. Hyaline degeneration occurs in forms of porphyria, lipoid proteinosis and sometimes in lichenoid tissue reactions. Epithelial structures may also show a similar type of change, for instance the tumour cells of cylindroma frequently undergo hyaline change.

Myxoid degeneration. This indicates the deposition or replacement of dermal connective tissue by amorphous, stringy, basophilic material. This pattern of degeneration is seen in localized myxoedema, papular mucinosis, scleredema and dermatomyositis, as well as being seen in various neural, epithelial and adnexal neoplasms.

Epidermal

Ballooning degeneration. This form of degeneration of keratinocytes is associated with marked swelling and pallor of individual cells, with loss of intercellular bridges. A blister forms as a result of the consequent acantholysis. Ballooning degeneration along with reticular degeneration is characteristic of virus disorders affecting epithelia, such as herpesvirus infections.

Hydropic degeneration. This is also known as liquefaction degeneration, and refers to a vacuolar change that affects the basal cell layer of the epidermis. Small droplets and vacuoles develop within and in between basal cells. The process is commonly associated with pigmentary incontinence, and when marked may lead to subepidermal blister formation. It occurs typically in the whole range of lichenoid tissue reactions, including lupus erythematosus, lichen planus, dermatomyositis, poikiloderma atrophicans vasculare and lichen sclerosus (Fig. 10.27).

Reticular degeneration. This indicates the development of large, multiple, intraepidermal vesicles, where there remains a ragged network of epidermal cell remnants. As mentioned above, reticular degeneration often occurs in association with ballooning degeneration in acute virus infections of the herpesvirus and poxvirus groups. This pattern of epidermal degeneration may also sometimes be seen in the acute bullous reaction of contact dermatitis.

Desmoplasia

This term describes a pattern of fibrosis or sclerosis of dermal connective tissue, usually in association with an epithelial or melanocytic proliferative lesion. Examples of the use of this term are in desmoplastic trichoepithelioma and desmoplastic malignant melanoma.

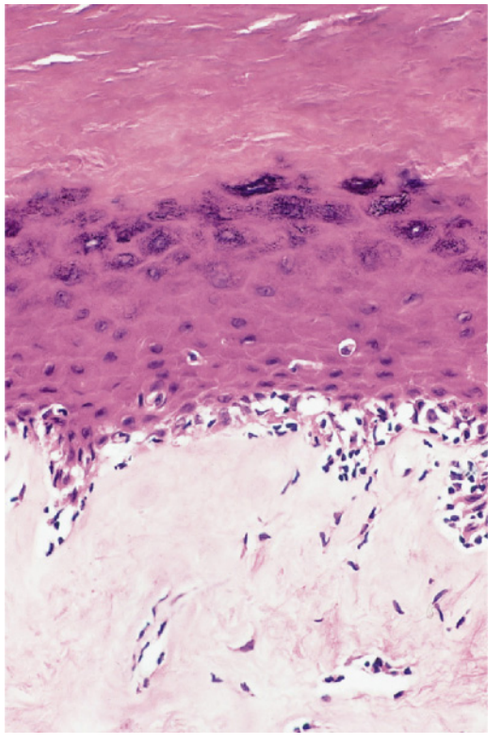


Fig. 10.27 Prominent liquefaction degeneration from a case of lichen sclerosus.

Dyskeratosis

This term relates to some abnormality in the process of epidermal cell keratinization. The changes usually consist of nuclear pyknosis and bright pink condensation of the cytoplasm of keratinocytes. The process occurs in two main contexts. Firstly, in malignant and premalignant epithelial lesions, such as squamous cell carcinoma, Bowen's disease and solar keratosis. Secondly, in various forms of acantholytic disorder such as Darier's disease. In this latter condition, specific types of dyskeratotic cell include corps ronds and grains (see Fig. 10.26).

Dysplasia

This term is a confusing one, especially when used to describe atypical melanocytic naevi, because if communication with the clinician is inadequate, it may be interpreted to mean different things. Its use normally reflects some abnormality in cell maturation, cytomorphology or the relationship between cells in epithelial structures. It has the connotation of possible progression to neoplastic disease.

Exocytosis

This term describes the migration of inflammatory cells from the blood vessels of the dermis into the overlying epidermis. The process may be associated with spongiosis, as in eczema, or occur in the absence of spongiosis, such as may be seen in mycosis fungoides. In the later setting, the word epidermotropism is usually preferred.

Granuloma

A granuloma describes circumscribed foci of inflammation containing monocytes, macrophages, lymphocytes and epithelioid cells. Multinucleated giant cells of foreign body, Langhans or Touton type may also be observed. Varying degrees of epidermal hyperplasia, capillary proliferation and dermal fibrosis are common accompanying changes. Granulomatous inflammation occurs in a wide variety of infectious and non-infectious conditions. Many different types of organism ranging from viruses through bacteria to fungi can produce a tissue granuloma. The presence of granulomas in a skin biopsy may indicate a systemic disease, such as sarcoidosis, or a localized dermatosis of unknown cause, such as granuloma annulare or acne agminata. The precise histological appearance of a dermal granuloma depends not only on the underlying cause, but on the period over which the disease has been active, and the immune status of the host.

Grenz zone

This comes from the German word for border, and in dermatopathology is applied to a narrow zone of normal dermis between the epidermis and pathological changes in the underlying dermis.

Hypergranulosis

This refers to an increase in thickness of the granular layer of the epidermis, and is commonly accompanied by hyperkeratosis and acanthosis. It is often seen in chronic lichenification and lichen planus and related disorders.

Hyperkeratosis

Hyperkeratosis refers to increased thickness of the stratum corneum, and may be associated with acanthosis of the Malpighian layer. Hyperkeratosis may occur in various disorders of keratinization, such as the keratodermas and some ichthyotic disorders, and relative hyperkeratosis is quite common in chronic discoid lupus erythematosus. In certain conditions, such as in Flegel's disease, in addition to increased thickness of the stratum corneum there is a change from the normal basket-weave pattern to a compact arrangement of the stratum corneum cells. When assessing the thickness of the stratum corneum, it is important to correlate the histological appearances with the site of the biopsy. The stratum corneum is normally thick on the palms and soles, and very thin, or even absent, around the eyelids and near mucous membrane junctions.

Epidermolytic hyperkeratosis

This particular change, also sometimes referred to as granular degeneration, is a peculiar and characteristic change seen in a number of skin disorders. There is an increase in the thickness of the granular layer, where keratinocytes appear to contain an increased number of keratohyalin granules. Perinuclear vacuolization occurs in this area, and the cell boundaries may be indistinct. The vacuolization may be marked, in some cases appearing to lead to intraepidermal vesicle formation. Although this change is best known as the characteristic histopathological feature of bullous ichthyosiform erythroderma (Fig. 10.28), it also occurs in many other inherited and acquired conditions, including a form of palmoplantar keratoderma, so-called epidermolytic acanthoma,

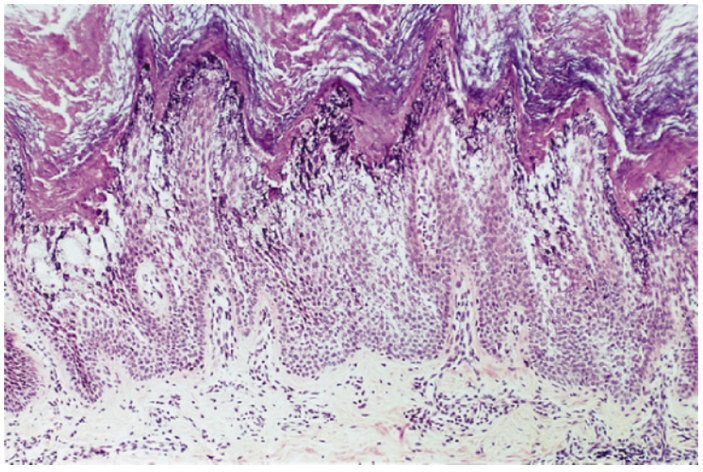


Fig. 10.28 Epidermolytic hyperkeratosis seen in a biopsy from a patient with congenital bullous ichthyosiform erythroderma.

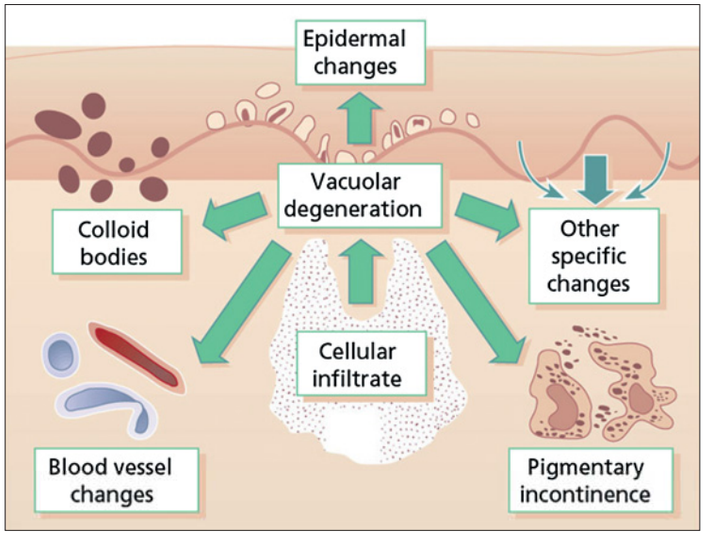


Fig. 10.29 The lichenoid tissue reaction. Various histopathological consequences follow damage to the dermal–epidermal junction. These histopathological changes are seen in a wide variety of lichenoid reactions, ranging from lichen planus to lupus erythematosus, poikiloderma atrophicans vasculare, lichen sclerosus and lichenoid drug eruptions.

and some forms of linear epidermal naevus. It is also occasionally seen as an incidental finding, either in normal skin or in association with a lesion, such as a naevus, a viral wart or a seborrhoeic keratosis.

Follicular hyperkeratosis

This describes varying degrees of hyperkeratosis and plugging of the ostia of hair follicles, and this change may be associated with the rupture of the follicular wall. It occurs in many conditions including pityriasis rubra pilaris, lupus erythematosus, lichen planopilaris and lichen sclerosus.

Kamino bodies (eosinophilic globules)

This term describes the eosinophilic globules seen in the epidermis or in the region of the dermal–epidermal junction in spindle- and epithelioid-cell (Spitz) naevi. They are almost always found in Spitz naevi but may also be seen in some cases of melanoma.

Karyorrhexis

This refers to the fragmentation of cell nuclei, and the process may be seen in various forms of neutrophilic dermatoses and cutaneous pyoderma. It is commonly seen in necrotizing vasculitic processes. The term leukocytoclasis specifically refers to the fragmentation of nuclei of neutrophil polymorphonuclear leukocytes. However, the term is sometimes used to refer to fragmentation of other inflammatory cells such as lymphocytes.

Lichenoid tissue reaction

This is a pattern of changes occurring both in the epidermis and especially the dermis, seen in a wide variety of conditions, ranging from lichen planus itself to lupus erythematosus, lichen sclerosus and the poikilodermas. Lichenoid changes may also be seen in some examples of cutaneous drug eruptions. In the upper dermis, there is a band-like infiltrate consisting predominantly of mononuclear cells. This is closely related to the dermal–epidermal junction, which itself may have a saw-toothed pattern. Liquefaction degeneration of the basal cell layer is seen, and colloid body formation may be present. There is often an increase in thickness of the overlying epidermis, affecting both the Malpighian layer and the stratum corneum (Fig. 10.29).

Metaplasia

This term is used to indicate an alteration of one type of tissue into another, such as the formation of bone in certain epithelial tumours, for example pilomatricoma.

Necrobiosis

Necrobiosis is an unsatisfactory term derived from words for life and death. It is applied to certain granulomatous disorders where the dermal connective tissue becomes homogenized and loses its normal staining characteristics, resulting in mucinous, fibrinoid or sclerotic alteration. The outlines of the normal architecture are usually still present, and the amount of inflammation varies. Changes of necrobiosis are normally surrounded by a palisading histiocytic granuloma. The condition is seen in association with granuloma annulare, necrobiosis lipoidica, rheumatoid nodule and acne agminata.

Necrolysis

This is used to describe the separation of tissue constituents as a consequence on cell death. Epidermal changes of necrolysis are seen in various inflammatory reactions such as erythema multiforme, toxic epidermal necrolysis and necrolytic migratory erythema seen in association with the glucagonoma syndrome.

Necrosis

This term describes the death of cells or tissue.

Papilloma

This term indicates a tumour or tumour-like proliferation exhibiting both papillomatosis and hyperkeratosis. Acanthosis is also

present. Examples of skin papillomas include viral warts, seborrhoeic keratoses and some epidermal naevi.

Papillomatosis
This change is characterized by elongation upwards of the dermal papillae, giving an accentuated and sometimes irregular, undulating configuration to the dermal–epidermal junction. The feature is commonly seen in psoriasis, and a wide variety of other inflammatory and neoplastic cutaneous disorders.

Parakeratosis
Parakeratosis can be defined as the retention of keratinocyte nuclei within the horny cell layer. It represents a disturbance of keratinization, and is normally associated with an absence or reduction in thickness of the granular cell layer. The histological feature of parakeratosis is commonly seen in many different forms of inflammatory dermatosis, and is closely associated either with increased epidermal cell turnover or with inflammatory changes in the epidermis itself. It is commonly seen in psoriasis and subacute eczematous reactions, and in conditions such as pityriasis lichenoides where the change reflects an earlier disturbance in the underlying epidermis. In chronic inflammatory conditions where epidermal turnover is unaffected, such as in lichenoid reactions, parakeratosis is rarely seen. Dysplastic epithelial changes, such as those occurring in actinic keratoses and Bowen's disease, are normally accompanied by parakeratosis.

Pigmentary incontinence
This refers to the loss of melanin from cells of the basal layer of the epidermis, and the accumulation of melanin, both free and within dendritic macrophages, in the underlying dermis. It is associated with damage to keratinocytes of the lower epidermis, and is commonly seen in lichenoid tissue reactions. Small amounts of melanin may be seen in the upper dermis in normal pigmented skin.

Pleomorphism
This describes variability in the appearance of cells, and in particular the nuclei of cells of the same type. Although it may be seen in malignant and premalignant conditions, marked pleomorphism may also be seen in benign lesions such as Spitz naevi.

Polymorphism
Conventionally this is used to describe a variation in types of cells in a cutaneous lesion. This term is not the same as pleomorphism.

Pustules and abscesses
These terms are used to describe cavities within the epidermis or dermis formed by collections of neutrophil or eosinophil polymorphonuclear cells. Occasionally, the term is used to describe collections of other leukocytes, as in the term Pautrier microabscesses (see below). Cutaneous pustules may be sterile, or associated with an infectious microorganism. Certain specific types of microabscess and pustule are of diagnostic value in dermatopathology.

Kogoj's spongiform pustule. This describes the multilocular micropustules that form in the superficial portions of the epidermis in pustular psoriasis. They form in a similar manner to Munro microabscesses but the process is more extensive.

Munro microabscesses. These lesions are small collections of neutrophil polymorphs usually found within the stratum corneum. They are normally seen in lesions of chronic established psoriasis, and the other histological features of the psoriatic reaction, such as irregular epidermal thickening and parakeratosis, are normally present.

Papillary tip microabscesses. These are small focal collections of neutrophil polymorphs or occasionally eosinophils, in the tips of dermal papillae. Although they are characteristic of dermatitis herpetiformis, they may occur in other bullous eruptions such as epidermolysis bullosa acquisita and the bullous form of lupus erythematosus.

Pautrier microabscesses. These small, intraepidermal collections of lymphoid cells in the absence of marked spongiosis are characteristic of mycosis fungoides. The cells within the epidermis may show some degree of nuclear hyperchromatism or atypia. Single cell colonization of the epidermis is more commonly seen than true Pautrier microabscess formation in many cases of early mycosis fungoides.

Subcorneal pustules. Large, subcorneal collections of neutrophil polymorphs usually represent either impetigo or subcorneal pustular dermatosis. Sometimes, the distinction of either of these two conditions from pustular psoriasis may be difficult.

Pyknosis
This term is used to refer to hyperchromatism and shrinkage of the cell nucleus. It is normally associated with cell death, and may be seen in a wide variety of conditions, including epithelial dysplasias, drug reactions and reactions to UV light.

Saw-toothing
This refers to an alteration in the pattern of the dermal–epidermal junction where dermal papillae are expanded and the tips of the rete pegs are pointed. The resulting pattern bears a superficial resemblance to the teeth of a saw and the change is seen in lichen planus and other lichenoid reactions.

Spongiosis
Spongiosis is also known as intercellular oedema, and describes the widening of intercellular spaces between keratinocytes due to fluid accumulation. Spongiosis is the characteristic histopathological change seen in acute and subacute eczematous reactions, but is also seen in a wide variety of other conditions; when spongiosis is marked it leads to intraepidermal vesiculation. Spongiosis of follicular epithelium may be associated with increased mucin deposition in the histopathological reaction pattern known as follicular mucinosis.

Storiform patterning
This is a pattern of proliferation commonly seen in various dermal and soft-tissue tumours, where strands of spindle-shaped tumour

cells or even collagen bundles are arranged so as to resemble the pattern seen in woven cloth. The term is also sometimes applied to the presence of strands of spindle-shaped tumour cells or connective tissue cells that appear to extend radially from a central hub, similar to the spokes of a wheel. Cartwheel patterning is probably a better term to describe this particular appearance. Storiform and cartwheel patterning, although commonly referred to in DFSP, are by no means specifically diagnostic (Fig. 10.20a).

Theque

This term is derived from French and Greek words for a box (*thèque*, θηκη) and is conventionally used in dermatopathology to describe small aggregates or nests of cells, particularly the collections of naevus cells at, and in the region of, the dermal–epidermal junction.

Villi

This term refers to elongated dermal papillae covered usually with a single layer of epidermal cells, and which form the base of a blister cavity that has resulted from the process of suprabasal acantholysis. Villi are seen in the various forms of pemphigus and Darier's disease (see Fig. 10.26), warty dyskeratoma, and transient and persistent acantholytic dermatosis.

Special problems that may be encountered in skin biopsies

Histological sections that reveal little or no abnormality

It is not uncommon for the diagnostic dermatopathologist to come across histological sections where at first sight the appearances resemble normal skin. It may be that the pathological changes have been missed. This can be the fault of the clinician who has perhaps taken too superficial a biopsy from a lesion of suspected panniculitis, or it can be the fault of the pathologist who has inappropriately blocked the biopsy specimen, or taken too few sections from the material. The importance of studying numerous serial sections in this situation cannot be overemphasized. There are a number of conditions, however, where subtle pathological abnormalities are present, but where a high index of suspicion is needed to make a correct diagnosis. The following list includes some of the more important of these.

Epidermal lesions

Fungal infections. In the presence of patchy epidermal spongiosis and focal overlying parakeratosis, it is always important to exclude the presence of a fungal infection with a PAS stain. Occasionally, a few neutrophil polymorphs may be seen in the upper Malpighian layer of stratum corneum, and this may provide a clue to the correct diagnosis. Pityriasis versicolor may be present in the absence of spongiosis, and is frequently missed.

Ichthyotic disorders. The dominant form of ichthyosis vulgaris is usually characterized by some degree of compact hyperkeratosis, and an absent or attenuated granular layer. If the hyperkeratosis is not significant, the diagnosis may be overlooked. When assessing the stratum corneum, it is always important to look at not only the thickness, but also the quality of the corneocytes. An alteration from the normal basket-weave pattern to a compact cornified layer usually indicates some pathological abnormality.

Porokeratosis. The epidermal changes, usually of atrophy, in the various forms of porokeratosis are often not striking, and the diagnostic cornoid lamella may not be seen on the first sections cut from the block. In diagnostic biopsies, the cornoid lamella may not be present. All forms of porokeratosis may be misdiagnosed, but the disseminated actinic form of the disorder is the most commonly overlooked.

Actinic keratoses. Some flat actinic keratoses may show very little evidence of keratinocyte atypia, and unless a reasonable amount of normal skin is included the biopsy material may be signed out as non-diagnostic.

Pigmentary disorders

Various disorders of epidermal pigmentation may be difficult to diagnose with certainty, particularly if one is not certain of the skin colour of the patient from whom the biopsy has been taken. The loss of pigment in established vitiligo is normally associated with absence or reduction in number of melanocytes. However, in café-au-lait spots and ephelides, melanocytes are normal in number. A melanin stain may reveal a difference between lesional and adjacent skin. In post-inflammatory hypo- or hyperpigmentation, the number of melanocytes remains normal with increase or decrease in melanin in basal cells. Often, melanophages are seen in the papillary dermis particularly in post-inflammatory hyperpigmentation.

Dermal deposits

The small amounts of amyloid seen in macular amyloidosis are often difficult to visualize with H&E stain. Special stains are indicated, but the presence of slightly expanded dermal papillae, together with a hint of lichenoid tissue reaction, may alert the pathologist to this possibility. A further useful clue is the presence of scattered apoptotic keratinocytes. The presence of iron pigment in small quantities in the dermis is easily missed, either in common conditions, such as bruising, or in rare situations, such as idiopathic haemochromatosis. A Perls' stain usually highlights iron deposits that have not been detected in slides stained with H&E. The deposits of silver in argyria are often best seen around the basement-membrane zone of dermal sweat ducts.

Connective tissue diseases

Scleroderma, particularly in the late stages, often shows little histopathological abnormality. The coarsening and hyalinization of collagen bundles, with a reduction in the space between them, is often not prominent particularly in the superficial form of morphoea. In the early stages of the condition, there is normally some increase in cellularity around dermal blood vessels. It is always important to try and assess normal skin if there is some present in the biopsy. Similar problems may be encountered with various forms of connective tissue naevi, and abnormalities of elastic tissue such as anetoderma. In atrophoderma, the elastic pattern is more or less normal, but there is a reduction in total thickness of the dermis, which may be difficult to evaluate. A solution to this

problem is to obtain an ellipse of skin in which half of the specimen represents clinically normal skin. To indicate the clinically normal skin, the clinician marks the specimen with a stitch.

Dermal infiltrates

Urticaria. In biopsies from urticarial lesions, there may be very little more than slight dermal oedema, which is often difficult to evaluate on processed tissue, together with a slight increase in inflammatory cells around upper dermal blood vessels. It should be remembered that, in normal skin, a few mononuclear cells, fibroblasts and other cells are present in the dermis. A clue to the diagnosis of urticaria is the presence of at least a few eosinophils.

Blue naevus and related disorders. The dendritic melanocytes seen in the dermal melanocytoses, particularly Mongolian spot, are often difficult to recognize without the use of special stains such as the S-100 immunohistochemical marker. The main problem resides in the distinction between melanophages and melanocytes, as most dermal melanocytoses excluding blue naevus contain only few scattered dermal pigmented melanocytes. The use of an immunohistochemical marker for melanocytes such as S-100 is useful, but the product obtained in the detection of the final peroxidase product is usually brown and this is very similar to melanin. This problem can be overcome by bleaching the slide before immunohistochemistry, or by changing the diaminobenzidine for amino-ethyl carbazole, which results in a red product.

Granuloma annulare. In the majority of cases this diagnosis is straightforward, with evidence of a dermal palisading granuloma with necrobiosis. However, in the disseminated form of the condition the changes are often very slight, and may be represented by just a few mononuclear cells dissecting bundles of collagen.

Mast cell disorders. The adult form of urticaria pigmentosa, and particularly its variant telangiectasia macularis eruptiva perstans, frequently shows only a relatively slight increase in numbers of mast cells within the dermis. In these forms of urticaria pigmentosa, the mast cells tend to be rather dendritic or short spindle-shaped. Their granules may not be obvious, and they may resemble normal connective tissue cells, such as fibroblasts. In mastocytoma and some juvenile forms of mastocytosis, the mast cells are larger, rounded cells with central nuclei and are easier to recognize.

Scalp disorders

Unless an adequate biopsy is available for examination, many disorders of the scalp may be difficult to evaluate. Conditions such as telogen effluvium and long-standing alopecia areata show very little sign of inflammation, and diagnosis may have to be made purely on the number of pilosebaceous structures, and the relative number of follicles in different phases of the hair cycle. The study of horizontally sectioned biopsies is the ideal method to study hair follicles with regards to their cycle, pathological alterations and numbers (see Chapter 66).

Conclusion

As mentioned at the start of this chapter, histopathological examination of a skin biopsy taken from an appropriate lesion is a great help in assisting the clinician to come to a correct diagnosis, and therefore to come to a decision regarding management of the patient. Light microscopic examination of sections from skin-biopsy tissue fixed in formalin and embedded in paraffin is likely to remain the single most useful diagnostic technique for the foreseeable future. The wide range of tissue and cytological changes that may be encountered within normal skin and inflammatory and neoplastic conditions mean that considerable experience is required for the dermatopathologist to contribute helpfully to patient management. Many excellent texts are now available on the histopathology of the skin, but there can be no substitute for personal study on a day-to-day basis of as much material as possible under the supervision of an experienced guide. Feedback and communication between clinician and pathologist is essential, and has been perhaps one of the most important factors in the advances in dermatopathology in the last decade. The light microscopist already has a very wide range of additional techniques available to assist in diagnosis and to study the anatomy and physiology of normal and diseased tissues, some of which are outlined above. The numerous new areas of investigation that have developed over the last few years, including molecular biological techniques, such as PCR, *in situ* hybridization and studies on biological response modifiers, cytokines and adhesion molecules, will no doubt continue to further major advances in our understanding of skin in health and disease.

Reference

1 Ackerman AB, Boer A, Bennin B *et al*. *Histologic Diagnosis of Inflammatory Skin Diseases*, 3rd edn. New York: Ardor Scribendi, 2004.

CHAPTER 11
Molecular Biology

E.A. O'Toole
Centre for Cutaneous Research, Barts and the London School of Medicine and Dentistry, London, UK

Basic molecular biology of the cell, 11.2
Structure of nucleic acids (DNA and RNA), 11.2
Molecular techniques, 11.3
Southern and northern blotting, 11.5
Polymerase chain reaction, 11.6
DNA sequencing, 11.6
RNA interference, 11.7
Genomics, 11.7
Proteomics, 11.8
Application of molecular techniques, 11.9
Strategies for identification of disease-causing genes, 11.11
Complex traits, 11.14
Pharmacogenetics, 11.16
Epigenetics, 11.16
Cancer genetics, 11.17
Putting it all together and future trends, 11.19
From genetics of disease to treatment, 11.20
Gene therapy, 11.20
Conclusion, 11.22

Introduction

There is no single, all-embracing definition of molecular biology. However, it is possible, certainly with hindsight, to plot and recognize the growth of a unique blend of biochemistry, genetics and cell biology—the subject we now call molecular biology—which is having a revolutionary impact on all areas of biology, not least clinical medicine. The Nobel Laureate James Watson and colleagues, writing in a preface to one of the standard texts of molecular biology, commented that whereas only 25 years ago it was possible for one individual to know all the important topics in molecular biology, this was no longer the case [1]. This explosion of knowledge is not just due to a revolution in our conceptual understanding, but owes as much to an astonishing expansion in our technical facility to characterize and manipulate nucleic acids (both DNA and RNA) and the resulting proteins. Several features of the organization and structure of nucleic acids go some way to explaining the power of this gene-centred approach to biology. Genetic information is conveyed in a *linear* sequence of only four bases; genes are *collinear* with proteins; and genes themselves are arranged in chromosomes in a fixed *linear* sequence, without which cloning of genes on the basis of position (so-called positional cloning or reverse genetics) would be impossible. What is still extraordinary, and was once not obvious, is how much biologically meaningful information can be revealed by merely understanding the linear base sequence of a particular gene [2].

The development of molecular biology as a discipline has not been a gradual, step-by-step process but, by contrast, has faltered at several stages [1–5]. Intellectual landmarks include Avery's work with *Pneumococcus*, demonstrating that nucleic acids (rather than protein) carry genetic information; Watson and Crick's Nobel Prize-winning description of the structure of DNA; and subsequent work by Crick, together with Brenner and others in the late 1950s and early 1960s, describing how information encoded by DNA was realized in protein structure [1–5]. In the early 1960s, however, there was a hiatus lasting until perhaps the mid 1970s. At this stage, many of the ground-breaking discoveries, whilst having a general applicability, were experimentally limited to simple organisms such as bacteriophages or bacteria. There were not the experimental tools to allow human genome analysis and, consequently, genetic approaches to disease were still beyond reach. In the 1970s, a number of fundamental advances in an area that would later become known as biotechnology changed this situation. The identification and experimental manipulation of plasmids and the identification of restriction, and other DNA-modifying, enzymes heralded a new era in our ability to study the human genome and start utilizing genetic approaches to human disease. In particular, combinations of techniques, together with considerable insight, led to the ability to study those rare but important differences between individuals' protein-coding DNA, which are the cause of most inherited disease. Perhaps counter-intuitively, the detection of variation in non-coding DNA (so-called 'junk DNA') was also to have a great influence; virtually all present-day mapping of disease-causing genes relies on such variation. In addition, an ever-enlarging armamentarium of techniques allowed the increased experimental manipulation of DNA, including the reintroduction of DNA into cells, firstly in culture and later into animals, leading to the development of transgenic technology. This new biology now permeates all areas of clinical medicine, and dermatology is no exception; there has been astonishing progress in identifying the genes for a host of skin disorders. As well as providing and hinting at explanations for the underlying pathophysiology of these diseases, these advances promise an increase in the speed of development of new therapeutic approaches, either those based on genes themselves, such as gene therapy, or by allowing a quickening of the pace of drug discovery. Finally, the Human Genome Project, an international effort using high throughput sequencing started in 1990 and completed in 2007, has led to sequence information on the estimated 3.1 billion base pairs of DNA and approximately 25 000 genes in the human genome [6].

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

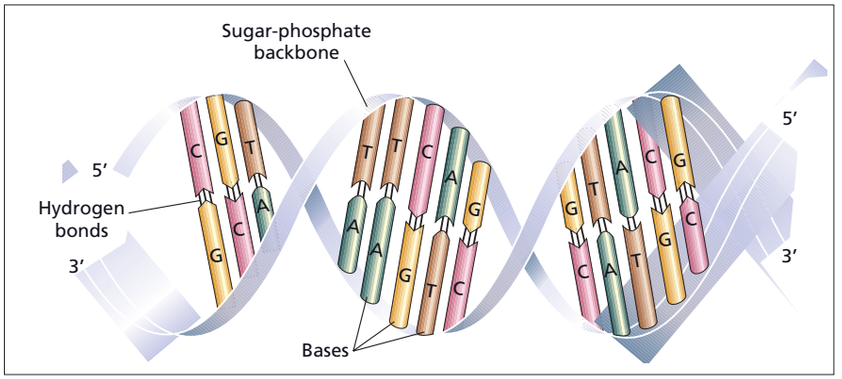


Fig. 11.1 Schematic of the DNA double helix. The backbone of the helix is made up of sugar and phosphate moieties that run in opposite directions (5′→3′ and 3′→5′). The strands are linked by the bases, which pair via hydrogen bonds in a particular fashion, cytosine with guanine, and adenine with thymine. Because of the specific nature of the base pairing, if the hydrogen bonds are broken, each strand can act as a template for the other, such as occurs at transcription of DNA into RNA or when DNA is replicated. It is also evident that because each strand of DNA is complementary to the other, then one strand can be used as a probe for the other.

It is not possible within this chapter to give a comprehensive or even fair treatment of the whole of molecular biology as it applies to dermatology. For those interested, there are some unusually readable (and exciting) books on molecular biology/genetics to which the reader is directed [1,2,4,6–8]. Nor can the chapter be viewed merely as a catalogue of genetic disorders of the skin; review of the Online Mendelian Inheritance in Man (OMIM) database suggests that up to one-third of the listed disorders may involve the skin. However, what I will try to do is: (i) briefly review the structure of nucleic acids; (ii) explain how the structure of DNA allows the development of a number of techniques, which in turn permits further analysis of the relation between genes and organisms; and (iii) give examples of how molecular biological approaches have been informative for the study of skin disease, including a section on cancer genetics. Finally, a brief summary is given of the use of molecular biological techniques in diagnosis and therapy.

References

1 Watson JD, Baker T, Bell S *et al. Molecular Biology of the Gene*, 6th edn. Menlo Park, CA: Benjamin Cummings, 2008.
2 Judson HF. *The Eighth Day of Creation: Makers of the Revolution in Biology*. 25th anniversary edn. New York: Simon and Schuster, 1996.
3 Alberts B, Johnson A, Lewis J *et al. Molecular Biology of the Cell*, 4th edn. New York: Garland Science, 2007.
4 Watson JD. *A Passion for DNA: Genes, Genomes and Society*. 50th anniversary edn. Oxford: Oxford University Press, 2001.
5 Strachan T, Read AP. *Human Molecular Genetics*, 3rd edn. New York: Garland Science, 2004.
6 Venter JC. *A Life Decoded: My Genome–My Life*. New York: Penguin Press, 2007.
7 Leroi AM. *Mutants: on the Form, Varieties and Errors of the Human Body*. London: Harper Collins, 2003.
8 Ridley M. *Genome. The Autobiography of a Species in 23 Chapters*. London: Harper Collins, 2000.

Basic molecular biology of the cell

Structure of nucleic acids (DNA and RNA) [1–3]

DNA is an antiparallel double helix in which the backbones of the helix are made from sugar and phosphate groups; these are linked by one of four bases (cytosine, guanine, thymine and adenine) that form hydrogen bonds with a complementary base on the opposing backbone (Fig. 11.1). The primary genetic information is coded by the pattern of these bases. Importantly, and central to the Watson and Crick model, cytosine always binds with guanine, and adenine with thymine. Because these base pairings are held together by hydrogen bonds only, one can imagine how, if the bonds are broken (such as by treatment with heat), each strand of DNA could act as a template for the opposing strand. Each cell in the human body contains 3.3 billion base pairs of DNA packaged into 46 chromosomes (22 pairs of autosomes and 2 sex chromosomes, X and Y). If DNA were unravelled, the length of DNA in each cell would be 2 m; that from a human body would stretch further than to the moon and back!

Surprisingly, perhaps 90% of the DNA on chromosomes does not appear to code for protein, and is therefore often referred to as 'junk DNA'. Much of this DNA is made up of repeated sequences of DNA, the function of which is unclear. It has, however, been experimentally fortuitous, in that this 'junk DNA' is a rich source of genetic variation between individuals, and forms the basis for genetic mapping of disease traits. Thus for any one chromosome, the genes residing on that chromosome will be diluted by a much larger volume of DNA that does not appear to code for protein. Finding genes is therefore sometimes like searching for a needle in a haystack, even when the area of a chromosome harbouring a gene for a particular disorder has been closely localized by mapping of the disorder in affected kindreds. Not only are genes arranged on chromosomes in an intermittent way, but while genes and proteins are collinear, the DNA that directly codes for particular groups of amino acids is in itself discontinuous on the chromosome, being arranged into introns and exons (Fig. 11.2).

With certain important exceptions (which are not central to this description), DNA in every cell in the body is identical in terms of its primary structure. The keratinocyte's DNA is the same as that in a red-cell precursor or a neurone. This immediately raises the problem of how a keratinocyte knows how to make keratins, a red-cell precursor globins and a neurone synapses. How do the different types of cells produce different proteins if they carry identical DNA? DNA is transcribed into RNA, which is then translated into protein. If one were to examine the RNAs produced in these different cell types, one would detect differences. A major area of interest in molecular biology has therefore been in understanding the control of such differences in *gene expression*. This control occurs at two main levels: first, transcription—whether particular RNAs are copied from a particular gene; and second,

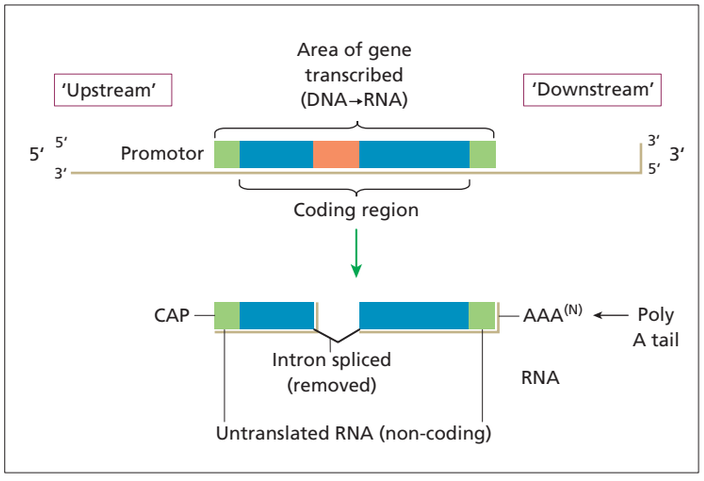


Fig. 11.2 Schematic of a gene and transcription to, and processing of, RNA. The gene comprises the transcribed region, which largely consists of the coding region (including the introns, which will be spliced out and do not code for protein) and the upstream and downstream regions. The promoter region is upstream, although sequences important in determining the level of gene expression in response to a variety of stimuli can be located upstream or downstream. DNA is transcribed into RNA by a DNA-dependent polymerase and the resulting RNA strand processed by removal (splicing) of introns, addition of a string of adenines at the 3′ end (polyA tail) and 'capping' of the 5′ end. Some of the RNA that is transcribed and not spliced out (the untranslated 5′ and 3′ sequences) does not code for protein, but appears to be important for RNA stability and translation into protein. The number of introns is extremely variable: some genes have no introns, whereas others have hundreds of introns, with the length of the introns greatly exceeding the length of the region that directly codes for protein.

translation—whether proteins are then made from any particular RNA molecule. Whether a particular gene is transcribed into RNA is determined by the interaction between a variety of proteins in the cell, and by extracellular signals mediated through a number of pathways that interact with RNA polymerases (enzymes that copy DNA into RNA) via the promoter region of the gene. The promoter, located (usually entirely) 5′ to the coding region of the gene ('upstream'), functions akin to an on/off and volume control on a CD player, controlling whether, and how much, gene transcription takes place in response to instructions received from a myriad of pathways. Transcription factors are proteins that bind to the promoter region of a gene to activate transcription. Various signalling pathways control the transcription of a gene, depending on the transcription factor that binds to the specific gene promoter, and this is a complex area of molecular biology. As mentioned above, the gene itself is likely to be discontinuous, such that the RNA produced may contain what are called introns (areas that do not code for protein), which are cut or spliced out once the RNA is made (see Fig. 11.2). The spliced version of the RNA then proceeds to the ribosome (in the cytoplasm) where protein synthesis occurs. Other changes to the RNA also occur, including the addition of a string of adenines (the so-called polyA tail, which appears to be important for the stability of the RNA) and a process termed capping at the 5′ end of the RNA (see Fig. 11.2). The structure of a protein from the same gene may therefore differ in different cells, depending on the splicing and any other changes to the RNA. Throughout this transfer of information, however, it is the linear sequence of bases within and around the gene that appears important in determining the structure of the protein. Within the coding region of the gene, each group of three adjacent bases ('triplet') specifies a particular amino acid. Outside the coding region, although the DNA may not code for protein directly, the pattern of bases, particularly that before the start of a transcription site in the promoter of the gene, is also important in determining the level of transcription (in response to a variety of stimuli). Primary sequence is therefore more than just a shorthand for the three-dimensional structure of the resulting protein.

Table 11.1 Differences between nuclear and mitochondrial genome (adapted from [5]).

Characteristic	Nuclear genome	Mitochondrial genome
Size of genome	3.3×10^9 bp	16569 bp
Number of genes	25000–30000	37 (13 encoding proteins, 22 transfer RNAs and 2 ribosomal RNAs)
Introns	Frequent	Absent
Transmission	Mendelian	Maternal
Transcription	Genes transcribed individually	Genes transcribed as large polycistrons
Coding DNA	Approximately 3%	93%

Mitochondrial DNA

Mitochondria are intracellular organelles that are involved in cellular aerobic respiration, including generation of ATP, and in cell signalling, particularly cell death pathways. Mitochondria contain their own DNA, which is inherited from an individual's mother [4]. Some of the differences between mitochondrial and nuclear DNA are given in Table 11.1.

Mitochondrial DNA mutations can contribute to ageing and associated disease such as type 2 diabetes, neurological disorders, photoageing and skin cancer [5,6].

References

1 Watson JD, Baker T, Bell S *et al. Molecular Biology of the Gene*, 6th edn. Menlo Park, CA: Benjamin Cummings, 2008.
2 Alberts B, Johnson A, Lewis J *et al. Molecular Biology of the Cell*, 4th edn. New York: Garland Science, 2007.
3 Strachan T, Read AP. *Human Molecular Genetics*, 3rd edn. New York: Garland Science, 2004.
4 Lane N. *Power, Sex, Suicide: Mitochondria and the Meaning of Life*. New York: Oxford University Press, 2005.
5 Taylor RW, Turnbull DM. Mitochondrial DNA mutations in human disease. *Nat Rev Genet* 2005; **6**: 389–402.
6 Birch-Machin MA. The role of mitochondria in ageing and carcinogenesis. *Clin Exp Dermatol* 2006; **31**: 548–52.

Molecular techniques

Extraction of nucleic acid is straightforward. Take a few millilitres of blood, or a small skin biopsy, treat with a proteinase overnight, separate the nucleic acid from protein using phenol and chloroform, and then precipitate the several hundred micrograms of DNA with cold alcohol. This procedure is straightforward but

time consuming and so kits, available from several manufactures, are now commonly used to extract DNA in as little as 30 min. The resulting DNA can be easily pelleted in a microcentrifuge, and appears as a slightly yellow, sticky substance that can subsequently be dissolved in water and assayed on the basis of its absorption of UV radiation. This isolated DNA is made up of the 3 billion bases of genomic DNA from each cell, multiplied by the 100 million or so cells from which the DNA has been extracted. However, at this level of analysis, the DNA from different individuals would look much the same. Mere examination with the eye does not provide any insight into the primary base sequence. The technical revolution in the last quarter century allows such analysis. While whole volumes are devoted to describing the techniques of molecular biology, the principles involved are usually straightforward, and it is often possible intuitively to appreciate how and why they work, and to see how they take advantage of the basic structure of DNA.

Restriction enzymes are naturally occurring enzymes that cleave DNA in a sequence-specific manner. They have been identified in a variety of bacteria, where their principal function seems to be to defend bacteria against particular forms of bacteriophage infection (the principle being that particular sequences might occur in an invading organism but not in the host, and that enzymes specific for these sequences would be able to defend the host from invasion). If the DNA isolated from blood or skin, which consists of pieces upwards of 50 kilobases (kb) in length, is suspended in buffer and incubated with a restriction enzyme, the DNA is cleaved into much smaller fragments. The exact size of the fragments depends on the particular restriction enzyme chosen; some might be expected to cut the DNA every few hundred base pairs, whereas others whose target sequence is not so common might only cut once every million base pairs or so. It is therefore possible to characterize the DNA in terms of its primary sequence structure based on the pattern of fragments obtained following restriction enzyme digests. Furthermore, differences between DNA from different individuals (which are particularly common in the non-coding region of DNA) may show up as differences in the size of the fragments following digestion with particular restriction enzymes (Fig. 11.3). An important feature of many restriction enzymes is that although their action depends on the presence of a particular sequence of bases, DNA is cleaved in such a way that, with another enzyme known as DNA ligase and a source of energy, it can be stuck together again—'cut and paste' in word-processing terminology. This 'cut-and-paste' facility allows small pieces of DNA (say a couple of kilobases long) that have been cut with the enzyme to be inserted into a vector such as a plasmid. The subject of vectors may appear confusing but, for present purposes, molecular biologists have identified and created a whole range of experimental vehicles that allow the propagation of DNA; very much the workhorses underlying the phrase 'cloning of DNA'. A commonly used vector is a plasmid. Plasmids are naturally occurring, extrachromosomal, circular pieces of DNA found in bacteria. Their medical importance is that they may carry antibiotic-resistance genes and transmit these from one bacterium to another. Experimental manipulation makes it possible to 'cut and paste' a piece (an 'insert') of DNA into a plasmid, *transfect* the plasmid back into a bacterium, and wherever the bacterium divides, the plasmid and insert will also be copied. Because bacteria can grow in an exponential fashion, this technique allows large amounts of the insert to be produced (cloned).

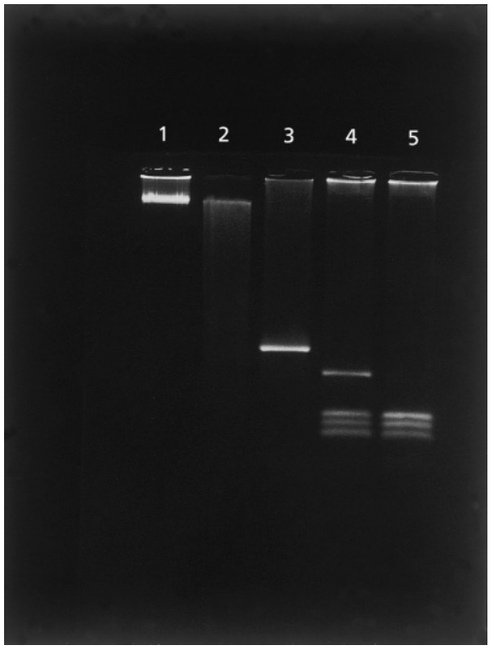


Fig. 11.3 DNA labelled with ethidium bromide and run through an agarose gel and examined under a UV radiation source. Ethidium bromide intercalates into DNA and fluoresces in response to short-wave UV radiation. The first two tracks show a sample of genomic DNA before and after digestion with a restriction enzyme (note the smearing present in track 2). Track 3 shows the human melanocortin 1 receptor (melanocyte-stimulating hormone receptor) amplified using the polymerase chain reaction (PCR). Tracks 4 and 5 show the PCR, shown in track 3, from two individuals digested with a restriction enzyme which reveals a polymorphism due to a mutation at codon 84 of the melanocortin receptor gene.

Additionally, it is possible to restrict (in other words, digest with a restriction enzyme) the DNA isolated from a cell, and 'paste' many of the resulting small pieces of DNA into plasmids (or other suitable vectors), such that each vector will contain only one insert of DNA and that the majority of plasmids would be expected to contain a unique insert. These plasmids can then be transfected back into bacteria, and the resulting collection of bacteria containing many different plasmids comprises a *DNA library*—a representation of a cell's DNA, now in a form that can be cloned, promulgated and used experimentally. An analogous technique can be used to make a complementary DNA (cDNA) library, that is a library that represents the RNA species expressed by a particular cell, in which each 'book' corresponds to a particular RNA molecule (Fig. 11.4). Unlike DNA, RNAs are not ordered in the cell in linear arrays like genes on chromosomes, but rather the RNA from a particular cell consists of hundreds of thousands of individual RNA molecules, each of which can be translated into a particular protein. Unlike DNA, RNAs are expected to differ dramatically between different cell types: keratinocytes will produce a large number of RNAs coding for keratins, whereas these would not be seen in a red-cell precursor, which by contrast will be rich in globin RNAs, and vice versa. Because RNA is diffi-

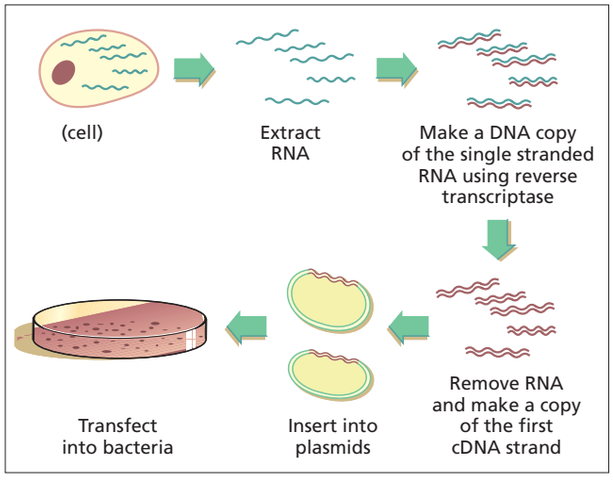


Fig. 11.4 Making a complementary DNA (cDNA) library. RNA (single stranded) is extracted and a cDNA copy of the RNA made using reverse transcriptase. The RNA is then removed, and the first strand of cDNA acts as a template for the second strand of DNA. The short fragments of double-stranded DNA (inserts) are then 'pasted' into plasmids, transfected into a suitable bacterial host, cultured and plated out on agarose. Each bacterial colony will contain a clone of bacteria that contains only one insert. The number of colonies expressing the same insert should reflect the frequency of the RNA species in the cells the library has been made from. Libraries can also be made from genomic DNA, in which case no cDNA synthesis is necessary, but because the desired fragments to be cloned are larger, a variety of other vectors (rather than plasmids) are used.

cult to manipulate experimentally, the RNA species can be converted using reverse transcriptase into a cDNA—very much the reverse of normal transcription, which converts DNA into RNA—and the resulting DNA inserted into a plasmid, such that the population of plasmids now represents the RNA species in any one cell. The resulting library is known as a cDNA library, 'c' because it is complementary to the RNAs in the original cell.

Southern and northern blotting

If the DNA extracted from a eukaryotic cell is cut with a particular restriction enzyme, the resulting fragments might be expected to differ between different individuals, the organization of the fragments therefore providing information about any DNA sequence differences. In order to display the DNA, it is possible to order the resulting fragments of DNA by passing them through an agarose gel within an electric field. The charged DNA molecules will migrate through the gel depending on their mass, with the smallest fragments travelling furthest. However, once the nucleic acid has migrated through the gel, it can be conveniently transferred to a nitrocellulose (or better still a nylon) membrane, in a process called Southern transfer (Fig. 11.5). The DNA is then fixed (cross-linked) to the membrane (which, while looking like a piece of paper, has similar tensile properties to a plastic carrier bag) using UV radiation. Importantly, although the nucleic acid is now covalently bound to the membrane, it is still free to take part in hydrogen-bond reactions. This transfer of DNA from an agarose gel to a membrane is known as Southern blotting, after its inventor Ed Southern; northern blotting (a pun on Southern!) refers to the transfer of RNA and western blotting to the transfer of proteins.

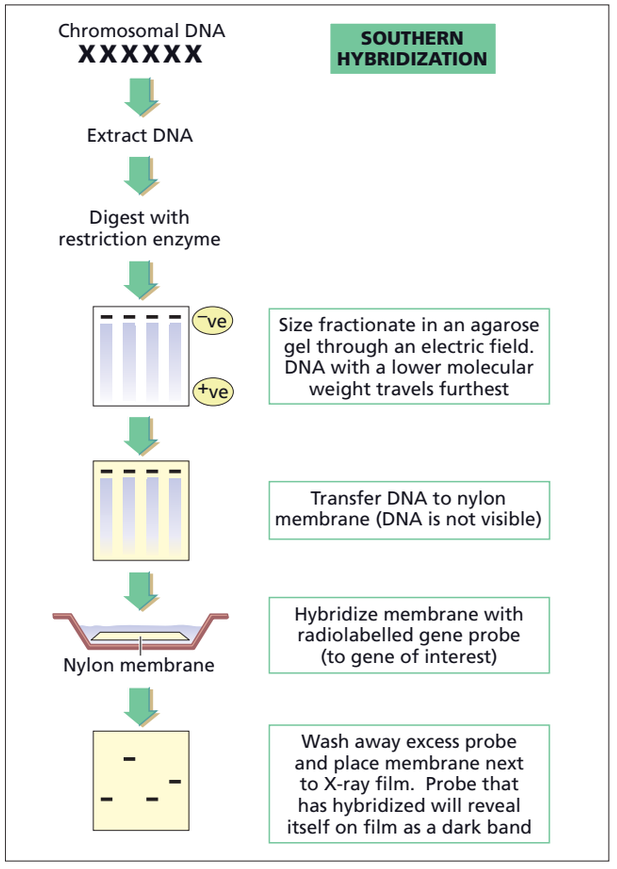


Fig. 11.5 Southern hybridization. Genomic DNA extracted from cells can be cut with a suitable restriction enzyme and then size-fractionated through an agarose gel within an electric field. The DNA in the gel can then be transferred (or blotted) to a nylon (or nitrocellulose) membrane, which is then hybridized with a radiolabelled probe complementary to the target sequence. Following hybridization, the membrane is washed to remove excess probe and sequences that have bound non-specifically. The membrane is then placed next to radiation-sensitive film overnight. Wherever the radiolabelled probe has bound to a complementary sequence, a band will be visible on the film. In this example, DNA from four individuals was run on the gel and hybridized. The differences in the position of the black bands on the autoradiograph reflect that the size of the DNA fragment containing the gene of interest differs between individuals. The most likely explanation for this polymorphism is that the restriction enzyme has cut the DNA differently because of variations in the DNA between the individuals close to, but probably not within, the gene of interest (see text). A similar procedure can be carried out to examine RNA expression and is called northern (as compared with Southern) blotting. Because RNA molecules exist individually rather than as large chromosomes (as for DNA), no restriction digestion is necessary; the details of the transfer of RNA to a nylon membrane also differ from that needed for DNA. When the membrane is placed next to film, the intensity of the resulting band will reflect the amount of that RNA species in the target cell of interest. More than one band may be seen in a single track, reflecting differences in how the RNA is spliced (there may be more than one splice variant in a particular cell).

Because RNAs exist as individual molecules rather than as long arrays on chromosomes like DNA, RNA extracted from cells is fractionated immediately, and does not have to be first digested with restriction enzymes.

Following Southern blotting, the DNA attached to the membrane will not be visible to the naked eye, although it is possible to see the DNA when it is size fractionated through an agarose gel

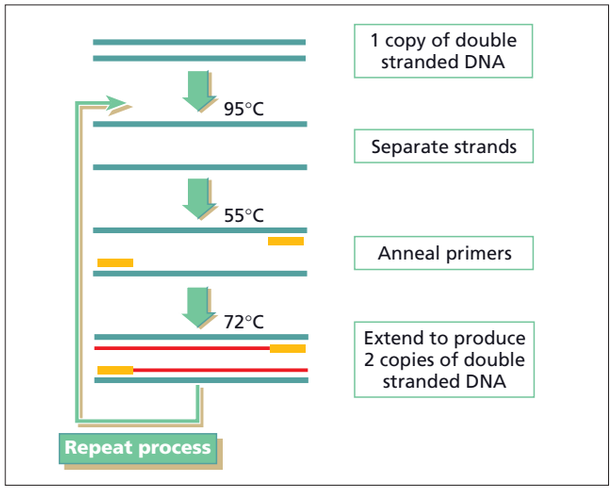


Fig. 11.6 Polymerase chain reaction (PCR). A double-stranded molecule of DNA is denatured into two complementary strands using heat (95°C). Primers are short stretches of DNA, usually 18–25 base pairs in length, complementary to sequences on the separated strands of DNA. For the primers to anneal, the temperature needs to be approximately 55°C, and the presence of a primer is essential for the polymerase (plus the necessary bases and energy) to make complementary copies of each strand of DNA ('extension'). The two double-stranded molecules that are produced can then act as templates for further rounds of replication; hence the term 'chain reaction'. The technical breakthrough that has made PCR so successful was the discovery of polymerases that are so heat stable that they are not destroyed during the denaturation (strand separation) step (such polymerases were found in bacteria that inhabit hot springs).

by virtue of the fact that dyes such as ethidium bromide intercalate in DNA and fluoresce under UV radiation (see Fig. 11.3). If such a gel or membrane is examined, a long smear comprising millions of molecules of DNA will be evident; for most purposes it will be necessary to characterize the DNA further, so that individual genes or stretches of DNA can be examined (see Fig. 11.3). This is usually accomplished by using a labelled gene probe that is complementary to the target of interest, which will bind to the target nucleic acid located somewhere within the smear (and which will comprise only a tiny fraction of the total DNA, for instance one gene out of 25 000).

Polymerase chain reaction (PCR)

Mention has already been made of the use of DNA or RNA polymerases, enzymes that allow copies of a nucleic acid to be made. For example, a DNA-dependent DNA polymerase will make complementary DNA copies of a DNA molecule, whereas reverse transcriptase is an RNA-dependent DNA polymerase and will therefore make DNA copies of RNA. As well as an energy source and the necessary nucleotide bases, most polymerases require a primer or short sequence of DNA complementary to the strand to be copied, from which to start the synthesis of the complementary copy. The most celebrated use of DNA polymerases is *PCR* (Fig. 11.6), application of which has revolutionized much of molecular biology and more recently clinical diagnostics. The principle underlying PCR is that if primary sequence information is available for a primer area (usually 15–25 bases long) outside the target area of interest, then once a copy of both strands is made using a DNA polymerase and the resulting daughter strands reanneal, heating the DNA to near 100°C causes the daughter strands to separate again and in turn act as templates for further rounds of replication. The technical breakthrough has been the identification of thermally stable DNA polymerases that are not destroyed by the high temperature needed to separate the complementary strands. Intuitively, one can see that this replication is logarithmic, and therefore PCR allows the amplification of DNA many millionfold. In practice, there are some constraints: amplifying short sequences of 400–500 bases is straightforward but the limit is reached at around 10–15 kb; the extreme sensitivity of the technique can also be a disadvantage, as laboratory contamination can be a major hazard, a drawback which should not be forgotten when PCR is used to diagnose infectious agents in clinical biopsies.

In *reverse transcription PCR* (RT-PCR), RNA is extracted from tissue or cells, converted to its corresponding cDNA and then this cDNA is subjected to PCR. The amplified PCR product is then run on an agarose gel (as in Fig. 11.3). The technique is extremely sensitive and has been of great use in the study of gene expression patterns in skin pathophysiology. Its utility in skin disease has partly been because of the difficulty of extracting high-quality RNA in large amounts from intact skin (as compared with cell culture). The main disadvantage of PCR is that because it is so sensitive, DNA species of little biological purpose may be amplified. *Real-time PCR* is identical except the progress of the reaction is monitored in real time. A fluorescent probe (e.g. Taqman-type probe), complementary to the gene of interest, binds to the DNA and fluorescence increases with the number of copies of DNA allowing quantitation of gene expression. A major advantage of real-time PCR is that running a gel is not necessary.

DNA sequencing

DNA-dependent polymerases also play a central role in the commonest method of sequencing DNA. As long as there is a cloned source of DNA, either from the gene being cloned in a plasmid or from PCR, it is possible to determine the primary base sequence. This makes use of a DNA polymerase and the four nucleotide bases, only one of which is labelled; in the original method a radioactive label was used. As well as bona fide bases, particular nucleotides ('terminators') are added to the mix; these cause the DNA polymerase to fall off the template, resulting in complementary strands that have terminated prematurely. These aborted transcripts will therefore reveal themselves as shorter fragments when the products of the reactions are run on a polyacrylamide gel, resulting in a ladder of lines that will reflect the primary sequence. If separate terminator bases are used in each of the four reactions, one for cytosine, one for guanine, one for thymine and one for adenine, and the resulting four reactions are run out side by side on a gel, then the resulting pattern of radiolabelled, prematurely terminated bands will correspond to the primary sequence (Fig. 11.7).

For large-scale sequencing, such as was necessary to sequence the human and mouse genomes, new technology had to be developed. In dye-terminator sequencing, each of the four dideoxynucleotide chain terminators is labelled with a different fluorescent dye, which emits fluorescence at a specific wavelength. This is



Fig. 11.7 An example of a DNA sequence obtained using the dideoxy method of sequencing for which Sanger was awarded a second Nobel prize. Essentially, copies of the template are made using a DNA polymerase only. The presence of dideoxynucleotides (instead of deoxynucleotides as in normal DNA) in the reaction causes the template copies to terminate prematurely. Four such copying reactions are carried out, one for each dideoxy base, such that the reaction terminates where the base was being added. When the products of all four reactions are run out on one gel, then reading across the bands reflects the order of premature termination products, which in turn reflects the primary sequence of the DNA strand being copied. This method is now mainly of historical interest only. (Courtesy of M. Birch-Machin, Department of Dermatology, University of Newcastle, Newcastle, UK.)

analysed by computer and the data output is a fluorescent peak trace chromatogram (Fig. 11.8). This technology reads about 67 000 base pairs per hour. However, newer higher-throughput sequencing technology is now available, such as 454 (Roche) or Solexa (Illumina) sequencing [1].

RNA interference

RNA interference (RNAi) is a mechanism that inhibits gene expression through degradation of specific mRNA molecules. This phenomenon of gene-specific silencing was described initially in petunia plants before its recognition as a widespread, possibly universal, mechanism. The discovery that RNAi is active in mammals opened the gates for the possibility of effectively silencing virtually any gene with a known sequence, either for basic scientific interest or for therapeutic purposes [2]. The RNAi pathway is triggered by double stranded RNA (dsRNA) molecules sharing sequence-specific homology to particular 'target' mRNAs. The RNase III enzyme, Dicer, is a key molecule in the RNAi pathway as it binds and cleaves long dsRNA molecules into short fragments, known as small interfering RNAs (siRNAs). siRNA duplexes are small, 19-bp dsRNA molecules, bearing two-nucleotide (nt) 3′ overhangs at each end. siRNA duplexes mimic the structure of mature *microRNA* (miRNA) duplexes, which are genomically encoded RNAs that do not code for proteins and are involved in regulating gene expression, particularly during development. It is estimated that there are about 500 miRNAs in mammalian cells, regulating about 30% of genes [3]. The RNA-induced silencing complex (RISC) (Fig. 11.9) incorporates one of the two strands of the siRNA duplex, known as the antisense or guide strand, where it acts as a guide RNA to direct the RISC to complementary mRNAs, while the second strand is degraded. A critical component of the RISC, the Argonaute-2 (Ago2) protein, then cleaves the targeted mRNA at a defined position; the targeted mRNA is then degraded by cellular RNAses, thereby preventing it from being used as a translation template. The exogenous introduction of synthetic siRNA duplexes (19–25 bp in length) directly into the cell is a simple and effective technique to induce transient RNAi. These siRNAs act catalytically at non-toxic, low nanomolar concentrations and are capable of cleaving up to 95% of the target mRNA in the cell (Fig. 11.9).

Genomics

Human genomics is the large-scale study of the entire human DNA sequence. Studying the human genome has required the development of appropriate technology to manipulate and sequence DNA and appropriate computer software to analyse the large amounts of information generated. A single nucleotide polymorphism (SNP, pronounced snip) is a single nucleotide substitution in DNA. There are over 10 million SNPs listed in the dbSNP database. A haplotype is a set of SNPs on a single chromosome that are likely, statistically, to be inherited together. The emergence of microarray chips has facilitated both the study of SNPs and gene expression, at the transcriptional level. A gene expression 'chip' has thousands of DNA probes at high density on silicone slides or beads on a slide. Target RNA is reverse-transcribed, fluorescently labelled and hybridized to the slides and the signal read as fluorescent intensity. Because more than one fluorescent label can be used, the relative intensity of RNA from different tissues or cells that have undergone an experimental intervention can be hybridized at the same time and the readout quoted as the ratio of expression in one sample to that in another (based on the ratio of fluorescence for each probe). This allows the characterization of gene expression from cells in culture or from tissue.

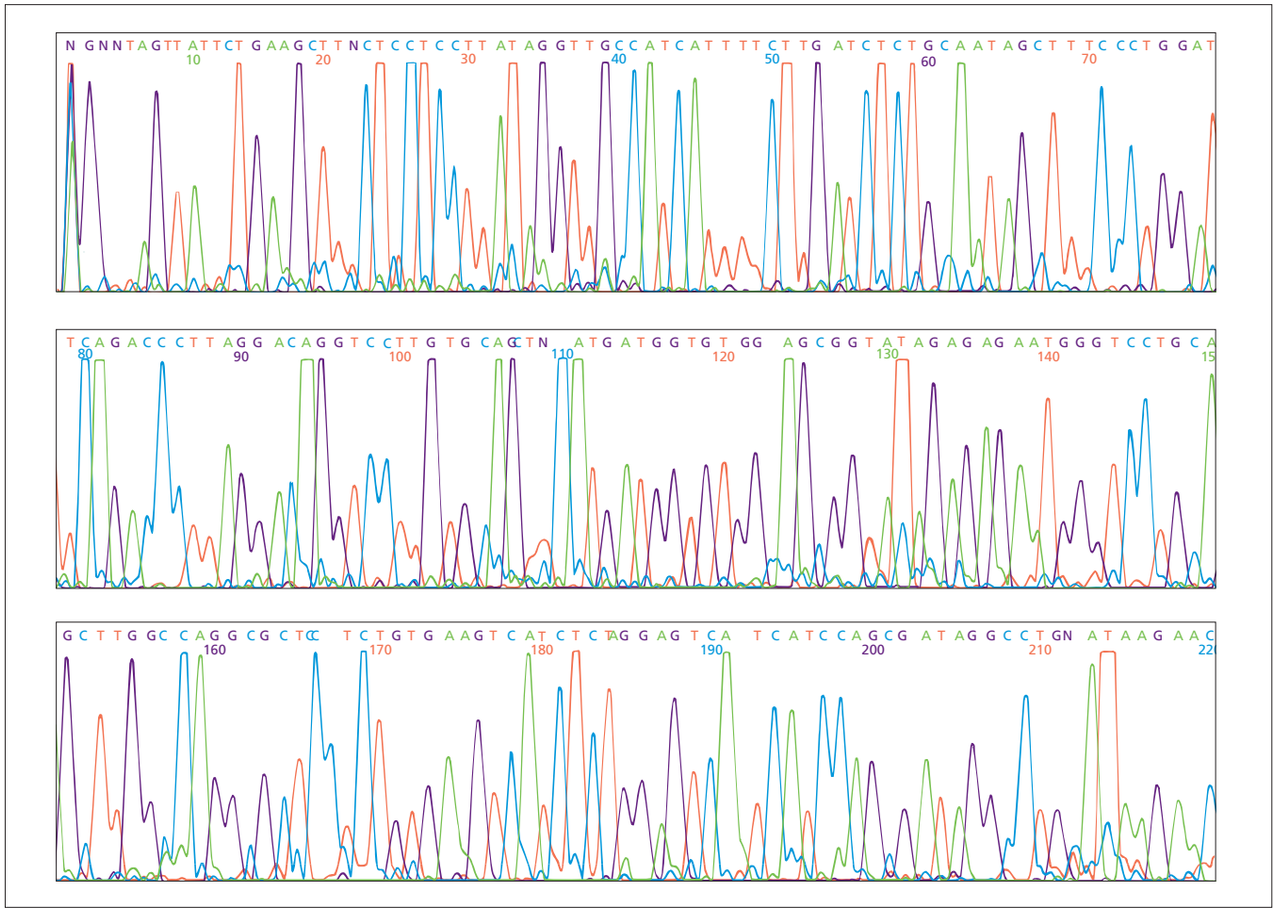


Fig. 11.8 An example of an automated sequence output using fluorescent primers. In this method, each base or primer pair is labelled with a fluorescent dye, the sequencing reaction carried out as described in Fig. 11.7, and the products run in one lane of a gel. A laser beam directed at one point of the gel causes the dyes to fluoresce as the DNA fragments move past, and because the maximum fluorescence occurs at a different wavelength for each of the four dyes, the sequence can be read by computer. (Courtesy of M. Birch-Machin, Department of Dermatology, University of Newcastle, Newcastle, UK.)

Pathway analysis can then be used to examine the patterns of gene expression under various conditions. Other microarray applications are outlined in Table 11.2.

Proteomics

The field of proteomics encompasses the study of all proteins expressed in a tissue at a given time, including their various isoforms, identification of post-translational modifications (for example, phosphorylation and glycosylation) and protein–protein interactions [4]. When a new gene is sequenced, it is of interest to find out where the gene-encoded mRNA transcripts and proteins are expressed and to find out their function. Interestingly, there is poor correlation between mRNA expression levels and protein expression. Genes can be variably expressed, gene splicing and mRNA editing are frequent and post-translational modification of the protein occurs, making proteomics a challenging field [5]. Also, although the genome of a cell is relatively constant, the proteome is in a constant state of change in response to the cell cycle, drug exposure, age, etc. Proteomic analysis can be simplified by isolation of a class of proteins with similar chemical properties. For example, proteins that are tyrosine phosphorylated can be immunoprecipitated with a phosphotyrosine antibody. An initial approach usually involves separation of the protein using one-dimensional (1-D) or two-dimensional (2-D) gel electrophoresis followed by excision of the band of interest and identification of peptides using mass spectrometry.

Bioinformatics

Bioinformatics is a science that combines molecular biology, computer science and information technology. This involves analysis of nucleotide and amino acid sequences, protein domains and protein structures [6]. In Table 11.3, some web resources are listed.

References

1 von Bubnoff A. Next-generation sequencing: the race is on. *Cell* 2008; **132**: 721–3.

2 Elbashir SM, Harborth J, Lendeckel W *et al.* Duplexes of 21-nucleotide RNAs mediate RNA interference in cultured mammalian cells. *Nature* 2001; **411**: 494–8.

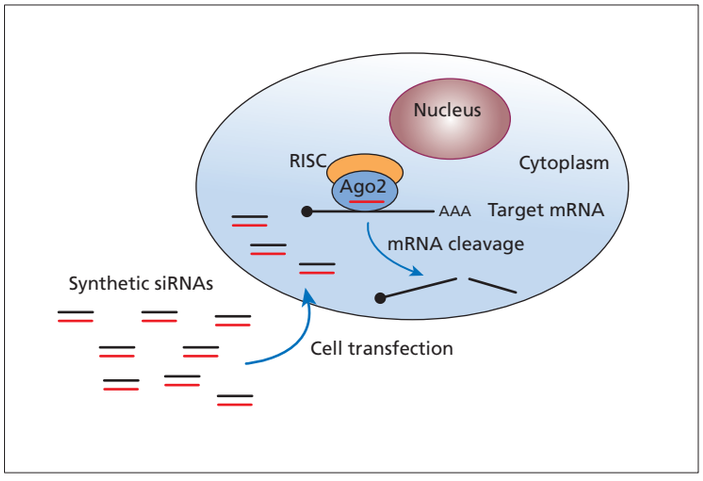


Fig. 11.9 RNA interference (RNAi) in mammalian cells by transfection with synthetic small interfering RNAs (siRNAs). Direct transfection of synthetic siRNAs (19-bp short interfering duplexes) into mammalian cells in culture can lead to cleavage of target mRNA, and subsequent transient suppression of gene expression. The antisense siRNA strand (represented in red) is incorporated into the RNA-induced silencing complex (RISC) and guides it to complementary mRNA sequences (target mRNA). When the RISC complex containing the siRNA antisense strand specifically pairs with complementary mRNA it induces cleavage of the target mRNA (mRNA cleavage). (Courtesy of Dr V. Martins, Centre for Cutaneous Research, Barts and the London School of Medicine and Dentistry, London, UK.)

Table 11.2 Microarray applications.

Type	Application
Comparative genomic hybridization	Examination of chromosomal loss or gain
Single nucleotide polymorphism array	Detection of polymorphisms and LOH
Chromatin immunoprecipitation on chip	Identification of DNA sequences binding to a protein
Expression arrays	Examination of gene expression

LOH, loss of heterozygosity

Table 11.3 Web resources on bioinformatics.

Name	Content	Link
BLAST	Comparison of sequences	http://blast.ncbi.nlm.nih.gov/Blast.cgi
UCSC	Genome bioinformatics	http://genome.ucsc.edu/
Entrez	NCBI databases	http://www.ncbi.nlm.nih.gov/sites/entrez
HapMap	Database of human haplotypes	http://www.hapmap.org
GEO	Array data repository	http://www.ncbi.nlm.nih.gov/geo/
Phosphosite	Database of phosphorylation sites	http://www.phosphosite.com
dbSNP	Database of human SNPs	http://www.ncbi.nlm.nih.gov/SNP

NCBI, National Centre for Biotechnology; GEO, Gene Expression Omnibus.

3 Boyd SD. Everything you wanted to know about small RNA but were afraid to ask. *Lab Invest* 2008; **88**: 569–78.
4 Pardanani A, Wieben ED, Spelsberg TC, Tefferi A. Primer on medical genomics. Part IV: Expression proteomics. *Mayo Clin Proc* 2002; **77**: 1185–96.
5 Guo Y, Fu Z, Van Eyk JE. A proteomic primer for the clinician. *Proc Am Thorac Soc* 2007; **4**: 9–17.
6 Elkin PL. Primer on medical genomics part V: bioinformatics. *Mayo Clin Proc* 2003; **78**: 57–64.

Application of molecular techniques

The utility of the techniques described above has in the recent past been extended in two particular directions. Firstly, it has been possible to marry the approaches of classical genetics and molecular biology to such a degree that mapping of human diseases characterized by a Mendelian pattern of inheritance is now very straightforward, and this will be discussed in the next section. Secondly, it has become possible to manipulate genes experimentally, such that they can be overexpressed or inhibited in either living cells in culture or, more recently, living organisms (transgenic animals).

When a gene for a particular disorder has been identified, it is frequently possible to obtain a good idea of the function of that gene, based on either sequence similarity to genes previously identified, or knowledge about similar genes in model organisms such as *Drosophila*, mouse or yeast. For example, *patched*, the gene underlying the naevoid basal cell carcinoma syndrome, once identified, was shown to have a homologue in *Drosophila*, and work in this 'model organism' had already provided important insights into the protein's cellular localization and participation in various signalling pathways [1,2].

Once a gene is identified, either through genetic linkage or candidate gene approaches, as described below (p. 11.11), a number of techniques facilitate studies of the gene's expression and function. A technique called *in situ* hybridization is used to examine expression of RNA in tissue and this is widely used in dermatology. In some instances, a gene can be transcribed into RNA but, perhaps surprisingly, little protein may be made. By contrast with *in situ* hybridization, immunohistochemistry detects protein expression, and therefore the two techniques can be considered complementary. For *in situ* hybridization tissue sections are prepared and exposed to a cDNA or RNA probe, which is tagged with either a radioisotope or a colour label (as used in immunocytochemistry), and the experimental conditions manipulated such that where there is base pairing between the probe and the target, the RNA signal is detected. Radioactive methods were popular historically, but colour detection methods such as digoxigenin are generally used today. The R-spondin 4 gene (*RSPO4*) is mutated in inherited anonychia and Fig. 11.10 elegantly demonstrates expression of *RSPO4* in nail using whole-mount *in situ* hybridization in a mouse embryo [3].

Cloned genes may be manipulated *in vitro* to elucidate the gene function. Although one may associate a particular change in DNA sequence with a particular disease state, at some stage it may be necessary to prove functionally how the mutation leads to disease. The ability to clone DNA in vectors such as plasmids allows the possibility of transferring these plasmids containing the target gene into human cells in the laboratory. If the plasmids are engineered with appropriate regulatory sequences (promoter and related upstream sequences) that will be recognized by eukaryotic cells, the cells may proceed to transcribe genes from the plasmid in a temporary fashion (*transient transfection*) or, if particular selection markers are encoded by the plasmid, the plasmids may stably

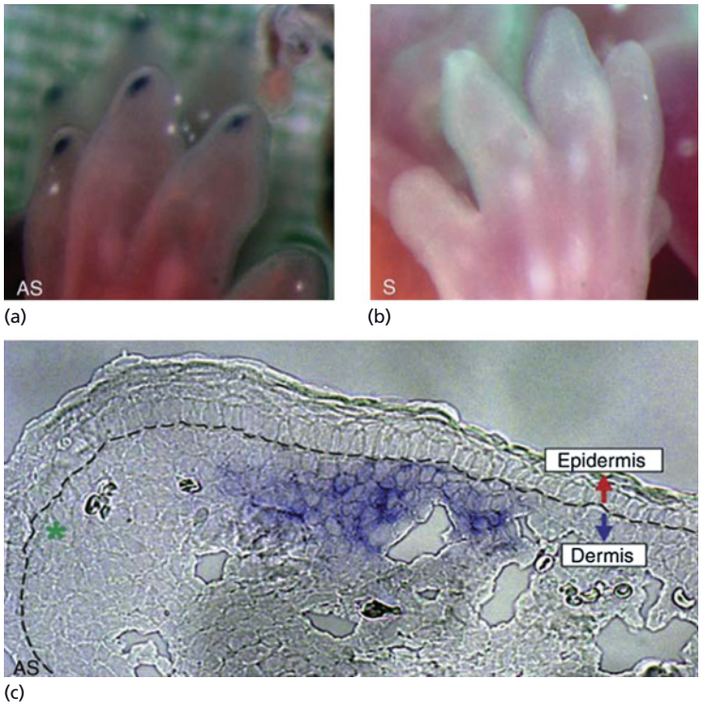


Fig. 11.10 Whole-mount *in situ* hybridization of E15.5 mouse embryos showing specific expression of Rspo4 at the sites of nail development. (a) Detection of Rspo4 expression (blue) using an antisense probe (AS). (b) The negative control using a sense probe (S). (c) A section through the nail region shows that expression is confined to the nail mesoderm. The boundary between dermis and epidermis is marked with a broken line, and the green asterisk denotes the tip of the finger (From Blaydon *et al.* [3]).

integrate into the host nuclear DNA (*stable transfection*). Genes can also be cloned into viral vectors, such as retroviral or lentiviral vectors, the plasmid DNA transfected into a packaging cell, and the secreted viral particles used to stably transduce cell lines or primary keratinocytes [4]. Use of such experimental systems allows examination of the effects of any cloned gene on cellular functions such as proliferation, migration, adhesion and apoptosis. A cDNA of interest may also be transfected into cultured cells simply to obtain large amounts of the resulting protein for further analysis. Mutated genes, either spontaneously occurring or constructed in the laboratory (usually using PCR-based site-directed mutagenesis), can also be transfected, and the influence of these mutations used to map out important domains of the protein's function [5]. A similar assay can be used to study the upstream regulatory regions that are important in controlling a gene's expression. Key regulatory sequences upstream of a gene's start site can be placed in a plasmid vector and transfected into cells. The gene's product itself can be assayed, or more often the gene of interest can be replaced with a gene called a 'reporter' that lends itself to experimental analysis. For instance, if one is interested in studying the regions upstream of a gene that are important in determining its expression (i.e. the regions of the promoter that mediate binding to a variety of other cellular proteins and signalling pathways), then one can clone this particular region of the genomic DNA, attach it to a reporter gene that codes for a fluorescent material such as luciferase, and transfect this into cells. The cells can then be treated with a variety of agents to discover whether they are able to induce, or alter, transcription of the reporter gene acting through the promoter sequence being studied.

The development of siRNA technology has allowed transient or stable knockdown of target mRNA using siRNA duplexes or short hairpin (sh) RNAs in retroviral vectors, respectively, followed by functional studies [6]. Microarray technology can be applied using very small amounts of RNA. As an example, cDNA libraries were generated from 50 pg of RNA from single putative epidermal stem cells. Gene expression profiling was performed using expression chips and a new putative stem cell marker was identified, called *Lrig1*, a known antagonist of the epidermal growth factor receptor (EGFr). Down-regulation of *Lrig1* increased EGFr expression and cell proliferation, consistent with the role of this gene in stem cell biology [7].

Techniques that allow the production of transgenic animals, which either carry an additional copy of the gene or, by taking advantage of the presence of endogenous recombinases, allow a particular gene to be deleted, are very powerful. Readers are directed to standard textbooks of molecular and cell biology for further details. For instance, imagine one wanted to examine the effects of a particular mutant form of a human keratin gene that had been associated with a particular skin disease. The mutated human gene, once identified, can be cloned and inserted into a plasmid with the appropriate upstream regulatory sequence (promoter), which means that the gene will only be expressed in a particular target situation. Obviously, for this particular experiment one would only wish to express the mutant gene in a physiologically appropriate manner and so ideally its own promoter should be used. Of course it is not necessary to wait for a spontaneous mutant in a human population from which to make a transgenic mouse. One could mutate a normal human gene and then insert this into a mouse to see what happens. In fact, it was this approach that first suggested that mutations of *K14* or *K5* cause epidermolysis bullosa; transgenic mice in which a mutated *K14* gene was expressed in the basal layer of skin showed a phenotype corresponding to that of epidermolysis bullosa simplex [8].

An added twist to these sorts of experiment is that it is possible, by using the appropriate regulatory regions that determine where a gene is expressed, to express a gene in an unphysiological context. This can be experimentally revealing. For instance, β1 integrin is normally expressed in the basal layer of skin, but when transgenic mice are produced in which β1 integrin is expressed suprabasally, by expressing the gene under the involucrin promoter, a phenotype resembling psoriasis is seen [9]. Because of the specificity of expression patterns of the various keratin genes, their promoters have been frequently used to regulate the expression of a variety of other genes within skin, including various cytokine genes.

An alternative transgenic experimental design is that of homologous recombination, in which endogenous recombinases allow wild-type sequence and a mutated vector sequence to be interchanged in embryonal stem cells. These cells can then be used to create chimeric mice, which later can be bred so that they are null for the relevant gene (i.e. they do not have any functional gene on

either chromosome) [10]. If a gene is necessary for normal development, then the null mouse may die *in utero*. The technique of Cre/*lox* recombination allows a focal knock-out of the gene product (i.e. not in the whole animal) such that frequently the mutation is not embryonically lethal and that some animals will survive into adulthood where a phenotype may be seen in at least part of the animal [11]. A more sophisticated approach to controlling gene expression has also been developed by combining Cre/*lox* with a tetracycline-regulated transcriptional system. In this combination system, expression of Cre occurs only when the drug tetracycline is administered, allowing scientists to switch gene expression on and off. A further approach is the generation of a hypomorphic mouse that expresses just enough of the gene of interest to be viable, but still has the disease phenotype [12]. A good example is the recessive dystrophic epidermolysis bullosa hypomorphic mouse that expresses about 10% of wild-type type VII collagen and survives, in contrast to the collagen VII null mouse that dies in the neonatal period [10,12]. Despite the expense and time required, these approaches are extremely powerful, and can go a long way to determining the function of a certain gene is at the physiological or whole-animal level, or how mutations of a gene contribute to a particular phenotype. However, perhaps the most striking observation in 'knock-out' animals made using homologous recombination is how often such animals are grossly normal. This has inevitably prompted re-examination of the amount of redundancy, and the biological significance of this redundancy, in various biological pathways.

References

1 Gailani MR, Ståhle-Bäckdahl M, Leffell DJ *et al.* The role of the human homologue of *Drosophila patched* in sporadic basal cell carcinomas. *Nat Genet* 1996; **14**: 78–81.

2 Hahn H, Christiansen J, Wicking C *et al.* A mammalian *patched* homolog is expressed in target tissues of *sonic hedgehog* and maps to a region associated with developmental abnormalities. *J Biol Chem* 1996; **271**: 12125–8.

3 Blaydon DC, Ishii Y, O'Toole EA *et al.* The gene encoding R-spondin 4 *(RSPO4)*, a secreted protein implicated in Wnt signaling, is mutated in inherited anonychia. *Nat Genet* 2006; **38**: 1245–7.

4 Chen M, O'Toole EA, Muellenhoff M *et al.* Development and characterization of a recombinant truncated type VII collagen 'minigene'. Implication for gene therapy of dystrophic epidermolysis bullosa. *J Biol Chem* 2000; **275**: 24429–35.

5 Woodley DT, Hou Y, Martin S, Li W, Chen M. Characterization of molecular mechanisms underlying mutations in dystrophic epidermolysis bullosa using site-directed mutagenesis. *J Biol Chem* 2008; **283**: 17838–45.

6 Sur R, Lyte PA, Southall MD. Hsp27 regulates pro-inflammatory mediator release in keratinocytes by modulating NF-kappaB signaling. *J Invest Dermatol* 2008; **128**: 1116–22.

7 Jensen KB, Watt FM. Single-cell expression profiling of human epidermal stem and transit-amplifying cells: Lrig1 is a regulator of stem cell quiescence. *Proc Natl Acad Sci USA* 2006; **103**: 11958–63.

8 Vassar R, Coulombe PA, Degenstein L *et al.* Mutant keratin expression in transgenic mice causes marked abnormalities resembling a human genetic skin disease. *Cell* 1991; **64**: 365–80.

9 Carroll JM, Romero MR, Watt FM. Suprabasal integrin expression in the epidermis of transgenic mice results in developmental defects and a phenotype resembling psoriasis. *Cell* 1995; **83**: 957–68.

10 Heinonen S, Männikkö M, Klement JF *et al.* Targeted inactivation of the type VII collagen gene *(COL7A1)* in mice results in severe blistering phenotype: a model for recessive dystrophic epidermolysis bullosa. *J Cell Sci* 1999; **112**: 3641–8.

11 Shirakata Y, Kimura R, Nanba D *et al.* Heparin-binding EGF-like growth factor accelerates keratinocyte migration and skin wound healing. *J Cell Sci* 2005; **118**: 2363–70.

12 Fritsch A, Loeckermann S, Kern JS *et al.* A hypomorphic mouse model of dystrophic epidermolysis bullosa reveals mechanisms of disease and response to fibroblast therapy. *J Clin Invest* 2008; **118**: 1669–79.

Strategies for identification of disease-causing genes

The spectacular advances in the application of molecular biology to the genetics of human disease have largely been confined to disorders characterized by a simple Mendelian inheritance pattern (such as autosomal dominant or autosomal recessive). Examples include the discovery that mutations in keratin genes can cause a range of skin diseases [1] and the identification of *patched* as the tumour-suppressor gene underlying Gorlin's syndrome and sporadic basal cell carcinoma [2,3]. There are two approaches to identifying the causative gene for a disorder that shows a Mendelian pattern of inheritance: genetic linkage (genome-wide analysis) and candidate gene approaches. In many instances, the successful identification of a disease-causing gene relies on a combination of these approaches, and such examples are discussed below.

In the candidate gene approach, a starting point is the suspicion that a particular gene may be implicated in a particular disorder. Clues may arise from the phenotype of affected individuals, histology, other similar diseases where the gene is known, etc. The candidate gene is then examined for the presence of mutations in an affected kindred. The obvious limitation of this approach is that it only works if understanding of the pathophysiology of a disorder is sufficient to allow a candidate to be identified, and if the relevant gene has been cloned. For instance, once the tyrosinase and tyrosinase-related genes were identified, they were obvious candidates to examine for mutation in individuals with albinism or other pigmentary disorders [4]. Mutation detection can be undertaken using a number of strategies, but the gold standard is DNA sequencing. Often, however, particularly when large genes are examined or a large number of individuals need to be studied, screening techniques are used that, while not providing full sequence information, can detect many, if not all, changes in comparison with the known sequence (e.g. PCR amplification of exons followed by conformational change analysis such as single-stranded conformational polymorphism or heteroduplex and melt-curve analysis) [5]. A possible strategy for searching for a mutation in a known or candidate gene is illustrated in Fig. 11.11. The disadvantage of the candidate gene approach is that, for many skin disorders, our knowledge of the underlying pathophysiology is so limited that we are unable to identify suitable candidates. A genomic approach can also be taken, for example microarray technology comparing gene expression from fibroblasts or keratinocytes from a normal and an affected individual, particularly in recessive conditions, might reveal a single gene with markedly reduced expression in the affected individual.

When little is known about the underlying pathophysiology of the disorder, the only viable strategy is that based on genetic linkage or genome-wide analysis. This requires a suitable kindred, preferably showing Mendelian inheritance of the trait, and traditionally the use of polymorphic microsatellite markers. A standard, commercially available panel consists of 400 microsatellite

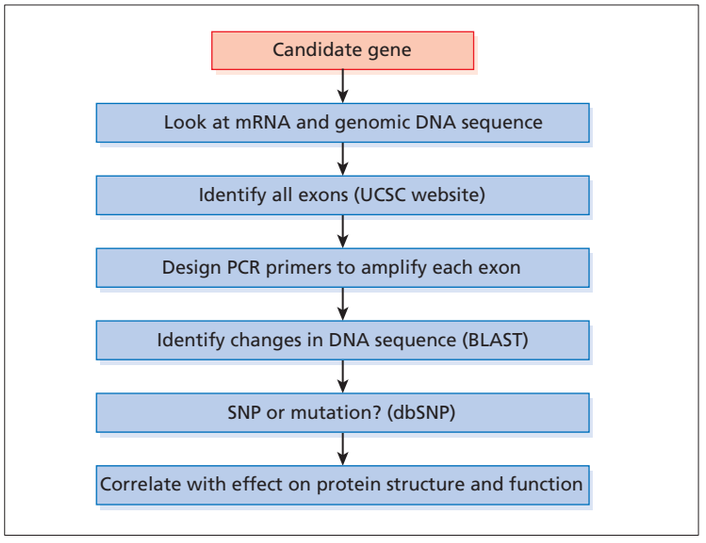


Fig. 11.11 Strategy for finding a mutation in a gene.

markers (fluorescently tagged primer pairs) covering the entire genome. Evidence of linkage may then be confirmed by selecting further microsatellite markers, at closer intervals, spanning the chromosomal area of interest. Genetic mapping compares the inheritance pattern of the trait with the inheritance pattern of a chromosome region, allowing one to find a chromosomal region that all the affected but none of the unaffected have in common. Ideally, large kindreds are needed, but if these are not available, then it may be possible to analyse several different kindreds, assuming that the same gene causes the disorder in the respective kindreds. This assumption is not always warranted; for instance, mutations of *K5* and *K14* located on different chromosomes both cause epidermolysis bullosa. When numerous loci are examined for linkage to a particular trait, statistical tests are required to determine whether the association between a particular trait and a particular chromosomal position could have occurred by chance. This is conventionally quoted as the log of the odds ratio (lod score), and as a rule of thumb a lod score of at least 3, and preferably higher, is required. (A lod score of 3 approaches a similar level of significance as that seen with a conventional statistical test with a value of $P = 0.05$.)

Although candidate gene approaches and genetic linkage/positional cloning have been described as alternative approaches, in practice they are often combined, and dermatology has already provided some pertinent examples of such experimental synergism, notably the identification of mutations in keratin genes as the cause of a range of cutaneous disorders. Keratin genes were among the first human genes identified, largely because their expressed RNA represents such a major proportion of the RNA species of a keratinocyte; early cDNA libraries from keratinocytes consisted predominantly of keratin cDNA clones. Despite the high levels of keratin expression in keratinocytes, the raising of antibodies, and numerous studies trying to relate keratin gene expression to disease states, the exact function of keratins remained uncertain. One can imagine two experimental approaches: (i) what disease would result from a mutated keratin ('gene looking for a disease'); and (ii) knowing that keratins are highly expressed in skin, would positional cloning of various skin diseases centre on the known clusters of keratin genes located on chromosomes 12 and 17 ('diseases looking for a gene')? As it turned out, for keratins and epidermolysis bullosa the answer to both these questions was the same, and arrived at within weeks of each other. Mice that had been born harbouring an experimentally mutated keratin showed a phenotype strikingly similar to that seen in epidermolysis bullosa simplex [6]. Almost simultaneously, positional cloning in kindreds mapped the cause of the same disorder literally on top of *K14*, a coincidence too good to ignore [7]. Because *K14* combines with *K5*, it was predicted and subsequently shown that the same phenotype could be produced from mutations in *K5* (even though *K5* and *K14* are located on different chromosomes). Because many keratin genes are clustered on chromosomes 12 and 17, it took little effort to examine whether other inherited blistering disorders might involve other keratin genes. Analysis of kindreds with bullous ichthyosiform erythroderma showed that this disorder also mapped to the keratin cluster and subsequently was found to be due to mutations of *K1* or *K10* [8]. It has been possible to extend this 'phenotypic walking' (by analogy with chromosome walking) even further. Given that bullous ichthyosiform erythroderma is the result of *K1* or *K10* mutations, it was no surprise when ichthyosis of Siemens, a condition with many similarities to bullous ichthyosiform erythroderma, was found to be due to mutations of *K2e* (expression of *K2e* is similar to that of *K1* or *K10*, but more superficial, in keeping with the histological features) [9]. Similarly, some of the cases of palmoplantar keratoderma, where the pattern of blistering is restricted to sites of maximal expression of *K9*, were shown to be secondary to *K9* mutations [10]. However, this process can be taken even further. Patients with pachyonychia congenita show similar involvement of the palms, and a collection of other phenotypic features suggestive of defects in *K17*. Candidate-directed mapping in several kindreds showed linkage to the keratin clusters [11], and pachyonychia congenita has subsequently been shown to arise (depending on the clinical subtype) from mutations of *K17*, *K16* or *K6* [12,13]. Patients with pachyonychia may also show changes in the mouth akin to those of white-sponge naevus and, on the basis of this overlap, mutations of *K4* or *K13* were found to underlie white-sponge naevus syndrome [14]. Similarly, some patients with pachyonychia have cysts like those seen in steatocystoma multiplex, which in turn can also be caused by mutations of *K17* [15]. Abnormal hair is also a feature of pachyonychia congenita and suggested to some that monilethrix might be secondary to a keratin mutation. Subsequently, mutations were found in monilethrix in the hair cortex keratin, hHb6 (Keratin 86) [16]. A mutation in the V1 domain of *K5* was found in the rare epidermolysis bullosa simplex with mottle pigmentation [17]. Mutations in the V1 domain of *K14* were recently found to cause Naegeli–Franceschetti–Jadassohn syndrome (NFJS) and dermatopathia pigmentosa reticularis (DPR), two closely related autosomal dominant ectodermal dysplasia syndromes with similar features, including complete absence of dermatoglyphics (fingerprint lines), a reticulate pattern of skin hyperpigmentation, palmoplantar keratoderma and abnormal sweating, providing a further link between altered skin pigmentation and keratin mutations [18]. The speed at which researchers

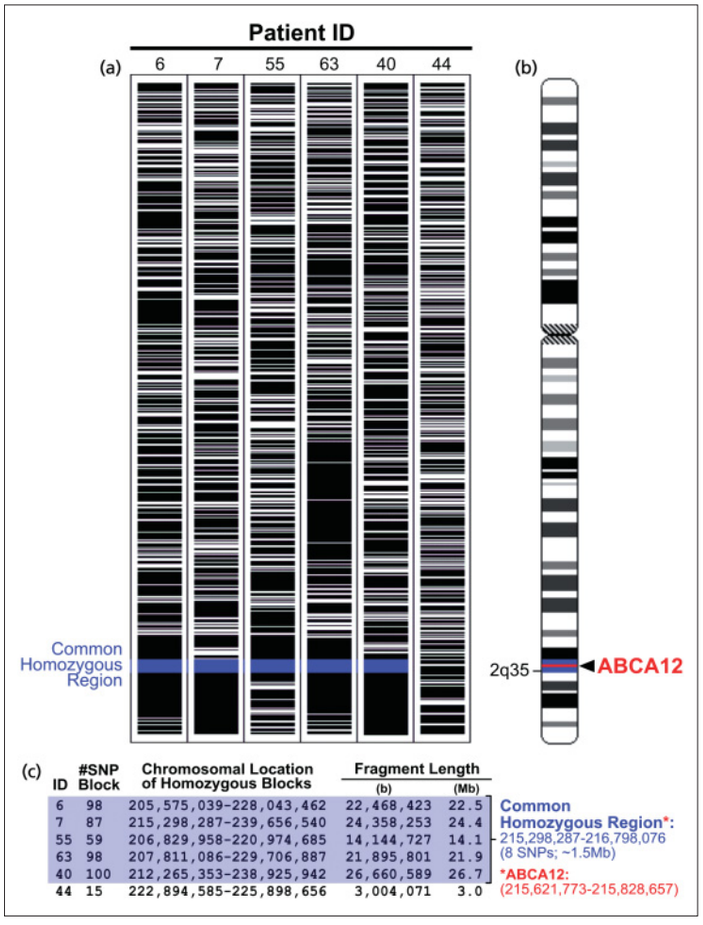


Fig. 11.12 Localization of the harlequin ichthyosis (HI) gene to chromosome 2q35 by the use of SNP-array mapping. (a) Homozygous SNP profiles of chromosome 2 in six patients with HI. Black bars indicate homozygous SNP call data. Blue bars indicate the minimal common region of homozygous SNPs in patients 1–5, a genetic distance of approximately 1.5 Mb. (b) Ideogram of chromosome 2 showing the position of *ABCA12* (red bar), located within the minimal common region of homozygous SNPs (blue) identified in panel (a). (c) The genetic interval of the homozygous SNP 'blocks' in each patient with HI, with clear indication that the *ABCA12* gene maps within the common homozygous region for five of the six patients. (From Kelsell *et al.* [19]).

have uncovered the genes responsible for so many cutaneous disorders attests to the power of the combination of mapping and candidate approaches.

Until recently, in the absence of a candidate gene, one of the bottlenecks in the identification of disease-causing genes was the difficulty moving from chromosomal position, which might encompass up to 10 million bases, to identification of the disease-causing gene. For autosomal recessive disorders in consanguineous families, arrays of 10 000 to 500 000 SNPs, available commercially from Illumina and Affymetrix, provide a rapid method of disease mapping. Finding the gene for harlequin ichthyosis (HI), the most severe congenital ichthyosis, was hampered by neonatal mortality and very few kindreds with more than one affected child. The HI gene, *ABCA12*, was identified in 2005 using SNP arrays, which showed an area of shared homozygosity on chromosome 2 in five out of six affected individuals (Fig. 11.12). Microsatellite markers were then used to confirm and refine the minimal region [19]. Of the six genes in this region, *ABCA12* was an obvious candidate, as missense mutations in *ABCA12* had been shown to underlie the less severe non-bullous ichthyosiform erythroderma/lamellar ichthyosis [20]. Sequencing confirmed *ABCA12* as the major genetic cause of HI [19]. Recently, SNP array technology was also used to map the genes for autosomal recessive anonychia and woolly hair [21,22].

Another array technique, high-resolution comparative genomic hybridization, was used to localize deletions on the X-chromosome in focal dermal hypoplasia, an X-linked dominant condition characterized by defective development of mesodermal and ectodermal tissues. Sequencing of genes in the area of deletion revealed mutations in *PORCN*, encoding a putative *O*-acyltransferase, involved in Wnt signalling, an important developmental pathway, as the cause of this condition [23].

If there are multiple, complex deletions or duplications in a gene, this may be difficult to identify with standard sequencing techniques. A truncated message (mRNA) may indicate a large deletion. In a recent study, several patients with harlequin ichthyosis appeared to have mutations on one allele only [24]. Multiplex PCR and copy number array analysis confirmed exon deletions on the other allele (Fig. 11.13).

References

1 Leigh IM, Lane EB. Mutations in the genes for epidermal keratins in epidermolysis bullosa and epidermolytic hyperkeratosis. *Arch Dermatol* 1993; **129**: 1571–7.

2 Hahn H, Wicking C, Zaphiropoulos PG *et al.* Mutations of the human homolog of *Drosophila patched* in the nevoid basal cell carcinoma syndrome. *Cell* 1996; **85**: 841–51.

3 Gailani MR, Ståhle-Bäckdahl M, Leffell DJ *et al.* The role of the human homologue of *Drosophila patched* in sporadic basal cell carcinomas. *Nat Genet* 1996; **14**: 78–81.

4 Spritz RA. Molecular genetics of oculocutaneous albinism. *Hum Mol Genet* 1994; **3**: 1469–75.

5 Common JE, O'Toole EA, Leigh IM *et al.* Clinical and genetic heterogeneity of erythrokeratoderma variabilis. *J Invest Dermatol* 2005; **125**: 920–7.

6 Vassar R, Coulombe PA, Degenstein L *et al.* Mutant keratin expression in transgenic mice causes marked abnormalities resembling a human genetic skin disease. *Cell* 1991; **64**: 365–80.

7 Bonifas JM, Rothman AL, Epstein EH Jr. Epidermolysis bullosa simplex: evidence in two families for keratin gene abnormalities. *Science* 1991; **254**: 1202–5.

8 Rothnagel JA, Dominey AM, Dempsey LD *et al.* Mutations in the rod domains of keratins 1 and 10 in epidermolytic hyperkeratosis. *Science* 1992; **257**: 1128–30.

9 McLean WHI, Morley SM, Lane EB *et al.* Ichthyosis bullosa of Siemens (IBS): a disease involving keratin 2e. *J Invest Dermatol* 1994; **103**: 277–81.

10 Reis A, Hennies HC, Langbein L *et al.* Keratin 9 gene mutations in epidermolytic palmoplantar keratoderma (EPPK). *Nat Genet* 1994; **6**: 174–9.

11 Munro CS, Carter S, Bryce S *et al.* A gene for pachyonychia congenita is closely linked to the keratin cluster on 17q12–q21. *J Med Genet* 1994; **31**: 675–8.

12 McLean WHI, Rugg EL, Lunny DP *et al.* Keratin 16 and keratin 17 mutations cause pachyonychia congenita. *Nat Genet* 1995; **9**: 273–8.

13 Bowden PE, Haley JL, Kansky A *et al.* Mutation of a type II keratin gene (K6a) in pachyonychia congenita. *Nat Genet* 1995; **10**: 363–5.

14 Rugg EL, McLean WHI, Allison WE *et al.* A mutation in the mucosal keratin K4 is associated with oral white sponge nevus. *Nat Genet* 1995; **11**: 450–2.

15 Smith FJD, Corden LD, Rugg EL *et al.* Missense mutations in keratin 17 cause either pachyonychia congenita type 2 or a phenotype resembling steatocystoma multiplex. *J Invest Dermatol* 1997; **108**: 220–3.

16 Winter H, Rogers MA, Langbein L *et al.* Mutations in the hair cortex keratin hHb6 cause the inherited hair disease monilethrix. *Nat Genet* 1997; **16**: 372–4.

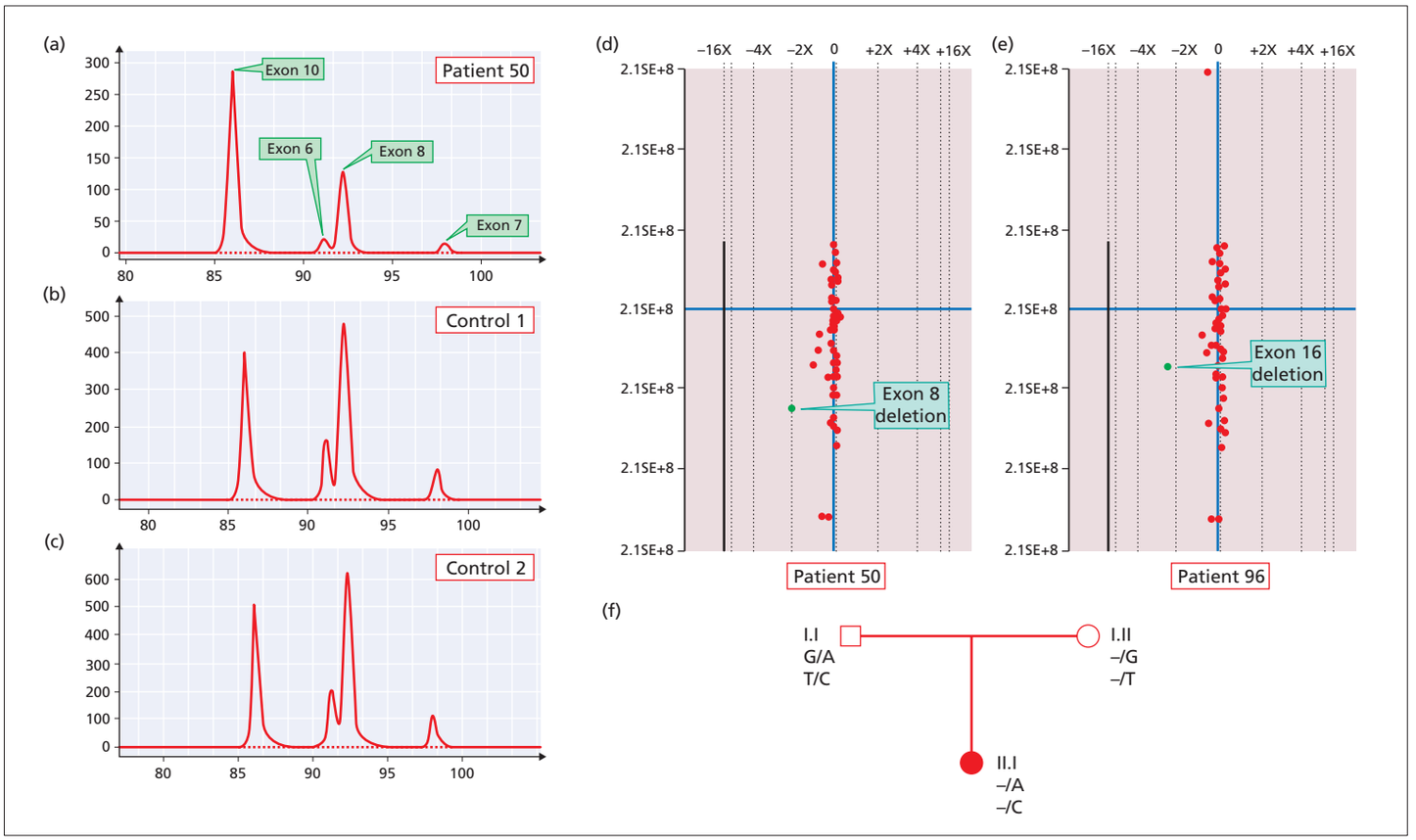


Fig. 11.13 Analysis of heterozygous exon deletions in patients with harlequin ichthyosis. (a–c) Multiplex PCR from an affected patient (Patient 50) and two unaffected individuals (Controls) showing changes in the exon profile. (d) Agilent oligo array data showing a reduction in copy number in exon 8 of Patient 50, and (e) the presence of a deletion in Patient 96. Deleted oligonucleotides are indicated by arrows. (f) Pedigree of Patient 50 with genotypes of exon 8 SNP (c. 888 G > A (V296V)) and an intron 8 SNP (c. 985 + 85 T > C). The genotypes clearly show non-maternal inheritance, supportive of a maternal deletion spanning exon 8. Deleted SNPs are depicted as –. (From Thomas *et al.* [24].)

17 Uttam J, Hutton E, Coulombe PA *et al.* The genetic basis of epidermolysis bullosa simplex with mottled pigmentation. *Proc Natl Acad Sci USA* 1996; **93**: 9079–84.
18 Lugassy J, Itin P, Ishida-Yamamoto A *et al.* Naegeli–Franceschetti–Jadassohn syndrome and dermatopathia pigmentosa reticularis: two allelic ectodermal dysplasias caused by dominant mutations in KRT14. *Am J Hum Genet* 2006; **79**: 724–30.
19 Kelsell DP, Norgett EE, Unsworth H *et al.* Mutations in ABCA12 underlie the severe congenital skin disease harlequin ichthyosis. *Am J Hum Genet* 2005; **76**: 794–803.
20 Lefévre C, Audebert S, Jobard F *et al.* Mutations in the transporter ABCA12 are associated with lamellar ichthyosis type 2. *Hum Mol Genet* 2003; **12**: 2369–78.
21 Blaydon DC, Ishii Y, O'Toole EA *et al.* The gene encoding R-spondin 4 (RSPO4), a secreted protein implicated in Wnt signaling, is mutated in inherited anonychia. *Nat Genet* 2006; **38**: 1245–7.
22 Shimomura Y, Wajid M, Ishii Y *et al.* Disruption of P2RY5, an orphan G protein-coupled receptor, underlies autosomal recessive woolly hair. *Nat Genet* 2008; **40**: 335–9.
23 Grzeschik KH, Bornholdt D, Oeffner F *et al.* Deficiency of PORCN, a regulator of Wnt signaling, is associated with focal dermal hypoplasia. *Nat Genet* 2007; **39**: 833–5.
24 Thomas AC, Cullup T, Norgett EE *et al.* ABCA12 is the major harlequin ichthyosis gene. *J Invest Dermatol* 2006; **126**: 2408–13.

Complex traits

The term 'complex trait' describes any pattern of inheritance of a phenotype that does not fit a classic Mendelian pattern. Examples in dermatology include atopic eczema and psoriasis. Although these disorders are inherited in families, gene–environment and gene–gene interactions, low penetrance, genetic heterogeneity and statistical power pose challenges for researchers. In an absolute sense, the distinction between complex and simple traits is artificial, as even a disorder with an apparently straightforward pattern of inheritance, such as epidermolysis bullosa simplex or Darier's disease, may show variations of clinical phenotype between

affected individuals that are the result of other modifying genes or differences in environmental exposure.

Whereas positional cloning, candidate gene analysis and linkage of Mendelian traits have had considerable success, genetic analysis of complex traits is a relatively new, but burgeoning area [1]. One can see that if a disorder is due to mutations at a number of different loci (i.e. it is polygenic), the influence of any one particular locus will tend to be modest, and conventional linkage analysis may be of limited utility. Allele-sharing methods tend to be more robust than linkage analysis, because no underlying model of inheritance is assumed. In allele-sharing methods, one tries formally to demonstrate that the inheritance pattern of a chromosomal region is *not* consistent with random Mendelian segregation (by showing that affected relatives inherit identical copies of the region more often than one would expect by chance). Examples of allele-sharing methods include affected sibling-pair analysis, where the frequency of sharing of particular regions is only compared in siblings affected with the disease (avoiding the problems of incomplete penetrance). Of course, for complex disorders the problem of moving from a highlighted chromosomal region to the actual gene is considerably more difficult than in highly penetrant disorders. This is because co-segregation of a marker and the disease may not be absolute; rather, one has to work with statistical confidence intervals. This raises the question of the number of individuals that need to be examined, because of the absence of the all-or-nothing principle of a gene that is both necessary and sufficient for a particular disease. In this situation, a variety of other strategies, such as linkage disequilibrium mapping, may be needed. Alternative strategies include association studies, which are in effect case–control studies based on the presence of a particular allele in affected and unaffected individuals, for example as in recent genetic studies on psoriasis [2,3]. Low power can be a limiting factor in case–control studies.

The use of genetically homogenous populations such as founder populations or isolated, island populations can increase statistical power considerably. A good example of this is the work of the biopharmaceutical company, deCODE (www.decode.com). Based in Iceland, with unique genealogical data and DNA samples from over half of the adult population, scientists are able to study very large, extended pedigrees. Genes are mapped by linkage analysis of affected large pedigrees, focusing in on chromosomal areas and using high-density markers to find which haplotypes are associated with disease.

Many research groups are now performing whole-genome association studies using DNA chips, which can genotype over a million SNPs in the human genome, encompassing about two-thirds of the common genetic variants. Using the typed SNPs and HapMap data, the statistical technique of imputation can be used to deduce genotypes at untyped SNPs [4]. The Wellcome Trust Case–Control Consortium using DNA SNP chips, with 3000 controls and 2000 cases of each of seven complex diseases, including Crohn's disease and diabetes, doubled the number of known genetic variants associated with these complex diseases in an initial study [5]. These findings have now been replicated in other populations. The deCODE group in a similar whole-genome study in the Icelandic population recently identified novel genetic determinants of hair, skin and eye colour [6,7]. Importantly, this study replicated the previous association of *MC1R* variation with hair colour. In a subsequent paper, they showed that variation in two of these genes, *TYR* (encoding tyrosinase) and *ASIP* (encoding agouti signalling protein), were associated with increased risk of basal cell carcinoma and malignant melanoma [8].

Genetics studies of Mendelian disorders can give clues to the pathogenesis of complex disease. Dermatologists know that ichthyosis vulgaris is more common in atopic individuals. Ichthyosis vulgaris was recently shown to be due to loss-of-function mutations in filaggrin, an important component of the epidermal barrier [9]. Subsequently, loss-of-function variants of filaggrin were shown to be a major risk factor for atopic eczema in Northern European white populations [10]. A further example is the finding of mutations in the gene coding for an exonuclease, *TREX1*, causing Aicardi–Goutières syndrome, a condition comprising encephalopathy with spasticity associated with chilblain lupus [11]. Mutations in *TREX1* were subsequently found to associate with systemic lupus erythematosus [12].

Copy number variation can also contribute to complex disease. This is where a segment of DNA, at least 500 bases in length, is found at different copy numbers in different individuals. This may be because of deletion or duplication [13]. It had been thought that individuals have two copies of each gene, but it has now been shown that about 12% of the human genome has variability in copy number [14]. A recent study found increased β-defensin copy number in psoriasis. β-defensins play a major role in innate immunity in the skin and an 'increased dose' of defensins could account for some of the inflammation seen in psoriatic skin [15].

References

1 McCarthy MI, Abecasis GR, Cardon LR *et al.* Genome-wide association studies for complex traits: consensus, uncertainty and challenges. *Nat Rev Genet* 2008; **9**: 356–69.

2 Liu Y, Helms C, Liao W *et al.* A genome-wide association study of psoriasis and psoriatic arthritis identifies new disease loci. *PLoS Genet* 2008; **4**: e1000041.

3 Capon F, Bijlmakers MJ, Wolf N *et al.* Identification of ZNF313/RNF114 as a novel psoriasis susceptibility gene. *Hum Mol Genet* 2008; **17**: 1938–45.

4 Marchini J, Howie B, Myers S *et al.* A new multipoint method for genome-wide association studies by imputation of genotypes. *Nat Genet* 2007; **39**: 906–13.

5 Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* 2007; **447**: 661–78.

6 Sulem P, Gudbjartsson DF, Stacey SN *et al.* Genetic determinants of hair, eye and skin pigmentation in Europeans. *Nat Genet* 2007; **39**: 1443–52.

7 Sulem P, Gudbjartsson DF, Stacey SN *et al.* Two newly identified genetic determinants of pigmentation in Europeans. *Nat Genet* 2008; **40**: 835–7.

8 Gudbjartsson DF, Sulem P, Stacey SN *et al.* ASIP and TYR pigmentation variants associate with cutaneous melanoma and basal cell carcinoma. *Nat Genet* 2008; **40**: 886–91.

9 Smith FJ, Irvine AD, Terron-Kwiatkowski A *et al.* Loss-of-function mutations in the gene encoding filaggrin cause ichthyosis vulgaris. *Nat Genet* 2006; **38**: 337–42.

10 Palmer CN, Irvine AD, Terron-Kwiatkowski A *et al.* Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet* 2006; **38**: 441–6.

11 Crow YJ, Hayward BE, Parmar R *et al.* Mutations in the gene encoding the 3′–5′ DNA exonuclease TREX1 cause Aicardi–Goutières syndrome at the AGS1 locus. *Nat Genet* 2006; **38**: 917–20.

12 Lee-Kirsch MA, Gong M, Chowdhury D *et al.* Mutations in the gene encoding the 3′–5′ DNA exonuclease TREX1 are associated with systemic lupus erythematosus. *Nat Genet* 2007; **39**: 1065–7.

13 Gonzalez E, Kulkarni H, Bolivar H *et al.* The influence of CCL3L1 gene-containing segmental duplications on HIV-1/AIDS susceptibility. *Science* 2005; **307**: 1434–40.
14 Redon R, Ishikawa S, Fitch KR *et al.* Global variation in copy number in the human genome. *Nature* 2006; **444**: 444–54.
15 Hollox EJ, Huffmeier U, Zeeuwen PL *et al.* Psoriasis is associated with increased beta-defensin genomic copy number. *Nat Genet* 2008; **40**: 23–5.

Pharmacogenetics

The field of pharmacogenetics encompasses the study of how genetic variation affects an individual's response to drugs. Both side effects and therapeutic failure of drugs may have a genetic component. A good example in dermatology is thiopurine methyl transferase (TPMT) genotyping prior to starting individuals on azathioprine [1]. Patients with TPMT alleles causing low enzyme activity are at high risk of myelotoxicity and azathioprine is avoided, whereas in patients with intermediate activity, the dose of azathioprine can be reduced. Identification of the patient's genotype, therefore, enables the decision that it would be safer to use an alternative drug or tailoring of the dose to suit the patient and this practice is now widespread.

The use of methotrexate in psoriasis can be limited by toxicity and lack of efficacy in a proportion of patients. Methotrexate is a potent inhibitor of dihydrofolate reductase and produces its toxic effect through inhibition of synthesis of purines and pyrimidines. Specific polymorphisms in thymidylate synthase have been associated with poor clinical response or increased toxicity in patients with psoriasis on methotrexate [2]. Furthermore, genetic variation within the ABC-binding cassette family genes, *ABCC1* and *ABCG2*, is associated with a favourable response to methotrexate therapy [3]. Genetic variation may also explain the poor response of some patients with psoriasis to anti-TNF therapy. Variations in the TNF gene, its receptor and associated cytokines have been demonstrated in patients with rheumatoid arthritis and Crohn's disease, which may explain the altered pharmacodynamics and lack of response in a subgroup of patients [4]. Stevens–Johnson syndrome and toxic epidermal necrolysis are very severe skin reactions that may develop in some individuals after administration of carbamazepine. There is a strong association of the HLA-B*1502 allele in Han Chinese individuals with carbamazepine-induced Stevens–Johnson syndrome [5].

References

1 Meggitt SJ, Gray JC, Reynolds NJ. Azathioprine dosed by thiopurine methyltransferase activity for moderate-to-severe atopic eczema: a double-blind, randomised controlled trial. *Lancet* 2006; **367**: 839–46.
2 Campalani E, Arenas M, Marinaki AM *et al.* Polymorphisms in folate, pyrimidine, and purine metabolism are associated with efficacy and toxicity of methotrexate in psoriasis. *J Invest Dermatol* 2007; **127**: 1860–7.
3 Warren RB, Smith RL, Campalani E *et al.* Genetic variation in efflux transporters influences outcome to methotrexate therapy in patients with psoriasis. *J Invest Dermatol* 2008; **128**: 1925–9.
4 Kooloos WM, de Jong DJ, Huizinga TW, Guchelaar HJ. Potential role of pharmacogenetics in anti-TNF treatment of rheumatoid arthritis and Crohn's disease. *Drug Discov Today* 2007; **12**: 125–31.
5 Chung WH, Hung SI, Hong HS *et al.* Medical genetics: a marker for Stevens–Johnson syndrome. *Nature* 2004; **428**: 486.

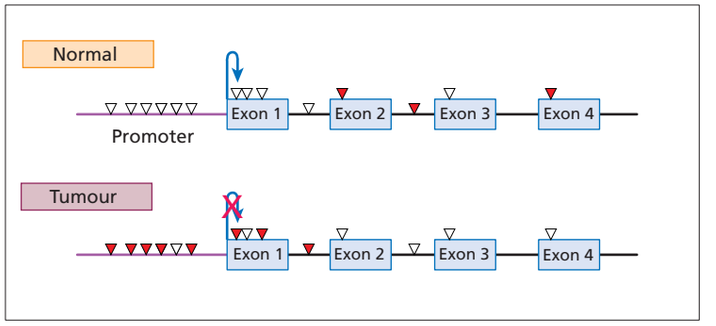


Fig. 11.14 Differences in methylation between normal and cancer cells. A sample human gene is shown, with exons 1–4, a continuous line representing gene introns, and a purple line representing the promoter region. Putative CpG islands are represented by triangles (red, methylated; white, unmethylated). In simple terms, in normal cells, the unmethylated state of CpG sites within the promoter permit active transcription, whereas the opposite is true in cancer cells.

Epigenetics

Epigenetic change is a modification to DNA or associated histone proteins, without variation in the DNA sequence [1]. This may be caused by environment, ageing or disease. The epigenetic state of cells and tissue varies depending on internal and external cues. There are two main mechanisms of epigenetic modification, *DNA methylation* (addition of a methyl [CH_3] group) and *chromatin* or *histone modification* [2]. DNA methylation occurs in cytosines that precede guanines, known as dinucleotide CpGs or CpG islands, which occur in the promoter regions of many genes (Fig. 11.14). DNA hypermethylation has been regarded as a mechanism of gene silencing (switching off gene expression); however, in cancer, DNA hypomethylation may also inactivate gene expression. The second major mechanism of epigenetic change is histone modification. Histones are the main proteins in chromatin that forms the core around which the DNA double helix is formed. Changes may involve methylation or covalent modifications of serine or lysine, such as phosphorylation or acetylation. Both monogenic and complex diseases may be modified by epigenetic change. The genetic skin disease, incontinentia pigmenti, and other X-linked disorders, may show variability in phenotype because of X-chromosome inactivation (XCI), a process in which females silence either the wild-type or mutant X-chromosome during embryogenesis [3,4]. In systemic lupus erythematosus, lymphocyte DNA hypomethylation can occur. Procainamide and hydralazine can both cause DNA hypomethylation and drug-induced lupus [5]. Current major areas of research include the epigenetics of cancer and development [2,6]. Unlike changes in the DNA sequence, epigenetic changes are reversible. The epigenome can be modified globally by drugs that inhibit DNA methylation or histone deacetylation. The histone deacetylation inhibitor (HDI), panobinostat, is well-tolerated and induces a clinical response in cutaneous T-cell lymphoma [7].

References

1 Feinberg AP. Epigenetics at the epicenter of modern medicine. *JAMA* 2008; **299**: 1345–50.
2 Esteller M. Epigenetics in cancer. *N Engl J Med* 2008; **358**: 1148–59.

3 Sun BK, Tsao H. X-Chromosome inactivation and skin disease. *J Invest Dermatol* 2008; **128**: 2753–9.
4 Happle R. X-chromosome inactivation: role in skin disease expression. *Acta Paediatr* 2006; **95** (Suppl.): 16–23.
5 Sekigawa I, Kawasaki M, Ogasawara H *et al.* DNA methylation: its contribution to systemic lupus erythematosus. *Clin Exp Med* 2006; **6**: 99–106.
6 Lunyak VV, Rosenfeld MG. Epigenetic regulation of stem cell fate. *Hum Mol Genet* 2008; **17** (R1): R28–36.
7 Ellis L, Pan Y, Smyth GK, George DJ *et al.* Histone deacetylase inhibitor panobinostat induces clinical responses with associated alterations in gene expression profiles in cutaneous T-cell lymphoma. *Clin Cancer Res* 2008; **14**: 4500–10.

Cancer genetics

Molecular biological approaches to understanding the mechanisms underlying cancer are increasingly fruitful [1,2]. Interest in the molecular biology of cancer not only reflects the importance of the disease to human health overall, but also the intrinsic interest in many of the physiological processes that are deranged in the cancer cell, including cell-cycle control, cell proliferation, invasion and differentiation, and the control of cell death. Molecular biological approaches have led to a new conceptual understanding of the genetic contribution to cancer, which can be summarized as follows. First, cancer is a genetic disease in which the accumulation of multiple genetic abnormalities, coupled with the selection of cells for a more and more malignant phenotype, leads to, and correlates with, the clinical behaviour of the tumour. Second, the underlying defective pathophysiological mechanisms in a wide range of human cancers are similar, and increasingly can be seen to relate to a few key cellular pathways, many of which appear to influence whether a cell cycles or not. Third, the same genes are often involved in sporadic tumours as in inherited tumours; for instance, the same gene *patched* is important in Gorlin's syndrome and in sporadic basal cell carcinomas [3,4].

Genetic abnormalities in cancer cells can be classified into two types: oncogenes and tumour-suppressor genes [5]. Oncogenes are mutated forms of cellular genes called proto-oncogenes that normally control how a cell divides and differentiates. When a proto-oncogene mutates into an oncogene through a point mutation, amplification or translocation, the gene becomes permanently activated, pushing the cell towards the adoption of a malignant phenotype. In genetic terms they are dominant, and therefore only one mutated copy per cell is enough to observe a different phenotype. Oncogenes were originally identified in animal models in which host genes had been hijacked by viruses and mutated. When these viruses infected animal cells, they contributed towards the adoption of a malignant phenotype. Although this is an interesting experimental paradigm, and within animal models of cancer viruses are not infrequently implicated, in humans the association between viruses and cancer is weaker, and, where it exists, it may not be because viruses harbour oncogenes. Early functional assays for oncogenes relied on extraction of DNA from a tumour, and then transfection of this DNA into cells that had been manipulated experimentally such that they were on the verge of neoplasia. If an oncogene were present, clones of these cultured cells would progress and adopt a malignant phenotype, which could be assayed on the basis of phenotypic characteristics (such as colony formation in soft agar). This sort of assay system is cumbersome, and many more oncogenes in human cancers have been identified either on the basis of homology to known oncogenes in other animal systems or by candidate approaches based on their physiological role.

A tumour-suppressor gene is a gene that, when functioning normally, acts so as to protect against the development of the malignant phenotype—the product of the gene possesses *tumour-suppressing* activity. These genes slow down cell division, repair mutations in DNA and trigger cell death to prevent cancer. As with oncogenes, many of these genes appear to be involved in interactions with regulatory proteins controlling the cell cycle. Unlike oncogenes, tumour-suppressor genes are (at the level of the cell) recessive, in that a homozygous mutation is required for them to lose their normal physiological role. Of particular importance has been the discovery that the same tumour-suppressor genes are frequently implicated in sporadic and familial tumours; mutations of *patched* are the cause of Gorlin's syndrome and sporadic basal cell carcinoma [6].

One aspect of tumour-suppressor genes that is not self-evident is that, although these genes are recessive at the level of the cell, when examined in a kindred the trait appears dominant. Based on observations of the epidemiology of retinoblastoma, Knudson [7] proposed a model in which a critical step in the development of tumourigenesis required the inactivation of both maternal and paternal alleles of a particular gene. Importantly, he showed that in an individual inheriting one faulty gene, a second 'hit' leading to loss of the remaining allele (in any particular gene) was far more likely to occur than in an individual who had inherited two wild-type genes. Implicit in this hypothesis was that the same genes were involved in familial and sporadic cancer [7]. This model is illustrated in Fig. 11.15. In Gorlin's syndrome, for instance, those with a family history inherit one abnormality in every cell in the body. If a second hit or mutation occurs (hence the name 'two-hit hypothesis') and if other genetic events are also present, then a tumour may result. In an individual who does not inherit one abnormal copy, a tumour may still result, but in this case both maternal and paternal alleles would have to be somatically inactivated, an event far less likely to occur. This explains why tumours are more common in those who inherit one faulty allele through the germ line. It is of interest to dermatologists that the origin of this idea was first proposed over 50 years ago in order to explain certain aspects of experimental skin carcinogenesis in the mouse [8].

There are a number of mechanisms by which a tumour-suppressor gene can be inactivated: the gene may be mutated; viral proteins may interact with the tumour-suppressor gene product, targeting it for degradation (as happens with some human papillomaviruses); or, quite commonly, the area of the chromosome harbouring the gene may be lost (for example by deletion) [9]. Researchers are now also focusing on epigenetic change as a further mechanism of tumour suppressor gene inactivation causing loss of protein expression [10]. Loss of genetic material can be easily detected using polymorphic PCR microsatellite markers identical to those used in positional cloning, so that instead of two bands—one representing the maternal chromosome and the other the paternal chromosome—being visible in the

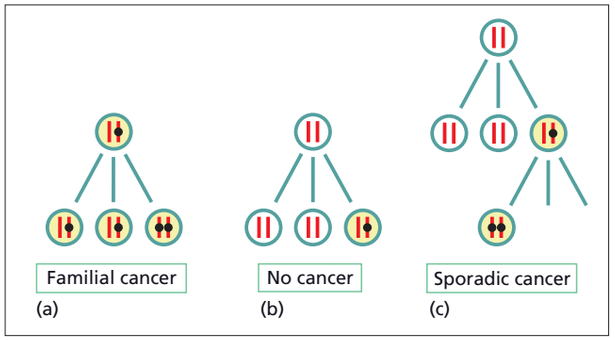


Fig. 11.15 Knudson two-hit hypothesis. Based on the epidemiology of retinoblastoma, Knudson hypothesized that the same genes are involved in familial cancer as in sporadic cancer and that they are recessive at the cellular level—two hits are required to observe a phenotype. Gorlin's syndrome appears to fall into this tumour-suppressor paradigm. A member of a Gorlin's kindred inherits one abnormal germ-line allele (*patched*) in every cell (a). Because tumour-suppressor genes are recessive at the cellular level, the phenotype of all the somatic cells is normal until the remaining wild-type allele is mutated. Once both alleles are inactivated, a rate-limiting step for cancer development has been passed. By comparison, in an individual with no cancer predisposition (b), both germ-line alleles are normal; if an occasional cell undergoes inactivation of one allele, no phenotype will be seen. For a tumour to develop without an inherited predisposition (c), both alleles would have to be inactivated somatically, an event orders of magnitude less likely to occur. This model explains why the frequency of basal cell cancer (in this example) is so much higher in a Gorlin's kindred than in other individuals. Note that despite the gene being recessive at the cellular level, the trait is inherited as a dominant.

tumour, loss of one allele will be evident as loss of one band. Rarely both alleles will be lost, although it is more common for both alleles to be inactivated by different mechanisms. This loss of genetic material, which is referred to as *loss of heterozygosity* (LOH), is one of the major methods by which tumour-suppressor genes may be identified. *Uniparental disomy* (UPD) occurs when two copies of a chromosome or a portion of a chromosome originate from one parent. If a parent is heterozygous for a mutation, the offspring will be recessive. Identification of areas of LOH and UPD can now be performed rapidly using SNP array technology, as recently demonstrated in non-melanoma skin cancer [11,12]. Online genetic databases can then be used to find genes of interest in the affected chromosomal region. Recently, sequencing of over 18000 genes in 11 breast and 11 colon tumours has identified 280 new possible cancer genes, some of which will be of interest in dermatology [13].

Besides oncogenes and tumour-suppressor genes, a third category of gene, the mismatch repair gene, is of relevance to human skin cancer. There are well-known associations between sebaceous carcinoma and a variety of systemic malignancies, particularly colorectal cancer (Muir–Torre/Lynch syndrome) [14]. Molecular studies showed microsatellite instability (MSI) in sebaceous gland tumours and colon carcinoma from Muir–Torre patients [15]. The microsatellite sequences were frequently abnormal in length, with additional bands being seen following PCR, caused by mutations in *MLH1* and *MSH2*. Subsequently, MSI and mismatch repair gene mutations have been found in sebaceous hyperplasia and sebaceous tumours from immunosuppressed transplant patients [16,17].

Efforts have intensified over the last 5 to 10 years to understand the molecular basis of melanoma and non-melanoma skin cancer. *Basal cell carcinoma* (BCC) is genetically quite homogeneous. About 90% of sporadic BCCs have identifiable mutations in the *PTCH1* gene, resulting in upregulation of hedgehog signalling [11]. In addition, about 10% have activating mutations in the *SMO* gene, encoding smoothened, another member of the hedgehog pathway [18]. About 40% of BCCs have UV-induced transition mutations in *TP53*, a tumour suppressor gene which repairs UV-induced mutations in DNA [19]. Polymorphisms in genes activated by exposure to UV, such as reactive oxygen species (*GST, CYP450*) or DNA repair (xeroderma pigmentosum genes) and genetic variants in *MC1R*, associated with fair skin, are also significantly associated with risk of BCC development (reviewed in [6]).

Squamous cell carcinoma (SCC) is very heterogeneous. Ultraviolet radiation-induced *TP53* mutations are found in up to 90% of SCCs [20]. Mutations in $p16^{INK4A}$ and $p14^{ARF}$ (genes controlling the cell cycle), and hypermethylation without mutation, have also been documented in SCC, as well as activating mutations in *HRAS* and *KRAS* [21–23]. A recent SNP array analysis examined genome-wide allele imbalance in SCC [12]. Loss of heterozygosity on chromosome 9p was observed in 13 out of 16 tumours. Other recurrent events included LOH on 3p, 2q, 8p and 13 in approximately 50% of the SCCs. This study also identified deletions within the protein tyrosine phosphatase receptor type D locus in three out of 16 tumours, with a possible association with metastasis.

The *NRAS* gene, encoding for a small guanine-nucleotide binding protein involved in activation of the mitogen-activated protein kinase pathway was the first gene found to be mutated in about 20% of malignant melanomas [24]. Subsequently mutations were found in *BRAF*, a downstream effector of *RAS*, in about 70% of malignant melanoma and benign naevi [25,26]. Melanocortin-1 receptor variants that cause red hair and freckling are associated with a small increase in melanoma risk (two- to threefold) and an increased risk of melanoma with *BRAF* mutations [27]. The growth factor stem cell factor binds to a receptor called KIT, which is mutated in 5–10% of melanomas, mainly from acral and mucosal sites [28]. There are at least four other genes that underlie predisposition to familial melanoma. The commonest is a gene on chromosome 9, *CDKN2A*, which codes for $p16^{INK4A}$, an inhibitor of the cyclin-dependent kinases 4 and 6 [29]. Fifty per cent of British families with three or more melanoma cases have *CDKN2A* mutations. There is also a rare, dominant, activating mutation in the *CDK4* gene rendering it insensitive to p16 inhibition [30]. Very rare deletions in $p14^{ARF}$, a second product of the *CDKN2A* locus, have also been shown to underlie susceptibility to melanoma and neural tumours [31].

References

1 Leary RJ, Lin JC, Cummins J *et al.* Integrated analysis of homozygous deletions, focal amplifications, and sequence alterations in breast and colorectal cancers. *Proc Natl Acad Sci USA* 2008; **105**: 16224–9.

2 Vogelstein B, Kinzler KW. Cancer genes and the pathways they control. *Nat Med* 2004; **10**: 789–99.

3 Hahn H, Wicking C, Zaphiropoulos PG *et al.* Mutations of the human homolog of Drosophila *patched* in the nevoid basal cell carcinoma syndrome. *Cell* 1996; **85**: 841–51.

4 Gailani MR, Ståhle-Bäckdahl M, Leffell DJ *et al.* The role of the human homologue of *Drosophila patched* in sporadic basal cell carcinomas. *Nat Genet* 1996; **14**: 78–81.
5 Croce CM. Oncogenes and cancer. *N Engl J Med* 2008; **358**: 502–11.
6 Epstein EH. Basal cell carcinomas: attack of the hedgehog. *Nat Rev Cancer* 2008; **8**: 743–54.
7 Knudson A. Genetic events in human carcinogenesis. In: Brugge J, Curran T, Harlow E, McCormick F, eds. *Origins of Human Cancer*. New York: Cold Spring Harbour Laboratory Press, 1991: 17–26.
8 Charles DR, Luce-Clausen EM. The kinetics of papilloma formation in benzpyrene-treated mice. *Cancer Res* 1942; **2**: 261–3.
9 Haupt S, Berger M, Goldberg Z, Haupt Y. Apoptosis—the p53 network. *J Cell Sci* 2003; **116**: 4077–85.
10 Chan TA, Glockner S, Yi JM *et al.* Convergence of mutation and epigenetic alterations identifies common genes in cancer that predict for poor prognosis. *PLoS Med* 2008; **5**: e114.
11 Teh MT, Blaydon D, Chaplin T *et al.* Genomewide single nucleotide polymorphism microarray mapping in basal cell carcinomas unveils uniparental disomy as a key somatic event. *Cancer Res* 2005; **65**: 8597–603.
12 Purdie KJ, Lambert SR, Teh MT *et al.* Allelic imbalances and microdeletions affecting the PTPRD gene in cutaneous squamous cell carcinomas detected using single nucleotide polymorphism microarray analysis. *Genes Chromosomes Cancer* 2007; **46**: 661–9.
13 Wood LD, Parsons DW, Jones S *et al.* The genomic landscapes of human breast and colorectal cancers. *Science* 2007; **318**: 1108–13.
14 Lynch HT, Fusaro RM, Roberts L *et al.* Muir–Torré syndrome in several members of a family with a variant of the cancer family syndrome. *Br J Dermatol* 1985; **113**: 295–301.
15 Kruse R, Rütten A, Lamberti C *et al.* Muir-Torre phenotype has a frequency of DNA mismatch-repair-gene mutations similar to that in hereditary nonpolyposis colorectal cancer families defined by the Amsterdam criteria. *Am J Hum Genet* 1998; **63**: 63–70.
16 Kruse R, Rütten A, Schweiger N *et al.* Frequency of microsatellite instability in unselected sebaceous gland neoplasias and hyperplasias. *J Invest Dermatol* 2003; **120**: 858–64.
17 Harwood CA, Swale VJ, Bataille VA *et al.* An association between sebaceous carcinoma and microsatellite instability in immunosuppressed organ transplant recipients. *J Invest Dermatol* 2001; **116**: 246–53.
18 Xie J, Murone M, Luoh SM *et al.* Activating *Smoothened* mutations in sporadic basal-cell carcinoma. *Nature* 1998; **391**: 90–2.
19 Ziegler A, Leffell DJ, Kunala S *et al.* Mutation hotspots due to sunlight in the *p53* gene of nonmelanoma skin cancers. *Proc Natl Acad Sci USA* 1993; **90**: 4216–20.
20 Brash DE, Rudolph JA, Simon JA *et al.* A role for sunlight in skin cancer: UV-induced *p53* mutations in squamous cell carcinoma. *Proc Natl Acad Sci USA* 1991; **88**: 10124–8.
21 Soufir N, Molès JP, Vilmer C *et al.* P16 UV mutations in human skin epithelial tumors. *Oncogene* 1999; **18**: 5477–81.
22 Pierceall WE, Goldberg LH, Tainsky MA *et al. Ras* gene mutation and amplification in human nonmelanoma skin cancers. *Mol Carcinog* 1991; **4**: 196–202.
23 Brown VL, Harwood CA, Crook T *et al. p16INK4a* and *p14ARF* tumor suppressor genes are commonly inactivated in cutaneous squamous cell carcinoma. *J Invest Dermatol* 2004; **122**: 1284–92.
24 Hocker T, Tsao H. Ultraviolet radiation and melanoma: a systematic review and analysis of reported sequence variants. *Hum Mutat* 2007; **28**: 578–88.
25 Davies H, Bignell GR, Cox C *et al.* Mutations of the *BRAF* gene in human cancer. *Nature* 2002; **417**: 949–54.
26 Pollock PM, Harper UL, Hansen KS *et al.* High frequency of *BRAF* mutations in nevi. *Nat Genet* 2003; **33**: 19–20.
27 Landi MT, Bauer J, Pfeiffer RM *et al. MC1R* germline variants confer risk for *BRAF*-mutant melanoma. *Science* 2006; **313**: 521–2.
28 Curtin JA, Busam K, Pinkel D, Bastian BC. Somatic activation of *KIT* in distinct subtypes of melanoma. *J Clin Oncol* 2006; **24**: 4340–6.
29 Hussussian CJ, Struewing JP, Goldstein AM *et al.* Germline p16 mutations in familial melanoma. *Nat Genet* 1994; **8**: 15–21.
30 Zuo L, Weger J, Yang Q *et al.* Germline mutations in the p16INK4a binding domain of CDK4 in familial melanoma. *Nat Genet* 1996; **12**: 97–9.
31 Randerson-Moor JA, Harland M, Williams S *et al.* A germline deletion of p14(ARF) but not *CDKN2A* in a melanoma–neural system tumour syndrome family. *Hum Mol Genet* 2001; **10**: 55–62.

Putting it all together and future trends

Perhaps one of the most astonishing aspects of the growth in technical prowess of molecular biology has been the way in which, from initial 'boot-strapping' methodology, there has been a roller-coaster of more powerful experimental techniques, allowing increasingly precise and ambitious questions to be answered. For instance, when a gene for a particular disorder has been identified using SNP array technology, it is frequently possible to obtain a good idea of the function of that gene, based on either sequence similarity to genes previously identified or knowledge about similar genes in model organisms such as *Drosophila*, mouse or yeast. Identification of new genes that do not bear some sequence similarity to known genes is becoming increasingly rare. The availability of sequencing data from the Human Genome Project now allows analogous prediction, based on what is described as *in silico* experimentation; human sequences can be screened using a variety of bioinformatic techniques in which expressed sequences can be predicted and similarities to known gene products scored and putative functions suggested.

In the 'post-genome era', the availability of genomic and proteomic technology allows scientists to catalogue changes in genes and proteins in disease pathophysiology. There is also optimism that even those disorders that show a more complex pattern of inheritance, such as atopic eczema, psoriasis and acne vulgaris, will also fall to currently available technologies. However, perhaps the most pressing force driving change is the desire to narrow the gap between the identification of disease-causing genes and the development of therapeutic agents.

In some instances, however, cloning of the gene does have immediate clinical implications; identification of the genes underlying the inherited bullous disorders and harlequin ichthyosis means that prenatal and even preimplantation diagnosis is now a reality [1,2]. For carriers of highly penetrant genes, modification of lifestyle may be appropriate, as for carriers of *p16* mutations who are at high risk of malignant melanoma. It is likely that better clinical and genetic data on the heterogeneous group of congenital ichthyosiform erythrodermas (there are now six known genes, including *TGM1, ABCA12, ichthyin, ALOXE3, ALOX12B* and *CYP4F22*) will eventually allow classification on a more rational basis [3].

Understanding the biological mechanism of both common and rare cutaneous disorders may also lead to new therapies. For example, acral and mucosal melanoma frequently have mutations in *KIT*. Inatamib mesylate is a receptor tyrosine kinase inhibitor that inhibits *BCR-ABL* and *KIT* and is effective in treating chronic myeloid leukaemia and neurogastrointestinal tumours [4]. Clinical trials of inatamib are currently in progress for patients with acral and mucosal melanomas who have *KIT* mutations. Rosacea is a common skin disorder characterized by inflammation and vascular abnormalities. A recent study identified two new features of this disorder: increased expression of cathelicidin antimicrobial

peptides and a related serine protease, molecules involved in innate immunity, which may be future specific targets [5]. Also, identification of abnormalities in vascular endothelial growth factor signalling have been found in infantile haemangioma, suggesting that this pathway may be a target for new topical therapies [6]. Merkel cell tumour, a rare cancer occurring in elderly individuals, were hypothesized to have an infectious aetiology. A recent study, using digital transcriptome subtraction, a high-throughput DNA sequencing method, identified a novel polyomavirus in these tumours, confirming this possibility [7]. Finally, cloning of human genes allows the production of recombinant pharmaceuticals, such as interferons, new monoclonal antibodies and vaccines, by genetic engineering.

References

1 Lesueur F, Bouadjar B, Lefèvre C *et al.* Novel mutations in *ALOX12B* in patients with autosomal recessive congenital ichthyosis and evidence for genetic heterogeneity on chromosome 17p13. *J Invest Dermatol* 2007; **127**: 829–34.

2 Thomas AC, Sinclair C, Mahmud N *et al.* Novel and recurring *ABCA12* mutations associated with harlequin ichthyosis: implications for prenatal diagnosis. *Br J Dermatol* 2008; **158**: 611–3.

3 Fassihi H, Eady RA, Mellerio JE *et al.* Prenatal diagnosis for severe inherited skin disorders: 25 years' experience. *Br J Dermatol* 2006; **154**: 106–13.

4 Hodi FS, Friedlander P, Corless CL *et al.* Major response to imatinib mesylate in KIT-mutated melanoma. *J Clin Oncol* 2008; **26**: 2046–51.

5 Yamasaki K, Di Nardo A, Bardan A *et al.* Increased serine protease activity and cathelicidin promotes skin inflammation in rosacea. *Nat Med* 2007; **13**: 975–80.

6 Jinnin M, Medici D, Park L *et al.* Suppressed NFAT-dependent VEGFR1 expression and constitutive VEGFR2 signaling in infantile hemangioma. *Nat Med* 2008; **14**: 1236–46.

7 Feng H, Shuda M, Chang Y, Moore PS. Clonal integration of a polyomavirus in human Merkel cell carcinoma. *Science* 2008; **319**: 1096–100.

From genetics of disease to treatment

Future work relating to the development of new therapeutic strategies lies in three directions: first, the detailed characterization of differences in gene expression; second, gene-based therapies; and finally, high-throughput screening of pharmacological compound libraries to identify drugs that modulate expression of the mutant gene, or related genes, and thus may compensate functionally for the mutant gene. In the 'post-genome era', automated approaches such as microarray chips are facilitating identification and description of gene expression in different cell types.

Thinking specifically of therapy, there are clear alternative, and perhaps complementary, strategies being pursued. For instance, the development of new, small-molecule pharmacological agents is now heavily dependent on molecular biological techniques. The identification of genes, the ability to study gene expression and the ability to produce large amounts of a protein experimentally, all facilitate functional studies of protein activity, identification of key domains and characterization of protein structure by crystallography. The identification of the myriad of isoforms for many receptors offers new targets for small-molecule design.

Gene therapy

Gene therapy traditionally describes a range of technologies that have in common the treatment of disease based on the introduction of genes or nucleic acids (including oligonucleotides), usually employing viral vectors expressing the DNA of interest. The virus can integrate into the human genome giving stable, long-term expression of the gene. Despite considerable media attention, success has been limited, and most work has concentrated on the development of the technology, toxicity assessment and *in vitro* work. In initial clinical trials of gene therapy for X-linked severe combined immunodeficiency, two children who were treated with retroviral vectors developed leukaemia [1]. It seemed likely that there was a causal relationship between integration of the virus and the development of the leukaemia, and this finding caused concern and a slowing down of clinical trials of similar approaches. In 2008, two groups reported safe administration of *RPE65* cDNA in an adenoviral vector to retinal epithelium in patients with Leber's optic amaurosis, the most severe form of inherited blindness, with subtle improvements in vision [2,3].

The approach to genetic therapy of skin disease can be summarized as follows. In recessive or compound heterozygous disorders, there is complete or almost complete absence of the protein, so replacement of the protein is necessary. This can be approached in two ways. The gene can be replaced by gene therapy (in the traditional sense) or the protein can be replaced by injection of recombinant protein or transplantation of cells expressing normal amounts of protein from a related donor. Examples of disorders that might benefit from this approach include recessive dystrophic epidermolysis bullosa (RDEB) and non-lethal forms of junctional epidermolysis bullosa. In dominant disorders, although generally less severe, gene therapy requires a different approach, as the patient has both mutant and wild-type copies of the gene. The mutant gene disrupts the function of the normal gene (dominant-negative effect). We know from parent and sibling carriers of recessive disorders that having 50% of the normal gene expression is sufficient. Therefore, inhibition of the mutant gene, using a small molecule or a molecular genetic approach such as a specific siRNA, could be sufficient to correct the problem. *In vitro* studies of siRNA for the skin disorder pachyonychia congenita have shown considerable promise (Fig. 11.16) and a clinical trial is currently in progress [4,5].

Many genetic diseases, including some forms of epidermolysis bullosa and neurofibromatosis, are due to nonsense mutations causing a premature stop codon in the messenger RNA, which results in a truncated protein. An American company, PTC Therapeutics (www.ptcbio.com), is developing small molecules that induce ribosomes to selectively read-through premature stop codons, resulting in production of full-length, functional protein. An example of this is PTC124, a new oral treatment for cystic fibrosis, which produced modest improvements in pulmonary function and chloride transport [6]. An understanding of how genes compensate and interact with each other may also facilitate development of therapy. In the keratin 14 null mouse model of epidermolysis bullous simplex (EBS), treatment with sulfurophane, a natural product derived from broccoli, improved blistering by increasing keratin 17 expression. Topical application of sulfurophane may be of value in EBS [7].

Genetic material may be passed to the cell of interest either *in vivo* or *in vitro*. With *in vitro* gene therapy, cells from the individual are cultured and genetic modification is carried out *in vitro*, before returning the cells to the patient. This is feasible in skin as kerati-

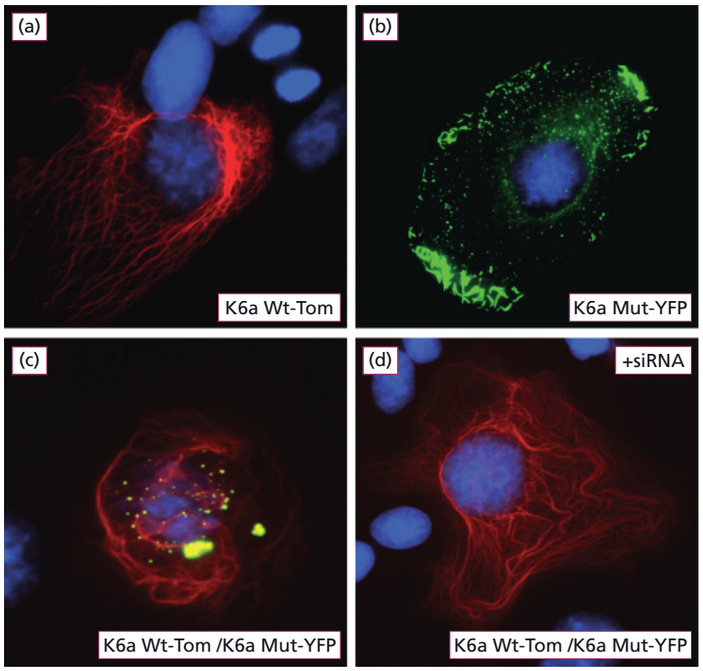


Fig. 11.16 Development of siRNA targeting of the mutant K6a present in pachyonychia congenita. Cells were transfected with fusion constructs coding for either (a) wild-type K6a and a red fluorescent reporter protein (K6a Wt–Tom), or (b) mutant K6a and a yellow/green fluorescent reporter protein (K6a Mut–YFP), or (c) both. Wild-type keratins produced intracellular filaments (red) and mutant keratins produced aggregates (yellow/green). (d) Transfection of cells with a specific siRNA targeting the single nucleotide mutation in K6a, in addition to K6a Wt–Tom and K6a Mut–YFP, resulted in loss of mutant K6a Mut–YFP. (Courtesy of R. Kaspar and R. Hickerson, TransDerm, CA, USA.)

nocytes and fibroblasts can be cultured relatively easily. With *in vivo* gene therapy, the gene of interest is applied to the skin using a delivery system such as a 'genecream' containing liposomes. Gene replacement can be achieved using various viral vectors that integrate their genome into the human genome. Retroviral particles generally only infect dividing cells; however, lentiviral vectors infect both dividing and non-dividing cells very efficiently, and are possibly the current vector of choice. A major success in genetic skin disease gene therapy was the successful treatment of a young man with junctional epidermolysis bullosa caused by a homozygous mutation in the *LAMB3* gene encoding the beta3 chain of laminin 332 [8]. A retroviral vector with a *LAMB3* gene insert was used to infect stem cells derived from the patient's palm and these cells were grafted onto surgically prepared regions on the patient's leg. The epidermis remained stable at 1-year follow-up. Small clinical trials are also planned in RDEB. Several RDEB patients in the USA have undergone allogeneic stem cell bone marrow transplant, after successful murine experiments [9], and this approach is promising for the future as a means of correcting both wounded epidermis and mucosae in RDEB (www.clinicaltrial.gov, identifier NCT00478244). A recent clinical trial of fibroblast therapy in five patients with RDEB achieved increased production of type VII collagen at the basement membrane zone [10]. Donor fibroblasts were injected into a small area of dermis, and although the fibroblasts were no longer present in skin after 2 weeks, significantly increased deposition of type VII collagen protein was seen up to 3 months in several of the patients. In a mouse model of RDEB, injection of human recombinant type VII collagen protein prolonged survival significantly, and this is also a possibility for future human clinical trials [11].

Molecular biology has allowed a genetic engineering approach to malignant melanoma. Peripheral blood lymphocytes from patients with melanoma were transduced with genes encoding the alpha and beta chains of the anti-MART-1 T-cell receptor. MART-1 is a tumour-associated antigen. These genes were cloned from a tumour-infiltrating lymphocyte (TIL) clone obtained from a patient who demonstrated almost complete regression of metastatic melanoma after adoptive cell transfer of TILs. Two patients out of 15 had sustained regression of their metastases 1 year after treatment and both had persisting, high, circulating engineered lymphocytes [12].

A final consideration with gene therapy is how generic the techniques can be made. This assumes importance because although studies on cancer using gene therapy have been well funded, to take gene therapy approaches through to the clinic, industrial-scale funding is probably necessary. For many rare dermatological disorders, as for development of new drug-based strategies, it is not clear that the size of the market will justify the necessary investment. A second limitation on application, particularly with respect to dermatological therapy, may be concern about safety. However, as stem-cell transplant and vector technology improve, this will be less of a concern. Obviously, since the vast majority of cutaneous diseases are not life-threatening, these sorts of approaches will, in the short term, be restricted to disorders that are potentially fatal, such as melanoma or some of the inherited blistering disorders.

References

1 Kohn DB, Sadelain M, Glorioso JC. Occurrence of leukaemia following gene therapy of X-linked SCID. *Nat Rev Cancer* 2003; **3**: 477–88.

2 Bainbridge JW, Smith AJ, Barker SS *et al.* Effect of gene therapy on visual function in Leber's congenital amaurosis. *N Engl J Med* 2008; **358**: 2231–9.

3 Maguire AM, Simonelli F, Pierce EA *et al.* Safety and efficacy of gene transfer for Leber's congenital amaurosis. *N Engl J Med* 2008; **358**: 2240–8.

4 Hickerson RP, Smith FJ, Reeves RE *et al.* Single-nucleotide-specific siRNA targeting in a dominant-negative skin model. *J Invest Dermatol* 2008; **128**: 594–605.

5 Leachman SA, Hickerson RP, Hull PR *et al.* Therapeutic siRNAs for dominant genetic skin disorders including pachyonychia congenita. *J Dermatol Sci* 2008; **51**: 151–7.

6 Kerem E, Hirawat S, Armoni S *et al.* Effectiveness of PTC124 treatment of cystic fibrosis caused by nonsense mutations: a prospective phase II trial. *Lancet* 2008; **372**: 719–27.

7 Kerns ML, DePianto D, Dinkova-Kostova AT *et al.* Reprogramming of keratin biosynthesis by sulforaphane restores skin integrity in epidermolysis bullosa simplex. *Proc Natl Acad Sci USA* 2007; **104**: 14460–5.

8 Mavilio F, Pellegrini G, Ferrari S *et al.* Correction of junctional epidermolysis bullosa by transplantation of genetically modified epidermal stem cells. *Nat Med* 2006; **12**: 1397–402.

9 Tolar J, Ishida-Yamamoto A, Riddle M *et al.* Amelioration of epidermolysis bullosa by transfer of wild-type bone marrow cells. *Blood* 2008; **113**: 1167–74.

10 Wong T, Gammon L, Liu L *et al.* Potential of fibroblast cell therapy for recessive dystrophic epidermolysis bullosa. *J Invest Dermatol* 2008; **128**: 2179–89.

11 Remington J, Wang X, Hou Y *et al.* Injection of recombinant human type VII collagen corrects the disease phenotype in a murine model of dystrophic epidermolysis bullosa. *Mol Ther* 2009; **17**: 26–33.

12 Morgan RA, Dudley ME, Wunderlich JR *et al*. Cancer regression in patients after transfer of genetically engineered lymphocytes. *Science* 2006; **314**: 126–9.

Conclusion

Molecular biology and the application of molecular biological techniques to the study of disease have come an astonishingly long way in a short period of time. Disease-causing genes continue to be identified at a significant pace. Molecular biological technology has opened up the study at increased speed of whole areas of medicine, because of both DNA-based diagnostics and an increased facility to carry out high-throughput biochemistry and pharmacology. In genetic skin disease, molecular biology is beginning at last to yield treatments that are likely to be successful. In psoriasis, genetic engineering of new monoclonal antibodies targeting important immune drivers of the disease is now routine.

New therapies do not always work in every patient, but this sometimes allows a further hypothesis to be generated in the laboratory, which eventually results in a better drug [1].

High-throughput technology is already producing thousands of biomarkers and putative targets in various cancers, including melanoma. Skin cells can be reprogrammed to behave like embryonic stem cells by transfection with four genes and subsequently directed to a tissue-specific lineage, for example cardiomyocytes [2]. Sequencing of an individual's genome may soon become more widely available. The majority of drugs may in the future be adjusted after examining an individual's genotype. However, the real skill will be translating all of this information into clinically useful tools for the dermatologist [3]. That is why it is important that some dermatologists remain as close to the bench as they do to the clinic.

References

1 Ledford H. Translational research: the full cycle. *Nature* 2008; **453**: 843–5.
2 Aasen T, Raya A, Barrero MJ *et al*. Efficient and rapid generation of induced pluripotent stem cells from human keratinocytes. *Nat Biotechnol* 2008; **26**: 1276–84.
3 Oro AE. Dermatology in the postgenomic era: harnessing human variation for personalized medicine. *Arch Dermatol* 2008; **144**: 389–91.

CHAPTER 12
Inflammation

M. Steinhoff[1], *R.W. Groves*[2], *P.E. LeBoit*[3] *& T.A. Luger*[1]

[1]Department of Dermatology, University of Münster, Münster, Germany
[2]St John's Institute of Dermatology, Guy's Hospital, London, UK
[3]Dermatopathology, University of California San Francisco, San Francisco, USA

Clinical characteristics of inflammation, 12.2
Phases of inflammation, 12.2
Innate defence mechanisms, 12.5
Antimicrobial peptides, 12.5
Toll-like receptors, 12.8
NBS-LRR (nucleotide-binding site and leucine-rich repeat) proteins, 12.9
Type 3 complement receptor, 12.10
Mannose receptor and other C-type lectins, 12.10
Cell apoptosis and inflammation, 12.11
Major histocompatibility complex and inflammation, 12.13
Cellular components of cutaneous inflammation, 12.14
Epidermis, 12.14
Keratinocytes, 12.14
Lymphocytes, 12.17
Natural killer cells, 12.18
Polymorphonuclear granulocytes, 12.20
Mast cells, 12.24
Monocytes and macrophages, 12.26
Fibroblasts, 12.30
Platelets, 12.32
Mediators of inflammation, 12.33
Acute-phase proteins, 12.34
Cytokines, 12.34
Interleukins, 12.35
Interferons, 12.41
Tumour necrosis factor, 12.42
Cytokine suppressors and inhibitors, 12.43
Chemokines, 12.44
Proteases, 12.49
Matrix metalloproteinases, 12.51
Lysosomal mediators, 12.53
Radical oxygen species (ROS), 12.54
Nitric oxide, 12.56
Histamine, 12.57
Platelet-activating factor, 12.59
Prostaglandins and leukotrienes, 12.60
Neuromediators, 12.62
Vasculature and inflammation, 12.68
Cell adhesion and adhesion molecules, 12.68
Endothelin 1, 12.75
Growth factors from cells other than keratinocytes, 12.76

Introduction [1–18]

Inflammation can be defined as a complex body defence mechanism to respond to dangerous endogenous or exogenous stimuli. From a very early stage in phylogenesis, inflammation is associated with the host defence against infectious agents or injury. A variety of exogenous and endogenous mediators are capable of inducing inflammatory responses, such as microbial agents, toxins or pH changes, resulting in an acute dermatitis. Exogenous physical stimuli, such as heat, cold, UV radiation or mechanical irritation, may also affect skin homeostasis and activate the release of inflammatory mediators such as radical oxygen species, nitric oxide derivates, cytokines, chemokines, eicosanoids, neuropeptides, etc. [19].

The inflammatory response consists of various cellular and molecular mechanisms that enable reconstitution of body integrity. The acute reaction is characterized by successive phases. An initial, clinically 'silent' phase involves release of immediate inflammatory mediators from resident cells of the damaged tissue, thereby initiating the tissue (activated tissue cells) and immune responses (early components include: macrophages, mast cells, platelets, basophils, dendritic cells; and later: neutrophils, eosinophils, lymphocytes, etc.) [20]. In a second phase, a vascular reaction, characterized by vasodilatation and increased permeability, can be observed, followed by a cellular phase, where inflammatory cells infiltrate the injured microenvironment. As will become apparent, many skin diseases involve inappropriate regulation of the inflammatory response.

Early inflammatory cells, such as mast cells or macrophages, release a variety of mediators including cytokines, chemokines or proteases, to remove or inactivate dead cells, detritus, microbiological organisms and toxins. Upon activation, endothelial cells release a plethora of cytokines, chemotactic agents or radical oxygen species, important mediators which orchestrate the subsequent inflammatory mechanisms, such as leukocyte recruitment, extracellular matrix reorganization, and stimulation of epithelial cells, and fibroblasts; they are also crucial to the control of intravascular mediators such as coagulation factors and proteases. Leukocytes closely interact with activated endothelial cells expressing cell adhesion molecules, to allow emigration into the inflammatory environment. In addition, other important mediators, such as kinins, biogenic amines, neuropeptides, nitric oxide

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

and other radical oxygen species (ROS), haemoxygenase (HO), growth factors, complement compounds, prostaglandins, leucotrienes and ADP, are released to fine tune the inflammatory response. Moreover, several cutaneous cells are capable of generating inflammatory mediators and their receptors in order to regulate the cellular response to released pro-inflammatory molecules, ultimately leading to tissue repair. Under normal circumstances, inflammatory effects are rapidly attenuated by anti-inflammatory mechanisms to protect the body from uncontrolled stimulation, which might otherwise result in prolonged activation and possibly disease. As a consequence of uncontrolled conditions, an inflammatory response may become chronic, resulting in chronic eczema, impaired wound healing or autoimmune disease, for example [21].

The molecular mechanisms underlying the acute and chronic phases of inflammation are different, and are only partly understood. During the last few years, however, our knowledge of the pathophysiology of inflammation and the mediators involved has expanded substantially. This chapter highlights some of the important recent advances in our understanding of the mechanisms of inflammation with special regard to the skin, and discusses the impact of modern therapeutic strategies on the treatment of cutaneous inflammation. Cellular constituents of the adaptive immune system (T cells, B cells, antigen presenting cells) are described in detail elsewhere (Chapter 13). Therefore, the main focus of this chapter is on the cells and mediators of the innate immune system and their role during inflammation.

Clinical characteristics of inflammation

Five characteristic signs of inflammation were described by Celsus centuries ago: redness, heat, pain, swelling and loss of function. However, not all signs may be necessarily observed in all skin lesions during a given inflammatory response.

Redness (rubor). This reflects the presence of red blood cells or haemoglobin in the skin. Increased redness may follow increased blood flow through superficial dilated vessels, resulting from stimuli leading to vasodilatation, or from obstruction in deeper vessels causing diversion or 'shunting' of blood through more superficial vessels. Redness in the skin may also result from stasis and congestion without increased flow of blood. Such partial stasis increases the chances for leukocytes to emigrate from vessels.

Heat (calor). This is a usual consequence of increased blood flow through the skin. In acute lesions, the temperature of the skin may increase as a direct result of an elevated local metabolic rate. In chronic inflammation, neither local metabolism nor blood flow may be increased, and the skin may feel cool. Heat loss cannot be correlated exactly with redness, because areas of fast flow may be on the border of a more congested and slow-flowing system. Thus, conduction of heat to the surface of the skin may be considerable over a large, deep arteriovenous fistula, while the upper dermis may show all the effects of severe stasis as a consequence of the raised venous pressure.

Pain (dolor). The sensations that accompany inflammation of the skin may vary in the various diseases and include pain (sunburn), burning (rosacea), stinging, itching (atopic dermatitis) and/or tenderness, and are thus more variable than in most internal organs. Which of these sensations predominates depends in part on the site, depth, intensity and duration of the inflammatory process. Thus, in urticaria stinging may accompany transient superficial lesions. Itching is the usual sensation in prurigo, atopic dermatitis or papular urticaria or in weals due to mediator release from mast cells (such as histamine, tryptase) or keratinocytes. Pain and tenderness may accompany deeper lesions of long duration, as observed in delayed pressure urticaria. Other mediators such as cytokines (e.g. interleukin-31), nerve-growth factor (NGF), bradykinin and proteases may also induce pain by activating specific receptors on primary afferent neurones.

Swelling (tumor). Rapid tissue swelling is due to extracellular oedema, the increased leakage of water and mineral salts (transudate), or proteins (oedema fluid) as a consequence of plasma extravasation from post-capillary venules. In acute forms of inflammation, fluid accumulates at the site of inflammation when the rate of exudation from venules and capillaries is greater than the rate of clearance by the lymphatic vessels. This process is normally transient and stops after 4–6 h. Here, neuropeptides, peptides, nitric oxide, cytokines and other vascular active mediators play a crucial role. In most lesions, swelling is mainly due to oedema, or to plasma constituents, for example fibrin in delayed hypersensitivity reactions. In chronic inflammation, swelling is also caused by an increase of extracellular matrix components. Even a dense leukocytic infiltration usually does not substantially contribute to swelling, except in the case of abscess or granuloma formation. Neutrophils may accumulate at a site in large numbers within 4 h, but macrophages and lymphocytes, which contribute to a firmer, more persistent swelling, usually accumulate more slowly over 48–72 h. The persistence of the leukocyte infiltration depends upon the nature of causative agent and the kinetics of the clearing process. Tissue hypertrophy with acanthosis, fibroblast proliferation and angiogenetic factor-induced formation of new vessels may also contribute to more persistent swelling and dysregulated termination of the inflammatory process.

Phases of inflammation

Inflammation induced by exogenous or endogenous stimuli can either occur as an acute response or develop into a chronic condition. Normally, the acute inflammatory response is terminated by several negative feedback mechanisms, such as receptor-antagonists for cytokines or protease inhibitors. Under certain conditions, however, an imbalance of the inflammatory response can lead to a persistence of pro-inflammatory stimuli, resulting in a chronic disease state (Fig. 12.1).

The acute phase (first 6 h) of inflammation consists of a vascular reaction, including vasodilatation, oedema formation, plasma extravasation, activation of endothelial cells and release of early inflammatory mediators from the injured tissue site. Subsequently, this site becomes a target for inflammatory cells aiming to

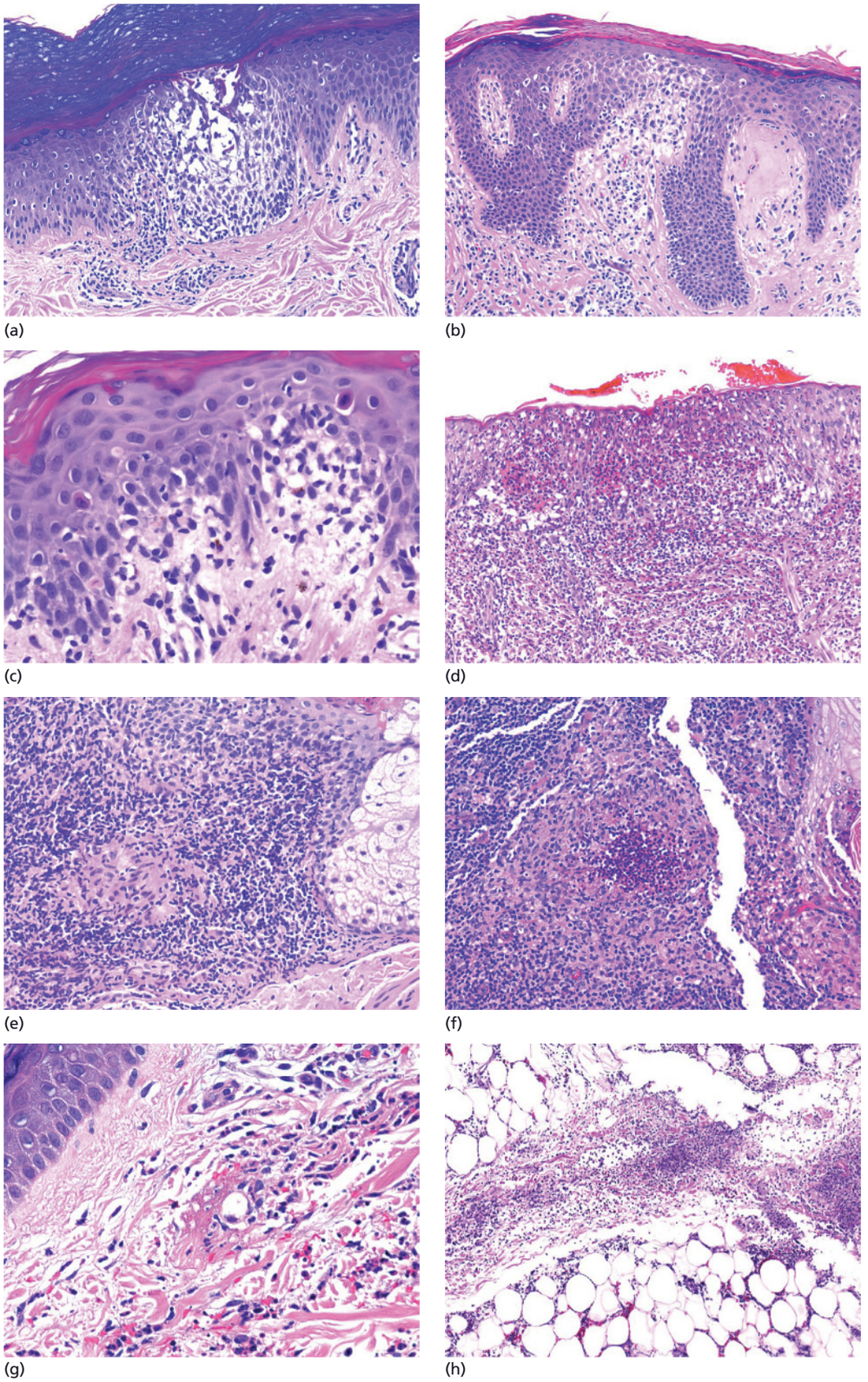


Fig. 12.1 Histopathological features of skin inflammation. (a) Subacute dyshidrosiform dematitis with intraepidermal intercellular oedema (spongiosis), and accumulation of inflammatory cells in the upper dermis around blood vessels. (b) Spongiotic dermatitis combined with regular epidermal hyperkeratosis (psoriasiform reaction pattern), as often observed in chronic inflammatory skin lesions. Note, epidermal hyperparakeratosis due to scratching, spongiosis, and in the dermis marked infiltration of T lymphocytes. In contrast to (c), there is no impairment of the basal membrane. (c) 'Interface' dermatitis in which inflammatory cells (e.g. T cells and eosinophils as here in graft-versus-host reaction) invade the damaged epidermal basal layer or above ('vacuolation'), closely associated with apoptotic ('eosinophilic') keratinocytes. (d) Eosinophilic dermatitis: high density of invading eosinophils in the superficial dermis, as observed in eosinophilic dermatitis of infancy. (e) Granulomatous dermatitis pattern: many lymphocytes surround a perifollicular granuloma consisting of macrophages, as observed in granulomatous rosacea. (f) Tuberculoid granuloma: masses of macrophages, epitheloid cells, giant cells as well as lymphocytes surrounding the granuloma, accumulation of acid mucopolysaccharides between collagen bundles, a loosened extracellular matrix, and occasional degeneration of fibroblasts due to apoptosis, as seen in tuberculosis. (g) Vasculopathic inflammatory tissue pattern: fibrinoid endothelial cell swelling, and increase in fibrohistiocytic cells. Leukocytes invade the connective tissue after transmigration through inflamed endothelial cell walls, as seen in leukocytoclastic vasculitis. (h) Septal panniculitis: inflammation of the deeper skin, and subcutaneous fat. Here, infiltrating neutrophils fill the septa in a patient with erythema nodosum.

eliminate the noxious agent. Vasodilatation of small vessels may be caused by several mediators, such as kinins (bradykinin), amines (serotonin), prostaglandins (PGE_2), and neuropeptides (e.g. calcitonin gene-related peptide, CGRP), which may be released by platelets, mast cells, endothelial cells or sensory nerves. Subsequently, plasma extravasation leads to oedema. Most of these effects are exerted via the up-regulation of specific receptors, such as the bradykinin-2 receptor, or the prostaglandin E_2-receptor. Conversely, peptidases released in the vicinity of the vessel wall may inhibit, and thereby effectively terminate, the vasodilatatory response to neuropeptides or endothelin. Nitric oxide (NO) synthase inhibitors may also block the effects of NO, thereby establishing tissue homeostasis.

Macrophages and neutrophils represent the first line of the host defence against microorganisms [19]. Sensors on these cells that recognize PAMPs (pathogen-associated molecular patterns), such as toll-like receptors (TLR) and nucleotide-binding oligomerization-domain protein-like receptors (NOD), play an essential role in the recognition of 'outside danger' molecules from pathogens [21]. By their recruitment, activation, phagocytosis and killing, the cells rapidly respond to infectious agents until the adaptive immune response is initiated. Subsequently, activated immune cells release cytokines and other mediators to direct the immune system towards the provision of a capable and effective host defence. Moreover, chemokines, which recruit leukocytes to the site of inflammation, can be released by most cutaneous cells. Infectious agents and the local inflammatory response activate the complement system, which initiates the production of plasma proteins capable of destroying pathogenic agents. Finally, the innate immune system also contributes substantially to activation of the adaptive immune response [22] and to resolution of inflammation [23].

The chronic phase of inflammation is characterized by a dysregulation of the homeostatic inflammatory–anti-inflammatory machinery, leading to a cellular phase with prolonged recruitment and enhanced immigration of inflammatory as well as immunocompetent cells to the site of inflammation. Finally, the resident and infiltrating cells are responsible for cell activation, phagocytosis, killing of pathogens, removal of debris, necrosis, apoptosis and modulated restoration of the tissue. The outcome of the inflammatory response is crucially determined by the removal of the primary pro-inflammatory stimulus. Thus, the progression of the acute into the chronic state of inflammation is due to the persistence of the stimulating agent. Exogenous factors may consist of toxins or pathogens, whereas endogenous factors could be autoantigens, for example. Microorganisms, via escaping immunosurveillance, can induce chronic inflammatory states, as observed in leishmaniasis or mycobacterial disease. On the other hand, chronic inflammation in autoimmune-mediated diseases, such as pemphigus vulgaris or lupus erythematosus, may be driven by defective down-regulatory mechanisms. The fine-tuned mechanisms of non-infectious chronic inflammation are poorly understood.

One of the intriguing recent findings which has increased our understanding of the endogenous-mediated processes of inflammation is the description of the NALP-3 inflammasome by ATP, K^+ ions, HMGB1 and S100 proteins, amongst others [24–28]. This is at least in part mediated by caspase-1 [29].

References

1 Janeway CA, Travers P, Walport M, Shlomchik M. *Immunobiology*, 5th edn. New York: Taylor & Francis Inc., 2001.
2 Ezekowitz RAB, Hoffmann JA. Innate immunity. *Curr Opin Immunol* 1996; **8**: 1–2.
3 Carroll MC, Prodeus AP. Linkages of innate and adaptive immunity. *Curr Opin Immunol* 1998; **10**: 36–40.
4 Alberts B, Johnson A, Lewis J *et al*. *Molecular Biology of the Cell*, 4th edn. New York and London: Garland Science, 2002.
5 May AE, Seizer P, Gawaz M. Platelets: inflammatory firebugs of vascular walls. *Arterioscler Thromb Vasc Biol* 2008; **28**: s5–10.
6 Thurmond RL, Gelfand EW, Dunford PJ. The role of histamine H1 and H4 receptors in allergic inflammation: the search for new antihistamines. *Nat Rev Drug Discov* 2008; **7**: 41–53.
7 Lin YT, Wang CT, Chiang BL. Role of bacterial pathogens in atopic dermatitis. *Clin Rev Allergy Immunol* 2007; **33**: 167–77.
8 Kallenberg CG. Pathogenesis of PR3-ANCA associated vasculitis. *J Autoimmun* 2008; **30**: 29–36.
9 Bradley J. TNF-mediated inflammatory disease. *J Pathol* 2008; **214**: 149–60.
10 Haskó G, Pacher P. A2A receptors in inflammation and injury: lessons learned from transgenic animals. *J Leukoc Biol* 2008; **83**: 447–55.
11 Rupprecht TA, Koedel U, Fingerle V, Pfister HW. The pathogenesis of Lyme neuroborreliosis—from infection to inflammation. *Mol Med* 2008; **14**: 205–12.
12 Lin JH, Dutz JP, Sontheimer RD, Werth VP. Pathophysiology of cutaneous lupus erythematosus. *Clin Rev Allergy Immunol* 2007; **33**: 85–106.
13 Nickoloff BJ, Qin JZ, Nestle FO. Immunopathogenesis of psoriasis. *Clin Rev Allergy Immunol* 2007; **33**: 45–56.
14 Ritchlin C. Psoriatic disease—from skin to bone. *Nat Clin Pract Rheumatol* 2007; **3**: 698–706.
15 Thielitz A, Ansorge S, Bank U *et al*. The ectopeptidases dipeptidyl peptidase IV (DP IV) and aminopeptidase N (APN) and their related enzymes as possible targets in the treatment of skin diseases. *Front Biosci* 2008; **13**: 2364–75.
16 Hantash BM, Zhao L, Knowles JA, Lorenz HP. Adult and fetal wound healing. *Front Biosci* 2008; **13**: 51–61.
17 Gilhar A, Paus R, Kalish RS. Lymphocytes, neuropeptides, and genes involved in alopecia areata. *J Clin Invest* 2007; **117**: 2019–27.
18 Kelly M, Hwang JM, Kubes P. Modulating leukocyte recruitment in inflammation. *J Allergy Clin Immunol* 2007; **120**: 3–10.
19 Medzhitov R. Origin and physiological roles of inflammation. *Nature* 2008; **454**: 428–35.
20 Nathan C. Neutrophils and immunity: challenges and opportunities. *Nat Rev Immunol* 2006; **6**: 173–82.
21 Medzhitov R, Janeway CA Jr. Innate immunity: the virtues of a nonclonal system of recognition. *Cell* 1997; **91**: 295–8.
22 Sokol CL, Barton GM, Farr AG, Medzhitov R. A mechanism for the initiation of allergen-induced T helper type 2 responses. *Nat Immunol* 2008; **9**: 310–8.
23 Serhan CN. Resolution phase of inflammation: novel endogenous anti-inflammatory and proresolving lipid mediators and pathways. *Annu Rev Immunol* 2007; **25**: 101–37.
24 Dostert C, Petrilli V, Van Bruggen R *et al*. Innate immune activation through Nalp3 inflammasome sensing of asbestos and silica. *Science* 2008; **320**: 674–7.
25 Mariathasan S, Weiss DS, Newton K *et al*. Cryopyrin activates the inflammasome in response to toxins and ATP. *Nature* 2006; **440**: 228–32.
26 Hofmann MA, Drury S, Fu C *et al*. RAGE mediates a novel proinflammatory axis: a central cell surface receptor for S100/calgranulin polypeptides. *Cell* 1999; **97**: 889–901.
27 Vogl T, Tenbrock K, Ludwig S *et al*. Mrp8 and Mrp14 are endogenous activators of Toll-like receptor 4, promoting lethal, endotoxin-induced shock. *Nat Med* 2007; **13**: 1042–9.
28 Rock KL, Kono H. The inflammatory response to cell death. *Annu Rev Pathol* 2008; **3**: 99–126.
29 Keller M, Ruegg A, Werner S, Beer HD. Active caspase-1 is a regulator of unconventional protein secretion. *Cell* 2008; **132**: 818–31.

Innate defence mechanisms

Innate immunity consists of a complex defence system which is highly conserved throughout the species and already present at birth. The response generated by the innate defence system to injurious agents is immediate, not antigen specific and not activated by pathogen molecular patterns (PAMPs) [1]. In contrast to the adaptive immune response, the innate defence response is not enhanced upon a second exposure and, most importantly, has no memory. The major components of the innate defence system are antimicrobial peptides, toll-like receptors, type 3 complement receptor (CR3), scavenger receptors (SR), mannose receptor (MR) and other C-type lectins [2,3]. In a broader sense, radical oxygen species, nitric oxide and its derivatives, and certain neuropeptides (truncated neuropeptides) may be regarded as components of the innate defence system.

Antimicrobial peptides

Antimicrobial peptides or proteins (AMPs) constitute a novel family of effector molecules with an important contribution to host defence, inflammation or cytotoxicity, and with substantial potential benefit for the treatment of infectious and inflammatory skin diseases. In humans, peptide antibiotics of three families have been identified, and defined as defensins, cathelicidins and histatins. All of the characterized antimicrobial peptides share the capacity to kill and/or to inactivate bacteria, fungi and enveloped viruses *in vitro*. They apparently kill mammalian target cells and microorganisms by a mechanism involving initial electrostatic interactions with negatively charged surface molecules on target cells, followed by insertion into the cell membranes, permeabilization and formation of voltage-regulated channels. In addition to their antimicrobial and cytotoxic properties, some defensins act as opsonins, while others inhibit signal transduction pathways such as protein kinase C, competitively inhibit receptor activation (e.g. ACTH receptor), block steroidogenesis, or act as selective chemoattractants for monocytes. Thus, in addition to their capacity for killing microbes, endogenous AMPs may also contribute to both innate host defence and adaptive immune responses. Many of these AMPs can be induced *in vitro* by pro-inflammatory cytokines, bacteria or fungi. They are rapidly released and synthesized during inflammation; some are also locally expressed in the skin in the absence of inflammation. This suggests that non-inflammatory stimuli of endogenous and/or exogenous origin can also stimulate AMP synthesis without inflammation. Thus, AMPs may become useful therapeutic tools for regulation of immune defence without causing inflammation [4].

Defensins

Defensins are antimicrobial and cytotoxic peptides which consist of 29–35 amino acids, including six invariant cysteines whose intramolecular disulphide bonds cyclize and stabilize them in a triple-stranded beta-sheet configuration. They are generated by proteolytic processing from 93–95 amino acid precursor prepropeptides and can be detected in plants, insects and various mammals [5,6]. The prosegment keeps the peptide in an inactive state and subsequently activation occurs by proteolysis. Matrilysin (MMP-7) was identified as the enzyme responsible for the generation of mature defensins in mice by proteolytic cleavage.

In general, defensins maintain body integrity when the skin is challenged by microbial agents. The generation of antimicrobial peptides is one of the first-line protective systems of the skin. For example, cathelicidins protect the skin through two distinct pathways: (i) direct antimicrobial activity and (ii) initiation of a host response resulting in cytokine release, inflammation, angiogenesis and re-epithelialization [7]. Cathelicidin and proteases have been implicated in the pathophysiology of skin diseases such as psoriasis, atopic dermatitis and rosacea and, as vitamin D_3 may be a key regulator of human cathelicidin, this has implications for the treatment of certain inflammatory and infectious diseases [8–11]. For example, rosacea patients express abnormally high levels of cathelicidin in their facial skin, and the proteolytically processed forms of cathelicidin peptides found in rosacea are different from those in normal individuals. These cathelicidin peptides are the result of a post-translational processing abnormality associated with an increase in stratum corneum tryptic enzyme (SCTE) in the epidermis. Addition of SCTE, and increasing protease activity and deletion of the serine protease inhibitor gene *Spink5*, increase inflammation in mouse skin. Thus, antimicrobial peptides and proteases may be involved in an exacerbated innate immune response in inflammatory skin diseases, including rosacea.

Interestingly, defensins make up to 5% of the total protein content in human neutrophils and are also produced by macrophages, keratinocytes and mucosal epithelial cells of the cutaneous, respiratory, digestive, urinary and reproductive systems [12–15]. In mammals, neutrophils are capable of generating and releasing all three classes of defensins. The antimicrobial spectrum of defensins includes Gram-positive as well as Gram-negative bacteria, mycobacteria, *T. pallidum*, many fungi and some enveloped viruses. Defensins exert non-specific cytotoxic activity against a wide range of normal and malignant targets, including cells resistant to tumour necrosis factor alpha (TNF-α) and natural killer (NK)-cytolytic factor.

α-defensins contain three disulphide bridges, and reveal a triple-stranded β-sheet structure with a β-hairpin that contains cationic amino acids. The first human α-defensin was isolated from neutrophils [16]. Six human α-defensins (termed human neutrophil peptide (HNP)-1 to -6) have been identified. Human neutrophils generate four α-defensins, HNP-1 to -4. They all are localized in the azurophilic granules of neutrophil granulocytes, where they are the principal proteins and contribute to the oxygen-independent killing of phagocytized microorganisms. In contrast, mouse neutrophil granules do not contain α-defensins. HNP-5 and -6 are primarily found in Paneth's cells of the small intestine and epithelial cells of the female urogenital tract.

*β-defensin*s were first isolated from cow tongue in 1991 and originally named tracheal antimicrobial peptide (TAP). They contain six cysteine residues connected by three disulphide bridges but spaced differently from those in α-defensins. The genes encoding β-defensins are localized in the same chromosomal region as α-defensins. They consist of 36–42 amino acids, and possess a different disulphide alignment as compared to other defensins.

Human β-defensin-1 (hBD-1) is expressed constitutively in epithelial cells of the skin, the gastrointestinal as well as urinary and respiratory tracts. Human β-defensin-2 (hBD-2) was also isolated from psoriatic skin [17]. hBD-1 and hBD-2 are diffusely expressed throughout different epithelial organs, as well as glandular cells of different tissues. hBD-3 was isolated from psoriatic keratinocytes, and has potent antimicrobial activity against many skin-pathogenic bacteria [18].

The expression of defensins is tightly regulated. While the expression of hBD-1 has been found to be constitutive, hBD-2 expression seems to be inducible by infectious and pro-inflammatory stimuli. In the skin *in vivo,* hBD-2 transcripts and peptide are found to be up-regulated during infectious diseases [19]. *In vitro,* pro-inflammatory cytokines such as IL-1α, IL-1β and TNF-α, but also lipopolysaccharide (LPS) and microorganisms (Gram-positive and Gram-negative bacteria, and *Candida albicans*) are able to induce hBD-2 production. hBD-1, hBD-2 and hBD-3 are expressed in human skin and immune cells. The expression of hBDs are differentially regulated. For example, hBD-3 up-regulation is mediated by transactivation of the epidermal growth factor receptor (EGFR). The expression of hBD-2 is IL-1-dependent [20], and hBD-3 can be induced by histamine [21]. hBD play a role in keratinocyte migration and cytokine production [22], barrier function and *Staphylococcus aureus* protection [23,24].

θ-Defensins constitute a novel class of defensins that have been isolated from Rhesus monkey neutrophils. The peptide Rhesus θ-defensin-1 is produced by the post-translational ligation of two truncated α-defensins, and demonstrates salt-independent antimicrobial activity. So far, θ-defensins have not been detected in the skin.

Cathelicidins

Peptide antibiotics of the cathelicidin ('cathe-lin' = cathepsin L inhibitor) family contain a highly conserved signal sequence, but show substantial heterogeneity in the C-terminal domain encoding the mature peptide, which can range in size from 12 to 80 amino acid residues. The only human cathelicidin, LL-37/hCAP-18, was originally isolated from human bone marrow [5,6] but expression of LL-37/hCAP-18 is up-regulated in inflamed skin and colocalizes with IL-6. LL-37/hCAP-18 has been found to be regulated by various inflammatory stimuli such as cytokines [19]. Interestingly, the LL-37/hCAP-18 gene contains several potential binding sites for transcription factors (acute-phase response factor and nuclear factor for IL-6 expression (NF IL-6)) that are possibly involved in the regulation of inflammation. However, the mechanisms that induce antimicrobial peptides and the corresponding signalling pathways are speculative at present.

As described above, cathelicidins interact with serine proteases and protease inhibitors, thereby regulating immune defence mechanisms in rosacea [11].

Histatins

Histatins are a family of histidine-rich peptides present in human saliva [25], consisting of about 38 to 32 amino acid residues. The five members of the histatin family are modulated by post-translational processing. A specific role for histatins in humans, however, is still under debate. Histatins seem to play an essential role in the antiviral defence of human saliva and in wound closure [26,27], as well as in gingivitis [28]. Their antimicrobial activity includes strong effects on *Candida albicans* [29]. Histatins may also play a role in experimentally induced sepsis in rats.

Role of antimicrobial peptides in immunity and skin pathophysiology

Antimicrobial peptides, including defensins, cathelicidins and histatins, have a broad spectrum of activity against Gram-positive and Gram-negative bacteria as well as against fungi and enveloped viruses. Antimicrobial peptides show synergistic activity with other host defence molecules such as lysozyme and lactoferrin. The microbicidal activity of defensins is based on permeabilization of anionic lipid bilayers and the subsequent release of cellular contents and the destruction of the cell membrane electrode potential. A second model of action describes the aggregation of peptides into positively charged patches, resulting in the formation of transient gaps. Additionally, defensin-related cell death has been linked to interference with protein synthesis or DNA damage.

Thus far, the evidence that defensins contribute to innate immunity in humans *in vivo* is largely indirect. Evidence for the host defence function of antimicrobial peptides includes a study involving MMP7-knockout mice with an increased susceptibility for infections. In addition to their antimicrobial activity, defensins and cathelicidins can bind to lipopolysaccharide and inactivate the biological functions of this endotoxin. Bacterial resistance to antimicrobial peptides is a rare phenomenon. Mechanisms that result in the development of resistance involve modifications of outer cell wall components, such as lipopolysaccharide, teichoic acids or phosphocholine, and the modulation of efflux pumps [6].

Beside their role as endogenous antibiotics, antimicrobial peptides have other functions in inflammation, wound repair and regulation of the adaptive immune system. Human neutrophil defensins have been described to be cytotoxic for various cell types and to induce cytokine synthesis in epithelial cells, monocytes and T cells. Further, they increase the binding of bacteria to epithelial cells and induce the liberation of histamine from mast cells. Finally, α-defensins are involved in the chemotaxis of monocytes and T cells, the modulation of cell proliferation and B-cell production, and the inhibition of complement activation and proteinase inhibitors [9,30,31]. The human β-defensins have recently been identified as potent ligands for the chemokine receptor CCR6 that is present on dendritic and T cells, suggesting a close functional link between the innate and adaptive immune systems [32].

There is strong evidence that antimicrobial peptides serve as mediators of host defence not only by direct antimicrobial activity, but also by their function as modulators of the inflammatory process. Defensins induce the release of pro-inflammatory mediators such as IL-8, IFN-γ, IL-6, IL-10 and LTB4. On the other hand, defensins might also exhibit anti-inflammatory activities by inducing the secretion of IL-10 [33]. Furthermore, defensins attract inflammatory cells such as neutrophils, B cells, T cells and macrophages, and activate epithelial cells, including keratinocytes, to release cytokines and chemokines. Neutrophil-derived defensins, for example, stimulate IL-8 production, which also helps to recruit

more neutrophils to the site of inflammation. This is in accordance with the report that *in vivo* administration of human neutrophil defensins increases the ability of mice to resist local infection by enhancing neutrophil recruitment to infected tissues. Human neutrophil defensins are reported to bind to complement component 1q [34]. Therefore, it is possible that defensins may participate in the regulation of complement activation. Human neutrophil α-defensins also enhance the antigen-specific humoral immune response. For example, $CD4^+$ T cells isolated from mice immunized with antigen in the presence of α-defensins displayed a higher antigen-specific proliferative response and an elevated production of IFN-γ, IL-5, IL-6 and IL-10 as compared to T cells from mice immunized with antigen alone. HNP1 enhances phagocytosis by cultured mouse peritoneal macrophages. Human defensins can degranulate mast cells, resulting in the release of histamine and tryptase, leading to the recruitment of more neutrophils to the site of inflammation. Conversely, mast cells release the cathelicidin LL-37 which is involved in the killing of bacteria [35].

Antimicrobial peptides are also involved in the induction and regulation of adaptive immune responses [6,14,30,31,36]. Defensins have been shown to modulate the cytokine profile of T cells; HNP-1 and HNP-2 are T-cell chemoattractants and induce the recruitment of T cells to sites of inflammation *in vivo*. Defensins also modulate dendritic cell function. Human α- and β-defensins are selectively chemotactic for human immature, but not mature, dendritic cells. Although *in vivo* neutrophil defensins are stored in azurophilic granules, they can be released into the extracellular environment by neutrophil disruption or degranulation [37]. Murine BD2 has been demonstrated to directly modulate dendritic cell function and maturation, indicating that defensins are involved in immunosurveillance. Thus, defensins, presumably present at sites of inflammation, form chemotactic gradients for immature dendritic cells. Since dendritic cells are crucial for the induction of adaptive immune responses, defensins may directly contribute to antigen-specific immune responses.

In the skin, defensins such as hBD2 are up-regulated in psoriasis [17], acne [38] and folliculitis [39]. In contrast, decreased expression and release of hBD2 and LL-37 was found in lesional skin of atopic dermatitis patients [40]. Interestingly, antimicrobial agents such as LL-37 and hBD1 are up-regulated in the inflamed skin of newborn infants during erythema toxicum neonatorum [41]. Moreover, growth factors such as insulin-like growth factor-1 (IGF-1) and transforming growth factor-α (TGF-α) enhance the expression of hCAP/LL-37 and hBD3, indicating an up-regulation of antimicrobial peptides during wound healing [42]. Accordingly, HNP1 increases the expression of pro-α-(I)-collagen and decreases MMP-1 release, supporting a role of defensins in wound repair [43]. Moreover, IL-1 seems to be an important inducer of hBD2 synthesis in human keratinocytes [44]. One of the defensins most recently described in the skin is hornerin (S100A16) a new calcium-binding, profilaggrin-related protein, which may play an important role in epidermal barrier function [45]. In summary, defensins play an essential role in inflammatory skin diseases such as rosacea, atopic dermatitis and psoriasis, and wound healing, as well as in bacterial, viral and fungal infections [46], and are important antimicrobial peptides in human tongue [47].

References

1 Netea MG, Brown GD, Kullberg BJ, Gow NA. An integrated model of the recognition of *Candida albicans* by the innate immune system. *Nat Rev Microbiol* 2008; **6**: 67–78.

2 Harder J, Glaser R, Schroder JM. Review: Human antimicrobial proteins effectors of innate immunity. *J Endotoxin Res* 2007; **13**: 317–38.

3 Carneiro L, Magalhaes J, Tattoli I *et al*. Nod-like proteins in inflammation and disease. *J Pathol* 2008; **214**: 136–48.

4 Lai Y, Gallo RL. Toll-like receptors in skin infections and inflammatory diseases. *Infect Disord Drug Targets* 2008; **8**(3): 144–55.

5 Bals R. Epithelial antimicrobial peptides in host defense against infection. *Respir Res* 2000; **1**: 141–50.

6 Chertov O, Yang D, Howard OM, Oppenheim JJ. Leukocyte granule proteins mobilize innate host defenses and adaptive immune responses. *Immunol Rev* 2000; **177**: 68–78.

7 Schauber J, Gallo RL. Antimicrobial peptides and the skin immune defense system. *J Allergy Clin Immunol* 2008; **122**: 261–6.

8 Schauber J, Oda Y, Buchau AS *et al*. Histone acetylation in keratinocytes enables control of the expression of cathelicidin and CD14 by 1,25-dihydroxyvitamin D3. *J Invest Dermatol* 2008; **128**: 816–24.

9 Fellermann K, Stange EF. Defensins—innate immunity at the epithelial frontier. *Eur J Gastroenterol Hepatol* 2001; **13**: 771–6.

10 Chromek M, Slamova Z, Bergman P *et al*. The antimicrobial peptide cathelicidin protects the urinary tract against invasive bacterial infection. *Nat Med* 2006; **12**: 636–41.

11 Yamasaki K, Di Nardo A, Bardan A *et al*. Increased serine protease activity and cathelicidin promotes skin inflammation in rosacea. *Nat Med* 2007; **13**: 975–80.

12 Bals R, Jany B. Identification of disease genes by expression profiling. *Eur Respir J* 2001; **18**: 882–9.

13 Bals R, Wilson JM. Cathelicidins—a family of multifunctional antimicrobial peptides. *Cell Mol Life Sci* 2003; **60**: 711–20.

14 Gallo RL, Murakami M, Ohtake T, Zaiou M. Biology and clinical relevance of naturally occurring antimicrobial peptides. *J Allergy Clin Immunol* 2002; **110**: 823–31.

15 Zasloff M. Antimicrobial peptides in health and disease. *N Engl J Med* 2002; **347**: 1199–200.

16 Ganz T, Selsted ME, Szklarek D *et al*. Defensins. Natural peptide antibiotics of human neutrophils. *J Clin Invest* 1985; **76**: 1427–35.

17 Harder J, Bartels J, Christophers E, Schroder JM. A peptide antibiotic from human skin. *Nature* 1997; **387**: 861.

18 Harder J, Bartels J, Christophers E, Schroder JM. Isolation and characterization of human beta-defensin-3, a novel human inducible peptide antibiotic. *J Biol Chem* 2001; **276**: 5707–13.

19 Frohm M, Agerberth B, Ahangari G *et al*. The expression of the gene coding for the antibacterial peptide LL-37 is induced in human keratinocytes during inflammatory disorders. *J Biol Chem* 1997; **272**: 15258–63.

20 Sorensen OE, Thapa DR, Rosenthal A *et al*. Differential regulation of beta-defensin expression in human skin by microbial stimuli. *J Immunol* 2005; **174**: 4870–9.

21 Kanda N, Watanabe S. Histamine enhances the production of human beta-defensin-2 in human keratinocytes. *Am J Physiol Cell Physiol* 2007; **293**: C1916–23.

22 Niyonsaba F, Ushio H, Nakano N *et al*. Antimicrobial peptides human beta-defensins stimulate epidermal keratinocyte migration, proliferation and production of proinflammatory cytokines and chemokines. *J Invest Dermatol* 2007; **127**: 594–604.

23 Jensen JM, Pfeiffer S, Akaki T *et al*. Barrier function, epidermal differentiation, and human beta-defensin 2 expression in tinea corporis. *J Invest Dermatol* 2007; **127**: 1720–7.

24 Kisich KO, Howell MD, Boguniewicz M *et al*. The constitutive capacity of human keratinocytes to kill *Staphylococcus aureus* is dependent on beta-defensin 3. *J Invest Dermatol* 2007; **127**: 2368–80.

25 Oppenheim FG, Xu T, McMillian FM *et al*. Histatins, a novel family of histidine-rich proteins in human parotid secretion. Isolation, characterization, primary structure, and fungistatic effects on *Candida albicans*. *J Biol Chem* 1988; **263**: 7472–7.

26 Hardestam J, Petterson L, Ahlm C *et al*. Antiviral effect of human saliva against hantavirus. *J Med Virol* 2008; **80**: 2122–6.

Table 12.1 Potential use of toll-like receptor (TLR) agonists in various diseases.

Disease/condition	TLR involved	Therapeutic approach	Comments and expected outcome
Acne	TLR-2	Antagonist	Suppression of *P. acnes*-induced cytokine production
Atopic dermatitis	Many	Bacterial vaccine Agonists	Shifting of a Th2 into a Th1 response
Pathogen invasion	TLR-7	Agonist	Reinstatement of cytokine-induced host defence and elimination of viruses
Acute inflammation	TLR-2, -4	Antagonist	Reduction in inflammation by inhibiting TLR-2, -4 expression and HSP-70 release
Chronic inflammation	TLR-2, -4	Antagonist	Reduction in TLR-induced release of inflammatory mediators (heat shock proteins, fatty acids, hyaluronic acids)
Autoimmune disease	TLR-9	Antagonist	Blocking of production of autoantibodies and proliferation of B cells induced by immune complexes containing DNA
Sepsis	Many	Soluble TLRs Antagonists Signalling inhibitors	Ligand neutralization Mediator blockade Receptor blockade

27 Oudhoff MJ, Bolscher JG, Nazmi K *et al.* Histatins are the major wound-closure stimulating factors in human saliva as identified in a cell culture assay. *FASEB J* 2008; **22**: 3805–12.

28 Paquette DW, Simpson DM, Friden P *et al*. Safety and clinical effects of topical histatin gels in humans with experimental gingivitis. *J Clin Periodontol* 2002; **29**: 1051–8.

29 Vylkova S, Jang WS, Li W *et al*. Histatin 5 initiates osmotic stress response in *Candida albicans* via activation of the Hog1 mitogen-activated protein kinase pathway. *Eukaryot Cell* 2007; **6**: 1876–88.

30 Yang YL, Li XM. The IAP family: endogenous caspase inhibitors with multiple biological activities. *Cell Res* 2000; **10**: 169–77.

31 Risso A. Leukocyte antimicrobial peptides: multifunctional effector molecules of innate immunity. *J Leukoc Biol* 2000; **68**: 785–92.

32 Yang D, Chertov O, Bykovskaia SN *et al*. Beta-defensins: linking innate and adaptive immunity through dendritic and T cell CCR6. *Science* 1999; **286**: 525–8.

33 Lillard JW Jr, Boyaka PN, Chertov O *et al*. Mechanisms for induction of acquired host immunity by neutrophil peptide defensins. *Proc Natl Acad Sci U S A* 1999; **96**: 651–6.

34 van den Berg RH, Faber-Krol MC, van Wetering S *et al*. Inhibition of activation of the classical pathway of complement by human neutrophil defensins. *Blood* 1998; **92**: 3898–903.

35 Di Nardo A, Vitiello A, Gallo RL. Cutting edge: mast cell antimicrobial activity is mediated by expression of cathelicidin antimicrobial peptide. *J Immunol* 2003; **170**: 2274–8.

36 Fellermann K, Wehkamp J, Stange EF. Antimicrobial peptides in the skin. *N Engl J Med* 2003; **348**: 361–3.

37 Ganz T. Extracellular release of antimicrobial defensins by human polymorphonuclear leukocytes. *Infect Immun* 1987; **55**: 568–71.

38 Chronnell CM, Ghali LR, Ali RS *et al.* Human beta defensin-1 and -2 expression in human pilosebaceous units: upregulation in acne vulgaris lesions. *J Invest Dermatol* 2001; **117**: 1120–5.

39 Oono T, Huh WK, Shirafuji Y *et al*. Localization of human beta-defensin-2 and human neutrophil peptides in superficial folliculitis. *Br J Dermatol* 2003; **148**: 188–91.

40 Ong PY, Ohtake T, Brandt C *et al.* Endogenous antimicrobial peptides and skin infections in atopic dermatitis. *N Engl J Med* 2002; **347**: 1151–60.

41 Marchini G, Lindow S, Brismar H *et al.* The newborn infant is protected by an innate antimicrobial barrier: peptide antibiotics are present in the skin and vernix caseosa. *Br J Dermatol* 2002; **147**: 1127–34.

42 Sorensen OE, Cowland JB, Theilgaard-Monch K *et al*. Wound healing and expression of antimicrobial peptides/polypeptides in human keratinocytes, a consequence of common growth factors. *J Immunol* 2003; **170**: 5583–9.

43 Oono T, Shirafuji Y, Huh WK *et al*. Effects of human neutrophil peptide-1 on the expression of interstitial collagenase and type I collagen in human dermal fibroblasts. *Arch Dermatol Res* 2002; **294**: 185–9.

44 Liu L, Roberts AA, Ganz T. By IL-1 signaling, monocyte-derived cells dramatically enhance the epidermal antimicrobial response to lipopolysaccharide. *J Immunol* 2003; **170**: 575–80.

45 Wu Z, Meyer-Hoffert U, Reithmayer K *et al.* Highly complex peptide aggregates of the s100 fused-type protein hornerin are present in human skin. *J Invest Dermatol* 2008; **129**: 1446–58.

46 Glaser R, Harder J, Lange H *et al*. Antimicrobial psoriasin (S100A7) protects human skin from *Escherichia coli* infection. *Nat Immunol* 2005; **6**: 57–64.

47 Meyer JE, Harder J, Sipos B *et al.* Psoriasin (S100A7) is a principal antimicrobial peptide of the human tongue. *Mucosal Immunol* 2008; **1**: 239–43.

Toll-like receptors

Toll-like receptors (TLRs) are key receptor molecules critically involved in microbial recognition by the immune system. At present, 12 members of the TLR family have been identified in mammals (Table 12.1). They recognize microbial structures such as bacterial lipopolysaccharides, bacterial DNA, viral double-stranded DNA as well as drugs or endogenous inflammatory molecules (S-100 protein MRP) [1]. There is also evidence that some probiotics which appear to be effective in allergy prevention may function via interaction with TLRs. Knowledge of the number of ligands for these receptors is growing, and it appears that multiple ligands exist for each receptor. TLRs activate common signalling pathways leading to the activation of the transcription factor nuclear factor-kappa B (NF-κB), as well as mitogen-activated protein kinases (MAPKs), which results in the production of pro-inflammatory cytokines and modulation of inflammatory processes, apoptosis or cell growth. On the other hand, individual TLRs, via their specific signalling systems, may induce immune responses to a single microbial agent. Thus, TLRs are crucial components of both the innate and adaptive immune responses.

TLRs are defined by the presence of a Toll/IL-1 receptor (TIR) domain in their cytosolic region and an extracellular domain comprising leucine-rich repeats. A key question concerns the signal transduction pathways, and whether different responses induced by different TLRs are important for the tailoring of the host defence against different microbes. In this regard, two TIR domain-containing adapter proteins, MyD88 and TIRAP/Mal, are of great interest. There is evidence from MyD88-deficient mice that MyD88 is an universal adapter for a wide range of the TIR domain-

containing receptors tested thus far [2], while TIRAP/Mal is implicated in signalling by the LPS sensor TLR-4, but not the bacterial cytosine-phosphate-guanine (CpG) DNA sensor TLR-9 or IL-1 [3,4]. Thus, TLRs are widely expressed on immunocompetent cells and thereby involved in the activation, as well as differentiation, of dendritic cells and T cells [5]. While undoubtedly important in downstream signalling responses and NF-κB activation, TLRs have not been shown to bind directly to ligands such as LPS or their complexes with LPS-binding protein (LBP) [6]. Instead, they bind to CD14, also implicated in apoptotic cell, heat shock protein and fibrinogen clearance. TLRs have recently been found to be expressed on various resident skin cells, including keratinocytes, in addition to immunocompetent cells.

The ligands so far identified that signal through TLR are mainly exogenous, but there are reports of drugs or endogenous ligands and of intracellular rather than surface engagement, through which selected TLRs may act. For example, imidazoquinolones such as imiquimod and resiquimod were found to bind to TLR-7 and TLR-8, respectively, and thereby activate macrophages. The resultant secretion of pro-inflammatory cytokines, predominantly IFN-γ, TNF-α and IL-12, was found to be responsible for an immunodeviation towards a T helper 1 (Th1) mediated response required for cytotoxicity and effective antiviral or antitumoral activity. Accordingly, topical imiquimod is successfully used for the treatment of anogenital warts and several types of skin tumour. A similar Th1-inducing effect has been observed for CpG oligodeoxynucleotides (ODN), and was found to be mediated via TLR-9. The efficacy of CpG ODN in the treatment of allergic diseases, or as an adjuvant immunotherapy for tumours, is currently under investigation. The potential for using TLRs for therapy of various inflammatory disorders is shown in Table 12.1.

TLRs play an essential role in many skin diseases such as mycobacteriosis and Wegener's syndrome. *Mycobacterium ulcerans* causes Buruli ulcer. Keratinocyte-derived toll-like receptors-2 and -4, as well as dectin-1, actively participate in the innate immune response to *M. ulcerans* by regulating internalization of bacteria, production of reactive oxygen species (ROS), and the expression of chemokines and the defensin LL-37 [7]. TLRs may be also involved in the pathophysiology of psoriasis, atopic dermatitis [8] and pityriasis rubra pilaris, which can be triggered by the TLR-9 agonist imiquimod [9]. Thus, the skin forms the outermost part of the innate immune system, by sensing danger from pathogen-associated molecule patterns (PAMPs) through toll-like receptors and other pattern-recognition receptors (PRRs). Hence, the skin may prevent inflammation by producing antimicrobial peptides or other antimicrobial intermediates before mediator release of cytokines, ROS or proteases can occur. For example, low-molecular weight hyaluronic acid induces TLR-2 and -4 activation, thereby regulating immune defence [10]. Secondly, TLRs communicate with the adaptive immune system, for example through activation of Langerhans' cells, dermal dendritic cells or T cells by TLR activation on keratinocytes. TLRs can influence the immune system in either stimulating or suppressing the immune response. For example, TLR-12 regulates susceptibility to contact hypersensitivity in mice [11]. Glucocorticoids induce TLR-2 activation on keratinocytes, suggesting that steroid-induced TLR-2 together with *P. acnes* plays a role in the exacerbation of acne vulgaris as well as corticosteroid-induced acne [12]. TLR-3 appears to be involved in antiviral defence in the skin [13].

NBS-LRR (nucleotide-binding site and leucine-rich repeat) proteins

While toll-like receptors are involved in detection of microbes in the extracellular compartment, a newly discovered family of proteins, the NBS-LRR (nucleotide-binding site and leucine-rich repeat) proteins (e.g. NODS, NALPS and NAIP) are involved in intracellular recognition of microbes and their products. Furthermore, NBS proteins may be involved in autoimmune diseases and atopic dermatitis. The NBS-LRR 'microbial-sensing' proteins participate in innate immune responses by recognizing conserved, often structural, components of microorganisms. NBS-LRR proteins are characterized by three structural domains: a C-terminal leucine-rich repeat (LRR) domain able to sense a microbial motif; an intermediary nucleotide binding site (NBS) essential for the oligomerization of the molecule, necessary for signal transduction induced by different N-terminal effector motifs, such as a pyrin domain (PYD); and a caspase-activating and recruitment domain (CARD) or a baculovirus inhibitor of apoptosis protein repeat (BIR) domain. Two of these family members, NOD1 and NOD2, play a role in the regulation of pro-inflammatory pathways through NF-κB induced by bacterial ligands. Recently, it was shown that NOD2 recognizes a specific peptidoglycan motif from bacteria, muramyl dipeptide (MDP). A surprising number of human genetic disorders have been linked to NBS-LRR proteins. For example, mutations in Nod2, which render the molecule insensitive to MDP and unable to induce NF-κB activation when stimulated, are associated with susceptibility to a chronic intestinal inflammatory disorder, Crohn's disease. Conversely, mutations in the NBS region of NOD2 induce a constitutive activation of NF-κB and are responsible for Blau syndrome, another autoinflammatory disease which includes inflammation of joints and the skin. NALP3 has been implicated in rare autoinflammatory disorders. In conclusion, NBS-LRR molecules appear as a new family of intracellular receptors of innate immunity, able to detect specific bacterial compounds and induce all inflammatory response; the dysregulation of these processes due to mutations in the genes encoding these proteins is involved in numerous autoinflammatory disorders [14].

NOD (nucleotide-binding oligomerization domain) proteins are members of a family that includes the apoptosis regulator APAF1 (apoptotic protease activating factor 1), mammalian NOD-LRR (leucine-rich repeat) proteins and plant disease-resistance gene products. Several NOD proteins have been implicated in the induction of NF-κB activity and in the activation of caspases. Two members of the NOD family, NOD1 and NOD2, mediate the recognition of specific bacterial components. Notably, genetic variation in the genes encoding the NOD proteins NOD2, cryopyrin and CIITA (MHC class II transactivator) in humans and Naip5 (neuronal apoptosis inhibitory protein 5) in mice is associated with inflammatory disease or increased susceptibility to bacterial infections. Mammalian NOD proteins seem to function as cytosolic sensors for the induction of apoptosis, as well as for innate recognition of microorganisms and regulation of inflammatory responses [15].

Type 3 complement receptor

Type 3 complement receptor (CR3) is a myeloid cell phagocytic receptor for complement-opsonized particles, responsible for direct interactions with pathogens such as *Mycobacterium tuberculosis* or yeast-derived zymosan, as well as for host ligands [16]. It is a β2-integrin also known as CD18/CD11b, critical to myelomonocytic cell recruitment to sites of inflammation, irrespective of the host or the microbial origin. The expression of CR3 by macrophages is tissue-selective, and is thus not generated by all immune cells. CR3 is promiscuous in its range of binding of ligands, including intercellular adhesion molecule-1 (ICAM-1) on endothelial cells or platelets, indicating a role at early stages of inflammation and wound healing. Moreover, CR3 contributes to clearance of apoptotic cells. Of note, the opsonic phagocytic mechanism differs from that mediated by Fc receptors, and CR3-mediated uptake by macrophages triggers cytokine release but does not trigger the release of prostaglandins or reactive oxygen species, indicating specific regulation of inflammatory processes.

Scavenger receptors

Scavenger receptors (SRs) represent a family of structurally unrelated membrane molecules expressed by macrophages and selected endothelial cells, with a broad specificity for polyanionic ligands such as low-density lipoprotein (LDL), suggesting a role in host defence and inflammation. SR-A, for example, contributes to the resistance of the host towards Gram-positive microbial infection *in vivo*. SR-A is also involved in the phagocytic uptake of unopsonized *Neisseria meningitidis* [17]. In contrast, LPS, a previously known ligand of SR-A, is not required for the uptake of *Neisseria* by macrophages, but is responsible for the TLR-4-mediated induction of pro-inflammatory responses. This is associated with an overproduction of TNF-α and other pro-inflammatory mediators, perhaps resulting from an imbalance between SR-A-dependent clearance of LPS and TLR-4-dependent pathways of secretory stimulation. Thus, the role of SRs during inflammation and infection has many interesting features. First, they are able to function as adhesion molecules, but can also mediate endocytosis and phagocytosis of modified-host components and of exogenous ligands (LPS, lipoteichoic acid, and others). The structural basis for receptor–ligand interactions remains unclear. Additionally, the signalling pathways induced by SR-A in the infected cell are poorly defined, and the ligands utilized in many studies can bind to a wide range of SR molecules. Future studies, with the availability of knockout mice for various SRs, will help to clarify their role within innate and adaptive immunity, as well as cutaneous diseases or skin homeostasis. Two novel surface scavenger receptors, SCART1 and SCART2, are related to CD5, CD6 and CD163 in developing and mature gamma delta T cells. SCART2 positive gamma delta T cells belong to a new IL-17-producing subset with distinct homing capabilities [18]. CD163 is a haemoglobin scavenger receptor and is a highly specific marker for monocytes, macrophages and histiocytes. Thus, CD163 expression is helpful in distinguishing between dermatofibroma, cellular fibrous histiocytoma and dermatofibrosarcoma protuberans [19]. Peroxisome proliferator-activated receptors (PPARs) and NF-κB may be involved in the pathophysiology of psoriasis, because deficient NF-κB activation permits unabated PPARδ-mediated transactivation, which may contribute to the pathological phenotype of psoriasis [20].

Mannose receptor and other C-type lectins

The mannose receptor (MR) is expressed by macrophages, dendritic cells and some endothelial cells. It is a multilectin, which binds mannosyl/fucosyl or GlcNAc-glycoconjugate ligands through its Ca^{2+}-dependent carbohydrate recognition domains (CRD) [21]. The ligands are present on several bacteria, fungi, virus-infected cells and parasites. Endogenous self-ligands for CRD include L-selectin, implicated in cell migration, and a number of mannose-terminal lysosomal hydrolases [22]. Recent data also suggest novel ligands for MR in peripheral lymphoid organs. Interestingly, macrophages are capable of releasing a soluble form of MR into the plasma. Thus, MR participates in complex functions related to tissue clearance, homeostasis, immunomodulation and host defence. The role of MR in inflammatory skin diseases is still obscure. MR is expressed by macrophages and dermal dendritic cells, and regulates the release of cytokines, transcription factors and receptors involved in inflammation [23] and *Candida albicans* infection [24]. MR also regulates the function of lymphatic vessels [25].

In other organs, such as the lung, it has been demonstrated that selective targeting of glucocorticoids to alveolar macrophages by applying mannosylated liposomes offers efficacious pharmacological intervention with minimal side effects, by inhibiting TNF-α, IL-1β, and cytokine-induced neutrophil chemoattractant-1 levels, suppression of neutrophil infiltration and myeloperoxidase activity, and inhibition of NF-κB [26].

References

1 Vogl T, Tenbrock K, Ludwig S *et al.* Mrp8 and Mrp14 are endogenous activators of Toll-like receptor 4, promoting lethal, endotoxin-induced shock. *Nat Med* 2007; **13**: 1042–9.

2 Janssens S, Beyaert R. A universal role for MyD88 in TLR/IL-1R-mediated signaling. *Trends Biochem Sci* 2002; **27**: 474–82.

3 Fitzgerald KA, Palsson-McDermott EM, Bowie AG *et al.* Mal (MyD88-adapter-like) is required for Toll-like receptor-4 signal transduction. *Nature* 2001; **413**: 78–83.

4 Horng T, Barton GM, Medzhitov R. TIRAP: an adapter molecule in the Toll signaling pathway. *Nat Immunol* 2001; **2**: 835–41.

5 Takeuchi O, Akira S. Genetic approaches to the study of Toll-like receptor function. *Microbes Infect* 2002; **4**: 887–95.

6 Tobias PS. Lipopolysaccharide-binding protein and CD14. In: Ezekowitz RAB, Hoffmann JA, eds. *Innate Immunity*. Totowa, NJ: Humana Press 2003: 255–65.

7 Lee HM, Shin DM, Choi DK *et al.* Innate immune responses to *Mycobacterium ulcerans* via toll-like receptors and dectin-1 in human keratinocytes. *Cell Microbiol* 2009; **11**: 678–92.

8 De Benedetto A, Agnihothri R, McGirt LY *et al.* Atopic dermatitis: a disease caused by innate immune defects? *J Invest Dermatol* 2009; **129**: 14–30.

9 Yang FC, Jessup C, Dahiya M, Reynolds R. Pityriasis rubra pilaris exacerbation with topical use of imiquimod. *Int J Dermatol* 2008; **47**: 1076–8.

10 Gariboldi S, Palazzo M, Zanobbio L *et al.* Low molecular weight hyaluronic acid increases the self-defense of skin epithelium by induction of beta-defensin 2 via TLR2 and TLR4. *J Immunol* 2008; **181**: 2103–10.

11 Martin SF, Dudda JC, Bachtanian E *et al.* Toll-like receptor and IL-12 signaling control susceptibility to contact hypersensitivity. *J Exp Med* 2008; **205**: 2151–62.

12 Shibata M, Katsuyama M, Onodera T *et al.* Glucocorticoids enhance Toll-like receptor 2 expression in human keratinocytes stimulated with *Propionibacterium acnes* or proinflammatory cytokines. *J Invest Dermatol* 2009; **129**: 375–82.

13 Kalali BN, Kollisch G, Mages J *et al.* Double-stranded RNA induces an antiviral defense status in epidermal keratinocytes through TLR3-, PKR-, and MDA5/RIG-I-mediated differential signaling. *J Immunol* 2008; **181**: 2694–704.
14 Chamaillard M, Girardin SE, Viala J, Philpott DJ. Nods, Nalps and Naip: intracellular regulators of bacterial-induced inflammation. *Cell Microbiol* 2003; **5**: 581–92.
15 Inohara N, Nunez G. NODs: intracellular proteins involved in inflammation and apoptosis. *Nat Rev Immunol* 2003; **3**: 371–82.
16 Ross GD. Regulation of the adhesion versus cytotoxic functions of the Mac-1/CR3/alphaMbeta2-integrin glycoprotein. *Crit Rev Immunol* 2000; **20**: 197–222.
17 Peiser L, Mukhopadhyay S, Gordon S. Scavenger receptors in innate immunity. *Curr Opin Immunol* 2002; **14**: 123–8.
18 Kisielow J, Kopf M, Karjalainen K. SCART scavenger receptors identify a novel subset of adult gammadelta T cells. *J Immunol* 2008; **181**: 1710–6.
19 Sachdev R, Sundram U. Expression of CD163 in dermatofibroma, cellular fibrous histiocytoma, and dermatofibrosarcoma protuberans: comparison with CD68, CD34, and Factor XIIIa. *J Cutan Pathol* 2006; **33**: 353–60.
20 Westergaard M, Henningsen J, Johansen C *et al.* Expression and localization of peroxisome proliferator-activated receptors and nuclear factor kappaB in normal and lesional psoriatic skin. *J Invest Dermatol* 2003; **121**: 1104–17.
21 East L, Isacke CM. The mannose receptor family. *Biochim Biophys Acta* 2002; **1572**: 364–86.
22 Lee SJ, Evers S, Roeder D *et al.* Mannose receptor-mediated regulation of serum glycoprotein homeostasis. *Science* 2002; **295**: 1898–901.
23 Ochoa MT, Loncaric A, Krutzik SR *et al.* 'Dermal dendritic cells' comprise two distinct populations: CD1+ dendritic cells and CD209+ macrophages. *J Invest Dermatol* 2008; **128**: 2225–31.
24 Cambi A, Netea MG, Mora-Montes HM *et al.* Dendritic cell interaction with *Candida albicans* critically depends on N-linked mannan. *J Biol Chem* 2008; **283**: 20590–9.
25 Marttila-Ichihara F, Turja R, Miiluniemi M *et al.* Macrophage mannose receptor on lymphatics controls cell trafficking. *Blood* 2008; **112**: 64–72.
26 Wijagkanalan W, Higuchi Y, Kawakami S *et al.* Enhanced anti-inflammation of inhaled dexamethasone palmitate using mannosylated liposomes in an endotoxin-induced lung inflammation model. *Mol Pharmacol* 2008; **74**: 1183–92.

Cell apoptosis and inflammation

Apoptosis (Greek: falling, as of leaves from a tree) is a physiological and programmed form of cell death that is characteristic for all nucleated cells, in plants, animals and humans. Apoptosis regulates the function of all skin cells and leukocytes by directly regulating various effector subtypes. It has to be substantially differentiated from the process of necrosis [1].

Apoptosis is the most common form of cell death in both innate and adaptive immunity. Central to the apoptotic process is a family of intracellular cysteine proteases with aspartate-specificity, defined as caspases. Caspases are intracellular proteases which are counter-regulated by multiple antiapoptotic molecules, and the expression of the latter in skin cells and immune cells is mainly dependent on survival factors. Thus, the steady state of apoptosis changes under different pathological conditions. During inflammation, the expression of survival factors is usually elevated, resulting in increased cell survival and consequently in the accumulation of the involved immune cells. In many inflammatory diseases, apoptosis is delayed, contributing to enhanced recruitment and survival of leukocytes at the site of inflammation. In keratinocytes, accelerated cell death can often be observed, a mechanism which amplifies or maintains chronic inflammatory reactions.

The first step of this fine-tuned cellular process is the induction of endogenous endonuclease activation and proteolysis. The intracellular activation machinery is very similar in all cells. Keratinocytes, for example, undergo apoptosis when irradiated with supraoptimal doses of ultraviolet light (UV light), during infection or in acute or chronic inflammation as well as in autoimmune diseases.

The pathways, regulators and counter-regulators of apoptosis are incompletely understood as of yet. In healthy tissues, cells that are no longer needed are rapidly eliminated without affecting the overall function of the tissue. In this process, cells undergo an active and spontaneous suicide, defined as programmed cell death. Most physiological cell death involves apoptosis. The morphological correlates of apoptosis include decrease of cell volume and condensation of the nucleus. However, intracellular organelles such as the mitochondria or lysosomes retain their normal morphology at this stage and are still active. Later, blebbing of the plasma membrane occurs, and the nucleus becomes fragmented. Finally, the cell itself fragments to form apoptotic bodies that are engulfed by nearby phagocytes. With respect to biochemical changes, it is known that the chromosomes become fragmented into nucleosome units.

At the cell surface, apoptosis is regulated by various receptors such as the TNF-α receptor or Fas receptor (so-called 'death signal' receptors). Survival factors include IL-3 and erythropoietin. The tumour suppressor gene *p53* plays a very important role in apoptosis induced by damage to DNA. This has been demonstrated by studying resistance to apoptosis of cells derived from *p53* knockout mice. Other molecules which have been strongly implicated as major players in apoptosis include the caspases, the Bcl-2 family proteins and the IL-1 converting enzyme (ICE). These proteins are highly conserved during evolution. Apoptosis occurs during viral, bacterial or fungal infections, neurogenic and non-neurogenic inflammation, physical trauma (e.g. UV radiation), etc. In contrast, inhibition of apoptosis in the immune system enables the survival of autoreactive B cells and T cells, and is therefore a cause of autoimmune disorders [1–3].

Fas ligand (FasL) causes apoptosis of epidermal keratinocytes and triggers the appearance of spongiosis in eczematous dermatitis. FasL also aggravates inflammation by triggering the expression of pro-inflammatory cytokines, chemokines and adhesion molecules in keratinocytes. FasL also triggers caspase activity, stimulates autocrine production of epidermal growth factor receptor (EGFR) ligands, and activation of EGFR and ERK1 and ERK2 mitogen-activated protein kinases. Subsequently, FasL regulates expression and release of CXCL8/interleukin-8, ICAM-1, IL-1α, IL-1, CCL20/MIP-3α and TSLP. Thus, FasL is involved in the regulation of epidermal inflammation [4,5]. FasL also triggers an NF-κB-dependent mRNA accumulation of inflammatory cytokines (such as TNF-α, IL-6, and IL-1β), chemokines (CCL2/MCP-1, CXCL1/GROα, CXCL3/GROγ, and CXCL8/IL-8), and the adhesion molecule ICAM-1. In the presence of caspase inhibitors, but not in their absence, FasL also triggers release of CCL5/RANTES mRNA. These findings identify a novel pro-inflammatory role of FasL in keratinocytes that is independent of caspase activity and is separable from apoptosis. Thus, in addition to causing spongiosis, FasL may play a direct role in triggering and/or sustaining inflammation in eczema [5].

In terms of the inflammatory process, recent knowledge indicates that inflammatory cells such as neutrophils, macrophages and dendritic cells are capable of directing the inflammatory response in both pro- or anti-inflammatory directions, depending on the signals which they receive. Thus, apoptosis may be either a pro- or anti-inflammatory process, depending on the microenvironment in which this interaction occurs [6].

During the past few years, it has become evident that apoptosis is not a 'passive' process in inflammatory terms, but is rather an active event in which apoptotic cells become phagocytosed, thereby inducing inflammatory responses. Thus, clearance of apoptotic cells can result in subsequent efficacious anti-inflammatory and immunosuppressive effects [7]. For example, the apoptosis of neutrophils infiltrating damaged tissue may contribute to the termination of inflammation or progression of wound healing. In the perturbed epidermis, particularly after ultraviolet (UV) light irradiation, physical trauma or certain cutaneous autoimmune diseases, apoptotic cell residues are known as Civatte cells (colloid bodies or sunburn cells) [8]. Recent data indicate that the clearance of apoptotic cells can also result in the generation of pro-inflammatory stimuli, which may ultimately lead to the amplification of chronic inflammation and also immune-mediated diseases [9].

During early stages of apoptosis in keratinocytes, the cell nuclei become convoluted and chromatin aggregates on the nuclear membrane, and cells shrink and separate from the contiguous cells (disaggregation). Subsequently, fragments of the nucleus and small apoptotic bodies become released from the cell surface ('apical blebbing'). Anatomically, apoptotic cells are composed of nuclear remnants, particles of organelles and the cytoplasm within a capsule of transglutaminase cross-linked proteins resembling differentiated involucrin in keratinocytes. Finally, the apoptotic cell residues may be ingested by professional phagocytes, such as macrophages or neutrophils [10,11].

Apoptosis differs from necrosis in that in necrosis single or very small groups of cells are affected. There is nuclear pyknosis, condensation of the cytoplasm and phagocytosis of the residual material without excitation of inflammation; resolution of the organized tissue without major structural change can occur. Nuclear pyknosis occurs in coagulative necrosis, but the change in apoptosis is caused by endonuclease splitting of the DNA, resulting in a 'ladder' pattern on separation in agarose gels, whereas necrotic cell DNA forms an amorphous smear [9].

In the skin, cell apoptosis of almost all resident or invading immune cells is induced during organ development, hypoxia, tissue injury, allergic reactions, exposure to toxins and drugs, after skin radiation with ions or UV light, and during autoimmune processes (e.g. pemphigus vulgaris). Thus, cell apoptosis can be regarded as a physiological defence mechanism against 'danger signals' threatening the skin, with the aim of clearance of the 'danger-induced' effects on tissue integrity. For example, distinct subsets of hapten-specific T cells are capable of inducing apoptosis in autologous keratinocytes. Moreover, nickel-specific $CD8^+$ and $CD4^+$ T-cell subsets can exert cytotoxic activity against keratinocytes. Finally, glucocorticoids and other immunosupressants, such as calcineurin inhibitors (tacrolimus, pimecrolimus), induce apoptotic pathways in several immune cells, thereby contributing to healing during inflammation or autoimmune diseases. Whether the induction of anti-apoptotic processes seen as a side effect during treatment with anti-inflammatory drugs is of importance for the observed amplification of infection by certain of these agents is currently unclear [10–14]. The mechanism of UV-light induced skin damage and exacerbation of lupus erythematosus has been a puzzle. Recent results demonstrate that sunlight triggers a colony stimulating factor (CSF-1)-dependent, macrophage-mediated destructive inflammation in the skin leading to cutaneous lupus erythema (LE) in LE-susceptible FAS-ligand mice but not LE-resistant mice [15]. Certain molecules have been identified in the last few years which regulate apoptosis in keratinocytes and skin immune cells. For example, Bid (BH3-interacting death domain protein) resists apoptosis and induces amplified immune responses after UVB exposure in Langerhans' cells and keratinocytes [16]. Matrix-metalloproteinases such as MMP21 are capable of inducing apoptosis in keratinocytes [17]. Thus, the skin contains an armada of proapoptotic as well as antiapoptotic instruments releasable in response to inflammatory stimuli, and which may endanger body integrity during infection or injury as well as during chronic inflammation and autoimmune diseases. Pemphigus foliaceus (PF) is an organ-specific autoimmune skin disease characterized by subcorneal epidermal cell detachment (acantholysis) and pathogenic autoantibodies against desmoglein 1. Apoptotic mechanisms in keratinocytes may be involved in PF, because proapoptotic factors such as caspases-3 and -6 as well as Bax are up-regulated, while antiapoptotic factors such as Bcl-x(L) are found to be down-regulated. Of note, caspase inhibitors such as Bok-D-fmk inhibit this effect. Thus, caspase activation and other apoptotic factors may contribute to apoptotic processes and therefore acantholytic blister formation in PF [18]. These mechanisms, however, may not be true for all subtypes of pemphigus [19].

Nucleotide-binding and oligomerization domain 2 (NOD2) belongs to the emerging NOD-like receptor (NLR) family, considered important in innate immunity. Mutations in NOD2 cause Blau syndrome, an inherited inflammation of eye, joints and skin. Mutations in a homologous region of another NLR member, NALP3, cause auto-inflammation, wherein IL-1β plays a critical role [20].

Other proteins, such as the cathelicidin LL-37, for example, may exert antiapoptotic effects on keratinocytes, thereby protecting the epidermal compartment during infection or inflammation [21].

References

1 Rathmell JC, Thompson CB. The central effectors of cell death in the immune system. *Annu Rev Immunol* 1999; **17**: 781–828.

2 Allen TD, Spence HM, Salyer KE. Reconstruction of external genitalia in bladder exstrophy. *RN* 1975; **38**: OR1-3, OR7-8, OR11.

3 Conus S, Simon HU. Cathepsins: key modulators of cell death and inflammatory responses. *Biochem Pharmacol* 2008; **76**: 1374–82.

4 Farley SM, Purdy DE, Ryabinina OP *et al*. Fas ligand-induced proinflammatory transcriptional responses in reconstructed human epidermis. Recruitment of the epidermal growth factor receptor and activation of MAP kinases. *J Biol Chem* 2008; **283**: 919–28.

5 Farley SM, Dotson AD, Purdy DE *et al*. Fas ligand elicits a caspase-independent proinflammatory response in human keratinocytes: implications for dermatitis. *J Invest Dermatol* 2006; **126**: 2438–51.

6 Krammer PH. CD95's deadly mission in the immune system. *Nature* 2000; **407**: 789–95.

7 Savill J, Fadok V. Corpse clearance defines the meaning of cell death. *Nature* 2000; **407**: 784–8.
8 Kulms D, Schwarz T. Molecular mechanisms involved in UV-induced apoptotic cell death. *Skin Pharmacol Appl Skin Physiol* 2002; **15**: 342–7.
9 Kerr JF, Winterford CM, Harmon BV. Apoptosis. Its significance in cancer and cancer therapy. *Cancer* 1994; **73**: 2013–26.
10 Caron E, Hall A. Identification of two distinct mechanisms of phagocytosis controlled by different Rho GTPases. *Science* 1998; **282**: 1717–21.
11 Hart SP, Dougherty GJ, Haslett C, Dransfield I. CD44 regulates phagocytosis of apoptotic neutrophil granulocytes, but not apoptotic lymphocytes, by human macrophages. *J Immunol* 1997; **159**: 919–25.
12 Herrmann M, Voll RE, Zoller OM *et al*. Impaired phagocytosis of apoptotic cell material by monocyte-derived macrophages from patients with systemic lupus erythematosus. *Arthritis Rheum* 1998; **41**: 1241–50.
13 Liu Y, Cousin JM, Hughes J *et al*. Glucocorticoids promote nonphlogistic phagocytosis of apoptotic leukocytes. *J Immunol* 1999; **162**: 3639–46.
14 Meagher LC, Cousin JM, Seckl JR, Haslett C. Opposing effects of glucocorticoids on the rate of apoptosis in neutrophilic and eosinophilic granulocytes. *J Immunol* 1996; **156**: 4422–8.
15 Menke J, Hsu MY, Byrne KT *et al*. Sunlight triggers cutaneous lupus through a CSF-1-dependent mechanism in MRL-Fas(lpr) mice. *J Immunol* 2008; **181**: 7367–79.
16 Pradhan S, Kim HK, Thrash CJ *et al*. A critical role for the proapoptotic protein bid in ultraviolet-induced immune suppression and cutaneous apoptosis. *J Immunol* 2008; **181**: 3077–88.
17 Skoog T, Elomaa O, Pasonen-Seppanen SM *et al*. Matrix metalloproteinase-21 expression is associated with keratinocyte differentiation and upregulated by retinoic acid in HaCaT cells. *J Invest Dermatol* 2009; **129**: 119–30.
18 Li N, Zhao M, Wang J *et al*. Involvement of the apoptotic mechanism in pemphigus foliaceus autoimmune injury of the skin. *J Immunol* 2009; **182**: 711–7.
19 Schmidt E, Gutberlet J, Siegmund D *et al*. Apoptosis is not required for acantholysis in pemphigus vulgaris. *Am J Physiol Cell Physiol* 2009; **296**: C162–72.
20 Rosenzweig HL, Martin TM, Planck SR *et al*. Activation of NOD2 *in vivo* induces IL-1beta production in the eye via caspase-1 but results in ocular inflammation independently of IL-1 signaling. *J Leukoc Biol* 2008; **84**: 529–36.
21 Chamorro CI, Weber G, Gronberg A *et al*. The human antimicrobial peptide LL-37 suppresses apoptosis in keratinocytes. *J Invest Dermatol* 2009; **129**: 937–44.

Major histocompatibility complex and inflammation

The genetic loci responsible for the rejection of non-self tissues are located in a region known as the major histocompatibility complex (MHC) on chromosome 6. The MHC genes encode for highly polymorphic cell surface structures termed MHC antigens or human leukocyte antigens (HLA). MHC antigens are critically involved in many immune processes and skin diseases such as genodermatoses, psoriasis, and various autoimmune diseases. Three classes of molecules (I–III) have been identified. The class I and II glycoproteins share a similar overall structure and are involved in antigen presentation. There are three main class I genes (HLA-A, HLA-B and HLA-C) and three main class II genes (HLA-DP, HLA-DQ and HLA-DR). The class III proteins, although encoded by genes residing in the same chromosomal region as those for the class I and II molecules, consist of components of the complement system and molecules that are involved in the processing of antigens, such as the proteasome-like genes and transporter genes [1–3].

Each class I MHC protein is expressed on the cell surface as a dimer composed of two non-covalently-linked polypeptide chains (heavy or α-chain associated with a non-MHC-encoded β_2-microglobulin). The peptide-binding capacity of the class I MHC is enormous because each individual carries six different HLA-A, HLA-B and HLA-C alleles, and each allelic gene product is capable of generating a variety of different peptides [2,3].

The class II MHC is highly polymorphic, with the polymorphic residues concentrated in the α_1 and β_1 domains, which are involved in peptide binding. Multimeric receptor forms are also possible for other molecules involved in cognate recognition (e.g. class I MHC, T-cell receptor), and probably increase the avidity of interaction of juxtaposed cells [1–3].

Class I MHC molecules bind cytoplasmic proteins (e.g. viral proteins from infected cells) that are degraded into peptides by a large cytoplasmic proteolytic complex derived from at least two genes in the HLA class II region [4]. Class II MHC molecules bind peptides derived from exogenous proteins that have been internalized in antigen-presenting cells in a coated pit into the endocytic pathway, where antigen degradation generates functional peptides. The resulting peptide–protein complex is then translocated to, and expressed on, the antigen-presenting cell surface [5].

Under normal circumstances, self-proteins are displayed, leading to a state of tolerant inactivity. However, deleterious intracellular events lead to the display of MHC class I molecules complexed with foreign peptides, fostering the activation of $CD8^+$ T cells and the generation of cytotoxic T cells. Similarly, extracellular exposure to foreign substances results in the cell-surface display of class II MHC molecules complexed with foreign peptides, leading to the activation of $CD4^+$ T cells, the induction of B cells through helper T-cell activity, or immunoglobulin production.

The $CD8^+$ class I pathway of T cells is associated with internal cellular events. Because virtually all nucleated cells express class I molecules, essentially all cells can act as antigen-presenting cells for $CD8^+$ T cells, providing an important protection against harmful intracellular processes such as inflammation, infection or tumour development. The $CD4^+$ class II pathway is responsive to external cellular events, but the relative restriction of constitutive class II expression and antigen-presenting capacity to B cells, macrophages, dendritic cells, venular endothelial cells and probably keratinocytes limits the possibilities and consequences of activating $CD4^+$ T cells.

Dysfunction or genetic alteration of MHC alleles has been found in various skin and immune diseases. MHC class I-restricted $CD8^+$ T cells play an important part in the pathophysiology of contact hypersensitivity (CHS). Class I-restricted $CD8^+$ T cells are sufficient for the induction of CHS, supporting the idea that MHC class II-restricted $CD4^+$ T cells down-regulate this inflammatory response. Moreover, $CD8^+$ T cells mediate the skin inflammation through their cytotoxic activity using either the perforin or the Fas–Fas ligand pathway. Thus, cytotoxic $CD8^+$ T cells directly contribute to delayed-type hypersensitivity reactions [6]. Inflammation-associated regulation of MHC function appears also to be crucial in microvascular endothelial cells (HDMEC). Thus, cytokines such as TNF-α or IFN-γ, but not IL-1α, increase MHC class I expression on HDMEC [7].

Skin diseases. MHC class II antigens have been implicated in the pathophysiology of lichen planus, graft-versus-host disease and

Behçet's disease. Histopathological analysis of the skin revealed marked hyperkeratosis of the epidermis and dramatic thickening of the granular layer, with slight infiltration of inflammatory cells in the dermis, in transgenic mice carrying MHC class I chain-related gene B (MICB) [8]. Moreover, the absence of MHC class II permitted the development of systemic autoimmune effects in a mouse model of acute graft-versus-host disease [9]. In general, variation among individuals in a cluster of genes encoding inflammation-related proteins, along with MHC genes, seems to be crucial for the development of MHC-associated diseases and their susceptibility to a variety of autoimmune disorders [10].

Modern anti-inflammatory therapeutic strategies appear to be effective in the treatment of MHC-associated inflammatory diseases. For example, recombinant human IL-11 therapy was associated with suppression of mucosal inflammation, and concomitant improvement of epithelial resistance and neurally mediated secretion, in a model of chronic HLA-B27 colitis; oral treatment of HLA-B27 rats with rhIL-11 reduced myeloperoxidase (MPO) activity in the colon and suppressed clinical signs of diarrhoea [11]. For detailed information on the role of MHC in the adaptive immune response see Chapter 13.

The expression of MHC Class II is differentially regulated in epithelial cells during bacterial infection [12], and varies markedly in different chronic inflammatory skin diseases, such as allergic or atopic dermatitis and psoriasis. Among different known psoriasis susceptibility loci (*PSORS*), *PSORS1* on chromosome 6 has the strongest association to this disease as of yet. Altered expression of some *PSORS1* candidate genes has been reported, but little is known about HLA-C expression in psoriasis. Although HLA-C is abundant in protein extracts from both eczema and psoriasis, a consistent and intriguing difference in the expression pattern can be found. In psoriasis, strong HLA-C immunoreactivity occurs in the basal cell layer, polarized towards the basement membrane, whereas HLA-C immunostaining is present mostly in suprabasal cells of eczema patients and in normal healthy skin. A similar pattern can be observed for HLA class Ia expression. The difference in the HLA-C expression patterns in psoriasis and eczema suggests different functional roles in the specific immune response in different chronic inflammatory skin diseases [13–15].

References

1 Baron S. *Medical Microbiology*, 4th edn. Texas: University of Texas Medical Branch at Galveston, 1996.

2 Janeway CA, Travers P, Walport M, Shlomchik M. *Immunobiology*, 5th edn. New York: Taylor & Francis Inc., 2001.

3 Lambrecht BN. Allergen uptake and presentation by dendritic cells. *Curr Opin Allergy Clin Immunol* 2001; **1**: 51–9.

4 Khare SD, Hansen J, Luthra HS, David CS. HLA-B27 heavy chains contribute to spontaneous inflammatory disease in B27/human beta2-microglobulin (beta2m) double transgenic mice with disrupted mouse beta2m. *J Clin Invest* 1996; **98**: 2746–55.

5 Khare SD, Luthra HS, David CS. Spontaneous inflammatory arthritis in HLA-B27 transgenic mice lacking beta 2-microglobulin: a model of human spondyloarthropathies. *J Exp Med* 1995; **182**: 1153–8.

6 Kehren J, Desvignes C, Krasteva M *et al.* Cytotoxicity is mandatory for CD8(+) T cell-mediated contact hypersensitivity. *J Exp Med* 1999; **189**: 779–86.

7 Swerlick RA, Garcia-Gonzalez E, Kubota Y *et al*. Studies of the modulation of MHC antigen and cell adhesion molecule expression on human dermal microvascular endothelial cells. *J Invest Dermatol* 1991; **97**: 190–6.

8 Nomura E, Sato M, Suemizu H *et al*. Hyperkeratosis and leukocytosis in transgenic mice carrying MHC class I chain-related gene B (MICB). *Tissue Antigens* 2003; **61**: 300–7.

9 Teshima T, Reddy P, Liu C *et al*. Impaired thymic negative selection causes autoimmune graft-versus-host disease. *Blood* 2003; **102**: 429–35.

10 Blum A, Miller H. The major histocompatibility complex and inflammation. *South Med J* 2000; **93**: 169–72.

11 Venkova K, Keith JC Jr, Greenwood-Van Meerveld B. Oral treatment with recombinant human interleukin-11 improves mucosal transport in the colon of human leukocyte antigen-B27 transgenic rats. *J Pharmacol Exp Ther* 2004; **308**: 206–13.

12 Han DC, Huang GT, Lin LM *et al*. Expression of MHC Class II, CD70, CD80, CD86 and pro-inflammatory cytokines is differentially regulated in oral epithelial cells following bacterial challenge. *Oral Microbiol Immunol* 2003; **18**: 350–8.

13 Carlen L, Sakuraba K, Stahle M, Sanchez F. HLA-C expression pattern is spatially different between psoriasis and eczema skin lesions. *J Invest Dermatol* 2007; **127**: 342–8.

14 Fan X, Yang S, Huang W *et al.* Fine mapping of the psoriasis susceptibility locus PSORS1 supports HLA-C as the susceptibility gene in the Han Chinese population. *PLoS Genet* 2008; **4**: e1000038.

15 Nair RP, Stuart PE, Nistor I *et al.* Sequence and haplotype analysis supports HLA-C as the psoriasis susceptibility 1 gene. *Am J Hum Genet* 2006; **78**: 827–51.

Cellular components of cutaneous inflammation

Epidermis

To avoid repetition, the function of cellular constituents belonging to the adaptive immune system, such as lymphocytes and dendritic antigen-presenting cells (Langerhans' cells, dermal dendritic cells) will not be discussed here, as they are described in depth in Chapter 13.

Keratinocytes

In the past, the keratinocyte was viewed as a passive 'brick' in the defensive wall surrounding the body. However, beside their role in producing cytokeratins and lipids, keratinocytes are capable of generating and releasing an armada of different inflammatory and immunomodulatory mediators. Upon stimulation during inflammation, keratinocytes actively secrete large amounts of cytokines, chemokines, peptides and growth factors, and express receptors for these mediators, as well as several co-stimulatory molecules (Table 12.2).

The formation of the epidermal barrier is one of the mainstays of keratinocyte function. The skin forms an effective barrier between the organism and the environment, preventing invasion of pathogens and defending against physical or chemical injuries, and regulates the loss of water, molecules and solutes. The physical barrier is mainly located in the stratum corneum and consists of protein-enriched cells (corneocytes with cornified envelope and cytoskeletal elements, as well as corneodesmosomes) and lipid-enriched intercellular spaces. The nucleated keratinocyte also contributes to the barrier through tight, gap and adherens junctions, as well as through desmosomes and cytoskeletal elements. During epidermal differentiation, lipids are synthesized in the keratinocytes and extruded into the extracellular space, where they form extracellular lipid-enriched layers. The cornified cell envelope, a tough protein–lipid polymer structure, resides below the cytoplasmic membrane on the exterior of the corneocytes. Ceramides A

Table 12.2 Some important human keratinocyte cytokines and pro-inflammatory mediators (a non-exhaustive list).

Agent	Abbreviation
Interleukins	
Interleukin-1α and β	IL-1α and β
Interleukin-3	IL-3
Interleukin-6	IL-6
Interleukin-8	IL-8
Interleukin-18	IL-18
Interleukin-23	IL-23
Interleukin-33	IL-33
Interferons	
Interferon-α	IFN-α
Interferon-β	IFN-β
Pro-inflammatory mediators	
Tumour necrosis factor-α	TNF-α
Macrophage migration inhibitory factor	MIF
Prostaglandin E_2*	PGE_2
Leukotriene B_4*	LTB_4
12-Hydroxyeicosatetraenoic acid	12-HETE
Epidermal proteases	Cathepsins
Serine protease	Trypsinogen
Lysozyme	—
Neuropeptides	SP, NKA
Chemokines †	
Monocyte chemotactic protein-1	MCP-1 (CCL2)
Cutaneous T-cell-attracting chemokine	CTACK (CCL-27)
Macrophage inflammatory protein-3	MIP3a (CCL20)
Stromal cell-derived factor-1	SDF1a (CXCL12)
Inducible protein-10	IP-10 (CXCL10)
Monokine induced by γ interferon	MIG (CXCL9)
Growth-regulated oncogene-α	GRO-α (CXCL1)
Regulated on activation normally T-cell expressed, secreted	RANTES (CCL5)
Anti-inflammatory mediators	
α-Melanocyte stimulating hormone	α-MSH
IL-1 receptor antagonist	IL-1RA
Interleukin-10	IL-10
Colony-stimulating factors	
Granulocyte–macrophage colony-stimulating factor	GM-CSF
Granulocyte colony-stimulating factor	G-CSF
Macrophage colony-stimulating factor	M-CSF
Growth regulators	
Transforming growth factor-α	TGF-α
Transforming growth factor-β	TGF-β
Platelet-derived growth factor	PDGF
Basic fibroblast growth factor	bFGF
Vascular endothelial growth factor	VEGF
Endothelin-1	ET-1

† Note that chemokines are now properly referred to by their CXC/CC etc. abbreviation rather than by names describing biological activity.

* Detection in skin *in vivo*, presumably from the epidermis.

and B are covalently bound to cornified envelope proteins and form the backbone for the subsequent addition of free ceramides, free fatty acids and cholesterol in the stratum corneum. Filaggrin is cross-linked to the cornified envelope and aggregates keratin filaments into macrofibrils. Formation and maintenance of barrier function is influenced by cytokines, 3′,5′-cyclic adenosine monophosphate and calcium. Changes in epidermal differentiation and lipid composition lead to a disturbed skin barrier, which allows the entry of environmental allergens, immunological reaction and inflammation in atopic dermatitis. A disturbed skin barrier has been implicated in many skin diseases such as contact dermatitis, ichthyosis, psoriasis and atopic dermatitis [1–3].

Lipid metabolism plays an essential role in the maintenance of epidermal homeostasis and skin inflammation. The keratinocyte is a very active producer of various lipids and a key regulatory pathway in this process is that of peroxisome proliferator-activated receptors (PPARs) and their ligands. Activation of PPARα, -β/δ, or -γ or the closely related liver X-receptors (LXRs), stimulates keratinocyte differentiation and induces an armada of transcription factors involved in inflammation and metabolic regulation of cells. This leads to stimulatory signals for lipid synthesis, lamellar body formation and secretion. Accordingly, the activity of proteases and enzymes required for the extracellular processing of lipids in the stratum corneum leads to the formation of lamellar membranes that mediate permeability barrier function. The stimulation of keratinocyte differentiation and permeability barrier formation also occurs during fetal development, resulting in accelerated epidermal development. PPAR and LXR activation regulates keratinocyte mediator release, regulation of adhesion molecules, and proliferation and apoptosis. With respect to inflammation, PPAR and LXR activation is anti-inflammatory as shown in animal studies of allergic and irritant contact dermatitis. Moreover, in both psoriatic epidermis and atopic dermatitis, the expression of both PPARα and PPARγ is decreased. PPARs suppress proliferation and induce differentiation of keratinocytes, growth arrest, apoptosis and terminal differentiation. Of note, clinical trials using gemfibrozil, a PPARα ligand, resulted in a significantly lower occurrence of melanoma as compared to controls. Thus, PPARs and LXRs may be targets for anti-inflammatory therapies for diseases such as psoriasis, atopic dermatitis and others [4–6].

Keratinocytes respond to both external stimuli and endogenous trigger factors. External stimuli include bacteria, fungi, house-dust mites, viruses, antigens, mechanical stress, UV light or temperature change. Moreover, endogenous inflammatory mediators such as cytokines, neuropeptides, proteases, eicosanoids, nitric oxygen or other free radicals may directly modulate keratinocyte function. Thus, cytokines and other factors derived from keratinocytes may play a crucial regulatory role in many physiological and pathophysiological conditions in the skin such as inflammation, immune defence and wound healing.

The response of keratinocytes to injury may be separated into two phases. In the first phase, pro-inflammatory mediators are released (e.g. IL-1 and TNF-α) that initiate immediate host defence, for example by induction of adhesion molecules on endothelium and inducing migration of Langerhans' cells to draining lymphatic tissue. In the second phase, keratinocytes induce cutaneous regeneration by activating fibroblasts and proliferation of endothelium in order to repair tissue damage and restore integrity to the skin.

One of the prototypic keratinocyte-derived cytokines is IL-1. In the skin, IL-1 is constitutively synthesized in basal, and also

suprabasal, keratinocytes, and is released upon various injurious stimuli. IL-1 release can be induced in an autocrine or paracrine fashion by IL-1 itself, or by other cytokines such as TNF-α or IL-6 [7]. Not only does IL-1 release lead to local endothelial activation with leukocyte recruitment, keratinocyte-derived IL-1 can stimulate the release of secondary cytokines such as granulocyte–macrophage colony-stimulating factor (GM-CSF), which serves as a crucial mediator for the activation and differentiation of Langerhans' cells, a key part of the adaptive immune response. Keratinocyte-derived cytokines such as TNF-α, IL-1 or IL-6 may enter the circulation and subsequently exert systemic effects such as fever and acute-phase protein production. Although resting keratinocytes do not constitutively synthesize TNF-α, this important cytokine can be induced by various stimuli. At low concentrations it may regulate keratinocyte proliferation and the maturation and migration of Langerhans' cells. During inflammation and wound repair, keratinocyte-derived TNF-α also participates in the modulation of T-cell activity and dendritic cell function [8]. Moreover, keratinocyte-derived cytokines such as TNF-α are involved in the regulation of dermal microvascular endothelial cells, via stimulation of the production of cytokines as well as chemokines, and up-regulation of cell adhesion molecule expression, such as E-selectin, ICAM-1 and vascular cell adhesion molecule (VCAM). Other growth factors generated by keratinocytes include transforming growth factors (TGF-α, TGF-β) and colony-stimulating growth factors (G-CSF, M-CSF, GM-CSF), which exert multiple functions in the skin.

Keratinocytes also release a range of chemokines such as CCL-8 (MCP-2), CCL-27 (CTACK), CCL-5 (RANTES), CXCL-1 (GRO-α, CCL-2 (MCP-1), CXCL-10 (IP-10), CCL-11 (eotaxin) and others, which regulate trafficking of lymphocytes, neutrophils, eosinophils, dendritic cells and mast cells. Thus, being able to initiate endothelial activation and then direct migration of inflammatory cells through the skin, keratinocytes are likely to actively participate in the regulation of many inflammatory skin diseases including psoriasis and atopic dermatitis. These pro-inflammatory effects, however, may be inhibited by regulatory molecules such as the suppressors of cytokine signalling (SOCS). SOCS1, SOCS2 and SOCS3 proteins are up-regulated in the epidermis of psoriasis and allergic contact dermatitis but not in atopic dermatitis patients [9]. They exert multiple anti-inflammatory effects on keratinocytes, such as down-regulation of HLA-DR, ICAM-1, IP-10 and MCP-1.

Growth factors, such as epidermal growth factor (EGF), also modulate keratinocyte function during inflammation and tissue repair. Recently, an autocrine loop of keratinocyte proliferation and migration was observed during wound healing, and found to be regulated by the receptor for EGF [10]. Increased TGF-β, basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) expression levels can be also observed in keratinocytes after injury and inflammatory stimuli, indicating that keratinocytes are autocrine and paracrine key regulators of growth factors during skin inflammation and remodelling.

In addition to these non-antigen-specific pathways, keratinocytes may also participate in antigen-specific immunological responses. For example, keratinocyte expression of co-stimulatory molecules such as CD80, an important signal for professional antigen-presenting cell and T-cell interactions, is up-regulated by allergens or irritants [11]. In addition, various inflammatory stimuli up-regulate the expression of MHC molecules such as MHC II or CD1d on keratinocytes, suggesting a potential role for keratinocytes in antigen presentation [12], though this remains controversial. Keratinocytes also provide a source of antigenic proteins to which chemical haptens can conjugate. Lymph node cells from hapten-sensitized mice were found to proliferate in the presence of a keratinocyte extract without hapten [13]. Keratinocyte-derived chemokines also have an essential role during the induction, regulating Langerhans' cell egress from epidermis, as well as the elicitation phase, of contact hypersensitivity [14].

UV radiation is an important factor that modulates keratinocyte function during inflammation. UV causes DNA damage and, via the activation of the transcription factor NF-κB, induces the production of cytokines, growth factors, proteases and matrix metalloproteinases, which regulate keratinocyte function. Keratinocyte- as well as mast cell-derived cytokines such as TNF-α have been demonstrated to be involved in UV-mediated cutaneous immune responses [15,16]. It was observed that UV failed to induce tolerance in mast cell-deficient mice, and that tolerance occurred if mast cells were triggered to degranulate after activation of the IgE receptor [13]. NF-κB target genes (IL-1, IL-6, TNF-α, VEGF) also have a role in sunburn reactions after UV [17]. Finally, UV also induces the production of suppressor factors, such as IL1-RA, IL-10, TGF-β and melanocyte-stimulating hormone (α-MSH), which exert an anti-inflammatory and immunosuppressive action. The secretion of these signals following UV usually occurs later, after the initiation of pro-inflammatory mediators, and may therefore reflect mechanisms for the down-regulation of inflammation and the prevention of chronic inflammation [18]. Up-regulation of adhesion molecules such as intercellular adhesion molecule 1 (ICAM-1) on the surface of keratinocytes may play an important role in the recruitment of monocytes and activated T cells into the epidermis during UVB-induced inflammation. Recent data suggests that UVB-induced reactive oxygen species (ROS) is involved in the translocation of NF-κB, which is responsible for expression of ICAM-1 and subsequent increased monocyte adhesion to human keratinocytes [19], probably alongside MAP kinases [20].

Various microbiological agents such as viruses, bacteria, fungi or house-dust mite antigens, via multiple mechanisms including proteases, proteins and glycoproteins, may also affect keratinocyte functions, ultimately resulting in an inflammatory response. For example, human papillomaviruses (HPV) are known to modulate the expression of signals in keratinocytes that regulate their proliferation, as well as the release of mediators of inflammation. HPV-16 down-regulates IFN-responsive genes and up-regulates NF-κB-responsive genes in keratinocytes, resulting in a modified immune response. Moreover, an HPV-16 protein was found to induce the secretion of chemokines such as IL-8, RANTES, macrophage inflammatory protein-1α (MIP-1α) and IFN-γ-inducible protein. IFN-inducible genes and STAT1 (an important interferon responsive transcription factor) appear to be crucial target genes for keratinocyte-targeting viruses [21]. Thus, keratinocytes may directly alter gene expression in response to pathogens, and thereby influence host resistance to infection and inflammation.

Bacterial infections of the skin are another example of the interaction of microbes with keratinocytes. Although keratinocytes express antibacterial molecules such as defensins, streptococci and staphylococci may infect the skin by using strategies to overcome keratinocyte defence mechanisms. For example, CD44 appears to have an important role as a receptor for the colonization of keratinocytes by group A streptococci. Thus, receptor-blocking strategies on keratinocytes (e.g. TLRs, CD44 or activation of anti-inflammatory systems such as PPARs) may prove to be novel tools for the treatment of cutaneous infections as well as inflammation [22]. In summary, keratinocytes, via the release of mediators and the expression of surface molecules, subserve multiple important functions in the skin during inflammation and infection, tissue repair and autoimmunity.

Cytokines and chemokines regulate the function keratinocytes, which are an abundant source, but also targets for, these inflammatory mediators. Pro- as well as anti-inflammatory molecules have been described, and are 'hot topics' with respect to the treatment of skin inflammation. They contribute to mediator release, and activation of critical signalling pathways involved in inflammation (e.g. NF-κB, MAP kinases), as well as regulation of epithelialization, migration and cell growth. In human skin explants, recent studies have demonstrated that the chemokine CXCR2 is expressed in wounded keratinocytes, and its expression correlates well with the modulation of the Th1/Th2 ratio in the inflammatory state during wound healing, and proliferation of keratinocytes [23]. Furthermore, keratinocytes generate 'homing factors' for T helper cells to recruit those to the site of inflammation [24].

A recently described illustration of the interaction between genetic and inflammatory mechanisms in the pathogenesis of genodermatoses is Kindler's syndrome [25]. This autosomal recessive disease is characterized by trauma-induced blistering, poikiloderma, skin atrophy, mucosal inflammation and varying degrees of photosensitivity. Kindler syndrome involves loss-of-function mutations in a newly recognized actin cytoskeleton-associated protein, defined as fermitin family homologue 1, encoded by the gene *FERMT1*. This protein mediates anchorage between the actin cytoskeleton and the extracellular matrix via focal adhesions, and thus the structural pathology differs from other forms of epidermolysis bullosa in which there is a disruption of the keratin intermediate filament–hemidesmosome network and the extracellular matrix. In the skin, fermitin family homologue 1 is mainly expressed in basal keratinocytes and binds to the cytoplasmic tails of β1- and β3-integrins, as well as to fermitin family homologue 2 and filamin-binding LIM protein 1. It also plays a crucial role in keratinocyte migration, proliferation and adhesion. Consequently, dysregulation of this gene leads to epidermal blistering and inflammation.

References

1 Bovenschen HJ, Seyger MM, Van de Kerkhof PC. Plaque psoriasis vs. atopic dermatitis and lichen planus: a comparison for lesional T-cell subsets, epidermal proliferation and differentiation. *Br J Dermatol* 2005; **153**: 72–8.

2 Jensen JM, Folster-Holst R, Baranowsky A *et al.* Impaired sphingomyelinase activity and epidermal differentiation in atopic dermatitis. *J Invest Dermatol* 2004; **122**: 1423–31.

3 Proksch E, Brandner JM, Jensen JM. The skin: an indispensable barrier. *Exp Dermatol* 2008; **17**: 1063–72.

4 Jiang YJ, Lu B, Kim P *et al.* PPAR and LXR activators regulate ABCA12 expression in human keratinocytes. *J Invest Dermatol* 2008; **128**: 104–9.

5 Schmuth M, Jiang YJ, Dubrac S *et al.* Thematic review series: skin lipids. Peroxisome proliferator-activated receptors and liver X receptors in epidermal biology. *J Lipid Res* 2008; **49**: 499–509.

6 Sertznig P, Seifert M, Tilgen W, Reichrath J. Peroxisome proliferator-activated receptors (PPARs) and the human skin: importance of PPARs in skin physiology and dermatologic diseases. *Am J Clin Dermatol* 2008; **9**: 15–31.

7 Luger TA, Stadler BM, Katz SI, Oppenheim JJ. Epidermal cell (keratinocyte)-derived thymocyte-activating factor (ETAF). *J Immunol* 1981; **127**: 1493–8.

8 Gottlieb AB. Infliximab for psoriasis. *J Am Acad Dermatol* 2003; **49**: S112–7.

9 Federici M, Giustizieri ML, Scarponi C *et al.* Impaired IFN-gamma-dependent inflammatory responses in human keratinocytes overexpressing the suppressor of cytokine signaling 1. *J Immunol* 2002; **169**: 434–42.

10 Tokumaru S, Higashiyama S, Endo T *et al.* Ectodomain shedding of epidermal growth factor receptor ligands is required for keratinocyte migration in cutaneous wound healing. *J Cell Biol* 2000; **151**: 209–20.

11 Wakem P, Burns RP Jr, Ramirez F *et al.* Allergens and irritants transcriptionally upregulate CD80 gene expression in human keratinocytes. *J Invest Dermatol* 2000; **114**: 1085–92.

12 Bonish B, Jullien D, Dutronc Y *et al.* Overexpression of CD1d by keratinocytes in psoriasis and CD1d-dependent IFN-gamma production by NK-T cells. *J Immunol* 2000; **165**: 4076–85.

13 Alard P, Kurimoto I, Niizeki H *et al.* Hapten-specific tolerance induced by acute, low-dose ultraviolet B radiation of skin requires mast cell degranulation. *Eur J Immunol* 2001; **31**: 1736–46.

14 Goebeler M, Trautmann A, Voss A *et al.* Differential and sequential expression of multiple chemokines during elicitation of allergic contact hypersensitivity. *Am J Pathol* 2001; **158**: 431–40.

15 Pfundt R, van Vlijmen-Willems I, Bergers M *et al.* In situ demonstration of phosphorylated c-jun and p38 MAP kinase in epidermal keratinocytes following ultraviolet B irradiation of human skin. *J Pathol* 2001; **193**: 248–55.

16 Schmitt DA, Walterscheid JP, Ullrich SE. Reversal of ultraviolet radiation-induced immune suppression by recombinant interleukin-12: suppression of cytokine production. *Immunology* 2000; **101**: 90–6.

17 Abeyama K, Eng W, Jester JV *et al.* A role for NF-kappaB-dependent gene transactivation in sunburn. *J Clin Invest* 2000; **105**: 1751–9.

18 Steinhoff M, Brzoska T, Luger TA. Keratinocytes in epidermal immune responses. *Curr Opin Allergy Clin Immunol* 2001; **1**: 469–76.

19 Park LJ, Ju SM, Song HY *et al.* The enhanced monocyte adhesiveness after UVB exposure requires ROS and NF-kappaB signaling in human keratinocyte. *J Biochem Mol Biol* 2006; **39**: 618–25.

20 Traore K, Sharma RB, Burek CL, Trush MA. Role of ROS and MAPK in TPA-induced ICAM-1 expression in the myeloid ML-1 cell line. *J Cell Biochem* 2007; **100**: 1010–21.

21 Chang YE, Laimins LA. Microarray analysis identifies interferon-inducible genes and Stat-1 as major transcriptional targets of human papillomavirus type 31. *J Virol* 2000; **74**: 4174–82.

22 Cywes C, Stamenkovic I, Wessels MR. CD44 as a receptor for colonization of the pharynx by group A Streptococcus. *J Clin Invest* 2000; **106**: 995–1002.

23 Zaja-Milatovic S, Richmond A. CXC chemokines and their receptors: a case for a significant biological role in cutaneous wound healing. *Histol Histopathol* 2008; **23**: 1399–407.

24 Soumelis V, Reche PA, Kanzler H *et al.* Human epithelial cells trigger dendritic cell mediated allergic inflammation by producing TSLP. *Nat Immunol* 2002; **3**: 673–80.

25 Lai-Cheong JE, Tanaka A, Hawche G *et al.* Kindler syndrome: a focal adhesion genodermatosis. *Br J Dermatol* 2009; **160**: 233–42.

Lymphocytes

T- and B-lymphocytes play a pivotal role in the pathogenesis and pathophysiology of many immune-mediated and inflammatory skin diseases, including psoriasis, atopic dermatitis, contact dermatitis and lichen planus. The role of T- and B-cells during

inflammation and the immune response is extensively discussed in Chapters 13 and 17, and these cells will not be discussed further here. However, the NK cell, a lymphocyte subset not discussed elsewhere, will be considered here.

Natural killer cells

Natural killer (NK) cells or large granular lymphocytes are bone marrow-derived lymphocytes that were initially characterized by their ability to lyse a variety of tumour targets and infected cells. Originally referred to as null cells, because they display neither T- nor B-cell-specific characteristics, NK cells typically express CD56, which is homologous to neural cell adhesion molecule, and sometimes express CD16, a low-affinity receptor for the Fc portion of IgG. CD16 is often associated with the CD3-ζ homodimer found in the T-cell receptor–CD3 complex. NK cells comprise approximately 10% of peripheral blood lymphocytes, and express neither B-cell-specific membrane immunoglobulins nor the T-cell receptor–CD3 complex. However, they may express some T-cell differentiation antigens, such as CD2 and CD8 (as an α/α homodimer), and myelomonocyte differentiation antigens, such as CD11b, CD11c, CD14 and CD15 [1].

It is well known that NK cells are able to secrete significant amounts of cytokines (IFN-γ and TNF-α) as well as chemokines. However, in contrast to T- and B-cell responses to antigen, which typically require a proliferation phase, the innate NK-cell response is immediate, implying that NK cells are involved in curbing pathogens during the initial hours and days of an infection. Indeed, there is strong evidence that NK cells contribute to the defence against intracellular bacteria and parasites and that they are crucial for controlling several types of viral infection. Moreover, their antitumour capacity is well established *in vitro* as well as *in vivo* [2–4].

Although NK cells do not possess the specialized gene rearrangement machinery that assembles T- and B-cell antigen receptor genes, they exhibit a clear capacity to discriminate between host and target cells. In the case of cellular targets, sensitivity to NK cells is correlated in many instances with decreased levels of MHC expression. NK cells are also able to reject MHC-incompatible bone marrow grafts. These observations led to the formulation of the 'missing self' hypothesis, by which NK cells ignore potential targets expressing normal levels of autologous class I molecules and attack cells that do not. However, 'missing self-recognition' is only one of several modes of NK cell–target cell discrimination [5–9].

NK cells preferentially kill target cells that lack surface expression of MHC class I molecules. This implies the existence of triggering receptors that recognize non-MHC ligands on these target cells. Unlike T lymphocytes that recognize MHC–peptide complexes using clonally distributed T-cell receptors generated by gene rearrangement, NK cells appear to use triggering receptors that do not require this genetic process. These triggering receptors can initiate NK-cell activation and target cell lysis, provided that NK cells are not turned off by activation of MHC class I-specific inhibitory receptors. These data suggest that triggering NK receptors involved in natural cytotoxicity recognize non-MHC ligands expressed not only by abnormal but also by normal cells [10,11].

NK receptors. NK cell activity is regulated by opposing signals from receptors that activate and inhibit their effector functions. Three distinct receptor families, Ly49, CD94/NKG2 and KIR (killer cell-inhibitory receptors), are involved in NK-cell recognition of polymorphic MHC class I molecules. Recent studies suggest these inhibitory NK-cell receptors are members of a larger superfamily containing immunoreceptor tyrosine-based inhibitory motif (ITIM), defined as the inhibitory receptor superfamily (IRS). Thus, NK cells are regulated by a balance of signalling via stimulatory receptors, specific for diverse ligands, and inhibitory receptors, specific for MHC class I molecules [12].

Three novel NK-specific triggering surface molecules that are involved in natural cytotoxicity have been identified (NKp46, NKp30 and NKp44). They represent the first members of a novel emerging group of receptors, collectively termed natural cytotoxicity receptors (NCRs) [13]. Interestingly, there exists coordinated surface expression of the three NCRs, their surface density varying in different individuals and also in the NK cells isolated from a given individual and altered expression or function of NCR or NKG2D is being explored as a possible cause of immunological disorders. Upon activation of NCRs, NK cells undergo blastogenesis, generate cytokines, enhance cytotoxicity and migrate. In contrast, inhibitory receptors prevent killing of normal cells and limit the production by NK cells of inflammatory cytokines, including TNF-α, IFN-γ and GM-CSF.

Other NK-cell receptors include the low-affinity receptor for IgG, CD16 (Fc RIII). The transmembrane-anchored CD16 isoform is expressed on the majority of (but not all) NK cells, as well as on activated monocytes and a subset of T cells. Upon CD16-mediated activation, NK cells secrete cytokines [14], mediate antibody-dependent cellular cytotoxicity and may undergo apoptosis as a consequence of Fas ligand-induced cell death [15]. CD2 may be a co-stimulatory receptor that augments primary activation of NK cells. NK specificity is derived from expression of a variety of MHC-specific receptors, such that each NK cell expresses several inhibitory and stimulatory receptors. Together these mechanisms ensure a self-tolerant and maximally discriminating NK-cell population.

Upon stimulation, NK cells produce high levels of certain cytokines and chemokines. They have a crucial role in the defence against a number of different infectious agents and tumours. The first evidence of this function came from observations that virus-induced interferons (IFN-α and -β) are potent inducers of NK-cell-mediated cytotoxicity, and that NK cells are important contributors to innate defence against viral infections. Subsequently, a wide range of other innate cytokines have been detected that mediate biological functions regulating the NK-cell responses of cytotoxicity, proliferation and IFN-γ or TNF-α production. For example, certain viral infections induce IL-12, which elicits IFN-γ production by NK cells, thereby inducing antiviral mechanisms. Thus, after microbial stimulation, NK cells have immediate effects resulting in host defence, especially with regard to viruses. In addition, chemokines such as MIP-1α are capable of stimulating migration of NK cells, probably via binding of the CCR5 chemokine receptor. Other chemokines that activate NK cells are CCL-4 (MIP-1β), CCL-2, CCL-8, CCL-7 (MCP-1, -2, -3) and CCL-5 (RANTES). In addition, numerous cytokines have been found to modulate

NK-cell function, including IFN-α and -β, which induce cytotoxic activity, stimulate proliferation and inhibit IL-12 production [13,16].

Unlike T and B cells, NK cells develop normally in scid mice or mice with disrupted rearrangement genes, indicating that gene rearrangement is not required for their differentiation or function. NK cells are clearly instrumental in innate immune responses, in particular providing for the early production of IFN-γ and possibly other cytokines necessary to control certain bacterial, parasitic and viral infections. The factors responsible for activation of NK cells during infection have remained elusive, but probably involve soluble factors such as IFN-α and -β, cytokines (TNF-α, IL-12, IL-15) and chemokines, as well as the presence of certain membrane-bound molecules on surrounding tissues. Although positive stimuli are required to activate NK-cell migration and effector function, the process is tightly regulated by inhibitory receptors and cytokines that limit and potentially terminate the response [17–19].

Signalling lymphocytic activating molecule (SLAM) family receptors and SLAM-associated protein (SAP)-related adapters play several important roles in the immune system. Natural killer (NK) cells express at least three members of the SLAM family. They are 2B4, NK, T- and B-cell antigen (NTB-A), and CD2-like receptor-activating cytotoxic cells (CRACC), which recognize their respective ligands CD48, NTB-A, and CRACC on target cells and possibly on other NK cells. In mature human NK cells, SLAM family receptors appear to have activating functions. In mature mouse NK cells, however, the only available information is for 2B4, which reportedly has the capacity to either stimulate or inhibit NK cell activation. The ability of SLAM family receptors to regulate NK cell functions seems to be largely dependent on their capacity to associate, by way of their cytoplasmic domain, with members of the SAP family of adapters, including SAP, Ewing's sarcoma-activated transcript-2 (EAT-2), and EAT-2-related transducer (ERT). By binding to SAP, SLAM family receptors are coupled to the Src kinase FynT, thereby evoking protein tyrosine phosphorylation signals. In human NK cells, SAP is likely to be crucial for the activating function of 2B4 and NTB-A, but not of CRACC, and SAP is also crucial for the activating function of 2B4 in mouse NK cells. Thus, SAP proteins and SLAM receptors have important functions in NK cell biology [20]. Mutations that affect the adaptor molecule SAP underlie the primary immunodeficiency disease X-linked lymphoproliferative syndrome. SAP is required for mediating signals from members of the SLAM family of immunomodulatory receptors. Recent data have highlighted a role for SAP in the development of innate-like T-cell lineages, including natural killer T cells, and in the regulation of the interactions between B cells and T cells that are required for germinal-centre formation and long-term humoral immunity. These data have revealed that SLAM family members and SAP have crucial roles in regulating lymphocyte interactions and adhesion, which are required for the normal development, homeostasis and function of the immune system [21].

In the skin, recent investigations have revealed that NK cells are involved in the pathophysiology of atopic dermatitis [22], contact dermatitis [23], sarcoidosis [24], transplant rejection [25] and infection [26].

Thus, NK cells serve as sentinels in the immune system, which is constantly assailed by pathogens as well as antigens, and where the achievement of a balance is crucial to permit elimination of pathogens but avoid autoimmunity. The potential for self-aggression is dramatically illustrated by the phenotype of mice with disrupted cytotoxic T-lymphocyte antigen 4 (CTLA-4) genes. In these animals, CD28 stimulation via CD80 or CD86 in the absence of negative regulation by CTLA4 [27,28] leads to a catastrophic T-cell lymphoproliferative disease that results in death. Receptors that possess the consensus ITIM (CD22, LAIR-1, gp49, LIR1, gp91/PIR, ILT1/2, ILT3) sequence seem to be crucial in this context [13,17,27,28].

References

1 Trinchieri G. Biology of natural killer cells. *Adv Immunol* 1989; **47**: 187–376.
2 Biron CA, Nguyen KB, Pien GC *et al*. Natural killer cells in antiviral defense: function and regulation by innate cytokines. *Annu Rev Immunol* 1999; **17**: 189–220.
3 Scharton-Kersten TM, Sher A. Role of natural killer cells in innate resistance to protozoan infections. *Curr Opin Immunol* 1997; **9**: 44–51.
4 Spits H, Lanier LL, Phillips JH. Development of human T and natural killer cells. *Blood* 1995; **85**: 2654–70.
5 Garrido F, Ruiz-Cabello F, Cabrera T *et al.* Implications for immunosurveillance of altered HLA class I phenotypes in human tumours. *Immunol Today* 1997; **18**: 89–95.
6 Liao NS, Bix M, Zijlstra M *et al*. MHC class I deficiency: susceptibility to natural killer (NK) cells and impaired NK activity. *Science* 1991; **253**: 199–202.
7 Moretta A, Bottino C, Vitale M *et al.* Activating receptors and coreceptors involved in human natural killer cell-mediated cytolysis. *Annu Rev Immunol* 2001; **19**: 197–223.
8 Raulet DH, Vance RE, McMahon CW. Regulation of the natural killer cell receptor repertoire. *Annu Rev Immunol* 2001; **19**: 291–330.
9 Tortorella D, Gewurz BE, Furman MH *et al*. Viral subversion of the immune system. *Annu Rev Immunol* 2000; **18**: 861–926.
10 Moretta A, Biassoni R, Bottino C *et al.* Major histocompatibility complex class I-specific receptors on human natural killer and T lymphocytes. *Immunol Rev* 1997; **155**: 105–17.
11 Moretta L, Ciccone E, Moretta A *et al*. Allorecognition by NK cells: nonself or no self? *Immunol Today* 1992; **13**: 300–6.
12 Blery M, Delon J, Trautmann A *et al.* Reconstituted killer cell inhibitory receptors for major histocompatibility complex class I molecules control mast cell activation induced via immunoreceptor tyrosine-based activation motifs. *J Biol Chem* 1997; **272**: 8989–96.
13 Lanier LL. NK cell receptors. *Annu Rev Immunol* 1998; **16**: 359–93.
14 Colonna M, Samaridis J. Cloning of immunoglobulin-superfamily members associated with HLA-C and HLA-B recognition by human natural killer cells. *Science* 1995; **268**: 405–8.
15 Wagtmann N, Biassoni R, Cantoni C *et al.* Molecular clones of the p58 NK cell receptor reveal immunoglobulin-related molecules with diversity in both the extra- and intracellular domains. *Immunity* 1995; **2**: 439–49.
16 Natarajan K, Dimasi N, Wang J *et al*. Structure and function of natural killer cell receptors: multiple molecular solutions to self, nonself discrimination. *Annu Rev Immunol* 2002; **20**: 853–85.
17 Biron CA. Activation and function of natural killer cell responses during viral infections. *Curr Opin Immunol* 1997; **9**: 24–34.
18 Moore JP, Trkola A, Dragic T. Co-receptors for HIV-1 entry. *Curr Opin Immunol* 1997; **9**: 551–62.
19 Scott P, Trinchieri G. The role of natural killer cells in host–parasite interactions. *Curr Opin Immunol* 1995; **7**: 34–40.
20 Veillette A. NK cell regulation by SLAM family receptors and SAP-related adapters. *Immunol Rev* 2006; **214**: 22–34.
21 Schwartzberg PL, Mueller KL, Qi H, Cannons JL. SLAM receptors and SAP influence lymphocyte interactions, development and function. *Nat Rev Immunol* 2009; **9**: 39–46.
22 De Benedetto A, Agnihothri R, McGirt LY *et al.* Atopic dermatitis: a disease caused by innate immune defects? *J Invest Dermatol* 2009; **129**: 14–30.

23 Gober MD, Gaspari AA. Allergic contact dermatitis. *Curr Dir Autoimmun* 2008; **10**: 1–26.
24 Noor A, Knox KS. Immunopathogenesis of sarcoidosis. *Clin Dermatol* 2007; **25**: 250–8.
25 Binet I, Wood KJ. *In vivo* models of inflammation: immune rejection and skin transplantation *in vivo*. *Methods Mol Biol* 2003; **225**: 239–48.
26 Smith SA, Kotwal GJ. Immune response to poxvirus infections in various animals. *Crit Rev Microbiol* 2002; **28**: 149–85.
27 Tivol EA, Borriello F, Schweitzer AN *et al*. Loss of CTLA-4 leads to massive lymphoproliferation and fatal multiorgan tissue destruction, revealing a critical negative regulatory role of CTLA-4. *Immunity* 1995; **3**: 541–7.
28 Waterhouse P, Penninger JM, Timms E *et al*. Lymphoproliferative disorders with early lethality in mice deficient in Ctla-4. *Science* 1995; **270**: 985–8.

Polymorphonuclear granulocytes

The polymorphonuclear granulocytes, basophils, eosinophils and neutrophils, are the mobile attack forces of the human body defence system to infection and injury as well as being involved in allergy. All cells arise from haematopoietic precursors, undergo maturation within the bone marrow and are released into the blood as mature leukocytes. Eosinophils and basophils are thought to arise from a common mononuclear stem cell, which is stimulated to divide by the cytokines IL-3 and GM-CSF acting in concert with stromal factors. While the production of these cells is limited under normal conditions, in allergy, increased levels of GM-CSF and IL-5 result in their increased production. Both eosinophils and basophils are primarily tissue cells with a very limited lifespan in the blood. For eosinophils, the lifespan in the blood is approximately 24 h and during injury the tissue:blood ratio is about 100:1. In contrast, neutrophils are constitutively generated by the bone marrow in large numbers. Because of the large number produced and the relatively short lifespan (less than 24 h), more than half of the work done by the bone marrow is dedicated to the production of neutrophils. In inflammation, increased levels of inflammatory cytokines stimulate enhanced neutrophil production. IL-3, IL-6, GM-CSF and TNF-α are the cytokines that are most likely to be involved.

Basophils

Although representing less than 1% of the circulating leukocytes, basophils can be purified from the blood and have been studied extensively *in vitro*. Like mast cells, basophils stain metachromatically with aniline dyes but can be distinguished from mast cells by their bilobed nucleus.

Structurally and functionally, basophils have a lot in common with mast cells. Perhaps the most important similarity is the presence of FcεRI, the high-affinity receptor for IgE, on their surface. Basophils derived from allergic patients contain up to 500 000 IgE receptors per cell [1]. However, they can be activated by cross-linkage of only approximately 1% of this number [2], making them exquisitely sensitive to allergen stimulation. It has been suggested that IgE on basophils may be in one of two forms, IgE^+ or IgE^- cells, with the former form being activated by IL-3 and histamine-releasing factors [3,4]. Furthermore, like skin mast cells, basophils are activated by the complement fraction, C5a. Other receptors on basophils are for IL-3, IL-4 and GM-CSF, which prolong their survival, and a histamine H_2 receptor, which down-regulates their function. The ease with which basophils can be obtained from patients has led to their widespread use *in vitro* in research and diagnosis of allergic disease (e.g. to detect circulating histamine-releasing autoantibodies in chronic urticaria [5]).

Basophils contain about 1 pg/cell of histamine, which, as in mast cells, is stored in modified lysosomal granules in combination with proteoglycans, predominantly chondroitin sulphate in the case of the basophil. Basophils contain very small amounts of tryptase, but no chymase. On stimulation, basophils generate relatively large amounts of the leukotrienes (LT) LTC_4, but not LTB_4 or the prostaglandin (PG) PGD_2 [6]. Another important function of the basophil is the generation of IL-4 and IL-13, which are critical for switching the B lymphocyte to IgE production [7,8].

In allergic diseases, basophils migrate from the bone marrow, enter the circulation as mature cells and infiltrate tissues in response to inflammatory stimuli. Knowledge of their role within the tissues is largely circumstantial. One reason is that basophils infiltrating an area of active allergic disease are likely to undergo degranulation quite rapidly and therefore be difficult to detect. Another is that until recently it has been difficult to distinguish tissue basophils from mast cells. However, monoclonal antibodies to a basophil granule protein have been described [9,10], which revolutionized basophil research; for example, evidence for basophil recruitment during late-phase allergic response is now unequivocal [11].

Eosinophils

The idea of an association between eosinophils and allergic disease, particularly asthma, has long history. Until the 1980s, it was thought that eosinophils might be anti-inflammatory. However, with the realization that eosinophil granule proteins are highly toxic, this view changed to one of eosinophils being considered as pro-inflammatory cells. Indeed, many of the features of asthma and related allergic diseases were considered to be mediated by eosinophil products. However, recent studies with anti-IL-5 and IL-12, which ablated eosinophils but failed to relieve asthma [12,13], have thrown doubt on the pivotal role ascribed to eosinophils in allergic diseases.

Coming from a common precursor, eosinophils and basophils are closely related. Eosinophils, like basophils, are approximately 8 μm in diameter, have a bilobed nucleus and use the blood merely as a transport system to reach the tissues. The eosinophil cytoplasm contains two types of granule, the most characteristic of which is the core-containing specific granule, which contains the basic proteins. Such granules avidly take up acidic dyes (e.g. eosin), giving eosinophils their characteristic microscopic appearance. The other granule is the so-called 'primary granule', which lacks a core and is of variable size. Also present in the cytoplasm are a number of lipid bodies, thought to be a store of arachidonic acid for eicosanoid synthesis.

The eosinophil membrane is particularly rich in receptors for adhesion proteins, chemokines and cytokines. For example, the coordinated action of IL-5, CCR3 binding chemokines and the adhesion molecules P-selectin and VCAM-1, acting in concert, cause selective recruitment of eosinophils into allergic tissue [14]. Once in the tissues, GM-CSF, IL-5 and eotaxin serve to both prime eosinophils for chemotactic and degranulatory responses and adhesion and cytotoxicity, and to prolong survival. Interestingly, eosinophils produce large quantities of GM-CSF and IL-5, so

ensuring their own survival [15]. Eosinophils also possess immunoglobulin receptors for IgA, IgG and IgE, and therefore have wide interactions with the immune system.

The major proteins of the eosinophil granule are major basic protein (MBP), eosinophil cationic protein (ECP), eosinophil peroxidase (EPO) and eosinophil-derived neurotoxin (EDN). To explain their presence, it must be remembered that the allergic response was originally developed as an immune defence system against helminth parasite infestation. All the above proteins are highly toxic to helminths. As they are also potentially toxic to mammalian cells, they may cause tissue damage in allergic responses. In addition, the peroxidase actions of EPO may lead to the generation of toxic oxygenated free radicals.

Eosinophils are probably the major producers of LTC_4 in allergic inflammation. Although this has profound implications for asthma, the importance in allergic responses in the skin is less clear. However, the beneficial effects of leukotriene receptor antagonists in atopic dermatitis [16] and urticaria [17] suggest an involvement.

In peripheral blood and non-inflamed tissue, eosinophils are in a resting state to prevent unwanted tissue damage from eosinophil-derived mediators. Thus, basophils are important regulators of immune cells such as eosinophils [18,19], and are critically involved in anaphylaxis [20]. In order to become activated, eosinophils must first be primed by exposure to the cytokines IL-5, GM-CSF and IL-3, or the lipid products platelet-activating factor (PAF) and LTB_4. As the majority of these substances are also chemoattractants, the end result is large numbers of degranulating eosinophils and heavy granule protein deposits at sites of allergic inflammation. Such a strategy would be ideal if the target was the surface of a large helminth parasite. However, in allergic skin disease, the stimulus is allergen and not a parasite. Even so, large deposits of extracellular eosinophil granule proteins are found in both urticaria [21] and atopic dermatitis [22,23], with raised MBP levels being found in the circulation [24].

Neutrophils

Neutrophilic polymorphonuclear leukocytes (or neutrophils) are approximately 7 μm in diameter and are easily recognized in conventional cytological preparations by their pinkish cytoplasm and distinctive polymorphic nuclei. When neutrophils are viewed under the electron microscope, a number of heterogeneous granules are obvious. The larger of these, the so-called primary or azurophilic granules, are peroxidase-positive, whereas the smaller ones, the so-called secondary or specific granules, are peroxidase-negative. Other subcellular structures, such as Golgi apparatuses, are scarce.

Neutrophils are the most numerous of the blood leukocytes and represent the first line of defence of the immune system against infection and tissue injury. As a consequence, it is necessary for them to be able to reach an inflammatory site very rapidly. Once released from the bone marrow, the majority of neutrophils are 'stored' intravascularly by the process of margination. It has been calculated for a 70-kg male that the number of marginated neutrophils is approximately 3×10^{10} [25]. The expression of a high density of adhesion proteins on their cell surface allows large numbers of neutrophils to move rapidly from their marginated sites into inflamed tissues. Indeed, evidence of their accumulation may be seen within minutes of a tissue stimulus. Several adhesion proteins have been identified on the neutrophil, the most important being the integrin LFA-1 (CD11a/CD18), which is the ligand for ICAM-1 [26]. In order to move rapidly to an inflammatory site once in the extravascular compartment, neutrophils must also express high levels of receptors for a wide range of chemotactic agents, such as IL-8 and LTB_4 (Fig. 12.2). Neurotrophins are also capable of modulating neutrophil function [27].

Like the other granulocytes, neutrophil mediators may either be preformed and stored in granules or be synthesized *de novo* on cell activation. The preformed mediators are mainly enzymes that facilitate the primary function of the neutrophils—to phagocytose and digest bacteria and other foreign particles. Neutrophil lysosomal granules contain more than 20 enzymes, including proteinases, elastase, gelatinase, collagenase, lysozyme, cathepsin G and defensins [28]. These enzymes may act either intracellularly to digest ingested bacteria or be released into the extracellular environment during inflammation. A further enzyme, myeloperoxidase, facilitates the bactericidal respiratory burst, which is characteristic of neutrophil activation [29]. In this reaction, oxygen radicals, hydrogen peroxide (H_2O_2) and superoxide (O_2^-) generated by the peroxidase converted into the even more toxic hypochloric acid (HOCl) and hydroxyl ($OH^\bullet$) radicals.

Evidence of the capacity of neutrophils to cause tissue damage is, for example, the tissue degradation around an implanted foreign body, such as a splinter, in order to facilitate its rejection as part of the healing process. Pus is an extreme example of neutrophil activity resulting from severe degradation of tissue and of dead leukocytes. However, the potential for neutrophils to cause overt tissue damage is limited by the presence of antiproteinases, such as α_2-antiproteinase, α_2-macroglobulin and antielastins, which penetrate the tissues from plasma during inflammation. Therefore, it is unlikely that neutrophils cause overt tissue damage in the presence of normal levels of antiproteinases. However, in antiproteinase deficiency, as has been suggested is the case in emphysema, the potential for neutrophil-induced tissue damage is enhanced [28]. Neutrophils also play an important role in *Staphylococcus aureus* infections and the onset of methicillin-resistant *S. aureus* infection [30,31].

The primary role of the newly generated mediators appears to be directed to the recruitment of more neutrophils. In the short term, this is facilitated by the synthesis and release of large quantities of LTB_4, a potent neutrophil attractant. *In vitro*, neutrophils certainly have the capacity to synthesize the cytokines IL-1β, TNF-α and IL-8, which would serve to recruit and activate further neutrophils, and IL-6, IL-12 and GM-CSF, which stimulate haematopoiesis of neutrophil precursors. However, bearing in mind that the peak production time for cytokines is often 12–24 h after cell stimulation, the clinical significance of their production in a cell with a tissue lifespan often less than 6 h is questionable.

The potential role(s) of neutrophils in inflammatory diseases is even less clear than that of basophils and eosinophils. In many situations when the neutrophils are present microscopically, it is difficult to evaluate whether their presence is a cause or consequence of the condition. Moreover, there is evidence that damage to the blood vessel wall in cutaneous leukocytoclastic vasculitis is

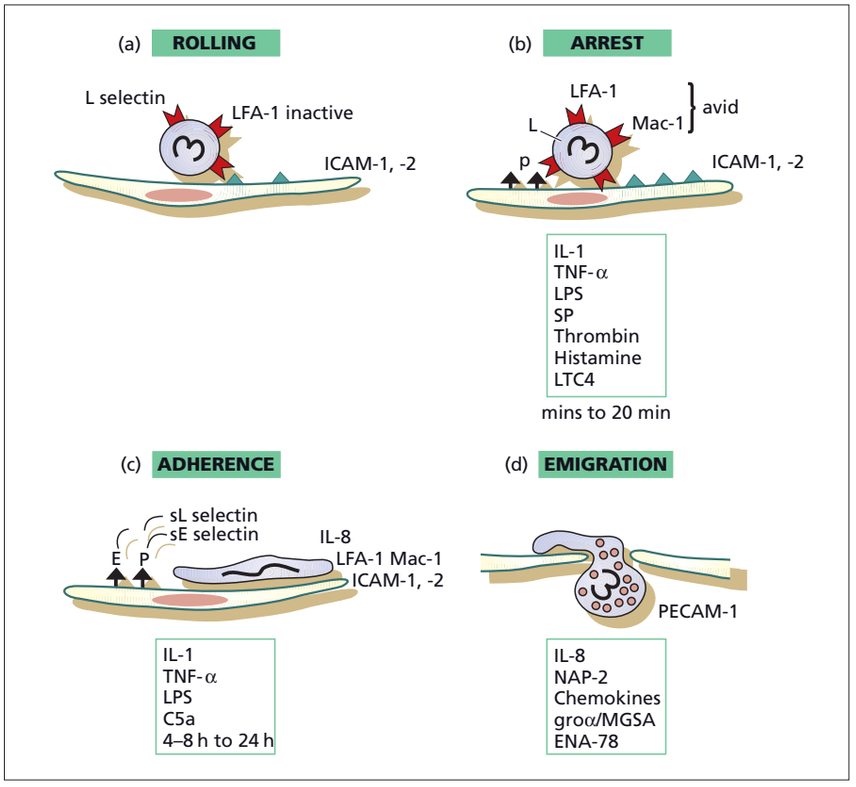


Fig. 12.2 Neutrophil emigration. (a) Rolling: cells roll over the endothelium by brief non-adherent contacts via the selectins, particularly L-selectin. The integrins are non-binding. (b) Arrest: on contact with activated endothelium, selectin binding briefly increases, integrins become avid and intercellular adhesion molecule 1 (ICAM-1) increases on the endothelial surface. (Monocytes and eosinophils also bind via α4β1 to vascular cell adhesion molecule 1 (VCAM-1).) (c) Adherence: the neutrophil flattens on the endothelium, affinity increases and motility response to chemokines is initiated. (d) Emigration: neutrophil leaves vessel through interendothelial cell junction, regulated by integrins, platelet/endothelium cell adhesion molecule 1 (PECAM-1) and chemokines.

caused by enzymes from activated neutrophils [32]. It has also been suggested that neutrophil elastase is involved in the dermal–epidermal cleavage observed in bullous pemphigoid [33].

The L-selectin molecule is localized to neutrophil microvilli and is cleaved or 'shed' during neutrophil activation, possibly permitting neutrophils to migrate from the intravascular lumen into sites of inflammation. After activation, P-selectin facilitates and supports neutrophil degranulation, superoxide (O_2^{2-}) production, and polarization in response to PAF and bacterial formylated peptides, such as formyl-methionyl-leucyl-phenylalanine (fMLP) [34]. In response to chemoattractant, cross-linking of L-selectin on neutrophils primes cells for increased O_2^{2-} production and calcium influx, and stimulates adhesion. Interaction of neutrophils with endothelial cells also results in increased mRNA levels for TNF-α and IL-8.

Many chemokines, including IL-8 and other chemoattractants such as formyl peptides, complement C5a, LTB_4 and PAF, cause rapid neutrophil adhesion, thereby supporting their emigration from the vasculature [35]. In contrast, the role of various mediators and chemokines in activation of the process of rolling of neutrophils in inflamed venules is still unclear. In certain *in vitro* systems, neutrophil arrest from rolling can be attributed to a single chemoattractant. For example, human umbilical vein endothelial cells (HUVEC) treated with histamine or thrombin support P-selectin-dependent neutrophil rolling and PAF-dependent activation [36]. However, in most inflammatory models *in vivo*, PAF synthesis or receptor antagonists have little or no effect.

Inflammatory or bacterial substances in sufficient amounts may depress the activities of neutrophils, as observed in patients with extensive leg ulcers, for example. Acquired defects in neutrophil chemotaxis are also observed in diabetes mellitus, which may be corrected *in vitro* by the addition of potassium, glucose and insulin. Thus, reduced random movement and response to chemotactic substances may be induced in previously normal neutrophils by severe bacterial infection, without obvious granule changes. This is reversible, because the reduced responsiveness of neutrophils returns to normal during effective treatment. In such cases, it is necessary to differentiate diminished activity induced in mature cells from the normal, lesser activity of immature cells mobilized as a result of the infection.

Abnormalities in neutrophils can have profound effects on resistance to disease. Several defects in enzyme activity have been observed. A deficiency in the H_2O_2–myeloperoxidase–halide system impairs the bactericidal activity of leukocytes. A very good example is chronic granulomatous disease, characterized by recurrent granulomas of skin and lymph nodes, which is associated with defective ability of neutrophils to kill bacteria [37]. An impairment in nicotinamide adenine dinucleotide (NADH) oxidase results in a failure to form H_2O_2 [38], which is critical for effective bactericidal activity. Moreover, deficiency of glucose-6-phosphate dehydrogenase (G6PD) results in the inability to kill catalase-active bacteria.

Several diseases have been revealed to be associated with defects in neutrophil function. In leukocyte adhesion deficiency-I (LAD-I),

patients lack CD18 and therefore all β2 integrins; their neutrophils can neither tightly adhere to endothelium nor exit from the circulation in response to infection. LAD-I patients have recurrent skin and mucosal infections, with most patients dying before the age of 10 years [39]. However, qualitative activation rather than quantitative expression of β2 integrins seems to be critical for stimulated neutrophil adhesion [40,41]. Another class of patient has defective carbohydrate fucosylation and lack of expression of sialyl Lewis X (sLex) ligands [42]. These 'LAD-II' patients have decreased neutrophil motility *in vitro*, neutrophilia and recurrent bacterial infections. Interestingly, classic drugs such as colchicine have been shown to decrease E-selectin density on endothelial cells and to down-modulate L-selectin expression on neutrophils [43]. Methotrexate inhibits neutrophil adhesion to connective tissues [40]. Corticosteroids lower adhesion molecule expression on both endothelium [44] and neutrophils [45]. Salicylates also inhibit neutrophil adhesion, probably by blocking activation of CD11b/CD18 [46].

Chédiak–Higashi disease is a rare autosomal recessive disease affecting neutrophils and all other lysosomal granule-containing cells in the body. The disease is secondary to mutations in *Lyst*, a gene encoding a cytoplasmic protein involved in lysosomal trafficking [47,48]. The neutrophils contain giant granules resulting from specific and azurophilic granule fusion. Patients have recurrent bacterial infections, neurological disease, partial albinism, platelet dysfunction and early death [39].

Another inherited granule disorder characterized by recurrent bacterial infection is specific granule deficiency, marked by the absence of neutrophil-specific granules and defensins. The disorder is probably secondary to the deficiency of transcription factor CCAAT/enhancer binding protein E, which has a critical role in normal myeloid cell development. Recently, a mutation in the gene encoding this protein has been characterized, and a knockout mouse for the gene has been engineered, showing impaired nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity [49], phagocytosis, intracellular killing and migration [50–52].

References

1 Conroy MC, Adkinson NF Jr, Lichtenstein LM. Measurement of IgE on human basophils: relation to serum IgE and anti-IgE-induced histamine release. *J Immunol* 1977; **118**: 1317–21.

2 MacGlashan D Jr, Lichtenstein LM. Studies of antigen binding on human basophils. I. Antigen binding and functional consequences. *J Immunol* 1983; **130**: 2330–6.

3 MacDonald SM. Human recombinant histamine-releasing factor. *Int Arch Allergy Immunol* 1997; **113**: 187–9.

4 Okayama Y, Begishvili TB, Church MK. Comparison of mechanisms of IL-3 induced histamine release and IL-3 priming effect on human basophils. *Clin Exp Allergy* 1993; **23**: 901–10.

5 Grattan CE, Francis DM, Hide M, Greaves MW. Detection of circulating histamine releasing autoantibodies with functional properties of anti-IgE in chronic urticaria. *Clin Exp Allergy* 1991; **21**: 695–704.

6 Warner JA, Freeland HS, MacGlashan DW *et al*. Purified human basophils do not generate LTB4. *Biochem Pharmacol* 1987; **36**: 3195–9.

7 Brunner T, Heusser CH, Dahinden CA. Human peripheral blood basophils primed by interleukin 3 (IL-3) produce IL-4 in response to immunoglobulin E receptor stimulation. *J Exp Med* 1993; **177**: 605–11.

8 Li H, Sim TC, Alam R. IL-13 released by and localized in human basophils. *J Immunol* 1996; **156**: 4833–8.

9 Kepley CL, Craig SS, Schwartz LB. Identification and partial characterization of a unique marker for human basophils. *J Immunol* 1995; **154**: 6548–55.

10 McEuen AR, Buckley MG, Compton SJ, Walls AF. Development and characterization of a monoclonal antibody specific for human basophils and the identification of a unique secretory product of basophil activation. *Lab Invest* 1999; **79**: 27–38.

11 Irani AM, Huang C, Xia HZ *et al.* Immunohistochemical detection of human basophils in late-phase skin reactions. *J Allergy Clin Immunol* 1998; **101**: 354–62.

12 Bryan SA, O'Connor BJ, Matti S *et al.* Effects of recombinant human interleukin-12 on eosinophils, airway hyper-responsiveness, and the late asthmatic response. *Lancet* 2000; **356**: 2149–53.

13 Leckie MJ, ten Brinke A, Khan J *et al.* Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response. *Lancet* 2000; **356**: 2144–8.

14 Wardlaw AJ, Brightling C, Green R *et al*. Eosinophils in asthma and other allergic diseases. *Br Med Bull* 2000; **56**: 985–1003.

15 Wardlaw AJ, Moqbel R, Kay AB. Eosinophils: biology and role in disease. *Adv Immunol* 1995; **60**: 151–266.

16 Capella GL, Grigerio E, Altomare G. A randomized trial of leukotriene receptor antagonist montelukast in moderate-to-severe atopic dermatitis of adults. *Eur J Dermatol* 2001; **11**: 209–13.

17 Erbagci Z. The leukotriene receptor antagonist montelukast in the treatment of chronic idiopathic urticaria: a single-blind, placebo-controlled, crossover clinical study. *J Allergy Clin Immunol* 2002; **110**: 484–8.

18 Amerio P, Frezzolini A, Feliciani C *et al.* Eotaxins and CCR3 receptor in inflammatory and allergic skin diseases: therapeutical implications. *Curr Drug Targets Inflamm Allergy* 2003; **2**: 81–94.

19 Shpacovitch V, Feld M, Hollenberg MD *et al*. Role of protease-activated receptors in inflammatory responses, innate and adaptive immunity. *J Leukoc Biol* 2008; **83**: 1309–22.

20 Ogawa Y, Grant JA. Mediators of anaphylaxis. *Immunol Allergy Clin North Am* 2007; **27**: 249–60, vii.

21 Haas N, Motel K, Czarnetzki BM. Comparative immunoreactivity of the eosinophil constituents MBP and ECP in different types of urticaria. *Arch Dermatol Res* 1995; **287**: 180–5.

22 Kiehl P, Falkenberg K, Vogelbruch M, Kapp A. Tissue eosinophilia in acute and chronic atopic dermatitis: a morphometric approach using quantitative image analysis of immunostaining. *Br J Dermatol* 2001; **145**: 720–9.

23 Leiferman KM, Fujisawa T, Gray BH, Gleich GJ. Extracellular deposition of eosinophil and neutrophil granule proteins in the IgE-mediated cutaneous late phase reaction. *Lab Invest* 1990; **62**: 579–89.

24 Morita H, Yamamoto K, Kitano Y. Elevation of serum major basic protein in patients with atopic dermatitis. *J Dermatol Sci* 1995; **9**: 165–8.

25 Kauder E, Boggs DR, Athens JW *et al*. Leukokinetic studies. XII. Kinetic studies of normal isologous neutrophilic granulocytes transfused into normal subjects. *Proc Soc Exp Biol Med* 1965; **120**: 595–9.

26 Haskard DO, Lee TH. The role of leukocyte-endothelial interactions in the accumulation of leukocytes in allergic inflammation. *Am Rev Respir Dis* 1992; **145**: S10–3.

27 Peters EM, Raap U, Welker P *et al.* Neurotrophins act as neuroendocrine regulators of skin homeostasis in health and disease. *Horm Metab Res* 2007; **39**: 110–24.

28 Weiss SJ. Tissue destruction by neutrophils. *N Engl J Med* 1989; **320**: 365–76.

29 Lehrer RI, Ganz T, Selsted ME, Babior BM, Curnutte JT. Neutrophils and host defense. *Ann Intern Med* 1988; **109**: 127–42.

30 Iwatsuki K, Yamasaki O, Morizane S, Oono T. Staphylococcal cutaneous infections: invasion, evasion and aggression. *J Dermatol Sci* 2006; **42**: 203–14.

31 Kollef MH, Micek ST. Methicillin-resistant *Staphylococcus aureus*: a new community-acquired pathogen? *Curr Opin Infect Dis* 2006; **19**: 161–8.

32 Groger M, Fischer GF, Wolff K, Petzelbauer P. Immune complexes from vasculitis patients bind to endothelial Fc receptors independent of the allelic polymorphism of FcgammaRIIa. *J Invest Dermatol* 1999; **113**: 56–60.

33 Liu Z, Shapiro SD, Zhou X *et al.* A critical role for neutrophil elastase in experimental bullous pemphigoid. *J Clin Invest* 2000; **105**: 113–23.

34 Lorant DE, Topham MK, Whatley RE *et al.* Inflammatory roles of P-selectin. *J Clin Invest* 1993; **92**: 559–70.

35 Ley K. Integration of inflammatory signals by rolling neutrophils. *Immunol Rev* 2002; **186**: 8–18.

36 Lorant DE, Patel KD, McIntyre TM *et al*. Coexpression of GMP-140 and PAF by endothelium stimulated by histamine or thrombin: a juxtacrine system for adhesion and activation of neutrophils. *J Cell Biol* 1991; **115**: 223–34.
37 Penniall R, Spitznagel JK. Chicken neutrophils: oxidative metabolism in phagocytic cells devoid of myeloperoxidase. *Proc Nat Acad Sci USA* 1975; **72**(12): 5012–15.
38 Segal AW, Peters TJ. Characterisation of the enzyme defect in chronic granulomatous disease. *Lancet* 1976; **1**: 1363–5.
39 Lekstrom-Himes JA, Gallin JI. Immunodeficiency diseases caused by defects in phagocytes. *N Engl J Med* 2000; **343**: 1703–14.
40 Philips MR, Buyon JP, Winchester R *et al*. Up-regulation of the iC3b receptor (CR3) is neither necessary nor sufficient to promote neutrophil aggregation. *J Clin Invest* 1988; **82**: 495–501.
41 Schleiffenbaum B, Moser R, Patarroyo M, Fehr J. The cell surface glycoprotein Mac-1 (CD11b/CD18) mediates neutrophil adhesion and modulates degranulation independently of its quantitative cell surface expression. *J Immunol* 1989; **142**: 3537–45.
42 Phillips ML, Schwartz BR, Etzioni A *et al*. Neutrophil adhesion in leukocyte adhesion deficiency syndrome type 2. *J Clin Invest* 1995; **96**: 2898–906.
43 Cronstein BN, Molad Y, Reibman J *et al*. Colchicine alters the quantitative and qualitative display of selectins on endothelial cells and neutrophils. *J Clin Invest* 1995; **96**: 994–1002.
44 Cronstein BN, Kimmel SC, Levin RI *et al*. A mechanism for the antiinflammatory effects of corticosteroids: the glucocorticoid receptor regulates leukocyte adhesion to endothelial cells and expression of endothelial-leukocyte adhesion molecule 1 and intercellular adhesion molecule 1. *Proc Natl Acad Sci U S A* 1992; **89**: 9991–5.
45 Filep JG, Delalandre A, Payette Y, Foldes-Filep E. Glucocorticoid receptor regulates expression of L-selectin and CD11/CD18 on human neutrophils. *Circulation* 1997; **96**: 295–301.
46 Pillinger MH, Capodici C, Rosenthal P *et al*. Modes of action of aspirin-like drugs: salicylates inhibit erk activation and integrin-dependent neutrophil adhesion. *Proc Natl Acad Sci U S A* 1998; **95**: 14540–5.
47 Barbosa MD, Nguyen QA, Tchernev VT *et al*. Identification of the homologous beige and Chediak–Higashi syndrome genes. *Nature* 1996; **382**: 262–5.
48 Nagle DL, Karim MA, Woolf EA *et al*. Identification and mutation analysis of the complete gene for Chediak–Higashi syndrome. *Nat Genet* 1996; **14**: 307–11.
49 Yamanaka R, Barlow C, Lekstrom-Himes J *et al*. Impaired granulopoiesis, myelodysplasia, and early lethality in CCAAT/enhancer binding protein epsilon-deficient mice. *Proc Natl Acad Sci U S A* 1997; **94**: 13187–92.
50 Lekstrom-Himes J, Xanthopoulos KG. CCAAT/enhancer binding protein epsilon is critical for effective neutrophil-mediated response to inflammatory challenge. *Blood* 1999; **93**: 3096–105.
51 Shpacovitch V, Feld M, Bunnett NW, Steinhoff M. Protease-activated receptors: novel PARtners in innate immunity. *Trends Immunol* 2007; **28**: 541–50.
52 Zaja-Milatovic S, Richmond A. CXC chemokines and their receptors: a case for a significant biological role in cutaneous wound healing. *Histol Histopathol* 2008; **23**: 1399–407.

Mast cells

Mast cells (MC) are a heterogeneous group of multifunctional, tissue-dwelling cells with roles in conditions as diverse as allergy, parasite infestation, inflammation, angiogenesis and tissue remodelling. The cells were named 'Mastzellen' (Greek *mastos*, breast) in 1876 by Paul Ehrlich because he believed that the intracellular granules, which appeared purple in colour when stained with aniline blue dyes, contained phagacytosed materials or nutrients [1]. This change in colour, or metachromasia, we now know to represent the interaction of the dyes with the highly acidic heparin contained within mast cell granules. Mast cells are haematopoietic in origin, entering the circulation from the bone marrow as mononuclear cell precursors that both express mRNA for stem cell factor (SCF) and have SCF receptors (SCFR, CD117) on their cell membranes [2]. From the blood, the precursors migrate into the tissues where, under the influence of local microenvironmental factors, they undergo their final phases of differentiation and maturation into recognizable mast cells. It is pertinent at this stage to distinguish mast cells from basophils, which were originally thought to be circulating mast cells, but are actually related more closely to eosinophils, developing in the bone marrow from granulocyte precursors and entering the circulation only when fully mature [3]. Mast cells and basophils differ in their repertoire of mediators released (Table 12.3).

Table 12.3 Comparison of mediators formed by human mast cells and basophils.

Mediator/product	Mast cells	Basophils
Histamine	+	+
Leukotriene C_4	+	+
Leukotriene B_4	–	(+)
Prostaglandin D_2 (PGD_2)	+	–
5-HETE	+	–
Thromboxane A_2 (TXA_2)	+	–
Platelet-activating factor (PAF)	+	–
Interleukin-1β	+	
Interleukin-3	+	
Interleukin-4	+ +	+
Interleukin-5	+	?
Interleukin-6	+	?
Interleukin-8	+	+
Interleukins-9, -10, -13, -14	+	
MCP-1α (chemokine)	+	
TNF-α	+ +	–
Tryptase/chymase	+	–
Carboxypeptidase	+	–
Heparin	+	–
Nerve growth factor (NGF)	+	
Eosinophil chemotactic factor	+	+
Neutrophil chemotactic factor	+	?

Mast cells are distinguished immunocytochemically by their neutral protease content, the MC_T phenotype containing only tryptase and the MC_{TC} phenotype containing both tryptase and chymase [4]. MC_T and MC_{TC} mast cells also express different receptors (Table 12.4). Initially, these respective subtypes were suggested to be the equivalents of the 'mucosal' and 'connective tissue' types previously described in experimental animals. However, it is now realized that variable amounts of both mast cell subtypes are present within any given tissue, their relative abundance changing with disease (e.g. in allergy or fibrosis). MC_T appear to be 'immune system-related' mast cells with a primary role in host defence, whereas MC_{TC} appear to be 'non-immune system-related' mast cells with functions in angiogenesis and tissue remodelling rather than immunological protection. However, it should be remembered that both phenotypes express Fc, εRI and may therefore participate fully in IgE-dependent allergic reactions.

In addition, there appears to be a functional heterogeneity between mast cells of different tissues, which is largely unrelated to immunocytochemical heterogeneity. For example, human skin mast cells alone express CD88, the receptor for the anaphylatoxin C5a, allowing them to be activated in a complement-mediated

Table 12.4 Receptors identified on the mast cell and basophil membrane.

Receptors	Mast cells		Basophil	Ligand/agonist
	MC_{TC}	MC_T		
FcεR1	+	+	+	IgE
CD32 FcγRI	–	–	+	IgG
CD88				
C5aR	+	(–)	+	C5a
C3aR	–	–	+	C3a
CD25				
IL-1R	+	–	–	IL-1
IL-2R	–	–	+	IL-2
IL-3R	–	+	+	IL-3
IL-5R	–	–	+	IL-5
CDw128 IL-8R	–	–	+	IL-8
GM-CSFR	–	–	+	GM-CSF
Toll-like receptor (TLR)				
TLR1	+	(–)	–	
TLR2	+	–	+	Bacterial peptides
TLR4	+	–	+	LPS
TLR6	+	–	–	Bacterial peptides
Chemokine receptors				
CCR1	+	(–)	(+)	MIP1-α
CCR2	–	–	+	MCP
CCR3	+	(–)	+	MCP
CCR4	+			
CD40L	+	–	+	CD40 : B cells
CD117 c-*kit* (KL)	+	+	(+)	Stem cell factor c-*kit* ligand

GM-CSF, granulocyte–macrophage colony-stimulating factor; IL, interleukin.

disease [5,6]. Also, skin mast cells alone respond to a variety of basic non-immunological secretagogues, including neuropeptides and drugs, such as morphine, codeine and muscle relaxants [7,8]. Interestingly, activation by these agents is incomplete, in that eicosanoid generation does not accompany degranulation [7]. The ability of human skin mast cells, but not those from other tissues, to respond to anaphylatoxins and basic non-immunological secretagogues explains the flushing reactions observed in sensitive individuals in the absence of overt rhinorrhoea or bronchoconstriction. Such responses may also be involved in physical urticarias.

The secretory granule of the human mast cell contains a crystalline complex of preformed inflammatory mediators ionically bound to a matrix of heparin proteoglycan. The mediator most readily associated with the mast cell, the simple diamine histamine, is present in the granules at approximately 100 mmol/L, equivalent to about 1–4 pg/cell. Histamine exerts many effects pertinent to the immediate phase of allergic responses, including initiation of the wheal and flare response [9]. However, these effects are normally of relatively short duration as histamine is rapidly metabolized, usually within 1–2 min, by histamine-*N*-methyltransferase (approximately 70%) and by diamine oxidase (histaminase) (approximately 30%). Interestingly, reduced diamine oxidase activity has been associated with recurrent urticaria [10].

The other 'early phase' mediators released from the skin mast cell are PGD_2 and LTC_4 [11]. While there is little evidence for a role of the former in skin inflammation, the success, particularly in individuals with a variant LTC_4 synthase allele [12], of leukotriene receptor antagonists in atopic dermatitis [13] and urticaria [14] suggests that this eicosanoid may be more important in skin disease than considered previously.

The major mast cell protease is tryptase, an approximately 130-kDa serine protease that is stored in a fully active form in the granule [15,16]. When released into the extracellular environment, the neutral pH allows tryptase to become enzymatically functional as a tetramer bound to heparin. The properties of tryptase pertinent to the skin include cleavage of the vasodilator calcitonin gene-related peptide (CGRP); a kallikrein-like activity; cleavage of matrix components, including 75-kDa gelatinase/type IV collagen, fibronectin and type VI collagen, and activation of stromelysin, which may, in turn, cleave other matrix components; and mitogenic activity for fibroblasts. While there appear to be no endogenous inhibitors of tryptase, it is likely to have very local effects because, in the absence of heparin, the biologically active tetrameric form of tryptase rapidly dissociates into inactive monomers. In addition to acting as an enzyme in the extracellular space, tryptase and other serine proteinases have been demonstrated to activate specific receptors by proteolytic cleavage. In the skin, tryptase activates proteinase-activated receptor-2 (PAR-2), which is constitutively expressed by keratinocytes and myofibroblasts. Upon inflammatory stimuli, endothelial cells, nerves and immune cells up-regulate PAR-2 expression. Interestingly, tryptase mimics various effects of histamine via activation of PAR-2 such as oedema, plasma extravasation, recruitment of neutrophils, and induction of pruritus. Thus, alongside histamine, tryptase is an important mediator of inflammatory responses, suggesting a role in inflammatory skin diseases such as atopic dermatitis, urticaria and angio-oedema [17,18].

Chymase is a 30-kDa monomeric protease stored in the same secretory granules as tryptase in the MC_{TC} subset of mast cells. Chymase degrades the neuropeptide neurotensin, but not substance P or VIP, cleaves angiotensin I to angiotensin II more effectively than angiotensin converting enzyme (ACE), and may also contribute to the splitting of the dermal–epidermal junction in bullous pemphigoid [15,19]. Two other proteinases, carboxypeptidase and cathepsin G, have been associated with the MC_{TC} subset of human mast cells. Carboxypeptidase is a unique 34.5-kDa metalloproteinase that removes the carboxyl terminal residues from a range of peptides, including angiotensin, leu^5-enkephalin, kinetensin, neuromedin N and neurotensin. Cathepsin G is a chymotryptic enzyme with a structure seemingly identical to that of neutrophil cathepsin G. When mast cells are activated, chymase, carboxypeptidase and cathepsin G are released together in a 400–500-kDa complex with proteoglycan, and are likely to act in concert with the other enzymes to degrade proteins.

With the discovery that polymorphisms in *SPINK5*, a gene encoding for a serine protease inhibitor, are associated with Netherton's syndrome and other allergic diseases [20], the potential role for proteases in skin disease seems to be extending.

Cytokines are responsible for the initiation and coordination of allergic inflammation. It is logical, therefore, that the mast cell is

a source of such cytokines. Of particular note are the NF-κB-dependent cytokines, TNF-α, GM-CSF and IL-8 [21,22] and the Th2 cytokines, IL-4, IL-5 and IL-13 [23,24]. Thus, not only have mast cells the capacity to initiate immediate phase allergic and anaphylactic reactions and tissue damage, they also have the capacity to stimulate allergic inflammation, which is characterized by the influx of basophils, eosinophils and neutrophils [25].

Histamine released by mast cells binds to and activates histamine receptors. Four of them (H1R to H4R) have been cloned so far. Besides its effects on sensory nerves and endothelial cells, histamine also modulates keratinocyte function directly, such as MMP-9 production and cell migration. Thus, histamine may contribute to epidermal dysregulation during the acute or chronic phase of inflammation [26].

The fact that many pathological processes affect the activation of mast cells in the skin and that the number of mast cells varies in different skin and allergic diseases, tumours and fibrotic diseases, indicates an important regulatory role of these cells in many diseases. Indeed, mast cells are capable of releasing more than 30 mediators with diverse roles, including pro- as well as anti-inflammatory cytokines/chemokines, TNF-α, growth factors, proteases and prostanoids [27]. In mutant mice which are profoundly mast-cell deficient or genetically altered, mast cells revealed features usually seen during inflammatory or immune responses, tissue remodelling, host defence and skin homeostasis [28,29].

References

1 Ehrlich P. Beitrage zur Kenntnis der Anilinfärbungen und ihrer Verwendung in der mikroskopischen Technik. *Arch Mikr Anat* 1876; **13**: 263–77.

2 Castells MC, Friend DS, Bunnell CA *et al.* The presence of membrane-bound stem cell factor on highly immature nonmetachromatic mast cells in the peripheral blood of a patient with aggressive systemic mastocytosis. *J Allergy Clin Immunol* 1996; **98**: 831–40.

3 Galli SJ. New insights into 'the riddle of the mast cells': microenvironmental regulation of mast cell development and phenotypic heterogeneity. *Lab Invest* 1990; **62**: 5–33.

4 Irani AA, Schechter NM, Craig SS *et al.* Two types of human mast cells that have distinct neutral protease compositions. *Proc Natl Acad Sci U S A* 1986; **83**: 4464–8.

5 el-Lati SG, Dahinden CA, Church MK. Complement peptides C3a- and C5a-induced mediator release from dissociated human skin mast cells. *J Invest Dermatol* 1994; **102**: 803–6.

6 Valent P, Schernthaner GH, Sperr WR *et al.* Variable expression of activation-linked surface antigens on human mast cells in health and disease. *Immunol Rev* 2001; **179**: 74–81.

7 Lowman MA, Benyon RC, Church MK. Characterization of neuropeptide-induced histamine release from human dispersed skin mast cells. *Br J Pharmacol* 1988; **95**: 121–30.

8 Stellato C, de Paulis A, Cirillo R *et al.* Heterogeneity of human mast cells and basophils in response to muscle relaxants. *Anesthesiology* 1991; **74**: 1078–86.

9 Petersen LJ, Church MK, Skov PS. Histamine is released in the wheal but not the flare following challenge of human skin *in vivo*: a microdialysis study. *Clin Exp Allergy* 1997; **27**: 284–95.

10 Lessof MH, Gant V, Hinuma K *et al.* Recurrent urticaria and reduced diamine oxidase activity. *Clin Exp Allergy* 1990; **20**: 373–6.

11 Robinson C, Benyon C, Holgate ST, Church MK. The IgE- and calcium-dependent release of eicosanoids and histamine from human purified cutaneous mast cells. *J Invest Dermatol* 1989; **93**: 397–404.

12 Sampson AP, Siddiqui S, Buchanan D *et al.* Variant LTC(4) synthase allele modifies cysteinyl leukotriene synthesis in eosinophils and predicts clinical response to zafirlukast. *Thorax* 2000; **55** (Suppl. 2): S28–31.

13 Capella GL, Grigerio E, Altomare G. A randomized trial of leukotriene receptor antagonist montelukast in moderate-to-severe atopic dermatitis of adults. *Eur J Dermatol* 2001; **11**: 209–13.

14 Erbagci Z. The leukotriene receptor antagonist montelukast in the treatment of chronic idiopathic urticaria: a single-blind, placebo-controlled, crossover clinical study. *J Allergy Clin Immunol* 2002; **110**: 484–8.

15 Church MK, Holgate ST, Shute JK *et al.* Mast cell derived mediators. In: Middleton E, Reed CE, Ellis EF *et al.*, eds. *Allergy: Principles and Practice*. New York: Mosby 1998: 146–61.

16 Schwartz LB. Tryptase from human mast cells: biochemistry, biology and clinical utility. *Monogr Allergy* 1990; **27**: 90–113.

17 Steinhoff M, Neisius U, Ikoma A *et al.* Proteinase-activated receptor-2 mediates itch: a novel pathway for pruritus in human skin. *J Neurosci* 2003; **23**: 6176–80.

18 Steinhoff M, Vergnolle N, Young SH *et al.* Agonists of proteinase-activated receptor 2 induce inflammation by a neurogenic mechanism. *Nat Med* 2000; **6**: 151–8.

19 Dimson OG, Giudice GJ, Fu CL *et al.* Identification of a potential effector function for IgE autoantibodies in the organ-specific autoimmune disease bullous pemphigoid. *J Invest Dermatol* 2003; **120**: 784–8.

20 Walley AJ, Chavanas S, Moffatt MF *et al.* Gene polymorphism in Netherton and common atopic disease. *Nat Genet* 2001; **29**: 175–8.

21 Coward WR, Okayama Y, Sagara H *et al.* NF-kappa B and TNF-alpha: a positive autocrine loop in human lung mast cells? *J Immunol* 2002; **169**: 5287–93.

22 Okayama Y, Kobayashi H, Ashman LK *et al.* Human lung mast cells are enriched in the capacity to produce granulocyte-macrophage colony-stimulating factor in response to IgE-dependent stimulation. *Eur J Immunol* 1998; **28**: 708–15.

23 Bradding P, Roberts JA, Britten KM *et al.* Interleukin-4, -5, and -6 and tumor necrosis factor-alpha in normal and asthmatic airways: evidence for the human mast cell as a source of these cytokines. *Am J Respir Cell Mol Biol* 1994; **10**: 471–80.

24 Kobayashi H, Okayama Y, Ishizuka T *et al.* Production of IL-13 by human lung mast cells in response to Fcepsilon receptor cross-linkage. *Clin Exp Allergy* 1998; **28**: 1219–27.

25 Von Stebut E. Immunology of cutaneous leishmaniasis: the role of mast cells, phagocytes and dendritic cells for protective immunity. *Eur J Dermatol* 2007; **17**: 115–22.

26 Gschwandtner M, Purwar R, Wittmann M *et al.* Histamine upregulates keratinocyte MMP-9 production via the histamine H1 receptor. *J Invest Dermatol* 2008; **128**: 2783–91.

27 Galli SJ, Tsai M. Mast cells: versatile regulators of inflammation, tissue remodeling, host defense and homeostasis. *J Dermatol Sci* 2008; **49**: 7–19.

28 Galli SJ, Grimbaldeston M, Tsai M. Immunomodulatory mast cells: negative, as well as positive, regulators of immunity. *Nat Rev Immunol* 2008; **8**: 478–86.

29 Metz M, Grimbaldeston MA, Nakae S *et al.* Mast cells in the promotion and limitation of chronic inflammation. *Immunol Rev* 2007; **217**: 304–28.

Monocytes and macrophages

The monocyte–macrophage system, formerly known as the 'reticuloendothelial system', represents a heterogeneous family of cell types that vary within different tissues. The range of functions of monocytes and macrophages is summarized in Table 12.5, and their receptor expressing and mediator repertoire is shown in Table 12.6. They all derive from identical progenitors in the bone marrow, where they mature from monoblasts to pro-monocytes. The maturation time is approximately 16 h in the rat and 19–25 h in humans. As mature cells, monocytes may remain in the blood for approximately 2–5 days. Following inflammatory stimuli, monocytes adhere to the endothelium and subsequently migrate into the site of inflammation where they differentiate into macrophages or dendritic cells (antigen-presenting cells). During acute inflammation, the rate of monocyte formation may be dramatically increased. This is important because resident macrophages show only a poor ability to divide [1,2].

Table 12.5 List of major functions of monocytes and macrophages, their receptors and secretory products.

Antitumour activity
Atherogenesis
Control of T and B lymphocytes
Control of dendritic cell function
Coagulation and fibrinolysis
Detoxification
Granuloma formation
Host defence
Metabolism and storage of lipids and iron
Mediation of acute and chronic inflammation
Modulation of keratinocyte function
Processing of antigens
Recruitment of leukocytes
Regulation of haematopoiesis
Release of enzymes for degradation
Scavenging of necrotic debris and effete cells
Wound healing

Table 12.6 List of major products released and receptors expressed by monocytes and macrophages.

Receptors (R)
IgG, IgE, IgA
C-reactive protein
C1q
C3b, C3bi
Fibrin
Fibronectin
Laminin
Transferrin
Heparin
IFN-α, -β, -γ
TNF-α
GM-CSF
Insulin
Insulin-like growth factor
Platelet-activating factor (PAF)
HLA-DR (class II MHC)
Macrophage inhibitory factor (MIF)
IL-2, -3, -4, -8, -10, -13, -16, -19, -23, -26
LTC, LTD_4, LTB_4
PGE_2
Histamine H_1, H_2
CCR4, CCR5
Angiotensin II
Toll-like receptors
α-adrenergic agents
β-adrenergic agents
Cholinergic agents
Products secreted
Atrial natriuretic peptide (ANP)
Lysozyme
Neutral proteases
Acid proteases
Lipases
Collagenase, elastase
α_2-Macroglobulin
α_1-Antiprotease
Complement C1, C2, C4, C3, C5
Factors B and D
NO
Prostaglandins E_2, $F_{2\alpha}$
Leukotrienes B, C, D, E
Thromboxane (TXA_2)
Glutathione
IL-1α, -1β, -1ra, -6, -8, -10, -12, -18
MIF
PAF
TNF-α
IFN-α/β
TGF-β
PDGF
GM-CSF, M-CSF, G-CSF
Respiratory burst reactive oxygen radicals

Macrophages rapidly recognize pathogens and 'danger signals' in the connective tissue by means of cell surface receptors [3] such as CD14, the mannose receptor, the SR, RAGE, protease-activated receptors [4] and TLRs (see above). These receptors recognize specific ligands released by microorganisms, leading to intracellular signal transduction pathways and ultimately initiating an inflammatory response. Macrophages also represent an important link to the adaptive immune system by generating immunomodulating cytokines such as interferons. In addition, they release IFN-γ and express MHC class II antigen HLA-DR, and may thus stimulate lymphocytes.

Macrophages have also been shown to utilize molecules from the complement system to interact with pathogens, and may subsequently undergo apoptosis or become degraded. Under pathophysiological conditions, macrophages may become incorporated into a granuloma or be converted into an epithelioid cell, with an increased ability to synthesize enzymes or other mediators of inflammation. Moreover, macrophages can also be incorporated into a giant cell by fusion with other macrophages. Such pathophysiological chronic inflammatory processes are observed in diseases that may affect the skin, such as tuberculosis, leprosy and sarcoidosis.

Macrophages are professional phagocytes; they recognize pathogens by specific receptors and subsequently phagocytose them. During this active, energy-driven process, macrophages generate acidic phagosomes and lysosomal mediators such as oxygen radicals. Macrophage-derived proteolytic enzymes, cathepsins D and G, acid phosphatases or matrix metalloproteinases are released during inflammation. Under normal circumstances, this network of defence molecules is a very effective barrier in the maintenance of tissue homeostasis. Under pathophysiological conditions, however, when defence mechanisms are impaired, these mediators may also have deleterious effects on the host, resulting in tissue destruction and fibrosis, as observed in various diseases such as arthritis.

Macrophage migration inhibitory factor (MIF) was originally described as a T-cell-derived lymphokine with the potential to inhibit the random migration of macrophages. However, recent reports have shown a much broader tissue distribution of

production, including the skin. Recently, an MIF has been localized to many skin cells such as keratinocytes [5], fibroblasts [6] and endothelial cells. An important role for MIF has been reported in several skin diseases such as lupus erythematosus [7], contact hypersensitivity [8], atopic dermatitis [9], psoriasis [10,11], wound healing [12], systemic sclerosis [13], graft-versus-host disease [14] and sepsis [15,16]. Thus, MIF may represent an important target molecule for the treatment of skin diseases in which macrophages are involved.

The production of arachidonic acid derivatives appears to be crucial for macrophage-mediated responses during inflammation. PGE_2, for example, is involved in lymphocyte activation by macrophages and also inhibits macrophages in an autocrine manner, indicating a negative-feedback system via specific prostaglandin receptors.

Macrophages are major targets for infection by human immunodeficiency virus type 1 (HIV-1). In addition to their role as productive viral reservoirs, inappropriate activation of infected and uninfected macrophages appears to contribute to pathogenesis. These responses establish a complex cytokine network, which may enhance or suppress HIV-1 replication. In addition, dysregulation of macrophage function by gp120–chemokine receptor signalling may contribute to local inflammation and injury and further recruit additional inflammatory and/or target cells [17].

Other receptors expressed by monocytes/macrophages are the peroxisome proliferator-activated receptors (PPARs). These are ligand-activated transcription factors that form a subfamily of the nuclear receptor gene family. This subfamily consists of three isotypes, PPARα (NR1C1), -γ (NR1C3) and -β/δ (NRC1C2) with a heterogeneous tissue distribution. PPARs are activated by ligands, such as naturally occurring fatty acids, which are activators of all three PPAR isotypes. In order to be transcriptionally active, PPARs need to heterodimerize with the retinoid-X-receptor (RXR). PPARs have a critical role in lipid and glucose homeostasis, but lately they have been implicated as regulators of inflammatory responses including in the skin. The first evidence of the involvement of PPARs in the control of inflammation came from PPARα knockout mice, which showed a prolonged inflammatory response. PPARα activation results in the repression of NF-κB signalling and inflammatory cytokine production in different cell types. A role for PPARγ in inflammation has also been reported in monocytes–macrophages, where ligands of this receptor inhibited the activation of macrophages and the production of inflammatory cytokines (TNF-α, IL-6 and IL-1β), although part of the anti-inflammatory effects of these ligands seems to be mediated by a mechanism not involving PPARγ. PPARs also regulate the gene expression of key proteins involved in vascular inflammation. By modulating transcription of pro-inflammatory genes such as cytokines, chemokines, endothelial cell adhesion molecules and metalloproteinases, PPARs directly affect inflammatory events. Together, these findings suggest a role of PPARs in the control of the inflammatory response, with potential therapeutic applications in inflammatory diseases such as acne, atopic dermatitis and psoriasis [18–22].

A novel family of monocyte-derived receptors has been described, which seems to be important in the regulation of inflammatory responses. This family of triggering receptors expressed by myeloid cells (TREMs) belongs to a rapidly expanding family of monocyte-derived receptors that include activating and inhibitory isoforms encoded by a gene cluster linked to the MHC. TREM1 and TREM2 activate myeloid cells by signalling through the adaptor protein DAP12. TREM1 triggers phagocyte secretion of pro-inflammatory chemokines and cytokines, amplifying the inflammation that is induced by bacteria and fungi [23].

Macrophages can remain within the tissue in a quiescent resting phase for months until stimulated through ligand binding to one or more of their numerous receptors (Fig. 12.3). They express receptors for IgG (FcγRI, FcγRII, FcγRIII) and complement components C3b and C3bi [24]. They also express receptors for C-reactive protein (CRP), which in blood monocytes induces synthesis of IL-1β and IL-1 receptor antagonist (IL-1RA).

There is evidence for a close interaction between T lymphocytes and macrophages. T-cell-derived IFN-γ both primes macrophages for an enhanced response to other cytokines and activates them to increase oxygen utilization and H_2O_2 formation. It also induces nitric oxide formation, increases phagocytic and tumouricidal activities, initiates or enhances MHC class II membrane antigen expression, and stimulates the synthesis of several cytokines and receptor expression. T-cell IL-2 stimulates macrophages, particularly if they are primed by IFN-γ. Macrophages also synthesize many cytokines such as IL-1, a potent pro-inflammatory signal.

Macrophages serve as an effective component of innate immunity by their ability to recognize, engulf and kill potential pathogens through lysosomal degradation. They also coordinate additional host responses by synthesizing a range of inflammatory mediators that can activate the adaptive immune response and establish protective immunity. Although they are a key component of the mammalian defence system, macrophage activity is not always beneficial to the host. The centrality of macrophages in disease processes makes macrophage regulation a major target in the prevention, control and cure of inflammatory processes. Consequently, macrophage-restricted genes may be crucial targets for therapeutic intervention. Large-scale cDNA microarrays have been used to compare macrophage inflammatory genes differentially expressed in two distinct macrophages populations (bone-marrow-derived macrophages and inflammatory thioglycolate-elicited peritoneal macrophages) with those in non-macrophage cell populations, such as primary embryonic fibroblasts and splenic non-adherent cells. Expression profiles indicate that macrophage inflammatory genes are associated with expected functional categories, such as lysosomal degradation, phagocytosis, host defence and homeostasis.

With respect to the molecular regulation of cytokine signalling in macrophages during inflammatory skin diseases, the Jak–Stat–Socs pathway has been shown to regulate all cell types involved in the initiation, propagation, and resolution of skin inflammation. The Jak–Stat pathway is negatively regulated by the suppressor of cytokine signalling (Socs) protein pathway. Thus, Jak–Stat–Socs signalling modulates developmental, pro- and anti-inflammatory outcomes depending on the cytokine receptor activated and which genes are accessible at the current state of inflammation [25].

Macrophages have been implicated in the regulation of T-cell function in the pathophysiology of psoriasis [26–30], atopic dermatitis, sarcoidosis, wound healing and Kawasaki disease [31], as

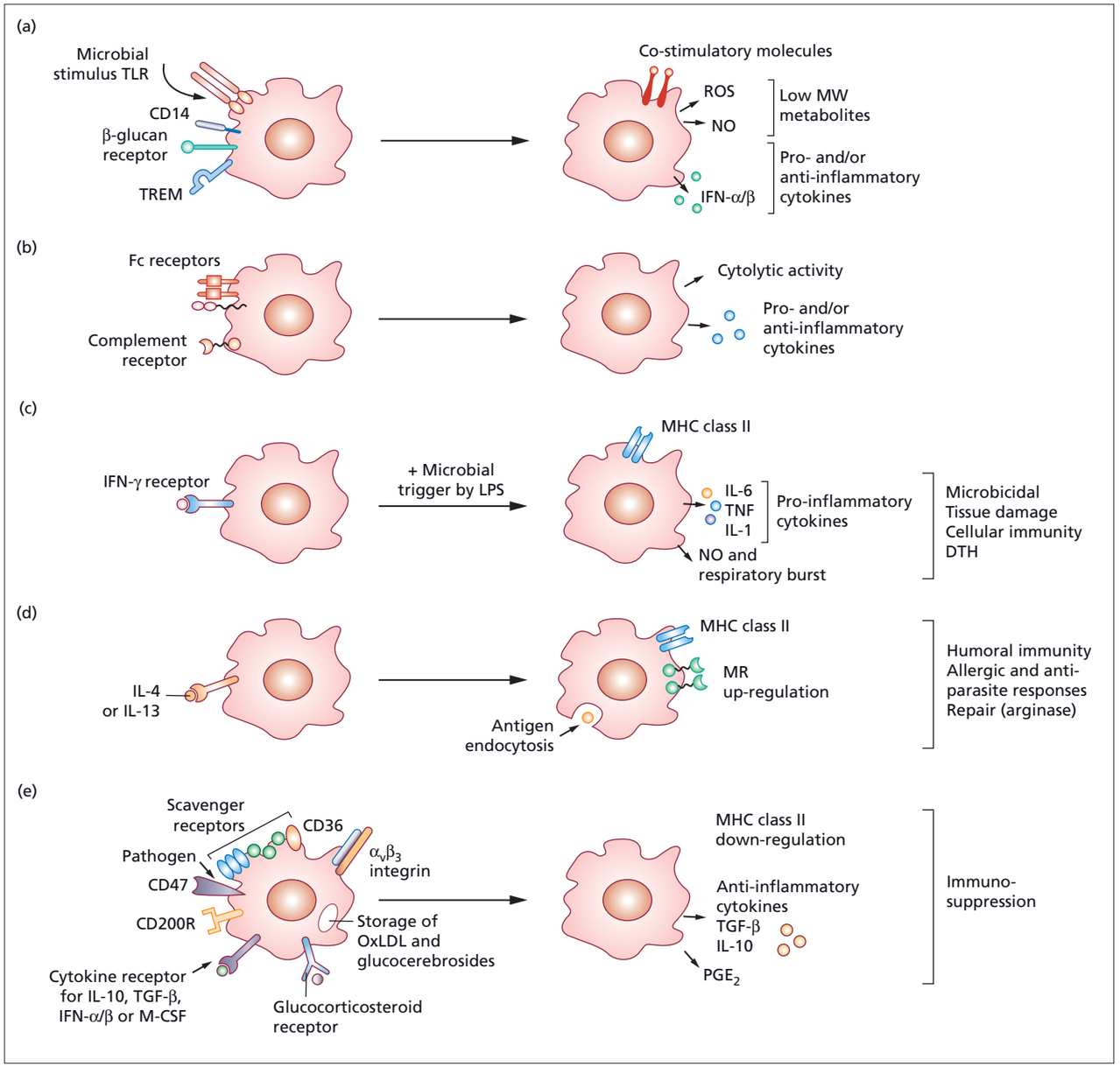


Fig. 12.3 Role of macrophages in innate and acquired immune function. (Modified from Gordon S. Alternative activation of macrophages. *Nature Rev Immunol* 2003; **3**: 23–35.) (a) Macrophages recognize pattern-recognition receptors such as toll-like receptors (TLRs), CD14–LPS-binding protein and others. These stimuli induce production of pro-inflammatory cytokines such as interferons, nitric oxide and reactive oxygen species. This is followed by a well-tuned anti-inflammatory response. Scavenger receptor (SR-A) and mannose receptor (MR) promote phagocytosis and endocytosis of host and of exogenous ligands. (b) Humoral activation and phagocytosis are mediated by some Fc and complement receptors, whereas other receptors down-regulate these responses. (c) Classical activation is triggered by the priming stimulus IFN-γ, followed by a microbial trigger (e.g. LPS). (d) Alternative activation is mediated by IL-4 and IL-13, acting through a common receptor chain (IL-4Rα). (e) Inactivation can be of innate as well as of acquired origin. Uptake of apoptotic cells or lysosomal storage of host molecules generates anti-inflammatory responses. Cellular activity is modulated by interactions of macrophages with T cells, fibroblast or extracellular matrix by activating specific receptors. Glucocorticoids and anti-inflammatory agents can suppress macrophage function. Pathogens can deactivate macrophages thereby contributing to infection. DTH, delayed-type hypersensitivity; M-CSF, macrophage colony-stimulating factor; OxLDL, oxidized low-density lipoprotein; PGE_2, prostaglandin E_2, TGF-β, transforming growth factor-β; TREM, triggering receptor expressed on myeloid cells.

well as in autoimmune diseases such as lupus erythematosus [32].

References

1 Janeway CA, Travers P, Walport M, Shlomchik M. *Immunobiology*, 5th edn. New York: Taylor & Francis Inc., 2001.

2 Travers P, Walport M, Shlomchik M. *Macrophages*. New York: Garland, 2001.

3 Heinzelmann M, Polk HC Jr, Chernobelsky A *et al*. Endotoxin and muramyl dipeptide modulate surface receptor expression on human mononuclear cells. *Immunopharmacology* 2000; **48**: 117–28.

4 Shpacovitch V, Feld M, Bunnett NW, Steinhoff M. Protease-activated receptors: novel PARtners in innate immunity. *Trends Immunol* 2007; **28**: 541–50.

5 Shimizu T, Abe R, Ohkawara A, Nishihira J. Ultraviolet B radiation upregulates the production of macrophage migration inhibitory factor (MIF) in human epidermal keratinocytes. *J Invest Dermatol* 1999; **112**: 210–5.

6 Watanabe H, Shimizu T, Nishihira J *et al*. Ultraviolet A-induced production of matrix metalloproteinase-1 is mediated by macrophage migration inhibitory factor (MIF) in human dermal fibroblasts. *J Biol Chem* 2004; **279**: 1676–83.
7 Hoi AY, Morand EF, Leech M. Is macrophage migration inhibitory factor a therapeutic target in systemic lupus erythematosus? *Immunol Cell Biol* 2003; **81**: 367–73.
8 Shimizu T, Abe R, Nishihira J *et al*. Impaired contact hypersensitivity in macrophage migration inhibitory factor-deficient mice. *Eur J Immunol* 2003; **33**: 1478–87.
9 Shimizu T, Abe R, Ohkawara A *et al*. Macrophage migration inhibitory factor is an essential immunoregulatory cytokine in atopic dermatitis. *Biochem Biophys Res Commun* 1997; **240**: 173–8.
10 Shimizu T, Nishihira J, Mizue Y *et al*. Histochemical analysis of macrophage migration inhibitory factor in psoriasis vulgaris. *Histochem Cell Biol* 2002; **118**: 251–7.
11 Steinhoff M, Meinhardt A, Steinhoff A *et al*. Evidence for a role of macrophage migration inhibitory factor in psoriatic skin disease. *Br J Dermatol* 1999; **141**: 1061–6.
12 Ashcroft GS, Mills SJ, Lei K *et al*. Estrogen modulates cutaneous wound healing by downregulating macrophage migration inhibitory factor. *J Clin Invest* 2003; **111**: 1309–18.
13 Selvi E, Tripodi SA, Catenaccio M *et al*. Expression of macrophage migration inhibitory factor in diffuse systemic sclerosis. *Ann Rheum Dis* 2003; **62**: 460–4.
14 Lo JW, Leung AY, Huang XR *et al*. Macrophage migratory inhibitory factor (MIF) expression in acute graft-versus-host disease (GVHD) in allogeneic hemopoietic stem cell transplant recipients. *Bone Marrow Transplant* 2002; **30**: 375–80.
15 Baugh JA, Bucala R. Macrophage migration inhibitory factor. *Crit Care Med* 2002; **30**: S27–S35.
16 Calandra T, Roger T. Macrophage migration inhibitory factor: a regulator of innate immunity. *Nat Rev Immunol* 2003; **3**: 791–800.
17 Lee C, Liu QH, Tomkowicz B *et al*. Macrophage activation through CCR5- and CXCR4-mediated gp120-elicited signaling pathways. *J Leukoc Biol* 2003; **74**: 676–82.
18 Cabrero A, Laguna JC, Vazquez M. Peroxisome proliferator-activated receptors and the control of inflammation. *Curr Drug Targets Inflamm Allergy* 2002; **1**: 243–8.
19 Chen W, Yang CC, Sheu HM *et al*. Expression of peroxisome proliferator-activated receptor and CCAAT/enhancer binding protein transcription factors in cultured human sebocytes. *J Invest Dermatol* 2003; **121**: 441–7.
20 Di-Poi N, Michalik L, Tan NS *et al*. The anti-apoptotic role of PPARbeta contributes to efficient skin wound healing. *J Steroid Biochem Mol Biol* 2003; **85**: 257–65.
21 Kuenzli S, Saurat JH. Peroxisome proliferator-activated receptors in cutaneous biology. *Br J Dermatol* 2003; **149**: 229–36.
22 Tham DM, Wang YX, Rutledge JC. Modulation of vascular inflammation by PPARs. *Drug News Perspect* 2003; **16**: 109–16.
23 Colonna M. TREMs in the immune system and beyond. *Nat Rev Immunol* 2003; **3**: 445–53.
24 Takahara M, Kang K, Liu L *et al*. iC3b arrests monocytic cell differentiation into CD1c-expressing dendritic cell precursors: a mechanism for transiently decreased dendritic cells in vivo after human skin injury by ultraviolet B. *J Invest Dermatol* 2003; **120**: 802–9.
25 O'Shea JJ, Murray PJ. Cytokine signaling modules in inflammatory responses. *Immunity* 2008; **28**: 477–87.
26 Clark RA, Kupper TS. Misbehaving macrophages in the pathogenesis of psoriasis. *J Clin Invest* 2006; **116**: 2084–7.
27 Li YY, Zollner TM, Schon MP. Targeting leukocyte recruitment in the treatment of psoriasis. *Clin Dermatol* 2008; **26**: 527–38.
28 Nickoloff BJ, Qin JZ, Nestle FO. Immunopathogenesis of psoriasis. *Clin Rev Allergy Immunol* 2007; **33**: 45–56.
29 Stratis A, Pasparakis M, Rupec RA *et al*. Pathogenic role for skin macrophages in a mouse model of keratinocyte-induced psoriasis-like skin inflammation. *J Clin Invest* 2006; **116**: 2094–104.
30 Wang H, Peters T, Kess D *et al*. Activated macrophages are essential in a murine model for T cell-mediated chronic psoriasiform skin inflammation. *J Clin Invest* 2006; **116**: 2105–14.
31 Matsubara T, Ichiyama T, Furukawa S. Immunological profile of peripheral blood lymphocytes and monocytes/macrophages in Kawasaki disease. *Clin Exp Immunol* 2005; **141**: 381–7.
32 Gaipl US, Kuhn A, Sheriff A *et al*. Clearance of apoptotic cells in human SLE. *Curr Dir Autoimmun* 2006; **9**: 173–87.

Fibroblasts

Under physiological conditions, fibroblasts are part of the connective tissue and the source of most of the extracellular matrix protein elements in the dermis. Intercellular substrates in the dermis are mainly composed of collagens, fibronectin, laminins, syndecans, decorin, hyaluronic acid, heparan sulphate and glycosaminoglycans (GAGs) (see Chapter 3). GAGs covalently bind to proteins to form proteoglycans, which are able to bind proteins such as cytokines, chemokines or growth factors in the extracellular space. Fibroblast-derived matrix molecules such as collagens, laminins and fibronectin are capable of modulating cell–cell interactions between fibroblasts and inflammatory cells. For example, migrating T cells or mast cells interact with extracellular matrix proteins via β2-integrin activation to regulate cell migration during inflammation or wound healing.

After stimulation, fibroblasts are able to transform into several types of specialized cell such as myofibroblasts, smooth-muscle cells, chondrocytes and osteocytes. It is not known if the different phenotypes arise from pluripotential stem cells or from subtypes with restricted properties of differentiation. Some differentiated fibroblasts can revert to the original mesenchymal state, whereas others persist as mature, committed cells. Therefore it is not surprising that fibroblast-derived cartilage and bone may occasionally be found in scar tissue induced by thus far unknown stimuli. Under normal circumstances in the skin, fibroblasts mature into dermal fibrocytes. After maturation, their function is merely restricted to the synthesis of extracellular matrix proteins such as collagens, elastin, hyaluronic acids and glycosaminoglycans. In the skin, collagens I, III, IV, VII, XVII, fibronectin and laminins are of special interest, due to their capability of regulating dermal–epidermal interactions via modulation of the basal lamina composition at the dermal–epidermal border, around vessels, and skin appendages. Thus, fibroblasts are critical cells for skin homeostasis but are also involved in inflammatory responses.

Under pathophysiological conditions, fibroblasts or fibrocytes can be involved in many diseases, such as connective tissues diseases (e.g. scleroderma, scleromyxoedema), vasculitis, graft-versus-host disease, wound repair, fibrosis, skin ageing, scar formation, keloids, autoimmunity and tumourgenesis.

During inflammation, the morphology and properties of fibroblasts are strictly dependent on the surrounding microenvironment. Dermal fibroblasts grown *in vitro* on different substrates, such as collagens or laminins, but maintained in the same medium, show differences in morphology, integrin expression and cytokine synthesis. Moreover, dermal fibroblasts cultured in contracting collagen gels form sixfold more PGE_2 than do cells cultured on plastic [1]. Fibroblasts in floating collagen gels are stellate with long cytoplasmic processes [2]. After gel contraction, the DNA synthesis is reduced [3] and collagenase synthesis is increased [4]. In contrast, fibroblasts grown on anchored (non-contracting) gels become elongated, bipolar and lie along lines of tension, similar

to fibrocytes [5]. They synthesize DNA, proliferate [3,6] and do not exhibit increased collagenase synthesis.

Alterations of the extracellular matrix generated by fibroblasts may depend on stimulation by certain cytokines, chemokines, proteases or growth factors. For example, the expression of β1-integrin chains α2, α3 and α5 in fibroblasts on fibronectin and fibrin substrates is regulated by platelet-derived growth factor (PDGF) and similar to that observed in fresh wounds. Moreover, PDGF also modulates the integrin synthesis in fibroblasts, resembling that of the granulating tissue of wounds [7]. Moreover, differences in the matrix composition alter PDGF-receptor phosphorylation [8]. Therefore, the responsiveness to PDGF is one of the most potent mediators controlling fibroblast proliferation and collagen formation.

During wound healing and scar formation, the surrounding environment of fibroblasts modulates freshly damaged tissues with fibrin clots (coagulation at early stages) to organized extracellular matrix at later stages. Moreover, hypertrophic scars are characterized by a stable phenotype of fibroblasts which differ from normal fibroblasts and exhibit a reduced response to epidermal growth factor (EGF) as well as an increased synthesis of collagens [9].

Inflammation plays an important role in the initiation and progression of scleroderma. In a study of systemic scleroderma, collagen formation was increased as the α2 chain of the α2β1 integrin was reduced [10]. Similarly, the down-regulation of collagen mRNA expression in fibroblasts of systemic scleroderma patients tended to be less than that in controls. This increased potential to form collagen was associated with a decrease in the α1β1 integrin [11]. Both α1β1 and α2β1 integrins, but particularly α2β1, recognize collagen-1 in the dermis, and the reduced integrin expression associated with increased collagen synthesis may reflect defective signalling between fibroblasts and their collagen matrix environment.

Dermal fibroblasts synthesize prostaglandins, leukotrienes and several cytokines or chemokines. As resident cells, fibrocytes release pro-inflammatory mediators as an early response to skin injury, and growth factors to promote subsequent healing. The production by fibroblasts *in vitro* of leukocyte activating/attracting agents is somewhat in contradiction to the *in vivo* histological findings, which rarely reveals accumulation of leukocytes round fibroblasts. Therefore, it is possible that proteoglycan binding of some of the cytokines results in a more diffuse leukocyte infiltration. Fibroblast proliferation is stimulated mainly by PDGF, TGF-β and fibroblast growth factor (FGF). The growth factor TGF-β may either stimulate or reduce proliferation, depending upon the state of cell activation [12]. Finally, synthesis of collagens or other connective tissue elements is induced by PDGF or TGF-β. In contrast, TNF-α may stimulate or repress synthesis depending on the state of activation [12]. In normal skin as well as during disease, a close interaction exists between fibroblast and keratinocyte activation which is regulated by cytokines, chemokines and growth factors.

Several *in vitro* studies suggest that eosinophils may have a role in fibrosis, remodelling and repair processes associated with IgE-mediated hypersensitivity. Eosinophil-derived TGF-β and IL-13 is temporarily associated with myofibroblast formation and deposition of tenascin and pro-collagen I, suggesting that both inflammatory mediators may contribute to repair and remodelling events of inflammatory skin diseases by modulating fibroblast function [13]. There is also evidence of a role for neuropeptides in the modulation of fibroblast functions. Thus, it has been shown that expression and cellular levels of SCF are up-regulated in fibroblasts by substance P (SP) [14]. In summary, fibroblasts contribute crucially to the interaction of epidermal and dermal components to maintain skin integrity.

In wounds involving the dermis, activated fibroblasts migrate on structures of the extracellular matrix such as collagens, fibronectin or fibrin, where they proliferate and synthesize new matrix proteins including collagens and elastin to form new granulation tissue. During this process, fibroblast (myofibroblast) proliferation becomes gradually reduced as the collagens mature and the wound contracts [6,15]. In the granulation tissue, the fibroblasts are transformed into myofibroblasts, with several morphological, chemical and antigenic differences as compared to resident mature fibroblasts [16,17]. Myosin in the activated cell is phosphorylated to expose actin-binding sites, to form actin–myosin contractile or stress fibres across the cell. Focal contacts or integrins exert tension forces on the extracellular matrix components. The first formed collagen gel is compacted and modified to form strands of dermal tissue fibres. The fibroblasts migrate to lie along the fibres as seen in normal dermis, at which time they lose their myosin stress fibres, although they continue to contribute to the overall tension of the skin.

References

1 Pentland AP. Collagen lattice effects on fibroblast arachidonic acid metabolism. *J Cell Physiol* 1989; **139**: 392–7.

2 Bellows CG, Melcher AH, Aubin JE. Contraction and organization of collagen gels by cells cultured from periodontal ligament, gingiva and bone suggest functional differences between cell types. *J Cell Sci* 1981; **50**: 299–314.

3 Nakagawa S, Pawelek P, Grinnell F. Extracellular matrix organization modulates fibroblast growth and growth factor responsiveness. *Exp Cell Res* 1989; **182**: 572–82.

4 Paye M, Nusgens BV, Lapiere CM. Modulation of cellular biosynthetic activity in the retracting collagen lattice. *Eur J Cell Biol* 1987; **45**: 44–50.

5 Bellows CG, Melcher AH, Aubin JE. Association between tension and orientation of periodontal ligament fibroblasts and exogenous collagen fibres in collagen gels in vitro. *J Cell Sci* 1982; **58**: 125–38.

6 Grinnell F. Fibroblasts, myofibroblasts, and wound contraction. *J Cell Biol* 1994; **124**: 401–4.

7 Xu J, Clark RA. Extracellular matrix alters PDGF regulation of fibroblast integrins. *J Cell Biol* 1996; **132**: 239–49.

8 Lin YC, Grinnell F. Decreased level of PDGF-stimulated receptor autophosphorylation by fibroblasts in mechanically relaxed collagen matrices. *J Cell Biol* 1993; **122**: 663–72.

9 Garner WL, Karmiol S, Rodriguez JL *et al*. Phenotypic differences in cytokine responsiveness of hypertrophic scar versus normal dermal fibroblasts. *J Invest Dermatol* 1993; **101**: 875–9.

10 Kozlowska E, Sollberg S, Mauch C *et al*. Decreased expression of alpha 2 beta 1 integrin in scleroderma fibroblasts. *Exp Dermatol* 1996; **5**: 57–63.

11 Ivarsson M, McWhirter A, Black CM, Rubin K. Impaired regulation of collagen pro-alpha 1(I) mRNA and change in pattern of collagen-binding integrins on scleroderma fibroblasts. *J Invest Dermatol* 1993; **101**: 216–21.

12 Kovacs EJ. Fibrogenic cytokines: the role of immune mediators in the development of scar tissue. *Immunol Today* 1991; **12**: 17–23.

13 Phipps S, Ying S, Wangoo A *et al*. The relationship between allergen-induced tissue eosinophilia and markers of repair and remodeling in human atopic skin. *J Immunol* 2002; **169**: 4604–12.

14 Toyoda M, Nakamura M, Morohashi M. Neuropeptides and sebaceous glands. *Eur J Dermatol* 2002; **12**: 422–7.

15 Clark RA. Regulation of fibroplasia in cutaneous wound repair. *Am J Med Sci* 1993; **306**: 42–8.
16 Gabbiani G, Rungger-Brändle E. The fibroblast. In: Glynn LE, ed. *Tissue Repair and Regeneration*. Amsterdam: Elsevier 1981: 1–50.
17 Skalli O, Gabbiani G. The biology of the myofibroblast: relationship to wound contraction and fibrocontractive disease. In: Clark RAF, Henson PM, eds. *The Molecular and Cellular Biology of Wound Repair*. New York: Plenum Press 1988: 373–402.

Platelets

Platelets are derived from megakaryocytes in the bone marrow and are the major components involved in blood clotting and homeostasis. Upon injury and inflammation, platelets regulate leukocyte aggregation and adherence to the endothelium, reflected by cell arrest and emigration into the tissue. Using video microscopy, transient platelet rolling on endothelium has recently been observed. Platelets accumulate in the vicinity of an injury, making them available for an immediate response [1]. Moreover, platelets contain a variety of potent inflammatory mediators and growth factors that contribute to normal homeostasis of blood cells, acute inflammation, tissue repair and immune responses. Accordingly, platelets release mediators such as eicosanoids, ADP, amines, proteolytic enzymes and cationic proteins. They are also a source of serotonin (5-HT), which is released during vascular injury, resulting in enhanced deposition of immune complexes on the endothelium. Thus, the formation of platelet aggregates and the subsequent release of mediators appear to have a role in tissue damage during cutaneous small vessel vasculitis [2].

In contrast to their classical role in coagulation, platelet production and activation appears to be a critical cell type at early stages of inflammation, injury and immunity. Platelets become activated and interact with endothelial cells, thereby stimulating the increase of inflammatory transcription factors and mediators such as NF-κB and interleukin-6. Thus, continuous activation of platelets leads to the perpetuation of inflammatory signalling and amplification of the inflammatory response, as observed in vasculitis.

Platelets are functionally closely associated with all types of leukocytes. Activated platelets secrete chemotactic substances, facilitate the binding of leukocytes to the endothelium as well as their subsequent extravasation, and may influence the inflammatory responses of leukocytes by both stimulation and inhibition. However, platelets also contain an array of potent pro-inflammatory substances, and are therefore effector cells of inflammation. Because of the role of platelets in IgE-dependent killing and eosinophil infiltration, they are currently considered to be directly involved in allergic IgE-mediated reactions [3].

Platelets express several receptors and can be activated by plasma products, immunoglobulins, complement, extracellular matrix components, leukocytes (particularly neutrophils) and endothelial cells. Receptors for soluble agonists include ADP [4], FcγRII [5,6] and complement component C3a [7]. They also express PARs belonging to a novel subfamily of G-protein-coupled receptors with seven transmembrane domains activated by serine proteases [8,9]. PAR-1, -3 and -4 are thrombin receptors in mice (PAR-3, PAR-4) and humans (PAR-1 and PAR-4). During inflammation, PARs become activated by thrombin on platelets, leading to mediator release and regulation of endothelial cell and leukocyte function. PAR-1 is critically involved in angiogenesis and leukocyte transmigration [8].

α11bβ3 (also designated glycoprotein 11b–111a or GP11b–111a) represents an important platelet-specific integrin. Upon activation, it is recruited to the cell surface, where it is capable of binding to thrombin, collagen or laminin [10]. The platelet integrin α2β1 (GP1a–11a) binds collagen [11], α5β1 and α6β1 (GP1c–11a) bind to fibronectin, collagen and laminin, while CD36 (GPIV) binds thrombospondin and possibly collagen [12]. Complement binds to the granule membrane protein 140 (GMP-140). Upon activation, GMP-140 expression is induced on platelets and endothelium, resulting in up-regulation of E-selectin and the promotion of leukocyte adherence [13].

Some receptors may bind to several ligands, and the activating potential of distinct ligands varies. Whereas 'strong agonists' (thrombin, collagen, thromboxane A_2 [TXA_2] and PAF) elicit a direct response, 'weak agonists' (9-ADP, adrenaline [epinephrine], vasopressin and serotonin) depend upon secretion to mediate a full response. Antagonists include PGI_2, PGD_2, endothelium-derived relaxing factor (EDRF) and nitric oxide [14]. Several of these are generated as the result of platelets activating other platelets (TXA_2, ADP and serotonin).

Receptors of normal platelets are either intracellular or, if on the cell surface, do not contact their ligands in undamaged tissue. On activation, rapid exposure and realignment of receptors stimulates second-messenger G proteins, protein tyrosine kinases and phospholipases [14]. The platelets change shape to develop numerous microspicules, which leads to aggregation of platelets and binding to other cells [15]. Platelets are reported *in vitro* to release microparticles that preferentially bind, activate and aggregate neutrophils, increasing expression of the CD11b receptor [16]; *in vivo* this would increase neutrophil–endothelium binding. Platelet–neutrophil interaction promotes formation of leukotrienes and lipoxins, the precursors of which are derived from both cells. Di-HETE is formed by the interaction of platelet 12-lipoxygenase (12-LO) and neutrophil 5-LO; neutrophils release LTD_4 and LTC_4 [17,18]. Such transcellular mediator synthesis results in concentrations of pro-inflammatory lipoxins and leukotrienes at the site of vascular damage. Using 12-LO-deficient mice, a role for platelet-type 12-LO in normal transepidermal permeability barrier function in mice was shown [16]. Other platelet pro-inflammatory mediators include TGF-α and -β, PDGF and prostaglandins; platelet aggregates in clots are the source of most prostaglandins in the blood during inflammation [19]. PDGF is both a pro-inflammatory mediator by virtue of activating neutrophils and monocytes, and a growth factor inducing tissue repair by regulating fibroblast proliferation, chemotaxis and collagen synthesis.

The expression receptors for immunoglobulins and complement on platelets may contribute to inflammation and to the removal of potential agonists. Thus, via signalling through IgG as well as IgE receptors [3,5,6], the release of pro-inflammatory mediators is enhanced, and the activation of C3a receptors induces release of serotonin and synthesis of thromboxane [5]. The IgG receptors bind IgG–antigen complexes, which are removed from

the circulation when the platelet complex is subsequently ingested by phagocytes in the spleen, liver and elsewhere.

Thrombospondin 1 (TSP-1), an adhesive glycoprotein expressed by endothelial cells, fibroblasts and macrophages, has an important role in platelet adhesion, inflammation and cell–cell interaction [20,21]. TSP-1 is up-regulated early during tissue injury, and is involved in angiogenesis, inflammation and vascular skin diseases by directly interacting with endothelial cells.

Recent data strongly suggest platelets to be directly involved in immune responses. Thus, blood platelets participate actively in immune defence and inflammatory processes. Upon activation via adenosine-triphosphate (purinergic receptors) or protease-activated receptor-1 (PAR-1), platelets release a variety of mediators, including cytokines, chemokines such as thymus and activation-regulated chemokine (TARC/CCL17) or RANTES, platelet factor 4 (PF-4), PDGF, β-thromboglobulin, serotonin, proteases, and arachidonic acid metabolites (prostanoids) [22,23]. Platelets also induce the expression of immunomodulatory and cell adhesive molecules such as CD154 and P-selectin. Conversely, inflammatory processes in the skin induce platelet activation, which contributes to acceleration and modulation of many inflammatory processes including vasculitis. Activated platelets are capable of facilitating leukocyte rolling in the skin and the release of inflammatory mediators in the skin. Platelets might be an important effector cell of the skin immune system, with modifications of platelet function contributing to the pathophysiology of certain inflammatory skin disorders such as urticaria or psoriasis [24,25]. The changes in platelet activity and reactivity have been demonstrated to impact on the pathophysiology of wound healing [26,27], urticaria, atopic dermatitis and psoriasis [3,28,29].

References

1 Mordon S, Begu S, Buys B *et al*. Study of platelet behavior in vivo after endothelial stimulation with laser irradiation using fluorescence intravital videomicroscopy and PEGylated liposome staining. *Microvasc Res* 2002; **64**: 316–25.

2 Meijer-Jorna LB, Mekkes JR, van der Wal AC. Platelet involvement in cutaneous small vessel vasculitis. *J Cutan Pathol* 2002; **29**: 176–80.

3 Klinger MH. Platelets and inflammation. *Anat Embryol (Berl)* 1997; **196**: 1–11.

4 Hourani SM, Hall DA. Receptors for ADP on human blood platelets. *Trends Pharmacol Sci* 1994; **15**: 103–8.

5 Anderson GP, Anderson CL. Signal transduction by the platelet Fc receptor. *Blood* 1990; **76**: 1165–72.

6 King M, McDermott P, Schreiber AD. Characterization of the Fc gamma receptor on human platelets. *Cell Immunol* 1990; **128**: 462–79.

7 Polley MJ, Nachman RL. Human platelet activation by C3a and C3a des-arg. *J Exp Med* 1983; **158**: 603–15.

8 Rattenholl A, Steinhoff M. Proteinase-activated receptor-2 in the skin: receptor expression, activation and function during health and disease. *Drug News Perspect* 2008; **21**: 369–81.

9 Takeuchi T, Harris JL, Huang W *et al*. Cellular localization of membrane-type serine protease 1 and identification of protease-activated receptor-2 and single-chain urokinase-type plasminogen activator as substrates. *J Biol Chem* 2000; **275**: 26333–42.

10 Hynes RO. Integrins: versatility, modulation, and signaling in cell adhesion. *Cell* 1992; **69**: 11–25.

11 Staatz WD, Fok KF, Zutter MM *et al*. Identification of a tetrapeptide recognition sequence for the alpha 2 beta 1 integrin in collagen. *J Biol Chem* 1991; **266**: 7363–7.

12 Huang MM, Bolen JB, Barnwell JW *et al*. Membrane glycoprotein IV (CD36) is physically associated with the Fyn, Lyn, and Yes protein-tyrosine kinases in human platelets. *Proc Natl Acad Sci U S A* 1991; **88**: 7844–8.

13 McEver RP. Properties of GMP-140, an inducible granule membrane protein of platelets and endothelium. *Blood Cells* 1990; **16**: 73–80.

14 Kroll MH, Schafer AI. Biochemical mechanisms of platelet activation. *Blood* 1989; **74**: 1181–95.

15 White JG, Leistikow EL, Escolar G. Platelet membrane responses to surface and suspension activation. *Blood Cells* 1990; **16**: 43–70.

16 Jy W, Mao WW, Horstman L *et al*. Platelet microparticles bind, activate and aggregate neutrophils in vitro. *Blood Cells Mol Dis* 1995; **21**: 217–31.

17 Edenius C, Forsberg I, Stenke L, Lindgren JA. Lipoxin formation in human platelets. *Adv Prostaglandin Thromboxane Leukot Res* 1991; **21A**: 97–100.

18 Fiore S, Romano M, Serhan CN. Lipoxin and leukotriene production during receptor-activated interactions between human platelets and cytokine-primed neutrophils. *Adv Prostaglandin Thromboxane Leukot Res* 1991; **21A**: 93–6.

19 Johnson EN, Nanney LB, Virmani J *et al*. Basal transepidermal water loss is increased in platelet-type 12-lipoxygenase deficient mice. *J Invest Dermatol* 1999; **112**: 861–5.

20 Chen ZS, Pohl J, Lawley TJ, Swerlick RA. Human microvascular endothelial cells adhere to thrombospondin-1 via an RGD/CSVTCG domain independent mechanism. *J Invest Dermatol* 1996; **106**: 215–20.

21 Lange-Asschenfeldt B, Weninger W, Velasco P *et al*. Increased and prolonged inflammation and angiogenesis in delayed-type hypersensitivity reactions elicited in the skin of thrombospondin-2-deficient mice. *Blood* 2002; **99**: 538–45.

22 Bonner JC. Regulation of PDGF and its receptors in fibrotic diseases. *Cytokine Growth Factor Rev* 2004; **15**: 255–73.

23 Steinhoff M, Buddenkotte J, Shpacovitch V *et al*. Proteinase-activated receptors: transducers of proteinase-mediated signaling in inflammation and immune response. *Endocr Rev* 2005; **26**: 1–43.

24 Ludwig RJ, Schultz JE, Boehncke WH *et al*. Activated, not resting, platelets increase leukocyte rolling in murine skin utilizing a distinct set of adhesion molecules. *J Invest Dermatol* 2004; **122**: 830–6.

25 Yang J, Furie BC, Furie B. The biology of P-selectin glycoprotein ligand-1: its role as a selectin counterreceptor in leukocyte-endothelial and leukocyte-platelet interaction. *Thromb Haemost* 1999; **81**: 1–7.

26 Anitua E, Andia I, Ardanza B *et al*. Autologous platelets as a source of proteins for healing and tissue regeneration. *Thromb Haemost* 2004; **91**: 4–15.

27 Martin P, Leibovich SJ. Inflammatory cells during wound repair: the good, the bad and the ugly. *Trends Cell Biol* 2005; **15**: 599–607.

28 Kasperska-Zajac A, Brzoza Z, Rogala B. Platelet function in cutaneous diseases. *Platelets* 2008; **19**: 317–21.

29 Michiels JJ. Platelet-mediated microvascular inflammation and thrombosis in thrombocythemia vera: a distinct aspirin-responsive arterial thrombophilia, which transforms into a bleeding diathesis at increasing platelet counts. *Pathol Biol (Paris)* 2003; **51**: 167–75.

Mediators of inflammation

The main role of the inflammatory response is the elimination of external noxious stimuli such as irritants, allergens and pathogens, or of endogenous stimuli such as toxic or infectious agents. There is also a necessity to avoid tissue disruption and cell destruction, and to restore tissue homeostasis. Balance between these potentially opposing requirements is achieved by generating a variety of inflammatory mediators, which may exert their effects in an autocrine, paracrine, juxtacrine or endocrine manner.

A wide variety of distinct mediators, including cytokines, phase proteins, kinins, prostanoids, leukotrienes, neuromediators, oxygen, nitrogen and carbon products, are involved in the orchestration of inflammation. Importantly, these mediators are not only released by leukocytes and lymphocytes, but also upon activation

during injury by almost any cell residing at the site of inflammation. The final outcome depends on the nature, severity and duration of the injurious stimuli, and reflects a cascade of well-tuned interactions between several mediators released by different cell types. Furthermore, the activation and up-regulation of specific receptors for each of these mediators is crucial for the outcome of any inflammatory reaction. Occasionally, some mediators can activate more than one receptor and, vice versa, some receptors can be activated by several ligands.

Acute-phase proteins

During the acute phase of inflammation, cytokines such as TNF-α, IL-1 and IL-6 rapidly stimulate the release of proteins from hepatocytes to coordinate tissue integrity. Acute-phase proteins (APPs) are defined as plasma proteins if their serum concentration increases by more than 25% after tissue destruction. They are released by the liver to opsonize pathogens, inhibit protease function and clear cell detritus. APPs such as CRP, mannan-binding lectin, complement proteins, fibrinogen, α_1-antitrypsin, α_1-antichymotrypsin, haptoglobin, serum amyloid A and acid α-glycoprotein may have several pro- or anti-inflammatory activities. Moreover, hormones (e.g. glucocorticoids) are capable of stimulating APP synthesis within hours.

CRP is an APP that can be detected in the serum during infection and tissue damage within 24–48 h. Because CRP correlates well with disease progression, it is a reliable activity marker for inflammatory or infectious processes. It binds phosphorylcholin of LPSs in the cell membrane of bacteria and fungi, activates the classical complement pathway [1], stimulates leukocyte chemokinesis and phagocytosis, and induces a spontaneous vasculitis [2]. It is proposed that one function of CRP is to mobilize cells rapidly to counteract infection, before specific antibody is formed.

Another APP that activates the complement pathway is mannan-binding lectin. Together with the pulmonary surfactant proteins, mannan-binding lectin belongs to the family of 'collectins' that contain a globular lectin-like domain which is able to bind the membrane of pathogens [3,4].

The classic complement pathway is initiated by CRP, heparin, protamine sulphate and DNA, and also by plasmin or trypsin action on C1s. The alternative pathway is initiated by bacterial and endogenous endotoxin and cell debris. Complement C5 is cleaved by leukocyte enzymes, particularly neutral proteases, neutrophil elastase and acidic protease cathepsin G [5]. Epidermal cells contain serine proteinases active at neutral pH, which appear to cleave C5, resulting in a greater neutrophilia than seen in similar tests with plasmin and trypsin [6]. C3 is activated by trypsin and neutrophil elastase. The processes of clotting, generation of kinins and fibrinolysis all activate complement. The pro-inflammatory properties of C5a, C3a and C4a on mast cells and basophils, as anaphylatoxins releasing cell mediators and, in the case of C5a, attracting and activating leukocytes, are described in Chapter 13.

Serum factors such as complement, DNase I, pentraxins (e.g. CRP) and IgM contribute to efficient opsonization and uptake of apoptotic and necrotic cells. Defects in these factors may impact the development of systemic lupus erythematosus (SLE) in humans and mice and may represent a central pathogenic process in the development and acceleration of SLE [7]. The status of acute phase proteins can be dramatically modified during cytokine therapy [8].

References

1 Osmand AP, Mortensen RF, Siegel J, Gewurz H. Interactions of C-reactive protein with the complement system. III. Complement-dependent passive hemolysis initiated by CRP. *J Exp Med* 1975; **142**: 1065–77.

2 Parish WE. Features of human spontaneous vasculitis reproduced experimentally in animals. Effects of antiglobulins, C-reactive protein and fibrin. Bayer Symposium. VI. *Experimental Models of Chronic Inflammatory Disease*. New York: Springer 1977: 117–51.

3 Spence JD, Norris J. Infection, inflammation, and atherosclerosis. *Stroke* 2003; **34**: 333–4.

4 Takahashi K, Gordon J, Liu H *et al.* Lack of mannose-binding lectin-A enhances survival in a mouse model of acute septic peritonitis. *Microbes Infect* 2002; **4**: 773–84.

5 Orr FW, Varani J, Kreutzer DL *et al*. Digestion of the fifth component of complement by leukocyte enzymes. Sequential generation of chemotactic activities for leukocytes and for tumor cells. *Am J Pathol* 1979; **94**: 75–83.

6 Lazarus GS, Farb RM, Thomas CA. Role of proteinases in cutaneous inflammation. In: Safai B, Good RA, eds. *Immunodermatology*. New York: Plenum Press 1981: 177–87.

7 Gaipl US, Kuhn A, Sheriff A *et al*. Clearance of apoptotic cells in human SLE. *Curr Dir Autoimmun* 2006; **9**: 173–87.

8 Asnis LA, Gaspari AA. Cutaneous reactions to recombinant cytokine therapy. *J Am Acad Dermatol* 1995; **33**: 393–410.

Cytokines

Cytokines are structurally related polypeptides or glycoproteins that exert their effects at concentrations within the pico- or nanomolar range. Originally, they were regarded as immunocompetent cell-derived immunomodulators. However, recent knowledge demonstrates that a clear-cut differentiation between cytokines, growth factors, neurotransmitters and hormones is not possible. The predominant role of cytokines is to mediate inflammatory and immune responses. Cytokines determine the direction of immune responses and control tissue integrity during injury. Thus, the quality and quantity of cytokine production within the injured tissue determines whether the immune system is directed into a humoral or cytotoxic cell-mediated allergic response. Moreover, cytokines (along with other mediators) determine the switch of the immune system from a pro- to an anti-inflammatory state.

Over the last decades, a large body of knowledge has accumulated on the role of cytokines in cutaneous inflammation. They are ultimately involved in all phases of inflammation. While pro-inflammatory cytokines induce the body response to external or internal danger, anti-inflammatory cytokines are capable of restoring tissue homeostasis by suppressing inflammatory processes. Various molecular biology and modern immunological techniques have been applied to cytokine research, and the genes for many of these factors have been cloned and characterized in the skin. Together, these studies clearly demonstrate that many cytokines exert pleiotropic functions. For example, IL-1 was originally described as a leukocytic pyrogen, endogenous pyrogen, B-cell-activating factor and lymphocyte-activating factor. Today it is well known that various skin cells, including keratinocytes, use IL-1 to communicate with neighbouring cells in the skin during inflammation [1]. Thus, the IL nomenclature was introduced to replace the older descriptive and often misleading names.

To understand fully the role of cytokines in skin inflammation, one has to collate information from human and animal studies as well as *in vitro* and *in vivo* data. The availability of recombinant cytokines and cytokine antagonists was of tremendous benefit in the verification of the specific effects of cytokines *in vivo*. Modern techniques, such as genomic and proteomic approaches, have given new insights into the regulatory mechanisms underlying the actions of cytokines. Moreover, the use of cytokine and cytokine receptor gene-deficient mice have helped in our understanding of the specific role of these molecules during cutaneous inflammation. It must be appreciated that *in vivo* a cocktail of several cytokines acts simultaneously or sequentially upon the inflammatory microenvironment. Thus, the biological activities of cytokines during inflammation are the sum of well-tuned synergistic and antagonistic processes.

Cytokines use different cell biological mechanisms to modulate inflammation. Some cytokines (e.g. IL-1, IL-2 or IL-4) exert their effects by exclusively binding to cell surface receptors. Others (e.g. TGF-β or IL-6) may additionally interact with components of the extracellular matrix to modulate skin function during inflammation.

Interleukins

Interleukins are polypeptides participating in all normal and reactive cell functions. So far, 35 interleukins have been described and characterized. Some prime cells, making them responsive to other agents, and most act in a synergistic way (see p. 12.28).

IL-1. The first cytokine detected in the skin was IL-1, originally named epidermal thymocyte-activating factor. Cytokines of the IL-1 family are key players in immunity and inflammation in virtually every organ of the body. Members of the IL-1 family discovered so far include IL-1α, IL-1β, IL-1 receptor antagonist (IL-1RA), IL-1H, IL-1F7b, IL-18 and IL-18-binding protein (BP). They may function as agonistic or antagonistic ligands for the members of the IL-1 receptor (IL-1R) family. IL-1 and IL-18 are structurally very closely related and both are synthesized as biologically inactive precursor molecules lacking a signal peptide. Almost all cells of the body, including keratinocytes, have been found to synthesize many of the IL-1 family members (see Table 12.2) upon stimulation. In some cells, such as macrophages, fibroblasts, endothelial and dendritic cells, IL-1 may also exist in a membrane-bound form.

The currently known 12 members of the IL-1R family are defined as membrane-spanning molecules that consist of at least one immunoglobulin-like domain exterior to the cell and, except for the IL-1RII, a Toll/IL-1R (TIR) domain in the cytoplasm. Type I IL-1R (IL-1R) binds both IL-1α and IL-1β. In addition, a homologue of the IL-1R, known as IL-1R accessory protein (AcP), which has no affinity on its own for either of the IL-1 forms, is required for IL-1 signalling. The second natural IL-1 binding protein is IL-1RII, which has a high affinity for IL-1α, but a much lower affinity for IL-1β or IL-1RA. IL-33 is a new member of the IL-1 family which exerts its effects in an autocrine and paracrine fashion, as does IL-1.

IL-1RI is expressed on keratinocytes, fibroblasts, endothelial cells, lymphocytes and other cells. IL-1RII can be detected on B lymphocytes and neutrophils. An endogenous soluble IL-1RA type I was found to act as a competitive IL-1R inhibitor. There is evidence of differences in responses mediated via each receptor. Cultured keratinocytes predominantly express mRNA for IL-1β, but *in vivo* in normal epidermis IL-1α is also detectable. IL-1 is present in the stratum granulosum, and considerable amounts have also been detected in psoriatic scales [1]. However, this is confined to IL-1β, which is functionally inactive, while active IL-1α is reduced [3].

IL-1 is a pro-inflammatory cytokine, stimulates repair and differentiation, and is an important mediator of immune regulation. It is mitogenic for thymocytes and T cells, induces IL-2 synthesis and receptor expression, proliferation and release of lymphokines (see Chapter 13). Furthermore, IL-1 is a growth factor for B cells, inducing proliferation and enhancing antibody formation, and it also increases NK cell activity. IL-1 also activates macrophages and neutrophils as well as the release of their enzymes, and induces prostaglandin synthesis.

It has been contended that, despite the large amounts of IL-1 being detected in epidermis, it is largely inactive and contributes little to the inflammatory response. Nevertheless, injection of keratinocyte IL-1 and recombinant IL-1 (rIL-1) into mice and rabbits induces oedema, erythema and neutrophil infiltration. There is also evidence that during wound healing, human keratinocyte IL-1 stimulates the synthesis of PGE_2 by subpopulations of human fibroblasts, which feeds back to result in the stimulation of keratinocyte proliferation and differentiation.

IL-1 is increased in the early phase of numerous skin diseases and induces the release of further cytokines and growth factors, and the recruitment of T lymphocytes, into the inflammatory tissue. IL-1 participates in the regulation of microvascular dermal endothelial cells by the up-regulation of cell adhesion molecules such as ICAM-1 or E-selectin. IL-1 also regulates the expression of ICAM-1 on keratinocytes, thus participating in the recruitment of lymphocytes into the epidermis, and activates IL-6 or NF-κB [3], which may be of considerable relevance in inflammatory dermatoses.

IL-1 is considered to be a key cytokine in the pathogenesis of autoimmune diseases such as pemphigus vulgaris. Increased levels of IL-1α and TNF-α have been detected in lesional skin of patients with pemphigus. Acantholysis of keratinocytes was found to be inhibited by antibodies directed against IL-1α and TNF-α. Furthermore, in IL-1-α and TNF-α receptor-deficient mice, a decreased susceptibility for pemphigus was observed. IL-1 also plays a crucial role by inducing keratinocyte apoptosis in pemphigus patients [4], and may be involved in vitiligo [5].

IL-2. IL-2, or T-cell growth factor, is an essential mediator for developing an immune response. Activated T lymphocytes secrete IL-2 and express IL-2 receptors, resulting in their proliferation and clonal expansion. IL-2 is also an important mediator for the proliferation of B lymphocytes and the activation of NK cells. Furthermore, IL-2 participates in the regulation of T-cell functions in Th1-mediated skin diseases such as psoriasis and cutaneous T-cell lymphoma [6–8]. The role of IL-2 in these diseases has recently been proven by the successful therapeutic use of specific anti-IL-2 strategies [7]. Another important regulator of memory

T-cell proliferation seems to be clofazimine, which inhibits Kv1.3 potassium channels, which has implications for the pathophysiology of autoimmune diseases and psoriasis [9]. Protein kinase C (PKC) isoforms (α, β, τ) play an essential role in the regulation of IL-2 expression levels. An oral PKC inhibitor (AEB071) blocked IL-2 mRNA expression and T-lymphocyte proliferation and achieved a significant decrease in the psoriasis severity score index, supporting the role of IL-2 and PKC in psoriasis [10].

IL-3. This belongs to the group of haematopoietic colony-stimulating factors (CSF), and promotes growth of T-cell lines and mast cells. It is synthesized by T lymphocytes, myeloid cell lines and keratinocytes. The IL-3 receptor (IL3R), like the IL-5R and the GM-CSFR, consists of two distinct chains of which the β-chain is identical for all three cytokine receptors. Although IL-3 has multi-CSF activity, in the skin it may activate both mast cells, contributing to fibrosis, as seen in scleroderma, and neutrophils, to release oxygen radicals cytotoxic for microorganisms. Moreover, monocyte proliferation, adherence to endothelium, secretion of IL-8 and the expression of LYVE-1 on lymphatic endothelial cells [11] is induced or enhanced by IL-3, as is eosinophil chemotaxis and phagocytosis [12,13]. IL-3 also regulates the activation status of human basophils [14]. Epidermal–dermal application of plasmid-encoded IL-3 by a gene gun resulted in enhanced infiltration of B cells, accumulation of dendritic cells, increase of TNF-α and IL-1β [15]. A ceramide derivate was able to inhibit skin inflammation and atopic dermatitis by suppressing IL-1 production [16].

IL-4. Originally named B-cell growth factor, IL-4 acts mainly on immunocompetent cells, and induces proliferation of activated mature T cells, and enhances T-cell cytotoxic properties, but suppresses cytokine formation by Th1 cells, thereby reducing delayed hypersensitivity responses. IL-4 stimulates MHC class II expression, and expression of the low-affinity IgE receptor (CD23) on B cells. IgE synthesis is regulated by IL-4 together with IL-13, and is inhibited by IFN-γ and TGF-β. Cytokines such as IL-2, IL-5, IL-6 and IL-9 synergize with IL-4 and IL-13 to enhance IgE production. On macrophages, however, IL-4 decreases CD23 expression. Mast cell growth is stimulated by IL-4, as is the growth of precursor haematopoietic cells, both directly and indirectly, by stimulating G-CSF and M-CSF production in monocytes. IL-4 is important for the differentiation towards a Th2 T-cell subtype. In contrast, cytokines such as IL-12, IL-18 and IL-23 inhibit the differentiation of IL-4-producing T cells. Although IL-4 is generated in high amounts by T cells, there is also evidence that IL-4 is released in the skin by keratinocytes or mast cells. The IL-4 receptor was detected on T and B cells, macrophages, dendritic cells, mast cells, fibroblasts and keratinocytes. IL-4 proved to be an essential mediator for the differentiation of dendritic cells [17]. *In vivo*, IL-4 has been found to mediate immunodeviation towards Th2 responses, and in preliminary studies has been successfully used for the treatment of Th1-mediated skin diseases such as psoriasis.

IL-5. IL-5, a helper T-cell lymphokine, induces growth and differentiation of activated B cells, and is a key mediator for the switching of immunoglobulin class synthesis. It is the most important promoter of eosinophil formation and differentiation. Mature eosinophils are activated and their survival is prolonged in parasitic infestations. IL-5 works synergistically with IL-3 and GM-CSF on eosinophils.

IL-6. This is mainly generated by monocytes, bone marrow cells, fibroblasts, endothelial cells, some T cells, B cells and keratinocytes [13]. IL-6 is involved in the regulation of the function of T, B and NK cells, which express both of the IL-6 receptor chains. It has an essential role in the maturation of B-cells, antibody production, and also participates in inflammation by inducing the formation of acute phase proteins (APP) by hepatocytes. In T cells, IL-6 mediates activation, growth and differentiation. Thus, IL-6 is an 'early' pro-inflammatory cytokine, which induces APP production, and the increased formation of IL-6 by fibroblasts, endothelial cells and keratinocytes stimulated by IL-1 and TNF-α may represent a significant amplifying process in inflammation [12,18]. Despite the finding of increased IL-6 serum levels in autoimmune diseases such as SLE, systemic scleroderma and pemphigus vulgaris, a specific role for IL-6 in any skin disease has not been established.

IL-7 and thymic stromal lymphopoietin (TSLP). IL-7, synthesized by monocytes and T cells, is a haematopoietic growth factor, stimulating T- and B-cell proliferation. Moreover, immune functions such as the proliferation of cytotoxic T and NK cells, as well as the activation of monocytes and macrophages, can be triggered by IL-7. Therefore, administration or neutralization of IL-7 may allow the modulation of immune functions in patients with lymphocyte depletion, tumours or autoimmune diseases [19].

Two different IL-7R have been characterized mainly on lymphoid and myeloid cells. There is evidence that mainly IL-7Rα but not IL-7Rβ expression is required for T-lymphocyte proliferation. Recently, an IL-7 like cytokine, TSLP, was described, which binds to a heterodimer consisting of the IL-7Rα chain and a common γ-like receptor chain also named TSLP receptor [20]. TSLP was found to be highly expressed in suprabasal keratinocytes from patients with inflammatory skin diseases such as atopic dermatitis. TSLP activates $CD11^+$ dendritic cells to migrate and to initiate a Th2 immune response [20,21]. TSLP activation is probably regulated synergistically by pro-inflammatory (TNF-α or IL-1α) and Th2 (IL-4 or IL-13) cytokines [22,23]. OX40 ligand was found to be the TSLP-induced molecule on dendritic cells that triggers inflammatory T(h)2 differentiation in the absence of IL-12. TSLP also regulates the innate phase of allergic immune responses through activating mast cells. Therefore, TSLP and OX40 ligand may be targets for therapeutic intervention in blockade of the initiation of allergic inflammatory responses [24].

IL-8. This is a member of the CXC subfamily of chemokines.

IL-9. This is produced by $CD4^+$ T lymphocytes and was originally described in the murine system as P40, T-cell growth factor III

(TCGF III) and mast cell growth enhancing activity (MEA). IL-9 is a growth factor for T-helper lymphocytes, mast cells and megakaryoblastic leukaemic cells, and stimulates the development of erythopoietic colonies as well as IL-4-induced IgE production by B lymphocytes. IL-9 transcripts have been detected in Hodgkin's lymphoma and large cell anaplastic lymphoma, suggesting a role for IL-9 in the pathogenesis of these tumours.

IL-10. This was originally described as a cytokine secreted by Th2 cells, which inhibits the release of cytokines from Th1 cells [25,26]. Later it was found that IL-10 can be synthesized by Th1 as well as Th2 lymphocytes, and also by cytotoxic T cells, mast cells, B cells and monocytes, the latter being the major source of IL-10 in humans [27]. There is now evidence for an IL-10 family of related cytokines, comprising different members of viral or cellular origin, including IL-19, IL-20, IL-22 (IL-10-related T-cell-derived inducible factor), IL-24 (melanoma differentiation-associated antigen 7) and IL-26 (AK155). The different receptors for the IL-10 family belong to the cytokine receptor family type 2, resulting, through the activation of signal transducer and activator of transcription (STAT) factors, in diverse biological effects [26].

IL-10 diminishes IFN-γ and IL-2 production by Th1 cells, as well as IL-4 and IL-5 generation by Th2 cells. IL-10 inhibits release of IL-1β, IL-6, IL-8, IL-12 and TNF-α in monocytes, as well as IFN-γ and TNF-α in NK cells. In monocytes or dendritic cells, IL-10 also down-regulates the expression and the release of MHC class II molecules, CD23, ICAM-I and the accessory B7 molecule. Thus, IL-10 is an important cytokine for the regulation of antigen presentation and suppression of Th1 as well as Th2 cytokine production.

The anti-inflammatory effect of IL-10 is a result of the inhibition of pro-inflammatory cytokines such as IL-1, IL-2, IL-6, TNF-α and IFN-γ, and the inhibition of chemokines (IL-8) and chemokine receptors such as CXC-2. In eosinophils, IL-10 inhibits eosinophil survival and IL-4-induced IgE synthesis, indicating an important role for this cytokine in allergic responses. In contrast, IL-10 activates the proliferation of, and immunoglobulin production by B cells. Thus, IL-10 is also a survival and differentiation factor for B cells. IL-10 contributes to inhibition of cellular and allergic immune responses while stimulating humoral and cytotoxic immune mechanisms [27].

Increased expression of IL-10 occurs in patients with allergic contact dermatitis [28], and IL-10-deficient mice show a delayed contact hypersensitivity immune response [29]. Stimulators of keratinocyte IL-10 synthesis include contact allergens and UVB light. The effect of IL-10 is mediated via a specific IL-10 receptor expressed on numerous skin cells. IL-10 has been proposed as a therapeutic target for the treatment of inflammatory diseases such as psoriasis, atopic dermatitis and asthma, and other autoimmune diseases [30,31].

IL-11. IL-11 stimulates precursor/progenitor haematopoietic blast cell mitosis, and synergizes with GM-CSF, IL-3 and IL-4. It also promotes an immunodeviation towards Th2, induces the formation of APPs by the liver, stimulates fibroblast functions, supports differentiation of lymphocytes but depresses differentiation of adipocytes, and inhibits abnormal keratinocyte differentiation. Accordingly, first clinical trials have shown that IL-11 appears to be effective in the treatment of psoriasis. Moreover, a role of IL-11 in tissue remodelling during severe asthma has been suggested [32].

IL-12. This cytokine is generated by monocytes, macrophages, dendritic cells, B cells, neutrophils, mast cells and keratinocytes. The active form is a heterodimer consisting of a p40 and a p35 subunit. Interestingly, homodimers and monomers of p40 serve as competitive antagonists by binding to the IL-12 receptor without activating the signal transduction cascade. There is now evidence for an IL-12 family of heterodimeric cytokines which share similar functions in innate as well as adaptive immunity but also have differentiated effects. Currently, the IL-12 family consists of five members, including IL-23, IL-27, cardiotrophin-like cytokine/soluble cyliary neutrotrophic factor receptor (CLC/sCNTFR) and CLC/cytokine-like factor 1 (CLC/CLF-1) [33].

IL-12 is an important activator of NK cells. It further increases IFN-γ production, modulates T-cell functions and inhibits tumour angiogenesis [34]. Stimulators of IL-12 secretion in skin include bacterial products or UV light. A protective effect of IL-12 on UV-induced DNA damage has been detected in keratinocytes [35].

IL-13. This is a cytokine with effects similar to IL-4, and was found to be released by T cells, mast cells and keratinocytes [36]. It affects the function of B cells as well as monocytes, and decreases production of pro-inflammatory cytokines in keratinocytes and endothelial cells. IL-13 also reduces chemokine-induced chemotaxis of T cells. IL-6 expression on monocytes is inhibited by both IL-4 and IL-13.

IL-14. IL-14 (high molecular weight [HMW], B-cell growth factor [BCGF]) is a cytokine implicated in the generation and maintenance of normal memory B cells. It is produced by malignant B cells and normal as well as malignant T cells [37].

IL-15. IL-15 shares many of the activities of IL-2 but is characterized by the use of a unique α-chain of its receptor. Both receptors use a common β- and γ-chain. The major sources of IL-15 are macrophages and epithelial cells, including keratinocytes and fibroblasts, whereas T cells do not express IL-15. Major stimuli for IL-15 production include IFN-α and -β. Like IL-2, IL-15 functions as a T-cell growth factor, is chemotactic for T cells, activates NK cells, stimulates B-cell growth as well as differentiation, and plays a role in the maturation of dendritic cells [38,39]. In human keratinocytes, IL-15 inhibits the anti-Fas and methylcellulose-induced apoptosis [40]. Because of its IFN-γ and IgE-synthesis-modulating function, a relevance in the pathophysiology of atopic dermatitis is attributed to IL-15.

IL-16. This is secreted from keratinocytes and Langerhans' cells amongst others, and is an important chemokine for the recruitment of $CD4^+$ T cells, monocytes, eosinophils and Langerhans' cells into inflamed skin. Serological levels of this cytokine correlate positively with the severity of atopic dermatitis [41].

IL-17. This is expressed by numerous immunocompetent cells. In keratinocytes, IL-17 initiates the release of growth-related oncogene-α (GRO-α), GM-CSF, IL-6 and the IFN-γ-induced expression of ICAM-1. In dermal endothelial cells, IL-17 induces IL-1 secretion and up-regulation of cell adhesion molecules. IL-17 activates skin fibroblasts [42] and results in increased IL-6 secretion and collagen synthesis. A pathophysiological role for IL-17 in systemic scleroderma has been proposed [43].

New evidence strongly supports the idea of an involvement of IL-17-producing T cells (TH_{17} T cells) in the pathophysiology of autoimmune diseases, psoriasis and contact dermatitis [44,45]. TH_{17} cells also express the hydrocarbon receptor which can be activated by dioxin derivates, linking TH_{17} T cells to environmental stimuli during immune responses and inflammation [46].

Although IL-17F is highly homologous to IL-17A and binds the same receptor, their functional roles are different. IL-17F plays only a marginal role in the development of delayed-type and contact hypersensitivities, autoimmune encephalomyelitis, and arthritis. Both IL-17F and IL-17A are involved in host defence against mucoepithelial infection by *Staphylococcus aureus* and *Citrobacter rodentium*. IL-17A is produced mainly in T cells, whereas IL-17F is produced in T cells, innate immune cells, and epithelial cells. Although only IL-17A efficiently induces cytokines in macrophages, both cytokines activated epithelial innate immune responses [47].

IL-18. The production of IL-18 has been described in dendritic cells, macrophages, keratinocytes, osteoblasts, microglia cells and fibroblasts, and IL-18 mRNA expression can be stimulated by LPS, GM-CSF and Fas ligand. IL-18 is also synthesized by human keratinocytes and was found be significantly up-regulated in inflammatory skin diseases. The receptor for IL-18 is expressed by keratinocytes, which implies an autocrine regulation by IL-18 [48]. Functional IL-18 requires activation by an IL-18 converting enzyme (ICE or caspase-1) or proteinase-3 [49].

Together with IL-12, IL-18 significantly stimulates the production of IFN-γ. IL-18 also induces the maturation of T cells and NK cells, and stimulates the release of cytokines and chemokines. It increases Fas-mediated NK-cell cytotoxicity, induces IgE production by B cells and synergizes with IL-2 to enhance IL-4 production. However, the effects of IL-18 on T cells seem to vary, dependent on endogenous and exogenous factors such as the maturation state and the micromilieu. In basophils, IL-18 contributes to IL-4 and IL-13 production and in macrophages IL-18 induces the production of cytokines such as IL-6 and IFN-γ, TNF-α and IL-1β. Moreover, IL-18 stimulates the synthesis of IL-6, IL-8, ICAM-1 and matrix metalloproteinases by endothelial cells.

IL-18 binds to a unique heterodimer receptor which is up-regulated by IL-12. IL-18-binding protein (IL-18BP) is a secreted protein able to bind IL-18 with high affinity, leading to inhibition of IL-18-induced IFN-γ and IL-8 production and NF-κB activation. Recently, another secreted protein, IL-1H, was observed also to have IL-18R antagonist activity.

In the skin, IL-18 modulates the migration of Langerhans' cells, the activity of T-helper cells and wound healing [50]. IL-18 also regulates ICAM-1 expression on microvascular endothelial cells, indicating a role in leukocyte–endothelial interactions during inflammation. The pathophysiological relevance of IL-18 for diseases such as atopic dermatitis [49] is currently debated. Enhanced expression of IL-18 was found in patients with lupus erythematosus and psoriasis. Finally, IL-18 also seems to be an important regulator during host defence in infections by viruses, bacteria, fungi and protozoa.

IL-19. This is a member of the IL-10 family that is released by monocytes and macrophages upon stimulation by LPS and GM-CSF. It can also be released by B cells. IL-19 exerts its effects by stimulating the receptors of IL-20 or IL-22.

IL-20. IL-20 shares a distinctive homology with IL-10, and is expressed in the skin and trachea. Overexpression of IL-20 in transgenic mice causes skin lesions similar to those of psoriasis. Two putative receptors for IL-20 were identified on keratinocytes. Moreover, IL-20 receptors are highly expressed in psoriatic skin, further providing evidence for a role of this cytokine in the disease [51].

IL-21. IL-21 is a new member of the type I cytokine superfamily which is mainly produced by activated T cells and has close structural similarities with IL-15, IL-2 and IL-4. It has a unique receptor chain, IL-21R, that pairs with the common γ-chain. The multiple biological functions of IL-21 include activation of NK cells, T cells and B cells, and it has also been found to inhibit the activation and maturation of dendritic cells [52].

IL-22. This IL-10-related, T-cell-derived inducible factor is synthesized by $CD4^+$ T and mast cells amongst others, and can be stimulated by IL-9 and LPS [51]. The IL-22 receptor has also been detected in the skin. There are two soluble IL-22 receptor antagonists (IL-22RA1 and -RA2). The IL-22RA2 is expressed by immunocompetent cells as well as epithelial cells. In contrast to other members of the IL-10 family of cytokines, IL-22 mediates acute-phase responses in inflamed tissue and hepatocytes.

IL-23. This cytokine is structurally closely related to other mediators such as IL-6, G-CSF and IL-12. Transgenic mice overexpressing IL-23 show an intense inflammatory infiltrate of lymphocytes and macrophages in numerous organs including the skin [53]. There is also evidence that IL-23, by increasing the number of Langerhans' cells with a more mature phenotype, enhances cutaneous immunity [33].

IL-24. IL-24 (melanoma differentiation-associated antigen 7) is a member of the IL-10 cytokine family, which is generated by Th2 cells in an IL-4 inducible manner. It is also produced by differentiated melanoma cells and LPS-stimulated monocytes. IL-24 has been shown to inhibit the proliferation of tumour cells, including melanoma, via the induction of apoptosis.

IL-25. Two new members of the IL-17 cytokine family, IL-17F and IL-25, have recently been described. IL-25 is produced by Th2 cells as well as mast cells, and by inducing the production of IL-4, IL-5 and IL-13 is capable of amplifying allergic-type inflammatory responses [54].

IL-26. IL-26 (AK155) is generated by monocytes and various T-cell types, and is involved in the transformed phenotype of human T cells after infection by herpes virus [55,56].

Our knowledge of its receptor expression, signalling mechanisms, biological effects and relevance to diseases is scant.

IL-27. This is a member of the IL-12 family of heterodimeric cytokines [57]. As an early product of activated antigen-presenting cells, IL-27 is able to induce the clonal expansion of naive $CD4^+$ T-cells. It synergistically with IL-12 induces the production of IFN-γ by Th1 and NK cells. IL-27 probably binds to the orphan-receptor WSX-1/TCCR belonging to the IL-6/IL-12 receptor family, identified as the IL-27R [58]. IL-27 is probably important for the proliferation and activation of naïve T cells [33].

IL-28 and IL-29. Three cytokines designated IL-28A, IL-28B and IL-29 [59] are induced by viral infection and are distantly related to type I interferons and the IL-10 family because of their antiviral activity. IL-28 and IL-29 bind to a heterodimeric class II cytokine receptor, consisting of IL-10Rβ, and an orphan class II receptor chain IL-28Rα.

IL-31. This has been found to be expressed mainly by Th2 lymphocytes. The IL-31 receptor (IL-31R) complex is composed of a heterodimer including the IL-31 RA and the oncostatin Mβ receptor (OSMRβ). Dimerization of IL-31RA and OSMRβ leads to IL-31-induced signalling (calcium, STAT3) in keratinocytes, macrophages and sensory neurones, suggesting a role in adaptive and innate immunity as well as neurogenic inflammation [60–62]. IL-31 is involved in inflammatory processes in the skin, gastrointestinal tract and lung [63]. Investigations in mice overexpressing IL-31 revealed this cytokine to be critically involved in dermatitis and pruritus [64]. Genetic and immunological studies support this also to be true for human skin, especially in atopic dermatitis and prurigo nodularis [65].

IL-32. IL-32 induces various cytokines/chemokines such as TNF-α, IL-8 and MIP-2. It activates the NF-κB and p38 mitogen-activated protein kinase pathway which is involved in inflammatory responses. IL-32 mRNA is highly abundant in immune tissue compared with other tissues. IL-32 can be induced in human peripheral lymphocyte cells after mitogen stimulation, in human epithelial cells by IFNγ, and in NK cells after exposure to the combination of IL-12 plus IL-18. IL-32 has been shown to play a role in viral infections and Wegener's granulomatosis, by interacting with neutrophil-derived proteinase-3 and proteinase-activated receptor-2; it may be involved in inflammatory, infectious and autoimmune diseases [66–69].

IL-33. IL-33 belongs to the IL-1-like cytokine family, and activates mast cells, Th2 lymphocytes and fibroblastic reticular cells of lymphoid tissues. It induces the production of Th2-associated cytokines such as IL-4, IL-5 and IL-13. IL-33 can activate immune cells in an autocrine or paracrine fashion. Of note, IL-33 is also a nuclear factor (NF-HEV) which is abundantly expressed in high endothelial venules from lymphoid organs, thereby acting as a nuclear transcriptional regulator. In the skin, IL-33 is also expressed in dermal endothelial cells and keratinocytes. It is abundantly expressed by skin vascular tumours. Thus, IL-33 receptor may act as a 'danger signal' receptor on keratinocytes, endothelial cells, T cells and mast cells during inflammation, trauma and infection [70,71].

IL-34. This is a novel cytokine which regulates monocytes via activation of an IL-34 receptor (known as macrophage colony-stimulating factor, M-CSF), followed by ERK1/2 activation [72].

IL-35. IL-35 is a heterodimeric novel cytokine of the IL-12 family, consisting of Ebi3 (Epstein–Barr virus induced gene-3) and IL-12α /p35. IL-35 is produced by specific subtypes of murine regulatory T cells (Tregs) and suppresses T-cell proliferation, making it a novel cytokine regulating adaptive immune responses during inflammation, autoimmune diseases and transplantation in mice [73]. This may not apply to humans, in which the role of IL-35 remains to be elucidated [74].

References

1 Camp RD, Fincham NJ, Cunningham FM *et al*. Psoriatic skin lesions contain biologically active amounts of an interleukin 1-like compound. *J Immunol* 1986; **137**: 3469–74.

2 O'Shea JJ, Murray PJ. Cytokine signaling modules in inflammatory responses. *Immunity* 2008; **28**: 477–87.

3 Abeyama K, Eng W, Jester JV *et al*. A role for NF-kappaB-dependent gene transactivation in sunburn. *J Clin Invest* 2000; **105**: 1751–9.

4 Rodrigues DB, Pereira SA, dos Reis MA *et al*. *In situ* detection of inflammatory cytokines and apoptosis in pemphigus foliaceus patients. *Arch Pathol Lab Med* 2009; **133**: 97–100.

5 Pehlivan S, Ozkinay F, Alper S *et al*. Association between IL4 (-590), ACE (I)/(D), CCR5 (Delta32), CTLA4 (+49) and IL1-RN (VNTR in intron 2) gene polymorphisms and vitiligo. *Eur J Dermatol* 2009; **19**: 126–8.

6 Jain S, Kaur IR, Das S *et al*. T helper 1 to T helper 2 shift in cytokine expression: an autoregulatory process in superantigen-associated psoriasis progression? *J Med Microbiol* 2009; **58**: 180–4.

7 Austin LM, Ozawa M, Kikuchi T *et al*. The majority of epidermal T cells in psoriasis vulgaris lesions can produce type 1 cytokines, interferon-gamma, interleukin-2, and tumor necrosis factor-alpha, defining TC1 (cytotoxic T lymphocyte) and TH1 effector populations: a type 1 differentiation bias is also measured in circulating blood T cells in psoriatic patients. *J Invest Dermatol* 1999; **113**: 752–9.

8 Saleh MN, LeMaistre CF, Kuzel TM *et al*. Antitumor activity of DAB389IL-2 fusion toxin in mycosis fungoides. *J Am Acad Dermatol* 1998; **39**: 63–73.

9 Ren YR, Pan F, Parvez S *et al*. Clofazimine inhibits human Kv1.3 potassium channel by perturbing calcium oscillation in T lymphocytes. *PLoS ONE* 2008; **3**: e4009.

10 Skvara H, Dawid M, Kleyn E *et al*. The PKC inhibitor AEB071 may be a therapeutic option for psoriasis. *J Clin Invest* 2008; **118**: 3151–9.

11 Groger M, Niederleithner H, Kerjaschki D, Petzelbauer P. A previously unknown dermal blood vessel phenotype in skin inflammation. *J Invest Dermatol* 2007; **127**: 2893–900.

12 Linker-Israeli M, Deans RJ, Wallace DJ *et al*. Elevated levels of endogenous IL-6 in systemic lupus erythematosus. A putative role in pathogenesis. *J Immunol* 1991; **147**: 117–23.

13 Turksen K, Kupper T, Degenstein L *et al*. Interleukin 6: insights to its function in skin by overexpression in transgenic mice. *Proc Natl Acad Sci U S A* 1992; **89**: 5068–72.

14 Lourenco FD, Azor MH, Santos JC *et al*. Activated status of basophils in chronic urticaria leads to interleukin-3 hyper-responsiveness and enhancement of histamine release induced by anti-IgE stimulus. *Br J Dermatol* 2008; **158**: 979–86.

15 Matthews K, Rhind SM, Gossner AG *et al*. The effects of gene gun delivered pIL-3 adjuvant on skin pathology and cytokine expression. *Vet Immunol Immunopathol* 2007; **119**: 233–42.

16 Kang JS, Lee CW, Lee K *et al.* Inhibition of skin inflammation and atopic dermatitis by topical application of a novel ceramide derivative, K112PC-5, in mice. *Arch Pharm Res* 2008; **31**: 1004–9.

17 Romani N, Gruner S, Brang D *et al.* Proliferating dendritic cell progenitors in human blood. *J Exp Med* 1994; **180**: 83–93.

18 Neuner P, Urbanski A, Trautinger F *et al.* Increased IL-6 production by monocytes and keratinocytes in patients with psoriasis. *J Invest Dermatol* 1991; **97**: 27–33.

19 Fry TJ, Mackall CL. Interleukin-7: from bench to clinic. *Blood* 2002; **99**: 3892–904.

20 Liu YJ. Thymic stromal lymphopoietin: master switch for allergic inflammation. *J Exp Med* 2006; **203**: 269–73.

21 Soumelis V, Reche PA, Kanzler H *et al.* Human epithelial cells trigger dendritic cell mediated allergic inflammation by producing TSLP. *Nat Immunol* 2002; **3**: 673–80.

22 Bogiatzi SI, Fernandez I, Bichet JC *et al.* Cutting edge: proinflammatory and Th2 cytokines synergize to induce thymic stromal lymphopoietin production by human skin keratinocytes. *J Immunol* 2007; **178**: 3373–7.

23 Soumelis V, Liu YJ. Human thymic stromal lymphopoietin: a novel epithelial cell-derived cytokine and a potential key player in the induction of allergic inflammation. *Springer Semin Immunopathol* 2004; **25**: 325–33.

24 Liu YJ. Thymic stromal lymphopoietin and OX40 ligand pathway in the initiation of dendritic cell-mediated allergic inflammation. *J Allergy Clin Immunol* 2007; **120**: 238–44; quiz 45–6.

25 Enk AH, Saloga J, Becker D *et al.* Induction of hapten-specific tolerance by interleukin 10 in vivo. *J Exp Med* 1994; **179**: 1397–402.

26 Fickenscher H, Hor S, Kupers H *et al*. The interleukin-10 family of cytokines. *Trends Immunol* 2002; **23**: 89–96.

27 Borish LC, Steinke JW. 2. Cytokines and chemokines. *J Allergy Clin Immunol* 2003; **111**: S460–75.

28 Nickoloff BJ, Fivenson DP, Kunkel SL *et al*. Keratinocyte interleukin-10 expression is upregulated in tape-stripped skin, poison ivy dermatitis, and Sezary syndrome, but not in psoriatic plaques. *Clin Immunol Immunopathol* 1994; **73**: 63–8.

29 Berg DJ, Leach MW, Kuhn R *et al.* Interleukin 10 but not interleukin 4 is a natural suppressant of cutaneous inflammatory responses. *J Exp Med* 1995; **182**: 99–108.

30 Asadullah K, Docke WD, Sabat RV *et al*. The treatment of psoriasis with IL-10: rationale and review of the first clinical trials. *Expert Opin Investig Drugs* 2000; **9**: 95–102.

31 Asadullah K, Sterry W, Volk HD. Interleukin-10 therapy—review of a new approach. *Pharmacol Rev* 2003; **55**: 241–69.

32 Zheng T, Zhu Z, Wang J *et al*. IL-11: insights in asthma from overexpression transgenic modeling. *J Allergy Clin Immunol* 2001; **108**: 489–96.

33 Trinchieri G, Pflanz S, Kastelein RA. The IL-12 family of heterodimeric cytokines: new players in the regulation of T cell responses. *Immunity* 2003; **19**: 641–4.

34 Lamont AG, Adorini L. IL-12: a key cytokine in immune regulation. *Immunol Today* 1996; **17**: 214–7.

35 Schwarz A, Stander S, Berneburg M *et al.* Interleukin-12 suppresses ultraviolet radiation-induced apoptosis by inducing DNA repair. *Nat Cell Biol* 2002; **4**: 26–31.

36 Obara W, Kawa Y, Ra C *et al*. T cells and mast cells as a major source of interleukin-13 in atopic dermatitis. *Dermatology* 2002; **205**: 11–7.

37 Ford R, Tamayo A, Martin B *et al.* Identification of B-cell growth factors (interleukin-14; high molecular weight-B-cell growth factors) in effusion fluids from patients with aggressive B-cell lymphomas. *Blood* 1995; **86**: 283–93.

38 Lodolce J, Burkett P, Koka R *et al.* Interleukin-15 and the regulation of lymphoid homeostasis. *Mol Immunol* 2002; **39**: 537–44.

39 Mohamadzadeh M, Knop J, Aliani S, Cruz PD Jr. Cytokine expression and antigen-presenting capacity of 4F7+ dendritic cells derived from dermis, spleen, and lymph nodes. *Arch Dermatol Res* 1997; **289**: 435–9.

40 Ruckert R, Asadullah K, Seifert M *et al.* Inhibition of keratinocyte apoptosis by IL-15: a new parameter in the pathogenesis of psoriasis? *J Immunol* 2000; **165**: 2240–50.

41 Frezzolini A, Paradisi M, Zaffiro A *et al.* Circulating interleukin 16 (IL-16) in children with atopic/eczema dermatitis syndrome (AEDS): a novel serological marker of disease activity. *Allergy* 2002; **57**: 815–20.

42 Katz Y, Nadiv O, Rapoport MJ, Loos M. IL-17 regulates gene expression and protein synthesis of the complement system, C3 and factor B, in skin fibroblasts. *Clin Exp Immunol* 2000; **120**: 22–9.

43 Kurasawa K, Hirose K, Sano H *et al.* Increased interleukin-17 production in patients with systemic sclerosis. *Arthritis Rheum* 2000; **43**: 2455–63.

44 Larsen JM, Bonefeld CM, Poulsen SS *et al*. IL-23 and T(H)17-mediated inflammation in human allergic contact dermatitis. *J Allergy Clin Immunol* 2009; **123**: 486–92.

45 Zhu B, Symonds AL, Martin JE *et al.* Early growth response gene 2 (Egr-2) controls the self-tolerance of T cells and prevents the development of lupuslike autoimmune disease. *J Exp Med* 2008; **205**: 2295–307.

46 Veldhoen M, Hirota K, Westendorf AM *et al.* The aryl hydrocarbon receptor links TH17-cell-mediated autoimmunity to environmental toxins. *Nature* 2008; **453**: 106–9.

47 Ishigame H, Kakuta S, Nagai T *et al.* Differential roles of interleukin-17A and -17F in host defense against mucoepithelial bacterial infection and allergic responses. *Immunity* 2009; **30**: 108–19.

48 Koizumi H, Sato-Matsumura KC, Nakamura H *et al.* Distribution of IL-18 and IL-18 receptor in human skin: various forms of IL-18 are produced in keratinocytes. *Arch Dermatol Res* 2001; **293**: 325–33.

49 Gracie JA, Robertson SE, McInnes IB. Interleukin-18. *J Leukoc Biol* 2003; **73**: 213–24.

50 Steinhoff M, Brzoska T, Luger TA. Keratinocytes in epidermal immune responses. *Curr Opin Allergy Clin Immunol* 2001; **1**: 469–76.

51 Xie MH, Aggarwal S, Ho WH *et al.* Interleukin (IL)-22, a novel human cytokine that signals through the interferon receptor-related proteins CRF2-4 and IL-22R. *J Biol Chem* 2000; **275**: 31335–9.

52 Parrish-Novak J, Foster DC, Holly RD, Clegg CH. Interleukin-21 and the IL-21 receptor: novel effectors of NK and T cell responses. *J Leukoc Biol* 2002; **72**: 856–63.

53 Wiekowski MT, Leach MW, Evans EW *et al.* Ubiquitous transgenic expression of the IL-23 subunit p19 induces multiorgan inflammation, runting, infertility, and premature death. *J Immunol* 2001; **166**: 7563–70.

54 Hurst SD, Muchamuel T, Gorman DM *et al.* New IL-17 family members promote Th1 or Th2 responses in the lung: in vivo function of the novel cytokine IL-25. *J Immunol* 2002; **169**: 443–53.

55 Conti P, Kempuraj D, Frydas S *et al.* IL-10 subfamily members: IL-19, IL-20, IL-22, IL-24 and IL-26. *Immunol Lett* 2003; **88**: 171–4.

56 Knappe A, Hor S, Wittmann S, Fickenscher H. Induction of a novel cellular homolog of interleukin-10, AK155, by transformation of T lymphocytes with herpesvirus saimiri. *J Virol* 2000; **74**: 3881–7.

57 Pflanz S, Timans JC, Cheung J *et al.* IL-27, a heterodimeric cytokine composed of EBI3 and p28 protein, induces proliferation of naive CD4(+) T cells. *Immunity* 2002; **16**: 779–90.

58 Chen Q, Ghilardi N, Wang H *et al.* Development of Th1-type immune responses requires the type I cytokine receptor TCCR. *Nature* 2000; **407**: 916–20.

59 Sheppard P, Kindsvogel W, Xu W *et al.* IL-28, IL-29 and their class II cytokine receptor IL-28R. *Nat Immunol* 2003; **4**: 63–8.

60 Cevikbas F, Steinhoff A, Homey B, Steinhoff M. Neuroimmune interactions in allergic skin diseases. *Curr Opin Allergy Clin Immunol* 2007; **7**: 365–73.

61 Dillon SR, Sprecher C, Hammond A *et al.* Interleukin 31, a cytokine produced by activated T cells, induces dermatitis in mice. *Nat Immunol* 2004; **5**: 752–60.

62 Sonkoly E, Muller A, Lauerma AI *et al.* IL-31: a new link between T cells and pruritus in atopic skin inflammation. *J Allergy Clin Immunol* 2006; **117**: 411–7.

63 Zhang Q, Putheti P, Zhou Q *et al*. Structures and biological functions of IL-31 and IL-31 receptors. *Cytokine Growth Factor Rev* 2008; **19**: 347–56.

64 Grimstad O, Sawanobori Y, Vestergaard C *et al.* Anti-interleukin-31-antibodies ameliorate scratching behaviour in NC/Nga mice: a model of atopic dermatitis. *Exp Dermatol* 2009; **18**: 35–43.

65 Bilsborough J, Leung DY, Maurer M *et al.* IL-31 is associated with cutaneous lymphocyte antigen-positive skin homing T cells in patients with atopic dermatitis. *J Allergy Clin Immunol* 2006; **117**: 418–25.

66 Cagnard N, Letourneur F, Essabbani A *et al.* Interleukin-32, CCL2, PF4F1 and GFD10 are the only cytokine/chemokine genes differentially expressed by *in vitro* cultured rheumatoid and osteoarthritis fibroblast-like synoviocytes. *Eur Cytokine Netw* 2005; **16**: 289–92.

67 Csernok E, Holle JU, Gross WL. Proteinase 3, protease-activated receptor-2 and interleukin-32: linking innate and autoimmunity in Wegener's granulomatosis. *Clin Exp Rheumatol* 2008; **26**: S112–7.
68 Kim SH, Han SY, Azam T *et al*. Interleukin-32: a cytokine and inducer of TNF-alpha. *Immunity* 2005; **22**: 131–42.
69 Netea MG, Lewis EC, Azam T *et al*. Interleukin-32 induces the differentiation of monocytes into macrophage-like cells. *Proc Natl Acad Sci U S A* 2008; **105**: 3515–20.
70 Kakkar R, Lee RT. The IL-33/ST2 pathway: therapeutic target and novel biomarker. *Nat Rev Drug Discov* 2008; **7**: 827–40.
71 Moussion C, Ortega N, Girard JP. The IL-1-like cytokine IL-33 is constitutively expressed in the nucleus of endothelial cells and epithelial cells *in vivo*: a novel 'alarmin'? *PLoS ONE* 2008; **3**: e3331.
72 Lin H, Lee E, Hestir K *et al*. Discovery of a cytokine and its receptor by functional screening of the extracellular proteome. *Science* 2008; **320**: 807–11.
73 Collison LW, Workman CJ, Kuo TT *et al*. The inhibitory cytokine IL-35 contributes to regulatory T-cell function. *Nature* 2007; **450**: 566–9.
74 Bardel E, Larousserie F, Charlot-Rabiega P *et al*. Human CD4+ CD25+ Foxp3+ regulatory T cells do not constitutively express IL-35. *J Immunol* 2008; **181**: 6898–905.

Interferons

Interferons (IFNs) were originally described as factors that 'interfere' with the replication of virus replication. They comprise a family of cytokines thought to be critical to the defence against cancer cells and viral infections. Moreover, IFNs are key regulatory agents with many activities in normal tissue physiology, inflammation and the immune responses, enhancing or depressing the activities of other cytokines.

IFN-α and IFN-β are rapidly released after viral infections upon stimulation by double-stranded RNA. In contrast, IFN-γ is induced indirectly during the inflammatory response against pathogens, but also contributes to host defence. The major cellular sources of IFN-α are macrophages and B cells, whereas IFN-β is produced by fibroblasts and IFN-γ is synthesized by activated T cells. A further member of the type I interferon family is defined as IFN-κ [1]. It induces the release of several cytokines from monocytes and dendritic cells, and inhibits IL-12 release from monocytes. The synthesis of IFN-κ is induced by IFN-γ in monocytes as well as dendritic cells. It also can be detected in these cells in lesional skin of atopic dermatitis and psoriasis.

The IFNs have specific receptors and different properties, which may act in a synergistic or antagonistic fashion. IFN-α and IFN-β exert their effects by inhibiting virus replication in host cells. Additionally, via binding to IFN receptors, both molecules not only affect infected cells, but also activate defence mechanisms in neighbouring 'healthy' cells in a paracrine manner. Activation of the receptor by IFN-α and IFN-β leads to the induction of intracellular signalling pathways involved in inflammation and host defence. For example, IFN-α and IFN-β activate STATs, P1-kinase and Mx-protein, all factors that increase the resistance of cells to viral replication [2].

IFN-γ alone induces the formation of MHC class II molecule HLA-DR on membranes of monocytes and keratinocytes [3–5], while IFN-α and IFN-β up-regulate expression of the MHC class I antigens on many cell types. This leads to optimal antigen presentation to cells of the adaptive immune system such as T cells. IFNs activate NK-cell activity, leading to the successful killing of infected cells. In contrast, IFNs save non-infected cells from destruction by NK cells by inducing MHC class I molecules on these cells. In addition, IFN-γ stimulates the activity of a proteinase, cathepsin S [6]. The release of VEGF is induced in keratinocytes and suppressed in fibroblasts by IFN-γ indicating that this cytokine is involved in the regulation of angiogenesis [7].

IFN-γ also augments monocyte secretion of TNF-α and TNF-β, which contribute to the antiviral and antiproliferative properties of IFNs [8], and increases the expression of IL-2R and ligand binding on human leukaemic and normal lymphocytes [9]. The IFNs augment activity of NK lymphocytes and macrophages [10], and stimulate macrophage synthesis of arachidonic acid products [11]. IFN-α may also stimulate the formation of IgG and IgM by B cells [12]. Thus, interferons directly function as important mediators of both the innate and the adaptive immune responses.

In inflammatory skin diseases such as atopic dermatitis, a beneficial effect of IFN-γ treatment has been reported. In mice, mast cells appear to contribute to the regulation of IFN-γ in the inflamed skin [13]. INF-γ has been implicated in autoimmune diseases such as lupus erythematosus; overexpression of IFN-γ in the epidermis leads to SLE-like skin alterations [14].

The pro-inflammatory effects of keratinocyte activation by IFN-γ can be inhibited by regulatory molecules defined as suppressors of cytokine signalling (SOCS). SOCS1, SOCS2 and SOCS3 proteins are up-regulated in the epidermis of psoriasis and allergic contact dermatitis but not in atopic dermatitis patients [15]. They exert multiple anti-inflammatory effects on keratinocytes, such as down-regulation of HLA-DR, ICAM-1, IP-10 and MCP-1.

Interferons are also involved in the response to infections, injury or exogenous triggering, such as UV-light leading to inflammation. Cells of the innate immune system activate adaptive immunity by means of multiple immunostimulatory cytokines including IFNs. IFNs can also induce specialized dendritic cells (DCs) expressing the tryptophan-catabolizing enzyme indoleamine (IDO), which confers potent T-cell suppressor activity. DCs also promote differentiation of naïve CD4 T cells into regulatory T cells (Tregs), and stimulate mature Tregs to acquire potent suppressor activity. pDCs up-regulate IDO by means of a mechanism that depends on cell-autonomous IFN type I signalling in response to CD80/86 (B7.1/2).

In summary, interferons not only act as antiviral agents but are also important mediators of inflammatory and immune responses within the skin.

References

1 Nardelli B, Zaritskaya L, Semenuk M *et al*. Regulatory effect of IFN-kappa, a novel type I IFN, on cytokine production by cells of the innate immune system. *J Immunol* 2002; **169**: 4822–30.
2 Janeway CA, Travers P, Walport M, Shlomchik M. *Immunobiology*, 5th edn. New York: Taylor & Francis Inc., 2001.
3 Basham TY, Nickoloff BJ, Merigan TC, Morhenn VB. Recombinant gamma interferon induces HLA-DR expression on cultured human keratinocytes. *J Invest Dermatol* 1984; **83**: 88–90.
4 Kaplan G, Witmer MD, Nath I *et al*. Influence of delayed immune reactions on human epidermal keratinocytes. *Proc Natl Acad Sci U S A* 1986; **83**: 3469–73.
5 Kelley VE, Fiers W, Strom TB. Cloned human interferon-gamma, but not interferon-beta or -alpha, induces expression of HLA-DR determinants by fetal monocytes and myeloid leukemic cell lines. *J Immunol* 1984; **132**: 240–5.
6 Schwarz G, Boehncke WH, Braun M *et al*. Cathepsin S activity is detectable in human keratinocytes and is selectively upregulated upon stimulation with interferon-gamma. *J Invest Dermatol* 2002; **119**: 44–9.

7 Trompezinski S, Denis A, Schmitt D, Viac J. IL-10 is unable to downregulate VEGF expression in human activated keratinocytes. *Arch Dermatol Res* 2002; **294**: 377–9.
8 Nedwin GE, Svedersky LP, Bringman TS *et al*. Effect of interleukin 2, interferon-gamma, and mitogens on the production of tumor necrosis factors alpha and beta. *J Immunol* 1985; **135**: 2492–7.
9 Herrmann F, Cannistra SA, Levine H, Griffin JD. Expression of interleukin 2 receptors and binding of interleukin 2 by gamma interferon-induced human leukemic and normal monocytic cells. *J Exp Med* 1985; **162**: 1111–6.
10 Herberman RB, Ortaldo JR, Djeu JY *et al.* Role of interferon in regulation of cytotoxicity by natural killer cells and macrophages. *Ann N Y Acad Sci* 1980; **350**: 63–71.
11 Boraschi D, Censini S, Bartalini M, Tagliabue A. Regulation of arachidonic acid metabolism in macrophages by immune and nonimmune interferons. *J Immunol* 1985; **135**: 502–5.
12 Rodriguez MA, Prinz WA, Sibbitt WL *et al*. Alpha-interferon increases immunoglobulin production in cultured human mononuclear leukocytes. *J Immunol* 1983; **130**: 1215–9.
13 Alenius H, Laouini D, Woodward A *et al.* Mast cells regulate IFN-gamma expression in the skin and circulating IgE levels in allergen-induced skin inflammation. *J Allergy Clin Immunol* 2002; **109**: 106–13.
14 Sasseville D, Ghamdi WA, Khenaizan SA. Interferon-induced cutaneous necrosis. *J Cutan Med Surg* 1999; **3**: 320–3.
15 Federici M, Giustizieri ML, Scarponi C *et al*. Impaired IFN-gamma-dependent inflammatory responses in human keratinocytes overexpressing the suppressor of cytokine signaling 1. *J Immunol* 2002; **169**: 434–42.

Tumour necrosis factor

Tumour necrosis factor (TNF), also defined as cachectin or endogenous pyrogen, is a protein of approximately 17 kDa that exists in a secreted and transmembrane form, and builds dimers or trimers after being released [1]. It is secreted by monocytes and macrophages, mast cells, fibroblasts, smooth muscle cells, endothelial cells, keratinocytes, T cells and certain NK cells. It has multiple pro- as well as anti-inflammatory activities, and is also a growth factor in normal physiological regeneration and wound healing [2,3]. Upon stimulation by exogenous factors such as bacterial LPS, staphylococcal toxin, viruses and other organisms, or by endogenous mediators such as C5a, IL-1, IL-2, GM-CSF, substance P, bradykinin and TNF itself, large amounts are released within minutes, and the synthesis is rapidly increased. The rate of synthesis is controlled by IFN-γ [4], but several other cytokines may antagonize and influence further release (e.g. TGF-β, IL-6, PGE_2 or vitamin D_3). TNF-α is activated after processing at the cell membrane by a transmembrane enzyme, TNF-α converting enzyme.

Three types of TNF receptors have been identified: TNF-R1 (CD 120a, p55) and TNF-R2 (CD 120b, p75), which are expressed by almost all cells and bind both TNF-α and TNF-β; and TNF-R3 which is only synthesized by human hepatocytes and which binds TNF-α. Each receptor appears to mediate different cellular responses [5]. TNF receptors also belong to the superfamily of death receptors which are able to induce apoptosis (e.g. in keratinocytes and leukocytes during cutaneous inflammation).

The soluble forms of the receptors, released from cell membranes, neutralize both forms of TNF, thereby preventing systemic effects resulting from local inflammation [6]. The soluble receptors occur in the blood and urine of normal persons, and were found to be markedly increased during various inflammatory disorders and sepsis [6–8]. TNF-binding proteins (TBPs) are also capable of regulating TNF function after release into the extracellular space.

TNF has many biological properties, similar to those of IL-1, which synergistically may enhance TNF activity. It induces septic shock and fever [9], cachexia [10] and is a potent mediator of inflammation, increasing macrophage and neutrophil chemotaxis, phagocytosis, cytotoxicity and respiratory burst activity [11–16]. The protective role of TNF is supported by the observation that mice that lack the gene for TNF do not develop septic arthritis but otherwise are lacking an efficient defence against systemic infection [17]. Thus, an important role of TNF is to protect tissues by localizing inflammation. On the other hand, once infection becomes systemic, TNF may have deleterious effects leading to sepsis and shock [16]. Some of these effects may be aggravated by the TNF being able to stimulate synthesis of many other cytokines and mediators, including IL-1, GM-CSF, PDGF, TGF-β, prostaglandins and leukotrienes.

In the skin, TNF-α has been found to exert numerous effects. Toxins, haptens as well as UV light are potent inducers of TNF-α release from keratinocytes. TNF receptors are involved in the regulation of keratinocyte apoptosis [18]. TNF-α also induces intense expression of ICAM-1 in keratinocytes. Via activation of NF-κB and C/EBPβ TNF-α regulates the synthesis of cytoskeletal proteins participating in epidermal responses to inflammation or wound healing. In contrast to its tissue-damaging properties, TNF is also a growth factor, stimulating fibroblast proliferation and synthesis, and exhibits synergy with EGF, by increasing the EGF receptor, PDGF and insulin [2].

In endothelial cells, TNF promotes leukocyte adherence by increasing the expression of E-selectin, ICAM-1 and VCAM, probably via activation of the transcription factor NF-κB. TNF-α is also a potent activator of neutrophils, leading to the regulation of cell recruitment, chemotaxis, degranulation and release of cytokines and oxidative burst mediators. TNF-α has been identified as one of the cytokines required for the maturation of DC and therefore also plays a role in the initiation of an immune response. The pathophysiological relevance of TNF-α has been demonstrated in various models of infection, inflammation and autoimmune disease [19,20]. This is further supported by the successful use of biologics targeting TNF-α for the treatment of T-cell mediated skin diseases such as psoriasis [21,22]. Moreover, diseases associated with mutations within the TNF-receptor type I have been described. Thus, the TNF-receptor-associated periodic syndrome (TRAPS) is a rare hereditary disease characterized by prolonged periodic fever attacks and severe, localized inflammatory reactions [23].

The observation that TNF-α appeared to be a crucial protein in many skin diseases, including psoriasis, led to novel therapeutic strategies aimed at blocking TNF-α function and/or TNF-α receptor activation. Several different agents that neutralize the pro-inflammatory cytokine TNF-α such as a humanized antibody (infliximab), a full human antibody (adalimumab) and a protein containing the TNF-α receptor (TNFαRII) fused with a humanized immunoglobulin fragment (etanercept) are available for the treatment of inflammatory diseases, with psoriasis or psoriatic arthritis as an approved indication in addition to rheumatoid arthritis and Crohn's disease. A pegylated form of a recombinant soluble human TNF-α receptor is currently under investigation (pegsunercept). By contrast, patients have developed atopic dermatitis

lesions after infliximab therapy. TNF-α does not appear to play an essential role in the pathophysiology of atopic dermatitis or even ameliorate this disease, but TNF-α blockers do seem to be beneficial in the treatment of psoriasis, lichen planus and forms of panniculitis.

References

1 Borish LC, Steinke JW. 2. Cytokines and chemokines. *J Allergy Clin Immunol* 2003; **111**: S460–75.
2 Balkwill FR. Tumour necrosis factor. *Br Med Bull* 1989; **45**: 389–400.
3 Tracey KJ, Vlassara H, Cerami A. Cachectin/tumour necrosis factor. *Lancet* 1989; **1**: 1122–6.
4 Beutler B, Tkacenko V, Milsark I *et al*. Effect of gamma interferon on cachectin expression by mononuclear phagocytes. Reversal of the lpsd (endotoxin resistance) phenotype. *J Exp Med* 1986; **164**: 1791–6.
5 Vilcek J, Lee TH. Tumor necrosis factor. New insights into the molecular mechanisms of its multiple actions. *J Biol Chem* 1991; **266**: 7313–6.
6 Van Zee KJ, Kohno T, Fischer E *et al*. Tumor necrosis factor soluble receptors circulate during experimental and clinical inflammation and can protect against excessive tumor necrosis factor alpha in vitro and in vivo. *Proc Natl Acad Sci U S A* 1992; **89**: 4845–9.
7 Aderka D, Wysenbeek A, Engelmann H *et al*. Correlation between serum levels of soluble tumor necrosis factor receptor and disease activity in systemic lupus erythematosus. *Arthritis Rheum* 1993; **36**: 1111–20.
8 Digel W, Porzsolt F, Schmid M *et al*. High levels of circulating soluble receptors for tumor necrosis factor in hairy cell leukemia and type B chronic lymphocytic leukemia. *J Clin Invest* 1992; **89**: 1690–3.
9 Tracey KJ, Beutler B, Lowry SF *et al*. Shock and tissue injury induced by recombinant human cachectin. *Science* 1986; **234**: 470–4.
10 Tracey KJ, Wei H, Manogue KR *et al*. Cachectin/tumor necrosis factor induces cachexia, anemia, and inflammation. *J Exp Med* 1988; **167**: 1211–27.
11 Beutler B, Cerami A. The biology of cachectin/TNF—a primary mediator of the host response. *Annu Rev Immunol* 1989; **7**: 625–55.
12 Djeu JY, Blanchard DK, Richards AL, Friedman H. Tumor necrosis factor induction by *Candida albicans* from human natural killer cells and monocytes. *J Immunol* 1988; **141**: 4047–52.
13 Perez C, Albert I, DeFay K *et al*. A nonsecretable cell surface mutant of tumor necrosis factor (TNF) kills by cell-to-cell contact. *Cell* 1990; **63**: 251–8.
14 Shalaby MR, Aggarwal BB, Rinderknecht E *et al*. Activation of human polymorphonuclear neutrophil functions by interferon-gamma and tumor necrosis factors. *J Immunol* 1985; **135**: 2069–73.
15 Tartaglia LA, Goeddel DV. Two TNF receptors. *Immunol Today* 1992; **13**: 151–3.
16 Tracey KJ, Fong Y, Hesse DG *et al*. Anti-cachectin/TNF monoclonal antibodies prevent septic shock during lethal bacteraemia. *Nature* 1987; **330**: 662–4.
17 Hultgren O, Eugster HP, Sedgwick JD *et al*. TNF/lymphotoxin-alpha double-mutant mice resist septic arthritis but display increased mortality in response to *Staphylococcus aureus*. *J Immunol* 1998; **161**: 5937–42.
18 Wakugawa M, Nakamura K, Akatsuka M *et al*. Interferon-gamma-induced RANTES production by human keratinocytes is enhanced by IL-1beta, TNF-alpha, IL-4 and IL-13 and is inhibited by dexamethasone and tacrolimus. *Dermatology* 2001; **202**: 239–45.
19 Nakayama T, Fujisawa R, Yamada H *et al*. Inducible expression of a CC chemokine liver- and activation-regulated chemokine (LARC)/macrophage inflammatory protein (MIP)-3 alpha/CCL20 by epidermal keratinocytes and its role in atopic dermatitis. *Int Immunol* 2001; **13**: 95–103.
20 Vestergaard C, Bang K, Gesser B *et al*. A Th2 chemokine, TARC, produced by keratinocytes may recruit CLA+CCR4+ lymphocytes into lesional atopic dermatitis skin. *J Invest Dermatol* 2000; **115**: 640–6.
21 Gottlieb AB. Infliximab for psoriasis. *J Am Acad Dermatol* 2003; **49**: S112–7.
22 Leonardi CL, Powers JL, Matheson RT *et al*. Etanercept as monotherapy in patients with psoriasis. *N Engl J Med* 2003; **349**: 2014–22.
23 Hentgen V, Reinert P. TNF receptor-associated periodic syndrome (TRAPS): clinical aspects and physiopathology of a rare familial disease. *Arch Pediatr* 2003; **10**: 45–53.

Cytokine suppressors and inhibitors

In addition to pro-inflammatory cytokines, certain cytokines including IL-1RA, TGF-β and members of the IL-10 family exert potent anti-inflammatory effects. The physical state of cytokines in body fluids has rarely been determined. Detection of a cytokine by immunological techniques allows only conclusions concerning its presence, but not about its potential activity. The cytokine may be coupled to another molecule that prevents binding to the specific receptor. Coupling may occur as: (i) dissociable complexes with a protective lipoprotein that releases the cytokine to react with its receptor; (ii) firmly bound complexes of cytokine and a carrier protein that interferes with receptor linkage [1,2]; or (iii) complexes of cytokine with its specific soluble receptor that blocks interaction with cell receptors [3].

Anti-inflammatory cytokines exert their effects by:

1 Regulation of cytokine secretion
2 Regulation of cytokine receptor expression
3 Receptor competition
4 Soluble binding factors and/or inhibitors
5 Regulation of proteases that activate the cytokine pro-form (converting enzymes).

This has led to novel therapeutic strategies in inflammatory and allergic diseases.

IL-1RA and IL-18RA

Two types of specific blocking agent for IL-1 activity have been identified. The first is a soluble receptor without a transmembrane structure that binds to free IL-1, inactivating its binding site. The second, IL-1 receptor antagonist (IL-1RA), is an inactive IL-1 homologue that blocks receptor sites on cells. IL-1RA is normally secreted during inflammatory reactions. Its production and release is modulated by many cytokines such as IL-4, IL-6, IL-13 or TGF-β. The important function of IL-1 RA is to potentially inhibit the deleterious effects of IL-1 during inflammation. Keratinocytes, fibroblasts and monocytes are also capable of generating an intracellular form of IL-1RA, the function of which is not understood [3].

IL-1α or IL-1β activity normally follows binding of the cytokine to the IL-1R type I receptor on all responding cells [4]. Other cells, such as B cells and neutrophils, express another IL-1R, the IL-1R type II [5]. It has been suggested that the IL-1RII can be shed from the cell surface and bind with free IL-1, thus ultimately blocking its ability to couple to cell-bound IL-R1. An alternative inhibitory molecule is an inactive homologue of IL-1, IL-1RA, which binds to cellular receptors without inducing a signal. The inert homologue therefore blocks the receptor, and subsequently prevents later binding of active IL-1 [6–9]. This type of antagonist is peculiar to IL-1. It is secreted mainly by monocytes and macrophages, but also by neutrophils and fibroblasts. It has been designated secreted interleukin-1 receptor antagonist (sIL-1RA).

Both the IL-1α and the IL-18 precursor require cleavage into an active mature molecule by an intracellular cysteine protease called IL-1α converting enzyme (ICE), also known as capsase-1. Thus ICE inhibitors may limit the activity of IL-1α as well as IL-18. IL-1RA is a physiological antagonist which has a similar structure to IL-1α as well as IL-β, and thus competes with the binding of the natural ligand to the receptor. IL-18BP is a naturally occurring

antagonist which is able to bind IL-18 with high affinity and to neutralize its activity, but not that of IL-1. Another IL-18 antagonist, IL-1H, has sequence homology with IL-1RA and binds the IL-18R but not the IL-1R. IL-1F7b shares sequence homology with IL-18, and binds the IL-18Rα but has no IL-18-like agonistic or antagonistic activity. IL-F7b binds to IL-18BP and subsequently may block the IL-18Rα, which ultimately results in the inhibition of IL-18 activity.

A non-receptor soluble protein that may function as a protective carrier protein or inhibitory substance is α_2M [10]; it is a carrier for IL-1, IL-6 and PDGF [11,12], but inactivates IL-2 and FGF [10]. Other soluble inhibitors, mainly against IL-1, have been found in the medium of UV-exposed keratinocyte cultures, and in the sera of UV-exposed mice and humans. The identity of this substance, and a related epidermal cell contra-IL-1, which blocks the activity of IL-1, is still to be determined [13].

TGF-β

TGF-β belongs to a family of peptides involved in growth and differentiation in almost all cells. It is involved in the regulation of fibroblasts and keratinocytes, as well as extracellular matrix proteins, in pathophysiological processes such as fibrosis, wound healing and scar formation. TGF-β is crucial to the transformation of fibroblasts into myofibroblasts, thereby promoting fibrosis.

Within the immune system, TGF-β is a potent anti-inflammatory molecule. It down-regulates the function of T cells, B cells, monocytes and NK cells. T cells undergoing apoptosis release TGF-β, leading to immunosuppressive effects in the inflammatory micromilieu [12]. TGF-β also diminishes mast cell function by inhibiting mast cell proliferation and IgE synthesis. TGF-β reduces the synthesis of IL-1 and IL-2. TGF-β, secreted in an inactive form, can bind weakly after exposure to acid pH in wound fluid to epidermal growth factor receptor (EGFR) on keratinocytes and endothelium, and compete with the stimulating molecules EGF and TGF-β thereby reducing keratinocyte and endothelial proliferation.

It is also critically involved in T-cell regulation and thus adaptive immunity. Furin cleaves TGF-β, thereby down-regulating the function of regulatory and effector T cells. Thus, furin might activate immune responses, and may result in a breakdown in peripheral tolerance [14].

IL-10 family of cytokines

Because of their similarity to IL-10 function, interleukins IL-10, IL-19, IL-20, IL-22, IL-24 and IL-26 have been grouped together as the IL-10 family. IL-28 and IL-29 share similarities to both type I interferons and IL-10 cytokines. Their function and role during inflammation and immune response are as described above.

References

1 Honda M, Chan C, Shevach EM. Characterization and partial purification of a specific interleukin 2 inhibitor. *J Immunol* 1985; **135**: 1834–9.

2 Larrick JW. Native interleukin 1 inhibitors. *Immunol Today* 1989; **10**: 61–6.

3 Fernandez-Botran R. Soluble cytokine receptors: their role in immunoregulation. *FASEB J* 1991; **5**: 2567–74.

4 Sims JE, Gayle MA, Slack JL *et al*. Interleukin 1 signaling occurs exclusively via the type I receptor. *Proc Natl Acad Sci U S A* 1993; **90**: 6155–9.

5 Dinarello CA. Interleukin-1 and interleukin-1 antagonism. *Blood* 1991; **77**: 1627–52.

6 Dripps DJ, Brandhuber BJ, Thompson RC, Eisenberg SP. Interleukin-1 (IL-1) receptor antagonist binds to the 80-kDa IL-1 receptor but does not initiate IL-1 signal transduction. *J Biol Chem* 1991; **266**: 10331–6.

7 Granowitz EV, Clark BD, Mancilla J, Dinarello CA. Interleukin-1 receptor antagonist competitively inhibits the binding of interleukin-1 to the type II interleukin-1 receptor. *J Biol Chem* 1991; **266**: 14147–50.

8 Hannum CH, Wilcox CJ, Arend WP *et al*. Interleukin-1 receptor antagonist activity of a human interleukin-1 inhibitor. *Nature* 1990; **343**: 336–40.

9 Kupper TS, Groves RW. The interleukin-1 axis and cutaneous inflammation. *J Invest Dermatol* 1995; **105**: 62S–6S.

10 James K. Interactions between cytokines and alpha 2-macroglobulin. *Immunol Today* 1990; **11**: 163–6.

11 Borth W, Luger TA. Identification of alpha 2-macroglobulin as a cytokine binding plasma protein. Binding of interleukin-1 beta to 'F' alpha 2-macroglobulin. *J Biol Chem* 1989; **264**: 5818–25.

12 Chen W, Frank ME, Jin W, Wahl SM. TGF-beta released by apoptotic T cells contributes to an immunosuppressive milieu. *Immunity* 2001; **14**: 715–25.

13 Krutmann J, Schwarz T, Kirnbauer R *et al*. Epidermal cell-contra-interleukin 1 inhibits human accessory cell function by specifically blocking interleukin 1 activity. *Photochem Photobiol* 1990; **52**: 783–8.

14 Li XH, Simon AE. *In vivo* accumulation of a turnip crinkle virus defective interfering RNA is affected by alterations in size and sequence. *J Virol* 1991; **65**: 4582–90.

Chemokines

Chemokines constitute a large family of soluble chemotactic cytokines with four conserved cysteines linked by disulphide bonds. Four subfamilies, CXC, CC, CX3C and C chemokines, are distinguished according to the position of the first two cysteines. More than 40 chemokines have been defined and characterized (Table 12.7). Most chemokine genes encode for proteins of approximately 90–125 amino acids. The different chemokine subfamilies are clustered on different chromosomes [1].

The main characteristic of chemokines is their potential to activate and attract leukocytes to the site of inflammation. Thus, chemokines have a pivotal role during inflammation and immunity. Interestingly, while CXC chemokines mainly attract neutrophils and lymphocytes, CC chemokines are capable of attracting monocytes, eosinophils, basophils and lymphocytes, but not neutrophils.

The classic role of chemokines is to attract leukocytes to the site of inflammation. For instance, $CD34^+$ dendritic cells (DCs) express ligands for chemokine receptors such as CCR1, CCR5, CCR6, CXCR4 or CCR9 to enter the target tissue. After maturation in epithelial tissues such as the epidermis, DCs change their phenotype by up-regulating CCR7, to traffic to lymph nodes [2]. In the skin, specific chemokines such as CCL27 attract a special subset of memory T cells normally expressing a cutaneous lymphocyte-associated antigen (CLA) which selectively traffics these cells to the skin. The CLA protein seems to be crucial for T-cell interaction with the endothelium, the extracellular matrix and other cell types in the skin [3].

In addition to attracting leukocytes, chemokines may also modulate leukocyte–endothelial interactions. They promote transendothelial emigration by supporting the binding of cell adhesion molecules with integrins (e.g. linkage of VCAM with α4β1 integrin on monocytes, eosinophils and basophils) or the binding of L-selectin to E-selectin on neutrophils. CC chemokines such as RANTES and MIP-1α may also induce the synthesis and release of inflammatory mediators such as histamine or leukotrienes from basophils [4–6].

Table 12.7 Nomenclature for human chemokines. (From Keystone Chemokine Conference, Keystone, CO, USA, January 18–23, 1999.)

Systematic name	Human ligand	Mouse ligand	Chemokine receptor(s)
CC chemokine/receptor family			
CCL1	I-309	TCA-3, P500	CCR8
CCL2	MCP-1, MCAF	MCP-1, JE	CCR2
CCL3	MIP-1α, LD78α, LD78β, AT464.1, AT464.2, GOS19-1, GOS19-2	MIP-1α	CCR1, CCR5
CCL4	MIP-1β, AT744.1, AT744.2, Act-2, G-26, HC21, H400, LAG-1	MIP-1β	CCR5
CCL5	RANTES	RANTES	CCR1, CCR3, CCR5
CCL6	Unknown	C10, MRP-1	Unknown
CCL7	MCP-3	NC28, FIC, MARC	CCR1, CCR2, CCR3
CCL8	MCP-2, HC14	MCP-2	CCR2, CCR3
CCL9, CCL10	Unknown	MRP-2, CCF18, MIP-1γ	Unknown
CCL11	Eotaxin	Eotaxin	CCR3
CCL12	Unknown	MCP-5	CCR2
CCL13	MCP-4, NCC-1, CKβ-10	Unknown	CCR2, CCR3
CCL14	HCC-1, HCC-3, NCC-2	Unknown	CCR1
CCL15	HCC-2, MIP-1δ, NCC-3, MIP-5, LKN-1	Unknown	CCR1, CCR3
CCL16	HCC-4, NCC-4, LEC, LMC	LCC-1	CCR1
CCL17	TARC, dendrokine	TARC	CCR4
CCL18	DC-Ck1, PARC, MIP-4, AMAC-1	Unknown	Unknown
CCL19	MIP-3β, ELC, exodus-3, CKβ-11	MIP-3β	CCR7
CCL20	MIP-3α, LARC, exodus-1	MIP-3α	CCR6
CCL21	6Ckine, SLC, exodus-2, TCA-4	6Ckine	CCR7
CCL22	MDC, STCP-1, DCtacin-β	ABCD-1	CCR4
CCL23	MPIF-1, MIP-3, CKβ8, CKβ8–1	Unknown	CCR1
CCL24	Eotaxin-2, MPIF-2, CKβ-6	Unknown	CCR3
CCL25	TECK	TECK	CCR9 (GPR9-6)
CCL26	Eotaxin-3	Unknown	CCR3
CCL27	CTACK/ALP	CTACK, ALP	Unknown
CXC chemokine/receptor family			
CXCL1	GRO-1, GROα, MGSA-α	GRO (KC)	CXCR2 > CXCR1
CXCL2	GRO2, GROβ, MIP2α, MGSA-β	GRO (KC)	CXCR2
CXCL3	GRO3, GROγ, MIP-2β	GRO (KC)	CXCR2
CXCL4	PF4	PF4var1, PF4alt	Unknown
CXCL5	ENA-78	LIX	CXCR2
CXCL6	GCP-2	CKα-3	CXCR1, CXCR2
CXCL7	NAP-2	Unknown	CXCR2
CXCL8	IL-8, MDNCF, NAP-1, NCF	Unknown	CXCR1, CXCR2
CXCL9	Mig, Humig	Mig	CXCR3
CXCL10	IP-10	crg-2, mob-1	CXCR3
CXCL11	I-TAC, H174, b-R1	Unknown	CXCR3
CXCL12	SDF-1α, SDF-1β, PBSF	SDF-1α/β	CXCR4
CXCL13	BLC, BCA-1	BLR1L, Angie	CXCR5
CXCL14	BRAK/bolekine	BRAK	Unknown
CXCL15	Unknown	Lungkine	Unknown
XC chemokine/receptor family			
XCL1	Lymphotactin, SCM-1α, ATAC	Lymphotactin	XCR1
XCL2	SCM-1β		XCR1
CX3C chemokine/receptor			
CX3CL1	Fractalkine, neurotactin	Fractalkine	CX3CR1

MDC, macrophage-derived chemokine; TARC, thymus and activation-regulated chemokine.

The effects of chemokines are mediated via binding and activating heptahelical G protein-coupled receptors. Chemokine activation instantly leads to rearrangement of the cell cytoskeleton, and activation of intracellular second messengers and integrins. Chemokine activation in neutrophils or monocytes results in the generation of inflammatory agents such as lipid mediators, NO, prostaglandins, amines, proteases and oxygen radicals [7].

Besides their specific ligand–receptor interaction, chemokines may also adhere to extracellular matrix proteins and the apical surface of endothelial cells. This appears to be crucial for the

migration of leukocytes to sites of inflammation. For example, CXCL8 and CCL19 attach to the endothelial cell surface, thereby stimulating transmigration [8]. In contrast, glycosaminoglycans such as heparan sulphate are capable of inactivating chemokine effects on endothelial cells [9].

Chemokine receptors are expressed by numerous cell types and modulate not only inflammation, but also embryogenesis and innate as well as adaptive immune responses. Chemokine receptors have been implicated in the pathophysiology of several diseases such as HIV infection, malaria, psoriasis and wound healing [10]. Moreover, viruses such as herpesvirus and poxvirus encode for chemokine receptors, thereby entering their hosts, indicating an important role for chemokines in certain infectious diseases [11].

CC chemokines

The CC-chemokine family currently comprises 28 members. Therefore, only those with a strong relation to skin inflammation will be briefly described here.

RANTES (CCL5). RANTES, an acronym for regulated upon activation, normal T cell expressed and secreted, is chemotactic for basophils, eosinophils, lymphocytes and monocytes. It induces granule release and leukotriene synthesis in basophils and eosinophils, and histamine release from basophils. The activity is enhanced by priming with IL-5. It is formed by macrophages, fibroblasts and T cells. RANTES is one of the more potent chemokines in inflammation and allergy, and is believed to be an important mediator of tissue eosinophilia. RANTES mRNA has been detected in skin of atopic subjects 6 h after challenge by antigen, and the secreted protein is present in atopic dermatitis skin scales [12].

Macrophage inflammatory protein 1a (CCL3). This is formed by monocytes, fibroblasts, activated T and B cells, and attracts monocytes, lymphocytes, basophils and eosinophils. When bound to endothelial cells, it is reported to increase binding of $CD8^+$ T cells. In mice, it releases histamine from mast cells and basophils, but histamine release from human basophils is little above control amounts.

Macrophage inflammatory protein 1b (CCL4). This is closely related to the α-form and shares many of its properties. It has been reported to increase the adhesion to endothelium of $CD8^+$ or $CD4^+$ T cells, via α4β1 integrin–VECAM binding.

Monocyte chemotactic proteins. MCPs are chemotactic for T cells, DCs and NK cells. They are also potent attractants of monocytes and modulate the expression of adhesion molecules. MCP-2 and MCP-3 (CCL7 and CCL8) also attract eosinophils, whereas MCP-1 (CCL2) and MCP-3 attract basophils, and induce histamine release and synthesis of LTC_4. Recently, MCP-2 has been reported to be as potent as MCP-3 in activating eosinophils and basophils [13]. These proteins contribute to leukocyte infiltration of damaged tissue, possibly especially in atopic disorders. Antibodies against MCP-1 rendered animals less susceptible to delayed-type hypersensitivity, indicating that they may provide a potential therapeutic strategy for the treatment of allergic reactions in the skin.

Eotaxin (CCL11). Eotaxin, a potent chemokine for eosinophils [14], has more than 50% amino acid homology MCP. It has been detected in the epithelium of nasal polyps and possibly contributes to the eosinophilia of allergic inflammation. Eotaxin attracts T cells and eosinophils to the skin in patients with atopic dermatitis. In eotaxin-deficient mice, allergen-induced attraction of eosinophils seems to be impaired; this effect, however, appears to be compensated for by other chemokines at later stages [15].

CCL18. CCL18 is constitutively present at high levels in human plasma and probably contributes to the physiological homing of lymphocytes and DC, as well as to the generation of primary immune responses. Increased CCL18 production is observed in several diseases, including inflammatory skin, joint and lung diseases or malignant tumours [16].

CCL27. This is a skin-associated CC chemokine member that binds the receptor CCR10 with high affinity. CCL27–CCR10 interactions are critical for skin-homing CLA-bearing memory T cells [17,18]. Data suggest that CCL27 directly contributes to cutaneous inflammation. For example, patients with psoriasis, atopic dermatitis and contact dermatitis express CCR10 on $CD4^+$ T cells, fibroblasts and endothelial cells. Intracutaneous application of CCL27 was found to attract lymphocytes into the skin [19].

CXC chemokines

IL-8. Among the 16 members of the CXC chemokine family, IL-8 was the first chemokine to be defined and is the most potent mediator for attracting neutrophils. IL-8 binds to and activates CXCR-1 and CXCR-2. CXCR-1 (IL-8R1) is exclusively activated by IL-8, while CXCR2 (IL-8R2) can also be activated by GRO-α (CXCL1), GRO-β (CXCL2), GRO-γ (CXCL3), NAP-2 (CXCL7), ENA-78 (CXCL5) and GCP-2 (CXCL6).

GRO-α (CXCL1). This product of a growth-regulated gene, which also has melanoma growth-stimulating activity (MGSA), attracts and activates neutrophils. It is formed by monocytes, fibroblasts, platelets, endothelial cells and melanoma cells. Increased amounts occur in psoriatic scales, together with IL-8 [20].

NAP-2 (CXCL7). This is a product cleaved from a basic protein derived from platelet granules. It attracts neutrophils, and induces influx of calcium ions, degranulation and the respiratory burst [21].

Interferon-inducible protein 10 (CXCL10). IP-10 is induced by IFN in monocytes, activated T cells, fibroblasts, endothelial cells and keratinocytes. It also attracts monocytes and T cells and promotes T-cell binding to endothelium; it may contribute to the cell changes of delayed hypersensitivity [22].

Epithelial neutrophil activating peptide 78 (CXCL5). ENA-78 attracts and activates neutrophils, resulting in the release of their granules and mediators. It is synthesized by platelets, type II alveolar epithelial cells stimulated by IL-1, as well as neutrophils, monocytes, endothelial cells, and vascular smooth-muscle cells stimulated by IL-1 or LPs. ENA-78 also has been detected in

lungs infiltrated by neutrophils in adult respiratory distress, and increased amounts are found in the sera of patients with rheumatoid arthritis [23].

Chemokine receptors

So far, five CXC receptor subtypes have been defined. Most receptors can be activated by more than one chemokine, and several chemokines bind to more than one receptor. Thus, a high variability can be observed following chemokine release leading to receptor redundancy which makes CRs relatively inaccessible to therapeutic intervention [1,10,16].

The first chemokine receptors for IL-8, defined as CXCR1 and CXCR2, are expressed by T cells, activated eosinophils, mast cells, basophils and dendritic cells, suggesting a role for IL-8 during acute inflammation and innate immunity. Both CXCR1 and CXCR2 can be activated by IL-2. CXCR1 appears to be the dominant receptor for chemotaxis, phospholipase D production and superoxide generation after IL-8 or NAP-2 activation. CXCR2 mediates neutrophil chemotaxis in response to low-concentration NAP-2 and GRO-α. Interestingly, human herpesvirus (HHV) and HHV8 both express functional CXCR2 receptors, although the significance of this remains unclear [24]. CXCR3 is a receptor for T-cell activation. It binds I-TAC (CXCL11), Mig (CXCL9) and IP-10 (CXCL10). CXCR3 is expressed mainly by Th1 cells and $CD45RO^+$ memory T cells. Interestingly, in sarcoidosis, virtually all T cells express CXCR3. CXCR4 has been detected on most hematopoietic cells such as B cells, dendritic cells, Langerhans' cells, macrophages and T cells. Moreover, CXCR4 has also been identified as an HIV virus co-receptor, in that the glycoprotein gp120 from the HIV envelope binds to CXCR4 in the presence of CD4 [25]. However, CD4 independent association of gp120 to CXCR4 has also been shown. Thus, CXCR4 may be involved in HIV infection and HIV neurotoxicity. CXCR5 is a B-cell chemokine receptor. After T-cell activation, CXCR5 is up-regulated on memory and/or effector T cells via the chemokine BCA-1 (CXCL13), suggesting a role in T–B cell interaction.

CCR1. This is a receptor for several chemokines such as MIP-1α, RANTES, MCP-2, MCP-3, MIP-5, MPIF-1 (CCL23) and HCC-1 (CCL14). MIP-1β and MCP-1 are also weak agonists. CCR1 is expressed by T cells, especially memory $CD45RO^+$ T cells. CCR1 knockout mice do not acquire spontaneous infections, but they exhibit increased mortality when infected with *Aspergillus fumigatus*, indicating a role for CCR1 in neutrophil-mediated diseases [26]. This receptor also appears to regulate granuloma formation and the Th1–Th2 cytokine balance. Data indicate that CCR1 is a receptor that can modulate inflammatory responses either positively or negatively, depending on the microenvironment.

CCR2. This is a leukocyte MCP-1 receptor expressed by monocytes, dendritic cells, NK cells and T cells, B cells and basophils. Mice lacking CCR2 develop normally but do not recruit macrophages in an experimental inflammation model. They fail to clear infections, have smaller granulomas and show defective recruitment of monocytes–macrophages to the site of inflammation. These results indicate a role for CCR2 in macrophage functions. Moreover, CCR2 also appears to be involved in HIV infection [1,5,10,25].

CCR3. This mediates the chemotaxis of eosinophils and may thus be important during allergic inflammation and hypersensitivity. This receptor can be activated by MIP-1α, MIP-1β and eotaxin, RANTES, MCP-3, MCP-4, MIP-5 and the TAT protein of HIV. Eotaxin appears to be the most potent agonist of CCR3. CCR3 can also be detected on basophils, mast cells, Th2-lymphocytes as well as DCs. Eotaxin knockout mice showed only weak responses after ovalbumin challenge. Using animal models, neutralization of eotaxin resulted in a partial blockade of eosinophilia after allergen challenge [27].

CCR4. This is expressed by Th2 cells and can be activated by macrophage-derived chemokine (MDC = CCL22) and thymus and activation-regulated chemokine (TARC = CCL17). This receptor may also be involved in dendritic cell functions, trafficking of T cells to the lymph nodes and T cell transmigration, as well as homing of memory T cells to inflamed skin [28].

CCR5. This has become well known as a major HIV-1 co-receptor that controls susceptibility to HIV-1 infection and disease [10]. CCR5 is expressed by T lymphocytes and macrophages as well as Langerhans' cells. CCR5 can be activated by MIP-1α, RANTES, MIP-1β and MCP-1. MCP-3 however, appears to be a CCR5 antagonist. Under normal conditions CCR5 knockout mice appear healthy. A role for CCR5 in down-modulating T-cell-dependent immune responses has been suggested. CCR5 is one of the first receptors for which use of receptor antagonists has been advocated in clinical trials in humans, in HIV infection [29].

CCR6. This mediates responsiveness of memory T cells to the chemokine LARC (CCL20). CCR6 seems to be important for the migration of memory T cells and DCs to secondary lymphoid organs. The chemokine MIP-3α has been shown to regulate the homing of Langerhans'-type dendritic cells to the epidermis by activating CCR6. The CCR6 ligand LARC can be released by macrophages, dendritic cells and endothelial cells. However, the human β-defensin 2 (HBD-2) has also been shown to functionally bind CCR6. HBD-2 is produced by enterocytes during infection and functions as an antimicrobial factor. It also attracts DCs and memory T cells via CCR6 activation. Together, these results indicate a role for this receptor as a link between the innate and adaptive immune systems [30].

CCR7. This is a homing receptor for B cells, T cells and DCs across high endothelial venules. CCR7 is activated by the chemokines ELC (CCL19) and SLC (CCL21), which are expressed in the T-cell area of lymphoid tissues but not in the B-cell area. This is supported by the finding that CCR7 knockout mice show defective B- and T-cell homing, whereas defective T-cell development is not found.

CCR8. This is critically associated with the function of Th2 lymphocytes. Reports of the activation of CCR8 by various agents such as TARC and MIP-1β are controversial. Interestingly,

CCR8 can be activated by viral chemokines from molluscum contagiosum [31]. CCR8 has also been described as an HIV-1 co-receptor.

CCR9. This is a recently described receptor that can be activated by TECK (CCL25), a chemokine for dendritic cells, T cells and activated macrophages. It also appears to be involved in the development of T cells within the thymus.

CCR10. This is a receptor for the skin-associated CC chemokine CCL27 (CTACK) that attracts skin-homing memory T cells to the site of inflammation [17].

CCR11. This is a receptor for MCP-1, MCP-2 and MCP-4. It has been described in the heart, small intestine and the lung.

CX3CR1. This is a receptor that is crucially involved in cell–cell adhesion and leukocyte trafficking. Its ligand fractalkine is a transmembrane protein that activates CX3R1 on neutrophils, monocytes, NK cells and T lymphocytes. This receptor has also been described as a co-receptor for HIV-1. Its role in the skin, however, is currently unknown.

A crucial role for chemokines and chemokine receptors in cutaneous inflammation has been demonstrated in several studies in which the relevant genes have been deleted by homologous recombination. For example, CXCR2 gene-deficient mice are incapable of mobilizing neutrophils *in vivo* [32]. Further results showing that CXCR2 ligand neutralization leads to impaired reactions during skin inflammation suggest a potential therapeutic potential for the use of chemokine receptor antagonists in inflammatory skin diseases such as psoriasis. CXCR2 knockout mice show defective neutrophil recruitment, an altered temporal pattern of monocyte recruitment and altered secretion of IL-1β, indicating a role for this chemokine receptor in wound healing [33].

Data suggest a role for chemokines in angiogenesis. IL-8 (CXCL8) has been shown to act as a growth factor in malignant melanoma. Melanoma cells overexpress certain chemokines that activate CXCL8, indicating an autocrine tumour-promoting effect of this chemokine. Many chemokines, including CCL20/MIP-3α, have been demonstrated to display antimicrobial activity comparable to defensins.

Chemokines may also be involved in the modulation of angiogenesis during tumour growth. For instance, CXCL8 (IL-8) and CXCL10 (IP-10) are angiostatic factors, while CXCL12 (SDF-1) has been shown to act as an angiogenic factor *in vivo* [2,8,10,34]. Interestingly, CXCL12 and VEGF appear to act synergistically to regulate angiogenesis. Other chemokines such as CXCL4, CXCL9 and CXCL10 decrease angiogenesis, and thereby may inhibit tumour growth. A role for chemokines in regulating blood vessel formation during chronic inflammation and injury awaits further clarification.

In summary, recent data indicate a crucial role for various chemokines in cutaneous inflammation, and receptor antagonists may prove useful in the treatment of several skin diseases including inflammation, autoimmunity, allergy, infection and tumour growth.

References

1 Baggiolini M, Dewald B, Moser B. Human chemokines: an update. *Annu Rev Immunol* 1997; **15**: 675–705.

2 Homey B, Muller A, Zlotnik A. Chemokines: agents for the immunotherapy of cancer? *Nat Rev Immunol* 2002; **2**: 175–84.

3 Santamaria LF, Perez Soler MT, Hauser C, Blaser K. Allergen specificity and endothelial transmigration of T cells in allergic contact dermatitis and atopic dermatitis are associated with the cutaneous lymphocyte antigen. *Int Arch Allergy Immunol* 1995; **107**: 359–62.

4 Baggiolini M, Dahinden CA. CC chemokines in allergic inflammation. *Immunol Today* 1994; **15**: 127–33.

5 Baggiolini M, Dewald B, Moser B. Interleukin-8 and related chemotactic cytokines–CXC and CC chemokines. *Adv Immunol* 1994; **55**: 97–179.

6 Bischoff SC, Krieger M, Brunner T, Dahinden CA. Monocyte chemotactic protein 1 is a potent activator of human basophils. *J Exp Med* 1992; **175**: 1271–5.

7 Kuna P, Reddigari SR, Rucinski D *et al*. Monocyte chemotactic and activating factor is a potent histamine-releasing factor for human basophils. *J Exp Med* 1992; **175**: 489–93.

8 Middleton J, Neil S, Wintle J *et al*. Transcytosis and surface presentation of IL-8 by venular endothelial cells. *Cell* 1997; **91**: 385–95.

9 Webb LM, Ehrengruber MU, Clark-Lewis I *et al*. Binding to heparan sulfate or heparin enhances neutrophil responses to interleukin 8. *Proc Natl Acad Sci U S A* 1993; **90**: 7158–62.

10 Murphy PM. International Union of Pharmacology. Update on chemokine receptor nomenclature. *Pharmacol Rev* 2002; **54**: 227–9.

11 Pease JE, Murphy PM. Microbial corruption of the chemokine system: an expanding paradigm. *Semin Immunol* 1998; **10**: 169–78.

12 Schroder JM, Noso N, Sticherling M, Christophers E. Role of eosinophil-chemotactic C-C chemokines in cutaneous inflammation. *J Leukoc Biol* 1996; **59**: 1–5.

13 Weber M, Uguccioni M, Ochensberger B *et al*. Monocyte chemotactic protein MCP-2 activates human basophil and eosinophil leukocytes similar to MCP-3. *J Immunol* 1995; **154**: 4166–72.

14 Gerber BO, Zanni MP, Uguccioni M *et al*. Functional expression of the eotaxin receptor CCR3 in T lymphocytes co-localizing with eosinophils. *Curr Biol* 1997; **7**: 836–43.

15 Rothenberg ME, MacLean JA, Pearlman E *et al*. Targeted disruption of the chemokine eotaxin partially reduces antigen-induced tissue eosinophilia. *J Exp Med* 1997; **185**: 785–90.

16 Schutyser E, Richmond A, Van Damme J. Involvement of CC chemokine ligand 18 (CCL18) in normal and pathological processes. *J Leukoc Biol* 2005; **78**: 14–26.

17 Morales J, Homey B, Vicari AP *et al*. CTACK, a skin-associated chemokine that preferentially attracts skin-homing memory T cells. *Proc Natl Acad Sci U S A* 1999; **96**: 14470–5.

18 Homey B, Wang W, Soto H *et al*. Cutting edge: the orphan chemokine receptor G protein-coupled receptor-2 (GPR-2, CCR10) binds the skin-associated chemokine CCL27 (CTACK/ALP/ILC). *J Immunol* 2000; **164**: 3465–70.

19 Homey B, Alenius H, Muller A *et al*. CCL27-CCR10 interactions regulate T cell-mediated skin inflammation. *Nat Med* 2002; **8**: 157–65.

20 Schroder JM, Gregory H, Young J, Christophers E. Neutrophil-activating proteins in psoriasis. *J Invest Dermatol* 1992; **98**: 241–7.

21 Walz A, Meloni F, Clark-Lewis I *et al*. [Ca^{2+}]i changes and respiratory burst in human neutrophils and monocytes induced by NAP-1/interleukin-8, NAP-2, and gro/MGSA. *J Leukoc Biol* 1991; **50**: 279–86.

22 Taub DD, Lloyd AR, Conlon K *et al*. Recombinant human interferon-inducible protein 10 is a chemoattractant for human monocytes and T lymphocytes and promotes T cell adhesion to endothelial cells. *J Exp Med* 1993; **177**: 1809–14.

23 Koch AE, Kunkel SL, Harlow LA *et al*. Epithelial neutrophil activating peptide-78: a novel chemotactic cytokine for neutrophils in arthritis. *J Clin Invest* 1994; **94**: 1012–8.

24 Arvanitakis L, Geras-Raaka E, Varma A *et al*. Human herpesvirus KSHV encodes a constitutively active G-protein-coupled receptor linked to cell proliferation. *Nature* 1997; **385**: 347–50.

25 Lapham CK, Zaitseva MB, Lee S *et al*. Fusion of monocytes and macrophages with HIV-1 correlates with biochemical properties of CXCR4 and CCR5. *Nat Med* 1999; **5**: 303–8.

26 Gao JL, Wynn TA, Chang Y *et al*. Impaired host defense, hematopoiesis, granulomatous inflammation and type 1-type 2 cytokine balance in mice lacking CC chemokine receptor 1. *J Exp Med* 1997; **185**: 1959–68.

27 Humbles AA, Conroy DM, Marleau S *et al.* Kinetics of eotaxin generation and its relationship to eosinophil accumulation in allergic airways disease: analysis in a guinea pig model in vivo. *J Exp Med* 1997; **186**: 601–12.
28 Campbell JJ, Haraldsen G, Pan J *et al.* The chemokine receptor CCR4 in vascular recognition by cutaneous but not intestinal memory T cells. *Nature* 1999; **400**: 776–80.
29 Zaitseva M, Blauvelt A, Lee S *et al.* Expression and function of CCR5 and CXCR4 on human Langerhans cells and macrophages: implications for HIV primary infection. *Nat Med* 1997; **3**: 1369–75.
30 Yang D, Chertov O, Bykovskaia SN *et al.* Beta-defensins: linking innate and adaptive immunity through dendritic and T cell CCR6. *Science* 1999; **286**: 525–8.
31 Damon I, Murphy PM, Moss B. Broad spectrum chemokine antagonistic activity of a human poxvirus chemokine homolog. *Proc Natl Acad Sci U S A* 1998; **95**: 6403–7.
32 Cacalano G, Lee J, Kikly K *et al.* Neutrophil and B cell expansion in mice that lack the murine IL-8 receptor homolog. *Science* 1994; **265**: 682–4.
33 Devalaraja RM, Nanney LB, Du J *et al.* Delayed wound healing in CXCR2 knockout mice. *J Invest Dermatol* 2000; **115**: 234–44.
34 Belperio JA, Keane MP, Arenberg DA *et al.* CXC chemokines in angiogenesis. *J Leukoc Biol* 2000; **68**: 1–8.

Proteases

Proteases constitute the largest family of enzymes, and comprise approximately 5% of the human genome, making them the largest protein family in humans. Although not known to be involved in multiple processes, proteases have in the past been regarded purely as destructive enzymes that merely degrade peptides. Proteases are in fact involved in almost all biological processes, such as embryogenesis, cell cycling, growth and differentiation, coagulation, inflammation, tumourigenesis, hair growth, secretion and tissue repair, and they also assist in cell–cell communication [1–4].

Proteases can be divided into five groups, depending on the type of molecule that mediates catalytic work (serine, threonine, cysteine, aspartyl, metalloproteinases). It is important to realize that the effect of a protease is irreversible, because hydrolysis cannot be reversed. Therefore, proteases are maintained in a precursor state (zymogen) and become activated only when needed. Proteinases are involved in inflammatory processes that are not appropriately regulated. Significant tissue destruction and impairment of repair mechanisms may occur after proteinase activation, or dysfunction of protease inhibitors. One of the best examples of a crucial part played by a protease-regulated system is the blood coagulation cascade. Another example is programmed cell death (apoptosis) in which cysteine proteases (caspases) are critically involved [5].

In the skin, exogenous proteases such as Der p3 or Der p9 from house-dust mite, bacterial (e.g. V8 protease from staphylococci) or fungal proteinases (aspartyl proteases) are capable of triggering the inflammatory response in the epidermis or dermis. Among the keratinocyte-derived enzymes that may contribute to inflammation are acid phosphatase, cathepsins (acid proteases) B, C and D, mainly distributed in lysosomes with acid phosphatase, and neutral serine proteinases such as squamous cell tryptic enzyme (SCTE), squamous cell chymotryptic enzyme (SCCE) and trypsin IV. Interestingly, enteropeptidase, the enzyme that cleaves trypsinogen and thereby activates trypsin, can be functionally expressed by keratinocytes. Keratinocytes also respond to protease inhibitors, indicating a complete proteinase-regulated machinery within the epidermis. Another enzyme, plasminogen activator, is generated throughout the epidermis, with some predominance within the granular layer.

Hereditary angio-oedema, characterized by episodic, localized angio-oedema of the skin or mucosa, results from heterozygous deficiency of a protease inhibitor from the plasma, C1 esterase inhibitor (C1INH). C1INH seems to be involved in preventing excessive vascular permeability, and is an important modulator of inflammatory responses via regulation of complement activation.

Converting enzymes, such as IL-1 converting enzyme or prohormone convertase, are important proteinases in the switching of a pro-form of a molecule to the active state. They are especially important during the inflammatory process, where dysfunction of such enzymes may result in a disease state.

Acid phosphatase occurs in large amounts, relative to other acid hydrolases, particularly in the upper keratinizing layers of the epidermis. It probably participates in nucleic acid degradation. Hyperplasia of human skin induced by UV radiation and vitamin A application is associated with an up-regulation of acid phosphatase. This increase, which also occurs in the stratum corneum, has found applications as a test for weak irritants; severe irritants result in a loss of acid phosphatase. Mild irritation of rat skin results in an increase of acid phosphatase, maximal on the third day, coinciding with acanthosis and thickening of the stratum granulosum.

Acidic protease cathepsins B, C and D occur in the human epidermis. In rabbits, cathepsin D was found to play a major role in intracellular protein digestion, and if released may degrade extracellular protein. Following irritation, proteases first degrade damaged cells via releasing lysosomal enzymes. Subsequently, via the activation of complement, Hageman factor, and cleavage of fibrin, the infiltration of leukocytes is initiated resulting in inflammation. Neutral protease in human skin, also present in fibroblasts, neutrophils and lymphocytes, has been shown to cleave complement and stimulate neutrophil chemotaxis in mice [6]. Thus, damage to the epidermis will initiate the generation of chemotactic substances by release of proteolytic enzymes and by activation of other acute phase proteins, resulting in infiltration by neutrophils and further inflammation.

Tryptase is released by mast cells during inflammation, allergic reactions and tissue repair, and stimulates the release of pro-inflammatory cytokines (IL-6, IL-8, GM-CSF) and other inflammatory mediators (NO, prostaglandins) [7–9]. Another protease released by mast cells during inflammation is chymase. This enzyme seems to be important as a regulator of vascular responses, leukocyte recruitment and the regulation of extracellular matrix proteins. Thus, chymase may be involved in the pathophysiology of allergic reactions, inflammation and tissue repair [10].

Many proteases are integral components of vital signalling networks. Besides their role as catalysts for extracellular matrix proteins, certain serine proteases have been demonstrated to activate specific receptors. The first protease-mediated receptor system identified was the thrombin receptor (PAR-1) [11]. Subsequently, two other thrombin receptors were characterized: PAR-3 and PAR-4 [12]. Thrombin not only plays an essential part in the coagulation cascade, but additionally activates platelets and

endothelial cells, thereby contributing to inflammation and tissue repair. PARs are G protein-coupled receptors with seven transmembrane domains. After activation, they mediate several inflammatory reactions, such as the release of cytokines, prostaglandins, NO or chemokines. Up-regulation of cell adhesion molecules on microvascular endothelial cells can also be mediated via PARs, indicating a direct role of proteases on leukocyte–endothelial interactions during inflammation [7]. *In vivo*, PAR-2 can be activated by skin-derived proteases such as tryptase and trypsin IV, leading to pruritus, oedema, plasma extravasation, and up-regulation of cell adhesion molecules followed by transendothelial migration of neutrophils [13–15]. Thus, activation of PARs appears to be a crucial event involved in many aspects of acute and chronic inflammation.

Plasminogen activation on the cell surface depends on the activation of urokinase type plasminogen activator (uPA) and its receptor. Such protease receptor families are defined as plasminogen activator receptors (also abbreviated PAR receptors). In contrast to the other PARs, these receptors are single-transmembrane receptors with protein kinase activity. One receptor, uPAR (urokinase receptor), can be activated by binding of urokinase and vitronectin [16]. Upon activation on endothelial cells, urokinase receptors mediate adhesion, proliferation and migration of inflammatory cells. For example, uPAR has been demonstrated to be highly expressed on leukocytes during HIV infection, and soluble uPAR (suPAR) in the serum is an effective predictor of survival in HIV infection [17]. In the skin, uPAR has been implicated in the pathophysiology of acantholysis in pemphigus [18]. uPA also activates metalloproteinases, thereby contributing to vascular damage [19]. The uPA–uPAR system is completed by the existence of plasminogen activator inhibitors (PAIs). Together, the orchestrated interaction of uPA, uPAR and PAI appears to have an essential role during inflammation, angiogenesis and cancer [20]. It is well known that protease inhibitor deficiency, or dysfunction, such as with α_1-antitrypsin, may result in airway disease [21]. An important finding has been that certain protease inhibitors are involved in cutaneous inflammation and disease. *SPINK5*, encoding the putative multidomain serine protease inhibitor LEKTI, has been identified as the gene defective in Netherton's syndrome [21]. LEKTI is strongly expressed in the granular and uppermost spinous layers of the epidermis, and in differentiated layers of stratified epithelia. Loss of LEKTI expression in the epidermis seems to be a diagnostic feature of Netherton's syndrome.

Protease inhibitors also have been identified as useful therapeutic agents. For example, inhibitors of angiotensin-converting enzyme are widely used for the treatment of hypertension but, via their pro-inflammatory capacity, may also cause the exacerbation of inflammatory skin diseases such as psoriasis. Moreover, HIV protease inhibitors recently have been introduced for the treatment of AIDS. The key role proteases play in the pathophysiology of many diseases makes them attractive targets for future drug development [22–25].

Matriptase is a trypsin-like proteinase which is produced by all types of epithelia, and was shown to be overexpressed in several carcinomas of epithelial origin. In human epidermis, matriptase is mainly produced by keratinocytes from the stratum granulosum and the first cornified layer. It is an important enzyme within the epidermis, allowing for the correct processing of profilaggrin. Filaggrin aggregates keratin inside the keratinocytes and facilitates cornified envelope as well as lipid matrix formation. Thus, matriptase may be involved in skin homeostasis, barrier function, inflammation and cancerogenesis. Indeed, mice lacking matriptase die shortly after birth due to fatal water loss. Moreover, hair follicle growth is impaired. Hepatocyte growth factor activator inhibitor-1 (HAI-1), the matriptase inhibitor, counteracts the enzyme activity of matriptase. There is strong evidence that the matriptase/HAI-1 ratio is dysregulated in epithelial cancers as well as under inflammatory conditions. Thus, protease/protease inhibitor systems may be involved in the development of cancer in chronic inflammatory conditions [26]. Kallikreins may play an essential role in epidermal homeostasis, Netherton's syndrome and barrier dysfunction [27–32].

Ectopeptidases such as dipeptidyl peptidase IV (DP IV) and aminopeptidase N (APN), as well as endopeptidases (NEP, neutral endopeptidase; ACE, angiotensin converting enzyme; ECE, endothelin-converting enzyme), and their related enzymes, have been considered as possible targets for the treatment of various inflammatory skin diseases [33–35].

Skin cells express dipeptidyl peptidase IV (DP IV) and aminopeptidase N (APN), and their related molecules of the DP IV-like family, DP2, DP6, DP8, DP9 and fibroblast activation protein (FAP), as well as the cytoplasmic alanyl aminopeptidase (cAAP). Inhibitors of DP IV-like activity, Lys(Z(NO2))-thiazolidide (LZNT) and Lys(Z(NO2))-pyrrolidide (LZNP), and the APN inhibitors actinonin and bestatin, affect proliferation, differentiation and cytokine production in keratinocytes as well as sebocytes, which are involved in the initiation of acne. Furthermore, they suppress proliferation of *Propionibacterium acnes*-stimulated T cells *ex vivo* and induce an anti-inflammatory cytokine profile. The inhibitors also suppress skin fibroblast proliferation, whereas only inhibition of DP IV-like activity decreases TGF-β1 expression, and abrogates the TGF-β1-mediated stimulatory effects on TGF-β1 and fibronectin production, collagen synthesis and matrix deposition in these cells [36].

In summary, proteases along with their inhibitors and receptors have an essential role in skin homeostasis and pathology. A well-tuned orchestra of these enzymes seems to be crucial for the maintenance of many inflammatory responses in the skin such as oedema, plasma extravasation, recruitment of leukocytes, cell–cell communication, extracellular matrix degradation, angiogenesis, cytoprotection, post-inflammatory pigmentation, spongiosis and keratinocyte desquamation. The significance of proteases to the treatment of skin diseases will be better understood once effective protease inhibitors, protease-receptor antagonists (or agonists) are available in the future.

References

1 Coughlin SR. Thrombin signalling and protease-activated receptors. *Nature* 2000; **407**: 258–64.

2 Ruf W, Dorfleutner A, Riewald M. Specificity of coagulation factor signaling. *J Thromb Haemost* 2003; **1**: 1495–503.

3 Tani K, Ogushi F, Shimizu T, Sone S. Protease-induced leukocyte chemotaxis and activation: roles in host defense and inflammation. *J Med Invest* 2001; **48**: 133–41.

4 Tomimori Y, Tsuruoka N, Fukami H *et al.* Role of mast cell chymase in allergen-induced biphasic skin reaction. *Biochem Pharmacol* 2002; **64**: 1187.
5 Fortini ME. Gamma-secretase-mediated proteolysis in cell-surface-receptor signalling. *Nat Rev Mol Cell Biol* 2002; **3**: 673–84.
6 Davis AE 3rd. The pathogenesis of hereditary angioedema. *Transfus Apher Sci* 2003; **29**: 195–203.
7 Shpacovitch VM, Brzoska T, Buddenkotte J *et al.* Agonists of proteinase-activated receptor 2 induce cytokine release and activation of nuclear transcription factor kappaB in human dermal microvascular endothelial cells. *J Invest Dermatol* 2002; **118**: 380–5.
8 Hou L, Kapas S, Cruchley AT *et al.* Immunolocalization of protease-activated receptor-2 in skin: receptor activation stimulates interleukin-8 secretion by keratinocytes in vitro. *Immunology* 1998; **94**: 356–62.
9 Wakita H, Furukawa F, Takigawa M. Thrombin and trypsin induce granulocyte-macrophage colony-stimulating factor and interleukin-6 gene expression in cultured normal human keratinocytes. *Proc Assoc Am Physicians* 1997; **109**: 190–207.
10 Abraham WM. Tryptase: potential role in airway inflammation and remodeling. *Am J Physiol Lung Cell Mol Physiol* 2002; **282**: L193–6.
11 Vu TK, Hung DT, Wheaton VI, Coughlin SR. Molecular cloning of a functional thrombin receptor reveals a novel proteolytic mechanism of receptor activation. *Cell* 1991; **64**: 1057–68.
12 Steinhoff M, Buddenkotte J, Shpacovitch V *et al.* Proteinase-activated receptors: transducers of proteinase-mediated signaling in inflammation and immune response. *Endocr Rev* 2005; **26**: 1–43.
13 Seeliger S, Derian CK, Vergnolle N *et al.* Proinflammatory role of proteinase-activated receptor-2 in humans and mice during cutaneous inflammation in vivo. *FASEB J* 2003; **17**: 1871–85.
14 Steinhoff M, Neisius U, Ikoma A *et al.* Proteinase-activated receptor-2 mediates itch: a novel pathway for pruritus in human skin. *J Neurosci* 2003; **23**: 6176–80.
15 Steinhoff M, Vergnolle N, Young SH *et al.* Agonists of proteinase-activated receptor 2 induce inflammation by a neurogenic mechanism. *Nat Med* 2000; **6**: 151–8.
16 Blasi F, Carmeliet P. uPAR: a versatile signalling orchestrator. *Nat Rev Mol Cell Biol* 2002; **3**: 932–43.
17 Sidenius N, Sier CF, Ullum H *et al.* Serum level of soluble urokinase-type plasminogen activator receptor is a strong and independent predictor of survival in human immunodeficiency virus infection. *Blood* 2000; **96**: 4091–5.
18 Xue W, Hashimoto K, Toi Y. Functional involvement of urokinase-type plasminogen activator receptor in pemphigus acantholysis. *J Cutan Pathol* 1998; **25**: 469–74.
19 Carmeliet P, Moons L, Lijnen R *et al.* Urokinase-generated plasmin activates matrix metalloproteinases during aneurysm formation. *Nat Genet* 1997; **17**: 439–44.
20 Blasi F. uPA, uPAR, PAI-1: key intersection of proteolytic, adhesive and chemotactic highways? *Immunol Today* 1997; **18**: 415–7.
21 Bitoun E, Micheloni A, Lamant L *et al.* LEKTI proteolytic processing in human primary keratinocytes, tissue distribution and defective expression in Netherton syndrome. *Hum Mol Genet* 2003; **12**: 2417–30.
22 Leung D, Abbenante G, Fairlie DP. Protease inhibitors: current status and future prospects. *J Med Chem* 2000; **43**: 305–41.
23 Puente XS, Sanchez LM, Overall CM, Lopez-Otin C. Human and mouse proteases: a comparative genomic approach. *Nat Rev Genet* 2003; **4**: 544–58.
24 Nakajima M, Naya N. Development of a chymase inhibitor: pharmacological characterization of a chymase inhibitor in inflamed tissue remodeling and fibrosis. *Jpn J Pharmacol* 2002; **90**: 206–9.
25 Hiemstra PS. Novel roles of protease inhibitors in infection and inflammation. *Biochem Soc Trans* 2002; **30**: 116–20.
26 Bocheva G, Rattenholl A, Vergnolle N, Steinhoff M. Role of matriptase, hepatocyte-growth factor inhibitor-1 and proteinase-activated receptor-2 in human skin cancer. *J Invest Dermatol* 2009; **129**: 1816–23.
27 Descargues P, Deraison C, Bonnart C *et al.* Spink5-deficient mice mimic Netherton syndrome through degradation of desmoglein 1 by epidermal protease hyperactivity. *Nat Genet* 2005; **37**: 56–65.
28 Eissa A, Diamandis EP. Human tissue kallikreins as promiscuous modulators of homeostatic skin barrier functions. *Biol Chem* 2008; **389**: 669–80.
29 Hachem JP, Man MQ, Crumrine D *et al.* Sustained serine proteases activity by prolonged increase in pH leads to degradation of lipid processing enzymes and profound alterations of barrier function and stratum corneum integrity. *J Invest Dermatol* 2005; **125**: 510–20.
30 Hachem JP, Wagberg F, Schmuth M *et al.* Serine protease activity and residual LEKTI expression determine phenotype in Netherton syndrome. *J Invest Dermatol* 2006; **126**: 1609–21.
31 Lundwall A, Brattsand M. Kallikrein-related peptidases. *Cell Mol Life Sci* 2008; **65**: 2019–38.
32 Voegeli R, Rawlings AV, Doppler S, Schreier T. Increased basal transepidermal water loss leads to elevation of some but not all stratum corneum serine proteases. *Int J Cosmet Sci* 2008; **30**: 435–42.
33 Padilla BE, Cottrell GS, Roosterman D *et al.* Endothelin-converting enzyme-1 regulates endosomal sorting of calcitonin receptor-like receptor and beta-arrestins. *J Cell Biol* 2007; **179**: 981–97.
34 Roosterman D, Cottrell GS, Padilla BE *et al.* Endothelin-converting enzyme 1 degrades neuropeptides in endosomes to control receptor recycling. *Proc Natl Acad Sci U S A* 2007; **104**: 11838–43.
35 Roosterman D, Goerge T, Schneider SW *et al.* Neuronal control of skin function: the skin as a neuroimmunoendocrine organ. *Physiol Rev* 2006; **86**: 1309–79.
36 Thielitz A, Ansorge S, Bank U *et al.* The ectopeptidases dipeptidyl peptidase IV (DP IV) and aminopeptidase N (APN) and their related enzymes as possible targets in the treatment of skin diseases. *Front Biosci* 2008; **13**: 2364–75.

Matrix metalloproteinases

Matrix metalloproteinases (MMPs) constitute a family of multidomain zinc endopeptidases that contain a catalytic domain with a common metzincin-like topology (Table 12.8). They are involved not only in extracellular matrix degradation, but also in a number of other biological processes. Classically, MMPs are known as key players in the regulation of the extracellular matrix (ECM), by mediating the responses of cells to their environment. By causing the proteolytic degradation or activation of a cell and the ECM, these proteases influence cell migration, proliferation and cell survival. They have overlapping activities, principally on collagen, fibronectin, laminin and elastin. The activity is tightly controlled, being stimulated by inflammatory mediators or growth factors such as IL-1, TNF-α, TGF-β, EGF, FGF as well as PDGF, and repressed by TGF-α and IL-4. The extracellular activity is inhibited by four different tissue inhibitors of metalloproteinases (TIMP-1–TIMP-4) and by the less selective α_1-antitrypsin (α_1-proteinase inhibitor) and α_2-macroglobulin [1–4].

Twenty-eight matrix metalloproteinases (MMP-1 to MMP-28), grouped according to domain structure as gelatinases, collagenases, stromolysins and matrilysin, are zinc-dependent endopeptidases present in small amounts in resting tissue, which are increased in normal tissue remodelling, and pathological changes including tumour infiltration and tissue repair. Secreted forms can be distinguished from transmembrane forms. Both forms have been implicated in proteolytic regulation of cell communication. TIMP-3 seems to be an inhibitor of the function of so-called ADAMs (adamalysin-like proteinases with metalloproteinase and desintegrin-like domains). Moreover, matrix-associated ADAMs exist that have a thrombospondin-like domain (ADAM-TS). In addition to TIMPs, ADAMs appear to be crucial regulators of MMP activity during skin homeostasis and disease. For example, TACE, ADAM-10 and ADAM-9 have been shown to be functionally expressed in keratinocytes. Activation of these ADAMs resulted in increased shedding of transmembrane collagen XVII from keratinocytes, indicating that it represents a substrate for ADAMs, thereby regulating extracellular matrix function in the skin during various subtypes of inflammation, wound healing,

Table 12.8 Vertebrate matrix metalloproteinases (MMPs).

MMP	Name	Group	Substrate
MMP1	Collagenase-1	Collagenases	Collagens I, II, III, VII, VIII, X, gelatine
MMP2	Gelatinase-A	Gelatinases	Collagens I, II, III, IV, V, VII, X, XI
MMP3	Stromelysin-1	Stromelysins	PG core protein, laminin, fibronectin
MMP7	Matrilysin-1	Matrilysins	Collagens I and IV, elastin, fibronectin, entactin, tenascin, aggrecan, vitronectin, decorin, versican, osteopontin, E-cadherin, Fas ligand, pro-TNF-α
MMP8	Neutrophil collagenase	Collagenases	Collagens I, II and III, aggrecan
MMP9	Gelatinase-B	Gelatinases	Collagens IV, V, XI and XIV, gelatine, elastin, fibronectin, vitronectin, laminin, aggrecan, versican, decorin
MMP10	Stromelysin-2	Stromelysins	Collagens III, IV and V, gelatine, elastin, fibronectin, aggrecan
MMP11	Stromelysin-3	Stromelysins	Collagin IV, gelatine, fibronectin, laminin, insulin-like growth factor-binding protein (IGFBP)
MMP12	Macrophage elastase	Metalloelastases	Collagens I, IV and V, gelatine, elastin, fibronectin, vitronectin, laminin, entactin, osteonectin, aggrecan
MMP13	Collagenase-3	Collagenases	Collagens I, II, III, IV, VI, IX, X and XIV, gelatine, fibronectin
MMP14	MT1-MMP	MT-MMPs	Collagens I, II and III, gelatine, fibronectin, tenascin, vitronectin, laminin, entactin, aggrecan, perlecan
MMP15	MT2-MMP	MT-MMPs	Fibronectin, tenascin, entactin, laminin, aggrecan, perlecan
MMP16	MT3-MMP	MT-MMPs	Collagen III, gelatine, fibronectin, vitronectin, laminin
MMP17	MT4-MMP	MT-MMPs	Gelatine, fibronectin, fibrillin
MMP18	Collagenase-4 (*Xenopus*)		
MMP19	RASI-1	Other MMPs	Collagen IV, gelatine, tenascin, fibronectin, aggrecan, entactin, laminin
MMP20	Enamelysin	Other MMPs	Amelogenin, aggrecan
MMP21	XMMP (*Xenopus*)		ND
MMP22	CMMP (chicken)		ND
MMP23	CA-MMP	Other MMPs	ND
MMP24	MT5-MMP	MT-MMPs	ND
MMP25	MT6-MMP	MT-MMPs	Collagen IV, gelatine, fibronectin
MMP26	Endometase, matrilysin-2	Matrilysins	Collagen IV, gelatine, fibronectin
MMP27			ND
MMP28	Epilysin	Other MMPs	ND

ND, not determined.

skin ageing or blistering diseases [5–9]. They are also involved in skin ageing which has an inflammatory component [10].

MMP activity seems to be enhanced in patients with inflammatory skin diseases such as psoriasis [11], and MMP-9 activity can be enhanced in human keratinocytes by UV irradiation [12] or even histamine from mast cells [13,14]. Moreover, matrix metalloproteinase gelatinase B (MMP-9) coordinates and effects epithelial regeneration during healing, as demonstrated in a mouse model [15]. MMP-1 also directly influences its own up-regulation by elastin peptides in cultured fibroblasts [16], and fibroblasts themselves are capable of generating MMP-2 and MMP-9 [17]. MMP-9 and -13 appear to modulate inflammatory responses during cutaneous inflammation, for example by regulating collagen function [18]. Increased levels of MMP-1, MMP-2 and MMP-13 were observed in lesional skin of inflammatory skin diseases such as stasis dermatitis. In contrast, TIMP-1 and TIMP-2 levels were diminished, indicating that MMPs are directly involved in the regulation of skin remodelling and inflammatory responses during stasis dermatitis [19]. MMP-2 seems to play a role in acne since the expression levels correlate with *Propionibacteria* infection [20]. Moreover, increased inflammation delays wound healing in mice deficient in collagenase-2 (MMP-8) [21].

MMP19 is important for cell proliferation, cell adhesion and migration. In mice, MMP-19 appears to be an important factor in cutaneous immune responses and influences the development of T cells [22]. Similar TNF-α, MMP-1, -9, -10 and -26 alterations are seen in both pyoderma gangrenosum and inflammatory bowel disease ulcers, suggesting a similar pathogenesis for cutaneous and mucosal inflammation in these two diseases, which may coexist in certain patients [23].

There is little difference in the enzymes present in tissues in acute and chronic wounds, the major enzymes being MMP-2 and MMP-9 (gelatinases and pro-collagenase) and MMP-1 (collagenase) [24,25]. Keratinocyte formation of collagenase occurs rapidly (within 4–6 h) during wound healing, reaching a maximum in uncomplicated wounds on days 3–5, and then declining by about day 9 when repair is complete. Collagenase digests native collagen to short peptide chains, which become susceptible to degradation by other non-specific proteases. At the wound edges, collagenase prepares the extracellular matrix bed for keratinocytes, and may contribute to keratinocyte migration [26–29]. In addition a decrease in the amount of TIMPs, the inhibitors of MMPs, in chronic wounds has been detected [27,30]. Fluid from acute wounds stimulates fibroblast proliferation, proteinase expression, matrix element formation and also was found to contain cytokines such as PDGF and βFGF [31,32].

MMPs may also play an important role in the mediation of UV-light-induced autoimmune diseases such as lupus erythematosus. Different subtypes of cutaneous lupus erythematosus are fairly similar in their MMP expression profile. MMP-3 and -10 mediate

both epidermal changes and dermal tissue remodelling but are not present in lymphocytes. Furthermore, the low expression of TIMP-1 suggests that lupus skin is characterized by proteolytic events, and targeted action using selective MMP inhibitors may reduce lupus-induced damage in inflamed tissues [33]. This needs to be further explored in more detail.

In patients with psoriatic arthritis, decreased levels of MMP-9 and angiogenic factors can be observed after anti-TNF-α treatment, strongly suggesting that MMP-9 may play a key role in the skin inflammatory process in psoriasis [34].

Thus, targeting MMPs and/or TIMPs may be beneficial for the treatment of various inflammatory skin diseases, Sjögren's syndrome and impaired wound healing. The anti-inflammatory effects of agents including glucocorticoids or antibiotics are only partly understood [35,36]. Tetracycline effects in various inflammatory skin diseases such as acne, rosacea, scleroderma, bullous dermatoses and pyoderma gangrenosum may be—at least in part—due to their inhibitory action on MMPs [37].

References

1 Bode W. Structural basis of matrix metalloproteinase function. *Biochem Soc Symp* 2003; **70**: 1–14.
2 Chase AJ, Newby AC. Regulation of matrix metalloproteinase (matrixin) genes in blood vessels: a multi-step recruitment model for pathological remodelling. *J Vasc Res* 2003; **40**: 329–43.
3 Visse R, Nagase H. Matrix metalloproteinases and tissue inhibitors of metalloproteinases: structure, function, and biochemistry. *Circ Res* 2003; **92**: 827–39.
4 Baker AH, Edwards DR, Murphy G. Metalloproteinase inhibitors: biological actions and therapeutic opportunities. *J Cell Sci* 2002; **115**: 3719–27.
5 Bedocs PM, Kumar V, Mahon MJ. Pemphigoid gestationis: a rare case and review. *Arch Gynecol Obstet* 2009; **279**: 235–8.
6 Kasperkiewicz M, Zillikens D. The pathophysiology of bullous pemphigoid. *Clin Rev Allergy Immunol* 2007; **33**: 67–77.
7 Raffetto JD, Khalil RA. Matrix metalloproteinases in venous tissue remodeling and varicose vein formation. *Curr Vasc Pharmacol* 2008; **6**: 158–72.
8 Sagi L, Sherer Y, Trau H, Shoenfeld Y. Pemphigus and infectious agents. *Autoimmun Rev* 2008; **8**: 33–5.
9 Franzke CW, Tasanen K, Schacke H *et al.* Transmembrane collagen XVII, an epithelial adhesion protein, is shed from the cell surface by ADAMs. *EMBO J* 2002; **21**: 5026–35.
10 Thornfeldt CR. Chronic inflammation is etiology of extrinsic aging. *J Cosmet Dermatol* 2008; **7**: 78–82.
11 Suomela S, Kariniemi AL, Impola U *et al.* Matrix metalloproteinase-19 is expressed by keratinocytes in psoriasis. *Acta Derm Venereol* 2003; **83**: 108–14.
12 Onoue S, Kobayashi T, Takemoto Y *et al*. Induction of matrix metalloproteinase-9 secretion from human keratinocytes in culture by ultraviolet B irradiation. *J Dermatol Sci* 2003; **33**: 105–11.
13 Gschwandtner M, Purwar R, Wittmann M *et al.* Histamine upregulates keratinocyte MMP-9 production via the histamine H1 receptor. *J Invest Dermatol* 2008; **128**: 2783–91.
14 Harvima IT. Induction of matrix metalloproteinase-9 in keratinocytes by histamine. *J Invest Dermatol* 2008; **128**: 2748–50.
15 Mohan R, Chintala SK, Jung JC *et al.* Matrix metalloproteinase gelatinase B (MMP-9) coordinates and effects epithelial regeneration. *J Biol Chem* 2002; **277**: 2065–72.
16 Brassart B, Fuchs P, Huet E *et al.* Conformational dependence of collagenase (matrix metalloproteinase-1) up-regulation by elastin peptides in cultured fibroblasts. *J Biol Chem* 2001; **276**: 5222–7.
17 Kobayashi T, Hattori S, Shinkai H. Matrix metalloproteinases-2 and -9 are secreted from human fibroblasts. *Acta Derm Venereol* 2003; **83**: 105–7.
18 Purwar R, Kraus M, Werfel T, Wittmann M. Modulation of keratinocyte-derived MMP-9 by IL-13: a possible role for the pathogenesis of epidermal inflammation. *J Invest Dermatol* 2008; **128**: 59–66.
19 Herouy Y, Mellios P, Bandemir E *et al.* Inflammation in stasis dermatitis upregulates MMP-1, MMP-2 and MMP-13 expression. *J Dermatol Sci* 2001; **25**: 198–205.
20 Choi JY, Piao MS, Lee JB *et al*. *Propionibacterium acnes* stimulates pro-matrix metalloproteinase-2 expression through tumor necrosis factor-alpha in human dermal fibroblasts. *J Invest Dermatol* 2008; **128**: 846–54.
21 Gutierrez-Fernandez A, Inada M, Balbin M *et al.* Increased inflammation delays wound healing in mice deficient in collagenase-2 (MMP-8). *FASEB J* 2007; **21**: 2580–91.
22 Beck IM, Ruckert R, Brandt K *et al.* MMP19 is essential for T cell development and T cell-mediated cutaneous immune responses. *PLoS ONE* 2008; **3**: e2343.
23 Bister V, Makitalo L, Jeskanen L, Saarialho-Kere U. Expression of MMP-9, MMP-10 and TNF-alpha and lack of epithelial MMP-1 and MMP-26 characterize pyoderma gangrenosum. *J Cutan Pathol* 2007; **34**: 889–98.
24 Moses MA, Marikovsky M, Harper JW *et al.* Temporal study of the activity of matrix metalloproteinases and their endogenous inhibitors during wound healing. *J Cell Biochem* 1996; **60**: 379–86.
25 Wysocki AB, Staiano-Coico L, Grinnell F. Wound fluid from chronic leg ulcers contains elevated levels of metalloproteinases MMP-2 and MMP-9. *J Invest Dermatol* 1993; **101**: 64–8.
26 Inoue M, Kratz G, Haegerstrand A, Stahle-Backdahl M. Collagenase expression is rapidly induced in wound-edge keratinocytes after acute injury in human skin, persists during healing, and stops at re-epithelialization. *J Invest Dermatol* 1995; **104**: 479–83.
27 Vaalamo M, Weckroth M, Puolakkainen P *et al.* Patterns of matrix metalloproteinase and TIMP-1 expression in chronic and normally healing human cutaneous wounds. *Br J Dermatol* 1996; **135**: 52–9.
28 Saarialho-Kere UK, Vaalamo M, Airola K *et al*. Interstitial collagenase is expressed by keratinocytes that are actively involved in reepithelialization in blistering skin disease. *J Invest Dermatol* 1995; **104**: 982–8.
29 Agren MS, Taplin CJ, Woessner JF *et al*. Collagenase in wound healing: effect of wound age and type. *J Invest Dermatol* 1992; **99**: 709–14.
30 Bullen EC, Longaker MT, Updike DL *et al.* Tissue inhibitor of metalloproteinases-1 is decreased and activated gelatinases are increased in chronic wounds. *J Invest Dermatol* 1995; **104**: 236–40.
31 Chen WY, Rogers AA, Lydon MJ. Characterization of biologic properties of wound fluid collected during early stages of wound healing. *J Invest Dermatol* 1992; **99**: 559–64.
32 Jalkanen M, Haapanen T, Lyytikainen AM, Larjava H. Wound fluids mediate granulation tissue growth phases. *Cell Biol Int Rep* 1983; **7**: 745–53.
33 Jarvinen TM, Kanninen P, Jeskanen L *et al.* Matrix metalloproteinases as mediators of tissue injury in different forms of cutaneous lupus erythematosus. *Br J Dermatol* 2007; **157**: 970–80.
34 Cordiali-Fei P, Trento E, D'Agosto G *et al*. Decreased levels of metalloproteinase-9 and angiogenic factors in skin lesions of patients with psoriatic arthritis after therapy with anti-TNF-alpha. *J Autoimmune Dis* 2006; **3**: 5.
35 Fox RI, Tornwall J, Maruyama T, Stern M. Evolving concepts of diagnosis, pathogenesis, and therapy of Sjogren's syndrome. *Curr Opin Rheumatol* 1998; **10**: 446–56.
36 Xue M, Le NT, Jackson CJ. Targeting matrix metalloproteases to improve cutaneous wound healing. *Expert Opin Ther Targets* 2006; **10**: 143–55.
37 Sapadin AN, Fleischmajer R. Tetracyclines: nonantibiotic properties and their clinical implications. *J Am Acad Dermatol* 2006; **54**: 258–65.

Lysosomal mediators

The role of lysosomes in skin inflammation—although underestimated—was highlighted by Winkelmann and Lazarus decades ago [1,2]. Recent research indicates lysosomal proteins to be involved in inflammation, wound healing, fibrosis, ageing and autoimmune diseases [3,4]. Many mediators of inflammation, particularly tissue-destructive enzymes, are derived from cellular lysosomes, which on release into the cytoplasm result in autolysis. Extracellularly, they degrade tissue elements (e.g. collagen and elastin) and dead cells [5,6]. These enzymes may also activate further mediators of inflammation in the plasma or tissue fluids

(e.g. the generation of kinins from kallikrein is induced by the trypsin-like activity of lysosomal proteases). Such proteases can also cleave complement C3 to activate the alternative pathway of complement.

Lysosomes are found in nearly all living cells, and comprise a semipermeable membrane surrounding a small vacuole, which contains acidic hydrolases and other enzymes and substances. There is some variation in the lysosomal components to be found in each type of cell [5,6]. In the developing neutrophil, lysosomes are derived from the Golgi complex; in macrophages and some other cells including keratinocytes, it is believed that they are derived from the rough endoplasmic reticulum and are transferred to special areas of the smooth endoplasmic reticulum situated within the Golgi complex.

Epidermal cells have lysosomes that contain acid phosphatases, aryl sulphatase, several proteases including the acidic protease cathepsin D, and other enzymes [7–9]. One of the difficulties in examining these enzymes is the presence of inhibitors, which inactivate enzymes of the epidermal cells, as well as of the dermis and plasma.

The lysosomes participate in the phagocytic functions of epidermal cells, particularly active during regeneration after wounds. They are also involved in pigmentation, as melanosomes are transferred to keratinocytes by a process analogous to phagocytosis. Epidermal cell derived lysosomes are involved in keratinization, responses to UV light and neoplasia [7,10]. Lysosomes also appear to be involved in sebum secretion, as they enlarge and rupture in the process of cell disintegration.

During inflammation the increase in extracellular acid phosphatase and protease is attributed to the release of epidermal lysosomes, because it occurs before leukocyte infiltration and is predominantly concentrated at the site of inflammation rather than in the serum. Leukocytes, particularly neutrophils, entering the lesion may be attracted by chemotactic factors generated by the activity of acid or neutral proteases, which cleave complement, kallikrein or Hageman factor. Accordingly, a neutral proteinase extracted from rabbit skin induced wealing within 15 min and acute neutrophil infiltration within 18 h when injected into the skin, indicating the possible participation of epidermal cell lysosome enzymes in inflammation [11].

Lysosomal proteins are also involved in the regulation of lymphatic vessel function [12], wound healing [4], regulation of T cell–Langerhans' cell interactions [13], keratinocyte function [14], granulomatous slack skin disease [15], mycobacteriosis [16] and Wegener's disease [3,17].

References

1 Lazarus GS, Hatcher VB. Lysosomes and the skin. *Front Biol* 1975; **43**: 111–43.

2 Winkelmann RK. Molecular inflammation of the skin. *J Invest Dermatol* 1971; **57**: 197–208.

3 Jennette JC, Falk RJ. Antineutrophil cytoplasmic autoantibodies and associated diseases: a review. *Am J Kidney Dis* 1990; **15**: 517–29.

4 Nurden AT, Nurden P, Sanchez M *et al*. Platelets and wound healing. *Front Biosci* 2008; **13**: 3532–48.

5 Alberts B, Johnson A, Lewis J *et al*. *Molecular Biology of the Cell,* 4th edn. New York and London: Garland Science, 2002.

6 Lodish B, Berk A, Zipursky SL *et al*. *Molecular Cell Biology,* 4th edn. New York: WH Freeman, 1999.

7 Lazarus GS, Hatcher VB, Levine N. Lysosomes and the skin. *J Invest Dermatol* 1975; **65**: 259–71.

8 Mier PD, van den Hurk JJ. Lysosomal hydrolases of the epidermis. 3. Peptide hydrolases. *Br J Dermatol* 1975; **93**: 509–17.

9 Mier PD, van den Hurk JJ. Lysosomal hydrolases of the epidermis. 2. Ester hydrolases. *Br J Dermatol* 1975; **93**: 391–8.

10 Honigsmann H, Wolff K, Konrad K. Epidermal lysosomes and ultraviolet light. *J Invest Dermatol* 1974; **63**: 337–42.

11 Lazarus GS, Barrett AJ. Neutral proteinase of rabbit skin: an enzyme capable of degrading skin protein and inducing an inflammatory response. *Biochim Biophys Acta* 1974; **350**: 1–12.

12 Johnson LA, Prevo R, Clasper S, Jackson DG. Inflammation-induced uptake and degradation of the lymphatic endothelial hyaluronan receptor LYVE-1. *J Biol Chem* 2007; **282**: 33671–80.

13 Bechetoille N, Andre V, Valladeau J *et al*. Mixed Langerhans cell and interstitial/dermal dendritic cell subsets emanating from monocytes in Th2-mediated inflammatory conditions respond differently to proinflammatory stimuli. *J Leukoc Biol* 2006; **80**: 45–58.

14 Schwarz G, Boehncke WH, Braun M *et al*. Cathepsin S activity is detectable in human keratinocytes and is selectively upregulated upon stimulation with interferon-gamma. *J Invest Dermatol* 2002; **119**: 44–9.

15 Tsang WY, Chan JK, Loo KT *et al*. Granulomatous slack skin. *Histopathology* 1994; **25**: 49–55.

16 Gutierrez MG, Mishra BB, Jordao L *et al*. NF-kappa B activation controls phagolysosome fusion-mediated killing of mycobacteria by macrophages. *J Immunol* 2008; **181**: 2651–63.

17 Fissolo N, Kraus M, Reich M *et al*. Dual inhibition of proteasomal and lysosomal proteolysis ameliorates autoimmune central nervous system inflammation. *Eur J Immunol* 2008; **38**: 2401–11.

Radical oxygen species (ROS)

Radical oxygen species (ROS) are critically involved in many processes during acute and chronic inflammation such as ageing, cell differentiation, apoptosis, release of inflammatory mediators, etc. They monitor oxygen tension for the control of cell homeostasis and mediator production, and are involved in many signal transduction pathways involving membrane receptors during various physiological and pathophysiological processes. Activation is caused by membrane stimulation, phagocytosis, immune complexes or aggregated immunoglobulins (IgG and IgA) as well as IFN-γ. Oxygen radicals may exist following generation only for seconds; they potentially act as toxic agents, although their effects may not always be significant, and depend on the availability of intracellular control mechanisms [1–4].

NO and ROS are typically generated by tightly regulated enzymes such as NO synthase (NOS) and NADPH oxidase, or from less well-regulated sources such as the mitochondrial electron-transport chain. The massive production of antimicrobial and tumoricidal ROS in an inflammatory environment is known as the 'oxidative burst' and plays an important role as first-line defence against environmental pathogens. The physiological relevance of NADPH oxidase as a defensive agent is suggested by the observation that mice lacking the NADPH oxidase components gp91phox or p47 exhibit reduced resistance to infection [5–7].

Various forms ('species') of activated oxygen and intermediates exist: superoxide anion O^-, a precursor of toxic products, H_2O_2, MPO particularly formed in phagocytes, and hydroxyl ($HO^\bullet$) and singlet oxygen ($^\bullet O_2$) radicals, which give rise to chemiluminescence. Oxygen (O_2) alone is not toxic, and H_2O_2 in small amounts is a normal cell signal molecule; both may be converted to reactive

factors. H_2O_2, particularly in the presence of iron, is converted to the very reactive hydroxyl radical HO•. The HO• mediates a chain reaction with lipid and cyclic peroxides as the end-products, and causes cell death and membrane lysis. Furthermore, the superoxide anion of the human monocyte oxidizes low-density lipoprotein and converts it into a cytotoxin, which damages fibroblast cell lines [8].

In mitochondria, ROS are generated as undesirable side products of the oxidative energy pathway. An excessive and/or sustained increase in ROS production has been implicated in the pathogenesis of UV damage, skin ageing, autoimmune diseases, cancer, injury and wound healing, and many other diseases. ROS have been implicated in the pathophysiology of skin ageing as there is increasing evidence that free radical-mediated events may alter the expression of genes coding for proteins such as NF-κB. Finally, a crucial role for oxygen-dependent cytotoxicity in cutaneous cancerogenesis, as well as in decreased control of DNA synthesis and cell division, has been described [9,10].

There is growing evidence that oxidative stress has a pivotal role in various diseases such as inflammation, tumour growth, metabolic diseases, atherosclerosis and thrombosis, and infections such as HIV. 'Mitochondrial oxidative stress' seems to be crucial in metabolic diseases and cancer, resulting in a pro-oxidative shift in the systemic thiol–disulphide redox state and elevated ROS production. In these cases, increased ROS levels or changes in the intracellular glutathione levels are often associated with pathological alterations. Accordingly, this may result in a dysregulation of signalling or gene expression in inflammation in relation to cell adhesion molecules or cytokines [11,12].

During inflammation, NO and ROS are capable of killing microorganisms, thereby contributing to host defence. The generation of their activity is associated with the respiratory burst when cells are exposed to foreign agents. In the skin, UV radiation may—alone or following exposure to phototoxic or photoallergic chemicals as in PUVA therapy—induce activation of NO and ROS species, leading to the production of various inflammatory mediators, including cytokines and kinins. Similar effects are observed in patients with porphyria who have been exposed to UV light. The poly (ADP-ribose) polymerase (PARP) pathway appears to have an important role in the regulation of inflammatory reactions in the skin [13]. Some of the inflammatory activities of monocyte–macrophages, neutrophils and eosinophils are the result of free radicals. There is growing evidence that the biochemical basis for the mechanism of action of dithranol at the molecular level is related to redox activity leading to the production of active oxygen species, including singlet oxygen, superoxide anion and hydroxyl radical [14]. ROS molecules have been implicated in regulating leukocyte–endothelial interactions. Thus, adhesion of neutrophils to endothelial cells involves the stimulation of ICAM-1 and L-selectin via ROS activation [15,16].

There also exist important physiological aspects of redox regulation. The enzyme-mediated production of superoxide and NO, respectively, is strictly regulated by cytokines and other inflammatory mediators. Subsequently, the resulting oxidative species act as secondary messengers to control a variety of physiological responses such as vascular relaxation or hormone production [17].

Enhancement of signal transduction pathways by stimulation of ROS leads to up-regulation of expression or receptors involved in inflammation, such as the angiotensin II receptor and the EGF receptor. Furthermore, H_2O_2 has a relatively long half-life and may directly cross the cell membrane to modulate cell function. For example, ROS from activated macrophages and neutrophils may contribute to the activation of antigen-specific immune responses to pathogens. Signalling pathways involving JNK, p38 MAPK, and the transcription factors AP-1 and NF-κB, are particularly responsive to redox regulation. Thus, various intracellular signalling cascades are modulated by ROS molecules [18–20].

The production of ROS by non-phagocytic NADPH oxidase isoforms also plays a part in the regulation of intracellular signalling within non-phagocytic cells, including fibroblasts. Moreover, activated macrophages and neutrophils can produce large amounts of superoxide and its derivatives via the phagocytic isoform of NADPH oxidase. Stimulated neutrophils and macrophages generate singlet oxygen by reactions that involve either MPO or NADPH oxidase, respectively. Importantly, physiologically relevant ROS concentrations can modulate redox-sensitive signalling cascades and enhance immunological functions of lymphocytes [20,21].

With regard to achieving a balanced inflammatory response, the activity of free radicals has to be rapidly terminated. Therefore, various endogenous and exogenous molecules rapidly inactivate the function of extracellular oxygen species, such as superoxide dismutase, catalase and glutathione peroxidase, free α-tocopherols and antioxidants.

In summary, ROS generated by many cells in the immune system and the skin can modulate inflammation and infection. Clinical interventions with ROS-modulating agents may help to attenuate oxidative stress that is directly attributable to inflammation.

References

1 Biasi D, Carletto A, Caramaschi P *et al.* Neutrophil functions and IL-8 in psoriatic arthritis and in cutaneous psoriasis. *Inflammation* 1998; **22**: 533–43.

2 Hussain SP, Hofseth LJ, Harris CC. Radical causes of cancer. *Nat Rev Cancer* 2003; **3**: 276–85.

3 Aslan M, Freeman BA. Oxidases and oxygenases in regulation of vascular nitric oxide signaling and inflammatory responses. *Immunol Res* 2002; **26**: 107–18.

4 Folkerts G, Kloek J, Muijsers RB, Nijkamp FP. Reactive nitrogen and oxygen species in airway inflammation. *Eur J Pharmacol* 2001; **429**: 251–62.

5 Morgenstern DE, Gifford MA, Li LL *et al.* Absence of respiratory burst in X-linked chronic granulomatous disease mice leads to abnormalities in both host defense and inflammatory response to *Aspergillus fumigatus*. *J Exp Med* 1997; **185**: 207–18.

6 Dinauer MC, Deck MB, Unanue ER. Mice lacking reduced nicotinamide adenine dinucleotide phosphate oxidase activity show increased susceptibility to early infection with *Listeria monocytogenes*. *J Immunol* 1997; **158**: 5581–3.

7 Gao XP, Standiford TJ, Rahman A *et al.* Role of NADPH oxidase in the mechanism of lung neutrophil sequestration and microvessel injury induced by Gram-negative sepsis: studies in p47phox-/- and gp91phox-/- mice. *J Immunol* 2002; **168**: 3974–82.

8 Gil-Lamaignere C, Roilides E, Lyman CA *et al.* Human phagocytic cell responses to *Scedosporium apiospermum* (*Pseudallescheria boydii*): variable susceptibility to oxidative injury. *Infect Immun* 2003; **71**: 6472–8.

9 Nakamura Y, Feng Q, Kumagai T *et al.* Ebselen, a glutathione peroxidase mimetic seleno-organic compound, as a multifunctional antioxidant. Implication for inflammation-associated carcinogenesis. *J Biol Chem* 2002; **277**: 2687–94.

10 Murakami A, Nakamura Y, Torikai K *et al.* Inhibitory effect of citrus nobiletin on phorbol ester-induced skin inflammation, oxidative stress, and tumor promotion in mice. *Cancer Res* 2000; **60**: 5059–66.

11 Nakamura Y, Murakami A, Ohto Y *et al*. Suppression of tumor promoter-induced oxidative stress and inflammatory responses in mouse skin by a superoxide generation inhibitor 1′-acetoxychavicol acetate. *Cancer Res* 1998; **58**: 4832–9.
12 Mulligan MS, Varani J, Warren JS *et al*. Roles of beta 2 integrins of rat neutrophils in complement- and oxygen radical-mediated acute inflammatory injury. *J Immunol* 1992; **148**: 1847–57.
13 Virag L, Szabo E, Bakondi E *et al*. Nitric oxide-peroxynitrite-poly(ADP-ribose) polymerase pathway in the skin. *Exp Dermatol* 2002; **11**: 189–202.
14 Swinkels OQ, Prins M, Gerritsen MJ *et al*. An immunohistochemical assessment of the response of the psoriatic lesion to single and repeated applications of high-dose dithranol cream. *Skin Pharmacol Appl Skin Physiol* 2002; **15**: 393–400.
15 Cooper D, Stokes KY, Tailor A, Granger DN. Oxidative stress promotes blood cell-endothelial cell interactions in the microcirculation. *Cardiovasc Toxicol* 2002; **2**: 165–80.
16 Ichimura H, Parthasarathi K, Quadri S *et al*. Mechano-oxidative coupling by mitochondria induces proinflammatory responses in lung venular capillaries. *J Clin Invest* 2003; **111**: 691–9.
17 Neuschwander-Tetri BA, Ferrell LD, Sukhabote RJ, Grendell JH. Glutathione monoethyl ester ameliorates caerulein-induced pancreatitis in the mouse. *J Clin Invest* 1992; **89**: 109–16.
18 Haddad JJ. Antioxidant and prooxidant mechanisms in the regulation of redox(y)-sensitive transcription factors. *Cell Signal* 2002; **14**: 879–97.
19 Kamata H, Hirata H. Redox regulation of cellular signalling. *Cell Signal* 1999; **11**: 1–14.
20 Gil L, Martinez G, Gonzalez I *et al*. Contribution to characterization of oxidative stress in HIV/AIDS patients. *Pharmacol Res* 2003; **47**: 217–24.
21 Calhoun WJ, Salisbury SM, Chosy LW, Busse WW. Increased alveolar macrophage chemiluminescence and airspace cell superoxide production in active pulmonary sarcoidosis. *J Lab Clin Med* 1988; **112**: 147–56.

Nitric oxide

Over the last few years, NO has been established as a versatile factor in the immune system. NO is involved in the pathophysiology and control of inflammation, infectious diseases, autoimmune processes, tumourigenesis and chronic degenerative diseases, and may be of considerable importance in a variety of skin diseases (Table 12.9). Originally, NO was perceived as a product of macrophages activated by cytokines and generated from the amino acid L-arginine by the enzymatic activity of inducible NO synthase (iNOS or NOS2). It is now known that NO functions are considerably more complex. NO has a wide distribution in immune cells such as dendritic cells, eosinophils and neutrophils, Kupffer cells, macrophages, mast cells, microglial and NK cells, as well as in other cells that may be involved in immune reactions, such as chondrocytes, endothelial cells, epithelial cells, hepatocytes, mesangial cells, Schwann cells and vascular smooth muscle cells [1,2]. Furthermore, additionally to iNOS, different isoforms of NO synthase have been identified—endothelial NOS (eNOS or NOS3), neuronal NOS (nNOS or NOS1), both also known as constitutive NOS (cNOS)—that all operate within the immune system and catalyse the same reaction, conversion of L-arginine to NO [2]. Importantly, the activity of NO is not restricted to the site of production. It is highly diffusible, and the ability of NO to form complexes allows it to bridge long distances. Circulating nitrite (NO_2^-), a stable product of the NOS reaction, can be reduced to $^{\bullet}NO$, which is the substrate for the peroxidase pathways of eosinophils and neutrophils, leading to the formation of novel NO-derived oxidants at distant sites [3,4]. Therefore, NOS-negative immune cells can both produce NO and become targets of NO action.

Table 12.9 Pathophysiological role of nitric oxide in human skin.

Disease	Functions
Contact dermatitis (CD)	Modified expression in allergic and irritant contact dermatitis NOS expression in irritant CD: focal staining in epidermis and dermis
Atopic dermatitis	Clinical application of NOS inhibitor for atopic dermatitis Enhanced staining in the spongiotic area of the epidermis and of the perivascular region (inflammatory cells?)
Acute urticaria	NOS expression co-localized with inflammatory cytokines and CD23
Psoriasis	iNOS mRNA and IL-8 mRNA co-localize in keratinocytes of psoriatic skin Overexpression of iNOS in keratinocytes of psoriatic lesions NO may account for reduced incidence of infections in psoriasis
Lupus erythematosus (LE)	iNOS expression in cutaneous and systemic LE. Aberrant timing of UVA-induced iNOS expression in LE patients Enhanced NO production, endothelial and keratinocyte iNOS production in LE patients
Systemic sclerosis (SSC)	Increased iNOS and eNOS expression by endothelial cells in SSC Enhanced iNOS synthesis in SSC patients Increased NO production and iNOS synthesis in mononuclear cells, endothelial cells and fibroblasts in lesional skin of SSC
Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN)	Expression of iNOS in inflammatory cells of SJS and TEN
Sunburn erythema	Topical application of NO inhibitors protects against UVB-induced erythema UVB acts as a potent stimulator of eNOS and xanthine oxidase in human keratinocytes
Leg ulcers	Increased NOS expression in chronic leg ulcers Increased NOS activity in diabetic foot ulcers (macrophages)
Burn injury	Enhanced NO production in skin lesions Expression of iNOS in burn wounds (keratinocytes, capillary endothelium)
Tinea pedis	Successful treatment with an NO-liberating cream (acidified nitrate)
Molluscum contagiosum	Successful treatment with an NO-liberating cream (acidified nitrate)

eNOS, endothelial nitric oxide synthase; iNOS, inducible nitric oxide synthase; NO, nitric oxide; NOS, nitric oxide synthase.

The expression of iNOS is regulated by cytokines, while nNOS and eNOS, constitutively expressed in the cell, are activated by elevation of intracellular Ca^{2+} concentration and binding of calmodulin. All three NOS isoforms are only active as homodimers. In low concentrations, NO itself activates NF-κB and upregulates iNOS, whereas high concentrations exert the opposite effect and therefore may help to prevent NO overproduction.

Another factor that determines NOS activity is the availability of its substrate, arginine. Generation of NO (e.g. by macrophages) depends on extracellular L-arginine even when an adequate level of intracellular arginine is present [2,5].

The use of NOS inhibitors, NO donors and NOS knockout mice has provided evidence that NO triggers a broad spectrum of reactions. Accordingly, NO inhibits the adhesion of platelets and leukocytes to endothelium [6], via down-regulating the expression of adhesion molecules such as E-selectin, P-selectin, ICAM-1 and VCAM-1 [7,8]. Moreover, NO can inhibit the expression of integrins such as LFA-1 on neutrophils [6–8] and influence the chemotactic response of leukocytes by modulating the production and activity of chemokines [2,9–11]. Additionally, differentiation, proliferation and apoptosis of immune cells is mediated by NO. In the thymus deletion of T-cell receptor-activated double-positive thymocytes is dependent on thymic stromal cell released NO [12–16].

There is also evidence for a complex role of NO in autoimmune diseases such as experimental autoimmune arthritis (EAA), encephalomyelitis (EAE), uveitis (EAU) and nephritis (EAN). According to animal studies, iNOS appears to function as a negative feedback regulator of autoimmune Th1 cell response and thereby protect the host against immunopathological sequelae [1,17]. However, it has to be pointed out that results obtained with iNOS knockout mice, and mice treated with NOS inhibitors, do not support this view [17–19]. A possible explanation derives from work by McCartney-Francis *et al*. [19] on the streptococcal cell wall-induced arthritis model in rats, in which eNOS and nNOS appear to mediate the acute and chronic erosive joint disease, whereas iNOS helped to limit inflammation. Furthermore, a protective anti-inflammatory function of iNOS has been demonstrated in a T-cell-dependent and B-cell-mediated myasthenia gravis-like autoimmune disease [20], in local carrageenan-induced pleurisy [21] and in TNF-induced shock in mice [22]. In humans, a role of NOS has been demonstrated in pemphigus vulgaris [23].

References

1 Bogdan C. The function of nitric oxide in the immune system. In: Balligand JL, Mayer BB, eds. *Handbook of Experimental Pharmacology Nitric Oxide*. Heidelberg: Springer 2000: 443–92.

2 Bogdan C. Nitric oxide and the immune response. *Nat Immunol* 2001; **2**: 907–16.

3 Eiserich JP, Hristova M, Cross CE *et al.* Formation of nitric oxide-derived inflammatory oxidants by myeloperoxidase in neutrophils. *Nature* 1998; **391**: 393–7.

4 MacPherson JC, Comhair SA, Erzurum SC *et al.* Eosinophils are a major source of nitric oxide-derived oxidants in severe asthma: characterization of pathways available to eosinophils for generating reactive nitrogen species. *J Immunol* 2001; **166**: 5763–72.

5 Chang CI, Liao JC, Kuo L. Arginase modulates nitric oxide production in activated macrophages. *Am J Physiol* 1998; **274**: H342–8.

6 Grisham MB, Granger DN, Lefer DJ. Modulation of leukocyte-endothelial interactions by reactive metabolites of oxygen and nitrogen: relevance to ischemic heart disease. *Free Radic Biol Med* 1998; **25**: 404–33.

7 Banick PD, Chen Q, Xu YA, Thom SR. Nitric oxide inhibits neutrophil beta 2 integrin function by inhibiting membrane-associated cyclic GMP synthesis. *J Cell Physiol* 1997; **172**: 12–24.

8 Hickey MJ, Sharkey KA, Sihota EG *et al.* Inducible nitric oxide synthase-deficient mice have enhanced leukocyte-endothelium interactions in endotoxemia. *FASEB J* 1997; **11**: 955–64.

9 Pfeilschifter J, Eberhardt W, Beck KF. Regulation of gene expression by nitric oxide. *Pflugers Arch* 2001; **442**: 479–86.

10 Mach F, Sauty A, Iarossi AS *et al.* Differential expression of three T lymphocyte-activating CXC chemokines by human atheroma-associated cells. *J Clin Invest* 1999; **104**: 1041–50.

11 Trifilieff A, Fujitani Y, Mentz F *et al*. Inducible nitric oxide synthase inhibitors suppress airway inflammation in mice through down-regulation of chemokine expression. *J Immunol* 2000; **165**: 1526–33.

12 Tai XG, Toyo-oka K, Yamamoto N *et al.* Expression of an inducible type of nitric oxide (NO) synthase in the thymus and involvement of NO in deletion of TCR-stimulated double-positive thymocytes. *J Immunol* 1997; **158**: 4696–703.

13 Aiello S, Noris M, Piccinini G *et al.* Thymic dendritic cells express inducible nitric oxide synthase and generate nitric oxide in response to self- and alloantigens. *J Immunol* 2000; **164**: 4649–58.

14 Moulian N, Truffault F, Gaudry-Talarmain YM *et al*. *In vivo* and *in vitro* apoptosis of human thymocytes are associated with nitrotyrosine formation. *Blood* 2001; **97**: 3521–30.

15 Fehsel K, Kroncke KD, Meyer KL *et al*. Nitric oxide induces apoptosis in mouse thymocytes. *J Immunol* 1995; **155**: 2858–65.

16 Brito C, Naviliat M, Tiscornia AC *et al.* Peroxynitrite inhibits T lymphocyte activation and proliferation by promoting impairment of tyrosine phosphorylation and peroxynitrite-driven apoptotic death. *J Immunol* 1999; **162**: 3356–66.

17 Bogdan C. The multiplex function of nitric oxide in (auto)immunity. *J Exp Med* 1998; **187**: 1361–5.

18 Gilkeson GS, Mudgett JS, Seldin MF *et al.* Clinical and serologic manifestations of autoimmune disease in MRL-lpr/lpr mice lacking nitric oxide synthase type 2. *J Exp Med* 1997; **186**: 365–73.

19 McCartney-Francis NL, Song X, Mizel DE, Wahl SM. Selective inhibition of inducible nitric oxide synthase exacerbates erosive joint disease. *J Immunol* 2001; **166**: 2734–40.

20 Shi FD, Flodstrom M, Kim SH *et al.* Control of the autoimmune response by type 2 nitric oxide synthase. *J Immunol* 2001; **167**: 3000–6.

21 Paul-Clark MJ, Gilroy DW, Willis D *et al*. Nitric oxide synthase inhibitors have opposite effects on acute inflammation depending on their route of administration. *J Immunol* 2001; **166**: 1169–77.

22 Cauwels A, Van Molle W, Janssen B *et al.* Protection against TNF-induced lethal shock by soluble guanylate cyclase inhibition requires functional inducible nitric oxide synthase. *Immunity* 2000; **13**: 223–31.

23 Marquina M, Espana A, Fernandez-Galar M, Lopez-Zabalza MJ. The role of nitric oxide synthases in pemphigus vulgaris in a mouse model. *Br J Dermatol* 2008; **159**: 68–76.

Histamine

Histamine (2-[4-imidazolyl]ethylamine) was the first mediator of anaphylaxis to be identified, in 1932. Its pharmacological description as an endogenous substance was even earlier, in 1910 [1]. Histamine is synthesized from histidine by the specific enzyme L-histidine decarboxylase (HDC). It can be generated by some neurones, mast cells, basophils and platelets, where it is intracellularly stored in vesicles, and rapidly released upon stimulation. However, it has been shown that HDC is inducible in a variety of tissues by a mechanism coupled with the cytokine network, leading to non-classical histamine generation. Histamine, like tryptase, is one of the mediators rapidly released from mast cells during inflammation and hypersensitivity. However, recent knowledge clearly indicates that histamine is not the only inflammatory mediator released by mast cells.

Histamine exerts a powerful effect on blood vessels, causing smooth muscle contraction, vasodilatation and plasma extravasation from capillaries. Classically, histamine is released upon an antigen–antibody reaction with IgE bridging on the cell surface of mast cells. Further studies have shown that histamine release can

be also triggered in an IgE-independent manner (e.g. by direct interaction of molecules with cell membrane-associated G proteins or transmembrane lipid mediators). Release of high concentrations of histamine, as during immediate-type hypersensitivity, leads to systemic shock symptoms such as vasodilatation, oedema, smooth muscle contraction, decreased blood pressure and subsequent cardiopulmonary dysfunction.

Histamine mediates itch responses, especially at the beginning of an inflammatory response by activating histamine receptors on cutaneous sensory nerves. However, histamine does not appear to be the crucial mediator of itch in inflammatory skin diseases such as atopic dermatitis. Thus, a variety of distinct mediators seem to be responsible for mediating pruritus in different inflammatory skin diseases. For example, cytokines or proteinases released during the inflammatory response also have been found to activate itch mediating nerve fibres [2].

Additionally, histamine can exert direct effects on immune cells, endothelial cells and primary efferent nerve fibres via activation of histamine receptors. Four histamine receptors (HRs) have been cloned and characterized so far, which belong to the G protein-coupled receptor family with seven transmembrane domains (H_1–H_4). Except for H_3R, which is exclusively expressed in the brain, histamine receptors are widely distributed throughout the body. Thus, H_4R is located in the thymus, small intestine, liver, spleen, colon, bone marrow and on peripheral blood leukocytes [3]. H_1R is found to be expressed by tissues including mammalian brain, retina, airway, skin [4], genitourinary tract, vascular smooth muscle, adrenal medulla, liver, endothelial cells, astrocytoma cells, cerebral microvessels and lymphocytes [5]. H_2R shows a similar expression pattern to H_1R, being detected in mammalian brain, pulmonary system, cardiovascular system, intestine, skin [4], endocrine as well as exocrine glands [6] and the immune system, in T cells [7,8], macrophage–monocytes and lymphocytes [9].

In the skin, H_1R is localized on fibroblasts [10] and endothelial cells [11], and both H_1R and H_2R are expressed on keratinocytes [12,13]. After histamine activation, H_1R mediates several vascular responses, such as increased vascular permeability, vasodilatation and constriction of smooth muscle cells. H_2R exerts various effects on immune cells, such as mediator release from basophils, neutrophils and lymphocytes. Interestingly, H_2R augments T-suppressor cell activity, whereas H_1R activates regulatory T cells with contradictory effects. H_3R function is implicated in neuroregulation in the central nervous system.

Immune cells (mast cells, basophils and probably others) as well as neurones serve as cellular sources of histamine in the human body, albeit with a large difference in respect to active molecule levels. H_4R is activated by histamine at relatively low concentrations (5 nM) and, notably, by synthetic agonists (4-methylhistamine, OUP16 and some others). H_4R function can be selectively antagonized by a small molecule: JNJ7777120 and its benzimidazole analogue VUF6002. H_4R is able to cause signs of inflammation (oedema and leukocyte recruitment), and pruritus. H_4R participates in histamine-induced chemotaxis of these cells. Moreover, histamine-induced effects on the expression of cell adhesion molecules appear to be mediated via H_4R. H_4R is also involved in histamine-induced scratching in mice [14]. Thus, H_4R may be involved in the pathophysiology of skin inflammation, allergy and pruritus.

Histamine action can be terminated by receptor down-regulation, enzymes and suppressor factors. One of the latter is histamine suppressor factor (HSF), synthesized for example by activated lymphocytes. In monocytes histamine also was found to induce the production of mediators inhibiting lymphocyte migration [15]. Apart from these direct activities of histamine, it enhances expression of cell receptors, and depending on the concentration either may inhibit or stimulate the outgrowth of epidermis from skin slices *in vitro* [16]. Thus, depending on the concentration of degrading enzymes and the receptor repertoire on the cells involved histamine may contribute to pro-inflammatory as well as regenerative changes in the tissue.

Histamine formation and release is regulated by several factors other than IgE, such as cytokines, prostaglandins, leukotrienes and neuropeptides. In contrast, histamine activity regulates the formation of cytokines. Accordingly, some cytokines and chemokines such as IL-1, IL-3, IL-5, IL-8 and MCP-1, are potent inducers of histamine synthesis and release. Histamine, through the H_2 receptor, reduces the production of IL-1, IL-6 and TNF-α from endotoxin-stimulated monocytes [17,18]. Histamine also inhibits the formation of IL-2, and possibly indirectly through IL-2 inhibition also reduces IFN-γ activity [17].

Histamine regulates T-cell and B-cell functions by differential expression of H_1 and H_2 receptors [8]. Accordingly, histamine enhances Th1 responses by triggering the H_1R, whereas both Th1 and Th2 responses are negatively regulated by H_2R via the activation of different intracellular signalling pathways. In mice, deletion of H_1R resulted in the suppression of IFN-γ and the dominant secretion of Th2 cytokines (IL-4 and IL-13) associated with an increased specific antibody response (IgE, IgG1, IgG2b and IgG3). Mutant mice lacking H_2R showed up-regulation of both Th1 and Th2 cytokines [8]. These findings indicate an important regulatory mechanism in the control of inflammatory and immune functions through release of histamine. Finally, histamine also modulates MMP-9 production by keratinocytes [19].

References

1 Dale HH, Laidlaw PP. The physiological action of beta-iminazolylethylamine. *J Physiol* 1910; **41**: 318–44.

2 Stander S, Steinhoff M. Pathophysiology of pruritus in atopic dermatitis: an overview. *Exp Dermatol* 2002; **11**: 12–24.

3 Oda T, Morikawa N, Saito Y *et al*. Molecular cloning and characterization of a novel type of histamine receptor preferentially expressed in leukocytes. *J Biol Chem* 2000; **275**: 36781–6.

4 Greaves MW, Davies MG. Histamine receptors in human skin: indirect evidence. *Br J Dermatol* 1982; **107** (Suppl. 23): 101–5.

5 Hill SJ. Distribution, properties, and functional characteristics of three classes of histamine receptor. *Pharmacol Rev* 1990; **42**: 45–83.

6 Hirata N, Takeuchi K, Ukai K *et al*. Expression and localization of histamine H2 receptor messenger RNA in human nasal mucosa. *J Allergy Clin Immunol* 1999; **103**: 944–9.

7 Kunzmann S, Mantel PY, Wohlfahrt JG *et al*. Histamine enhances TGF-beta1-mediated suppression of Th2 responses. *FASEB J* 2003; **17**: 1089–95.

8 Jutel M, Watanabe T, Klunker S *et al*. Histamine regulates T-cell and antibody responses by differential expression of H1 and H2 receptors. *Nature* 2001; **413**: 420–5.

9 Sachs B, Hertl M, Merk HF. Histamine receptors on lymphocytes: distribution and functional significance. *Skin Pharmacol Appl Skin Physiol* 2000; **13**: 313–23.

10 Johnson CL, Johnson CG. Inhibition of human skin fibroblast proliferation by histamine and phorbol esters is mediated by protein kinase C. *Cell Signal* 1990; **2**: 105–13.
11 Baenziger NL, Fogerty FJ, Mertz LF, Chernuta LF. Regulation of histamine-mediated prostacyclin synthesis in cultured human vascular endothelial cells. *Cell* 1981; **24**: 915–23.
12 Koizumi H, Ohkawara A. H2 histamine receptor-mediated increase in intracellular Ca^{2+} in cultured human keratinocytes. *J Dermatol Sci* 1999; **21**: 127–32.
13 Kanda N, Watanabe S. Histamine inhibits the production of interferon-induced protein of 10 kDa in human squamous cell carcinoma and melanoma. *J Invest Dermatol* 2002; **119**: 1411–9.
14 Rossbach K, Wendorff S, Sander K *et al*. Histamine H4 receptor antagonism reduces hapten-induced scratching behaviour but not inflammation. *Exp Dermatol* 2009; **18**: 57–63.
15 Berman JS, McFadden RG, Cruikshank WW *et al*. Functional characteristics of histamine receptor-bearing mononuclear cells. II. Identification and characterization of two histamine-induced human lymphokines that inhibit lymphocyte migration. *J Immunol* 1984; **133**: 1495–504.
16 Aoyagi T, Adachi K, Halprin KM *et al*. The effect of histamine on epidermal outgrowth: its possible dual role as an inhibitor and stimulator. *J Invest Dermatol* 1981; **76**: 24–7.
17 Falus A, Meretey K. Histamine: an early messenger in inflammatory and immune reactions. *Immunol Today* 1992; **13**: 154–6.
18 Kuna P, Reddigari SR, Rucinski D, Kaplan AP. Further characterization of histamine releasing chemokines present in fractionated supernatants derived from human mononuclear cells. *Clin Exp Allergy* 1996; **26**: 926–33.
19 Harvima IT. Induction of matrix metalloproteinase-9 in keratinocytes by histamine. *J Invest Dermatol* 2008; **128**: 2748–50.

Platelet-activating factor

PAF (1-*O*-alkyl-2-acetyl-sn-glycero-3-phosphocholine) is a phospholipid with diverse biological functions, particularly during inflammation. It is rapidly synthesized on stimulation, probably by activation of phospholipase A_2 hydrolysing fatty acid acyl groups as in arachidonic acid, followed by reacetylation. PAF binds to and activates a specific PAF receptor that is expressed by many inflammatory cells. Inactivation of PAF is regulated primarily by the rate of degradation, which is catalysed by PAF-acetylhydrolase. Beside its role as an inflammatory mediator, PAF is also capable of functioning as a hormone and transmitter in the nervous system. PAF is formed concomitantly with other arachidonic acid derivatives, the prostaglandins and leukotrienes.

In humans, PAF is synthesized by monocyte–macrophages, neutrophils, eosinophils, endothelial cells, mast cells, basophils and platelets, in response to immunological, infective or acute inflammatory mediators. PAF stimulates platelet aggregation, as well as synthesis and release of mediators [1], such as serotonin, thromboxane and PAF, within minutes of activation. In neutrophils, PAF induces chemokinesis (activated mobility), chemotaxis (attraction), secretion of lysosomal products, synthesis of 12-HETE and LTB_4 and initiation of the respiratory burst [2,3]. In monocytes PAF induces NF-κB activation and alterations in gene expression [4]. Eosinophils and endothelial cells are particularly responsive to PAF, especially *in vivo*. Moreover, PAF mediates the contraction in postcapillary venules with transient increased vascular permeability, followed by a late phase of erythema. In humans, intradermal injection of PAF has been shown to induce local eosinophilia [5] and a significant neutrophilia with a late-phase erythema [6]. In the skin, PAF is involved in growth of melanocytic tumours, and is known to mediate skin inflammation. In PAF-transgenic animals, an increased mortality was observed upon challenge with endotoxin. In addition these animals developed melanocytic tumours of the skin, and had increased bronchial hyperreactivity [7].

PAF signals the priming and activation of leukocytes at the cell surface of activated human microvascular endothelial cells. Moreover, PAF and the cell adhesion molecule P-selectin are coordinately displayed on stimulated human endothelial cells. P-selectin tethers the leukocyte to the endothelial cell, which allows PAF to bind to its receptors on the endothelial cell and on the polymorphonuclear leukocyte. This constitutes a form of juxtacrine signalling that may be a general way to spatially restrict the actions of a potent pleiotropic mediator such as PAF [8]. The PAF-receptor belongs to a subfamily of G protein-coupled receptors with seven transmembrane domains. It is expressed by many immune cells as well as epithelial cells. PAF-induced signalling is mediated via NF-κB and protein kinase C.

Dysregulated signalling by PAF may result in disease states. For example, developmental deficiency of PAF acetylhydrolase may lead to unregulated pro-inflammatory signalling by PAF in infants with neonatal necrotizing enterocolitis [9]. Dysregulated signalling by PAF also contributes to the severity of asthma in patients genetically deficient in PAF acetylhydrolase. Recently, strategies with exogenous recombinant PAF acetylhydrolase or PAF receptor antagonists demonstrated that PAF is a juxtacrine signalling molecule at the surfaces of activated human platelets, which—like endothelial cells—are critical in cell–cell interactions in inflammatory and thrombotic responses [10].

A role of PAF in inflammatory skin diseases is well documented. For example, PAF is involved in inflammatory response and pain transmission during UV-induced dermatitis [11], contact hypersensitivity [12], psoriasis [13], pruritus [14] and probably acne [15].

References

1 Kloprogge E, de Haas GH, Gorter G, Akkerman JW. Properties of PAF-acether-induced platelet aggregation and secretion. Studies in gel-filtered human platelets. *Thromb Res* 1983; **29**: 595–608.
2 Henson PM. Platelet-activating factor (PAF) as a mediator of neutrophil-platelet interactions in inflammation. *Agents Actions* 1981; **11**: 545–7.
3 Lin AH, Morton DR, Gorman RR. Acetyl glyceryl ether phosphorylcholine stimulates leukotriene B4 synthesis in human polymorphonuclear leukocytes. *J Clin Invest* 1982; **70**: 1058–65.
4 Weyrich AS, McIntyre TM, McEver RP *et al*. Monocyte tethering by P-selectin regulates monocyte chemotactic protein-1 and tumor necrosis factor-alpha secretion. Signal integration and NF-kappa B translocation. *J Clin Invest* 1995; **95**: 2297–303.
5 Henocq E, Vargaftig BB. Accumulation of eosinophils in response to intracutaneous PAF-acether and allergens in man. *Lancet* 1986; **1**: 1378–9.
6 Archer CB, Page CP, Morley J, MacDonald DM. Accumulation of inflammatory cells in response to intracutaneous platelet activating factor (Paf-acether) in man. *Br J Dermatol* 1985; **112**: 285–90.
7 Prescott SM, McIntyre TM, Zimmerman GA. In: Gallin JI, Snyderman R, eds. *Inflammation: Basic Principles and Clinical Correlates*. Philadelphia: Lippincott Williams & Wilkins 1999: 387–96.
8 Prescott SM, Zimmerman GA, Stafforini DM, McIntyre TM. Platelet-activating factor and related lipid mediators. *Annu Rev Biochem* 2000; **69**: 419–45.
9 Caplan MS, Hedlund E, Adler L *et al*. The platelet-activating factor receptor antagonist WEB 2170 prevents neonatal necrotizing enterocolitis in rats. *J Pediatr Gastroenterol Nutr* 1997; **24**: 296–301.
10 Weber C, Springer TA. Neutrophil accumulation on activated, surface-adherent platelets in flow is mediated by interaction of Mac-1 with fibrinogen bound to

alphaIIbbeta3 and stimulated by platelet-activating factor. *J Clin Invest* 1997; **100**: 2085–93.
11 Zhang Q, Sitzman LA, Al-Hassani M *et al.* Involvement of platelet-activating factor in ultraviolet B-induced hyperalgesia. *J Invest Dermatol* 2009; **129**: 167–74.
12 Fukunaga A, Khaskhely NM, Sreevidya CS *et al*. Dermal dendritic cells, and not Langerhans cells, play an essential role in inducing an immune response. *J Immunol* 2008; **180**: 3057–64.
13 Wolf P, Nghiem DX, Walterscheid JP *et al.* Platelet-activating factor is crucial in psoralen and ultraviolet A-induced immune suppression, inflammation, and apoptosis. *Am J Pathol* 2006; **169**: 795–805.
14 Thomsen JS, Sonne M, Benfeldt E *et al*. Experimental itch in sodium lauryl sulphate-inflamed and normal skin in humans: a randomized, double-blind, placebo-controlled study of histamine and other inducers of itch. *Br J Dermatol* 2002; **146**: 792–800.
15 Zhang Q, Seltmann H, Zouboulis CC, Travers JB. Activation of platelet-activating factor receptor in SZ95 sebocytes results in inflammatory cytokine and prostaglandin E2 production. *Exp Dermatol* 2006; **15**: 769–74.

Prostaglandins and leukotrienes

Prostaglandins and thromboxanes

Prostaglandins (PG) and thromboxanes (TX) comprise a diverse family of autacoids, whose synthesis is initiated by cyclo-oxygenase-mediated metabolism of the unsaturated 20-carbon fatty acid arachidonic acid to the endoperoxide intermediates, PGG_2 and PGH_2 [1]. Prostaglandins were first discovered in the 1930s by Von Euler, who investigated the blood pressure lowering potential of compounds from semen. Prostaglandins are products of the cyclo-oxygenase activity on arachidonic acid, and to a much lesser extent other unsaturated fatty acids, and through intermediate products release PGE_2 and PGD_2 by different isomerases, and $PGF_2\alpha$ by a reductase. They are synthesized by many cell types leading to the generation of five bioactive prostanoids: TXA_2, PGD_2, PGE_2, PGF_2 and PGI_2. They function as mediators of inflammation, tumour growth and cardiovascular homeostasis. Each of the prostanoids is generated via activation of specific synthetases. Because prostanoids are either chemically or metabolically unstable, it is believed that they exert their effects very locally [2].

After being released, prostanoids exert their effects by binding and activating a subfamily of eight heptical G protein-coupled receptors, defined as EP (four subtypes for PGE_2) and FP, DP, IP or TP for PGF_2, PGD_2, $PGI_2\alpha$ and TXA_2, respectively [3]. Although each receptor subtype shows the highest affinity to the prospective ligand, cross-reactivity between the family members can be observed [4]. Moreover, splice variants of certain PG receptors can be observed, leading to altered receptor function and probably disease. PG receptors signal via stimulation of IP-3, diacylglycerol, and inhibition of adenylyl cyclase or Gi. In addition to PG transmembrane receptors, the nuclear peroxisome proliferator-activated receptor γ (PPARγ) has been identified as a prostanoid receptor. Interestingly, PPARγ can inactivate NF-κB, thereby modulating inflammatory responses [5].

Prostanoids and their receptors are widely distributed and have a biological role in many cell types. They may exert synergistic but also contradictory effects on specific cell types, such as epithelial cells or smooth muscle cells. In the airways, for example, PGE_2 has a relaxing effect, whereas $PGI_2\alpha$ is a potent vasoconstrictor. PGE_2 shows strong immunosuppressive effects on T cells and facilitates IgE switching in B cells by synergistically acting with LPS or IL-4. $PGI_2\alpha$ induces contraction of smooth muscle cells, and thereby mediates broncho- and vasoconstriction. Moreover, $PGI_{2\alpha}$ also inhibits PGE_2-mediated cutaneous permeability.

Thus, $PGI_2\alpha$ counteracts PGE_2 activity. In normal tissues, concentrations of both mediators seem to be balanced. Under pathophysiological conditions, however, the vasodilator PGE_2 is increased, resulting in pro-inflammatory effects. However, the balance is normalized during tissue regeneration.

In the skin, PGE_2 induces vasodilatation, and potentiates the pro-inflammatory effects of histamine, serotonin as well as bradykinin, and thus induces oedema, plasma extravasation, pruritus and pain [6]. Moreover, PGE_2 has important immunoregulatory functions in decreasing the proliferation of Th1 cells or stimulating the synthesis of IFN-γ [7]. This has clinical implications in patients with atopic dermatitis, who show increased synthesis of PGE_2 in peripheral blood monocytes, decreased Th1 lymphocyte proliferation and reduced synthesis of IFN-γ. PGE_2 also contributes to the synthesis of IL-4, thereby regulating IgE synthesis and affecting the Th1/Th2 balance [8,9]. *In vivo*, prostaglandins also contribute to cutaneous inflammation, such as contact dermatitis or UV-induced inflammation, and they potentiate the itch induced by histamine.

Prostacyclin (PGI_2), the common designation of epoprostenol, is the main metabolic product of arachidonic acid in vascular tissue, particularly in the endothelium [10]. It is an unstable substance with a half-life time of 2–3 min. PGI_2 is the most potent endogenous inhibitor of platelet aggregation, and also disperses aggregated platelets, inhibits thrombus formation, increases cutaneous bleeding time and is a strong vasodilator.

12-HETE and 15-HETE are products of arachidonic acid, converted by the 12- and 15-lipoxygenase enzymes via intermediate peroxy forms. Both are formed by fibroblasts and keratinocytes. 12-HETE is pro-inflammatory, attracting neutrophils, eosinophils as well as monocytes *in vitro*, and aggregates leukocytes [11]. It also stimulates epidermal DNA synthesis. When applied to skin, 12-HETE induces erythema followed by neutrophil and monocyte infiltration, but not eosinophil infiltration [12]. Physiological amounts occur in psoriatic skin and after UV irradiation. As it is much less potent than LTB_4 and other chemoattractants, the significance of 12-HETE in lesional skin is unknown. 15-HETE is the main arachidonic acid metabolite in homogenized dermis, and is almost certainly derived from fibroblasts; it inhibits mitogen-induced DNA synthesis by T lymphocytes and 12-HETE formation by platelets and keratinocytes. It is therefore anti-inflammatory, regulating the pro-inflammatory changes mediated by 12-HETE. Keratinocytes also form 15-HETE, but the significance of this in the control of 12-HETE production is unknown [13–15].

Pharmacological and genetic approaches have further defined the role of prostaglandin receptors in inflammation and the immune response. EP2-deficient mice show a loss of PGE_2-induced bronchodilatation, and EP3-deficient mice demonstrate impaired febrile responses to pyrogens and mucosal integrity. A decreased inflammatory response can be observed in EP4- and IP-deficient mice, indicating a direct role of this receptor during inflammation [16,17]. PGI_2, via IP activation, seems to be critically involved in acute oedematous responses [18]. PG receptors such as IP, EP1,

EP3 and EP4 are expressed by sensory neurones and contribute to pain during inflammation.

In addition, allergic reactions are associated with an increase in prostanoid secretion. Thus PGD_2 is a major PG released by mast cells during allergen challenge, and is abundantly produced in atopic diseases such as atopic dermatitis and asthma.

Prostanoid synthesis critically depends on the action of cyclo-oxygenase. Two isoforms exist: COX-1 and COX-2. Whereas COX-1 is localized in the endoplasmic reticulum close to the plasma membrane, COX-2 can be found in the perinuclear region. COX-1 is constitutively expressed by most cells but can be slightly increased by growth factors, cytokines or tumour-promoting agents [5]. Although COX-1 was not thought to be involved in inflammation, COX-1-deficient mice display reduced experimentally induced inflammation, such as ear oedema and allergic airway disease. COX-2 expression is inducible by various factors such as cytokines, growth factors and endotoxins. Surprisingly, COX-2-deficient mice do not exhibit marked differences in inflammatory responses as compared to wild-type mice. Thus, COX-1 may contribute more to inflammation than previously thought. Overexpression of the COX-2 gene in epithelial cells resulted in increased adhesion to the extracellular matrix, diminished E-cadherin expression, enhanced Bcl-2 levels and enhanced resistance to butyrate-induced apoptosis. Moreover, COX-1 appears to be essential for endothelial tube formation, whereas COX-2 is essential for the production of angiogenic factors. Thus, cyclo-oxygenases exert several effects on endothelial cells during inflammation and tumour growth [19].

Recently, a number of PG receptor compounds and COX-2 inhibitors have been developed. Most of these compounds are not selective, but activate or inactivate several receptor subtypes [20,21]. The classic COX-inhibitor, aspirin, blocks both, but preferentially COX-1 over COX-2. In contrast, COX-2 inhibitors such as rofecoxib and celecoxib are effective anti-inflammatory agents, while showing considerably less gastrotoxicity than COX-1 inhibitors and other non-steroidal anti-inflammatory drugs.

Leukotrienes

Cleavage of arachidonic acid by 5-lipoxygenase (5-LO) followed by further degradation results in several chemically related leukotrienes. They are generated by many cell types and may be divided chemically and biologically into two substances: LTB_4 and LTC_4 [20–23]. These may be further transformed into metabolites LTD_4 and LTE_4. LTB_4 stimulates chemokinesis of polymorphonuclear leukocytes, and induces exudation of plasma. Leukotrienes induce prolonged contraction of smooth muscle, and hence constriction of small airways. They stimulate mucus secretion and induce post-capillary oedema. LTB_4 has also been isolated from the skin of patients with psoriasis and atopic dermatitis.

The 5-LO pathway leading to leukotriene formation plays a pivotal part in the pro-inflammatory cascade during inflammation [21]. For example, LTB_4 promotes neutrophil chemotaxis and adhesion to vascular endothelium through specific integrins. The cysteinyl leukotrienes cause plasma leakage from postcapillary venules and enhance mucus secretion. LTD_4 and another 5-LO-derived eicosanoid, 5-oxo-ETE, are eosinophil chemoattractants. The use of murine models in which specific genes such as '5-lipoxygenase' of the leukotriene pathway have been deleted by homologous recombination firmly support their crucial role in allergic inflammation.

5-LO has been identified as an inducer of ROS production in lymphocytes. However, our knowledge on the physiological relevance of this in redox signalling is still incomplete. The oxidized metabolites generated by 5-LO have been found to change the intracellular redox balance and to induce signal transduction pathways and gene expression. LTB_4 controls cytotoxic effector T-cell recruitment to inflamed tissues [22]. Moreover, Th2 cytokines coordinately regulate IgE-dependent cysteinyl leukotriene production by human mast cells; IL-4 induces leukotriene C4 synthase expression, and thereby regulates T-cell–mast cell interactions [23–25].

Leukotrienes exert their effects by binding and activating specific heptical G protein-coupled receptors (GPCRs). Four receptor subtypes have been cloned and characterized. The high-affinity B-LT1 receptor on leukocytes binds LTB_4 in the subnanomolar range, and stimulates neutrophil secretion. Two subtypes of cysteinyl leukotriene receptors, CysLT1 and CysLT2, mediate the actions of LTC_4 and LTD_4. CysLT1 is found on airway smooth muscle cells and vascular endothelial cells, and promotes bronchoconstriction and up-regulation of endothelial cell adhesion molecules. However, our knowledge of the role of leukotrienes receptors under physiological and pathophysiological conditions in these tissues is far from complete.

The lipoxins are chemically and functionally different from the leukotrienes. Although LXA_4 and LXB_4 are similar in structure, these mediators display biological activities that are quite distinct. LXA_4 interactions with neutrophils involve binding sites that are not recognized by LXB_4 [26,27]. LXB_4 is a potent agonist for stimulating the proliferation and differentiation of granulocyte–monocyte colonies from human mononuclear cells [28], and increases the S-phase in the cell cycle and enhances nuclear protein kinase C activity [29]; such effects have not been reported for LXA_4. However, both LXA_4 and LXB_4 selectively stimulate human peripheral blood monocytes [30] and enhance growth of myeloid progenitor cells [31].

There is increasing interest in a potential therapeutic effect of leukotriene modifiers or antileukotrienes such as 5-LO inhibitors (zileuton [Zyflo]) and CysLT1 receptor antagonists (zafirlukast [Accolate] or montelukast [Singulair]). They have been used clinically in long-term studies in asthma therapy [32]. However, there is still much debate about their clinical efficacy. Their efficacy in exercise-induced asthma and aspirin-intolerant asthma is well documented. Clinical trials show bronchodilatory effects beyond those provided by β-agonists, as well as reduced eosinophil numbers in the sputum. On the other hand, a number of non-responding patients have been observed. This may be explained—at least in part—by non-leukotriene-dependent mechanisms involved in different forms of asthma or by pharmacogenetic factors. Thus, leukotriene-modulating agents may provide novel tools for the treatment of certain inflammatory diseases. For instance, a steroid-sparing benefit in mild to moderate asthma was described. However, whether antileukotriene agents may be of help for the treatment of inflammatory skin diseases such as urticaria and allergic reactions is still unclear [33].

Thus, targeting various pro-inflammatory or anti-inflammatory prostanoid receptors may be beneficial for treating inflammatory dermatoses including psoriasis or eczema. Administration of a small molecule antagonist, Compound A (Cmpd A), effectively blocked oedema formation and greatly reduced the inflammatory infiltrate in an allergic contact dermatitis model by down-regulating IL-4, IL-1β, TNF-α, TNF-β, GRO-α, MIP-2 and thymic stromal lymphopoietin (TSLP) [34,35]. In contrast, PGE_2 is a major soluble factor released by fibroblasts which suppresses inflammatory cytokine production from dendritic cells [36].

References

1 Guan Y, Zhang Y, Schneider A *et al*. Urogenital distribution of a mouse membrane-associated prostaglandin E(2) synthase. *Am J Physiol Renal Physiol* 2001; **281**: F1173–7.

2 Narumiya S, FitzGerald GA. Genetic and pharmacological analysis of prostanoid receptor function. *J Clin Invest* 2001; **108**: 25–30.

3 Coleman RA, Smith WL, Narumiya S. International Union of Pharmacology classification of prostanoid receptors: properties, distribution, and structure of the receptors and their subtypes. *Pharmacol Rev* 1994; **46**: 205–29.

4 Narumiya S, Sugimoto Y, Ushikubi F. Prostanoid receptors: structures, properties, and functions. *Physiol Rev* 1999; **79**: 1193–226.

5 Versteeg HH, van Bergen en Henegouwen PM *et al*. Cyclooxygenase-dependent signalling: molecular events and consequences. *FEBS Lett* 1999; **445**: 1–5.

6 Salmon JA, Higgs GA. Prostaglandins and leukotrienes as inflammatory mediators. *Br Med Bull* 1987; **43**: 285–96.

7 Snijdewint FG, Kalinski P, Wierenga EA *et al*. Prostaglandin E2 differentially modulates cytokine secretion profiles of human T helper lymphocytes. *J Immunol* 1993; **150**: 5321–9.

8 Chan S, Henderson WR Jr, Li SH, Hanifin JM. Prostaglandin E2 control of T cell cytokine production is functionally related to the reduced lymphocyte proliferation in atopic dermatitis. *J Allergy Clin Immunol* 1996; **97**: 85–94.

9 Chan SC, Kim JW, Henderson WR Jr, Hanifin JM. Altered prostaglandin E2 regulation of cytokine production in atopic dermatitis. *J Immunol* 1993; **151**: 3345–52.

10 Moncada S, Vane JR. Prostacyclin and the vascular endothelium. *Bull Eur Physiopathol Respir* 1981; **17**: 687–701.

11 Goetzl EJ, Gorman RR. Chemotactic and chemokinetic stimulation of human eosinophil and neutrophil polymorphonuclear leukocytes by 12-L-hydroxy-5,8,10-heptadecatrienoic acid (HHT). *J Immunol* 1978; **120**: 526–31.

12 Dowd PM, Kobza Black A, Woollard PM *et al*. Cutaneous responses to 12-hydroxy-5,8,10,14-eicosatetraenoic acid (12-HETE). *J Invest Dermatol* 1985; **84**: 537–41.

13 Gualde N, Atluru D, Goodwin JS. Effect of lipoxygenase metabolites of arachidonic acid on proliferation of human T cells and T cell subsets. *J Immunol* 1985; **134**: 1125–9.

14 Vanderhoek JY, Bryant RW, Bailey JM. 15-hydroxy-5,8,11,13-eicosatetraenoic acid: a potent and selective inhibitor of platelet lipoxygenase. *J Biol Chem* 1980; **255**: 5996–8.

15 Kragballe K, Pinnamaneni G, Desjarlais L *et al*. Dermis-derived 15-hydroxy-eicosatetraenoic acid inhibits epidermal 12-lipoxygenase activity. *J Invest Dermatol* 1986; **87**: 494–8.

16 Murata T, Ushikubi F, Matsuoka T *et al.* Altered pain perception and inflammatory response in mice lacking prostacyclin receptor. *Nature* 1997; **388**: 678–82.

17 Miyaura C, Inada M, Suzawa T *et al*. Impaired bone resorption to prostaglandin E2 in prostaglandin E receptor EP4-knockout mice. *J Biol Chem* 2000; **275**: 19819–23.

18 Matsuoka T, Hirata M, Tanaka H *et al*. Prostaglandin D2 as a mediator of allergic asthma. *Science* 2000; **287**: 2013–7.

19 Tilley SL, Coffman TM, Koller BH. Mixed messages: modulation of inflammation and immune responses by prostaglandins and thromboxanes. *J Clin Invest* 2001; **108**: 15–23.

20 Yopp AC, Randolph GJ, Bromberg JS. Leukotrienes, sphingolipids, and leukocyte trafficking. *J Immunol* 2003; **171**: 5–10.

21 Funk CD. Prostaglandins and leukotrienes: advances in eicosanoid biology. *Science* 2001; **294**: 1871–5.

22 Goodarzi K, Goodarzi M, Tager AM *et al*. Leukotriene B4 and BLT1 control cytotoxic effector T cell recruitment to inflamed tissues. *Nat Immunol* 2003; **4**: 965–73.

23 Hsieh FH, Lam BK, Penrose JF, Austen KF, Boyce JA. T helper cell type 2 cytokines coordinately regulate immunoglobulin E-dependent cysteinyl leukotriene production by human cord blood-derived mast cells: profound induction of leukotriene C(4) synthase expression by interleukin 4. *J Exp Med* 2001; **193**: 123–33.

24 Ott VL, Cambier JC, Kappler J *et al*. Mast cell-dependent migration of effector CD8+ T cells through production of leukotriene B4. *Nat Immunol* 2003; **4**: 974–81.

25 Tager AM, Bromley SK, Medoff BD *et al*. Leukotriene B4 receptor BLT1 mediates early effector T cell recruitment. *Nat Immunol* 2003; **4**: 982–90.

26 Nigam S, Fiore S, Luscinskas FW, Serhan CN. Lipoxin A4 and lipoxin B4 stimulate the release but not the oxygenation of arachidonic acid in human neutrophils: dissociation between lipid remodeling and adhesion. *J Cell Physiol* 1990; **143**: 512–23.

27 Fiore S, Ryeom SW, Weller PF, Serhan CN. Lipoxin recognition sites. Specific binding of labeled lipoxin A4 with human neutrophils. *J Biol Chem* 1992; **267**: 16168–76.

28 Khshivo AL, Nekrasov AS, Lankin VZ *et al*. [Lipoxin B, an enhancing factor of spontaneous platelet aggregation in whole blood.] *Biull Eksp Biol Med* 1989; **108**: 26–8.

29 Beckman BS, Despinasse BP, Spriggs L. Actions of lipoxins A4 and B4 on signal transduction events in Friend erythroleukemia cells. *Proc Soc Exp Biol Med* 1992; **201**: 169–73.

30 Maddox JF, Serhan CN. Lipoxin A4 and B4 are potent stimuli for human monocyte migration and adhesion: selective inactivation by dehydrogenation and reduction. *J Exp Med* 1996; **183**: 137–46.

31 Stenke L, Edenius C, Samuelsson J, Lindgren JA. Deficient lipoxin synthesis: a novel platelet dysfunction in myeloproliferative disorders with special reference to blastic crisis of chronic myelogenous leukemia. *Blood* 1991; **78**: 2989–95.

32 Brink C. Leukotriene receptors: state of the art. *Adv Exp Med Biol* 2003; **525**: 7–10.

33 Drazen JM. Anti-leukotrienes as novel anti-inflammatory treatments in asthma. *Adv Exp Med Biol* 2002; **507**: 217–21.

34 Boehme SA, Chen EP, Franz-Bacon K *et al*. Antagonism of CRTH2 ameliorates chronic epicutaneous sensitization-induced inflammation by multiple mechanisms. *Int Immunol* 2009; **21**: 1–17.

35 Boehme SA, Franz-Bacon K, Chen EP *et al*. A small molecule CRTH2 antagonist inhibits FITC-induced allergic cutaneous inflammation. *Int Immunol* 2009; **21**: 81–93.

36 Shiraishi H, Yoshida H, Saeki K *et al*. Prostaglandin E2 is a major soluble factor produced by stromal cells for preventing inflammatory cytokine production from dendritic cells. *Int Immunol* 2008; **20**: 1219–29.

Neuromediators

Accumulating evidence indicates the existence of an interactive network between the cutaneous neuronal system, the neuroendocrine axis and the immune system. Neurocutaneous interactions influence a variety of physiological and pathophysiological biological functions in the skin, such as development, growth, differentiation, immunity, inflammation, pruritus and wound healing (Table 12.10). Different types of cutaneous nerve fibre release neuromediators and activate specific receptors on target cells in the skin, such as keratinocytes, mast cells, Langerhans' cells, microvascular endothelial cells, fibroblasts and infiltrating immune cells, thereby modulating inflammation [1–4].

Neuropathic pain is defined as symptoms associated with a primary lesion, or a dysfunction of the central or peripheral system. The neurophysiological base of neuronal signalling occurs exclusively in skin sensory endings, cutaneous nerves or central nervous tissue, as a consequence of an adequate sensory stimulus, and depends on the induction of an electric potential difference at

Table 12.10 Neuromediators in the skin; sources and target cells of neurotransmitters/neuropeptides.

Neuromediator	Receptor	Source	Target cells/function
Acetylcholine	Nicotinergic and muscarinergic acetylcholine receptors	Autonomic cholinergic nerves, keratinocytes, lymphocytes, melanocytes	Innervation of sweat glands and arteriovenous anastomoses; keratinocyte and lymphocyte differentiation; proliferation, adhesion; migration
Catecholamine, norepinephrine	Adrenergic receptors	Autonomic adrenergic nerves, keratinocytes, melanocytes	Innervation of blood vessels, arrector pili muscles; pain transmission; regulation of activity of natural killer cells and monocytes; apoptosis induction in lymphocytes
Substance P	Tachykinin (neurokinin) receptors (NK1-, NK2-, NK3R)	Sensory nerve fibres	Mediates skin erythema, oedema, pruritus; up-regulates cell adhesion molecule expression on keratinocytes and endothelial cells; release of IL-8, TNF-α, histamine, leukotriene B4, prostaglandin D_2
Neurokinin A	Tachykinin (neurokinin) receptors	Sensory nerve fibres	Up-regulation of keratinocyte nerve growth factor expression
VIP	VPAC receptors	Sensory nerve fibres, Merkel cells	Sweat secretion, vasodilatation; proliferation, migration of keratinocytes; histamine release from mast cells
PACAP	VPAC receptors	Autonomic and sensory nerve fibres, lymphocytes, dermal endothelial cells	Vasodilatation, immunomodulatory effect on T cells and macrophages; modulates mast cell function, inhibits antigen-induced apoptosis on mature T lymphocytes, down-regulates pro-inflammatory cytokines and chemokines in T cells, up-regulates cytokines and cell adhesion molecules in dermal microvascular endothelial cells
CGRP	CGRP receptors	Sensory nerve fibres	Keratinocyte and endothelial cell proliferation, stimulates cytokine production
POMC	Melanocortin receptors	Melanocytes, keratinocytes, endothelial cells, Langerhans' cells, mast cells, fibroblasts, monocytes, macrophages	Antagonizes effects of pro-inflammatory cytokines (IL-1α, IL-1β, IL-6, TNF-α, endotoxins); up-regulates Il-10; releases histamine from mast cells; regulates dendritic cell function

the nerve endings, mediated—at least in part—by induction of ion channels. A nerve action potential begins after depolarization involving transient membrane modification. In addition, calcium channels contribute to depolarization processes through activation of protein kinases. Thus, understanding the role of ion channels will lead to novel therapeutic strategies for the treatment of inflammation, pain and/or pruritus [5].

Hair follicle unit. The human hair follicle is a unique miniorgan, capable of life-long cycles of massive growth (anagen), regression (catagen) and resting (telogen). Recent work has identified complex, stringently localized signalling mechanisms between skin neuroectoderm and mesoderm that drive the hair cycle. Pilosebaceous units are both prominent targets and sources of stress mediators. Thus, the nervous system plays an essential role in the regulation of the hair cycle and melanogenesis [6].

Stress. Stress is linked to exacerbation and amplification of inflammation, allergic reactions, pruritus, sensitive skin, stinging and burning and delayed wound healing. Neuropeptides such as substance P (SP) may play a role in these processes. Stress, probably via SP and other mediators, is associated with neurogenic inflammation and increased apoptosis in the murine hair follicle. After exposure to sonic stress, for example, the number of SP-positive nerve fibres is significantly increased. There was strong association of nerve fibres to mast cells; the percentage of degranulated mast cells increased significantly, associated with a rise in apoptotic cells in the skin. Increased numbers of peptidergic nerve fibres correlated with increased numbers of growth-associated protein 43 $(Gap\text{-}43)^+$ nerve fibres, a marker for growing nerves. Thus, neuronal plasticity and increased neuroimmune interaction occur under stress and may alter the state of inflammatory skin diseases [7].

Atopic dermatitis and allergic reactions. Similarly, exposure to sonic stress in murine atopic dermatitis-like allergic dermatitis (AD) equipotently raised the number of SP^+ cutaneous nerve fibres. Stress increased AD histological parameters (eosinophil infiltration, vascular cell adhesion molecule-positive blood vessels, epidermal thickness) by at least 30%, associated with increased neurogenic inflammation (degranulated mast cells, interstitial neuropeptidergic dense core granules, mast cell apoptosis, endothelial gaping). Key features of AD exacerbation could not be induced in mice lacking the neurokinin-1 SP receptor (NK1). Interestingly, stress had no significant additional effect on $CD4^+$ cell number, but shifted the cytokine profile toward Th2 in the skin. Thus, stress primarily exacerbates AD via SP-dependent cutaneous neurogenic inflammation [8,9]. The number of sensory as well as autonomous nerves appears to be enhanced in chronic inflammation [10].

Cutaneous neuropeptides and neurohormones include a large family of small peptides such as substance P, CGRP, somatostatin, vasoactive intestinal peptide (VIP), pituitary adenylate cyclase activating peptide (PACAP), melanocyte-stimulating hormone (MSH) and β-endorphin. Moreover, neurotrophic factors such as

nerve growth factor may affect the skin. Such neuromediators can be released from both sensory and (rarely) autonomic nerve fibres, which terminate predominantly in the dermis but also in the epidermis, and thus are in close anatomical proximity to a variety of different cutaneous cell types during inflammation. Additionally, several skin cells generate neuropeptide receptors during the inflammatory response. Most of these belong to the G protein-coupled heptical transmembrane receptor family coupled to heterotrimeric G proteins. Because sensory neurones also express specific receptors for neuropeptides, prostaglandins, histamine, neurotrophins, proteases and cytokines, an interactive communication network between sensory nerves and immune cells probably exists during cutaneous inflammation [1,11,12]. Some neuropeptides have been demonstrated to be also capable of direct activation of intracellular G proteins. Endopeptidases such as neutral endopeptidase (NEP), endothelin-converting enzyme (ECE) or angiotensin-converting enzyme (ACE) are transmembrane molecules that regulate neuropeptide function by extracellular degradation or intracellular endosomal receptor-ligand control, thereby leading to the inhibition of neuropeptide function [13]. NEP appears to be an essential mediator both of pain and acute or chronic inflammation [14]. They have also been shown to modulate neurogenic inflammation by limiting the effects of neuropeptides in the skin [15]. Hence, a complex network of neuromediators, neurotransmitter receptors and peptidases exists to regulate cutaneous inflammation.

The axon reflex response in the skin is complex, and is dependent on the anatomical distribution of the cutaneous axon reflexes and release of different types of neuropeptide [15]. In the skin, at least 30% of the cutaneous afferent nerves belong to a subtype of sensory nerves with dual sensory afferent and efferent function, which mediate neurogenic inflammation. Capsaicin-sensitive C-fibres, and to a lesser extent Aδ–fibres, are not only capable of transporting impulses to the central nervous system (orthodromic signal) but also release neuropeptides (antidromic signal), which result in inflammatory activities in the skin. Neuropeptides released from cutaneous nerves are capable of acting on target cells via a paracrine, juxtacrine or endocrine pathway. These target cells express specific neuropeptide receptors that are appropriately coupled to an intracellular signal transduction pathway, or ion channels that, when activated, may result in activation of biological responses such as erythema, oedema, hyperthermia and pruritus. Because of their anatomical association to cutaneous nerves, mast cells and their released products appear to play an important part in mediating neuronal antidromic responses in the skin, although the precise role of these cells in cutaneous inflammation remains to be determined.

The tachykinin substance P strongly induces inflammatory responses and pruritus. Accordingly, SP is capable of mediating the release of the pro-inflammatory cytokine TNF-α, as well as the secretion of histamine from mast cells, which results in vasodilatation via activation of H1 receptors on vascular smooth muscle cells. SP may also induce the release of leukotrienes and prostaglandins. Acute immobilization stress triggers skin mast cell degranulation via SP, corticotropin releasing hormone and neurotensin [16]. This could be the explanation for the frequent observation that stress, via release of certain neuropeptides, may trigger skin mast cell degranulation and influence cutaneous inflammation and pruritus. Previous studies using antagonists against the SP receptor (neurokinin 1R, NK1R) indicate that cutaneous oedema can be modulated by SP via NK1R activation, independently of histamine effects [17].

Neuropeptides may also regulate vascular responses in the skin during inflammation. For example, PACAP is a potent vasodilatator and oedema potentiator in rabbit skin, and mediates plasma extravasation in rat skin [18,19]. PACAP is a relatively newly recognized member of the VIP–secretin-peptide family, present in autonomic and sensory nerve fibres of the spinal cord and dorsal root ganglia, where it may influence inflammation and nociception [20]. PACAP was detected in cutaneous nerve fibres co-localized with VIP, substance P or CGRP, respectively, all of which may play a part during cutaneous inflammation. PACAP produces a long-lasting depression of a C-fibre-evoked flexion reflex in rats [21]. PACAP may also be involved in immunomodulation via down-regulating pro-inflammatory responses such as IL-2 or IL-6 production, and up-regulating anti-inflammatory mediators such as IL-10 [22], indicating that PACAP may have a role in neurogenic inflammation of the skin.

Substance P and nerve growth factor (NGF) may be also involved in neurogenic inflammation, and its regulation, in hair follicle epithelial stem cells (HFeSC) [23]. The neuropeptide CGRP has been shown to modulate immune responses and inflammation *in vitro* as well as *in vivo*. It is one of the most potent vasodilatators in humans [24], and is critically involved in vasodilatation during neurogenic inflammation and acute inflammatory responses such as sunburn and acute contact dermatitis. In general, CGRP predominantly mediates anti-inflammatory and neurotrophic effects. CGRP was found to regulate Langerhans' cell function [25], and increases the phagocytotic ability of macrophages, indicating a regulatory role of CGRP on monocyte–macrophage–dendritic cell function. CGRP also stimulated adhesion of human neutrophils and monocytes to HUVEC and dermal microvascular endothelial cells [26]. In addition, CGRP potentiated the accumulation of neutrophils and oedema formation induced by IL-1 [27], and induced mast cells to release TNF-α which resulted in inflammatory effects on surrounding skin cells [28]. On the other hand, CGRP induced the production of IL-10 and blocked sensitization in a murine model of CHS, and induced specific immune tolerance [25]. In Langerhans' cells, CGRP inhibited the production of Th1-associated chemokines (CXCL9, CXCL10), but stimulated the generation of Th2-associated chemokines (CCL17, CCL22). Thus, neuronal derived CGRP drives LC to stimulate T cells towards a Th2 phenotype, as observed in atopic dermatitis [29].

Somatostatin (SOM) is an inhibitor of immunity and inflammation [30]. Somatostatin exerts its affects through five distinct subtypes of G-protein-coupled receptors (SSTR1–5). While SSTR1–3 are strongly expressed in the epidermis of healthy skin, and in the skin of patients with psoriasis or atopic dermatitis, SSTR4 and 5 were strongly expressed in the epidermis of psoriasis patients, but weakly expressed in the epidermis of those with atopic dermatitis and normal skin. The intensity of the staining also varied considerably between the different layers of the epidermis, especially in psoriasis patients. Dendritic cells, found mostly in the papillary and upper reticular dermis, showed strong expression of SSTR1–4,

but weak expression of SSTR5. SSTR1–5 were strongly expressed in the sweat glands in all skin biopsies. Hair follicles and sebaceous glands expressed all five subtypes. Striated muscle fibres showed intense expression of SSTR1–4, but weak or negative expression of SSTR5 [31]. SSTRs are rapidly internalized and recycle, where they can be reactivated [32]. Somatostatin is regarded as a predominantly antiproliferative molecule, having cancer-inhibiting properties mediated by tyrosine phosphatases, and inhibitory effects on the proliferation of T lymphocytes [33]. The inhibitory effects of SOM may not be generalized, because SOM also stimulates histamine release of human skin mast cells. SOM, and the SOM analogue angiopeptin, also decrease adhesion by monocytes to unstimulated and IL-1-stimulated endothelial cells by a cyclic adenosine monophosphate (cAMP) dependent mechanism that does not involve ICAM-1. SOM may therefore attenuate recruitment of distinct leukocyte subpopulations during the initial phase of inflammation [34]. There is evidence for the participation of SOM in the pathophysiology of atopic dermatitis and mastocytosis [35–37].

Proopiomelanocortin (POMC) peptides are widely distributed in the skin and are expressed by melanocytes, keratinocytes, microvascular endothelial cells, Langerhans' cells, mast cells and fibroblasts, as well as by immune cells such as monocytes and macrophages. Post-translational processing of a POMC prohormone generates up to eight different POMC peptides after cleavage by prohormone convertase 1 and 2 (PC1, 2).

α-MSH belongs to the family of POMC peptides. α-MSH is a tridecapeptide derived from proopiomelanocortin, with marked body-protective and anti-inflammatory effects. These effects can be elicited via centrally expressed melanocortin receptors that orchestrate descending neurogenic anti-inflammatory pathways. α-MSH modulates various signalling pathways, such as NF-κB activation, expression of adhesion molecules and chemokine receptors, production of pro-inflammatory cytokines and mediators, IL-10 synthesis, T-cell proliferation and activity, inflammatory cell migration, expression of antioxidative enzymes, and apoptosis. The anti-inflammatory effects of α-MSH have been validated in animal models of experimentally induced fever; irritant and allergic contact dermatitis, vasculitis, and fibrosis; ocular, gastrointestinal, brain, and allergic airway inflammation; and arthritis, as well as in models of organ injury. Due to its anti-inflammatory effect without pigmentary activity, the C-terminal tripeptide of α-MSH, KPV, has been proposed as an anti-inflammatory therapeutic agent in skin diseases [4]. In particular, α-MSH antagonizes the effects of pro-inflammatory cytokines such as IL-1α, IL-1β, IL-6 and TNF-α [38], suggesting that the immunomodulating capacity of α-MSH is also mediated through its effects on monocyte and macrophage functions. α-MSH down-regulates the production of pro-inflammatory cytokines and accessory molecules on antigen-presenting cells, while production of suppressor factors such as IL-10 is up-regulated by α-MSH [39]. It is well established that α-MSH ameliorates contact hypersensitivity, leading to hapten-specific tolerance by inducing anti-inflammatory cytokines. Moreover, α-MSH recently was found to exert anti-inflammatory activity in a murine model of asthma.

The neurotransmitters acetylcholine (ACh) and norepinephrine (noradrenaline) are also involved in inflammatory processes in the skin. ACh is released by autonomic nerves, but can be also produced by melanocytes, keratinocytes [40] and lymphocytes. It regulates different activities in keratinocytes such as proliferation, adhesion, migration and differentiation. ACh was shown to be crucial to sustain the viability of keratinocytes *in vitro*, and cholinergic drugs were capable of modulating keratinocyte function such as adhesion and motility. Both choline acetyltransferase and acetylcholinesterase appear to regulate the function of ACh in keratinocytes. Intracutaneous application of ACh has been demonstrated to modulate various inflammatory responses [41].

ACh and its derivatives exert their effects by activating nicotinergic or muscarinergic cell surface receptors. The nicotinic receptors for ACh are transmembrane ion channels. Muscarinic receptors belong to a subfamily of G protein-coupled heptical receptors, defined as m_1, m_2, m_3, m_4 and m_5 receptors. Muscarinergic as well as nicotinergic receptors are widely expressed and are involved in epithelial differentiation, cell survival of keratinocytes, and inflammation [42–44]. As expected, nicotine leads to marked effects on microcirculation (vasoconstriction) via activation of nACh receptors [45] but also influences inflammatory responses [46]. The precise role of Ach and smoking on inflammation in the skin, however, remains to be elucidated.

Catecholamines, their regulating enzymes and adrenergic receptors (ARs), have been detected in nerve fibres, keratinocytes [47] and melanocytes [48,49]. Certainly, the classic function of norepinephrine and other pharmacologically active derivatives is vasoregulation. Iontophoresed norepinephrine causes vasoconstriction, and it partially restores vascular reactivity in heat-induced vasodilated human skin [50]. Catecholamines also regulate the activity of certain lymphocytes (NK cells) and monocytes, and induce apoptosis in lymphocytes. In contrast, catecholamine release may be induced by lymphocytes such as T and B cells. During delayed-type hypersensitivity, norepinephrine may also serve as an immunoenhancing agent. α- and β-ARs have been detected in human skin. AR agonists inhibit TNF-α release from mast cells [51], and are potent inhibitors of the IgE-mediated release of tryptase mediators from human mast cells *in vitro* [52]. α- and β-ARs may also regulate important vascular responses in the skin such as vasoconstriction. Decreased levels of β-ARs were observed in lesional and non-lesional psoriatic skin [53], whereas increased levels of α-ARs were observed in arterioles of patients with scleroderma [54]. Norepinephrine is able to increase LPS-induced IL-6 production in human microvascular endothelial cells via ARs. Data suggest that catecholamines, in addition to CGRP, regulate Langerhans' cell function in the skin [55]. Taken together, these results clearly indicate a role for classic autonomic neurotransmitters during inflammation and the immune response.

Capsaicin (*trans*-8-methyl-*N*-vanillyl-6-nonenamide), a vanillyl-alkaloid found in chilli peppers and other solanaceae, has been used as an anti-inflammatory agent for many years. Topically applied, capsaicin elicits a rapid sensation of burning pain by selectively activating sensory C-fibres, and triggers a cascade of inflammatory events such as erythema, and the release of pro-inflammatory mediators in skin and mucosa. While capsaicin at lower concentrations activates sensory nerves to release neuropeptides, repeated application renders nerves in the treated area insensitive to further stimulation at higher concentrations. This is

probably caused by capsaicin receptor-mediated depletion of neuronal-derived neuropeptides within a certain subdivision of sensory nerves [56].

Chronic application of capsaicin leads to neurotoxic effects in sensory nerves, causing nerve desensitization and decreased release of neuropeptides to the site of inflammation. Thus, constant application may have an anti-inflammatory and anti-pruritic effect in the skin. These effects are at least partly mediated by activation of the capsaicin (vanilloid) receptor, TRPV1 [57]. TRPV1 is a non-selective cation channel with six transmembrane domains, now defined as the first member of the TRPV (transient receptor potential of vanilloid type) superfamily, TRPV1. To date, six members exist; these play a role in pain transmission induced by temperature, chemicals and inflammatory mediators (e.g. lipids, endocannabinoids) and chemicals. TRPV1 can be directly activated by exposure to heat, protons and the cannabinoid anandamide, conditions which participate in inflammation and injury. In the skin, TRPV1 is expressed by sensory nerves and keratinocytes and may induce the release of neuropeptides, prostaglandins (PGE_2) and cytokines such as IL-8. Of note, TRPV1 is up-regulated in keratinocytes of patients with atopic dermatitis, indicating a role for TRPV1 and its ligands (certain prostanoids, endocannabinoids, etc.) in cutaneous inflammation. Other important TRPV effects on skin homeostasis and inflammation may be subserved by TRPV2 (expressed by nerves and lymphocytes), and TRPV3, -4 and -6 (expressed by nerves and keratinocytes). TRPV3 appears to be involved in pruritic inflammatory skin diseases in mice [58]. This effect may be mediated by TRPV3-induced PGE_2 activation in keratinocytes [59].

Data suggest that proteases as neuromediators contribute to cutaneous inflammation, pruritus and barrier function by activating PARs. Activation of PARs by thrombin or mast cell tryptase results in vasodilatation, extravasation of plasma proteins and infiltration of neutrophils [60], by releasing neuropeptides such as CGRP and SP from sensory nerve endings. Thus, mast cells may regulate inflammatory responses in the skin by communicating with sensory nerves, not only via histamine receptors but also via PARs. Neutrophils release proteinase-3 which activates PAR-2, thereby playing a potential role in the exacerbation of the autoimmune disease, Wegener's syndrome [61]. In the skin, PARs are localized in keratinocytes, endothelial cells, nerve fibres and myoepithelial cells of sweat glands. Mast cells themselves express PAR-2, indicating a potential autocrine regulatory role for tryptase in cutaneous neurogenic inflammation via activation of PAR-2. *In vivo*, PAR-2 mediates oedema, plasma extravasation and up-regulation of cell adhesion molecules, and promotes the transendothelial migration of neutrophils [62], in part by a neurogenic mechanism. PAR-2 mediates pro-inflammatory responses and itch, indicating a role of PAR-2 during the pruritic response in inflammatory skin lesions [63]. Finally, PAR2 is involved in barrier function and probably ichthyosis [64,65].

The role of nociceptive processes in relation to chronic, tissue-damaging self-injury among individuals with neurodevelopmental disorders is poorly understood. Recent evidence strongly suggests implication of the sensory nervous system in injury, wound healing and self-destructive behaviour (artefacts, self-mutilation). Scientific investigation has been limited, in part, by the clinical reality that the majority of individuals with severe intellectual impairment have co-morbid communicative impairment, making it difficult to ascertain information regarding pain, pruritus and other sensations. Of note, there exists an abnormal pattern of peripheral epidermal nerve fibre innervation and increased neuropeptide (substance P) content, and modified neural neuroimmune activity, specific to a subset of individuals with chronic self-injury. These individuals had significantly more degranulated mast cells and were more responsive to tactile stimulation during a sensory testing procedure. Thus, nociceptive mechanisms and peripheral afferent sensitization may play a part in mediating and maintaining chronic self-injury [66,67].

References

1 Steinhoff M, Stander S, Seeliger S *et al*. Modern aspects of cutaneous neurogenic inflammation. *Arch Dermatol* 2003; **139**: 1479–88.

2 Steinhoff M, Bienenstock J, Schmelz M *et al*. Neurophysiological, neuroimmunological, and neuroendocrine basis of pruritus. *J Invest Dermatol* 2006; **126**: 1705–18.

3 Roosterman D, Goerge T, Schneider SW *et al*. Neuronal control of skin function: the skin as a neuroimmunoendocrine organ. *Physiol Rev* 2006; **86**: 1309–79.

4 Brzoska T, Luger TA, Maaser C *et al*. Alpha-melanocyte-stimulating hormone and related tripeptides: biochemistry, antiinflammatory and protective effects *in vitro* and *in vivo*, and future perspectives for the treatment of immune-mediated inflammatory diseases. *Endocr Rev* 2008; **29**: 581–602.

5 Golz R, Mendling W. Candidosis of the prostate: a rare form of endomycosis. *Mycoses* 1991; **34**: 381–4.

6 Paus R. Frontiers in the (neuro-)endocrine controls of hair growth. *J Investig Dermatol Symp Proc* 2007; **12**: 20–2.

7 Peters EM, Kuhlmei A, Tobin DJ *et al*. Stress exposure modulates peptidergic innervation and degranulates mast cells in murine skin. *Brain Behav Immun* 2005; **19**: 252–62.

8 Huang CH, Kuo IC, Xu H *et al*. Mite allergen induces allergic dermatitis with concomitant neurogenic inflammation in mouse. *J Invest Dermatol* 2003; **121**: 289–93.

9 Pavlovic S, Daniltchenko M, Tobin DJ *et al*. Further exploring the brain–skin connection: stress worsens dermatitis via substance P-dependent neurogenic inflammation in mice. *J Invest Dermatol* 2008; **128**: 434–46.

10 Almarestani L, Longo G, Ribeiro-da-Silva A. Autonomic fiber sprouting in the skin in chronic inflammation. *Mol Pain* 2008; **4**: 56.

11 Brain SD. New feelings about the role of sensory nerves in inflammation. *Nat Med* 2000; **6**: 134–5.

12 Ansel JC, Kaynard AH, Armstrong CA *et al*. Skin–nervous system interactions. *J Invest Dermatol* 1996; **106**: 198–204.

13 Roosterman D, Cottrell GS, Padilla BE *et al*. Endothelin-converting enzyme 1 degrades neuropeptides in endosomes to control receptor recycling. *Proc Natl Acad Sci U S A* 2007; **104**: 11838–43.

14 Kramer HH, He L, Lu B *et al*. Increased pain and neurogenic inflammation in mice deficient of neutral endopeptidase. *Neurobiol Dis* 2009; **35**: 177–83.

15 Scholzen TE, Steinhoff M, Bonaccorsi P *et al*. Neutral endopeptidase terminates substance P-induced inflammation in allergic contact dermatitis. *J Immunol* 2001; **166**: 1285–91.

16 Singh LK, Pang X, Alexacos N *et al*. Acute immobilization stress triggers skin mast cell degranulation via corticotropin releasing hormone, neurotensin, and substance P: a link to neurogenic skin disorders. *Brain Behav Immun* 1999; **13**: 225–39.

17 Palframan RT, Costa SK, Wilsoncroft P *et al*. The effect of a tachykinin NK1 receptor antagonist, SR140333, on oedema formation induced in rat skin by venom from the *Phoneutria nigriventer* spider. *Br J Pharmacol* 1996; **118**: 295–8.

18 Warren JB, Larkin SW, Coughlan M *et al*. Pituitary adenylate cyclase activating polypeptide is a potent vasodilator and oedema potentiator in rabbit skin in vivo. *Br J Pharmacol* 1992; **106**: 331–4.

19 Cardell LO, Stjarne P, Wagstaff SJ *et al*. PACAP-induced plasma extravasation in rat skin. *Regul Pept* 1997; **71**: 67–71.

20 Steinhoff M, McGregor GP, Radleff-Schlimme A *et al*. Identification of pituitary adenylate cyclase activating polypeptide (PACAP) and PACAP type 1 receptor in human skin: expression of PACAP-38 is increased in patients with psoriasis. *Regul Pept* 1999; **80**: 49–55.

21 Odum L, Petersen LJ, Skov PS, Ebskov LB. Pituitary adenylate cyclase activating polypeptide (PACAP) is localized in human dermal neurons and causes histamine release from skin mast cells. *Inflamm Res* 1998; **47**: 488–92.

22 Martinez C, Delgado M, Gomariz RP, Ganea D. Vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide-38 inhibit IL-10 production in murine T lymphocytes. *J Immunol* 1996; **156**: 4128–36.

23 Paus R, Arck P, Tiede S. (Neuro-)endocrinology of epithelial hair follicle stem cells. *Mol Cell Endocrinol* 2008; **288**: 38–51.

24 Zeller J, Poulsen KT, Sutton JE *et al.* CGRP function-blocking antibodies inhibit neurogenic vasodilatation without affecting heart rate or arterial blood pressure in the rat. *Br J Pharmacol* 2008; **155**: 1093–103.

25 Hosoi J, Murphy GF, Egan CL *et al.* Regulation of Langerhans cell function by nerves containing calcitonin gene-related peptide. *Nature* 1993; **363**: 159–63.

26 Ichinose M, Sawada M. Enhancement of phagocytosis by calcitonin gene-related peptide (CGRP) in cultured mouse peritoneal macrophages. *Peptides* 1996; **17**: 1405–14.

27 Scholzen TE, Kalden DH, Brzoska T *et al.* Expression of proopiomelanocortin peptides in human dermal microvascular endothelial cells: evidence for a regulation by ultraviolet light and interleukin-1. *J Invest Dermatol* 2000; **115**: 1021–8.

28 Niizeki H, Alard P, Streilein JW. Calcitonin gene-related peptide is necessary for ultraviolet B-impaired induction of contact hypersensitivity. *J Immunol* 1997; **159**: 5183–6.

29 Ding W, Stohl LL, Wagner JA, Granstein RD. Calcitonin gene-related peptide biases Langerhans cells toward Th2-type immunity. *J Immunol* 2008; **181**: 6020–6.

30 Reichlin S. Somatostatin. *N Engl J Med* 1983; **309**: 1495–501.

31 Hagstromer L, Emtestam L, Stridsberg M, Talme T. Expression pattern of somatostatin receptor subtypes 1–5 in human skin: an immunohistochemical study of healthy subjects and patients with psoriasis or atopic dermatitis. *Exp Dermatol* 2006; **15**: 950–7.

32 Roosterman D, Kreuzer OJ, Brune N *et al.* Agonist-induced endocytosis of rat somatostatin receptor 1. *Endocrinology* 2007; **148**: 1050–8.

33 Payan DG, Hess CA, Goetzl EJ. Inhibition by somatostatin of the proliferation of T-lymphocytes and Molt-4 lymphoblasts. *Cell Immunol* 1984; **84**: 433–8.

34 Leszczynski D, Josephs MD, Fournier RS, Foegh ML. Angiopeptin, the octapeptide analogue of somatostatin, decreases rat heart endothelial cell adhesiveness for mononuclear cells. *Regul Pept* 1993; **43**: 131–40.

35 Pincelli C, Fantini F, Massimi P *et al*. Neuropeptides in skin from patients with atopic dermatitis: an immunohistochemical study. *Br J Dermatol* 1990; **122**: 745–50.

36 Johansson O. Morphological characterization of the somatostatin-immunoreactive dendritic skin cells in urticaria pigmentosa patients by computerized image analysis. *Scand J Immunol* 1985; **21**: 431–9.

37 Johansson O, Nordlind K. Immunohistochemical localization of somatostatin-like immunoreactivity in skin lesions from patients with urticaria pigmentosa. *Virchows Arch B Cell Pathol Incl Mol Pathol* 1984; **46**: 155–64.

38 Hartmeyer M, Scholzen T, Becher E *et al*. Human dermal microvascular endothelial cells express the melanocortin receptor type 1 and produce increased levels of IL-8 upon stimulation with alpha-melanocyte-stimulating hormone. *J Immunol* 1997; **159**: 1930–7.

39 Grabbe S, Bhardwaj RS, Mahnke K *et al*. Alpha-melanocyte-stimulating hormone induces hapten-specific tolerance in mice. *J Immunol* 1996; **156**: 473–8.

40 Grando SA, Kist DA, Qi M, Dahl MV. Human keratinocytes synthesize, secrete, and degrade acetylcholine. *J Invest Dermatol* 1993; **101**: 32–6.

41 Banwell BL, Russel J, Fukudome T *et al*. Myopathy, myasthenic syndrome, and epidermolysis bullosa simplex due to plectin deficiency. *J Neuropathol Exp Neurol* 1999; **58**: 832–46.

42 Peralta EG, Ashkenazi A, Winslow JW *et al*. Distinct primary structures, ligand-binding properties and tissue-specific expression of four human muscarinic acetylcholine receptors. *EMBO J* 1987; **6**: 3923–9.

43 Grando SA, Horton RM, Mauro TM *et al*. Activation of keratinocyte nicotinic cholinergic receptors stimulates calcium influx and enhances cell differentiation. *J Invest Dermatol* 1996; **107**: 412–8.

44 Grando SA. Biological functions of keratinocyte cholinergic receptors. *J Investig Dermatol Symp Proc* 1997; **2**: 41–8.

45 Edvinsson ML, Andersson SE, Xu CB, Edvinsson L. Cigarette smoking leads to reduced relaxant responses of the cutaneous microcirculation. *Vasc Health Risk Manag* 2008; **4**: 699–704.

46 Breivik T, Gundersen Y, Gjermo P *et al*. Nicotinic acetylcholine receptor activation mediates nicotine-induced enhancement of experimental periodontitis. *J Periodontal Res* 2000; **44**: 297–304.

47 Ndoye A, Buchli R, Greenberg B *et al*. Identification and mapping of keratinocyte muscarinic acetylcholine receptor subtypes in human epidermis. *J Invest Dermatol* 1998; **111**: 410–6.

48 Schallreuter KU, Korner C, Pittelkow MR *et al*. The induction of the alpha-1-adrenoceptor signal transduction system on human melanocytes. *Exp Dermatol* 1996; **5**: 20–3.

49 Schallreuter KU, Wood JM, Pittelkow MR *et al.* Regulation of melanin biosynthesis in the human epidermis by tetrahydrobiopterin. *Science* 1994; **263**: 1444–6.

50 Beed M, O'Connor MB, Kaur J *et al*. Transient hyperaemic response to assess skin vascular reactivity: effects of heat and iontophoresed norepinephrine. *Br J Anaesth* 2009; **102**: 205–9.

51 Bissonnette EY, Befus AD. Anti-inflammatory effect of beta 2-agonists: inhibition of TNF-alpha release from human mast cells. *J Allergy Clin Immunol* 1997; **100**: 825–31.

52 Suzuki H, Ueno A, Takei M *et al*. The effects of S1319, a novel marine sponge-derived beta2-adrenoceptor agonist, on IgE-mediated activation of human cultured mast cells. *Inflamm Res* 2000; **49**: 86–94.

53 Steinkraus V, Steinfath M, Stove L *et al*. Beta-adrenergic receptors in psoriasis: evidence for down-regulation in lesional skin. *Arch Dermatol Res* 1993; **285**: 300–4.

54 Flavahan NA, Flavahan S, Liu Q *et al.* Increased alpha2-adrenergic constriction of isolated arterioles in diffuse scleroderma. *Arthritis Rheum* 2000; **43**: 1886–90.

55 Seiffert K, Hosoi J, Torii H *et al.* Catecholamines inhibit the antigen-presenting capability of epidermal Langerhans cells. *J Immunol* 2002; **168**: 6128–35.

56 Holzer P. Neurogenic vasodilatation and plasma leakage in the skin. *Gen Pharmacol* 1998; **30**: 5–11.

57 Caterina MJ, Schumacher MA, Tominaga M *et al*. The capsaicin receptor: a heat-activated ion channel in the pain pathway. *Nature* 1997; **389**: 816–24.

58 Yoshioka T, Imura K, Asakawa M *et al.* Impact of the Gly573Ser substitution in TRPV3 on the development of allergic and pruritic dermatitis in mice. *J Invest Dermatol* 2009; **129**: 714–22.

59 Huang SM, Lee H, Chung MK *et al.* Overexpressed transient receptor potential vanilloid 3 ion channels in skin keratinocytes modulate pain sensitivity via prostaglandin E2. *J Neurosci* 2008; **28**: 13727–37.

60 Dery O, Corvera CU, Steinhoff M, Bunnett NW. Proteinase-activated receptors: novel mechanisms of signaling by serine proteases. *Am J Physiol* 1998; **274**: C1429–52.

61 Csernok E, Ai M, Gross WL *et al.* Wegener autoantigen induces maturation of dendritic cells and licenses them for Th1 priming via the protease-activated receptor-2 pathway. *Blood* 2006; **107**: 4440–8.

62 Steinhoff M, Vergnolle N, Young SH *et al.* Agonists of proteinase-activated receptor 2 induce inflammation by a neurogenic mechanism. *Nat Med* 2000; **6**: 151–8.

63 Steinhoff M, Neisius U, Ikoma A *et al.* Proteinase-activated receptor-2 mediates itch: a novel pathway for pruritus in human skin. *J Neurosci* 2003; **23**: 6176–80.

64 Demerjian M, Hachem JP, Tschachler E *et al.* Acute modulations in permeability barrier function regulate epidermal cornification: role of caspase-14 and the protease-activated receptor type 2. *Am J Pathol* 2008; **172**: 86–97.

65 Hachem JP, Houben E, Crumrine D *et al.* Serine protease signaling of epidermal permeability barrier homeostasis. *J Invest Dermatol* 2006; **126**: 2074–86.

66 Symons FJ, Wendelschafer-Crabb G, Kennedy W *et al*. Evidence of altered epidermal nerve fiber morphology in adults with self-injurious behavior and neurodevelopmental disorders. *Pain* 2008; **134**: 232–7.

67 Symons FJ, Wendelschafer-Crabb G, Kennedy W *et al*. Degranulated mast cells in the skin of adults with self-injurious behavior and neurodevelopmental disorders. *Brain Behav Immun* 2009; **23**: 365–70.

Table 12.11 Integrin β1 and β2 families regulating cell–cell and cell–extracellular matrix binding.

	Family	α: CD number	Ligands	Integrin occurrence/responding cells
VLA-β1				
α1β1	VLA-1	CD49a	Laminin, type IV collagen	Fibroblasts
α2β1	VLA-2	CD49b	Laminin, collagens	Keratinocytes (basal), fibroblasts, platelets
α3β1	VLA-3	CD49c	Laminin, collagen, fibronectin	Fibroblasts, keratinocytes (basal)
α4β1	VLA-4	CD49d	Fibronectin VCAM-1	Fibroblasts, leukocytes (not neutrophils), Langerhans' cells
α5β1	VLA-5	CD49e	Fibronectin	Fibroblasts, endothelium, platelets, macrophages, keratinocytes
α6β1	VLA-6	CD49f	Laminin	Fibroblasts, keratinocytes
α7β1			Laminin	
α8β1				
α9β1			Fibronectin, VCAM-1	Fibroblasts, leukocytes, Langerhans' cells
α10β1			Collagens	Fibroblasts
α11β1			Collagens	Fibroblasts
αvβ1		CD51	Fibronectin, vitronectin	Fibroblasts, keratinocytes
LEUCAM-β2 (mainly cell–cell)				
α1β2	LFA-1	CD11a/CD18	ICAM-1, -2, -3	Leukocytes
αmβ2	Mac-1	CD11b/CD18	ICAM-1, fibrinogen, C3bi	Leukocytes
αxβ2	p150.95	CD11c/CD18	Fibrinogen, C3bi	Leukocytes, endothelium
αdβ2			ICAM-3	Macrophages

See text for abbreviation definitions. β1 integrins stated to bind to basal keratinocytes may be expressed weakly in suprabasal cells of normal epidermis; expression is increased during inflammation.
LEUCAM, leukocyte (cell) adhesion molecules.

Vasculature and inflammation

Cell adhesion and adhesion molecules

Cell–cell and cell–substrate adhesion is an essential function of cell membranes. Adhesion molecules participate in every cell activity, although they may be latent, that is not expressed until the cell is stimulated, as in platelets, or expressed very transiently, as for the selectins, between leukocytes and endothelium, for example. Over a longer duration, integrins can be up-regulated or down-regulated, thereby controlling interactions between basal keratinocytes and the basement membrane, skin cells and leukocytes or leukocyte–leukocyte interactions during inflammation. Tissue growth, differentiation and repair are tightly regulated by adhesion molecules, because leukocyte recruitment and function is critically dependent upon adhesion molecule functions. Practically, a leukocyte sequentially up-regulates several different surface molecules during its passage through the endothelium to the site of inflammation or injury. Accordingly, endothelial cells have to up-regulate their counterpartners on their cell surface, suggesting a close communication between leukocytes and endothelial cells through inducing mediators such as cytokines and chemokines. Thus, adhesion molecule expression is a complex process, associated with, or induced by, the contiguous cells or substrate. Adhesion molecules can be subdivided as members of the integrin family, the selectin family and the immunoglobulin superfamily.

The recruitment of immunocytes to cutaneous tissues, a complex multistep cascade mediated by a large variety of cytokines, chemokines, and adhesion molecules, is thought to be a pivotal process in the pathophysiology, development, perpetuation or termination of skin inflammation. Thus, defining the mechanisms and molecules, and targeting leukocyte trafficking, remains an attractive approach for the treatment of skin diseases. It is increasingly recognized that during the pathogenesis of psoriasis, for example, multiple interactions between T cells, dendritic cells, macrophages, mast cells, endothelial cells and keratinocytes play a role in the outcome of the inflammatory response. Biologics specifically inhibiting key molecules involved in cutaneous leukocyte recruitment have been approved for the treatment of various skin diseases [1]. However, the existence of certain redundant and/or functional overlaps limits their therapeutic success [2–4].

Integrins

Integrins, first recognized by Hynes in 1987 [5], are the best studied members of the cell adhesion receptor superfamily. Integrins and their ligands are key to embryogenesis, tissue development and differentiation, immune responses, leukocyte trafficking, cancer metastasis and tissue homeostasis. However, integrins are not only binding partners but also regulate release of mediators during inflammation [6]. Integrins also modulate T-cell function [7], contact hypersensitivity [8], recruitment of eosinophils [9], psoriasiform dermatitis in mice [10] and impaired wound healing [11].

Integrins are α- and β-heterodimers but are of considerable diversity, there being eight β chains and 18 α subunits; one α subunit non-covalently links with one β subunit [12], assembling into 24 distinct integrins (Table 12.11). Some α subunits (e.g. αv) may link with more than one β chain, enabling binding to different substrates (e.g. vitronectin, fibronectin or collagens). Partner recognition is specific for the tripeptide sequence Arg-Gly-Asp (RGD) [13]. Ligand substrates have been identified experimentally. *In vivo*, it is probable that there is diversity in adhesion molecules; a

cell may vary expression of integrins depending upon the nature either of the substrate or the stimulus [12].

In addition to their roles in adhesion to extracellular matrix ligands, integrins act as links between the intracellular cytoskeleton and extracellular milieu. All integrins, apart from α6β4, link to actin, whereas the β4 subunit with its large (1000 amino acid compared to 50 amino acid) cytoplasmic domain links to intermediate filaments. Ligation of integrins initiates a plethora of signal transduction events which serve to modulate cell behaviour, including proliferation, apoptosis, up-regulation of genes involved in inflammation, cell polarity and migration [14]. Many integrin-stimulated cell signalling pathways are similar to those triggered by growth factor receptors and cytokine/chemokine receptors.

Knockout mice studies have helped to elucidate the specific, non-redundant function of each of the 24 integrins. Indeed, genes for all β subunits and α subunits which have been knocked out reveal that the role of each integrin is markedly distinct. The phenotypes range from perinatal lethality (α3, α6, α8, αv, β4 and β8) to defects in leukocyte function (αL, αM, αE, β2 and β7), inflammation (β6) and angiogenesis (α1 and β3) [15].

The β1 chain integrins, also known as VLA (very late antigens of activation, being late in appearance on T-cell activation) bind cells to cell substrates (Table 12.11). The β1 integrins have important cell–cell and cell–membrane linking functions in the epidermis. The distribution of integrins in epidermal cultures is fairly consistent. The α2, α3, α5 and β1 chains are present in basal cells, particularly at cell–cell junctions; α6β4 integrin tends to be most strongly expressed on the base of the basal cells, as is αvβ1, which is weakly and irregularly expressed. These two integrins bind to fibronectin, laminin and vitronectin of the basement membrane [13–18]. If the culture substrate in the initial stages of development is changed from laminin to collagen, the dominant integrin in the basal–substrate zone changes from α3 to α2β1 [16]. The half-life of integrins in culture is 12–15 h. Disappearance of integrins in suprabasal cells occurs because they are not replaced, and is associated with terminal differentiation. Upward cell migration from the basal layer involves loss of adhesion to the basement-membrane proteins, which precedes the decrease and loss of the α5β1 integrins and fibronectin [19,20].

In normal epidermis *in vivo*, the highest expression of integrins is on basal cells, either at cell–cell contacts, where α2 and α3β1 are particularly found, or the basal cell–basement-membrane interface, with α3β1 being strongly expressed and αvβ1 and α1β1 being less evident [16,21,22]. Integrin α6β4, a laminin receptor, is strongly expressed in hemidesmosomes [23]. Opinion varies about the presence of α5 on normal basal cells, or the persistence of integrins in the suprabasal layers; discrepancies in the literature may be a result of different epitope specificities of the test antibodies, or to activation of the skin before or during sampling. The β1 chain persists on the cell surface in suprabasal layers, but at a lower level than on basal cells [13,16]. Reported identification of α2β1 and α3β1 on suprabasal cells of normal epidermis [16] may be caused by recognition of the β1 chain rather than the α chains. As described in the culture studies on α5β1, there is first loss of binding to the extracellular matrix components and then loss of the integrin during differentiation [20], with possibly greater persistence of the β1 cell–cell links.

During epidermal wound healing, there is increased expression in the wound of α2β1, α3β1, α5β1, αvβ4 and α6β4 integrins [21,24,25]; some differences in relative expression have been reported during repair of punch-biopsy wounds [25] as compared with suction blisters [21]. The migrating keratinocytes in punch-biopsy repair strongly express α3 and β1, α6 and β4, while after day 2 α5 activity is increased. The α3 and β1 pattern extends into the unwounded peripheral tissue [25]. In suction-blister repair, the blister roof expresses clusters of several α chains and β1 and β4 chains. On day 2, the migrating keratinocytes express the normal basal cell pattern. By day 6 in the healed hyperproliferative suprabasal epithelium, α2, α3, α6 and β1 are present, and there are low amounts of αv. The α5 and β4 integrins are confined to the basal layer, and in the case of β4 also to the next layer. The staining pattern distal to the wounds is normal [21]. These changes reflect the more rapid upward and lateral migration of hyperproliferative keratinocytes, and synthesis of extracellular substances (e.g. fibronectin and vitronectin). Changes in the granulating basement membrane of full epidermal thickness wounds [25] stimulate formation of the corresponding integrins. In 7-day wounds, formation of fibronectin and tenascin is associated with expression of αvβ6, and of the specific integrins beneath the basal cells at the dermal interface [26]. Hyperproliferation of epidermal keratinocytes in psoriasis is associated with discrete clusters of suprabasal α6 and β1 [18], and also with α3 and α5, particularly at the rete ridges [27].

Human Thy-1 is a receptor on endothelial cells which binds the interin Mac-1 on neutrophils. Thus, Mac-1 may contribute to neutrophil recruitment to sites of inflammation. Binding of neutrophils to human Thy-1 also stimulates release of MMP-9 and CXCL8 from neutrophils, resulting in enhanced migration, indicating that integrins are not only binding partners but also active drivers of mediator release [28], TNF-α blockers [29] and 1α,25-dihydroxyvitamin D_3 (vitamin D_3) [30].

References

1 Li YY, Zollner TM, Schon MP. Targeting leukocyte recruitment in the treatment of psoriasis. *Clin Dermatol* 2008; **26**: 527–38.

2 Homey B, Steinhoff M, Ruzicka T, Leung DY. Cytokines and chemokines orchestrate atopic skin inflammation. *J Allergy Clin Immunol* 2006; **118**: 178–89.

3 Kupper TS, Fuhlbrigge RC. Immune surveillance in the skin: mechanisms and clinical consequences. *Nat Rev Immunol* 2004; **4**: 211–22.

4 Schon MP, Zollner TM, Boehncke WH. The molecular basis of lymphocyte recruitment to the skin: clues for pathogenesis and selective therapies of inflammatory disorders. *J Invest Dermatol* 2003; **121**: 951–62.

5 Hynes RO. Integrins: a family of cell surface receptors. *Cell* 1987; **48**: 549–54.

6 Kelly M, Hwang JM, Kubes P. Modulating leukocyte recruitment in inflammation. *J Allergy Clin Immunol* 2007; **120**: 3–10.

7 Aoki T, Ueno T, Toyonaga A *et al*. Radiographic evidence of cholecystokinin octapeptide receptors in the hamster gallbladder. *Scand J Gastroenterol* 1991; **26**: 1165–72.

8 Siewert C, Menning A, Dudda J *et al.* Induction of organ-selective $CD4^+$ regulatory T cell homing. *Eur J Immunol* 2007; **37**: 978–89.

9 Okigami H, Takeshita K, Tajimi M *et al.* Inhibition of eosinophilia in vivo by a small molecule inhibitor of very late antigen (VLA)-4. *Eur J Pharmacol* 2007; **559**: 202–9.

10 Wang H, Peters T, Kess D *et al*. Activated macrophages are essential in a murine model for T cell-mediated chronic psoriasiform skin inflammation. *J Clin Invest* 2006; **116**: 2105–14.

11 Peters T, Sindrilaru A, Wang H *et al*. CD18 in monogenic and polygenic inflammatory processes of the skin. *J Investig Dermatol Symp Proc* 2006; **11**: 7–15.

12 Hynes RO. Integrins: bidirectional, allosteric signaling machines. *Cell* 2002; **110**: 673–87.
13 Larjava H, Peltonen J, Akiyama SK *et al*. Novel function for beta 1 integrins in keratinocyte cell–cell interactions. *J Cell Biol* 1990; **110**: 803–15.
14 Schwartz LB. Clinical utility of tryptase levels in systemic mastocytosis and associated hematologic disorders. *Leuk Res* 2001; **25**: 553–62.
15 Sheppard D. In vivo functions of integrins: lessons from null mutations in mice. *Matrix Biol* 2000; **19**: 203–9.
16 Carter WG, Wayner EA, Bouchard TS, Kaur P. The role of integrins alpha 2 beta 1 and alpha 3 beta 1 in cell-cell and cell-substrate adhesion of human epidermal cells. *J Cell Biol* 1990; **110**: 1387–404.
17 Sonnenberg A, Linders CJ, Daams JH, Kennel SJ. The alpha 6 beta 1 (VLA-6) and alpha 6 beta 4 protein complexes: tissue distribution and biochemical properties. *J Cell Sci* 1990; **96**: 207–17.
18 Adams JC, Watt FM. Expression of beta 1, beta 3, beta 4, and beta 5 integrins by human epidermal keratinocytes and non-differentiating keratinocytes. *J Cell Biol* 1991; **115**: 829–41.
19 Adams JC, Watt FM. Changes in keratinocyte adhesion during terminal differentiation: reduction in fibronectin binding precedes alpha 5 beta 1 integrin loss from the cell surface. *Cell* 1990; **63**: 425–35.
20 Nicholson LJ, Watt FM. Decreased expression of fibronectin and the alpha 5 beta 1 integrin during terminal differentiation of human keratinocytes. *J Cell Sci* 1991; **98**: 225–32.
21 Hertle MD, Kubler MD, Leigh IM, Watt FM. Aberrant integrin expression during epidermal wound healing and in psoriatic epidermis. *J Clin Invest* 1992; **89**: 1892–901.
22 Ryynanen J, Jaakkola S, Engvall E *et al*. Expression of beta 4 integrins in human skin: comparison of epidermal distribution with beta 1-integrin epitopes, and modulation by calcium and vitamin D3 in cultured keratinocytes. *J Invest Dermatol* 1991; **97**: 562–7.
23 Stepp MA, Spurr-Michaud S, Tisdale A *et al*. Alpha 6 beta 4 integrin heterodimer is a component of hemidesmosomes. *Proc Natl Acad Sci U S A* 1990; **87**: 8970–4.
24 Juhasz I, Murphy GF, Yan HC *et al*. Regulation of extracellular matrix proteins and integrin cell substratum adhesion receptors on epithelium during cutaneous human wound healing in vivo. *Am J Pathol* 1993; **143**: 1458–69.
25 Cavani A, Zambruno G, Marconi A *et al*. Distinctive integrin expression in the newly forming epidermis during wound healing in humans. *J Invest Dermatol* 1993; **101**: 600–4.
26 Haapasalmi K, Zhang K, Tonnesen M *et al.* Keratinocytes in human wounds express alpha v beta 6 integrin. *J Invest Dermatol* 1996; **106**: 42–8.
27 Kellner I, Konter U, Sterry W. Overexpression of extracellular matrix receptors (VLA-3, 5 and 6) on psoriatic keratinocytes. *Br J Dermatol* 1991; **125**: 211–6.
28 Saalbach A, Arnhold J, Lessig J *et al*. Human Thy-1 induces secretion of matrix metalloproteinase-9 and CXCL8 from human neutrophils. *Eur J Immunol* 2008; **38**: 1391–403.
29 Shear NH, Langley RG, Ho V. Efalizumab, a reversible T-cell modulator for psoriasis. *J Cutan Med Surg* 2006; **9** (Suppl. 1): 4–9.
30 Muller K, Schinn M, Reichrath J, Meineke V. 1alpha,25-Dihydroxyvitamin D3 modulates the response of human keratinocytes to ionizing radiation exposure. *Anticancer Res* 2006; **26**: 2735–41.

Avidity of integrins (β2)

Cell migration, and cell–cell or cell–substrate binding in tissue repair, are associated with increased cell adhesion, integrin avidity and cytoskeleton actin polymerization. Members of the β2 integrin leukocyte cell adhesion molecule (LEUCAM) subfamily (also known as CD11/18) are expressed on most leukocytes, becoming inactive when they are 'resting'. Leukocyte function associated antigen-1 (LFA-1) (CD11a/CD18; α1β2) illustrates the changes in conformation and increase in binding sites after activation of the cell. The adhesion molecules of mobile non-activated leukocytes do not bind to endothelial cell ligands, thus avoiding spontaneous cell aggregation and vascular damage. On leukocyte activation, rapid changes in LFA-1 promote binding to the endothelial ligands (immunoglobulin superfamily members) ICAM-1 and ICAM-2, resulting in leukocyte arrest at the site, emigration or local inflammatory change [1,2]. New epitopes appear in the α and β chains [3,4] and there is an influx of calcium ions resulting in an increase in expression of the binding sites [2,5]. Strong support for the importance of β2 to leukocyte trafficking and inflammation comes from the phenotypes of mice lacking one or more β2 integrins on their ligands (e.g. skin infections), and the genetic disease leukocyte adhesion deficiency (LAD), which results from mutations in the gene for β2 integrin. LAD patients suffer from leukocytosis and failure to recruit leukocytes to sites of infection [6]. Blockade of β2 integrins is a highly promising line of biological therapy for skin inflammation, particularly psoriasis [7].

Low-avidity integrins are not closely associated with the cytoskeleton, but upon ICAM-1 contact stimulation, membrane protein kinase C (PKC) initiates phosphorylation of the cytoskeletal proteins, and the α and β chains of LFA-1. This results in reorganization of the vinculin, talin and α-actinin molecules that link actin fibrils to the cell membrane and the integrin, and induces polymerization of the actin fibrils, thereby increasing the cytoskeleton matrix essential to the adaptation of the cell to its environment. The changes in conformation result in increased avidity of the integrins [1,2]. Leukocyte activation results in high-avidity transformation of LFA-1, coupling to the actin intermediate proteins, and polymerization of the actin fibrils, which stabilizes binding to ICAM-1 and promotes adherence to the endothelium. Activation of integrins also stimulates cell synthesis of cytokines and receptors to chemokines, contributing to cell emigration.

Mac-1 (CD11b/CD18) on the membranes of neutrophils, eosinophils and monocytes has a wider range of ligand binding than LFA-1 although it has the same β2 chain (Table 12.11). In normal cells it is inactive but, like LFA-1, the binding affinity for the endothelial cell membrane and other ligands becomes expressed on leukocyte stimulation.

References

1 Pardi R, Inverardi L, Bender JR. Regulatory mechanisms in leukocyte adhesion: flexible receptors for sophisticated travelers. *Immunol Today* 1992; **13**: 224–30.
2 Lub M, van Kooyk Y, Figdor CG. Ins and outs of LFA-1. *Immunol Today* 1995; **16**: 479–83.
3 van Kooyk Y, Weder P, Hogervorst F *et al.* Activation of LFA-1 through a $Ca^{2(+)}$-dependent epitope stimulates lymphocyte adhesion. *J Cell Biol* 1991; **112**: 345–54.
4 Shattil SJ, Ginsberg MH, Brugge JS. Adhesive signaling in platelets. *Curr Opin Cell Biol* 1994; **6**: 695–704.
5 van Kooyk Y, Weder P, Heije K, Figdor CG. Extracellular Ca^{2+} modulates leukocyte function-associated antigen-1 cell surface distribution on T lymphocytes and consequently affects cell adhesion. *J Cell Biol* 1994; **124**: 1061–70.
6 Etzioni A, Doerschuk CM, Harlan JM. Of man and mouse: leukocyte and endothelial adhesion molecule deficiencies. *Blood* 1999; **94**: 3281–8.
7 Gordon KB, Papp KA, Hamilton TK *et al.* Efalizumab for patients with moderate to severe plaque psoriasis: a randomized controlled trial. *JAMA* 2003; **290**: 3073–80.

Selectins

Selectins are calcium-dependent transmembrane glycoproteins with an amino-group terminal portion that binds to sialylated carbohydrate counter-receptors on other cells. Selectin binding is a key transient link between leukocytes and vascular endothelium, thereby mediating the initial steps of leukocyte tethering

Table 12.12 Selectin family.

Molecule	Cells	Function	Activation
P-selectin			
CD62P GMP 140 PADGEM LECAM-3	Platelets, endothelial cells	Links neutrophils and monocytes to platelets and endothelium	Thrombin, histamine oncostatin M, IL-4, IL-13, free radicals, peroxides
E-selectin			
CD26E ELAM-1 LECAM-2	Endothelial cells	Links neutrophils, monocytes, and CLA^+ T-cell subsets to endothelium	IL-1β, TNF-α, LPS, substance P
L-selectin			
CD62L LAM-1 LECAM-1 $Gp90^{MEL}$ DREG	Neutrophils, basophils, eosinophils, monocytes, lymphocytes	Leukocyte rolling on endothelium; transient arrest	Constitutive activation by endothelium

and rolling. The selectin family comprises three members: P-, E- and L-selectin—the genes for which are clustered on chromosome 1 (Table 12.12) [1]. Each selectin has a lectin-like domain at the amino (NH_2) terminal followed by an EGF-like domain and consensus repeats.

P-selectin. P-selectin (CD62P, GMP-140, PADGEM, LECAM-3) is stored intracellularly in the α-granules of platelets and Weibel–Palade bodies of endothelial cells [2,3]. Surface expression of P-selectin on endothelium follows fusion of Weibel–Palade bodies with the plasma membrane. This follows stimulation by histamine, IL-4, IL-13, oncostatin M or thrombin [4–6]. Expression of P-selectin occurs rapidly, within 30 min. Transient expression on endothelium contributes to early leukocyte recruitment [7]. More sustained expression of P-selectin occurs when platelets and endothelium are activated by thrombin, histamine or free radicals, resulting in adhesion of platelets to neutrophils or monocytes and further adhesion of leukocytes, which is enhanced by PAF [8–10]. Once expressed on the cell surface, P-selectin is rapidly internalized by endocytosis [11].

The main ligand for P-selectin is P-selectin glycoprotein ligand-1 (PSGL-1) expressed on myeloid, lymphoid and dendritic cells [12]. P-selectin–PSGL-1 binding is crucial to neutrophil rolling, in that targeted gene disruption of PSGL-1 abrogates this process [13]. The other P-selectin ligand is CD24, which can mediate cell rolling on inflamed endothelium independent of PSGL-1 [14]. Recently, it has been shown that adhesion of P-selectin to leukocytes activates intracellular signalling pathways [15]. For instance, adhesion to T lymphocytes leads to tyrosine phosphorylation of proteins including paxillin [16].

Soluble P-selectin has been detected in plasma but its role is uncertain.

E-selectin. E-selectin (CD62E, ELAM-1, LECAM-2) is synthesized and expressed solely by endothelium and, unlike P-selectin, is not constitutively expressed. Expression is transcriptionally regulated by TNF-α, IL-1 LPS and substance P [17–19]. Following stimulation, peak expression of E-selectin occurs within 4 h and wanes in 24–48 h [17]. E-selectin ligand-1 (ESL-1), the main receptor for E-selectin, is expressed only on myeloid cells [20]. Both PSGL-1 and L-selectin are able to bind E-selectin [21,22]. Leukocytes do not require activation to bind to E-selectin, but as a result of binding there is activation of the β_2 integrin LFA-1 receptors on neutrophils [23]. E-selectin differentiates between neutrophil and eosinophil binding through differences in amount and dimeric form of ESL-1; eosinophil binding is about half that of neutrophils [24].

E-selectin expression is detectable on dermal endothelium in all inflammatory dermatoses, indeed it is preferentially expressed in skin [25]. Cutaneous lymphocyte antigen (CLA) is a glycoprotein molecule expressed on T cells that home specifically to the skin [26]. The expression of CLA by T cells is dependent on induction of glycosylation enzymes that modify pre-existing PSGL-1 during transition of T cells from non-activated to memory phenotype [27,28]. T cells in inflammatory skin disease express CLA, whereas T cells in non-cutaneous inflammation are mainly CLA-negative [27]. The skin specificity of E-selectin–CLA binding makes this an attractive target for biological therapy of inflammatory skin disease [29]. However, a systemically administered antibody directed to E-selectin was ineffective in the treatment of psoriasis [29]. A soluble form of E-selectin is released, which can also induce β2 integrin expression on neutrophils. Levels of soluble E-selectin in plasma are increased in scleroderma, polyarteritis nodosa, SLE, psoriasis and atopic dermatitis [30]. Correlation between levels of soluble E-selectin and disease activity has been observed in atopic dermatitis, psoriasis and palmoplantar pustulosis [31,32]. Whether soluble E-selectin has any direct pathogenic role in psoriasis or is merely a reflection of skin inflammation is debatable.

L-selectin. L-selectin (CD62L, LAM-1, LECAM-1, $gp90^{MEL}$, DREG) is constitutively expressed on the surface of leukocytes during maturation, and expression persists until binding of leukocyte to endothelium [33]. L-selectin is important in the initial phases of leukocyte–endothelial cell binding (Fig. 12.2). L-selectin is unique in that it is the only selectin known to be involved in trafficking of lymphocytes into lymphatic tissue. Upon leukocyte activation (binding), L-selectin is shed from the cell surface [34]. During the later stages of the inflammatory response L-selectin is an important mediator of neutrophil recruitment [35]. Four L-selectin ligands have been identified to date:

1. *Glycosylation-dependent cell adhesion molecule-1* (GlyCAM-1): a secreted protein not found on high endothelial venules (HEV)
2. *Mucosal addressin cell adhesion molecule-1* (MadCAM-1): important in tethering and rolling of lymphocytes in the HEV of Peyer's patches in the gut
3. *CD34*: has a role in lymphocyte rolling in the tonsil
4. *Sgp200*: as for the other two selectins, PSGL-1 may also be a ligand for L-selectin.

Although selectins were originally investigated as adhesion molecules, there is now considerable interest in their role as signalling molecules. For instance, activation via cross-linking of

L-selectin on leukocytes leads to up-regulation of surface expression of β1 and β2 on naïve but not memory T cells, and calcium flux in peripheral blood mononuclear cells [36–38]. In neutrophils in particular, L-selectin cross-linking leads to activation of MAP kinases involving Erk 1 and 2 activation [39].

Down-modulating selectin function has been shown to be an effective therapeutic paradigm, at least in various animal models of inflammation [40–43]. For example, L-selectin diminishes T-cell-mediated allergic reactions during the early sensitization phase of contact dermatitis [44].

Blockers of selectin function have been recently developed for the treatment of various inflammatory dermatoses including psoriasis and atopic dermatitis. β-1, 3-glucan sulphate (PS3) has been shown to have inhibitory activity towards L and P-selectin function [45].

References

1 Watson ML, Kingsmore SF, Johnston GI *et al*. Genomic organization of the selectin family of leukocyte adhesion molecules on human and mouse chromosome 1. *J Exp Med* 1990; **172**: 263–72.

2 Hsu-Lin S, Berman CL, Furie BC *et al*. A platelet membrane protein expressed during platelet activation and secretion. Studies using a monoclonal antibody specific for thrombin-activated platelets. *J Biol Chem* 1984; **259**: 9121–6.

3 McEver RP, Beckstead JH, Moore KL *et al*. GMP-140, a platelet alpha-granule membrane protein, is also synthesized by vascular endothelial cells and is localized in Weibel-Palade bodies. *J Clin Invest* 1989; **84**: 92–9.

4 Modur V, Feldhaus MJ, Weyrich AS *et al.* Oncostatin M is a proinflammatory mediator. In vivo effects correlate with endothelial cell expression of inflammatory cytokines and adhesion molecules. *J Clin Invest* 1997; **100**: 158–68.

5 Yao L, Pan J, Setiadi H *et al*. Interleukin 4 or oncostatin M induces a prolonged increase in P-selectin mRNA and protein in human endothelial cells. *J Exp Med* 1996; **184**: 81–92.

6 Woltmann G, McNulty CA, Dewson G *et al*. Interleukin-13 induces PSGL-1/P-selectin-dependent adhesion of eosinophils, but not neutrophils, to human umbilical vein endothelial cells under flow. *Blood* 2000; **95**: 3146–52.

7 Lawrence MB, Springer TA. Leukocytes roll on a selectin at physiologic flow rates: distinction from and prerequisite for adhesion through integrins. *Cell* 1991; **65**: 859–73.

8 Tsuji T, Nagata K, Koike J *et al*. Induction of superoxide anion production from monocytes and neutrophils by activated platelets through the P-selectin-sialyl Lewis X interaction. *J Leukoc Biol* 1994; **56**: 583–7.

9 Lorant DE, Patel KD, McIntyre TM *et al*. Coexpression of GMP-140 and PAF by endothelium stimulated by histamine or thrombin: a juxtacrine system for adhesion and activation of neutrophils. *J Cell Biol* 1991; **115**: 223–34.

10 Tedder TF, Steeber DA, Chen A, Engel P. The selectins: vascular adhesion molecules. *FASEB J* 1995; **9**: 866–73.

11 Hattori R, Hamilton KK, Fugate RD *et al*. Stimulated secretion of endothelial von Willebrand factor is accompanied by rapid redistribution to the cell surface of the intracellular granule membrane protein GMP-140. *J Biol Chem* 1989; **264**: 7768–71.

12 Laszik Z, Jansen PJ, Cummings RD *et al.* P-selectin glycoprotein ligand-1 is broadly expressed in cells of myeloid, lymphoid, and dendritic lineage and in some nonhematopoietic cells. *Blood* 1996; **88**: 3010–21.

13 Yang J, Hirata T, Croce K *et al.* Targeted gene disruption demonstrates that P-selectin glycoprotein ligand 1 (PSGL-1) is required for P-selectin-mediated but not E-selectin-mediated neutrophil rolling and migration. *J Exp Med* 1999; **190**: 1769–82.

14 Aigner S, Ramos CL, Hafezi-Moghadam A *et al.* CD24 mediates rolling of breast carcinoma cells on P-selectin. *FASEB J* 1998; **12**: 1241–51.

15 Hidari KI, Weyrich AS, Zimmerman GA, McEver RP. Engagement of P-selectin glycoprotein ligand-1 enhances tyrosine phosphorylation and activates mitogen-activated protein kinases in human neutrophils. *J Biol Chem* 1997; **272**: 28750–6.

16 Haller H, Kunzendorf U, Sacherer K *et al.* T cell adhesion to P-selectin induces tyrosine phosphorylation of pp125 focal adhesion kinase and other substrates. *J Immunol* 1997; **158**: 1061–7.

17 Bevilacqua MP, Stengelin S, Gimbrone MA Jr, Seed B. Endothelial leukocyte adhesion molecule 1: an inducible receptor for neutrophils related to complement regulatory proteins and lectins. *Science* 1989; **243**: 1160–5.

18 Matis WL, Lavker RM, Murphy GF. Substance P induces the expression of an endothelial-leukocyte adhesion molecule by microvascular endothelium. *J Invest Dermatol* 1990; **94**: 492–5.

19 Klein LM, Lavker RM, Matis WL, Murphy GF. Degranulation of human mast cells induces an endothelial antigen central to leukocyte adhesion. *Proc Natl Acad Sci U S A* 1989; **86**: 8972–6.

20 Steegmaier M, Levinovitz A, Isenmann S *et al.* The E-selectin-ligand ESL-1 is a variant of a receptor for fibroblast growth factor. *Nature* 1995; **373**: 615–20.

21 Asa D, Raycroft L, Ma L *et al.* The P-selectin glycoprotein ligand functions as a common human leukocyte ligand for P- and E-selectins. *J Biol Chem* 1995; **270**: 11662–70.

22 Picker LJ, Warnock RA, Burns AR *et al*. The neutrophil selectin LECAM-1 presents carbohydrate ligands to the vascular selectins ELAM-1 and GMP-140. *Cell* 1991; **66**: 921–33.

23 Lo SK, Lee S, Ramos RA *et al.* Endothelial-leukocyte adhesion molecule 1 stimulates the adhesive activity of leukocyte integrin CR3 (CD11b/CD18, Mac-1, alpha m beta 2) on human neutrophils. *J Exp Med* 1991; **173**: 1493–500.

24 Bochner BS, Sterbinsky SA, Bickel CA *et al*. Differences between human eosinophils and neutrophils in the function and expression of sialic acid-containing counterligands for E-selectin. *J Immunol* 1994; **152**: 774–82.

25 Groves RW, Ross E, Barker JN *et al*. Effect of in vivo interleukin-1 on adhesion molecule expression in normal human skin. *J Invest Dermatol* 1992; **98**: 384–7.

26 Picker LJ, Michie SA, Rott LS, Butcher EC. A unique phenotype of skin-associated lymphocytes in humans. Preferential expression of the HECA-452 epitope by benign and malignant T cells at cutaneous sites. *Am J Pathol* 1990; **136**: 1053–68.

27 Picker LJ, Treer JR, Ferguson-Darnell B *et al*. Control of lymphocyte recirculation in man. II. Differential regulation of the cutaneous lymphocyte-associated antigen, a tissue-selective homing receptor for skin-homing T cells. *J Immunol* 1993; **150**: 1122–36.

28 Fuhlbrigge RC, Kieffer JD, Armerding D, Kupper TS. Cutaneous lymphocyte antigen is a specialized form of PSGL-1 expressed on skin-homing T cells. *Nature* 1997; **389**: 978–81.

29 Bhushan M, Bleiker TO, Ballsdon AE *et al.* Anti-E-selectin is ineffective in the treatment of psoriasis: a randomized trial. *Br J Dermatol* 2002; **146**: 824–31.

30 Carson CW, Beall LD, Hunder GG *et al*. Serum ELAM-1 is increased in vasculitis, scleroderma, and systemic lupus erythematosus. *J Rheumatol* 1993; **20**: 809–14.

31 Szepietowski J, Wasik F, Bielicka E *et al*. Soluble E-selectin serum levels correlate with disease activity in psoriatic patients. *Clin Exp Dermatol* 1999; **24**: 33–6.

32 Kitamura T, Tamada Y, Kato M *et al.* Soluble E-selectin as a marker of disease activity in pustulosis palmaris et plantaris. *Acta Derm Venereol* 1999; **79**: 462–4.

33 Gallatin WM, Weissman IL, Butcher EC. A cell-surface molecule involved in organ-specific homing of lymphocytes. *Nature* 1983; **304**: 30–4.

34 Jung TM, Dailey MO. Rapid modulation of homing receptors (gp90MEL-14) induced by activators of protein kinase C. Receptor shedding due to accelerated proteolytic cleavage at the cell surface. *J Immunol* 1990; **144**: 3130–6.

35 Ley K, Bullard DC, Arbones ML *et al.* Sequential contribution of L- and P-selectin to leukocyte rolling in vivo. *J Exp Med* 1995; **181**: 669–75.

36 Po JL, Mazer B, Jensen GS. The L-selectin antibody FMC46 mediates rapid, transient increase in intracellular calcium in human peripheral blood mononuclear cells and Daudi lymphoma cells. *Biochem Biophys Res Commun* 1995; **217**: 1145–50.

37 Giblin PA, Hwang ST, Katsumoto TR, Rosen SD. Ligation of L-selectin on T lymphocytes activates beta1 integrins and promotes adhesion to fibronectin. *J Immunol* 1997; **159**: 3498–507.

38 Hwang ST, Singer MS, Giblin PA *et al.* GlyCAM-1, a physiologic ligand for L-selectin, activates beta 2 integrins on naive peripheral lymphocytes. *J Exp Med* 1996; **184**: 1343–8.

39 Waddell TK, Fialkow L, Chan CK *et al.* Signaling functions of L-selectin. Enhancement of tyrosine phosphorylation and activation of MAP kinase. *J Biol Chem* 1995; **270**: 15403–11.

40 Barthel SR, Gavino JD, Descheny L, Dimitroff CJ. Targeting selectins and selectin ligands in inflammation and cancer. *Expert Opin Ther Targets* 2007; **11**: 1473–91.

41 Catalina MD, Estess P, Siegelman MH. Selective requirements for leukocyte adhesion molecules in models of acute and chronic cutaneous inflammation: participation of E- and P- but not L-selectin. *Blood* 1999; **93**: 580–9.
42 Constantin G. PSGL-1 as a novel therapeutic target. *Drug News Perspect* 2004; **17**: 579–86.
43 Rossi B, Constantin G. Anti-selectin therapy for the treatment of inflammatory diseases. *Inflamm Allergy Drug Targets* 2008; **7**: 85–93.
44 Oostingh GJ, Ludwig RJ, Enders S *et al.* Diminished lymphocyte adhesion and alleviation of allergic responses by small-molecule- or antibody-mediated inhibition of L-selectin functions. *J Invest Dermatol* 2007; **127**: 90–7.
45 Alban S, Ludwig RJ, Bendas G *et al.* PS3, a semisynthetic beta-1,3-glucan sulfate, diminishes contact hypersensitivity responses through inhibition of L- and P-selectin functions. *J Invest Dermatol* 2009; **129**: 1192–202.

Immunoglobulin superfamily

CAM are the ligands or counter-receptors for the integrins (Table 12.13). They have one or more immunoglobulin-like domains, hence the designation immunoglobulin superfamily, and have repeat sequences resembling those of fibronectin. Their chief function is to bind leukocytes to cells expressing them, or to endothelium to facilitate vascular emigration, or to cytokine-activated fibroblasts and keratinocytes, to aggregate leukocytes at sites of inflammation.

ICAM-1 has five immunoglobulin-like domains, and is expressed weakly on normal endothelium, but is much increased by stimulation by IL-1, TNF-α or the complement component C5a [1]. On other cells (e.g. keratinocytes and fibroblasts) ICAM-1 is not expressed constitutively, but appears following stimulation by TNF-α or IFN-γ. ICAM-2, present constitutively on endothelium, is not increased by inflammatory stimulation. The third member, ICAM-3, contains five immunoglobulin-like domains and is expressed constitutively by resting monocytes, lymphocytes and epidermal Langerhans' cells [2]. Its expression is increased upon stimulation (e.g. treatment *in vitro*) and it binds with LFA-1 (CD11a/CD18). ICAM-1 contributes to leukocyte adhesion via the LFA-1 and Mac-1 β2 integrins (Table 12.13) [3]. The related VCAM-1 molecule expression is increased after cytokine stimulation, and it binds the α4β1 integrin mediating extravascular migration, principally of monocytes and eosinophils. Another variant, the platelet–endothelial cell adhesion molecule (PECAM-1 or CD31), is found in platelets and at the intercellular junctions of endothelium, where it contributes to leukocyte passage from blood vessels (Fig. 12.2) [4].

Table 12.13 The immunoglobulin superfamily of adhesion molecules.

Adhesion molecule	Cells	Ligand/ counter-receptors	Cells
LFA-3 (CD 58)	Most cell types	CD2	T lymphocytes
ICAM-1	Endothelium	LFA-1	Leukocytes
	Fibroblasts	(α1β2)	
	Activated leukocytes	Mac-1	Monocytes
	Activated keratinocytes	(αnβ2)	
ICAM-2	Endothelium	LFA-1	Leukocytes
ICAM-3	Activated leukocytes	LFA-1	Leukocytes
	Dendritic cells		
	Langerhans' cells		
VCAM-1	Endothelium	VLA-4	Leukocytes
	Macrophages	(α4β1)	(not neutrophils)
	Dendritic cells		Langerhans' cells
	Fibronectin		
PECAM-1	Platelets, leukocytes	PECAM-1, CD31	
	Endothelium		

Like the selectins, the extracellular regions of ICAMs and VCAM are released into tissue fluids in a soluble form (sICAM-1, sVCAM). *In vitro* studies of ICAM-1 indicate that its soluble form is released from blood mononuclear cells, but not from epithelium, fibroblasts or endothelium. In normal persons, up to 450 ng/mL sICAM-1 is detectable in serum, but this may be increased two- or threefold in inflammation (e.g. in disorders such as diabetes, idiopathic pulmonary fibrosis and liver disease); sICAM-1 is also detectable in the synovial fluid of patients with rheumatoid arthritis [5]. sICAM-1 is significantly elevated in the serum of a number of dermatological diseases including atopic dermatitis, psoriasis and metastatic melanoma [6–8] and correlates with clinical severity in untreated disease. sICAM-2 does not exist. sICAM-3 is increased in the sera of patients with psoriasis and atopic dermatitis but is less relevant than sICAM-1 to disease activity [9]. sVCAM is present in normal sera, and is increased in cancer and inflammation, including rheumatoid arthritis. Serum levels of sVCAM are elevated in advanced cutaneous melanoma, localized scleroderma, systemic sclerosis and SLE [10–12]. The role of soluble adhesion molecules is poorly understood—they may compete in cell–cell binding or they may activate cells that possess the cognate ligand.

The L1 cell adhesion molecule (L1CAM) belongs to the immunoglobulin superfamily and was originally identified in the nervous system. Recent studies demonstrated L1CAM expression in various types of cancer, predominantly at the invasive front of tumours and in metastases, suggesting its involvement in advanced stages of tumour progression [13].

A new member of the Ig superfamily, activated leukocyte cell adhesion molecule (ALCAM), has been detected in subsets of haematopoietic cells and endothelial cells during embryogenesis. ALCAM supports the development of haematopoietic cells and increases capillary tube formation. The soluble form, sALCAM, also appears to regulate human microvascular endothelial cells (HMVEC), upon TNF-α stimulation. ALCAM significantly enhanced tube formation of endothelial-like cells on Matrigel, and inhibited their migration. sALCAM completely abolished the effects of ALCAM, suggesting a role as a decoy receptor. sALCAM also enhanced migration of HMVEC, suggesting an important role of this adhesion molecule in the regulation of endothelial cell function [14].

CEACAM1 appears to be an essential CAM for the regulation of T-cell function and cytokine regulation. It is also a co-inhibitory receptor after T-cell activation.

Another cell adhesion molecule regulating skin endothelial cell function is CD99, a highly *O*-glycosylated cell-surface protein expressed on most leukocytes. It is also expressed at endothelial cell contacts and participates in the process of transendothelial migration of monocytes and neutrophils. In a mouse model of delayed-type hypersensitivity (DTH) reaction, anti-CD99 antibodies inhibited the recruitment of *in vivo*-activated T cells into

inflamed skin as well as oedema formation, suggesting CD99 to be a potential therapeutic target in skin inflammation [15].

References

1 Rothlein R, Dustin ML, Marlin SD, Springer TA. A human intercellular adhesion molecule (ICAM-1) distinct from LFA-1. *J Immunol* 1986; **137**: 1270–4.
2 de Fougerolles AR, Springer TA. Intercellular adhesion molecule 3, a third adhesion counter-receptor for lymphocyte function-associated molecule 1 on resting lymphocytes. *J Exp Med* 1992; **175**: 185–90.
3 Smith CW, Marlin SD, Rothlein R *et al*. Cooperative interactions of LFA-1 and Mac-1 with intercellular adhesion molecule-1 in facilitating adherence and transendothelial migration of human neutrophils in vitro. *J Clin Invest* 1989; **83**: 2008–17.
4 Muller WA, Weigl SA, Deng X, Phillips DM. PECAM-1 is required for transendothelial migration of leukocytes. *J Exp Med* 1993; **178**: 449–60.
5 Gearing AJ, Newman W. Circulating adhesion molecules in disease. *Immunol Today* 1993; **14**: 506–12.
6 Wolkerstorfer A, Laan MP, Savelkoul HF *et al.* Soluble E-selectin, other markers of inflammation and disease severity in children with atopic dermatitis. *Br J Dermatol* 1998; **138**: 431–5.
7 Hirai S, Kageshita T, Kimura T *et al.* Soluble intercellular adhesion molecule-1 and soluble E-selectin levels in patients with atopic dermatitis. *Br J Dermatol* 1996; **134**: 657–61.
8 De Pita O, Frezzolini A, Cianetti A *et al*. Squamous cell carcinoma-related antigen (SCCr-Ag), sICAM-1 and beta 2-microglobulin are useful markers of disease activity in psoriasis. *Acta Derm Venereol* 1999; **79**: 132–5.
9 Griffiths CE, Boffa MJ, Gallatin WM, Martin S. Elevated levels of circulating intercellular adhesion molecule-3 (cICAM-3) in psoriasis. *Acta Derm Venereol* 1996; **76**: 2–5.
10 Vuoristo MS, Laine S, Huhtala H *et al*. Serum adhesion molecules and interleukin-2 receptor as markers of tumour load and prognosis in advanced cutaneous melanoma. *Eur J Cancer* 2001; **37**: 1629–34.
11 Shahin AA, Anwar S, Elawar AH *et al.* Circulating soluble adhesion molecules in patients with systemic sclerosis: correlation between circulating soluble vascular cell adhesion molecule-1 (sVCAM-1) and impaired left ventricular diastolic function. *Rheumatol Int* 2000; **20**: 21–4.
12 Yamane K, Ihn H, Kubo M *et al.* Increased serum levels of soluble vascular cell adhesion molecule 1 and E-selectin in patients with localized scleroderma. *J Am Acad Dermatol* 2000; **42**: 64–9.
13 Raveh S, Gavert N, Ben-Ze'ev A. L1 cell adhesion molecule (L1CAM) in invasive tumors. *Cancer Lett* 2009; **282**: 137–45.
14 Ikeda K, Quertermous T. Molecular isolation and characterization of a soluble isoform of activated leukocyte cell adhesion molecule that modulates endothelial cell function. *J Biol Chem* 2004; **279**: 55315–23.
15 Bixel G, Kloep S, Butz S *et al*. Mouse CD99 participates in T-cell recruitment into inflamed skin. *Blood* 2004; **104**: 3205–13.

Adhesion molecules regulating leukocyte emigration

Leukocyte emigration at a site of inflammation is regulated by a complex sequence of interacting changes. A leukocyte rolling over endothelium is arrested by an activated endothelial cell, binds to it, and passes through an endothelial intercellular junction, attracted by chemokines and other chemotactic agents [1–4], a process known as the endothelial cell–leukocyte adhesion cascade (Fig. 12.2).

Neutrophils, eosinophils and monocytes in the blood may flow mid-stream, or roll down the endothelium, when both leukocytes and endothelium are unstimulated. Contact between the rolling leukocyte and endothelium is regulated by constitutive L-selectin (neutrophils) or by L-selectin and α4β1 integrins (eosinophils and monocytes). On contact between the leukocyte, and endothelium activated by TNF-α, IL-1, IL-4 or LPS endotoxin, the leukocytes are rapidly activated. Differences in the integrins expressed in the leukocyte types contribute to the selectivity of the resulting leukocyte infiltrate. The initial adhesion is enhanced by other products resulting from endothelial activation: thrombin, histamine, bradykinin, H_2O_2 and LTC_4. Similarly, neutrophils become further activated by endothelial inflammatory products, particularly PAF, enhanced by platelet aggregation.

The rolling activated neutrophil is arrested by the activated endothelium. The L-selectin molecules are shed. P-selectin from endothelium and platelets is rapidly mobilized, linking the neutrophil to the endothelium; adherence is enhanced by E-selectin on the endothelium binding to sialyl Lewis groups on the neutrophils (Fig. 12.2). Arrest is followed by firm adhesion, during which the neutrophil spreads on the endothelium, adhesion forces are progressively increased, and the neutrophil begins to respond to chemokines and other attracting agents. A rapid change occurs in the conversion of LFA-1 integrins to an avid state, to bind with ICAM-1 and ICAM-2 on the endothelium, which increases expression of ICAM-1. A second β2 integrin, Mac-1, also has functional increased activity and binds to ICAM-1 only (Fig. 12.2).

Adherence changes to migration as the neutrophil responds to IL-8, neutrophil activating peptide-2 (NAP-2), growth-regulated gene/melanoma growth stimulating activity (GRO/MGSA), C5a and other attracting agents. Vascular emigration is most evident in the post-capillary endothelium, but occurs elsewhere in the venous system with sufficient loss of vessel wall integrity. Emigration appears to be mediated by the neutrophil flowing over the ICAM molecules and inserting itself into an intercellular junction, where PECAM-1 is localized; this appears essential for passage of the cell (Fig. 12.2).

Emigration of monocytes and eosinophils is similar, but with some differences in the adhesion molecules and chemokines involved. The α4β1 integrin is expressed constitutively, and contributes to leukocyte rolling, and also to adhesion by binding to VCAM-1 [2]. Monocytes express all three of the CD11/CD18 β2 integrins, and also some ICAM-1 [5]. This may regulate the binding of monocytes to unstimulated endothelium, but adhesion to and emigration from stimulated endothelium is much stronger [5]. A greater number of chemokines contribute to monocyte and eosinophil emigration than emigration by neutrophils, particularly RANTES, MIP-1α, MCP-2 and MCP-3, and additionally MIP-1β and MCP-1 attract monocytes.

Detailed knowledge of the adhesion molecules has an application in the development of blocking ligands, which may offer the potential for control of tissue damaging inflammation.

References

1 Hogg N, Berlin C. Structure and function of adhesion receptors in leukocyte trafficking. *Immunol Today* 1995; **16**: 327–30.
2 Stewart M, Thiel M, Hogg N. Leukocyte integrins. *Curr Opin Cell Biol* 1995; **7**: 690–6.
3 Williams MJ, Hughes PE, O'Toole TE, Ginsberg MH. The inner world of cell adhesion: integrin cytoplasmic domains. *Trends Cell Biol* 1994; **4**: 109–12.
4 Albelda SM, Smith CW, Ward PA. Adhesion molecules and inflammatory injury. *FASEB J* 1994; **8**: 504–12.
5 Meerschaert J, Furie MB. The adhesion molecules used by monocytes for migration across endothelium include CD11a/CD18, CD11b/CD18, and VLA-4 on monocytes and ICAM-1, VCAM-1, and other ligands on endothelium. *J Immunol* 1995; **154**: 4099–112.

Adhesion molecules on activated keratinocytes

Leukocytes emerging from blood vessels move through tissue and bind to activated cells by the same adhesion molecules. ICAM-1 is expressed on fibroblasts, activated thymic epithelial cells and activated keratinocytes [1–4]. As for endothelial cells, ICAM-1 is inducible on fibroblasts by IL-1, IFN-γ and TNF-α, which are cytokines activated or released in damaged tissue [4,5].

It is well known that adhesion molecules critically regulate immune responses [6], cell proliferation and migration [7], and inflammatory signalling pathways in endothelial and epithelial cells [8].

Normal keratinocytes do not express ICAM-1 when examined by usual immunohistochemical methods, although extremely small amounts are detectable by immunoelectron microscopy; this expression may be sufficient for normal leukocyte and Langerhans' cell migration, but avoids leukocyte-mediated damage [9]. The expression of ICAM-1 on keratinocytes is induced by IFN-γ and TNF-α, which are products released by lymphocytes infiltrating inflamed skin [10]. Activated lymphocyte IFN-γ induces keratinocyte expression of ICAM-1 and HLA-DR, promoting inflammatory and allergic epidermal responses [11,12]. ICAM-1 expression is induced in the basal and lower suprabasal layers; decreased expression in the upper layers is associated with greater differentiation and formation of involucrin [13]. When ICAM-1 is found in the upper suprabasal layers, it probably reflects the presence of relatively undifferentiated hyperproliferative epidermis. Among the disorders in which keratinocytes express ICAM-1 are allergic contact dermatitis [14–16], irritant contact dermatitis [17], psoriasis [18–20], lichen planus, bullous pemphigoid, exanthems and urticaria [21].

References

1 Dustin ML, Singer KH, Tuck DT, Springer TA. Adhesion of T lymphoblasts to epidermal keratinocytes is regulated by interferon gamma and is mediated by intercellular adhesion molecule 1 (ICAM-1). *J Exp Med* 1988; **167**: 1323–40.

2 Griffiths CE, Voorhees JJ, Nickoloff BJ. Gamma interferon induces different keratinocyte cellular patterns of expression of HLA-DR and DQ and intercellular adhesion molecule-I (ICAM-I) antigens. *Br J Dermatol* 1989; **120**: 1–8.

3 Pober JS, Gimbrone MA Jr, Lapierre LA *et al*. Overlapping patterns of activation of human endothelial cells by interleukin 1, tumor necrosis factor, and immune interferon. *J Immunol* 1986; **137**: 1893–6.

4 Vejlsgaard GL, Ralfkiaer E, Avnstorp C *et al*. Kinetics and characterization of intercellular adhesion molecule-1 (ICAM-1) expression on keratinocytes in various inflammatory skin lesions and malignant cutaneous lymphomas. *J Am Acad Dermatol* 1989; **20**: 782–90.

5 Dustin ML, Rothlein R, Bhan AK *et al*. Induction by IL 1 and interferon-gamma: tissue distribution, biochemistry, and function of a natural adherence molecule (ICAM-1). *J Immunol* 1986; **137**: 245–54.

6 Sugimoto N, Rui T, Yang M *et al*. Points of control exerted along the macrophage-endothelial cell-polymorphonuclear neutrophil axis by PECAM-1 in the innate immune response of acute colonic inflammation. *J Immunol* 2008; **181**: 2145–54.

7 Joachim RA, Handjiski B, Blois SM *et al*. Stress-induced neurogenic inflammation in murine skin skews dendritic cells towards maturation and migration: key role of intercellular adhesion molecule-1/leukocyte function-associated antigen interactions. *Am J Pathol* 2008; **173**: 1379–88.

8 Morris MA, Dawson CW, Wei W *et al*. Epstein-Barr virus-encoded LMP1 induces a hyperproliferative and inflammatory gene expression programme in cultured keratinocytes. *J Gen Virol* 2008; **89**: 2806–20.

9 Lonati A, Mommaas MA, Pasolini G *et al*. Keratinocytes resident in normal human skin constitutively express, at low levels, the intercellular adhesion molecule-1. An in situ immunoelectronmicroscopy study. *Br J Dermatol* 1996; **135**: 32–5.

10 Barker JN, Allen MH, MacDonald DM. The effect of *in vivo* interferon-gamma on the distribution of LFA-1 and ICAM-1 in normal human skin. *J Invest Dermatol* 1989; **93**: 439–42.

11 Volc-Platzer B, Majdic O, Knapp W *et al*. Evidence of HLA-DR antigen biosynthesis by human keratinocytes in disease. *J Exp Med* 1984; **159**: 1784–9.

12 Wikner NE, Huff JC, Norris DA *et al*. Study of HLA-DR synthesis in cultured human keratinocytes. *J Invest Dermatol* 1986; **87**: 559–64.

13 Little MC, Gawkrodger DJ, Mac Neil S. Differentiation of human keratinocytes is associated with a progressive loss of interferon gamma-induced intercellular adhesion molecule-1 expression. *Br J Dermatol* 1996; **135**: 24–31.

14 Garioch JJ, Mackie RM, Campbell I, Forsyth A. Keratinocyte expression of intercellular adhesion molecule 1 (ICAM-1) correlated with infiltration of lymphocyte function associated antigen 1 (LFA-1) positive cells in evolving allergic contact dermatitis reactions. *Histopathology* 1991; **19**: 351–4.

15 Brasch J, Sterry W. Expression of adhesion molecules in early allergic patch test reactions. *Dermatology* 1992; **185**: 12–7.

16 Griffiths CE, Nickoloff BJ. Keratinocyte intercellular adhesion molecule-1 (ICAM-1) expression precedes dermal T lymphocytic infiltration in allergic contact dermatitis (Rhus dermatitis). *Am J Pathol* 1989; **135**: 1045–53.

17 Willis CM, Stephens CJ, Wilkinson JD. Selective expression of immune-associated surface antigens by keratinocytes in irritant contact dermatitis. *J Invest Dermatol* 1991; **96**: 505–11.

18 Lisby S, Ralfkiaer E, Rothlein R, Vejlsgaard GL. Intercellular adhesion molecule-I (ICAM-I) expression correlated to inflammation. *Br J Dermatol* 1989; **120**: 479–84.

19 de Boer OJ, Wakelkamp IM, Pals ST *et al*. Increased expression of adhesion receptors in both lesional and non-lesional psoriatic skin. *Arch Dermatol Res* 1994; **286**: 304–11.

20 Li YY, Zollner TM, Schon MP. Targeting leukocyte recruitment in the treatment of psoriasis. *Clin Dermatol* 2008; **26**: 527–38.

21 Lange Wantzin G, Ralfkiaer E, Lisby S, Rothlein R. The role of intercellular adhesion molecules in inflammatory skin reactions. *Br J Dermatol* 1988; **119**: 141–5.

Endothelin 1

Endothelin 1 (ET-1), a 21-amino acid peptide, was first identified as a vascular endothelial cell product [1] with potent vasoconstrictor activity, which contributes to endothelial turnover and integrity. It is also synthesized by keratinocytes [2]. ET-1 is mitogenic for fibroblasts [3], smooth muscle cells including vascular cells [3,4], melanocytes, in which it also stimulates tyrosinase activity [5], and renal mesangial cells.

Endothelin (ET-1) has been shown to contribute crucially to UV-induced skin responses such as tanning. ET-1 skin levels in UV-irradiated mice increased substantially and continually in correlation with the levels of UV-induced skin inflammation. Moreover, blockade of ET-1 receptors (ETA) resulted in significantly decreased cutaneous inflammation following UV irradiation. Intracutaneous ET-1 injection caused prominent mast cell degranulation and mast cell-dependent inflammation. ETA blockade did not decrease UV-induced inflammation in mast cell-deficient mice, unless these mice had been adoptively transferred with mast cells before irradiation. This indicates that skin inflammation due to UV irradiation is caused in part by ET-1 acting on skin mast cells [6].

ET-1 has been implicated in diverse physiological or pathological processes, including the vascular changes associated with sepsis. However, the factors that regulate ET-1-associated toxicity during bacterial infections and in other settings are not fully understood. Both the pathology associated with certain allergic and autoimmune disorders, and optimal host defence against bacterial and parasitic infections are mediated by mast cells. *In vitro*, mast cells can produce ET-1, undergo ET-1-dependent

and endothelin-A receptor (ET(A))-dependent activation, and release proteases that degrade ET-1. ET(A)-dependent mast-cell activation can diminish both ET-1 levels and ET-1-induced pathology *in vivo*, and can also contribute to optimal survival during acute bacterial peritonitis. These findings identify a new biological function for mast cells: promotion of homeostasis by limiting the toxicity associated with an endogenous mediator [7].

ET-1 was described over a decade ago as belonging to the group of mast cell-derived and mast cell-bound cytokines. Mast cell subtype- and environment-dependent, ET-1 acts as a potent non-immunological mast-cell activator, which leads to degranulation and mediator release. Studies in mast cell-deficient mice have provided convincing evidence that mast cells counteract the toxicity induced by high concentrations of ET-1, and thereby promote homeostasis [8].

References

1 Yanagisawa M, Kurihara H, Kimura S *et al.* A novel potent vasoconstrictor peptide produced by vascular endothelial cells. *Nature* 1988; **332**: 411–5.

2 Yohn JJ, Morelli JG, Walchak SJ *et al.* Cultured human keratinocytes synthesize and secrete endothelin-1. *J Invest Dermatol* 1993; **100**: 23–6.

3 Muldoon LL, Rodland KD, Forsythe ML, Magun BE. Stimulation of phosphatidylinositol hydrolysis, diacylglycerol release, and gene expression in response to endothelin, a potent new agonist for fibroblasts and smooth muscle cells. *J Biol Chem* 1989; **264**: 8529–36.

4 Hirata Y, Takagi Y, Fukuda Y, Marumo F. Endothelin is a potent mitogen for rat vascular smooth muscle cells. *Atherosclerosis* 1989; **78**: 225–8.

5 Yada Y, Higuchi K, Imokawa G. Effects of endothelins on signal transduction and proliferation in human melanocytes. *J Biol Chem* 1991; **266**: 18352–7.

6 Metz M, Lammel V, Gibbs BF, Maurer M. Inflammatory murine skin responses to UV-B light are partially dependent on endothelin-1 and mast cells. *Am J Pathol* 2006; **169**: 815–22.

7 Maurer M, Wedemeyer J, Metz M *et al.* Mast cells promote homeostasis by limiting endothelin-1-induced toxicity. *Nature* 2004; **432**: 512–6.

8 Hultner L, Ehrenreich H. Mast cells and endothelin-1: a life-saving biological liaison? *Trends Immunol* 2005; **26**: 235–8.

Growth factors from cells other than keratinocytes

Potent cytokines stimulating regeneration of skin are synthesized by cells of the dermis. TGF-α and TGF-β, PDGF and βFGF are synthesized by several types of cell, and the epidermis probably contributes only a small proportion of that synthesized in a healing lesion. Other potent cytokines are EGF, insulin-like growth factor-1 (IGF-1), IGF-2, FGF, αFGF and βFGF.

CHAPTER 13

Clinical Immunology, Allergy and Photoimmunology

G.P. Spickett[1] *& T. Schwarz*[2]

[1]Regional Department of Immunology, Royal Victoria Infirmary, Newcastle upon Tyne, UK
[2]Department of Dermatology, Venerology and Allergology, University Hospital Schleswig-Holstein Campus, Kiel, Germany

Overview of structure and function of the immune system, 13.1
Innate immunity, 13.1
Acquired immunity, 13.6
Components of acquired immunity, 13.6
Structure and development of the immune system, 13.7
Lymphocyte function, activation and regulation, 13.9
Overview of immunological disease, 13.11
Immunodeficiency, 13.11
Primary immunodeficiency, 13.12
Secondary immunodeficiency, 13.12
Autoimmunity and allergy (hypersensitivity), 13.12
Immunity at extremes of age, 13.15
Immunity and malignancy, 13.15
Overview of diagnostic testing for immunological and allergic disease, 13.15
Immunochemistry, 13.16
Detection of autoimmunity, 13.19
Cellular tests, 13.22
Molecular immunology, 13.23
Immunological therapy, 13.23
Further reading, 13.26
Photoimmunology, 13.26
UV radiation induces local and systemic immunosuppression, 13.27
Effect of UV radiation on antigen presentation, 13.28
UV radiation induces immunologic tolerance, 13.29
UV radiation induces T cells with regulatory/suppressor activity, 13.30
UV radiation induces the release of immunosuppressive mediators, 13.31
UV radiation induces immunosuppression in humans, 13.32
Molecular targets mediating UV-induced immunosuppression, 13.32
UVA-induced immunosuppression, 13.33
Implications of UV-induced immunosuppression, 13.33

Overview of structure and function of the immune system

G.P. Spickett, pp. 13.1–13.26

The immune system plays a key role in the protection of an organism against infection and has evolved in parallel with pathogens, which seek to circumvent the organism's defensive strategies. The structure and function of the immune system is complex, rivalled in complexity only by the nervous system with which it shares considerable structural and functional homology. Both organs extend through the body and are reliant on chemical mediators to transmit information between cells. There are complex links between the two systems, manifest by shared receptors and common mediators. The immune system is divided into innate and acquired immunity, which between them provide both immediate defence and long-term immunological memory respectively. Both systems are interlinked to provide effective protection against infection. Disease can arise through immunodeficiency, malignancy and deviation (autoimmunity and allergy).

Traditionally, the immune system is divided into two parts, the innate or non-adaptive and acquired or adaptive, the difference being in the ability of the acquired immune system to learn from exposure to pathogens. The requirement for the innate system is to provide generic protection during the time required for the acquired immune system to generate a specific response. The main feature of the adaptive system is long-lived, specific immunological memory. The two parts are linked through shared mediators (cytokines and chemokines) as well as shared receptors. In many respects, both systems amplify the other's response through released mediators.

In a short chapter it is not possible to give an in-depth view of all aspects of the immune system and the interested reader is directed to more detailed sources of information. A brief overview of the immune system follows as an introduction to the clinical aspects later in the chapter.

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

Innate immunity

Innate immunity describes all of the body's defensive strategies that do not have the capacity for learnt responses or immunological memory. The system includes surface defences, soluble mediators and non-specific cells. These do not operate in isolation but are closely integrated with acquired immunity. Figure 13.1 gives an overview of the main features and how they are integrated.

Non-specific defence mechanisms

The non-specific defence mechanisms include the structural design of the organism, aimed at reducing the capacity for microorganisms to gain entry. These include: the structure of the skin itself, together with the secretions it produces; enzymes in tears and other secretions, such as lysozyme and complement, that have a bactericidal effect; stomach acid, which is extremely effective

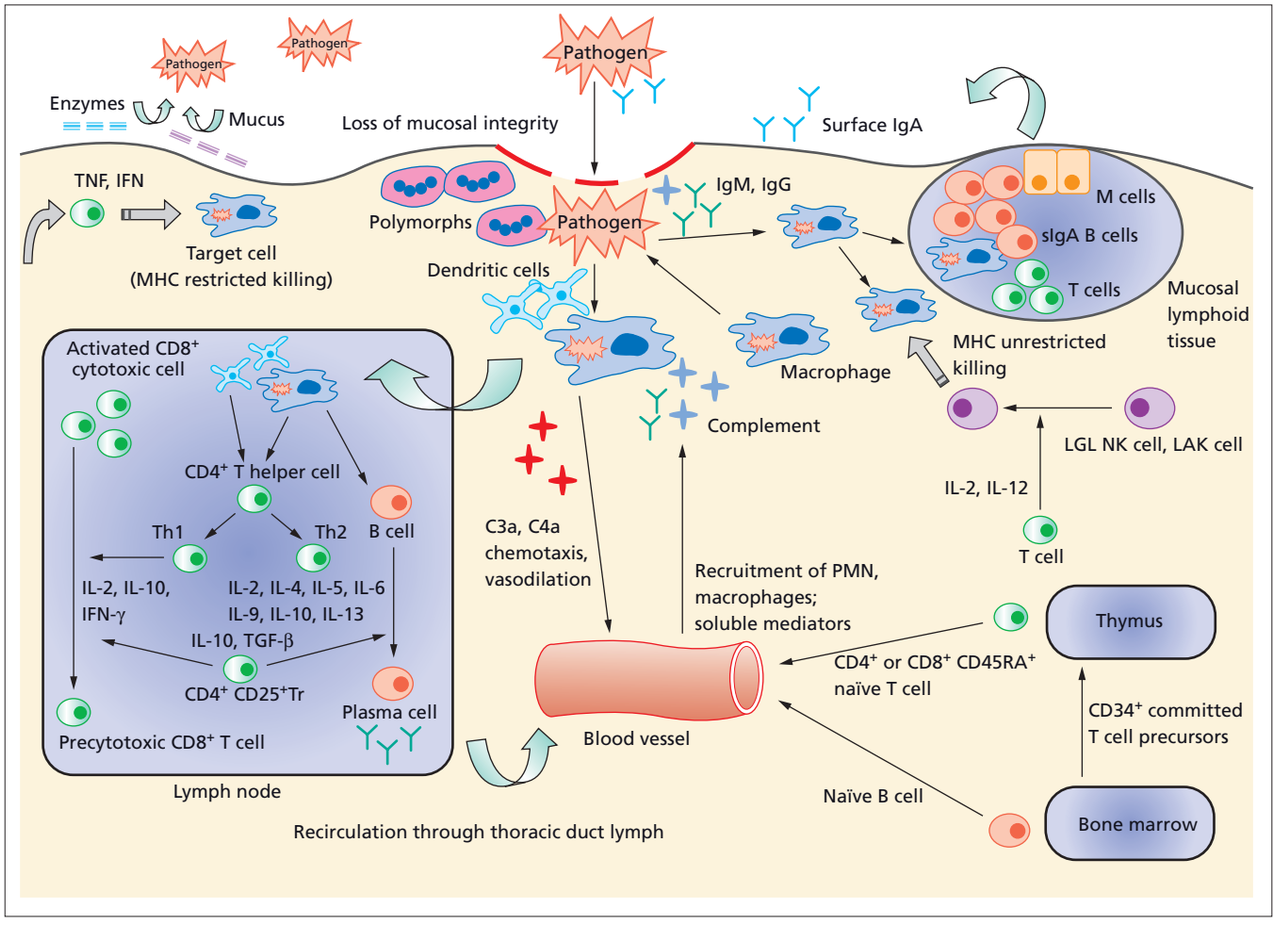


Fig. 13.1 Integration of the various aspects of the immune system, both innate and acquired, in dealing with pathogens. IFN, interferon; IL, interleukin; LAK, lymphokine-activated killer; LGL, large granular lymphocyte; TGF, transforming growth factor.

at reducing bacterial counts entering the upper gastrointestinal tract; and surface mucus in the respiratory tract, which traps bacteria and allows them to be removed by the ciliary escalator. The importance of these mechanisms is demonstrated in illnesses where these protective mechanisms are disrupted, for example: burns lead to easy passage of bacteria into deeper tissues; Sjögren's syndrome, with reduced secretions in eyes, mouth and lungs, is accompanied by increased bacterial infections at all these sites; achlorhydria, either due to gastric atrophy or induced by drugs such as proton-pump inhibitors, is associated with reduced resistance to enteric infections and also to *Candida*; cystic fibrosis and ciliary dyskinesia both disrupt the interaction between mucus and cilia and lead to progressive and severe lung disease due to infection. These examples clearly demonstrate that these non-specific features play a significant role in host defence and cannot be replaced, no matter how effective other aspects of the innate and acquired immune systems might be.

Soluble factors

The main soluble factors involved in host defence are the components of the complement and kinin cascades which are linked, through shared regulatory components, with the clotting cascade. There are three pathways of complement activation (Fig. 13.2): the classical pathway, triggered by interaction of an antibody–antigen complex with C1q; the lectin pathways, triggered by binding of mannose-binding lectin (MBL) to mannose residues on bacterial surfaces; and the alternate pathway, triggered by interaction of lipopolysaccharides of appropriate surface charge with alternate pathway proteins. The alternate pathway is also responsible for the 'tick-over' low-level activation of the complement system. All three pathways converge at the level of C3 to activate the terminal lytic sequence, which inserts a pore comprising the C5–8 proteins and polymerized C9. These pore-forming proteins are structurally very similar to the proteins produced in natural killer (NK) cells and cytotoxic T cells. Complement is a major opsonin, and the presence of C1q and C3 on bacterial surfaces increases phagocytosis through binding to complement receptors. Activation of the complement system also increases recruitment of phagocytic cells by the split products released during activation, that is C4a, C3a and C5a, the anaphylatoxins, which increase vascular permeability and are chemotactic for neutrophils. A specific receptor for C5a (CD88) has been identified, which activates cells via tyrosine phosphorylation and MAP kinases.

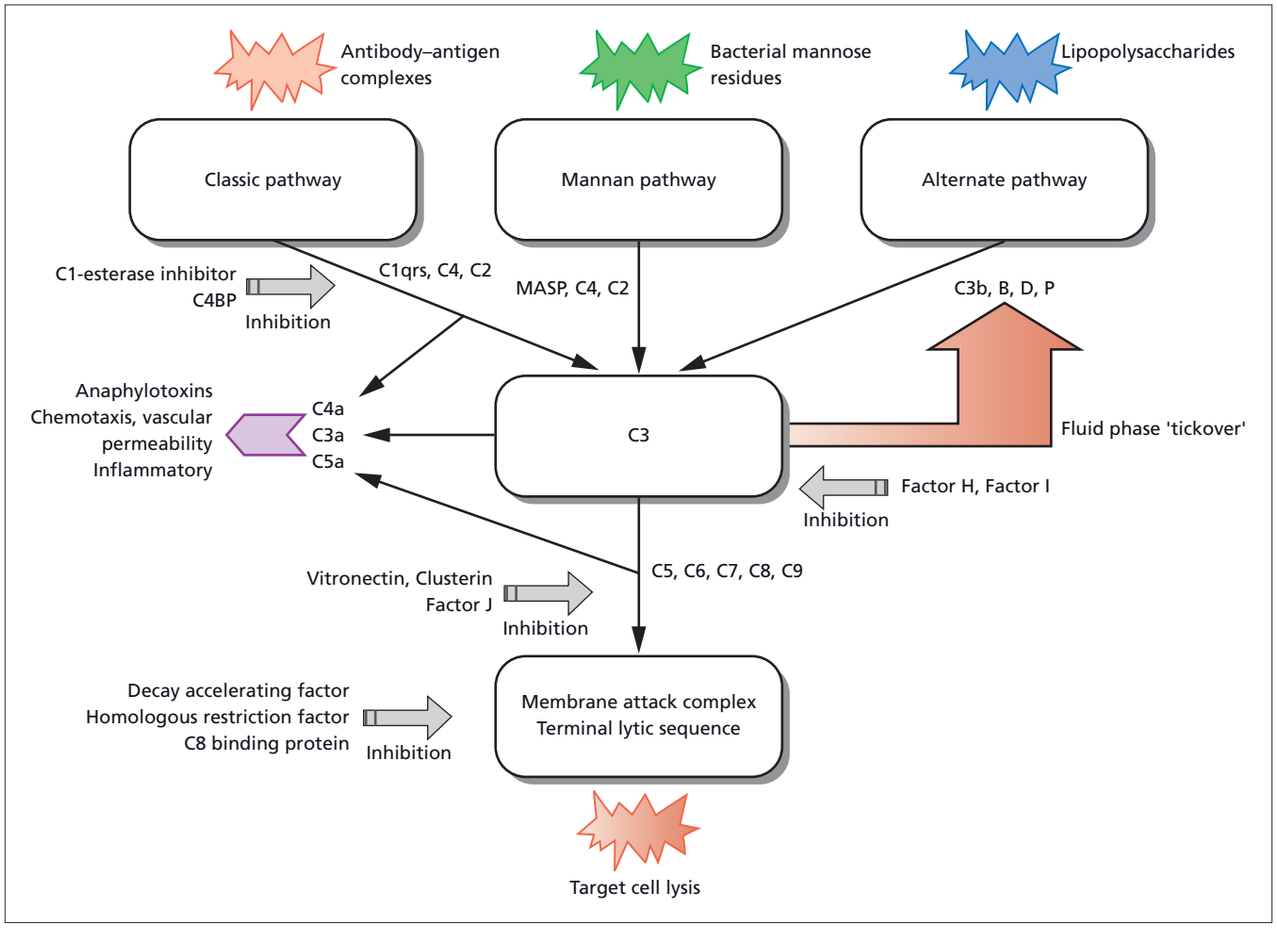


Fig. 13.2 Pathways of complement activation and their control. MASP, mannan-binding protein associated serine protease.

Complement receptors play a crucial role in linking the innate and acquired systems. Complement receptor 1 (CR1, CD35) is widely expressed on neutrophils, macrophages, follicular dendritic cells and B cells. Its presence on phagocytic cells is directly coupled to the process of phagocytosis, while on follicular dendritic cells it plays a pivotal role in antigen trapping and therefore persistence of antigen for subsequent presentation to T cells and B cells to maintain immunological memory. On B cells it is involved in activation and also in presentation of antigen to T cells. It is present on erythrocytes and is therefore involved in the removal of immune complexes to the spleen for subsequent phagocytosis and destruction. CR2 (CD21, EBV receptor) is expressed mainly on B cells, and forms part of the B-cell antigen receptor complex with surface immunoglobulin, CD19 and the immunoglobulin α chain (CD81). CR2 binds C3 degradation fragments iC3b and C3d, and co-ligation of these with antigen to the B-cell receptor reduces the threshold for B-cell activation 100-fold. CD21 is also essential for the development and maintenance of B1 ($CD5^+$) B cells, which are involved in the spontaneous production of IgM and play a role in recognition of lipid antigens. It is also a receptor for soluble CD23, an autocrine B-cell growth factor involved in IgE production. CR3 and CR4 are β integrins, expressed on phagocytic cells and directly involved in signalling for phagocytosis.

The complement system is an enzymatic cascade of proteases, with each step providing amplification. There are key checkpoints at which regulatory proteins act to ensure that the process is controlled. C1-esterase inhibitor inhibits C1r and C1s and also mannan-binding protein (MBP)-associated serine protease from the lectin pathway, as well as acting as a regulatory protein in the clotting and kinin cascades. Factor H is an inhibitor of C3 and C4-binding protein inhibits activated C4; these are both large molecules with multiple binding sites and are therefore capable of inactivating multiple activated complement proteins simultaneously. Both also act as co-factors for factor I, an inhibitor of activated C3 and C4. Deficiency of factor H has been associated with haemolytic–uraemic syndrome. Key molecules involved in the regulation of the classical pathway are CD55 (decay accelerating factor), which binds C4b and C3b, and C4 binding protein (C4bp) which binds C4b. The complement receptor CR1 also inhibits the activities of the convertases. In the alternate pathway, the cell bound molecule CD46 (membrane co-factor protein, MCP), which is similar to DAF, and works in a similar way to Factor H, promotes Factor I inactivation of C3b and C3i.

Newly described regulators of the terminal lytic sequence include vitronectin and clusterin, which interact mainly with C5b67. Host cells also have regulatory proteins CD59 (membrane inhibitor of reactive lysis (MIRL); protectin) and C8-binding protein (homologous restriction factor, HRF) expressed on their surface to prevent accidental bystander destruction by the terminal lytic sequence.

In paroxysmal nocturnal haemoglobinuria, there is a somatic clonal mutation in the *pig*A gene that prevents proteins, such as DAF, MCP and protectin, which contain the glycosylphosphatidylinositol (GPI) anchor, from being expressed through disruption of the transmembrane glycolipid tail. This causes the production of erythrocytes susceptible to complement-mediated lysis and night-time haemolysis, when the blood pH drops.

Deficiency of nearly all components of the complement system has been described, and most lead to increased susceptibility to infection, particularly with *Neisseria* species. The significance of MBP deficiency is uncertain, as deficiency alleles have been identified in healthy subjects. It is thought likely that MBP deficiency is only clinically important when other aspects of the humoral immune system are defective and the levels of MBL are significantly reduced.

The kinin cascade is also a critical pathway in inflammation, particularly in rhinitis and asthma, and also in generation of angio-oedema in hereditary angio-oedema. The end-product of the cascade is bradykinin, which acts through specific bradykinin receptors on smooth muscle, endothelial cells, neurones and synovial cells. C1-esterase inhibitor and α_2-macroglobulin inhibit activated kallikrein and therefore reduce bradykinin production; C1-esterase inhibitor also inhibits factor XIa in the clotting cascade and Hageman factor in the kinin cascade. Carboxypeptidase N breaks down bradykinin to des-arg-bradykinin, which retains some vasoactive properties: deficiency of carboxypeptidase N has been reported as a cause of angio-oedema. Des-arg-bradykinin is inactivated by angiotensin-converting enzyme (ACE), which explains why angio-oedema and cough are common complications of therapy with ACE inhibitors. Experimental drugs such as icatibant and FR173657 are available that block bradykinin receptors, and may therefore have a major role in the management of angio-oedema.

The pentraxin family of molecules includes C-reactive protein (CRP) and serum amyloid A (SAA). These are acute-phase proteins that bind directly to microbial polysaccharides as well as matrix proteins. CRP also scavenges DNA released from dead cells by binding to chromatin. It binds to C1q, thus facilitating the removal of the DNA–immune complex. It acts as an opsonin, but inhibits the convertases that activate the terminal lytic sequence. CRP is clearly an essential molecule, as deficiency has never been reported.

Defensins are newly described, small polypeptide molecules with a direct ability to lyse bacteria. The α-defensins are produced in neutrophils and also in gastrointestinal Paneth cells, while the β-defensins are produced by epithelial cells of the airway and the urothelium.

Many cells of the innate system produce inflammatory compounds derived from the arachidonic acid pathway. These include the prostaglandins, thromboxanes and leukotrienes. These agents have a diverse array of inflammatory properties, including increasing vascular permeability, local blood flow, chemotaxis of neutrophils and smooth muscle constriction, and effects on platelets. The different metabolic pathways include mutually antagonistic agents, prostacyclins and lipoxins. Abnormalities of the enzymes of the synthetic pathways for prostaglandins account for the adverse effects of aspirin in some individuals. The pharmaceutical industry has been active in producing inhibitors of leukotriene synthesis, inhibitors of lipoxygenase (Zileuton) and 5-lipoxygenase activating protein being the most effective, while drugs such as monteleukast and zafirlukast are leukotriene antagonists that are effective in asthma but also in urticaria and other inflammatory conditions.

Cellular components

Polymorphonuclear leukocytes (neutrophils) play a critical role in the immediate defence against bacteria. They develop in the bone marrow under the influence of the specific cytokines SCF, IL-3, G-CSF and GM-CSF. The bone marrow contains a large reserve pool of mature cells, which can be released by stress such as infection; 60% of bone marrow capacity is devoted to neutrophil production. Neutrophils remain in the circulation for only a few hours before emigrating into tissues. Abundant expression of leukocyte adhesion molecules, such as L-selectin, P-selectin and cutaneous lymphocyte antigen (CLA), ensures the margination of neutrophils along the endothelial surface. In the presence of activating and chemotactic factors binding to specific surface receptors such as *N*-formylmethionine-containing peptides derived from bacteria, platelet-activating factor (PAF), the chemokines MIP-1α, RANTES and IL-8, and the anaphylatoxins C3a and C5a, adhesion to endothelium occurs. This process involves integrins of the CD11/CD18 family, with subsequent emigration and migration of neutrophils to the site of inflammation, following the chemotactic gradient. Phagocytosis is stimulated by binding of antibody to Fc receptors and complement to complement receptors, leading to the formation of the phagocytic vacuole. Fusion of the vacuole with the primary neutrophil granules then exposes the bacterium to an array of enzymes and bactericidal proteins, including myeloperoxidase, lysozyme, elastase, cathepsin G, proteinase-3, azurocidin and α-defensins. Three types of granule are recognized: specific granules containing the enzymes, gelatinase granules containing predominantly gelatinase and NADPH oxidase, and secretory granules. Inducible enzyme systems also contribute, producing nitric oxide and superoxide. The oxidative burst that forms superoxide is produced by the NADPH oxidase system, a multicomponent enzyme. Genetic deficiencies of the subunits of this enzyme cause the X-linked and autosomal forms of chronic granulomatous disease. In X-linked chronic granulomatous disease (63% of cases) mutations occur in the gp91-phox protein, while the autosomal forms are due to mutations in p47-phox, p22-phox and p67-phox. Myeloperoxidase is responsible for the production of hypochlorous acid, a potent oxidizing agent formed from hydrogen peroxide and chlorine; myeloperoxidase deficiency has been reported and leads to increased infections. Neutrophils have multiple bactericidal pathways, so defects in one pathway

will not necessarily lead to failure to kill bacteria. Neutrophils are also biosynthetically active, secreting an array of cytokines and chemokines, including tumour necrosis factor (TNF)-α, IL-1, IL-12, interferon (IFN)-γ, transforming growth factor (TGF)-β and IL-8, that amplify the inflammatory response.

Neutrophils

Neutrophils express high levels of pattern recognition receptors (PRR) which recognize cell wall components of pathogens, viral DNA and RNA and lipoproteins. These include CD14, the lipopolysaccharide receptor and toll-like receptors (TLR) of which there are a large number. Binding of antigens activates a cell through complex interlinked cascades. Deficiency of components of the TLR cascades has now been identified as causing increased susceptibility to bacterial infection. Neutrophils also express scavenger receptors which bind low density lipoproteins, particularly if they have been oxidized. In mice, deficiency of these receptors can increase susceptibility to staphylococcal infection.

Macrophage–monocytes

Macrophage–monocytes are mononuclear phagocytic cells, also derived from the bone marrow and under similar differentiation control to neutrophils. They are longer lived than neutrophils and are actively migratory, being found in all tissues in the body. Control of migration is similar to that for neutrophils, although there are a range of chemokines specifically involved in recruitment, such as MCP-1, MDC, PF4 and MIP-1α. As well as expressing complement and Fc receptors, enabling them to phagocytose immune complexes, they also express an array of scavenger receptors, including lipopolysaccharide (LPS) and TLR, which bind LPS complexed with soluble CD14. Other TLR bind proteolytic cleavage fragments from the complement and kinin systems. Activation through TLR leads to oxidative burst and release of the cytokines IL-1 and TNF-α, which drive the systemic inflammatory reaction, stimulating the acute phase response and causing pyrexia via effects on the hypothalamus. Macrophages have similar enzyme systems to neutrophils, although the activity of the NADPH oxidase system is lower. Macrophages can act as antigen-presenting cells (APCs) and major histocompatibility complex (MHC) class II antigens on the cell surface are up-regulated by activation. These cells play an essential role in type IV delayed-type hypersensitivity reactions, as part of granuloma formation, often with cell fusion to create multinucleate giant cells. This is mediated through IFN-γ. Mutations in the IFN-γ receptor, leading to either non-expression or expression but loss of function, have been associated with increased susceptibility to mycobacterial infection, due to failure of macrophage function despite good T-cell immunity. Defects in the receptor for IL-12, which is involved in the induction of IFN-γ, also lead to a similar clinical picture.

Macrophages, together with dendritic cells, form an essential bridge between the innate and acquired immune systems. Phagocytosis of antigen by macrophages leads to internalization, digestion of antigen and re-expression of derived peptides on the cell surface bound to MHC class II antigens. This provides essential stimulation to $CD4^+$ T cells. Dendritic cells have direct phagocytic capacity but acquire antigen through transfer from macrophages, with which they form tight complexes during the immune process.

Eosinophils

Eosinophils are derived from the same bone marrow lineage as neutrophils, but differentiate under the influence of IL-5; their main role in host defence is against parasitic infections. Their granules contain: eosinophil peroxidise; the Charcot–Leyden crystal protein, a cytotoxic phosphatase; eosinophil cationic protein (ECP); major basic protein; and eosinophil-derived neurotoxin. The latter is an important mediator of the neuropathy seen in Churg–Strauss syndrome. Eosinophils have surface receptors for IgE (low affinity, CD23), IgG Fc receptors and complement receptors. Recruitment to sites of inflammation is through similar use of selectins and integrins. The anaphylatoxins and PAF are chemotactic and there are specific eosinophil chemoattractants of the chemokine family, eotaxin-2 and eotaxin-3. Activation of an eosinophil leads to an oxidative burst and production of leukotrienes as well as an array of cytokines, including IL-1, IL-6, TNF-α and the chemokine IL-8, thus promoting an acute inflammatory reaction. Release of eosinophil granule components contributes to bronchial damage in asthma, and promotes the chronic phase of inflammation through the release of cytokines active on lymphocytes. MHC class II is expressed, indicating that the cells can also function as APCs.

Mast cells

Mast cells are derived from a distinct lineage of bone marrow cells and express high levels of high-affinity IgE receptors on their surface. Mast cells also express receptors for C3a and C5a, as well as multiple chemokine receptors, ensuring that they are attracted to sites of inflammation regardless of the initiating event. Similar adhesion molecules are expressed as on neutrophils and eosinophils. Their granules contain large amounts of histamine, heparin, tryptase and TNF-α. Cross-linking of the IgE receptor by allergen triggers degranulation. Mast cells produce both leukotrienes and prostaglandins, contributing to the inflammatory response, and also synthesize IL-3, IL-4, IL-5 and GM-CSF. Mast cells in lung and gastrointestinal mucosa can be differentiated from those in skin and gastrointestinal submucosa by the presence of chymase in the latter.

Basophils

Basophils are circulating cells with similar properties to tissue mast cells and have high-affinity receptors for IgE. Despite this, they are derived from the same bone marrow precursor as eosinophils, whereas mast cells are a distinct lineage. Basophils circulate for several days in the bloodstream. They produce leukotrienes but not prostaglandins. Basophils are about 100-fold more sensitive to activation via the IgE receptor compared with mast cells, and are also more sensitive to non-IgE stimuli, including *N*-formyl-methyonyl-leucylphenylalanine (fMLP), C3a and C5a, and phospholipase A. They appear to be involved in the late phase of allergic reactions in tissues and produce IL-4 and IL-13, which increase synthesis of IgE. Interestingly, the release of these

cytokines is dependent on the calcineurin pathway, which can be inhibited by ciclosporin and tacrolimus, accounting for the effectiveness of these drugs in treating allergic reactions.

Natural killer cells

Natural killer cells are large, granular lymphocytes derived from bone marrow precursors. Their granules contain perforin, a cytotoxic protein closely related to complement proteins of the terminal lytic sequence. Although of lymphocyte lineage, these cells do not express CD3/T-cell receptor (TCR) complexes on their surface, nor do they rearrange their TCR genes. Some cells express CD8, but mainly they express CD16, a low-affinity IgG Fc receptor, and CD56, a variant of the neural cell adhesion molecule. They express a range of specific NK-cell receptors, including NKp46 and NKG2D (binds to MHC class I chain-related A and B molecules, MICA and MICB), and cytotoxicity is enhanced by exposure to IL-2. It is thought that the default for NK cells is to kill cells that they come into contact with, unless the cells express sufficient levels of MHC class I antigens to interact with killer-inhibitory receptors (KIRs) expressed on the surface of NK cells. Binding of MHC class I to KIRs is independent of the presence of bound peptide. There are a variety of different KIRs, some of which recognize non-classical MHC antigens (HLA-E, HLA-G). This reactivity explains the abundance of NK cells in the placenta that express high levels of non-classical MHC as they are involved in tolerance to the fetal allograft. Expression of IgG receptors enables them to kill antibody-coated targets via antibody-dependent cell-mediated cytotoxicity. They produce IFN-γ, TNF-α and granulocyte macrophage colony stimulating factor (GM-CSF), contributing to acute inflammation and stimulating T-helper type 1 (Th1) responses in the acquired system (see below). NK cells contribute to tumour surveillance, seeking out cells with reduced class I expression, and also provide protection against viral infections, as viruses often block surface expression of MHC class I antigens, thereby preventing T-cell recognition. Very rare, primary NK-cell deficiency has been reported, with increased susceptibility to all types of herpesviruses. Functional abnormalities of NK cells are seen in the X-linked lymphoproliferative syndrome, due to signalling lymphocyte activation molecule (SLAM)—associated protein (SAP) deficiency, and in Chédiak–Higashi syndrome.

γδ T cells

γδ T cells are thought to represent an evolutionarily early form of T cell and comprise only a minority of T cells, located mainly in mucosae and skin. They never express αβ TCR and even their γδ TCR are of limited diversity and tend to be more cross-reactive. Their pattern of antigen recognition is more in keeping with other cells of the innate immune system. They do not require antigen processing for recognition. MICA and MICB are targets for NKG2D recognition. Effector functions are similar to $\alpha\beta TCR^+$ T cells.

NK T cells

NK T cells are cells with characteristics of both T cells and NK cells and carry a very limited diversity αβ TCR and also express NKG2D receptors and KIRs. They appear to recognize CD1d, a molecule with similarity to MHC antigens, and interact specifically with dendritic cells. Antigens recognized include glycosylsphingolipids. Their effector functions are more in keeping with NK cells but they may also play a role in limiting autoimmunity.

$CD5^+$ B cells

These cells (B1 cells, see below) comprise a small population of very long-lived B cells that are involved in the production of natural antibodies, predominantly IgM class, with a structure close to germ-line configuration, and are broadly polyreactive. The presence of these natural antibodies may facilitate early antibody-mediated opsonization and lysis, before a more specific immune response can develop. These cells thus act as a bridge between the innate and acquired immune systems. Self-reactivity is a problem with natural antibodies and B1 cells are frequently the cell type identified in chronic lymphocytic leukaemia.

Acquired immunity

The key features of the acquired immune system are: (i) the responses are specific to a particular pathogen or antigen; and (ii) there is long-lived immunological memory that persists after the first encounter. This is manifest in the antibody responses to antigen on first exposure, where the response is small and comprises predominantly IgM (primary immune response), whereas re-challenge after a suitable interval leads to a large and predominantly IgG response (secondary immune response). The process is accompanied by an expansion of the antigen-reactive cells, together with the generation of long-lived memory B cells. A similar process takes place in T cells. During the process somatic mutation takes place in the antigen receptors to enhance their affinity for antigen. The immune system is a dynamic surveillance system, with constant recirculation of the constituent cells through the bloodstream, organs and lymphoid tissue. Lymph nodes and spleen remain the primary sites of encounter with antigen-bearing APCs and are also the sites of major antigen-driven proliferation. The recirculation process is tissue-specific and targeted through specific receptors expressed on vascular endothelium.

Components of acquired immunity

The key components of the acquired immune system are the B cells, which produce antibody, and T cells, which serve helper, cytotoxic and regulatory functions. Both have specific receptors based on recombination of multiple genes to give an enormous range of potential specificities. Both cell types use the recombinase-activating genes (*RAG-1* and *RAG-2*) to carry out this process. The antigen receptors on T and B cells differ in their recognition requirements. Antibody binds to conformational epitopes in whole molecules and these will not usually be contiguous, but are represented as surface binding sites on the target molecule. In contrast, the TCR recognizes short linear peptide sequences (7–15 amino acids), only in the context of binding of the peptide to MHC antigens. These linear sequences may be anywhere in the molecule but are usually deeply buried within the structure and not accessible on the surface. This means that B cells can be stimulated by free antigen whereas T cells in the main require processed antigen, presented by APCs such as macrophages and dendritic

cells. As B cells themselves express MHC class II antigens, they can function as APCs, presenting peptides to $CD4^+$ T cells in return for help through T-cell cytokine production. Both T-cell and B-cell antigen receptors occur in clusters with co-receptor molecules, which confer additional recognition functions (complement, MHC class), and transmembrane signalling molecules linked to cascades of intracellular enzymes. Activation signals are usually delivered by phosphotyrosine kinases, while inhibitory signals dephosphorylate tyrosine.

B lymphocytes

B lymphocytes develop in the marrow and then migrate to secondary lymphoid tissue, where they encounter antigen. Antigen-stimulated B cells develop into plasma cells, producing quantities of serum immunoglobulins that are representative of the surface antibody receptor of the cell. B cells exist in two forms, B1 and B2, distinguished by their pattern of surface antigens. B1 cells have low/absent surface IgD, CD45, CD23 and can be $CD5^+$ (B1a) and $CD5^-$ (B1b). B1 cells are long-lived cells, producing naturally occurring low-affinity antibodies, usually IgM, against bacteria and autoantigens. Early in life a high percentage of cells are B1, but this falls with age; however, it is this population that is expanded in most chronic lymphocytic leukaemias. B2 cells are 'conventional' B cells and have high levels of surface IgM and IgD as well as CD45 and CD23, but do not express CD5.

Immunoglobulins

Serum immunoglobulins comprise five classes, IgM, IgD, IgG, IgA and IgE (in order of expression), determined by the heavy chain. Each can have either κ or λ light chains. IgD operates primarily as a surface receptor and has no known function as a secreted molecule. High levels have been associated with a syndrome of recurrent fevers, arthritis and infections (hyper-IgD syndrome) that appears to be caused by a defect in mevalonate kinase. IgM exists as a membrane receptor and as a soluble pentameric form, in which the five IgM molecules are joined by a J chain. IgM is the antibody produced in the first phase of an immune response. IgG exists as four subclasses, and comprises, by concentration, the major serum immunoglobulin. IgG1 and IgG3 are mainly antiprotein antibodies, while IgG2 is mainly antipolysaccharide. IgG4 is present only in low concentrations and its precise role is uncertain, although deficiency of it and other subclasses do not necessarily give rise to clinical disease; measurement of IgG subclasses is therefore not a useful predictor of underlying humoral immune deficiency. In Sjögren's syndrome, IgG1 is preferentially increased in the polyclonal elevation of IgG seen in this condition; the other subclasses are relatively reduced. IgA exists in two forms, IgA1 (the predominant serum form) and IgA2. IgA is the antibody of mucosal surfaces, and is secreted in the form of dimers and trimers, with an associated J chain. In the process of secretion, which involves active transport through the epithelial cells mediated by the poly Ig receptor, a secretory piece is added, which slows the rate of breakdown. Secretory piece deficiency has been reported very rarely. In the absence of IgA, IgG and IgM can be transported to the mucosal surface and provide effective protection. Thus selective IgA deficiency may be asymptomatic in respect of infection, although it increases the risk of developing a range of autoimmune diseases, including coeliac disease and connective tissue diseases. IgE is primarily involved in antiparasite immunity, acting as a passively adsorbed receptor on mast cells and basophils. Serum concentrations are extremely low in comparison with the other classes of immunoglobulins.

T lymphocytes

Mature T cells develop in the thymus from T-lineage committed precursors derived from bone marrow. In the thymus, the process of development of functional TCRs takes place in an analogous way to the process in B cells. As well as the TCR, the cells also develop the co-receptor molecules of the CD3 complex (five separate chains) and CD4 and CD8 surface expression. In the periphery, T-cell function is defined to a certain extent by expression of CD4 and CD8, which define the class of MHC recognized. $CD4^+$ T cells are 'helper-effector cells', which recognize predominantly MHC class II antigens and thus interact mainly with a restricted array of MHC class II-positive cells, such as B cells and APCs, or other cells which may have induced class II, for example thyrocytes during thyroiditis. Functions ascribed to $CD4^+$ T cells include provision of T-cell help through cognate interactions and cytokine release to B cells and also cytotoxicity towards class II-bearing targets. $CD8^+$ T cells recognize MHC class I antigens, which are expressed on all cells except erythrocytes, and are particularly involved in the recognition of virally infected targets. These cells are actively cytotoxic, using the same enzymes found in NK-cell granules (perforins and granzymes). T cells also perform regulatory functions, cross-suppressing other types of T cells (see below).

Structure and development of the immune system

Although diffused throughout the body, the immune system functions as an integrated organ in much the same way as the nervous system, with which it shares a number of key molecular concepts. However, the immune system has an enormous task as the surface area of the skin is about 2 m^2, that of the lung 100 m^2 (the size of a soccer pitch) and that of the gastrointestinal tract 400 m^2 (four soccer pitches!). The mucosal surfaces have to be 'painted' with a contiguous film of secreted IgA. This explains why the total daily production of IgA is tenfold higher than that of IgG, even though the serum level of IgA is five times less than that of IgG.

Primary lymphoid tissue

The primary lymphoid tissue comprises the sites in which lymphocytes and other cells involved in immunological function develop. In humans this comprises the yolk sac and fetal liver during embryogenesis, with seeding of pluripotent precursors to the bone marrow. These stem cells may be either $CD34^+$ or $CD34^-$, although in clinical transplantation CD34 is used to enrich for stem-cell activity. B-cell development takes place in the bone marrow while committed T-cell precursors, which are $CD7^+$, migrate to the thymus. In birds the bursa of Fabricius and in lagomorphs the sacculus rotundus and the appendix are specific organs involved in the generation of B cells and are analogous to the thymus. However, humans do not appear to have homologous structures. In all these organs there is a complex interaction

between stromal epithelium and developing immunocytes, with production of key growth factors by the epithelial cells and presentation of self-antigens involved in tolerance induction.

B-cell development takes place in the bone marrow in humans, with 10^9 new B cells produced each day. During the process of B-cell development, the immunoglobulin genes undergo rearrangement to form the basis of the enormous repertoire of antibodies. This process is dependent on the presence of the recombinase enzymes *RAG-1/RAG-2*. Recombination occurs first in the heavy-chain genes, involving the V, D and J regions. There is a significant wastage as 50% of cells fail to produce viable recombinations. Initially the cells produce a membrane form of the μ heavy chain, which appears on the surface, coupled with the surrogate light chains, V pre-B and λ5. At the same time the invariant chains Igα and Igβ are also produced and combine on the surface as part of the receptor complex. The role of the surrogate light chains is purely to allow expression of the heavy chain and to permit the continued development of the B cell, with recombinations of the κ and λ light chains, and the expression of a fully formed receptor. During this process, the other components of the receptor complex (CD19 and CD21) also appear, and cells become dual positive for surface IgM and IgD. B-cell development is a complex process, and defects in some of the essential enzymes and genes have been identified as causing primary immunodeficiencies. These include deficiencies of surrogate light chain, μ chain, Igα BLNK (B-cell linker protein) and BTK (B-cell tyrosine kinase), which give B-lineage specific defects, while *RAG-1/RAG-2* defects cause severe combined immunodeficiency (SCID) due to their involvement in TCR rearrangement. Use of knock-out mice has enabled rapid strides to be made in the assessment of the enzymes critical to B-cell development. It is likely that further genetic abnormalities will be described in humans.

Within the thymus, committed T-cell precursors undergo rearrangement first of their TCR β genes; *RAG-1/RAG-2* are critical for this process. In order for the gene product to be expressed a surrogate α chain, invariant TCR pre-α, is produced that permits the next stage of α-chain rearrangement. A small proportion of cells express γδ TCR rather than αβ TCR. Failure to rearrange a functioning β chain leads to cell death. It has been calculated that the process of gene rearrangement can lead to 10^8 potential recombinations. Numerous genes are involved in the control of this process, including *Ikaros* and *Notch-1*. During this process, expression of CD44 (hyaluronate receptor) is lost and expression of CD25 (low-affinity IL-2 receptor) is gained. Cells then express CD3 and both CD4 and CD8 (dual-positive cells), and lose one or the other as development proceeds to become either $CD4^+$ or $CD8^+$ T cells. The enzyme ZAP-70 kinase is essential to this process and its genetic deficiency leads to failure of production of $CD8^+$ T cells and reduced numbers of $CD4^+$ T cells; this disorder is a variant of SCID. T cells leave the thymus in a naïve state. During the process of T-cell development two key events take place: positive selection of T cells that recognize self-MHC and negative selection of those that recognize self-peptides. As the recombination process is essentially random, the majority of developing T cells do not develop appropriate TCRs. Cells that do not recognize MHC die by 'neglect' while those that recognize self-peptides are stimulated to proliferate and die (activation-induced cell death or apoptosis). Accordingly, the thymus has a huge turnover of T cells, the majority of which die *in situ*. Any failure in the process of eliminating self-peptide reactive T cells contributes to later development of autoimmune disease.

Failure of thymic development has been described and is due to as yet uncharacterized gene defects located at chromosome 22q11, which control the development of the branchial arches and pouches; this leads to failure of T-cell production as well as cardiac abnormalities. The severe form with immunodeficiency is recognized as DiGeorge syndrome, analogous to the nude mouse mutation. However, milder variants without immunodeficiency are also identified: velocardiofacial syndrome and conotruncal anomaly face syndrome.

Although early dogma denied the possibility of extrathymic generation of T cells, it is now clear that certain specific classes of T cells can develop independently of the thymus. These include intestinal intraepithelial lymphocytes, which are usually γδ TCR^+ and often express an unusual homodimeric αα CD8. Extrathymic γδ TCR^+ cells appear to have specificity for non-protein phosphate containing antigens, particularly triphosphate nucleic acids and hydrocarbon phosphates derived from mycobacteria. Recognition of these antigens does not appear to require conventional processing and the cells can recognize whole antigen.

Secondary lymphoid tissue

Spleen

The largest lymphoid organ is the spleen, containing about 25% of the body's lymphocytes, and comprises white pulp surrounding central arterioles (peri-arteriolar lymphoid sheath) and red pulp through which blood is filtered. Red pulp contains sinusoids with abundant macrophages, which are important in stripping off immune complexes bound to the surface of red blood cells and also for removing aged red blood cells. The white pulp comprises both T and B cells and also contains follicles consisting mainly of B cells. In primary follicles the B cells are predominantly resting cells, whereas in secondary follicles a change in morphology identifies the presence of germinal centres, where active B-cell development takes place in response to antigenic stimulation. This process is stimulated by the presence of APCs and activated T cells expressing high levels of CD40 ligand (CD154). The marginal zone occurs at the interface of red and white pulp and contains a distinct population of B cells, expressing surface IgM but little IgD.

Lymph nodes

Lymph nodes occur in chains beginning at the extremities and are linked by lymphatic channels that eventually coalesce to form the thoracic duct, which drains into the left subclavian vein. Flow along the lymphatics is centripetal, draining lymph-containing antigen, inflammatory mediators and cells to regional lymph nodes and thence to the general circulation. Lymph enters the cortex of the node, filtering through the kidney-shaped node to leave by the medulla. The cortex comprises the mainly B-cell area with primary and secondary follicles, as in the white pulp of the spleen, while the medullary area comprises mainly T and B cells in the process of emigration from the node. However, T cells and APCs are spread through the whole structure of the lymph node

and the paracortical area surrounding the B-cell follicles is rich in T cells, macrophages and dendritic cells. Specialized follicular dendritic cells are found in the follicles and are responsible for holding antigen on their surface to provide continuous stimulation of B cells recruited into the follicle. These cells have abundant Fc receptors for IgG and use passively bound antibody to sequester antigen in abortive endocytic vacuoles called iccosomes, which protect it from proteolytic degradation. This feature explains why antibody levels decline but not usually to zero after a secondary immune response, as there is continuous restimulation from the sequestered antigen.

Specialized lymphoid tissue is present in the upper respiratory tract, including the tonsils and adenoids (Waldeyer's ring). These are particularly rich in B cells and have a structure similar to lymph nodes. Absence of tonsillar tissue in a small child should always raise suspicion of a B-cell deficiency, particularly a genetic abnormality such as X-linked agammaglobulinaemia, in which mature B cells cannot be produced. The tonsils atrophy in early adult life and it is most unusual to see persistent tonsillar tissue in adults over the age of 25 years. The gut is well supplied with lymphoid tissue in the form of Peyer's patches, located in the lamina propria, particularly around the ileum, and containing many follicles. Isolated follicles also occur scattered through the lamina propria. The surface epithelium overlying the follicles and Peyer's patches is modified with the presence of M cells, which take up particulate antigen and express MHC class II antigens. Peyer's patches contain all the elements found in peripheral lymph nodes, except that a high proportion of the differentiated B cells express IgA. As well as the defined structures, the lamina propria also contains large numbers of free-ranging lymphocytes, including IgA^+ B cells, and specialized intraepithelial lymphocytes, mainly $CD8^+$ or $CD4^-CD8^-$ T cells, γδ T cells and NKT cells. There is an increased proportion of γδ TCR^+ cells with cytotoxic activity. The lymphoid structure in the lower respiratory tract is less well developed, although small aggregates similar to Peyer's patches may be found. The difference is related to the burden of microbes in the two sites, as the lung under normal conditions is relatively free of infection, with most foreign material trapped in the upper airway or removed by the mucociliary escalator.

In the skin, Langerhans' cells are scattered through the epidermis. These are potent APCs, migrating in the lymph to the regional lymph nodes to stimulate B and T cells and secreting IL-1 and chemokines. Keratinocytes are also directly involved in immune responses through the production of cytokines, including IL-1, IL-6, TNF-α and TGF-β. As noted below, blood vessels in the skin express specific receptors for recruiting skin-homing lymphocytes that express CLA.

Lymphocyte trafficking

A key feature of immune function is the traffic of lymphocytes and other cells involved in the immune response from sites of storage or rest to sites of inflammation. As an estimate of the size of the population of cells on the move, the total number of lymphocytes is estimated at 10^{12} while 10^{11} are in circulation at any one time. Recruitment of lymphocytes into secondary lymphoid tissue occurs through specialized vessels in lymph nodes, the high endothelial venule (HEV); 80% of the lymphocytes enter lymph nodes using the HEV, with the remaining 20% arriving in afferent lymph from tissues. Entry is controlled by expression of L-selectin (CD62L) on the lymphocyte and its cognate receptor on the HEV. The integrins of the lymphocyte function associated antigen (LFA-1) family are also crucial in neutrophil trafficking but are less so for lymphocytes, which can use other cognate pairs; clinical deficiency of LFA-1 family members leads to an inability of neutrophils to leave the circulation. A range of different receptors occurs on lymphoid tissue in different tissues and the skin that allow selective recruitment of either naïve cells or cells that have been primed to antigens occurring in these locations. For example, binding of L-selectin to the mucosal addressin MAdCAM causes recruitment of naïve cells to Peyer's patches, while the interaction of an $\alpha_4\beta_7$ integrin with MadCAM and vascular cell adhesion molecule (VCAM)-1 recruits naïve cells to Peyer's patches but memory cells to the lamina propria of the gut. Interaction of CLA and E-selectin on endothelium in skin recruits memory cells to the skin. Binding of lymphocyte very late antigen (VLA)-1 to VCAM-1 attracts lymphocytes to inflammation, as does interaction of lymphocyte-expressed CD44 with hyaluronate. Chemokines and their receptors are also involved, such as secondary lymphoid chemokines, which bind to T cells bearing CCR7; fractalkine, expressed on HEV is also a potent chemoattractant for T cells. T and B cells have discrete and non-overlapping patterns of chemokine responses, and are therefore recruited to different areas within the lymph nodes. Many other molecules involved in cellular adhesion have been identified and it is thought that other molecular pairs exist which confer additional tissue specificity on lymphocytes. Once memory cells are recruited in one area, they are thought to retain that homing response for the reminder of their life.

As well as deficiencies of LFA-1 such as leukocyte adhesion molecule deficiency (LAD)-1, clinical examples of other adhesion molecule deficiencies have been described. LAD-2 is caused by a defect in fucosylation that leads to an inability of the receptors for selectins to bind to their cognate molecules, causing recurrent infections, neutrophilia and mental retardation. These patients can be treated successfully with oral fucose. A clinical deficiency of E-selectin has also been described, with recurrent infections but no neutrophilia.

Lymphocyte function, activation and regulation

Antigen presentation

Professional APCs, including macrophages and dendritic cells, undertake antigen presentation to T cells and B cells that express MHC class II antigens constitutively and to other cells on which class II can be induced by inflammation. Although dendritic cells are not phagocytic, they can take up processed antigen transferred from macrophages via pinocytosis in clathrin-coated pits and receptor-mediated endocytosis. Antigen presentation through the class II (or exogenous) pathway targets antigen to the $CD4^+$ T cells. Newly synthesized class II molecules are directed to the endosomal compartment by the invariant chain Ii where they are loaded with peptides. A peptide sequence in Ii called CLIP blocks the peptide-binding groove in the class II molecule until it reaches the endosome, where the enzyme DM removes it. The peptide-binding groove in class II is open-ended, allowing peptides to

overhang the ends, provided that the correct sequence binds in the middle. Once loaded, the class II molecule is transferred to the cell surface. The process is a continuous one, and class II is recycled off the surface and can be reloaded with peptide.

Antigen presented via the class I (or endogenous) pathway is loaded in a different compartment, the endoplasmic reticulum, with proteolysis taking place in proteosomes in the cytosol and governed by ubiquitin. The peptide-binding groove on class I has closed ends, which means that the peptide has to be exactly the right length and sequence to bind. Trimming of over-length peptides is carried out in the cytosol by leucine aminopeptidase. The proteins involved in peptide loading are the TAP (transporter associated with antigen processing) proteins. Once correctly loaded, the class I molecule is inserted in the endoplasmic reticulum membrane in association with calnexin and then with β_2-microglobulin. Finally, a large multi-molecular complex is formed and transported to the Golgi body and then to the surface membrane. Any class I molecules not loaded with peptide are destroyed prior to transfer to the Golgi. Evidence for recycling is less clear than for class II.

A third pathway of antigen presentation exists, based on the non-MHC molecular family CD1, which is coded separately from MHC but has similarities to class I, including the use of β_2-microglobulin as a light chain. CD1 molecules also present antigen to T cells, although the antigens are predominantly lipids, particularly those derived from mycobacteria. At least four isoforms are known, each with different lipid specificities. Loading of CD1 molecules with lipid takes place in the endocytic pathway.

B cells

Mature B cells leaving the bone marrow circulate through the blood and tissues or enter lymph nodes directly via HEVs, where they form the follicles. On encounter with antigen and with T cells recognizing components of the same antigen, B cells are stimulated to proliferate and to develop further to plasma cells. Two further key processes are involved: class switching, in which the B cell changes the heavy chain associated with a given antibody binding specificity; and somatic hypermutation, which permits an increase in affinity of the antibody (affinity maturation).

Class switching allows the immune system to develop IgG and IgA responses from the initial primary IgM response. This process depends on the interaction of CD40 on the B cell with CD40 ligand (CD154) on activated T cells. Genetic defects in CD154 lead to the X-linked hyper-IgM syndrome, where there is failure of the class switch and IgG and IgA antibody are not produced but high levels of IgM are produced. Deficiency of CD40 itself causes a similar but autosomal disease. CD40 is also expressed on APCs and hence T-cell function is also impaired, leading to the typical occurrence of opportunistic infections such as *Pneumocystis jiroveci* pneumonia and cryptosporidiosis. One of the enzymes involved in class switching is activation-induced cytidine deaminase (AID); mutations in this enzyme give rise to autosomal hyper-IgM syndrome. Other enzymes involved are the Ku family of DNA phosphokinases, which are targets in the autoimmune process in systemic lupus erythematosus (SLE).

Affinity maturation only takes place in B cells proliferating in the germinal centres, and occurs at hotspots within the variable regions of heavy and light chains, targeting residues that form part of the antibody-binding site. The process is random, and it appears that the enzyme AID is also involved in this process. The process is actively driven by exposure to antigen: cells that hypermutate to produce antibodies of lower affinity are less stimulated and will therefore cease to proliferate, whereas those with higher affinity will continue to receive positive feedback stimuli.

Memory B cells have a different phenotype from naïve B cells, expressing high levels of CD27, a member of the TNF-receptor gene family. Conversion to memory phenotype is dependent on the CD40–CD40 ligand interaction in the presence of IL-4. Subsequent activation of memory B cells can take place through interaction of CD27 with its ligand, CD70, expressed on activated T cells; IL-2 and IL-10 augment this process. Naïve B cells can be induced to form plasma cells through OX40 and its interaction with OX40 ligand on T cells.

B-cell responses to antigen have been divided on the basis of requirement for T-cell help. T-dependent antigens include most proteins; T-independent (TI) antigens are mostly polysaccharide antigens. TI-1 antigens include LPS and endotoxin, which at low doses stimulate B cells directly to produce specific antibody, but at high doses stimulate polyclonal B-cell proliferation through interaction with specific receptors. T-independent type 2 (TI-2) antigens such as capsular polysaccharides only stimulate specific antibody production. For all TI responses, however, responses are greater in the presence of T cells, so T-cell independence is relative.

Regulation of B-cell activation takes place through negative feedback loops of cytokines produced by activated B cells. It is also thought that the production of idiotypic antibodies, that is antibodies that bind to the antigen-binding site of other antibodies, form complex regulatory networks that down-regulate antibody production. Rheumatoid factors are antibodies that recognize the Fc regions of other antibodies; these also appear during infections and are thought to play a role in control of the immune response, presumably by forming immune complexes, which are known to switch off antibody production when present in high concentrations. This explains why antibody responses to antigens are reduced in small children when maternal antibody is still present. This normal occurrence of rheumatoid factors during the immune response explains why measurement of rheumatoid factors as a diagnostic screening test is usually unhelpful unless a patient has clinical signs of rheumatoid arthritis.

T cells

Recent T-cell emigrants from the thymus are naïve and are distinguished by expression of high levels of CD45RA. After antigen exposure, the phenotype changes, with reduction in CD45RA and expression of CD45RO. CD45RA and CD45RO are isoforms of the leukocyte common antigen CD45 and are generated by alternate splicing of the RNA transcript. Exposure to antigen via the TCR/CD3 complex must occur in the context of the appropriate co-stimulatory molecules for T-cell activation to occur. If exposure to antigen occurs in the absence of co-stimulation, then non-responsiveness to the antigen is generated (anergy) or the cell is switched to the apoptotic pathway. The best-known co-stimulatory molecule is T-cell CD28. This interacts with B7.1

(CD80) and B7.2 (CD86) expressed on APCs. As noted above, interaction between CD40 and CD40 ligand is also important. Inducible co-stimulator (ICOS) is another T-cell co-stimulatory molecule that interacts with B7RP-1 to activate T cells. Conversely, a related T-cell molecule, cytotoxic T lymphocyte-associated antigen (CTLA)-4, binds to B7.2 and leads to inhibition of T-cell activation. Surface receptors for cytokines are also required for T-cell activation. Mutations in the common γ chain for cytokine receptors lead to SCID. The intracellular kinase cascade is complex, and is being unravelled through studies on knock-out mice and human genetic immunodeficiencies. The kinase JAK-3, linked upstream to cytokine receptors and downstream to signalling transduction and activator of transcription (STAT) kinase, is critical since defects in this molecule also lead to SCID. Other defects in intracellular signal transduction occur in Wiskott–Aldrich syndrome, where mutations in the *WASP* gene interfere with signalling through the rho-GTPases; ataxia telangiectasia, in which a phosphatidylinositol 3-kinase is defective; and the X-linked lymphoproliferative syndrome in which the defect is in the SAP protein. Intracellular calcium is essential for activity of some of the kinases and this is controlled via the calcineurin pathway, which provides the target for ciclosporin and tacrolimus, immunosuppressive drugs that prevent T-cell activation.

Apoptosis plays a key role in the control of lymphocyte activation and the prevention of autoimmunity. Two processes exist: apoptosis triggered by lack of signals (intrinsic cell death pathway, controlled by Bcl) and apoptosis triggered by activation via CD95. CD95 is expressed on T cells activated via the TCR/CD3 complex. Interaction of CD95 ligand with CD95 (fas) on the T cell activates the caspase pathways and leads to DNA fragmentation. The importance of this pathway is demonstrated in the Canale–Smith syndrome, in which there are defects in the apoptotic pathways at the level of either CD95 or the caspases. The syndrome is characterized by excessive, uncontrolled lymphoproliferation accompanied by features of autoimmunity.

$CD4^+$ Th cells have been divided on the basis of cytokine production, and latterly chemokine receptor expression, into Th1 and Th2 cells. Th1 cells are involved primarily in 'help' for cytotoxic or cell-mediated T-cell responses, while Th2 cells are predominantly responsible for the support of antibody-mediated responses, including IgE-mediated allergic responses. There is cross-regulation of the two subsets, with Th1 cytokines down-regulating Th2 cells and vice versa. Th1 cells produce IL-2 and IFN-γ, while Th2 cells produce IL-4, IL-5, IL-9, IL-10 and IL-13. Th1 responses require signalling through the IL-12 receptor and the IFN-γ receptor; in the absence of function in these pathways, Th1 responses essential for handling mycobacteria are abolished and recurrent infection occurs. Polarization of naïve $CD4^+$ T cells to either a Th1 or Th2 response occurs through the release of cytokines from the cells of the innate system, such as macrophages, NK cells, mast cells, eosinophils and basophils. Conversely, the cytokines released by activated Th1 and Th2 cells further stimulate the innate cells. IL-9 appears to have an important role in governing the class switch in B cells to IgE production. In evolutionary terms, the Th2–IgE axis plays an important role in the control of parasitic infections, particularly worm infections of the bowel. One proposal for the increasing prevalence of allergic disease suggests that the disappearance of parasitic worm infections in developed countries releases the IgE system to respond inappropriately to other antigens.

$CD8^+$ cytotoxic T (Tc) cells have also been divided into two populations based on cytokine production: Tc1 produce IFN-γ, while Tc2 produce IL-4 and IL-5. Two discrete mechanisms are used by Tc cells for killing targets recognized via interaction of target cell class I with the CD3/TCR/CD8 complex. Co-stimulation is required for optimum killing activity, especially via CD2 and LFA-1 (CD11a/CD18). The first pathway triggers cell death in the target using the fas–fas ligand pathway of apoptosis, as discussed above. The other pathway uses granzyme and perforin, exocytosed from granules in the Tc. Perforin forms pores in the target cell membrane and allows the entry of granzymes into the cell, which completes cell destruction. Under certain circumstances $CD4^+$ T cells can also be shown to possess cytolytic activity.

Other classes of T cells have been described that play an important role in down-regulation and control of activated T cells. These include Th3, Tr1 and T regulatory (Treg) cells, not to be confused with the old concept of 'suppressor cells'. The role of CTLA-4 in inhibiting activation has already been noted. IL-10 and TGF-β produced by these T cells is also inhibitory. The best documented population of Treg cells is CD4+CD25+FoxP3+; L-selectin and OX-40 are also expressed. FoxP3 is expressed specifically on Treg in the thymus and in the periphery, but is not expressed on other types of T cells. Deficiency of this type of T cell is seen in the IPEX syndrome, an immunodeficiency with high levels of autoimmune diseases.

Overview of immunological disease

Immunological disease can arise as a result of genetic deficiency of key components, hyperreactivity (allergy/hypersensitivity), immune deviation (autoimmunity) and immunological malignancy. In addition, there are changes in immunological function arising from extremes of age, malignancy in other organs, pregnancy and environmental exposures (e.g. cigarette smoke, drug administration).

Understanding immune-mediated disease is dependent on understanding both the development and function of the immune system. However, multiple mechanisms may be active. For example, in primary immunodeficiencies due to genetic defects, there is often aberrant immunological development that leads to autoimmunity and eventually in many cases to lymphoid malignancy.

Immunodeficiency

Immunodeficiency is subdivided into primary and secondary (Tables 13.1–13.3). Over the last 10 years an increasing number of genetic abnormalities of the immune system have been described. A key feature is the lack of correlation between the genetic abnormalities and the clinical phenotype. In some cases this is due to redundancy within the immune system, allowing compensatory mechanisms to provide protection. Some immunological diseases that are classified as 'primary' do not yet have a clearly defined genetic basis, such as common variable immunodeficiency,

Table 13.1 Summary of major immune defects (not exhaustive).

B-cell defects
X-linked agammaglobulinaemia
μ-chain deficiency; surrogate light-chain deficiency
SWAP-70 deficiency
Hyper-IgE syndrome (includes secondary neutrophil disorder)
CD79a (Igα chain) deficiency
BLNK deficiency
ICOS deficiency
TACI deficiency
T-cell defects
Wiskott–Aldrich syndrome (*WASP* gene mutations)
Ataxia telangiectasia (*ATM* mutations)
Chronic mucocutaneous candidiasis (AIRE, FoxP3 deficiency)
X-linked hyper-IgM (CD40 ligand deficiency); autosomal hyper-IgM syndrome (multiple defects)
Cartilage–hair hypoplasia
Idiopathic $CD4^+$ T-cell lymphopenia
Combined defects
Severe combined immunodeficiency (*RAG-1*/*RAG-2* mutations, common γ-chain deficiency; CD3ε deficiency)
Adenosine deaminase deficiency
Purine nucleoside phosphorylase deficiency
DNA repair defects (DNA ligase IV); Bloom's syndrome; xeroderma pigmentosum
Canale–Smith syndrome (autoimmune lymphoproliferative syndromes; fas, fas-ligand, caspase deficiencies)
X-linked lymphoproliferative syndrome (SAP deficiency; includes NK disorder)
MHC class I and MHC class II deficiency
Neutrophil defects
Chronic granulomatous disease (X-linked, autosomal)
Cyclic neutropenia
Leukocyte adhesion molecule deficiency (LAD-1, LAD-2)
Chédiak–Higashi syndrome (including NK cells)
Complement defects
C1–9 deficiency, properdin deficiency
C1-esterase inhibitor deficiency
C4-binding protein deficiency
Factor H deficiency
Chemokine deficiency
WHIM syndrome (CCR7 deficiency)
Toll Receptor Pathway deficiencies
STAT-1 deficiency
IRAK-4 deficiency
Interferon-γ receptor deficiency
Unclassified
Common variable immunodeficiency
Selective IgA deficiency
Specific antibody deficiency
Hyper-IgD syndrome (mevalonate kinase deficiency); periodic fever syndromes (TNF-receptor associated protein deficiency)

selective IgA deficiency and specific antibody deficiency. Most primary immunodeficiencies are rare, in contrast with secondary immunodeficiency, which is common and becoming increasingly so due to widespread use of immunomodulating drugs to control immune-mediated disease.

Primary immunodeficiency

Primary immunodeficiency is defined as immunodeficiency due to genetic defects or where no secondary cause can be identified. Advances in molecular genetics over the last 10 years have meant that clinically well-described syndromes have been identified genetically, increasing our understanding of the immune system through natural knock-out experiments. This has also led to a re-evaluation of some diseases, for example X-linked hyper-IgM syndrome, previously thought to be a B-cell defect, is now known to be a T-cell defect impairing B-cell development.

The type of cell or protein affected by the defect determines the likely clinical sequelae. In most cases this will include infection, although other problems such as autoimmunity and malignancy also arise.

Investigation for primary immunodeficiency is an increasingly complex field and specialist advice from an immunologist interested in this type of disorder is required at an early stage to assist with both diagnosis and management.

Secondary immunodeficiency

Secondary immunodeficiency represents the most likely type of immunodeficiency that will be encountered by clinical practitioners. The causes are extensive but can be categorized according to primary triggers. In most cases the effects are on T and B cells, although some triggers lead to damage to neutrophils and other parts of the innate immune system, leading to a more complex immunodeficiency. The dermatological manifestations tend to be cutaneous infection and an increase in cutaneous neoplastic change, often at multiple sites. Investigation may be required to prove the cause, but in most cases identification of the primary cause is enough to explain the problem.

Autoimmunity and allergy (hypersensitivity)

These represent overactivity of the immune system. In the case of allergy this is directed against external antigens (allergens), while in autoimmunity the targets are host antigens. Gell and Coombs originally classified the pathogenic mechanisms and no one has produced a better classification since (Table 13.4). However, it is worth noting that pathological reactions frequently involve more than one mechanism so the classification represents a simplification of the true nature of immunological disease.

Allergic disease

Atopic disease in particular is now thought to be a complex phenomenon, with both immediate type I and delayed type IV mechanisms active at different times within the evolution of the disease process. This applies particularly to asthma and has important ramifications for therapy. Previously, treatment has focused on the immediate responses in the airway, while ignoring the T-cell-mediated damage, which is not apparent until secondary lung fibrosis occurs due to T-cell-stimulated collagen deposition. Thus although good initial control is obtained, the disease gradually progresses to irreversible lung disease. Adapting treatment to deal with all the pathogenic mechanisms involved is therefore critical.

In clinical practice, classification of a disease is dependent on demonstrating the presence of appropriate components of the

Table 13.2 Dermatological consequences of some primary immunodeficiencies.

	Key clinical features	Dermatological features
B-cell defects		
X-linked agammaglobulinaemia	Bacterial infections of upper and lower respiratory tracts, joints, gastrointestinal tract	Cutaneous bacterial infection
Common variable immunodeficiency	Bacterial infections of upper and lower respiratory tracts, joints, gastrointestinal tract; autoimmunity; granulomatous disease, lymphoma; nodular lymphoid hyperplasia	Cutaneous bacterial infection, vitiligo, alopecia, cutaneous granulomas
Hyper-IgE syndrome	Eczema, staphylococcal infections of skin and lung (pneumatoceles), osteopenia	Extensive impetigo, recurrent boils
T-cell defects		
Chronic mucocutaneous candidiasis (including APCED: autoimmune polyendocrinopathy, candidiasis and ectodermal dysplasia, due to *AIRE* gene mutations)	Chronic candidiasis; endocrinopathy; systemic infections with bacteria, mycobacteria and herpesviruses	Candidiasis of nails, Norwegian scabies
Wiskott–Aldrich syndrome (mutations in *WASP* gene)	Thrombocytopenia, small platelets, recurrent bacterial and viral infections, eczema, lymphoma	Eczema (distribution atypical compared with atopic eczema); often infected; cutaneous viral infections, papillomavirus, molluscum contagiosum (both extensive)
Ataxia telangiectasia	Cerebellar ataxia (progressive), cutaneous telangiectasia, viral and bacterial infections	Cutaneous viral infections, papillomavirus, molluscum contagiosum (both extensive); telangiectasia (conjunctivae, ears especially)
Cartilage–hair hypoplasia	Short-limbed dwarfism, fine hair, recurrent bacterial infections	Abnormal (fine) hair
Combined immunodeficiencies		
Severe combined immunodeficiency (all variants)	Early onset of infections: bacterial, viral, fungal	Rashes (Omenn variant, maternofetal engraftment)
DNA repair defects (xeroderma pigmentosum, Nijmegen breakage syndrome)	Malignancy, recurrent infections	Keratoses, cutaneous malignancy
Neutrophil disorders		
Chronic granulomatous disease	Bacterial and fungal infections	Cutaneous bacterial infections, ulceration of mouth
Cyclic neutropenia	Bacterial and fungal infections	Cyclic mouth ulceration (gingivitis)
Rare disorders		
Chédiak–Higashi syndrome and Griscelli's syndrome	NK cell defect, abnormal neutrophils, recurrent infections, lymphohistiocytosis	Silver streaks in hair, oculocutaneous albinism
Dyskeratosis congenita	Malignancy, bone marrow failure, recurrent infections (bacterial) with hypogammaglobulinaemia	Cutaneous pigmentation, nail dystrophy, oral leukoplakia
Anhidrotic ectodermal dysplasia	Respiratory infections	Hypohidrosis, abnormal dentition
Papillon–Lefèvre syndrome	Recurrent bacterial infections, impaired neutrophil function	Hyperkeratosis and pyoderma
Complement disorders		
C2 deficiency	SLE-like disease, recurrent bacterial infections	Extensive cutaneous lupus erythematosus
C1-esterase inhibitor deficiency	Angio-oedema	Angio-oedema without urticaria
C4-binding protein deficiency	Angio-oedema, features of Behçet's syndrome	Angio-oedema, ulceration

NK, natural killer; SLE, systemic lupus erythematosus.

immune response, such as allergen-specific IgE, autoantibodies and complement abnormalities. However, detection of abnormal T cells is more difficult, except in the context of patch-testing for contact hypersensitivity.

The development of allergic disease is multifactorial. In principle, however, allergens are no different to any other antigen in the way in which they are processed and presented to T cells. The propensity to develop a Th2–IgE response appears to be genetically controlled, although more than one gene is involved. Candidate genes include those for the Th2 cytokines IL-4, IL-5 and their receptors, IgE and MHC antigens. Allergic reactions are commoner in developed countries, although allergic sensitization occurs in all populations. However, in communities in developing countries it appears that the cytokines produced as a result of endemic infections suppress the clinical manifestations of allergic disease. Where food allergens are concerned, it appears that

Table 13.3 Causes of secondary immunodeficiency.

Infection
Human immunodeficiency virus
Epstein–Barr virus and other herpesviruses
Measles, rubella, influenza
Chronic bacterial sepsis, tuberculosis
Parasitic and protozoal infections

Drugs
Immunosuppressive drugs: corticosteroids, cyclophosphamide, azathioprine, ciclosporin A, tacrolimus, sirolimus, mycophenolate (all affect T- and B-cell function)
Biologicals: anti-CD3, anti-CD4, anti-CD52, efalizumab, alefacept anti-TNF (etanercept, infliximab, adalimumab)
Anticonvulsants: phenytoin, valproate, carbamazepine (hypogammaglobulinaemia, neutrophil dysfunction)
Carbimazole (agranulocytosis)
Chloramphenicol, penicillins (aplastic anaemia)
Transfusion therapy (blood components, including intravenous immunoglobulin)

Malignancy
Lymphoma, leukaemia, myeloma and other plasma cell dyscrasias, myelofibrosis (neutrophil dysfunction)
Solid tumours

Physical
Irradiation
Plasmapheresis, immunopheresis
Surgery (especially if thoracic duct damaged)

Medical/metabolic
Diabetes mellitus, glycogen storage disease (neutrophil dysfunction)
Chronic renal failure
Protein-losing enteropathy
Myotonic dystrophy
Nutritional deficiency (iron, zinc, vitamin B_{12})

Miscellaneous
Asplenia
Burns
Toxins (alcohol, cigarettes, solvents)
Extremes of age (prematurity, old age)
Pregnancy

TNF, tumour necrosis factor.

Table 13.4 Gell and Coombs classification of immunological reactions.

Gell and Coombs classification	Immunological mechanisms	Examples of clinical disease
Type I (immediate hypersensitivity)	Allergen-specific IgE, mast cells, histamine, leukotrienes, Th2 cells, cytokines involved in IgE production (IL-4), eosinophil production (GM-CSF, IL-3, IL-5)	Anaphylaxis, urticaria (some types), allergic rhinoconjunctivitis, asthma (immediate but not chronic)
Type II	IgG-antibody mediated, direct effects (complement-mediated lysis), Th2 cells	Antibody-mediated autoimmune disease (thyroid, haemolytic anaemia, thrombocytopenia, myasthenia gravis, etc.)
Type III	Immune complex disease, IgG and IgM antibodies, complement, complement receptors	Serum sickness, SLE (abnormal complement, complement receptors), complement deficiency (abnormal immune complexes)
Type IV (delayed hypersensitivity)	T-cell mediated, Th1 cells, cytokines (IL-2, IFN-γ, TNF-α), macrophages, $CD8^+$ cytotoxic T cells	Contact (delayed-type) hypersensitivity, eczema, graft rejection

GM-CSF, granulocyte–macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; SLE, systemic lupus erythematosus; TNF, tumour necrosis factor.

exposure at times when the immune system is relatively immature in the first 2 years of life can lead to inappropriate responses. This may be augmented by the fact that many of the foods concerned contain naturally occurring lectins (e.g. wheatgerm agglutinin, peanut agglutinin), which have profound proliferative effects on lymphocytes. Exposure to infections in early childhood also has a protective effect against the development of allergic disease, as demonstrated in German children brought up on farms (hygiene hypothesis). Changes in the way we live are also important, for example the move to centrally heated, double-glazed houses with poor ventilation and fitted carpets provide optimum growth conditions for house-dust mites. Keeping pets indoors also contributes, although there is some evidence that keeping pets can have a protective effect against pet allergy. Other environmental factors include changes in diet, for example peanuts are now a common source of protein whereas they were rarely consumed 30 years ago, and the contribution of pollution, especially diesel fumes.

Autoimmune disease

Autoimmunity can arise through failure of the initial negative selection process for T and B cells or it can occur through the breaking of peripheral tolerance. As pathogens have evolved in parallel with humans, and in order to reduce the risk of elimination by the immune system they have developed antigenic structures similar to those present in their preferred host. Accordingly, there is a risk that the immune response may generate both antibodies and effector T cells that are cross-reactive with components of self, for example coxsackieviruses and diabetes mellitus, and *Klebsiella* and $HLA\text{-}B27^+$ arthritis. Evolutionary selection pressure will determine that individuals who can respond to pathogens with an effective immune response will survive, even though this may be at a later cost of autoimmune disease. The pathogen will eliminate those whose immune response fails. The need to present such antigens then drives the evolutionary pressure on the selection of certain MHC haplotypes in stable populations and accounts for the widely differing patterns of MHC antigens in different parts of the world. Today's long-distance travel means that this equilibrium is disturbed: individuals are exposed to pathogens whose antigens cannot be presented effectively because those infected do not possess the appropriate MHC molecules. Other genes also contribute to the generation of autoimmunity, for example there is an increased incidence of autoimmunity in

complement deficiencies and a high incidence of autoimmunity in defects of apoptosis such as fas deficiency and caspase deficiency, deficiencies in Treg cells (IPEX syndrome) and in thymic development (AIRE gene defects). Autoimmunity may also be triggered by the release of sequestered antigen from privileged sites (e.g. the eye) and by the generation of neoantigens by chemicals and toxins (e.g. autoimmune haemolytic anaemia caused by penicillins). One suspects that the root cause of most autoimmune diseases will be infection, although like a hit-and-run accident the culprit is long gone even though the effects of the 'accident' may be lifelong.

Immunity at extremes of age

The immune system is incompletely developed at birth; while all the components are present, the acquired immune system requires antigen exposure to develop the full repertoire of both T- and B-cell antigen receptors through recombination and somatic mutation and class switching. While this process takes place, protection is provided for the first 6 months of life by maternally transmitted antibody, transferred across the placenta by an active process in the last trimester. Breastfeeding also provides important amounts of IgA for protection of the gut. Stimulation to the acquired system can be provided by either natural infection or programmes of immunization. However, virulence factors in certain classes of bacteria, notably pneumococci, *Haemophilus influenzae* and *Neisseria meningitidis*, are capsular polysaccharides. These antigens are difficult for the immune system to recognize in the first 2 years of life, hence the high incidence of invasive disease caused by these organisms in this age group. Normally the bulk of antipolysaccharide antibody is IgG2 subclass. Interestingly, this defect can be bypassed by covalently conjugating the polysaccharide antigen to a protein, with the immune system producing a protective but mainly IgG1 antibody response to the polysaccharide. As the immune system ages, this inability to recognize polysaccharide antigens returns and there is a second peak of disease in the older population.

Ageing of the immune system is not chronologically related. Studies of the immune system in the elderly have been hampered by the need to define healthy elderly, free of other illness and medication. In fact the immune system remains remarkably effective, with good vaccine responses in the healthy elderly. However, protection of at-risk groups is less effective by virtue of their coexisting disease. Thus targeting influenza vaccine at those with, for example, chronic respiratory disease or chronic lymphocytic leukaemia targets the vaccines at those least able to respond. It was previously assumed that beyond the age of about 25 years, the ability of the immune system to reconstitute from thymus and bone marrow declined rapidly. However, newer evidence has shown that thymus is capable of functioning well into old age, albeit with a reduced capacity for generation of mature T cells. Much of the immune dysfunction of the elderly is related to other disease processes, either directly or through their treatment. Immune regulatory function becomes less effective with age and this is manifest by increasing levels of rheumatoid factors and other autoantibodies, usually in the absence of clinical disease. Low-level monoclonal gammopathies also develop due to failure to suppress antibody-producing clones at the end of an immune response (monoclonal gammopathy of uncertain significance; MGUS). These may remain stable for decades, although the current view is that all will eventually develop into myeloma, given sufficient time.

Immunity and malignancy

The immune system has an important role to play in immune surveillance for malignancy through the activities of NK cells (see above) and in control of established tumours by infiltrating cytotoxic T cells. Tumours often escape immune surveillance and cytotoxicity by loss of key antigens on the cell surface or production of immunosuppressive mediators. Tumours of the immune system, either lymphomas (including chronic lymphocytic leukaemia) or myelomas, have a direct effect on immunological responsiveness, with reduction in humoral immunity especially and an increase in bacterial infections. In the case of lymphomas, the abnormalities of humoral immune function may persist for years after apparently curative therapy. The importance of the acquired immune system in tumour control is well demonstrated by the significant increase in cutaneous tumours seen in patients treated with immunosuppressive drugs such as ciclosporin and cyclophosphamide over long periods.

Overview of diagnostic testing for immunological and allergic disease

Accurate immunological diagnosis depends on access to appropriate immunology laboratory services. Such services need to be run to high quality standards, verified by external peer review inspection. In the UK this is carried out by Clinical Pathology Accreditation (CPA); similar organizations exist in other countries. Laboratories are inspected at regular intervals to ensure compliance with agreed standards. These standards verify the organization, testing and reporting of laboratory testing. Participation in external quality assurance for the tests offered is essential, although rarely requested tests may not have national schemes in place. Under these circumstances the laboratory must satisfy itself that it is taking reasonable steps to quality assure the results. In all cases, laboratories should run internal controls with defined parameters and only report results when these internal controls meet their predetermined values. Clinical governance standards require clinicians to assure themselves that they are using appropriate diagnostic services. Where academic departments are providing in-house tests for diagnostic clinical use, they have the responsibility, under product liability legislation, for any errors or problems arising from the assay. It is essential therefore that scrupulous internal quality control data are collected, together with validation data.

Good clinical practice requires that test selection should be appropriate to the disease under investigation. The laboratory is responsible for selecting the most appropriate methodology and ensuring that clinicians have a clear understanding of the performance of the test, through derivation of normal ranges appropriate to the population under study and interpretative comment. Each laboratory for each test should define normal ranges, although in practice nationally established ranges may be used. Ranges should be adjusted for age, sex and racial background.

Table 13.5 Allergy tests.

	Advantages	Disadvantages
Skin prick tests	Cheap Results available in 15 min Useful positive and negative reinforcement Can be used with *ad hoc* allergens (e.g. fresh foods, drugs)	Cannot be done in patients receiving antihistamines, calcium channel blockers, phenothiazines, or those with extensive dermatitis Inadvisable as first-line test in patients with suspected anaphylaxis to test reagents (except where resuscitation facilities available) Requires skilled staff for reproducible results
Radioallergosorbent test (RAST)	Clinically useful for inhalants and some foods only Automated analysis Can be used in patients where skin prick testing is contraindicated	Expense (staff and analyser) Results not immediately available No reinforcement of clinical message Not suitable for many allergens (fruits, drugs)
Flow cytometric tests	Research tools	Very expensive, labour-intensive

Immunochemistry

Immunochemistry covers the measurement and identification of serum proteins, including abnormal ones. Usually this is undertaken using automated analysers, which are readily quality controlled. International standards have been established for all major serum proteins, and there are long-established external quality assurance schemes. Results in principle should vary little from laboratory to laboratory.

Allergy tests (Table 13.5)

Total IgE and allergen-specific IgE are readily measured in the diagnostic laboratory. However, total IgE levels correlate poorly with the allergic symptomatology; elevated levels suggest inheritance of the atopic tendency but do not predict the form this may take. Levels greater than 1000 kU/L are usually seen in atopic dermatitis. Levels more than 50 000 kU/L are seen in the hyper-IgE syndrome. However, levels in the range 10 000–50 000 kU/L may be seen in either condition and the differential diagnosis is then dependent on associated clinical and immunological features. Levels of total IgE within the normal range do not exclude severe allergic disease, although this is usually mono-allergenic. Total IgE levels are geometrically rather than normally distributed and there is considerable variation in ranges with age. It is essential to check that the laboratory has reported the appropriate range for age.

Allergen-specific IgE can be detected by many techniques, although the earliest technique was the radioallergosorbent test (RAST): this acronym has entered common usage as a term for allergen-specific IgE. Few, if any, laboratories use this technique now, having moved to colorimetric or fluorimetric assays. Complex array-based assays, in development, may make detailed screening much more cost effective. These assays tend to be expensive. Direct testing by skin prick is cheaper and is the preferred method of testing, provided that staff experienced in the technique are available. Results of skin prick testing are operator dependent. Correlation between skin prick testing and RAST is dependent on the allergen. For inhalant allergens and strongly allergenic food allergens, such as shrimp, peanut and tree nuts, there is good correlation. In the case of fruit allergens, as seen in the oral allergy syndrome, RAST results are unreliable and should not be used. Of those patients with latex allergy, 15% will have negative RAST results. RAST for drug allergy, with the exception of suxamethonium, is also unreliable and skin prick or intradermal testing is required. Newer assays include the Flow-CAST, and assays of stimulated histamine release compare well in some respects but are very expensive in comparison with existing tests. Allergy testing should be targeted to allergens identified on the basis of clinical symptoms, as routine screening with extended panels often leads to positive results of uncertain clinical significance, which is confusing to clinicians and patients alike. Very high total IgE levels (>1000 kU/L) have always been suspected of causing false-positive reactions in RAST, especially to food allergens, although most modern assays seem to be less susceptible to this effect. Biological cross-reactivity is also common, where similar allergenic proteins occur in many species of plant or animal. This may be clinically relevant, for example prawn allergy in patients allergic to house-dust mite, or irrelevant, as in the detection of IgE to wheat in patients allergic to grass pollen. Interpretation of results is therefore dependent on a clear understanding of the patient's history.

Mast cell tryptase is a useful marker of mast cell degranulation and can therefore be used to discriminate between acute allergic reactions and non-immunological mimics. It is a stable protein whose levels remain elevated for up to 24 h after a reaction and is easily and reliably measured on a clotted blood sample. Eosinophil cationic protein (ECP) has also been used to demonstrate activation of eosinophils, particularly in the context of asthma, where it has been proposed as a useful marker of chronic eosinophilic inflammation. Unfortunately it is less stable than mast cell tryptase, and has a strict sampling protocol involving timed centrifugation, which renders it useless for diagnostic use.

Mast cell tryptase is also helpful in suspected mastocytosis, although 24-h urinary methylhistamine is probably more sensitive, albeit more awkward to collect. At present, the only commercial assay for urinary methylhistamine has been withdrawn by the manufacturer.

Immunoglobulins (Table 13.6)

Automated analysers, using nephelometry or turbidimetry, can measure serum immunoglobulins and IgG subclasses accurately

Table 13.6 Patterns of immunoglobulins.

Pattern of immunoglobulins and electrophoresis	Clinical associations
IgG, IgA, IgM all low; electrophoresis shows agammaglobulinaemia	X-linked agammaglobulinaemia (children), light-chain myeloma (elderly), gross unselective nephrotic syndrome (all serum proteins reduced), burns, immunosuppressive drugs (excess), acute severe bacterial infection
IgG and IgM normal, IgA absent; electrophoresis normal	IgA deficiency; may be associated with IgG subclass deficiency and specific antibody deficiency. Also associated with gluten sensitivity (dermatitis herpetiformis, coeliac disease), connective tissue diseases
IgG and IgA low/absent, IgM normal/low; electrophoresis shows reduced γ region	Common variable immunodeficiency, protein-losing enteropathy; selective nephrotic syndrome (albumin reduced)
IgG and IgA low/absent, IgM high/normal; electrophoresis shows reduced γ region	Hyper-IgM syndrome, acute viral infection (repeat in convalescence)
Raised IgG; IgA and IgM low; electrophoresis shows monoclonal band on background of reduced γ region	IgG myeloma, lymphoma
Raised IgA; IgG and IgM low; electrophoresis shows monoclonal band on background of reduced γ region	IgA myeloma
Raised IgM; IgG and IgA low; electrophoresis shows monoclonal band on background of reduced γ region	Waldenström's macroglobulinaemia, lymphoma
IgG, IgA and IgM low; electrophoresis shows monoclonal band on background of reduced γ region	IgD or IgE myeloma, light-chain myeloma with free light chains in serum (also think of AL amyloid)
Raised IgG, normal/raised IgA, normal IgM; electrophoresis shows polyclonal increase in γ	Chronic infections (bacterial, viral), chronic inflammatory disease (RhA, SLE), sarcoidosis, autoimmune hepatitis
Very raised IgG (predominantly IgG1), raised IgA and IgM; electrophoresis shows polyclonal increase in γ	Sjögren's syndrome, hypergammaglobulinaemic purpura
Very raised IgM, normal IgG or IgA; electrophoresis shows polyclonal increase in γ region with or without small IgM bands	Primary biliary cirrhosis
Very raised IgA, normal/raised IgG, normal IgM; polyclonal increase in γ with β–γ bridging	Liver disease, especially cirrhosis due to alcohol

RhA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

and reproducibly. The only indications for measurement of these parameters are the investigation of suspected immunodeficiency, liver disease, lymphomas and plasma cell dyscrasias. Normal ranges must be age specific and in adults the range for IgM is also modified by sex, with the lower limit of normal for IgM being higher in females than males. Measurement of immunoglobulins should always be accompanied by electrophoresis, both as an internal quality control and also to permit the detection of paraproteins (monoclonal immunoglobulins). If the latter are detected, then immunofixation should be carried out to identify the nature of the band, and urine requested for analysis for free light chains (Bence Jones proteins). Paraproteins may react abnormally with antisera used for the quantification, leading to falsely low or high results. This may be due to polymerization of the paraproteins or the presence of monomeric, as opposed to pentameric, IgM. Paraproteins should therefore also be quantified by scanning densitometry.

Table 13.7 Cryoglobulins.

Type	Composition	Associations
I	Monoclonal immunoglobulin	Myeloma, Waldenström's macroglobulinaemia, lymphoma
II	Monoclonal immunoglobulin with rheumatoid factor activity, precipitate contains both monoclonal and polyclonal immunoglobulins	Myeloma, Waldenström's macroglobulinaemia, lymphoma, mixed essential cryoglobulinaemia (HCV infection), subacute bacterial endocarditis, connective tissue diseases
III	Polyclonal immunoglobulins with rheumatoid factor activity	Chronic infections, chronic inflammatory diseases

HCV, hepatitis C virus.

Cryoglobulins and cryofibrinogen

Cryoglobulins are abnormal immunoglobulins that precipitate at a higher temperature than normal (Table 13.7). Normal immunoglobulins may precipitate from serum that is cooled to 4–6°C, but cryoglobulins precipitate at temperatures found in the extremities, that is above 26°C, causing obstruction to small blood vessels and a vasculitic-looking rash on cooler parts of the bodies, typically the hands and feet but also nose and ears. The higher the temperature at which they precipitate, the worse the symptoms will be. The appearance of cutaneous vasculitis on extremities, particularly in cooler weather, should always raise suspicions of cryoglobulins. The detection of a type II cryoglobulin in the absence of evidence for myeloma should raise the possibility of hepatitis C infection; complement C4 is invariably markedly reduced. Pyroglobulins are extremely rare and precipitate when the temperature is raised. Cryofibrinogen is an abnormal fibrinogen precipitated by cold; the significance of cryofibrinogen is less certain, but it is often associated with malignancy. Cryoglobulins are often

confused with cold agglutinins, which are antibodies that agglutinate erythrocytes in the cold and are strongly associated with *Mycoplasma* infection.

Detection of cryoglobulins requires a clotted blood sample to be taken and kept at 37°C until clot retraction has taken place; in practice this means transporting samples in a vacuum flask containing water at 37°C. Cryofibrinogen can be detected in samples containing ethylenediamine tetra-acetic acid (EDTA); heparin should not be used because some fibrinogens are heparin insoluble.

Specific antibodies

Specific antibodies to bacterial, viral and fungal allergens are useful diagnostic tests for the assessment of the appropriateness of the humoral immune response. Tests can be carried out to exposure antigens and to deliberate challenges with vaccines (no live vaccines should be used in patients with any form of known or suspected immunodeficiency). The use of polysaccharide antigens such as pneumococcal capsular polysaccharide is particularly valuable as a robust test for humoral immune deficiency, as failure of responsiveness may occur even when total immunoglobulins and IgG subclasses are normal.

Precipitating antibodies to fungi are useful as diagnostic tests for fungal infection, although chronic mucocutaneous candidiasis is often accompanied by very high levels of *Candida* precipitins despite poor or absent T-cell responses, demonstrated by delayed hypersensitivity testing or *in vitro* antigen-specific T-cell proliferation (see below).

Complement assays

Complement components C3 and C4 are usually measured routinely by nephelometry or turbidimetry and can be assayed rapidly. Both are acute-phase proteins and will rise in chronic infection or inflammation by about 10%. C4 null alleles are common, resulting in reduced C4; as there is an ancestral gene duplication there are two C4 genes (four alleles), C4A and C4B. As a rule of thumb, two null alleles give a C4 level at the lower end of the normal range, while three null alleles give a level of half the lower end of the normal range, assuming there is no excess consumption. Factor B, from the alternate pathway, can be measured by automated analyser, although in routine practice this adds little useful clinical information. Mannan-binding lectin (MBL) from the lectin pathway can also be readily measured but the clinical utility is uncertain, except in the investigation of recurrent infections, where deficiency in MBL may be a co-factor with other immunological deficiency.

There is no role for measurement of immune complexes, as they can be readily detected in normal healthy individuals and the assays are difficult to standardize. Measurement of stable complement breakdown products such as C3d is more valuable as a determinant of complement turnover (Table 13.8).

Investigation of complement component deficiencies, which are associated with increased susceptibility to neisserial infection and atypical SLE-like disease, should be undertaken with haemolytic assays of complement that test both the classical and alternate pathways: CH_{100}/CH_{50} and $APCH_{100}/APCH_{50}$. These assays demonstrate intact complement cascade pathways through lysis of red cells. In the case of CH_{100}/CH_{50}, antibody-coated red cells are used to fix complement via the classical pathway; for the alternate pathway $APCH_{100}/APCH_{50}$, guinea pig erythrocytes are used, which can uniquely bind the alternate pathway components. Both tests rely on an intact terminal lytic sequence. Both tests must be done in parallel to identify the site of any deficient component. Reduced haemolytic function will be seen where there is excessive complement consumption, although absent haemolysis will be found where there is a component deficiency. The exception is C9 deficiency, which permits slow haemolysis via the membrane attack complex C5–8. This deficiency is rare in Caucasians but is common in Japan. Individual components can then be measured depending on which part of the complement cascade is likely to be affected. It is difficult to identify C2 deficiency, which often presents with atypical cutaneous lupus (Ro antibody positive), because active lupus without C2 deficiency will reduce C2 levels due to activation of the classical pathway by antigen–autoantibody complexes. Ideally one needs to carry out testing at a time when clinical disease is quiescent, although this is often difficult to achieve.

Table 13.8 Patterns of complement abnormalities.

Complement pattern	Associated conditions
C3, C4 raised	Acute phase: infection, inflammation
C3, C4 reduced, C3d increased	Increased complement turnover via classical pathway (antibody or MBP mediated)
C3 reduced, C4 normal/high, C3d increased	Increased complement turnover via alternate pathway (endotoxin) Post-streptococcal glomerulonephritis (up to 6 weeks); C3 nephritic factor (>6 weeks: type II membranoproliferative glomerulonephritis)
C3 normal, C4 reduced, C3d normal	C4 null alleles, C1-esterase inhibitor deficiency, C4-nephritic factor, mixed essential cryoglobulinaemia (HCV)

HCV, hepatitis C virus; MBP, mannan-binding protein.

C1-esterase inhibitor deficiency leads to a clinical syndrome of angio-oedema *without* urticaria, that is hereditary angio-oedema, an autosomal dominant condition. There is no value in screening patients for C1-esterase inhibitor deficiency where typical urticaria is seen. Patients with hereditary angio-oedema all have reduced C4 levels even between attacks; during attacks, C4 levels become undetectable. Measurement of C1-esterase inhibitor is therefore unlikely to be helpful if C4 is normal. Individuals with type I hereditary angio-oedema (85%) have a non-functioning C1-esterase inhibitor gene, while in type II (15%) there is a point mutation at the enzyme active site, leading to loss of function of the protein. Both immunochemical and functional assays for C1-esterase inhibitor are available. Angio-oedema has also been reported as a consequence of the rare deficiency of C4-binding protein and due to gain of function mutations in clotting Factor XII.

Acquired angio-oedema may be seen in the older population, in association with the presence of paraproteins or autoimmune disease (although more commonly it is due to drug treatment,

typically with ACE inhibitors). In such cases checking for autoantibodies associated with SLE and measuring immunoglobulins and performing serum electrophoresis will give clues to the underlying diagnosis. C2 levels are said to be reduced in hereditary angio-oedema but normal in acquired angio-oedema, but this is not reliable.

Acute-phase proteins

Measurement of acute-phase proteins is an essential part of the investigation of sick patients. Measures of the acute phase include erythrocyte sedimentation rate (ESR), plasma viscosity, C-reactive protein (CRP), orosomucoid (α_1-acid glycoprotein), serum amyloid A (SAA) and albumin. However, these measures are *not* interchangeable, and more than one marker is usually required. Albumin is a negative acute-phase protein, that is serum levels decrease during the inflammatory process. Transferrin behaves similarly. Most other proteins increase during an inflammatory process, although the increase may only be of the order of 10%, for example C3 and C4. In selecting suitable measures for clinical use, it is essential to choose markers that are easily measurable (preferably with automated equipment) and cheap and which have a wide dynamic range, that is there is a large difference between normal and abnormal values. The ESR has a dynamic range of 15 (10–150), while the CRP has a dynamic range of 100 (4–400). SAA has a similar dynamic range to CRP but is a less widely available and more expensive test, so has little additional value. Orosomucoid has a dynamic range of 2 so is unsuitable for routine use, although it has been previously supported as a more specific marker in inflammatory bowel disease. There is, however, no evidence that it performs better than CRP. Plasma viscosity has been promoted as equivalent to ESR but also has a poor dynamic range (2); its use is specifically for investigation and monitoring of hyperviscous states occurring in myeloma, especially IgA myeloma, and Waldenström's macroglobulinaemia.

Contrary to popular belief, CRP and ESR are not interchangeable. The relationship between ESR and CRP is similar to that between HbA_{1c} and glucose. The ESR rises only slowly after the onset of an acute insult and remains raised for several weeks after, being largely dependent on serum fibrinogen levels, a long-lived circulating protein. CRP on the other hand rises within hours and has a short half-life (6–8 h), meaning that levels also fall rapidly after a successful therapeutic intervention. Accordingly, CRP is appropriate for day-to-day monitoring, whereas ESR changes little in this time frame. At any given time, CRP gives a picture of events of the previous 12 h, while ESR clarifies events of the previous 2 weeks. There are diseases, such as active SLE, where the two markers move asynchronously, with a significantly elevated ESR but little if any rise in CRP, unless infection is also present. Occasional patients have been described whose CRP range is reset, so that their acute-phase response takes place within the 'accepted' normal range. This is seen sometimes in giant cell arteritis, and makes monitoring difficult.

Detection of autoimmunity

Detection of the presence of autoantibodies can be performed by direct or indirect immunofluorescence (usually the cheapest and easiest method), solid phase assays, enzyme-linked immunosorbent assay (ELISA) and radioimmunoassay and, in some cases, flow cytometry. High throughput analysers using luminex or array-based technology are now increasingly used and may well supplant other techniques, including immunofluorescence. In all cases it is essential that the assay system has an appropriate threshold to reduce the risk of false-positive results. A number of autoantibodies may be found at low levels in apparently healthy individuals (e.g. rheumatoid factors, anti-Ro antibodies) and the prevalence of incidental positives rises with increasing age.

Nuclear and related antigens

A very large range of nuclear antigens have been identified as targets for autoimmune processes. Not all of these have identifiable clinical utility. Table 13.9 identifies the most important antigens and their clinical significance. Most of these can be detected by immunofluorescence using either rodent tissue or a human epithelial cell line (Hep2) (Fig. 13.3). Hep2 cells have the advantage of having a large nucleus in which patterns of staining can be readily identified. Genetically modified Hep2 cells are also available, engineered to have higher levels of expression of Ro antigen. Rodent tissue tends to have low levels of Ro antigen and it is also saline soluble so can be lost during the staining procedure. When rodent tissue was used exclusively for the detection of antibodies to nuclear antigens, this loss of Ro accounted for the high percentage of patients classified as antinuclear antibody-negative lupus. The increased use of Hep2 cells has significantly reduced the number of lupus patients in whom no antinuclear antibodies can be detected. Antibodies to extractable nuclear antigens were originally identified by counter-current immunoelectrophoresis; however, with the availability of cloned recombinant antigens, solid phase assays are widely used to identify specificities of nuclear antibodies. The wide variety of different assays has meant that there is often no good agreement between the different assays and there is no currently accepted 'gold standard'. Similar problems have arisen with antibodies to double-stranded DNA (dsDNA), although here the gold standard has been the Farr assay; ELISA does not always produce satisfactory results due to degradation of dsDNA to single-stranded DNA or reverse-wound DNA (Z-DNA). Immunofluorescence on *Crithidia* has been proposed as a suitable test for dsDNA as its kinetochore contains pure dsDNA. The assay is, however, relatively insensitive and is now less widely used.

Detection of antibodies to nuclear components is diagnostically valuable. However, with the exception of antibodies to dsDNA, serial monitoring of antibody titres or arbitrary ELISA units provides no clinically useful information. Changes in levels of dsDNA antibodies do have some predictive value: a rising titre frequently heralds relapse, while a falling titre is usual where therapy has been successful. However, the absolute value has no relevance to disease activity. It is likely that there are subgroups of dsDNA antibodies, as not all patients with SLE develop renal disease. Currently available diagnostic tests do not yet distinguish these different anti-DNA antibodies.

The significance of the titre of an antinuclear antibody is dependent on the age of the patient: low-titre and clinically insignificant antibodies are seen in healthy elderly patients; conversely,

Table 13.9 Nuclear and related antigens.

Staining pattern on rodent liver and Hep2 cells	Antigens recognized	Clinical associations
Homogeneous nuclear staining	dsDNA	SLE
	Histones (H2A, H2B)	SLE, drug-induced LE
	Mi-2	Steroid-responsive dermatomyositis
Fine speckled nuclear staining	Ro (52 kDa, 60 kDa antigens, distinguished using immunoblotting)	Sjögren's syndrome, SLE
	La (48 kDa protein)	Primary Sjögren's syndrome, SLE
Coarse speckled nuclear staining	U1-RNP	Undifferentiated connective tissue disease (anti-dsDNA and anti-Sm negative)
	Sm (B′/B and D proteins shared between U1, U2 and U4–U6 RNPs)	SLE
	Nuclear matrix (coarse speckles indicates multiple proteins)	SLE, undifferentiated connective tissue disease
Atypical speckled nuclear staining	Scl-70	Systemic sclerosis (severe form)
Nucleolar staining	RNA Pol I (speckled nucleolar staining)	Diffuse systemic sclerosis
	PM-Scl (PM-1) (homogeneous nucleolar staining)	Myositis–scleroderma overlap
	Fibrillarin (clumpy nucleolar staining)	Systemic sclerosis (lung and heart but few joint problems)
Cell-cycle-specific nuclear speckles	PCNA	SLE
Centromere (dividing cells)	CENA, CENB, CENC	Limited scleroderma (CREST syndrome)
Fine cytoplasmic speckled staining	tRNA synthetases (Jo-1, PL-7, PL-12, EJ, OJ)	Myositis (antisynthetase syndrome)
Coarse cytoplasmic speckled staining	Signal recognition peptide	Myositis
Ribosomal staining	rRNP	SLE (nephritis)
	Ribosomal P protein	SLE (cerebral)

CREST, calcinosis, Raynaud's phenomenon, (o)esophageal involvement, sclerodactyly, telangiectasia; dsDNA, double-stranded DNA; LE, lupus erythematosus; PCNA, proliferating cell nuclear antigen; RNP, ribonucleoprotein; SLE, systemic lupus erythematosus.

low-titre antibodies are often significant in children. Laboratories should provide age-specific ranges.

Antinuclear antibodies of varying specificities and sometimes in high titre have been reported in association with infection, especially adenovirus and Gram-negative bacteria. Antibodies to dsDNA are rarely found under these circumstances. It is critically important to interpret the laboratory results in the light of the full clinical picture. Similarly, antibodies can appear in association with malignancy. In some cases, these markers are useful identifiers of paraneoplastic phenomena (anti-Hu, anti-Yo, anti-Ri in neurological disease).

ANCA antigens and the diagnosis of vasculitis

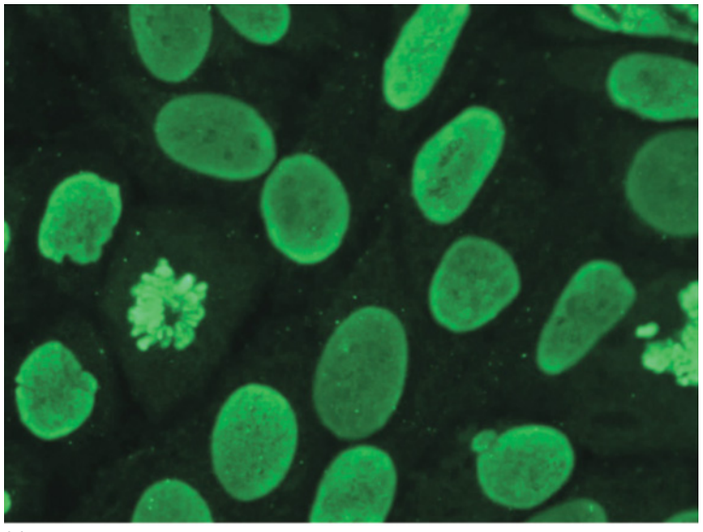
The detection of antineutrophil cytoplasmic antibodies (ANCA) has been an important step forward in the diagnosis of autoimmune vasculitis. The substrate for detection is ethanol-fixed human neutrophils. Other fixation techniques such as formaldehyde and acetone are not reliable and should not therefore be used. Three patterns are recognized: cytoplasmic granular staining (C-ANCA), atypical cytoplasmic staining (X-ANCA) and perinuclear staining (P-ANCA). As the latter can be difficult to distinguish from nuclear staining, Hep2 cells should also be used as a control for the presence of nuclear antibodies. Target antigens have been identified: proteinase 3 is the main target antigen for C-ANCA and myeloperoxidase is the main antigen for P-ANCA. Solid phase confirmatory assays are now available for these antigens. Other target antigens that have been identified include cathepsins, lactoferrin and neutrophil elastase. It is important to identify X-ANCA, as laboratories frequently confuse this pattern (which is not associated with antibodies to proteinase 3) with a true C-ANCA.

Of patients with Wegener's granulomatosis, 85% have C-ANCA, 10% P-ANCA and 5% will be seronegative. Of patients with Churg–Strauss syndrome, 10% have C-ANCA and 60% P-ANCA. In microscopic polyangiitis, 45% have C-ANCA and 45% have P-ANCA.

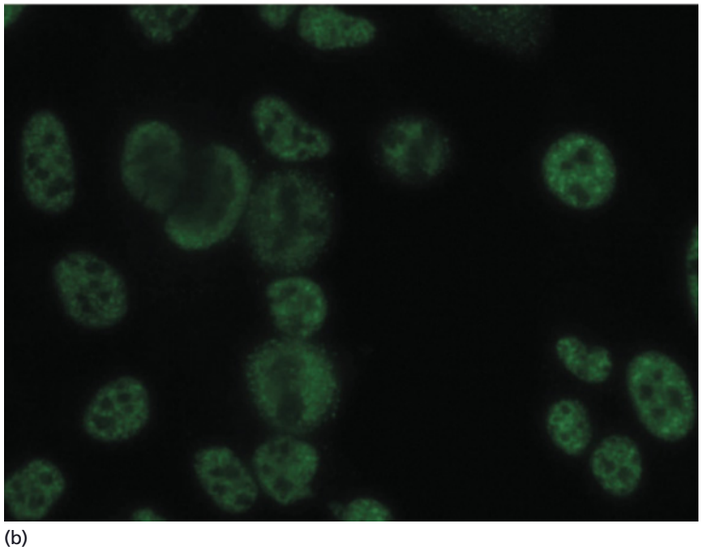
ANCA may also be seen in non-vasculitic conditions, including inflammatory bowel disease and sclerosing cholangitis. Prolonged neutrophil activation, as in infection, may also cause ANCA to appear, for example in cystic fibrosis. Careful interpretation of results is therefore required. It appears that ANCA do not appear as part of the ageing process, and therefore their detection in the elderly is likely to be significant. There is no correlation between disease severity and ANCA titre, although rising titres are thought to herald relapse. IgA ANCA have been reported in some IgA-related vasculitides such as Henoch–Schönlein purpura and IgA nephropathy, although the significance of this is uncertain.

Rheumatoid factor

As previously noted, rheumatoid factors are seen as part of the normal immune response to infection. They also occur in the



(a)



(b)

Fig. 13.3 (a) Homogeneous antinuclear antibody demonstrated by indirect immunofluorescence on Hep2 cells; (b) Coarse speckled pattern seen with anti-RNP antibodies on Hep2 cells.

ageing population, without clinical significance, and as a specificity of monoclonal proteins (often with cryoglobulin properties). Although the assay is widely requested, its utility as a screening test is nil. Its major value is as a predictor of severe extra-articular disease in those patients with known clinical rheumatoid arthritis, where high levels of rheumatoid factors are predictive. Increasingly, antibodies to cyclic citrullinated peptide (CCP) are being used as an early marker of rheumatoid arthritis, as these are more specific than rheumatoid factor.

Other organ-non-specific antigens

Immunofluorescence using composite tissue blocks containing kidney, liver and stomach will also identify other organ-non-specific antibodies such as mitochondrial antibodies (primary biliary cirrhosis), liver–kidney microsomal antibodies (drug-induced hepatitis), ribosomal antibodies (see Table 13.9), smooth muscle antibodies (autoimmune hepatitis) and gastric parietal cell antibodies (pernicious anaemia).

Table 13.10 Autoimmune syndromes.

Syndrome	Major criteria	Minor criteria
Type I (autoimmune polyendocrinopathy, candidiasis, ectodermal dysplasia)	Candidiasis, adrenal failure, hypoparathyroidism	Gonadal failure, alopecia, malabsorption, chronic hepatitis
Type II (Schmidt's syndrome)	Adrenal failure, thyroid disease, type I diabetes mellitus	Gonadal failure, vitiligo, non-endocrine autoimmunity (myasthenia gravis)
Type III	Thyroid disease	Type I diabetes mellitus *or* pernicious anaemia *or* non-endocrine autoimmunity (myasthenia gravis)

Organ-specific antigens (including skin)

Organ-specific autoantibodies can be detected by direct immunofluorescence on biopsies and also by indirect techniques using animal tissues (primate or rodent). These include autoantibodies against endocrine tissues, as seen in the autoimmune polyglandular syndromes, some of which are associated with chronic mucocutaneous candidiasis (Table 13.10).

Autoantibodies to skin (see Chapter 40) are detected on primate oesophagus by indirect immunofluorescence. Titres and serial monitoring do not appear to have any great clinical significance. The same substrate is also used to detect endomysial antibodies of the IgA class, as a diagnostic test of high sensitivity and specificity in gluten-sensitive enteropathy, including dermatitis herpetiformis. As coeliac disease is associated with an increased incidence of IgA deficiency, screening for such is required; under these circumstances, IgG endomysial antibodies carry the same diagnostic significance. The target antigen has been identified as tissue transglutaminase (tTG), and solid phase assays for antibodies to this enzyme are available. There is no evidence that these are diagnostically superior to endomysial antibodies. Gliadin antibodies (IgG and IgA) are non-specific tests that should not be used for the diagnosis of gluten-sensitive enteropathy. Endomysial and tTG antibodies disappear gradually when strict gluten avoidance is instituted, but reappear after gluten challenge; they are therefore valuable as a tool to monitor compliance.

Autoimmunity in urticaria

It has been claimed that a significant proportion of patients (up to 35%) with chronic urticaria may have autoantibodies to the α subunit of the IgE receptor, and a further 5–10% may have autoantibodies to IgE itself. Unfortunately, the solid phase assays used to demonstrate the presence of these autoantibodies have lacked appropriate controls. Studies using immunoblots have confirmed that such autoantibodies may occur but have shown them to be commonly present in low concentrations in the serum of otherwise healthy individuals and also at higher titre in patients

Table 13.11 Surface markers on leukocytes.

Surface marker	Cell type	Examples of abnormalities
CD19 (or CD20)	B lymphocytes	Absent in X-linked agammaglobulinaemia, BLNK deficiency and B^- SCID; reduced in common variable immunodeficiency
CD16/56	NK cells	Elevated in acute infections; rare deficiency reported
CD3	T cells	Reduced/absent in severe combined immunodeficiency
CD4	T helper cells	Reduced in viral infections including HIV
CD8	T cytotoxic cells	Raised in acute/chronic viral infections; reduced/absent in ZAP-70 deficiency
CD25	IL-2 receptor	Expression measured on $CD4^+$ cells as marker of T-cell activation (inflammation and infection); high levels are expressed on Treg, with FoxP3
MHC class II (DR common)	Constitutively expressed on B cells, activation marker on T cells	Measured on $CD4^+$ cells as marker of T-cell activation (inflammation and infection); absent in class II MHC deficiency
MHC class I (W6/32, common)	All nucleated cells	Absent in MHC class I deficiency
CD45RA	Naïve T cells	Monitoring reconstitution post BMT
CD45RO	Memory T cells	Monitoring reconstitution post BMT
CD11a,b,c/CD18	Adhesion molecules (lymphocytes, neutrophils)	Leukocyte adhesion molecule deficiency type I
CD15	Adhesion molecule (macrophages, neutrophils)	Leukocyte adhesion molecule deficiency type II
CD21/CD35	Complement receptors (with CD11b, c) on phagocytic cells and B lymphocytes	Complement receptor deficiency

BLNK, B-cell linker protein; BMT, bone marrow transplantation; HIV, human immunodeficiency virus; IL, interleukin; MHC, major histocompatibility complex; NK, natural killer; SCID, severe combined immunodeficiency.

with blistering skin diseases and connective tissue diseases. Their clinical utility is doubtful and there are no commercial validated assays available.

A small proportion of patients with chronic urticaria have hypocomplementaemic urticarial vasculitis. These patients have systemic features and may also suffer from angio-oedema, ocular inflammation and chronic obstructive pulmonary disease in the absence of a smoking history. It may be associated with evidence of an underlying connective tissue disorder. C3 and C4 are usually reduced and autoantibodies to the collagenous region of C1q can be demonstrated, although these are also found in patients with SLE (especially if glomerulonephritis is present) who do not have urticarial lesions. However, all patients with clinical features of hypocomplementaemic urticarial vasculitis have the antibody. Routine assays are available for anti-C1q antibodies, although these are prone to interference from immune complexes and DNA fragments.

Cellular tests

Delayed-type hypersensitivity testing

In vivo testing for type IV reactions is commonly practised in dermatology departments in the form of patch testing for contact dermatitis. This is a useful and reliable test, and is the type IV counterpart of skin prick testing. Allergens are applied under aluminium discs taped to the back for 48 h and then removed. Allergen-specific T cells are then recruited by allergen-bearing APCs in the epidermis, accumulating over the next 48–72 h. The infiltrate is palpable, and there is often blistering and inflammation at the site due to cytokine release and recruitment of inflammatory cells. In the case of photoallergy, allergens are applied in duplicate, with one panel being exposed to UV light after removal of the discs, while the duplicate panel is protected from light.

Variants of this type of test include the well-known Heaf test for T-cell immunity to *Mycobacterium tuberculosis*, in which a multipronged applicator introduces purified protein derivative (PPD) into the dermis. Similar tests are used by clinical immunologists to test for T-cell immunity to *Candida* and other protein antigens, as part of the work-up for suspected T-cell immunodeficiency. Access to antigens in a form suitable for (unlicensed) clinical use limits the usefulness of this type of testing.

Cell marker analysis (whole blood) (Table 13.11)

Lymphocyte subpopulations in peripheral blood are readily measurable. This test is carried out by flow cytometry, ideally using a single platform instrument capable of producing absolute counts for the major lymphocyte populations. There is a wide range of available surface markers, but in clinical practice a relatively restricted panel provide all the required information. This type of testing has no intrinsic diagnostic value in the absence of a clear clinical question, such as whether a child has immunological features compatible with SCID. Testing lymphocyte subsets is often carried out as a surrogate (without informed consent) for retroviral disease. As well as being ethically unjustified, this is inappropriate because changes in $CD4^+$ T cells are seen in a wide range of acute and chronic viral infections as well as in acutely sick patients and are not specific to human immunodeficiency virus (HIV) disease. In patients with known HIV infection, monitoring of cell counts provides important information on risks of opportunistic infections, as different infections appear at different points in the decline of the $CD4^+$ T-lymphocyte count. Monitoring is also important in assessing the immune reconstitution seen in response to treatment with highly active antiretroviral therapy. Patients on immunosuppressive therapy with cytotoxic agents should in the first instance be monitored with absolute lymphocyte counts obtained from a standard full blood count, but if very

low counts occur then checking the subpopulations is helpful for determining whether any additional prophylaxis against infection is required.

It is important to remember that analysis of peripheral blood lymphocytes provides a snapshot of lymphocytes in transit only, and gives no information about immunological processes going on in other tissues. Furthermore, there are circadian changes in blood lymphocytes, so the timing of samples has a significant effect on cell counts; this is particularly important for serial monitoring.

More extensive panels are used for the identification of leukaemias and this is usually done in parallel with examination of bone marrow. Here absolute counts are not necessary as the phenotype of the bulk population is required.

In vitro proliferation assays

In vitro T-cell function testing is complex, labour-intensive, time-consuming and difficult to quality control. Lymphocytes must be purified from blood by density gradient centrifugation and set up in sterile culture for periods of 3–7 days. Accordingly, its use is restricted to diagnosis and monitoring of primary immunodeficiencies. Abnormalities in these assays are not necessarily translated into clinical symptoms. The gold standard is still tritiated thymidine uptake. Alternative methods using flow cytometry have been developed based on analysis of cellular DNA content and expression of activation markers such as CD69 and transferrin receptor, but these do not provide the same information or have the same clinical correlations as tritiated thymidine incorporation. Panels of polyclonal stimuli are used that activate T or B cells at different points in the cascade, enabling the cellular location of defects to be identified. These include phytohaemagglutinin A, pokeweed mitogens and concanavalin A, plant lectins that bind to oligosaccharides on cell surface proteins; anti-CD3 (±IL-2), which mimics activation via the TCR; and phorbol esters, which activate the intracellular enzyme protein kinase C in the presence of calcium (calcium ionophores are used). Antigen can also be used but as the frequency of antigen-specific T-cell precursors in peripheral blood is extremely low, responses are very small compared with polyclonal stimuli. Typically, *Candida* antigens, tetanus toxoid and viral antigens such as those from herpes simplex virus (HSV), cytomegalovirus (CMV) and varicella-zoster virus (VZV) are used.

Results are expressed in counts per minute (cpm) and also as a stimulation index (SI) calculated by comparing the control incorporation with the stimulated incorporation. It is essential that a medium control is always performed and that a normal healthy control is run in parallel as a reagent check. There is a large range of normal responses and laboratories should develop their own acceptable ranges. However, as a general principle, polyclonal stimuli should give an SI greater than 10, while for antigen an SI of 2–4 is acceptable.

Other functional assays have been developed for the flow cytometer, including assays for apoptosis, valuable in the Canale–Smith syndrome, and activation-induced expression of CD40 ligand (CD154), valuable in the X-linked hyper-IgM syndrome.

Neutrophil function tests

Robust assays exist for the identification of defects of neutrophil oxidative metabolism. The historic assay is the nitroblue tetrazolium reduction test, which was performed as a slide assay. This has been modified by the application of similar fluorescent dyes for use on the flow cytometer. Similarly, flow cytometric assays exist for measuring neutrophil and macrophage phagocytosis, using fluoresceinated opsonized bacteria. However, these assays are highly susceptible to the clinical state of the patient, and abnormal results are obtained in patients with active or recent infection. Assays of neutrophil chemotaxis are described but these are impossible to standardize and there is such a wide range of 'normal' results that interpretation of clinical results is no better than guesswork.

Cytokine assays

Measurement of cytokines by solid phase assays is well-established as a research tool. However, measurement of cytokines in clinical material has not been shown to be diagnostically helpful as the assays are unreliable when used in this way, mainly due to the natural occurrence of soluble cytokine receptors and anticytokine antibodies in body fluids that interfere with binding. The use of surrogates such as CRP is more robust. Cytokine production *in vitro* can be used as an adjunct to T-cell proliferation assays. Intracellular cytokine production can be measured using the flow cytometer, and cytokine production can be tied to particular cell types by simultaneous surface staining with monoclonal antibodies. There seems to be little gain in clinically useful information over and above that derived from lymphocyte subset analysis.

Molecular immunology

The use of molecular genetic techniques to identify immunoglobulin and TCR gene rearrangements has been essential in developing the understanding of lymphoproliferative conditions. These techniques can be as easily applied to solid tissue extracts as to peripheral blood cells. Flow cytometric methods have also been used to identify clonality of T cells in peripheral blood by examining Vβ chain usage with panels of monoclonal antibodies.

Immunological therapy

Immunological therapy has for many years rested on a small group of cytotoxic drugs supplemented with corticosteroids. These remain important, but advances in our understanding of basic immunology and parallel technical advances have opened the door to new and exciting immunological therapies with potentially fewer side effects. Nonetheless, steroids and cytotoxics will remain important for the foreseeable future.

Corticosteroids

These have both anti-inflammatory and immunosuppressive effects. The anti-inflammatory effect is mediated by increased production of lipomodulin, an inhibitor of phospholipase A_2, the enzyme essential to the formation of the arachidonic acid pathway metabolites involved in inflammation (leukotrienes and

prostaglandins). Phagocytosis is also inhibited, and production of IL-1 and TNF-α is reduced. At higher doses, corticosteroids are lymphotoxic, via increased apoptosis. Lymphocyte proliferation is inhibited and cytokine production is reduced, especially by Th1 cells.

Methotrexate

Methotrexate is a folate antagonist, used in weekly (low) doses as an immunosuppressant. It is converted to long-lived intracellular polyglutamate metabolites, which are potent inhibitors of dihydrofolate reductase; this accounts for the cumulative toxicity. However, it is not clear if this activity accounts for the immunosuppressive and anti-inflammatory activities. One suggested mechanism is blockade of transmethylation reactions, with increased lymphotoxic concentrations of *S*-adenosylhomocysteine (one of the toxic metabolites that accumulates in adenosine deaminase deficiency, a cause of SCID). Another postulated mechanism involves the inhibition of aminoimidazole carboxamide ribonucleotide (AICAR) transformylase, which leads to an increase in cellular AICAR riboside, which also inhibits adenosine deaminase and leads to an increase in adenosine, a powerful inhibitor of lymphocyte proliferation and cytokine production that acts via specific adenosine receptors.

Azathioprine

Azathioprine, a pro-drug of 6-mercaptopurine, inhibits DNA synthesis and also the purine salvage pathway. Its conversion to thio-IMP suppresses the conversion of inosine monophosphate (IMP) to adenosine monophosphate (AMP), and metabolism of thio-IMP to thioguanine leads to the latter's incorporation into, and consequent damage to, DNA. Azathioprine has a broad range of immunological activities: reduced NK-cell function; reduction in $CD8^+$ T cells; inhibition of lymphocyte proliferation and cytokine production; inhibition of antibody responses (primary > secondary) and impaired neutrophil chemotaxis. Side effects are related to levels of the enzyme thiopurine methyltransferase (TPMT). Patients with a homozygous deficiency of TPMT are highly susceptible to prolonged bone marrow toxicity even from tiny doses of azathioprine, whereas heterozygotes can tolerate reduced doses of the drug with care. Checking red cell TPMT levels before treatment allows identification of those who will develop severe toxicity so they can be spared a trial of therapy. Long-term use may cause a persistent profound lymphopenia and severe hypogammaglobulinaemia.

Other drugs operating on these pathways are fludarabine and cladribine. These have been mainly used in the treatment of haematological malignancies, but their potent immunosuppressive effects are likely to be of considerable value in managing autoimmune disease, with appropriate tailoring of the doses.

Mycophenolate mofetil

Mycophenolate is a potent inhibitor of the enzyme IMP dehydrogenase and therefore works on both *de novo* synthesis as well as salvage of purine, that is the same pathways affected by azathioprine. Its range of effects is therefore very similar to azathioprine. In addition, the reduction in the guanine nucleotide pool decreases the synthesis of oligosaccharide chains on surface receptors involved in adhesion and migration.

Cyclophosphamide

Cyclophosphamide is a pro-drug converted by the liver into phosphoramide mustard, an alkylating agent that acts on guanine residues in DNA and which increases cross-linking of DNA strands, thus preventing DNA replication and transcription. It is a potent inhibitor of lymphocyte proliferation, reducing antibody production, particularly primary antibody responses. It is more active against $CD4^+$ T cells, and has minimal effects on NK cells. Significant lymphopenia occurs on treatment with cyclophosphamide, and prophylactic antibiotics to prevent opportunistic infections are recommended.

Leflunomide

This is a pro-drug that is converted *in vivo* into a potent inhibitor of the enzyme dihydro-orotate dehydrogenase, an enzyme required for the synthesis of pyrimidines. It prevents lymphocyte proliferation. As T cells are dependent on *de novo* synthesis of pyrimidines, they are uniquely sensitive to leflunomide. At high doses it is also thought to inhibit tyrosine kinases, inhibiting the cascade linked to the IL-2 receptor. It has a very long half-life, as it is highly protein bound.

Hydroxychloroquine and mepacrine

The actions of the antimalarials are not entirely certain, although they reduce the production of cytokines, particularly the pro-inflammatory cytokines IL-1, TNF-α and IFN-γ. They are also concentrated into lysosomes, where they alter pH and interfere with antigen processing.

Thalidomide

Thalidomide is a potent inhibitor of TNF-α production by monocytes, interfering with gene transcription. It also decreases adhesion molecule expression and inhibits IFN-γ production through preferential stimulation of Th2 cells. Oxypentifylline has similar but weaker properties.

Ciclosporin, tacrolimus and sirolimus

Ciclosporin binds to cyclophilin, an intracellular peptidyl-prolyl *cis-trans* isomerase, and the resulting complex inhibits cytoplasmic calcineurin, a calcium-activated serine–threonine phosphatase. This in turn prevents dephosphorylation of NF-AT (nuclear factor of activated T cells), which normally binds to DNA to enhance the transcription of IL-2 and other cytokines, and CD40 ligand in activated T cells. Dephosphorylation prevents the normal translocation of NF-AT from cytoplasm to nucleus, and inhibits the production of IL-2 and other molecules normally associated with activation of T cells. T cells are particularly sensitive to the effects of ciclosporin, because of low levels of calcineurin. NK cells and B cells are also affected by ciclosporin. The effect is reversible, so overenthusiastic immunosuppression can be rapidly reversed if required. Monitoring of trough blood levels is possible and enables doses to be accurately controlled; levels required for control of autoimmune diseases are lower than those required to prevent allograft rejection.

Tacrolimus binds to a similar peptidyl-prolyl *cis-trans* isomerase, FKBP12, and this has a similar effect on calcineurin. Clinically and immunologically, the effects of tacrolimus are similar to those of ciclosporin.

Sirolimus (rapamycin) also binds to FKBP12, but appears to inhibit an enzyme called mTOR, which is involved in transmission of signals via the IL-2 receptor. Sirolimus and ciclosporin appear therefore to be able to act synergistically by inhibition both of IL-2 production and signalling via IL-2.

Topical formulations of these drugs and related novel compounds are now being introduced for use in immunologically mediated skin disease.

Biological therapy (monoclonal antibodies, chimeric molecules, cytokines, cytokine antagonists, intravenous immunoglobulin; see Chapter 76)

There has been great interest in the use of monoclonal antibodies for the treatment of disease. The first agent used clinically was a murine anti-CD3 (muromonab), although its use was limited by its murine origin, which usually led rapidly to the development of neutralizing antibodies. However, it was recognized as a potent immunosuppressive agent and used in clinical allograft rejection. Genetic engineering of monoclonal antibodies now allows the murine binding site to be inserted into a human immunoglobulin framework, while retaining its original specificity. This reduces, but does not completely abolish, the antimouse response. Antibodies to the pan-leukocyte antigen CD52 are potent immunosuppressive agents (Campath), producing a prolonged lymphopenia. An anti-CD20 (B cell) monoclonal antibody, rituximab, originally introduced to treat lymphomas, has also been found to be a useful therapy in a variety of autoimmune conditions including pemphigus. Many surface molecules are now the targets of experimental monoclonal antibody therapies. A humanized monoclonal antibody to LFA-1 (CD 11a), efalizumab, is a licensed therapy for psoriasis. Particular targets of interest are the co-stimulatory molecules B7–CD28 and CD40–CD40 ligand. Because of its inhibitory nature, CTLA-4 has also been used in the form of a hybrid fusion molecule with human immunoglobulin. Fusion proteins such as LFA-3/IgG (alefacept) and denileukin diftitox have been used to treat psoriasis and cutaneous T-cell lymphoma, respectively.

An alternative strategy has been to target the cytokines or their receptors. The most effective examples of this have been the use of the humanized anti-TNF monoclonal antibody (infliximab), the fully human anti-TNF monoclonal antibody (adalimumab) and the TNF-receptor Ig Fc fusion protein (etanercept), which are highly active in suppressing TNF-based inflammatory reactions such as psoriasis, Crohn's disease and rheumatoid arthritis. There has been concern, however, that use of these agents may increase autoimmunity and also susceptibility to infection, particularly mycobacterial infection. Other cytokine antagonists, such as the naturally occurring IL-1 receptor antagonist, which binds to IL-1 receptor but does not signal, are also being tested in clinical trials. Other targets for monoclonal antibodies in trials include IL-6 and IL-8.

There is a long history to the administration of cytokines in pharmacological doses, starting with IL-2, as adjuncts to chemotherapy for malignant disease. However, the benefits have been small and the side effects considerable. There may be some benefit from IL-2 in common variable immunodeficiency, used in a pegylated form to lengthen the circulating half-life, and in acquired immune deficiency syndrome (AIDS), to improve T-cell function. Administration of IFN-γ has been shown to be beneficial in chronic granulomatous disease, although the precise mechanism of action is unclear. IFN-α is valuable in treatment of chronic hepatitis C infection, with best results coming from combination therapy with the antiviral ribavirin. On the whole, however, cytokine therapy has been a disappointment. This is partly due to the considerable cytokine redundancy, with overlapping functions from multiple cytokines, and partly because most of the cytokines act as short-range messengers; also, the total cytokine and chemokine milieu that a cell experiences determines its response. The same cytokine may therefore have different effects depending on which other cytokines are present. This scenario is difficult to replicate by pharmacological administration of single cytokines.

High-dose intravenous immunoglobulin is widely used as an immunomodulatory agent for autoimmune disease. It is likely that multiple mechanisms of action are involved, including modulation of cytokine release and function, antiproliferative effects, suppression of antibody production via idiotypic antibodies, inhibition of complement-mediated tissue damage and Fc receptor blockade. Problems with this type of therapy are that it is in short supply and has to be derived from human material, which poses risks of infection; the risks of transmission of prion disease are as yet unquantified. It has been widely used, including the treatment of bullous skin diseases, resistant urticaria and atopic dermatitis. None of these uses are yet licensed. In a shortage, priority for supplies should be given to its use in licensed indications and in properly conducted clinical trials.

Physical therapy (plasmapheresis, photopheresis, irradiation, immunoadsorption)

Plasmapheresis provides a rapid way of removing pathogenic autoantibodies. However, it must be combined with immunosuppressive therapy, as there is usually a rebound increase in autoantibody levels immediately following plasmapheresis. Modifications of plasmapheresis include the use of specific immunoadsorption columns in the extracorporeal circuit. These columns comprise a biocompatible substrate to which either protein A or specific antigen is coupled, enabling specific antibodies to be removed without removing essential antibodies necessary for host defence against pathogens. A further development is the use of photopheresis, in which psoralen-like drugs are administered and the extracorporeal circuit is then irradiated with UV light; this provides a potent method of suppression of lymphocytes. The main drawback of these methods is the need for expensive equipment and trained staff.

Low-dose irradiation is also immunosuppressive in doses below those used in the management of malignant disease. This can prove valuable where there is localized immunological disease, for example locally aggressive Wegener's granulomatosis.

Allergy therapy

The mainstay of symptomatic allergy relief is the reduction of mediator output by the use of steroids and mast-cell stabilizing

drugs such as disodium cromoglycate and nedocromil, and the antagonism of released mediators by the use of antihistamines and leukotriene antagonists.

Reduction or abolition of allergic reactivity can be undertaken by specific allergen immunotherapy, using purified and standardized allergen extracts. The precise mechanism by which tolerance is induced is unclear. Initially, IgE levels increase before declining slowly. IgG4 antibodies are also produced and may have a blocking role. Alterations in T-cell function are also likely. The process is slow and optimum schedules have yet to be established. Maintenance therapy is required, usually for several years. Most therapy is given by injection but there is evidence that the sublingual route can be used with good effect, albeit requiring much larger doses of allergen. It is, however, very effective for seasonal allergic rhinitis due to grass and tree pollens, and is also effective for house-dust mite, cats (but less so dogs) and venoms. There is some risk of anaphylaxis and therefore the treatment is suitable only for hospital use by experienced personnel. Current trials are investigating the use of peptides derived from key allergens as a way of inducing T-cell tolerance and therefore abolishing the IgE response. The peptides induce tolerance when injected because they are not presented in the correct way with co-stimulation. This effect may be enhanced by co-administration of IL-12 or IL-18, which induce IFN-γ and bias the immune response towards Th1.

Monoclonal antibodies to IgE have also been introduced into clinical trials with some success. These have been tested first in asthma, where the effects are modest, probably because non-IgE mechanisms are also prominent, but are likely to be more effective in rhinitis. Significant reductions in circulating IgE levels have been documented.

Transplantation

Stem cell transplantation after bone marrow ablative therapy as a treatment for severe autoimmune disease refractory to conventional immunosuppressive therapy is now being undertaken. Diseases include juvenile chronic arthritis and other severe connective tissue diseases such as scleroderma.

Further reading

The field of immunology is a colossal one and provision of up-to-date references in a textbook that takes 2 years from submission to publication is impossible. Accordingly, the list below indicates useful immunological reference works that provide more detailed discussion of the topics covered. Use of PubMed and Medline to obtain the latest information is strongly recommended, particularly in regard to diagnosis and management of clinical conditions.

Basic immunology

1 Paul WE, ed. *Fundamental Immunology*, 6th edn. Philadelphia: Lippincott, Williams & Wilkins, 2008.

Basic and clinical immunology

1 Austen KF, Frank MM, Atkinson JP, Cantor H, eds. *Samter's Immunologic Diseases*, 6th edn. Philadelphia: Lippincott, Williams & Wilkins, 2001.
2 Mak TW, Saunders ME. *The Immune Response: Basic and Clinical Principles*. Academic Press, 2004.
3 Rich RR, Fleischer TA, Shearer WT, Schroeder HW, Frew AJ, Weyard CM. *Clinical Immunology, Principles and Practice*, 3rd edn. Mosby Elsevier 2008.

Allergic disease

1 Brostoff J, Challacombe SJ, eds. *Food Allergy and Intolerance*, 2nd edn. London: Saunders, 2002.
2 Metcalfe DD, Sampson HA, Simon RA. *Food Allergy: Adverse Reactions to Foods and Food Additives*, 4th edn. Boston: Blackwell Science, 2008.
3 Adkinson NF, Bochner BS, Busse WW, Holgate ST, Lemanske JR, Simons FER. *Middleton's Allergy, Principles and Practice*, 7th edn. Mosby Elsevier 2009.

Autoimmune disease

1 Ball GV, Bridges SL, eds. *Vasculitis*. Oxford: Oxford University Press, 2002.
2 Lahita RG, Chiorazzi N, Reeves WH, eds. *Textbook of the Autoimmune Diseases*. Philadelphia: Lippincott, Williams & Wilkins, 2000.
3 Rose NR, Mackay IR, eds. *The Autoimmune Diseases*, 3rd edn. San Diego: Academic Press, 1998.

Primary immunodeficiency diseases

1 Stiehm ER, Ochs HD, Winkelstein JA. *Immunologic Disorders in Infants and Children*, 5th edn. Philadelphia: Elsevier Saunders 2004.

Immunological therapy

1 Austen KF, Burakoff SJ, Rosen F, Strom TB, eds. *Therapeutic Immunology*, 2nd edn. Boston: Blackwell Science, 2001.

Laboratory diagnosis

1 Detrick B, Hamilton RG, Folds JD, eds. *Manual of Clinical and Laboratory Immunology*, 7th edn. Washington DC: ASM Press, 2006.
2 Shoenfeld Y, Gershwin ME, Meroni PL, eds. *Autoantibodies*, 2nd edn. Amsterdam: Elsevier, 2007.
3 Spickett GP. *Oxford Handbook of Clinical Immunology and Allergy*, 2nd edn. Oxford: Oxford University Press, 2006.

Photoimmunology

T. Schwarz, pp. 13.26–13.34

It is more than 25 years since the discovery that ultraviolet (UV) radiation can influence the immune system. Since then numerous studies in the field of photoimmunology have tried to identify, first, the biological impacts of UV-induced immunosuppression and, second, the underlying mechanisms. The immunosuppressive effects of solar radiation are mostly due to the medium wavelength range (UVB, 290–320 nm). Accordingly, the vast majority of photoimmunological studies have used UVB. There is also recent evidence that the long wave-length range (UVA, 320–400 nm) can affect the immune system, although its effects are less pronounced and more heterogeneous. Hence, in the following section the term UV refers mostly to UVB. If other spectra, for example UVA or UVC, were used it will be mentioned specifically.

UVB inhibits antigen presentation, induces the release of immunosuppressive cytokines and the generation of T cells with suppressive activities. This does not cause general immunosuppression but rather an inhibition of immune reactions in an antigen-specific fashion, mediated by suppressor/regulatory T cells. UVB-induced DNA damage is a major molecular trigger of UV-mediated immunosuppression. Further studies addressing the molecular mechanisms underlying UV-induced immunosuppression will contribute

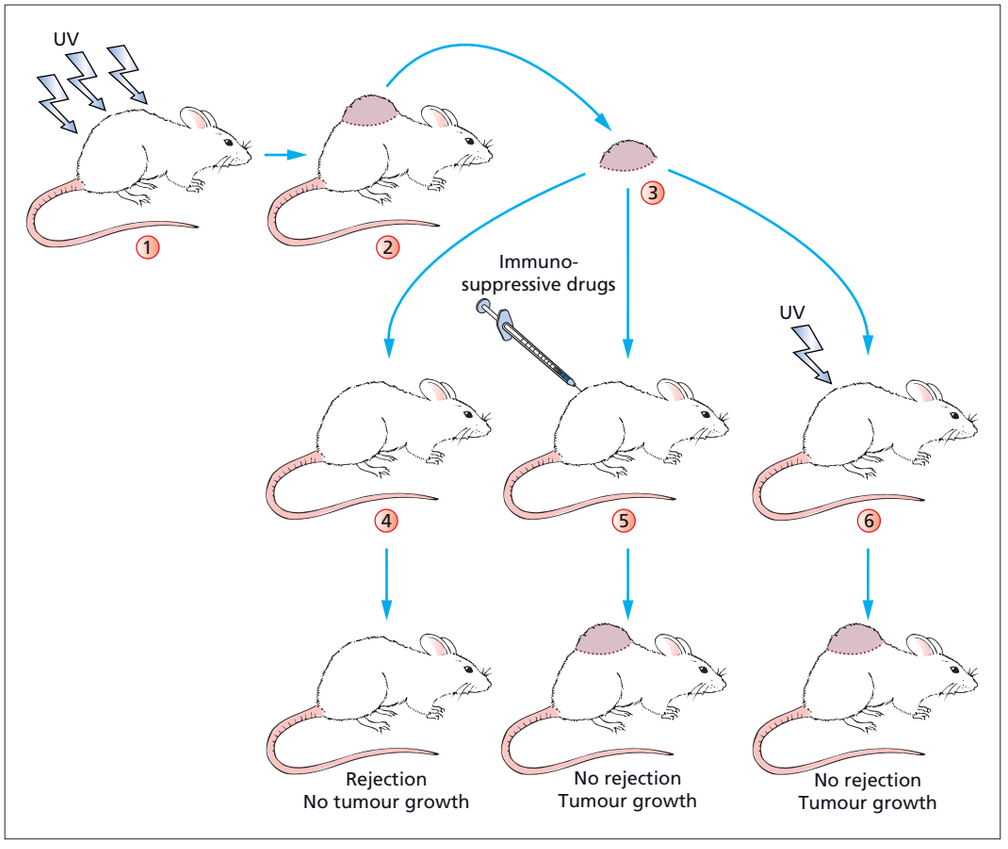


Fig. 13.4 UV radiation inhibits the rejection of immunogenic skin tumours. Chronic UV exposure (1) induces skin tumours (2). Upon transplantation (3) these tumours are rejected by naïve syngeneic recipient mice (4). If recipient mice are treated with immunosuppressive drugs (5) or exposed to UV radiation (6) these tumours are not rejected but grow.

to a better understanding of how UV acts both as a pathogen and as a therapeutic tool.

Until recently, photoimmunology has exclusively concentrated on studying the effects of UV radiation on the acquired immune response. There are very recent indications that UV radiation might also influence the innate immune response. Since these studies are just at the beginning and the impact of the alteration by UV radiation is not yet clear, the following chapter will almost exclusively focus on the effect of UV radiation on the acquired immune response.

UV radiation induces local and systemic immunosuppression

Initial evidence that UV radiation influences the immune system was provided by the observation that UV radiation inhibits the immunological rejection of transplanted tumours. Skin tumours induced by chronic UV exposure in mice are highly immunogenic since they are rejected following transplantation into naïve, syngeneic hosts [1]. However, if the recipient animal is treated with immunosuppressive drugs, the inoculated tumours are not rejected but grow, implying that the rejection is immunological in nature. Rejection can also be prevented when the recipient mice are exposed to UV radiation instead of immunosuppressive drugs, clearly indicating that UV radiation can act in an immunosuppressive fashion (Fig. 13.4).

A similar effect can be observed in another immunological *in vivo* model, namely the induction of contact hypersensitivity (CHS). CHS represents a particular kind of delayed type hypersensitivity response which is induced by epicutaneous application of low molecular weight chemical compounds. Since these substances have to bind to proteins to exert antigenic features they are called haptens. Painting of haptens on areas of skin that have been exposed to low (suberythemogenic) UV doses does not induce CHS, whereas administration of the same compound to an unexposed site causes a normal CHS response [2].

Since the areas of hapten application and UV exposure are identical, this type of immunosuppression is called local (Fig. 13.5). Inhibition of CHS induction by UV radiation is associated with a reduction in the number of Langerhans' cells (LC) at the site of exposure [2,3]. This appeared logical since in those days LC were regarded as the primary antigen-presenting cells in the skin [4] and thus suggested that UV radiation interferes with antigen presentation. However, this concept has recently been challenged by the findings that LC may be dispensable for sensitization [5–7].

Higher doses of UV can also affect immune reactions initiated at distant, non-UV-exposed sites. Accordingly, CHS cannot be induced in mice that are exposed to high doses of UV radiation even if the hapten is applied at unirradiated sites [8]. This type is called systemic immunosuppression (Fig. 13.6). Systemic immunosuppression is certainly mediated by mechanisms other than

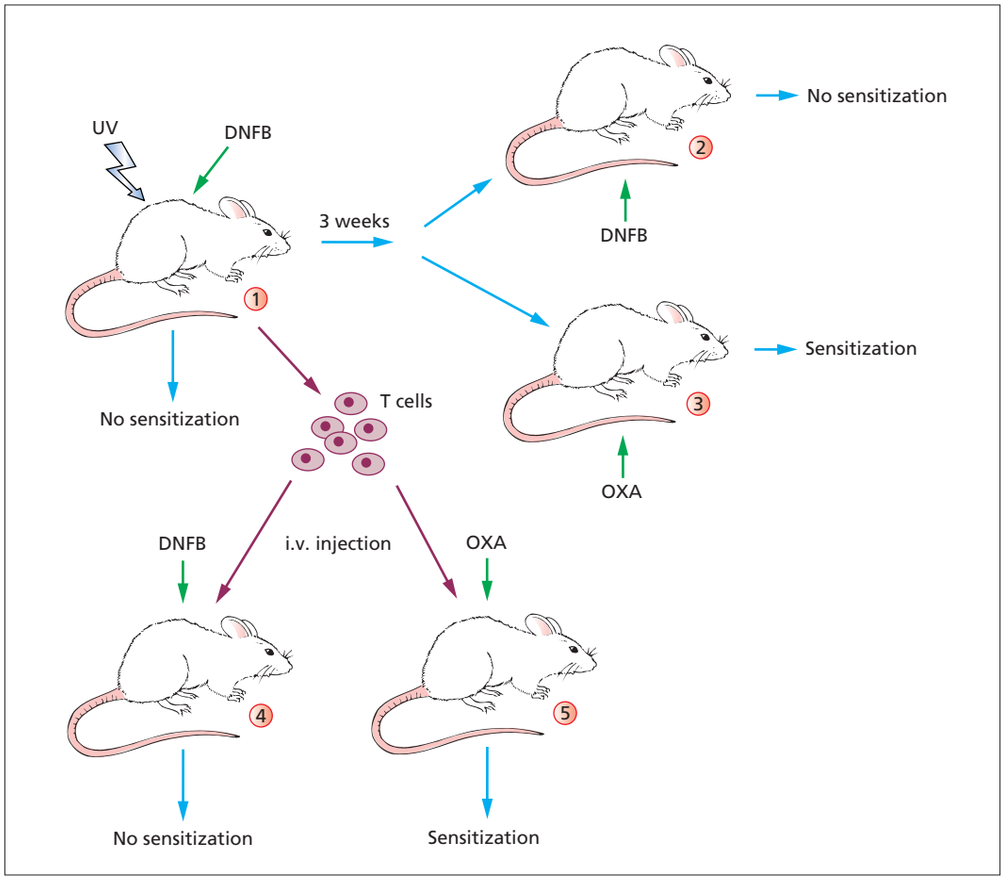


Fig. 13.5 UV radiation induces hapten-specific tolerance which can be adoptively transferred. Application of the hapten dinitrofluorobenzene (DNFB) onto UV-exposed skin does not result in sensitization (1). Reapplication of DNFB onto non-UV-exposed skin of the same mice 3 weeks later again does not cause sensitization (2), indicating that tolerance has developed. However, animals can be sensitized against the unrelated hapten oxazolone (OXA), indicating that tolerance is hapten-specific (3). Intravenous (i.v.) injection of T cells obtained from mice that received DNFB onto UV-exposed skin inhibits sensitization against DNFB of recipient mice (4). However, recipients can be sensitized against OXA (5), indicating that transfer of suppression is hapten-specific.

local immunosuppression. The question as to how UV radiation could interfere with the induction of an immune response at a distant, non-UV-exposed skin area remained unanswered for a long time. It is now clear that UV radiation stimulates keratinocytes to release immunosuppressive soluble mediators which enter the circulation and cause systemic immunosuppression [9].

Effect of UV radiation on antigen presentation

Within the epidermis, LC are the major antigen-presenting cell [10], although other dendritic cells resident in the skin may also be capable of inducing sensitization [5–7]. Exposure of skin to UV radiation results in a profound depletion of LC (Fig. 13.7) which seems to be responsible for inhibition of the induction of contact hypersensitivity following UV irradiation [2]. Depending on the dose of UV applied, the disappearance of LC may be due to either their emigration out of the epidermis and/or induction of apoptotic cell death. UV-damaged LC are still able to migrate into the regional lymph nodes [11] and on their arrival they are still capable of presenting antigen to T cells. Nevertheless, due to the UV stress LC seem to be so damaged that they are unable to present antigen properly, which results in tolerance but not sensitization.

UV radiation certainly alters the antigen-presenting capacity of LC [12]. Inhibition of expression of the adhesion molecule intercellular adhesion molecule-1 (ICAM-1) by UV radiation may be responsible for impaired adherence between LC and T cells. Accordingly, inhibition of antigen presentation by UV radiation was proven both *in vitro* and *in vivo*. Injection of antigen-loaded LC or dendritic cells that have been exposed to UV radiation does not result in sensitization, while injection of antigen-pulsed cells mounts an immune response [13]. In addition, UV-exposed antigen-presenting cells (APCs) are unable to induce a response *in vitro*, for example proliferation in the mixed leucocyte reaction [14]. *In vitro,* UV exposure differentially affects LC in their capacity to stimulate different subsets of $CD4^+$ T-cell clones. While UV-treated LC are unable to stimulate T-cell clones of the Th1 type, their ability to stimulate Th2 clones is unaffected [15]. This may explain why UV radiation preferentially suppresses Th1-mediated immune responses.

References

1 Romerdahl CA, Okamoto H, Kripke ML. Immune surveillance against cutaneous malignancies in experimental animals. *Immunol Series* 1989; **46**: 749–67.

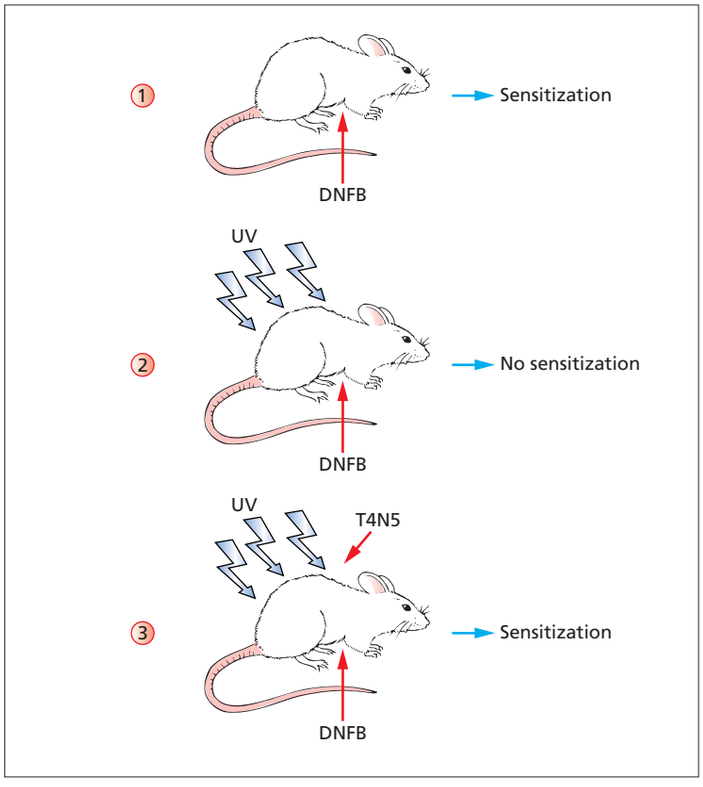


Fig. 13.6 UV radiation induces systemic immunosuppression. Application of allergens (e.g. dinitrofluorobenzene; DNFB) on normal skin induces sensitization (1). Higher doses of UV radiation inhibit sensitization (2) even upon application of the allergen on non-UV-exposed skin (e.g. abdomen). Reduction of UV-induced DNA damage by topical application of the DNA repair enzyme T4N5 endonuclease on the UV-exposed skin area enables sensitization (3), demonstrating that UV-induced DNA damage is causally responsible for the UV-induced immunosuppression.

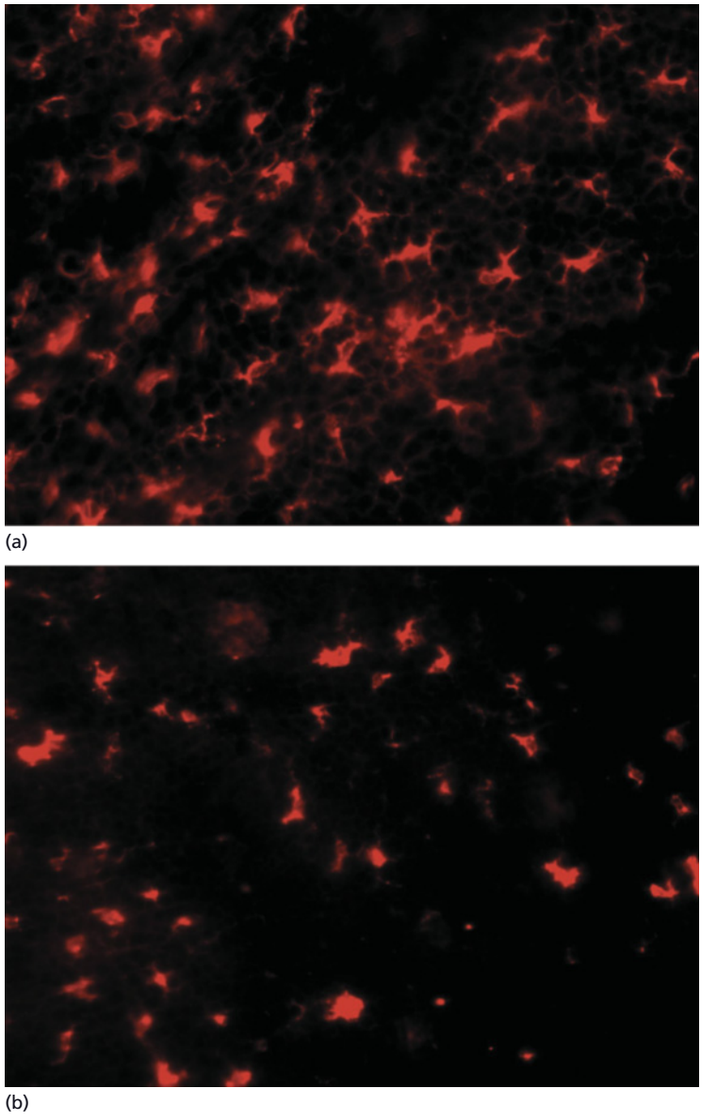


Fig. 13.7 UV radiation depletes Langerhans' cells from the epidermis. (a) In a sheet preparation of normal murine skin numerous Langerhans' cells can be detected by staining with an antibody against MHC class II (Ia) molecules. (b) The number of Langerhans' cells is significantly reduced by UV exposure (2 J/m^2).

2 Toews GB, Bergstresser PR, Streilein JW. Epidermal Langerhans cell density determines whether contact hypersensitivity or unresponsiveness follows skin painting with DNFB. *J Immunol* 1980; **124**: 445–53.

3 Aberer W, Schuler G, Stingl G *et al*. Ultraviolet light depletes surface markers of Langerhans cells. *J Invest Dermatol* 1981; **76**: 202–10.

4 Stingl G, Tamaki K, Katz SI. Origin and function of epidermal Langerhans cells. *Immunol Rev* 1980; **53**: 149–74.

5 Kissenpfennig A, Henri S, Dubois B *et al*. Dynamics and function of Langerhans cells in vivo: dermal dendritic cells colonize lymph node areas distinct from slower migrating Langerhans cells. *Immunity* 2005; **22**: 643–54.

6 Bennett CL, van Rijn E, Jung S *et al*. Inducible ablation of mouse Langerhans cells diminishes but fails to abrogate contact hypersensitivity. *J Cell Biol* 2005; **169**: 569–76.

7 Kaplan DH, Jenison MC, Saeland S *et al*. Epidermal Langerhans cell-deficient mice develop enhanced contact hypersensitivity. *Immunity* 2005; **23**: 611–20.

8 Noonan FP, DeFabo EC, Kripke ML. Suppression of contact hypersensitivity by UV radiation: an experimental model. *Springer Semin Immunopathol* 1981; **4**: 293–304.

9 Walterscheid JP, Nghiem DX, Ullrich SE. Determining the role of cytokines in UV-induced immunomodulation. *Methods* 2002; **28**: 71–8.

10 Stingl G, Tamaki K, Katz SI. Origin and function of epidermal Langerhans cells. *Immunol Rev* 1980; **53**: 149–74.

11 Schwarz A, Maeda A, Kernebeck K *et al*. Prevention of UV radiation-induced immunosuppression by IL-12 is dependent on DNA repair. *J Exp Med* 2005; **201**: 173–9.

12 Stingl LA, Sauder DN, Iijima M *et al*. Mechanism of UV-B-induced impairment of the antigen-presenting capacity of murine epidermal cells. *J Immunol* 1983; **130**: 1586–91.

13 Fox IJ, Sy MS, Benacerraf B, Greene MI. Impairment of antigen-presenting cell function by ultraviolet radiation. II. Effect of in vitro ultraviolet irradiation on antigen-presenting cells. *Transplantation* 1981; **31**: 262–5.

14 Aberer W, Stingl G, Stingl-Gazze LA, Wolff K. Langerhans cells as stimulator cells in the murine primary epidermal cell-lymphocyte reaction: alternation by UV-B irradiation. *J Invest Dermatol* 1982; **79**: 129–35.

15 Simon JC, Cruz PC, Bergstresser PR, Tigelaar RE. Low dose ultraviolet B-irradiated Langerhans cells preferentially activate CD4$^+$ cells of the T helper 2 subset. *J Immunol* 1990; **145**: 2087–91.

UV radiation induces immunologic tolerance

Application of haptens onto UV-exposed murine skin does not result in the induction of contact hypersensitivity. If the same contact allergen is applied, several weeks later, to an area of skin which was not exposed to UV radiation, again no contact hypersensitivity response is induced [1]. This indicates that the initial

application of the hapten onto UV-exposed skin induces long-term unresponsiveness (Fig. 13.5). However, the mice are not generally immunosuppressed by the initial UV exposure since an immune response against another, unrelated, hapten can be induced perfectly in these animals. This indicates that the immunological unresponsiveness caused by UV radiation is hapten-specific, a state called hapten-specific tolerance. Induction of UV-mediated tolerance can be also observed in systemic immunosuppression [2]. Long-term immunosuppression by UV radiation is also observed in the tumour transplantation model. UV exposure suppresses rejection of transplanted skin tumours. If mice are treated for several weeks with repeated doses of UV radiation and then treatment is stopped, the animals remain susceptible to tumour challenge for at least one year, perhaps even for the rest of their lives [3].

The phenomenon of UV-induced tolerance is also demonstrable in humans although some interindividual susceptibility appears to exist. [4]. The fact that UV radiation suppresses the immune system in a specific rather than a general fashion might explain why phototherapy exerts much lower side effects than conventional immunosuppressive drugs which compromise the immune system in a broad manner.

References

1 Toews GB, Bergstresser PR, Streilein JW. Epidermal Langerhans cell density determines whether contact hypersensitivity or unresponsiveness follows skin painting with DNFB. *J Immunol* 1980; **124**: 445–53.

2 Kripke ML, Morison WL. Studies on the mechanism of systemic suppression of contact hypersensitivity by ultraviolet B radiation. *Photodermatol* 1986; **3**: 4–14.

3 Kripke ML. Immunology and photocarcinogenesis. *J Am Acad Dermatol* 1986; **14**: 149–55.

4 Yoshikawa T, Rae V, Bruins-Slot W *et al*. Susceptibility to effects of UVB radiation on induction of contact hypersensitivity as a risk factor for skin cancer in humans. *J Invest Dermatol* 1990; **95**: 530–6.

UV radiation induces T cells with regulatory/suppressor activity

UV radiation-induced hapten-specific tolerance appears to be due to the induction of T cells with inhibitory/suppressive activity. Injection of splenocytes from mice which have been tolerized by application of a hapten onto UV-exposed skin into naïve syngeneic mice renders the recipients unresponsive to this particular antigen [1]. Immune responses against other non-related antigens are unaffected (Fig. 13.5). Transfer of suppression is mediated via T cells since their depletion from splenocytes is associated with a loss of transfer. Thus, sensitization in combination with UV exposure induces the generation of T cells with hapten-specific suppressor activity. Transfer of tolerance can be observed both in local [1] and systemic models [2]. Nevertheless, different types of T cells seem to be involved. In the systemic form of UV-induced suppression, transfer of tolerance is mediated by the induction of antigen-specific, $CD3^+CD4^+CD8^-$ suppressor cells [3]; in the local form of suppression, both $CD4^+$ and $CD8^+$ cells appear to be involved. These differences may be due to a variety of factors including: the different systems used; strain of mice; the type of haptens; and the UV doses applied.

Although the adoptive transfer experiments appear convincing, attempts to purify and clone these transferred cells have been unsuccessful. For this reason, the term 'T suppressor cells' was almost banned in general immunology and the entire concept of UV-induced tolerance and suppressor cells was drawn into question by many immunologists [4]. The subject of T suppressor cells experienced a renaissance by the finding that chronic activation of both human and murine $CD4^+$ T cells in the presence of interleukin (IL)-10 induces $CD4^+$ T cell clones which release high levels of IL-10, low levels of IL-2 and no IL-4 [5]. These antigen-specific T cell clones suppress the proliferation of $CD4^+$ T cells in response to antigen, and prevent a T cell-mediated colitis in an immunodeficient mouse model of this condition [5]. This $CD4^+$ T cell subset is referred to as T regulatory cells 1 (Tr1).

Another subset of $CD4^+$ regulatory T (Treg) cells is characterized by the constitutive expression of the α chain of the IL-2 receptor (CD25). After antigen-specific activation, $CD4^+CD25^+$ T cells suppress immune reactions both *in vitro* and *in vivo* in an antigen-non-specific way [6]. There is also evidence that $CD4^+CD25^+$ Treg may be involved in the mediation of UV-induced tolerance. The area of Treg is currently one of the most extensively studied subjects in general immunology and future studies will increase knowledge about the mediation of tolerance and active suppression. Whether these T cells are termed suppressor or regulatory seems to be more of a semantic issue. The term regulatory T cells or Treg is usually preferred, since the existence of these cells is becoming accepted even by those investigators who previously denied the existence of suppressor T cells.

Due to the different tolerance models (local, systemic, induction, memory, high dose, low dose) different subtypes of UV-induced Treg (UV-Treg) may exist. Currently best characterized are the Treg involved in the low-dose suppression of CHS. These cells belong to the $CD4^+CD25^+$ subtype, express CTLA-4, and in contrast to the classical $CD4^+CD25^+$ T cells release high amounts of IL-10 upon antigen-specific activation [7]. Thus, they may represent a separate subtype of Treg since they exhibit characteristics of naturally occurring Treg (expression of CD4 and CD25) but also of type 1 regulatory T (Tr1) cells (release of IL-10).

Intravenous injection of hapten-specific Treg into naïve mice inhibits sensitization in an antigen-specific fashion as immune reactions against other antigens are not suppressed [1]. Treg suppress immune reactions in an antigen-specific manner thus these cells carry quite a therapeutic potential, as via their administration general immunosuppression may be avoided. In comparison with conventional immunosuppressive drugs, this would have great benefits for the patients as the side effects of general immunosuppression, including secondary infections and increased risk of developing malignancies, could be avoided or prevented. Therapeutic administration, however, would only make sense if these cells are able not only to prevent sensitization but also to inhibit the elicitation in sensitized hosts. In general, the aim of immunosuppression is not to prevent but to treat and to cure diseases.

Interestingly, intravenous injection of UV-Treg into naïve mice inhibits the sensitization, but not the elicitation, of CHS when injected intravenously into already sensitized mice [8]. However, upon intracutaneous injection of UV-Treg into the ears of sensitized mice the ear challenge is inhibited [9]. This proves that UV-induced Treg once they have reached the area of inflammation can suppress not only the induction but also the elicitation of

immune reactions. This process is critically dependent on the expression pattern of tissue homing receptors. UV-Treg express lymph node but not skin homing receptors. Hence upon intravenous injection, they migrate into the lymph nodes but not into the periphery and thus only inhibit sensitization but not elicitation. Thus, it is of crucial importance whether it will be possible to manipulate the expression pattern of homing receptors in such a way that Treg can gain access to the periphery. If this proves not to be the case, the therapeutic potential of Treg will be limited.

Cellular-mediated suppression appears to play a role in the inhibition of tumour immune responses by UV radiation. However, in this setting natural killer T (NKT) cells, but not Treg, appear to be involved [10]. UV-induced NKT cells suppress a delayed type hypersensitivity reaction against tumour antigens. In addition, they support the growth of inoculated UV-induced tumour cells which are rejected in normal mice. This indicates that NKT cells may play a critical role in regulating the growth of UV-induced skin cancers.

References

1 Elmets CA, Bergstresser PR, Tigelaar RE *et al*. Analysis of the mechanism of unresponsiveness produced by haptens painted on skin exposed to low dose ultraviolet radiation. *J Exp Med* 1983; **158**: 781–94.

2 Noonan FP, DeFabo EC, Kripke ML. Suppression of contact hypersensitivity by UV radiation and its relationship to UV-induced suppression of tumor immunity. *Photochem Photobiol* 1981; **34**: 683–9.

3 Ullrich SE, McIntryre WB, Rivas JM. Suppression of the immune response to alloantigen by factors released from ultraviolet-irradiated keratinocytes. *J Immunol* 1990; **145**: 489–98.

4 Beissert S, Schwarz A, Schwarz T. Regulatory T cells. *J Invest Dermatol* 2006; **126**: 15–24.

5 Groux H, O'Garra A, Bigler M *et al*. A $CD4^+$ T-cell subset inhibits antigen-specific T-cell responses and prevents colitis. *Nature* 1997; **389**: 737–42.

6 Maloy KJ, Powrie F. Regulatory T cells in the control of immune pathology. *Nat Immunol* 2001; **2**: 816–22.

7 Schwarz T. 25 years of UV-induced immunosuppression mediated by T cells—from disregarded T suppressor cells to highly respected regulatory T cells. *Photochem Photobiol* 2008; **84**: 10–8.

8 Glass MJ, Bergstresser PR, Tigelaar RE, Streilein JW. UVB radiation and DNFB skin painting induce suppressor cells universally in mice. *J Invest Dermatol* 1990; **94**: 273–8.

9 Schwarz A, Maeda A, Wild MK *et al*. Ultraviolet radiation-induced regulatory T cells not only inhibit the induction but can suppress the effector phase of contact hypersensitivity. *J Immunol* 2004; **172**: 1036–43.

10 Moodycliffe AM, Nghiem D, Clydesdale G, Ullrich SE. Immune suppression and skin cancer development: regulation by NKT cells. *Nat Immunol* 2000; **1**: 459–60.

UV radiation induces the release of immunosuppressive mediators

The finding that mice exposed to higher doses of UV radiation cannot be sensitized, even when the antigen is applied to an area of skin which has not been exposed to UV [1,2], clearly indicates that UV radiation has the capacity to suppress the immune system in a systemic manner (Fig. 13.6). How events at the irradiated site lead to a suppressed response to an antigen applied at a distant area of non-UV-exposed skin remained unresolved for many years. Keratinocytes have been recognized as a potent source of various soluble mediators, including immunostimulatory and pro-inflammatory cytokines. Cytokine release by keratinocytes can be effectively induced by UV radiation [3]. UV radiation, however, may also stimulate the release of immunosuppressive mediators since intravenous injection of supernatants obtained from UV-exposed keratinocytes into naïve mice renders the recipients unresponsive to hapten sensitization [4]. Therefore, UV-induced keratinocyte-derived immunosuppressive mediators may enter the circulation and inhibit immune responses at areas of skin not directly exposed to UV radiation, thereby explaining the phenomenon of systemic immunosuppression.

Several mediators appear to be involved in UV-induced immunosuppression. The major player appears to be IL-10, whose release by keratinocytes is induced by UV radiation [5]. IL-10 abrogates the ability of LC to present antigens [6] and injection of IL-10 into an area of skin where hapten has been applied prevents the induction of CHS and induces hapten-specific tolerance [7]. In turn, injection of an anti-IL-10 antibody into UV-irradiated mice prevents systemic UV-induced suppression of the induction of delayed type hypersensitivity [5]. Furthermore, IL-10 induces a shift from a Th1 to a Th2 response; this may explain why UV radiation inhibits primarily Th1 immune reactions and favours development of Th2 reactions [8].

IL-12 is a cytokine which induces a Th1 immune response and which may be regarded as a counter-balance to IL-10 [9]. Thus, it is not surprising that IL-12 has the capacity to prevent UV-induced immunosuppression. Injection of IL-12 before UV exposure enables sensitization even if the antigen is applied onto UV-irradiated skin [10–12]. Even more importantly IL-12 is able to break established UV-induced tolerance, since its injection into UV-tolerized mice renders these animals susceptible to the antigen against which they were tolerized [10,12].

Other soluble mediators, besides IL-10, which appear to be involved in UV-induced immunosuppression are: tumour necrosis factor-α [13,14]; IL-4 [15]; prostaglandin E_2 [15]; calcitonin gene related peptide [16], α melanocyte stimulating hormone [17]; and platelet activating factor (PAF) [18].

References

1 Noonan FP, DeFabo EC, Kripke ML. Suppression of contact hypersensitivity by UV radiation: an experimental model. *Springer Semin Immunopathol* 1981; **4**: 293–304.

2 Noonan FP, DeFabo EC, Kripke ML. Suppression of contact hypersensitivity by UV radiation and its relationship to UV-induced suppression of tumor immunity. *Photochem Photobiol* 1981; **34**: 683–9.

3 Schwarz T, Urbanski A, Luger TA. Ultraviolet light and epidermal cell derived cytokines. In: Luger TA, Schwarz T, eds. *Epidermal Growth Factors and Cytokines*. New York: Marcel Dekker, 1994: 303–63.

4 Schwarz T, Urbanska A, Gschnait F, Luger TA. Inhibition of the induction of contact hypersensitivity by a UV-mediated epidermal cytokine. *J Invest Dermatol* 1986; **87**: 289–91.

5 Rivas JM, Ullrich SE. Systemic suppression of DTH by supernatants from UV-irradiated keratinocytes: an essential role for IL-10. *J Immunol* 1992; **148**: 3133–9.

6 Enk AH, Angeloni VL, Udey MC, Katz SI. Inhibition of Langerhans' cell antigen-presenting function by IL-10. A role for IL-10 in tolerance induction. *J Immunol* 1993; **151**: 2390–8.

7 Enk AH, Saloga J, Becker D *et al*. Induction of hapten-specific tolerance by interleukin 10 in vivo. *J Exp Med* 1994; **179**: 1397–402.

8 Ullrich SE. Mechanisms involved in the systemic suppression of antigen-presenting cell function by UV irradiation. Keratinocyte-derived IL-10 modulates antigen-presenting cell function of splenic adherent cells. *J Immunol* 1994; **152**: 3410–6.

9 Trinchieri G. Interleukin-12 and its role in the generation of Th1 cells. *Immunol Today* 1993; **14**: 335–8.
10 Schmitt DA, Owen-Schaub L, Ullrich SE. Effect of IL-12 on immune suppression and suppressor cell induction by ultraviolet radiation. *J Immunol* 1995; **154**: 5114–20.
11 Müller G, Saloga J, Germann T *et al*. IL-12 as mediator and adjuvant for the induction of contact sensitivity in vivo. *J Immunol* 1995; **155**: 4661–8.
12 Schwarz A, Grabbe S, Aragane Y *et al*. Interleukin-12 prevents UVB-induced local immunosuppression and overcomes UVB-induced tolerance. *J Invest Dermatol* 1996; **106**: 1187–91.
13 Moodycliffe AM, Kimber I, Norval M. Role of tumour necrosis factor-alpha in ultraviolet B light-induced dendritic cell migration and suppression of contact hypersensitivity. *Immunol* 1994; **81**: 79–84.
14 Kurimoto I, Streilein JW. Deleterious effects of cis-urocanic acid and UVB radiation on Langerhans cells and on induction of contact hypersensitivity are mediated by tumor necrosis factor alpha. *J Invest Dermatol* 1992; **99**: 69S–70S.
15 Shreedar V, Giese T, Sung VW, Ullrich SE. A cytokine cascade including prostaglandin E_2, IL-4, and IL-10 is responsible for UV-induced systemic immune suppression. *J Immunol* 1998; **160**: 3783–9.
16 Gillardon F, Moll I, Michel S *et al*. Calcitonin gene-related peptide and nitric oxide are involved in ultraviolet radiation-induced immunosuppression. *Eur J Pharmacol* 1995; **293**: 395–400.
17 Luger TA, Schwarz T, Kalden H *et al*. Role of epidermal cell-derived alpha-melanocyte stimulating hormone in ultraviolet light mediated local immunosuppression. *Ann N Y Acad Sci* 1999; **885**: 209–16.
18 Walterscheid JP, Ullrich SE, Nghiem DX. Platelet-activating factor, a molecular sensor for cellular damage, activates systemic immune suppression. *J Exp Med* 2002; **195**: 171–9.

UV radiation induces immunosuppression in humans

The vast majority of studies in the field of photoimmunology have been performed *in vivo* in animal, usually murine, models. Although numerous *in vitro* studies have been performed with human cells, the key question is whether the observations made in animal models are relevant to the human situation and whether humans are immunosuppressed by UV radiation in a similar fashion. UV-induced tolerance has been shown to occur in humans as well as in animals. Upon low-dose UV radiation, about 45% of UV immunosuppressed humans become tolerant. Tolerance is hapten-specific, since the individuals respond normally upon subsequent immunization against other non-related haptens [1]. Higher doses of UV appear to increase the proportion of individuals that can develop tolerance [2]. However, it is unclear whether all humans can be rendered tolerant by UV radiation; this may be critically dependent on the spectrum, the dose, the timing and on individual predisposition. It remains to be determined whether the UV-susceptible population is at higher risk of developing skin cancer. Indeed, sensitivity to sunburn appears to be associated with susceptibility to UV radiation-induced suppression of cutaneous cell-mediated immunity in humans [3]. Recently, UV-induced immunosuppression has started to be used as a tool to evaluate the potency of sunscreens [4,5].

References

1 Yoshikawa T, Rae V, Bruins-Slot W *et al*. Susceptibility to effects of UVB radiation on induction of contact hypersensitivity as a risk factor for skin cancer in humans. *J Invest Dermatol* 1990; **95**: 530–6.
2 Cooper KD, Oberhelman L, Hamilton TA *et al*. UV exposure reduces immunization rates and promotes tolerance to epicutaneous antigens in humans: Relationship to dose, CD1a-DR^+ epidermal macrophage induction, and Langerhans cell depletion. *Proc Natl Acad Sci USA* 1992; **89**: 8497–501.
3 Kelly DA, Young AR, McGregor JM *et al*. Sensitivity to sunburn is associated with susceptibility to ultraviolet radiation-induced suppression of cutaneous cell-mediated immunity. *J Exp Med* 2000; **191**: 561–6.
4 Damian DL, Halliday GM, Barnetson RS. Broad-spectrum sunscreens provide greater protection against ultraviolet-radiation-induced suppression of contact hypersensitivity to a recall antigen in humans. *J Invest Dermatol* 1997; **109**: 146–51.
5 Moyal DD, Fourtanier AM. Broad-spectrum sunscreens provide better protection from the suppression of the elicitation phase of delayed-type hypersensitivity response in humans. *J Invest Dermatol* 2001; **117**: 1186–92.

Molecular targets mediating UV-induced immunosuppression

Nuclear DNA is a perfect chromophore for both UVB and UVC radiation. UV radiation primarily induces two types of DNA lesions, pyrimidine dimers and (6-4)-photoproducts. Thus UV-induced DNA lesions have been regarded as the major, and for a long time the only, molecular target via which UV radiation exerts its biological effects. UV-induced DNA damage also appears to be critically involved in signalling photoimmunosuppression. This conclusion is supported by studies using DNA repair enzymes applied topically in a liposome-based cream (Fig. 13.6). Application of T4N5 endonuclease, a bacterial DNA repair enzyme, restores the immune response when applied immediately after UV exposure [1]. Similar findings were obtained in humans when the repair enzyme photolyase was applied topically [2].

Despite clear-cut evidence for the crucial role of UV-induced DNA damage in photoimmunosuppression, there are indications that UV radiation may also affect cytoplasmic and membrane targets [3]. UV radiation can directly trigger surface receptors either by inducing their oligomerization [4] or phosphorylation [5].

In addition, the involvement of *cis*-urocanic acid (UCA) indicates that UV-induced immunosuppression can be mediated independently of DNA damage. UCA is an epidermal chromophore involved in mediating UV-induced immunosuppression [6]. UCA, a metabolite of the essential amino acid histidine, accumulates in the epidermis as epidermal cells are devoid of the necessary enzymes to further catabolize it. Two tautomeric forms of UCA exist, *trans* (E)- and *cis* (Z)-UCA. Upon UV exposure UCA is photoisomerized from *trans*- into *cis*-UCA. Tape-stripping of the epidermis, which removes the majority of UCA, prevents UV-induced suppression of the induction of CHS, indicating that *cis*-UCA is involved in photoimmunosuppression [7]. Furthermore, injection of *cis*-UCA partially mimics the immunoinhibitory activity of UV radiation [8]. *Vice versa*, anti-*cis*-UCA antibodies restore particular immune responses after UV exposure [9]. *cis*-UCA also inhibits the presentation of tumour antigens by Langerhans' cells [10]. This effect can be reversed by IL-12 [11]. In addition, injection of *cis*-UCA antibodies reduces the incidence of UV-induced skin tumours in a photocarcinogenesis model indicating the involvement of *cis*-UCA in the generation of UV-induced skin cancer [11].

References

1 Kripke ML, Cox PA, Alas LG, Yarosh DB. Pyrimidine dimers in DNA initiate systemic immunosuppression in UV-irradiated mice. *Proc Natl Acad Sci USA* 1992; **89**: 7516–20.

2 Stege H, Roza L, Vink AA *et al*. Enzyme plus light therapy to repair DNA damage in ultraviolet-B-irradiated human skin. *Proc Natl Acad Sci USA* 2000; **97**: 1790–5.
3 Schwarz T. UV light affects cell membrane and cytoplasmic targets. *J Photochem Photobiol B* 1998; **44**: 91–6.
4 Sachsenmaier C, Radler-Pohl A, Zinck R *et al*. Involvement of growth factor receptors in the mammalian UVC response. *Cell* 1994; **78**: 963–72.
5 Aragane Y, Kulms D, Kothny G *et al*. Ultraviolet light induces apoptosis via direct activation of CD95 (FAS/APO-1) independently from its ligand CD95L. *J Cell Biol* 1998; **140**: 171–82.
6 Norval M, Gibbs NK, Gilmour J. The role of urocanic acid in UV-induced immuno-suppression: recent advances (1992–1994). *Photochem Photobiol* 1995; **62**: 209–17.
7 DeFabo EC, Noonan FP. Mechanism of immune suppression by ultraviolet irradiation in vivo. I. Evidence for the existence of a unique photoreceptor in skin and its role in photoimmunology. *J Exp Med* 1983; **158**: 84–98.
8 Kondo S, Sauder DN, McKenzie RC *et al*. The role of cis-urocanic acid in UVB-induced suppression of contact hypersensitivity. *Immunol Lett* 1995; **48**: 181–6.
9 Moodycliffe AM, Bucana CD, Kripke ML *et al*. Differential effects of a monoclonal antibody to cis-urocanic acid on the suppression of delayed and contact hypersensitivity following ultraviolet irradiation. *J Immunol* 1996; **157**: 2891–9.
10 Beissert S, Mohammad T, Torri H *et al*. Regulation of tumor antigen presentation by urocanic acid. *J Immunol* 1997; **159**: 92–6.
11 Beissert S, Ruhlemann D, Mohammad T *et al*. IL-12 prevents the inhibitory effects of cis-urocanic acid on tumor antigen presentation by Langerhans cells: implications for photocarcinogenesis. *J Immunol* 2001; **167**: 6232–8.

UVA-induced immunosuppression

While UVB is universally found to be immunosuppressive, this is not the case for UVA. There are reports that UVA may protect the immune system from the suppressive effects of UVB [1]. This effect seems to be mediated via interferon-γ [2]. Unlike UVB which has a dose response showing increased levels of immunosuppression with increasing dose, UVA, at least under some circumstances, has a bell-shaped dose–response curve so that after the maximum immunosuppressive dose has been reached, higher doses cause lower levels of immunosuppression until a dose is reached which is no longer suppressive [3]. This refers to dose ranges to which humans can be exposed during normal daily outdoor activities. While this might appear to indicate that UVB is the more important waveband in sunlight for causing immunosuppression, solar-simulated UV-induced immunosuppression dose responses have been reported to be identical to UVA, since absorption of UVB from the irradiation source has no discernible effect on solar-simulated UV-induced immunosuppression [4,5]. Furthermore, numerous studies using sunscreens to filter UVB from solar-simulated UV have shown the importance of UVA within the sunlight spectrum for causing immunosuppression in humans and mice [6,7]. Thus, UVA-1 induced immunosuppression has been used to determine the UVA-1 filtering capacity of sunscreens [8].

References

1 Reeve VE, Bosnic M, Boehm-Wilcox C *et al*. Ultraviolet A radiation (320–400 nm) protects hairless mice from immunosuppression induced by ultraviolet B radiation (280–320 nm) or cis-urocanic acid. *Int Arch Allergy Immunol* 1998; **115**: 316–22.
2 Reeve VE, Bosnic M, Nishimura N. Interferon-gamma is involved in photoimmuno-protection by UVA (320–400 nm) radiation in mice. *J Invest Dermatol* 1999; **112**: 945–50.
3 Byrne SN, Spinks N, Halliday GM. The induction of immunity to a protein antigen using an adjuvant is significantly compromised by ultraviolet A radiation. *J Photochem Photobiol B* 2006; **84**: 128–34.
4 Nghiem DX, Kazimi N, Clydesdale G *et al*. Ultraviolet a radiation suppresses an established immune response: implications for sunscreen design. *J Invest Dermatol* 2001; **117**: 1193–9.
5 Byrne SN, Spinks N, Halliday GM. Ultraviolet A irradiation of C57BL/6 mice suppresses systemic contact hypersensitivity or enhances secondary immunity depending on dose. *J Invest Dermatol* 2002; **119**: 858–64.
6 Bestak R, Barnetson RS, Nearn MR, Halliday GM. Links Sunscreen protection of contact hypersensitivity responses from chronic solar-simulated ultraviolet irradiation correlates with the absorption spectrum of the sunscreen. *J Invest Dermatol* 1995; **105**: 345–51.
7 Damian DL, Halliday GM, Barnetson RS. Broad-spectrum sunscreens provide greater protection against ultraviolet-radiation-induced suppression of contact hypersensitivity to a recall antigen in humans. *J Invest Dermatol* 1997; **109**: 146–51.
8 Moyal DD, Fourtanier AM. Broad-spectrum sunscreens provide better protection from the suppression of the elicitation phase of delayed-type hypersensitivity response in humans. *J Invest Dermatol* 2001; **117**: 1186–92.

Implications of UV-induced immunosuppression

The biological implications of UV-induced immunosuppression may be several-fold. In experimental models it has been demonstrated that UV radiation can inhibit the protective immune response against viral, bacterial and fungal infections. The most frequently used infectious agents to study these phenomena are herpes simplex virus, *Listeria*, *Leishmania*, mycobacteria and *Candida* [1]. Based on these studies there is clear cut-evidence that UV radiation can compromise an immune response against these agents both in a local and a systemic fashion. These models have contributed in an essential way to the further understanding of how UV radiation suppresses the immune system. However, from daily clinical practice we know that acute and severe exacerbations of infectious diseases following solar exposure are extremely rare in humans. The only exception is herpes simplex infection, in which recurrences are frequently observed after solar exposure.

In contrast, bacterial infections are only observed rarely. For defence against bacterial infections the innate immune response which involves granulocytes, complement and, in particular, antimicrobial peptides is much more relevant than the classic adaptive immune response [2]. Preliminary data exist that UV radiation might induce the release of antimicrobial peptides. This could explain why bacterial superinfections are not a major problem upon solar and artificial UV exposures. In this context, it is important to mention that vitamin D, the production of which is induced by UV, has been found to exert antimicrobial activity against mycobacteria via the release of the antimicrobial peptide cathelicidin [3]. Therefore, at this stage, the clinical implications of UV-induced immunosuppression for infectious diseases may be limited.

The immune system protects not only against infection but also malignancy. Transformed cells, particularly in the early stages, can be recognized as 'foreign' and attacked by the immune system (tumour immunology). This may specifically apply to both non-melanoma skin cancer and malignant melanoma. There is clear evidence of an association of susceptibility to skin cancer and immunosuppression. Chronically immunosuppressed individuals, like transplant patients, exhibit a significantly increased risk

of developing skin cancer [4]. This risk increases with the cumulative UV load. In addition, the ability of UV radiation to negate host defences against skin tumours has been convincingly demonstrated in various experimental animal models. Furthermore, restoration or even enhancement of an immune response, for example by topical or systemic application of immunomodulators (interferons, imiquimod), has become an established alternative therapeutic option for the treatment of skin cancer [5]. Taken together, the immunosuppressive impact of UV radiation is probably much more relevant for carcinogenesis than for the exacerbation of infectious diseases.

It is striking that UV radiation at low doses can suppress an immune response [6]. Thus, one may speculate that a certain degree of immunosuppression may be beneficial. The skin is an organ that is constantly exposed to potential allergens; in addition autoimmune responses may be generated within the skin [7,8]. Hence, it is tempting to speculate that a certain degree of regular immunosuppression by daily sun exposure may prevent the induction of these immune responses.

The immunosuppressive effects of UV radiation, however, can also be exploited therapeutically. Phototherapy is a major therapeutic strategy in the treatment of inflammatory skin disease (Chapter 29). Although the mechanisms underlying the beneficial effects of solar/UV exposure in certain diseases remain to be determined, it is obvious that the immunosuppressive properties are essential in this respect [9]. Accordingly, the majority of dermatoses, for example psoriasis and atopic dermatitis, which can be treated with immunosuppressive drugs, respond favourably to phototherapy.

References

1 Chapman RS, Cooper KD, De Fabo EC *et al*. Solar ultraviolet radiation and the risk of infectious disease: summary of a workshop. *Photochem Photobiol* 1995; **61**: 223–47.

2 Harder J, Gläser R, Schröder JM. The role and potential therapeutical applications of antimicrobial proteins in infectious and inflammatory diseases. *Endocr Metab Immune Disord Drug Targets* 2007; **7**: 75–82.

3 Liu PT, Stenger S, Li H *et al*. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. *Science* 2006; **311**: 1770–3.

4 Euvrard S, Kanitakis J, Pouteil-Noble C *et al*. Skin cancers in organ transplant recipients. *Ann Transplant* 1997; **2**: 28–32.

5 Woodmansee C, Pillow J, Skinner RB Jr. The role of topical immune response modifiers in skin cancer. *Drugs* 2006; **66**: 1657–64.

6 Toews GB, Bergstresser PR, Streilein JW. Epidermal Langerhans cell density determines whether contact hypersensitivity or unresponsiveness follows skin painting with DNFB. *J Immunol* 1980; **124**: 445–53.

7 Mehling A, Loser K, Varga G *et al*. Overexpression of CD40 ligand in murine epidermis results in chronic skin inflammation and systemic autoimmunity. *J Exp Med* 2001; **194**: 615–28.

8 Casciola-Rosen LA, Anhalt G, Rosen A. Autoantigens targeted in systemic lupus erythematosus are clustered in two populations of surface structures on apoptotic keratinocytes. *J Exp Med* 1994; **179**: 1317–23.

9 Weichenthal M, Schwarz T. Phototherapy—how does UV work? *Photodermatol Photoimmunol Photomed* 2005; **21**: 260–6.

CHAPTER 14
Wound Healing

E.A. O'Toole[1] *& J.E. Mellerio*[2]

[1]Centre for Cutaneous Research, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK
[2]Genetic Skin Disease Group, St John's Institute of Dermatology, Guy's and St Thomas' NHS Foundation Trust, London, UK

Biological aspects of wound healing, 14.1	Fibroblast recruitment, matrix synthesis and scarring, 14.7	Chronic wounds, 14.11
Inflammation and the immune response, 14.2	Age-related changes in wound healing, 14.9	Leg ulcers, 14.12
Re-epithelialization, 14.4	**Clinical aspects of wound healing, 14.9**	Pressure ulcers, 14.13
Angiogenesis, 14.6	Burns, 14.10	Complications of wound healing, 14.15
		Principles of treating wounds, 14.19

Biological aspects of wound healing

E.A. O'Toole, pp. 14.1–14.9

Introduction

Skin, the largest organ in the body, is vital for humans and animals to protect against dehydration, bleeding and environmental microorganisms. Humans and animals have evolved a sophisticated mechanism of wound healing to plug any gap in skin integrity quickly, re-epithelialize over the defect and rapidly replace the lost dermis with new matrix. The final product is not normal skin, for adult human skin does not regenerate, but rather is a repair in the form of a scar, which is visible on the skin surface.

Adult wound repair consists of a series of overlapping stages [1], beginning with aggregation and degranulation of platelets, blood clotting and the formation of a fibrin plug (eschar), which initially fills the wound (Fig. 14.1). This is followed by the inflammatory phase, where initially polymorphonuclear leukocytes appear, which stimulate the recruitment of monocytes, macrophages and lymphocytes that kill microorganisms and secrete a wide variety of growth factors and cytokines, which modulate the remaining wound healing response. These immune cells invade the fibrin-filled wound space and, together with fibroblasts and blood vessels from the deep fascia and surrounding dermis, begin to lay down a temporary matrix of granulation tissue consisting initially of a proteoglycan- and fibronectin-rich tissue, which serves as a guiding substratum for the migrating and proliferating cells. Cellular behaviour and coordination of the wound response is controlled during this granulation phase by a wide range of growth factors, extracellular matrix molecules and their receptors. There are extensive cell–cell and cell–matrix interactions. Epidermal cells proliferate and move down the edge of the wound until they reach the new granulation tissue, where they dissect between the overlying fibrinous eschar and the underlying granulation tissue to close the wound. At the same time, the wound contracts predominantly by forces exerted by contractile elements contained within myofibroblasts. The transitory granulation tissue phase ends as immune cells, fibroblasts and endothelial cells undergo apoptosis, while the remaining fibroblasts lay down collagen (mostly types I and III), a process that continues for some time. In the final remodelling stage of wound healing, the matrix is remodelled with a decrease in the relative levels of fibronectin, proteoglycans and type III collagen and an increase in the levels of predominantly type I collagen, which is organized into thick bundles and extensively cross-linked to form the mature scar.

Acute wound healing proceeds quickly and with few problems in the vast majority of cases. Clearly, the speed of wound healing depends upon many factors, including the size of the wound (incisional or excisional), blood supply to the area, presence of foreign bodies and microorganisms, age and health of the patient, nutritional status of the patient, drugs that the patient may be taking and a variety of systemic diseases. Oxygen plays a critical part in wound healing [2,3], as does nitric oxide [4]. Leptin may be another regulator of wound healing [5]. Wound healing is subject to regulation by a large number of different cytokines and growth factors [6,7]. Oestrogens promote wound healing, while androgens inhibit it [8–11]. Opioid peptides may also favour wound healing [12].

Sometimes, the wound-healing process does not proceed normally and chronic wounds result. The most common forms of chronic wounds in humans include venous ulcers, diabetic ulcers and pressure sores. In each of these cases there is normally an underlying pathology, such as venous insufficiency in the case of venous ulcers, or abnormal microvasculature and high blood sugar levels in diabetic ulcers. These underlying pathologies create a situation where the wound-healing response is impaired. Thus, for example, in the case of venous stasis ulcers, there is often a chronic ischaemia–reperfusion injury resulting in high levels of local cytokines, complex cuffs forming around the blood vessels and increased levels of wound proteases, particularly metalloproteinase-8 (MMP-8), MMP-26 and elastase, and decreased levels of protease inhibitors such as tissue inhibitor of matrix metalloproteinases (TIMP-2) [13–16]. In the case of diabetic ulcers, there are often extensive abnormalities in the microcirculation, thickening of the blood vessel wall, thrombi and areas of focal necrosis [17].

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

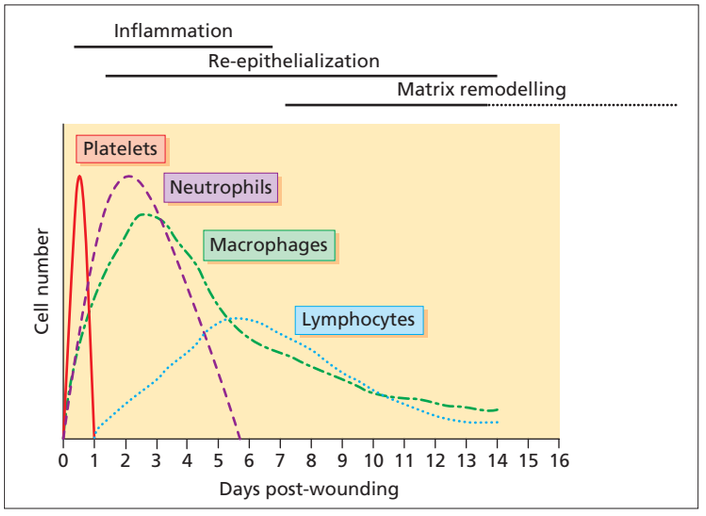


Fig. 14.1 Wound inflammatory cells during the first 2 weeks of wound healing.

In such chronic wounds, it is necessary to treat the underlying pathology if long-term non-recurrent healing of the ulcer is to be achieved. Understanding the molecular pathogenesis of these chronic wound-healing states can lead to novel therapeutic targets for pharmacological intervention (e.g. application of dressings containing protease inhibitors or 'smart matrix'). The wound-healing response can also be disrupted by excessive healing (adverse scarring), which is represented at the extremes by hypertrophic scars or keloids. These excessive wound-healing states result from the abnormal deposition of connective tissue within the healing wound, such that the scar is elevated and may extend beyond the boundaries of the original wound. Excessive scarring shows a clear genetic basis with racial tendencies (e.g. it is more common in black and oriental people than it is in white people).

Finally, the acute wound-healing response varies with the age of the individual. Wounds made on very early embryos heal by complete regeneration, while wounds made on later embryos or early fetuses (in the middle trimester of pregnancy) display scar-free healing but absence of regeneration of dermal appendages. Embryonic wounds exhibit a markedly reduced inflammatory response, alterations in cellular mediators, cytokines, growth factors, extracellular matrix modulators, tyrosine phosphorylation patterns and homeobox gene expression [18]. Wounds in children and young adults often heal quickly with excessive scarring, while elderly patients show specific disruptions in the wound-healing cascade, such as elevated levels of proteases, altered ratios of growth factors and their receptors and a slower rate of healing but often with enhanced quality (reduced scarring). Age-related changes in the inflammatory response to wounding have been reported [19]. Wound healing is impaired by stress, possibly due to increased serum cortisol [20].

Despite the fact that the various phases of wound healing overlap, it is convenient to consider the principal cellular and molecular mechanisms regulating the basic biology of wound healing in three phases: inflammation and the immune response, re-epithelialization, and matrix remodelling (see Fig. 14.1).

References

1 Clark RAF, ed. *The Molecular and Cellular Biology of Wound Repair*, 2nd edn. New York: Plenum Press, 1996: 3–50.
2 Albina JE, Reichner JS. Oxygen and the regulation of gene expression in wounds. *Wound Repair Regen* 2003; **11**: 445–51.
3 Gordillo GM, Sen CK. Revisiting the essential role of oxygen in wound healing. *Am J Surg* 2003; **186**: 259–63.
4 Schffer M, Bongartz M, Fischer S *et al*. Nitric oxide restores impaired healing in normoglycaemic diabetic rats. *J Wound Care* 2007; **16**: 311–6.
5 Murad A, Nath AK, Cha ST *et al*. Leptin is an autocrine/paracrine regulator of wound healing. *FASEB J* 2003; **17**: 1895–7.
6 Werner S, Grose R. Regulation of wound healing by growth factors and cytokines. *Physiol Rev* 2003; **83**: 835–70.
7 Li J, Chen J, Kirsner R. Pathophysiology of acute wound healing. *Clin Dermatol* 2007; **25**: 9–18.
8 Ashcroft GS, Mills SJ, Lei K *et al*. Estrogen modulates cutaneous wound healing by downregulating macrophage migration inhibitory factor. *J Clin Invest* 2003; **111**: 1309–18.
9 Gilliver SC, Ashworth JJ, Ashcroft GS. The hormonal regulation of cutaneous wound healing. *Clin Dermatol* 2007; **25**: 56–62.
10 Gilliver SC, Ashworth JJ, Mills SJ *et al*. Androgens modulate the inflammatory response during acute wound healing. *J Cell Sci* 2006; **119**: 722–32.
11 Ashcroft GS, Mills SJ. Androgen receptor-mediated inhibition of cutaneous wound healing. *J Clin Invest* 2002; **110**: 615–24.
12 Poonawala T, Levay-Young BK, Hebbel RP, Gupta K. Opioids heal ischemic wounds in the rat. *Wound Repair Regen* 2005; **13**: 165–74.
13 Etufugh CN, Phillips TJ. Venous ulcers. *Clin Dermatol* 2007; **25**: 121–30.
14 Herrick SE, Ashcroft G, Ireland G *et al*. Up-regulation of elastase in acute wounds of healthy aged humans and chronic venous leg ulcers are associated with matrix degradation. *Lab Invest* 1997; **77**: 281–8.
15 Pirilä E, Korpi JT, Korkiamäki T *et al*. Collagenase-2 (MMP-8) and matrilysin-2 (MMP-26) expression in human wounds of different etiologies. *Wound Repair Regen* 2007; **15**: 47–57.
16 Vaalamo M, Leivo T, Saarialho-Kere U. Differential expression of tissue inhibitors of metalloproteinases (TIMP-1, -2, -3, and -4) in normal and aberrant wound healing. *Hum Pathol* 1999; **30**: 795–802.
17 Ferguson MWJ, Herrick SE, Spencer MJ *et al*. The histology of diabetic ulcers. *Diabet Med* 1996; **13**: 530–3.
18 Yannas IV, Kwan MD, Longaker MT. Early fetal healing as a model for adult organ regeneration. *Tissue Eng* 2007; **13**: 1789–98.
19 Gosain A, DiPietro LA. Aging and wound healing. *World J Surg* 2004; **28**: 321–6.
20 Ebrecht M, Hextall J, Kirtley LG *et al*. Perceived stress and cortisol levels predict speed of wound healing in healthy male adults. *Psychoneuroendocrinology* 2004; **29**: 798–809.

Inflammation and the immune response

Following wounding, there is almost immediate release of inflammatory mediators from damaged cells, degranulating platelets or resident tissue macrophages and mast cells. Furthermore, wounding causes a transient permeabilization of cells near the wound margin, with the rapid exchange of extracellular and intracellular ions, resulting in the switching on of early response genes in such cells within seconds following wounding. These mediators initially cause arteriole dilatation, resulting in an increased blood flow into the wound area. This process is further aided by growth factors such as vascular endothelial growth factor (VEGF), which causes hyperpermeability of endothelial cells [1]. This results in an influx of fluid and plasma components into the wound space, while inflammatory cells adhere to the vascular endothelium and migrate through the vascular wall into the wound.

Neutrophils are the predominant, initial inflammatory cells recruited to the wound, which together with platelets release a complex mixture of cytokines and growth factors. These amplify

the inflammatory response resulting in an influx of monocytes and lymphocytes, the proliferation of monocyte precursors within the wound and their differentiation into mature macrophages [2]. The use of knock-out mouse models to dissect the contribution of individual cytokines to wound repair revealed important roles for tumour necrosis factor-alpha (TNF-α), interleukin-1 signalling, CXCR2, IP-10, Smad3 and secretory leukocyte protease inhibitor in the inflammatory cell recruitment in acute wound healing [2,3].

Platelets respond very quickly, and when they reach the wound they adhere through selectin and integrin receptors [4], degranulate and release a variety of factors, including thromboxanes, prostaglandins, 12-lipoxygenase products, serotonin, adhesive glycoproteins including fibrinogen, Von Willebrand factor, fibronectin and thrombospondin and growth factors including platelet-derived growth factor (PDGF), epidermal growth factor (EGF) and transforming growth factor-β1 (TGF-β1). These factors both contribute to the initial fibrin plug that closes the wound and modulate subsequent cellular behaviour, including attachment, migration, proliferation and matrix deposition. However, wound closure, angiogenesis and collagen synthesis are not significantly impaired in thrombocytopenic mice [5].

These signals from the wound site, together with changes in vascular permeability, cause leukocytes to pavement in the blood vessels, undergo rolling and attachment to activated endothelial P- and E-selectins and integrins, for example heterodimers of CD18 (β2 integrin) and variable α subunits [4,6]. Neutrophils, recruited early in wound healing, are responsible for destroying invading bacteria by phagocytosis and release of reactive oxygen species, eicosanoids and proteolytic enzymes (elastase, cathepsin G, urokinase-type plasminogen activator), which may cause further tissue damage and inflammation. Once in the wound, neutrophils may be activated by cytokines such as granulocyte–macrophage colony-stimulating factor (GM-CSF) and tumour necrosis factor-α (TNF-α), complement or proteases such as thrombin. Unless stimuli for neutrophil recruitment persist, after a few days neutrophils are eliminated by macrophage phagocytosis or apoptopic cell death [7]. Monocytes and macrophages are recruited in large numbers to the healing wound as neutrophil numbers begin to decline. Classic studies by Leibovich and Ross [8] demonstrated the importance of these cells in wound healing; experimental depletion of wound macrophages resulted in prolonged inflammation and delays in fibroblast proliferation, matrix deposition and subsequent wound closure. The transition from a resting to an active state in monocytes and macrophages is controlled by cytokines such as TNF-α and IFN-γ, as well as bacterial products such as lipopolysaccharide. Monocytes and macrophages produce a range of cytokines in response to pro-inflammatory signals, including TGF-β and TGF-α, basic fibroblast growth factor, VEGF and PDGF. The interactions between these growth factors and monocyte/macrophage differentiation/activation is complex and often self-regulatory. Thus, TGF-β1 acts as a pro-inflammatory cytokine early in the wound-healing phase, as it is chemotactic to immature monocytes, which are recruited to the wound site, and synthesize and secrete more TGF-β1, due to a self-inducing response element in the TGF-β1 promoter. However, TGF-β1 is anti-inflammatory to mature or activated monocytes/macrophages, because it inhibits their activation and modulates receptor expression. Although wound healing is initially normal in the TGF-β1 knockout mouse, accumulation of inflammatory cells and reduction in angiogenesis and collagen deposition lead to delayed epithelial closure [9].

In addition to the production of cytokines, wound macrophages also produce a range of extracellular matrix molecules, which, together with fibrinogen and fibrin from the blood clot, matrix molecules from degranulating platelets, recruited fibroblasts and endothelial cells, form the granulation tissue or provisional matrix. This provisional matrix is rich in molecules, such as fibronectin, vitronectin, thrombospondin, SPARC (osteonectin), tenascin and proteoglycans such as dermatan, chondroitin and heparan sulphate. It acts as an early scaffold for the re-establishment of the dermis and for the migration of epidermis as it promotes both cell migration and proliferation [10]. Regulation of this provisional matrix is complex, and achieved partially through control at the transcriptional level, for example with alternative splicing of the primary transcript for fibronectin resulting in embryonic-like cellular fibronectins being deposited within the wound space, which better facilitate cell migration and proliferation [11].

Pro-inflammatory cytokines such as TNF-α and IFN-γ can stimulate the production of chemokines by endothelial cells [12]. Endothelial and macrophage chemokines (e.g. IL-8, IP-10, PF-4, MIP-1α, MIP-1β, RANTES and MCP-1) attract lymphocytes to the wound area, and may have a role in the progression of healing to fibrosis [3]. These lymphocytes include both B and T lymphocytes, and there is growing evidence that the particular type of T-lymphocyte response (Th1 or Th2), each characterized by a different profile of cytokine secretion, may be one of the factors underlying abnormal fibrosis and scarring [13]. Human γ/δ T lymphocytes express and synthesize connective tissue growth factor (CTGF), known to regulate fibrogenesis and wound healing, as well as FGF-7, -10 and IGF-1 regulating keratinocyte differentiation and proliferation [14]. In addition, this T-cell subgroup regulates keratinocyte hyaluronic acid deposition in the provisional matrix, and subsequent macrophage infiltration into the wound [15]. The type of T-lymphocyte response itself may be determined by the profile of growth factors in the early wound. Thus, for example, natural killer (NK) cell migration out of blood vessels is promoted by VEGF but inhibited by FGF-2 [16]. IL-6 also has a crucial role in wound healing, probably by regulating early leukocyte infiltration and tissue remodelling in the later stages of wound repair [17]. Recent *in vivo* functional studies reveal the roles of different transcriptional regulators in wound repair. Mice deficient for PU.1 transcription factor, that lack macrophages and functional neutrophils, surprisingly showed normal scar-free healing of incisional wounds [18]. Mice deficient in Nrf2, a leucine zipper transcription factor involved in detoxification of reactive oxygen species, have increased and prolonged macrophage infiltration in wounds, suggesting that Nrf2 regulates resolution of inflammation [19].

These early inflammatory responses clear the wound of foreign antigens such as bacteria and supply combinations of growth factors and extracellular matrix molecules, which orchestrate the subsequent healing of the provisional matrix by providing the signals and scaffold for fibroblast, endothelial and keratinocyte influx. Inflammatory cells such as monocytes and macrophages

decrease towards the end of the inflammatory phase, largely through apoptosis resulting from diminution of the levels of survival factors (e.g. specific cytokines and matrix molecules).

References

1 Eming SA, Krieg T. Molecular mechanisms of VEGF-A action during tissue repair. *J Invest Dermatol Symp Proc* 2006; **11**: 79–86.
2 Eming SA, Krieg T, Davidson JM. Inflammation in wound repair: molecular and cellular mechanisms. *J Invest Dermatol* 2007; **127**: 514–25.
3 Ishida Y, Kondo T, Kimura A, Matsushima K, Mukaida N. Absence of IL-1 receptor antagonist impaired wound healing along with aberrant NF-kappaB activation and a reciprocal suppression of TGF-beta signal pathway. *J Immunol* 2006; **176**: 5598–606.
4 Subramaniam M, Saffaripour S, Van De Water L *et al.* Role of endothelial selectins in wound repair. *Am J Pathol* 1997; **150**: 1701–9.
5 Szpaderska AM, Egozi EI, Gamelli RL, DiPietro LA. The effect of thrombocytopenia on dermal wound healing. *J Invest Dermatol* 2003; **120**: 1130–7.
6 Peters T, Sindrilaru A, Hinz B *et al*. Wound-healing defect of CD18(−/−) mice due to a decrease in TGF-beta1 and myofibroblast differentiation. *EMBO J* 2005; **24**: 3400–10.
7 Haslett C, Henson P. Resolution of inflammation. In: Clark RAF, ed. *The Molecular and Cellular Biology of Wound Repair*. New York: Plenum Press, 1996: 143–96.
8 Leibovich SJ, Ross R. The role of the macrophage in wound repair. *Am J Pathol* 1975; **78**: 71–100.
9 Wang XJ, Han G, Owens P *et al.* Role of TGF beta-mediated inflammation in cutaneous wound healing. *J Investig Dermatol Symp Proc* 2006; **11**: 112–7.
10 Yamada KM, Clark RAF. Provisional matrix. In: Clark RAF, ed. *The Molecular and Cellular Biology of Wound Repair*. New York: Plenum Press, 1996: 51–83.
11 Muro AF, Chauhan AK, Gajovic S *et al.* Regulated splicing of the fibronectin EDA exon is essential for proper skin wound healing and normal lifespan. *J Cell Biol* 2003; **162**: 49–60.
12 Gillitzer R, Goebeler M. Chemokines in cutaneous wound healing. *J Leukoc Biol* 2001; **69**: 513–21.
13 Park JE, Barbul A. Understanding the role of immune regulation in wound healing. *Am J Surg* 2004; **187**: 11S–6S.
14 Sharp LL, Jameson JM, Cauvi G *et al.* Dendritic epidermal T cells regulate skin homeostasis through local production of insulin-like growth factor 1. *Nat Immunol* 2005; **6**: 73–9.
15 Jameson JM, Cauvi G, Sharp LL *et al.* Gammadelta T cell-induced hyaluronan production by epithelial cells regulates inflammation. *J Exp Med* 2005; **201**: 1269–79.
16 Melder RJ, Koenig GC, Witver BP *et al.* During angiogenesis, vascular endothelial growth factor and basic fibroblast growth factor regulate natural killer cell adhesion to tumor endothelium. *Nat Med* 1996; **2**: 992–7.
17 Gallucci RM, Lee EG, Tomasek JJ. IL-6 modulates alpha-smooth muscle actin expression in dermal fibroblasts from IL-6-deficient mice. *J Invest Dermatol* 2006; **126**: 561–8.
18 Martin P, D'Souza D, Martin J *et al*. Wound healing in the PU.1 null mouse-tissue repair is not dependent on inflammatory cells. *Curr Biol* 2003; **13**: 1122–8.
19 Braun S, Hanselmann C, Gassmann MG *et al.* Nrf2 transcription factor, a novel target of keratinocyte growth factor action which regulates gene expression and inflammation in the healing skin wound. *Mol Cell Biol* 2002; **22**: 5492–505.

Re-epithelialization

The process of re-epithelialization commences about 24 hours after wounding when keratinocytes migrate from the wound edge or hair follicles across the provisional wound matrix to invade the wound bed, where they proliferate to form new epidermis [1]. Keratinocyte injury alters the ratio of magnesium and calcium ions, which induces keratinocytes to adopt a migratory phenotype [2]. The migrating keratinocyte flattens and elongates with formation of lamellipodia to aid cell movement, loss of cell–cell (desmosomes) and cell–matrix contacts and rearrangement of the actin filament network. The K1 and K10 suprabasal cytokeratin filaments are replaced by the flexible cytokeratins K6 and K16, whose expression is regulated by growth factors such as EGF, TGF-α and TGF-β present at high levels within the provisional matrix [3].

Following wounding, signals from the matrix and growth factors induce phosphorylation of numerous keratinocyte proteins, including focal adhesion kinase, c-Met, the small guanine triphosphatase, Rac, extracellular signal-regulated kinases 1/2, phosphatidylinositol 3-kinase, mitogen-activated protein kinase kinase kinase 1 and p38 mitogen-activated protein kinase, and the downstream AP-1 and Stat3 families of transcription factors which regulate many of the genes involved in keratinocyte migration, for example integrins, MMPs and growth factors [4–10]. TNF-α stimulates transcription of the PPARβ/δ (peroxisome-proliferator-activated receptor β/δ) gene, also via an AP-1 site in its promoter, with subsequent up-regulation of the expression of integrin-linked kinase and 3-phosphoinositide-dependent kinase-1, which activates the anti-apoptotic protein, Akt [11]. Keratinocytes in the basal layer some 300–400 cell diameters away from the wound margin proliferate extensively; such proliferation peaks within 1–2 days post-wounding and then falls back again to reach basal levels about 14 days post-wounding. The transcription factor, c-Myc, is a potent regulator of keratinocyte proliferation during wound healing [12]. Suprabasal cells derived from this extensive proliferation roll over the attached basal cells to form new basal cells at the wound margin, a process repeated by successive basal cells until re-epithelialization is complete.

To reach the wound bed, migrating keratinocytes express metalloproteinases (MMPs) (enzymes that degrade basement membrane components and interstitial collagens) and urokinase-type plasminogen activator, an enzyme which activates plasmin for fibrinolysis of fibrin [13,14]. Up-regulation of MMP-9 and urokinase plasminogen activator, induced by hypoxia, result in increased keratinocyte migration [15,16]. This up-regulation is mirrored by the concurrent up-regulation of plasminogen-activator inhibitors, which control the extent of plasminogen activation [16]. This suggests a key role for the plasmin–plasminogen system in wound healing, an assertion given experimental weight by wound-healing studies on mice with targeted disruption of the plasminogen gene [17]. These mice show substantial delays in wound re-epithelialization and the aberrant persistence of fibrin within the wound matrix, demonstrating the importance of the plasminogen–plasmin system for fibrin removal during wound healing. Syndecan-1 is a cell-surface proteoglycan that enhances keratinocyte proliferation and re-epithelialization [18].

During wound healing, the migrating keratinocytes come into contact with dermal collagens and the fibrin clot constituents fibrin, fibronectin and vitronectin. Thus, α5, β1, αV and β5 integrins, the primary keratinocyte receptors for fibronectin and vitronectin, are up-regulated in migrating keratinocytes during re-epithelialization [19]. Expression of these integrins may be induced by TGF-β1 [20]. Once re-epithelialization is complete, the keratinocytes switch from the vitronectin/fibronectin receptor (αVβ5) to the tenascin/fibronectin receptor (αVβ6), a switch that may be involved in the redifferentiation of the epidermis, as the β6 integrin has been associated with epithelial remodelling during

Table 14.1 Main source of growth factors/cytokines during wound healing.

	Platelet	Macrophage	Lymphocyte	Keratinocyte	Fibroblast	Endothelial cells
PDGF	X	X			X	X
VEGF	X	X			X	X
EGF	X	X				
FGF-1/2		X	X			X
FGF-7					X	
IGF-1	X				X	
HGF					X	
TNF-α		X	X			X
TGF-α	X	X		X		
TGF-β		X	X	X	X	
GM-CSF		X				
IFN-γ			X	X		
IL-1β		X	X	X		
IL-2		X	X	X		
IL-6		X	X	X		
IL-8		X	X	X		

Table 14.2 Function of cytokines/growth factors in acute wounds.

	Leukocyte chemotaxis	Re-epithelialization	Angiogenesis	Wound remodelling
PDGF	+	++	++	++
VEGF			+	
EGF	+	+++	+	+
FGF-1/2		+	+++	+
FGF-7		+++		+
HGF	+	+++	++	+
IGF-1			++	
TNF-α	++			
TGF-α		++	++	
TGF-β		+	+	
GM-CSF	+			
IFN-γ	+			
IL-1β	+++	+		++
IL-6				+
IL-8	++	++	++	

development and tumourigenesis [21]. Because keratinocytes do not express the fibrin-specific integrin, αVβ3, instead of invading the fibrin clot, the migrating cells dissect the fibrin clot from the wound bed [22].

A number of growth factors secreted by keratinocytes, fibroblasts or inflammatory cells promote keratinocyte proliferation and migration (see Table 14.1 and Table 14.2 and references [23–26]). Fibroblast growth factor-7 (FGF-7/KGF) stimulates hyaluronan synthesis, which also promotes keratinocyte migration [27]. The antimicrobial peptides, human beta-defensins, stimulate epidermal keratinocyte migration, proliferation and production of pro-inflammatory cytokines [28]. Secreted heat shock protein-90α induced by TGF-α, promotes both epidermal and dermal cell migration [29]. Keratinocytes can stimulate FGF-7 production by underlying dermal cells, which then acts specifically on the overlying epidermal cells expressing the FGF-7 receptor [30]. During wounding, cells come into contact with human serum, which promotes keratinocyte motility via p38 MAP kinase and induction of epidermal MMP expression [31].

In normal skin, the basement membrane separates the epidermis from the dermis. Following wounding, this dermal–epidermal junction must be reconstituted as part of the re-epithelialization process. Basal lamina components, such as type IV collagen, laminin and heparan sulphate, are synthesized and deposited into the dermal–epidermal junction by both the fibroblasts and the keratinocytes, and a scanty basement membrane is usually present by 7 to 9 days after wounding [32,33]. Maturation of anchoring fibrils may take up to 3 years [34].

References

1 Coulombe PA. Wound epithelialization: accelerating pace of discovery. *J Invest Dermatol* 2003; **121**: 219–30.

2 Satish L, Blair HC, Glading A, Wells A. Interferon-inducible protein 9 (CXCL11)-induced cell motility in keratinocytes requires calcium flux-dependent activation of mu-calpain. *Mol Cell Biol* 2005; **25**: 1922–41.

3 Jiang CK, Magnaldo T, Ohtsuki M *et al.* Epidermal growth factor and transforming growth factor-α specifically induce the activation- and hyperproliferation-associated keratins 6 and 16. *Proc Natl Acad Sci USA* 1993; **90**: 6786–90.

4 Fitsialos G, Chassot AA, Turchi L *et al.* Transcriptional signature of epidermal keratinocytes subjected to *in vitro* scratch wounding reveals selective roles for ERK1/2, p38, and phosphatidylinositol 3-kinase signaling pathways. *J Biol Chem* 2007; **282**: 15090–102.

5 Chmielowiec J, Borowiak M, Morkel M *et al*. c-Met is essential for wound healing in the skin. *J Cell Biol* 2007; **177**: 151–62.

6 Tscharntke M, Pofahl R, Chrostek-Grashoff A *et al*. Impaired epidermal wound healing *in vivo* upon inhibition or deletion of Rac1. *J Cell Sci* 2007; **120**: 1480–90.

7 Deng M, Chen WL, Takatori A *et al*. A role for the mitogen-activated protein kinase kinase kinase 1 in epithelial wound healing. *Mol Biol Cell* 2006; **17**: 3446–55.

8 Li W, Nadelman C, Henry G *et al.* The p38-MAPK/SAPK pathway is required for human keratinocyte migration on dermal collagen. *J Invest Dermatol* 2001; **117**: 1601–11.

9 Sano S, Itami S, Takeda K *et al.* Keratinocyte specific ablation of Stat3 exhibits impaired skin remodelling but does not affect skin morphogenesis. *EMBO J* 1999; **18**: 4657–68.

10 Yates S, Rayner TE. Transcription factor activation in response to cutaneous injury: role of AP-1 in re-epithelialization. *Wound Repair Regen* 2002; **10**: 5–15.

11 Di-Poi N, Tan NS, Michalik L *et al*. Anti-apoptotic role of PPARβ in keratinocytes via transcriptional control of the Akt1 pathway. *Mol Cell* 2002; **10**: 721–33.

12 Zanet J, Pibre S, Jacquet C *et al*. Endogenous Myc controls mammalian epidermal cell size, hyperproliferation, endoreplication and stem cell amplification. *J Cell Sci* 2005; **118**: 1693–704.

13 Morris VL, Chan BM. Interaction of epidermal growth factor, Ca^{2+}, and matrix metalloproteinase-9 in primary keratinocyte migration. *Wound Repair Regen* 2007; **15**: 907–15.

14 Romer J, Lund LR, Eriksen J *et al.* Differential expression of urokinase-type plasminogen activator and its type-1 inhibitor during healing of mouse skin wounds. *J Invest Dermatol* 1991; **97**: 803–11.

15 O'Toole EA, van Koningsveld R, Chen M, Woodley DT. Hypoxia induces epidermal keratinocyte matrix metalloproteinase-9 secretion via the protein kinase C pathway. *J Cell Physiol* 2008; **214**: 47–55.

16 Daniel RJ, Groves RW. Increased migration of murine keratinocytes under hypoxia is mediated by induction of urokinase plasminogen activator. *J Invest Dermatol* 2002; **119**: 1304–9.

17 Romer J, Bugge TH, Pyke C *et al.* Impaired wound healing in mice with a disrupted plasminogen gene. *Nat Med* 1996; **2**: 287–92.

18 Ojeh N, Hiilesvuo K, Wärri A *et al*. Ectopic expression of syndecan-1 in basal epidermis affects keratinocyte proliferation and wound re-epithelialization. *J Invest Dermatol* 2008; **128**: 26–34.

19 Clark RAF. Fibronectin matrix deposition and fibronectin receptor expression in healing and normal skin. *J Invest Dermatol* 1990; **94**: 128–34S.

20 Gailit G, Welch MP, Clark RAF. TGF-β1 stimulates expression of keratinocyte integrins during re-epithelialization of cutaneous wounds. *J Invest Dermatol* 1994; **103**: 221–7.

21 Clark RAF, Ashcroft GS, Spencer MJ *et al.* Re-epithelialization of normal excisional wounds is associated with a switch from αVβ5 to αVβ6 integrins. *Br J Dermatol* 1996; **13**: 46–51.

22 Kubo M, Van De Water L, Plantefaber LC *et al.* Fibrinogen and fibrin are anti-adhesive for keratinocytes: a mechanism for fibrin eschar slough during wound repair. *J Invest Dermatol* 2001; **117**: 1369–81.

23 Li Y, Fan J, Chen M, Li W, Woodley DT. Transforming growth factor-alpha: a major human serum factor that promotes human keratinocyte migration. *J Invest Dermatol* 2006; **126**: 2096–105.

24 Bandyopadhyay B, Fan J, Guan S *et al.* A 'traffic control' role for TGFbeta3: orchestrating dermal and epidermal cell motility during wound healing. *J Cell Biol* 2006; **172**: 1093–105.

25 Shirakata Y, Kimura R, Nanba D *et al.* Heparin-binding EGF-like growth factor accelerates keratinocyte migration and skin wound healing. *J Cell Sci* 2005; **118**: 2363–70.

26 Broughton G 2nd, Janis JE, Attinger CE. The basic science of wound healing. *Plast Reconstr Surg* 2006; **117**: 12S–34S.

27 Karvinen S, Pasonen-Seppanen S, Hyttinen JM *et al.* Keratinocyte growth factor stimulates migration and hyaluronan synthesis in the epidermis by activation of keratinocyte hyaluronan synthases 2 and 3. *J Biol Chem* 2003; **278**: 49495–504.

28 Niyonsaba F, Ushio H, Nakano N *et al*. Antimicrobial peptides human beta-defensins stimulate epidermal keratinocyte migration, proliferation and production of proinflammatory cytokines and chemokines. *J Invest Dermatol* 2007; **127**: 594–604.

29 Cheng CF, Fan J, Fedesco M *et al*. Transforming growth factor alpha (TGFalpha)-stimulated secretion of HSP90alpha: using the receptor LRP-1/CD91 to promote human skin cell migration against a TGFbeta-rich environment during wound healing. *Mol Cell Biol* 2008; **28**: 3344–58.

30 Werner S, Peters KG, Lonkager MT *et al.* Large induction of keratinocyte growth factor expression in the dermis during wound healing. *Proc Natl Acad Sci USA* 1992; **89**: 6896–900.

31 Henry G, Li W, Garner W *et al.* Migration of human keratinocytes in plasma and serum and wound re-epithelialization. *Lancet* 2003; **361**: 574–6.

32 Regauer S, Seiler GR, Barrandon Y *et al.* Epithelial origin of cutaneous anchoring fibrils. *J Cell Biol* 1990; **111**: 2109–15.

33 Fleischmajer R, Utani A, MacDonald ED *et al.* Initiation of skin basement membrane formation at the epidermo-dermal interface involves assembly of laminins through binding to cell membrane receptors. *J Cell Sci* 1998; **111**: 1929–40.

34 Compton CC, Press W, Gill JM *et al.* The generation of anchoring fibrils by epidermal keratinocytes: a quantitative long-term study. *Epithelial Cell Biol* 1995; **4**: 93–103.

Angiogenesis

Formation of new blood vessels within the provisional matrix is stimulated by day 2 of the inflammatory stage of wound healing. Immediately following injury, angiogenic growth factors including VEGF, PDGF, FGFs and TGF-β are secreted by platelets, fibroblasts, wounded keratinocytes and macrophages [1,2]. Vascular endothelial growth factor induces endothelial cell proliferation and migration through three receptors, VEGFR-1/Flt1, VEGFR-2 and Neuropilin-1 [3,4]. Periostin, a known inducer of VEGFR-2 expression which plays a role in regulating vascular smooth muscle cell migration, was recently shown to be 96-fold upregulated in wound vessels compared to normal blood vessels [5]. The sprouting endothelial cells participate in granulation tissue formation (the capillary loops within the provisional matrix give granulation tissue its red granular appearance). Hypoxia and reactive oxygen species also regulates VEGF expression via the activation of hypoxia-inducible factor-1α, which is strongly expressed by keratinocytes at the wound edge, and the Sp1 transcription factor, respectively [6,7]. Endothelial cells from nearby blood vessels and, in larger wounds, endothelial progenitor cells from bone marrow, activated by VEGF and mobilized by the CXCR4 ligand, SDF-1 (stromal cell-derived factor 1), move to the wound bed [8].

Laminin 411 (laminin 8) and laminin 511 (laminin 10) are the major laminin isoforms in the basement membrane of dermal microvascular endothelial cells [9]. Laminin 8 promotes endothelial cell attachment, migration and tubule formation. Endothelial cells use both β1-containing and αvβ3 integrins in their interactions with the G1-3 domains of the α4 chain of laminin 8 [10,11]. Proteolytic enzymes, for example MMPs, are released at the growing tips of capillaries, degrading the ECM for forward movement [12]. Ephrin ligand–receptor interactions guide the patterning of vascular loops and tubes [13].

Adequate revascularization of the wound is essential for healing; ineffective angiogenesis results in impaired wound healing. At the end of the provisional matrix phase, the numbers of blood vessels within the healing wound decrease by a process of apoptosis,

probably induced by depletion of vascular survival factors, such as VEGF, and the appearance of pro-apoptotic factors such as TGF-β [14].

References

1 Li J, Chen J, Kirsner R. Pathophysiology of acute wound healing. *Clin Dermatol* 2007; **25**: 9–18.
2 Nissen NN, Polverini PJ, Koch AE *et al.* Vascular endothelial growth factor mediates angiogenic activity during the proliferative phase of wound healing. *Am J Pathol* 1998; **152**: 1445–52.
3 Ferrera N. VEGF: basic science and clinical progress. *Endocr Rev* 2004; **25**: 581–611.
4 Matthies AM, Low QE, Lingen MW, DiPietro LA. Neuropilin-1 participates in wound angiogenesis. *Am J Pathol* 2002; **160**: 289–96.
5 Roy S, Patel D, Khanna S *et al*. Transcriptome-wide analysis of blood vessels laser captured from human skin and chronic wound-edge tissue. *PNAS* 2007; **104**: 14472–7.
6 Schafer M, Werner S. Transcriptional control of wound repair. *Annu Rev Cell Dev Biol* 2007; **23**: 69–92.
7 Sen CK, Khanna S, Babior BM *et al.* Oxidant-induced vascular endothelial growth factor expression in human keratinocytes and cutaneous wound healing. *J Biol Chem* 2002; **277**: 33284–90.
8 Grunewald M, Avraham I, Dor Y *et al*. VEGF-induced adult neovascularization: recruitment, retention, and role of accessory cells. *Cell* 2006; **124**: 175–89.
9 Li J, Zhou L, Tran HT *et al.* Overexpression of laminin 8 in human dermal microvascular cells promotes angiogenesis-related functions. *J Invest Dermatol* 2006; **126**: 432–40.
10 Feng X, Clark RA, Galanakis D *et al*. Fibrin and collagen differentially regulate human dermal microvascular endothelial cell integrins: stabilization of alphaV/beta3 mRNA by fibrin 1. *J Invest Dermatol* 1999; **113**: 913–9.
11 Gonzales M, Weksler B, Tsurata D *et al*. Structure and function of a vimentin-associated matrix adhesion in endothelial cells. *Mol Biol Cell* 2001; **12**: 85–100.
12 Cornelius LA, Nehring LC, Roby JE *et al*. Human dermal microvascular endothelial cells produce matrix metalloproteinases in response to angiogenic factors and migration. *J Invest Dermatol* 1995; **105**: 170–6.
13 Cheng N, Brantley DM, Chen J. The ephrins and Eph receptors in angiogenesis. *Cytokine Growth Factor Rev* 2002; **13**: 75–85.
14 Gerber HP, Dixit V, Ferrara N. Vascular endothelial growth factor induces expression of the antiapoptotic proteins Bcl-2 and A1 in vascular endothelial cells. *J Biol Chem* 1998; **273**: 13313–6.

Fibroblast recruitment, matrix synthesis and scarring

The fibroblasts migrate into, and proliferate within, the provisional wound matrix, depositing additional extracellular matrix molecules. Most wound fibroblasts are derived from proliferation of fibroblast progenitor cells in the deep dermis and the septae of the underlying fat; relatively few cells are derived from the margins of the surrounding dermis [1]. Like the keratinocytes, they alter their integrin profile, expressing receptors for fibronectin, fibrin and vitronectin and down-regulating receptors for collagen during the early phases of migration [2,3]. During the early stages of provisional matrix deposition, collagen synthesis in the surrounding unwounded skin is suppressed, while fibronectin synthesis is enhanced [2]. Fibroblasts within the provisional matrix secrete and assemble a complex extracellular matrix. Initially, this consists predominantly of fibronectin and proteoglycans, but later consists of mature type I collagen bundles. The ratio of collagen types during wound healing varies, the early wound being characterized by elevated levels of type III collagen, whereas later in wound healing type I collagen predominates. Minor collagens, such as types 12 and 14, as well as proteoglycans such as decorin, are also present in the early healing wound and play a key part in collagen fibril organization. The degree of collagenous cross-linking also varies with time after wounding: the early wound has fewer and more immature cross-links compared with the later wound, which has extensive mature cross-links, resulting in a more insoluble collagenous matrix. Both mesenchymal and epidermal secreted factors stimulate fibroblast proliferation, migration and extracellular matrix synthesis in a paracrine and autocrine fashion, including the TGF-β family, IGF-1, PDGF, CTGF and hypoxia-induced heat shock protein 90 [4–6]. There is extensive cross-talk between the extracellular matrix-derived signals and growth factor signalling in this process. Thus, for example, clustering of integrin receptors on the fibroblast leading edge leads to associated clustering of growth factor receptors, which then interact with the growth factors bound to the matrix.

The early granulation tissue is characterized by transformed wound fibroblasts called myofibroblasts, which show elevated levels of α-smooth muscle actin and are morphologically and functionally intermediate between fibroblasts and smooth muscle cells. Differentiation into myofibroblasts is induced by growth factors such as TGF-β1 and IL-6, coagulation protease factor (F)Xa, extracellular matrix proteins such as the fibronectin splice variant ED-A FN and tenascin, and the mechanical microenvironment [7,8]. Myofibroblasts may contribute to the contractile forces involve in wound contraction, and their persistence can lead to abnormal scar contracture. They are preferentially eliminated during the apoptopic phase of wound healing which may be induced by wound relaxation [7]. The Smad family of proteins mediates signal transduction of the TGF-β superfamily, including induction of CTGF expression and synthesis of collagens and TIMP-1, and TGF-β induces fibroblast contraction necessary for efficient wound healing [9]. Turnover of the extracellular matrix is facilitated by a range of proteases and protease inhibitors, including plasmin, matrix metalloproteinases, hyaluronidase and elastase [10]. Levels of these active proteases are carefully and focally controlled both by growth factors, for example, IL-6, and by proteolytic inhibitors such as TIMP and syndecans [11,12]. IL-10 and bFGF both regulate remodelling of the ECM during wound healing [13,14].

As healing proceeds, the numbers of fibroblasts, endothelial and inflammatory cells decrease, and the predominantly collagenous matrix becomes organized into thicker, more heavily cross-linked bundles. This marks the establishment of the mature scar. Scars continue to remodel for a long time after wounding, and cannot be considered to be in a steady-state condition until at least 2 years post-wounding. Cutaneous scarring is defined as a macroscopic disturbance of the normal structure and function of the skin architecture, resulting from the end-product of a healed wound [15]. Scarring may manifest itself as an elevated or depressed site, with an alteration of skin texture (e.g. hard), colour (e.g. hyperpigmentation or erythema), vascularity, nerve supply, reflectance and biomechanical (e.g. elasticity) properties. Histologically, dermal scars are characterized by thickened epidermis with a flattened dermal–epidermal junction, and an abnormal organization of the dermal matrix into parallel bundles of scar-tissue collagen, as opposed to the normal basket-weave appearance of dermal collagen. The scar collagen fibres are usually smaller, more densely

packed and often have higher proportions of type III collagen and fibronectin compared with surrounding normal skin. Elastin appears early in the wound-healing process but then disappears (presumably because of the activity of elastase) to reappear again later in the scar [16]. However, the elastin is abnormally organized into fragmented and chaotic structures, as opposed to the normal elastin fibre arcades that characterize normal dermis [16]. Epidermal appendages such as hair follicles and sebaceous glands do not regenerate in scars, although experimental addition of dermal papilla fibroblasts to a wound can induce hair follicle formation [17]. Recent evidence from a mouse model suggest that wounding, in association with Wnt signalling, can induce hair follicles from epidermal progenitor cells [18]. Proliferative scarring or chronic wounds may result from overexpression or dysregulated activity of the fibrogenic isoforms of TGF-β (1 and 2) [19,20]. All three isoforms of TGF-β, and its receptors, are strongly expressed in adult wounds, but not in fetal wounds, which do not scar [21].

The severity of scarring can be assessed clinically using visual analogue scales, and the severity of macroscopic scarring correlates with histological abnormalities predominantly in the epidermis and in the papillary dermis [22]. Scar redness or erythema lasts on average for about 7 months after excisional wounding [23]. The initial inflammatory phase of wounding is thought to be critical to the morphology and severity of scarring. Application of antiscarring therapies, such as neutralizing antibodies to the profibrotic TGF-β isoforms, TGF-β1 or TGF-β2, or exogenous TGF-β3, which is elevated in non-scarring fetal epidermis, is necessary at the time of, or shortly after, wounding to achieve maximum antiscarring effect [24,25]. Smad3 is a key mediator of the TGF-β pathway and the Smad3 null mouse exhibits impaired wound healing, suggesting that inhibition of TGF-β may not always have beneficial effects [26]. Mannose-6-phosphate, an inhibitor of activation of TGF-β1 and TGF-β2, has been reported to reduce scarring in mouse models, and provides a further therapeutic approach [27].

Gap junctions, intercellular communication channels composed of connexin isoforms, are present in epidermis. Application of Connexin 43 antisense oligonucleotides reduced the inflammatory cell infiltrate with accelerated healing in murine wounds and reduced scarring after cutaneous thermal injury [28,29]. Short bioengineered peptides derived from the Cx43 carboxyl terminus accelerate wound healing and reduce scarring [30]. Scarring of skin is a major clinical problem resulting in adverse cosmesis, loss of function particularly if over joints, and interference with growth in children. Strategies to reduce scarring in skin may also be beneficial in the eye, the central nervous system and other organs where cytokine secretion or gap junction communication play a role in fibrosis.

References

1 Mori L, Bellini A, Stacy MA *et al*. Fibrocytes contribute to the myofibroblast population in wounded skin and originate from the bone marrow. *Exp Cell Res* 2005; **304**: 81–90.

2 Grieling D, Clark RAF. Fibronectin provides a conduit for fibroblast transmigration from collagenous stroma into fibrin clot provisional matrix. *J Cell Sci* 1997; **110**: 861–70.

3 Clark RA, An JQ, Greiling D *et al.* Fibroblast migration on fibronectin requires three distinct functional domains. *J Invest Dermatol* 2003; **121**: 695–705.

4 Werner S, Krieg T, Smola H. Keratinocyte-fibroblast interactions in wound healing. *J Inv Dermatol* 2007; **127**: 998–1008.

5 Werner S, Grose R. Regulation of wound healing by growth factors and cytokines. *Physiol Rev* 2003; **83**: 835–70.

6 Li W, Fan J, Chen M *et al.* Mechanism of human dermal fibroblast migration driven by type I collagen and platelet-derived growth factor-BB. *Mol Biol Cell* 2004; **15**: 294–309.

7 Hinz B. Formation and function of the myofibroblast during tissue repair. *J Invest Dermatol* 2007; **127**: 526–37.

8 Borensztajn K, Stiekema J, Nijmeijer S *et al.* Factor Xa stimulates proinflammatory and profibrotic responses in fibroblasts via protease-activated receptor-2 activation. *Am J Pathol* 2008; **172**: 309–20.

9 Sumiyoshi K, Nakao A, Setoguchi Y *et al.* Smads regulate collagen gel contraction by human dermal fibroblasts. *Br J Dermatol* 2003; **149**: 464–70.

10 Mignatti P, Rifkin DB, Welgus HG, Parks WC. Proteinases and tissue remodelling. In: Clark RAF, ed. *The Molecular and Cellular Biology of Wound Repair*. New York: Plenum Press, 1996: 427–75.

11 Young PK, Grinell F. Metalloproteinase activation cascade after burn injury: a longitudinal analysis of the human wound environment. *J Invest Dermatol* 1994; **103**: 660–4.

12 Luckett LR, Gallucci RM. Interleukin-6 (IL-6) modulates migration and matrix metalloproteinase function in dermal fibroblasts from IL-6KO mice. *Br J Dermatol* 2007; **156**: 1163–71.

13 Moroguchi A, Ishimura K, Okano K *et al.* Interleukin-10 suppresses proliferation and remodelling of extracellular matrix of cultured human skin fibroblasts. *Eur Surg Res* 2004; **36**: 39–44.

14 Xie J, Bian H, Qi S *et al.* Effects of basic fibroblast growth factor on the expression of extracellular matrix and matrix metalloproteinase-1 in wound healing. *Clin Exp Dermatol* 2008; **33**: 176–82.

15 Bayat A, McGrouther DA, Ferguson MW. Skin scarring. *BMJ* 2003; **326**: 88–92.

16 Ashcroft GS, Kielty CM, Horan MA, Ferguson MWJ. Age-related changes in the temporal and spatial distributions of fibrillin and elastin mRNAs and proteins in acute cutaneous wounds of healthy humans. *J Pathol* 1997; **183**: 80–9.

17 Jahoda CA, Reynolds AJ, Oliver RF. Induction of hair growth in ear wounds by cultured dermal papilla cells. *J Invest Dermatol* 1993; **101**: 584–90.

18 Ito M, Yang Z, Andl T *et al*. Wnt-dependent *de novo* hair follicle regeneration in adult mouse skin after wounding. *Nature* 2007; **447**: 316–20.

19 Hakkinen L, Koivisto L, Gardner H *et al.* Increased expression of β6-integrin in skin leads to spontaneous development of chronic wounds. *Am J Pathol* 2004; **164**: 229–42.

20 Cha J, Kwak T, Butmarc J *et al.* Fibroblasts from non-healing human chronic wounds show decreased expression of beta ig-h3, a TGF-beta inducible protein. *J Dermatol Sci* 2008; **50**: 15–23.

21 Cowin AJ, Holmes TM, Brosnan P, Ferguson MW. Expression of TGF-β and its receptors in murine fetal and adult dermal wounds. *Eur J Dermatol* 2001; **11**: 424–31.

22 Beausang E, Floyd H, Dunn KW *et al*. A new quantitative scale for clinical scar assessment. *Plast Reconstr Surg* 1998; **102**: 1954–61.

23 Bond JS, Duncan JA, Mason T *et al*. Scar redness in humans: how long does it persist after incisional and excisional wounding? *Plast Reconstr Surg* 2008; **121**: 487–96.

24 Shah M, Foreman DM, Ferguson MWJ. Neutralizing antibody to TGF-β1,2 reduces scarring in adult rodents. *J Cell Sci* 1994; **107**: 1137–57.

25 Shah M, Foreman DM, Ferguson MWJ. Neutralization of TGF-β1 and TGF-β2 or exogenous addition of TGF-β3 to cutaneous rat wounds reduces scarring. *J Cell Sci* 1995; **108**: 985–1002.

26 Arany PR, Flanders KC, Kobayashi T *et al*. Smad3 deficiency alters key structural elements of the extracellular matrix and mechanotransduction of wound closure. *Proc Natl Acad Sci USA* 2006; **103**: 9250–5.

27 Miller MC, Nanchahal J. Advances in the modulation of cutaneous wound healing and scarring. *BioDrugs* 2005; **19**: 363–81.

28 Mori R, Power KT, Wang CM *et al.* Acute downregulation of connexin43 at wound sites leads to a reduced inflammatory response, enhanced keratinocyte proliferation and wound fibroblast migration. *J Cell Sci* 2006; **119**: 5193–203.

29 Coutinho P, Qiu C, Frank S *et al*. Limiting burn extension by transient inhibition of Connexin43 expression at the site of injury. *Br J Plast Surg* 2005; **58**: 658–67.

30 Rhett JM, Ghatnekar GS, Palatinus JA *et al.* Novel therapies for scar reduction and regenerative healing of skin wounds. *Trends Biotechnol* 2008; **26**: 173–80.

Age-related changes in wound healing

Wounds even of a very substantial size created in certain lower vertebrates (e.g. amphibians) heal by complete regeneration. Similarly, wounds made in early (first-trimester) embryos also heal by complete regeneration [1]. However, these wounds tend to be made before the skin has established even a simple differentiated structure. During the second trimester, experimental studies in numerous animals have shown that late embryonic and early fetal dermal wounds heal with the absence of scarring, but without the regeneration of dermal appendages such as hair follicles or sebaceous glands [2]. This scar-free embryonic wound healing then gradually turns into a scarring healing phenotype during the last trimester and after birth. Scar-free embryonic wounds lack fibrin clots and platelet degranulation, have altered matrix components, including increased tenascin-C and hyaluronic acid, and have a sparse, poorly-differentiated inflammatory response [3]. Consequently, the growth factor profile at the embryonic wound site is different, with reduced levels, for example, of TGF-β1 and TGF-β2, but increased levels of TGF-β3 [4]. Early fetal dermal fibroblasts also display a differential gene response to TGF-β1 compared with postnatal fibroblasts [5]. These observations of scar-free fetal healing have led to experimental studies to manipulate TGF-β isoforms to try and mimic the fetal situation with good results [6]. These interesting experimental findings have now been translated into possible therapies, which are undergoing evaluation in clinical trials.

Interestingly, ageing during adult life also brings alterations to the wound-healing process [7]. Many studies of human age-related changes in the wound-healing profile are methodologically flawed because of failure to control for concurrent morbidity and disease. However, experimental investigations on health status in defined human subjects of varying ages have shown profound alterations in the wound-healing process with age [7]. Elderly subjects heal their wounds more slowly, with a reduced inflammatory response, an altered cytokine profile and an increased level of active proteases [8–10]. Of major interest is the observation that, in normal ageing skin, the levels of proteases such as matrix metalloproteinases and elastase increase, while the levels of proteolytic inhibitors (e.g. TIMP) decrease, tipping the balance towards proteolytic digestion of the dermis [11]. This may account for some of the age-related changes seen in normal skin structure. It may also predispose certain individuals to ulcer formation, as chronic venous ulcers are characterized by an excessive proteolytic profile [12]. By contrast, the quality of wound healing in elderly subjects is markedly improved with reduced scarring. In part, this correlates with the altered inflammatory and growth factor response, which to some extent mimics that seen in embryonic skin [8]. These ageing studies have also shown marked differences between how males and females heal their wounds, and between the healing of pre- and postmenopausal females [13,14]. In general, postmenopausal women heal more slowly but with a better scar quality than premenopausal women. Exogenous therapeutic addition of topical oestrogen to the healing wounds of postmenopausal women causes a marked acceleration of wound healing and reverses the age-related changes in speed and quality [15]. Selective oestrogen receptor modulators, such as tamoxifen, appear to act as oestrogen receptor agonists in skin, accelerating cutaneous wound healing in a murine model [16]. These results have significant implications for the treatment of wounds in older individuals.

References

1 Martin P. Wound healing: aiming for perfect skin regeneration. *Science* 1997; **276**: 75–81.
2 Ferguson MWJ, Whitby DJ, Shah M *et al.* Scar formation: the spectral nature of fetal and adult wound repair. *Plast Reconstr Surg* 1996; **97**: 854–60.
3 Metcalfe AD, Ferguson MW. Tissue engineering of replacement skin: the crossroads of biomaterials, wound healing, embryonic development, stem cells and regeneration. *J R Soc Interface* 2007; **4**: 413–37.
4 Whitby DJ, Ferguson MWJ. Immunohistochemical localization of growth factors in fetal wound healing. *Dev Biol* 1991; **147**: 207–15.
5 Rolfe KJ, Irvine LM, Grobbelaar AO, Linge C. Differential gene expression in response to transforming growth factor-beta1 by fetal and postnatal dermal fibroblasts. *Wound Repair Regen* 2007; **15**: 897–906.
6 Shah M, Foreman DM, Ferguson MWJ. Control of scarring in adult wounds by neutralizing antibodies to transforming growth factor-β (TGF-β). *Lancet* 1992; **339**: 213–4.
7 Ashcroft GS, Horan MA, Ferguson MWJ. The effect of ageing on cutaneous wound healing. *J Anat* 1995; **187**: 1–26.
8 Ashcroft GS, Horan MA, Ferguson MWJ. Ageing is associated with reduced deposition of specific extracellular matrix components, an up-regulation of angiogenesis and an altered inflammatory response in a murine incisional wound-healing model. *J Invest Dermatol* 1997; **108**: 430–7.
9 Ashcroft GS, Horan MA, Ferguson MWJ. The effects of ageing on wound healing: immunolocalization of growth factors and their receptors in a murine incisional model. *J Anat* 1997; **190**: 351–65.
10 Ashcroft GS, Horan MA, Herrick SE *et al.* Age-related differences in the temporal and spatial regulation of matrix metalloproteinases (MMPs) in normal skin and acute cutaneous wounds of healthy humans. *Cell Tissue Res* 1997; **31**: 1–11.
11 Ashcroft GS, Herrick SE, Tarnuzzer RW *et al.* Human ageing impairs injury induced *in vivo* expression of tissue inhibitor of matrix metalloproteinases (TIMP)-1 and -2 proteins and mRNA. *J Pathol* 1997; **183**: 169–76.
12 Herrick SE, Ashcroft GS, Ireland G *et al.* Up-regulation of elastase in acute wounds of healthy aged humans and chronic venous leg ulcers are associated with matrix degradation. *Lab Invest* 1997; **77**: 281–8.
13 Gilliver SC, Ashcroft GS. Sex steroids and cutaneous wound healing: the contrasting influences of estrogens and androgens. *Climacteric* 2007; **10**: 276–88.
14 Gilliver SC, Ruckshanthi JP, Atkinson SJ, Ashcroft GS. Androgens influence expression of matrix proteins and proteolytic factors during cutaneous wound healing. *Lab Invest* 2007; **87**: 871–81.
15 Ashcroft GS, Dodsworth J, Van Boxtel E *et al.* Estrogen accelerates cutaneous wound healing associated with an increase in TGF-β1 levels. *Nat Med* 1997; **3**: 1209–15.
16 Hardman MJ, Emmerson E, Campbell L, Ashcroft GS. Selective estrogen receptor modulators accelerate cutaneous wound healing in ovariectomized female mice. *Endocrinology* 2008; **149**: 551–7.

Clinical aspects of wound healing

J.E. Mellerio, pp. 14.9–14.25

Acute wounds result from a breach in the integrity of the skin, which occurs with incisional and excisional surgical wounds and traumatic skin injury including burns. At a cellular level, acute wounding results in activation of mitogen-activated protein kinase pathways and activator-protein 1 [1].

Healing by primary intention refers to wounds where the edges have been brought into apposition by sutures, which is possible when there is a good blood supply and no contamination or necrotic debris. Optimal healing requires the wound edges to be everted, carefully aligned and free from tension. Epidermis will

cross the gap by 24 h, but by 5 days the tensile strength is only about 5% that of normal skin. Thus, sutures help to take some tension off the wound. Buried absorbable sutures are helpful in reducing dead space and supporting the wound for longer, as the tensile strength is still only about 20% that of normal skin at 3 weeks [2]. Staples or clips may be used for primary wound closure, especially post-operatively, and have the advantage of producing a good cosmetic result. Tissue adhesives and sterile skin closure strips may also be used, particularly for traumatic lacerations where sutures would increase tissue tension and threaten viability, and have the advantage of not requiring suture removal.

Healing by secondary intention occurs when a wound is allowed to heal from the edge without surgical closure [3], so re-epithelialization is a crucial process. This technique is often used when there is wound contamination and a risk of infection, for example following excision of a pilonidal sinus or hidradenitis suppurativa. The depth of the wound is critical to the manner of healing. In a partial-thickness wound, not only will part of the dermis remain intact, but retention of critical regions of hair follicles and other skin appendages will also provide a rapid source of epidermal regeneration. The density of skin appendages therefore influences the rate of healing. In contrast, full-thickness wounds will have lost dermal and appendageal components and can only be healed from the wound edge, requiring a stimulation of granulation tissue; a mixture of proliferating microvasculature, fibroblasts and the deposition of matrix components. Wound contraction occurs after 1–2 weeks, via activated fibroblasts or myofibroblasts, which decreases the surface area to be closed. Different body sites vary in the results of secondary intention healing, concave surfaces being better than convex, and the face being better than extremities.

In open wounds, the normal water-retaining properties of the skin are lost, and the inflammatory exudate on the surface dries to form a crust or scab. This acts as a barrier to external infection, but it prevents epidermal migration across the surface of the wound. A wound that is kept moist by an appropriate dressing will epithelialize faster than a wound that has been allowed to form a crust. Accelerated epithelial healing under an occlusive non-permeable dressing is associated with a gelatinous coagulum containing fibrin and fibronectin, which provides a suitable matrix for epidermal cell migration [4].

Tertiary healing or delayed primary closure [5] involves allowing some healing by secondary intention and then closing the wound primarily. This may be indicated when infection is present and needs to be cleared by antibacterial treatment, or if skin grafting is intended. Delaying primary closure in this way reduces morbidity, but does not delay the development of wound strength [6]. Indeed, there is some evidence that by the 60th day, wounds healed by delayed primary closure are considerably stronger than those closed immediately [7]. This may be because of better oxygenation and blood flow with delayed closure [8].

References

1 Turchi L, Chassot AA, Rezzonico R *et al.* Dynamic characterization of the molecular events during *in vitro* epidermal wound healing. *J Invest Dermatol* 2002; **119**: 56–63.

2 Dunphy JE, Jackson DS. Practical applications of experimental studies in the care of the primarily closed wound. *Am J Surg* 1982; **104**: 273–82.

3 Bernstein G. Healing by secondary intention. *Dermatol Clin* 1989; **7**: 645–61.

4 Jonkman MF, Hoeksma EA, Niewenhuis P. Accelerated epithelialization under a highly water vapour permeable wound dressing is associated with increased precipitation of fibrin (ogen) and fibronectin. *J Invest Dermatol* 1990; **94**: 477–84.

5 Dimick AR. Delayed wound closure: indications and techniques. *Ann Emerg Med* 1988; **17**: 1303–4.

6 Hugo NE, Epstein L, Cone A. The effect of primary wounding on the tensile strength of secondary wounds. *Surg Gynaecol Obstet* 1970; **131**: 516–8.

7 Fogdestam I. A biomechanical study of healing rat skin incisions after delayed primary closure. *Surg Gynaecol Obstet* 1981; **153**: 191–9.

8 Scott PG, Chambers M, Johnson BW *et al.* Experimental wound healing: increased breaking strength and collagen synthetic activity in abdominal fascial wounds healing with secondary closure of the skin. *Br J Surg* 1985; **72**: 777–9.

Burns

Burns may be classified according to the depth of thermal injury: partial-thickness burns affect the epidermis only (superficial or first-degree burns) or involve the epidermis and dermis (second-degree), where they may be superficial or deep dermal. Full-thickness (third-degree) burns extend to the subcutaneous tissues [1] (Fig. 14.2). Most burns have a mixture of different depths of involvement within them which requires careful assessment. Superficial burns are red, moist and blanche easily, but deeper dermal burns are mottled red, dry and non-blanching. Full-thickness burns are dry, chalky white or charred. More superficial burns are extremely painful whereas full-thickness burns are anaesthetic. The extent of injury is determined by the rule of nines [1,2]. The head and upper limbs are each 9% of the total body surface area (TBSA), whereas each lower limb, the anterior and posterior trunk is 18% TBSA. A minor burn is either superficial or involves less than 20% TBSA. The speed of healing of dermal burns depends on the number of viable hair follicles and other appendages. Deep burns result in longer healing times, severe scarring and contractures, so surgical practice has evolved to excise burn wounds and close with a skin graft as soon as practicable, usually within the first 5 days after the injury.

Wound healing in burns is affected by particular complications of the burn injury in the cutaneous vasculature [3]. The depth of burns tends to increase after 24–48 h as a result of progressive vascular occlusion. Thermal injury produces a zone of coagulative

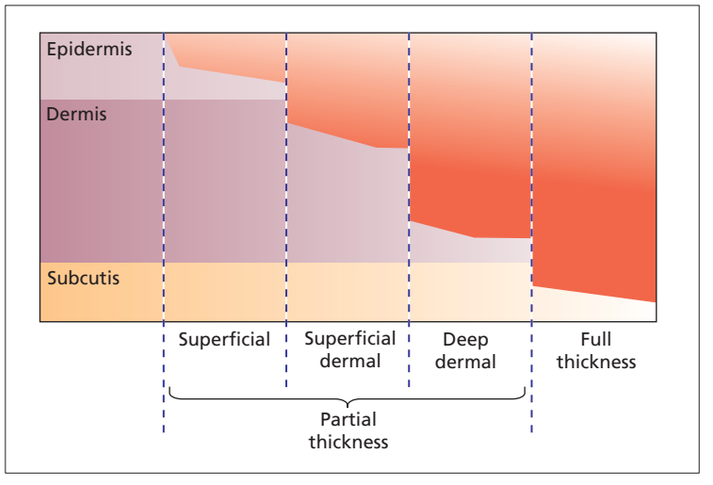


Fig. 14.2 Different depths of cutaneous burns.

necrosis surrounded by an area of hyperaemia, as histamine release after burning gives initial vasodilatation followed by bradykinin-mediated vasoconstriction. Leukocyte adhesion to vessel walls produces progressive thrombotic occlusion, which causes extension and deepening of the burn. Continued leukocyte activation leads to free-radical-mediated tissue damage, and produces prolonged inflammation for 1–4 weeks, which prevents healing. Release of proteases from leukocytes, keratinocytes and macrophages also delays healing by inactivating growth factors, and by destroying newly regenerating tissue.

Early management of thermal burns [4] includes removal from the heat source and immersion in or irrigation with tepid (15°C) water for at least 20 min to limit further thermal damage, minimize oedema and provide analgesia. Polyvinyl chloride (PVC) film (Clingfilm) may be placed over the wound as an initial wound covering, or hands and feet placed in a clear plastic bag. A variety of dressings (e.g. Vaseline impregnated gauze or soft silicone dressings (e.g. Mepitel®)) may be used for the first 24–48 h until wound depth can be clarified. Biological dressings such as human allografts, porcine heterografts or synthetic skin equivalents are very effective in reducing pain. Occlusive dressings may be helpful on small burns, but are not practical for large surface-area burns. One per cent silver sulfadiazine cream is widely used in burns units to reduce the risk of secondary infection, especially *Pseudomonas* species. Dressings are generally changed every 3 to 5 days, or more frequently if there are signs of infection.

Chemical burns resulting from contact with corrosive substances tend to be deep because coagulative necrosis of tissues usually continues until the chemical is removed. Alkalis, such as cement, and acids such as hydrofluoric acid used in glass etching, are commonly implicated. Clothing over affected sites should be removed and the area thoroughly irrigated with water before undertaking assessment and management as for thermal burns [5].

In a deep dermal or full-thickness circumferential burn, early escharotomy may be needed to prevent ischaemia in a limb or respiratory compromise with extensive chest burns. Surgical excision down to bleeding with immediate grafting is the treatment of choice on any burn not likely to heal in 2–3 weeks. Tangential excision and split-thickness sheet or mesh grafts are generally used, either autologous grafts, cadaveric allografts or cultured epithelial autografts. Synthetic skin equivalents (e.g. Integra®, TransCyte®, Apligraf®) may be particularly useful if the extent of the burns limits suitable autologous donor skin, but are costly. Cultured autologous epithelial suspensions which can be applied to the wound bed (e.g. ReCell®) are a further option which has become available recently [6]. There may be significant blood loss (200 mL/1% TBSA) from wound bed excision, which must be replaced. Pressure garments are widely used to prevent excessive scarring, as are silicone gel sheets and occlusive membranes.

References

1 Heimbach DM, Afromowitz MA, Engrav LH *et al*. Burn depth estimation: man or machine. *J Trauma* 1984; **24**: 373–7.

2 Masterson JP. Burns. In: Ellis BW and Paterson-Brown S, eds. *Hamilton Bailey's Emergency Surgery*. Oxford: Butterworth–Heinemann, 1995: 140–52.

3 Mileski WI, Borgstrom D, Lightfood S *et al*. Inhibition of leukocyte endothelial adherence following thermal injury. *J Surg Res* 1992; **52**: 334–9.

4 Deitch EA. The management of burns. *N Engl J Med* 1990; **323**: 1249–54.

5 Edlich RF, Farinholt HM, Winters KL *et al*. Modern concepts of treatment and prevention of chemical injuries. *J Long-Term Eff Med Implants* 2005; **15**: 303–18.

6 Gravante G, Di Fede MC, Araco A *et al*. A randomized trial comparing ReCell system of epidermal cells delivery versus classic skin grafts for the treatment of deep partial thickness burns. *Burns* 2007; **33**: 966–72.

Chronic wounds

The series of biological events that close any defect in the skin may be impaired by factors interfering with inflammation, angiogenesis, re-epithelialization and wound remodelling. Most wounds will have a tendency to heal, however long standing, but this process may be very slow and suffer from many complications. Recurrent injury over a previous scar, as in a leg ulcer or pressure sore, and recurrent breakdown following healing, can give rise to chronic skin wounds or ulcers that appear to have lost the capacity to heal. Although the mechanisms of skin ulceration are understood, the biological profile of the chronic wound is not clear.

The chronic wound environment may, for example, be deficient in stimulatory growth factors, growth factor receptors or proteolytic enzymes required for growth factor activation, or may be overproducing any of these factors [1–3]. Growth activation in the edge of a wound bed is particularly associated with overexpression of TGF-α, heparin-binding epidermal growth factor (HB-EGF) and EGF receptor [4]. The chronic wound may produce a hostile microenvironment to cells requiring activation in the wound-healing process. Chronic wound fluid has been shown to decrease proliferation of fibroblasts, endothelial cells and keratinocytes, in part mediated through Ras- and mitogen-activated protein kinase (MAPK) signalling pathways [5–9]. In contrast, acute wound fluid stimulates growth of these cells [10]. Wound fluid from venous ulcers contains active collagenases and degraded fibronectin and vitronectin, and decreases cell adhesion. Fibrin accumulates in chronic wounds (unlike acute wounds), and forms complexes that may bind or inactivate other molecules such as growth factors.

Metalloproteinases (MMPs) are pro-enzymes requiring activation [11]. Three classes of MMPs are collagenases, gelatinases and stromelysins, single-chain proteins the production of which is stimulated by soluble factors and matrix proteins, and inhibited by TIMP [12,13]. There may be abnormalities of MMPs and TIMP in the chronic wound [2,14,15]. Collagenases are probably important in tissue remodelling following healing. Keratinocytes in the edge of a chronic wound are stimulated to produce collagenase by type I collagen.

Keratinocytes in chronic wounds fail to migrate across a wound bed despite a hyperplastic epithelium, and may lack specific matrix proteins in the wound bed to permit cell movement. Keratinocytes migrate most effectively on fibronectin, usually present in the wound bed, and on type I and IV collagens, but not on laminin [16]. Keratinocyte mesenchymal interactions therefore require a vascularized appropriate matrix, and they are impaired in chronic persistent wounds.

The chronic wounds that pose the most significant clinical problems are chronic leg ulcers and pressure sores. These wounds are also of high economic importance, as caring for them consumes a huge amount of health-care resources [17].

References

1 Claudy AI, Mirshahi M, Soria C, Soria J. Detection of undegraded fibrin and tumour necrosis factor-α in venous leg ulcers. *J Am Acad Dermatol* 1991; **25**: 623–7.
2 Silver IA. Cellular microenvironment in healing and non-healing wounds. In: Pine E, Hunt TK, Rovee D, eds. *Hard and Soft Tissue Injury*. New York: Praeger, 1984: 50–66.
3 Falanga V. Growth factors and chronic wounds: the need to understand the microenvironment. *J Dermatol* 1992; **19**: 667–72.
4 Martin P. Wound healing: aiming for perfect skin regeneration. *Science* 1997; **276**: 75–81.
5 Bucalo B, Eaglstein WH, Falanga V. Inhibition of cell proliferation by chronic wound fluid. *Wound Repair Regen* 1993; **1**: 181–6.
6 Phillips TJ, al-Amoudi HO, Leverkus M, Park HY. Effect of chronic wound fluid on fibroblasts. *J Wound Care* 1998; **7**: 527–32.
7 De Mattei M, Ongaro A, Magaldi S *et al*. Time- and dose-dependent effects of chronic wound fluid on human adult dermal fibroblasts. *Dermatol Surg* 2008; **34**: 347–56.
8 Seah CC, Phillips TJ, Howard CE *et al*. Chronic wound fluid suppresses proliferation of dermal fibroblasts through a Ras-mediated signaling pathway. *J Invest Dermatol* 2005; **124**: 466–74.
9 Raffetto JD, Vasquez R, Goodwin DG, Menzoian JO. Mitogen-activated protein kinase pathway regulates cell proliferation in venous ulcer fibroblasts. *Vasc Endovascular Surg* 2006; **40**: 59–66.
10 Katz MH, Alvarez AF, Kirsner RS *et al*. Human wound fluid from acute wounds stimulates fibroblast and endothelial cell growth. *J Am Acad Dermatol* 1991; **25**: 1054–8.
11 Parks WC. Matrix metalloproteinases in repair. *Wound Repair Regen* 1999; **7**: 423–32.
12 Saarialho-Kere UK, Chang ES, Welgus HG, Parks WC. Distinct localization of collagenase and tissue inhibitor of metalloproteinases expression in wound healing associated with ulcerative pyogenic granuloma. *J Clin Invest* 1992; **90**: 1952–7.
13 Pilcher BK, Wang M, Qin XJ *et al*. Role of matrix metalloproteinases and their inhibition in cutaneous wound healing and allergic contact hypersensitivity. *Ann NY Acad Sci* 1999; **878**: 12–24.
14 Saarialho-Kere UK. Patterns of matrix metalloproteinase and TIMP expression in chronic ulcers. *Arch Dermatol Res* 1998; **290** (Suppl.): S47–54.
15 Herouy Y, Trefzer D, Zimpfer U *et al*. Matrix metalloproteinases and venous leg ulceration. *Eur J Dermatol* 2000; **10**: 173–80.
16 O'Toole EA. Extracellular matrix and keratinocyte migration. *Clin Exp Dermatol* 2001; **26**: 525–30.
17 Harding K, Cutting K, Price P. The cost-effectiveness of wound management protocols of care. *Br J Nurs* 2000; **9** (Suppl.): S6–24.

Leg ulcers

Leg ulcers are becoming more common as the population ages, as they particularly afflict the elderly. Prevalence figures suggest up to 1% of the population may be affected [1–4]. The health-care cost of non-healing ulcers is immense, in view of the high use of community nursing resources, consuming an estimated 1–2% of the annual health-care budget of European countries [5,6]. Chronic leg ulcers also cause significant morbidity and reductions in quality of life for those affected [7–10]. The most common cause of leg ulcers (80–85%) is chronic venous insufficiency, with arterial disease and diabetic neuropathy accounting for the majority of the remainder (Table 14.3).

Venous ulcers result from valve incompetence in the perforating veins connecting superficial and deep venous systems, so that venous pressure does not fall during exercise and as a result capillary proliferation occurs [11]. An increased permeability to macromolecules produces a pericapillary fibrin cuff, which binds growth factors and matrix proteins and may impede oxygenation [12]. Trapped leukocytes occluding capillaries may add to tissue ischaemia through the release of inflammatory mediators that increase vascular permeability [13]. The skin develops purpura resulting from extravasated red cells, and pigmentation from collections of haemosiderin and melanin. There may be pitting oedema, or changes of lipodermatosclerosis, with induration and fibrosis of the dermis and subcutaneous tissues, skin atrophy and pigmentation. Eczematization is also commonly observed. Ulceration typically develops in the gaiter area above the malleoli with irregular, gently sloping edges. Ulcers usually heal initially but there is a high recurrence rate. The resultant scarring, repeated episodes of infection and chronic lymphoedema tend to promote the chronicity of ulceration [14,15] (Fig. 14.3). The most important factor in the aetiology of venous ulcers is venous hypertension, resulting from valve incompetence, loss of calf muscle pump, or both. Venous thrombosis may also lead to venous hypertension.

Table 14.3 Causes of leg ulcers.

Venous (chronic venous insufficiency)
Arterial
Atherosclerosis
Hypertensive
Trauma (+above)
Mixed arteriovenous
Vasculitis (arteritis and allergic vasculitis)
Pyoderma gangrenosum
Bacterial infections (including tropical ulcer, acid-fast bacilli, ecthyma)
Malignancy
Necrobiosis lipoidica
Vasospastic (including sickle cell anaemia, cryoglobulinaemia)



Fig. 14.3 Chronic venous ulcers with surrounding chronic edge.

In familial cases of venous leg ulcers there may be an inherited resistance to activated protein C, leading to thrombosis and subsequent ulceration. Most cases of activated protein C resistance are caused by a specific mutation in exon 10 of the clotting factor V gene, known as the factor V Leiden mutation [16]. Less commonly, a polymorphic variant in the prothrombin gene (G20210A) may also be associated with increased risk of venous leg ulceration [17]. Management of venous leg ulcers centres around the use of appropriate compression bandaging or hosiery to reduce the effects of venous hypertension, suitable wound dressings and treating infection, when present [18,19].

Arterial ulceration tends to occur in patients with other symptoms and signs of peripheral vascular disease, such as intermittent claudication, rest pain and loss of peripheral pulses. The ulcers tend to occur at acral sites such as the tips of toes or over bony prominences. They are punched out with a demarcated border which may be haemorrhagic, usually with a dry, necrotic base. Surrounding skin may be smooth, hairless, cool and demonstrate reduced capillary refill. Ischaemic ulcers are extremely painful, especially at night. Besides local wound care, management may include surgical intervention to increase arterial perfusion, modification of risk factors for peripheral vascular disease, and increasing exercise to encourage collateral circulation to the legs and feet.

Diabetic ulcers are most commonly associated with diabetic neuropathy, although microvascular occlusive disease may also contribute [20–22]. They often result from unnoticed injury on the plantar surface of the foot, particularly over bony prominences, and are prone to infection. Healing tends to be slow and difficult to achieve; underlying osteomyelitis may occur and amputation is an unfortunately common outcome. Neuropathy may be associated with paraesthesia, anaesthesia and pain. Light touch, vibration and then position sense are usually lost in the affected foot. Little is known about how endothelial and metabolic abnormalities in diabetes affect wound repair. Hyperglycaemia may affect neutrophil activity. Loss of neuropeptide homoeostasis may be relevant, as intact neurosensory activity is essential for inflammation. Management of diabetic ulcers requires a multidisciplinary approach, and should address wound management, glycaemic control, arterial disease, infection and orthotics for relief of pressure areas [23,24].

References

1 Dale JJ, Callam MJ, Ruckley CV *et al*. Chronic ulcers of the leg: a study of prevalence in a Scottish community. *Health Bull (Edinb)* 1983; **41**: 310–4.

2 Callum MJ, Ruckley CV, Harper DR, Dale JJ. Chronic ulceration of the leg: extent of the problem and provision of care. *Br Med J* 1985; **290**: 1855–6.

3 Margolis DJ, Bilker W, Santanna J, Baumgarten M. Venous leg ulcer: incidence and prevalence in the elderly. *J Am Acad Dermatol* 2002; **46**: 381–6.

4 Moffatt CJ, Franks PJ, Doherty DC *et al*. Prevalence of leg ulceration in a London population. *QJM* 2004; **97**: 431–7.

5 Ruckley CV. Socioeconomic impact of chronic venous insufficiency and leg ulcers. *Angiology* 1997; **48**: 67–9.

6 Drew P, Posnett J, Rusling L. Wound Care Audit Team. The cost of wound care for a local population in England. *Int Wound J* 2007; **4**: 1491–55.

7 Persoon A, Heinen MM, van der Vleuten CJ *et al*. Leg ulcers: a review of their impact on daily life. *J Clin Nurs* 2004; **13**: 341–54.

8 Goodridge D, Trepman E, Embil JM. Health-related quality of life in diabetic patients with foot ulcers: literature review. *J Wound Ostomy Continence Nurs* 2005; **32**: 368–77.

9 Jones J, Barr W, Robinson J, Carlisle C. Depression in patients with chronic venous ulceration. *Br J Nurs* 2006; **15**: S17–23.

10 Guarnera G, Tinelli G, Abeni D *et al*. Pain and quality of life in patients with vascular leg ulcers: an Italian multicentre study. *J Wound Care* 2007; **16**: 347–51.

11 Browse NL, Burnand KG. The cause of venous ulceration. *Lancet* 1982; **2**: 243–5.

12 Burnand KG, Whimster I, Naidoo A *et al*. Pericapillary fibrin deposition in the ulcer bearing skin of the lower limb: the cause of lipodermatosclerosis and venous ulceration. *BMJ* 1982; **285**: 1071–2.

13 Coleridge-Smith PD, Thomas P, Scurr JH *et al*. Causes of venous ulceration: a new hypothesis. *BMJ* 1988; **296**: 1726–7.

14 Cornwall JV, Dore CJ, Lewis JD. Leg ulcers, epidemiology and aetiology. *Br J Surg* 1986; **73**: 693–6.

15 Phillips TJ, Dover JS. Leg ulcers. *J Am Acad Dermatol* 1991; **25**: 965–87.

16 Procopciuc LM, Has C, Drugan C *et al*. Genetic analysis of factor V Leiden in a family with history of thrombosis and venous leg ulcers. *J Cell Mol Med* 2000; **4**: 297–302.

17 Jebeleanu G, Procopciuc LM. G20210A prothrombin mutation identified in patients with venous leg ulcers. *J Cell Mol Med* 2001; **5**: 397–401.

18 Cullum N, Nelson EA, Fletcher AW, Sheldon TA. Compression for venous leg ulcers. *Cochrane Database Syst Rev* 2001; **2**: CD000265.

19 Palfreyman SJ, Nelson EA, Lochiel R, Michaels JA. Dressings for healing venous leg ulcers. *Cochrane Database Syst Rev* 2006; **3**: CD001103.

20 Cotton LT, Higton DI, Berry HE. Diabetes and vascular surgery. *Postgrad Med J* 1971; **47**: 84–5.

21 Gibbons GW. The diabetic foot: amputations and drainage of infection. *J Vasc Surg* 1987; **5**: 791–3.

22 Logerfo FW, Coffman JD. Vascular and microvascular disease of the foot in diabetes: implications for foot care. *N Engl J Med* 1984; **311**: 1615–9.

23 Edmonds M, Foster AVM, Sanders L. *A Practical Manual of Diabetic Foot Care*. Oxford: Blackwell Science, 2004.

24 National Institute for Clinical Excellence. *Type 2 Diabetes. Prevention and Management of Foot Problems*. NICE, London, 2004. (www.nice.org.uk/nicemedia/pdf/CG010NICEguideline.pdf)

Pressure ulcers

Pressure ulcers (bed sores, decubitus ulcers) are areas of localized tissue necrosis caused by pressure, friction or shearing forces, acting alone or in combination, resulting in soft tissue compression between a bony prominence and a rigid external surface [1–4]. The presence of moisture, from wound exudate or urinary or faecal incontinence, further exacerbates damage to the tissues. The overall prevalence of pressure ulcers in hospital inpatients has been estimated to be as high as 30% and is associated with a significant morbidity, mortality and economic cost [5–7].

The mean capillary pressure in healthy individuals is 25 mmHg, and external compression with pressures of 30 mmHg will occlude blood vessels so that tissues become anoxic and undergo ischaemic necrosis. Toleration of high tissue pressures depends on the patient's health and the extent and time of application, but short intervals of pressure relief will allow longer resistance. Any patient who is severely and acutely ill can develop pressure sores, because dehydration and hypotension will add to tissue destruction. Patient immobility is the major risk factor, but loss of sensory perception, including loss of consciousness, will contribute. Factors predisposing to pressure ulcers are listed in Table 14.4.

The depth of ulcer is used to classify pressure sores, and there are a number of classification systems, for example the European Pressure Ulcer Advisory Panel (EPUAP) scheme (Table 14.5). Eighty per cent are superficial and 20% deep, but even superficial sores will progress if left unrelieved. The most common sites are the areas of highest compression in the supine patient: 60% of all

Table 14.4 Factors predisposing to pressure ulcers.

Immobility especially post-operatively
Hypotension
Dehydration
Reduced sensory perception including neurological disease and spinal injury
Loss of consciousness
Elderly
General ill health
Ischaemic heart disease
Peripheral vascular disease
Smoking
Pyrexia
Poor nutrition especially hypoalbuminaemia and low zinc
Drugs reducing mobility, sensation or blood flow

Table 14.5 Staging of pressure sores (EPUAP classification scheme).

I	Non-blanching erythema of intact skin
II	Partial-thickness skin loss involving epidermis and/or dermis
III	Full-thickness skin loss with necrosis of subcutaneous tissue down to but not through underlying fascia
IV	Full-thickness with penetration to fascia, muscle, bone

sores are over the sacrum (Fig. 14.4a), while the ischial tuberosities, greater trochanter and heel (Fig. 14.4b) account for 15%. Less common sites are elbows, knees, ankles and occiput. Heels erode when individuals sit immobile with heels supported.

Assessment of at-risk patients should be undertaken and may help prevent pressure ulcers. A variety of tools exist which assess factors such as age, mobility, level of consciousness, nutritional status, continence and severity of illness, although these should be used in conjunction with clinical judgement [8–10]. Patients considered to be at risk of developing pressure ulcers should be encouraged to mobilize regularly or, where this is not possible, should be turned or repositioned at least every 1–2 hours. Care should be taken when moving patients not to increase shearing or frictional forces on the skin. A variety of pressure-relieving devices such as static or dynamic mattresses and mattress overlays are available and may be indicated in those at particular risk of developing pressure ulcers or those with established areas of ulceration [11]. Faecal or urinary incontinence should be managed to reduce moisture at pressure sites as much as possible. Existing pressure ulcers should be managed with appropriate dressings but deeper or extensive lesions may require surgical intervention with debridement, with or without reconstuction.

Early active mobilization not only relieves pressure, but also increases blood flow and muscle tone. When pressure is relieved, sores go through a process of debridement, where necrotic slough forms a hard dry black eschar. This later separates by natural proteolysis, followed by wound contraction, re-epithelialization and scar remodelling. The pathology of the pressure ulcer shows wedge-shaped infarcts of the subcutaneous tissue, capillary obstruction by microthrombi, and endothelial cell swelling and necrosis, with widespread inflammation.

Infection and osteomyelitis may follow wound breakdown, but significant tissue infection will be associated with redness, heat, oedema and tenderness, and systemic features such as leukocytosis, fever and pain, with an offensive exudate. Rapid debridement is particularly important in those at increased risk of infection, such as diabetics and the immunosuppressed.



(a)



(b)

Fig. 14.4 (a) Full-thickness sacral pressure sore with necrotic debris (stage III) in a patient with neurological coma. (b) Full-thickness heel pressure sore: clean and granulating in an immobile elderly patient.

References

1 Allman RD. Pressure sores among the elderly. *N Engl J Med* 1989; **320**: 850–3.
2 Shea JD. Pressure sores: classification and management. *Clin Orthop* 1975; **112**: 89–100.
3 Allman RD, Laprode CA, Noel IB *et al*. Pressure sores among hospitalized patients. *Ann Intern Med* 1986; **105**: 337–42.
4 Leigh IM, Bennet G. Pressure ulcers: prevalence, etiology and treatment modalities—a review. *Am J Surg* 1994; **67**: 25–30S.
5 Vanderwee K, Clark M, Dealey C *et al*. Pressure ulcer prevalence in Europe: a pilot study. *J Eval Clin Pract* 2007; **13**: 227–35.
6 Woodbury MG, Houghton PE. Prevalence of pressure ulcers in Canadian healthcare settings. *Ostomy Wound Manage* 2004; **50**: 22–4, 26, 28, 30, 32, 34, 36–8.
7 Bennett G, Dealey C, Posnett J. The cost of pressure ulcers in the UK. *Age Ageing* 2004; **33**: 230–5.
8 NICE. *Pressure Ulcer Risk Assessment and Prevention*. Clinical guidelines, 2001. (www.nice.org.uk/nicemedia/pdf/clinicalguidelinepressuresoreguidancercn.pdf)

9 Pancorbo-Hidalgo PL, Garcia-Fernandez FP, Lopez-Medina IM, Alvarez-Nieto C. Risk assessment scales for pressure ulcer prevention: a systematic review. *J Adv Nurs* 2006; **54**: 94–110.
10 Balzer K, Pohl C, Dassen T, Halfens R. The Norton, Waterlow, Braden and Care Dependency Scales: comparing their validity when identifying patients' pressure sore risk. *J Wound Ostomy Continence Nurs* 2007; **34**: 389–98.
11 Cullum N, McInnes E, Bell-Syer SE, Legood R. Support surfaces for pressure ulcer prevention. *Cochrane Database Syst Rev* 2004; **3**: CD001735.

Complications of wound healing

Hypertrophic and keloid scarring

Keloids and hypertrophic scars are abnormal fibrous reactions to trauma, inflammation, surgery or burns in predisposed individuals, particularly in Afro-Caribbean skin, and most occur between the ages of 10 and 30 years. Hypertrophic scars remain restricted to the original wound, but keloids extend beyond the original wound and rarely regress. Trauma, skin tension and hormones are aetiological factors. Most keloids commence within a year of trauma in areas of highest skin tension: on the upper back, shoulders, anterior chest and upper arms. Reducing wound tension by orientating the wound along lines of relaxed tension may reduce scar formation. Familial predisposition to keloid formation is suggested by reports of recessive and dominant inheritance. Although no human leukocyte antigen (HLA) association or polymorphic variants in TGF-β genes have been found [1], linkage studies have identified susceptibility loci on chromosomes 2p23 and 7p11 in two families with autosomal dominant keloids [2]. Some skin diseases give keloidal scarring, including acne conglobata, acne keloidalis nuchae, hidradenitis suppurativa and certain infections such as chickenpox.

Keloids present clinically because they are disfiguring, painful or pruritic, especially when actively growing. The clinical course is variable, with keloids appearing from weeks to months after the initiating lesion, growing to exceed the wound limits and then stabilizing. Suppurative necrosis occasionally complicates the lesion from vascular damage or pilosebaceous occlusion, particularly in acneiform lesions. Keloids seldom regress spontaneously, but may soften in the elderly.

Hypertrophic scars are distinguished from keloids by growth course and outcome. They occur soon after the trauma or inflammation, are limited to the site of the wound and regress in months to years, but may be difficult to distinguish from keloids in their early actively growing phase. Pathological distinction is not easy. Normal healing involves fibroplasia following the inflammatory phase. In keloids, this is progressive and forms nodular vascular proliferations surrounded by fibroblasts. These nodules transform into avascular collagenous bundles with persistent swirls of fibroblasts; myofibroblasts are prevalent in active keloids. The collagen bundles are randomly aligned and not orientated to the skin surface, whereas in normal scars the bundles lie parallel to the epithelial surface. There are suggestions from *in vitro* studies that abnormal collagen cross-linking, degradation or regulation by TGF-β may be involved in the pathogenesis [1,3–5]. Other cellular changes identified include alterations in α1β1 integrin collagen receptor expression [6] and in the regulation of fibroblast apoptosis [7]. *In vitro* studies also suggest that keloid keratinocytes may also influence keloid fibroblasts (and normal fibroblasts) to increase procollagen I and III gene and protein expression [8]. Increased fibronectin gene expression and expression of IL-6 have been demonstrated in keloid fibroblasts, in addition to increased vascular endothelial growth factor (VEGF) in keloid keratinocytes [9–12].

Treatment of keloids and hypertrophic scars initially involves intralesional corticosteroid injection, although hypopigmentation and local subcutaneous atrophy are possible local side effects. Mechanistically, triamcinolone acetonide has been shown to directly stimulate basic fibroblast growth factor (bFGF) expression and to inhibit TGF-β1 production [13], changes that are both recognized to reduce scarring. However, repeated injections of corticosteroids are always necessary, and seldom completely successful. Surgical therapy with excision or enucleation has a high recurrence rate in the absence of adjunct therapy, such as intralesional steroids, radiotherapy, pressure devices, silicone gels or other less proven agents including intralesional IFN-γ, IFN-α2 and retinoids. Prevention by minimizing trauma and surgery in predisposed individuals is important, as most treatments are unsatisfactory, although surgery combined with radiation has the lowest recurrence rates [14,15]. Other possible treatment options include laser therapy (585-nm pulsed-dye or Nd:YAG), electron beam irradiation, cryotherapy, intralesional 5-fluorouracil, intralesional verapamil and topical imiquimod [16–27]. *In vitro* studies suggest that the anti-inflammatory drug lysine acetylsalicylate also decreases proliferation and extracellular matrix gene expression (procollagen I and II) in keloid fibroblasts [28].

References

1 Bayat A, Bock O, Mrowietz U *et al*. Genetic susceptibility to keloid disease and transforming growth factor β2 polymorphisms. *Br J Plast Surg* 2002; **55**: 283–6.
2 Marneros AG, Norris JEC, Watanabe S *et al*. Genome scans provide evidence for keloid susceptibility loci on chromosomes 2q23 and 7p11. *J Invest Dermatol* 2004; **122**: 1126–32.
3 Diegelmann RF, Cohen IK, McCoy BJ. Growth kinetics and collagen synthesis of normal skin, normal scar and keloid fibroblasts *in vitro*. *J Cell Physiol* 1979; **98**: 341–6.
4 Hunt TK, Banda MJ, Silver IA. Cell interactions in post traumatic fibrosis. *Fibrosis*. *Ciba Found Symp* 1985; **114**: 127–49.
5 Russell JD, Witt WS. Cell size and growth characteristics of cultured fibroblasts isolated from normal and keloid tissue. *Plast Reconstr Surg* 1976; **57**: 207–12.
6 Szulgit G, Rudolph R, Wandel A *et al*. Alterations in fibroblast α1β1 integrin collagen receptor expression in keloids and hypertrophic scars. *J Invest Dermatol* 2002; **118**: 409–15.
7 Akasaka Y, Fujita K, Ishikawa Y *et al*. Detection of apoptosis in keloids and a comparative study on apoptosis between keloids, hypertrophic scars, normal healed flat scars, and dermatofibroma. *Wound Repair Regen* 2001; **9**: 501–6.
8 Lim IJ, Phan TT, Bay BH *et al*. Fibroblasts cocultured with keloid keratinocytes: normal fibroblasts secrete collagen in a keloid-like manner. *Am J Physiol Cell Physiol* 2002; **283**: C212–22.
9 Oliver N, Babu M, Diegelmann R. Fibronectin gene transcription is enhanced in abnormal wound healing. *J Invest Dermatol* 1992; **99**: 579–86.
10 Xue H, McCauley RL, Zhang W. Elevated interleukin-6 expression in keloid fibroblasts. *J Surg Res* 2000; **89**: 74–7.
11 Ghazizadeh M. Essential role of IL-6 signaling pathway in keloid pathogenesis. *J Nippon Med Sch* 2007; **74**: 11–22.
12 Gira AK, Brown LF, Washington CV *et al*. Keloids demonstrate high-level epidermal expression of vascular endothelial growth factor. *J Am Acad Dermatol* 2004; **50**: 850–3.
13 Carroll LA, Hanasonon MM, Mikulec AA *et al*. Triamcinolone stimulates bFGF production and inhibits TGF-β1 production by human dermal fibroblasts. *Dermatol Surg* 2002; **28**: 704–9.
14 Murray JC. Scars and keloids. *Dermatol Clin* 1993; **11**: 697–708.
15 Akita S, Akino K, Yakabe A *et al*. Combined surgical excision and radiation therapy for keloid treatment. *J Craniofac Surg* 2007; **18**: 1164–9.

16 Manuskiatti W, Fitzpatrick RE. Treatment response of keloidal and hypertrophic sternotomy scars: comparison among intralesional corticosteroid, 5-fluorouracil, and 585-nm flashlamp-pumped pulsed dye laser treatments. *Arch Dermatol* 2002; **138**: 1149–55.
17 Kumar K, Kapoor BS, Rai P, Shukla HS. *In situ* irradiation of keloid scars with Nd:YAG laser. *J Wound Care* 2000; **9**: 313–5.
18 Maarouf M, Schleicher U, Schmachtenberg A, Ammon J. Radiotherapy in the management of keloids: clinical experience with electron beam irradiation and comparison with X-ray therapy. *Strahlenther Onkol* 2002; **178**: 330–5.
19 Yosipovitch G, Widijanti Sugeng M, Goon A *et al*. A comparison of the combined effect of cryotherapy and corticosteroid injections versus corticosteroids and cryotherapy alone on keloids: a controlled study. *J Dermatolog Treat* 2001; **12**: 87–90.
20 Gupta S, Kalra A. Efficacy and safety of intralesional 5-fluorouracil in the treatment of keloids. *Dermatology* 2002; **204**: 130–2.
21 Nanda S, Reddy BS. Intralesional 5-fluorouracil as a treatment modality of keloids. *Dermatol Surg* 2004; **30**: 54–6.
22 D'Andrea F, Brongo S, Ferraro G, Baroni A. Prevention and treatment of keloids with intralesional verapamil. *Dermatology* 2002; **204**: 60–2.
23 Stashower ME. Successful treatment of earlobe keloids with imiquimod after tangential shave excision. *Dermatol Surg* 2006; **32**: 380–6.
24 Chuangsuwanich A, Gunjittisomram S. The efficacy of 5% imiquimod cream in the prevention of recurrence of excised keloids. *J Med Assoc Thai* 2007; **90**: 1363–7.
25 Panabiere-Castaings MH. Retinoic acid in the treatment of keloids. *J Dermatol Surg Oncol* 1988; **14**: 1275–6.
26 Berman B, Duncan MR. Short-term keloid treatment *in vivo* with human interferon alfa-2b results in a selective and persistent normalization of keloidal fibroblast collagen, glycosaminoglycan, and collagenase production *in vitro*. *J Am Acad Dermatol* 1989; **21**: 694–702.
27 O'Brien L, Pandit A. Silicon gel sheeting for preventing and treating hypertrophic and keloid scars. *Cochrane Database Syst Rev* 2006; **1**: CD003826.
28 Petri JB, Haustein UF. Lysine acetylsalicylate decreases proliferation and extracellular matrix gene expression rate in keloid fibroblasts *in vitro*. *Eur J Dermatol* 2002; **12**: 231–5.

Wound infection

Wounds may be contaminated or colonized with microorganisms without overt infection or impairment of healing, although multiplication of these organisms may lead to critical colonization and frank infection. This mediates adverse events in the wound following binding of microorganisms to tissue and triggering of a host immune response. Wounds that contain more than 10^5 bacteria per gram of tissue are likely to lead to clinical infection [1,2]. Bacteria compete for metabolites (glucose and oxygen), release toxins and proteases (leading to cell damage), and activate complement (prolonging inflammation). Patients with systemic problems such as diabetes mellitus, steroid therapy, increasing age, local ischaemia and oedema, and immunosuppression are more prone to develop infection. Fibronectin in the wound bed is known to predispose to bacterial adhesion. Foreign material, such as necrotic eschar, non-vital tissue, dressing fibres or sutures further predispose to bacterial contamination.

Failure of a chronic wound to decrease in size may be the first clinical sign of infection [3]. Exudate will typically increase in quantity, first clear or serous but becoming purulent or haemorrhagic as infection progresses. Commonly, Gram-positive organisms such as *Staphylococcus aureus* are isolated (56% leg ulcers and 51% pressure sores [4]). Infections with Gram-negative bacilli and anaerobic organisms, particularly *Pseudomonas* and *Proteus*, are also commonly implicated, especially in more chronic wounds (greater than a month in duration), and give a characteristic offensive odour. Friable or beefy red granulation tissue in the wound bed is suggestive of superficial wound infection. Indicators of deeper infection include increasing pain, warmth, swelling and pyrexia [5]. In deeply infected wounds, there may be probing to underlying bone, and, in such cases, it is necessary to consider the possibility of osteomyelitis. Whilst more superficial wound infections will usually respond to topical antimicrobial agents, signs of deeper or systemic infection necessitate systemic antimicrobial therapy.

The gold standard for identifying causative organisms in wound infections is a biopsy of the wound bed for culture and sensitivity of organisms, although this is seldom practicable in standard clinical practice. Rather, a bacteriology swab should be taken from the wound base after removal of slough and exudate, rotated through 360° and sent to the laboratory in transport medium. Culture and sensitivity will identify pathogenic organisms, including resistant bacteria, and guide the choice of antimicrobial therapy. Bacterial counts are often elevated under occlusive dressings, and there is no good explanation for the low incidence of clinical infection, although limiting exogenous pathogenic organisms by the barrier of the dressing may play a part [6–8].

In recent years, emergence of multiple antibiotic resistance of methicillin-resistant strains of *Staphylococcus aureus* (MRSA) has become a major clinical problem worldwide [9–12]. Although hospital-acquired MRSA infections have been implicated in causing many nosocomial infections, community-acquired reservoirs of MRSA are now identified in a greater number of wound infections [13]. MRSA bacteraemia rates have increased worldwide over recent years, and are associated with a higher mortality than bacteraemias of methicillin-sensitive *Staphylococcus aureus* [14]. At a cellular level, the key determinant of the broad-spectrum beta-lactam resistance in MRSA strains is the activity of the penicillin-binding protein 2a (PBP2a) [15]. Patients with chronic wounds are also frequently treated with oral antibiotics when suspected of clinical infection, which predisposes to the development of resistance of other organisms. Notably, widespread use of ciprofloxacin for its anti-*Pseudomonas* activity has given rise to resistant isolates from leg ulcers [10,12,16].

References

1 Krizek TJ, Robson MC. Evolution of quantitative bacteriology in wound management. *Am J Surg* 1975; **130**: 579–84.
2 Dow G, Browne A, Sibbald RG. Infection in chronic wounds: controversies in diagnosis and treatment. *Ostomy Wound Manage* 1999; **45**: 23–7, 29–40.
3 Sibbald RG, Woo K, Ayello EA. Increased bacterial burden and infection: The story of NERDS and STONES. *Adv Skin Wound Care* 2006; **19**: 447–61.
4 Daltrey DC, Rhodes B, Chattwood JG. Investigation into the microbial flora of healing and non-healing decubitus ulcers. *J Clin Pathol* 1981; **34**: 701–5.
5 Gardner SE, Frantz RA, Doebbeling BN. The validity of the clinical signs and symptoms used to identify localized chronic wound infection. *Wound Repair Regen* 2001; **9**: 178–86.
6 Lookingbill DP, Miller SM, Knowles RC. Bacteriology of chronic leg ulcers. *Arch Dermatol* 1978; **114**: 1765–8.
7 Mertz PM, Marshall DA, Eaglestein WH. Occlusive wound dressings to prevent bacterial invasion and wound infection. *J Am Acad Dermatol* 1985; **12**: 662–8.
8 Varghese MC, Balin AK, Carter M, Caldwell D. Local environment of chronic wounds under synthetic dressings. *Arch Dermatol* 1986; **122**: 52–7.
9 MacKinnon MM, Allen KD. Long-term MRSA carriage in hospital patients. *J Hosp Infect* 2000; **46**: 216–21.

10 Colsky AS, Kirsner RS, Kerdel FA. Analysis of antibiotic susceptibilities of skin wound flora in hospitalized dermatology patients. *Arch Dermatol* 1998; **134**: 1006–9.
11 Tiemersma EW, Bronzwaer SLAM, Lyytikäinen O *et al*. Methicillin-resistant *Staphylococcus aureus* in Europe, 1999–2002. *Emerg Infect Dis* 2004; **10**: 1627–35.
12 Valencia IC, Kirsner RS, Kerdel FA. Microbiologic evaluation of skin wounds: alarming trend toward antibiotic resistance in an inpatient dermatology service during a 10-year period. *J Am Acad Dermatol* 2004; **50**: 845–9.
13 Demling RH, Waterhouse B. The increasing problem of wound bacterial burden and infection in acute and chronic soft-tissue wounds caused by methicillin-resistant *Staphylococcus aureus*. *J Burns Wounds* 2007; **7**: e8.
14 Melzer M, Eykyn SJ, Gransden WR, Chinn S. Is methicillin-resistant *Staphylococcus aureus* more virulent than methicillin-susceptible *S. aureus*? A comparative cohort study of British patients with nosocomial infection and bacteraemia. *Clin Infect Dis* 2003; **37**: 1453–60.
15 Lim D, Strynadka NC. Structural basis for the beta-lactam resistance of PBP2a from methicillin-resistant *Staphylococcus aureus*. *Nat Struct Biol* 2002; **9**: 870–6.
16 Teng P, Falanga V, Kerdel FA. The microbiological evaluation of leg ulcers and infected dermatoses in patients requiring hospitalization. *Wounds* 1993; **5**: 133–136.

Other local factors influencing wound healing

Desiccation of the wound allows the formation of a dry eschar, leading to slower re-epithelialization. Indeed, covered acute wounds resurface up to 40% faster than those exposed to the air [1–3]. A moist wound environment also encourages more rapid angiogenesis and dermal repair [4–6]. Occlusion of chronic wounds may also increase healing rates over the first 4 weeks.

Haematoma formation may impede wound healing because of local tissue hypoxia as well as providing a medium for accumulation and growth of bacteria and other microorganisms [7]. Haemostasis is therefore important in surgical procedures, as is good wound handling because crushed tissue or over-tight sutures may cause ischaemia and promote inflammation and secondary infection.

Foreign bodies in wounds tend to lower pH, reduce oxygen tension and activate complement, thereby delaying wound healing [3,7].

Contact dermatitis may develop to a variety of topical preparations applied to wounds. There is a tendency towards a greater incidence with increasing age and many patients will have positive patch tests to multiple allergens [8–11]. Commonly identified medicament allergens include aminoglycoside antibiotics, fragrance allergens, lanolin, topical corticosteroids, rubber accelerators and hydrocolloid gels. Contact allergy or cell toxicity to a number of herbal or complementary wound preparations are also recognized [12–15]. Superimposed contact dermatitis usually delays wound repair and some vehicles of topically applied medications may also affect epithelialization [16].

References

1 Eaglstein WH. Experiences with biosynthetic dressings. *J Am Acad Dermatol* 1985; **12**: 434–40.
2 Levine R, Agren MS, Mertz PM. Effect of occlusion on cell proliferation during epidermal healing. *J Cutan Med Surg* 1998; **2**: 19319–8.
3 Agren MS, Karlsmark T, Hansen JB, Rygaard J. Occlusion versus air exposure on full-thickness biopsy wounds. *J Wound Care* 2001; **10**: 301–4.
4 Goslen JB. Wound healing for the dermatologic surgeon. *Dermatol Surg Oncol* 1988; **14**: 959–72.
5 Dyson M, Young SR, Pendle L *et al.* Comparison of moist and dry conditions on dermal repair. *J Invest Dermatol* 1989; **92**: 434–9.
6 Dyson M, Young SR, Hart J *et al.* Comparison of moist and dry conditions on the process of angiogenesis during dermal repair. *J Invest Dermatol* 1992; **99**: 729–33.
7 Reed BR, Clark RAF. Cutaneous tissue repair: practical implications of current knowledge II. *J Am Acad Dermatol* 1985; **13**: 919–41.
8 Travadia S, Bianchi J, Dawe RS *et al*. Allergic contact dermatitis in venous leg ulcer patients. *Contact Dermatitis* 2003; **48**: 261–5.
9 Machet L, Couhé C, Perrinaud A *et al*. A high prevalence of sensitization still persists in leg ulcer patients: a retrospective series of 106 patients tested between 2001 and 2002 and a meta-analysis of 1975–2003 data. *Br J Dermatol* 2004; **150**: 929–35.
10 Saap L, Fahim S, Arsenault E *et al*. Contact sensitivity in patients with leg ulcerations. *Arch Dermatol* 2004; **140**: 1241–6.
11 Green CM, Holden CR, Gawkrodger DJ. Contact allergy to topical medicaments becomes more common with advancing age: an age-stratified study. *Contact Dermatitis* 2007; **56**: 229–31.
12 Prashar A, Locke IC, Evans CS. Cytotoxicity of lavender oil and its major components to human human skin cells. *Cell Prolif* 2004; **37**: 221–9.
13 Ferreira M, Teixeira M, Silva E, Selores M. Allergic contact dermatitis to Aloe vera. *Contact Dermatitis* 2007; **57**: 278–9.
14 Rutherford T, Nixon R, Tam M, Tate B. Allergy to tea tree oil: retrospective review of 41 cases with positive patch tests over 4.5 years. *Australas J Dermatol* 2007; **48**: 83–7.
15 Sköld M, Hagvall L, Karlberg AT. Autoxidation of linyl acetate, the main component of lavender oil, creates potent contact allergens. *Contact Dermatitis* 2008; **58**: 9–14.
16 Eaglstein WH, Mertz PM. Inert vehicles do affect wound healing. *J Invest Dermatol* 1980; **74**: 90–1.

Wound healing and ageing

Wound healing in the elderly progresses more slowly, and it is thought that all phases of the wound-healing process are affected, with decreased proliferative responses, delayed angiogenesis, delayed remodelling and slower re-epithelialization [1–6]. Age-related reductions are seen in keratinocyte and fibroblast migration (especially in poorly oxygenated wounds), integrin function, actin cytoskeletal organization and inflammatory chemokine responses [7–11]. Incisional wounds in older individuals have a lower tensile strength, and postoperative surgical dehiscence rates are higher [12]. However, elderly patients do successfully heal after major surgery, such as open heart surgery, and so the differences from younger individuals are not contraindications to surgical procedures. Other factors adversely affecting wound healing, such as peripheral vascular disease, cardiac problems, diabetes mellitus and poor nutrition, are also more likely to occur in the elderly.

Superficial wounds heal more slowly among the elderly, with unroofed blisters and split-thickness wounds, such as donor sites, showing the same pattern [3,13]. Meshed autografts greatly accelerated healing (10 days) compared with Vaseline gauze (10–36 days) in the treatment of donor sites in the elderly, which suggests that reducing the need for re-epithelialization is of considerable benefit [14]. New techniques of wound healing, such as cultured epidermal grafts, are particularly applicable to the elderly, but care must be taken to treat vigorously underlying medical conditions.

References

1 Eaglstein WH. Wound healing and ageing. *Clin Geriatr Med* 1989; **5**: 183–8.
2 Gosain A, DiPietro LA. Aging and wound healing. *World J Surg* 2004; **28**: 321–6.
3 Holt DR, Kirk SJ, Regan MC *et al*. Effect of age on wound healing in healthy human beings. *Surgery* 1992; **112**: 293–8.

4 Kligman AM. Perspectives and problems in cutaneous gerontology. *J Invest Dermatol* 1979; **73**: 39–46.
5 Orentreich N, Salmanowitz VJ. Levels of biological functions with ageing. *Trans NY Acad Sci* 1969; **2**: 992–1012.
6 Quirinia A, Viidik A. The influence of age on the healing of normal and ischaemic incisional wounds. *Mech Ageing Dev* 1991; **58**: 221–32.
7 Xia YP, Zhao Y, Tyrone JW *et al.* Differential activation of migration by hypoxia in keratinocytes isolated from donors of increasing age: implication for chronic wounds in the elderly. *J Invest Dermatol* 2002; **116**: 50–6.
8 Reed MJ, Ferara NS, Vernon RB. Impaired migration, integrin function, and actin cytoskeletal organization in dermal fibroblasts from a subset of aged human donors. *Mech Ageing Dev* 2001; **122**: 1203–20.
9 Swift ME, Burns AL, Gray KL, DiPietro LA. Age-related alterations in the inflammatory response to dermal injury. *J Invest Dermatol* 2001; **117**: 1027–35.
10 Mogford JE, Tawil N, Chen A *et al.* Effect of age and hypoxia on TGF-β1 receptor expression and signal transduction in human dermal fibroblasts: impact on cell migration. *J Cell Physiol* 2002; **190**: 259–65.
11 West MD. The cellular and molecular biology of skin ageing. *Arch Dermatol* 1994; **130**: 87–95.
12 Halasz NA. Dehiscence of laparotomy wounds. *Am J Surg* 1968; **116**: 210–4.
13 Grove GL. Age-related differences in healing of superficial skin wounds in humans. *Arch Dermatol Res* 1982; **272**: 381–5.
14 Fatah MF, Ward CM. The morbidity of split-skin graft donor sites in the elderly: the case for mesh grafting the donor site. *Br J Plast Surg* 1984; **37**: 184–90.

Systemic factors affecting wound healing

Systemic diseases, including vascular disorders (e.g. congestive cardiac failure, hypertension, atherosclerosis, venous insufficiency or lymphoedema), as well as metabolic disorders (e.g. chronic renal failure, chronic liver disease or diabetes mellitus) may all interfere with wound healing.

Underlying unrecognized or untreated diseases may also retard healing. For example, ulceration of the skin may result from ischaemic necrosis secondary to a primary vasculitis such as polyarteritis nodosa, rheumatoid vasculitis or neutrophilic inflammation such as pyoderma gangrenosum. Although the early stages of such lesions often have a prominent haemorrhagic component, they may result in indolent chronic ulcers. The site and distribution of lesions are often a clue to the underlying pathology, as are signs of inflammation, haemorrhage or undermining of the edge. Vasculitic lesions particularly affect acral sites and areas of impaired vascularity, and signs of livedo or palpable purpura may be present. Although lesions in necrotizing venulitis may be in the stasis areas, they will also occur on arms, legs and buttocks. Active treatment of the underlying disease will often stimulate surprisingly rapid healing, and intralesional steroids in the edge of a chronic wound help even chronic pyoderma gangrenosum lesions. Genetic abnormalities may also contribute to impaired wound healing, in particular abnormalities of connective tissue, as found in Marfan syndrome, Ehlers–Danlos syndrome and prolidase deficiency, and defects of the epidermis and appendages, such as epidermolysis bullosa and ankyloblepharon–ectodermal dysplasia–clefting syndrome.

Malignancy may be relevant to impaired wound healing, either because of ulceration occurring within a tumour or because malignancy arises on a background of chronic ulceration. Non-melanoma skin cancers, both basal cell and squamous cell carcinomas, as well as malignant melanoma, may ulcerate. Many of these lesions will be on sun-exposed sites, but they may be extensive in patients exposed to carcinogens, and lesions on the legs may be misdiagnosed, although this is a common site of actinic lesions in women. A malignant ulcer will continually grow in size, be irregular in shape and usually have a thickened edge. The site may be atypical for a chronic ulcer, which provides an important clue. A diagnostic biopsy of the edge should always be considered in any ulcer increasing in size. Excision and grafting will often be required on the lower leg. Malignant change can develop in a chronic non-healing ulcer, particularly following burns or pressure ulcers: this is referred to as a Marjolin ulcer. Suspicion is raised by failure to heal, progressive enlargement and changes in the ulcer edge, and a diagnostic biopsy is indicated. Tumours arising in chronic ulcers are usually squamous cell carcinomas and are typically aggressive with frequent local and distant metastasis, and an accompanying poor prognosis [1–3].

Protein malnutrition is a major factor affecting wound healing, and malnourished patients have an increased risk of surgical complications [4]. Surgery, trauma or sepsis may lead to relative protein deficiency and a negative nitrogen balance. This is particularly the case for patients following burns in whom nitrogen loss, malnutrition and loss of trace elements can be profound and have a negative effect on wound healing, morbidity and mortality if not adequately and promptly addressed [5,6]. Protein malnutrition causes inhibition of angiogenesis, and impairment of fibroblast proliferation and collagen synthesis; these abnormalities are reversed on protein replacement. Nutritional support also maintains immune function, decreases the risk of infection and facilitates wound healing [7]. Serum levels of albumin, transferrin and IGF-1 are indicators of the status of protein stores [8].

Vitamin deficiency may have adverse effects on wound healing, particularly in the case of vitamins A, C and K. Vitamin A modulates cell differentiation and can reverse inhibitory effects of glucocorticoids on healing of some wounds. Lack of vitamin A also compromises epithelialization, collagen synthesis and inflammation [9]. Vitamin C deficiency seriously impairs the speed and strength of wound healing because of markedly reduced collagen synthesis, formation of fragile capillaries and decreased resistance to infection [10]. Supplementation may improve rates of healing of chronic wounds [11]. Vitamin K is essential in the synthesis of blood clotting factors II, VII, IX and X. Deficiency of vitamin K impairs haemostasis and may result in haematoma formation.

Trace element deficiency usually occurs in combination with other deficiencies, particularly in chronic malabsorption and alcoholism. Zinc is a component of many coenzyme complexes, and severe deficiency results in abnormal lymphocyte function, increased susceptibility to infection and delayed wound healing [12,13]. Zinc-deficient wounds are also abnormally weak. Although zinc metabolism and distribution may be abnormal in patients with non-healing leg ulcers, oral zinc supplementation probably only accelerates healing in individuals with zinc deficiency. Topical zinc, however, may reduce infections and promote wound healing [13]. Iron deficiency interferes with wound healing by causing anaemia and tissue hypoxia, but also interferes with bacterial killing, increasing the risk of wound infection. Clearly, most deficiency states are multiple and it is difficult to distinguish which deficiency is causing the problem in healing. Local nutritional problems are also of importance in consideration of delayed healing, and loss of an adequate blood supply accounts for the bulk of the 'non-healing wounds' seen in clinical practice,

including decubitus ulcers and ulcers of the lower legs resulting from various types of vascular disease.

Drugs, such as corticosteroids, reduce DNA synthesis in the epidermis and induce morphological changes in fibroblasts [14,15]. In addition, it is well established that they induce dermal atrophy (probably by inhibiting synthesis of collagen) and retard re-epithelialization. It is therefore not surprising that long-term administration of these drugs either systemically or topically impedes the healing of wounds, and predisposes both to wound dehiscence and to chronic ulceration. Other drugs such as anticoagulants, cytotoxic agents, aspirin, colchicine, penicillamine, ciclosporin and phenylbutazone [16–18] may have adverse effects on wound healing, from direct effects on cells taking part in the healing process (as in cytotoxic agents), effects on vascularization or the enhancement of infection.

It is well-established that cigarette smoking has an adverse effect on wound healing [19]. It causes restriction of cutaneous blood flow and carboxyhaemoglobin further limits oxygenation of the skin. There are also reductions in dermal fibroblast proliferation and migration which impair healing and cause increased scarring. Surgical scars, flaps and grafts are at particular risk of breakdown and smokers should therefore be encouraged strongly to stop smoking before elective procedures [20].

References

1 Ozek C, Cankayali R, Bilkay U *et al.* Marjolin's ulcers arising in burn scars. *J Burn Care Rehabil* 2001; **22**: 384–9.

2 Enoch S, Miller DR, Price PE, Harding KG. Early diagnosis is vital in the management of squamous cell carcinomas associated with chronic non healing ulcers: a case series and review of the literature. *Int Wound J* 2004; **1**: 165–75.

3 Combemale P, Bousquet M, Kanitakis J *et al*. Malignant transformation of leg ulcers: a retrospective study of 85 cases. *J Eur Acad Dermatol Venereol* 2007; **21**: 935–41.

4 Law NW, Ellis H. The effect of parenteral nutrition on the healing of abdominal wall wounds and colonic anastamoses in protein malnourished rats. *Surgery* 1990; **107**: 449–54.

5 De-Souza DA, Greene J. Pharmacological nutrition after burn injury. *J Nutr* 1998; **128**: 797–803.

6 Berger MM, Shenkin A. Trace element requirements in critically ill burned patients. *J Trace Elem Med Biol* 2007; **21** (Suppl. 1): 44–8.

7 Breslow RA, Hallfrisch J, Guy DG *et al*. The importance of dietary protein in healing pressure ulcers. *J Am Geriatr Soc* 1993; **41**: 357–62.

8 Moller S, Jenson M, Svensson P *et al.* Insulin-like growth factor 1 (IGF-1) in burn patients. *Burns* 1991; **17**: 279–81.

9 Hunt TK. Vitamin A and wound healing. *J Am Acad Dermatol* 1986; **15**: 817–21.

10 Hunt AH. The role of vitamin C in wound healing. *Br J Surg* 1940; **28**: 436.

11 Desneves KJ, Todorovic BE, Cassar A, Crowe TC. Treatment with supplementary arginine, vitamin C and zinc in patients with pressure ulcers: a randomized controlled trial. *Clin Nutr* 2005; **24**: 979–87.

12 Haley JV. Zinc sulphate and wound healing. *J Surg Res* 1979; **27**: 168–74.

13 Lansdown AB, Mirastschijski U, Stuubs N *et al*. Zinc in wound healing: theoretical, experimental, and clinical aspects. *Wound Repair Regen* 2007; **15**: 2–16.

14 Devitt H, Clark M, Macks R *et al*. A quantitative approach to epidermal wound healing: the effect of dexamethasone on regenerating epithelium. *Br J Dermatol* 1978; **98**: 315–23.

15 Eaglstein WH, Mertz PM. New method for assessing epidermal wound healing: the effects of triamcinolone acetonide and polyethylene film occlusion. *J Invest Dermatol* 1978; **71**: 382–4.

16 Fishel R, Barbul A, Wasserkrug HL. Cyclosporin A impairs wound healing in rats. *J Surg Res* 1983; **34**: 572–5.

17 Morton D. Effect of colchicine on wound healing in rats. *Surg Forum* 1974; **25**: 47–9.

18 Pollack SV. Systemic drugs and nutritional aspects of wound healing. *Clin Dermatol* 1984; **2**: 68–80.

19 Freiman A, Bird G, Metelitsa AI *et al*. Cutaneous effects of smoking. *J Cutan Med Surg* 2004; **8**: 415–23.

20 Goldminz D, Bennett RG. Cigarette smoking and flap and full-thickness graft necrosis. *Arch Dermatol* 1991; **127**: 1012–5.

Principles of treating wounds

Assessment and wound bed preparation

Assessment of any wound should include investigation of possible primary pathology, such as Doppler studies of arterial pressure if ischaemic aetiology is suspected. Any potential factors that may be delaying healing, for example poorly controlled diabetes mellitus, malnutrition or systemic corticosteroid use, should also be explored and corrected where possible. It is important to be able to assess wounds objectively so that progress can be monitored at successive visits. Accurate wound measurement to establish the area, shape and volume of the wound, however, is often difficult. Serial photography and computerized planimetry are not practicable to use in standard practice in the community, but a simple photographic record with a scale measurement included can provide a useful reference in the patient's clinical records over successive visits. Alternatively, in approximately circular wounds, the longest diameter in one direction may be multiplied by the diameter at 90 degrees to give an approximation of wound size. In more irregularly shaped wounds, tracings on gridded acetate films can be used and the area approximated by counting squares within the grid. This technique is prone to error, however, since it may not take account of islands of re-epithelialization within the wound, nor encompass wound depth. Since this technique also involves direct wound contact, it may be unacceptably painful to use. Deep, flask-shaped pressure ulcers are particularly difficult, but the volume of fluid under an occluding membrane can be roughly measured. Research studies may use a variety of techniques, including laser Doppler assessment of blood flow, ultrasound measurement of depth, optical coherence tomography, wound pH and direct measurement of arterial or venous pressures [1–3].

Thorough assessment of chronic wounds is fundamental to establishing potential causes of delayed healing and many tools for recording features such as size, exudate, wound bed and edge exist. A number of different schemes have been employed to use information from these clinical signs to address factors that are impeding healing. One that is commonly used is the TIME system, which examines a number of parameters that need to be optimized to prepare the wound bed for healing (Tissue, Infection/Inflammation, Moisture, Edge) [4,5]. Tissue in the wound bed is assessed for viability: necrotic tissue, slough or adherent eschar delays healing and acts as a focus for microorganisms, and needs removal before healing can progress. Infection and inflammation will also impair healing, so if infection is present, as assessed clinically and microbiologically, it should be treated with appropriate topical or systemic antimicrobial agents. Moisture balance is extremely important in chronic wounds: a desiccated wound will have delayed healing, but, similarly, excess exudate will cause maceration of surrounding skin with the potential for extension

of the wound. A variety of topical agents and dressings are available to achieve good moisture balance in different types of wound. The wound edge should be assessed if it is failing to advance or is undermined, and options such as debridement or grafting considered to encourage healing.

In addition to the wound itself, assessment of surrounding skin is essential to identify changes such as cellulitis, eczema or maceration. If callus is present it should be debrided to prevent increased tissue breakdown and ulceration underneath it. Pain should also be assessed: this may be procedural related to dressing changes or bathing, or constant, particularly if there is ischaemia, infection or neuropathy. A variety of pain assessment tools exist to record the nature, site and severity of pain.

References

1 Dyson M, Moodley S, Verjee L *et al*. Wound healing assessment using 20 MHz ultrasound and photography. *Skin Res Technol* 2003; **9**: 116–21.

2 Shukla VK, Shukla D, Tiwary SK *et al*. Evaluation of pH measurement as a method of wound assessment. *J Wound Care* 2007; **16**: 291–4.

3 Cobb MJ, Chen Y, Underwood RA *et al*. Noninvasive assessment of cutaneous wound healing using ultrahigh-resolution optical coherence tomography. *J Biomed Opt* 2006; **11**: 064002.

4 Falanga V. Classifications for wound bed preparation and stimulation of chronic wounds. *Wound Repair Regen* 2000; **8**: 347–52.

5 Schultz G, Sibbald RG, Falanga V *et al*. Wound bed preparation: a systematic approach to wound management. *Wound Repair Regen* 2003; **11**: S1–28.

Compression bandaging

Compression bandaging and elastic stockings are of proven benefit in reversing the effects of chronic venous hypertension, by raising the local hydrostatic pressure and reducing superficial venous pressure [1–4] (Table 14.6). Indeed, a systematic review of venous leg ulcer compression bandaging trials has found that compression increases ulcer healing rates compared with no compression, that multilayered systems are more effective than single layer dressings, and that high compression is more effective than low compression [5]. The compression increases flow velocity, and results in the restoration of fibrinolysis and breakdown of fibrin cuffs. The optimal external pressure of 35–40 mmHg may not be tolerated, but lower pressures may enhance ulcer healing. It is essential not to deliver such levels of pressure to an ischaemic leg, as necrosis or gangrene may result [6]. For this reason, Doppler pressures should always be measured and compression dressings only used if the ankle brachial pressure index is greater than 0.8.



Fig. 14.5 Application of a four-layer bandage.

Traditional crêpe bandaging, etc., provides little external compression, but newer short-stretch and high-performance bandages are much more effective. There is variation in pressure according to the technique of the user. A large community programme tested a four-layer bandaging technique (Fig. 14.5) designed to deliver sustained, consistent compression for a week between dressing changes (crêpe/Velband/Elset/Coban) [1]. The excellent healing rate (80% of ulcers in 12 weeks) in this study has led to the widespread adoption of the technique in the UK, but the success rates depend on the local clinical profile; specialist wound-care units often collect patients who have failed all conventional treatments. Combining compression therapy with surgery to correct superficial venous reflux does not lead to improved healing rates compared with compression alone, but reduces ulcer recurrence and increases ulcer-free time [7].

Table 14.6 Compression hosiery and bandages.

	Class	Ankle pressure (mmHg)	Indication
Compression hosiery	1	14–17	Varicose veins
	2	18–24	Mild oedema and prevention of recurrence venous ulcers in slim legs
	3	25–35	Oedema and chronic venous insufficiency in large legs
Single-layer bandages	3a	14–17	Uncomplicated venous leg ulcers, e.g. Elset, K-Plus
	3b	18–24	Venous leg ulcers and lymphoedema, e.g. Coban
	3c	25–35	Venous leg ulcers and lymphoedema in large legs, e.g. Tensopress, Setopress
	3d	36–50	Extensive venous leg ulcers, ulcers secondary to lymphoedema, venous insufficiency following venous thrombosis in very large or oedematous legs, e.g. elastic web bandages
Multilayer bandages		36–50	Venous leg ulcers and ulcers secondary to lymphoedema, e.g. Padding, crepe plus Class 3a and 3b bandages

References

1 Blair SD, Wright DDI, Backhouse CM *et al.* Sustained compression and healing of chronic venous ulcers. *BMJ* 1988; **297**: 1159–61.
2 Burnand KG, Layr GT. Graduated elastic stockings. *BMJ* 1986; **293**: 224–5.
3 Burnand KG, Clemenson G, Morland M *et al.* Venous lipodermatosclerosis: treatment by fibrinolytic enhancement and elastic compression. *BMJ* 1980; **280**: 7–11.
4 Hendricks WM, Swallow RT. Management of stasis ulcers with Unna's boots versus elastic support stockings. *J Am Acad Dermatol* 1985; **12**: 90–8.
5 Cullum N, Nelson EA, Fletcher AW, Sheldon TA. Compression for venous leg ulcers. *Cochrane Database Syst Rev* 2001; **2**: CD000265.
6 Callam MJ, Ruckley CV, Dale JJ *et al.* Hazards of compression treatment of the leg: an estimate from Scottish surgeons [Editorial]. *BMJ* 1987; **295**: 1382.
7 Gohel MS, Barwell JR, Tayler M *et al.* Long term results of compression therapy alone versus compression plus surgery in chronic venous ulceration (ESCHAR): randomized controlled trial. *BMJ* 2007; **335**: 83–7.

Organization of wound care services

Over the last couple of decades, there has been a move towards managing chronic wounds in community-based settings with district nurses providing the vast majority of care for patients. Admission for inpatient care and leg elevation is not practical due to lack of inpatient beds and high cost. Furthermore, leg ulcers healed by intensive inpatient treatment tend to recur following discharge, and admission is associated with a loss of independence in this largely elderly group. Using a research-based approach to optimize leg ulcer management, community leg ulcer clinics have increased wound healing rates as well as reducing costs for this care. This model also ensures that only patients with wounds requiring special expertise, such as skin grafting, vascular surgery or medical treatment, are referred to more expensive hospital facilities. Schemes, such as the Leg Club Foundation in the UK, provide valuable community-based treatment for patients, as well as education and social support (www.legclub.org).

Topical therapy

Antiseptics. Antiseptic antimicrobial agents have been widely used to cleanse infected wounds for many years. The advent of systemic antibiotics for infection control has led to a reappraisal of antiseptic usage, as they have now been shown to retard re-epithelialization and slow healing [1,2]. However, this must be balanced against the emergence of bacteria resistant to systemic and topical antibiotics, in which setting appropriate use of antiseptic preparations may be extremely useful.

Saline dressings can be used to irrigate and clean a wound, removing cellular and bacterial debris, and are safe but pharmacologically inactive. Hexachlorophene and chlorhexidine are tissue toxic, and tend to be painful to apply to open wounds. Hydrogen peroxide is rapidly broken down to give molecular oxygen and, as with sodium hypochlorite, is rapidly inactivated by tissue exudate, although the physical effervescence may help surface debridement. A cream formulation of stabilized hydrogen peroxide has broad antimicrobial effects and, in addition, improves the microcirculation in chronic venous ulcers with a beneficial effect on healing [3]. Povidone–iodine solution is also toxic in high concentrations, but can maintain bactericidal activity at low concentration. Its effect on wound healing is not clearly established, but there is some evidence to suggest a beneficial effect on chronic wounds [4,5]. Cadexomer-iodine has beneficial effects in wound healing through its antimicrobial action, although it also increases levels of VEGF in wounds [6,7]. As iodine can cause contact dermatitis, it should be used with caution.

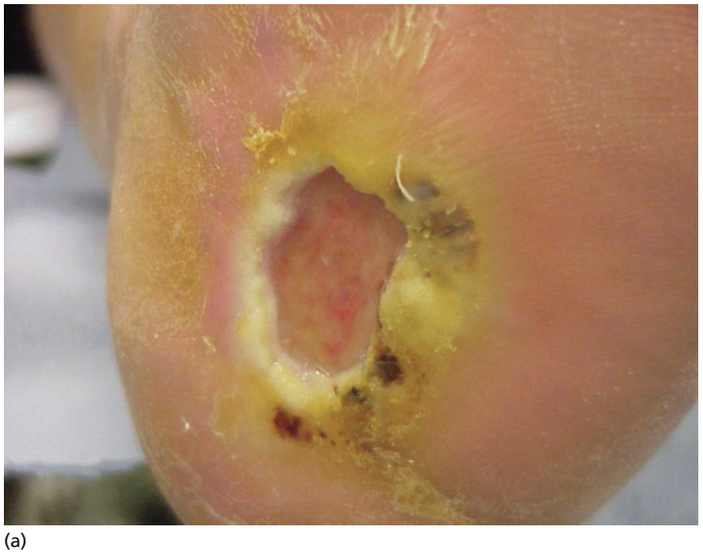
Silver sulfadiazine compounds are widely used in burn care, being effective against *Staphylococcus aureus* and *Pseudomonas aeruginosa*, and possibly having an effect by enhancing epithelialization [8].

Antibiotics. Topical antibiotics have also been used to reduce tissue infection in wounds and are often incorporated into dressing materials, but they are frequent causes of contact dermatitis, particularly neomycin and gentamicin. Use of systemic antibiotics for true tissue infection is now preferred, particularly with the development of antibiotic-resistant organisms. Mupirocin appears to sensitize infrequently but, as it may be effective in multiresistant *Staphylococcus aureus* (MRSA), it should not be generally used. Topical antibiotic use should be strictly limited to appropriate clinical settings and not used for prolonged periods of time.

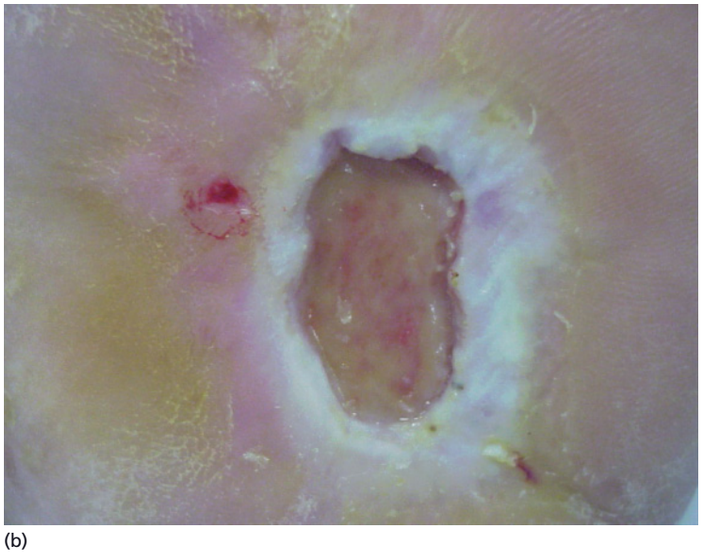
Traditional. Honey mixed with butter was applied to wounds by the Ancient Egyptians as 'Balm of Gilead', and both honey and cane sugar are still used as wound dressings [9,10]. Honey stimulates tissue growth and epithelialization, as well as reducing inflammation and infection, debriding and deodorizing wounds [11]. It is also effective against antibiotic resistant bacteria, including MRSA [12]. A systematic review of randomized trials of topical honey in superficial burns and wounds has concluded that honey may be a useful treatment [13]. Cane sugar containing sucrose, which is not metabolized outside the gastrointestinal tract, prevents bacterial growth by decreasing available water, and it has also been claimed that it might stimulate granulation tissue [14].

References

1 Brennan SS, Leaper DJ. The effect of antiseptics on the healing wound: a study using the rabbit ear chamber. *Br J Surg* 1985; **72**: 780–2.
2 Lineweaver W, Howard R, Soucy D *et al.* Topical antimicrobial toxicity. *Arch Surg* 1985; **120**: 267–70.
3 Belcaro G, Cesarone MR, Errichi BM *et al.* Improvement of microcirculation and healing of venous hypertension and ulcers with Crystacide: evaluation with a microcirculatory model, including free radicals, laser doppler flux, and PO2/PCO2 measurements. *Angiology* 2007; **58**: 323–8.
4 Kramer SA. Effect of povidone-iodine on wound healing: a review. *J Vasc Nurs* 1999; **17**: 17–23.
5 Eming SA, Smola-Hess S, Kurschat P *et al.* A novel property of povidon-iodine: inhibition of excessive protease levels in chronic non-healing wounds. *J Invest Dermatol* 2006; **126**: 2731–3.
6 Lamme EN, Gustafsson TO, Middelkoop E. Cadexomer-iodine ointment shows stimulation of epidermal regeneration in experimental full-thickness wounds. *Arch Dermatol Res* 1998; **290**: 18–24.
7 Ohtani T, Mizuashi M, Ito Y, Aiba S. Cadexomer as well as cadexomer iodine induces the production of proinflammatory cytokines and vascular endothelial growth factor by human macrophages. *Exp Dermatol* 2007; **16**: 318–23.
8 Geronomus RG, Mertz PM, Eaglstein W. Wound healing: the effects of topical antimicrobial agents. *Arch Dermatol* 1979; **115**: 1311–4.
9 Bergman A. Acceleration of wound healing by topical application of honey. *Am J Surg* 1983; **145**: 374–6.
10 Gordon HL. Sugar and wound healing. *Lancet* 1985; **2**: 663–4.
11 Molan PC. Re-introducing honey in the management of wounds and ulcers—theory and practice. *Ostomy Wound Manage* 2002; **48**: 28–40.
12 Blaser G, Santos K, Bode U *et al.* Effect of medical honey on wounds colonized or infected with MRSA. *J Wound Care* 2007; **16**: 325–8.



(a)



(b)

Fig. 14.6 Neuropathic ulcer of the sole before (a) and after (b) debridement. (Courtesy of the Diabetic Foot Clinic, King's College Hospital, London.)

13 Moore OA, Smith LA, Campbell F *et al*. Systematic review of the use of honey as a wound dressing. *BMC Complement Altern Med* 2001; **1**: 2.
14 Chirife J, Herszage L, Joseph A. Microbiological basis for the use of sugar in treating infected wounds. *Antimicrob Agents Chemother* 1983; **23**: 766–73.

Wound debridement

When there has been necrosis or progression in a chronic ulcer, necrotic debris which accumulates on the surface of or around a wound may impair healing by forming a physical barrier to re-epithelialization, as well as acting as a focus for infection. Debridement is the removal of this tissue and can be undertaken using a variety of techniques [1]. Surgical debridement under local or general anaesthetic may be required to promote healing, and entails removal of necrotic tissue and a margin of viable tissue. This may need to be repeated at intervals. Conservative sharp dissection does not usually require anaesthetic as it involves removal of necrotic tissue only, without viable wound margin (Fig. 14.6).

Non-surgical methods of debridement include irrigation with water or saline, which can also be performed under pressure in a whirlpool. Wet-to-dry dressings involve application of saline-soaked gauze to a wound and removal when it has dried out, taking with it adherent slough and necrotic tissue. This may be painful for the patient, however, limiting its usefulness. Autolytic debridement exploits the presence of endogenous collagenases and proteases present in a wound to break down necrotic tissue. Appropriate dressings to maintain a moist wound environment, such as hydrogels, films and hydrocolloid dressings in dry wounds, and foams, alginates or hydrofibres in more sloughy wounds, may be used. Care must be taken to protect surrounding skin from damaging effects of these enzymes, however.

Proteolytic enzymes can also be applied to wounds to facilitate debridement, and, again, care must be exercised to protect surrounding tissues. The two enzymes most commonly used in Europe are fibrinolysin/desoxyribonuclease and collagenase. Studies in necrotic ulcer animal models have shown the effectiveness of collagenase in wound debridement, but no clinical efficacy for fibrinolysin/DNAse in this model [2]. Streptokinase/streptodornase is the topical enzyme preparation most commonly used in the UK. Proteolytic enzymes derived from Antarctic krill have also been shown to be effective in wound debridement [3], and papain is also used in some countries.

Larval therapy has made a reappearance on the therapeutic scene [4]. Sterile maggots of the green bottle fly, *Lucilia (Phaenicia) sericata*, are used for debridement. Up to 1000 maggots are introduced into the wound and left for 1–3 days before a dressing change. Secretions from the maggots have a proteolytic effect and their movement in the wound bed is thought to stimulate granulation tissue. It is now also possible to use maggots contained in mesh bags for application to the wound bed which appears effective and may be more acceptable to the patient. One advantage of this therapy is that the maggots effectively separate necrotic from living tissue, thereby making subsequent surgical debridement unnecessary or much easier [5].

References

1 Anderson I. Debridement methods in wound care. *Nurs Stand* 2006; **20**: 65–72.
2 Mekkes JR, Zeegelaar JE, Westerhof W. Quantitative and objective evaluation of wound débriding properties of collagenase and fibrinolysin/desoxyribonuclease in a necrotic ulcer animal model. *Arch Dermatol Res* 1998; **290**: 152–7.
3 Mekkes JR, Le Poole IC, Das PK *et al*. *In vitro* tissue-digesting properties of krill enzymes compared with fibrinolysin/DNAse, papain and placebo. *Int J Biochem Cell Biol* 1997; **29**: 703–6.
4 Reames MK. The use of maggots in wound debridement. *Ann Plast Surg* 1988; **21**: 388–91.
5 Mumcuoglu KY. Clinical applications for maggots in wound care. *Am J Clin Dermatol* 2001; **2**: 219–27.

Wound dressings

Wound dressings protect the surface of wounds and prevent bacterial and viral contamination of healing wounds. Studies have shown that occlusive dressings maintaining a moist environment have beneficial effects on wound healing through accumulation of endogenous growth factors in wound fluid, and other biological effects on angiogenesis, generation of granulation tissue and re-epithelialization [1–5]. The main concern about wound occlusion has been a perceived increased risk of tissue infection, and indeed

occlusion of wounds can lead to higher bacterial counts. However, rates of tissue infection are low and there appears to be no impairment of re-epithelialization [6].

An ideal dressing should be able to maintain a good moisture balance at the wound bed, be easy to remove without damaging the wound or surrounding skin, be impermeable to bacteria, confer mechanical protection to the wound and be non-toxic and non-allergenic. Comfort for the patient, conformability, cost-effectiveness and a long shelf life are other important considerations. There are many different types of synthetic dressing available with different physical properties, depending on their composition. These comprise: polyurethane films, hydrogels, hydrocolloids, foams and alginates. In addition, newer dressings have emerged that have specific clinically relevant qualities, including collagens, hydrofibres, antimicrobial dressings, debriding agents, odour-absorbing dressings, biosynthetic dressings and hyaluronic acid dressings [7]. A dressing should be selected according to the properties of the wound it is to be applied to, and this choice may need to be re-evaluated depending on how the wound progresses.

Clinical indications for optimal selection of appropriate dressings are outlined in Table 14.7.

Semipermeable films (e.g. Biocclusive®, Opsite®, Tegaderm®) are thin polyurethane transparent sheets that are often coated with adhesive to stick to the margins of the wounds, although they do not adhere to the wound itself. They are impermeable to bacteria and fluids but are air and water vapour permeable. Films allow inspection of the wound without need for removal and can be left *in situ* for up to several days at a time. They promote a moist wound environment but are not able to cope with large amounts of exudate and provide little mechanical protection of the wound. Films are useful for superficial wounds or as dressings around catheter sites. Care must be taken when removing film dressings because new epithelium can easily be stripped [8–10].

Low-adherence dressings (e.g. Bactigras®, Jelonet®, Mepitel®, NA Ultra®, Urgotul®) maintain a moist wound environment, but allow exudate to pass through from the wound to a secondary dressing. They have very low adherence to the wound bed and surrounding skin, so are a valuable choice in patients with fragile skin. Low-adherence dressings may come in the form of tulles, textiles or perforated or layered plastic films.

Hydrogels (e.g. ActiformCool®, Intrasite®, Sterigel®) are translucent, jelly-like non-adhesive matrices of insoluble polymers. They are able to donate water to the wound surface to maintain a moist environment, but, since they are only partially hydrated, can also absorb low to moderate amounts of exudate. They are semipermeable to gas and water vapour. Hydrogels are usually used in gel form, in sheets or impregnated into gauze with a secondary dressing applied over them. They often have a soothing, cooling and analgesic effect because the cross-linked polymers tend to entrap water and reduce the skin surface temperature by up to 5°C. Hydrogels are useful in superficial wounds as well as deeper wounds, sinuses and cavities, although care must be taken to avoid maceration of surrounding skin [11].

Hydrocolloids (e.g. DuoDERM Extra Thin®, Granuflex®, Tegasorb®) comprise an opaque mixture of adhesive absorbent polymers and gelling agents such as gelatin, pectin and sodium carboxymethylcellulose. They adhere well to the wound edge and have an impermeable polyurethane backing. Hydrophilic particles in the dressing interact with the wound exudate to form a yellow gel next to the wound. This can be confused with a purulent wound discharge, but the acidic microenvironment forms an antibacterial and antiviral barrier and is helpful in autolytic wound debridement. Hydrocolloid dressings can adhere to any dry or moist site, allowing the patient to bathe or shower. They are widely used in shallow or cavity wounds, especially on difficult areas to dress such as the sacrum and heels. Side effects from these dressings include an increased amount of granulation tissue and tissue maceration [12,13].

Hydrofibres (e.g. Aquacel®) are composed of carboxymethylcellulose fibres in a non-woven sheet that form a soft gel when exposed to heavily exudative wounds. They are extremely absorbent, up to three times more so than alginates (see below). They are well-suited to flat, cavity or sinus wounds and require a secondary dressing.

Alginates (e.g. Kaltostat®, Sorbsan®) are made from brown seaweed and are highly hydrophilic, changing from fibrous to gel form on absorbing water. Indeed, alginates can absorb up to 20 times their own weight. The ingredients include calcium salts of alginic, mannuronic and guluronic acids. When exposed to sodium-rich solutions (such as wound exudate) calcium and sodium ions interchange resulting in increased amounts of free calcium. This leads to amplification of the normal wound clotting cascade. Alginates are available in sheets or rope forms and are suitable for dressing heavily exudative wounds, deep wounds and cavities. In addition, they can be easily moved without damage to

Table 14.7 Selection of appropriate wound dressings.

Types of wound	Suitable dressings
Acute	
Abrasions, lacerations	Films, hydrocolloids, thin foams
Catheter or cannula sites	Films
Burns	Hydrocolloids, hydrogels, biosynthetic dressings
Donor sites	Films, hydrocolloids
Dermabrasion, chemical peels	Hydrogels
Surgical wounds	Films, hydrocolloids, hydrogels, alginates
Chronic	
Venous ulcer	
Heavy exudates	Foams, alginates, hydrofibres
Moderate exudates	Hydrocolloids, foams
Mild exudates	Hydrogels, hydrocolloids
Malodorous	Foams, alginates, hydrocolloid charcoal
Arterial	Hydrogels
Neuropathic	
Moist	Hydrogels, alginates, hydrofibres
Dry	Hydrogels, hydrocolloids
Pressure ulcers	
Stage I	Films, thin hydrocolloids
Stage II–III	Hydrocolloids, foams, hydrogels, debriding agents
Stage IV	Alginates, hydrofibres, debriding agents
Fungating	Hydrocolloids, hydrogels, alginates, foams, charcoal

the wound surface when well hydrated [13]. They require a secondary dressing and should be changed daily.

Foams (e.g. Allevyn®, Mepilex®) are absorbent, opaque polyurethane or silicone sheets that are permeable to gas and water vapour. They may be of variable thickness and are suitable for moderately or heavily exudative wounds. Foams often have a semi-permeable backing to prevent exudate seeping through. Conventional foam dressings may stick and be difficult to remove if the exudate dries out, but silicone-coated foams avoid this problem and protect surrounding skin.

Collagen dressings (e.g. Catrix®, Promogran®) are made from cowhide and are available as sheets, pads, particles or gels. Sometimes they are also combined with alginates or hydrogels. These dressings accelerate wound healing by providing a collagenous matrix to enhance cell migration during wound healing.

Antimicrobial dressings (e.g. Acticoat®, Aquacel Ag®, Inadine®, Iodosorb®) are designed to counter the anti-healing effects of bacterial colonization and infection in chronic wounds. While it is recognized that topical antimicrobials in high concentration interfere with wound healing, antiseptics such as povidone–iodine 0.001% have been shown to maintain bactericidal activity but without any cytotoxic effects on the healing wound. Slow-release iodine preparations such as cadexomer–iodine are suitable for chronic venous ulcers [14]. Thyroid function may be affected and should therefore be monitored in patients using iodine dressings. Silver compounds have also been shown to prevent chronic wound colonization by bacteria and are now widely available in a variety of different wound dressings including low adherence dressings, hydrofibres, hydrocolloids, alginates and foams [15]. Metronidazole gel is commonly used with other dressings to control odour and infections from anaerobic organisms that may be particularly problematic in fungating malignant wounds.

Debriding dressings in the form of chemical or enzymatic looseners can be used to remove necrotic tissue, often to supplement hydrocolloid dressings.

Odour-absorbing dressings (e.g. CliniSorb®, Lyofoam C®) are based on activated charcoal that absorbs bacterial breakdown products. These dressings are often combined with foam, alginate or hydrocolloid dressings.

Hyaluronic acid dressings (e.g. Hyalofill®) are made of biodegradable absorbent bipolymers that form a hydrophilic mesh with the wound exudate. Hyaluronic acid accelerates granulation tissue formation and re-epithelialization and these dressings help stabilize the clot and attract inflammatory cells crucial to the wound healing process.

References

1 Winter GD, Scales JT. Effect of air drying and dressings on the surface of a wound. *Nature* 1963; **197**: 91–2.

2 Dyson M, Young S, Pendle C *et al.* Comparison of the effects of moist and dry conditions on dermal repair. *J Invest Dermatol* 1988; **91**: 434–9.

3 Falanga V. Occlusive wound dressings: why, when, which? *Arch Dermatol* 1988; **124**: 872–906.

4 Hinman CP, Maibach H. Effect of air exposure and occlusion on experimental human skin wounds. *Nature* 1963; **200**: 377–8.

5 Reed BR, Clark RAF. Cutaneous tissue repair: practical implications of current knowledge. *J Am Acad Dermatol* 1985; **13**: 919–41.

6 Hutchinson JJ. Prevalence of wound infection under occlusive dressings: a collective survey of reported research. *Wounds* 1990; **1**: 23–33.

7 Bello YM, Phillips TJ. Therapeutic dressings. In: James WD, Cockerell CJ, Dzubow LM, Paller AS, Yancey KB, eds. *Advances in Dermatology*, Vol. 16. Mosby, New York, 2000: 253–72.

8 Alper JC, Welch EA, Ginsberg M *et al.* Moist wound healing under a vapour permeable membrane. *J Am Acad Dermatol* 1983; **8**: 347–53.

9 Jonkman MF, Bruin P, Hoeksma A *et al.* A clot-inducing wound dressing with high water vapor permeability: enhancing effects on epidermal wound healing in partial thickness wounds in guinea pigs. *Surgery* 1988; **104**: 537–45.

10 Jonkman MF, Hoeksma EA, Niewenhuis P. Accelerated epithelialization under a highly water vapour permeable wound dressing is associated with increased precipitation of fibrin (ogen) and fibronectin. *J Invest Dermatol* 1990; **94**: 477–84.

11 Hampton S. A small study in healing rates and symptom control using a new sheet hydrogel dressing. *J Wound Care* 2004; **13**: 297–300.

12 Friedman SJ, Wu PD. Management of leg ulcers with hydrocolloid occlusive dressing. *Arch Dermatol* 1984; **120**: 1329–36.

13 Gorse GJ, Mesner RL. Improved pressure sore healing with hydrocolloid dressings. *Arch Dermatol* 1987; **123**: 766–71.

14 Zhou LH, Nahm WK, Badiavas E *et al.* Slow release iodine preparation and wound healing: *in vitro* effects consistent with lack of *in vivo* toxicity in human chronic wounds. *Br J Dermatol* 2002; **146**: 365–74.

15 Leaper DJ. Silver dressings: their role in wound management. *Int Wound J* 2006; **3**: 282–94.

Other pharmacological and physical modalities

Pentoxifylline increases fibrinolysis, decreasing blood viscosity, increasing red cell deformity and inhibiting platelet aggregation. It is used to reduce symptoms of ischaemia in patients with occlusive arterial disease, and a number of studies indicate it may be beneficial with or without concurrent compression in the treatment of chronic venous leg ulcers [1].

Prostaglandins E1 and I2, iloprost and calcium-channel blockers such as nifedipine, show conflicting results in peripheral vascular disease and venous ulceration [2], although some calcium-channel blockers may have a direct effect on keratinocyte migration [3]. The serotonin antagonist, ketanserin has been shown to be of benefit when applied topically to diabetic foot and leg ulcers [4,5].

Ascorbic acid is a co-factor for proline hydroxylase necessary for collagen synthesis, but it is of doubtful benefit in patients who are not vitamin deficient. In accordance with the Pauling concept that most individuals do not have enough vitamin C in their diet, large dietary supplements of ascorbic acid were given to a group of patients with pressure sores in a double-blind study; considerable increase in the rate of healing was noted in the treated group [6]. Ascorbic acid has also been shown to have an important function in the preparation of *in vitro* skin substitutes, with direct effects on epidermal barrier formation, basement-membrane integrity and the quality of skin contracture after grafting [7].

The precise role of zinc in wound healing is unclear at present. Early studies claiming that systemic zinc therapy accelerated wound healing in humans and other animals have been supported by some workers and refuted by others [8,9]. This discrepancy may be partly explained by studies that have shown that systemic zinc reduces the healing time in patients with venous and arterial leg ulcers, but only if the patients are initially zinc deficient. Topical zinc may be beneficial in wound healing through local actions reducing infection and promoting epithelialization [9–11]. Zinc also appears to have an important antioxidant role in skin [12], and mutations in the zinc transport gene, *SLC39A4*, have recently been demonstrated in the zinc-deficiency disorder,

acrodermatitis enteropathica, an autosomal recessive condition associated with chronic superficial skin ulceration and poor wound healing [13].

Treatment of wounds with oxygen has been considered to be helpful in some wounds, although recent studies have focused on the state of the redox environment of wounds and the role of nitric oxide in wound repair [14,15]. Nitric oxide is a small radical, formed from the amino acid L-arginine by three distinct forms of nitric acid synthase. The inducible form (iNOS) is synthesized in the early stages of normal wound healing, and experimental knockout of the gene leads to delayed wound healing. By contrast, improved wound healing can be obtained by the addition of nitric oxide or arginine to wounds. Nitric oxide has also been shown to regulate collagen synthesis, cell proliferation and wound contraction [14]. Hyperbaric oxygen therapy increases wound nitric oxide levels which is thought to promote healing of chronic wounds, particularly diabetic foot ulcers [16–18]. Although not yet of practical widespread therapeutic value, manipulation of nitric oxide in skin using hyperbaric oxygen or other means may have future relevance to improving normal or abnormal wound healing.

In vacuum-assisted closure, negative pressure is used to assist wound closure, particularly deep wounds, chronic leg ulcers and diabetic ulcers [19,20]. It helps remove wound fluid and is thought to promote healing by increasing local tissue oxygenation, blood flow and formation of granulation tissue. Low-frequency, non-contact ultrasound has also been used to promote healing in chronic wounds and pressure ulcers, although efficacy of this modality has not hitherto been confirmed [21,22].

References

1 Jull A, Arroll B, Parag V, Waters J. Pentoxifylline for treating venous leg ulcers. *Cochrane Database Syst Rev* 2007; **3**: CD001733.
2 Coffman JD. Vasodilator drugs in peripheral vascular disease. *N Engl J Med* 1979; **300**: 713–17.
3 Trollinger DR, Isseroff RR, Nuccitelli R. Calcium-channel blockers inhibit galvanotaxis in human keratinocytes. *J Cell Physiol* 2002; **193**: 1–9.
4 Martínez-de Jesús FR, Morales-Guzmán M, Castaáeda M *et al*. Randomized single-blind trial of topical ketanserin for healing acceleration of diabetic foot ulcers. *Arch Med Res* 1997; **28**: 95–9.
5 Quatresooz P, Kharfi M, Paquet P *et al*. Healing effect of ketanserin on chronic leg ulcers in patients with diabetes. *J Eur Acad Dermatol Venereol* 2006; **20**: 277–81.
6 Taylor TV, Rimmer S, Day B. Ascorbic acid supplementation in pressure sores. *Lancet* 1974; **2**: 544–6.
7 Boyce ST, Supp AP, Swope VB, Warden GD. Vitamin C regulates keratinocyte viability, epidermal barrier, and basement membrane *in vitro*, and reduces wound contraction after drafting of cultured skin substitutes. *J Invest Dermatol* 2002; **118**: 565–72.
8 Greaves MW, Ive FA. Double blind trial of zinc sulphate in treatment of chronic venous leg ulceration. *Br J Dermatol* 1972; **87**: 632–4.
9 Lansdowne ABG, Mirastschijski U, Stubbs N *et al*. Zinc in wound healing: theoretical, experimental, and clinical aspects. *Wound Repair Regen* 2007; **15**: 2–16.
10 Stromberg HE, Agren MS. Topical zinc oxide treatment improves arterial and venous leg ulcers. *Br J Dermatol* 1984; **111**: 461–8.
11 Ågren MS, Ostenfeld U, Kallehave F *et al*. A randomized, double-blind, placebo-controlled multicenter trial evaluating topical zinc oxide for acute open wounds following pilonidal disease excision. *Wound Repair Regen* 2006; **14**: 526–35.
12 Rostan EF, DeBuys HV, Madey DL, Pinnell SR. Evidence supporting zinc as an important antioxidant for skin. *Int J Dermatol* 2002; **41**: 606–11.
13 Kury S, Dreno B, Bezieau S *et al*. Identification of *SLC39A4*, a gene involved in acrodermatitis enteropathica. *Nat Genet* 2002; **31**: 239–40.
14 Sen CK, Khanna S, Gordillo G *et al*. Oxygen, oxidants, and antioxidants in wound healing: an emerging paradigm. *Ann NY Acad Sci* 2002; **957**: 239–49.
15 Witte MB, Barbul A. Role of nitric acid in wound repair. *Am J Surg* 2002; **183**: 406–12.
16 Boykin JV Jr. The nitric oxide connection: hyperbaric oxygen therapy, becaplermin, and diabetic ulcer management. *Adv Skin Wound Care* 2000; **13**: 169–74.
17 Kranke P, Bennett M, Roeckl-Wiedmann I, Debus S. Hyperbaric oxygen therapy for chronic wounds. *Cochrane Database Syst Rev* 2004; **1**: CD004123.
18 Boykin JV Jr, Baylis C. Hyperbaric oxygen therapy mediates increased nitric oxide production associated with wound healing: a preliminary study. *Adv Skin Wound Care* 2007; **20**: 382–8.
19 Eginton MT, Brown KR, Seabrook GR *et al*. A prospective randomized evaluation of negative-pressure wound dressings for diabetic foot wounds. *Ann Vasc Surg* 2003; **17**: 645–9.
20 Vuerstaek JDD, Vainas T, Wuite J *et al*. State-of-the-art treatment of chronic leg ulcers: a randomized controlled trial comparing vacuum-asssisted closure (V.A.C.) with modern wound dressings. *J Vasc Surg* 2006; **44**: 1029–38.
21 Baba-Akbari Sari A, Flemming K, Cullum NA, Wollina U. Therapeutic ultrasound for pressure ulcers. *Cochrane Database Syst Rev* 2006; **3**: CD001275.
22 Kavros SJ, Schenck EC. Usage of noncontact low-frequency ultrasound in the treatment of chronic foot and leg ulcerations: a 51-patient analysis. *J Am Podiatr Med Assoc* 2007; **97**: 95–101.

Skin grafts

E.A O'Toole, pp. 14.25–14.27

Pinch grafts and split-thickness skin grafts

For pinch grafts, small (2–3 mm^2) pieces of partial-thickness skin can be removed under local anaesthetic, as an outpatient procedure or by a specialist nurse within the home, and planted across the wound bed to form islands for re-epithelialization with greatly increased healing (Fig. 14.7). The time-consuming nature of the procedure is the major problem, but repeated grafts can be performed, and the donor sites heal very rapidly. The approach may benefit both arterial and venous leg ulcers, and its suitability for primary care settings has been demonstrated [1].

For split-thickness skin grafts, a large sheet of partial-thickness skin is removed using a dermatome. The plane of cleavage may be variable, either within the papillary or reticular dermis. The graft is usually meshed before application as this tends to reduce the chances of the graft subsequently detaching as a result of the wound exudate. Split-thickness skin graft donor sites are often painful.

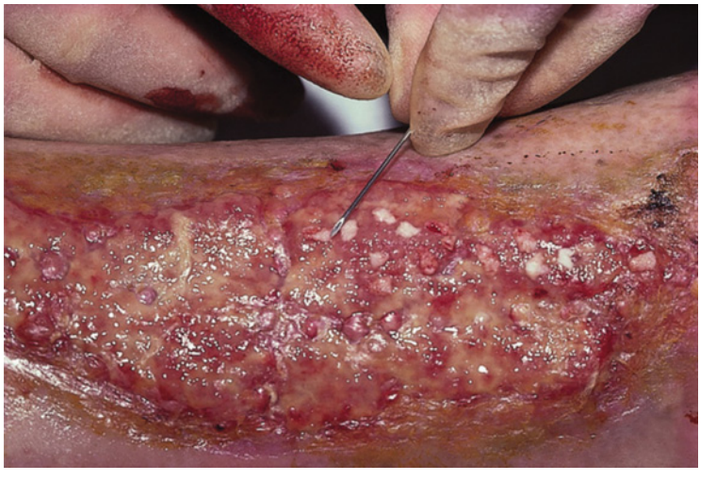
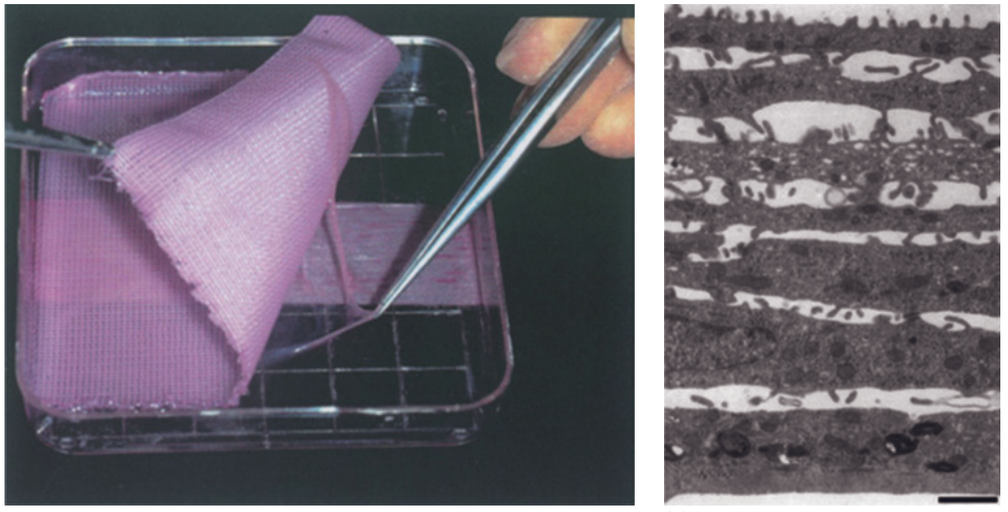


Fig. 14.7 Application of pinch grafts to a leg ulcer.



(a) (b)

Fig. 14.8 (a) Cultured keratinocyte allograft prepared for clinical use. (b) Ultrastructure of allograft.

In vitro-prepared skin grafts

The feasibility of growing human keratinocytes in culture was first established in 1975 [2] and the possibility of expanding a small donor site up to 10 000-fold led to the application of cultured keratinocytes for grafting [3]. Grafts established from the patient's own skin (autografts) or from allogeneic donors (allografts) have subsequently been formulated for clinical use (Fig. 14.8).

The earliest clinical use was to treat major burns patients, and the translucent sheets became a permanent stable epidermis, visible after 12–14 days [4]. The resulting graft remained fragile, and remodelling of the dermis occurred slowly [5]. Without a well-vascularized dermis, cultured keratinocytes alone are of limited use, and provision of a dermal equivalent in the graft on the wound bed appears to enhance graft take [6]. Cultured epidermal autografts have also been used to treat epidermolysis bullosa wounds [7], wound beds of congenital naevi [8], and chronic leg ulcers [9], where repeated grafting from passaged cultures is a major advantage. Preparation of a cultured keratinocyte sheet can take 2–3 weeks. Keratinocytes can also be suspended in fibrin and sprayed onto wounds or delivered on polymer carrier systems, such as hyaluronate membranes, allowing earlier grafting than previously possible [10–11]. Allografts of cultured keratinocytes do not survive long term [12–13], but have been shown to have a wound-healing effect in chronic leg ulcers [14], probably because of the production of appropriate growth factors and extracellular matrix proteins.

The field of tissue engineering to generate skin in the laboratory using keratinocytes, fibroblasts, growth factors and biomaterials has advanced considerably [15,16]. Available products can be categorized into three groups: (i) epidermal substitutes, (ii) dermal substitutes and (iii) combined epidermal and dermal substitutes (Fig. 14.9). Full-thickness wounds require replacement of both the epidermis and dermis. Current skin substitutes lack a vascular plexus, a major challenge for this area of research.

Pluripotent stem cells, such as mesenchymal cells from bone marrow, are recruited into the dermis during wound healing [17,18]. Stem cells derived from bone marrow or adipose tissue accelerate wound healing in both murine and human wounds, providing an exciting prospect for future therapy [19,20].

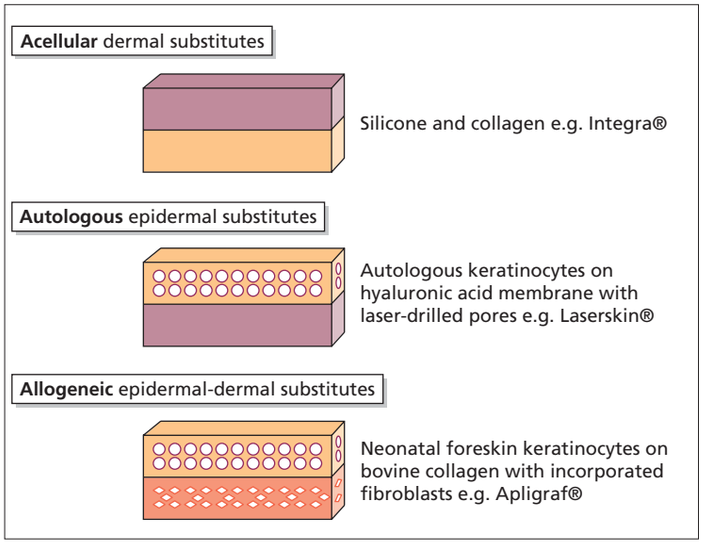


Fig. 14.9 Biological skin substitutes.

References

1 Oien RF, Hakansson A, Hansen BU, Bjellerup M. Pinch grafting of chronic leg ulcers in primary care: fourteen years' experience. *Acta Derm Venereol Stockh* 2002; **82**: 275–8.

2 Rheinwald J, Green H. Serial cultivation of strains of human epidermal keratinocytes: formation of keratinizing colonies from single cells. *Cell* 1975; **6**: 331–4.

3 Green H, Kehinde O, Thomas J. Growth of cultured human epidermal cells into multiple epithelia suitable for grafting. *Proc Natl Acad Sci USA* 1979; **76**: 5665–8.

4 O'Connor NE, Mulliken JB, Banks-Schlegel S *et al*. Grafting of burns with cultured epithelium prepared from autologous epidermal cells. *Lancet* 1981; **i**: 75–8.

5 Compton CC, Gill JM, Bradford DA *et al*. Skin regenerated from cultured epithelial autografts on full thickness burn wounds from 6 days to 5 years after graft-

ing: a light, electron microscopic and immunohistochemical study. *Lab Invest* 1989; **60**: 600–12.
6 Cuono C, Langdon R, McGuire J. Use of cultured epidermal autograft and dermal allografts as skin replacement after burn injury. *Lancet* 1986; **i**: 1123–4.
7 Collin B, Balderson D, Papini R, Marsden J, Moss C. Cultured autologous keratinocyte grafting of chronic erosions in three patients with epidermolysis bullosa. *Clin Exp Dermatol* 2006; **31**: 718–9.
8 Gallico GG, O'Connor NE, Compton CC *et al*. Cultured epithelial autografts for giant congenital naevi. *Plast Reconstr Surg* 1989; **84**: 1–9.
9 Limova M, Mauro T. Treatment of leg ulcers with cultured epithelial autografts: clinical study and case reports. *Osteotomy Wound Manage* 1995; **41**: 54–60.
10 Scuderi N, Onesti MG, Bistoni G *et al*. The clinical application of autologous bioengineered skin based on a hyaluronic acid scaffold. *Biomaterials* 2008; **29**: 1620–9.
11 Magnusson M, Papini RP, Rea SM *et al*. Cultured autologous keratinocytes in suspension accelerate epithelial maturation in an *in vivo* wound model as measured by surface electrical capacitance. *Plast Reconstr Surg* 2007; **119**: 495–9.
12 Brain A, Purkis PE, Coates P *et al*. Survival of cultured allogeneic keratinocytes transplanted to deep dermal bed assessed with probe specific for Y chromosome. *BMJ* 1989; **298**: 917–9.
13 Karawach WF, Oliver AM, Weiler-Mithoff E *et al*. Survival assessment of cultured epidermal allografts applied over partial thickness burn wounds. *Br J Plast Surg* 1991; **44**: 321–4.
14 Leigh IM, Purkis PE, Navsaria HA, Phillips TJ. Treatment of chronic venous ulcers with sheets of cultured allogeneic keratinocytes. *Br J Dermatol* 1987; **117**: 591–7.
15 MacNeil S. Progress and opportunities for tissue-engineered skin. *Nature* 2007; **445**: 874–80.
16 Wong T, McGrath JA, Navsaria HA. The role of fibroblasts in tissue engineering and regeneration. *Br J Dermatol* 2007; **156**: 1149–55.
17 Sasaki M, Abe R, Fujita Y *et al*. Mesenchymal stem cells are recruited into wounded skin and contribute to wound repair by transdifferentiation into multiple skin cell type. *J Immunol* 2008; **180**: 2581–7.
18 Wu Y, Chen L, Scott PG, Tredget EE. Mesenchymal stem cells enhance wound healing through differentiation and angiogenesis. *Stem Cells* 2007; **25**: 2648–59.
19 Altman AM, Matthias N, Yan Y *et al*. Dermal matrix as a carrier for *in vivo* delivery of human adipose-derived stem cells. *Biomaterials* 2008; **29**: 1431–42.
20 Yoshikawa T, Mitsuno H, Nonaka I *et al*. Wound therapy by marrow mesenchymal cell transplantation. *Plast Reconstr Surg* 2008; **121**: 860–77.

Growth factors to augment wound healing

All cells involved in the wound-healing process (inflammatory cells, epidermal keratinocytes and mesenchymal cells) can synthesize a wide range of membrane-bound and free growth factors, whose effects are mediated by specific growth factor receptors for each family of growth factor. Growth factors are multifunctional and have differing effects on different cell types, and can induce expression of other cytokines and their receptors in an autocrine and paracrine fashion. Growth factor activity can also be regulated via ECM components and proteolytic activation. The addition of exogenous growth factors in pharmacological amounts may have measurable effects in wound-healing models, but can be disappointing in the clinical arena [1–3]. Furthermore, elevated metalloproteinases and bacterial superinfection of wounds may completely obliterate any possibility of a useful therapeutic response from exogenous growth factors because of rapid degradation of the recombinant protein [4].

In animal models, a number of growth factors have positive effects on granulation tissue formation and angiogenesis, including PDGF, FGFs and TGF-β [5,6]. EGF family members appear to enhance re-epithelialization, as well as having mesenchymal effects [7–9]. Repifermin, a truncated form of recombinant KGF-2 (FGF-10), showed promise in a Phase 2A randomized clinical trial on venous ulcers [10], but in a subsequent trial failed to meet its primary endpoint [11]. PDGF (becaplermin gel) is currently the only licensed recombinant growth factor for treating recalcitrant wounds, and its usefulness in the management of chronic neuropathic diabetic ulcers has been demonstrated in clinical trials [12]. However, use of becaplermin is limited by cost and the requirement for daily applications.

The clinical success of delivery of growth factors to wounds has been disappointing. Gene therapy is a promising method of delivery of growth factors to epithelium. In a rabbit ischaemic ear wound model, one injection of an adenoviral vector containing DNA for human PDGF-AA increased wound closure and re-epithelialization compared to both ischaemic and non-ischaemic controls [13]. The promising results of the first human gene therapy trial using PDGF have recently been reported [14].

References

1 Leahy PJ, Lawrence WT. Biologic enhancement of wound healing. *Clin Plast Surg* 2007; **34**: 659–71.
2 Braund R, Hook S, Medlicott NJ. The role of topical growth factors in chronic wounds. *Curr Drug Deliv* 2007; **4**: 195–204.
3 Wong T, McGrath JA, Navsaria H. The role of fibroblasts in tissue engineering and regeneration. *Br J Dermatol* 2007; **156**: 1149–55.
4 Trengove NJ, Stacey MC, MacAuley S *et al*. Analysis of the acute and chronic wound environments: the role of proteases and their inhibitors. *Wound Repair Regen* 1999; **7**: 442–52.
5 Schweigerer L. Basic fibroblast growth factor as a wound healing hormone. *TIPS* 1988; **9**: 427–8.
6 Mustoe TA, Pierce GF, Thomason A *et al*. Accelerated healing of incisional wounds in rats induced by transforming growth factor β. *Science* 1987; **237**: 1333–6.
7 Brown GL, Nanney LB, Griffen J *et al*. Enhancement of healing by topical treatment with epidermal growth factor. *N Engl J Med* 1989; **321**: 76–9.
8 Laato N, Niinikoski J, Gerbin B *et al*. Stimulation of wound healing by epidermal growth factor. *Ann Surg* 1986; **203**: 379–81.
9 Schultz GS, White MW, Mitchell R *et al*. Epithelial wound healing enhanced by transforming growth factor-α and vaccinia growth factor. *Science* 1987; **235**: 350–2.
10 Robson MC, Phillips TJ, Falanga V *et al*. Randomized trial of topically applied repifermin (recombinant human keratinocyte growth factor-2) to accelerate wound healing in venous ulcers. *Wound Repair Regen* 2001; **9**: 347–52.
11 Goldman R. Growth factors and chronic wound healing: past, present, and future. *Adv Skin Wound Care* 2004; **17**: 24–35.
12 Wieman TJ, Smiell JM, Su Y. Efficacy and safety of a topical gel formulation of recombinant platelet-derived growth factor-BB (becaplermin) in patients with chronic neuropathic diabetic ulcers: a phase III randomized placebo-controlled double-blind study. *Diabetes Care* 1998; **21**: 822–7.
13 Liechty KW, Nesbit M, Herlyn M *et al*. Adenoviral-mediated overexpression of platelet-derived growth factor-B corrects ischemic impaired wound healing. *J Invest Dermatol* 1999; **113**: 375–83.
14 Margolis D, Crombleholme T, Thom S *et al*. Phase I gene transfer study of H5.020CMV.PDGF-b in venous leg ulcer. *J Invest Derm* 2007; **127**: S55 (abstr. 327).

CHAPTER 15
Genetics and Genodermatoses

A.D. Irvine[1] *& J.E. Mellerio*[2]

[1]Our Lady's Hospital for Sick Children, and Trinity College Dublin, Dublin, Ireland
[2]St John's Institute of Dermatology, St Thomas' Hospital, London, UK

Genetics and disorders of the skin, 15.1
Nosology of genetics in skin disease, 15.2
Principles of medical genetics, 15.2
Histocompatibility antigens and disease association, 15.8
Genetic counselling, 15.9
Chromosomal disorders, 15. 9
Autosomal chromosome defects, 15.10
Sex chromosome defects, 15.12
Noonan's syndrome, 15.14
Familial multiple tumour syndromes, 15.15
Ectodermal dysplasias, 15.27
Syndromes associated with DNA instability, 15.70
Poikilodermatous syndromes, 15.78
Miscellaneous syndromes, 15.83
Future directions, 15.97

Genetics and disorders of the skin

Progress in the field of genetics in medicine continues rapidly. Most of the known single-gene disorders (e.g. genodermatoses) have at least been mapped to a particular chromosomal region and, in ever-increasing number, the causal genes have been isolated and studied [1]. In contrast, progress towards unravelling the molecular genetic basis of the more common and complex disorders (e.g. psoriasis and atopic eczema) has been somewhat slower. However, recent progress with the human sequencing effort together with radically improved computerized analytical strategies offer the prospect of progress in understanding the pathogenesis of these important dermatological disorders. The extraordinary rate of such developments has contributed to the parallel progress in understanding of the fundamental aspects of human skin characteristics. In combination, this revolution offers enormous opportunity and excitement for future research, together with the prospect of improved therapies for skin disease.

The Human Genome Project, an international effort to describe the entire human genetic sequence (3×10^9 bases), has hit targets ahead of expectation, and the release of the first draft [2] has necessitated a radical readjustment of the likely number of human genes within the genome (20 000–25 000). The genome sequences of a range of other organisms, including the nematode worm *Caenorhabditis elegans*, the fruit fly *Drosophila melanogaster* and the mouse, have now been completed. These act as important models for exploring gene structure and function in relation to tissues or the whole organism and have been extensively investigated in relation to a number of important genodermatoses.

The Internet provides the most satisfactory window on all this activity and a number of the more informative sites are listed below.

- UK Human Genetics Unit (http://www.hgu.mrc.ac.uk). Access to a wide range of databases and resources for genetic studies.
- The National Center for Biotechnology Information (http://ncbi.nlm.nih.gov/guide/). Main entry point for information about the Human Genome Project.
- Mutation Database, Cardiff (http://www.hgmd.cf.ac.uk/ac/index.php).
- Online Mendelian Inheritance in Man (OMIM) (http://www.ncbi.nlm.nih.gov/omim/). OMIM is a catalogue of over 12 000 known human Mendelian characters, and was created by Dr Victor McKusick of Johns Hopkins Hospital, Baltimore, USA. OMIM is an excellent starting point for acquiring up-to-date information on human Mendelian characters or *phenotypes*. Each character is given a six-digit MIM number, which is widely used to identify inherited disorders in the medical literature. The first digit of the MIM number indicates the mode of inheritance (historical): 1, autosomal dominant; 2, autosomal recessive; 3, X-loci or phenotype; 4, Y-loci or phenotype; 5, mitochondrial loci; and 6, autosomal loci or phenotypes added after 1994.

References

1 Leech SN, Moss CA. Current and online genodermatosis database. *Br J Dermatol* 2007; **156**: 1115–48.
2 International Human Genome Sequencing Consortium. Initial sequencing of the human genome. *Nature* 2001; **409**: 860–921.

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

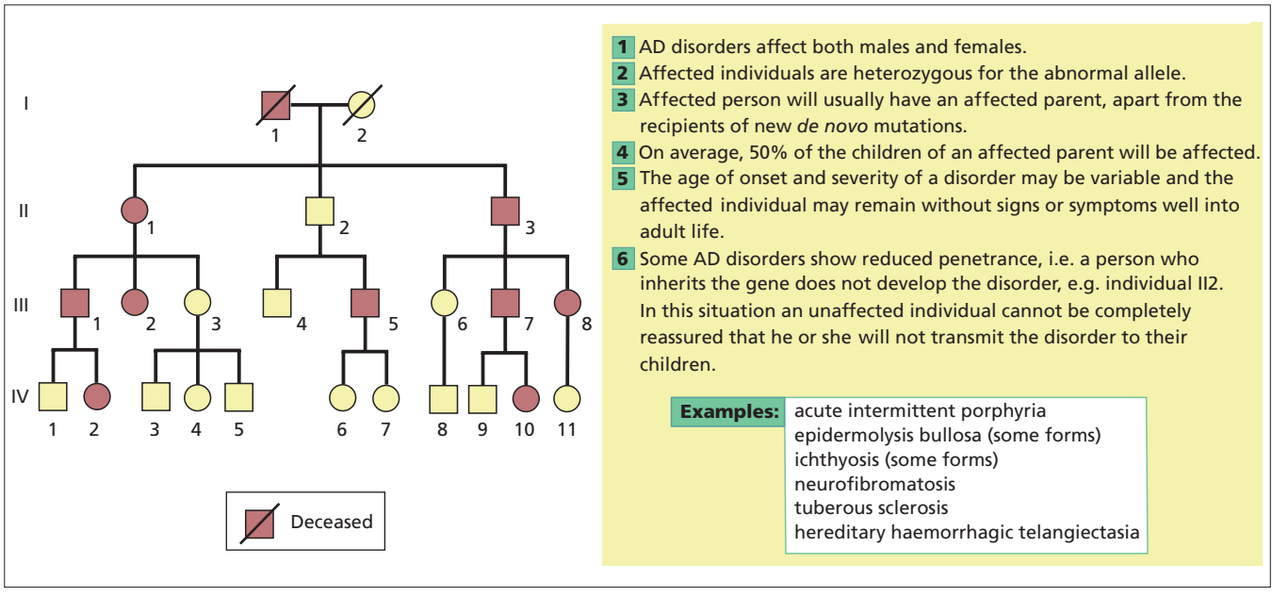


Fig. 15.1 Autosomal dominant (AD) inheritance.

Nosology of genetics in skin disease

The terms 'familial', 'inherited' and 'congenital' are frequently misunderstood and misused. *Familial* refers to the clustering of a disorder, with more close relatives affected than predicted by the population prevalence of the condition. *Inherited* disorders require the transmission of genetic variants from one generation to the next. The term *congenital* simply means that the character was present at or detectable before birth; such abnormalities may not be genetically determined, and include developmental defects due to environmental infectious agents (e.g. rubella) and deformations arising from physical insults (e.g. amniotic bands). Only a proportion of inherited disorders reveal themselves at birth (i.e. are congenital), with many having their onset in later life. Such age dependence may result from a wide number of factors, including maturation of cells or tissue-specific functions, exposure to exogenous agents or accumulation of a noxious substance. A further and important example of adult age of onset is provided by hereditary cancer syndromes, such as neurofibromatosis (NF) type 2, in which a second mutation impacting upon the normal allele of a so-called *tumour-suppressor gene* (e.g. *Merlin*) is required to lead to tumour formation. Such a mutation occurs as a 'somatic' change.

Of the inherited skin abnormalities, the largest group is the single-gene disorders, which require an alteration in the function of a gene and are known commonly as the genodermatoses. The inheritance patterns for classical genodermatoses are illustrated in Figs 15.1–15.4. Each disorder is relatively uncommon, and more detailed descriptions of a number of important examples are presented in this chapter and elsewhere. Predisposition to the more common skin disorders, including atopic eczema and psoriasis, is determined by the action of more than one gene, with significant evidence for further modulation by environmental factors. Such disorders display complex patterns of clustering in families, and are referred to as *multifactorial*. Chromosomal abnormalities, either in number (*aneuploidy*) or form (*translocation*, *complex rearrangements* or *microdeletions*) are important to the clinician, particularly if the patient presents a range of abnormalities including mental retardation. However, chromosomal anomalies rarely present solely with dermatological problems and hence are only briefly mentioned.

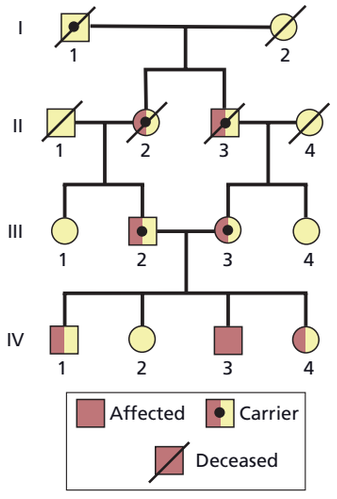
The study of rare disorders, including the genodermatoses, has also provided insight into fundamental aspects of human genetic principles and mechanisms. Essential terms and principles are described, with the intention of helping the reader understand relevant genetic concepts referred to throughout this book and to aid in the interpretation of the rapidly emerging literature in this field [1–4].

References

1 Harper J. *Inherited Skin Disorders: the Genodermatoses*. Oxford: Butterworth–Heinemann, 1999.
2 Moss C, Savin J. *Dermatology and the New Genetics*. Oxford: Blackwell Science, 1995.
3 Novice FM, Collison DW, Burgdorf WHC, Esterly NB. *Handbook of Genetic Skin Disorders*. Philadelphia: Saunders, 1994.
4 *Online Mendelian Inheritance in Man (OMIM)*. Welch Medical Library, Johns Hopkins University. http://www.ncbi.nlm.nih.gov/omim.

Principles of medical genetics

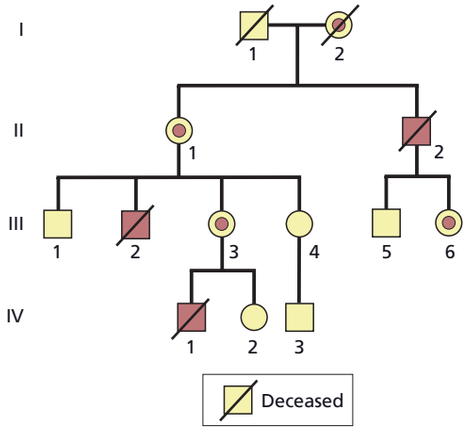
Inherited characteristics are transmitted from one generation to the next by chromosomes, composed of double-helix strands of DNA. A *gene* is a sequence of bases in DNA encoding a polypeptide. The precise position of the gene on a genetic map is known as its *locus*. In females, the 46 chromosomes found in most somatic cells present in homologous pairs; hence two copies of every gene exist, one maternal and the other paternal in origin. In males, the Y chromosome only pairs with the X chromosome at the pseudo-



1 AR disorders affect both males and females.
2 Affected individuals are homozygous for an abnormal allele and typically are born to unaffected parents.
3 On average, 1 in 4 of the children of heterozygous parents will be affected.
4 Typically, no family history is seen.
5 Consanguinity increases the risk of an AR disorder because both parents are more likely to carry the same mutant allele, inherited from a common ancestor.
6 The offspring of an affected person will be healthy heterozygotes and can be affected only if the other parent is also a gene carrier. This is unlikely except in consanguineous marriages or in ethnic groups in which particular alleles are common (e.g. isolated populations).
7 AR disorders are often severe; for example, many of the inborn errors of metabolism are AR.

Examples:
epidermolysis bullosa (the more severe forms)
ichthyosis (the more severe forms)
acrodermatitis enteropathica
phenylketonuria
xeroderma pigmentosum

Fig. 15.2 Autosomal recessive (AR) inheritance.



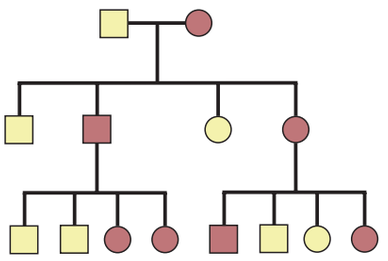
1 Usually only males are affected.
2 The disorder is transmitted through healthy female carriers; occasionally a heterozygous female may show some features of the condition (as a result of non-random X inactivation).
3 A female carrier will transmit the disorder to half her sons, and half her daughters will be carriers.
4 When a male is affected, all his daughters will be carrier heterozygotes.
5 The trait cannot be transmitted from father to son.
6 An XLR condition should be considered when the family history indicates affected males in different generations of the same family. Family history is not always positive as new *de novo* mutations are fairly common.

Examples:
anhidrotic ectodermal dysplasia
Fabry's disease
Menke's syndrome
ocular albinism

Fig. 15.3 X-linked recessive (XLR) inheritance.

autosomal region. *Meiosis* is the process of cell division by which male and female gametes (germ cells) are produced. Alternative genes at a single locus are called *alleles*. An individual with two different alleles at a particular locus is *heterozygous*; where both alleles are identical, the individual is described as *homozygous* at that locus. Genes on the X chromosome are not one of a pair in males and when such a gene is abnormal in a male, the term *hemizygous* is used. Nuclear DNA accounts for 99.995% of the total genetic pool. As with all complex mammalian genomes, the human sequence is made up of considerable amounts of repetitive DNA (Fig. 15.5). The total number of genes is now estimated to be approximately 20 000, with an average size, including introns, of between 10 and 15 kb.

An allele is regarded as *dominant* (Fig. 15.1) if it manifests as a phenotype when present on only one member of the chromosome pair (heterozygous state) and as *recessive* (Fig. 15.2) if it must be present at both corresponding loci (homozygous state) before it can exert its full effect. Hence, it is apparent that the terms 'domi-



1. An XLD disorder will give rise to a disorder in both hemizygous males and heterozygous females.
2. Affected males will transmit the disorder to their daughters, but not to their sons.
3. Affected females will transmit the disorder to half their sons and half their daughters.
4. In some disorders the condition is lethal in hemizygous males; so only female patients are encountered in clinical practice.

Examples: incontinentia pigmenti
X-linked form of oro-facial-digital syndrome

Fig. 15.4 X-linked dominant (XLD) inheritance.

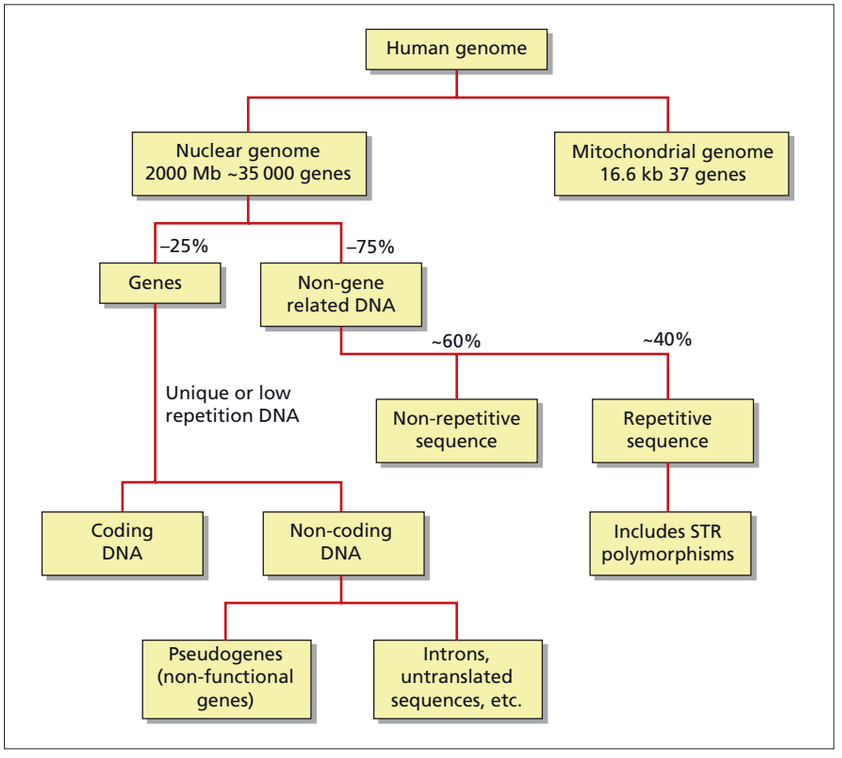


Fig. 15.5 Human genome organization.

nance' and 'recessivity' refer to a phenotypic characteristic rather than a gene [1].

Those genes borne on chromosomes other than the sex chromosomes (X and Y) are known as *autosomal*. Characters controlled by genes borne on the X or Y chromosomes are termed *sex-linked* (Figs 15.3 & 15.4). The Y chromosome is much smaller than the X chromosome. The great majority of sex-linked genes are exclusive to the X chromosome, having no active counterpart on the Y chromosome. For these traits the term 'recessive' applies to males who carry only one (mutant) allele. Females who carry X-linked mutations are typically heterozygous and with rare exceptions, including markedly skewed X inactivation, display no clinical abnormalities.

A region of homology sufficient for pairing between the X and Y chromosomes exists on the end of the short arm of the X chromosome, known as the *pseudo-autosomal region*, enabling sex-linked transmission comparable to autosomal traits [2]. Genes that are Y-linked are primarily involved in male sex determination (e.g. *SRY* gene controlling the testis determining factor) or spermatogenesis. Girls affected with MIDAS syndrome (microphthalmia, dermal aplasia and sclerocornea) and showing anomalies of the genitalia may display an *SRY*-positive status, indicating a translocation between the pseudo-autosomal region of Xp and Yp [3]. Hairy pinnae is another phenotype that is Y-linked [4].

The effects of a mutant allele are not necessarily constant; the degree to which the effects are variable is a measure of the *expression* of the character in question, and the frequency with which a gene produces any effect at all is a measure of its *penetrance*.

In addition to nuclear DNA, mitochondria contain a circular chromosome comprising 14 protein-coding regions [5]. The mito-

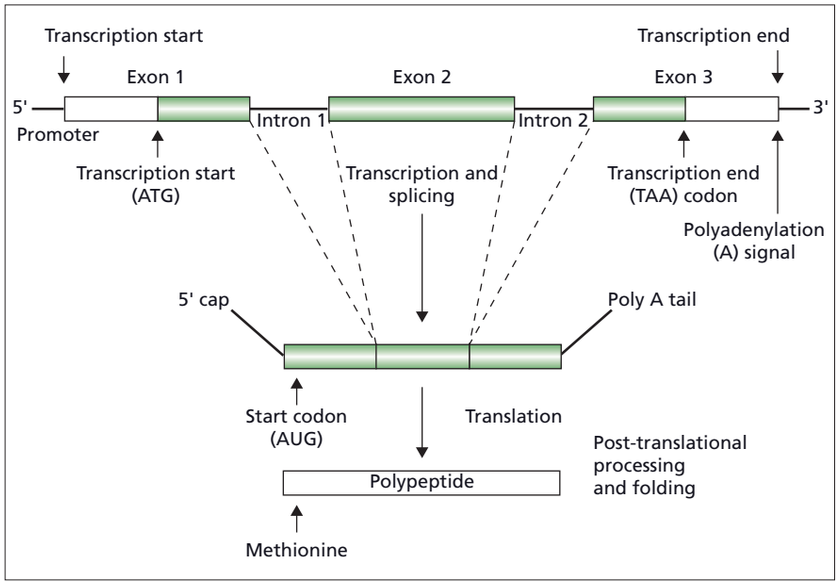


Fig. 15.6 Features of a typical human structural gene.

chondrial DNA codes for enzymes involved in the respiratory chain and oxidative phosphorylation. Mitochondrial disorders are essentially muscular, neurological and ophthalmological diseases and transmission is almost exclusively matrilineal [6].

Genetic heterogeneity

Genetic heterogeneity is the term used to describe clinically similar disorders (phenotypes) that result from different genetic defects. The concept of genetic heterogeneity is important for several reasons: (i) disorders that appear the same can be due to entirely different molecular defects, with a different natural history and requiring different treatment; (ii) for accurate genetic counselling, as defects may have different inheritance patterns; and (iii) because genetic heterogeneity plays a significant role in common complex disease states. Different alleles at the same locus (allelic) and genes at different loci (non-allelic) can give rise to similar phenotypes. Recognizing this, one can differentiate similar disorders by careful clinical distinction, as Wells and Kerr [7] did in distinguishing between autosomal dominant and X-linked ichthyosis. The use of both clinical findings and family history has helped to delineate heterogeneity in the epidermolysis bullosa and Ehlers–Danlos syndromes. Xeroderma pigmentosum illustrates phenotypic homogeneity but with marked genetic heterogeneity, with at least seven different genetic variants.

Mutations and disease

Most mutations are spontaneous and unexplained; however, certain factors such as mutagenic chemicals and ionizing radiation can increase the rate. In the absence of such agents, the mutation rate is of the order of 1 base pair (bp) substitution for every 10^9–10^{10} bp replicated. If a mutation occurs in a somatic cell (*somatic mutation*), only the descendants of that cell are affected and there will be no transmission of the abnormality to further generations. Only mutations occurring in the gametes or their precursors can be transmitted to offspring.

Normally, replication of DNA is accurate but mutations can occur, either induced by exposure to mutagenic agents or spontaneously through errors in the process of DNA replication and repair during meiosis.

Mutations that impinge on the function of a gene most commonly occur within the coding regions (exons) and may alter the amino-acid sequence and hence structure and function of the protein (Fig. 15.6). In addition to gross structural chromosomal changes, submicroscopic alterations including substitutions (replacement of a single nucleotide by another), deletions (loss of one or more nucleotides) and insertions (addition of one or more nucleotides) may occur. Single-base substitutions, often referred to as point mutations, have been most extensively characterized (see Cardiff Human Mutation Database). The majority are either missense or nonsense mutations. These mutations alter a codon so that either a different amino acid is encoded (missense), or a codon specifying an amino acid in a normal individual is altered to code for the stop codon TGA, leading to premature termination of the protein (nonsense). Deletions and insertions (up to 20 bp of DNA) other than multiples of three will lead to disruption of the reading frame for RNA translation, resulting in a frameshift mutation and premature termination (Fig. 15.6). Point mutations may also affect splicing, the process by which mature messenger RNA (mRNA) is produced from RNA that has been transcribed directly from the gene [1].

Two-hit progression to tumour formation

Through pioneering observations on the familial and sporadic occurrence of rare tumours, Knudson [8] proposed that germ-line mutation of one allele of a tumour-suppressor gene, although required to explain an autosomal dominant pattern of inheritance, was not in itself sufficient to lead to tumour formation. Hence, in a target tissue, acquired mutations known as somatic mutations need to occur and lead to complete loss of function of the gene. Molecular genetic evidence to support this important concept has

recently emerged for a number of disorders, including NF1 and tuberous sclerosis.

Contiguous gene syndromes

Large genome deletions may involve several neighbouring genes, for example a well-established 'set' of contiguous gene disorders involve the steroid sulphatase locus (Xp22.3). Deletions of different sizes and location within Xp22.3 give varying combinations of X-linked ichthyosis, Kallman's syndrome (hypogonadotrophic hypogonadism and anosmia), chondrodysplasia punctata, ocular albinism, mental retardation and short stature [9].

Functional impact of mutations and polymorphisms

Mutations exert their effects by leading to a loss or gain of function of the gene's protein product. In general, loss-of-function mutations lead to either reduced activity or complete loss of the protein. Gain-of-function mutations result in either increased levels of expression or the acquisition of a new function of a protein. The term 'mutation' has traditionally been applied to genetic variation causative of a Mendelian disorder. As further studies are undertaken to unravel the genetic contribution of common and complex disorders, understanding the subtle functional consequences of all genetic variation, including polymorphisms, will be increasingly important [1].

High-throughput genetic analysis

Studies of human genetic disease have been substantially facilitated by the introduction of rapid and increasingly low-cost methods of DNA analysis. Genome-wide screens of polymorphic markers and global analysis of gene transcripts can readily be achieved. DNA microarray represents one emerging technology likely to impact on the application of molecular genetics to clinical dermatology. A microarray or DNA chip represents multiple DNA sequences immobilized on a solid surface, using either a photolithographic process or simple 'spotting' of DNA sequences onto a glass slide. Such chips allow high-throughput parallel analysis, which can be used to uncover point mutations in single genes or larger genomic deletions, as well as detecting changes in gene expression associated with disease states or response to treatment.

Mosaicism, lyonization and the lines of Blaschko

Mosaicism describes an individual with two or more cell lines of different genotypes derived from the same zygote. In health, all females exhibit functional mosaicism with regard to their X chromosomes. One of the two X chromosomes in the cells of normal females undergoes inactivation at an early stage of embryonic development (12–16 days after fertilization), a process known as lyonization [10]. The inactive X remains condensed as a densely stained mass of chromatin known as the Barr body. For each somatic cell it is random whether the paternal X or the maternal X is inactivated, but the choice is fixed for all subsequent descendants of that cell. Thus, a female has a mixture of two populations of cells, some of which have an active paternal X chromosome and some of which have an active maternal X chromosome. The relative proportions vary from female to female (even in identical twins) due to the randomness of the inactivation process. As a result of lyonization, the heterozygous state of various X-linked gene defects may give rise to a mosaic pattern of cutaneous lesions, which conforms to the system of lines on the skin first described by Blaschko in 1901 [11] (Fig. 15.7). The original description by Blaschko referred to a 'system of lines on the human skin which the linear naevi and dermatoses follow'. Many naevoid skin lesions display an arrangement following these lines. The lines do not correspond to any known nervous, vascular or lymphatic structures, but represent the developmental growth pattern of the skin [12].

Many genetic skin diseases reflect mosaicism, with mutation occurring after fertilization (post-zygotic). Important features to be considered in mosaicism and their impact on phenotype relate to the proportion of cells that harbour the mutation and tissue distribution. In general, the greater the proportion of cells that are abnormal, the greater the severity of the resultant phenotype. Furthermore, phenotype is influenced by the portion of mutant cells in a specific tissue. If a mutation has little impact on the normal function of the tissue, the phenotypic consequences are likely to be minimized. Women heterozygous for the gene of X-linked recessive ichthyosis do not display any mosaic pattern of skin changes, and it has been suggested that some genes on the X chromosome may escape inactivation [13,14].

It is likely that all naevi reflect genetic mosaicism [15]. Streaky or patchy pigmentary skin changes may be a clue to the presence of mosaicism. The pigmentary patterns associated with mosaicism are reviewed by Happle [16].

Gonadal mosaicism and recurrence risk

An autosomal dominant trait may occur in more than one sibling, even though both parents are apparently unaffected. This phenomenon may be explained by gonadal mosaicism, due to the presence of a mutation in germ-line but not somatic cells [17]. Evidence of gonadal mosaicism exists in tuberous sclerosis [18], bullous ichthyosiform erythroderma [19] and NF1 [20]. Gonadal mosaicism for the X-linked disorder incontinentia pigmenti has been reported in a healthy male [21].

Genomic imprinting

This term is used to describe the phenomenon whereby a DNA sequence derived from one parent acts in a different way compared with that derived from the other parent [22,23]. Imprinting (coding or non-coding) carries a signal or imprint that indicates to nuclear transcription machinery the parent of origin for that sequence. For the majority of the human genome, no distinction is made between paternal and maternal copies, with the exclusion of polymorphic variation. The molecular basis of imprinting is thought to be methylation, the process whereby a methyl group (CH_3) is added to DNA nucleotides (typically cytosine). Methylation is usually associated with reduced levels of expression of a gene, and for certain genes is applied exclusively to either the paternal or maternal copies. Examples of dermatological disorders subject to imprinting include familial glomus tumour [24] and Albright's hereditary osteodystrophy [25], and the phenomenon may also play a role in the genetic basis of atopy [26,27] and psoriasis [28].

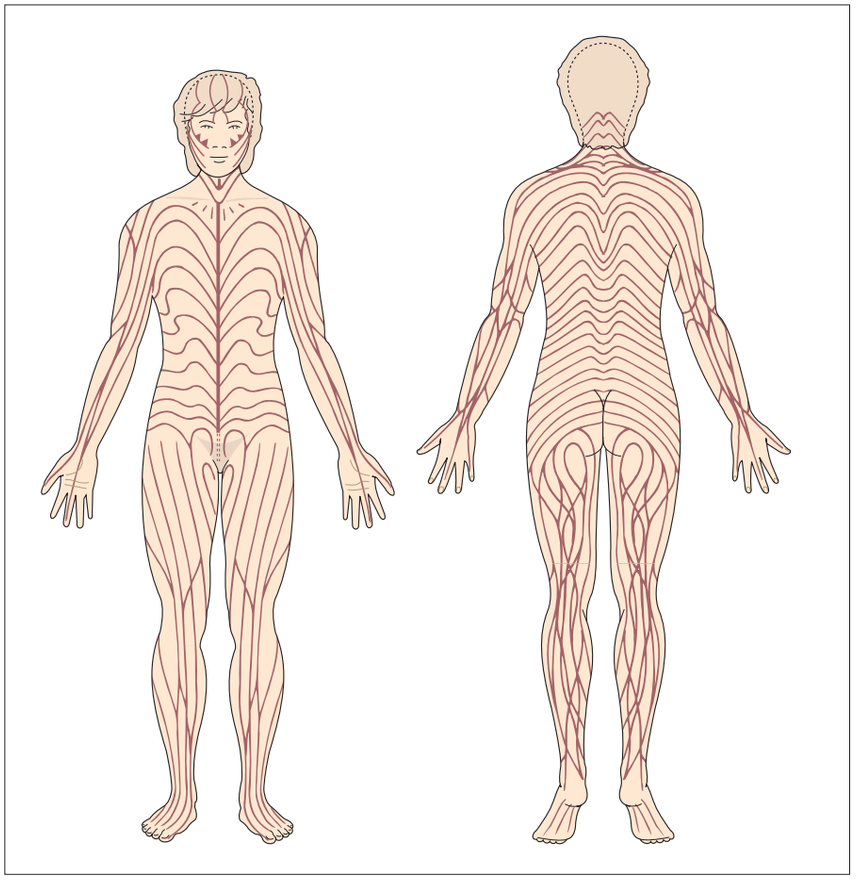


Fig. 15.7 Blaschko's lines as illustrated in his 1901 article 'A system of lines on the surface of the human body which the linear naevi and dermatoses follow'.

Uniparental disomy

For the vast majority of individuals, one chromosome of a pair has been inherited from each parent. Rarely, uniparental disomy may occur when an offspring receives both copies of a chromosome pair from one of its parents. For some chromosomes this results in recognizable phenotypes, for example uniparental disomy of the maternal copies of chromosome 15 leads to Prader–Willi syndrome. For other chromosomes, uniparental disomy does not appear to be of obvious phenotypic value, unless by chance the identical chromosomes harbour a recessive mutation, which would then be present in the homozygous state [29,30].

Twin spotting

This hypothesis has been proposed, based on the genetic concept of somatic recombination, to explain the frequent coexistence of two separate and distinct naevi, for example a telangiectatic naevus and naevus anaemicus and phacomatosis pigmentovascularis [31–33]. Twin spotting has been extensively studied in plants and animals.

Genome sequence and analysis of inherited disorders

Completion of the human genome sequencing effort has led to phenomenal progress in gene mapping techniques, with thousands of DNA markers now available, each defined and covering all chromosomes. These markers have greatly facilitated linkage studies within families with Mendelian disorders. Linkage analysis questions whether each DNA marker co-inherits with the disease more often than expected by chance. The statistical test of linkage is the logarithm of the odds (lod) score. A lod score of 3 or greater is accepted as significant evidence of linkage, whereas a score of –2 excludes linkage at that location. The traditional DNA marker is a *restriction fragment length polymorphism* (RFLP) analysed by Southern blotting of restricted (digested) DNA, with the fragments detected by a radioactive probe. Most genetic markers are now detected rapidly by polymerase chain reaction (PCR)-based methods of analysis, exploiting an abundant class of DNA sequence variation known as simple tandem repeats or single nucleotide polymorphisms. *Gene tracking* is the term given to the use of a known linkage between a marker and a disease locus to predict the genotype at the disease locus in a particular family member, such as in asymptomatic carrier testing or prenatal diagnosis. Linkage studies are just the first step in positional cloning of a disease gene.

Genetic linkage, linkage disequilibrium and disease association

Alleles at gene loci residing close to each other on the same chromosome remain linked in transmission so long as the chromosome remains intact; however, during reduction division (meiosis), such linkages may be disrupted if *crossing-over* occurs. The closer two

gene loci are situated on a chromosome, the less likely they are to be separated by crossing-over and the more likely they are to be inherited together. Two such gene loci are said to be linked and it is possible to demonstrate genetic linkage in a family using appropriate genetic markers. When two alleles occur together more frequently, or less frequently, in a population than would have been expected from the individual allele frequencies, they are said to be in *linkage disequilibrium*. This may arise as a result of a recent mutation or for a particular combination of DNA sequences, which may have, for example, a selective advantage and hence achieve disequilibrium by natural selection. Linkage disequilibrium is one important cause of disease association.

The nail–patella syndrome is a clinical example of a disorder that shows genetic linkage with the blood group ABO locus; the ABO and the disease gene loci are both situated on chromosome 9. Because of eventual crossing-over, over a number of generations recombination will occur, leading to different affected families; alternatively, independent mutations causing nail–patella syndrome may arise *de novo*. Thus, there is genetic linkage between the loci for blood groups and nail–patella syndrome, but no association with a particular blood group. Genetic linkage is a phenomenon demonstrable within families. In contrast, association due to linkage disequilibrium is a phenomenon demonstrated by comparing a population of affected individuals with a control population [1].

References

1 Strachan T, Reed AP. *Human Molecular Genetics*, 2nd edn. Oxford: BIOS Scientific, 1999.
2 Skaletsky H, Kuroda-Kawaguchi T, Minx PJ *et al.* The male-specific region of the human Y chromosome is a mosaic of discrete sequence classes. *Nature* 2003; **423**: 825–37.
3 Mücke J, Hoepffner W, Thamm B *et al.* MIDAS syndrome (microphthalmia, dermal aplasia and sclerocornea): an autonomous entity with linear skin defects within the spectrum of focal hypoplasias. *Eur J Dermatol* 1995; **5**: 197–203.
4 Stern C, Centerwall WR, Sarkar SS. New data on the problem of Y-linkage of hairy pinnae. *Am J Hum Genet* 1964; **16**: 455–71.
5 Anderson S, Bankier AT, Barrell BG *et al.* Sequence and organization of the human mitochondrial genome. *Nature* 1981; **290**: 457–65.
6 Richly E, Chinnery PF, Leister D. Evolutionary diversification of mitochondrial proteomes: implications for human disease. *Trends Genet* 2003; **19**: 356–62.
7 Wells RS, Kerr CB. Genetic classification of ichthyosis. *Arch Dermatol* 1965; **92**: 33–55.
8 Knudson AG. Mutation and cancer: statistical study of retinoblastoma. *Proc Natl Acad Sci USA* 1971; **68**: 820–3.
9 Paige DG, Emilion GG, Bouloux PMG *et al.* A clinical and genetic study of X-linked ichthyosis and contiguous gene defects. *Br J Dermatol* 1994; **131**: 622–9.
10 Lyon MF. Sex chromatin and gene action in the mammalian X-chromosome. *Am J Hum Genet* 1962; **14**: 135–48.
11 Blaschko A. *Die Nervenverteilung in der Haut in Ihrer Beziehung Zu Den Erkrankungen der Haut*. Vienna, Leipzig: Braumuller, 1901.
12 Happle R. Mosaicism in human skin: understanding the pattern and mechanisms. *Arch Dermatol* 1993; **129**: 1460–70.
13 Happle R. Cutaneous manifestation of X-linked genes escaping inactivation. *Clin Exp Dermatol* 1992; **17**: 69–73.
14 Disteche CM. Escape from X inactivation in human and mouse. *Trends Genet* 1995; **11**: 17–22.
15 Happle R. What is a nevus? A proposed definition of a common medical term. *Dermatology* 1995; **191**: 1–5.
16 Happle R. Pigmentary patterns associated with human mosaicism: a proposed classification. *Eur J Dermatol* 1993; **3**: 170–4.
17 Hall JG. Somatic mosaicism: observations related to clinical genetics. *Am J Hum Genet* 1988; **43**: 355–63.
18 Verhoef S, Vrtel R, van Essen T *et al.* Somatic mosaicism and clinical variation in tuberous sclerosis complex. *Lancet* 1995; **345**: 202.
19 Paller AS, Syder AJ, Chan YM *et al.* Genetic and clinical mosaicism in a type of epidermal nevus. *N Engl J Med* 1994; **331**: 1408–15.
20 Lázaro C, Ravella A, Gaona A *et al.* Neurofibromatosis type 1 due to a germ-line mosaicism in a clinically normal father. *N Engl J Med* 1994; **331**: 1403–7.
21 Kirchman TTT, Levy ML, Lewis RA *et al.* Gonadal mosaicism for incontinentia pigmenti in a healthy male. *J Med Genet* 1995; **32**: 887–90.
22 Wilkins JF, Haig D. What good is genomic imprinting: the function of parent-specific gene expression. *Nat Rev Genet* 2003; **4**: 359–68.
23 Hall JG. Genomic imprinting: review and relevance to human diseases. *Am J Hum Genet* 1990; **46**: 857–73.
24 Van der May AGL, Maaswinkel-Mooy PD, Cornelisse CJ *et al.* Genomic imprinting in hereditary glomus tumours: evidence for new genetic theory. *Lancet* 1989; **ii**: 1291–4.
25 Aldred MA, Trembath RC. Activating and inactivating mutations in the human GNAS1 gene. *Hum Mutat* 2000; **16**: 183–9.
26 Cookson WOCM, Young RP, Sandford AJ *et al.* Maternal inheritance of atopic IgE responsiveness on chromosome 11q. *Lancet* 1992; **340**: 381–4.
27 Coleman R, Trembath RC, Harper JI. Chromosome 11q13 and atopy underlying atopic eczema. *Lancet* 1993; **341**: 1121–2.
28 Traupe H, van Gurp PJM, Happle R *et al.* Psoriasis vulgaris, fetal growth and genomic imprinting. *Am J Med Genet* 1992; **42**: 649–54.
29 Engel E. A new genetic concept: the uniparental disomy and its potential effect, the isodisomy. *J Genet Hum* 1980; **28**: 11–22.
30 Spence JE, Perciaccante RG, Greig GM *et al.* Uniparental disomy as a mechanism for human genetic disease. *Am J Hum Genet* 1988; **42**: 217–26.
31 Happle R, Steijlen PM. Phacomatosis pigmentovascularis gedeutet als ein Phänomen der Zwillingsflecken. *Hautarzt* 1989; **40**: 721–4.
32 Happle R, Koopman R, Mier PD. Hypothesis: vascular twin naevi and somatic recombination in man. *Lancet* 1990; **335**: 376–8.
33 Happle R. Allelic somatic mutations may explain vascular twin naevi. *Hum Genet* 1991; **86**: 321–2.

Histocompatibility antigens and disease association

Human leukocyte antigens are glycoproteins on the cell surface of most nucleated human cells. These differ in subtle ways from person to person and uniquely fingerprint each person's cells. These fingerprints allow a person's immune system to recognize if a given cell is its own. The importance of the human leukocyte antigen (HLA) system has been highlighted by the need to match donors and recipients in the transplantation of human tissues.

The HLA region is located on the short arm of chromosome 6, referred to as the major histocompatibility complex (MHC). A person inherits HLA as a set, one set (haplotype) from each parent. There are at least four or five genetic loci that produce HLA, termed A, B, C, D and DR (in order of their discovery not their location), and their gene products are called HLA-A, HLA-B, HLA-C, HLA-D and HLA-DR. Each locus has multiple allelic determinants (polymorphism). Each allele at each locus controls an antigen, which is identified by a number placed after the letter of that series, for example HLA-A1, HLA-B5. The letter 'w' in front of a number indicates that its specificity was studied in an international workshop, and continues to undergo further definition.

HLAs that code at the A, B and C loci are determined by serological cytotoxicity methods, whereas those occurring at the D locus are detected by the mixed lymphocyte reaction. The HLA-DR antigens are serologically determined and are similar, if not identical, to the D locus antigens. DNA-based methods for typing at all HLA loci are now available.

The association of an HLA with a given disease means that there is a higher incidence of that antigen in a group of patients with the disease than in a group of people without the disease. There are various ways in which the presence of a particular HLA might be involved in the pathogenesis of a disease.

1 *Molecular mimicry*. An infective agent may have a similar configuration to the HLA, so that the agent is then not attacked by the body's defence system. Alternatively, the agent might differ only slightly from the HLA, so that antibodies are produced that attack both the infective agent and the cells containing the HLA, thus inducing autoimmune damage.
2 *Receptor effects*. Many chemicals, including drugs and toxins, bind to the cell surface before they are taken into the cytoplasm. As HLAs are present on the cell surface, they could modify the binding of these potentially toxic substances, and the specificity for such binding may be determined, at least in part, by DNA variation for HLA molecules.
3 *Genetic linkage*. The HLA may be close to another gene on the same chromosome that produces a disease, either directly (e.g. due to an enzyme deficiency) or indirectly due to an effect on the immune response, which may be abnormally enhanced, leading to autoimmunity, or abnormally decreased, leading to infection.

The association between an HLA and a particular disease is rarely absolute. Ankylosing spondylitis is strongly associated with the B27 antigen, but some patients with this disease are B27 negative and many patients with B27 do not develop ankylosing spondylitis. There are many possible explanations for this, including the role of environmental factors or triggers, such as chemicals or infective agents, in disease causation. Non-HLA-linked genes are probably also important, including some that may confer resistance to disease. The relative risk is the numerical answer to the question 'How many times is a person with a given HLA phenotype more likely to develop a given disease than a person without that HLA phenotype?' The relationship between HLA and skin disease is the subject of several reviews [1–4] (Table 15.1).

Table 15.1 Some skin diseases known to be associated with particular human leukocyte antigens (HLA).

Disease	Antigen	Relative risk
Dermatitis herpetiformis	B8	15
	Dw3/DRw3	>15
Pemphigus	DRw4	10
Reiter's disease	B27	35
Behçet's disease	B5	10
Psoriasis	B13	4
	B17	5
	B37	5
	Cw6	12
	Dw7	10
Psoriatic arthropathy (central)	B27	10
Psoriatic arthropathy (peripheral)	Bw38	9

There is a genetic predisposition to pemphigoid (herpes) gestationis; 90% of patients express either HLA-DR3 or HLA-DR4 [5].

References

1 Lobitz WC Jr. The HLA system in dermatology. In: Rook A, Savin J, eds. *Recent Advances in Dermatology*, Vol. 5. Edinburgh: Churchill Livingstone, 1980: 35–57.
2 Rowell N. Histocompatibility antigens (HLA) in dermatology. *Br J Dermatol* 1984; **111**: 347–57.
3 Thomson G. HLA disease associations: models for the study of complex human genetic disorders. *Crit Rev Clin Lab Sci* 1995; **32**: 183–219.
4 Elder JT, Henseler T, Christophers E *et al*. Of genes and antigens: the inheritance of psoriasis. *J Invest Dermatol* 1994; **103** (Suppl.): 150–3.
5 Shornick JK. Herpes gestationis. *Dermatol Clin* 1993; **11**: 527–33.

Genetic counselling [1–3]

Advice to parents or prospective parents must be based on an accurate diagnosis and a detailed family history. It is essential to establish a diagrammatic representation of the family pedigree. Genetic counselling depends upon the recurrence risk to parents of having an affected child. The risk that any pregnancy will produce a child with a serious abnormality is about 1 in 50 (2%). A risk greater than 10% is high, whereas a risk of less than 5% is considered low. However, the impact such a risk has upon a couple or extended family depends on the severity of the disorder and any prior experience relatives may have of a condition. The offspring and recurrence risks for known forms of Mendelian disorders are illustrated in Figs 15.1–15.4.

Many different definitions of genetic counselling have been proposed, but all include the concept of a process of communication, where patients or relatives are informed of the probability of developing or transmitting a genetic disorder. This process should also include discussion about the consequences of such disorders and the possibilities for disease prevention. Hence, it is apparent that counselling is a complex process that requires a range of skills, which increasingly includes integration of complex information regarding DNA analysis. However, it remains important to realize that it is the burden of disease rather than the precise numerical value of risk that concerns most patients and prospective parents. Genetic counselling has recently emerged as a distinct specialty in medicine and many dermatology centres work in close collaboration over the provision of accurate and comprehensive advice.

References

1 Baraitser M. Genetic counselling in skin disorders. In: Harper J, ed. *Inherited Skin Disorders: the Genodermatoses*. Oxford: Butterworth–Heinemann, 1996: 319–25.
2 Royal College of Physicians Working Party. *Prenatal Diagnosis and Genetic Screening*. London: Royal College of Physicians, 1989.
3 Harper PS. *Practical Genetic Counselling*, 5th edn. Oxford: Butterworth-Heinemann, 1998.

Chromosomal disorders

Chromosomal disorders may be due to abnormalities of chromosome number or structure and may involve autosomes or sex chromosomes. Somatic cells are *diploid*, with a complement of 46 chromosomes, whereas gametes (ova and sperm) are *haploid*, with only 23 chromosomes following reduction division in meiosis. Numerical abnormalities that involve the gain or loss of one or

more chromosomes are known as aneuploidies. Structural chromosome rearrangements result from chromosome breakage with subsequent reunion in a different configuration. They may be balanced or unbalanced, depending on whether or not gain (or loss) of genetic material occurs. Approximately 7.5% of all conceptions have a chromosomal disorder, but most of these are spontaneously aborted, so the birth frequency is 0.6%. Among early spontaneous abortions, the frequency of chromosomal disorders is 60%, whereas in late spontaneous abortions and stillbirths the frequency is 5%. Chromosomal abnormalities generally cause multiple congenital malformations. Children with more than one physical abnormality, particularly if retarded, should undergo chromosomal analysis as part of their investigation. Chromosomal disorders are incurable but can be reliably detected by prenatal diagnostic techniques. Amniocentesis or chorionic villous sampling should be offered to women whose pregnancies are at increased risk, namely women over the age of 35 years and couples with an affected child.

Autosomal chromosome defects

Down's syndrome [1–3]

Synonym
- Trisomy 21

Down [1] described this syndrome in 1866. In 1959, it became the first recognized chromosomal anomaly [4]. It is the most common autosomal abnormality, with a frequency of about 1 per 700 live births [5].

Aetiology [2]. Most cases (95%) result from trisomy of chromosome 21, in which the extra chromosome is derived by nondisjunction at meiosis, usually from the mother; the incidence of this type rises with maternal age. Less common, and clinically indistinguishable, is the type that shows no relation to maternal age and is sometimes familial. The affected child has the normal number of 46 chromosomes but one of the clinically normal parents carries a translocation of part of chromosome 21. A few patients are themselves mosaics and tend to have less marked physical stigmata and higher intelligence [6].

Pathology. Congenital heart defects are common and the brain is small with flat convolutions. Renal tract anomalies are less common.

Immunological defects are frequent. Autoimmune disease is common in Down's syndrome, T-cell function is impaired and the atopic state is often associated [7]. There is an increased risk of developing acute leukaemia, usually under the age of 5 years.

The lichenified patches of skin show no distinctive pattern, with hyperkeratosis, acanthosis and a dermal inflammatory infiltrate.

Clinical features [8]. The facial appearance often permits a clinical diagnosis. The head is small, the face flat, the nose short and squat and the ears small and misshapen. The eyes are usually conspicuously mongoloid, with slanting palpebral fissures. The eyelids are thickened and the eyelashes short and sparse. Epicanthic folds are frequent in early childhood but tend to become less noticeable with age. The iris tends to be hypoplastic and may show light areas in its outer third (Brushfield's spots). The limbs are stumpy and the joint ligaments lax. The fingers are short and cone-shaped and are sometimes webbed. The little finger is often curved. The presence of these features varies in affected individuals, and a diagnostic index has been proposed [9].

Mental retardation is a serious complication: the IQ is usually less than 50, and if it is not mosaicism should be suspected. Congenital heart malformations, especially endocardial cushion defects, are present in 40%, and duodenal atresia may occur. Other complications include cataracts (2%), epilepsy (10%), hypothyroidism (3%), leukaemia (1%), atlantoaxial instability (2–3%) and recurrent respiratory infections. When serious malformations are present, death during infancy is usual, but otherwise life expectancy is little reduced. Down's syndrome accounts for about one-third of all moderate and severe mental disability in children of school age. Most will walk and develop simple language. Puberty is often delayed and incomplete, with adult heights about 150 cm. Presenile dementia commonly supervenes after 40 years of age.

The skin is normal at birth and in early childhood is soft and velvety [8,10]. Between the ages of 5 and 10 years it becomes increasingly dry and less elastic, and by the age of 15 over 70% show generalized xerosis of mild to moderate degree, with evidence of accelerated skin ageing [11]. Patchy lichenification is present in some 30% under 10 years and more than 80% over 20 years of age. The patches resemble lichen simplex and most commonly occur on the upper arm, the wrists, the fronts of the thighs, the back of the ankle and the back of the neck, and are probably correctly regarded as manifestations of atopic dermatitis, the incidence of which some authorities [10] have considered to be low.

A chronic follicular papular eruption of the presternal and interscapular regions is frequently present, consistent with *Malassezia* folliculitis. In a clinical trial, oral itraconazole produced a significant clinical improvement accompanied by a decrease in the skin *Malassezia* count, but relapse occurred when therapy was discontinued and was accompanied by a return of the *Malassezia* yeasts [12].

The hair may be normal but is often fine and may be hypopigmented. The prevalence of alopecia areata is high and it tends to be extensive and persistent [7,13]. The teeth are hypoplastic and late to erupt. Fissuring and thickening of the lips are frequent and increase in prevalence and severity with age [14]. The tongue is scrotal in almost all cases. Elastosis perforans serpiginosa [15,16] and syringomas, especially in adult females with Down's syndrome [17,18], occur more often than in normal subjects.

Skin infections, angular cheilitis, chronic blepharitis and a purulent nasal discharge are common. There is a high prevalence of onychomycosis [7,19]. The cheeks are often red. The peripheral circulation is poor, acrocyanosis is frequent and livedo reticularis is often conspicuous throughout the year, on the thighs, buttocks and trunk.

Dermatoglyphic features include a single flexion crease on the fifth finger, the simian palmar crease and an increased incidence of ulnar loops on the fingers.

There is no evidence that the prevalence of other dermatoses is significantly different in individuals with Down's syndrome

compared with individuals with mental retardation from other causes. Psoriasis runs its normal course, although an unusual hyperkeratotic form has been described [20]. Acral lentiginous melanoma has been described in association with Down's syndrome [21].

References

1 Down JLH. Observations on an ethnic classification of idiots. *Clin Lect Rep London Hosp* 1866; **3**: 259–62.
2 Smith DW, Wilson AA. *The Child with Down's Syndrome*. Philadelphia: Saunders, 1973.
3 Salmon MA. *Developmental Defects and Syndromes*. Aylesbury, UK: HM & M, 1978: 346–56.
4 Lejeune J, Gautier M, Turpin R. Les chromosomes somatiques des enfants mongoliens. *C R Acad Sci (Paris)* 1959; **248**: 1721–2.
5 Fabia J. Illegitimacy and Down's syndrome. *Nature* 1969; **221**: 1157–8.
6 Wilson MG, Towner JW, Forsman I. Decreasing mosaicism in Down's syndrome. *Clin Genet* 1980; **17**: 335–40.
7 Carter DM, Jegosothy BV. Alopecia areata and Down's syndrome. *Arch Dermatol* 1976; **112**: 1397–9.
8 Kersting DW, Rapaport IF. A clinico-pathologic study of the skin in mongolism. *Arch Dermatol* 1958; **77**: 319–23.
9 Rex AP, Preus M. A diagnostic index for Down's syndrome. *J Pediatr* 1982; **100**: 903–6.
10 Rapaport I. Oligophrenie mongolienne et ectodermoses congenitales. *Ann Dermatol Syphiligr* 1960; **87**: 263–78.
11 Brugge KL, Grove GL, Clopton P *et al.* Evidence for accelerated skin wrinkling among developmentally delayed individuals with Down's syndrome. *Mech Ageing Dev* 1993; **70**: 213–25.
12 Kavanagh GM, Leeming JP, Marshman GM *et al.* Folliculitis in Down's syndrome. *Br J Dermatol* 1993; **129**: 696–9.
13 Du Vivier A, Munro DD. Alopecia areata, autoimmunity and Down's syndrome. *BMJ* 1975; **i**: 191–2.
14 Butterworth T, Leoni EP, Beerman H *et al.* Cheilitis of mongolism. *J Invest Dermatol* 1960; **35**: 347–52.
15 Rasmussen JE. Disseminated elastosis perforans serpiginosa in four mongoloids. Recognition of residual changes. *Br J Dermatol* 1972; **86**: 9–13.
16 Langeveld-Wildschut EG, Toonstra J, van-Vloten WA *et al.* Familial elastosis perforans serpiginosa. *Arch Dermatol* 1993; **129**: 205–7.
17 Rhodes LE, Verbov JL. Widespread syringomata in Down's syndrome. *Clin Exp Dermatol* 1993; **18**: 333–4.
18 Schepis C, Siragusa M, Palazzo R *et al.* Palpebral syringomas and Down's syndrome. *Dermatology* 1994; **189**: 248–50.
19 Velthuis PJ, Nijenhuis M. Treatment of onychomycosis with terbinafine in patients with Down's syndrome. *Br J Dermatol* 1995; **133**: 144–6.
20 Rotchford JP, Hyman AB. Extreme hyperkeratotic psoriasis in a mongoloid. *Arch Dermatol* 1961; **83**: 973–6.
21 Nakano J, Muto M, Arikawa K *et al.* Acral lentiginous melanoma associated with Down's syndrome. *J Dermatol* 1993; **20**: 59–60.

Trisomy 18 [1–3]

Synonym
- Edwards' syndrome

This is the second most common multiple malformation syndrome. It occurs in about 1 per 3000 live births; 95% of affected fetuses abort spontaneously. Parental non-disjunction at either the first or second meiotic division results in the extra copy of chromosome 18. Rarely, a parental translocation is responsible. Occasionally, mosaicism is seen with a milder phenotype and can give rise to pigmentary skin changes, as seen in hypomelanosis of Ito [4,5]. The syndrome comprises severe mental deficiency, a characteristic skull shape with a small chin and prominent occiput, low-set malformed ears, clenched hands with overlapping index and fifth fingers, single palmar crease, 'rocker-bottom' feet and a short sternum. Malformations of the heart, kidneys and other organs are frequent. Cutaneous features include cutis laxa of the neck, hypertrichosis of the forehead and back, and capillary haemangiomas. Fingerprints show a distinctive low-arch dermal ridge pattern. Death within a month occurs in 30%. Only 10% survive beyond the first year and these infants show profound developmental delay.

References

1 Butler LJ, Snodgrass GJAI, Sinclair NE *et al.* E (16–18) trisomy syndrome: analysis of 13 cases. *Arch Dis Child* 1965; **40**: 600–11.
2 Edwards JH, Harnden DG, Cameron AH *et al.* A new trisomic syndrome. *Lancet* 1960; **i**: 787–9.
3 Hodes ME, Cole J, Palmer CG *et al.* Clinical experience with trisomies 18 and 13. *J Med Genet* 1978; **15**: 48–60.
4 Chitayat D, Friedman JM, Johnston MM. Hypomelanosis of Ito—a nonspecific marker of somatic mosaicism: report of case with trisomy 18 mosaicism. *Am J Med Genet* 1990; **35**: 422–4.
5 Sybert VP. Hypomelanosis of Ito: a description, not a diagnosis. *J Invest Dermatol* 1994; **103** (Suppl.): 141–3.

Trisomy 13 [1–4]

Synonym
- Patau's syndrome

The incidence of trisomy 13 is 1 per 5000 live births. Non-disjunction at either the first or second meiotic division in either parent may cause trisomy 13. In about 20% of cases, one parent is a translocation carrier. In about 5% of patients, mosaicism is present. The characteristic features of the syndrome are mental retardation, sloping forehead reflecting underlying holoprosencephaly (a developmental defect of the forebrain), eye defects including microphthalmia or anophthalmia, cleft palate and cleft lip, low-set ears, 'rocker-bottom' feet, cardiac defects and a variety of other visceral abnormalities. Survival for more than 6 months is unusual. Cutaneous features include vascular anomalies, especially of the forehead, hyperconvex nails and localized defects of the scalp. Cutis laxa of the neck has also been reported. The palm print shows a distal palmar axial triradius.

References

1 Patau K, Smith DW, Therman E *et al.* Multiple congenital anomaly caused by an extra autosome. *Lancet* 1960; **i**: 790–2.
2 Lubs HA Jr, Koenig EU, Brandt IK. Trisomy 13–15: a clinical syndrome. *Lancet* 1961; **ii**: 1001–2.
3 Hodes ME, Cole J, Palmer CG *et al.* Clinical experience with trisomies 18 and 13. *J Med Genet* 1978; **15**: 48–60.
4 Strani GF, Tomidei M, Cagna-Vallino G *et al.* Patau's syndrome. Description of a clinical case with special reference to its dermatologic aspects. *G Ital Dermatol Venereol* 1986; **121**: 25–8.

Other autosomal abnormality syndromes

Although the syndromes to which these autosomal abnormalities give rise include distinctive craniofacial malformations, they do not exhibit constant or frequent dermatological features, apart from abnormal dermatoglyphics. Other chromosomal disorders are reviewed elsewhere [1,2].

Chromosome 4, short-arm deletion syndrome [3]
These children have microcephaly, mental retardation, hypospadias and multiple malformations, such as cleft lip and/or palate, low-set ears and pre-auricular pits. There are scalp defects in some cases.

Chromosome 5, short-arm deletion syndrome [4–6]

Synonym
- *Cri du chat* syndrome

This is a clinically heterogeneous syndrome. The patients are mentally deficient microcephalics with a cat-like cry. In some cases a pre-auricular skin tag accompanies low-set malformed ears. There may be premature greying of the hair.

Long-arm 18, deletion syndrome [7]
Hypoplasia of the mid-face gives these children deep-set eyes. The antihelix is very prominent and there are multiple skeletal and ocular abnormalities. Eczema has been reported to occur in 25% of cases.

References
1 Clarke Fraser F. Gross chromosomal aberrations. In: Avery ME Taeusch HW, eds. *Diseases of the Newborn*, 5th edn. Philadelphia: Saunders, 1984.
2 Borgaonkar DS. *Chromosomal Variation in Man: a Catalogue of Chromosomal Variants and Anomalies*, 4th edn. New York: Liss, 1984.
3 Wolf U, Reinwein H. Clinical and cytogenetic differential diagnosis of the anomalies of the short arms of the B chromosomes. *Z Kinderheilk* 1967; **98**: 235–45.
4 Laurent C, Robert JM. Etude genetique et clinique d'une famille de sept enfants dans laquelle trois sujets sont atteints de la 'maladie du cri du chat'. *Ann Genet* 1966; **9**: 113–22.
5 Smith DW. Compendium on shortness of stature. *J Pediatr* 1967; **70**: 463–519.
6 Wilkins LE, Brown JA, Nance WE *et al*. Clinical heterogeneity in 80 home-reared children with cri du chat syndrome. *J Pediatr* 1983; **102**: 528–33.
7 Insley J. Syndrome associated with a deficiency of part of the long arm of chromosome 18. *Arch Dis Child* 1967; **42**: 140–6.

Sex chromosome defects

Turner's syndrome [1,2]
Turner's syndrome is defined as a gonadal dysgenesis due to a missing or structurally defective X chromosome. In 1938, Turner described this syndrome in seven girls [1].

Aetiology [2]. The frequency of Turner's syndrome is 1 per 2500 female births [3]. In some 80% of cases there are 45 chromosomes with an X0 sex chromosome complement. Such cases are chromatin negative in buccal smears. It is assumed that the missing chromosome was lost before or at fertilization. The incidence of 45X was reported to be increased in the offspring of teenage mothers [4], but in a study from Denmark there was no significant relation between mother's age and risk of Turner's syndrome [5].

Most of the remaining 20% of cases are chromatin positive. Some have 46 chromosomes but with partial deletion of one X chromosome [6]. Such individuals may not differ significantly in their phenotype from the common X0 but they may be less severely affected [7]. Other cases have shown mosaicism of various types (XX/X0 or XXX/X0) [8].

Pathology [8]. In place of the normal gonads, ovarian streaks are present that are composed of stroma-like cells and quiescent germinal epithelium without follicular activity or germ cells. However, both follicles and germ cells have occasionally been present.

Lymphangiographic studies have shown hypoplasia of cutaneous and subcutaneous lymphatics [9].

A lack of feedback inhibition by hormones from the defective ovaries produces elevated levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) in the serum by 5 days of age [10].

Clinical features [7,11–13]. Turner's syndrome results in early spontaneous loss of the fetus in over 95% of cases. Severely affected fetuses who survive to the second trimester can be detected by ultrasonography, which shows cystic hygroma, chylothorax, ascites and hydrops.

Growth failure is a consistent finding at birth in infants with Turner's syndrome, which begins in early gestation and is well established by mid-pregnancy [14]. The diagnosis may be suggested in the newborn by redundant neck skin and peripheral oedema. However, the diagnosis is usually made later as a result of investigation for short stature and primary amenorrhoea.

The characteristic clinical features of Turner's syndrome include: small stature; a broad shield-shaped chest with widely spaced nipples; a wide carrying angle of the arms; a webbed neck (pterygium colli); a low posterior hairline; low, misshapen ears; high, arched palate; cutis laxa, especially on the neck and buttocks; short fourth, and sometimes fifth, metacarpals and metatarsals; hypoplastic nails; and a tendency to keloidal scar formation.

Individuals with Turner's syndrome have increased numbers of melanocytic naevi and therefore have an increased risk for melanoma [15]. Lymphangiectatic oedema of the hands and feet may be present at birth and clear in the first 2 years. Skeletal abnormalities are a common feature [6], but are also very variable. Among the most frequent are cubitus valgus, kyphoscoliosis and epiphyseal defects and pathological fractures. Cardiovascular abnormalities [16] are present in some 25% of cases, especially coarctation of the aorta. Ocular defects, squints or ptosis, are also a feature of some cases. Intelligence is usually normal, although a few girls have educational problems.

Endocrinological investigations reveal an increased output of pituitary gonadotrophins accompanied by low oestrogen levels. Thus there is usually primary amenorrhoea with failure to develop full secondary sexual characteristics. Some patients menstruate and, exceptionally, may be fertile. Adrenal androgens are present, and pubic and axillary hair may be present in the absence of other manifestations of normal pubertal development. A few examples are known [17] in which otherwise typical Turner's syndrome (X0 chromosome complement) is accompanied by some degree of genital virilization and hirsutism.

Diagnosis. Diagnosis may be made prenatally by amniocentesis [5]. The somatic abnormalities may suggest the diagnosis in infancy or childhood, but if they are inconspicuous or absent, the diagnosis may be unsuspected until puberty. Increased urinary excretion of FSH supports the diagnosis, which can be confirmed

by examination of buccal smears supplemented by chromosome studies.

Treatment. Oestrogen replacement will allow the development of secondary sexual characteristics but does not seem to influence stature or infertility. Treatment with human growth hormone may improve the ultimate adult height; long-term, randomized, controlled studies are in progress [18]. Melanocytic naevi may grow more rapidly during growth hormone therapy [19]. Therefore, individuals with Turner's syndrome, especially those on growth hormone therapy, should have periodic skin examinations and be advised on the regular use of sunscreens [15].

References

1 Turner HH. A syndrome of infantilism, congenital webbed neck and cubitus valgus. *Endocrinology* 1938; **23**: 566–74.
2 Lindsten J. *Turner's Syndrome*. Uppsala: Almquist, 1963.
3 Maclean N, Harnden DG, Court Brown WM. Abnormalities of sex chromosome constitution in newborn babies. *Lancet* 1961; **ii**: 406–8.
4 Warburton D, Kline J, Stein Z. Monosomy X: a chromosomal anomaly associated with young maternal age. *Lancet* 1980; **i**: 167–9.
5 Gravholt CH, Juul S, Naeraa RW *et al.* Prenatal and postnatal prevalence of Turner's syndrome: a registry study. *BMJ* 1996; **312**: 16–21.
6 Bowen P. Chromosomal abnormalities. *Clin Orthop* 1964; **3**: 40–58.
7 Grumbach MM, Conte FA. Disorders of sex differentiation. In: Williams RH, ed. *Textbook of Endocrinology*. Philadelphia: Saunders, 1981.
8 Ashby DIB. *Human Intersex*. Edinburgh: Livingstone, 1962.
9 Alvin A, Dieh J, Lindsten J *et al.* Lymph vessel hypoplasia and chromosome aberrations in six patients with Turner's syndrome. *Acta Derm Venereol (Stockh)* 1967; **47**: 25–33.
10 Conte FA, Grumbach MM, Kaplan SL *et al.* Correlation of luteinizing hormone-releasing-factor-induced luteinizing hormone and follicle-stimulating hormone release from infancy to 19 years with the changing pattern of gonadotrophin secretion in agonadal patients: relation to the restraint of puberty. *J Clin Endocrinol Metab* 1980; **50**: 163–8.
11 Rossi E, Caflisch A. Le syndrome du pterygium Status Bonnevie-Ullrich, dystrophia brevicolli congenita, syndrome de Turner et arthromyodysplasia congenita. *Helv Paediatr Acta* 1951; **6**: 119–48.
12 Grumbach MM, Van Wyk JJ, Wilkins L. Chromosomal sex in gonadal dysgenesis (ovarian agenesis): relationship to male pseudohermaphrodism and theories of human sex differentiation. *J Clin Endocrinol Metab* 1955; **15**: 1161–93.
13 Andersson M, Bjersing L, Rafstedt S. Early diagnosis of gonadal dysgenesia (Turner's syndrome). *Acta Paediatr (Stockh)* 1958; **47**: 132–41.
14 FitzSimmons J, Fantel A, Shepard TH. Growth parameters in mid-trimester fetal Turner syndrome. *Early Hum Dev* 1994; **38**: 121–9.
15 Becker B, Jospe N, Goldsmith LA. Melanocytic nevi in Turner syndrome. *Pediatr Dermatol* 1994; **11**: 120–4.
16 De La Chapelle A. Cytogenetical and clinical observations in female gonadal dysgenesis. *Acta Endocrinol Suppl* 1962; **65**: 1–122.
17 Gordon GE, Overstreet EW, Traut HF *et al.* A syndrome of gonadal dysgenesis: a variety of ovarian agenesis with androgenic manifestations. *J Clin Endocrinol Metab* 1955; **15**: 1–12.
18 Taback SP, Collu R, Deal CL *et al.* Does growth-hormone supplementation affect adult height in Turner's syndrome? *Lancet* 1996; **348**: 25–7.
19 Bourguignon JP, Pierard GE, Ernould C *et al.* Effects of human growth hormone therapy on melanocytic naevi. *Lancet* 1993; **341**: 1505–6.

Klinefelter's syndrome [1,2]

Aetiology. The frequency of Klinefelter's syndrome is 1 per 600 male births [2]. In buccal smears the nuclei are chromatin positive and indistinguishable from those of the normal female, but in cultures there are seen to be 47 chromosomes with an XXY sex chromosome complement [3]. The differentiation of the developing gonad proceeds along male lines but the testis fails to develop fully, and many seminiferous tubules are replaced by fibrous tissue. Leydig cells are present in normal or increased numbers.

Clinical features [1,2,4–6]. There are no clinical manifestations before puberty, which occurs at the normal age. The testes are small and fail to produce adult levels of testosterone, which leads to poorly developed secondary sexual characteristics and infertility. Hair growth on the trunk, limbs and face tends to be below average. Psychiatric disorders are common but mental deficiency is not. Some patients retain eunuchoid body proportions. They are tall, obese and may develop gynaecomastia. Associated features include osteoporosis [7] and taurodontism (vertical enlargement of the molar pulp chamber) [8]. Various minor dermatoglyphic changes have been recorded [9].

An association between systemic lupus erythematosus (SLE) and Klinefelter's syndrome has been postulated [10], and this is interesting in view of the fact that SLE is more frequent in women than men and that oestrogens may provoke SLE in some patients [11]. In a case report of SLE in a hypogonadal male with Klinefelter's syndrome treated with testosterone in doses sufficient to normalize the serum level of this hormone to the adult male range, haematological and serological abnormalities, including elevated levels of anti-DNA antibodies and depressed complement levels, returned to normal within 9 months of increasing the testosterone dose [12].

There are two reports of incontinentia pigmenti in boys with Klinefelter's syndrome [13,14]. As incontinentia pigmenti trait is usually lethal in males, it has been proposed that the second X chromosome protects against fetal death.

Patients with Klinefelter's syndrome have an increased risk of developing leg ulcers, especially in combination with hyperpigmentation or atrophie blanche [15,16]. Some authors have attributed the cause of leg ulceration to venous insufficiency, others have implicated increased activity of plasminogen activator inhibitor 1 [17]. It seems likely that androgens may protect against the development of leg ulcers, because ulcers are more common in women than men, and it may be relevant that men who do develop leg ulcers tend to be taller, heavier and less fertile than age-matched control subjects [18].

Testosterone replacement therapy will improve secondary sexual characteristics, but infertility is the rule, except in mosaic patient.

Diagnosis. The association of gynaecomastia with small testes and otherwise apparently normal genitalia should suggest the diagnosis, which is supported by finding an increased urinary excretion of gonadotrophin. The diagnosis is confirmed by chromosome studies.

References

1 Klinefelter HF, Reifenstein EC Jr, Albright F. Syndrome characterized by gynaecomastia, aspermatogenesis with A-Leydigism and increased excretion of follicle-stimulating hormone. *J Clin Endocrinol* 1942; **2**: 615–27.
2 Bandmann H-J, Breit R. *Klinefelter's Syndrome*. Berlin: Springer, 1984.
3 Thompson MW. *Genetics in Medicine*, 3rd edn. Philadelphia: Saunders, 1980: 174–6.

4 Stewart JSS, Mack WS, Govan ADT *et al.* Klinefelter's syndrome: clinical and hormonal aspects. *QJM* 1959; **28**: 561–71.
5 Becker KL, Hoffman DL, Albert A *et al.* Klinefelter's syndrome. Clinical and laboratory findings in 50 patients. *Arch Intern Med* 1966; **118**: 314–21.
6 Gerald PS. Current concepts in genetics. Sex chromosome disorders. *N Engl J Med* 1976; **294**: 706–8.
7 Horowitz M, Nordin BEC, Aaron J *et al.* Osteoporosis and Klinefelter's syndrome. In: Bandmann H-J, Breit R, eds. *Klinefelter's Syndrome*. Berlin: Springer, 1984: 51–61.
8 Rossiwall B. Taurodontism in Klinefelter's syndrome. In: Bandmann H-J, Breit R, eds. *Klinefelter's Syndrome*. Berlin: Springer, 1984: 80–4.
9 Saldana-Garcia P. Dermatoglyphics of Klinefelter's syndrome. In: Bandmann H-J, Breit R, eds. *Klinefelter's Syndrome*. Berlin: Springer, 1984: 85–100.
10 Stern R, Fishman J, Brusman H *et al.* Systemic lupus erythematosus associated with Klinefelter's syndrome. *Arthritis Rheum* 1977; **20**: 18–22.
11 Alarcon-Segovia D, Sauza J. SLE and Klinefelter's syndrome. In: Bandmann H-J, Breit R, eds. *Klinefelter's Syndrome*. Berlin: Springer, 1984: 109–14.
12 Olsen NJ, Kovacs WJ. Case report: testosterone treatment of systemic lupus erythematosus in a patient with Klinefelter's syndrome. *Am J Med Sci* 1995; **310**: 158–60.
13 Kunze J, Frenzel UH, Huttig E *et al.* Klinefelter's syndrome and incontinentia pigmenti. *Hum Genet* 1977; **35**: 237–40.
14 Omerod AD, White MI, McKay E *et al.* Incontinentia pigmenti in a boy with Klinefelter's syndrome. *J Med Genet* 1987; **24**: 439–41.
15 Howell R. Hypostatic ulceration and Klinefelter's syndrome. *BMJ* 1978; **ii**: 95–6.
16 Campbell WA, Price WH. Venous thromboembolic diseases in Klinefelter's syndrome. *Clin Genet* 1981; **19**: 275–80.
17 Veraart JC, Hamulyak K, Neumann HA *et al.* Increased plasma activity of plasminogen activator inhibitor 1 (PAI-1) in two patients with Klinefelter's syndrome complicated by leg ulcers. *Br J Dermatol* 1994; **130**: 641–4.
18 Howell R, Burton JL. Decreased fertility in men with venous stasis of the legs. *Lancet* 1982; **ii**: 630–1.

Other abnormalities of the sex chromosomes

XXYY [1]

These individuals show many of the main features of Klinefelter's syndrome, including sparse body hair. Additional features reported are multiple cutaneous angiomas, acrocyanosis and early peripheral vascular disease.

XYY syndrome [2]

These patients are phenotypic males, often tall and with, perhaps, an increased incidence of severe acne (see Chapter 42). They may be mentally retarded, and have a reputation for aggressive behaviour [3], not accepted by all authorities. There is no evidence of increased secretion of FSH or LH [4].

XXXXY syndrome [5]

These patients, of low birth weight, are slow to grow physically and are mentally defective. There are multiple skeletal defects, of which limited elbow pronation is the most characteristic. The ears are large, low-set and malformed. There is hypogenitalism. No consistent dermatological defects are reported, but some patients have hypotrichosis.

Fragile X syndrome [6–8]

Fragile X syndrome is associated with a folate-sensitive fragile site in band Xq27.3 due to a triplet DNA repeat that is expanded and unstable. Subjects have mental retardation and mild dysmorphic features, with mild connective tissue abnormality that leads to fine skin, hyperextensible joints and flat feet. Males are more commonly affected than females. The disorder is common, with about 1 in 2000 children affected.

References

1 Peterson WC, Gorlin RJ, Paegler F *et al.* Cutaneous aspects of the XXYY genotype. A variant of Klinefelter's syndrome. *Arch Dermatol* 1966; **94**: 695–8.
2 Voorhees JJ, Hayes E, Wilkins J *et al.* The XYY chromosomal complement and nodulocystic acne. *Ann Intern Med* 1970; **73**: 271–6.
3 Alam MT, Deschamps R, Gaba E *et al.* The XYY syndrome in an adolescent male exhibiting prominent behavioural problems. *Clin Genet* 1972; **3**: 162–8.
4 Christiansen P, Nielsen J. Urinary follicle stimulating hormone and luteinizing hormone in six males with the XYY syndrome. *Acta Endocrinol* 1973; **74**: 625–30.
5 Zaleski WA, Houston CS, Pozsonyi J. The XXXXY chromosome anomaly: report of three new cases and review of 30 cases from the literature. *Can Med Assoc J* 1966; **194**: 1143–54.
6 Yu S, Kremer E, Pritchard M *et al.* The fragile X genotype is characterized by an unstable region of DNA. *Science* 1991; **252**: 1179–81.
7 Oberlé I, Rousseau F, Heitz D *et al.* Instability of a 550bp DNA segment and abnormal methylation in fragile X syndrome. *Science* 1991; **252**: 1097–102.
8 Sutherland GR, Haan EA, Kremer E *et al.* Hereditary unstable DNA: a new explanation for some old genetic questions? *Lancet* 1991; **338**: 289–92.

Noonan's syndrome (MIM 163950) [1,2]

This autosomal dominant syndrome, which occurs in both sexes, phenotypically resembles Turner's syndrome. Clinically, patients are of short stature and have a broad short neck, which may be webbed. The facies are characteristic and have an association of hypertelorism, blepharoptosis, epicanthic folds and a small chin. Skeletal defects, including spinal deformity in 30%, are frequent [3]. Congenital heart defects, such as pulmonary stenosis and cardiomyopathy, may be present. Intelligence may be normal but some degree of intellectual impairment is usual. Children with Noonan's syndrome (NS) tend to be clumsy, stubborn, irritable and have communication difficulties [4]. In 70% of males, the testes are undescended.

Dermatological manifestations are common. Lymphoedema of the feet and legs is common and more severe than in Turner's syndrome [5]. Orbital oedema is sometimes seen and can be an unusual presentation of NS [6]. Widespread leukokeratosis of the lips and gingiva has been described [7]. The hair is usually coarse, light coloured and curly, with a low posterior hairline. Downy hypertrichosis may occur on the cheeks or shoulders. Pubic hair is scanty in the male and beard growth is poor [8]. Ulerythema oophryogenes may be a cutaneous marker for NS [9,10].

The genetic basis of NS in many cases is now known to be due to mutations in *PTPN11*, a gene encoding the non-receptor protein tyrosine phosphatase SHP2, which contains two Src homology-2 (SH2) domains [11]. Tartaglia *et al.* [11] found that mutations in the *PTPN11* gene accounted for about 50% of the patients studied. Mutations in the neurofibromin gene (*NF1*), which is the site of mutations causing classic NF1, have been found in neurofibromatosis–Noonan syndrome. Acute leukaemia has been reported in a few cases of NS [12]. After germ-line mutations in *PTPN11* were demonstrated in NS, a search has been performed for defects in *PTPN11* in myeloid disorders, including cases of juvenile myelomonocytic leukaemia (JMML) in children with NS. Specific mutations in *PTPN11* associated with isolated JMML occur as somatic

changes and have never been observed as germ-line defects, leading to speculation that these molecular defects have a greater functional impact and may be associated with embryonic lethality.

Patients with overlapping features of NF1 and NS have also been described (see p. 15.20), and in some of these cases mutations in the *NF1* gene have been detected.

In contrast with Turner's syndrome, short stature and infertility are not constant features. The diagnosis of NS must be suspected in all patients labelled as Turner's syndrome if they are of normal height, intellectually impaired, have a cardiac valve defect or manifest normal gonadal function. Individuals with NS who are of short stature may benefit from treatment with growth hormone [13].

Less common forms of Noonan's syndrome

De novo germline mutations of the *KRAS* gene have also been found in individuals with a variant of Noonan's syndrome (designated NS3; MIM 609942), but these account for less than 5% of Noonan's syndrome cases [14]. Although this mutation was initially identified in an individual with juvenile myelomonocytic leukaemia-like myeloproliferative disorder, further screening of NS cases revealed additional mutations in this gene in the absence of myeloproliferative problems.

Mutations in the *KRAS* gene have also been found in cardiofaciocutaneous syndrome [15].

Further uncommon forms of Noonan's syndrome have been designated NS4 and NS5. NS4 (MIM 610733) is caused by gain-of-function mutations in the *SOS1* gene, which may account for up to 28% of all cases of NS and is therefore the second most common gene defect in NS [16,17].

Some genotype–phenotype correlations are emerging in NS, in that those patients with *SOS1* mutations (NS4) appear to have a more frequent occurrence of pulmonary stenosis compared with NS patients in general, and a lower incidence of atrial septal defects compared with those with *PTPN11* mutation [16]. Additionally, ectodermal features including keratosis pilaris and curly hair were significantly more prevalent among individuals with *SOS1* mutation compared with other Noonan patients. Reduced height, seen in 70% of the general Noonan population, occurred in relatively few patients with *SOS1* mutations (height below the third percentile in only two of 15 individuals with a *SOS1* mutation). In contrast, macrocephaly was overrepresented among those with *SOS1* mutations. Only one individual with an *SOS1* mutation had mental retardation, potentially attributable to critical illness as a newborn. In comparison, 30% of all children with Noonan's syndrome require special education [16].

NS5 (MIM 611553) is caused by mutations in the *RAF1* gene [18], a serine–threonine kinase that activates MEK1 and MEK2. Pandit *et al*. [18] sequenced the *RAF1* gene in 231 individuals with Noonan's syndrome who did not have mutations in the *PTPN11*, *KRAS* or *SOS1* genes. These authors identified 13 different missense mutations in 18 unrelated patients with NS and found that hypertrophic cardiomyopathy was present in 94% of patients carrying a mutation in one of two hotspots. Simultaneously with this report, another group sequenced the *RAF1* gene in 30 patients with NS and again found a strong association with cardiomyopathy [19].

References

1 Noonan JA. Hypertelorism with Turner phenotype. A new syndrome with associated congenital heart disease. *Am J Dis Child* 1968; **116**: 373–80.
2 Mendez HM, Opitz JM. Noonan syndrome: a review. *Am J Med Genet* 1985; **21**: 493–506.
3 Lee CK, Chang BS, Hong YM *et al.* Spinal deformities in Noonan syndrome: a clinical review of sixty cases. *J Bone Joint Surg Am* 2001; **83A**: 1495–502.
4 Wood A, Massarano A, Super M *et al.* Behavioural aspects and psychiatric findings in Noonan's syndrome. *Arch Dis Child* 1995; **72**: 153–5.
5 Minikin W, Frank SB, Wolman SR, Cohen HJ. Lymphedema in Noonan's syndrome. *Int J Dermatol* 1974; **13**: 179–83.
6 Phillips WG, Dunnill MG, Kurwa AR *et al.* Orbital oedema: an unusual presentation of Noonan's syndrome. *Br J Dermatol* 1993; **129**: 190–2.
7 Lucker GP, Steijlen PM. Widespread leucokeratosis in Noonan's syndrome. *Clin Exp Dermatol* 1994; **19**: 414–7.
8 Wyre HU. Cutaneous manifestations of Noonan's syndrome. *Arch Dermatol* 1978; **114**: 929–30.
9 Nield VS, Pegum JS, Wells RS. The association of keratosis pilaris atrophicans and woolly hair with and without Noonan's syndrome. *Br J Dermatol* 1984; **110**: 357–62.
10 Pierini JD, Pierini AM. Keratosis pilaris atrophicans faciei (ulerythema oophryogenes): a cutaneous marker in the Noonan syndrome. *Br J Dermatol* 1979; **100**: 409–16.
11 Tartaglia M, Mehler EL, Goldberg R *et al.* Mutations in PTPN11, encoding the protein tyrosine phosphatase SHP-2, cause Noonan syndrome. *Nat Genet* 2001; **29**: 465–8.
12 Johannes JM, Garcia ER, DeVaan GA *et al.* Noonan's syndrome in association with acute leukemia. *Pediatr Hematol Oncol* 1995; **12**: 571–5.
13 Thomas BC, Stanhope R. Long-term treatment with growth hormone in Noonan's syndrome. *Acta Paediatr* 1993; **82**: 853–5.
14 Schubbert S, Zenker M, Rowe SL *et al.* Germline *KRAS* mutations cause Noonan syndrome. *Nat Genet* 2006; **38**: 331–6.
15 Niihori T, Aoki Y, Narumi Y *et al.* Germline *KRAS* and *BRAF* mutations in cardio-facio-cutaneous syndrome. *Nat Genet* 2006; **38**: 294–6.
16 Roberts AE, Araki T, Swanson KD *et al*. Germline gain-of-function mutations in *SOS1* cause Noonan syndrome. *Nat Genet* 2007; **39**: 70–4.
17 Tartaglia M, Pennacchio LA, Zhao C *et al.* Gain-of-function *SOS1* mutations cause a distinctive form of Noonan syndrome. *Nat Genet* 2007; **39**: 75–9.
18 Pandit B, Sarkozy A, Pennacchio LA *et al.* Gain-of-function *RAF1* mutations cause Noonan and LEOPARD syndromes with hypertrophic cardiomyopathy. *Nat Genet* 2007; **39**: 1007–12.
19 Razzaque MA, Nishizawa T, Komoike Y *et al*. Germline gain-of-function mutations in *RAF1* cause Noonan syndrome. *Nat Genet* 2007; **39**: 1013–7.

Familial multiple tumour syndromes

The neurofibromatoses

The neurofibromatoses comprise several distinct genetic disorders that lead to the formation of tumours surrounding nerves and many other pathological features. The two main forms are NF1 and NF2. The most common type (NF1) is characterized by multiple café-au-lait macules and the occurrence of neurofibromas along peripheral nerves. The second type (NF2) is characterized by vestibular schwannomas (acoustic neuromas), usually bilateral, as well as meningiomas and other tumours of the nervous system. NF2 does not have significant cutaneous manifestations and is not reviewed here. The spectrum of these disorders has been reviewed [1–6].

Neurofibromatosis 1 (MIM 162200)

Synonym

- von Recklinghausen's neurofibromatosis



Fig. 15.8 Neurofibromatosis: axillary freckling and multiple neurofibromas. (Courtesy of Professor J. Harper, Great Ormond Street Hospital, London, UK.)



Fig. 15.9 Neurofibromatosis: extensive neurofibroma of the foot. (Courtesy of Professor J. Harper, Great Ormond Street Hospital, London, UK.)



Fig. 15.10 Neurofibromatosis: Lisch nodules (pigmented iris hamartomas). (Courtesy of Professor J. Harper, Great Ormond Street Hospital, London, UK.)

Definition, history and aetiology [7–9]. In 1882, Friedrich von Recklinghausen published a monograph describing this disease and pointing out that the skin tumours were derived from peripheral nerves [10]. In retrospect, Virchow [11] first reported a family with more than one affected member. It is now recognized that NF1 is an inherited neuroectodermal abnormality, characterized by the presence of six or more café-au-lait spots, axillary freckles, multiple neurofibromas and Lisch nodules (pigmented iris hamartomas) (Figs 15.8–15.10). The mode of inheritance is autosomal dominant, with almost 100% penetrance by the age of 5 years [9,12]. Sporadic cases result from a high gene mutation rate and account for up to 50% of all cases [7–9]. The prevalence of NF1 has been estimated at about 1 in 2500–3300 births [9]. Incomplete or monosymptomatic forms are frequent.

The gene for NF1 is located on chromosome 17 [13,14]. The *NF1* gene has now been cloned and encodes a protein named neurofibromin [15–17]. The gene spans 335 kb and has at least 59 exons, producing four major alternatively spliced transcripts. It is widely expressed in a variety of human tissues. The neurofibromin protein shows significant regions of similarity to the GTPase-activating protein and is capable of down-regulating Ras activity. The majority of *NF1* germ-line mutations alter the reading frame or insert a premature stop codon. No hotspot for mutations has been identified, making the genetic screening highly challenging as each affected individual and family has specific mutations. The impact of these mutations is effective haploinsufficiency for neurofibromin, that is only 50% of the normal protein is produced by cells. Further investigation supports the contention that the *NF1* gene acts as a suppressor of tumour activity, with a variety of somatic inactivating mutations identified in neurofibromas, in keeping with the classical Knudson 'two-hit' hypothesis of tumour genesis. The random acquisition of somatic mutation partly explains the delayed age of onset of the tumours associated with NF1 and the variability of expression [18]. Mouse models with disrupted *NF1* genes have been shown to have an increased susceptibility to certain tumours, giving further support to the role of the *NF1* gene as a tumour suppressor [19,20]. Neurofibromin has been shown to be present in both keratinocytes and melanocytes in normal adult human skin [21].

Mast cells are increased in neurofibromas and may be involved in the development and growth of these tumours by producing

several growth factors, such as histamine and tumour necrosis factor-α (TNF-α) [22,23].

Pathology. Cutaneous neurofibromas are derived from peripheral nerves and their supporting structures, including neurilemmal cells. Ultramicroscopically, they are seen to consist of arborizing Schwann cells in collagenous interstitial tissue. The fibroblast-like cells in cutaneous neurofibromas are thought to be derived from factor XIIIa and HLA-DR-positive connective tissue cells in peripheral nerves [24]. In both café-au-lait spots and clinically unaffected skin, giant pigment granules are occasionally found in epidermal cells and melanocytes [25–29]. They are rarely found in McCune–Albright syndrome, and never in normal skin. They can, however, be found in other conditions, and their presence cannot be regarded as pathognomonic.

Clinical features [7,8,30–32]. The National Institutes of Health Consensus Development Conference Statement, developed in 1988, has proved to be very useful and is widely employed in clinical practice [33]. This requires two or more of the following criteria to be fulfilled.

1. Six or more café-au-lait macules of over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in postpubertal individuals
2. Two or more neurofibromas of any type or one plexiform neurofibroma
3. Freckling in the axillary or inguinal regions
4. Optic glioma
5. Two or more Lisch nodules
6. A distinctive osseous lesion such as sphenoid dysplasia or thinning of the long bone cortex with or without pseudoarthrosis
7. A first-degree relative (parent, sibling, offspring) with NF1 by the above criteria.

Café-au-lait macules (CALMs) are sharply defined, light-brown patches that vary in size from 0.5 to 50 cm, although the majority are 10 cm or less in size. CALMs are the first feature of the disease to appear in all children [8,34]. In a population study, parents noted café-au-lait macules for the first time at 4 years of age or less in all affected children and within the first year of life in 82%. The macules increase in size and number during the first decade.

Cutaneous neurofibromas (previously termed mollusca fibrosa) are soft, lilac-pink tumours, sessile and dome-shaped, sometimes pedunculated. These lesions are most numerous on the trunk and limbs; hundreds may be present, ranging from a few millimetres to several centimetres in diameter. In women, they are prominent on the areola of the breast. Small, firm nodules may develop in relation to peripheral nerves. Blue–red macules and pseudoatrophic macules also occur [35] and are often variants of neurofibromas.

The plexiform neurofibroma is a diffuse elongated fibroma along the course of a nerve, frequently involving the trigeminal or upper cervical nerves and usually noticeable within the first 2 years of life. Plexiform neurofibromas have a distinctive 'bag of worms' feeling on palpation. Elephantiasis neurofibromatosa is a similar diffuse neurofibromatosis of nerve trunks associated with overgrowth of the subcutaneous tissue and of the skin, which is wrinkled and pendulous and may produce gross disfigurement. Neurofibromas may also involve the viscera and blood vessels.

Freckling occurs frequently in the axillae, when it is virtually pathognomonic (Crowe's sign) [36]. It is present in about 70% of affected subjects and appears a little later than the café-au-lait spots, the youngest case in one series being 3 years old [34]. It may also occur in other intertriginous areas, especially the groin. There may also be darker pigmented patches over an underlying plexiform neurofibroma, and if these extend to the midline of the spine, it may indicate that the tumour involves the spinal cord [37].

Lisch nodules (pigmented iris hamartomas) appear as dome-shaped lesions found superficially around the iris on slit-lamp examination. They occur in over 90% of patients and increase in incidence with age [8,34]. They are asymptomatic but help to confirm the diagnosis. They do not occur in segmental or bilateral acoustic NF [31].

Oral lesions are present in 5–10% of cases, as papillomatous tumours of palate, buccal mucous membrane, tongue and lips, or as macroglossia, which is usually asymmetrical [38].

Skeletal abnormalities are well described in NF1, possibly due to a defect in osteoblast differentiation secondary to NF1 ± status [39]. Kyphoscoliosis occurs in 2% of cases. Early-onset, high-level lesions may progress inexorably, leading to cardiorespiratory disease, unless aggressive surgery is performed. Pseudoarthrosis involving the tibia or radius occurs in 1%, but may be asymptomatic [31]. Sphenoid wing dysplasia is a characteristic abnormality.

Recently, in addition to the well characterized skeletal abnormalities, a generalized bone metabolic defect due to loss of the function of neurofibromin has been identified [40]. Early identification of NF1 patients with osteoporosis may permit more timely and aggressive treatments to prevent the likely substantial morbidity associated with increased fracture risk later in life. Short stature and macrocephaly [41] are also uncommon features of the condition.

Other organs: the severity of cutaneous involvement gives no reliable indication of the extent of the disease in other organs. Between 25 and 30% of children may exhibit learning difficulties [34,42] and physical development may be impaired. Speech impediments, hypertelorism and headaches are also common [31,43].

Endocrine disturbances of many types may be associated [44]: precocious puberty, acromegaly [45], Addison's disease, hyperparathyroidism, gynaecomastia and phaeochromocytoma. Renovascular hypertension may occur in children [46,47]. Osteomalacia when present is the result of a congenital defect of the renal tubules.

Involvement of the lower urinary tract [48] may give rise to urinary symptoms. Constipation occurs due to dysfunction of the colonic musculature. Gastrointestinal lesions may also cause recurrent haemorrhage or obstruction. There is a high prevalence of cardiovascular abnormalities [49,50] and NF1 can be complicated by pulmonary hypertension [51].

Neurological manifestations are found in some 40% of patients [38,52]. The most common solitary intracranial tumour is an

optic nerve glioma; astrocytomas and schwannomas also occur. Tumours may arise in peripheral nerves and within the spinal cord. Intracranial tumours may cause epilepsy, although fits may occur in the absence of any demonstrable focal lesion.

Sarcomatous change within a neurofibroma varies from 1.5 to 15% of cases, more often in deeper than in cutaneous lesions [34,53]. It is rare before the age of 40 years, but has occurred in early childhood. Growth is often slow and metastasis late, but local recurrence is frequent. In contrast, malignant peripheral nerve sheath tumours (MPNST) are highly aggressive [54]. MPNST associated with NF1 have a poorer prognosis than spontaneous MPSNT [55]. Malignant change may occur simultaneously in several lesions. Enlargement or pain should suggest the possibility of malignant change, although rapid enlargement may also occur secondary to intralesional haemorrhage.

Other malignant diseases associated with NF include Wilms' tumour, rhabdomyosarcoma, several types of leukaemia [56], retinoblastoma [57] and malignant melanoma [58].

Pruritus may be a symptom of NF. The presence of large numbers of mast cells in the skin in this condition, and the response of the itching to antihistamines, suggest that histamine is the cause of the pruritus [37]. In addition, a beneficial effect of the mast cell blocking agent ketotifen has been reported [22].

Course and prognosis [7,31,38,59]. The course of the condition varies considerably in individual patients and the majority will have a benign course without developing major complications. In fact, a diagnosis of NF1 is often made in middle age or later in life. The wide variability in presentation appears to be at least partially genetically determined and is unrelated to the unaffected NFI allele [60].

Characteristically, café-au-lait spots are present at birth or, more commonly, develop in early childhood and increase in number throughout life. Cutaneous neurofibromas appear during childhood and increase rapidly in number at puberty, suggesting a possible hormonal influence. However, lesions may be present at birth and become progressively more extensive. Although early onset and rapid progression before puberty usually indicate a poor prognosis, minimal cutaneous involvement in the young child does not necessarily imply a favourable course, although many cases remain limited. Extensive involvement of the urinary or gastrointestinal tract or the central nervous system carries a poor prognosis.

Pregnancy, in which unexplained hypertension frequently occurs, sometimes appears to induce rapid progression of existing lesions and the development of new ones [31,61], again suggesting hormonal sensitivity.

At presentation, a detailed clinical assessment is essential and must include examination of all other members of the family. Suggested investigations should include a neurophysiological assessment, a skeletal survey, audiography and slit-lamp ocular examination. Parents and siblings should also have their eyes examined for the presence of Lisch nodules. It is recommended that individuals with NF1 have an annual clinical review, which must include measurement of blood pressure. Further investigations will depend upon the detection of complications. Magnetic resonance imaging (MRI) should be performed in children who have macrocephaly or who demonstrate focal neurological signs or symptoms. Routine cranial imaging is the subject of debate. The detection of an asymptomatic brain lesion will increase patient and parental anxiety and would not alter clinical management. Patients with NF should be monitored by a number of different specialists, with one physician acting as the coordinator. The ideal situation is a multidisciplinary clinic, now established in a number of centres [62].

Long-term follow-up information on cohorts of NF1 patients has shown a reduced life expectancy related to the development of malignancy and other complications, such as hypertension due to renal artery stenosis or phaeochromocytoma [63–65].

Diagnosis. Diagnosis is established on the basis of clinical criteria. Molecular genetic testing is feasible, but the large size of the gene and wide range of pathogenic mutations have so far impeded the widespread diagnostic use of genetic testing [66]. Cutaneous neurofibromas are clinically and histologically distinctive, although a plexiform neurofibroma in an infant can clinically resemble a congenital melanocytic naevus. Café-au-lait spots, usually the earliest manifestation in children, are present in 10–20% of normal individuals and about 35% of patients with McCune–Albright syndrome [7,25]. If only one or two are present, they have little diagnostic significance in the absence of other signs or of a family history of the disease; if six or more are present, the probability of NF is high. Identification of the *NF1* gene means that prenatal/presymptomatic diagnosis for this disease is now possible, with greater than 95% accuracy in families with a suitable structure [34]. However, in a disorder showing such varied expression and complications, the decision to undergo prenatal diagnosis is far from clear. Prenatal diagnosis is also not an option for the approximately 50% of cases who represent new mutations.

Treatment. Treatment is symptomatic. The more disfiguring lesions can be excised if not too diffuse [67]. Carbon dioxide laser surgery is a treatment modality for cutaneous neurofibromas, but hypertrophic and atrophic scars can result and a preliminary test treatment is recommended [68]. Surgery is also indicated when an increase in size and pain suggests possible malignant change. Epilepsy should be thoroughly investigated, as neurosurgical relief is sometimes practicable. Prolonged follow-up with routine checks every 6–12 months is advisable.

NF1 has a significant impact on quality of life through alteration of health and appearance [69]. Adolescence is a particularly difficult time when neurofibromas may grow rapidly in response to hormonal changes.

Genetic counselling is important. Informing families about the varied complications of NF1 is a difficult counselling task, and there is a fine balance between providing adequate information and causing unnecessary alarm. It should be made clear to patients that 50% of their children are likely to be affected and the disease may be severe. First-degree relatives (e.g. siblings and offspring) who have no stigmata of the disease are unlikely to carry the gene and the risk for their offspring is small but not absent, as gonadal mosaicism has been observed [70,71].

References

1 Riccardi VM. Neurofibromatosis: clinical heterogeneity. *Curr Probl Cancer* 1982; 7: 1–34.

2 Riccardi VM. *Neurofibromatosis: Phenotype, Natural History and Pathogenesis*, 2nd edn. Baltimore: Johns Hopkins University Press, 1992.
3 Viskochil D, Carey JC. Nosological considerations of the neurofibromatoses. *J Dermatol* 1992; **19**: 873–80.
4 Viskochil D, Carey JC. Alternate and related forms of the neurofibromatoses. In: Huson SM, Hughes RAC, eds. *The Neurofibromatoses: a Clinical and Pathogenetic Overview*. London: Chapman & Hall, 1994: 445–574.
5 Von Deimling A, Krone W, Menon AG. Neurofibromatosis type 1: pathology, clinical features and molecular genetics. *Brain Pathol* 1995; **5**: 153–62.
6 Huson SM, Rosser E. The phakomatoses. In: Rimoin DL, Connor JM, Pyeritz RE, eds. *Principles and Practice of Medical Genetics*. New York: Churchill Livingstone, 1997: 2269–302.
7 Crowe FW, Schull WJ, Neel JV. *A Clinical, Pathological and Genetic Study of Multiple Neurofibromatosis*. Springfield, IL: Thomas, 1956.
8 Huson SM, Harper PS, Compston DAS. Von Recklinghausen neurofibromatosis. A clinical and population study in South East Wales. *Brain* 1988; **111**: 1355–81.
9 Huson SM, Compston DAS, Clark P *et al.* A genetic study of Von Recklinghausen neurofibromatosis in South East Wales. I. Prevalence, fitness, mutation rate, and effect of parental transmission on severity. *J Med Genet* 1989; **26**: 704–11.
10 von Recklinghausen FD. *Uber die Multiplen Fibrome der Haut und Ihre Beziehung Zu Den Multiplen Neuromen*. Berlin: A. Hirschwald, 1882.
11 Virchow R. Ueber die Reform der patologischen und therapeutischen Anschauungen durch die mikroskopischen Untersuchungen. *Virchow Arch Pathol Anat Physiol Klin Med* 1847; **1**: 345–9.
12 Riccardi VM, Lewis RA. Penetrance of von Recklinghausen neurofibromatosis: a distinction between predecessors and descendants. *Am J Hum Genet* 1988; **42**: 284–9.
13 Barker D, Wright E, Nguyen K *et al.* Gene for von Recklinghausen neurofibromatosis is in the pericentromeric region of chromosome 17. *Science* 1987; **236**: 1100–2.
14 Seizinger BR, Rouleau GA, Ozelius LG *et al.* Genetic linkage of von Recklinghausen neurofibromatosis to the nerve growth factor gene. *Cell* 1987; **49**: 589–94.
15 Cawthorn RM, Weiss R, Xu G *et al.* A major segment of the neurofibromatosis type 1 gene: cDNA sequence, genomic structure and point mutations. *Cell* 1990; **62**: 193–201.
16 Viskochil D, Buchberg AM, Xu G *et al.* Deletions or translocation interrupt a cloned gene at the neurofibromatosis type 1 locus. *Cell* 1990; **62**: 187–92.
17 Wallace MR, Marchuk DA, Anderson LB *et al.* Type 1 neurofibromatosis gene: identification of a large transcript disrupted in three NF1 patients. *Science* 1990; **249**: 181–6.
18 Shen MH, Harper PS, Upadhyaya M. Molecular genetics of neurofibromatosis type 1 (NF1). *J Med Genet* 1996; **33**: 2–17.
19 Brannan CI, Perkins AS, Vogel KS *et al.* Targeted disruption of the neurofibromatosis type 1 gene leads to development abnormalities in heart and various neural crest-derived tissues. *Genes Dev* 1994; **8**: 1019–29.
20 Jacks T, Shih TS, Schmitt EM *et al.* Tumour predisposition to mice heterozygous for a targeted mutation in NF1. *Nat Genet* 1994; **7**: 353–61.
21 Malhotra R, Ratner N. Localization of neurofibromin to keratinocytes and melanocytes in developing rat and human skin. *J Invest Dermatol* 1994; **102**: 812–8.
22 Riccardi VM. Mast cell stabilization to decrease neurofibroma growth. Preliminary experience with ketotifen. *Arch Dermatol* 1988; **123**: 1011–6.
23 Nürnberger M, Moll I. Semiquantitative aspects of mast cells in normal skin and in neurofibromas of neurofibromatosis types 1 and 5. *Dermatology* 1994; **188**: 296–9.
24 Takata M, Imai T, Hirone T. Factor-XIIIa-positive cells in normal peripheral nerves and cutaneous neurofibromas of type 1 neurofibromatosis. *Am J Dermatopathol* 1994; **16**: 37–43.
25 Benedict PH, Szabo G, Fitzpatrick TB *et al.* Melanotic macules in Albright's syndrome and in neurofibromatosis. *JAMA* 1968; **205**: 618–26.
26 Johnson BL, Charneco DR. Café au lait spot in neurofibromatosis and in normal individuals. *Arch Dermatol* 1970; **102**: 442–6.
27 Jimbow K, Szabo G, Fitzpatrick TB. Ultrastructure of giant pigment granules (macromelanosomes) in the cutaneous pigmented macules of neurofibromatosis. *J Invest Dermatol* 1973; **61**: 300–9.
28 Silvers DN, Greenwood RS, Helwig EB. Café au lait spots without giant pigment granules. Occurrence in suspected neurofibromatosis. *Arch Dermatol* 1974; **110**: 87–8.
29 Fitzpatrick TB. Melanin synthesis pathways in the pathogenesis of neurofibromatosis. *Adv Neurol* 1981; **29**: 209–11.
30 Basset A, Collomb H, Quere NA *et al.* Quelques aspects de la maladie de Recklinghausen en Afrique de l'Ouest. A propos de 35 cas observés a Dakar de 1959 à 1964. *Ann Dermatol Siphiligr* 1966; **93**: 43–51.
31 Riccardi VM. Von Recklinghausen neurofibromatosis. *N Engl J Med* 1981; **305**: 1617–27.
32 Riccardi VM. Neurofibromatosis. In: Gomez MR, ed. *Neurocutaneous Diseases*. Boston: Butterworth, 1987: 11–29.
33 National Institutes of Health Consensus Development Conference Statement. Neurofibromatosis. *Arch Neurol* 1988; **45**: 575–8.
34 Huson SM, Compston DAS, Harper PS. A genetic study of Von Recklinghausen neurofibromatosis in South East Wales. II. Guidelines for genetic counselling. *J Med Genet* 1989; **26**: 712–21.
35 Westerhof W, Konrad K. Blue–red macules and pseudoatrophic macules. *Arch Dermatol* 1982; **118**: 577–81.
36 Crowe FW. Axillary freckling as a diagnostic aid in neurofibromatosis. *Ann Intern Med* 1964; **61**: 1142–3.
37 Riccardi VM. Pathophysiology of neurofibromatosis. *J Am Acad Dermatol* 1980; **3**: 157–66.
38 Canale DJ, Bebin J. In: Vinken PJ, Bruyn GW, eds. *Handbook of Clinical Neurology*, Vol. 14. Amsterdam: Elsevier, 1972: 132–62.
39 Wu X, Estwick SA, Chen S *et al.* Neurofibromin plays a critical role in modulating osteoblast differentiation of mesenchymal stem/progenitor cells. *Hum Mol Genet* 2006; **15**: 2837–45.
40 Brunetti-Pierri N, Doty SB, Hicks J *et al.* Generalized metabolic bone disease in neurofibrosis type 1. *Mol Genet Metab* 2008; **94**: 105–11.
41 Weichert KA, Dine MS, Benton C *et al.* Macrocranium and neurofibromatosis. *Radiology* 1973; **107**: 163–6.
42 Ferner RE, Hughes RA, Weinman J. Intellectual impairment in neurofibromatosis 1. *J Neurol Sci* 1996; **138**: 125–33.
43 Westerhof W, Delleman JW, Wolters E *et al.* Neurofibromatosis and hypertelorism. *Arch Dermatol* 1984; **120**: 1579–81.
44 Saxena KM. Endocrine manifestations of neurofibromatosis in children. *Am J Dis Child* 1970; **120**: 265–71.
45 Hartemann P, Schmitt J, Arnould G. Acromegalie et neurofibromatose de Recklinghausen. A propos de dix cas. *Ann Endocrinol* 1964; **25**: 601–18.
46 Mena E, Bookstein JJ, Holt JF *et al.* Neurofibromatosis and renovascular hypertension in children. *Am J Roentgenol* 1973; **118**: 39–45.
47 Nakhoul F, Green J, Angel A *et al.* Renovascular hypertension associated with neurofibromatosis: two cases and review of the literature. *Clin Nephrol* 2001; **55**: 322–6.
48 Gonzalez-Argulo A. Neurofibromatosis involving the lower urinary tract. *J Urol* 1963; **89**: 804–11.
49 Friedman JM, Arbiser J, Epstein JA *et al.* Cardiovascular disease in neurofibromatosis 1: report of the NF1 Cardiovascular Task Force. *Genet Med* 2002; **4**: 105–11.
50 Tedesco MA, Di Salvo G, Natale F *et al.* The heart in neurofibromatosis type 1: an echocardiographic study. *Am Heart J* 2002; **143**: 883–8.
51 Aoki Y, Kodama M, Mezaki T *et al.* von Recklinghausen disease complicated by pulmonary hypertension. *Chest* 2001; **119**: 1606–8.
52 Kramer W. Lesions of the central nervous system in multiple neurofibromatosis. *Psychiatr Neurol Neurochir* 1971; **74**: 349–68.
53 D'Agostino AN, Soule EH, Miller RH. Sarcomas of the peripheral nerves and somatic soft tissues associated with multiple neurofibromatosis (Von Recklinghausen's disease). *Cancer* 1963; **16**: 1015–27.
54 Leroy K, Dumas V, Martin-Garcia N *et al.* Malignant peripheral nerve sheath tumors associated with neurofibromatosis type 1: a clinicopathologic and molecular study of 17 patients. *Arch Dermatol* 2001; **137**: 908–13.
55 Zou C, Smith KD, Liu J *et al.* Clinical, pathological, and molecular variables predictive of malignant peripheral nerve sheath tumor outcome. *Ann Surg* 2009; **249**: 1014–22.
56 Hope DG, Mulvihill JJ. Malignancy in neurofibromatosis. *Adv Neurol* 1981; **29**: 33–56.
57 Hasanreisoglu B, Or M, Akbatur H. Neurofibromatosis associated with retinoblastoma: case report. *Br J Ophthalmol* 1988; **72**: 139–41.
58 Duve S, Rakoski J. Cutaneous melanoma in a patient with neurofibromatosis: a case report and review of the literature. *Br J Dermatol* 1994; **131**: 290–4.

59 Brasfield RD, Das Gupta TK. Von Recklinghausen's disease: a clinico-pathological study. *Ann Surg* 1972; **175**: 86–104.
60 Sabbagh A, Pasmant E, Laurendeau I *et al*. Unravelling the genetic basis of variable clinical expression in neurofibromatosis 1. *Hum Mol Genet* 2009; **18**: 2768–78.
61 Swapp GH, Main RA. Neurofibromatosis in pregnancy. *Br J Dermatol* 1973; **80**: 431–5.
62 Ferner RE, Huson SM, Thomas N *et al.* Guidelines for the diagnosis and management of individuals with neurofibromatosis 1. *J Med Genet* 2007; **44**: 81–8.
63 Sorensen SA, Mulvihill JT, Nielsen A. Long-term follow-up of von Recklinghausen neurofibromatosis: survival and malignant neoplasms. *N Engl J Med* 1986; **314**: 1010–5.
64 Zöller M, Rembeck B, Akesson HO *et al.* Life expectancy, mortality and prognostic factors in neurofibromatosis type 1: a 12 year follow-up of an epidemiological study in Göteborg, Sweden. *Acta Derm Venereol (Stockh)* 1995; **75**: 136–40.
65 Imaizumi Y. Mortality of neurofibromatosis in Japan, 1968–92. *J Dermatol* 1995; **22**: 191–5.
66 Korf BR. Diagnosis and management of neurofibromatosis type 1. *Curr Neurol Neurosci Rep* 2001; **1**: 162–7.
67 Griffith BH, McKinney P, Monroe CW *et al.* Von Recklinghausen's disease in children. *Plast Reconstr Surg* 1972; **49**: 647–53.
68 Ostertag JU, Theunissen CC, Neumann HA. Hypertrophic scars after therapy with CO_2 laser for treatment of multiple cutaneous neurofibromas. *Dermatol Surg* 2002; **28**: 296–8.
69 Wolkenstein P, Zeller J, Revuz J *et al.* Quality-of-life impairment in neurofibromatosis type 1: a cross-sectional study of 128 cases. *Arch Dermatol* 2001; **137**: 1421–5.
70 Sestini R, Vivarelli R, Balestri P *et al*. Neurofibromatosis type 2 attributable to gonosomal mosaicism in a clinically normal mother, and identification of seven novel mutations in the *NF2* gene. *Hum Genet* 2000; **107**: 366–71.
71 Consoli C, Moss C, Green S *et al*. Gonosomal mosaicism for a nonsense mutation (*R1947X*) in the *NF1* gene in segmental neurofibromatosis type 1. *J Invest Dermatol* 2005; **125**: 463–6.

NF1, juvenile xanthogranulomas and juvenile chronic myeloid leukaemia

The association of juvenile xanthogranulomas with NF1 has been noted in many patients [1]. It is now recognized that children with NF1 and juvenile xanthogranulomas have a 20–32-fold higher risk for juvenile chronic myeloid leukaemia than do patients with NF1 who do not have juvenile xanthogranulomas [2]. Juvenile chronic myeloid leukaemia is a rare type of leukaemia and accounts for about 1–2% of childhood leukaemias. A rare association of NF1, juvenile xanthogranulomas, and juvenile myelomonocytic leukaemia (JMML), initially presenting with features of haemophagocytic lymphohistiocytosis has been described [3].

References

1 Jensen NE, Sabharwal S, Walker AE. Naevoxanthoendothelioma and neurofibromatosis. *Br J Dermatol* 1971; **85**: 326–30.
2 Zvulunov A, Barak Y, Metzker A. Juvenile xanthogranuloma, neurofibromatosis, and juvenile chronic myelogenous leukemia. World statistical analysis. *Arch Dermatol* 1995; **131**: 904–8.
3 Shin HT, Harris MB, Orlow SJ. Juvenile myelomonocytic leukemia presenting with features of hemophagocytic lymphohistiocytosis in association with neurofibromatosis and juvenile xanthogranulomas. *J Pediatr Hematol Oncol* 2004; **26**: 591–5.

Segmental neurofibromatosis [1–7]

This condition is characterized by café-au-lait spots, cutaneous neurofibromas and sometimes visceral neurofibromas, limited to a circumscribed body segment. The condition probably represents a somatic mosaicism of the *NF1* gene. Rubenstein *et al.* [8] reported two patients with segmental NF in which signs of generalized NF appeared in a single member of the next generation. It is difficult, in the light of these and other anecdotal examples, to reassure patients with apparent segmental NF that there is no risk of NF1 occurring in their offspring, although the risk is small.

References

1 Miller RM, Sparkes RS. Segmental neurofibromatosis. *Arch Dermatol* 1977; **113**: 837–8.
2 Dawson TAJ. Regional eruptive neurofibromatosis. *Br J Dermatol* 1984; **111** (Suppl. 26): 65.
3 Oranje AP, Vuzevski VD, Kalis TJ *et al.* Segmental neurofibromatosis. *Br J Dermatol* 1985; **112**: 107–12.
4 Roth MRR, Martines MAJR, James WD. Segmental neurofibromatosis. *Arch Dermatol* 1987; **123**: 917–20.
5 Viskochil D, Carey JC. Alternate and related forms of the neurofibromatoses. In: Huson SM, Hughes RAC, eds. *The Neurofibromatoses: a Clinical and Pathogenetic Overview*. London: Chapman & Hall, 1994: 445–574.
6 Moss C, Green SH. What is segmental neurofibromatosis? *Br J Dermatol* 1994; **130**: 106–10.
7 Ruggieri M, Huson SM. The clinical and diagnostic implications of mosaicism in the neurofibromatoses. *Neurology* 2001; **56**: 1433–43.
8 Rubenstein AE, Bader JE, Aron AA *et al.* Familial transmission of segmental neurofibromatosis. *Neurology* 1983; **33** (Suppl. 2): 76.

Café-au-lait spots and pulmonary stenosis (MIM 193520) [1,2]

Synonym
- Watson's syndrome

In three families, café-au-lait macules were associated with pulmonary stenosis and low intelligence. Some affected individuals also had freckling in the axillae, perineum and elsewhere. There was no other evidence of NF [2]. Café-au-lait spots are present in about 60% of patients with this syndrome [1]. Allanson *et al.* [3] demonstrated linkage with markers for the *NF1* gene, and Tassabehji *et al.* [4] identified an *NF1* mutation in a family with features of Watson's syndrome and NS. The pathogenesis of this distinct phenotype is as yet unclear.

References

1 Ortonne JP, Brocard E, Floret D *et al.* Valeur diagnostique des taches café-au-lait. *Ann Dermatol Vénéréol* 1980; **107**: 313–27.
2 Watson GH. Pulmonary stenosis, café au lait spots and dull intelligence. *Arch Dis Child* 1967; **42**: 303–7.
3 Allanson JE, Upadhyaya M, Watson G *et al.* Watson syndrome: is it a subtype of type 1 neurofibromatosis? *J Med Genet* 1991; **28**: 752–6.
4 Tassabehji M, Strachan T, Sharland M *et al.* Tandem duplication within a neurofibromatosis type 1 (NF1) gene exon in a family with features of Watson syndrome and Noonan syndrome. *Am J Hum Genet* 1993; **53**: 90–5.

Neurofibromatosis–Noonan syndrome (MIM 601321)

Patients with features of both NF1 and NS have been described, although considerable variability of phenotypic expression exists. Whether a specific NF–NS phenotype exists is unclear at present. In a survey of the Noonan phenotype in a series of NF1 patients, it was concluded that this was not a distinct syndrome [1]. More recently, De Luca *et al.* screened a case collection with clinically well-characterized NF–NS for mutations in the entire coding sequence of the *NF1* and *PTPN11* genes [2]. Heterozygous *NF1* defects were identified in 16 of the 17 unrelated subjects studied, thus providing evidence that mutations in *NF1* represent the

major molecular event underlying this condition. Several in-frame defects affecting exons 24 and 25, which encode a portion of the GAP-related domain of the protein, were observed. On the other hand, no defect in *PTPN11* was observed and no lesion affecting exons 11 through 27 of the *NF1* gene was identified in 100 *PTPN11* mutation-negative subjects with NS, providing further evidence that NF–NS and NS are genetically distinct disorders. These results support the view that NF–NS is a variant of *NF1* and is caused by mutations of the *NF1* gene, some of which have been demonstrated to cause classic *NF1* in other individuals.

References

1 Colley A, Donnai D, Evans DGR. Neurofibromatosis/Noonan phenotype: a variable feature of type 1 neurofibromatosis. *Clin Genet* 1996; **49**: 59–64.
2 De Luca A, Bottillo I, Sarkozy A *et al*. *NF1* gene mutations represent the major molecular event underlying neurofibromatosis-Noonan syndrome. *Am J Hum Genet* 2005; **77**: 1092–101.

Diffuse neurofibroma [1]

Diffuse neurofibroma is a relatively recently recognized distinct clinical entity. A report of four adult cases [1] described 3–8-cm, hard, sclerotic plaques with an irregular surface but without protruding nodules, present for 1–12 years. Histologically, the tumours consisted of spindle cells with wavy fibrillar cytoplasm and elongated nuclei. Electron microscopy and special stains confirmed their neural origin. Excision revealed infiltration well beyond the clinical margins, and malignant transformation in one. Early diagnosis is important, as prompt surgical treatment is recommended.

Reference

1 Dahl MGC, Malcolm AJ. Diffuse neurofibroma: unrecognised and undertreated? *Br J Dermatol* 1989; **121** (Suppl. 34): 24.

NF1-like syndrome (MIM 611431)

Synonym
- Legius syndrome

In 2007, an important disorder that closely resembles NF1 was described. The cardinal features are multiple CALMs, macrocephaly and axillary freckling. Five families that were negative for *NF1* gene mutational analysis were used for linkage analysis and a region identified on chromosome 15; subsequently, mutations in the *SPRED1* gene were identified [1]. Legius syndrome appears to be distinguished clinically by the absence of Lisch nodules or neurofibromas and genetically by the absence of *NF1* gene mutations.

Reference

1 Brems H, Chmara M, Sahbatou M *et al.* Germline loss-of-function mutations in *SPRED1* cause a neurofibromatosis 1-like phenotype. *Nat Genet* 2007; **39**: 1120–6.

Tuberous sclerosis complex (MIM 191100)

Synonyms
- Epiloia
- Bourneville's disease

Definition, history and aetiology. Tuberous sclerosis complex (TSC) is now the preferred name for the condition previously known as tuberous sclerosis and represents a genetic disorder of hamartoma formation in many organs, particularly the skin, brain, eye, kidney and heart. Characteristic skin lesions are numerous and include angiofibromas, the shagreen patch, periungual fibromas and 'ash-leaf' white macules, classically, although not invariably, seen in association with epilepsy and mental retardation. The term 'complex' emphasizes the multisystem involvement and highly variable expression of the disease.

TSC was first recognized in the 19th century [1]. Rayer [2] gave the first description of the fibrovascular papules, and Bourneville [3] reported the case of a mentally retarded girl who also suffered from hemiplegia and epilepsy. He did not recognize her facial eruption or kidney tumour as being part of the disease. Sherlock [4] coined the now outmoded term 'epiloia', a contraction capturing the diagnostic clinical triad of *epi*lepsy, *l*ow *i*ntelligence and *a*denoma sebaceum.

Early population studies greatly underestimated the prevalence of TSC. More recent studies have shown the incidence to be 1 in 10 000 in the Oxford region [5] and 1 in 27 000 in the west of Scotland [6]. Osborne *et al.* [7] have estimated that the birth incidence may be in the region of 1 in 5800, which makes TSC, along with NF1, one of the more common single-gene disorders.

The inheritance of TSC is determined by a single autosomal dominant gene, showing great variability of expression, even within a single family. Genetic linkage studies first mapped the *TSC* gene to chromosome 9 [8,9]. It is now recognized that about half the TSC families are linked to 9q34 (*TSC1*) and the other half to 16p13 (*TSC2*) [10,11]. The proportion of families who do not link to either chromosome 9 or 16 is small. *TSC1* encodes hamartin and the *TSC2* gene encodes a protein named tuberin. Tuberin shows one area of homology to the catalytic domain of the GTPase-activating protein Rap1. Rap1 is a member of the same group of GTPases as *RAS* and is involved in the regulation of cell proliferation and differentiation. This suggests that some of the biological functions of tuberin and neurofibromin are similar.

Loss of tuberin activity is thought to lead to activation of Rap1 in tumours of patients with TSC [12]. Further support for a putative tumour-suppressor role is derived from the study of loss of heterozygosity studies for the *TSC1* and *TSC2* gene regions in various hamartomas from TSC patients [13–15]. No obvious phenotypic differences have been found between families linked to *TSC1* and *TSC2* [16]. Analysis of deletions of the *TSC2* locus has identified one specific correlation, namely severe polycystic kidney disease, for which the causal gene is contiguous [17].

Approximately 60–70% of TSC cases are thought to be the result of new mutations, but before genetic counselling of the normal parents of an affected child, both parents should be fully investigated, including a full skin examination using the Wood's lamp, and possibly computed tomography (CT) [18], renal ultrasound or intravenous pyelography, and expert ophthalmological examination. A study using these investigations showed that about 30% of apparently unaffected parents had TSC [19].

Pathology [20]. The defect in organogenesis may affect almost any tissue. Most of the lesions are hamartomas, and in many organs the cells resemble embryonic cells, suggesting that the defect occurs at an early stage in embryogenesis. In many lesions, for example angiomyolipoma of the kidney, there is malformation of vascular and mesenchymal tissue. The lesions are slow growing and tend to produce symptoms by pressure effects, although occasionally there is haemorrhage from a vascular lesion.

Most of the cutaneous lesions show an excess of collagen. The shagreen patches show no other change and cannot be identified on the histological findings alone. Angiofibromata (formerly misnamed adenoma sebaceum) consist of hyperplastic blood vessels and sebaceous glands of immature hair follicles. Collagen synthesis is increased in the angiofibroma, although total collagen content is decreased, suggesting that there may be an increased turnover of collagen [21]. Histopathology of the periungual fibromas shows a distal part with loose collagen and many blood vessels and a larger proximal part composed of dense collagen bundles and fewer capillaries [22]. The white ash-leaf-shaped macules contain abnormal melanocytes with reduced tyrosinase activity [23], and electron microscopy shows defective melanization of melanosomes [24,25].

The characteristic tuberosclerotic nodules of glial proliferation may occur anywhere in the cerebral cortex, basal ganglia and ventricular walls, but are rare in the cerebellum, medulla or cord [20]. Gliomas are not uncommon and almost always develop in the striothalamic region. Renal tumours of embryonic type, usually multiple, subcapsular and benign, are found in about 80% of cases at post-mortem but are frequently asymptomatic. The angiomyolipoma is the characteristic lesion but cystic renal disease also occurs [26]. The so-called congenital rhabdomyoma of the heart is an abnormal and premature differentiation of embryonic myocardium into atypical Purkinje cells. The lungs may show interstitial fibrosis or fibroleiomyomatosis with cystic changes [27–29]. Lymphoblastoid cell lines and fibroblasts from patients with TSC are abnormally sensitive to radiation and radiomimetic chemicals [30].

Clinical features [31–36]. The characteristic features of the syndrome are skin lesions, mental retardation and epilepsy, but these show very wide variation in age of onset and severity. Onset before the age of 5 years with cutaneous changes or with epilepsy is usual, although the disease may remain latent until adolescence or adult life. Diagnostic criteria determined by a committee of the then US National Tuberous Sclerosis Association (now the TS Alliance) [37,38] have since been modified [39,40]. A definitive diagnosis of TSC requires two major features (Table 15.2). Brain MRI or non-enhanced CT, renal ultrasound or echocardiogram may be necessary.

Skin lesions are found in 60–70% of cases. Lesions of four types are pathognomonic.

1. Angiofibromas (Fig. 15.11) may rarely be present at birth or develop in infancy, but usually appear between the ages of 3 and 10 years, and sometimes later. They often become more extensive at puberty and then remain unchanged. Firm, discrete, red-brown, telangiectatic papules, 1–10 mm in diameter, extend from the nasolabial furrows to the cheeks and chin, and are occasionally found in the ears. They may be numerous and conspicuous, and very rarely may form large cauliflower-like masses. In many cases they are easily overlooked, being confined to a small area on each side of the nose or the chin.
2. Periungual fibromas (Koenen's tumours) appear at or after puberty as smooth, firm, flesh-coloured excrescences emerging from the nail folds. They are usually 5–10 mm in length, but may be very large. This can be the only clinically evident abnormality.
3. The shagreen patch is an irregularly thickened, slightly elevated, soft, skin-coloured plaque, usually in the lumbosacral region.
4. White ovoid or ash-leaf-shaped macules [23,41–43] 1–3 cm in length, most easily detectable by examination under Wood's light, are frequently present on the trunk or limbs. They are a valuable physical sign, as they may be found at birth or in early infancy, some years before other signs of the disease develop, and may suggest the correct diagnosis in infants with convulsions. However, it is important to appreciate that hypopigmented macules are seen in 2–3 per 1000 of apparently normal newborn babies and therefore alone their presence is not indicative of TSC [44].

Table 15.2 Revised diagnostic criteria for tuberous sclerosis complex [39,40].

Major features
Facial angiofibromas or forehead plaque
Non-traumatic ungual or periungual fibroma
Hypomelanotic macules (more than 3)
Shagreen patch (connective tissue nevus)
Multiple retinal nodular hamartomas
Cortical tuber*
Subependymal nodule
Subependymal giant cell astrocytoma
Cardiac rhabdomyoma, single or multiple
Lymphangiomyomatosis†
Renal angiomyolipoma†
Minor features
Multiple randomly distributed pits in dental enamel
Hamartomatous rectal polyps‡
Bone cysts§
Cerebral white matter migration lines*§¶
Gingival fibromas
Non-renal hamartoma‡
Retinal achromic patch
'Confetti' skin lesions
Multiple renal cysts‡
Definite TSC: either 2 major features or 1 major feature with 2 minor features
Probable TSC: 1 major feature and 1 minor feature
Possible TSC: either 1 major feature or 2 or more minor features

* When cerebral cortical dysplasia and cerebral white matter migration tracts occur together, they should be counted as one rather than two features of TSC.

† When both lymphangiomyomatosis and renal angiomyolipomas are present, other features of TSC should be present before a definitive diagnosis is assigned.

‡ Histological confirmation is suggested.

§ Radiographic confirmation is sufficient.

¶ One panel member recommended three or more radial migration lines constitute a major feature.



Fig. 15.11 Tuberous sclerosis: angiofibromas. (Courtesy of Professor J. Harper, Great Ormond Street Hospital, London, UK.)



Fig. 15.12 Tuberous sclerosis: fibromatous nodule on the forehead. (Courtesy of Professor J. Harper, Great Ormond Street Hospital, London, UK.)

Other cutaneous manifestations include firm fibromatous plaques, especially on the forehead [45] and scalp (Fig. 15.12), soft pedunculated fibromas around the neck and axillae, and poliosis [46].

Fibromatous tumours are occasionally present on the gums and palate and rarely are found on the tongue, larynx and pharynx [47]. Small pits commonly occur in the tooth enamel in adult patients; although less obvious in the deciduous teeth, these pits have been used as an early diagnostic sign in children with TSC [48].

Learning difficulties is present in 60–70% of cases and may be progressive, but if mental development has been normal throughout childhood subsequent deterioration is uncommon [34]. Some cases have presented gross behaviour disorders, although they have been of normal intelligence. In particular, self injury behaviour is quite common, occurring in up to 10% of patients [49]. Psychotic symptoms, including schizophrenia, sometimes develop [50].

Epilepsy [51] is seen in almost all mentally retarded patients and in some 70% of those with average intelligence. It usually begins in infancy or early childhood, thus often preceding the skin lesions by many years. Less frequently, the onset of epilepsy is delayed until puberty or adult life. The attacks may be focal and often become progressively more frequent and severe, but there may be long remissions. Treatment can be quite challenging and in some cases requires surgery. Intracranial malignant change occurs in a few patients. Symptoms and signs of raised intracranial pressure usually result from obstruction by a tumour at the foramen of Monro. Very rarely, cord lesions produce focal neurological signs.

Ocular signs [52,53] occur in 50% of cases but may be hard to detect. Retinal phacomas are seen as white streaks along the vessels or as small, rounded tumours near the disc. Pigmentary and other retinal abnormalities can occur. Symptoms are rare but there may be scotomas or amaurosis. Hypopigmented spots in the iris also occur and these may be analogous to the ash-leaf macule in the skin [54].

Cardiac and renal tumours are often asymptomatic unless by reason of their size or site. Cardiac rhabdomyomas, detected by echocardiography, occur in over 50% of infants [55–57]. These tumours may result in early death; however, recent evidence suggests that in the majority these tumours regress in early infancy and again in adolescence [57]. Prenatal detection of these tumours is now possible by fetal echocardiography [58,59] and is often the initial clue to the diagnosis. Renal involvement includes angiomyolipoma [60], a benign tumour of the renal parenchyma and, less commonly, renal cysts [61,62]. Rarely, the presenting symptoms may be of renal origin, usually haematuria [63].

Pulmonary changes [28] are rare and seldom cause symptoms, but if extensive can result in increasing dyspnoea and recurrent spontaneous pneumothorax. Lymphangioleiomyomatosis is occasionally seen. These respiratory complications occur much more frequently in females and tend to become clinically manifest in the second decade [27,29]. They may result in death from tension pneumothorax or cor pulmonale. The rare association of TSC with chylothorax resulting from lymphangiomyoma appears to be significant [64].

Gastrointestinal tumours may occur [65]. These are usually hamartomatous colonic polyps. Colonoscopy should be considered in the investigation of patients with TSC.

Endocrine and other metabolic disturbances may be present [66]. Most frequently reported are pituitary–adrenal dysfunction, thyroid disorders and premature puberty.

Associated abnormalities. These include primary localized gigantism [67,68] and diffuse cutaneous reticulohistiocytosis [69].

Partial forms. In some cases, only one component of the syndrome is clinically evident, although post-mortem findings in such cases often show involvement of other organs. Unilateral, multiple, facial angiofibromas have been reported in two patients and the authors hypothesized that this represented a mosaic form of TSC [70].

Radiological findings [71]. These are delineated below.

Skull. Calcification is seen on plain skull X-ray in about 50% of patients, although it is not usually apparent until later

childhood or adult life. Investigation should now include CT and MRI [72]. The characteristic CT findings include periventricular (subependymal) nodules, parenchymal hamartomas (cortical tubers), ventriculomegaly and, rarely, subependymal giant cell astrocytomas. The typical CT appearance of TSC consists of calcified periventricular nodules that project into the lateral ventricles and hypoattenuated parenchymal lesions. MRI is more sensitive in the detection of parenchymal lesions. The periventricular lesions may not be seen initially and can progress to calcified lesions with time. This is also true of the parenchymal lesions.

Hands and feet [73]. Cyst-like lesions of the phalanges and irregular thickening of the cortex of metatarsals and metacarpals have been reported, and similar lesions localized in vertebrae, pelvis or long bones are not uncommon.

Lungs. There may be irregular reticulation of the lung fields, not radiologically distinguishable from other types of interstitial fibrosis.

Kidneys. Investigation includes ultrasound and CT [74]. Angiography is helpful in differentiating renal hamartomas from other lesions [75].

Electroencephalographic findings. The proportion of cases showing abnormal findings is high and increases with age, but there is no diagnostic pattern.

Course and prognosis. The expectation of life for a severely affected infant is poor: 3% die in the first year, 28% under 10 years and 75% before age 25 years. Death is usually due to epilepsy or intercurrent infection, but occasionally it is due to a tumour, cardiac failure or pulmonary fibrosis. The prognosis for the older child or young adult with the cutaneous stigmata and epilepsy is unpredictable. Each case must be investigated in detail and individually assessed.

Diagnosis [36]. The telangiectasia and the lack of comedones and pustules distinguish angiofibromas from acne vulgaris. The firm, skin-coloured papules of epithelioma adenoides cysticum must also be differentiated. The full syndrome presents few problems. Difficulties arise in infancy when the classical triad is not evident. The identification of white ash-leaf-shaped macules under Wood's light, in the presence of unexplained epilepsy, retinal phacomas, or radiological or electroencephalographic findings, or a positive family history will help establish the diagnosis. The partial forms are often unsuspected until post-mortem. Any child of a person diagnosed as having TSC has a 50% chance of inheriting the disease. Family screening and genetic counselling should be carried out by referral to a clinical genetics service. DNA testing is available in 85% of cases and should be discussed. Gonadal mosaicism is possible in around 3% of families where parents are not known to have overt TSC. Prenatal diagnosis is not an option for the 60–70% of cases who represent new mutations.

Treatment. The cosmetic appearance may be improved by treating angiofibromas with the pulsed dye vascular laser (wavelength 585 nm), which reduces redness. The more papular/nodular lesions are best treated with the carbon dioxide laser or other débriding techniques in the first instance [76]. The treatment of lesions in other organs is unsatisfactory, and surgical procedures may be required for relief of symptoms. Neurosurgery should be considered when epilepsy is uncontrolled by drugs and there is a fixed, circumscribed, electroencephalographic focus [77].

References

1 Morgan JE, Wolfort F. The early history of tuberous sclerosis. *Arch Dermatol* 1979; **115**: 1317–9.
2 Rayer PFO. *Treatise*: *Maladies de la Peau*, 2nd edn. Philadelphia: Willis, 1835: 656–9.
3 Bourneville DM. Contribution a l'étude de l'idiotie: Sclèrose tubéreuse des circonvolutions cérébrale: Idiote et épilepsie hemiplegique. *Arch Neurol* 1880; **1**: 81–91.
4 Sherlock EB. *The Feeble-Minded: a Guide to Study and Practice*. London: MacMillan, 1911: 235–47.
5 Hunt A, Lindenbaum RH. Tuberous sclerosis: a new estimate of prevalence within the Oxford region. *J Med Genet* 1984; **21**: 272–7.
6 Sampson JR, Scahill SJ, Stephenson JBP *et al.* Genetic aspects of tuberous sclerosis in the west of Scotland. *J Med Genet* 1989; **26**: 28–31.
7 Osborne JP, Fryer A, Webb D. Epidemiology of tuberous sclerosis. *Ann NY Acad Sci* 1991; **615**: 125–7.
8 Connor JM, Pirrit LA, Yates JRW *et al.* Linkage of the tuberous sclerosis locus to a DNA polymorphism detected by v-abl. *J Med Genet* 1987; **24**: 544–6.
9 Fryer AE, Connor JM, Povey S *et al.* Evidence that the gene for tuberous sclerosis is on chromosome 9. *Lancet* 1987; **i**: 659–61.
10 Kwiatowski DJ, Short MP. Tuberous sclerosis. *Arch Dermatol* 1994; **130**: 348–54.
11 Sampson JR, Harris PC. The molecular genetics of tuberous sclerosis. *Hum Mol Genet* 1994; **3**: 1477–80.
12 Wienecke R, Konig A, Declue JE. Identification of tuberin, the tuberous sclerosis-2 product. Tuberin possesses specific Rap1 GAP activity. *J Biol Chem* 1995; **270**: 16409–14.
13 Green AJ, Smith M, Yates JRW. Loss of heterozygosity on chromosome 16p13.3 in hamartomas from tuberous sclerosis patients. *Nat Genet* 1994; **6**: 193–6.
14 Green AJ, Johnson PH, Yates JRW. The tuberous sclerosis gene on chromosome 9q34 acts as a growth suppressor. *Hum Mol Genet* 1994; **3**: 1833–4.
15 Henske EP, Neumann HPH, Scheithauer BW *et al.* Loss of heterozygosity in the tuberous sclerosis (TSC2) region on chromosome band 16p13 occurs in sporadic as well as TSC associated renal angiomyolipomas. *Genes Chromosomes Cancer* 1995; **13**: 295–8.
16 Povey S, Burley MW, Attwood J *et al.* Two loci for tuberous sclerosis: one on 9q34 and one on 16p13. *Ann Hum Genet* 1994; **58**: 107–27.
17 Brook-Carter PT, Peral B, Ward CJ *et al.* Deletion of the TSC2 and PKDI genes associated with severe infantile polycystic kidney disease, a contiguous gene syndrome. *Nat Genet* 1994; **8**: 328–32.
18 Flinter FA, Neville BGR. Examining the parents of children with tuberous sclerosis. *Lancet* 1986; **ii**: 1167.
19 Cassidy SB, Pagon RA, Pepin M *et al.* Family studies in tuberous sclerosis. Evaluation of apparently unaffected parents. *JAMA* 1983; **249**: 1302–4.
20 Bender BL, Yunis EJ. The pathology of tuberous sclerosis. *Pathol Annu* 1982; **17**: 339–82.
21 Oikarinen A, Palatsi R, Linna SL *et al.* Types I and II collagens and the activities of prolyl hydroxylase and galactosylhydroxylysylglucosyl-transferase in skin lesions of tuberous sclerosis. *Br J Dermatol* 1982; **107**: 659–64.
22 Kint A, Baran R. Histopathologic study of Koenen tumors. Are they different from acquired digital fibrokeratoma? *J Am Acad Dermatol* 1988; **18**: 369–72.
23 Fitzpatrick TB, Szabo G, Hori Y *et al.* White leaf-shaped macules. Earliest visible sign of tuberous sclerosis. *Arch Dermatol* 1968; **98**: 1–6.
24 Jimbow K, Fitzpatrick TB, Szabo G *et al.* Congenital circumscribed hypomelanosis: a characterization based on electron microscopic study of tuberous sclerosis, nevus depigmentosus and piebaldism. *J Invest Dermatol* 1975; **64**: 50–62.
25 Tilgen W. Ultrastructure of white leaf-shaped macules in tuberous sclerosis. *Arch Dermatol Forsch* 1973; **248**: 13–27.
26 Mitnick JS, Bosniak MA, Hilton S *et al.* Cystic renal disease in tuberous sclerosis. *Radiology* 1983; **147**: 85–7.
27 Dwyer JM. Pulmonary tuberous sclerosis. Report of three patients and a review of the literature. *QJM* 1971; **40**: 115–25.

28 Milledge RD, Gerald BE, Carter WJ. Pulmonary manifestations of tuberous sclerosis. *Am J Roentgenol* 1966; **98**: 734–8.
29 Rudolph RI. Pulmonary manifestations of tuberous sclerosis. *Cutis* 1981; **27**: 82–4.
30 Scudiero DA, Moshell AN, Scarpinato RG *et al.* Lymphoblastoid lines and skin fibroblasts from patients with tuberous sclerosis are abnormally sensitive to ionizing radiation and to a radiomimetic chemical. *J Invest Dermatol* 1981; **78**: 234–8.
31 Fryer AE, Osbourne JP. Tuberous sclerosis: a clinical appraisal. *Pediatr Rev Commun* 1987; **1**: 239–55.
32 Gomez MR. Tuberous sclerosis. In: Gomez MR, ed. *Neurocutaneous Diseases*. Boston: Butterworth, 1987: 30–52.
33 Hunt A. Tuberous sclerosis: a survey of 97 cases. Part I. Seizures, pertussis immunization and handicap. Part II. Physical findings. Part III. Family aspects. *Dev Med Child Neurol* 1983; **25**: 346–9, 350–2, 353–7.
34 Lagos JC, Gomez MR. Tuberous sclerosis: reappraisal of a clinical entity. *Mayo Clin Proc* 1967; **42**: 26–49.
35 Osborne JP. Diagnosis of tuberous sclerosis. *Arch Dis Child* 1988; **63**: 1423–5.
36 Reed WB, Nickel WR, Campion G. Internal manifestations of tuberous sclerosis. *Arch Dermatol* 1963; **87**: 715–28.
37 Roach ES, Smith M, Huttenlocher P *et al.* Diagnostic criteria: tuberous sclerosis complex. *J Clin Neurol* 1992; **7**: 221–4.
38 Huson SM, Rosser E. The phakomatoses. In: Rimoin DL, Connor JM, Pyeritz RE, eds. *Principles and Practice of Medical Genetics*. New York: Churchill Livingstone, 1997: 2269–302.
39 Roach ES, Gomez MR, Northrup H. Tuberous sclerosis complex consensus conference: revised clinical diagnostic criteria. *J Child Neurol* 1998; **13**: 624–8.
40 Gomez MR, Sampson JR, Whittemore EH. *Tuberous Sclerosis Complex*, 3rd edn. Oxford: Oxford University Press, 1999.
41 Fois A, Pindinelli CA, Berardi R. Early signs of tuberous sclerosis in infancy and childhood. *Helv Paediatr Acta* 1973; **28**: 313–21.
42 Gold AP, Freeman JM. Depigmented nevi: the earliest sign of tuberous sclerosis. *Pediatrics* 1965; **35**: 1003–5.
43 Hurwitz S, Braverman IM. White spots in tuberous sclerosis. *J Pediatr* 1970; **77**: 587–94.
44 Alper JC, Holmes LB. The incidence and significance of birthmarks in a cohort of 4141 newborns. *Pediatr Dermatol* 1983; **1**: 58–68.
45 Fryer AE, Osborne JP, Schutt W. Forehead plaque: a presenting skin sign in tuberous sclerosis. *Arch Dis Child* 1987; **62**: 292–3.
46 Nickel WR, Reed WB. Tuberous sclerosis. Special reference to the microscopic alterations in the cutaneous hamartomas. *Arch Dermatol* 1962; **85**: 209–26.
47 Papanayotou P, Verzirtzi E. Tuberous sclerosis with gingival lesions. Report of a case. *Oral Med Oral Surg Oral Pathol* 1975; **39**: 578–82.
48 Weits-Binnerts JJ, Hoff M, Van Grunsven MF. Dental pits in deciduous teeth, an early sign of tuberous sclerosis. *Lancet* 1982; **ii**: 1344–5.
49 Staley BA, Montenegro MA, Major P *et al.* Self-injurious behavior and tuberous sclerosis complex: frequency and possible associations in a population of 257 patients. *Epilepsy Behav* 2008; **13**: 650–3.
50 Herkert EE, Wald A, Romero O. Tuberous sclerosis and schizophrenia. *Dis Nerv Syst* 1972; **33**: 439–45.
51 Curatolo P, Verdecchia M, Bombardieri R. Tuberous sclerosis complex: a review of neurological aspects. *Eur J Paediatr Neurol* 2002; **6**: 15–23.
52 Grover WD, Harley RD. Early recognition of tuberous sclerosis by fundoscopic examination. *J Pediatr* 1969; **75**: 991–5.
53 Rowley SA, O'Callaghan FJ, Osborne JP. Ophthalmic manifestations of tuberous sclerosis: a population based study. *Br J Ophthalmol* 2001; **85**: 420–3.
54 Gutman I, Dunn D, Behrens M *et al.* Hypopigmented iris spot. An early sign of tuberous sclerosis. *Ophthalmology* 1982; **89**: 1155–9.
55 Bass JL, Breningstal G, Swaiman KF. Echocardiographic incidence of cardiac rhabdomyoma in tuberous sclerosis. *Am J Cardiol* 1985; **55**: 1379–82.
56 Gibbs JL. The heart and tuberous sclerosis: an echocardiographic and electrocardiographic study. *Br Heart J* 1985; **54**: 596–9.
57 Smith HC, Watson GH, Patel RG *et al.* Cardiac rhabdomyomata in tuberous sclerosis: their course and diagnostic value. *Arch Dis Child* 1989; **64**: 196–200.
58 Chitayat D, McGillivray BC, Diamant S *et al.* Role of prenatal detection of cardiac tumours in the diagnosis of tuberous sclerosis: report of two cases. *Prenat Diagn* 1988; **8**: 577–84.
59 Journel H, Roussey M, Plais MH *et al.* Prenatal diagnosis of familial tuberous sclerosis following detection of cardiac rhabdomyoma by ultrasound. *Prenat Diagn* 1986; **6**: 283–9.
60 Blute ML, Malek RS, Segura JW. Angiomyolipoma: clinical metamorphosis and concepts for management. *J Urol* 1988; **139**: 20–3.
61 Moss JG, Hendry GMA. The natural history of renal cysts in an infant with tuberous sclerosis: evaluation with ultrasound. *Br J Radiol* 1988; **61**: 1074–6.
62 O'Callaghan A, Edwards JA, Tobin M *et al.* Tuberous sclerosis with striking renal involvement in a family. *Arch Intern Med* 1975; **135**: 1082–7.
63 Wandschneider G, Haas P, Vilits P *et al.* The Bourneville–Pringle syndrome from an urological and radiological viewpoint. *Urol Int* 1973; **28**: 393–404.
64 Jao J, Gilbert S, Messer R. Lymphangiomyoma and tuberous sclerosis. *Cancer* 1972; **29**: 1188–92.
65 Devroede G, Lemieux B, Masse S *et al.* Colonic hamartomas in tuberous sclerosis. *Gastroenterology* 1988; **94**: 182–8.
66 Holtzmann M, Reider-Groswasser I, Harel S. An unusual association of tuberous sclerosis and adrenogenital syndrome. *Brain Dev* 1983; **5**: 46–8.
67 Ortonne JP, Jeune R, Fulton R *et al.* Primary localised gigantism and tuberous sclerosis. *Arch Dermatol* 1982; **118**: 877–8.
68 Sahoo B, Handa S, Kumar B. Tuberous sclerosis with macrodactyly. *Pediatr Dermatol* 2000; **17**: 463–5.
69 Caputo R, Ermacora E, Gelmetti C. Diffuse cutaneous reticulohistiocytosis in a child with tuberous sclerosis. *Arch Dermatol* 1988; **124**: 567–70.
70 Silvestre JF, Banuls J, Ramon R *et al.* Unilateral multiple facial angiofibromas: a mosaic form of tuberous sclerosis. *J Am Acad Dermatol* 2000; **43**: 127–9.
71 Evans JC, Curtis J. The radiological appearances of tuberous sclerosis. *Br J Radiol* 2000; **73**: 91–8.
72 Altman NR, Purser RK, Post MJD. Tuberous sclerosis: characteristics at CT and MR imaging. *Radiology* 1988; **167**: 527–32.
73 Hasegawa J, Ihrke RE. Tuberous sclerosis complex. Unusual case of adenoma sebaceum, tuberous sclerosis and extensive bone lesions. *JAMA* 1960; **173**: 150–3.
74 Narla LD, Slovis TL, Watts FB *et al.* The renal lesions of tuberosclerosis (cysts and angiomyolipoma): screening with sonography and computerized tomography. *Pediatr Radiol* 1988; **18**: 205–9.
75 Viamonte M, Ravel R, Politano V *et al.* Angiographic findings in a patient with tuberous sclerosis. *Am J Roentgenol* 1966; **98**: 723–33.
76 Papadavid E, Markey A, Bellaney G *et al.* Carbon dioxide and pulsed dye laser treatment of angiofibromas in 29 patients with tuberous sclerosis. *Br J Dermatol* 2002; **147**: 337–42.
77 Perot P, Weir B, Rasmussen T. Tuberous sclerosis: surgical therapy for seizures. *Arch Neurol* 1966; **15**: 498–506.

Gardner's syndrome (MIM 175100)

Aetiology. The syndrome comprises multiple epidermoid cysts, fibrous tissue tumours, osteomas and polyposis of the colon; its inheritance is determined by an autosomal dominant gene of variable expressivity [1–4]. The Gardner's syndrome gene is located on chromosome 5q, near bands 5q21–q22 [5,6]. It is now thought that Gardner's syndrome and familial polyposis coli are allelic disorders, caused by mutation in the *APC* (adenomatous polyposis coli) gene.

Congenital hypertrophy of the retinal pigment epithelium is a frequent finding in Gardner's syndrome and is a valuable clue to the presence of the gene in persons who have not yet developed other manifestations [7,8].

Turcot's syndrome, in which polyposis of the colon is associated with malignant tumours of the central nervous system [9], was present in the uncle of a patient with gastric polyposis and multiple epidermoid cysts [10]. It has been suggested that Turcot's syndrome represents a variant of Gardner's syndrome.

Pathology. The pathology and natural history of the polyposis are essentially similar to familial polyposis coli. The syndrome in which polyposis of the colon is associated with perifollicular fibrosis is probably distinct [11]. Several groups have reported the association of hepatoblastoma with polyposis coli [12,13].

Histology and immunohistochemistry of cutaneous cysts suggest that these are derived from follicular stem cells [14].

Clinical features [3,11,15–17]. Polyposis of the colon or rectum usually arises during the second decade, but may occur in early childhood. It is present in about 50% of cases by the age of 20 years. There are few symptoms and intussusception is not a feature. Malignant change develops some 15–20 years later in over 40% of reported cases.

The variable expressivity of the gene must be remembered when a family is investigated [18]. Cutaneous and skeletal changes may be present without polyposis, and polyposis may be present when one or more of the other features of the syndrome is lacking [19].

Epidermoid cysts, which may be numerous, are usually irregularly distributed on the face, scalp and extremities, and are less frequent on the trunk. They may first appear between the ages of 4 and 10 years, but often considerably later, and are ultimately present in almost all cases.

Osteomas develop mainly in the maxilla, mandible and sphenoid bones, but also in other bones of the skull and, less frequently, in the long bones. They are usually small, multiple and present in some 50% of cases. The age of onset is often not accurately known, but they may be present at puberty.

Fibromas or desmoid tumours are less frequently present. They are usually poorly localized tumours in incisional scars of the abdomen, but may occur at other sites. Fibrosarcomas have also been associated with the syndrome. Fibromatous growths of the mesentery may be discovered at operation, and severe peritoneal scarring may follow surgery. A very large desmoid tumour extensively involving the chest wall and the left anterior abdominal wall has been described in a patient with a family history of Gardner's syndrome. The desmoid arose at the site of a thoracotomy scar following the removal of a large aneurysm of the left atrial appendage 5 years before [20].

Lipomas in the subcutaneous tissues, and in other organs, have frequently been noted.

Leiomyomas of the stomach or ileum, or retroperitoneal tissue, are sometimes present.

Diagnosis. Because multiple epidermoid or sebaceous cysts may be inherited as an isolated abnormality and may thus have no sinister significance, their discovery is an indication for a detailed family history and a careful examination for osteomas, including radiological examination of the skull, and for other dermal tumours. The cutaneous lesions are an important indicator of possible asymptomatic polyposis.

References

1 Gardner EJ. Follow-up study of a family group exhibiting dominant inheritance for a syndrome including intestinal polyps, osteomas, fibromas and epidermal cysts. *Am J Hum Genet* 1962; **14**: 376–90.

2 Gardner EJ. Discovery of the Gardner syndrome. *Birth Defects* 1972; **2**: 48–51.

3 Gardner EJ, Richards RC. Multiple cutaneous and subcutaneous lesions occurring simultaneously with hereditary polyposis and osteomatosis. *Am J Hum Genet* 1953; **5**: 139–47.

4 Gorlin RJ, Chaudhry AP. Multiple osteomatosis, fibromas, lipomas and fibrosarcomas of the skin and mesentery, epidermoid inclusion cysts of the skin, leiomyomas and multiple intestinal polyposis. A heritable disorder of connective tissue. *N Engl J Med* 1960; **263**: 1151–8.

5 Bodmer WF, Bailey CJ, Bodmer J *et al.* Localisation of the gene for familial adenomatous polyposis on chromosome 5. *Nature* 1987; **328**: 614–6.

6 Leppert M, Dobbs M, Scambler P *et al.* The gene for familial polyposis coli maps to the long arm of chromosome 5. *Science* 1987; **238**: 1411–3.

7 Blair NP, Trempe CL. Hypertrophy of the retinal pigment epithelium associated with Gardner's syndrome. *Am J Ophthalmol* 1980; **90**: 661–7.

8 Traboulsi EI, Krush AJ, Gardner EJ *et al.* Prevalence and importance of pigmented ocular fundus lesions in Gardner's syndrome. *N Engl J Med* 1987; **316**: 661–7.

9 Turcot J, Despres JP, St Pierre F. Malignant tumors of the central nervous system associated with familial polyposis of the colon: report of two cases. *Dis Colon Rectum* 1959; **2**: 465–8.

10 Yaffee HS. Gastric polyposis and soft tissue tumors. A variant of Gardner's syndrome. *Arch Dermatol* 1964; **89**: 806–8.

11 Hornstein OP, Knickenberg M. Perifollicular fibromatosis cutis with polyps of the colon: a cutaneo-intestinal syndrome sui generis. *Arch Dermatol Res* 1975; **253**: 161–75.

12 Kingston JE, Draper GJ, Mann JR. Hepatoblastoma and polyposis coli. *Lancet* 1982; **i**: 475.

13 Li FP, Thurber WA, Seddon J *et al.* Hepatoblastoma in families with polyposis coli. *JAMA* 1987; **257**: 2475–7.

14 Narisawa Y, Kohda H. Cutaneous cysts of Gardner's syndrome are similar to follicular stem cells. *J Cutan Pathol* 1995; **22**: 115–21.

15 Danes BS. The Gardner syndrome. *Cancer* 1975; **36**: 2327–33.

16 McKusick VA. Genetic factors in intestinal polyposis. *JAMA* 1962; **182**: 271–7.

17 Weary PE, Linthicum A, Cawley EP *et al.* Gardner's syndrome: a family group study and review. *Arch Dermatol* 1964; **90**: 20–30.

18 Danes BS. The Gardner's syndrome: increased tetraploidy in cultured skin fibroblasts. *J Med Genet* 1976; **13**: 52–6.

19 Thomas KE, Watne AL, Johnson JG *et al.* Natural history of Gardner's syndrome. *Am J Surg* 1968; **115**: 218–26.

20 Mole MT, Goldstraw P, Sheppard MN. Desmoid tumour in thoracotomy scar 5 years after excision of a left giant atrial appendage aneurysm in female with a family history of Gardner's syndrome. *Thorac Cardiovasc Surg* 1992; **40**: 300–2.

Cowden's disease (MIM 158350)

Synonyms

- Cowden's syndrome
- Multiple hamartoma syndrome

Definition. In this rare disorder, multiple hamartomatous lesions of ectodermal, endodermal and mesodermal origins are associated with a predisposition to malignant tumours, particularly of the breast. Cowden was the name of the family in whom the disease was first described [1].

The condition is characterized by mucosal and cutaneous papillomatosis and fibromatosis, with fibrocystic breast disease in the female and thyroid goitre or adenoma.

Aetiology. Inheritance of the disease is determined by an autosomal dominant gene of variable expressivity. Germ-line mutations of the *PTEN1* gene, located on chromosome 10, have been identified in a proportion of kindreds. However, Cowden's disease, like so many other inherited disorders, shows locus heterogeneity,

with some families developing the disease due to heterozygous mutation of the transforming growth factor (TGF)-β type 1 receptor, known as bone morphogenetic receptor type 1 (*BMPR1A*). Both genes encode proteins required in regulation of cell proliferation, and loss of the wild-type allele has been detected in tumour tissue, in accord with the Knudson 'two-hit' hypothesis [2]. About 100 cases have been reported [3].

Pathology [4,5]. The skin lesions around the mouth, eyes and chin are trichilemmomas [6]. The breast lesions are fibroadenomas, which are liable to undergo malignant degeneration. A unique fibroma on the face and other sites has been described [5,7], composed of broad acellular collagen bundles in a lamellar or whorl-like pattern with occasional giant cells. This has been referred to by Barax *et al.* [3] as 'Cowden's fibroma'. An immunohistochemical study of the sclerotic fibroma has shown strong staining with an antibody directed at human type I procollagen [8]. There is a report of amyloid in association with multiple hamartoma syndrome [3].

Clinical features [9–14]. Mucocutaneous lesions have been present in all reported cases of this disease, but they have varied in their distribution, extent and age of onset. Skin-coloured, lichenoid papules up to 4 mm in diameter, tending to coalesce to give a cobblestone appearance, are distributed on and around the eyes and mouth. On the dorsa of hands and wrists are lesions like those of acrokeratosis verruciformis. On palms and soles and on palmar and plantar aspects of fingers and toes are small translucent keratoses. Multiple angiomas and lipomas have been found in several cases. Malignant melanoma has occurred [15].

Verrucous and papillomatous lesions are seen in some patients on the labial and buccal mucosa, fauces and oropharynx, and may extend to the larynx.

In a series of 21 patients [14], craniomegaly was noted to be the most frequent extracutaneous finding, affecting 70% of patients.

Of the many other abnormalities that have been reported in this syndrome, the most frequent involve the thyroid and breasts. Approximately 30% of reported female cases developed breast cancer [14]. Fibrocystic disease of the breast sometimes leads to massive hyperplasia. Goitre or thyroid adenoma is present in many cases and thyroid carcinoma has been reported [7,9]. Adenocarcinoma of the uterus has been reported in 6% of women with multiple hamartoma syndrome [14]. Less frequent associations include adenoid facies, high-arched palate, vitiligo, café-au-lait spots, skeletal abnormalities, retinal glioma, pseudotumour cerebri, gastrointestinal polyposis and various gynaecological disorders (menstrual irregularity, uterine fibroids). An association with renal cell adenocarcinoma and primary neuroendocrine carcinoma of the skin (Merkel cell carcinoma) in one patient has been documented [16].

Ruschak *et al.* [17] described a patient with this syndrome who had a deficiency of T-lymphocyte function, with recurrent cellulitis and abscess formation, and the eventual development of acute myeloid leukaemia.

Differential diagnosis. The combination of clinical and histological findings is pathognomonic. It seems possible that the skin lesions have in the past been confused with Darier's disease, and some cases may have been reported as TSC with mucosal involvement [7]. The relationship between Cowden's syndrome and gingival fibromatosis with hypertrichosis [18] is uncertain, but they are probably separate conditions.

Treatment. Cosmetic surgery may be helpful. The possibility of carcinoma of breast or thyroid must be borne in mind. Female patients with this syndrome should avoid oestrogen therapy and should have frequent breast investigations, including mammography, or even prophylactic mastectomy [19].

References

1 Lloyd KM, Dennis M. Cowden's disease: a possible new symptom complex with multiple system involvement. *Ann Intern Med* 1963; **58**: 136–42.
2 Liaw D, Marsh DJ, Li J *et al.* Germline mutations of the PTEN gene in Cowden disease, an inherited breast and thyroid cancer syndrome. *Nat Genet* 1997; **16**: 64–7.
3 Barax CN, Lebwohl M, Phelps RG. Multiple hamartoma syndrome. *J Am Acad Dermatol* 1987; **17**: 342–6.
4 Brownstein MH, Mehregan AM, Bikowski B *et al.* The dermatopathology of Cowden's syndrome. *Br J Dermatol* 1979; **100**: 667–73.
5 Starink TM, Meijer CJLM, Brownstein MH. The cutaneous pathology of Cowden's disease: new findings. *J Cutan Pathol* 1985; **12**: 83–93.
6 Salem OS, Steck WD. Cowden's disease (multiple hamartoma and neoplasia syndrome). *J Am Acad Dermatol* 1983; **8**: 686–96.
7 Weary PE, Gorlin RJ, Gentry WC *et al.* Multiple hamartoma syndrome (Cowden's disease). *Arch Dermatol* 1972; **106**: 682–90.
8 Shitabata PK, Crouch EC, Fitzgibbon JF *et al.* Cutaneous sclerotic fibroma. Immunohistochemical evidence of a fibroblastic neoplasm with ongoing type I collagen synthesis. *Am J Dermatopathol* 1995; **17**: 339–43.
9 Burnett JW, Goldner R, Calton GJ. Cowden disease. Report of two additional cases. *Br J Dermatol* 1975; **93**: 329–36.
10 Gentry WC, Eskitt NR, Gorlin RJ. Multiple hamartoma syndrome (Cowden disease). *Arch Dermatol* 1974; **109**: 521–5.
11 Nuss DD, Aeling JL, Clemons DE *et al.* Multiple hamartoma syndrome (Cowden's disease). *Arch Dermatol* 1978; **114**: 743–6.
12 Ocana Sierra J. Cowden's syndrome. *Acta Dermosifiliogr* 1974; **65**: 117–28.
13 Starink TM. Cowden's disease: analysis of fourteen new cases. *J Am Acad Dermatol* 1984; **11**: 1127–41.
14 Starink TM, Van der Veen JPW, Arwert F *et al.* The Cowden syndrome: a clinical and genetic study in 21 patients. *Clin Genet* 1986; **29**: 222–33.
15 Siegel JM. Cowden's disease: report of a case with malignant melanoma. *Cutis* 1975; **16**: 255–8.
16 Haibach H, Burns TW, Carlson HE *et al.* Multiple hamartoma syndrome (Cowden's disease) associated with renal cell carcinoma and primary neuroendocrine carcinoma of the skin (Merkel cell carcinoma). *Am J Clin Pathol* 1992; **97**: 705–12.
17 Ruschak PJ, Kauh YC, Luscombe HA. Cowden's disease associated with immunodeficiency. *Arch Dermatol* 1981; **117**: 573–5.
18 Jorgenson RJ, Cocker ME. Variation in the inheritance and expression of gingival fibromatosis. *J Periodontol* 1974; **45**: 472–7.
19 Walton BJ, Morain WD, Baughman RD *et al.* Cowden's disease: a further indication for prophylactic mastectomy. *Surgery* 1986; **99**: 82–6.

Ectodermal dysplasias

The ectodermal dysplasias are a complex and highly diverse group of heritable disorders. By some authors' estimations the broader definition of ectodermal dysplasias encompasses some 170 to 200 individual conditions. Any approach to summarizing current knowledge about this group of conditions presents several challenges. Firstly and most importantly, how is an ectodermal

dysplasia defined, and which distinct conditions are encompassed by this broad term? The history of the terminology throughout the literature is instructive. The first clinical cases with features of what would now be classified as ectodermal dysplasia were reported as early as 1792, when Danz described two Jewish boys with congenital absence of hair and teeth [1]. In 1875 Charles Darwin reported the case '. . . communicated to me by a Mr. Wedderburn, of a Hindoo family in Scinde in which ten men, in the course of four generations, were furnished, in both jaws taken together, with only four small and weak incisor teeth and with eight posterior molars. The men thus affected have very little hair on the body, and become bald early in life. They also suffer much during hot weather from excessive dryness of the skin.' [2]. This family would now be recognized as having X-linked hypohidrotic ectodermal dysplasia but the term 'ectodermal dysplasia' did not appear until 1929 [3]. Prior to this report a small series of cases with hypotrichosis, hypodontia, onychodysplasia and anhidrosis had been described under various names such as 'dystrophy of hair and nails', 'imperfect development of skin, hair and teeth', and 'congenital ectodermal defect'. The designation outlined by Weech specified three essential aspects of ectodermal dysplasias: (i) most of the disturbances must affect tissues of ectodermal origin; (ii) these disturbances must be developmental; and (iii) heredity plays a causal role. Weech had in mind the X-linked anhidrotic form (Christ–Siemens–Touraine syndrome (CST) or hypohidrotic ectodermal dysplasia (HED) MIM: 305100) in males but noted that it had also been reported in females; he also noted that this pattern of involvement was occasionally inherited as a non-sex-linked trait. For some authors and clinicians, the term ectodermal dysplasia is still used specifically with reference to CST syndrome and the autosomal dominant and recessive forms of HED. As more clinical reports of patients with similar but subtly distinct patterns of anomalies were recorded, the term 'ectodermal dysplasia' became extended to include many different genetic entities. In an attempt to encapsulate this heterogeneity and diversity of symptoms seen, Touraine [4] suggested the expression 'ectodermal polydysplasia'. Attempts at more formal classification soon followed; initially conditions were classified as hidrotic or anhidrotic, but this simple classification failed to reflect the complexity of nail, hair and dental anomalies associated with the various forms of ED.

Currently, the most widely accepted and used definition of the ectodermal dysplasias is of a group of inherited disorders that share in common developmental abnormalities of two or more of the following: hair, teeth, nails, sweat glands and other ectodermal structures. Other structures derived from embryonic ectoderm include the mammary gland, thyroid gland, thymus, anterior pituitary, adrenal medulla, central nervous system, external ear, melanocytes, cornea, conjunctiva, lacrimal gland and lacrimal duct. There are merits and demerits of this approach to definition. One definite benefit is that the problems encountered by many patients and families are similar regardless of the specific subtype of ED; parents and children can benefit by being part of larger support networks exemplified by the Ectodermal Dysplasia Society (UK-based; URL: http://www.ectodermaldysplasia.org) and the National Foundation for Ectodermal Dysplasias (US-based; URL: http://www.nfed.org). This wide-ranging classification is also helpful in concentrating the minds of research workers in the field and several EDs are now known to have shared genetic mechanisms. Although the broader definition has the benefit of reach and inclusivity, many conditions encompassed by this broad definition are not usually considered as primarily ectodermal dysplasias. For example, inherited conditions as diverse as incontinentia pigmenti, dyskeratosis congenita, trichothiodystrophies, cardiofaciocutaneous syndrome, pachyonychia congenita and Goltz syndrome by this definition are ectodermal dysplasias, but common practice has been to consider many of these as separate entities. In excess of 190 different conditions come under the umbrella term of 'ectodermal dysplasia', if the widest definition of 'an inherited disorder involving two or more of the following ectodermal appendages: teeth, hair, eccrine sweat glands' is used. For a recent detailed summary of most of these conditions see Table 15.3.

Classification: clinical approaches

Having accepted the broadest definition of an ectodermal dysplasia, the second challenge presented by this group of conditions is that of designing a meaningful and functional classification system. Until the end of the 20th century, classification systems for ectodermal dysplasias were, due to lack of molecular understanding, based on clinical manifestations. Several authors addressed the issue of delineating nosological groups of conditions linked by shared phenotypic traits. The most comprehensive accounts of clinical phenotypes and inheritance patterns of ectodermal dysplasia were produced by Freire-Maia and Pinheiro in their classic monograph [5] and in subsequent writings [25]. Their classification designated conditions by groups depending on presence of hair, nail, tooth or sweat gland abnormalities, and assigned conditions to groups using a '1-2-3-4 system' to collate conditions that had involvement of hair (1), teeth (2), nails (3) or sweat glands (4). This classification was a comprehensive attempt to bring order to an unwieldy group of conditions but was difficult to use and grouped together disparate clinical entities such as Goltz syndrome and pachyonychia congenita. In common with any other classification of ectodermal dysplasias based on clinical findings, this system is confounded by the subtleties of inheritance such as incomplete penetrance and variable expressivity of phenotype. This is especially true in the ectodermal dysplasias, in which sweating is often not formally measured and tooth or nail anomalies may be subtle. For a comprehensive contemporaneous consideration of the breadth of ED conditions in the tradition of Freire-Maia and Pinheiro please see [26]. Clinical classifications now need to become more focused, user-friendly, and better integrated with emerging molecular data. Difficult decisions will need to be made to balance inclusiveness (of every possible ectodermal dysplasia) with accessibility and practicality of usage.

Classification: molecular approaches

The last decade has seen several important insights into the molecular basis of a number of the ectodermal dysplasias. In some cases the molecular data have confirmed clinical impressions, for example Hay–Wells syndrome and ectrodactyly, ectodermal dysplasia, clefting (EEC) syndrome have ectodermal dysplasia and clefting of the palate and lip as common clinical findings and these

Table 15.3 The ectodermal dysplasias. (Modified from Harper J, Oranje A, Prose N, eds. *Textbook of Pediatric Dermatology*, 2nd edn. Blackwell Publishing, with permission.)

Name (alternative names)	MIM number/ primary ref.	Inh	Phenotypic characteristics				
			Nails	Hair	Teeth	Sweat glands	Other
Absence of dermal ridge patterns, onychodystrophy, and palmoplantar anhidrosis (Basan syndrome)	129200	AD	Fingernails attached distally to the hyponychium; rough in texture; horiz & vert grooved	Normal	Normal	Palmoplantar anhidrosis	**Skin:** at birth, multiple milia (on chin); several vesicular/bullous lesions (on fingers & soles); leather-like texture & callosities in adults; simian creases in some patients
Ackerman syndrome (dento-oculocutaneous syndrome)	200970	AR?	Horiz ridging of the fingernails with dist onychoschizia	Scanty body hair; vellus hairs in the moustache & beard areas	Taurodontia, pyramidal or fused molar roots	Normal	**Skin:** indurated & hyperpigmented over the interphalangeal joints of the fingers **Face:** upper lip characterized by abs of 'Cupid's bow'; thickening & widening of the philtrum; ectropion of both lower lids **Other:** complete sensorineural hearing loss; juvenile glaucoma; syndactyly (third & fourth fingers); clinodactyly of the fifth finger
Acro-dermato-ungual-lacrimal-tooth syndrome (ADULT syndrome)	103285	AD	Finger- & toenail dysplasia	Frontal alopecia	Hypodontia; loss of permanent teeth	Normal	**Skin:** intensive freckling **Other:** lacrimal duct atresia; ectrodactyly, syndactyly; hypoplastic breasts & nipples
Acrorenal field defect, ectodermal dysplasia, lipoatrophic diabetes (AREDYLD syndrome)	207780	AR	Normal	Scalp hypotrichosis, scant axillary & pubic hair; normal eyebrows & lashes	2 natal & 4 deciduous teeth with enamel dysplasia; abs of permanent teeth buds; anodontia by 11 years	Normal	**Skin:** hypoplastic & hypopigmented areolae; abs of DIP extension & flexion creases **Face:** prom forehead & bridge of nose; sl mongoloid slant of palpebral fissures; short nasal septum with flat tip of nose; short upper lip; relatively flat philtrum; prom chin with mandibular prognathism; posteriorly angulated auricles with broad intertragal incisure; hypoplastic tragus & small groove at antitragus **Other:** short stature; difficulty in grasping with left hand; limb abnormalities; lipoatrophic diabetes; hypoplasia of mammary gland; lumbar scoliosis; hyperostosis of cranial vault; cranial dysostosis; prom subcutaneous leg veins; hypoplasia of the middle right major renal calyx & hypotonia of the right ureter
Agammaglobulinaemia–dwarfism–ectodermal dysplasia (Swiss type ectodermal dysplasia); ? same as cartilage–hair hypoplasia (see below)	200900	AR?	Normal	Slow growing, in one family failed to grow after initial pelage	No data	No data	**Skin:** erythroderma; mild hyperkeratosis; generalized scaliness; ichthyosiform lesions; redundant, esp on the limbs, suggesting cutis laxa; biopsy showed keratosis, fissuring of keratotic layer, & thickening of granular layer **Other:** dyschondroplastic (short-limbed) dwarfism; lymphopenia; gammaglobulinaemia; prom eosinophilia; hypoplastic thymus; microscopic alterations of thymus, spleen, lymph nodes, gastrointestinal tract, bones

(Continued)

Table 15.3 *Continued*

Name (alternative names)	MIM number/ primary ref.	Inh	Phenotypic characteristics				
			Nails	Hair	Teeth	Sweat glands	Other
Alopecia–anosmia–deafness–hypogonadism (Johnson neuroectodermal syndrome)	147770	AD	Normal	Abs or sp scalp hair, eyebrows & lashes, axillary & pubic hair	Carious, leading to extensive premature loss	Hypohidrosis	**Skin:** multiple café-au-lait spots **Other:** conductive hearing loss; hypogonadism; occas cong heart defects; cleft palate; choanal stenosis; anosmia or hyposmia; mental retardation; speech impairment; hypodontia; unilateral facial palsy; retro/micrognathia
Alopecia–onychodysplasia–hypohidrosis	F-M & P [5]	NK	Severely dyst (thick & yellow)	Abs scalp & body hair; no eyebrows or lashes; virtually no body hair	Normal	Hypohidrosis with hyperthermia	**Skin:** thick, scaly skin in patches over most of the body (the scalp, soles & legs are more severely affected); eczema; scaly lesions with crusting & some open sores most pronounced around orifices **Other:** photophobia; horiz nystagmus, legal blindness; short stature; low IQ, seizures; hypospadias; non-palpable testes
Alopecia–onychodysplasia–hypohidrosis–deafness	F-M & P [5]	NK	Normal fingernails; thick, sl deformed toenails, with subungual hyperkeratosis; cong anonychia	Extensive scalp hypotrichosis; abs of eyebrows	Normal	Hypohidrosis	**Skin:** hyperpigmented, dry & sl rough, with hyperkeratosis of palms, soles, knees & elbows; dermatoglyphics with extensive ridge dissociation **Face:** unusual, with prom nose; sl anteverted auricles with broad upper antihelical region; mongoloid palpebral slanting & narrow palpebral fissures **Other:** sensorineural deafness; bilateral ectropia; photophobia; short stature; pectus excavatum; retarded bone age
Alopecia universalis–onychodystrophy–total vitiligo	Lerner [6]	AR?	Dyst fingernails & toenails with transverse ridging	Prog loss of body & scalp hair, eyebrows, & lashes	Normal	Hyperhidrosis	**Skin:** total vitiligo; skin becomes light & translucent & prone to sunburn
Amelo-cerebrohypohidrotic syndrome	226750	AR?	Normal	Normal	Yellow due to enamel hypoplasia	Hypohidrosis	**Skin:** Scarce sebaceous glands & nerve fibres **Other:** Myopia, prog CNS degeneration with severe epileptiform seizures appearing between 11 months & 4 years of age; muscle spasticity; abn EEG
Amelo-onychohypohidrotic dysplasia	104570	AD	Onycholysis with subungual hyperkeratosis	Normal	Hypocalcified-hypoplastic enamel	Hypohidrosis	**Skin:** gen xerotic with keratosis pilaris over the buttocks & extensor surfaces of the limbs; seborrhoeic dermatitis of scalp
Ankyloblepharon-ectodermal defects—cleft lip and palate (AEC) syndrome	106260	AD	Severe dystrophy	Hypotrichosis; abs or scanty eyebrows & lashes	Poorly formed & pointed; widely spaced; carious; severe hypodontia	Hypohidrosis; no hyperthermia	**Skin:** dry & smooth; palmoplantar hyperkeratosis with obliteration of dermatoglyphic patterns; occas reticulate hyperpigmentation; supernumerary nipples, severe recurrent scalp pustulation **Face:** ankyloblepharon filiforme adnatum with partial fusion of eyelids at birth; broad nasal bridge; hypoplastic maxilla; auricular abnormalities; cleft lip **Other:** lacrimal duct atresia; photophobia

Anonychia–onychodystrophy with brachydactyly type b and ectrodactyly	106990	AD	Anonychia; onychodystrophy	Normal	Normal	Normal	**Limbs:** ectrodactyly; absent/hypoplastic metacarpals; absent/hypoplastic distal phalanges; hypoplastic metatarsals
Anonychia with bizarre flexural pigmentation	106750	AD	Gen abs on the fingers & toes; in a few instances rudimentary	Slow growing & coarse scalp hair, thinning early in adult life	Highly carious	Mild hypohidrosis without hyperthermia	**Skin:** hypo- & hyperpigmentation, particularly in the groins, axillae, & breasts; distortion of epidermal ridges on palms & soles; mild palmoplantar hyperkeratosis; increased palmar markings; distorted fingertip patterns; small macular telangiectases in a few regions
Arthrogryposis and ectodermal dysplasia (trichooculodermovertebral syndrome)	601701	NK	Abs at birth; later normal length; tendency toward longitudinal breaks	Hypotrichosis of scalp (atrichia at birth) & body; scanty eyebrows & lashes	Enamel hypoplasia	Hypohidrosis	**Skin:** dry; tendency to excessive bruising & scarring after injuries & scratching **Other:** bilateral epicanthic folds; sl mongoloid slant; short stature; probable low–normal intelligence level; arthrogryposis of all joints; bilateral clinodactyly; sl bilateral syndactyly of second & third toes; diabetes mellitus
Autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED) syndrome; autoimmune polyendocrinopathy syndrome, type I	240300	AD	Thickened & dystrophic	Occas alopecia areata	Normal	Normal	Oral candidiasis; autoimmune endocrinopathies (hypergonadotropic hypogonadism, insulin-dependent diabetes mellitus, autoimmune thyroid diseases & pituitary defects); autoimmune or immunomediated gastrointestinal diseases (chronic atrophic gastritis, pernicious anaemia & malabsorption); chronic active hepatitis; autoimmune skin diseases (vitiligo & alopecia); keratoconjunctivitis; immunological defects (cellular & humoral); asplenia & cholelithiasis
Baisch syndrome	Baisch [7]	NK	Almost total abs of the finger & toenails	Normal	Delayed eruption; abs of lateral incisors	Normal	**Limbs:** polydactyly with syndactyly in the hands (6/7 fingers); hypoplasia of the dist interphalangeal joints of fingers & toes; short & wide hands & feet; adduction of feet; delayed bone age
Blepharocheilodontic syndrome (clefting, ectropion, and conical teeth syndrome)	119580	AD	Normal	Normal	Conical teeth	Normal	Cleft lip & palate; hypertelorism; ectropia; euryblepharon
Book dysplasia	112300	AD	Normal	Normal	Hypodontia of the premolar region	Palmoplantar hyperhidrosis	**Eyes:** blue irides
Brachymetapody–anodontia-hypotrichosis–albinoidism (oculo-osteocutaneous syndrome; Tuomaala syndrome)	211370	AR	Normal	Poor hair growth	Cong anodontia	Normal	**Skin:** albinoidism **Other:** multiple ocular abnormalities including strabismus, nystagmus, distichiasis, lenticular opacities, high-grade myopia; mandibular prognathism; short stature; short metacarpals

(Continued)

Table 15.3 *Continued*

Name (alternative names)	MIM number/ primary ref.	Inh	Phenotypic characteristics				
			Nails	Hair	Teeth	Sweat glands	Other
Camarena syndrome	F-M & P [5]	AD? XD?	Dysplastic	Thin; hypopigmented & very sp; poor growth	Anodontia	Abs of sweat glands in the scalp; anhidrosis on face & scalp	**Skin:** thin & smooth; palmoplantar erythema; nevus vascularis on the right lid & above the nose; euhidrosis on the rest of the body; mild 'cara de vieja' (old woman's face) **Other:** hypertelorism; abn auricles; micrognathia; microstomia; bilateral clinodactyly of the fifth fingers; high arched palate
Cardiofaciocutaneous syndrome	115150	AD	Normal	Sparse, slow-growing curly hair; absence of eyebrows & eyelashes	Normal	Normal	**Skin:** severe atopic dermatitis, ichthyosis; multiple palmar & plantar creases, hyperkeratosis (especially extensor surfaces), keratosis pilaris **Face:** coarse facial features, similar to Noonan syndrome; relative macrocephaly; prominent forehead; bitemporal narrowing; shallow orbital ridges; prominent philtrum; posteriorly rotated ears; down-slanting palpebral fissures; hypertelorism; exophthalmos; short upturned nose; depressed nasal bridge; submucous cleft palate; high-arched palate **Other:** postnatal short stature; hearing loss; nystagmus; strabismus; atrial septal defects; pulmonary stenosis; splenomegaly; hyperextensible fingers; mild to moderate mental retardation; seizures; hypotonia or hypertonia; hydrocephalus; cortical atrophy; frontal lobe hypoplasia; brain stem atrophy
Carey syndrome	F-M & P [5]	NK	Dyst from early childhood	Thin, hypopigmented & very sp	Discoloration; microdontia; hypodontia	Decreased number of sweat pore openings	**Skin:** aplasia cutis congenita-like scalp defects **Other:** moderate conductive hearing loss; abs of tear ducts; displacement of the inner canthi; U-shaped mouth; flat nasal bridge; maxillary hypoplasia; incomplete 2–3 toe syndactyly; cleft palate
Cartilage–hair hypoplasia syndrome	250250	AR	Normal	Sp eyebrows, eyelashes, beard, lt coloured hair	Normal	Normal	Increased malign risk; short-limbed dwarfism, mild scoliosis, short hands, limited elbow extension; Hirschsprung's disease, oesophageal atresia

Cataract–alopecia–sclerodactyly syndrome	212360	AR	Normal	Total alopecia	Normal	Normal	**Skin:** sclerodactyly, hyperkeratosis **Other:** congenital bilateral cataracts; contractures digits; pseudoainhum; patients from Rodrigues in the Indian Ocean
Cataract, hypertrichosis, mental retardation syndrome (CAHMR syndrome)	211770	AR	Normal	Gen hypertrichosis	Normal	Normal	Mental retardation; cong lamellar cataracts
Cleft lip/palate–ectodermal dysplasia syndrome (CLEPD1; Roselli–Gulienetti syndrome; Zlotogora–Ogur syndrome) (allelic to Margarita Island ectodermal dysplasia, see below)	225000	AR	Subungual hyperkeratosis, sulci; transverse & longitudinal striae; irregularities of free margins; hallucal nails with abs of the lamina	Woolly, thin, coarse, opaque, & short	Hypodontia; transverse striation; irregularities of the free margins	? mild tendency to perspiration	**Skin:** tendency to desquamation with erythematous patches **Face:** cleft lip; hypoplasia of the auricular lobes; flat nasal pyramid **Other:** cleft palate; malformation of the genitourinary system; abs or fusion of the last lumbar vertebra; aplasia or hypoplasia of thumb
Coffin–Siris syndrome	135900	AR? AD?	Abs to hypoplastic fifth fingernails & toenails; other nails occas hypoplastic or abs	Sp scalp hair; bushy eyebrows & lashes; hirsutism of limbs, forehead & back	Delayed eruption; microdontia	Normal	**Skin:** dermatoglyphic changes; simian crease **Other:** coarse face with thick lips, wide mouth & nose, anteverted nostrils, & low nasal bridge; retardation of psychomotor & growth development; hypotonia; lax joints; clinodactyly of the fifth fingers; general abs of terminal phalanges of fifth fingers & toes; general aplasia or variable hypoplasia of middle & prox phalanges of other fingers & toes; bilateral or unilateral dislocation of the radial heads; small or abs patella; frequent respiratory infections; umbilical & inguinal hernias; cleft palate; feeding problems in infancy; six lumbar vertebrae; short sternum; microcephaly
Conductive deafness, with ptosis and skeletal anomalies	221320	AR	Normal	Delayed hair growth	Dysplastic teeth	Normal	**Other:** conductive hearing loss from combined atresia of the external auditory canal & the middle ear space, complicated by chronic infection; ptosis; thin, pinched-nose facial appearance **Skeletal:** internal rotation of hips; dislocation of the radial heads & fifth finger clinodactyly
Congenital hypotrichosis with juvenile macular dystrophy (HJMD)	601553	AR	Normal	Cong hypotrichosis; normal eyelashes/ eyebrows	Normal	Normal	Juvenile macular dystrophy

(Continued)

Table 15.3 *Continued*

Name (alternative names)	MIM number/ primary ref.	Inh	Phenotypic characteristics				
			Nails	Hair	Teeth	Sweat glands	Other
Congenital insensitivity to pain with anhidrosis (CIPA; familial dysautonomia, type II)	256800	AR	Normal	Hypotrichosis in areas of the scalp	Enamel aplasia	Hypohidrosis with hyperthermia	**Skin:** dry; scars from self-inflicted bites may be present on the fingers & arms; chronic sores are common on the hands, feet, & pressure points, such as the buttocks **Other:** irregular lacrimation; mental retardation; multiple fractures from trauma resulting in deformities; joint degeneration (Charcot joints); universal sensory loss; abs pain perception & physiological responses to painful stimuli; impaired temperature & touch perception; diminished tendon reflexes; occas encopresis & enuresis; ulceration of the mouth & scars from biting the tongue & lips
Cook's syndrome	106995	AD	Onychodystrophy; anonychia	Normal	Normal	Normal	Fifth finger brachydactyly; digitalization of thumbs; absent/hypoplastic distal phalanges of hands & feet
Corneodermatoosseous syndrome	122440	AD	Distal onycholysis	Normal	Soft teeth; early tooth decay	Normal	**Eyes:** corneal dystrophy; photophobia; burning/watering of eyes **Skin:** palmoplantar hyperkeratosis, erythematous scaly skin; generalized erythroderma **Other:** brachydactyly; short distal phalanges; short stature; medullary narrowing of hand bones
Cranio-ectodermal syndrome (Levin syndrome I; Sensenbrenner syndrome)	218330	AR	Broad & short	Thin, sp & slow-growing; abn structure	Microdontia; hypodontia; widely spaced; enamel hypoplasia; taurodontism	Normal	**Skin:** dimples over elbows & knees; bilateral hallucal creases; single flexion crease on each toe; bilateral single palmar creases **Skeletal:** rhizomelic shortness (greatest in upper limbs); disproportionate shortness of the fibulae; pronounced shortness of middle & dist phalanges of toes & fingers; cutaneous syndactyly; clinodactyly; increased space between first & second toes; hallux valgus; dolichocephaly; gen osteoporosis; highly arched palate; sagittal suture synostosis; short & narrow thorax; pectus excavatum **Other:** hyperopia; myopia; nystagmus; frontal bossing; epicanthal folds & antimongoloid slant; full cheeks; posteriorly angulated pinnae with hypoplastic antihelix; hypotelorism; broad nasal bridge; anteverted nares; everted lower lip; capillary naevus on the forehead; multiple oral frenula; cong heart defects

Curly hair–ankyloblepharon–nail dysplasia (CHANDS)	214350	AR	Hypoplastic finger & toe nails	Curly	Normal	Normal	**Eyes:** fused eyelids at birth (ankyloblepharon)
Deafness and onychodystrophy (DOOR syndrome)	220500	AR	Hypoplastic & dyst finger & toenails; anonychia	Normal	Hypoplastic & discoloured; irregular placement	Normal	**Skin:** dermatoglyphic abnormalities **Other:** sensorineural deafness; apparently low-set ears; seizures & mental retardation; triphalangy of both thumbs & halluces; hypoplasia or aplasia of terminal phalanges of fingers & toes; occas clinodactyly & camptodactyly
Deafness and onychodystrophy (Robinson syndrome)	124480	AD	Hypoplastic & dyst finger & toenails	Normal	Coniform; hypodontia, delayed primary & secondary dentition	Normal	**Other:** syndactyly of toes; severe sensorineural hearing loss (high frequency)
Dermo-odonto-dysplasia	125640	AD	Dysplastic; brittle	Dry; slow-growing (scalp, moustache & beard); circumscribed area of alopecia; normal eyebrows & lashes; sp axillary & pubic hair	Hypodontia; microdontia; persistence of deciduous teeth	Normal	**Skin:** dry & thin to variable degree (esp. on palmoplantar regions); simian crease **Face:** left palpebral ptosis; prognathic mandible
Dermotrichic syndrome ? related to IFAP syndrome (308205) (see below)	F-M & P [5]	XR	Dyst & hyperconvex fingernails	Gen atrichia from birth	Normal	Hypohidrosis without hyperthermia	**Skin:** gen ichthyosiform lesions; including palmoplantar area & scalp **Face:** prom forehead; large ears; small nose with mildly low nasal bridge; blepharophimosis **Other:** severe psychomotor retardation; abnormal EEG; frequent apyretic seizures; short stature; hemivertebrae at the dorsolumbar region; cong aganglionic megacolon; narrow arched palate; positive Benedict & glucoseoxydase tests; discrete increase of tyrosinaemia; discrete anaemia

(Continued)

Table 15.3 *Continued*

Name (alternative names)	MIM number/ primary ref.	Inh	Phenotypic characteristics				
			Nails	Hair	Teeth	Sweat glands	Other
Dubovitz syndrome	223370	AR	Normal	Sp scalp hair, sp lateral eyebrows	Delayed eruption; caries	Normal	**Skin:** eczema **Face:** elongation of face with age; shallow supraorbital ridge; facial asymmetry; micrognathia; high, sloping forehead; prom ears; short palpebral fissures; ptosis; blepharophimosis; microphthalmia; broad nasal tip; high-arched palate; submucous cleft palate; velopharyngeal insufficiency **Other:** growth retardation; short stature; microcephaly; mild mental retardation with behaviour problems; high-pitched voice; recurrent infections; hypogammaglobulinaemia; IgA deficiency; neoplasia including aplastic anaemia; acute lymphatic leukaemia, lymphoma & neuroblastoma
Dyskeratosis congenita (X-linked) (Zinsser–Cole–Engman syndrome)	305000	XR	Dystrophy with late onset paronychia occas leading to anonychia; hypoplasia	Hypotrichosis; loss of cilia due to blepharitis & ectropion; abs of eyebrows & lashes; premature canities	Poorly aligned; early carious degeneration	Gen hyperhidrosis elsewhere	**Skin:** hyper- & hypomelanosis, telangiectatic erythema; ulcers; dry desquamation; atrophy; hyperkeratotic plaques (palmoplantar & over joints); premalignant lesions; abs fingerprints **Eyes:** blepharitis; ectropion of the lower lids; obliteration of the punctalacrimalia; bullous conjunctivitis; continuous lacrimation **Other:** sharp facial features; occas mental & growth retardation; Fanconi-like pancytopenia; premalignant leukoplakia on lips, mouth, anus, urethra & conjunctiva; frail skeletal structure; genital anomalies; oesophageal dysfunction and/or diverticulum; atrophic lingual papillae; gingivitis
Dyskeratosis congenita (autosomal dominant/ Scoggins type)	127550	AD	Dystrophic	Hypotrichosis	Carious	No data	**Skin:** hyper- & hypomelanosis, telangiectatic erythema; ulcers; dry desquamation; atrophy; hyperkeratotic plaques (palmoplantar & over joints); premalignant lesions; abs fingerprints **Eyes:** Blepharitis; ectropion of the lower lids; obliteration of the puncta lacrimalia; bullous conjunctivitis; continuous lacrimation **Other:** sharp facial features; occas mental & growth retardation; Fanconi-like pancytopenia; premalignant leukoplakia on lips, mouth, anus, urethra & conjunctiva; frail skeletal structure; genital anomalies; oesophageal dysfunction and/or diverticulum; atrophic lingual papillae; gingivitis

Dyskeratosis congenita (autosomal recessive)	224230	AR	Dystrophic	Hypotrichosis	Carious	No data	**Skin:** hyper- & hypomelanosis, telangiectatic erythema; ulcers; dry desquamation **Other:** pancytopenia; thrombocytopenia; small platelets; T-cell abnormalities; dystrophic fingers & toes
Ectodermal defect with skeletal abnormalities	Wallace [8]	NK	Finger & toenails poorly developed & foreshortened	Scalp hair is sl coarse; very sp axillary hair	Hypodontia; hypoplastic teeth	Normal	**Skin:** thin, fine & dry; fine, light, granular pigmentation; translucent appearance; rudimentary nipples **Face:** striking appearance; central portion is relatively underdeveloped; the cheeks, upper jaw & nose are sunken with the 'inverted, dish-shaped deformity' & somewhat prom eyes **Other:** low intelligence; short metacarpals; some absorption of the terminal tufts of the dist phalanges; flexion anomalies of hands & feet, abs of breasts; narrow & highly arched palate
Ectodermal dysplasia with natal teeth (Turnpenny type)	601345	AD	Normal	Thin scalp hair; scanty body hair	Oligodontia by late adolescence	Variable heat tolerance	**Skin:** flexural acanthosis nigricans
Ectodermal dysplasia with palatal paralysis	Wesser & Vistnes [9]	NK	No data	Abs of frontal hair, eyebrows & lashes	Stunted & peg-shaped; enamel hypoplasia	Anhidrosis on face (abs sweat glands)	**Skin:** abs of sebaceous glands on the face **Other:** conductive loss; otitis; frontal bossing; depressed nasal bridge; highly arched palate; palatal paralysis; diminished sensation in the palate, the posterior pharyngeal wall & the tonsillar pillar area; abn & distorted speech with a marked nasal component
Ectodermal dysplasia with severe mental retardation	Kirman [10]	NK	Almost abs from fingers & toes	Abs scalp (except for a small wisp in the centre of the head) & body hair	Normal	Hypohidrosis without hyperthermia	**Skin:** fine, thin & shiny with some desquamation over the hands, feet & the top of the head; abs of both nipples **Other:** blindness with bilateral cataract; abn ears; severe mental retardation; abs of menstruation; prepubertal vulva
Ectodermal dysplasia with mental retardation and syndactyly	600906	NK	Severe onychogryphosis	Short, abundant, & stiff, sparse eyebrows	No data	Hypohidrosis	**Skin:** dry **Other:** syndactyly involving the third & fourth fingers & the second & third toes; mild mental retardation; large scalp defect, a peculiar face with large palpebral fissures, broad nasal bridge & constantly open mouth, abnormally modelled ears; mild, & toes

(Continued)

Table 15.3 *Continued*

Name (alternative names)	MIM number/ primary ref.	Inh	Phenotypic characteristics				
			Nails	Hair	Teeth	Sweat glands	Other
Ectodermal dysplasia with syndactyly	Wiedemann *et al.* [11]	AR	Yellowish & partially thickened	Hypotrichosis; brittle scalp hair; pili torti; sp eyebrows & lashes	Severe crown hypoplasia; delayed & atypical eruption of permanent teeth	Normal	**Skin:** dry with hyperkeratosis, esp at the dist third of the trunk, lower limbs, & palmoplantar regions (axillae & elbows are normal); transverse crease on both palms **Other:** mild crowding of the lenses; discrete hypermetropia; syndactyly on both fingers & toes to variable degrees; lordosis; highly arched palate
Ectodermal dysplasia syndrome with tetramelic deficiencies	F-M & P [5]	NK	Platonychia; mildly dysplastic toenails	Scalp hypotrichosis; sp eyebrows & lashes	Hypodontia; peg-shaped teeth	Normal	**Skin:** hypoplastic areolae & nipples **Limbs:** bipartite right clavicle; short & distally curved left clavicle; coxa valga; steep femoral necks; synostosis of cuboid & lateral cuneiform bones; cutaneous syndactyly **Other:** esotropia; malformed auricles; protruding lips; wide nasal root; mild mental retardation; short stature; microcephaly; constant tearing & repeated infections of the conjunctivae; atresia of the naso-lacrimal ducts
Ectodermal dysplasia with adrenal cyst (odonto-onycho-hypohidrotic dysplasia with mid-line scalp defect)	129550	AD	Dyst fingernails	Alopecia cutis verticis	Delayed eruption; diastemata; minor shape alterations	Hypohidrosis as determined by pilocarpine iontophoresis	**Skin:** midline scalp defect (aplasia cutis verticis); hypoplastic areolae & nipples **Other:** breast hypoplasia (inability to lactate); hypertension of undetermined pathogenesis
Ectodermal dysplasia with distinctive facies & preaxial polydactyly	129540	AD	Rounded nails	Scalp alopecia; body alopecia; sp eyebrows; sp eyelashes	Thin enamel; dental caries	Normal	Micrognathia; flat philtrum; malar hypoplasia; dystopia canthorum; flat nasal bridge; thin upper lip; thickened frenulum; fifth finger clinodactyly; preaxial polydactyly; duplicated halluces; duplicated first metatarsals; language delay
Ectodermal dysplasia with ectrodactyly & macular dystrophy	225280	AR	Dysplastic	Hypotrichosis	Normal	Normal	Ectrodactyly; syndactyly; cleft hand; macular dystrophy
Ectodermal dysplasia, pure hair & nail type	602032	AD	Congenital onychodystrophy; micronychia; onycholysis; onychorrhexis	Brittle hair; temporal hypotrichosis	Normal	Normal	**Skin:** folliculitis decalvans of neck
Ectrodactyly–ectodermal dysplasia–cleft lip/palate (EEC) syndrome	129900	AD	Dysplastic, thin, pitted, brittle & striated	Hypotrichosis of scalp & body; fair & dry; scanty or abs eyebrows & lashes	Anodontia; hypodontia; microdontia; enamel hypoplasia; poorly formed; peg-shaped incisors	Occas hypohidrosis without hyperthermia	**Skin:** dry, translucent, palmoplantar hyperkeratosis; eczematous patches; pigmented naevi **Face:** cleft lip; broad nose; defective auricles; pointed chin; malar hypoplasia **Other:** conductive hearing loss; tear duct anomaly or malfunction; speckled iris; photophobia; strabismus; blepharitis; clouding of the cornea; cong adhesions between the eyelids; ectrodactyly; syndactyly; clinodactyly; cleft palate; renal abnormalities; rhinitis; respiratory infections; genital anomalies

Ectrodactyly–ectodermal dysplasia (possible variant expression of EEC, see below)	129810	AD	Normal	Hypotrichosis	Normal	Abnormal dentition	**Other:** no clefting of the lip or palate, as seen in classic EEC syndrome
Ellis–van Creveld syndrome (chondroectodermal dysplasia, mesoectodermal dysplasia) See Weyer's acrofacial dysostosis, below	225500	AR	Dysplastic (brittle, furrowed & underdeveloped)	Thin, brittle, & hypochromic; abs or scanty eyebrows & lashes	Natal teeth; precocious exfoliation; hypodontia; occas hypoplastic enamel	Normal	**Skin:** eczema, petechiae are described in different patterns **Other:** occas strabismus, cataract, coloboma of the iris, microphthalmia; exophthalmia; short-limbed dwarfism; bilateral postaxial polydactyly (gen of the hands); brachymetacarpy; thick & short bones of limbs; fusion of the hamate & capitate; clubfoot; genua valga; syndactyly; occas mild mental retardation; cong heart disease; respiratory difficulties; gingivolabial fusion; cleft palate; epispadia; hypospadias; hypoplastic genitalia **Face:** broad nose; occas cleft lip, frontal bossing & hypertelorism
Fischer syndrome (Fischer–Volavsek syndrome)	Fischer [12]	AD	Onychogryposis; onycholysis	Sp scalp hair, eyebrows, & lashes	Normal	Palmoplantar hyperhidrosis	**Skin:** occas xeroderma; palmoplantar keratosis **Other:** eyelid oedema; occas mental deficiency; clubbing of dist phalanges of the fingers & toes; syringomyelia; apathy
Focal dermal hypoplasia syndrome (Goltz syndrome)	305600	XL	Thin, spooned, narrow, grooved hypopigmented or abs	Hypotrichosis	Hypodontia; microdontia; enamel hypoplasia; delayed eruption; irregular placement	Hypohidrosis or hyperhidrosis	**Skin:** abs of skin from various parts at birth; areas of underdevelopment or thinness; linear hypo- or hyperpigmentation; telangiectasia; herniation of subcutaneous fat; multiple papillomas of mucous membranes and periorificial skin; follicular hyperkeratotic papules; angiofibromatous nodules around lips & anus; palmoplantar hyperkeratosis; occas dermatoglyphic changes **Other:** occas hearing loss; colobomas; microphthalmia; irregularity of pupils; clouding of cornea or vitreous; blue sclerae; lip papillomas; malformed auricles; asymmetry & notching of the alae nasi; pointed chin; triangular face; hypertelorism; mental retardation; short stature; syndactyly; polydactyly; hypoplasia of the external genitalia; umbilical and/or inguinal hernia; vertebral anomalies (scoliosis, spina bifida etc) highly arched palate; gum papillomas; small breasts

(Continued)

Table 15.3 *Continued*

Name (alternative names)	MIM number/ primary ref.	Inh	Phenotypic characteristics				
			Nails	Hair	Teeth	Sweat glands	Other
Focal facial dermal dysplasia, type I (FFDD-type I, focal facial dermal dysplasia, bitemporal aplasia cutis, Brauer syndrome) ? same as FFDD type II	136500	AD	Normal	Alopecia areata; gen sp eyebrows & lashes or multiple rows of lashes on upper lids; normal to abs lashes on lower lids	Normal	Localized hypohidrosis (scarce to abs sweat glands in the focal lesions)	**Skin:** round, focal temporal lesions that have a smooth or wrinkled surface & may be hyperpigmented; occas multiple vertic linear depressions on the lower forehead; abs of sebaceous glands in the temporal lesions **Eyes:** chronic bilateral blepharitis in a few cases **Face:** leonine appearance; wrinkles periorbitally; wide nasal bridge; fleshy nose with the tip bent down; bilateral epicanthic folds
Focal facial dermal dysplasia, type II (FFDD-type II, facial ectodermal dysplasia, bitemporal forceps marks syndrome, Setleis syndrome) ? same as FFDD type I	227260	?AR	Normal	Alopecia areata; gen sp eyebrows & lashes or multiple rows of lashes on upper lids; normal to abs lashes on lower lids	Normal	Localized hypohidrosis (scarce to abs sweat glands in the focal lesions)	**Skin:** round, focal temporal lesions that have a smooth or wrinkled surface & may be hyperpigmented; occas multiple vertic linear depressions on the lower forehead; abs of sebaceous glands in the temporal lesions **Eyes:** chronic bilateral blepharitis in a few cases **Face:** leonine appearance; wrinkles periorbitally; wide nasal bridge; fleshy nose with the tip bent down; bilateral epicanthic folds
Fried tooth and nail syndrome	Fried [13]	AR	Small, thin & sl concave	Fine & short; scanty eyebrows	Hypodontia; peg-shaped teeth	Normal	**Face:** prom lips & chin **Other:** branchial cyst on the left side of the neck
Gingival fibromatosis and hypertrichosis	135400	AD	Normal	Gen hypertrichosis; black & coarse	Delayed eruption; occas microdontia & premature exfoliation	Normal	**Skin:** occas pigmented nevi & hyperelasticity **Other:** occas large ears, peculiar nose & coarse features; mental retardation; epilepsy; gingival fibromatosis; occas hypoplastic breasts
Gingival fibromatosis–sparse hair–malposition of teeth	Jorgenson [14]	AR	No data	Excessively thick in childhood; begins to thin out during early teens; sp later	Malpositioned & malformed; serrated incisors	No data	**Face:** coarse appearance; protruding lips (secondary to gingival fibromatosis); prognathic mandible; broad & flat nasal alae **Other:** alternating strabismus; rotating nystagmus; myopia; abn EEG; low IQ; large hands; broad & relatively short feet; highly arched palate
Gorlin–Chaudhry–Moss syndrome	233500	AR?	No data	Hypertrichosis	Hypodontia; microdontia; some pulp chambers small or missing	Normal	**Face:** characteristic with 'dished out' appearance of middle face; ectropion of lower lid; antimongoloid slant; short stature **Other:** mild bilateral conductive loss; hyperopia; microphthalmia; horiz nystagmus; corneal ulcers; defective eyelid development; craniofacial dysostosis; patent ductus arteriosus; hypoplasia of labia majora; highly arched palate; mild umbilical hernia

Growth retardation–alopecia–pseudoanodontia–optic atrophy (GAPO)	230740	AR	Hyperconvexity on fingers & toes is referred to in two patients	Generalized atrichia	Pseudoanodontia of both primary & permanent dentition with abs of alveolar ridges	Normal	**Skin:** Dry; redundant; fragile with inadequate wound healing (small, depressed scars); depigmented areas; unusual wrinkles; leatherlike & thick on nape & upper back; abn dermatoglyphics **Face:** 'small' & 'characteristic'; asymmetrical; craniofacial dysostosis; micrognathia; protruding & thickened lips; protruding auricles; prom supraorbital ridges; depressed nasal bridge; minor auricular malformations **Other:** sensorineural hypoacusia; optic atrophy; glaucoma; keratoconus; nystagmus; photophobia; dwarfism; occas mental retardation; symmetrical prox shortening of humeri; hyperextensible fingers; second & third toes smaller than the fourth; wide gap between hallux & second toes; wide anterior fontanelle; prom scalp veins; hepatosplenomegaly; bilateral choanal atresia; hyperplasia of sublingual connective tissue; hypoplasia of mammary glands; pectus excavatum; umbilical hernia; delayed bone maturation through childhood & adolescence
Hallerman–Streiff syndrome (Francois dyscephalic syndrome)	234100	AR Heterogeneity? AD?	Normal	Thin & light; gen or sutural alopecia of scalp	Natal; supernumerary; hypodontia; deciduous; premature caries; coniform teeth; hypoplastic enamel	Normal	**Skin:** cutaneous atrophy largely limited to the face and/or scalp; telangiectases; xerosis **Face:** characteristically bird-like; the head has an abn shape, usually brachycephalic or scaphocephalic with frontal & parietal bossing; micrognathia; microstomia with thin lips; apparently low-set ears; 'double chin' **Other:** bilateral microphthalmia; cong cataract; cong corectopia; occas nystagmus; strabismus; blue sclerae; optic disc coloboma; various chorioretinal pigment alterations; occas syndactyly; winging of the scapulae; proportionate short stature; intelligence ranges from normal to mental retardation; narrow & highly arched palate; delayed ossification of craniofacial sutures; microcephaly; cardiac defects; hypogenitalism; cryptorchidism; vertebral anomalies; funnel chest

(Continued)

Table 15.3 *Continued*

Name (alternative names)	MIM number/ primary ref.	Inh	Phenotypic characteristics				
			Nails	Hair	Teeth	Sweat glands	Other
Hayden syndrome	F-M & P [5]	NK	Severe pachyonychia (hands & feet)	No scalp hair, eyebrows, or lashes; virtually no body hair	Normal	Severe hypohidrosis	**Skin:** follicular & plaque-like hyperkeratosis; ichthyosis-like hyperkeratosis on the shins; extremely severe palmoplantar hyperkeratosis to the point of almost complete stiffness of the fingers & toes; severe chronic scalp infection with many pustules **Other:** Chronic external otitis leading to virtual deafness; severe chronic conjunctivitis leading to virtual blindness; saddle nose; narrow palpebral fissures
Hereditary mucoepithelial dysplasia	158310	AD	Chronic monilial nail infection	Non-scarring alopecia	Gingival inflammation	Normal	**Skin:** flat red periorificial mucosal lesions; follicular keratosis **Other:** photophobia; nystagmus; keratoconjunctivitis; keratitis; pannus; cataracts; repeated pneumonia; fibrocystic lung disease; cor pulmonale; mucocutaneous candidiasis; diarrhoea in infancy; T & B cell abnormalities; abnormal PAP smears; vulvovaginal erythema
Hidrotic ectodermal dysplasia (Clouston syndrome/ED2)	129500	AD	Variable degrees of dystrophy; thickened & sl discoloured; paronychia	Dry, fine, usually blonde, slow-growing; hypotrichosis; abs/scanty eyebrows & lashes	Occas hypodontia, anodontia, widely spaced; natal teeth; caries	Normal	**Skin:** dry & rough; tendency toward scaliness; hyperpigmentation of some areas; thick dyskeratotic palms & soles **Other:** occas strabismus, cataract & myopia; occas mental deficiency & short stature; speech difficulties; tufting of terminal phalanges; clubbing of fingers; thickening of skull bones
Hidrotic ectodermal dysplasia, Christianson–Fourie type	601375	AD	Dystrophic thickened nails; unattached distal half of nails	Short, thin, sp, pale scalp hair; absent eyebrows; short, sparse eyelashes; sp axillary & pubic hair	Normal	Normal	Episodic supraventricular tachycardia; bradycardia
Hypertrichosis and dental defects	F-M & P [5]	AD	Normal	Generalized hypertrichosis (except on palms, soles & mucous membranes)	Occas persistence of deciduous teeth, delayed eruption, hypodontia, anodontia	Normal	

Hypohidrotic ectodermal dysplasia–X-linked (ED1; Christ–Siemens–Touraine (CST) syndrome)	305100	XR	Gen normal; sometimes dyst or abs at birth and/or fragile & brittle with incomplete development & celonychia	Fine & dry; hypochromic; hypotrichosis of scalp & body; abs or scanty eyebrows & lashes; moustache & beard gen normal	Hypodontia; peg-shaped incisors and/or canines; persistence of deciduous teeth; delayed eruption; occas anodontia	Hypohidrosis with or without hyperthermia; abs or decreased number of epidermal ridge sweat pores	**Skin:** thin, smooth & dry due to hypoplasia or abs of sebaceous glands; occas pigmentation & dermatoglyphic changes; abs or supernumerary nipples & areolae **Face:** highly characteristic in persons who are severely affected (gen males) with thick & prom lips, depressed nasal bridge (saddle nose), frontal bossing, hypoplasia of the maxilla, wrinkles beneath the eyes, or around the eyes, nose & mouth & minor alterations of the auricles; the periorbital region is often more darkly pigmented than the rest of the body **Other:** occas conductive loss; photophobia; decreased function of the lacrimal glands; aplasia or hypoplasia of the lacrimal ducts; atrophic rhinitis; otitis media; decreased sense of taste and/or smell; atrophied mucous glands of the upper respiratory tract; respiratory difficulties; chronic pharyngitis & laryngitis; aplasia or hypoplasia of the mammary glands
Hypohidrotic ectodermal dysplasia–autosomal dominant (EDA3); includes Jorgenson syndrome	129490	AD	Gen normal; sometimes hypoplastic	Sp, fuzzy, lightly pigmented scalp hair; abs or scanty eyebrows, lashes & body hair	Hypodontia; anodontia; conical teeth	Hypohidrosis with hyperthermia	**Skin:** smooth, thin, dry & hypoplastic **Other:** photophobia; hypoplasia of lacrimal ducts; decreased function of the lacrimal glands; saddle nose; thick & protruding lips; frontal bossing & prom auricles; chronic rhinitis, frequent respiratory infections
Hypohidrotic ectodermal dysplasia (autosomal recessive)	224900	AR	Gen normal; sometimes hypoplastic	Sp, fuzzy, lightly pigmented scalp hair; abs or scanty eyebrows, lashes & body hair	Hypodontia; anodontia; conical teeth	Hypohidrosis with hyperthermia	**Skin:** smooth, thin, dry & hypoplastic **Other:** photophobia; hypoplasia of lacrimal ducts; decreased function of the lacrimal glands; saddle nose; thick & protruding lips; frontal bossing & prom auricles; chronic rhinitis, frequent respiratory infections
HED with immune deficiency	300291	XD	Gen normal; sometimes hypoplastic	Sp, fuzzy, lightly pigmented scalp hair; abs or scanty eyebrows, lashes & body hair	Hypodontia; anodontia; conical teeth	Hypohidrosis with hyperthermia	Milder ectodermal dysplasia features than classic HED; failure to thrive, recurrent infections of digestive tract; recurrent respiratory infections; dysgammaglobulinaemia

(Continued)

Table 15.3 *Continued*

Name (alternative names)	MIM number/ primary ref.	Inh	Phenotypic characteristics				
			Nails	Hair	Teeth	Sweat glands	Other
HED with immune deficiency, osteopetrosis and lymphoedema	300301	XD	Gen normal; sometimes hypoplastic	Sp, fuzzy, lightly pigmented scalp hair; abs or scanty eyebrows, lashes & body hair	Hypodontia; anodontia; conical teeth	Hypohidrosis with hyperthermia	Milder ectodermal dysplasia features than classic HED; failure to thrive, recurrent infections of digestive tract; recurrent respiratory infections; dysgammaglobulinaemia; osteopetrosis Generally more severe phenotype than 300291
HED with deafness	125050	AD	Gen normal; sometimes hypoplastic	Sp, fuzzy, lightly pigmented scalp hair; abs or scanty eyebrows, lashes & body hair	Hypodontia; anodontia; conical teeth	Hypohidrosis with hyperthermia	Progressive hearing loss
Hypohidrotic ectodermal dysplasia with hypothyroidism and ciliary dyskinesia (possibly a CGS with 225040, see below) (? same as ANOTHER syndrome)	225050	NK	Dyst, ridged finger- & toenails with a shrivelled appearance	Scanty & wispy scalp hair with a hard, hay-like consistency; scanty eyebrows & normal lashes	Normal	Hypohidrosis with hyperthermia; low number of sweat gland pores in the palms	**Skin:** poorly developed palmar dermal ridges; mottled brownish skin pigmentation of the trunk during the first months of life; urticaria pigmentosa-like skin & mucosal pigmentation **Other:** lacrimal ducts frequently blocked with resultant bilateral epiphora; frequent conjunctivitis; short stature; structural ciliary abnormalities of the respiratory tract; recurrent & severe upper & lower respiratory infections; severe cow's milk intolerance in infancy; elevated thyrotrophin; decreased thyroid hormone production from early childhood; no evidence of thyroid tissue shown by radiolabelled iodine studies
Hypohidrotic ectodermal dysplasia with hypothyroidism and agenesis of the corpus callosum	225040	NK ?CGS	Dyst, ridged finger & toenails with a shrivelled appearance	Scanty & wispy scalp	Normal	Hypohidrosis with hyperthermia	**Other:** severe mental retardation; agenesis of corpus callosum; primary hypothyroidism; absent normal thyroid & ectopic goiter on technetium 99 thyroid scintigram
Hypohidrotic ectodermal dysplasia with papillomas and acanthosis nigricans (Lelis' syndrome)	Lelis [15]	AR?	Short & dyst	Gen hypotrichosis; scalp hair is dry, fine, lustreless & slow growing; also scanty axillary, pubic hair, moustache/ beard, eyebrows & lashes	Hypoplastic & carious	Hypohidrosis, small number of sweat glands (detected by biopsy)	**Skin:** dry; palmoplantar hyperkeratosis; hyperpigmented & hyperkeratotic skin with wrinkles, papillomas & acanthosis nigricans in the neck, axillae, & genito-femoral regions; increased cornification & presence of follicular plugs on the 'normal' skin; unusual wrinkles around lips **Other:** plicate tongue with papillomatosis

Hypotrichosis-osteolysis-periodontitis-palmoplantar keratoderma syndrome	607658	AD?	Onychogryphosis	Hypotrichosis; pili torti et annulati	Caries & periodontitis	Normal	**Skin:** striate palmoplantar keratoderma; acroosteolysis; psoriasis-like skin lesions **Other:** periodontitis
Ichthyosis follicularis, atrichia, and photophobia syndrome (IFAP) ? related to dermotrichicic syndrome (see below)	308205	XR ? CGS	Normal	Cong atrichia	Enamel dysplasia	Hypohidrosis	**Skin:** ichthyosis follicularis **Other:** photophobia; short stature; mental retardation; seizures; congenital aganglionic megacolon; inguinal hernia; vertebral anomalies; renal anomalies; recurrent respiratory infections
Incontinentia pigmenti (familial male-lethal type IP, Bloch–Sulzberger syndrome)	308300	XL	Dyst in all or most of the fingers & toes in about one tenth of cases	Scarring alopecia in one third	Hypodontia; anodontia; peg-shaped; delayed eruption; both deciduous & permanent teeth are affected	Normal	**Skin:** vesicular-bullous eruption in the neonatal period followed or accompanied by verrucous lesions & bizarre pigmentation; pigmented macules may be present **Other:** occas cong hearing loss; ophthalmological alterations in about one fifth of the patients include blindness, strabismus, cataract, uveitis, retrolental fibroplasias, optic nerve atrophy, microphthalmia; occas clubfoot, cleft palate, microcephaly; about one-third of the cases present severe CNS anomalies: spastic tetraplegia, hemiplegia, diplegia; epilepsy; mental retardation; occas short stature
Johanson–Blizzard syndrome	243800	AR	No data	Sp, dry & fine or coarse; marked frontal upsweep	Oligodontia of both dentitions; peg-shaped teeth	Normal	**Skin:** pale & smooth; café-au-lait spots on lower limbs & abdomen; patches of vitiligo on the lower back & abdomen; midline scalp defects (aplasia cutis congenita); tiny nipples with almost no areolae; transverse palmar creases **Other:** cong sensorineural deafness; aplasia of the inferior puncta; strabismus; aplastic alae nasi, beak-like appearance to nose; severe mental retardation; occas akinetic seizures; microcephaly; hypothyroidism; pancreatic dysfunction; imperforate anus; genitourinary defects; failure to thrive/oedema; malabsorption; epiphyseal dysgenesis; nasolacrimocutaneous fistulae; highly arched palate; delayed bone age; hyperextensibility

(Continued)

Table 15.3 *Continued*

Name (alternative names)	MIM number/ primary ref.	Inh	Phenotypic characteristics				
			Nails	Hair	Teeth	Sweat glands	Other
Keratitis ichthyosis and deafness (KID) syndrome, incorporates hystrix-like ichthyosis with deafness (HID) syndrome 602540	148210	AD	Abs at birth; delayed development; leukonychia & thickening (most marked in the fingernails); destructive dystrophy	Hair loss varies from alopecia to fine, thin scalp hair; scanty or abs eyebrows & lashes; occas trichorrhexis nodosa in some scalp hairs	Delayed eruption of deciduous teeth; brittleness; tendency to develop caries; unspecified defects	Hypohidrosis (with hyperthermia)	**Skin:** ichthyosiform erythroderma with sebaceous dysfunction; furrowing around mouth & chin; erythematous hyperkeratotic plaques on elbows, knees, & the dorsa of hands & feet; marked thickening (leather-like consistency) of palms & soles; increased susceptibility to squamous cell carcinoma **Other:** cong sensorineural deafness; vascularisation of the cornea with pannus formation resulting in loss of vision; keratitis; occas decreased tear production; photophobia; bilateral flexion contractures at knees & elbows with tight heel cords
Kirghizian dermato-osteolysis	221810	AR?	Some dyst fingernails	Normal	Hypodontia; abnormally shaped	Normal	**Skin:** multiple ulcerations on face, trunk, & limbs, with healing of the more superficial ones & fistulous cicatrisation of the deeper ones **Other:** recurrent keratitis with corneal scarring leading to visual impairment; acromegaloid enlargement of hands & feet; claw hands; enlarged & deformed joints; short fingers; flexion contractures in some fingers
Limb–mammary syndrome	603543	AD	Nail dysplasia	Normal	Variable degrees of hypodontia	Hypohidrosis	Hypoplasia/aplasia of the mammary glands; cleft lip/palate +/– bifid uvula; lacrimal duct atresia
Margarita Island ED (allelic to cleft lip/palate–ectodermal dysplasia syndrome (CLEPD1))	225060	AR	Dysplastic	Sp, short scalp hair; sp eyebrows	Hypodontia, esp upper lateral incisors	Normal	Cleft lip/palate; syndactyly of fingers;
Marshall syndrome (allelic to Stickler syndrome (108300), but no ectodermal dysplasia in Stickler syndrome)	154780	AD	Normal	Sparse scalp hair & eyelashes in some families	Occas hypodontia, microdontia, abnormalities of eruption, & malposition	Occas mild hypohidrosis	**Face:** characteristic, with cong & persistently severe flat nasal bridge, anteversion of nostrils, malar hypoplasia, frontal bossing, & sometimes hypertelorism **Other:** occas mental retardation; short-to-normal stature; hypoextensible joints; cranial & spondyloepiphyseal abnormalities; prog cong sensorineural deficit; myopia; fluid vitreous; cong & juvenile cataracts with spontaneous & sudden maturation & absorption
McGrath syndrome (ectodermal dysplasia–skin fragility syndrome)	604536	AR	Thickened & dystrophic	Short & sparse, some improvement with time	Normal	Hypohidrosis, some improvement with age	**Skin:** at birth blistering & desquamation especially on the face, limbs, & buttocks; lifelong fragility, with trauma-induced tearing & blisters on the pressure points of the soles after prolonged standing or walking; plantar hyperkeratosis

Melanoleucoderma	246500	AR	Normal	Dry & abundant scalp hair; sp lateral eyebrows; normal eyelashes; axillary & pubic hair almost normal in women, abs in men	Delayed eruption of deciduous & permanent teeth; hypodontia	Mild palmoplantar hyperhidrosis	**Skin:** pale, thin, dry, smooth, pliable & feminine; gen mottled dyschromia consisting of various shades of hyper- & hypopigmentation; anetopoikiloderma-like lesions over the elbows, knees & prox phalangeal articulations; pyoderma over the lower regions of the legs leading to atrophic scars; palmoplantar hyperkeratosis **Face:** typical 'family' face with flat saddle nose, thick lips with sl telangiectasia & deep furrows around the eyes & mouth **Other:** mental retardation; short stature; hyperextensibility of the fingers; slender legs; sexual underdevelopment in men (hypospadias, small penis & scrotum, atrophy of the testes, abs of secondary sexual characteristics)
Mesomelic dwarfism–skeletal abnormalities–ectodermal dysplasia	Brunoni *et al.* [16]	NK	Hypoplastic toenails	Hypotrichosis	Dysmorphic; irregular eruption; malpositioned	Normal	**Skin:** extremely hypoplastic papillary dermal ridges; bilateral transitional palmar flexion creases **Face:** depressed nasal root; micrognathia; hypertelorism; antimongoloid palpebral slanting; epicanthal folds; long philtrum; thin lips **Limbs:** short forearms & hands; broad thumbs; brachymesophalangy; camptodactyly of both fifth fingers; short legs; flattened acetabular margins; broad halluces **Other:** esotropia; short stature; mild psychomotor retardation; brachycephaly; narrow & highly arched palate; retarded ossification of the anterior fontanelle with the presence of Wormian bones
Mikaelian syndrome (ectodermal dysplasia and neurosensory deafness)	224800	AR	Normal	Coarse & brittle; hypotrichosis of scalp	Caries	Normal	**Skin:** hyperkeratotic; increased melanin in the basal layer **Other:** bilateral sensorineural loss; coarse facial features; arachnodactyly; kyphoscoliosis
Monilethrix	158000	AD	Occas dystrophic	Brittle, beaded, highly variable degrees of alopecia	Normal	Normal	**Skin:** keratosis pilaris, especially over nape of neck

(Continued)

Table 15.3 *Continued*

Name (alternative names)	MIM number/ primary ref.	Inh	Phenotypic characteristics				
			Nails	Hair	Teeth	Sweat glands	Other
Naegeli–Franceschetti–Jadassohn syndrome	161000	AD	Normal	Normal	Carious & yellowish spotted	Hypohidrosis; discomfort in heat	**Skin:** reticular cutaneous pigmentation (appearing at age 2 & disappearing with age), palmoplantar hyperkeratosis, absent dermatoglyphics
Oculo-dentodigital (ODD) syndrome	164200	AD	Normal	Brittle, sp & dry; slow-growing	Generalized enamel hypoplasia; occas hypodontia; microdontia, & premature loss	Normal	**Eyes:** microcornea; microphthalmia with small orbits; reduced lid apertures; occas findings: optic atrophy, synechiae, disc coloboma, persistence of papillary membrane, nystagmus, cong cataract, glaucoma, strabismus & epicanthal folds **Limbs:** syndactyly & camptodactyly of the fourth & fifth fingers & of one or more toes; occas ulnar clinodactyly of the fifth fingers & syndactyly of the third & fourth toes; hip dislocation; cubitus valgus **Other:** face characterized by a thin nose, hypoplastic alae & narrow nostrils; cleft lip; orbital hypotelorism; occas micrognathia & mild pinna defects; microcephaly; cranial hyperostosis; cleft palate; osteopetrosis; occas conductive impairment
Oculotrichodysplasia	257960	AR	Brittle finger & toenails	Generalized hypotrichosis, sparse scalp, axillary & pubic hair; scanty eyelashes & sparse eyebrows in distal 2/3	Hypodontia; carious with extensive extractions	Normal	**Other:** retinitis pigmentosa
Odontomicronychial dysplasia	601319	AR	Short, thin, slow growing nails	Normal	Precocious eruption & shedding of deciduous teeth; precocious eruption of secondary teeth	Normal	
Odonto-onychodermal dysplasia	257980	AR	Dystrophic	Dry & sparse with thinning of eyebrows in some	Misshapen teeth; peg-shaped incisors	Hyperhidrosis	**Skin:** thickening of the palms & soles; erythematous lesions of face; thickening of the palmar skin with painful chafing **Other:** mild mental deficiency

Onychotrichodysplasia and neutropenia	258360	AR	Hypoplastic finger & toenails; koilonychia; onychorrhexis	Dry, fine, lustreless, short, curly, sp on scalp, eyebrows & lashes; trichorrhexis; abs axillary & pubic hair	Normal	Normal	**Skin:** thin & wrinkled on the palms & soles; pustules on the palms **Other:** chronic irritative conjunctivitis; delayed psychomotor development; mild generalized hypotonia; chronic neutropenia; recurrent infections (mainly tonsillitis, sinusitis, & otitis)
Orofaciodigital (OFD) syndrome type I	311200	XD	Normal	Dryness and/or variable degree of alopecia (65%)	Abs of the lower lateral incisors (50%); malposition; occas supernumerary canines & enamel hypoplasia	Normal	**Skin:** evanescent facial milia **Face:** broad nasal root; hypoplasia of alae nasi; median cleft of the upper lip; occas short philtrum, frontal bossing; ear abnormalities **Limbs:** several types of malformations including brachydactyly, clinodactyly, syndactyly, polydactyly **Other:** dystopia canthorum; occas mental retardation (usually mild), trembling & short stature; multiple hypertrophied lingual & labial frenula; lateral grooving of maxillary alveolar process; grooved ankyloglossia; cleft palate; hypoplasia of malar bone; hypoplasia of the base of the skull; renal abnormalities
Pachyonychia congenita type 1 (Jadassohn–Lewandowsky type)	167200	AD	Severe wedge-shaped thickening	Usually normal	No natal teeth	Palmoplantar hyperhidrosis	**Skin:** Focal palmoplantar keratoderma; verrucous lesions on the knees, elbows, buttocks, ankles, & popliteal regions; follicular keratoses/keratosis pilaris **Other:** oral leukokeratosis; hoarseness
Pachyonychia congenita type 2 (Jackson–Lawler type)	167210	AD	Severe wedge-shaped thickening	Usually normal	Natal teeth	Palmoplantar hyperhidrosis	**Skin:** focal palmoplantar keratoderma; verrucous lesions on the knees, elbows, buttocks, ankles & popliteal regions; follicular keratoses/keratosis pilaris; multiple pilosebaceous cysts (steatocysts) with onset at puberty distinguish this form from PC type 1 **Other:** oral leukokeratosis; hoarseness
Palmoplantar hyperkeratosis and alopecia	104100	AD	Short & dyst with onycholysis	Hypotrichosis to alopecia; abs of eyebrows & lashes; hypotrichosis of axillae & pubic regions	Normal	Normal	**Skin:** palmoplantar hyperkeratosis

(Continued)

Table 15.3 *Continued*

Name (alternative names)	MIM number/ primary ref.	Inh	Phenotypic characteristics				
			Nails	Hair	Teeth	Sweat glands	Other
Papillon–Lefèvre syndrome	245000	AR	Occas dyst (spoon-shaped & striated; onychogryphosis)	Occas thin & loose	Periodontal degeneration with consequent shedding of all teeth	Palmoplantar hyperhidrosis; occas gen hypohidrosis	**Skin:** Hyperkeratosis of the palmar & plantar surfaces with a tendency towards fissuring & cracking; dry & dirty-appearing on the dorsal surface of the arms & the ventral surface of the legs; occas eczema & erythema of the face as well as of the sacral & gluteal regions **Other:** severe gingivostomatitis; occas intracranial calcifications; abn liver function; renal abnormalities; gen osteoporosis
Pili torti and developmental delay	261990	AR	Normal	Pili torti	Normal	Normal	Growth & developmental delay, mild to moderate neurological abnormalities
Pili torti and onychodysplasia (Beare type)	Beare [17]	AD	Short, fragile & brittle	Initially normal, followed by hypotrichosis on the scalp, axillary & pubic areas; pili torti	Normal	Normal	**Skin:** normal, dry or greasy; sl atrophy on the top of the scalp **Other:** low IQ; severe mental retardation; 'irresponsible personality'
Pili torti and onychodysplasia	Calzavara-Pinton *et al.* [18]	AD	Distal nail dystrophy	Pili torti of scalp, beard, pubic & axillary hair; absent eyebrows, eyelashes & body hair	Normal	Normal	
Pilodental dysplasia with refractive errors	262020	AR	Normal	Scalp hypotrichosis; pili annulati	Hypodontia, abnormally shaped teeth	Normal	Follicular hyperkeratosis of trunk & limbs & marked hyperopia
Poikiloderma with neutropenia (Navajo poikiloderma)	604173	AR	Thickened & dystrophic	Normal	Normal	Normal	**Skin:** eczematous rash at birth, becomes poikilodermatous over first 2 years of life **Other:** non-cyclical neutropenia, recurrent upper respiratory tract infections & chest infections Similarity to Rothmund–Thompson syndrome (see below) but no mutations in *RECQL4*
Polyposis, skin pigmentation, alopecia and fingernail changes (Cronkhite–Canada syndrome)	175500	?AD	Onychodystrophy	Alopecia	Normal	Normal	**Skin:** hyperpigmentation **Other:** cachexia; cataracts; xerostomia; glossitis; diminution of sense of taste; gastrointestinal hamartomatous polyps (stomach, small bowel, colon); gastrointestinal carcinoma; protein-losing enteropathy; malabsorption; haematochezia; clubbing of fingers; peripheral neuropathy; thromboembolism; hypocalcaemia; hypomagnesaemia; hypokalaemia

Rapp–Hodgkin syndrome	129400	AD?	Small narrow & dysplastic	Coarse & stiff on scalp; pili torti; abs or scarcity on scalp & body; sp eyebrows & lashes	Conically shaped; short, square incisors & canines; hypoplastic enamel; extensive caries; hypodontia	Hypohidrosis; lower number of sweat glands	**Skin:** dry & coarse; thickened over the extensor surface of the elbows & knees; hypoplastic dermatoglyphics **Face:** cleft lip; hypoplastic maxilla; mild frontal prominence; microstomia; mildly depressed nasal bridge; prom & malformed auricles **Other:** conductive loss (secondary to otitis media); chronic epiphora; corneal opacities; photophobia; atresia of puncta; ectropion; lacrimal papillae; short stature; occas syndactyly Absence of ankyloblepharon & severe erosive scalp dermatitis may distinguish Rapp–Hodgkin syndrome from AEC syndrome (see above)
Rothmund–Thomson syndrome	268400	AR	Frequently dyst	Hypotrichosis of scalp & body; eyebrows & lashes usually fall out during the first year of life & remain sp or abs	Hypodontia; microdontia; supernumerary teeth; pronounced caries; delayed eruption	Normal	**Skin:** poikiloderma including atrophy, irregular pigmentation & telangiectasias beginning during the first 3–6 months; palmoplantar hyperkeratosis; sensitivity to sunlight; initial rash is red, elevated with oedematous patches appearing symmetrically on the cheeks, hands, forearms & buttocks & subsequently on the trunk & lower limbs; after a few years dry, scaling & atrophic skin develops with areas of hyperpigmentation, hypopigmentation & telangiectasia **Other:** cataract, usually bilateral (onset 3–6 years); occas degenerative lesions of the cornea; small hands & feet; short terminal phalanges, syndactyly: abs of metacarpals, rudimentary ulna & radius; increased risk of osteosarcoma; short stature; occas mental retardation; hypogonadism; cryptorchidism; skull abnormalities; scoliosis
Sabinas brittle hair and mental deficiency syndrome (?same as those described elsewhere as the Pollitt syndrome, MIM #275550)	211390	AR	Dyst (splitting & cracking proximally)	Dry, brittle, coarse, wiry in texture; reduced eyebrows & lashes; abs of axillary & pubic hair	No data	Normal	**Skin:** scalp hyperkeratosis on exposed areas **Other:** pigmentary retinopathy; unilateral cong tortuosity of the retinal vessels; pale optic discs & hyperopic astigmatism; maxillary hypoplasia; mental retardation; delayed bone age

(Continued)

Table 15.3 *Continued*

Name (alternative names)	MIM number/ primary ref.	Inh	Phenotypic characteristics				
			Nails	Hair	Teeth	Sweat glands	Other
Scalp–ear–nipple syndrome (Finlay–Marks syndrome)	181270	AD	Brittle fingernails	Congenitally denuded areas on scalp, sp axillary & secondary sexual hair	Widely spaced/ missing teeth	Reduced apocrine secretion	**Skin:** raised firm scalp nodules **Other:** small tragi; cupped & protruding ears; absent/rudimentary nipples; breast aplasia; partial third/fourth finger syndactyly
Schinzel–Giedion midface-retraction syndrome	269150	AR?	Narrow, deeply set, triangular & hyperconvex	Gen hypertrichosis	Delayed eruption	No data	**Skin:** abundant on the neck; hypoplastic nipples; hypoplastic dermal ridges; simian creases **Face:** saddle nose with depressed root & short bridge; high/protruding forehead; orbital hypertelorism; small/malformed auricles; anteverted nostrils; midface hypoplasia; facial haemangiomata **Limbs:** mesomelic brachymelia; hypoplasia of dist phalanges in hands & feet; short metacarpals of thumbs; talipes **Other:** severe mental retardation; growth retardation; abn EEG & seizures; spasticity; recurrent apnoeic spells; multiple Wormian bones; wide cranial sutures & fontanelles; broad ribs, broad cortex & increased density of long tubular bones & vertebrae, hypoplastic/aplastic pubic bones; choanal stenosis; short & broad neck; short penis with hypospadias
Schopf–Schulz–Passarge syndrome (cystic eyelids–palmoplantar keratosis–hypodontia–hypotrichosis)	224750	AR	Brittle with longitudinal & oblique furrows; onycholysis	Generalized hypotrichosis of scalp & body	Extensive hypodontia; persistence of deciduous teeth	Normal	**Skin:** palmoplantar keratosis; telangiectatic facial skin; papules; multiple tumours with follicular differentiation **Other:** bilateral early senile cataract; arteriosclerotic fundi; myopia; cysts of eyelids developing late
Sener syndrome (frontonasal dysplasia and dilated Virchow–Robin spaces)	606156	NK	Dystrophic nails	Thin hair	Hypodontia; dental occlusion; natal teeth	Normal	**Face:** hypertelorism with a wide mouth, long, smooth philtrum & small posteriorly rotated ears **Other:** multiple cystic areas within the white matter radiating from the ventricles into oval lobes with sparing of the basal ganglia, brainstem, & corpus callosum
Sensorineural hearing loss, enamel hypoplasia & nail defects (Heimler syndrome)	234580	AR	Beau's lines (toenails); leukonychia (fingernails)	Normal	Gen enamel hypoplasia	Normal	Sensorineural hearing loss

Skeletal anomalies–ectodermal dysplasia–growth and mental retardation	Schinzel [19]	NK	Hypoplastic toenails	Almost complete abs of body hair; a few curled hairs are present in the parieto-occipital & pubic regions	Normal	Normal	**Skin:** dry & hyperkeratotic with rhomboid type of scaling, esp on the lower legs; abs of flexion creases on thumbs; fifth fingers with single flexion creases **Face:** large, prom nose; upslanting palpebral fissures; short upper lip; large, poorly formed ears **Other:** microbrachycephaly; multiple uni- or bilateral fusion of vertebral bodies in the lower thoracic & upper lumbar regions; multiple limb abnormalities; syndactyly; bone fusions
Taurodontia, absent teeth, and sparse hair (?Same as Witkop syndrome 189500, see below)	272980	AR	Slow-growing nails; thin, spoon-shaped nails	Sparse hair; slow-growing hair	Congenital hypodontia; taurodontia	Normal	
Tetramelic deficiencies, ectodermal dysplasia, deformed ears, and other abnormalities (odontotrichomelic syndrome)	273400	AR	Hypoplastic?	Severe hypotrichosis of scalp & body	Hypodontia; microdontia; coniform teeth; persistence of deciduous teeth	Normal	**Skin:** thin, dry & shiny; an unusual number of wrinkles are formed when patients smile or grimace; dermatoglyphic disturbances; hypoplastic nipples; hypoplastic or abs areolae **Face:** protruding lips; enlarged nose; large, thin, prom & deformed auricles; incomplete right cleft lip in one patient **Other:** EEG abnormalities; growth retardation; extensive tetramelic deficiencies; metabolic abnormalities; ECG abnormalities
Thumb deformity and alopecia	188150	AD	Normal	Alopecia	Single central upper incisor	Normal	Hypoplastic thumbs; short stature; mental retardation; increased groin pigmentation with raindrop depigmentation
Trichodental dysplasia	601453	AD	Normal	Fine & lustreless appearance; relatively thin shafts with a sl beading effect; scanty or abs dist eyebrows & sp eyelashes	Hypodontia; peg-shaped teeth; retained deciduous teeth	No data	

(Continued)

Table 15.3 *Continued*

Name (alternative names)	MIM number/ primary ref.	Inh	Phenotypic characteristics				
			Nails	Hair	Teeth	Sweat glands	Other
Trichodentoosseous syndrome	190320	AD	Flat, thickened, misshapen & striated; brittle	Dry, thick, tough with short curls, often straightens in childhood; balding may occur with age in men	Thin enamel; small, widely spaced teeth; teeth pits; taurodontism; periapical abscesses	Normal	**Face:** occas frontal bossing **Others:** occas clinodactyly; some of the calvarial sutures show evidence of premature fusion leading to mild to moderate dolichocephaly
Tricho-odonto-onychial dysplasia (tricho-odonto-onychial dysplasia with amastia)	129510	AR?	Variable degree of dystrophy of finger & toenails	Alopecia totalis; peripheral fringe of hair on the temporal & occipital regions, sp eyebrows & eyelashes	Enamel hypoplasia in both dentitions; secondary anodontia	Normal	**Skin:** increased number of pigmented naevi; supernumerary nipples; keratotic actinic lesions; crusts, ephelides in the scalp; mild palmoplantar hyperkeratosis; dermatoglyphic alterations **Other:** one patient had a mixed mild hearing deficit on the left; short stature
Tricho-odonto-onycho-dermal syndrome	Pinheiro *et al.* [20]	NK	Severely dyst or abs finger & toenails	Parieto-occipital hypotrichosis; aplasia cutis congenita; sp eyelashes; sp & irregular eyebrows	Hypodontia; persistence of deciduous teeth; enamel hypoplasia; delayed eruption	Normal	**Skin:** dry with hypochromic, atrophic & poikiloderma-like spots; irregular areolae; wrinkled back of hands; palmar keratosis; dermatoglyphic alterations; aplasia cutis congenita of the scalp **Face:** long philtrum; microstomia with thin lips; hyperpigmented eyelids & periorbital regions **Limbs:** bilateral clinodactyly; syndactyly; hypoplastic thumb; pronounced manus cava; hypoplastic dist & middle phalanges of both second fingers; abs middle phalanges of all toes **Other:** mild asymmetry of the skull; cong hypertrophy of the frenum linguae
Tricho-odonto-onychial dysplasia	275450	?AR	Dystrophic	Severe hypotrichosis	Enamel hypoplasia; secondary anodontia	Normal	**Skin:** supernumerary nipples; naevus pigmentosus **Other:** bone deficiency in the frontoparietal region
Tricho-onycho-dental (TOD) dysplasia	Koshiba *et al.* [21]	AD	Thin with longitudinal striations & cracks	Scanty, fine, curled; sp eyebrows & lashes	Taurodontic molars; hypoplastic–hypomature enamel; hypodontia	Hypohidrosis with hyperthermia	**Skin:** fine textured

Trichorhinophalangeal syndrome types I & III	190350 190351	AD	Occas thin, short, with long longitudinal grooves; flattened, koilonychia-like & normal in colour, racket thumbnails	Fine, usually blond & sp (esp in the fronto-temporal areas); sp or abs eyebrows	Occas supernumerary incisors; microdontia; poorly aligned	Normal	**Other:** pear-shaped nose; long & wide philtrum; large, prom ears; occas exotropia & photophobia; short stature; increased susceptibility to upper respiratory tract infections; narrow palate; scoliosis; lordosis or kyphosis; pectus carinatum **Limbs:** brachymesophalangy; brachymetacarpy; brachymetatarsy; peripheral dysostosis with type 12 cone-shaped epiphyses at some of the middle phalanges of the hands (the joints are thickened); ulnar & radial deviation of the fingers; occas clinodactyly; winged scapulae; coxa valga; Perthes-like abnormalities (Type III: severe brachydactyly, short metacarpals, severe short stature)
Trichorhinophalangeal syndrome type II (Langer–Giedion syndrome)	150230	AD	Occas thin, short, with long longitudinal grooves; flattened, koilonychia-like & normal in colour; racket thumbnails	Fine, usually blond & sp (esp in the fronto-temporal areas); sp or abs eyebrows	Occas supernumerary incisors; microdontia; poorly aligned	Normal	As above plus multiple cartilaginous exostoses; mental retardation is common
Trichorrhexis nodosa syndrome (Pollitt syndrome) (? same as Sabinas brittle hair and mental deficiency syndrome (211390))	275550	?AR	Hypoplastic nails; spoon-shaped nails	Trichorrhexis nodosa; short, woolly hair; stubby eyebrow hair	No data	Normal	**Skin:** ichthyotic skin, flexural eczema; photosensitivity **Other:** mental retardation; hypotonia; titubation; spastic diplegia; extensor plantar reflexes; absent deep tendon reflexes; partial agenesis of the corpus callosum; central nuclear cataracts; jerky ocular pursuit movements; growth retardation; microcephaly; receding chin; protruding ears
Ulnar mammary syndrome (Schinzel syndrome)	601621	AD	Normal	Sparse axillary hair; scant lateral eyebrows	Ectopic upper canines; hypodontia	Axillary apocrine gland hypoplasia	**Other:** delayed growth; obesity; subglottic stenosis; hypoplastic scapula; hypoplastic clavicle; breast hypoplasia; nipple hypoplasia; anal atresia or stenosis; pyloric stenosis; small penis; delayed puberty; shawl scrotum; imperforate hymen **Limbs:** hypoplastic/absent/deformed ulna; hypoplastic/absent/deformed radius; hypoplastic humerus; absent 3rd, 4th, & 5th ulnar rays; postaxial polydactyly; short fourth & fifth toes

(Continued)

Table 15.3 *Continued*

Name (alternative names)	MIM number/ primary ref.	Inh	Phenotypic characteristics				
			Nails	Hair	Teeth	Sweat glands	Other
Uncombable hair, retinal pigmentary dystrophy, dental anomalies, and brachydactyly (Bork syndrome)	191482	AD	Normal	Uncombable hair; congenital hypotrichosis	Oligodontia; supernumerary inferior lateral incisors; microdontia	Normal	Juvenile cataracts; retinal pigmentary dystrophy; brachymetacarpy; mild mental retardation
Walbaum–Dehane–Schlemmer syndrome	Walbaum *et al.* [22]	AR	Normal	Initially thin & blond; alopecia later; hypotrichosis of body	Hypodontia; supernumerary teeth; microdontia; malposition	Normal	**Skin:** abn dermatoglyphics **Face:** Swollen, with flat nasal bridge & enlarged tip of nose **Other:** Mild gingival hypertrophy; growth retardation
Weyer acrofacial dysostosis (? milder AD form of Ellis van Creveld, MIM 225500, see above)	193530	AD	Hypoplastic/ dysplastic	Normal	Incisors abnormal in shape & number; single central incisor; conical	Normal	**Other:** short stature; postaxial polydactyly; short limbs; acrofacial dysostosis; abnormal mandible; hypotelorism; prominent ear antihelices
Witkop syndrome (tooth and nail syndrome) (? same as taurodontia, absent teeth, and sparse hair 272980, see above)	189500	AD	Koilonychia; longitudinal ridging; nail pits, toenails more affected than fingernails	Normal	Partial or total anodontia	Normal	Lip eversion
Woolly hair, hypotrichosis, everted lower lip, and outstanding ears (Salamon syndrome)	278200	AR	Highly dyst; brittle; ungues plicatae; toenails more severely affected; onycholysis	Gen hypotrichosis of scalp & body; woolly hair	Extensive hypodontia (rudimentary permanent teeth); persistence of deciduous teeth	Normal	**Skin:** palmoplantar keratosis; telangiectatic facial skin; papules; multiple tumours with follicular differentiation **Other:** bilateral early senile cataract; arteriosclerotic fundi; myopia; eyelid cysts; everted lower lip; protruding ears
Xeroderma–talipes–enamel defect (XTE syndrome)	Moynahan [23]	NK	Deformed on fingers +/– toes	Coarse & dry; slow-growing; hypotrichosis; no lashes on lower lids	Poorly formed; yellow enamel	Hypohidrosis	**Skin:** gen dry, scaling with numerous bullae on face & limbs; scanty hair follicles **Other:** photophobia; hypoplasia of the ocular puncta leading to epiphora & blepharitis; EEG alterations; mild mental retardation; bilateral club foot; cleft palate
Zanier–Roubicek syndrome (? same as AD HED (129490), see above)	Zanier & Roubicek [24]	AD	Occas brittle	Hypotrichosis; normal eyebrows & lashes	Hypodontia; conical teeth; early loss of deciduous teeth	Hypohidrosis, often severe hyperthermia in infancy	**Skin:** smooth & dry **Other:** reduced lacrimation; normal or sl reduced stature; hypoplasia of the mammary glands

Abn: abnormal; abs: absence; AD: autosomal dominant; AR: autosomal recessive; CGS: contiguous gene syndrome; cong: congenital; dist: distally; dyst: dystrophic; esp: especially; gen: generally/generalized; horiz: horizontal; inh: inheritance; lt: light; malign: malignancy; NK: not known; occas: occasionally/occasional; MIM: Mendelian Inheritance in Man; prog: progressive; prom: prominent; prox: proximal; ref: reference; sl: slight; sp: sparse; vert: vertical; XL: X-linked.

conditions are now known to be allelic [27]. Prompted by the great advances in molecular knowledge, several authors have proposed new molecular-based approaches [28–30]. These proposed approaches classify conditions based on the class of molecule responsible for the disorder, for example categorizing together those with mutations in structural or developmental molecules. This approach has many advantages, especially for characterization of defects in preparation for molecular diagnostics and, hopefully, molecular therapy. These systems, however, need to be integrated with clinical findings and need to be accessible to all clinicians involved in the care of these patients. Importantly, it has to be realized that currently it is not possible to provide a molecular diagnosis for all patients, even in those with classical clinical features of conditions well characterized at a molecular level. Molecular factors, such as unusual mutation mechanisms, can frustrate conventional mutation identification as can health-care service delivery factors such as access to and affordability of molecular diagnostics; these and other confounders are likely to remain the case in the foreseeable future.

The following section reviews some of the commoner ectodermal dysplasias, considered by their genetic mechanisms, namely ectodermal dysplasias due to mutations in tumour necrosis factor (TNF)-like/NF-κB signalling pathways, the p63-related ectodermal dysplasias, ectodermal dysplasias due to other transcription factors and ectodermal dysplasias due to mutations in gap junction proteins.

References

1 Danz D. Sechste Bemerkung. Von Menschen ohne Haare und Zahne. *Stark Arch Geburth Frauen Neugeb Kinderkr* 1792; **4**: 684.

2 Darwin C. *The Variations of Animals and Plants under Domestication*, 2nd edn, Vol. 2. London: John Murray, 1875: 319.

3 Weech A. Hereditary ectodermal dysplasia (congenital ectodermal defect). A report of two cases. *Am J Dis Child* 1929; **37**: 766–90.

4 Touraine A. L'anidrose héréditaire avec hypotrichose et anodontie (polydysplasie ectodermique héréditaire). *Presse Méd* 1936; **44**: 145–9.

5 Freire-Maia N, Pinheiro M. *Ectodermal Dysplasias: A Clinical and Genetic Study*. New York: Alan R. Liss, 1984.

6 Lerner AB. Three unusual pigmentary syndromes. *Arch Dermatol* 1961; **83**: 151–9.

7 Baisch A. Anonychia congenita, Kombiniert mit Polydaktykie and verzogertem abnormen Zahndurchbruch. *Dtsch Z Chir* 1931; **232**: 450–7.

8 Wallace HJ. Ectodermal defect with skeletal abnormalities. *Proc R Soc Med* 1958; **51**: 707–8.

9 Wesser DW, Vistnes LM. Congenital ectodermal dysplasia, anhidrotic, with palatal paralysis and associated chromosome abnormality. *Plast Reconstr Surg* 1969; **8**: 396–8.

10 Kirman BH. Idiocy and ectodermal dysplasia. *Br J Dermatol* 1955; **67**: 303–7.

11 Wiedemann HR, Grosse FR, Dibbern H. *Caracteristicas das Sindromes em Pediatria. Atlas de Diagnostico Diferencial*. (transl. of Das Charakteristische Syndrom by H Fürstenau). São Paulo: Manole. 1978.

12 Fischer H. Familiar hereditares Vorkommen von Keratoma palamare et plantare, Nagelverandergungen, Haaranomalien und Verdickung der Endglieder der Finger und Zehen in 5 Generationen. (die Beziehungen dieser Veranderungen zur inneren Sekretion.) *Dermatol Zeitschr* 1921; **32**: 114–42.

13 Fried K. Autosomal recessive hydrotic ectodermal dysplasia. *J Med Genet* 1977; **14**: 137–9.

14 Jorgenson RJ. Gingival fibromatosis. *Birth Defects* 1971; **7**: 278–80.

15 Lelis I. [Autosomal-recessive ectodermal dysplasia—a separate nosological entity]. *Vestn Dermatol Venereol* 1978; **12**: 56–9.

16 Brunoni D, Lederman H, Ferrari S *et al*. Uma sindrome malformativa com nanismo mesomelico, malformacoes esqueleticas, displasia ectodermica e facies tipica. *Cienc Cult* 1982; **34**: 694.

17 Beare JM. Congenital pilar defect showing features of pili torti. *Br J Dermatol* 1952; **64**: 366–72.

18 Calzavara-Pinton P, Carlino A, Benetti A *et al*. Pili torti and onychodysplasia. Report of a previously undescribed hidrotic ectodermal dysplasia. *Dermatologica* 1991; **182**: 184–7.

19 Schinzel A. A case of multiple skeletal anomalies, ectodermal dysplasia, and severe growth and mental retardation. *Helv Paediatr Acta* 1980; **35**: 243–51.

20 Pinheiro M, Pereira LC, Freire-Maia N. A previously undescribed condition: tricho-odonto-onycho-dermal syndrome. A review of the tricho-odonto-onychial subgroup of ectodermal dysplasias. *Br J Dermatol* 1981; **105**: 371–82.

21 Koshiba H, Kimura O, Nakata M *et al*. Clinical, genetic, and histologic features of the trichoonychodental (TOD) syndrome. *Oral Surg Oral Med Oral Pathol* 1978; **46**: 376–85.

22 Walbaum R, Dehaene P, Schlemmer H. Dysplasie ectodermique: une forme autosomique recessive? *Arch Fr Pediatr* 1971; **28**: 435–42.

23 Moynahan EJ. XTE syndrome (xeroderma, talipes and enamel defect): a new heredo-familial syndrome. *Proc R Soc Med Lond* 1970; **63**: 1–2.

24 Zanier JM, Roubicek MM. Hypohidrotic ectodermal dysplasia with autosomal dominant transmission. *Fifth Int Congress Hum Genet, Mexico* 1976; Communication 273.

25 Pinheiro M, Freire-Maia N. Ectodermal dysplasias: a clinical classification and a causal review. *Am J Med Genet* 1994; **53**: 153–62.

26 Irvine AD. Ectodermal dysplasias. In: Harper JI, Oranje OP, Prose N, eds. *Textbook of Pediatric Dermatology*, 2nd edn. Oxford: Blackwell Scientific; 2005: 1412–66.

27 McGrath JA, Duijf P, Doetsch V *et al*. Hay-Wells syndrome is caused by heterozygous missense mutations in the SAM domain of p63. *Hum Mol Genet* 2001; **10**: 221–9.

28 Itin PH, Fistarol SK. Ectodermal dysplasias. *Am J Med Genet C Semin Med Genet* 2004; **131C**: 45–51.

29 Lamartine J. Towards a new classification of ectodermal dysplasias. *Clin Exp Dermatol* 2003; **28**: 351–5.

30 Priolo M, Lagana C. Ectodermal dysplasias: a new clinical-genetic classification. *J Med Genet* 2001; **38**: 579–85.

Ectodermal dysplasias due to mutations in TNF-like/NF-κB signalling pathways

The transcription factor NF-κB regulates the expression of multiple genes with functions in controlling the immune and stress responses, cell adhesion, protection against apoptosis and inflammatory reactions [1,2]. NF-κB is composed of homo- or heterodimers of five proteins belonging to the Rel family. NF-κB is usually maintained in an inactive state within the cytoplasm by association with inhibitory proteins of the IκB family: IκBα, IκBβ and IκBε. IκB molecules are phosphorylated on two critical serine residues in response to multiple stimuli such as cytokines, various stress signals, and viral and bacterial infections. Phosphorylation at these sites enables recognition of IκB molecules by a ubiquitation complex. Following polyubiquitation, IκBs are degraded by proteasomes, thus releasing free NF-κB to enter the nucleus and activate target genes [3]. The kinase that phosphorylates IκB has been designated IκK (for IκB kinase) and has been shown to consist of two catalytic subunits (IκKα/IκK1 and IκKβ/IκK2) and a third component IκKγ (more usually known as NEMO) that provides a structural and regulatory function to the complex. Cell lines lacking NEMO are unable to activate NF-κB in response to most stimuli [4]. Extensive work with mouse models has confirmed the centrality of the NF-κB pathway in apoptosis, inflammatory and immune functions [5]. Complete absence of NF-κB leads to prenatal death due to massive TNF-induced liver apoptosis and more subtle knockouts that alter NF-κB activity all lead to immune defects. The NF-κB pathway has recently generated

much interest in the ectodermal dysplasias and defects at various levels have been identified in several EDs. In many cases these predominantly phenotype-driven, mouse–human comparison studies have yielded significant new insights into molecular pathways [1]. One of the best characterized pathways in NF-κB activation is the ectodysplasin pathway, an upstream activator. Since 1997, defects in this pathway have been demonstrated in the X-linked, autosomal dominant and recessive subtypes of hypohidrotic ED. Subsequently, mutations in downstream components have been shown to underlie familial incontinentia pigmenti and HED associated with immunodeficiency and/or osteopetrosis.

The X-linked HED gene, *EDA*, which maps to Xq12-13.1 and is also mutated in the mouse orthologue *tabby* [6], was first described in 1996 [7]. *EDA* encodes two isoforms of a trans-membrane protein, ectodysplasin-A, that has homology to the tumour necrosis factor (TNF) family. The extracellular domain of ectodysplasin-A has a collagen-like repeat and a furin cleavage site, unique in TNF proteins. Cleavage is necessary to enable solubility and functionality of EDA. The two longest isoforms, EDA-A1 and EDA-A2, bind to two different receptors: EDA-A1 binds to the EDAR protein and EDA-A2 binds to another X-linked receptor, XEDAR [8]. Mutations have been identified in all domains of ectodysplasin-A in patients with HED, and many of these mutations are thought to have an effect on solubility or cleavage of ectodysplasin-A, rendering it non-functional [9]. The physiological role of EDA in hair follicle morphogenesis was reinforced by the isolation of the gene for autosomal dominant/recessive HED. Patients with autosomal dominant or recessive HED are phenotypically identical to those with X-linked HED. The mutated gene, named *downless* (*DL*) after the mouse homologue, encodes a member of the tumour necrosis-factor receptor (TNFR) superfamily which functions as an ectodysplasin receptor (EDAR) [10]. Loss-of-function mutations throughout *dl* have been reported in autosomal recessive HED and dominant negative mutations have been reported in autosomal dominant HED within the death domain of this trans-membrane protein [11].

The EDA:EDAR pathway was further refined when the molecular basis of a third mouse homologue was identified. The *crinkled* mouse (*cr*) is a spontaneous mouse mutant with an identical phenotype to *downless* and *tabby*. Using positional cloning techniques, the causative gene was identified in an adapter protein (EDAR-associated death domain, termed EDARADD) for the EDA:EDAR complex [12]. The same group also identified mutations in a family with autosomal recessive HED [12]. The EDARADD interacts with the intracellular death domain of EDAR, linking it to downstream signals, leading to NFκB activation [12]. EDARADD associates with TRAF 1, 2 and 3. NFκB activation by the EDAR pathway is NEMO-dependent [13], and the relevance of this interaction to human ectodermal dysplasias became clarified when loss-of-function mutations were identified in the IKKγ gene (more usually known as *NEMO*) in incontinentia pigmenti [14]. This discovery was followed by identification of less critical mutations in *NEMO* in several male patients with an unusual phenotype of HED associated with immune deficiency (EDA–ID) [13,15]. Mutations in the coding region are associated with the EDA–ID phenotype and specific mutations in the stop codon of *NEMO* cause a more severe syndrome of osteoporosis and/or lymphoedema associated with EDA–ID [13].

Two other EDAR-related members of the TNFR superfamily, X-linked ectodysplasin-A2 receptor (XEDAR) [8] and TROY/TAJ [16,17] have been reported. Signals from each of these receptors were shown to activate NFκB, providing further candidate genes and candidate signalling systems for human HED. The TNFR-associated factor 6 *(TRAF-6)* is a cytoplasmic adapter protein that links signals from members of the TNFR superfamily to activation of transcription factors such as NFκB through IKK activation. TRAF-6 –/– mice display HED, revealing yet more complexity to these signalling systems [18]. It is likely that several of these genes will, in time, be shown to have relevance in human HED.

X-linked, autosomal dominant and recessive hypohidrotic ectodermal dysplasia

The phenotypic appearances of the X-linked (MIM 305100) and autosomal types (MIM 129490 and 224900) are identical.

Definition. X-linked HED is the most common of the ectodermal dysplasias and is characterized by hypotrichosis, hypodontia, hypohidrosis and distinctive facial features. Autosomal recessive HED is clinically identical to X-linked HED and females are as severely affected as males.

Pathology. The epidermis is thin with effacement of rete ridges. Affected males have absent or sparse eccrine glands and ducts [19,21]. Hair follicles and sebaceous glands are variably reduced in number [19–21]. Apocrine glands may be absent, sparse or even normal. Mucous glands of the upper respiratory tract may be sparse or absent [19]. Light and scanning electron microscope findings of hair shaft abnormalities are variable and include longitudinal clefts or grooves and transverse fissuring. The bulb of the hair shaft is dystrophic in some individuals [22]. Radiographs of the mandible reveal dental hypoplasia or aplasia [19,23].

Clinical features

Hair. Scalp hair is sparse, fine, lightly pigmented and grows slowly. Eyebrows are scanty or absent; occasionally just the outer two-thirds are missing. The eyelashes may be normal, sparse or completely absent. Secondary sexual hair in the beard, pubic and axillary regions is variably present and may be normal. Hair on the torso and extremities is usually absent [19,20,24,25]. Approximately 70% of obligate female carriers of X-linked HED describe their hair as being sparse or fine [24].

Teeth. A wide range of dental abnormalities may be associated, ranging from complete absence of teeth (anodontia) to sparse, abnormally shaped teeth. Studies reveal a mean of 24 missing teeth, out of a total of 28, in affected males [24,26]. Dentition is delayed and the erupted teeth tend to be small, widely spaced and frequently conical or peg-shaped (Fig. 15.13). Both deciduous and permanent teeth are affected. The alveolar ridges are hypoplastic, which gives rise to full, everted lips [23,27]. About 80% of obligate female carriers of X-linked HED have distinct dental abnormalities including absent permanent teeth and small or peg-shaped teeth [24].



Fig. 15.13 Conical teeth in X-linked hypohidrotic ectodermal dysplasia. (Courtesy of Professor J. Harper, Great Ormond Street Hospital, London, UK.)

Nails. The nails are normal in most individuals.

Sweat glands. Sweating is severely diminished or absent due to a paucity or absence of eccrine glands. An absence of sweating leads to an inability to thermoregulate by evaporative cooling, and hyperthermia can occur with physical exertion or in a warm environment. Due to a lower body surface area ratio, thermoregulation is most problematic in infants and young children who may experience recurrent bouts of fever as high as 42°C. Heat intolerance does occur in older children and adults, but is less problematic as they are better able to control their body temperature by drinking cold liquids, wetting their skin or clothing and seeking out cool surroundings [24]. Up to 25% of heterozygote females experience heat intolerance and almost half notice their ability to sweat is reduced [24]. The hypohidrotic areas of skin in carrier females of X-linked HED occur in defined linear patterns corresponding to the lines of Blaschko [28].

Skin. At birth, affected males may demonstrate marked scaling or peeling of their skin which may be mistaken for a collodion membrane [29]. In children and adults, the skin is fine, smooth and dry. Periorbital hyperpigmentation and fine wrinkling around the eyes are characteristic features of the disorder. Eczema is common and is prominent in flexural areas [25,30]. Small milia-like papules may be found on the face [21,31].

Other ectodermal structures. Diminished or absent salivary glands and mucous glands of the nose, mouth and ears cause numerous otolaryngological complications including nasal obstruction caused by thick, fetid nasal discharge and adherent nasal crusts, sinusitis, recurrent upper respiratory tract infections, feeding problems in infancy, xerostomia, hoarse voice and impacted cerumen [21,30–32]. Diminished production of tear film from the lacrimal glands may cause dry eyes, photophobia and corneal damage [31,33]. A third of affected males have abnormalities of the nipples including absent, simple or accessory nipples [24,34]. Female carriers may also be affected with marked breast asymmetry, inadequate breast milk production or absence of the breast (athelia). Both pituitary and adrenal insufficiency have been reported [31].

Craniofacial features. Affected patients have a distinctive facies with relative frontal bossing, concave midface, saddle nose and everted lips [19,21,23]. Around 30% of affected males have ears that are described as simple or satyr [24]. The distinctive facial features may not be obvious at birth, but become more noticeable with age. Carrier females may exhibit similar facial features.

Other clinical features. Diminished or absent mucous glands of the tracheal, bronchial, oesophageal, gastric and colonic mucosa cause problems with recurrent bronchitis, pneumonia, dysphagia and gastro-oesophageal reflux and constipation [24,29,31]. Reactive airways associated with wheezing is a common problem [24].

Prognosis. Failure to thrive occurs in up to 40% of affected males [24]. Height and weight are compromised in early childhood but appear to normalize with time. Mortality in infancy and early childhood is historically 25%, primarily due to hyperthermia, failure to thrive and respiratory infections [27], but these figures are likely to have greatly improved in recent years.

Differential diagnosis. Affected infants with scaling skin may be misdiagnosed as collodion babies with lamellar ichthyosis. Once the characteristic facies and lack of sweating are evident, there are very few disorders to consider in the differential diagnosis. HED with hypothyroidism displays hypohidrosis with hyperthermia and hypotrichosis, but the teeth are normal, the nails are significantly dystrophic and the skin has mottled-brown areas of pigmentation [35]. Fried tooth and nail syndrome manifests hypotrichosis, hypodontia and prominent everted lips, but the sweating is normal [35]. Basan syndrome is characterized by hypotrichosis, hypodontia and hypohidrosis, but also by severe nail dystrophy and congenital absence of dermatoglyphics [24]. For the purposes of genetic counselling and reproductive planning it is possible to perform DNA-based molecular genetic diagnosis in a large number of patients. This can help to conclusively distinguish between X-linked and autosomal forms where there is no family history to indicate the mode of inheritance.

Treatment. A multidisciplinary approach is best [35]. Early diagnosis facilitates avoidance of life-threatening complications in infancy and planning of long-term management. Accurate diagnosis enables informed genetic counselling for families [36]. Female carriers may be detected in most cases by careful clinical examination for patchy distribution of scalp and body hair, sweat pores and hypodontia [30]. DNA-based molecular diagnosis on affected families can detect female carriers of X-linked HED. DNA-based prenatal diagnosis is also possible in families at risk for the disorder, but it is not widely practised.

Prevention of hyperthermia is critical. This is done by avoiding heat and physical overexertion, cooling the body with wet clothing and cool drinks and by air-conditioning home and school environments. Early dental restoration with bonding, overdentures or implants is imperative [32,37,38]. Nasal crusting and

discharge can be managed with saline nose drops and a home humidifier. Consumption of large amounts of liquids or artificial saliva preparations minimize dry mouth and swallowing difficulties [39]. Dry eyes may be treated with artificial tears. The daily use of lubricating drops facilitates the removal of impacted ear wax. Pulmonary difficulties are managed by avoidance of smoky, dusty environments, adequate humidification, and the use of chest physiotherapy and antibiotics when appropriate [40].

Future treatments may involve gene correction or administration of recombinant EDA protein. Proof of principle has been achieved in a dog model for this approach [41].

Hypohidrotic ectodermal dysplasia with immunodeficiency (EDA–ID; MIM 300291); hypohidrotic ectodermal dysplasia with immunodeficiency, osteopetrosis and lymphoedema (EDA-ID-OP; MIM 300301)

The observation of unusually severe recurrent infections in a small subset of patients with otherwise typical HED features led to the suggestion that there may be a specific syndrome of HED and immunodeficiency (EDA–ID). The EDA–ID syndrome was first reported in a boy with miliary tuberculosis [42], and the second reported case had recurrent life-threatening infections caused by *Pseudomonas aeruginosa*, *Mycobacterium avium* and cytomegalovirus [43]. A third child had a milder phenotype with repeated infections due to *Staphylococcus aureus* and *Streptococcus pneumoniae* [44], and three further siblings from a different kindred had recurrent severe infections with *Streptococcus pneumoniae*, with impaired response to polysaccharide antigens [45]. All of these cases were in males, suggesting X-linked inheritance. Further cases have extended knowledge of the phenotype, and severe life-threatening or recurrent bacterial infections have been reported in the lower respiratory tract, skin, soft tissues, bones and gastrointestinal tract, as well as meningitis and septicaemia in early childhood. Overall, the causative pathogens have most often been Gram-positive bacteria (*S. pneumoniae* and *S. aureus*), followed by Gram-negative bacteria (*Pseudomonas* spp. and *Haemophilus influenzae*) and mycobacteria. Most patients have severe hypogammaglobulinaemia, with low serum IgG levels and varied levels of other immunoglobulin isotypes (IgA, IgM and IgE) [4]. Some patients have massively elevated IgM levels [13,15,46], and an impaired antibody response to polysaccharides is the most consistent feature of this condition [4]. Impaired NK cell activity is reported in some, but not all, patients with EDA–ID [47,48]; the degree and range of immunological abnormalities seen may relate to the type of *NEMO* mutation involved.

Familial incontinentia pigmenti (incontinentia pigmenti type 2; MIM 308300)

Please see Chapter 58 for a full discussion of this condition.

References

1 Ghosh S, May MJ, Kopp EB. NF-kappa B and Rel proteins: evolutionarily conserved mediators of immune responses. *Annu Rev Immunol* 1998; **16**: 225–60.

2 Kaufman CK, Fuchs E. It's got you covered. NF-kappaB in the epidermis. *J Cell Biol* 2000; **149**: 999–1004.

3 Karin M, Ben-Neriah Y. Phosphorylation meets ubiquitination: the control of NF-[kappa]B activity. *Annu Rev Immunol* 2000; **18**: 621–63.

4 Smahi A, Courtois G, Rabia SH *et al.* The NF-kappaB signalling pathway in human diseases: from incontinentia pigmenti to ectodermal dysplasias and immune-deficiency syndromes. *Hum Mol Genet* 2002; **11**: 2371–5.

5 Gerondakis S, Grossmann M, Nakamura Y *et al.* Genetic approaches in mice to understand Rel/NF-kappaB and IkappaB function: transgenics and knockouts. *Oncogene* 1999; **18**: 6888–95.

6 Ferguson BM, Brockdorff N, Formstone E *et al.* Cloning of Tabby, the murine homolog of the human EDA gene: evidence for a membrane-associated protein with a short collagenous domain. *Hum Mol Genet* 1997; **6**: 1589–94.

7 Kere J, Srivastava AK, Montonen O *et al.* X-linked anhidrotic (hypohidrotic) ectodermal dysplasia is caused by mutation in a novel transmembrane protein. *Nat Genet* 1996; **13**: 409–16.

8 Yan M, Wang LC, Hymowitz SG *et al.* Two-amino acid molecular switch in an epithelial morphogen that regulates binding to two distinct receptors. *Science* 2000; **290**: 523–7.

9 Chen Y, Molloy SS, Thomas L *et al.* Mutations within a furin consensus sequence block proteolytic release of ectodysplasin-A and cause X-linked hypohidrotic ectodermal dysplasia. *Proc Natl Acad Sci U S A* 2001; **98**: 7218–23.

10 Barsh G. Of ancient tales and hairless tails. *Nat Genet* 1999; **22**: 315–6.

11 Headon DJ, Overbeek PA. Involvement of a novel Tnf receptor homologue in hair follicle induction. *Nat Genet* 1999; **22**: 370–4.

12 Headon DJ, Emmal SA, Ferguson BM *et al.* Gene defect in ectodermal dysplasia implicates a death domain adapter in development. *Nature* 2001; **414**: 913–6.

13 Doffinger R, Smahi A, Bessia C *et al.* X-linked anhidrotic ectodermal dysplasia with immunodeficiency is caused by impaired NF-kappaB signaling. *Nat Genet* 2001; **27**: 277–85.

14 Smahi A, Courtois G, Vabres P *et al.* Genomic rearrangement in NEMO impairs NF-kappaB activation and is a cause of incontinentia pigmenti. The International Incontinentia Pigmenti (IP) Consortium. *Nature* 2000; **405**: 466–72.

15 Zonana J, Elder ME, Schneider LC *et al.* A novel X-linked disorder of immune deficiency and hypohidrotic ectodermal dysplasia is allelic to incontinentia pigmenti and due to mutations in IKK-gamma (NEMO). *Am J Hum Genet* 2000; **67**: 1555–62.

16 Kojima T, Morikawa Y, Copeland NG *et al.* TROY, a newly identified member of the tumor necrosis factor receptor superfamily, exhibits a homology with Edar and is expressed in embryonic skin and hair follicles. *J Biol Chem* 2000; **275**: 20742–7.

17 Eby MT, Jasmin A, Kumar A *et al.* TAJ, a novel member of the tumor necrosis factor receptor family, activates the c-Jun N-terminal kinase pathway and mediates caspase-independent cell death. *J Biol Chem* 2000; **275**: 15336–42.

18 Naito A, Yoshida H, Nishioka E *et al.* TRAF6-deficient mice display hypohidrotic ectodermal dysplasia. *Proc Natl Acad Sci U S A* 2002; **99**: 8766–71.

19 Clouston H. The major forms of hereditary ectodermal dysplasia (with an autopsy and biopsies on the anhydrotic type). *Canad Med Assoc J* 1939; **40**: 1–7.

20 Weech A. Hereditary ectodermal dysplasia (congenital ectodermal defect). A report of two cases. *Am J Dis Child* 1929; **37**: 766–90.

21 Arnold ML, Rauskolb R, Anton-Lamprecht I *et al.* Prenatal diagnosis of anhidrotic ectodermal dysplasia. *Prenat Diagn* 1984; **4**: 85–98.

22 Micali G, Cook B, Blekys I *et al.* Structural hair abnormalities in ectodermal dysplasia. *Pediatr Dermatol* 1990; **7**: 27–32.

23 Vierucci S, Baccetti T, Tollaro I. Dental and craniofacial findings in hypohidrotic ectodermal dysplasia during the primary dentition phase. *J Clin Pediatr Dent* 1994; **18**: 291–7.

24 Clarke A, Phillips DI, Brown R *et al.* Clinical aspects of X-linked hypohidrotic ectodermal dysplasia. *Arch Dis Child* 1987; **62**: 989–96.

25 Reed WB, Lopez DA, Landing B. Clinical spectrum of anhidrotic ectodermal dysplasia. *Arch Dermatol* 1970; **102**: 134–43.

26 Crawford PJ, Aldred MJ, Clarke A. Clinical and radiographic dental findings in X linked hypohidrotic ectodermal dysplasia. *J Med Genet* 1991; **28**: 181–5.

27 Levin LS. Dental and oral abnormalities in selected ectodermal dysplasia syndromes. *Birth Defects Orig Artic Ser* 1988; **24**: 205–27.

28 Happle R, Frosch PJ. Manifestation of the lines of Blaschko in women heterozygous for X-linked hypohidrotic ectodermal dysplasia. *Clin Genet* 1985; **27**: 468–71.

29 The Executive and Scientific Advisory Boards of the National Foundation for Ectodermal Dysplasias M, Illinois. Scaling skin in the neonate: a clue to the early diagnosis of X-linked hypohidrotic ectodermal dysplasia (Christ-Siemens-Touraine syndrome). *J Pediatr* 1989; **114**: 600–2.

30 Clarke A. Hypohidrotic ectodermal dysplasia. *J Med Genet* 1987; **24**: 659–63.
31 Butterworth T, Ladda R. *Clinical Gendodermatology*. Westpoint, CT: Praeger; 1981: 208–17.
32 Coston GN, Salinas CF. Speech characteristics in patients with hypohidrotic ectodermal dysplasia. *Birth Defects Orig Artic Ser* 1988; **24**: 229–34.
33 Wright JT, Finley WH. X-linked recessive hypohidrotic ectodermal dysplasia. Manifestations and management. *Ala J Med Sci* 1986; **23**: 84–7.
34 Soderholm AL, Kaitila I. Expression of X-linked hypohidrotic ectodermal dysplasia in six males and in their mothers. *Clin Genet* 1985; **28**: 136–44.
35 Freire-Maia N, Pinheiro M. *Ectodermal Dysplasias: A Clinical and Genetic Study*. New York: Alan R. Liss, 1984.
36 Sybert VP. Early diagnosis in the ectodermal dysplasias. *Birth Defects Orig Artic Ser* 1988; **24**: 277–8.
37 Nowak AJ. Dental treatment for patients with ectodermal dysplasias. *Birth Defects Orig Artic Ser* 1988; **24**: 243–52.
38 Guckes AD, Brahim JS, McCarthy GR *et al*. Using endosseous dental implants for patients with ectodermal dysplasia. *J Am Dent Assoc* 1991; **122**: 59–62.
39 Myer CM, 3rd. The role of an otolaryngologist in the care of ectodermal dysplasia. *Pediatr Dermatol* 1987; **4**: 34–5.
40 Myer CM, 3rd. Otolaryngologic manifestations of the ectodermal dysplasias–clinical note. *Int J Pediatr Otorhinolaryngol* 1986; **11**: 307–10.
41 Casal ML, Lewis JR, Mauldin EA *et al.* Significant correction of disease after postnatal administration of recombinant ectodysplasin A in canine X-linked ectodermal dysplasia. *Am J Hum Genet* 2007; **81**: 1050–6.
42 Frix CD, 3rd, Bronson DM. Acute miliary tuberculosis in a child with anhidrotic ectodermal dysplasia. *Pediatr Dermatol* 1986; **3**: 464–7.
43 Sitton JE, Reimund EL. Extramedullary hematopoiesis of the cranial dura and anhidrotic ectodermal dysplasia. *Neuropediatrics* 1992; **23**: 108–10.
44 Abinun M, Spickett G, Appleton AL *et al*. Anhidrotic ectodermal dysplasia associated with specific antibody deficiency. *Eur J Pediatr* 1996; **155**: 146–7.
45 Schweizer P, Kalhoff H, Horneff G *et al*. [Polysaccharide specific humoral immunodeficiency in ectodermal dysplasia. Case report of a boy with two affected brothers]. *Klin Pediatr* 1999; **211**: 459–61.
46 Jain A, Ma CA, Liu S *et al*. Specific missense mutations in NEMO result in hyper-IgM syndrome with hypohydrotic ectodermal dysplasia. *Nat Immunol* 2001; **2**: 223–8.
47 Orange JS, Brodeur SR, Jain A *et al*. Deficient natural killer cell cytotoxicity in patients with IKK-gamma/NEMO mutations. *J Clin Invest* 2002; **109**: 1501–9.
48 Dupuis-Girod S, Corradini N, Hadj-Rabia S *et al*. Osteopetrosis, lymphedema, anhidrotic ectodermal dysplasia, and immunodeficiency in a boy and incontinentia pigmenti in his mother. *Pediatrics* 2002; **109**: e97.

TP63-related phenotypes: overview of molecular pathway

The *p53* gene family is a key regulator of the cell cycle and is mutated in more than 50% of human cancers. *p63* and *p73* are related genes that share high amino acid identity with *p53* [1–5]. The role of p63 and p73 in human cancers has been extensively studied but neither molecule is felt to play a significant role in tumorigenesis. Both p63 and p73 are distinct from p53 in that they each have a C-terminal protein–protein interacting motif (sterile-alpha-motif; SAM domain) that is not present in p53. The *p63* and *p73* genes also differ from *p53* in that they each can encode several different isoforms by utilizing two different transcription initiation sites (for review see [6]). The expression of *p63* is more restricted than the ubiquitous nature of *p53* expression and is restricted to the embryonic ectoderm and the basal regenerative layers of epithelial tissues in adults (skin, cervix, tongue, oesophagus, mammary glands, prostate and urothelium) [5]. *p63* –/– mice die at birth and have truncation of limbs (especially the forelimbs, with complete absence of phalanges and carpals), and absence of ectodermal derivatives including the epidermis and appendages (whiskers, hair etc.), the prostate, lacrimal, breast and urothelial tissues [7,8]. Limb defects are best explained by a failure of the apical ectodermal ridge to develop [8].

Mutations in *p63* have now been identified in five distinct human phenotypes, all of which have ectodermal dysplasia as a key feature. Some genotype–phenotype correlation is possible in that there is clustering of mutations in some of the phenotypes to specific sites of the p63 molecule (for review see [6]). *p63* mutations account for most cases of ectrodactyly, ectodermal dysplasia, clefting syndrome (EEC syndrome). In an authoritative paper, van Bokhoven *et al.* [9] were able to demonstrate mutations in 40 out of 43 families with EEC; all but one of these mutations were sited within the DNA-binding domain, and five amino acid residues accounted for 75% of all mutations. In ankyloblepharon–ectodermal dysplasia–clefting syndrome (AEC syndrome, also known as Hay–Wells syndrome), where the limb abnormalities are absent or minimal, mutations have been exclusively detected within the SAM domain and are associated with complex gain-of-function as well as loss- and change-of-function effects [9]. In limb–mammary syndrome (LMS), *p63* frameshift mutations leading to truncations of p63 protein have been reported in exon 13 in two unrelated patients [9], and an N-terminal mutation in a further family [6]. Mutations in acro-dermato-ungual-tooth syndrome (ADULT syndrome) have yielded interesting insights in that the first mutation was identified in exon 3′, which is only expressed in the transactivating (TA) isotypes of p63 and causes an amino acid substitution outside the DNA binding domain [10]. A subsequent report has demonstrated a mutation that confers significant transactivation activity on ΔN-p63γ, an otherwise inert isoform of p63 [6]. Non-syndromic split-hand split-foot syndrome (SHFM) is a genetically heterogeneous group of conditions, but some cases (possibly around 10%) are attributable to *p63* mutations [9]. Some of these mutations seem specific for SHFM but others underlie both EEC and SHFM [6].

The clustering of mutations in specific sites observed in the TP63-related syndromes suggests that the mechanism is due to gain-of-function rather than loss-of-function [11]. Although clustering of mutations is determined in part by the characteristics of the mutated residue, whether it is a CpG site, etc., the degree of clustering in this group of conditions suggests that each condition has a specific pathogenetic mechanism. This site-specificity also presumably suggests that the p63 protein has several functions, each with a specific site within the molecule, and that each of these functions can be disturbed in isolation from the others.

Ankyloblepharon–ectodermal dysplasia–clefting syndrome (MIM 106260)

Synonym
- Hay–Wells syndrome

Definition. Ankyloblepharon–ectodermal dysplasia–clefting (AEC) syndrome is characterized by cleft lip/palate, severe scalp erosions and abnormalities of the epidermal appendages, including hypotrichosis, hypodontia, absent or dystrophic nails and mild hypohidrosis. One distinctive feature is ankyloblepharon filiforme adnatum—partial thickness fusion of the eyelid margins.

History. In 1976, Hay and Wells described seven patients from four families with an inherited disorder characterized by congenital filiform fusion of the eyelids, dysplasia of the epidermal appendages and cleft lip/palate. Five of these original seven patients had ankyloblepharon filiforme adnatum and one had small nodules removed from her eyelids as a child, presumably remnants of spontaneously lysed ankyloblepharon [12].

Pathology. Scanning electron microscopy of the affected hair shaft shows various defects including fractures of the cuticle and pili torti, none of which is specific for the disorder [13]. Skin biopsy of involved scalp tissue shows a thin granular layer and stratum corneum. Hair follicles are reduced in size and arrector pili muscles appear hypertrophic [14]. Sweat stimulation tests reveal a patchy loss of sweat glands over most of the body [12].

Clinical features

Hair. Scalp hair is wiry, coarse and sparse; alopecia is common. The eyebrows and eyelashes are short, brittle and sparse. Body, pubic and axillary hair may be sparse or absent [12,13,15].

Teeth. Hypodontia is common. Those teeth that are present are frequently small, conical and discoloured [12,13,15,16].

Nails. Nail abnormalities are variable, even within an individual, and include distal hypoplasia and thickened hyperconvex plates. Complete absence of nails is a frequent finding [12]. Chronic paronychia has been reported [13].

Sweat glands. Heat intolerance is described by a significant number of individuals, but hyperpyrexia is not a problem [15]. Sweat pores are reduced in number in affected individuals [12].

Skin. At birth, over three-quarters of affected newborns have red, eroded, peeling skin like a collodion membrane (Fig. 15.14) [15]. This resolves over the first few weeks and the underlying skin is dry (Fig. 15.15). Over two-thirds of individuals have chronic problems with severe, recurrent scalp erosions and scalp infections which are a major feature of AEC syndrome (Fig. 15.16) [15]. Palmoplantar keratoderma was reported in four of the original seven patients described by Hay and Wells [12]. It is not a common finding in affected children but may be more pronounced in adults.

Other ectodermal structures. Ankyloblepharon filiforme adnatum (strands of epithelial tissue between the eyelids) are a cardinal feature of the disorder but are noted in only 70% of patients (Fig. 15.17) [12,13,15]. The strands may lyse spontaneously and may be difficult to detect. Lacrimal duct atresia or obstruction occurs in over half of affected individuals [15]. Supernumerary nipples may be present [13,15].

Craniofacial features. Typical craniofacial features include a broadened nasal bridge and maxillary hypoplasia (Fig. 15.18) [17]. The ears may be small and low-set, with deformities of the auricle [15]. The ear canals may be webbed and abnormally shaped [13].



Fig. 15.14 Peeling, red, parchment-like skin in a newborn with AEC syndrome. (Courtesy of Dr V.P. Sybert, Seattle, WA, USA.)



Fig. 15.15 The parchment skin resolves over the first few weeks of life and the underlying skin is dry as seen in this 1-month-old baby with AEC syndrome. (Courtesy of Dr V.P. Sybert, Seattle, WA, USA.)

Cleft lip is a variable feature but cleft palate is seen in most individuals [12,13,15].

Other abnormalities. Other features seen occasionally in AEC syndrome include cutaneous syndactyly of the second and third toes, hypospadias and vaginal dryness and erosions [15].

Prognosis. Abnormalities of the external ear canals and palate frequently cause problems with chronic otitis media and secondary hearing loss. Atresia of the lacrimal duct can lead to epiphora,



Fig. 15.16 Severe scalp erosions and extensive granulation tissue in a 5-year-old girl with AEC syndrome. (Courtesy of Dr V.P. Sybert, Seattle, WA, USA.)



Fig. 15.17 Ankyloblepharon filiforme adnaturm (strands of epithelial tissue between the eyelids) in a newborn with AEC syndrome. (Courtesy of Dr V.P. Sybert, Seattle, WA, USA.)

chronic conjunctivitis and photophobia. Scalp erosions and chronic scalp infections may be severe enough to warrant surgical intervention with skin engraftment [15]. Prenatal diagnosis may be possible in affected families by ultrasound of cleft palate/lip [18].

Differential diagnosis. CHANDS is a rare autosomal recessive ectodermal dysplasia with curly, kinky hair, hypoplastic nails and the defining feature of ankyloblepharon. It can be distinguished from AEC by absence of cleft palate and lack of typical craniofacial



Fig. 15.18 The characteristic craniofacial features of a broad nasal bridge and maxillary hypoplasia are seen in this young girl with AEC syndrome. (Courtesy of Dr V.P. Sybert, Seattle, WA, USA.)

features [19,20]. In the newborn period, the eroded, peeling skin seen in AEC syndrome may be mistaken for epidermolysis bullosa [21].

Treatment. Emollients are appropriate for the collodion-like membrane in the newborn. Neonates with AEC often have extreme skin fragility and they should be handled with extreme care. Neonatal intensive care nursing protocols such as those used for neonates with epidermolysis bullosa should be used. The ankyloblepharon filiforme adnatum may require surgical correction or may lyse spontaneously. The lacrimal duct atresia may be surgically correctable [22]. The scalp requires aggressive wound care and treatment with topical or systemic antibiotics as warranted [15]. Other abnormalities such as cleft lip/palate, hypospadias and the maxillary hypoplasia may be surgically corrected [17]. Teeth preservation and restoration is imperative [16].

Ectrodactyly, ectodermal dysplasia, clefting syndrome (EEC syndrome; MIM 12990)

Definition. The main features of the EEC syndrome are ectrodactyly (split hand or foot deformity), cleft lip/palate, tear duct anomalies and abnormalities of the epidermal appendages including hypotrichosis, hypodontia, dystrophic nails and occasional hypohidrosis.

History. The association of ectrodactyly, cleft lip/palate and ectodermal dysplasia was initially described by Rüdiger *et al*. [23] who recognized this combination of defects represents a specific syndrome termed EEC syndrome. Over 150 cases have subsequently been described [14].

Pathology. Radiographs of hand or foot deformities show missing or hypoplastic metacarpals and metatarsals [24]. Scanning

electron microscopic studies of hair shafts of affected individuals show longitudinal grooves, distorted bulbs and cuticular defects [25,26]. These findings can be seen in a number of other ectodermal dysplasias and are not specific to EEC syndrome.

Clinical features

Hair. The scalp hair is fine and sparse, light-coloured and may be wiry in texture. Eyebrows and eyelashes are short, thin and sparse. Axillary, pubic and body hair may also be affected [23–25,27].

Teeth. Teeth may be small, abnormally shaped or missing [23–25,27]. Premature loss of secondary teeth is common, presumably due to multiple caries from enamel hypoplasia.

Nails. The nail plates may be dystrophic, hypoplastic or completely absent, even when there are no bony defects of the involved digit [27,28].

Sweat glands. Sweating is usually normal, but heat intolerance is noted by a few individuals [24,27,29].

Skin. Dry skin and hyperkeratosis, particularly of the legs, are reported in some individuals [30,31]. Scalp dermatitis is seen rarely [25,31].

Other ectodermal structures. Atresia or hypoplasia of the lacrimal duct are seen in over 90% of affected individuals [14,30,32]. Secretions from the lacrimal gland may be diminished [32]. Nipple anomalies are reported in a few individuals [30].

Craniofacial features. The nose may be broad, and the chin pointed, and there may be minor variable ear anomalies, but the facies are not distinct. Cleft palate, with or without cleft lip, occurs in three-quarters of affected individuals and is a major feature of this disorder [30]. Choanal atresia has been reported [33].

Other abnormalities. Ectrodactyly (lobster claw deformity) is a major feature of this disorder and occurs in over 90% of affected individuals (Fig. 15.19). About three-quarters of individuals with ectrodactyly have both hand and foot involvement [30]. Structural abnormalities of the genitourinary tract occur in about one-third of individuals; the most common structural finding is megaureter [34,35]. Abnormalities of the external genitalia have also been described [35]. Mental retardation is a variable and uncommon feature of the disorder, occurring in less than 10% of affected individuals [30], and may be limited to those with chromosomal deletions as part of a contiguous gene syndrome. Hearing loss occurs in about 15% of individuals [30]. It is uncertain whether this is primary or secondary to recurrent otitis media. Isolated growth hormone deficiency has been reported in one individual [36].

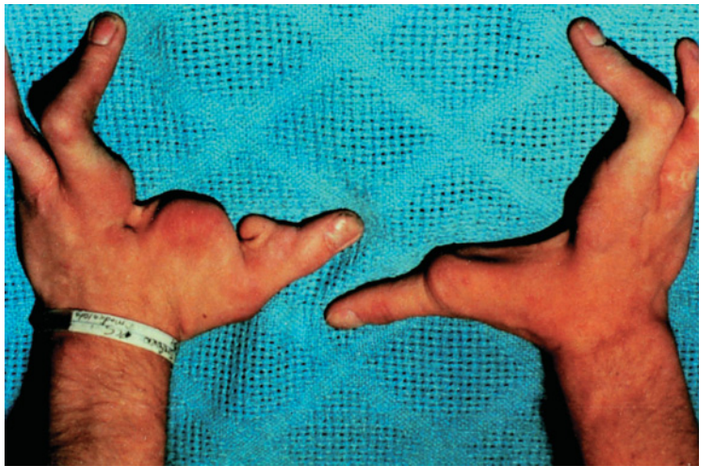


Fig. 15.19 Ectrodactyly of the hands in a young man with EEC syndrome. (Courtesy of Dr V.P. Sybert, Seattle, WA, USA.)

Prognosis. A significant number of affected individuals experience epiphora, conjunctivitis and blepharitis as a result of lacrimal duct hypoplasia. Photophobia, corneal ulcers and corneal scarring and perforation, may occur as a result of lacrimal gland hypoplasia [32]. Recurrent urinary tract infections, both symptomatic and asymptomatic, may be a problem in individuals with genitourinary anomalies [34].

Differential diagnosis. A few other ectodermal dysplasias manifest limb abnormalities and cleft palate/lip. Although clefting is not a constant feature, odentotrichomelic syndrome may be differentiated by severe tetramelic reductions and autosomal recessive mode of inheritance [14]. Other rare syndromes such as Martinez syndrome, Zlotogora–Ogur syndrome and Rosselli–Gulienetti syndrome can be differentiated from EEC by specific limb abnormalities and mode of inheritance (see Table 15.3).

Treatment. Treatment involves surgical correction of the cleft lip/palate, lacrimal duct, limb defects and genitourinary abnormalities, as indicated. DNA-based prenatal diagnosis is available for selected families where the gene defect is known.

Acro-dermato-ungual–tooth (ADULT syndrome; MIM 103285)

Acro-dermato-ungual–tooth syndrome is a rare condition distinguished from EEC syndrome by an absence of facial clefting. Patients have, in addition, excessive freckling and exfoliative dermatitis of the digits [37].

Limb mammary syndrome (LMS; MIM 603543)

This previously unrecognized autosomal dominant syndrome was reported in a Dutch family with a constellation of features that had not previously been reported. The major features were a combination of hand and foot anomalies and mammary gland aplasia/hypoplasia. The skin and hair were normal in all affected individuals, but some had lacrimal duct atresia, nail dysplasia, hypohidrosis, hypodontia or cleft palate [6]. LMS is distinguished from EEC syndrome by the consistent finding of mammary anomalies in LMS (infrequent in EEC) and the much more frequent finding of skin, nail and tooth anomalies in EEC syndrome. The clefting in LMS is of the palate only, whereas in EEC syndrome the lip and palate are affected [6].

Non-syndromic split hand–split foot syndrome (SHFM; MIM 183600)

This condition has no dermatological features and therefore is not discussed in detail here.

Defects in transcription factors other than p63

In addition to the p63 pathway, several other EDs have now been attributed to defects in transcription factors that control the expression of several target genes important in ectodermal morphogenesis. In many cases, positional cloning studies have yielded the primary mutation in a specific gene but the detailed molecular signalling pathways have yet to be delineated. Ellis van Creveld syndrome (EvC) is a recessive ED that is characterized by a skeletal dysplasia with short limbs, short ribs, postaxial polydactyly and congenital heart defects [38]. The gene has recently been identified [39] and the function, although not fully characterized, is most likely a transcription factor, given the hypothetical structural characteristics (nuclear localization, two DNA-binding domains, leucine-rich zipper domain). Witkop syndrome (MIM 189500) is an autosomal dominant ED with primary manifestation in the teeth (taurodontia, partial or complete anodontia) and nails (koilonychia, longitudinal ridging, and nail pits) [40]. Mutations have been identified in the *MSX1* gene, a member of the homeobox gene family and an important regulator of transcription [40].

Of the EDs more likely to be seen by a dermatologist, trichodentoosseous (TDO) syndrome and trichorhinophalangeal (TRPS) syndrome have both been attributed to mutations in transcription factors. The causative gene for TDO is *DLX3* [41], a homeodomain transcription factor that is developmentally expressed in many structures derived from epithelial–mesenchymal interactions, such as teeth, hair follicles and limb buds [42]. The *TRPS1* gene underlies TRPS types I and III [43], and a microdeletion syndrome (8q42.11 to 8q24.1), that includes *TRPS1* and *EXT1*, underlies TRPS type II [44,45]. Computer analysis of *TRPS1* suggests that it is a novel transcription factor with an unusual composition of nine putative zinc-finger motifs of four different types [46]. All of the mutations in *TRPS1* probably act as loss-of-function mutations, meaning that haploinsufficiency is the likely mechanism in TRPS.

TDO and TRPS are discussed in detail below.

Trichodentoosseus syndrome (MIM 190320)

Definition. TDO syndrome is a well-defined ectodermal dysplasia, with kinky hair, hypoplasia of tooth enamel and asymptomatic sclerotic bone changes.

History. Lichtenstein *et al.* [47] defined the features of this disorder in 107 individuals and proposed the name tricho-dento-osseous (TDO) syndrome. Robinson and Miller [48] were the first authors to describe this syndrome, but did not detect bone involvement as part of the disorder. Some authors argue that the clinical manifestations observed in some families are varied enough to suggest genetic heterogeneity, and they classify TDO syndrome into three subtypes differing from each other primarily by the degree of bone involvement [49,50]. Other authors consider that variable expression of a single gene seems a more plausible explanation [51].

Pathology. On dental radiographs, unerupted teeth and taurodontia (increased size of the tooth pulp chamber) are found [52]. Scanning electron microscopic analysis of affected teeth shows pits and depressions in the tooth enamel, uniformly thin tooth enamel, and an abnormal collagenous membrane around the open apices [53]. Radiographs of the skull reveal sclerosis and sometimes thickening of the calvarium. The long bones may also be sclerotic [51].

Clinical features [47,48,50,51,53]

Hair. At birth, the scalp hair is thick and kinky or curly; it may straighten in later life. The eyelashes may also be curly.

Teeth. Teeth abnormalities are present in all patients and include pitted, hypoplastic enamel with brownish-yellow discoloration of both primary and permanent teeth, and taurodontia. Tooth eruption may be delayed, and abscesses are common. Dental caries occurs and leads to early loss of teeth.

Nails. Fingernails are thin, brittle and peel readily. Toenails may be thickened or normal.

Sweat glands. Sweating abnormalities are not found in this disorder.

Skin. The skin is normal and other ectodermal structures are normal.

Craniofacial features. There is frontal bossing, the jaw is square and the head is elongated. Partial premature fusion of the cranial sutures occurs in three-quarters of affected individuals. The bones of the skull are radiographically dense and may be thick. This is not problematic for the patient and may be found incidentally when radiographs of the skull are obtained for unrelated reasons.

Other abnormalities. Clinodactyly is rarely seen.

Prognosis. Affected individuals are healthy, but lose most of their teeth by the age of 30 years [47].

Differential diagnosis. Curly hair and nail dysplasia is also seen in CHANDS syndrome (curly hair, ankyloblepharon and nail dysplasia), but ankyloblepharon makes this disorder distinct. Tooth and nail syndrome lacks kinky or curly hair.

Treatment. This includes appropriate dental restoration.

Trichorhinophalangeal syndrome type I (MIM 190350), type II (MIM 150230) and type III (MIM 190531)

Synonyms

- Langer–Giedion syndrome; MIM 150230
- Sugio–Kajii syndrome; MIM 190531

Definition. The trichorhinophalangeal syndrome (TRPS) is characterized by sparse scalp hair, bulbous, pear-shaped nose, small teeth with dental malocclusion, thin nails, cone-shaped epiphyses, short stature and occasional skeletal abnormalities.

Clinical features [54,55]

Hair. The hair is usually fine, blond and sparse; the most prominently affected areas are the fronto-temporal areas. The eyebrows are sparse or absent.

Teeth. Dental abnormalities are frequent, with supernumerary incisors, microdontia and poorly aligned teeth.

Nails. The nails are occasionally thin and short, with long longitudinal grooves. They can be flattened, koilonychia-like and normal in colour. 'Racket' thumbnails have been described.

Sweat glands and skin. There are no abnormalities of sweat glands or skin.

Other ectodermal structures. There is occasional exotropia and photophobia.

Craniofacial features. Many patients have a characteristic facies, with a pear-shaped nose, a long and wide philtrum, and large, prominent ears. A narrow palate is often noted.

Other features. Short stature is common, and a wide range of skeletal abnormalities have been described including brachymesophalangy, brachymetacarpy, brachymetatarsy and peripheral dysostosis, with type 12 cone-shaped epiphyses on some of the middle phalanges of the hands. Joints are often thickened, ulnar and radial deviation of the fingers is seen, and there are occasional abnormalities such as clinodactyly, winged scapulae and coxa valga. Perthes-like abnormalities have been reported in a few cases [56]. Chest wall deformities, such as pectus carinatum, lordosis or kyphoscoliosis are occasional features.

Type II TRPS shares many characteristics with types I and III, but is more significantly associated with mental retardation. In addition, there are multiple cutaneous exostoses and markedly redundant or loose skin, and more marked joint laxity. Type III TRPS differs from type I by the presence of severe brachydactyly, due to short metacarpals, and more severe short stature [57,58]. There is an emerging genotype–phenotype correlation in that mutations in the GATA DNA-binding zinc finger seem to predict a type III phenotype, whereas mutations elsewhere in *TRPS1* are associated with TRPS type I [59].

References

1 Jost CA, Marin MC, Kaelin WG Jr. p73 is a simian [correction of human] p53-related protein that can induce apoptosis. *Nature* 1997; **389**: 191–4.

2 Kaghad M, Bonnet H, Yang A *et al*. Monoallelically expressed gene related to p53 at 1p36, a region frequently deleted in neuroblastoma and other human cancers. *Cell* 1997; **90**: 809–19.

3 Osada M, Ohba M, Kawahara C *et al*. Cloning and functional analysis of human p51, which structurally and functionally resembles p53. *Nat Med* 1998; **4**: 839–43.

4 Senoo M, Seki N, Ohira M *et al*. A second p53-related protein, p73L, with high homology to p73. *Biochem Biophys Res Commun* 1998; **248**: 603–7.

5 Yang A, Kaghad M, Wang Y *et al*. *p63*, a *p53* homolog at 3q27-29 encodes multiple products with transactivating, death-inducing, and dominant-negative activities. *Mol Cell* 1998; **2**: 305–16.

6 Brunner HG, Hamel BC, van Bokhoven H. P63 gene mutations and human developmental syndromes. *Am J Med Genet* 2002; **112**: 284–90.

7 Mills AA, Zheng B, Wang X-J *et al*. *p63* is a *p53* homolog required for limb and epidermal morphogenesis. *Nature* 1999; **398**: 708–13.

8 Yang A, Schweizer R, Sun D *et al*. p63 is essential for regenerative proliferation in limb, craniofacial and epithelial development. *Nature* 1999; **398**: 7147–8.

9 van Bokhoven H, Hamel BC, Bamshad M *et al*. p63 Gene mutations in eec syndrome, limb-mammary syndrome, and isolated split hand-split foot malformation suggest a genotype-phenotype correlation. *Am J Hum Genet* 2001; **69**: 481–92.

10 Amiel J, Bougeard G, Francannet C *et al*. TP63 gene mutation in ADULT syndrome. *Eur J Hum Genet* 2001; **9**: 642–5.

11 Cummings CJ, Zoghbi HY. Fourteen and counting: unravelling trinucleotide repeat diseases. *Hum Mol Genet* 2000; **9**: 909–16.

12 Hay RJ, Wells RS. The syndrome of ankyloblepharon, ectodermal defects and cleft lip and palate: an autosomal dominant condition. *Br J Dermatol* 1976; **94**: 277–89.

13 Greene SL, Michels VV, Doyle JA. Variable expression in ankyloblepharon-ectodermal defects-cleft lip and palate syndrome. *Am J Med Genet* 1987; **27**: 207–12.

14 Fosko SW, Stenn KS, Bolognia JL. Ectodermal dysplasias associated with clefting: significance of scalp dermatitis. *J Am Acad Dermatol* 1992; **27**: 249–56.

15 Vanderhooft SL, Stephan MJ, Sybert VP. Severe skin erosions and scalp infections in AEC syndrome. *Pediatr Dermatol* 1993; **10**: 334–40.

16 Rule DC, Shaw MJ. The dental management of patients with ankyloblepharon (AEC) syndrome. *Br Dent J* 1988; **164**: 215–8.

17 Satoh K, Tosa Y, Ohtsuka S *et al*. Ankyloblepharon, ectodermal dysplasia, cleft lip and palate (AEC) syndrome: surgical corrections with an 18-year follow-up including maxillary osteotomy. *Plast Reconstr Surg* 1994; **93**: 590–4.

18 Bronshtein M, Gershoni-Baruch R. Prenatal transvaginal diagnosis of the ectrodactyly, ectodermal dysplasia, cleft palate (EEC) syndrome. *Prenat Diagn* 1993; **13**: 519–22.

19 Baughman FA Jr. CHANDS: the curly hair-ankyloblepharon-nail dysplasia syndrome. *Birth Defects Orig Artic Ser* 1971; **7**: 100–2.

20 Toriello HV, Lindstrom JA, Waterman DF *et al*. Re-evaluation of CHANDS. *J Med Genet* 1979; **16**: 316–7.

21 Taieb A, Legrain V, Surleve-Bazeille JE *et al*. Generalized epidermolysis bullosa with congenital synechiae, associated malformations and unusual ultrastructure: a new entity? *Dermatologica* 1988; **176**: 76–82.

22 Hicks C, Pitts J, Rose GE. Lacrimal surgery in patients with congenital cranial or facial anomalies. *Eye* 1994; **8**: 583–91.

23 Rüdiger RA, Haase W, Passarge E. Association of ectrodactyly, ectodermal dysplasia, and cleft lip-palate. *Am J Dis Child* 1970; **120**: 160–3.

24 Bixler D, Spivack J, Bennett J *et al*. The ectrodactyly-ectodermal dysplasia-clefting (EEC) syndrome. Report of 2 cases and review of the literature. *Clin Genet* 1972; **3**: 43–51.

25 Trueb RM, Bruckner-Tuderman L, Wyss M *et al*. Scalp dermatitis, distinctive hair abnormalities and atopic disease in the ectrodactyly-ectodermal dysplasia-clefting syndrome. *Br J Dermatol* 1995; **132**: 621–5.

26 Micali G, Cook B, Blekys I *et al*. Structural hair abnormalities in ectodermal dysplasia. *Pediatr Dermatol* 1990; **7**: 27–32.

27 Kuster W, Majewski F, Meinecke P. EEC syndrome without ectrodactyly? Report of 8 cases. *Clin Genet* 1985; **28**: 130–5.

28 Rosenmann A, Shapira T, Cohen MM. Ectrodactyly, ectodermal dysplasia and cleft palate (EEC syndrome). Report of a family and review of the literature. *Clin Genet* 1976; **9**: 347–53.

29 Richieri-Costa A, de Vilhena-Moraes SA, Ferrareto I *et al*. Ectodermal dysplasia/ectrodactyly in monozygotic female twins. Report of a case-review and comments on the ectodermal dysplasia/ectrodactyly (cleft lip/palate) syndromes. *Rev Brasil Genet* 1986; **9**: 349–74.

30 Rodini ES, Richieri-Costa A. EEC syndrome: report on 20 new patients, clinical and genetic considerations. *Am J Med Genet* 1990; **37**: 42–53.

31 Trueb RM, Bruckner-Tuderman L, Burg G. Ectrodactyly-ectodermal dysplasia-clefting syndrome with scalp dermatitis. *J Am Acad Dermatol* 1993; **29**: 505–6.

32 McNab AA, Potts MJ, Welham RA. The EEC syndrome and its ocular manifestations. *Br J Ophthalmol* 1989; **73**: 261–4.
33 Christodoulou J, McDougall PN, Sheffield LJ. Choanal atresia as a feature of ectrodactyly-ectodermal dysplasia-clefting (EEC) syndrome. *J Med Genet* 1989; **26**: 586–9.
34 Nardi AC, Ferreira U, Netto Junior NR *et al*. Urinary tract involvement in EEC syndrome: a clinical study in 25 Brazilian patients. *Am J Med Genet* 1992; **44**: 803–6.
35 Rollnick BR, Hoo JJ. Genitourinary anomalies are a component manifestation in the ectodermal dysplasia, ectrodactyly, cleft lip/palate (EEC) syndrome. *Am J Med Genet* 1988; **29**: 131–6.
36 Knudtzon J, Aarskog D. Growth hormone deficiency associated with the ectrodactyly-ectodermal dysplasia-clefting syndrome and isolated absent septum pellucidum. *Pediatrics* 1987; **79**: 410–2.
37 Propping P, Zerres K. ADULT-syndrome: an autosomal-dominant disorder with pigment anomalies, ectrodactyly, nail dysplasia, and hypodontia. *Am J Med Genet* 1993; **45**: 642–8.
38 Ellis RWB, van Creveld S. A syndrome characterized by ectodermal dysplasia, polydactyly, chondrodysplasia and congenital morbus cordis: report of three cases. *Arch Dis Child* 1940; **15**: 65–84.
39 Ruiz-Perez VL, Ide SE, Strom TM *et al*. Mutations in a new gene in Ellis-van Creveld syndrome and Weyers acrodental dysostosis. *Nat Genet* 2000; **24**: 283–6.
40 Jumlongras D, Bei M, Stimson JM *et al*. A nonsense mutation in MSX1 causes Witkop syndrome. *Am J Hum Genet* 2001; **69**: 67–74.
41 Price JA, Bowden DW, Wright JT *et al*. Identification of a mutation in DLX3 associated with tricho-dento-osseous (TDO) syndrome. *Hum Mol Genet* 1998; **7**: 563–9.
42 Robinson GW, Mahon KA. Differential and overlapping expression domains of Dlx-2 and Dlx-3 suggest distinct roles for Distal-less homeobox genes in craniofacial development. *Mech Dev* 1994; **48**: 199–215.
43 Momeni P, Glockner G, Schmidt O *et al*. Mutations in a new gene, encoding a zinc-finger protein, cause tricho-rhino-phalangeal syndrome type I. *Nat Genet* 2000; **24**: 71–4.
44 Ludecke HJ, Wagner MJ, Nardmann J *et al*. Molecular dissection of a contiguous gene syndrome: localization of the genes involved in the Langer-Giedion syndrome. *Hum Mol Genet* 1995; **4**: 31–6.
45 Hou J, Parrish J, Ludecke HJ *et al*. A 4-megabase YAC contig that spans the Langer-Giedion syndrome region on human chromosome 8q24.1: use in refining the location of the trichorhinophalangeal syndrome and multiple exostoses genes (TRPS1 and EXT1). *Genomics* 1995; **29**: 87–97.
46 Dai KS, Liew CC. Characterization of a novel gene encoding zinc finger domains identified from expressed sequence tags (ESTs) of a human heart cDNA database. *J Mol Cell Cardiol* 1998; **30**: 2365–75.
47 Lichtenstein J, Warson R, Jorgenson R *et al*. The tricho-dento-osseous (TDO) syndrome. *Am J Hum Genet* 1972; **24**: 569–82.
48 Robinson GC, Miller JR. Hereditary enamel hypoplasia: its association with characteristic hair structure. *Pediatrics* 1966; **37**: 498–502.
49 Freire-Maia N, Pinheiro M. *Ectodermal Dysplasias: A Clinical and Genetic Study*. New York: Alan R. Liss, 1984.
50 Shapiro SD, Quattromani FL, Jorgenson RJ *et al*. Tricho-dento-osseous syndrome: heterogeneity or clinical variability. *Am J Med Genet* 1983; **16**: 225–36.
51 Quattromani F, Shapiro SD, Young RS *et al*. Clinical heterogeneity in the tricho-dento-osseous syndrome. *Hum Genet* 1983; **64**: 116–21.
52 Levin LS. Dental and oral abnormalities in selected ectodermal dysplasia syndromes. *Birth Defects Orig Artic Ser* 1988; **24**: 205–27.
53 Melnick M, Shields ED, El-Kafrawy AH. Tricho-dento-osseous syndrome: a scanning electron microscopic analysis. *Clin Genet* 1977; **12**: 17–27.
54 Giedion A, Burdea M, Fruchter Z *et al*. Autosomal dominant transmission of the tricho-rhino-phalangeal syndrome. Report of 4 unrelated families, review of 60 cases. *Helv Paediatr Acta* 1973; **28**: 249–59.
55 Beals RK. Tricho-rhino-phalangeal dysplasia. Report of a kindred. *J Bone Joint Surg Am* 1973; **55**: 821–6.
56 Sugiura Y. Tricho-rhino-phalangeal syndrome associated with Perthes-disease-like bone change and spondylolisthesis. *Jinrui Idengaku Zasshi* 1978; **23**: 23–30.
57 Sugio Y, Kajii T. Ruvalacaba syndrome: autosomal dominant inheritance. *Am J Med Genet* 1984; **19**: 741–53.
58 Niikawa N, Kamei T. The Sugio-Kajii syndrome, proposed tricho-rhino-phalangeal syndrome type III. *Am J Med Genet* 1986; **24**: 759–60.
59 Ludecke HJ, Schaper J, Meinecke P *et al*. Genotypic and phenotypic spectrum in tricho-rhino-phalangeal syndrome types I and III. *Am J Hum Genet* 2001; **68**: 81–91.

Defects in gap junction proteins

Gap junctions facilitate efficient cell–cell communication between all cells in multicellular organisms. This system facilitates a synchronized cellular response to a variety of intercellular signals by regulating the direct passage of low-molecular-weight metabolites (<1000 Da) and ions between the cytoplasm of adjacent cells [1]. In humans, gap junction channels are formed by a polygenic family of 20 different connexin proteins with a predicted molecular mass of 25–62 kDa. Six connexin units oligomerize to rosette-like hemichannels (connexons) that dock end-to-end with an opposing cell. Connexins are integral membrane proteins that couple with four α-helical transmembrane domains, two rigid extracellular domains that couple with those of a partner connexon, and three cytoplasmic portions of variable length and sequence that determine connexin specificity and selective channel properties. Gap junction channels may be composed of two similar hemichannels formed by the same type of connexin (homotypic) or two distinct hemichannels, each formed by a different connexin protein (heterotypic). In addition, each connexon could be assembled from different connexin subunits (heterotypic heterochannels). Each combination of connexins has different qualities of permeability and this is likely highly significant in terms of function. Most cell types express more than one type of connexin, but the skin and inner ear have a particularly high number of gap junctions and utilize up to 10 of the 20 different connexin proteins. In the skin, they appear to have a role in the coordination of keratinocyte growth and differentiation [2]. Connexins may be classified in three major groups (*GJA*, *GJB* and *GJC*) based on sequence homology. Mutations in connexins result in hereditary peripheral neuropathy, complex conotruncal heart malformations, autosomal dominant forms of cataract and hearing loss. The first connexin mutations associated with skin disease were identified in *GJB3*, encoding Cx31, leading to erythrokeratoderma variabilis [3]. Mutations associated with distinct skin phenotypes were subsequently identified in three additional connexins, *GJB3*, *GJB4* and *GJB6*, encoding the β connexins Cx26, Cx30.3 and Cx30, respectively [4,5]. Most of these connexins are also expressed in the inner ear, and the relationship between epidermal disease and deafness is complex—three out of the four autosomal dominant connexin mutations that are associated with epidermal disease are also associated with hearing loss.

In 1996, Clouston's syndrome was linked to chromosome 13q11-q12.1 [6], and subsequent studies have shown genetic homogeneity to this locus [7–9]. Mutations in *GJB6*, encoding the connexin Cx30, were identified in all available kindreds [10]. Several dominant-negative mutations have now been identified within the amino-terminus and transmembrane domains of Cx30. Mutations in *GJB6* had previously been identified in a small family with dominant non-syndromic hearing loss [11], emphasizing the complexity and diversity of phenotypes caused by dominant-acting connexin mutations. Several dominant-negative mutations have

been reported within the first extracellular loop and in the cytoplasmic aminoterminus of the closely related Cx26 in patients with the keratitis–ichthyosis–deafness (KID) syndrome [12]. A D50N mutation in Cx26 is particularly common. Mutations in Cx26 had previously been documented in patients with the mutilating keratoderma Vohwinkel's syndrome (see below). To emphasize the overlap in genotype–phenotype correlation in the connexin disorders, patients carrying identical mutations in Cx30 (V37E) have been shown to have classical Clouston's syndrome [13] and a KID syndrome-like phenotype. The role of connexins in ectodermal dysplasias was further expanded with the identification of mutations in the α connexin, *GJA1*, encoding Cx43 in oculodentodigital dysplasia [14].

Clouston's syndrome (MIM 129500)

Synonym
- Hidrotic ectodermal dysplasia

Definition. Hidrotic ectodermal dysplasia is an autosomal dominant ectodermal dysplasia defined by generalized hypotrichosis, dystrophic nails and hyperkeratosis of the palms and soles.

History. This distinct ectodermal dysplasia is named after Clouston, a doctor in Quebec, Canada, who defined much of what we know about the disorder [15,16]. Several reports describe a large kindred originally from France, who then migrated to Canada, the USA and Scotland [15–19]. Five generations of a large Malaysian-Chinese kindred have also been reported [20].

Pathology. Various abnormal physical properties of the hair shaft have been found, including low disulphide-bonded protein content, increased water content, altered birefringence in polarized light, reduced elastic modulus and reduced tensile strength. The hair shaft is abnormally shaped; it may be twisted, small, have longitudinal grooves and be square in cross-section. The pigment may be absent [21]. Cells of the cuticle are atrophic or even absent near the tips of the hair shafts, although relatively normal near the base. The cortex of the hair shaft is more fibrillar, coarse and disorganized compared with normal hair shafts [21]. Hair follicles in skin biopsies are reduced in number, and when present may appear dystrophic, with thickened connective tissue sheaths surrounding them [22]. Sebaceous glands are sparse and apocrine glands are sparse or absent. Eccrine glands are normal in number; in one affected individual, a single, rather than a double, layer of eccrine ductal cells was present [22]. Skin biopsy of the palmoplantar thickening shows acanthosis, orthohyperkeratosis and hypergranulosis [22].

Clinical features

Hair. Scalp hair is sparse, fine, brittle, pale in colour and slow growing (Fig. 15.20). Hair loss may become more pronounced over time and total alopecia can occur. The eyebrows and eyelashes are thin or absent. Body, pubic and axillary hair are also affected.

Teeth. The teeth are normal but caries is common.



Fig. 15.20 The scalp hair is sparse, fine and brittle in this woman with hidrotic ectodermal dysplasia. (Courtesy of Dr V.P. Sybert, Seattle, WA, USA.)



Fig. 15.21 The nail plates are thick, short and discolored in this individual with hidrotic ectodermal dysplasia. (Courtesy of Dr V.P. Sybert, Seattle, WA, USA.)

Nails. Nail dystrophy is characteristic of HED but can be variable. Generally, the nail plate is short, thick, slow growing and discolored (Fig. 15.21). The nail plate may be completely absent. Frequent infections of the nail folds can occur.

Sweat glands. Sweating is normal in affected individuals.

Skin. The skin tends to be dry and rough; it is unclear how this is related to the paucity of sebaceous glands described in some



Fig. 15.22 Diffuse palmoplantar hyperkeratosis is seen frequently in hidrotic ectodermal dysplasia. This individual exhibits mild plantar hyperkeratosis. (Courtesy of Dr V.P. Sybert, Seattle, WA, USA.)

affected individuals. Diffuse, stippled palmar and plantar hyperkeratosis is a frequent finding (Fig. 15.22), and can be severe. It may extend onto the dorsum of the hands and feet, and fissuring can occur. The skin may also be thickened over the knees, elbows, joints of the fingers and knuckles. Localized hyperpigmentation of the skin is a striking finding and may occur over the knuckles, elbows, axillae, areolae and bony prominences. In the original kindred, cutaneous carcinomas of the nail bed and palmar tissue were observed in several affected individuals [15,16].

Other ectodermal structures. Various eye abnormalities have been described, including conjunctivitis, strabismus and congenital cataract. In one family, five affected individuals developed bilateral premature cataracts [23]. Oral leukoplakia has been described in a number of families [24,25]. Diffuse eccrine poromatosis was reported in one patient [26]. Sensorineural hearing loss has rarely been reported.

Craniofacial features. There are no characteristic craniofacial features. Thickened skull bones have been described.

Other features. Tufting of the terminal phalanges was described in Clouston's original report [15].

Prognosis. The nail and skin dystrophies can become more pronounced over time. Physical development and life span are unaffected.

Differential diagnosis. Pachyonychia congenita shares the features of palmoplantar hyperkeratosis, oral leukoplakia and thickened, discolored nails, but the hair is usually normal and the teeth erupt prematurely [24,27]. Individuals with Coffin–Siris syndrome have sparse hair and absent or hypoplastic nails, most notably the fifth fingernail and toenail. They lack the palmoplantar hyperkeratosis, their facial features are characteristic and they have associated mental retardation [24].

Treatment. Nail ablation may sometimes be necessary, emollients for hyperkeratosis sometimes helpful and artificial hair pieces useful in some individuals.

Keratitis ichthyosis and deafness syndrome (MIM 242150)

Definition. The constellation of vascularizing keratitis, ichthyosiform hyperkeratosis and neurosensory deafness are the characteristic features of KID syndrome. This was probably first reported as early as 1915 [28], with the acronym being coined relatively recently in 1981 [29]. There is a broad clinical spectrum of manifestations.

Pathology. Biopsy of skin shows non-specific acanthosis with papillomatosis and basketweave hyperkeratosis. Hair follicles may be atrophic.

Clinical features

Hair. Alopecia occurs in 80% of patients, ranging from minimal loss of eyebrows or eyelashes to total scalp alopecia; in 25% of patients, the alopecia is congenital. An additional 17% of patients have sparse, fine hair without frank alopecia.

Teeth. No abnormalities.

Nails. Nails are dystrophic in the majority of patients.

Sweat glands. Sweating may be decreased or absent.

Skin. Patients with KID syndrome are usually born with erythematous or erythrokeratodermatous skin that is mildly scaling; in 7% of patients these skin features develop during the first 4 weeks of life [30]. The sharply demarcated, erythematous plaques are symmetrically distributed on the face and extremities. The characteristic thick, leathery skin with tiny stippled papules develops during the first year of life, particularly during the first 3 months. Well-defined, verrucous, hyperkeratotic plaques develop in 90% of patients, often localized to the face and limbs. Diffuse palmoplantar hyperkeratosis with a stippled or leathery pattern also occurs in almost all patients; occasionally, knuckle pads are noted. After puberty, follicular occlusion syndrome, occasionally with severe acne, may develop, accompanied by sinuses in the axillae, groins and perianal region.

Other ectodermal structures. Ophthalmological features are progressive, and most commonly develop in childhood or early adolescence, although photophobia from birth has been described. The keratoconjunctivitis sicca with corneal vascularization leads to pannus formation and markedly decreased visual acuity.

Craniofacial features. There are no characteristic cranioectodermal features.

Other features. The hearing loss is neurosensory, congenital and non-progressive. It can be detected in the neonate by brainstem-evoked auditory potential testing. Approximately 45%

of patients have recurrent infections, especially bacterial and candidal infections of the skin, auditory canals and eyes. Some patients have shown evidence of immunodeficiency, with moderate increases in IgE levels, defective chemotaxis, and absent lymphocyte proliferative responses to *Candida albicans* [31]. Squamous cell carcinoma of the skin and of the tongue have been described in more than 10% of patients, and may occur during childhood.

Prognosis. Ophthalmological manifestations are progressive. The hearing loss is generally not felt to change with time, but in this author's experience progressive hearing loss may occur. Vigilance is required for development of squamous carcinoma.

Differential diagnosis. The stippled palmoplantar keratoderma and alopecia are reminiscent of Clouston's syndrome.

Treatment. Therapy is supportive. Corneal transplants have been successfully performed to treat corneal vascularization. Cochlear implants [32] have been used to treat the hearing loss, but the sustainability of these in persons with such abnormally healing skin has yet to be proven. Oral fluconazole therapy of recalcitrant fungating candidiasis resulted in complete resolution and remission for at least a year [33].

References

1 Pitts JD. The discovery of metabolic co-operation. *Bioessays* 1998; **20**: 1047–51.
2 Choudhry R, Pitts JD, Hodgins MB. Changing patterns of gap junctional intercellular communication and connexin distribution in mouse epidermis and hair follicles during embryonic development. *Dev Dyn* 1997; **210**: 417–30.
3 Richard G, Smith LE, Bailey RA *et al*. Mutations in the human connexin gene GJB3 cause erythrokeratodermia variabilis. *Nat Genet* 1998; **20**: 366–9.
4 Kelsell DPWL, Houseman MJ. Connexin mutations in skin disease and hearing loss. *Am J Hum Genet* 2001; **68**: 559–68.
5 Richard G. Connexins: a connection with the skin. *Exp Dermatol* 2000; **9**: 77–96.
6 Kibar Z, Der Kaloustian VM, Brais B *et al*. The gene responsible for Clouston hidrotic ectodermal dysplasia maps to the pericentromeric region of chromosome 13q. *Hum Mol Genet* 1996; **5**: 543–7.
7 Radhakrishna U, Blouin JL, Mehenni H *et al*. The gene for autosomal dominant hidrotic ectodermal dysplasia (Clouston syndrome) in a large Indian family maps to the 13q11–q12.1 pericentromeric region. *Am J Med Genet* 1997; **71**: 80–6.
8 Taylor TD, Hayflick SJ, McKinnon W *et al*. Confirmation of linkage of Clouston syndrome (hidrotic ectodermal dysplasia) to 13q11–q12.1 with evidence for multiple independent mutations. *J Invest Dermatol* 1998; **111**: 83–5.
9 Kibar Z, Dube MP, Powell J *et al*. Clouston hidrotic ectodermal dysplasia (HED): genetic homogeneity, presence of a founder effect in the French Canadian population and fine genetic mapping. *Eur J Hum Genet* 2000; **8**: 372–80.
10 Lamartine J, Munhoz Essenfelder G, Kibar Z *et al*. Mutations in GJB6 cause hidrotic ectodermal dysplasia. *Nat Genet* 2000; **26**: 142–4.
11 Grifa A, Wagner CA, D'Ambrosio L *et al*. Mutations in GJB6 cause nonsyndromic autosomal dominant deafness at DFNA3 locus. *Nat Genet* 1999; **23**: 16–8.
12 Richard G, Rouan F, Willoughby CE *et al*. Missense mutations in GJB2 encoding connexin-26 cause the ectodermal dysplasia keratitis–ichthyosis–deafness syndrome. *Am J Hum Genet* 2002; **70**: 1341–8.
13 Smith FJD, Morely SM, McLean WH. A novel connexin 30 mutation in Clouston syndrome. *J Invest Dermatol* 2002; **118**: 530–2.
14 Paznekas WA, Boyadjiev SA, Shapiro RE *et al*. Connexin 43 (GJA1) mutations cause the pleiotropic phenotype of oculodentodigital dysplasia. *Am J Hum Genet* 2003; **72**: 408–18.
15 Clouston H. A hereditary ectodermal dystrophy. *Can Med Assoc J* 1929; **21**: 18–31.
16 Clouston H. The major forms of hereditary ectodermal dysplasia (with an autopsy and biopsies on the anhydrotic type). *Canad Med Assoc J* 1939; **40**: 1–7.
17 Joachim H. Hereditary dystrophy of the hair and nails in six generations. *Ann Intern Med* 1936; **10**: 400–2.
18 Wilkey WD, Stevenson GH. A family with inherited ectodermal dystrophy. *Can Med Assoc J* 1945; **53**: 226–30.
19 Williams M, Fraser FC. Hydrotic ectodermal dysplasia—Clouston's family revisited. *Can Med Assoc J* 1967; **96**: 36–8.
20 Rajagopalan K, Tay CH. Hidrotic ectodermal dysplasia: study of a large Chinese pedigree. *Arch Dermatol* 1977; **113**: 481–5.
21 Escobar V, Goldblatt LI, Bixler D *et al*. Clouston syndrome: an ultrastructural study. *Clin Genet* 1983; **24**: 140–6.
22 Pierard GE, Van Neste D, Letot B. Hidrotic ectodermal dysplasia. *Dermatologica* 1979; **158**: 168–74.
23 Hazen PG, Zamora I, Bruner WE *et al*. Premature cataracts in a family with hidrotic ectodermal dysplasia. *Arch Dermatol* 1980; **116**: 1385–7.
24 Levin LS. Dental and oral abnormalities in selected ectodermal dysplasia syndromes. *Birth Defects Orig Artic Ser* 1988; **24**: 205–27.
25 George DI Jr, Escobar VH. Oral findings of Clouston's syndrome (hidrotic ectodermal dysplasia). *Oral Surg Oral Med Oral Pathol* 1984; **57**: 258–62.
26 Wilkinson RD, Schopflocher P, Rozenfeld M. Hidrotic ectodermal dysplasia with diffuse eccrine poromatosis. *Arch Dermatol* 1977; **113**: 472–6.
27 Freire-Maia N, Pinheiro M. *Ectodermal Dysplasias: a Clinical and Genetic Study*. New York: Alan R. Liss, 1984.
28 Burns FS. A case of generalized congenital keratoderma with unusual involvement of the eyes, ears and nasal and buccal mucous membranes. *J Cutan Dis* 1915; **33**: 255–60.
29 Skinner BA, Greist MC, Norins AL. The keratitis, ichthyosis, and deafness (KID) syndrome. *Arch Dermatol* 1981; **117**: 285–9.
30 Caceres-Rios H, Tamayo-Sanchez L, Duran-Mckinster C *et al*. Keratitis, ichthyosis, and deafness (KID syndrome): review of the literature and proposal of a new terminology. *Pediatr Dermatol* 1996; **13**: 105–13.
31 Harms M, Gilardi S, Levy PM *et al*. KID syndrome (keratitis, ichthyosis, and deafness) and chronic mucocutaneous candidiasis: case report and review of the literature. *Pediatr Dermatol* 1984; **2**: 1–7.
32 Hampton SM, Toner JG, Small J. Cochlear implant extrusion in a child with keratitis, ichthyosis and deafness syndrome. *J Laryngol Otol* 1997; **111**: 465–7.
33 Shiraishi S, Murakami S, Miki Y. Oral fluconazole treatment of fungating candidiasis in the keratitis, ichthyosis and deafness (KID) syndrome. *Br J Dermatol* 1994; **131**: 904–7.

Syndromes associated with DNA instability

Xeroderma pigmentosum (MIM 278700, 278720, 278730, 278740, 278750, 278760, 278780 and 610651)

Definition [1]. Xeroderma pigmentosum (XP) is a rare autosomal recessive disease characterized by photosensitivity, pigmentary changes, premature skin ageing, neoplasia and abnormal DNA repair. Some patients with XP also have neurological complications.

Aetiology. The initial report of this disorder was made by Hebra and Kaposi in 1874 [2], and the term 'xeroderma pigmentosum', meaning pigmented dry skin, was introduced in 1882 [3].

XP is found worldwide in all races, with an equal sex incidence. It occurs with a frequency of approximately 1 in 250 000 in Europe and the USA [4]. In Japan, the frequency has been reported to be higher (1 in 40 000) [5].

Inheritance is autosomal recessive; parents of affected individuals, who are thus obligate heterozygotes, are clinically normal. XP demonstrates considerable genetic heterogeneity; there are at least eight different subtypes recognized, designated complementation groups A–G and XP variant (Table 15.4).

Table 15.4 Nucleotide excision repair disorders. (Data compiled from published literature by A.R. Lehmann, Genome Damage and Stability Centre, University of Sussex, UK.)

Complementation group	Gene	Chromosome localization	Size of gene product (amino acids)	Activity	Comments
Xeroderma pigmentosum (XP)					
XP-A	*XPA*	9q22	273 (31 kDa)	Binds damaged DNA	Most common group; severe skin and neurological abnormalities
XP-B	*XPB*	2q21	782 (89 kDa)	Helicase; part of TFIIH	Rare; only three kindreds, two with XP/CS, one with TTD
XP-C	*XPC*	3p25	940 (106 kDa)	Damage recognition	Common; severe skin abnormalities
XP-D	*XPD*	19q13	760 (87 kDa)	Helicase; part of TFIIH	Common; severe + neurological abnormalities; also includes two cases of XP/CS and most cases of TTD
XP-E	*XPE*	11p12	427 (48 kDa)	Damaged DNA binding	Rare; mild features
XP-F	*XPF*	16p13	905 (103 kDa)	Nuclease subunit with ERCC1	Rare; fairly mild
XP-G	*XPG*	13q33	1196 (133 kDa)	Nuclease	Rare; severe + neurological abnormalities; half of cases have XP/CS
XP-V	*POLH*	6p21	713 (78 kDa)	Postreplication repair	20% of XP cases; mild skin abnormalities
*Cockayne syndrome (CS)**					
CS-A	*CSA*	5q12–q31	396 (44 kDa)	Transcription-coupled repair	Rare; milder features
CS-B	*CSB*	10q11	1493 (168 kDa)	Transcription-coupled repair	Common; more severe features
Trichothiodystrophy (TTD)					
Most TTD patients are in XP-D group, less commonly XP-B group. TTD-A group have mutations in *TFB5* subunit of TFIIH. Non-photosensitive TTDs have no repair defect but mutations in *TTDN1* gene.					

* CS also found rarely in combination with XP in XP-B, XP-D and XP-G groups.

Cleaver first reported in 1968 [6], and in subsequent studies [7–9], that fibroblasts from most patients with typical XP lack the normal capacity to repair UV radiation damage to DNA. In 1970, Epstein *et al.* [10] showed that DNA repair was defective *in vivo*. Approximately 80% of patients with XP show a defect in the initiation of DNA excision repair of UV photoproducts [11–13]. In these patients, repair replication is reduced in all cell types examined—epidermal cells, dermal fibroblasts, lymphocytes, conjunctival cells, corneal cells, liver cells, basal cell carcinoma cells and amniocytes [14,15].

The unscheduled DNA synthesis assay (following UV irradiation of cells in culture) is the standard laboratory method for diagnosis of XP [16]. The complementation group can be determined by using cell fusion techniques to identify the XP repair defect [17]. Cultured fibroblasts from two different patients with XP are fused so that their nuclei coexist in the same cytoplasm (forming a heterokaryon). If both nuclei have the same defect, then the heterokaryon shows defective DNA repair after UV irradiation and the patients are in the same complementation group. If the nuclei have different defects, then each will supply what the other is lacking and DNA repair within the heterokaryon will be normal. Seven distinct complementation groups are recognized in XP patients (A–G).

Nucleotide excision repair [18–19]. This process, whereby damaged DNA is removed and replaced with new DNA using the intact strand as a template, involves the products of some 30 genes [20]. The genes involved in nucleotide excision repair (NER) have now been cloned (Table 15.4). The excision repair cross-complementing (ERCC) genes are so called because of their ability to complement DNA repair in mutant rodent cells. The names of the XP genes have superseded those of the corresponding ERCC genes. The complete process of NER has now been reconstructed [21] (Fig. 15.23). The initial step in the process involves recognition of damaged DNA by the XP-C protein together with its partner HR23B [22]. This results in the recruitment of the dual function transcription factor TFIIH, composed of at least six subunits, including XP-B and XP-D proteins, which both have helicase activity. These helicases open out the structure at the site of DNA damage. The exact function of XP-A protein is not clear, but it seems to have a role in verifying the positions of the other proteins on the damaged structure, enabling the structure-specific nucleases to incise the DNA. ERCC1-XP-F and XP-G are both structure-specific nucleases, which cut the DNA on either side of the damage. The repair–synthesis step requires DNA polymerase ε (polε), the replication accessory factor proliferating-cell nuclear antigen (PCNA) and replication factor C (RFC); the new DNA is then joined to the old by DNA ligase. As well as these proteins, the incision reaction is stimulated by the product of the *XPE* gene, which is the smaller subunit of a dimeric protein that binds specifically to UV-irradiated DNA and is thought to assist in the early recognition of cyclobutane pyrimidine dimers.

Deficiency of NER is also associated with Cockayne's syndrome (CS) and trichothiodystrophy.

XP variant [23]. Twenty per cent of patients have XP variant, with normal NER but a defect in an alternative repair process, known as post-replication or daughter-strand repair. This manifests as a

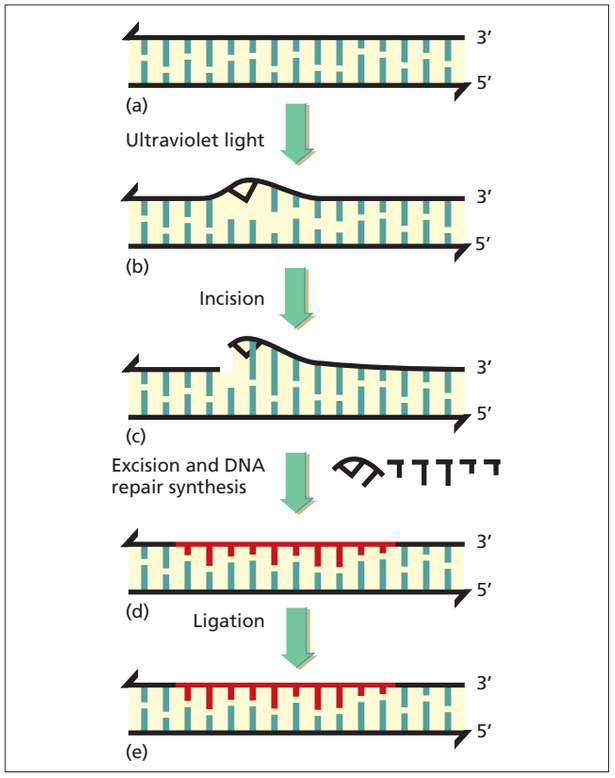


Fig. 15.23 Excision repair of pyrimidine dimers. Distortion in DNA double helix by pyrimidine dimer is located (b), the damaged strand excised (c), the dimer removed together with neighbouring nucleotides and the gap filled with new DNA (d); ligation (e) completes repair. (From Pawsey *et al.* [1].)

reduced molecular weight of newly synthesized DNA in UV-irradiated cells and a delay in the production of intact high-molecular-weight DNA strands following UV irradiation [24]. The genetic defect in XP variant is in *POHL* which encodes a DNA polymerase, designated polη, which is able to replicate DNA past UV-induced cyclobutane thymine dimers and some other types of DNA damage, in most cases inserting the 'correct' nucleotides opposite the damaged bases [25–27]. This property contrasts with that of the DNA polymerases that carry out normal DNA replication. These are extremely accurate, but are blocked by most types of DNA damage.

Clinical diversity. Despite substantial increases in our understanding of the genetic mechanisms underlying different forms of XP, the reasons for marked clinical variability have not been fully elucidated. Different subtypes of XP show clinical and epidemiological differences. Most patients are in group C, which is most common in Europe and the USA, and show no neurological defects. However, those in group A tend to develop neurological disease before the age of 7 years, and those in group D usually develop neurological problems after this age. There is evidence of genotype–phenotype correlation in some XP groups, with more severe phenotypes resulting from truncating mutations in critical domains of the relevant gene, whereas missense mutations in less critical regions tend to result in milder disease [28,29].

Skin photosensitivity. XP is very variable in expression of sun sensitivity and this is reflected in tests for light sensitivity. Some cases of typical XP show a papular and vesicular reaction, mainly to light in the 290–320 nm range [30]. The minimal erythema dose may be reduced or normal.

XP and neoplasia. Cultured dermal fibroblasts from XP patients exhibit increased UV-induced mutagenesis. The neoplasms in XP patients, which occur predominantly on sun-exposed surfaces, are thought to be the result of UV-induced mutations [16]. Indeed, skin tumours from XP patients carry mutations bearing a 'UV signature' in the *p53* and *PTCH* genes [31,32]. UV exposure also triggers a complex series of signal transduction pathways that result in immunosuppression of the skin, which may also be an important factor [33,34].

Pathology. The histological changes in the fully developed atrophic stage closely resemble those of senile skin. The epidermis is thin and flattened, and dermal collagen shows basophilic degeneration. Irregular proliferation of rete pegs, heavily laden with pigment, is a distinctive feature. The keratoses and the malignant tumours that ultimately complicate all but the mildest cases show no specific histological characteristics.

Electron microscopic studies [35] show shrinkage of keratinocytes and their nuclei, and abnormalities of nuclear morphology. Melanocytes are also abnormal, with polymorphic melanosomes, and there may be giant pigment granules in melanocytes or keratinocytes. There are also abnormalities of desmosomes, the endoplasmic reticulum and mitochondria. Dermal fibroblasts appear to behave like macrophages and engulf melanosomes within vacuoles. In hypopigmented macules the melanocytes are scanty, but Langerhans cells are numerous [36].

Clinical features [4,37] (Fig. 15.24). The skin is normal at birth; the first symptoms are noticed between the sixth month and the third year in over 75% of cases, but may appear in very early infancy or later childhood. Although the disease always advances through its successive stages, the rate of progression is unpredictable and bears no constant relationship to the age of onset. Most cases beginning in early childhood reach the tumour stage before the age of 20 years, although a few run a more benign course and some cases of later onset may develop multiple tumours within a few years.

Freckling and increasing dryness on light-exposed surfaces are usually the earliest manifestations; they may follow an acute sunburn or more persistent erythema. Freckles appear first on the face and hands and later on other exposed parts, the neck and lower legs, lips and conjunctivae; in severe cases the trunk is affected. Varying in colour from light to dark brown and in size from a pinpoint to a centimetre or more, they may fuse to form irregular patches of pigmentation. Fading at first in the winter months, they soon become permanent. As they increase progressively in number, telangiectases and small angiomas appear interspersed among them. Telangiectases and angiomas on unexposed skin and on the lingual and buccal mucous membranes have been reported. Small, round or irregular, white, atrophic macules also develop. Some follow crusted vesiculobullous lesions; others arise



Fig. 15.24 Xeroderma pigmentosum. (From Harper J. *Handbook of Paediatric Dermatology*, 2nd edn. Oxford: Butterworth-Heinemann, 1990.)

independently. Superficial ulcers, slow to heal, leave disfiguring scars, and on the eyelids may produce ectropion. Keratoacanthomas may form, even in the mildest cases, and resolve spontaneously in a few months. Actinic keratoses are frequent; they may resolve spontaneously or may undergo malignant change.

The first malignant tumours may develop as early as the third or fourth year, with a median age of onset of 8 years. Patients up to the age of 20 years have a 1000 times greater incidence of melanoma and non-melanoma skin cancers than the general population [38]. Basal cell carcinoma is common, and large numbers, sometimes pigmented, may appear over the course of years. Squamous cell carcinoma is also common and may arise on the anterior tongue, in the portion that may be exposed to UV radiation [38,39]. Melanomas may be multiple; they may lead to early death from widespread metastases or run a more benign course, even in adults, although histologically malignant. Other malignant tumours, such as angiosarcoma and fibrosarcoma, may rarely occur.

The disease is often fatal before the age of 10 years, and worldwide two-thirds die before 20 years of age. These statistics have improved in countries where children are adequately protected from the sun. Multiple metastases of squamous cell carcinoma or melanoma are one cause of death, but many patients die from infection, to which they are abnormally susceptible, or from neurological complications [40]. Survival beyond middle age is sometimes possible in mild cases or with adequate treatment. Striking interfamily variation in expectation of life has been reported.

Ocular lesions [4,37]. The eyes are affected in some 80% of cases. Photophobia and conjunctivitis are common early symptoms. Ectropion and destruction of the lower lids expose the bulbar conjunctiva, and symblepharon and ulceration may occur. Pigmented macules on the conjunctiva are common. Vascular pterygium, corneal opacities and epitheliomas of the lids, conjunctiva or cornea may also develop.

Neurological complications. Progressive neurological abnormalities occur in approximately 20% of XP patients [37,41], with one or more of the following: mental retardation, areflexia or hyporeflexia, spasticity, ataxia, sensorineural deafness, peripheral neuropathy, dysphasia and abnormal electroencephalographic findings. Patients with neurological abnormalities usually have group A or D XP, although a few have been reported with group C, group G or XP variant disease [37,41]. Neurological involvement is thought to arise from accumulation of DNA damage in the absence of adequate NER, ultimately leading to neuronal death. The severity of neurological disease depends on the complementation group and the failure of recovery of RNA synthesis in XP fibroblasts after UV irradiation, but does not necessarily correlate with the severity of skin disease [41].

De Sanctis–Cacchione syndrome [42]. This term has been applied to XP with severe, early onset neurological involvement and can arise in the context of several different complementation groups, but most notably complementation group A. It has also been described in siblings with a homozygous mutation in the CS gene, *CSB* [43]. Microcephaly, severe mental deficiency, dwarfism, hypogonadism, deafness, choreoathetosis and ataxia have been reported. Post-mortem findings show cerebral and olivopontocerebellar atrophy from neurone loss, without primary damage to white matter, or gliosis.

XP with CS. Rarely, CS can occur in combination with XP in XP-B [44], XP-D [45], and XP-G [46,47]. These patients have variability in clinical features and severity which are not fully understood, but generally, those with CS and XP-B have milder disease than those with XP-D and XP-G [48].

Autosomal dominant XP. An autosomal dominant form of XP has been described in two kindreds [49,50]. These patients had a mild clinical course and, in one family, there was reduced fibroblast DNA repair synthesis after UV exposure [50].

Diagnosis. In the fully developed case, the diagnosis of XP is unmistakable. Mild or early cases must be differentiated from ordinary freckling. Other forms of photosensitivity and premature ageing, including progeria, acrogeria, Rothmund–Thomson syndrome, Bloom's syndrome, CS, Hartnup syndrome and hydroa vacciniforme, must be excluded.

Prenatal diagnosis by assessment of UV-induced DNA repair synthesis from cultured amniocytes or chorionic villi is possible [51].

Treatment. As soon as the diagnosis is established, patients must be protected from sunlight by every possible means. They must not go outdoors during daylight hours, except in the early morning or evening, and even then they should wear two layers of clothing and a broad-brimmed hat. All uncovered skin surfaces must be

protected by a total sun-block cream, and sunglasses with side shields should be worn. UV radiation is harmful up to at least 320 nm, and some fluorescent lights can emit radiation below this wavelength. Chemical light screens can combine a cosmetic and protective function.

Early and adequate excision of all tumours is essential, and is to be preferred to radiotherapy because of the atrophic and degenerate state of the skin. Topical 5-fluorouracil may be useful for early or premalignant lesions. Chemical peeling and dermabrasion can also be helpful [52]. Plastic surgery and grafting of large areas of facial skin may sometimes be required [53]. Photodynamic therapy should not be used as the irradiation involved is likely to result in further skin damage and carcinogenesis [54].

There is now substantial evidence to suggest that oral retinoids reduce the occurrence of skin cancer in XP [55,56]. A trial of prophylactic therapy should therefore be considered.

The eyes may need to be treated with artificial tears, soft contact lenses or even corneal transplant. The relatives of known cases should be carefully examined and tested [30] so that mildly affected individuals may be detected at the earliest possible stage.

A clinical trial used the microbial enzyme T4 endonuclease V applied regularly as a topical liposome lotion. This enzyme is able to bypass the defect in XP cells. Employed over a period of 1 year, it significantly reduced the onset of both new basal cell carcinomas and actinic keratoses [57].

In vitro and *ex vivo* experiments have established that correction of the underlying genetic defect in different forms of XP is possible. Animal studies using viral vectors have also established that gene therapy approaches for patients with this disease should soon become possible [58,59].

References

1 Pawsey SA, Magnus IA, Ramsay CA *et al.* Clinical, genetic and DNA repair studies on a consecutive series of patients with xeroderma pigmentosum. *QJM* 1979; **48**: 179–210.

2 Hebra F, Kaposi M. *On Diseases of the Skin Including the Exanthemata*, Vol. 3 (translated by W. Tay). London: The New Sydenham Society, 1874: 252–8.

3 Kaposi M. Xeroderma pigmentosum. *Med Jahrb Wien* 1882: 619–33. (French translation, *Ann Dermatol Syphiligr* 1883; **4**: 29–38.)

4 Robbins JH, Kraemer KH, Lutzner MA *et al.* Xeroderma pigmentosum: an inherited disease with sun sensitivity, multiple cutaneous neoplasms and abnormal DNA repair. *Ann Intern Med* 1974; **80**: 221–48.

5 Neel JV, Kodai M, Brewer R *et al.* The incidence of consanguineous matings in Japan: with remarks on the estimation of comparative gene frequencies and the expected rate of appearance of induced recessive mutations. *Am J Hum Genet* 1949; **1**: 156–78.

6 Cleaver JE. Defective repair replication of DNA in xeroderma pigmentosum. *Nature* 1968; **218**: 652–6.

7 Cleaver JE. DNA damage and repair in light-sensitive human skin disease. *J Invest Dermatol* 1970; **54**: 181–95.

8 Cleaver JE. Xeroderma pigmentosum: progress and regress. *J Invest Dermatol* 1973; **60**: 374–80.

9 Cleaver JE, Carter DM. Xeroderma pigmentosum variants: influence of temperature on DNA repair. *J Invest Dermatol* 1973; **60**: 29–32.

10 Epstein JH, Fukuyama K, Reed WB *et al.* Defect in DNA synthesis in skin of patients with xeroderma pigmentosum demonstrated *in vivo*. *Science* 1970; **168**: 1477–8.

11 Cook PR, Brazell IA, Pawsey SA *et al.* Changes induced by ultraviolet light in the superhelical DNA of lymphocytes for subjects with xeroderma pigmentosum and normal controls. *J Cell Sci* 1978; **29**: 117–27.

12 Hayakawa H, Ishizaki K, Inoue M *et al.* Repair of ultraviolet radiation damage in xeroderma pigmentosum cells belonging to complementation group F. *Mutat Res* 1981; **80**: 381–8.

13 Giannelli F, Pawsey SA, Avery JA. Differences in patterns of complementation of the more common groups of xeroderma pigmentosum: possible implications. *Cell* 1982; **29**: 451–8.

14 Kraemer KH. Xeroderma pigmentosum. In: Demis DJ, Dobson RL, McGuire J, eds. *Clinical Dermatology*, Vol. 4. Hagerstown, MD: Harper & Row, 1980: 1–33.

15 Ramsey CA, Coltart TM, Blunt S *et al.* Prenatal diagnosis of xeroderma pigmentosum: report of the first successful case. *Lancet* 1974; **ii**: 1109–12.

16 Clark Lambert W. Genetic diseases associated with DNA and chromosomal instability. *Dermatol Clin* 1987; **5**: 85–108.

17 De Weerd-Kastelein EA, Keijzer W, Bootsma D. Genetic heterogeneity of xeroderma pigmentosum demonstrated by somatic cell hybridization. *Nature* 1972; **238**: 80–3.

18 de Laat WL, Jaspers NG, Hoeijmakers JH. Molecular mechanism of nucleotide excision repair. *Genes Dev* 1999; **13**: 768–85.

19 Berneburg M, Lehmann AR. Xeroderma pigmentosum and related disorders: defects in DNA repair and transcription. *Adv Genet* 2001; **43**: 71–102.

20 Lehmann AR. Nucleotide excision repair and the link with transcription. *Trends Biochem Sci* 1995; **20**: 402–5.

21 Aboussekhra A, Biggerstaff M, Shivji MK *et al.* Mammalian DNA nucleotide excision repair reconstituted with purified protein components. *Cell* 1995; **80**: 859–68.

22 Volker M, Mone MJ, Karmakar P *et al.* Sequential assembly of the nucleotide excision repair factors in vivo. *Mol Cell* 2001; **8**: 213–24.

23 Itoh T, Ono T, Yamaizumi M. A simple method for diagnosing xeroderma pigmentosum variant. *J Invest Dermatol* 1996; **107**: 349–53.

24 Lehmann AR, Kirk-Bell S, Arlett CF *et al.* Xeroderma pigmentosum cells with normal levels of excision repair have a defect in DNA synthesis after UV-irradiation. *Proc Natl Acad Sci USA* 1975; **72**: 219–23.

25 Masutani C, Kusumoto R, Yamada A *et al.* The XPV (xeroderma pigmentosum variant) gene encodes human DNA polymerase eta. *Nature* 1999; **399**: 700–4.

26 Tanioka M, Masaki T, Ono R *et al.* Molecular analysis of DNA polymerase eta gene in Japanese patients diagnosed as xeroderma pigmentosum variant type. *J Invest Dermatol* 2007; **127**: 1745–51.

27 Inui H, Oh K-S, Nadem C *et al.* Xeroderma pigmentosum-variant patients from America, Europe, and Asia. *J Invest Dermatol* 2008; **128**: 2055–68.

28 Cleaver JE, Thompson LH, Richardson AS, States JC. A summary of mutations in the UV-sensitive disorders: xeroderma pigmentosum, Cockayne syndrome, and trichothiodystrophy. *Hum Mutat* 1999; **14**: 9–22.

29 Oh K-S, Khan SG, Jaspers NGJ *et al.* Phenotypic heterogeneity in the XPB DNA helicase gene (ERCC3): xeroderma pigmentosum without and with Cockayne syndrome. *Hum Mutat* 2006; **27**: 1092–103.

30 Ramsay CA, Giannelli F. The erythemal action spectrum and deoxyribonucleic acid repair synthesis in xeroderma pigmentosum. *Br J Dermatol* 1975; **92**: 49–56.

31 Dumaz N, Drougar C, Sarasin A *et al.* Specific UV-induced mutation spectrum in the p53 gene of skin tumors from DNA repair deficient xeroderma pigmentosum patients. *Proc Natl Acad Sci USA* 1993; **90**: 10529–33.

32 Bodak N, Queille S, Avril MF *et al.* High levels of patched gene mutations in basal-cell carcinomas from patients with xeroderma pigmentosum. *Proc Natl Acad Sci USA* 1999; **96**: 5117–22.

33 Miyauchi-Hashimoto H, Tanaka K, Horio T. Enhanced inflammation and immunosuppression by ultraviolet radiation in xeroderma pigmentosum group A (XPA) model mice. *J Invest Dermatol* 1996; **107**: 343–8.

34 Streilein JW, Taylor JR, Vincek V *et al.* Relationship between ultraviolet-induced immunosuppression and carcinogenesis. *J Invest Dermatol* 1994; **103**: 107S–11S.

35 Plotnick H, Lupulescu A. Ultrastructural studies of xeroderma pigmentosum. *J Am Acad Dermatol* 1983; **9**: 876–82.

36 Cesarini JP, Bioulac G, Moreno G *et al.* Hypopigmented macules of sun exposed skin in xeroderma pigmentosum. An electron microscopic study. *J Cutan Pathol* 1975; **2**: 128–39.

37 Kraemer KH, Lee MM, Scotto J. Xeroderma pigmentosum: cutaneous, ocular, and neurologic abnormalities in 830 published cases. *Arch Dermatol* 1987; **123**: 241–50.

38 Kraemer KH, Lee MM, Andrews AD, Lambert WC. The role of sunlight and DNA repair in melanoma and nonmelanoma skin cancer. The xeroderma pigmentosum paradigm. *Arch Dermatol* 1994; **130**: 1018–21.
39 Harper JI, Copeman PWM. Carcinoma of the tongue in a boy with xeroderma pigmentosum. *Clin Exp Dermatol* 1981; **6**: 601–4.
40 English JSC, Swerdlow AJ. The risk of malignant melanoma, internal malignancy and mortality in xeroderma pigmentosum patients. *Br J Dermatol* 1987; **117**: 457–61.
41 Anttinen A, Koulu L, Nikoskelainen E *et al*. Neurological symptoms and natural course of xeroderma pigmentosum. *Brain* 2008; **131**: 1979–89.
42 De Sanctis C, Cacchione A. L'idioza xerodermica. *Riv Sper Freniatr* 1932; **56**: 269–92.
43 Colella S, Nardo T, Botta E *et al*. Identical mutations in the CSB gene associated with either Cockayne syndrome or the DeSanctis-Cacchione variant of xeroderma pigmentosum. *Hum Mol Genet* 2000; **9**: 1171–5.
44 Brumback RA, Yoder FW, Andrews AD *et al*. Normal pressure hydrocephalus: recognition and relationship to neurological abnormalities in Cockayne's syndrome. *Arch Neurol* 1978; **35**: 337–45.
45 Broughton BC, Thompson AF, Harcourt SA *et al*. Molecular and cellular analysis of the DNA repair defect in a patient in xeroderma pigmentosum complementation group D who has the clinical features of xeroderma pigmentosum and Cockayne syndrome. *Am J Hum Genet* 1995; **56**: 167–74.
46 Hamel BC, Raams A, Schuitema-Dijkstra AR *et al*. Xeroderma pigmentosum–Cockayne syndrome complex: a further case. *J Med Genet* 1996; **33**: 607–10.
47 Moriwaki S, Stefanini M, Lehmann AR *et al*. DNA repair and ultraviolet mutagenesis in cells from a new patient with xeroderma pigmentosum group G and Cockayne syndrome resemble xeroderma pigmentosum cells. *J Invest Dermatol* 1996; **107**: 647–53.
48 Rapin I, Lindenbaum Y, Dickson DW *et al*. Cockayne syndrome and xeroderma pigmentosum. *Neurology* 2000; **55**: 1442–9.
49 Anderson T, Begg M. Xeroderma pigmentosum of mild type. *Br J Dermatol* 1950; **62**: 402–7.
50 Imray FP, Hockey A, Relf W *et al*. Sensitivity to ultraviolet radiation in a dominantly inherited form of xeroderma pigmentosum. *J Med Genet* 1986; **23**: 72–8.
51 Kleijer WJ, van der Sterre ML, Garritsen VH *et al*. Prenatal diagnosis of xeroderma pigmentosum and trichothiodystrophy in 76 pregnancies at risk. *Curr Gene Ther* 2007; **7**: 163–74.
52 Nelson BR, Fader DJ, Gillard M *et al*. The role of dermabrasion and chemical peels in the treatment of patients with xeroderma pigmentosum. *J Am Acad Dermatol* 1995; **32**: 623–6.
53 Gleason MC. Xeroderma pigmentosum: five-year arrest after total resurfacing of the face. *Plast Reconstr Surg* 1970; **46**: 577–81.
54 Procianoy F, Cruz AA, Baccega A *et al*. Aggravation of eyelid and conjunctival malignancies following photodynamic therapy in DeSanctis-Cacchione syndrome. *Ophthal Plast Reconstr Surg* 2006; **22**: 498–9.
55 Berth-Jones J, Graham-Brown RAC. Xeroderma pigmentosum variant: response to etretinate. *Br J Dermatol* 1990; **122**: 559–61.
56 Kraemer KH, DiGiovanna JJ, Moshell AN *et al*. Prevention of skin cancer in xeroderma pigmentosum with the use of oral isotretinoin. *N Engl J Med* 1988; **318**: 1630–7.
57 Yarosh D, Klein J, O'Connor A *et al*. Effect of topically applied T4 endonuclease V in liposomes on skin cancer in xeroderma pigmentosum: a randomised study. *Lancet* 2001; **357**: 926–9.
58 Marchetto MC, Muotri AR, Burns DK *et al*. Gene transduction in skin cells in preventing cancer in xeroderma pigmentosum mice. *Proc Natl Acad Sci USA* 2004; **101**: 17759–64.
59 Marchetto MC, Correa RG, Menck CF, Muotri AR. Functional lentiviral vectors for xeroderma pigmentosum gene therapy. *J Biotechnol* 2006; **126**: 424–30.

Cockayne's syndrome (MIM 216400 and 133540)

Definition. An inherited syndrome characterized by short stature, mental retardation, photosensitivity, premature skin ageing, disproportionately large hands, feet and ears, ocular defects and extensive demyelination.

Aetiology [1]. In this rare autosomal recessive syndrome skin fibroblasts are abnormally sensitive to UV irradiation [2–4]. Unlike XP, the global NER process occurs normally in CS cells *in vivo* and *in vitro*. However, CS cells are defective in an important subpathway of NER. Following DNA damage, it is of prime importance for the cell to remove damage from actively transcribed regions of DNA, and in human cells repair is more rapid in transcribed than in untranscribed regions. This preferential repair is referred to as transcription-coupled repair, and it is this rapid preferential repair that is specifically defective in CS cells [5]. The associated failure of cells to restore normal levels of RNA synthesis after UV irradiation [6] has provided a means for carrying out complementation tests on CS cells, and two complementation groups have been identified, CS-A (accounting for approximately 20% of CS patients) and CS-B [7] (Table 15.4). The products of the two known CS genes, *CSA* (chromosome 5) and *CSB* (chromosome 10q11–q21), are envisaged to fulfil a transcription-coupled repair function [8]. CS can rarely be found in combination with XP (see p. 15.73).

Clinical features [9–11]. Although very early onset has been reported in a significant minority of cases, the child usually appears normal for the first year, when facial erythema in the butterfly distribution develops after exposure to sunlight. The sensitivity to light is eventually lost, but not before mottled pigmentation and atrophic scars have given the patient a prematurely senile appearance, which is enhanced by the progressive loss of subcutaneous fat on the face and the sunken eyes. The skin elsewhere shows little change. The ears tend to protrude, and hair is normal or sparse and has sometimes been prematurely grey. In contrast with XP, patients with CS do not have an increased incidence of skin cancer or infection [10].

Physical and mental development are greatly delayed and the child remains growth retarded. The limbs are disproportionately long, with large hands and feet that may be blue and cold. Skeletal deformities and flexion contractures of the limbs commonly develop [12]. Sexual maturation occurs in some cases [13]. Optic atrophy, retinal degeneration and cataracts [14] lead to loss of vision, and progressive deafness is usual but variable in degree. There is extensive, diffuse demyelination of the peripheral nerves and the central nervous system [10]. Survival beyond the second decade is unusual, although two affected brothers, aged 42 and 55 years, have been reported [15]. In general, CS-A is milder in clinical course than CS-B, but within each type no clear genotype–phenotype correlation has been established [16].

Diagnosis. Progeria has frequently caused confusion, as dwarfism and a prematurely senile appearance are characteristic of both syndromes, and in both the child appears normal in its first year. The light sensitivity, ocular defects, normal hair and disproportionately large extremities are typical of CS. In Rothmund–Thomson syndrome, the cutaneous changes begin in early infancy and affect the buttocks and extremities as well as the face. In Bloom's syndrome, the erythema of face and hands is associated with growth retardation, but mental development is normal. The condition is distinguished from XP by the unusual facies, the

demyelination with delayed nerve conduction velocity, the lack of cutaneous malignancy [10] and the normal level of global NER. Prenatal diagnosis is possible by amniocentesis [16–18] or from chorionic villus samples [19], using the RNA synthesis recovery test.

References

1 Lehmann AR. Nucleotide excision repair and the link with transcription. *Trends Biochem Sci* 1995; **20**: 402–5.
2 Mayne LV, Lehmann AR, Waters R. Excision repair in Cockayne syndrome. *Mutat Res* 1982; **106**: 179–89.
3 Rainbow AJ, Howes M. A deficiency in the repair of UV and gamma-ray damaged DNA in fibroblasts from Cockayne's syndrome. *Mutat Res* 1982; **93**: 235–47.
4 Yatani R, Kusano I, Shiraishi T *et al.* DNA synthesis and hypersensitivity to ultraviolet radiation in Cockayne's syndrome. *Exp Mol Pathol* 1982; **36**: 361–72.
5 Venema J, Mullenders LH, Natarajan AT *et al.* The genetic defect in Cockayne syndrome is associated with a defect in repair of UV-induced DNA damage in transcriptionally active DNA. *Proc Natl Acad Sci USA* 1990; **87**: 4707–11.
6 Mayne LV, Lehmann AR. Failure of RNA synthesis to recover after UV-irradiation: an early defect in cells from individuals with Cockayne's syndrome and xeroderma pigmentosum. *Cancer Res* 1982; **42**: 1473–8.
7 Stefanini M, Fawcett H, Botta E *et al.* Genetic analysis of twenty-two patients with Cockayne syndrome. *Hum Genet* 1996; **97**: 418–23.
8 Henning KA, Li L, Iyer N *et al.* The Cockayne syndrome group A gene encodes a WD repeat protein that interacts with CSB protein and a subunit of RNA polymerase II TFIIH. *Cell* 1995; **82**: 555–64.
9 Macdonald WB, Fitch KD, Lewis IC. Cockayne's syndrome. A heredo-familial disorder of growth and development. *Pediatrics* 1960; **25**: 997–1007.
10 Nance MA, Berry SA. Cockayne syndrome: review of 140 cases. *Am J Med Genet* 1992; **42**: 68–84.
11 Lehmann AR, Thompson AF, Harcourt SA *et al.* Cockayne's syndrome: correlation of clinical features with cellular sensitivity of RNA synthesis to UV-irradiation. *J Med Genet* 1993; **30**: 679–82.
12 Riggs W, Seibert J. Cockayne's syndrome: roentgen findings. *Am J Roentgenol* 1972; **116**: 623–33.
13 Schönenberg H, Frohn K. Das Cockayne-Syndrom. *Monatsschr Kinderheilk* 1969; **117**: 103–8.
14 Lieberman WJ, Schimek RA, Snyder CH. Cockayne's disease. A report of a case. *Am J Ophthalmol* 1961; **52**: 116–8.
15 Miyauchi H, Horio T, Akaeda T *et al.* Cockayne syndrome in two adult siblings. *J Am Acad Dermatol* 1994; **30**: 329–35.
16 Bertola DR, Cao H, Albano LM *et al.* Cockayne syndrome type A: novel mutations in eight typical patients. *J Hum Genet* 2006; **51**: 701–5.
17 Lehmann AR, Francis AJ, Giannelli F. Prenatal diagnosis of Cockayne's syndrome. *Lancet* 1985; **i**: 486–8.
18 Cleaver JE, Volpe JP, Charles WC *et al.* Prenatal diagnosis of xeroderma pigmentosum and Cockayne syndrome. *Prenat Diagn* 1994; **14**: 921–8.
19 Falik-Zaccai TC, Laskar M, Kfir N *et al.* Cockayne syndrome type II in a Druze isolate in northern Israel in association with an insertion mutation in ERCC6. *Am J Med Genet* 2008; **146A**: 1423–9.

Bloom's syndrome (MIM 210900) [1]

Synonym
- Congenital telangiectatic erythema and stunted growth

Definition. The syndrome is characterized by photosensitivity, telangiectatic facial erythema, proportionate pre- and postnatal growth deficiency, distinctive facies, abnormal immune response and predisposition to malignancy.

Aetiology. Bloom's syndrome is a rare autosomal recessive disorder. Cultured lymphocytes and fibroblasts from patients show a high incidence of chromosomal aberrations and cells with abnormally high rates of sister-chromatid exchange (SCE) are uniquely characteristic of Bloom's syndrome [2,3]. The gene for Bloom's syndrome (*BLM*) has been mapped to chromosome 15q26.1 [4] and encodes a DNA helicase, RecQ protein-like-3 [5,6]. This helicase is thought to be involved in resolving abnormal structures that can arise during DNA replication, and may additionally be involved in transcriptional regulation [7]. Bloom's syndrome occurs with greater frequency in Ashkenazi Jews; a common ancestral mutation has been identified in most of these patients along with other founder mutations in patients from other geographical regions [8,9].

Clinical features [2,10–14]. Bloom's syndrome patients have a characteristic appearance. There is moderate and proportionate growth deficiency both *in utero* and postnatally. Patients have a narrow, slender, delicate facies with a relatively prominent nose. They may have mild microcephaly with dolichocephaly (the head is proportionately longer and narrower than expected). Telangiectatic erythema of the face develops during infancy or early childhood as red macules or plaques, which may simulate lupus erythematosus. They are most numerous on the 'butterfly' area of the nose and cheeks, but may involve the margins of the eyelids, the forehead and the ears, and sometimes the dorsa of hands and forearms. There may be slight scaling. Exacerbation after exposure to sunlight is usual but not invariable, and light may also provoke bullae, bleeding and crusting of the lips.

Other associated abnormalities include café-au-lait patches, clinodactyly, syndactyly, congenital heart disease, bronchiectasis, annular pancreas and a high-pitched voice, possibly due to the craniofacial anatomy and high-arched palate [12,15]. Many associated developmental defects have been reported.

Testicular atrophy is common and adult male patients are infertile. Although the tubular elements of the testes function poorly, the androgen-secreting portions are spared, thus permitting normal puberty [16]. Fertility in female patients appears reduced, although full-term pregnancies have been reported [17,18]. Bloom's syndrome patients have an increased incidence of type II diabetes mellitus [19]. Neurological development is normal.

The mortality from neoplastic disease, particularly acute leukaemia, during the second or third decade is significantly increased [3–5,20]. Cancers of the types and sites seen in the general population arise frequently and unusually early, as do rare malignancies of early childhood [20]. They are predominantly internal rather than cutaneous malignancies [14]. Reported associations include B-cell [21] and Hodgkin's lymphoma [13], and Wilms' tumour [22,23]. Ionizing radiation from cancer surveillance or treatment may predispose to further DNA damage and carcinogenesis in Bloom's syndrome patients and should therefore be minimized as much as possible [24]. There is no increased frequency of malignancies in heterozygote carriers of *BLM* mutations.

Prenatal testing for Bloom's syndrome has been successfully undertaken by SCE analysis in chorionic villus cell cultures [25].

References

1 Bloom D. The syndrome of congenital telangiectatic erythema and stunted growth. *J Pediatr* 1966; **68**: 103–13.

2 Giannelli F, Benson PF, Pawsey SA *et al.* Ultraviolet light sensitivity and delayed DNA-chain maturation in Bloom's syndrome fibroblasts. *Nature* 1977; **265**: 466–9.
3 Dicken CH, Dewald G, Gordon H. Sister chromatid exchanges in Bloom's syndrome. *Arch Dermatol* 1978; **114**: 755–60.
4 Ellis NA, German J. Molecular genetics of Bloom's syndrome. *Hum Mol Genet* 1996; **5**: 1457–63.
5 Ellis NA, Groden J, Ye TZ *et al.* The Bloom's syndrome gene product is homologous to RecQ helicases. *Cell* 1995; **83**: 655–66.
6 Passarge E. A DNA helicase in full Bloom. *Nat Genet* 1995; **11**: 356–7.
7 Foucault F, Vaury C, Barakat A *et al.* Characterization of a new BLM mutation associated with a topoisomerase IIα defect in a patient with Bloom's syndrome. *Hum Mol Genet* 1997; **6**: 1427–34.
8 Ellis NA, Ciocci S, Proytcheva M *et al.* The Ashkenazic Jewish Bloom syndrome mutation blmAsh is present in non-Jewish Americans of Spanish ancestry. *Am J Hum Genet* 1998; **63**: 1685–93.
9 German J, Sanz MM, Ciocci S *et al.* Syndrome-causing mutations of the BLM gene in persons in the Bloom's Syndrome Registry. *Hum Mutat* 2007; **28**: 743–53.
10 Landau JW, Sasaki MS, Newcomer VD *et al.* Bloom's syndrome. The syndrome of telangiectatic erythema and growth retardation. *Arch Dermatol* 1966; **94**: 687–94.
11 German J. Bloom's syndrome. I. Genetical and clinical observations in the first twenty-seven patients. *Am J Hum Genet* 1969; **21**: 196–227.
12 Gretzula JC, Oscar Hevia BS, Weber PJ. Bloom's syndrome. *J Am Acad Dermatol* 1987; **17**: 479–88.
13 Passarge E. Bloom's syndrome: the German experience. *Ann Genet* 1991; **34**: 179–97.
14 German J. Bloom's syndrome. *Dermatol Clin* 1995; **13**: 7–18.
15 Wolf J. Congenital telangiectatic erythema resembling lupus erythematosus in dwarfs: Bloom's syndrome. *Arch Dermatol* 1963; **87**: 764.
16 Kauli R, Prager-Lewin R, Kaufman H *et al.* Gonadal function in Bloom's syndrome. *Clin Endocrinol* 1977; **6**: 285–9.
17 Mulcahy MT, French M. Pregnancy in Bloom's syndrome. *Clin Genet* 1981; **19**: 156–8.
18 Chisolm CA, Bray MJ, Karns LB. Successful pregnancy in a woman with Bloom syndrome. *Am J Med Genet* 2001; **102**: 136–8.
19 Mori S, Kondon N, Motoyoshi F *et al.* Diabetes mellitus in a young man with Bloom's syndrome. *Clin Genet* 1990; **38**: 387–90.
20 German J. Bloom's syndrome. XX. The first 100 cancers. *Cancer Genet Cytogenet* 1997; **93**: 100–6.
21 Oto S, Miyamoto S, Kudoh F *et al.* Treatment for B-cell-type lymphoma in a girl associated with Bloom's syndrome. *Clin Genet* 1992; **41**: 46–50.
22 Cairney AE, Andrews M, Greenberg M *et al.* Wilms tumour in three patients with Bloom syndrome. *J Pediatr* 1987; **111**: 414–6.
23 Berger C, Frappaz D, Leroux D *et al.* Wilm's tumour and Bloom syndrome. *Arch Pediatr* 1996; **3**: 802–5.
24 Thomas ER, Shanley S, Walker L, Eeles R. Surveillance and treatment of malignancy in Bloom syndrome. *Clin Oncol (R Coll Radiol)* 2008; **20**: 375–9.
25 Howell RT, Davies T. Diagnosis of Bloom's syndrome by sister chromatid exchange in chorionic villus cultures. *Prenat Diagn* 1994; **14**: 1071–3.

Werner's syndrome (MIM 277700)

Definition. The syndrome is characterized by premature ageing with sclerodermatous skin changes, subcutaneous calcification, short stature, prematurely aged facies, premature arteriosclerosis, diabetes mellitus and a predisposition to malignancy.

Aetiology. Werner's syndrome is a rare autosomal recessive disorder caused by mutations in *WRN (RECQL2)*, a DNA helicase gene on 8p12–p11.2 [1–5]. There is an increased incidence of spontaneous chromosomal deletions and rearrangements in cultured cell lines from affected individuals [6,7]. The mechanism for DNA instability in Werner's syndrome appears to be due to replication-associated telomere loss that is greatly increased in the absence of WRN helicase activity [8]. Clinically normal heterozygous carriers of *WRN* mutations have also been shown to have increased genetic instability compared with normal controls [9,10]. Werner's syndrome occurs worldwide, but there appears to be a higher frequency of reported cases from Japan, where the incidence is estimated at approximately 3 per million [11,12].

Clinical features [11–13]. The cutaneous features of Werner's syndrome include sclerodermatous skin changes, particularly on the face and extremities, and subcutaneous calcification. The face has a prematurely aged appearance with beaking of the nose. Hair may be sparse and prematurely grey. Stature is short with slender limbs. Patients tend to develop early arteriosclerosis, diabetes mellitus, osteoporosis and hypogonadism, and are at risk of cataracts and retinal degeneration. Importantly, Werner's syndrome patients are predisposed to developing malignancies, in particular myeloid disorders, meningiomas, melanomas, thyroid cancers and osteosarcomas [12].

A subset of patients have been described with 'atypical' Werner's syndrome, in whom clinical features have been more severe. In this group, heterozygous mutations of the lamin A/C gene (*LMNA*) have been identified [14], and therefore this should probably be more correctly considered a milder, later onset variant of Hutchinson–Gilford progeria syndrome [15].

References

1 Yu C-E, Oshima J, Fu Y-H *et al.* Positional cloning of the Werner's syndrome gene. *Science* 1996; **272**: 258–62.
2 Oshima J, Yu C-E, Piussan C *et al.* Homozygous and compound heterozygous mutations at the Werner syndrome locus. *Hum Mol Genet* 1996; **5**: 1909–13.
3 Goto M, Imamura O, Kuromitsu J *et al.* Analysis of helicase gene mutations in Japanese Werner's syndrome patients. *Hum Genet* 1997; **99**: 191–3.
4 Yu C-E, Oshima J, Wijsman EM *et al.* Mutations in the consensus helicase domains of the Werner syndrome gene. *Am J Hum Genet* 1997; **60**: 330–41.
5 Moser MJ, Oshima J, Monnat RJ Jr. WRN mutations in Werner syndrome. *Hum Mutat* 1999; **13**: 271–9.
6 Fuckuchi K, Martin GM, Monnat RJ Jr. Mutator phenotype of Werner syndrome is characterised by extensive deletions. *Proc Natl Acad Sci* 1989; **86**: 7994.
7 Scappaticci S, Forabosco A, Borroni G *et al.* Clonal structural chromosomal rearrangements in lymphocytes of four patients with Werner's syndrome. *Ann Genet* 1990; **33**: 5–8.
8 Crabbe L, Jauch A, Naeger CM *et al.* Telomere dysfunction as a cause of genomic instability in Werner syndrome. *Proc Natl Acad Sci* 2007; **104**: 2205–10.
9 Ogburn CE, Oshima J, Poot M *et al.* An apoptosis-inducing genotoxin differentiates heterozygotic carriers for Werner helicase mutations from wild-type and homozygous mutants. *Hum Genet* 1997; **101**: 121–5.
10 Moser MJ, Bigbee WL, Grant SG *et al.* Genetic instability and hematologic disease risk in Werner syndrome patients and heterozygotes. *Cancer Res* 2000; **60**: 2492–6.
11 Goto M, Tanimoto K, Horiuchi Y, Sasazuki T. Family analysis of Werner's syndrome: a survey of 42 Japanese families with a review of the literature. *Clin Genet* 1981; **19**: 8–15.
12 Goto M, Miller RW, Ishikawa Y, Sugano H. Excess of rare cancers in Werner syndrome (adult progeria). *Cancer Epidermiol Biomarkers Prev* 1996; **5**: 239–46.
13 Epstein CJ, Martin GM, Schultz AL, Motulsky AG. Werner's syndrome: a review of its symptomatology, natural history, pathologic features, genetics and relationship with the natural aging process. *Medicine* 1966; **45**: 177–222.
14 Chen L, Lee L, Kudlow BA *et al.* LMNA mutations in atypical Werner's syndrome. *Lancet* 2003; **362**: 440–5.
15 Haegle RA. Drawing the line in progeria syndromes. *Lancet* 2003; **362**: 416–7.

Poikilodermatous syndromes

Dyskeratosis congenita: X-linked recessive (MIM 305000), autosomal dominant (MIM 127550) and autosomal recessive (MIM 224230)

Definition. Dyskeratosis congenita (DKC) is a group of rare inherited disorders characterized by pigmentation and atrophy of the skin, nail dystrophy, leukoplakia, bone marrow failure and a predisposition to malignancy. Genes known to be mutated in this heterogeneous disorder have an important role in maintaining telomere length during cell division [1]. DKC therefore appears to be a disorder of telomere maintenance.

Aetiology. DKC is rare, but distributed worldwide. It was first described in 1906 by Zinsser [2], and later by Cole *et al.* [3] and Engmann [4]. X-linked recessive DKC is the most common form [5,6] although autosomal inheritance, both dominant [7–10] and recessive [11], is observed in other pedigrees. The clinical severity, somatic and haematological abnormalities, age at onset and age of death vary greatly in different individuals with DKC; in general terms, the X-linked recessive form is more severe than autosomally-inherited disease. In a significant number of families with DKC, the underlying genetic defect remains to be elucidated [1,11].

Telomeres consist of nucleotide repeats and a protein complex at the ends of chromosomes that are required to maintain integrity of the chromosomes. A number of different proteins are involved in telomere maintenance, including telomerase reverse transcriptase (encoded by *TERT*), its RNA component (*TERC*) and a number of proteins that form a complex known as shelterin that recognizes telomere DNA and telomeres from DNA repair pathways [12–14]. With every cell division, telomeres are shortened by loss of nucleotide repeats. If this shortening becomes critical, cells may undergo senescence with apoptosis, genetic instability or reduced potential for proliferation [15]. In DKC, the telomeres are greatly shortened (< 1st percentile), a phenomenon also observed in inherited and acquired haematological diseases such as some inherited bone marrow failure, aplastic anaemia and myelodysplasia [1]. The first mutations in patients with X-linked DKC were identified in 1998 by Heiss *et al.* [16] in the dyskerin gene, *DKC1*. Dyskerin is a component of H/ACA small nucleolar ribonucleoprotein (snoRNP) particles and is involved in modification of ribosomal RNA, and is also a component of the telomerase complex; one or both of these mechanisms may be affected by *DKC1* mutations in X-linked DKC [17,18]. Female carriers of X-linked DKC show skewed X-inactivation, suggesting that wild-type haematopoietic cells have a growth and survival advantage over cells carrying *DKC1* mutations [19]. More recently, mutations in *TERC*, *TERT* and *TINF2* (which encodes a component of shelterin) have been delineated in families with autosomal dominant DKC [10,20,21]. In addition, there is evidence of anticipation in families with *TERC* mutations, which has been attributed to progressive telomere shortening in successive generations [9]. *TERC* and *TERT* mutations have also been demonstrated in families with adult-onset aplastic anaemia and shortened telomeres but no other features of DKC [9,22–24].



Fig. 15.25 Dyskeratosis congenita: reticulate pigmentation on the neck.

Mutations in two other components of telomerase and snoRNP complexes, *NOP10* and *NHP2*, have been identified in a subset of patients with autosomal recessive DKC [11,25], although the causative molecular pathology in many other cases remains elusive.

Pathology. The cutaneous changes are not pathognomonic and are unimpressive. The epidermis is flattened; the dermis is vascular and contains pigment-laden macrophages and an inconstant lymphocytic infiltrate. The connective tissue is usually normal.

Clinical features [6,26–30]. The essential features of the syndrome are reticulate pigmentation and atrophy of the skin, nail dystrophy and mucosal leukoplakia. The nail changes are usually the first to appear. Between the ages of 5 and 13 years, the nails become dystrophic and are shed; they may be reduced to horny plugs or be completely destroyed. There may be recurrent episodes of suppurative paronychia.

The pigmentary changes may appear simultaneously or 2 or 3 years later, and reach their full development in 3–5 years. Fine, reticulate, grey–brown pigmentation is most conspicuous on the neck (Fig. 15.25) and thighs, but involves the greater part of the trunk. The skin is atrophic, and telangiectases may be sufficiently numerous to give a poikilodermatous appearance. The skin of the face is red and atrophic, with irregular macular pigmentation, and that of the dorsa of the hands and feet is diffusely atrophic, transparent and shiny. The palms and soles may be thickened and hyperhidrotic, and may form bullae with trauma. Premature cavities and cicatricial alopecia have occasionally been noted [28]. The teeth tend to be defective and irregularly implanted, and periodontal disease and early caries are usual.

The onset of the mucous membrane lesions may coincide with, or follow, the nail and skin changes. Small blisters and erosions of the lingual and buccal mucous membranes are succeeded by irregular patches of leukoplakia (Fig. 15.26). Similar changes on the tarsal conjunctiva may obliterate the lacrimal puncta, resulting in epiphora, and soreness and scarring of the lids. Anorectal, oesophageal or urethral leukoplakia may produce stenosis. Similar changes may occur throughout the gastrointestinal tract and on the urogenital mucous membranes. Pulmonary and hepatic fibro-



Fig. 15.26 Dyskeratosis congenita: the development of leukoplakia.

sis have also been described [10]. Interestingly, mutations in *TERC* and *TERT* have also been identified in some patients with isolated pulmonary fibrosis [31,32].

General physical and mental development is sometimes delayed, and osteoporosis may occur. Immunodeficiency, intrauterine growth retardation, microcephaly, cerebellar hypoplasia and intracranial calcification have also been reported, particularly in the Hoyeraal–Hreidarsson syndrome, a severe form of X-linked DKC [33]. Revesz syndrome is characterized by nail dystrophy, fine hair, cerebellar hypoplasia, exudative retinopathy, growth retardation and bone marrow hypoplasia [34]. Identification of a mutation in *TINF2* in an individual with Revesz syndrome supports it as a variant of DKC [21].

Malignancy. The incidence of carcinoma in the areas of leukoplakia appears to be high; it may prove fatal between the ages of 30 and 50 years. Carcinoma has also developed on other mucosal surfaces and in atrophic skin. Other neoplasms reported include pancreatic carcinoma and Hodgkin's disease. In a review of 104 cases [35], 12% had developed one or more tumours at the time of reporting (mean age of patients at reporting was 21 years).

Haematological abnormalities. The incidence of bone marrow failure in DKC is high: in one series, it arose in 93% of patients and pancytopenia was the cause of death in 71% [6]. The timing of onset is variable but the risk increases from age 10 years. Myelodysplasia and acute myeloid leukaemia have been reported in other patients. Bone marrow and stem cell transplantation have been undertaken in many patients over recent years, although short- and long-term complications occur with high frequency, particularly hepatic and pulmonary complications as a result of conditioning radiotherapy and chemotherapy [36–40].

Prognosis. The prognosis is usually poor, as either the blood dyscrasia or carcinoma may prove fatal. However, in some patients only nail dystrophy and pigmentation are present [41], and in such cases the expectation of life is normal.

Diagnosis. Because of the relatively late onset of the characteristic features of this syndrome, their relationship may be overlooked for some years and diagnosis delayed. It has often been confused with Rothmund–Thomson syndrome. In this, erythema of the face, buttocks and limbs in infancy is progressively succeeded by poikiloderma, nail changes are unusual, and leukoplakia does not occur. In anhidrotic ectodermal dysplasia the dental changes, distinctive facies, sparse or absent hair and normal nails provide points of differentiation.

Treatment. The aplastic anaemia associated with DKC can be successfully treated by allogeneic bone marrow transplantation; however, this approach does not reverse the other systemic manifestations of the syndrome [36–40]. Granulocyte colony-stimulating factor has been used successfully to improve haematological parameters in the short term [41].

Retinoids have been reported to cause regression of lesions in leukoplakia [42], and so may reduce the incidence of malignancy.

References

1 Savage SA, Alter BP. The role of telomere biology in bone marrow failure and other disorders. *Mech Ageing Dev* 2008; **129**: 35–47.

2 Zinsser F. Atrophia cutis reticularis cum pigmentatione, dystrophia unguium et leukokeratosis oris. *Ikonogr Dermatol (Hyoto)* 1906; **5**: 219–23.

3 Cole HN, Rauschkolb JC, Toomey J. Dyskeratosis congenita with pigmentation, dystrophia unguis and leukokeratosis oris. *Arch Dermatol Syphilol* 1930; **21**: 71–95.

4 Engmann MF. A unique case of reticular pigmentation of the skin with atrophy. *Arch Dermatol Syphilol* 1926; **13**: 685–7.

5 Davidson HR, Connor JM. Dyskeratosis congenita. *J Med Genet* 1988; **25**: 843–6.

6 Knight S, Vulliamy T, Copplestone A *et al.* Dyskeratosis Congenita (DC) Registry: identification of new features of DC. *Br J Haematol* 1998; **103**: 990–6.

7 Scoggins RB, Prescott KJ, Asher GH *et al.* Dyskeratosis congenita with Fanconi-type anemia: investigations of immunologic and other defects. *Clin Res* 1971; **19**: 409.

8 Tchou PK, Kohn T. Dyskeratosis congenita: an autosomal dominant disorder. *J Am Acad Dermatol* 1982; **6**: 1034–9.

9 Vulliamy T, Marrone A, Szydlo R *et al.* Disease anticipation is associated with progressive telomere shortening in families with dyskeratosis congenita due to mutations in TERC. *Nat Genet* 2004; **36**: 447–9.

10 Armanios M, Chen J-L, Chang Y-PC *et al.* Haploinsufficiency of telomerase reverse transcriptase leads to anticipation in autosomal dominant dyskeratosis congenita. *Proc Natl Acad Sci USA* 2005; **102**: 15960–4.

11 Walne AJ, Vulliamy T, Marrone A *et al.* Genetic heterogeneity in autosomal recessive dyskeratosis congenita with one subtype due to mutations in the telomerase-associated protein NOP10. *Hum Mol Genet* 2007; **16**: 1619–29.

12 Nakamura TM, Cech TR. Reversing time: origin of telomerase. *Cell* 1998; **92**: 587–90.

13 Collins K, Mitchell JR. Telomerase in the human organism. *Oncogene* 2002; **21**: 564–79.

14 de Lange T. Shelterin: the protein complex that shapes and safeguards human telomeres. *Genes Dev* 2005; **19**: 2100–10.

15 Maser RS, DePinho RA. Connecting chromosomes, crisis and cancer. *Science* 2002; **297**: 565–9.

16 Heiss NS, Knight SW, Vulliamy TJ *et al.* X-linked dyskeratosis congenita is caused by mutations in a highly conserved gene with putative nucleolar functions. *Nat Genet* 1998; **19**: 32–8.

17 Mochizuki Y, He J, Kulkarni S *et al.* Mouse dyskerin mutations affect accumulation of telomerase RNA and small nucleolar RNA, telomerase activity, and ribosomal RNA processing. *Proc Natl Acad Sci USA* 2004; **101**: 10756–61.

18 Yoon A, Peng G, Brandenberger Y *et al.* Impaired control of IRES-mediated translation in X-linked dyskeratosis congenita. *Science* 2006; **312**: 902–5.

19 Vulliamy TJ, Knight SW, Dokal I, Mason PJ. Skewed X-inactivation in carriers of X-linked dyskeratosis congenita. *Blood* 1997; **90**: 2213–6.
20 Vulliamy T, Marrone A, Goldman F *et al.* The RNA component of telomerase is mutated in autosomal dominant dyskeratosis congenita. *Nature* 2001; **413**: 432–5.
21 Savage SA, Giri N, Baerlocher GM *et al.* TINF2, a component of the shelterin telomere protection system, is mutated in dyskeratosis congenita. *Am J Hum Genet* 2008; **82**: 501–9.
22 Yamaguchi H, Baerlocher GM, Lansdorp PM *et al.* Mutations of the human telomerase RNA gene (TERC) in aplastic anemia and myelodysplastic syndrome. *Blood* 2003; **102**: 916–8.
23 Yamaguchi H, Caldo RT, Ly H *et al.* Mutations in TERT, the gene for telomerase reverse transcriptase, in aplastic anemia. *N Engl J Med* 2005; **352**: 1413–24.
24 Fogarty PF, Yamaguchi H, Wiestner A *et al.* Late presentation of dyskeratosis congenita as apparently acquired aplastic anaemia due to mutations in telomerase RNA. *Lancet* 2003; **362**: 1628–30.
25 Vulliamy T, Beswick R, Kirwan M *et al.* Mutations in the telomerase component NHP2 cause the premature ageing syndrome dyskeratosis congenita. *Proc Natl Acad Sci USA* 2008; **105**: 8073–8.
26 Bryan HG, Nixon RK. Dyskeratosis congenita and familial pancytopenia. *JAMA* 1965; **192**: 203–8.
27 Connor JM, Teague RH. Dyskeratosis congenita: report of a large kindred. *Br J Dermatol* 1981; **105**: 321–5.
28 Milgrom H, Stoll HJ, Crissey JT. Dyskeratosis congenita. A case with new features. *Arch Dermatol* 1964; **89**: 345–9.
29 Drachtman RA, Alter BP. Dyskeratosis congenita. *Dermatol Clin* 1995; **13**: 33–9.
30 Vulliamy TJ, Marrone A, Knight SW *et al.* Mutations in dyskeratosis congenita: their impact on telomere length and the diversity of clinical presentation. *Blood* 2006; **107**: 2680–5.
31 Armanios MY, Chen JJ, Cogan JD *et al.* Telomerase mutations in families with idiopathic pulmonary fibrosis. *N Engl J Med* 2007; **356**: 1317–26.
32 Tsakiri KD, Cronkhite JT, Kuan PJ *et al.* Adult-onset pulmonary fibrosis caused by mutations in telomerase. *Proc Natl Acad Sci USA* 2007; **104**: 7552–7.
33 Sznajer Y, Baumann C, David A *et al.* Further delineation of the congenital form of X-linked dyskeratosis congenita (Hoyeraal-Hreidarsson syndrome). *Eur J Pediatr* 2003; **162**: 863–7.
34 Revesz T, Fletcher S, al Gazali LI, DeBuse P. Bilateral retinopathy, aplastic anaemia, and central nervous system abnormalities: a new syndrome? *J Med Genet* 1992; **29**: 673–5.
35 Davidson HR, Connor JM. Dyskeratosis congenita. *J Med Genet* 1988; **25**: 843–6.
36 Yabe M, Yabe H, Hattori K *et al.* Fatal interstitial pulmonary disease in a patient with dyskeratosis congenita after allogeneic bone marrow transplantation. *Bone Marrow Transplant* 1997; **19**: 389–92.
37 Nobili B, Rossi G, De Stefano P *et al.* Successful umbilical cord blood transplantation in a child with dyskeratosis congenita after a fludarabine-based reduced-intensity conditioning regimen. *Br J Haematol* 2002; **119**: 573–4.
38 Brazzola P, Duval M, Fournet JC *et al.* Fatal diffuse capillaritis after hematopoietic stem-cell transplantation for dyskeratosis congenita despite low-intensity conditioning regimen. *Bone Marrow Transplant* 2005; **36**: 847–50.
39 de la Fuente J, Dokal I. Dyskeratosis congenita: advances in the understanding of the telomerase defect and the role of stem cell transplantation. *Pediatr Transplant* 2007; **11**: 584–94.
40 Mills SE, Cooper PH, Beacham BE *et al.* Intracranial calcifications and dyskeratosis congenita. *Arch Dermatol* 1979; **115**: 1437–9.
41 Pritchard SL, Junker AK. Positive response to granulocyte-colony-stimulating factor in dyskeratosis congenita before matched unrelated bone marrow transplantation. *Am J Pediatr Hematol Oncol* 1994; **16**: 186–7.
42 Koch HF. Effect of retinoids on precancerous lesions of oral mucosa. In: Orfanos CE, Braun-Falco O, Farber EM *et al.*, eds. *Retinoids. Advances in Basic Research and Therapy*. Berlin: Springer, 1981: 307–12.

Rothmund–Thomson syndrome (MIM 268400)

Synonym
- Poikiloderma congenitale

Aetiology. Rothmund–Thomson syndrome (RTS) is a rare autosomal recessive disorder. The initial description by Rothmund [1] referred to children with cataracts and a peculiar degeneration of the skin. Thomson [2] described sisters with similar skin changes, and subsequently [3] labelled the disorder as 'poikiloderma congenitale'. Cataracts were not a feature of his cases. Taylor [4] reviewed the literature and proposed the eponym of Rothmund–Thomson syndrome. Kitao *et al.* [5] reported three patients with RTS who carried two types of compound heterozygous mutations in a DNA helicase gene, known as *RECQL4*, on chromosome 8q24.3. Subsequently, many more *RECQL4* mutations have been identified in individuals with RTS, although in around 40% of patients with this clinical diagnosis, no mutations have been identified, indicating a degree of genetic heterogeneity [6,7]. It has been suggested that patients can be classified depending on the presence or absence of *RECQL4* mutations: patients with RTS type I have poikiloderma and may have juvenile cataracts but the gene defect(s) has not been identified; in RTS type II, in which *RECQL4* mutations are found, patients have the typical poikiloderma and an increased risk of osteosarcoma [7]. Identification of *RECQL4* mutations in patients with a clinical diagnosis of RTS, therefore, may have implications for the need for ongoing surveillance for malignancy. Trisomy 8 mosaicism has also been described in some Rothmund–Thomson patients [8,9].

Mutations in *RECQL4* have also been identified in two other disorders which exhibit some clinical overlap with RTS. Firstly, Baller–Gerold syndrome (BGS) (MIM 218600), which is characterized by craniosynostosis and radial defects, and in which poikiloderma may be a feature. It has been proposed that the clinical and genetic similarities between RTS and BGS may indicate that these are a single entity [10]. Secondly, RAPADILINO syndrome (MIM 266280), which encompasses growth retardation, bony abnormalities, particularly radial defects, and an increased risk of certain malignancies, but no poikiloderma [11]. Genotype–phenotype correlation has been shown for a number of families with these disorders and *RECQL4* mutations [7].

The *RECQL4* protein is essential for the initiation of DNA replication and is necessary for efficient removal of UV-induced DNA damage [12]. Reduced DNA-repair capacity and increased sensitivity to UVC have been reported in individual patients with RTS [13,14].

Pathology [15]. In childhood, the histological changes are flattening and atrophy of the epidermis, with oedema of the dermal–epidermal junction. There may be some vasodilatation and perivascular lymphocytic infiltration in the dermis. In adults, exposed skin shows a combination of fragmentation of elastic tissue in the dermis and patchy Bowenoid dyskeratosis of the epidermis.

Clinical features [4,16–20]. The skin appears normal at birth. The earliest lesions usually develop between the third and sixth month, but sometimes as late as the second year. Plaques of erythema and oedema, or more transitory diffuse erythema, are succeeded by varying combinations of atrophy, telangiectasia, pigmentation and depigmentation. The pigmentation, dull brown in colour,

irregularly macular or reticulate, develops later than the atrophy and telangiectasia on which it is superimposed, although it may extend much beyond these areas, especially on the neck and trunk, where it may be the only change. On the face and hands telangiectasia predominates. Ultimately, the lesions closely resemble chronic radiodermatitis.

The cheeks are first and most severely involved, but the forehead, chin and ears seldom escape. The hands, forearms and lower legs are next affected, and the buttocks and thighs are frequently involved. Light sensitivity is a feature of many cases, and exposure to sunlight may extend the distribution of the eruption on the upper trunk; however, it is not limited to light-exposed skin, and the poikiloderma may develop without preceding erythema. Light sensitivity may be so severe that a bullous response is elicited, and although this tends to diminish after early childhood, it may persist into adult life [15,17].

Once they have reached their full development in early life, the skin lesions tend to remain unchanged, but in many cases keratoses develop on exposed skin from adolescence onwards, and large warty keratoses of hands, wrists, feet, ankles and elsewhere may restrict the patient's activities [21]. Squamous or basal cell carcinoma may develop in the keratoses or in the surrounding atrophic skin [22].

Scalp hair is often sparse and fine, and may be absent. Eyebrows and eyelashes, and pubic and axillary hair are often sparse or absent. Nails are normal or small and dystrophic. Teeth are often normal, but microdontia and early caries have been reported.

Bilateral cataracts have developed, usually between the fourth and seventh year, in 10–40% of reported cases, and are more frequent in some families than in others.

Physical development is frequently delayed; most patients are of proportionate small stature, with slender delicate limbs, small hands and feet, and short fingers. The skull may be small and the features bird-like, sometimes with a saddle nose. Hypogonadism of slight or severe degree is frequent, and the incidence of hyperparathyroidism appears also to be increased [23]. The association of RTS and Addison's disease has also been reported [24].

Skeletal abnormalities include radial ray defects [25], which may present as thumb hypoplasia with an abnormal radial head, or complete absence of the radius. There is a recognized risk of osteosarcoma, notably in patients with *RECQL4* mutations, especially in the bones of the lower leg, which can present in childhood [7,18,26–28]. In a series of 41 patients with RTS, Wang *et al.* [29] identified osteosarcoma in 32% (higher than previous estimates) and radial defects in 20% [29].

Other associations reported include myelodysplastic syndrome [30], malignant eccrine poroma [31], malignant fibrous histiocytoma [32] and annular pancreas with duodenal stenosis [33].

Individuals with Rothmund–Thomson syndrome are usually of normal intelligence. Life expectancy depends on the development of an associated malignancy; otherwise it appears to be normal.

Diagnosis. The essential features in differential diagnosis are the age of onset, the distribution of the lesions and the combination of atrophy, telangiectasia and mottled pigmentation, most intense on light-exposed skin but not necessarily confined to it.

In Werner's syndrome, the skin changes are essentially sclerodermatous, and both skin and ocular lesions develop later than in RTS. In DKC, reticulate pigmentation develops between the ages of 5 and 13 years, and is most marked on the neck, trunk and thighs. Atrophy and telangiectasia may appear later. The nail changes are constant and severe. In progeria, the child is often small but otherwise normal during the first year; thereafter, development is delayed. Scalp hair, eyebrows and eyelashes are lost and the skin assumes an increasingly senile appearance. In CS, light sensitivity is a conspicuous feature after the first year, but there is no poikiloderma. Hypohidrotic ectodermal dysplasia should be identified by the association, in variable combinations, of conical teeth, hypotrichosis and partial or complete anhidrosis. The skin is atrophic but not poikilodermatous. XP should not cause confusion: in mild forms, only freckle-like macules are present, whereas in mild forms of RTS, telangiectasia is the conspicuous feature. Telangiectasia, often irregular, linear and present at birth, is a feature of focal dermal hypoplasia. In Bloom's syndrome, erythema, and not poikiloderma, is the essential change.

Treatment. Protection against sunlight is important. Careful supervision is essential to ensure detection of malignancy. Baseline radiography of the long bones by the age of 5 years has been recommended, because underlying skeletal dysplasias can make X-ray interpretation difficult if there is later suspicion of osteosarcoma [29]. It is not known whether patients with RTS have increased sensitivity to chemotherapy and radiotherapy. Improvement of cutaneous changes has been described with retinoids [34]. Telangiectasia, especially on the face, can be improved significantly by treatment with the vascular pulsed dye laser [35].

References

1 Rothmund A. Über Kataracte in Verbindung mit einer eigentümlichen Hautdegeneration. *Graefes Arch Ophthalmol* 1868; **14**: 159–82.
2 Thomson MS. An hitherto undescribed familial disease. *Br J Dermatol* 1923; **35**: 455–62.
3 Thomson MS. Poikiloderma congenitale. *Br J Dermatol* 1936; **48**: 221–34.
4 Taylor WB. Rothmund's syndrome–Thomson's syndrome. *Arch Dermatol* 1957; **75**: 236–44.
5 Kitao S, Shimamoto A, Goto M *et al.* Mutations in RECQL4 cause a subset of cases of Rothmund–Thomson syndrome. *Nat Genet* 1999; **22**: 82–4.
6 Wang LL, Gannavarapu A, Kozinetz CA *et al.* Association between osteosarcoma and deleterious mutations in the RECQL4 gene in Rothmund–Thomson syndrome. *J Natl Cancer Inst* 2003; **95**: 669–74.
7 Siitonen HA, Sotkasiira J, Biervliet M *et al.* The mutation spectrum in *RECQL4* diseases. *Eur J Hum Genet* 2009; **17**: 151–8.
8 Ying KL, Olzumi J, Curry CJ. Rothmund–Thomson syndrome associated with trisomy 8 mosaicism. *J Med Genet* 1990; **27**: 258–60.
9 Lindor NM, Devries EM, Michels VV *et al.* Rothmund–Thomson syndrome in siblings: evidence for acquired in vivo mosaicism. *Clin Genet* 1996; **49**: 124–9.
10 Van Maldergem L, Siitonen HA, Jalkh N *et al.* Revisiting the craniosynostosis-radial ray hypoplasia association: Baller-Gerold syndrome caused by mutations in the RECQL4 gene. *J Med Genet* 2006; **43**: 148–52.
11 Siitonen HA, Kopra O, Kääriäinen H *et al.* Molecular defect of RAPADILINO syndrome expands the phenotype spectrum of RECQL diseases. *Hum Mol Genet* 2003; **12**: 2837–44.
12 Fan W, Luo J. RecQ4 facilitates UV-induced DNA damage repair through interaction with nucleotide excision repair factor XPA. *J Biol Chem* 2008; **283**: 29037–44.
13 Smith PJ, Paterson MC. Enhanced radiosensitivity and defective DNA repair in cultured fibroblasts derived from Rothmund–Thomson patients. *Mutat Res* 1982; **94**: 213–28.

14 Shinya A, Nishigori C, Moriwaki S *et al.* A case of Rothmund–Thomson syndrome with reduced DNA repair capacity. *Arch Dermatol* 1993; **129**: 332–6.
15 Tritsch H, Lischka G. Zur Histopathologie der kongenitalen Poikilodermie Thomson. *Z Haut Geschlechtskr* 1968; **43**: 155–66.
16 Simmons IJ. Rothmund–Thomson syndrome: a case report. *Australas J Dermatol* 1980; **21**: 96–9.
17 Berg E, Chuang T-Y, Cripps D. Rothmund–Thomson syndrome. A case report, phototesting, and literature review. *J Am Acad Dermatol* 1987; **17**: 332–8.
18 Moss C. Rothmund–Thomson syndrome: a report of two patients and a review of the literature. *Br J Dermatol* 1990; **122**: 821–9.
19 Vennos EM, Collins M, James WD. Rothmund–Thomson syndrome: review of the world literature. *J Am Acad Dermatol* 1992; **27**: 750–62.
20 Mak RKH, Griffiths WAD, Mellerio JE. An unusual patient with Rothmund-Thomson syndrome, porokeratosis and bilateral iris dysgenesis. *Clin Exp Dermatol* 2006; **31**: 401–3.
21 Kanitakis C, Ktenides MA. Lésions kératosiques et verruqueuses au cours du syndrome de Thomson. *Ann Dermatol Syphiligr* 1972; **99**: 269–76.
22 Stinco G, Governatori G, Mattighello P, Patrone P. Multiple cutaneous neoplasms in a patient with Rothmund-Thomson syndrome: case report and published work review. *J Dermatol* 2008; **35**: 154–61.
23 Werder EA, Mürset G, Illig R *et al.* Hypogonadism and parathyroid adenoma in congenital poikiloderma (Rothmund–Thomson syndrome). *Clin Endocrinol* 1975; **4**: 75–82.
24 Lapunzina P, Fonseca E, Gracia R *et al.* Rothmund–Thomson syndrome and Addison disease. *Pediatr Dermatol* 1995; **12**: 164–9.
25 Moss C, Bacon CJ, Mueller RF. 'Isolated' radial ray defect may be due to Rothmund–Thomson syndrome. *Clin Genet* 1990; **38**: 318–9.
26 Judge MR, Kilby A, Harper JI. Rothmund–Thomson syndrome and osteosarcoma. *Br J Dermatol* 1993; **129**: 723–5.
27 Leonard A, Craft AW, Moss C, Malcolm AJ. Osteogenic sarcoma in the Rothmund–Thomson syndrome. *Med Pediatr Oncol* 1996; **26**: 249–53.
28 Cumin I, Cohen JY, David A *et al.* Rothmund–Thomson syndrome and osteosarcoma. *Med Pediatr Oncol* 1996; **26**: 414–6.
29 Wang LL, Levy ML, Lewis RA *et al.* Clinical manifestations in a cohort of 41 Rothmund-Thomson syndrome patients. *Am J Med Genet* 2001; **102**: 11–7.
30 Rizzari C, Bacchiocchi D, Rovelli A *et al.* Myelodysplastic syndrome in a child with Rothmund–Thomson syndrome: a case report. *J Pediatr Hematol Oncol* 1996; **18**: 96–7.
31 Van-Hees CL, Van-Duinen CM, Bruijin JA *et al.* Malignant eccrine poroma in a patient with Rothmund–Thomson syndrome. *Br J Dermatol* 1996; **134**: 813–5.
32 Ilhan I, Arikan U, Buyukpamukcu M. Rothmund–Thomson syndrome and malignant fibrous histiocytoma: a case report. *Pediatr Hematol Oncol* 1995; **12**: 103–5.
33 Blaustein HS, Stevens AW, Stevens PD *et al.* Rothmund–Thomson syndrome associated with annular pancreas and duodenal stenosis: a case report. *Pediatr Dermatol* 1993; **10**: 159–63.
34 Shuttleworth D, Marks R. Congenital poikiloderma: treatment with etretinate. *Br J Dermatol* 1988; **118**: 729–30.
35 Potozkin JR, Geronemus RG. Treatment of the poikilodermatous component of the Rothmund–Thomson syndrome with the flashlamp-pumped pulsed dye laser: a case report. *Pediatr Dermatol* 1991; **8**: 162–5.

Acrokeratotic poikiloderma of Weary (MIM 173700) [1]

Synonym
- Hereditary sclerosing poikiloderma

This syndrome, probably determined by an autosomal dominant gene, appears to be a distinct entity that has been described in a handful of families [1–3]. It is characterized by generalized poikiloderma with accentuation in the flexures and sparing of the face, scalp and ears, sclerosis of the palms and soles, linear hyperkeratosis and sclerosis of the flexures, and finger clubbing. Tissue calcinosis, Raynaud's phenomenon and cardiac abnormalities have also been described [1,3].

References

1 Weary PE, Hsu YT, Richardson DR *et al.* Hereditary sclerosing poikiloderma: report of two families with an unusual and distinctive genodermatosis. *Arch Dermatol* 1969; **100**: 413–22.
2 Fazio M, Lisi S, Amantea A *et al.* [Weary. Hereditary sclerosing poikiloderma]. *Ann Dermatol Venereol* 1995; **122**: 618–20.
3 Grau Salvat C, Pont V, Cors JR, Aliaga A. Hereditary sclerosing poikiloderma of Weary: report of a new case. *Br J Dermatol* 1999; **140**: 366–8.

Kindler's syndrome (MIM 173650) [1]

Kindler's syndrome is an autosomal recessive disorder characterized by trauma-induced blistering, sun sensitivity, skin atrophy, poikiloderma and mucosal inflammation [1,2]. Although it is now considered to be a form of epidermolysis bullosa, it is clinically and pathologically distinct [3]. Loss-of-function mutations in the gene encoding fermitin family homologue 1 (kindlin 1) (*FERMT1*) on chromosome 20p12.3 have been identified in many affected families [2,4,5]. This is an actin cytoskeleton-associated protein which links the actin cytoskeleton to the extracellular matrix via focal adhesions, with a role in keratinocyte adhesion, migration and proliferation [2]. In the past there has been some confusion between Kindler's syndrome and acrokeratotic poikiloderma of Weary, although these are now considered distinct entities.

Pathology. Histopathology of poikilodermatous areas of skin shows hyperkeratosis, epidermal atophy, loss of rete ridges, dermal pigmentary incontinence, colloid bodies and blood vessel ectasia. Ultrastructurally, there may be reduplication of the lamina densa and clefts around the basement membrane zone, which may be at the level of the basal keratinocyte, within the lamina lucida, or beneath the lamina densa [6].

Clinical features. In neonates and infants, skin fragility and blistering are the most prominent findings, and the condition may be mistaken for other forms of epidermolysis bullosa [2,7]. The blistering tends to improve through childhood, as does the photosensitivity that is a feature in the majority of cases. There is progressive poikiloderma and atrophy, particularly on sun-exposed sites such as the dorsa of the hands and face [1,5,7]. Many patients have nail dystrophy and pseudosyndactyly of the digits. Periodontal disease with erosive gingivitis occurs early [4,8]. Oesophageal, anal, urethral and vaginal stenosis may occur, and an increased risk of squamous cell carcinoma of the skin or mucosae is also well recognized [9–11]. A number of patients have also had colitis and diarrhoea as a feature of their disease [12].

Differential diagnosis. In infancy, the main differential diagnosis is epidermolysis bullosa, although the development of photosensitivity and poikiloderma means that it should be possible to distinguish between these conditions. However, the presence of pseudosyndactyly, scarring, mucosal stenoses and mucocutaneous squamous cell carcinoma may overlap considerably with dystrophic epidermolysis bullosa. Later, Kindler's syndrome must be distinguished from other poikilodermatous conditions.

Treatment. The management of Kindler's syndrome centres around protection of the skin from mechanical trauma, as well as sun avoidance in view of the photosensitivity and predisposition

to skin cancer. Close attention should be paid to oral hygiene to minimize dental loss from periodontal disease. Mucosal strictures may require dilatation, although, generally, non-essential instrumentation should be avoided to minimize the risk of worsening stenoses.

References

1 Kindler T. Congenital poikiloderma with traumatic bulla formation and progressive cutaneous atrophy. *Br J Dermatol* 1954; **66**: 104–11.
2 Lai-Cheong JE, Tanaka A, Hawche G *et al.* Kindler syndrome: a focal adhesion genodermatosis. *Br J Dermatol* 2009; **160**: 233–42.
3 Fine JD, Eady RA, Bauer EA *et al.* The classification of inherited epidermolysis bullosa (EB): report of the Third International Consensus Meeting on Diagnosis and Classification of EB. *J Am Acad Dermatol* 2008; **58**: 931–50.
4 Siegel DH, Ashton GH, Penagos HG *et al.* Loss of kindlin-1, a human homolog of the *Caenorhabditis elegans* actin–extracellular-matrix linker protein UNC-112, causes Kindler syndrome. *Am J Hum Genet* 2003; **73**: 174–87.
5 Jobard F, Bouadjar B, Caux F *et al.* Identification of mutations in a new gene encoding a FERM family protein with a plekstrin homology domain in Kindler syndrome. *Hum Mol Genet* 2003; **12**: 925–35.
6 Hovnanian A, Blanchet-Bardon C, de Prost Y. Poikiloderma of Theresa Kindler: report of a case with ultrastructural study, and review of the literature. *Paediatr Dermatol* 1989; **6**: 82–90.
7 Penagos H, Jaen M, Sancho MT *et al.* Kindler syndrome in native Americans from Panama: report of 26 cases. *Arch Dermatol* 2004; **140**: 939–44.
8 Wiebe CB, Silver JG, Larjava HS. Early-onset periodontitis associated with Weary-Kindler syndrome: a case report. *J Periodontol* 1996; **67**: 1004–10.
9 Mansur AT, Elcioglu NH, Aydingoz IE *et al.* Novel and recurrent *KIND1* mutations in two patients with Kindler syndrome and severe mucosal involvement. *Acta Derm Venereol* 2007; **87**: 563–5.
10 Emanuel PO, Rudikoff D, Phelps RG. Aggressive squamous cell carcinoma in Kindler syndrome. *Skinmed* 2006; **5**: 305–7.
11 Lotem M, Raben M, Zeltser R *et al.* Kindler syndrome complicated by squamous cell carcinoma of the hard palate: successful treatment with high-dose radiation therapy and granulocyte-macrophage colony-stimulating factor. *Br J Dermatol* 2001; **144**: 1284–6.
12 Kern JS, Herz C, Haan E *et al.* Chronic colitis due to an epithelial barrier defect: the role of kindlin-1 isoforms. *J Pathol* 2007; **213**: 462–70.

Miscellaneous syndromes

Bazex–Dupré–Christol syndrome (MIM 301845)

Synonyms
- BDC syndrome
- Bazex syndrome
- Follicular atrophoderma and basal cell carcinomas

First described by Bazex *et al.* in 1964 [1,2], the mode of inheritance is now known to be X-linked dominant with evidence of linkage to Xq24–q27 [3]. This represents the identification of a gene presumed to be involved in hair follicle development and skin tumour formation. Several large family pedigrees have been studied [4–7]. The essential features are follicular atrophoderma, present from birth, and the development of multiple basal cell carcinomas of the face from adolescence onwards. In infancy and childhood, milia are often present. The follicular atrophoderma affects the dorsa of the hands and feet, and sometimes large areas on the extensor surfaces or lower back are affected. The exaggerated follicular funnels ('ice-pick' marks) are caused by deep and lax follicular ostia rather than a true atrophy. The basal cell carcinomas present as lightly-pigmented papules, which resemble melanocytic naevi.

Inconstant features include facial hypohidrosis with or without generalized hypohidrosis [8]; congenital hypotrichosis, which in males is diffuse and affects all scalp hairs, whereas females tend to have normal hairs intermingled with abnormal hairs; and hair-shaft abnormalities, such as pili torti and trichorrhexis nodosa [6,9]. Genital trichoepitheliomas and hidradenitis suppurativa have also been described [10]. There is some clinical overlap with Rombo syndrome, characterized by facial follicular atrophy, multiple milia and hypotrichosis. However, these cases also show erythema, telangiectases and dermal collagen or elastin abnormalities, and the inheritance pattern appears to be autosomal dominant [11,12]. Bazex–Dupré–Christol syndrome is easily distinguished from Gorlin's syndrome (see Chapter 52). It must not be confused with a completely different disorder, acrokeratosis paraneoplastica, a cutaneous marker of malignancy, that has also been labelled as Bazex syndrome [13].

References

1 Bazex A, Dupré A, Christol B. Genodermatose complexe de type indeterminé associant une hypotrichose, un état atrophodermique generalisé et des degenerescences cutanées multiples (epitheliomas-basocellulaires). *Bull Soc Fr Dermatol Syphiligr* 1964; **71**: 206.
2 Bazex A, Dupré A, Christol B. Atrophodermic folliculaire, proliferations basocellulaires et hypotrichose. *Ann Dermatol Syphilol* 1964; **93**: 241–54.
3 Vabres P, Lacombe D, Rabinowitz LG *et al.* The gene for Bazex–Dupré–Christol syndrome maps to chromosome Xq. *J Invest Dermatol* 1995; **105**: 87–91.
4 Kidd A, Carson L, Gregory DW *et al.* A Scottish family with Bazex–Dupré–Christol syndrome: follicular atrophoderma, congenital hypotrichosis, and basal cell carcinoma. *J Med Genet* 1996; **33**: 493–7.
5 Moreau-Cabarrot A, Bonafe JL, Hachich N *et al.* Atrophodermie folliculaire, proliferations baso-cellulaires et hypotrichose (syndrome de Bazex–Dupré–Christol). Etude de deux familles. *Ann Dermatol Vénéréol* 1994; **121**: 297–301.
6 Goeteyn M, Geerts ML, Kint A *et al.* The Bazex–Dupré–Christol syndrome. *Arch Dermatol* 1994; **130**: 337–42.
7 Herges A, Stieler W, Stadler R. Das Bazex–Dupré–Christol–Syndrom. Follikulare Atrophodermie, multiple Basaliome und Hypotrichose. *Hautarzt* 1993; **44**: 385–91.
8 Viksnins P, Berlin A. Follicular atrophoderma and basal cell carcinomas. The Bazex syndrome. *Arch Dermatol* 1977; **113**: 948–51.
9 Meynadier J, Guilhou J-J, Barneon G *et al.* Atrophodermie folliculaire, hypotrichose, grains de milium multiples associés a des dystrophies ostéo-cartilagineuses minimes. Etude familiale de 3 cas. *Ann Dermatol Syphilol Venereol* 1979; **106**: 497–501.
10 Yung A, Newton-Bishop JA. A case of Bazex-Dupré-Christol syndrome associated with multiple genital trichoepitheliomas. *Br J Dermatol* 2005; **153**: 682–4.
11 Michaelsson G, Olsson E, Westermark P. The Rombo syndrome: a familial disorder with vermiculate atrophoderma, milia, hypotrichosis, trichoepitheliomas, basal cell carcinomas and peripheral vasodilation with cyanosis. *Acta Derm Venereol* 1981; **61**: 497–503.
12 Van Steensel MAM, Jaspers NGJ, Steijlen PM. A case of Rombo syndrome. *Br J Dermatol* 2001; **144**: 1215–8.
13 Pecora AL, Landsman L, Imgrund SP *et al.* Acrokeratosis paraneoplastica (Bazex syndrome). *Arch Dermatol* 1983; **119**: 820–6.

Focal facial dermal dysplasia (MIM 136500)

Synonym
- Bitemporal aplasia cutis

The focal facial dermal dysplasias (FFDDs) are a genetically heterogeneous group of disorders characterized by congenital,

bitemporal, round, scar-like lesions with or without associated facial anomalies. Kowalski and Fenske [1] proposed a classification for this group of disorders: type 1, autosomal dominant; type 2, autosomal recessive; and type 3 with other facial features (Setleis syndrome). The genetic basis for the FFDDs is not clear, but it has been suggested that all forms represent a single autosomal dominant disorder with variable penetrance and expression [2].

Brauer [3] originally reported a large kindred with autosomal dominant inheritance. The facial lesions were described as scar-like and varied in size. Hair was absent in the lesions and no sweating could be demonstrated. Apart from the temporal defects, no other abnormalities were noted.

Setleis *et al.* [4] subsequently described five children from three apparently unrelated Puerto Rican families with scar-like defects on each temple and other features including an aged, leonine appearance, absent or multiple rows of eyelashes, eyebrows that slanted sharply upwards and outwards, puckered skin around the eyes, a scar-like median furrow on the chin and a rubbery nose and chin. Histology revealed a thin epidermis and dermis with little elastic tissue and an absence or scarcity of adnexae. Inheritance was assumed to be autosomal recessive.

McGeoch and Reed [5] documented 31 affected persons in six generations of an Australian family with pigmented atrophic lesions on the temples and linear radiating depressions on the forehead. In addition, clefting and hairless depressions on the chin were described. Autosomal dominant inheritance was clearly demonstrated.

A number of cases of FFDD have been described in whom the atrophic, round areas of skin, with or without a hair collar, were located on the cheeks and extended from the preauricular area towards the chin [1,6,7]. The position of these lesions has led to the suggestion that they may result from incomplete maxillary and mandibular ectodermal fusion during embryonic development.

References

1 Kowalski DC, Fenske NA. The focal facial dermal dysplasias: report of a kindred and a proposed new classification. *J Am Acad Dermatol* 1992; **27**: 575–82.
2 Ward KA, Moss C. Evidence for genetic homogeneity of Setleis' syndrome and focal facial dermal dysplasia. *Br J Dermatol* 1994; **130**: 645–9.
3 Brauer A. Hereditaerer symmetrischer systematisierter Naevus aplasticus bei 38 Personen. *Dermatol Wochenschr* 1929; **89**: 1163–8.
4 Setleis H, Kramer B, Valcarcel M, Einhorn AH. Congenital ectodermal dysplasia of the face. *Pediatrics* 1963; **32**: 540–8.
5 McGeoch AH, Reed WB. Familial focal facial dermal dysplasia. *Arch Dermatol* 1973; **107**: 591–5.
6 Stone N, Burge S. Focal facial dermal dysplasia with a hair collar. *Br J Dermatol* 1998; **139**: 1136–7.
7 Wells JM, Weedon D. Focal facial dermal dysplasia or aplasia cutis congenita: a case with hair collar. *Australas J Dermatol* 2001; **42**: 129–31.

Focal dermal hypoplasia (MIM 305600)

Synonyms
- Goltz syndrome
- Goltz–Gorlin syndrome

Definition and aetiology. Focal dermal hypoplasia (FDH) is a rare multisystem condition in which developmental defects of the skin are associated with ocular, dental and skeletal abnormalities. Over 200 cases have been reported, although the incidence is likely to be underestimated, as mildly affected subjects may go unrecognized. FDH is an X-linked dominant disorder, although rare male cases have been reported, as has father to daughter transmission, thought to reflect paternal X chromosome mosaicism [1–3]. The causative gene in this disorder has been identified as *PORCN* on chromosome Xp11.23 [4,5]. This is thought to encode an *O*-acyltransferase involved in Wnt signalling which is important in ectodermal–mesodermal development during embryogenesis. In a number of affected individuals, heterozygous deletions involving *PORCN* have been identified, whereas nonsense, missense and splice site mutations have been implicated in other patients [4–7]. Skewed X-inactivation has been observed in some patients with FDH, indicating a survival advantage for cells expressing the normal X chromosome over those carrying a *PORCN* mutation or deletion [3–5].

Pathology [8,9]. The foci of dermal hypoplasia show extreme reduction in thickness of the dermis, so that subcutaneous fat is situated almost immediately beneath the epidermis. There is debate about whether the defect is primarily an atrophy of the dermis, with secondary fat 'herniation', or a complex developmental abnormality of connective tissue causing both dermal hypoplasia and the development of fat hamartomas [10]. Wnt signalling is known to promote fibroblast proliferation [11] but also inhibit adipogenesis [12]. Inhibition of Wnt signalling pathways resulting from *PORCN* mutations might, therefore, favour mesodermal development of adipocytes in preference to dermal fibroblasts. Papillomatous lesions of FDH show markedly acanthotic epithelium overlying a core of vascular connective tissue.

Clinical features [6–8,13,14]. Findings vary from easily overlooked, mild skin atrophy to severe limb deformity and life-threatening complications. Skin involvement has been present in all but two of the reported cases [15] and is usually regarded as essential for the diagnosis. It remains possible that undiagnosed gene carriers occur with non-cutaneous features alone.

The typical skin lesions, which are present at birth, consist of asymmetrical linear streaks of atrophy and telangiectasia that follow Blaschko's lines. In racially pigmented skin, the lesions may be hypopigmented or hyperpigmented rather than erythematous. Soft reddish-yellow nodules represent the so-called 'fat herniations' (Fig. 15.27). Raspberry-like papillomas are common on the lips, perineum and at other sites, including the ears, fingers, toes, buccal mucosa and oesophagus [16]. Multiple giant papillomas have been reported [17]. In addition, generalized dryness of the skin and pruritus may be features. Nails may be absent or dystrophic. The hair is usually sparse and brittle, and there may be patchy alopecia of the scalp or pubic area. A case of FDH presenting as congenital localized alopecia has been reported [18]. Dental abnormalities are relatively frequently seen and include enamel hypoplasia, hypodontia, microdontia and irregular spacing of the teeth, with malocclusion [19].

Short stature and slender build are usual, and mental development is sometimes delayed. The facial features are characteristic: the skull is small and rounded, the chin is pointed and the facial



Fig. 15.27 Focal dermal hypoplasia: herniation at the site of skin atrophy.

outline is triangular, with protruding ears. The alae nasi may be asymmetrical and notched. The face, trunk and limbs may be asymmetrical. Other skeletal malformations include scoliosis, but most characteristic are syndactyly, polydactyly, ectrodactyly or absence of one or more digits. Facial clefting has also been described [20,21]. Ocular defects [16,22,23] are frequent and include microphthalmos, anophthalmos, coloboma, strabismus, keratoconus and corneal opacification. Intestinal malrotation and mediastinal dextroposition have been described in association with FDH [24].

On radiological examination, osteopathia striata, seen as fine, parallel, vertical, radio-opaque stripes in the metaphyses of the long bones, is found in a large proportion of cases [25,26]. This finding is not pathognomonic, but is present in approximately 20% of gene carriers and can be a useful feature, particularly if the condition is suspected in minimally affected subjects. Skeletal lesions, including giant cell tumours and osteochondromas, are also seen in some cases [27–29].

Diagnosis. The presence of the lesions from birth and the association of linear streaks of atrophy and telangiectasia with soft fatty nodules and malformations of the digits confirms the diagnosis. MIDAS syndrome (*mi*crophthalmia, *d*ermal *a*plasia and *s*clerocornea) has been reported as distinct from focal dermal hypoplasia [30,31].

Treatment. Patients with FDH often require reconstructive surgery for anatomical abnormalities. Intubation for general anaesthesia must be undertaken cautiously, as papillomas may be present in the upper respiratory tract [32].

Airway papillomas have been treated successfully with endoscopic laser treatment [33], and similar cutaneous lesions may respond to curettage and photodynamic therapy [34]. The telangiectatic skin lesions can be improved cosmetically with the vascular pulsed dye laser [35].

References

1 Staughton RCD. Focal dermal hypoplasia (Goltz's syndrome) in a male. *Proc R Soc Med* 1976; **69**: 232–3.
2 Burgdorf WH, Dick GF, Soderberg HD, Goltz RW. Focal dermal hypoplasia in a father and daughter. *J Am Acad Dermatol* 1981; **4**: 273–7.
3 Gorski JL. Father-to-daughter transmission of focal dermal hypoplasia associated with non-random X-inactivation: support for X-linked inheritance and paternal X chromosome mosaicism. *Am J Med Genet* 1991; **40**: 332–7.
4 Grzeschik K-H, Bornholdt D, Oeffner F *et al.* Deficiency of PORCN, a regulator of Wnt signaling, is associated with focal dermal hypoplasia. *Nat Genet* 2007; **39**: 833–5.
5 Wang X, Sutton VR, Peraza-Llanes JO *et al.* Mutations in X-linked PORCN, a putative regulator of Wnt signaling, cause focal dermal hypoplasia. *Nat Genet* 2007; **39**: 836–8.
6 Leoyklang P, Suphapeetiporn K, Wananukul S, Shotelersuk V. Three novel mutations in the PORCN gene underlying focal dermal hypoplasia. *Clin Genet* 2008; **73**: 373–9.
7 Clements SE, Wessagowit V, Lai-Cheong JE *et al.* Focal dermal hypoplasia resulting from a new nonsense mutation, p.E300X, in the PORCN gene. *J Dermatol Sci* 2008; **49**: 39–42.
8 Gorlin RJ, Meskin LH, Peterson WC *et al.* Focal dermal hypoplasia syndrome. *Acta Derm Venereol (Stockh)* 1963; **43**: 421–40.
9 Ishii N, Baba N, Kanaizuka I *et al.* Histopathological study of focal dermal hypoplasia (Goltz syndrome). *Clin Exp Dermatol* 1992; **17**: 24–6.
10 Howell JB, Freeman RG. Cutaneous defects of focal dermal hypoplasia: an ectomesodermal dysplasia syndrome. *J Cutan Pathol* 1989; **16**: 237–58.
11 Cheon SS, Cheah AY, Turley S *et al.* Beta-catenin stabilization dysregulates mesenchymal cell proliferation, motility, and invasiveness and causes aggressive fibromatosis and hyperplastic cutaneous wounds. *Proc Natl Acad Sci USA* 2002; **99**: 6973–8.
12 Ross SE, Hemati N, Longo KA *et al.* Inhibition of adipogenesis by Wnt signaling. *Science* 2000; **289**: 950–3.
13 Goltz RW, Peterson WC, Gorlin RJ *et al.* Focal dermal hypoplasia. *Arch Dermatol* 1962; **86**: 708–17.
14 Goltz RW, Henderson RR, Hitch JM *et al.* Focal dermal hypoplasia syndrome. A review of the literature and report of two cases. *Arch Dermatol* 1970; **101**: 1–11.
15 Ayme S, Fraser FC. Possible examples of the Goltz syndrome (focal dermal hypoplasia) without linear areas of skin hypoplasia. *Birth Defects* 1982; **18**: 59–65.
16 Zala L, Ettlin C, Krebs A. Fokale dermale Hypoplasie mit Keratokonus, Osophaguspapillomen und Hidrokystomen. *Dermatologica* 1975; **150**: 176–85.
17 Kore-Eda S, Yoneda K, Ohtani T *et al.* Focal dermal hypoplasia (Goltz syndrome) associated with multiple giant papillomas. *Br J Dermatol* 1995; **133**: 997–9.
18 Terashi H, Kurata S, Hashimoto H *et al.* A case of Goltz syndrome presenting as congenital incomplete alopecia. *J Dermatol* 1994; **21**: 122–4.
19 Baxter AM, Shaw MJ, Warren K. Dental and oral lesions in two patients with focal dermal hypoplasia (Goltz syndrome). *Br Dent J* 2000; **189**: 550–3.
20 Rodini ES, Nardi A, Guion-Almeida ML *et al.* Ectodermal dysplasia, ectrodactyly, clefting, anophthalmia/microphthalmia, and genitourinary anomalies: nosology of Goltz–Gorlin syndrome versus EEC syndrome. *Am J Med Genet* 1992; **42**: 276–80.
21 Rodini ES, Machado-Paula LA, Vendramini S, Guion-Almeida ML. Atypical facial clefting in a patient with Goltz syndrome. *Am J Med Genet* 2006; **140**: 1616.
22 Willetts GS. Focal dermal hypoplasia. *Br J Ophthalmol* 1974; **58**: 620–4.
23 Lueder GT, Steiner RD. Corneal abnormalities in a mother and daughter with focal dermal hypoplasia (Goltz–Gorlin syndrome). *Am J Ophthalmol* 1995; **120**: 256–8.
24 Irvine AD, Stewart FJ, Bingham EA *et al.* Focal dermal hypoplasia (Goltz syndrome) associated with intestinal malrotation and mediastinal dextroposition. *Am J Med Genet* 1996; **62**: 213–5.

25 Howell JB, Reynolds J. Osteopathia striata. A diagnostic osseous marker of focal dermal hypoplasia. *Trans St John's Hosp Dermatol Soc* 1974; **60**: 178–82.
26 Happle R, Lenz W. Striation of bones in focal dermal hypoplasia: manifestation of functional mosaicism? *Br J Dermatol* 1977; **96**: 133–8.
27 Lynch RD, Leshner RT, Nicholls PJ *et al.* Focal dermal hypoplasia (Goltz's syndrome) with an expansile iliac lesion. A case report. *J Bone Joint Surg* 1981; **63A**: 470–3.
28 Joannides T, Pringle JAS, Shaw DG *et al.* Case reports: giant cell tumour of bone in focal dermal hypoplasia. *Br J Radiol* 1983; **56**: 684–5.
29 Cox NH, Paterson WD. Osteochondroma of humerus in focal dermal hypoplasia (Goltz) syndrome. *Clin Exp Dermatol* 1991; **16**: 283–4.
30 Happle R, Daniels O, Koopman RJ. MIDAS syndrome (microphthalmia, dermal aplasia, and sclerocornea): an X-linked phenotype distinct from Goltz syndrome. *Am J Med Genet* 1993; **47**: 710–3.
31 Mucke J, Happle R, Theile H. MIDAS syndrome respectively MLS syndrome: a separate entity rather than a particular lyonization pattern of the gene causing Goltz syndrome. *Am J Med Genet* 1995; **57**: 117–8.
32 Holzman RS. Airway involvement and anesthetic management in Goltz's syndrome. *J Clin Anesth* 1991; **3**: 422–5.
33 Gordjani N, Herdeg S, Ross UH *et al.* Focal dermal hypoplasia (Goltz-Gorlin syndrome) associated with obstructive papillomatosis of the larynx and hypopharynx. *Eur J Dermatol* 1999; **9**: 618–20.
34 Mallipeddi R, Chaudhury SI, Darley CR, Kurwa HA. A case of focal dermal hypoplasia (Goltz) syndrome with exophytic granulation tissue treated by curettage and photodynamic therapy. *Clin Exp Dermatol* 2006; **31**: 228–31.
35 Alster TS, Wilson F. Focal dermal hypoplasia (Goltz's syndrome). Treatment of cutaneous lesions with the 585-nm flashlamp-pumped pulsed dye laser. *Arch Dermatol* 1995; **131**: 143–4.

Nail–patella syndrome (MIM 161200)

Synonym
- Hereditary onycho-osteodysplasia (Hood) syndrome

First described by Turner in 1933 [1] and Aschner in 1934 [2], nail–patella syndrome was the first human disorder to be mapped by linkage [3]. Linkage to the ABO blood group was subsequently narrowed to an interval on chromosome 9q34.1 [4,5]. The condition shows autosomal dominant inheritance with variable expressivity but high penetrance. The causative gene, *LMX1B*, encodes an LIM-homeodomain protein, a presumed transcription factor with a role in dorsal/ventral limb patterning, and the development of the glomerular basement membrane, the anterior segment of the eye, and serotoninergic and dopaminergic neurones. Heterozygous loss-of-function mutations have been described in many families with nail–patella syndrome [6–10].

The syndrome combines nail and skeletal defects [10–14]. The nails are dystrophic in 95% of cases, either from birth or early childhood. The thumbnails are most severely involved and may be absent or small, thickened and depressed. Nails of other fingers, and sometimes of the toes, may also be affected. The lunulae are often triangular and may be the only nail change seen.

In only 20% of cases is there aplasia of the patella, but in another 70% there is subluxation of the patella. Other skeletal defects include the presence of posterior iliac horns [15,16], clavicular horns [17], dislocation of the radial heads, scoliosis and thickened scapulae [18–20].

Various renal abnormalities have been recorded, with glomerulonephritis seen most commonly, in 30–55%. It may remain asymptomatic for many years, although end-stage renal failure may occur [21–24]. In cases with glomerulonephritis, there is damage to the basement membrane, with deposition of C3 and IgM in the mesangium. Genotype–phenotype correlation for *LMX1B* mutations has been demonstrated: mutations within the homeodomain are associated with more frequent occurrence and greater levels of proteinuria compared with individuals with mutations in the LIM domains [10].

Hyperpigmentation of the pupillary margin of the iris (Lester iris) occurs in approximately half of all cases. Glaucoma and ocular hypertension may also occur [14,25].

Other features described in nail–patella syndrome include a 'glove and stocking' distribution of numbness or tingling, epilepsy, poor peripheral circulation [14] and sensorineural hearing loss [10]. Reduced bone mineral density compared with controls has been suggested to account for an increased risk of skeletal fractures and scoliosis [26].

References

1 Turner JW. An hereditary arthrodysplasia associated with hereditary dystrophy of the nails. *JAMA* 1933; **100**: 882–4.
2 Aschner B. A typical hereditary syndrome: dystrophy of the nails, congenital defect of the patella and congenital defect of the head of the radius. *JAMA* 1934; **102**: 2017–20.
3 Renwick JH, Lawler SD. Genetical linkage between the ABO and nail-patella loci. *Ann Hum Genet* 1955; **19**: 312–31.
4 Campeau E, Watkins D, Rouleau GA *et al.* Linkage analysis of the nail–patella syndrome. *Am J Hum Genet* 1995; **56**: 243–7.
5 McIntosh I, Clough MV, Schaffer AA *et al.* Fine mapping of the nail-patella syndrome locus at 9q34. *Am J Hum Genet* 1997; **60**: 133–42.
6 Dreyer SD, Zhou G, Baldini A *et al.* Mutations in LMX1B cause abnormal skeletal patterning and renal dysplasia in nail patella syndrome. *Nat Genet* 1998; **19**: 47–50.
7 Vollrath D, Jaramillo-Babb VL, Clough MV *et al.* Loss-of-function mutations in the LIM-homeodomain gene, LMX1B, in nail-patella syndrome. *Hum Mol Genet* 1998; **7**: 1091–8.
8 McIntosh I, Dreyer SD, Clough MV *et al.* Mutation analysis of LMX1B gene in nail-patella syndrome patients. *Am J Hum Genet* 1998; **63**: 1651–8.
9 Hamlington J, Jones C, McIntosh I. Twenty-two novel LMX1B mutations identified in nail patella syndrome (NPS) patients. *Hum Mutat* 2001; **18**: 458.
10 Bongers EMHF, Huysmans FT, Levtchenko E *et al.* Genotype-phenotype studies in nail-patella syndrome show that LMX1B mutation location is involved in the risk of developing nephropathy. *Eur J Hum Genet* 2005; **13**: 935–46.
11 Gibbs RC, Berczeller PH, Hyman AB. Nail–patella–elbow syndrome. *Arch Dermatol* 1964; **89**: 196–9.
12 Pillay VK. Onycho-osteodysplasia (nail–patella syndrome). Study of a Chinese family with this condition. *Ann Hum Genet* 1965; **28**: 301–7.
13 Downey N. A case report of an Irish family displaying nail–patella syndrome. *Ir J Med Sci* 1993; **162**: 86–7.
14 Sweeney E, Fryer A, Mountford R *et al.* Nail patella syndrome: a review of the phenotype aided by developmental biology. *J Med Genet* 2003; **40**: 153–62.
15 Fong EE. 'Iliac horns' (symmetrical bilateral central posterior iliac processes): a case report. *Radiology* 1946; **47**: 517–8.
16 Karabulut N, Ariyurek M, Erol C *et al.* Imaging of 'iliac horns' in nail–patella syndrome. *J Comput Assist Tomogr* 1996; **20**: 530–1.
17 Yarali HN, Erden GA, Karaarslan F *et al.* Clavicular horn: another bony projection in nail–patella syndrome. *Pediatr Radiol* 1995; **25**: 549–50.
18 Burkhart CG, Bhumbra R, Iannone AM. Nail–patella syndrome. *J Am Acad Dermatol* 1980; **3**: 251–6.
19 Duncan JG, Souter WA. Hereditary onycho-osteodysplasia. The nail–patella syndrome. *J Bone Joint Surg* 1963; **45B**: 242–58.
20 Guidera KJ, Satterwhite Y, Ogden JA *et al.* Nail patella syndrome: a review of 44 orthopaedic patients. *J Pediatr Orthop* 1991; **11**: 737–42.
21 Bennett WM, Musgrave JE, Campbell RA *et al.* The nephropathy of the nail–patella syndrome. Clinicopathologic analysis of 11 kindred. *Am J Med* 1973; **54**: 304–19.

22 Curtis JJ, Bhathena D, Leach RP *et al.* Goodpasture's syndrome in a patient with the nail–patella syndrome. *Am J Med* 1976; **61**: 401–6.
23 Hawkins CF, Smith OE. Renal dysplasia in a family with multiple hereditary abnormalities including iliac horns. *Lancet* 1950; **1**: 803–8.
24 Morita T, Laughlin LO, Kawano K *et al.* Nail–patella syndrome. Light and electron microscopic studies of the kidney. *Arch Intern Med* 1973; **131**: 271–7.
25 Lichter PR, Richards JE, Downs CA *et al.* Cosegregation of open-angle glaucoma and the nail-patella syndrome. *Am J Ophthalmol* 1997; **124**: 506–15.
26 Towers AL, Clay CA, Sereika SM *et al.* Skeletal integrity in patients with nail patella syndrome. *J Clin Endocr Metab* 2005; **90**: 1961–5.

Clubbing of the fingers and toes (MIM 119900)

Synonyms
- Hippocratic fingers
- Acropachy

Definition. Clubbing results from swelling of the soft tissues of the terminal phalanx of a digit that obliterates the angle between the base of the nail and the digit [1]. Hypertrophic osteoarthropathy (HOA) (see below) is often associated with clubbing, but can occur without it. In thyroid acropachy, clubbing is associated with thickening of the soft tissues of the hands and feet, and periosteal new bone formation occurs in the hands and feet rather than the long bones [2].

Aetiology. Clubbing may occur early as a hereditary defect in otherwise healthy individuals, or in association with underlying systemic disease. Autosomal inheritance with variable penetrance and expressivity has been proposed in familial cases [3,4], and there is suggestive evidence [5] that hereditary predisposition may play some part in the more common acquired forms. Recently, Tariq *et al.* [6] identified a homozygous missense mutation in the *HPGD* gene in a consanguineous family with isolated congenital clubbing. This gene, on chromosome 4q34–q35, encodes NAD^+ dependent 15-hydroxyprostaglandin dehydrogenase, an enzyme involved in the regulation of prostaglandin metabolism. Mutations in the same gene have also been identified in families with primary hypertrophic osteoarthropathy [7].

Acquired clubbing may be associated with pulmonary (empyema, lung abscess, cystic fibrosis, bronchial carcinoma, etc.), cardiovascular (cyanotic heart disease, subacute bacterial endocarditis, atrial myxoma, etc.), gastrointestinal (inflammatory bowel disease, coeliac disease, etc.) or metabolic (thyroid acropachy, Grave's disease) disease [8–10].

Pathology and pathogenesis. Increased fibrous tissue separates the nail from the phalanx, and there may be perivascular lymphocytic infiltration. The bone is not usually affected, but spurs of bone may occasionally form on the terminal phalanx. Many studies have shown that the blood flow to clubbed fingers is increased, except in hereditary clubbing [10]. The flow returns to normal if the clubbing improves after elimination of the underlying pathology. It is possible that the increased blood flow travels through the central Suquet–Hoyer canals of the digital arteriovenous anastomoses. There is at present no single satisfactory theory to account for the hyperaemia and soft-tissue overgrowth, and there may be several mechanisms. Identification of *HPGD* mutations in isolated clubbing and primary hypertrophic osteoarthropathy may support a role of prostaglandins in the aetiology of clubbing [6,7], although other vasodilators have been proposed, including ferritin [10], bradykinin and serotonin [11]. Tissue hypoxia [10] and neural factors [6] have also been suggested.

Clinical features [1,5]. The normal nail projects from the digit at an obtuse angle of about 160°, most clearly seen on the thumbs. In clubbing, this angle is obliterated, and sometimes reversed. The nail plate usually shows increased curvature in one or both planes and the volume of the distal phalanx may be increased.

In hereditary clubbing, these changes may be congenital [6,12] or begin gradually at, or soon after, puberty. They commonly involve all fingers and toes, particularly the thumbs, although occasionally some digits may be spared. In acquired clubbing, the onset is usually insidious and may occur at any age, but even in severe cyanotic congenital heart disease it is seldom noticeable before the second year. It may be bilateral or unilateral, or may affect only one or two digits. In malignant pulmonary disease, the onset may be rapid and painful.

Diagnosis. The distinction between hereditary and acquired clubbing may be of great clinical significance, as clubbing may precede any other evidence of pulmonary neoplasm by many months. Hypertrophic osteoarthropathy always shows bone and often joint changes, and clubbing is merely one feature of the syndrome. Familial osteoarthropathy [13], a manifestation of avascular necrosis of phalangeal epiphyses, presents before puberty as enlargement and impaired mobility of interphalangeal joints.

Pseudoclubbing may be produced by shortening of the fingernail, which accompanies osteolysis of the terminal phalanges, such as has occurred in workers engaged in the polymerization of vinyl chloride [14].

Unilateral or unidigital clubbing is usually due to a vascular abnormality, such as an aneurysm in the affected limb. Unilateral clubbing can also be caused by neural damage, for example a Pancoast tumour, or prolonged hemiplegia.

Treatment. The secondary form may show some regression if the provocative disease is treated [15].

References

1 Marrie TJ, Brown N. Clubbing of the digits. *Am J Med* 2007; **120**: 940–1.
2 McCarthy J, Twersky J, Lion M. Thyroid acropachy. *J Can Assoc Radiol* 1975; **26**: 199–202.
3 Curth HO, Firschein IL, Alpert M. Familial clubbed fingers. *Arch Dermatol* 1961; **83**: 828–36.
4 Lees E. Hippocratisme familial avec coloration jaunâtre des paumes, associé dans un cas à une hypercarotinémie temporaire. *J Genet Hum* 1958; **6**: 304.
5 Fischer DS, Singer DH, Feldman SM. Clubbing, a review, with emphasis on hereditary acropachy. *Medicine (Baltimore)* 1964; **43**: 459–79.
6 Tariq M, Azeem Z, Ali G *et al.* Mutation in the HPGD gene encoding NAD+ dependent 15-hydroxyprostaglandin dehydrogenase underlies isolated congenital nail clubbing (ICNC). *J Med Genet* 2009; **46**: 14–20.
7 Uppal S, Diggle CP, Carr IM *et al.* Mutations in 15-hydroxyprostaglandin dehydrogenase cause primary hypertrophic osteoarthropathy. *Nat Genet* 2008; **40**: 789–93.
8 Mauer EF. On the etiology of clubbing of the fingers. *Am Heart J* 1947; **34**: 852–9.

9 Kitis G, Thompson H, Allan RN. Finger clubbing in inflammatory bowel disease: its prevalence and pathogenesis. *BMJ* 1979; **ii**: 825–8.
10 Schneerson JM. Digital clubbing and hypertrophic osteoarthropathy: the underlying mechanism. *Br J Dis Chest* 1981; **75**: 113–31.
11 Audebert AA, Aubriot A, Krulik M *et al.* Hypertrophic pulmonary osteoarthropathy with paraneoplastic secretion of four hormones. Considerations on pathogenesis. *Semin Hôp* 1982; **58**: 529–30.
12 DeSèze S, Jurmand SH. Pachydermopériostose. Hippocratisme digital chez le père atteint de bronchopneumopathie chronique et chez lefrère bien portant. Réflexions sur le rôle du facteur héréditaire et familial dans la genèse des hypertrophies des extrémités. *Soc Med Hôp Paris* 1950; **66**: 860–4.
13 Allison AC, Blumberg BS. Familial osteoarthropathy of the fingers. *J Bone Joint Surg* 1958; **40B**: 538–45.
14 Harris DK, Adams WGF. Acro-osteolysis occurring in men engaged in the polymerization of vinyl chloride. *BMJ* 1967; **iii**: 712–4.
15 Lopez-Majano V, Layon J, Britt T. Pulmonary hypertrophic osteoarthropathy: its modification by therapy. *Eur J Nucl Med* 1982; **7**: 419–21.

Pachydermoperiostosis (MIM 167100, 1259100)

(see also Chapters 45 & 62)

Synonym
- Hypertrophic osteoarthropathy

Definition and terminology. Pachydermoperiostosis is a syndrome characterized by hypertrophic changes involving predominantly the skin and bones of the extremities. The term 'cutis verticis gyrata' describes a folded hyperplasia of the scalp that may accompany pachydermoperiostosis but also has other causes.

Aetiology [1–4]. *Primary pachydermoperiostosis* (synonym Touraine–Solente–Golé syndrome) is a rare inherited disorder that has been reported in many ethnic groups and which occurs predominantly in males. In some families, autosomal dominant inheritance with incomplete penetrance and variable expressivity has been proposed [3]. In other families, however, autosomal recessive inheritance has been demonstrated [3,4], and mutations in the *HPGD* gene, encoding NAD^+ dependent 15-hydroxyprostaglandin dehydrogenase, have been identified [4]. Affected individuals with homozygous truncating mutations of *HPGD* have been found to have greatly increased levels of urinary prostaglandin E2; a number of these patients also had a persistent patent ductus arteriosus, presumed secondary to the elevated prostaglandin levels [4]. Heterozygous carriers of *HPGD* mutations may have mild clubbing of the digits [4].

Cranio-osteoarthropathy shares some features with primary pachydermoperiostosis, namely clubbing and hypertrophic osteoarthropathy, but patients do not have pachydermia. They typically present earlier in childhood and have delayed neurocranial ossification, with delayed closure of the fontanelles, and may also have congenital heart disease. The overlap of clinical features suggests that primary pachydermoperiostosis and cranio-osteoarthropathy are allelic in some cases, and this has been confirmed by the identification of homozygous missense mutations in *HPGD* in two families with the latter condition [4].

Secondary pachydermoperiostosis (synonym secondary hypertrophic osteoarthropathy) is usually provoked by severe pulmonary disease, adenocarcinoma or epidermoid carcinoma of the bronchus, pleural mesothelioma, bronchiectasis, lung abscess or, less often, carcinoma of the stomach, oesophagus or thymus. In cyanotic congenital heart disease with clubbing, bone changes rarely develop.

Pathology [2,5]. Proliferative periostitis of the leg bones, especially in the diaphyses of the tibia, fibula, radius and ulna, leads to diffuse irregular periosteal ossification, increasing the circumference of affected bones without increasing their length. In severe cases, almost all bones may be involved, and ligaments, tendons and interosseous membranes may ossify. Abnormal ossification of the skull has been reported [6]. In the early stages, but not the later stages, there is increased blood flow to the clubbed fingers [7,8]. The skin shows hypertrophy of collagen and of epidermis and epidermal appendages, and an increase of acid mucopolysaccharide.

Clinical features [3,4,9–12]. Primary pachydermoperiostosis usually begins soon after puberty. The skin of the face, forehead and scalp becomes grossly thickened and thrown into folds. The folding of the scalp produces one of the forms of cutis verticis gyrata. The skin of the hands and feet is also thickened, but usually not folded. Seborrhoea of the face and scalp, and hyperhidrosis of hands and feet may be troublesome.

Thickening of the phalanges and of the bones of the limbs produces spade-like hands and feet with increased circumference of arms and legs. The fingers and toes are clubbed. Acro-osteolysis of the fingers and toes may occasionally occur [8].

Skin and bone changes become progressively more severe for 5–10 years and then usually remain unchanged throughout life; exceptionally, they may continue to progress and the degree of sebaceous hyperplasia may become extreme. Sparse facial and pubic hair and gynaecomastia are present in some cases, but evidence of endocrine disturbance is equivocal. Many patients have learning difficulties, which may be profound. Expectation of life is reduced in such patients, although reliable figures for the less severely affected are not available. Cranio-osteoarthropathy is characterized by clubbing, hypertrophic osteoarthropathy, delayed cranial ossification and closure of the fontanelles, and, in some cases, congenital heart disease, but not by the skin changes seen in primary pachydermoperiostosis [12–14]. These changes usually start early in childhood.

Secondary pachydermoperiostosis occurs predominantly in men aged 30–70 years. The bone changes are the most obvious feature, develop more rapidly, and are often painful. The skin changes may be absent and are often relatively mild. If the primary disease can be treated effectively, the bone and skin changes will regress.

Radiological changes. The greatest periosteal thickening is seen in the diaphyses of metatarsals and metacarpals and the long bones of the limbs. There is some thickening of the cortex (Fig. 15.28).

Diagnosis. The primary and secondary forms of pachydermoperiostosis must be differentiated by the age of onset, the rate of progression and the presence of underlying pulmonary pathol-



Fig. 15.28 Pachydermoperiostosis: radiograph of the ankle. (Courtesy of the late Dr J. Savin, Edinburgh, UK.)

ogy. Although skin changes are more frequent in the primary form, their presence does not exclude a tumour.

In acromegaly, the facial skeleton, jaw and skull as a whole are enlarged, and visual defects may be detectable. In thyroid acropachy, enlargement is confined to hands and feet, and exophthalmos and pretibial myxoedema are often present, with other signs of hyperthyroidism.

References

1 Fischer DS, Singer DH, Feldman SM. Clubbing, a review, with emphasis on hereditary acropachy. *Medicine (Baltimore)* 1964; **43**: 459–79.
2 Vogel A, Goldfischer S. Pachydermoperiostosis. Primary or idiopathic hypertrophic osteoarthropathy. *Am J Med* 1962; **33**: 166–87.
3 Castori M, Sinibaldi L, Mingarelli R *et al.* Pachydermoperiostosis: an update. *Clin Genet* 2005; **68**: 477–86.
4 Uppal S, Diggle CP, Carr IM *et al.* Mutations in 15-hydroxyprostaglandin dehydrogenase cause primary hypertrophic osteoarthropathy. *Nat Genet* 2008; **40**: 789–93.
5 Hambrick GW, Carter M. Pachydermoperiostosis. Touraine–Solente–Golé syndrome. *Arch Dermatol* 1966; **94**: 594–608.
6 Bartolozzi G, Bernini G, Maggini M. Hypertrophic osteoarthropathy without pachydermia. Idiopathic form. *Am J Dis Child* 1975; **129**: 849–51.
7 Jajic I, Pecina M, Kistulovic B *et al.* Primary hypertrophic osteoarthropathy (PHO) and changes in the joints. Clinical, X-ray, scintigraphic, arteriographic and histologic examination of 19 patients. *Scand J Rheumatol* 1980; **9**: 89–96.
8 Fam AG, Chin-Sang H, Ramsay CA. Pachydermoperiostosis: scintigraphic, thermographic, plethysmographic, and capillaroscopic observations. *Ann Rheum Dis* 1983; **42**: 98–102.
9 Touraine A, Solente G, Golé L. Un syndrome ostéo-dermopathique: la pachydermie plicaturée avec pachypériostose des extrémitiés. *Presse Med* 1958; **92**: 1820–4.
10 Lubach D, Freyschmidt J, Bolten D. Pachydermoperiostosis (Touraine–Solente–Golé syndrome). Clinical and radiological differential diagnosis. *Z Hautkr* 1980; **56**: 175–86.
11 Schneider I, Szabo L, Endrody K *et al.* Pachydermoperiostosis (Touraine–Solente–Golé Syndrom). *Hautarzt* 1982; **33**: 221–3.
12 O'Connell S, Suri M, Duff D *et al.* Congenital cardiac disease as a core feature of cranio-osteoarthropathy. *Clin Dysmorphol* 2004; **13**: 213–9.
13 Dabir T, Sills AM, Hall CM *et al.* Cranio-osteoarthropathy in sibs. *Clin Dysmorphol* 2007; **16**: 197–201.
14 Latos-Bielenska A, Marik I, Kuklik M *et al.* Pachydermoperiostosis—critical analysis with report of five unusual cases. *Eur J Pediatr* 2007; **166**: 1237–43.

Cutis verticis gyrata

This condition is characterized by convoluted ridges and folds of skin affecting the scalp. It may occur as a primary condition, either in isolation (rarely) or in association with other abnormalities, notably impaired cognition and learning difficulties, cerebral palsy, schizophrenia, microcephaly, deafness, cataracts, retinitis pigmentosa and strabismus. Cutis verticis gyrata may also be secondary to a number of other diseases including cerebriform intradermal naevi, cylindromas, neurofibromatosis, dermatofibromas, connective tissue naevi, acromegaly, inflammatory conditions of the scalp, Noonan's and Turner's syndrome, and acanthosis nigricans.

Acromegaloid phenotype with cutis verticis gyrata and corneal leukoma (MIM 102100) [1]

Synonym
- Rosenthal–Kloepfer syndrome

In this rare, autosomal dominant syndrome, there are acromegaloid facial features but the sella turcica is normal in size. There may be hyperplasia and folding of the facial skin. The scalp is enlarged, causing gyrate folds in the skin, and the dermal ridges in the palms are split longitudinally. During the first decade of life, the cornea becomes opaque, often bilaterally. No endocrine abnormality has been detected.

Reference

1 Rosenthal JW, Kloepfer HW. An acromegaloid, cutis verticis gyrata, corneal leukoma syndrome. A new medical entity. *Arch Ophthalmol* 1962; **68**: 722–6.

Cutis verticis gyrata and mental deficiency (MIM 219300)

Cutis verticis gyrata has been identified with a frequency of up to 5% in institutionalized patients with severe cognitive impairment and learning difficulties [1,2]. Chromosomal fragility has been described in a significant proportion of affected individuals [2].

References

1 Akesson HO. Cutis verticis gyrata and mental deficiency in Sweden. I. Epidemiologic and clinical aspects. *Acta Med Scand* 1964; **175**: 115–27.
2 Schepis C, Palazzo R, Cannavo SP *et al.* Prevalence of primary cutis verticis gyrata in a psychiatric population: association with chromosomal fragile sites. *Acta Derm Venereol* 1990; **70**: 483–6.

Cutis verticis gyrata, retinitis pigmentosa and sensorineural deafness (MIM 605685) [1]

This disorder, described in two brothers, comprises primary cutis verticis gyrata, microcephaly, retinitis pigmentosa, cataracts, sensorineural hearing loss and impaired cognition.

Reference

1 Megarbane A, Waked N, Chouery E *et al.* Microcephaly, cutis verticis gyrata of the scalp, retinitis pigmentosa, cataracts, sensorineural deafness, and mental retardation in two brothers. *Am J Med Genet* 2001; **98**: 244–9.

Table 15.5 The main craniosynostosis syndromes.

Syndrome	Other features in addition to craniosynostosis	Chromosomal localization	Gene	Reference
Apert	Mid-face malformations, syndactyly of hands and feet, acne	10q26	*FGFR2*	[2]
Crouzon	Proptosis, acanthosis nigricans (AN)	10q26	*FGFR2*	[3]
		4p16.3	*FGFR3* (with AN)	[4]
Pfeiffer	Broad halluces and thumbs	8p11.2–11.1/10q26	*FGFR1/FGFR2*	[5,6]
Saethre–Chotzen	Ptosis, facial asymmetry, low hairline	7p21	*TWIST*	[7,8]
Beare–Stevenson	Cutis gyrata	10q26	*FGFR2*	[9]

FGFR, fibroblast growth factor receptor gene; *TWIST*, the human counterpart of the murine *Twist* gene, a basic helix–loop–helix transcription factor.

The craniosynostoses

Craniosynostosis is the premature fusion of skull sutures in infancy causing craniofacial malformation, often in association with other abnormalities. More than 100 syndromic forms of craniosynostosis have been described [1]. Most notable are the eponymously named, autosomal dominantly inherited syndromes of Apert, Crouzon, Pfeiffer, Saethre–Chotzen and Beare–Stevenson. There have been significant advances in understanding of the genetic basis of many of these disorders, especially in relation to fibroblast growth factor receptor genes (Table 15.5). This group of disorders displays allelic heterogeneity in addition to phenotypic variability and overlap.

References

1 Reardon W, Winter RM. The molecular pathology of syndromic craniosynostosis. *Mol Med Today* 1995; **1**: 432–7.
2 Wilkie AOM, Slaney SF, Oldridge M *et al.* Apert syndrome results from localised mutations of FGFR2 and is allelic with Crouzon syndrome. *Nat Genet* 1995; **9**: 165–72.
3 Reardon W, Winter RM, Rutland P *et al.* Mutations in the fibroblast growth factor receptor 2 gene cause Crouzon syndrome. *Nat Genet* 1994; **8**: 98–104.
4 Meyers GA, Orlow SJ, Munro IR *et al.* Fibroblast growth factor receptor 3 (FGFR3) transmembrane mutation in Crouzon syndrome with acanthosis nigricans. *Nat Genet* 1995; **11**: 462–4.
5 Muenke M, Schell U, Hehr A *et al.* Mutations in the fibroblast growth factor receptor-1 gene in Pfeiffer syndrome. *Nat Genet* 1994; **8**: 269–74.
6 Rutland P, Pulleyn LJ, Reardon W *et al.* Identical mutations in the *FGFR2* gene cause both Pfeiffer and Crouzon syndrome phenotypes. *Nat Genet* 1995; **9**: 173–6.
7 Howard TD, Paznekas WA, Green ED *et al.* Mutations in *TWIST*, a basic helix–loop–helix transcription factor, in Saethre–Chotzen syndrome. *Nat Genet* 1997; **15**: 36–41.
8 El Ghouzzi V, Le Merrer M, Perrin-Schmitt F *et al.* Mutations of the *TWIST* gene in the Saethre–Chotzen syndrome. *Nat Genet* 1997; **15**: 36–41.
9 Przylepa KA, Paznekas W, Zhang M *et al.* Fibroblast growth factor receptor 2 mutations in Beare–Stevenson cutis gyrata syndrome. *Nat Genet* 1996; **13**: 492–4.

Apert's syndrome (MIM 101200) [1–4]

Synonym
- Acrocephalosyndactyly

Apert's syndrome is characterized by craniosynostosis, mid-facial malformations and a characteristic syndactyly of the hands with a 'mitten-like' appearance caused by fusion of the fingers (and sometimes the thumb). Moderate or severe acne develops in all cases at puberty, with comedones on the arms and forearms as well as in the commonly affected sites [5,6]. Hyperhidrosis is common, and excess wrinkling of the forehead skin is also described [6]. In a report by Henderson *et al.* [7], severe acne in two patients with Apert's syndrome responded well to isotretinoin therapy. Immunohistochemical studies of the skin showed no difference in the number of cells expressing androgen receptors between the patients with Apert's syndrome and controls.

Most cases of Apert's syndrome are sporadic, although autosomal dominant transmission is reported. The vast majority of cases result from one of two missense mutations in the *FGFR2* gene [8–10]. One of these recurrent mutations has also been identified in lesional skin from an acneiform naevus, indicating somatic mosaicism [11].

References

1 Apert ME. De l'acrocephalosyndactylie. *Bull Mem Soc Méd Hôp Paris* 1906; **23**: 1310–30.
2 Blank CE. Apert's syndrome (a type of acrocephalosyndactyly): observations on a British series of 39 cases. *Ann Hum Genet* 1960; **24**: 151–64.
3 Musallam SS, Poley JR, Riley HD. Apert's syndrome (acrocephalosyndactyly). A description and a report on seven cases. *Clin Pediatr* 1975; **14**: 1054–62.
4 McNaughton PZ, Rodman OG. Apert's syndrome. *Cutis* 1980; **25**: 538–40.
5 Solomon LM, Fretzin D, Pruzansky S. Pilosebaceous abnormalities in Apert's syndrome. *Arch Dermatol* 1970; **102**: 381–5.
6 Cohen MM Jr, Kreiborg S. Cutaneous manifestations of Apert syndrome. *Am J Med Genet* 1995; **58**: 94–6.
7 Henderson CA, Knaggs H, Clark A *et al.* Apert's syndrome and androgen receptor staining of the basal cells of sebaceous glands. *Br J Dermatol* 1995; **132**: 139–43.
8 Wilkie AOM, Slaney SF, Oldridge M *et al.* Apert syndrome results from localised mutations of *FGFR2* and is allelic with Crouzon syndrome. *Nat Genet* 1995; **9**: 165–72.
9 Lajeunie E, Cameron R, El Ghouzzi V *et al.* Clinical variability in patients with Apert's syndrome. *J Neurosurg* 1999; **90**: 443–7.
10 Oldridge M, Zackai EH, McDonald-McGinn DM *et al.* De novo Alu-element insertions in FGFR2 identify a distinct pathological basis for Apert syndrome. *Am J Hum Genet* 1999; **64**: 446–61.
11 Munro CS, Wilkie AOM. Epidermal mosaicism producing localized acne: somatic mutation in *FGFR2*. *Lancet* 1998; **352**: 704–5.

Crouzon's syndrome (MIM 123500) [1]

Synonym
- Craniofacial dysostosis

Crouzon's syndrome is characterized by craniosynostosis, maxillary hypoplasia, shallow orbits and ocular proptosis. Like Apert's syndrome, it is an autosomal dominant disorder resulting from mutations in the *FGFR2* gene [2]. Some patients with features of

Crouzon's syndrome also have acanthosis nigricans, which is of early onset before puberty, and wide in its distribution (neck, axillae, chest, abdomen, perioral, periorbital and nasolabial folds). There is a female preponderance for this disorder [3]. Patients with this form of Crouzon's syndrome have been shown to have a specific missense mutation in the *FGFR3* gene [4].

References

1 Crouzon O. Dysostose cranio-faciale héréditaire. *Bull Soc Méd Hôp Paris* 1912; **33**: 545–55.
2 Reardon W, Winter RM, Rutland P *et al.* Mutations in the fibroblast growth factor receptor 2 gene cause Crouzon syndrome. *Nat Genet* 1994; **8**: 98–104.
3 Arnaud-Lopez L, Fragoso R, Mantilla-Capacho J, Barros-Nunez P. Crouzon with acanthosis nigricans: further delineation of the syndrome. *Clin Genet* 2007; **72**: 405–10.
4 Meyers GA, Orlow SJ, Munro IR *et al.* Fibroblast growth factor receptor 3 (FGFR3) transmembrane mutation in Crouzon syndrome with acanthosis nigricans. *Nat Genet* 1995; **11**: 462–4.

Pfeiffer's syndrome (MIM 101600)

In 1964, Pfeiffer [1] described a syndrome comprising craniosynostosis, broad thumbs, broad great toes and, in some, partial soft-tissue syndactyly of the hands. Other features may include umbilical hernia, malpositioned anus, bifid scrotum, widely spaced nipples, proptosis of eyelids, pre-auricular tag, absent external auditory canals, bifid uvula, supernumerary teeth and gingival hypertrophy. There is evidence of genetic heterogeneity, with the majority of cases caused by mutations in *FGFR2* [2], but some resulting from *FGFR1* mutations [3].

References

1 Pfeiffer RA. Dominant erbliche Akrocephalosyndaktylie. *Z Kinderheilkd* 1964; **90**: 301–20.
2 Rutland P, Pulleyn LJ, Reardon W *et al.* Identical mutations in the *FGFR2* gene cause both Pfeiffer and Crouzon syndrome phenotypes. *Nat Genet* 1995; **9**: 173–6.
3 Muenke M, Schell U, Hehr A *et al.* Mutations in the fibroblast growth factor receptor-1 gene in Pfeiffer syndrome. *Nat Genet* 1994; **8**: 269–74.

Saethre–Chotzen syndrome (MIM 101400)

This syndrome is characterized by a broad and variable pattern of malformations, including craniosynostosis, low-set frontal hairline, facial asymmetry, ptosis, deviated nasal septum, brachydactyly, partial cutaneous syndactyly, especially of the second and third fingers, and various skeletal anomalies [1,2]. Women with the disorder may be at increased risk of breast cancer [3]. It results from mutations in the *TWIST* transcription factor gene [4,5].

References

1 Saethre H. Ein Beitrag zum Turmschädelproblem (Pathogenese, Erblichkeit und Symptomologie). *Dtsch Z Nervenheilkd* 1931; **117**: 533–55.
2 Chotzen F. Eine eigenartige familiäre Entwicklungsstörung (Akrocephalo-syndaktylie, Dysostosis craniofacialis und Hypertelorismus). *Monatsschr Kinderheilkd* 1932; **55**: 97–122.
3 Sahlin P, Windh P, Lauritzen C *et al.* Women with Saethre-Chotzen syndrome are at increased risk of breast cancer. *Genes Chromosomes Cancer* 2007; **46**: 656–60.
4 Howard TD, Paznekas WA, Green ED *et al.* Mutations in *TWIST*, a basic helix–loop–helix transcription factor, in Saethre–Chotzen syndrome. *Nat Genet* 1997; **15**: 36–41.
5 El Ghouzzi V, Le Merrer M, Perrin-Schmitt F *et al.* Mutations of the *TWIST* gene in the Saethre–Chotzen syndrome. *Nat Genet* 1997; **15**: 36–41.

Beare–Stevenson cutis gyrata syndrome (MIM 123790) [1]

Beare–Stevenson cutis gyrata syndrome is characterized by cutis gyrata, acanthosis nigricans, craniosynostosis, craniofacial dysmorphism, digital anomalies, umbilical and anogenital abnormalities and early death. *FGFR2* mutations have been identified in some but not all patients with the syndrome, indicating possible genetic heterogeneity [2].

Reference

1 Hall BD, Cadle RG, Golabi M *et al.* Beare–Stevenson cutis gyrata syndrome. *Am J Med Genet* 1992; **44**: 82–9.
2 Przylepa KA, Paznekas W, Zhang M *et al.* Fibroblast growth factor receptor 2 mutations in Beare–Stevenson cutis gyrata syndrome. *Nat Genet* 1996; **13**: 492–4.

Curry–Jones syndrome (MIM 601707) [1,2]

This is characterized by an asymmetrical facial appearance, craniosynostosis, pre-axial polydactyly, syndactyly, agenesis of the corpus callosum, streaky skin atrophy, gut abnormalities, variable developmental delay and eye defects. Trichoblastoma of the skin has been described in one case [2].

References

1 Temple IK, Eccles DM, Winter RM *et al.* Craniofacial abnormalities, agenesis of the corpus callosum, polysyndactyly and abnormal skin and gut development: the Curry Jones syndrome. *Clin Dysmorphol* 1995; **4**: 116–29.
2 Grange DK, Clericuzio CL, Bayliss SJ *et al.* Two new patients with Curry-Jones syndrome with trichoblastoma and medulloblastoma suggest an etiologic role of the sonic hedgehog-patched-GLI pathway. *Am J Med Genet* 2008; **146A**: 2589–97.

Craniosynostosis and porokeratosis (MIM 603116)

Synonym
- CDAGS syndrome

This rare disorder comprises craniosynostosis, anal and genitourinary abnormalities, clavicular hypoplasia and skin eruptions. In most cases, the cutaneous abnormality is porokeratosis with onset in infancy, although more psoriasiform or lichenoid changes have also been reported [1]. The eyebrows and eyelashes tend to be sparse. This autosomal recessive condition has been mapped to 22q12–q13.

Reference

1 Mendoza-Londono R, Lammer E, Watson R *et al.* Characterization of a new syndrome that associates craniosynostosis, delayed fontanel closure, parietal foramina, imperforate anus, and skin eruption: CDAGS. *Am J Hum Genet* 2005; **77**: 161–8.

Cranio-ectodermal dysplasia (MIM 218330)

Synonym
- Sensenbrenner syndrome

This autosomal recessive syndrome comprises dolichocephaly, epicanthal folds, hypertelorism, hypodontia and microdontia, growth retardation, limb shortening and short, fine hair [1–4]. Renal and hepatic abnormalities have also been described [4].

References

1 Sensenbrenner JA, Dorst JP, Owens RP. New syndrome of skeletal, dental and hair anomalies. *Birth Defects* 1975; **11**: 372–9.
2 Levin LS, Perrin JC, Ose L *et al.* A heritable syndrome of craniosynostosis, short thin hair, dental abnormalities, and short limbs: cranioectodermal dysplasia. *J Pediatr* 1977; **90**: 55–61.
3 Lammer EJ, Baden H, Margolis RJ. Phenotype of cranioectodermal dysplasia with different hair and bone abnormalities. *Am J Med Genet* 1993; **45**: 9–13.
4 Zaffanello M, Diomedi-Camassei F, Melzi ML *et al.* Sensenbrenner syndrome: a new member of the hepatorenal fibrocystic family. *Am J Med Genet* 2006; **140A**: 2336–40.

Cornelia de Lange syndrome (MIM 122470)

Synonym
- Typus amstelodamensis

Aetiology. This syndrome was originally described in 1933 by Cornelia de Lange [1]. Recently, it has been shown to arise from mutations in genes involved in the cohesin complex that has a role in chromosomal cohesion and coordinated segregation of sister chromatids. Approximately half of all cases result from autosomal dominant mutations in the *NIPBL* gene on 5p13.1, that encodes a cohesin regulator protein [2,3]. Milder cases of Cornelia de Lange syndrome may result from mutations in cohesin complex protein genes, *SMC1L1* on Xp11.22-p11.21 [4], or *SMC3* on chromosome 10q25 [5].

Clinical features [2–13]. The syndrome is characterized by distinctive facial features that can be used in many cases to make the diagnosis [6]. The face is often expressionless, with arched eyebrows, long eyelashes, a long philtrum with a thin upper lip and down-turned angles of the mouth, and a small nose with a depressed bridge and anteverted nostrils. The teeth are small and widely spaced. Microcephaly, micrognathia and low-set, posteriorly-rotated ears are found. There is marked pre- and postnatal growth retardation, and limb reduction abnormalities are common. Cognitive impairment and learning disability are usually severe. Other features described include cleft and high-arched palate, cardiac septal defects, hypoplastic genitalia, gastrointestinal disorders and a variety of skeletal abnormalities. Respiratory and feeding difficulties are frequent in infancy and the cry is weak and low-pitched.

The hairline is low on the neck and forehead and there is hypertrichosis, which may be prominent on the forehead, the sides of the face, the back, shoulders and extremities. Cutis marmorata is common and persistent, and the skin around the eyes and nose may show a bluish tinge.

Life expectancy is generally poor and most patients die in infancy or childhood, often from infections to which they are susceptible. However, some mildly affected individuals have shown relatively normal development.

References

1 De Lange C. Sur un type nouveau de degenerescence (typus Amstelodamensis). *Arch Med Enfants* 1933; **36**: 713–9.
2 Krantz ID, McCallum J, DeScipio C *et al.* Cornelia de Lange syndrome is caused by mutations in *NIPBL*, the human homolog of Drosophila *melanogaster* Nipped-B. *Nat Genet* 2004; **36**: 631–5.
3 Tonkin ET, Wang T-J, Lisgo S *et al.* NIPBL, encoding a homolog of fungal Scc2-type sister chromatid cohesion proteins and fly Nipped-B, is mutated in Cornelia de Lange syndrome. *Nat Genet* 2004; **36**: 636–41.
4 Musio A, Selicorni A, Focarelli ML *et al.* X-linked Cornelia de Lange syndrome owing to *SMC1L1* mutations. *Nat Genet* 2006; **38**: 528–30.
5 Deardoff MA, Kaur M, Yaeger D *et al.* Mutations in cohesin complex members SMC3 and SMC1A cause a mild variant of Cornelia de Lange syndrome with predominant mental retardation. *Am J Hum Genet* 2007; **80**: 483–94.
6 Ireland M, Burn J. Cornelia de Lange syndrome—photo essay. *Clin Dysmorphol* 1993; **2**: 151–60.
7 Salazar FN. Dermatological manifestations of the Cornelia de Lange syndrome. *Arch Dermatol* 1966; **94**: 38–43.
8 Schuster DS, Johnson SAM. Cutaneous manifestations of the Cornelia de Lange syndrome. *Arch Dermatol* 1966; **93**: 702–7.
9 Milot J, Demay F. Ocular anomalies in de Lange syndrome. *Am J Ophthalmol* 1972; **74**: 394–9.
10 MacDonald DM, Greaves M. Cornelia de Lange syndrome. *Br J Dermatol* 1976; **95**: 37–9.
11 Lee FA, Kenny FM. Skeletal changes in the Cornelia de Lange syndrome. *Am J Roentgenol* 1967; **100**: 27–39.
12 Bianchine JW. Hypertrichosis of the Cornelia de Lange syndrome. *Birth Defects* 1971; **7**: 259–60.
13 Jackson L, Kline AD, Barr MA, Koch S. De Lange syndrome: a clinical review of 310 individuals. *Am J Med Genet* 1993; **47**: 940–6.

Rubinstein–Taybi syndrome (MIM 180849) [1–3]

Synonym
- Broad thumb–hallux syndrome

Aetiology. Rubinstein–Taybi syndrome is an autosomal dominant disorder that, in the majority of cases, arises in the context of cytogenetic abnormalities involving chromosome 16p13.3 [4–6]. The causative gene at this locus, *CREBBP*, encodes CREB-binding protein (CBP), a nuclear protein that participates as a coactivator in cyclic AMP-regulated gene expression [7]. Less commonly, individuals with this condition have been found to harbour mutations in the *EP300* gene on 22q13 that encodes a histone acetyltransferase involved in regulation of transcription [8].

Clinical features. The essential features of this complex and variable developmental syndrome are impaired cognition and learning difficulties, microcephaly, growth retardation, broad thumbs and great toes, and facial abnormalities. The palate may be high and narrow, and teeth crowded and irregular [9]. Syndactyly of the hands and accessory nipples may also occur.

A capillary naevus of the forehead or nape has been noted in over 50% of cases, and about the same proportion are said to develop hypertrichosis, especially of the back. The eyebrows may be heavy and highly arched, and the eyelashes long. Dermatoglyphic abnormalities are common. Patients with Rubinstein–Taybi syndrome seem to be prone to develop keloids [10–12]. There have been individual case reports of this syndrome associated with multiple pilomatricomas [13] and piebaldism [14].

Approximately one-third of cases have cardiac defects [15], and the use of neuromuscular blocking agents such as succinylcholine during anaesthesia can provoke cardiac arrhythmias [16]. Joint laxity and dislocations [17], and an increased risk of tumours, especially of the nervous system, have also been reported [18].

References

1 Rubinstein JH, Taybi H. Broad thumbs and toes and facial abnormalities. *Am J Dis Child* 1963; **105**: 588–608.
2 Walker AC, Cox DW. The Rubinstein–Taybi syndrome. *Med J Aust* 1969; **ii**: 99–101.
3 Filippi G. The Rubinstein–Taybi syndrome. Report of 7 cases. *Clin Genet* 1972; **3**: 303–18.
4 Breuning MH, Dauwerse HG, Fugazza G *et al.* Rubinstein–Taybi syndrome caused by submicroscopic deletions within 16p13.3. *Am J Hum Genet* 1993; **52**: 249–54.
5 Hennekam RC, Tilanus M, Hamel BC *et al.* Deletion at chromosome 16p13.3 as a cause of Rubinstein–Taybi syndrome: clinical aspects. *Am J Hum Genet* 1993; **52**: 255–62.
6 Hennekan RCM. Rubinstein-Taybi syndrome. *Eur J Hum Genet* 2006; **14**: 981–5.
7 Petrij F, Giles RH, Dauwerse HG *et al.* Rubinstein–Taybi syndrome caused by mutations in the transcriptional co-activator CBP. *Nature* 1995; **376**: 292–3.
8 Roelfsema JH, White SJ, Ariyurek Y *et al.* Genetic heterogeneity in Rubinstein-Taybi syndrome: mutations in both the CBP and EP300 genes cause disease. *Am J Hum Genet* 2005; **76**: 572–80.
9 Bloch-Zupan A, Stachtou J, Emmanouil D *et al.* Oro-dental features as useful diagnostic tool in Rubinstein-Taybi syndrome. *Am J Med Genet* 2007; **143A**: 570–3.
10 Kurwa AR. Rubinstein–Taybi syndrome and spontaneous keloids. *Clin Exp Dermatol* 1979; **4**: 251–4.
11 Selmanowitz VJ, Stiller MJ. Rubinstein–Taybi syndrome. Cutaneous manifestations and colossal keloids. *Arch Dermatol* 1981; **117**: 504–6.
12 Hendrix JD Jr, Greer KE. Rubinstein–Taybi syndrome with multiple flamboyant keloids. *Cutis* 1996; **57**: 346–8.
13 Cambiaghi S, Ermacora E, Brusasco A *et al.* Multiple pilomatricomas in Rubinstein–Taybi syndrome: a case report. *Pediatr Dermatol* 1994; **11**: 21–5.
14 Herranz P, Borbujo J, Martinez W *et al.* Rubinstein–Taybi syndrome with piebaldism. *Clin Exp Dermatol* 1994; **19**: 170–2.
15 Stevens CA, Bhakta MG. Cardiac abnormalitites in the Rubinstein-Taybi syndrome. *Am J Med Genet* 1995; **59**: 346–8.
16 Stirt JA. Succinylcholine in Rubinstein–Taybi syndrome (letter). *Anesthesiology* 1982; **57**: 429.
17 Bonioli E, Bellini C, Senes FM *et al.* Slipped capital femoral epiphysis associated with Rubinstein-Taybi syndrome. *Clin Genet* 1993; **44**: 79–81.
18 Miller RW, Rubinstein JH. Tumors in Rubinstein-Taybi syndrome. *Am J Med Genet* 1995; **56**: 112–5.

Cartilage–hair hypoplasia (MIM 250250)

Synonym
- Metaphyseal chondrodysplasia of McKusick

This autosomal recessive syndrome was first identified in Amish communities of the USA, among whom it occurs in around 1 in 700 live births [1]. It has also been described in other communities and its prevalence is high in Finland [2].

It is characterized by a high degree of dwarfism, abnormal bone and cartilage development giving rise to multiple skeletal deformities, abnormal hair, and a variable degree of defective immune function giving rise to an increased susceptibility to infection as well as a predisposition to cancers, particularly non-Hodgkin lymphoma [1,3–6]. There may be gastrointestinal tract involvement and anaemia [1,3,7].

The hair is sparse, short, of very fine calibre and lighter in colour than in unaffected siblings, and is often very brittle [8,9]. Some affected individuals are almost bald. The filamentous and matrix proteins of the hair have no gross structural defects; decreased reactivity of some disulphide bonds may account for its abnormal biophysical and biochemical properties [8,10].

Cartilage–hair hypoplasia is caused by mutations in the *RMRP* gene [11]. This nuclear gene encodes RNA rather than DNA. The RNA is not translated but is an essential component of an RNA-processing enzyme, RNase MRP, that is required for copying mitochondrial DNA [12], and for protein translation from ribosomal RNA [13]. Investigation of different *RMRP* mutations reveals genotype–phenotype correlation, with some mutations predisposing to more severe skeletal effects, and others to immune deficiency, hair abnormalities and cancer [14].

References

1 McKusick VA, Eldridge R, Hostetler JA *et al.* Dwarfism in the Amish. II. Cartilage–hair hypoplasia. *Bull Johns Hopkins Hosp* 1965; **116**: 285–326.
2 Virolainen M, Savilahti E, Kaitila I *et al.* Cellular and humoral immunity in cartilage–hair hypoplasia. *Pediatr Res* 1978; **12**: 961–6.
3 Makitie O. Cartilage-hair hypoplasia in Finland: epidemiological and genetic aspects of 107 patients. *J Med Genet* 1992; **29**: 652–5.
4 Makitie O, Kaitila I, Savilahti E. Susceptibility to infections and in vitro immune functions in cartilage-hair hypoplasia. *Eur J Pediatr* 1998; **157**: 816–20.
5 Kavadas FD, Giliani S, Gu Y *et al.* Variability of clinical and laboratory features among patients with ribonuclease mitochondrial RNA processing endoribonuclease gene mutations. *J Allergy Clin Immunol* 2008; **122**: 1178–84.
6 Makitie O, Pukkala E, Teppo L, Kaitila I. Increased incidence of cancer in patients with cartilage-hair hypoplasia. *J Pediatr* 1999; **134**: 315–8.
7 Williams MS, Ettinger RS, Hermanns P *et al.* The natural history of severe anemia in cartilage-hair hypoplasia. *Am J Med Genet* 2005; **138A**: 35–40.
8 Coupe RL, Lowry RB. Abnormality of the hair in cartilage–hair hypoplasia. *Dermatologica* 1970; **141**: 329–34.
9 Pinto L, Nobili B, Scarano G *et al.* Cartilage–hair hypoplasia: clinical and immunological study. *Pediatra* 1981; **89**: 41–51.
10 Kelling C, Goldsmith LA, Baden HP. Biophysical and biochemical studies of the hair in cartilage–hair hypoplasia. *Clin Genet* 1973; **4**: 500–6.
11 Ridanpää M, van Eenennaam H, Pelin K *et al.* Mutations in the RNA component of RNase MRP cause a pleiotropic human disease, cartilage–hair hypoplasia. *Cell* 2001; **104**: 195–203.
12 Chang DD, Clayton DA. A mammalian mitochondrial RNA processing activity contains nucleus-encoded RNA. *Science* 1987; **235**: 1178–84.
13 Thiel CT, Horn D, Zabel B *et al.* Severely incapacitating mutations in patients with extreme short stature identify RNA-processing endoribonuclease PMRP as an essential cell growth regulator. *Am J Hum Genet* 2005; **77**: 795–806.
14 Thiel CT, Mortier G, Kaitila I *et al.* Type and level of RMRP functional impairment predicts phenotype in the cartilage hair hypoplasia-anauxetic dysplasia spectrum. *Am J Hum Genet* 2007; **81**: 519–29.

Van der Woude syndrome (MIM 119300) [1]

Synonyms
- Cleft lip/palate with mucous cysts of the lower lip
- Lip-pit syndrome

This is an autosomal dominant condition in which there are lower lip pits, cleft lip and/or palate and hypodontia [2]. The penetrance is close to 100%, with variable expression [3,4]. It is the commonest form of syndromic clefting, accounting for approximately 2% of all cases of cleft lip and/or palate. Clefting occurs in around one-fifth of affected individuals [3]. Lip pits are the most common manifestation of the syndrome, present in almost 90% of affected cases, and are the only manifestation in over 60% [3]. The pits, which vary from mere depressions to deep channels, may secrete small quantities of viscous saliva. Other developmental defects, for example syndactyly, are sometimes associated.

Popliteal pterygium syndrome (MIM119500) is another autosomal dominant disorder with variable expressivity that shares phenotypic overlap with van der Woude syndrome. In addition to clefting and lower lip pits, features of the syndrome include lower limb pterygium formation, syndactyly, cryptorchidism, hypoplasia or aplasia of the labia majora, hypoplasia or agenesis of digits and filiform ankyloblepharon [5–9]. In around one-third of patients, there is a pyramidal skin fold over the nails, particularly affecting the great toes. Underscoring their phenotypic similarities [10], these syndromes are allelic, resulting from mutations in the *IRF6* gene on 1q32–q41, that encodes interferon regulatory factor-6, a transcription factor with a role in orofacial development [11]. Interestingly, polymorphisms in *IRF6* have been associated with cases of non-syndromic cleft lip and palate [12,13].

The recognition of lip pits, or a family history of lip pits, in association with clefting is important for genetic counselling because a diagnosis of van der Woude syndrome indicates a higher recurrence risk compared with non-syndromic clefting [14].

References

1 Van der Woude A. Fistula labii inferioris congenita and its association with cleft lip and palate. *Am J Hum Genet* 1954; **6**: 244–56.
2 Velez A, Alamillos FJ, Dean A *et al.* Congenital lower lip pits (Van der Woude syndrome). *J Am Acad Dermatol* 1995; **32**: 520–1.
3 Janku P, Robinow M, Kelly T *et al.* The van der Woude syndrome in a large kindred: variability, penetrance, genetic risks. *Am J Med Genet* 1980; **5**: 117–23.
4 Shprintzen RJ, Goldberg RB, Sidoti EJ. The penetrance and variable expression of the van der Woude syndrome: implications for genetic counselling. *Cleft Palate J* 1980; **17**: 52–7.
5 Trelot U. Sur un vice conformation très rare de la levre inferieure. *J Méd Chir Prot* 1869; **40**: 442–5.
6 Gorlin RJ, Sedano HO, Cervenka J. Popliteal pterygium syndrome: a syndrome comprising cleft lip-palate, popliteal and intercrural pterygia, digital and genital anomalies. *Pediatrics* 1968; **41**: 503–9
7 Cunningham LN, Keating MA, Snyder HM *et al.* Urological manifestations of the popliteal pterygium syndrome. *J Urol* 1989; **141**: 910–2.
8 Khan SN, Hufnagle KG, Pool R. Intrafamilial variability of popliteal pterygium syndrome: a family description. *Cleft Palate J* 1986; **23**: 233–6.
9 Lees MM, Winter RM, Malcolm S *et al.* Popliteal pterygium syndrome: a clinical study of three families and report of linkage to the van der Woude syndrome locus on 1q32. *J Med Genet* 1999; **36**: 888–92.
10 Soekarman D, Cobben JM, Vogels A *et al.* Variable expression of the popliteal pterygium syndrome in two 3-generation families. *Clin Genet* 1995; **47**: 169–74.
11 Kondon S, Schutte BC, Richardson RJ *et al.* Mutations in IRF6 cause Van der Woude and popliteal pterygium syndromes. *Nat Genet* 2002; **32**: 285–9.
12 Zucchero TM, Cooper ME, Maher BS *et al.* Interferon regulatory factor 6 (IRF6) gene variants and the risk of isolated cleft lip or palate. *N Engl J Med* 2004; **351**: 769–80.
13 Scapoli L, Palmieri A, Martinelli M *et al.* Strong evidence of linkage disequilibrium between polymorphisms at the IRF6 locus and nonsyndromic cleft lip with or without cleft palate, in an Italian population. *Am J Hum Genet* 2005; **76**: 180–3.
14 Birnbaum S, Reutter H, Lauster C *et al.* Mutation screening in the IRF6-gene in patients with apparently nonsyndromic orofacial clefts and a positive family history suggestive of autosomal-dominant inheritance. *Am J Med Genet* 2008; **146A**: 787–90.

Dowling–Degos disease (MIM 179850) [1,2]

Synonym

- Reticular pigmented anomaly of the flexures

This rare autosomal dominant condition usually presents postpubertally with multiple small, round pigmented macules that resemble freckles. They become progressively more numerous and may become reticulate with time. The axillae and groins are the usual sites, although other areas may be involved, including the intergluteal and inframammary folds, neck, scalp, trunk and arms [1–3]. Involvement of the genitalia, particularly pigmented lesions of the vulva, has been described [4]. Pigmentation is symmetrical and progressive, but is otherwise asymptomatic. The degree of pigmentation varies, but in some patients the lesions are almost confluent, giving a brown or black lace-like pattern. Dark brown papules may also develop at affected sites. Nails and hair are normal. Other features that may be present include scattered comedo-like lesions (dark dot follicles) and pitted acneiform scars near the angles of the mouth. Dowling–Degos disease may be associated with hidradenitis suppurativa [5,6].

The histology is diagnostic, with a distinctive form of acanthosis, characterized by an irregular elongation of thin branching rete ridges, with a concentration of melanin at the tips. The condition involves the follicular infundibulum, and in some cases there is follicular plugging. The melanocyte count is normal [7,8].

Dowling–Degos disease is caused by loss of function mutations in the keratin 5 gene (*KRT5*) situated in the keratin gene cluster on 12q13, resulting in haploinsufficiency [9]. Similar pigmentary changes are observed as a result of a specific *KRT5* mutation in epidermolysis bullosa simplex with mottled pigmentation (MIM 131960) [10], underscoring a function of this basal epidermal keratin in melanosome uptake and transport.

Histology of Dowling–Degos disease distinguishes it from conditions such as acanthosis nigricans, multiple basal cell papillomas, epidermal naevi and the axillary freckles of neurofibromatosis. There is clinical overlap between the disease and two other autosomal dominant conditions, reticulate acropigmentation of Kitamura [11–14] and Haber's syndrome [15,16].

The latter is characterized by a rosacea-like eruption with keratotic plaques and pitted scars.

References

1 Dowling GB, Freudenthal W. A case of acanthosis nigricans. *Br J Dermatol* 1938; **50**: 467–71.
2 Degos R, Ossipowski B. Dermatose pigmentaire réticulée de plis (discussion de l'acanthosis nigricans). *Ann Dermatol Syphiligr* 1954; **81**: 147–51.
3 Bardach HG. Dowling–Degos disease with involvement of the scalp. *Hautarzt* 1981; **32**: 182–6.
4 Milde P, Goerz G, Plewig G. Morbus Dowling–Degos mit ausschliesslich genitaler Manifestation. *Hautarzt* 1992; **43**: 369–72.
5 Weber LA, Kantor GR, Bergfeld WF. Reticulate pigmented anomaly of the flexures (Dowling–Degos disease): a case report associated with hidradenitis suppurativa and squamous cell carcinoma. *Cutis* 1990; **45**: 446–50.
6 Fenske NA, Groover CE, Lober CW *et al.* Dowling–Degos disease, hidradenitis suppurativa, and multiple keratoacanthomas. A disorder that may be caused by a single underlying defect in pilosebaceous epithelial proliferation. *J Am Acad Dermatol* 1991; **24**: 888–92.
7 Howell JB, Freeman RG. Reticular pigmented anomaly of the flexures. *Arch Dermatol* 1978; **114**: 400–3.
8 Wilson-Jones E, Grice K. Reticulate pigmented anomaly of the flexures (Dowling–Degos): a new genodermatosis? *Br J Dermatol* 1974; **91** (Suppl. 36): 6.
9 Betz RC, Planko L, Eigelshoven S *et al.* Loss-of-function mutations in the keratin 5 gene lead to Dowling-Degos disease. *Am J Hum Genet* 2006; **78**: 510–9.

10 Uttam J, Hutton E, Coulombe PA *et al.* The genetic basis of epidermolysis bullosa simplex with mottled pigmentation. *Proc Natl Acad Sci USA* 1996; **93**: 9079–84.
11 Kitamura K, Akamatsu S, Hirokawa K. Eine besondere Form der Akropigmentation: Acropigmentatio reticularis. *Hautarzt* 1953; **4**: 152–6.
12 Crovato F, Desirello G, Rebora A. Is Dowling–Degos disease the same disease as Kitamura's reticulate acropigmentation? *Br J Dermatol* 1983; **109**: 105–10.
13 Berth-Jones J, Graham-Brown RAC. A family with Dowling Degos disease showing features of Kitamura's reticulate acropigmentation. *Br J Dermatol* 1989; **120**: 463–6.
14 Cox NH, Long E. Dowling–Degos disease and Kitamura's reticulate acropigmentation: support for the concept of a single disease. *Br J Dermatol* 1991; **125**: 169–71.
15 Sanderson KV, Wilson HTH. Haber's syndrome. Familial rosacea-like eruption with intraepidermal epithelioma. *Br J Dermatol* 1965; **77**: 1–8.
16 McCormack CJ, Cowen P. Haber's syndrome. *Australas J Dermatol* 1997; **38**: 82–4.

Dyschromatosis symmetrica hereditaria (MIM 127400)

Synonym
- Reticulate acropigmentation of Dohi

This is an autosomal dominant disorder that occurs worldwide but is mostly described in Japanese and Chinese individuals. It comprises hyper- and hypopigmented macules on the dorsa of the extremities and the face, with onset in infancy or childhood [1–3]. Ultrastructurally, there is increased melanin pigment in the basal layer and enlarged melanocytes with long dendrites in pigmented skin, but reduced numbers of melanocytes in hypopigmented areas [4]. The differential diagnosis includes forms of xeroderma pigmentosum, although patients with dyschromatosis symmetrica hereditaria have normal DNA repair and no increased susceptibility to cutaneous malignancy. It is caused by mutations in the *ADAR1* gene on chromosome 1q21.3 that encodes a double-stranded RNA-specific adenosine deaminase [4,5].

References

1 Komaya G. Symmetrische Pigmentanomalie der Extremitaeten. *Arch Derm Syph* 1924; **147**: 389–93.
2 Patrizi A, Manneschi V, Pini A *et al.* Dyschromatosis symmetrica hereditaria associated with idiopathic torsion dystonia: a case report. *Acta Derm Venereol* 1994; **74**: 135–7.
3 Oyama M, Shimizu H, Ohata Y *et al.* Dyschromatosis symmetrica hereditaria (reticulate acropigmentation of Dohi): report of a Japanese family with the condition and a literature review of 185 cases. *Br J Dermatol* 1999; **140**: 491–6.
4 Kondo T, Suzuki T, Mitsuhashi Y *et al.* Six novel mutations of the ADAR1 gene in patients with dyschromatosis symmetrica hereditaria: histological observation and comparison of genotypes and clinical phenotypes. *J Dermatol* 2008; **35**: 395–406.
5 Miyamura Y, Suzuki T, Kono M *et al.* Mutations of the RNA-specific adenosine deaminase gene (*DSRAD*) are involved in dyschromatosis symmetrica hereditaria. *Am J Hum Genet* 2003; **73**: 693–9.

Dyschromatosis universalis hereditaria (MIM 127500)

This is another autosomal dominant pigmentary condition described predominantly in Japanese families [1,2]. In contrast with dyschromatosis symmetrica hereditaria, hyper- and hypopigmented macules arise mainly on the trunk and the onset is usually earlier, in the first year of life. Light and electron microscopy demonstrate differences in fully melanized melanosomes in affected areas of skin rather than altered melanocyte numbers [2]. The condition has been linked to 6q24.2–q25.2 in two Chinese families [3]. Autosomal recessive inheritance with linkage to 12q21–q23 has also been described in one pedigree [4].

References

1 Suenaga M. Genetical studies on skin diseases. VII. Dyschromatosis universalis hereditaria in five generations. *Tohoku J Exp Med* 1952; **55**: 373–6.
2 Nuber UA, Tinschert S, Mundlos S, Hausser I. Dyschromatosis universalis hereditaria: familial case and ultrastructural skin investigation. *Am J Med Genet* 2004; **125A**: 261–6.
3 Xing Q, Wang M, Chen X *et al.* A gene locus responsible for dyschromatosis symmetrica hereditaria (DSH) maps to chromosome 6q24.2–q25.2. *Am J Hum Genet* 2003; **73**: 377–82.
4 Stuhrmann M, Hennies HC, Bukhari IA *et al.* Dyschromatosis universalis hereditaria: evidence for autosomal recessive inheritance and identification of a new locus on chromosome 12q21–q23. *Clin Genet* 2008; **73**: 566–72.

Chronic, infantile, neurological, cutaneous, articular (CINCA) syndrome (MIM 607115), Muckle–Wells syndrome (MIM 191900) and familial cold autoinflammatory syndrome (MIM 120100)

Chronic, infantile, neurological, cutaneous, articular syndrome was originally described by Ansell *et al.* in 1975 [1], and later termed CINCA syndrome by Prieur *et al.* [2]. It is characterized by a triad of rash, arthropathy and CNS involvement. The rash, which usually starts from birth, is persistent, urticarial and migratory, with perivascular polymorphonuclear inflammation histologically. Arthropathy may be severe and progressive, with epiphyseal abnormalities, periosteal elevation along the shafts of the long bones and early patella ossification radiologically. There is chronic meningitis, with progressive hearing loss. Other features include short stature, delayed fontanelle closure, frontal bossing and a broad nasal bridge.

Muckle–Wells syndrome and familial cold autoinflammatory syndrome (synonym familial cold urticaria) have overlapping clinical features, including episodic inflammatory rash, arthralgias and fever [3,4]. Late-onset sensorineural deafness and renal amyloidosis may occur but are more common in Muckle–Wells syndrome.

These three syndromes with phenotypic similarities have been shown to be allelic, caused by heterozygous mutations in the CIAS1 gene, *NLPR3*, on 1q44, that encodes a pyrin-like protein mainly expressed in peripheral blood leukocytes [5–8]. Interleukin-1 antagonists are emerging as a potentially effective therapy for all three syndromes [9,10].

References

1 Ansell BM, Bywaters EG, Elderkin FM. Familial arthropathy with rash, uveitis and mental retardation. *Proc R Soc Med* 1975; **68**: 584–5.
2 Prieur AM, Griscelli C, Lambert F *et al.* A chronic, infantile, neurological, cutaneous, and articular (CINCA) syndrome. A specific entity analysed in 30 patients. *Scand J Rheumatol* 1987; **66** (Suppl.): 57–68.
3 Muckle TJ, Wells M. Urticaria, deafness and amyloidosis: a new heredo-familial syndrome. *QJM* 1962; **31**: 235–48.
4 Kile RL, Rusk HA. A case of cold urticaria with unusual family history. *JAMA* 1940; **114**: 1067–8.
5 Hoffman HM, Mueller JL, Broide DH *et al.* Mutation of a new gene encoding a putative pyrin-like protein causes familial cold autoinflammatory syndrome and Muckle-Wells syndrome. *Nat Genet* 2001; **29**: 301–5.

6 Dode C, Le Du N, Cuisset L *et al.* New mutations of CIAS1 that are responsible for Muckle-Wells syndrome and familial cold urticaria: a novel mutation underlies both syndromes. *Am J Hum Genet* 2002; **70**: 1498–506.
7 Feldmann J, Prieur A-M, Quartier P *et al.* Chronic infantile neurological cutaneous and articular syndrome is caused by mutations in CIAS1, a gene highly expressed in polymorphonuclear cells and chondrocytes. *Am J Hum Genet* 2002; **71**: 198–203.
8 Neven B, Calleebaut I, Prieur AM *et al.* Molecular basis of the spectral expression of CIAS1 mutations associated with phagocytic cell-mediated autoinflammatory disorders CINCA/NOMID, MWS and FCU. *Blood* 2004; **103**: 2809–15.
9 Boschan C, Witt O, Lohse P *et al.* Neonatal-onset multisystem inflammatory disease (NOMID) due to a novel S331R mutation of the CIAS1 gene and response to interleukin-1 receptor antagonist treatment. *Am J Med Genet* 2006; **140A**: 883–6.
10 Hoffman HM, Throne ML, Amar NJ *et al.* Efficacy and safety of rilonacept (interleukin-1 Trap) in patients with cryopyrin-associated periodic syndromes: results from two sequential placebo-controlled studies. *Arthritis Rheum* 2008; **58**: 2443–52.

Dermo-chondro-corneal dystrophy (MIM 221800)

Synonym
- François' syndrome

Patients with this very rare disorder have firm nodular skin lesions on the dorsa of the hands and on the nose and ears, osteochondrodystrophy of the bones of the hands and feet, resulting in limitation of movement and deformity, and corneal dystrophy with white or brownish opacities. A number of case reports suggest autosomal recessive inheritance [1–5], although non-familial cases with marked gingival involvement have also been described [6,7]. The underlying defect has not been identified.

References

1 François J. Distrophie dermo-chondro-cornéenne familiale. *Ann Oculist* 1949; **182**: 409–41.
2 Jensen JV. Dermo-chondro-corneal dystrophy: report of a case. *Acta Ophthalmol* 1958; **36**: 71–8.
3 Wiedmann HR. Zur François'schen Krankheit. *Arzt Wochenschr* 1958; **41**: 905–9.
4 Remky VH, Engelbrecht G. Dystrophya dermo-chondro-cornealis (François). *Monattsbl Augenheilkd* 1967; **151**: 319–31.
5 Maldonado R, Tamayo L, Velazquez E. Dystrophie dermo-chondro–cornéenne familiale (syndrome de François). *Ann Dermatol Vénéréol* 1977; **104**: 475–8.
6 Caputo R, Sambvani N, Monti M *et al.* Dermochondrocorneal dystrophy (François' syndrome). *Arch Dermatol* 1988; **124**: 424–8.
7 Sardella A, Carrassi A, Caputo R *et al.* Gingival lesions in a patient with dermochondrocorneal dystrophy (François syndrome). A case report. *J Clin Periodontol* 1998; **25**: 1047–9.

Congenital scalp defects with distal limb anomalies (MIM 100300)

Synonym
- Adams–Oliver syndrome

Individuals with this disorder have congenital scalp defects, often involving the underlying bone, and limb malformations, ranging from hypoplasia of the fingers and toes to absence of the legs below the knees [1–4]. Variable features include vascular defects, cutis marmorata telangiectatica congenita, cardiac defects and central nervous system anomalies [5–8]. The inheritance pattern in the majority is autosomal dominant with variable expression, although autosomal recessive inheritance has also been proposed, especially in patients with CNS involvement [8,9].

References

1 Adams FH, Oliver CP. Hereditary deformities in man due to arrested development. *J Hered* 1945; **36**: 3–7.
2 Burton BK, Hauser L, Nadler HL. Congenital scalp defects with distal limb anomalies: report of a family. *J Med Genet* 1976; **13**: 466–8.
3 Bonafede RP, Beighton P. Autosomal dominant inheritance of scalp defects with ectrodactyly. *Am J Med Genet* 1979; **3**: 35–41.
4 Fryns JP. Congenital scalp defects with distal limb reduction anomalies. *J Med Genet* 1987; **24**: 493–6.
5 Farrell SA, Warda LJ, LaFlair P, Szymonowicz W. Adams-Oliver syndrome: a case with juvenile chronic myelogenous leukemia and chylothorax. *Am J Med Genet* 1993; **47**: 1175–9.
6 Ishikiriyama S, Kaou B, Udagawa A, Niwa K. Congenital heart defect in a Japanese girl with Adams-Oliver syndrome: one of the most important complications. *Am J Med Genet* 1992; **43**: 900–1.
7 Fryns JP, de Cock P, van den Berghe H. Occipital scalp defect associated with valvular pulmonary stenosis: a new entitiy? *Clin Genet* 1992; **42**: 97–9.
8 McGoey RR, Lacassie Y. Adams-Oliver syndrome in siblings with central nervous system findings, epilepsy, and developmental delay: refining the features of a severe autosomal recessive variant. *Am J Med Genet* 2008; **146A**: 488–91.
9 Klinger G, Merlob P. Adams-Oliver syndrome: autosomal recessive inheritance and new phenotypic-anthropometric findings. *Am J Med Genet* 1998; **79**: 197–9.

FG syndrome-1 (MIM 305450)

Synonym
- Opitz–Kaveggia syndrome

The FG syndrome is an X-linked recessive syndrome comprising a number of congenital anomalies and developmental delay, first described by Opitz and Kaveggia [1]. The major features are impaired cognition and learning disability, mild facial dysmorphism, 'cowlicks' of the hairline, congenital hypotonia, relative macrocephaly and constipation [2]. Elia *et al.* [3] reported a boy with FG syndrome, who also had gingival hyperplasia and keloids. Hyper- and hypopigmented streaks on the trunk have also been reported in some cases [4]. A recurrent mutation in the *MED12* gene on Xp13 that encodes a thyroid hormone receptor-associated protein has been identified in some families [5]. Other forms of FG syndrome with linkage to other loci on the X chromosome have been described: these share phenotypic features with FG syndrome-1.

References

1 Opitz JM, Kaveggia EG. Studies of malformation syndromes of man XXXIII: the FG syndrome. An X-linked recessive syndrome of multiple congenital anomalies and mental retardation. *Z Kinderheilkd* 1974; **117**: 1–18.
2 Romano C, Baraitser M, Thompson E. A clinical follow-up of British patients with FG syndrome. *Clin Dysmorphol* 1994; **3**: 104–14.
3 Elia M, Lello R, Romano C *et al.* A case of FG syndrome with gingival hyperplasia and keloids. *Pediatr Dermatol* 1995; **12**: 387–9.
4 Opitz JM, Richieri-da Costa A, Aase JM, Benke PJ. FG syndrome update 1988: note of 5 new patients and bibliography. *Am J Med Genet* 1988; **30**: 309–28.
5 Risheg H, Graham JM Jr, Clark RD *et al.* A recurrent mutation in MED12 leading to R961W causes Opitz-Kaveggia syndrome. *Nat Genet* 2007; **39**: 451–3.

Future directions

Every attempt has been made to provide an up-to-date overview of progress in the field of clinical and molecular genetics relevant to contemporary dermatological practice. However, no other field of medicine is changing more rapidly than our understanding of the genetic basis of human diseases. The interested reader is strongly encouraged to consult the online information sources described, as these sites are continually updated.

Through information gained from our rapidly increasing knowledge of genetic diseases comes greater awareness about the structure, development and function of the skin and other organs. It also opens the possibility for translational benefits for patients and families, including better means of diagnosis, assessing prognosis, and novel therapeutic options for this wide range of disorders.

Acknowledgement

The authors wish to recognize the work of the previous authors on this chapter, Professors Richard Trembath and John Harper. We also thank Professor Virginia Sybert for use of photographs.

CHAPTER 16

Prenatal Diagnosis of Genetic Skin Disease

J.A. McGrath

St John's Institute of Dermatology, King's College London, Guy's Campus, London, UK

Prenatal diagnosis in practice, 16.1	**Fetal ultrasound, 16.7**	**Ethical aspects of prenatal diagnosis, 16.10**
DNA-based methods, 16.1	**Preimplantation genetic diagnosis, 16.7**	
Fetoscopy and fetal skin biopsy, 16.5	**Non-invasive molecular strategies, 16.9**	

Prenatal diagnosis in practice

In most countries, sustained improvements in obstetric and perinatal care have meant that congenital malformations, single-gene defects and chromosomal abnormalities are increasing in their relative importance as causes of infant mortality and morbidity. Up to 5% of live-born infants may be affected by congenital defects or hereditary disease, and approximately 20% of all infant deaths today are the result of such disorders. Congenital defects and hereditary diseases can have a huge impact on individual sufferers and families at risk of genetic disease as well as creating substantial health, economic and financial burdens for health-care providers and society in general.

Over the last 30 years, there have been major advances in defining specific structural, biological, chemical and, in particular, molecular pathologies that either cause certain inherited skin diseases or which act as pathognomonic markers of these disorders [1]. This plethora of information provides new opportunities to improve diagnostic accuracy, to refine genetic counselling, and to provide a rationale for the development of new treatments, including gene, protein and cell-based therapies. The discoveries also make feasible a choice of options for prenatal testing in families at risk of recurrence for several forms of inherited skin disease [2].

Today, any couple planning to have a child cannot afford to ignore these new advances. Prenatal diagnosis with appropriate counselling should be an integral part of the management of individuals or couples at risk of having children with a congenital or genetic disorder. Access to genetic counsellors is important for anyone seeking information about these risks, and the available management options after the risk has been determined.

The purpose of prenatal diagnosis is the detection or exclusion of a hereditary disease or congenital defect *in utero*. The option of an elective abortion of affected pregnancies can help parents at risk of having affected children to produce normal offspring. A consequence of early prenatal diagnosis is that many pregnancies can proceed to term with the delivery of a normal child, instead of being terminated on the basis of a high risk.

The prenatal diagnosis of several genodermatoses is now well established. Over the past three decades, the techniques used have changed from being heavily reliant on the analysis of fetal skin biopsy samples acquired during the second half of the mid-trimester, to the examination of fetal DNA from first-trimester chorionic villus samples [3]. Preimplantation genetic diagnosis (PGD) and preimplantation genetic haplotyping (PGH) are additional options that have been recently introduced [4].

Further technical advances are likely to lead to the development of less invasive forms of fetal screening, such as analysis of free fetal DNA in the maternal circulation [5]. Advances in technology, however, also bring with them new financial costs as well as fundamental ethical and moral considerations, all of which need to be considered carefully in discussing and planning appropriate strategies for prenatal diagnosis in inherited skin diseases.

References

1 Leech SN, Moss C. A current and online genodermatosis database. *Br J Dermatol* 2007; **156**: 1115–48.
2 Ashton GH, Eady RA, McGrath JA. Prenatal diagnosis for inherited skin diseases. *Clin Dermatol* 2000; **18**: 643–8.
3 Fassihi H, Eady RA, Mellerio JE *et al.* Prenatal diagnosis for severe inherited skin disorders: 25 years' experience. *Br J Dermatol* 2006; **154**: 106–13.
4 Braude P, Pickering S, Flinter F, Ogilvie CM. Preimplantation genetic diagnosis. *Nat Rev Genet* 2002; **3**: 941–55.
5 Norbury G, Norbury CJ. Non-invasive prenatal diagnosis of single gene disorders: how close are we? *Sem Fetal Neonatal Med* 2008; **13**: 76–83.

DNA-based methods

At present, the majority of prenatal diagnosis tests for inherited skin disorders are performed by analysis of fetal DNA that is usually extracted from chorionic villi [1]. After implantation of the embryo, the chorionic plate, which is derived from the trophoblast layer of the blastocyst, attaches to the uterine wall. Chorionic villi are of fetal origin and therefore a useful source of fetal DNA, as

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.



Fig. 16.1 Chorionic villi for DNA-based prenatal diagnosis.

are amniotic cells that are released from various fetal epithelia [2]. Chorionic villus biopsy can be performed either transcervically or by the transabdominal route. These procedures allow for approximately 10–50 mg of tissue to be biopsied or aspirated. The risk of fetal loss following chorionic villus sampling (CVS) (performed after 10 weeks) is approximately 1–2%. Initially, some reports suggested that CVS might increase the risk of severe limb reduction defects, but this has not been borne out in subsequent, more extensive international studies [2]. Nevertheless, it is recommended that CVS is not performed before 10 weeks. Tissue obtained from CVS needs to be cleaned under a dissecting microscope to exclude maternal cells (decidua, blood) that could contaminate polymerase chain reaction (PCR) or biochemical analyses (Fig. 16.1).

It is also important that villi are collected in an appropriate medium. For example, the presence of heparin (beyond the initial cleaning phase) may inhibit the activity of the Taq polymerase enzyme that is fundamental to PCR amplification. Chorionic villi can also be cultured for diagnostic confirmation of the findings obtained from direct analysis of the villi. It usually takes about 2 weeks to culture chorionic villi for the confirmatory tests: this may improve diagnostic accuracy but there is an inevitable delay that adds to the gestational age at final diagnosis.

Apart from CVS, fetal DNA can also be extracted from fetal cells obtained by amniocentesis, usually performed at about 16 weeks' gestation [3]. Amniocentesis is a means of obtaining amniotic fluid and its cells for morphological, cytogenetic, biochemical or molecular analysis. Amniotic fluid cells are derived from fetal epidermis, alimentary and genitourinary mucosa, and amnion. These cells have been used to assess diseases associated with abnormalities of DNA synthesis and repair, as well as metabolic disorders that result in abnormal protein synthesis. However, now that the molecular basis of nearly all these conditions is known, such approaches are rarely necessary and the vast majority of prenatal tests can be performed by direct analysis of genomic DNA pathology in fetal DNA following CVS or amniocentesis [4].

Faced with a couple who have had a previously affected child with any form of inherited skin disease and who wish to consider prenatal diagnosis in the next pregnancy, it is vital to have an accurate diagnosis of the condition and to be aware of the pattern of inheritance that will determine the genetic risk. Involvement of specialist dermatology centres, clinical geneticists and genetic counsellors is helpful in determining the feasibility of prenatal diagnostic testing. In preparation for DNA-based prenatal testing, DNA samples should be available from both parents and the affected family member(s) to screen for the pathogenic mutations or informative genetic markers. The possibility of *de novo* mutations, non-paternity, uniparental disomy and germline mutations must all be considered in determining the suitability of the prenatal test. Uniparental disomy refers to the inheritance of both copies of a chromosome pair from just one parent (paternal or maternal). In essence, uniparental isodisomy allows two copies of a recessive mutation to be transmitted from a heterozygous carrier parent. Uniparental disomy has been reported in both junctional and recessive dystrophic epidermolysis bullosa (EB), emphasizing the importance of screening DNA from both parents to check carrier status [5,6]. It is also important to stress that delineation of informative gene mutations or genetic markers should be determined in advance of all requests for prenatal testing. It is not appropriate to undertake a DNA-based test without prior knowledge of the genetic information that is pertinent to a particular case or family.

Table 16.1 lists the disorders for which DNA-based prenatal testing has been performed. It is likely that the number of conditions tested for in this way will expand over the next few years, given that the molecular basis of over 350 single gene disorders with a skin phenotype has now been determined [7]. Over the last 15 years, the most common indications for DNA-based prenatal testing have been Hallopeau–Siemens recessive dystrophic EB and Herlitz junctional EB [4].

Because mutations in only one gene (the type VII collagen gene, *COL7A1*) are known to cause both recessive and dominant forms of dystrophic EB, prenatal diagnosis can be performed by linkage analysis using a combination of intragenic and flanking markers for the gene locus on chromosome 3p21 [8]. These genetic markers can be combined with microsatellite markers for haplotype analysis in predicting whether the fetus carries one, two or neither mutant *COL7A1* allele (Fig. 16.2).

A potential pitfall of haplotype analysis using polymorphic markers is the possibility of a *de novo* mutation or parental germline mosaicism in one of the alleles inherited in a previously affected sibling. To increase the accuracy of the test, DNA analysis of pregnancies at risk of recessive dystrophic EB should also, where possible, be based on direct mutation screening of both *COL7A1* alleles (Fig. 16.3).

Under optimal conditions, the DNA analysis of key family members, including testing for informative polymorphic and microsatellite markers, in addition to mutational analysis, can be completed within 2 weeks. The analysis of fetal DNA can sub-

Table 16.1 DNA-based prenatal diagnosis.

Genodermatosis	MIM	Protein (*Gene*)	Gene locus
Junctional epidermolysis bullosa (Herlitz)	226700	Laminin-332 α3 chain (*LAMA3*)	18q11.2
		Laminin-332 β3 chain (*LAMB3*)	1q32.2
		Laminin-332 δ2 chain (*LAMC2*)	1q25.3
Junctional epidermolysis bullosa (with pyloric atresia)	226730	β4 integrin (*ITGB4*)	17q25.1
Non-Herlitz junctional epidermolysis bullosa	226650	Type XVII collagen (*COL17A1*)	10q25.1
Dystrophic epidermolysis bullosa (recessive)	226600	Type VII collagen (*COL7A1*)	3p21.33
Dystrophic epidermolysis bullosa (dominant)	131750	Type VII collagen (*COL7A1*)	3p21.33
Epidermolysis bullosa simplex (Dowling–Meara)	131760	Keratin 14 (*KRT14*)	17q21.2
Bullous congenital ichthyosiform erythroderma	113800	Keratin 10 (*KRT10*)	17q21.2
Pachyonychia congenita (type 1)	167200	Keratin 16 (*KRT16*)	17q21.2
Netherton's syndrome	256500	Serine protease inhibitor (*SPINK5*)	5q33.1
Lamellar ichthyosis	242300	Transglutaminase 1 (*TGM1*)	14q11.2
Sjögren–Larsson syndrome	270200	Fatty aldehyde dehydrogenase (*FALDH*)	17p11.2
Ehlers–Danlos syndrome type VI	225400	Lysyl hydroxylase I (*PLOD*)	1p36.22
Oculocutaneous albinism (tyrosinase-negative, OCA1A)	203100	Tyrosinase (*TYR*)	11q14.3
Congenital erythropoietic porphyria	263700	Uroporphyrinogen III cosynthetase (*UROS*)	10q26.2
Ectrodactyly, ectodermal dysplasia, clefting (EEC) syndrome	129900	TP63 (*p63*)	3q28
Smith–Lemli–Opitz syndrome	270400	Sterol δ7-reductase (*DHCR7*)	11q13.4
Mucopolysaccharidosis (Hunter, type II)	309900	Iduronate-2-sulphatase (*IDS*)	Xq28
Sialidosis (type II)	256550	Lysosomal alpha-*N*-acetyl-neuraminidase (*NEU1*)	6p21.33
Infantile neuronal ceroid lipofuscinosis (INCL)	256730	Lysosomal palmitoyl-protein thioesterase (*CLN1*)	1p32
Late-infantile neuronal ceroid lipofuscinosis (LINCL)	204500	Lysosomal tripeptidyl peptidase I (*CLN2*)	11p15.4
Thanatophoric dysplasias (types I, II)	151210	Fibroblast growth factor receptor 3 (*FGFR3*)	4p16.3
Achondroplasia–hypochondroplasia	100800	Fibroblast growth factor receptor 3 (*FGFR3*)	4p16.3
Conradi–Hunermann–Happle syndrome	302960	Emopamil binding protein (*EBP/CDPX2*)	Xp11.23
Xeroderma pigmentosum group A	278700	DNA-binding protein (*XPA*)	9q22.3
Oculocutaneous tyrosinaemia	276600	Tyrosine aminotransferase (*TAT*)	16q22.1
Harlequin ichthyosis	242500	Lipid transporter (*ABCA12*)	2q34

sequently, in most cases, be accomplished within 48–72 h after its receipt in the laboratory.

Because junctional EB shows considerable molecular heterogeneity (see Table 16.1), DNA-based prenatal diagnosis of this disorder is dependent on direct mutation analysis instead of genetic linkage [9]. In pregnancies at risk for the Herlitz form of junctional EB, prenatal testing includes analysis of the relevant one of the three laminin-332 genes, *LAMA3*, *LAMB3* and *LAMC2*. Mutations in other genes encoding molecular components of the hemidesmosome-anchoring filament complex are also known to cause subtypes of EB. For example, mutations in the genes encoding the α6 or β4 integrin chains (*ITGA6*, *ITGB4*) underlie a form of junctional EB associated with pyloric atresia and defects in the type XVII collagen gene, *COL17A1*, cause a non-Herlitz variant of junctional EB. Clues to the relevant candidate gene/protein in individual cases of junctional EB can usually be derived from immunolabelling of the skin of the previously affected child using antibodies to these different proteins [10].

References

1 Wapner RJ. Invasive prenatal diagnostic techniques. *Semin Perinatol* 2005; **29**: 401–4.

2 Brambati B, Tului L. Chorionic villus sampling and amniocentesis. *Curr Opin Obstet Gynecol* 2005; **17**: 197–201.

3 Evans MI, Andriole S. Chorionic villus sampling and amniocentesis in 2008. *Curr Opin Obstet Gynecol* 2008; **20**: 164–8.

4 Fassihi H, Eady RA, Mellerio JE *et al.* Prenatal diagnosis for severe inherited skin disorders: 25 years' experience. *Br J Dermatol* 2006; **154**: 106–13.

5 Fassihi H, Wessagowit V, Ashton GH *et al.* Complete paternal uniparental isodisomy of chromosome 1 resulting in Herlitz junctional epidermolysis bullosa. *Clin Exp Dermatol* 2005; **30**: 71–4.

6 Fassihi H, Lu L, Wessagowit V *et al.* Complete maternal isodisomy of chromosome 3 in a child with recessive dystrophic epidermolysis bullosa but no other phenotypic abnormalities. *J Invest Dermatol* 2006; **126**: 2039–43.

7 Leech SN, Moss C. A current and online genodermatosis database. *Br J Dermatol* 2007; **156**: 1115–48.

8 Christiano AM, LaForgia S, Paller AS *et al.* Prenatal diagnosis for recessive dystrophic epidermolysis bullosa in 10 families by mutation and haplotype analysis in the type VII collagen gene (*COL7A1*). *Mol Med* 1996; **2**: 59–76.

9 Christiano AM, Pulkkinen L, McGrath JA, Uitto J. Mutation based prenatal diagnosis of Herlitz junctional epidermolysis bullosa. *Prenatal Diag* 1997; **17**: 343–54.

10 McGrath JA, Eady RA. The role of immunohistochemistry in the diagnosis of the non-lethal forms of junctional epidermolysis bullosa. *J Dermatol Sci* 1997; **14**: 68–75.

11 McGrath JA, Dunnill MG, Christiano AM *et al.* First trimester DNA-based exclusion of recessive dystrophic epidermolysis bullosa from chorionic villus sampling. *Br J Dermatol* 1996; **134**: 734–9.

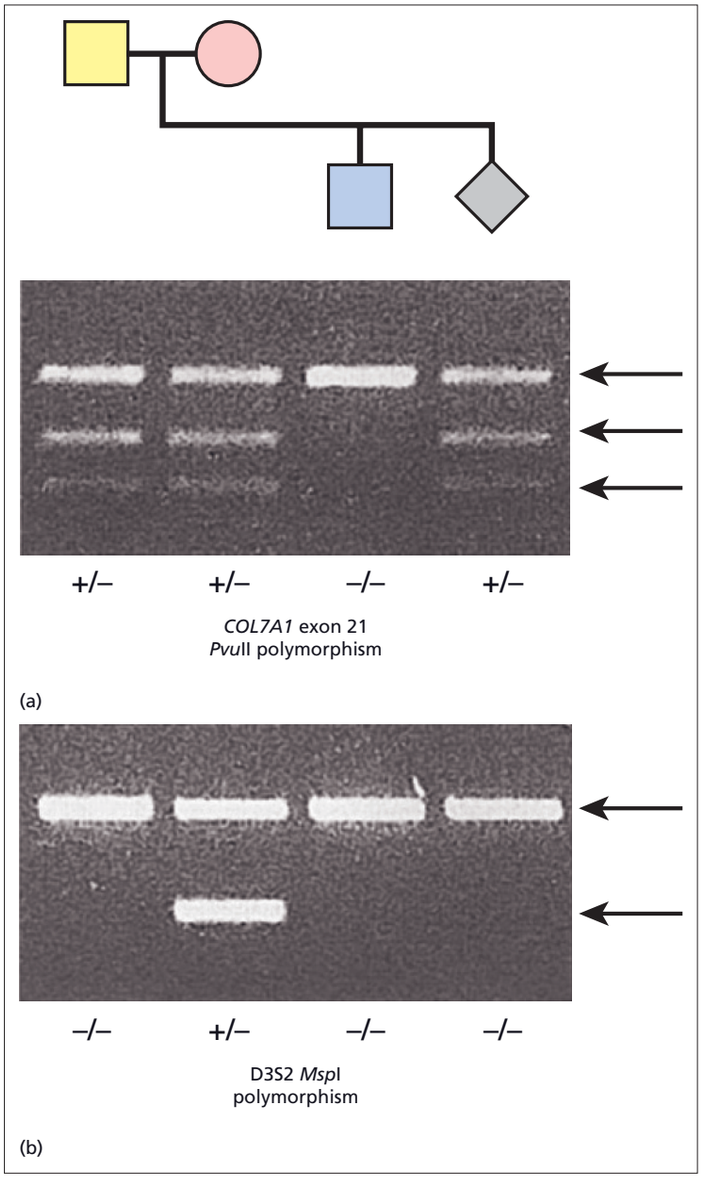


Fig. 16.2 Prenatal exclusion of dystrophic epidermolysis bullosa by linkage analysis. (a) *Pvu*II restriction endonuclease digestion for an intragenic *COL7A1* polymorphism in exon 21 shows a +/– haplotype in the maternal, paternal and fetal DNA in contrast to a –/– haplotype in the previously affected child's DNA. (b) *Msp*I restriction endonuclease digestion for a flanking polymorphism (D3S2) shows a +/– haplotype in the maternal DNA in contrast to a –/– haplotype in the paternal, previously affected child and fetal DNA. These findings indicate that the fetus has inherited the normal paternal *COL7A1* allele and the mutant maternal *COL7A1* allele, and is therefore predicted to be an unaffected carrier of one mutant *COL7A1* allele. (From McGrath *et al.* [11].)

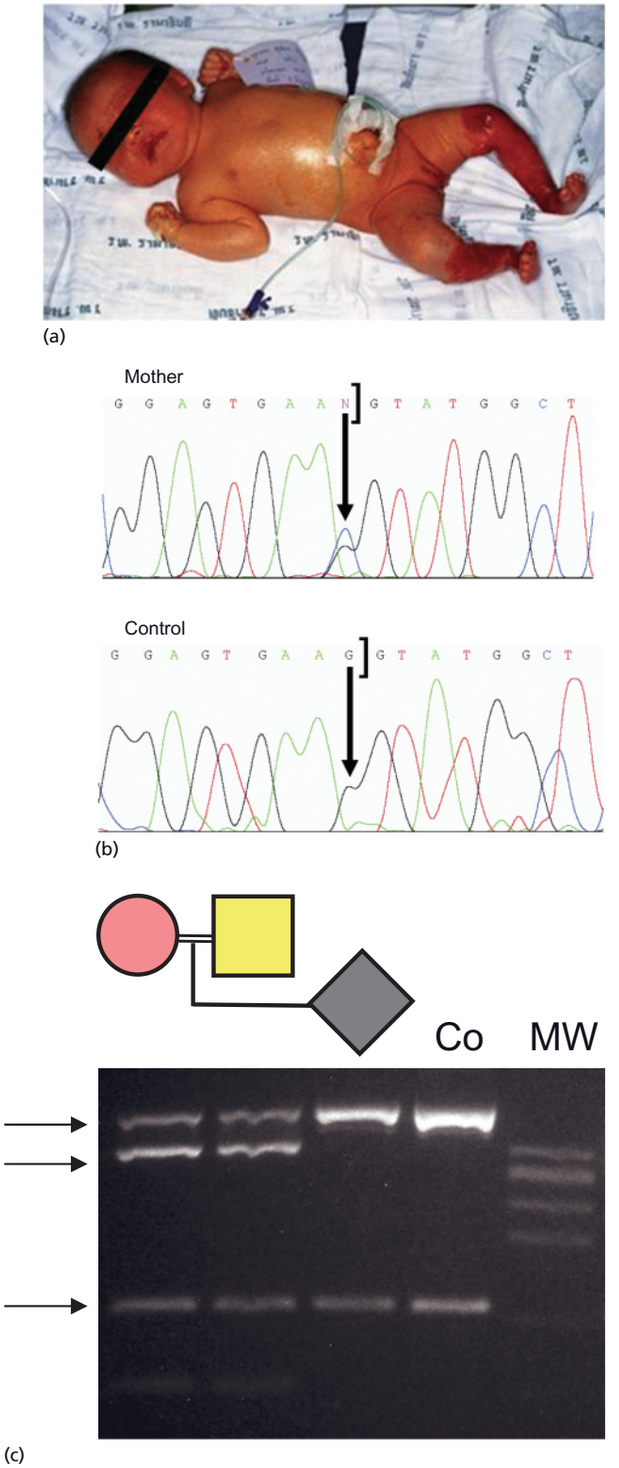


Fig. 16.3 Prenatal exclusion of dystrophic epidermolysis bullosa by mutation analysis. (a) Blistering and erosions in the previously affected child with recessive dystrophic epidermolysis bullosa. (b) Nucleotide sequencing of the PCR products from both parents (here illustrated in the maternal DNA) shows a heterozygous G > C substitution at the end of exon 18 of the *COL7A1* gene: the mutation is designated +/– c.2440G→C. (c) Restriction endonuclease digestion with *HpyCH4*IV and prenatal diagnosis. The mutation introduces a novel cutting site for *HpyCH4*IV. In control DNA (Co), the PCR product is cleaved into two clear fragments. In contrast, in both parents who are heterozygous carriers of c.2440G→C, additional digested bands are present. However, the fetal PCR products are digested similarly to the control DNA, indicating that the fetus has inherited two wild-type *COL7A1* alleles with respect to this mutation and is therefore predicted to be clinically unaffected with RDEB. MW = ΦX174 *Hae*III molecular weight marker.

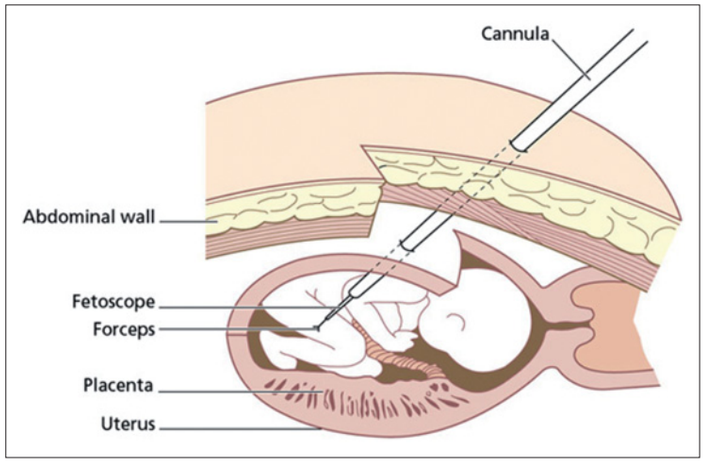


Fig. 16.4 Illustration of fetoscopy and fetal skin biopsy procedure.

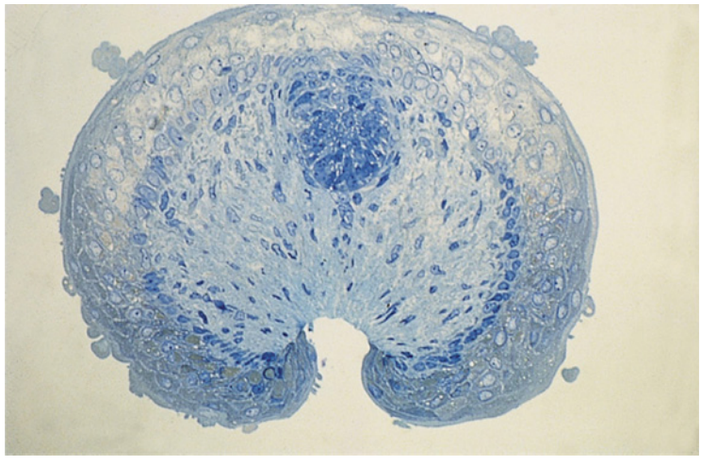


Fig. 16.6 Photomicrograph of a semithin section of a normal fetoscopic skin sample at 18 weeks' gestation (×295).

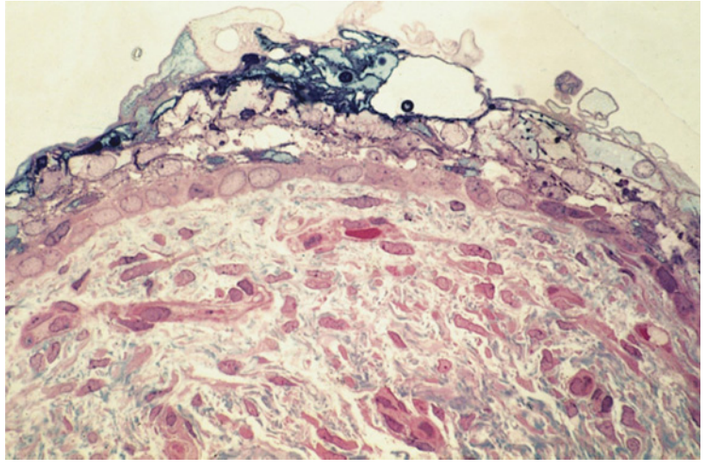


Fig. 16.5 Photomicrograph of a semithin section of a skin sample from 20-week fetus affected with bullous congenital ichthyosiform erythroderma. Note that severe vacuolation of the intermediate cell layers is present, even before the stratum corneum is formed. Periderm blebs are still evident at the epidermal surface (×380).

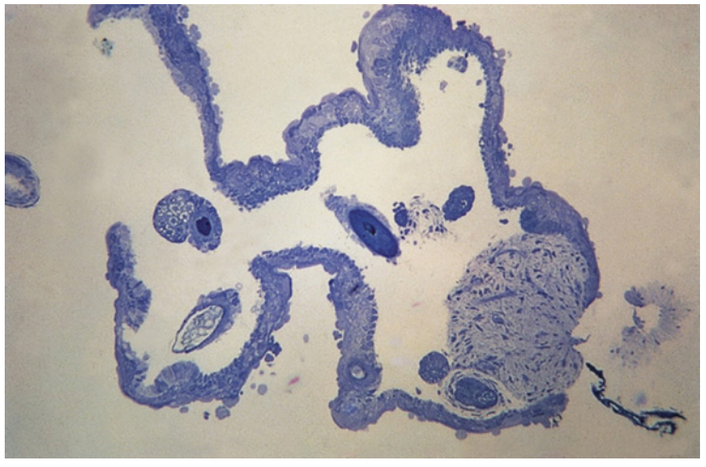


Fig. 16.7 Photomicrograph of a fetoscopic skin sample from an 18-week fetus affected with recessive dystrophic epidermolysis bullosa. Note the extensive dermal–epidermal separation. Subsequent electron microscopy confirmed that the split was beneath the level of the lamina densa. Richardson's stain (×150).

Fetoscopy and fetal skin biopsy

Fetoscopy involves the insertion of a fibreoptic endoscope into the pregnant uterus (Fig. 16.4), using sedation and local anaesthesia, normally at 16–20 weeks' gestation.

The main indications for fetoscopy have been to enable direct visualization of the uterine contents, fetal blood sampling (usually from the umbilical cord) and tissue biopsy (e.g. from skin, liver or other organs). Direct inspection has been of particular value in identifying defects of facial features, limbs and digits, head and spine, anterior abdominal wall and genitalia. With respect to inherited skin disorders, in current clinical practice, fetoscopy has a limited use.

Biopsies of fetal skin represent the earliest form of prenatal testing for inherited skin diseases but this approach has largely been superseded by DNA-based methods. Fetal skin biopsy was first performed in the early 1980s for the diagnosis of congenital bullous ichthyosiform erythroderma (Fig.16.5) and Herlitz junctional epidermolysis bullosa (EB) [1,2].

These initial biopsies were performed with the aid of a fetoscope to visualize the fetus. However, with improvements in sonographic imaging, biopsies of fetal skin started to be taken under ultrasound guidance [3]. Fetal skin biopsy samples obtained during the early 1980s could be examined only by light microscopy and transmission electron microscopy (Figs 16.6 and 16.7).

However, the introduction of a number of monoclonal and polyclonal antibodies to various basement membrane components during the mid-1980s led to the development of immunohistochemical tests to help complement ultrastructural analysis in establishing accurate diagnoses [4], especially in cases of EB, which has been the main clinical indication for performing fetal skin biopsies over the last 25 years [5] (Fig. 16.8).

In such cases, fetal skin biopsy samples are usually obtained between 15 and 22 weeks' gestation. It has been normal practice to take four full-thickness pieces of skin: two for electron microscopy and two for immunofluorescence microscopy. The sites most commonly biopsied are the buttocks, back or thorax. Indirect immunofluorescence microscopy using an antibody (or

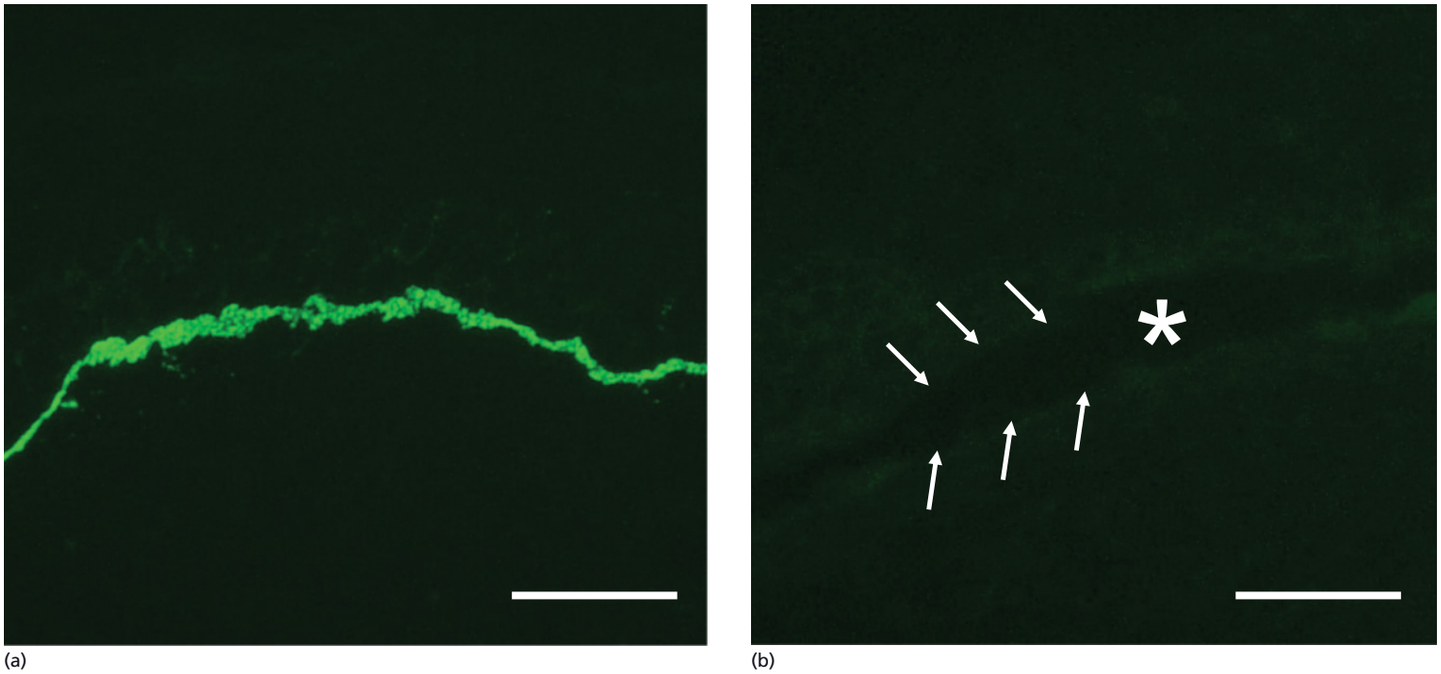


Fig. 16.8 Immunofluorescence microscopy following fetal skin biopsy using an antibody to type VII collagen. (a) In normal fetal skin at 16 weeks' gestation there is bright linear labelling at the dermal–epidermal junction; (b) in contrast, in a fetus affected with severe recessive dystrophic EB there is a complete absence of type VII collagen immunoreactivity (asterisk depicts blister cavity and arrows indicate roof and base of blister at the dermal–epidermal junction). Bar = 25 μm.

antibodies) to specific structural components of the dermal–epidermal junction, that is to those proteins that had shown absent, attenuated or altered immunostaining patterns in the previously affected child, is also part of the prenatal testing for EB.

Historically, another major indication for prenatal testing by fetal skin biopsy has been ichthyosis, especially harlequin ichthyosis. In sampling fetal skin at risk for harlequin ichthyosis, biopsies are not usually taken before 22 weeks' gestation because the structural abnormalities only start to appear at this stage in the pregnancy [6]. Slightly earlier diagnosis, at 19 weeks' gestation, has been attempted by examining keratinized hair canals and amniotic fluid cells [7]. With the discovery of mutations in the *ABCA12* gene as the molecular basis of harlequin ichthyosis, however, most cases can now be considered for much earlier DNA-based prenatal diagnosis instead [8]. Fetal skin biopsies have also been used in the diagnosis of oculocutaneous albinism. During the second trimester, melanogenesis is more active in hair bulbs than in interfollicular epidermis, and therefore fetal skin biopsies are preferentially taken from hairy regions, such as the fetal scalp or eyebrows [9]. Ultrastructural assessment of oculocutaneous tyrosinase-negative albinism has also subsequently been assisted by immunohistochemical methods in which skin samples were incubated with L-DOPA solution to assess tyrosinase activity [10], but DNA-based diagnosis is now also feasible [11].

For all fetal skin biopsy tests, sampling error, inadequacy of samples for analysis, and difficulty in interpreting the morphological and immunohistochemical features can pose problems, according to the experience of the obstetrician and microscopist. Artefact caused by the biopsy procedure, and by processing the very small fetal skin samples, can be severe or mimic true pathology. Nevertheless, fetal skin biopsy has an excellent track record, with a high degree of sensitivity and specificity of the analytical techniques used. Postnatal scars from prenatal skin sampling are usually inconspicuous. The rate of fetal loss is probably no more than 1% over the background incidence of spontaneous abortions. However, the procedure is invasive, which will always be a concern to both the medical team and the patient. Since the mid-1990s, the number of fetal skin biopsies performed has fallen by more than 95%, largely due to the introduction of alternative molecular screening methods [5]. The current indications for fetal skin biopsies, however, are:

1. Where the causative gene is unknown but prenatal diagnosis has been shown to be possible in similar cases using fetal skin biopsies
2. Where the causative gene is known, but informative DNA markers are unavailable, perhaps because an affected offspring had died before appropriate DNA samples could be obtained
3. Where previously attempted DNA-based prenatal diagnosis has been equivocal or technically unsatisfactory.

References

1 Golbus MS, Sagebiel RW, Filly RA *et al*. Prenatal diagnosis of congenital bullous ichthyosiform erythroderma (epidermolytic hyperkeratosis) by fetal skin biopsy. *N Engl J Med* 1980; **302**: 93–5.

2 Rodeck CH, Eady RA, Gosden CM. Prenatal diagnosis of epidermolysis bullosa letalis. *Lancet* 1980; **i**: 949–52.

3 Rodeck CH, Nicolaides KH. Fetoscopy and fetal tissue sampling. *Br Med Bull* 1983; **39**: 332–7.

4 Heagerty AH, Kennedy AR, Gunner DB *et al*. Rapid prenatal diagnosis and exclusion of epidermolysis bullosa using novel antibody probes. *J Invest Dermatol* 1986; **86**: 60–5.

5 Fassihi H, Eady RA, Mellerio JE *et al*. Prenatal diagnosis for severe inherited skin disorders: 25 years' experience. *Br J Dermatol* 206; **154**: 106–13.

6 Blanchet-Bardon C, Dumez Y. Prenatal diagnosis of harlequin fetus. *Semin Dermatol* 1984; **3**: 225–8.
7 Akiyama M, Suzumori K, Shimizu H. Prenatal diagnosis of harlequin ichthyosis by the examination of keratinized hair canals and amniotic fluid cells at 19 weeks' estimated gestational age. *Prenatal Diag* 1999; **19**: 167–71.
8 Akiyama M, Titeux M, Sakai K *et al.* DNA-based prenatal diagnosis of harlequin ichthyosis and characterization of *ABCA12* mutation consequences. *J Invest Dermatol* 2007; **127**: 568–73.
9 Eady RA, Gunner DB, Garner A *et al.* Prenatal diagnosis of oculocutaneous albinism by electron microscopy of fetal skin. *J Invest Dermatol* 1983; **80**: 210–12.
10 Shimizu H, Ishiko A, Kikuchi A *et al.* Prenatal diagnosis of tyrosinase-negative oculocutaneous albinism by an electron microscopic dopa reaction test of fetal skin. *Prenatal Diag* 1994; **14**: 442–50.
11 Shimizu H, Niizeki H, Suzumori K *et al.* Prenatal diagnosis of oculocutaneous albinism by analysis of the fetal tyrosinase gene. *J Invest Dermatol* 1994; **103**: 104–6.

Fetal ultrasound

Ultrasound images of the fetus and other uterine contents can be very informative in the detection of heart, bone or central nervous system abnormalities but the gross pathology of most inherited skin disorders is usually too subtle and beyond the resolution of this approach. Nevertheless, the 'snowflake sign' in the amniotic cavity may be a marker of fetal skin sloughing in certain disorders, including junctional EB with pyloric atresia and harlequin ichthyosis [1,2]. Three-dimensional ultrasound, however, enables a greatly improved analysis of morphology and has been used in the prenatal diagnosis of harlequin ichthyosis by screening for atypical facial dysmorphism, abnormal ear morphology, a wide open mouth with protruding tongue, large joint contractures and flexion deformities of the fetal digits [3]. Other cutaneous abnormalities diagnosed prenatally by this method include hypohidrotic ectodermal dysplasia, linear naevus sebaceus and cutis verticis gyrata [4–6]. Fetal ultrasonography can also be used for prenatal diagnosis of genodermatoses by identification of associated non-cutaneous features, such as gastric dilatation and associated polyhydramnios in junctional EB with pyloric atresia [7], and, in one case, a combination of severe oligohydramnios, hydrops fetalis and a large nephrogenic cyst in ectrodactyly–ectodermal dysplasia–clefting (EEC) syndrome [8]. These examples illustrate the value of ultrasonography in the prenatal diagnosis of some cutaneous disorders. However, at present this technique can only be used as a prenatal diagnostic tool after about 18 weeks' gestation, often too late in pregnancy to become an acceptable and established method of assessment. With further refinement, non-invasive ultrasound examination of the fetus may become more useful earlier in pregnancy for conditions characterized by gross morphological abnormalities, but for now it has a limited role in clinical practice with regard to inherited skin diseases.

References

1 Dolan CR, Smith LT, Sybert VP. Prenatal detection of epidermolysis bullosa letalis with pyloric atresia in a fetus by abnormal ultrasound and elevated alpha-fetoprotein. *Am J Med Genet* 1993; **47**: 395–400.
2 Bongain A, Benoit B, Ejnes L *et al.* Harlequin fetus: three-dimensional sonographic findings and new diagnostic approach. *Ultrasound Obstet Gynecol* 2002; **20**: 82–5.
3 Holden S, Ahuja S, Ogilvy-Stuart A *et al.* Prenatal diagnosis of harlequin ichthyosis presenting as distal arthrogryposis using three-dimensional ultrasound. *Prenatal Diag* 2007; **27**: 566–7.
4 Sepulveda W, Sandoval R, Carstens E *et al.* Hypohidrotic ectodermal dysplasia: prenatal diagnosis by three-dimensional ultrasonography. *J Ultrasound Med* 2003; **22**: 731–5.
5 Neis AE, Johansen KL, Harms RW *et al.* Sonographic characteristics of linear nevus sebaceous sequence. *Ultrasound Obstet Gynecol* 2006; **27**: 323–4.
6 Nas T, Biri A, Gursoy R *et al.* Prenatal ultrasonographic appearance of isolated cutis verticis gyrata. *Ultrasound Obstet Gynecol* 2005; **26**: 97–8.
7 Azarian M, Dreux S, Vuillard E *et al.* Prenatal diagnosis of inherited epidermolysis bullosa in a patient with no family history: a case report and literature review. *Prenatal Diag* 2006; **26**: 57–9.
8 Chuangsuwanich T, Sunsaneevithayakul P, Muangsomboon K, Limwongse C. Ectrodactyly-ectodermal dysplasia-clefting (EEC) syndrome presenting with a large nephrogenic cyst, severe oligohydramnios and hydrops fetalis: a case report and review of the literature. *Prenatal Diag* 2005; **25**: 210–5.

Preimplantation genetic diagnosis

For some couples, termination at any stage of pregnancy is unacceptable. Others may find the stress of abortion after skin biopsy prenatal testing in the mid-trimester or even after chorionic villus biopsy in the first trimester is too great to bear, especially if they have experienced a termination previously. Preimplantation genetic diagnosis (PGD) is an alternative method that is able to provide information about the genetic status of an early embryo [1]. PGD refers to the removal of a single cell from an embryo generated *in vitro* for genetic testing to diagnose a recurrent, serious, heritable condition and thereby to avoid the implantation of affected embryos (Fig. 16.9).

The procedure involves assisted conception techniques to generate embryos *in vitro* (Fig. 16.10). A single cell is then sampled as tissue representative of the whole embryo (Fig. 16.11) and is analysed for the presence of a specific genetic or chromosomal abnormality.

Only embryos found to be free of a specific genetic defect are then implanted in the uterus. The technique was developed in the UK in the late 1980s and was first used to avoid transmission of adrenoleucodystrophy and X-linked mental retardation [2]. Selection of female embryos to avoid X-linked disease was first carried out by polymerase chain reaction and then subsequently by fluorescence *in situ* hybridization (FISH), which can also be applied to testing for chromosomal rearrangements and translocations [3]. Successful clinical application of PGD for an inherited skin disorder has also been described. In that case, PGD testing was performed in embryos at risk of the autosomal recessive disorder, ectodermal dysplasia-skin fragility syndrome (OMIM604536). Testing involved direct sequencing of family-specific mutations in the *PKP1* gene encoding the desmosomal protein plakophilin 1 [4].

Other testing protocols have also been established for dystrophic EB. A generic test based on amplification of microsatellite markers centromeric and telomeric to the *COL7A1* gene is available for clinical use [5]. Tests that can screen for junctional EB resulting from mutations in the *LAMA3* or *LAMB3* genes (which encode the α3 and β3 polypeptide chains of laminin-332, respectively) are also in clinical practice. The tests for junctional EB involve recent technological advances in which template DNA

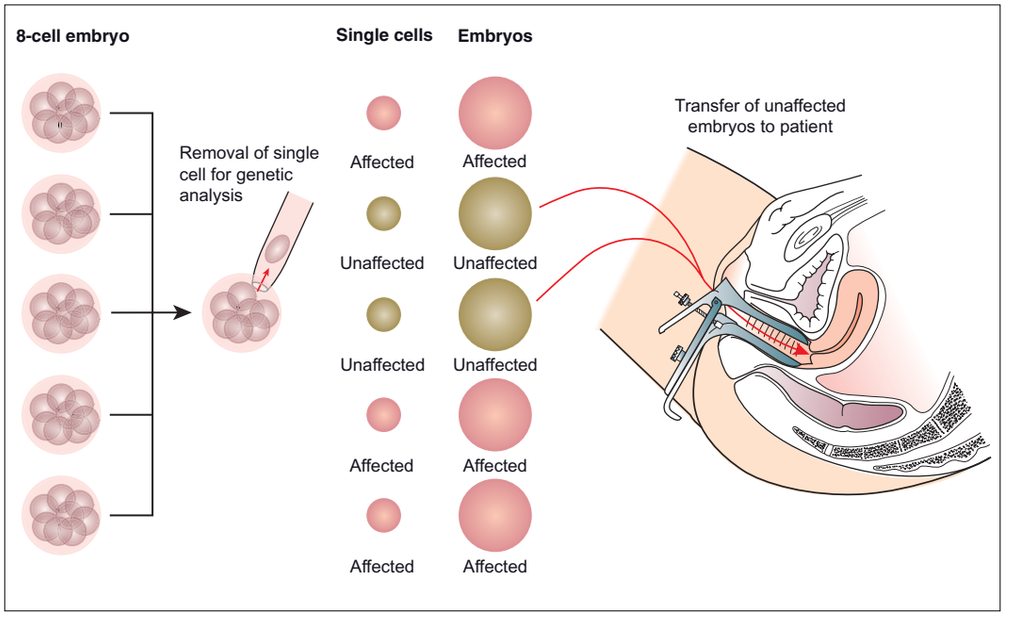


Fig. 16.9 Approach to PGD. Embryos are created with the use of *in vitro* fertilization. On the third day after fertilization, a single cell is removed from each embryo for genetic testing. Up to two mutation-free embryos are considered for transfer back to the uterus.



Fig. 16.10 *In vitro* fertilization using intracellular sperm injection (ICSI), as a prerequisite for preimplantation diagnosis. (Courtesy of the Assisted Conception Unit, Guy's and St Thomas' Hospital, London, UK.)



Fig. 16.11 Biopsy of a single cell from a blastocyst (3-day-old embryo) for preimplantation diagnosis. (Courtesy of the Assisted Conception Unit, Guy's and St Thomas' Hospital, London, UK.)

(typically approximately 6 ng from a single cell) can undergo initial whole genome amplification through multiple displacement amplification to create a much larger amount of DNA (approximately 6 µg) for genetic testing. This means that more markers of mutant or wild-type alleles can be examined, which improves both diagnostic scope and accuracy. The approach is known as preimplantation genetic haplotying (PGH) [6]. The main advantage of PGH is that it does not require precise details of the mutation to be known: only the gene which is implicated and the mode of inheritance are required. This makes the development of a specific test for a disease faster and the diagnosis from a single-cell biopsy more secure.

The clinical success of PGD/PGH is most strongly related to the number of embryos available for biopsy, which in turn is related to the number of good quality eggs obtained after gonadotrophin stimulation. If suitable embryos are available, clinical pregnancy rates are usually about 25% in most centres [7].

In the UK, there are strict regulations governing PGD. In 1990, the UK government passed the Human Fertilization and Embryology Act which gives some protection to human embryos. It limits the time they can be kept *in vitro* to 14 days and requires licences to be obtained for assisted reproductive therapy and for the storage of embryos and research involving them. The Act also established the Human Fertilization and Embryology Authority (HFEA) as

the appropriate regulatory agency and the HFEA is responsible for granting licences for PGD tests for specific diseases. The HFEA decides whether a disease is sufficiently serious to warrant interference with embryos and whether the licence applicants are competent to carry out the testing. In 2006, the HFEA also provided instruction and guidance on PGD testing for genetic susceptibility to certain diseases [8]. Approval was granted for certain subtypes of breast cancer, ovarian cancer, hereditary non-polyposis colon cancer and familial adenomatous polyposis, in which these potentially serious genetic conditions could be predetermined on the basis of single gene tests. Skin conditions such as psoriasis or atopic dermatitis, in which several genes may be implicated and for which medical treatments are available, are not currently deemed appropriate for PGD susceptibility screening. Whether the recent discovery of specific, frequent filaggrin gene mutations in individuals with (usually more severe) atopic dermatitis will challenge the recent testing boundaries, however, remains to be seen. Regulation of PGD varies throughout the world, and this method of prenatal testing is not permitted in several countries (e.g. Argentina, Austria, Switzerland or Taiwan) and is restricted in others (e.g. France or Germany).

References

1 Braude P, Pickering S, Flinter F, Ogilvie CM. Preimplantation genetic diagnosis. *Nat Rev Genet* 2002; **3**: 941–55.

2 Handyside AH, Kontogianni EH, Hardy K, Winston RM. Pregnancies from human preimplantation embryos sexed by Y-specific DNA amplification. *Nature* 1990; **344**: 768–70.

3 Ogilvie CM, Braude PR, Scriven PN. Preimplantation genetic diagnosis—an overview. *J Histochem Cytochem* 2005; **53**: 255–60.

4 Fassihi H, Grace J, Lashwood A *et al.* Preimplantation genetic diagnosis of skin fragility-ectodermal dysplasia syndrome. *Br J Dermatol* 2006; **154**: 546–50.

5 Fassihi H, Renwick PJ, Black C, McGrath JA. Single cell PCR amplification of microsatellites flanking the COL7A1 gene and suitability for preimplantation genetic diagnosis of Hallopeau-Siemens recessive dystrophic epidermolysis bullosa. *J Dermatol Sci* 2006; **42**: 241–8.

6 Renwick PJ, Trussler J, Ostad-Saffari E *et al.* Proof of principle and first cases using preimplantation genetic haplotyping—paradigm shift for embryo diagnosis. *Reprod Biomed Online* 2006; **13**: 110–9.

7 Grace J, El-Toukhy T, Scriven P *et al.* Three hundred and thirty cycles of preimplantation genetic diagnosis for serious genetic disease: clinical considerations affecting outcome. *BJOG* 2006; **113**: 1393–401.

8 Braude P. Preimplantation diagnosis for genetic susceptibility. *N Engl J Med* 2006; **355**: 541–3.

Non-invasive molecular strategies

Currently available methods for prenatal testing of fetal DNA or skin all involve invasive procedures and therefore attempts are also being made to develop less invasive screening strategies. One approach that is still at an experimental stage is assessment of fetal DNA in the maternal circulation by means of a simple blood test. This involves isolation of fetal cells in the maternal circulation or analysis of free fetal DNA in the maternal plasma.

In the late 19th century, placentally-derived trophoblasts were first demonstrated in pregnant mothers and in the 1960s it was established that nucleated fetal cells could be isolated from the maternal circulation [1]. Several fetal cell populations can be present in maternal peripheral blood, including erythrocytes, lymphocytes and trophoblasts but typically there is only about one fetal cell per ml of maternal blood. This makes isolation and detection of these fetal cells very difficult, despite the more recent introduction of laboratory techniques such as fluorescence- or magnetic-activated cell sorting, or microdissection, to improve fetal cell capture. Sensitivity rates for fetal cell detection in maternal blood are only approximately 40% and false positive detection rates are often more than 10%. Nucleated fetal cells may also persist in the maternal circulation for months or years, thus rendering their detection of dubious value for prenatal testing [2].

In 1997, it was established that cell-free circulating fetal DNA was also present in the maternal circulation [3]. This fetal DNA constitutes approximately 3–6% of cell-free DNA in the maternal plasma (which corresponds to 25–50 genome equivalents per ml) and mostly consists of short fragments (80% is shorter than 200-bp in length and all is shorter than 300-bp) [1]. It is detectable as early as 4 weeks' gestation and its concentration increases as gestation progresses. Unlike nucleated fetal cells, there is no long-term persistence of free fetal DNA in the maternal circulation. Indeed, free fetal DNA is cleared rapidly with a mean half-life of 16 minutes [4]. The main source of free fetal DNA in the maternal plasma is the placenta, from syncytiotrophoblasts in the form of apoptotic fragments packaged into microvesicles [5]. Normal cell turnover events in the placenta may be responsible for its release into the circulation, which provides an explanation for raised circulating free fetal DNA levels in multiple pregnancies and in pregnancy-associated disorders such as pre-eclampsia.

The main limitation of using free fetal DNA for prenatal diagnosis is its very low concentration in the maternal plasma. One approach to selectively enrich fetal DNA is by using gel electrophoresis to separate the smaller molecular weight fetal DNA from the maternal plasma [6]. An alternative method is to try to reduce the release of maternal DNA from cells during venepuncture. This can be done by collecting the blood in tubes containing formaldehyde; background maternal DNA levels are thereby reduced [7]. This approach, however, has not been widely employed and most maternal blood samples for free fetal DNA extraction are collected in standard EDTA tubes.

Once free fetal DNA is isolated, chromosomes, genes or genetic polymorphisms and mutations, inherited from the father, can be targeted. It is important to remember, however, that fetal cell or cell free DNA cannot be used to screen for maternal alleles because of masking of the maternal allele by maternal DNA. Nevertheless, prenatal diagnosis, based on screening for paternally-derived mutations, has been reported for some types of muscular dystrophy and beta thalassaemia [6]. Moreover, the use of free fetal DNA is now the basis of a widely used clinical assay to test for Rhesus blood group antigen D (i.e. from a RhD positive fetus in the plasma of a RhD negative mother) [8], as well as fetal sex determination in women at high risk for X-linked conditions or congenital adrenal hyperplasia. Current testing by this method is usually carried out at about 7 weeks' gestation and false-positive rates (for fetal sexing) are approximately 2%. As yet, however, there are no maternal blood testing methods currently in use for prenatal testing of severe inherited skin disorders.

In 2000, fetal RNA was also identified in maternal plasma [9]. The placenta is the main source of circulating fetal RNA and so

far approximately 10 specific placental transcripts (i.e. expressed in the placenta but absent in the maternal blood cells) have been characterized. Unlike most RNA, fetal RNA is surprisingly stable against RNase digestion. In future, it may be feasible to detect aneuploidies via the quantitative assessment of placentally-derived cell-free mRNA of certain chromosomes (e.g. chromosome 21-specific genes such as *PLAC4* in the detection of trisomy 21) [10]. Another approach may be to try to establish epigenetic signatures for fetal DNA (e.g. based on differential DNA methylation status) which will allow for the detection of both maternal and paternal markers. Copy numbers of free fetal placental-derived mRNAs could also provide a basis for novel non-invasive disease screening. There is also interest in post-genomics technologies that explore the proteins (proteomics) and transcripts (transcriptomics) released by the placenta to try to identify new biomarkers of disease [11].

Analysis of cell-free fetal DNA in maternal plasma provides a potential opportunity to develop reliable, timely, safe and cost-effective prenatal diagnosis for single gene disorders. To date, non-invasive first-trimester analysis for these conditions has been limited by assay sensitivity and specificity, mostly due to the background maternal DNA. However, the identification of fetal RNA in the maternal circulation and the detection of fetal epigenetic markers has greatly increased the number of molecular markers that could be developed for prenatal diagnosis and monitoring [12]. When testing very early in gestation, however, it is important to perform careful ultrasound examination to determine the number of gestational sacs because of the risk of discordant pregnancies. Nevertheless, overall, it is likely that in the future these basic molecular biology and technical advances will be translated into clinical prenatal tests for couples at reproductive risk of severe inherited skin disorders, thus increasing screening choice for couples at risk.

References

1 Norbury G, Norbury CJ. Non-invasive prenatal diagnosis of single gene disorders: how close are we? *Sem Fetal Neonatal Med* 2008; **13**: 76–83.

2 Bianchi DW, Simpson JL, Jackson LG *et al.* Fetal gender and aneuploidy detection using fetal cells in maternal blood: analysis of NIFTY I data. National Institute of Child Health and Development Fetal Cell Isolation Study. *Prenatal Diag* 2002; **22**: 609–15.

3 Lo YM, Corbetta N, Chamberlain PF *et al.* Presence of fetal DNA in maternal plasma and serum. *Lancet* 1997; **350**: 485–7.

4 Lo YM, Zhang J, Leung TN *et al.* Rapid clearance of fetal DNA from maternal plasma. *Am J Hum Genet* 1999; **64**: 218–24.

5 Alberry M, Maddocks D, Jones M *et al.* Free fetal DNA in maternal plasma in anembryonic pregnancies: confirmation that the origin is the trophoblast. *Prenatal Diag* 2007; **27**: 415–8.

6 Li Y, Di Naro E, Vitucci A *et al.* Detection of paternally inherited fetal point mutations for beta-thalassemia using size-fractionated cell-free DNA in maternal plasma. *JAMA* 2005; **293**: 843–9.

7 Dhallan R, Au WC, Mattagajasingh S *et al.* Methods to increase the percentage of free fetal DNA recovered from the maternal circulation. *JAMA* 2004; **291**: 1135–7.

8 Finning KM, Martin PG, Soothill PW, Avent ND. Prediction of fetal D status from maternal plasma: introduction of a new noninvasive fetal RHD genotyping service. *Transfusion* 2002; **42**: 1079–85.

9 Poon LL, Leung TN, Lau TK, Lo YM. Presence of fetal RNA in maternal plasma. *Clin Chem* 2000; **46**: 1832–4.

10 Lo YM, Chiu RW. Prenatal diagnosis: progress through plasma nucleic acids. *Nat Rev Genet* 2007; **8**: 71–7.

11 Avent ND, Plummer ZE, Madgett TE *et al.* Post-genomics studies and their application to non-invasive prenatal diagnosis. *Sem Fetal Neonatal Med* 2008; **13**: 91–8.

12 Hahn S, Zhong XY, Holzgreve W. Recent progress in non-invasive prenatal diagnosis. *Semin Fetal Neonatal Med* 2008; **13**: 57–62.

Ethical aspects of prenatal diagnosis

There is currently a lack of regulatory controls for prenatal diagnostic testing. In the UK, the only statutory requirement is that physicians report the occurrence of any subsequent pregnancy termination and the reasons for it. Termination may be performed at any time during the gestation if 'there is a substantial risk that if the child were born it would suffer from such physical or mental abnormalities as to be severely handicapped'. The upper age limit for abortions, which was set at 28 weeks in the 1967 Abortion Act, was changed to 24 weeks in the 1990 Human Fertilization and Embryology Act, but the change of timing does not apply 'in cases in which the child could have serious mental or physical handicaps'.

In contrast, there are very tight regulatory controls and cumbersome licensing requirements for any work that interferes with 3-day-old eight-cell embryos, which includes all PGD/PGH analyses. Additional restrictions also apply for using human embryos for research, including dissection of the inner cell mass to extract embryonic stem cells.

Present and future trends in prenatal and preimplantation diagnosis are bound to raise questions concerning moral, ethical, legal and economic aspects of these procedures. Major questions concern the degree of fetal abnormality and the consequent level of physical or mental disability that may be considered as a justification for abortion. Further issues will be raised now that preimplantation diagnosis is feasible for genetic susceptibility to certain disorders, usually malignancies, that occur in adult life [1,2]. Familial melanoma is not yet a licensed indication but if a specific single susceptibility gene abnormality is identified in some individuals then it may well become a feasible and licensed screening test. Likewise, psoriasis or atopic dermatitis families with clear single gene causation might also be candidates for preimplantation diagnosis for genetic susceptibility in the future.

For inherited skin diseases such as the various forms of EB, genetic tests are now available for variants of this disorder that generally might be regarded as mild, certainly in comparison with those associated with greater clinical severity or worse prognosis. For example, prenatal testing is now possible for the Weber–Cockayne form of EB simplex. However, such a test has not yet been reported, probably because it has not been requested. Most health-care personnel may feel that aborting a fetus that has tested positive for one of the 'milder' disorders is unjustified [3]. However, society might say that any couple at risk has the right to know what options are available and possibly the right to have prenatal diagnosis with the intention of terminating an affected pregnancy. Ethical implications on informed choice will also need to be considered. It is evident that although informed choice is highly valued in Western, individualistically orientated countries,

it is less highly valued in non-Western, more collectivist countries [4]. How these and other issues are to be resolved based on moral, ethical and legal considerations is by no means clear and will continue to be debated, along with other major issues involving genetic testing, created or influenced by recent advances in biomedical technology and reproductive medicine. For example, the introduction of new technologies for prenatal testing, such as non-invasive approaches, may raise further concerns about the appropriateness (or not) of screening for sex selection, paternity testing, particular physical traits or other genetic information [5].

References

1 Retchitsky S, Verlinsky O, Chistokhina A *et al.* Preimplantation genetic diagnosis for cancer predisposition. *Reprod Biomed Online* 2002; **5**: 148–55.

2 Braude P. Preimplantation diagnosis for genetic susceptibility. *N Engl J Med* 2006; **355**: 541–3.

3 Gare M, Gosme-Seguret S, Kaminski M, Cuttini M. Ethical decision-making in prenatal diagnosis and termination of pregnancy: a qualitative survey among physicians and midwives. *Prenatal Diag* 2002; **22**: 811–7.

4 van den Heuvel A, Marteau TM. Cultural variation in values attached to informed choice in the context of prenatal diagnosis. *Semin Fetal Neonatal Med* 2008; **13**: 99–102.

5 Newson AJ. Ethical aspects arising from non-invasive fetal diagnosis. *Semin Fetal Neonatal Med* 2008; **13**: 103–8.

CHAPTER 17
The Neonate

D.G. Paige[1], A.R. Gennery[2] & A.J. Cant[2]

[1]Department of Dermatology, Barts and the Royal London NHS Trust, London, UK
[2]Children BMT Unit, Newcastle General Hospital, Newcastle upon Tyne, UK

Skin disorders in the neonate, 17.1
Nomenclature, 17.1
Skin function in the neonate, 17.1
The appearance of neonatal skin, 17.4
Toxic erythema of the newborn, 17.6
Miliaria, 17.7
Transient pustular melanosis, 17.8
Infantile acropustulosis, 17.9
Eosinophilic pustulosis, 17.10
Neonatal pustulosis of transient myeloproliferative disorder, 17.10
Congenital erosive and vesicular dermatosis healing with reticulated supple scarring, 17.11
'Cradle cap', 17.11
Complications of prematurity, 17.11
Complications of medical procedures on the fetus and neonate, 17.11
Atrophic lesions of neonates, 17.15
Congenital annular limb lesions/amniotic bands, 17.15
Neonatal adnexal polyp, 17.15
Infantile pedal papules, 17.15
Disorders caused by transplacental transfer of maternal autoantibodies, 17.15
Neonatal lupus erythematosus, 17.16
Neonatal pemphigus vulgaris, 17.18
Transplacental pemphigoid (herpes) gestationis, 17.19
Transplacental transfer of maternal malignant disease, 17.19
Disorders caused by transfer of toxic substances in maternal milk, 17.19
'Collodion' baby, 17.19
Eczematous eruptions in the newborn, 17.22
Contact dermatitis in the neonatal period, 17.22
Infantile 'seborrhoeic' dermatitis, 17.28
Infantile psoriasis and napkin psoriasis, 17.31
'Blueberry muffin' baby (dermal erythropoiesis), 17.32
Neonatal purpura fulminans, 17.33
Acute haemorrhagic oedema of childhood, 17.33
Disorders of subcutaneous fat, 17.34
Cold panniculitis, 17.35
Neonatal cold injury, 17.35
Subcutaneous fat necrosis of the newborn, 17.36
Sclerema neonatorum, 17.38
Infections, 17.39
Viral infections, 17.39
Bacterial infections, 17.42
Fungal infections, 17.46
Primary immunodeficiency disorders, 17.48
The innate immune system, 17.48
The adaptive immune system, 17.49
Immunodeficiency disorders: general principles, 17.51
Diagnosis and investigation of immunodeficiency, 17.51
Disorders of cell-mediated immunity, 17.57
DNA repair defects and immunodeficiency, 17.67
Other immunodeficiencies, 17.70
Defects of antibody production, 17.70
Defects in innate immunity, 17.73

Skin disorders in the neonate

D. Paige, pp. 17.1–17.48

Nomenclature

The neonatal or newborn period is the first 4 weeks of extrauterine life, whereas infancy is the whole first year.

Infants born alive before the 37th week of gestation (i.e. 37 weeks after the first day of the mother's last menstrual period) are considered to be premature or preterm. Infants born with a birth weight of less than 2500 g are considered to be low-birth-weight infants; this state may be the consequence of prematurity, a less than expected rate of intrauterine growth (small for gestational age), or a combination of both. The term intrauterine growth retardation is used when birth weight is low for gestational age; such infants are commonly described as dysmature or small-for-dates.

Infants born after 42 weeks' gestation are described as post-term, irrespective of birth weight. This expression is often used synonymously with postmature. Because the true period of gestation may not be known exactly by dates, the diagnoses of prematurity, smallness-for-dates and maturity are made principally on clinical grounds; the relevant cutaneous features are considered later.

Skin function in the neonate

Barrier function

Great interest has focused on skin barrier function, both in preterm and full-term neonates, because of the evidence that both are at high risk of toxicity from topically applied substances [1].

It is believed that the normal full-term infant has a completely functional stratum corneum, with fully developed barrier function [2–6]. Toxicity resulting from percutaneous absorption in the full-term neonate is therefore more often related to: (i) the greatly increased ratio of surface area to volume; (ii) the frequent presence of occlusive conditions, such as exist under waterproof nappy covers; and (iii) high ambient temperatures and humidity, than to any impairment of barrier function *per se*.

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

There is, in contrast, definite evidence of impaired barrier function in preterm infants, especially those of less than 34 weeks' gestation, mirroring the anatomical immaturity of the epidermis and stratum corneum [3–5,7–11]. Percutaneous absorption correlates inversely with gestational age, but barrier function appears to improve rapidly after birth in the preterm infant, and will generally be normal by the end of the second or third week after birth [3,5,10,12].

It is clear that nothing should be applied to the skin of any baby without careful consideration of the potential hazards of percutaneous absorption, particularly in those with skin diseases. In the case of small, preterm neonates, one should be hesitant to apply anything at all to the skin. The best documented hazards relate to aniline dyes [13], hexachlorophene and related antiseptics [14–17], alcohol [18–21] and corticosteroids [22]. A number of other substances should never be used in neonates, especially not in preterm neonates; these include neomycin [23], boric acid [6,24–26], resorcinol (e.g. in Castellani's solution) [27,28], γ-benzene hexachloride [6,29], benzyl alcohol [30], benzyl benzoate [6], urea [31] and salicylic acid [6,32]. Antiseptics such as chlorhexidine [7] and iodine [33–35] should be used with the greatest caution and alcohol-based products should be avoided in view of the risk of 'chemical burns' [36,37]. Low-dose (0.25%) aqueous chlorhexidine applied to term babies has been shown to decrease mortality from sepsis in a study of 17 500 neonates from Nepal but only in low-birth-weight babies, and no differences were seen in those with birth weights over 2500 g [38]. Care should also be taken with agents used to launder, sterilize or mark nappies and bed linen [13,39–42], also with mothballs used in their storage [43].

Even the routine use of topical petrolatum-based emollients in preterms has been challenged recently, as whilst they can reduce transepidermal water loss (TEWL), a Cochrane review of four studies showed their use was associated with increased coagulase-negative staphylococcal infection and nosocomial infection [44]. Further studies in Bangladesh have confirmed this increase in nosocomial infection in preterm infants with use of petrolatum emollients, but have shown a significant reduction in infections with use of sunflower oil as an alternative [45,46]. No data yet exist on the use of emollients in preterm infants with severe skin disease, such as Netherton's syndrome or harlequin ichthyosis, where nosocomial infection is such a common problem and often lethal.

In view of the risk, it is of concern that a study undertaken in the USA a few years ago revealed that parents had applied over 48 different chemicals in over-the-counter preparations to the skin of their 1-month-old babies [47].

Conversely, the increased permeability of the skin in the preterm neonate has potential value for percutaneous administration of drugs [48].

TEWL is greatly increased in preterm compared with full-term babies [3,49–51]. The resulting outward passage of water can lead to high rates of heat loss by evaporation, which may even exceed the baby's resting rate of heat production. These losses can be reduced by increasing the ambient humidity [49,46,52], although this leads to an increased risk of infection, by covering the child with a plastic bubble blanket [53,54], a Perspex shield [55], or by applying a lipid barrier [56,57]. Whilst nursing the child in a high relative humidity environment helps lessen TEWL in the acute stage, it slows down the maturation and recovery of the skin barrier, so that abnormal TEWL takes longer to recover than in those nursed in low relative humidity environments [58].

It has been shown that oxygen absorption and carbon dioxide excretion rates through intact skin during the first few days of life are inversely correlated with gestational age [59]. There is, however, no increase in gas exchange in full-term neonates compared with adults, and rates in preterm neonates rapidly fall within 2 weeks of birth to those observed in full-term neonates. These studies raise the possibility of utilizing this increased gas permeability of preterm neonatal skin to deliver oxygen in the respiratory distress syndrome, particularly where there is severe pulmonary hypertension, when adequate oxygenation is exceedingly difficult to achieve.

It is possible that immaturity of the skin also predisposes the premature neonate to penetration of the skin by microorganisms, leading to systemic infection. This may be the reason that the premature infant with congenital cutaneous candidiasis is at greater risk of disseminated candidiasis [60].

Eccrine sweating

A full complement of anatomically normal eccrine sweat glands is present by the 28th week of gestation [61], but these appear to be functionally immature in neonates born before the 36th week, in terms of their responses to intradermal injection of acetylcholine and epinephrine (adrenaline) [62], and to thermal stress [63]. However, responsiveness usually develops in such babies by 2 weeks after birth [62,64]. Neonates born after the 36th week of gestation sweat in response to thermal stress from birth [65,66], although such sweating is initially relatively inefficient as a thermoregulatory mechanism. Care must therefore be taken not to overheat any neonate, but particularly the preterm neonate, and although severe overheating leading to hyperpyrexia is probably rare, lesser degrees of iatrogenic overheating appear to be common and may even induce apnoeic attacks [67].

The forehead appears to be the principal site of thermally induced sweating in the neonate [66]. The palms and soles, however, are sites of 'emotional' sweating, occurring in response to arousal, which appears to be well developed at birth in full-term but not preterm neonates [63]. The rate of such 'emotional sweating' can provide a measure of stress in small babies [68].

Sebaceous gland secretion

The secretions of the fetal sebaceous glands make a significant contribution to the vernix caseosa [69]. Vernix caseosa acts as a naturally occurring 'barrier cream' which also contains antimicrobial peptides and is formed from week 24 gestation [70,71]. Sebum secretion rates are high in neonates compared with older pre-adolescent children [72], and it is assumed that this sebaceous gland activity reflects stimulation by placentally transferred maternal androgen, particularly by dehydroepiandrosterone [72]. Sebaceous gland activity decreases from about the end of the first month to reach a stable level by the end of the first year [72].

References

1 West DP, Worobec S, Solomon LM. Pharmacology and toxicology of infant skin. *J Invest Dermatol* 1981; **76**: 147–50.

2 Fairley JA, Rasmussen JE. Comparison of stratum corneum thickness in adults and children. *J Am Acad Dermatol* 1983; **8**: 652–4.
3 Harpin VA, Rutter N. Barrier properties of the newborn infant's skin. *J Pediatr* 1983; **102**: 419–25.
4 McCormack JJ, Boisits EK, Fisher LB. An *in vitro* comparison of adult versus neonatal skin. In: Maibach JI, Boisits EK, eds. *Neonatal Skin*. New York: Marcel Dekker, 1982: 149–64.
5 Nachman RL, Esterley NB. Increased skin permeability in preterm infants. *J Pediatr* 1971; **79**: 628–32.
6 Rasmussen JE. Percutaneous absorption in children. In: Dobson RL, ed. *Year Book of Dermatology*. Chicago: Year Book, 1979: 15–38.
7 Aggett PJ, Cooper LV, Ellis SH *et al.* Percutaneous absorption of chlorhexidine in neonatal cord care. *Arch Dis Child* 1981; **56**: 878–91.
8 Barker N, Hadgraft J, Rutter N. Skin permeability in the newborn. *J Invest Dermatol* 1987; **88**: 409–11.
9 Greaves SJ, Ferry DG, McQueen EG *et al.* Serial hexachlorophene blood levels in the premature infant. *NZ Med J* 1975; **81**: 334–6.
10 West DP, Halket JM, Harvey DR *et al.* Percutaneous absorption in preterm infants. *Pediatr Dermatol* 1987; **4**: 234–7.
11 Rutter N. The immature skin. *Br Med Bull* 1988; **44**: 957–70.
12 Evans NJ, Rutter N. Development of the epidermis in the newborn. *Biol Neonate* 1986; **49**: 74–80.
13 Kagan BM, Mirman B, Calvin J *et al.* Cyanosis in premature infants due to aniline dye intoxication. *J Pediatr* 1949; **34**: 574–8.
14 Curley A, Hawk RE, Kimbrough RD *et al.* Dermal absorption of hexachlorophane in infants. *Lancet* 1971; **ii**: 296–7.
15 Martin-Bouyer G, Lebreton R, Toga M *et al.* Outbreak of accidental hexachlorophene poisoning in France. *Lancet* 1982; **i**: 91–5.
16 Powell H, Swarner O, Gluck L *et al.* Hexachlorophene myelinopathy in premature infants. *J Pediatr* 1973; **82**: 976–81.
17 Schuman RM, Leech RW, Alvord EC Jr. Neurotoxicity of hexachlorophene in the human. *Arch Neurol* 1975; **32**: 320–5.
18 Giminez ER, Vallejo NE, Roy E *et al.* Percutaneous alcohol intoxication. *Clin Toxicol* 1968; **1**: 39–48.
19 Harpin VA, Rutter N. Percutaneous alcohol absorption and skin necrosis in a premature infant. *Arch Dis Child* 1982; **57**: 477–9.
20 Puschel K. Percutaneous alcohol intoxication. *Eur J Pediatr* 1981; **136**: 317–8.
21 Sxhick J, Milstein J. Burn hazard of isopropyl alcohol in the neonate. *Pediatrics* 1981; **68**: 587–8.
22 Feinblatt BI, Aceto T, Beckhorn G *et al.* Percutaneous absorption of hydrocortisone in children. *Am J Dis Child* 1966; **112**: 218–24.
23 Morrell P, Hey E, Mackee IW *et al.* Deafness in a preterm baby associated with topical antibiotic spray containing neomycin. *Lancet* 1985; **i**: 1167–8.
24 Jensen JPA. Transkutan absorption af bor fra bornesalve anvendt profylaktisk mod bledermatitis. *Nord Med* 1971; **86**: 1425–9.
25 Skipworth GB, Goldstein N, McBride WP. Boric acid intoxication from 'medicated talcum powder'. *Arch Dermatol* 1967; **95**: 83–6.
26 Valdes-Dapena MA, Arey JB. Boric acid poisoning. *J Pediatr* 1962; **61**: 531–46.
27 Cunningham AA. Resorcin poisoning. *Arch Dis Child* 1956; **31**: 173–6.
28 Lundell E, Nordman R. A case of infantile poisoning by topical application of Castellani's solution. *Ann Clin Res* 1973; **5**: 404–6.
29 Solomon LM, Fahrner L, West DP. Gamma-benzene hexachloride toxicity: a review. *Arch Dermatol* 1977; **113**: 353–7.
30 Gershanik J, Boecler B, Ensley H *et al.* The gasping syndrome and benzyl alcohol poisoning. *N Engl J Med* 1982; **307**: 1384–8.
31 Beverley DW, Wheeler D. High plasma urea concentrations in collodion babies. *Arch Dis Child* 1986; **61**: 696–8.
32 Galea P, Goel KM. Salicylate poisoning in dermatological treatment. *Arch Dis Child* 1990; **65**: 335.
33 Chabrolle JP, Rossier A. Goitre and hypothyroidism in the newborn after cutaneous absorption of iodine. *Arch Dis Child* 1978; **53**: 495–8.
34 Mitchell IM, Pollock JC, Jamieson MPG *et al.* Transcutaneous iodine absorption in infants undergoing cardiac operation. *Ann Thorac Surg* 1991; **52**: 1138–40.
35 Pyati SP, Ramamurthy RS, Krauss MT *et al.* Absorption of iodine in the neonate following topical use of povidone iodine. *J Pediatr* 1977; **91**: 825–8.
36 Upadhyayula S, Kambalapalli M, Harrison CJ. Safety of anti-infective agents for the skin preparation in premature infants. *Arch Dis Child* 2007; **92**: 646–7.
37 Reynolds PR, Banerjee S, Meek JH. Alcohol burns in extremely low birthweight infants: still occurring. *Arch Dis Child Fetal Neonatal Edition* 2005; **90**: F10.
38 Tielsch JM, Darmstadt GL, Mullany LC *et al.* Impact of newborn skin-cleansing with chlorhexidine on neonatal mortality in southern Nepal: a community-based, cluster-randomized trial. *Pediatrics* 2007; **119**: e330–40.
39 Armstrong RW, Eichner EW, Klein DF *et al.* Pentachlorophenol poisoning in a nursery for newborn infants. II. Epidemiologic and toxologic studies. *J Pediatr* 1969; **75**: 317–25.
40 Brown BW. Fatal phenol poisoning from improperly laundered diapers. *Am J Public Health* 1970; **60**: 901–2.
41 Fisch RO, Berglund EB, Bridge AG *et al.* Methemoglobinemia in a hospital nursery. *JAMA* 1963; **185**: 760–3.
42 Robson AM, Kissane JM, Elvick NH *et al.* Pentachlorophenol poisoning in a nursery for newborn infants. I. Clinical features and treatment. *J Pediatr* 1969; **75**: 309–16.
43 Schafer WB. Acute hemolytic anemia related to naphthalene. *Pediatrics* 1951; **7**: 172–4.
44 Conner JM, Soll RF, Edwards WH. Topical ointment for preventing infection in preterm infants. *Cochrane Database Syst Rev* 2004; (1): CD001150.
45 Darmstadt GL, Saha SK, Ahmed ASM *et al.* Effect of topical treatment with skin barrier-enhancing emollients on nosocomial infections in preterm infants in Bangladesh: a randomised controlled trial. *Lancet* 2005; **365**: 1039–45.
46 Darmstadt GL, Saha SK, Ahmed ASM *et al.* Effect of topical treatment of preterm neonates in Bangladesh on invasion of pathogens into the bloodstream. *Pediatr Res* 2007; **61**: 588–93.
47 Cetta F, Lambert GH, Ros SP. Newborn chemical exposure from over-the-counter skin care products. *Clin Pediatr (Phila)* 1991; **30**: 286–9.
48 Evans NJ, Rutter N, Hadgraft J *et al.* Percutaneous administration of theophylline in the preterm infant. *J Pediatr* 1985; **107**: 307–11.
49 Hammarlund K, Sedin G. Transepidermal water loss in newborn infants. III. Relation to gestational age. *Acta Paediatr Scand* 1979; **68**: 795–801.
50 Rutter N, Hull D. Water loss from the skin of term and preterm babies. *Arch Dis Child* 1979; **54**: 858–68.
51 Wilson DR, Maibach HI. Transepidermal water loss *in vivo*. *Biol Neonate* 1980; **37**: 180–5.
52 Sulyok E, Jequier E, Ryser G. Effect of relative humidity on thermal balance of the newborn infant. *Biol Neonate* 1972; **21**: 210–8.
53 Brice JEH, Rutter N, Hull D. Reduction of skin water loss in the newborn. II. Clinical trial of two methods in very low birthweight babies. *Arch Dis Child* 1981; **56**: 673–5.
54 Marks KH, Friedman Z, Maisels MJ. A simple device for reducing insensible water loss in low birth-weight infants. *Pediatrics* 1977; **60**: 223–6.
55 Fitch CW, Korones SB. Heat shield reduces water loss. *Arch Dis Child* 1984; **59**: 886–8.
56 Rutter N, Hull D. Reduction of skin water loss in the newborn. I. Effect of applying topical agents. *Arch Dis Child* 1981; **56**: 669–72.
57 Nopper AJ, Horii KA, Sookdeo-Drost S *et al.* Topical ointment therapy benefits premature infants. *J Pediatr* 1996; **128**: 660–9.
58 Ågren J, Sjörs G, Sedin G. Ambient humidity influences the rate of skin barrier maturation in extremely preterm infants. *J Pediatr* 2006; **148**: 613–7.
59 Evans NJ, Rutter N. Percutaneous respiration in the newborn infant. *J Pediatr* 1986; **108**: 282–6.
60 Baley JE, Silverman RA. Systemic candidiasis: cutaneous manifestations in low birth weight infants. *Pediatrics* 1988; **82**: 211–5.
61 Szabo G. The number of eccrine sweat glands in human skin. *Adv Biol Skin* 1962; **3**: 1–5.
62 Behrendt H, Green M. Drug-induced localised sweating in full-size and low-birth-weight neonates. *Am J Dis Child* 1969; **117**: 299–306.
63 Harpin VA, Rutter N. Development of emotional sweating in the newborn infant. *Arch Dis Child* 1982; **57**: 691–5.
64 Harpin VA, Rutter N. Sweating in preterm babies. *J Pediatr* 1982; **100**: 614–8.
65 Green M, Behrendt H. Sweating responses of neonates to local thermal stimulation. *Am J Dis Child* 1973; **125**: 20–5.
66 Rutter N, Hull D. Response of term babies to a warm environment. *Arch Dis Child* 1979; **54**: 178–83.
67 Perlstein PH, Edwards NK, Sutherland JM. Apnea in premature infants and incubator-air-temperature changes. *N Engl J Med* 1970; **282**: 461–6.

68 Gladman G, Chiswick ML. Skin conductance and arousal in the newborn. *Arch Dis Child* 1990; **65**: 1063–6.
69 Rissman R, Groenink HWW, Weerheim AM *et al.* New insights into ultrastructure, lipid composition and organization of vernix caseosa. *J Invest Dermatol* 2006; **126**: 1823–33.
70 Visscher MO, Narendran V, Pickens WL *et al.* Vernix caseosa in neonatal adaptation. *J Perinatol* 2005; **25**: 440–6.
71 Marchini G, Lindow S, Brismar H *et al.* The newborn infant is protected by an innate antimicrobial barrier: peptide antibiotics are present in the skin and vernix caseosa. *Br J Dermatol* 2002; **147**: 1127–34.
72 Agache P, Blanc D, Barrand C *et al.* Sebum levels during the first year of life. *Br J Dermatol* 1980; **103**: 643–9.

The appearance of neonatal skin

A variety of skin lesions commonly seen in the newborn are regarded as 'physiological'. Their frequency has been studied by several authors, and varies somewhat in different racial groups [1–5].

At birth, the skin is covered with a whitish, greasy film, the *vernix caseosa*. The vernix may cover the entire skin surface, or it may be present only in body folds such as the groins. It normally dries rapidly and starts to flake off within a few hours of birth. The vernix appears to be comprised of lipids [6,7]. Little is known of its function, though recent evidence of its content of the peptide antibiotic LL-37 and of lysozyme support an antimicrobial role [8]. Its colour may reflect intrauterine problems, such as haemolytic disease of the newborn and postmaturity, both of which result in golden yellow staining. Fetal distress *in utero* may lead to staining of the vernix by the bile pigments present in meconium.

Peripheral cyanosis (or acrocyanosis) is a feature of the newborn, particularly the full-term newborn, and is usually particularly marked on the palms and soles and around the mouth. In the absence of cyanosis of warm central parts such as the tongue, this may be regarded as normal during the first 48 h or so. It is made more obvious by hypothermia, and is improved by warming.

A few hours after birth, many babies develop a striking generalized hyperaemia usually known as *erythema neonatorum*, which fades spontaneously within 24–48 h.

In as many as 15% of neonates, a vivid colour difference may appear along the midline at some time during the first week of life [9–12]. This phenomenon occurs when the baby is lying on its side, the upper half of the body becoming pale, the lower half a deep-red colour, with a sharp midline demarcation between the two. The duration of the attack is highly variable, but generally is between half a minute and 20 min. If the baby is turned on the other side, the colour change may reverse. An individual neonate may have only a single episode, or it may recur on several occasions. This curious phenomenon has been called *harlequin colour change*. It appears to have no pathological significance in the great majority of cases, and is considered to reflect immaturity of hypothalamic centres responsible for the control of peripheral vascular tone [9]. If it persists beyond the end of the fourth week, it may be associated with hypoxia due to cardiovascular anomalies [13].

Newborn infants who are subjected to cooling will show distinct marbling of the skin. Although this more or less disappears on rewarming, many normal neonates demonstrate faint marbling, even under optimal environmental conditions. The marbling comprises a reticulate blue vascular pattern, which has often been called *cutis marmorata*. This response is a physiological one, and may be seen throughout infancy. *Cutis marmorata telangiectatica congenita* is an entirely distinct vascular developmental disorder, and is easily distinguished (see Chapter 18). Cutaneous marbling may be seen in older children with a variety of disorders, particularly athyrotic (congenital) hypothyroidism [14], the de Lange syndrome, the Adams–Oliver syndrome, in trisomy 18, trisomy 21, homocystinuria and the Divry–Van Bogaert syndrome (see Chapters 15 and 18).

Rather superficial cutaneous desquamation, often termed physiological scaling of the newborn, occurs in up to 75% of normal neonates [5,15]. This usually first appears around the ankles on the first day of life, and is most commonly more or less confined to the hands and feet [5]. It may remain very localized or may gradually become more widespread, usually reaching its maximum extent and intensity by the eighth day. Although it has been reported that this type of desquamation is unusual in babies born earlier than the 39th week of gestation, and that it occurs with increasing frequency the greater the gestational age [15], this was not confirmed in a later study, in which it was found to occur with equal prevalence at all gestational ages [5]. It tends always to be more severe in neonates who are small-for-dates, whatever their gestational age. Physiological scaling may occasionally be fairly pronounced, not generally sufficiently so to lead to confusion with any of the more serious types of congenital ichthyosis, but milder varieties of ichthyosis, such as ichthyosis vulgaris, may be difficult to distinguish, and it should be borne in mind that X-linked hypohidrotic ectodermal dysplasia may present with scaling of the skin in the neonatal period [16].

One or two solitary blisters or erosions are occasionally present at birth on the fingers, lips or forearms, and are believed to be caused by vigorous sucking *in utero*; hence the term sucking blister is often applied. These heal rapidly without sequelae [17].

The scalp hair is shed synchronously during the fifth month of fetal life, and having regrown enters telogen in a wave from front to back, starting about 12 weeks before term. After shedding of the telogen hairs from the frontal and parietal areas, the roots again enter the anagen phase in a similar wave from front to back [18–20]. The roots in the occipital area do not enter telogen until term, and therefore rather conspicuous alopecia may appear at this site at birth or within the first 2 months ('neonatal occipital alopecia') [21].

There appear to be two waves of hair loss and regrowth from front to back during early infancy, but by the end of the first year the typical mosaic pattern of hair growth is established [22]. In some babies, there is unusually synchronous hair loss during the neonatal period, resulting in obvious diffuse alopecia (telogen effluvium of the newborn), but, by the end of the first 6 months of life, most babies have a full head of hair [23]. At this stage, the hairline often extends to the lateral ends of the eyebrows, but the terminal hairs comprising this extension gradually convert to vellus hairs during the remainder of the first year of life, causing the hairline to recede to its characteristic childhood position.

Sebaceous gland hyperplasia is a physiological event in the newborn, reflecting the influence of maternal androgens. It is visible to the naked eye in the great majority of infants as multiple, uniform, pinpoint, yellowish papules that are most prominent on

the nose, cheeks, upper lip and forehead, but may also be visible on the upper trunk, especially the areolae, the genitalia and the limbs. The phenomenon is associated in about 40% of infants with *milia*, which represent minute follicular epidermal cysts [24]. The number of milia present may vary from one or two to many hundreds. They comprise 1–3 mm, white, globular papules, which occur at the same sites. Rather larger and usually single milia, often termed pearls, are seen sometimes on the areolae, scrotum and labia majora. Both the sebaceous gland hyperplasia and the milia tend to disappear spontaneously during the first weeks of life, though a few may persist longer. Milia which are exceptionally extensive or persistent, or whose distribution is atypical, may be features of the orofacial–digital syndrome type I, Marie–Unna type congenital hypotrichosis or the X-linked Bazex–Dupré–Christol syndrome, which features hypotrichosis and milia [25] (see Chapter 15).

The influence on the fetus of maternal and placental hormones gives rise to a group of phenomena, varying greatly in degree, sometimes described as 'miniature puberty'. In the newborn female, the genitalia appear succulent, and the size of the clitoris in particular may lead the inexperienced to suspect intersex. A mucoid vaginal discharge is common. Vaginal smears at this stage may be indistinguishable from those of pregnant women. A few days after birth, the hyperplastic vaginal epithelium desquamates to leave a more normal infantile mucosa; this desquamation may be manifest as a creamy white discharge. Frank withdrawal bleeding may occur from the uterus on the third of fourth day, usually lasting 2 or 3 days. The male genitalia appear similarly large and well-developed at birth.

Both sexes show hypertrophy of the mammary glands at birth. After 2 or 3 days the breasts may become engorged and lactation of so-called 'witch's milk' may occur. The swelling subsides during the second week and has usually become undetectable by the end of the fourth week. In some girls, however, it may be more persistent, and it is these girls in particular who are at risk of infection because of the presence of stagnant milk, leading to mastitis and abscess formation.

In about 8% of babies, the linea alba becomes pigmented, and this pigmentation may persist for 2 or 3 months. Mongolian spots occur in about 85% of oriental neonates [2,26], and the frequency in black babies is also high [27]. Mongolian spots are rare in white neonates, around 3% [27]. Exaggerated pigmentation of the scrotum occurs in about 30% of oriental neonates [26]. A rare type of congenital linear and/or reticulate pigmentation has been reported on the limbs and/or trunk of black neonates [28].

One or more 1–2 mm, yellowish white, keratinous cysts, known as *Epstein's pearls*, may be seen in the mouths of up to 85% of all neonates, along the alveolar ridges and/or in the midline at the junction of the hard and soft palate [5,29,30]. These generally disappear without treatment within a few weeks. Other common oral findings in the neonate [30] include rather succulent gums, analogous to the hypertrophic gingivitis often seen in pregnant women, a whitish hue to the oral mucosa (termed 'leukoedema', but probably synonymous with what other authors have called 'suckling pads' [31]), alveolar lymphangioma [32], ankyloglossia, commissural lip pits [33,34] and a median alveolar notch.

References

1 Cordova A. The mongolian spot: a study of ethnic differences and a literature review. *Clin Pediatr (Phila)* 1981; **20**: 714–9.
2 Hidano A, Purwoko R, Jitsukawa K. Statistical survey of skin changes in Japanese neonates. *Pediatr Dermatol* 1986; **3**: 140–4.
3 Nanda A, Kaur S, Bhakoo ON *et al.* Survey of cutaneous lesions in Indian newborns. *Pediatr Dermatol* 1989; **6**: 39–42.
4 Saracli T, Kenney JA, Scott RB. Common skin disorders in the newborn Negro infant. *J Pediatr* 1963; **63**: 358–62.
5 Rivers JK, Frederiksen PC, Dibdin C. A prevalence survey of dermatoses in the Australian neonate. *J Am Acad Dermatol* 1990; **23**: 77–81.
6 Downing DT, Strauss JS. Synthesis and composition of surface lipids of human skin. *J Invest Dermatol* 1974; **62**: 228–44.
7 Karkkainen J, Nikkari T, Ruponen S *et al.* Lipids of the vernix caseosa. *J Invest Dermatol* 1965; **44**: 333–8.
8 Marchini G, Lindow S, Brismar H *et al.* The newborn infant is protected by an innate antimicrobial barrier: peptide antibiotics are present in the skin and vernix caseosa. *Br J Dermatol* 2002; **147**: 1127–34.
9 Herlitz G. Unilateral skin vessel crises in the newborn. *Acta Paediatr Scand* 1953; **42**: 506–13.
10 Mortensen O, Stougard-Andresen P. Harlequin colour change in the newborn. *Acta Obstet Gynecol Scand* 1959; **38**: 352–8.
11 Nelligan GA, Strang LB. A 'harlequin' colour change in the newborn. *Lancet* 1952; **ii**: 1005–7.
12 Selimoglu MA, Dilmen U, Karakelleoglu C *et al.* Harlequin color change. *Arch Pediatr Adolesc Med* 1995; **149**: 1171–2.
13 Pearson HA, Cone TE. Harlequin color change in a young infant with tricuspid atresia. *Pediatrics* 1957; **50**: 609–12.
14 Jones KL. Athyrotic hypothyroidism sequence. In: *Smith's Recognizable Patterns of Human Malformation*, 5th edn. Philadelphia: Saunders, 1997: 614–5.
15 Griffiths AD. Skin desquamation in the newborn. *Biol Neonate* 1966; **10**: 127–39.
16 Executive and Scientific Advisory Boards of the National Foundation for Ectodermal Dysplasias. Scaling skin in the neonate: a clue to the early diagnosis of hypohidrotic ectodermal dysplasia (Christ–Siemens–Touraine syndrome). *J Pediatr* 1989; **114**: 600–2.
17 Murphy WF, Langley AL. Common bullous lesions, presumably self-inflicted, occurring *in utero* in the newborn infant. *Pediatrics* 1963; **32**: 1099–101.
18 Barman JM, Pecoraro V, Astore I *et al.* The first stage in the natural history of the human scalp hair cycle. *J Invest Dermatol* 1967; **48**: 138–42.
19 Kostanecki W, Pawlowski A, Lozinska D. Der haarwurzelstatus bei neugeborenen. *Arch Klin Exp Dermatol* 1965; **221**: 162–5.
20 Pecoraro V, Astore I, Barman JM. Cycle of the scalp hair of the newborn child. *J Invest Dermatol* 1964; **43**: 145–7.
21 Cutrone M, Grimalt R. Transient neonatal hair loss: a common transient neonatal dermatosis. *Eur J Pediatr* 2005; **164**: 630–2.
22 Barth JH. Normal hair growth in children. *Pediatr Dermatol* 1987; **4**: 173–84.
23 Kligman AM. Pathologic dynamics of human hair loss. *Arch Dermatol* 1961; **83**: 175–98.
24 Gordon I. Miliary sebaceous cysts and blisters in the healthy newborn. *Arch Dis Child* 1949; **24**: 286–8.
25 Vabres P, Lacombe D, Anderson CE *et al.* The gene for Basex syndrome maps to chromosome Xq. *J Invest Dermatol* 1995; **105**: 87–91.
26 Tsai F-J, Tsai C-H. Birthmarks and congenital skin lesions in Chinese newborns. *J Formos Med Assoc* 1993; **92**: 838–41.
27 Osburn K, Schosser RH, Everett MA. Congenital pigmented and vascular lesions in newborn infants. *J Am Acad Dermatol* 1987; **16**: 788–92.
28 Halper S, Rubinstein D, Prose N, Levy M. Pigmentary lines of the newborn. *J Am Acad Dermatol* 1993; **28**: 893–4.
29 Cataldo E, Berkman MD. Cysts of the oral mucosa in newborns. *Am J Dis Child* 1968; **116**: 44–8.
30 Jorgenson RJ, Shapiro SD, Salinas CF *et al.* Intraoral findings and anomalies in neonates. *Pediatrics* 1982; **69**: 577–82.
31 Heyl T. The skin of the pre-term baby—a visual appraisal. *Clin Exp Dermatol* 1986; **11**: 584–93.
32 Levin LS, Jorgenson RJ, Jarvey BA. Lymphangiomas of the alveolar ridges in neonates. *Pediatrics* 1976; **58**: 881–4.
33 Everett FG, Westcott WB. Commissural lip pits. *Oral Surg Oral Med Oral Pathol* 1961; **14**: 202–9.

34 Baker BR. Pits of the lip commissures in Caucasoid males. *Oral Surg Oral Med Oral Pathol* 1966; **21**: 56–60.

The appearance of the preterm neonate

The skin of the preterm neonate tends to have a rather translucent, gelatinous quality, and the so-called 'miniature puberty' features are much less prominent.

Preterm infants are often covered in quite obvious lanugo hairs, which tend to be most dense on the face, limbs and trunk. This hair would normally be shed *in utero* about 1 month before term [1], to be replaced by a second coat of shorter lanugo, which is present at birth in full-term infants. Like the terminal scalp hair, this downy lanugo is shed during the first months of life and is itself replaced by vellus hair.

Reference

1 Kligman AM. Pathologic dynamics of human hair loss. *Arch Dermatol* 1961; **83**: 175–98.

Appearance of small-for-dates and postmature neonates

The small-for-dates or dysmature neonate presents a characteristic appearance due to relative prenatal malnutrition. The baby is small and, from the dermatological point of view, the most striking feature is the lack of subcutaneous fat, which causes the baby to look thin and wrinkled. Vernix is absent in the extremely immature infant, but may be profuse nearer to term. The skin and vernix are often stained yellowish green by meconium. After birth, the skin dries quickly and becomes 'crazed' with long transverse splits on the trunk. It then peels off to reveal more normal-appearing skin beneath. The fingernails are often long.

The postmature infant is longer, but of otherwise similar appearance to the small-for-dates neonate, having also experienced intrauterine malnutrition due to placental insufficiency. Vernix is often absent [1].

Reference

1 Clifford SH. Postmaturity—with placental dysfunction. Clinical syndrome with pathologic findings. *J Pediatr* 1954; **44**: 1–13.

Toxic erythema of the newborn

Synonym

- Erythema toxicum neonatorum

Terminology. The most widely used term for this condition is inappropriate in view of the complete absence of any evidence of a toxic cause.

Aetiology. The cause of toxic erythema of the newborn is unknown. It was at one time believed that the frequent finding of an associated blood eosinophilia implied an allergic origin, but there has never been any convincing support for the view that the condition is a manifestation of hypersensitivity to milk or drugs transmitted to the infant before birth via the placenta, or to vaginal secretions. Furthermore, the demonstration that tissue eosinophilia is a non-specific feature of inflammatory responses in neonates [1] adds little weight to such a view.

The intrafollicular location of mature pustules has led to the suggestion that the inflammatory response is elicited by some component of sebum [2].

Attempts to culture pathogenic bacteria from the lesions have always proved fruitless [3].

The suggestion has been made that toxic erythema of the newborn might represent a mild and self-limited, acute graft-versus-host reaction due to maternal lymphocyte transfer to the neonate [4], but evidence for this is poor; in particular the histopathological features do not resemble those that have been demonstrated in acute graft-versus-host reactions in the skin.

Pathology [5,6]. Histologically, the macular erythema shows oedema in the upper dermis, associated with a sparse and largely perivascular inflammatory infiltrate comprising principally eosinophils. Papular lesions are characterized, in addition, by eosinophil infiltration of the outer root sheath of one or more hair follicles, above the point of entry of the sebaceous duct. Pustular lesions show intrafollicular accumulation of eosinophils immediately below the stratum corneum. Smears of the pustule contents demonstrate inflammatory cells, more than 90% of which are eosinophils [7,8].

There is an associated blood eosinophilia of up to 20% of the white cell count in around half the cases, and this is generally more marked when there is a prominent pustular element to the eruption [3,7].

Clinical features [3,7–11]. Up to 50% of full-term infants of all racial types will manifest some degree of toxic erythema during the first few days of life [9,12–15]. The incidence appears to decrease with both prematurity and smallness-for-dates [16]. In the majority of cases, the onset is during the first 48 h after birth, but it may occur at any time until about the fourth day. It is in rare instances present at birth [9,17,18].

Most commonly, the eruption initially takes the form of a blotchy, macular erythema, the number of individual lesions varying from one or two to several hundred. They are most profuse on the trunk, particularly the anterior trunk, but also commonly appear on the face and proximal parts of the limbs, especially the thighs. Lesions have been recorded, however, at almost any site except the palms and soles. In the mildest cases, these macules fade within a day. In more severe cases, urticarial papules arise within the erythematous areas, or, occasionally, independently of them (particularly on the back and buttocks). These papules are, in about 10% of cases, surmounted by small pustules 1–2 mm in diameter.

Presentation with scrotal pustules present at birth has been reported more recently [18].

The infant appears well, and unperturbed by the eruption. Spontaneous recovery occurs rapidly, usually within 3 days, but recurrences are occasionally seen, and have been reported as late as the sixth week of life [19,20].

Diagnosis. Toxic erythema of the newborn has to be distinguished from several other disorders featuring pustular lesions during the neonatal period, particularly miliaria, transient neonatal pustular melanosis, incontinentia pigmenti, and, most importantly, herpes

simplex virus (HSV) infection, varicella, impetigo neonatorum and *Malassezia furfur* pustulosis. Of these, perhaps pustular miliaria is the one most often confused clinically with toxic erythema. Toxic erythema can be rapidly distinguished from all of these by microscopic examination of a smear of pustule contents, stained with Giemsa, and by bacterial and viral culture.

Treatment. No treatment is required.

References

1 Eitzman DV, Smith RT. The non-specific inflammatory cycle in the neonatal infant. *Am J Dis Child* 1959; **97**: 326–34.
2 Luders D. Histologic observations in erythema toxicum neonatorum. *Pediatrics* 1960; **26**: 219–24.
3 Levy HL, Cothran F. Erythema toxicum neonatorum present at birth. *Am J Dis Child* 1962; **103**: 617–9.
4 Bassukas ID. Is erythema toxicum neonatorum a mild, self-limited acute cutaneous graft-versus-host reaction from maternal-to-fetal lymphocyte transfer? *Med Hypotheses* 1992; **38**: 334–8.
5 Duperrat B, Bret AJ. Erythema neonatorum allergicum. *Br J Dermatol* 1961; **73**: 300–2.
6 Freeman RG, Spiller R, Knox JM. Histopathology of erythema toxicum neonatorum. *Arch Dermatol* 1960; **82**: 586–9.
7 Harris R, Schick B. Erythema neonatorum. *Am J Dis Child* 1956; **92**: 27–33.
8 Marino LJ. Toxic erythema present at birth. *Arch Dermatol* 1965; **92**: 402–3.
9 Nanda A, Kaur S, Bhakoo ON *et al*. Survey of cutaneous lesions in Indian newborns. *Pediatr Dermatol* 1989; **6**: 39–42.
10 Taylor WB, Bondurant CP. Erythema neonatorum allergicum. *Arch Dermatol* 1957; **76**: 591–4.
11 Berg FJ, Solomon LM. Erythema neonatorum toxicum. *Arch Dis Child* 1987; **62**: 327–8.
12 Hidano A, Purwoko R, Jitsukawa T. Statistical survey of skin changes in Japanese neonates. *Pediatr Dermatol* 1986; **3**: 140–4.
13 Rivers JK, Frederiksen PC, Dibdin C. A prevalence survey of dermatoses in the Australian neonate. *J Am Acad Dermatol* 1990; **23**: 77–81.
14 Tsai F-J, Tsai C-H. Birthmarks and congenital skin lesions in Chinese newborns. *J Formos Med Assoc* 1993; **92**: 838–41.
15 Prigent F, Vige P, Martinet C. Lésions cutanées au cours de la première semaine de vie chez 306 nouveau-nés consécutifs. *Ann Dermatol Vénéréol* 1991; **118**: 697–9.
16 Carr JA, Hodgman JE, Freedman RI *et al*. Relationship between toxic erythema and infant maturity. *Am J Dis Child* 1966; **122**: 129–34.
17 Keitel HG, Yadav V. Etiology of toxic erythema. *Am J Dis Child* 1963; **106**: 306–9.
18 Maffei FA, Michaels MG, Wald ER. An unusual presentation of erythema toxicum with scrotal pustules present at birth. *Arch Pediatr Adolesc Med* 1996; **150**: 649–50.
19 Pohlandt F, Harnisch R, Meigel WN *et al*. Bild des Erythema neonatorum. *Hautarzt* 1977; **28**: 469–74.
20 Hidano A, Purwoko R, Jitsukawa K. Statistical survey of skin changes in Japanese neonates. *Pediatr Dermatol* 1986; **3**: 140–4.

Miliaria

Aetiology. Miliaria occurs when the flow of eccrine sweat is impeded by obstruction of the intraepidermal portion of the sweat duct. Its aetiology and pathogenesis are presumed to be similar at all ages and are considered in Chapter 44. Relative immaturity of the sweat duct may be an important predisposing factor in early infancy, as may a tendency for infants to be nursed in excessively warm and humid conditions.

Miliaria crystallina appears to reflect obstruction of the sweat duct within the stratum corneum itself. It is particularly common during the neonatal period, probably principally because of delayed patency of the sweat pore.



Fig. 17.1 Miliaria crystallina on the upper arm of a 7-day-old infant.

Miliaria rubra appears to be caused by sweat duct obstruction deeper within the epidermis, induced perhaps by increased activity of the intraductal microflora [1,2].

Pathology. Miliaria crystallina is characterized by the presence of intracorneal or subcorneal vesicles in communication with sweat ducts [3]. In miliaria rubra, focal areas of spongiosis and spongiotic vesicle formation are seen in close proximity to sweat ducts, which often contain an amorphous, periodic acid–Schiff (PAS) stain-positive plug [1,4].

Clinical features [5]. Miliaria crystallina presents as crops of clear, thin-walled, superficial vesicles 1–2 mm in diameter, without associated erythema (Fig. 17.1), resembling drops of water. These are exceedingly delicate, and generally rupture within 24 h, and are followed by branny desquamation. They arise most frequently during the first 2 weeks of life, and are particularly likely to be seen on the forehead, scalp, neck and upper trunk. Though rare during the first 4 days, congenital cases have been reported [6,7].

Miliaria rubra ('prickly heat') comprises erythematous papules and papulovesicles about 1–4 mm in diameter, on a background of macular erythema. Sometimes, quite large, weal-like lesions occur. Frequently, some of the lesions are pustular (*miliaria pustulosa*), but this does not necessarily indicate secondary infection. Nevertheless, staphylococcal secondary infection of miliaria (periporitis) is not infrequent, and may lead to sweat gland abscesses.

Miliaria rubra is common and, although it may be seen throughout infancy, it probably occurs most frequently during the neonatal period. Crops of lesions arise fairly symmetrically, most often in flexural areas, especially around the neck and in the groins and axillae. The face, scalp and upper trunk are also frequently affected. It may also occur rather locally at sites that have been occluded, for example where there has been direct contact between skin and a plastic mattress cover or plastic pants. Where the eruption is profuse, the child may be restless and distressed. Each crop of

lesions will subside within 2–3 days, but recurrences are common, unless the provocative environmental conditions are modified.

Recurrent bouts of miliaria pustulosa appear to be a rather specific finding in type 1 pseudohypoaldosteronism [8,9].

Diagnosis. Miliaria crystallina is distinguishable from viral infections of the skin by the lack of background erythema, and by the absence of inflammatory cells or giant keratinocytes on cytological examination of vesicle contents. When it occurs during the first few days of life, miliaria rubra is often confused with toxic erythema. However, miliaria rubra can generally be distinguished by its flexural predominance, by the frequent presence of vesicular lesions and by its tendency to recur. Where pustular lesions are seen in toxic erythema, a smear of their contents will reveal large numbers of eosinophils.

When pustular lesions are prominent in miliaria, there may be confusion with infantile acne or with folliculitis, but careful clinical examination of the individual lesions will show that they do not have a follicular distribution.

References

1 Holzle E, Kligman AM. The pathogenesis of miliaria rubra. Role of the resident flora. *Br J Dermatol* 1978; **99**: 117–37.
2 Singh G. The role of bacteria in anhidrosis. *Dermatologica* 1973; **146**: 256–61.
3 Loewenthal LJA. The pathogenesis of miliaria. The role of sodium chloride. *Arch Dermatol* 1961; **84**: 2–17.
4 Perlstein MA. Evaluation of certain preparations for care of the skin of newborn infants. *Am J Dis Child* 1948; **75**: 385–94.
5 Shelley WB, Horvath PN. Experimental miliaria in man. *J Invest Dermatol* 1950; **14**: 9–20.
6 Arpey CJ, Nagashima-Whalen LS, Chren MT. Congenital miliaria crystallina: case report and literature review. *Pediatr Dermatol* 1992; **9**: 283–7.
7 Straka BF, Cooper PH, Greer KE. Congenital miliaria crystallina. *Cutis* 1991; **47**: 103–6.
8 Urbatsch A, Paller AS. Pustular miliaria rubra: a specific cutaneous finding of type 1 pseudohypoaldosteronism. *Pediatr Dermatol* 2002; **19**: 317–9.
9 Argoubi H, Fitchner C, Richard O *et al*. Pustular miliaria rubra and systemic type 1b pseudohypoaldosteronism in a newborn. *Ann Dermatol Venereol* 2007; **134**: 253–6.

Transient pustular melanosis

Synonym
- Transient neonatal pustular melanosis

Terminology and aetiology. Despite having first been described more than 30 years ago [1], whether this is really an entity remains unresolved. Nothing is known of its aetiology other than that it would appear, like toxic erythema of the newborn, to be non-infectious. It was first reported in black Americans, and appears to be commoner in, but not confined to, black neonates (4.4% in black US neonates against 0.6% in white US neonates) [1]. This probably reflects the fact that its diagnosis is currently based on the appearance of typical macular post-inflammatory pigmentation, as the name seems to require. It has been suggested that it is merely a variant of toxic erythema of the newborn [2].

Pathology [1]. Pustular lesions show intra- or subcorneal collections of neutrophils and a few eosinophils. The underlying dermis may show no abnormality, or a sparse perivascular and perifollicular inflammatory infiltrate, also mainly of neutrophils with a few eosinophils.

The pigmented macules demonstrate basal and suprabasal increase in pigmentation only, apparently without pigmentary incontinence.

Smears of pustular contents show predominantly neutrophils, and bacterial culture is negative.

Clinical features [1,3–7]. Lesions are almost invariably present at birth. The most characteristic component of the eruption is 1–3 mm flaccid, superficial, fragile pustules, with no surrounding erythema. These pustules may occur at any site, but favour the chin, neck, forehead, back and buttocks. Sites where they have ruptured are marked initially by a detachable brown crust, and subsequently by a small collarette of scale, which may surmount a pigmented macule. Sometimes, pigmented macules are already present at birth. The pigmented macules are a prominent element in black infants, and are seen more rarely in other races [5]. The pigmentation may persist for about 3 months. Affected infants are otherwise entirely well.

It has been suggested that this condition is responsible for the freckling or '*lentigines neonatorum*' that have been reported in some 15% of black neonates [8].

Diagnosis. It remains to be established whether this is really just an early-onset variant of toxic erythema of the newborn occurring in the dark-skinned. Stained smears and microbiological studies will distinguish staphylococcal and herpetic infections. The differential diagnosis of neonatal pustular eruptions is given in Table 17.1.

Table 17.1 Pustular eruptions in the neonate.

Infantile acne
Impetigo
Congenital syphilis
Neonatal listeriosis
Herpes simplex virus (HSV) infection
Congenital or neonatal candidiasis
Malassezia pustulosis
Scabies
Miliaria
Eosinophilic pustulosis
Toxic erythema of the newborn
Infantile acropustulosis
Transient pustular melanosis
Pustular psoriasis
Neonatal pustulosis of transient myeloproliferative disorder

References

1 Ramamurthy RS, Reveri M, Esterly NB *et al*. Transient neonatal pustular melanosis. *J Pediatr* 1976; **88**: 831–5.
2 Ferrándiz C, Coroleu W, Ribera M *et al*. Sterile transient neonatal pustulosis is a precocious form of erythema toxicum neonatorum. *Dermatology* 1992; **185**: 18–22.
3 Auster B. Transient neonatal pustular melanosis. *Cutis* 1978; **22**: 327–8.

4 Barr RJ, Globerman LM, Werber FA. Transient neonatal pustular melanosis. *Int J Dermatol* 1979; **18**: 636–8.
5 Merlob P, Metzker A, Reisner SH. Transient neonatal pustular melanosis. *Am J Dis Child* 1982; **136**: 521–2.
6 Wyre HW Jr, Murphy MO. Transient neonatal pustular melanosis. *Arch Dermatol* 1979; **115**: 458.
7 Piccinno R, Menni S. Melanosi pustulosa neonatale transitoria. *G Ital Dermatol Venereol* 1985; **120**: 409–12.
8 Fox JN, Walton RG, Gottlieb B, Castellano A. Pigmented skin lesions in black newborn infants. *Cutis* 1979; **24**: 399–402.

Infantile acropustulosis

Aetiology. Infantile acropustulosis is an uncommon disorder of unknown aetiology. It occurs in all races [1], though it was first described in black infants [2,3]. It has been suggested that eosinophilic pustular folliculitis and infantile acropustulosis may be different manifestations of the same disease [4,5]. It has also been suggested that, at least in some cases, infantile acropustulosis occurs following successful treatment of scabies [6–8]. Interestingly, it has been reported in a 2-month-old infant whose mother was treated for scabies 4 months previously [9]. It has also been reported in siblings [9], and in only one of a pair of identical twins [10].

Pathology [2,11–13]. Biopsies of fully developed pustules have revealed well-circumscribed subcorneal or intraepidermal aggregations of neutrophils, with a sparse perivascular lymphohistiocytic infiltrate in the underlying papillary dermis. Biopsy of pre-pustular lesions shows focal intraepidermal vesiculation [13,14] with keratinocyte necrosis. This intraepidermal vesicle is subsequently invaded by neutrophils and/or eosinophils. The pustule starts its life deep in the epidermis, but does not become clinically fully developed until it reaches a subcorneal location.

Direct and indirect immunofluorescence is negative in lesional, perilesional and normal skin [1,3,15].

Stained smears of pustule contents generally show a predominance of neutrophils, but there may be a preponderance of eosinophils early in the course of the disorder [3]. The pustules are sterile [2,11,16]. Peripheral blood eosinophilia has been reported [14,17,18], but is not invariable [9,13,17].

Clinical features [2,3,9,12,15,19,20]. Recurrent crops of intensely itchy, 1–4-mm vesicopustules appear principally on the soles and sides of the feet, and on the palms, but may also occur on the dorsa of the feet, hands and fingers, and on the ankles, wrists and forearms. Scattered lesions may also be seen on the face, scalp and trunk, but a predominantly acral distribution is characteristic. Mucosal lesions do not occur.

Individual lesions appear to start as tiny, red papules, which evolve into vesicles and then pustules over about 24 h. Excoriation results in erosions and then crusts. Healing is frequently succeeded by macular post-inflammatory hyperpigmentation.

Pruritus may be intense, with restlessness, loss of appetite and interference with sleep.

In the majority of cases, the onset is in the first year of life, particularly during the first 6 months [9]; lesions may be present at birth. Each crop lasts for 7–14 days. They tend to occur at intervals of 2–4 weeks in most cases, often being more frequent and more numerous in the summer months. The attacks occur with gradually diminishing numbers of lesions, and with decreasing frequency, until they cease altogether, usually within 2 years of the onset [8].

Treatment. The early use of fairly potent, topical corticosteroids with [9] or without [12] occlusion appears to abort attacks.

The intense pruritus may be lessened by large doses of oral antihistamines [2].

Though rarely justified, dapsone is usually effective in controlling this condition in a dose of 1–2 mg/kg/day in two divided doses [3], and usually reduces pruritus within 24 h. Higher doses are occasionally required [17]. Too hasty withdrawal of treatment may provoke severe exacerbations [11].

Diagnosis. The predilection for the palms and soles and the recurrent attacks differentiate this disorder from most other pustular eruptions seen in the neonatal period, particularly toxic erythema, miliaria and transient pustular melanosis.

Persistent palmoplantar pustulosis may be similar histologically but characteristically has a much later onset, a more persistent course, and the skin surrounding the pustules is dusky red and glazed.

Subcorneal pustular dermatosis may also resemble infantile acropustulosis histologically, and has occasionally had its onset during the first 3 months of life [21]. It is, however, likely to be associated with fever and neutrophilia, and has a different distribution, favouring the proximal flexures, although lesions on the palms and soles have been described.

Scabies may initially be extremely difficult to exclude, and where there is any doubt a therapeutic trial of an appropriate acaricide is clearly justified. The persistence of acral pustulosis for many months in children aged less than 3 years, and previously treated for scabies, has been reported [22].

References

1 Palungwachira P. Infantile acropustulosis. *Australas J Dermatol* 1989; **30**: 97–100.
2 Jarratt M, Ramsdell W. Infantile acropustulosis. *Arch Dermatol* 1979; **115**: 834–6.
3 Kahn G, Rywlin AM. Acropustulosis of infancy. *Arch Dermatol* 1979; **115**: 831–3.
4 Taïeb A, Bassan-Andrieu L, Maleville J. Eosinophilic pustulosis of the scalp in childhood. *J Am Acad Dermatol* 1992; **27**: 55–60.
5 Vicente J, Espana A, Idoate M *et al.* Are eosinophilic pustular folliculitis of infancy and infantile acropustulosis the same entity? *Br J Dermatol* 1996; **135**: 807–9.
6 Humeau S, Bureau B, Litioux P *et al.* Infantile acropustulosis in six immigrant children. *Pediatr Dermatol* 1995; **12**: 211–4.
7 Prendiville JS. Infantile acropustulosis: how often is it a sequela of scabies? *Pediatr Dermatol* 1995; **12**: 275–6.
8 Nguyen J, Strobel M, Arnaud JP *et al.* Acropustulose infantile: expression inhabituelle de la gale chez le nourrison? *Ann Pediatr (Paris)* 1991; **38**: 479–83.
9 Dromy R, Raz A, Metzker A. Infantile acropustulosis. *Pediatr Dermatol* 1991; **8**: 284–7.
10 Monk B. Acropustulosis of infancy in a twin (Letter). *Clin Exp Dermatol* 1990; **15**: 77.
11 Findlay RJ, Odom RB. Infantile acropustulosis. *Am J Dis Child* 1983; **137**: 455–7.
12 Jennings JL, Burrows WM. Infantile acropustulosis. *J Am Acad Dermatol* 1983; **9**: 733–8.

13 Vignon-Pennamen D-D, Wallach D. Infantile acropustulosis. *Arch Dermatol* 1986; **122**: 1155–60.
14 Lucky AW, McGuire JS. Infantile acropustulosis with eosinophilic pustules. *J Pediatr* 1982; **100**: 428–9.
15 McFadden N, Falk ES. Infantile acropustulosis. *Cutis* 1985; **36**: 49–51.
16 Newton JA, Salisbury J, Marsden A, McGibbon DH. Acropustulosis of infancy. *Br J Dermatol* 1986; **115**: 735–9.
17 Bundino S, Zina AM, Ubertalli S. Infantile acropustulosis. *Dermatologica* 1982; **165**: 615–9.
18 Falanga V. Infantile acropustulosis with eosinophilia. *J Am Acad Dermatol* 1985; **13**: 826–8.
19 Kahana M, Schewach-Millet M, Feinstein A. Infantile acropustulosis—report of a case. *Clin Exp Dermatol* 1987; **12**: 291–2.
20 Laudren A, Chavrent-Brenton J, Lancien G. Acropustulose infantile. *Ann Dermatol Vénéréol* 1985; **112**: 251–2.
21 Johnson SAM, Cripps DJ. Subcorneal pustular dermatosis in children. *Arch Dermatol* 1974; **109**: 73–7.
22 Bjornberg A, Friis B. Persistent pustulosis in children adopted from Asia: a sequela of scabies? *Int J Dermatol* 1978; **17**: 69–73.

Eosinophilic pustulosis

Synonym
- Eosinophilic pustular folliculitis

Aetiology. This entity is now recognized as a characteristic skin disorder of infancy, with typical cases described from many different countries [1–5]. Its aetiology and its relationship to eosinophilic pustular folliculitis of adults [6] are unknown. It has been suggested that this condition and infantile acropustulosis may be different manifestations of a single disorder [5,7].

Pathology. Biopsy shows a dense perifollicular infiltrate of eosinophils, with some lymphocytes and histiocytes, in the mid- and upper dermis. The hair follicles themselves show spongiotic degeneration of the outer root sheath, and infiltration with eosinophils. The centre of the follicles is necrotic, and filled with eosinophils and eosinophilic debris. Smears of pustule contents show plentiful eosinophils. There is mild to moderate peripheral blood eosinophilia, and occasionally, neutrophilia.

Clinical features. The condition generally has its onset in infancy. Lesions occur predominantly in the scalp [2,4,5,7], comprising mildly pruritic, 1–3-mm-diameter pustules on an erythematous base, with prominent secondary crusting. However, pustules may also occur at almost any other site except the mucosae, occasionally even in areas lacking hair follicles [3]. Annular lesions resembling those seen in adults were reported in a 5 year old [8], but this is perhaps more likely to have been an early case of the adult form of eosinophilic pustular folliculitis. Patients are not systemically unwell.

A pattern of cyclical recurrences is characteristic, but the likely duration of the disease is unknown.

Diagnosis. Conditions that need to be considered in the differential diagnosis include infections, particularly impetigo and candidosis, and other non-infective pustuloses of infancy, particularly toxic erythema, infantile acropustulosis and transient neonatal pustulosis.

Infections are principally excluded by the sterile pustule contents, the absence of eosinophils in smears of pustule contents, and the lack of peripheral blood eosinophilia. While toxic erythema may initially be clinically and histologically similar, it does not show any predilection for the scalp, and lacks the cyclical recurrent course. Similarly, the pustular phase of transient neonatal pustulosis is confined to the neonatal period. Also, the pustules contain neutrophils rather than eosinophils. The lesions of infantile acropustulosis, while they do generally occur in recurring crops, tend to be larger and are located principally on acral sites including the palms and soles, rather than in the scalp.

Treatment. There is some evidence that higher-potency topical corticosteroids and oral erythromycin may have some suppressive effect on the lesions seen in infants [3,4], but little treatment is required since the prognosis for spontaneous remission appears excellent.

References

1 Duarte AM, Kramer J, Yusk JW *et al.* Eosinophilic pustular folliculitis in infancy and childhood. *Am J Dis Child* 1993; **147**: 197–200.
2 Darmstadt GL, Tunnessen WW, Swerer RJ *et al.* Eosinophilic pustular folliculitis. *Pediatrics* 1992; **89**: 1095–8.
3 Giard F, Marcoux D, McCuaig C *et al.* Eosinophilic pustular folliculitis (Ofuji disease) in childhood: a review of four cases. *Pediatr Dermatol* 1991; **8**: 189–93.
4 Lucky AW, Esterley NB, Heskel N *et al.* Eosinophilic pustular folliculitis in infancy. *Pediatr Dermatol* 1984; **1**: 202–6.
5 Taïeb A, Bassan-Andrieu L, Maleville J. Eosinophilic pustulosis of the scalp in childhood. *J Am Acad Dermatol* 1992; **27**: 55–60.
6 Ofuji S, Ogino A, Horio T *et al.* Eosinophilic pustular folliculitis. *Acta Derm Venereol (Stockh)* 1970; **50**: 195–203.
7 Vicente J, España A, Idoate M *et al.* Are eosinophilic pustular folliculitis of infancy and infantile acropustulosis the same entity? *Br J Dermatol* 1996; **135**: 807–9.
8 Dekio S, Jidoi J, Kawasaki Y. Eosinophil-infiltrating folliculitis in childhood. *J Dermatol* 1989; **16**: 388–91.

Neonatal pustulosis of transient myeloproliferative disorder

There have been several reports of neonates with trisomy 21 (and mosaic trisomy 21) developing pustules and vesicles (on an erythematous background), predominantly on the face, as part of congenital leukaemia or transient myeloproliferative disorder (TMD) [1,2]. They may also pustulate at sites of trauma, such as venepuncture sites or under adhesive tape. There is an associated high white blood cell count, often with the presence of blasts. Skin biopsy shows intraepidermal pustules with a perivascular dermal infiltrate of neutrophils, eosinophils and atypical mononuclear cells. The lesions often resolve spontaneously over a few weeks paralleled by a decreasing white cell count.

Mutations in the transcription factor GATA1 seem to underlie TMD but a second genetic hit is needed to develop leukaemia [3].

Up to 20% of patients with TMD will go on to develop an acute megakaryoblastic leukaemia within the first 4 years of life.

References

1 Burch JM, Weston WL, Rogers M *et al.* Cutaneous pustular leukemoid reactions in trisomy 21. *Pediatr Dermatol* 2003; **20**: 232–7.
2 Viros A, Garcia-Patos V, Aparicio G *et al.* Sterile neonatal pustulosis associated with transient myeloproliferative disorder in twins. *Arch Dermatol* 2005; **141**: 1053–4.

3 Groet J, Mc Elwaine S, Spinelli M *et al.* Acquired mutations in GATA 1 in neonates with Down's syndrome with transient myeloid disorder. *Lancet* 2003; **361**: 1617–20.

Congenital erosive and vesicular dermatosis healing with reticulated supple scarring

Synonym

- Extensive congenital erosions and vesicles healing with reticulate scarring

This is a rare disorder of unknown aetiology [1–6]. There is no evidence of genetic transmission. It appears possible that the condition reflects an as yet unidentified intrauterine infection.

The majority of affected infants have been premature. Some have also had microcephaly and neurological problems, including convulsions and developmental delay.

At birth, there are extensive, superficial erosions, with scattered vesicles and bullae, affecting up to 75% of the body surface [1–6]. These heal fairly quickly within the first few weeks of life, leaving rather characteristic soft, reticulated scarring. The trunk and limbs tend to be more severely affected than the face and scalp. Following healing of the skin lesions, there may be residual loss of eccrine sweating in scarred areas, with the potential for hyperthermia under appropriate conditions, patchy alopecia, partial loss of eyelashes, and absence or hypoplasia of nails. Teeth have been normal. Mild, localized, recurrent vesiculation may occur [6].

Biopsies of vesicular areas have shown spongiosis or epidermal necrosis with dermal haemorrhage and inflammation [6]. In another report, an eroded area showed loss of the epidermis with a superficial and deep dermal inflammatory infiltrate comprising mostly neutrophils [4]. Scarred areas have shown an increased density of dermal collagen, and absence of eccrine sweat glands [1,5]. Direct immunofluorescence does not show any specific pattern of deposition of immunoglobulins, C3 or fibrin [4]. Electron microscopy and immunohistochemical mapping of perilesional skin have shown nothing to suggest that this is a variant of epidermolysis bullosa [5].

References

1 Cohen BA, Esterley NB, Nelson PF. Congenital erosive and vesicular dermatosis healing with reticulated supple scarring. *Arch Dermatol* 1985; **121**: 361–7.
2 Gupta AK, Rasmussen JE, Headington JT. Extensive congenital erosions and vesicles healing with reticulate scarring. *J Am Acad Dermatol* 1987; **17**: 369–76.
3 Plantin P, Delaire P, Guillois B, Guillet G. Congenital erosive dermatosis with reticulated supple scarring: first neonatal report. *Arch Dermatol* 1990; **126**: 544–6.
4 Sadick NS, Shea CR, Schlessel JS. Congenital erosive and vesicular dermatosis with reticulated supple scarring: a neutrophilic dermatosis. *J Am Acad Dermatol* 1995; **32**: 873–7.
5 Sidhu-Malik NK, Resnick SD, Wilson BB. Congenital erosive and vesicular dermatosis healing with reticulated supple scarring: report of three new cases and review of the literature. *Pediatr Dermatol* 1998; **15**: 214–8.
6 Stein S, Stone S, Paller AS. Ongoing blistering in a boy with congenital erosive and vesicular dermatosis healing with reticulated supple scarring. *J Am Acad Dermatol* 2001; **45**: 946–8.

'Cradle cap'

This term is applied, rather loosely, to almost any situation in which there is adherent scaling of the scalp during infancy. This type of scaling is very common, particularly on the vertex, during the first few weeks of life, and is generally believed to represent persisting vernix.

However, there is little doubt that such scaling may appear in early infancy in babies in whom the scalp was clear at birth [1]. The eyebrows are frequently affected in this acquired type of cradle cap, and lesions may also appear on the forehead and temples, the retroauricular area and the folds of the neck. This rash is generally considered to be a manifestation of infantile seborrhoeic dermatitis.

If scaling or crusting is present during the neonatal period, the scalp should be regularly oiled with olive oil or arachis oil. In the more refractory case, Emulsifying Ointment BP, Aqueous Cream BP or any other water-dispersible emollient should be massaged into the scalp once or twice a day, left for several hours, and then rinsed out. Applications containing salicylic acid, and shampoos containing potentially toxic substances, such as selenium sulphide, should not be used on the scalp in neonates because of the dangers posed by their percutaneous absorption.

Reference

1 Bonifazi E. Infantile seborrheic dermatitis: pathogenetic considerations and nosological aspects. *Pediatr Dermatol News* 1988; **7**: 16–21.

Complications of prematurity

Anetoderma of prematurity [1]

A series of infants have recently been described in whom nummular areas of cutaneous atrophy appeared on the trunk and/or proximal limbs within a few weeks or months of birth. All these babies had been born between the 24th and 29th weeks of gestation and in almost all cases the lesions had first appeared while the child was still in the neonatal intensive care unit. Histologically, these lesions demonstrated reduction or absence of elastic tissue, consistent with anetoderma. An aetiological role for trauma resulting from care procedures seems likely and two cases have been described in association with the use of gel ECG electrodes [2].

References

1 Prizant TL, Lucky AW, Frieden IJ *et al.* Spontaneous atrophic patches in extremely premature infants: anetoderma of pregnancy. *Arch Dermatol* 1996; **132**: 671–4.
2 Colditz PB, Dunster KR, Joy GJ *et al.* Anetoderma of prematurity in association with electrocardiographic electrodes. *J Am Acad Dermatol* 1999; **41**: 478–81.

Complications of medical procedures on the fetus and neonate

Scarring following antenatal procedures

Amniocentesis comprises the insertion of a needle into the amniotic sac through the abdominal wall for the removal of amniotic fluid. Punctate scars and dimples may result from accidental puncture of the fetal skin during the procedure [1–4], although the frequency of such lesions can be greatly reduced by the routine use of ultrasound guidance. Generally, injuries are minor, but more substantial trauma can occur.

Other antenatal procedures on the fetus that may result in scarring include biopsies of skin, liver or tumours, aspiration of fluid

collections, and a variety of therapeutic procedures, all of which are undertaken with ultrasound guidance.

References

1 Broome DL, Wilson MG, Weiss B *et al*. Needle puncture of fetus: a complication of second-trimester amniocentesis. *Am J Obstet Gynecol* 1976; **126**: 247–52.
2 Bruce S, Duffy JO, Wolf JE. Skin dimpling associated with midtrimester amniocentesis. *Pediatr Dermatol* 1984; **2**: 140–2.
3 Epley SL, Hansen JW, Cruickshank DP. Fetal injury with mid-trimester diagnostic amniocentesis. *Obstet Gynecol* 1979; **53**: 77–80.
4 Raimer SS, Raimer BG. Needle puncture scars from mid-trimester amniocentesis. *Arch Dermatol* 1984; **120**: 1360–2.

Intrauterine blood transfusion

Gangrene of the skin of the abdominal wall has been reported following intrauterine red cell transfusion for haemolytic disease of the fetus due to rhesus incompatibility [1].

Reference

1 Shelton LW. Gangrenous skin defect after intrauterine transfusion. *Am J Dis Child* 1969; **117**: 593–6.

Scarring acquired due to procedures during delivery

Scalp electrodes are very widely employed to monitor fetal heart rate during labour. The most commonly used type of electrode is curved and is implanted by being 'screwed' into the scalp. Lacerations are not an uncommon sequela [1]. Although these generally heal rapidly, they may leave localized areas of permanent scarring in the scalp, which may later be confused with cutis aplasia. Cephalohaematoma has also been reported [2].

Scalp blood samples are also often taken to establish fetal acid–base status; these are taken via small incisions using a special lancet. Either type of injury can lead to abscesses in up to 4% of neonates [3], usually becoming evident by the third day of life. These are generally a minor problem [4], but osteomyelitis [5] and necrotizing fasciitis [6] may, however, occur. Infecting bacteria have included group A streptococci and *Neisseria gonorrhoeae* [7]. HSV infection may also occur at the site of electrode implantation, reflecting infection of the mother's genital tract [8]. Vesicles appear within 4–10 days of birth. Recognition of such lesions is important, as localized infection of this type has occasionally been complicated by meningoencephalitis [9,10] and by lethal dissemination [11].

Forceps delivery may occasionally result in local subcutaneous fat necrosis. Vacuum extractors (ventouse) may rarely cause permanent alopecia, most typically in a circle that clearly corresponds to the site of its application. Marked caput succedaneum is usually present at delivery [12]. Scalpel laceration during caesarean delivery may require suturing and will generally result in scarring.

References

1 Ashkenazi S, Metzker A, Merlob P *et al*. Scalp changes after fetal monitoring. *Arch Dis Child* 1985; **60**: 267–9.
2 Kaufman HH, Hochberg J, Anderson RP *et al*. Treatment of calcified cephalohematoma. *Neurosurgery* 1993; **32**: 1037–9.
3 Okada DM, Chow AW, Bruce VT. Neonatal scalp abscess and fetal monitoring: factors associated with infection. *Am J Obstet Gynecol* 1977; **129**: 185–9.
4 Cordero L, Anderson CW, Zuspan FP. Scalp abscess: a benign and infrequent complication of fetal monitoring. *Am J Obstet Gynecol* 1983; **146**: 126–30.
5 McGregor JA, McFarren T. Neonatal cranial osteomyelitis: a complication of fetal monitoring. *Obstet Gynecol* 1989; **73**: 490–2.
6 Siddiqi SF, Taylor PM. Necrotizing fasciitis of the scalp. *Am J Dis Child* 1982; **136**: 226–8.
7 Reveri M, Krishnamurthy C. Gonococcal scalp abscess. *J Pediatr* 1979; **94**: 819–20.
8 Parvey LS, Ch'ien LT. Neonatal herpes simplex virus infection introduced by fetal monitor scalp electrodes. *Pediatrics* 1980; **65**: 1150–3.
9 Kaye EM, Dooling EC. Neonatal herpes simplex meningoencephalitis associated with fetal monitor scalp electrodes. *Neurology* 1981; **31**: 1045–6.
10 Freedman RM, Baltimore R. Fatal *Streptococcus viridans* septicemia and meningitis: relationship to fetal scalp electrode monitoring. *J Perinatol* 1990; **10**: 272–4.
11 Golden SM, Merenstein GB, Todd WA *et al*. Disseminated herpes simplex neonatorum: a complication of fetal monitoring. *Am J Obstet Gynecol* 1977; **123**: 917–8.
12 Lykoudis EG, Spyropoulou GA, Lavasidis LG *et al*. Alopecia associated with birth injury. *Obstet Gynecol* 2007; **110**: 487–90.

Complications of phototherapy

Phototherapy with blue light at 420–460 nm leads to the transcutaneous photo-oxidation of bilirubin, and has become firmly established as a safe and effective treatment for neonatal jaundice [1].

A number of minor cutaneous side effects have been described. Some babies develop a macular erythematous rash as the serum bilirubin level falls [2].

Darkening of treated areas of skin lasting for several months has been reported in racially black babies [3]. This effect may initially be due to the immediate pigment-darkening reaction, which is induced by visible as well as by long-wave UV radiation. However, the persistence of hyperpigmentation in these babies over several months implies that increased melanogenesis must also occur.

Unexplained UV burns have also been reported after phototherapy for neonatal jaundice [4].

Phototoxic reactions

Phototoxic reactions to a number of drugs given to the neonate, or injected into the amniotic cavity, may occur following phototherapy for neonatal jaundice. The best known of these drugs is furosemide [5].

Methylene blue is sometimes injected into the amniotic cavity to detect premature rupture of the fetal membranes at the end of pregnancy. Methylene blue is a photosensitizing compound, and the use of phototherapy for hyperbilirubinaemia in a neonate that has been exposed *in utero* can lead to erythema and blistering [6].

'Bronze baby' syndrome

This is a rare complication of neonatal phototherapy, in which a dark-grey-brown ('bronze') pigmentation of the skin, serum and urine follows phototherapy, and remains as the hyperbilirubinaemia fades [7,8]. Hepatic disease appears to be a prerequisite for the development of this complication, and is thought to cause abnormal accumulation of the responsible pigment. This pigment has not yet been precisely identified, but it has been suggested that it might be a photoisomer of bilirubin [9]. The abnormal hepatic function also leads to increased serum levels of porphyrin and copper, which in turn form copper–porphyrin complexes.

Photodestruction of these complexes leads to the production of brown pigments, which might also be responsible for the 'bronze' colour [10]. A third suggestion has been that the pigment is biliverdin, which might accumulate as a consequence of reduced conversion of haem to bilirubin [11].

In making the diagnosis, other causes of similar pigmentation need to be considered, particularly central cyanosis secondary to congenital heart disease, the 'carbon baby' syndrome [12] and the 'grey baby' syndrome, due to chloramphenicol overdosage [13]. These can be ruled out, where appropriate, by skin biopsy, serum chloramphenicol level, blood gas analysis and serum spectophotometry [7].

The bronze pigmentation gradually fades after discontinuation of phototherapy, but death has been reported in several affected neonates, either from kernicterus or from extrahepatic biliary duct atresia [14].

References

1 Polin RA. Management of neonatal hyperbilirubinemia: rational use of phototherapy. *Biol Neonate* 1990; **58** (Suppl. 1): 32–4.
2 Giunta F. Bilirubin rash in the newborn. *JAMA* 1969; **208**: 1703.
3 Woody NC, Brodkey MJ. Tanning from phototherapy for neonatal jaundice. *J Pediatr* 1973; **82**: 1042–3.
4 Siegfried EC, Stone MS, Madison KC. Ultraviolet light burn: a cutaneous complication of visible light phototherapy for neonatal jaundice. *Pediatr Dermatol* 1992; **9**: 278–82.
5 Burry JN, Lawrence JR. Phototoxic blisters from high frusemide dosage. *Br J Dermatol* 1976; **94**: 495–9.
6 Porat R, Gilbert S, Magilner D. Methylene blue-induced phototoxicity: an unrecognised complication. *Pediatrics* 1996; **97**: 717–21.
7 Ashley JR, Littler CM, Burgdorf WHC. Bronze baby syndrome. *J Am Acad Dermatol* 1985; **12**: 325–8.
8 Kopelman AE, Brown RS, Odell GB. The 'bronze baby syndrome': a complication of phototherapy. *J Pediatr* 1972; **81**: 466–72.
9 Onishi S, Itoh S, Isobe K *et al.* Mechanism of development of bronze baby syndrome in neonates treated with phototherapy. *Pediatrics* 1982; **69**: 273–6.
10 Rubaltelli FF, Jori G, Reddi E. Bronze baby syndrome: a new porphyrin-related disorder. *Pediatr Res* 1983; **17**: 327–30.
11 Purcell SM, Wians FH, Ackerman NB *et al.* Hyper-biliverdinaemia in the bronze baby syndrome. *J Am Acad Dermatol* 1987; **16**: 172–7.
12 Ruiz-Maldonado R, Tamayo L, Fernandez-Diaz J. Universal acquired melanosis: the carbon baby. *Arch Dermatol* 1978; **114**: 775–8.
13 Krasinki K, Perkin R, Rutledge J. The grey baby syndrome revisited. *Clin Pediatr (Phila)* 1982; **21**: 571–2.
14 Clark CF, Torii S, Hamamoto Y *et al.* The 'bronze baby' syndrome: postmortem data. *J Pediatr* 1976; **88**: 461–4.

Bullous and purpuric eruptions resulting from transient porphyrinaemia

Bullous photosensitivity reactions may be seen in neonates with congenital erythropoietic porphyria, hepatoerythropoietic porphyria, erythropoietic protoporphyria and harderoporphyria [1,2].

It is clear that under certain, probably exceptional, circumstances, a bullous eruption closely resembling epidermolysis bullosa may develop following phototherapy in a neonate, due to transient porphyrinaemia [3]. The circumstances in which porphyrinaemia may occur in neonates who do not have inborn errors of porphyrin metabolism are not fully defined, but probably include prematurity, cholestasis, disturbed hepatocellular function and renal failure.

More recently, localized purpuric eruptions have been described at exposed sites in a number of neonates who had all been transfused prior to phototherapy; it was proposed that the cause may also have been transient porphyrinaemia [4,5].

References

1 Smith SG. Hepatoerythropoietic porphyria. *Semin Dermatol* 1986; **5**: 125–37.
2 Nordmann Y, Grandchamp B, de Verneuil H *et al.* Harderoporphyria: a variant coproporphyria. *J Clin Invest* 1983; **72**: 1139–49.
3 Mallon E, Wojnarowska F, Hope P *et al.* Neonatal bullous eruption as a result of transient porphyrinemia in a premature infant with hemolytic disease of the newborn. *J Am Acad Dermatol* 1995; **33**: 333–6.
4 Crawford RI, Lawlor ER, Wadsworth LD, Prendiville JS. Transient erythroporphyria of infancy. *J Am Acad Dermatol* 1996; **35**: 833–4.
5 Paller AS, Eramo LR, Farrell EE *et al.* Purpuric phototherapy-induced eruption in transfused neonates: relation to transient porphyrinemia. *Pediatrics* 1997; **100**: 360–4.

Umbilical artery catheterization

Umbilical artery catheters are often used in neonatal intensive care, for frequent blood sampling, for continuous Po_2 and blood pressure monitoring, for administration of fluids and drugs, and for exchange transfusions. Vascular complication may ensue, including aortic thrombosis, embolization and spasm. These may result in lower limb ischaemia, which may progress to gangrene or necrosis [1–7]. Analogous ischaemic changes may occur in the lower arm or hand following cannulation of the brachial and radial arteries, respectively.

References

1 Cutler VE, Stretcher GS. Cutaneous complications of central umbilical artery catheterization. *Arch Dermatol* 1977; **113**: 61–3.
2 Du JHN, Briggs JN, Young G. Disseminated intravascular coagulopathy in hyaline membrane disease: massive thrombosis following umbilical artery catheterization. *Pediatrics* 1970; **45**: 287–9.
3 Kitterman JA, Phibbs RH, Tooley WH. Catheterization of umbilical vessels in newborn infants. *Pediatr Clin North Am* 1970; **17**: 895–912.
4 Lobe TE, Richardson CJ, Boulden TF *et al.* Mycotic thromboaneurysmal disease of the abdominal aorta in preterm infants. *J Pediatr Surg* 1992; **27**: 1054–9.
5 Mann NP. Gluteal skin necrosis after umbilical artery catheterisation. *Arch Dis Child* 1980; **55**: 815–7.
6 Purohit DM, Levkoff AH, Devit PC. Gluteal necrosis with foot drop. *Am J Dis Child* 1978; **132**: 897–9.
7 Rudolph N, Wang H-H, Dragutsky D. Gangrene of the buttock: a complication of umbilical artery catheterization. *Pediatrics* 1974; **53**: 106–9.

Transcutaneous oxygen monitoring

Transcutaneous oxygen monitoring is frequently used in neonatal intensive care. This uses an electrode applied to the skin and maintained at 44°C in order to increase cutaneous blood flow. This generally causes a superficial burn, which usually resolves within 60 h [1], but occasionally, after longer periods of monitoring, there may be a more severe burn [2], sometimes with vesiculation [3]; such lesions may result in permanent scarring [2]. Measures have been recommended to reduce the risk of these injuries [4], but the transcutaneous Po_2 monitor has now been largely superseded by pulse oximetry, which uses an unheated sensor with no risk of burning.

References

1 Boyle RJ, Oh W. Erythema following transcutaneous Po_2 monitoring. *Pediatrics* 1980; **65**: 333–4.

2 Golden SM. Skin craters—a complication of transcutaneous oxygen monitoring. *Pediatrics* 1981; **67**: 514–6.
3 Eberhard P, Mindt W, Kreuzer F. Cutaneous oxygen monitoring in the newborn. *Paediatrician* 1976; **5**: 335–69.
4 Evans NJ, Rutter N. Reduction of skin damage from transcutaneous oxygen electrodes using a spray-on dressing. *Arch Dis Child* 1986; **61**: 881–4.

Electrocardiographic electrodes [1]

Raised, skin-coloured lesions, approximately 5 mm in diameter, on the forehead have been described at the age of 3 months following the use of electrocardiographic electrodes in intensive care monitoring of premature neonates. Biopsy demonstrated reduction of elastic fibres; hence the lesions were interpreted as an iatrogenic form of anetoderma, possibly provoked by hypoxia secondary to skin pressure.

Reference

1 Colditz PB, Dunster KR, Joy GJ *et al*. Anetoderma of prematurity in association with electrocardiographic electrodes. *J Am Acad Dermatol* 1999; **41**: 478–81.

Transillumination blisters [1]

Transillumination is used in neonatal intensive care units as a way of diagnosing pneumothorax and for finding arteries and veins for blood sampling. Occasionally, this procedure provokes discrete 2–4-mm blisters with necrotic bases in acral locations close to common venous access sites, such as the wrists and the lateral malleoli. The occurrence of such lesions should arouse suspicions that the transilluminator unit may be faulty, or that the infrared filters might be missing or switched off.

Reference

1 Sajben FP, Gibbs NF, Friedlander SF. Transillumination blisters in a neonate. *J Am Acad Dermatol* 1999; **41**: 264–5.

Cutaneous necrosis following extravasation of intravenous medications

Leakage of total parenteral nutrition and of a variety of medications have led to local skin and subcutaneous tissue necrosis in the neonate [1–4]. It appears that the risk is highest when intravenous cannulae are inserted in the lower limbs, particularly above the ankle. Severe lesions may lead to joint contractures requiring plastic surgical correction. Alopecia may result from extravasation from cannulae placed in the scalp.

References

1 Hironaga M, Fujigaki T, Tanaka S. Cutaneous calcinosis in a neonate following extravasation of calcium gluconate. *J Am Acad Dermatol* 1982; **6**: 392–5.
2 Vaidya UV, Hegde VM, Bhave SA *et al*. Reduction in parenteral nutrition-related complications in the newborn. *Indian Pediatr* 1991; **28**: 477–84.
3 Gault DT. Extravasation injuries. *Br J Plast Surg* 1993; **46**: 91–6.
4 Cartlidge PH, Fox PE, Rutter N. The scars of newborn intensive care. *Early Hum Dev* 1990; **21**: 1–10.

Iatrogenic dystrophic calcification

Iatrogenic dystrophic cutaneous calcification has been reported in three situations:

1 On the heel due to heel pricks during neonatal care [1–3]
2 At the site of extravasation of calcium-containing solutions given intravenously or by intramuscular injection [4–6]
3 On the scalps of children who have undergone electroencephalography with calcium chloride-containing paste on abraded skin [7].

References

1 Sell EJ, Hansen RC, Struck-Pierce S. Calcified nodules on the heel: a complication of neonatal intensive care. *J Pediatr* 1980; **96**: 473–5.
2 Williamson D, Holt PJA. Calcified cutaneous nodules on the heels of children: a complication of heel sticks as a neonate. *Pediatr Dermatol* 2001; **18**: 138–40.
3 Rho NK, Youn SJ, Park HS *et al*. Calcified nodule on the heel of a child following a single heel stick in the neonatal period. *Clin Exp Dermatol* 2003; **28**: 502–3.
4 Goldminz D, Barnhill R, McGuire J *et al*. Calcinosis cutis following extravasation of calcium gluconate. *Arch Dermatol* 1988; **124**: 922–5.
5 Hironaga M, Fujigaki T, Tanaka S. Cutaneous calcinosis in a neonate following extravasation of calcium gluconate. *J Am Acad Dermatol* 1982; **6**: 392–5.
6 Sahn EF, Smith DJ. Annular dystrophic calcifinosis cutis in an infant. *J Am Acad Dermatol* 1992; **26**: 1015–7.
7 Mancuso G, Tosti A, Fanti PA *et al*. Cutaneous necrosis and calcinosis following encephalography. *Dermatologica* 1990; **181**: 324–6.

Needle marks [1]

Children who have received neonatal intensive care will frequently have punctate white scars at sites of needle insertion. Individual lesions will generally be imperceptible, but groups of lesions at particular sites may be more apparent, resulting in curious speckled scarring.

Reference

1 Cartlidge PH, Fox PE, Rutter N. The scars of newborn intensive care. *Early Hum Dev* 1990; **21**: 1–10.

Damage following use of chest drains for pneumothorax

These chest drains can cause substantial scarring [1] and permanent damage to the breast in females.

Reference

1 Cartlidge PH, Fox PE, Rutter N. The scars of newborn intensive care. *Early Hum Dev* 1990; **21**: 1–10.

Cutaneous necrosis following chemical burns

Cutaneous necrosis has been reported following skin contact with a variety of antiseptics in premature neonates, reflecting the increased rate of percutaneous absorption that is a feature in this age group [1–5]. The alcohol base can also have a directly toxic effect on the skin so this can occur around a surgical site (e.g. umbilical catheter) and often on the back or buttocks where the cleanser has pooled or soaked onto drapes [6].

References

1 Harpin VA, Rutter N. Percutaneous alcohol absorption and skin necrosis in a premature infant. *Arch Dis Child* 1982; **57**: 477–9.
2 Pyati SP, Ramamurthy RS, Krauss MT, Pildes RS. Absorption of iodine in the neonate following topical use of povidone–iodine. *J Pediatr* 1977; **91**: 825–8.
3 Puschel K. Percutaneous alcohol intoxication. *Eur J Pediatr* 1981; **136**: 317–8.
4 Schick JB, Milstein JM. Burn hazard of isopropyl alcohol in the neonate. *Pediatrics* 1981; **68**: 587–8.
5 Wilkinson AR, Baum JD, Keeling JW. Superficial skin necrosis in babies prepared for umbilical arterial catheterisation. *Arch Dis Child* 1981; **56**: 237–8.
6 Mannan K, Chow P, Lissauer T *et al*. Mistaken identity of skin cleansing solution leading to extensive chemical burns in an extremely preterm infant. *Acta Paediatr* 2007; **96**: 1536–7.

Table 17.2 Causes of atrophic lesions in neonates.

Morphoea
Atrophic dermatofibrosarcoma protuberans
Cutis marmorata telangiectatica congenita
Aplasia cutis congenita
Anetoderma of prematurity
Congenital erosive and vesicular dermatosis healing with reticulate supple scarring
Medallion-like dermal dendrocyte hamartoma
Congenital infection (HSV and VZV; maybe zosteriform)
Focal dermal hypoplasia of Goltz
Neonatal lupus erythematosus

Atrophic lesions of neonates

There are a number of causes of atrophic lesions in neonates (Table 17.2).

Medallion-like dermal dendrocyte hamartoma

First described in 2004 in female neonates, this rare condition presents with a reddish-brown, congenital, atrophic lesion of the skin on the upper trunk or neck. Lesions are typically round or oval, measure 2–6 cm across and persist. They may show a slight increase in hair growth and visible underlying blood vessels under a wrinkled epidermis [1–3]. Histology differentiates this disorder from other causes of neonatal cutaneous atrophy such as aplasia cutis congenita, congenital dermatofibrosarcoma protuberans (in early life before it becomes nodular), morphoea, cutis marmorata telangiectatica congenita and anetoderma of prematurity. It shows epidermal atrophy, spindle cell proliferation in the dermis and to a lesser degree the subcutis, and reduced adnexal structures. Spindle cells stain positive for CD34, Factor X111a, vimentin and fascin, suggesting a dermal dendritic origin. Atrophic DFSP is also CD34 positive, but is factor X111a negative.

References

1 Rodriguez-Jurado R, Palacios C, Duran-McKinster C *et al.* Medallion-like dermal dendrocyte hamartoma: a new clinically and histopathologically distinct lesion. *J Am Acad Dermatol* 2004; **51**: 359–63.

2 Martin JM, Jorda E, Monteagudo C *et al.* Atrophic congenital lesion on the back. *Arch Dermatol* 2006; **142**: 921–6.

3 Martin L, Combemale P, Dupin M *et al.* The atrophic variant of dermatofibrosarcoma protuberans in childhood: a report of six cases. *Br J Dermatol* 1998; **139**: 719–25.

Congenital annular limb lesions/amniotic bands

Congenital annular limb lesions usually cause constrictions and may lead to limb malformations, lymphoedema and even ischaemia and autoamputation ('congenital pseudoainhum'). They may occur in a number of conditions, including Michelin tyre baby syndrome and amniotic band syndrome. The latter occurs due to premature rupture of the amniotic sac which fails to grow normally and leads to fibrous strands developing on the outer amnion and chorion. The fetus can get 'trapped' in the bands and oligohydramnios can cause further compression. If this occurs early *in utero* malformations tend to be more extensive and include alopecia, aplasia cutis, neural tube defects, craniofacial defects as well as limb constriction bands [1].

Treatment is difficult and is by surgical correction when possible [2].

Raised limb bands occurring later in infancy seem to behave in a more benign fashion even if associated with amniotic bands [3,4].

References

1 Higginbottom MC, Jones KL, Hall BD *et al.* The amniotic band disruption complex: timing of amniotic rupture and variable spectra of consequence of defects. *J Pediatr* 1979; **95**: 544–9.

2 Rossillon D, Rombouts JJ, Verllen-Dumoulin C *et al.* Congenital ring-constriction syndrome of the limbs; a report of 19 cases. *Br J Plast Surg* 1988; **41**: 270–7.

3 Latteo SA, Taylor AE, Meggitt SJ. Raised limb bands developing in infancy. *Br J Dermatol* 2006; **154**: 791–2.

4 Dyer JA, Chamlin S. Acquired raised bands of infancy: association with amniotic bands. *Pediatr Dermatol* 2005; **22**: 346–9.

Neonatal adnexal polyp

Solitary, self-healing, polypoid lesions have been observed in some 4% of neonates in a Japanese survey [1,2]; their occurrence in other racial groups has yet to be documented. These lesions are firm, pink, polypoid nodules, about 1 mm in diameter, usually found close and medial to one or other nipple. Histology shows a normal epidermis, a vascular dermis containing prominent hair follicles with vestigial sebaceous glands and well-developed eccrine glands. These lesions generally separate from the skin spontaneously after a few days.

References

1 Hidano A, Kobayashi T. Adnexal polyp of neonatal skin. *Br J Dermatol* 1975; **92**: 659–62.

2 Hidano A, Purwoko R, Jitsukawa K. Statistical survey of skin changes in Japanese neonates. *Pediatr Dermatol* 1986; **3**: 140–4.

Infantile pedal papules

Infantile pedal papules [1,2] are a common finding in neonates (6%) and infants (39%). They are benign, asymptomatic, flesh-coloured nodules (0.5–1 cm) on the medial aspect of the foot often anterior to the heel. They are frequently symmetrical and usually disappear by age 3 years. They have been described under various different names: precalcaneal congenital fibrolipomatous hamartomas, adipose plantar nodules, congenital piezogenic-like pedal papules and bilateral congenital fatty heel pads.

References

1 Greenberg S, Krafchik BR. Infantile pedal papules. *J Am Acad Dermatol* 2005; **53**: 333–4.

2 Ortega-Monzo C, Molina-Gallardo I, Monteagudo-Castro C *et al.* Precalcaneal congenital fibrolipomatous hamartoma: a report of four cases. *Pediatr Dermatol* 2000; **17**: 429–31.

Disorders caused by transplacental transfer of maternal autoantibodies

Clinical manifestations in the neonate have now been reported in a number of maternal disorders that are believed to be induced by circulating autoantibodies. Of particular interest to the dermatologist are those reports concerning lupus erythematosus (LE)

(see below), pemphigus vulgaris [1–5], pemphigus foliaceus [6,7], herpes gestationis [8] and aphthosis [9].

Because IgA, IgM and IgE antibodies do not cross the placenta in significant amounts, this phenomenon is restricted to diseases caused by autoantibodies of IgG class. Where complement is also involved in pathogenesis, this must be provided by the fetus, as it does not pass across the placenta. Complement can be detected in the fetus from about the 11th week of gestation [9]. Maternal IgG is catabolized more or less completely within the first 3–6 months of life, and antibody-mediated transplacental diseases can be expected to remit spontaneously within this period.

References

1 Hup JM, Bruinsma RA, Boersma ER, de Jong MC. Neonatal pemphigus vulgaris: transplacental transmission of antibodies. *Pediatr Dermatol* 1986; **3**: 468–72.

2 Merlob P, Metzker A, Hazaz B *et al.* Neonatal pemphigus. *Pediatrics* 1986; **78**: 1102–5.

3 Middelkamp HJ, Bruinsma RA, Boersma ER *et al.* Neonatal pemphigus vulgaris: transplacental transmission of antibodies. *Pediatr Dermatol* 1986; **3**: 468–72.

4 Ross MG, Kane B, Frieder R *et al.* Pemphigus in pregnancy: a re-evaluation of fetal risk. *Am J Obstet Gynecol* 1986; **155**: 30–3.

5 Grunwald MH, Zamora E, Avinoach I *et al.* Pemphigus neonatorum. *Pediatr Dermatol* 1993; **10**: 169–70.

6 Walker DC, Kolar KA, Hebert AA *et al.* Neonatal pemphigus foliaceus. *Arch Dermatol* 1995; **131**: 1308–11.

7 Avalos-Diaz E, Olague-Marchan M, Lopez-Swiderski A *et al.* Transplacental passage of maternal pemphigus foliaceus autoantibodies induces neonatal pemphigus. *J Am Acad Dermatol* 2000; **43**: 1130–4.

8 Chen SH, Chopra K, Evans TY *et al.* Herpes gestationis in a mother and child. *J Am Acad Dermatol* 1999; **40**: 847–9.

9 Thivolet J, Cambazard F, Genvo MF. Grande aphtose néonatale de transmission maternelle. *Ann Dermatol Vénéréol* 1982; **109**: 815–6.

Neonatal lupus erythematosus

Definition. Neonatal LE is a rare syndrome comprising transient skin lesions resembling subacute cutaneous LE, and/or congenital heart block, occurring in the babies of mothers with clinical or subclinical autoimmune connective tissue disease, and associated with the transplacental passage of maternal autoantibodies to the ribonucleoproteins (RNPs), Ro-SSA, La-SSB or U_1-RNP [1].

Aetiology. It is now accepted that this disease is provoked in the fetus or newborn infant by maternal IgG autoantibodies that have crossed the placenta [2,3]. In 95% of cases, these are of IgG1 class [4] and are directed against the Ro RNP antigen [5]. These antibodies are relatively prevalent in young women, and appear to be compatible with apparently normal health. For these reasons, neonatal LE is seen more commonly than neonatal pemphigus vulgaris or neonatal herpes gestationis. La, anti-native DNA, anticardiolipin or antinuclear antibodies, or rheumatoid factor, may be present in addition to Ro antibodies [6,7]. A small proportion of affected infants do not have detectable Ro antibodies but do have La, U_1-RNP (nRNP) antibodies [6–8]. Many affected infants fail to demonstrate a significant titre of circulating antinuclear antibodies, unless human tissue is used, when a speckled fluorescence pattern will be seen [9].

The presence of Ro and La antigens has been demonstrated in fetal skin and cardiac conducting tissue [10,11].

Up to 60% of the mothers of infants with neonatal LE have no clinical evidence of connective tissue disease at the time of the birth [3,7,12]. However, there is a substantial risk of subsequent development of symptoms of autoimmune connective tissue disease [13]. About 40% of the mothers do have signs or symptoms of systemic lupus erythematosus (SLE), subacute cutaneous LE or the sicca syndrome [14–17], although these may be minimal. More recently, it has been recognized that about 5% of women of child-bearing age who present with leukocytoclastic vasculitis will have Ro antibodies [18], and it is probable that about 5% of babies with neonatal LE have mothers with leukocytoclastic vasculitis [13,19].

Pathology. Skin biopsy specimens from infants with cutaneous lesions generally demonstrate the features of LE, that is epidermal atrophy, liquefaction degeneration of basal keratinocytes, colloid bodies and a perivascular and periappendageal lymphohistiocytic inflammatory infiltrate in the dermis [14,20,21].

Direct immunofluorescence is positive in about 50% of cases, showing dermal–epidermal junction and perivascular deposition of IgG, IgM and C3 [14,21].

Autoimmune haemolytic anaemia and thrombocytopenia are seen in a small proportion of affected infants [14].

Cardiac abnormalities occur in about 60% of infants with neonatal LE [1], although there appear to be some racial differences in this frequency, which is reported to be smaller, for example, in Japan [22]. Fibrosis of the conducting tissue of the heart commonly results in congenital heart block. It has recently been shown that anti-Ro antibodies can bind to cardiac conduction cells during mid- to late fetal development, leading to altered membrane repolarization and selective damage to the atrioventricular (AV) node [23]. Other developmental abnormalities of the heart may also occasionally occur, including subendocardial fibroelastosis and fibrinous pericarditis [24,25].

Asymptomatic central nervous system vasculopathy has been demonstrated in neonatal LE by ultrasound and colour Doppler flow imaging, but its longer term significance is unknown [26].

These antibodies disappear from the infant's serum within about 6 months, but are more persistent in the mother [14,21,27].

Clinical features [9,14–17,22,28–31]. Most infants with neonatal LE have either skin lesions or cardiac lesions; approximately 10% have both [13,32]. About 90% of infants with neonatal erythematosus have only skin lesions.

In about two-thirds of those infants who develop cutaneous lesions, these are already present at birth [15,30]. In the remainder, the lesions appear during the first 2–3 months, although their appearance may be delayed as long as 5 months [13].

The skin lesions of neonatal LE generally take the form of well-defined areas of macular or slightly elevated erythema, frequently annular, occurring predominantly on the face, particularly the forehead, temples and upper cheeks, and on the scalp and neck (Fig. 17.2). A 'spectacle'-like distribution of lesions around the eyes is especially characteristic. The chest, back or limbs may also be affected.



Fig. 17.2 Neonatal lupus erythematosus (LE): fading facial lesions in characteristic periorbital distribution, with residual atrophy, in a 4-month-old infant.

Less commonly, lesions take the form of annular erythema without an epidermal component; this type of presentation has predominantly been reported in Japanese infants [22,27].

Subcutaneous lesions have also been described [33].

Occasionally, neonatal LE presents as extensive reticulate erythema with atrophy, closely resembling cutis marmorata telangiectatica congenita [34,35].

Depigmentation may be very prominent in racially pigmented infants [36].

Provocation or exacerbation of lesions by sun exposure has been reported in some cases.

Follicular plugging is not prominent, but scaling is a common early feature, and a degree of atrophy and/or telangiectasia are frequent long-term sequelae. Permanent hair loss may occur.

Lesions resembling morphoea have been reported [37].

In most cases, the skin lesions have resolved within the first year, but areas of atrophy and/or telangiectasia may be more persistent [38,39]. Long-standing depressions have followed subcutaneous lesions [33]. The most frequent sites for such lesions are the temples and scalp.

Systemic features are detectable in over half of all affected infants, of which cardiac involvement is the commonest, occurring in about 50% of cases. Cardiac involvement tends to affect a different group of infants, heart and skin abnormalities occurring together in only about 10% [9,13,32]. The reasons for this are unclear. Congenital heart block can be detected as early as the 18th week of gestation by ultrasound or electrocardiography [40]. The block is generally permanent, and is not associated with structural cardiac abnormalities such as septal defects. About a half of affected infants require pacemakers [29,40].

A smaller proportion of infants have combinations of hepatomegaly, splenomegaly, lymphadenopathy, autoimmune haemolytic anaemia, thrombocytopenia and pneumonitis, which are generally mild in degree and fairly transient.

Prognosis [41]. Infants with skin lesions alone, or with skin lesions and systemic features other than heart block, generally show little sign of residual disease after the age of 1 year. However, their long-term prognosis must remain slightly guarded in the light of reports of the later development by some of full-blown connective tissue disease [25,29,42–44]. Conduction defects of the heart tend to be permanent, and when severe are associated with a significant mortality [13,29,45].

The risk of recurrence in further pregnancies appears to be about 25% [13,46]. This risk appears to be influenced by immunogenetic factors [47]. Spontaneous abortion and stillbirth do not appear to be more frequent in further pregnancies of mothers who have had a previous child with neonatal LE [13]. Mothers with Ro antibody may experience recurrent fetal loss if they do not have SLE, but do not appear to do so if they do have SLE [48].

Diagnosis [7]. The lesions of congenital rubella or cytomegalovirus infection may need to be considered, although these are of purplish colour and purpura is generally prominent. Congenital syphilis may also need to be excluded, but whereas mucosal, periorificial, and palmar and plantar lesions are common in congenital syphilis, these features are rare in neonatal LE. However, confusion may be caused by the false-positive antibody tests that are as much a feature of neonatal as of acquired LE.

Atrophy and telangiectasia of the cheeks is seen with photosensitivity in Bloom's syndrome, and without photosensitivity, in most cases, in the Rothmund–Thomson syndrome (see Chapter 15). In these disorders, skin lesions are not present at birth and generally appear later than in neonatal LE.

A skin biopsy will usually allow an accurate diagnosis of neonatal LE, particularly if combined with direct immunofluorescence studies, and tests for the appropriate circulating autoantibodies in both the mother and the child.

Treatment. The skin lesions of neonatal LE require no treatment, but sun protection is essential. Occasionally, thrombocytopenia, haemolytic anaemia or hepatitis may warrant systemic steroid therapy [49]. Up to 50% of infants with cardiac involvement will require a pacemaker [22].

The pregnancy of a woman who has Ro, La or U_1-RNP antibodies should be monitored to detect a slow fetal heart rate [50,51]. Treatment with high-dose systemic steroids may be indicated for fetal bradycardia where there are signs of heart failure [52].

References

1 Petri M, Watson R, Hochberg MC. Anti-Ro antibodies and neonatal lupus. *Rheum Dis Clin North Am* 1989; **15**: 335–60.

2 Provost TT. Commentary: neonatal lupus erythematosus. *Arch Dermatol* 1983; **119**: 619–22.

3 Weston WL, Harmon C, Peebles C *et al*. A serological marker for neonatal lupus erythematosus. *Br J Dermatol* 1982; **107**: 377–82.

4 Bennion SD, Ferris C, Lieu T-S *et al*. IgG subclasses in the serum and skin in subacute cutaneous lupus erythematosus and neonatal lupus erythematosus. *Arch Dermatol* 1990; **95**: 643–6.

5 Sontheimer RD, McCauliffe DP. Pathogenesis of anti-Ro/SS-A autoanti-body-associated cutaneous lupus erythematosus. *Dermatol Clin* 1990; **8**: 751–8.

6 Dugan EM, Tunnessen WW, Honig PJ, Watson RM. U_1RNP antibody positive neonatal lupus. *Arch Dermatol* 1992; **128**: 1490–4.

7 Neidenbach PJ, Sahn EE. La(SSB)-positive neonatal lupus erythematosus: report of a case with unusual features. *J Am Acad Dermatol* 1993; **29**: 848–52.
8 Provost TT, Watson RM, Gammon WR. The neonatal lupus syndrome associated with U_1RNP (nRNP) antibodies. *N Engl J Med* 1987; **316**: 1135–8.
9 Lee LA, Norris DA, Weston WL *et al.* Neonatal lupus and the pathogenesis of cutaneous lupus. *Pediatr Dermatol* 1986; **3**: 491–2.
10 Lee LA, Harmon CE, Huff JC *et al.* The demonstration of SS-A/Ro antigen in human fetal tissues and in neonatal and adult skin. *J Invest Dermatol* 1985; **85**: 143–6.
11 Horsfall AC, Venables PJ, Taylor PV, Maini RN. Ro and La antigens and maternal autoantibody idiotype on the surface of myocardial fibers in congenital heart block. *J Autoimmun* 1991; **4**: 165–76.
12 Lee LA, Weston WL. New findings in neonatal lupus syndrome. *Am J Dis Child* 1984; **138**: 233–6.
13 McCune AB, Weston WL, Lee LA. Maternal and fetal outcome in neonatal lupus syndrome. *Ann Intern Med* 1987; **106**: 518–23.
14 Franco HL, Weston WL, Peebles C *et al.* Autoantibodies directed against sicca syndrome antigens in the neonatal lupus syndrome. *J Am Acad Dermatol* 1981; **4**: 67–72.
15 Draznin TH, Esterly NB, Furey NL *et al.* Neonatal lupus erythematosus. *J Am Acad Dermatol* 1979; **1**: 437–42.
16 Korkij W, Soltani K. Neonatal lupus erythematosus: a review. *Pediatr Dermatol* 1984; **1**: 189–95.
17 Rendall JRS, Wilkinson JD. Neonatal lupus erythematosus. *Clin Exp Dermatol* 1978; **3**: 69–76.
18 De Argila D, Revenga F, Llamas R *et al.* Cutaneous vasculitis with anti-Ro SSA antibodies not associated to connective tissue disease. *Actas Dermosifiliogr* 1995; **86**: 499–505.
19 Borrego L, Rodriguez J, Soler E *et al.* Neonatal lupus erythematosus related to maternal leukocytoclastic vasculitis. *Pediatr Dermatol* 1997; **14**: 221–5.
20 Maynard B, Lieferman KM, Peters MS. Neonatal lupus erythematosus syndrome. *J Cutan Pathol* 1991; **18**: 333–8.
21 Watson RM, Lane AT, Barnett NK *et al.* Neonatal lupus erythematosus: a clinical, serological and immunogenetic study with review of the literature. *Medicine (Baltimore)* 1984; **63**: 362–78.
22 Kaneko T, Tanji O, Hasegawa T *et al.* Neonatal lupus erythematosus in Japan. *J Am Acad Dermatol* 1992; **26**: 397–403.
23 Alexander E, Buyon JP, Provost TT, Guarieri T. Anti-Ro/RR-A antibodies in the pathophysiology of congenital heart block in neonatal lupus syndrome: an experimental model. *Arthritis Rheum* 1992; **35**: 176–89.
24 Doshi N, Smith B, Klionski B. Congenital pericarditis due to maternal lupus erythematosus. *J Pediatr* 1980; **96**: 699–701.
25 McCue CM, Mantakas ME, Tingelstad JB *et al.* Congenital heart block in newborn of mother with connective tissue disease. *Circulation* 1977; **56**: 82–90.
26 Cabañas F, Pellicer A, Valverde E *et al.* Central nervous system vasculopathy in neonatal lupus erythematosus. *Pediatr Neurol* 1996; **15**: 124–6.
27 Miyagawa S, Kitamura W, Yoshioka J *et al.* Placental transfer of anticytoplasmic antibodies in annular erythema of newborns. *Arch Dermatol* 1981; **117**: 569–72.
28 Chameides L, Trurex R, Vetter V *et al.* Association of maternal systemic lupus erythematosus with congenital complete heart block. *N Engl J Med* 1977; **297**: 1204–7.
29 Esscher E, Scott JS. Congenital heart block and maternal systemic lupus erythematosus. *BMJ* 1979; **1**: 1235–8.
30 Soltani K, Pacernick LJ, Lorincz AL. Lupus erythematosus-like lesions in newborn infants. *Arch Dermatol* 1974; **110**: 435–7.
31 Vonderheid EC, Koblenzer PJ, Ming PML *et al.* Neonatal lupus erythematosus. *Arch Dermatol* 1976; **112**: 698–705.
32 Lee LA. Neonatal lupus erythematosus. *J Invest Dermatol* 1993; **100**: S9–13.
33 Nitta Y. Lupus erythematosus profundus associated with neonatal lupus erythematosus. *Br J Dermatol* 1997; **136**: 112–4.
34 Carrascosa JM, Ribera M, Bielsa I *et al.* Cutis marmorata telangiectatica congenita or neonatal lupus? *Pediatr Dermatol* 1996; **13**: 230–2.
35 Greist MC, Probst E. Cutis marmorata telangiectatica congenita or neonatal lupus. *Arch Dermatol* 1980; **116**: 1102–3.
36 Jenkins RE, Kurwa AR, Atherton DJ, Black MM. Neonatal lupus erythematosus. *Clin Exp Dermatol* 1994; **19**: 409–11.
37 Ohtaki N, Miyamoto C, Orita M *et al.* Concurrent multiple morphea and neonatal lupus erythematosus in an infant boy born to a mother with SLE. *Br J Dermatol* 1986; **115**: 85–90.
38 Bourquelique C, Debillon T, Mesnard B *et al.* Neonatal lupus presenting as telangiectasia and atrophic lesions. *Pediatrie* 1990; **45**: 251–4.
39 Thornton C, Eichenfield L, Shinall E *et al.* Cutaneous telangiectases in neonatal lupus erythematosus. *J Am Acad Dermatol* 1995; **33**: 19–25.
40 Litsey SE, Noonan JA, O'Connor WN *et al.* Maternal connective tissue disease and congenital heart block. *N Engl J Med* 1985; **312**: 98–100.
41 Brucato A, Franceschini F, Buyon JP. Neonatal lupus: long-term outcome of mothers and children and recurrence rate. *Clin Exp Dermatol* 1997; **15**: 467–73.
42 Fox RJ Jr, McCuistion CH, Schoch EP Jr. Systemic lupus erythematosus: association with previous neonatal lupus erythematosus. *Arch Dermatol* 1979; **115**: 340.
43 Jackson R, Gulliver M. Neonatal lupus erythematosus: a 15 year follow-up. *Br J Dermatol* 1979; **101**: 81–6.
44 Lanham JG, Walport MJ, Hughes GR. Congenital heart block and familial connective tissue disease. *J Rheumatol* 1983; **10**: 823–5.
45 Waltuck J, Buyon JP. Autoantibody-associated congenital heart block: outcome in mothers and children. *Ann Intern Med* 1994; **120**: 544–51.
46 Lee LA, Lillis PJ, Fritz KA *et al.* Neonatal lupus syndrome in successive pregnancies. *J Am Acad Dermatol* 1983; **9**: 401–6.
47 Lee LA, Bias WB, Arnett FC *et al.* Immunogenetics of the neonatal lupus syndrome. *Ann Intern Med* 1983; **99**: 592–6.
48 Mavragani CP, Dafni UG, Tzioufas AG, Moutsopoulos HM. Pregnancy outcome and anti-Ro/SSA in autoimmune disease: a retrospective cohort study. *Br J Rheumatol* 1998; **37**: 740–5.
49 Rider LG, Buyon JP, Rutledge J *et al.* Treatment of neonatal lupus. *J Rheumatol* 1993; **20**: 1208–11.
50 Buyon JP. Neonatal lupus. *Curr Opin Rheumatol* 1996; **8**: 485–90.
51 Silverman ED. Congenital heart block and neonatal lupus erythematosus: prevention is the goal. *J Rheumatol* 1993; **20**: 1101–4.
52 Ishimaru S, Izaki S, Kitamura K *et al.* Neonatal lupus erythematosus: dissolution of atrioventricular block after administration of corticosteroids to the pregnant mother. *Dermatology* 1994; **189** (Suppl. 1): 6–10.

Neonatal pemphigus vulgaris

Pemphigus vulgaris is unusual in pregnancy, because it is largely a disease of an older age group and because affected individuals receiving systemic treatment rarely become pregnant. Nevertheless, several cases of transplacentally transmitted pemphigus vulgaris have been reported [1–6]. Not all mothers have had clinically apparent disease during pregnancy [7]; in other cases the disease has been mild [8].

Affected infants have had cutaneous and/or mucosal erosions or bullae. Several have been stillborn [1,6]. Direct immunofluorescence has been positive in skin biopsies from all affected infants, and circulating IgG pemphigus antibodies have been found in the majority.

No treatment is required; lesions have resolved spontaneously within about 3 weeks, and circulating IgG antibodies have become undetectable by the end of the second month of life.

References

1 Green D, Maize JC. Maternal pemphigus vulgaris with *in vivo* bound antibodies in the stillborn fetus. *J Am Acad Dermatol* 1982; **7**: 388–92.
2 Hup JM, Bruinsma RA, Boersma ER *et al.* Neonatal pemphigus vulgaris: transplacental transmission of antibodies. *Paediatr Dermatol* 1986; **3**: 468–72.
3 Merlob P, Metzker A, Hazaz BA *et al.* Neonatal pemphigus vulgaris. *Pediatrics* 1986; **78**: 1102–5.
4 Moncada B, Kettelsen S, Hernandez-Moctezuma JL *et al.* Neonatal pemphigus vulgaris: role of passively transferred pemphigus antibodies. *Br J Dermatol* 1982; **106**: 465–8.

5 Storer JS, Galen WK, Nesbitt LT *et al.* Neonatal pemphigus vulgaris. *J Am Acad Dermatol* 1982; **6**: 929–32.
6 Wasserstrum N, Laros RK. Transplacental transmission of pemphigus. *JAMA* 1983; **249**: 1480–2.
7 Tope WD, Kamino H, Briggaman RA *et al.* Neonatal pemphigus vulgaris in a child born to a woman in remission. *J Am Acad Dermatol* 1993; **29**: 480–5.
8 Chowdhury MMU, Natarajan S. Neonatal pemphigus vulgaris associated with mild oral pemphigus in the mother during pregnancy. *Br J Dermatol* 1998; **139**: 500–3.

Transplacental pemphigoid (herpes) gestationis

Cutaneous lesions occur in about 10% of infants born to mothers with pemphigoid gestationis, although maternal IgG antibasement-membrane autoantibody can be found in all infants of affected mothers [1,2]. The lesions may be present at birth or they may appear at any time up to the third day of life [3,4]. These lesions may vary from evanescent, non-specific, erythematous or urticarial papules to fully developed bullae [5,6]. Lesions in the infant may be extensive [7]. Spontaneous regression of lesions within 3 weeks is the rule. Direct immunofluorescence is normal by the end of the first month, and circulating IgG anti-basement-membrane-zone antibody can no longer be found.

Earlier reports of increased fetal and infant morbidity and mortality when mothers have pemphigoid gestationis [8] have not been confirmed [9–11]. However, there does appear to be an increased risk of premature delivery when a mother has herpes gestationis [10,11]. The risk of adrenal insufficiency should be considered in neonates whose mothers have been treated with prednisolone for prolonged periods.

References

1 Katz A, Minta JO, Toole JWP *et al.* Immunopathologic study of herpes gestationis in mother and infant. *Arch Dermatol* 1982; **113**: 1069–72.
2 Shornick JK. Herpes gestationis. *J Am Acad Dermatol* 1987; **17**: 539–56.
3 Chorzelski TP, Jablonska S, Beutner EH *et al.* Herpes gestationis with identical lesions in the newborn. Passive transfer of the disease? *Arch Dermatol* 1976; **112**: 1129–31.
4 Rimbaud P, Jean R, Bonnet H *et al.* Herpes gestationis: éruption bulleuse chez le nouveauné. *Bull Soc Fr Dermatol Syphiligr* 1971; **78**: 419–25.
5 Kolodny KC. Herpes gestationis: a new assessment of incidence, diagnosis and fetal prognosis. *Am J Obstet Gynecol* 1969; **104**: 39–45.
6 Bonifazi E, Meneghini CL. Herpes gestationis with transient bullous lesions in the newborn. *Pediatr Dermatol* 1984; **1**: 215–8.
7 Chen SH, Chopra K, Evans TY *et al.* Herpes gestationis in a mother and child. *J Am Acad Dermatol* 1999; **40**: 847–9.
8 Lawley TJ, Stinzl G, Katz SI *et al.* Fetal and maternal risk factors in herpes gestationis. *Arch Dermatol* 1978; **114**: 552–5.
9 Schornick JK, Bangert JL, Freeman RG *et al.* Herpes gestationis: clinical and histologic features of twenty-eight cases. *J Am Acad Dermatol* 1983; **8**: 214–24.
10 Shornick JK, Black NM. Fetal risks in herpes gestationis. *J Am Acad Dermatol* 1992; **26**: 63–8.
11 Mascaró JM, Lecha M, Mascaró JM. Fetal morbidity in herpes gestationis. *Arch Dermatol* 1995; **131**: 1209–10.

Transplacental transfer of maternal malignant disease

Transplacental transfer of maternal malignant disease is fortunately extremely rare, despite the fact that malignancy occurs in 1 in 1000 pregnancies [1,2], and it is well established that maternal cells regularly reach the fetus [3].

The malignancy transferred in this way has been malignant melanoma in about 90% of cases, although this particular malignancy accounts for only about 8% of those occurring in pregnant women [4]. Malignant melanoma transmitted in this way may result in the appearance of nodular skin deposits in the neonate. Spontaneous regression of transplacentally transferred malignant melanoma has been reported [5,6].

Transplacental transmission of acute monocytic leukaemia [7] and of natural killer (NK) cell lymphoma [8] have also been reported.

References

1 Antonelli NM, Dotters DJ, Katz VL, Kuller JA. Cancer in pregnancy: a review of the literature. *Obstet Gynecol Surv* 1996; **51**: 125–42.
2 Dildy GAA, Moise KJ, Carpenter RJ, Klima T. Maternal malignancy metastatic to the products of conception: a review. *Obstet Gynecol Surv* 1989; **44**: 535–40.
3 Pollack MS, Kirkpatrick D, Kapoor N *et al.* Identification by HLA typing of intrauterine derived maternal T cells in four patients with severe combined immunodeficiency. *N Engl J Med* 1982; **307**: 662–6.
4 Potter JF, Schoeneman M. Metastases of maternal cancer to the placenta and fetus. *Cancer* 1970; **25**: 380–8.
5 Aronson S. A case of transplacental tumour metastasis. *Acta Paediatr Scand* 1963; **52**: 123–4.
6 Cavell B. Transplacental metastasis of malignant melanoma. *Acta Paediatr Scand* 1963; **146** (Suppl.): 37–40.
7 Osada S, Horibe K, Oiwa K *et al.* A case of infantile acute monocytic leukaemia caused by vertical transmission of the mother's leukemic cells. *Cancer* 1990; **65**: 1146–9.
8 Catlin EA, Roberts JD, Erana R *et al.* Transplacental transmission of natural-killer-cell lymphoma. *New Engl J Med* 2000; **136**: 875–80.

Disorders caused by transfer of toxic substances in maternal milk

When considering the cause of any rash in a young infant, the possibility that it reflects exposure of the mother to a toxic substance that has been transferred in her milk needs to be borne in mind. A good example is provided by two reports of bromoderma occurring in neonates whose mothers had taken bromide medicinally [1] or had been accidentally exposed in a photographic laboratory [2].

References

1 Yeung GTC. Skin eruption in newborn due to bromism derived from mother's milk. *BMJ* 1950; **1**: 769.
2 Mangurten HH, Kaye CI. Neonatal bromism secondary to maternal exposure in a photographic laboratory. *J Pediatr* 1982; **100**: 596–8.

'Collodion' baby

Synonym

- Lamellar desquamation/exfoliation of the newborn

Aetiology and nomenclature. This term describes a highly characteristic clinical entity. It precedes the development of one of a variety of ichthyoses, the commonest of which are the autosomal recessive ichthyoses termed lamellar ichthyosis and non-bullous ichthyosiform erythroderma [1–3] (see Chapter 19). The collodion baby phenotype has been reported in the rarer autosomal dominant form of lamellar ichthyosis [4] and a possibly autosomal

dominant form of non-bullous ichthyosiform erythroderma [5]. It is also characteristic of the trichothiodystrophy–ichthyosis syndrome [6,7].

There are other ichthyoses in which an initial collodion baby phase has occasionally been reported. These include ichthyosis vulgaris [2], X-linked ichthyosis [8], Netherton's syndrome [9], neutral lipid storage disease [10] and the Sjögren–Larsson syndrome [2], but the great majority of neonates with these disorders do not demonstrate the collodion baby phenotype. A transient collodion membrane has also been reported in two neonates with Gaucher's disease [11,12].

In at least 10% of cases, the collodion baby phase is followed by a relatively mild ichthyosis of lamellar type; this may be so mild as to be considered more or less normal [2,3,13–19]. Autosomal recessive inheritance has been reported in this type of case [17], but it remains possible that these cases are genetically heterogeneous.

Pathology [1,2,20,21]. It was at one time popular to regard the collodion membrane as retained periderm (epitrichium) [22]. Histologically, however, the membrane is essentially orthokeratotic, rather than parakeratotic like the periderm [1,2,16,21], making this a highly improbable explanation. Apart from a compact, thickened orthokeratotic stratum corneum, the epidermis is fairly normal, similarly the dermis.

Although the histology of the skin is identical at birth whether the child later develops a severe ichthyosis or not, at about 15 days it may be possible to make a prediction on histological grounds [16], even though the clinical features are still indistinguishable.

Electron microscopy of the epidermis at 2 days in a baby whose skin later became clinically normal showed several distinctive features [14]. The upper two-thirds of the stratum corneum were of abnormal appearance; the corneocytes were convoluted and irregular in shape, and contained unusual, small, dense intracellular granules. There were large numbers of intercellular lamellar (Odland) bodies and exceptionally well-preserved desmosomes.

Clinical features [1–3,9,21,23,24]. The severely affected infant is bright red and encased in a taut, glistening, yellowish translucent covering resembling collodion (Fig. 17.3). The face is immobilized; tension on the skin results in ectropion, eversion of the lips (eclabion), producing a rather fish-like appearance of the mouth, and effacement of the nose and ears. The nostrils may be blocked. The skin over the fingers, hands, toes and feet may result in immobility and may interfere with blood flow, occasionally resulting in the loss of parts of digits.

Within hours, this membrane dries and cracks, and bleeding may occur along the resulting fissures. Within 1 or 2 days, it starts to peel off, either in extensive sheets or as large, light-brown scales, but may reform several times. The shedding will generally be more or less complete within 4 weeks. Subsequently, the typical features of one of several varieties of ichthyosis gradually emerge over a period of weeks or months.

During the first day or two, tightness of the skin on the thorax may interfere with respiration, and very occasionally, respiratory distress may be caused by nasal obstruction.



Fig. 17.3 Lamellar desquamation of the newborn in a 7-day-old infant. This child required peritoneal dialysis for acute renal failure secondary to inadequate hydration. A year later, the skin was normal apart from minimal fine scaling.

Diagnosis. The appearance of the collodion baby is unmistakable.

A degree of cracking and desquamation is a characteristic cutaneous finding in babies who are small for gestational age and/or post-term, presumably due to placental insufficiency, but this is unlikely to be mistaken for true lamellar desquamation of the newborn because of the lesser severity of the skin changes and the presence of other clinical features of these two states. Babies who are erythrodermic at birth, due, for example, to Netherton's syndrome, or to the Conradi–Hünermann syndrome, may be mistaken for collodion babies, but careful examination will reveal no collodion membrane.

The appearance of the neonate with harlequin ichthyosis (see below) has much in common with the collodion baby, the principal difference being the greater thickness of the stratum corneum, which typically encases the baby like a suit of armour. However, clinical differentiation may be less straightforward in milder cases.

Restrictive dermopathy also results in a neonate with tight and immobilizing skin, but in this condition, the skin appears thin and transparent, with prominent underlying blood vessels. The mouth is also open, but ectropion is not generally present. The skin does not dry out and come away. Death occurs rapidly as a consequence of respiratory failure.

Neonates with the lethal autosomal recessive Neu–Laxova syndrome [25] may have skin changes closely resembling a collodion membrane. The condition is characterized by intrauterine growth

retardation, and central nervous system, skeletal and cranial abnormalities.

Boys with hypohidrotic ectodermal dysplasia may show lamellar scaling at birth, but it is unlikely that this would be mistaken for a collodion membrane.

Prognosis. The collodion baby is at risk, largely because of the consequences of loss of skin barrier function, resulting in:

- impaired temperature regulation
- increased insensible water loss [26–28], which may lead to acute renal failure and/or permanent brain damage [29] if fluid replacement is neglected
- septicaemia [27].

Respiration may become compromised as a result of intrapartum aspiration of squamous debris shed into the amniotic fluid [30]. Interestingly, this debris can be seen on fetal ultrasound, and in such cases, early delivery by caesarean section may be protective of life.

Immobility of the chest may also compromise respiratory function, and predispose to pneumonia.

In the short term, mortality from these causes is substantial.

The longer-term outlook depends on which type of ichthyosis develops, and it is important to be aware that there is no correlation between initial severity in a collodion baby and the gravity of the ichthyosis that follows. At present, only observation over a period of months will reveal the ultimate fate of the skin in collodion babies. It has, however, been suggested that a skin biopsy at about the 15th day may be helpful in this respect [16].

Treatment. The most important element in treatment is an awareness of the possible complications, as outlined above.

The baby should be nursed in an incubator in a high-humidity atmosphere, with careful monitoring of body temperature. Great attention needs to be given to fluid and electrolyte balance. In severe cases, fluid therapy should be given intravenously, but in less severe cases oral or nasogastric fluid supplementation will suffice. Peritoneal dialysis may be indicated if renal failure occurs.

Fluid loss can be reduced by frequent applications of lipid; a 50:50 mixture of white soft paraffin and liquid paraffin is ideal for this purpose. Frequent oiling of the skin increases mobility and comfort, accelerates healing of fissures and may reduce the risk of infection.

Prevention of infection is of the greatest importance in saving these babies. Great attention should be paid to this aspect of care. Skin punctures should be kept to a minimum, and vascular access should be avoided as far as possible. Deeper fissures are more likely to become infected especially if inflamed, so regular swabs should be done for bacteria and candida as septicaemia is a common complication [31].

Bands of tight skin constricting digits, hands or feet may occasionally require surgical division.

References

1 Larregue M, Gharbi R, Daniel J *et al.* Le bébé collodion: évolution à propos de 29 cas. *Ann Dermatol Syphiligr (Paris)* 1976; **103**: 31–56.

2 Larregue M, Ottavy M, Bressieux J-M *et al.* Bébé collodion: trente-deux nouvelles observations. *Ann Dermatol Vénéréol* 1986; **113**: 773–85.

3 Lentz CL, Altman J. Lamellar ichthyosis: the natural clinical course of collodion baby. *Arch Dermatol* 1968; **97**: 3–13.

4 Traupe H, Kolde G, Happle R. Autosomal dominant lamellar ichthyosis: a new skin disorder. *Clin Genet* 1984; **26**: 457–61.

5 Rossmann-Ringdahl I, Anton-Lamprecht I, Swanbeck G. A mother and two children with non-bullous ichthyosiform erythroderma. *Arch Dermatol* 1986; **122**: 559–64.

6 Happle R, Traupe H, Grobe H *et al.* The Tay syndrome (congenital ichthyosis with trichothiodystrophy). *Eur J Pediatr* 1984; **141**: 147–52.

7 Jorizzo JL, Atherton DJ, Crounse RG *et al.* Ichthyosis, brittle hair, impaired intelligence, decreased fertility and short stature (IBIDS syndrome). *Br J Dermatol* 1982; **106**: 705–10.

8 Wells RS, Jennings MC. X-linked ichthyosis and ichthyosis vulgaris. Clinical and genetic distinctions in a second series of families. *JAMA* 1967; **202**: 485–8.

9 Larregue M, Bressieux JM, Founet JP. Collodion baby. *Mod Probl Paediatr* 1978; **20**: 40–9.

10 Wolf R, Zaritzky A, Pollak S. Value of looking at leukocytes in every case of ichthyosis. *Dermatologica* 1988; **177**: 237–40.

11 Lui K, Commens C, Choong R, Jaworski R. Collodion babies with Gaucher's disease. *Arch Dis Child* 1988; **63**: 854–6.

12 Ince Z, Coban A, Peker O *et al.* Gaucher disease associated with congenital ichthyosis in the neonate. *Eur J Pediatr* 1995; **154**: 418.

13 Arlette J. Collodion membrane in the premature infant. *Pediatr Dermatol* 1987; **4**: 269–70.

14 De Dobbeleer G, Heenen M, Song M *et al.* Collodion baby skin: ultrastructural and autoradiographic study. *J Cutan Pathol* 1982; **9**: 196–202.

15 Finlay HVL, Bound JP. Collodion skin in the neonate due to lamellar ichthyosis. *Arch Dis Child* 1952; **27**: 438–41.

16 Frenk E. A spontaneous healing collodion baby: a light and electron microscopical study. *Acta Derm Venereol (Stockh)* 1981; **61**: 169–71.

17 Frenk E, De Techtermann F. Self-healing collodion baby: evidence for autosomal recessive inheritance. *Pediatr Dermatol* 1992; **9**: 95–7.

18 Ghosh TK. Collodion baby: report of a case. *Arch Dermatol* 1969; **100**: 39–41.

19 Langer K, Konrad K, Weninger M, Wolff K. Kollodiumbaby mit Uebergang in milde lamellare Ichthyose. *Hautarzt* 1991; **42**: 34–8.

20 Frenk E, Mevorah B. The keratinization disorder in collodion babies evolving into lamellar ichthyosis. *J Cutan Pathol* 1977; **4**: 329–37.

21 Scott OLS, Stone DGH. Lamellar desquamation of the newborn ('collodion baby'). *Br J Dermatol* 1955; **67**: 189–95.

22 Cockayne EA. Lamellar ichthyosis. In: *Inherited Abnormalities of the Skin and its Appendages*. London: Oxford University Press, 1933: 159–61.

23 Bloom D, Goodfried MS. Lamellar ichthyosis of the newborn, the collodion baby: a clinical and genetic entity; report of a case and review of the literature with special consideration of pathogenesis and classification. *Arch Dermatol* 1962; **86**: 336–42.

24 Shelmire JB. Lamellar exfoliation of the newborn. *Arch Dermatol* 1955; **71**: 471–5.

25 Hickey P, Piantanida E, Lentz-Kapua S, Kenner J. Neu–Laxova syndrome: a case report. *Pediatr Dermatol* 2002; **20**: 25–7.

26 Buyse L, Graves C, Marks R *et al.* Collodion baby dehydration: the danger of high transepidermal water loss. *Br J Dermatol* 1993; **129**: 86–8.

27 Garty BZ, Wiseman Y, Metzker A *et al.* Hypernatremic dehydration and hypothermia in congenital lamellar ichthyosis. *Pediatr Dermatol* 1985; **3**: 65–8.

28 Kiistala R, Lauharanta J, Kanerva L. Transepidermal water loss and sweat gland response in lamellar ichthyosis before and during treatment with etretinate: report of three cases. *Acta Derm Venereol (Stockh)* 1981; **62**: 268–70.

29 Hogan GR. Hypernatremia: problems in management. *Pediatr Clin North Am* 1976; **23**: 569–74.

30 Perlman M, Bar-Ziv J. Congenital ichthyosis and neonatal pulmonary disease. *Pediatrics* 1974; **53**: 573–5.

31 Larregue M, Bieder C, Guillet G *et al.* Cutaneous fissures in collodion babies: incidence and treatment. *Ann Dermatol Venereol* 2008; **135**: 279–85.

Eczematous eruptions in the newborn

Eczematous eruptions are extremely common during the newborn period. Few are severe, and most are transient. However, in some babies they herald more chronic and possibly severe atopic dermatitis, and, in a few instances, they may provide an important clue to serious internal disease, as for example in the cases of zinc deficiency and the Wiskott–Aldrich syndrome (WAS). The following varieties of neonatal eczematous eruption will be considered here: contact dermatitis, particularly primary irritant napkin dermatitis and perianal dermatitis, intertrigo and infantile seborrhoeic dermatitis.

Contact dermatitis in the neonatal period

The skin of the newborn is particularly sensitive to irritants. Factors that contribute to the high incidence of primary irritant reactions in this age group include the widespread use of inappropriate toxic applications such as antiseptics, prolonged skin contact with urine and faeces, and the frequent presence of occlusive conditions. The commonest clinical patterns of primary irritant dermatitis seen in the newborn period are perianal dermatitis and napkin dermatitis. A non-allergic form of contact dermatitis to plastic identification bracelets has also been described in neonates [1]. The alcohol burn is a less common, but very important, form of acute irritant reaction.

True allergic contact dermatitis is exceedingly unusual in the neonatal period [2], partly because of the relative difficulty of sensitizing the skin for type IV hypersensitivity responses at this age [3,4] and partly because of the lack of appropriate antigen contact. Many authors have argued that reports of allergic contact dermatitis in neonates based on positive patch-test results require cautious interpretation, because the concentrations of allergens generally used for such tests may elicit irritant responses in small children [5–7], but relevant positive results have been described in early infancy to allergens such as nickel (from earrings), epoxy resin (from a plastic identification bracelet), and the components of various topical applications, particularly those used for the treatment of napkin dermatitis [7].

References

1 Schulsinger C, Mollgaard K. Polyvinyl chloride dermatitis not caused by phthalates. *Contact Dermatitis* 1980; **6**: 477–80.
2 Hjorth N. Contact dermatitis in children. *Acta Dermatol Venereol (Stockh)* 1981; **95**: 36–9.
3 Cassimos C, Kanakoudi-Tsakalidis F, Spyroglou K *et al*. Skin sensitization to 2,4 dinitrochlorobenzene (DNCB) in the first months of life. *J Clin Lab Immunol* 1980; **3**: 111–3.
4 Epstein WL. Contact type delayed hypersensitivity in infants and children: induction of the *Rhus* sensitivity. *Pediatrics* 1961; **27**: 51–3.
5 Marcussen PV. Primary irritant patch-test reactions in children. *Arch Dermatol* 1963; **87**: 378–82.
6 Muller E, Rockl H. Lappchentests bei Kindern und Jugendlichen. *Hautarzt* 1975; **26**: 85–7.
7 Fisher AA. Allergic contact dermatitis in early infancy. *Cutis* 1985; **35**: 315–6.

Perianal dermatitis of the newborn

Aetiology. Perianal dermatitis has been reported to have an overall incidence of 5–20% [1]. The incidence is lower in breastfed infants than in those fed cow's milk formulae [2,3]. It has been suggested that this difference might be explained by the higher faecal pH of the formula-fed infants [3], but this has not been confirmed [4]. Although the precise cause of perianal dermatitis in the newborn remains unknown, it is assumed that it represents an irritant response to faecal constituents. It is likely that there is considerable variation in susceptibility.

Clinical features. In the great majority of cases, erythema of the perianal skin makes its initial appearance during the first 8 days of life [2]. In the mildest cases, the erythema is confined to a zone some 2 cm in diameter around the anus, but commonly it extends to 4 cm or more. In the more severe forms, the affected skin may be oedematous and superficially eroded. Healing occurs spontaneously in 7–8 weeks. Although it usually occurs alone, perianal dermatitis may sometimes be associated with primary irritant napkin dermatitis or seborrhoeic dermatitis of infancy.

Diagnosis. The site and the early age of onset usually establish the diagnosis, but other dermatoses that appear in the napkin area need to be considered. The presence of pain and bleeding suggests a possible developmental defect of the anal papillae [5].

Treatment. Little treatment is usually needed, other than attention to hygiene. The affected area should be washed with water and a water-miscible emollient as soon as possible after defecation, and a protective lubricant such as White Soft Paraffin BP should be applied immediately afterwards.

References

1 Hidano A, Purwoko R, Jitskawa K. Statistical survey of skin changes in Japanese neonates. *Pediatr Dermatol* 1986; **3**: 140–4.
2 Pratt AG. Perianal dermatitis of the newborn. *Am J Dis Child* 1951; **82**: 429–32.
3 Pratt AG, Reed WT. Influence of type of feeding on pH of stool, pH of skin and the incidence of perianal dermatitis in the newborn infant. *J Pediatr* 1955; **46**: 539–43.
4 Tanino J, Steiner M, Benjamin B. The relationship of perianal dermatitis to fecal pH. *J Pediatr* 1959; **54**: 793–800.
5 Nichamin SJ, Kallet HI. Anomalous anal papillae in infants and children. *J Pediatr* 1951; **38**: 468–71.

Primary irritant napkin dermatitis

Synonym
- Diaper dermatitis

Terminology. The term napkin dermatitis implies an inflammatory eruption of the napkin area. Such an eruption may have many causes. The term is therefore best avoided except in this more general sense, and the term primary irritant napkin dermatitis should be preferred for the condition described here, even though its exact aetiology remains unestablished.

Aetiology [1–6]. It seems unlikely that every case of primary irritant napkin dermatitis has precisely the same combination of causes. It is, however, exceedingly rare in the absence of napkin wearing, and at least a degree of urinary or faecal incontinence.

The following factors need to be considered in any discussion of the aetiology of primary irritant dermatitis.

Maceration by water. The stratum corneum is almost exclusively responsible for the water barrier function of the epidermis, containing cells that are continuously sloughed off and renewed in a cycle of 12–24 days [7]. The hydrophobic extracellular matrix acts as the water barrier, preventing water loss from the body, and the entry of water and other hydrophilic substances, while the hydrophilic cells of the stratum corneum ('corneocytes') provide mechanical protection from the external environment in the form of a waxy layer.

Excessive wetness has several effects on the stratum corneum. Firstly, it makes the skin surface more fragile, and therefore more sensitive to frictional damage [4,8]. Secondly, it interferes with the protective barrier function [8–10], allowing increased permeation of irritant substances into the sensitive living layers of the skin below the stratum corneum, and exposure of these layers to the drying effect of the air and to the entry of harmful microorganisms.

Prolonged occlusion of the skin can itself produce erythema, particularly if water is kept in contact with the skin surface [1], and it has been suggested that prolonged contact with water alone can provoke dermatitis [11].

Friction. It seems likely that friction between the skin and the fabric of the napkin will also be an important factor in most cases. This is supported by the frequent predilection of the eruption for sites where such friction would be maximal, that is the inner surfaces of the thighs, the convex surfaces of the genitalia, the buttocks and the waistline. Friction would be able to breach the stratum corneum in the presence of maceration.

Urine. Newborn babies pass urine more than 20 times in 24 h. This frequency reduces through infancy to an average of seven times in 24 h at 12 months [12].

For many years it was believed that ammonia, produced by bacterial degradation of urea in the infants' urine, was the major cause of primary irritant napkin dermatitis [13,14]. It is now clear that this is not the case [4,15]. Neither the ammonia levels found in the first morning napkin nor the prevalence of urea-splitting microorganisms differ between infants with or without primary irritant napkin dermatitis [4]. The microorganisms isolated from affected infants are not able to release ammonia either faster or in greater quantity than those from unaffected infants [4]. It has been shown that urine containing various concentrations of ammonia does not cause significant erythema when applied under occlusion for 24 h to intact infants' skin, although it can do so when the skin has previously been abraded [4]. However, only about one in four of infants with primary irritant napkin dermatitis in this study had napkin ammonia levels in excess of the minimum concentration shown to cause such erythema. It appears, therefore, that the presence of ammonia is not mandatory, although it almost certainly will aggravate the eruption when the integrity of the skin is already compromised.

It has been suggested that urinary degradation products other than ammonia might also play a role. One study has shown that urine allowed to stand for 18 h at 37°C could induce dermatitis when applied to infants' skin, whereas fresh urine could not [16]. The effect was not related either to the pH or to the ammonia concentration, but the identity of the relevant irritant could not be established.

It is now clear that the role of urinary pH is critical. The higher the pH of the urine (i.e. the greater the alkalinity) the more liable an infant is to develop irritant napkin dermatitis. However, it seems that alkaline urine is not directly harmful; its harmful effect results from its interaction with faecal material in the napkin (see below). In addition, urine appears to increase epidermal permeability more effectively than water alone [9].

Faeces. It has been known for many years that human faeces have an irritant effect on skin [17]. Infants' faeces contain substantial amounts of pancreatic protease and lipase, and similar enzymes are produced within the gut by a variety of bacteria [18,19]. These faecal enzymes appear to be important skin irritants [20,21]. The irritant effect of such enzymes may be enhanced by many factors, particularly impaired barrier function and high pH. One of the factors that have been shown to affect faecal pH is the infant's diet, a higher pH being found in the cow's milk formula-fed infant [22].

Ureases are produced by a variety of faecal bacteria [18], and have the effect of increasing pH when mixed with urine. Increased pH enhances the activity of faecal lipases and proteases [9]. This perhaps provides an explanation for the anecdotal observation that cow's milk formula-fed infants appear more liable to primary irritant napkin dermatitis than breastfed infants, as the faeces of the former group have been shown to be more heavily colonized by urease-producing bacteria [23].

A variety of other factors may lower the infant's threshold for development of irritant napkin dermatitis; or may worsen the eruption once it is established. These include:

Poor or misguided skin care. The use of liquid soap for washing [24] and of talcum powder remain surprisingly common; both will increase risk of an irritant dermatitis.

Microorganisms. Although it has often been claimed that bacterial infection plays an important role in the common primary irritant type of napkin dermatitis, quantitative studies have consistently shown that the bacterial flora isolated from such eruptions does not differ materially from that isolated from the same area of skin in normal infants [15,25,26]. Neither does the type of napkin appear to influence the bacterial flora [27].

On the other hand, the evidence for an aetiological role for *Candida albicans* seems somewhat stronger. This organism has been isolated from the affected area in many infants with the primary irritant type of napkin dermatitis, but only very infrequently from the same area in normal infants [15,26,28,29]. Furthermore, there appears to be a good correlation between the severity of primary irritant napkin dermatitis and the level of *C. albicans* in the faeces [3].

The question of a role for *C. albicans* is complicated by the issue of the relationship between primary irritant napkin dermatitis and the classical form of napkin candidiasis. It is possible that, in most

cases, the latter is a complication of the former, and this view is supported by the fact that maceration of the skin is virtually a prerequisite for the establishment of *C. albicans* infections in human skin [30,31]. It is likely, therefore, that this organism will become established in the napkin area of infants who have primary irritant napkin dermatitis if it is present in the faeces.

Antibiotics. The use of broad-spectrum antibiotics in infants for conditions such as otitis media and respiratory tract infections has been shown to lead to an increased incidence of irritant napkin dermatitis [32]. This appears to parallel increased recovery of *C. albicans* from the rectum and skin in such infants.

Diarrhoea. The production of frequent liquid faeces is associated with shortened transit times, and such faeces are therefore likely to contain greater amounts of residual digestive enzymes.

Developmental anomalies of the urinary tract. Those anomalies that result in constant passage of urine will predispose to urinary tract infections.

In summary, the precise aetiology of primary irritant napkin dermatitis remains unestablished. Maceration and friction appear to be important in breaching the epidermal barrier. Faecal proteolytic and lipolytic enzymes appear able to act as irritants in skin whose barrier function is impaired, particularly if the ambient pH is high. The main factors in increasing the pH appear to be the action of faecal urease on urine, and the infant's diet. Secondary invasion by *C. albicans* appears to be a risk where this organism is present in faeces.

Pathology. The histological picture is generally that of primary irritant dermatitis with epidermal spongiosis and mild inflammatory changes in the dermis.

Clinical features [33,34]. Primary irritant napkin dermatitis is not often seen during the first 3 weeks of life. The onset is most often during the third to the 12th week, and the peak prevalence is seen between the seventh and 12th months [3,35]. Essentially the same condition has been reported in older children and adults who are incontinent of urine [36–38].

The overall incidence of the condition is difficult to establish, and may now be less than in the past, due to a general change to disposable napkins, but there is evidence that some 50% of infants are affected to some degree at some stage [3]. Another index of the degree of the problem is provided by the fact that in one survey it accounted for some 20% of all skin consultations in children aged under 5 years in the UK [39]. Both sexes and all races appear to be equally affected.

The most common form of primary irritant napkin dermatitis comprises confluent erythema of the convex surfaces in closest contact with the napkin, that is the buttocks, the genitalia, the lower abdomen and pubic area, and the upper thighs. The deeper parts of the groin flexures are generally spared (Fig. 17.4).

In some infants, the eruption is more or less confined to the margins of the napkin area ('tidemark dermatitis') and may reflect either chafing against the edge of the napkin or prolonged skin contact with the edges of impervious napkin covers or pants.



Fig. 17.4 Primary irritant napkin dermatitis, affecting the convexities predominantly with sparing of the groin creases.

Another distinctive pattern that has recently been described is one where the eruption is localized to the lateral parts of the upper thigh and buttock, most often unilaterally, but not infrequently bilaterally, in a position that corresponds to the areas where direct contact may occur with the bands that fasten the napkin [40,41]. It appears most often to be due to an irritant effect, but may also be a reflection of contact sensitization to rubber or glue chemicals [42].

Where the reaction is acute, the erythema may have a glazed appearance and be followed by peeling of the skin in sheets. A finer scaling is more commonly present in more long-standing cases. Post-inflammatory hypopigmentation may be a striking feature in racially pigmented infants.

Occasionally, an erosive form of primary irritant napkin dermatitis is seen, in which small vesicles and erosions may develop into rather characteristic, shallow, round ulcers with raised crater-like edges ('Jacquet's dermatitis').

In both sexes, involvement of the genitalia may lead to dysuria and occasionally, where the glans penis is severely affected, male infants may experience acute retention of urine [33].

Several fairly distinctive variants of primary irritant napkin dermatitis occur. When secondary invasion by *C. albicans* is present [15], the erythema may be more intense, and will no longer spare the deeper parts of the flexural folds. The margin tends to become more defined, scalloped with peripheral scaling. Within the marginal area small pustules are often visible, and these may also be seen scattered beyond the periphery of the erythema—so-called 'satellite' lesions. This clinical appearance is associated with faecal carriage of *C. albicans* [43].

In the second, less common variant, the erythematous areas are similarly well marginated but take on a markedly psoriasiform aspect with prominent scaling of a rather more adherent and micaceous type [39,44,45]. The onset of this eruption, commonly termed *napkin psoriasis*, may be quite sudden and its extension rapid. The relationship of this eruption to true psoriasis is discussed in Chapter 20.

A herpetiform presentation of primary irritant napkin dermatitis has occasionally been described [46]. This takes the form of an

eruption of vesicles and pustules followed by shallow erosions, closely resembling herpes simplex clinically, but showing no evidence of this infection pathologically.

Rather rarely, one may see domed, reddish brown or purple nodules as an additional feature. These lesions, usually known as infantile gluteal granulomas, are discussed later in this chapter.

Not infrequently, primary irritant napkin dermatitis affects areas beyond the confines of the napkin area itself. This appears particularly likely where there has been prolonged contact between the skin, urine and an occlusive surface such as a plastic cot sheet. Thus, the lateral aspects of the thighs, the calves and the heels are especially commonly affected.

In other babies, rapid dissemination of the rash occurs without any clear explanation, most characteristically in the form of expanding nummular lesions on the trunk, and more confluent erythematosquamous plaques in the flexures of the axillae and neck. An 'id' reaction to *C. albicans* has been proposed as the explanation for some of these rashes, but without any convincing evidence being provided to support such a view [28,45,47]. Where a rash in the napkin area is the first manifestation of psoriasis, other lesions of psoriasis may eventually make their appearance elsewhere. Similarly, napkin dermatitis may be the first sign of atopic dermatitis (see Chapter 24), or of 'seborrhoeic dermatitis of infancy'.

In infants with racially pigmented skin, hypopigmentation may be very prominent, and is sometimes the parents' principal anxiety. When there is an associated eczematous eruption on the face, this may similarly feature marked hypopigmentation, and this may be the presenting problem [48].

Prognosis. Primary irritant napkin dermatitis will almost always show some response to therapy, and, in the longer term, it will resolve when napkins are no longer worn. However, in some children the napkin area eruption is merely the first sign of a susceptibility to chronic skin disorders, particularly psoriasis and atopic dermatitis. Since atopic dermatitis often initially presents with a napkin dermatitis indistinguishable from simple primary irritant napkin dermatitis, one has to be cautious not to give too optimistic a prognosis to parents of any child with such a rash.

Differential diagnosis. A wide variety of skin disorders present with lesions in the napkin area during infancy.

A confluent, glistening, sharply marginated erythematous rash with peripheral desquamation and/or pustulation, and usually with satellite pustules, is, together with oral candidiasis, the typical presentation of neonatal candidiasis, a superficial *Candida* infection transmitted to the baby during birth [49]. The rash normally appears during the second week of life, and is aetiologically distinct from napkin-area *Candida* infections secondary to primary irritant napkin dermatitis.

In the past, congenital syphilis was relatively common, and had to be considered seriously in any infant with a dermatosis in the napkin area. Congenital syphilis is now rare in many countries, but its continued existence must constantly be borne in mind. Reddish brown macules, sometimes slightly raised, arise principally on the extremities including the palms and soles, and on the face mainly around the mouth. The napkin area is also frequently affected. Bullous or erosive lesions may occur in the napkin area. Flexural condylomas, rhinitis, hepatosplenomegaly and low birth weight are regular features.

The important diagnosis of zinc deficiency must be considered in any infant with a napkin dermatitis which fails to respond to appropriate treatment. A history of prematurity should increase one's suspicion, and a normal plasma zinc level does not rule out the diagnosis. Infants with napkin eruptions caused by zinc deficiency usually have a concurrent facial dermatitis extending from the perioral area, an erosive paronychia and erosive lesions in the palmar creases of the hands.

Multiple carboxylase deficiency is a rare cause of rashes in the napkin area; however, the rash most characteristically starts on the face with a presentation resembling seborrhoeic dermatitis.

In infancy, one of the commonest presentations of Langerhans' cell histiocytosis (see Chapter 55) is intertrigo, which tends to be very persistent and to become eroded as the disease progresses. Although the intertriginous eruption of Langerhans' cell histiocytosis may appear very early, more often it does not do so until after the third month. Initially, the eruption comprises small, yellowish papules, which become confluent and subsequently may become ulcerated. The scalp is almost always concurrently affected, particularly the retroauricular area.

Some diagnostic difficulty may be encountered by the occasional occurrence of dermatophyte infections in the napkin area [50–52]. It is important to bear in mind that the clinical appearances of such infections are likely to have been substantially modified by the application of topical corticosteroids.

Primary HSV infection of the genital area occurs from time to time in both boys and girls. The eruption is acute and accompanied by malaise and pyrexia.

Unusual infections causing eruptions in the napkin area should alert one to the possibility of primary or acquired immunodeficiency [53].

Treatment. Successful treatment of primary irritant napkin dermatitis depends on recognition of the relevant aetiological factors in the individual child, but can nevertheless generally follow a fairly standard pattern. The provision of topical medications without attention to such details as the frequency of napkin changes is often associated with therapeutic failure. The elements of successful treatment include the following:

Attention to the napkins

(a) *Disposable versus washable cloth napkins*. The use of good-quality disposable napkins, particularly those containing absorbent gelling materials ('super-absorbent' disposable napkins), is associated with a lower incidence and with lesser severity of napkin dermatitis compared with washable cloth napkins [3,54–56]. These gels are able to absorb about 80 times their own weight of water, and their use therefore results in reduced wetting, and, therefore, less maceration of the skin [57]. The use of such napkins is also associated with more normal skin pH values [54]. Highly absorbent napkins with an added 'breathable' microporous film membrane have been shown to reduce the prevalence of *Candida albicans* and napkin dermatitis [58].

(b) *Continuous administration of emollient from certain disposable napkins*. Disposable napkins are now available in which the layer next to the skin (the 'topsheet') is impregnated with an emollient, usually predominantly white soft paraffin. The use of this type of napkin has been shown to reduce the severity of irritant napkin dermatitis [59].

(c) *Frequency of napkin changes*. The frequency of napkin changes is also important, but probably less so now, because the absorbency of disposable napkins has increased greatly over recent years. It remains important however to change napkins as soon as possible after defaecation.

(d) *Care of washable napkins*. The use of antiseptic solutions for the storage of cloth napkins prior to washing is more or less universal, and is safe as long as suitable agents are used and washing and rinsing procedures are adequate. Poisoning of infants by antiseptics used in the laundering of napkins is well documented [60–62]. The quaternary ammonium compounds are now regarded as the best choice, of which benzalkonium chloride is perhaps the most widely employed. Antiseptics should never be used during the rinsing process.

Machine washing is generally preferable, as the cleaning and rinsing processes are reliable and thorough. A lower incidence of primary irritant napkin dermatitis has been demonstrated in babies whose napkins were laundered commercially rather than domestically [35]. 'Biological' detergents are best avoided, as are fabric 'conditioners' added during the rinsing. Tumble drying is preferable to air drying because it leaves the napkins softer, and therefore less liable to chafe.

Routine skin care in the napkin area. A routine of skin care should be instituted that will help prevent recurrence after the eruption has been successfully cleared. At each napkin change, a water-repellent emollient such as White Soft Paraffin BP, a half-and-half mixture of White Soft Paraffin BP and Liquid Paraffin BP, Zinc and Castor Oil Cream BP, or Bepanthen® [63] ointment should be applied.

When the napkin has been soiled, the area should be cleansed with water and a water-miscible emollient such as Aqueous Cream BP, and dried before applying a water-repellent emollient. Traditionally, cotton-wool balls have been used for this purpose. However, prewetted wipes are now available commercially which combine a very soft fabric with water, without the additives such as alcohol and fragrance that made such products undesirable in the past. It is very important that cleansing of the skin be undertaken as gently as possible, with the minimum of friction.

During remission, the baby should be bathed daily with a dispersible or semidispersible bath oil added to the water, and a water-miscible emollient should be used as a cleansing agent. While the eruption is under treatment, such baths should ideally be given twice a day.

The use of talcs and proprietary over-the-counter preparations containing potential irritants should be discouraged.

Specific therapy. Topical corticosteroids are helpful, and are indicated in all but the mildest cases. There is, however, virtually never any need to use applications containing anything more potent than 1% hydrocortisone. Such an application should be used twice a day after the bath, ideally in an ointment base.

It must be borne in mind that the rate of percutaneous absorption of corticosteroid from topical application in the napkin area will be considerably enhanced by the occlusive conditions found at this site. Fears that corticosteroid absorption might interfere with descent of the testes in male infants have not been confirmed in those of normal birth weight, but the possibility remains that such a problem could arise in low birth-weight babies [64].

As the eruption is often secondarily infected with *C. albicans*, the use of an ointment containing an anticandidal agent such as miconazole is justified and has been shown to be effective [65]. Systemic antibiotics are very rarely indicated, and there is no convincing evidence that oral nystatin has any additional therapeutic or prophylactic value when used in combination with a topical anticandidal agent [1,29,66].

In cases where flow of urine and especially of faeces over the skin is more or less continuous, topical sucralfate has been reported to provide a particularly effective barrier [37].

References

1 Boisits EK, McCormack JJ. Diaper dermatitis and the role of predisposition. In: Maibach H, Boisits EK, eds. *Neonatal Skin*. New York: Marcel Dekker, 1982: 191–204.

2 Burgoon CF, Urbach F, Grover WD. Diaper dermatitis. *Pediatr Clin North Am* 1961; **8**: 835–6.

3 Jordan WE, Lawson KD, Berg RW *et al.* Diaper dermatitis: frequency and severity among a general infant population. *Pediatr Dermatol* 1986; **3**: 198–207.

4 Leyden JJ, Katz S, Stewart R *et al.* Urinary ammonia and ammonia-producing micro-organisms in infants with and without diaper dermatitis. *Arch Dermatol* 1977; **113**: 1678–80.

5 Warin RP, Faulkner KE. Napkin psoriasis. *Br J Dermatol* 1961; **73**: 445–7.

6 Wiener F. The relationship of diapers to diaper rashes in the 1 month old infant. *J Pediatr* 1979; **95**: 422–4.

7 Williams ML, Elias PM. From basket weave to barrier: unifying concepts for the pathogenesis of disorders of cornification. *Arch Dermatol* 1993; **129**: 626–8.

8 Zimmerer RE, Lawson KD, Calvert CJ. The effects of wearing diapers on skin. *Pediatr Dermatol* 1986; **3**: 95–101.

9 Berg RW, Buckingham KW, Stewart RL. Etiologic factors in diaper dermatitis: the role of urine. *Pediatr Dermatol* 1986; **3**: 102–6.

10 Suskind RR, Ishihara M. The effects of wetting on cutaneous vulnerability. *Arch Environ Health* 1965; **11**: 529–37.

11 Willis J. The effects of prolonged water exposure on human skin. *J Invest Dermatol* 1973; **60**: 166–71.

12 Jordan WE, Blaney TL. Factors influencing infant diaper dermatitis. In: Maibach H, Boisits EK, eds. *Neonatal Skin*. New York: Marcel Dekker, 1982: 205–21.

13 Cooke JV. The etiology and treatment of ammonia dermatitis of the gluteal region of children. *Am J Dis Child* 1921; **22**: 481–92.

14 Zahorsky J. The ammoniacal diaper in infants and young children. *Am J Dis Child* 1915; **10**: 436–40.

15 Leyden JJ, Kligman AM. The role of microorganisms in diaper dermatitis. *Arch Dermatol* 1978; **114**: 56–9.

16 Rapp GW. The etiology of urine diaper rash. *Arch Pediatr* 1955; **72**: 113–8.

17 Caplan RM. The irritant role of feces in the genesis of perianal itch. *Gastroenterology* 1966; **50**: 19–23.

18 Donaldson RM. Normal bacterial populations of the intestine and their relation to intestinal function. *N Engl J Med* 1964; **270**: 938–45.

19 Gall LS. Normal fecal flora of man. *Am J Clin Nutr* 1970; **23**: 1457–65.

20 Bidmead MC, Rodger MN. The effect of enzymes on stratum corneum. *J Soc Cosmet Chem* 1973; **24**: 493–500.

21 Buckingham KW, Berg RW. Etiologic factors in diaper dermatitis: the role of feces. *Pediatr Dermatol* 1986; **3**: 107–12.

22 Pratt AG, Reed WT. Influence of type of feeding on pH of stool, pH of skin and the incidence of perianal dermatitis in the newborn infant. *J Pediatr* 1955; **46**: 539–43.
23 Yoshioka H, Iseki K, Fujita K. Development and differences of intestinal flora in the neonatal period in breast-fed and bottle-fed infants. *Pediatrics* 1983; **72**: 317–21.
24 Patrizi A, Neri I, Marzaduri S, Fiorillo L. Pigmented and hyperkeratotic napkin dermatitis: a liquid detergent irritant dermatitis. *Dermatology* 1996; **193**: 36–40.
25 Brookes DB, Hubbert RM, Sarkany I. Skin flora of infants with napkin rash. *Br J Dermatol* 1971; **85**: 250–3.
26 Montes LF, Pittillo RF, Hunt D *et al.* Microbial flora of infant's skin: comparison of types of microorganisms between normal skin and diaper dermatitis. *Arch Dermatol* 1971; **103**: 640–8.
27 Keswick BH, Seymour JL, Milligan MC. Diaper area skin microflora of normal children and children with atopic dermatitis. *J Clin Microbiol* 1987; **25**: 216–21.
28 Dixon PN, Warin RP, English MP. Role of *Candida albicans* infection in napkin rashes. *BMJ* 1969; **2**: 23–7.
29 Munz D, Powell KR, Pai CH. Treatment of candidal diaper dermatitis: a double blind controlled comparison of topical nystatin with topical plus oral nystatin. *J Pediatr* 1982; **101**: 1022–5.
30 Maibach HI, Kligman AM. The biology of experimental human cutaneous moniliasis (*Candida albicans*). *Arch Dermatol* 1962; **85**: 233–57.
31 Rebora A, Marples RR, Kligman AM. Experimental infection with *Candida albicans*. *Arch Dermatol* 1973; **108**: 69–73.
32 Honig PJ, Gribetz B, Leyden JL *et al.* Amoxicillin and diaper dermatitis. *J Am Acad Dermatol* 1988; **19**: 275–9.
33 Jacobs AH. Eruptions in the diaper area. *Pediatr Clin North Am* 1978; **25**: 209–24.
34 Koblenzer PJ. Diaper dermatitis: an overview. *Clin Pediatr (Phila)* 1973; **12**: 386–92.
35 Grant WW, Street L, Fearnow RG. Diaper rashes in infancy. *Clin Pediatr (Phila)* 1973; **12**: 714–6.
36 Hara M, Watanabe M, Tagami H. Jacquet erosive diaper dermatitis in a young girl with urinary incontinence. *Pediatr Dermatol* 1991; **8**: 160–1.
37 Markham T, Kennedy F, Collins P. Topical sucralfate for erosive irritant diaper dermatitis. *Arch Dermatol* 2000; **136**: 1199–200.
38 Virgili A, Corazza M, Califano A. Diaper dermatitis in an adult: a case of erythema papuloerosive of Sevestre and Jacquet. *J Reprod Med* 1998; **43**: 949–51.
39 Verbov JL. Skin problems in children. *Practitioner* 1976; **217**: 403–15.
40 Roul S, Ducombs G, Leaute-Labreze C, Taieb A. 'Lucky Luke' contact dermatitis due to the rubber components of diapers. *Contact Dermatitis* 1998; **38**: 363–4.
41 Larralde M, Raspa ML, Silvia H, Lamas F. Diaper dermatitis: a new clinical feature. *Pediatr Dermatol* 2001; **18**: 167–8.
42 Belhadjali H, Giordano-Labadie F, Rance F, Bazex J. 'Lucky Luke' contact dermatitis from diapers: a new allergen? *Contact Dermatitis* 2001; **44**: 248.
43 Rebora A, Leyden JJ. Napkin (diaper) dermatitis and gastro-intestinal carriage of *Candida albicans*. *Br J Dermatol* 1981; **105**: 551–5.
44 Farber EM, Jacobs AH. Infantile psoriasis. *Am J Dis Child* 1977; **131**: 1266–9.
45 Ferguson AG, Fraser NG, Grant PW. Napkin dermatitis with psoriasiform 'ide'. A review of fifty two cases. *Br J Dermatol* 1966; **78**: 289–96.
46 Graham-Brown RA, Lister DM, Burns DA. Herpetiform napkin dermatitis: napkin dermatitis simulating an acute herpes simplex infection. *Br J Dermatol* 1986; **114**: 746–7.
47 Jefferson J. Napkin psoriasis. *Br J Dermatol* 1966; **78**: 614–5.
48 Pegum JS. Facial depigmentation as a presenting symptom of napkin dermatitis in Negro infants. *Br J Clin Pract* 1968; **22**: 241–2.
49 Resnick SD, Greenberg RA. Autoinoculated palmar pustules in neonatal candidiasis. *Pediatr Dermatol* 1989; **6**: 206–9.
50 Congly H. Infection of the diaper area caused by *Epidermophyton floccosum*. *Can Med Assoc J* 1983; **129**: 410–1.
51 Kahana M, Levi A, Cohen M *et al.* Dermatophytosis of the diaper area. *Clin Pediatr (Phila)* 1987; **26**: 149–51.
52 Parry EL, Foshee WS, Marks JG. Diaper dermatophytosis. *Am J Dis Child* 1982; **136**: 273–4.
53 Thiboutot D, Beckford A, Mart C *et al.* Cytomegalovirus diaper dermatitis. *Arch Dermatol* 1991; **127**: 396–8.
54 Campbell R, Seymour JL, Stone LC *et al.* Clinical studies with disposable diapers containing absorbent gelling materials: evaluation of effects on infant skin condition. *J Am Acad Dermatol* 1987; **17**: 978–87.
55 Campbell RL, Bartlett AV, Sarbaugh FC *et al.* Effects of diaper types on diaper dermatitis associated with diarrhea and antibiotic use in children in day-care centers. *Pediatr Dermatol* 1988; **5**: 83–7.
56 Lane AT, Rehder PA, Helm K. Evaluations of diapers containing absorbent gelling material with conventional disposable diapers in newborn infants. *Am J Dis Child* 1990; **144**: 315–8.
57 Wilson PA, Dallas MJ. Diaper performance: maintenance of healthy skin. *Pediatr Dermatol* 1990; **7**: 179–84.
58 Akin F, Spraker M, Aly R *et al.* Effects of breathable disposable diapers: reduced prevalence of *candida* and common diaper dermatitis. *Pediatr Dermatol* 2001; **18**: 282–90.
59 Odio MR, O'Connor RJ, Sarbaugh F, Baldwin S. Continuous topical administration of a petrolatum formulation by a novel disposable diaper. *Dermatology* 2000; **200**: 238–43.
60 Brown BW. Fatal phenol poisoning from improperly laundered diapers. *Am J Public Health* 1970; **60**: 901–2.
61 Fisch RO, Berglund EB, Bridge AG *et al.* Methaemoglobinaemia in a hospital nursery: a search for causative factors. *JAMA* 1963; **185**: 760–3.
62 Robson AM, Kissane JM, Elvick NH *et al.* Pentachlorophenol poisoning in a nursery for newborn infants. I. Clinical features and treatment. *J Pediatr* 1969; **75**: 309–16.
63 Putet G, Guy B, Andres P *et al.* Effect of bepanthen ointment in the prevention and treatment of diaper rash on premature and full-term babies. *Realités Pediatr* 2001; **63**: 33–8.
64 John Radcliffe Hospital Cryptorchidism Study Group. Effect of corticosteroid creams on descent of testes in infants. *BMJ* 1990; **301**: 214–5.
65 Colcannon P, Gisoldi E, Phillips S, Grossman R. Diaper dermatitis: a therapeutic dilemma. Results of a double-blind, placebo-controlled trial of miconazole nitrate 0.25%. *Pediatr Dermatol* 2001; **18**: 149–55.
66 Dixon PN, Warin RP, English MP. Alimentary *Candida albicans* and napkin rashes. *Br J Dermatol* 1972; **86**: 458–62.

Infantile gluteal granulomas

This term has been applied to a condition that arises as a complication of the primary irritant type of napkin dermatitis [1]. The apparent absence of any reports of the disorder before 1971, in contrast to the substantial number published throughout the world during the next decade, implied that this may have been a modern phenomenon, perhaps related to changes in the care of the napkin area in general, and the treatment of napkin dermatitis in particular. Conversely, a decrease in the number of case reports during the last decade may reflect a real improvement in these aspects of infant care.

In most, but certainly not all [2,3] of the reported cases, rather potent topical corticosteroids had been used, and the authors believed them to have been important precipitating factors [4–7]. *Candida albicans* has also been considered as an aetiological factor [6], but cannot be isolated from the napkin area in such infants any more often than in uncomplicated cases of napkin dermatitis [5]. Intracutaneous intradermal tests to *C. albicans* antigen have not shown evidence of either immediate or delayed hypersensitivity, and serum precipitins to *C. albicans* and *C. parapsilosis* have not been found [8]. A role has also been proposed for the use of occlusive pants, but these are now rather rarely used in the developed parts of the world. Starch particles were found within lesions in one case [9], but were sought and not identified in others [3].

Histologically, there is a dense granulomatous infiltrate occupying the full depth of the dermis, comprising lymphocytes, plasma cells, neutrophils, eosinophils and histiocytes [4,5,8,10].



Fig. 17.5 Infantile gluteal granulomas in the pubic area of a 6-month-old infant.

The characteristic lesions most commonly make their appearance between the fourth and ninth months of life in a child with primary irritant napkin dermatitis. There is no correlation between the severity of the napkin dermatitis and the incidence of these lesions, and they frequently appear to arise at a time when the napkin dermatitis is improving. The lesions comprise one or several, rather uniform, livid purple nodules, which are usually oval in outline with their long axis parallel to the skin creases [5] and up to about 3 cm in length. They tend to occur on the convexities of the napkin area, not in the flexures themselves, and are definitely not confined to the gluteal region, as the name might be taken to imply (Fig. 17.5). They have occasionally also occurred at other sites in affected infants [5]. They persist for some weeks and appear to regress spontaneously, even if the use of potent corticosteroid applications is continued [11], and may leave atrophic scars [5]. Analogous lesions have been described in incontinent older patients [12,13].

These lesions require little treatment other than the removal of likely provocative factors, especially the withdrawal of topical corticosteroid therapy other than hydrocortisone alone, if this is required for the treatment of persisting napkin dermatitis, and the restriction to a minimum of the wearing of occlusive plastic pants. Napkin-area care should be as outlined above for primary irritant napkin dermatitis.

These lesions have a superficial resemblance clinically and histologically to Kaposi's sarcoma [10]. However, the latter more commonly arises on the extremities, even in infants [14], and histologically shows characteristic interweaving bands of spindle cells, at least in well-developed cases.

References

1 Tappeiner J, Pfleger L. Granuloma gluteale infantum. *Hautarzt* 1971; **2**: 383–8.

2 Bluestein J, Furner B, Phillips D. Granuloma gluteale infantum: case report and review of the literature. *Pediatr Dermatol* 1990; **7**: 196–8.

3 Konya, J, Gow E. Granuloma gluteale infantum. *Australas J Dermatol* 1996; **37**: 57–8.

4 Bazex A, Dupre A, Christol B *et al.* Le granulome glutéal infantile (Tappeiner et Pfleger). *Ann Dermatol Syphiligr (Paris)* 1972; **99**: 121–34.

5 Bonifazi E, Garofalo L, Lospalluti M *et al.* Granuloma gluteale infantum with atrophic scars: clinical and histological observations in eleven cases. *Clin Exp Dermatol* 1981; **6**: 23–9.

6 Delacretaz J, Grigoriu D, de Crousaz H *et al.* Candidose nodulaire de la region inguino-genitale et des fesses (granuloma gluteale infantum). *Dermatologica* 1972; **144**: 144–55.

7 Uyeda K, Nakayasu K, Takaishi Y *et al.* Kaposi sarcoma-like granuloma on diaper dermatitis. *Arch Dermatol* 1973; **107**: 605–7.

8 Lovell CR, Atherton DJ. Infantile gluteal granuloma. *Clin Exp Dermatol* 1984; **9**: 522–5.

9 Kelly R, Campbell PE. Granuloma gluteale infantum with starch granules in the lesions. *Med J Aust* 1973; **2**: 438–9.

10 Uyeda K, Nakayasu K, Takaishi Y *et al.* Electron-microscopic observations of the so-called granuloma gluteale infantum. *J Cutan Pathol* 1974; **1**: 26–32.

11 Kituchi I, Jono M. Flurandrenolide-impregnated tape for granuloma gluteale infantum. *Arch Dermatol* 1976; **112**: 564.

12 Maekawa Y, Sakazaki Y, Hayashibara T. Diaper area granuloma of the aged. *Arch Dermatol* 1978; **114**: 382–3.

13 Fujita K, Ortone F, Danno K, Miyachi Y. Two cases of diaper area granuloma of the adult. *J Dermatol* 1991; **18**: 671–5.

14 Dutz W, Stout AP. Kaposi's sarcoma in infants and children. *Cancer* 1960; **13**: 684–94.

Infantile 'seborrhoeic' dermatitis

Definition and nomenclature. The term infantile 'seborrhoeic' dermatitis is widely used to describe an allegedly distinctive eczematous or psoriasiform eruption seen in infants, having a predilection for the scalp and the proximal flexures, and a favourable prognosis compared with atopic dermatitis. The term nevertheless remains unsatisfactory, as the condition has no established relationship with seborrhoea or even with sebum; neither is there any convincing evidence that it is analogous to seborrhoeic dermatitis of adults. There must be some doubt whether the condition exists at all as a separate entity.

Aetiology. The authors regard the term *infantile seborrhoeic dermatitis* as a description of a somewhat distinctive but nevertheless highly variable clinical presentation rather than a single disease. It may be a presentation that can reflect a variety of different skin disorders, and that may therefore have a number of different causes. The term is used to describe cases that others would consider to be examples of cradle cap with intertriginous lesions, intertrigo, primary irritant napkin dermatitis with dissemination, atopic dermatitis, infantile psoriasis and multiple carboxylase deficiency, as well as rashes that may reflect primary immunodeficiency infants. Once all these have been excluded, how many cases of a genuinely distinct seborrhoeic dermatitis of infancy would remain is not clear. However, as there remains a considerable body of opinion that there is a true infantile seborrhoeic dermatitis, the condition is described in this chapter. It appears possible that disagreements on this subject might to some extent reflect regional variations in incidence, and possibly a dramatic fall in incidence in recent years.

The relationship between infantile seborrhoeic dermatitis and atopic dermatitis has been the subject of debate for many years. Some authorities have proposed that infantile seborrhoeic dermatitis is merely a characteristic pattern of atopic dermatitis and not a separate entity [1], on the basis of the observation that apparently typical infantile seborrhoeic dermatitis not infre-

quently transforms into equally typical atopic dermatitis. The occurrence of such transformation is not disputed, only its frequency and interpretation. A prevalence of atopic dermatitis of 27.5% was reported in a group of children reviewed 5–13 years after a diagnosis of seborrhoeic dermatitis had been made in infancy [2]. In another study [3], it was shown that 19% of a group of children, diagnosed as having seborrhoeic dermatitis of infancy about 12 years earlier, had atopic dermatitis on review, compared with a prevalence of 10% in a control group, and of 45% in a group of children diagnosed as having atopic dermatitis in infancy. Scientific resolution of this controversy is hampered by clinical overlap between the two conditions, at least in their earliest stages [4]. Furthermore, the incidence of atopic dermatitis is so high that a proportion of infants with infantile seborrhoeic dermatitis would in any case be expected to develop atopic dermatitis. Because the age of onset is similar, this would often occur before the seborrhoeic dermatitis had resolved. The most valid reasons for continuing to regard the two conditions as distinct entities are, firstly, a relative lack of association between infantile seborrhoeic dermatitis and atopic status in infancy [5] and, secondly, a better prospect of early resolution in infantile seborrhoeic dermatitis [4].

These problems are highlighted by the reported prevalence of psoriasis of about 27% in a group of children reviewed 2–13 years after a diagnosis of infantile seborrhoeic dermatitis had been made [6].

Controversy also surrounds the relationship between infantile seborrhoeic dermatitis and seborrhoeic dermatitis of adults. Sebum is no longer considered an important aetiological factor in the adult condition, although it is considered possible that seborrhoea plays a part in the seborrhoeic dermatitis seen in a relatively high proportion of patients with Parkinson's disease. As infants do secrete some sebum, at least in the first few months of life [7], an aetiological role for sebum in infantile seborrhoeic dermatitis is not entirely excluded and, it has been argued, without any scientific support, that the typical early resolution of the disorder is the direct result of decreasing levels of sebum production during the last 6 months of infancy. There is no evidence of an increased prevalence of seborrhoeic dermatitis in adult life among those who previously had a diagnosis of infantile seborrhoeic dermatitis.

A favoured view in the past was that infantile seborrhoeic dermatitis is an 'id' reaction to *C. albicans* skin and intestinal infection [8,9], but no convincing evidence has been put forward to support this hypothesis.

An aetiological role for *M. furfur* has been convincingly argued in adult seborrhoeic dermatitis [10], and is supported by the therapeutic benefit that follows therapy with ketoconazole [11]. It has been demonstrated that this organism can activate complement *in vitro* by the alternative pathway [12]. *Pityrosporum ovale* is part of the normal skin flora in adults, but is rare in prepubertal children; it is generally found in greatest density in the scalp and proximal flexures. The proportion of the normal scalp flora represented by *P. ovale* is increased in adults with seborrhoeic dermatitis [13], and the organism has been isolated with an increased frequency from several body sites in infants with infantile seborrhoeic dermatitis [14,15]. A possible aetiological role for this yeast in infantile seborrhoeic dermatitis is supported by reports of therapeutic response to topical ketoconazole [15,16].

In the past, there was a strong feeling that nutritional factors might be important in the aetiology of infantile seborrhoeic dermatitis, an impression that was strengthened by a report from Czechoslovakia of an increased incidence of the condition during the post-Second World War period of food shortage [17]. The appearance of an intertriginous dermatitis with some resemblance to infantile seborrhoeic dermatitis was described in infants fed a diet deficient in essential fatty acids [18], but evidence of essential fatty acid deficiency has not been demonstrated in infants with seborrhoeic dermatitis [19]. Data have been reported, however, that were interpreted as suggesting that affected children may have transiently impaired activity of the enzyme, δ-6-desaturase [20]. Seborrhoeic dermatitis has also been reported in breast-fed babies of malnourished mothers, in whom it improved when biotin injections were given to the mothers [21]. Dramatic responses have been described in infants with generalized seborrhoeic dermatitis who were themselves given oral or parenteral biotin [22,23]. In contrast, subsequent controlled trials of biotin treatment provided no support for such claims [19,24], and biotin deficiency in infancy does not result in the clinical picture of seborrhoeic dermatitis [25,26].

Pathology. There have been very few studies of the histopathology of infantile seborrhoeic dermatitis. However, it seems clear that one finds patchy parakeratosis, with epidermal microvesicles and slight spongiosis, occasional lymphocytes, moderate acanthosis (often psoriasiform) and a poorly developed granular layer [27]. The dermis features a mild, patchy perivascular lymphocytic inflammatory infiltrate and prominent perivascular oedema. Direct immunofluorescence has been negative, and candidal antigen has not been identified.

Clinical features [4,28,29]. The eruption generally first appears between the second week of life and the sixth month, but perhaps most frequently between the third and eighth weeks. In some cases, it starts in the napkin area; in others, it starts on the face and scalp. Occasionally, the eruption first appears on the trunk outside the napkin area. Often, the rash occurs almost simultaneously on the face, scalp and in the napkin area at its onset. It tends to spread fairly rapidly to involve the scalp, face, neck, napkin area and axillae. On the scalp, the vertex and frontal areas are the sites of predilection. On the face, the forehead, eyebrows, eyelids and nasolabial folds tend to be the worst affected areas. The eruption is often confluent around the neck and up the sides of the face to the temples, the area behind the ears tending to be the most severely affected. In the napkin area, the folds are confluently involved. On the trunk, the umbilical area is a favourite site.

The rash comprises well-defined areas of erythema and scaling with tiny vesicles. Papular and lichenified lesions are not seen. On the scalp and in the flexures, the eruption is confluent, but, elsewhere, the individual lesions usually start as small, round or oval areas, subsequently extending and coalescing to form patterns. The scales are rather adherent; they are yellow-brown in colour, large and greasy in the scalp, but smaller, whiter and drier in other areas.

Typically the infant is well, and pruritus appears to be relatively mild, in contrast to atopic dermatitis. As a consequence, feeding and sleep are generally undisturbed.

Differential diagnosis. The diagnostic features of seborrhoeic dermatitis are said to be its distribution in the scalp and proximal flexures, and the relative absence of pruritus, but these are not really sufficiently specific to define the disorder clinically.

Many of those diagnosed as having infantile seborrhoeic dermatitis could be given more satisfactory alternative diagnoses. These include cradle cap, intertrigo, disseminated primary irritant napkin dermatitis, atopic dermatitis, infantile psoriasis, zinc deficiency, multiple carboxylase deficiency and primary immunodeficiencies.

Perhaps the situation in which the diagnosis of infantile seborrhoeic dermatitis is most often incorrectly applied is that of disseminated primary irritant napkin dermatitis (see above). Some babies with typical primary irritant napkin dermatitis may experience progressive spread of the eruption beyond the confines of the napkin area. This generally only occurs when the napkin dermatitis is relatively intense. The pattern of dissemination in such cases may closely resemble the distribution of lesions regarded as characteristic for infantile seborrhoeic dermatitis.

It is likely that in a small proportion of cases, infantile seborrhoeic dermatitis is an early manifestation of psoriasis. There is certainly a suspicion that the dissemination of primary irritant napkin dermatitis is at least occasionally a reflection of underlying predisposition to psoriasis.

As discussed earlier in this chapter, there is a common, acquired type of cradle cap that is frequently associated with scaling lesions in the eyebrows, forehead and temples, and the retroauricular area and neck, and occasionally with intertriginous lesions in the axillae and groins. This rash starts on the scalp and manifests relatively little inflammation. To some, this is a form of infantile seborrhoeic dermatitis; to others, it is a different entity.

Differentiation from atopic dermatitis may be particularly problematic, directly mirroring uncertainties about the existence of such an entity as infantile seborrhoeic dermatitis. There can be no doubt that rashes having the clinical characteristics of infantile seborrhoeic dermatitis may gradually transform into one that has the typical appearances of infantile atopic dermatitis, an observation that has led many to regard infantile seborrhoeic dermatitis as nothing more than a 'seborrhoeic pattern' of atopic dermatitis in infants [1]. The presence or absence of a family history of atopic disorders appears to be unhelpful in discrimination, as is the age of onset [4]. Pruritus is commoner and more severe in atopic dermatitis, but it should be borne in mind that pruritus may not in any case be evident in early infancy.

Langerhans' cell histiocytosis (see Chapter 55) may present with an eruption having features in common with infantile seborrhoeic dermatitis, particularly its distribution in the scalp, groins and axillae. However, careful examination will demonstrate that the eruption of Langerhans' cell histiocytosis comprises clusters of small, translucent, flesh-coloured papules, although these may become confluent at certain sites, particularly in the proximal flexures and in the retroauricular area. There is often a petechial element in addition. Although the child may be pallid and unwell, this is not invariably the case. There may of course be other manifestations of the disease such as oral or anogenital lesions, soft masses in the scalp, or hepatosplenomegaly. Where there is any suspicion of Langerhans' cell histiocytosis, a skin biopsy should be undertaken.

Multiple carboxylase deficiency may present in infancy with a well-marginated erythematosquamous rash that starts in the scalp, on the eyebrows and at the eyelid margins, extending later to the perioral, perianal areas and to other flexural sites. There may be associated blepharitis, and keratoconjunctivitis causing photophobia. Vomiting is common. Neurological symptoms tend to be prominent, particularly convulsions, developmental delay, hypotonia and ataxia.

Certain primary immunodeficiency disorders may present with a progressive eczematous eruption having a predilection for the proximal flexures. Similar rashes may occur in secondary immunodeficiency disorders such as congenital human immunodeficiency virus (HIV) infection.

Prognosis. The outlook, even without treatment, is good, and clearance can be anticipated within a few weeks in the majority of cases. Relapses are unusual after clearance. Persistence suggests that the correct diagnosis is atopic eczema, psoriasis, zinc deficiency, Langerhans' cell histiocytosis or immunodeficiency.

Treatment. The treatment of this condition is similar to that of atopic dermatitis. Affected infants should be bathed at least once a day, and a dispersing bath oil may be added to the water. During the bath, affected areas should be cleaned with a water-dispersible emollient such as Ung. Emulsificans BP or Aqueous Cream BP. Soap should be avoided. After bathing, a topical antiyeast agent should be given, because 2% ketoconazole cream has been shown to be effective in a high proportion of cases [16]. Treatment should be applied once or twice a day for 10–14 days. At other times during the day, a simple emollient cream or ointment should be applied, especially in the napkin area.

The scalp should be cleaned with 2% ketoconazole shampoo. Applications containing salicylic acid or corticosteroids should not be used, because of the very efficient absorption of these molecules at this site in infancy.

While it is reasonable to assess the nutritional value of the infant's diet, there is no evidence that either biotin or essential fatty acids are generally beneficial [19,24].

References

1 Vickers CFH. The natural history of atopic eczema. *Acta Derm Venereol (Stockh)* 1980; **92** (Suppl.): 113–5.

2 Neville EA, Finn OA. Psoriasiform napkin dermatitis: a follow-up study. *Br J Dermatol* 1975; **92**: 279–85.

3 Podmore P, Burrows D, Eedy DJ *et al.* Seborrhoeic dermatitis—a disease entity or a clinical variant of atopic eczema? *Br J Dermatol* 1986; **115**: 341–50.

4 Yates VM, Kerr REI, MacKie R. Early diagnosis of infantile seborrheic dermatitis and atopic dermatitis—clinical features. *Br J Dermatol* 1983; **108**: 633–8.

5 Yates VM, Kerr REI, Freier K *et al.* Early diagnosis of infantile seborrheic dermatitis and atopic dermatitis—total and specific IgE levels. *Br J Dermatol* 1983; **108**: 639–45.

6 Menni S, Piccinno R, Baietta S *et al.* Infantile seborrheic dermatitis: 7-year follow-up and some prognostic criteria. *Pediatr Dermatol* 1989; **6**: 13–5.

7 Pochi PE. The sebaceous gland. In: Maibach H, Boisits EK, eds. *Neonatal Skin*. New York: Marcel Dekker, 1982: 67–80.

8 Seebacher C. Zur Ätiologie und Pathogenese der Dermatitis seborrhoides infantum. *Mykosen* 1981; **24**: 209–15.
9 Oranje AP, van Joost T, Stolz E. Superficial fiungal infections in children in the Netherlands. *J Drug Ther Res* 1984; **9**: 436–9.
10 Shuster S. The aetiology of dandruff and mode of action of therapeutic agents. *Br J Dermatol* 1984; **111**: 235–42.
11 Ford GP, Farr PM, Ive FA *et al.* The response of seborrhoeic dermatitis to ketoconazole. *Br J Dermatol* 1984; **111**: 603–7.
12 Belew PW, Rosenberg EW, Jennings BR. Activation of the alternative pathway of complement by *Malassezia ovalis* (*Pityrosporum ovale*). *Mycopathologia* 1980; **70**: 187–91.
13 McGinley KJ, Leyden JJ, Marples RR *et al.* Quantitative microbiology of the scalp in non-dandruff, dandruff and seborrheic dermatitis. *J Invest Dermatol* 1975; **64**: 401–5.
14 Broberg A, Faergeman J. Infantile seborrhoeic dermatitis and *Pityrosporum ovale*. *Br J Dermatol* 1989; **120**: 359–62.
15 Ruiz-Maldonado R, Lopez-Matinez R, Chavarria ELP *et al. Pityrosporum ovale* in infantile seborrheic dermatitis. *Pediatr Dermatol* 1989; **6**: 16–20.
16 Taieb A, Legrain V, Palmier C *et al.* Topical ketoconazole for infantile seborrheic dermatitis. *Dermatologica* 1990; **181**: 26–32.
17 Svejcar J, Homolka J. Experimental experiences with biotin in babies. *Ann Pediatr (Paris)* 1950; **174**: 175–93.
18 Hansen AE, Haggard ME, Boelsche AN *et al.* Essential fatty acids in infant nutrition. III. Clinical manifestations of linoleic acid deficiency. *J Nutr* 1958; **66**: 565–76.
19 Erlichman M, Goldstein R, Levi E *et al.* Infantile flexural seborrhoeic dermatitis. Neither biotin nor essential fatty acid deficiency. *Arch Dis Child* 1981; **56**: 560–2.
20 Tolleson A, Frithz A, Berg A, Karlman G. Essential fatty acids in infantile seborrheic dermatitis. *J Am Acad Dermatol* 1993; **22**: 957–61.
21 Nisenson A. Seborrheic dermatitis in infants: treatment with biotin injections for the nursing mother. *Pediatrics* 1969; **44**: 1014–5.
22 Nisenson A. Seborrheic dermatitis of infants and Leiner's disease: a biotin deficiency. *J Pediatr* 1957; **51**: 537–48.
23 Messaritakis J, Katamis C, Karabula C *et al.* Generalised seborrheic dermatitis: clinical and therapeutic data of 25 patients. *Arch Dis Child* 1975; **50**: 871–4.
24 Keipert JA. Oral use of biotin in seborrhoeic dermatitis of infancy: a controlled trial. *Med J Aust* 1976; **1**: 584–5.
25 Anon. Clinical nutrition cases. Biotin deficiency as a complication of incomplete parenteral nutrition. *Nutr Rev* 1981; **39**: 274–7.
26 Nyhan WL. Inborn errors of biotin metabolism. *Arch Dermatol* 1987; **123**: 1696–8.
27 Oranje A, van Joost TH, van Reede EC *et al.* Infantile seborrhoeic dermatitis: morphological and immunopathological study. *Dermatologica* 1986; **172**: 191–5.
28 Bonifazi E. Infantile seborrhoeic dermatitis: pathogenetic considerations and nosological aspects. *Pediatr Dermatol News* 1988; **7**: 16–21.
29 Tachao P. Problems of so-called infantile eczema. III. Seborrhoeic dermatitis. *Acta Derm Venereol (Stockh)* 1939; **20**: 232–47.

Infantile psoriasis and napkin psoriasis

While it is uncommon for psoriasis to appear in infancy, this undoubtedly does happen [1–3], and there is some evidence suggesting the occasional occurrence of congenital psoriasis [1,4,5]. However, the term napkin psoriasis has been used rather loosely to describe what should probably more correctly have been called *psoriasiform napkin dermatitis* or *psoriasiform seborrhoeic dermatitis of infancy* [6–8]. In some infants with primary irritant napkin dermatitis and infantile seborrhoeic dermatitis, the eruption shows psoriasiform features clinically (Fig. 17.6) [9–12]; it has been demonstrated that these children have an increased risk of genuine psoriasis many years later [9,12–15].

True psoriasis occurs in infancy, most typically in the napkin area as an isomorphic (Koebner) response in a genetically predisposed child with primary irritant napkin dermatitis [1]. While a fairly confident diagnosis of psoriasis can sometimes be made in such a case, it is more often appropriate to use the term 'psoriasiform' in this situation, as most infants with psoriasiform napkin dermatitis do not appear to go on to develop psoriasis [16]. Furthermore, it has been shown that the frequency of the three human leukocyte antigens (HLA), B13, B17 and BW37, is no different in infants with psoriasiform napkin dermatitis from their frequency in normal infants, whereas they are found with very significantly increased frequency in true psoriatics [17].



Fig. 17.6 Napkin psoriasis: confluent dry erythema with a sharp, scalloped margin in a 7-month-old infant.

Psoriasiform napkin dermatitis has a mean onset at about 2 months, and generally lasts for 2–4 months [9,16]. The rash comprises psoriasiform plaques in the napkin area with smaller papular satellites of similar appearance. It frequently disseminates, to involve the trunk and limbs, where lesions will have the same morphology, and to the face and scalp, where affected areas tend to be more diffuse and covered with denser, adherent scale or crust. Frankly pustular lesions have been described in disseminated napkin psoriasis [18].

Generalized pustular psoriasis has also been described occasionally in infancy, including a case in which lytic bone lesions were present due to chronic, recurrent, multifocal osteomyelitis [19].

References

1 Farber EM, Jacobs AH. Infantile psoriasis. *Am J Dis Child* 1977; **131**: 1266–9.
2 Nyfors A, Lemholt K. Psoriasis in children: a short review and a survey of 245 cases. *Br J Dermatol* 1975; **92**: 437–42.
3 Nyfors A. Psoriasis in children: characteristics, prognosis and therapy. *Acta Derm Venereol (Stockh)* 1981; **95** (Suppl.): 47–53.
4 Henriksen L, Zachariae H. Pustular psoriasis and arthritis in congenital psoriasiform erythroderma. *Dermatologica* 1972; **144**: 12–8.
5 Lerner MR, Lerner AB. Congenital psoriasis: report of three cases. *Arch Dermatol* 1972; **105**: 598–601.
6 Warin RP. Napkin psoriasis. *Br J Dermatol* 1967; **78**: 613–4.
7 Warin RP. Napkin psoriasis followed by psoriasis. *Br J Dermatol* 1967; **79**: 711.
8 Warin RP, Faulkner KE. Napkin psoriasis. *Br J Dermatol* 1961; **73**: 445–7.
9 Andersen SLC, Thomsen K. Psoriasiform napkin dermatitis. *Br J Dermatol* 1971; **84**: 316–9.
10 Fergusson AG, Fraser NG, Grant PW. Napkin dermatitis with psoriasiform 'ide': a review of 52 cases. *Br J Dermatol* 1966; **78**: 289–96.

11 Jefferson J. Napkin psoriasis. *Br J Dermatol* 1966; **78**: 614–5.
12 Neville EA, Finn OA. Psoriasiform napkin dermatitis: a follow-up study. *Br J Dermatol* 1975; **92**: 279–85.
13 Rasmussen HB, Hagdrup H, Schmidt H. Psoriasiform napkin dermatitis. *Acta Derm Venereol (Stockh)* 1986; **66**: 534–6.
14 Morris A, Rogers M, Fischer G, Williams K. Childhood psoriasis: a clinical review of 1262 cases. *Pediatr Dermatol* 2001; **18**: 188–98.
15 Farber EM, Mullen RH, Jacobs AH *et al.* Infantile psoriasis: a follow-up study. *Pediatr Dermatol* 1986; **3**: 237–43.
16 Boje RH, Hagdrup H, Schmidt H. Psoriasiform napkin dermatitis. *Acta Dermatol Venereol (Stockh)* 1986; **66**: 534–6.
17 Skoven IG, Hjortshoj A. HLA-antigens and psoriasiform napkin dermatitis. *Dermatologica* 1978; **157**: 225–8.
18 Watanabe M, Tabata N, Tagami H. Explosive diaper pustular psoriasis (Letter). *Pediatr Dermatol* 2002; **19**: 564–5.
19 Ivker RA, Grin-Jorgensen CM, Vega VK *et al.* Infantile generalised psorisis associated with lytic lesions of the bone. *Pediatr Dermatol* 1993; **10**: 277–82.

'Blueberry muffin' baby (dermal erythropoiesis)

Definition. This term has been used to describe a characteristic eruption in neonates, often present at birth, comprising widespread, purple, erythematous, oval or circular macules, papules and nodules reflecting dermal erythropoiesis.

Aetiology and pathology (Table 17.3). The 'blueberry muffin' type of lesion has been recorded in a number of congenital viral and bacterial infections, notably rubella [1–5], cytomegalovirus [1,6–9], coxsackie B2 infection, parvovirus B19 [10], and in congenital syphilis and toxoplasmosis [7,11]. These lesions have also been described in a variety of congenital haematological disorders, notably hereditary spherocytosis [12], rhesus incompatibility [13,14], ABO blood group incompatibility [6] and twin–twin transfusion syndrome [6,15]. Occasionally, clinically identical lesions have occurred in infants who appeared to have no underlying cause [6].

In the congenital infections and haematological disorders, the lesions have been shown histologically to comprise foci of dermal erythropoiesis [1,6,12,15,16]. The reticular dermis contains aggregates of nucleated and non-nucleated erythrocyte precursors, but generally no cells of myeloid or megakaryocytic type. It is possible that this process represents persistence and exaggeration of the dermal erythropoiesis that is a normal occurrence in early fetal development, but the reasons behind this persistence are unclear [8,12].

Table 17.3 Differential diagnosis of the 'blueberry muffin' baby.

Dermal erythropoiesis
Congenital infections (rubella, cytomegalovirus, coxsackie B2, syphilis, toxoplasmosis)
Hereditary spherocytosis
Rhesus haemolytic anaemia
ABO blood group incompatibility
Twin–twin transfusion syndrome
Neoplastic infiltrates
Congenital leukaemia
Neuroblastoma
Congenital rhabdomyosarcoma
Other disorders
Neonatal lupus erythematosus (LE)

Clinical features. The skin lesions of dermal erythropoiesis are present at birth, comprising widespread or sometimes more local collections of macules and infiltrated, domed papules up to about 1 cm in diameter, having a colour that is generally purple, but may vary from dark blue to magenta. There may be frank petechiae on the surface of some of the lesions. Favoured sites include the trunk, head and neck. The lesions generally fade into light-brown macules within a few weeks of birth. Late-onset blueberry muffin syndrome has been reported in a 3-month-old child following congenital rubella [17].

Diagnosis. Clinically rather similar but more nodular lesions have occurred in a number of situations. Whether such lesions should be called 'blueberry muffin' lesions is debatable, as they do not show dermal erythropoiesis, but a variety of other histological appearances, in each case characteristic for their cause. Examples include congenital leukaemia [18–25], neonatal neuroblastoma [26,27], congenital rhabdomyosarcoma [28], congenital Langerhans' cell histiocytosis [29] and neonatal LE.

References

1 Brough AJ, Jones D, Page RH *et al.* Dermal erythropoiesis in neonatal infants: a manifestation of intrauterine viral disease. *Pediatrics* 1967; **40**: 627–35.
2 Cooper LZ, Green RH, Krugman S *et al.* Neonatal thrombocytopenic purpura and other manifestations of rubella contracted *in utero*. *Am J Dis Child* 1965; **110**: 416–27.
3 Cooper LZ, Ziring PR, Cockerse AB *et al.* Rubella: clinical manifestations and management. *Am J Dis Child* 1969; **118**: 18–29.
4 McIntosh ED, Menser MA. A fifty-year follow-up of congenital rubella. *Lancet* 1992; **340**: 414–5.
5 Rudolph AJ, Yow MD, Phillips A *et al.* Transplacental rubella infection in newly born infants. *JAMA* 1965; **191**: 843–5.
6 Bowden JB, Hebert AA, Rapini RP. Dermal hematopoiesis in neonates: report of five cases. *J Am Acad Dermatol* 1989; **20**: 1104–10.
7 Fine JD, Arndt KA. The TORCH syndrome: a clinical review. *J Am Acad Dermatol* 1985; **12**: 697–706.
8 Groark SP, Jampel RM. Violaceous papules and macules in a newborn: dermal erythropoiesis associated with congenital cytomegalovirus infection. *Arch Dermatol* 1989; **125**: 114–7.
9 Labeille B, Kremp O, Gontier MF *et al.* Erythropoièse intradermique néonatale. *Ann Dermatol Vénéréol* 1988; **115**: 1135–6.
10 Silver MM, Hellmann J, Zielenska M *et al.* Anemia, blueberry muffin rash and hepatomegaly in a newborn infant. *J Pediatr* 1996; **128**: 579–86.
11 Schachner L, Press S. Vesicular, bullous and pustular disorders in infancy and childhood. *Pediatr Clin North Am* 1983; **30**: 609–29.
12 Argyle JC, Zone JJ. Dermal erythropoiesis in neonatal infants. *Pediatrics* 1981; **117**: 492–4.
13 Hebert AA, Esterly NB, Gardner TH. Dermal erythropoiesis in Rh hemolytic disease of the newborn. *J Pediatr* 1985; **107**: 799–801.
14 Pizarro A, Elorza D, Gamallo C *et al.* Neonatal dermal erythropoiesis associated with severe rhesus immunization: amelioration by high-dose intravenous immunoglobulin. *Br J Dermatol* 1995; **133**: 334–5.
15 Schwartz JL, Maniscalco WM, Lane AT *et al.* Twin transfusion syndrome causing cutaneous erythropoiesis. *Pediatrics* 1984; **74**: 527–9.
16 Klein HZ, Markarian M. Dermal erythropoesis in congenital rubella: description of an infected newborn who had purpura associated with marked extramedullary erythropoesis in the skin and elsewhere. *Clin Pediatr (Phila)* 1969; **8**: 604–7.
17 Vozza A, Tolone C, Carrano EM *et al.* Late onset blueberry muffin syndrome following congenital rubella. *J Eur Acad Dermatol Venereol* 2003; **17**: 204–5.

18 Torrelo A, Madero L, Mediero IG *et al.* Aleukemic congenital leukemia cutis. *Pediatr Dermatol* 2004; **21**: 458–61.
19 Francis JS, Sybert VP, Benjamin DR. Congenital monocytic leukemia: report of a case with cutaneous involvement, and review of the literature. *Pediatr Dermatol* 1989; **6**: 306–11.
20 Gottesfeld E, Silverman RA, Coccia PF *et al.* Transient blueberry muffin appearance of a newborn with congenital monoblastic leukemia. *J Am Acad Dermatol* 1989; **21**: 347–51.
21 Hansen RM, Barnett J, Hanson G *et al.* Aleukaemic leukemia cutis. *Arch Dermatol* 1986; **122**: 812–4.
22 Meuleman V, Degreef H. Acute myelomonocytic leukemia with skin localizations. *Dermatology* 1995; **190**: 346–8.
23 Monpoux F, Lacour J-P, Hatchuel Y *et al.* Congenital leukemia cutis preceding monoblastic leukemia by 3 months. *Paediatr Dermatol* 1996; **13**: 472–6.
24 Ohno S, Yokoo T, Ohta M *et al.* Aleukemic leukemia cutis. *J Am Acad Dermatol* 1990; **22**: 374–7.
25 Resnik KS, Brod BB. Leukemia cutis in congenital leukemia. *Arch Dermatol* 1993; **129**: 1301–6.
26 Hawthorne HC, Nelson JS, Witzleben CL *et al.* Blanching subcutaneous nodules in neonatal neuroblastoma. *J Pediatr* 1970; **77**: 297–300.
27 Shown TE, Durfee MF. Blueberry muffin baby: neonatal neuroblastoma with subcutaneous metastases. *J Urol* 1970; **104**: 193–5.
28 Kitagawa N, Arata J, Ohtsuki Y *et al.* Congenital alveolar rhabdomyosarcoma presenting as blueberry muffin baby. *J Dermatol* 1989; **16**: 409–11.
29 Shaffer MP, Walling HW, Stone MS. Langerhans cell histiocytosis presenting as blueberry muffin baby. *J Am Acad Dermatol* 2005; **53** (Suppl. 1): S143–6.

Neonatal purpura fulminans

Definition. Neonatal purpura fulminans is a potentially lethal disorder characterized by progressive haemorrhagic necrosis of the skin associated with cutaneous vascular thrombosis. It is usually due to a genetically transmitted thrombophilic disorder.

Aetiology. In the older child, purpura fulminans is a highly characteristic feature of meningococcal septicaemia, where it results from acquired deficiency of protein C or S [1], and it may occur as a sequel to a number of other infections, including common infections such as streptococcal infections, varicella and measles [2].

However, the occurrence of purpura fulminans in the neonate is almost always a reflection of homozygous deficiency of protein C or, less frequently, of protein S [3,4]. Protein C resistance has also been reported, due to mutations in the factor V gene [5,6].

Clinical features. The skin lesions most characteristically appear within the first 12 h of life [5,7], but their initial development may occasionally be delayed until later in infancy [8]. They generally comprise more or less symmetrical and well-defined 'lakes' of confluent ecchymosis, without petechiae. The lesions occur most often on the limbs, particularly at sites of pressure, but may also appear on the trunk and on the face and scalp. The onset is sudden, and the lesions enlarge rapidly, with coalescence and the development of haemorrhagic bullae and central necrosis. There is surrounding erythema and the lesions are tender. The patient is frequently febrile. These infants are also at risk of thrombosis in the central nervous system, and in the retinal vessels [7,9–11]. There is a substantial danger of internal haemorrhage, shock and death.

Diagnosis. Disseminated intravascular coagulation can also occur in association with severe bacterial infections in infants as well as in older children [12].

Treatment. Initially, fresh frozen plasma should be given with the minimum delay, in a dose of 10–15 ml/kg/12 h. If protein C deficiency is confirmed, onward therapy with protein C concentrate should continue until the skin lesions have healed [13]. Longer-term treatment is with oral anticoagulants. Liver transplantation has been undertaken successfully [14].

References

1 Powars DR, Rogers ZR, Patch MJ *et al.* Purpura fulminans in meningococcaemia associated with acquired deficiencies of proteins C and S. *N Engl J Med* 1987; **317**: 571–2.
2 Darmstadt GL. Acute infectious purpura fulminans: pathogenesis and medical management. *Pediatr Dermatol* 1998; **15**: 169–83.
3 Aiach M, Borgel D, Gaussem P *et al.* Protein C and protein S deficiencies. *Semin Hematol* 1997; **34**: 205–17.
4 Clouse LH, Comp PC. The regulation of hemostasis: the protein C system. *N Engl J Med* 1986; **314**: 1298–304.
5 Pipe SW, Schmaier AH, Nichols WC *et al.* Neonatal purpura fulminans in association with factor V R506Q mutation. *J Pediatr* 1996; **128**: 706–9.
6 Dahlbäck B. Resistance to activated protein C as risk factors for thrombosis: molecular mechanisms, laboratory investigation and clinical management. *Semin Hematol* 1997; **34**: 217–34.
7 Marlar RA, Neumann A. Neonatal purpura fulminans due to homozygous protein C or S deficiencies. *Semin Thromb Hemost* 1990; **16**: 299–309.
8 Tuddenham EG, Takase T, Thomas AE *et al.* Homozygous protein C deficiency with delayed onset of symptoms at 7 to 10 months. *Thromb Res* 1989; **53**: 475–84.
9 Marciniak E, Wilson HD, Marlar RA. Neonatal purpura fulminans: a genetic disorder related to the absence of protein C in blood. *Blood* 1985; **65**: 15–20.
10 Seligsohn U, Berger A, Abend M *et al.* Homozygous protein C deficiency manifested by massive venous thrombosis in the newborn. *N Engl J Med* 1984; **310**: 559–62.
11 Sills RH, Marlar RA, Montgomery RR *et al.* Severe homozygous protein C deficiency. *J Pediatr* 1984; **105**: 409–13.
12 Chuansumrit A, Hotrakitya S, Kriuavit A. Severe acquired neonatal purpura fulminans. *Clin Pediatr (Phila)* 1996; **35**: 373–6.
13 Muller F-M, Ehrenthal W, Hafner G, Schranz D. Purpura fulminans in severe congenital protein C deficiency: monitoring of treatment with protein C concentrate. *Eur J Pediatr* 1996; **155**: 20–5.
14 Casella JF, Lewis JH, Bontempo FA. Successful treatment of homozygous protein C deficiency by hepatic transplantation. *Lancet* 1988; **1**: 435–8.

Acute haemorrhagic oedema of childhood

Synonym
- Finkelstein's disease

Definition. Acute haemorrhagic oedema of infancy is a distinctive type of leukocytoclastic vasculitis occurring in children under the age of 2 years. It was first described under this title by Finkelstein [1]. Clinically it is manifest by a combination of purpura, often in a cockade pattern, and an inflammatory oedema of the limbs and face, with a tendency to recurrence in the short term and subsequent spontaneous resolution [2].

Aetiology. The cause of infantile acute haemorrhagic oedema remains unknown, and there has been considerable debate about its relationship to Henoch–Schönlein purpura. Many regard it as an analogue of Henoch–Schönlein purpura, occurring in the very young, and this view is to some degree supported by a report of associated haematuria and proteinuria [3,4]. It is generally believed that infections, drugs and vaccines might all be precipitating factors in individual cases [2,5], and a recent case report provided evidence of provocation by a primary cytomegalovirus infection [6].

Pathology. Histopathology of the skin lesions has shown changes varying from a perivascular lymphocytic and histiocytic infiltrate with erythrocyte extravasation, to fully developed leukocytoclastic vasculitis with fibrinoid necrosis [4,7–12].

Direct immunofluorescence has generally demonstrated fibrin and C3 in and around dermal vessels [5]. IgM has been found in about three-quarters of cases and IgA in about one-quarter.

Haematological studies have invariably shown normal platelet counts and no abnormalities of coagulation. Serum complement levels have been normal.

Transient renal involvement may be revealed by the occurrence of microscopic haematuria and mild proteinuria [3,4].

Clinical features. The condition is seen almost exclusively in children between the ages of 4 months and 2 years. It is manifest by the sudden appearance of oedematous papules that feature petechial haemorrhage, and that extend to form ecchymotic plaques. These lesions most typically occur on the face, especially the cheeks, eyelids and ears, and the limbs, particularly the hands and feet. These plaques are usually of cockade (rosette) type, with scalloped margins, but occasionally small lesions join up to produce a more reticulate pattern. The lesions often follow immunizations or an upper respiratory tract infection (URTI). Accompanying oedema of the hands, feet or whole limbs is common.

Associated oedema of the penis and scrotum [3,13,14] or oral petechial lesions [13] have also been reported. Other occasional cutaneous findings have included ecchymotic [13] or necrotic lesions of the ear [9,11] and urticarial lesions [3,10,14].

In contrast to the rather dramatic cutaneous lesions, the patient generally remains well, apart from the frequent presence of pyrexia, which is usually mild. Visceral lesions are conspicuous by their general absence, although gastrointestinal complications have very occasionally been reported, including melaena [2] and lethal intussusception [9].

Differential diagnosis. Awareness of this disease should make diagnosis fairly straightforward. Meningococcal septicaemia will require consideration, but the well-defined symmetrical areas of confluent ecchymosis seen in this disorder are highly distinctive. Certain other disorders may produce annular lesions in infants, particularly urticaria and erythema multiforme, but these generally lack a haemorrhagic element and do not usually take on a rosette configuration with scalloped margins. The same is true of the lesions of Sweet's syndrome, which may also occur occasionally in very young children [15,16]. Kawasaki disease characteristically causes oedematous induration of the hands and feet, and may result in a rash in which annular erythema may be a feature, but the skin lesions themselves are not as indurated, nor are they purpuric. One of the most important differential diagnoses to consider in any disorder presenting with intracutaneous haemorrhage in the very young is non-accidental injury.

Prognosis. Recurring crops of lesions may occur, but spontaneous resolution normally follows within about 2 weeks. Recurrence must be rare, but has occasionally occurred [13]. No significant long-term sequelae have been reported.

Treatment. No specific therapy is required.

References

1 Finkelstein H. *Lehrbuch der Säulingkrankheiten*, 4th edn. Amsterdam: Auff, 1938: 814–30.

2 Legrain V, Lejean S, Taieb A *et al.* Infantile acute hemorrhagic edema of the skin: study of ten cases. *J Am Acad Dermatol* 1991; **24**: 17–22.

3 Castel Y, Masse R, le Fur JM *et al.* L'oedème aigu hémorragique de la peau du nourrisson. *Ann Pediatr (Paris)* 1976; **23**: 653–66.

4 Gelmetti C, Barbagallo C, Cerri D *et al.* Acute hemorrhagic oedema of the skin in infants: clinical and pathogenic observations in seven cases. *Pediatr Dermatol News (Bari)* 1985; **4**: 23–34.

5 Saraclar Y, Tinaztepe K, Adalioglu G, Tuncer A. Acute hemorrhagic edema of infancy (AHEI)—a variant of Henoch–Schönlein purpura or a distinct clinical entity? *J Allergy Clin Immunol* 1990; **86**: 473–83.

6 Kuroda K, Yabunami H, Hisanaga Y. Acute haemorrhagic oedema of infancy associated with cytomegalovirus infection. *Br J Dermatol* 2002; **147**: 1254–7.

7 Krause I, Lazarov A, Rachmel A *et al.* Acute haemorrhagic oedema of infancy: a benign variant of leucocytoclastic vasculitis. *Acta Paediatr* 1996; **85**: 114–7.

8 Lambert D, Laurent R, Bouilly D *et al.* Oedème aigu hémorragique du nourrisson: données immunologiques et ultrastructurales. *Ann Dermatol Vénéréol* 1979; **106**: 975–87.

9 Larregue M, Lorette G, Prigent F *et al.* Oedème aigu hémorragique du nourrisson avec complication léthale digestive. *Ann Dermatol Vénéréol* 1980; **107**: 901–5.

10 Lesage B, Larregue M, Bouillet F *et al.* Oedème aigu hémorragique du nourrisson (purpura en cocarde avec oedème post-infectieux de Seidlmayer) et vascularité allergique. *Ann Pediatr (Paris)* 1975; **22**: 599–606.

11 Maleville J, Alt J, Grosshans E *et al.* Oedème aigu hémorragique du nourrisson: vascularité allergique dermique. *Bull Soc Fr Dermatol Syphiligr* 1973; **80**: 432–5.

12 Neri I, Patrizi A, Costa AM *et al.* Four cases of acute hemorrhagic edema of the skin in infants. *Pediatr Dermatol News (Bari)* 1987; **6**: 107–10.

13 Dubin BA, Bronson DM, Eng AN. Acute hemorrhagic edema of childhood: an unusual variant of leukocytoclastic vasculitis. *J Am Acad Dermatol* 1990; **23**: 347–50.

14 Laugier P, Hunziker N, Reiffers J *et al.* L'oedème aigu hémorragique de la peau du nourrisson (purpura en cocarde avec oedème). *Dermatologica* 1970; **141**: 113–8.

15 Dunn TR, Saperstein HW, Biederman A *et al.* Sweet syndrome in a neonate with aseptic meningitis. *Pediatr Dermatol* 1992; **9**: 288–92.

16 Hassouna L, Nabulsi-Khalil M, Mroueh SM *et al.* Multiple erythematous tender papules and nodules in an 11-month-old boy. *Arch Dermatol* 1996; **132**: 1507–10.

Disorders of subcutaneous fat

Terminological confusion has bedevilled the literature on disorders of subcutaneous fat in the newborn. The four conditions described below are essentially separate entities, although not without some clinical and pathological overlap.

Cold panniculitis (see also Chapter 46)

Definition. Cold panniculitis is a distinctive form of panniculitis provoked directly by cold exposure, to which infants appear particularly predisposed.

Aetiology. The fat of the newborn appears to be more highly saturated than that of older children and adults, with the effect that it solidifies at a higher temperature [1,2]. The possible clinical relevance of this phenomenon was demonstrated by experiments in which young pigs were fed fats of various degrees of saturation, producing corresponding differences in the saturation of their own subcutaneous fat [3]. The subsequent application of ice to the skin induced panniculitis only in the pigs fed saturated fat.

Applying ice for 50 seconds causes panniculitis in all newborn infants, in only 40% of 6-month-olds and almost never in 9-month-olds [4].

Cold panniculitis in infancy has most often followed exposure of the cheeks to: (i) extremely cold air [5–7]; (ii) ice bags applied as a therapy for supraventricular tachycardia [8,9]; or (iii) lollipops [10–12].

Pathology [10,13]. An early feature in skin biopsies is a lymphohistiocytic infiltrate around blood vessels at the junction of the dermis and subcutaneous fat. After a few days, lipocyte rupture leads to the formation of cystic cavities surrounded by areas of marked infiltration by lymphocytes and histiocytes, with a few neutrophils and eosinophils.

Clinical features. Indurated, warm, red, subcutaneous plaques and nodules appear within hours or days of appropriate cold exposure.

The lesions have generally occurred on the cheeks in infants, although they may be seen elsewhere in older children and adults [13,14].

Prognosis and treatment. The induration resolves over a period of a week or so, often leaving some residual post-inflammatory hyperpigmentation. No treatment is required, although it is clearly advisable for the child to avoid further cold exposure of the type that precipitated the lesions.

References

1 Hirsch J, Farquar JW, Ahrens EH *et al.* Studies of adipose tissue in man: a microtechnique for sampling and analysis. *Am J Clin Nutr* 1960; **8**: 499–511.

2 Sweeney MJ, Etteldorf JN, Throop LJ *et al.* Diet and fatty acid distribution in subcutaneous fat and in the cholesterol–triglyceride fraction of serum in young infants. *J Clin Invest* 1963; **42**: 1–9.

3 Adams JE, Foster JH, Faulk WH *et al.* Experimental production of subcutaneous fat necrosis by general hypothermia: relation to the chemical composition of fat. *Surg Forum* 1954; **5**: 556–63.

4 Lemez L. Beitrag zur Pathogenese der subcutanen Fettgewebsnecrose neugeborener (Sog. Sclerodermia neonatorum) an der Hand einer Kaltereaktion des subcutanen Fettgewebes bei neugeborenen und jungen Sauglingen: II Mitteilung. *Z Kinderheilkd* 1928; **46**: 323–69.

5 Haxthausen H. Adiponecrosis e frigore. *Br J Dermatol* 1941; **53**: 83–9.

6 Rotman H. Cold panniculitis in children: adiponecrosis e frigore of Haxthausen. *Arch Dermatol* 1966; **94**: 720–1.

7 Lowe LB. Cold panniculitis in children. *Am J Dis Child* 1968; **115**: 709–13.

8 Mimouni F, Merlob P, Metzker A, Reisner SH. Supraventricular tachycardia: the icebag technique may be harmful in newborn infants? *J Pediatr* 1983; **103**: 337.

9 Ter Poorten JC, Hebert AA, Ilkiw R. Cold panniculitis in a neonate. *J Am Acad Dermatol* 1995; **33**: 383–5.

10 Duncan WC, Freeman RG, Heaton CL. Cold panniculitis. *Arch Dermatol* 1966; **94**: 722–4.

11 Epstein EH, Oren ME. Popsicle panniculitis. *N Engl J Med* 1970; **282**: 966–7.

12 Rajkumar SV, Laude TA, Russo RM *et al.* Popsicle panniculitis of the cheeks. *Clin Pediatr (Phila)* 1976; **15**: 619–21.

13 Solomon LM, Beerman H. Cold panniculitis. *Arch Dermatol* 1963; **88**: 897–900.

14 Beacham BE, Cooper PH, Buchanan CS *et al.* Equestrian cold panniculitis in women. *Arch Dermatol* 1980; **116**: 1025–7.

Neonatal cold injury

Definition. Neonatal cold injury is a disorder, now rare in developed countries, in which cold exposure of a small-for-dates neonate causes hypothermia associated with lethargy and generalized pitting oedema of the skin, clinically and pathologically distinct from sclerema neonatorum.

Aetiology [1–4]. Low environmental temperature has been the principal cause of virtually all reported cases of this disorder. Other factors that appear to have predisposed babies to this complication of cold exposure include intrauterine growth retardation, which results in a relatively thin panniculus, and tight wrappings, which would restrict muscular activity. Immaturity of either reflex shivering mechanisms or of protective vasomotor responses would also increase the risk. The condition seems to be much less common in the UK now than it was 40 years ago, probably because of improved heating in homes, very much reduced frequency of home delivery and abandonment of the previous habit of bathing babies at birth.

Pathology [5]. The panniculus is generally thin. Otherwise, there is little obvious abnormality apart from dilatation of dermal blood vessels. Profuse exudation of clear fluid from the cut surface at post-mortem suggests that the induration is due to oedema.

The dominant post-mortem finding in fatal cases has been massive pulmonary haemorrhage [2,4].

Clinical features [1–4]. The infant is usually a full-term neonate, born at home, but small for gestational age. In the great majority of cases, presentation is within the first 4 days of life, and usually during the first 24 h. The most striking features are intense erythema or cyanosis of the face and extremities, and firm, pitting oedema beginning at the extremities and spreading centrally, and becoming progressively more indurated in a proportion of cases. Petechiae have occasionally been observed.

The skin feels cold, and the baby is usually hypothermic. Associated non-cutaneous features of cold injury are generally present, and may occur in the absence of skin changes. These include immobility, drowsiness, poor feeding, vomiting, oliguria and gastrointestinal bleeding with vomiting of altered blood or melaena.

The condition appears to have been associated with a high mortality, around 25%.

Diagnosis. The main source of diagnostic confusion is with sclerema neonatorum. The generally healthy state of the infant

before the onset of the cutaneous induration, its pitting nature, the history of cold exposure and a low rectal temperature all help to distinguish the two disorders. It is possible that the late non-pitting induration of the skin, which supervenes in some cases [2], may in fact be genuine sclerema.

References

1 Arneil GC, Kerr MM. Severe hypothermia in Glasgow infants in winter. *Lancet* 1963; **ii**: 756–9.
2 Bower RD, Jones LF, Weeks MM. Cold injury in the newborn: a study of 70 cases. *BMJ* 1960; **1**: 303–9.
3 Mann TP. Hypothermia in the newborn: a new syndrome? *Lancet* 1955; **i**: 613–4.
4 Mann TP, Elliott RIK. Neonatal cold injury due to accidental exposure to the cold. *Lancet* 1957; **i**: 229–34.
5 Elliott RIK. Sclerema. *Proc R Soc Med* 1959; **52**: 1018–21.

Subcutaneous fat necrosis of the newborn

Definition. Subcutaneous fat necrosis of the newborn is an uncommon and transient disorder of neonates in which focal areas of fat necrosis cause nodular skin lesions. This nodular necrosis of subcutaneous fat may be associated with hypercalcaemia.

Aetiology. Subcutaneous fat necrosis generally occurs in full-term or post-term infants of normal birth weight during the first 6 weeks of life. The precise cause is unestablished, but a variety of insults appear to have contributed in individual cases. These have included birth asphyxia [1–4], maternal pre-eclampsia [5,6], maternal diabetes [7], obstetric trauma [8–10] and hypothermia [11–13]. In many cases, there is no convincing history of any of these putative predisposing causes. It has been suggested that localized tissue hypoxia—albeit transient—may be the common link in every case [14]. This might explain the predominant localization of lesions to sites such as the shoulders and buttocks, where mechanical pressure might further compromise the circulation. However, intermittent reports of an analogous type of fat necrosis occurring in infants undergoing hypothermic cardiac surgery implies that the common factor is perhaps more likely to be cold.

It has been suggested that another important predisposing factor for the development of subcutaneous fat necrosis might be a protease inhibitor deficiency, analogous to the α_1-antitrypsin deficiency seen in some patients with panniculitis [15]. Such a deficiency might allow trauma to trigger development of lesions, but perhaps it would be more likely that lesions developing in this way would show the pathological features of panniculitis rather than fat necrosis.

An interesting concept [13] is that subcutaneous fat necrosis of the newborn might be a disorder of brown fat, which is present in those areas most frequently affected [16].

The appearance of subcutaneous fat necrosis has been reported after intravenous prostaglandin E_1 (PGE_1) administration for congenital heart disease, and the suggestion was made that the PGE_1 may have been responsible [17].

A number of infants have now been reported in whom subcutaneous fat necrosis was associated with hypercalcaemia [18–26]. This complication probably occurs in around a quarter of all cases, and appears to occur more frequently in infants with more extensive disease, and almost exclusively when the trunk is affected [4].

The cause of the hypercalcaemia is unknown. Suggested mechanisms have been reviewed by Hicks *et al.* [27] and by Burden and Krafchik [4]. It currently appears most likely that it reflects increased calcium absorption due to extrarenal production of 1,25-dihydroxyvitamin D, which has been observed in other granulomatous disorders including sarcoidosis [4,19,28,29]. Elevated parathormone levels have been reported in one case [24], but post-mortem studies have not revealed any evidence of parathyroid hyperplasia. The finding of increased urinary excretion of PGE_1 led to the suggestion that increased bone calcium resorption might be responsible [25,30].

Pathology [3,31–33]. Biopsies of the affected subcutaneous tissue show patchy fat necrosis, with a granulomatous inflammatory reaction of foreign-body type, and fibrosis. Both the fat cells and the giant cells contain needle-shaped clefts, which may be radially arranged. Fibrotic obliteration of small arterioles has also been observed [34]. Calcium deposits are commonly found in the necrotic fat.

Ultrastructural examination has shown parallel aggregations of electron-lucent needle-shaped spaces within adipocytes [33].

Similar changes in visceral adipose tissue have been reported in post-mortem studies of affected infants [5,9]. Widespread calcium deposition in internal organs has also been shown in post-mortem specimens from hypercalcaemic cases [6,21] and nephrocalcinosis has been observed in such infants during life [23,35].

Transient thrombocytopenia has been reported during the period of initial development of the lesions, possibly due to sequestration of platelets [6,14,36].

Plasma lipid abnormalities have been reported in a neonate with subcutaneous fat necrosis, but their relevance was unclear [37].

Clinical features. Infants who develop subcutaneous fat necrosis are generally full-term or post-term neonates of normal weight. Nodular thickening of the subcutaneous tissues is usually first detected between the second and 21st days of life. Sometimes, the changes are present at birth, and, rarely, they may appear as late as the sixth week. The nodules tend to be symmetrically distributed, and show a predilection for buttocks, thighs, shoulders, back, cheeks and arms. Lesions may be single or multiple, rounded or oval, and pea-sized or many centimetres in diameter. They are initially discrete, but may fuse to form large plaques. The overlying skin is often red or bluish red. The nodules feel rubbery or hard, and are not attached to the deeper structures. The lesions may be painful [38]. New nodules may continue to develop for a week or more.

In most cases, the child's health is not substantially impaired, and within a few months the nodules disappear. Where calcium deposition is marked, the lesions may take rather longer to resolve [39]. Usually no trace of the nodules remains, but there may be slight atrophy [12]. Rarely, the nodules may ulcerate, discharge their fatty contents and leave scars.

The condition has occasionally been fatal, particularly when visceral fat has been involved [5], or where there has been complicating hypercalcaemia [24].

Diagnosis. Neonates delivered by forceps may develop subcutaneous nodules where the forceps were applied, presumably as a result of traumatic fat necrosis.

Subcutaneous fat necrosis of the newborn was in the past frequently confused with sclerema neonatorum. Occasionally, the two conditions may occur simultaneously [40].

All infants who have experienced subcutaneous fat necrosis should have their serum calcium measured on presentation and a few weeks later. If hypercalcaemia is present, its cause requires thorough investigation to exclude disorders such as primary hyperparathyroidism and vitamin D intoxication.

Treatment. None is generally required.

Hypercalcaemia may warrant treatment by administration of furosemide, dietary restriction of calcium and vitamin D, and sometimes also by oral corticosteroid administration. There may be a role for bisphosphonate administration in some cases [41].

References

1 Holtzel A. Subcutaneous fat necrosis of the newborn. *Arch Dis Child* 1951; **26**: 89–91.
2 Mogilner BM, Alkalay A, Nissim F *et al.* Subcutaneous fat necrosis of the newborn. *Clin Pediatr (Phila)* 1981; **20**: 748–50.
3 Tsuji T. Subcutaneous fat necrosis of the newborn: light and electron microscopic studies. *Br J Dermatol* 1976; **95**: 407–16.
4 Burden AD, Krafchik BR. Subcutaneous fat necrosis of the newborn: a review of 11 cases. *Pediatr Dermatol* 1999; **16**: 384–7.
5 Flory CM. Fat necrosis of the newborn. Report of a case with necrosis of the subcutaneous and visceral fat. *Arch Pathol* 1948; **45**: 278–88.
6 Ostwalt GC, Montes LF, Cassady G. Subcutaneous fat necrosis of the newborn. *J Cutan Pathol* 1978; **5**: 193–9.
7 Steiness I. Subcutaneous fat necrosis of the newborn (adiponecrosis subcutanea neonatorum) and maternal diabetes mellitus. *Acta Med Scand* 1961; **170**: 411–6.
8 McDonald R. Subcutaneous fat necrosis and sclerema neonatorum. *S Afr Med J* 1955; **29**: 1007–12.
9 Kohnstam GLS, Herbert FK. Sclerema neonatorum and its relation to fat necrosis. *Arch Dis Child* 1927; **2**: 349–57.
10 Noojin RO, Pace BF, Davis HG. Subcutaneous fat necrosis of the newborn: certain etiologic considerations. *J Invest Dermatol* 1949; **12**: 331–4.
11 Blake HA, Goyette EM, Lyter CS. Subcutaneous fat necrosis complicating thermia. *J Pediatr* 1955; **46**: 78–80.
12 Duhn R, Schoen EJ, Siu M. Subcutaneous fat necrosis with extensive calcification after hypothermia in two newborn infants. *Pediatrics* 1968; **41**: 661–4.
13 Taieb A, Douard D, Sarlangue J *et al.* Trois cas de cystostéatonécrose néonatale: discussion physiopathologique. *Presse Méd* 1986; **15**: 2197–200.
14 Chen TH, Shewmake SW, Hansen DD *et al.* Subcutaneous fat necrosis of the newborn: a case report. *Arch Dermatol* 1981; **117**: 36–7.
15 Silverman AK. Panniculitis in infants. *Arch Dermatol* 1985; **121**: 834.
16 Nedergaard J, Lindberg O. The brown fat cell. *Int Rev Cytol* 1982; **74**: 187–286.
17 Sharata H, Postellon DC, Hashimoto K. Subcutaneous fat necrosis, hypercalcemia and prostaglandin E. *Pediatr Dermatol* 1995; **12**: 43–7.
18 Barltrop D. Hypercalcaemia associated with neonatal subcutaneous fat necrosis. *Arch Dis Child* 1963; **38**: 516–8.
19 Cook JS, Stone MS, Hansen JR. Hypercalcaemia in association with subcutaneous fat necrosis of the newborn: studies of calcium regulating hormones. *Pediatrics* 1992; **90**: 93–6.
20 Fernandez-Lopez E, Garcia-Dorado J, de Unamuno P *et al.* Subcutaneous fat necrosis of the newborn and idiopathic hypercalcemia. *Dermatologica* 1990; **180**: 250–4.
21 Martin MM, Steven EM. Subcutaneous fat necrosis of the newborn with calcification of the tissues. *Arch J Dis Child* 1957; **32**: 146–8.
22 Norwood-Galloway A, Lebwohl M, Phelps RG *et al.* Subcutaneous fat necrosis of the newborn with hypercalcemia. *J Am Acad Dermatol* 1987; **16**: 435–9.
23 Sharlin DO, Koblenzer P. Necrosis of subcutaneous fat with hypercalcaemia: a puzzling and multifaceted disease. *Clin Pediatr (Phila)* 1970; **9**: 290–4.
24 Thomsen RJ. Subcutaneous fat necrosis of the newborn and idiopathic hypercalcaemia: report of a case. *Arch Dermatol* 1980; **116**: 1155–8.
25 Veldhuis JD, Kulin HE, Demers LM *et al.* Infantile hypercalcaemia with subcutaneous fat necrosis: endocrine studies. *J Pediatr* 1979; **95**: 460–2.
26 Yasuda T, Sunami S, Ogura N *et al.* Infantile hypercalcaemia with subcutaneous fat necrosis. *Acta Paediatr Scand* 1986; **75**: 1042–5.
27 Hicks MJ, Levy ML, Alexander J, Flaitz CM. Subcutaneous fat necrosis of the newborn and hypercalcemia; case report and review of the literature. *Pediatr Dermatol* 1993; **10**: 271–6.
28 Finne PH, Sanderud J, Aksnes L *et al.* Hypercalcemia with increased and unregulated 1,25-dihydroxyvitamin D production in a neonate with subcutaneous fat necrosis. *J Pediatr* 1988; **112**: 792–4.
29 Kruse K, Irle U, Uhlig R. Elevated 1,25-dihydroxy-vitamin D serum concentrations in infants with subcutaneous fat necrosis. *J Pediatr* 1993; **122**: 460–3.
30 Sharata H, Postellon DC, Hashimoto K. Subcutaneous fat necrosis of the newborn, hypercalcemia and prostaglandin E. *Pediatr Dermatol* 1995; **12**: 43–7.
31 Balazs M. Subcutaneous fat necrosis of the newborn with emphasis on ultrastructural studied. *Int J Dermatol* 1987; **26**: 227–30.
32 Pasyk K. Studies on subcutaneous fat necrosis of the newborn. *Virchows Arch* 1978; **379**: 243–59.
33 Friedman SJ, Winkelman RK. Subcutaneous fat necrosis of the newborn: light, ultrastructural and histochemical microscopic studies. *J Cutan Pathol* 1989; **16**: 99–105.
34 Taieb A, Douard D, Maleville J. Subcutaneous fat necrosis and brown fat deficiency. *J Am Acad Dermatol* 1987; **26**: 227–30.
35 Michael AF, Hong R, West CD. Hypercalcaemia in infancy associated with subcutaneous fat necrosis and calcification. *Am J Dis Child* 1962; **104**; 235–44.
36 Wolach B, Raas-Rothchild A, Vogel R *et al.* Subcutaneous fat necrosis with thrombocytopenia in a newborn infant. *Dermatologica* 1990; **181**: 54–5.
37 Vonk J, Janssens PMW, Demacker PNM, Folkers E. Subcutaneous fat necrosis in a neonate, in association with aberrant plasma lipid and lipoprotein values. *J Pediatr* 1993; **123**: 462–4.
38 Rosbotham JL, Johnson A, Haque KN, Holden CA. Painful subcutaneous fat necrosis of the newborn associated with the intra-partum use of a calcium channel blocker. *Clin Exp Dermatol* 1998; **23**: 19–21.
39 Shackelford GD, Barton LL, McAlister WH. Calcified subcutaneous fat necrosis in infancy. *J Can Assoc Radiol* 1975; **26**: 203–7.
40 Jardine D, Atherton DJ, Trompeter RS. Sclerema neonatorum and subcutaneous fat necrosis of the newborn in the same infant. *Eur J Pediatr* 1990; **150**: 125–6.
41 Rice AM, Rivkees SA. Etidronate therapy for hypercalcemia in subcutaneous fat necrosis of the newborn. *J Pediatr* 1999; **134**: 349–51.

Subcutaneous fat necrosis following hypothermic cardiac surgery in infancy

There have been several reports of the occurrence of lesions analogous to those of subcutaneous fat necrosis of the newborn in children who have had cardiac surgery [1–5], and this may be a relatively frequent complication of such surgery. It appears likely that the principal provocative factor in these cases was the cutaneous application of ice to induce hypothermia, although trauma and/or hypoxia may have contributed. It is noteworthy that these children appear to have developed lesions of subcutaneous fat necrosis rather than cold panniculitis. The ages of the children at the time of surgery varied from 12 days to 20 months. Lesions appeared between 14 and 30 days later, principally at the sites subjected to the greatest cold exposure. Hypercalcaemia may occur [3]. The lesions resolve within a few weeks and no treatment is required.

References

1 Blake HA, Goyette EM, Lyter CS *et al.* Subcutaneous fat necrosis complicating hypothermia. *J Pediatr* 1955; **46**: 78–80.
2 Collins HA, Stahlman M, Scott HW. The occurrence of subcutaneous fat necrosis in an infant following induced hypothermia used as an adjuvant in cardiac surgery. *Ann Surg* 1953; **133**: 880–5.
3 Glover MT, Catterall MD, Atherton DJ. Subcutaneous fat necrosis in two infants after hypothermic cardiac surgery. *Pediatr Dermatol* 1991; **8**: 210–2.
4 Silverman AK, Michels EH, Rasmussen JE. Subcutaneous fat necrosis in an infant occurring after hypothermic cardiac surgery. *J Am Acad Dermatol* 1986; **15**: 331–6.
5 Chuang S-D, Chiu H-C, Chang C-C. Subcutaneous fat necrosis of the newborn complicating hypothermic cardiac surgery. *Br J Dermatol* 1995; **132**: 805–10.

Sclerema neonatorum

Aetiology. Sclerema neonatorum is a very rare disorder that almost always appears during the first week of life, although it has occasionally been recorded later in infants born preterm. It has generally been considered a non-specific sign of grave illness, and has been associated with a mortality up to 75% [1,2]. Prematurity and smallness-for-dates appear to be frequent predisposing factors [2]. It has been recorded as already present at birth in infants subjected to placental insufficiency [3]. The disorder does not seem to occur in otherwise healthy infants, and most characteristically develops during the course of one of a wide variety of severe illnesses, particularly serious infections, congenital heart disease and other major developmental defects [2]. A proportion of these infants has been hypothermic, and occasionally sclerema has been described as a complication of neonatal cold injury [4]; nevertheless, cold does not appear to be an important aetiological factor in the majority of cases.

Lipolytic mechanisms are poorly developed in the newborn, particularly in those born preterm [5]. The maturation of these enzyme systems might be further compromised by major infection or hypoxia. It has been suggested that sclerema might reflect defective lipolysis within adipose tissue, which would result in failure of fat mobilization, and an impaired capacity to maintain body temperature. It has been reported that the ratio of saturated to unsaturated fatty acids is relatively high in the adipose tissue of all neonates, and that this ratio was even higher in an infant with sclerema [6,7]. This would lead to a raised melting point, and it is possible that the induration of subcutaneous fat, which is the major clinical feature of sclerema, might reflect its solidification due to a fall in the temperature of the adipose tissue during peripheral circulatory collapse [8].

Pathology [7–9]. Often, surprisingly little abnormality has been apparent histologically. However, in most cases the subcutaneous fat layer appears to be thickened, due to an increased size of the individual lipocytes and to an increased width of the intersecting bands of connective tissue, probably due to oedema. There is very little evidence of fat necrosis and, generally, only the slightest indication of inflammation. The most characteristic histological feature of sclerema neonatorum is the presence of radially arranged, needle-shaped clefts in adipocytes and, occasionally, in multinucleate giant cells, reflecting the presence of crystals prior to processing.

Clinical features [8,10]. The affected infant is generally severely ill at the time of onset of sclerema. Woody induration of the skin starts on the buttocks, thighs or calves and extends rapidly and symmetrically to involve almost the whole surface, with the exception of the palms, soles and genitalia. This skin is hard and cold to touch, and yellowish white in colour, often with purplish mottling. It will not pit with pressure. Mobility is limited, and as a result the face may take on a mask-like expression.

The prognosis is poor, and is largely determined by the nature of the underlying disease. In spite of advances in the treatment of many of the predisposing disorders, particularly sepsis, the mortality probably remains in excess of 50%. In infants who survive, the appearance of the skin returns to normal without long-term complications such as calcification.

Diagnosis. The main area of diagnostic confusion has been between sclerema and subcutaneous fat necrosis. It is now clear that the two disorders are distinct pathologically and clinically [10], although they can occur together on occasions [11]. Table 17.4 outlines their distinguishing features.

Scleroedema has been reported in an infant at 2 weeks of age, and was distinguished from sclerema principally on histological grounds [12]. Turner's syndrome is often recognizable at birth by the presence in a female of firm, non-pitting lymphoedema of the dorsa of the hands and feet, associated with low birth weight and loose folds of skin around the neck. Where primary lymphoedema occurs in neonates, it will already be clinically evident at birth.

Table 17.4 Distinctions between neonatal cold injury, sclerema and subcutaneous fat necrosis.

	Neonatal cold injury	Sclerema	Subcutaneous fat necrosis
Frequency	Previously common, now rare	Rare, usually seen in neonatal intensive care units	Uncommon
Patient	Full-term neonates often small-for-dates, born at home	Usually severely ill neonates, often preterm or small-for-dates or post-term	Healthy infants, usually full term
Onset	During the first week	Almost always during the first week	1–6 weeks
Sites	Extremities, spreading centrally	Lower limbs initially becoming generalized	Trunk, buttocks, thighs, arms, face
Appearance	Pitting oedema initially with erythema or cyanosis of face and extremities	Diffuse, yellow-white woody induration with immobility of limbs	Firm, reddish-violet, subcutaneous nodules
Histology	Thin panniculus	Subtle; thickened connective tissue trabeculae; radial needle-like clefts	Granulomatous inflammation and fat necrosis
Prognosis	Mortality around 25%	Poor, mortality greater than 50% in past	Generally excellent

The condition may be familial, and generally first affects the legs, particularly the lower legs. The presence of oedema at birth, and its very slow progression in an otherwise healthy neonate, distinguish primary lymphoedema from sclerema.

Treatment. Treatment is primarily that of any underlying disease. Systemic corticosteroids are probably not effective [1], but there is evidence that repeated exchange transfusions may substantially reduce mortality [13,14].

References

1 Levin SE, Bakst CM, Isserow L. Sclerema neonatorum treated with corticosteroids. *BMJ* 1961; **2**: 1533–6.
2 Warwick W, Ruttenberg HD, Quie PG. Sclerema neonatorum: a sign not a disease. *JAMA* 1963; **184**: 680–3.
3 Molteni RA, Ames MR. Sclerema neonatorum and joint contractures at birth as a potential complication of chronic *in utero* hypoxia. *Am J Obstet Gynecol* 1986; **155**: 380–1.
4 Bower BD, Jones LF, Weeks MM. Cold injury of the newborn: a study of 70 cases. *BMJ* 1960; **1**: 303–9.
5 Rafstedt S. Studies in serum lipids and lipoproteins in infancy and childhood. *Acta Paediatr Scand* 1955; **44** (Suppl. 102): 1906–7.
6 Channon HJ, Harrison GA. The chemical nature of the subcutaneous fat in the normal and sclerematous infant. *Biochem J* 1926; **20**: 84–92.
7 Kellum RE, Ray TL, Brown GR. Sclerema neonatorum: report of a case and analysis of subcutaneous and epidermal lipids by chromatographic methods. *Arch Dermatol* 1968; **97**: 372–80.
8 Hughes WE, Hammond ML. Sclerema neonatorum. *J Pediatr* 1948; **32**: 676–92.
9 Pasyk K. Sclerema neonatorum: light microscopic studies. *Virchows Arch* 1980; **388**: 87–103.
10 Fretzin DF, Arias AM. Sclerema neonatorum and subcutaneous fat necrosis of the newborn. *Pediatr Dermatol* 1987; **4**: 112–22.
11 Jardine D, Atherton DJ, Trompeter RS. Sclerema neonatorum and subcutaneous fat necrosis of the newborn in the same infant. *Eur J Pediatr* 1990; **150**: 125–6.
12 Heilbron B, Saxe N. Scleredema in an infant. *Arch Dermatol* 1986; **122**: 1417–9.
13 Pearse RG, Sauer PJ. Exchange transfusion in treatment of serious infection in the newborn and sclerema neonatorum. *Arch Dis Child* 1978; **53**: 262.
14 Pelet B. C3, factor B, α_1-antitrypsin in neonatal septicaemia with sclerema. *Arch Dis Child* 1980; **55**: 782–8.

Infections

Although infectious diseases affecting the skin are described in detail elsewhere in this book, the clinical features of some of the more important infections affecting the skin during the neonatal period will be briefly considered here, because of their importance in the differential diagnosis of other dermatoses.

Viral infections

Neonatal herpes simplex

HSV infection in the newborn is generally a serious disease with a high mortality. The incidence is about 7/100 000 life births and up to 40% of such infants are premature [1]. The majority of such infections result from transmission of HSV type 1 (20%) and HSV type 2 (80%), by contact with an infected genital tract during delivery [1–3]. However, intrauterine HSV infection rarely occurs (5% of all neonatal HSV) [4], due either to transmission across the placenta [5], or to ascending infection related to prolonged rupture of the fetal membranes [6]. Intrauterine HSV is usually due to HSV type 2 and is more common when the HSV is a primary and/or disseminated infection in the mother.



Fig. 17.7 Neonatal herpes simplex: congenital ulceration and scarring at 10 days. This infant responded rapidly to aciclovir therapy and is now entirely healthy apart from residual atrophy.

Infection may also occur postnatally by contact with non-genital sites, both maternal and non-maternal [7].

Most infants with neonatal HSV are born to mothers who have no previous history of genital HSV and who show no overt clinical signs of herpes at delivery.

Over 70% of all infants with neonatal HSV have skin or mucosal lesions [8–10], but only in about 10% will the disease be confined to the skin. The skin lesions appear between day 2 and 20, unless intrauterine infection has occurred, in which case they will generally already be present at birth [4,11,12].

Isolated or grouped vesicles are the most common type of lesion, and the scalp and face are the most commonly affected sites, although lesions can occur at virtually any site (Fig. 17.7). Occasionally, the eruption may be generalized and bullous, and widespread erosions may occur without obvious vesicles or bullae, mimicking epidermolysis bullosa [12]. When infection is acquired during birth, the initial lesions have a predilection for the scalp in vertex presentations, and the perianal area in breech presentations [13]. Lesions may also be localized to areas of intrauterine or intrapartum skin damage [14], such as the area in which a fetal scalp electrode has been sited. Areas of cutaneous atrophy or scarring are not infrequent in the intrauterine form, and vesicular lesions may continue to appear within or at the periphery of these areas [4,15]. A zosteriform pattern has also been described [16], and, in some cases, localized or generalized non-vesicular erythematous macules. Congenital cutaneous calcification has been reported in a child with intrauterine HSV infection [17].

Oral lesions are also frequent, and take the form of erosions on the tongue, palate, gingivae and buccal mucosa.

A fatal outcome is unusual when infection is limited to the skin, mouth and eyes, but mortality and long-term damage are more likely when the central nervous system is involved or when infection is disseminated, even when appropriate antiviral therapy is given. Mortality is higher when infection is with HSV-2 [2].

Early recognition and adequate early treatment with aciclovir does appear to protect infants from dissemination of infection, where this is initially confined to the skin [14,15,18].

Herpes simplex infection in premature infants is even more severe in terms of clinical outcomes. In one study, nine of 12 infants died and the other three had neurological sequelae [19]. It is also more difficult to diagnose as vesicular lesions are found in less than half of cases. It often presents with respiratory distress and thrombocytopenia. Non-specific signs such as lethargy, hypotension, raised aspartate transaminase and fits have also been observed. Diagnosis is by culture/PCR but treatment with intravenous aciclovir should not be delayed if HSV is suspected.

References

1 Sauerbrei A, Wutzler P. Herpes simplex and varicella-zoster virus infections during pregnancy: current concepts of prevention, diagnosis and therapy. Part 1: Herpes simplex virus infections. *Med Microbiol Immunol* 2007; **196**: 89–94.
2 Malm G, Berg U, Forsgren M. Neonatal herpes simplex: clinical findings and outcome in relation to type of maternal infection. *Acta Paediatr* 1995; **84**: 256–60.
3 Nahmias AJ, Josey WE, Naib ZM. Neonatal herpes simplex infection: role of genital infection in mother as the source of virus in the newborn. *JAMA* 1967; **199**: 164–8.
4 Hutto C, Arvin A, Jacobs R *et al.* Intrauterine herpes simplex virus infections. *J Pediatr* 1987; **110**: 97–101.
5 Seiber OF, Fulginiti VA, Brazie J *et al. In utero* infection of the fetus by herpes simplex virus. *J Pediatr* 1966; **69**: 30–4.
6 Nahmias AJ, Josey WE, Naib ZM *et al.* Perinatal risk associated with maternal genital herpes simplex virus infection. *Am J Obstet Gynecol* 1971; **110**: 825–37.
7 Light IJ. Postnatal acquisition of herpes simplex virus by the newborn infant: a review of the literature. *Pediatrics* 1979; **63**: 480–2.
8 Nahmias AJ, Alford CA, Korones SB. Infection of the newborn with *herpesvirus hominis*. *Adv Pediatr* 1970; **17**: 185–226.
9 Whitley RJ, Nahmias AJ, Visintine AM *et al.* The natural history of herpes simplex virus infection of the mother and newborn. *Pediatrics* 1980; **66**: 489–94.
10 Whitley RJ, Corey L, Arvin A *et al.* Changing presentation of herpes simplex virus infections in neonates. *J Infect Dis* 1988; **158**: 109–16.
11 Hanshaw JB. *Herpesvirus hominis* infections in the fetus and the newborn. *Am J Dis Child* 1973; **126**: 546–55.
12 Honig PJ, Brown D. Congenital herpes simplex virus infection initially resembling epidermolysis bullosa. *J Pediatr* 1982; **101**: 958–60.
13 Hodgman JE, Freedman RI, Levan NE. Neonatal dermatology. *Pediatr Clin North Am* 1971; **18**: 713–56.
14 Lauber J, Eerkes K, Storer J. Herpes simplex virus infection complicating amniotic band syndrome in a newborn. *Cutis* 1989; **44**: 64–6.
15 Glover MT, Atherton DJ. Congenital infection with herpes simplex virus type 1. *Pediatr Dermatol* 1987; **4**: 336–40.
16 Music SI, Fine EM, Togo Y. Zoster-like disease in the newborn due to herpes simplex virus. *N Engl J Med* 1971; **284**: 24–6.
17 Beers BB, Flowers FP, Sherertz EF *et al.* Dystrophic calcinosis cutis secondary to intrauterine herpes simplex. *Pediatr Dermatol* 1986; **3**: 208–11.
18 Englund JA, Fletcher CV, Balfour HH. Acyclovir therapy in neonates. *J Pediatr* 1991; **119**: 129–35.
19 O'Riordan DP, Golden WC, Aucott SW *et al.* Herpes simplex virus infections in premature infants. *Pediatrics* 2006; **118**: 1612–20.

Fetal varicella syndrome (FVS)

Approximately 90% of adults are seropositive for the varicella-zoster virus antibody. If a woman is seronegative, she may develop chickenpox during pregnancy; this occurs in up to 10 per 10 000 pregnancies [1–3]. The infection may be transmitted to the fetus, probably in about 25% of cases. Such transmission of varicella-zoster virus infection to the fetus is considered to be very rare in mothers who develop herpes zoster during pregnancy [4].

Table 17.5 Principal clinical features of the fetal varicella syndrome.

Low birth weight
Cutaneous lesions:
Localized absence of skin, usually on a limb
Scars, often of dermatomal outline
Papular lesions resembling connective tissue naevi
Hypoplasia of one or more limbs (usually the limb affected by localized absence of skin or scarring), and/or malformed digits
Ocular anomalies, including chorioretinitis, cataracts, microphthalmia, Horner's syndrome
Central nervous system abnormalities, including seizures, mental retardation, hydrocephalus, cortical atrophy, encephalitis, encephalomyelitis, dorsal radiculitis

When a mother develops varicella between the seventh and 20th week of pregnancy, spontaneous abortion may follow, or the child may be born with a variety of abnormalities considered characteristic of FVS [5–7] (Table 17.5), and this appears to be most frequent when maternal infection has occurred between weeks 13 and 20 [3]. This syndrome was first described in 1947 [8]; many other cases have been reported since [9–13]. However, most children of such mothers are born with no detectable abnormality, despite laboratory confirmation of intrauterine infection [7]. FVS therefore appears to be a relatively rare complication of maternal varicella early in pregnancy, with a fetal risk of approximately 2% [1,4,7,14]. Some authors have argued that occasionally FVS can occur as late as 28 weeks into pregnancy [15].

Localized scarring, presumed to be the sequel to intrauterine ulceration, is the most common cutaneous feature of the FVS. The larger single lesions have characteristically occurred on a limb, and have frequently been associated with hypoplasia of that limb; these lesions have generally followed infections occurring in early pregnancy [5,14–17]. Their segmental outline may be a direct consequence of damage to the fetal nervous system [6,16], as the varicella-zoster virus is known to be strongly neurotropic, or to fetal herpes zoster [9]. The occurrence of larger numbers of smaller lesions appears to result in the main from varicella later in pregnancy; their antecedents seem likely to be vesicular lesions, essentially the same as those occurring in postnatal varicella. If fetal infection has occurred in the last trimester, these smaller skin lesions, reflecting fetal varicella, may still be ulcerated at birth [18].

Areas of congenital localized absence of skin, without associated limb hypoplasia or other neurological abnormalities, have been a less well recognized consequence of intrauterine varicella [19,20], and may reflect fetal herpes zoster later in gestation. Similar skin lesions have been reported in cases of intrauterine infection with human HSV [21].

Skin-coloured papular lesions have been described in children with FVS [22], which are likely to be a direct response to cutaneous injury by intrauterine chickenpox. More verrucous lesions have been described in one immunocompetent neonate more reminiscent of 'verrucous herpes' seen in immunocompromised patients [23].

If a child is born with 'full blown FVS' the mortality is about 25% in the first 3 months of life [3].

Herpes zoster occurring in early infancy is likely to indicate that the child has been infected with the varicella-zoster virus *in utero* [24,25].

Pregnant women who are not immune (on the basis of history, and, preferably, serologically), and who experience exposure to varicella-zoster, should be given varicellazoster immune globulin (VZIG) [26]. Although this can prevent or modify clinical varicella if given up to 3 days after contact, there is no definite evidence that it prevents fetal infection or damage [4]. Giving VZIG to neonates of mothers who have chickenpox at the time of delivery does not appear to reduce the incidence of clinical infection but may reduce its severity [27]. But, as the risk of fetal damage is small, termination of pregnancy is not indicated. Ultrasound examinations can be performed to detect some of the abnormalities that occur in the cardiovascular system [28], but several of the important ocular and neurological sequelae cannot be diagnosed in this way. Amniocentesis, fetal blood and chorionic villus sampling can be performed to isolate the virus or to detect specific IgM, but may fail to identify infection [25,29].

There are no reports that establish a role for aciclovir therapy in the prevention of FVS. Therefore, the decision whether to treat the mother should be based solely on the severity of her illness [26].

A potentially dangerous situation relates to maternal development of varicella in the 4 days either side of delivery [30]. In this case, neonatal varicella may also occur, but, in the absence of the protection offered by the maternal immune system, mortality may be as high as 30%. Where maternal infection occurs at this time, VZIG is recommended for the newborn. If overt varicella develops in the child, intravenous aciclovir should be added to the VZIG [31].

References

1 McIntosh D, Isaacs D. Varicella-zoster virus infection in pregnancy. *Arch Dis Child* 1993; **68**: 1–2.

2 Dufour P, de Bièvre P, Vinatier D *et al.* Varicella and pregnancy. *Eur J Obstet Gynecol Reprod Biol* 1996; **66**: 119–23.

3 Sauerbrei A, Wutzler P. Herpes simplex and varicella-zoster virus infections during pregnancy: current concepts of prevention, diagnosis and therapy. Part 2: Varicella-zoster virus infections. *Med Microbiol Immunol* 2007; **196**: 95–102.

4 Enders G, Miller E, Craddock-Watson J *et al.* Consequences of varicella and herpes zoster in pregnancy: prospective study of 1739 cases. *Lancet* 1994; **343**: 1548–51.

5 Paryani SG, Arvin AM. Intrauterine infection with varicella-zoster virus after maternal varicella. *N Engl J Med* 1986; **314**: 1542–6.

6 Alkalay AL, Pomerance JJ, Rimoin DL. Fetal varicella syndrome. *J Pediatr* 1987; **111**: 320–3.

7 Pastuszak AL, Levy M, Schick B *et al.* Outcome after maternal varicella infection in the first 20 weeks of pregnancy. *N Engl J Med* 1994; **330**: 901–5.

8 La Foret E, Lynch CL. Multiple congenital defects following maternal varicella: report of a case. *N Engl J Med* 1947; **236**: 534–7.

9 Higa K, Dan K, Manabe H. Varicella-zoster virus infection during pregnancy: hypothesis concerning the mechanism of congenital malformations. *Obstet Gynecol* 1987; **69**: 214–22.

10 Hammad E, Helin I, Pacsa A. Early pregnancy varicella and associated congenital anomalies. *Acta Paediatr Scand* 1989; **78**: 963–4.

11 Mendivil A, Mendivil MP, Cuartero V. Ocular manifestations of the congenital varicella-zoster syndrome. *Ophthalmologica* 1992; **205**: 191–3.

12 Scharf A, Scherr O, Enders G, Helftenbein E. Virus detection in the fetal tissue of a premature delivery with congenital varicella syndrome: a case report. *J Perinat Med* 1990; **18**: 317–22.

13 Scheffer IE, Baraitser M, Brett EM. Severe microcephaly associated with congenital varicella infection. *Dev Med Child Neurol* 1991; **33**: 916–20.

14 Gilbert G. Chickenpox during pregnancy. *BMJ* 1993; **306**: 1079–80.

15 Anon. Chickenpox, pregnancy and the newborn. *Drug Ther Bull* 2005; **43**: 69–72, 94–5.

16 Srabstein JC, Morris N, Larke RPB *et al.* Is there a congenital varicella syndrome? *J Pediatr* 1974; **84**: 239–43.

17 Borzyskowski M, Harris RF, Jones RWA. The congenital varicella syndrome. *Eur J Pediatr* 1981; **137**: 335–8.

18 Bai BVA, John TJ. Congenital skin ulcers following varicella in late pregnancy. *J Pediatr* 1979; **94**: 65–7.

19 Essex-Cater A, Heggarty H. Fatal congenital varicella syndrome. *J Infect Dis* 1983; **7**: 77–8.

20 Bailie F. Aplasia cutis congenita of neck and shoulder requiring a skin graft: a case report. *Br J Plast Surg* 1983; **36**: 72–4.

21 Honig PJ, Brown D. Congenital herpes simplex virus infection initially resembling epidermolysis bullosa. *J Pediatr* 1982; **101**: 958–60.

22 White MI, Daly BM, Moffat MA, Rankin R. Connective tissue naevi in a child with intra-uterine varicella infection. *Clin Exp Dermatol* 1990; **15**: 149–51.

23 Boussault P, Boralevi F, Labbe L *et al.* Chronic varicella-zoster skin infection complicating the congenital varicella syndrome. *Pediatr Dermatol* 2007; **24**: 429–32.

24 Brunell PA, Kotchmar GS. Zoster in infancy: failure to maintain virus latency following intrauterine infection. *J Pediatr* 1981; **98**: 71–3.

25 Lecuru F, Taurelle R, Bernard J-P *et al.* Varicella-zoster infection during pregnancy: the limits of prenatal diagnosis. *Eur J Obstet Gynecol Reprod Biol* 1994; **56**: 67–8.

26 Prober CG, Gershon AA, Grose C *et al.* Consensus: varicella-zoster infections in pregnancy and the perinatal period. *Pediatr Infect Dis* 1990; **9**: 865–9.

27 Miller E, Cradock-Watson JE, Ridehalgh MK. Outcome in newborn babies given anti-varicella-zoster immunoglobulin after perinatal maternal infection with varicella-zoster virus. *Lancet* 1989; **2**: 371–3.

28 Pons JC, Rozenberg F, Imbert MC *et al.* Prenatal diagnosis of second-trimester congenital varicella syndrome. *Prenat Diagn* 1992; **12**: 975–6.

29 Hartung J, Enders G, Chaoui R *et al.* Prenatal diagnosis of congenital varicella syndrome and detection of varicella-zoster virus in the fetus: a case report. *Prenat Diagn* 1999; **19**: 163–6.

30 Meyers JD. Congenital varicella in term infants: risk reconsidered. *J Infect Dis* 1974; **129**: 215–7.

31 Rothe MJ, Feder HM, Grant-Kels JM. Oral acyclovir therapy for varicella and zoster infections in pediatric and pregnant patients: a brief review. *Pediatr Dermatol* 1991; **8**: 236–42.

Congenital rubella

Rubella contracted by the fetus before the 20th week of gestation may result in disseminated infection, causing intrauterine growth retardation, microcephaly, microphthalmia and a wide variety of other abnormalities [1]. Cutaneous lesions are among the most prominent clinical features of congenital rubella [2–4]. The typical lesions are present at birth, or make their appearance during the first 48 h. They comprise discrete, rounded, red or purple infiltrated macules, 3–8 mm in diameter. Although such lesions may be seen at any site, they generally occur in largest numbers on the face, scalp, back of the neck and on the trunk. Occasionally, the lesions are slightly raised. They tend to fade over a period of weeks. These lesions have often been described as 'purpuric', and have generally been attributed to thrombocytopenia, which is another common feature of congenital rubella [3]. However, histological examination has shown them to comprise foci of dermal erythropoiesis [2,5,6]. Such lesions have frequently been described as 'blueberry muffin'

lesions. Genuine thrombocytopenic purpura is probably rather uncommon.

Other reported skin manifestations of congenital rubella have included cutis marmorata, seborrhoea and hyperpigmentation of the forehead, cheeks and umbilical area [7], and discrete deep dimples over bony prominences, particularly the patellae [8].

References

1 Hanshaw JB, Dudgeon JA, Marshall WC. Rubella. In: Hanshaw JB, ed. *Viral Diseases of the Fetus and Newborn*. Philadelphia: Saunders, 1985: 13–91.

2 Brough AJ, Jones D, Page RH *et al.* Dermal erythropoiesis in neonatal infants: a manifestation of intrauterine viral disease. *Pediatrics* 1967; **40**: 627–35.

3 Cooper LZ, Green RH, Krugman S *et al.* Neonatal thrombocytopenic purpura and other manifestations of rubella contracted *in utero*. *Am J Dis Child* 1965; **110**: 416–27.

4 Rudolph AJ, Yow MD, Phillips A *et al.* Transplacental rubella infection in newly born infants. *JAMA* 1965; **191**: 843–5.

5 Klein HZ, Markarian M. Dermal erythropoesis in congenital rubella: description of an infected newborn who had purpura associated with marked extramedullary erythropoesis in the skin and elsewhere. *Clin Pediatr (Phila)* 1969; **8**: 604–7.

6 Naeye RL, Blanc W. Pathogenesis of congenital rubella. *JAMA* 1965; **194**: 1277–83.

7 Desmond MM, Wilson GS, Melnick JL *et al.* Congenital rubella encephalitis: course and early sequelae. *J Pediatr* 1967; **71**: 311–31.

8 Hammond K. Skin dimples and rubella. *J Pediatr* 1967; **39**: 291–2.

Human immunodeficiency virus (HIV) infections

HIV infection may be transmitted to the infant *in utero*, during delivery or through breast-feeding. Because most infections are probably transmitted around the time of birth, clinical manifestations are not commonly seen for the first few months, and some infected infants will remain asymptomatic for many years before manifestations first appear.

Mucocutaneous manifestations are common in infant HIV infection and frequently have an infective aetiology [1–3].

Persistent mucocutaneous candidiasis is the commonest of all. In addition to infection of oral and napkin areas, there may be extensive cutaneous involvement. Dermatophyte fungal infections are also characteristic, and infection with more unusual fungi may occur, including *Aspergillus* [4]. Bacterial infections include unusually severe or recurring impetigo, folliculitis, cellulitis and abscesses. Problems with viruses include atypical chickenpox, herpes zoster, herpes simplex, and unusually severe molluscum and human papillomavirus infections. Norwegian scabies may present in infancy.

A wide variety of non-infectious manifestations of HIV infection may also occur. Perhaps the most characteristic in infancy is seborrhoeic dermatitis affecting the face and scalp, often also proximal flexures, occasionally disseminating more widely. Drug eruptions are also rather frequent, especially with trimethoprim–sulfamethoxazole.

References

1 Prose NS. Cutaneous manifestations of HIV infection in children. *Dermatol Clin* 1991; **9**: 543–50.

2 Straka BF, Whitaker DL, Morrison SH *et al.* Cutaneous manifestations of the acquired immunodeficiency syndrome in children. *J Am Acad Dermatol* 1988; **18**: 1089–102.

3 Wananukul S, Deekajorndech T, Panchareon C *et al.* Mucocutaneous findings in pediatric AIDS related to degree of immunosuppression. *Pediatr Dermatol* 2003; **20**: 289–94.

4 Shetty D, Giri N, Gonzalez CE *et al.* Invasive aspergillosis in human immunodeficiency virus-infected children. *Pediatr Infect Dis J* 1997; **16**: 216–21.

Bacterial infections

Staphylococcus aureus infections

As in older children and adults, *S. aureus* causes a wide variety of cutaneous lesions in neonates.

Bullous impetigo

The neonate is peculiarly liable to the development of bullous impetigo, which is most often caused by phage group II strains of *S. aureus* [1]. The disorder in neonates differs in no significant way from that in older children and adults, although it was formerly distinguished by the rather confusing term, *pemphigus neonatorum*. Epidemics of bullous impetigo, in which some infants may develop staphylococcal scalded skin syndrome, have occurred in neonates due to transmission of infection in the nursery, principally via nursing or medical staff [2–4]. Although the infection is acquired in hospital following delivery, the lesions do not generally appear until the second week of life, when the child will now usually have left hospital.

The perineum, periumbilical area and the neck creases are predilection sites for the initial lesions. Rapidly enlarging bullae with thin, delicate walls and a narrow, red areola contain clear fluid at first, which may later become turbid or frankly purulent. The condition may remain localized or become widespread. Untreated generalized bullous impetigo in the neonate is associated with a significant mortality, and serious complications including lung abscess, staphylococcal pneumonia and osteomyelitis have been reported, even in cases treated with antibiotics [5,6].

The differential diagnosis of bullae and erosions in the neonate is illustrated in Table 17.6 [7–12].

Staphylococcal scalded skin syndrome

The staphylococcal scalded skin syndrome was first described in neonates by a German, Ritter von Rittershain [13]. It is caused by epidermolytic toxin A and/or B, which are elaborated by certain strains of *S. aureus*, most commonly of phage group II [1], particularly strains 71 and 55. These toxins reach the skin via the circulation from a distant focus of infection, usually in the umbilicus, breast, conjunctiva or the site of circumcision [14] or herniorrhaphy [15]. Transmission of the causative toxin through human milk has been reported [16].

Both these toxins attack desmoglein 1 (a desmosomal protein) so mucosal involvement does not occur (this is analogous to pemphigus foliaceus which has the same target antigen) [17].

The disorder is most often seen in young children, and particularly in neonates. The very much greater incidence of this condition in neonates is believed to reflect less efficient metabolism and excretion of the toxin [18]. Multiple cases can occur in a neonatal unit [19]. Cases occurring in later childhood tend to be associated with underlying disease, especially immunosuppression and renal failure [20].

It does not present at birth, although it may first appear within the first few hours thereafter [21]. The first sign of the disease is a faint, macular, orange-red, scarlatiniform eruption. The eruption

Table 17.6 Differential diagnosis of bullae and/or erosions in the neonate.

More common disorders
Miliaria crystallina
Bullous impetigo
Thermal or chemical burns
Sucking blisters
Mastocytosis
Rare disorders
Epidermolysis bullosa
Incontinentia pigmenti
Bullous ichthyosiform erythroderma
Neonatal herpes simplex
Fetal varicella syndrome (FVS)
Herpes zoster
Congenital syphilis
Passively transferred
Pemphigus vulgaris
Herpes gestationis
Bullous pemphigoid [7]
Extensive congenital erosions and vesicles healing with reticulate scarring
Congenital erythropoietic porphyria
AEC syndrome
Congenital absence of skin
Porphyrias and transient porphyrinaemia [8]
Langerhans' cell histiocytosis [9]
Weary syndrome/Kindler syndrome [10,11]
Ectodermal dysplasia–skin fragility syndrome (plakophilin-1 deficiency) [12]

generally becomes more extensive, and, over the next 24–48 h, turns to a more confluent, deep erythema with oedema. The surface then becomes wrinkled before starting to separate, leaving raw, red erosions. Sites of predilection for the development of erosions are the central part of the face, the axillae and the groins.

Extreme tenderness of the skin is an early feature, and may occur at a stage where cutaneous signs are not yet striking. The child is pyrexial and distressed. These features can lead to a suspicion that the child has arthritis or an acute abdomen. The presence of impetiginous crusting around the nose and mouth can be diagnostically helpful. Recovery is usually rapid, even without antibiotic therapy, although infants occasionally die in spite of such treatment [22]. Healing occurs without scarring.

The scalded appearance of the skin differentiates the disease from bullous impetigo, and the rapid onset with marked cutaneous tenderness distinguishes it from most of the other causes of erythroderma in infancy. The rarity of clinically apparent bullae and the confluent nature of the rash help differentiate it from those bullous disorders likely to be seen in young children.

The only real problem in differential diagnosis would be with toxic epidermal necrolysis, which, although clinically similar, has a worse prognosis. In the past, the staphylococcal scalded skin syndrome and toxic epidermal necrolysis were confused, but it is now clear that they are entirely distinct entities. Genuine toxic epidermal necrolysis does occur in young children but is relatively rare, and differs clinically by virtue of mucosal involvement. Wherever there is any doubt, the two conditions may be reliably distinguished by histology, as the level of skin separation is intraepidermal in the staphylococcal scalded skin syndrome and at the dermal–epidermal junction in toxic epidermal necrolysis. If the child's condition arouses anxiety, a frozen section will provide rapid differentiation [23].

Treatment is with either a penicillinase-resistant penicillin analogue, such as flucloxacillin or methicillin, or with an appropriate cephalosporin or sodium fusidate. If the attack is severe, the drug should initially be given intravenously. Systemic corticosteroids are contraindicated, on the basis of experimental [24] and clinical [25] evidence that they aggravate the disease. Appropriate compensation must be made for heat and fluid losses. Pain will also require treatment, and affected infants will generally be much more comfortable if the lesions are dressed rather than left open. In severe cases, it may occasionally be justifiable to ventilate the patient in order to obtain adequate relief of pain.

Periporitis staphylogenes and sweat gland abscesses

Periporitis staphylogenes is the term applied to pustular lesions appearing in neonatal skin as a result of secondary infection of miliaria by *S. aureus* [26–29]. Such lesions may progress to sweat gland abscesses, although it is not clear whether sweat gland abscesses are always a complication of miliaria. These disorders have in the past been incorrectly called 'folliculitis and furunculosis of the newborn'. Sweat gland abscesses are distinguished from furuncles clinically by a lack of any tendency to 'point', 'coldness' and absence of tenderness.

Periporitis must be distinguished from miliaria pustulosa, which is not an infective disorder, and from bacterial folliculitis, which in the neonate is usually caused by *S. aureus*. *Candida albicans* and *M. furfur* may also cause pustulosis in the neonate, and a number of non-infective conditions may cause confusion, such as eosinophilic pustulosis.

Mastitis and breast abscesses

Infection of the breast is common and is usually associated with *S. aureus*, but a variety of other bacteria may be responsible [30]. It is almost always unilateral; it occurs most commonly in the second or third week of life, more often in girls than boys, and only very rarely in the preterm infant. The affected breast is swollen, and often red and hot. Systemic toxicity is usually absent. Fluctuation implies abscess formation, which will require surgical drainage. The development of a breast abscess may lead to loss of breast tissue in the longer term [31].

References

1 Murano K, Fujita K, Yoshioka H. Microbiologic characteristics of exfoliative toxin-producing *Staphylococcus aureus*. *Pediatr Infect Dis J* 1988; **7**: 313–5.
2 Curran JP, Al-Salihi FL. Neonatal staphylococcal scalded skin syndrome: massive outbreak due to an unusual phage type. *Pediatrics* 1980; **66**: 285–90.
3 Dancer SJ, Simmons NA, Poston SM *et al.* Outbreak of staphylococcal scalded skin syndrome among neonates. *J Infect* 1988; **16**: 87–103.
4 Wolinsky E, Lipsitz PJ, Mortimer EA *et al.* Acquisition of staphylococci by newborns: direct versus indirect transmission. *Lancet* 1960; **ii**: 620–2.
5 Forfar JO, Bale CL, Elias-Jones TF *et al.* Staphylococcal infection of the newborn. *BMJ* 1953; **2**: 170–4.
6 Hardyment AF. Control of infections of newborn infants. *Pediatr Clin North Am* 1958; **5**: 287–300.
7 Marsden RA. Bullous pemphigoid in a child. *Clin Exp Dermatol* 1983; **8**: 329–32.

8 Crawford RI, Lawlor ER, Wadsworth LD, Prendiville JS. Transient erythroporphyria of infancy. *J Am Acad Dermatol* 1996; **35**: 833–4.
9 Lerner LH, Bailey EM. A newborn with multiple hemorrhagic vesicles, lymphadenopathy and respiratory distress. *N Engl J Med* 1996; **334**: 1591–7.
10 Burch JM, Fassihi H, Jones CA *et al.* Kindler syndrome. A new mutation and new diagnostic possibilities. *Arch Dermatol* 2006; **142**: 620–4.
11 Ashton GHS. Kindler syndrome. *Clin Exp Dermatol* 2004; **29**: 116–21.
12 Ersoy-Evans S, Erkin G, Fassihi H *et al.* Ectodermal dysplasia–skin fragility syndrome resulting from a new homozygous mutation, 888delC, in the desmosomal protein plakophilin 1. *J Am Acad Dermatol* 2006; **55**: 157–61.
13 Ritter von Rittershain G. Die exfoliative Dermatitis jungerer Sauglinge. *Central Zeitung Kinderheilk* 1878; **2**: 3–23.
14 Annunziata D, Goldblum LM. Staphylococcal scalded skin syndrome: a complication of circumcision. *Am J Dis Child* 1978; **132**: 1187–8.
15 Artman M, Shanks GD. Staphylococcal scalded skin syndrome after herniorrhaphy. *Am J Dis Child* 1981; **135**: 471–2.
16 Raymond J, Bingen E, Brahimi N *et al.* Staphylococcal scalded skin syndrome in a neonate. *Eur J Clin Microbiol Infect Dis* 1997; **16**: 453–4.
17 Stanley JR *et al.* Pemphigus, bullous impetigo and the staphylococcal scalded-skin syndrome. *N Eng J Med* 2006; **355**: 1800–10.
18 Fritsch P, Elias P, Varga J. The fate of staphylococcal exfoliation in the newborn and adult mice. *Br J Dermatol* 1976; **95**: 275–84.
19 Saiman L, Jakob K, Holmes KW *et al.* Molecular epidemiology of staphylococcal scalded skin syndrome in premature infants. *Pediatr Infect Dis J* 1998; **17**: 329–34.
20 Borchers SL, Gomez EC, Isseroff RR. Generalized staphylococcal scalded skin syndrome in an anephric boy undergoing hemodialysis. *Arch Dermatol* 1984; **120**: 912–8.
21 Loughead JL. Congenital staphylococcal scalded skin syndrome: report of a case. *Pediatr Infect Dis J* 1992; **11**: 413–4.
22 Rasmussen JE. Toxic epidermal necrolysis: a review of 75 cases in children. *Arch Dermatol* 1975; **111**: 1135–9.
23 Amon RB, Dimond RL. Toxic epidermal necrolysis: rapid differentiation between staphylococcal and drug-induced disease. *Arch Dermatol* 1975; **111**: 1433–7.
24 Melish ME, Glasgow LA, Turner MD. The staphylococcal scalded skin syndrome; isolation and partial characterisation of the exfoliative toxin. *Br J Dermatol* 1982; **125**: 129–40.
25 Rudolph RI, Schwartz W, Leyden JJ. Treatment of staphylococcal toxic epidermal necrolysis. *Arch Dermatol* 1974; **110**: 559–62.
26 Lubowe II, Perlman HH. Periporitis staphylogenes and other complications of miliaria in infants and children. *AMA Arch Dermatol Syphilol* 1954; **69**: 543–53.
27 Maibach HI, Kligman AM. Multiple sweat gland abscesses. *JAMA* 1960; **174**: 140–2.
28 Mopper C, Pinkus H, Iacobell P. Multiple sweat gland abscesses of infants. *Arch Dermatol* 1955; **71**: 177–83.
29 Tudor RB. Sweat gland abscesses of infancy. *Lancet* 1957; **77**: 307–8.
30 Brook I. The aerobic and anaerobic microbiology of neonatal breast abscess. *Pediatr Infect Dis J* 1991; **10**: 785–6.
31 Rudoy RL, Nelson JD. Breast abscess during the neonatal period: a review. *Am J Dis Child* 1975; **129**: 1031–4.

Omphalitis

Omphalitis is rare in the developed world (0.7% births) but is more of a problem for developing countries (up to 6% births). It is characterized by redness, oedema and discharge of the 'stump'. Cases can progress to cellulitis and deeper tissue infection. It is more common in protracted labour, non-sterile delivery and cord care, prematurity, low birth weight and some cultural practices such as application of tobacco ash [1].

The umbilical cord may become colonized by a variety of potentially pathogenic bacteria, and an equally wide variety of topical antiseptics and antibiotics have been used in an attempt to reduce this colonization. The use of hexachlorophane was popular until it became apparent that this could lead to serious neurotoxicity, particularly in the preterm infant [2]. The best substitute may be chlorhexidine, applied as a dusting powder rather than as an alcoholic solution [3]. In developing countries, 4% chlorhexidine has been shown to reduce omphalitis (and indeed reduce neonatal mortality if given on day 1) in a community based study in Nepal [4].

Occasionally, infection of the umbilical cord becomes disseminated, either by bloodstream invasion or by direct extension via the umbilical vessels to the peritoneal cavity. Tetanus, diphtheria and necrotizing fasciitis [5] may also occur as complications of umbilical infection. Such infections are still responsible for a high proportion of deaths in the neonatal period in developing countries.

References

1 Fraser NIA, Davies BW, Cusack J. Neonatal omphalitis: a review of its serious complications. *Acta Paediatrica* 2006; **95**: 519–22.
2 Shuman RM, Leech RW, Alvord EC. Neurotoxicity of hexachlorophene in the human. I. A clinicopathologic study of 248 children. *Pediatrics* 1974; **54**: 689–95.
3 Aggett PJ, Cooper LV, Ellish SH *et al.* Percutaneous absorption of chlorhexidine in neonatal cord care. *Arch Dis Child* 1981; **56**: 878–91.
4 Mullany LC, Darmstadt GL, Khatry SK *et al.* Topical application of chlorhexidine to the umbilical cord for prevention of omphalitis and neonatal mortality in southern Nepal: a community-based, cluster-randomized trial. *Lancet* 2006; **367**: 910–8.
5 Lally KP, Atkinson JB, Wooley MM *et al.* Necrotising fasciitis: a serious sequela of omphalitis in the newborn. *Ann Surg* 1984; **199**: 101–3.

Preorbital and orbital cellulitis

Preorbital cellulitis is restricted to the part of the orbit anterior to the orbital septum and is manifest by eyelid swelling. Orbital cellulitis involves the structures deep to the septum and presents with painful proptosis, eyelid oedema and conjunctival erythema. A variety of bacteria can cause these infections, including *S. aureus*, group A and other streptococci. One should always be alert to the possibility of group B *Streptococcus* as a rare cause of periorbital cellulitis or any form of cellulitis in a neonate, in view of their high risk of septicaemia with this organism [1,2].

Necrotizing fasciitis

This name is given to a distinctive form of cellulitis, in which infection tracks along the fascial planes, causing thrombosis of blood vessels running through the fascia with resulting necrosis of the skin, subcutaneous fat and even muscle [3,4]. In neonates, it may arise spontaneously, but most often is a complication of physical birth trauma, omphalitis [5], breast abscess, or iatrogenic skin wounds such as result from scalp electrodes [6] or circumcision [7]. The mother's genital tract is probably often the source of the infection [8].

Initially, the infant develops what appears to be straightforward cellulitis usually affecting the abdominal wall. However, the child becomes disproportionately toxic, and the area affected becomes indurated, discoloured and extends progressively [4,9]. The surface may show a peau d'orange appearance. Purpura and, occasionally bullae, may develop in the centre of the indurated area, often followed quite rapidly by frank necrosis. Destruction of superficial nerves results in local cutaneous anaesthesia. Gas and crepitation may be clinically apparent, or may be seen radiologically. Fever is not invariably present.

A wide variety of bacteria have been associated with necrotizing fasciitis, most commonly group A streptococci, but also group B streptococci, *S. aureus* and *Escherichia coli* [3,9–11]. In many cases, a synergistic infection by aerobic and anaerobic organisms appears to be responsible. Occasionally, fungi have been responsible. Antibiotic therapy appears to be of limited value in this potentially lethal situation. The most important aspect of treatment is early surgical excision of necrotic tissue [5,11].

References

1 Mittal MK, Shah SS, Friedlaender EY. Group B streptococcal cellulitis in infancy. *Pediatr Emerg Care* 2007; **23**: 324–5.
2 Hauger SB. Facial cellulitis: an early indicator of group B streptococcal bacteremia. *Pediatrics* 1981; **67**: 376–7.
3 Goldberg GN, Hansen RC, Lynch PJ. Necrotizing fasciitis in infancy: report of three cases and review of the literature. *Pediatr Dermatol* 1984; **2**: 55–63.
4 Hsieh WS, Yang PH, Chao HC *et al.* Neonatal necrotizing fasciitis: a report of three cases and review of the literature. *Pediatrics* 1999; **103**: e53.
5 Lally KP, Atkinson JB, Wooley MM *et al.* Necrotising fasciitis: a serious sequela of omphalitis in the newborn. *Ann Surg* 1984; **199**: 101–3.
6 Siddiqi SF, Taylor PM. Necrotizing fasciitis of the scalp. *Am J Dis Child* 1982; **136**: 226–8.
7 Woodside JR. Necrotising fasciitis after neonatal circumcision. *Am J Dis Child* 1980; **134**: 301–2.
8 Nutman J, Henig E, Wilunsky E *et al.* Acute necrotising fasciitis due to streptococcal infection in a newborn infant. *Arch Dis Child* 1979; **54**: 637–9.
9 Ramamurthy RS, Srinivasan G, Jacobs NM. Necrotizing fasciitis and necrotizing cellulitis due to group B *Streptococcus*. *Am J Dis Child* 1977; **131**: 1169–70.
10 Weinberger M, Haynes RE, Morse TS. Necrotizing fasciitis in a neonate. *Am J Dis Child* 1972; **123**: 591–4.
11 Wilson HD, Haltalin KC. Acute necrotising fasciitis in childhood: report of 11 cases. *Am J Dis Child* 1973; **125**: 591–5.

Neonatal listeriosis

Listeriosis during the neonatal period is uncommon, but dangerous. The responsible organism, *Listeria monocytogenes*, may be transmitted to humans principally through contaminated foods [1]. In pregnancy, it causes a rather non-specific and generally mild, influenza-like illness in the mother [2], but it may lead to transplacental infection of the fetus. Maternal HIV infection may predispose to neonatal listeriosis [3]. Adult listeriosis has increased in a number of European countries during the early 2000s, but mostly in the elderly and not as yet in pregnancy-related cases [4].

Clinically, there are early-onset and late-onset forms of neonatal listeriosis [5]. The early-onset form results from the development of miliary granulomas following blood-borne dissemination of infection. Severely affected babies tend to be born prematurely, and there is a high mortality [6,7]. Post-mortem studies reveal miliary granulomas in many organs. A few infants will have analogous miliary skin lesions during life, manifest as scattered, discrete grey or white papules or pustules, about 1–2 mm in diameter, with a red margin [8,9], which will provide a source of organisms for culture [10]. The back appears to be the site of predilection for such lesions, which are also seen in the mouth and on the conjunctiva. Other cutaneous lesions have been described in such babies, including purpura and morbilliform rashes [4,6].

The late form of the disease is commoner, taking the form of meningitis, occurring a week or two after birth [11].

Diagnosis is by culturing the organism from a variety of sites, including cerebrospinal fluid, blood, urine and from biopsy material, including the skin. Treatment is most frequently with a combination of parenteral ampicillin and gentamicin or kanamycin [6], followed by a longer course of ampicillin or penicillin given alone.

References

1 Schlech WF, Lavigne PM, Bortolussi RA *et al.* Epidemic listeriosis: evidence for transmission by food. *N Engl J Med* 1983; **203**: 203–6.
2 Robertson MH. Listeriosis. *Postgrad Med J* 1977; **53**: 618–22.
3 Smith KJ, Skelton HG, Angritt P *et al.* Cutaneous lesions of listeriosis in a newborn. *J Cutan Pathol* 1991; **18**: 474–6.
4 Koch J, Stark K. Significant increase of listeriosis in Germany—epidemiological patterns 2001–2005. *Eurosurveillance* 2006; **11**: pii=631.
5 Gray ML, Killinger AH. *Listeria monocytogenes* and listeric infections. *Bacteriol Rev* 1966; **30**: 309–82.
6 Ahlfors C, Goetzman BW, Halsted CC *et al.* Neonatal listeriosis. *Am J Dis Child* 1977; **131**: 405–8.
7 Canfield MA, Walterspiel JA, Edwards MS *et al.* An epidemic of perinatal listeriosis serotype 1b in Hispanics in a Houston hospital. *Pediatr Infect Dis* 1985; **4**: 106.
8 Dincsoy MY, Booker CR, Scott RB. Skin manifestation in *Listeria* infection. *J Natl Med Assoc* 1965; **57**: 290–6.
9 Smith K, Yeager J, Skelton H *et al.* Diffuse petechial pustular lesions in a newborn: disseminated *Listeria monocytogenes*. *Arch Dermatol* 1994; **130**: 245–8.
10 Gray ML. *Listeria monocytogenes* and listeric infection in the diagnostic laboratory. *Ann NY Acad Sci* 1962; **98**: 686–99.
11 Nichols W, Wooley PV. *Listeria monocytogenes* meningitis. *J Pediatr* 1962; **61**: 337–50.

Pseudomonas aeruginosa infections

Ecthyma gangrenosum [1–3]

Pseudomonas aeruginosa is common in the hospital environment and infections are encouraged by the widespread use of broad-spectrum antibiotics. Most, but not all, neonates who develop the skin lesions of ecthyma gangrenosum have *P. aeruginosa* septicaemia, usually in the context of predisposing factors that include prematurity, neutropenia and other immunodeficiencies, necrotizing enterocolitis and bowel surgery. Occasionally the lesions develop directly at the site of direct inoculation of the causative organism.

Histologically, the presence of vasculitis, due to bacterial infiltration of vessel walls, is characteristic [4], together with haemorrhage and necrosis; for this reason skin biopsy can be very helpful in diagnosis.

Clinically, lesions initially take the form of painful macular erythema or purple ecchymosis. The centre then generally develops either vesicles (or less commonly bullae) or pustules which rapidly ulcerate. One subsequently sees one or more ulcers with a depressed, necrotic, often black, crusted centre and a raised edge. The perioral and perianal areas may show grouped lesions.

This infection is potentially dangerous when it occurs in the setting of septicaemia. Appropriate parenterally administered combination antibiotic therapy will be required.

Noma neonatorum

Noma neonatorum is a gangrenous disorder of the nose, lips, mouth, perianal area and, occasionally, the scrotum and eyelids, occurring in low birth weight and/or premature neonates, almost



Fig. 17.8 Congenital syphilis: nummular erythematosquamous lesions in a 4-week-old infant.

exclusively in underdeveloped parts of the world. It is frequently caused by *P. aeruginosa* and is almost invariably lethal in the absence of appropriate antibiotic treatment [5]. A similar condition may be seen in older children and adults in the context of severe immunodeficiency [6].

Purpura fulminans

Although in the newborn this condition is most often a reflection of genetically transmitted thrombophilic disorder, it may be caused by acute infections, particularly with endotoxin-associated, Gram-negative bacteria such as *Neisseria meningitidis* [7,8].

Congenital syphilis

Congenital syphilis is described in detail in Chapter 34, but its cutaneous manifestations in the neonate will be considered here briefly, because of their importance in differential diagnosis [9].

The skin is clinically affected in about 40% of neonates with congenital syphilis. In such cases, the skin is usually of normal appearance at birth, the initial lesions occurring between the second and eighth week, and occasionally later. Sites of predilection are the anogenital area, the face and the palms and soles. The lesions themselves are reddish brown in colour; they may be macular or papular, and tend to be larger and firmer than those seen in acquired secondary syphilis (Fig. 17.8). In about 3% of cases the lesions are bullous. Paronychia is commonly present. Small, round, moist, papular lesions, traditionally termed mucous patches, are frequently present in the mouth and on other mucosal surfaces. Condylomata lata may be present in the anogenital flexures or at other flexural sites, for example between the toes or in the angles of the mouth.

Birth weight is below 2500 g in approximately 50% of affected infants. Apart from the cutaneous features, the most frequent clinical manifestations of congenital syphilis in the newborn are hepatomegaly, splenomegaly, jaundice, pneumonia and rhinitis, often with a blood-stained discharge.

The recent resurgence in the incidence of syphilis in many countries may lead to an increase in cases of congenital disease, especially where antenatal care is poor [10].

Congenital tuberculosis

Tuberculosis in the newborn due to transmission of infection *in utero* is relatively rare. The lungs and/or liver tend to be the predominant sites of involvement, and skin manifestations are unusual. However, cutaneous lesions have occasionally occurred, in the form of small numbers of discrete, umbilicated, erythematous papules up to 4 mm in diameter [11].

References

1 Boisseau AM, Sarlangue J, Perel Y *et al.* Perineal ecthyma gangrenosum in infancy and early childhood: septicemic and nonsepticemic forms. *J Am Acad Dermatol* 1992; **27**: 415–8.

2 Hughes JR, Newbould M, du Vivier AWP, Greenough A. Fatal *Pseudomonas* septicemia and vasculitis in a premature infant. *Pediatr Dermatol* 1998; **15**: 122–4.

3 Chan YH, Chong CY, Puthucheary J *et al.* Ecthyma gangrenosum: a manifestation of *Pseudomonas* sepsis in three paediatric patients. *Singapore Med J* 2006; **47**: 1080–3.

4 Teplitz C. Pathogenesis of *Pseudomonas* vasculitis and septic lesions. *Arch Pathol* 1965; **80**: 297–307.

5 Ghosal SP, Sen Gupta PC, Mukherjee AK *et al.* Noma neonatorum: its aetiopathogenesis. *Lancet* 1978; **2**: 289–91.

6 Rotbart HA, Levin MJ, Jones J *et al.* Noma in children with severe combined immunodeficiency. *J Pediatr* 1986; **109**: 596–600.

7 Clegg HW, Todres ID, Moylan FM *et al.* Fulminant neonatal meningococcemia. *Am J Dis Child* 1980; **134**: 354–5.

8 Darmstadt G. Acute infectious purpura fulminans: pathogenesis and medical management. *Pediatr Dermatol* 1998; **15**: 169–83.

9 Chawla V, Pandit P, Nkrumah FK. Congenital syphilis in the newborn. *Arch Dis Child* 1988; **63**: 1393–4.

10 Chakraborty R, Luck S. Syphilis is on the increase: the implications for child health. *Arch Dis Child* 2008; **93**: 105–9.

11 McCray MK, Esterley NB. Cutaneous eruptions in congenital tuberculosis. *Arch Dermatol* 1981; **117**: 460–4.

Fungal infections

Candida infections in the neonate

There are two distinct forms of candidiasis seen in the first weeks of life, which have been called *neonatal candidiasis*, which appears after birth, and *congenital candidiasis*, which is present at birth.

Neonatal candidiasis

This is a relatively common disorder that occurs in the early weeks after birth, in the form of oral candidiasis with or without candidiasis in the napkin area. The rash is usually focused in the perianal area, and is a deep 'beefy' red colour, with a moist appearance, often with pustules at the periphery, which is often scalloped in outline. Just beyond the margin, in as yet unaffected skin, there may be punctate erythematous lesions, sometimes pustular ('satellite' lesions).

It is assumed that the infection is acquired during delivery from the mother's genital tract, and it should be borne in mind that the frequency of vaginal candidiasis at the time of delivery is between 20% and 25% [1].

Occasionally, the rash may become more generalized. The occurrence of localized palmar pustules in an infant with neonatal oral candidiasis was believed to reflect the inoculation of *Candida* from the mouth into the skin as a result of sucking [2].

The most reliable treatment is generally a combination of a non-absorbed oral anticandidal agent, usually amphotericin drops or

miconazole 2% oral gel, and a topical anticandidal agent such as ketoconazole 2% cream.

Congenital candidiasis

This is a rarer condition, seen at birth, which is generally believed to reflect maternal *Candida* chorioamnionitis resulting from ascending infection from the genital tract [3–9]. It appears that *Candida* is, however, able to find its way into the amniotic fluid without prior rupture of membranes [10]. Foreign bodies in the uterus or the cervix increase the risk, particularly intrauterine contraceptive devices [10,11]. There is no evidence that maternal antibiotic therapy or immunodeficiency in the infant play a role in predisposition [9,12].

An extensive eruption of scattered pinkish red macules and papules is present at birth or appears within a few hours. The lesions generally progress to a vesicular phase, and then either to a pustular or a bullous phase, over a period of 1–3 days. More or less any part of the skin surface may be affected, including the nails, palms and soles. In fact, palmar and plantar pustules are regarded as a hallmark of congenital cutaneous candidiasis. Isolated involvement of the nail plates has been described [13]. Oral involvement is usually absent, and the napkin area tends to be spared, at least initially.

Very-low-birth-weight infants may have a scalded appearance, and are particularly at risk of systemic infection.

When infection is confined to the skin, affected infants have generally been otherwise well, and the rash clears within a week with appropriate topical antifungal therapy, for example with topical ketoconazole. The rash clears with prominent post-inflammatory desquamation.

Skin and mucosal involvement may be complicated by systemic candidiasis, particularly in the premature [4,14]. The lungs may be affected [15]; hepatosplenomegaly and abnormal liver function have also been recorded [9]. Candidal meningitis is another potential complication [16]. Criteria have been proposed that indicate high risk of systemic involvement. Systemic antifungal therapy should be considered in at-risk infants [12]; amphotericin B is probably the drug of choice [11,14].

Studies have shown that intravenous fluconazole prophylaxis in very-low-birth-weight infants reduces both invasive candidiasis and mortality rates [17,18] but a Cochrane review of three other studies using oral antifungal prophylaxis in preterm infants has not shown any convincing benefit [19].

References

1 Stuart S, Lane A. *Candida* and *Malassezia* as nursery pathogens. *Semin Dermatol* 1992; **11**: 19–23.

2 Resnick SD, Greenberg RA. Autoinoculated palmar pustules in neonatal candidiasis. *Pediatr Dermatol* 1989; **6**: 206–9.

3 Chapel TA, Gagliardi C, Nichols W. Congenital cutaneous candidiasis. *J Am Acad Dermatol* 1982; **6**: 926–8.

4 Gibney MD, Siegfried EC. Cutaneous congenital candidiasis: a case report. *Pediatr Dermatol* 1995; **12**: 359–63.

5 Perel Y, Taieb A, Fontan I *et al.* Candidose cutanée congénitale: une observation avec revue de la litérature. *Ann Dermatol Vénéréol* 1986; **113**: 125–30.

6 Raval DS, Barton LL, Hansen RC, Kling PJ. Congenital cutaneous candidiasis: case report and review. *Pediatr Dermatol* 1995; **12**: 355–8.

7 Rudolph N, Tariq AA, Reale MR *et al.* Congenital cutaneous candidiasis. *Arch Dermatol* 1977; **113**: 1101–3.

8 Darmstadt GL, Dinulos JG, Miller Z. Congenital cutaneous candidiasis: clinical presentation, pathogenesis and management guidelines. *Pediatrics* 2000; **105**: 438–44.

9 Cosgrove BF, Reeves K, Mullins D *et al.* Congenital cutaneous candidiasis associated with respiratory distress and elevation of liver function tests: a case report and review of the literature. *J Am Acad Dermatol* 1997; **37**: 817–23.

10 Bruner JP, Elliott JP, Kilbride HW *et al.* Candida chorioamnionitis diagnosed by amniocentesis with subsequent fetal infection. *Am J Perinatol* 1986; **3**: 213–8.

11 Rowen JL, Tate JM. Management of neonatal candidiasis. *Pediatr Infect Dis J* 1998; **17**: 1007–11.

12 Johnson DE, Thompson TR, Ferrieri P. Congenital candidiasis. *Am J Dis Child* 1981; **135**: 273–5.

13 Argebast KD, Lamberty LF, Koh JK *et al.* Congenital candidiasis limited to the nail plates. *Pediatr Dermatol* 1990; **7**: 310–2.

14 Waguespack-LaBiche J, Chen S-H, Yen A. Disseminated congenital candidiasis in a premature infant. *Arch Dermatol* 1999; **135**: 510–2.

15 Glassman BD, Muglia JJ. Widespread erythroderma and desquamation in a neonate: congenital cutaneous candidiasis. *Arch Dermatol* 1993; **129**: 899–902.

16 Barone SR, Krilov LR. Neonatal candidal meningitis in a full-term infant with congenital cutaneous candidiasis. *Clin Pediatr (Phila)* 1995; **34**: 217–9.

17 Healy CM, Campbell JR, Zaccaria E *et al.* Fluconazole prophylaxis in extremely low birth weight neonates reduces invasive candidiasis mortality rates without emergence of fluconazole-resistant *candida* species. *Pediatrics* 2008; **121**: 703–10.

18 McGuire W, Clerihew L, Austin N. Prophylactic intravenous antifungal agents to prevent mortality and morbidity in very low birth weight infants. *Cochrane Database Syst Rev* 2004; **1**: CD003850.

19 Austin NC, Darlow B. Prophylactic oral antifungal agents to prevent systemic candida infection in preterm infants. *Cochrane Database Syst Rev* 2004; **1**: CD003478.

Malassezia pustulosis

Colonization of the skin by *M. furfur* starts soon after birth and progresses until the age of about 3 months, probably reflecting the activity of the sebaceous glands during this period [1–3]. This yeast has been a cause of systemic infections in infants receiving intravenous lipids, and it is presumed that the source of organisms in such cases was the skin [4].

It is now believed that *M. furfur and M. sympodialis* may be a frequent cause of erythematous papulopustular eruptions occurring on the face and scalp in neonates, a condition now widely termed *neonatal cephalic pustulosis* [3,5–7], though not all neonates with this clinical presentation had detectable *Malassezia* in the lesions [8]. This type of rash was reported to have a frequency of 10% in neonates seen as outpatients in a paediatric dermatology department [7], with pustule contents showing *M. furfur* yeasts in over half of these, associated with a good therapeutic response to topical application of 2% ketoconazole cream for 15 days in almost every case. A frequency of 66% was reported in one study, with 62% being culture-positive for *Malassezia* [8].

There is reason to believe that some of the *Malassezia*-negative cases in these studies may have had genuine neonatal acne, which is generally easily distinguished by the concurrent presence of comedones.

Certainly, *Malassezia* pustulosis clearly needs to be considered in neonates presenting with pustular lesions on the face and/or in the scalp, in cases that might otherwise be diagnosed as eosinophilic pustulosis of the scalp, transient pustular melanosis, scabies, neonatal acne vulgaris, or cutaneous infections such as *S. aureus* or *C. albicans* [9].

References

1 Koseki S, Takahashi S. Serial observation on the colonization of *Pityrosporum orbiculare* (*ovale*) on the facial skin surface of newborn infants. *Jpn J Med Mycol* 1988; **29**: 209–15.
2 Borderon JC, Langier J, Vaillant MC. Colonisation du nouveau-né par *Malassezia furfur*. *Bull Soc Fr Mycol Med* 1989; **1**: 129–32.
3 Niamba P, Weill FX, Sarlangue J *et al.* Is common neonatal cephalic pustulosis (neonatal acne) triggered by *Malassezia sympodialis*? *Arch Dermatol* 1998; **134**: 995–8.
4 Alpert G, Bell LM, Campos JM *et al. Malassezia furfur* fungemia in infancy. *Clin Pediatr (Phila)* 1987; **26**: 528–31.
5 Aractingi S, Cadranel S, Reygagne P, Wallach D. Pustulose néonatale induite par *Malassezia furfur*. *Ann Dermatol Vénéréol* 1991; **118**: 856–8.
6 Plantin P, Cartier H, Geffroy F, Broussine L. Une pustulose néonatale a reconnaitre: la pustulose induite par *Malassezia furfur. Arch Pediatr* 1995; **2**: 1016.
7 Rapelmanoro R, Mortureux P, Couprie B *et al.* Neonatal *Malassezia furfur* pustulosis. *Arch Dermatol* 1996; **132**: 190–3.
8 Bernier V, Weill FX, Hirigoyen V *et al.* Skin colonisation by *Malassezia* species in neonates: a prospective study and relationship with neonatal cephalic pustulosis (neonatal acne). *Arch Dermatol* 2002; **138**: 215–8.
9 Moisson YF, Wallach D. Les dermatoses pustuleuses de la période néonatale. *Ann Pediatr (Paris)* 1992; **39**: 397–406.

Primary immunodeficiency disorders

A.R. Gennery & A.J. Cant, pp. 17.48–17.85

Introduction

The immune system protects against a huge variety of infective agents, which bear many different surface proteins or antigens. To achieve this a series of defence mechanisms have evolved, from simple mechanical barriers, through non-specific second line defences which recognize certain highly conserved microbial proteins to highly specific responses with 'memory' which are refined on repeated exposure and afford long-term protection. The interaction of man and microbe is ongoing through evolution, so that as existing systems become redundant, new defensive pathways evolve. New understandings of immune mechanisms give better insight into the causes of primary and secondary immunodeficiency and many aspects of immune function have been elucidated by the recognition of specific defects in immunodeficient individuals. Here, immune response mechanisms will be briefly described with examples of specific defects that result in primary or secondary immunodeficiency. Immunodeficiency states will then be reviewed in detail with particular reference to their dermatological manifestations. It is much easier to understand the dermatological features of immunodeficiency if the immune defect is also understood. Not surprisingly, the more severe primary defects of immunity present early in life, and so the dermatological features of these disorders will be considered in this chapter.

The innate immune system

Physical and chemical barriers such as epithelial surfaces and mucous membranes, hair, cilia, the secretion of sticky mucus, enzymes and acids, as well as antibiotics produced by commensal flora, are all highly effective at excluding pathogens by their antimicrobial effects, or by preventing microbial attachment. The importance of these barriers is demonstrated by the greatly increased risk of sepsis that occurs when they are significantly breached, such as occurs following severe burns or in epidermolysis bullosa.

If these barriers are breached and tissues invaded, pathogens are confronted by the innate immune response, an early evolutionary adaptation; this lacks immunological memory, so that the magnitude of response is the same no matter how many times the antigen is encountered. Pathogens are recognized by genetically predetermined receptors such as Toll-like receptors (TLRs) on the surface of phagocytic cells, which detect a limited range of highly conserved structures, such as bacterial lipopolysaccharide, mannan and peptidoglycan, present on many micro-organisms but not on the host. Recognition of one of these molecules causes immediate activation and cytokine release, accounting for the rapid response of the innate system. New understanding of defects in signalling in this part of the innate immune system have revealed associations with anhidrotic ectodermal dysplasia and incontinentia pigmenti.

Neutrophils are part of the innate response, endocytosing and killing invading pathogens. Macrophages and monocytes also endocytose pathogens, but in addition process antigen and present it to T lymphocytes to initiate the adaptive response. Soluble plasma proteins such as mannan binding protein and complement play an important first line role in innate defence once the epithelial surfaces are breached. Complement is a series of plasma proteins that act in a cascading sequence to attack extracellular organisms. Direct activation by microorganisms proceeds through the alternative pathway, whilst the classical pathway requires activation by antibody bound to antigen. Complement coating microorganisms can kill pathogens directly, or can facilitate pathogen removal by phagocytes, which bind complement to complement receptors. Non-function or absence of components of the alternative pathway or terminal pathway leads to recurrent infection with extracellular pathogens, particularly *Neisseria* species. Defects in the classical pathway, which plays a role in the clearance of immune complexes, leads to immune-complex mediated disease, chronic inflammation and systemic lupus erythematosis. Neutrophil defects include severe congenital neutropenia (Kostmann's syndrome), associated with an absolute neutrophil count below 500 cells/mm^3, and cyclical neutropenia, in which neutropenia occurs at roughly 3-weekly intervals. Patients with these conditions are at risk of bacterial and fungal infection. Once activated, neutrophils normally migrate from blood vessels to the site of infection. In leukocyte adhesion deficiency, neutrophils lack integrin molecules, which are necessary for their adherence to blood vessel walls and migration between vascular endothelial cells to the site of infection. Affected patients mobilize very large numbers of neutrophils, but they are unable to migrate into tissues. Patients present with delayed umbilical cord separation, rapidly enlarging infected skin ulcers with no pus, and recurrent soft tissue, respiratory and gastrointestinal infection. To eliminate infection, phagocytes must both ingest microorganisms and kill them once ingested. Intracellular killing is defective in chronic granulomatous disease, where patients cannot generate intracellular hydrogen peroxidase, as the enzyme NADPH oxidase is defective. Affected patients are susceptible to recurrent infections with catalase-positive bacteria and fungi, and suffer recurrent soft tissue, respiratory and

gastrointestinal infection with tissue scarring due to granuloma formation.

Much of the immune response is mediated by soluble protein messengers called cytokines, which are secreted by the liver, vascular endothelium and white blood cells. Defects in cytokine signalling pathways can have serious consequences. Macrophages produce interleukin (IL)-12 in response to infection, leading to interferon gamma (IFN-γ) release by T lymphocytes and natural killer cells, which in turn activates hydrogen peroxide production by the macrophages. Defects in IL-12, IL-12 receptor chains and IFN-γ have been identified in patients with severe or recurrent atypical mycobacterial or BCG infection. Overproduction of cytokines due to genotypic polymorphisms can also lead to problems. Increased tumour necrosis factor alpha (TNF-α) production gives increased protection to mycobacterial infection, but leads to an overwhelming pro-inflammatory cascade and severe septic shock in meningococcal infection. Defects in components of the TLR signalling pathway have recently been described in a few patients, leading to recurrent infection, predominantly with polysaccharide-encapsulated bacteria.

The adaptive immune system

T (thymus-derived) and B (bone marrow-derived) lymphocytes, which constitute the adaptive immune response, are generated in specialized lymphoid organs, namely lymph nodes, spleen and mucosal-associated lymphoid tissue. Characteristics of the adaptive response include proliferation of antigen-specific T and B lymphocytes, following activation by cells of the innate system. T lymphocytes act directly whilst B lymphocytes produce specific antibody. To respond to the vast number of possible antigens, B lymphocytes produce approximately 10^{18} different antibody variable regions, with a similar number of T-lymphocyte (or cell) receptor (TCR) variable regions, from fewer than 400 germline genes. This remarkable diversity means that there is a T or B lymphocyte with a receptor to complement every protein antigen that could be made. This variety is achieved by promiscuous recombination processes that cut, splice and modify variable region receptor genes. This randomly generated receptor diversity produces self-reactive lymphocytes as well as lymphocytes generated against specific microorganisms. Early lymphocyte development enables receptor rearrangement, but, following expression of a mature receptor, continued survival is antigen dependent and self-reactive lymphocytes are usually eliminated.

B-lymphocyte development

The diverse repertoire of T- and B-lymphocyte receptors is generated by recombination of a small number of gene segments. B-lymphocyte receptors (BCR) are membrane-bound immunoglobulin. Immunoglobulins are composed of two identical heavy (H) chains and two identical light (L) chains, held together by disulphide bonds. Immunoglobulins have two separate functions, firstly to bind to specific antigen, through the variable (V) domain, and secondly to recruit other cells to the immunoglobulin-bound antigen to affect killing and destruction. The second function is mediated through the constant (C) domain. The constant region is invariant for each immunoglobulin class, although it has five main forms or isotopes which determine the immunoglobulin class (IgM, G, A, E, D). Small variations lead to four IgG and two IgA subclasses. Both heavy and light chains have C and V domains.

Variable domains are constructed from the recombination of gene segments from two or three 'families' of genes. In light chains, a V (variable) segment is joined to a J (joining) segment. These are joined to the light chain C domain. A similar process occurs in the heavy chain, but there are three different gene segments in the variable region, a V (variable) segment, a J (joining) segment and a D (diversity) segment, which join to the heavy chain C domain. There are a number of different gene segments in each 'family' and so diversity is generated by varying the combination in which the V (D) J segments are arranged. Further diversity is introduced by pairing different heavy and light chain variable regions, and by imprecise splicing and rejoining of different gene segments, which give rise to different nucleotide sequences at the joining junction. These recombination events occur in the bone marrow. 'Fine tuning' of the response to produce antibody exactly complementary to antigen (somatic hypermutation) requires T-cell cooperation (see below). This unique and complex system is very prone to genetic faults, which are not lethal *in utero*. Mutations in genes encoding B-cell heavy or light chains, or in the associated signalling molecules necessary for their development, lead to absence of B cells and agammaglobulinaemia, as seen in X-linked agammaglobulinaemia (Bruton's disease) or to hypogammaglobulinaemia due to μ-chain deficiency. Defects in specific immunoglobulin heavy or light chain translation lead to individual class or subclass deficiency, although some humoral immunity is preserved.

T-lymphocyte development

T-lymphocyte receptor (TCR) development is very similar to that of B lymphocytes, but occurs in a specialized microenvironment, the thymus. Precursor cells migrate to the thymus and undergo TCR chain rearrangements. The TCR consists of α/β or γ/δ heterodimers. Each α, β, γ, δ chain contains a variable and a constant domain. As in the BCR, the variable domains are constructed from gene segments from different V, (D) and J 'families'. TCR α and γ loci do not contain D segments. The TCR differs from the BCR in that TCRs only recognize antigen that is bound to an individual's own major histocompatibility complex (MHC) tissue type molecule expressed on the surface of their cells. Thus, during thymic development, only T lymphocytes that recognize antigen presented by self MHC complex are allowed to survive positive selection (self MHC restriction); then, those that recognize self-antigen–MHC complex are destroyed (negative selection—self-tolerance). Only about 2% of T-lymphocyte precursors entering the thymus pass this rigorous selection process and leave as mature, naïve T lymphocytes.

T and B lymphocytes use similar signalling and enzymatic processes to rearrange gene segments and construct antigen receptors. These enzymes have evolved from those used to repair DNA damaged by UV light or ionizing radiation, hence the occurrence of photosensitivity in certain DNA repair disorders. Many of these enzymes are critical to lymphocyte development, which cannot occur in their absence, explaining the various forms of severe combined immunodeficiency (SCID), for example as when

recombination activating genes (*RAG1* and *2*) are mutated resulting in T-negative, B-negative SCID. The important role of the thymus is illustrated by complete DiGeorge syndrome or CHARGE syndrome, where congenital thymic absence leads to a SCID phenotype with absence of T lymphocytes. A number of signalling molecules and their receptors, particularly those for cytokines and their receptors, are also critical in lymphocyte development and survival. Thus, absence of the common cytokine receptor γ chain, which is integral to the IL-2, -4, -7, -9 and -15 receptors, leads to T-lymphocyte-negative, B-lymphocyte-positive, NK-lymphocyte-negative SCID, as does absence of Janus-associated kinase (JAK)-3, which is a signalling molecule associated with the cytokine receptors. Other defects can lead to dysregulation of thymic selection.

A lymphocyte that fails either negative or positive selection undergoes apoptosis. Defects in the apoptosis pathway, such as Fas or Fas ligand molecules or in the downstream caspases, leads to the escape of autoreactive lymphocytes, which can lead to autoantibody production and autoimmune disease.

Antigen presentation and lymphocyte interaction

Mature T and B lymphocytes circulate through the blood, lymphatics and tissues looking for the antigen that is specific for their particular receptor. Microorganisms are taken up by cells of the innate response, such as macrophages. They are broken down in lysosomes to small polypeptide fragments of 8–12 amino-acids long, combined with MHC class I or II molecules and presented at the cell surface as an antigen/MHC complex, with antigen bound within the groove of the MHC molecule. Defects in the MHC class II transcription molecules, or in the MHC class I transporter proteins (which transport antigen peptide to MHC I molecules) occur and although affected individuals have functionally normal lymphocytes, they suffer repeated, life-threatening infections because antigen cannot be presented to their T and B lymphocyte receptors.

Most adaptive immune responses occur in lymphoid tissue, where lymphocytes and antigen-presenting cells (macrophages, dendritic cells) are concentrated. There are at most only a few hundred lymphocytes with a receptor complementary to a specific antigen. When a T lymphocyte interacts with a matching antigen/MHC complex (MHC class I with CD8 cytotoxic T lymphocytes, for intracellular organisms, MHC class II with CD4 helper T lymphocytes for extracellular organisms), a second signal is delivered from the antigen-presenting cell (APC) to the T lymphocytes via a B7 molecule on the APC interacting with a CD28 molecule on the T lymphocyte. The combination of these two signals (TCR/MHC–antigen and B7/CD28) activates the T lymphocyte, causing repeated replication of T lymphocytes bearing the same antigen-specific receptor; a process called clonal expansion. Conversely, delivery of the first signal without the second renders the T lymphocyte unable to respond to antigen, and this unresponsive state is known as T-lymphocyte anergy. Because only a few T lymphocytes have the receptor for the specific antigen, only a few are activated for that antigen. However, as each microorganism carries many antigens, infection will cause the proliferation and clonal expansion of many different T lymphocytes, leading to a polyclonal response. As well as triggering clonal T-lymphocyte proliferation, an activated CD4 T lymphocyte can interact with a B lymphocyte carrying the BCR specific for the antigen, triggering clonal B-lymphocyte expansion. Initially the B lymphocyte responds by secreting IgM. In lymph node germinal centres, as the adaptive response matures, interactions between T lymphocytes via CD40 ligand (expressed on T lymphocytes) and CD40 expressed on B lymphocytes, enables B lymphocytes to switch from making IgM to making IgA, IgG and IgE, through substitution of the appropriate C domain on the heavy and light chains, encoding for IgM, A, G or E respectively, a process known as isotype switching. Point mutations, deletions and insertions in the variable domain of the immunoglobulin molecule (somatic hypermutation) modify the immunoglobulin molecule further (the fourth method of creating antibody diversity) and B lymphocytes making immunoglobulin that 'fits' the antigen most precisely are generated in great number (affinity maturation), whilst B lymphocytes that produce immunoglobulin of a 'less good' fit undergo apoptosis. Once activated, these T lymphocytes and B lymphocytes are long lived and act as memory lymphocytes. Thus, when the same antigen is encountered again, these lymphocytes immediately react and do not require activation by the innate system. The immunoglobulin that is produced attaches to the microorganism via the antigen-binding region. The effector portion of the immunoglobulin attaches to immunoglobulin receptors on phagocytes and macrophages, facilitating phagocytosis and antigen processing and elimination. Defects in these mechanisms illustrate their importance. In X-linked hyper-IgM syndrome, CD40 ligand is deficient, so B lymphocytes are unable to switch from making IgM to other immunoglobulin isotypes. T lymphocytes are also unable to interact with macrophages (which also express CD40), which are unable to kill ingested intracellular pathogens such as *Pneumocystis jiroveci* and *Cryptosporidium parvum*, thus allowing opportunistic infection with these organisms. An autosomal recessive form of hyper-IgM syndrome is due to mutations in the activation-induced cytidine deaminase gene, which encodes a protein involved in the isotype switching and hypermutation processes.

Once switched on by antigen presentation, T lymphocytes develop in different ways, and two routes are fairly well characterized; the Th1 route with production of IL-2 and IFN-γ, whose main role is in stimulating macrophage function and cell-mediated immunity, but which also induces B lymphocytes to switch the class of antibody produced, particularly to IgG2. Th2 cells, on the other hand, produce predominantly IL-4 and IL-10, which promote antibody responses and class switching, particularly towards IgG1, IgG4 and IgE. Allergic responses and those against parasites are of Th2 type. Responses to an antigen may follow a Th1 or Th2 route depending on a complex set of circumstances. Once established, these responses are self-amplifying in that production of IFN-γ or IL-4 promotes Th1 and Th2 responses, respectively, and inhibits the other.

Over-activation of the antigen/TCR or BCR binding process can also cause disease; bacterial toxins and some viruses act as so called superantigens, which bind to the outside of the MHC molecule, and in particular to the outside of a V-chain (one of the V segments of the β chain of the TCR), regardless of the antigenic specificity of the V domain of the β chain, or of the DJ segments of the V domain of the β chain. Thus instead of activating, say,

only 20 out of 10^{16} naïve T lymphocytes, one superantigen is able to activate up to 20% of the T-lymphocyte pool, which leads to massive lymphocyte activation and cytokine release, accounting for the features of marked inflammation (inducing polymorphic and vasculitic rashes) seen in superantigen-mediated diseases such as toxic shock syndrome and Kawasaki disease.

Elucidation of the molecular pathways enhances our understanding of the immune response, and identification and clarification of precise molecular mechanisms enables us to better understand and treat primary immune deficiencies. Thus, X-linked hyper-IgM used to be considered an antibody deficiency, although immunoglobulin replacement did not prevent liver disease secondary to *Cryptosporidium parvum* infection. Recognition that it is a primary T-lymphocyte defect has led to haematopoietic transplantation in selected patients. Identification of the genetic defect in X-linked SCID has led to successful gene therapy for this condition.

The skin is a vital component of the innate immune system and the site where many innate and adaptive immune responses to infection are seen. It is not surprising, therefore, that skin sepsis and other dermatological manifestations are common features of primary immunodeficiency. Understanding the context of these responses ought to give a clearer view of these conditions and their treatment.

Immunodeficiency disorders: general principles

Classification and genetics

The overall incidence of any significant immune deficiency disorder (excluding selective IgA deficiency) has been estimated at 1 in 10 000. The WHO working party on immunodeficiency [1] has classified the primary disorders (Table 17.7).

Reference

1 Geha RS, Notarangelo LD, Casanova JL *et al*. Primary immunodeficiency diseases: an update from the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee. *J Allergy Clin Immunol* 2007; **120**: 776–94.

Diagnosis and investigation of immunodeficiency

A careful history and examination should precede laboratory tests as the clues obtained should determine which children should be investigated and which tests performed.

History

Taking a careful family history may reveal other children with unusual or fatal infectious complications suggestive of an autosomal recessive or X-linked pattern of inheritance. A history of consanguinity within the family should be sought. Delayed separation of the umbilical cord, in the absence of local infection, may suggest a neutrophil defect. Most children will present because of an infective problem. An immunodeficient child is likely to have more infections compared to normal children, which take longer to resolve or follow an atypical course. The type of organism involved, especially atypical ones, should direct further investigation. Cutaneous infections in immunodeficient patients are either caused by microorganisms not usually pathogenic in normal individuals, or follow a more severe course with the same microorganism than in those with normal immunity. Such infections may not immediately suggest a primary immunodeficiency unless this diagnosis is actively considered. Conversely, the familial

Table 17.7 Combined immunodeficiencies and defects of phagocytic function.

Immunodeficiency	Defect	Inheritance
CD40 ligand deficiency	CD40 ligand (CD154)	XL
Wiskott–Aldrich syndrome	WAS protein	XL
X-linked lymphoproliferative disease	SLAM-associated protein	XL
	X-linked inhibitor of apoptosis	XL
DiGeorge syndrome	Chromosomal deletion (usually 22q11.2 deletion, occasionally 10p deletion)	Sporadic (some AD)
CHARGE syndrome	*CHD7*	Sporadic (some AD)
Cartilage hair hypoplasia	*RMRP* gene	AR
Immunodeficiency with albinism:		
Chediak–Higashi syndrome	Lyst gene	AR
Griscelli syndrome	*RAB27A*	AR
Hermansky–Pudlak syndrome type 2	*AP3B1*	AR
Endosomal adaptor protein deficiency	p14	AR
Familial haemophagocytic lymphohistiocytosis	Perforin gene	AR
	UNC13D	AR
	Syntaxin 11	AR
Ataxia–telangiectasia	*ATM* gene	AR
Nijmegen breakage syndrome	*NBS1* gene	AR
Ligase IV deficiency	DNA ligase IV	AR
Fanconi's anaemia	*FAND2* gene	AR
Ectodermal dysplasia–immunodeficiency	*NEMO* gene	XL
	IRAK-4	AR
	IκBα	AR
XL chronic granulomatous disease	p91phox	XL
AR chronic granulomatous disease	p22phox	AR
	p47phox	AR
	p67phox	AR
Leukocyte adhesion deficiency Type I	β integrin (CD18)	AR
Leukocyte adhesion deficiency Type II	CD15	AR
Leukocyte adhesion deficiency Type III	RAP1A activation defect	AR
Neutrophil G6PD deficiency	Neutrophil G6PD	XL
Myeloperoxidase deficiency	Myeloperoxidase	AR
Severe congenital neutropenia	Elastase 2	AR
	HAX1	AR
	WAS activating mutation	XL
Mycobactericidal defect	IFN-γ receptor 1 deficiency	AR
	IFN-γ receptor 2 deficiency	AR
	IL-12 receptor deficiency	AR
	IL-12 deficiency	AR
	STAT 1 deficiency	AR
	NFκB signalling pathway defects (NEMO)	XL

XL, X-linked; AD, autosomal dominant; AR, autosomal recessive.

presentations of cutaneous staphylococcal infection in the absence of infection at other sites is much more likely to be due to nasal carriage of staphylococci, and cross infection, than immunodeficiency. Frequent upper respiratory tract infections (URTI) alone in a young child are not indicative of an underlying immune defect unless associated with frequent bacterial infections, clinical experience suggesting that up to eight URTI per year is normal in the pre-school years [1]. Infections with common organisms may run an atypical course that is unusually severe (e.g. haemorrhagic chicken pox) or they fail to respond to standard treatments (e.g. a bacterial pneumonia which fails to respond to appropriate antibiotic therapy). Alternatively, infections may be caused by uncommon (atypical) organisms which are in themselves highly suggestive of immunodeficiency, such as *Pneumocystis jiroveci* pneumonia [2]. Failure to thrive is a common finding, and this may or may not be associated with diarrhoea due to chronic or recurrent infection or autoimmune enteropathy [3]. Evidence of end-organ damage, such as a cough productive of sputum consistent with bronchiectasis, should also be sought. Allergic/atopic problems are common and may be unusually severe. Autoimmune and malignant diseases, though not common, have an increased incidence. Photosensitivity rashes may be a particular feature in some disorders, for example the immunodeficiencies associated with DNA repair disorders.

In some disorders, for example IgA deficiency, there may be a family history of collagen vascular or other immunopathological disease [4]. Older relatives who are carriers of an inherited immunodeficiency or who are affected by milder variants of primary immune defects may have autoimmune manifestations (e.g. mouth ulcers and systemic lupus erythematosus variant in chronic granulomatous disease (CGD) [5]) or have a history of malignant disease (lymphoma in X-linked lymphoproliferative disease (XLP) or Wiskott–Aldrich syndrome (WAS)).

Furuncular lesions or abscesses can be an overlooked manifestation of a primary immunodeficiency. They are most characteristically seen in neutrophil disorders (Table 17.7) such as CGD [6], Chediak–Higashi syndrome, leukocyte adhesion deficiency [7] and neutrophil-specific granule deficiency, but also in hyper-IgE syndrome [8] and antibody deficiencies such as XLP or in complement disorders. In these disorders it is, however, usual for infections of the skin to be accompanied by infection at other sites.

Cutaneous and mucosal ulceration are features of several immunodeficiency states and are the hallmark of leukocyte adhesion deficiency. Although infection is believed likely to be the cause of the ulceration, it can be difficult to identify the microorganisms responsible, and the accumulation of neutrophils in small blood vessels to the point where blockage and tissue necrosis occurs probably plays a big part in their genesis. Such ulcers are a characteristic feature of disorders featuring neutropenia, including congenital neutropenia, cyclical neutropenia and the Chediak–Higashi syndrome. Gradually extending cutaneous ulcers due to herpes simplex virus (HSV) (Fig. 17.9) are suggestive of T-lymphocyte defects, but have also been reported in X-linked agammaglobulinaemia.

Unusually severe or extensive infections with HSV or varicella-zoster virus, including the haemorrhagic vesicles seen in haemorrhagic chickenpox, are characteristic of T-lymphocyte defects.



Fig. 17.9 Progressive cutaneous ulceration due to herpes simplex in a 9-year-old child with T-lymphocyte immunodeficiency.



Fig. 17.10 Unusually large and rapidly proliferating viral warts in a child with combined immune deficiency.

Bullous impetigo with clear blisters may be a presentation of neutropenia. A vesicular presentation of the hyper-IgE syndrome in infancy has been described [9].

Ordinary viral warts are virtually never indicative of immunodeficiency. However, exceptionally rapid growth of warts, exceptionally large size or unusually extensive infections are suggestive of underlying defects of immunity (Fig. 17.10). Severe, extensive, persistent molluscum contagiosum is seen in similar disorders such as WAS, CD40 ligand deficiency and less well characterized combined immune deficiencies (Fig. 17.11).



Fig. 17.11 Severe molluscum contagiosum in a child with an undefined T-lymphocyte defect. (Courtesy of the Paediatric Immunology Unit, Newcastle General Hospital, UK.)

Refractory mucosal and cutaneous *Candida* infections are a characteristic presenting sign of several immunodeficiency disorders, particularly severe combined immunodeficiency and severe T-lymphocyte defects. Surprisingly, systemic *Candida* infections are rather rare in these conditions. Persistent mucosal and cutaneous *Candida* infection, which responds poorly to systemic treatment, suggests chronic mucocutaneous candidiasis.

Non-infectious, non-specific manifestations of immunodeficiency

If atopic eczema is considered to be an immunodeficiency disease, eczema would certainly be the commonest of all cutaneous manifestations of immunodeficiency. Eczema is also a characteristic cutaneous feature of some primary immunodeficiencies disorders such as WAS, and has been recorded as occurring more frequently than one would expect in various other disorders, including selective IgA deficiency, selective IgM deficiency, ataxia–telangiectasia and combined immunodeficiency.

Morbilliform eruptions are sometimes caused by viral infections, as in other children, but in severe combined immunodeficiency they are quite frequently manifestations of acute graft-versus-host disease (GvHD), due either to maternofetal engraftment, or to engraftment of viable lymphocytes from a third party after the transfusion of non-irradiated blood products after birth (Fig. 17.12). A rash may be seen after vaccination with live vaccines, such as measles, mumps and rubella or varicella, in patients with severe T-lymphocyte immunodeficiency, who develop disease.

Petechiae, due to thrombocytopenia, are a highly characteristic feature of WAS and may also occur in Fanconi's anaemia, dyskeratosis congenita, Schwachman's syndrome and the Chediak–Higashi syndrome.



Fig. 17.12 Acute graft-versus-host disease following transfusion of non-irradiated blood in a child with severe combined immunodeficiency.

Vasculitic lesions may rarely be seen as an autoimmune manifestation and have been documented in XLP, autoimmune lymphoproliferative syndrome (ALPS) and the immunodysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome, as well as common variable immunodeficiency (CVID).

A combination of erythroderma of early onset with failure to thrive in early infancy is highly suggestive of immunodeficiency, and often results from dysregulated, activated T lymphocytes invading the skin. In some cases these are maternally derived and represent true GvHD [10], whilst in other cases aberrant clones of the infant's own T lymphocytes cause a similar reaction, which results in the condition known as Omenn syndrome, a 'leaky' form of SCID.

Patients with several different primary immunodeficiencies have featured indurated erythematous papules and plaques with central scaling, scarring, atrophy or ulceration, which demonstrated caseating granulomas histologically. The conditions in which these have been reported include common variable immunodeficiency [11], X-linked agammaglobulinaemia [12], ataxia-telangiectasia [13] chronic granulomatous disease [14] and patients with atypical *RAG* mutations [15].

As well as classical systemic and discoid lupus erythematosus, a syndrome resembling systemic lupus erythematosus from the cutaneous point of view, but having only very mild non-cutaneous manifestations and either absent or very low-titre plasma antinuclear antibodies, has been described in patients with a variety of complement deficiencies, most commonly C2 deficiency but also C3, C4, C9 and C1 esterase inhibitor deficiency. In such patients, this syndrome can occasionally have its onset as early as the first year of life, and, because many of these patients are susceptible to certain infections such as meningococcal meningitis, the association of a disorder resembling lupus erythematosus and recurrent infections of appropriate type is highly suggestive of a hereditary complement deficiency.

There is an increased incidence of systemic lupus erythematosus in patients with IgA deficiency, and skin lesions closely resembling discoid lupus erythematosus have occurred in female carriers of the gene for X-linked chronic granulomatous disease.

References

1 Chapel HM. Consensus on diagnosis and management of primary antibody deficiency. *BMJ* 1994; **308**: 581–5.
2 Berrington JE, Flood TJ, Abiniun M *et al.* Unsuspected *Pneumocystis jiroveci* pneumonia at presentation of severe primary immunodeficiency. *Arch Dis Child* 2000; **82**: 144–7.
3 Cavazzana-Calvo M, Fischer A. Gene therapy for severe combined immunodeficiency: are we there yet? *J Clin Invest* 2007; **117**: 1456–65.
4 Cunningham Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. *Clin Immunol* 1999; **92**: 34–48.
5 Brandrup F, Koch C, Petri M *et al.* Discoid lupus erythematosus-like lesions and stomatitis in female carriers of X-linked chronic granulomatous disease. *Br J Dermatol* 1981; **104**: 495–505.
6 Jones LBKR, McGrogan P, Flood TJ *et al.* Chronic granulomatous disease in the UK and Ireland—a comprehensive national patient based registry. *Clin Exp Immunol* 2008; **152**: 211–8.
7 Paller AS, Nanda V, Spates C *et al.* Leukocyte adhesion deficiency: recurrent childhood skin infections. *J Am Acad Dermatol* 1994; **31**: 316–9.
8 Grimbacher B, Holland SM, Gallin JI *et al.* Hyper-IgE syndrome with recurrent infections—an autosomal dominant multisystem disorder. *N Eng J Med* 1999; **340**: 692–702.
9 Chamlin SL, McCalmont TH, Cunningham BB *et al.* Cutaneous manifestations of hyper-IgE syndrome in infants and children. *J Pediatr* 2002; **141**: 572–5.
10 Muller SM, Ege M, Pottharst A *et al.* Transplacentally acquired maternal T lymphocytes in severe combined immunodeficiency: a study of 121 patients. *Blood* 2001; **98**: 1847–51.
11 Torrelo A, Medeiro IG, Zambrano A. Caseating cutaneous granulomas in a child with common variable immunodeficiency. *Pediatr Dermatol* 1995; **12**: 170–3.
12 Fleming MG, Gewurz AT, Pearson RW. Caseating granulomas in a patient with X-linked infantile hypogammaglobulinaemia. *J Am Acad Dermatol* 1991; **24**: 629–33.
13 Joshi RK, Al Asiri RH, Haleem A *et al.* Cutaneous granuloma with ataxia telangiectasia. *Clin Exp Dermatol* 1993; **18**: 458–61.
14 Johnston RB, Baehner RL. Chronic granulomatous disease: correlation between pathogenesis and clinical findings. *Pediatrics* 1971; **48**: 730–9.
15 Schuetz C, Huck K, Gudowius S *et al.* An immunodeficiency disease with RAG mutations and granulomas. *N Engl J Med* 2008; **358**: 2030–8.

Table 17.8 Features of skin disease in primary immunodeficiency.

Dermatological abnormality	Disease
Autoimmune or immune-mediated	Vasculitis–XLP
	Petechiae secondary to thrombocytopenia–WAS
	CGD carriers
	ALPS
	MFE–SCID
	Omenn's syndrome
Malignancy	DNA repair disorders
Chemical or radiation damage	Photosensitivity–DNA repair disorders
	CGD carriers
Plantar warts, molluscum contagiosum	WAS
	WHIM syndrome
	AR HIES
Abscesses	Neutrophil disorder, e.g. CGD
	Antibody deficiency, e.g. XLA
	HIES
Candida	CMC
	SCID
	HIES
Pigmentation disorders	Chediak–Higashi syndrome
	Griscelli syndrome
	Hermansky–Pudlak syndrome Type 2
	Endosomal adaptor protein p14 deficiency
	NEMO
Photosensitivity	DNA repair disorders, e.g. DNA ligase 4 deficiency

ALPS, autoimmune lymphoproliferative syndrome; AR, autosomal recessive; CGD, chronic granulomatous disease; CMC, chronic mucocutaneous candidiasis; HIES, hyper-IgE syndrome; MFE, maternofetal engraftment; SCID, severe combined immunodeficiency; WAS, Wiskott–Aldrich syndrome; WHIM, wart hypogammaglobulinaemia infection, and myelokathexis syndrome; XLP, X-linked lymphoproliferative syndrome.

Examination

General physical examination should be directed towards examination of potential sites of infection, including the throat, ears and sinuses, and the oral cavity and nappy area for candidiasis. The presence or absence of lymphoid tissue should be noted, as should cutaneous problems consistent with an immune defect. In more severe antibody states such as X-linked agammaglobulinaemia, there is a lack of tonsils and lymphoid tissues. Signs of end-organ damage from infections, such as clubbing and respiratory abnormalities must be sought. Some diseases may have specific physical signs, such as oculocutaneous albinism in Chediak–Higashi syndrome, typical facies and/or cleft palate in DiGeorge or CHARGE syndrome, typical facies in immunodeficiency, centromeric instability, facial dysmorphism (ICF) syndrome, telangiectasia or neurological abnormalities in ataxia-telangiectasia, and disproportionate short stature in some forms of combined immune deficiency (see Immunodeficiency and short-limbed dwarfism, below). Specific skin lesions can give clues to the underlying immunological disorder (Table 17.8).

Radiological evaluation

Evidence of bony abnormalities may support a diagnosis of adenosine deaminase deficiency [1], Schwachman–Diamond syndrome [2] or other dysplasias associated with immune defects. Dilatation of the common bile duct may be suggestive of sclerosing cholangitis, associated with a number of combined immune deficiencies especially X-linked hyper IgM syndrome [3]. Careful review of chest radiographs may suggest bronchiectasis, and should prompt high resolution computed tomograph imaging. Although absence of a thymus on anterior posterior and lateral chest radiographs is consistent with a combined immune defect in infants and young children, thymic atrophy may also occur in response to stress (e.g. infection) and this finding is not diagnostic.

References

1 Wortmann RL, Tekkanat KK, Veum JA *et al.* Basis for the chondro-osseous dysplasia associated with adenosine deaminase deficiency: selective toxicity to immature chondrocytes. *Adv Exp Med Biol* 1991; **309B**: 265–8.
2 Berrocal T, Simón MJ, al-Assir I *et al.* Shwachman-Diamond syndrome: clinical, radiological and sonographic aspects. *Pediatr Radiol* 1995; **25**: 289–9.
3 Levy J, Espanol-Boren T, Thomas A *et al.* Clinical spectrum of X-linked hyperIgM syndrome. *J Pediatr* 1997; **131**: 47–54.

Laboratory investigation

Two main questions need to be addressed: which children to investigate, and how extensively to investigate selected children [1]. Investigation should be triggered by one or more of the warning signs (Table 17.9). Laboratory investigations can be

Table 17.9 Warning signs of immunodeficiency.

Eight or more new infections within 12 months
Two or more serious sinus infections or episodes of pneumonia within 1 year
Two or more months on antibiotics with little effect
Failure of an infant to gain weight or grow normally
Recurrent deep skin or organ abscesses
Persistent superficial candidiasis after age 1 year
Episode of opportunistic infection
Complication associated with live vaccination
Need for intravenous antibiotics to clear infections

Table 17.10 Examples of association between most likely type of immune defect and infecting organisms.

Candidate immune defect	Typical infecting organism
Antibody	*Streptococcus pneumoniae, Haemophilus influenzae, Giardia lamblia, Mycoplasma* spp., Enteroviruses
Cell mediated	*Salmonella, Cryptosporidium, Giardia lamblia, Candida albicans*, herpesviruses (e.g. CMV), other viruses e.g. measles, Bacille Calmette-Guerin, *Pneumocystis jirovecii*
Neutrophil	*Staphylococcus* Gram-negative bacteria, *Candida albicans, Aspergillus* spp., Bacille Calmette-Guerin
Type-1 cytokine defects	*Salmonella, Mycobacteria* (typical and atypical), Bacille Calmette-Guerin
Monocyte	*Candida albicans*
Natural killer cell	Herpesviruses
Complement	*Neisseria meningitidis, Streptococcus pneumoniae, Haemophilus influenzae*

directed to a certain extent by the organism causing infection (Table 17.10) and the age of the child. Laboratory investigations range from those readily available in all centres, to highly specialized tests performed in research centres. Only a small proportion of children presenting with recurrent infections require complex investigation; most can be adequately investigated with a few relatively straightforward tests (Table 17.11).

A full blood count and film can be very revealing. Neutropenia is readily detected, and a bone marrow aspiration will distinguish failure of production from increased peripheral destruction, and also exclude a myelodysplastic or malignant process. Neutrophilia in the absence of overt infection may suggest a neutrophil adhesion defect or functional problem (e.g. CGD). Lymphopenia, using appropriate age-related ranges, strongly suggests a combined immune deficiency of primary or secondary aetiology [2], although SCID can occur in the presence of a normal lymphocyte count. Nucleated red cells in infants and abnormal leukocyte morphology in sick children may be detected as lymphocytes on the automated cell counter, and thus erroneously suggest a normal lymphocyte count. Abnormal leukocyte granules are seen in Chediak–Higashi syndrome, whilst a platelet volume is invariably low in WAS, making this the most rapid and reliable diagnostic pointer in this condition [3].

Table 17.11 Investigations in children with suspected primary immunodeficiency.

First line investigation	Second line investigation
FBC and WCC differential	Chromosomal studies
Lymphocyte subsets	Genetic studies
IgM, A, G and IgG subclasses	HRCT of chest
Specific tetanus, HiB antibodies	Bronchoscopy
Pneumococcal antibodies (if >2 years)	Tissue biopsy
Simple spirometry (if >5 years)	Radiation sensitivity studies
Plain chest radiograph	Specific lymphocyte marker studies
Microbiological investigations (culture, IF, PCR)	Lymphocyte proliferation investigations
Complement C3, C4 levels	Neutrophil oxidative burst investigations
Functional complement investigations	

FBC, full blood count; WCC, white cell count; HiB, *Haemophilus influenzae* type B; IF, immunofluorescence; PCR, polymerase chain reaction; HRCT, high resolution computed tomograph.

References

1 Slatter MA, Gennery AR. Clinical immunology review series: an approach to the patient with recurrent infections in childhood. *Clin Exp Immunol* 2008; **152**: 389–96.

2 Hague RA, Rassam S, Morgan G *et al*. Early diagnosis of severe combined immune deficiency syndrome. *Arch Dis Child* 1994; **70**: 260–3.

3 Oda A, Ochs HD. Wiskott-Aldrich syndrome protein and platelets. *Immunol Rev* 2000; **178**: 111–7.

Tests of innate immunity

Complement

C3 and C4 are easily measured; however, null alleles for C4 are relatively common, so that the significance of an isolated low C4 in an individual with recurrent infections is less certain. Furthermore, normal levels of C3 and C4 do not exclude deficiencies of other complement components. It is better to screen the whole complement system by assessing the functional integrity of the classical and alternative complement pathway using assays which test the ability of patient serum to lyse sensitized red blood cells (CH50/100 and AP50 respectively). Deficiency in any one component will result in a failure of lysis. Low values may be seen in the presence of active infection, when complement components are being consumed, or if degradation of complement components has occurred because the sample was not separated and frozen within 2 h of venesection. If repeat testing shows a persistent abnormality, measurement of the levels of individual complement components should be performed until the defective component is identified.

Neutrophil function tests

Neutrophil function has three main components: chemically mediated movement towards microorganisms (chemotaxis); ingestion of microorganisms into a phagocytic vacuole (phagocytosis); and activation of the respiratory burst within the phagolysosome to produce free oxygen radicals that kill microorganisms. Neutrophil function tests are fraught with technical pitfalls, as neutrophils rapidly activate upon venesection and also die quickly.

Neutrophil chemotaxis is unreliable and only performed in a research setting. Chemiluminescence measures all three phases of neutrophil activity; such assays have been superseded by flow cytometric assays (see below). Nitroblue tetrazolium (NBT) is a yellow dye that is readily taken up by phagocytes and, upon stimulation (for example with phorbol myristate acetate) is reduced to the purple dye formazan by the oxidative burst. Normally, at least 95% of neutrophils should contain a purple deposit in stimulated cells. In CGD, less than 1% of neutrophils reduce NBT. Carrier mothers of X-linked CGD can also be detected by this method as they show an intermediate level of NBT reduction (20–80%). In experienced hands, this is a rapid and sensitive test for CGD, but false normal results can be seen when the test is performed infrequently.

Flow cytometric assays of neutrophil function

The flow cytometer, widely used in the cellular immunology laboratory, counts the absolute number and proportion of cells bearing a fluorescent marker which scatters light with a distinctive pattern.

Fluorescently labelled microorganisms can be used to assess the phagocytic ability of neutrophils, seeing what proportion of cells have ingested the labelled organisms. Comparison of phagocytosis using the patient's own serum with that using control serum gives a measure of the effectiveness of patients' antibody and complement systems to aid phagocytosis (opsonization).

Phagocytosis of organisms by neutrophils and monocytes normally leads to activation of the respiratory burst and the production of free oxygen radicals. If neutrophils take up dihydrorhodamine and, using a suitable stimulus, the dihydrorhodamine is reduced, it fluoresces within cells, which can be assessed using the flow cytometer; absence of fluorescence indicating failure of the respiratory burst. This is the best test for identifying patients with CGD and will also detect carriers for X-linked CGD, who exhibit a dual population of normal and abnormal cells. The test has the advantage that more laboratories are experienced in the interpretation of flow cytometric readouts than reading slide NBT tests and so false-normal results are much less likely. It is, however, more sensitive than an NBT test so neutrophil function defects other than CGD may also be detected. Neutrophil killing defects may also occur in deficiency states of myeloperoxidase and glucose-6-phosphate dehydrogenase, which can be assayed separately.

Tests of the adaptive immune system

Test of humoral immunity

Immunoglobulins IgG, A and M are routinely measured by nephelometry which measures light scattering, the amount of light scattered being proportional to the quantity of immunoglobulin within the sample. Results must be evaluated with reference to age-specific normal ranges, as production of all five classes of immunoglobulin is low at birth and gradually matures over the first 5 years of life [1]. Low levels of Ig can only be attributed to a production defect if gut or renal losses have been excluded and the serum albumin is within the normal range. Catabolic states, such as myotonic dystrophy, can also lower total immunoglobulin levels.

IgE is measured using a variety of techniques, including enzyme-linked immunosorbent assays (ELISA) and automated solid-phase ELISAs. IgG subclasses are commonly measured by nephelometry or radial immunodiffusion. Results should be compared with age-specific normal ranges.

Reference

1 Insel RA and Looney RJ. The B-lymphocyte system. In: Stiehm RE, Ochs HD, Winkelstein JA, eds. *Immunologic Disorders in Infants and Children*, 5th edn. Philadelphia: Elsevier Saunders, 2004.

Measures of in vivo antibody responses

The ability of the immune system to produce functional antibody is more important than the amount of circulating antibody. Functional tests of IgG production rely on measuring antibody titres to antigens to which the child is known to have been exposed either naturally or by vaccination. Responses to protein antigens such as tetanus, diphtheria and the conjugated (*Haemophilus influenzae* type B) Hib vaccine are widely available. However, although normal ranges for antibody titres exist, these are not well validated for antigens other than Hib, and may not be a true reflection of immunological memory. If antibody titres are low, booster vaccinations should be given to assess the memory response. In children over 2 years of age, administration of 23-valent polysaccharide pneumococcal vaccine is useful to assess the ability to respond to carbohydrate antigens. Interpretation of these responses has become more difficult since the introduction of the 7-valent conjugated pneumococcal vaccine into the national immunization schedule. Measurement of individual serotypes, contained in the 7-valent conjugate pneumococcal polysaccharide vaccine, as well as those found only in the 23-valent pneumococcal polysaccharide vaccine, gives most useful information [1,2]. Loss of the polysaccharide response may be the first sign of an evolving immune deficiency in patients with common variable immunodeficiency or WAS. Assessment of antibody responses to common respiratory viral pathogens and varicella zoster may also provide useful additional information, although negative tests in the absence of microbiologically proven disease are difficult to interpret.

The optimal test of *in vivo* antibody production is assessment of IgM and IgG responses and rate of clearance to a novel antigen whose clearance is dependent on opsonization by a specific antibody. IgM isohaemagglutinin responses to ABO blood group antigens can be a useful measure of intrinsic IgM production.

References

1 Balmer P, Cant AJ, Borrow R. Anti-pneumococcal antibody titre measurement: what useful information does it yield? *J Clin Pathol* 2007; **60**: 345–5.

2 Lakshman R, Gennery AR, Arkwright PD *et al.* Assessing immune responses to pneumococcal vaccines. *Arch Dis Child* 2003; **88**: 648–9.

Cell mediated immunity

Cell mediated (T lymphocyte) defects are rarely isolated defects, and are usually accompanied by a degree of humoral immune deficiency, as T lymphocyte help is crucial in making an antibody response with memory.

Quantification of cell numbers. Lymphocytes can be enumerated using flow cytometry, which detects the different light scatter

properties of cells passed through a laser beam, and enables populations of neutrophils, monocytes and lymphocytes to be differentiated. Lymphocytes can be characterized further by their cell surface markers, which are identified by specific monoclonal antibodies. The number of cells staining with a particular monoclonal antibody can be expressed either as a percentage of the lymphocyte pool or as an absolute number. As with all immunological parameters, both proportions of different T lymphocytes and absolute numbers vary with age and reference should be made to published age-related normal ranges [1,2]. Approximately 60–80% of circulating lymphocytes are T lymphocytes, with 10–20% B lymphocytes and 5–15% NK cells.

References

1 Comans-Bitter WM, de Groot R, van den Beemd R *et al*. Immunophenotyping of blood lymphocytes in childhood. Reference values for lymphocyte subpopulations. *J Pediatr* 1997; **130**: 388–93.

2 Berrington JE, Barge D, Fenton AC *et al*. Lymphocyte subsets in term and significantly preterm UK infants in the first year of life analysed by single platform flow cytometry. *Clin Exp Immunol* 2005; **140**: 289–92.

Functional tests of cell mediated immunity. When lymphocytes encounter antigen *in vivo*, they respond by upregulation of activation markers and proliferation, without which an effective immune response cannot occur. This can be mimicked *in vitro* by culturing lymphocytes with a non-specific stimulus, such as plant lectins, and using the incorporation of tritiated thymidine or a non-radioactive marker such as bromodeoxyuridine into the DNA of dividing cells as a surrogate measure of cell proliferation.

Definition of molecular defects

Protein assays

The genetic basis of an increasing number of immune deficiencies is now well defined; many occur because a surface or cytoplasmic signalling protein is absent or defective. These abnormalities can be detected using a combination of western blotting and flow cytometry [1,2].

References

1 Gilmour KC, Cranston T, Jones A *et al*. Diagnosis of X-linked lymphoproliferative disease by analysis of SLAM-associated protein expression. *Eur J Immunol* 2000; **30**: 1691–7.

2 Gilmour KC, Cranston T, Loughlin S *et al*. Rapid protein-based assays for the diagnosis of T-B+ severe combined immunodeficiency. *Br J Haematol* 2001; **112**: 671–6.

Genetics

In the presence of an appropriate history or abnormal protein expression, genetic analysis may be undertaken. Genes can be screened using single stranded conformational polymorphism analysis, or by direct sequencing using automated sequencers. Once mutations have been defined, parents can be tested for carrier status. Carrier testing of siblings raises a number of ethical issues, and children should reach the age of informed consent before any tests are undertaken.

Table 17.12 Molecular defects and immunophenotype in severe combined immunodeficiency.

Defect	Molecular defect	Inheritance	T, B, NK cells
Cytokine signalling	CγC	XL	− + −
	JAK 3	AR	− + −
	IL7 Rα	AR	− + +
Defects associated with the salvage pathway of nucleotide biosynthesis	ADA	AR	T_{low} B_{low} NK_{low}
	PNP	AR	$T_{low}B_{low}NK_{low}$
Defects affecting signalling through the T-cell antigen receptor	CD45	AR	− + −
	CD3δ	AR	− + −
	CD3ε	AR	− + −
	CD3ζ	AR	− + +
	ZAP70 kinase	AR	+ + + (absent CD8)
VDJ recombination defects	RAG 1 and 2	AR	− − +
	Artemis	AR	− − +
	Cernunnos	AR	T_{low} B_{low} NK+
	DNA ligase 4	AR	T_{low} B_{low} NK+
Other	Reticular dysgenesis	AR	− − − (+ myeloid dysfunction)
	MHC class II deficiency	AR	+++ (absent CD4)

XL, X-linked; AR, autosomal recessive.

Disorders of cell-mediated immunity

Severe combined immunodeficiencies (SCID)

Failure to develop normal T lymphocytes, usually due to a range of specific X-linked or autosomal recessive gene defects affecting early T-lymphocyte development or signalling pathways, leads to T-lymphocyte immunodeficiency, usually with concomitant humoral deficiency. The severity of the humoral deficiency varies from a subtle defect of specific antibody response to complete hypogammaglobulinaemia. In the most severe phenotype, severe combined immunodeficiency (SCID), profound T lymphopenia and panhypogammaglobulinaemia cause early infective death. In the classic SCID presentation, lymphocyte numbers and responses to mitogens are absent, but may be present in attenuated forms where immunoglobulin may also be produced. Patients usually have a limited diversity of T-lymphocyte receptors and immunoglobulin gene rearrangements. Identifying the molecular defect in individual patients is important for prognosis, treatment, genetic counselling and increasing our knowledge about these rare diseases.

Types of severe combined and combined immunodeficiencies

SCID can be subdivided according to the presence or absence of T, B and NK lymphocytes, each phenotype being due to a number of distinct molecular defects, also enabling classification by mechanism (Table 17.12) [1–7].

References

1 Puck JM, Deschenes SM, Porter JC *et al*. The interleukin-2 receptor gamma chain maps to Xq13.1 and is mutated in X-linked severe combined immunodeficiency, SCIDX1. *Hum Mol Genet* 1993; **2**: 1099–104.

2 Macchi P, Villa A, Giliani S *et al.* Mutations of Jak-3 gene in patients with autosomal severe combined immune deficiency (SCID). *Nature* 1995; **377**: 65–8.
3 Puel A, Ziegler SF, Buckley RH *et al.* Defective IL7R expression in T-B+NK+ severe combined immunodeficiency. *Nat Genet* 1998; **20**: 394–7.
4 Schwarz K, Glaus GH, Ludwig L *et al.* RAG mutations in human B cell-negative SCID. *Science* 1996; **274**: 97–9.
5 Moshous D, Callebaut I, de Chasseval R *et al.* ARTEMIS, a novel DNA double-strand break repair/V(D)J recombination protein, is mutated in human severe combined immune deficiency. *Cell* 2001; **105**: 177–86.
6 Buck D, Malivert L, de Chasseval R *et al.* Cernunnos, a novel nonhomologous end-joining factor, is mutated in human immunodeficiency with microcephaly. *Cell* 2006; **124**: 287–9.
7 Roberts JL, Lauritsen JP, Cooney M *et al.* T-B+NK+ severe combined immunodeficiency caused by complete deficiency of the CD3zeta subunit of the T-cell antigen receptor complex. *Blood* 2007; **109**: 3198–206.

General features of severe combined immunodeficiency

Although appearing well at birth, affected infants fail to clear normally 'minor' infections [1]. Rotavirus can cause chronic diarrhoea and failure to thrive whilst *respiratory syncitial virus* or parainfluenza infection leads to a persistent bronchiolitis like illness. An insidiously progressive, persistent respiratory infection with radiological evidence of interstitial pneumonitis suggests *Pneumocystis jiroveci* infection, often a co-pathogen with respiratory viruses. Other presentations include prolonged otitis media and invasive bacterial infections, particularly staphylococcal or pseudomonas septicaemia and pneumonia, which may respond poorly to appropriate treatment (Table 17.13). Severe, invasive fungal infection is rare, but often fatal. Persistent, treatment-resistant, superficial candidiasis is the commonest dermatological feature. This may start in the napkin area, but will often extend rapidly to produce a picture resembling severe seborrhoeic dermatitis. Systemic *Candida* infections do not usually occur unless central venous lines are used. Pyogenic cutaneous infection due to *Staphylococcus aureus* or group A streptococci are not uncommon, and will often provoke lesions having a necrotic, ecthymatous appearance. Resistance to appropriate antibiotic therapy should raise suspicion [2].

Occasionally, babies present with disseminated BCG (Fig. 17.13). Children presenting within the first 6 months or so of life are more likely to have SCID or a severe T-lymphocyte defect. Dysmorphic features may suggest a diagnosis of DiGeorge or CHARGE syndrome. Microcephaly is a feature of some patients with DNA ligase 4 or cernunnos deficiency.



Fig. 17.13 Disseminated BCG in a child with severe combined immunodeficiency given BCG vaccination at birth. (Courtesy of the Paediatric Immunology Unit, Newcastle General Hospital, UK.)

Table 17.13 Presenting features of severe combined immunodeficiency.

Common presentations	Common pathogens	Rare presentations
Persistent viral gastroenteritis	Norovirus Rotavirus Astrovirus Adenovirus Respiratory syncitial virus	Bacterial septicaemia Disseminated BCG infection
Persistent viral lower respiratory tract infection	Parainfluenzae virus Cytomegalovirus	Haemophagocytosis Lymphoid malignancy Autoimmune cytopenias
Pneumocystis jiroveci pneumonitis		
Recurrent or recalcitrant candidiasis		
Failure to thrive		

Isohaemagglutinins are a useful measure of *in vitro* IgM production and absence is significant. If SCID is suspected, lymphocyte phenotyping is more reliable than immunoglobulin estimation. Chest radiographs show an absent thymus with hyperinflation and/or interstitial pneumonia when respiratory infection is present. Without treatment, patients die from infection by about 12 months of age. Currently, the only curative treatment is haematopoietic stem cell transplantation [3,4]. Clinical gene therapy trials for common gamma chain and adenosine deaminase deficiency are in progress; they have produced mixed results. Supportive interim treatments include antibiotic prophylaxis with co-trimoxazole as antipneumocystis treatment, antifungal prophylaxis and immunoglobulin replacement. Live vaccines should be avoided. The diagnosis of SCID is a paediatric emergency, and suspected cases should be urgently referred to a designated treatment centre for further assessment and treatment.

References

1 Fischer A. Severe combined immunodeficiencies (SCID). *Clin Exp Immunol* 2000; **122**: 143–9.
2 De Raeve L, Song M, Levy J *et al.* Cutaneous lesions as a clue to severe combined immunodeficiency. *Pediatr Dermatol* 1992; **9**: 49–51.
3 Buckley RH, Schiff SE, Schiff RI *et al.* Hematopoietic stem-cell transplantation for the treatment of severe combined immunodeficiency. *N Engl J Med* 1999; **340**: 508–16.

4 Antoine C, Muller S, Cant A *et al.* Long-term survival and transplantation of haemopoietic stem cells for immunodeficiencies: a report of the European experience 1968–99. *Lancet* 2003; **361**: 553–60.

Dermatological features of SCID

Two atypical forms of SCID with maternofetal graft-versus-host disease (MFGvHD) and Omenn syndrome have distinct manifestations and are commonly seen by dermatologists who can play a key role in early diagnosis, which in turn offers better outcome from stem cell transplantation. In both conditions, the skin is infiltrated by abnormal T-lymphocyte clones. As SCID infants lack functional T cells they cannot reject foreign lymphocytes acquired either from the mother *in utero* or from an unirradiated blood transfusion (Fig. 17.12). Engraftment of transplacentally acquired maternal lymphocytes (MFGvHD) sometimes, but not always, provokes the clinical signs of GvHD, typically with a mild reticular skin rash with or without slightly deranged liver function tests. Surprisingly, up to 50% of children with SCID have clinically silent MFGvHD [1] although GvHD can be severe or fatal, when the skin rash is more severe and lymphadenopathy and hepatosplenomegaly may be present; these cases may be clinically indistinguishable from Omenn syndrome, but identification of maternal cells by karyotype or DNA fingerprinting will distinguish MFGvHD from Omenn syndrome [2].

Omenn syndrome is characterized by a generalized, thickened erythematous rash, often with scaling and erythroderma. The cutaneous abnormality is often the first sign of the disorder; an erythematous, exfoliating, protein-losing rash appearing and evolving into a confluent erythema. The initial appearances may be papular, becoming confluent, and the skin often becomes thickened with a 'leathery' consistency. Hair, including eyebrows, is often lost as the rash evolves (Fig. 17.14). The rash may be present at birth or evolve over the first few weeks of life. There is also lymphadenopathy, particularly of the axillary and inguinal nodes, as well as increased serum IgE levels with a marked eosinophilia and combined immunodeficiency [3]. Children usually present in early infancy but atypical forms may present later in the first year of life. As well as the clinical features described, children usually suffer diarrhoea, failure to thrive and persistent infection, as seen in other forms of SCID. There are normally high numbers of activated, oligoclonal, poorly functional T lymphocytes of the Th2 phenotype, explaining the eosinophilia and exclusive IgE production [4]. Peripheral B lymphocyte numbers are low or absent, as are levels of immunoglobulin classes other than IgE. The syndrome has been called a 'leaky' form of SCID in that small numbers of very abnormal T lymphocytes 'leak' past the block in T lymphocyte development [5]. The underlying defect, at least in some cases, is a mutation in the recombination activating genes [6]. In some families, one affected individual has presented with T^- B^-NK^+ SCID whilst another has presented with Omenn syndrome [7]. Other genes that have been implicated include Artemis, IL7Ra, RMRP, CHD7 and CgC [8–12]. The clinical picture may resemble SCID with maternofetal engraftment, when maternal T lymphocytes crossing the placenta cause a graft-versus-host disease-like reaction in an immunoincompetent patient. Activated oligoclonal lymphocytes in skin seemingly provoke Langerhans' cells to migrate to lymph nodes, liver and spleen where lymphoid tissue architecture is severely disrupted. It has been suggested that IFN-γ may ameliorate the clinical symptoms, but bone marrow transplantation is the only curative treatment [13].



Fig. 17.14 Newborn infant with Omenn syndrome due to a mutation in the *RAG1* gene. Note the confluent erythematous exfoliating, thickened rash with a 'leathery' consistency, and loss of hair and eyebrows. (Courtesy of the Paediatric Immunology Unit, Newcastle General Hospital, UK.)

Histology of the skin shows a dense, dermal perivascular lymphohistiocytic infiltrate, comprising activated T lymphocytes, with numerous eosinophils. S100-staining Langerhans' cells are usually absent, and there is no epidermotropism. Lymph node architecture is disordered, being replaced by a similar massive infiltrate of cells of S100-staining interdigitating reticulum cells with absence of germinal centres, absent B cells and a paucity of T lymphocytes [14].

In the older literature this condition has been confused with Langerhans' cell histiocytosis (Letterer–Siwe disease). It is likely that several cases reported in the literature under other names were in fact examples of this disorder [15].

References

1 Muller SM, Ege M, Pottharst A *et al.* Transplacentally acquired maternal T lymphocytes in severe combined immunodeficiency: a study of 121 patients. *Blood* 2001; **98**: 1847–51.
2 Appleton AL, Curtis A, Wilkes J *et al.* Differentiation of materno-foetal GVHD from Omenn's syndrome in pre-BMT patients with severe combined immunodeficiency. *Bone Marrow Transpl* 1994; **14**: 157–9.
3 Notarangelo LD, Villa A, Schwarz K. RAG and RAG defects. *Curr Opin Immunol* 1999; **11**: 435–42.
4 Schandene L, Ferster A, Mascart-Lemone F *et al.* T-helper type 2-like cells and therapeutic effects of interferon-γ in combined immunodeficiency with hypereosinophilia (Omenn's syndrome). *Eur J Immunol* 1993; **23**: 53–60.
5 Rieux-Laucat F, Bahadoran P, Brousse N *et al.* Highly restricted human T-cell repertoire beta (TCRB) chain diversity in peripheral blood and tissue-infiltrating lymphocytes in Omenn's syndrom (severe combined immunodeficiency with hypereosinophilia). *J Clin Invest* 1998; **102**: 312–21.

6 Villa A, Santagata S, Bozzi F *et al.* Partial V(D)J recombination activity leads to Omenn syndrome. *Cell* 1998; **93**: 885–96.
7 Corneo B, Moshous D, Gungor T *et al.* Identical mutations in RAG1 or RAG2 genes leading to defective V(D)J recombinase activity can cause either T-B-severe combined immune deficiency or Omenn syndrome. *Blood* 2001; **97**: 2772–6.
8 Ege M, Ma Y, Manfras B *et al.* Omenn syndrome due to ARTEMIS mutations. *Blood* 2005; **105**: 4179–86.
9 Giliani S, Bonfim C, de Saint Basile G *et al.* Omenn syndrome in an infant with IL7RA gene mutation. *J Pediatr* 2006; **148**: 272–4.
10 Roifman CM, Gu Y, Cohen A. Mutations in the RNA component of RNase mitochondrial RNA processing might cause Omenn syndrome. *J Allergy Clin Immunol* 2006; **117**: 897–903.
11 Shibata F, Toma T, Wada T *et al.* Skin infiltration of CD56(bright) CD16(-) natural killer cells in a case of X-SCID with Omenn syndrome-like manifestations. *Eur J Haematol* 2007; **79**: 81–5.
12 Gennery AR, Slatter MA, Rice J *et al.* Mutations in *CHD7* in patients with CHARGE association cause T-B+NK+ severe combined immune deficiency and may cause Omenn-like syndrome. *Clin Exp Immunol* 2008; **153**: 75–80.
13 Mazzolari E, Moshous D, Forino C *et al.* Hematopoietic stem cell transplantation in Omenn syndrome: a single-center experience. *Bone Marrow Transpl* 2005; **36**: 107–14.
14 Martin JV, Willoughby PB, Giusti V *et al.* The lymph node pathology of Omenn's syndrome. *Am J Surg Pathol* 1995; **19**: 1082–7.
15 Wyss M, Von Fliedner V, Jacot-des-Combes E *et al.* A lymphoproliferative syndrome: cutaneous dystrophy and combined immunodeficiency with lack of helper T-cell function. *Clin Immunol Immunopathol* 1982; **23**: 34–49.

SCID due to metabolic defects

Adenosine deaminase (ADA) deficiency [1] and purine nucleoside phosphorylase (PNP) deficiency [2] are both single-gene defects inherited in an autosomal recessive manner, which result in defective metabolism of the DNA break-down products, allowing the accumulation of toxic purine metabolites that destroy immature lymphocytes. Skeletal abnormalities (cupping deformities of the ends of the ribs, as well as abnormalities of the transverse vertebral processes and the scapulae) are reported in up to 50% of cases of ADA deficiency [3]. Neurodevelopmental problems may also occur in some patients [4]. Very rarely, partial forms of ADA deficiency occur, where some lymphocyte function is preserved. Interestingly, such patients have clinical features similar to those seen in hyper-IgE syndrome [5]. Treatment is by bone marrow transplantation [6] or by use of replacement polyethylene glycol-coupled ADA [7]. Gene therapy is being attempted in this condition [8].

PNP is initially less severe than ADA deficiency [9]. Most cases present in early childhood with recurrent and severe infections, particularly with viruses and fungi, accompanied by diarrhoea and failure to thrive. There is a marked tendency to autoimmune disease, especially haemolytic anaemia [10], which can progress to red cell aplasia, and also to GvHD following non-irradiated blood transfusion. Skeletal abnormalities do not occur, but neurodevelopmental problems are found in over half of all patients, particularly spastic paresis, dysequilibrium and ataxia [10]. There may also be more general neurodevelopmental and behavioural problems. In one series, 20% of patients presented primarily with neurological disorder [11]. Serum uric acid levels are very low. The diagnosis is confirmed by demonstrating absent PNP activity in red cells or fibroblasts and deoxyinosine and deoxyguanosine in the urine. The prognosis without haematopoietic stem cell transplantation is poor.

References

1 Hirschhorn R, Vauter GF, Kirkpatrick JA Jr *et al.* Adenosine deaminase deficiency frequency and comparative pathology in autosomally recessive severe combined immunodeficiency. *Clinical Immunol Immunopathol* 1979; **14**: 107–20.
2 Giblett ER, Ammann AJ, Wara DW *et al.* Nucleoside-phosphorylase deficiency in a child with severely defective T-cell immunity and normal B-cell immunity. *Lancet* 1975; **1**: 1010–3.
3 Cederbaum SD, Kartila I, Runoin DL *et al.* The chondro-osseous dysplasia of adenosine deaminase deficiency with severe combined immunodeficiency. *J Pediatr* 1976; **89**: 737–42.
4 Rogers M, Lwin R, Fairbanks L *et al.* Cognitive and behavioural abnormalities in adenosine deaminase deficient severe combined deficiency. *J Pediatr* 2001; **139**: 44–50.
5 Ozsahin H, Arredondo FX, Santisteban I *et al.* Adenosine deaminase deficiency in adults. *Blood* 1997; **89**: 2849–55.
6 Antoine C, Muller S, Cant A *et al.* Long-term survival and transplantation of haemopoietic stem cells for immunodeficiencies: a report of the European experience 1968–99. *Lancet* 2003; **361**: 553–60.
7 Hershfield MS. PEG-ADA replacement therapy for adenosine deaminase deficiency. An update after 8.5 years. *Clin Immunol Immunopathol* 1995; **76**: S228–32.
8 Aiuti A, Slavin S, Aker M *et al.* Correction of ADA-SCID by stem cell gene therapy combined with nonmyeloablative conditioning. *Science* 2002; **296**: 2410–3.
9 Carpenter PA, Ziegler JB, Vowels MR. Late diagnosis and correction of purine nucleoside phosphorylase deficiency with allogeneic bone marrow transplantation. *Bone Marrow Transpl* 1996; **17**: 121–4.
10 Markert ML. Purine nucleoside phosphorylase deficiency. *Immunodefic Rev* 1991; **3**: 45–81.
11 Soutar RL, Day RE. Dysequilibrium/ataxic diplegia with immunodeficiency. *Arch Dis Child* 1991; **66**: 982–3.

Other combined immunodeficiencies

Other rare immunodeficiencies have been described in only a few patients to date with defects in other surface and signalling molecules (Table 17.12). It is likely that these will become increasingly recognized as more laboratories are able to offer diagnostic testing.

Major histocompatibility complex antigen deficiency

Major histocompatibility complex class II (Bare lymphocyte syndrome)

Major histocompatibility complex class II (MHC II) antigens (HLA-DR, DP, DQ) are expressed on a limited repertoire of cells and present antigen to $CD4^+$ T lymphocytes which, with the help of an appropriate second signal, activate T-helper lymphocytes specific for that antigen. Expression of MHC II in the thymus is also essential for positive selection of $CD4^+$ T lymphocytes. Since HLA antigens are of vital importance for lymphocyte development and function, lack of MHC II expression, previously described as 'bare lymphocyte syndrome', results in a profound susceptibility to viral, bacterial, fungal and protozoal infections [1]. Lack of MHC II expression results from defects in genes coding for regulatory factors that control transcriptional activation of MHC II molecules [2].

Most patients will have a CD4 lymphopenia and hypogammaglobulinaemia; lymphocyte proliferation responses are usually normal. The diagnosis can be confirmed by flow cytometry showing absent or significantly reduced levels of class II molecules, for example HLA-DR, on cells that constitutively express



Fig. 17.15 Necrotizing skin lesion on the elbow of a patient with MHC class I deficiency. Biopsy of the lesion showed granulomata, but mycobacteria were not identified or isolated. (Courtesy of the Paediatric Immunology Unit, Newcastle General Hospital, UK.)

class II (B lymphocytes and monocytes). Haematopoietic stem cell transplantation is the definitive treatment [3].

MHC I deficiency

Although described before MHC II deficiency, SCID due to abnormal expression of the A, B and C components of the MHC I complex is much less common. MHC I is required for development of $CD8^+$ T lymphocytes, and affected children have low numbers of these cells. Mitogen responses are frequently normal [4]. MHC I deficiency is due to mutations in the peptide transporter genes, which code for proteins that transport degraded protein antigen from the cytosol to the endoplasmic reticulum where they associate with the MHC I complex [5].

Clinically, this disease has a milder phenotype than MHC II deficiency, with symptoms often not beginning until late childhood. Recurrent respiratory tract infections leading to bronchiectasis and sinus problems are common. Gastrointestinal disease is rare. The most striking clinical manifestation is necrotizing granulomatous skin lesions which are located on the extremities (Fig. 17.15) [6,7] and also at the midface [8]. The skin manifestations begin with a small pustule or subcutaneous nodule which slowly expands and ulcerates. The lesions are slow to heal, and usually leave hyperpigmented scars. Midface lesions can be particularly mutilating and resemble midline granuloma. Diagnosis is confirmed by showing absent HLA class I expression in peripheral blood. Treatment is directed towards prevention/limitation of lung disease with judicious use of antibiotics (directed by sputum cultures), physiotherapy and bronchodilators as required. Prophylactic continuous antibiotics are of unproven benefit, but may be helpful. The majority of cases do not require replacement immunoglobulin therapy or haematopoietic stem cell transplantation.

References

1 Klein C, Lisowska-Grospierre B, LeDeist F *et al*. Major histocompatibility complex class II deficiency: clinical manifestations, immunologic features, and outcome. *J Pediatr* 1993; **123**: 921–8.

2 Reith W, Steimle V, Lisowska-Grospierre B *et al*. Molecular basis of major histocompatibility complex class II deficiency. In: Ochs HD, Smith CIE, Puck JM, eds. *Primary Immunodeficiency Diseases; A molecular and genetic approach*. New York: Oxford University Press, 1999.

3 Renella R, Picard C, Neven B *et al*. Human leucocyte antigen-identical haematopoietic stem cell transplantation in major histocompatibility complex class II immunodeficiency: reduced survival correlates with an increased incidence of acute graft-versus-host disease and pre-existing viral infections. *Br J Haematol* 2006; **134**: 510–6.

4 de la Salle H, Hanau D, Fricker D *et al*. Homozygous human TAP peptide transporter mutation in HLA class I deficiency. *Science* 1994; **265**: 237–41.

5 Gadola SD, Moins-Teisserenc HT, Trowsdale J *et al*. TAP deficiency syndrome. *Clin Exp Immunol* 2000; **121**: 173–8.

6 Plebani A, Monafo V, Cattaneo R *et al*. Defective expression of HLA class I and CD1a molecules in a boy with Marfan-like phenotype and deep skin ulcers. *J Am Acad Dermatol* 1996; **35**: 814–8.

7 Watanabe S, Iwata M, Maeda H *et al*. Immunohistochemical studies of major histocompatibility antigens in a case of the bare lymphocyte syndrome without immunodeficiency. *J Am Acad Dermatol* 1987; **17**: 895–902.

8 Moins-Teisserenc HT, Gadola SD, Cella M *et al*. Association of a syndrome resembling Wegener's granulomatosis with low surface expression of HLA class-I molecules. *Lancet* 1999; **354**: 1598–603.

Combined immunodeficiency forming part of other syndromes

DiGeorge syndrome

This condition results from abnormal cephalic neural crest cell migration into the third and fourth pharyngeal arches in early embryological development. A microdeletion at chromosome 22q11.2 is present in 90% of cases, while the remainder are associated with other chromosomal anomalies, particularly 10p–. DiGeorge syndrome belongs to a group of disorders that have been described as developmental field defects [1]. The syndrome is extremely heterogeneous with partial forms more common than the complete phenotype [2]. Whilst classically recognized by the triad of congenital heart defects, immunodeficiency secondary to thymic hypoplasia and hypocalcaemia secondary to parathyroid gland hypoplasia, an expanded phenotype is increasingly recognized, with dysmorphic facies (low-set, abnormally formed ears, hypertelorism and antimongoloid slant, micrognathia, short philtrum to the upper lip and high arched palate), palatal abnormalities (cleft palate, velopharyngeal insufficiency), autoimmune phenomena such as autoimmune cytopenia, vitiligo, autoimmune thyroiditis, learning difficulties (particularly speech delay), renal anomalies, neuropsychiatric disorders and short stature. Conotruncal heart defects are classically associated with the syndrome, but

other defects are seen including tetralogy of Fallot, septal defects, pulmonary atresia and aberrant subclavian vessels. Some patients have normal hearts.

Severe T-lymphocyte immunodeficiency presenting with a SCID phenotype of profound lymphopenia and poor lymphocyte proliferation is rare, and accounts for less than 1.5% of cases [3]. Humoral immunodeficiency is more common than previously thought, presenting with recurrent sinopulmonary infection, which may improve with time [4]. Occasionally, significant lung damage may occur due to repeated infection. Autoimmune features are increasingly recognized, including juvenile chronic arthritis and autoimmune cytopenias [5,6]. The long-term immunological outlook is not well defined, particularly in children with mild cardiac or palatal phenotypes. An Omenn syndrome phenotype has been described in patients with DiGeorge syndrome [7], and at least some of these have been secondary to engraftment of maternal T cells causing a MFGvHD [8]. CHARGE syndrome has recently been linked with SCID, and as in patients with DiGeorge syndrome, the primary immunological defect is an absent thymus [9,10].

References

1 Lammer EJ, Opitz JM. The DiGeorge anomaly as a developmental field defect. *Am J Genet* 1986; **2** (Suppl.): 113–27.

2 Muller W, Peter HH, Kallfelz HC *et al.* The DiGeorge sequence: immunologic findings in partial and complete forms of the disorder. *Eur J Pediatr* 1989; **149**: 96–103.

3 Ryan AK, Goodship JA, Wilson DA *et al.* Spectrum of clinical features associated with interstitial chromosome 22q11 deletions: a European collaborative study. *J Med Genet* 1997; **34**: 798–804.

4 Gennery AR, Barge D, O'Sullivan JJ *et al.* Antibody deficiency and autoimmunity in 22q11.2 deletion syndrome. *Arch Dis Child* 2002; **86**: 422–5.

5 Sullivan KE, McDonald-McGinn DM, Driscoll DA *et al.* Juvenile rheumatoid arthritis-like polyarthritis in chromosome 22q11.2 deletion syndrome (DiGeorge anomalad/velocardiofacial syndrome/conotruncal anomaly face syndrome). *Arthritis Rheum* 1997; **40**: 430–6.

6 DePiero AD, Lourie EM, Berman BW *et al.* Recurrent immune cytopenias in two patients with DiGeorge/velocardiofacial syndrome. *J Pediatr* 1997; **131**: 484–6.

7 Collard HR, Boeck A, McLaughlin TM *et al.* Possible extrathymic development of nonfunctional T cells in a patient with complete DiGeorge Syndrome. *Clin Immunol* 1999; **91**: 156–62.

8 Ocejo-Vinyals JG, Lazano MJ, Sanchez-Velasco P *et al.* An unusual concurrence of graft versus host disease caused by engraftment of maternal lymphocytes with DiGeorge anomaly. *Arch Dis Child* 2000; **83**: 165–9.

9 Writzl K, Cale CM, Pierce CM *et al.* Immunological abnormalities in CHARGE syndrome. *Eur J Med Genet* 2007; **50**: 338–45.

10 Gennery AR, Slatter MA, Rice J *et al.* Mutations in *CHD7* in patients with CHARGE association cause T-B+NK+ severe combined immune deficiency and may cause Omenn-like syndrome. *Clin Exp Immunol* 2008; **153**: 75–80.

Wiskott–Aldrich syndrome (WAS)

Immunodeficiency, thrombocytopenia, eczema and an increased risk of autoimmune disorders and malignancy characterize this X-linked recessive condition. The gene responsible for WAS codes for the Wiskott–Aldrich syndrome protein (WASP) [1], which is only found in bone marrow-derived cells and is implicated in actin cytoskeleton polymerization [2]. Mutations in the same gene are found in patients with X-linked thrombocytopenia (XLT) [3], and also in X-linked severe congenital neutropenia [4]. Patients usually exhibit the classical triad of thrombocytopenia, recurrent infections and eczema (Fig. 17.16) but these vary in severity and in some patients the eczema is surprisingly mild [5]. In general, it is indistinguishable from atopic eczema apart from the presence of purpura and bleeding from excoriation in many patients. The condition usually presents in early life with bruising, petechiae and bleeding; thrombocytopenia and bleeding episodes may require platelet transfusions. In XLT, thrombocytopenia with small platelet volume is the only symptom, perhaps with mild eczema. In WAS, bacterial and/or viral infections of the upper and lower respiratory tract are common [6] and opportunistic infection, such as *Pneumocystis jiroveci*, may occur. Herpes viruses, including *Herpes simplex* and *varicella-zoster* virus, are poorly handled and may cause severe and recurrent disease. Impetigo, cellulitis and skin abscesses are surprisingly common, molluscum contagiosum and viral warts may be very extensive and together with excessive bruising help to clinically distinguish WAS from uncomplicated eczema. Indeed, very extensive molluscum contagiosum is quite characteristic of WAS (Fig. 17.11). Infection exacerbates the bleeding tendency, and early death may result from bleeding. With increasing age, infective problems replace bleeding as the major cause of death [7]. Immunization with polysaccharide and typhoid vaccines is ineffective [8] and can cause severe, even fatal, reactions. The median survival is between 3 and 15 years. Autoimmunity, particularly autoimmune haemolytic anaemia and vasculitis, and malignancy, particularly of the lymphoreticular system, become more common with increasing age [6] and in many cases are related to abnormal persistence of Epstein–Barr viral infection [9]. Scoring systems have been used to distinguish the milder phenotype of XLT from classical WAS. Heterozygous



Fig. 17.16 Severe eczema in a patient with Wiskott–Aldrich syndrome. (Courtesy of the Paediatric Immunology Unit, Newcastle General Hospital, UK.)

female carriers are clinically normal and demonstrate non-random X-inactivation in all haemopoietic cells.

Thrombocytopenia with an abnormally small mean platelet volume (less than 5 fl) is pathognomic [8]. The severity of immunodeficiency is variable, but affects cellular and humoral responses. T lymphopenia is progressive with depressed responses to mitogens and antigens and delayed-type hypersensitivity skin test responses [6]. Serum immunoglobulins show a characteristic pattern with a very low IgM, normal IgG and raised IgA and IgE [8]. Antibody responses to tetanus, *Haemophilus influenzae* type B and *Pneumococcus* are often low, as are isohaemagglutinin titres. The direct antiglobulin test is frequently positive, with or without a haemolytic anaemia. *In vivo* neutrophil and monocyte chemotaxis is impaired [8]. Electron microscopy shows greatly reduced numbers of microvilli on lymphocytes and platelets due to failure of the normal binding of actin bundles which is critical to the organization of the cytoskeleton. Lymphoid and myeloid cell lines are all affected so that phagocytes migrate poorly to sites of inflammation and do not put out normal filopodia, dendritic cells do not present antigen effectively, lymphocytes do not signal to each other normally and platelets form imperfectly from megakaryocytes [10]. WASP has a number of unique domains, suggesting multiple functions, which may explain the complex phenotype of a single gene mutation. Missense mutations in exons 1–3 which lead to normal or truncated sized protein result in the milder phenotype of XLT, whereas most other mutations result in the classic WAS phenotype.

Treatment. Acute bleeding episodes may be controlled by platelet transfusions (irradiated to prevent graft-versus-host disease). Splenectomy and systemic steroids should be avoided if possible as they will increase the risk of infection. Topical steroids are required for the eczema. Intravenous immunoglobulin, with or without prophylactic antibiotics, reduces bacterial sinopulmonary infections and in high dose may help treat autoimmune phenomena [11].

With only these supportive measures the prognosis remains poor. Immunological and haematological reconstitution can be achieved by haematopoietic stem cell transplantation [12]. Autoimmune manifestations can complicate partial donor chimerism post-transplant. Whilst cytopenias are most common, dermatological manifestations include Addison's disease and vasculitis [13].

References

1 Derry JMJ, Ochs HD, Francke U. Isolation of a novel gene mutated in Wiskott-Aldrich syndrome. *Cell* 1994; **78**: 635–44.

2 Symons M, Derry JMJ, Karlak B *et al.* Wiskott-Aldrich syndrome protein, a novel effector for the GTPase CDC42Hs, is implicated in actin polymerization. *Cell* 1996; **84**: 723–34.

3 Zhu Q, Zhang M, Blaese RM *et al.* Isolated Wiskott-Aldrich syndrome and X-linked congenital thrombocytopenia are caused by mutations of the same gene. *Blood* 1995; **86**: 3797–804.

4 Devrient K, Kim AS, Mathijs G *et al.* Constitutively activating mutation in WASP causes X-linked severe congenital neutropenia. *Nat Genet* 2001; **27**: 313–7.

5 Schindelhauer D, Weiss M, Hellebrand H *et al.* Wiskott-Aldrich syndrome: no strict genotype-phenotype correlations but clustering of missense mutations in the amino-terminal part of the WASP gene product. *Hum Genet* 1996; **98**: 68–76.

6 Sullivan KE, Mullen CA, Blaese RM *et al.* A multiinstitutional survey of the Wiskott-Aldrich syndrome. *J Pediatr* 1994; **125**: 876–85.

7 Mullen CA, Anderson KD, Blaese RM. Splenectomy and/or bone marrow transplantation in the management of the Wiskott-Aldrich syndrome; long-term follow-up of 62 cases. *Blood* 1993; **82**: 2961–6.

8 Ochs HD, Schlicter SJ, Harker LA *et al.* The Wiskott-Aldrich syndrome: studies of lymphocytes, granulocytes and platelets. *Blood* 1980; **55**: 243–52.

9 Nonoyama S, Ochs HD. Characterization of the Wiskott-Aldrich syndrome protein and its role in the disease. *Curr Opin Immunol* 1998; **10**: 407–12.

10 Thrasher AJ, Kinnon C. The Wiskott-Aldrich syndrome. *Clin Exp Immunol* 2000; **120**: 2–9.

11 Wodzinski MA, Lilleyman JS. High-dose immunoglobulin therapy of Wiskott-Aldrich syndrome. *Pediatr Hamatol Oncol* 1987; **4**: 345–8.

12 Filipovich AH, Stone JV, Tomany SC *et al.* Impact of donor type on outcome of bone marrow transplantation for Wiskott-Aldrich syndrome: collaborative study of the International Bone Marrow Transplant Registry and the National Marrow Donor Program. *Blood* 2001; **97**: 1598–603.

13 Ozsahin H, Cavazzana-Calvo M, Notarangelo LD *et al.* Long-term outcome following hematopoietic stem-cell transplantation in Wiskott-Aldrich syndrome: collaborative study of the European Society for Immunodeficiencies and European Group for Blood and Marrow Transplantation. *Blood* 2008; **111**: 439–45.

X-linked hyper-IgM syndrome (CD40 ligand deficiency)

X-linked hyper-IgM syndrome is a T-lymphocyte immunodeficiency due to a defect in the gene encoding for the CD40 ligand glycopeptide (CD154) expressed on activated T lymphocytes [1,2]. CD40L binds to CD40, expressed on B lymphocytes and monocyte/macrophage derived cells [3]. Lack of binding prevents immunoglobulin isotype switching from IgM to IgA, IgG and IgE, as well as activation of Kupffer cells and pulmonary macrophages. Lack of IgA and IgG results in a similar clinical picture to X-linked agammaglobulinaemia (XLA) with sinopulmonary and invasive bacterial infection but, in contrast to XLA, opportunistic infections also occur. Failure of T lymphocytes to activate pulmonary macrophages results in *Pneumocystis jiroveci* pneumonia whilst ineffective Kupffer cell function allows repeated infections of bowel, pancreas and biliary tree with *Cryptosporidium parvum* and similar organisms, leading to sclerosing cholangitis, cirrhosis, pancreatitis and hepatic malignancy, which becomes clinically apparent in the second or third decade [4]. Neutropenia with oral ulceration is seen in as many as 66% of patients; fatal CMV infection or enteroviral meningoencephalitis can occur [5]; autoimmune phenomena are relatively common, and include haemolytic anaemia, thrombocytopenia, hypothyroidism, arthritis and liver disorders [4]. Severe soft tissue infection due to *Pseudomonas aeruginosa* may occur [6].

Laboratory findings include low or absent IgA and IgG with normal or raised levels of IgM [7]. Neutropenia may be present, but T and B lymphocyte numbers are normal.

Patients should receive co-trimoxazole prophylaxis for *Pneumocystis jiroveci* and immunoglobulin replacement therapy. The neutropenia sometimes responds to granulocyte colony-stimulating factor (G-CSF) and intravenous immunoglobulin. All drinking water, including bottled water, should be boiled. Azithromycin prophylaxis may lessen the risks of *Cryptosporidium parvum* infection. Despite conventional treatment, many patients do not survive beyond the second decade of life, but a few patients with a common variable immunodeficiency-like clinical course and no biliary or liver disease are relatively well in middle life. Bone marrow transplantation is increasingly being recommended for this condition

and combined bone marrow and liver transplantation has been successful [8,9].

References

1 Korthauer U, Graf D, Mages HW *et al.* Defective expression of T-cell CD40 ligand causes X-linked immunodeficiency with hyper-IgM. *Nature* 1993; **361**: 539–41.
2 Disanto JP, Bonnefoy JY, Gauchat JF *et al.* CD40 Ligand mutations in X-linked immunodeficiency with hyper-IgM. *Nature* 1993; **361**: 541–3.
3 Van Kooten C, Banchereau J. Functions of CD40 on B cells, dendritic cells and other cells. *Curr Opin Immunol* 1997; **9**: 330–7.
4 Levy J, Espanol-Boren T, Thomas A *et al.* Clinical spectrum of X-linked hyperIgM syndrome. *J Pediatr* 1997; **131**: 47–54.
5 Cunningham CK, Bonville CA, Ochs HD *et al.* Enteroviral meningoencephalitis as a complication of X-linked hyper-IgM syndrome. *J Pediatr* 1999; **134**: 584–8.
6 Kyong CU, Virella G, Fudenburg HH *et al.* X-linked immunodeficiency with increased IgM: clinical, ethnic and immunologic heterogeneity. *Pediatr Res* 1978; **12**: 1024–6.
7 Notarangelo LD, Duse M, Ugazio AG. Immunodeficiency with hyper-IgM (HIM). *Immunodefic Rev* 1992; **3**: 101–22.
8 Gennery AR, Khawaja K, Veys P *et al.* Treatment of CD40 ligand deficiency by hematopoietic stem cell transplantation: a survey of the European experience, 1993–2002. *Blood* 2004; **103**: 1152–7.
9 Hadzic N, Pagliuca A, Rela M *et al.* Correction of the hyper-IgM syndrome after liver and bone marrow transplantation. *N Engl J Med* 2000; **342**: 320–3.

X-linked lymphoproliferative diseases (XLP)

An X-linked immunodeficiency associated with fulminant fatal Epstein–Barr virus (EBV)-driven infectious mononucleosis was first recognized in the Duncan kindred [1]. There are three common clinical presentations: fulminant infectious mononucleosis (58%); dysgammaglobulinaemia, often evolving to common variable immunodeficiency (31%); and EBV-driven B-lymphocyte lymphoma, usually extranodal, and affecting the gastrointestinal tract or central nervous system (20%). Less commonly, patients present with vasculitis, aplastic anaemia, haemophagocytic lymphohistiocytosis, pulmonary lymphomatoid granulomatosis or vasculitis [2]. Few cases of XLP-associated vasculitis have been published (Fig. 17.17). Polyarteritis nodosa-like vasculitis has been reported in one case [3]. Vasculitic changes in small and medium-sized muscular arteries have also been reported [4]. The prognosis is poor with a high risk of death during initial EBV infection, and no recorded survivors after 40 years of age [5]. Most patients are well until infected with Epstein–Barr virus, although other viruses may act as triggers. The gene responsible for the disease, on the X chromosome, codes for a small protein, SAP (signalling lymphocyte activation molecule (SLAM) associated protein), which is expressed on the surface of T lymphocyte and is critical for T lymphocyte and NK cell control of EBV-infected B lymphocytes [6,7]. Confirmation of the diagnosis involves demonstrating EBV genome in blood by PCR, together with immune defects outlined above and an abnormal response to EBV, with absent antibody response to EBV nuclear antigen (EBNA). SAP protein is absent or abnormally expressed in many cases, although a gene mutation is not apparent in up to 40% of patients. Haemophagocytic lymphohistiocytic episodes are treated with immunosuppression with ciclosporin, and intravenous immunoglobulin is beneficial particularly when hypogammaglobulinaemia is present.

More recently, a defect in X-linked inhibitor of apoptosis (XIAP) has been described [8]. Clinical presentation is similar to that of XLP, although haemorrhagic colitis has also been described. The clinical course seems similar to those with classical XLP. Haematopoietic stem cell transplantation is the only curative treatment for either genetic defect.



Fig. 17.17 Vasculitic lesion in a boy with X-linked lymphoproliferative disease. (Courtesy of the Paediatric Immunology Unit, Newcastle General Hospital, UK.)

References

1 Purtilo DT, Cassel CK, Yang JPS *et al.* X-linked recessive progressive combined variable immunodeficiency (Duncan's disease). *Lancet* 1975; **I**: 935–40.
2 Morra M, Howie D, Simarro Grande M *et al.* X-linked lymphoproliferative disease: a progressive immunodeficiency. *Ann Rev Immunol* 2001; **19**: 657–82.
3 Dutz JP, Benoit L, Wang X *et al.* Lymphocytic vasculitis in X-linked lymphoproliferative disease. *Blood* 2001; **97**: 95–100.
4 Loeffel S, Chang CH, Heyn R *et al.* Necrotizing lymphoid vasculitis in X-linked lymphoproliferative syndrome. *Arch Pathol Lab Med* 1985; **109**: 546–50.
5 Purtilo DT, Grierson HL, Davis JR *et al.* The X-linked lymphoproliferative disease: from autopsy toward cloning the gene 1975–1990. *Pediatr Pathol* 1991; **11**: 685–710.
6 Coffey AJ, Brooksbank RA, Brandau O *et al.* Host response to EBV infection in X-linked lymphoproliferative disease results from mutations in an SH2-domain encoding gene. *Nat Genet* 1998; **20**: 129–35.
7 Sayos J, Wu C, Morra M *et al.* The X-linked lymphoproliferative-disease gene product SAP regulates signals induced through the co-receptor SLAM. *Nature* 1998; **395**: 462–9.
8 Rigaud S, Fondanèche MC, Lambert N *et al.* XIAP deficiency in humans causes an X-linked lymphoproliferative syndrome. *Nature* 2006; **444**: 110–4.

Immunodeficiency and short-limbed dwarfism

Cartilage hair hypoplasia, the best described of the osteochondrodysplasias, is inherited in an autosomal recessive manner and is associated with mutations in the *RMRP* gene, which encodes mitochondrial RNA-processing endoribonuclease [1]. Severe short-limbed, short stature (–11.8 SD to 2.1 SD) with X-ray appearances of metaphyseal and spondyloepiphyseal dysplasia are always present, and most patients have sparse light hair [2]. Severe anaemia and Hirschsprung's disease [3] are less common but well-recognized associations, as are malignancies, notably lymphoma and skin carcinoma [4]. The immunodeficiency is surprisingly variable; most have T lymphopenia, and impaired *in vitro* mitogen proliferative responses, but only half suffer recurrent infection [5]. However, some have IgA and/or IgG subclass deficiencies with frequent ear infections. Patients are excessively vulnerable to viral infections, particularly varicella-zoster, EBV and other human

herpes virus infections, and the risk of infective death is 300 times greater than normal [2]. This condition should be considered in any child with severe chickenpox or herpes simplex infections who is short and has fine sparse hair. Severely affected patients should be assessed for haematopoietic stem cell transplantation, which has been successful in correcting the immunodeficiency.

References

1 Ridanpaa M, van Eenennaam H, Pelin K *et al*. Mutations in the RNA component of the Rnase MRP cause a pleiotropic human disease, cartilage-hair hypoplasia. *Cell* 2001; **104**: 195–203.

2 Makitie O, Kaitila I. Cartilage-hair hypoplasia—clinical manifestations in 108 Finnish patients. *Eur J Pediatr* 1993; **152**: 211–7.

3 Makitie O, Kaitila I, Rintala R. Hirschsprung disease associated with severe cartilage-hair hypoplasia. *J Pediatr* 2001; **138**: 929–31.

4 Makitie O, Pukkala E, Teppo L *et al*. Increased incidence of cancer in patients with cartilage–hair hypoplasia. *J Pediatr* 1999; **134**: 315–8.

5 Makitie O, Kaitla I, Savilahti E. Susceptibility to infections and in vitro immune functions in cartilage–hair hypoplasia. *Eur J Pediatr* 1998; **157**: 816–20.

Immunodeficiency, centromeric instability, facial dysmorphism (ICF) syndrome

ICF syndrome is an autosomal recessive disorder in which there are characteristic, structural chromosomal abnormalities in chromosomes 1, 9 and 16 in lymphocytes. Other cells do not show these changes. Affected children develop severe, recurrent infections and have immunoglobulin deficiency, often with agammaglobulinaemia but with normal T- and B-lymphocyte numbers [1]. T-lymphocyte immunity is not normal, and *Pneumocystis jiroveci* infection, severe viral warts and cutaneous fungal infection are described (Fig. 17.18). Patients have no immunoglobulin class-switched B lymphocytes. Facial dysmorphism is variable, but common features include low set ears, hypertelorism, flat nasal bridge, epicanthic folds, tongue protrusion and micrognathia. Triangular facies are described. Mental retardation has been described, with speech delay being a common feature. This diagnosis should be considered in a child with very extensive warts, or spreading cutaneous fungal infection and the characteristic facial features.



Fig. 17.18 Extensive, chronic fungal infection of the nail bed in a patient with ICF syndrome. (Courtesy of the Paediatric Immunology Unit, Newcastle General Hospital, UK.)

The differential diagnosis is CVID. Mental retardation may occur. Some patients have mutations in the *DNMT3B* gene, which regulates chromosomal methylation [2]. Haematopoietic stem cell transplantation has been performed successfully for this condition [3].

References

1 Brown DC, Grace E, Sumner AT *et al*. ICF syndrome (immunodeficiency, centromeric instability and facial anomalies): investigation of heterochromatin abnormalities and review of outcome. *Hum Genet* 1995; **96**; 411–6.

2 Hagleitner MM, Lankester A, Maraschio P *et al*. Clinical spectrum of immunodeficiency, centromeric instability and facial dysmorphism (ICF-syndrome). *J Med Genet* 2008; **45**: 93–9.

3 Gennery AR, Slatter MA, Bredius RG *et al*. Hematopoietic stem cell transplantation corrects the immunologic abnormalities associated with immunodeficiency-centromeric instability-facial dysmorphism syndrome. *Pediatrics* 2007; **120**: e1341–4.

Disorders of immune regulation

Increasingly, patients with complex autoimmune manifestations are being recognized, often with coexistent infectious problems. Patients with classical primary immunodeficiency, such as WAS or DiGeorge's syndrome, present with autoimmune manifestations, and it is logical to consider genetic disorders of immune regulation as primary immunodeficiencies in the broadest sense.

Defects of lymphocyte apoptosis (autoimmune lymphoproliferative syndrome, ALPS)

Apoptosis, or programmed cell death, is important for regulating immune responses once an infection has been countered. Defects in this process lead to marked autoimmune and lymphoproliferative features which characterize ALPS [1]. There are a number of pathways through which apoptosis can be induced [2]; one of the most important is initiated through a cell surface molecule Fas (CD95). Ligation of this molecule initiates a cascade of intracellular reactions culminating in apoptosis, induced by proteolytic enzymes including caspases. Mutations in molecules in this cascade result in molecularly distinct but clinically similar forms of ALPS. Fas is expressed as a trimeric surface protein. Heterozygotes with a Fas mutation in one allele often develop the full clinical syndrome, as one abnormal protein chain is sufficient to significantly impair the trimer's function, a so-called dominant-negative effect. Most of the cases are heterozygotes, though a few homozygous cases are also reported.

Many patients present in early childhood, but adult presentation and asymptomatic cases may occur. Patients usually remain well, until the disease is triggered, often by human herpes virus infection [3]. Haematological autoimmunity is most common [4], but any system can be involved. One patient developed a blistering dermatosis that was shown to be childhood linear IgA disease (Fig. 17.19) [5]. Other dermatological manifestations include vasculitis and urticaria [6]. Lymphoproliferation leads to massive, asymmetric, anterior cervical lymphadenopathy together with splenomegaly in nearly all cases, and hepatomegaly in some [4,6,7]. Malignant disease of the lymphoid system (both Hodgkin's and non-Hodgkin's lymphoma) is reported with increased frequency, but has probably been over diagnosed because the histological picture of proliferation resembles malignancy; clonality



Fig. 17.19 Tense bullae arising from erythematous plaques confirmed histologically as linear IgA disease with the presence of a subepidermal split and linear deposition of IgA at the dermoepidermal junction in a boy with *Fas*-deficient autoimmune lymphoproliferative syndrome. (Courtesy of the Paediatric Immunology Unit, Newcastle General Hospital, UK.)

studies distinguish the two [8]. Affected individuals usually have high lymphocyte counts and normal or high immunoglobulin levels. Autoantibodies are usually present. The occurrence of circulating CD3-positive T lymphocytes expressing the α/β receptor but not expressing CD4 or CD8 (so called double-negative T lymphocytes) and usually constituting between 5 and 20% of the total CD3 cell count, is a very important diagnostic clue.

Autoimmune phenomena usually respond to standard treatments, including corticosteroids and dapsone in the case of ALPS-associated juvenile bullous dermatosis. Splenectomy should be avoided if possible, as severe infective complications may follow. Haematopoietic stem cell transplantation has been successful in patients with homozygous Fas deficiency, but currently not enough is known of the long-term prognosis to justify its elective use in (milder) heterozygous case, especially as some patients improve with age.

References

1 Bleesing JHJ, Straus SE, Fleisher TA. Autoimmune lymphoproliferative syndrome: a human disorder of abnormal lymphocyte survival. *Pediatric Clin N Amer* 2000; **47**: 1291–310.

2 Vaux DL, Flavell RA. Apoptosis genes and autoimmunity. *Curr Opin Immunol* 2000; **12**: 719–24.

3 Arkwright PD, Rieux-Laucat F, Le Deist F *et al.* Cytomegalovirus infection in infants with autoimmune lymphoproliferative syndrome (ALPS). *Clin Exp Immunol* 2000; **121**: 353–7.

4 Sneller MC, Wang J, Dale JK *et al.* Clinical, immunologic and genetic features of an autoimmune lymphoproliferative syndrome associated with abnormal lymphocyte apoptosis. *Blood* 1997; **89**: 1341–8.

5 Wong CS, Arkwright PD, Rieux-Laucat F *et al.* Childhood linear IgA disease in association with autoimmune lymphoproliferative syndrome. *Br J Dermatol* 2004; **150**: 578–80.

6 Rieux-Laucat F, Blachere S, Danielan S *et al.* Lymphoproliferative syndrome with autoimmunity: a possible genetic basis for dominant expression of the clinical manifestations. *Blood* 1999; **94**: 2575–82.

7 LeDeist F, Emile JF, Rieux-Laucat F *et al.* Clinical, immunological and pathological consequences of Fas-deficient conditions. *Lancet* 1996; **348**: 719–23.

8 Straus SE, Jaffe ES, Puck JM *et al.* The development of lymphomas in families with autoimmune lymphoproliferative syndrome with germline Fas mutation defective apoptosis. *Blood* 2001; **98**: 194–200.

Chronic mucocutaneous candidiasis

Chronic mucocutaneous candidiasis (CMC) describes a heterogeneous group of primary or secondary disorders characterized by chronic infection of skin, nails and mucous membranes by organisms of the genus *Candida*, most commonly *Candida albicans*. The precise molecular defect is not known for most forms of primary CMC. Recurrent and persistent candida of the mouth, napkin area, skins and nails are the hallmark of this condition, but the severity varies considerably and invasive disease almost never occurs. Failure of usually effective antifungal drugs to clear *Candida* distinguishes primary CMC from other conditions that predispose to *Candida*, such as secondary immunodeficiency, steroid treatment or systemic antibiotics. Candidiasis is usually first noticed early in infancy and in severe cases gross oesophageal involvement causes dysphagia, gastro-oesophageal reflux and failure to thrive, whilst skin lesions may be extremely disfiguring and distressing. As a patient becomes older, *Candida* infection may become less severe. In about half the patients there is an associated endocrinopathy (in order of frequency, hypoparathyroidism, Addison's disease, pernicious anaemia, hypothyroidism and diabetes mellitus) which becomes apparent from the second to third decades onward. Cases may be familial or sporadic with recessive or dominant patterns of inheritance. For some patients, nail dystrophy and dental enamel hypoplasia, and autoimmune endocrinopathy, are associated with CMC—part of the autosomal recessive autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy (APECED) disorder [1]. In these patients, defects in the gene autoimmune regulator 1 *(AIRE-1)* are described [2]. The AIRE-1 protein is expressed in the thymus and is important for presenting host proteins to developing T lymphocytes. Normally, autoreactive T lymphocytes are eliminated before they emerge from the thymus, but in patients with *AIRE* deficiency, autoreactive lymphocytes survive and are released into the peripheral circulation, where they cause autoimmune endocrinopathy. There are decreased numbers of regulatory T lymphocytes in these patients [3]. The mechanism by which these patients develop CMC is unknown.

A minority of patients with CMC suffer from invasive bacterial sepsis, opportunistic infection, autoimmune haemolytic anaemia, malabsorption and chronic active hepatitis. Bronchiectasis and restrictive lung disease can occur [4]. The underlying defect is poorly defined and immunological abnormalities are very variable. There may be diminished T-lymphocyte proliferation and cytokine production in response to *Candida* antigens with impaired antibody production to polysaccharide antigens, and sometimes IgG2 subclass deficiency [5]. There is evidence for impaired cellular immunity to *Candida* species, including negative delayed-type

hypersensitivity skin tests and absent or low T-cell proliferation *in vitro*, as well as impaired production of macrophage inhibitory factor. Studies have demonstrated inadequate production of Th1 cytokines (IFN-γ, IL-2, IL-12) in response to *Candida* species [6].

Treatment with azole antifungals such as fluconazole can be very effective, even in severe cases, but may not completely eradicate infection, since infection often recurs on stopping treatment. Continuous treatment is necessary in severe cases. It should be noted that patients with the hyper-IgE syndrome can also present with persistent superficial candidiasis.

References

1 Ahonen P, Myllarniemi S, Sipila I *et al.* Clinical variation of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) in a series of 68 patients. *N Engl J Med* 1990; **322**: 1829–36.

2 Perheentupa J. Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. *J Clin Endocrinol Metab* 2006; **91**: 2843–50.

3 Ryan KR, Lawson CA, Lorenzi AR *et al.* CD4+CD25+ T-regulatory cells are decreased in patients with autoimmune polyendocrinopathy candidiasis ectodermal dystrophy. *J Allergy Clin Immunol* 2005; **116**: 1158–9.

4 Kirkpatrick CH. Chronic mucocutaneous candidiasis. *Pediatr Infect Dis J* 2001; **20**: 197–206.

5 Lilic D, Calvert JE, Cant AJ *et al.* Chronic mucocutaneous candidiasis. II. Class and subclass of specific antibody responses in vivo and in vitro. *Clin Exp Immunol* 1996; **105**: 213–9.

6 Lilic D, Cant AJ, Abinun M *et al.* Chronic mucocutaneous candidiasis: I. Altered-antigen stimulated IL-2, IL-4, IL-6 and IFNg production. *Clin Exp Immunol* 1996; **105**: 205–12.

Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome

The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome [1] is characterized by early-onset type I insulin-dependent diabetes mellitus, infantile ichthyosiform dermatitis, protracted diarrhoea and severe enteropathy and thyroiditis. Mutations in the *FOXP3* gene have been described in affected patients [2,3]. Insulin-dependent diabetes develops in early infancy. Atopic eczema and exfoliative dermatitis are the third most common presenting features after diabetes and enteropathy. Bruising may occur, leading to thrombocytopenia. Pemphigoid nodularis has been described as a feature of the condition [4], as well as psoriasiform dermatitis [5]. Females with very similar presentations have been described, and other gene defects are clearly implicated. Mutations in CD25 have recently been described in patients with IPEX-like disease. Haematopoietic stem cell transplantation has been tried as a curative treatment [6].

References

1 Peake JE, McCrossin RB, Byrne G *et al.* X linked immune dysregulation, neonatal insulin dependent diabetes and intractable diarrhoea. *Arch Dis Child* 1996; **74**: F195–9.

2 Wilden RS, Ramsdell F, Peake J *et al.* X-linked neonatal diabetes mellitus, enteropathy and endocrinopathy syndrome is the human equivalent of mouse scurfy. *Nat Genet* 2001; **27**: 18–20.

3 Bennett CL, Christie J, Ramsdell F *et al.* The immune dysregulation, polyendocrinopathy, enteropathy X-linked syndrome (IPEX) is caused by mutations of FOXP3. *Nat Genet* 2001; **27**: 20–1.

4 McGinness JL, Bivens MM, Greer KE *et al.* Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) associated with pemphigoid nodularis: a case report and review of the literature. *J Am Acad Dermatol* 2006; **55**: 143–8.

5 Nieves DS, Phipps RP, Pollock SJ *et al.* Dermatologic and immunologic findings in the immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome. *Arch Dermatol* 2004; **140**: 466–72.

6 Baud O, Goulet O, Canioni D *et al.* Treatment of the immune dysregulation, polyendocrinopathy, enteropathy X-linked syndrome (IPEX) by allogeneic bone marrow transplantation. *N Engl J Med* 2001; **344**: 1758–62.

DNA repair defects and immunodeficiency

As previously described, a huge number of genetically diverse lymphocytes, each bearing a unique receptor, are needed for recognition of a wide array of foreign antigens. These are created by rearranging the variable (V), diversity (D) and joining (J) gene segments that code for T- or B-lymphocyte receptor genes (VDJ recombination). To do this, DNA double-strand breaks are made between the gene segments, and then rejoined after the segments have been re-arranged. This uses the DNA repair machinery found in all cells, which originally evolved to repair DNA damaged by UV light or toxic agents, but which the immune system has utilized to generate the diversity of specific immune responses. Without fully effective DNA repair mechanisms, cells with damaged DNA are more likely to apoptose or undergo malignant proliferation. Thus individuals with defective DNA repair mechanisms have a predisposition to photosensitivity, skin abnormality, neurodegeneration, developmental anomalies and cancer as well as defective immunity [1]. Some have psoriasis-like lesions. As DNA repair mechanisms involve many control proteins, there is scope for many single-gene defects to cause distinct clinical entities; only a few of these conditions are well understood, but several manifest both dermatological and immunological features, and with the rapidly increasing understanding of their molecular bases it is likely that these conditions will now be better delineated.

Reference

1 Gennery AR. Human primary immunodeficiency syndromes associated with defective DNA double strand break repair. *Br Med Bull* 2006; **77–8**: 71–85.

Ataxia-telangiectasia

This multisystem, autosomal recessive disorder, the best known of the DNA repair disorders, is characterized by progressive cerebellar ataxia, oculocutaneous telangiectasiae, variable immunodeficiency and an increased risk of lymphoid malignancy [1]. It is associated with chromosomal instability and cellular radiosensitivity. Diagnosis remains chiefly clinical and depends on the age of presentation. In the absence of a family history, patients usually present with gait anomalies before telangiectasiae appear. Ataxia and cerebellar signs are always present, usually by the second year of life. Neurological degeneration is progressive, resulting in severe disability by late childhood, although intellectual function is usually preserved. Telangiectases usually appear between 2 and 8 years of age, first on the bulbar conjunctivae but later elsewhere, particularly on the nose, the ears, and in the antecubital and popliteal fossae. Other cutaneous manifestations include patches of hypo- or hyperpigmentation, cutaneous atrophy and atopic dermatitis [2–5]. Gonadal atrophy occurs in both sexes, and growth failure is also prominent in the later stages. Cellular and humoral immunodeficiency affects 60–80% of cases, with low levels of IgA, IgG2 and poor antibody responses to viruses and *Pneumococcus*

being seen most often [5]. Recurrent sinopulmonary infection is common and may lead to bronchiectasis and clubbing, but clinical manifestations are extremely variable [6]. Atrophic skin lesions with granuloma have been described [7]. Lymphoreticular malignancies and, unusually for immunodeficient patients, carcinomas, occur with increased frequency [8]. Radiosensitivity means that treatment with radiotherapy is toxic and often lethal. Irrespective of the development of malignancy, survival beyond early adult life is unusual. Heterozygosity for the *AT* gene confers an increased risk of developing breast cancer [9].

A raised serum α-fetoprotein (abnormal in 90%) supports the diagnosis, as does increased chromosome breakage on exposure to ionizing radiation. The *ATM* gene codes for a phosphatidyl kinase involved in meiotic recombination and cell cycle control [10]. This protein detects DNA damage, and signals to proteins involved in DNA repair and cell cycle control, ensuring that the defective DNA is repaired before cells can divide [11]. Prophylactic antibiotics or immunoglobulin replacement can reduce the morbidity of sinopulmonary infection in some patients.

References

1 Shiloh Y. Ataxia-telangiectasia: closer to unraveling the mystery. *Eur J Hum Genet* 1995; **3**: 116–38.
2 Cohen LE, Tanner DJ, Schaefer HG *et al*. Common and uncommon cutaneous findings in patients with ataxia-telangiectasia. *J Am Acad Dermatol* 1984; **10**: 431–8.
3 Epstein WI, Reed W, Boder E *et al*. Dermatological aspects of ataxia telangiectasia. *Cutis* 1968; **4**: 1324–32.
4 Reed W, Epstein WI, Boder E. Cutaneous manifestations of ataxia telangiectasia. *JAMA* 1966; **195**: 746–53.
5 McFarlin DE, Stober W, Waldmann TA. Ataxia telangiectasia. *Medicine* 1972; **51**: 281–314.
6 Oxelius V-A, Berkel AI, Hanson LA. IgG2 deficiency in ataxia-telangiectasia. *N Engl J Med* 1982; **306**: 515–7.
7 Joshi RK, al Asiri RH, Haleem A *et al*. Cutaneous granuloma with ataxia telangiectasia—a case report and review of literature. *Clin Exp Dermatol* 1993; **18**: 458–61.
8 Taylor AMR, Metcalfe JA, Thick J *et al*. Leukaemia and lymphoma in ataxia telangiectasia. *Blood* 1996; **87**: 423–38.
9 Athma P, Rappaport R, Swift M. Molecular genotyping shows that ataxia-telangiectasia heterozygotes are predisposed to breast cancer. *Cancer Genet Cytogenet* 1996; **92**: 130–4.
10 Savitsky K, Bar-Shira A, Gilad S *et al*. A single ataxia telangiectasia gene with a product similar to PI-3 kinase. *Science* 1995; **268**: 1749–53.
11 Lavin MF, Kozlov S. ATM activation and DNA damage response. *Cell Cycle* 2007; **6**: 931–42.

Nijmegen breakage syndrome

Other DNA repair defect disorders include Nijmegen breakage syndrome (NBS), an autosomal recessive disorder described in the Dutch town of that name, and characterized by microcephaly with mild to moderate mental retardation, 'bird-like' facies, immunodeficiency, clinical radiation sensitivity and chromosomal instability. Bacterial sinopulmonary infection is common, as is hypogammaglobulinaemia and $CD4^+$ T lymphopenia with diminished T-lymphocyte proliferative responses. Absence of ataxia, together with normal α-fetoprotein levels, distinguishes NBS from ataxia-telangiectasia. Specific dermatological features include café-au-lait spots and vitiligo [1], as well as skin infections due to fungal infection, and cutaneous manifestations of viral infection, particularly due to herpes viruses [2]. Sun sensitivity of the eyelids and occasional cutaneous telangiectasia have been described [1]. Treatment with antibiotic prophylaxis or immunoglobulin replacement can be helpful. Haematopoietic stem cell transplantation has been successfully performed on rare occasions [3].

References

1 Hiel JA, Weemaes CM, van den Heuvel LP *et al*. Nijmegen breakage syndrome. *Arch Dis Child* 2000; **82**: 400–6.
2 Resnick IB, Kondratenko I, Togoev O *et al*. Nijmegen breakage syndrome: clinical characteristics and mutation analysis in eight unrelated Russian families. *J Pediatr* 2002; **140**: 355–61.
3 Gennery AR, Slatter MA, Bhattacharya A *et al*. Bone marrow transplantation for Nijmegen breakage syndrome. *J Pediatr Hematol Oncol* 2005; **27**: 239.

Other disorders of DNA repair associated with immunodeficiency

Defects in DNA ligase 4, Artemis and cernunnos have been described above. As well as presenting with SCID, patients may present with features of combined immunodeficiency. Skin photosensitivity and psoriasis and multiple psoriasiform erythrodermic and squamous skin patches have been reported [1]. Many patients have microcephaly with associated developmental delay. Bloom's syndrome, a rare autosomal recessive disorder, is associated with increased sister chromatid exchange, severe growth failure, increased malignancy and immunodeficiency. Affected individuals may develop facial telangiectases and photosensitivity of the face, dorsa of the hands and forearms. Hypo- and hyperpigmented lesions may also present (Fig. 17.20). Recurrent bacterial sinopulmonary infections associated with hypogammaglobulinaemia, most often low IgM, are the most common clinical manifestation of immunodeficiency, and may lead to bronchiectasis. Bloom's protein, the gene for which is mutated in the disease, unwinds the DNA helix, but the exact mechanism by which this causes immunodeficiency is unclear [2]. Mutations in DNA ligase I have been described in an immunodeficient individual with photosensitivity who developed venous dilatation on the skin, mainly on the limbs. Bulbar telangiectasia was also present [3].

References

1 Gennery AR, Cant AJ, Seidel J *et al*. Mutations in DNA ligase IV cause radiosensitivity, growth failure, microcephaly, myelodysplasia and combined immunodeficiency (abstract). *Arch Dis Child* 2003; **88** (Suppl. 1): A54.
2 Wegner RD, German JJ, Chrzanowska KH *et al*. In: Ochs HD, Smith CIE, Puck JM, eds. *Primary Immunodeficiency Diseases; A Molecular and Genetic Approach*, 2nd edn. Oxford University Press, 2007: 427–53.
3 Webster ADB, Barnes DE, Arlett CF *et al*. Growth retardation and immunodeficiency in a patient with mutations in the DNA ligase I gene. *Lancet* 1992; **339**: 1508–9.

Fanconi's anaemia

Fanconi's anaemia is a chromosomal instability disorder characterized by developmental defects, progressive bone marrow failure and cancer susceptibility. Children with Fanconi's anaemia are generally small, and elfin-like and of low birth weight. The central clinical manifestation of Fanconi's syndrome is progressive bone-marrow failure during childhood and adolescence [1–3]. Easy bruising is generally the presenting symptom, and most often first becomes apparent between the ages of 4 and 10 years.

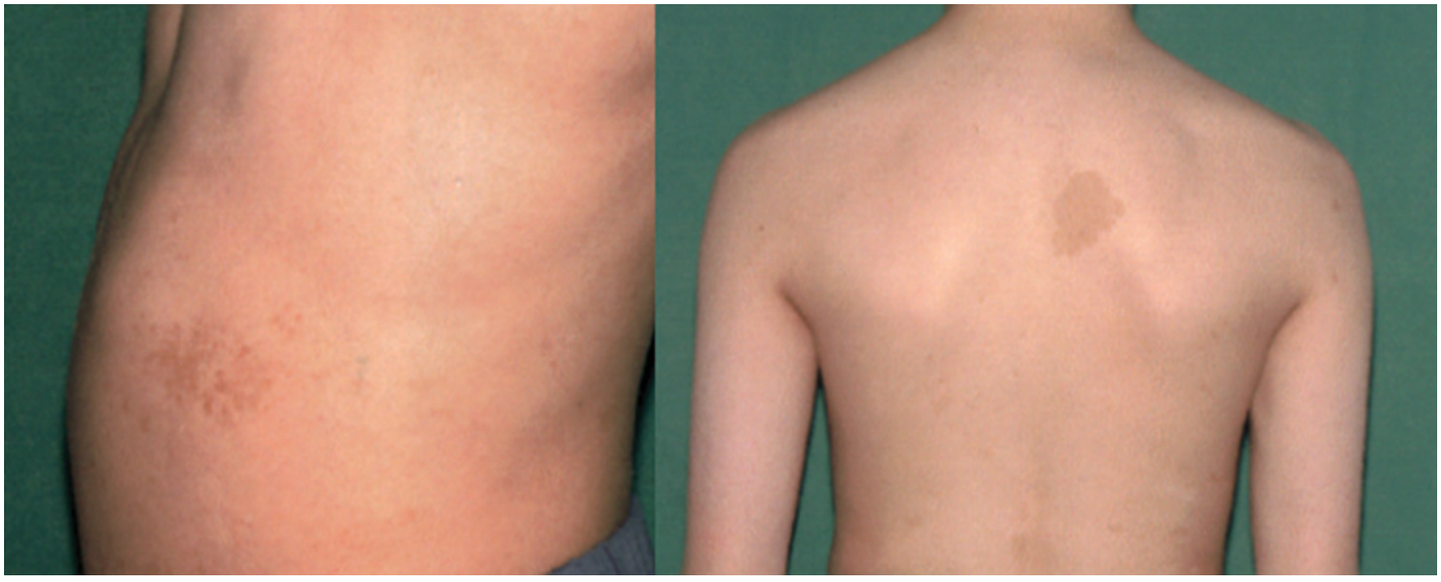


Fig. 17.20 Areas of truncal hyperpigmentation in a patient with Bloom's syndrome. (Courtesy of the Paediatric Immunology Unit, Newcastle General Hospital, UK.)

In addition to thrombocytopenia, anaemia and leukopenia are usual, and the bone marrow is aplastic.

Cutaneous hyperpigmentation and skeletal anomalies are characteristic. Unfortunately, the dermatological findings are not well described in the older literature, and there is considerable confusion with dyskeratosis congenita. However, they comprise macular brownish pigmentation, either resembling freckles and occurring mainly in sun-exposed areas, or more diffusely, in which case the abdomen, genital area and flexures appear to be predominantly affected [4]. Guttate macular hypopigmentation is often also present in affected areas. Hypopigmentation and café-au-lait spots are reported. Persistent and exceptionally severe viral wart infection can occur [4].

The principal skeletal abnormality is absence or hypoplasia of at least one of the thumbs; hypoplasia or absence of the radius is also common. Structural renal abnormalities, endocrinopathies, genital hypoplasia, microcephaly and microphthalmia are other common features.

There is a high risk of leukaemia and other malignancies in these children [5], probably due to the structural instability of chromosomes observed in Fanconi's anaemia, which leads to a high frequency of chromosomal breaks and rearrangements [6]. Cultured cells are unusually sensitive to DNA cross-linking agents such as mitomycin C, but they are not generally sensitive to ionizing radiation, although cells from the Fanconi's D2 subgroup do show ionizing radiation sensitivity.

The disorder is transmitted as an autosomal recessive trait. Thirteen complementation groups (A–N) have been described [7] and the gene defects have now been discovered. The Fanconi's proteins are involved in repair of DNA cross-linking damage, and some interact with other DNA repair pathways. In particular, the Fanconi's D2 subgroup appears to interact with ATM and nibrin, mutated in ataxia-telangiectasia and Nijmegen breakage syndrome respectively [8,9]. The induction of chromosomal breakage by the alkylating agent, diepoxybutane, can be used to detect heterozygotes and for prenatal diagnosis [10], although chorionic villus biopsy and genetic diagnosis is now possible if the specific gene defect within the family is known. There is a high incidence of diabetes [11], and of neoplastic disease [12], in heterozygotes.

The outlook for untreated patients with Fanconi's anaemia is poor, with death usually occurring within a few years of the first signs of marrow failure. Initially, bone-marrow function can be stimulated with corticosteroids and with the androgenic steroid, oxymethalone. Haematopoietic stem cell transplantation has been used successfully to treat patients, but care must be taken to avoid the use of alkylating agents in pretransplant conditioning [13]. Patients are at increased risk of secondary malignancy post-transplantation.

References

1 Auerbach AD. Fanconi's anaemia. *Dermatol Clin* 1995; **13**: 41–9.
2 Butturini A, Gale RP, Verlander PC *et al*. Hematologic abnormalities in Fanconi anemia. *Blood* 1994; **84**: 1650–5.
3 Nilsson LR. Chronic pancytopenia with multiple congenital abnormalities (Fanconi's anemia). *Acta Paediatr* 1960; **49**: 518–29.
4 Johansson E, Niemi K-M, Siimes M *et al*. Fanconi's anemia. *Arch Dermatol* 1982; **118**: 249–52.
5 Kutler DI, Singh B, Satagopan J *et al*. A 20-year perspective on the international Fanconi anemia registry (IFAR). *Blood* 2003; **101**: 341–52.
6 Schroeder TM, German J. Bloom's syndrome and Fanconi's anemia: demonstration of two distinctive patterns of chromosomal disruption and rearrangement. *Humangenetik* 1974; **25**: 1249–56.
7 Joenje H, Patel KJ. The emerging genetic and and molecular basis of Fanconi anaemia. *Nat Rev Genet* 2001; **2**: 446–57.
8 Taniguchi T, Garcia-Higuera I, Xu B *et al*. Convergence of the Fanconi anemia and ataxia teleangectasia signaling pathways. *Cell* 2002; **109**: 459–72.
9 Nakanishi K, Taniguchi T, Ranganathan V *et al*. Interaction of FANCD2 and NBS1 in the DNA damage response. *Nat Cell Biol* 2002; **4**: 913–20.
10 Auerbach AD, Min Z, Gosh R *et al*. Clastogen-induced chromosomal breakage as a marker for first trimester prenatal diagnosis of Fanconi anemia. *Hum Genet* 1986; **73**: 86–8.

11 Swift M, Sholman L, Gilmour D. Diabetes mellitus and the gene for Fanconi's anemia. *Science* 1972; **178**: 308–10.
12 Swift M. Fanconi's anemia in the genetics of neoplasia. *Nature* 1971; **230**: 370–3.
13 Guardiola P, Pasquini R, Dokal I *et al*. Outcome of 69 allogeneic stem cell transplantations for Fanconi anemia using HLA-matched unrelated donors: a study on behalf of the European Group for Blood and Bone Marrow Transplantation. *Blood* 2000; **95**: 422–9.

Other immunodeficiencies

A number of syndromes have been described which include primary immunodeficiency as part of the phenotype. In some, the syndrome is well described, and in a few the underlying molecular defect has recently been elucidated. Most lack clear definition.

Hoyeraal–Hreidarrson syndrome

This X-linked disorder is characterized by microcephaly, cerebellar hypoplasia, aplastic anaemia and growth retardation [1,2]. A progressive combined immunodeficiency, with hypogammaglobulinaemia and lymphopenia is a well-recognized association [3]. Mutations in the dyskeratosis congenita gene (*DKC1*) have been found and at least some cases of Hoyeraal–Hreidarsson syndrome represent a severe phenotype of dyskeratosis congenita [4]. Cutaneous manifestations include leukoplakia, oral and gastointestinal ulceration, and reticulated hyperpigmentation, primarily in the regions of the neck, upper thorax and upper extremities [5]. Other cutaneous features include nail dystrophy, which begins with longitudinal striations, increasing brittleness, deformation, onychoclasis and nail loss [6]. Palmar and plantar hyperhidrosis, blistering, hyperkeratosis, acrocyanosis and alopecia may also occur.

References

1 Hoyeraal HM, Lamvik J, Moe PJ. Congenital hypoplastic thrombocytopenia and cerebral malformations in two brothers. *Acta Paediatr Scand* 1970; **59**: 185–91.
2 Hreidarrson S, Kristjansson K, Johannesson G *et al*. A syndrome of progressive pancytopenia with microcephaly, cerebellar hypoplasia, and growth failure. *Acta Paediatr Scand* 1988; **77**: 773–7.
3 Berthet F, Caduff R, Schaad UB *et al*. A syndrome of primary combined immunodeficiency with microcephaly, cerebellar hypoplasia, growth failure and progressive pancytopenia. *Eur J Pediatr* 1994; **153**: 333–8.
4 Knight SW, Heiss NS, Vulliamy TJ *et al*. Unexplained aplastic anaemia, immunodeficiency, and cerebellar hypoplasia (Hoyeraal-Hreidarsson syndrome) due to mutations in the dyskeratosis congenita gene, DKC1. *Br J Haematol* 1999; **107**: 335–9.
5 Solder B, Weiss M, Jager A *et al*. Dyskeratosis congenita: multisystemic disorder with special consideration of immunologic aspects. *Clin Pediatr* 1998; **37**: 521–30.
6 Ozdemir MA, Karakukcu M, Kose M *et al*. The longest surviving child with Hoyeraal–Hreidarsson syndrome. *Haematologica* 2004; **89**: ECR38.

Netherton's syndrome

This triad of generalized infantile erythroderma, diarrhoea and failure to thrive may be associated with a variable immunodeficiency, including mild lymphopenia and polysaccharide antibody deficiency [1]. The clinical features are similar to those seen in Omenn syndrome and SCID and maternofetal engraftment, with erythroderma and ichthyosis characterized by abnormal cornification, dryness and fish-like scaling of the skin. Hair shaft abnormalities (trichorrhexis invaginata) are described which may not be seen until several months of age [2]. Distinguishing these entities is important, as the other conditions are treated by bone marrow transplantation, whereas Netherton's syndrome is not. Hair shaft abnormalities are diagnostic (bamboo hairs). Squamous cell carcinoma has been described in Netherton's syndrome [3]. Mutations in the serine protease inhibitor gene *SPINK5* have been described [4,5].

References

1 Stryk S, Siegfried EC, Knutsen AP. Selective antibody deficiency to bacterial polysaccharide antigens in patients with Netherton syndrome. *Pediatr Dermatol* 1999; **16**: 19–22.
2 Netherton EW. A unique case of trichorrhexis inodosa—bamboo hairs. *Arch Dermatol* 1958; **78**: 483–7.
3 Saghari S, Woolery-Lloyd H, Nouri K. Squamous cell carcinoma in a patient with Netherton's syndrome. *Int J Dermatol* 2002; **41**: 415–6.
4 Chavanas S, Bodemer C, Rochat A *et al*. Mutations in SPINK5, encoding a serine protease inhibitor, cause Netherton syndrome. *Nat Genet* 2000; **25**: 141–2.
5 Komatsu N, Saijoh K, Jayakumar A *et al*. Correlation between SPINK5 gene mutations and clinical manifestations in Netherton syndrome patients. *J Invest Dermatol* 2008; **128**: 1148–59.

Defects of antibody production (Table 17.14)

X-linked agammaglobulinaemia (XLA, Bruton's disease)

First described by Bruton in 1952 [1], this X-linked intrinsic B-cell defect prevents B-lymphocyte development beyond the pre-B-lymphocyte stage. It is caused by a defective gene that encodes

Table 17.14 Classification of antibody deficiency.

Antibody deficiency	Molecular defect	Inheritance
X-linked agammaglobulinaemia (Bruton's disease)	Btk	XL
XL hyper-IgM (see CD40L deficiency, p. 17.63)		
Autosomal recessive hyper-IgM syndrome	Activation-induced cytidine deaminase (AID)	AR
	CD40	AR
	UNG	AR
	NEMO	XL
Autosomal recessive agammaglobulinaemia	mu chain	AR
	BLNK	AR
	λ5/14.1 gene	AR
	Iga (CD79a)	AR
Ig heavy-chain deletions	Chromosome 14q32 deletion	AR
Selective Ig deficiency:	Defect of isotype differentiation	Unknown
IgG subclass deficiency IgA deficiency	Terminal differentiation failure in IgA+ B cells	Unknown
Polysaccharide antibody deficiency	Variable, described in some btk, NEMO, DGA patients	Unknown, specific diseases XL
CVID	See Table 17.15	Variable, may be AD, AR, XL
Transient hypogammaglobulinaemia of infancy	Unknown	Unknown

XL, X-linked; AR, autosomal recessive; AD, autosomal dominant.



Fig. 17.21 Cellulitis due to *Pseudomonas aeruginosa* in a patient with X-linked agammaglobulinaemia. (Courtesy of the Paediatric Immunology Unit, Newcastle General Hospital, UK.)

a cytoplasmic enzyme, Bruton tyrosine kinase (btk) [2,3]. Classically, affected boys produce no immunoglobulins and make no antibody responses, but have normal cell-mediated immunity. Since the molecular basis has been defined, milder phenotypes have been recognized where some antibody function is present [4]. Typically, recurrent pyogenic infections commence in the latter half of the first year of life, once maternal IgG levels have declined. The diagnosis is often made surprisingly late; in one series, the average age at diagnosis was 3 and a half years, and 2 years when there was a positive family history [5]. Sinopulmonary infections are most common, but pyoderma, gastroenteritis, arthritis, meningitis and osteomyelitis may be presenting features. Boils or impetigo are the most common dermatological features, frequently due to *Staphylococcus aureus* or *Pseudomonas* (Fig. 17.21) and usually associated with neutropenia. Chronic, ulcerative, cutaneous HSV infection has been reported [6]. Asymptomatic papular lesions developed on the trunk and arms of a 34-year-old patient in which caseating granulomas were demonstrated on biopsy, but no infectious agent was identified [7]. Pyoderma gangrenosum may be a feature [8], and Stevens–Johnson syndrome [9], vitiligo [9] and total alopecia areata [10] have also been described. Recovery from viral infections is normal with the notable exception of those caused by enteroviruses (especially echoviruses) [11], which can cause a chronic meningoencephalitis or dermatomyositis-like picture [12]. Non-purulent arthritis affecting predominantly large joints is occasionally seen, in some cases due to mycoplasma infection. Amyloidosis is an infrequent complication.

Usually there is absence or severe depletion of all serum immunoglobulin classes, and antibody responses to vaccines are absent. There are normal numbers of T lymphocytes, but no B lymphocytes in peripheral blood, although pre-B lymphocytes (containing cytoplasmic μ chains) are found in bone marrow. Lymph nodes show absent follicles and germinal centres, and plasma cells cannot be demonstrated at any site. The diagnosis can be rapidly confirmed by demonstrating absence of the btk protein in cell lysates [13].

Immunoglobulin replacement therapy is the mainstay of treatment. Chronic lung damage and sinus disease may also progress on treatment, and for this reason vigorous and early antibiotic therapy should be used for respiratory tract infections. Since the introduction of intravenous immunoglobulin therapy, lung disease seems less common and the patients developing progressive lung and sinus disease while on treatment appear to be those with damage sustained before immunoglobulin therapy was commenced [14], which emphasizes the importance of early diagnosis and treatment.

References

1 Bruton OC. Agammaglobulinaemia. *Pediatrics* 1952; **9**: 722–7.
2 Tsukada S, Saffran DC, Rawlings DJ *et al*. Deficient expression of a B cell cytoplasmic tyrosine kinase in human X-linked agammaglobulinemia. *Cell* 1993; **72**: 279–90.
3 Vetrie D, Vorechovsky I, Sideras P *et al*. The gene involved in X-linked agammaglobulinemia is a member of the Src family of protein-tyrosine kinases. *Nature* 1993; **361**: 226–33.
4 Wood PMD, Mayne A, Joyce H *et al*. A mutation in Bruton's tyrosine kinase as a cause of selective anti-polysaccharide antibody deficiency. *J Pediatr* 2001; **139**: 148–51.
5 Lederman HM, Winkelstein JA. X-linked agammaglobulinaemia: an analysis of 96 patients. *Medicine* 1985; **64**: 145–56.
6 Olsen NY, Hall JC. Chronic cutaneous herpes simplex and X-linked hypogammaglobulinemia. *Pediatr Dermatol* 1987; **4**: 225–8.
7 Flemiing MG, Gewurz AT, Pearson RW. Caseating granulomas in a patient X-linked infantile hypogammaglobulinemia. *J Am Acad Dermatol* 1991; **24**: 629–33.
8 Conley ME, Howard V. Clinical findings leading to the diagnosis of X-linked agammaglobulinemia. *J Pediatr* 2002; **141**: 566–71.
9 Hermaszweski RA, Webster ADB. Primary hypogammaglobulinaemia: a survey of clinical manifestations and complications. *QJM* 1993; **86**: 31–42.
10 Ipp MM, Gelfand EW. Antibody deficiency and alopecia. *J Pediatr* 1976; **89**: 728–31.
11 Wilfert CM, Buckley RH, Mohanakumar T *et al*. Persistent and fatal central nervous system echovirus infections in patients with agammaglobulinemia. *N Engl J Med* 1977; **296**: 1485–9.
12 Bardelas JA, Winkelstein JA, Seto DS *et al*. Fatal ECHO 24 infection in a patient with hypogammaglobulinemia: relationship to dermatomyositis-like syndrome. *J Pediatr* 1977; **90**: 396–8.
13 Gaspar HB, Lester T, Levinsky RJ *et al*. Bruton's tyrosine kinase expression and activity in X-linked agammaglobulinaemia (XLA). *Clin Exp Immunol* 1998; **111**: 334–8.
14 Quartier P, Debre M, De Blic J *et al*. Early and prolonged intravenous immunoglobulin replacement therapy in childhood agammaglobulinaemia: a retrospective survey of 31 patients. *J Pediatr* 1999; **134**: 589–96.

Autosomal recessive forms of agammaglobulinaemia

When hypogammaglobulinaemia is found in a girl or a child with consanguineous patients one of the autosomal recessive genetic defects affecting B-lymphocyte differentiation should be considered. Mutations have been described so far in genes coding for: μ heavy chain [1], Igα (part of the signal transduction complex of the B lymphocyte antigen receptor) [2], λ5 light chain [3] and B-lymphocyte linker protein (BLNK) [4]. These molecules are all required for early B-lymphocyte development from pro-B-lymphocyte to pre-B-lymphocyte stage. Unlike in XLA, pre-B lymphocytes are therefore not detectable in marrow samples. Other families have also been described in whom the molecular defect is yet to be identified. In all cases, the defect is B-lymphocyte specific. The number of cases described is too small to draw firm

conclusions, but the clinical picture would seem to be similar to XLA, although patients with μ heavy chain deficiency may have more serious life-threatening infections than those with XLA with an earlier onset of symptoms [5]. Skin sepsis is described as a feature, but less commonly than in XLA.

References

1 Yel L, Minegishi Y, Coustan-Smith E *et al*. Mutations in the mu heavy chain gene in patients with agammaglobulinemia. *N Eng J Med* 1996; **335**: 1486–93.
2 Minegishi Y, Coustan-Smith E, Rapalus L *et al*. Mutations in Igα (CD79a) result in a complete block in B-cell development. *J Clin Invest* 1999; **104**: 1115–21.
3 Minegishi Y, Coustan-Smith E, Wang Y-H *et al*. Mutations in the human λ5/14.1 gene result in B cell deficiency and with agammaglobulinemia. *J Exp Med* 1998; **187**: 71–7.
4 Minegishi Y, Rohrer J, Coustan-Smith E *et al*. An essential role for BLNK in human B cell development. *Science* 1999; **286**: 1954–7.
5 Grunebaum E. Agammaglobulinaemia caused by defects other than btk. *Immunol Allergy Clin* 2001; **21**: 45–63.

Common variable immune deficiency

Common variable immune deficiency (CVID) is a poorly defined entity characterized by the presence of quantitative or qualitative hypogammaglobulinaemia. The incidence is described as between 1:10 000 and 1:50 000 of the population, and although the onset of symptoms typically occurs in adolescence or early adult life, CVID is increasingly being diagnosed in childhood.

Selective IgA deficiency with or without IgG2 deficiency may be one end of the spectrum of this disease [1], and families are described where some members have CVID whilst others have selective IgA and/or IgG2 deficiency. Now that other immune deficiencies are being defined by their molecular defects, it has become apparent that some patients with CVID have mild phenotypes of other immune deficiencies such as X-linked agammaglobulinaemia, CD40 ligand deficiency or X-linked lymphoproliferative disease [2,3]. Autoimmune diseases, such as rheumatoid arthritis, dermatomyositis and systemic lupus erythematosus [4,5] also have an increased incidence in these kindreds. However, over recent years, five genetic defects have been more specifically linked with CVID (Table 17.15), although the underlying molecular problem has yet to be defined for the majority of patients.

Inducible co-stimulator (ICOS) is essential for T-lymphocyte-dependent B-lymphocyte responses, including the switch of immunoglobulin class from IgM to IgA and IgG. ICOS deficiency results in impaired germinal centre development, terminal B-lymphocyte differentiation and hypogammaglobulinaemia [6,7]. CD19 is only expressed on B lymphocytes, and deficiency which leads to impaired antigen-induced B-lymphocyte activation with hypogammaglobulinaemia has been described in only a few patients [8]. Transmembrane activator and calcium-modulating cyclophilin ligand interactor (TACI) is a tumour necrosis factor-like receptor expressed on B lymphocytes, involved in the control of B-lymphocyte apoptosis, survival and differentiation. Other molecules involved in this pathway include the B-cell-activating factor receptor (BAFF-R). Defects in both of these molecules have been found in CVID patients and those with IgA deficiency [9,10]. The MutS homologue 5 (MSH5) is critical in DNA mismatch repair and has a role in the switch of immunoglobulin class. Defects have been found in patients with CVID and associated IgA deficiency [11], but there appears to be incomplete penetrance, as healthy controls have been found with the same mutations.

Table 17.15 Genetic defects implicated in common variable immunodeficiency (CVID).

Genes (and deficiency) associated with CVID	Genes (and deficiency) associated with other immunodeficiencies that may mimic CVID
TNFRSF13B (transmembrane activator and calcium-modulating cyclophilin ligand interactor, TACI)	*ADA* (adenosine deaminase)
BAFFR (B-cell-activating factor receptor, BAFF-R)	*SH2D1A* (X-linked lymphoproliferative disease, XLA)
ICOS (inducible co-stimulator, ICOS)	*BTK* (X-linked agammaglobulinaemia, XLA)
CD19 (B-lymphocyte CD19)	*CD40LG* (CD40 ligand)
MSH5 (MutS homologue 5, MSH5)	

As with all patients with humoral immune defects, patients often present with recurrent sinopulmonary and gastrointestinal infections. Other clinical manifestations in this disease exemplify the inherent immune deregulation, with an increased incidence of autoimmune disease, particularly autoimmune haemolytic anaemia, thrombocytopenia and neutropenia. Non-malignant granulomatous lymphadenopathy, hepatosplenomegaly and involvement of the GI tract is a frequent finding in a subgroup of patients [12], and clinical differentiation from malignancy may be difficult, although histologically lesions resemble those seen in sarcoidosis. These granulomata are normally sensitive to steroid treatment. Patients with CVID also have a significantly increased risk of lymphoreticular and gastrointestinal malignancies [13,14]. Cutaneous manifestations are common and non-specific and include impetigo, boils, furuncles and cellulitis. Severe viral wart infection has been reported. Atopic eczema, vitiligo, alopecia areata and psoriasis have also been described in CVID patients, and are probably more common than expected. Skin manifestations with other associated symptoms should raise suspicion of this diagnosis.

All patients have defective antibody function, in which hypogammaglobulinaemia varies from a failure to respond to vaccines to panhypogammaglobulinaemia. B-lymphocyte numbers are frequently normal, but a significant proportion of patients have T-lymphocyte abnormalities, in particular a reversed CD4/8 ratio and generalized lymphopenia. Mild phenotypes may require only prophylactic antibiotics. Significant degrees of hypogammaglobulinaemia should be treated with immunoglobulin replacement therapy. Granulomatous lesions and autoimmune phenomena may respond to treatment with steroids.

References

1 Vorechovsky I, Cullen M, Carrington M *et al*. Fine mapping of IGAD1 in IgA deficiency and common variable immunodeficiency: identification and characterization of haplotypes shared by affected members of 101 multiple-case families. *J Immunol* 2000; **164**: 4408–16.
2 Kanegane H, Tsukada S, Iwata T *et al*. Detection of Bruton's tyrosine kinase mutations in hypogammaglobulinaemic males registered as common variable immunodeficiency (CVID) in the Japanese Immunodeficiency Registry. *Clin Exp Immunol* 2000; **120**: 512–7.

3 Gilmour KC, Cranston T, Jones A *et al*. Diagnosis of X-linked lymphoproliferative disease by analysis of SLAM-associated protein expression. *Eur J Immunol* 2000; **30**: 1691–7.
4 Conley ME, Park CL, Douglas SD. Childhood common variable immunodeficiency with autoimmune disease. *J Pediatr* 1986; **108**: 915–22.
5 Lee AH, Levinson AI, Schumacher HR. Hypogammaglobulinaemia and rheumatic disease. *Semin Arthr Rheum* 1993; **22**: 252–64.
6 Grimbacher B, Hutloff A, Schlesier M *et al*. Homozygous loss of ICOS is associated with adult-onset common variable immunodeficiency. *Nat Immunol* 2003; **4**: 261–8.
7 Warnatz K, Bossaller L, Salzer U *et al*. Human ICOS deficiency abrogates the germinal center reaction and provides a monogenic model for common variable immunodeficiency. *Blood* 2006; **107**: 3045–52.
8 Kanegane H, Agematsu K, Futatani T *et al*. Novel mutations in a Japanese patient with CD19 deficiency. *Genes Immun* 2007; **8**: 663–70.
9 Castigli, E, Wilson SA, Garibyan L *et al*. TACI is mutant in common variable immunodeficiency and IgA deficiency. *Nat Genet* 2005; **37**: 829–34.
10 Warnatz K, Salzer U, Gutenberger S *et al*. Finally found: human BAFF-R deficiency causes hypogammaglobulinemia. *Clin Immunol* 2005; **115** (Suppl. 1): S20.
11 Sekine H, Ferreira RC, Pan-Hammarström Q *et al*. Role for Msh5 in the regulation of Ig class switch recombination. *Proc Natl Acad Sci USA* 2007; **104**: 7193–8.
12 Spickett GP, Farrant J, North ME *et al*. Common variable immunodeficiency: how many diseases? *Immunol Today* 1997; **18**: 325–8.
13 Hermaszweski RA, Webster ADB. Primary hypogammaglobulinaemia: a survey of clinical manifestations and complications. *QJM* 1993; **86**: 31–42.
14 Cunningham-Rundles C, Siegal FP, Cunningham-Rundles S *et al*. Incidence of cancer in 98 patients with common varied immunodeficiency. *J Clin Immunol* 1987; **7**: 294–9.

IgA deficiency

Studies on healthy blood donors have shown that 1 in 600–700 Caucasians have no demonstrable serum IgA, and whilst there is almost always concomitant lack of salivary IgA, many affected individuals are asymptomatic [1]. However there is increased incidence of IgA deficiency in populations of patients with chronic lung disease and autoimmune diseases [2,3], suggesting that it may be associated with disease, perhaps when there are other, ill-defined immunological abnormalities.

Recurrent upper respiratory tract and ear infections are the commonest symptoms in young children with IgA deficiency; in the majority the frequency and severity of infections improves with age, regardless of the IgA level [4].

There is a strong correlation between autoimmune disease of all types and IgA deficiency [3], which appears independent of the infection suffered. It may be that abnormalities of antigen handling in the gut account for these autoimmune phenomena, and the increased incidence of gastrointestinal infection and coeliac disease seen in IgA deficiency, although the true incidence of these problems has not been well defined. Skin manifestations may be non-specific, and include atopic eczema, in association with sinopulmonary disease. Cutaneous features due to autoimmune disease, including psoriasis, vitiligo and dermatomyositis, have been reported [5].

References

1 Koistinen J. Selective IgA deficiency in blood donors. *Vox Sang* 1975; **29**: 192–202.
2 Burkes AW, Steele RW. Selective IgA deficiency. *Ann Allergy* 1986; **57**: 3–13.
3 Liblau RS, Bach JF. Selective IgA deficiency and autoimmunity. *Int Arch Allerg Immunol* 1992; **99**: 16–27.
4 Dalal I, Reid B, Nisbet-Brown E *et al*. The outcome of patients with hypogammaglobulinaemia in infancy and early childhood. *J Pediatr* 1998; **133**: 144–6.
5 Cunningham-Rundles C. Selective IgA deficiency. In: Stiehm RE, Ochs HD, Winkelstein JA, eds. *Immunologic Disorders in Infants and Children*, 5th edn, 2004. Philadelphia: Elsevier Saunders.

Other forms of antibody deficiency

Other forms of antibody deficiency are described (Table 17.14) but the cutaneous features are no different to those described above.

Defects in innate immunity

Disorders of phagocytic cells

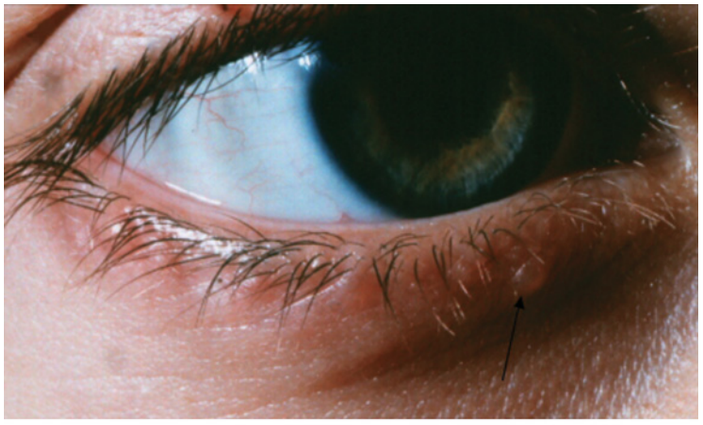
Chronic granulomatous disease

Chronic granulomatous disease (CGD) is an inherited defect of the phagocyte nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzyme complex, which generates reactive oxygen species that cause potassium ions to ingress and release lysosyme granules into phagosomes containing ingested microbes. The gene defect for the most common form, found on the X chromosome and coding for the major membrane component $gp91^{phox}$, accounts for up to 60% of cases. Defects in the genes coding for the cytoplasmic components $p67^{phox}$, $p47^{phox}$ and $p22^{phox}$ are inherited in an autosomal recessive pattern [1].

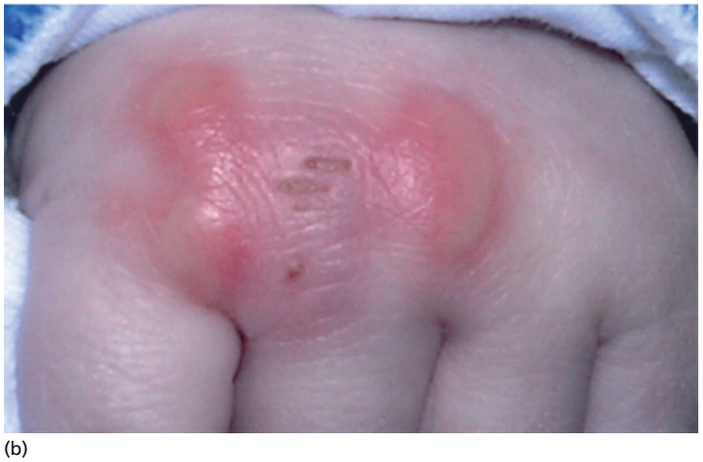
The disease has protean clinical manifestations, but the hallmark is acute, and potentially fatal, bacterial or fungal infection [2]. The disease becomes apparent during the first 2 years of life in the great majority of cases [3], but the onset may occasionally be delayed into the second decade [4–6]. The earliest manifestations are often seen in the skin. Neonatal pustulosis is commonly the first sign of the disease. Subsequently, a rather non-specific, impetiginized periorificial rash is highly characteristic. This is most commonly seen around the nostrils, ears, mouth and eyes, and has sometimes been described as 'eczematous' or 'seborrhoeic'. Any area where the skin has been broken, by abrasion for example, tends to become impetiginized or ecthymatous. Nodular lesions may follow, and these frequently break down to form necrotic ulcers.

Firm, translucent, papular lesions around the nose, eyes (Fig. 17.22a), lips and on the cheeks may mimic lupus vulgaris or sarcoidosis. A common manifestation is acute, suppurative lymphadenitis in the neck, axilla or groin. Other frequent pyogenic infections include liver abscesses, osteomyelitis, arthritis, pneumonia, skin sepsis and perianal abscesses. Pathogens, such as *Staphylococcus aureus*, *Burkholderia cepacia*, *Aspergillus* species and *Serratia marcerens*, are most commonly seen [7].

Subcutaneous nodules may develop at immunization or cannulation sites, and these also tend in time to ulcerate (Fig. 17.22b). Poor healing of surgical wounds, and of these discharging nodular skin lesions, is highly characteristic. Perianal abscesses are a regular feature. Other frequent findings include chronic suppurative paronychia, folliculitis of the scalp and ulcerative stomatitis. Acute febrile neutrophilic dermatosis (Sweet's syndrome) has been rarely described [8], as has chronic bullous disease of childhood [9]. Fungal infection often causes pulmonary disease with pneumonia, and lung abscess formation, followed by empyema and spread across tissues planes into paraspinal tissue and



(a)



(b)

Fig. 17.22 (a) A granulomatous translucent papule around the eye. (b) Ulcerating subcutaneous nodule at the site of insertion of an intravenous cannula in a child with chronic granulomatous disease. (Courtesy of the Paediatric Immunology Unit, Newcastle General Hospital, UK.)

vertebrae [10,11]. Discrete areas of persistent consolidation may be seen radiologically and are often termed 'encapsulating pneumonia'; this sign is highly distinctive. Less specific reticulonodular shadowing and hilar lymphadenopathy are also frequent. Liver abscesses are rare in childhood, and when seen CGD should always be looked for [12,13].

The importance of non-infectious inflammatory complications is increasingly recognized. These include inflammatory bowel disease, which clinically and histologically can be indistinguishable from Crohn's disease, restrictive lung defects, genitourinary obstruction and cutaneous granulomata, particularly at the vaccination sites. These non-infective manifestations sometimes respond well to corticosteroid treatment [14], but this may increase the risk of infectious complications. Discoid lupus has been described rarely in patients with CGD [15].

Female carriers of X-linked CGD frequently develop erythematous macular, papular and urticarial skin lesions following light exposure, and discoid lupus erythematosus or Jessner's lymphocytic infiltrate [7]. The carrier state for X-linked CGD should be considered in all women presenting with discoid lupus erythematosus, and appropriate attention should be paid to their family history. Identification of the carrier state offers such women the possibility of genetic counselling, and prenatal diagnosis of CGD in their sons. Female carriers of X-linked CGD do not generally show increased susceptibility to infection. However, some carriers have subcutaneous abscess, hidradenitis suppurativa and ulcerative stomatitis [16].

Diagnosis is suggested by failure of reduction of nitroblue tetrazolium or dihydrorhodamine by neutrophils. X-linked carriers have both normal and abnormal neutrophils and the presence of abnormal neutrophils may lead to abnormal clearance of cellular debris, which may in turn account for their excess risk of autoimmune disease.

Prophylactic antibiotics, in particular co-trimoxazole which is concentrated in neutrophils, has significantly reduced morbidity and mortality from bacterial infections in CGD [3]. Children should also be given antifungal prophylaxis; itraconazole is currently the best available agent, which may help reduce the risk of fatal fungal disease in these patients [14].

Infections or unexplained fevers should be treated aggressively. IFN-γ is a useful adjunctive treatment in severe bacterial or fungal infections. Although used as prophylactic therapy in the US, in Europe it is mainly used for prophylaxis only after documented failure of oral antibacterial and antifungal agents [2]. White cell infusions may also be used as adjunctive therapy in severe infection. Registry data suggest that the outlook in early childhood has improved considerably in recent years, but considerable morbidity and mortality occur [7].

Survival is variable, but improving, with prophylactic administration of antibacterial and antifungal agents; the risk of severe or fatal fungal infection resistant to antifungal prophylaxis remains. Increasingly, haematopoietic stem cell transplantation is recommended, and even in those with active fungal infection, a good outcome can be achieved [17].

References

1 Curnette JT. Molecular basis of the autosomal recessive forms of chronic granulomatous disease. *Immunodefic Rev* 1992; **3**: 149–72.

2 Fischer A, Segal AW, Seger R *et al*. The management of chronic granulomatous disease. *Eur J Pediatr* 1993; **152**: 896–9.

3 Finn A, Hadzic N, Morgan G *et al*. Prognosis of chronic granulomatous disease. *Arch Dis Child* 1990; **65**: 942–5.

4 Barriere H, Litoux P, Stalder J-F *et al*. Chronic granulomatous disease: late onset of skin lesions only in two siblings. *Arch Dermatol* 1981; **117**: 683–4.

5 Chusid MJ, Parrillo JE, Fauci AS. Chronic granulomatous disease. Diagnosis in a 27 year old man. *JAMA* 1975; **233**: 1295–6.

6 Liese JG, Jendrossek V, Jansson A *et al*. Chronic granulomatous disease in adults. *Lancet* 1995; **346**: 220–3.

7 Jones LB, McGrogan P, Flood TJ *et al*. Special article: chronic granulomatous disease in the United Kingdom and Ireland: a comprehensive national patient-based registry. *Clin Exp Immunol* 2008; **152**: 211–8.

8 Elliot SP, Mallory SB. Sweet syndrome. An unusual presentation of chronic granulomatous disease in childhood. *Ped Infect Dis J* 1999; **18**: 568–70.

9 Sillevis Smith JH, Leusen JHW, Stas HG *et al*. Chronic bullous disease of childhood and a Paecilomyces lung infection in chronic granulomatous disease. *Arch Dis Child* 1997; **77**: 150–2.

10 Jabado N, Casanova J-L, Haddad E *et al*. Invasive pulmonary infection due to *Scedosporium apiospermum* in two children with chronic granulomatous disease. *Clin Infect Dis* 1998; **27**: 1437–41.

11 Cohen MS, Isturiz RE, Malech HL *et al*. Fungal infection in chronic granulomatous disease. The importance of the phagocyte in defense against fungi. *Am J Med* 1981; **71**: 59–66.

12 Ament ME, Ochs HD. Gastrointestinal manifestations of chronic granulomatous disease. *N Engl J Med* 1973; **288**: 382–7.
13 Hague RA, Eastham EJ, Lee RE *et al*. Resolution of hepatic abscess after interferon gamma in chronic granulomatous disease. *Arch Dis Child* 1993; **69**: 443–5.
14 Cale CM, Jones AM, Goldblatt D. Follow up of patients with chronic granulomatous disease diagnosed since 1990. *Clin Exp Immunol* 2000; **120**: 351–5.
15 Roos D, Kuijpers TW, Curnette JT. Chronic granulomatous disease. In: Ochs DH, Smith CIE, Puck JM, eds. *Primary Immunodeficiency Diseases: A Molecular and Genetic Approach*, 2nd edn. Oxford University Press: Oxford, 2007.
16 Brandrup F, Koch C, Petri M *et al*. Discoid lupus erythematosus-like lesions and stomatitis in female carriers of X-linked chronic granulomatous disease. *Br J Dermatol* 1981; **104**: 495–505.
17 Seger RA, Gungor T, Belohradsky BH *et al*. Treatment of chronic granulomatous disease with myeloablative conditioning and an unmodified hematopoietic allograft: a survey of the European experience 1985–2000. *Blood* 2002; **100**: 4344–50.

Neutropenia

Neutropenia can result from reduced bone marrow production or increased peripheral destruction, which can be distinguished by bone marrow examination. Neutropenia most frequently follows decreased production induced by disease processes or drug treatments. Increased consumption may occur in autoimmune states, including those associated with immune deficiency. The degree of neutropenia will influence the clinical picture: neutrophil counts of less than 0.5×10^9/l carry a major risk of infection, whilst counts below 0.2×10^9/l are associated with a significant incidence of life-threatening sepsis.

Cyclical neutropenia

In cyclical neutropenia, decreases in haematopoiesis at intervals of about 3 weeks (range 13–35 days) lead to neutropenia and susceptibility to infection. Patients are normally asymptomatic, but during the period of severe neutropenia, aphthous ulcers, gingivitis, stomatitis and cellulitis may develop. Death from overwhelming infection occurs in a small proportion of patients. Symptoms resolve over 3 to 4 days as the neutrophil count rises, thus neutrophil counts taken after the onset of symptoms are usually normal; to make the diagnosis, neutrophil counts should be taken two or three times a week over a 4- or 5-week period. In some families, this is inherited in an autosomal dominant manner, and mutations in the neutrophil elastase gene (*ELA2*) have been identified in patients with cyclical neutropenia [1].

Reference

1 Horwitz M, Benson KF, Person RE *et al*. Mutations in ELA2, encoding neutrophil elastase, define a 21-day biological block in cyclic haematopoiesis. *Nat Genet* 1999; **23**: 433–6.

Severe congenital neutropenia

This was originally described by Kostmann in 1956 as an autosomal recessive disease [1]. Onset is within the first year of life, with recurrent and life-threatening infections. Symptoms include omphalitis, cellulitis, perirectal abscesses, peritonitis, stomatitis and meningitis. Examination of bone marrow shows an arrest at the promyelocyte to myelocyte maturation stage. Treatment with G-CSF results in increased counts and fewer infections in almost all patients with neutropenia not secondary to peripheral destruction. Concerns about the induction of leukaemias with prolonged use of G-CSF have not been borne out, although pre-treatment and annual bone marrow aspirates are recommended to screen for the development of myeloid leukaemia [2]. Some patients have defects in the *ELA2* gene. More recently, defects in *HAX1* have been described in other families [3]. Haematopoietic stem cell transplantation may be indicated in selected cases. A small number of patients with congenital neutropenia inherited in an X-linked manner have mutations that result in over-activity of WASP (Wiskott–Aldrich syndrome protein) [4], whilst dysregulated expression of the GTPases RhoA and Rac2 has been described in families where inheritance is autosomal recessive [5].

References

1 Kostmann R. Infantile genetic agranulocytosis. A review with presentation of ten new cases. *Acta Paediatr Scand* 1956; **64**: 362–6.
2 Zeidler C, Boxer L, Dale DC *et al*. Management of Kostmann syndrome in the G-CSF era. *Br J Haematol* 2000; **109**: 490–5.
3 Klein C, Grudzien M, Appaswamy G *et al*. HAX1 deficiency causes autosomal recessive severe congenital neutropenia (Kostmann disease). *Nat Genet* 2007; **39**: 86–92.
4 Devrient K, Kim AS, Mathijs G *et al*. Constitutively activating mutation in WASP causes X-linked severe congenital neutropenia. *Nat Genet* 2001; **27**: 313–7.
5 Kasper B, Tidow N, Grothues D *et al*. Differential expression and regulation of GTPases (RhoA and Rac2) and GDIs (LyGDI and RhoGDI) in neutrophils from patients with severe congenital neutropenia. *Blood* 2000; **95**: 2947–53.

Shwachman–Diamond syndrome

This rare, autosomal recessive disorder is characterized by exocrine pancreatic insufficiency, metaphyseal chondrodysplasia with associated skeletal abnormalities, bone marrow dysfunction and recurrent infections [1]. Skin sepsis is a feature. Neutropenia occurs in all patients, whilst 10–25% of patients also have pancytopenia. There is an increased incidence of myeloid leukaemia inherent to this condition. Cutaneous features are common, although not well documented. They may be due to pancreatic insufficiency with resultant malabsorption of fat-soluble vitamins, essential fatty acids and other nutrients. Patients may show xerosis and follicular keratosis. Facial skin in particular may be dry with associated perioral dermatitis. A widespread, symmetrical eczematous rash has been reported and with associated thrombocytopenic purpura, the diagnosis of WAS may be erroneously suggested. Palmoplantar hyperkeratosis and nail thickening may occur. A defect in the *SBDS* gene, a possible RNA-processing gene, has been described in these patients [2]. Haematopoietic stem cell transplantation has been successfully performed in this condition [3].

References

1 Ginzberg H, Shin J, Ellis L *et al*. Shwachman syndrome; phenotypic manifestations of sibling sets and isolated cases in a large patient cohort are similar. *J Pediatr* 1999; **135**: 81–8.
2 Boocock GRB, Morrison JA, Popovic M *et al*. Mutations in SBDS are associated with Shwachman-Diamond syndrome. *Nat Genet* 2003; **33**: 97–101.
3 Faber J, Lauener R, Wick F *et al*. Shwachman–Diamond syndrome: early bone marrow transplantation in a high risk patient and new clues to pathogenesis. *Eur J Pediatr* 1999; **158**: 995–1000.

Neutrophil-specific granule deficiency

This rare disorder is characterized by recurrent skin and lung infections with staphylococci and enteric bacteria [1]. Electron microscopy of patients' neutrophils shows reduced or absent

secondary granules; specific stains demonstrate lack of the secondary granule proteins such as lactoferrin and vitamin B_{12} binding protein. Proteins that reside in azurophilic (primary) granules, such as lysozyme and myeloperoxidase, are present. Neutrophils also show abnormalities in migration and nuclear morphology. Mice lacking the transcription factor CCAAT/enhancer binding protein have a similar phenotype, and case reports of patients with mutations in this gene have now been published [2].

The clinical course of patients is variable. Treatment options include prompt institution of antibiotic therapy for infections and prophylactic antibiotic treatment. Haematopoietic stem cell transplantation should be considered in patients with a severe phenotype.

References

1 Gallin JI. Neutrophil specific granule deficiency. *Ann Rev Med* 1985; **36**: 263–74.
2 Lekstrom-Himes JA, Dorman SE, Kopar P *et al*. Neutrophil-specific granule deficiency results from a novel mutation with loss of function of the transcription factor CCAAT/Enhancer Binding Protein. *J Exp Med* 1999; **189**: 1847–52.

Hyper-IgE syndrome

The hyper-IgE syndrome (HIES) (previously Job's syndrome) is of special relevance to the dermatologist, as the initial presentation may be cutaneous. It is a complex disorder, characterized by extreme elevation of the serum IgE level (usually in the range 2000–40 000 U/l), chronic dermatitis and repeated lung and skin infections [1]. The initial description was of severe, recurrent staphylococcal skin abscesses in fair-skinned, red-headed girls with eczema [2]. Both sexes and all races are affected equally.

These patients are frequently described as having eczema, although this is different from typical atopic eczema [3]. Affected children develop a rather non-specific, excoriated, papular and pustular eruption in the first year of life, often within the first month, particularly over the scalp, the scalp margins, the buttocks and the proximal flexures, such as the axillae, groins and neck [4,5]. The rash may appear as early as the first few days of life, at which stage it may be vesicular [6], but crusting becomes a prominent feature. Features of lichenification or scales are absent or mild in HIES. Psoriasiform lesions have been described in these patients [7].

There is almost invariably a history of furunculosis and staphylococcal lung infections, abscesses and empyema. Many patients develop staphylococcal pneumatoceles, which strongly suggest the diagnosis [8,9]. Although skin and lung infections predominate, infections of the ears, sinuses, joints and viscera are not uncommon. Skin abscesses tend to favour the scalp, face and neck, and are sometimes cold (i.e. with little surrounding inflammation) but this is not always the case. Ulceration is frequently present. Lymphadenopathy may be complicated by the development of lymph-node abscesses. *Staphylococcal aureus* is the predominant pathogen, but infection is also seen with *Haemophilus influenzae*, pneumococci, group A streptococci and with *Candida*. Oral candidiasis and *Candida* nail infections are common [9]. Pneumatocoeles may provide the focus for the development of aspergillomas. Molluscum contagiosum and verruca plana have been described as co-existing in patients with HIES [10].

Non-immunological features of the condition, which are variably present, include: abnormal, coarse facies with a wide nasal bridge and large head (Fig. 17.23); hypodense bones leading to frequent fractures; joint laxity; a high incidence of scoliosis; and delayed resorption of primary dentition with consequent delayed eruption of secondary teeth [9]. Coronary artery aneurysms have also been described [11]. The mode of inheritance can be autosomal dominant or recessive. Patients with recessive disease have the classic triad of recurrent skin infections, pneumonia and elevated serum IgE, but do not have the characteristic facial features or bony abnormalities. Additionally, they suffer from severe viral infections, including chronic refractory molluscum contagiosum and herpes simplex virus infections.



Fig. 17.23 A patient with hyper-IgE syndrome, who presented with staphylococcal pneumatocoeles. Coarse facial features and an infected eczematous-like rash are demonstrated. (Courtesy of the Paediatric Immunology Unit, Newcastle General Hospital, UK.)

Peripheral blood eosinophilia may be marked, up to 50–60%. Serum IgE levels are consistently very high (more than 10 times the upper limit of normal), although they may be normal in infancy. Most patients also have elevated IgD levels; total IgE levels may fall in adults, however IgG, IgA and IgM levels are usually unremarkable. In a significant proportion of patients, there is a failure of antibody response to polysaccharide antigens, which contributes to the susceptibility to infection [9]. In keeping with the great increase in circulating total IgE, patients show strongly positive, immediate weal-and-flare responses on skin-prick testing with foods and commonly inhaled allergens, as well as bacterial and fungal antigens [12]. Circulating levels of IgG anti-IgE are also high, as they are in atopic eczema [13]. It is rather characteristic for patients to have excessive production of IgE specific for *Staphylococus aureus* [14].

The molecular pathophysiology of HIES has remained elusive for more than 30 years, but a genetic cause for both forms has now

been described. Recently, patients with autosomal dominant HIES were found to be defective in signal transducer and activator of transcription 3 (STAT3), downstream of Tyk2, and important in the transcription of IL-6 and -10, but not IL-12 or IFNα [15,16]. All mutations were in the SRC homology 2 or DNA binding domains, which do not affect protein levels. Many of the systemic features found in HIES can now be explained; in mice, stat3 deficiency in the lung leads to excessive lung inflammation and airway enlargement, consistent with pneumatocoele formation in patients. Down-regulation of Th2 cytokines, including IL-6 and IL-10, impairs inflammatory responses, causing 'cold abscesses'. The defect causing autosomal recessive inherited disease is tyrosine kinase 2 (Tyk2) deficiency [17]. Tyk2 is a janus kinase family kinase involved in signalling through many cytokine pathways. Cells from affected patients show severe defects in response to type 1 cytokines including IFN-γ, IL-6, -10, -12 and -23. The predisposition to viral infections may be explained by the defects in type I (IFN) signalling.

Hyper-IgE syndrome is not merely atopic eczema with predisposition to cutaneous staphylococcal infections, but a very characteristic immunodeficiency disorder with specific diagnostic criteria, which include staphylococcal lung infections with an onset in infancy. However, individuals have been reported who appear to have a milder variant of the hyper-IgE syndrome, with a later onset, and with typical cutaneous and immunological abnormalities but without lung involvement [3]. Nevertheless, it must be borne in mind when considering this diagnosis that the disorder does not feature atopic eczema, but a recurrent pyodermatous eruption often associated with ulceration and/or lymph-node abscesses. The serum IgE level alone does not allow clear differentiation between atopic eczema and the hyper-IgE syndrome, because it can be equally high in both disorders. A similar clinical picture has been described in older patients with partial ADA deficiency [18].

The mainstay of treatment is long-term antistaphylococcal antibiotic prophylaxis, usually with flucloxacillin. Attention to skin hygiene is important, with judicial use of topical antimicrobials. *Candida* infections should be treated topically or, when refractory, with oral ketoconazole or fluconazole [19].

Histamine 2 receptor blockers such as cimetidine have been used, though their value is disputed. IFN-γ treatment has been tried in a few patients, but although there was some lowering of the IgE levels, there was no clinical benefit [20]. Intravenous immunoglobulin therapy may be useful in those with a demonstrable antibody production deficit and progressive bronchiectasis, which can lead to respiratory failure and death in early adulthood. Fungal infection is an important cause of death [21]. Persistent pneumatocoeles should be excised. Haematopoietic stem cell transplantation has been attempted in severe cases, and although the somatic features and high IgE levels were not corrected, the infectious problems were significantly reduced [22], possibly in keeping with the concept that the gene defects result in defective innate immune signalling responses.

References

1 Buckley RH. The hyper-IgE syndrome. *Clin Rev Allergy Immunol* 2001; **20**: 139–54.

2 Davies SD, Schaller J, Wedgewood RJ. Job's syndrome: recurrent 'cold' staphylococcal abscesses. *Lancet* 1966; **I**: 1013–5

3 Hochreutener H, Wuthrich B, Huwyler T *et al*. Variant of hyper-IgE syndrome: the differentiation from atopic dermatitis is important because of treatment and prognosis. *Dermatologica* 1991; **182**: 7–11.

4 Donabedian H, Gallin JI. The hyperimmunoglobulin E recurrent infection (Job's) syndrome. *Medicine* 1983; **62**: 195–208.

5 Chamlin SL, McCalmont TH, Cunningham BB *et al*. Cutaneous manifestations of hyper-IgE syndrome in infants and children. *J Pediatr* 2002; **141**: 572–5.

6 Kamei R, Honig PJ. Neonatal Job's syndrome featuring a vesicular eruption. *Pediatr Dermatol* 1988; **5**: 75–82.

7 Li XL, Geng SM, Lei XB *et al*. Unusual psoriasiform lesions in a patient with hyper-IgE syndrome. *J Eur Acad Dermatol Venereol* 2007; **21**: 424–6.

8 Merton DF, Buckley RH, Pratt PC *et al*. Hyperimmunoglobulin E syndrome; radiographic observations. *Radiology* 1979; **132**: 71–8.

9 Grimbacher B, Holland SM, Gallin JI *et al*. Hyper-IgE syndrome with recurrent infections—an autosomal dominant multisystem disorder. *N Eng J Med* 1999; **340**: 692–702.

10 Lei XB, Geng SM, Zeng WH *et al*. Unusual coexistence of molluscum contagiosum and verruca plana in a hyper-IgE syndrome. *Int J Dermatol* 2006; **45**: 1199–201.

11 Ling JC, Freeman AF, Gharib AM *et al*. Coronary artery aneurysms in patients with hyper IgE recurrent infection syndrome. *Clin Immunol* 2007; **122**: 255–8.

12 Buckley RH, Sampson HA. The hyperimmunoglobulin E syndrome. In: Franklin ED, ed. *Clinical Immunology Update*. New York: Elsevier, 1981: 147–67.

13 Quinti I, Bozek C, Wood N *et al*. Circulating IgG autoantibodies to IgE in atopic syndromes. *J Allergy Clin Immunol* 1986; **77**: 586–94.

14 Berger M, Kirkpatrick CH, Goldsmith PK *et al*. IgE antibodies to *Staphylococus aureus* and *Candida albicans* in patients with the syndrome of hyperimmunoglobulin E and recurrent infections. *J Immunol* 1980; **125**: 2437–43.

15 Minegishi Y, Saito M, Tsuchiya S *et al*. Dominant-negative mutations in the DNA-binding domain of STAT3 cause hyper-IgE syndrome. *Nature* 2007; **448**: 1058–62.

16 Holland SM, DeLeo FR, Elloumi HZ *et al*. STAT3 mutations in the hyper-IgE syndrome. *N Engl J Med* 2007; **357**: 1608–19.

17 Minegishi Y, Saito M, Morio T *et al*. Human tyrosine kinase 2 deficiency reveals its requisite roles in multiple cytokine signals involved in innate and acquired immunity. *Immunity* 2006; **25**: 745–55.

18 Shovlin CL, Hughes JMB, Simmonds HA *et al*. Adult presentation of adenosine deaminase deficiency. *Lancet* 1993; **341**: 1471.

19 Aihara Y, Mori M, Yokota S. Sucessful treatment of onychomycosis with fluconazole in two patients with hyperimmunoglobulinemia E syndrome. *Pediatr Dermatol* 1996; **13**: 493–5.

20 King CL, Gallin JI, Malech HL *et al*. Regulation of immunoglobulin production in hyperimmunoglobulin E recurrent-infection syndrome by interferon gamma. *Proc Natl Acad Sci USA* 1989; **86**: 10085–9.

21 Freeman AF, Kleiner DE, Nadiminti H *et al*. Causes of death in hyper-IgE syndrome. *J Allergy Clin Immunol* 2007; **119**: 1234–40.

22 Gennery AR, Flood TJ, Abinun M *et al*. Bone marrow transplantation does not correct the hyper IgE syndrome. *Bone Marrow Transpl* 2000; **25**: 1303–5.

Leukocyte adhesion disorders

To meet infection in tissues, leukocytes egress from the circulation toward sites of inflammation. To do this, cells roll along the capillary endothelium, then adhere to endothelial cells and finally pass between endothelial cells into tissues. A range of cell surface adhesion molecules are responsible for different stages of this process, as well as binding of different leukocytes to each other whilst immune responses occur. It is therefore not surprising that defects in the cell surface molecules responsible for the process result in life-threatening infection and dramatic cutaneous manifestations. In leukocyte adhesion deficiency (LAD) type I, absence of the 95-kDa β chain (CD18), common to the β2 integrin family of cell surface adhesive molecules, leads to a profound immunodeficiency affecting the function of neutrophils, monocytes,



Fig. 17.24 Deep perianal ulceration in a patient with leukocyte adhesion deficiency type I. (Courtesy of the Paediatric Immunology Unit, Newcastle General Hospital, UK.)

T lymphocytes and NK cytotoxic cells [1,2]. Inheritance is autosomal recessive. Chemotaxis, adherence and phagocytosis are markedly depressed. Different mutations result in phenotypes of variable severity, and occasional patients express normal levels of CD18 but have a non-functional molecule. The β2 integrin family is also involved in the platelet function molecule Gp2b3a, and patients with a combined leukocyte and platelet defect have been found [3]. The clinical picture is almost entirely explained by the way in which leukocytes are attracted to areas of infection and attach to the vessel walls at sites of inflammation in the usual way, but cannot pass out into the tissues. This leads to blockage of small vessels and rapidly expanding necrotic lesions without pus. Individuals with the most severe phenotype (<1% expression) present in the first weeks of life with delayed umbilical cord separation (the cord fails to shrink down and may not separate until 3–4 weeks of age) and omphalitis, together with rapidly progressive, erosive perianal ulcers (Fig. 17.24). Delayed umbilical cord separation does not seem to occur in patients with some expression of the molecule (usually in the range 2–10% of normal expression). In all forms there is excessive susceptibility to bacterial and fungal infections, with recurrent cellulitis and abscesses in the skin and other soft tissues. Deep-seated infections of bone, respiratory and gastrointestinal tracts are also seen. Gingivitis, ulcerative stomatitis and periodontitis are common and severe, leading to loss of teeth. Inflammatory lesions, particularly affecting the skin and resembling pyoderma gangrenosum, can occur in the partial forms of the deficiency, and may respond to steroids. Investigations almost invariably show a circulating neutrophilia (because of failure of the cells to migrate out of the circulation) and a profound neutrophil chemotactic defect. Diagnosis is confirmed by demonstrating the absence of the cell surface markers recognized by the anti-CD11/CD18 monoclonal antibodies. Treatment is with antibiotics in the first instance. Surgery should be avoided because of the poor healing. Neutrophil infusions appear helpful in the control of severe infections, but their use is limited by the production of alloantibodies to the transfused cells.

In the severe form, early death from infection is the rule unless a successful haematopoietic stem cell transplantation can be performed. In the partial forms, supportive and expectant management is pursued in the first instance, but haematopoietic stem cell transplantation may become necessary.

LAD type II is extremely rare, and results from defective fucose metabolism, whereby a failure to generate sialyl lewis X (CD15s) and other ligand molecules prevents binding of selectin molecules. This results in a failure of the 'rolling' type weak adhesion of leukocytes to endothelium which normally slows down the circulating leukocytes before β2 integrin binding can occur. There is a neutrophilia, and neutrophil chemotaxis and migration from the circulation is severely impaired. There is no deficiency in specific immune responses. As in LAD I deficiency, patients have a neutrophilia and suffer repeated bacterial infections and periodontal disease. Delayed umbilical cord separation is however not seen, and other features peculiar to LAD II include mental retardation, short stature and the Bombay (hh) blood phenotype [4].

A further entity, LAD type III, is also described [5,6], where leukocytes have normal β2 integrin expression, but an impaired ability to generate high avidity to their endothelial ligands at vascular endothelial contacts in response to rapid endothelial chemoattractant signals. Clinical features are similar to those in LAD types I and II.

References

1 Crowley CA, Curnutte JT, Rosin RE *et al*. An inherited abnormality of neutrophil adhesion: its genetic transmission and its association with a missing protein. *N Engl J Med* 1980; **302**: 1163–8.

2 Fischer A, Lisowska-Grospierre B, Anderson DC *et al*. Leukocyte adhesion deficiency: molecular basis and functional consequences. *Immunodefic Rev* 1988; **1**: 39–54.

3 Inwald D, Davies EG, Klein NJ. Demystified . . . adhesion molecule deficiencies. *Mol Pathol* 2001; **54**: 1–7.

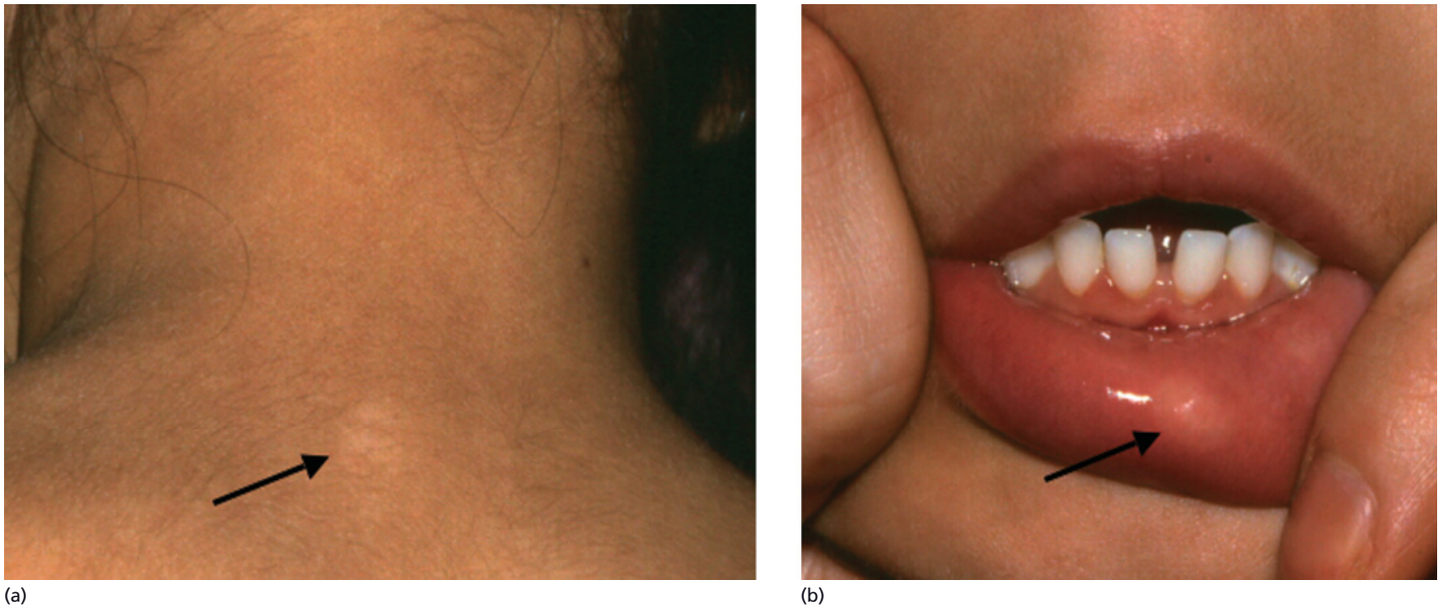
4 Etzioni A, Frydmon M, Pollack S *et al*. Recurrent severe infections caused by a novel leucocyte adhesion deficiency. *N Engl J Med* 1992; **327**: 1789–92.

5 Pasvolsky R, Feigelson SW, Kilic SS *et al*. A LAD-III syndrome is associated with defective expression of the Rap-1 activator CalDAG-GEFI in lymphocytes, neutrophils, and platelets. *J Exp Med* 2007; **204**: 1571–82.

6 Kinashi T, Aker M, Sokolovsky-Eisenberg M *et al*. LAD-III, a leukocyte adhesion deficiency syndrome associated with defective Rap1 activation and impaired stabilization of integrin bonds. *Blood* 2004; **103**: 1033–6.

Disorders of cellular cytotoxicity with oculocutaneous pigmentary defects

Congenital neutropenia or neutrophil dysfunction with associated hypopigmentation is recognized in patients with Chediak–Higashi syndrome [1], Griscelli syndrome [2] and Hermansky–Pudlak syndrome type 2 [3]. The common feature of these diseases is defects in proteins which control lysosomal secretion in melanocytes and immune cells. An important presentation of these diseases is haemophagocytic lymphohistiocytosis (HLH), universally fatal without treatment. Patients present with high swinging fevers, hepatosplenomegaly, jaundice and erythematous rash, respiratory distress and pancytopenia; they appear septic but blood cultures are usually sterile. Cytophagic histiocytic panniculitis has been described rarely [4]. Laboratory findings include an acute phase response, elevated ferritin and elevated fasting triglycerides with prolonged prothrombin time and reduced fibrinogen levels. Examination of bone marrow, cerebrinospinal fluid, pleural effusions or ascitic fluid may demonstrate haemophagocytosis. This may be very difficult to find, and repeated sampling



(a) (b)

Fig. 17.25 Subtle hypopigmentation on the nape (a) and lower labial mucosa (b) in a child with Chediak–Higashi syndrome. (Courtesy of the Paediatric Immunology Unit, Newcastle General Hospital, UK.)

may be required. Haemophagocytosis may occur secondary to a number of infections, in particular viral infections, and careful exclusion of infections by serology/PCR should be undertaken. Haemophagocytosis is also seen in a number of immunodeficient states including Griscelli syndrome, Chediak–Higashi syndrome and XLP. Diagnosis of familial HLH should be suspected in an infant with an appropriate clinical picture. Older children are more likely to have secondary HLH.

Twenty to thirty per cent of patients with familial HLH will have a mutation in the gene coding for perforin, normally found in the granules of NK and cytotoxic T lymphocytes. Perforin is important for cell lysis and apoptosis, and so may be important for all cells that regulate immune responses; its absence allows dysregulated immune activation [5]. More recently, other gene defects leading to HLH have been identified. *PFR1* defects lead to impaired perforin production, and cytolytic effector molecules cannot be introduced into the target cell, thereby triggering apoptosis. *UNC13D* mutations impair granule exocytosis after docking at the membrane. Recently, a third gene, *STX11*, was identified in familial HLH. The encoded protein, t-SNARE syntaxin 11, plays a role in intracellular trafficking. Since the protein has only been detected in monocytes, *STX11* mutations may impair cytolytic activity involving the interaction between dendritic and killer cells. Other, as yet unidentified, genetic defects also lead to HLH.

Treatment with a combination of chemotherapeutic agents, steroids and monoclonal antibodies that deplete lymphocytes may induce remission, but only haematopoietic stem cell transplantation is curative.

References

1 Kaplan J, De Domenico I, Ward DM. Chediak–Higashi syndrome. *Curr Opin Hematol* 2008; **15**: 22–9.

2 Menasche G, Feldmann J, Houdusse A *et al.* Biochemical and functional characterization of Rab27a mutations occurring in Griscelli syndrome patients. *Blood* 2003; **101**: 2736–42.

3 Wei ML. Hermansky–Pudlak syndrome: a disease of protein trafficking and organelle function. *Pigment Cell Res* 2006; **19**: 19–42.

4 Chen RL, Hsu YH, Ueda I *et al*. Cytophagic histiocytic panniculitis with fatal haemophagocytic lymphohistiocytosis in a paediatric patient with perforin gene mutation. *J Clin Pathol* 2007; **60**: 1168–9

5 Stepp SE, Dufourcq-Lagelouse R, Le Deist F *et al*. Perforin gene defects in familial hemophagocytic lymphohistiocytosis. *Science* 1999; **286**: 1957–9.

Chediak–Higashi syndrome

Chediak–Higashi syndrome (CHS) is a rare, autosomal recessive disease with partial oculocutaneous albinism, recurrent bacterial infections with organisms such as *Staphylococcus aureus*, streptococci and pneumococci, and approximately 85% of patients develop an accelerated lymphocyte and macrophage activation syndrome (similar to that seen in haemophagocytic lymphohistiocytosis (HLH) and XLP), which untreated is usually fatal. Skin, hair and eyes are affected in most cases [1]. Recurrent skin infections are common, generally starting in early childhood [2]. Deficient cutaneous pigmentation may be obvious (Fig. 17.25), but in some cases it is more subtle, and only apparent if nipples and genitalia are carefully examined. The hair generally has a silver sheen and shows clumped pigment on microscopy. Photophobia and nystagmus are regular features, due to ocular pigment dilution. Severe gingivitis and oral mucosal ulceration are well described [3].

Patients usually, but not invariably, enter an accelerated phase of the disease, with widespread infiltration with activated lymphocytes and macrophages, resulting in rapid enlargement of liver, spleen and lymph nodes, together with jaundice, hepatic failure, respiratory distress, pancytopenia and bleeding, and so death usually occurs in the first decade; survival into the second

and third decades has been recorded. Progressive neurological deterioration is common in patients who survive early childhood [4].

Characteristic giant lysosomal granules are seen in the cytoplasm of all cells containing these organelles, and are easily detected on a peripheral blood film. The gene for this disease codes for a regulator of lysosomal transport [5]; proteins normally transported through lysosomes enter these organelles but cannot exit, with subsequent lysosomal hypertrophy. In melanocytes, this results in abnormal melanin transport and consequent albinism. Neutrophil lysosomes cannot degenerate and release bactericidal proteins into the phagosome, and so intracellular killing is defective. NK cell function is also defective, as is monocyte function, probably because giant lysosomes interfere with processing of MHC II in endosomes, and thus antigen presentation is defective. The activation syndrome may result from failure to transport inhibitory molecules such as CTLA4 to the surface of leukocytes, with consequent failure of negative feedback mechanisms after T-lymphocyte and macrophage activation.

Prophylactic co-trimoxazole should be given to prevent bacterial infection. The accelerated phase cannot be predicted, and patients should be closely monitored, particularly if febrile. Symptoms, signs, laboratory and clinical findings and diagnosis and treatment of the accelerated phase are as for HLH. The only definitive treatment is haematopoietic stem cell transplantation. This should be considered early if there is a matched sibling donor. Although haematopoietic stem cell transplantation prevents further episodes of macrophage activation, it may not prevent later neurological deterioration.

References

1 Stolz W, Graubner V, Gerstmeier J *et al*. Chediak–Higashi syndrome: approaches in diagnosis and treatment. *Curr Probl Dermatol* 1989; **18**: 93–100.
2 Weary PE, Bender AS. Chediak–Higashi syndrome with severe cutaneous involvement. *Arch Intern Med* 1987; **119**: 381–6.
3 Hamilton RE, Giansanti JS. The Chediak–Higashi syndrome. *Oral Surg* 1974; **37**: 754–61.
4 Sung JH, Meyers JP, Stadlan EM *et al*. Neuropathological changes in Chediak–Higashi disease. *J Neuropathol Exp Neurol* 1969; **28**: 86–118.
5 Barbosa MDFS, Barrat FJ, Tchernev VT *et al*. Identification of mutations in two major mRNA isoforms of the Chediak–Higashi syndrome gene in human and mouse. *Hum Mol Genet* 1997; **6**: 1091–8.

Griscelli syndrome

This rare, autosomal recessive disorder results in a partial albinism and a combined immunodeficiency [1]. Individuals with Griscelli syndrome resemble those with CHS in that they have variable hypopigmentation of the skin and hair and recurrent pyogenic infections. Skin colour seems to have been more or less unremarkable, without photosensitivity, in the few patients so far reported, but affected individuals are paler than their siblings [2] and the hair, including eyebrows and eyelashes, is silvery grey from early childhood (Fig. 17.26).

Delayed-type cutaneous hypersensitivity is absent, T-cell numbers may be reduced and natural killer cell function is impaired. Hypogammaglobulinaemia is often seen as a secondary phenomenon, although B-cell numbers are usually normal. In contrast to CHS, large lysozomal granules are not seen and examination of hair by electron microscopy shows large clumps of pigment, with the accumulation of normal mature melanosomes in basal layer melanocytes in the epidermis. The liver, spleen and lymph nodes are infiltrated with histiocytic cells. Neurological abnormalities do not occur, but patients do develop an accelerated phase, which is fatal unless treated by haematopoietic stem cell transplantation [3]. Two male siblings have been reported in whom immunodeficiency was combined with partial albinism, as in Griscelli's syndrome, but in which agenesis of the corpus callosum, cleft lip and palate and bilateral congenital cataracts were also features [4].



Fig. 17.26 Generalized hypopigmentation of skin and characteristically silvery grey hair, present from birth. (Courtesy of the Paediatric Immunology Unit, Newcastle General Hospital, UK.)

Three gene defects have been described in Griscelli's syndrome: *MYO5A*, which codes for myosin 5a [5], *RAB27A* [6] and *MLPH*, which codes for melanophilin [7]. Immune defects are only reported in patients with *RAB27A* mutations.

References

1 Griscelli C, Durandy A, Guy-Grand D. A syndrome associating partial albinism and immunodeficiency. *Am J Med* 1978; **65**: 691–702.
2 Schneider LC, Berman RS, Shea CR *et al*. Bone marrow transplantation for the syndrome of pigmentary dilution and lymphohistiocytosis (Griscelli's syndrome). *J Clin Immunol* 1990; **10**: 146–53.
3 Klein C, Phillipe N, LeDeist F *et al*. Partial albinism with immunodeficiency (Griscelli Syndrome). *J Pediatr* 1994; **125**: 886–95.
4 Vici CD, Sabetta G, Gambarara M *et al*. Agenesis of the corpus callosum, combined immunodeficiency, bilateral cataract and hypopigmentation in two brothers. *Am J Med Genet* 1988; **29**: 1–8.
5 Pastural E, Barrat FJ, Dufourcq-Lagelouse R *et al*. Griscelli disease maps to chromosome 15q21 and is associated with mutations in the Myosin-Va gene. *Nat Genet* 1997; **16**: 289–92.
6 Menasche G, Pastural E, Feldmann J *et al*. Mutations in RAB27A cause Griscelli syndrome associated with haemophagocytic syndrome. *Nat Genet* 2000; **25**: 173–6.

7 Ménasché G, Ho CH, Sanal O *et al*. Griscelli syndrome restricted to hypopigmentation results from a melanophilin defect (GS3) or a MYO5A F-exon deletion (GS1). *J Clin Invest* 2003; **112**: 450–6.

Hermansky–Pudlak syndrome

Hermansky–Pudlak syndromes predominantly present as bleeding disorders. One patient, with clinical features consistent with Griscelli syndrome, including skin and hair hypopigmentation, was found to have a pathogenic homozygous mutation in the *AP3B1* gene, mutated in Hermansky–Pudlak syndrome type 2. In addition to recurrent infection associated with neutropenia, he developed fulminant HLH [1].

Reference

1 Enders A, Zieger B, Schwarz K *et al*. Lethal hemophagocytic lymphohistiocytosis in Hermansky–Pudlak syndrome type II. *Blood* 2006; **108**: 81–7.

Endosomal adaptor protein p14 deficiency

A new defect causing skin hypopigmentation, with severe congenital neutropenia and B-lymphocyte dysfunction with short stature, has been described. Patients suffer recurrent pneumococcal bronchopulmonary infection [1]. The affected protein, p14, is an adaptor molecule that is involved in control of the late endosome trafficking. The method by which this leads to neutropenia remains unclear.

Reference

1 Bohn G, Allroth A, Brandes G *et al*. A novel human primary immunodeficiency syndrome caused by deficiency of the endosomal adaptor protein p14. *Nat Med* 2007; **13**: 38–45.

Warts, hypogammaglobulinaemia, infection, myelokathexis (WHIM) syndrome

This rare, autosomal dominantly inherited immunodeficiency is characterized by numerous confluent warts, commonly on hands, although they may also be found on mucosal surfaces including the mouth. They can appear as cervical papillomatosis and vulval condylomata accuminata. They are caused by human papilloma virus and may be premalignant. They normally appear during late teens, but may be seen in early childhood. The warts respond poorly to treatment. Other clinical features include recurrent sinopulmonary bacterial infections from early childhood, which may lead to bronchiectasis in later life. Severe neutropenia is usual, and lymphopenia is described. Bone marrow examination is normocellular with marked granulocyte hyperplasia (myelokathexis—failure of leukocytes to emigrate from the marrow) [1]. The genetic defect is in the chemokine receptor *CXCR4*, important for chemotaxis of progenitor and mature haemopoietic cells [2]. Treatment is supportive with G-CSF and immunoglobulin replacement.

References

1 Gorlin RJ, Gelb B, Diaz GA *et al*. WHIM syndrome, an autosomal dominant disorder: clinical, hematological, and molecular studies. *Am J Med Genet* 2000; **91**: 368–76.

2 Hernandez PA, Gorlin RJ, Lukens JN *et al*. Mutations in the chemokine receptor gene CXCR4 are associated with WHIM syndrome, a combined immunodeficiency disease. *Nat Genet* 2003; **34**: 70–4.

Defects in the IL-12-dependent IFN-γ pathway

Defects in the IL-12 dependent IFN-γ pathway have been described in affected patients with persistent, severe bone and soft tissue abscesses and discharging sinuses due to Bacille Calmette-Guérin (BCG), or weakly pathogenic environmental non-tuberculous mycobacteria, which can be fatal [1]. There is also susceptibility to invasive non-typhi salmonella infections and severe viral infection, particularly due to herpesvirus. Oral ulceration and cutaneous vesicular eruptions have been described in those with viral infection [2]. Two patients with lesions mimicking those seen in Langerhans' cell histiocytosis, who were subsequently shown to have IFN-γ receptor deficiency, have been described. Osteolytic lesions were present in the skull and humerus, with granulomatous inflammation and central necrosis on biopsy [3], from which BCG was cultured. Infections result from a failure of upregulation of macrophage killing. The clinical picture depends on the precise molecular defect that is present. Defects have been described in a number of constituents of the IL-12/IFN-γ pathway, including complete or partial IFNγ-R1 deficiency, IL-12p40 subunit deficiency, and complete IL-12b1 deficiency. The outcome of patients with complete IFNγ-R1 deficiency is poor, but haematopoietic stem cell transplantation has been successfully attempted.

References

1 Remus N, Reichenbach J, Picard C *et al*. Impaired interferon gamma-mediated immunity and susceptibility to mycobacterial infection in childhood. *Pediatr Res* 2001; **50**: 8–13.

2 Dorman SE, Uzel G, Roesler J *et al*. Viral infections in interferon-γ receptor deficiency. *J Pediatr* 1999; **135**: 640–3.

3 Edgar JDM, Smyth AE, Pritchard J *et al*. Interferon gamma-receptor deficiency mimicking Langerhans' cell histiocytosis. *J Pediatr* 2001; **139**: 600–3.

Anhydrotic ectodermal dysplasia, incontinentia pigmenti, susceptibility to infection and defects in the *NEMO* gene and downstream signalling pathway

The transcription factors of the NF-κB family are activated by signals received when innate immune responses are triggered in cells such as neutrophils and macrophages. They play an important role in regulating immune and stress responses, inflammatory reactions and immunity to infection in humans, and are critical for transmitting signals to the nucleus from cell surface receptors that detect microbes or viruses. A number of diseases are associated with defects in this pathway, including incontinentia pigmenti and ectodermal dysplasia. X-linked anhydrotic ectodermal dysplasia and immunodeficiency have been associated in an ill-defined manner for some time, but only recently has the pathology begun to be elucidated. Patients present with sparse scalp hair, conical teeth and absent sweat glands. Some suffer from recurrent sinopulmonary infection, often with encapsulated organisms, and have poor antibody responses to polysaccharide antigens, or frank hypogammaglobulinaemia [1]. Such infants share many of the clinical features of anhydrotic ectodermal dysplasia (EDA), although they appear less severe than in children with 'classical' EDA without immunodeficiency. Incontinentia pigmenti is a rare X-linked dominant condition characterized by developmental abnormalities in skin, hair, teeth and the central nervous system. Carrier mothers demonstrate well-recognized cutaneous features of Blaschko linear skin lesions occurring in

four successive, sometimes overlapping, stages: (i) erythema, vesicules and pustules; (ii) verrucous hyperkeratotic lesions; (iii) hyperpigmented whorls and streaks following lines of Blaschko; and (iv) pallor and scarring. In other respects, affected females are healthy. Previously, affected males were all reported to die soon after birth, but some have now been described who survive, albeit with a progressive combined immunodeficiency [2]. Hypomorphic mutations in *NEMO*, which codes for NF-κB essential modulator, were subsequently discovered in a number of patients [2,3]. Stop codon mutations in the same gene are responsible for osteopetrosis and/or lymphoedema with ectodermal dysplasia and immunodeficiency (OL-EDA-ID) [2–6]. Subsequently, immunodeficiency without ectodermal dysplasia has also been described in patients with mutations in *NEMO* [7,8]. Only a few of the mothers of affected boys from EDA-ID kindreds showed variable features of EDA or incontinentia pigmenti (dry and/or hyperpigmented skin, hypodontia, conical teeth), as well as elevated IgA levels, whilst mothers of both children with OL-EDA-ID phenotype showed mild features of incontinentia pigmenti. Hypermorphic mutations in IκBα, a protein that acts downstream of NF-κB, have been described in a patient with ectodermal dysplasia and immunodeficiency [9]. The mutation impairs NF-κB activation, resulting in a similar clinical phenotype to *NEMO* defects. A further patient deficient in IκBα, who presented with ectodermal dysplasia and immunodeficiency, has also been described [10]. Invasive *Streptococcus pneumoniae* infections are also seen in patients with IRAK-4 deficiency [11]. IRAK-4, a kinase downstream of Toll-like receptors, is important for the onset and propagation of inflammation, and patients have a poor or delayed inflammatory response. Whilst potentially life-threatening in childhood, infections are rare as patients reach adulthood.

References

1 Abinun M, Spickett G, Appleton AL *et al*. Anhidrotic ectodermal dysplasia associated with specific antibody deficiency. *Eur J Pediatr* 1996; **155**: 146–7.

2 Smahi A, Courtois G, Vabres P *et al*. Genomic rearrangement in NEMO impairs NF-κB activation and is a cause of incontinentia pigmenti. *Nature* 2000; **405**: 466–72.

3 Doffinger R, Smahi A, Bessia C *et al*. X-linked anhidrotic ectodermal dysplasia with immunodeficiency is caused by impaired NF-kB signalling. *Nat Genet* 2001; **27**; 277–85.

4 Dupuis-Girod S, Corradini N, Hadj-Rabia S *et al*. Osteopetrosis, lymphedema, anhidrotic ectodermal dysplasia and immunodeficiency in a boy and incontinentia pigmenti in his mother. *Pediatrics* 2002; **109**: e97.

5 Mansour S, Woffendin H, Mitton S *et al*. Incontinentia pigmenti in a surviving male is accompanied by hypohidrotic ectodermal dysplasia and recurrent infection. *Am J Med Genet* 2001; **99**: 172–7.

6 Zonana J, Elder ME, Schneider LC *et al*. A novel X-linked disorder of immune deficiency and hypohidrotic ectodermal dysplasia is allellic to incontinentia pigmenti and due to mutations in IKK-gamma (NEMO). *Am J Hum Genet* 2000; **67**: 1555–62.

7 Niehues T, Reichenbach J, Neubert J *et al*. Nuclear factor kappaB essential modulator-deficient child with immunodeficiency yet without anhidrotic ectodermal dysplasia. *J Allergy Clin Immunol* 2004; **114**: 1456–62.

8 Orange JS, Levy O, Brodeur SR *et al*. Human nuclear factor kappa B essential modulator mutation can result in immunodeficiency without ectodermal dysplasia. *J Allergy Clin Immunol* 2004; **114**: 650–6.

9 Courtois G, Smahi A, Reichenbach J *et al*. A hypermorphic IkappaBalpha mutation is associated with autosomal dominant anhidrotic ectodermal dysplasia and T cell immunodeficiency. *J Clin Invest* 2003; **112**: 1108–15.

10 Janssen R, van Wengen A, Hoeve MA *et al*. The same IkappaBalpha mutation in two related individuals leads to completely different clinical syndromes. *J Exp Med* 2004; **200**: 559–68.

11 Ku CL, von Bernuth H, Picard C *et al*. Selective predisposition to bacterial infections in IRAK-4-deficient children: IRAK-4-dependent TLRs are otherwise redundant in protective immunity. *J Exp Med* 2007; **204**: 2407–22.

Toll-like receptor pathway deficiencies

There are 10 Toll-like receptors (TLR) in humans, each of which recognizes a distinct, but limited, repertoire of conserved microbial products which, when bound by the relevant TLR on neutrophils or macrophages, triggers a number of signalling pathways that, involving NF-κB, activate cells, stimulate proliferation and cause cytokine release. Defects have been discovered in one TLR and the signalling pathway. The first to be discovered was in individuals who had experienced herpes simplex encephalitis, but no other unusual infectious disease, and who had controlled other viral infections. Defects were found in *UNC-93B*, which encodes a protein expressed in the endoplasmic reticulum, involved in signalling through the Toll-like receptor (TLR)-3, -7, -8 and -9 [1]. More recently, defects in the gene encoding TLR-3 have been identified in children who appear susceptible only to herpes simplex encephalitis [2].

References

1 Casrouge A, Zhang SY, Eidenschenk C *et al*. Herpes simplex virus encephalitis in human UNC-93B deficiency. *Science* 2006; **314**: 308–12.

2 Zhang SY, Jouanguy E, Ugolini S *et al*. TLR3 deficiency in patients with herpes simplex encephalitis. *Science* 2007; **317**: 1522–7.

Complement disorders

Complement deficiencies

Deficiencies of isolated complement components are rare, deficiency of C2 being the most frequent, and, with the exception of properdin and C1 esterase inhibitor deficiency, are generally transmitted in an autosomal recessive manner, severe disease occurring when both alleles are defective. However, heterozygosity results in approximately half normal levels of the protein which can sometimes be clinically important. A number of clinical patterns can occur depending upon which factor is deficient.

Deficiency of the early components of the classical complement activation pathway, that is C1, 4 and 2, tend to predispose to autoimmune disease, particularly systemic lupus erythematosus [1]. Photosensitivity and cutaneous manifestations of lupus erythematosus occur in association with mild non-cutaneous disease and absent or unimpressive plasma levels of antinuclear antibody.

Evidence, based on the finding that null alleles for a number of complement components (notably C2 and C4) occur with greater frequency in patients with autoimmune diseases such as systemic lupus erythematosus, suggests that heterozygosity for deficiency is also a risk factor. In general, the course of these diseases is similar to that in patients without complement deficiency. Partial deficiencies of certain complement components, particularly C2 and C4, is associated with an increased risk of certain diseases, notably systemic lupus erythematosus, discoid lupus erythematosus, juvenile rheumatoid arthritis, membranous glomerulonephritis and angio-oedema [2–4].

Recurrent pyogenic infections are a feature of complement deficiencies. Organisms such as streptococci and *Haemophilus influenzae* are the main problem, as opsonization/binding of antibody and complement to bacteria is critical for their elimination. C3 deficiency is the most severe. Deficiency of the classical pathway components C1q and C2, and of factor D in the alternative pathway, also predisposes to infection, and the first two also carry a predisposition to autoimmune phenomena. Deficiencies of the alternative pathway control proteins, factors H or I, lead to uncontrolled consumption of C3, resulting in increased susceptibility to pyogenic infections including meningococcal disease [5].

Deficiency of one of the later complement components, C5–C9 (leading to failure of membrane lysis), or of the control factor properdin (the only deficiency inherited in an X-linked manner) leads to a specific deficiency in handling neisserial species (*N. meningitidis* and *N. gonorrhoeae*) but not to a generalized increase in susceptibility to pyogenic infections. There is a predominance of disease caused by rare serogroups of meningococci (W135, X, Y and Z) in these patients. In one study [6], complement deficiency (most commonly late components or properdin) was found in 33% of survivors of meningococcal disease due to rare serogroups, compared to 2, 0 and 7% in patients who suffered group A, B and C disease, respectively. Recurrent attacks of meningococcal septicaemia/meningitis, and severe invasive gonococcal disease, are also associated with late complement deficiencies. C9 deficiency in Japan affects up to 0.1% of the population [5], but is less common in Caucasians. Screening for deficiencies should be undertaken in patients and their immediate families where there has been recurrent meningococcal disease due to common serogroups, or single episodes caused by a rare serogroup. In the UK, screening children with single episodes of meningococcal disease due to common serotypes is unlikely to reveal a complement defect [7]. Where infections occur in children with deficiencies of the early complement components, these are predominantly caused by encapsulated bacteria, such as *Pneumococcus*.

Several proteins have been identified that have regulatory effects on the complement system. The existence of these activities has generally come to light through the profound clinical effects that may result from their deficiency. The best known of these deficiencies is that of C1 esterase inhibitor, which results in hereditary angio-oedema (see Chapter 22). Deficiency of factor 1, previously termed C3b inactivator, leads to unchecked cleavage of C3, and therefore to clinical manifestations closely resembling those seen in C3-deficient individuals [8,9]. In this condition, plasma infusions may provoke anaphylaxis, because the contained C3 is so rapidly cleaved to form the anaphylotoxin, C3a [10].

References

1 Bowness P, Davies KA, Norsworthy PJ *et al*. Hereditary C1q deficiency and systemic lupus erythematosus. *QJM* 1994; **87**: 455–64.

2 Agnello V, Gell J, Tye MJ. Partial genetic deficiency of the C4 component of complement in discoid lupus erythematosis and urticaria/angiodema. *J Am Acad Dermatol* 1983; **9**: 894–8.

3 Coleman TH, Forristal J, Kosaka T *et al*. Inherited complement deficiencies in membranoproliferative glomerulonephritis. *Kidney Int* 1983; **24**: 681–90.

4 Glass D, Raum D, Gibson D *et al*. Inherited deficiency of the second component of complement: rheumatic disease associations. *J Clin Invest* 1976; **58**: 853–61.

5 Tedesco F, Nürnberger W, Perissutti S. Inherited deficiencies of the terminal complement components. *Int Rev Immunol* 1993; **10**: 51–64.

6 Fijen CAP, Kuijper EJ, Bulte MT *et al*. Assessment of complement deficiency in patients with meningococcal disease in the Netherlands. *Clin Infect Dis* 1999; **28**: 98–105.

7 Hoare S, El-Shazali O, Clark JE *et al*. Investigation for complement deficiency following meningococcal disease. *Arch Dis Child* 2002; **86**: 215–7.

8 Alper CA, Abramson N, Johnston RB *et al*. Increased susceptibility to infection associated with abnormalities of complement-mediated functions and of the third component of complement (C3). *N Engl J Med* 1970; **282**: 350–54.

9 Barrett DJ, Boyle MDP. Restoration of complement function in vivo by plasma infusion in factor 1 (C3b inactivator) deficiency. *J Pediatr* 1984; **104**: 76–81.

10 Wahn V, Gobel U, Day NK. Restoration of complement function by plasma infusion in factor 1 (C3b inactivator) deficiency. *J Pediatr* 1984; **105**: 673–4.

C1q deficiency

A variety of clinical manifestations have been described in patients with C1q deficiency, including cutaneous vasculitis, systemic lupus erythematosus, membranous glomerulonephritis and problems with infections, particularly meningitis and septicaemia, but also including stomatitis, pyoderma and persistent candidiasis of mouth and nails [1–5].

References

1 Berkel AI, Loos M, Sanal O *et al*. Clinical and immunological studies in a case of selective complete C1q deficiency. *Clin Exp Immunol* 1979; **8**: 52–63.

2 Figueroa JE, Densen P. Infectious diseases associated with complement deficiencies. *Clin Microbiol Rev* 1991; **4**: 359–95.

3 Minta JO, Winkler CJ, Biggar WD *et al*. A selective and complete absence of C1q in a patient with vasculitis and nephritis. *Clin Immunol Immunopathol* 1982; **22**: 225–37.

4 Nishino H, Shibuya K, Nishida Y *et al*. Lupus erythematosus-like syndrome with selective complete deficiency of C1q. *Ann Intern Med* 1981; **95**: 322–4.

5 Steinsson K, McLean RH, Merrow M *et al*. Selective complete C1q deficiency associated with systemic lupus erythematosus. *J Rheumatol* 1983; **10**: 590–4.

C1r and C1s deficiencies

Systemic lupus erythematosus, or a disorder clinically suggestive of systemic lupus erythematosus but lacking confirmatory serological findings, and/or membranous glomerulonephritis, have similarly been reported in patients with deficiencies either of C1r [1] or C1s [2]. Infections have not been prominent except in the case of an infant with C1r deficiency who had lung infections and hepatic abscesses [3].

References

1 Rick KC, Hurley J, Gewurz H. Inborn C1r deficiency with a mild lupus-like syndrome. *Clin Immunol Immunopathol* 1979; **13**: 77–84.

2 Pondman KW, Stoop JW, Cormane RH *et al*. Abnormal C1r in a patient with systemic lupus erythematosus. *J Immunol* 1968; **101**: 811.

3 Johnston RB. Disorders of the complement system. In: Stiehm ER, ed. *Immunologic Disorders in Infants and Children*, 4th edn. Philadelphia: WB Saunders, 1996: 490–509.

C4 deficiency

The majority of patients reported with C4 deficiency have been children or adolescents [1]. Their principal clinical abnormalities have comprised systemic lupus erythematosus, or a systemic lupus erythematosus-like syndrome, Henoch–Schönlein purpura or Sjögren's syndrome. Infections have only occasionally been a problem [2,3].

References

1 Ross SC, Densen P. Complement deficiency states and infection: epidemiology, pathogenesis, and consequences of neisserial and other infections in an immune deficiency. *Medicine* 1984; **63**: 243–73.

2 Tappeiner G, Hintner H, Scholz S *et al*. Systemic lupus erythematosus in hereditary deficiency of the fourth component of complement. *J Am Acad Dermatol* 1982; **7**: 66–79.

3 Figueroa JE, Densen P. Infectious diseases associated with complement deficiencies. *Clin Microbiol Rev* 1991; **4**: 359–95.

C2 deficiency

This is the commonest complement deficiency. It has now been shown to be associated with a variety of diseases, but deficient individuals are often entirely healthy. Disorders occurring in C2-deficient patients have included systemic lupus erythematosus, discoid lupus erythematosus, membranous glomerulonephritis, Henoch–Schönlein purpura, rheumatoid arthritis, dermatomyositis, Crohn's disease and idiopathic thrombocytopenic purpura [1–5]. Serious bacterial infections may also occur, particularly pneumococcal, *Haemophilus influenzae* and meningococcal infections, in that order, although it is unclear why some patients are prone to such infections and others are not.

References

1 Agnello V. Association of systemic lupus erythematosus and SLE-like syndrome with hereditary and acquired complement deficiency states. *Arthritis Rheum* 1978; **21**: 146–52.

2 Guenther LC. Inherited disorders of complement. *J Am Acad Dermatol* 1983; **9**: 815–39.

3 Johnston RB. Disorders of the complement system. In: Stiehm ER, ed. *Immunologic Disorders in Infants and Children*, 4th edn. Philadelphia: WB Saunders, 1996: 490–509.

4 Ross SC, Densen P. Complement deficiency states and infection: epidemiology, pathogenesis, and consequences of neisserial and other infections in an immune deficiency. *Medicine* 1984; **63**: 243–73.

5 Steinsson K, Erlendsson K, Valdimarsson H. Successful plasma infusion treatment of a patient with C2 deficiency and systemic lupus erythematosus: clinical experience over 45 months. *Arthritis Rheum* 1989; **32**: 906–13.

C3 deficiency

C3 deficiency is the most serious of all the isolated complement deficiency states. Infections are the main hazard, particularly infections with organisms that require opsonization. Thus, meningococcal meningitis and pneumococcal pneumonia have been major problems [1]. The clinical picture is in many ways similar to that of hypogammaglobulinaemia. Transient maculopapular rashes have been reported to occur in association with infections; histologically, these have shown the features of leukocytoclastic vasculitis [2]. Other manifestations, such as systemic lupus erythematosus and membranous glomerulonephritis, have also been reported [1].

References

1 Ross SC, Densen P. Complement deficiency states and infection: epidemiology, pathogenesis, and consequences of neisserial and other infections in an immune deficiency. *Medicine* 1984; **63**: 243–73.

2 Roord JJ, Daha M, Kuis W *et al*. Inherited deficiency of the third component of complement associated with recurrent pyogenic infections, circulating immune complexes, and vasculitis in a Dutch family. *Pediatrics* 1983; **71**: 81–7.

C5, C6, C7, C8 and C9 deficiency

Recurrent meningococcal meningitis and disseminated gonococcal infections have been the principal clinical consequence of deficiencies of all these complement components [1–3]. One patient has been reported in whom frequent cutaneous infections and subcutaneous abscesses were the presenting problem, as one would expect from the defective generation of C5a chemoattractant [4], but it is now clear that cutaneous infections are generally not a problem in these patients [5].

Systemic lupus erythematosus, discoid lupus erythematosus, Sjögren's syndrome, rheumatoid arthritis and ankylosing spondylitis have also been associated with these deficiencies [1,4]. An affected 43-year-old woman has been reported in whom Raynaud's phenomenon, sclerodactyly and telangiectasia were associated with hereditary deficiency of C7 [6].

References

1 Ross SC, Densen P. Complement deficiency states and infection: epidemiology, pathogenesis, and consequences of neisserial and other infections in an immune deficiency. *Medicine* 1984; **63**: 243–73.

2 Vogler LB, Newman SL, Stroud RM *et al*. Recurrent meningococcal meningitis with absence of the sixth component of complement: an evaluation of underlying immunologic mechanisms. *Pediatrics* 1979; **64**: 465–7.

3 Weinstein MP, Gocke DJ, Gewurz A. Complement deficiency and sporadic meningococcal disease. *N Engl J Med* 1983; **309**: 615.

4 Rosenfeld SI, Kelly ME, Leddy JP. Hereditary deficiency of the fifth component of complement in man. I. Clinical, immunochemical and family studies. *J Clin Invest* 1976; **57**: 1626–34.

5 Figueroa JE, Densen P. Infectious diseases associated with complement deficiencies. *Clin Microbiol Rev* 1991; **4**: 359–95.

6 Boyer JT, Gall EP, Norman ME *et al*. Hereditary deficiency of the seventh component of complement. *J Clin Invest* 1975; **56**: 905–13.

Interaction of antibody and complement deficiencies

Deficiency of the early classical pathway complement components has been shown to be associated with poor antibody responses, presumably because the resulting poor opsonization leads to impaired antigen penetration. Later components are not implicated.

Alternative pathway opsonization is less efficient in the absence of specific antibody to bacterial surfaces. There is evidence that antibody may 'neutralize' surface molecules, such as sialic acid, which otherwise inhibit alternative pathway activation.

Deficiencies of C3 receptors

The distribution and function of cell surface receptors for C3b and its derivatives have been described above. Specific clinical syndromes have been attributed to deficiencies of some of these receptors. A dominantly inherited CR1 deficiency is associated with SLE and other immune complex disorders, presumably related to failure of the immune complex clearing function of this molecule.

Deficient expression of the CR3 receptor occurs as part of the leukocyte adhesion deficiency type I syndrome since it is a member of the β integrin family affected in this disorder, though what contribution this makes to the overall clinical picture in that condition is unclear.

Management of complement deficiencies

Apart from C1 esterase inhibitor, there are no specific replacement factor preparations. Fresh plasma infusions have been used prophylactically or can be reserved for the treatment of serious episodes of infection. Lifelong prophylactic penicillin and meningococcal vaccination are advised in those complement deficiencies resulting in susceptibility to neisserial infections. A polyvalent vaccine (A,C,W135 and Y) should be given. Prophylactic co-trimoxazole can be used in deficiencies that result in an increased susceptibility to a wider range of organisms. Clinical monitoring may allow earlier diagnosis and treatment of autoimmune disorders, should they emerge.

CHAPTER 18
Naevi and other Developmental Defects

C. Moss[1] *& H. Shahidullah*[2]

[1]Department of Dermatology, Birmingham Children's Hospital, Birmingham, UK
[2]Department of Dermatology, Derbyshire Royal Infirmary, Derby, UK

Definitions, 18.1
Aetiology, 18.2
Classification of naevi, 18.3
Blaschko's lines, 18.4
Epidermal naevi, 18.4
Verrucous epidermal naevus, 18.5
Sebaceous naevus, 18.8
Follicular naevi, 18.10
Apocrine naevi, 18.14
Eccrine naevi, 18.15
Becker's naevus, 18.17
Inflammatory epidermal naevi, 18.19
Other naevoid epidermal disorders, 18.23
The epidermal naevus syndromes, 18.27
Dermal and subcutaneous naevi, 18.30
Connective tissue naevi, 18.30
Proteoglycan naevi, 18.34
Fibrous tissue naevi, 18.34
Muscle naevi, 18.35
Fat naevi, 18.37
Vascular naevi, 18.40
Vascular tumours, 18.40
Vascular malformations, 18.60
Other developmental defects, 18.80
Complex defects of the first and second branchial arches, 18.80
Other defects of relevance to dermatology, 18.87
Posterior midline cutaneous lesions associated with defects of the cranium, vertebrae and spinal cord, 18.95
Congenital absence of skin, 18.98
Amniotic bands and adhesions, 18.106

Definitions

Developmental defects are errors in morphogenesis arising during intrauterine life. Most are *congenital*, that is present at birth, and some are inherited. The term embraces *malformations*, *deformations* and *disruptions* [1]. There is clearly considerable overlap between these three categories.

A *malformation* is a primary anatomical defect resulting from abnormal development of an organ or tissue. It may be *isolated*, occurring in an otherwise normal child, or multiple, affecting several body systems. A *malformation syndrome* is the occurrence of multiple malformations in a recognizable pattern, frequently accompanied by mental retardation, for example Down's syndrome. A *malformation sequence* occurs when a primary malformation produces secondary defects, for example hydrocephalus secondary to spina bifida.

Deformation reflects abnormal intrauterine moulding by mechanical forces, for example positional deformation of the legs and feet in spina bifida. Severe oligohydramnios may result in a characteristic combination of congenital deformations referred to as Potter's syndrome, one cause of which is renal agenesis [2].

Disruption indicates intrauterine damage or destruction to a developed organ by agents such as infection, circulatory compromise or amniotic bands.

A *teratogen* (from the Greek, *teres*, a monster) is any extrinsic factor operative during fetal life that is capable of inducing developmental abnormalities.

Naevus is the Latin word for 'maternal impression' or 'birthmark' and indicates a circumscribed, non-neoplastic skin or mucosal lesion, usually present at or soon after birth, and fixed. The term should always be qualified according to the cell or tissue of origin, for example 'connective tissue naevus' and 'vascular naevus'. Confusingly, 'naevus', 'naevo-' and 'naevoid' are often used without qualification to imply melanocytic naevus. Thus 'naevus cell' means the cell type found in a melanocytic naevus, 'naevocytic naevus' means a melanocytic naevus, and 'naevoid basal cell carcinomas' look like melanocytic naevi.

The term 'naevus' is synonymous with *cutaneous hamartoma* (e.g. smooth muscle naevus/hamartoma), both comprising an abnormal mixture of a tissue's usual components (the word 'hamartoma' derives from the Greek word *hamartia*, meaning 'to err').

Many, possibly all, naevi represent clones of genetically altered cells arising from mosaicism [3–7]. *Genetic mosaicism* (see also Chapter 15) denotes the presence of two or more genetically different cell populations in an individual derived from a single zygote. The differences can be between single genes, groups of genes or entire chromosomes. *Chimerism* denotes the presence of two or more genetically distinct cell populations in an individual derived from two different zygotes. Chimeras can result from the fusion of dizygotic twin embryos, or from the fertilization by two spermatozoa, and subsequent splitting, of an ovum containing a polar body. While mosaicism generally involves an abnormal clone within a normal individual, chimerism involves two different normal clones. Cutaneous anomalies due to mosaicism affect any skin cell type, but the cutaneous abnormalities observed in human chimeras are always pigmentary [8–10].

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

The word 'naevoid' is sometimes applied to mosaic forms of inherited skin conditions following Blaschko's lines, for example naevoid psoriasis.

The imprecise term *systematized*, applied to an extensive naevus, implies a linear, segmental or dermatomal distribution. The terms *segmental* and *zosteriform* should be confined to naevi following body segments and dermatomes respectively. In practice, 'segmental' usually conceals ignorance about whether the pattern follows dermatomes or Blaschko's lines.

References

1 Jones KL. *Smith's Recognizable Patterns of Human Malformation*, 6th edn. Philadelphia: Elsevier Saunders, 2006.
2 Thomas IT, Smith DW. Oligohydramnios, cause of the non-renal features of Potter's syndrome, including pulmonary hypoplasia. *J Pediatr* 1974; **84**: 811–4.
3 Happle R. What is a nevus? *Dermatology* 1995; **191**: 1–5.
4 Bolognia JL, Orlow SJ, Glick SA. Lines of Blaschko. *J Am Acad Dermatol* 1994; **31**: 157–90.
5 Moss C, Jones DO, Blight A, Bowden PE. Birthmark due to cutaneous mosaicism for keratin 10 mutation. *Lancet* 1995; **345**: 596.
6 Paller AS. Expanding our concepts of mosaic disorders of the skin. *Arch Dermatol* 2001; **137**: 1236–8.
7 Stosiek N, Ulmer R, von den Driesch P *et al.* Chromosomal mosaicism in two patients with epidermal verrucous nevi. *J Am Acad Dermatol* 1994; **30**: 622–5.
8 Findlay GH, Moores PP. Pigment anomalies of the skin in the human chimaera: their relations to systematised naevi. *Br J Dermatol* 1980; **103**: 489–98.
9 Goudie RB, Jack AS, Goudie BM. Genetic and developmental aspects of pathological pigmentation patterns. *Curr Top Pathol* 1985; **74**: 103–39.
10 Thomas IT, Frias JL, Cantu ES *et al.* Association of pigmentary abnormalities with chromosomal and genetic mosaicism and chimerism. *Am J Hum Genet* 1989; **45**: 193–205.

Aetiology

Congenital malformations may be caused by environmental or genetic factors, or combinations of the two independently or interacting. Some abnormalities have different causes in different patients, for example aplasia cutis. It is important to recognize parents' tendencies to attribute neonatal defects to antenatal and perinatal events: the question 'What did you think might have caused this?' may reveal surprising and irrational concerns.

Environmental factors. Those provoking congenital malformations (teratogens) are listed below. In fact, remarkably few cutaneous developmental defects have been attributed to teratogens [1]: they include aplasia cutis congenita of the scalp due to methimazole and segmental aplasia cutis following first-trimester varicella.

1 *Intrauterine infections*: rubella [2–5], cytomegalovirus [6], toxoplasmosis [7] and herpes simplex virus [8], are well-known causes of non-cutaneous defects. Varicella infection before 20 weeks gestation can cause segmental aplasia cutis [9].
2 *Ionizing radiation* from X-rays, radiotherapy or accidental contamination [10,11].
3 *Drugs taken during pregnancy* [12–15], particularly cytotoxic and immunosuppressive agents, anticonvulsants, anticoagulants, androgens, lithium carbonate, thalidomide, vitamin A derivatives and antithyroid drugs. Carbimazole and methimazole [16] can cause aplasia cutis congenita of the scalp.
4 *Alcohol* [17–19] *use during pregnancy* may result in a characteristic dysmorphic appearance (fetal alcohol syndrome) an occasional feature of which is neonatal hypertrichosis. Haemangiomas (mostly small, raised strawberry angiomas) were found in 12/41 (29%) infants with fetal alcohol syndrome [17].
5 *Trace metal excesses or deficiency during pregnancy*, particularly mercury exposure which causes widespread neurological disease [20], and zinc deficiency which is associated with neural tube defects [21].
6 *Exposure to other toxins during pregnancy*. Congenital polychlorinated biphenyl (PCB) poisoning occurred following exposure of mothers in two industrial accidents, in Japan and Taiwan, in which cooking oil was contaminated during its manufacture [22]. Affected babies had 'cola-coloured skin', with dark brown pigmentation of flexures, nails, mouth and sclerae that cleared in 2–5 months.
7 *Maternal diseases*, such as diabetes mellitus [23] and phenylketonuria [24].
8 *Paternal occupational exposure to toxins* can adversely affect the fetus either by direct effects on spermatozoa, or indirectly by maternal contamination. Paternal occupations that have been linked with birth defects include janitors, painters, printers, and occupations related to solvents or agriculture [25].

Genetic factors. Most developmental defects involving the skin probably have a genetic basis. The types of genetic abnormality, in descending order of size of the mutation, are summarized below:

1 *Chromosomal syndromes*: major abnormalities of chromosome number include trisomy 21 (Down's syndrome), and sex chromosome defects. Syndromes due to structural anomalies of chromosomes include Wolf–Hirschhorn syndrome, in which there is loss of the short arm of chromosome 4. Chromosomal syndromes involving an autosome are usually accompanied by mental retardation. Skin anomalies are unusual in this group, but include keratosis pilaris in Down's syndrome. Localized skin anomalies are even more unusual: an example is aplasia cutis in Wolf–Hirschhorn syndrome. Chromosomal anomalies may be inherited, or may arise after conception from chromosomal non-disjunction during mitosis, in which case they will be mosaic.
2 *Microdeletion syndromes*: submicroscopic deletion of contiguous genes can produce syndromes combining features caused by the individual genes. A dermatological example is X-linked ichthyosis with hypogonadotrophic hypogonadism, due to a microdeletion at Xp22 affecting both the steroid sulphatase and Kallmann's syndrome loci. Microdeletions are detected by fluorescence *in situ* hybridization (FISH).
3 *Mutations in specific genes*: this is the major cause of both inherited and mosaic syndromes and anomalies.

Genetic mechanisms in localized and isolated defects

Genetic skin disorders are usually generalized. The patchy and localized conditions that are the subject of this chapter can be produced and transmitted by the following genetic mechanisms:

1 Mutations in genes acting on morphogenesis may cause abnormal cell migration, resulting in patchy defects. Examples include dominantly inherited scalp aplasia cutis, and white patches in autosomal dominant piebaldism.
2 Patchy skin manifestations in some generalized autosomal dominant and recessive disorders may be attributable to a genetic

'second hit' [26] (loss of heterozygosity), e.g. hamartomas in tuberous sclerosis, and the tumours of xeroderma pigmentosum. However, other mechanisms have been postulated [27].

3 Some localized anomalies represent a '*forme fruste*' or minimal expression of a generalized disorder. For example, lower-lip sinuses, which most often occur alone, represent the minimal manifestation of an autosomal dominant gene, whose full expression results in Van der Woude's syndrome, with associated cleft lip and palate [28]. It is possible that isolated ash-leaf macules and café-au-lait macules have a similar significance.

4 Genetic mosaicism resulting from somatic mutation is probably the major cause of naevi and other localized skin defects [29–32]. The embryo is normal at conception, but at some point during early embryogenesis a mutation gives rise to a clone of cells in which the genetic change manifests as a localized cutaneous abnormality. Naevi caused by genetic mosaicism arising after conception are by definition not inherited from the parents. Occasional reports of familial clustering of mosaic conditions (such as epidermal naevus and segmental neurofibromatosis) may be attributable to inheritance of an unstable premutation. Happle has suggested two other mechanisms to explain familial clustering of mosaic conditions: 'paradominant inheritance' [33] in which a recessive gene is unmasked by loss of heterozygosity, and the silencing and activation of different genes by 'transposable elements' [34]. A particular risk of mosaic disorders is transmission of the generalized condition to the patient's offspring (e.g. generalized neurofibromatosis type 1 in offspring of patients with segmental neurofibromatosis). Some localized defects (e.g. Sturge–Weber syndrome) have been attributed to serious mutations compatible with survival only in the mosaic state, so that if the mutation were passed on it would cause miscarriage [35]: this has never been documented. Epidermal mosaicism is manifest as Blaschko's lines (see below).

References

1 Boccardi D, Menni S, Ferraroni M *et al*. Birthmarks and transient skin lesions in newborns and their relationship to maternal factors: a preliminary report from northern Italy. *Dermatology* 2007; **215**: 53–8.

2 McIntosh ED, Menser MA. A fifty-year follow-up of congenital rubella. *Lancet* 1992; **340**: 414–15.

3 Miller E, Cradock-Watson JE, Pollock TM. Consequences of confirmed maternal rubella at successive stages of pregnancy. *Lancet* 1982; **ii**: 781–4.

4 Sever JL, Nelson KB, Gilkeson MR. Rubella epidemic 1964: effect on 6000 pregnancies. *Am J Dis Child* 1965; **110**: 395–407.

5 Atreya CD, Mohan KV, Kulkarni S. Rubella virus and birth defects: molecular insights into the viral teratogenesis at the cellular level. *Birth Defects Res A Clin Mol Teratol* 2004; **70**: 431–7.

6 Ornoy A, Diav-Citrin O. Fetal effects of primary and secondary cytomegalovirus infection in pregnancy. *Reprod Toxicol* 2006; **21**: 399–409.

7 Montoya JG, Liesenfeld O. Toxoplasmosis. *Lancet* 2004; **363**: 1965–76.

8 Sauerbrei A, Wutzler P. Herpes simplex and varicella-zoster virus infections during pregnancy: current concepts of prevention, diagnosis and therapy. Part 1: herpes simplex virus infections. *Med Microbiol Immunol* 2007; **196**: 89–94.

9 Sauerbrei A, Wutzler P. Herpes simplex and varicella-zoster virus infections during pregnancy: current concepts of prevention, diagnosis and therapy. Part 2: Varicella-zoster virus infections. *Med Microbiol Immunol* 2007; **196**: 95–102.

10 Griem MI, Meier P, Dobben GD. Analysis of the morbidity and mortality of children irradiated in fetal life. *Radiology* 1967; **88**: 347–9.

11 Czeizel A. Infant mortality after Chernobyl. *Lancet* 1990; **335**: 161.

12 Briggs GG, Freeman RK, Yaffe SJ. *Drugs in Pregnancy and Lactation*, 7th edn. Baltimore: Lippincott Williams & Wilkins, 2005.

13 Lenz W. Malformations caused by drugs in pregnancy. *Am J Dis Child* 1966; **112**: 99–106.

14 Shephard TH. *Catalog of Teratogenic Agents*, 8th edn. Baltimore: Johns Hopkins University Press, 1995.

15 Ferner RE. Disorders of the fetus and infant. In: Davies DM, Ferner RE, de Glanville H, eds. *Davies' Textbook of Adverse Drug Reactions*, 5th edn. London: Chapman & Hall, 1998: 82–118.

16 Karg E, Bereg E, Gaspar L *et al*. Aplasia cutis congenita after methimazole exposure in utero. *Pediatr Dermatol* 2004; **21**: 491–4.

17 Hanson JW, Jones KL, Smith DW. Fetal alcohol syndrome. Experience with 41 patients. *JAMA* 1976; **235**: 1458–60.

18 Mukherjee RA, Hollins S, Turk J. Fetal alcohol spectrum disorder: an overview. *J R Soc Med* 2006; **99**: 298–302.

19 Ferraro F, Dehaene P. Cutaneous tuberous angioma in children with fetal alcohol syndrome. *Arch Pediatr* 1996; **3**: 511–2.

20 Amin-Zaki L, El-Hassani S, Majeed MA *et al*. Intra-uterine methylmercury poisoning in Iraq. *Pediatrics* 1974; **54**: 587–95.

21 Golalipour MJ, Mansourian AR, Keshtkar A. Serum zinc levels in newborns with neural tube defects. *Indian Pediatr* 2006; **43**: 809–12.

22 Miller RW. Congenital PCB poisoning: a reevaluation. *Environ Health Perspect* 1985; **60**: 211–4.

23 Dunn PM. Congenital malformations and maternal diabetes. *Lancet* 1964; **ii**: 644–5.

24 National Institutes of Health. Consensus Development Conference Statement: phenylketonuria: screening and management, October 16–18, 2000. *Pediatrics* 2001; **108**: 972–82.

25 Chia S-E, Shi L-M. Paternal occupation and risk of birth defect. *Occup Environ Med* 2001; **59**: 149–55.

26 Knudsen AG Jr. Mutation and cancer: a statistical study of retinoblastoma. *Proc Natl Acad Sci USA* 1971; **68**: 820–3.

27 Tucker T, Friedman JM. Pathogenesis of hereditary tumors: beyond the 'two-hit' hypothesis. *Clin Genet* 2002; **62**: 345–57.

28 Ziai MN, Benson AG, Djalilian HR. Congenital lip pits and van der Woude syndrome. *J Craniofac Surg* 2005; **16**: 930–2.

29 Happle R. What is a nevus? *Dermatology* 1995; **191**: 1–5.

30 Bolognia JL, Orlow SJ, Glick SA. Lines of Blaschko. *J Am Acad Dermatol* 1994; **31**: 157–90.

31 Moss C, Jones DO, Blight A, Bowden PE. Birthmark due to cutaneous mosaicism for keratin 10 mutation. *Lancet* 1995; **345**: 596.

32 Paller AS. Expanding our concepts of mosaic disorders of the skin. *Arch Dermatol* 2001; **137**: 1236–8.

33 Happle R. Klippel–Trenaunay syndrome: is it a paradominant trait? *Br J Dermatol* 1993; **128**: 465–6.

34 Happle R. Transposable elements and the lines of Blaschko: a new perspective. *Dermatology* 2002; **204**: 4–7.

35 Happle R. Lethal genes surviving by mosaicism: a possible explanation for sporadic birth defects involving the skin. *J Am Acad Dermatol* 1987; **16**: 899–906.

Classification of naevi

The classification of naevi is historical and not entirely logical. In general, naevi are classified according to the component cell, tissue or organ, and subdivided according to the macroscopic or histological nature of the abnormality (Table 18.1). The existing categories have stood the test of time, enabling dermatologists to distinguish naevi with different biological behaviour, and to advise patients accordingly. However, there are many areas of uncertainty, reflecting variability within and between lesions and patients. As we learn more about the molecular basis of naevi some of these uncertainties resolve. For example, we now know that epidermolytic and non-epidermolytic verrucous epidermal naevi are different entities, while Darier-like and acantholytic epidermal naevi are probably the same. The classification used here combines established clinical divisions with newer molecular definitions.

Table 18.1 Classification of non-vascular naevi.

Epidermal naevi	Dermal and subcutaneous naevi
Keratinocyte naevi	*Connective tissue naevi*
Verrucous epidermal naevus	Collagen naevi
Epidermolytic verrucous epidermal naevus	Familial cutaneous collagenoma
Non-epidermolytic verrucous epidermal naevus	Eruptive collagenoma
Sebaceous naevi	Shagreen patch
Naevus sebaceus	Other collagenomas
Follicular naevi	Elastic naevi
True hair-follicle naevus	Perforating elastoma
Comedo naevus	Juvenile elastoma and the Buschke–Ollendorff syndrome
'Acne-free' naevus	Papular elastorrhexis
Basaloid follicular hamartoma	Naevus anelasticans
Dilated pore naevus	Other elastomas
Hairy malformation of the palms and soles	Proteoglycan naevi
Apocrine naevi	Mucinous naevus
True apocrine naevus	Fibrous hamartoma of infancy
Syringocystadenoma papilliferum	*Muscle naevi*
Eccrine naevi	Infantile myofibroma
True eccrine naevus	Congenital smooth muscle hamartoma
Eccrine angiomatous hamartoma	Diffuse smooth muscle hamartoma
Porokeratotic eccrine ostial and dermal duct naevus	Congenital leiomyoma
Becker's naevus	Striated muscle naevi
Inflammatory epidermal naevi	*Fat naevi*
ILVEN	Naevi lipomatodes cutaneous superficialis
CHILD naevus	Lipoblastoma
Other naevoid epidermal disorders	Encephalocraniocutaneous lipomatosis
Linear lichen planus	Congenital lipoma
Naevoid psoriasis	Congenital lipomatosis
Darier-like epidermal naevus	Neurolipomatosis
Hailey–Hailey-like epidermal naevus	'Michelin tyre' baby
Linear porokeratosis	
Atrophoderma of Moulin	
'Blaschkitis'	
Epidermal naevus syndrome	

Blaschko's lines

Almost all epidermal naevi follow the pattern of lines painstakingly documented by Blaschko from drawings of epidermal naevi [1]. Blaschko's lines are characteristic of mosaic conditions of the epidermis and probably represent the routes of ectodermal cell migration from the neural crest [2,3]. On the trunk, these lines tend to take the form of transverse bands, differing from dermatomes in being more numerous, and in their S-shaped wave form on the lateral trunk (Fig. 18.1) and V-shape in the middle of the back. On the arms and legs, lesions follow lines roughly parallel with the axis of the limb. The lines spiral on the scalp, are vertical in the mid-face, and extend laterally from the angles of the mouth [4–6]. They never cross the anterior truncal midline, but run along it. Posteriorly, the 'Blaschko' midline is often shifted from the anatomical midline.



Fig. 18.1 Multiple verrucous epidermal naevi with the histological changes of epidermolytic hyperkeratosis.

The shape and distribution of epidermal naevi probably reflect not only paths of cell migration but also the timing of mosaicism and cell type. Abnormal clones arising at the very early blastocyst stage will be widely distributed along the paths of migrating cells and appear linear, while those arising in the fully formed fetus are more likely to be single, small, round or oval lesions. Keratinocytes, which migrate by directional proliferation, produce linear lesions, whereas melanocytes which migrate singly more often form leaf-shaped (phylloid) or block-like lesions.

References

1 Blaschko A. Die Nervenverteilung in der Haut in ihrer Beziehung zu den Erkrankungen der Haut. *Beilage zu den Verhandlungen der Deutschen Dermatologischen Gesellschaft VII Congress. Breslau*. Wien: Braumuller, 1901.

2 Montgomery DW. The cause of the streaks in naevus linearis. *J Cutan Genitourinary Dis* 1901; **19**: 455–64.

3 Moss C. Cytogenetic and molecular evidence for cutaneous mosaicism: the ectodermal origin of Blaschko lines. *Am J Med Genet* 1999; **85**: 330–3.

4 Bolognia JL, Orlow SJ, Glick SA. Lines of Blaschko. *J Am Acad Dermatol* 1994; **31**: 157–90.

5 Happle R, Assim A. The lines of Blaschko on the head and neck. *J Am Acad Dermatol* 2001; **44**: 612–5.

6 Restano L, Cambiaghi S, Tadini G *et al*. Blaschko lines of the face: a step closer to completing the map. *J Am Acad Dermatol* 1998; **39**: 1028–30.

Epidermal naevi

The term epidermal naevus is used for naevi composed of keratinocytes. Recently, the molecular causes of certain epidermal naevi have been elucidated, enabling us to differentiate between them. However, the older literature does not differentiate between, for

example, epidermolytic and non-epidermolytic naevi, and therefore clinical descriptions must be read in this light.

Probably all epidermal naevi comprise an abnormal clone of cells, reflecting genetic mosaicism arising from somatic mutation (see above). The clinical implications of mosaicism are firstly that it is unlikely to recur in the same family, and secondly that there is a theoretical risk of the condition being passed on to the patient's offspring in a severe or even lethal generalized form. Curiously, these predictions are not always borne out, as is discussed under the individual headings.

Verrucous epidermal naevus

Synonyms
- Naevus verrucosus
- Naevus unius lateris

Definition. Verrucous epidermal naevi are congenital, non-inflammatory cutaneous hamartomas composed of keratinocytes. They are distinct from inflammatory, acantholytic and porokeratotic epidermal naevi, from sebaceous naevi, and from epidermal naevi derived from skin appendages. Their prevalence in adults is probably 0.1–0.5%, and they occur equally in males and females. They are divided into epidermolytic and non-epidermolytic types.

Epidermolytic verrucous epidermal naevus

Aetiology. The histological similarity between epidermolytic verrucous epidermal naevi and autosomal dominant bullous ichthyosiform erythroderma (BIE) led to the idea that the former represents a clone of cells expressing a mutation in one of the BIE genes *KRT1* and *KRT10*. This was confirmed by finding mutations in *KRT10* [1,2] and *KRT1* [3] in such naevi but not in the adjacent normal skin and in lymphocytes of a woman with verrucous epidermal naevi whose son had BIE [4]. Such epidermal naevi are sporadic and cannot be passed on from parent to child. However a parent with an epidermolytic verrucous epidermal naevus is likely to have gonadal mosaicism as well as cutaneous mosaicism, and can therefore produce offspring with generalized BIE [1,4,5].

Pathology. Epidermolytic verrucous epidermal naevi show hyperkeratosis, acanthosis and papillomatosis with epidermolytic hyperkeratosis [5] identical to that seen in BIE. This comprises perinuclear vacuolization of the keratinocytes, associated with premature and excessive formation of irregular keratohyalin granules, indistinct cell borders and hyperkeratosis.

Clinical features [1–5]. By analogy with BIE, epidermolytic verrucous epidermal naevi at birth would be expected to be blistered, and only later to become verrucous. However, there is no specific report of this. In young children they appear as slightly pigmented velvety or warty streaks or plaques. With age they darken and the surface becomes more warty (Fig. 18.2), sometimes with an erythematous base. They may be single or multiple, and size and site are variable. *KRT1* but not *KRT10* is expressed in palmoplantar skin, so theoretically mutations in the former but not the latter might cause lesions in those sites. Flexural lesions may become macerated and foul smelling, causing discomfort and psychological problems. Striate palmoplantar keratoderma and ainhum occurred in a child with extensive systematized epidermolytic verrucous epidermal naevi [6]. Epidermolytic verrucous epidermal naevi are not associated with extracutaneous abnormalities (epidermal naevus syndrome: see below) because keratin genes are expressed only in epithelia. They probably do not have the malignant potential of sebaceous naevi [7].



Fig. 18.2 Linear verrucous epidermal naevus on the neck.

Diagnosis. Epidermolytic and non-epidermolytic verrucous epidermal naevi are sometimes indistinguishable except on histology. Their lack of inflammation, presence at birth, warty, brown appearance and persistence distinguish them from most other types of epidermal naevus. They may be confused with linear viral warts, particularly filiform or digitate warts on the neck, scalp or body folds.

References

1 Paller AS, Syder AJ, Chan Y-M *et al.* Genetic and clinical mosaicism in a type of epidermal nevus. *N Engl J Med* 1994; **331**: 1408–15.
2 Moss C, Jones DO, Blight A, Bowden PE. Birthmark due to cutaneous mosaicism for keratin 10 mutation. *Lancet* 1995; **345**: 596.
3 Tsubota A, Akiyama M, Sakai K *et al.* Keratin 1 gene mutation detected in epidermal nevus with epidermolytic hyperkeratosis. *J Invest Dermatol* 2007; **127**: 1371–4.
4 Nomura K, Umeki K, Hatayama I, Kuronuma T. Phenotypic heterogeneity in bullous congenital ichthyosiform erythroderma: possible somatic mosaicism for keratin gene mutation in the mildly affected mother of the proband. *Arch Dermatol* 2001; **137**: 1192–5.
5 Nazarro V, Ermacora E, Santucci B *et al.* Epidermolytic hyperkeratosis: generalised form in children from parents with systematised linear form. *Br J Dermatol* 1990; **122**: 417–22.
6 Pandhi D, Reddy BS. A rare association of epidermal nevus syndrome and ainhum-like digital constrictions. *Pediatr Dermatol* 2002; **19**: 349–52.
7 Gosain AK, Santoro TD, Larson DL, Gingrass RP. Giant congenital nevi: a 20-year experience and an algorithm for their management. *Plast Reconstr Surg* 2001; **108**: 622–31.

Non-epidermolytic verrucous epidermal naevus

Aetiology. Non-epidermolytic verrucous epidermal naevi are probably heterogeneous, representing mosaicism for different,

and as yet unidentified, mutations. Stosiek *et al.* [1] reported chromosomal mosaicism in two otherwise normal men with non-epidermolytic verrucous epidermal naevi. Several chromosomal abnormalities were found in the abnormal skin, with a breakpoint common to both patients at 1q23. This lies intriguingly close to a locus known as the epidermal differentiation complex, which includes a cluster of over 25 genes encoding structural components of the cornified envelope [2]. Other candidates for acanthosis nigricans-like epidermal naevi [3,4] include the fibroblast growth factor receptor (FGFR) genes [5]. There are now several reports of *FGFR3* mutations in verrucous epidermal naevi [6–8], in one case associated with craniofacial anomalies similar to those seen in craniosynostosis syndromes caused by *FGFR3* mutation [7]. The commonest mutation is R248C. Mutations in the oncogene *PIC3CA* have recently been reported in epidermal naevi [9]. *PTEN* is also implicated in verrucous epidermal naevi: two patients with Proteus-like syndrome and a germ-line mutation in *PTEN* showed loss of heterozygosity for the *PTEN* mutation in DNA tissue from an epidermal naevus [10,11]. A palmoplantar verrucous naevus has been reported which was due to mosaicism for a mutation in keratin 16, the gene responsible for pachyonychia congenita [12], but since hyperkeratosis in pachyonychia congenita is confined to the palms and soles, it is unlikely that verrucous epidermal naevi at other sites are caused by pachyonychia congenita gene mutations. Mosaic chromosome 6 trisomy has also been found in the skin of a patient with an epidermal naevus in addition to extensive linear hypopigmentation [13].

Pathology [14,15]. The most common histological pattern is sharply demarcated hyperkeratosis and acanthosis, often associated with papillomatosis, and occasionally by focal hypergranulosis and/or columns of parakeratosis. About 10% of lesions show a distinctive 'church-spire' pattern of acanthosis and hyperkeratosis, resembling acrokeratosis verruciformis, and about 5% show features resembling seborrhoeic keratoses, that is hyperkeratosis, papillomatosis, acanthosis and horn pseudocysts, with a flat lower base. Rarely, they may show histological features more characteristic of common viral warts, acanthosis nigricans [3,4], or of the verrucous phase of incontinentia pigmenti [16].

Several other changes have been reported in verrucous epidermal naevi. Appendageal anomalies seen in early childhood include immature hair follicles, sebaceous, eccrine or apocrine glands. In later childhood and adult life, comedo-like dilated follicles, and sebaceous, eccrine and apocrine hyperplasia occur [17,18]. It is not at all clear to what extent these represent age- and site-related differences in the same disorder [18,19] or different naevi. The same difficulty applies to occasional reports of basal cell [20–22], squamous [22–28], verrucous [29] and adnexal carcinomas [30], and Bowen's disease [19], within epidermal naevi: usually they are those showing sebaceous or apocrine differentiation.

Clinical features. Verrucous epidermal naevi are usually present at birth but may appear or extend during childhood. A verrucous epidermal naevus in a 60-year-old woman reported to have developed only 5 years previously was highly atypical, with bilateral crusted, hyperkeratotic plaques on the head and upper trunk and histological signs of inflammation [31]. At birth they have a white, macerated appearance, but within a few days take the form of pink or slightly pigmented, velvety streaks or plaques. Later, they darken and the surface becomes more warty (see Fig. 18.2), sometimes with an erythematous base. Their extent and distribution are highly variable, but sebaceous naevi are especially common on the face and scalp. They may extend on to an adjacent mucosal surface [32]. Nail ridging, splitting, discoloration or dystrophy may occur where the nail fold is involved. The lesions are as a rule asymptomatic, except, for example, when they impinge upon the nail fold, where they may cause recurrent paronychia, and may split or distort the nail plate. Flexural lesions may become macerated and foul smelling. Verrucous epidermal naevi have been associated with scalp woolly hair naevi [33], and in some cases the woolly hair directly overlies a verrucous epidermal naevus [34,35]. Tumours may develop within the naevi (see above). While most of the patients in whom this has occurred have been over 40 years of age, malignant tumours have been reported in patients as young as 17 years of age [23].

A wide variety of developmental anomalies may occur in association with verrucous epidermal naevi and are discussed in more detail in the section on epidermal naevus syndrome. They include localized anomalies such as megalopinna [36] and aplasia cutis of the scalp [37], and syndromes such as epidermal naevus syndrome, Proteus syndrome, McCune–Albright syndrome [38,39], Klippel–Trenaunay syndrome [40], and phakomatosis pigmentokeratotica. Hypophospataemic rickets and osteomalacia sometimes accompany verrucous epidermal naevi [41] and are discussed under epidermal naevus syndrome.

Diagnosis. Epidermolytic and non-epidermolytic verrucous epidermal naevi must be distinguished histologically. Non-epidermolytic verrucous epidermal naevi can be differentiated clinically from other types of epidermal naevus as they are usually present at birth, asymptomatic, non-inflammatory and persistent. If the age of onset is uncertain they can be confused with viral warts [42]. Historically, verrucous epidermal naevi have been confused with a variety of epidermal naevi whose true identity has been recognized more recently, for example CHILD (*c*ongenital *h*emidysplasia with *i*chthyosiform naevus and *l*imb *d*efects) naevus.

References

1 Stosiek N, Ulmer R, von den Driesch P *et al.* Chromosomal mosaicism in two patients with epidermal verrucous nevi. *J Am Acad Dermatol* 1994; **30**: 622–5.

2 Christiano AM. Frontiers in keratodermas: pushing the envelope. *Trends Genet* 1997; **13**: 227–33.

3 Curth HO. Unilateral epidermal naevus resembling acanthosis nigricans. *Br J Dermatol* 1976; **95**: 433–6.

4 Ersoy-Evans S, Sahin S, Mancini AJ *et al*. The acanthosis nigricans form of epidermal nevus. *J Am Acad Dermatol* 2006; **55**: 696–8.

5 Torley D, Bellus GA, Munro CS. Genes, growth factors and acanthosis nigricans. *Br J Dermatol* 2002; **147**: 1096–101.

6 Hafner C, van Oers JM, Vogt T *et al*. Mosaicism of activating FGFR3 mutations in human skin causes epidermal nevi. *J Clin Invest* 2006; **116**: 2201–7.

7 Collin B, Taylor IB, Wilkie AO, Moss C. Fibroblast growth factor receptor 3 (FGFR3) mutation in a verrucous epidermal naevus associated with mild facial dysmorphism. *Br J Dermatol* 2007; **156**: 1353–6.

8 Hernandez S, Toll A, Baselga E *et al*. Fibroblast growth factor receptor 3 mutations in epidermal nevi and associated low grade bladder tumors. *J Invest Dermatol* 2007; **127**: 1664–6.

9 Hafner C, López-Knowles E, Luis NM *et al*. Oncogenic PIK3CA mutations occur in epidermal nevi and seborrheic keratoses with a characteristic mutation pattern. *Proc Natl Acad Sci U S A* 2007; **104**: 13450–4.

10 Loffeld A, McLellan NJ, Cole T *et al*. Epidermal naevus in Proteus syndrome showing loss of heterozygosity for an inherited *PTEN* mutation. *Br J Dermatol* 2006; **154**: 1194–8.

11 Caux F, Plauchu H, Chibon F *et al*. Segmental overgrowth, lipomatosis, arteriovenous malformation and epidermal nevus (SOLAMEN) syndrome is related to mosaic PTEN nullizygosity. *Eur J Hum Genet* 2007; **15**: 767–73.

12 Terrinoni A, Puddu P, Didona B *et al*. A mutation in the VI domain of K16 is responsible for unilateral palmoplantar verrucous nevus. *J Invest Dermatol* 2000; **114**: 1136–40.

13 Sobey GJ, Quarrell OW, Williams S, McGrath HM. Mosaic chromosome 6 trisomy in an epidermal nevus. *Pediatr Dermatol* 2007; **24**: 144–6.

14 Su WPD. Histopathologic varieties of epidermal nevus. *Am J Dermatopathol* 1982; **4**: 161–70.

15 Solomon LM, Esterly NB. Epidermal and other congenital organoid nevi. *Curr Probl Pediatr* 1975; **6**: 1–55.

16 Fletcher V, Williams ML, Lane AT. Histologic changes resembling the verrucous phase of incontinentia pigmenti within epidermal nevi: report of two cases. *Pediatr Dermatol* 1985; **3**: 69–74.

17 Rechdouni A, Urata MM, Saadat P, Vadmal MS. Multifocal papillary apocrine adenoma arising in a systematized linear epidermal nevus. *Cutis* 2004; **73**: 348–52.

18 Mehregan AH, Pinkus H. Life history of organoid nevi. *Arch Dermatol* 1965; **91**: 574–88.

19 Waltz KM, Helm KF, Billingsley EM. The spectrum of epidermal nevi: a case of verrucous epidermal nevus contiguous with nevus sebaceus. *Pediatr Dermatol* 1999; **16**: 211–3.

20 Goldberg HS. Basal cell epitheliomas developing in a localized linear epidermal nevus. *Cutis* 1980; **25**: 295–9.

21 Horn MS, Sausker WF, Pierson DL. Basal cell epithelioma arising in a linear epidermal nevus. *Arch Dermatol* 1981; **117**: 247.

22 Kono E, Izumi Y, Hirai A *et al.* A case of squamous cell carcinoma and basal cell carcinoma arising in a linear epidermal nevus. *Rinsho Shinkeigaku* 1992; **34**: 687–91.

23 Cramer SF, Mandel MA, Hauler R *et al.* Squamous cell carcinoma arising in a linear epidermal nevus. *Arch Dermatol* 1981; **117**: 222–4.

24 Dogliotti M, Frenkel A. Malignant changes in a verrucous nevus. *Int J Dermatol* 1978; **17**: 225–7.

25 Ichikawa T, Saiki M, Kaneko M *et al.* Squamous cell carcinoma arising in a verrucous epidermal nevus. *Dermatology* 1996; **193**: 135–8.

26 Levin A, Amazon K, Rywlin AM. A squamous cell carcinoma that developed in an epidermal nevus. *Am J Dermatopathol* 1984; **6**: 51–5.

27 Swint RB, Klaus SN. Malignant degeneration of an epithelial nevus. *Arch Dermatol* 1970; **101**: 56–8.

28 Affleck AG, Leach IH, Varma S. Two squamous cell carcinomas arising in a linear epidermal naevus in a 28-year-old female. *Clin Exp Dermatol* 2005; **30**: 382–4.

29 Kitikawa K, Kawashima J, Miyakawa T *et al.* Verrucous carcinoma arising in an epidermal nevus. *Nishinihon J Dermatol* 1988; **50**: 549.

30 Martin PC, Smith JL, Pulitzer DR *et al.* Compound (primordial) adnexal carcinoma arising in a systematized compound epithelial nevus. *Am J Surg Pathol* 1992; **16**: 417–25.

31 Adams BB, Mutasim DF. Adult onset verrucous epidermal nevus. *J Am Acad Dermatol* 1999; **41**: 824–6.

32 Brown HM, Gorlin RJ. Oral mucosal involvement in nevus unius lateris (ichthyosis hystrix). *Arch Dermatol* 1960; **81**: 509–15.

33 Wright S, Lemoine NR, Leigh IM. Woolly hair naevi with systematized linear epidermal naevus. *Clin Exp Dermatol* 1986; **11**: 179–82.

34 Al-Harmozi SA, Mahmoud SF, Ejeckam GC. Woolly hair nevus syndrome. *J Am Acad Dermatol* 1992; **27**: 259–60.

35 Peteiro C, Oliva NP, Zulaica A *et al.* Woolly hair nevus; report of a case associated with a verrucous epidermal nevus in the same area. *Pediatr Dermatol* 1989; **6**: 188–90.

36 Mahakrishnan A. Megalopinna in naevus unius lateris: a case report. *Acta Derm Venereol (Stockh)* 1981; **61**: 365–7.

37 Happle R, Konig A. Didymosis aplasticosebacea: coexistence of aplasia cutis congenita and nevus sebaceus may be explained as a twin spot phenomenon. *Dermatology* 2001; **202**: 246–8.

38 Pierini AM, Ortonne JP, Floret D. Signes dermatologiques du syndrome de McCune–Albright: à propos d'un cas. *Ann Dermatol Vénéréol* 1981; **108**: 969–76.

39 Yu AC, Ng V, Dicks-Mireaux C, Grant DB. Epidermal naevus syndrome associated with polyostotic fibrous dysplasia and central precocious puberty. *Eur J Pediatr* 1995; **154**: 102–4.

40 Wikler J, Starink TM. Acanthosis nigricans-like epidermal naevus and Klippel–Trenaunay syndrome. *Br J Dermatol* 1990; **123**: 539.

41 Tokatli A, Coskun T, Ozalp I. Hypophosphatemic vitamin-D resistant rickets associated with epidermal nevus syndrome. *Turk J Pediatr* 1997; **39**: 247–51.

42 Bandyopadhyay D, Sen S. Perianal verrucous epidermal naevus mimicking perianal warts. *Sex Transm Infect* 2003; **79**: 424.

Management of epidermolytic and non-epidermolytic epidermal naevi

Reports of the responses of epidermal naevi to various therapies have rarely distinguished between the different histological types. Therefore both are considered together here.

Topical applications are rarely curative and therefore have a limited place in the treatment of verrucous epidermal naevi [1]. Preparations containing salicylic acid, lactic acid or retinoic acid [2] may decrease the keratotic element to some extent but require persistent application to maintain any improvement. Podophyllum may help [3] but its toxicity precludes its use in larger lesions [4]. Successful treatment with topical 5-fluorouracil and retinoic acid [5,6], calcipotriol and calcitriol have been reported.

Cosmetically significant lesions may justify systemic retinoid therapy. Isotretinoin [7], etretinate [8] and acitretin [9] can produce worthwhile reduction of hyperkeratosis (in epidermolytic lesions). Patients and carers must understand that drug therapy is not curative and the condition will relapse if the treatment is stopped.

Even surgery is not curative unless underlying dermis is removed or destroyed at the same time as the epidermal component. Large lesions may require multistage, multimodality procedures, adapted according to anatomical site [10]. Skin-shaving procedures or dermabrasion thus tend to produce only temporary benefit. Cryotherapy is a simple alternative for smaller lesions. Laser is used increasingly, and improvements in technology and better selection of modality, are gradually overcoming problems such as hypertrophic scarring, pigmentary changes and partial recurrence. The argon laser is helpful for softer, less hyperkeratotic lesions [11]. Continuous-wave carbon dioxide laser vaporization has been used successfully for extensive verrucous epidermal nevus [12]. Pulsed carbon dioxide laser is better for thinner and softer verrucous epidermal naevi [13–16]. Small lesions have been vaporized in a single session but for larger lesions multiple treatment sessions are required. Staged carbon dioxide laser treatment using different modalities for thick and thin lesions cleared an extensive verrucous epidermal naevus with no recurrence in 2 years of follow-up [10]. Newer erbium : yttrium aluminium garnet (Er : YAG) lasers with greater coagulative capacity can also be used with good effect. A single treatment can produce good clearance with minimal tissue destruction and scarring [17], although in one series of 20 patients five lesions recurred within a year [18]. The pulsed ruby laser may reduce and lighten dark-coloured epidermal naevi, but patients with a darker skin type risk post-irradiation depigmentation [19].

Patients with epidermolytic verrucous epidermal naevi are at risk of parenting a child with BIE. If the patient is a child the carers

should probably be informed of this risk, and of the possibility of first-trimester antenatal diagnosis. Arrangements should be made to counsel the affected individual at a suitable age. Currently, we lack data that allow quantification of the risk. Patients with non-epidermolytic epidermal naevi can be counselled that these are sporadic lesions and are not passed on as a generalized skin condition. It has been suggested that the generalized condition is lethal [20], and affected individuals survive only if they are 'rescued' by mosaicism.

References

1 Fox BJ, Lapins NA. Comparison of treatment modalities for epidermal nevus: a case report and review. *J Dermatol Surg Oncol* 1983; **11**: 879–85.
2 Gunther SH. Retinoic acid versus placebo in linear verrucous naevi, scaly lichenified eczema and verrucae plantaris. *Br J Dermatol* 1973; **89**: 317.
3 Garb J. Nevus verrucosus unilateris cured with podophyllin ointment. *Arch Dermatol* 1960; **81**: 606–9.
4 Cassidy DE, Drewery J, Fanning JP. Podophyllum toxicity: report of a fatal case and review of the literature. *J Toxicol Clin Toxicol* 1982; **19**: 35–44.
5 Nelson BR, Kolansky G, Gillard M *et al.* Management of linear verrucous epidermal nevus with topical 5-fluorouracil and tretinoin. *J Am Acad Dermatol* 1994; **30**: 287–8.
6 Kim JJ, Chang MW, Shwayder T. Topical tretinoin and 5-fluorouracil in the treatment of linear verrucous epidermal nevus. *J Am Acad Dermatol* 2000; **43**: 129–32.
7 Herman AR, Scott RA. Systematized epidermal nevus treated with isotretinoin. *J Drugs Dermatol* 2002; **1**: 195–6.
8 Happle R, Kastru W, Macher E. Systemic retinoid therapy of systematized verrucous epidermal nevus. *Dermatologica* 1977; **155**: 200–5.
9 Taskapan O, Dogan B, Baloglu H, Harmanyeri Y. A case of verrucous epidermal naevus successfully treated with acitretin. *Acta Derm Venereol* 1998; **78**: 475–6.
10 Gosain AK, Santoro TD, Larson DL, Gingrass RP. Giant congenital nevi: a 20-year experience and an algorithm for their management. *Plast Reconstr Surg* 2001; **108**: 622–31.
11 Hohenleutner U, Landthaler M. Laser therapy of verrucous epidermal naevi. *Clin Exp Dermatol* 1993; **18**: 124–7.
12 Losee JE, Serletti JM, Pennino RP. Epidermal nevus syndrome: a review and case report. *Ann Plast Surg* 1999; **43**: 211–4.
13 Michel J-L, Has C, Has V. Resurfacing CO_2 laser treatment of linear verrucous epidermal naevus. *Eur J Dermatol* 2001; **11**: 436–9.
14 Alam M, Arndt KA. A method for pulsed carbon dioxide laser treatment of epidermal nevi. *J Am Acad Dermatol* 2002; **46**: 554–6.
15 Paradela S, Del Pozo J, Fernandez-Jorge B *et al*. Epidermal nevi treated by carbon dioxide laser vaporization: a series of 25 patients. *J Dermatolog Treat* 2007; **18**: 169–74.
16 Boyce S, Alster TS. CO_2 laser treatment of epidermal nevi: long-term success. *Dermatol Surg* 2002; **28**: 611–4.
17 Pearson IC, Harland CC. Epidermal naevi treated with pulsed erbium:YAG laser. *Clin Exp Dermatol* 2004; **29**: 494–6.
18 Park JH, Hwang ES, Kim SN, Kye YC. Er:YAG laser treatment of verrucous epidermal nevi. *Dermatol Surg* 2004; **30**: 378–81.
19 Baba T, Narumi H, Hanada K, Hashimoto I. Successful treatment of dark-colored epidermal nevus with ruby laser. *J Dermatol* 1995; **22**: 567–70.
20 Happle R. Lethal genes surviving by mosaicism: a possible explanation for sporadic birth defects involving the skin. *J Am Acad Dermatol* 1987; **16**: 899–906.

Sebaceous naevus

Synonym
- Naevus sebaceus of Jadassohn

Definition and aetiology. Sebaceous naevi are epidermal hamartomas comprised predominantly of sebaceous glands. The view that sebaceous naevi and verrucous epidermal naevi are variants of the same disorder, those on the head and neck being more sebaceous and those elsewhere more verrucous, is supported by the occurrence of both types in the same individual and in the epidermal naevus syndrome [1–3].

Sebaceous naevi are usually sporadic, probably reflecting lethal genes rescued by mosaicism (see above). There have been occasional reports of familial cases [4–6], perhaps reflecting inheritance of an unstable premutation, but attributed by Happle and Konig to paradominant inheritance [7]. Because sebaceous naevi have a tendency to develop tumours, various tumour genes have been implicated in their aetiology. Constitutive activation of the patched-hedgehog signalling pathway (involved in Gorlin's syndrome and basal cell carcinomas) was suggested by Xin *et al.* [8] who found loss of heterozygosity at the *PTCH* locus 9q22.3 in sebaceous naevi. However, this finding was refuted by Takata *et al.* [9] who also found lack of expression of *Gli-1*, another gene in the patched-hedgehog signalling pathway expressed in basal cell carcinomas. Mutations in the oncogene *PIC* have recently been reported in epidermal naevi [10].

Pathology [11,12]. Before puberty, the sebaceous and apocrine glands in these lesions are sparse and underdeveloped, so that the lesions may be indistinguishable from verrucous epidermal naevi. Cords and buds of poorly differentiated epithelial cells representing primordial pilosebaceous follicles are, however, a distinctive and diagnostic feature at this stage [11]. After puberty the characteristic mature sebaceous glands and associated papillomatous hyperplasia of the overlying epidermis are seen. Hair follicles are inconspicuous. Buds of undifferentiated epithelial cells resembling foci of basal cell carcinoma probably represent primordial hair follicles [12]. Merkel cells may be abundant [13]. Some lesions feature hypoplastic sebaceous glands, or sebaceous glands situated at an abnormally high level in the dermis. Ectopic apocrine glands are very commonly observed deep in the dermis beneath the sebaceous glands [11,12].

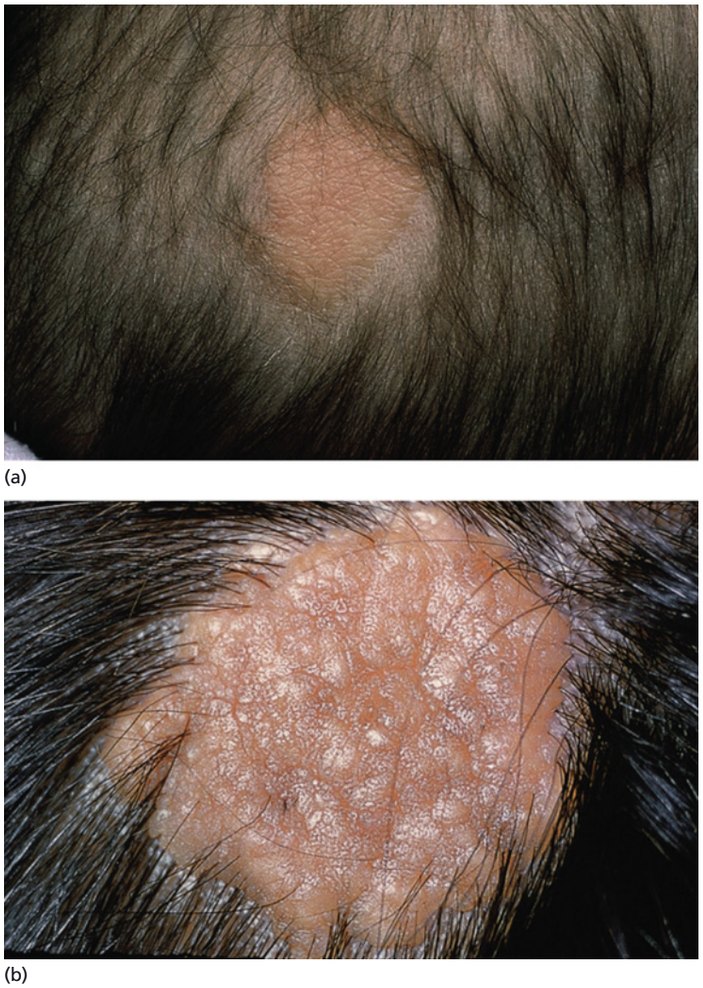
A variety of appendageal tumours, sometimes multiple, may develop within sebaceous naevi [14–31]. The most commonly reported are syringocystadenoma papilliferum and trichoblastoma [14]; less common tumours include nodular hidradenoma [15], apocrine cystadenoma [16], syringoma, infundibuloma and trichoadenoma [17] and trichilemmoma and pilomatricoma [18]. Locally invasive and malignant tumours include keratoacanthoma [19], proliferating trichilemmal cyst [20], and basal cell [21–24], sebaceous, apocrine [25], eccrine [26] and squamous carcinomas [17,23] and malignant melanoma [27]. Leiomyosarcoma occurred with trichoblastoma and syringocystadenoma papilliferum in one case [28]. The true incidence of malignancy in sebaceous naevi is difficult to determine for several reasons, but mainly because different criteria were used to gather cases in each of the larger series. Furthermore basaloid proliferation has almost certainly been misinterpreted as basal cell carcinoma, the commonest malignancy reported in sebaceous naevi (see below). Takata *et al.* [9] found clear molecular differences between the basal cell carcinoma-like trichoblastomas arising in sebaceous naevi and true basal cell carcinomas.

Clinical features. Sebaceous naevi occur in about 0.3% of all neonates [32,33]. They comprise circumscribed, slightly raised,

pinkish, yellow, orange or tan plaques, with a smooth or somewhat velvety surface. Although usually congenital, they are occasionally first reported later in life [34]. The sex incidence is equal.

The lesions may be round, oval or linear, varying in length from under 1 to over 10 cm. Their shape may be determined by the stage at which they arise, early lesions conforming to embryonic epidermal migratory lines, while later lesions arising in a more fixed epidermis are round (see Blaschko's lines, above). They most commonly occur singly, but may be multiple and extensive, like verrucous epidermal naevi. Most occur on the head and neck, favouring the scalp, the areas around the ears, the temples, forehead and the central part of the face. They can extend on to the oral mucosa [35]. Sebaceous naevi of the scalp are devoid of hair, and usually present with the complaint of a bald patch (Fig. 18.3).

Following birth, the lesions tend to become less prominent and then to remain unchanged until puberty, when they become thickened and more elevated. For this reason, many patients present at this stage. Gradually they become more nodular during adult life (Fig. 18.3). A sebaceous naevus of the external auditory canal presented with deafness due to secondary cerumen impaction in adulthood [36].



(a)

(b)

Fig. 18.3 Sebaceous naevus: (a) in a 6-month-old infant; (b) in an adult.

Development of an exophytic nodule on a naevus sebaceous usually represents a benign appendageal tumour or viral wart [31]. Rapid, circumscribed enlargement or ulceration should arouse suspicion of malignant transformation. This usually occurs in middle age, but can undoubtedly occur in adolescence, or even in childhood [19,37,38]. The lifetime risk of malignant transformation is probably less than 5%, but is difficult to establish with any precision because the major studies have varied considerably in methods of selection and in ages of the patients [11,12,29,31]. The most common malignancy is basal cell carcinoma, but the incidence of this tumour has been overestimated because of misinterpretation of trichoblastoma [14] and basaloid proliferation as basal cell carcinoma. Other malignant tumours reported include squamous [17,23,39], sebaceous [40], tricholemmal [41] and apocrine [25] carcinomas, and malignant melanoma [27]. Leiomyosarcoma occurred with trichoblastoma and syringocystadenoma papilliferum in one case [28]. Despite occasionally aggressive histopathological features, most of these tumours are of low-grade malignancy. Nevertheless, local recurrence after excision, metastasis and a lethal outcome have all been reported [29]. It is not unusual to find several different types of tumour arising from naevus sebaceous [17,18,28,41].

Associated abnormalities occur in a small proportion of cases: these are considered under the heading of 'epidermal naevus syndrome'.

Diagnosis. Diagnosis is usually straightforward on clinical grounds alone. In early infancy, lesions in the scalp must be distinguished from aplasia cutis, which has a smoother papyraceous surface. Syringocystadenoma papilliferum may be very difficult to distinguish clinically, although the surface tends to be pink and nodular, rather than yellow and velvety. Early juvenile xanthogranulomas may be similar in their clinical appearance, although these generally develop rapidly into distinctive domed, papular or nodular lesions. Solitary mastocytomas may also be confused clinically during infancy, but histological examination will clearly identify all these disorders. Multiple pigmented trichoblastomas arising in a naevus sebaceous resembled malignant melanoma [42].

Very rarely, heterotopic brain tissue or an encephalocoele may result in a congenital bald patch overlying a subcutaneous nodule [43]. They may communicate with the brain so it is important to distinguish them from sebaceous naevus.

Treatment. Removal during childhood may be necessary for cosmetic reasons but is difficult to justify on grounds of risk of malignancy [44]. Excision of scalp lesions with primary closure gives an excellent cosmetic result, but larger lesions may require tissue expansion. Simple excision is generally adequate even in the presence of histological malignancy. Superficial removal by dermabrasion or carbon dioxide laser is likely to be followed by partial recurrence but may be helpful where excision is not feasible [45]. An extensive naevus sebaceus of face and scalp in a 38-year-old

woman was cleared with 13 sessions of photodynamic therapy, with no recurrence 16 months later [46].

References

1 Rogers M, McCrossin I, Commens C. Epidermal nevi and the epidermal nevus syndrome. *J Am Acad Dermatol* 1989; **20**: 476–88.
2 Solomon LM, Esterly NB. Epidermal and other congenital organoid nevi. *Curr Probl Pediatr* 1975; **6**: 1–55.
3 Waltz KM, Helm KF, Billingsley EM. The spectrum of epidermal nevi: a case of verrucous epidermal nevus contiguous with nevus sebaceous. *Pediatr Dermatol* 1999; **16**: 211–3.
4 Benedetto L, Sood U, Blumenthal N *et al.* Familial nevus sebaceus. *J Am Acad Dermatol* 1990; **23**: 130–2.
5 Laino L, van Steensel MAM, Innocenzi D, Camplone G. Familial occurrence of naevus sebaceus of Jadassohn: another case of paradominant inheritance? *Eur J Dermatol* 2001; **11**: 97–8.
6 Hughes SM, Wilkerson AE, Winfield HL, Hiatt KM. Familial nevus sebaceus in dizygotic male twins. *J Am Acad Dermatol* 2006; **54** (2 Suppl.): S47–8.
7 Happle R, Konig A. Familial nevus sebaceus may be explained by paradominant transmission. *Br J Dermatol* 1999; **141**: 377.
8 Xin H, Matt D, Qin JZ *et al.* The sebaceous nevus: a nevus with deletions of the *PTCH* gene. *Cancer Res* 1999; **59**: 1834–6.
9 Takata M, Tojo M, Hatta N *et al.* No evidence of deregulated patched-hedgehog signaling pathway in trichoblastomas and other tumors arising within nevus sebaceus. *J Invest Dermatol* 2001; **117**: 1666–70.
10 Hafner C, López-Knowles E, Luis NM *et al.* Oncogenic PIK3CA mutations occur in epidermal nevi and seborrheic keratoses with a characteristic mutation pattern. *Proc Natl Acad Sci USA* 2007; **104**: 13450–4.
11 Mehregan AH, Pinkus H. Life history of organoid nevi: special reference to nevus sebaceus of Jadassohn. *Arch Dermatol* 1975; **91**: 574–88.
12 Wilson-Jones E, Heyl T. Naevus sebaceus: a report of 140 cases with special regard to the development of secondary malignant tumours. *Br J Dermatol* 1970; **82**: 99–117.
13 Schulz T, Hartschuh W. Merkel cells in nevus sebaceus. *Am J Dermatopathol* 1995; **17**: 570–9.
14 Jaqueti G, Requena L, Sanchez-Yus E. Trichoblastoma is the most common neoplasm developed in nevus sebaceus of Jadassohn. *Am J Dermatopathol* 2000; **22**: 108–18.
15 Ioannides G, Simonson L. Nodular hidradenoma in nevus sebaceus of Jadassohn. *Arch Dermatol* 1964; **89**: 250–2.
16 Campbell JP, Solomon AR, Woo TY. Apocrine cystadenoma arising in a nevus sebaceus of Jadassohn. *Cutis* 1984; **34**: 510–2.
17 Miller CJ, Ioffreda MD, Billingsley EM. Sebaceous carcinoma, basal cell carcinoma, trichoadenoma, trichoblastoma, and syringocystadenoma papilliferum arising within a nevus sebaceus. *Dermatol Surg* 2004; **30**: 1546–9.
18 Miyake H, Hara H, Shimojima H, Suzuki H. Follicular hybrid cyst (trichilemmal cyst and pilomatricoma) arising within a nevus sebaceus. *Am J Dermatopathol* 2004; **26**: 390–3.
19 Ujiie H, Kato N, Natsuga K, Tomita Y. Keratoacanthoma developing on nevus sebaceous in a child. *J Am Acad Dermatol* 2007; **56** (2 Suppl.): S57–8.
20 Rahbari H, Mehregan A. Development of proliferating trichilemmal cyst in an organoid nevus. *J Am Acad Dermatol* 1986; **14**: 123–6.
21 Goldstein GD, Whitaker DC, Argenyi ZB *et al.* Basal cell carcinoma arising in a sebaceous nevus during childhood. *J Am Acad Dermatol* 1988; **18**: 429–30.
22 Westfried M, Mikhail GR. Multifocal basal cell carcinomas in a nevus sebaceus of Jadassohn. *J Dermatol Surg Oncol* 1981; **7**: 420–2.
23 Ball EA, Hussain M, Moss AL. Squamous cell carcinoma and basal cell carcinoma arising in a naevus sebaceous of Jadassohn: case report and literature review. *Clin Exp Dermatol* 2005; **30**: 259–60.
24 Winer LH, Levin GH. Pigmented basal cell carcinoma in verrucous nevi. *Arch Dermatol* 1961; **83**: 960–4.
25 Dalle S, Skowron F, Balme B, Perrot H. Apocrine carcinoma developed in nevus sebaceus of Jadassohn. *Eur J Dermatol* 2003; **13**: 487–9.
26 Tarkhan II, Domingo J. Metastasizing eccrine porocarcinoma developing in a sebaceous nevus of Jadassohn: report of a case. *Arch Dermatol* 1985; **121**: 413–5.
27 Abe S, Yamamoto Y, Uno S *et al.* Malignant melanoma arising in a sebaceous nevus of the scalp. *Br J Plast Surg* 2003; **56**: 171–3.
28 Premalata CS, Kumar RV, Malathi M *et al.* Cutaneous leiomyosarcoma, trichoblastoma, and syringocystadenoma papilliferum arising from nevus sebaceus. *Int J Dermatol* 2007; **46**: 306–8.
29 Domingo J, Helwig EB. Malignant neoplasms associated with nevus sebaceus of Jadassohn. *J Am Acad Dermatol* 1979; **1**: 545–56.
30 Weschler HL, Fisher ER. A combined polymorphic epidermal and adnexal tumor in nevus unius lateris. *Dermatologica* 1965; **130**: 158–64.
31 Cribier B, Scrivener Y, Grosshans E. Tumors arising in nevus sebaceus: a study of 596 cases. *J Am Acad Dermatol* 2000; **42**: 263–8.
32 Alper J, Holmes LB, Mihm MC. Birthmarks with serious medical significance: nevocellular nevi, sebaceous nevi, and multiple café-au-lait spots. *J Pediatr* 1979; **95**: 696–700.
33 Tsai F-J, Tsai C-H. Birthmarks and congenital skin lesions in Chinese newborns. *J Formos Med Assoc* 1993; **92**: 838–41.
34 Conner AE, Bryan H. Nevus sebaceus of Jadassohn. *Am J Dis Child* 1967; **114**: 626–30.
35 Warnke PH, Russo PA, Schimmelpenning GW *et al.* Linear intraoral lesions in the sebaceous nevus syndrome. *J Am Acad Dermatol* 2005; **52**: 62–4.
36 Bothwell NE, Willard CC, Sorensen DM, Downey TJ. A rare case of a sebaceous nevus in the external auditory canal. *Ear Nose Throat J* 2003; **82**: 38–41.
37 Turner CD, Shea CR, Rosoff PM. Basal cell carcinoma originating from a nevus sebaceus on the scalp of a 7-year-old boy. *J Pediatr Hematol Oncol* 2001; **23**: 247–9.
38 Dunkin CS, Abouzeid M, Sarangapani K. Malignant transformation in congenital sebaceous naevi in childhood. *J R Coll Surg Edinb* 2001; **46**: 303–6.
39 Hidvegi NC, Kangesu L, Wolfe KQ. Squamous cell carcinoma complicating naevus sebaceous of Jadassohn in a child. *Br J Plast Surg* 2003; **56**: 50–2.
40 Matsuda K, Doi T, Kosaka H *et al.* Sebaceous carcinoma arising in nevus sebaceus. *J Dermatol* 2005; **32**: 641–4.
41 Misago N, Narisawa Y. Tricholemmal carcinoma in continuity with trichoblastoma within nevus sebaceus. *Am J Dermatopathol* 2002; **24**: 149–55.
42 De Giorgi V, Massi D, Trez E *et al.* Multiple pigmented trichoblastomas and syringocystadenoma papilliferum in naevus sebaceous mimicking a malignant melanoma: a clinical dermoscopic-pathological case study. *Br J Dermatol* 2003; **149**: 1067–70.
43 Tanii T, Hamada T. A variant of encephalomeningocoele: heterotopic brain tissue on the scalp. *Dermatologica* 1984; **169**: 354–8.
44 Santibanez-Gallerani A, Marshall D, Duarte AM *et al.* Should nevus sebaceus of Jadassohn in children be excised? A study of 757 cases, and literature review. *J Craniofac Surg* 2003; **14**: 658–60.
45 Ashinoff R. Linear nevus sebaceus of Jadassohn treated with the carbon dioxide laser. *Pediatr Dermatol* 1993; **10**: 189–91.
46 Dierickx CC, Goldenhersh M, Dwyer P *et al.* Photodynamic therapy for nevus sebaceus with topical δ-aminolevulinic acid. *Arch Dermatol* 1999; **135**: 637–40.

Follicular naevi

True hair-follicle naevus

Synonym
- Congenital vellus hamartoma

In the past, the lesions that are now more usually termed trichofolliculomas were often described as 'hair-follicle naevi' [1]. The term should be confined to a hamartoma comprising an excessive concentration of normal hair follicles [2,3]. This rare tumour, sometimes also called *congenital vellus hamartoma* [4], generally takes the form of a small, skin-coloured papule on the face, usually present from birth. Histologically, the lesion contains numerous small but well-differentiated vellus hair follicles in the dermis, with a few sebaceous glands and eccrine sweat glands. Hair follicle naevi following Blaschko's lines have been reported [5], in one case in association with epidermal naevi [6]. Subepidermal calcified nodule of the ear has been reported in a child with hair follicle

naevus [7]. These naevi can be differentiated from eruptive vellus hair cysts which arise later in childhood and usually occur on the chest. The treatment of choice is simple excision.

References

1 Davis DA, Cohen PR. Hair follicle nevus: case report and review of the literature. *Pediatr Dermatol* 1996; **13**: 135–8.
2 Choi EH, Ahn SK, Lee SH, Bang D. Hair follicle nevus. *Int J Dermatol* 1992; **31**: 578–81.
3 Komura A, Tani M. Hair follicle nevus. *Dermatology* 1992; **185**: 154–5.
4 Grouls V. Hair follicle nevus or congenital vellus hamartoma. *Am J Dermatopathol* 1985; **7**: 304.
5 Germain M, Smith KJ. Hair follicle nevus in a distribution following Blaskho's lines. *J Am Acad Dermatol* 2002; **46**: S125–7.
6 Ikeda S, Kawada J, Yaguchi H, Ogawa H. A case of unilateral, systematized linear hair follicle nevi associated with epidermal nevus-like lesions. *Dermatology* 2003; **206**: 172–4.
7 Won JH, Ahn SK, Lee SH. Subepidermal calcified nodule of the ear in a child with hair follicle nevus. *Int J Dermatol* 1994; **33**: 505–6.

Comedo naevus

Synonyms
- Comedone naevus
- Naevus comedonicus
- Follicular naevus
- Acne naevus

Definition. First described in 1895 [1], the comedo naevus is a linear lesion comprising numerous keratin-filled pits, sometimes with acneiform pustules.

Aetiology. This is a rare naevus, fewer than 200 having been reported [2]. In a series of 235 epidermal naevi, Rogers found only four comedo naevi [3]. This is probably a mixed group, reflecting mosaicism for a variety of mutations that can predispose to acne. Acneiform naevi with predominantly inflammatory lesions may represent a clonal sensitivity to androgens [4–6]. The occasional histological finding of rudimentary hair follicles, sebaceous glands and trichilemmal cysts suggests a primary defect within the pilosebaceous gland. In naevi where comedones predominate, interfollicular histological changes typical of common verrucous epidermal naevi [7] or epidermolytic hyperkeratosis [8] suggest that follicular blockage is secondary to a keratinocyte defect. Comedo naevus on hair-bearing limbs contiguous with lesions involving eccrine ducts on the palms and soles, resembling *porokeratotic eccrine ostial and dermal duct naevus* [9–12], and glans penis [13], also supports a non-appendage-specific epidermal problem causing duct blockage.

Munro and Wilkie hypothesized that mosaicism for a dominantly inherited disorder featuring severe acne might account for some acneiform naevi [14]. Apert's syndrome, characterized by acne, craniosynostosis and other bony defects, seemed a good candidate. This would explain the occasional association with skeletal abnormalities [2], as well as the linear distribution of acneiform lesions, and was confirmed by demonstrating an *FGFR2* mutation in lesional epidermis but not in adjacent normal skin [14]. Comedo naevi might also result from mosaicism for mutations, as yet unidentified, causing two other autosomal disorders featuring widespread comedones. The first of these is most commonly called *familial diffuse comedones* [15,16], but has been reported under the term 'nevus comedonicus' [17]. The comedo-like lesions appear progressively and in a diffuse bilateral distribution. In the second, called *familial dyskeratotic comedones*, the comedones are less extensive and demonstrate dyskeratosis histologically [18–21].

Pathology [2,9,22]. The characteristic histological feature of a comedo naevus is an aggregation of deep, wide invaginations of acanthotic epidermis, filled with concentric lamellae of keratin. These probably represent dilated hair follicles, as hair shafts are occasionally seen in the lower part of the invagination [7,22,23], and rudimentary sebaceous glands may open into them [22]. Arrector pili muscles are absent. The interfollicular epidermis may be histologically normal, acanthotic and hyperkeratotic [7], or even epidermolytic [8,24,25]. Schecter [26] showed epidermolytic hyperkeratosis in the follicular epithelium. Other reported histological associations have included trichilemmal cysts [27,28].

Clinical features [29]. Comedo naevus comprises groups of pits filled with black keratinous plugs resembling blackheads with inflammatory acne lesions developing later. The intervening epidermis may appear normal, hyperkeratotic, or slightly hypo- or hyperpigmented [22,30]. Areas of more marked hypopigmentation have been reported by several authors [11,31]. There may be one or several lesions in a linear, unilateral [30,32–34] or, more rarely, bilateral distribution [23,35]. Lesions may be very extensive [2,31,35]. The commonest site is the face, followed by the neck, trunk and upper arm. Palms, soles [9–12] and the glans penis [13], from which pilosebaceous follicles are normally absent, may occasionally be involved, usually in association with lesions in more characteristic sites, and often contiguous with them [31,36]. Curiously, the scalp is rarely affected [34,36,37].

Predominantly comedonal naevi are occasionally present at birth, but inflammatory acneiform naevi more often appear during childhood [3,35] or adolescence [32]. They may be complicated by acneiform chronic inflammation, suppuration, fistula formation and hypertrophic scarring [2,7,30,34,35,38,39]. The development of multiple nodules within a comedo naevus may reflect the presence of associated trichilemmal cysts [27] or basal cell carcinomas [40].

There have been occasional reports of associated developmental anomalies, including ipsilateral cataract [3,41,42], extensive naevus flammeus [43], transverse myelitis [44] and perforating elastoma [45]. While some of these are probably coincidental, skeletal malformations [31,44,46–48] may be manifestations of mosaicism for an *FGFR2* mutation, causing patchy manifestations of Apert's syndrome. The characteristic features of Apert's syndrome include craniosynostosis, mid-face hypoplasia, syndactyly and broad distal phalanx of thumb. The patient reported by Patrizi *et al.* [47] with a comedo naevus on the right cheek, syndactyly and a broad right thumb, is very likely to have been mosaic for Apert's syndrome, although this was not investigated. Rogers' patient with extensive comedo naevus and syndactyly [3] may also have been mosaic for Apert's syndrome. An association with Page's disease of the bone and breast cancer was probably coincidental [42].

Diagnosis. Porokeratotic eccrine ostial and dermal duct naevus can be distinguished clinically by its occurrence on the palms and soles, and also histologically. Familial diffuse comedones and familial dyskeratotic comedones may be pathogenetically identical to comedo naevi (see above) but are symmetrical and widespread rather than linear. Atrophoderma vermiculata and keratosis pilaris atrophicans may show comedones, but can be distinguished from comedo naevus by their symmetry. The dilated pore naevus [49] can only be distinguished histologically. Comedones may occur in linear basal cell naevus. Comedo naevi have been reported historically as sequelae of lichen planus [50], herpes zoster [51], vaccination [52] and trauma [53], but the lesions described in these reports may simply represent an unusual pattern of scarring. Extensive comedones due to chloracne and sun damage are distinguishable from comedo naevus by their non-linearity.

Treatment. As with other epidermal naevi, surgical excision, if necessary with tissue expansion [54], is more effective in the long term than superficial shaving or dermabrasion [30], but the latter can occasionally be useful cosmetically if the lesions are extensive [53], as can the regular use of a comedo extractor [27]. Both topical retinoic acid and 12% ammonium lactate may sometimes improve the appearance of lesions [39,55], and may help prevent secondary inflammation. Tacalcitol [56], and tazarotene 0.05% with calcipotriene 0.005% daily [57] have also been used effectively. Although oral isotretinoin has been reported to be ineffective [58,59], it is logical to treat extensive, inflamed acneiform naevi with antiacne medication instead of, or in preparation for, surgical treatment.

References

1 Kofmann S. Ein Fall von seltener Lokalisation und Verbreitung von Comedonen. *Arch Dermatol Syphilol* 1895; **32**: 177–8.
2 Guldbakke KK, Khachemoune A, Deng A, Sina B. Naevus comedonicus: a spectrum of body involvement. *Clin Exp Dermatol* 2007; **32**: 488–92.
3 Rogers M. Epidermal nevi and the epidermal nevus syndromes. *Pediatr Dermatol* 1992; **9**: 342–4.
4 Gonzales-Hermosa MR, Escario E, de la Heras C *et al.* Acne naevus. *Clin Exp Dermatol* 1990; **15**: 154–5.
5 Hughes BR, Cunliffe WJ. An acne naevus. *Clin Exp Dermatol* 1987; **12**: 357–9.
6 Cooper MF, Hay JB, McGibbon D *et al.* Androgen metabolism and sebaceous activity in clonal acne. *J Invest Dermatol* 1976; **66**: 261.
7 Kim SC, Kang WH. Nevus comedonicus associated with epidermal nevus. *J Am Acad Dermatol* 1989; **21**: 1085–8.
8 Lookingbill DP, Ladda RL, Cohen C. Generalized epidermolytic hyperkeratosis in the child of a parent with nevus comedonicus. *Arch Dermatol* 1984; **120**: 223–6.
9 Harper KE, Spiel Vogel RL. Nevus comedonicus of the palm and wrist. *J Am Acad Dermatol* 1985; **12**: 185–8.
10 Leppard BJ, Marks R. Comedone naevus: a report of nine cases. *Trans St John's Hosp Dermatol Soc* 1973; **59**: 45–51.
11 Wood MG, Thew MA. Nevus comedonicus: a case with palmar involvement and a review of the literature. *Arch Dermatol* 1968; **98**: 111–6.
12 Marsden RA, Fleming K, Dawber RPR. Comedo naevus of the palm: a sweat duct naevus. *Br J Dermatol* 1979; **101**: 717–22.
13 Abdel-Aal H, Abdel-Aziz AHM. Nevus comedonicus: report of three cases localised on glans penis. *Acta Derm Venereol (Stockh)* 1975; **55**: 78–80.
14 Munro CS, Wilkie AO. Epidermal mosaicism producing localised acne: somatic mutation in *FGFR2*. *Lancet* 1998; **352**: 704–5.
15 Cantu JM, Gomez-Bustamente MO, Gonzalez-Mendoza A *et al.* Familial comedones: evidence for autosomal dominant inheritance. *Arch Dermatol* 1978; **114**: 1807–9.
16 Rodin HH, Blankenship ML, Berstein G. Diffuse familial comedones. *Arch Dermatol* 1967; **95**: 145–6.
17 Giam YC, Ong BH, Rajan VS. Nevus comedonicus in homozygous twins. *Dermatologica* 1981; **162**: 249–53.
18 Hallermann C, Bertsch HP. Two sisters with familial dyskeratotic comedones. *Eur J Dermatol* 2004; **14**: 214–5.
19 Van Geel NA, Kockaert M, Neumann HA. Familial dyskeratotic comedones. *Br J Dermatol* 1999; **140**: 956–9.
20 Hall JR, Holder W, Knox JM *et al.* Familial dyskeratotic comedones: a report of three cases and review of the literature. *J Am Acad Dermatol* 1987; **17**: 808–14.
21 Price M, Russell-Jones R. Familial dyskeratotic comedones. *Clin Exp Dermatol* 1985; **10**: 147–53.
22 Nabai H, Mehregan AH. Nevus comedonicus: a review of the literature and report of twelve cases. *Acta Derm Venereol (Stockh)* 1973; **53**: 71–4.
23 Fritsch P, Wittels W. Ein Fall von bilateralem Naevus comedonicus. *Hautarzt* 1971; **22**: 409–12.
24 Aloi FG, Molinero A. Nevus comedonicus with epidermolytic hyperkeratosis. *Dermatologica* 1987; **174**: 140–3.
25 Barsky S, Doyle JA, Winkelmann RK. Nevus comedonicus with epidermolytic hyperkeratosis. *Arch Dermatol* 1981; **117**: 86–8.
26 Schecter AK, Lester B, Pan TD, Robinson-Bostom L. Linear nevus comedonicus with epidermolytic hyperkeratosis. *J Cutan Pathol* 2004; **31**: 502–5.
27 Leppard BJ. Trichilemmal cysts arising in an extensive comedo naevus. *Br J Dermatol* 1977; **96**: 545–8.
28 Tantcheva-Poor I, Reinhold K, Krieg T, Happle R. Trichilemmal cyst nevus: a new complex organoid epidermal nevus. *J Am Acad Dermatol* 2006; **57** (5 Suppl.): S72–7.
29 Lefkowitz A, Schwartz RA, Lambert WC. Nevus comedonicus. *Dermatology* 1999; **199**: 204–7.
30 Beck MH, Dave VK. Extensive nevus comedonicus. *Arch Dermatol* 1980; **116**: 1048–50.
31 Cripps DJ, Bertram JR. Nevus comedonicus bilateralis et verruciformis. *J Cutan Pathol* 1976; **3**: 273–81.
32 Kirtak N, Inaloz HS, Karakok M *et al*. Extensive inflammatory nevus comedonicus involving half of the body. *Int J Dermatol* 2004; **43**: 434–6.
33 Cestari TF, Rubim M, Valentini BC. Nevus comedonicus: case report and review of the literature. *Pediatr Dermatol* 1991; **8**: 300–5.
34 Rodriguez JM. Nevus comedonicus. *Arch Dermatol* 1975; **111**: 1363–4.
35 Vasiloudes PE, Morelli JG, Weston WL. Inflammatory nevus comedonicus in children. *J Am Acad Dermatol* 1998; **38**: 834–6.
36 Suarez TI, Prado A, Cordero AA. El nevo comedonico. *Med Cutan Ibero Lat Am* 1985; **13**: 371–6.
37 Ghaninezhad H, Ehsani AH, Mansoori P, Taheri A. Naevus comedonicus of the scalp. *J Eur Acad Dermatol Venereol* 2006; **20**: 184–5.
38 Anderson NP, Ayres S, Kane LM. Comedone naevus. *Arch Derm Venereol (Stockh)* 1933; **14**: 229–312.
39 Milton GP, DiGiovanna JJ, Peck GL. Treatment of nevus comedonicus with ammonium lactate lotion. *J Am Acad Dermatol* 1989; **20**: 324–8.
40 Alpsoy E, Durusoy C, Ozbilim G *et al*. Nevus comedonicus syndrome: a case associated with multiple basal cell carcinomas and a rudimentary toe. *Int J Dermatol* 2005; **44**: 499–501.
41 Whyte HJ. Unilateral comedo nevus and cataract. *Arch Dermatol* 1968; **97**: 533–5.
42 Martinez M, Levrero P, Bazzano C *et al*. Nevus comedonicus syndrome in a woman with Paget bone disease and breast cancer: a mere coincidence? *Eur J Dermatol* 2006; **16**: 697–8.
43 Rook AJ. Nevus comedonicus unilateralis with partial Sturge–Weber syndrome and extensive vascular naevi with haemangiectatic hypertrophy of leg. In: *Proceedings of the Tenth International Congress of Dermatology*. London: British Medical Association, 1953: 421–2.
44 Engber PB. The nevus comedonicus syndrome: case report with emphasis on associated internal manifestations. *Int J Dermatol* 1978; **17**: 745–9.
45 Rupec M. Nevus follicularis keratosus (Nevus comedonicus) mit Elastoma intrapapillare. *Dermatol Wochenschr* 1963; **147**: 141–8.
46 Schneider C. Ein Beitrag zur Klinik Naevus comedonicus. *Hautarzt* 1975; **26**: 153–4.
47 Patrizi A, Neri I, Fiorentini C, Marzaduri S. Nevus comedonicus syndrome: a new case. *Pediatr Dermatol* 1998; **15**: 304–6.

48 Seo YJ, Piao YJ, Suhr KB *et al*. A case of nevus comedonicus syndrome associated with neurologic and skeletal abnormalities. *Int J Dermatol* 2001; **40**: 648–50.
49 Resnik KS, Kantor GR, Howe NR *et al*. Dilated pore nevus: a histologic variant of nevus comedonicus. *Am J Dermatopathol* 1993; **15**: 169–71.
50 Bernucci F. Considerazione su di un nevo-acromio lineare a comedoni. *Arch Ital Dermatol Sifilogr Venereol* 1930; **6**: 26–32.
51 Blaschko A. Acne zosteriformis. *Arch Dermatol Syphilol* 1916; **123**: 242–50.
52 Senear FE, Perlstein MO. Nevus unilateris comedonicus. *Arch Dermatol Syphilol* 1935; **32**: 680–1.
53 Grimalt R, Caputo R. Posttraumatic nevus comedonicus. *J Am Acad Dermatol* 1993; **28**: 273–4.
54 Marcus J, Esterkly NB, Bauer BS. Tissue expansion in a patient with extensive nevus comedonicus. *Ann Plast Surg* 1992; **29**: 362–6.
55 Loria PR, Hailey CW. Nevus follicularis keratosis (comedo nevus). *Arch Dermatol* 1961; **83**: 991–4.
56 Wakahara M, Kiyohara T, Kumakiri M *et al*. Bilateral nevus comedonicus: efficacy of topical tacalcitol ointment. *Acta Derm Venereol* 2003; **83**: 51.
57 Deliduka SB, Kwong PC. Treatment of Nevus comedonicus with topical tazarotene and calcipotriene. *J Drugs Dermatol* 2004; **3**: 674–6.
58 Decherd JW, Mills O, Leyden JJ. Naevus comedonicus: treatment with retinoic acid. *Br J Dermatol* 1972; **86**: 528–9.
59 Peck GL, Yoder FW. Treatment of disorders of keratinization with an oral stereoisomer of retinoic acid. In: Marks R, Dykes PJ, eds. *The Ichthyoses*. Lancaster: MTP Press, 1978: 193.

'Acne-free' naevus

A single case has been reported of an adolescent male with severe papulopustular acne vulgaris of the back, who had, within the affected area, four well-defined bilaterally symmetrical zones, which were completely free of acne [1]. Investigation revealed smaller sebaceous glands, reduced sebum excretion rate, decreased counts of *Propionibacterium acnes* in the pilosebaceous ducts and reduced conversion of testosterone to 5α-dihydrotestosterone in the 'acne-free' zones. This may be another type of 'functional' naevus, possibly due to abnormal end-organ androgen responsiveness, and could be regarded as the converse of the situation in acne naevi.

Reference

1 Cunliffe WJ, Ead RD, Perera WHD *et al*. An acne-free naevus. *Br J Dermatol* 1977; **96**: 287–90.

Linear basaloid follicular hamartomas

Definition. A rare variety of epidermal naevus composed of multiple, benign, follicular basal cell hamartomas. The literature has not always differentiated this from linear basal cell naevi.

Aetiology. Some cases may represent mosaicism for autosomal dominant generalized basaloid follicular hamartomas [1–4].

Clinical features [5–8]. This benign, localized naevus is generally present from birth and may be extensive. The linear form consists of numerous, translucent or brown nodules or plaques, which occasionally demonstrate central ulceration, often associated with small areas of macular hypopigmentation. Other reported abnormalities in the affected area have included cysts, verrucous papules, basal cell carcinomas [9] and stria-like areas of cutaneous atrophy [10]. Solitary and plaque-like lesions occur in the scalp, usually associated with localized alopecia [7]. Normal hair growth on a scalp follicular hamartoma has been reported but the histology in that case was also atypical [8].

Pathology. Basaloid follicular hamartoma is characterized by anastomosing strands of well-differentiated basaloid or squamoid cells extending from the upper portions of follicles into a loose connective tissue stroma [5,7,8]. There may be trichoblastomatous proliferation [11]. It can be distinguished from basal cell carcinoma by its low proliferative index (Ki-67 expression) and by circumferential expression of CD34 around the epithelial strands [12].

Differential diagnosis. Confusion may arise with other adnexal tumours, particularly on the face. It must be differentiated from linear basal cell naevus.

Treatment. Treatment, if required, is usually surgical.

References

1 Wheeler CE, Carroll MA, Groben PA *et al*. Autosomal dominantly inherited basaloid follicular hamartoma syndrome: report of a new disease in a North Carolina family. *J Am Acad Dermatol* 2000; **43**: 189–206.
2 Girardi M, Federman GL, McNiff JM. Familial mutiple basaloid follicular hamartomas: a report of two affected sisters. *Pediatr Dermatol* 1999; **16**: 281–4.
3 Ricks M, Elston DM, Sartori CR. Multiple basaloid follicular hamartomas associated with acrochordons, seborrhoeic keratoses and chondrosarcoma. *Br J Dermatol* 2002; **146**: 1068–70.
4 Lee PL, Lourduraj LT, Palko MJ 3rd *et al*. Hereditary basaloid follicular hamartoma syndrome. *Cutis* 2006; **78**: 42–6.
5 El-Darouti MA, Marzouk SA, Abdel-Halim MR *et al*. Basaloid follicular hamartoma. *Int J Dermatol* 2005; **44**: 361–5.
6 Jiminez-Acosta FJ, Redondo E, Baez O *et al*. Linear unilateral basaloid follicular hamartoma. *J Am Acad Dermatol* 1992; **27**: 316–9.
7 Mehregan AH, Baker S. Basaloid follicular hamartoma: three cases with localized and systematized unilateral lesions. *J Cutan Pathol* 1985; **12**: 55–65.
8 Morohashi M, Sakamoto F, Takenouchi T *et al*. A case of localised follicular hamartoma: an ultrastructural and immunohistochemical study. *J Cutan Pathol* 2000; **27**: 191–8.
9 Yoshida Y, Urabe K, Mashino T *et al*. Basal cell carcinomas in association with basaloid follicular hamartoma. *Dermatology* 2003; **207**: 57–60.
10 Lee MW, Choi JH, Moon KC, Koh JK. Linear basaloid follicular hamartoma on the Blaschko's line of the face. *Clin Exp Dermatol* 2005; **30**: 30–4.
11 Kaiser A, Spence RJ, Parwani A *et al*. Basaloid follicular hamartoma with trichoblastomatous proliferations. *J Cutan Med Surg* 2003; **7**: 395–8.
12 Naeyaert JM, Pauwels C, Geerts ML, Verplancke P. CD-34 and KI-67 staining patterns of basaloid follicular hamartoma are different from those in fibroepithelioma of Pinkus and other variants of basal cell carcinoma. *J Cutan Pathol* 2001; **28**: 538–41.

Linear basal cell naevus

Synonym
- Basal cell naevus with comedones

Definition. A linear collection of macules and papules histologically similar to basal cell carcinoma.

Aetiology. Some cases may reflect mosaicism for Gorlin's syndrome (linear basal cell naevus syndrome); however, Brailey *et al*. could not find mutations in *PTCH* in DNA from a linear basal cell naevus [1].

Clinical features. Unilateral smooth or warty papules [1,2], skin tag-like lesions and occasionally comedones [3–5] occur in a linear

distribution usually on the trunk or a limb. Malformations of the spine are rarely associated [4]. Skeletal malformations and palmar pits may reflect mosaicism for Gorlin syndrome [6].

Pathology. There is basaloid proliferation, peripheral palisading and surface erosion as seen in basal cell carcinoma. Distinction may rely on the young age of the patient. There may be stromal condensation around the basal cell nests [1].

References

1 Brailey LL, Davis T, Kolker SE *et al*. Congenital linear unilateral basal cell nevus: a case report with patched gene molecular studies. *J Cutan Pathol* 2007; **34**: 65–70.
2 Willis D, Rapini RP, Chernosky ME. Linear basal cell nevus. *Cutis* 1990; **46**: 493–4.
3 Bleiberg J, Brodkin RH. Linear unilateral basal cell nevus with comedones. *Arch Dermatol* 1969; **100**: 187–90.
4 Carney RG. Linear unilateral basal cell nevus with comedones: report of a case. *Arch Dermatol Syphilol* 1952; **65**: 471–6.
5 Horio T, Komura J. Linear unilateral basal cell nevus with comedo-like lesion. *Arch Dermatol* 1978; **114**: 95–7.
6 Camisa C, Rossana C, Little L. Naevoid basal cell carcinoma syndrome with unilateral neoplasms and pits. *Br J Dermatol* 1985; **113**: 365–7.

Dilated pore naevus

While clinically indistinguishable from comedo naevus, histologically the dilated pore naevus shows aggregated dilated follicular cysts [1]. These cysts individually are indistinguishable from the dilated pore of Winer, a solitary lesion usually occurring on the face in middle-age. Steffen [2] has argued that the dilated pore of Winer is a primary neoplasm (infundibloma) rather than a cyst. A dilated pore naevus has also been described with onset in adulthood [3].

References

1 Resnik KS, Kantor GR, Howe NR *et al.* Dilated pore nevus: a histologic variant of nevus comedonicus. *Am J Dermatopathol* 1993; **15**: 169–71.
2 Steffen C. Winer's dilated pore: the infundibuloma. *Am J Dermatopathol* 2001; **23**: 246–53.
3 Konohana A, Kobayashi T. Aggregated dilated pores. *J Dermatol* 1999; **26**: 332–3.

Hairy malformation of the palms and soles

This rare disorder appears to be transmitted as an autosomal dominant trait. Asymptomatic areas of skin, having a somewhat altered texture and bearing hairs, are present bilaterally on the palms near the wrists, and on the medial aspect of the longitudinal arch of the feet [1,2]. Histologically, these show no abnormality other than the presence of hair follicles. A sporadic case has been reported in which the abnormality occurred on one palm only [3]. Differential diagnosis will include congenital melanocytic naevus and smooth muscle hamartoma.

References

1 Jackson CE, Callies QC, Krull EA, Mehregan A. Hairy cutaneous malformations of palms and soles: a hereditary condition. *Arch Dermatol* 1975; **111**: 1146–9.
2 Schnitzler ML. Dysembryoplasie pilaire circonscrite des paumes: un cas familial. *Bull Soc Fr Dermatol Syphiligr* 1973; **80**: 323–4.
3 Camacho F, Campora RG. Circumscribed pilary dysembryoplasia of the palms. *Dermatologica* 1991; **182**: 63–4.

Apocrine naevi

True apocrine naevi

Synonym
- Apocrine gland hamartoma

True apocrine naevi are rare, although apocrine structures are frequently seen in sebaceous naevi [1] and syringocystadenoma papilliferum. The clinical appearance is variable and includes solitary nodules on the scalp [2], pigmented vulval papules [3], a plaque on the face [4,5] and bilateral soft tumours in the axillae or upper chest [6–9]. In a patient with focal dermal hypoplasia, the lesions comprised multiple papules in the sternal area [10]. Histologically, true apocrine naevi comprise large numbers of mature apocrine glands extending from the upper dermis to the subcutaneous fat. Decapitation secretion and periodic acid–Schiff (PAS)-positive diastase-resistant granules in the luminal cells differentiate apocrine from eccrine gland differentiation [5]. There is only one report of malignant transformation: an apocrine gland carcinoma was excised within an area of skin histologically consistent with apocrine nevus, but a preceding clinical lesion was not described [11].

References

1 Ng WK. Nevus sebaceus with apocrine and sebaceous differentiation. *Am J Dermatopathol* 1996; **18**: 420–3.
2 Civatte J, Tsoitis G, Preaux J. Le naevus apocrine: étude de 2 cas. *Ann Dermatol Syphiligr* 1974; **101**: 251–61.
3 Chen KT. Pigmented apocrine hamartoma of the vulva: a report of two cases. *Int J Gynecol Pathol* 2005; **24**: 85–7.
4 Lee Y, Kim BJ, Lee JH *et al*. Congenital apocrine hamartoma. *Pediatr Dermatol* 2007; **24**: 346–7.
5 Herrmann JJ, Eramo LR. Congenital apocrine hamartoma: an unusual clinical variant of organoid nevus with apocrine diffrentiation. *Pediatr Dermatol* 1995; **12**: 248–51.
6 Ando K, Hashikawa Y, Nakashima M *et al*. Pure apocrine nevus. *Am J Dermatopathol* 1991; **13**: 71–6.
7 Kim JH, Hur H, Lee CW *et al*. Apocrine nevus. *J Am Acad Dermatol* 1988; **18**: 579–81.
8 Neill JSA, Park HK. Apocrine nevus: light microscopic, immunohistochemical and ultrastructural studies of a case. *J Cutan Pathol* 1993; **20**: 79–83.
9 Rabens SF, Naness JI, Gottlieb BF. Apocrine gland organic hamartoma (apocrine nevus). *Arch Dermatol* 1976; **112**: 520–2.
10 Vakilzadeh F, Happle R, Peters P *et al*. Fokale dermale Hypoplasie mit apokrinen Naevi und streifenformiger Anomalie der Knochen. *Arch Dermatol Res* 1976; **256**: 189–95.
11 Nishikawa Y, Tokusashi Y, Saito Y *et al*. A case of apocrine adenocarcinoma associated with hamartomatous apocrine gland hyperplasia of both axillae. *Am J Surg Pathol* 1994; **18**: 832–6.

Syringocystadenoma papilliferum

Synonym
- Naevus syringocystadenomatosus papilliferus

Definition. Syringocystadenoma papilliferum is a skin hamartoma with predominantly apocrine differentiation.

Aetiology. The histogenesis of these lesions is controversial. They show features of apocrine glands, or occasionally eccrine glands.

Syringocystadenoma papilliferum is a frequent component of sebaceous naevi and associated hamartomatous malformations of hair follicles and sebaceous glands are common. Yamamoto *et al.* [1] postulated an origin in pluripotent cells on immunohistochemical and ultrastructural grounds. Boni *et al.* [2] showed mutations in *PTCH* or *P16* tumour suppressor genes in syringocystadenoma papilliferum. Kazakov *et al.* noted an overlap with tubular adenoma [3].

Pathology. Histologically, cystic invaginations extend downwards from a papillomatous epidermis, with numerous villous projections extending into the lumen. The lining is glandular epithelium, comprising an outer cuboidal layer and an inner cylindrical layer occasionally demonstrating 'decapitation' secretion. Prominent apocrine glands deep to the invaginations, can be shown by serial sectioning to be connected [4]. A plasma cell infiltrate is present, particularly in the stroma of the papillary projections. Syringocystadenoma papilliferum shows focal positivity to CK15, a relatively specific marker of hair follicle stem cells in the bulge [5]. Basal cell carcinoma may develop [2], and rarely secondary adenocarcinoma (syringocystadenocarcinoma papilliferum) [6] and apocrine ductal carcinoma [7].

Clinical features. These lesions occur either as a nodular plaque, a linear group of nodules or a solitary nodule. The plaque and linear varieties are usually present at birth, or appear during infancy [8], and may become more elevated and nodular, verrucous or crusted at puberty. The less common solitary nodular form usually develops at puberty. The plaque form usually presents as a hairless area in the scalp, while the linear form is commoner on the neck or face. A mature lesion comprises clusters of pinkish brown nodules 2–10 mm in diameter, which are domed, umbilicated or pedunculated, often with a friable or crusted surface. Several lesions may be scattered over an area. The solitary nodular form predominates on the trunk, particularly the shoulders, the axillae and genital areas, and occasionally the limbs.

Ulceration or rapid enlargement may indicate malignant transformation, usually to basal cell carcinoma [2], but occasionally adenocarcinoma. In most such cases, there is a coexistent sebaceous naevus.

Naevi of this histological type may be associated with non-cutaneous abnormalities (see epidermal naevus syndrome).

Diagnosis. The plaque and linear forms on the head and neck may be difficult to distinguish clinically from sebaceous naevus, although syringocystadenoma papilliferum tends to be pinker and more nodular. The umbilication of individual nodules, particularly in the linear form, may cause confusion with molluscum contagiosum [8]. There is histological overlap with tubular adenoma [3].

Management. Because of the not infrequent development of secondary basal cell carcinoma, these lesions should be excised wherever possible. Pulsed carbon dioxide laser treatment of a surgically difficult lesion in and below the ear in a 2½-week-old baby produced 'reasonable cosmesis' with minimal recurrence at 3 years [9]. Secondary syringocystadenocarcinoma papilliferum occurs very rarely and has been treated successfully with Mohs micrographic surgery [6].

References

1 Yamamoto O, Hamada T, Hisaoka M, Sasaguri Y. An immunohistochemical and ultrastructural study of syringocystadenoma papilliferum. *Br J Dermatol* 2002; **147**: 936–45.
2 Boni R, Xin H, Hohl D *et al*. Syringocystadenoma papilliferum: a study of potential tumour suppressor genes. *Am J Dermatopathol* 2001; **23**: 87–9.
3 Kazakov DV, Bisceglia M, Calonje E *et al*. Tubular adenoma and syringocystadenoma papilliferum: a reappraisal of their relationship. An interobserver study of a series, by a panel of dermatopathologists. *Am J Dermatopathol* 2007; **29**: 256–63.
4 Krinitz K. Naevus syringocystadenomatosus papilliferus in linearer Anordnung. *Hautarzt* 1966; **17**: 260–5.
5 Misago N, Narisawa Y. Cytokeratin 15 expression in apocrine mixed tumors of the skin and other benign neoplasms with apocrine differentiation. *J Dermatol* 2006; **33**: 2–9.
6 Chi CC, Tsai RY, Wang SH. Syringocystadenocarcinoma papilliferum: successfully treated with Mohs micrographic surgery. *Dermatol Surg* 2004; **30**: 468–71.
7 Hugel H, Requena L. Ductal carcinoma arising from a syringocystadenoma papilliferum in a nevus sebaceus of Jadassohn. *Am J Dermatopathol* 2003; **25**: 490–3.
8 Goldberg NS, Esterly NB. Linear papules on the neck of a child. *Arch Dermatol* 1985; **121**: 1197–202.
9 Jordan JA, Brown OE, Biavati MJ, Manning SC. Congenital syringocystadenoma papilliferum of the ear and neck treated with the CO_2 laser. *Int J Pediatr Otorhinolaryngol* 1996; **38**: 81–7.

Eccrine naevi

Pure eccrine naevi

Synonyms
- Naevus sudoriferus
- Sudoriferous hamartoma

Although an eccrine component is commonly found in sebaceous naevus, purely eccrine naevi are very rare. They can present at any age and the clinical appearance is variable. In one case a solitary pore that discharged a mucoid secretion showed histologically numerous coils, comprising both secretory and ductal elements, situated deeply in the dermis and leading to a central dilated pore on the surface [1]. Two cases presented as nodules comprising numerous normally structured sweat glands and ducts surrounded by mucin, and were termed mucinous eccrine naevus [2,3]. An otherwise unremarkable area of diffusely increased sweat production, with histologically prominent eccrine glands, has been termed 'naevus sudoriferus' [4,5]. Other cases have taken the form of a small plaque [6], a congenital perianal skin tag [7], and grouped skin-coloured or brown papules, sometimes in a linear distribution [8].

References

1 Herzberg JJ. Ekkrines Syrincystadenom. *Arch Klin Exp Dermatol* 1962; **214**: 600–21.
2 Park HS, Lee UH, Choi JC, Chun DK. Mucinous eccrine nevus. *J Dermatol* 2004; **31**: 687–9.
3 Llombart B, Molina I, Monteagudo C *et al*. Mucinous eccrine nevus: an unusual lesion in a child. *Pediatr Dermatol* 2003; **20**: 137–9.
4 Goldstein N. Ephidrosis (local hyperhidrosis): nevus sudoriferus. *Arch Dermatol* 1967; **96**: 67–8.
5 Kawaoka JC, Gray J, Schappell D, Robinson-Bostom L. Eccrine nevus. *J Am Acad Dermatol* 2004; **51**: 301–4.

6 Pippione M, Depaoli MA, Sartoris S. Naevus eccrine. *Dermatologica* 1976; **152**: 40–6.
7 Mahdavy M, Smoller BR. Eccrine nevus presenting as a perianal skin tag: a case report and review of the literature. *Am J Dermatopathol* 2002; **24**: 361–3.
8 Morris ES, Scheel MM, Lundquist KF, Raimer SS. Grouped papules on the arm of an infant. Eccrine nevus. *Arch Dermatol* 2000; **136**: 542–9.

Eccrine angiomatous naevus

Synonyms
- Eccrine angiomatous hamartoma
- Sudoriparous angioma

Definition. Eccrine angiomatous naevus is a rare condition characterized histologically by numerous eccrine structures and capillary channels, most commonly found in acral skin where eccrine glands are numerous. The term covers a spectrum of lesions ranging from the predominantly angiomatous 'sudoriparous angioma' [1] up to the normally vascularized naevus sudoriferus.

Pathology. Histologically, lesions show nests of large, but otherwise normal eccrine glands [2,3], enmeshed in loose fibrous tissue, which contains numerous thin-walled blood vessels and lymphatics [4]. There may be a very intimate association between the glandular and vascular elements [5,6]. The overlying epidermis may be mildly acanthotic. Other components, particularly hair follicles, may also be closely associated with the eccrine angiomatous complexes [7,8]. Some have shown fat [9,11,12] or mucin deposition [3,10]. Immunohistochemical findings are similar to normal eccrine glands [9].

Clinical features. This is very rare with only 42 cases in the English language literature [13]. These lesions appear at birth or during childhood in 77% of cases and affect both sexes equally [9,14]. They take the form of a nodule or plaque, flesh-coloured or with a bluish colour and angiomatous appearance. Eighty per cent occur on the extremities [14], particularly the palm and sole, but also on other parts of the feet, on the face, neck and on the trunk. Occasionally, there are multiple lesions [1,14–17]. Most are painful on pressure [4,9,18]. Nail destruction with underlying osteolysis has been reported [13]. Some demonstrate hypertrichosis [15] and/or hyperhidrosis [3], but not all [19]. Generally, they enlarge very gradually; more rapid growth has been described during pregnancy and adolescence [20]. One atypical case presented at the age of 73 years, on the buttock, and was verrucous [21]. They are usually unassociated with other anomalies but accompanied Cowden syndrome in one case [22] and neurofibromatosis in another [23]. A familial occurrence was noted in one report [17].

Treatment. Painful lesions may require removal, particularly those on the palm or sole; this has been successfully achieved by deep excision with full-thickness grafting [4], or by amputation [20]. Pulsed dye laser was helpful in only one of two patients [24]. Spontaneous regression has been reported [25].

References

1 Domonkos AN, Suarez LS. Sudoriparous angioma. *Arch Dermatol* 1967; **96**: 552–3.
2 Sulica RL, Kao GF, Sulica VI, Penneys NS. Eccrine angiomatous hamartoma (nevus): immunohistochemical findings and review of the literature. *J Cutan Pathol* 1994; **21**: 71–5.
3 Martinelli PT, Tschen JA. Eccrine angiomatous hamartoma: a case report and review of the literature. *Cutis* 2003; **71**: 449–55.
4 Kikuchi I, Kuroki Y, Inoue S. Painful eccrine angiomatous nevus on the sole. *J Dermatol* 1982; **9**: 329–32.
5 Challa VR, Jone J. Eccrine angiomatous hamartoma: a rare skin lesion with diverse histological features. *Dermatologica* 1977; **155**: 206–9.
6 Hyman AB, Harris H, Brownstein MH. Eccrine angiomatous hamartoma. *NY State J Med* 1968; **68**: 2803–6.
7 Zeller DJ, Goldman RL. Eccrine-pilar angiomatous hamartoma. *Dermatologica* 1971; **143**: 100–4.
8 Velasco JA, Almeida V. Eccrine pilar angiomatous nevus. *Dermatologica* 1988; **177**: 317–22.
9 Cebreiro C, Sanchez-Aguilar D, Gomez Centeno P, Fernandez-Redondo V, Toribio J. Eccrine angiomatous hamartoma: report of seven cases. *Clin Exp Dermatol* 1998; **23**: 267–70.
10 Tsunemi Y, Shimazu K, Saeki H *et al*. Eccrine angiomatous hamartoma with massive mucin deposition. *Eur J Dermatol* 2005; **15**: 291–2.
11 Nakatsui TC, Schloss E, Krol A, Lin AN. Eccrine angiomatous hamartoma: report of a case and literature review. *J Am Acad Dermatol* 1999; **41**: 109–11.
12 Smith VC, Montesinos E, Revert A *et al*. Eccrine angiomatous hamartoma: report of three patients. *Pediatr Dermatol* 1996; **13**: 139–42.
13 Sezer E, Koseoglu RD, Filiz N. Eccrine angiomatous hamartoma of the fingers with nail destruction. *Br J Dermatol* 2006; **154**: 1002–4.
14 Morrell DS, Ghali FE, Stahr BJ, McCauliffe DP. Eccrine angiomatous hamartoma: a report of symmetric and painful lesions of the wrists. *Pediatr Dermatol* 2001; **18**: 117–9.
15 Sugimoto Y, Araki E, Inoguchi N *et al*. Adult-onset multiple eccrine angiomatous hamartoma in enlarging hairy plaques. *Acta Derm Venereol (Stockh)* 2007; **87**: 180–1A.
16 Foshee JB, Grau RH, Adelson DM, Crowson N. Eccrine angiomatous harmartoma in an infant. *Pediatr Dermatol* 2006; **23**: 365–8.
17 Garcia-Arpa M, Rodriguez-Vazquez M, Cortina-de la Calle P *et al*. Multiple and familial eccrine angiomatous hamartoma. *Acta Derm Venereol (Stockh)* 2005; **85**: 355–7.
18 Wolf R, Krakowski A, Dorfman B. Eccrine angiomatous hamartoma: a painful step. *Arch Dermatol* 1989; **125**: 1489–90.
19 Pelle MT, Pride HB, Tyler WB. Eccrine angiomatous hamartoma. *J Am Acad Dermatol* 2002; **47**: 429–35.
20 Gabrielsen T-Ø, Elgjo K, Sommerschild H. Eccrine angiomatous hamartoma of the finger leading to amputation. *Clin Exp Dermatol* 1991; **16**: 44–5.
21 Tsuji T, Sawada H. Eccrine angiomatous hamartoma with verrucous features. *Br J Dermatol* 1999; **141**: 167–9.
22 Oh JG, Yoon CH, Lee CW. Case of Cowden syndrome associated with eccrine angiomatous hamartoma. *J Dermatol* 2007; **34**: 135–7.
23 Castilla EA, Schwimer CJ, Bergfeld WF *et al*. Eccrine angiomatous hamartoma in a neurofibromatosis type-1 patient. *Pathology* 2002; **34**: 378–80.
24 Lee S-Y, Chang S-E, Choi J-H *et al*. Congenital eccrine angiomatous hamartoma: report of two patients. *J Dermatol* 2001; **28**: 338–40.
25 Tay YK, Sim CS. Eccrine angiomatous hamartoma associated with spontaneous regression. *Pediatr Dermatol* 2006; **23**: 516–7.

Porokeratotic eccrine ostial and dermal duct naevus

Definition. Porokeratotic eccrine ostial and dermal duct naevus (PEODDN) is a localized area of plugged pores usually on the palm or sole. It has been recognized only since 1980 [1], early cases having been reported as comedo naevus of the palm [2], or linear eccrine naevus with comedones [3]. Several cases have been reported since [4].

Aetiology. This is presumably a mosaic genetic defect. As for comedo naevus, debate centres on whether the primary abnormal-

ity involves the epidermis or the appendage. Staining with carcinembryonic antigen (CEA) which labels the acrosyringium and dermal eccrine duct suggests that PEODDN represents an abnormally keratinizing epidermal invagination traversed by an acrosyringium-like duct, rather than a primary abnormality of the acrosyringium and dermal duct [5].

Pathology. Histologically, these lesions are characterized by dilated comedo-like epidermal invaginations filled with parakerotic plugs. The neighbouring epidermis demonstrates parakeratotic columns, which protrude above the rest of the stratum corneum. The granular layer is absent at the base of these columns, and in the lining of the comedo-like structures; keratinocytes with vacuolated cytoplasm and pyknotic nuclei may also be a feature. In the lower portion of the invaginations, intraepidermal eccrine ducts are generally visible, and there may be associated hyperplastic intradermal eccrine ducts with comma-shaped extensions. However many cases show no connection between the parakeratotic columns and eccrine ducts [6]. Bowen's disease was found in one case [7], and linear psoriasis in two others, in one case partially overlapping with the palmar lesion [8].

Clinical features. The lesions are asymptomatic and are usually present from birth, although onset later in childhood is reported in 26% [9,10]. PEODDN resembles comedo naevus, comprising small keratotic papules, with a central plugged pit, in a linear distribution, usually on the palms and soles [11]. At other sites, the lesions tend to be more verrucous, resembling verrucous epidermal naevi, sometimes with filiform vegetations [6]. PEODDN is occasionally quite extensive [1]. Involvement of all four limbs has been reported [12]. The lesions may be anhidrotic [1] or hyperhidrotic [2,10]. There are no known associated abnormalities.

Diagnosis. The entity described as *porokeratotic eccrine duct and hair follicle nevus* [13,14] is probably very closely related, the only real distinction being that hair follicles were affected as well as eccrine sweat ducts. Comedo naevi can be distinguished histologically, because they lack the characteristic intraepidermal and dermal eccrine ducts, and the parakeratotic columns. This disorder also appears to be distinct from *punctate porokeratosis* [15] in which multiple punctate, seed-like keratoses and/or pits are present on the palms and soles, occasionally in a linear configuration, and sometimes associated with linear porokeratosis. Punctate porokeratosis does not resemble comedones, either clinically or histologically, and the cornoid lamellae are not obviously associated with eccrine duct ostia.

Treatment. As for other epidermal naevi, simple excision is usually the treatment of choice. An adult-onset lesion on the hand resistant to topical keratolytics and cryotherapy responded to four treatments with the carbon dioxide laser and remained clear 9 months later [16]. Spontaneous involution has been reported over 24 years [17].

References

1 Abell E, Read SI. Porokeratotic eccrine ostial and dermal duct naevus. *Br J Dermatol* 1980; **103**: 435–41.

2 Marsden RA, Fleming K, Dawber RPR. Comedo naevus of the palm: a sweat duct naevus. *Br J Dermatol* 1979; **101**: 717–22.

3 Blanchard L, Hodge SJ, Owen LG. Linear eccrine nevus with comedones. *Arch Dermatol* 1981; **117**: 357–9.

4 Sassmanshausen J, Bogomilsky J, Chaffins M. Porokeratotic ostial and dermal duct naevus: a case report and review of the literature. *J Am Acad Dermatol* 2000; **43**: 364–7.

5 Jiminez J, Gomez I, Gonzalez C *et al*. Porokeratotic eccrine ostial and dermal duct naevus. *Br J Dermatol* 1995; **132**: 490–1.

6 Cambiaghi S, Gianotti R, Caputo R. Widespread porokeratotic eccrine ostial and dermal duct nevus along Blaschko lines. *Pediatr Dermatol* 2007; **24**: 162–7.

7 Coras B, Vogt T, Roesch A *et al*. Bowen's disease on porokeratotic eccrine ostial and dermal duct nevus. *Dermatol Surg* 2007; **33**: 496–9.

8 Yu HJ, Ko JY, Kwon HM, Kim JS. Linear psoriasis with porokeratotic eccrine ostial and dermal duct nevus. *J Am Acad Dermatol* 2004; **50** (5 Suppl.): S81–3.

9 Valks R, Abajo P, Fraga J *et al*. Porokeratotic eccrine ostial and dermal duct nevus of late onset: more frequent than previously suggested? *Dermatology* 1996; **193**: 138–40.

10 Birol A, Erkek E, Bozdoethan O *et al*. A case of porokeratotic eccrine ostial and dermal duct naevus of late onset. *J Eur Acad Dermatol Venereol* 2004; **18**: 619–21.

11 Warren KJ, Baselga E, Fleming MG, Esterly NB. Keratotic papules on the palm of a 12-year-old boy. *Pediatr Dermatol* 1998; **15**: 140–2.

12 Cobb MW, Vidmar DA, Dilaimy MS. Porokeratotic eccrine ostial and dermal duct nevus: a case of systematized involvement. *Cutis* 1990; **46**: 495–7.

13 Coskey RJ, Mehregan AH, Hashimoto K. Porokeratotic eccrine duct and hair follicle nevus. *J Am Acad Dermatol* 1982; **6**: 940–3.

14 Kroumpouzos G, Stefanato CM, Wilkel CS *et al*. Systematised porokeratotic eccrine and hair follicle naevus: report of a case and review of the literature. *Br J Dermatol* 1999; **141**: 1092–6.

15 Sakas EL, Gentry RH. Porokeratosis punctata palmaris et plantaris (punctate porokeratosis). *J Am Acad Dermatol* 1985; **13**: 908–12.

16 Del Pozo J, Martinez W, Verea MM *et al.* Porokeratotic eccrine ostial and dermal duct naevus: treatment with carbon dioxide laser. *Br J Dermatol* 1999; **141**: 1144–5.

17 Mazuecos J, Ortega M, Rios JJ, Camacho F. Long-term involution of unilateral porokeratotic eccrine ostial and dermal duct naevus. *Acta Derm Venereol* 2003; **83**: 147–9.

Becker's naevus

Synonyms
- Becker's melanosis
- Pigmented hairy epidermal naevus

Definition. An acquired and persistent asymmetrical area of skin pigmentation [1], sometimes showing evidence of increased androgen sensitivity, and co-localizing with other developmental anomalies.

Aetiology. The sporadic occurrence and asymmetrical distribution of most Becker's naevi suggest cutaneous mosaicism. Indeed, chromosomal mosaicism was reported in one patient with Becker's naevus [2]. A Becker's naevus has been reported to follow Blaschko's lines [3], but the usual lack of conformity to Blaschko's lines may be due to the relatively late occurrence of a causative mutation (see above). The mutant skin clone is presumably predisposed not only to pigmentation but also to androgen sensitivity, since Becker's naevus is prone to acne and hypertrichosis [4]. While most cases occur sporadically, Becker's naevus has been reported in siblings [5], father and son [6], and uncle and nephew [7]. As discussed above, familial occurrence of a mosaic disorder can be reconciled with mosaicism by mechanisms such as inheritance of an unstable premutation, paradominant inheritance [8]

and chance. Co-localization with other developmental anomalies suggests a clonal defect in morphogenesis. Becker's naevus may be pathogenetically related to congenital smooth muscle hamartoma, which also shows hypertrichosis, hyperpigmentation and increased smooth muscle, albeit in different proportions [6].

Clinical features. Becker's naevus is a relatively common anomaly, affecting most racial groups, and about five times more frequent in males than females [9]. It is rarely congenital [3,10], and may present in childhood, but is usually first noticed during adolescence, initially pale in colour and becoming more conspicuous after sun-exposure. Becker's naevus was found in 0.25% of 28 000 18-year-old Italian men enlisted for the navy [11], the reported age of onset being 5–17 years, mean 11.9 years. A higher prevalence, 0.52%, in 19 000 French recruits aged 17–26 [9], suggests that Becker's naevus may sometimes appear later. Once present, Becker's naevus remains indefinitely. The usual site is shoulder, anterior chest or scapular region, but lesions on face, neck and distal limbs have been reported [9,12]. It starts as an area of irregular macular pigmentation, which spreads to a diameter of several centimetres, new macules developing beyond the margin and fusing with it, giving a geographical contour. The skin may thicken towards the centre of the lesion. Increased terminal hairs may appear on and around the lesion, and were observed in 70% of the Italian cases [11].

Becker's naevus is more prone to acne vulgaris than the adjacent normal skin [4,13,14]. Other cutaneous anomalies reported to co-localize with Becker's naevus include tinea versicolor [15], eczema [16], granuloma annulare [17], basal cell carcinoma [18], lymphangioma [19] and hypohidrosis [20]. Becker's naevus was associated with generalized lichen planus in one case [10], and in another lichen planus was confined to a large Becker's naevus affecting the whole of one lower limb [21]. Lesions on the face may be associated with asymmetric growth of scalp or beard hair [22].

Although Becker's naevi generally occur without any associated pathology, several ipsilateral developmental abnormalities have been described, particularly breast hypoplasia [12,14,23–26] and supernumerary nipples [27], and also aplasia of the pectoralis major muscle [28], limb reduction [12], segmental odontomaxillary dysplasia [29] and lipoatrophy [24]. Spina bifida [23,30], scoliosis [28], pectus carinatum [23], congenital adrenal hyperplasia [2] and an accessory scrotum [31] have also been reported. The term *Becker's naevus syndrome* has been proposed to describe the association of a Becker's naevus with ipsilateral non-cutaneous abnormalities [25,32,33]. Hoon *et al.* [26] hypothesized that hypoplastic breast, like Becker's naevus, reflects increased androgen receptors; in their case spironolactone, an antiandrogen agent, effectively treated the breast hypoplasia but had no effect on the pigmentation. A report of a diffuse Becker's naevus on the face associated with ipsilateral hemimaxillary enlargement [34] supports the concept of Becker's naevus syndrome as a 'field defect', the associated anomalies usually co-localizing with the naevus.

The possibility of an increased risk of malignant melanoma in patients with Becker's naevus has been raised [35].

Pathology. Histological changes may be subtle. Well-developed lesions show hyperkeratosis, acanthosis and papillomatosis, with hyperplasia of hair follicles and sebaceous glands. The basal and suprabasal keratinocytes are heavily pigmented, and melanocyte density is variably reported as increased [36] or normal [37], with a few melanophages in the upper dermis. There are no junctional or intradermal naevus cells. The dermis is thickened, and contains numerous, but often inconspicuous, bundles of smooth muscle fibres, unrelated to hair follicles or blood vessels [37]. Ultrastructurally, there is evidence of enhanced melanin synthesis, with increased melanocyte activity and increased numbers of melanosome complexes in keratinocytes [38,39]. Giant melanosomes have been reported both in melanocytes and keratinocytes [40]. Increased numbers of androgen receptors [4] and androgen receptor messenger RNA (mRNA) [41] have been found in lesional skin.

Diagnosis. A well-developed Becker's naevus is unmistakeable. In early lesions, age of onset, geographical outline and site help to distinguish Becker's naevus from a café-au-lait macule and from linear and whorled naevoid hypermelanosis. Acquired smooth muscle hamartoma has similar clinical and histological features, but in different proportions, with less pigmentation and more smooth muscle [42]. Whether *progressive cribriform and zosteriform hyperpigmentation* [43] should be regarded as a non-hypertrichotic variant of Becker's naevus is unclear.

Treatment. Benefit from the Q-switched ruby laser has been reported [44], but reactive patchy hyperpigmentation may recur [45]. In a 27-year-old man, three treatments with the 694-nm long-pulsed ruby laser decreased hair density as well as pigmentation, the improvement lasting for the 10 months of follow-up [46]. Trelles *et al.* [47] used either a single treatment with the Er:YAG laser or three treatments with the Q-switched Nd:YAG laser in 22 patients with Becker's naevus, and followed patients up for 2 years. Both groups reported excellent clearance at 1 month. However after 2 years, pigment clearance was rated nearly 80% in the Er:YAG group, with six patients completely clear and the remainder improved by more than 50%. By contrast, pigment clearance in the Nd:YAG group had dropped to 20%. Expert skin camouflage advice can be helpful [48].

References

1 Becker SW. Concurrent melanosis and hypertrichosis in distribution of nevus unius lateris. *Arch Dermatol* 1949; **60**: 155–60.

2 Lambert JR, Willems P, Abs R, Van Roy B. Becker's nevus associated with chromosomal mosaicism and congenital adrenal hyperplasia. *J Am Acad Dermatol* 1994; **30**: 655–7.

3 Ro YS, Ko JY. Linear congenital Becker nevus. *Cutis* 2005; **75**: 122–4.

4 Person JR, Longcope C. Becker's naevus: an androgen-mediated hyperplasia with increased androgen receptors. *J Am Acad Dermatol* 1984; **10**: 235–8.

5 Fretzin DF, Whitney D. Familial Becker's nevus. *J Am Acad Dermatol* 1985; **12**: 589–90.

6 Book SE, Glass AT, Laude TA. Congenital Becker's nevus with a familial association. *Pediatr Dermatol* 1997; **14**: 373–5.

7 Panizzon R, Schnyder UW. Familial Becker's nevus. *Dermatologica* 1988; **176**: 275–6.

8 Happle R. Paradominant inheritance: a possible explanation for Becker's pigmented hairy nevus. *Eur J Dermatol* 1992; **2**: 39–40.

9 Tymen R, Forestier J-F, Boutet B *et al.* Naevus tardif de Becker: à propos d'une série de 100 observations. *Ann Dermatol Vénéréol* 1981; **108**: 41–6.

10 Puri S, Nanda S, Grover C *et al*. Congenital becker nevus with lichen planus. *Pediatr Dermatol* 2005; **22**: 328–30.
11 Ingordo V, Gentile C, Iannazzone S *et al*. The 'EpiEnlist' project: a dermo-epidemiologic study on a representative sample of young Italian males. Prevalence of selected pigmentary lesions. *J Eur Acad Dermatol Venereol* 2007; **21**: 1091–6.
12 Copeman PWM, Wilson-Jones EWJ. Pigmented hairy epidermal nevus (Becker). *Arch Dermatol* 1965; **92**: 249–51.
13 Agrawal S, Garg VK, Sah SP, Agarwalla A. Acne in Becker's nevus. *Int J Dermatol* 2001; **40**: 583–5.
14 Santos-Juanes J, Galache C, Curto JR *et al.* Acneiform lesions in Becker's nevus and breast hypoplasia. *Int J Dermatol* 2002; **41**: 699–700.
15 Wright RC. Another association with Becker's nevus. *Arch Dermatol* 1979; **115**: 1035.
16 Lockshin BN, Brogan B, Billings S. Eczematous dermatitis and prurigo nodularis confined to a Becker's nevus. *Int J Dermatol* 2006; **45**: 1465–6.
17 Weinberg JM, Scheinfeld N, Tishler HR. Granuloma annulare restricted to Becker's naevus. *Br J Dermatol* 2004; **151**: 245–6.
18 Patrizi A, Medri M, Neri I, Fanti PA. Becker naevus associated with basal cell carcinoma, melanocytic naevus and smooth-muscle hamartoma. *J Eur Acad Dermatol Venereol* 2007; **21**: 130–2.
19 Oyler RM, Davis DA, Woosley JT. Lymphangioma associated with Becker's nevus: a report of coincident hamartomas in a child. *Pediatr Dermatol* 1997; **14**: 376–9.
20 Do JE, Kim YJ, Kang HY. Hypohidrosis colocalized with Becker's naevus. *Br J Dermatol* 2007; **156**: 766–7.
21 Terheyden P, Hornschuh B, Karl S *et al*. Lichen planus associated with Becker's nevus. *J Am Acad Dermatol* 1998; **38**: 770–2.
22 de Almeida HL Jr, Happle R. Two cases of cephalic Becker nevus with asymmetrical growth of beard or scalp hair. *Dermatology* 2003; **207**: 337–8.
23 Glinick SE, Alper JC, Bogaars H *et al*. Becker's melanosis: associated abnormalities. *J Am Acad Dermatol* 1983; **9**: 509–14.
24 Van Gerwen HJ, Koopman RJ, Steijlen PM, Happle R. Becker's naevus with localized lipoatrophy and ipsilateral breast hypoplasia. *Br J Dermatol* 1993; **129**: 213.
25 Angelo C, Grosso MG, Stella P *et al*. Becker's nevus syndrome. *Cutis* 2001; **68**: 123–4.
26 Hoon Jung J, Chan Kim Y, Joon Park H, Woo Cinn Y. Becker's nevus with ipsilateral breast hypoplasia: improvement with spironolactone. *J Dermatol* 2003; **30**: 154–6.
27 Urbani CE. Paradominant inheritance, supernumerary nipples and Becker's nevus: once again. *Eur J Dermatol* 2001; **11**: 597.
28 Moore JA, Schosser RH. Becker's melanosis and hypoplasia of the breast and pectoralis major muscle. *Pediatr Dermatol* 1985; **3**: 34–7.
29 Jones AC, Ford MJ. Simultaneous occurrence of segmental odontomaxillary dysplasia and Becker's nevus. *J Oral Maxillofac Surg* 1999; **57**: 1251–4.
30 Naranjo R, Delgado V, De Dulanto F *et al.* Melanosis de Becker. *Actas Dermosifiliogr* 1980; **71**: 331–6.
31 Szylit J-A, Grossman ME, Luyando Y *et al.* Becker's nevus and an accessory scrotum. *J Am Acad Dermatol* 1986; **14**: 905–7.
32 Happle R, Koopman RJ. Becker nevus syndrome. *Am J Med Genet* 1997; **68**: 357–61.
33 Danarti R, Konig A, Salhi A *et al*. Becker's nevus syndrome revisited. *J Am Acad Dermatol* 2004; **51**: 965–9.
34 Welsch MJ, Stein SL. A syndrome of hemimaxillary enlargement, asymmetry of the face, tooth abnormalities, and skin findings (HATS). *Pediatr Dermatol* 2004; **21**: 448–51.
35 Fehr B, Panizzon RG, Schnyder UW. Becker's nevus and malignant melanoma. *Dermatologica* 1991; **182**: 77–80.
36 Tate PR, Hodge SJ, Owen LG. A quantitative study of melanocytes in Becker's nevus. *J Cutan Pathol* 1980; **7**: 404–9.
37 Haneke E. The dermal component in melanosis naeviformis Becker. *J Cutan Pathol* 1979; **6**: 53–8.
38 Frenk E, Delacretaz J. Zur Ultrastrucktur der Beckerschen Melanose. *Hautarzt* 1970; **21**: 397–400.
39 Gebhart W, Kidd RL, Niebauer G. Beckersche Melanose: eine ultrastruukterelle Untersuchung der Pigmentveranderung. *Arch Dermatol Forsh* 1971; **241**: 166–78.
40 Bhawan J, Chang WH. Becker's melanosis: an ultrastructural study. *Dermatologica* 1979; **159**: 221–30.
41 Nirde P, Dereure O, Belon C *et al*. The association of Becker nevus with hypersensitivity to androgens. *Arch Dermatol* 1999; **135**: 212–4.
42 ul Bari A, Rahman SB. Acquired smooth muscle hamartoma. *Indian J Dermatol Venereol Leprol* 2006; **72**: 178.
43 Rower JM, Carr RD, Lowney ED. Progressive cribriform and zosteriform hyperpigmentation. *Arch Dermatol* 1978; **114**: 98–9.
44 Nelson JS, Applebaum J. Treatment of superficial cutaneous pigmented lesions by melanin-selective photothermolysis using the Q-switched ruby laser. *Ann Plast Surg* 1992; **29**: 231–7.
45 Kopera D, Hohenleutner U, Landthaler H. Quality-switched ruby laser treatment of solar lentigines and Becker's nevus: a histopathological and immunohistochemical study. *Dermatology* 1997; **194**: 338–43.
46 Nanni CA, Alster TS. Treatment of a Becker's naevus using a 694-nm long-pulsed ruby laser. *Dermatol Surg* 1998; **24**: 1032–4.
47 Trelles MA, Allones I, Moreno-Arias GA, Velez M. Becker's naevus: a comparative study between erbium:YAG and Q-switched neodymium:YAG; clinical and histopathological findings. *Br J Dermatol* 2005; **152**: 308–13.
48 Tedeschi A, Dall'Oglio F, Micali G *et al*. Corrective camouflage in pediatric dermatology. *Cutis* 2007; **79**: 110–2.

Inflammatory epidermal naevi

Inflammatory linear verrucous epidermal naevus (ILVEN) and CHILD naevus present at or soon after birth and usually persist lifelong. They can thus be distinguished from naevoid variants of inflammatory dermatoses which occur later and often resolve, including linear lichen planus, naevoid psoriasis, lichen striatus and adult Blaschkitis. However, all comprise hyperkeratotic lesions following Blaschko's lines, with histological evidence of inflammation. Probably all reflect genetic mosaicism, the former for potentially lethal dominant mutations rescued by mosaicism, and the latter for multifactorial dermatoses with an autosomal dominant component.

Inflammatory linear verrucous epidermal naevus

Synonym
- Dermatitic epidermal naevus

Definition. A pruritic, erythematous scaly lesion following Blaschko's lines [1].

Aetiology. ILVEN is probably due to mosaicism for a dominant mutation, as yet unidentified, which would be lethal if it affected all cells and is 'rescued' by mosaicism [2]. More recently, Happle [3] has suggested that linear skin disorders such as ILVEN might reflect the action of a retroviral transposable element ('retrotransposon') that is partly expressed and partly silenced at an early developmental stage. ILVEN is usually sporadic, in keeping with both hypotheses, but there have been reports of familial cases, including two in which mother and daughter were affected [4,5] and one involving mother, two sons and (reportedly) maternal grandfather [6]. Two cases in patients positive for human immunodeficiency virus 1 (HIV-1) [7], suggested clonal dysregulation of growth triggered by infection. However, the histology of these two lesions resembled psoriasis, which is known to be associated with HIV infection. Absent involucrin expression in the parakeratotic epidermis has been reported, a finding that appears to distinguish ILVEN from psoriasis [8].

Pathology. The characteristic histology shows columns of hypergranulosis with orthokeratotic hyperkeratosis alternating with equally well-defined columns of agranulosis and parakeratotic hyperkeratosis [9]. Other cases simply show a rather psoriasiform chronic eczema. Spongiosis is occasionally seen. An associated upper dermal lymphohistiocytic inflammatory infiltrate is regularly present.

Clinical features. About 75% of ILVENs appear during the first 5 years of life, most often in the first 6 months, although later onset has been recorded [4,5,10,11]. About 25% extend beyond their initial presentation, usually over a few months, but in one case over 9 years [12]. They are characterized by pruritus, which may be intense. The lesions are linear, most commonly on a limb, and comprise eczematous or psoriasiform papules (Fig. 18.4). ILVEN can be of any length, occasionally extending the whole length of a limb. As with other epidermal naevi, nail dystrophy may occur when the nail fold is affected [13]. Occasionally, ILVEN is bilateral and widespread [13–15]. Occasional reports of limb reduction anomalies associated with ILVEN on the adjacent skin have led to the suggestion that ILVEN represents a limited form of CHILD naevus, and that ILVEN and CHILD would more appropriately be named, respectively, PEN and PENCIL, indicating *p*soriasiform *e*pidermal *n*aevus with or without *c*ongenital *i*psilateral *l*imb defects [16]. In one case, ILVEN on the scrotum and penis was associated with ipsilateral undescended testicle [17]. A report of two girls with ILVEN and arthritis suggested a new association [18], but linear psoriasis with psoriatic arthropathy seems a more likely diagnosis for their symmetrical, distal, methotrexate-responsive arthritis; skin histology was not reported.

Although generally persistent and resistant to treatment, some lesions have been reported to resolve spontaneously [10].



Fig. 18.4 Inflammatory linear verrucous epidermal naevus on the posterior thigh.

Differential diagnosis. Earlier reports confused ILVEN with naevoid psoriasis, and with epidermal naevi in which psoriasis had developed as an isomorphic phenomenon [19–22]. Several patients have been reported in whom naevoid psoriasis and ILVEN both appeared to be present [23–25]. Transient inflammation of an ILVEN coinciding with an outbreak of guttate psoriasis probably reflects koebnerization of the ILVEN by psoriasis [12,25,26]. ILVEN can be distinguished from true naevoid psoriasis by pruritus and lack of response to antipsoriatic treatments [23,27]. Sodium dodecyl sulphate polyacrylamide gel electrophoresis (SDS-PAGE) has identified stratum corneum fibrous polypeptide patterns distinct from those seen in psoriasis [28,29]. In ILVEN lesions, Vissers *et al.* found increased keratin 10 expression and reduced Ki-67, CD4, CD8, CD450RO, CD2, CD25, CD94 and CD161 positive cells compared with psoriasis; a case of ILVEN with psoriasis was histologically intermediate [30]. Lichen striatus is distinguished by its rapid development, generally after the first year of life, by its relative lack of pruritus, by its more lichenoid clinical and histological features, and, eventually, by its spontaneous involution. The distinction between CHILD syndrome and ILVEN is uncertain [16,31,32]. An ILVEN-like lesion present for 6 months on one arm of an 11-year-old boy showed features of mycosis fungoides histologically [33].

Treatment. ILVEN is notoriously resistant to treatment, although occasionally spontaneous resolution occurs. Potent topical corticosteroids applied under occlusion, or intralesional steroid injections, provide little more than temporary symptomatic relief [11]. Similarly, topical retinoids appear to provide no benefit [34]. Successful treatment with dithranol [23] suggested that the true diagnosis was naevoid psoriasis. Calcipotriol or tacalcitol in some cases merely reduce the redness and itching, while in others have produced prolonged clearance [35–39]. Calcitriol used for 8 months completely cleared a lesion on the leg [40]. A lesion on the leg of an 11-year-old girl, that had proved resistant to topical steroids alone, resolved completely with tacrolimus and fluocinonide under occlusion for 2 weeks, then without occlusion for 8 weeks, and remained clear 2 years later; part of the lesion extending on to the foot responded less well [41]. Effective systemic treatments have included acitretin [42] and etanercept [43].

Cryotherapy may be a reasonable approach, particularly for smaller lesions [44]. Surgical excision tends to be followed by rapid recurrence unless a generous depth of underlying dermis is removed [13,45]. Successful treatment has been reported with the flashlamp-pumped pulsed tuneable dye laser [46]. ILVENs treated with the carbon dioxide resurfacing laser have remained clear for up to 2 years of follow-up [47–49], but this laser is less effective for ILVEN than for non-inflammatory verrucous epidermal naevi [49].

References

1 Altman J, Mehregan AH. Inflammatory linear verrucose epidermal nevus. *Arch Dermatol* 1971; **104**: 385–9.

2 Happle R. Lethal genes surviving by mosaicism: a possible explanation for sporadic birth defects involving the skin. *J Am Acad Dermatol* 1987; **16**: 899–906.
3 Happle R. Transposable elements and the lines of Blaschko: a new perspective. *Dermatology* 2002; **204**: 4–7.
4 Hamm H, Happle R. Inflammatory linear verrucous epidermal nevus (ILVEN) in a mother and her daughter. *Am J Med Genet* 1986; **24**: 685–90.
5 Goldman K, Don PC. Adult onset of inflammatory linear epidermal nevus in a mother and her daughter. *Dermatology* 1994; **189**: 170–2.
6 Alsaleh QA, Nanda A, Hassab-el-Naby MM, Hsakr MF. Familial linear verrucous epidermal naevus (ILVEN). *Int J Dermatol* 1994; **33**: 52–4.
7 Welch M, Smith KJ, Skelton HG *et al*. Immunohistochemical features in inflammatory linear verrucous epidermal nevi suggest a distinctive pattern of clonal dysregulation of growth. *J Am Acad Dermatol* 1993; **29**: 242–8.
8 Ito M, Shimuzu N, Fujiwara H *et al*. Histopathogenesis of inflammatory linear verrucous epidermal naevus. *Arch Dermatol Res* 1991; **283**: 491–9.
9 Dupre A, Christol B. Inflammatory linear verrucose epidermal nevus: a pathologic study. *Arch Dermatol* 1977; **113**: 767–9.
10 Hodge SJ, Barr JM, Owen LG. Inflammatory linear verrucose epidermal nevus. *Arch Dermatol* 1978; **114**: 436–8.
11 Morag C, Metzker A. Inflammatory linear epidermal nevus: report of seven new cases and review of the literature. *Pediatr Dermatol* 1985; **3**: 15–8.
12 Lee SH, Rogers M. Inflammatory linear verrucous epidermal naevi: a review of 23 cases. *Australas J Dermatol* 2001; **42**: 252–6.
13 Landwehr AJ, Starinck TM. Inflammatory linear verrucous epidermal naevus. *Dermatologica* 1983; **166**: 107–9.
14 Cheesbrough MJ, Kilby PE. The inflammatory linear verrucous epidermal naevus: a case report. *Clin Exp Dermatol* 1978; **3**: 293–8.
15 Dupre A, Christol B. Naevus épidermique verruqueux inflammatoire linéaire (NEVIL) bilatéral avec localisation labiale et lésions histologiques à minima. *Ann Dermatol Vénéréol* 1977; **104**: 163–4.
16 Moss C, Burn J. CHILD + ILVEN = PEN or PENCIL. *J Med Genet* 1990; **27**: 390–1.
17 Oskay T, Kutluay L. Inflammatory linear verrucous epidermal naevus associated with ipsilateral undescended testicle. *Clin Exp Dermatol* 2003; **28**: 557–8.
18 Al-Enezi S, Huber AM, Krafchik BR, Laxer RM. Inflammatory verrucous epidermal nevus and arthritis: a new association. *J Pediatr* 2001; **138**: 602–4.
19 Bennett RG, Burns L, Wood SG. Systematised epidermal nevus: a determinant for the localisation of psoriasis. *Arch Dermatol* 1973; **108**: 705–7.
20 Bondi EE. Psoriasis overlying an epidermal nevus. *Arch Dermatol* 1979; **115**: 624–5.
21 Goujon C, Pierini AM, Thivolet J. Le psoriasis linéaire, existe-t-il? *Ann Dermatol Vénéréol* 1981; **108**: 643–50.
22 Sugai T, Shimotoge M, Saito T. Psoriasis and systematized epidermal nevus. *Arch Dermatol* 1970; **102**: 656–60.
23 De Mare S, Van der Kerhof PCM, Happle R. Dithranol in the treatment of inflammatory linear verrucous epidermal nevus. *Acta Dermatol Venereol (Stockh)* 1989; **69**: 77–80.
24 Oram Y, Arisoy AE, Gurer I *et al*. Bilateral inflammatory linear verrucous epidermal nevus associated with psoriasis. *Cutis* 1996; **57**: 275–8.
25 Menni S, Restano L, Gianotti R, Boccardi D. Inflammatory linear verrucous epidermal nevus (ILVEN) and psoriasis in a child? *Int J Dermatol* 2000; **39**: 30–2.
26 Hofer T. Does inflammatory linear verrucous epidermal nevus represent a segmental type 1/type 2 mosaic of psoriasis? *Dermatology* 2006; **212**: 103–7.
27 Atherton DJ, Kahana M, Russell-Jones R. Naevoid psoriasis. *Br J Dermatol* 1989; **120**: 837–41.
28 Adrian RM, Baden HP. Analysis of epidermal fibrous proteins in inflammatory linear verrucous epidermal nevus. *Arch Dermatol* 1980; **116**: 1179–80.
29 Bernhard JD, Owen WR, Steinman HK *et al*. Inflammatory linear verrucous epidermal nevus—epidermal protein analysis in four patients. *Arch Dermatol* 1984; **120**: 214–5.
30 Vissers WH, Muys L, Erp PE *et al*. Immunohistochemical differentiation between inflammatory linear verrucous epidermal nevus (ILVEN) and psoriasis. *Eur J Dermatol* 2004; **14**: 216–20.
31 Golitz LE, Weston WL. Inflammatory linear verrucous epidermal nevus: association with epidermal nevus syndrome. *Arch Dermatol* 1979; **115**: 1208–9.
32 Grosshans E, Laplanche G. Verruciform xanthoma or xanthomatous transformation of inflammatory epidermal nevus? *J Cutan Pathol* 1981; **8**: 382–4.
33 Jang JG, Sim HJ, Kim SH *et al*. Mycosis fungoides mimicking inflammatory linear verrucous epidermal nevus. *J Eur Acad Dermatol Venereol* 2004; **18**: 218–20.
34 Rulo HFC, Van der Kerkhof PCM. Treatment of inflammatory linear verrucous epidermal nevus. *Dermatologica* 1991; **182**: 112–4.
35 Micali G, Nasca MR, Musumeci ML. Effect of topical calcipotriol on inflammatory linear verrucous epidermal nevus. *Pediatr Dermatol* 1995; **12**: 386–7.
36 Mitsuhashi Y, Katagiri Y, Kondo S. Treatment of inflammatory linear verrucous epidermal naevus with topical vitamin D_3. *Br J Dermatol* 1997; **136**: 132–48.
37 Gatti S, Carrozzo AM, Orlandi A, Nini G. Treatment of inflammatory linear verrucous epidermal naevus with calcipotriol. *Br J Dermatol* 1995; **132**: 837–9.
38 Zvulunov A, Grunwald MH, Halvy S. Topical calcipotriol for treatment of inflammatory linear verrucous epidermal nevus. *Arch Dermatol* 1997; **133**: 567–8.
39 Bohm I, Bieber T, Bauer R. Successful therapy of an ILVEN in a 7-year old girl with calcipotriol. *Hautarzt* 1999; **50**: 812–4.
40 Bohm M, Luger TA, Traupe H. Successful treatment of inflammatory linear verrucous epidermal naevus with topical natural vitamin D3 (calcitriol). *Br J Dermatol* 2003; **148**: 824–5.
41 Mutasim DF. Successful treatment of inflammatory linear verrucous epidermal nevus with tacrolimus and fluocinonide. *J Cutan Med Surg* 2006; **10**: 45–7.
42 Renner R, Rytter M, Sticherling M. Acitretin treatment of a systematized inflammatory linear verrucous epidermal naevus. *Acta Derm Venereol* 2005; **85**: 348–50.
43 Bogle MA, Sobell JM, Dover JS. Successful treatment of a widespread inflammatory verrucous epidermal nevus with etanercept. *Arch Dermatol* 2006; **142**: 401–2.
44 Dupre A, Christol B, Vialars ML. Naevus épidermique verruqueux inflammatoire linéaire (NEVIL). *Ann Dermatol Syphiligr* 1973; **100**: 261–74.
45 Lee BJ, Mancini AJ, Renucci J *et al*. Full-thickness surgical excision for the treatment of inflammatory linear verrucous epidermal nevus. *Ann Plast Surg* 2001; **47**: 285–92.
46 Alster TS. Inflammatory linear verrucous epidermal nevus: successful treatment with the 585 nm flashlamp-pumped pulsed tunable dye laser. *J Am Acad Dermatol* 1994; **31**: 513–4.
47 Ulkur E, Celikoz B, Yuksel F, Karagoz H. Carbon dioxide laser therapy for an inflammatory linear verrucous epidermal nevus: a case report. *Aesthetic Plast Surg* 2004; **28**: 428–30.
48 Molin L, Sarhammar G. Perivulvar inflammatory linear verrucous epidermal nevus (ILVEN) treated with CO_2 laser. *J Cutan Laser Ther* 1999; **1**: 53–6.
49 Michel JL, Has C, Has V. Resurfacing CO_2 laser treatment of linear verrucous epidermal nevus. *Eur J Dermatol* 2001; **11**: 436–9.

The CHILD naevus

Definition. CHILD is an acronym for *c*ongenital *h*emidysplasia with *i*chthyosiform naevus and *l*imb *d*efects [1]. Internal organs are often hypoplastic on the affected side. The CHILD naevus is the characteristic skin lesion observed in this disorder.

Aetiology. CHILD syndrome is an X-linked dominant trait, with a strong female predominance and antenatal lethality in males. Survival of a karyotypically normal male can be attributed to a somatic mutation on the X chromosome [2]. It is usually sporadic but mother-to-daughter transmission has been reported in several cases [3] with considerable variation in severity within families [4]. Initially it was thought to be allelic to X-linked dominant Conradi–Hünermann syndrome. Both conditions share the clinical features of linear scaling and asymmetric limb reductions, with peroxisomal deficiency in fibroblasts from involved areas of skin [5] and elevated plasma 8-dehydrocholesterol and 8(9)-cholesterol levels [6]. Grange *et al*. [6] indeed found a nonsense mutation in the X-linked dominant Conradi–Hünermann syndrome gene, 3β-hydroxysteroid-δ8,δ7 isomerase, or emopamil binding protein

(EBP) at Xp11.22–23 , in a patient with CHILD syndrome. However, this finding has not been repeated, and Grange's patient may in fact have had X-linked dominant Conradi–Hünermann syndrome, a diagnosis in keeping with improvement in her ichthyosis. Simultaneously, Konig *et al.* [7] found, in both sporadic and familial patients with CHILD syndrome, mutations in *NSDHL* (NAD(P)H steroid dehydrogenase-like protein) gene at Xq28. Several further reports have confirmed this as the CHILD syndrome gene [8–10].

NSDHL functions upstream of EBP in cholesterol biosynthesis. CHILD syndrome and X-linked Conradi–Hünermann syndrome are examples of inborn errors of cholesterol biosynthesis, manifesting profound abnormalities of early embryogenesis. Smith–Lemli–Opitz syndrome is another example, and these disorders demonstrate the importance of cholesterol in early embryonic development [11,12], known to be via the hedgehog signalling pathway. *NSDHL* mutations in mice produce the 'bare patches' and 'striated' phenotypes [13]. Microarray studies of mutant mouse fibroblasts show changes in expression of numerous other cholesterol-related genes [14]. Male lethality in mice is associated with a thinner placenta with fewer fetal vessels [15]. The extreme lateralization of CHILD syndrome contrasts with symmetry of X-linked dominant Conradi–Hünermann syndrome and has not yet been explained satisfactorily; it is curiously not a feature of the female mouse *NSHDL* mutants [8]. CHILD syndrome might be an extreme form of ILVEN, an alternative name covering the whole spectrum being PEN or PENCIL [16]. This idea has been contested by Happle [17]. It could now be tested, knowing the defect in CHILD syndrome.

Pathology. Light microscopy [18] shows marked acanthosis, and areas of parakeratosis within a largely orthokeratotic epidermis. There is exocytosis of neutrophils, with focal collections resembling Munro microabscesses. The dermis contains a patchy lymphohistiocytic infiltrate. Some biopsies, particularly those taken from flexural sites, may show enlarged dermal papillae containing foamy lipid-laden histiocytes (verruciform xanthoma) [17,19,20]. Although verruciform xanthoma is very characteristic of CHILD naevi, it can also occasionally be seen in severe dystrophic epidermolysis bullosa and pemphigus vulgaris, and it may also be a feature of biopsies taken from the mouth, vulva or penis. Two of seven verruciform xanthomas showed mutations in *NSDHL* [21]; not all exons were examined.

Ultrastructurally [18,22], many corneocytes contain lipid vacuoles. Vesicular structures, probably abnormal lamellar granules, are seen in the intercellular spaces of the epidermis, and become more numerous as cornification progresses. Large intracytoplasmic vacuoles are seen within papillary dermal foamy cells [22]. Confocal microscopy localized tagged proteins encoded by mutant and wild-type *NSDHL* to lipid droplets as well as the endoplasmic reticulum [23,24].

Clinical features. Most affected individuals are female. CHILD naevi are usually present at birth, but occasionally first appear during the first few months of life or even later. Lesions may extend during life, and rarely regress. The lesions are generally asymptomatic, comprising well-circumscribed areas of erythema covered in waxy scales, sometimes with a verrucous surface. There is a marked preference for flexural areas (*ptychotropism*) [25], where oozing vegetations may develop. Squamous carcinoma has been reported [26]. Characteristically, lesions are confined or concentrated on one side of the body, with sharp midline demarcation. In more severe cases, one side of the body may be diffusely affected, usually but not always [27] with sparing of the face and the oral mucosa. Sometimes the distribution is more streaky, following Blaschko's lines, and sometimes both linear and diffuse unilateral patterns coexist in the same patient. Manifestations may be extremely mild, even confined to the skin of a single digit, when the diagnosis is only recognized in the presence of a severely affected proband [4]. Konig *et al.* [28] reported bilateral, almost symmetrical involvement in a woman with a novel missense mutation of *NSDHL*.

A wide variety of non-cutaneous anomalies have been reported in the CHILD syndrome [1,27,29,30]. Unilateral bone defects are particularly characteristic, and most likely to affect the long bones. The severity of limb lesions varies from hypoplasia of a few metacarpals or phalanges to complete absence of an entire limb. Hands or feet may be grossly deformed. Scoliosis may be present. In some cases, punctate epiphyseal calcifications have been shown radiologically in the first few months after birth; these disappear later.

Unilateral hypoplasia of the brain, cranial nerves or spinal cord may be present, with mental retardation, electroencephalogram (EEG) abnormalities and sensory defects.

Congenital cardiac defects may be present, and are perhaps the main cause of early death of children with CHILD syndrome. Other anomalies of the kidneys, lungs and other internal organs have been described.

Diagnosis. Naevoid psoriasis, ILVEN and epidermal naevus syndrome can be confused with CHILD syndrome. Psoriasis is less persistent and does not show waxy scales clinically or verruciform xanthoma histologically. In contrast to CHILD naevi, ILVEN does not show flexural preference, and tends to be exclusively linear. The distinction from epidermal naevus syndrome is perhaps semantic. CHILD syndrome when first delineated had to be distinguished from epidermal naevus syndrome as it was then understood [31]. More recently, Happle has reclassified CHILD syndrome as an epidermal naevus syndrome [32].

Treatment. CHILD naevi appear to be highly refractory to all treatment, except occasionally oral retinoids [3,26].

References

1 Happle R, Koch H, Lenz W. The CHILD syndrome: congenital hemidysplasia with ichthyosiform erythroderma and limb defects. *Eur J Pediatr* 1980; **134**: 27–33.

2 Happle R, Efendy I, Megahed M *et al*. CHILD syndrome in a boy. *Am J Med Genet* 1996; **62**: 192–4.

3 Happle R, Karlic D, Steijen PM. CHILD Syndrome bei Mutter und Tochter. *Hautarzt* 1990; **41**: 105–8.

4 Bittar M, Happle R, Grzeschik KH *et al*. CHILD syndrome in 3 generations: the importance of mild or minimal skin lesions. *Arch Dermatol* 2006; **142**: 348–51.

5 Emami S, Rizzo WB, Hanley KP *et al*. Peroxisomal abnormality in fibroblasts from involved skin of CHILD syndrome. *Arch Dermatol* 1992; **128**: 1213–22.

6 Grange DK, Kratz LE, Braverman NE, Kelley RI. CHILD syndrome caused by deficiency of 3β-hydroxysteroid-δ8,δ7 isomerase. *Am J Med Genet* 2000; **90**: 328–35.

7 Konig A, Happle R, Bornholdt D *et al*. Mutations in the *NSDHL* gene, encoding a 3β-hydroxysteroid dehydrogenase, cause CHILD syndrome. *Am J Med Genet* 2000; **90**: 339–46.
8 Hummel M, Cunningham D, Mullett CJ *et al*. Left-sided CHILD syndrome caused by a nonsense mutation in the NSDHL gene. *Am J Med Genet A* 2003; **122**: 246–51.
9 Kim CA, Konig A, Bertola DR *et al*. CHILD syndrome caused by a deletion of exons 6–8 of the NSDHL gene. *Dermatology* 2005; **211**: 155–8.
10 Bornholdt D, Konig A, Happle R *et al*. Mutational spectrum of NSDHL in CHILD syndrome. *J Med Genet* 2005; **42**: e17.
11 Porter FD. Human malformation syndromes due to inborn errors of cholesterol synthesis. *Curr Opin Pediatr* 2003; **15**: 607–13.
12 Herman GE. Disorders of cholesterol biosynthesis: prototypic metabolic malformation syndromes. *Hum Mol Genet* 2003; **12**: R75–88.
13 Liu XY, Dangel AW, Kelley RI *et al*. The gene mutated in bare patches and striated mice encodes a novel 3 β-hydroxysteroid dehydrogenase. *Nat Genet* 1999; **22**: 182–7.
14 Cunningham D, Swartzlander D, Liyanarachchi S *et al*. Changes in gene expression associated with loss of function of the NSDHL sterol dehydrogenase in mouse embryonic fibroblasts. *J Lipid Res* 2005; **46**: 1150–62.
15 Caldas H, Cunningham D, Wang X *et al*. Placental defects are associated with male lethality in bare patches and striated embryos deficient in the NAD(P)H Steroid Dehydrogenase-like (NSDHL) Enzyme. *Mol Genet Metab* 2005; **84**: 48–60.
16 Moss C, Burn J. CHILD + ILVEN = PEN or PENCIL. *J Med Genet* 1990; **27**: 390–1.
17 Happle R. CHILD naevus is not ILVEN. *J Med Genet* 1991; **28**: 214.
18 Hebert AA, Esterly NB, Holbrook KA, Hall JC. The CHILD syndrome: histologic and ultrastructural studies. *Arch Dermatol* 1987; **123**: 503–9.
19 Grosshans E, Laplanche G. Verruciform xanthoma or xanthomatous transformation of inflammatory epidermal nevus? *J Cutan Pathol* 1981; **8**: 382–4.
20 Zamora-Martinez E, Martin-Moreno L, Barat-Cascante A *et al*. Another CHILD syndrome with xanthomatous pattern. *Dermatologica* 1990; **180**: 263–6.
21 Mehra S, Li L, Fan CY, Smoller B *et al*. A novel somatic mutation of the 3beta-hydroxysteroid dehydrogenase gene in sporadic cutaneous verruciform xanthoma. *Arch Dermatol* 2005; **141**: 1263–7.
22 Ishibashi M, Matsuda F, Oka H, Ishiko A. Abnormal lamellar granules in a case of CHILD syndrome. *J Cutan Pathol* 2006; **33**: 447–53.
23 Caldas H, Herman GE. NSDHL, an enzyme involved in cholesterol biosynthesis, traffics through the Golgi and accumulates on ER membranes and on the surface of lipid droplets. *Hum Mol Genet* 2003; **12**: 2981–91.
24 Ohashi M, Mizushima N, Kabeya Y, Yoshimori T. Localization of mammalian NAD(P)H steroid dehydrogenase-like protein on lipid droplets. *J Biol Chem* 2003; **278**: 36819–29.
25 Happle R. Ptychotropism as a cutaneous feature of the CHILD syndrome. *J Am Acad Dermatol* 1990; **23**: 763–6.
26 Jacyk WK, La Cock A. Squamous cell carcinoma arising in CHILD syndrome. *J Eur Acad Dermatol Venereol* 2006; **20**: 311–3.
27 Moulin G, Barrut D, Franc MP *et al*. CHILD syndrome: naevus épidermique et hémidysplasie corporelle hypoplasique homolatérale. *Ann Dermatol Vénéréol* 1982; **109**: 793–4.
28 Konig A, Happle R, Fink-Puches R *et al*. A novel missense mutation of *NSDHL* in an unusual case of CHILD syndrome showing bilateral, almost symmetric involvement. *J Am Acad Dermatol* 2002; **46**: 594–6.
29 Laplanche G, Grosshans E, Gabriel-Robez O *et al*. Hyperplasie épidermique et hémidysplasie corporelle hypoplasique congénitales homolatérales (démembrement du syndrome de Solomon). *Ann Dermatol Vénéréol* 1980; **107**: 729–39.
30 Christiansen JV, Petersen HO, Sogaard H. The CHILD syndrome—congenital hemidysplasia with ichthyosiform erythroderma and limb defects. *Acta Derm Venereol (Stockh)* 1984; **64**: 165–8.
31 Golitz LE, Weston WL. Inflammatory linear verrucous epidermal nevus: association with epidermal nevus syndrome. *Arch Dermatol* 1979; **115**: 1208–9.
32 Happle R. Epidermal nevus syndromes. *Semin Dermatol* 1995; **14**: 111–21.

Other naevoid epidermal disorders

Several generalized dermatoses occasionally follow Blaschko's lines, probably reflecting a clonal 'susceptibility mutation'. Linear lichen planus, psoriasis, Darier's disease, Hailey–Hailey disease, porokeratosis, atrophoderma of Moulin, and 'adult Blaschkitis' or BLAISE (*B*laschko *l*inear *a*cquired *i*nflammatory *s*kin *e*ruption) are described below. Linear lichen nitidis [1], lichen striatus (eczema) [2], segmental vitiligo [3] and linear morphoea [4] are discussed elsewhere in relation to the appropriate generalized disorder. The following have also been reported in a linear or naevoid distribution: lupus erythematosus [5], fixed drug eruption [6], chronic graft-versus-host disease [7] and mycosis fungoides [8].

References

1 Prigent F, Cavelier-Balloy B, Lemarchand-Venencie F, Civatte J. Linear lichen nitidis. *Ann Dermatol Vénéréol* 1989; **116**: 814–5.
2 Zhang Y, McNutt NS. Lichen striatus: histological, immunohistochemical and ultrastructural study of 37 cases. *J Cutan Pathol* 2001; **28**: 65–71.
3 Hann SK, Lee HJ. Segmental vitiligo: clinical findings in 208 patients. *J Am Acad Dermatol* 1996; **35**: 671–4.
4 Hauser C, Skaria A, Harms M, Saurat JH. Morphoea following Blaschko's lines. *Br J Dermatol* 1996; **134**: 594–5.
5 Heid E, Grosshans E, Gonda J *et al*. Eruption Blaschko lineaire avec biologie lupique. *Ann Dermatol Vénéréol* 1996; **123**: 331–3.
6 Happle R, Effendy I. Coexisting linear and disseminated drug eruption: a clinical clue to the understanding of the genetic basis of drug eruptions. *Eur J Dermatol* 2001; **11**: 89.
7 Beers B, Kalish RS, Kaye VN, Dahl MV. Unilateral linear lichenoid eruption after bone marrow transplantation: an unmasking of tolerance to an abnormal keratinocyte clone? *J Am Acad Dermatol* 1993; **28**: 888–92.
8 Jang JG, Sim HJ, Kim SH *et al*. Mycosis fungoides mimicking inflammatory linear verrucous epidermal nevus. *J Eur Acad Dermatol Venereol* 2004; **18**: 218–20.

Linear lichen planus

Some acquired linear lesions resemble lichen planus in all but their distribution [1,2]. They can occur at any age and resolve leaving post-inflammatory pigmentation. In some cases there is no history of preceding inflammatory lesions, and the appearance is indistinguishable from linear ashy dermatosis [3]. If linear lichen planus extends to the end of a digit there may be associated nail dystrophy, and similarly there may be mucous membrane involvement [4]. Linear lichen planus is sometimes mutifocal [5] and in one female recurred three times after successive deliveries [6]. Linear lichen planus affecting the left chest and shoulder and progressing down the left arm was reported in a patient with metastatic carcinoma of the left breast [7]. Linear lichen plano-pilaris has also been reported, usually on the face [8].

Histologically, linear lichen planus shows a lichenoid band-like lymphohistiocytic infiltrate at the dermal–epidermal junction, plus Civatte bodies and dermal melanophages [1,2]. Severe epidermal apoptosis has been observed [9]. It seems likely that linear lichen planus represents lichen planus localized to Blaschko's lines by a clonal 'susceptibility mutation'.

References

1 Brownstein MH, Silverstein L, Lefing W. Lichenoid epidermal nevus: 'linear lichen planus'. *J Am Acad Dermatol* 1989; **20**: 913–5.
2 Kabbash C, Laude TA, Weinberg JM, Silverberg NB. Lichen planus in the lines of Blaschko. *Pediatr Dermatol* 2002; **19**: 541–5.
3 Yokozeki H, Ueno M, Komori K, Nishioka K. Multiple linear erythema dyschromicum perstans (ashy dermatosis) in the lines of Blaschko. *Dermatology* 2005; **210**: 356–7.
4 Hartl C, Steen KH, Wegne H *et al*. Unilateral linear lichen planus with mucous membrane involvement. *Acta Derm Venereol (Stockh)* 1999; **79**: 145–6.

5 Long CC, Finlay AY. Multiple linear lichen planus in the lines of Blaschko. *Br J Dermatol* 1996; **136**: 275–6.
6 Krasowska D, Pietrzak A, Lecewicz-Torun B. Unilateral multiple linear lichen planus following the Blaschko lines recurring after deliveries. *Dermatology* 2001; **202**: 340.
7 Sciallis GF, Loprinzi CL, Davis MD. Progressive linear lichen planus and metastatic carcinoma. *Br J Dermatol* 2005; **152**: 399–401.
8 Baker K, Pehr K. Linear lichen planopilaris of the trunk: first report of a case. *J Cutan Med Surg* 2006; **10**: 136–8.
9 Akagi A, Ohnishi Y, Tajima S, Ishibashi A. Linear hyperpigmentation with extensive epidermal apoptosis: a variant of linear lichen planus pigmentosus? *J Am Acad Dermatol* 2004; **50**: S78–80.

Naevoid psoriasis

Psoriasis occasionally occurs in a 'naevoid' form [1], possibly reflecting mosaicism for a gene responsible for psoriasis. Linear psoriasis coexisting with generalized psoriasis may represent loss of heterozygosity for a psoriasis gene, or invasion of a verrucous epidermal naevus by psoriasis as a result of the isomorphic phenomenon [2–5]. Onset is usually during childhood, but some otherwise typical cases have presented at birth [6–8]. The lesions are clinically indistinguishable from ordinary psoriasis other than in their distribution, and are histologically identical. Linear psoriasis can be associated with nail pits [9] and psoriatic arthritis [10]. This condition responds to antipsoriatic therapy such as ultraviolet radiation [9] or dithranol [11]. A boy with extensive linear psoriasis associated with severe psoriatic arthritis showed dramatic improvements of joints but not skin with infliximab, while neither responded to etanercept [10]. Linear psoriasis has been reported in association with PEODDN [12] and can be distinguished from ILVEN [13] by its minimal pruritus and therapeutic responsiveness.

References

1 Atherton DJ, Kahana M, Russell-Jones R. Naevoid psoriasis. *Br J Dermatol* 1989; **120**: 837–41.
2 Bennett RG, Burns L, Wood SG. Systematised epidermal nevus: a determinant for the localisation of psoriasis. *Arch Dermatol* 1973; **108**: 705–7.
3 Bondi EE. Psoriasis overlying an epidermal nevus. *Arch Dermatol* 1979; **115**: 624–5.
4 Goujon C, Pierini AM, Thivolet J. Le psoriasis linéaire, existe-t-il? *Ann Dermatol Vénéréol* 1981; **108**: 643–50.
5 Sugai T, Shimotoge M, Saito T. Psoriasis and systematized epidermal nevus. *Arch Dermatol* 1970; **102**: 656–60.
6 Al-Fouzan AS, Hassab-el-Naby HMM, Nanda A. Congenital linear psoriasis: a case report. *Pediatr Dermatol* 1990; **7**: 303–6.
7 Lehners-Weber C, de la Brassinne M, Dezfoulian B *et al*. Congenital psoriasis following the lines of Blaschko. *Pediatr Dermatol* 1996; **13**: 219–21.
8 Ghorpade A. Linear naevoid psoriasis along lines of Blaschko. *J Eur Acad Dermatol Venereol* 2004; **18**: 726–7.
9 Saraswat A, Sandhu K, Shukla R, Handa S. Unilateral linear psoriasis with palmoplantar, nail, and scalp involvement. *Pediatr Dermatol* 2004; **21**: 70–3.
10 Rott S, Kuster RM, Mrowietz U. Successful treatment of severe psoriatic arthritis with infliximab in an 11-year-old child suffering from linear psoriasis along lines of Blaschko. *Br J Dermatol* 2007; **157**: 191–2.
11 De Mare S, Van der Kerhof PCM, Happle R. Dithranol in the treatment of inflammatory linear verrucous epidermal nevus. *Acta Dermatol Venereol (Stockh)* 1989; **69**: 77–80.
12 Yu HJ, Ko JY, Kwon HM, Kim JS. Linear psoriasis with porokeratotic eccrine ostial and dermal duct nevus. *J Am Acad Dermatol* 2004; **50**: S81–3.
13 Vissers WH, Muys L, Erp PE *et al*. Immunohistochemical differentiation between inflammatory linear verrucous epidermal nevus (ILVEN) and psoriasis. *Eur J Dermatol* 2004; **14**: 216–20.

Linear Darier's disease

Synonym
- Acantholytic dyskeratotic epidermal naevus

Several patients have been reported with acantholytic epidermal naevi comprising crusted keratotic papules, clinically and histologically resembling Darier's disease, but with no family history of Darier's disease [1–10]. Such naevi usually appear after the age of 20 years. The lesions can extend over many years and are aggravated by UV exposure [1,3]. If the affected area includes the nails, typical nail changes of Darier's disease may occur [4], and if the hands are affected, pits and keratoses may be observed within the involved zone [4]. One patient developed herpes zoster in the same distribution [11].

The suggestion that such naevi represent mosaicism for Darier's disease has now been confirmed by finding a mutation in the Darier's disease gene *ATP2A2* in the naevus, but not in unaffected skin [7]. The existence of a 'non-Darier' congenital linear acantholyitic naevus remains uncertain [12]. Mutation analysis of *ATP2A2* was negative in DNA from involved skin in one such case [13].

Treatment is as for other linear epidermal naevi. It appears that topical retinoic acid may be useful [1], and it would be anticipated that oral acitretin might be of value where the distribution is extensive.

References

1 Starink TM, Woerdeman MJ. Unilateral systematised keratosis follicularis: a variant of Darier's disease or an epidermal naevus (acantholytic dyskeratotic epidermal naevus)? *Br J Dermatol* 1981; **105**: 207–14.
2 Thomas I, Shockman J, Epstein JD. Linear keratosis follicularis: a specific entity? *J Am Acad Dermatol* 1989; **20**: 1122–3.
3 Van der Wegen-Keijser MH, Prevoo RMLH, Bruynzeel DP. Acantholytic dyskeratotic epidermal naevus in a patient with guttate psoriasis on PUVA therapy. *Br J Dermatol* 1991; **124**: 603–5.
4 Munro CS, Cox NH. An acantholytic dyskeratotic epidermal naevus with other features of Darier's disease on the same side of the body. *Br J Dermatol* 1992; **127**: 168–71.
5 Cambiaghi S, Brusasco A, Grimalt R, Caputo R. Acantholytic dyskeratotic epidermal naevus as a mosaic form of Darier's disease. *J Am Acad Dermatol* 1995; **32**: 284–6.
6 O'Malley MP, Haake A, Goldsmith L, Berg D. Localised Darier disease. Implications for genetic studies. *Arch Dermatol* 1997; **133**: 1134–8.
7 Sakuntabhai A, Dhitavat J, Burge S, Hovnanian A. Mosaicism for *ATP2A2* mutations causes segmental Darier's disease. *J Invest Dermatol* 2000; **115**: 1144–7.
8 Goldberg EI, Lefkovits AM, Sapadin AN. Zosteriform Darier's disease versus acantholytic dyskeratotic epidermal nevus. *Mt Sinai J Med* 2001; **68**: 339–41.
9 Reese DA, Paul AY, Davis B. Unilateral segmental Darier disease following Blaschko lines: a case report and review of the literature. *Cutis* 2005; **76**: 197–200.
10 Gilaberte M, Puig L, Vidal D, Alomar A. Acantholytic dyskeratotic naevi following Blaschko's lines: a mosaic form of Darier's disease. *J Eur Acad Dermatol Venereol* 2003; **17**: 196–9.
11 Abraham S, Jones A, Toutous-Trellu L *et al*. Linear Darier disease with herpes zoster superinfection treated successfully by brivudine. *Br J Dermatol* 2006; **154**: 365–7.
12 Bergua P, Puig L, Fernandez-Figueras MT *et al*. Congenital acantholytic dyskeratotic dermatosis: localized Darier disease or disseminated benign papular acantholytic dermatosis? *Pediatr Dermatol* 2003; **20**: 262–5.
13 Huh WK, Fujiwara K, Takahashi H, Kanitakis J. Congenital acantholytic dyskeratotic epidermal naevus following Blaschko's lines versus segmental Darier's disease. *Eur J Dermatol* 2007; **17**: 130–2.

Linear Hailey–Hailey disease

Synonym
- Relapsing linear acantholytic dermatosis

A distinctive form of epidermal naevus has been reported, in which well-defined linear erythematous plaques demonstrate vesiculation, erosion and crusting, and the typical histological features of benign familial chronic pemphigus (Hailey–Hailey disease) [1,2]. This type of naevus has an early onset, and a highly characteristic course, with periods of spontaneous improvement followed by relapse. It is likely that this represents mosaicism for a mutation in the Hailey–Hailey disease gene *ATP2C1* [3].

A 5-year-old patient apparently inherited the condition from her mother and grandmother, in whom the disease was manifest only in the perianal area [1]. A possible explanation was that the Hailey–Hailey mutation was transmitted in the usual autosomal dominant manner, with limited flexural disease presenting in early adult life, while the child was mosaic for a loss-of-heterozygosity (Happle type 2 mosaicism [4]), and accordingly developed more severe and earlier onset disease in a linear distribution. This patient later developed typical symmetrical flexural disease, and molecular analysis confirmed a germline *ATP2C1* mutation with loss of heterozygosity in the linear lesion [5].

A single case of a distinctive type of keratinocyte naevus has been reported as 'naevus corniculatus' [6]. Clinically, the naevus featured filiform and horn-like keratoses, and giant comedones. Histologically, the lesion showed acantholytic changes more closely resembling those seen in Hailey–Hailey disease than in Darier's disease.

References

1 Vakilzadeh F, Kolde G. Relapsing linear acantholytic dermatosis. *Br J Dermatol* 1985; **112**: 349–55.
2 Duschet P, Happle R, Schwarz T, Gschnait F. Relapsing linear acantholytic dermatosis. *J Am Acad Dermatol* 1995; **33**: 920–2.
3 Sudbrak R, Brown J, Dobson-Stone C *et al.* Hailey–Hailey disease is caused by mutations in *ATP2C1* encoding a novel Ca^2 pump. *Hum Mol Genet* 2000; **9**: 1131–40.
4 Happle R. A rule concerning the segmental manifestation of autosomal dominant skin disorders. *Arch Dermatol* 1997; **133**: 1505–9.
5 Poblete-Gutierrez P, Wiederholt T, Konig A *et al.* Allelic loss underlies type 2 segmental Hailey-Hailey disease, providing molecular confirmation of a novel genetic concept. *J Clin Invest* 2004; **114**: 1467–74.
6 Happle R, Steijlen PM, Kolde J. Naevus corniculatus: a new acantholytic disorder. *Br J Dermatol* 1990; **122**: 107–12.

Linear porokeratosis

Definition. This naevus, distributed along Blaschko's lines, is characterized by annular plaques clinically and histologically indistinguishable from the lesions of generalized porokeratosis [1].

Aetiology. Linear porokeratosis probably reflects mosaicism for a gene responsible for generalized porokeratosis. This idea is supported by the fact that the generalized forms of porokeratosis (porokeratosis of Mibelli, disseminated superficial actinic porokeratosis (DSAP), and porokeratosis plantaris palmaris et disseminata) can be inherited as autosomal dominant genes, whereas the linear variant usually occurs sporadically. The report of linear porokeratosis in monozygotic twins [2] can be reconciled with the idea of mosaicism by postulating that a somatic mutation in the porokeratosis gene occurred before the twinning division, so that the aberrant clone was present in both embryos. Reports of pre-existing linear porokeratosis in patients later developing DSAP [3–9], and the occasional occurrence of linear porokeratosis in the children or siblings of patients with DSAP [3,4,9,10] can be explained by loss of heterozygosity for this dominant gene, that is Happle type 2 mosaicism [7,11]. According to this hypothesis, an individual with inherited generalized porokeratosis undergoes a somatic mutation affecting the normal allele resulting in clonal loss of heterozygosity. The resultant line contrasts with the background skin because it has 'double the dose' of porokeratosis. Skin cancers in porokeratosis are particularly associated with the linear variant [12–15], in keeping with Happle's suggestion of loss of heterozygosity [11]. The role of *p53* is uncertain: overexpression of *p53* has been reported in linear porokeratosis [16,17] and in a superimposed squamous carcinoma, but not in the adjacent porokeratosis [14].

Generalized porokeratosis can be provoked by immune suppression [1]. Hunt *et al.* [18], however, reported exacerbations of linear porokeratosis during episodes of liver failure, and improvement following transplantation.

Clinical features. The lesions of linear porokeratosis comprise grouped and confluent hyperkeratotic plaques, each with a fine, rounded, annular rim and an atrophic centre. Lesions may be hyper- or hypopigmented and/or erythematous, and are disposed in an interrupted linear fashion along Blaschko's lines. They may be widespread [19] and can occur on the soles [20] or face [21]. Lesions affecting a distal limb may be associated with nail dystrophy such as pterygium and longitudinal ridging [19,22,23], and in one case there was bony narrowing of the digit [23]. The lesions are often present at birth, when they may be ulcerated [24]. Occasional spontaneous resolution has been described [25,26], but generally the lesions are lifelong, with increasing hyperkeratosis. There is a predisposition to skin cancer within the lesions, including squamous cell carcinomas [12] which may be multiple [15], and Bowen's disease [27].

Management. A variety of treatments has been used with variable success; of these the most consistently successful have been surgical excision [12,28] and ablation with the carbon dioxide laser [29]. Other helpful topical treatments have included cryotherapy [30], dermabrasion [28,31], 5-fluorouracil [32,33], tretinoin [33], 5% imiquimod [34], vitamin D analogues, urea [35], dithranol [2], and 0.05% tretinoin [19]. Many of these topical agents caused initial inflammation which was followed by resolution. Oral retinoids proved helpful in two cases [36,37], but etretinate in another case worsened the porokeratosis [38].

References

1 Schamroth JM, Zlotogorski A, Gilead L. Porokeratosis of Mibelli. Overview and review of the literature. *Acta Derm Venereol (Stockh)* 1997; **77**: 207–13.
2 Guillot P, Taieb A, Fontan I *et al.* Porokératose de Mibelli linéaire chez des jumelles monozygotes. *Ann Dermatol Vénéréol* 1991; **118**: 519–24.

3 Commens CA, Shumack SP. Linear porokeratosis in two families with disseminated superficial actinic porokeratosis. *Pediatr Dermatol* 1987; **4**: 209–14.
4 Dover JS, Phillips TJ, Burns DA *et al.* Disseminated superficial actinic porokeratosis: coexistence with other porokeratotic variants. *Arch Dermatol* 1986; **122**: 887–9.
5 Feldman SR, Crosby DL, Tomsick RS. Scaly atrophic lesions both scattered and in linear arrays. Disseminated superficial actinic porokeratosis in a patient with linear porokeratosis. *Arch Dermatol* 1991; **127**: 1219, 1222.
6 Suh DH, Lee HS, Kim SD *et al.* Coexistence of disseminated superficial porokeratosis in childhood with congenital linear porokeratosis. *Pediatr Dermatol* 2000; **17**: 466–8.
7 Freyschmidt-Paul P, Hoffmann R, Konig A, Happle R. Linear porokeratosis superimposed on disseminated superficial actinic porokeratosis: report of two cases exemplifying the concept of type 2 segmental manifestation of autosomal dominant skin disorders. *J Am Acad Dermatol* 1999; **41**: 644–7.
8 Suarez-Amor O, Pereiro-Ferreiros M, Ginarte M *et al.* Coexistence of linear porokeratosis and disseminated superficial actinic porokeratosis: a type 2 segmental manifestation. *Acta Derm Venereol (Stockh)* 2007; **87**: 363–4.
9 Boente Mdel C, López-Baró AM, Frontini Mdel V, Asial RA. Linear porokeratosis associated with disseminated superficial actinic porokeratosis: a new example of type II segmental involvement. *Pediatr Dermatol* 2003; **20**: 514–8.
10 Moreland ME, Wyre HW. Porokeratosis: two morphologic forms in one family. *Arch Dermatol* 1981; **117**: 245–6.
11 Happle R. Cancer proneness of linear porokeratosis may be explained by allelic loss. *Dermatology* 1997; **195**: 20–5.
12 Lozinski AZ, Fisher BK, Walter JB *et al.* Metastatic squamous cell carcinoma in linear porokeratosis of Mibelli. *J Am Acad Dermatol* 1987; **16**: 448–51.
13 Murata Y, Kumano K, Takai T. Type 2 segmental manifestation of disseminated superficial porokeratosis showing a systematized pattern of involvement and pronounced cancer proneness. *Eur J Dermatol* 2001; **11**: 191–4.
14 Anzai S, Takeo N, Yamaguchi T *et al.* Squamous cell carcinoma in a renal transplant recipient with linear porokeratosis. *J Dermatol* 1999; **26**: 244–7.
15 Curnow P, Foley P, Baker C. Multiple squamous cell carcinomas complicating linear porokeratosis. *Australas J Dermatol* 2003; **44**: 136–9.
16 Sasaki S, Urano Y, Nakagawa K *et al.* Linear porokeratosis with multiple squamous cell carcinomas: study of *p53* expression in porokeratosis and squamous carcinoma. *Br J Dermatol* 1996; **134**: 1151–2.
17 Quinn AG. *p21*Wafl/Cipl and *p53* expression in the skin—intertwined but not inseparable. *Br J Dermatol* 1999; **141**: 614–6.
18 Hunt SJ, Sharra WG, Abell E. Linear and punctate porokeratosis associated with end-stage liver disease. *J Am Acad Dermatol* 1991; **25**: 937–9.
19 Dervis E, Demirkesen C. Generalized linear porokeratosis. *Int J Dermatol* 2006; **45**: 1077–9.
20 Witkowski JA, Parish LC. Linear porokeratosis presenting as mosaic plantar warts. *Int J Dermatol* 1982; **21**: 40–1.
21 Zhang ZH, Xiang LH, Chen LJ *et al.* Congenital facial linear porokeratosis. *Clin Exp Dermatol* 2005; **30**: 361–2.
22 Chen HH, Liao YH. Onychodystrophy in congenital linear porokeratosis. *Br J Dermatol* 2002; **147**: 1272–3.
23 Tseng SS, Levit EK, Ilarda I *et al.* Linear porokeratosis with underlying bony abnormalities. *Cutis* 2002; **69**: 309–12.
24 Fisher CA, Leboit PE, Frieden I. Linear porokeratosis presenting as erosions in the newborn period. *Pediatr Dermatol* 1995; **12**: 318–22.
25 Bogaert MA, Hogan DJ. Linear porokeratosis in a 74-year-old woman. *J Am Acad Dermatol* 1991; **25**: 338.
26 Bogaert MA, Hogan DJ. Linear porokeratosis. *Int J Dermatol* 1993; **32**: 75–6.
27 Guenova E, Hoetzenecker W, Metzler G *et al.* Multicentric Bowen disease in linear porokeratosis. *Eur J Dermatol* 2007; **17**: 439–40.
28 Eyre WG, Carson WE. Linear porokeratosis of Mibelli. *Arch Dermatol* 1972; **105**: 426–9.
29 Barnett JH. Linear porokeratosis: treatment with the carbon dioxide laser. *J Am Acad Dermatol* 1986; **14**: 902–4.
30 Bhushan M, Craven NM, Beck MH, Chalmers RJ. Linear porokeratosis of Mibelli: successful treatment with cryotherapy. *Br J Dermatol* 1999; **141**: 389.
31 Cohen PR, Held JL, Katz B. Linear porokeratosis: successful treatment with diamond fraise dermabrasion. *J Am Acad Dermatol* 1990; **23**: 975–7.
32 Hubler WR, Michaelson JD, Knox JM. Linear porokeratosis. *Cutis* 1974; **14**: 61–4.
33 Grover C, Goel A, Nanda S *et al.* A case of extensive linear porokeratosis with evaluation of topical tretinoin versus 5-flourouracil as treatment modalities. *J Dermatol* 2005; **32**: 1000–4.
34 Ahn SJ, Lee HJ, Chang SE *et al.* Case of linear porokeratosis: successful treatment with topical 5% imiquimod cream. *J Dermatol* 2007; **34**: 146–7.
35 Taniguchi Y, Yuasa T, Shimuzu M. Linear porokeratosis. *J Dermatol* 1993; **20**: 489–92.
36 Goldman GD, Milstone LM. Generalized linear porokeratosis treated with etretinate. *Arch Dermatol* 1995; **131**: 496–7.
37 Pehamberger H, Konrad K. Treatment with an oral aromatic retinoid in linear porokeratosis. *Dermatologica* 1980; **160**: 270–4.
38 Knobler RM, Neuman RA. Exacerbation of porokeratosis during etretinate therapy. *Acta Derma Venereol (Stockh)* 1990; **70**: 319–22.

Linear atrophoderma of Moulin

In some patients, clearly demarcated cutaneous atrophy and hyper- or hypopigmentation with minimal inflammation and sclerosis is distributed along Blaschko's lines [1–3]. Histologically, there is variable atrophy and some inflammation. It usually appears during childhood or adolescence. Variability in presentation suggests that this is not a single entity [4], and some cases might represent a linear variant of atrophoderma of Pierini and Pasini, mosaicism for a *COL3A1* mutation (i.e. linear Ehlers–Danlos syndrome type IV) or a late 'burnt out' stage of linear morphoea. One atypical congenital case showed no inflammation or sclerosis [5]. Psoriasiform histology was reported in another case [6]. Linear atrophy with telangiectasia has been reported in linear atrophoderma of Moulin [7] but is more commonly seen in Goltz focal dermal hypoplasia. An association of right-sided linear atrophoderma with leukonychia of both hands may have been coincidental [8].

References

1 Rompel R, Mischke AL, Langner C, Happle R. Linear atrophoderma of Moulin. *Eur J Dermatol* 2000; **10**: 611–3.
2 Wollenberg A, Baumann L, Plewig G. Linear atrophoderma of Moulin: a disease which follows Blaschko's lines. *Br J Dermatol* 1996; **135**: 277–9.
3 Danarti R, Bittar M, Happle R, Konig A. Linear atrophoderma of Moulin: postulation of mosaicism for a predisposing gene. *J Am Acad Dermatol* 2003; **49**: 492–8.
4 Ang GC, Lee JB. Linear atrophoderma of Moulin: is it a single disease? *J Am Acad Dermatol* 2005; **52**: 923–4.
5 Ang G, Hyde PM, Lee JB. Unilateral congenital linear atrophoderma of the leg. *Pediatr Dermatol* 2005; **22**: 350–4.
6 Browne C, Fisher BK. Atrophoderma of moulin with preceding inflammation. *Int J Dermatol* 2000; **39**: 850–2.
7 Utikal J, Keil D, Klemke CD *et al.* Predominant telangiectatic erythema in linear atrophoderma of Moulin: novel variant or separate entity? *Dermatology* 2003; **207**: 310–5.
8 Atasoy M, Aliagaoglu C, Sahin O *et al.* Linear atrophoderma of Moulin together with leuconychia: a case report. *J Eur Acad Dermatol Venereol* 2006; **20**: 337–40.

Adult Blaschkitis

Synonyms

- Blaschko linear acquired inflammatory skin eruption
- BLAISE

This remitting and relapsing eruption of itchy inflammatory vesicles and papules occurs usually on the trunk in adults [1]. The histology is more eczematous (spongiotic) than lichenoid. It would be difficult to distinguish from linear Grover's disease [2]. Brinkmeier *et al.* [3] reported Blaschkitis after 2 days of metronidazole

therapy. Rechallenge with two oral doses of metronidazole 3 months later provoked a relapse after 3 days. Lipsker *et al.* found mosaicism for various anomalies of chromosome 18 in a woman with Blaschkitis [4]. Taieb *et al.* [5] and Hofer [6] considered that 'adult Blaschkitis' represents an adult version of lichen striatus and Taieb proposed the acronym BLAISE to cover both. BLAISE should perhaps be regarded as a description rather than a diagnosis, a useful category for many of the disorders in this section, pending more precise identification.

References

1 Grosshans EM. Acquired Blaschkolinear dermatoses. *Am J Med Genet* 1999; **85**: 334–7.

2 Fantini F, Kovacs E, Scarabello A. Unilateral transient acantholytic dermatosis (Grover's disease) along Blaschko's lines. *J Am Acad Dermatol* 2002; **47**: 319–20.

3 Brinkmeier T, Herbst RA, Schaller J *et al.* Drug-induced blaschkitis. *Acta Derm Venereol* 2004; **84**: 314–5.

4 Lipsker D, Cribier B, Girard-Lemaire F *et al.* Genetic mosaicism in an acquired inflammatory dermatosis following the lines of Blaschko. *Arch Dermatol* 2000; **136**: 805–7.

5 Taieb A, El Youbi A, Grosshans E, Maleville J. Lichen striatus: a Blaschkolinear acquired inflammatory skin eruption. *J Am Acad Dermatol* 1991; **25**: 637–42.

6 Hofer T. Lichen striatus in adults or 'adult blaschkitis'? There is no need for a new naming. *Dermatology* 2003; **207**: 89–92.

The epidermal naevus syndromes

Non-epidermolytic epidermal naevi can be associated with a wide range of abnormalities in other systems (epidermolytic verrucous epidermal naevi are not, as the causative keratin gene mutations are expressed only in skin). Historically [1,2], the term 'epidermal naevus syndrome' referred to the association of sebaceous naevus with neurological, ocular and sometimes other abnormalities. Later, the term was extended to cover almost any multisystem disorder featuring sebaceous or verrucous epidermal naevus [3]. More recently, Happle has used the term 'the epidermal naevus syndromes' to include at least six separate disorders, namely: Schimmelpenning's syndrome, Proteus syndrome, comedo naevus syndrome, CHILD syndrome, Becker's naevus syndrome and phakomatosis pigmentokeratotica [4,5]. This has created two difficulties: firstly, most dermatologists would not regard Becker's naevus as an epidermal naevus; secondly, changing the meaning of 'epidermal naevus syndrome' leaves us without a name for the entity well established in the literature as 'epidermal naevus syndrome' [6], none of the historical eponyms being satisfactory.

Therefore, this account maintains the original and well-established use of the term 'epidermal naevus syndrome' as 'the association of sebaceous and/or verrucous epidermal naevi with other developmental defects, particularly of the CNS, eye and skeleton'. The term 'epidermal naevus syndrome' as used here does not include syndromes where the naevus is not a sebaceous or verrucous epidermal naevus (e.g. Becker's naevus, CHILD naevus). Neither does it include those conditions which feature epidermal naevi but are sufficiently distinctive to merit their own name (Proteus syndrome and phakomatosis pigmentokeratotica). We can also separate out those syndromes which lack neurological manifestations and have been defined in molecular terms, including comedo naevus syndrome (due to mosaic *FGFR2* mutations), the association of facial asymmetry with epidermal naevus due to mosaicism for the *FGFR3* mutation R248C [7] and a Proteus-like syndrome with loss of heterozygosity for a *PTEN* mutation [8]. Even after excluding all these, epidermal naevus syndrome remains a heterogeneous group, within which further conditions will be defined in the future. Eventually, when all the different mutations responsible for epidermal naevus syndrome have been defined, the term may become redundant, but for the moment it remains useful.

Epidermal naevus syndrome

Synonyms
- Sebaceous naevus syndrome
- Schimmelpenning's syndrome
- Feuerstein–Mims syndrome
- Organoid naevus syndrome
- Jadassohn's naevus phakomatosis

Definition. Epidermal naevus syndrome [9] describes the association of sebaceous and/or verrucous naevi with other developmental defects, particularly of the central nervous system (CNS), eye and skeleton, first reported by Feuerstein and Mims [1] and Schimmelpenning [2]. Other authors have used the term *Jadassohn's naevus phakomatosis* to describe this association [10]. Although early reports only included sebaceous naevi, the term is now used to include patients with verrucous naevi. The associations with both types of naevi are very similar, and some patients have both verrucous and sebaceous naevi, differentiation depending largely on the site, lesions on the head and neck being more often sebaceous [9].

Aetiology. Epidermal naevus syndrome is a sporadic disorder, probably reflecting genetic mosaicism for an autosomal dominant mutation which would be lethal if not 'rescued' by mosaicism [11]. To explain discordance in monozygotic twins, the mosaicism must have arisen after conception [12] and after the division into twin zygotes; the limited involvement (right eye and right side of the scalp only) in the affected twin is also consistent with a relatively late mutation. Occasional occurrence in successive generations can be explained by inheritance of an unstable pre-mutation, or by loss of heterozygosity for a recessive mutation ('paradominant inheritance' [13]).

Clinical features. The cutaneous element of epidermal naevus syndrome can be sebaceous naevus, verrucous epidermal naevus [3,9,14–16] or syringocystadenoma papilliferum [17]. The naevus may grow abnormal hair, such as woolly hair [18], long, pale 'angora' type hair [19] or hair associated with follicular hyperkeratosis [20].

Additional cutaneous abnormalities seen in some patients include infantile haemangiomas, naevi flammei, hypochromic naevi, café-au-lait macules [21,22], congenital melanocytic naevi [22–24], Spitz naevi [25,26], follicular hyperkeratosis and dermatomegaly [14,16]. One infant had a large congenital turban tumour (cylindroma) considered to have developed within the apocrine structures of the naevus sebaceous [27]. Ipsilateral facial lipoma with hemimegalencephaly has been reported in three cases of epidermal nevus syndrome [28] and intracranial and orbital lipomas have also occurred [29].

Sometimes, the epidermal naevus involves the mucosae of the mouth, anus or genitalia [9,16,30,31]. Oral involvement may include dental enamel hypoplasia, malformations of the teeth and hypodontia [14,30] and maxillary giant cell granuloma [32].

Significant developmental anomalies occur in approximately 1.7% of all neonates [33] and 10% of children with epidermal naevi, the risk correlating poorly with number and extent of lesions. Skeletal deformities reported in the epidermal naevus syndrome include kyphosis, scoliosis, cystic and lytic changes, hypertrophy and atrophy, short limbs and syndactyly [9,14,16,34].

A wide variety of neurological abnormalities has been identified in about 50% of patients with epidermal naevus syndrome [10,16,17,35–42]. Neurological abnormalities are much more frequent in patients who have sebaceous naevi on the head and neck [15,16,35,42], but the location of the skin lesions does not provide reliable prediction of the laterality of intracranial brain anomalies [43]. Seizures, especially infantile spasms, occur in some 50% of patients, many of whom have underlying structural abnormalities of the CNS [44]. Mental retardation also occurs in about 50% of cases; it varies in degree, but may be profound. Spastic hemiparesis affects about 20% of patients and may have its onset at any time from birth to adolescence; spastic tetraparesis has also been described. Conductive [45] and sensorineural deafness [14] occur. The commonest structural CNS abnormalities have been ipsilateral gyral malformations and complete or partial hemimegalencephaly [37,44,46–49], but others have included vascular malformations [29,36,50–53], hemiatrophy [38,40,54,55], posterior fossa abnormalities, lateral ventricle enlargement [38,56], porencephaly [57], agenesis of the corpus callosum [44], hamartoma [58], intracranial [29] or intraspinal lipomas [59,60] and basal ganglia malformation [49]. Neuroimaging is surprisingly often normal, even in patients with clinical neurological abnormalities [42] and multiple modalities may be required [61]. Conversely, a neurologically normal child had neuroradiological abnormalities [62]. Cranial nerve palsies have also been described fairly commonly.

Some 35–70% of patients have ocular abnormalities [6,14,16,38, 40,51,52,54–56,63–66], the commonest of which is involvement of the eyelid or conjunctiva by the epidermal naevus, sometimes causing trichiasis or interfering with lid closure. Other ocular problems have included colobomas of the eyelid, iris and retina, conjuctival lipodermoids and choristomas. Optic nerve hypoplasia, retinal dysplasia, cortical blindness, microphthalmia, macrophthalmia, anophthalmia, corneal opacities and cataracts have also been reported.

Many other non-cutaneous abnormalities have now been reported in association with epidermal naevi, including aortic coarctation and other vascular anomalies [53], cardiac, genitourinary [10,14,15], hepatic and renal [67] abnormalities and endocrine disease [68,69], including inappropriate antidiuretic hormone (ADH) secretion [68] and precocious puberty [24,70,71]. In several patients, bone disease and/or muscle weakness has occurred secondary to hypophosphataemic vitamin D-resistant rickets [16,25,26,54,70,72–81]; some of these patients [25,76,78] had radiolucent bone lesions shown in one case to be angiomatous [78]. Debulking the epidermal naevi leads to biochemical improvement [70], suggesting that these epidermal naevi, or the associated intraosseous angiomatous tumours, secrete a substance that induces renal phosphate loss. A similar phenomenon occurs with a variety of benign mesenchymal tumours, melanocytic naevi [80] and occasionally malignant tumours [82]. A strong candidate gene for 'phosphatonin', the postulated humoral factor responsible for tumour-induced rickets/osteomalacia, was fibroblast growth factor-23, localized to 12p13 [82]. Elevated FGF-23 has been reported [83,84]. One patient suffered both hypophosphataemic vitamin-D resistant rickets and precocious puberty [70]. An overlap has been suggested with the McCune–Albright syndrome [21], but radiologically the polyostotic fibrous dysplasia of the McCune–Albright syndrome is distinguishable from the intraosseous angiomas reported with epidermal naevi [78].

Benign and malignant transformation may occur in these patients' epidermal naevi, exactly as it may when such naevi exist without associated abnormalities. However, insufficient attention has been drawn to the relatively high incidence of systemic malignancies that have arisen in patients with epidermal naevi, often at a very early age [16]. These have included nephroblastoma [16,34,39], salivary gland carcinomas [85], carcinoma of the oesophagus and stomach and breast [86], astrocytoma [87], glioma [88], mandibular ameloblastoma [89], transitional cell carcinoma of the bladder [90], rhabdomyosarcoma of the bladder [91] and testicle [92], parotid adenocarcinoma [92] and intrathoracic teratoma [14].

Diagnosis. Epidermal naevus syndrome overlaps with other syndromes characterized by verrucous epidermal naevi, such as Proteus syndrome, naevus comedonicus syndrome and phakomatosis pigmentokeratotica. CNS lipoma may lead to confusion with encephalocraniocutaneous lipomatosis [59].

Treatment. The treatment of epidermal naevi is discussed elsewhere, and management of the associated anomalies is beyond the scope of this book. However, an apparently healthy child with epidermal naevus is likely to present to a dermatologist and management requires careful clinical judgment. Most children with epidermal naevi are otherwise perfectly well and it is inappropriate to investigate a child who is thriving and developmentally normal. Parents can be informed of the 10% risk of associated abnormalities, but also reminded that most of these will be picked up on routine child health surveillance, such as problems with vision, hearing, growth and neurological development. There should be a low threshold for following up any reported problems, for example a disproportionate rise in head circumference, which may be the first sign of raised intracranial pressure. Children with epidermal naevus syndrome tend to have several associated abnormalities, so if a second developmental anomaly is detected it is appropriate to look for others. Reasonable non-invasive investigations would include ophthalmological assessment and cranial ultrasound. If the naevus is extensive, serum calcium and phosphate should be measured to exclude tumour-induced osteomalacia/rickets.

References

1 Feuerstein RC, Mims LC. Linear nevus sebaceus with convulsions and mental retardation. *Am J Dis Child* 1962; **104**: 675–9.

2 Schimmelpenning GW. Klinischer Beitrag zur Symptomatologie der Phakomatosen. *Fortschr Geb Rontgenstr* 1957; **87**: 716–20.

3 Rogers M. Epidermal nevi and the epidermal nevus syndromes: a review of 233 cases. *Pediatr Dermatol* 1992; **9**: 342–4.
4 Happle R. How many epidermal naevus syndromes exist? *J Am Acad Dermatol* 1991; **25**: 550–6.
5 Happle R. Epidermal nevus syndromes. *Semin Dermatol* 1995; **14**: 111–21.
6 Vujevich JJ, Mancini AJ. The epidermal nevus syndromes: multisystem disorders. *J Am Acad Dermatol* 2004; **50**: 957–61.
7 Collin B, Taylor IB, Wilkie AO, Moss C. Fibroblast growth factor receptor 3 (FGFR3) mutation in a verrucous epidermal naevus associated with mild facial dysmorphism. *Br J Dermatol* 2007; **156**: 1353–6.
8 Loffeld A, McLellan NJ, Cole T *et al.* Epidermal naevus in Proteus syndrome showing loss of heterozygosity for an inherited PTEN mutation. *Br J Dermatol* 2006; **154**: 1194–8.
9 Solomon LM, Fretzin DF, Dewald RL. The epidermal nevus syndrome. *Arch Dermatol* 1968; **97**: 273–85.
10 Zaremba J. Jadassohn's naevus phakomatosis: 2. A study based on a review of thirty-seven cases. *J Ment Defic Res* 1978; **22**: 103–23.
11 Happle R. Lethal genes surviving by mosaicism: a possible explanation for sporadic birth defects involving the skin. *J Am Acad Dermatol* 1987; **16**: 899–906.
12 Schworm HD, Jedel KB, Holinski E *et al.* Discordant monozygotic twins with the Schimmelpenning–Feuerstein–Mims syndrome. *Clin Genet* 1996; **50**: 393–7.
13 Happle R. Klippel–Trenaunay syndrome: is it a paradominant trait? *Br J Dermatol* 1993; **128**: 465–6.
14 Rogers M, McCrossin I, Commens C. Epidermal nevi and the epidermal nevus syndrome. *J Am Acad Dermatol* 1989; **20**: 476–88.
15 Grebe TA, Rimsza ME, Richter SF *et al.* Further delineation of the epidermal nevus syndrome: two cases with new findings and review of the literature. *Am J Med Genet* 1993; **47**: 24–30.
16 Solomon LM, Esterly NB. Epidermal and other congenital organoid nevi. *Curr Probl Pediatr* 1975; **6**: 1–55.
17 Jancar J. Naevus syringocystadenomatosus papilliferus, with skull and brain lesions, hemiparesis, epilepsy and mental retardation. *Br J Dermatol* 1970; **82**: 402–5.
18 Al-Harmozi SA, Mahmoud SF, Ejeckam GC. Woolly hair nevus syndrome. *J Am Acad Dermatol* 1992; **27**: 259–60.
19 Schauder S, Hanefeld F, Noske UM, Zoll B. Depigmented hypertrichosis following Blaschko's lines associated with cerebral and ocular malformations: a new neurocutaneous, autosomal lethal gene syndrome from the group of epidermal naevus syndromes? *Br J Dermatol* 2000; **142**: 1204–7.
20 Gobello T, Mazanti C, Zambruno G, Chinni LM. New type of epidermal naevus syndrome. *Dermatology* 2000; **201**: 51–3.
21 Yu AC, Ng V, Dicks-Mireaux C, Grant DB. Epidermal naevus syndrome associated with polyostotic fibrous dysplasia and central precocious puberty. *Eur J Pediatr* 1995; **154**: 102–4.
22 Eichler C, Flowers FP, Ross J. Epidermal nevus syndrome: case report and review of clinical manifestations. *Pediatr Dermatol* 1989; **6**: 316–20.
23 Mimouni F, Han BK, Barnes L *et al.* Multiple hamartomas associated with intracranial malformation. *Pediatr Dermatol* 1986; **3**: 219–25.
24 Moss C, Parkin JM, Comaish JS. Precocious puberty in a boy with widespread linear epidermal naevus. *Br J Dermatol* 1991; **125**: 178–82.
25 Goldblum JR, Headington JT. Hypophosphatemic vitamin D-resistant rickets and multiple spindle and epithelioid nevi associated with linear nevus sebaceus syndrome. *J Am Acad Dermatol* 1993; **29**: 109–11.
26 Kishida ES, Muniz Silva MA, da Costa Pereira F *et al.* Epidermal nevus syndrome associated with adnexal tumors, spitz nevus, and hypophosphatemic vitamin D-resistant rickets. *Pediatr Dermatol* 2005; **22**: 48–54.
27 Regalado JJ. A novel epidermal nevus syndrome with congenital cylindromatous turban tumor. *J Cutan Pathol* 2003; **30**: 586–90.
28 Egan CA, Meadows KP, Van Orman CB, Vanderhooft SL. Neurologic variant of epidermal nevus syndrome with a facial lipoma. *Int J Dermatol* 2001; **40**: 189–90.
29 Canyigit M, Oguz KK. Epidermal nevus syndrome with internal carotid artery occlusion and intracranial and orbital lipomas. *AJNR Am J Neuroradiol* 2006; **27**: 1559–61.
30 Kelly JE, Hibbard ED, Giansanti JS. Epidermal nevus-syndrome. Report of a case with unusual oral manifestations. *Oral Surg* 1972; **34**: 774–80.
31 Lovejoy FH, Boyle WE. Linear nevus sebaceus syndrome: report of two cases and a review of the literature. *Pediatrics* 1973; **52**: 382–7.
32 Kaplan I, Metzker A, Calderon S. Epidermal nevus syndrome with maxillary involvement. *Int J Oral Maxillofac Surg* 1993; **22**: 298–300.
33 Marden PM, Smith DW, McDonald MI. Congenital anomalies in the newborn infant, including minor variations. *J Pediatr* 1964; **64**: 357–71.
34 Ross HE. Multiple lytic bone lesions. *J Am Osteopath Assoc* 1969; **69**: 338–45.
35 Baker RS, Ross PA, Baumann RJ. Neurologic complications of the epidermal nevus syndrome. *Arch Neurol* 1987; **44**: 227–32.
36 Dobyns WB, Garg BP. Vascular abnormalities in the epidermal nevus syndrome. *Neurology* 1991; **41**: 276–8.
37 El Shanti H, Bell WE, Waziri MH. Epidermal nevus syndrome: subgroup with neuronal migration defects. *J Clin Neurol* 1992; **7**: 29–34.
38 Holden KR, Dekaban AS. Neurological involvement by nevus unius lateris and nevus linearis sebaceus. *Neurology* 1972; **22**: 879–87.
39 Lansky LL, Fuderburk S, Cuppage FE *et al.* Linear sebaceous nevus syndrome: a hamartoma variant. *Am J Dis Child* 1972; **123**: 587–90.
40 Moynahan EJ, Wolff OH. A new neurocutaneous syndrome consisting of linear naevus, bilateral lipodermoid of the conjunctivae, cranial thickening, cerebral cortical atrophy and mental retardation. *Br J Dermatol* 1967; **79**: 651–2.
41 Pavone L, Curatolo P, Rizzo R *et al.* Epidermal nevus syndrome: a neurologic variant with hemimegalencephaly, gyral malformation, mental retardation, seizures and facial hemihypertrophy. *Neurology* 1991; **41**: 266–71.
42 Davies D, Rogers M. Review of neurological manifestations in 196 patients with sebaceous naevi. *Australas J Dermatol* 2002; **43**: 20–3.
43 Gurecki PJ, Holden KR, Sahn EE, Dyer DS, Cure JK. Developmental neural abnormalities and seizures in epidermal nevus syndrome. *Dev Med Child Neurol* 1996; **38**: 716–23.
44 Dodge NN, Dobyns WB. Agenesis of the corpus callosum and Dandy–Walker malformation associated with hemimegalencephaly in the sebaceous nevus syndrome. *Am J Med Genet* 1995; **56**: 147–50.
45 Yu KCY, Lalwani AK. Inner ear malformations and hearing loss in linear nevus sebaceous syndrome. *Int J Pediatr Otorhinolaryngol* 2000; **56**: 211–6.
46 Kwa VI, Smitt JH, Verbeeten BW *et al.* Epidermal nevus syndrome with isolated enlargement of one temporal lobe: a case report. *Brain Dev* 1995; **17**: 122–5.
47 Levin S, Robinson RO, Aicardi J, Hoare RD. Computed tomography appearance in the linear sebaceous naevus syndrome. *Neuroradiology* 1984; **26**: 469–72.
48 Sakuta R, Aikawa H, Takashima S, Ryo S. Epidermal nevus syndrome with hemimegalencephaly: neuropathological study. *Brain Dev* 1991; **13**: 260–5.
49 Abdelhalim AN, Moritani T, Richfield E *et al.* Epidermal nevus syndrome: megalencephaly with bihemispheric and cerebellar involvement: imaging and neuropathologic correlation. *J Comput Assist Tomogr* 2003; **27**: 534–7.
50 Kang WH, Koh YJ, Chun SI. Nevus sebaceus syndrome associated with intracranial arteriovenous malformation. *Int J Dermatol* 1987; **26**: 382–4.
51 Clancy RR, Kurtz MB, Baker D *et al.* Neurological manifestations of the organoid nevus syndrome. *Arch Neurol* 1985; **42**: 236–40.
52 Mollica F, Pavone L, Nuciforo G. Linear sebaceous nevus syndrome in a newborn. *Am J Dis Child* 1974; **128**: 868–71.
53 Kotulska K, Jurkiewcz E, Jozwiak S, Kuczynski D. Epidermal nevus syndrome and intraspinal hemorrhage. *Brain Dev* 2006; **28**: 541–3.
54 Sugarman GL, Reed WB. Two unusual neurocutaneous disorders with facial cutaneous signs. *Arch Neurol* 1969; **21**: 242–7.
55 Marks JG, Tomasovic JJ. Linear nevus sebaceus syndrome. *J Am Acad Dermatol* 1980; **2**: 31–2.
56 Marden PM, Venters HD. A new neurocutaneous syndrome. *Am J Dis Child* 1966; **112**: 79–81.
57 Chalhub EG, Volpe JJ, Gado MH. Linear nevus sebaceous syndrome associated with porencephaly and non-functioning major cerebral venous sinuses. *Neurology* 1975; **25**: 857–60.
58 Moskowitz R, Honig PJ. Nevus sebaceus in association with an intracranial mass. *J Am Acad Dermatol* 1982; **6**: 1078–80.
59 Mall V, Heinen F, Uhl M *et al.* CNS lipoma in patients with epidermal nevus syndrome. *Neuropediatrics* 2000; **31**: 175–9.
60 Booth TN, Rollins NK. MR imaging of the spine in epidermal nevus syndrome. *AJNR Am J Neuroradiol* 2002; **23**: 1607–10.
61 Zhang W, Simos PG, Ishibashi H *et al.* Neuroimaging features of epidermal nevus syndrome. *AJNR Am J Neuroradiol* 2003; **24**: 1468–70.
62 Neumann LM, Scheer I, Kunze J, Stover B. Cerebral manifestations, hemihypertrophy and lymphoedema of one leg in a child with epidermal nevus syndrome (Schimmelpenning-Feuerstein-Mims). *Pediatr Radiol* 2003; **33**: 637–40.

63 Diven DG, Solomon AR, McNeeley MC *et al.* Nevus sebaceus associated with major ophthalmologic abnormalities. *Arch Dermatol* 1987; **123**: 383–6.
64 Lambert HM. Linear nevus sebaceus syndrome. *Ophthalmology* 1987; **99**: 278–82.
65 Loff HJ, Bardenstein DS, Levine MR. Systematized epidermal nevi: case report and review of clinical manifestations. *Ophthal Plast Reconstr Surg* 1994; **10**: 262–6.
66 Mansour AM, Laibson PD, Reinecke RD *et al.* Bilateral total corneal and conjunctival choristomas associated with epidermal nevus. *Arch Ophthalmol* 1986; **104**: 245–8.
67 Kaur T, Kumar B, Chawwla YK. Epidermal naevi associated with extrahepatic portal venous obstruction, hypoplastic kidney and lymphangiectasia: a new syndromic variant? *Br J Dermatol* 2004; **150**: 618–9.
68 Yu TW, Tsau YK, Young C *et al.* Epidermal nevus syndrome with hypermelanosis and chronic hyponatremia. *Pediatr Neurol* 2000; **22**: 151–4.
69 Abouzeid SA, Khalil SA, Meheesen MA *et al.* Epidermal nevus with cutaneous endocrinal associations. *Arch Dermatol* 1979; **115**: 625–6.
70 Ivker R, Resnick SD, Skidmore RA. Hypophosphatemic vitamin-D resistant rickets, precocious puberty, and the epidermal nevus syndrome. *Arch Dermatol* 1997; **13**: 1557–61.
71 Tay YK, Weston WL, Ganong CA, Klingensmith GJ. Epidermal nevus syndrome: association with central precocious puberty and woolly hair nevus. *J Am Acad Dermatol* 1996; **35**: 839–42.
72 Aschinberg LC, Solomon LM, Zeis PM *et al.* Vitamin D-resistant rickets associated with epidermal nevus syndrome. *J Pediatr* 1977; **91**: 55–60.
73 Besser FS. Linear sebaceous naevi with convulsions and mental retardation (Feuerstein–Mims' syndrome), vitamin-D-resistant rickets. *Proc R Soc Med* 1976; **69**: 518–22.
74 Carey DE, Drezner MK, Hamden JA *et al.* Hypophosphatemic rickets/osteomalacia in linear sebaceous nevus syndrome: a variant of tumor-induced osteomalacia. *J Pediatr* 1986; **109**: 994–1000.
75 Oranje AP, Przyrembel H, Meradji M *et al.* Solomon's epidermal nevus syndrome (type: linear nevus sebaceus) and hypophosphatemic vitamin D-resistant rickets. *Arch Dermatol* 1994; **130**: 1167–71.
76 Rustin MHA, Bunker CB, Gilkes JJH *et al.* Polyostotic fibrous dysplasia associated with extensive linear epidermal naevi. *Clin Exp Dermatol* 1989; **14**: 371–5.
77 Skovby F, Sveljgaard E, Moller J. Hypophosphatemic rickets in linear sebaceous nevus syndrome. *J Pediatr* 1987; **111**: 855–7.
78 Stosiek N, Hornstein OP, Hiller D *et al.* Extensive linear epidermal nevus associated with hemangiomas of bones and vitamin-D-resistant rickets. *Dermatology* 1994; **189**: 278–82.
79 Tokatli A, Coskun T, Ozalp I. Hypophosphatemic vitamin-D resistant rickets associated with epidermal nevus syndrome. *Turk J Pediatr* 1997; **39**: 247–51.
80 Chou YY, Chao SC, Shiue CN *et al.* Hypophosphatemic rickets associated with epidermal nevus syndrome and giant hairy nevus. *J Pediatr Endocrinol Metab* 2005; **18**: 93–5.
81 Hosalkar HS, Jones DH, Offiah A, Hall C. Linear sebaceous naevus syndrome and resistant rickets. *J Bone Joint Surg Br* 2003; **85**: 578–83.
82 Fukumoto S, Yamashita T. Fibroblast growth factor-23 is the phosphaturic factor in tumour-induced osteomalacia and may be phosphatonin. *Curr Opin Nephrol Hypertens* 2002; **11**: 385–9.
83 Heike CL, Cunningham ML, Steiner RD *et al.* Skeletal changes in epidermal nevus syndrome: does focal bone disease harbor clues concerning pathogenesis? *Am J Med Genet A* 2005; **139**: 67–77.
84 Hoffman WH, Jueppner HW, Deyoung BR *et al.* Elevated fibroblast growth factor-23 in hypophosphatemic linear nevus sebaceous syndrome. *Am J Med Genet A* 2005; **134**: 233–6.
85 Berkeley WT. Nevus sebaceus (Jadassohn) complicated by bilateral salivary gland adenocarcinoma. *Plast Reconstr Surg* 1959; **23**: 55–63.
86 Pack GT, Sunderland DA. Naevus unius lateris. *Arch Surg* 1941; **43**: 341–75.
87 Meyerson LB. Nevus unius lateralis, brain tumour, and diencephalic syndrome. *Arch Dermatol* 1967; **95**: 501–4.
88 Andriola M. Nevus unius lateris and brain tumor. *Am J Dis Child* 1976; **130**: 1259–60.
89 Bazopoulou-Kyrkanisou E, Alexandridis C, Tosios KI *et al.* Epidermal nevus syndrome with development of a mandibular ameloblastoma. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2000; **90**: 64–70.
90 Rosenthal D, Fretzin DF. Epidermal nevus syndrome: report of association with a transitional cell carcinoma of the bladder. *Pediatr Dermatol* 1986; **3**: 455–8.
91 Dimond RL, Amon RB. Epidermal nevus and rhabdomyosarcoma. *Arch Dermatol* 1976; **112**: 1424–6.
92 Vidaurri-de la Cruz H, Tamayo-Sanchez L, Duran-McKinster C *et al.* Epidermal nevus syndromes: clinical findings in 35 patients. *Pediatr Dermatol* 2004; **21**: 432–9.

Phakomatosis pigmentokeratotica

The concurrence of sebaceous or verrucous epidermal naevus with speckled lentiginous naevus has been called 'phacomatosis pigmentokeratotica' [1–3]. It could be argued that speckled lentiginous naevus is simply one of the many localized anomalies associated with verrucous and sebaceous epidermal naevi, and that there is no justification for separating this particular association from epidermal naevus syndrome. The occurrence of extracutaneous anomalies in phakomatosis pigmentokeratotica supports this idea [4]. Furthermore, multiple melanocytic naevi have frequently been reported in association with epidermal naevus syndrome (see above) and hypophosphataemic rickets, which has been reported in several patients with multiple melanocytic naevi and widespread verrucous epidermal naevi, also occurs in phakomatosis pigmentokeratotica [2,5,6]. Malignant change has been reported within both naevoid elements [7], as has association with rhabdomyosarcoma [4].

Happle and colleagues have argued not only that phakomatosus pigmentokeratotica is a distinct syndrome with its own spectrum of associated abnormalities, but further that the lentiginous element might occur without the verrucous element as the 'speckled lentiginous naevus syndrome' [8,9]. Happle suggests that phakomatosis pigmentokeratotica represents twin-spotting [1,2,8].

References

1 Happle R, Hoffmann R, Restano L *et al.* Phacomatosus pigmentokeratotica: a melanocytic epidermal twin naevus syndrome. *Am J Med Genet* 1996; **65**: 363–5.
2 Tadini G, Restano L, Gonzales-Perez R *et al.* Phakomatosis pigmentokeratotica: review of new cases and further delineation of the syndrome. *Arch Dermatol* 1998; **134**: 333–7.
3 Boente C, Pizzi de Parra N, Larralde de Luna M *et al.* Phacomatosus pigmentokeratotica: another epidermal naevus syndrome and a distinctive type of twin spotting. *Eur J Dermatol* 2000; **10**: 190–4.
4 Gruson LM, Orlow SJ, Schaffer JV. Phacomatosis pigmentokeratotica associated with hemihypertrophy and a rhabdomyosarcoma of the abdominal wall. *J Am Acad Dermatol* 2006; **55**: S16–20.
5 Bouthors J, Vantyghem MC, Manouvrier-Hanu S *et al.* Phacomatosis pigmentokeratotica associated with hypophosphataemic rickets, pheochromocytoma and multiple basal cell carcinomas. *Br J Dermatol* 2006; **155**: 225–6.
6 Saraswat A, Dogra S, Bansali A, Kumar B. Phakomatosis pigmentokeratotica associated with hypophosphataemic vitamin D-resistant rickets: improvement in phosphate homeostasis after partial laser ablation. *Br J Dermatol* 2003; **148**: 1074–6.
7 Martinez-Menchon T, Mahiques Santos L, Vilata Corell JJ *et al.* Phacomatosis pigmentokeratotica: a 20-year follow-up with malignant degeneration of both nevus components. *Pediatr Dermatol* 2005; **22**: 44–7.
8 Happle R. Speckled lentiginous naevus syndrome: delineation of a new distinct neurocutaneous phenotype. *Eur J Dermatol* 2002; **12**: 133–5.
9 Vente C, Neumann C, Bertsch H *et al.* Speckled lentiginous nevus syndrome: report of a further case. *Dermatology* 2004; **209**: 228–9.

Dermal and subcutaneous naevi

Connective tissue naevi

Connective tissue naevi are circumscribed hamartomatous malformations of the dermal extracellular matrix, that is of collagen,

Table 18.2 Classification of connective tissue naevi.

Naevi of reticular connective tissue
Collagen naevi
Familial cutaneous collagenoma
Eruptive collagenoma
Plantar cerebriform collagenoma
Shagreen patch (tuberous sclerosis)
Linear connective tissue naevus
Knuckle pads
Other collagenomas
Elastic naevi
Pseudoxanthoma elasticum
Perforating elastoma
Juvenile elastoma and the Buschke–Ollendorff syndrome
Papular elastorrhexis
Naevus anelasticus
Other elastic naevi
Proteoglycan naevi
Mucinous naevus
Dermal nodules in Hunter's syndrome
Naevi of adventitial connective tissue
Fibrous papule of the face
Angiofibromas and subungual fibromas in tuberous sclerosis
Pearly papules of the penis
Perifollicular fibromas and trichodiscomas

elastic fibres or glycosaminoglycans [1,2]. They form a characteristic component of a number of well-defined inherited disorders, such as tuberous sclerosis and the Buschke–Ollendorff syndrome, but also occur as isolated sporadic lesions.

There are many different types of connective tissue naevi. The provisional classification in Table 18.2 is based on that of Uitto *et al.* [1]. Pierard and Lapiere further subdivided these naevi according to whether they arise from reticular or adventitial connective tissue [2]. The category 'elastic naevi' includes those characterized by a deficiency of elastin [3]. It is sometimes unclear whether an apparent deficiency of elastin simply reflects an excess of collagen [3].

References

1 Uitto J, Santa Cruz DJ, Eisen AZ. Connective tissue nevi of the skin. *J Am Acad Dermatol* 1980; **3**: 441–61.

2 Pierard GE, Lapiere CM. Nevi of connective tissue. A reappraisal of their classification. *Am J Dermatopathol* 1985; **7**: 325–33.

3 Lewis KG, Bercovitch L, Dill SW, Robinson-Bostom L. Acquired disorders of elastic tissue: Part II. decreased elastic tissue. *J Am Acad Dermatol* 2004; **51**: 165–85.

Collagen naevi

Familial cutaneous collagenoma

To date six families have been reported showing autosomal dominant inheritance of cutaneous collagenomas [1–4]. Affected individuals present with multiple, asymptomatic, indurated dermal nodules distributed symmetrically on the trunk and upper arms, particularly on the upper two-thirds of the back. Lesions vary in diameter from a few millimetres to a few centimetres, and in number from a dozen to more than a hundred. The condition first becomes manifest before or during adolescence, and an increased rate of appearance of new lesions has been noted during pregnancy. Spontaneous resolution has not been reported.

Histologically, the nodules showed an accumulation in the dermis of dense, coarse collagen fibres, with an apparent reduction in the number of elastic fibres [5].

Cardiological abnormalities reported in some patients include idiopathic myocardiopathy, left ventricular dilatation with thickened aorta and atrial septal defect [4], and might reflect fibrosis within the heart.

A mutation in the Buschke-Ollendorff gene, *LEMD3*, has been reported in one family with familial cutaneous collagenomas [6], raising the possibility that this is an allelic variant lacking the characteristic osteopoikilosis of Buschke–Ollendorff syndrome. Histologically, the reduction in elastic fibres distinguishes the lesions from the elastomas of Buschke–Ollendorff syndrome. Lesions on the scalp [7] must be distinguished from hypertrophic lesions of aplasia cutis congenital, which can also be familial.

Eruptive collagenoma

Sometimes cutaneous nodules, similar to those of familial cutaneous collagenoma, arise in the absence of any family history. The lesions tend to be earlier in onset and smaller than those of familial cutaneous collagenoma [8]. Although onset is usually in childhood, it has been reported in the seventh decade [9]. Exacerbation has been reported during pregnancy [8]. The term *eruptive collagenoma* has generally been applied to such cases, because of the abrupt development of these lesions [9–12]. The same term has been used, however, for cases which would seem, on clinical and histological grounds, to fall more correctly into the category of *lichen myxoedematosus* [13]. Hypertrophic chickenpox scars are easily mistaken for eruptive collagenomas.

Plantar cerebriform collagenoma

This rare lesion, imaginatively termed 'paving-stone naevus' [14], comprises a flesh-coloured cerebriform mass on the sole of variable size. It may occur in isolation [15–18], but is more often a component of the Proteus syndrome, in which it is associated with a variety of other anomalies including macrodactyly and hemihypertrophy [19].

Shagreen patch

The shagreen patch is a mamillated plaque-type collagenoma occurring, most often in the lumbosacral area, as a common and highly characteristic component of tuberous sclerosis [20].

Linear connective tissue naevus

Linear or zosteriform connective tissue naevus has been reported [21–24]. Onset is usually in childhood, and single or multiple lesions are distributed along Blaschko's lines [21]. Lesions may be nodular or cobblestone-like plaques.

Other collagenomas

A variety of other clinical types of collagenous connective tissue naevus has been described. Association with Down's syndrome [25,26] has been recorded. A large collagenoma resembling

a shagreen patch has been reported in a patient with multiple fibrofolliculomas [27]. A family has been reported in which scalp lesions diagnosed histologically as collagenomas were associated with cardiomyopathy and hypogonadism [28].

References

1 Uitto J, Santa Cruz DJ, Eisen A. Familial cutaneous collagenoma: genetic studies on a family. *Br J Dermatol* 1979; **101**: 185–95.
2 Phillips JC, Knautz MA, Sangueza OP *et al.* Familial cutaneous collagenoma. *J Am Acad Dermatol* 1999; **40**: 255–7.
3 Amato L, Mei S, Gallerani I *et al.* Familial cutaneous collagenoma: report of an affected family. *Int J Dermatol* 2005; **44**: 315–7.
4 Gurel MS, Mulayim MK, Ozardali I, Bitiren M. Familial cutaneous collagenoma: new affected family with prepubertal onset. *J Dermatol* 2007; **34**: 477–81.
5 Boente Mdel C, Primc NB, Asial RA, Winik BC. Familial cutaneous collagenoma: a clinicopathologic study of two new cases. *Pediatr Dermatol* 2004; **21**: 33–8.
6 Hershkovitz D, Amitai B, Sprecher E. Familial cutaneous collagenomas resulting from a novel mutation in LEMD3. *Br J Dermatol* 2007; **156**: 375–7.
7 Aroni K, Kyriazi E, Aivaliotis M, Davaris P. Familial localized connective tissue nevus of the scalp with alopecia (report of a very unusual case). *J Eur Acad Dermatol Venereol* 2004; **18**: 340–1
8 McClung AA, Blumberg MA, Huttenbach Y *et al.* Development of collagenomas during pregnancy. *J Am Acad Dermatol* 2005; **53**: S150–3.
9 Amaya M, Okubo Y, Koga M. A case of eruptive collagenoma localized on the neck and shoulders. *J Dermatol* 2002; **29**: 79–85.
10 Berberian BB, Wood C. Asymptomatic nodules on the back and abdomen: connective tissue nevi, eruptive collagenoma type. *Arch Dermatol* 1987; **123**: 811–2.
11 Padova-Elder S, Mols-Akowalczewski BL, Lambert WC. Multiple connective tissue nevi. *Cutis* 1988; **42**: 222–4.
12 Lee MW, Choi JH, Sung KJ *et al.* A case of eruptive collagenoma. *Pediatr Dermatol* 2002; **19**: 565–7.
13 Metz J, Schubert E. Das sog 'eruptive Kollagenom'—ein Lichen myxoedematosus? *Arch Dermatol Forsch* 1971; **240**: 148–59.
14 Lipschutz B. Über eine bisher nicht beschriebene Naevusform (pflastersteinformiger Bindegewebsnaevus). *Arch Dermatol Syphilol* 1922; **139**: 477–82.
15 Uitto J, Bauer EA, Santa Cruz DJ *et al.* Decreased collagenase production by regional fibroblasts cultured from the skin of a patient with connective tissue nevi of the collagen type. *J Invest Dermatol* 1982; **78**: 136–40.
16 Choi JC, Lee MW, Chang SE *et al.* Isolated plantar collagenoma. *Br J Dermatol* 2002; **146**: 164–5.
17 Altinyazar HC, Kargi E, Gun BD *et al.* Isolated plantar collagenoma: a case report. *J Dermatol* 2002; **29**: 508–11.
18 Nico MM, Valente NY, Machado KA. Isolated plantar collagenoma. *Acta Derm Venereol (Stockh)* 2003; **83**: 144.
19 Turner JT, Cohen MM Jr, Biesecker LG. Reassessment of the Proteus syndrome literature: application of diagnostic criteria to published cases. *Am J Med Genet* 2004; **130A**: 111–22.
20 Schwartz RA, Fernández G, Kotulska K, Jóźwiak S. Tuberous sclerosis complex: advances in diagnosis, genetics, and management. *J Am Acad Dermatol* 2007; **57**: 189–202.
21 Asano Y, Ihn H, Tamaki K. Linear connective tissue nevus. *Pediatr Dermatol* 2007; **24**: 439–41.
22 Amjadi M, Khorrami-Arani N, Mashman G, Allen PW. Zosteriform connective tissue nevus: a case report. *Am J Dermatopathol* 2007; **29**: 303–5.
23 Yeh SW, Magalhaes AM, Vasconcellos MR *et al.* Zosteriform connective tissue nevus: a case report. *Int J Dermatol* 2003; **42**: 720–2.
24 Kozminsky M, Bronson DM, Barsky S. Zosteriform connective tissue nevus. *Cutis* 1985; **2**: 77–8.
25 Kopec AV, Levine N. Generalized connective tissue nevi and ichthyosis in Down's syndrome. *Arch Dermatol* 1979; **115**: 623–4.
26 Togawa Y, Nohira G, Shinkai H, Utani A. Collagenoma in Down syndrome. *Br J Dermatol* 2003; **148**: 596–7.
27 Weintraub R, Pinkus H. Multiple fibrofolliculomas (Birt–Hogg–Dubé) associated with a large connective tissue nevus. *J Cutan Pathol* 1977; **4**: 289–99.
28 Sacks HN, Crawley IS, Ward JA *et al.* Familial cardiomyopathy, hypogonadism and collagenoma. *Ann Intern Med* 1980; **93**: 813–7.

Elastic naevi

Juvenile elastoma and the Buschke–Ollendorff syndrome

Synonym
- Dermatofibrosis lenticularis disseminata

The association between connective tissue naevi of the skin and osteopoikilosis, inherited as an autosomal dominant trait, is known eponymously as the Buschke–Ollendorff syndrome [1–3].

Histology of the skin lesions is highly characteristic [2–5]. While haematoxylin and eosin stained sections may appear normal, elastin stains show thick, interlacing tracts of elastic fibres running between fairly normal collagen in the reticular dermis, an appearance to which the term juvenile elastoma has been applied. Ultrastructurally, the elastin comprises clumps, coated with fine fibrils, and the fibroblasts contain swollen endoplasmic reticulum containing abnormal fibrillar material [5–8].

Two different clinical presentations have been described in the Buschke–Ollendorff syndrome. Some patients show a symmetrical eruption of uniform, small, lichenoid papules, reminiscent of pseudoxanthoma elasticum [2,6,9], and termed *dermatofibrosis lenticularis disseminata*. However, the more usual cutaneous presentation comprises asymmetrical groups of larger, yellowish nodules, sometimes coalescing to form plaques [3,10–12] (Fig. 18.5). The lesions may appear at any age, although most are present before puberty. Mixtures of these two types of lesions probably also occur. Although usually asymptomatic, occasionally patients complain of pain, tenderness or pruritus in affected areas of skin [12–14].



Fig. 18.5 Juvenile elastoma in the sacral area in the Buschke–Ollendorff syndrome.



Fig. 18.6 Osteopoikilosis in the Buschke–Ollendorff syndrome (X-ray of femoral head).

The second component of the Buschke–Ollendorff syndrome is a radiological abnormality termed *osteopoikilosis*, which comprises multiple, circumscribed, roundish or oval areas of increased opacity within bones, each usually measuring between 1 and 10 mm across [2,3] (Fig. 18.6). Such areas are found particularly frequently in the carpal and tarsal bones, in the phalanges, the epiphyses and metaphyses of the long bones and in the pelvis. They take several years to develop, but, after puberty, the appearances change very little. Histologically, these lesions are foci of tightly meshed bony trabeculae [15]. Some patients also demonstrate melorheostosis, a radiological appearance of long bones likened to dripping candle-wax [16].

Elevated elastin production [5] and elastin mRNA levels [8] in cultured fibroblasts from individuals with the syndrome, suggested a defect in pre-translational control of elastin production. However, the Buschke–Ollendorff syndrome is now known to be caused by mutations in the gene *LEMD3* encoding an inner nuclear membrane protein [16,17]. Osteopoikilosis in otherwise normal relatives of patients with the Buschke–Ollendorff syndrome, and characteristic skin lesions in the absence of osteopoikilosis, even after puberty [11,18] presumably represent incomplete expression of the Buschke–Ollendorff gene. There is no increase in morbidity or mortality in this syndrome, although a number of possible associations have been reported. Otosclerosis [19,20] and muscle fibrosis or contractures have been reported in several cases [2,11,13,21] and there have been individual patients with spinal anomalies [19,22] or short stature with or without precocious puberty [19,22]. Associations with peptic ulceration [13], and protein C deficiency [23] were presumably coincidental. In one family the Buschke–Ollendorff syndrome segregated to some extent with nail patella syndrome [24]. Osteopoikilosis was associated with short stature and mental retardation in three unrelated individuals with microdeletions involving *LEMD3* and flanking markers [25]. One of the three had raised, yellowish lesions on the upper chest and flank.

Papular elastorrhexis

Papular elastorrhexis is the name given in 1987 to a distinctive type of elastic tissue naevus [26]. The clinical presentation [27,28] is with multiple small (1–3 mm) white papules, which are not follicular and are symmetrically distributed, predominantly on the trunk and, to a lesser extent, on the limbs. The condition tends to appear in the second decade of life but has been reported in a 4 year old [29]. The lesions show no tendency to group, or to merge into plaques. Biopsies consistently demonstrate diminution and fragmentation of dermal elastic fibres.

This can be distinguished from the Buschke–Ollendorff syndrome by histology, absence of osteopoikilosis, and sporadic occurrence, although one reported case was familial [30]. It has been suggested that papular elastorrhexis, naevus anelasticus and eruptive collagenoma are the same entity [31]. Treatment with intralesional steroid was only transiently effective in one case [29], and in another resulted in cutaneous atrophy [31].

Naevus anelasticus

Several authors have reported cases in whom groups of small, yellowish or pink, perifollicular papules were present on the trunk, sometimes resulting in a 'wrinkled' appearance of the skin [32–34]. Histologically, these lesions have demonstrated focal absence of elastic fibres [35]. In the past, this condition was known inaccurately as *naevus elasticus of Lewandowsky* [33].

Other elastomas

Cases reported historically as juvenile elastoma and naevus elasticus [34,36,37] may represent *formes frustes* of the Buschke–Ollendorff syndrome, but they may alternatively be genuinely unrelated forms of elastoma. An exophytic form has been reported [38].

A distinctive condition comprising bilateral, thickened and furrowed plaques on the cheeks with an increase in elastic tissue histologically has been described in two separate reports [39,40]. The patients were both young, with no relevant family history. Sun exposure may have played a part in these.

References

1 Buschke A, Ollendorff H. Ein Fall von Dermatofibrosis lenticularis disseminata und Osteopathia condensans disseminata. *Dermatol Wochenschr* 1928; **86**: 257–62.
2 Verbov J, Graham R. Buschke–Ollendorff syndrome: disseminated dermatofibrosis with osteopoikilosis. *Clin Exp Dermatol* 1986; **11**: 17–26.
3 Kawamura A, Ochiai T, Tan-Kinoshita M, Suzuki H. Buschke-Ollendorff syndrome: three generations in a Japanese family. *Pediatr Dermatol* 2005; **22**: 133–7.
4 Cole GW, Barr RJ. An elastic tissue defect in dermatofibrosis lenticularis disseminata: Buschke–Ollendorff syndrome. *Arch Dermatol* 1982; **118**: 44–6.
5 Uitto J, Santa Cruz DJ, Starcher BC *et al.* Biochemical and ultrastructural demonstration of elastin accumulation in the skin lesions of the Buschke–Ollendorff syndrome. *J Invest Dermatol* 1981; **76**: 284–7.
6 Danielsen L, Midtgaard K, Christiensen HE. Osteopoikilosis associated with dermatofibrosis lenticularis disseminata. *Arch Dermatol* 1969; **100**: 465–70.
7 Reymond JL, Stoebner P, Beani JC *et al.* Buschke–Ollendorff syndrome: an electron-microscopic study. *Dermatologica* 1983; **166**: 64–8.
8 Giro GM, Duvic M, Smith LT *et al.* Buschke–Ollendorf syndrome associated with elevated elastin production by affected skin fibroblasts in culture. *J Invest Dermatol* 1992; **99**: 129–37.
9 Ramme K, Kolde G, Stadler R. Dermatofibrosis lenticularis disseminata mit Osteopoikilie. *Hautarzt* 1993; **44**: 312–4.
10 Atherton DJ, Wells RS. Juvenile elastoma and osteopoikilosis (the Buschke–Ollendorff syndrome). *Clin Exp Dermatol* 1982; **7**: 109–13.
11 Morrison JGL, Wilson-Jones E, MacDonald DM. Juvenile elastoma and osteopoikilosis (the Buschke–Ollendorff syndrome). *Br J Dermatol* 1977; **97**: 417–22.
12 Verbov J. Buschke–Ollendorff syndrome (disseminated dermatofibrosis with osteopoikilosis). *Br J Dermatol* 1977; **96**: 87–90.
13 Reinhardt LA, Rountree CB, Wilkin JK. Buschke–Ollendorff syndrome. *Cutis* 1983; **31**: 94–6.

14 Trattner A, David M, Rothem A *et al.* Buschke–Ollendorff syndrome of the scalp: histologic and ultrastructural findings. *J Am Acad Dermatol* 1991; **24**: 822–4.
15 Smith AD, Waisman M. Connective tissue nevi: familial occurrence and association with osteopoikilosis. *Arch Dermatol* 1960; **81**: 249–52.
16 Hellemans J, Debeer P, Wright M *et al.* Germline LEMD3 mutations are rare in sporadic patients with isolated melorheostosis. *Hum Mutat* 2006; **27**: 290.
17 Hellemans J, Preobrazhenska O, Willaert A *et al.* Loss-of-function mutations in LEMD3 result in osteopoikilosis, Buschke-Ollendorff syndrome and melorheostosis. *Nat Genet* 2004; **36**: 1213–8.
18 Berlin R, Hedensio B, Lilja B *et al.* Osteopoikilosis: a clinical and genetic study. *Acta Med Scand* 1967; **181**: 305–14.
19 Schnur RE, Grace K, Herzberg A. Buschke–Ollendorff syndrome, otosclerosis and congenital spinal stenosis. *Pediatr Dermatol* 1994; **11**: 31–4.
20 Piette-Brion B, Lowy-Motulsky M, Ledoux-Corbusier M, Achten G. Dermatofibromas, elastomas and deafness: a new case of the Buschke–Ollendorff syndrome? *Dermatologica* 1984; **168**: 255–8.
21 Walpole IR, Manners PJ. Clinical considerations in Buschke–Ollendorff syndrome. *Clin Genet* 1990; **37**: 59–63.
22 Schorr WF, Opitz JM, Reyes CN. The connective tissue nevus–osteopoikilosis syndrome. *Arch Dermatol* 1972; **106**: 208–14.
23 Dela Salmoniere P, Janier M, Chemlal K *et al.* Buschke–Ollendorff syndrome. *Ann Dermatol Vénéréol* 1994; **121**: 718–20.
24 Drouin CA, Grenon H. The association of Buschke-Ollendorf syndrome and nail-patella syndrome. *J Am Acad Dermatol* 2002; **46**: 621–5.
25 Menten B, Buysse K, Zahir F *et al.* Osteopoikilosis, short stature and mental retardation as key features of a new microdeletion syndrome on 12q14. *J Med Genet* 2007; **44**: 264–8.
26 Bordas X, Ferrandiz C, Ribera M, Calofre E. Papular elastorrhexis: a variant of nevus anelasticus? *Arch Dermatol* 1987; **123**: 433–4.
27 Sears JK, Stone MS, Argenyi Z. Papular elastorrhexis: a variant of connective tissue nevus. *J Am Acad Dermatol* 1988; **29**: 409–14.
28 Choonhakarn C, Jirarattanapochai K. Papular elastorrhexis: a distinct variant of connective tissue nevi or an incomplete form of Buschke–Ollendorff syndrome. *Clin Exp Dermatol* 2002; **27**: 454–7.
29 Lee SH, Park SH, Song KY *et al.* Papular elastorrhexis in childhood improved by intralesional injections of triamcinolone. *J Dermatol* 2001; **28**: 569–71.
30 Schirren H, Schirren CG, Stolz W *et al.* Papular elastorrhexis: a variant of dermatofibrosis lenticularis disseminate (Buschke–Ollendorff syndrome)? *Dermatology* 1994; **189**: 368–72.
31 Ryder HF, Antaya RJ. Nevus anelasticus, papular elastorrhexis, and eruptive collagenoma: clinically similar entities with focal absence of elastic fibers in childhood. *Pediatr Dermatol* 2005; **22**: 153–7.
32 Crivellato E. Disseminated nevus anelasticus. *Int J Dermatol* 1986; **25**: 171–3.
33 Lewandowsky F. Uber einem eigentumlichen Nevus der Brustgegend. *Arch Dermatol Syphilol* 1921; **131**: 90–4.
34 Staricco R, Mehregan AH. Nevus elasticus and nevus elasticus cascularis. *Arch Dermatol* 1961; **84**: 943–7.
35 Lewis KG, Bercovitch L, Dill SW, Robinson-Bostom L. Acquired disorders of elastic tissue: Part II. Decreased elastic tissue. *J Am Acad Dermatol* 2004; **51**: 165–85.
36 De Graciansky P, Leclercq R. Le 'naevus elasticus' en tumeurs disséminées. *Ann Dermatol Syphiligr* 1960; **87**: 5–25.
37 Weidman FD, Anderson NP, Ayres S. Juvenile elastoma. *Arch Dermatol Syphilol* 1933; **28**: 182–9.
38 Fork HE, Sanchez RL, Wagner RF *et al.* A new type of connective tissue nevus: isolated exophytic elastoma. *J Cutan Pathol* 1991; **18**: 457–63.
39 Becke RFA, Musso LA. An unusual epithelial-connective tissue naevus with perifollicular mucinosis. *Aust J Dermatol* 1978; **19**: 118–20.
40 Sosis AC, Johnson WC. Connective tissue nevus. *Dermatologica* 1972; **144**: 57–62.

Proteoglycan naevi

Mucinous naevus

Synonyms
- Naevus mucinosus
- Linear connective tissue naevus of the proteoglycan type

This rare naevus may in the past have been reported as cutaneous or papular mucinosis of infancy [1]. Histologically [2], these lesions are characterized by large amounts of proteoglycan in the superficial dermis, with variable overlying hyperkeratosis, acanthosis and elongation of rete ridges. Van Gieson staining shows a broad band in the upper third of the dermis in which elastic and collagen fibres are virtually absent, and alcian blue staining at pH 2.5 shows accumulation of proteoglycan in this area, which disappears following pre-treatment with hyaluronidase. It seems that proteoglycan synthesis is upregulated in fibroblasts of the upper dermis [3].

Clinically, the lesions comprise asymptomatic groups of flesh-coloured or slightly pigmented papules having a firm velvety surface and a tendency to coalesce to form plaques [3–5]. They are generally linear in disposition. Lesions may be present from birth [1,2] but may also develop some years later.

Clinically, the differential diagnosis of mucinous naevus includes connective tissue naevi of other types and the skin lesions of Hunter's syndrome (mucopolysaccharidosis type II) [6]. Histologically, one would need to consider papular mucinosis (lichen myxoedematosus), acral persistent papular mucinosis, self-healing juvenile cutaneous mucinosis and cutaneous focal mucinosis.

References

1 McGrae JD. Cutaneous mucinosis of infancy: a congenital and linear variant. *Arch Dermatol* 1983; **119**: 272–3.
2 Chang SE, Kang SK, Kim ES *et al.* A case of congenital mucinous nevus: a connective tissue nevus of the proteoglycan type. *Pediatr Dermatol* 2003; **20**: 229–31.
3 Yokogawa M, Kamakura T, Ishiguro H *et al.* Mucinous nevus. *J Dermatol* 2005; **32**: 30–3.
4 Redondo Bellon P, Vasquez-Doval J, Idoate M, Quintanilla E. Mucinous nevus. *J Am Acad Dermatol* 1993; **28**: 797–8.
5 Brakman M, Starink THM, Tafelkruyer J, Bos JD. Linear connective tissue naevus of the proteoglycan type ('naevus mucinosus'). *Br J Dermatol* 1994; **131**: 368–70.
6 Demitsu T, Kakurai M, Okubo Y *et al.* Skin eruption as the presenting sign in Hunter syndrome IIB. *Clin Exp Dermatol* 1999; **24**: 179–82.

Fibrous tissue naevi

Fibrous hamartoma of infancy

Definition. Fibrous hamartoma of infancy is a benign superficial mesenchymal tumour.

Clinical features. This lesion appears during the first 2 years of life, and can be present at birth [1,2]. It may be more common in boys [1,3]. It presents characteristically as a slowly enlarging, asymptomatic, dermal nodule on the trunk, particularly in the axilla, and the upper limbs [2,3] but it may occur at almost any site, including the scrotum [4] and hand [5]. It may be several centimetres in diameter with the overlying skin stretched and shiny [6]. Occasionally there are multiple lesions [5,7]. Coarse hairs may be present [7–9].

Pathology. Histologically, fibrous hamartoma of infancy comprises a mixture of spindle cells forming fascicles, clumps of round cells resembling immature mesenchyme, and mature adipose tissue, located in the deeper part of the dermis and/or the subcutis [1,10]. Eccrine changes are often present in the overlying epidermis [11]. Various chromosomal anomalies reported in two lesions

are difficult to interpret [12]. Occurrence in a child with Williams syndrome suggests a possible link with the elastin gene [8].

Treatment. It can be cured by local excision, which need not be radical [10]. Recurrence rarely occurs [9].

References

1 Sotelo-Avila C, Bale PM. Subdermal fibrous hamartoma of infancy. *Pediatr Pathol* 1994; **14**: 39–52.
2 Scott DM, Pena JR, Omura EF. Fibrous hamartoma of infancy. *J Am Acad Dermatol* 1999; **41**: 857–9.
3 Paller AS, Gonzalez-Crussi F, Sherman JO. Fibrous hamartoma of infancy. *Arch Dermatol* 1989; **125**: 88–91.
4 Thami GP, Jaswal R, Kanwar AJ. Fibrous hamartoma of infancy in the scrotum. *Pediatr Dermatol* 1998; **15**: 326.
5 Keskin M, Tosun Z, Toy H, Savaci N. Subdermal fibrous hamartoma of infancy in the hand. *Scand J Plast Reconstr Surg Hand Surg* 2007; **41**: 211–4.
6 Arioni C, Bellini C, Oddone M *et al.* Congenital fibrous hamartoma of the knee. *Pediatr Radiol* 2006; **36**: 453–5.
7 Yoon TY, Kim JW. Fibrous hamartoma of infancy manifesting as multiple nodules with hypertrichosis. *J Dermatol* 2006; **33**: 427–9
8 Togo T, Araki E, Ota M *et al.* Fibrous hamartoma of infancy in a patient with Williams syndrome. *Br J Dermatol* 2007; **156**: 1052–5.
9 Imaji R, Goto T, Takahashi Y *et al.* A case of recurrent and synchronous fibrous hamartoma of infancy. *Pediatr Surg Int* 2005; **21**: 119–20.
10 Carretto E, Dall'Igna P, Alaggio R *et al.* Fibrous hamartoma of infancy: an Italian multi-institutional experience. *J Am Acad Dermatol* 2006; **54**: 800–3.
11 Grynspan D, Meir K, Senger C, Ball NJ. Cutaneous changes in fibrous hamartoma of infancy. *J Cutan Pathol* 2007; **34**: 39–43.
12 Rougemont AL, Fetni R, Murthy S, Fournet JC. A complex translocation (6;12;8)(q25;q24.3;q13) in a fibrous hamartoma of infancy. *Cancer Genet Cytogenet* 2006; **171**: 115–8.

Infantile myofibroma

Infantile myofibroma is a tumour composed of a mixture of myofibroblasts and haemangiopericytoma-like areas [1]. It may occur as a solitary lesion, multiple lesions or diffusely in the skin and other organs. It appears in the first 2 years, sometimes at birth, usually on the head, neck or upper trunk. It may grow rapidly in the neonatal period, with ischaemic necrosis of the overlying skin, but despite their sometimes alarming appearance single congenital lesions usually regress spontaneously.

Reference

1 Jurcic V, Perkovic T, Pohar-Marinsek Z *et al.* Infantile myofibroma in a prematurely born twin: a case report. *Pediatr Dermatol* 2003; **20**: 345–9.

Differential diagnosis of connective tissue naevi

Conditions to be considered in the differential diagnosis of connective tissue naevi can broadly be separated on the basis of shape. Papular lesions might be confused with congenital smooth muscle hamartoma, leiomyomas, and neurofibromas, while linear lesions must be differentiated from epidermal naevi and naevus lipomatodes superficialis.

Muscle naevi

Congenital smooth muscle hamartoma

Synonym

- Congenital arrector pili hamartoma

Definition. Congenital smooth muscle hamartoma is a malformation of pilar smooth muscle, first described by Sourreil *et al.* [1]. It is relatively common, occurring in about one in 3000 births [2]. Familial cases have been reported [3], but most are sporadic.

Pathology. The histology shows well-defined bundles of smooth muscle fibres, which stain with Masson's trichrome [4–6]. The fibres themselves are generally long and straight, and extend in different directions. Each bundle is surrounded in turn by a clear space and by collagen. They are scattered over a wide area in the reticular dermis, and may extend into the subcutaneous fat. They may show a relationship to hair follicles [7]. Sometimes, there is associated hyperkeratosis, papillomatosis and increased epidermal pigmentation [6]. Electron microscopy has shown characteristic wavy or whorled myofilaments within the smooth muscle cells, and axons, mostly unmyelinated, adjacent to the smooth muscle bundles [4,5,8,9]. Immunohistochemistry shows that the muscle cells express smooth muscle actin and desmin, and there is a proliferation of CD34 positive dermal dendritic cells [7].

Clinical features. Smooth muscle hamartoma presents at birth or during the first few weeks of life, most often on the trunk or proximal limbs, as a variably indurated asymptomatic plaque, with irregular poorly defined margins, 1–10 cm across (Fig. 18.7), often showing prominent follicular papules [2,4–8,10–12]. Usually skin-coloured or faintly erythematous initially, subtle bluish brown pigmentation is a feature of the established lesion [13]. Firm stroking may provoke temporarily increased induration or piloerection, sometimes called the 'pseudo-Darier sign' [2,7,10,14]; this may diminish with age [15]. Exposure to cool or warm air can produce the same effect [7]. Occasionally, fasciculation has been reported [11,16]. In the majority of cases, there is a single plaque, but more extensively distributed, multiple lesions have also been reported [3,14,17,18].

Linear variants of congenital smooth muscle hamartoma have been reported, either with an atrophic appearance [19], or with hyperpigmentated perifollicular papules [20].



Fig. 18.7 Congenital smooth muscle hamartoma on the thigh.

Congenital smooth muscle hamartomas probably persist indefinitely [8], perhaps with gradual slight diminution in induration and hypertrichosis [2]. No significant associated abnormalities have been reported.

Diagnosis. Differential diagnosis is from solitary mastocytomas, pilar leiomyomas and connective tissue naevi, which are not hypertrichotic, and from congenital melanocytic naevi [13], simple hypertrichotic naevi and Becker's naevi. The greatest confusion has been with Becker's naevi, which may feature smooth muscle bundles in the dermis [21]. Lesions described in the literature as '*congenital Becker's naevi*' have been congenital smooth muscle hamartomas [22,23], and the two conditions are generally distinguishable by their age of onset, and by their characteristic histological features [4,14]. Acquired smooth muscle hamartoma [24–26] is distinct from congenital smooth muscle hamartoma. Congenital plexiform neurofibromas are frequently hypertrichotic [27], but are generally softer than congenital smooth muscle hamartomas, and are of course histologically distinctive.

References

1 Sourreil MMP, Beylot MC, Delfour MM. Hamartome par hyperplasie des muscles arrecteurs des poils chez un nourrison d'un mois. *Bull Soc Fr Dermatol Syphilol* 1969; **76**: 602.
2 Zvulunov A, Rotem A, Merlob P *et al.* Congenital smooth muscle hamartoma. *Am J Dis Child* 1990; **144**: 782–4.
3 Gualandri L, Cambiaghi S, Ermacora E *et al.* Multiple familial smooth muscle hamartomas. *Pediatr Dermatol* 2001; **18**: 17–20.
4 Berger TG, Levin MW. Congenital smooth muscle hamartoma. *J Am Acad Dermatol* 1984; **11**: 709–12.
5 Goldman MP, Kaplan RP, Heng MC. Congenital smooth muscle hamartoma. *Int J Dermatol* 1987; **26**: 448–52.
6 Johnson MD, Jacobs AH. Congenital smooth muscle hamartoma. *Arch Dermatol* 1989; **125**: 820–2.
7 Viglizzo G, Nemelka O, Nozza P *et al.* Congenital smooth muscle hamartoma presenting with an unusual pseudo-Darier's sign. *Clin Exp Dermatol* 2006; **31**: 148–9.
8 Bronson DM, Fretzin DF, Farrell LN. Congenital pilar and smooth muscle nevus. *J Am Acad Dermatol* 1983; **8**: 111–4.
9 Tsambaos D, Orfanos CE. Cutaneous smooth muscle hamartoma. *J Cutan Pathol* 1982; **9**: 33–42.
10 Gagne EJ, Su WP. Congenital smooth muscle hamartoma of the skin. *Pediatr Dermatol* 1993; **10**: 142–5.
11 Metzker A, Amir J, Rotem A *et al.* Congenital smooth muscle hamartoma of the skin. *Pediatr Dermatol* 1984; **2**: 45–8.
12 Holst VA, Junkins-Hopkins JM, Elenitsas R. Cutaneous smooth muscle neoplasms: clinical features, histologic findings, and treatment options. *J Am Acad Dermatol* 2002; **46**: 477–90.
13 Hanke CW, O'Brian JJ, Peters WC *et al.* Congenital smooth muscle hamartoma masquerading as congenital pigmented nevus. *J Dermatol Surg Oncol* 1985; **11**: 714–7.
14 Slifman NR, Harrist TJ, Rhodes AR. Congenital arrector pili hamartoma. *Arch Dermatol* 1985; **121**: 1034–7.
15 Berberian BJ, Burnett JW. Congenital smooth muscle hamartomas: a case report. *Br J Dermatol* 1986; **115**: 711–4.
16 Fine HL, Possick PA, Myrow RE. Transient rippling of the skin (smooth muscle hamartoma?). *Arch Dermatol* 1974; **110**: 141.
17 Guillot B, Huet P, Joujoux JM, Lorette G. Hamartomes musculaires lisses congenitaux multiples. *Ann Dermatol Vénéréol* 1998; **125**: 118–20.
18 Prigent F. Hamartome musculaire lisse hemicorporel congenital. *Rev Eur Dermatol MST* 1990; **2**: 461–5.
19 Grau-Massanes M, Raimer S, Colome-Grimmer M *et al.* Congenital smooth muscle hamartomas presenting as a linear atrophic plaque: case report and review of the literature. *Pediatr Dermatol* 1996; **13**: 222–5.
20 Jang H-S, Kim M-B, Oh C-K *et al.* Linear congenital smooth muscle hamartoma with follicular spotted appearance. *Br J Dermatol* 2000; **142**: 138–42.
21 Haneke E. The dermal component in melanosis naeviformis Becker. *J Cutan Pathol* 1979; **6**: 53–8.
22 Chapel TA, Tavafoghi V, Mehregan AH *et al.* Becker's melanosis: an organoid hamartoma. *Cutis* 1981; **27**: 405–6.
23 Karo KR, Gange RW. Smooth muscle hamartoma: possible congenital Becker's nevus. *Arch Dermatol* 1981; **117**: 678–9.
24 De la Espriella J, Grossin M, Marinho E, Belaich S. Smooth muscle hamartoma. *Ann Dermatol Vénéréol* 1993; **120**: 879–83.
25 Darling TN, Kamino H, Murray JC. Acquired cutaneous smooth muscle hamartoma. *J Am Acad Dermatol* 1993; **28**: 844–5.
26 Hsiao GH, Chen J-S. Acquired genital smooth muscle hamartoma. *Am J Dermatopathol* 1995; **17**: 67–70.
27 Riccardi VM, Eichner JE. Von Recklinghausen NF: overview; general growth and development. In: Riccardi VM, Eichner JF, eds. *Neurofibromatosis*. Baltimore: Johns Hopkins University Press, 1986: 37–55.

Diffuse smooth muscle hamartoma

Several children have now been reported with an unusual, diffuse type of smooth muscle hamartoma, presenting a unique clinical appearance [1–8]. Histology shows changes identical to the solitary type of congenital smooth muscle hamartomas, frequently associated with fragmented elastic fibres [7]. The baby is born with excess folds of rather firm skin on the limbs, particularly at the ankles and wrists, giving a 'Michelin baby' appearance. There is associated diffuse hypertrichosis, which may be especially marked at birth [1]. The palmar skin may have a rather cerebriform appearance [1]. One child also had cutaneous mastocytosis of urticaria pigmentosa type [9], and another had a paracentric inversion of chromosome 7q [10]. A brother and sister were described who also had facial anomalies and mental retardation [11]. The hypertrichosis and dermatomegaly in the case reported by Glover *et al.* gradually diminished with time [David Atherton, personal communication].

The term 'Michelin tyre baby' has also been applied to a similar appearance caused by diffuse lipomatous infiltration [8,12] and associated with a variety of anomalies. It is not a single entity.

References

1 Glover MT, Malone M, Atherton DJ. Michelin tyre baby syndrome resulting from diffuse smooth muscle hamartoma. *Pediatr Dermatol* 1989; **6**: 329–31.
2 Larregue M, Vabre P, Cavaroc Y *et al.* Hamartome diffus des muscles arrecteurs et hypertrichose lanuguineuse congénitale. *Ann Dermatol Vénéréol* 1991; **11**: 796–8.
3 Oku T, Iwasaki K, Fujita H. Folded skin with an underlying cutaneous smooth muscle hamartoma. *Br J Dermatol* 1993; **129**: 606–8.
4 Truhan AP, Esterley NB. Hypertrichotic skin-colored patches in an infant. *Arch Dermatol* 1985; **121**: 1197–202.
5 Wallach D, Sorin M, Saurat J-H. Naevus musculaire généralisé avec aspect clinique de 'bébé Michelin'. *Ann Dermatol Vénéréol* 1980; **107**: 923–7.
6 Prigent F. Smooth muscle hamartoma and congenital hypertrichosis. *Ann Dermatol Vénéréol* 1992; **119**: 489.
7 Sato M, Ishikawa O, Miyachi Y *et al.* Michelin tyre syndrome: a congenital disorder of elastic fibre formation. *Br J Dermatol* 1997; **136**: 583–6.
8 Palit A, Inamadar AC. Circumferential skin folds in a child: a case of Michelin tire baby syndrome. *Indian J Dermatol Venereol Leprol* 2007; **73**: 49–51.
9 Patrizi A, Neri I, Varotti C. Un autre cas de naevus musculaire généralisé avec aspect clinique de 'bébé Michelin' associé à une mastocytose cutanée. *Ann Dermatol Vénéréol* 1989; **116**: 551–4.
10 Schnur RE, Herzberg AJ, Spinner N *et al.* Variability in the Michelin tire syndrome. *J Am Acad Dermatol* 1993; **28**: 364–70.
11 Kharfi M, Zaraa I, Chaouechi S *et al.* Michelin tire syndrome: a report of two siblings. *Pediatr Dermatol* 2005; **22**: 245–9.

12 Sardana K, Mendiratta V, Kakar N *et al.* Spontaneously improving Michelin tire baby syndrome. *Pediatr Dermatol* 2003; **20**: 150–2.

Congenital leiomyoma

Cutaneous leiomyomas are only very rarely present at birth. However, a case has been reported recently of a neonate born with a pedunculated, firm, purple, spherical mass attached to the heel, which proved to be a pilar-type leiomyoma histologically [1].

Reference

1 Lupton GP, Naik DG, Rodman OG. An unusual congenital leiomyoma. *Pediatr Dermatol* 1986; **3**: 158–60.

Striated muscle hamartoma

Synonyms

- Congenital rhabdomyomatous mesenchymal hamartoma
- Congenital midline hamartoma

This entity, recognized since 1986 [1–8], is usually congenital and solitary. It occurs at sites where striated muscle is found superficially. Most reported cases have occurred on the face, particularly on the chin [4,7–9], in a nostril [10] or on a lip [1], but others have been recorded on the anterior chest and in the perianal area [3]. They are usually soft and pedunculated or polypoid. Some may be elongated, and some have been branched. Rare plaque-like lesions occur in adults [2].

Histologically, these lesions show disordered bundles of striated muscle fibres in the reticular dermis and the subcutis. They may also contain well-developed appendageal structures such as hair follicles, sebaceous glands, eccrine glands and ducts, nerve bundles and intradermal lobules of fat. It is the characteristic presence of these elements that is highlighted by the term rhabdomyomatous mesenchymal hamartoma [11].

Many of the cutaneous appendages that are a major cutaneous feature of *Delleman's syndrome* are striated muscle hamartomas, and any child in whom striated muscle hamartoma has been found should be examined carefully for other features of this syndrome [12]. Some cases of striated muscle hamartoma have occurred in association with a limited number of features that suggest the child may have had an incomplete form of Delleman's syndrome [13]. In one child, a lesion on the forehead contained a dermoid cyst and was associated with an underlying nasofrontal bone defect [14].

Striated muscle hamartomas need particularly to be distinguished from *fetal rhabdomyoma* and *neuromuscular hamartoma*. Fetal rhabdomyoma is a tumour of the subcutis that occurs in the neonate, and comprises a myxoid stroma containing undifferentiated mesenchymal cells with some that show differentiation towards embryonic skeleton [15]. Neuromuscular hamartoma, or a Triton tumour, occurs as a nodule in the subcutis comprising striated muscle mixed with nerves [16].

References

1 Hendrick SJ, Sanchez RL, Blackwell SJ *et al.* Striated muscle hamartoma: description of two cases. *Pediatr Dermatol* 1986; **3**: 153–7.
2 Kim HS, Kim YJ, Kim JW, Yu DS. Rhabdomyomatous mesenchymal hamartoma. *J Eur Acad Dermatol Venereol* 2007; **21**: 564–5.
3 Scrivener Y, Petiau P, Rodier-Bruant C *et al.* Perianal striated muscle hamartoma associated with hemangioma. *Pediatr Dermatol* 1998; **15**: 274–6.
4 Mills AE. Rhabdomyomatous mesenchymal hamartoma of the skin. *Am J Dermatopathol* 1989; **11**: 58–63.
5 Farris PE, Manning S, Vuitch F. Rhabdomyomatous mesenchymal hamartoma. *Am J Dermatopathol* 1994; **16**: 73–5.
6 Rosenberg AS, Kirk J, Morgan MB. Rhabdomyomatous mesenchymal hamartoma: an unusual dermal entity with a report of two cases and a review of the literature. *J Cutan Pathol* 2002; **29**: 238–43.
7 Ashfaq R, Timmons CF. Rhabdomyomatous mesenchymal hamartoma of skin. *Pediatr Pathol* 1992; **12**: 731–5.
8 Elgart GW, Patterson JW. Congenital midline hamartoma: case report with histochemical and immunohistochemical findings. *Pediatr Dermatol* 1990; **7**: 199–204.
9 Ortak T, Orbay H, Unlu E *et al.* Rhabdomyomatous mesenchymal hamartoma. *J Craniofac Surg* 2005; **16**: 1135–7.
10 Nakanishi H, Hashimoto I, Takiwaki H *et al.* Striated muscle hamartoma of the nostril. *J Dermatol* 1995; **22**: 504–7.
11 White G. Congenital rhabdomyomatous mesenchymal hamartoma. *Am J Dermatopathol* 1992; **14**: 64–5.
12 Sanchez RL, Raimer SS. Clinical and histological features of striated muscle hamartoma: a possible relationship to Delleman's syndrome. *J Cutan Pathol* 1994; **16**: 40–6.
13 Sahn EE, Garen PD, Pai GS *et al.* Multiple rhabdomyomatous mesenchymal hamartomas of the skin. *Am J Dermatopathol* 1990; **12**: 485–91.
14 Takeyama J, Hayashi T, Sanada T *et al.* Rhabdomyomatous mesenchymal hamartoma associated with nasofrontal meningocele and dermoid cyst. *J Cutan Pathol* 2005; **32**: 310–3.
15 Di Sant'Agnese PA, Knowles DM. Extracardiac rhabdomyomatous tumors. *Cancer* 1980; **46**: 780–9.
16 Marckel SF, Enzinger FM. Neuromuscular hamartoma—a benign 'triton tumor' composed of mature neural and striated muscle elements. *Cancer* 1982; **49**: 140–4.

Fat naevi

Naevus lipomatodes cutaneus superficialis

In this rare disorder, collections of mature lipocytes are situated ectopically within the dermis [1]. Associated histological abnormalities of the dermal connective tissue, blood vessels and epidermal appendages may also be seen within the lesions [2,3]. Folliculosebaceous cystic hamartoma was reported within the naevus in two cases [4,5], with dermoid cysts as well in one [5]. Electron microscopy has shown that the lipocytes are closely associated with capillaries, and it has been suggested that they may originate from pericytes, as in fetal lipogenesis [6].

Clinically, there are two principal presentations [3]. In the classic form originally described by Hoffman and Zurhelle [7], a cluster of soft, fleshy, skin-coloured or yellow nodules is found, most commonly on the lower trunk, especially on the back, buttocks or hips or abdomen, and on the upper posterior thighs [1,3,5,8–10]. Lesions have also been reported less frequently at other sites including the face [4,11], scalp [12], neck [13], eyelid [14] and clitoris [15]. They are generally present at birth, but may first appear during childhood or adolescence [8,16], and usually remain unchanged thereafter. These nodules may be domed, sessile or pedunculated. Their surface is most often smooth, but can be wrinkled, cerebriform or they may have a peau d'orange texture. They can measure over 20 cm in diameter. They are occasionally hairy [8], may contain comedo-like plugs [3,17] and have been associated with café-au-lait [18] or hypopigmented [19] macules and occasionally ulceration [20]. One patient also had angiokeratomas of the scrotum

[21]. In another patient naevus lipomatosis superficialis mosaicism for a 2p24 deletion was found [22].

The second form comprises a solitary, domed or sessile papule, which develops in adult life, and has been reported at sites other than the lower trunk, including the knee, axilla, arm, ear and scalp [3,23–26].

Histologically, naevus lipomatodes cutaneus superficialis must be differentiated from dermal collections of fat sometimes seen in intradermal melanocytic naevi [3], and pedunculated lipofibroma [27]. Fat also lies very superficially in the skin lesions of focal dermal hypoplasia, although clinically this condition is unlikely to be mistaken for naevus lipomatodes superficialis.

References

1 Abel R, Dougherty JW. Nevus lipomatosus cutaneus superficialis (Hoffman–Zurhelle). *Arch Dermatol* 1962; **85**: 132–4.
2 Mehregan AH, Tavafoghi V, Ghandchi A. Nevus lipomatosus cutaneus superficialis. *J Cutan Pathol* 1975; **2**: 307–13.
3 Wilson Jones E, Marks R, Pongsehirun D. Naevus superficialis lipomatosus. *Br J Dermatol* 1975; **93**: 121–33.
4 Kang H, Kim SE, Park K *et al.* Nevus lipomatosus cutaneous superficialis with folliculosebaceous cystic hamartoma. *J Am Acad Dermatol* 2007; **56**: S55–7.
5 Brasanac D, Boricic I. Giant nevus lipomatosus superficialis with multiple folliculosebaceous cystic hamartomas and dermoid cysts. *J Eur Acad Dermatol Venereol* 2005; **19**: 84–6.
6 Reymond JL, Stoebner P, Amblard P. Nevus lipomatosus cutaneus superficialis: an electron microscopic study of four cases. *J Cutan Pathol* 1980; **7**: 295–301.
7 Hoffman E, Zurhelle E. Uber einen Naevus lipomatodes cutaneus superficialis der linken Glutaalgegend. *Arch Dermatol Syphilol* 1921; **130**: 327–33.
8 Finley AG, Musso LA. Naevus lipomatosus cutaneus superficialis (Hoffman–Zurhelle). *Br J Dermatol* 1972; **87**: 557–64.
9 Dotz W, Prioleau PG. Nevus lipomatosus cutaneus superficialis: a light and electron microscopic study. *Arch Dermatol* 1984; **120**: 376–9.
10 Lane JE, Clark E, Marzec T. Nevus lipomatosus cutaneus superficialis. *Pediatr Dermatol* 2003; **20**: 313–4.
11 Park HJ, Park CJ, Yi TY *et al.* Nevus lipomatosis superficialis on the face. *Int J Dermatol* 1997; **36**: 435–7.
12 Chanoki M, Sugamoto I, Suzuki S, Hamada T. Naevus lipomatosis cutaneus superficialis of the scalp. *Cutis* 1989; **43**: 143–4.
13 Das JK, Sengupta S, Gangopadhyay AK. Nevus lipomatosus superficialis over neck, an atypical site. *Indian J Dermatol Venereol Leprol* 2006; **72**: 66–7.
14 Kaw P, Carlson A, Meyer DR. Nevus lipomatosus (pedunculated lipofibroma) of the eyelid. *Ophthal Plast Reconstr Surg* 2005; **21**: 74–6.
15 Hattori R, Kubo T, Yano K *et al.* Nevus lipomatosus cutaneous superficialis of the clitoris. *Dermatol Surg* 2003; **29**: 1071–2.
16 Holtz KH. Beutrag zur Histologie des Naevus lipomatodes cutaneus superficialis (Hoffman–Zurhelle). *Arch Dermatol Syphilol* 1955; **199**: 275–86.
17 Cramer HJ. Zur nosologischen Stellung des Naevus lipomatodes cutaneus superfialis (Hoffman–Zurhelle). *Dermatol Wochenschr* 1960; **142**: 1218–22.
18 Pierini DO, Abulafia J, Lebedinsky J. Nevo lipomatoso cutaneus superficial (Hoffman–Zurhelle). *Arch Argent Dermatol* 1970; **20**: 33–8.
19 Robinson HM, Ellis FA. Nevus lipomatosus subepidermalis seu superficialis cutis. *Arch Dermatol Syphilol* 1937; **35**: 485–8.
20 Girglia HS, Bhattacharya SK. Naevus lipomatosus cutaneus superficialis. *Int J Dermatol* 1975; **14**: 273–6.
21 Al-Mutairi N, Joshi A, Nour-Eldin O. Naevus lipomatosus cutaneous superficialis of Hoffmann-Zurhelle with angiokeratoma of Fordyce. *Acta Derm Venereol* 2006; **86**: 92–3.
22 Cardot-Leccia N, Italiano A, Monteil MC *et al.* Naevus lipomatosus superficialis: a case report with a 2p24 deletion. *Br J Dermatol* 2007; **156**: 380–1.
23 Knoth W von. Über Naevus lipomatosus cutaneous superficialis Hoffman–Zurhelle und über Naevus naevocellularis partim lipomatodes. *Dermatologica* 1962; **125**: 161–73.
24 Sathyanarayana V, Weitzner S. Solitary nevus lipomatosus cutaneus superficialis of the knee. *Arch Dermatol* 1978; **114**: 1226–7.
25 Weitzner S. Solitary naevus lipomatosus cutaneus superficialis of scalp. *Arch Dermatol* 1968; **97**: 540–2.
26 Orteu CH, Hughes JR, Rustin MHA. Naevus lipomatosis cutaneus superficialis: overlap with connective tissue naevi (letter). *Acta Derm Venereol (Stockh)* 1996; **76**: 243–5.
27 Nogita T, Wong T-Y, Hidano A *et al.* Pedunculated lipofibroma. *J Am Acad Dermatol* 1994; **31**: 235–40.

Lipoblastoma

Lipoblastoma is a rare, benign tumour of embryonic white fat. The term lipoblastomatosis is used for the diffuse variant. Around 90% of cases present in the first 2 years of life [1], and occasionally at birth [2,3]. There appears to be a male : female preponderance of about 3 : 1 [4]. Most lesions occur on the extremities [1] but are also found on the trunk, and in the neck [5], groin [6] and scalp [7], and present as slowly enlarging flesh-coloured or reddish soft-tissue swellings that are asymptomatic unless they compress important structures such as the spinal cord [8].

The diagnosis is based on histology and cytogenetics. The tumour may be encapsulated and well-circumscribed or infiltrative [2]. Lobules of lipocytes and lipoblasts are mixed with spindle and stellate mesenchymal cells, separated by fibrous septa. Serial biopsies have demonstrated maturation of the immature lipoblasts into lipocytes [1,9]. There may be foci of extramedullary haematopoiesis and prominent capillaries [3,4]. Sometimes an Alcian blue-positive myxoid stroma [10] may cause confusion with myxoid liposarcoma, a tumour that is extremely rare in early childhood. Cytogenetic study reveals abnormalities of the long arm of chromosome 8 (8q11.13), leading to rearrangement of the PLAG1 gene [11,12].

Ultrasound usually shows a homogeneous hyperechoic mass, and CT conclusively identifies the fatty component [13]. Magnetic resonance imaging (MRI) can be helpful in gauging the degree of infiltration of these tumours [13,14].

Both localized and diffuse variants of this condition are benign; neighbouring tissues may be infiltrated but metastasis has never been reported. Treatment is surgical, but recurrence may occur [6], particularly in the diffuse variant [1,10].

References

1 Chung EB, Enzinger FM. Benign lipomatosis: an analysis of 35 cases. *Cancer* 1959; **12**: 912.
2 Mentzel T, Calonje E, Fletcher CDM. Lipoblastoma and lipoblastomatosis: a clinicopathological study of 214 cases. *Histopathology* 1993; **23**: 527–33.
3 Calobrisi SD, Garland JS, Esterly NB. Congenital lipoblastomatosis of the lower extremity in a neonate. *Pediatr Dermatol* 1998; **15**: 210–3.
4 Stringel G, Shandling B, Mancer K, Ein SH. Lipoblastoma in infancy and childhood. *J Pediatr Surg* 1982; **17**: 277–80.
5 Sakaida M, Shimizu T, Kishioka C, Majima Y. Lipoblastoma of the neck: a case report and literature review. *Am J Otolaryngol* 2004; **25**: 266–9.
6 Jung SM, Chang PY, Luo CC *et al.* Lipoblastoma/lipoblastomatosis: a clinicopathologic study of 16 cases in Taiwan. *Pediatr Surg Int* 2005; **21**: 809–12.
7 Singh V, Raju R, Singh M, Singh TH. Congenital lipoblastoma of the scalp. *Am J Perinatol* 2004; **21**: 377–81.
8 Sun JJ, Rasgon BM, Hilsinger RL Jr. Lipoblastomatosis of the neck causing hemiparesis: a case report and review of the literature. *Head Neck* 2003; **25**: 337–40.
9 Van Meurs DP. The transformation of an embryonic lipomas to a common lipomas. *Br J Surg* 1947; **34**: 282–5.
10 Chien AL, Song DH, Stein SL. Two young girls with lipoblastoma and a review of the literature. *Pediatr Dermatol* 2006; **23**: 152–6.

11 Brandal P, Bjerkehagen B, Heim S. Rearrangement of chromosomal region 8q11-13 in lipomatous tumours: correlation with lipoblastoma morphology. *J Pathol* 2006; **208**: 388–94.
12 Bourelle S, Viehweger E, Launay F *et al.* Lipoblastoma and lipoblastomatosis. *J Pediatr Orthop B* 2006; **15**: 356–61.
13 Moholkar S, Sebire NJ, Roebuck DJ. Radiological-pathological correlation in lipoblastoma and lipoblastomatosis. *Pediatr Radiol* 2006; **36**: 851–6.
14 Jabra AA, Taylor GA. MRI evaluation of superficial soft tissue lesions in children. *Pediatr Radiol* 1993; **23**: 425–8.

Encephalocraniocutaneous lipomatosis

This neurocutaneous disorder, recognized since 1970 [1], occurs sporadically and affects both sexes equally [1–5]. Its asymmetry and sporadic occurrence suggest a lethal autosomal mutation rescued by mosaicism [6]. A *de novo* mutation in the neurofibromatosis type 1 gene was found in one case [7]. Severity is variable, particularly with regard to neurological disability [8].

The characteristic cutaneous feature is multiple lipomatous hamartomas, usually present from birth [4,5]. These soft, skin-coloured or yellow, domed papules and nodules vary in diameter from a few millimetres to several centimetres. Most are on the head and neck, particularly in the scalp, where they may appear as hairless plaques. Lesions are usually unilateral, but bilateral lesions do occur [9]. Histologically, there is dermal fibrosis with increased subcutaneous fat extending into the reticular dermis. Smaller papular lesions may show changes more closely resembling angiofibromas [5,10]. Associated aplasia cutis congenita of the scalp [11] has been reported.

Associated non-cutaneous anomalies include fleshy desmoid tumours of the eye [12], mental retardation with or without convulsions, and maxillary odontomas [10]. Intracerebral abnormalities tend to be ipsilateral to the cutaneous lesions, the most characteristic being unilateral cerebral atrophy with ventricular dilatation. Lipomatous hamartomas may be present in the brain, leptomeninges [1] and spinal cord [13].

Differential diagnosis includes focal dermal hypoplasia, oculo-auriculovertebral dysplasia (Goldenhar syndrome), oculocerebrocutaneous syndrome (Delleman's syndrome), Proteus syndrome and epidermal naevus syndrome.

References

1 Haberland C, Perou M. Encephalocraniocutaneous lipomatosis. *Arch Neurol* 1970; **22**: 144–55.
2 Fishman MA, Chang CSC, Miller JE *et al.* Encephalocraniocutaneous lipomatosis. *Pediatrics* 1978; **61**: 580–2.
3 Grimalt R, Ermacora E, Mistura L *et al.* Encephalocraniocutaneous lipomatosis: case report and review of the literature. *Pediatr Dermatol* 1993; **10**: 164–8.
4 Nosti-Martinez D, del Castillo V, Duran-McKinster C *et al.* Encephalocraniocutaneous lipomatosis: an uncommon neurocutaneous syndrome. *J Am Acad Dermatol* 1995; **32**: 387–9.
5 Sanchez NP, Rhodes AR, Mandell F *et al.* Encephalocraniocutaneous lipomatosis: a new neurocutaneous syndrome. *Br J Dermatol* 1981; **104**: 89–96.
6 Happle R, Steijlen PM. Enzephalokraniokutane Lipomatose: ein nichterblicher Mosaikphänotyp. *Hautarzt* 1993; **43**: 19–22.
7 Legius E, Wu R, Eyssen M *et al.* Encephalocraniocutaneous lipomatosis with mutation in the *NF1* gene. *J Med Genet* 1995; **32**: 316–9.
8 Sofiatti A, Cirto AG, Arnone M. Encephalocraniocutaneous lipomatosis: clinical spectrum of systemic involvement. *Pediatr Dermatol* 2006; **23**: 27–30.
9 Rubegni P, Risulo M, Sbano P *et al.* Encephalocraniocutaneous lipomatosis (Haberland syndrome) with bilateral cutaneous and visceral involvement. *Clin Exp Dermatol* 2003; **28**: 387–90.
10 Andreadis DA, Rizos CB, Belazi M *et al.* Encephalocraniocutaneous lipomatosis accompanied by maxillary compound odontoma and juvenile angiofibroma: report of a case. *Birth Defects Res A Clin Mol Teratol* 2004; **70**: 889–91.
11 Torrelo A, Boente Mdel C, Nieto O *et al.* Nevus psiloliparus and aplasia cutis: a further possible example of didymosis. *Pediatr Dermatol* 2005; **22**: 206–9.
12 Kodsi SR, Bloom KE, Egbert JE *et al.* Ocular and systemic manifestations of encephalocraniocutaneous lipomatosis. *Am J Ophthalmol* 1994; **118**: 77–82.
13 Lasierra R, Valencia I, Carapeto FJ *et al.* Encephalocraniocutaneous lipomatosis: neurologic manifestations. *J Child Neurol* 2003; **18**: 725–9.

Congenital lipoma

Morphologically and histologically a congenital lipoma is the same as an acquired lipoma: it is a rounded, soft, smooth, skin-coloured mass. However, the location and significance are different. The most characteristic sites for lipoma in the neonate are the back [1] and the perineum [2–4]. Lipomas overlying the lumbosacral area often cause deviation of the upper end of the gluteal cleft and have particular significance as they may extend through bony defects into the spinal canal and attach to the spinal cord [2–10]. Other associated spinal abnormalities include tethered cord and tight filum terminale [11].

Lumbosacral lipomas may show some characteristic histological features, including absence of a capsule, fibrous tissue scattered within the mass, and a variety of unusual ectopic neuroectodermal and mesodermal tissues [12].

The same phenomenon, of a subcutaneous lipoma connecting with a lipoma within the nervous system, has been described for an intracerebral lipoma [13].

References

1 Enjolras O, Boukobza M, Jdid R. Cervical occult spinal dysraphism: MRI findings and the value of a vascular birthmark. *Pediatr Dermatol* 1995; **12**: 256–9.
2 Fukamizu H, Matsumoto K, Inoue K *et al.* Large vulvar lipoma. *Arch Dermatol* 1982; **118**: 447.
3 Tsoutsoplides GC. Surgical management of extensive congenital hemangiofibrolipoma of the vulva in an infant. *Am J Obstet Gynecol* 1980; **136**: 260–1.
4 Bataille D, Donner C, Cassart M *et al.* Perineal lipoma in a newborn boy—a case report. *Eur J Pediatr Surg* 2007; **17**: 136–8.
5 Colak A, Tahta K, Ozcan DE *et al.* Congenital lumbosacral lipomas presenting as a form of occult spinal dysraphism. *Z Neurochir* 1992; **53**: 15–9.
6 Tavafoghi V, Ghandchi A, Hambrick GW *et al.* Cutaneous signs of spinal dysraphism: report of a case with a tail-like lipomas and review of 200 cases in the literature. *Arch Dermatol* 1978; **114**: 573–7.
7 Pierre-Kahn A, Lacombe J, Pichon J *et al.* Intraspinal lipomas with spina bifida: prognosis and treatment in 73 cases. *J Neurosurg* 1986; **65**: 756–61.
8 Serna MJ, Vasquez-Doval J, Vanaclocha V *et al.* Occult spinal dysraphism: a neurological problem with a dermatologic hallmark. *Pediatr Dermatol* 1993; **10**: 149–52.
9 Llowe D, Ehrlich MC, Chapman PH *et al.* Congenital intraspinal lipomas: clinical presentation and response to therapy. *J Pediatr Orthop* 1987; **7**: 531–7.
10 Kang HS, Wang KC, Kim KM *et al.* Prognostic factors affecting urologic outcome after untethering surgery for lumbosacral lipoma. *Childs Nerv Syst* 2006; **22**: 1111–21.
11 Bao N, Chen ZH, Gu S *et al.* Tight filum terminale syndrome in children: analysis based on positioning of the conus and absence or presence of lumbosacral lipoma. *Childs Nerv Syst* 2007; **23**: 1129–34.
12 Walsh JW, Markesberry WR. Histological features of congenital lipomas of the lower spinal canal. *J Neurosurg* 1980; **52**: 564–9.
13 Given CA, Fields TM, Pittman T. Interhemispheric lipoma connected to subcutaneous lipoma via lipomatous stalk. *Pediatr Radiol* 2005; **35**: 1110–2.

Congenital lipomatosis

Congenital lipomatosis is a rare adipose tissue malformation in which accumulations of mature lipocytes are present in the

subcutis, sometimes infiltrating adjacent tissues, especially muscle [1,2]. The commonest sites are the trunk, particularly the chest, and the face [3,4]. The subcutaneous lesions form soft, usually mobile masses, which may be of substantial size. There may be underlying hypertrophy of bone and hemihypertrophy [5]. Facial infiltrating lipomatosis may be associated with intracranial abnormalities [6].

Such lesions may be associated with haemangiomas and with macrodactyly; the relationship between this disorder and the Proteus and Bannayan–Riley–Ruvalcaba syndromes is uncertain.

References

1 Lachman RS, Finklestein J, Mehringer CM *et al.* Congenital aggressive lipomatosis. *Skeletal Radiol* 1983; **9**: 248–54.
2 Nixon HH, Scobie WG. Congenital lipomatosis: a report of four cases. *J Pediatr Surg* 1971; **6**: 742–4.
3 Haloi AK, Ditchfield M, Penington A, Phillips R. Facial infiltrative lipomatosis. *Pediatr Radiol* 2006; **36**: 1159–62.
4 Malik A, Jagmohan P, Thukral BB *et al.* Congenital infiltrating lipomatosis of the face and neck. *Acta Radiol* 2004; **45**: 556–60.
5 Zienowicz RJ, Karacaoglu E, Woo A. Massive diffuse congenital lipomatosis of the lower extremity. *Plast Reconstr Surg* 2006; **118**: 63e–66e.
6 Aydingoz U, Emir S, Karli-Oguz K *et al.* Congenital infiltrating lipomatosis of the face with ipsilateral hemimegalencephaly. *Pediatr Radiol* 2002; **32**: 106–9.

Neurolipomatosis

Synonyms
- Neural fibrolipoma
- Fibrolipomatous hamartoma of nerve

This is a rare condition of young adults in which mature fat and fibrous tissue accumulate around peripheral nerves of an extremity [1–3]; the median nerve is most often affected. The presenting symptoms include pain, diminished sensation and a sausage-shaped tumour in the skin without muscle infiltration.

References

1 Silverman TA, Enzinger FM. Fibrolipomatous hamartoma of nerve. *Am J Surg Pathol* 1985; **9**: 7–14.
2 Yildirim S. Neural fibrolipoma of the ulnar nerve in the hand: a case report. *Hand Surg* 2005; **10**: 323–6.
3 Kim YJ, Kim SY, Kang SJ, Kim GM. Neural fibrolipoma. *J Am Acad Dermatol* 2005; **53**: 528–9.

'Michelin tyre' baby

Synonyms
- Generalized folded skin
- Michelin tyre baby syndrome

In this rare congenital anomaly, generalized rolls of redundant skin produce an appearance fancifully likened to the symbol of the French tyre manufacturer [1,2]. Most infants are otherwise normal and some improve spontaneously [3–5]. One baby girl with a localized area of folded lipomatous skin also had microcephaly, mental retardation and deletion of the short arm of chromosome 11 [6,7].

Histology usually shows diffuse lipomatous hypertrophy. However, some cases are due to generalized smooth muscle hamartomatosis, in which the redundant skin folds are associated with hypertrichosis. In one case, no histological abnormality was identifiable, but a distinctive associated clinical feature was the presence of widespread stellate scarring [8]. Two familial reports suggested autosomal dominant transmission [9,10].

Congenital generalized folding of the skin also occurs in the Beare–Stevenson cutis gyrata syndrome [11], in which corrugation of the skin is usually confined to the scalp, forehead, face and neck with furrowing of the palms and soles. Associated features include acanthosis nigricans, craniofacial anomalies, anogenital anomalies, skin tags and a prominent umbilical stump.

References

1 Ross CM. Generalised folded skin with an underlying lipomatous nevus: 'the Michelin tire baby'. *Arch Dermatol* 1969; **100**: 320–3.
2 Palit A, Inamadar AC. Circumferential skin folds in a child: a case of Michelin tire baby syndrome. *Indian J Dermatol Venereol Leprol* 2007; **73**: 49–51.
3 Sardana K, Mendiratta V, Kakar N *et al.* Spontaneously improving Michelin tire baby syndrome. *Pediatr Dermatol* 2003; **20**: 150–2.
4 Ross CM. Generalised folded skin with underlying lipomatosus nevus: the Michelin tyre baby. *Arch Dermatol* 1972; **106**: 766.
5 Ohtsuka H, Miyauchi S, Miki Y. Folded skin with lipomatous nevus in the forehead and scalp. *Ann Plast Surg* 1984; **12**: 364–8.
6 Gardner EW, Miller HM, Lowney ED. Folded skin associated with underlying nevus lipomatosus. *Arch Dermatol* 1979; **115**: 978–9.
7 Gardner EW, Miller HM, Lowney ED. Deletion of chromosome 11 in babies with Michelin tyre syndrome. *Arch Dermatol* 1980; **116**: 622.
8 Burgdorf WHC, Doran CK, Worret W-I. Folded skin with scarring: Michelin tyre baby syndrome? *J Am Acad Dermatol* 1982; **7**: 90–3.
9 Kunze J, Riehm H. A new genetic disorder: autosomal dominant multiple benign ring-shaped skin crease. *Eur J Pediatr* 1982; **138**: 301–3.
10 Niikawa N, Ishikiriyama S, Shikimani T. The Michelin tire baby syndrome—an autosomal dominant trait. *Am J Med Genet* 1985; **22**: 637–8.
11 Hall BD, Cadle RG, Morris CA, Cohen MM. Beare–Stevenson cutis gyrata syndrome. *Am J Med Genet* 1992; **44**: 82–9.

Vascular naevi

Classification. In previous years the classification of cutaneous vascular abnormalities has been beset by confusion, and has concentrated on the pathology of the vessel involved. In 1982, the classification was greatly improved by integrating the biological behaviour and natural history of vascular birthmarks [1–3]. This binary classification into haemangiomas and malformations continues to form the basis of terminology used today (Table 18.3). It was further modified in 1996 by the International Society for the Study of Vascular Anomalies (ISSVA) and will be used in this chapter.

Vascular tumours

Infantile haemangioma

Synonyms
- Haemangioma of infancy
- Strawberry naevus
- Capillary haemangioma

Definition. Infantile haemangiomas (IH) are benign vascular tumours that appear during the first months of life characterized

Table 18.3 Classification of vascular birthmarks [1,2,3].

Vascular tumours	Vascular malformations
Infantile haemangioma	High flow
Hepatic haemangioma	Arteriovenous
Neonatal haemangiomatosis	+ associated syndromes
Congenital haemangiomas	Low flow
Rapidly involuting congenital haemangioma (RICH)	Capillary
	+ associated syndromes
Non-involuting congenital haemangioma (NICH)	Venous malformations
	+ associated syndromes
Tufted angioma	Lymphatic malformations
Kaposiform haemangioendothelioma	+ associated syndromes
Haemangiopericytoma	Mixed/combined: capillary/venous/arterial/lymphatic
Angiokeratoma	
Syndromes with vascular tumours	
Bannayan–Riley–Ruvalcalba syndrome	

Table 18.4 Vascular birthmarks in childhood.

	Infantile haemangioma	Vascular malformation
Clinical features	Usually present at birth—precursor lesion, or within first week	Usually present at birth
	Proliferates rapidly	Proportionate growth
	Involutes over years	Present in adulthood
Epidemiology	More common in: girls > boys 3 : 1 premature infants <1500 g	No gender bias
	Infants who have had chronic villus sampling	
Immunohistochemistry	GLUT-1 positive	GLUT-1 negative

by a pattern of rapid proliferation, followed by a slower period of involution.

Classification. The reason for the confusion surrounding the nomenclature of infantile vascular tumours existed because of clinical confusion between haemangiomas and vascular malformations (Table 18.4). Terms such as strawberry naevi/haemangiomas, capillary/cavernous haemangiomas although still popular amongst the public and non-dermatologists, should be abandoned. This classification is by no means totally inclusive as both haemangiomas and vascular malformations can coexist in the same patient [4].

Infantile haemangiomas are the most common paediatric tumour, affecting 10–12% of infants by the first year of life [5,6] and a prevalence of 1–3% in the first few days of life [7–9]. They are seen more commonly in girls than boys with preponderance between 3 and 5 : 1 [10–12]. It is also apparent that haemangiomas are more common in premature infants, appearing in up to 30% of babies less than 1000 g and 15% of babies less than 1500 g [6,13–14].

References

1 Mulliken JB, Glowacki J. Hemangiomas and vascular malformations in infants and children: a classification based on endothelial characteristics. *Plast Reconstr Surg* 1982; **69**: 412–20.

2 Enjolras O, Mulliken JB. Vascular tumours and vascular malformations (new issues). *Adv Dermatol* 1997; **13**: 375–423.

3 Mulliken JB. Classification of vascular birthmarks. In: Mulliken JB, Young AE, eds. *Vascular Birthmarks*: *Hemangiomas and Malformations*. Philadelphia: Saunders; 1988: 24–37.

4 Garzon MC, Enjolras O, Frieden IJ. Vascular tumours and vascular malformations: evidence for an association. *J Am Acad Dermatol* 2000; **42**: 275–9.

5 Jacobs AH. Strawberry hemangiomas: the natural history of the untreated lesion. *Calif Med* 1957; **86**: 8–10.

6 Holmdahl K. Cutaneous hemangiomas in premature and mature infants. *Acta Paediatr* 1955; **44**: 370–9.

7 Hidano A, Purwoko R, Jitsukawa K. Statistical survey of skin changes in Japanese neonates. *Pediatr Dermatol* 1986; **3**: 140–4.

8 Jacobs AH, Walton RG. The incidence of birthmarks in the neonate. *Pediatrics* 1976; **58**: 218–22.

9 Pratt AG. Birthmarks in infants. *Arch Dermatol Syphilol* 1953; **67**: 302–5.

10 Esterly NB. Cutaneous hemangiomas, vascular stains and malformations, and associated syndromes. *Curr Prob Dermatol* 1995; **7**: 69–107.

11 Finn MC, Glowacki J, Mulliken JB. Congenital vascular lesions: clinical application of a new classification. *J Pediatr Surg* 1983; **18**: 894–9.

12 Moroz B. In: Williams HB, ed. *Symposium on Vascular Malformations and Melanotic Lesion.* St Louis: Mosby, 1983; 162–71.

13 Amir J, Metzker A, Krikler R *et al.* Strawberry hemangioma in preterm infants. *Pediatr Dermatol* 1987; **3**: 331–2.

14 Mulliken JB. Diagnosis and natural history of hemangiomas. In: Mulliken JB, Young AE, eds. *Vascular Birthmarks: Hemangiomas and Malformations*. Philadelphia: Saunders; 1988: 41–62.

Pathogenesis. The pathogenesis has yet to be fully elucidated but clues are evident from a better understanding of vascular biology. Haemangiomas are proliferative lesions composed of endothelial cells (EC), supporting pericytes, myeloid cells and other cells such as fibroblasts and mast cells [1,2]. Examination of isolated haemangioma EC and whole tumours suggests that haemangiomas arise from uncontrolled clonal expansion of EC [3]. The signals for this proliferation may come from abnormal local cellular signals and somatic mutations in EC or pericytes [4,5]. The processes leading to the development of new blood vessels is complex and poorly understood. In proliferating haemangiomas, there is increased expression of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor [6,7]. Other growth factors such as insulin growth factor and integrins relevant to angiogenesis, $\alpha5\beta3$ and $\alpha5\beta1$ are expressed in the proliferative phase of haemangiomas [2,8]. In involuting haemangiomas, VEGF expression is reduced with a concomitant rise in the expression of apoptosis-associated proteins [9]. Examination of mRNA expression patterns of angiogenic genes in haemangioma-derived EC showed high expression of VEGF receptor-2 and the angiopoetin receptors Tie-1, Tie-2 and angiopoetin-2 [10]. Interestingly, infantile haemangioma endothelium is distinct from normal vasculature because it expresses myeloid markers CD14, CD15, CD32 and CD83, which may imply that myeloid cells are important in growth of tumours [11]. Although little attention has been focused on mesenchymal stem cells in the development of IH, stem cells isolated from IH were not shown to be clonal, and found to differentiate into adipose tissue. This may be relevant to the development of the fibro-fatty residuum that remains after involution [12].

Although specific gene mutations have not yet been isolated for IH, evidence exists of non-random X-inactivation in endothelial cells from proliferating haemangiomas [3,4] and mutations of VEGF receptors in 2/15 proliferating haemangiomas [4].

It is now apparent that EC from IH can be distinguished from other vascular tumours and malformations by surface markers such as GLUT-1 , an erythrocyte-type glucose transporter protein, Lewis Y antigen, Fc gamma receptor II and merosin [13,14]. These markers are also expressed at high levels on placental vasculature, leading workers to postulate that this placental phenotype may be due to either a somatic mutation of a regulatory gene in endothelial precursor cells or that placental endothelial cells embolize to the fetal circulation [14]. There has been further evidence to support the placental origin theory, with very high levels of transcriptome similarity between tissue derived from placenta and haemangioma [15]. However, using highly sensitive molecular genetic techniques, with fluorescent *in situ* hybridization of haemangioma EC followed by PCR, genotyping of mother–child pairs showed no evidence of maternal–fetal chimerism [16,17]. Immunohistochemical studies examining the expression of vascular lineage-specific markers show that haemangioma EC coexpress CD34 and LYVE-1, a marker for lymphatic vessels, but are negative for Prox-1, a lymphatic lineage-specific homeobox protein. As this resembles the phenotype of the cardinal vein during embryogenesis, IH are possibly arrested in an early stage of vascular differentiation [18]. Clearly, the understanding of the pathogenesis of infantile haemangiomas is still evolving.

References

1 Gonzales-Crussi F, Reyes-Mugica M. Cellular hemangiomas ('hemangioendotheliomas') in infants: light microscopic, immunochemical and ultrastructural observations. *Am J Surg Pathol* 1991; **15**: 769–78.

2 Nguyen VA, Furhapter C, Romani N *et al.* Infantile hemangioma is a proliferation of beta 4-negative endothelial cells adjacent to HLA-DR-positive cells with dendritic cell morphology. *Hum Pathol* 2004; **35**: 739–44.

3 Boye E, Yu Y, Paranya G *et al.* Clonality and altered behaviour of endothelial cells from hemangiomas. *J Clin Invest* 2001; **107**: 745–52.

4 Walter JW, North PE, Waner M *et al.* Somatic mutation of vascular endothelial growth factor receptors in juvenile hemangioma. *Genes Chrom Cancer* 2002; **33**: 295–303.

5 Bielenberg DR, Bucana CD, Sanchez R *et al.* Progressive growth of infantile cutaneous haemangiomas is directly correlated with hyperplasia and angiogenesis of adjacent epidermis and inversely correlated with expression of the endogenous angiogenesis inhibitor, IFN-β. *Int J Oncol* 1999; **14**: 401–8.

6 Takahashi K, Mulliken JB, Kozakewich HPW *et al.* Cellular markers that distinguish the phases of hemangioma during infancy and childhood. *J Clin Invest* 1994; **93**: 2357–64.

7 Chang J, Most D, Bresnick S *et al.* Proliferative hemangiomas: analysis of cytokine gene expression and angiogenesis. *Plast Reconstr Surg* 1999; **103**: 1–9.

8 Ritter MR, Dorrell MI, Edmonds J *et al.* Insulin-like growth factor 2 and potential regulators of haemangioma growth and involution identified by large-scale expression analysis. *Proc Natl Acad Sci USA* 2002; **99**: 7455–60.

9 Razon MJ, Kräling BM, Mulliken JB *et al.* Increased apoptosis coincides with onset of involution in infantile hemangioma. *Microcirculation* 1998; **5**: 189–95.

10 Yu Y, Varughese J, Brown LF *et al.* Increased Tie2 expression, enhanced response to angiopoetin-1, and dysregulated angiopoetin-2 expression in hemangioma-derived endothelial cells. *Am J Pathol* 2001; **159**: 2271–80.

11 Ritter MR, Reinisch J, Friedlander SF *et al.* Myeloid cells in infantile hemangioma. *Am J Pathol* 2006; **168**: 621–8.

12 Yu Y, Fuhr J, Boye E *et al.* Mesenchymal stem cells and apidogenesis in hemangioma involution. *Stem Cells* 2006; **24**: 1605–12.

13 North PE, Waner M, Mizeracki A *et al.* GLUT1: A newly discovered immunohistochemical marker for juvenile hemangiomas. *Hum Pathol* 2000; **31**: 11–22.

14 North PE, Waner M, Mizeracki A *et al.* A unique microvascular phenotype shared by juvenile haemangiomas and human placenta. *Arch Dermatol* 2001; **137**: 559–70.

15 Barnes CM, Huang S, Kaipainen A *et al.* Evidence by molecular profiling of a placental origin of infantile hemangioma. *Proc Natl Acad Sci USA* 2005; **102**: 19097–102.

16 Pittman KM, Losken W, Kleinman ME *et al.* No evidence for maternal-fetal microchimerism in infantile haemangioma: a molecular genetic investigation. *J Invest Dermatol* 2006; **126**: 2533–8.

17 Régnier S, Dupin N, le Danff C *et al.* Endothelial cells in infantile haemangiomas originate from the child and not from the mother (a fluorescence *in situ* hybridization- based study). *Br J Dermatol* 2007; **157**: 158–60.

18 Dadras SS, North PE, Bertoncini J *et al.* Infantile hemangiomas are arrested in an early developmental vascular differentiation state. *Mod Pathol* 2004; **17**: 1068–79.

Pathology. During the early phase of growth, haemangiomas have solid groups of endothelial cells with few lumina and non-pleomorphic nuclei. The endothelial cells then flatten out as lumina develop and start to bulge outward. The cells are surrounded by a thickened basement membrane. As involution proceeds, the haemangioma has a more obvious lobular appearance, with islands of fibrous and fatty tissue separating these lobules. Mast cells are also seen at all phases of haemangiomas, as ultrastructural studies show an apparent interaction with connective tissue cells [1], although it is unclear whether they play a significant role. Immunohistochemical studies of IH show positive staining of markers for factor VIII, CD31 and VwF, as one would expect for vascular endothelium. In the growth phase, cells express proliferating cell nuclear antigen, VEGF and the integrin E-selectin. As involution proceeds, apoptosis is clearly evident [2].

Even though the diagnosis is usually based on clinical grounds, GLUT1 staining is a valuable confirmatory tool in difficult cases, such as congenital haemangiomas. Other less commonly used, specific markers that help to differentiate IH from venous malformations include merosin, Lewis Y antigen and FcgRIII [3].

References

1 Dethlefsen SM, Mulliken JB, Glowacki J. An ultrastructural study of mast cell interactions in hemangiomas. *Ultrastruct Pathol* 1986; **10**: 175–83.

2 Razon MJ, Kräling BM, Mulliken JB *et al.* Increased apoptosis coincides with onset of involution in infantile hemangioma. *Microcirculation* 1998; **5**: 189–95.

3 North PE , Waner M, Mizeracki A *et al.* A unique microvascular phenotype shared by juvenile haemangiomas and human placenta. *Arch Dermatol* 2001; **137**: 559–70.

Clinical features. Haemangiomas usually appear within the first month of life although they present as a precursor lesion in the immediate perinatal period. This can be very subtle, with a faint telangiectatic patch or even a patch of naevus anemicus-like pallor (Fig. 18.8). These signs can readily be missed and the former sign can mimic a capillary malformation. An exception to this is congenital haemangioma (see below) where it appears to be fully developed at birth. Soon after this, the precursor lesion begins to become palpable, often in a cluster giving rise to the 'strawberry' appearance. They may occur anywhere on the skin or mucosal surface [1]. The overall clinical appearance is dependent on how deep into the skin they extend. This may be superficial (50–60%),

where they are bright red in the period of proliferation, deep, in which they have a more blue appearance, or a combination of both superficial and deep (25–35%) [2]. The deeper lesions are located in the deep dermis and/or subcutis and do not have any overlying skin changes, which may make diagnosis more difficult or even delay diagnosis.

In addition to size, some IH involve a broad anatomic region or a recognized developmental unit such as the ear or nasal tip. Others are more discrete and well localized [3]. It is apparent that IH are not randomly distributed [4]. More than 50% of hamangiomas affect the head and neck, and their distribution may correspond to sites of embryological fusion lines and facial developmental metameres [4]. The anatomical location is of major importance in determining the potential for complications such as airway obstruction, visual disturbance and ulceration [5–8]. However, segmental patterns are not precisely defined, although four facial segments were identified when photographic data was analysed from a retrospective analysis of 294 facial haemangiomas [9].

The natural progression of haemangiomas can be divided into proliferation and involution (an artificial division but clinically useful). The mean period of proliferation is 5 months (ISSVA data, 2006) with deeper lesions often proliferating up to 12 months of age (Fig. 18.9). In this phase, lesions are more solid to the touch, especially during activity or crying. Involution may begin in the first year and may occur in one part, whilst other parts are still proliferating. Clinically, the lesion changes from bright red to a dull grey-red with a flattening of the surface. The plaques often break up into smaller islands and involution can continue for up to 10 years. The seminal studies of natural history of untreated IH, from which much of current day prognosis is based, showed that involution is completed in 50% by 5 years, 70% by 7 years and 90% by 9 years [10,11]. There is a wide variation in what remains after involution, ranging from complete disappearance (Fig. 18.10), telangiectasia (Fig. 18.11) or, more commonly, a fibrofatty residuum. There are several variables that may affect this outcome. Lesions that start to involute late tend to regress incompletely. In addition, certain sites, such as the lips, nose, and cheeks, leave cosmetically more disfiguring residua. IH with ulceration tend to leave white or yellow scars.



Fig. 18.8 Haemangioma precursor.

References

1 Margileth AM, Museles M. Cutaneous hemangiomas in children: diagnosis and conservative management. *JAMA* 1965; **194**: 523–6.

2 Esterly NB. Cutaneous hemangiomas, vascular stains and malformations, and associated syndromes. *Curr Prob Dermatol* 1995; **7**: 69–107.

3 Metry DW, Dowd CF, Barkovich AJ *et al.* The many faces of PHACE syndrome. *J Pediatr* 2001; **139**: 117–23.

4 Waner M, North PE, Scherer KA *et al.* The nonrandom distribution of facial hemangiomas. *Arch Dermatol* 2003; **139**: 869–75.

5 Zide BM, Glat PM, Stile FL *et al.* Vascular lip enlargement, I: haemangiomas—tenets of therapy. *Plast Reconstr Surg* 1997; **100**: 1664–73.

6 Haik BG, Karcioglu ZA, Gordon RA *et al.* Capillary hemangioma (infantile periocular haemangioma). *Surv Ophthalmol* 1994; **38**: 399–426.

7 Metry DW, Herbert AA. Benign cutaneous vascular tumours: when to worry, what to do. *Arch Dermatol* 2000; **136**: 905–14.



(a) (b) (c) (d)

Fig. 18.9 Evolution of facial and neck haemangiomas: (a) and (b) Day 1; (c) and (d) Day 10.



(a) (b)

Fig. 18.10 Resolution of infantile haemangioma on lower leg: (a) 6 months old; (b) 4 years.



(a) (b) (c)

Fig. 18.11 Large mixed infantile haemangioma at: (a) 3 months; (b) 16 months; and (c) 3 years. A course of oral prednisolone was given at 3 months.

8 Garzon MC, Frieden IJ. Hemangiomas: when to worry. *Pediatric Ann* 2000; **29**: 58–67.
9 Haggstrom AN, Drolet BA, Baselga E *et al.* Prospective study of infantile hemangiomas: clinical characteristics predicting complications and treatment. *Pediatrics* 2006; **118**: 882–7.
10 Mulliken JB. Diagnosis and natural history of hemangiomas. In: Mulliken JB, Young AE, eds. *Vascular Birthmarks*: *Hemangiomas and malformations*. Philadelphia: Saunders; 1988: 41–62.
11 Bowers RE, Graham EA, Tomlinson KM. The natural history of the strawberry nevus. *Arch Dermatol* 1960; **82**: 667–80.

Diagnosis. This is not usually difficult if the classical signs of a precursor lesion are present followed by a period of growth and involution. However, deep haemangiomas may pose more difficulty with differentiation from vascular malformations. The latter tend to stay fixed and may enlarge during physiological stimuli, for example puberty and pregnancy, and do not go through a period of involution. The use of CT and MRI scanning is not particularly helpful in aiding diagnosis, as both IH and vascular malformations are reported as haemangiomas. There is evidence to support the use of scanning in the delineation of the extent of a haemangioma, and its response to therapy, for example steroids or interferon [1,2]. There may be instances where histological samples may have to be sent for immunohistochemical analysis, as IH are GLUT1 positive (as well as merosin, Fcg receptor II and Lewis Y antigen positive). Other benign vascular lesions such as pyogenic granuloma, tufted angioma and kaposiform haemangioendothelioma, venous malformations and congenital haemangioma are GLUT1 negative [3].

References

1 Dubois J, Garel L, Grignon A *et al.* Imaging of hemangiomas and vascular malformations in children. *Acad Radiol* 1998; **5**: 390–400.
2 Burrows PE, Laor T, Paltiel H *et al.* Diagnostic imaging in the evaluation of vascular birthmarks. *Dermatol Clin* 1998; **16**: 455–88.
3 North PE , Waner M, Mizeracki A *et al.* A unique microvascular phenotype shared by juvenile haemangiomas and human placenta. *Arch Dermatol* 2001; **137**: 559–70.

Complications (Table 18.5). Even though most haemangiomas do not cause any significant problem to the individual in the short or long term, they can pose significant morbidity in a notable minority, as outlined below.

Ulceration (Fig. 18.12)
Ulceration is a common complication in up to 8–13% of IH [1], and is usually a problem during the proliferative phase. The pathogenesis of ulceration is not known, but possible contributory factors include friction, local bacterial colonization or tissue hypoxia due to rapid expansion [2]. It is one of the commonest reasons for referral to a specialist, and may cause pain, scarring and disfigurement. It occurs more commonly in haemangiomas of the head and neck and perineal areas (especially the lips and intertriginous regions). Large segmental haemangiomas are more prone to ulceration than focal haemangiomas [2]. It may also occur later in the life cycle of a haemangioma as a result of treatment with pulse dye laser or imiquimod. Haemorrhage, whilst a common worry amongst parents, is rarely heavy unless ulceration occurs over a large artery.

Secondary infection may occur as a consequence of ulceration or treatment and may rarely lead to septicaemia or osteomyelitis. There are usually other signs to alert the physician such as fever, local tenderness and discharge.

Table 18.5 Complications of infantile haemangiomas.

Ulceration
Heart failure
Visual impairment
Airway obstruction
Auditory canal obstruction
Disfigurement
Associated abnormalities:
Spinal dysraphism
PHACE syndrome

Heart failure
This may occur in large hepatic haemangiomas with arteriovenous or portovenous shunting leading to congestive cardiac failure [2] (see p. 18.52, Hepatic haemangioma).

References

1 Kim HJ, Colombo M, Frieden IJ. Ulcerated hemangiomas, clinical characteristics and response to therapy. *J Am Acad Dermatol* 2001; **44**: 962–72.
2 Frieden IJ, Haggstrom AN, Drolet BA. Infantile hemangiomas: Current knowledge, future directions. Proceedings of a research workshop on infantile hemangiomas. *Ped Dermatol* 2005; **22**: 383–406.

Visual disturbance [1–3] (Fig. 18.13)
Periocular haemangiomas usually involve the upper eyelid, but involvement of the lower eyelid is not uncommon. The most worrying complication is amblyopia, which occurs as a result of inadequate visual stimuli to the visual cortex. The ensuing visual



Fig. 18.12 Large segmental ulcerated infantile haemangioma.



Fig. 18.13 Eyelid haemangioma in line of vision.

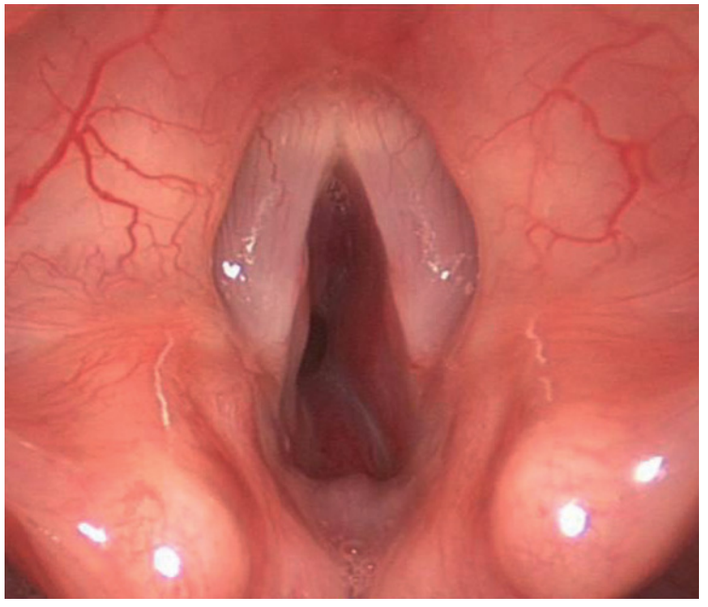


Fig. 18.14 Circumferential airway haemangioma.

impairment can be permanent if not detected early. It has been suggested that even a few days of visual loss can result in permanent loss. Astigmatism may also occur in haemangiomas through direct pressure on the globe. Strabismus leading to amblyopia is also a possibility if the haemangioma affects the movement of the extraocular muscles. Another relatively common complication is lacrimal duct obstruction due to direct pressure, leading to persistent epiphora. Less common complications include proptosis, exposure keratitis and ptosis.

References

1 Kusher BJ. Infantile orbital hemangiomas. *Int Pediatr* 1990; **5**: 249–57.
2 Haik BG, Jakobiec FA, Ellsworth RM *et al.* Capillary hemangioma of the lids and orbit: an analysis of the clinical features and therapeutic results in 101 cases. *Ophthalmology* 1979; **86**: 760–92.
3 Goldberg NS, Rosanova MA. Periorbital haemangiomas. *Dermatol Clin* 1992; **10**: 653–61.

Airway obstruction

Upper airway haemangiomas can be a cause for great concern. They may be focal or diffuse and lead to airway obstruction or feeding difficulty (Fig. 18.14). Affected children usually present with hoarseness, stridor, cyanosis or cough [1,2]. The beard distribution can be a useful indicator of subglottic involvement [3]. These children should be referred to an otolaryngologist and examined by direct laryngoscopy.

References

1 Shikani AH, Marsh BR, Jones MM *et al.* Infantile subglottic hemangiomas: an update. *Ann Otol Rhinol Laryngol* 1986; **95**: 336–47.
2 Riding K. Subglottic hemangioma: a practical approach. *J Otolaryngol* 1992; **22**: 419–21.
3 Orlow SJ, Isakoff MS, Blei F. Increased risk of symptomatic haemangiomas of the airway in association with cutaneous haemangiomas in a 'beard' distribution. *J Pediatr* 1997; **131**: 643–6.



Fig. 18.15 Residuum from nasal tip haemangioma.

Obstruction of the auditory canal

This is a possibility with some facial haemangiomas but is unlikely to cause any permanent hearing loss unless there is bilateral involvement.

Cosmetic disfigurement

Rarely some haemangiomas grow at an alarming rate and lead to some or many of the problems above as well as major cosmetic disfigurement [1]. These are the children in whom intervention should be started early and in whom multiple modalities may be required. Other sites are known not to fare well in the long term, such as the nose (sometimes referred to as the 'Cyrano nose') (Fig. 18.15) and the lower cheeks.

Reference

1 Enjolras O, Riche MC, Merland JJ *et al.* Management of alarming haemangiomas in infancy: a review of 25 cases. *Pediatrics* 1990; **85**: 491–7.

Associated abnormalities

A small but significant number of haemangiomas may be associated with structural abnormalities, and two recognized syndromes will be discussed.

Lumbosacral haemangiomas. These are usually present at birth as a telangiectatic patch which typically evolves into a plaque or vascular swelling in the midline or asymmetrically in the paraspinal region but always crosses the midline (Fig. 18.16). As with all midline lesions, one should consider the possibility of underlying defects such as a tethered spinal cord, and genitourinary anomalies including imperforate anus, renal defects, genital or sacral skin tags and genital abnormalities. The acronym PELVIS has been proposed to cover the association of large perineal haemangiomas (P) with the following congenital abnormalities: external genitalia malformations (E), lipomyelomeningocoele (L), vesicorenal abnormalities (V), imperforate anus (I) and skin tags (S) [1]. A different group has proposed the acronym SACRAL for a similar association of perineal haemangiomas and spinal dysraphism (S), anogenital anomalies (A), cutaneous anomalies (C), renal and urologic anomalies (R), associated with angioma (A) of lumbosacral localization (L) [2]. The absence of congenital defects does not negate the risk of tethered cord, and affected children should be investigated even though they appear to be neurologically normal. It is recommended that under the age of 4 months ultrasound is suitable for screening and above the age of 4 months MRI of the spine is preferable.



Fig. 18.16 Lumbosacral haemangioma overlying midline.

References

1 Girard C, Bigorre M, Guillot B *et al.* PELVIS syndrome. *Arch Dermatol* 2006; **142**: 884–8.

2 Stockman A, Boralevi F, Taieb A *et al.* SACRAL syndrome: spinal dysraphism, anogenital, cutaneous, renal and urologic anomalies, associated with an angioma of lumbosacral localization. *Dermatology* 2007; **214**: 40–5.

PHACE syndrome (OMIM #606519). Large facial segmental haemangiomas can be associated with other defects and the acronym PHACES was coined in 1996 referring to the association of posterior fossa defects, haemangiomas, arterial anomalies, cardiac defects (of which coarctation of the aorta is the commonest), eye abnormalities, sternal clefting or supraumbilical raphe. Only one extracutaneous feature is found in 70% of cases [1,2] and in a large prospective study was present in 20% of infants with large facial haemangiomas [3]. There is a striking sex preponderance of 90% [1,2] in favour of girls. The precise definition of what constitutes a large facial haemangioma is debatable and is something which is not measurable. However, it often affects several facial segments, may be bilateral and is often plaque-like with ulceration in multiple sites. The diagnosis of PHACES syndrome is made by the presence of a segmental facial infantile haemangioma in association with only one other congenital abnormality, because affected infants rarely suffer from the complete spectrum [2].

There appears to be a link between haemangiomas affecting the upper half of the face and the structural brain, cerebrovascular and eye abnormalities. Conversely, there appears to be a strong correlation between haemangiomas affecting the lower half of the face and the ventral developmental defects (Table 18.6).

The most common brain abnormality is a posterior fossa Dandy–Walker malformation. Less common findings may include hypogenesis of the cerebrum, corpus collosum or septum pellucidum, arachnoid cysts or microcephaly. Various vascular abnormalities may be found, such as hypoplastic vessels, anomalous branches or stenosis of the internal carotid artery. Over 50% of these abnormalities may lead to neurological sequelae: developmental

Table 18.6 Anomalies associated with PHACE syndrome [3,4].

System involved	Incidence	Specific type of abnormality
Structural brain	40%	Posterior fossa: Dandy–Walker malformation
		Hypoplasia of cerebellum, cerebrum, corpus callosum
Cerebrovascular abnormalities	40%	Carotid arterial anomalies
Cardiovascular	30%	Coarctation of the aorta
		Patent ductus arteriosus
		Ventricular or atrial septal defects
		Anomalous pulmonary vessels
Eye	<20%	Optic atrophy
		Retinal vascular abnormalities
		Congenital cataracts
Ventral developmental	20%	Sternal clefts or pits
		Supraumbilical raphe

delay, fits or strokes. In clinical terms, a posterior fossa malformation may be heralded by an increase in the head circumference. Eye abnormalities include iris hypoplasia, congenital cataracts, lens coloboma, optic atrophy or retinal vascular expansion. Cardiac defects include coarctation of the aorta, aneurysms and valvular stenosis, septal defects and anomalous pulmonary veins.

The suggested screening for a patient with a large facial haemangioma should therefore include: (i) an ultrasound of the head if less than 4 months, or preferably wait until an MRI can be performed, with additional MRI angiography at the same sitting, looking for vascular brain anomalies; and (ii) a cardiac examination looking for signs of coarctation, and an echocardiogram by a paediatric cardiologist. Any suspected eye abnormalities should trigger referral to a paediatric ophthalmologist.

References

1 Frieden IJ, Reese V, Cohen D. PHACE syndrome: the association of posterior fossa brain malformations, hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, and eye abnormalities. *Arch Dermatol* 1996; **132**: 307–11.

2 Metry DW, Dowd CF, Barkovich AJ *et al.*The many faces of PHACE syndrome. *J Pediatr* 2001; **139**: 117–23.

3 Metry DW, Haggstrom AN, Drolet BA *et al.* A prospective study of PHACE syndrome in infantile hemangiomas: demographic features, clinical findings and complications. *Am J Med Genet Part A* 2006; **140A**: 975–86.

4 Metry DW. A newborn girl with a large red plaque on her face. *Pediatr Ann* 2006; **35**: 423–6.

Management [1–3] (Table 18.7). The management of children with haemangiomas is open to debate, as the common belief amongst many general practitioners and paediatricians is that the natural history of by far the majority of lesions is spontaneous involution, albeit slow in a large number of children. However, a significant but very important minority of haemangiomas may cause functional problems or even permanent cosmetic disfigurement.

They are biologically diverse in their position and heterogeneous in their behaviour, making it difficult to establish protocols to suit all circumstances. However, a guiding principle should be as with all good medical practice— 'first do the patient no harm'.

In the 1950s and 1960s the outcomes of treatment with radiotherapy and surgery turned physicians away from intervention, and early results with argon lasers were not ideal [4–6]. New therapeutic modalities are now available and will be discussed below.

The decision to treat is obvious when IH are potentially life threatening, or function threatening, as in those haemangiomas with heart failure, ocular compromise or respiratory distress. The site and size of the haemangioma will dictate the need for treatment. Sites such as the lips, nose or ears are more likely to lead to permanent anatomical distortion and scarring [7,8]. The scarring from large plaque-like segmental haemangiomas on the face is potentially more serious than a similar lesion on the trunk.

Table 18.7 The major goals of management of infantile haemangiomas [1].

Prevention or reversal of life-threatening complications
Prevention of permanent disfigurement from skin changes following involution
Reduction of psychological distress to a minimum
Reduction of toxicity and resultant sequelae from systemic therapy
Avoidance of excessive scarring from aggressive surgery
Treatment of ulceration to minimize scarring.

The point in evolution of the haemangioma will also be relevant to management, and is closely linked with the age of the child. Haemangiomas of similar appearance may be in involution in an older child whilst in the growth phase in a child at 4 months old. The decision to treat surgically, for example, should normally be taken after the haemangioma has completed its growth phase.

The developmental stage of the child must also be taken into account, as children start becoming body aware at 2–3 years of age, but realization of a problem leading to stigmatization rarely occurs before 4–5 years of age. The decision to continue a wait and see approach must be balanced against the emotional consequences of this decision [9]. All children must be treated on an individual basis, but the parents should have information to help guide their decision. This may take the form of serial photographs, examples of previous cases with before and after photos, and a full discussion of the risks and benefits of any treatment modality.

References

1 Frieden IJ. Which hemangiomas to treat and how? *Arch Dermatol* 1997; **133**: 1593–5.

2 Frieden IJ. Management of hemangiomas. *Pediatr Dermatol* 1997; **14**: 757–83.

3 Frieden IJ, Eichenfield LF, Esterly NB *et al.* Guidelines for care of hemangiomas of infancy. *J Am Acad Dermatol* 1997; **37**: 631–7.

4 Margileth AM, Museles M. Cutaneous hemangiomas in children: diagnosis and conservative management. *JAMA* 1965; **194**: 523–6.

5 Bowers RE, Graham EA, Tomlinson KM. The natural history of the strawberry nevus. *Arch Dermatol* 1960; **82**: 667–80.

6 Simpson JR. Natural history of cavernous haemangiomata. *Lancet* 1959; **2**: 1057–9.

7 Esterly NB. Cutaneous hemangiomas, vascular stains and malformations, and associated syndromes. *Curr Probl Dermatol* 1995; **7**: 65–108.

8 Enroljas O, Mulliken JB. The current management of vascular birthmarks. *Pediatrics* 1993; **10**: 311–3.

9 Tanner JL, Dechert MP, Frieden IJ. Growing up with a facial hemangioma: parental coping and adaptation. *Pediatrics* 1998; **101**: 446–52.

Active non-intervention

This term was coined to show this was an active decision to treat in a non-interventional manner, as long-term, prospective, observational studies show that many haemangiomas will regress and leave a fairly reasonable cosmetic result [1,2]. The difficulty arises with multiple sources of information and conflicting opinion amongst health professionals, friends and relatives. The cosmetic appearance at an early age may push parents to desire early intervention to remove the lesion as soon as possible.

Once again, the role of an experienced dermatologist is invaluable, in reassuring the parents about the natural history and talking through their anxieties. A common worry, for example, is the concern about the lesion bleeding if caught—something which rarely happens. The use of serial photography, as mentioned previously, can help to show changes which are not always appreciated when parents are seeing the child every day.

References

1 Margileth AM, Museles M. Cutaneous hemangiomas in children: diagnosis and conservative management. *JAMA* 1965; **194**: 523–6.

2 Bowers RE, Graham EA, Tomlinson KM. The natural history of the strawberry nevus. *Arch Dermatol* 1960; **82**: 667–80.

Ulceration

There are multiple methods for treating ulceration, with no one therapy considered first line [1]. The aims should be to treat the ulceration, infection and pain. The ulceration may be treated conservatively with local antibiotics such as mupirocin or systemic antibiotics (if there is crusting, weeping and spreading erythema) and occlusive dressings (Fig. 18.17). Non-adherent, paraffin-based dressings with occlusive dressings can then be overlaid. Specific therapy, such as oral corticosteroids and pulsed dye laser [2], may be used alone or in combination, as discussed below, although the results of pulsed dye laser are not always positive [1]. The author's personal experience suggests that pulsed dye laser is very helpful in managing pain associated with ulceration which does not respond to conservative measures. The use of 0.01% becalpermin gel (a recombinant platelet-derived growth factor used in treating diabetic ulcers) has induced healing of ulceration, but the safety of this unlicensed product is not clear [3,4]. Another modality reported is a polyurethane film which helped ulceration and pain [5].

The most important symptom to address in ulceration is pain. Adequate analgesia (paracetamol suspension with or without ibuprofen or short-term codeine) on a regular basis and prior to dressing is vital to reduce the distress to the child. Advice from other health professionals often neglects this issue.



(a)



(b)

Fig. 18.17 (a) Ulcerated haemangioma and (b) healed with conservative management.

References

1 Kim HJ, Colombo M, Frieden IJ. Ulcerated hemangiomas: clinical characteristics and response to therapy. *J Am Acad Dermatol* 2001; **44**: 962–72.

2 Morelli JG, Tan OT, Weston WL. Treatment of ulcerated hemangiomas with the pulsed tunable dye laser. *Am J Dis Child* 1991; **145**: 1062–4.

3 Sugarman JL, Mauro TM, Frieden IJ. Treatment of an ulcerated hemangioma with recombinant platelet-derived growth factor. *Arch Dermatol* 2002; **138**: 314–6.

4 Metz BJ, Rubinstein MC, Levy ML *et al*. Response of ulcerated perineal hemangiomas of infancy to becalpermin gel, a recombinant human platelet-derived growth factor. *Arch Dermatol* 2004; **140**: 867–70.

5 Oranje AP, de Waard-van der Spek FB, Devillers ACA *et al*. Treatment and pain relief of ulcerative hemangiomas with a polyurethane film. *Dermatology* 2000; **200**: 31–4.

Therapeutic intervention

There are several possible treatments available and these are summarized in Table 18.8 and are discussed in more detail below.

Corticosteroids. Systemic corticosteroids have been used in the treatment of haemangiomas for more than 30 years [1–3] and their use is highlighted in Table 18.9. Their precise mechanism of action is not clear, but it is known that corticosteroids reduce

Table 18.8 Therapeutic interventions for infantile haemangiomas.

Therapy	Comment
Corticosteroids	Oral—for expanding, function- or life-threatening haemangiomas
	Topical not commonly used
Interferon	Second line for expanding, function- or life-threatening haemangiomas but used in children older than 1 year
Vincristine	Second line for expanding, function- or life-threatening haemangiomas in combination with oral corticosteroids
Propranol	For expanding function threatening haemangiomas
Pulsed dye laser	May be used for residual or large plaque haemangiomas but does not accelerate resolution
Surgery	May be used for areas which are known to leave poor cosmetic outcome such as nose and cheeks
Topical immunomodulators	Limited evidence of benefit for small haemangiomas

Table 18.9 Indications for steroid therapy to infantile haemangiomas.

Life- or function-threatening, affecting airway or vision
Congestive cardiac failure
Anatomical sites with a high risk of permanent disfigurement, e.g. nose, lip
If large or ulcerated (in some cases)

angiogenesis, induce vasoconstriction and reduce vascular permeability. More recent evidence shows increased apoptosis, which would seem biologically plausible as one mode of action [4]. There are no randomized controlled studies looking at dosing or efficacy, although a meta-analysis of steroid use in problematic haemangiomas showed a mean dose of 2.9 mg/kg/day and a response rate of 84% (excluding hepatic haemangiomas) [5]. This analysis also showed that 3 mg/kg/day was more effective than 2 mg/kg/day. An empirical dose of 2–5 mg/kg/day is used as a single morning dose and maintained for 1–3 months, followed by a gradual taper. A positive response is usually seen within 2–3 weeks if the tumour is going to respond. The speed of taper is not formalized and depends on the age of the child. A reduction that is carried out too rapidly will result in a rebound if the IH is still proliferating. In such cases, one has to restart at a higher dose and reduce more slowly. As with some chronic steroid-responsive dermatoses, an alternate day dosage may be used to circumvent potential side effects of growth and adrenal axis suppression.

Corticosteroid side effects include general irritability, poor sleep, behavioural changes, gastric irritation, glucose intolerance, weight gain, growth disturbance and adrenal suppression. The most common of these were cushingoid facies and personality change in a large study of haemangiomas treated in this manner [6]. The growth was suppressed in 35% of these patients, but catch up growth ensued in the majority. Other potential complications of steroids include cataracts, glaucoma, osteoporosis, increased risk of infections (including *Pneumocystis* pneumonia).

Patients with haemangiomas on systemic corticosteroids should ideally be under the joint care of a dermatologist and a paediatrician to monitor mood, sleep, blood pressure, height and weight, length and developmental milestones. For those patients on long-term therapy one should consider a low-dose corticotrophin stimulation test. Other factors to be considered include increasing the dose of steroids during illnesses with high fever, traumatic accidents or surgery. In addition, live vaccines should not be given during steroid therapy and zoster immune globulin should be administered with aciclovir if the child is exposed to varicella.

Intralesional steroids are sometimes used to treat orbital haemangiomas or other localized, for example, airway haemangiomas. Both triamcinolone and dexamethasone are used and can be repeated if necessary, with response rates of 80% [7]. One of the potential benefits is the lack of the side effects, discussed earlier. However, this is something which should only be done by experienced ophthalmologists as rare but serious side effects include eyelid necrosis [8] and retinal artery embolization with resulting blindness [9,10].

There is limited experience of using superpotent topical steroid (clobetasone propionate) in the treatment of infantile haemangiomas [11–13], and although easier to administer, the benefits of halting growth, shrinkage or flattening the lesion are likely to be applicable to only small superficial haemangiomas at risk of ulceration, or small periocular lesions [13].

References

1 Fost NC, Esterly NB. Successful treatment of juvenile hemangiomas with prednisone. *J Pediatr* 1968; **72**: 351–7.
2 Brown SH, Neerhout RC, Fonkalsrud EW. Prednisone therapy in the management of large hemangiomas in infants and children. *Surgery* 1972; **71**: 168–73.
3 Zarem HA, Edgerton MT. Induced resolution of cavernous hemangiomas following prednisolone therapy. *Plast Reconstr Surg* 1967; **39**: 76–83.
4 Hasan Q, Tan ST, Gush J *et al.* Steroid therapy of a proliferating haemangioma: histochemical and molecular changes. *Pediatrics* 2000; **105**: 117–21.
5 Bennett ML, Fleischer AB, Chamlin SL *et al.* Oral corticosteroid use is effective for cutaneous hemangiomas. *Arch Dermatol* 2001; **137**: 1208–13.
6 Boon LM, MacDonald DM, Mulliken JB. Complications of systemic corticosteroid therapy for problematic hemangioma. *Plast Reconstr Surg* 1999; **104**: 1616–23.
7 Chen MT, Yeong EK, Horng SY. Intralesional corticosteroid therapy in proliferating head and neck hemangiomas: a review of 155 cases. *J Pediatr Surg* 2000; **35**: 420–3.
8 Sutula FC, Glover AT. Eyelid necrosis following intralesional corticosteroid injection for capillary hemangioma. *Ophthalmic Surg* 1987; **18**: 103–5.
9 Shorr N, Seiff SR. Central retinal artery occlusion associated with periocular corticosteroid injection for juvenile hemangioma. *Ophthalmic Surg* 1986; **17**: 229–31.
10 Ruttum MS, Abrams GW, Harris GJ *et al.* Bilateral retinal embolization associated with steroid injection for capillary hemangioma of infancy. *J Pediatr Ophthalmol Strabismus* 1993; **30**: 4–7.
11 Elsas FJ, Lewis AR. Topical treatment of periocular capillary hemangioma. *J Pediatr Ophthalmol Strabismus* 1994; **31**: 153–6.
12 Cruz OA, Zarnegar SR, Myers SE. Treatment of periocular capillary hemangioma with topical clobetasol propionate. *Ophthalmology* 1995; **102**: 2012–85.
13 Garzon MC, Lucky AW, Hawrot A *et al.* Ultrapotent corticosteroid treatment of hemangiomas of infancy. *J Am Acad Dermatol* 2005; **52**: 281–6.

Interferon-α. There is no doubt that interferon-α is an effective anticancer drug and can inhibit angiogenesis in tumours. It has been shown to halt the growth of proliferative haemangiomas [1–6] with reported regression rates of 50% [4]. It is normally given as a subcutaneous injection at doses ranging from 1 to 3 million units/m^2/day over several months. However, initial enthusiasm has been tempered by reports of severe neurotoxicity, including spastic diplegia [7]. In some but not all cases this was reversible. A large meta-analysis of patients with vascular lesions given interferon-α showed 11/441 with spastic diplegia and 16/441 with motor developmental disturbance. Most importantly, these severe complications only occurred in children under the age of 1; children over 1 year of age were not affected [8]. The more predictable side effects of interferon-α include fever, general malaise, anaemia, neutropenia, elevated transaminases, and are not usually an indication to stop therapy. It should also be remembered that some haemangiomas do not respond to interferon-α [9].

It is suggested, therefore, that interferon-α should be reserved as a second-line treatment for infants with aggressive or life-threatening haemangiomas that are not responding to systemic corticosteroids; patients should be monitored by a neurologist.

References

1 White CW, Sondheimer HM, Crouch EC *et al.* Treatment of pulmonary hemangiomatosis with recombinant interferon alfa-2a. *N Eng J Med* 1989; **320**: 1197–200.
2 Orchard PJ, Smith CM III, Wood WG *et al.* Treatment of hemangioendotheliomas with alpha interferon. *Lancet* 1989; **ii**: 565–7.

3 Blei F, Orlow SJ, Geronemus RG. Interferon alfa-2a therapy for extensive perianal and lower extremity hemangioma. *J Am Acad Dermatol* 1993; **29**: 98–9.
4 Ezekowitz RAB, Mulliken JB, Folkman J. Interferon alfa-2a therapy for life-threatening hemangiomas of infancy. *N Engl J Med* 1992; **326**: 1456–63.
5 Ricketts RR, Hatley RM, Corden BJ *et al.* Interferon-α2a for the treatment of complex hemangiomas of infancy and childhood. *Ann Surg* 1994; **219**: 605–14.
6 Chang E, Boyd A, Nelson CC *et al.* Successful treatment of infantile hemangioma with interferon-α-2b. *J Pediatr Hematol Oncol* 1997; **19**: 237–44.
7 Barlow CF, Priebe CJ, Mulliken JB *et al.* Spastic diplegia as a complication of interferon-α-2a treatment of hemangiomas of infancy. *J Pediatr* 1998; **132**: 527–30.
8 Michaud A-P, Bauman NM, Burke DK *et al.* Spastic diplegia and other motor disturbances in infants receiving interferon-alpha. *Laryngoscope* 2004; **114**: 1231–6.
9 Teillac Hamel D, de Prost Y, Bodemer C *et al.* Serious childhood angiomas: unsuccessful α-2b interferon treatment. *Br J Dermatol* 1993; **129**: 473–6.

Vincristine. Vincristine has been used effectively to treat Kasabach–Merritt phenomenon in association with tufted angiomas and kaposiform haemangioendotheliomas [1]. Vincristine requires a central line and is given at a dose of 0.025–0.05 mg/kg (if <10 kg), or 1.5 mg/m^2 (if >10 kg). The side effects of therapy include peripheral neuropathy, constipation, jaw pain and inappropriate secretion of antidiuretic hormone. It has also been used in life threatening haemangiomas [2–5] and is now considered the initial second line therapy, because of the neurotoxicity associated with interferon-α.

References

1 Haisley-Royster C, Enjolras O, Frieden IJ *et al.* Kasabach-Merritt phenomenon: a retrospective study of treatment with vincristine. *J Pediatr Hematol Oncol* 2002; **24**: 459–62.
2 Payarols JP, Masferrer JP, Bellvert CG. Treatment of life-threatening hemangiomas with vincristine. *Lancet* 1995; **333**: 69.
3 Boehm DK, Kobrinsky NL. Treatment of cavernous hemangioma with vincristine. *Ann Pharmacother* 1993; **27**: 98.
4 Moore J, Lee M, Garzon M *et al.* Effective therapy of a vascular tumour of infancy with vincristine. *J Pediatr Surg* 2001; **36**: 1273–6.
5 Perez J, Pardo J, Gomez C. Vincristine: an effective treatment of corticosteroid-resistant life-threatening infantile haemangiomas. *Acta Oncol* 2002; **41**: 197–9.

Propranolol. This is a new therapy which came about by chance when heart failure in a child with a haemangioma was being treated with propanolol [1]. In this interesting case series, propranolol at a dose of 2 mg/kg was used for severe, non-corticosteroid-responsive infantile haemangiomas. There was evidence of regression, in some instances quite dramatically, after several months of therapy. The study was not controlled and in some of the children, steroids blockade has been shown to induce apoptosis in endothelial cells of capillaries [2]. This is clearly an exciting area for controlled and comparative studies in the future.

References

1 Leaute-Labreze C, Roque ED, Hubiche T *et al.* Propranolol for severe haemangiomas of infancy. *N Engl J Med* 2008; **358**: 2649–51.
2 Sommers Smith SK, Smith DM. Beta blockade induces apoptosis in cultured capillary endothelial cells. *In Vitro Dev Biol Anim* 2002; **38**: 298–304.

Laser therapy. The use of lasers in the treatment of haemangiomas remains controversial, unlike their use in vascular malformations (port-wine stains), which is not open to question. Laser therapy is the only area of haemangioma management examined by a prospective, randomized controlled trial [1,2]. This landmark study compared the outcome of early pulsed dye laser (PDL-585 nm) treatment of uncomplicated haemangiomas in 60 infants, with observation alone after 12 months. Even though there were greater numbers of patients who initially cleared completely with laser therapy, there was no difference in clearance or minimal residual signs at the age of 1 year. This study proved controversial, because many laser specialists felt that use of a cooling device and newer variable wavelength PDL would have led to a different conclusion. Another non-randomized comparative trial showed similar results [3]. Despite these reservations, the findings reflect the clinical experience of many paediatric dermatologists. The side effects of laser treatment include focal scars, possible ulceration, pain and pigmentary changes [1,3,4].

It is accepted that laser therapy may be useful in the treatment of ulcerated haemangiomas, and for the residual erythematous changes that are left after involution, although evidence from large studies is notably lacking.

References

1 Batta K, Goodyear HM, Moss C *et al.* Randomised controlled study of early pulsed dye laser treatment of uncomplicated childhood haemangiomas: results of a 1-year analysis. *Lancet* 2002; **360**: 521–7.
2 Batta K, Moss C, Waters R *et al.* Early pulsed dye laser treatment of childhood haemangiomas. *Lancet* 2003; **361**: 348.
3 Kono T, Sakurai H, Groff WF *et al.* Comparison study of a traditional pulsed dye laser versus a long-pulsed dye laser in the treatment of early childhood hemangiomas. *Lasers Surg Med* 2006; **38**: 112–5.
4 Witman PM, Wagner AM, Scherer K *et al.* Complications following pulsed dye laser treatment of superficial haemangiomas. *Lasers Surg Med* 2006; **38**: 116–23.

Surgery. The use of aggressive surgery in the past was followed by poor outcomes with marked scarring. There is, however, a subset of haemangiomas which benefit from surgical intervention [1]. The age of the child should be taken into account since facial image awareness occurs around 2.5–3 years of age. In the proliferative phase, surgery should be considered for obstruction (airway or visual), deformity (e.g. retroauricular) and ulceration not responding to medical therapy. In the involuting phase, surgery is indicated provided the size and appearance of the scar would not be less if the resection were postponed, and if the scar is easily concealable. In the involuted phase, the indications are an abnormal contour due to a fibrofatty residuum and distortion of an important anatomic structure [1–3]. Nasal tip haemangiomas warrant a special mention, as they are treated surgically more than any other anatomical site. It is recommended that once early lesions have been medically managed (with intralesional or systemic steroids if necessary), they should be resected in a staged fashion with alar apposition [4].

The traditional surgical technique of lenticular excision with a linear closure has been demonstrated to be less effective than circular excision with a purse string closure, which is considered to be the technique of choice [5].

References

1 Mulliken JB, Fishman SJ, Burrows PE. Vascular anomalies. *Curr Probl Surg* 2000; **37**: 517–84.
2 Demiri EC, Pelissier P, Genin-Etcheberry T *et al.* Treatment of facial haemangiomas: the present status of surgery. *Br J Plast Surg* 2001; **54**: 665–74.
3 McHeik JN, Renauld V, Duport G *et al.* Surgical treatment of haemangioma in infants. *Br J Plast Surg* 2005; **58**: 1067–72.

4 Hochman M, Mascareno A. Management of nasal hemangiomas. *Arch Facial Plast Surg* 2005; **7**: 295–300.
5 Mulliken JB, Rogers GF, Marler JJ. Circular excision of hemangioma and purse-string closure: the smallest possible scar. *Plast Reconstr Surg* 2002; **109**: 1544–54.

Embolization. As with other treatment for life threatening haemangiomas, this is a technique reserved for lesions that have not responded to medical therapy, as sometimes required in hepatic haemangiomas that have led to congestive cardiac failure [1].

Reference

1 Mulliken JB, Fishman SJ, Burrows PE. Vascular anomalies. *Curr Probl Surg* 2000; **37**: 517–84.

Radiotherapy. The use of radiotherapy is now extremely rare and cannot be justified for cutaneous haemangiomas in view of the risk of malignancy and disturbance of bone growth. It has been used for systemic, for example liver [1], haemangiomas and for life-threatening lesions [2].

References

1 Larcher VF, Howard ER, Mowatt AP. Hepatic haemangiomata: diagnosis and management. *Arch Dis Child* 1981; **56**: 7–14.
2 Ogino I, Torikai K, Kobayasi S *et al.* Radiation therapy for life- or function-threatening infant haemangioma. *Radiology* 2001; **218**: 834–9.

Topical immunomodulators. Imiquimod is a immune response modifier with the ability to induce interferon-γ, interferon-α, tumour necrosis factor-α and the antiangiogenesis factor, tissue inhibitor of matrix metalloproteinase [1]. There have been small open studies showing clinical resolution of small, superficial infantile haemangiomas [2–5]. The main side effects included local erythema, scaling and occasionally marked crusting. Unfortunately, none of these studies were controlled and the use of this treatment for haemangiomas is unlicensed.

References

1 Hurwitz DJ, Pincus L, Kupper TS. Imiquimod: a topically applied link between innate and acquired immunity. *Arch Dermatol* 2003; **139**: 1347–50.
2 Martinez MI, Sanchez-Carpintero I, North PE *et al.* Infantile hemangioma: clinical resolution with 5% imiquimod cream. *Arch Dermatol* 2002; **138**: 881–4.
3 Welsh O, Olazaran Z, Gomex M *et al.* Treatment of infantile hemangiomas with short term application of imiquimod 5% cream. *J Am Acad Dermatol* 2004; **51**: 639–42.
4 Hazen PG, Carney JF, Engstrom CW *et al.* Proliferating hemangioma of infancy: successful treatment with topical 5% imiquimod cream. *Pediatr Dermatol* 2005; **22**: 254–6.
5 Ho NTC, Lansang P, Pope E. Topical imiquimod in the treatment of infantile hemangiomas: a retrospective study. *J Am Acad Dermatol* 2007; **56**: 63–8.

Other modalities. Cryotherapy is popular in Germany and parts of South America [1,2]. Compression bandaging or intermittent pneumatic compression can provide a reduction in the bulk of large haemangiomas [3,4] although it can lead to serious complications of heart failure or respiratory distress [5]. The lack of a formal evidence base explains why these modalities are rarely used.

References

1 Cremer H. Cryosurgery for hemangiomas. *Pediatr Dermatol* 1998; **15**: 410–1.
2 Reischle S, Schuller-Petrovic S. Treatment of capillary hemangiomas in early childhood with a new method of cryosurgery. *J Am Acad Dermatol* 2000; **42**: 809–13.
3 Stringel G. Giant hemangioma: treatment with intermittent pneumatic compression. *J Pediatr Surg* 1987; **22**: 7–10.
4 Kaplan M, Paller AS. Clinical pearl: use of self-adhesive, compressive wraps in the treatment of limb hemangiomas. *J Am Acad Dermatol* 1995; **32**: 117–8.
5 Currie BG, Schell D, Bowring AC. Giant hemangioma of the arm associated with cardiac failure and Kasabach–Merritt syndrome in a neonate. *J Pediatr Surg* 1991; **26**: 734–7.

Hepatic haemangioma (HH)

Most infantile haemangiomas are cutaneous tumours, but visceral involvement may also occur, often in the setting of multiple lesions—haemangiomatosis. Infantile hepatic haemangiomas are proliferative endothelial cell neoplasms of the liver. Like their cutaneous counterpart, they share the same characteristic phases of rapid growth followed by spontaneous involution. Most hepatic haemangiomas are clinically silent and may be detected on routine prenatal ultrasound screening, or postnatal imaging for another reason [1]. A subset becomes symptomatic, presenting with heart failure secondary to high volume shunting. Less common presentations include hypothyroidism resulting from overproduction of type III iodothyroninedeiodinase [2–4], fulminant liver failure [5] and abdominal compartment syndrome [1]. The literature has been very confusing, as infantile HH is commonly referred to as hepatic haemangioendothelioma. The latter is a malignant tumour which does not involute. It also differs from adult hepatic haemangioma, which is a venous malformation and does not regress. One group has proposed three subtypes: focal, multifocal and diffuse, and suggested each subtype has its own distinctive imaging, pathological and physiological features [1].

Infantile HH may be imaged by ultrasound, CT or MRI scanning. The classic ultrasound appearance of small (<3 cm) haemangiomas is a strongly echogenic mass, whereas larger tumours may contain calcification, cystic spaces or fibrosis [6]. CT imaging shows an area of well-defined hypoattenuation on unenhanced scans and peripheral contrast enhancement on dynamic scans. MRI findings include hypointense areas on TI-weighted images, and markedly hyperintense areas on T2-weighted images, probably due to the slow blood flow through multiple, small vascular channels [7].

The management of hepatic haemangiomas usually is guided by the presence or absence of heart failure. Asymptomatic patients with focal or multifocal disease, without heart failure or haemodynamically significant shunting, may be followed up with periodic ultrasound to document regression. If heart failure is present, this should be treated medically. Infants with significant shunting are initially treated with systemic corticosteroids, but many do not respond [8–10]. As with cutaneous haemangiomas, interferon-α and vincristine is also used. However, if pharmacological therapy fails, embolization is often the next step, with hepatic artery ligation, or liver transplantation for rapidly deteriorating, symptomatic, diffuse haemangiomas [1,8,9,11].

The long-term prognosis varies on the extent and haemodynamic compromise, with mortality rates of up to 80% in untreated cases [12] and 20% in treated cases [9].

References

1 Christison-Lagay ER, Burrows PE, Alomari A *et al.* Hepatic haemangiomas: subtype classification and development of a clinical practice algorithm and registry. *J Pediatr Surg* 2007; **42**: 62–8.
2 Huang SA, Tu HM, Harney JW *et al.* Severe hypothyroidism caused by type 3 iodothyronine deiodinase in infantile hemangiomas. *N Engl J Med* 2000; **343**: 185–9.

3 Guven A, Aygun C, Ince H *et al.* Severe hypothyroidism caused by hepatic haemangioendothelioma in an infant of a diabetic mother. *Horm Res* 2005; **63**: 86–9.
4 Ho J, Kendrick V, Dewey D *et al.* New insight into the pathophysiology of severe hypothyroidism in an infant with multiple hepatic hemangiomas. *J Pediatr Endocrinol Metab* 2005; **18**: 511–4.
5 Lu CC, Ko SF, Liang CD *et al.* Infantile hemangioendothelioma presenting as early heart failure: report of two cases. *Chang Gung Med J* 2002; **25**: 405–10.
6 Reiger TS, Ramji FG. Pediatric hepatic haemangioma. *Radiographics* 2004; **24**: 1719–24.
7 Powers C, Ros P, Stoupis C *et al.* Primary liver neoplasms: MR imaging with pathologic correlation. *Radiographics* 1994; **14**: 459–82.
8 Stanley P, Geer GD, Miller GH *et al.* Infantile hepatic haemangiomas. Clinical features, radiologic investigations, and treatment of 20 patients. *Cancer* 1989; **64**: 936–9.
9 Boon LM, Burrows PE, Paltiel HJ *et al.* Hepatic vascular anomalies in infancy: a twenty-seven-year experience. *J Pediatr* 1996; **129**: 346–54.
10 Kassarjian A, Zurakowski D, Dubois J *et al.* Infantile hepatic haemangiomas: clinical and imaging findings and their correlation with therapy. *Am J Roentgenol* 2004; **182**: 785–95.
11 Daller JA, Bueno J, Gutierrez J *et al.* Hepatic hemangioendothelioma: clinical experience and management strategy. *J Pediatr Surg* 1999; **34**: 98–106.
12 Berman B, Lim HW-P. Concurrent cutaneous and hepatic hemangiomata in infancy: report of a case and a review of the literature. *J Dermatol Surg* 1978; **4**: 869–73.

Neoantal haemangiomatosis

Synonym
- Multifocal/benign neonatal haemangiomatosis

Children may sometimes be born with large numbers of small infantile haemangiomas ranging in number from a few to hundreds. This has been referred to as benign neonatal haemangiomatosis in the literature. They are usually small in size, ranging from 2 mm to 2 cm in diameter [1,2]. They are more common in girls than boys [2,3] and increase in size for the first few months before starting to involute [4]. In most cases the haemangiomas resolve spontaneously during the first 2–3 years of life [5]. Histologically, they are identical to solitary infantile haemangiomas with multilobular vascular proliferations composed of thin-walled vascular channels lined by normal endothelium [1]. The only investigation required in children less than 6 months of age is an ultrasound to detect the presence of an asymptomatic hepatic haemangioma.

It is important to differentiate this 'benign' form from the more serious diffuse (synonym miliary, disseminated) neonatal haemangiomatosis. It is highly probable that these two forms represent a spectrum of the same underlying disease.

References

1 Stern JK, Wolf JE, Jarratt M. Benign neonatal hemangiomatosis. *J Am Acad Dermatol* 1981; **4**: 442–5.
2 Stenninger E, Schollin J. Diffuse neonatal haemangiomatosis in a newborn child. *Acta Paediatr* 1993; **82**: 102–4.
3 Enjolras O, Garzon MC. Vascular stains, malformations and tumours. In: Eichenfeld LF, Frieden IJ, Esterly NB, eds. *Textbook of Neonatal Dermatology*. Philadelphia: WB Saunders; 2001: 336–52.
4 Golitz LE, Rudikoff J, O'Meara OP. Diffuse neonatal hemangiomatosis. *Pediatr Dermatol* 1986; **3**: 145–52.
5 Leung AKC, Rafaat M. Benign neonatal hemangiomatosis. *Pediatr Dermatol* 2003; **20**: 161–3.

Multifocal/diffuse neonatal haemangiomatosis (NH)

This is a rare disorder characterized by multiple cutaneous and visceral haemangiomas which appear at birth or early after birth



Fig. 18.18 Miliary haemangiomatosis causing cardiac failure in a 3-month-old infant.

(Fig. 18.18). A minimum of three criteria were deemed necessary for the diagnosis: an onset in the neonatal period, lack of malignant transformation and involvement of three or more organs [1]. The cutaneous presentation is the same as the multifocal benign form as described earlier. The most common symptom which should alert the physician that this may be the diffuse variant is an enlarging abdominal girth secondary to hepatomegaly [2]. The lungs, brain and gastrointestinal tract are also frequently affected [3]. A large meta-analysis of complications arising from diffuse NH showed that the most common were congestive cardiac failure in 38%, haemorrhage in 11% and multiorgan failure in 9%. The mortality of patients who received no treatment was 77% compared with 27% who were treated conservatively or surgically [3]. The management of such patients is still controversial [4]. The patient should have a thorough history and examination. The combination of hepatomegaly and heart failure is investigated with abdominal imaging and it has been suggested that any infant with five or more cutaneous haemangiomas should have an abdominal ultrasound [5]. Evidence of other organ involvement may be investigated by faecal occult blood analysis, CNS imaging and urinalysis. Guidelines state that corticosteroids should be the initial treatment, and if no improvement is seen in 2–4 weeks, interferon-α should be added [6]. Operative treatment with either hepatic artery ligation or embolization is indicated for large hepatic haemangiomas and severe congestive heart failure not responding to medical treatment. The presence of heart failure (relative risk 3.2) and the involvement of five or more organs (relative risk 1.6) were associated with a higher mortality rate [3].

References

1 Holden KR, Alexander F. Diffuse neonatal hemangiomatosis. *Pediatrics* 1970; **46**: 411–21.
2 Berman B, Lim HW-P. Concurrent cutaneous and hepatic hemangiomata in infancy: report of a case and a review of the literature. *J Dermatol Surg* 1978; **4**: 869–73.
3 Lopriore E, Markhorst DG. Diffuse neonatal haemangiomatosis: new views on diagnostic criteria and prognosis. *Acta Paediatr* 1999; **88**: 93–7.
4 Esterly NB, Margileth AM, Kahn G *et al.* Management of disseminated eruptive hemangiomata in infants. *Pediatr Dermatol* 1984; **1**: 312–7.

5 Mulliken JB, Fishman SJ, Burrows PE. Vascular anomalies. *Curr Probl Surg* 2000; **37**: 519–84.
6 Stratte EG, Tope WD, Johnson CL *et al.* Multimodal management of diffuse neonatal hemangiomatosis. *J Am Acad Dermatol* 1996; **34**: 337–42.

Congenital haemangiomas

A congenital haemangioma is a vascular tumour that has grown to its maximum size at birth and does not show a proliferative postnatal growth phase [1]. Congenital haemangiomas do not look like the typical precursor lesions of infantile haemangiomas and behave differently biologically. There are two major recognized subgroups, rapidly involuting congenital haemangiomas (RICH) [2] and non-involuting congenital haemangiomas (NICH) [3].

RICH grow in a similar pattern to IH but regress more rapidly, often by the first year. The NICH growth pattern is one of intrauterine growth and a plateau throughout life with no regression postnatally. Histologically, NICH are composed of large lobules of small vessels with intervening fibrosis and dermal arteriovenous (AV) microfistulae. A large stellate vessel is often seen centrally with thin basement membranes [2,3]. RICH are made up of lobules of variable size, large extralobular vessels, and plump endothelium with thick basement membranes after regression. Immunohistochemical staining for GLUT1 is negative in both RICH and NICH.

Both RICH and NICH have an equal sex distribution (unlike the female preponderance of IH), are usually solitary, and located on the head or limbs or near a joint. RICH typically present as a bluish or purple plaque or tumour with telangiectasia and peripheral pallor. They rapidly involute by 1 year of age, leaving noticeable dermal or subcutaneous atrophy [1]. They have characteristic ultrasound features with a uniform hypo-echoic mass and centrilobular draining vessels [4].

NICH are round or ovoid, and pink or purple in colour, showing peripheral pallor and coarse overlying telangiectasia (Fig. 18.19). Their size can vary from a few to several centimetres and they are often doughy in consistency and warm to touch. They do not show signs of involution and Doppler examination shows a fast flow lesion. They have been mistaken for arteriovenous malformations (AVM), because angiography will show fast flow and rapid filling, but no early venous opacification typical of AVM. They are best managed surgically and do not recur, unlike AVM [3].

Differentiating RICH from NICH is not always so clear cut, because both a congenital haemangioma and an acquired infantile haemangioma may coexist in the same patient [5]. In addition, a few tumours initially diagnosed as RICH may transform into NICH [5].

References

1 Boon LM, Enjolras O, Mulliken JB. Congenital hemangiomas: evidence for accelerated involution. *J Pediatr* 1996; **128**: 329–35.
2 Berenguer B, Mulliken JB, Enjolras O *et al.* Rapidly involuting congenital hemangioma: clinical and histopathological features. *Pediatr Develop Pathol* 2003; **6**: 495–510.
3 Enjolras O, Mulliken JB, Boon LM *et al.* Non-involuting congenital hemangioma: a rare cutaneous vascular anomaly. *Plast Reconstr Surg* 2001; **107**: 1647–54.
4 Rogers M, Lam A, Fischer G. Sonographic findings in a series of rapidly involuting congenital hemangiomas. *Pediatr Dermatol* 2002; **19**: 5–11.
5 Mulliken JB, Enjolras O. Congenital hemangiomas and infantile hemangioma: missing links. *J Am Acad Dermatol* 2004; **50**: 875–82.

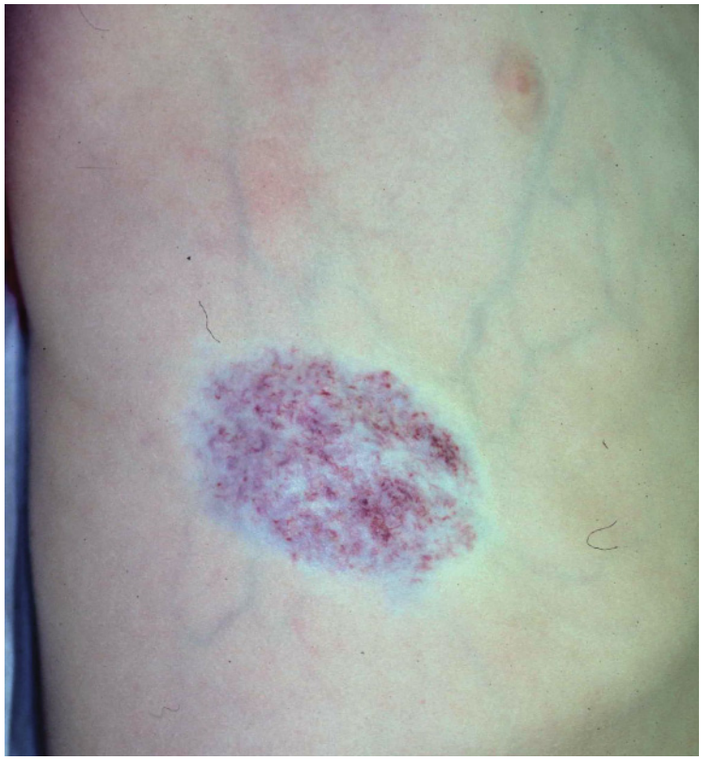


Fig. 18.19 Non-involuting congenital haemangioma (NICH) in an 11-year-old.

Tufted angioma (TA)

This is a rare tumour which occurs most commonly in prepubertal children [1–3]. It was, however, originally described in adults [4]. Less commonly it has been described in pregnancy and in an immunosuppressed individual [5,6].

Histologically, there is a lobular proliferation of plump, oval cells surrounding tiny slit-like lumina [7]. These blood vessels are tightly packed and organized in rounded tufts scattered in the dermis, often described as resembling cannon-balls. The tufts may occur deeply in the dermis, and into the subcutis [8,9]. Thin-walled lymphatic channels may be seen at the periphery of the cellular masses or throughout the dermis. Immunohistochemical stains show strong positivity for Ulex europaeus I lectin and EN4 [10] and unlike IH, negative staining for GLUT1 [11].

In children, they often appear before 1 year of age, with an ill-defined pink macule which evolves into a purple indurated nodule or plaque, but they can also vary in colour from a red to blue hue. They can reach up to 20 cm in diameter, and may cause confusion in their early stage with port-wine stains, connective tissue naevi, smooth muscle hamartoma and sarcoma. They may have localized hypertrichosis or hyperhidrosis on their surface. A useful clinical feature is that they are usually tender.

Even if the diagnosis is suspected clinically, a biopsy is recommended for confirmation. Their natural history shows that after a period of expansion they stabilize and may either resolve spontaneously [1,12,13] or more rarely progressively worsen [14]. Malignant transformation has not been reported. The differential diagnosis of TA includes infantile haemangioma, Kaposiform haemangioendothelioma (KHE), venous malformations, glomuve-

nous malformations and subcutaneous fat necrosis of the newborn [1]. As with KHE, it may be associated with the Kasabach–Merritt phenomenon.

The management of tufted angiomas is related to the age of the patient, size, symptoms and whether a coagulopathy is present. Excision is often performed but recurrence is common if this is incomplete. Some TA extend deeply into the subcutis, fascia and into muscle [15]. Other modalities reported to achieve effective resolution include soft X-ray [16], pulsed dye laser [17], interferon-α [18–20] and high-dose corticosteroids [21]. Low-dose aspirin may be of benefit in mild thrombocytopenia [9]. More significant thrombocytopenia and the Kasabach–Merritt phenomenon are discussed later.

References

1 Herron MD, Coffin CM, Vanderhooft SL. Tufted angiomas: variability of the clinical morphology. *Pediatr Dermatol* 2002; **19**: 394–401.
2 Wong SN, Tay YK. Tufted angioma: a report of five cases. *Pediatr Dermatol* 2002; **19**: 388–93.
3 Satter EK, Graham BS, Gibbs NF. Congenital tufted angioma. *Pediatr Dermatol* 2002; **19**: 445–7.
4 Wilson Jones E, Orkin M. Tufted angioma (angioblastoma). *J Am Acad Dermatol* 1989; **20**: 214–25.
5 Kim YK, Kim HJ, Lee KG. Acquired tufted angioma associated with pregnancy. *Clin Exp Dermatol* 1992; **17**: 458–9.
6 Chu P, Leboit PE. An eruptive vascular proliferation resembling acquired tufted angioma in the recipient of a liver transplant. *J Am Acad Dermatol* 1992; **26**: 322–5.
7 Kumakiri M, Muramoto F, Tsukinaga I *et al.* Crystalline lamellae in the endothelial cells of a type of hemangioma characterized by the proliferation of immature endothelial cells and pericytes—angioblastoma. *J Am Acad Dermatol* 1983; **8**: 68–75.
8 Enjolras O, Mulliken JB, Wassef M *et al.* Residual lesions after Kasabach–Merritt phenomenon in 41 patients. *J Am Acad Dermatol* 2000; **42**: 225–35.
9 Léauté-Labrèze C, Bioulac-Sage P, Labbé L *et al.* Tufted angioma with platelet trapping syndrome: response to aspirin. *Arch Dermatol* 1997; **133**: 1077–9.
10 Requena L, Sangueza OP. Cutaneous vascular proliferation. Part II. Hyperplasias and benign neoplasms. *J Am Acad Dermatol* 1997; **37**: 887–922.
11 North PE, Waner M, Mizeracki A *et al.* GLUT1: a newly discovered immunohistochemical marker for juvenile hemangiomas. *Hum Pathol* 2000; **31**: 11–22.
12 Miyamoto T, Mihara M, Mishima E *et al.* Acquired tufted angioma showing spontaneous regression. *Br J Dermatol* 1992; **127**: 458–9.
13 Lam WY, Mac-Moune Lai F, Look CN *et al.* Tufted angioma with complete regression. *J Cutan Pathol* 1994; **21**: 461–6.
14 Catteau B, Enjolras O, Delaporte E *et al.* Angiome en touffes sclérosant: a propos de 4 observations aux membres inférieurs. *Ann Dermatol Vénéréol* 1998; **15**: 682–5.
15 Bernstein EF, Kantor G, Howe N *et al.* Tufted angioma of the thigh. *J Am Acad Dermatol* 1994; **31**: 307–11.
16 Kimura S. Ultrastructure of so-called angioblastoma of the skin before and after soft X-ray therapy. *Jpn J Dermatol B* 1981; **8**: 235–43.
17 Mahendran R, White SI, Clark AH *et al.* Response of childhood tufted angioma to the pulsed-dye laser. *J Am Acad Dermatol* 2002; **47**: 620–2.
18 Suarez SM, Pensler JM, Paller AS. Response of deep tufted angioma to interferon alfa. *J Am Acad Dermatol* 1995; **33**: 124–6.
19 Park KC, Ahn PS, Lee YS *et al.* Treatment of angioblastoma with recombinant interferon-α2. *Pediatr Dermatol* 1995; **12**: 184–6.
20 Wilmer A, Kaatz M, Bocker T, Wollina U. Tufted angiomas. *Eur J Dermatol* 1999; **9**: 51–3.
21 Munn SE, Jackson JE, Russell-Jones R. Tufted haemangioma responding to high dose systemic steroids: a case report and review of the literature. *Clin Exp Dermatol* 1994; **19**: 511–4.

Kaposiform haemangioendothelioma [1]

Kaposiform haemangioendothelioma (KHE) is a rare vascular proliferation of childhood that can show local aggressive progression and may have associated systemic findings, the most common of which is the Kasabach–Merritt phenomenon (KMP). The clinical presentation of KHE falls into those which are retroperitoneal, presenting around 10 months of age [2], and those which present with cutaneous superficial (Fig. 18.20) or deep lesions [1]. In the cutaneous form, KHE tends to be a solitary vascular stain which starts to proliferate rapidly. Lesions generally manifest at a later date than simple infantile haemangiomas and are often complicated by KMP [1]. Congenital cases are also described [3–6].

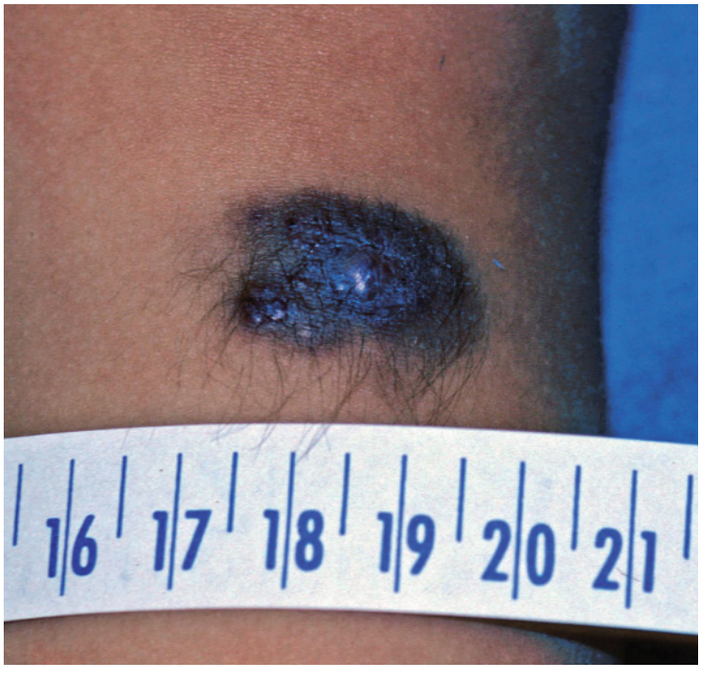


Fig. 18.20 Kaposiform haemangioendothelioma on lower leg.

Histologically, KHE is composed of lobules or sheets of tightly packed spindled or more rounded endothelial cells and pericytes, with an infiltrative pattern in the dermis, subcutaneous fat and muscles. They contain few vascular lumina, rare mitoses and minimal or absent hyperchromasia [7]. KHE has many pathological characteristics of a Kaposi's sarcoma, but demonstrates a more lobular pattern, a greater tendency to form complete vascular spaces and scattered fibrin thrombi [1]. In addition, KHE has not been shown to harbour human herpes virus-8, unlike most forms of Kaposi's sarcoma [8]. There is some possible histological overlap with tufted angioma as both tend to have endothelial cell proliferation leading to the formation of crescentic vascular spaces [1].

The rarity of the tumour does not allow for guideline-based management. If feasible, excision is the most successful of the reported treatments [7]. Other treatments include radiation therapy, interferon and ticlodine and aspirin [5]. If the KMP occurs, vincristine is used in combination with oral steroids. The prognosis is worse for retroperitoneal tumours than for cutaneous lesions, because of later diagnosis, more difficult access to the tumour or bleeding locally [5]. A rapidly growing cutaneous or soft-tissue vascular tumour in a child beyond the normal age of proliferation of an infantile haemangioma, if complicated by KMP, should be biopsied to rule out KHE.

References

1 Vin-Christian K, McCalmont TH, Frieden IJ. Kaposiform hemangioendothelioma. *Arch Dermatol* 1997; **133**: 1573–8.
2 Tsang WYW, Chan JKC. Kaposi-like infantile hemangioendothelioma: a distinctive vascular neoplasm of the retroperitoneum. *Am J Surg Pathol* 1991; **15**: 982–9.
3 Kasabach HH, Merritt KK. Capillary haemangioma with extensive purpura: report of a case. *AJDC* 1940; **59** 1063–70.
4 Fukunaga M, Ushigome S, Ishikawa E. Kaposiform hemangioendothelioma associated with Kasabach–Merritt syndrome. *Histopathology* 1996; **28**: 281–4.
5 Enjolras O, Wassef M, Mazoyer E *et al.* Infants with Kasabach–Merritt syndrome do not have 'true' hemangioma. *J Pediatr* 1997; **130**: 631–40.
6 Gianotti R, Gelmetti C, Alessi E. Congenital cutaneous multifocal kaposiform hemangioendothelioma. *Am J Dermatopathol* 1999; **21**: 557–61.
7 Zukerberg LR, Nickoloff BJ, Weiss SW. Kaposiform hemangioendothelioma of infancy and childhood: an aggressive neoplasm associated with Kasabach–Merritt syndrome and lymphangiomatosis. *Am J Surg Pathol* 1993; **17**: 321–8.
8 Lebbe C, Agbalika F, De Cremoux P *et al.* Detection of human herpes virus 8 and human T-cell lymphotropic virus type 1 sequences in Kaposi's sarcoma. *Arch Dermatol* 1997; **133**: 25–30.

Kasabach–Merritt phenomenon (KMP) [1]

The original description of the syndrome in 1940, linking thrombocytopenia, microangiopathic haemolytic anaemia and a consumptive coagulopathy with a rapidly enlarging vascular tumour [1], reported tumours with histological features of KHE. For many years, it was felt this phenomenon could occur with infantile haemangiomas, but it is now accepted this is usually a complication of tufted angiomas and kaposiform haemangioendotheliomas. Other less common tumours causing KMP include haemangiopericytomas [2–4]. Angiomas leading to KMP may be cutaneous [3], intrathoracic, most often mediastinal, abdominal (retroperitoneal or intrahepatic) [5], pelvic [6] or skeletal [7–9].

The typical presentation is a tumour either present at birth or one that starts to enlarge rapidly. They are usually solitary red/blue plaques or tumours with a blue hue and may involve large areas of skin. They rarely look like the 'strawberry' of an infantile haemangioma. They are commonly found on the trunk, neck and proximal limbs with a predilection for the thighs and shoulders (Fig. 18.21). One should suspect the phenomenon when a tumour rapidly increases in volume and ecchymoses appear, sometimes extending way beyond the margins of the tumour. The texture is also more woody and the overlying inflammation looks almost cellulitic. The bleeding diathesis may also present at other sites with haematuria, epistaxis, or prolonged bleeding at sites of trauma. Occasionally, the coagulation defect is present at birth [10], but is apparent by the age of 1 in most cases.

The coagulation status of suspected KMP should be checked by a platelet count and fibrinogen level. The degree of thrombocytopenia may be misleading initially, as the platelet count may be only marginally low, but it may fall to as low as 5000/mm^3. Other evidence of activation of the fibrinolytic system includes positive D-dimers and evidence of a haemolytic anaemia. The prothrombin time (PT) and activated partial thromboplastin time (PTT) may be elevated.

The low platelet count is due to a combination of increased destruction and sequestration of platelets within the expanding vascular tumour [11]. This has been confirmed by radiolabelling platelets with chromium-51 or indium-111 [12,13]. A coagulopathy may occur with some mixed venous–lymphatic malformations, but this is different, because it is often lifelong and haematologically characterized by reduced fibrinogen and a platelet count which may or may not be reduced, rarely falling below 70 000/mm^3. There is a state of intravascular coagulation resulting in consumption of clotting factors and elevated D-dimers, elevated PT and PTT [14,15].



Fig. 18.21 Kasabach–Merritt phenomenon from tufted angioma.

As a result of the coagulopathy, bleeding may occur at a wide number of sites and mortality as a consequence may be as high as 20–40% [11,16]. The coagulopathy, however, resolves spontaneously in the majority of patients in 1–6 years (mean 3 years) [3]. The residual tumour is often mild or inconspicuous. Unfortunately, a significant proportion of patients is left with permanent sequelae of a residual tumour or fibrosis causing joint or muscle functional disability [4,17].

The management of KMP is dependent on the severity of the coagulation defect, the site of tumour and the presence or absence of the physical effects of compression of surrounding tissues. One should remember that most cases resolve spontaneously and that there are iatrogenic complications of therapy. Only when life-threatening complications are likely, is treatment absolutely necessary. Like many cases of treatment of haemangiomas, there is no one standard protocol to guide paediatricians or dermatologists. For instance, mild thrombocytopenia is not a problem in young infants, although aspirin has been used [18] and can usually be monitored with regular platelet counts. There is an instinctive temptation to give platelet transfusions, but this may have a detrimental effect [19], as may heparin. Active bleeding and operative procedures may require platelet transfusions and fresh frozen plasma. Other treatments used to improve the coagulopathy include antithrombin III [5].

The major focus of therapy is reduction in the volume of tumour, and oral corticosteroids 2–5 mg/kg/day can induce both shrink-

age of the tumour and restoration of the platelet count [20–22]. The outcome of steroid therapy is less encouraging when there are severe coagulation abnormalities [23,24]. IFN-α has been shown to be effective, although its action is relatively slow [25–28]. It is therefore not an option where the coagulopathy is of a severe, acute onset. The most encouraging second-line medical therapy has been vincristine which binds to platelets and therefore homes in on sites of platelet sequestration [3,29]. The recommended dose is 1.0–1.5 mg/m^2/week by slow intravenous infusion. Most cases will show a response by 4 weeks, with an average of 12 weeks of treatment [30]. This treatment appears to have a rapidly beneficial effect on the coagulopathy, and can be expected to induce shrinkage of the underlying tumour over a period of months [29]. Other therapies reported to help include ticlopidine and aspirin [18], aspirin and dipyridamole [31], cyclophosphamide [32], pentoxifylline [33] and the antifibrinolytic agents tranexamic acid [33] and ε-aminocaproic acid [34].

Surgical excision of the causative tumour may be very effective in reversing the coagulation defect [5,35–37], but is not without its hazards, as bleeding may be profuse during surgery. It is often reserved for small accessible tumours. Another useful adjunct prior to surgery is tumour embolization, which has the added benefit of reducing intraoperative bleeding [16,38].

Radiotherapy has its advocates [16,39,40] but is generally not contemplated due to the risk of long-term complications [41,42]. It may be an option in difficult cases.

In summary, the management of KHE is initially conservative, with regular monitoring of platelets, clotting studies, fibrinogen and D-dimers. If there is a worsening of the coagulopathy, oral corticosteroids should then be used and consideration given to vincristine or IFN-α in children older than 1 year of age, and surgical treatment (with pre-embolization). The likely outcome of long-term tumour regression and normal coagulation should be borne in mind when contemplating aggressive intervention [3].

References

1 Kasabach HH, Merritt KK. Capillary haemangioma with extensive purpura: report of a case. *AJDC* 1940; **59**: 1063–70.
2 Vin-Christian K, McCalmont TH, Frieden IJ. Kaposiform hemangioendothelioma. *Arch Dermatol* 1997; **133**: 1573–8.
3 Enjolras O, Wassef M, Mazoyer E *et al.* Infants with Kasabach–Merritt syndrome do not have 'true' hemangioma. *J Pediatr* 1997; **130**: 631–40.
4 Enjolras O, Mulliken JB, Wassef M *et al.* Residual lesions after Kasabach–Merritt phenomenon in 41 patients. *J Am Acad Dermatol* 2000; **42**: 225–35.
5 Schulz AS, Urban J, Gessler P *et al.* Anaemia, thrombocytopenia and coagulopathy due to occult diffuse infantile haemangiomatosis of spleen and pancreas. *Eur J Pediatr* 1999; **158**: 379–83.
6 Dabashi Y, Eisen RN. Infantile hemangioendothelioma of the pelvis associated with Kasabach–Merritt syndrome. *Pediatr Pathol* 1990; **10**: 407–15.
7 Sadan N, Horowitz I, Choc L *et al.* Giant hemangioma with thrombocytopenia and osteolysis successfully treated with prednisone. *J Pediatr Orthop* 1989; **9**: 472–5.
8 Carrington PR, Rowley MJ, Fowler M *et al.* Kasabach–Merritt syndrome with bone involvement: the pseudomalignant sign of Gorham. *J Am Acad Dermatol* 1993; **29**: 117–9.
9 Biswal BM, Anand AK, Aggarwal HN *et al.* Vertebral haemangioma presenting as Kasabach–Merritt syndrome. *Clin Oncol (R Coll Radiol)* 1993; **5**: 187–8.
10 Bowles LJ, Kostopoulos-Farri E, Papageorgiou AN. Perinatal hemorrhage associated with the Kasabach–Merritt syndrome. *Clin Pediatr (Phila)* 1981; **20**: 428–9.
11 Hall GW. Kasabach–Merritt syndrome: pathogenesis and management. *Br J Haematol* 2001; **112**: 851–62.
12 Warrell RP, Kempin SJ, Benua RS *et al.* Intratumoral consumption of indium-111 labelled platelets in a patient with hemangiomatosis and intravascular coagulation (Kasabach–Merritt syndrome). *Cancer* 1983; **52**: 2256–60.
13 Doi O, Takada Y. Kasabach–Merritt syndrome in two neonates. *J Pediatr Surg* 1992; **27**: 1507–8.
14 Maceyko RF, Camisa C. Kasabach–Merritt syndrome. *Pediatr Dermatol* 1991; **8**: 133–6.
15 Mazoyer E, Enjolras O, Laurian C *et al.* Coagulation abnormalities associated with extensive venous malformations of the limbs: differentiation from Kasabach–Merritt syndrome. *Clin Lab Haematol* 2002; **24**: 243–51.
16 El-Dessouky M, Azmy AF, Raine PAM *et al.* Kasabach–Merritt syndrome. *J Pediatr Surg* 1988; **23**: 109–11.
17 Mac-Moune Lai F, To KF, Choi PC *et al.* Kaposiform haemangioendothelioma: five patients with cutaneous lesion and long follow-up. *Mod Pathol* 2001; **14**: 1087–92.
18 Léauté-Labrèze C, Bioulac-Sage P, Labbé L *et al.* Tufted angioma with platelet trapping syndrome: response to aspirin. *Arch Dermatol* 1997; **133**: 1077–9.
19 Phillips WG, Marsden JR. Kasabach–Merritt syndrome exacerbated by platelet transfusion. *J R Soc Med* 1993; **86**: 231–2.
20 Esterly NB. Kasabach–Merritt syndrome. *J Am Acad Dermatol* 1983; **8**: 504–13.
21 Evans J, Batchelor ADR, Start G *et al.* Haemangioma with coagulopathy: sustained response to prednisone. *Arch Dis Child*; **60**: 809–12.
22 Enjolras O, Mulliken JB. The current management of vascular birthmarks. *Pediatr Dermatol* 1993; **10**: 311–33.
23 Sadan N, Wolach B. Treatment of hemangiomas of infants with high doses of prednisone. *J Pediatr* 1996; **128**: 141–6.
24 Boon LM, MacDonald DM, Mulliken JB. Complications of systemic corticosteroid therapy for problematic hemangioma. *Plast Reconstr Surg* 1999; **104**: 1616–23.
25 White CW, Wolf SJ, Korones DN *et al.* Treatment of childhood angiomatous diseases with recombinant interferon alpha-2a. *J Pediatr* 1991; **118**: 59–66.
26 Klein C, Hauser M, Hadorn HB. Interferon α-2a therapy of consumptive coagulopathy in Kasabach–Merritt syndrome. *Pediatrics* 1992; **151**: 919.
27 Ezekowitz RAB, Mulliken JB, Folkman J. Interferon alfa-2a therapy for life-threatening hemangiomas of infancy. *N Engl J Med* 1992; **326**: 1456–63.
28 Hatley RM, Sabio H, Howell CG *et al.* Successful management of an infant with a giant hemangioma of the retroperitoneum and Kasabach–Merritt syndrome with α-interferon. *J Pediatr Surg* 1993; **28**: 1356–9.
29 Enjolras O, Wassef M, Dosquet CH *et al.* Syndrome de Kasabach–Merritt sur angiome en touffes congénital. *Ann Dermatol Vénéréol* 1998; **125**: 257–60.
30 Haisley-Royster C, Enjolras O, Frieden IJ *et al.* Kasabach-Merritt phenomenon: a retrospective study of treatment with vincristine. *J Pediatr Hematol Oncol* 2002; **24**: 459–62.
31 Koerper MA, Addiego JE, Ad A *et al.* Use of aspirin and dipyridamole in children with platelet trapping syndromes. *J Pediatr* 1983; **102**: 311–4.
32 Hurvits CH, Alkalay AL, Sloninsky L *et al.* Cyclophosphamide in life threatening vascular tumours. *J Pediatr* 1986; **109**: 360–3.
33 De Prost Y, Teillac D, Bodemer C *et al.* Successful treatment of Kasabach–Merritt syndrome with pentoxyfylline. *J Am Acad Dermatol* 1991; **25**: 854–5.
34 Morad AB, McClain KL, Ogden AK. The role of tranexamic acid in the treatment of giant hemangiomas in newborns. *Am J Pediatr Hematol Oncol* 1993; **15**: 383–5.
35 Hagerman LJ, Czapek EE, Donnellan WL *et al.* Giant hemangioma with consumption coagulopathy. *J Pediatr* 1975; **87**: 766–8.
36 Drolet BA, Scott LA, Esterly NB *et al.* Early surgical intervention in a patient with Kasabach-Merritt phenomenon. *J Pediatr* 2001; **138**: 756–8.
37 George M, Singhal V, Sharma V, Nopper AJ. Successful surgical extirpation of a complex vascular lesion in an infant with Kasabach–Merritt syndrome. *Pediatr Dermatol* 2002; **19**: 340–4.
38 Tanaka K, Shimao S, Okada T *et al.* Kasabach–Merritt syndrome with disseminated intravascular coagulopathy treated by exchange transfusion and surgical excision. *Dermatologica* 1986; **173**: 90–4.
39 Schild SE, Buskirk SJ, Frick LM *et al.* Radiotherapy for large symptomatic hemangiomas. *Int J Radiat Oncol Biol Phys* 1991; **21**: 729–35.
40 Miller JG, Orton CI. Long-term follow-up of a case of KMS treated with radiation and corticosteroids. *Br J Plast Surg* 1992; **45**: 559–61.
41 Furst CJ, Silfversward C, Holm LE. Mortality in a cohort of radiation treated childhood skin haemangiomas. *Acta Oncol* 1989; **28**: 789.

42 Caldwell JB, Ryan MT, Benson PM *et al*. Cutaneous angiosarcoma arising in the radiation site of a congenital hemangioma. *J Am Acad Dermatol* 1995; **33**: 865–70.

Haemangiopericytoma

This is still a controversial neoplasm as it is difficult to distinguish pericytes from endothelial cells or fibroblasts on light microscopy alone [1]. However, most authors believe it is a distinct entity [2]. Haemangiopericytoma rarely originates in the skin, and is often separated into adult and congenital or infantile types [3]. The congenital and infantile form typically presents as a multilobulated mass in the subcutis [1–4]. Lesions are found anywhere on the body and have a deep red colour, suggesting a vascular origin. Histopathology of these neoplasms shows tightly packed cellular areas surrounding endothelium-lined branching vessels. The cells show round to oval nuclei and cytoplasm with ill-defined borders. The vascular channels form a continuous network in a staghorn like arrangement [1]. There is evidence of mitotic activity, but the clinical behaviour is benign [3]. Immunostaining shows these tumours are positive for alpha smooth muscle actin, desmin, cytokeratin, and *Ulex europaeus* 1 lectin but negative for factor VIII-related antigen [1].

They may resolve spontaneously or be treated by excision [5].

References

1 Requena L, Sangueza OP. Cutaneous vascular proliferation. Part II. Hyperplasias and benign neoplasms. *J Am Acad Dermatol* 1997; **37**: 887–922.
2 Nappi O, Ritter JH, Pettinato G *et al*. Hemangiopericytoma: histopathological pattern or clinicopathological entity. *Semin Diagn Pathol* 1995; **12**: 221–32.
3 Enzinger FM, Smith BH. Hemangiopericytoma: an analysis of 106 cases. *Hum Pathol* 1976; **7**: 61–82.
4 Chen KTK, Kassel SH, Medrano VA. Congenital hemangiopericytoma. *J Surg Oncol* 1986; **31**: 127–9.
5 Resnick SD, Lacey S, Jones G. Hemorrhagic complications in a rapidly growing congenital hemangiopericytoma. *Pediatr Dermatol* 1993; **10**: 267–70.

Angiokeratomas [1]

Angiokeratomas are hyperkeratotic vascular cutaneous lesions which may be localized or diffuse. The localized forms are angiokeratoma circumscriptum, angiokeratoma of Mibelli, solitary angiokeratomas and angiokeratoma of the scrotum or vulva. The diffuse variant, angiokeratoma corporis diffusum, is a rare disorder commonly found in Fabry's disease (see Chapter 59).

Reference

1 Schiller PI, Itin PH. Angiokeratomas: an update. *Dermatology* 1996; **193**: 275–82.

Angiokeratoma circumscriptum

Aetiology and pathology. Angioma circumscriptum is a vascular malformation of ectatic vessels in the papillary dermis, which may or may not be thrombosed. The epidermis has varying degrees of acanthosis, papillomatosis and compact hyperkeratosis. The rete ridges are elongated and surround the dilated vascular channels [1,2].

Clinical features [3]. This is a rare condition which is comprised of a hyperkeratotic vascular plaque, usually present from birth. They are commonly situated on the lower leg and have a blue–black colour with a segmental distribution. With time, the lesion tends to develop more warty papules which may bleed if traumatized. The lesions are fixed and do not remit with age.

Diagnosis. The diagnosis is usually established by the combination of the early onset and clinical appearance of aggregated papules forming a hyperkeratotic plaque. There may be some confusion with verrucous haemangiomas. The latter have deeper vascular elements and capillary endothelial proliferation on histological examination. Other differential diagnoses include localized lymphatic malformations (microcystic) which are not hyperkeratotic and the more rare condition acral pseudolymphomatous angiokeratoma of children (APACHE). The latter is a distinctive entity affecting the feet and has pseudolymphomatous histology rather than a true angiokeratoma [4].

Treatment. The size of the lesions will determine the therapy used. Small lesions can be treated with curettage and cautery, and larger lesions treated with laser removal or even excision.

References

1 Fabry J. Über einen Fall von Angiokeratoma circumscription am linken Oberschenkel. *Dermatol Zeitschr* 1915; **22**: 1–4.
2 Goldman L, Gibson SH, Richfield DF. Thrombotic angiokeratoma circumscriptum simulating melanoma. *Arch Dermatol* 1981; **117**: 138–9.
3 Mittal R, Aggarwal A, Srivastava G. Angiokeratoma circumscriptum: a case report and review of the literature. *Int J Dermatol* 2005; **44**: 1031–4.
4 Hara M, Matsunaga J, Tagami H. Acral pseudolymphomatous angiokeratoma of children (APACHE): a case report and immunohistological study. *Br J Dermatol* 1991; **124**: 387–8.

Angiokeratoma of Mibelli

Aetiology and pathology. Angokeratoma of Mibelli is transmitted as an autosomal dominant trait with highly variable penetrance [1,2], affecting girls more than boys. The lesions are commonly associated with acrocyanosis and chilblains, which suggests that cold injury is important in the aetiology.

The histopathological features are essentially the same as those of angiokeratoma circumscriptum, that is marked ectasia of vessels within the papillary dermis, with associated acanthosis, papillomatosis and hyperkeratosis of the overlying epidermis [3]. Elongated rete ridges tend to encircle and enclose the vascular lacunae.

Clinical features [4,5]. The lesions commonly develop between the ages of 10 and 15 years, but both earlier and later onset has been recorded. A history of recurrent chilblains is usual, but not invariable. The earliest lesions are minute, bright-red macules, which slowly increase in size and become elevated, warty and darker in colour. They reach a diameter of 5 mm or more in some cases. The dorsal and lateral aspects of fingers and toes are most often affected, but lesions also occur on the dorsa of hands and feet (Fig. 18.22) and occasionally on the knees and elbows. On the calves, lesions resembling erythema induratum may be present [2]. The lesions, which are often numerous, may be disfiguring but seldom cause symptoms except for instances associated with ulceration of the fingertips [1,4]. There is little tendency to spontaneous resolution.



Fig. 18.22 Angiokeratoma of Mibelli in a 9-year-old child.

Treatment. The lesions can be treated, if desired, with liquid nitrogen, electrodesiccation, laser ablation [6] or by local excision.

References

1 Pringle JJ. Four cases of angiokeratoma from one family. *Br J Dermatol* 1913; **25**: 40–53.
2 Smith RBW, Prior IAM, Park RG. Angiokeratoma of Mibelli: a family with nodular lesions of the legs. *Aust J Dermatol* 1968; **9**: 329–34.
3 Imperial R, Helwig EB. Angiokeratoma: a clinicopathological study. *Arch Dermatol* 1967; **95**: 166–75.
4 Dave VK, Main RA. Angiokeratoma of Mibelli with necrosis of the fingertips. *Arch Dermatol* 1972; **106**: 726–8.
5 Haye KR, Rebello DJA. Angiokeratoma of Mibelli. *Acta Dermatol Venereol (Stockh)* 1961; **41**: 56–60.
6 Sommer S, Merchant WJ, Sheehan-Dare R. Severe predominantly acral variant of angiokeratoma of Mibelli: response to long-pulse Nd:YAG (1064 nm) laser treatment. *J Am Acad Dermatol* 2001; **45**: 764–6.

Solitary papular angiokeratoma [1]

This entity has been convincingly distinguished from the other angiokeratomas, particularly from angiokeratoma circumscriptum [2]. Solitary papular angiokeratoma is an acquired disorder, probably arising as a response to trauma. Even though it is not strictly a developmental anomaly, it is included in this chapter because of clinical and histopathological similarities with the other angiokeratomas.

Histologically, solitary papular angiokeratomas are more or less indistinguishable both from angiokeratoma circumscriptum and angiokeratoma of Mibelli. Solitary angiokeratomas differ clinically mainly by their later onset, usually between the age of 10 and 40 years, often with a history of preceding trauma. They occur in both sexes anywhere on the body, although the legs are the site of predilection. Although usually single, multiple lesions may occur. The patient often presents with a history of sudden enlargement, darkening or bleeding in a long-standing lesion, leading to suspicion of a malignant melanoma [2]. The lesions have the appearance of warty papules, generally between 2 and 10 mm in diameter, and dark red to blue–black in colour.

Solitary papular angiokeratomas are frequently mistaken clinically for viral warts, melanocytic naevi or, more importantly, malignant melanoma. Local excision is recommended if there is any doubt about the diagnosis.

References

1 Imperial R, Helwig EB. Angiokeratoma: a clinicopathological study. *Arch Dermatol* 1967; **95**: 166–75.
2 Goldman L, Gibson SH, Richfield DN. Thrombotic angiokeratoma circumscriptum simulating melanoma. *Arch Dermatol* 1981; **117**: 138–9.

Angiokeratoma of the scrotum

Synonym
- Angiokeratoma of Fordyce

Aetiology and pathology. The most common of the angiokeratomas, angiokeratoma of the scrotum, becomes more frequent with increasing age [1]. In a study in Japan, the prevalence was shown to increase from 0.6% in 16 year olds to 17% in those over 70 years of age [2]. It should probably be regarded as a degenerative disorder, and there is evidence that local venous hypertension plays a part in its development [1,3].

The histological features are similar to those observed in angiokeratoma of Mibelli and solitary papular angiokeratoma [4].

Clinical features [1,3,5,6]. Small, 1–4 mm, bright-red vascular papules may develop on the scrotum as early as late adolescence. With increasing age they become larger, darker and more numerous. Symptoms include itching, soreness or bleeding [7]. Identical lesions may also occur on the penis, upper thighs and in the groins. Well-circumscribed, macular, telangiectatic lesions have been described on the oral mucosa in patients with angiokeratomas of the scrotum [8].

The diagnosis of angiokeratoma corporis diffusum should be considered in any patient presenting with scrotal angiokeratomas.

Treatment. Liquid nitrogen cryotherapy, diathermy or laser ablation [9] can be used to treat symptomatic lesions. Evidence of associated disorders capable of increasing the scrotal venous pressure should be sought, particularly varicocoele, treatment of which may lead to regression of the angiokeratomas [3].

References

1 Imperial R, Helwig EB. Angiokeratoma of the scrotum (Fordyce type). *J Urol* 1967; **98**: 379–87.
2 Izaki M. Angiokeratoma of the scrotum (Fordyce). *Keio J Med* 1952; **1**: 61–8.
3 Agger P, Osmundsen PE. Angiokeratoma of the scrotum (Fordyce). *Acta Dermatol Venereol (Stockh)* 1970; **50**: 221–4.
4 Gioglio L, Porta C, Moroni M *et al.* Scrotal angiokeratoma (Fordyce): histopathological and ultrastructural findings. *Histol Histopathol* 1992; **7**: 47–55.
5 Evans HW. Angioma of the scrotum (Fordyce lesion). *Arch Intern Med* 1962; **110**: 520–2.
6 Robinson SS, Tasker S. Angiomas of the scrotum (angiokeratoma, Fordyce): compilation of cases and discussion of nomenclature. *Arch Dermatol* 1946; **54**: 667–74.
7 Taniguchi S, Inoue A, Hamada T. Angiokeratoma of Fordyce: a cause of scrotal bleeding. *Br J Urol* 1994; **73**: 589–90.
8 Rappaport I, Shiffman MA. Multiple phlebectasia involving jejunum, oral cavity and scrotum. *JAMA* 1963; **185**: 437–40.
9 Lapidoth M, Ad ED, David M *et al.* Treatment of angiokeratoma of Fordyce with pulsed dye laser. *Dermatol Surg* 2006; **32**: 1147–50.

Angiokeratoma of the vulva

Lesions entirely analogous to scrotal angiokeratomas may occur on the labia majora in older women [1,2] or in younger women from the use of the oral contraceptive pill [3].

References

1 Blair C. Angiokeratoma of the vulva. *Br J Dermatol* 1970; **83**: 409–11.
2 Imperial R, Helwig EB. Angiokeratoma of the vulva. *Obstet Gynecol* 1967; **29**: 307–12.
3 Novick NL. Angiokeratoma vulvae. *J Am Acad Dermatol* 1985; **12**: 561–3.

Syndromes with vascular tumours

Bannayan–Riley–Ruvalcaba syndrome [1–7] (OMIM#153480)

Synonyms

- Bannayan–Zonana syndrome
- Riley–Smith syndrome
- Ruvalcaba–Myhre–Smith syndrome

Bannayan–Riley–Ruvalcaba syndrome (BRRS) is an autosomal dominant condition which is comprised of macrocephaly, penile lentigines and hamartomatous tumours including lipomas, haemangiomas and gastrointestinal polyps. It was found that BRRS shared many clinical features with Cowden's syndrome, such as intestinal polyposis, macrocephaly, facial trichilemmomas and lipomas [2]. They share a common genetic basis as both have been shown to have mutations in the *PTEN* gene [8–10].

The commonest skin findings are penile lentiginosis and haemangiomas, although arteriovenous malformations [10] and lipomas have been noted. The lentiginosis may not develop until mid-childhood [11]. The typical cutaneous findings are deep lipomatous swellings on the trunk and proximal limbs, which may enlarge to a considerable size.

It is now accepted that BRRS patients should be monitored for cancer surveillance in the same way that patients with Cowden's are monitored for thyroid, breast and gastrointestinal cancer [9,11].

References

1 Bannayan GA. Lipomatosis, angiomatosis and macrencephalia: a previously undescribed congenital syndrome. *Arch Pathol* 1971; **92**: 1–5.
2 Fargnoli MC, Orlow S, Semel-Concepcion J *et al.* Clinicopathologic findings in the Bannayan–Riley–Ruvalcaba syndrome. *Arch Dermatol* 1996; **132**: 1214–8.
3 Gorlin RJ, Cohen MM, Condon LM *et al.* Bannayan–Riley–Ruvalcaba syndrome. *Am J Med Genet* 1992; **44**: 307–14.
4 Miles HR, Zonana J, MacFarland J. Macrocephaly with hamartomas: Bannayan–Zonana syndrome. *Am J Med Genet* 1984; **19**: 225–34.
5 Riley HD, Smith WR. Macrocephaly, pseudopapilledema and multiple hemangiomata: a previously undescribed heredofamilial syndrome. *Pediatrics* 1960; **26**: 293–300.
6 Zonana J, Rimoin DL, Davis DC. Macrocephaly with multiple lipomas and hemangiomas. *J Pediatr* 1976; **89**: 600–3.
7 Cohen MM. Bannayan–Riley–Ruvalcaba syndrome: renaming three formerly recognized syndromes as one etiologic entity. *Am J Med Genet* 1990; **35**: 291.
8 Celebi JT, Tsou HC, Chen FF *et al.* Phenotypic findings of Cowden syndrome and Bannayan–Zonana syndrome in a family associated with a single germline mutation in PTEN. *J Med Genet* 1999; **36**: 360–4.
9 Marsh DJ, Kum JB, Lunetta KL *et al. PTEN* mutation spectra and genotype–phenotype correlations in Bannayan–Riley–Ruvalcaba syndrome suggest a single entity with Cowden syndrome. *Hum Mol Genet* 1999; **8**: 1461–72.
10 Naidich JJ, Rofsky NM, Rosen R *et al.* Arteriovenous malformation in a patient with Bannayan–Zonana syndrome. *Clin Imaging* 2001; **25**: 130–2.
11 Parisi MA, Dinulos MB, Leppig KA *et al.* The spectrum and evolution of phenotypic findings in *PTEN* mutation positive cases of Bannayan–Riley–Ruvalcaba syndrome. *J Med Genet* 2001; **38**: 52–8.

Vascular malformations

Vascular malformations are localized defects of vascular development without evidence of endothelial cell proliferation, which are present at birth and never regress. They may also expand in certain situations, for example during surgery, trauma or pregnancy. They are commonly classified according to which type of anomalous vessel is involved and their flow characteristics (Table 18.10).

Table 18.10 Classification of vascular malformations [1,2].

High/fast flow

Arteriovenous malformation (AVM)
- Syndromes with AVM:
  - Parkes Weber syndrome
  - Wyburn–Mason syndrome
  - Cobb syndrome

Low/slow flow

Capillary malformation (CM)
- Salmon patch
- Port-wine stain
- Naevus anaemicus
- Syndromes with CM
  - Sturge–Weber syndrome
  - Cutis marmorata talangiectatica congenita (CMTC)
  - Macrocephaly-CMTC
  - Adams-Oliver syndrome
  - Phakomatosis pigmentovascularis
  - Beckwith-Wiedemann
  - Thrombocytopenia absent radii syndrome
  - Roberts syndrome
  - Rubinstein-Taybi syndrome
  - Cardiofaciocutaneous syndrome

Venous malformation (VM)
- Syndromes with VM
  - Mafucci's syndrome
  - Blue rubber bleb naevus syndrome
  - Glomuvenous malformation
  - CMVM
  - Cerebral cavernous malformation
- Verrucous haemangioma

Lymphatic malformation (LM–previously lymphangioma)
- Microcystic and macrocystic
- Syndromes with LM
  - Gorham's disease

Mixed/complex

Any combination of CM/VM/AVM/LM
- Klippel–Trenaunay syndrome
- Proteus syndrome
- Hereditary neurocutaneous angiomatosis
- CM-AVM syndrome
- Divry–Bogaert

Others
- Hereditary haemorrhagic telangiectasia
- Ataxia telangiectasia

Vascular malformations may occur on any part of the body and may extend into deep visceral locations. They may be localized or diffuse or occur as part of a syndrome, for example Parkes Weber, and Klippel–Trenaunay syndromes. Management will vary in terms of investigation methods and treatment modalities used. The lesions do not regress and will often require multidisciplinary care from dermatologists, plastic surgeons, interventional radiologists, neurosurgeons, and head and neck surgeons, as well as ongoing care in adult life.

References

1 Enjolras O, Mulliken JB. Vascular tumors and vascular malformations (new issues). *Adv Dermatol* 1997; **13**: 375–423.

2 Enjolras O, Mulliken JB. The current management of vascular birthmarks. *Pediatr Dermatol* 1993; **10**: 311–33.

Arteriovenous malformation (AVM)

This is the most common high-flow vascular malformation, which is composed of a direct communication between arteries and veins called a nidus. The malformation arises during fetal development as a result of primitive arteriovenous channels in the retiform plexus failing to regress [1]. These channels may not canalize for many years; expansion is secondary to increased blood flow through the malformation and dilatation of adjacent arteries and veins [1].

Pathology. An AVM is made up of distorted arteries and veins with irregular thickened fibromuscular walls, and elastic fibres which are not continuous. The communication channels between the two vessels involved in shunting are a mixture of capillaries and stromal fibrosis [2].

Clinical features. AV malformations are rare, but are often the most serious of all the vascular anomalies. They are present at birth and have no gender predominance. They may be confused in childhood with capillary malformations or infantile haemangiomas. The common triggers for expansion include trauma, puberty and pregnancy. In 1990, the ISSVA adopted the Schobinger staging classification system (Table 18.11) for clinical severity.

The natural history of these malformations serves as a guide for intervention. An AVM may remain stable for years in stage I and a bruit is of little significance unless its intensity increases [1]. The onset of pain or enlargement heralds the likely progression to ulceration or haemorrhage [1,3]. The head is the commonest site, accounting for 70% of cases in one large series [3].

An AVM affecting the face overlying the mandible may cause asymmetry and gingival bleeding. On other sites such as the digits, bony involvement may be accompanied by ischaemic skin necrosis.

Table18.11 Schobinger classification for arteriovenous malformations.

Stage I Dormant, quiescent stage	Macular/cutaneous blush Warm
Stage II Expansion	Warm mass, thrill or bruit present
Stage III Destruction	As for stage II plus pain, ulceration, bleeding, bone-lytic lesions
Stage IV	Stage III and cardiac failure

There are different radiological investigations that allow one to delineate the extent of the lesion. Ultrasound is the simplest method to confirm a diagnosis, and it is usually combined with Doppler, which shows high-velocity arterial flow and pulsatile venous flow [1]. MRI is superior to CT with contrast and MR angiography will highlight anomalous vasculature. Arteriography is only used prior to embolization.

Differential diagnosis. In the early phase, AV malformations may be mistaken for capillary malformations, whereas in later stages the signs are rarely mistaken for anything else.

Treatment. For stage I and early stage II lesions, a conservative observation approach may be employed. However, at this stage localized AVMs are easier to excise and reconstruct. Surgical excision remains controversial since the risk of progression to other stages is not quantifiable. Large lesions may be incompletely excised and the cosmetic outcome of the reconstruction may be worse than the original lesion [1]. For any AVM the treatment of choice would be wide excision [1,4]. Arterial embolization is employed to occlude shunts and is carried out with various agents such as glues, ethanol, particles, implantable coils or spheres. Proximal ligation of arterial feeding vessels is not advisable as the surrounding vessels are recruited to supply the nidus. This also prevents easy access to the nidus when embolization is necessary [5]. Wide surgical excision is carried out a few days after preoperative arterial embolization, which reduces the extent of perioperative haemorrhage [6]. Despite apparently successful embolization in limb AVM, the lesions may still recur months or years later [7]. It is therefore advisable to warn patients and their families that a cure is rarely possible and that management is aimed at keeping the AVM under control.

References

1 Kohout MP, Hansen M, Pribaz JJ *et al.* Arteriovenous malformations of the head and neck: natural history and management. *Plast Reconstr Surg* 1998; **102**: 643–54.

2 Enjolras O, Boon LM, Mulliken JB. Vascular malformations. In: Harper J, Oranje A, Prose N, eds. *Textbook of Pediatric Dermatology*, 2nd edn. Oxford: Blackwell, 2006: 1153–74.

3 Enjolras O, Logeart, Gelbert F *et al.* Malformations arterioveineuses: étude de 200 cas. *Ann Dermatol Vénéréol* 2000; **127**: 17–22.

4 McClinton MA. Tumours and aneurysms of the upper extremity. *Hand Clin* 1993; **9**: 151–69.

5 Coldwell DM, Stokes KR, Yakes WF *et al.* From the RSNA refresher courses. Embolotherapy: agents, clinical applications and techniques. *Radiographics* 1994; **14**: 623–46.

6 Burrows PE, Fellows KE. Techniques for management of pediatric vascular anomalies. In: Cope C, ed. *Current Techniques in Interventional Radiology*, Vol 2. Philadelphia: Current Medicine, 1995: 12–27.

7 White RI, Pollak J, Persing J *et al.* Long-term outcome of embolotherapy and surgery for high-flow extremity arteriovenous malformations. *J Vasc Intervent Radiol* 2000; **11**: 1285–95.

Syndromes with arteriovenous malformation

Parkes Weber syndrome (OMIM #608355) [1]

This is an uncommon syndrome characterized by overgrowth of a limb associated with a high flow capillary AVM or capillary–lymphatic AVM with multiple AV fistulae along the affected limb. It is more common in the lower limb and is characterized by a

congenital vascular stain (a quiescent stage I AVM) and increasing limb length and girth. Investigation with ultrasound and Doppler or MR angiography reveals the fistulae and often shows enlarged arteries and some areas of hypervascularity. The differential diagnosis is usually between Klippel–Trenaunay and Proteus syndrome, but there are no true AVMs in either of these diagnoses, and other features such as epidermal and connective tissue naevi will help to distinguish Proteus syndrome.

The disease may be complicated by leg length discrepancy, which may be treated by epiphyseal stapling [2,3]. If lymphatic anomalies are present, they can lead to lymphoedema and the associated features of chronic lymphatic congestion such as papillomatosis and infection. The treatment for any lymphoedema is usually conservative with compression bandaging or stockings.

References
1 Enjolras O, Chapot R, Merland JJ. Vascular anomalies and the growth of limbs: a review. *J Pediatr Orthop B* 2004; **13**: 349–57.
2 Gabriel KR, Crawford AH, Roy DR *et al.* Percutaneous epiphyseodesis. *J Pediatr Orthop* 1994; **14**: 358–62.
3 Rogalski R, Hensinger R, Loder R. Vascular abnormalities of the extremities, clinical findings and management. *J Pediatr Orthop* 1993; **13**: 9–14.

Wyburn–Mason syndrome [1–5]

Synonym
- Bonnet–Decahaume–Blanc syndrome

The original syndrome was described by Bonnet in 1937 [1], and it was later described by Wyburn-Mason in the English literature [2]. The main features of this rare disorder include cerebral midbrain arteriovenous malformations (AVMs), ipsilateral retinal AVM and ipsilateral cutaneous vascular abnormalities. The latter may be mistaken for a capillary malformation but it is a stage I AVM. However, the vascular malformation is not always unilateral; there are reports of bilateral and centrofacial vascular stains, extending from the glabella down to the upper lip. The visual tract abnormalities may occur anywhere between the orbit, optic nerve or optic tract. Patients may present with headaches, seizures or visual symptoms. Investigation with MRI and MR angiography will outline the AVM. Unfortunately, there is no consensus on the treatment for such a rare disorder and patients are typically managed conservatively by observation.

References
1 Bonnet P, Dechaume J, Blanc E. L'aneurysme cirsoide de la retine (aneurysme vasemeaux). *J Med Lyon* 1937; **18**: 165–78.
2 Wyburn-Mason R. Arteriovenous aneurysm of midbrain and retina, facial naevi and mental changes. *Brain* 1943; **66**: 163–203.
3 Patel U, Gupta SC. Wyburn–Mason syndrome: case report and review of the literature. *Neuroradiology* 1990; **31**: 544–6.
4 Theron J, Newton TH, Hoyt WF. Unilateral retinocephalic vascular malformations. *Neuroradiology* 1974: **7**: 185–96.
5 Dayani PN, Sadun AA. A case report of Wyburn-Mason syndrome and review of the literature. *Neuroradiology* 2007; **49**: 445–56.

Cobb syndrome

This is a rare idiopathic condition consisting of a segmental capillary malformation with an AVM of the spinal cord within two segments of the involved dermatome [1]. The capillary malformation is actually a quiescent AVM and may be quite faint in appearance or verrucous [2]. Spinal involvement may include the vertebral column, dura, spinal cord and nerve roots [3]. The importance of detecting the underlying spinal AVM is that the latter becomes symptomatic in childhood and leads to neurological complications such as spastic paralysis. There have been cases of successful treatment with embolization [4,5].

References
1 Cobb S. Hemangioma of the spinal cord associated with skin naevi of the same metamere. *Ann Surg* 1915; **62**: 641–9.
2 Clinton TS, Cooke LM, Graham BS. Cobb syndrome associated with a verrucous (angiokeratoma-like) vascular malformation. *Cutis* 2003; **71**: 283–7.
3 Jessen RT, Thompson S, Smith EB. Cobb syndrome. *Arch Dermatol* 1977; **113**: 1587–90.
4 Miyatake SI, Kikuchi H, Koide T *et al.* Cobb's syndrome and its treatment with embolization. *J Neurosurg* 1990; **72**: 497–9.
5 Matullo KS, Samdani A, Betz R. Low back pain and unrecognized Cobb syndrome in a child resulting in paraplegia. *Orthopedics* 2007; **30**: 237–8.

Capillary malformations

There are two common types of vascular malformation with a macular erythematous patch, the salmon patch and port-wine stain.

Salmon patch

Synonyms
- Nuchal stain
- Stork mark
- Stork bite

Salmon patches are extremely common vascular anomalies and are found in all types of races. Their prevalence varies from 20–60% [1–5]. There is evidence to suggest a genetic aetiology in some cases, as both facial and nuchal stains may be inherited as an autosomal dominant trait [6,7].

They present clinically with irregular pink/red macular patches with or without fine telangiectasia. The commonly affected sites are the nape of the neck extending up to the occipital scalp (Fig. 18.23) and anteriorly on the forehead, from the glabella to the upper eyelids or bridge of nose [8–11]. The less common sites include the sacral region [11] and sometimes multiple sites may be involved.

The natural history of these anomalies is that the majority of the facial stains will fade within the first year of life [8,12] whereas the other sites may persist into adulthood [12,13]. The sacral lesions are often a site for concern as they may be associated with occult spinal dysraphism [11,14]. The lesions are often triangular or rhomboidal in shape [11]. If a sacral salmon patch is present with a second abnormality such as a lipoma, pit, dimple, sinus, hypertrichosis, cutis aplasia or haemangioma, further investigation with an ultrasound or MRI is recommended [15].

References
1 Alper JC, Holmes LB. The incidence and significance of birthmarks in a cohort of 4641 newborns. *Pediatr Dermatol* 1983; **73**: 31–3.
2 Hidano A, Purwoko R, Jitsukawa K. Statistical survey of skin changes in Japanese neonates. *Pediatr Dermatol* 1986; **3**: 140–4.



Fig. 18.23 Nuchal capillary malformation in infant.

3 Kahana M, Feldman M, Abudi Z, Yurman S. The incidence of birthmarks in Israeli neonates. *Int J Dermatol* 1995; **34**: 704–6.
4 Nanda A, Kaur S, Bhakoo ON *et al*. Survey of cutaneous lesions in Indian newborns. *Pediatr Dermatol* 1989; **6**: 39–42.
5 Rivers JK, Fredericksen PC, Dibdin C. A prevalence survey of dermatoses in the Australian neonate. *J Am Acad Dermatol* 1990; **23**: 77–81.
6 Merlob P, Reisner SH. Familial nevus flammeus of the forehead and Unna's nevus. *Clin Genet* 1985; **27**: 165–6.
7 Selmanowitz VJ. Nevus flammeus of the forehead. *J Pediatr* 1968; **73**: 755–7.
8 Leung AKC, Telmesani AMA. Salmon patches in Caucasian children. *Pediatr Dermatol* 1989; **6**: 185–7
9 Pratt AG. Birthmarks in infants. *Arch Dermatol Syphilol* 1953; **67**: 302–5.
10 Tan KL. Nevus flammeus of the nape, glabella and eyelids: a clinical study of frequency, racial distribution, and association with congenital abnormalities. *Clin Pediatr (Phila)* 1972; **11**: 112–8.
11 Ben-Amitai D, Davidson S, Schwartz M *et al*. Sacral nevus flammeus simplex: the role of imaging. *Pediatr Dermatol* 2000; **17**: 469–71.
12 Smith MA, Manfield PA. The natural history of salmon patches in the first year of life. *Br J Dermatol* 1962; **74**: 31–3.
13 Bettley FR. Erythema nuchae. *Br J Dermatol* 1940; **52**: 363–70.
14 Harris HW, Miller F. Midline cutaneous and spinal defects. Midline cutaneous abnormalities associated with occult spinal disorders. *Arch Dermatol* 1996; **112**: 1724–8.
15 Enjolras O, Boukobza M, Jdid R. Cervical occult spinal dysraphism: MRI findings and the value of a vascular birthmark. *Pediatr Dermatol* 1995; **12**: 256–9.

Port-wine stains

A port-wine stain (PWS) is defined as a macular telangiectatic patch (CM) which is present at birth and remains throughout life. They may be localized or extensive, affecting a whole limb. They are often associated with an underlying disorder (see below).

Pathology and pathogenesis. These lesions are rarely biopsied but show regular, ectatic, small venule and capillary channels in the papillary and reticular dermis. Later-stage lesions develop progressive fibrosis around the vessels and dilatation of the channels. The thickness of vessels has proved of interest when trying to understand the response to treatment. It has been shown that facial V2 region vessels are deep, like those of limb CM, whereas the V1 are more superficial [1]. Immunohistochemical analysis of the abnormal vasculature has revealed a reduction in neurone density, which has been postulated to account for the dilatation of the vessels in CM [2,3].

Even though one could speculate that abnormality of vasculogenesis regulatory genes would lead to the development of anomalies such as CM, only *RASA1* (on chromosome 5q) has been linked to families with autosomal dominant CM–arteriovenous malformations. The gene product is a protein (p120-rasGAP) believed to be important in vascular endothelial cell proliferation [4].



Fig. 18.24 Extensive capillary malformation/port-wine stain affecting V1 and V2 distribution.

References

1 Eubanks LE, McBurney EI. Videomicroscopy of port wine stains: correlation of location and depth of lesion. *J Am Acad Dermatol* 2001; **44**: 948–51.
2 Smoller BR, Rosen S. Port-wine stains. A disease of altered neural modulation of blood vessels? *Arch Dermatol* 1986; **122**: 177–9.
3 Selim MM, Kelly KM, Nelson JS *et al*. Confocal microscopy study of nerves and blood vessels in untreated and treated port wine stains: preliminary observations. *Dermatol Surg* 2004; **30**: 892–7.
4 Eerola I, Boon LM, Watanabe S *et al*. Capillary malformation-arteriovenous malformation, a new clinical and genetic disorder caused by *RASA1* mutations. *Am J Hum Genet* 2003; **73**: 1240–9.

Clinical features. These are best considered as low-flow vascular malformations which may occur on any part of the body but commonly affect the face in the distribution of the trigeminal nerve (V1, V2, V3) (Fig. 18.24). The incidence varies between 0.1 and 2% [1–6]. If they affect the face they may extend into the mucosal surfaces such as the lips and gingiva. Initially, the lesions are pale pink patches, but with time they may mature into a violaceous colour (facial CM), remain static or even lighten (trunk or limb CM). Facial CMs typically evolve into thicker areas with vascular blebs, occasionally pyogenic granulomas [7,8] and underlying

tissue hypertrophy. This may include bony overgrowth and eruption of early dentition. Limb CM may also be associated with unilateral limb hypertrophy. If the borders are very well defined ('geographic CM') they are more commonly associated with underlying lymphatic abnormalities and limb hypertrophy [9].

The diagnosis of a CM is usually straightforward but in the early phase it may be mistaken for an evolving infantile haemangioma, early arteriovenous malformation or tufted angioma. Infantile haemangiomas will usually reveal their proliferative phase and tufted angiomas are often more plaque-like and tender. If one suspects an AVM, Doppler examination will be useful in confirming the diagnosis.

References

1 Alper JG, Holmes LB. The incidence and significance of birthmarks in a cohort of 4641 newborns. *Pediatr Dermatol* 1983; **1**: 58–66.

2 Jacobs AH, Walton RG. The incidence of birthmarks in the neonate. *Pediatrics* 1976; **58**: 218–22.

3 Nanda A, Kaur S, Bhakoo ON *et al*. Survey of cutaneous lesions in Indian newborns. *Pediatr Dermatol* 1989; **6**: 39–42.

4 Osburn K, Schosser RH, Evert MA. Congenital pigmented and vascular lesions in newborn infants. *J Am Acad Dermatol* 1987; **16**: 788–92.

5 Pratt AG. Birthmarks in infants. *Arch Dermatol Syphilol* 1953; **67**: 302–5.

6 Rivers JK, Fredericksen PC, Dibdin C. A prevalence survey of dermatoses in the Australian neonate. *J Am Acad Dermatol* 1990; **23**: 77–81.

7 Klapman MH, Yao F. Thickening and nodules in port-wine stains. *J Am Acad Dermatol* 2001; **44**: 300–2.

8 Valeyrie L, Lebrun-Vignes B, Descamps V *et al*. Pyogenic granuloma within port-wine stains: an alarming clinical presentation. *Eur J Dermatol* 2002; **12**: 373–5.

9 Maari C, Frieden IJ. Klippel–Trenaunay syndrome: the importance of 'geographic stains' in identifying lymphatic disease and risk of complications. *J Am Acad Dermatol* 2004; **51**: 391–8.

Treatment. The pulsed tuneable dye laser (PDL) has become the treatment of choice for CM (Fig. 18.25). PDL achieves lightening of the malformation by reducing the number and size of erythrocytes in vessels by selective photothermolysis. First generation PDLs operated at 577 nm or 585 nm and were effective and had relatively few side effects [1,2]. The success rate varied from 50 to 90% [3,4]. These studies also showed that not all CMs respond fully to PDL. A better understanding of the interaction between lasers and CM has led to modification of PDLs—the second-generation machines. The modifications include longer pulse widths, longer wavelengths, higher fluences and the addition of cooling devices [5]. The rationale for alteration in treatment parameters comes from studies of laser–CM interactions using non-invasive confocal microscopy [6,7] and animal models [8]. In comparative studies, the modified second-generation PDL devices were found to induce superior lightening of CM [9,10].

The side effects of PDL include bruising (in nearly all cases), pain, swelling, crusting, bleeding, pyogenic granuloma and pigmentary change, both hypo- and hyperpigmentation. The incidence of atrophic scarring is between 1 and 3% [11,12]. Despite the apparent successful response to therapy with PDL, long-term redarkening of the CM recurs up to 10 years later [13], something which should be explained to any parent putting their child forward for treatment. In addition, not all CMs respond to PDL. Second-generation PDL has been shown to help cases resistant to first-generation devices. One study showed a benefit in 6/9 cases with a range of 25–50% lightening [5]. The potassium titanyl phosphate (KTP) laser has also been shown to produce extra lightening in PDL-resistant CM, but only in approximately 15% of cases [14]. The patients in these studies experienced less discomfort and post-treatment purpura, but at the expense of a greater rate of scarring of up to 7% [14]. Other lasers such as the Nd:YAG (longer wavelength 1064 nm) have achieved good results compared with the second-generation PDL [15]. Additional methods for treating resistant lesions include multiple pass irradiation with two PDL passes: the first at 590–600 nm and the second at 585 nm. A small case series showed that this benefited hypertrophic CM [16]. The use of non-coherent light sources, such as intense pulsed light (e.g. Photoderm®), is an alternative method which uses broadband light, employing filters to remove any unwanted wavelengths. This source was better for pink and red CM, but also caused lightening of purple CM [17]. The identification of prognostic factors that determine the response to any of the above therapies should enable more targeted treatment. Clearly the size of vessel, its depth and density will influence response to PDL. The presence of more superficially located vessels infers a good response to therapy [18].



(a) (b)

Fig. 18.25 (a) Pre and (b) post pulsed dye laser therapy.

In clinical practice it is clear that red lesions respond better than pink or purple CM. The site of involvement is an important prognostic indicator, with the head and neck faring better than other body sites, although peripheral facial lesions respond better than centrofacial areas [19].

The timing of treatment is controversial. Older children may experience stinging and may require local anaesthesia, whereas all young children will require general anaesthesia. There is no evidence to show that deferring treatment until later childhood has any detrimental effect on the response to laser therapy [20]. The main reason for early treatment is to reduce the harmful effects of disfiguring CM on psychological development [21] and ideally should be completed before starting school. The number of treatments required to treat a CM is not standardized, and despite mathematical models using non-invasive methods such as the SIAscope (reflectance measurements) [22] it may still be related to cost, availability, side effects and the experience of the laser surgeon.

References

1 Levine VJ, Geronemus RG. Adverse effects associated with the 577- and 585-nanometer pulsed dye laser in the treatment of cutaneous vascular lesions: a study of 500 patients. *J Am Acad Dermatol* 1995; **32**: 613–7.

2 Katugampola GA, Lanigan SW. Five years experience of treating port wine stains with the flashpump-pumped pulsed dye laser. *Br J Dermatol* 1997; **137**: 750–4.

3 Reyes BA, Geronemus R. Treatment of port-wine stains during childhood with the flashpump-pumped pulsed dye laser. *J Am Acad Dermatol* 1990; **23**: 1142–8.

4 Orten SS, Waner M, Flock S *et al.* Port-wine stains. An assessment of 5 years of treatment. *Arch Otolaryngol-Head Neck Surg* 1996; **122**: 1174–9.

5 Lanigan SW, Taibjee SM. Recent advances in laser treatment of port-wine stains. *Br J Dermatol* 2004; **151**: 527–33.

6 Motley RJ, Katugampola G, Lanigan SW. Microvascular abnormalities in port wine stains and response to 585 nm pulsed dye laser. *Br J Dermatol* 1996; **135** (Suppl. 47): 13–27.

7 Selim MM, Kelly KM, Nelson JS *et al.* Confocal microscopy study of nerves and blood vessels in untreated and treated port wine stains: preliminary observations. *Dermatol Surg* 2004; **30**: 892–7.

8 Kimel S, Svaasand LO, Cao D *et al.* Vascular response to laser photothermolysis as a function of pulse duration, vessel type, and diameter: implications for port wine stain laser therapy. *Lasers Surg Med* 2002; **30**: 160–9.

9 Geronemus RG, Quintana AT, Lou WW *et al.* High fluence modified pulsed dye laser photocoagulation with dynamic cooling of port wine stains in infancy. *Arch Dermatol* 2000; **136**: 942–3.

10 Scherer K, Lorenz S, Wimmershoff M *et al.* Both the flashpump-pumped dye laser and the long-pulsed tunable dye laser can improve results in port-wine stain therapy. *Br J Dermatol* 2001; **145**: 79–84.

11 Lanigan SW. Patient-reported morbidity following flashlamp-pumped pulsed tunable dye laser treatment of port wine stains. *Br J Dermatol* 1995; **133**: 423–5.

12 Wlotzke U, Hohenleutner U, Abd-el-Raheem TA *et al.* Side effects and complications of flashlamp-pumped pulsed dye laser therapy of port-wine stains: a prospective study. *Br J Dermatol* 1996; **134**: 475–80.

13 Huikeshoven M, Petra HL, de Borgie CAJM *et al.* Redarkening of port-wine stains 10 years after pulsed-dye-laser treatment. *N Eng J Med* 2007; **356**: 1235.

14 Chowdhury MM, Harris S, Lanigan SW. Potasssium titanyl sulphate laser treatment of resistant port wine stains. *Br J Dermatol* 2001; **144**: 814–7.

15 Yang MU, Yaroslavsky AN, Farinelli WA *et al.* Long pulsed Nd:YAG laser treatment for port wine stains. *Lasers Surg Med* 2003; **15** (Suppl.): 28 (Abstr.).

16 Bencini PL. The multilayer technique: a new and fast approach for flashpump-pumped pulsed dye laser treatment of port wine stains (preliminary reports). *Dermatol Surg* 1999; **25**: 786–9.

17 Raulin C, Schroeter CA, Weiss RA *et al.* Treatment of port wine stains with a non-coherent pulsed light source: a retrospective study. *Arch Dermatol* 1999; **135**: 679–83.

18 Fiskrstrand EJ, Svaasand LO, Kopstad G *et al.* Laser treatment of port wine stains: therapeutic outcome in relation to morphological parameters. *Br J Dermatol* 1996; **134**: 1039–43.

19 Nguyen CM, Yohn JJ, Huff C *et al.* Facial port wine stains in childhood: prediction of the rate of improvement as a function of the age of the patient, size and location of the port wine stain and the number of treatments with the pulsed dye (585 nm) laser. *Br J Dermatol* 1998; **138**: 821–5.

20 van der Horst CM, Koster PH, de Borgie CA *et al.* Effect of the timing of treatment of port wine stains with the flash-pump-pumped pulsed-dye laser. *N Engl J Med* 1998; **338**: 1028–33.

21 Lanigan SW, Cotterill JA. Psychological disabilities amongst patients with port-wine stains. *Br J Dermatol* 1989; **121**: 209–15.

22 Laube S, Taibjee SM, Lanigan SW. Treatment of resistant port wine stains with the V beam® pulsed dye laser. *Lasers Surg Med* 2003; **33**: 282–7.

Naevus anaemicus (NA)

Naevus anaemicus is an uncommon, localized, congenital vascular malformation consisting of a macule/patch with an irregular margin most commonly found on the upper trunk [1]. This was first described by Vörner in 1906 to differentiate this from partial albinism [2]. It is a clinical diagnosis and if the lesion is examined by diascopy the skin appears indistinguishable from the surrounding normal skin. Rubbing the skin causes reactive hyperaemia in the adjacent skin, but no change within the lesion itself. It may present at birth or early childhood, and is more common in males than females [3]. Histological and ultrastructural examination shows no abnormalities [4]. The lesion is a physiological anomaly as various agents such as bradykinin, acetylcholine, and histamine fail to induce vasodilatation, but erythema is produced after an axillary sympathetic block. It is believed that naevus anaemicus is primarily an oversensitivity to vasoconstrictor stimuli [5].

Naevus anaemicus is more commonly found in association with port-wine stains [1] and neurofibromatosis [3]. Treatment is not necessary.

References

1 Katugampola GA, Lanigan GA. The clinical spectrum of naevus anaemicus and its association with port wine stains: report of 15 cases and review of the literature. *Br J Dermatol* 1996; **134**: 292–5.

2 Vörner H. Weber naevus anaemicus. *Arch Dermatol Syphilol* 1906; **82**: 391.

3 Fleisher TL, Zeligman I. Nevus anemicus. *Arch Dermatol* 1959; **100**: 750–5.

4 Greaves MW, Birkett D, Johnson C. Nevus anemicus: a unique catecholamine-dependent nevus. *Arch Dermatol* 1970; **102**: 172–6.

5 Daniel RH, Hubler WR, Wolf JE, Holder WR. Nevus anemicus: donor dominant defect. *Arch Dermatol* 1977; **113**: 53–6.

Sturge–Weber syndrome (OMIM 185300)

The syndrome is classically defined as a facial port-wine stain (PWS) in association with an ipsilateral vascular malformation of the leptomeninges and eye. Even though the original description of the syndrome had eye involvement [1], some authors do not consider eye involvement as mandatory for the diagnosis [2]. There is no evidence to suggest a genetic basis [3], although facial PWSs have been reported in first-degree relatives [4].

The pathology of the PWS is identical to those of other CMs. The brain abnormalities include increased leptomeningeal vascularity, especially affecting the occipital lobe, and on occasion, the whole hemisphere. The changes are usually unilateral, but may be bilateral in 15% of cases [5]. The long-term pathological changes include calcification, atrophy and demyelination [6].



Fig. 18.26 Port-wine stains on the face and trunk in a 3-year-old with Sturge–Weber syndrome.

The commonest cutaneous feature is a CM in the V1 and V2 distribution of the trigeminal nerve and it is believed that the ophthalmic branch must be involved in part or its entirety for the true syndrome [7] (Fig. 18.26). In clinical terms, at least part of the PWS extends to the forehead and upper eyelid [7] and it should be remembered that there is overlap in V1 and V2 over the bridge of the nose. Ocular and central nervous system problems were found to occur in PWSs affecting the upper and lower lids in 90% but only in 9% in PWSs affecting the lower lid alone [8]. The PWS can cross over the midline and is bilateral in around 50% [3,9]. There may be additional CMs on the trunk and limbs in up to 40% of cases [10]. The oral and nasal mucosae may be affected, leading to gingival hypertrophy and accelerated dentition [11].

Epileptic seizures are the most common neurological complication and occur in 55–90% of cases [3,4,9,12]. The seizures occur within the first 7 months of life in the majority, but may start later in adulthood. An early onset is associated with a poorer prognosis and higher incidence of mental retardation [13]. The seizures usually begin as focal seizures but may progress to generalized or even start as generalized seizures. The incidence of mental retardation is as high as 60% [3,12,14] and is more likely in those patients with bilateral brain involvement. Developmental delay is not universal and is present in around 50% [3,15]. Initially, seizures are followed by transient hemiplegia, and homonymous hemianopia, but later this may become permanent [2].

There are many different ocular complications of SWS (as with any facial CM). The most significant of these is glaucoma which can be present in up to 60% of cases [7]. The aetiology of glaucoma is not fully clear, but it is postulated that choroidal angiomas lead to an overproduction of aqueous fluid. Furthermore, anatomical abnormalities of the anterior chamber angle impair drainage, and raised episcleral pressure due to anomalous arteriovenous communications adds to this poor drainage [16,17]. Glaucoma is nearly always unilateral and is present at birth in over 60% [14,16]. Glaucoma is unlikely unless the PWS affects the upper eyelid, but more often than not, both upper and lower eyelids are affected [3,10]. When it presents at birth, the eye is enlarged (buphthalmos) and the cornea appears cloudy. Patients at later ages present with increasing myopia. The importance of treatment cannot be overemphasized, as failure to treat will eventually lead to optic nerve damage, field defects and ultimately blindness. It is therefore imperative that any at-risk patient is seen by a paediatric ophthalmologist as soon as possible.

The investigation of SWS is both radiological and neurological. Plain X-rays show sinuous tramline opacification typical of intracranial cortical calcification although CT scanning with contrast is more commonly used. Both MRI and CT scanning highlight the extent of both eye and leptomeningeal involvement. Even though CT scanning is superior to MRI in highlighting calcification [6], gadolinium-enhanced MRI is considered to be superior to CT scanning for earlier detection, delineating the extent, showing any associated vascular abnormalities and for assessing parenchymal atrophy, ischaemic damage and choroids plexus enlargement [15,18,19]. More specialized investigation with photon emission tomography (PET) can be used to show areas of ischaemia [20]. Electroencephalography is not used as frequently as it was in the past, but shows suppression of cortical activity over the affected area, with or without focal epileptiform spike discharges [21].

The management of patients with SWS is directed at control of seizures (when present) with anticonvulsants, regular follow up by an ophthalmologist for detection of glaucoma, and treatment of the PWS by laser as for any CM.

References

1 Sturge WA. A case of partial epilepsy apparently due to a lesion of one of the vasomotor centres of the brain. *Clin Soc Trans* 1879; **12**: 162–7.

2 Atherton DJ, Moss C. Naevi and other developmental defects. In: Burns T, Breathnach SM, Cox NH, Griffiths C, eds. *Rook's Textbook of Dermatology*, 7th ed. Oxford: Blackwell Science, 2004: 15.1–15.144.

3 Sujansky E, Conradi S. Outcome of Sturge–Weber syndrome in 52 adults. *Am J Med Genet* 1995; **57**: 35–45.

4 Pascual-Castroviejo I, Diaz-Gonzalez C, Garcia-Melian R *et al.* Sturge–Weber syndrome: study of 40 patients. *Pediatr Neurol* 1993; **76**: 48–51.

5 Boltshauser E, Wilson J, Hoare RD. Sturge–Weber syndrome with bilateral intracranial calcification. *J Neurol Neurosurg Psychiatry* 1976; **39**: 429–35.

6 Marti-Bonmati L, Menor F, Mulas F. The Sturge–Weber syndrome: correlation between the clinical status and radiological CT and MRI findings. *Childs Nerv Syst* 1993; **9**: 107–9.

7 Enjolras O, Riche MC, Merland JJ. Facial port wine stains and the Sturge–Weber syndrome. *Pediatrics* 1985; **76**: 48–51.

8 Tallman B, Tan OT, Morelli JG *et al.* Location of port wine stains and the likelihood of ophthalmic and/or central nervous system complications. *Pediatrics* 1991; **87**: 323–7.

9 Uram M, Zubillaga C. The cutaneous manifestations of Sturge–Weber syndrome. *J Clin Neuroophthalmol* 1982; **2**: 145–8.

10 Yingkun F, Yinchang Y. Sturge–Weber syndrome: a report of 22 cases. *Chin Med J* 1980; **93**: 697–708.

11 Wilson S, Venzel JM, Miller R. Angiography gingival hyperplasia and Sturge–Weber syndrome: report of case. *ASDC J Dent Child* 1986; **53**: 283–6.

12 Paller AS. The Sturge–Weber syndrome. *Pediatr Dermatol* 1987; **4**: 300–4.

13 Bebin EM, Gomez MR. Prognosis in Sturge–Weber disease: comparison of unihemispheric and bihemispheric involvement. *J Child Neurol* 1988; **3**: 181–5.

14 Sujansky E, Conradi M. Sturge–Weber syndrome: age of onset of seizures and glaucoma and prognosis for affected children. *J Child Neurol* 1995; **10**: 49–58.
15 Thomas-Sohl KA, Vaslow DF, Maria BL. Sturge–Weber syndrome: a review. *Pediatr Neurol* 2004; **30**: 303–10.
16 Greenwald MJ, Weiss A. Ocular manifestations of neurocutaneous syndromes. *Pediatr Dermatol* 1984; **2**: 98–117.
17 Cibis GW, Tripathi R, Tripathi BJ. Glaucoma in Sturge–Weber syndrome. *Ophthalmology* 1984; **91**: 1061–71.
18 Marti-Bonmati L, Menor F, Poyatos C *et al.* Diagnosis of Sturge–Weber syndrome: comparison of the efficacy of CT and MR imaging in 14 cases. *Am J Roentgenol* 1992; **158**: 867–71.
19 Elster AD, Chen MY. MR imaging of Sturge–Weber syndrome: role of gadopentetate dimeglumine and gradient-echo techniques. *Am J Neuroradiol* 1990; **11**: 685–9.
20 Griffiths PD. Sturge–Weber syndrome revisited: the role of neuroradiology. *Neuropediatrics* 1996; **27**: 284–94.
21 Brenner RP, Sharborough FW. Electroencephalographic evaluation in Sturge–Weber syndrome. *Neurology* 1976; **26**: 629–32.

Cutis marmorata telangiectatica congenita (OMIM 219250)

Synonyms
- Reticulate vascular naevus
- van Lohuizen's syndrome

Definition. Cutis marmorata telangiectatica congenita (CMTC) is an uncommon, congenital, vascular malformation, first described by Van Lohuizen [1], comprising a fixed reticulate erythema which may resemble physiological cutis marmorata.

Aetiology. The aetiology of CMTC is unknown. It is a sporadic disorder but familial cases have been reported [2,3]. Different groups have suggested an autosomal dominant inheritance with variable penetrance [2] or paradominant inheritance in which homozygous post-zygotic mutations in a mosaic population of cells accounts for the syndrome [4]. There is close overlap with Adams–Oliver syndrome (see below).

Pathology [1,2,5,6]. Histopathology of the vascular abnormality reveals dilated capillaries, venous and capillary lakes, and dilated veins in the dermis and subcutis. There is also evidence of endothelial swelling and a sparse perivascular lymphocytic infiltrate.

Clinical features. The vascular abnormality is a reticulate erythema producing the marbling that is akin to the physiological marbling seen in neonates (Fig. 18.27a). However, this is fixed and does not disappear after warming (unlike physiological cutis marmorata). The erythema is variable and can be a livid purple. The skin may be atrophic or even ulcerated in the vascular areas [6] (Fig. 18.27b).

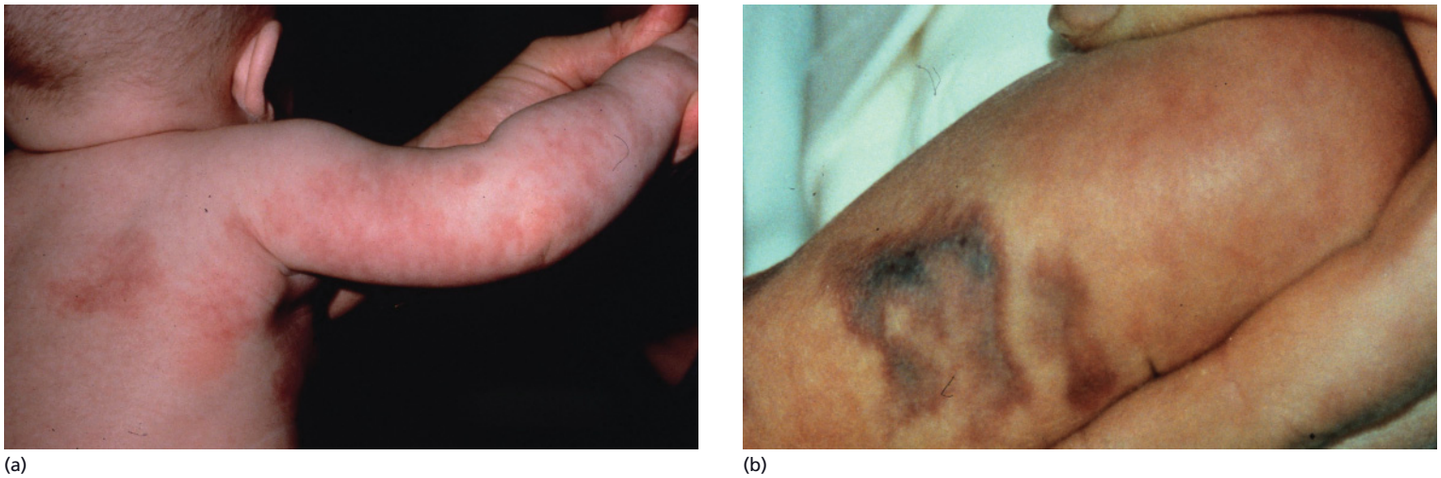
The affected areas may range from a few centimetres to a whole limb or hemitruncal involvement. The limbs are more commonly affected than other sites, and a sharp demarcation line is common. When the face is involved the lesions may be indistinguishable from PWS [6].

There may be associated atrophy (more common) or hypertrophy of the underlying subcutaneous tissue. This may manifest as reduced girth of the affected limb [5,7,8] and rarely bony hypoplasia [9].

There are numerous other congenital anomalies which have been reported in association with CMTC with a prevalence of 20–70% [6,10–12]. There is debate about the true prevalence of these abnormalities, as there is a tendency to reporting bias, such that it is probably at the lower end of this range. The most common defects are aplasia cutis, developmental delay and cleft palate [6,11,12]. Less common associations include macrocephaly [13], glaucoma [6,14], hypothyroidism [1], scoliosis and anogenital abnormalities [11,12]. The macrocephaly–CMTC and Adams–Oliver syndromes are discussed separately (see below).

The natural history of CMTC is lightening of the vascular markings and long-term, spontaneous resolution in the majority of cases [11,15,16], although residual reticulate erythema has also been reported [6,10,12]. Ulceration tends to heal without specialized treatment and limb length abnormalities become less apparent with time [7].

Diagnosis. CMTC should be easy to differentiate from physiological cutis marmorata, but is not as pronounced as the more



(a) (b)

Fig. 18.27 Cutis marmorata telangiectatica congenita; (a) back and arm, (b) leg. Note necrotic areas within lesion on leg.

persistent congenital livedo seen in Cornelia de Lange syndrome, trisomy 21 and homocystinuria. Neonatal lupus erythematosus and other vasculitides may also enter the differential diagnosis because of the reticulate telangiectatic atrophy, but congenital lupus is bilateral and symmetrical with a greater frequency of facial lesions. Some uncommon forms of patchy port-wine stains may cause confusion, but these lesions would not be associated with limb hypoplasia (or hypertrophy).

Treatment. The patients rarely require treatment as many children improve in the first 2 years of life [12] and therapy should be deferred to await any spontaneous improvement. It is suggested that limb girth and length measurements should be monitored, and a thorough physical examination for any associated abnormalities undertaken, including an eye examination if the abnormality extends to the eyelids, to exclude glaucoma. For those with persistent reticulate erythema, pulsed dye laser may be used to further lighten the affected patches.

References

1 Van Lohuizen CHJ. Uber eine seltene angeborene Hautanomalie (Cutis marmorata telangiectatica congenita). *Acta Dermatol Venereol (Stockh)* 1922; **3**: 202–11.
2 Andreev VC, Pramatarov K. Cutis marmorata telangiectatica congenita in two sisters. *Br J Dermatol* 1979; **101**: 345–50.
3 Kurczinski TW. Hereditary cutis marmorata telangiectatica congenita. *Pediatrics* 1982; **70**: 52–3.
4 Danarti R, Happle R, Konig A. Paradominant inheritance may explain familial occurrence of cutis marmorata telangiectatica congenita. *Dermatology* 2001; **203**: 208–11.
5 Way BH, Herrmann J, Gilbert EF *et al.* Cutis marmorata telangiectatica congenita. *J Cutan Pathol* 1974; **1**: 10–25.
6 Picascia DD, Esterly NB. Cutis marmorata telangiectatica congenita: report of 22 cases. *J Am Acad Dermatol* 1989; **20**: 1098–104.
7 Rogers M, Poyzer KG. Cutis marmorata telangiectatica congenita. *Arch Dermatol* 1982; **118**: 895–9.
8 Spraker MK, Stack C, Esterly NB. Congenital generalized fibromatosis: a review of the literature and report of a case associated with porencephaly, hemiatrophy and cutis marmorata telangiectatica congenita. *J Am Acad Dermatol* 1984; **10**: 365–71.
9 Farrell SA, Warda LJ, Laflair P *et al.* Adams–Oliver syndrome: a case with juvenile chronic myelogenous leukemia and chylothorax. *Am J Med Genet* 1993; **47**: 1175–9.
10 South DA, Jacobs AH. Cutis marmorata telangiectatica congenita (congenital generalised phlebectasia). *Pediatrics* 1978; **93**: 944–9.
11 Pehr K, Moroz B. Cutis marmorata telangiectatica congenita: long-term follow-up, review of the literature and report of a case in conjunction with congenital hypothyroidism. *Pediatr Dermatol* 1993; **10**: 6–11.
12 Devillers ACA, de Waard-van der Spek FB, Oranje AP. Cutis marmorata telangiectatica congenita: clinical features in 35 cases. *Arch Dermatol* 1999; **135**: 34–8.
13 Stephan MJ, Hall BD, Smith DW *et al.* Macrocephaly in association with unusual cutaneous angiomatosis. *J Pediatr* 1975; **87**: 353–9.
14 Weilepp AE, Eichenfeld LF. Association of glaucoma with cutis marmorata telangiectatica congenita: a localized anatomic malformation. *J Am Acad Dermatol* 1996; **35**: 276–8.
15 Powell ST, Su WPD. Cutis marmorata telangiectatica congenita: a report of nine cases and review of the literature. *Cutis* 1984; **34**: 305–12.
16 Amitai DB, Fichman S, Merlob P *et al.* Cutis marmorata telangiectatica congenita: clinical findings in 85 patients. *Pediatr Dermatol* 2000; **17**: 100–4.

Macrocephaly–cutis marmorata telangiectatica congenita (M-CMTC) (OMIM 602501)

This has been recognized as a separate entity from CMTC since 1996 [1,2]. It is defined as a CMTC-like vascular malformation with macrocephaly, neonatal hypotonia and developmental delay. The vascular malformation does not have any areas of atrophy seen in CMTC alone. There are numerous other associations including syndactyly, hemihypertrophy, hyperelastic skin and joint laxity, short stature, hydrocephalus and post-axial polydactyly [2–9].

References

1 Toriello H, Moore C, Dobyns W. Macrocephaly-cutis marmorata telangiectatica congenita: description of twelve patients with this previously undescribed common multiple congenital anomaly syndrome. *Eur J Hum Genet* 1996; **4**: 2.
2 Moore CA, Toriello HV, Abuelo DN *et al.* Macrocephaly-cutis marmorata telangiectatica congenita: a distinct disorder with developmental delay and connective tissue abnormalities. *Am J Med Genet* 1997; **70**: 67–73.
3 Reardon W, Harding B, Winter R *et al.* Hemihypertrophy, hemimegalencephaly and polydactyly. *Am J Med Genet* 1996; **66**: 144–9.
4 Clayton-Smith J, Kerr B, Brunner H *et al.* Macrocephaly with cutis marmorata, hemangioma and syndactyly—a distinctive overgrowth syndrome. *Clin Dysmorphol* 1997; **6**: 291–302.
5 Roberton SP, Gattas M, Rogers M *et al.* Macrocephaly-cutis marmorata congenita: report of five patients and a review of the literature. *Clin Dysmorphol* 2000; **9**: 1–9.
6 Barnicoat A, Salman M, Chitty L *et al.* A distinctive overgrowth syndrome with polysyndactyly. *Clin Dysmorphol* 1996; **5**: 339–46.
7 Baralle D, Firth H. A case of the new overgrowth syndrome—macrocephaly with cutis marmorata, haemangioma and syndactyly. *Clin Dysmorphol* 2000; **9**: 209–11.
8 Carcao M, Blaser SI, Grant RM *et al.* MRI findings in macrocephaly-cutis marmorata telangiectatica congenita. *Am J Med Genet* 1998; **76**: 165–7.
9 Moffitt DL, Kennedy CTC, Newbury-Ecob R. Macrocephaly with cutis marmorata, hemangioma and syndactyly syndrome. *Pediatr Dermatol* 1999; **16**: 235–77.

Adams–Oliver syndrome [1,2]

This is a rare syndrome characterized by a combination of aplasia cutis congenita, transverse limb abnormalities, skull defects and cutis marmorata telangiectatica congenita. The commonest limb malformations include syndactyly, polydactyly and brachydactyly. The aplasia cutis occurs most frequently on the vertex of the scalp and may have underlying bony skull defects. The presence of CMTC in Adams–Oliver syndrome may imply a disruption of embryonic vascular development as one of the potential underlying causes [3]. There have been reports of both autosomal dominant and recessive inheritance, but no specific gene mutations have been identified to date.

References

1 Adams FH, Oliver CP. Hereditary deformities in man due to arrested development. *J Hered* 1945; **36**: 3–7.
2 Verdyck P, Holder-Espinasse M, Van Hul W *et al.* Clinical and molecular analysis of nine families with Adams–Oliver syndrome. *Eur J Hum Genet* 2003; **11**: 457–63.
3 Swartz EN, Sanatani S, Sandor GG *et al.* Vascular abnormalities in Adams–Oliver syndrome: cause or effect? *Am J Med Genet* 1999; **82**: 49–52.

Phakomatosis pigmentovascularis [1–4]

This is a syndrome characterized by the combination of a capillary malformation with pigmented naevi of various types, as shown in Table 18.12. The term phakomatosis refers to a developmental malformation simultaneously affecting the eye, skin and central nervous system.

The classification of this disorder has been simplified [4]; it has been reported that a fifth type is defined by cutis marmorata and

Table 18.12 Classification of phakomatosis pigmentovascularis [2].

Subtype A: Cutaneous forms
Type 1A: port-wine stain/capillary malformation (CM) + epidermal naevus
Type 2A: CM + Mongolian blue spots + naevus anaemicus
Type 3A: CM + naevus spilus + naevus anemicus
Type 4A: CM + naevus spilus + naevus anaemicus + aberrant Mongolian blue spots
Subtype B: Systemic/syndromic form
Types 1–4 B as above plus Sturge–Weber syndrome or naevus of Ota or Klippel–Trenaunay syndrome



(a)



(b)

Fig. 18.28 Type 2 phakomatosis pigmentovascularis showing (a) extensive capillary malformation and (b) extensive Mongolian blue spots.

aberrant Mongolian blue spots [5]. The condition is uncommon and arises sporadically. It has been hypothesized that twin spots account for this phenotype [6]. In this hypothesis, somatic mutations on nearby genes lead to mosaic spots in close proximity to one another. Type 2 is reported to account for 80% of all cases [7] (Fig. 18.28). The capillary malformation may occur anywhere on the body, and can be segmental. The aberrant Mongolian blue spots occur on atypical sites and tend to persist, unlike conventional Mongolian blue spots. Affected cases should be investigated depending upon the sites involved, for example, for glaucoma if the CM affects the eyelids or for KTS if there is limb involvement.

References

1 Ota M, Kawamura T, Ito N. Phacomatosis pigmentovascularis (Ota). *Jpn J Dermatol B* 1947; **52**: 1–3.
2 Ruiz-Maldonado R, Tamayo L, Laterza AM *et al.* Phacomatosis pigmentovascularis: a new syndrome? *Pediatr Dermatol* 1987; **4**: 189–96.
3 Hasegawa Y, Yasuhara M. Phakomatosis pigmentovascularis type IVa. *Arch Dermatol* 1985; **121**: 651–3.
4 Happle R. Phacomatosis pigmentovascularis revisited and reclassified. *Arch Dermatol* 2005; **141**: 385–8.
5 Torrelo A, Zambrano A, Happle R. Cutis marmorata telangiectatica congenita and extensive mongolian spots: type 5 phacomatosis pigmentovascularis. *Br J Dermatol* 2003; **148**: 342–5.
6 Danarti R, Happle R. Paradominant inheritance of twin spotting: phacomatosis pigmentovascularis as a further possible example. *Eur J Dermatol* 2003; **13**: 612.
7 Sawada Y, Iwata M, Mitsuhashi Y. Nevus pigmentovascularis. *Ann Plast Surg* 1990; **25**: 142–5.

Beckwith–Wiedemann syndrome (BWS) (OMIM #130650) [1–3]

Synonym

- Exomphalos–macroglossia–gigantism syndrome

The main features of this overgrowth syndrome include exomphalos, macroglossia and gigantism in the neonate. The affected individuals have a propensity to develop specific tumours, including hepatoblastoma, Wilms tumour, neuroblastoma and rhabdomyosarcoma [4]. They also have a greater incidence of non-malignant renal abnormalities such as medullary cysts and hydronephrosis [5]. Infants have centrofacial capillary malformations in the majority of cases, which may extend to the upper eyelids, upper lip and nose. One of the characteristic findings is posterior helical ear pits. Neonatal hypoglycaemia is common and should be anticipated to prevent neurological sequelae.

The syndrome is caused by mutations in the *p57(KIP2)* gene or in the *NSD1* gene on chromosome 11p15.5 or 5q35 [6]. The syndrome is sporadic and the mode of inheritance is complex, with autosomal dominant inheritance with variable expressivity, or contiguous gene duplication being possible modes of transmission. It is believed that insulin growth factor 2 (*IGF2*) overexpression is central to the role of somatic overgrowth and the development of embryonal tumours. The importance of *IGF2* in the pathogenesis of BWS has been highlighted in mouse models where overexpression of *IGF2* and underexpression of *p57(KIP2)* resulted in macroglossia, gigantism and exomphalos but not in tumours or hypoglycaemia [7]. Prenatal diagnosis is possible by ultrasound [8]. Management is directed towards treatment of neonatal hypoglycaemia and long-term follow up of patients for tumour development. The capillary malformation may fade with age.

References

1 Irving JM. Exomphalos with macroglossia: a study of eleven cases. *J Pediatr Surg* 1967; **2**: 499–507.
2 Best LG, Hoekstra RE. Wiedemann–Beckwith syndrome: autosomal dominant inheritance in a family. *Am J Med Genet* 1981; **9**: 291–9.
3 Filippi G, McKusick VA. The Beckwith–Wiedemann syndrome (the exomphalos–macroglossia–gigantism syndrome): report of two cases and review of the literature. *Medicine* 1970; **49**: 279–98.

4 DeBaun MR, Tucker MA. Risk of cancer during first four years of life in children with Beckwith–Wiedemann syndrome. *J Pediatr* 1998; **132**: 398–400.
5 Choyke PL, Siegel MJ, Oz O *et al.* Non-malignant renal disease in pediatric patients with Beckwith–Wiedemann syndrome. *Am J Roentgen* 1998; **171**: 733–7.
6 Ping AJ, Reeve AE, Law DJ *et al.* Genetic linkage of Beckwith–Wiedemann syndrome to 11pl5. *Am J Hum Genet* 1989; **44**: 720–3.
7 Sun FL, Dean WL, Kelsey G *et al.* Transactivation of IGF2 in a mouse model of Beckwith-Wiedemann syndrome. *Nature* 1997; **389**: 809–15.
8 Nivelon-Chevalier A, Mavel A, Michiels R *et al.* Syndrome de Wiedemann–Beckwith familial: diagnostic antenatal echographique et confirmation histologique. *J Genet Hum* 1983; **31**: 397–402.

Thrombocytopenia–absent radii syndrome [1–4]

Synonyms
- TAR syndrome
- Tetraphocomelia–thrombocytopenia syndrome

This syndrome is a combination of congenital thrombocytopenia and absent radii (usually bilateral). Affected individuals may have capillary malformations on the head and neck. Other associated abnormalities include food intolerance, renal abnormalities (axial malrotation of the kidney, horseshoe kidney) and cardiac anomalies (coarctation of the aorta). The thrombocytopenia may be severe in infancy with a high mortality of 40% from haemorrhage. It has been shown that megakaryocyte colony growth *in vitro* was virtually absent in optimally stimulated cultures of a patient's bone marrow progenitors [5]. The inheritance of TAR syndrome is unclear and frequently sporadic. Pulsed dye laser treatment of the vascular stain proved disappointing; the lack of efficacy was attributed to thrombocytopenia with impaired production of platelet thrombi, and resultant inhibition of the effects of laser therapy [6].

References

1 Hall JG, Levin J, Kuhn JP *et al.* Thrombocytopenia with absent radius (TAR). *Medicine* 1969; **48**: 411–39.
2 Gounder DS, Pullon HW, Ockelford PA *et al.* Clinical manifestations of the thrombocytopenia and absent radii (TAR) syndrome. *Aust NZ J Med* 1989; **19**: 479–82.
3 Hedberg VA, Lipton JM. Thrombocytopenia and absent radii: a review of 100 cases. *Am J Pediatr Hematol Oncol* 1988; **10**: 51–64.
4 Greenhalgh KL, Howell RT, Bottani A *et al.* Thrombocytopenia–absent radius syndrome: a clinical genetic study. *J Med Genet* 2002; **39**: 876–81.
5 Homans AC, Cohen JL, Mazur EM. Defective megakaryocytopoiesis in the syndrome of thrombocytopenia with absent radii. *Brit J Haemat* 1988; **70**: 205–10.
6 Ashinoff R, Geronemus RG. Thrombocytopenia—absent radii syndrome and lack of response to the pulsed dye laser. *Arch Dermatol* 1990; **126**: 1520–1.

Roberts syndrome (OMIM #268300) [1–3]

Synonyms
- SC phocomelia
- Pseudothalidomide syndrome

This rare disorder was described in 1919 [1] and is characterized by craniofacial abnormalities, tetraphocomelia, growth retardation, sparse, silvery blond hair and a mid-facial capillary vascular malformation. The latter extends from the forehead to the philtrum. The craniofacial abnormalities include cleft lip and/or palate, micrognathia, hypoplastic ear lobes, hypertelorism and shallow orbits. The eyes are prominent with blue-tinged sclerae.

The genetic abnormality is characteristically a loss of cohesion of heterochromatic regions of centromeres and the Y chromosome. The genetic defect has recently been identified as mutations in the *ESCO2* gene (*RBS1* gene located on chromosome 8p21). The gene product is a member of a conserved protein family that is necessary for sister chromatid cohesion during S phase [4].

References

1 Roberts JB. A child with double cleft lip and palate, protrusion of the intermaxillary portion of the upper jaw, and imperfect development of the bones of the four extremities. *Ann Surg* 1919; **70**: 252–4.
2 Romke C, Froster-Iskenius U, Heyne K *et al.* Roberts syndrome and SC phocomelia: a single genetic entity. *Clin Genet* 1987; **31**: 170–7.
3 Van Den Berg DJ, Francke U. Roberts syndrome: a review of 100 cases and a new rating system for severity. *Am J Med Genet* 1993; **47**: 1104–23.
4 Vega H, Waisfisz Q, Gordillo M *et al.* Roberts syndrome is caused by mutations in ESCO2, a human homolog of yeast ECO1 that is essential for the establishment of sister chromatid cohesion. *Nat Genet* 2005; **37**: 468–70.

Rubinstein–Taybi syndrome (OMIM #180849) [1]

Rubinstein–Taybi syndrome is a rare sporadic condition first described in 1963 [2] characterized by mental retardation, broad thumbs and toes, and facial abnormalities. The cutaneous features include capillary malformations, scar formation and café-au-lait macules [3]. The gene abnormality has been found to be located on chromosome 16p13.3 and is caused by mutations in the gene encoding the transcriptional coactivator CREB-binding protein (CREBBP).

It has been suggested that about 5% of RTS patients develop neoplasms, including central nervous system tumours, leukaemias and rhabdomyosarcomas [4].

References

1 Hennekam RCM. Rubinstein–Taybi syndrome. *Europ J Hum Genet* 2006; **14**: 981–5.
2 Rubinstein JH, Taybi H. Broad thumbs and toes and facial abnormalities. *Am J Dis Child* 1963; **105**: 588–608.
3 Hennekam RCM, Stevens CA, Van de Kamp JJP. Etiology and recurrence risk in Rubinstein-Taybi syndrome. *Am J Med Genet* 1990; **6**: 56–64.
4 Miller RW, Rubinstein JH. Tumors in Rubinstein–Taybi syndrome. *Am J Med Genet* 1995; **56**: 112–5.

Cardiofaciocutaneous syndrome (OMIM #115150) [1]

This syndrome is characterized by a distinctive facies, heart defects (including pulmonary stenosis, atrial septal defect and hypertrophic cardiomyopathy) and mental retardation. The cutaneous features include capillary malformations, patchy hyperkeratosis or even ichthyosis, sparse hair and keratosis pilaris. The syndrome may be caused by mutations in one of the following genes: *KRAS, BRAF, MEK1* or *MEK2.* There is both genotypic and phenotypic overlap with Noonan's syndrome.

Reference

1 Roberts A, Allanson J, Jadico SK *et al.* The cardiofaciocutaneous syndrome. *J Med Genet* 2006; **43**: 833–42.

Venous malformations

Venous malformations (VM) are slow-flow anomalies defined as abnormal venous networks present at birth. The majority of cases are sporadic although familial cases have been reported [1].

Histologically, they are composed of ectatic channels which connect to form a vascular network with mitotically inactive, flat lining endothelium and scant mural smooth muscle [2]. It is very common to find evidence of thrombosis and calcification (phleboliths).

Clinical features. Venous malformations are easily identified by their blue discoloration, show evidence of swelling when dependent or during exercise and are soft and compressible (Fig. 18.29). They can affect any point between the skin surface and bone and usually are segmental in their distribution, although they can occur in multiple sites. They are often confused with infantile haemangiomas and, unlike AVMs, do not have a thrill/bruit or feel warm to the touch. The most common symptoms are pain, swelling or burning. VM of the limbs and trunk may cause functional problems if they extend deep into muscles and joints [3], and are often a cause of cosmetic disfigurement. Distal involvement of the limbs may lead to excess saggy skin and an engorged blue appearance of the digits. Larger malformations are more likely to result in differences in limb girth compared with the contralateral limb. Muscle involvement may lead to pain, especially in the morning and after exercise. It is believed that pain is caused by thromboses which eventually lead to phlebolith formation. Venous malformations tend to worsen in later childhood and adolescence. Those VM which involve joints may cause sudden onset of pain and swelling due to effusion and haemarthrosis. Stiffness and difficulty with mobility are other important sequelae [3], and a serious complication is pathological fracture due to weakening of the adjacent bone [3]. It is important to be aware of the increase in haemarthrosis secondary to the associated chronic disseminated intravascular coagulation found in VM (see below).

Head and neck VM are relatively common and may not only be cutaneous, but also affect the mucosal surfaces of the lips, cheeks, tongue and floor of mouth. They may lead to facial asymmetry and dental malalignment, dysphagia, and obstructive sleep apnoea. Intraorbital VM may cause enophthalmos when standing, or exophthalmos when lying down [4], but rarely lead to optic nerve compression.

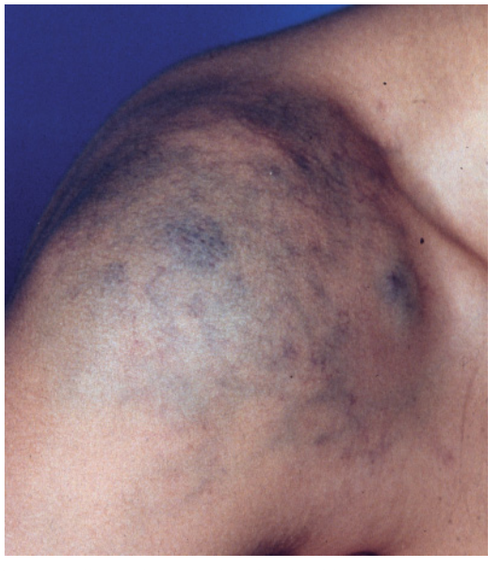


Fig. 18.29 Venous malformation affecting the shoulder.

Investigation. Radiological investigation of VM with a plain X-ray (rarely performed) often shows calcified opacities (phleboliths) whereas CT scanning with contrast highlights soft tissue and/or bony involvement. However, the investigation of choice is T2 weighted MRI: VM show up as high signal, well-defined or lobulated sacs and MRI will also show the extent of any bony involvement.

Patients with large head and neck VM may have a developmental venous anomaly in 20% of cases. This is an ectatic collection of dilated veins which drain into the deep brain, which is only found in less than 1% of the population [5]. These anomalies are easily identified with MR angiography. Fortunately, they do not confer an increased risk of cerebral haemorrhage, seizures or important neurological deficit.

A very important association of VM is an intravascular coagulopathy that is manifested by a low fibrinogen level, elevated D-dimers, increased fibrinogen degradation products and thrombocytopenia. Coagulation studies are recommended in all children with extensive VM and those VM involving muscle [6]. The intravascular coagulation may be chronic and localized but may switch to disseminated intravascular coagulation (DIC) during pregnancy, surgery, immobilization or at the onset of menses. This is a potentially serious problem, as life-threatening internal bleeding may occur [7]. It should be prophylactically managed with low molecular weight heparin prior to surgery as this may reduce the risk of intraoperative and post-operative bleeding [6] and in some instances, with long-term warfarin [7]. Furthermore, life-threatening complications of deep venous thrombosis and pulmonary embolus have been reported with fatal outcomes [8].

Treatment. The treatment of choice for those symptomatic lesions requiring intervention is sclerotherapy [9–12]. There are many types of sclerosant: ethanol, sodium tetradecylsulphate, Ethibloc®, Lauromacrogol® 400 and Bleomycin. This may or may not be combined with intralesional coil insertion to prevent outflow into the systemic circulation. The side effects of all forms of sclerotherapy include local tissue necrosis, ulceration, oedema, blistering, nerve damage and scarring. More serious side effects include renal damage and cardiac failure. Most intervention is undertaken with fluoroscopic control under general anaesthesia. In some instances, for example large limb VM, surgical excision is used in combination with sclerotherapy. Compression garments also offer symptomatic benefit.

References

1 Vikkula M, Boon LM, Carraway KL *et al.* Vascular dysmorphogenesis caused by an activating mutation in the receptor tyrosine kinase TIE2. *Cell* 1996; **87**: 1181–90.

2 Elluru RG, Azizkhan RG. Cervicofacial abnormalities. II. Vascular malformations. *Sem Pediatr Surg* 2006; **15**: 133–9.

3 Enjolras O, Ciabrini D, Mazoyer E *et al.* Extensive pure venous malformations in the upper or lower limb: a review of 27 cases. *J Am Acad Dermatol* 1997; **36**: 219–25.

4 Enjolras O, Boon LM, Mulliken JB. Vascular malformations. In: Harper J, Oranje A, Prose N, eds. *Textbook of Pediatric Dermatology*, 2nd edn. Oxford: Blackwell, 2006: 1153–74.
5 Boukobza M, Enjolras O, Guichard JP *et al.* Cerebral developmental venous anomalies associated with head-and-neck venous malformations. *Am J Neuroradiol* 1996; **17**: 987–94.
6 Mazoyer E, Enjolras O, Laurian C *et al.* Coagulation abnormalities associated with extensive venous malformations of the limbs: differentiation from Kasabach–Merritt syndrome. *Clin Lab Haematol* 2002; **24**: 243–51.
7 Mazereeuuw-Hautier J, Syed S, Leisner RI *et al.* Extensive venous/lymphatic malformations causing life-threatening haematological complications. *Br J Dermatol* 2007; **157**: 558–62.
8 Feighery C, Hoey SHE, Corbett JR *et al.* Potential life threatening complications of venous malformations. *Br J Dermatol* 2007; **156**: 1406–7.
9 Dubois J, Sebag G, De Prosty Y *et al.* Soft tissue venous malformations in children: percutaneous sclerotherapy with Ethibloc. *Radiology* 1991; **180**: 195–8.
10 Burrows PE, Fellows KE. Techniques for management of pediatric vascular anomalies. In: Cope C, ed. *Current Techniques in Interventional Radiology*, Vol 2, 2nd edn. Philadelphia: Current Medicine, 1995: 12–27.
11 Berenguer B, Burrows PE, Zurakowski D *et al.* Sclerotherapy of craniofacial malformations. *Plast Reconstr Surg* 1999; **104**: 1–11.
12 Muir T, Kirsten M, Fourie P *et al.* Intralesional bleomycin injection (IBI) treatment for haemangiomas and congenital vascular malformations. *Pediatr SurgInt* 2004; **19**: 766–73.

Syndromes with venous malformations

Maffucci's syndrome (OMIM# 166000)

Synonym
- Dyschondroplasia with haemangiomas

Maffucci's syndrome comprises the association of cutaneous venous malformations with enchondromas [1–8]. Most cases are sporadic and have no gender bias.

Cutaneous lesions are composed of thick- and thin-walled dermal and subcutaneous vascular spaces, with a single endothelial lining. Previously they have been mislabelled as haemangiomas, but are complex venous malformations.

Lesions are rarely present at birth but present as multiple cutaneous vascular swellings in infancy. These lesions generally take the form of soft, bluish, and sometimes tender exophytic nodules. The skin lesions show no tendency to resolve, and grow proportionately with the child. Grotesque grape-like masses may develop on the hands and feet [6]. Macrocystic lymphatic malformations are also frequently seen [7], and may be the sole cutaneous manifestation [9].

Other cutaneous features reported have included pigmentary changes, particularly café-au-lait macules [5]. At the same time as the development of cutaneous vascular swellings, the patient develops hard nodules—enchondromas—arising from the bones, especially on the fingers and toes, and the metaphyses of the long bones of the arms and legs. These are round or ovoid and are radiolucent. They are caused by abnormal transformation of cartilage into bone and may be unilateral or asymmetrical. The epiphyseal cartilage is affected and may lead to delay in bone growth and pathological fractures. Cutaneous and bone lesions may result in gross deformity of the hands or feet [6].

A variety of other benign and malignant mesodermal tumours have been reported in Maffucci's syndrome, and the disease has a very high malignant potential [4]. The most common malignant tumour is the chondrosarcoma, which arises from malignant transformation in enchondromas, and probably occurs in some 15% of patients [4,10,11]. Other malignant mesodermal tumours have included fibrosarcoma [12], angiosarcoma [10], lymphangiosarcoma [13] and osteosarcoma [2]. Both benign and malignant ovarian tumours have also been reported [4,5]. In addition, several non-mesodermal tumours have been described in these patients, including gliomas [3,4] and adenocarcinoma of the pancreas [12]. Multiple primary malignancies may also occur [2,4,12].

In Ollier's disease similar enchondromas are found, but unlike Maffucci's syndrome, there are no venous malformations. Other features of the two conditions are indistinguishable. A report of malignancy in Ollier's disease [14] adds weight to the belief that these two conditions are different parts of the same spectrum.

Long-term follow up of these patients is recommended because of the malignancy risk. A biopsy or radiological investigation of any lesions that enlarge rapidly or cause symptoms should be performed to exclude sarcomatous change. In some instances, surgical excision of skin lesions may improve the cosmetic appearance, but these lesions are not radiosensitive.

References

1 Bean WB. Dyschondroplasia and hemangiomata (Maffucci's syndrome). *Arch Intern Med* 1955; **95**: 767–78.
2 Bean WB. Dyschondroplasia and hemangiomata (Maffucci's syndrome). II. *Arch Intern Med* 1958; **102**: 544–50.
3 Carleton A, Elkington J, Greenfield JG *et al.* Maffucci's syndrome (dyschondroplasia with haemangiomata). *QJM* 1942; **11**: 203–28.
4 Lewis RJ, Ketcham AS. Maffucci's syndrome: functional and neoplastic significance: case report and review of the literature. *J Bone Joint Surg Am* 1973; **55**: 1465–79.
5 Loewinger RJ, Lichenstein J, Dodson WE *et al.* Maffucci's syndrome: a mesenchymal dysplasia and multiple tumour syndrome. *Br J Dermatol* 1977; **96**: 317–22.
6 Tilsley DA, Burden PW. A case of Maffucci's syndrome. *Br J Dermatol* 1981; **105**: 331–6.
7 Unroe BJ, Kissel CG, Rosenberg JC. Maffucci's syndrome: review of the literature and case report. *J Am Podiatr Med Assoc* 1992; **82**: 532–6.
8 Kuwahara RT, Skinner RB. Maffucci syndrome: a case report. *Cutis* 2002; **69**: 21–2.
9 Auyeung J, Mohanty K, Tayton K. Maffucci lymphangioma syndrome: an unusual variant of Ollier's disease, a case report and a review of the literature. *J Pediatr Orthop* 2003; **12**: 147–50.
10 Strang C, Rannie I. Dyschondroplasia with haemangiomata (Maffucci's syndrome): report of a case complicated by intracranial chondrosarcoma. *J Bone Joint Surg Br* 1950; **32**: 376–83.
11 Sun TC, Swee RG, Shives TC, Unni KK. Chondrosarcoma in Maffucci's syndrome. *J Bone Joint Surg Am* 1985; **67**: 1214–8.
12 Johnson JL, Webster JR, Sippy HI. Maffucci's syndrome (dyschondroplasia with hemangiomas). *Am J Med* 1960; **28**: 864–6.
13 Nardell SG. Ollier's disease: dyschondroplasia. *BMJ* 1950; **2**: 555–7.
14 Braddock GTF, Hadlow VD. Osteosarcoma in enchondromatosis (Ollier's disease): report of a case. *J Bone Joint Surg Br* 1966; **48**: 145–9.

Blue rubber bleb naevus syndrome (Bean's syndrome)

This is an uncommon condition with multiple venous malformations of the skin, gastrointestinal tract and other visceral sites including the liver, spleen, bladder, spinal cord, lungs and bones [1,2]. The majority of cases are sporadic but autosomal dominant families have been reported [3,4], although the latter have similarities to familial cutaneomucosal venous malformation (see below).

Clinically, the lesions are characteristically blue/purple soft compressible nodules with a rubbery feel. They are dome shaped, almost nipple-like 'rubber blebs' which may coalesce to form large

masses. They may be solitary or be present in large numbers throughout the body, especially on the upper limbs and trunk [5,6], and affect the mucosal surfaces of the mouth and genitalia. They may be tender or painful and typically appear during childhood but occasionally are present at birth or form in adulthood [4].

Histologically, the blebs are large, blood-filled vascular lumina in the dermis and subcutis. The superficial lesions have simple endothelial lining whereas the deeper channels have smooth muscle lining [7]. There are no glomus cells present.

The gastrointestinal tract is the most common visceral site affected and lesions share the same pathology as the cutaneous lesions. They are sessile or polypoid and affect all levels of the gastrointestinal tract, in particular the small intestine. They are prone to bleeding and may cause a significant anaemia requiring transfusion and iron replacement therapy [6,8]. Endoscopic investigation of suspected cases is performed for symptoms related to anaemia or bleeding. It is debatable whether other visceral sites should be investigated in the absence of symptoms.

The prognosis of blue rubber bleb syndrome is, like many other VM, persistence throughout life. The differential diagnosis of the syndrome includes multiple haemangiomatosis, glomuvenous malformation (glomangiomas), and angiokeratomas.

The vascular lesions may be treated with Nd:YAG laser, excision or even sclerotherapy [2]. Gastrointestinal bleeding may require endoscopic laser photocoagulation or surgical resection of extensively affected bowel segments. Iron supplements and/or transfusions are often necessary [8]. If a VM-associated coagulopathy is present, this may be treated with low molecular weight heparin.

References

1 Oranje AP. Blue rubber bleb nevus syndrome. *Pediatr Dermatol* 1986; **3**: 304–10.
2 Moodley M, Ramdial P. Blue rubber bleb nevus syndrome: case report and review of the literature. *Pediatrics* 1993; **92**: 160–2.
3 Munkvad M. Blue rubber bleb nevus syndrome. *Dermatologica* 1983; **167**: 307–9.
4 Talbot S, Wyatt EH. Blue rubber bleb naevi: report of a family in which only males were affected. *Br J Dermatol* 1970; **82**: 37–9.
5 Morris SJ, Kaplan SR, Ballan K, Tedesco FJ. Blue rubber bleb nevus syndrome. *JAMA* 1978; **239**: 1887.
6 Ertem D, Acar Y, Kotiloglu E *et al.* Blue rubber bleb nevus syndrome. *Pediatrics* 2001; **107**: 418–21.
7 Fretzin DF, Potter B. Blue rubber bleb nevus. *Arch Intern Med* 1965; **116**: 924–9.
8 Goraya JS, Marwaha KK, Vatve M *et al.* Blue rubber bleb nevus syndrome: a cause for recurrent episodic severe anemia. *Pediatr Hematol Oncol* 1998; **15**: 261–4.

Glomuvenous malformation (OMIM#138000)

Synonyms
- Multiple glomus tumours
- Glomangiomas

Glomus tumours are encapsulated proliferations of glomus cells which line vascular lumina. Glomus cells are thought to be modified smooth muscle cells [1,2] which line endothelial walls of structures known as glomus bodies. These are small, round cells with eosinophilic cytoplasm and centrally placed nuclei [3]. There are localized (segmental) and multiple forms which are probably all part of the same spectrum. The inherited multiple form is due to a germline mutation in the glomulin gene, a gene important for the differentiation of vascular smooth muscle. The mutation has been linked to 1p21-p22 [4–6]. It has been shown that a second hit in one GVM lesion suggests paradominant inheritance [7].



Fig. 18.30 Plaque-type glomangiomas on the back of a 14-year-old girl, which enlarged progressively.

Plaque-like glomuvenous malformations are extremely rare congenital lesions comprising many red/blue compressible papules coalescing into single or multiple plaques. They may be up to 20 cm [8–10] in diameter, with a central depression [11]. Like most glomus tumours, they tend to be painful. Their natural history is of continued growth and development of new lesions at different sites (Fig. 18.30). In the disseminated multiple form, the lesions are much smaller than the plaque ones, usually less than 1 cm, and can occur anywhere on the skin. Rather surprisingly they are often less tender than solitary glomus tumours [12].

The large lesions may be confused with tufted angiomas or other simple venous malformations, but are delineated on T2-weighted and TI-gadolinium enhanced MRI [13].

Unfortunately, treatment is not ideal as surgical excision may be followed by recurrence and sclerotherapy has proved disappointing [13].

References

1 Taafee A, Barker D, Wyatt EH *et al.* Glomus tumors: a clinicopathological survey. *Clin Exp Dermatol* 1980; **5**: 219–25.
2 Iqbal A, Cormack GC, Scerri G. Hereditary multiple glomangiomas. *Br J Plast Surg* 1998; **51**: 32–7.
3 Baselga E, Drolet BA, Fleming MS *et al.* Multiple acquired vascular nodules. *Pediatr Dermatol* 1997; **14**: 327–9.
4 Boon LM, Brouillard P, Irrthum A *et al.* A gene for inherited cutaneous venous anomalies ('glomangiomas') localizes to chromosome 1p21–22. *Am J Hum Genet* 1999; **65**: 125–33.
5 Irrthum A, Brouillard P, Enjolras O *et al.* Linkage disequilibrium narrows locus for venous malformations with glomus cells (VMGLOM) to a single 1.48Mbp YAC. *Eur J Hum Genet* 2001; **9**: 34–8.
6 Brouillard P, Boon LM, Mulliken JB *et al.* Mutations in a novel factor, glomulin, are responsible for glomuvenous malformations ('glomangiomas'). *Am J Hum Genet* 2002; **70**: 866–74.
7 Boon LM, Mulliken JB, Enjolras O *et al.* Glomuvenous malformation (glomangioma) and venous malformation: distinct clinicopathologic and genetic entities. *Arch Dermatol* 2004; **140**: 971–6.
8 Glick SA, Markstein EA, Herreid P. Congenital glomangiomas: case report and review of the literature. *Pediatr Dermatol* 1995; **12**: 242–4.

9 Landthaler M, Braun-Falco O, Eckert F *et al.* Congenital multiple plaquelike glomus tumor. *Arch Dermatol* 1990; **126**: 1203–7.
10 Carvalho VO, Taniguchi K, Giraldi S *et al.* Congenital plaquelike glomus tumor in a child. *Pediatr Dermatol* 2001; **18**: 223–6.
11 Yoon T-Y, Lee H-T, Chang S-H. Giant congenital multiple patch-like glomus tumors. *J Am Acad Dermatol* 1999; **40**: 826–8.
12 Parsons ME, Russo G, Fucich L *et al.* Multiple glomus tumors. *Int J Dermatol* 1997; **36**: 894–900.
13 Mounayer C, Wassef M, Enjolras O *et al.* Facial glomangiomas: large facial venous malformations with glomus cells. *J Am Acad Dermatol* 2001; **45**: 239–45.

Cutaneomucosal venous malformation (CMVM) (OMIM 600915)

This is an autosomal dominant disorder in which children have multiple, small VM. They have some clinical similarity to those seen in blue rubber bleb naevus syndrome, but lack the rubbery consistency and gastrointestinal involvement of the latter. The genetic abnormality of this rare condition has been previously mapped to a mutation of the *TIE2* gene localized to 9p21. This gene is required for blood vessel formation and maintenance [1,2].

References

1 Vikkula M, Boon LM, Carraway KL *et al.* Vascular dysmorphogenesis caused by an activating mutation in the receptor tyrosine kinase TIE2. *Cell* 1996; **87**: 1181–90.
2 Boon LM, Mulliken JB, Vikkula M *et al.* Assignment of a locus for dominantly inherited venous malformations to chromosome 9p. *Hum Mol Genet* 1994; **3**: 1583–7.

Cerebral cavernous malformation (CCM) (OMIM #116860) [1]

These are uncommon disorders characterized by multiple, cerebral capillary venous malformations. They can be asymptomatic or present with seizures, haemorrhage or focal neurological deficit. Retinal malformations are also reported. Familial cerebral cavernous malformation, with an autosomal dominant inheritance, has been mapped to the *CCM1* gene on chromosome 7q11.2 which encodes for the KRIT1 protein [2–4]. In some families a rare variant is defined by the association of CCM and hyperkeratotic cutaneous capillary venous malformations (HCCVMs). The latter are purple, irregular malformations which may be several centimetres in length, extending deep into the dermis [5,6].

References

1 Labauge P, Laberge S, Brunerau L *et al.* Hereditary cereberal cavernous angiomas: clinical and genetic features in 57 French families. *Lancet* 1998; **352**: 1892–7.
2 Dubovsky J, Zabramski JM, Kurth J *et al.* A gene responsible for cavernous malformations of the brain maps to chromosome 7q. *Hum Mol Genet* 1995; **4**: 453–8.
3 Gunel M, Awad IA, Anson J *et al.* Mapping a gene causing cerebral cavernous malformation to 7q11.2-q21. *Proc Nat Acad Sci* 1995; **92**: 6620–4.
4 Laberge-le Couteulx S, Jung HH, Labauge P *et al.* Truncating mutations in CCM1, encoding KRIT1, cause hereditary cavernous angiomas. *Nat Genet* 1999; **23**: 189–93.
5 Labauge P, Enjolras O, Bonerandi JJ *et al.* An association between autosomal dominant cerebral cavernomas and a distinctive hyperkeratotic cutaneous vascular malformation in 4 families. *Ann Neurol* 1999; **45**: 250–4.
6 Ostlere L, Hart Y, Misch KJ. Cutaneous and cerebral haemangiomas associated with eruptive angiokeratomas. *Br J Dermatol* 1996; **135**: 98–101.

Verrucous haemangioma

The ISSVA scheme of binary classification of vascular anomalies into vascular malformations and vascular tumours [1] breaks down for some vascular lesions, of which verrucous haemangioma is one type. Congenital vascular anomalies which develop a rough, warty surface have been differentiated from other similar tumours such as angiokeratomas on histological grounds and referred to as verrucous haemangioma [2]. They are usually present at birth but may present in adulthood. They are commonly found on the legs and may be linear [3,4], multiple or disseminated [5] and sometimes confined to the digits [2] (Fig. 18.31). In the early phase of evolution the lesions are non-keratotic, soft, blue/red plaques, but gradually become increasingly hyperkeratotic [6].



Fig. 18.31 Verrucous haemangioma on the distal arm.

Histologically, verrucous haemangiomas are characterized by epidermis with irregular papillary acanthosis, parakeratosis and hyperkeratosis. There is enlargement of adnexal structures and abnormal vessels are present in the dermis and subcutis. The abnormal vessels are separated by dermal fibrous tissue and have round, thick walls and a multilamellated basement membrane. The endothelial cells are flat and stain strongly for CD34 [6,7]. Verrucous haemangiomas persist indefinitely (hence the inclusion with vascular malformations) and are usually treated by excision. This may have to be done serially with a wide margin to prevent local recurrence, because involvement may extend deep into the fascia [6–9].

References

1 Enjolras O, Mulliken JB. Vascular tumors and vascular malformations (new issues). *Adv Dermatol* 1997; **13**: 375–423.
2 Kohda H, Narisawa Y. Digital verrucous fibroangioma. *Acta Dermatol Venereol (Stockh)* 1992; **72**: 303–4.
3 Imperial R, Helwig EB. Verrucous hemangioma: a clinicopathologic study of 21 cases. *Arch Dermatol* 1967; **96**: 247–53.
4 Wentscher U, Happle R. Linear verrucous hemangioma. *J Am Acad Dermatol* 2000; **42**: 516–8.
5 Cruces MJ, Dela Torre C. Multiple eruptive verrucous hemangiomas. *Dermatologica* 1985; **171**: 106–11.
6 Rossi A, Bozzi M, Barra E. Verrucous hemangioma and angiokeratoma circumscriptum: clinical and histologic differential characteristics. *J Dermatol Surg Oncol* 1989; **15**: 88–91.
7 Tennant LB, Mulliken JB, Perez-Atayde AR *et al.* Verrucous haemangioma revisited. *Pediatr Dermatol* 2006; **23**: 208–15.

8 Wong DS, Hunt ST, Inserra DW *et al.* Unilateral keratotic vascular lesion on the leg. *Arch Dermatol* 1996; **132**: 705, 708.
9 Tan YY, Seah CS, Tan PH. Verrucous haemangioma—a case report. *Ann Acad Med Singap* 1998; **27**: 255–7.

Lymphatic malformation

Lymphatic malformations (LM) are defined as benign lesions composed of vesicles or cystic cavities containing lymphatic fluid. They arise from embryological disturbances during the development of the lymphatic system. They are usually classified into microcystic (synonym lymphangioma circumscriptum) or macrocystic (synonym cystic hygroma) variants, although combined micro- and macrocystic lesions coexist.

Pathology. Histologically, lymphatic malformations are comprised of vascular spaces filled with eosinophilic and protein-rich fluid. Microcystic LM are lined by a single layer of flattened endothelium. The dilated vessel creates a vesicle within the dermal papilla and collections of lymphocytes are seen in the surrounding connective tissue [1]. Blood within the cystic spaces is not uncommon, and indicates recent trauma or spontaneous intralesional bleeding [2] or even a combined lymphatic–capillary malformation. In larger macrocystic LM, the fibrovascular vessel walls are of variable thickness, with striated and smooth muscle components [1]. Vascular endothelium expresses a variety of lymphatic vessel markers including VEGFR-3, LYVE-1 and M2A oncofetal antigen [3]. These cells are thought to trigger expression of the homeobox gene *PROX1* and the cells which express VEGFR-3, LYVE-1 and the product for *PROX1* are committed to form lymphatic vessels [4]. Mutations of VEGFR-3 or its ligands VEGF-C or VEGF-D or *PROX1* could be responsible for lymphatic malformations [5].

Clinical features. Cystic LM can be found in any part of the body, but are more commonly seen in lymphatic-rich areas such as the head and neck, axilla, mediastinum, groin, and retroperitoneum. Microcystic LM can affect the mucosa and skin and are comprised of clear, colourless fluid or darker (bloodstained) vesicles in a plaque or area of diffuse swelling (Fig. 18.32). Microcystic LM are prone to intermittent bruising or swelling and are often more widespread than initially suspected. The larger macrocystic LM are non-compressible, smooth, translucent masses under normal or bluish skin. Macrocystic LM are often found below the level of the mylohyoid bone and involve the anterior and posterior cervical triangles [2].

Large lesions may be picked up *in utero* during detailed ultrasound scans, although many are detected at birth. The majority of lesions are clinically apparent by 2 years of age and transillumination can help to differentiate some cystic lesions from solid masses. Even though ultrasound is useful for superficial lesions, MRI or CT scanning is better at demonstrating their full anatomical extent and their relationship to surrounding soft tissue, muscle and vascular structures. Lesions on MRI are bright on T2-weighted sequences, and isointense for fluid on T1-weighted sequences. Only the margins of the cysts enhance, and thrombi or fluid levels are common findings [6].

LM may cause numerous complications. Cutaneous involvement may result in spontaneous leakage, with a ready portal of entry for bacteria leading to acute or recurrent cellulitis. Very rarely this may result in life-threatening sepsis and cellulitis in these circumstances should therefore be treated aggressively with appropriate antibiotics [7]. For large head and neck LM, respiratory and tracheal obstruction is potentially very serious, requiring tracheostomy [8].



Fig. 18.32 Close up of microcystic lymphatic malformation in axilla.

Extensive limb LM may cause lymphoedema, lymph leakage or even elephantiasis. Pelvic LM may result in vulvar lymphangiectasia and gut LM may lead to a protein losing enteropathy [9].

References

1 Elluru RG, Azizkhan RG. Cervicofacial abnormalities. II. Vascular malformations. *Sem Pediatr Surg* 2006; **15**: 133–9.
2 Rahbar R, McGill TJ, Mulliken J. Vascular tumours and malformations of the head and neck. In: Cummings CW, ed. *Cummings Otolaryngology-Head and Neck Surgery*, 4th edn. Philadelphia, PA: Mosby, 2005: 4013–26.
3 Mentzel T, Kutzner H. Tumours of the lymphatic vessel of the skin and soft tissue. *Derm Pathol* 2002; **23**: 118–27.
4 Chang L, Kaipainen A, Folkman J. Lymphangiogenesis: new mechanisms. *Ann N Y Acad Sci* 2002; **979**: 111–9.
5 Garzon MC, Huang JT, Enjolras O *et al.* Vascular malformations Part I. *J Am Acad Dermatol* 2007; **56**: 353–70.
6 Burrows PE, Mason KP. Percutaneous treatment of low flow vascular malformations. *J Vasc Interv Radiol* 2004; **15**: 431–45.
7 Hancock BJ, Dickens S, Luks FI *et al.* Complications of lymphangioma in children. *J Pediatr Surg* 1992; **27**: 220–6.
8 Hartl DM, Roger G, Denoyelle F *et al.* Extensive lymphangioma presenting with upper airway obstruction. *Arch Otolaryngol Head Neck Surg* 2000; **126**: 1378–82.
9 Enjolras O, Boon LM, Mulliken JB. Vascular malformations. In: Harper J, Oranje A, Prose N, eds. *Textbook of Pediatric Dermatology*, 2nd edn. Oxford: Blackwell, 2006: 1153–74.

Differential diagnosis. The differential diagnosis of LM is wide and includes venous malformations, deep haemangiomas and

infantile fibrosarcoma. The latter present as soft, infiltrated pink plaques with pseudovesicles. They too have a cystic appearance on MRI scans, although only one-third are present at birth [1].

Treatment. In the past macrocystic LM were treated with excision [2]. The potential for cure is compromised by the difficulty in defining clear anatomical boundaries, resulting in incomplete excision and loss of normal tissue. The complications of excision include fistula formation, infection, recurrence and scarring. However, over the last decade, excision has no longer been considered the treatment of first choice. It has become apparent that sclerotherapy has a good success rate and confers a much lower morbidity [3,4]. In contrast, microcystic LM do not respond as well to sclerotherapy, but this should always be considered in symptomatic individuals. Sclerotherapy agents include ethanol, doxycycline, bleomycin, Ethibloc®, OK-432 (a killed strain of *Strep pyogenes*) and 3% sodium tetradecylsulphate (STS). Each agent has its advocates, and often the agent used is determined by the experience of the interventional radiologist. OK-432 causes an inflammatory reaction and subsequent shrinkage of cysts and has a success rate of 80–90% [5,6]. The side effects of this are few, with postoperative swelling being the most common. Ethibloc® is also very effective at sclerosing macrocystic LM, but can lead to skin necrosis due to extrusion from the cyst. Ethanol is similar in efficacy, but has the added problem of potential nerve damage. If large LM require treatment, doxycycline is used because large volumes are well tolerated [7].

Microcystic LM have been treated with Nd:YAG or CO_2 laser with partial success [8,9]. LM-related swelling also responds to compression bandaging and pneumatic compression.

Other issues which must be addressed include antibiotic therapy for secondary infection and recurrent sepsis due to leakage, adequate analgesia and treatment of any coexisting coagulopathy (as with venous malformations) with low molecular weight heparin.

References

1 Enjolras O, Boon LM, Mulliken JB. Vascular malformations. In: Harper J, Oranje A, Prose N, eds. *Textbook of Pediatric Dermatology*, 2nd edn. Oxford: Blackwell, 2006: 1153–74.
2 Young AE. Combined vascular malformations. In: Mulliken JB, Young AE, eds. *Vascular Birthmarks*: *Haemangiomas and Malformations*. Philadelphia: WB Saunders, 1988: 246–74.
3 Sung MW, Lee DW, Kim DY *et al.* Sclerotherapy with picibanil (OK-432) for congenital lymphatic malformation in the head and neck. *Laryngoscope* 2001; **111**: 1430–33.
4 Giguere CM, Bauman NM, Smith RJH. New treatment options for lymphangioma in infants and children. *Ann Otol Rhinol Laryngol* 2002; **111**: 1066–75.
5 Giguere CM, Bauman NM, Satoy *et al.* Treatment of lymphangiomas with OK-432 (Picibanil) sclerotherapy: a prospective multi-institutional trial. *Arch Otolaryngol Head Neck Surg* 2002; **128**: 1137–44.
6 Laranne J, Keski-Nisula L, Rautio R *et al.* OK-432 (Picibanil) therapy for lymphangiomas in children. *Eur Arch Otorhinolaryngol* 2002; **259**: 274–8.
7 Burrows PE, Mason KP. Percutaneous treatment of low flow vascular malformations. *J Vasc Interv Radiol* 2004; **15**: 431–45.
8 Alqahtani A, Nguyen LT, Flageole H *et al.* 25 years experience with lymphangiomas in children. *J Pediatr Surg* 1999; **34**: 1164–8.
9 Huilgol SC, Neill S, Barlow RJ. CO_2 laser therapy of vulval lymphangiectasia and lymphangioma circumscriptum. *Dermatol Surg* 2002; **28**: 575–7.

Gorham's disease [1–3]

Synonyms
- Gorham–Stout syndrome
- Vanishing bone disease
- Massive osteolysis

This is a rare disorder characterized by a proliferation of vascular channels that results in destruction and resorption of osseus matrix. The exact mechanism of bone resorption is still not clear, but in late stages of the disease, the dissolution of the bone leads to massive osteolysis and eventually the bone is replaced by fibrous tissue.

It affects men and women equally, and may involve the appendicular or axial skeleton and skull. The clinical features depend on the site affected. On the extremities it may present with a sudden onset of pain and swelling, or more slowly with reduction in the range of movement or progressive weakness in the involved limb. All types of malformations have been reported, but lymphatic malformations are probably the most common [4]. If the disease affects the ribs, scapulae or vertebrae, lymphangiectasia may extend into the pleural cavity resulting in chylothorax.

Gorham's disease can be treated medically with radiotherapy, bisphosphonates and interferon-α. However, surgical resection of the affected bone and reconstruction with bone grafts continues to be the mainstay of management.

References

1 Gorham LW, Wright AW, Schultz HH *et al.* Disappearing bones: a rare form of massive osteolysis: report of two cases, one with autopsy findings. *Am J Med* 1954; **17**: 674–82.
2 Gorham LW, Stout AP. Massive osteolysis (acute spontaneous absorption of bone, phantom bone, disappearing bone): its relationship to hemangiomatosis. *J Bone Joint Surg (Am)* 1955; **37**: 985–1004.
3 Bruch-Gerharz D, Gerharz CD, Stege H *et al.* Cutaneous vascular malformations in disappearing bone (Gorham–Stout) disease. *JAMA* 2003; **289**: 1479–80.
4 Patel DV. Gorham's disease or masssive osteolysis. *Clin Med Res* 2005; **3**: 65–74.

Mixed/complex malformations

Klippel–Trenaunay syndrome (KTS)

Definition and nomenclature. The commonly accepted definition of Klippel–Trenaunay syndrome is a cutaneous capillary malformation on a limb in association with soft tissue swelling, with or without bony hypertrophy. Interestingly, the original description also included venous varicosities of the affected limb [1]. The term is still in use despite the absence of any aetiological information in its derivation. A more useful definition would be based on the type of vessel involved and its flow characteristics, something which is suggested by those interested in the study of vascular anomalies. Thus KTS would be classed as a slow-flow, complex combined capillary–venous malformation (CVM) or capillary–venous–lymphatic malformation (CVLM). This would avoid the confusion with Parkes Weber syndrome, an entirely different high-flow abnormality with arteriovenous anastomoses in the affected limb (capillary–AVM or capillary–AV lymphatic malformation) [2,3].

Aetiology. The aetiology of KTS is unknown. It has been suggested that a mesodermal defect leading to abnormal vasculature is likely [4]. A genetic cause has not been found although familial cases have been reported [5]. A subgroup of patients with KTS were found to have a gene mutation of E133K causing an increased expression of VG5Q, a pro-angiogenic factor [6].

Clinical features. The cutaneous feature is classically a capillary malformation which may be a large stain or multiple smaller stains, and which ranges from pink to deep purple in colour. CM are present on the affected limb in 75% [7,8], with extension to the whole of the ipsilateral side of the body in 20% [7,8], and in 15% of cases to the contralateral limb [9]. If the stain is sharply demarcated this has been reported to signify an underlying lymphatic malformation and a greater risk of complications [10]. Such geographic stains are purple and are commonly found on the lateral aspect of the thighs, knees and lower legs [10]. The legs are more commonly affected than the arms [11].

Limb hypertrophy is the result of a combination of soft tissue and bony overgrowth and the underlying lymphatic abnormality (Fig. 18.33). Hypertrophy may occur in the limb only or affect the whole half of the body if the thorax is involved [12]. The increased limb size may be present at birth or develops rapidly until the end of puberty [7,9].

Other vascular anomalies may coexist, including localized lymphatic malformations (lymphangioma circumscriptum), angiokeratomas and pseudo-Kaposi's sarcoma lesions [13]. Venous varicosities of the affected limb are also common and form in late childhood or adolescence. A lateral venous anomaly is the most common abnormality [11], although other deep venous anomalies have been reported [14]. The varicosities have many associated problems including bleeding, thrombophlebitis and pain. More serious complications include deep venous thrombosis and pulmonary embolism [7]. Other associations are less common and are mainly developmental. These include poly/syndactyly [7,15] and macrocephaly [16]. Varicosities have been found in the lung, bladder, bowel and rectum [7,17–19].



Fig. 18.33 Klippel–Trenaunay syndrome with limb hypertrophy and lymphatic–venous malformation.

Differential diagnosis. The most common differentials include Parkes Weber and Proteus syndromes. In the former, the limb tends to be warm and there may be audible bruits. The arm is more commonly affected than the leg [20] and is less likely to be deformed than in patients with KTS [21]. The difficulty is usually distinguishing KTS from Proteus syndrome, but the differential has been eased by more recent diagnostic criteria for the latter (Table 18.13). Less common differential diagnoses include cutis marmorata telangiectatica congenita.

The use of radiological investigations is important in the investigation of suspected KTS. Duplex and doppler scans will show up any underlying venous abnormality and arteriovenous shunts, respectively. An MRI scan is useful in outlining the extent of the soft tissue and bone hypertrophy, as well as the lymphatic abnormality.

Treatment/management. The management of patients with KTS includes regular monitoring for limb length discrepancy, prevention of deep venous thrombosis/pulmonary emboli, and dealing with symptoms and signs of venous insufficiency. If limb length discrepancy is found with objective measurements, a paediatric orthopaedic opinion must be sought. Simple measures such as orthotic shoe appliances can be useful, and if more significant discrepancy is present, epiphyseal stapling is performed. Severe limb deformity, on rare occasions, is treated with full or part amputation of the affected limb [14,21]. The use of low molecular weight heparin as thromboprophylaxis is recommended prior to any surgical procedures.

The management of the venous abnormalities is essentially conservative with compression hosiery and, if the lymphatic abnormalities are severe, compression bandaging is useful. Surgical intervention with vein stripping may relieve pain, but worsen symptoms in patients with hypoplasia or absence of the deep system [20]. Surgery to reshape the limb is not recommended, as

Table 18.13 Diagnostic criteria for Proteus syndrome [13].

General	Mosaic distribution
	Progressive course
	Sporadic occurrence
plus	
Specific	Connective tissue naevus or 2 or more of the following criteria:
	Epidermal naevi
	Either bilateral ovarian cystadenomas or parotid adenoma
	Disproportionate overgrowth
	Lipomas
	Capillary, venous or lymphatic malformation
	Lung cysts

it is likely to result in fibrosis and worsening lymphoedema [22]. Bleeding from internal visceral involvement may necessitate surgical intervention [19]. Minor but symptomatic abnormalities, such as bleeding from angiokeratomas or localized lymphatic malformations, can be treated with lasers. Other complications such as infection, cellulitis and superficial thrombophlebitis should be managed with standard medical treatment.

References

1 Klippel M, Trenaunay P. Du naevus variqueux ostéohypertrophique. *Arch Gén Méd* 1900; **3**; 641–72.
2 Parkes Weber F. Angioma formation in connection with hypertrophy of limbs and hemi-hypertrophy. *Br J Dermatol* 1907; **19**: 231–5.
3 Parkes Weber F. Haemangiectatic hypertrophy of the limbs: congenital phlebarteriectasis and so-called congenital varicose veins. *Br J Child Dis* 1918; **15**: 13–7.
4 Baskerville PA, Ackroyd JS, Browse NL. The etiology of Klippel Trenaunay syndrome. *Ann Surg* 1985; **202**: 624–7.
5 Aelvoet GE, Jorens PG, Roelen LM. Genetic aspects of the Klippel–Trenaunay syndrome. *Br J Dermatol* 1992; **126**: 603–7.
6 Tian XL, Kadaba R, You SA *et al.* Identification of an angiogenic factor that when mutated causes susceptibility to Klippel–Trenaunay syndrome. *Nature* 2004; **427**: 640–5.
7 Baskerville PA, Ackroyd JS, Thomas ML *et al.* The Klippel–Trenaunay syndrome: clinical, radiological and haemodynamic features and management. *Br J Surg* 1985; **72**: 232–6.
8 Samuel M, Spitz L. Klippel–Trenaunay syndrome: clinical features, complications and management in children. *Br J Surg* 1995; **82**: 757–61.
9 Gloviczki P, Hollier LH, Telander RL *et al.* Surgical complications of Klippel–Trenaunay syndrome. *Ann Surg* 1983; **197**: 353–62.
10 Maari C, Frieden IJ. Klippel–Trenaunay syndrome: the importance of 'geographic stains' in identifying lymphatic disease and risk of complications. *J Am Acad Dermatol* 2004; **51**: 391–8.
11 Young AE. Combined vascular malformations. In: Mulliken JB, Young AE, eds. *Vascular Birthmarks*: *Haemangiomas and Malformations*. Philadelphia: WB Saunders, 1988: 246–74.
12 Rose LM. Hypertrophy of the lower limbs with cutaneous naevus and varicose veins. *Arch Dis Child* 1950; **25**: 162–9.
13 Kofoed ML, Klemp P, Thestrup-Pedersen K. The Klippel–Trenaunay syndrome with acro-angiodermatitis (pseudo-Kaposi's sarcoma). *Acta Dermatol Venereol (Stockh)* 1985; **65**: 75–7.
14 Gloviczki P, Stanson AW, Stickler GB *et al.* Klippel–Trenaunay syndrome: the risks and benefits of vascular interventions. *Surgery* 1991; **110**: 469–79.
15 McGrory BJ, Amadio PC. Klippel–Trenaunay syndrome: orthopaedic considerations. *Orthop Rev* 1993; **11**: 41–50.
16 Stephan MJ, Hall BD, Smith DW *et al.* Macrocephaly in association with unusual cutaneous angiomatosis. *J Pediatr* 1975; **87**: 353–9.
17 Kuffer FR, Starzynski TE, Girolami A *et al.* Klippel–Trenaunay syndrome, visceral angimatosis and thrombocytopenia. *J Pediatr Surg* 1968; **3**: 65–72.
18 Hall BD. Bladder hemangioma in Klippel–Trenaunay syndrome. *N Engl J Med* 1971; **285**: 1032–3.
19 Servelle M, Bastin R, Loygue J *et al.* Hematuria and rectal bleeding in the child with Klippel and Trenaunay syndrome. *Ann Surg* 1976; **183**: 418–28.
20 Lindenauer SM. Congenital arteriovenous fistula and the Klippel–Trenaunay syndrome. *Ann Surg* 1971; **174**: 248–63.
21 Kinmonth JB, Young AE, Edwards JM *et al.* Mixed vascular deformities of the lower limbs, with particular reference to lymphography and surgical treatment. *Br J Surg* 1976; **63**: 899–906.
22 Enjolras O, Boon LM, Mulliken JB. Vascular malformations. In: Harper J, Oranje A, Prose N, eds. *Textbook of Pediatric Dermatology*, 2nd edn. Oxford: Blackwell, 2006: 1153–74.

Proteus syndrome (OMIM #176920)

Definition. This syndrome was first described as a separate entity in 1983 [1], and is comprised of asymmetrical overgrowth of any part of the body, exostosis, cranial hyperostosis, verrucous epidermal naevi, vascular malformations and lipoma-like hamartomas. The name is derived from the Greek mythology sea god Proteus, who was able to change his shape at will.

Aetiology. There is no definite genetic inheritance, although *PTEN* tumour suppressor gene abnormalities have been described in cases of the syndrome [2]. It has been postulated that Proteus syndrome is caused by a mutation leading to somatic mosaicism, which would otherwise be lethal in the non-mosaic state [3,4]. There has been some support for this theory as the cutaneous lesions can occur in a mosaic pattern, and because of the lack of concordance in identical twins [5].

Pathology. The verrucous epidermal naevi are no different to similar naevi outwith the syndrome [6]. The subcutaneous masses, which are clinically lipomatous, are in fact complex hamartomas containing elements of adipose, vascular and lymphatic tissue [7–9]. Histopathology of the cerebriform plantar lesions shows increased collagen content with reduced elastic fibres consistent with a collagenoma [10,11].

Clinical features. There are usually some manifestations present at birth. The original description proposed that the important diagnostic features were enlarged hands and feet, raised pigmented naevi, hemihypertrophy, subcutaneous masses, skull abnormalities, visceral abnormalities and accelerated growth [1]. There have been a number of attempts to clarify the diagnostic criteria [12,13] (Table 18.13).

The characteristic form of overgrowth is asymmetrical hypertrophy of the face, whole or part of a limb or the trunk, a combination of these, or even hemihypertrophy of one side of the body. The most distinctive signs are cerebriform overgrowth of the soft tissues of the palms or soles. Macrodactyly and macrocephaly are also common.

The epidermal naevi are usually linear and verrucous, and can be both hypo- or hyperpigmented [6–10,14]. The vascular lesions may be extensive capillary malformations or more complex combined capillary–venous–lymphatic malformations akin to Klippel–Trenaunay syndrome. Other less significant findings include café-au-lait patches, and linear or whorled hypo- or hyperpigmentation [7,14]. Venous varicosities are also common [9].

Many extracutaneous findings have been reported, including lung and renal cysts [16], skeletal abnormalities (kyphosis, scoliosis, spinal cord stenosis), dental abnormalities (hypoplastic enamel, misshapen teeth, hypodontia), seizures and eye abnormalities (congenital blindness, squint, cataract and bulbar hypertrophy) [6,7,9,15,16]. Affected individuals have characteristic facies including a long face, dolicocephaly, a low nasal bridge, ptosis, and downward slanted palpebral fissures [16]. The majority of patients are of normal intelligence.

Diagnosis. The main differential diagnosis is with Klippel–Trenaunay syndrome, but the presence of the connective tissue and epidermal naevi and the cerebriform changes of the hands or feet make it easier to rule out KTS. Other syndromes with a cutaneous vascular anomaly and limb hypertrophy include Parkes

Weber syndrome, cutis marmorata telangiectatica congenita (CMTC), macrocephaly-CMTC, and Bannayan–Riley–Ruvalcaba syndrome. There are usually distinctive features which allow Proteus syndrome to be differentiated from these alternative diagnoses.

Treatment. As with many of these complex syndromes, the treatment is supportive with the aim of minimizing any disability. Overgrowth problems will require a multidisciplinary approach from orthopaedic surgeons, orthodontists, physiotherapists, plastic surgeons and ophthalmologists.

References

1 Weidemann HR, Burgio GR, Aldenhoff P *et al.* The Proteus syndrome. *Eur J Pediatr* 1983; **140**: 5–12.
2 Zhou X, Hampel H, Thiele H *et al.* Association of germline mutation in the *PTEN* tumour suppressor gene and Proteus and Proteus-like syndromes. *Lancet* 2001; **358**: 210–1.
3 Happle R. Lethal genes surviving by mosaicism: a possible explanation for sporadic birth defects involving the skin. *J Am Acad Dermatol* 1987; **16**: 899–906.
4 Lacombe D, Taieb A, Vergnes P *et al.* Proteus syndrome in seven patients: clinical and genetic considerations. *Genet Couns* 1991; **2**: 93–101.
5 Cohen MM Jr, Turner JT, Biesecker LG. Proteus syndrome: misdiagnosis with *PTEN* mutations. *Am J Med Genet A* 2003: **122**: 323–4.
6 Viljoen DL, Saxe N, Temple-Camp C. Cutaneous manifestations of the Proteus syndrome. *Pediatr Dermatol* 1988; **5**: 14–21.
7 Costa T, Fitch N, Azouz EM. Proteus syndrome: report of two cases with pelvic lipomatosis. *Pediatrics* 1985; **76**: 984–9.
8 Mucke J, Willgerodt H, Kunzel R *et al.* Variability in the Proteus syndrome: report of an affected child with progressive lipomatosis. *Eur J Pediatr* 1985; **143**: 320–3.
9 Clark RD, Donnai D, Rogers J *et al.* Proteus syndrome: an expanded phenotype. *Am J Med Genet* 1987; **27**: 99–117.
10 Samlaska CP, Levin S, James WD *et al.* Proteus syndrome. *Arch Dermatol* 1989; **125**: 1109–14.
11 Pierard GE, Pierard-Franchimont C, Mosbah TB *et al.* Common aspects of connective tissue hyperplasia of Proteus syndrome and collagenomas. *Ann Dermatol Vénéréol* 1991; **118**: 788–90.
12 Biesecker LG, Happle R, Mulliken JB *et al.* Proteus syndrome: diagnostic criteria, differential diagnosis, and patient evaluation. *Am J Med Genet* 1999; **84**: 389–95.
13 Turner JT, Cohen MM Jr, Biesecker LG. Reassessment of the Proteus syndrome literature: application of diagnostic criteria to published cases. *Am J Med Genet A* 2004; **130**: 111–22.
14 Viljoen DL, Nelson MM, de Jong G *et al.* Proteus syndrome in Southern Africa: natural history and clinical manifestations in six individuals. *Am J Med Genet* 1987; **27**: 87–97.
15 Mayatepek E, Kurczyndki TW, Ruppert ES *et al.* Expanding the phenotype of the Proteus syndrome: a severely affected patient with new findings. *Am J Med Genet* 1989; **32**: 402–6.
16 Cohen MM Jr. Proteus syndrome: clinical evidence for somatic mosaicism and selective review. *Am J Med Genet* 1993; **47**: 645–52.

Hereditary neurocutaneous angioma

This familial disorder was first described in 1979 [1] as an autosomal dominant trait. All the affected individuals had one or more port-wine stains, at almost any site, associated with localized vascular malformations within the CNS. These CNS vascular lesions showed a marked tendency to bleed, resulting in a variety of neurological manifestations with a high morbidity and mortality.

Reference

1 Zaremba J, Stepien M, Jelowicka M *et al.* Hereditary neurocutaneous angioma: a new genetic entity? *J Med Genet* 1979; **16**: 443–7.

Capillary malformation–arteriovenous malformation syndrome (CM–AVM) (OMIM #608354) [1]

This relatively new syndrome was described in 2003, and is comprised of a capillary malformation in association with an AVM or AV fistula, leading to soft tissue or skeletal tissue hypertrophy. The capillary malformations are atypical because they are multiple and small (1–2 cm), round or oval lesions.

The genetic abnormality has been isolated to mutations in the *RASA1* gene which codes for the p120-RasGAP protein. This protein is important in signalling for growth factor receptors that control proliferation, survival and migration of many cell types, including vascular endothelial cells.

Reference

1 Eerola I, Boon L, Mulliken JB *et al.* Capillary malformation-arteriovenous malformation, a new clinical and genetic disorder caused by *RASA1* mutations. *Am J Hum Genet* 2003; **73**: 1240–9.

Divry–van Bogaert syndrome [1,2]

This very rare disorder is characterized by diffuse corticomeningeal angiomatosis and livedo-like marbling of the skin. Presentation is with various neurological signs and symptoms including seizures, visual field defects, migraines, mental disturbances and progressive dementia. The prognosis is generally poor, with death in early adulthood.

References

1 Divry P, Van Bogaert L. Une maladie familiale caractérisée par une angiomatose diffuse cortico-méningée non calcifiante et une démyélinisation progressive de la substance blanche. *J Neurol Neurosurg Psychiatry* 1946; **9**: 41–54.
2 Martin JJ, Navarro C, Roussel JM *et al.* Familial capillaro-venous leptomeningeal angiomatosis. *Europ Neurol* 1973; **9**: 202–15.

Heritary haemorrhagic telangiectasia (Osler–Weber–Rendu syndrome) (OMIM #600376)

This is an autosomal dominant disorder comprising visceral telangiectasia, arteriovenous malformations, and cutaneous and mucous membrane telangiectasia. The genes mapped by linkage studies show that there are two types of abnormality. The most common, HHT-type 1, has been mapped to a transforming growth factor-beta (TGF-β) receptor (endoglin) loss of function mutation on chromosome 9q34-1. The second less common HHT-type 2, is caused by a loss of function mutation of the ALK-1 gene, which is another TGF-β receptor glycoprotein [1,2]. These gene products are expressed on vascular endothelium, and modulate vascular development via their effects on extracellular matrix production [3].

The cutaneous clinical features are telangiectases which may affect the cheeks, lips, tongue, nose, oral mucous membranes and fingers. The most common presenting symptom, however, is recurrent epistaxis, which may predate the cutaneous signs and usually develops in late adolescence [4]. The other common symptom is gastrointestinal (GI) bleeding which manifests itself in adulthood and is a result of GI telangiectasia and AV malformations. Other AVMs may occur in the liver, lung and central nervous system. Lung involvement may present with haemoptysis or significant haemothorax; CNS involvement presents with brain abscesses, emboli and stroke, and seizures [5].

The diagnosis of HHT is made by the presence of three or more of the following features [6]:

1 Epistaxis—spontaneous and recurrent
2 Multiple telangiectases—facial, peri- and intraoral
3 Visceral lesions—lungs, GI tract, brain, spinal cord
4 Family history with first-degree relative with HHT.

In children with multiple telangiectase, who may not present with visceral lesions, the diagnosis is more difficult and may require genetic testing. The common differential diagnosis is systemic sclerosis (CREST variant), but the latter has other manifestations such as sclerodactyly and Raynaud's phenomenon.

The investigation of HHT will depend upon the symptoms, with endoscopy for GI involvement and MR imaging for CNS disease. The management of affected individuals includes electrodesiccation, laser ablation (CO_2 and Nd:YAG), sclerotherapy and embolization to stop or reduce bleeding. Antibiotic prophylaxis is recommended for invasive procedures due to the risk of bacteraemia in patients with pulmonary AVMs.

References

1 McAllister KA, Grogg KM, Johnson DW *et al.* Endoglin, a TGF-beta binding protein of endothelial cells, is the gene for hereditary haemorrhagic telangiectasia type 1. *Nat Genet* 1994; **8**: 345–51.
2 Johnson DW, Berg JN, Baldwin MA *et al.* Mutations in the activin receptor-like kinase 1 gene in hereditary haemorrhagic telangiectasia type 2. *Nat Genet* 1996; **13**: 189–95.
3 Fuchizaki U, Miyamori H, Kitawaga S *et al.* Hereditary haemorrhagic telangiectasia (Rendu-Osler-Weber disease). *Lancet* 2003; **362**: 1490–4.
4 Porteous ME, Burn J, Proctor SJ. Hereditary haemorrhagic telangiectasia: a clinical analysis. *J Med Genet* 1992; **29**: 527–30.
5 Guttmacher AE, Marchuk DA, White RI Jr. Hereditary hemorrhagic telangiectasia. *N Engl J Med* 1995; **333**: 918–24.
6 Shovlin CL, Guttmacher AE, Buscarini E *et al.* Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu–Osler–Weber syndrome). *Am J Med Genet* 2000; **91**: 66–7.

Ataxia telangiectasia (OMIM #208900) [1]

Synonym
- Louis–Bar syndrome

Definition and aetiology. Ataxia telangiectasia is an autosomal recessive disorder consisting of cerebellar ataxia, oculocutaneous telangiectases, and a predisposition to malignancy. It is caused by mutations in the ataxia-telangiectasia mutated gene (*ATM*), localized to chromosome 11q22.3 [2].

Clinical features. Cerebellar ataxia tends to develop early, within the first 2 years, followed by the development of multiple telangiectases. These are usually seen on the bulbar conjunctiva but may also be seen in other sites such as the face, neck and dorsa of the hands and feet. The neurological features begin with truncal ataxia, which precedes appendicular ataxia, and the majority of patients develop choreoathetosis and/or dystonia [3]. Patients with ataxia telangiectasia have a strong predisposition to malignancy. There are reports of leukaemia [4], lymphoma [5] and higher rates of breast cancer [6]. The cells from patients with ataxia telangiectasia have an increased sensitivity to ionizing radiation, which should therefore be used with great caution in patients requiring radiotherapy or radioactive drugs. Other features include immunodeficiency, which may present with recurrent sinus or chest infections [7].

Diagnosis and management. Ataxia telangiectasia is diagnosed clinically on the basis of neurological signs and ocular telangiectasia. Immune deficiency may be demonstrated by low levels of IgG2, or IgM. The condition is progressive and has no known cure.

References

1 Taylor AMR, Byrd PJ. Molecular pathology of ataxia telangiectasia. *J Clin Pathol* 2005; **58**: 1009–15.
2 Gatti RA, Berkel I, Boder E *et al.* Localization of an ataxia-telangiectasia gene to chromosome 11q22–23. *Nature* 1988; **336**: 577–80.
3 Woods CG, Taylor AMR. Ataxia telangiectasia in the British Isles: the clinical and laboratory features of 70 affected individuals. *QJM* 1992; **82**: 169–79.
4 Saxon A, Stevens RH, Golde DW. Helper and suppressor T-lymphocyte leukemia in ataxia-telangiectasia. *New Eng J Med* 1979; **300**: 700–4.
5 Rosen, FS, Harris, NL. Case records of the Massachusetts General Hospital: a 30-year-old man with ataxia-telangiectasia and dysphagia. *New Eng J Med* 1987; **316**: 91–100.
6 Morrell D, Chase CL, Swift M. Cancers in 44 families with ataxia-telangiectasia. *Cancer Genet Cytogenet* 1990; **50**: 119–23.
7 Gatti RA, Boder E, Vinters HV *et al.* Ataxia-telangiectasia: an interdisciplinary approach to pathogenesis. *Medicine* 1991; **70**: 99–117.

Other developmental defects

Complex defects of the first and second branchial arches

Embryonic facial development is intimately linked to that of the skin in two respects. Firstly, the facial processes and skin share a common origin in the neural crest; secondly, facial epithelium maintains FGFR2 levels in the underlying mesenchyme essential for facial process morphogenesis and fusion [1]. The complex disorders resulting from defective development of the first and second branchial arch [1,2] include the following of relevance to dermatologists:

1 mandibulofacial dysostosis (synonym Treacher Collins syndrome)
2 oculomandibulodyscephaly with hypotrichosis (synonym Hallermann–Streiff syndrome)
3 oculoauriculovertebral dysplasia (synonym Goldenhar syndrome) and hemifacial microsomia.

Defects in development of the other branchial arches result in cysts, sinuses and fistulae, which are discussed later.

Mandibulofacial dysostosis

Synonyms
- Treacher Collins syndrome
- Franceschetti–Klein syndrome

Definition. An autosomal dominant disorder of craniofacial development resulting from defective development of the first branchial arch [2].

Aetiology. Treacher Collins syndrome is caused by mutations in the gene *TCOF1* at chromosomal locus 5q31.3 [3–6]. The gene

product 'treacle' is a nucleolar trafficking protein, essential during craniofacial development. Over 120 mutations have been identified, most being deletions, suggesting haplo-insufficiency during embryogenesis of the first and second branchial arches as the molecular mechanism [7,8]. Deficiency of 'treacle' results in apoptosis of neural crest cell precursors migrating into the craniofacial complex [9]. Treacher Collins syndrome is a dominant trait, with highly variable expression and no apparent genotype–phenotype correlation. Ellis *et al.* [5] found mutations in *TCOF1* in 52 of 97 patients with Treacher Collins syndrome. Others have identified mutations in *TCOF1* in only half of familial cases [6,8,10].

It will be of interest to dermatologists that the malformations observed in this disorder are similar to those produced in fetal mice by retinoids given at day 11.5 post-fertilization, corresponding to week 4 in humans [11,12]. Furthermore, Lungarotti *et al.* [13] described facial changes resembling mandibulofacial dysostosis in an infant whose mother took vitamin A during pregnancy. Mice deficient in endothelin-1 show craniofacial abnormalities strikingly similar to those seen in humans with the Treacher Collins syndrome [14].

Sixty per cent of patients with Treacher Collins syndrome have no family history, and some cases may result from gonadal mosaicism in a parent. Mosaicism for a *TCOF1* mutation was found in the clinically unaffected mother of an affected child; the mutation was detected in her leucocytes, hair bulb and buccal cells but not in skin fibroblasts [15].

Clinical features. Treacher Collins syndrome is characterized by hypoplasia of the facial bones, cleft palate, and middle and external ear defects [16]. The clinical presentation is highly variable with sometimes subtle manifestations [16,17]. The facial anomalies are usually symmetrical and include antimongoloid slanting palpebral fissures, coloboma of the lower lid, absence of lower eyelid lashes, malformation of the pinnae with stenosis of the external auditory meati, micrognathia, hypoplastic zygomatic arches and extension of scalp hair on to the cheeks [3,4,16,17]. Blind fistulae and skin tags are sometimes present between the ear and the angle of the mouth. The mouth itself is unusually large with missing and ectopic teeth [18], and the palate high and often cleft. Circumscribed scarring alopecia is an occasional finding. Most affected individuals are of normal intelligence but conductive-type deafness is a common problem.

Treatment. The facial appearance tends to improve as the child grows, and may be enhanced by surgery [1,8]. Early airway compromise caused by micrognathia may be helped by mandibular distraction surgery, but occasionally requires tracheostomy [8,19]. Intubation may be impossible. Deafness requires early recognition and correction with hearing aids and, where possible, surgery. Adolescents can show remarkably good social adjustment [20].

Prenatal diagnosis by ultrasound may not be possible until the second trimester [21]. In some families, a diagnosis can be made in the first trimester by linkage [22] or mutation analysis [5].

References

1 Rice DP. Craniofacial anomalies: from development to molecular pathogenesis. *Curr Mol Med* 2005; **5**: 699–722.

2 Hunt JA, Hobar PC. Common craniofacial anomalies: the facial dysostoses. *Plast Reconstr Surg* 2002; **110**: 1714–26.

3 Dixon MJ. Treacher Collins syndrome *Hum Mol Genet* 1996; **5**: 1391–6.

4 Marszalek B, Wojcicki P, Kobus K, Trezeciak WH. Clinical features, treatment and genetic background of Treacher Collins syndrome. *J Appl Genet* 2002; **43**: 223–33.

5 Ellis PE, Dawson M, Dixon MJ. Mutation testing in Treacher Collins syndrome. *J Orthod* 2002; **29**: 293–8.

6 Dixon J, Trainor P, Dixon MJ. Treacher Collins syndrome. *Orthod Craniofac Res* 2007; **10**: 88–95.

7 Isaac C, Marsh KL, Paznekas WA *et al.* Characterization of the nucleolar gene product, treacle, in Treacher Collins syndrome. *Mol Biol Cell* 2000; **11**: 3061–71.

8 Kobus K, Wojcicki P. Surgical treatment of Treacher Collins syndrome. *Ann Plast Surg* 2006; **56**: 549–54.

9 Dixon J, Jones NC, Sandell LL *et al.* Tcof1/Treacle is required for neural crest cell formation and proliferation deficiencies that cause craniofacial abnormalities. *Proc Natl Acad Sci USA* 2006; **103**: 13403–8.

10 Splendore A, Silva EO, Alonso LG *et al.* High mutation detection rate in *TCOF1* among Treacher Collins syndrome patients reveals clustering of mutations and 16 novel pathogenic changes. *Hum Mutat* 2000; **16**: 315–22.

11 Sulik KK, Johnston MC, Smiley SJ *et al.* Mandibulo-facial dysostosis (Treacher Collins syndrome): a new proposal for its pathogenesis. *Am J Med Genet* 1987; **27**: 359–72.

12 Emmanouil-Nikoloussi EN, Goret-Nicaise M, Foroglou CH *et al.* Craniofacial abnormalities induced by retinoic acid: a preliminary histological and scanning electron microscopic study. *Exp Toxicol Pathol* 2000; **52**: 445–53.

13 Lungarotti MS, Marinelli D, Mariani T, Calabro A. Multiple congenital abnormalities associated with apparently normal maternal intake of vitamin A: a phenocopy of the isotretinoin syndrome? *Am J Med Genet* 1987; **27**: 245–8.

14 Kurihara Y, Kurihara H, Suzuki HT *et al.* Elevated blood pressure and craniofacial abnormalities in mice deficient in endothelin-1. *Nature* 1994; **368**: 703–10.

15 Shoo BA, McPherson E, Jabs EW. Mosaicism of a TCOF1 mutation in an individual clinically unaffected with Treacher Collins syndrome. *Am J Med Genet A* 2004; **126**: 84–8.

16 Teber OA, Gillessen-Kaesbach G, Fischer S *et al.* Genotyping in 46 patients with tentative diagnosis of Treacher Collins syndrome revealed unexpected phenotypic variation. *Eur J Hum Genet* 2004; **12**: 879–90.

17 Hayashi T, Sasaki S, Oyama A *et al.* New grading system for patients with Treacher Collins syndrome. *J Craniofac Surg* 2007; **18**: 113–9.

18 da Silva Dalben G, Costa B, Gomide MR. Prevalence of dental anomalies, ectopic eruption and associated oral malformations in subjects with Treacher Collins syndrome. *Oral Surg Oral Med Oral Pathol* 2006; **101**: 588–92.

19 Shprintzen RJ, Berkman MD. Pharyngeal hypoplasia in Treacher Collins syndrome. *Arch Otolaryngol* 1979; **105**: 127–31.

20 Beaune L, Forrest CR, Keith T. Adolescents' perspectives on living and growing up with Treacher Collins syndrome: a qualitative study. *Cleft Palate Craniofac J* 2004; **41**: 343–50.

21 Crane JP, Beaver HA. Midtrimester sonographic diagnosis of mandibulo-facial dysostosis. *Am J Med Genet* 1986; **25**: 251–5.

22 Edwards SJ, Fowlie A, Cust MP *et al.* Prenatal diagnosis in Treacher Collins syndrome using combined linkage analysis and ultrasound imaging. *J Med Genet* 1996; **33**: 603–6.

Hallermann–Streiff syndrome

Synonyms
- Oculomandibulodyscephaly with hypotrichosis
- Dysencephalic syndrome of François

Definition. A craniofacial dysostosis comprising skeletal, ophthalmological and cutaneous defects.

Aetiology. Hallermann–Streiff syndrome is usually sporadic. The data from familial cases has been variably interpreted as indicating an autosomal dominant gene, with most cases reflecting new mutations [1] or autosomal recessive inheritance [2].

Clinical features [3–9]. The head is short (brachycephalic), the mandible hypoplastic and the nose beaked, producing a characteristic bird-like appearance. Ocular abnormalities are a major problem, particularly bilateral microphthalmia and cataracts. The mouth is small with a high-arched palate. Teeth are often present at birth; partial anodontia, hypoplasia and malimplantation of the teeth are also common [7]. There is proportionate dwarfism, and psychomotor retardation in 15–31% [5].

Cutaneous abnormalities are a striking feature. The scalp hair may be normal at birth, but soon becomes diffusely sparse, fair and brittle, with lack of hair particularly along the sides and back of the head. A highly characteristic finding is alopecia along the lines of the cranial sutures. The eyebrows, eyelashes, and pubic and axillary hair are also scanty. The facial skin is atrophic, particularly in the central part of the face, and telangiectasia may be prominent. Vitiligo and livedo have been reported [8].

Pathology. Histologically, the skin shows a rather loose-weave arrangement of dermal collagen and fragmented elastic fibres [3]. Scanning electron microscopy of hairs demonstrates circumferential grooving or absence of the cuticle [4].

Diagnosis. This condition must be differentiated from progeria, in which atrophy of the skin is more generalized, and alopecia both more pronounced and more diffuse. There is clinical overlap with oculo-dental-digital dysplasia, and a homozygous *GJA1* (connexin 43) mutation was found in one patient with features of both conditions [10].

Treatment. Airway compromise can be life-threatening and requires early intervention [8]. Affected children require expert ophthalmological and dental care. Reconstructive procedures are dealt with later and sometimes a wig may be helpful. Aesthetic surgery is difficult because the skin is generally thin and prone to scarring [8].

References

1 Guyard M, Perdreil G, Ceruti F. Sur deux cas de syndrome dysencéphalique à tête d'oiseau. *Bull Soc Ophtalmol Fr* 1962; **62**: 443–7.

2 François J. François' dysencephalic syndrome. *Birth Defects Orig Artic Ser* 1982; **18**: 595–619.

3 François J, Pierard J. The François' dysencephalic syndrome and skin manifestations. *Am J Ophthalmol* 1971; **71**: 1241–50.

4 Golomb RS, Porter PS. A distinct hair shaft abnormality in the Hallermann–Streiff syndrome. *Cutis* 1975; **16**: 122–8.

5 Cohen MM Jr. Hallermann–Streiff syndrome: a review. *Am J Med Genet* 1991; **41**: 488–99.

6 Amichai B, Finkelstein E, Grunebaum M, Metzker A. What syndrome is this? *Pediatr Dermatol* 1996; **13**: 255–7.

7 Hutchinson D. Oral manifestations of oculomandibulodyscephaly with hypotrichosis (Hallermann–Streiff syndrome). *Oral Surg Oral Med Oral Pathol* 1971; **31**: 234–44.

8 David LR, Finlon M, Genecov D, Argenta LC. Hallermann–Streiff syndrome: experience with 15 patients and review of the literature. *J Craniofac Surg* 1999; **10**: 160–8.

9 Mirshekari A, Safar F. Hallermann–Streiff syndrome: a case review. *Clin Exp Dermatol* 2004; **29**: 477–9.

10 Pizzuti A, Flex E, Mingarelli R *et al.* A homozygous GJA1 gene mutation causes a Hallermann–Streiff/ODDD spectrum phenotype. *Hum Mutat* 2004; **23**: 286.

Goldenhar syndrome

Synonyms
- Oculoauriculovertebral spectrum
- Facioauriculovertebral syndrome
- Hemifacial microsomia

Definition. A heterogeneous disorder characterized by anomalies, usually unilateral, of ear, eye, face and vertebral column.

Aetiology. Goldenhar syndrome is relatively common, with an incidence of about one in 5600 [1]. Genetic analysis has been hampered by phenotypic heterogeneity [2], particularly with regard to severity. Autosomal dominant inheritance has been reported [3] although most cases are sporadic [4]. A minor related anomaly, such as pre-auricular skin tag, occurs in 8% of first-degree relatives [5]. Goldenhar syndrome appears to be the result of abnormal development of both the first and second branchial arches. Suggested causes [6] include 'over-ripeness ovopathy' [7], haemorrhage involving the first and second branchial arches, and ectodermal non-disjunction and subsequent mesodermal tethering [8]. The last of these best explains the multisystem nature of this condition: involvement of the otic placode accounts for the ear anomaly and a similar process over the neuraxis explains the association with occult spinal dysraphism. Infants of diabetic mothers appear to be at increased risk [9]. Retinoic acid administered to rats on gestational days 10–12 produces similar anomalies [10]. Several patients have had chromosomal anomalies affecting, variously, 1, 5p, 6q, 7, 8, 9, 11, 18, 21, 22q and X [11,12]. A translocation between chromosomes 4 and 8 implicated the homeobox gene *BAPX1* [13]. A heterozygous mutation in the Townes–Brocks syndrome gene *SALL1* was found in a mother and two daughters, one of whom had the phenotype of Goldenhar syndrome; her sister and mother had the phenotype of Townes–Brocks syndrome [14]. The Treacher Collins gene *TCOF1* has also been implicated [15]. An association with carrier status for X-linked ichthyosis [16] was probably coincidental.

Clinical features [2,3,17,18]. The facial, auricular and ocular abnormalities are variable in severity and unilateral in 70% of cases. Ear abnormalities affect 94% and include a small, deformed pinna, and conductive deafness, often with accessory auricles and pits occurring along a line between the ear and the corner of the mouth [19]. Mandibular hypoplasia is usually ipsilateral to the abnormal ear. A low hairline on the forehead and temples has occasionally been reported.

Ocular abnormalities found in 65% are highly characteristic, particularly microphthalmia, upper eyelid coloboma, epibulbar dermoids and lipodermoids. Dermoids and lipodermoids present as yellow or white swellings at the limbus or corneal margin, dermoids usually in the lower outer quadrant and lipodermoids in the upper outer quadrant.

Vertebral anomalies include hypoplasia of vertebrae or hemivertebrae, most often in the cervical spine, and occult spinal dysraphism. Developmental delay, and cardiac, renal, genitourinary and gastroenterological anomalies also occur.

Diagnosis. There is phenotypic overlap with Townes–Brocks syndrome, and with the oculocerebrocutaneous syndrome, in which ear anomalies are less common and focal skin defects more common than in Goldenhar anomaly [20].

References

1 Gorlin RJ. Branchial arch and oro-acral disorders. In: Gorlin RJ, Cohen MM Jr, Hennekam RCM, eds. *Syndromes of the Head and Neck*, 4th edn. London: Oxford University Press, 2001: 790–8.
2 Tasse C, Bohringer S, Fischer S *et al.* Oculo-auriculo-vertebral spectrum (OAVS): clinical evaluation and severity scoring of 53 patients and proposal for a new classification. *Eur J Med Genet* 2005; **48**: 397–411.
3 Tasse C, Majewski F, Bohringer S *et al.* A family with autosomal dominant oculo-auriculo-vertebral spectrum. *Clin Dysmorphol* 2007; **16**: 1–7
4 Kaye CI, Martin AO, Rollnick BR *et al.* Oculoauriculovertebral anomaly: segregation analysis. *Am J Med Genet* 1992; **43**: 913–7.
5 Rollnick BR, Kaye CI, Nagatoshi K *et al.* Oculoauriculovertebral dysplasia and variants: phenotypic characteristics of 294 patients. *Am J Med Genet* 1987; **26**: 361–75.
6 Hartsfield JK. Review of the etiologic heterogeneity of the oculo-auriculo-vertebral spectrum (hemifacial microsomia). *Orthod Craniofac Res* 2007; **10**: 121–8
7 Jongbloet PH. Goldenhar syndrome and overlapping dysplasias, *in vitro* fertilisation and ovopathy. *J Med Genet* 1987; **24**: 616–20.
8 Lam CH. A theory on the embryogenesis of oculo–auriculo–vertebral (Goldenhar) syndrome. *J Craniofac Surg* 2000; **11**: 547–52.
9 Wang R, Martinaz-Frias ML, Graham JM Jr. Infants of diabetic mothers are at increased risk for the oculo–auriculo–vertebral sequence: a case-based and case-control approach. *J Pediatr* 2002; **141**: 611–7.
10 Emmanouil-Nikoloussi EN, Goret-Nicaise M, Foroglou CH *et al.* Craniofacial abnormalities induced by retinoic acid: a preliminary histological and scanning electron microscopic study. *Exp Toxicol Pathol* 2000; **52**: 445–53.
11 Balci S, Engiz O, Yilmaz Z, Baltaci V. Partial trisomy (11;22) syndrome with manifestations of Goldenhar sequence due to maternal balanced t(11;22). *Genet Couns* 2006; **17**: 281–9.
12 Josifova DJ, Patton MA, Marks K. Oculoauriculovertebral spectrum phenotype caused by an unbalanced t(5;8)(p15.31;p23.1) rearrangement. *Clin Dysmorphol* 2004; **13**: 151–3.
13 Fischer S, Ludecke HJ, Wieczorek D *et al.* Histone acetylation dependent allelic expression imbalance of BAPX1 in patients with the oculo-auriculo-vertebral spectrum. *Hum Mol Genet* 2006; **15**: 581–7.
14 Kosaki R, Fujimaru R, Samejima H *et al.* Wide phenotypic variations within a family with SALL1 mutations: isolated external ear abnormalities to Goldenhar syndrome. *Am J Med Genet A* 2007; **143**: 1087–90.
15 Su PH, Yu JS, Chen JY *et al.* Mutations and new polymorphic changes in the TCOF1 gene of patients with oculo-auriculo-vertebral spectrum and Treacher-Collins syndrome. *Clin Dysmorphol* 2007; **16**: 261–7.
16 Rivera-Vega MR, Duenas E, Jimenez-Vaca AL *et al.* A novel association in a family with oculo-auriculo-vertebral spectrum and x-linked ichthyosis. *Pediatr Dermatol* 2003; **20**: 182–4.
17 Touliatou V, Fryssira H, Mavrou A *et al.* Clinical manifestations in 17 Greek patients with Goldenhar syndrome. *Genet Couns* 2006; **17**: 359–70.
18 Stromland K, Miller M, Sjogreen L *et al.* Oculo-auriculo-vertebral spectrum: associated anomalies, functional deficits and possible developmental risk factors. *Am J Med Genet A* 2007; **143**: 1317–25.
19 Miller TD, Metry D. Multiple accessory tragi as a clue to the diagnosis of the oculo-auriculo-vertebral (Goldenhar) syndrome. *J Am Acad Dermatol* 2004; **50** (Suppl. 2): S11–3.
20 McCandless SE, Robin NH. Severe oculocerebrocutaneous (Delleman) syndrome: overlap with Goldenhar anomaly. *Am J Med Genet* 1998; **78**: 282–5.

Pre-auricular cysts and sinuses

Synonyms
- Congenital auricular fistulae
- Ear pits

Aetiology. The auricle is formed by the fusion of six small tubercles, three from each of the first two branchial arches. Imperfect fusion leads to entrapment of the epithelium to form pre-auricular cysts, which connect with the skin via pre-auricular sinuses. Such cysts and sinuses may occur as an isolated autosomal dominant trait [1]. Pre-auricular pits and sinuses also occur in the first and second branchial arch syndromes discussed above. They are frequent also in the following syndromes: cat eye [2], cervico-oculo-acoustic, 3p-, 4p-, Kabuki's, Nager's acrofacial dysostosis, Peters'-plus, Townes–Brocks [3] and branchio-oto-renal (BOR). BOR syndrome can be caused by mutations in the *EYA1* gene [4]. Posterior ear pits occur in the Beckwith–Wiedemann syndrome [5].

Clinical features. Asymptomatic pre-auricular cysts and sinuses are very common (Fig. 18.34) [6,7], occurring in 6.2 per 1000 live births in Israel [8], more often in black populations, and in 2.5% of the Chinese population [9]. These congenital, often bilateral, lesions may go unnoticed until infection develops, when they present as an acutely tender swelling anterior, or sometimes posterior [10], to the ear, with pus draining through a small opening just in front of the ascending limb of the helix. In most cases infection is recurrent, and an asymptomatic sinus is present on the other side. Very occasionally, the patient may present with a granulomatous nodule at the mouth of the sinus.

Hearing impairment is found in 17% of neonates with isolated pre-auricular pits or tags [11]. Associated developmental anomalies of the branchial apparatus may coexist, particularly malformations of the auricle, accessory auricles and branchial fistulae. CT scanning is more useful than MRI in the delineation of these anomalies [12]. Although pre-auricular sinuses coexist with renal anomalies in certain syndromes, for example BOR syndrome [4,13], isolated pre-auricular tags or pits are not associated with renal anomalies [6,8,13].

Diagnosis. First branchial arch sinuses usually exit lower down over the parotid gland. Granulomatous lesions may be confused with lupus vulgaris [14].



Fig. 18.34 Pre-auricular sinus.

Treatment. Hearing tests are indicated in neonates with isolated ear pits [11], but renal investigations are not [8]. Surgical excision is required when secondary infection has occurred, but should be delayed until the acute infection has been treated with systemic antibiotics. Recurrence is usually due to incomplete excision. The lesion most typically comprises several cysts arranged along a longitudinal tract which blends with the periosteum of the auditory canal. Occasionally a post-auricular sinus is also present. Methylene blue injection [15] facilitates full visualization, which is necessary for complete excision.

References

1 Bhalla V, Roy S, Inam AS. Familial transmission of preauricular fistula in a seven generation Indian pedigree. *Hum Genet* 1979; **48**: 339–41.
2 Llistosella E, Pujol RM. Brachio-oto-renal syndrome. *Pediatr Dermatol* 1996; **13**: 507–8.
3 Jones KL. *Smith's Recognizable Patterns of Human Malformation*, 5th edn. Philadelphia: Saunders, 1997: 1–7.
4 Rickard S, Boxer M, Trompeter R, Bitner-Glindzicz M. Importance of clinical evaluation and molecular testing in the branchio-oto-renal (BOR) syndrome and overlapping phenotypes. *J Med Genet* 2000; **37**: 623–7.
5 Barr CL, Best L, Weksberg R. Linkage studies in families with posterior helical ear pits and Beckwith–Wiedemann syndrome. *Am J Med Genet* 2001; **104**: 120–6.
6 Scheinfeld NS, Silverberg NB, Weinberg JM, Nozad V. The preauricular sinus: a review of its clinical presentation, treatment, and associations. *Pediatr Dermatol* 2004; **21**: 191–6.
7 Huang XY, Tay GS, Wansaicheong GK, Low WK. Preauricular sinus: clinical course and associations. *Arch Otolaryngol Head Neck Surg* 2007; **133**: 65–8.
8 Kugelman A, Tubi A, Bader D *et al.* Pre-auricular tags and pits in the newborn: the role of renal ultrasonography. *J Pediatr* 2002; **141**: 388–91.
9 Tsai F-J, Tsai C-H. Birthmarks and congenital skin lesions in Chinese newborns. *J Formos Med Assoc* 1993; **92**: 838–41.
10 Chang PH, Wu CM. An insidious preauricular sinus presenting as an infected postauricular cyst. *Int J Clin Prac* 2005; **59**: 370–2.
11 Kugelman A, Hadad B, Ben-David J *et al.* Preauricular tags and pits in the newborn: the role of hearing tests. *Acta Paediatr* 1997; **86**: 170–2.
12 Muckherji SK, Tart RP, Slattery WH *et al.* Evaluation of first branchial arch anomalies by CT and MR. *J Comput Assist Tomogr* 1993; **17**: 576–81.
13 Wang RY, Earl DL, Ruder RO, Graham JM Jr. Syndromic ear anomalies and renal ultrasounds. *Pediatrics* 2001; **108**: E32.
14 Scherwitz C, Dorn M. Zur lupus-vulgaris-artigen Fremdkorperreaktion auf kongenitaler preauricularer Fistel. *Hautarzt* 1973; **24**: 397–9.
15 Martin-Granizo R, Perez-Herrero MC, Sanchez-Cuellar A. Methylene blue staining and probing for fistula resection: application in a case of bilateral congenital preauricular fistulas. *Int J Oral Maxillofac Surg* 2002; **31**: 439–41.

Accessory tragus

Synonyms
- Accessory auricle
- Ear tag
- Cartilage naevus

Aetiology. The tragus (the cartilaginous bump anterior to the external auditory meatus) is derived from the dorsal portion of the first branchial arch. During embryonic life, the first arches grow ventrally to join in the midline, and accessory tragi may be found anywhere along this migratory course, from tragus to sternoclavicular joint. Isolated accessory auricles may be inherited as an autosomal dominant trait [1], mapped to 14q11.2–12 [2].



Fig. 18.35 Accessory tragi.

Pathology. Numerous, tiny hair follicles and eccrine sweat glands are conspicuous in the dermal core of accessory tragi, which are covered by normal epidermis. There is a prominent connective tissue framework in the subcutaneous fat [3]. Cartilage is almost always present. They may be difficult to differentiate from hair follicle naevi [4].

Clinical features. Accessory tragi are small, skin-coloured tags or nodules, arising on or near the tragus, along a line between the tragus and the corner of the mouth, or on the neck (*cervical auricles* or *wattles*) along the anterior edge of the sternomastoid muscle [5]. Vellus hairs often protrude from the surface. They may be unilateral or bilateral, single or multiple (Fig. 18.35), and either soft or cartilaginous in consistency. Like pre-auricular cysts and sinuses, they most commonly occur as a solitary abnormality [6], present in about 1% of neonates [7]. They also occur with other malformations and syndromes of the first branchial arch, such as Treacher Collins, Goldenhar, Nager's acrofacial dysostosis, 4p-, oculocerebrocutaneous and Townes' syndromes.

Similar lesions have very occasionally been described at other sites on the face such as the glabella [8].

Treatment. Accessory tragi are best removed surgically, with careful dissection and excision of any associated cartilage that may extend more deeply [5,9].

References

1 Tadini G, Cambiaghi S, Scarabelli G *et al.* Familial occurrence of isolated accessory tragi. *Pediatr Dermatol* 1993; **10**: 26–8.

2 Yang Y, Guo J, Liu Z *et al.* A locus for autosomal dominant accessory auricular anomaly maps to 14q11.2-q12. *Hum Genet* 2006; **120**: 144–7.
3 Satoh T, Tokura Y, Katsumata M *et al.* Histological diagnostic criteria for accessory tragi. *J Cutan Pathol* 1990; **17**: 206–10.
4 Ban M, Kamiya H, Yamada T, Kitajima Y. Hair follicle nevi and accessory tragi: variable quantity of adipose tissue in connective tissue framework. *Pediatr Dermatol* 1997; **14**: 433–6.
5 Kim SW, Moon SE, Kim JA. Bilateral accessory tragi on the suprasternal region. *J Dermatol* 1997; **24**: 543–5.
6 Jansen T, Romiti R, Altmeyer P. Accessory tragus: report of two cases and review of the literature. *Pediatr Dermatol* 2000; **17**: 391–4.
7 Tsai F-J, Tsai C-H. Birthmarks and congenital skin lesions in Chinese newborns. *J Formos Med Assoc* 1993; **92**: 838–41.
8 Sayama S, Tagami H. Cartilaginous nevus on the glabella. *Acta Dermatol Venereol (Stockh)* 1982; **62**: 180–1.
9 Sebben JE. The accessory tragus: no ordinary skin tag. *J Dermatol Surg Oncol* 1985; **11**: 745.

Cervical tab

Synonyms
- Cervical auricle
- Wattle
- Congenital cartilaginous rests of the neck

Cervical tabs simply represent accessory tragi at the ventral end of the migratory path of the first branchial arch [1,2].

Histologically, they comprise lobules of mature cartilage embedded in dense collagen.

Clinically, cervical tabs take the form of an irregular, often pedunculated papule or nodule up to 15 mm in diameter, occurring on the neck along the line of the anterior border of the lower third of the sternomastoid muscle. They may be unilateral or bilateral, and are usually noted during infancy. These lesions are not associated with fistulous tracts or connections to deeper structures, but cartilage may extend deeply.

References

1 Sperling LC. Congenital cartilaginous rests of the neck. *Int J Dermatol* 1986; **25**: 186–7.
2 Bendet E. A wattle (cervical accessory tragus). *Otolaryngol Head Neck Surg* 1999; **121**: 508–9.

Branchial cysts, sinuses and fistulae

Synonyms
- Branchial cleft cyst
- Lateral cervical cyst
- Cervical cyst, sinus, fistula

Aetiology. During weeks 4 and 5 of human embryological development, complex tissue movements produce the facial structures [1–3]. A 35-day-old human embryo has four gill-like branchial clefts on the sides of the neck, separating the branchial arches. The first cleft persists as the external auditory meatus, the others normally disappear by fusion. The second branchial arch fuses with the fifth arch, enclosing the second, third and fourth arches and their respective clefts to form an ectodermal pocket, termed the cervical sinus. Incomplete fusion results in fistulae (tracts with two openings), sinuses (tracts with one opening), or cysts (tracts with no openings). Sinuses and fistulae communicate with skin or internal mucosa according to whether the anomaly affects, respectively, the branchial cleft (ectoderm) or branchial pouch (endoderm).

Pathology [4]. First branchial arch anomalies are lined by keratinizing stratified squamous epithelium, and may contain cartilage, reflecting their relationship to the external auditory meatus [3]. Second and third branchial remnants have either non-keratinizing squamous epithelium or mucus secreting respiratory-type ciliated, columnar epithelium. Beneath the epithelium there is usually lymphoid tissue, often with germinal centres and subcapsular lymph sinuses. Thymic or parathyroid tissue may be found in third arch remnants, and thymic or thyroid tissue in fourth arch remnants, reflecting the origin of these organs.

Clinical features [2,3]. Branchial anomalies usually present at birth or in early childhood, sinuses and fistulae earlier than cysts. They are sometimes bilateral. Girls and boys are affected equally. Familial occurrence has been recorded [5,6]. Most branchial anomalies are derived from the second branchial cleft; third and fourth branchial anomalies are rare. Sinuses are the most common type of branchial anomaly reported, and fistulae the least common.

Branchial sinuses opening externally are usually apparent from birth as pits or blind-ending tracts. Those derived from the first branchial cleft are found over the parotid gland, below the angle of the mandible and occasionally on the back of the earlobe [7]; second, third and fourth sinuses exit in the lower third of the neck along the anterior border of the sternomastoid muscle. The external opening may become more prominent later because of mucous secretion, inflammation, infection or granulation tissue. A skin tag, sometimes containing cartilage, may mark the site of the opening. The tract itself may be palpable, running upwards in the neck from the cutaneous opening. Branchial sinuses are features of several syndromes including Treacher Collins, Goldenhar, Townes–Brocks, branchio-oto-renal and branchio-oculo-facial.

Branchial fistulae share the same cutaneous distribution as branchial sinuses, but also open internally [2]. First branchial pouch anomalies open into the external auditory canal [8,9] or middle ear, and can present with discharge from the ear [8]. There may be a membranous band from ear drum to auditory canal. Second branchial pouch remnants open into the tonsillar fossa, and third and fourth pouch remnants into the pharynx at the pyriform fossa. Branchial fistula can occur as an isolated anomaly [9], but is also a characteristic component of the autosomal dominant branchio-oto-renal (BOR) syndrome due to *EYA1* mutations, in which it is associated with pre-auricular pits, deafness and renal anomalies [10]. Branchial fistulae also occur with pre-auricular pits, deafness, commissural lip pits and rib anomalies in the autosomal recessive branchio-oto-costal syndrome [11].

Branchial cyst may present any time up to the third decade, as a pre- or post-auricular swelling [12] or a lump in the neck. In some cases, the swelling is painful, usually because of secondary infection. Branchial cysts vary from less than 1 cm to about 10 cm in diameter. On palpation they may feel cystic or solid. Pressure symptoms may occur, for example fourth arch cysts can cause thyroiditis [13,14], or recurrent laryngeal nerve paralysis [13,15]. Rarely, squamous cell carcinoma develops in the wall of a

branchial cyst [16]. Thyroid carcinoma has been reported in ectopic thyroid tissue in a branchial cyst [17].

Diagnosis. Ultrasound examination, CT scanning with contrast, and fistulography with thin barium [3] can be used to define branchial cleft remnants. Direct laryngoscopy may be used to detect fistulae, which are sometimes missed on flexible nasal pharyngoscopy [14]. Otological and MRI examination are important to exclude associated anomalies [12]. The differential diagnosis of lateral neck swellings includes unilateral lymphadenopathy, particularly malignant and tuberculous [18], parotid and thyroid tumours, thymopharyngeal cyst, thyroglossal cyst, lymphoepithelial cyst, dermoid cyst, teratoma, carotid body tumour, infantile haemangioma and neurofibroma. Cystic hygroma occurs in the posterior triangle of the neck, that is posterior to the sternomastoid muscle, and is usually apparent from birth or shortly afterwards. Histologically, third and fourth branchial anomalies may resemble cysts derived from rests of thymic or parathyroid tissue [2].

Treatment. Branchial remnants are usually removed surgically under general anaesthesia [3,8], first arch remnants through a standard parotidectomy incision, dissecting out the facial nerve, and others via a lateral neck incision. Injection of methylene blue into the cutaneous opening of sinuses and fistulae, or cannulation with a suture can be used to guide surgical removal [2,9]. Recurrence is likely if excision is incomplete; branchial cysts are more likely to recur if no epithelial lining is identified in the surgical specimen [3]. Ideally, surgery should be carried out before infection distorts the anatomy and hinders complete excision. However, a period of watchful waiting may be reasonable for asymptomatic lesions. Fistulae can be tackled by avulsion through the mouth using a varicose vein stripper [19], or endoscopic diathermy to the internal opening [13]. Sclerotherapy with OK-432 has been used successfully for branchial cleft cysts in adults [20].

References

1 Mukherji SK, Fatterpekar G, Castillo M *et al.* Imaging of congenital anomalies of the branchial apparatus. *Neuroimaging Clin N Am* 2000; **10**: 75–93, viii.
2 Waldhausen JH. Branchial cleft and arch anomalies in children. *Semin Pediatr Surg* 2006; **15**: 64–9.
3 Schroeder JW Jr, Mohyuddin N, Maddalozzo J. Branchial anomalies in the pediatric population. *Otolaryngol Head Neck Surg* 2007; **137**: 289–95.
4 Crocker J, Jenkins R. An immunohistochemical study of branchial cysts. *J Clin Pathol* 1985; **38**: 784–90
5 Martins AG. Lateral cervical and preauricular sinuses: their transmission as dominant characters. *BMJ* 1961; **1**: 255–6.
6 Wheeler CE, Shaw RF, Cawley EP. Branchial anomalies in three generations of one family. *Arch Dermatol* 1958; **77**: 715–9.
7 Elsurer C, Yilmaz T. First branchial cleft fistula presenting with external opening on earlobe. *Eur Arch Otorhinolaryngol* 2006; **263**: 685–7.
8 Triglia JM, Nicollas R, Ducroz V *et al.* First branchial cleft anomalies: a study of 39 cases and a review of the literature. *Arch Otolaryngol Head Neck Surg* 1998; **124**: 291–5.
9 Ang AH-C, Pang KP, Tan LK-S. Complete branchial fistula: case report and review of the literature. *Ann Otol Rhinol Laryngol* 2001; **110**: 1077–9.
10 Rickard S, Boxer M, Trompeter R, Bitner-Glindzicz M. Importance of clinical evaluation and molecular testing in the branchio-oto-renal (BOR) syndrome and overlapping phenotypes. *J Med Genet* 2000; **37**: 623–7.
11 Clementi M, Mammi I, Tenconi R. Family with branchial arch anomalies, hearing loss, ear and commissural lip pits, and rib anomalies. A new autosomal recessive condition: branchio-oto-costal syndrome? *Am J Med Genet* 1997; **68**: 91–3.
12 Marchioni D, Cuzzola E, Masone F, Ghidini A. Congenital postauricular swelling in a child. *Pediatr Dermatol* 2002; **19**: 246–9.
13 Rea PA, Hartley BE, Bailey CM. Third and fourth branchial pouch anomalies. *J Laryngol Otol* 2004; **118**: 19–24.
14 Garrel R, Jouzdani E, Gardiner Q *et al.* Fourth branchial pouch sinus: from diagnosis to treatment. *Otolaryngol Head Neck Surg* 2006; **134**: 157–63.
15 Hoyt BJ, Lee B, Taylor SM, Bullock M. Fourth branchial cyst presenting with right-sided vocal cord paralysis. *J Otolaryngol* 2004; **33**: 273–5.
16 Zimmermann CE, von Domarus H, Moubayed P. Carcinoma in situ in a lateral cervical cyst. *Head Neck* 2002; **24**: 965–9.
17 Lanzafame S, Caltabiano R, Puzzo L, Imme A. Expression of thyroid transcription factor 1 (TTF-1) in extra thyroidal sites: papillary thyroid carcinoma of branchial cleft cysts and thyroglossal duct cysts and struma ovarii. *Pathologica* 2006; **98**: 640–4.
18 Foote JE, Anderson PC. Branchial cleft remnants suggesting tuberculous lymphadenitis. *Arch Dermatol* 1968; **97**: 536–9.
19 Taylor PH, Bicknell PG. Stripping of branchial fistulae: a new technique. *J Laryngol Otol* 1977; **91**: 141–9.
20 Roh JL, Sung MW, Hyun Kim K, Il Park C. Treatment of branchial cleft cyst with intracystic injection of OK-432. *Acta Otolaryngol* 2006; **126**: 510–4.

Midline cervical cleft

Aetiology. This rare anomaly probably results from imperfect first or second branchial arch fusion in the midline. The histology could be explained by mesodermal cells destined for the tongue being deposited in the anterior neck [1].

Clinical features [1–5]. This is commoner in females. This lesion takes the form of a vertically orientated atrophic area, several centimetres in length, and several millimetres in width, in the lower anterior midline of the neck. There may be a polypoid skin protruberance at the upper end and a sinus tract at the caudal end. Fibrous bands may connect the lesion with the underlying platysma, causing contractures of the neck and lower jaw. Traction on the growing mandible may produce a bony spur. It may be associated with labial or mandibular clefting, and with thyroglossal and other branchial cleft anomalies.

Pathology. There is an unusual mixture of skin, skeletal muscle, and fibrous and salivary tissue.

Treatment. Treatment is surgical [3], via a series of Z-plasty incisions, ideally in the first year of life. Deep fibrous remnants should also be removed to avoid contracture.

References

1 Gardner RO, Moss AL. The congenital cervical midline cleft. Case report and review of literature. *Br J Plast Surg* 2005; **58**: 399–403.
2 Smith RM Jr, Barth PC, Castillo J *et al.* Congenital midline cervical cleft: a report of 3 cases. *Ear Nose Throat J* 2006; **85**: 119–20, 125.
3 Cochran CS, DeFatta RJ, Brenski AC. Congenital midline cervical cleft: a practical approach to Z-plasty closure. *Int J Pediatr Otorhinolaryngol* 2006; **70**: 553–9.
4 Maschka DA, Clemons JE, Janis JF. Congenital midline cervical cleft. Case report and review. *Ann Otol Rhinol Laryngol* 1995; **104**: 808–11.
5 Eastlack JP, Howard RM, Frieden IJ. Congenital midline cervical cleft: case report and review of the English language literature. *Pediatr Dermatol* 2000; **17**: 118–22.

Thyroglossal cysts

Aetiology. The embryonic thyroglossal duct normally obliterates by week 5, remaining only as the foramen caecum at the base of

the tongue, and the pyramidal lobe of the thyroid [1]. Thyroglossal duct remnants take the form of fistulae, cysts or solid masses of ectopic thyroid tissue, and may occur anywhere along its length. Thyroglossal duct cyst is sometimes inherited as an autosomal dominant trait [2] sometimes manifesting as congenital hypothyroidism [3]. The cysts gradually enlarge because of internal secretions from the epithelial lining.

Pathology. Thyroglossal cysts are lined by stratified squamous or mucus-secreting columnar epithelium, and may contain ectopic thyroid tissue.

Clinical features [1,2]. Thyroglossal cyst usually presents during the first 5 years of life but may not be diagnosed until adult life [4]. It is the commonest cause of midline anterior neck swellings in children. It usually presents as a soft mass in the midline of the neck, 1–3 cm in diameter and close to the hyoid bone. It moves upwards on swallowing or on protrusion of the tongue. There may be an opening in the mouth at the foramen caecum, leading to fetor or an unpleasant taste. Occasionally, it drains externally, often as a result of previous surgical procedures. Thyroglossal cyst may present acutely as an infected neck mass, dysphagia, hoarseness, airway obstruction [5], and even fatal asphyxia if the mass is at the base of the tongue [6]. Infection tends to be recurrent. Very large thyroglossal cysts may be displaced laterally and not move on swallowing [7].

Ectopic thyroid tissue in the throglossal remnant may be the only thyroid tissue present. This is an important consideration before excising thyroglossal duct cysts. Such patients may already be hypothyroid. Malignant degeneration occurs in 1–2% of thyroglossal duct remnants, including children [8,9]. Generally this is associated with a good prognosis following excision. It is sometimes multifocal, affecting also the thyroid gland.

Diagnosis. The differential diagnosis includes enlarged lymph nodes, dermoid cyst, lymphoma [10] and haematoma [11]. Bronchogenic cysts may occur in the midline at the suprasternal notch, but are rare.

Treatment. Fine-needle aspiration may be needed for decompression, histology and microbiological sampling. Acute infection is treated initially with antibiotics. Solid masses, particularly in hypothyroid patients, are usually scintiscanned to identify distribution of thyroid tissue prior to surgical excision, since the thyroglossal remnant may contain the patient's only functioning thyroid tissue. Surgery is deferred until any infection and inflammation have completely settled [12]. Surgical treatment is by dissection of the cyst and tract, and removal of the hyoid bone and base of tongue musculature [13]. Ethanol sclerosis therapy has also been used [14]. If malignant cells are found on fine-needle aspiration, a pre-operative MRI scan and wide excision are required. The roles of ablative radio-iodine and thyroidectomy in thyroglossal duct carcinoma are debated [9].

References

1 Foley DS, Fallat ME. Thyroglossal duct and other congenital midline cervical anomalies. *Semin Pediatr Surg* 2006; **15**: 70–5.

2 Schader I, Robertson S, Maoate K, Beasley S. Hereditary thyroglossal duct cysts. *Pediatr Surg Int* 2005; **21**: 593–4.

3 Leger J, Marinovic D, Garel C *et al*. Thyroid developmental anomalies in first degree relatives of children with congenital hypothyroidism. *J Clin Endocrinol Metab* 2002; **87**: 575–80.

4 Mohan PS, Chokshi RA, Moser RL, Razvi SA. Thyroglossal duct cysts: a consideration in adults. *Am Surg* 2005; **71**: 508–11.

5 Purdom E, Robitschek J, Littlefield PD, Cable B. Acute airway obstruction from a thyroglossal duct cyst. *Otolaryngol Head Neck Surg* 2007; **136**: 317–8.

6 Sauvageau A, Belley-Cote EP, Racette S. Fatal asphyxia by a thyroglossal duct cyst in an adult. *J Clin Forensic Med* 2006; **13**: 349–52.

7 Prasad KC, Dannana NK, Prasad SC. Thyroglossal duct cyst: an unusual presentation. *Ear Nose Throat J* 2006; **85**: 454–6.

8 Falvo L, Giacomelli L, Vanni B *et al*. Papillary thyroid carcinoma in thyroglossal duct cyst: case reports and literature review. *Int Surg* 2006; **91**: 141–6.

9 Plaza CP, Lopez ME, Carrasco CE *et al*. Management of well-differentiated thyroglossal remnant thyroid carcinoma: time to close the debate? Report of five new cases and proposal of a definitive algorithm for treatment. *Ann Surg Oncol* 2006; **13**: 745–52.

10 Tarnaris A, Giridharan W, Aird DW. Lymphoma mimicking a thyroglossal duct cyst in an adolescent. *J Laryngol Otol* 2005; **119**: 216–8.

11 Persaud R, Short M, Kothari P, Robinson A. Thyroglossal duct cyst masquerading as a haematoma. *J Laryngol Otol* 2004; **118**: 240–1.

12 Kaselas CH, Tsikopoulos G, Chortis CH, Kaselas B. Thyroglossal duct cyst's inflammation. When do we operate? *Pediatr Surg Int* 2005; **21**: 991–3.

13 Perkins JA, Inglis AF, Sie KC, Manning SC. Recurrent thyroglossal duct cysts: a 23-year experience and a new method for management. *Ann Otol Rhinol Laryngol* 2006; **115**: 850–6.

14 Baskin HJ. Percutaneous ethanol injection of thyroglossal duct cysts. *Endocr Pract* 2006; **12**: 355–7.

Other defects of relevance to dermatology

Bronchogenic cyst

Synonym
- Presternal ciliated cyst

Definition. An isolated cyst lined with respiratory epithelium.

Aetiology. Bronchogenic cysts usually occur in the chest or mediastinum, but are very occasionally found in the skin [1–3]. They are assumed to develop from tracheal buds at the time of division of the foregut into its tracheal and oesophageal components. At this stage, the right and left mesenchymal bars of the sternum are still unfused. The characteristic suprasternal site may reflect pinching off of bronchogenic tissue by the closing sternal plates. The other locations may be reached by migration of this tissue [2]. Alternative explanations for bronchogenic cysts include lymphatic or haematogenous spread of respiratory tissue [4] and *in situ* anomalous tissue differentiation (heteroplasia) [5].

Pathology. The cysts occur in the dermis or subcutis. The mucosal lining comprises lamina propria and a pseudostratified columnar ciliated epithelium with goblet cells. The cyst wall frequently contains smooth muscle and mucous glands. Lymphoid tissue may be present, particularly when secondary infection has occurred. Cartilage is occasionally seen, in keeping with the bronchogenic origin of this lesion. Gastric mucosa was seen as well as respiratory and squamous epithelium in a lesion on the upper back [6]. There is no connection to underlying structures.

Clinical features. Bronchogenic cysts are solitary and four times more common in males [7]. They are apparent at birth or shortly afterwards, usually as a pinpoint orifice, or a soft, asymptomatic, mobile nodule that very slowly increases in size and may eventually discharge mucoid fluid through a small fistula. Other morphologies include a papillomatous nodule [8] and an area with the appearance of aplasia cutis, and linear, erythematous pruritic hyperkeratotic papules resembling ILVEN [7]. Cutaneous bronchogenic cysts are characteristically located close to the suprasternal notch or over the manubrium sterni [9,10]. Occasionally, they occur in the shoulder [11] and scapular area [4,12], or in the thyroid gland. Lesions have also been reported on the chin [13–15] and abdominal wall [16]. Malignant transformation has been reported in non-cutaneous bronchogenic cysts but not in cutaneous bronchogenic cysts [7,15], apart from a single report of malignant melanoma arising in a bronchogenic cyst on the scapular area of a middle-aged Japanese man [17].

Diagnosis. Differential diagnosis includes branchial cysts, sinuses and fistulae, thyroglossal cysts, teratomas and heterotopic salivary gland tissue.

Treatment. Treatment comprises surgical excision.

References

1 Bagwell CE, Schiffman RJ. Subcutaneous bronchogenic cysts. *J Pediatr Surg* 1988; **23**: 993–5.
2 Fraga S, Helwig EB, Rosen SH. Bronchogenic cysts in the skin and subcutaneous tissue. *Am J Clin Pathol* 1971; **56**: 230–8.
3 Jona JZ. Extramediastinal bronchogenic cysts in children. *Pediatr Dermatol* 1995; **12**: 304–6.
4 Singer G, Haag E, Anabitarte M. Cutaneous lung tissue heterotopia. *Histopathology* 1998; **32**: 60–2.
5 Ramon R, Betloch I, Guijarro J *et al.* Bronchogenic cyst presenting as a nodular lesion. *Pediatr Dermatol* 1999; **16**: 285–7.
6 Vlodavsky E, Czernobilsky B, Bar Y, Lifschitz-Mercer B. Gastric mucosa in a bronchogenic cutaneous cyst in a child: case report and review of literature. *Am J Dermatopathol* 2005; **27**: 145–7.
7 Zvulunov A, Amichai B, Grunwald MH *et al.* Cutaneous bronchogenic cyst: delineation of a poorly recognised lesion. *Pediatr Dermatol* 1998; **15**: 277–81.
8 Miller OF, Tyler W. Cutaneous bronchogenic cyst with papilloma and sinus presentation. *J Am Acad Dermatol* 1984; **11**: 367–71.
9 Patterson JW, Pittman DL, Rich JD. Presternal ciliated cyst. *Arch Dermatol* 1984; **120**: 240–2.
10 Kural YB, Ergun S, Buyukbabani N *et al.* Cutaneous bronchogeneic cysts. *Int J Dermatol* 1998; **37**: 128–44.
11 Matsuda K, Hikita H, Ito N *et al.* Bronchogenic cyst of the shoulder. *Scand J Plast Reconstr Surg Hand Surg* 2004; **38**: 365–9.
12 Ozel SK, Kazez A, Koseogullari AA, Akpolat N. Scapular bronchogenic cysts in children: case report and review of the literature. *Pediatr Surg Int* 2005; **21**: 843–5.
13 Ambivaga PC, Rosen Y. Cutaneous ciliated cyst of the chin. *Arch Dermatol* 1979; **115**: 895–6.
14 Kotsuji-Maruyama T, Umebayashi Y, Imakado S, Otsuka F. Cutaneous bronchogenic cyst of the chin. *Dermatology* 2001; **203**: 192–3.
15 Calb IL, Haas E, Lewandowski MG, Maler L. Cutaneous bronchogenic cyst: an unusual localisation and review of the literature. *Br J Dermatol* 2000; **143**: 1353–5.
16 Kim NR, Kim HH, Suh YL. Cutaneous bronchogenic cyst of the abdominal wall. *Pathol Int* 2001; **51**: 970–3.
17 Tanita M, Kikuchi-Numagami K, Ogoshi K *et al.* Malignant melanoma arising from cutaneous bronchogenic cyst of the scapular area. *J Am Acad Dermatol* 2002; **46**: S19–21.

Cutaneous associations with sternal clefts

Sternal clefts are rare congenital anomalies, which are, however, frequently associated with a variety of cutaneous abnormalities, including fistulae [1,2], an area of ulceration or scarring [3–5], supra-umbilical midline raphe [6] and facial haemangiomas. Congenital aortic aneurysm is one of the more serious extracutaneous associations. Recognized syndromes include the PHACE association [7] and the sternal malformation/vascular dysplasia association [8], which may overlap [9].

Bifid sternum and incomplete fusion of the ribs in the midline are features of mice lacking glycogen synthase kinase-3beta (GSK-3beta) [10]. The mutant phenotype can be 'rescued' by administering GSK-3beta at two specific times in gestation. This model may shed light on sternal cleft and related anomalies.

References

1 Matsunaga W, Ishihara T, Yasuno K. Congenital dermoid fistula of the anterior chest region. *Nishinihon J Dermatol* 1994; **56**: 34–9.
2 Miyamoto T, Hosoda Y, Fujimoto Y *et al.* Congenital skin fistula with sternal cleft. *Br J Dermatol* 1995; **132**: 492–4.
3 Firmin RK, Fragomeni LS, Lennox SC. Complete cleft sternum. *Thorax* 1980; **35**: 303–6.
4 Maeda K, Yoshimura H, Furuoka H *et al.* Congenital upper sternal cleft: report of a case. *Jpn J Pediatr Surg* 1991; **23**: 679–82.
5 Stoll C, Vivier M, Renaud R. A supraumbilical midline raphe with sternal cleft in a 47XXX woman. *Am J Med Genet* 1987; **27**: 229–31.
6 Greenberg BM, Becker JM, Pletcher BA. Congenital bifid sternum: repair in early infancy and literature review. *Plast Reconstr Surg* 1991; **88**: 886–9.
7 Slavotinek AM, Dubovsky E, Dietz HC, Lacbawan F. Report of a child with aortic aneurysm, orofacial clefting, haemangioma, upper sternal defect, and marfanoid features: possible PHACE syndrome. *Am J Med Genet* 2002; **110**: 283–8.
8 Yapicioglou H, Narli N, Satar M, Soyupak S, Kucukosmanoglou O. A newborn infant with sternal malformation/vascular dysplasia association. *Genet Couns* 2002; **13**: 35–9.
9 Vermeer S, van Oostrom CG, Boetes C *et al.* A unique case of PHACES syndrome confirming the assumption that PHACES syndrome and the sternal malformation-vascular dysplasia association are part of the same spectrum of malformations. *Clin Dysmorphol* 2005; **14**: 203–6.
10 Liu KJ, Arron JR, Stankunas K *et al.* Chemical rescue of cleft palate and midline defects in conditional GSK-3beta mice. *Nature* 2007; **446**: 79–82.

Congenital dermoid cysts and sinuses

Aetiology and nomenclature [1]. A dermoid cyst is a *choristoma*, that is a benign tumour consisting of mature tissue derived from germ cell layers foreign to that site. The term 'dermoid' is sometimes used incorrectly for a benign cystic *teratoma*, that is a tumour with mature tissue derived from all three germ layers. Most cutaneous dermoid cysts develop from epithelium trapped along lines of embryonic fusion. There may be an associated sinus tract extending superficially or deeply or both. They are usually sporadic but there are several reports of familial dermoid cysts of the nose. Midline dermoids have occurred in a mother and daughter, external angular dermoids have been reported in siblings [2], and occipital dermoid sinuses in a mother and son [3].

Pathology. Cutaneous dermoid cysts are located in the subcutis; they are often adherent to periosteum, and may invade or erode underlying bone. The cysts are lined by keratinizing stratified squamous epithelium, complete with hair follicles, sebaceous and sweat glands. The lumen contains lipid, keratin and hair.



Fig. 18.36 Midline dermoid cyst on the bridge of the nose.

Clinical features. About 40% of dermoid cysts are present at birth, and about 70% by the age of 5 years. They enlarge because of the secretory activity of the epidermal lining. They typically appear as subcutaneous 'doughy' spherical nodules varying from around 0.5 to 6.0 cm in diameter, largely depending on site. Usually they are white, pearly or erythematous nodules, but occasionally appear as a yellow plaque [4]. A sinus opening, sometimes with projecting hairs, may be the only cutaneous sign of an intracranial dermoid [5]. They are usually found on the head and neck [6–8]. Predilection sites are the outer third of the eyebrow, the so-called *external angle dermoid*, the midline of the nose, usually near the bridge (Fig. 18.36), the scalp, the submental area, the anterior neck, the anterior chest wall and the occipital area.

Deep periorbital lesions derived from the orbital suture may displace the eyelid, cause proptosis, and erode the orbital bones, the intracranial extension sometimes creating an hour-glass shape [8]. In a series of 18 midline nasal dermoids, 12 had extensions to the septum and two to the skull base [9]. Recurrent infection may be a problem, and osteomyelitis and meningitis are occasional complications [10]. Pressure erosion of bone may also occur [1]. Dermoid cysts and sinuses of the head and neck require MRI and CT imaging prior to surgery, to reveal the anatomical extent of the tract and its relationship to the anterior cranial fossa [11]. Dermoids of the head and neck are usually isolated lesions but may be associated with other craniofacial anomalies [11].

Diagnosis. In the neck, the dermoid cyst is only slightly less common than the thyroglossal cyst and may be clinically indistinguishable. It must likewise be differentiated preoperatively from ectopic thyroid gland and branchial cyst.

Cysts at the bridge of the nose must particularly be distinguished from nasal gliomas, which present at birth as firm, reddish tumours at the side of the bridge, and meningoencephalocoeles which may pulsate and may be associated with an underlying skull defect [12]. Infected nasofrontal dermoid sinus may present as recurrent sinusitis [10].

It is essential to use MRI scanning [11–13] and/or high-resolution ultrasound [14] to evaluate midline facial masses, and thyroid function tests and ^{99m}Tc or ^{123}I scintillation scanning to identify any possible ectopic thyroid tissue prior to surgical excision of neck lesions [15].

Treatment. Surgical excision may be complicated by the presence of deep tracts adherent to underlying periosteum, or to the septum in the case of nasal lesions, or communicating intracranially. Failure to excise these tracts leads to recurrence, and treatment of these lesions is therefore best undertaken under general anaesthesia by a craniofacial, plastic or ENT surgeon after appropriate imaging [11,16].

References

1 Pensler JM, Baur BS, Naidich TP. Craniofacial dermoids. *Plast Reconstr Surg* 1988; **82**: 953–8.
2 McIntyre JD, Rannan-Eliya SV, Wall SA. Familial external angular dermoid: evidence for a genetic link. *J Craniofac Surg* 2002; **13**: 311–4.
3 Ansari S, Dadmehr M, Nejat F. Possible genetic correlation of an occipital dermal sinus in a mother and son. Case report. *J Neurosurg* 2006; **105** (Suppl. 4): 326–8.
4 Julapalli MR, Cohen BA, Hollier LH, Metry DW. Congenital, ill-defined, yellowish plaque: the nasal dermoid. *Pediatr Dermatol* 2006; **23**: 556–9.
5 Scolozzi P, Lombardi T, Jaques B. Congenital intracranial frontotemporal dermoid cyst presenting as a cutaneous fistula. *Head Neck* 2005; **27**: 429–32.
6 McAvoy JM, Zucherbraun L. Dermoid cysts of the head and neck in children. *Arch Otolaryngol* 1976; **102**: 529–31.
7 Pollard ZF, Harley RD, Clahoun J. Dermoid cysts in children. *Pediatrics* 1976; **57**: 379–82.
8 Ahuja R, Azar NF. Orbital dermoids in children. *Semin Ophthalmol* 2006; **21**: 207–11.
9 Sreetharan V, Kangesu L, Sommerlad BC. Atypical congenital dermoids of the face: a 25-year experience. *J Plast Reconstr Aesthet Surg* 2007; **60**: 1025–9.
10 Edmonds LD, Ahluwalia JS, Fortman BJ *et al.* Infected dermoid sinus tract mimicking recurrent sinusitis in an adolescent male. *Curr Probl Diagn Radiol* 2007; **36**: 43–7.
11 Hanikeri M, Waterhouse N, Kirkpatrick N *et al.* The management of midline transcranial nasal dermoid sinus cysts. *Br J Plast Surg* 2005; **58**: 1043–50.
12 Paller AS, Pensler JM, Tomita T. Nasal midline masses in infants and children. *Arch Dermatol* 1991; **127**: 362–6.
13 Barkovich AJ, Vandermarck P, Edwards MSB *et al.* Congenital nasal masses: CT and MR imaging features in 16 cases. *Am J Neuroradiol* 1991; **12**: 105–16.
14 Glasier CM, Brodsky MC, Lesither RE *et al.* High resolution ultrasound with Doppler: a diagnostic adjunct in orbital and ocular lesions in children. *Pediatr Radiol* 1992; **22**: 174–8.
15 Conklin WT, Davis RM, Dabb RW *et al.* Hypothyroidism following removal of a 'thyroglossal duct cyst'. *Plast Reconstr Surg* 1981; **68**: 930–2.
16 Blake WE, Chow CW, Holmes AD, Meara JG. Nasal dermoid sinus cysts: a retrospective review and discussion of investigation and management. *Ann Plast Surg* 2006; **57**: 535–40.

Nasal glioma

Nasal gliomas are rare childhood lesions, not true gliomas but rather encephalocoeles that have lost their intracranial connection [1]. They comprise heterotopic neuroectoderm and derive from the nasofrontal dural diverticulum: failure to obliterate this embryonic connection between dura and skin results in a nasal glioma

or a midline nasal dermoid, depending, respectively, on whether dural elements are retained externally or cutaneous elements internally. The heterotopic neural tissue may be amputated by closure of the craniofrontal sutures, or a stalk of fibroglial tissue may remain. Most nasal gliomas are intranasal, but some appear externally.

Histology shows astrocytes and neuroglial fibres interspersed with dense connective tissue trabeculae, sometimes containing striated muscle fibres, within the dermis [2]. In one case all three components of neural tissue were present, that is leptomeninges, glia and neurones, as well as sweat duct hyperplasia [3].

External nasal gliomas are usually present at birth, and grow in proportion to the child. They are asymptomatic and appear as a firm, red or bluish, smooth, domed swelling on the bridge or side of the nose. Hypertelorism may be present. Unlike true encephalocoeles, they do not increase in size with crying or the Valsalva manoeuvre. Intranasal gliomas take the form of a polypoid mass in the nose or pharynx, causing upper respiratory tract obstruction. Of a surgical series of 10 cases, two were external [2].

Differential diagnosis includes the true nasal encephalocoele and meningoencephalocoele [4], other cutaneous neural and meningeal heterotopias [5], congenital dermoid cyst, lacrimal duct cyst, neuroblastoma and rhabdomyosarcoma, but nasal gliomas are probably most often confused with infantile haemangioma [6,7].

Treatment is surgical excision. Biopsy and fine-needle aspiration are contraindicated because of the possibility of intracranial extension. If preoperative imaging reveals an intracranial connection, neurosurgical collaboration is required.

References

1 Hedlund G. Congenital frontonasal masses: developmental anatomy, malformations, and MR imaging. *Pediatr Radiol* 2006; **36**: 647–62.
2 Penner CR, Thompson L. Nasal glial heterotopia: a clinicopathologic and immunophenotypic analysis of 10 cases with a review of the literature. *Ann Diagn Pathol* 2003; **7**: 354–9.
3 Gambini C, Rongioletti F, Rebora A. Proliferation of eccrine sweat ducts associated with heterotopic neural tissue (nasal glioma). *Am J Dermatopathol* 2000; **22**: 179–82.
4 Bagger-Sjoback D, Bergstrand G, Edner G *et al.* Nasal meningoencephalocoele: a clinical problem. *Clin Otolaryngol* 1983; **8**: 329–35.
5 Argenyi ZB. Cutaneous neural heterotopias and related tumours relevant for the dermatopathologist. *Semin Diagn Pathol* 1996; **13**: 60–71.
6 Levine MR, Kellis A, Lash R. Nasal glioma masquerading as a capillary hemangioma. *Ophthal Plast Reconstr Surg* 1993; **9**: 132–4.
7 Hoeger PH, Schaefer H, Ussmueller J, Helmke K. Nasal glioma presenting as capillary haemangioma. *Eur J Pediatr* 2001; **160**: 84–7.

Transverse nasal groove

Synonym
- Nasal crease

Definition. A horizontal crease across the nose where cartilage meets bone.

Aetiology. The appearance of this lesion may be explained by differential growth of the alar and septal cartilages of the nose during childhood or as a residual embryonic groove in the frontonasal cartilage [1,2]. It is probably not rare, but is seldom noticed. It is often hereditary [1], possibly determined by an autosomal dominant gene [3]. This is probably the same as the nasal crease associated with allergic rhinitis and thought to be caused by repeated upwards rubbing of the nose: the 'allergic salute' [4,5]. No studies have been reported that seek to determine whether this lesion is in fact more frequent in children with allergic rhinitis.

Clinical features. A reddish pink, transverse streak or a shallow groove appears at the junction of the middle and lower thirds of the nose, generally at about the age of 10 years and most often in girls. It is obliterated spontaneously during early adult life. The presence of milia and comedones along this nasal groove [1,6–9] has been termed pseudoacne of the nasal crease [9].

References

1 Shelley WB, Shelley ED, Pansky B. The transverse nasal line: an embryonic fault line. *Br J Dermatol* 1997; **137**: 963–5.
2 Wimmershof MB, Hohenleutner U, Landthaler M. Transverse nasal groove. A rare embryological error in nature. *Hautazt* 2001; **52**: 828–30.
3 Anderson PC. Familial transverse nasal groove. *Arch Dermatol* 1961; **84**: 316–7.
4 Myers WA. The 'nasal crease': a physical sign of allergic rhinitis. *JAMA* 1960; **174**: 1204–6.
5 Berger WE. Allergic rhinitis in children: diagnosis and management strategies. *Paediatr Drugs* 2004; **6**: 233–50.
6 Akinduro OM, Burge SM. Congenital milia in the nasal groove. *Br J Dermatol* 1994; **130**: 800.
7 Del Rio E, Pena J, Aguilar A. Milia cysts along the nasal groove in a child. *Clin Exp Dermatol* 1993; **18**: 289–90.
8 Piqué E, Olivares M, Fariña MC *et al.* Congenital nasal comedones. *Clin Exp Dermatol* 1996; **21**: 220–1.
9 Risma KA, Lucky AW. Pseudoacne of the nasal crease: a new entity? *Pediatr Dermatol* 2004; **21**: 427–31.

Lip pits and sinuses

There are three types of lip pits: commissural pits, sinuses of the upper lip and lower lip pits, also known as lip sinuses.

Commissural lip pits

These are the commonest type of lip pits, and are found in about 2% of neonates, the highest frequency being found in black neonates [1]. Pits are visible just within the oral cavity at the angle of the mouth. These pits are generally bilateral, and should be regarded as sinuses, ending blindly within a few millimetres of their openings. They probably arise as a result of locally incomplete fusion of the maxillary and mandibular prominences. Histologically, the sinuses comprise stratified squamous epithelium identical to that of the vermilion border. Ducts having a cuboidal epithelium have occasionally been noted to open into the main sinus lumen, but associated glands have not been identified. Commissural lip pits are frequently inherited as an autosomal dominant trait [2]. They may be associated with pre-auricular sinuses [3], and may rarely communicate with the parotid duct [4]. They have occasionally been reported in association with other defects particularly deafness, external ear anomaly [5–7], rib anomalies [8], with branchio-oto-renal (BOR) syndrome, and with a variant of BOR syndrome without renal anomalies which mapped to 1q31 rather than to the established BOR gene (*EYA1*) locus at 8q13 [6,7,9]. Van der Woude's syndrome also features lip pits and maps to 1q31, but the two loci are distinct [9].

Sinuses of the upper lip

Congenital sinuses of the upper lip are extremely rare. One-third are lateral, rarely symmetrical [10], while the rest occur in the midline above the vermilion border, between the philtrum and the frenulum [11–13]. The embryology of these sinuses is unclear. Lateral sinuses may represent a *forme fruste* of cleft lip due to failure of fusion of the maxillary processes, or aberrations in the normal mesodermal merging process [12]. However, cleft lip is more often lateral, whereas upper lip pit is more often medial [14]. The idea that upper lip sinuses arise from a burrowing process analogous to that which forms the nasal cavities [11] is supported by the facts that the upper lip and nasal cavities are formed at the same embryological stage, that both anterior nasal cavities and upper lip sinuses are lined by stratified squamous epithelium, and that the sinus never goes right through to the oral cavity [14].

Congenital midline sinus of the upper lip may present with recurrent swelling or cellulitis around the frenulum [14,15].

Occasionally, upper lip sinuses are associated with other developmental anomalies such as hypertelorism, nasal fistula and lip fistula [10,16,17].

Lower lip pits

Synonyms
- Congenital lip sinuses
- Congenital lip fistulae

These take the form of bilateral openings in the vermilion border, at the peaks of the lower lip convexities, and may be associated with nipple-like protruberances [18]. Secretions may be expelled from these sinuses under the same conditions that stimulate secretion of saliva, and there may be a fistulous link to the salivary gland [19,20]. Histologically, the pits are blind sinuses, about 2–15 mm in length, lined by stratified squamous epithelium identical to that of the lip [21]. At the blind end, mucous glands may be present.

Lower lip pits are a characteristic component of the Van der Woude syndrome, an autosomal dominant trait with very variable expression. When fully expressed, the syndrome comprises cleft lip, cleft palate and uvula, hypodontia and lower lip pits [22–24], but some patients and families have only lip pits [25–27]. Lower lip pits are also a characteristic feature of the popliteal pterygium syndrome, in which they are also associated with cleft lip and/or palate [28,29]. Van der Woude and popliteal pterygium syndromes share the facial phenotype and are in fact allelic variants, both caused by mutations in *IRF6* at 1q32 [30]. *IRF6* mutations can also cause non-syndromic cleft lip and palate: studies in mice and chick embryos suggest a role for *IRF6* during the fusion events that occur during development of the lip and palate [31]. A variety of other anomalies have occasionally been reported in association with lower lip pits [32,33], including type I orofaciodigital syndrome [34] and Kabuki syndrome [35].

References

1 Jorgenson RJ, Shapiro SD, Salinas CF *et al.* Intraoral findings and anomalies in neonates. *Pediatrics* 1982; **69**: 577–82.

2 Everett FG, Wescott WB. Commissural lip pits. *Oral Surg* 1961; **14**: 202–9.

3 Baker BR. Pits of the lip commissures in Caucasoid males. *Oral Surg* 1966; **21**: 56–60.

4 Arriaga MA, Dindzans LJ, Bluestone CD. Parotid duct communicating with a labial pit and ectopic salivary cyst. *Arch Otolaryngol Head Neck Surg* 1990; **116**: 1445–7.

5 Ohishi M, Kai S, Ozeki S *et al.* Alveolar synechia, ankyloblepharon and ectodermal disorders: an autosomal recessive disorder? *Am J Med Genet* 1991; **38**: 13–5.

6 Marres HA, Cremers CWRJ, Huygen PLM, Joosten FBM. Congenital conductive or mixed deafness, preauricular sinus, external ear anomaly and commissural lip pits: an autosomal dominant inherited syndrome. *Ann Otol Rhinol Laryngol* 1991; **100**: 928–32.

7 Marres HA, Cremers CW, Huygen PL, Joosten FB. The deafness, preauricular sinus, external ear anomaly and commissural lip pits syndrome—otological, vestibular and radiological findings. *J Laryngol Otol* 1994; **108**: 13–8.

8 Clementi M, Mammi I, Tenconi R. Family with branchial arch anomalies, hearing loss, ear and commissural lip pits, and rib anomalies. A new autosomal recessive condition: branchio-oto-costal syndrome? *Am J Med Genet* 1997; **68**: 91–3.

9 Kumar S, Deffenbacher K, Marres HA *et al.* Genomewide search and genetic localisation of a second gene associated with autosomal dominant branchio-oto-renal syndrome: clinical and genetic implications. *Am J Hum Genet* 2000; **66**: 1715–20.

10 Ozgue F, Tuncbilek G. Bilateral congenital pits of the upper lip. *Ann Plast Surg* 2000; **45**: 658–61.

11 Miller CJ, Smith JM. Midline sinus of the upper lip and a theory concerning etiology. *Plast Reconstr Surg* 1980; **65**: 674–5.

12 Illing HM, Field D, McNamara CM, Sandy JR. Congenital sinus of the upper lip. A case report. *Int J Oral Maxillofac Surg* 1999; **28**: 29–30.

13 Millard DR, Williams S. Median lip clefts of the upper lip. *Plast Reconstr Surg* 1968; **42**: 4–14.

14 Assahina I, Sakakibara T, Miyashin M *et al.* Congenital midline sinus of the upper lip: case report and review of the literature. *Cleft Palate Craniofac J* 1997; **34**: 83–5.

15 Al-Qattan MM. Conenital midline sinus of the upper lip. *Ann Plast Surg* 2000; **44**: 76–8.

16 Bartels RJ, Howard RC. Congenital midline sinus of the upper lip. *Plast Reconstr Surg* 1973; **52**: 665–8.

17 Holbrook LA. Congenital midline sinus of the upper lip. *Br J Plast Surg* 1970; **23**: 155–60.

18 Michaelides AC, Hay RJ, Wells RS. Congenital sinuses of the lower lip. *Trans St John's Hosp Dermatol Soc* 1975; **61**: 82–6.

19 Souto LR. Congenital bilateral lower lip pits associated with fistulae of the minor salivary glands: case report of the principal Van Der Woude syndrome's trait. *Aesthetic Plast Surg* 2008; **32**: 172–4.

20 Ziai MN, Benson AG, Djalilian HR. Congenital lip pits and van der Woude syndrome. *J Craniofac Surg* 2005; **16**: 930–2.

21 Watanabe Y, Otake IM, Tomida K. Congenital fistulas of the lower lip: five cases with special reference to the etiology. *Oral Surg* 1951; **4**: 709–22.

22 Schinzel A, Klauser M. The Van der Woude syndrome (dominantly inherited lip pits and clefts). *J Med Genet* 1986; **23**: 291–4.

23 Nagore E, Sanchez-Motilla JM, Febrer MI *et al.* Congenital lower lip pits (Van der Woude syndrome): presentation of 10 cases. *Pediatr Dermatol* 1998; **15**: 443–5.

24 Vignale R, Araujo J, Pascal G *et al.* Van der Woude syndrome. A case report. *Pediatr Dermatol* 1998; **15**: 459–63.

25 Calista D. Congenital lower lip pits. *Pediatr Dermatol* 2002; **19**: 363–4.

26 Martelli-Junior H, Chaves MR, Swerts MS *et al.* Clinical and genetic features of Van der Woude syndrome in two large families in Brazil. *Cleft Palate Craniofac J* 2007; **44**: 239–43.

27 Zarandy MM, Givehchi G, Mohammadi M. A familial occurrence of lip anomaly. *Am J Otolaryngol* 2005; **26**: 132–4.

28 Gorlin RJ, Sedano HO, Cervenka J. Popliteal pterygium syndrome: a syndrome comprising cleft lip-palate, popliteal and intercrural pterygia, digital and genital anomalies. *Pediatrics* 1968; **41**: 503–9.

29 Rintala AE, Lahti AY, Gylling S. Congenital sinuses of the lower lip in connection with cleft lip and palate. *Cleft Palate J* 1970; **7**; 336–45.

30 Kondo S, Schutte BC, Richardson RJ *et al.* Mutations in *IRF6* cause Van der Woude and popliteal pterygium syndromes. *Nat Genet* 2002; **32**: 285–9.

31 Knight AS, Schutte BC, Jiang R, Dixon MJ. Developmental expression analysis of the mouse and chick orthologues of IRF6: the gene mutated in Van der Woude syndrome. *Dev Dyn* 2006; **235**: 1441–7.
32 Pauli RM, Hall JG. Lip pits, cleft lip and/or palate and congenital heart disease. *Am J Dis Child* 1980; **134**: 293–5.
33 Giampietro PF, Babu D, Koehn MA *et al.* New syndrome: focal dermal hypoplasia, morning glory anomaly, and polymicrogyria. *Am J Med Genet A* 2004; **124**: 202–8.
34 Salinas CF, Pai GS, Vera CL. Variability of expression of the orofaciodigital syndrome type 1 in black females: six cases. *Am J Med Genet* 1991; **38**: 574–82.
35 Schrander-Stumpel CT, Spruyt L, Curfs LM *et al.* Kabuki syndrome: Clinical data in 20 patients, literature review, and further guidelines for preventive management. *Am J Med Genet A* 2005; **132**: 234–43.

Polydactyly

Synonyms
- Accessory digit
- Supernumerary digit

Polydactyly can occur as an isolated trait, but also occurs in many syndromes [1]. The genes for polydactyly provide remarkable insights into normal fetal development [2].

The commonest form of supernumerary digit is postaxial polydactyly (PAP), in which the additional digit, which may be well-formed (PAP-A) or rudimentary (PAP-B), arises from the ulnar border of the hand, at or near the base of the fifth digit. Isolated postaxial polydactyly is ten times more common in black people than in white people: the US estimates of incidence are 1/3300–1/630 live births in white people and 1/300–1/100 in black people. It is transmitted as an autosomal dominant trait, possibly modified by a sex-linked recessive modifier gene [3]. The prevalence is 44% in the offspring of affected black fathers and 31% in the offspring of black mothers. In the offspring of non-black fathers and mothers it is 34% and 33% respectively [1]. PAP-A is genetically heterogeneous, and can be caused by mutations in the *GLI3* gene (*PAPA1*) at 7p15 [4], *PAPA2* at 13q31-q32 and *PAPA3* at 19p13.1–13.2 [5]. PAP occurs in 75% of patients with trisomy 13 (particularly those involving q31–q34) [4] suggesting a locus on chromosome 13. There are several genes for polysyndactyly including *HOXD* [6].

Preaxial polydactyly, with accessory digits on the radial side of the hand, is also heterogeneous. It is a feature of 25 different syndromes and can occur in isolation [2]. Clinically it is divided into type 1 (thumb polydactyly), type 2 (triphalangeal thumb polydactyly), type 3 (polydactyly of index finger) and type 4 (polysyndactyly). Genes include *GLI3* and *LMBR3* [7]. Crossed polydactyly is when the polydactyly is preaxial in the hands and postaxial in the feet or vice versa.

Polydactyly is often bilateral. The rudimentary lesion is a small, skin-coloured, sometimes pedunculated nodule, which may contain cartilage or be capped by a vestigial nail. Sometimes the lesion is soft and globular, in other cases warty.

The presence of numerous nerve bundles is a histological feature [8], which may also be seen at sites from which supernumerary digits have been amputated spontaneously, or traumatically, in early life [9].

Solitary ectopic nails may occur on the palmar aspect of fingers, usually the little finger. This anomaly is distinct from supernumerary digits [10]. In adults, such lesions must be distinguished from acquired digital fibrokeratomas [11].

Treatment. Polydactyly may be the presenting or sole abnormality in the proband with a familial syndrome. Therefore a careful family history must be taken, and genetic referral may be indicated. Supernumerary digits may be excised on cosmetic grounds. Neonatal paediatricians commonly ligate rudimentary accessories that have a narrow pedicle [12].

References

1 Jones KL. *Smith's Recognizable Patterns of Human Malformation*, 6th edn. Philadelphia: Elsevier Saunders, 2006.
2 Biesecker LG. What you can learn from one gene: *GLI3*. *J Med Genet* 2006; **43**: 465–9.
3 Orioli IM. Segregation distortion in the offspring of Afro-American fathers with post-axial polydactyly. *Am J Hum Genet* 1995; **56**: 1207–11.
4 Radhakrishna U, Blouin J-L, Mehenni H *et al.* Mapping one form of autosomal dominant postaxial polydactyly type A to chromosome 7p15–q11.23 by linkage analysis. *Am J Hum Genet* 1997; **60**: 597–604.
5 Zhao H, Tian Y, Breedveld G *et al.* Postaxial polydactyly type A/B (PAP-A/B) is linked to chromosome 19p13.1–13.2 in a Chinese kindred. *Eur J Hum Genet* 2002; **10**: 162–6.
6 Goodman FR, Majewski F, Collins AL, Scambler PJ. A 117-kb microdeletion removing HOXD9-HOXD13 and EVX2 causes synpolydactyly. *Am J Hum Genet* 2002; **70**: 547–55.
7 Gurnett CA, Bowcock AM, Dietz FR *et al.* Two novel point mutations in the long-range SHH enhancer in three families with triphalangeal thumb and preaxial polydactyly. *Am J Med Genet* 2007; **143A**: 27–32.
8 Chung J, Nam IW, Ahn SK *et al.* Rudimentary polydactyly. *J Dermatol* 1994; **21**: 54–5.
9 Shapiro L, Juhlin EA, Brownstein MH. 'Rudimentary polydactyly'; an amputation neuroma. *Arch Dermatol* 1973; **108**: 223–5.
10 Katayama I, Maeda M, Nishioka K. Congenital ectopic nail of the fifth finger. *Br J Dermatol* 1984; **111**: 231–3.
11 Bart RS, Andrade R, Kopf AW *et al.* Acquired digital fibrokeratomas. *Arch Dermatol* 1968; **97**: 120–9.
12 Dodd JK, Jones PM, Chinn DJ *et al.* Neonatal accessory digits: a survey of practice amongst paediatricians and hand surgeons in the United Kingdom. *Acta Paediatr* 2004; **93**: 200–4.

Supernumerary nipples

Synonym
- Polythelia

Supernumerary areolae and nipples are very common, occurring in about 6% of a German population [1]. They usually occur along the embryonic milk line that runs from axilla to groin. There is some evidence that they are commoner in males than in females, and that they are commoner on the left side [1]. The supernumerary nipple can occur with or without an areola and glandular tissue; sometimes an areola with or without glandular tissue occurs without a nipple. About 6% of cases are familial, the condition being transmitted as an autosomal dominant trait with incomplete penetrance. There is an unresolved debate as to whether there is [2–5], or is not [6–8], an association between supernumerary nipples and urinary tract malformations. They may be associated with Becker's naevus [9], and have been reported in children with haematological disorders [10].

Supernumerary nipple often passes un-noticed, but is susceptible to hormonal changes, infection and malignancy, particularly if there is associated breast tissue.

References

1 Schmidt H. Supernumerary nipples: prevalence size, sex and side predilection: a prospective clinical study. *Eur J Pediatr* 1998; **157**: 821–3.
2 Hersh JH, Bloom AS, Cromer AD *et al.* Does a supernumerary nipple/renal defect exist? *Am J Dis Child* 1987; **141**: 989–91.
3 Matesanz R, Teruel JL, Martin FG *et al.* High incidence of supernumerary nipples in end-stage renal failure. *Nephron* 1987; **44**: 385–6.
4 Meggyessy V, Mehes K. Association of supernumerary nipples with renal anomalies. *J Pediatr* 1987; **111**: 412–3.
5 Brown J, Schwartz RA. Supernumerary nipples and renal malformations: a family study. *J Cutan Med Surg* 2004; **8**: 170–2.
6 Jojart G, Seres E. Supernumerary nipples with renal anomalies. *Int Urol Nephrol* 1994: **26**: 141–4.
7 Leung AKC. Familial supernumerary nipples. *Am J Med Genet* 1988; **31**: 631–5.
8 Grotto I, Browner-Elhanan K, Mimouni D *et al.* Occurrence of supernumerary nipples in children with kidney and urinary tract malformations. *Pediatr Dermatol* 2001; **18**: 291–4.
9 Happle R, Koopman RJ. Becker nevus syndrome and supernumerary nipples. *Am J Med Genet* 1998; **77**: 78.
10 Aslan D, Gursel T, Kaya Z. Supernumerary nipples in children with hematologic disorders. *Pediatr Hematol Oncol* 2004; **21**: 461–3.

Developmental anomalies of the umbilicus

Clinically significant developmental anomalies in the region of the umbilicus are rare but present important diagnostic problems for the dermatologist [1]. The commonest umbilical lesion in the neonate after detachment of the umbilical cord is umbilical granuloma (Fig. 18.37) [2,3]; this has become less common since the routine application of talc to the umbilical stump was discontinued. A persistent umbilical lump or discharge not responding to silver nitrate therapy may be connected to the gastrointestinal or urinary systems (Table 18.14) and requires investigation by ultrasonography or CT before considering surgical treatment [3–6]. A retrospective series of 130 umbilical lesions excised over a 10-year period at a children's hospital in Ohio showed 14 vitelline remnants, seven urachal remnants, and three cases where both were present [7].



Fig. 18.37 Umbilical granuloma.

Anomalies of the omphalomesenteric (vitelline) duct [8]

The omphalomesenteric (or vitelline) duct connects the yolk sac with the embryonic digestive tract via the umbilical cord. It is normally obliterated between the fourth and seventh weeks. Anomalies have been classified (Table 18.14) as: (i) complete patency; (ii) partial patency (enteric, intermediate or peripheral); (iii) mucosal remnant at the umbilicus (umbilical polyp); or (iv) congenital band due to a fibrous remnant of either the vitelline duct or artery which can cause intestinal obstruction.

Completely patent omphalomesenteric duct [8–10]. Complete patency is clinically apparent soon after birth. The base of the cord separates to leave a sinus or a red nodule at the opening of an umbilical enteric fistula, the faecal discharge from which irritates the surrounding skin. Very rarely, ileum may prolapse through the fistula [8,11]. Treatment of these ducts requires excision of the umbilicus and tract. Unusually the appendix may be present inside the vitelline duct and present at the umbilicus as an appendico-umbilical fistula [12] or mass [13].

Patency of the enteric portion of the duct [8]. Persisting patency of the proximal vitelline duct constitutes a Meckel's diverticulum. The duct may be patent throughout its length and closed peripherally only by skin or granulation tissue.

Patency of the mid-portion of the duct. A cyst along the course of a fibrosed vitelline cord presents as a periumbilical lump.

Patency of the peripheral portion of the duct [1,10,12]. This may present to dermatologists as a sinus 1.0–2.5 cm in depth intermittently discharging mucus, or a red, polypoid nodule (*umbilical polyp*) comprising ectopic gastrointestinal mucosa. Symptoms may be very slight, so that persistence of these lesions into adult life is not unusual. Occasionally the mucoid, serous or blood-stained discharge gives rise to troublesome dermatitis.

Omphalomesenteric umbilical polyp must be differentiated from umbilical granuloma (see above) and prolapsed urachal

Table 18.14 Developmental anomalies of the umbilicus.

	Gastrointestinal system	Urinary system
Embryonic structure	Omphalomesenteric (vitelline) duct	Urachus
Complete patency	Umbilicoenteric fistula	Patent urachus
Partial patency: enteric	Meckel's diverticulum	Vesicourachal diverticulum (normal)
Partial patency: intermediate	Vitelline cyst	Urachal cyst
Partial patency: peripheral	Umbilical sinus	Umbilical urachal sinus
Mucosal remnant at umbilicus	Umbilical polyp	Umbilical polyp
Fibrous band remnant	Fibrosed vitelline cord	Median umbilical ligament (normal)

mucosa (see below). Fibrous umbilical polyp presents in childhood, more commonly in boys, and is composed of fibrous tissue [14]. Treatment is by simple excision, having checked radiologically that there is no associated patent omphalomesenteric duct or urachus.

Anomalies of the urachus [4,5,15]
The elongation of the body stalk to form the umbilical cord obliterates the part of the allantoic cavity within it. The urachus is the residual intra-abdominal portion of the allantois, from the umbilicus to the vertex of the bladder. After birth it forms a fibrous cord, the median umbilical ligament. Persistence of epithelial remnants within the fibrous end is frequent. The urachus may remain patent throughout all or part of its length forming cysts, sinuses or fistulae leading from the umbilicus or bladder. Carcinoma may develop in a urachal remnant in adult life [16]. However, of a retrospective paediatric radiological series of 56 urachal anomalies, only 20 were symptomatic and 36 were found incidentally; nine anomalies (including two that were symptomatic) disappeared spontaneously during follow-up [15].

Complete patency of the urachus. This presents within days of birth by intermittent dribbling of urine from the umbilicus. The umbilicus may appear normal or the prolapsed distal portion of the urachal duct may form a globular nodule, covered partly by skin and partly by urachal epithelium. The surrounding skin may be irritated, but usually less severely than by a faecal fistula. The diagnosis may be confirmed radiologically. Surgical excision should be carried out as soon as possible, on account of the risk of urinary tract infection in the short term, and the risk of malignant change in adult life [16].

Partial patency of the urachus. This presents differently according to the site of the defect [4,5]. Peripheral patency (umbilical–urachal sinus) appears as a small opening or a granuloma-like lesion at the umbilicus. The lower portion of the urachus remains patent in about 33% of persons (vesico–urachal diverticulum), often involutes spontaneously and requires no treatment unless it is symptomatic [15]. Cysts are the commonest urachal anomaly and may form at any point along the course of the urachus; they may communicate with the umbilicus, the bladder or with neither. Unless they discharge their contents externally, they are seldom clinically evident unless large or infected. They may present at birth as a giant umbilical cord [5,6] or later as tender midline swellings between the umbilicus and the symphysis pubis. If they communicate with the umbilicus, the discharged contents may consist of urine or mucus, pus or blood. In one case an epithelial-lined umbilical cyst draining into the urachus was thought to have derived from the allantois [17].

Cutaneous urachal remnant must be differentiated from umbilical granuloma and omphalomesenteric polyp. Congenital clear-cell acanthoma has also occurred at this site [18].

References

1 Armstrong DK, Thornton C, Bingham EA. Infantile umbilical polyp: important diagnostic considerations. *Dermatology* 1998; **197**: 94.
2 McCallum DI, Hall GFM. Umbilical granulomas: with particular reference to talc granuloma. *Br J Dermatol* 1970; **83**: 151–5.
3 Boothroyd AE, Cudmore RE. Ultrasound of the discharging umbilicus. *Pediatr Radiol* 1996; **26**: 362–4.
4 Yu JS, Kim KW, Lee HJ *et al.* Urachal remnant diseases: spectrum of CT and US findings. *Radiographics* 2001; **21**: 451–61.
5 Carlisle EM, Mezhir JJ, Glynn L *et al.* The umbilical mass: a rare neonatal anomaly. *Pediatr Surg Int* 2007; **23**: 821–4.
6 Snyder CL. Current management of umbilical abnormalities and related anomalies. *Semin Pediatr Surg* 2007; **16**: 41–9.
7 Kranbuhl KH, Lucky AW, Warner BW *et al.* Combined omphalomesenteric and urachal remnants in an 18-month-old girl. *Pediatr Dermatol* 2007; **24**: 65–8.
8 Moore TC. Omphalomesenteric duct malformations. *Semin Pediatr Surg* 1996; **5**: 116–23.
9 Howard S, Moss PD, O'Domhnaill S. Patent vitello-intestinal duct with associated fistula and prolapse. *Lancet* 1953; **ii**: 968–9.
10 Larralde de Luna M, Cicioni V, Herrera A *et al.* Umbilical polyps. *Pediatr Dermatol* 1987; **4**: 341–3.
11 Kling S. Patent omphalomesenteric duct: a surgical emergency. *Arch Surg* 1968; **96**: 545–8.
12 Crankson SJ, Ahmed GS, Palkar V. Patent omphalomesenteric duct of the vermiform appendix in a neonate: congenital appendicoumbilical fistula. *Pediatr Surg Int* 1998; **14**: 229–30.
13 Fuijkschot J, Wijnen RM, Gerrits GP *et al.* A neonate with an intact congenital umbilical appendix: an alternative theory on the etiology of the appendicoumbilical fistula. *Pediatr Surg Int* 2006; **22**: 689–93.
14 Vargas SO. Fibrous umbilical polyp: a distinct fasciitis-like proliferation of early childhood with a marked male predominance. *Am J Surg Pathol* 2001; **25**: 1438–42.
15 Ueno T, Hashimoto H, Yokoyama H. Urachal anomalies: ultrasonography and management. *J Pediatr Surg* 2003; **38**: 1203–7.
16 Cothren C, Ferucci P, Harken AH *et al.* Urachal carcinoma: key points for the general surgeon. *Am Surg* 2002; **68**: 201–3.
17 Jona JZ. Allantoic cyst and persistent urachal-allantoic communication: a rare umbilical anomaly. *J Pediatr Surg* 1998; **33**: 1441–2.
18 Hsu HC, Yang CH, Kuo TT *et al.* Urachal duct remnant-like umbilical clear cell acanthoma in an infant: an unusual presentation and pitfall in clinical practice. *Int J Dermatol* 2007; **46**: 615–8.

Congenital sinuses and cysts of the genitoperineal raphe

Synonyms
- Mucous cysts of the penile skin
- Parameatal cysts

Median raphe cyst of the penis takes the form of a translucent or blue cyst, a tender nodule or an indurated cord at any site along the ventral midline between the urethral meatus and the anus, usually near the glans. Several theories have been proposed to explain their occurrence [1]. They may result from incomplete ventral fusion of the urethral or genital folds. Alternatively they may represent ectopic periurethral glands of Littre (*mucoid cysts*) [2,3], or separated outgrowths of urethral endoderm (*urethroid cysts*) [4].

Median raphe cysts of the penis are usually lined by pseudostratified columnar epithelium, except in the distal portion of the raphe where they are lined by squamous epithelium [5]. Ciliated epithelium, similar to that of a bronchogenic cyst, has been reported in some cases [6,7]. Melanocytes were found in the lining of multiple median raphe cysts in two unrelated Japanese boys [8]. Apocrine cystadenoma of the penis is sometimes considered to be the same as median raphe cyst, but can be distinguished by positive expression of human milk fat globulin 1, a marker for breast and apocrine tissue [9].

In most cases, median raphe cysts of the penis remain asymptomatic until after puberty [1], and present only when they become the site of staphylococcal or gonococcal infections [10]. Parameatal cysts can present because they obstruct or distort urine flow in either males [11] or females [12]. However, they may present incidentally as an asymptomatic papule at any age, in some cases as late as the seventh decade [5,13]. Surgery is indicated where infection is not controllable by antibiotics.

Mucous cysts occasionally develop in the retrorectal space and are probably derived from hind-gut remnants. These may discharge via a sinus along the posterior part of the raphe.

References

1 Nagore E, Sanchez-Motilla JM, Febrer MI, Aliaga A. Median raphe cysts of the penis: a report of five cases. *Pediatr Dermatol* 1998; **15**: 191–3.
2 Otsuka T, Ueda Y, Terauchi M, Kinoshita Y. Median raphe (parameatal) cysts of the penis. *J Urol* 1998; **159**: 1918–20.
3 Cole LA, Helwig EB. Mucoid cysts of the penile skin. *Urology* 1976; **115**: 397–9.
4 Paslin D. Urethroid cyst. *Arch Dermatol* 1983; **119**: 89–90.
5 Dini M, Baroni G, Colafranceschi M. Median raphe cyst of the penis: a report of two cases with imunohistochemical investigation. *Am J Dermatopathol* 2001; **23**: 320–4.
6 Romani J, Barnados MA, Miralles J *et al.* Median raphe cyst of the penis with ciliated cells. *J Cutan Pathol* 1995; **22**: 378–81.
7 Park CO, Chun EY, Lee JH. Median raphe cyst on the scrotum and perineum. *J Am Acad Dermatol* 2006; **55** (5 Suppl.): S114–5.
8 Urahashi J, Hara H, Yamaguchi Z, Morishima T. Pigmented median raphe cysts of the penis. *Acta Derm Venereol (Stockh)* 2000; **80**: 297–8.
9 Ohnishi T, Watanabe S. Immunohistochemical analysis of human milk fat globulin 1 and cytokeratin expression in median raphe cyst of the penis. *Clin Exp Dermatol* 2001; **26**: 88–92.
10 Sowmini CN, Vijayalakshmi K, Chellamuthiah C *et al.* Infections of the median raphe of the penis. *Br J Vener Dis* 1973; **49**: 469–74.
11 Onaran M, Tan MO, Camtosun A *et al.* Parameatal cyst of urethra: a rare congenital anomaly. *Int Urol Nephrol* 2006; **38**: 273–4.
12 Vecchioli Scaldazza C. Acute urinary retention in a young woman by parameatal urethral cyst. *Arch Ital Urol Androl* 2006; **78**: 27–8.
13 Scelwyn M. Median raphe cyst of the perineum presenting as a perianal polyp. *Pathology* 1996; **28**: 201–2.

Anomalous anal papillae

Disturbance of the normal embryological development of the anus may rarely result in the appearance of one or more polypoid projections at the anus. These may be asymptomatic, but often become complicated by ulceration, faecal retention and constipation [1]. These can be distinguished from infantile perianal pyramidal protrusion, a transient lesion in infants possibly resulting from constipation [2]. The latter is always anterior to the anus and commoner in girls than boys.

References

1 Nichamin SJ, Kallet HI. Anomalous anal papillae in infants and children. *J Pediatr* 1951; **38**: 468–71.
2 Miyamoto T, Inoue S, Hagari Y, Mihara M. Infantile perianal pyramidal protrusion with hard stool history. *Br J Dermatol* 2004; **151**: 229.

Posterior midline cutaneous lesions associated with defects of the cranium, vertebrae and spinal cord

Dorsal midline birthmarks have great significance as markers of underlying neural tube and bone defects [1].

Aetiology. Failure of the caudal neuropore to close at the end of the fourth week of intrauterine life results in neural tube defects (*spinal dysraphism*), which may also involve tissues overlying the spinal cord, including the meninges, vertebral arch (*spina bifida*) and skin. Defective closure of the rostral neuropore, also during the fourth week, may result in analogous malformations in the occipital area. Genetic factors are undoubtedly involved, the recurrence risk of <25% suggesting multiple factors. Spina bifida is commoner in infants of obese mothers, where obesity is defined as body mass index (BMI) >29 kg/m^2 [2]. Folic acid supplementation before and during pregnancy reduces the risk of open neural tube defects [3].

Classification [4]. Neural tube defects can be classified according to whether the CNS is exposed (open or closed), whether neural tissue protrudes externally, and whether their position is caudal or cranial. Of 986 children referred to a spina bifida centre in Italy, 353 had open spinal dysraphism (OSD) and 633 had closed spinal dysraphism (CSD) [4]. The most common OSD was myelomeningocele, which was always accompanied by an Arnold–Chiari (Chiari II) malformation in which the cerebellum and fourth ventricle are displaced downwards. CSD was associated with a subcutaneous lipomatous mass, dural defects and meningoceles in 18.8% of cases. CSD without a mass was classified as simple (tight filum terminale, intradural lipoma) or complex (split cord malformations, caudal regression).

Clinical features.

Open lesions. A *myelomeningocoele* is an open defect of the caudal neural tube, with neural tissue widely exposed on the surface. This presents as a skin defect over the back, bordered laterally by the unfused dorsal portions of the vertebrae, and covered by a transparent membrane, which initially leaks cerebrospinal fluid. It soon dries and ceases to leak, the fluid accumulation causing the membrane to bulge. Spinal cord function is variably impaired, and there may be hydrocephalus due to the *Arnold–Chiari malformation*. An open defect at the cranial end of the neural tube (*cranium bifidum*) may similarly be associated with protrusion of meninges (*meningocoele*) or brain tissue (*meningoencephalocoele* or *encephalocoele*). *Meningocoeles* contain dura and arachnoid, but no neural tissue. Meningocoele can be identified by transilluminescence [5].

Islands of ectopic neural tissue may persist externally as 'rests' overlying intact bone [6]. In the occipital and parietal areas of the scalp they are sometimes termed 'atretic' meningocoeles or meningoencephalocoeles [6], 'meningiomas' [7] or meningothelial hamartomas [8]. Such lesions generally take the form of domed, hairless nodules with a collar of surrounding hypertrichosis (the 'hair collar' sign) [6,8], or sometimes just a tuft of hair [9], and sometimes an associated vascular stain [8]. They are not necessarily confined to the midline. They may look like areas of membranous aplasia cutis congenita. Ependymal rests may also be found in the sacrococcygeal area [10].

A *dorsal dermal sinus* is an open tract with no protrusion of neural or meningeal tissues. It appears as a deep dimple, the bottom of which cannot be seen. It may occur at any level from the occiput downwards, most commonly in the suboccipital and

lumbosacral areas [11,12], only 1% and 10% occurring in the cervical and thoracic areas, respectively [13]. The skin around the exit is often normal but may be dimpled, hairy or the site of a lipoma, abnormal pigmentation, port-wine stain or haemangioma [14–17]. Sometimes the cutaneous anomaly obscures the ostium of the sinus. In the occipital area, the exit site near the external protruberance of the occipital bone [12] is usually hidden by hair, which may be more luxuriant than elsewhere on the scalp. This insignificant dermatological anomaly is an important marker for serious associated complications including infection, underlying CNS anomaly and inclusion tumour. Entry of infection into the subarachnoid space may lead to meningitis, cerebellar abscess [18] or spinal abscess [15]. Spina bifida, spinal dysraphism or tethered cord may coexist with dorsal dermal sinus [13]. Congenital inclusion dermoid cysts are commonly associated [18] and may cause spinal cord compression [14,19]. In one case a dermal sinus opening over the lumbar spine communicated with the posterior mediastinum [16].

Closed lesions. In *spina bifida occulta* there is a defect in the vertebral arch but the lesion is closed and not associated with protrusion of the spinal cord or meninges. The cord may be normal, malformed or hypoplastic, or it may be damaged by transfixation by a bony spicule or fibrous septum arising from a vertebra, usually in the lumbar spine (*diastematomyelia*). Occult spinal dysraphism may occur in as many as 20% of cases, but only a small percentage of these will have a significant associated neurological defect. While most common in the lumbosacral area, spina bifida occulta may occur at any level of the vertebral column [20].

Closed defects with overlying cutaneous malformations are of particular importance to dermatologists to whom they may present first [5,21]. In a series of 1449 healthy American neonates, 70 (4.8%) had dorsal cutaneous stigmata [22]. In 207 infants with midline dorsal cutaneous stigmata, there was associated occult spinal dysraphism in 16 (8%) diagnosed on ultrasonography [22]. A Spanish study [23] reported minor midline dorsal cutaneous lesions in 7.2% of 2010 neonates, and of these 8% had underlying lesions on ultrasound examination, most commonly dermoid sinus. A retrospective French study of 54 children with congenital midline lumbosacral cutaneous lesions investigated by magnetic resonance imaging or ultrasound showed occult spinal dysraphism in three of 36 patients with an isolated lesion and 11 of 18 patients with two or more different skin lesions [1]. In about 50% of cases of spina bifida occulta there is an overlying cutaneous abnormality [11,24–26]. Cutaneous anomalies reported include dermal dimple or sinus, deviation of the gluteal cleft, lipoma [26,27], a tuft of long, soft, silky hair (often called a *faun-tail*) [28], small areas of atrophic or hypertrophic skin, pigmented or depigmented macule, skin tag, tail-like protrusion [29,30], dermoid cyst, macular vascular stain [31,32], 'twin' naevus of vascular stain and naevus anaemicus [33] and aplasia cutis congenita [34,35]. Infantile haemangioma [36,37] can be associated with tethered cord and other anomalies, in the so-called SACRAL [38] or PELVIS [39] syndrome, but the literature is confused by use of the term 'haemangioma' for macular capillary malformations [40,41]. Solitary haemangioma (strawberry naevus) may not be a marker of spinal dysraphism [42] but sometimes coexists with dermal sinus tract and associated haemangioma of the spinal cord [17]. Spinal lipoma is the commonest anomaly underlying a cutaneous mass lesion [5]. A *lipomyelomeningocoele* is a subcutaneous lipoma extending through the bony defect to the dura and attached to the cord. An association between cockade naevi at various body sites and spinal dysraphism has been suggested [43]. Rarely, intradermal ectopic renal tissue (nephrogenic rest) overlies spinal dysraphism [44]. There is some correlation between specific skin lesions and the nature of the underlying anomaly [5], but no clear rules [40].

Even without any bony defect, a dorsal midline anomaly may overlie a spinal abnormality, for example tethered cord with lumbosacral haemangioma, and vascular malformation of the spinal cord with an overlying port-wine stain (Cobb's syndrome).

A variety of other tumours and cysts, representing residual nonregressed distal cord and associated tissues, may occur in the retrorectal space, or subcutaneously over the sacrum [45,46]. They include hamartomas [47], teratomas [48], lipomas [27], ependymomas [10,49] and vestigial tails largely composed of adipose tissue [30,50,51]. Non-neoplastic perirectal inflammatory conditions and giant cell tumours of the sacrum also occur. These may occasionally be associated with overlying cutaneous lesions such as skin tags and epidermal naevi [24].

About 4% of all children have deep sacrococcygeal dimples and pits, or congenital pilonidal sinuses [52,53]. In the absence of other cutaneous anomalies or neurological signs such lesions within the gluteal cleft require no investigation [22,54]. Two patients with plexiform neurofibroma or mastocytoma overlying the lumbosacral spine did not have any underlying anomaly [55]. Collagenoma was found overlying occult spinal dysraphism in a child who also had lumosacral hypertrichosis and a sacral dimple [56], but has not been reported as an independent marker. However, a giant lumbosacral shagreen patch was associated with spina bifida occulta in a child with tuberous sclerosis and scoliosis [57]. An association of spina bifida with three pilomatricomas on the left side of the body was probably coincidental [58].

Diagnosis of occult spinal dysraphism. The likelihood of a spinal defect underlying a posterior midline skin lesion depends, firstly, on age at presentation; a neurologically normal child or adult is unlikely to have a functionally significant spinal defect but might still have a sinus with risk of infection. Secondly, it depends on the nature of the defect; small postanal dimples are very common and those <5 mm diameter or <2.5 cm from the anus are usually uncomplicated. It has been argued that ultrasound examination of such minor lesions only heightens parental anxiety unnecessarily [59]. True sinuses are more likely above the gluteal cleft. The following midline dorsal lesions warrant investigation: atypical dimples (>5 mm diameter or >2.5 cm from the anus), sinuses, masses, sacral hypertrichosis, two or more skin abnormalities, haemangioma, port-wine stain, and sacral telangiectasia even in an infant with an obvious naevus flammeus in the usual glabellar and occipital sites [22,32,40,60]. Ultrasound [61] or X-ray of the spine may be sufficient in the absence of a history of meningitis or neurological impairment. Ultrasound is most useful in neonates up to 3–4 months of age, before the posterior spinous elements ossify [23,59,61]. MRI is the investigation of choice for any suspicious lesions, allowing visualization of the tract and its termina-

tion as well as spinal anomalies and tumours compressing the cord [13,62].

Treatment. The treatment of large and open defects is beyond the scope of this book. Suspected dorsal dermal sinus should be investigated preoperatively with MRI to see whether it connects with the subarachnoid space. Probing and sinography are inadvisable and may lead to meningitis. Usually, no further action is required for asymptomatic single lesions in the lumbosacral area noted in infancy if the plain spine X-ray is normal. However, any suggestion of neurological deficit should be investigated with a spinal MRI.

References

1 Guggisberg D, Hadj-Rabia S, Viney C *et al.* Skin markers of occult spinal dysraphism in children: a review of 54 cases. *Arch Dermatol* 2004; **140**: 1109–15.
2 Shaw GM, Todoroff K, Finnell RH, Lammer EJ. Spina bifida phenotypes in infants or fetuses of obese mothers. *Teratology* 2000; **61**: 376–81.
3 Ray JG, Meier C, Vermeulen MJ *et al.* Association of neural tube defects and folic acid food fortification in Canada. *Lancet* 2002; **360**: 2047–8.
4 Tortori-Donati P, Rossi A, Cama A. Spinal dysraphism: a review of neuroradiological features with embryological correlations and proposal for a new classification. *Neuroradiology* 2000; **42**: 471–91.
5 Schropp C, Sörensen N, Collmann H, Krauss J. Cutaneous lesions in occult spinal dysraphism–correlation with intraspinal findings. *Childs Nerv Syst* 2006; **22**: 125–31.
6 Drolet BA, Clowry LA, McTigue MK, Esterly NB. The hair collar sign: a marker for cranial dysraphism. *Pediatrics* 1995; **96**: 309–13.
7 Sibley DA, Cooper PH. Rudimentary meningocoele: a variant of 'primary cutaneous meningioma'. *J Cutan Pathol* 1989; **16**: 72–80.
8 Herron MD, Coffin CM, Vanderhooft SL. Vascular stains and hair collar sign associated with congenital anomalies of the scalp. *Pediatr Dermatol* 2005; **22**: 200–5.
9 Khallouf R, Fetissof F, Machet MC *et al.* Sequestered meningocele of the scalp: diagnostic value of hair anomalies. *Pediatr Dermatol* 1994; **11**: 315–8.
10 Bale PM. Ependymal rests and subcutaneous sacrococcygeal ependymoma. *Pathology* 1980; **12**: 237–43.
11 Powell KR, Cherry JD, Hougen TJ *et al.* A prospective search for congenital dermal abnormalities of the craniospinal axis. *J Pediatr* 1975; **87**: 744–50.
12 Soto-Ares G, Vinchon M, Delmaire C *et al.* Report of eight cases of occipital dermal sinus: an update and MRI findings. *Neuropediatrics* 2001; **32**: 153–8.
13 Ackerman LL, Menezes AH, Follett KA. Cervical and thoracic dermal sinus tracts. A case series and review of the literature. *Pediatr Neurosurg* 2002; **37**: 137–47.
14 Lee JK, Kim JH, Kim JS *et al.* Cervical dermal sinus associated with dermoid cyst. *Childs Nerv Syst* 2001; **17**: 491–3.
15 Hung PC, Wang HS, Wu CT *et al.* Spinal intramedullary abscess with an epidermoid secondary to a dermal sinus. *Pediatr Neurol* 2007; **37**: 144–7.
16 Tubbs RS, Frykman PK, Harmon CM *et al.* An unusual sequelae of an infected persistent dermal sinus tract. *Childs Nerv Syst* 2007; **23**: 569–71.
17 Karikari IO, Selznick LA, Cummings TJ, George TM. Spinal capillary hemangioma in infants: report of two cases and review of the literature. *Pediatr Neurosurg* 2007; **43**: 125–9.
18 Akhaddar A, Jiddane M, Chakir N *et al.* Cerebellar abscesses secondary to occipital dermoid cyst with dermal sinus: case report. *Surg Neurol* 2002; **58**: 266–70.
19 Matson DD, Ingraham FD. Intracranial complications of congenital dermal sinuses. *Pediatrics* 1951; **8**: 463–74.
20 James CCM, Lassman LP. Spinal dysraphism: an orthopaedic syndrome in children accompanying occult forms. *Arch Dis Child* 1960; **35**: 315–27.
21 Antony FC, Holden CA. Diffuse hypertrichosis and faun-tail naevus as cutaneous markers of spinal dysraphism. *Clin Exp Dermatol* 2002; **27**: 645–8.
22 Kriss VM, Desai NS. Occult spinal dysraphism in neonates: assessment of high-risk cutaneous stigmata on sonography. *AJR Am J Roentgenol* 1998; **171**: 1687–92.
23 Henriques JG, Pianetti G, Henriques KS *et al.* Minor skin lesions as markers of occult spinal dysraphisms–prospective study. *Surg Neurol* 2005; **63** (Suppl. 1): S8–12.
24 Harrist TJ, Gang DL, Kleinman GM *et al.* Unusual sacrococcygeal embryologic malformations with cutaneous manifestations. *Arch Dermatol* 1982; **118**: 643–8.
25 Eid K, Hochberg J, Saunders DE. Skin abnormalities of the back in diastematomyelia. *Plast Reconstr Surg* 1982; **63**: 534–9.
26 Tavafoghi V, Ghandchi A, Hambrick GW *et al.* Cutaneous signs of spinal dysraphism: report of a patient with a tail-like lipoma and review of 200 cases in the literature. *Arch Dermatol* 1978; **114**: 573–7.
27 Colak A, Tahta K, Ozcan DE *et al.* Congenital lumbosacral lipomas presenting as a form of occult spinal dysraphism. *Zentralbl Neurochir* 1992; **53**: 15–9.
28 Thursfield WRR, Aitken Ross A. Faun tail (sacral hirsuties) and diastematomyelia. *Br J Dermatol* 1961; **73**: 328–36.
29 Miyamoto T, Hagari S, Mihara M, Hagari Y, Shimao S. Tail-like protrusion on the nape with cervical spina bifida. *Arch Dermatol* 1993; **129**: 918–9.
30 Lin PJ, Chang YT, Tseng HI *et al.* Human tail and myelomeningocele. *Pediatr Neurosurg* 2007; **43**: 334–7.
31 Enjolras O, Boukobza M, Jdid R. Cervical occult spinal dysraphism: MRI findings and the value of a vascular birthmark. *Pediatr Dermatol* 1995; **12**: 256–9.
32 Boyvat A, Yazar T, Ekmekci P, Gurgey E. Lumbosacral vascular malformation: a hallmark for occult spinal dysraphism. *Dermatology* 2000; **201**: 374–6.
33 Tatli MM, Kumral A, Duman N *et al.* An unusual cutaneous lesion as the presenting sign of spinal dysraphism in a preterm infant. *Pediatr Dermatol* 2004; **21**: 664–6.
34 Higginbottom MC, Jones KL, James HE *et al.* Aplasia cutis congenita: a cutaneous marker of occult spinal dysraphism. *J Pediatr* 1980; **96**: 687–9.
35 Izci Y, Gönül M, Secer HI, Gönül E. Aplasia cutis congenita: a rare cutaneous sign of split cord malformations. *Int J Dermatol* 2007; **46**: 1031–5.
36 Albright AL, Gartner JC, Wiener ES. Lumbar cutaneous hemangiomas as indicators of tethered spinal cords. *Pediatrics* 1989; **83**: 977–80.
37 Goldberg NS, Hebert AA, Esterly NB. Sacral hemangiomas and multiple congenital abnormalities. *Arch Dermatol* 1986; **122**: 684–7.
38 Stockman A, Boralevi F, Taïeb A, Léauté-Labrèze C. SACRAL syndrome: spinal dysraphism, anogenital, cutaneous, renal and urologic anomalies, associated with an angioma of lumbosacral localization. *Dermatology* 2007; **214**: 40–5.
39 Girard C, Bigorre M, Guillot B, Bessis D. PELVIS Syndrome. *Arch Dermatol* 2006; **142**: 884–8.
40 Drolet BA, Boudreau C. When good is not good enough: the predictive value of cutaneous lesions of the lumbosacral region for occult spinal dysraphism. *Arch Dermatol* 2004; **140**: 1153–5.
41 Tubbs RS, Wellons JC 3rd, Iskandar BJ, Oakes WJ. Isolated flat capillary midline lumbosacral hemangiomas as indicators of occult spinal dysraphism. *J Neurosurg* 2004; **100** (Suppl. 2 Pediatrics): 86–9.
42 Allen RM, Sandquist MA, Piatt JH Jr, Selden NR. Ultrasonographic screening in infants with isolated spinal strawberry nevi. *J Neurosurg* 2003; **98** (Suppl. 3): 247–50.
43 Capella GL, Altomare G. Cockade nevi and spinal dysraphism. *Int J Dermatol* 2000; **39**: 318–20.
44 Horenstein MG, Manci EA, Walker AB, Dehner LP. Lumbosacral ectopic nephrogenic rest unassociated with spinal dysraphism. *Am J Surg Pathol* 2004; **28**: 1389–92.
45 Lemire RJ, Graham CB, Beckwith JB. Skin-covered sacrococcygeal masses in infants and children. *J Pediatr* 1971; **79**: 948–54.
46 Mallory FB. Sacrococcygeal dimples, sinuses and cysts. *Am J Med Sci* 1982; **103**: 263–73.
47 Tibbs P, James H, Rorke L *et al.* Midline hamartomas masquerading as meningomyelocoeles or teratomas in the newborn infant. *J Pediatr* 1976; **89**: 928–33.
48 Pantoja E, Rodriguez-Ibanez I. Sacrococcygeal dermoids and teratomas: historical review. *Am J Surg* 1976; **132**: 377–83.
49 Vagaiwala MR, Robinson JS, Galicich JH *et al.* Metastasizing ependymoma of the sacrococcygeal region: case report and review. *Cancer* 1979; **44**: 326–33.
50 Svatek M, Stevens S, Ment LR. Caudal appendage in a full-term infant. *Curr Opin Pediatr* 1998; **10**: 635–9.
51 Lu FL, Wang PJ, Teng RJ, Yau KI. The human tail. *Pediatr Neurol* 1998; **19**: 230–3.
52 Haworth JD, Zachary RB. Congenital dermal sinuses in children: their relation to pilonidal sinuses. *Lancet* 1955; **ii**: 10–4.

53 Lewin RA. Pilonidal sinus of infancy. *Pediatrics* 1965; **35**: 795–7.
54 Weprin BE, Oakes WJ. Coccygeal pits. *Pediatrics* 2000; **105**: E69.
55 Martínez-Lage JF, Niguez BF, Pérez-Espejo MA *et al.* Midline cutaneous lumbosacral lesions: not always a sign of occult spinal dysraphism. *Childs Nerv Syst* 2006; **22**: 623–7.
56 Senayli A, Sezer E, Sezer T *et al.* Coexistence of sacral dimple, solitary collagenoma and mid-dorsal hypertrichosis in a child with occult spinal dysraphism. *Br J Dermatol* 2007; **156**: 1065–6.
57 Thappa DM, Jeevankumar B, Karthikeyan K *et al.* Giant shagreen patch associated with spina bifida occulta in tuberous sclerosis. *Pediatr Dermatol* 2003; **20**: 453–4.
58 Pielop JA, Metry D. Multiple pilomatricomas in association with spina bifida. *Pediatr Dermatol* 2005; **22**: 178–9.
59 Szyszko TA, Watson M. The value of ultrasonographic examination of the lumbar spine in infants with specific reference to cutaneous markers of occult spinal dysraphism. *Clin Radiol* 2005; **60**: 935.
60 Drolet B. Birthmarks to worry about. Cutaneous markers of dysraphism. *Dermatol Clin* 1998; **16**: 447–53.
61 Dick EA, Patel K, Owens CM, De Bruyn R. Spinal ultrasound in infants. *Br J Radiol* 2002; **75**: 384–92.
62 Tortori-Donati P, Rossi A, Biancheri R, Cama A. Magnetic resonance imaging of spinal dysraphism. *Top Magn Reson Imaging* 2001; **12**: 375–409.

Congenital absence of skin

Synonym
- Aplasia cutis congenita

The term 'aplasia cutis congenita' implies a failure of skin development, while the broader term 'congenital absence of skin' includes situations where the skin developed but has subsequently been lost. The appearance at birth is extremely variable, in terms of site, extent, depth, and degree of healing and scarring, and there are probably many different causes [1–3]. From careful review of the literature, a number of distinctive clinical disorders have emerged, many of which are genetic [2–5]. Frieden's classification has proved helpful [2] and a modified version will be used here. The term 'congenital absence of skin' is preferable to 'aplasia cutis' for Frieden types 5, 6 and 8, where skin was probably present at an early stage but was subsequently damaged and lost.

Few histological descriptions are available [1,6]. The epidermis is absent, and usually the dermis. Where the dermis remains, the connective tissue lacks appendages and elastic fibres. The subcutaneous fat may also be partly or wholly missing and there may be an underlying skull and dural defect. Where re-epithelialization has occurred the epidermis is flat, characteristically lacking appendages [7,8]; hypertrophic scarring may also occur [9].

References

1 Demmel U. Clinical aspects of congenital skin defects. *Eur J Pediatr* 1975; **121**: 21–50.
2 Frieden IJ. Aplasia cutis congenita: a clinical review and proposal for classification. *J Am Acad Dermatol* 1986; **14**: 646–60.
3 Moss C. Syndromes affecting the skin and mucosa. In: Hennekam R, Allanson J, Krantz I, eds. *Gorlin's Syndromes of the Head and Neck*, 5th edn. Oxford: Oxford University Press, 2009: in press.
4 Sybert VP. Aplasia cutis congenita: a report of 12 new cases and review of the literature. *Pediatr Dermatol* 1985; **3**: 1–14.
5 Evers ME, Steijlen PM, Hamel BC. Aplasia cutis congenita and associated disorders: an update. *Clin Genet* 1995; **47**: 295–301.
6 Walker JC, Koenig JA, Irwin L *et al.* Congenital absence of skin (aplasia cutis congenita). *Plast Reconstr Surg* 1960; **26**: 209–18.
7 Farmer AW, Maxmen MD. Congenital absence of skin. *Plast Reconstr Surg* 1960; **25**: 291–7.
8 Scott FP. Congenital scalp defects. *Dermatologica* 1967; **135**: 84–9.
9 Moschella SL. Congenital defects of scalp with keloid formation: cousins show similar defects. *Arch Dermatol* 1962; **86**: 63–4.

Type 1: non-syndromic aplasia cutis congenita of the scalp

Non-syndromic aplasia cutis congenita of the scalp is the commonest pattern of congenital absence of skin. It sometimes shows autosomal dominant inheritance [1–9] with reports of concordant [10,11] and discordant [12] monozygotic twins. The usual position at or adjacent to the parietal hair whorl may be explained by this being the site of maximum scalp tension during the period of rapid brain growth from the 10th to the 18th week of gestation [7].

About 80% of all lesions of congenital absence of skin occur on the scalp [7,13]. Scalp lesions are single in about 70% of cases, double in about 20% and triple in about 5%. Lesions vary enormously in diameter (from 0.5 to over 10.0 cm), shape and depth. They may initially appear deeply ulcerated, superficially eroded, scarred or bullous, and sometimes heal with hypertrophic scarring [5,14]. The larger lesions are often the deeper ones, and may extend to the dura or even to the meninges [15–17]. Such deep lesions may be associated with haemorrhage, sagittal sinus thrombosis or meningitis [16,18–20]. Up to one-third of cases involve the underlying bone [6,9,17,21]. Locally dilated scalp veins reported in several cases [11,17,22,23] suggest that the scalp defect may result from a vascular developmental abnormality [23,24]. An isolated patch of congenital absence of scalp skin is often mistakenly attributed to birth trauma, particularly from fetal scalp electrodes [25].

Lesions of aplasia cutis congenita surrounded by a zone of hypertrichosis, the so-called hair-collar sign, particularly those with a bullous appearance, may be clinically and histologically indistinguishable from atretic meningocoele in which rests of neural tissue are left on the outside of the intact cranium [26,27].

Severe aplasia cutis congenita of the scalp regenerates spontaneously but has also been repaired with engineered skin [28] and bone grafts.

References

1 Cutlip BD, Cryan DM, Vineyard WR. Congenital scalp defects in mother and child. *Am J Dis Child* 1967; **113**: 597–9.
2 Fisher M, Schneider R. Aplasia cutis congenita in three successive generations. *Arch Dermatol* 1973; **108**: 252–3.
3 Fukamizu H, Matsumoto K, Inoue K *et al.* Familial occurrence of aplasia cutis congenita. *J Dermatol Surg Oncol* 1982; **8**: 1068–70.
4 Guillen PS-P, Pichardo AR, Martinez FC. Aplasia cutis congenita. *J Am Acad Dermatol* 1985; **13**: 429–33.
5 Lassman LP, Sims DG. Congenital midline scalp and skull defect. *Arch Dis Child* 1975; **50**: 958–60.
6 Pap GS. Congenital defect of scalp and skull in three generations of one family. *Plast Reconstr Surg* 1970; **46**: 194–6.
7 Stephan MJ, Smith DW, Ponzi JW *et al.* Origin of scalp vertex aplasia cutis. *J Pediatr* 1982; **101**: 850–3.
8 Gucuyener K, Tunaoglu FS, Demirsoy S *et al.* Aplasia cutis congenita of the scalp without other defects in three siblings. *Acta Paediatr* 1992; **81**: 182.
9 Baselga E, Torrelo A, Drolet BA *et al.* Familial nonmembranous aplasia cutis of the scalp. *Pediatr Dermatol* 2005; **22**: 213–7.
10 Hodgman JE, Mathies AW, Levan NE. Congenital scalp defects in twin sisters. *Am J Dis Child* 1965; **110**: 293–5.

11 Kosnik EJ, Sayers MP. Congenital scalp defects: aplasia cutis congenita. *J Neurosurg* 1975; **42**: 32–6.
12 Yagupsky P, Reuveni H, Karplus M *et al.* Aplasia cutis congenita in one of monozygotic twins. *Pediatr Dermatol* 1986; **3**: 403–5.
13 Frieden IJ. Aplasia cutis congenita: a clinical review and proposal for classification. *J Am Acad Dermatol* 1986; **14**: 646–60.
14 Moschella SL. Congenital defects of scalp with keloid formation: cousins show similar defects. *Arch Dermatol* 1962; **86**: 63–4.
15 Argenta LC, Dingman RO. Total reconstruction of aplasia cutis congenita involving scalp, skull and dura. *Plast Reconstr Surg* 1986; **77**: 650–3.
16 Glasson DW, Duncan GM. Aplasia cutis congenita: delayed closure complicated by massive haemorrhage. *Plast Reconstr Surg* 1985; **75**: 423–5.
17 Vinocur CD, Weintraub WH, Wilensky RJ *et al.* Surgical management of aplasia cutis congenita. *Arch Surg* 1976; **111**: 1160–4.
18 Abbott R, Cutting CB, Wisoff JH *et al.* Aplasia cutis congenita of the scalp; issues in its management. *Pediatr Neurosurg* 1991–2; **17**: 182–4.
19 Peer LA, van Duyn J. Congenital defect of the scalp: report of a case with fatal termination. *Plast Reconstr Surg* 1948; **3**: 722–6.
20 Schneider BM, Berg RA, Kaplan AM. Aplasia cutis congenita complicated by sagittal sinus thrombosis. *Pediatrics* 1980; **66**: 948–50.
21 Muakkassa KF, King RB, Stark DB. Nonsurgical approach to congenital scalp and skull defects. *J Neurosurg* 1982; **56**: 711–5.
22 McMurray BR, Martin LW, Dignan PStJ *et al.* Hereditary aplasia cutis congenita and associated defects: three instances in one family and a survey of reported cases. *Clin Pediatr (Phila)* 1977; **16**: 610–4.
23 Resnik SS, Koblenzer PJ, Pitts FW. Congenital absence of the scalp with associated vascular anomaly. *Clin Pediatr (Phila)* 1965; **4**: 322–4.
24 Vasconez LO. Congenital defect of the skull and scalp due to an arteriovenous malformation. *Plast Reconstr Surg* 1973; **51**: 692–5.
25 Dunn PM. Litigation over congenital scalp defects. *Lancet* 1992; **339**: 440.
26 Drolet BA, Prendiville J, Golden J *et al.* 'Membranous aplasia cutis' with hair collars: congenital absence of skin or neuroectodermal defect? *Arch Dermatol* 1995; **131**: 1427–31.
27 Colon-Fontanez F, Fallon Friedlander S, Newbury R, Eichenfield LF. Bullous aplasia cutis congenita. *J Am Acad Dermatol* 2003; **48** (Suppl. 5): S95–8.
28 Donati V, Arena S, Capilli G *et al.* Reparation of a severe case of aplasia cutis congenita with engineered skin. *Biol Neonate* 2001; **80**: 273–6.

Type 2: congenital absence of skin on the scalp with limb reduction abnormalities

Synonym
- Adams–Oliver syndrome

Adams–Oliver syndrome is characterized by congenital midline scalp defects, asymmetrical distal limb reduction anomalies, cutis marmorata and cardiovascular anomalies. It is usually inherited as an autosomal dominant trait with highly variable penetrance and expression [1,2]. Autosomal recessive inheritance has also been described [3,4]. Many isolated cases have been reported [5]. The gene has not yet been identified [6].

Typically, the skin lesions are solitary or multiple bald scars near the vertex. They vary in diameter, from about 0.5 to 10.0 cm, larger lesions being disproportionately common. The lesions also vary considerably in depth, sometimes penetrating the skull to the dura. Dilated scalp veins [1] are frequently associated, and may be the sole abnormality [7]. Intellect is normal [1].

Hypoplastic or absent distal phalanges are the most common limb anomalies, but defects range from hypoplastic nails to absent hands or lower legs [1,5]. The lower limbs are generally more severely affected than the upper limbs.

Persistent cutis marmorata is reported in about 12% of cases [1,7,8] and may be the sole feature in an obligate gene carrier. Congenital heart disease affects about 8% of cases [9], and pulmonary hypertension occurs in some families [10,11]. A vascular aetiology seems likely [1,10–13], and an abnormality of pericyte recruitment has been postulated [11].

Incomplete forms of Adams–Oliver syndrome frequently occur, and any neonate presenting with a large area of scalp aplasia cutis congenita should be examined carefully for the associated anomalies, which may be limited to cutis marmorata [14] or coarctation of the aorta [2]. Sometimes there are no associated anomalies, only a familial aggregation of diverse cardiovascular anomalies [2]. Antenatal diagnosis has been achieved by ultrasound [4]. Adams–Oliver syndrome must be differentiated from focal dermal hypoplasia, trisomy 13 and the amniotic band sequence. Congenital absence of skin with split hand deformities [5,15], and congenital absence of skin with postaxial polydactyly [16,17] probably represent distinct genetic disorders.

Spontaneous osseous regeneration has been reported in a patient with a large skull and scalp defect due to the Adams–Oliver syndrome [18].

References

1 Whitley CB, Gorlin RJ. Adams–Oliver syndrome revisited. *Am J Med Genet* 1991; **40**: 319–26.
2 Heras Mulero C, Bartralot Soler R, Rodríguez-Cano L *et al.* Aplasia cutis associated with coarctation of the aorta: could this be an incomplete form of Adams-Oliver syndrome? *Br J Dermatol* 2007; **157**: 836–7.
3 Temtamy SA, Aglan MS, Ashour AM, Zaki MS. Adams–Oliver syndrome: further evidence of an autosomal recessive variant. *Clin Dysmorphol* 2007; **16**: 141–9.
4 Becker R, Kunze J, Horn D *et al.* Autosomal recessive type of Adams–Oliver syndrome: prenatal diagnosis. *Ultrasound Obstet Gynecol* 2002; **20**: 506–10.
5 Sybert VP. Aplasia cutis congenita: a report of 12 new cases and review of the literature. *Pediatr Dermatol* 1985; **3**: 1–14.
6 Verdyck P, Blaumeiser B, Holder-Espinasse M *et al.* Adams–Oliver syndrome: clinical description of a four-generation family and exclusion of five candidate genes. *Clin Genet* 2006; **69**: 86–92.
7 Toriello HV, Graff RG, Florentine MF *et al.* Scalp and limb defects with cutis marmorata telangiectatica congenita: Adams–Oliver syndrome? *Am J Med Genet* 1988; **29**: 269–76.
8 Frank RA, Frosch PJ. Adams–Oliver syndrome: cutis marmorata telangiectatica congenita with multiple anomalies. *Dermatology* 1993; **187**: 205–8.
9 Farrell SA, Warda LJ, LaFlair P, Szymonowicz W. Adams–Oliver syndrome: a case with juvenile chronic myelogenous leukemia and chylothorax. *Am J Med Genet* 1993; **47**: 1175–9.
10 Maniscalco M, Zedda A, Faraone S *et al.* Association of Adams-Oliver syndrome with pulmonary arterio-venous malformation in the same family: a further support to the vascular hypothesis. *Am J Med Genet A* 2005; **136**: 269–74.
11 Patel MS, Taylor GP, Bharya S *et al.* Abnormal pericyte recruitment as a cause for pulmonary hypertension in Adams-Oliver syndrome. *Am J Med Genet A* 2004; **129**: 294–9.
12 Swartz EN, Sanatani S, Sandor GG, Schreiber RA. Vascular abnormalities in Adams-Oliver syndrome: cause or effect? *Am J Med Genet* 1999; **82**: 49–52.
13 Piazza AJ, Blackston D, Sola A. A case of Adams-Oliver syndrome with associated brain and pulmonary involvement: further evidence of vascular pathology? *Am J Med Genet A* 2004; **130**: 172–5.
14 South DA, Jacobs AH. Cutis marmorata telangiectatica congenita (congenital generalized phlebectasia). *J Pediatr* 1978; **93**: 944–9.
15 Wilson WG, Harcus SJ. Variable expression of a congenital scalp defects/limb malformations syndrome in three generations. *Birth Defects Orig Artic Ser* 1982; **18**: 123–8.
16 Buttiens M, Fryns JP, Jonckheere P *et al.* Scalp defect associated with postaxial polydactyly: confirmation of a distinct entity with autosomal dominant inheritance. *Hum Genet* 1985; **71**: 86–8.
17 Fryns JP. Congenital scalp defects with distal limb reduction anomalies. *J Med Genet* 1987; **24**: 493–6.

18 Rhee ST, Colville C, Buchman SR, Muraszko K. Complete osseous regeneration of a large skull defect in a patient with cutis aplasia: a conservative approach. *J Craniofac Surg* 2002; **13**: 497–500.

Type 3: congenital absence of skin on the scalp with epidermal naevi

Sebaceous naevi occasionally occur next to areas of congenital absence of skin in the scalp [1]. Multiple areas of bullous congenital absence of skin have also been reported in a child with extensive unilateral verrucous epidermal naevi on the trunk and limbs [2].

Some of these cases have had associated either ophthalmological or neurological abnormalities identical to those seen in the epidermal naevus syndrome [1,3–5]. Happle and Konig suggest that the co-occurrence of aplasia cutis congenita and nevus sebaceous is a twin spot phenomenon [4], as is the association of aplasia cutis congenita with a fatty scalp naevus (naevus psiloliparus) in encephalocraniocutaneous lipomatosis [6].

References

1 Frieden I, Golabi M. Aplasia cutis congenita and the epidermal nevus syndrome: a previously unrecognized association. *Clin Res* 1985; **33**: 130.
2 Fryburg JS, Greer KE. Epidermal naevi and bullous aplasia cutis congenita in the newborn. *J Med Genet* 1993; **30**: 962–3.
3 Hogler W, Sidoroff A, Weber F *et al.* Aplasia cutis congenita, uvula bifida and bilateral retinal dystrophy in a girl with naevus sebaceous syndrome. *Br J Dermatol* 1999; **140**: 542–3.
4 Happle R, Konig A. Didymosis aplasticosebacea: coexistence of aplasia cutis congenita and nevus sebaceus may be explained as a twin spot phenomenon. *Dermatology* 2001; **202**: 246–8.
5 Demerdjieva Z, Kavaklieva S, Tsankov N. Epidermal nevus syndrome and didymosis aplasticosebacea. *Pediatr Dermatol* 2007; **24**: 514–6.
6 Torrelo A, Boente Mdel C, Nieto O *et al.* Nevus psiloliparus and aplasia cutis: a further possible example of didymosis. *Pediatr Dermatol* 2005; **22**: 206–9.

Type 4: congenital absence of skin overlying developmental malformations

Congenital absence of skin naturally occurs over large, open defects of the body wall such as spina bifida, meningomyelocoele and gastroschisis. However, it may also overlie smaller herniations or extracranial 'rests' of neural tissue, where it is sometimes the presenting feature. In the occipital and parietal areas of the scalp, heterotopic neural and/or meningeal tissue appears as a domed, hairless nodule with a collar of surrounding hypertrichosis (the 'hair collar' sign) [1,2]. The surface of the lesion is typically translucent and 'membranous' [3] and this diagnosis should always be considered in cases of 'membranous aplasia cutis congenita'. The lesion may be flat or depressed rather than raised, and will not always be sited in the midline. There may be an associated port-wine stain [1,4]. Ultrasound examination is essential to establish whether there is an underlying bony defect (as in meningoencephalocoele) or not (as in 'sequestrated' or 'atretic' meningocoele).

The skin is also characteristically absent or hypoplastic over a number of other developmental malformations, including spinal dysraphism [5,6], omphalocoele and sternal clefts [7–9]. Congenital absence of skin has also been reported over other cranial [10] and intracranial developmental anomalies, including arteriovenous fistula [11], leptomeningeal angiomatosis [12], congenital midline porencephaly [13] and cranial stenosis [14].

References

1 Drolet BA, Clowry LA, McTigue MK, Esterly NB. The hair collar sign: a marker for cranial dysraphism. *Pediatrics* 1995; **96**: 309–13.
2 Harrington BC. The hair collar sign as a marker for neural tube defects. *Pediatr Dermatol* 2007; **24**: 138–40.
3 Drolet BA, Prendiville J, Golden J *et al.* 'Membranous aplasia cutis' with hair collars: congenital absence of skin or neuroectodermal defect? *Arch Dermatol* 1995; **131**: 1427–31.
4 Herron MD, Coffin CM, Vanderhooft SL. Vascular stains and hair collar sign associated with congenital anomalies of the scalp. *Pediatr Dermatol* 2005; **22**: 200–5.
5 Higginbottom MC, Jones KL, James HE *et al.* Aplasia cutis congenita: a cutaneous marker of occult spinal dysraphism. *J Pediatr* 1980; **96**: 687–9.
6 Izci Y, Gönül M, Secer HI, Gönül E. Aplasia cutis congenita: a rare cutaneous sign of split cord malformations. *Int J Dermatol* 2007; **46**: 1031–5.
7 Firmin RK, Fragomeni LS, Lennox SC. Complete cleft sternum. *Thorax* 1980; **35**: 303–6.
8 Maeda K, Yoshimura H, Furuoka H *et al.* Congenital upper sternal cleft: report of a case. *Jpn J Pediatr Surg* 1991; **23**: 679–82.
9 Stoll C, Vivier M, Renaud R. A supraumbilical midline raphe with sternal cleft in a 47XXX woman. *Am J Med Genet* 1987; **27**: 229–31.
10 Preis S, Engelbrecht V, Lenard H-G. Aplasia cutis congenita and enlarged parietal foramina (Catlin marks) in a family. *Acta Paediatr* 1995; **84**: 701–2.
11 Singman R, Asaikar S, Hotson G, Prose NS. Aplasia cutis congenita and arteriovenous fistula. *Arch Neurol* 1990; **47**: 1255–8.
12 Pozzati E, Podovani R, Frank F *et al.* Leptomeningeal angiomatosis and aplasia congenita of the scalp. *J Neurosurg* 1983; **58**: 937–40.
13 Yokata A, Matsukado Y. Congenital midline porencephaly: a new brain malformation associated with scalp anomaly. *Childs Brain* 1979; **5**: 380–97.
14 Spear SL, Mickel JP. Simultaneous cutis aplasia congenita of the scalp and cranial stenosis. *Plast Reconstr Surg* 1983; **71**: 413–7.

Type 5: congenital absence of skin associated with fetus papyraceus

Congenital absence of skin has been observed in a number of infants whose birth was accompanied by the delivery of a *fetus papyraceus*, that is a twin or triplet that had died *in utero* during the second trimester [1–5]. In these cases, multiple, mostly symmetrical, linear or stellate areas of congenital absence of skin were present on the limbs and trunk (Fig. 18.38). Some also showed fibrous constriction bands on the limbs [1].This type of congenital absence of skin may represent cutaneous infarction due to release



Fig. 18.38 Congenital absence of skin in an infant with a stillborn twin of fetus papyraceus type.

of thromboplastin into a shared placenta after an intrauterine death [6]. Symmetry of the skin lesions is hard to explain by this mechanism. Associated hyperechogenic areas diagnosed as haematomas in the liver of one patient were thought to support the idea of a vascular aetiology [3].

The practice of selective feticide in multiple pregnancies complicated by fetal or maternal disease creates an iatrogenic fetus papyraceus. As predicted [7], there are increasing numbers of reports of aplasia cutis congenita in surviving co-twins following selective feticide. Similar skin lesions in one of surviving twins [8], and in singletons with no fetus papyraceus [9–12] might reflect *in utero* death of an unrecognized twin or triplet. In other, similar cases without mention of a twin, placental infarction has occurred [13], or the placenta has been described as pale and large [14,15].

References

1 Markman L, Sugar L, Zuker RM. Association of aplasia cutis congenita and fetus papyraceus in a triplet pregnancy. *Aust Paediatr J* 1982; **18**: 294–6.
2 Lemke RP, Machin G, Muttitt S *et al.* A case of aplasia cutis congenita in dizygotic twins. *J Perinatol* 1993; **13**: 22–7.
3 Cambiaghi S, Schiera A, Tasin L, Gelmetti C. Aplasia cutis congenita in surviving co-twins: four unrelated cases. *Pediatr Dermatol* 2001; **18**: 511–5.
4 Kelly BJ, Samolitis NJ, Xie D-L, Skidmore RA. Aplasia cutis congenita of the trunk with fetus papyraceus. *Pediatr Dermatol* 2002; **19**: 326–9.
5 Fagan LL, Harris PA, Coran AG, Cywes R. Sporadic aplasia cutis congenita. *Pediatr Surg Int* 2002; **18**: 545–7.
6 Schinzel AAGL, Smith DW, Miller JR. Monozygotic twinning and structural defects. *J Pediatr* 1979; **95**: 921–30.
7 Da-Silva SS, Fagbongbe EO. Aplasia cutis congenita in an infant of an initial triplet gestation: a case report. *Am J Perinatol* 1999; **16**: 531–5.
8 Sutton RL. Congenital defect of the skin of the newborn. *Arch Dermatol Syphilol* 1935; **31**: 855–7.
9 Harari Z, Pasmanik A, Dvoretzky I *et al.* Aplasia cutis congenita with dystrophic nail changes. *Dermatologica* 1976; **153**: 363–8.
10 Muakkassa KF, King RB, Stark DB. Nonsurgical approach to congenital scalp and skull defects. *J Neurosurg* 1982; **56**: 711–5.
11 Ruiz-Maldonado R, Tamayo L. Aplasia cutis congenita, spastic paralysis and mental retardation. *Am J Dis Child* 1974; **128**: 699–703.
12 Sharma LK. Congenital skin aplasia affecting trunk. *Arch Dis Child* 1973; **48**: 813–4.
13 Levin DL, Nolan KS, Esterly NB. Congenital absence of skin. *J Am Acad Dermatol* 1980; **2**: 203–6.
14 Munkvad JM, Nielsen AO, Asmussen T. Aplasia cutis congenita: a follow-up evaluation after 25 years. *Arch Dermatol* 1981; **117**: 232–3.
15 Dowler VB. Congenital defect of the skin in a newborn infant. *Am J Dis Child* 1932; **44**: 1279–84.

Type 6: congenital absence of skin with epidermolysis bullosa

Synonym
- Bart's syndrome

The term 'aplasia cutis congenita' is a misnomer for Type 6, which represents antenatal loss of skin rather than failure of skin development. Bart *et al.* [1] reported a dominantly inherited disorder in 26 members of a large kindred, characterized by congenital absence of skin on the lower legs, widespread blistering of skin and mucous membranes, and nail dystrophy. Further ultrastructural and genetic studies of this family confirmed dominant dystrophic epidermolysis bullosa due to a glycine substitution in type VII collagen [2,3]. We now recognize 'Bart's syndrome' as a non-specific feature of epidermolysis bullosa, not only the dominant dystrophic type, but also junctional epidermolysis bullosa (particularly the type associated with pyloric atresia) [4] and recessive EB simplex caused by plectin mutations [5]. In at least one family with dominant dystrophic epidermolysis bullosa, some affected members had 'Bart's syndrome' while others did not [6]. Where this pattern of congenital absence of skin has been reported without epidermolysis bullosa being diagnosed [7–9], it is possible that skin fragility was simply less apparent after birth than before.

The lesions usually present as extensive, well-defined, glistening, red ulcerations on the dorsum and medial aspect of the foot, often extending up the shin. They may be unilateral or, less frequently, bilateral and probably result from rubbing one shin and foot with the other heel, perhaps in response to pruritus. The idea that the lesions are determined by Blaschko's lines [10] seems less likely. Extensive aplasia cutis congenita affecting the trunk and neck has been reported in infants severely affected by junctional epidermolysis bullosa with pyloric atresia [11].

References

1 Bart BJ, Gorlin RJ, Anderson VE *et al.* Congenital localised absence of skin and associated abnormalities resembling epidermolysis bullosa: a new syndrome. *Arch Dermatol* 1966; **93**: 296–303.
2 Zelickson B, Matsumura K, Kist D, Epstein EH, Bart BJ. Bart's syndrome. Ultrastructure and genetic linkage. *Arch Dermatol* 1995; **131**: 663–8.
3 Christiano AM, Bart BJ, Epstein EH, Uitto J. Genetic basis of Bart's syndrome: a glycine substitution mutation in type VII collagen gene. *J Invest Dermatol* 1996; **106**: 778–80.
4 Morrell DS, Rubenstein DS, Briggaman RA *et al.* Congenital pyloric atresia in a newborn with extensive aplasia cutis congenita and epidermolysis bullosa simplex. *Br J Dermatol* 2000; **143**: 1342–3.
5 Charlesworth A, Gagnoux-Palacios L, Bonduelle M *et al.* Identification of a lethal form of epidermolysis bullosa simplex associated with a homozygous genetic mutation in plectin. *J Invest Dermatol* 2003; **121**: 1344–8.
6 Wakasugi S, Mizutari K, Ono T. Clinical phenotype of Bart's syndrome seen in a family with dominant dystrophic epidermoysis bullosa. *J Dermatol* 1998; **25**: 517–22.
7 Rauschkolb RR, Enriquez SI. Aplasia cutis congenita. *Arch Dermatol* 1962; **86**: 54–7.
8 Freire-Maia N, Pinheiro M, Ortega CC. Recessive aplasia cutis congenita of the limbs. *J Med Genet* 1980; **17**: 123–6.
9 Portnoy Y, Metzker A. Extraordinary aplasia cutis congenita, or a new entity? *Helv Paediatr Acta* 1981; **36**: 281–5.
10 Duran-McKinster C, Rivera-Franco A, Tamayo L *et al.* Bart syndrome: the congenital localized absence of skin may follow the lines of Blaschko. Report of six cases. *Pediatr Dermatol* 2000; **17**: 179–82.
11 Akhtar J, Batool T, Jalil S *et al.* Congenital pyloric atresia: isolated and associated with aplasia cutis congenita. *J Coll Physicians Surg Pak* 2005; **15**: 505–6.

Type 7: isolated congenital absence of skin localized to the extremities

This is a diagnosis of exclusion: a careful family history and clinical examination may reveal epidermolysis bullosa or associated anomalies characteristic of other types [1]. Type 7 congenital absence of skin may be associated with amniotic band [2] or ischaemia, as in Volkmann's ischaemic contracture [3,4].

References

1 Bigliardi PL, Braschler C, Kuhn P *et al.* Unilateral aplasia cutis congenita on the leg. *Pediatr Dermatol* 2004; **21**: 454–7.

2 Nagore E, Sánchez-Motilla JM, Febrer MI *et al.* Radius hypoplasia, radial palsy, and aplasia cutis due to amniotic band syndrome. *Pediatr Dermatol* 1999; **16**: 217–9.
3 Caouette-Laberge L, Bortoluzzi P, Egerszegi EP *et al.* Neonatal Volkmann's ischaemic contracture of the forearm: a report of five cases. *Plast Reconstr Surg* 1992; **90**: 621–8.
4 Cham PM, Drolet BA, Segura AD, Esterly NB. Congenital Volkmann ischaemic contracture: a case report and review. *Br J Dermatol* 2004; **150**: 357–63.

Type 8a: congenital absence of skin caused by specific teratogens

Several cases have been reported of congenital absence of midline scalp skin in children whose mothers took methimazole or carbimazole for treatment of hyperthyroidism during early pregnancy [1–5]. It is now regarded as highly likely that these drugs were responsible, although the risk appears to be low [3,4]. This defect was found in only one of monozygotic twins exposed to methimazole between weeks 11 and 17 [6]. Infants exposed to methimazole antenatally may have other anomalies including flared eyebrows, broad nasal bridge, choanal and oesophageal atresia, in the so-called 'methimazole embryopathy' [7]. There have been isolated reports of scalp aplasia cutis congenita following first trimester intake of the prostaglandin misoprostol, and in one case benzodiazepines [8]. Low molecular weight heparin has also been implicated [9].

References

1 Farine D, Maidman J, Rubin S, Chao S. Elevated α-fetoprotein in pregnancy complicated by aplasia cutis after exposure to methimazole. *Obstet Gynecol* 1988; **71**: 996–7.
2 Kalb RE, Grossman ME. The association of aplasia cutis congenita with therapy of maternal thyroid disease. *Pediatr Dermatol* 1986; **3**: 327–30.
3 Vogt T, Stolz W, Landthaler M. Aplasia cutis congenita after exposure to methimazole: a causal relationship? *Br J Dermatol* 1995; **133**: 994–6.
4 Diav-Citrin O, Ornoy A. Teratogen update: antithyroid drugs—methimazole, carbimazole and propylthiouracil. *Teratology* 2002; **65**: 38–44.
5 Karg E, Bereg E, Gaspar L *et al.* Aplasia cutis congenita after methimazole exposure in utero. *Pediatr Dermatol* 2004; **21**: 491–4.
6 Iwayama H, Hosono H, Yamamoto H *et al.* Aplasia cutis congenita with skull defect in a monozygotic twin after exposure to methimazole in utero. *Birth Defects Res A Clin Mol Teratol* 2007; **79**: 680–4.
7 Valdez RM, Barbero PM, Liascovich RC *et al.* Methimazole embryopathy: a contribution to defining the phenotype. *Reprod Toxicol* 2007; **23**: 253–5.
8 Martinez-Lage JF, Almagro MJ, Hernandez FL, Pozo M. Aplasia cutis congenita of the scalp. *Childs Nerv Syst* 2002; **18**: 634–7.
9 Sharif S, Hay CR, Clayton-Smith J. Aplasia cutis congenita and low molecular weight heparin. *BJOG* 2005; **112**: 256–8.

Type 8b: congenital absence of skin following intrauterine infections

Congenital absence of skin may occur in neonates with intrauterine herpes simplex infection [1–4], but is a more characteristic finding in intrauterine varicella-zoster virus (VZV) infection [5–10], where it may be associated with other features of the 'congenital varicella syndrome'. The cutaneous ulceration or scarring is unilateral and linear, usually occurring in a zosteriform distribution. Such lesions are most often a sequel to maternal chickenpox during the first or second trimester [9,10]. Confirmation of the diagnosis rests on the persistence of VZV IgG antibodies beyond 7 months of age when maternal antibodies [9,10] should have disappeared. Maternal chickenpox in the last trimester may also result in congenital ulcerations in the neonate, usually multiple and no larger than about 1 cm in diameter [11].

References

1 Harris HH, Foucar E, Anderson RD *et al.* Intrauterine herpes simplex infection resembling mechanobullous disease in a newborn infant. *J Am Acad Dermatol* 1986; **15**: 1148–55.
2 Honig PJ, Brown D. Congenital herpes simplex virus infection initially resembling epidermolysis bullosa. *J Pediatr* 1982; **101**: 958–60.
3 Tomer A, Harel A. Congenital absence of scalp skin and herpes simplex virus. *Isr J Med Sci* 1983; **19**: 950–1.
4 Sauerbrei A, Wutzler P. Herpes simplex and varicella-zoster virus infections during pregnancy: current concepts of prevention, diagnosis and therapy. Part 1: herpes simplex virus infections. *Med Microbiol Immunol* 2007; **196**: 89–94.
5 Bailie F. Aplasia cutis congenita of neck and shoulder requiring a skin graft: a case report. *Br J Plast Surg* 1983; **36**: 72–4.
6 Borzyskowski M, Harris RF, Jones RWA. The congenital varicella syndrome. *Eur J Pediatr* 1981; **137**: 335–8.
7 Essex-Cater A, Heggarty H. Fatal congenital varicella syndrome. *J Infect* 1983; **7**: 77–8.
8 Paryani SG, Arvin AM. Intrauterine infection with varicella-zoster virus after maternal varicella. *N Engl J Med* 1986; **314**: 1542–6.
9 Sauerbrei A, Wutzler P. The congenital varicella syndrome. *J Perinatol* 2000; **20**: 548–54.
10 Sauerbrei A, Wutzler P. Herpes simplex and varicella-zoster virus infections during pregnancy: current concepts of prevention, diagnosis and therapy. Part 2: Varicella-zoster virus infections. *Med Microbiol Immunol* 2007; **196**: 95–102.
11 Bai PVA, John TJ. Congenital skin ulcers following varicella in late pregnancy. *J Pediatr* 1979; **94**: 65–7.

Type 9: congenital absence of skin as a feature of malformation syndromes

This is a very heterogeneous group because congenital absence of the skin has been reported in numerous malformation syndromes, sometimes only in a single case [1,2]. The major disorders in which aplasia cutis congenita is a recognized feature are listed in Table 18.15. Those in which it is a characteristic feature include Adams–Oliver syndrome (see Type 2 above) and others described below.

Trisomy 13

Synonym
- Patau syndrome

Table 18.15 Major syndromes in which congenital absence of skin occurs.

Chromosomal disorders	Patau syndrome (trisomy 13)
	Wolf–Hirschhorn syndrome (4p-)
Autosomal dominant disorders	Adams–Oliver syndrome
	Focal facial dermal dysplasia
	Ectrodactyly, ectodermal defects, clefting (EEC) syndrome
	Ankyloblepharon, ectodermal defects, clefting (AEC) syndrome
Autosomal recessive disorders	Adams–Oliver syndrome (autosomal recessive type)
	Johanson–Blizzard syndrome
	Setleis syndrome
X-linked disorders	Goltz focal dermal dysplasia
	MIDAS syndrome
Possibly mosaic disorders	Delleman–Oorthuys (oculocerebrocutaneous) syndrome
	Epidermal naevus syndrome

Infants with this chromosomal abnormality rarely survive beyond their first year. Congenital absence of skin in the parietal or occipital scalp occurs in 38% of cases [3]. Other characteristic findings include holoprosencephaly (a developmental anomaly of the forebrain), microphthalmia, iris colobomas, cleft lip and/or palate, polydactyly, narrow and excessively convex nails, and a port-wine stain on the forehead. Interestingly, patients with mosaic trisomy 13 may present as hypomelanosis of Ito with a rather characteristic 'phylloid' pattern of hypopigmentation [4], together with mental retardation and other features of trisomy 13 syndrome. There are several pigment genes on chromosome 13 [5]; dyspigmentation has not been reported in full-blown trisomy 13, but might not have been noticed in the presence of other serious defects.

Deletion of the short arm of chromosome 4 (the 4p- syndrome)

Synonym
- Wolf–Hirschhorn syndrome

This syndrome is characterized by severe growth and mental retardation, seizures, craniofacial malformations and high childhood mortality. Congenital absence of skin in the posterior midline scalp is a frequent finding [6,7]. Other typical features include ocular hypertelorism, a beaked or broad nose, microcephaly, low-set, simple ears and pre-auricular tags or pits. Most patients have deletions involving large segments of 4p. Wolf–Hirschhorn syndrome is a contiguous gene syndrome [6,7], but exact genotype–phenotype correlations have not been established. A small critical region on 4p has been identified in patients with growth retardation and minor facial features but no aplasia cutis [6,8,9].

Focal facial dermal dysplasias

Symmetrical congenital atrophic lesions of the face resembling scars have been described under a number of different titles, including bitemporal aplasia cutis congenita, congenital ectodermal dysplasia of the face and hereditary symmetrical systemic aplastic naevi. The disorder may be isolated or associated with other facial anomalies. A review of published cases [10] suggested three distinct subgroups: (i) autosomal dominant focal facial dermal dysplasia without other facial anomalies; (ii) autosomal recessive focal facial dermal dysplasia without other facial anomalies; and (iii) focal facial dermal dysplasia with other facial anomalies (synonym Setleis' syndrome).

Autosomal dominant focal facial dermal dysplasia without other facial anomalies. A number of families have been reported in which the disorder is transmitted as an autosomal dominant trait [11–13]. The skin lesions appear to be the sole abnormality, and take the form of congenital, hairless, scarred areas on the face which are usually, but not always, oval in outline and symmetrical, and may be either hyper- or hypopigmented. These lesions may occur on the temple, or on the cheeks, where they tend to be disposed along a line that runs from the ear to the corners of the mouth. The size of the lesions is variable. There may be a surrounding rim of fine, lanugo-like hairs [14,15]. There may be a distinctly puckered appearance to the affected skin.

Histologically, there is atrophy of the dermis and subcutaneous fat, an absence of pilosebaceous follicles and eccrine glands but a normal epidermis. Striated muscle may be placed very close to the epidermis, and could be partly responsible for the occasionally reported puckering of the affected skin.

Autosomal recessive focal facial dermal dysplasia without other facial anomalies. Essentially identical skin lesions have been reported in other families in which inheritance appeared to be of autosomal recessive type [10]. There have been reports of clinically indistinguishable but sporadic cases whose pattern of inheritance is uncertain [15,16].

Focal facial dermal dysplasia with other facial anomalies (Setleis' syndrome). Since the first report by Setleis *et al.* [17], several families have been reported in which children demonstrated a leonine, aged facies with absent or abnormal eyelashes and eyebrows, puckered periorbital skin, a rubbery feel to the nose and chin, and scar-like defects on each temple [18–22]. While most reported patients have been Puerto-Rican, other ethnic groups have been affected [22–24]. Both autosomal recessive [23,25] and autosomal dominant inheritance with variable penetrance and expressivity [21,23,26,27] have been reported.

Rare, non-cutaneous manifestations include imperforate anus [22,28], megaureter [22], mental retardation [22], Fallot's tetralogy [17], iris coloboma, limb malformations and recurrent digital fibromas [28], and developmental delay [29].

Johanson–Blizzard syndrome

This rare, autosomal recessive disorder is characterized by pre- and postnatal growth deficiency, microcephaly, variable intellectual impairment, deafness, thyroid dysfunction, pancreatic insufficiency and rectourogenital abnormalities. Hypoplastic alae nasi are characteristic and congenital absence of skin in the posterior midline scalpis is seen in 76% [30]. It is caused by mutations in the ubiquitin ligase gene *UBR1* [31]. There are several features of ectodermal dysplasia, including sparse hair with a marked frontal upsweep, absent eyebrows and eyelashes [32], hypodontia of both dentitions, peg-like deformity of remaining teeth [33] and hypoplastic nipples and areolae. Café-au-lait macules and dilated scalp veins may be observed.

*MIDAS syndrome (**m**icrophthalmia, **d**ermal **a**plasia, **s**clerocornea) (MLS syndrome [**m**icrophthalmia with **l**inear **s**kin **d**efects])*

Since the first description in 1990 [34] several cases of this syndrome have been reported [35–38]. This X-linked dominant condition is associated with heterozygous deletions on the X chromosome at Xp22.31. This region contains the gene *HCCS*, which encodes human holocytochrome *c*-type synthetase. Mutations in *HCCS* cause MIDAS syndrome [39] and have been found in most patients with a normal karyotype [40]. There is considerable inter- and intrafamilial phenotypic variability, with in one case a mutation found in some cells of the asymptomatic mother of a typically affected daughter [41]. Rare affected males usually have an extra X chromosome [42,43]. The twin boys reported by Anguiano [42] were subsequently described by Cape [44].

Patients with this syndrome have ocular abnormalities with linear skin defects of face and neck, as well as variable brain, genital and cardiac anomalies. The skin defects comprise asymmetric erythematous atrophic lesions distributed in Blaschko's lines, similar to those seen in focal dermal hypoplasia but limited to the face, scalp, neck and upper trunk. Unlike in focal dermal hypoplasia, there are no exophytic fatty protrusions. With age they heal with pigmentation.

Ocular defects include microphthalmia and corneal opacities which may be bilateral, and sclerocornea which is usually unilateral [44]. Genital abnormalities [37] and cardiac anomalies occur, including life-threatening arrythmias [42,45]. Brain anomalies include corpus callosum agenesis.

Oculocerebrocutaneous syndrome

Synonym
- Delleman–Oorthuys syndrome

This distinctive malformation syndrome [46–57] occurs sporadically and in both sexes. Twenty eight cases had been reported by 2005 [51]. No familial cases have been reported, and the scattered, asymmetrical nature of the characteristic abnormalities suggests mosaicism for a mutant gene that would be lethal if the zygote were affected [52]. Linear dyspigmentation in one case supports the idea that this is a mosaic disorder [53]. The severity is variable [54].

Typical ocular manifestations include orbital cysts, eyelid colobomas, microphthalmia and anophthalmia [55]. There may be skull defects and dysmorphic facial features. CNS abnormalities include cerebral malformations, particularly cystic spaces (porencephaly), and agenesis of the corpus callosum, with developmental delay and seizures. The cutaneous features comprise a highly characteristic combination of areas of cutis aplasia and cutaneous appendages. The cutaneous appendages are usually around the eyes, nose and ear, and may take bizarre finger-like or tubular forms. They are histologically indistinguishable from striated muscle hamartomas [56]. Multiple focal skin defects occur mainly on the scalp, face, neck and lumbosacral area and comprise cutis aplasia, areas of atrophy and punched-out defects [49,54]. These usually appear hypopigmented, and, in one case, normal skin markings and lanugo hair within the lesions were regarded as evidence that they were not scars [49]. As well as hair within the atrophic lesions [54] a ring of more profuse hair growth around scalp lesions has also been noted [57].

Delleman's syndrome overlaps clinically with encephalocraniocutaneous lipomatosis (fatty naevi, with ocular and neurologic defects) [53,58–61]. It requires differentiation from focal dermal hypoplasia, and from Goldenhar syndrome [62], and oculoectodermal syndrome (aplasia cutis, epibulbar dermoids and cutaneous hyperpigmentation) [63].

Other disorders

Numerous other conditions have featured areas of absent skin at birth. Extensive symmetrical congenital erosions were reported in *congenital erosive and vesicular dermatosis healing with reticulate supple scarring* [64,65]. Aplasia cutis congenita can occur at any site in the amniotic band disruption sequence [66,67], and on the scalp in tricho-odonto-onychodermal ectodermal dysplasia [68]. Extensive congenital areas of absent skin resembling epidermolysis bullosa have been described in cases of ectodermal dysplasia with cleft lip and/or palate, in the EEC syndrome (*e*ctrodactyly, *e*ctodermal dysplasia, *c*lefting) [69], and in the AEC syndrome (*a*nkyloblepharon, *e*ctodermal defects, *c*left lip/palate) [70]. Areas of absent skin at birth have been recorded in a familial disorder featuring *lumpy scalp, odd ears and rudimentary nipples* [71]. Multiple scalp erosions at birth occurred in two phenotypic females with 46XY gonadal dysgenesis, associated with cleft lip and palate, ear deformity and pre-auricular pits [72].

Single families have been reported with conditions associated with congenital absence of skin. A disorder comprising congenital absence of skin, nipple and breast hypoplasia, nail dysplasia and delayed dental eruption has been described in a mother and her son [73]. Ear deformities and pre-auricular pits were also present in members of another family in association with unilateral facial paresis, dermal sinuses and congenital absence of skin [74]. Posterior midline scalp absence of skin and intestinal lymphangiectasia, leading to hypoproteinaemia and oedema, occurred in two siblings [75].

Single cases have been reported of a syndrome comprising bilateral scarring above the ears, linear submental scars, craniosynostosis, polydactyly, syndactyly, low-set, deformed ears, hypoplastic tibias and cardiac disease [76], and of a syndrome comprising extensive congenital erosions of the skin, anonychia and an atrophic lesion on the tongue [77]. Extensive aplasia cutis congenita occurred in a baby with an unbalanced translocation, being monosomic for distal 12q and trisomic for distal 1q [78]. Aplasia cutis congenita was associated with intestinal lymphangiectasia, skull defect and brain heterotopia [79]. In one fatal case with some features of very severe Johanson–Blizzard syndrome, almost complete congenital absence of skin was associated with absent ears, choanal atresia, syndactyly, imperforate anus, pulmonary hypoplasia and other anomalies [80]. A female with complete absence of skin died soon after birth with hypoplastic lungs, syndactyly, skull defect, oesophageal atresia, intestinal malrotation, calcifications of the hepatic capsule and other anomalies [81].

References

1 Evers ME, Steijlen PM, Hamel BC. Aplasia cutis congenita and associated disorders: an update. *Clin Genet* 1995; **47**: 295–301.

2 Moss C. Syndromes affecting the skin and mucosa. In: Hennekam R, Allanson J, Krantz I, eds. *Gorlin's Syndromes of the Head and Neck*, 5th edn. Oxford: Oxford University Press, 2009: in press.

3 Hsu HF, Hou JW. Variable expressivity in Patau syndrome is not all related to trisomy 13 mosaicism. *Am J Med Genet A* 2007; **143**: 1739–48.

4 Happle R. Phylloid hypomelanosis and mosaic trisomy 13: a new etiologically defined neurocutaneous syndrome. *Hautarzt* 2001; **52**: 3–5.

5 Taibjee SM, Bennett DC, Moss C. Abnormal pigmentation in hypomelanosis of Ito and pigmentary mosaicism: the role of pigmentary genes. *Br J Dermatol* 2004; **151**: 269–82.

6 Concolino D, Rossi E, Strisciuglio P *et al.* Deletion of a 760 kb region at 4p16 determines the prenatal and postnatal growth retardation characteristic of Wolf–Hirschhorn syndrome. *J Med Genet* 2007; **44**: 647–50.

7 Maas NM, Van Buggenhout G, Hannes F *et al.* Genotype–phenotype correlation in 21 patients with Wolf-Hirschhorn syndrome using high-resolution array comparative genome hybridization (CGH). *J Med Genet* 2008; **45**: 71–80.

8 Rauch A, Schellmoser S, Kraus C *et al.* First known microdeletion within the Wolf–Hirschhorn syndrome critical region refines genotype–phenotype correlations. *Am J Med Genet* 2001; **99**: 338–42.

9 Rodriguez L, Zollino M, Climent S *et al.* The new Wolf–Hirschhorn syndrome critical region (WHSCR-2): a description of a second case. *Am J Med Genet* 2005; **136A**: 175–8.

10 Kowalski DC, Fenske NA. The focal facial dermal dysplasias: report of a kindred and a proposed new classification. *J Am Acad Dermatol* 1992; **27**: 575–82.

11 Brauer A. Hereditaerer symmetrischer systemisierter Naevus aplasticus bei 38 Personen. *Dermatol Wochenschr* 1929; **89**: 1163–8.

12 McGeoch AH, Reed WB. Familial focal facial dermal dysplasia. *Birth Defects Orig Artic Ser* 1971; **7**: 96–9.

13 McGeoch AH, Reed WB. Familial focal facial dermal dysplasia. *Arch Dermatol* 1973; **107**: 591–6.

14 Stone N, Burge S. Focal facial dermal dysplasia with a hair collar. *Br J Dermatol* 1998; **139**: 1136–7.

15 Wells JM, Weedon D. Focal facial dermal dysplasia or aplasia cutis congenita: a case with a hair collar. *Australas J Dermatol* 2001; **42**: 129–31.

16 Majid ML, Prendiville JS, Esterley NB. Focal facial dermal dysplasia: bitemporal lesions resembling aplasia cutis congenita. *J Am Acad Dermatol* 1988; **18**: 1203–7.

17 Setleis H, Kramer B, Valcarcel M *et al.* Congenital ectodermal dysplasia of the face. *Pediatrics* 1965; **32**: 540–8.

18 Marion RW, Chitayat D, Hutcheon G *et al.* Autosomal recessive inheritance in the Setleis bitemporal 'forceps marks' syndrome. *Am J Dis Child* 1987; **141**: 895–7.

19 Rudolph RI, Schwartz W, Leyden J. Bitemporal aplasia cutis congenita: occurrence with other cutaneous abnormalities. *Arch Dermatol* 1974; **110**: 615–8.

20 Rudolph RI, Schwartz W, Leyden JJ. Emendation to 'bitemporal aplasia cutis congenita'. *Arch Dermatol* 1974; **110**: 636.

21 Di Lernia, Neri I, Patrizi I. Focal facial dermal dysplasia: two familial cases. *J Am Acad Dermatol* 1991; **25**: 389–91.

22 Clark RD, Golabi M, Lacassiey Y *et al.* Expanded phenotype and ethnicity in Setleis syndrome. *Am J Med Genet* 1989; **34**: 354–7.

23 Masuno M, Imaizumi K, Makita Y *et al.* Autosomal dominant inheritance in Setleis syndrome. *Am J Med Genet* 1995; **57**: 57–60.

24 Tay Y-K, Morelli JG, Weston WL. Focal facial dermal hypoplasia: report of a case with associated cardiac defects. *Br J Dermatol* 1996; **135**: 607–8.

25 al-Gazali LI, al-Talabani J. Setleis syndrome: autosomal recessive or autosomal dominant inheritance? *Clin Dysmorphol* 1996; **5**: 249–53.

26 Ward KA, Moss C. Evidence for genetic heterogeneity of Setleis syndrome and focal facial dermal dysplasia. *Br J Dermatol* 1994; **130**: 645–9.

27 Kent JS, Romanchuk KG, Lemire EG. Ophthalmic findings in Setleis syndrome: two new cases in a mother and son. *Can J Ophthalmol* 2007; **42**: 471–3.

28 Breuning MH, Oranje AP, Langemeijer RA *et al.* Recurrent digital fibroma, focal dermal hypoplasia, and limb malformations. *Am J Med Genet* 2000; **94**: 91–101.

29 McGaughran J, Aftimos S. Setleis syndrome: three new cases and a review of the literature. *Am J Med Genet* 2002; **111**: 376–80.

30 Zenker M, Mayerle J, Reis A, Lerch MM. Genetic basis and pancreatic biology of Johanson-Blizzard syndrome. *Endocrinol Metab Clin North Am* 2006; **35**: 243–53.

31 Zenker M, Mayerle J, Lerch MM *et al.* Deficiency of UBR1, a ubiquitin ligase of the N-end rule pathway, causes pancreatic dysfunction, malformations and mental retardation (Johanson-Blizzard syndrome). *Nat Genet* 2005; **37**: 1345–50.

32 Alpay F, Gul D, Lenk MK, Ogur G. Severe intrauterine growth retardation, aged facial appearance and congenital heart disease in a newborn with Johanson–Blizzard syndrome. *Pediatr Cardiol* 2000; **21**: 389–90.

33 Zerres K, Holtgrave EA. The Johanson–Blizzard syndrome: report of a new case with special reference to the dentition and review of the literature. *Clin Genet* 1986; **30**: 177–83.

34 Al-Gazali LI, Mueller RF, Caine A *et al.* Two 46,XX,t(X;Y) females with linear skin defects and congenital microphthalmia: a new syndrome at Xp22.3. *J Med Genet* 1990; **27**: 59–63.

35 Happle R, Daniëls O, Koopman RJJ. MIDAS syndrome (microphthalmia, dermal aplasia and sclerocornea): an X-linked phenotype distinct from Goltz syndrome. *Am J Med Genet* 1993; **47**: 710–3.

36 Lindsay EA, Grillo A, Ferrero GB *et al.* Microphthalmia with linear skin defects (MLS) syndrome: clinical, cytogenetic, and molecular characterization. *Am J Med Genet* 1994; **49**: 229–34.

37 Mucke J, Happle R, Theile H. MIDAS syndrome respectively MLS syndrome. *Am J Med Genet* 1995; **57**: 117–8.

38 Enright F, Campbell P, Stallings RL *et al.* Xp22.3 microdeletion in a 19-year-old girl with clinical features of MLS syndrome. *Pediatr Dermatol* 2003; **20**: 153–7.

39 Wimplinger I, Morleo M, Rosenberger G *et al.* Mutations of the mitochondrial holocytochrome c-type synthase in X-linked dominant microphthalmia with linear skin defects syndrome. *Am J Hum Genet* 2006; **79**: 878–89.

40 Morleo M, Pramparo T, Perone L *et al.* Microphthalmia with linear skin defects (MLS) syndrome: clinical, cytogenetic, and molecular characterization of 11 cases. *Am J Med Genet* 2005; **137A**: 190–8.

41 Wimplinger I, Rauch A, Orth U *et al.* Mother and daughter with a terminal Xp deletion: implication of chromosomal mosaicism and X-inactivation in the high clinical variability of the microphthalmia with linear skin defects (MLS) syndrome. *Eur J Med Genet* 2007; **50**: 421–31.

42 Anguiano A, Yang X, Felix JK, Hoo JJ. Twin brothers with MIDAS syndrome and XX karyotype. *Am J Med Genet A* 2003; **119**: 47–9.

43 Stratton RF, Walter CA, Paulgar BR *et al.* Second 46,XX male with MLS syndrome. *Am J Med Gene* 1998; **76**: 37–41.

44 Cape CJ, Zaidman GW, Beck AD, Kaufman AH. Phenotypic variation in ophthalmic manifestations of MIDAS syndrome (microphthalmia, dermal aplasia, and sclerocornea). *Arch Ophthalmol* 2004; **122**: 1070–4.

45 Paul T, Laohakunakorn P, Long B, Saul JP. Complete elimination of incessant polymorphic ventricular tachycardia in an infant with MIDAS syndrome: use of endocardial mapping and radiofrequency catheter ablation. *J Cardiovasc Electrophysiol* 2002; **13**: 612–5.

46 Bleeker-Wagemakers LM, Hamel BC, Hennekam RCM *et al.* Oculocerebrocutaneous syndrome. *J Med Genet* 1990; **27**: 69–70.

47 Hoo JJ, Kapp-Simon K, Rollnick B *et al.* Oculocerebrocutaneous (Delleman) syndrome: a pleiotropic disorder affecting ectodermal tissues with unilateral predominance. *Am J Med Genet* 1991; **40**: 290–3.

48 Wilson RD, Traverse L, Hall JG *et al.* Oculocerebrocutaneous syndrome. *Am J Ophthalmol* 1985; **99**: 142–8.

49 Ming JE, Katowitz J, McDonald-McGinn DM *et al.* Hemifacial microsomia in a newborn with hypoplastic skin lesions, an eyelid skin tag, and microphthalmia: an unusual presentation of Delleman syndrome. *Clin Dysmorphol* 1998; **7**: 279–83.

50 Scholz TA, Vanderhooft SL, Meyer LJ. What syndrome is this? *Pediatr Dermatol* 1999; **16**: 403–5.

51 Moog U, Jones MC, Bird LM, Dobyns WB. Oculocerebrocutaneous syndrome: the brain malformation defines a core phenotype. *J Med Genet* 2005; **42**: 913–21.

52 Happle R. Lethal genes surviving by mosaicism: a possible explanation for sporadic birth defects involving the skin. *J Am Acad Dermatol* 1987; **16**: 899–906.

53 Pascual-Castroviejo I, Pascual-Pascual SI, Velazquez-Fragua R, Lapunzina P. Oculocerebrocutaneous (Delleman) syndrome: report of two cases. *Neuropediatrics* 2005; **36**: 50–4.

54 Cambiaghi S, Levet PS, Guala G *et al.* Delleman syndrome: report of a case with a mild phenotype. *Eur J Dermatol* 2000; **10**: 623–6.

55 Divizia MT, Priolo M, Priolo E *et al.* How wide is the ocular spectrum of Delleman syndrome? *Clin Dysmorphol* 2004; **13**: 33–4.

56 Sanchez RL, Raimer SS. Clinical and histological features of striated muscle hamartoma: a possible relationship to Delleman's syndrome. *J Cutan Pathol* 1994; **16**: 40–6.

57 Ferguson JW, Hutchinson HT, Rouse BM. Ocular, cerebral and cutaneous malformations: confirmation of an association. *Clin Genet* 1984; **25**: 464–9.

58 Hennekam RC. Scalp lipomas and cerebral malformations: overlap between encephalocraniocutaneous lipomatosis and oculocerebrocutaneous syndrome. *Clin Dysmorphol* 1994; **3**: 87–9.

59 Moog U, Kruger G, Stengel B *et al.* Oculocerebrocutaneous syndrome: a case report, follow-up, and differential diagnosis considerations. *Genet Couns* 1996; **7**: 257–65.

60 Hunter AG. Oculocerebrocutaneous and encephalocraniocutaneous lipomatosis syndromes: blind men and an elephant or separate syndromes? *Am J Med Genet A* 2006; **140**: 709–26.

61 Torrelo A, Boente Mdel C, Nieto O *et al.* Nevus psiloliparus and aplasia cutis: a further possible example of didymosis. *Pediatr Dermatol* 2005; **22**: 206–9.

62 McCandless SE, Robin NH. Severe oculocerebrocutaneous (Delleman) syndrome: overlap with Goldenhar anomaly. *Am J Med Genet* 1998; **78**: 282–5.

63 Lee TK, Johnson RL, MacDonald IM *et al.* A new case of oculoectodermal syndrome. *Ophthalmic Genet* 2005; **26**: 131–3.
64 Cohen BA, Esterley NB, Nelson PF. Congenital erosive and vesicular dermatosis healing with reticulated supple scarring. *Arch Dermatol* 1985; **121**: 361–7.
65 Gupta AK, Rasmussen JE, Headington JT. Extensive congenital erosions and vesicles healing with reticulate scarring. *J Am Acad Dermatol* 1987; **17**: 369–76.
66 Baker CJ, Rudolph AJ. Congenital ring constrictions and intrauterine amputations. *Am J Dis Child* 1971; **121**: 393–400.
67 Higginbottom MC, Jones KL, Hall BD *et al.* The amniotic band disruption complex: timing of amniotic rupture and variable spectra of consequent defects. *J Pediatr* 1979; **95**: 544–9.
68 Pinheiro M, Pereira LC, Freire-Maia N. A previously undescribed condition: tricho-odonto-onycho-dermal syndrome: a review of the tricho-odonto-onychial subgroup of ectodermal dysplasias. *Br J Dermatol* 1981; **105**: 371–82.
69 Duillo MT, De Toni T, Cavaliere G *et al.* Associazione tra sindrome EEC e aplasia congenita delle cute con epidermolisi bollosa. *Minerva Pediatr* 1982; **34**: 627–32.
70 Vanderhooft SL, Stephan MJ, Sybert VP. Severe skin erosions and scalp infections in AEC syndrome. *Pediatr Dermatol* 1993; **10**: 334–40.
71 Finlay AY, Marks R. An hereditary syndrome of lumpy scalp, odd ears and rudimentary nipples. *Br J Dermatol* 1978; **99**: 423–30.
72 Brosnan PG, Lewandowsky RC, Toguri AG *et al.* A new familial syndrome of 46XY gonadal dysgenesis with anomalies of ectodermal and mesodermal structures. *J Pediatr* 1980; **97**: 586–90.
73 Tuffli GA, Laxova R. New autosomal dominant form of ectodermal dysplasia. *Am J Med Genet* 1983; **14**: 381–4.
74 Anderson CE, Hollister D, Szalay GC. Autosomal dominantly inherited cutis aplasia congenita, ear malformations, right sided facial paresis and dermal sinuses. *Birth Defects Orig Artic Ser* 1979; **15**: 265–70.
75 Bronspiegel N, Zelnick N, Rabinowitz H *et al.* Aplasia cutis congenita and intestinal lymphangiectasia: an unusual association. *Am J Dis Child* 1985; **139**: 509–13.
76 Sakati N, Nyhan WL, Tisdale WK. A new syndrome with acrocephalosyndactyly, cardiac disease and distinctive defects of the ear, skin and lower limbs. *J Pediatr* 1971; **79**: 104–9.
77 Sequeiros J, Sack GH. Linear skin atrophy, scarring alopecia, anonychia and tongue lesion: a new syndrome? *Am J Med Genet* 1985; **21**: 669–80.
78 Khan JY, Moss C, Roper HP. Aplasia cutis congenita with chromosome 12q abnormality. *Arch Dis Child Fetal Neonatal Ed* 1995; **72**: F205–6.
79 Bonioli E, Hennekam RC, Spena G *et al.* Aplasia cutis congenita, skull defect, brain heterotopia, and intestinal lymphangiectasia. *Am J Med Genet A* 2005; **132**: 202–5.
80 Park MS, Hahn SH, Hong CH *et al.* Extensive form of aplasia cutis congenita: a new syndrome? *J Med Genet* 1998; **35**: 609–11.
81 Sugiura T, Kouwaki M, Kiyosawa S *et al.* A case of systemic aplasia cutis congenita: a newly recognized syndrome? *Eur J Pediatr* 2008; **167**: 409–13.

Differential diagnosis. In the neonatal period parents sometimes mistake congenital absence of skin for obstetric trauma due to forceps or scalp electrodes [1,2], a confusion which may have significant medicolegal repercussions [3].

During childhood, congenital absence of scalp skin may be confused with sebaceous naevus, traumatic scarring, cicatricial alopecia, the linear scarring alopecia seen in *en coup de sabre* morphoea, and the alopecia along scalp suture lines characteristic of the Hallermann–Streiff syndrome.

Cases have been described of congenital bald patches in the scalp with histologically normal skin apart from absent appendages [4]. These 'aplastic naevi' might represent the minimal end of the spectrum of congenital absence of skin.

References

1 Ashkenazi S, Metzker A, Merlob P *et al.* Scalp changes after fetal monitoring. *Arch Dis Child* 1985; **60**: 267–9.
2 Brown ZA, Jung AL, Stenchever MA. Aplasia cutis congenita and the fetal scalp electrode. *Am J Obstet Gynecol* 1977; **129**: 351–2.
3 Dunn PM. Litigation over congenital scalp defects. *Lancet* 1992; **339**: 440.
4 Schoenfeld RJ, Mehregan AH. Aplastic naevus—the 'minus nevus'. *J Pediatr* 1973; **12**: 386–9.

Treatment. Most lesions will heal spontaneously from the margins, to leave a smooth, yellowish, hairless, papery scar. Underlying defects in the cranium generally resolve spontaneously during infancy even when large [1]. Occasionally, hypertrophic scarring occurs [2], and linear lesions on the limbs may lead to joint contracture. In the vast majority of cases, the prognosis is excellent if attention is paid to the prevention of both secondary infection and further trauma.

Small residual lesions can be treated by excision of the abnormal skin margins followed by primary closure [3]. Larger scalp defects are probably best treated by early grafting or flap rotation [4,5], as delayed closure may be complicated by infection or haemorrhage from the sagittal sinus, which may be lethal [6–8]. Composite ('engineered') skin grafts have been used successfully, using allogeneic keratinocytes [9], or autologous fibroblasts followed by keratinocytes a week later [10]. Bone grafts may be required to reconstruct large cranial defects [11,12]. However, some authors have recommended a conservative approach even for extensive lesions [1], with later excision of scars. Tissue expansion [12] has proved very valuable for this type of procedure.

References

1 Rhee ST, Colville C, Buchman SR, Muraszko K. Complete osseous regeneration of a large skull defect in a patient with cutis aplasia: a conservative approach. *J Craniofac Surg* 2002; **13**: 497–500.
2 Moschella SL. Congenital defects of scalp with keloid formation: cousins show similar defects. *Arch Dermatol* 1962; **86**: 63–4.
3 Martinez-Lage JF, Almagro MJ, Hernandez FL, Pozo M. Aplasia cutis congenita of the scalp. *Childs Nerv Syst* 2002; **18**: 634–7.
4 Sargent LA. Aplasia cutis congenita of the scalp. *J Pediatr Surg* 1990; **25**: 1211–3.
5 Başterzi Y, Bağdatoğlu C, Sari A, Demirkan F. Aplasia cutis congenita of the scalp and calvarium: conservative wound management with novel wound dressing materials. *J Craniofac Surg* 2007; **18**: 427–9.
6 Glasson DW, Duncan GM. Aplasia cutis congenita: delayed closure complicated by massive haemorrhage. *Plast Reconstr Surg* 1985; **75**: 423–5.
7 Irons GB, Olson RM. Aplasia cutis congenita. *Plast Reconstr Surg* 1980; **66**: 199–203.
8 Peer LA, Duyn JV. Congenital defect of the scalp: report of a case with fatal termination. *Plast Reconstr Surg* 1948; **3**: 722–6.
9 Verhelle NA, Heymans O, Deleuze JP *et al.* Abdominal aplasia cutis congenita: case report and review of the literature. *J Pediatr Surg* 2004; **39**: 237–9.
10 Donati V, Arena S, Capilli G *et al.* Reparation of a severe case of aplasia cutis congenita with engineered skin. *Biol Neonate* 2001; **80**: 273–6.
11 Argenta LC, Dingman RO. Total reconstruction of aplasia cutis congenita involving scalp, skull and dura. *Plast Reconstr Surg* 1986; **77**: 650–3.
12 Hockley AD. Aplasia cutis congenita of the scalp. *Childs Nerv Syst* 2002; **18**: 638.

Amniotic bands and adhesions

Synonyms
- Congenital ring constrictions
- Intrauterine amputation
- Adam complex syndrome (amniotic deformities adhesions mutilation)
- Raised limb bands

Definition. These are circumferential bands, appearing at birth or soon after, usually on limbs, and occasionally associated with other anomalies, particularly distal limb reductions.

Aetiology. Aetiology and classification of these disorders is confused [1–3]. Some undoubtedly result from antenatal rupture of the amniotic membrane: this produces tough bands which encircle developing limbs, resulting in annular constrictions [4,5], secondary syndactyly [6], and intrauterine amputations [7,8] in about one in 10 000 neonates. Amniotic bands may also result from amniotic membrane adhering to an abnormal fetal surface, particularly craniofacial defects [9] and cleft lip [10]. Occasionally, similar limb bands, appearing at birth or later, occur with an intact amnion, suggesting a localized abnormality in limb development rather than external constriction [1,2]. Tight socks have been suggested as a cause of bands appearing around the lower legs in infants [11–13]. Both ring constrictions [14] and congenital amputations [15] are occasionally familial.

Pathology. Biopsies of raised bands showed no specific abnormalities [2].

Clinical features. The most characteristic appearance is ring constrictions of digits, limbs, neck or trunk. The groove is usually about 1–3 mm wide and 2–4 mm deep. Beyond the constriction, there is often lymphoedema. Raised, narrow, scar-like bands can occur [16] and may coexist with the more typical grooves [1,2]. Distal limb deformities, such as syndactyly [6], polydactyly, talipes and distal limb reduction, not necessarily of the same limb, are also frequent, as is peripheral nerve palsy [17]. *In utero* amputation may also occur. Neonatal herpes simplex has been reported localized to an area of ulceration at the site of amniotic band compression [18].

Diagnosis. In the Michelin tyre baby syndrome there is abnormal limb enlargement with folds, rather than primary constrictions. Histology of the folds may show diffuse smooth muscle hamartoma or lipomatous naevus.

Treatment. Plastic surgery is indicated for residual constrictive grooves in a limb or digit, where there is interference with vascular or lymphatic circulation.

References

1 Lateo SA, Taylor AE, Meggitt SJ. Raised limb bands developing in infancy. *Br J Dermatol* 2006; **154**: 791–2.
2 Meggitt SJ, Harper J, Lacour M, Taylor AEM. Raised limb bands developing in infancy. *Br J Dermatol* 2002; **147**: 359–63.
3 Cohen MM Jr, Gorlin RJ, Clark R *et al.* Multiple circumferential skin folds and other anomalies: a problem in syndrome delineation. *Clin Dysmorphol* 1993; **2**: 39–46.
4 Dyer JA, Chamlin S. Acquired raised bands of infancy: association with amniotic bands. *Pediatr Dermatol* 2005; **22**: 346–9.
5 Miller ME, Graham JM, Higginbottom MC, Smith DW. Compression-related defects from early amnion rupture: evidence for mechanical teratogenesis. *J Pediatr* 1981; **98**: 292–7.
6 Ornoy A, Sekeles E, Sadovsky E. Amniogenic bands as a cause of syndactyly in a young human fetus. *Teratology* 1975; **9**: 129–34.
7 Baker CJ, Rudolph AJ. Congenital ring constrictions and intrauterine amputations. *Am J Dis Child* 1971; **121**: 393–400.
8 Torpin R, Faulkner A. Intrauterine amputation with the missing member found in the fetal membranes. *JAMA* 1966; **198**: 185–7.
9 Moerman P, Fryns JP, Vanderberghe K *et al.* Constrictive amniotic bands, amniotic adhesions and limb–body wall complex: discrete disruption sequences with pathogenetic overlap. *Am J Med Genet* 1992; **42**: 470–9.
10 Ray M, Hendrick S. Amniotic band syndrome. *Int J Dermatol* 1988; **27**: 312–4.
11 Marque MM, Guillot B, Le Gallic G, Bessis D. Raised limb bands in infancy: a post-traumatic aetiology? *Br J Dermatol* 2007; **156**: 578–9.
12 Berk DR, Bayliss SJ. Sock-line bands in infancy. *Br J Dermatol* 2007; **157**: 1063–4.
13 Berk DR, Tapia B, Lind A, Bayliss SJ. Sock-line hyperpigmentation: case series and literature review. *Arch Dermatol* 2007; **143**: 428–30.
14 Kunze J, Riehm H. A new genetic disorder: autosomal dominant multiple benign ring-shaped creases. *Eur J Pediatr* 1982; **138**: 301–13.
15 Etches PC, Stewart AR, Ives EJ. Familial congenital amputations. *J Pediatr* 1982; **101**: 448–9.
16 Russi DC, Irvine AD, Paller AS. Raised limb bands developing in infancy. *Br J Dermatol* 2003; **149**: 436–7.
17 Uchida Y, Sugioka Y. Peripheral nerve palsy associated with congenital constriction band syndrome. *J Hand Surg (Am)* 1991; **16**: 109–12.
18 Lauber J, Eerkes K, Storer J. Herpes simplex virus infection complicating amniotic band syndrome in the newborn. *Cutis* 1989; **44**: 64–6.

CHAPTER 19
Disorders of Keratinization

M.R. Judge[1], *W.H.I. McLean*[2] *& C.S. Munro*[3]

[1]Department of Dermatology, Salford Royal Hospital, Manchester, UK
[2]University of Dundee and Ninewells Hospital and Medical School, Dundee, UK
[3]Alan Lyell Centre for Dermatology, Southern General Hospital, Glasgow, UK

The molecular genetics of keratinizing disorders, 19.1
Ichthyosis, 19.4
Congenital ichthyoses, 19.6
Ichthyosis vulgaris, 19.6
X-linked recessive ichthyosis, 19.9
Multiple sulphatase deficiency, 19.13
Collodion baby, 19.13
Non-bullous ichthyosiform erythroderma, 19.17
Lamellar ichthyosis, 19.21
Harlequin ichthyosis, 19.25
Bullous ichthyosiform erythroderma, 19.29
Ichthyosis bullosa of Siemens, 19.34
Ichthyosis hystrix, 19.35
Netherton's syndrome, 19.37
Sjögren–Larsson syndrome, 19.42
Refsum's disease, 19.45
IBIDS/PIBIDS syndrome, 19.47
Conradi–Hünermann–Happle syndrome, 19.49
Neutral lipid storage disease with ichthyosis, 19.52
KID syndrome and HID syndrome, 19.54
CHILD syndrome, 19.57
Ichthyosis follicularis with alopecia and photophobia, 19.58
Neu–Laxova syndrome, 19.59
CHIME syndrome, 19.60
Sporadic genetic syndromes with ichthyosis, 19.60
Acquired ichthyoses, 19.63
Ichthyosis associated with malignancy, 19.63
Ichthyosis and non-malignant disease, 19.63
Drug-induced ichthyosis, 19.63
Pityriasis rotunda, 19.65
Peeling skin syndromes, 19.66
Acral peeling skin syndromes, 19.66
Familial peeling skin syndromes, 19.66
Oudtshoorn disease, 19.68
Erythrokeratoderma, 19.69
Erythrokeratoderma variabilis, 19.69
Progressive symmetrical erythrokeratoderma, 19.70
Other syndromes featuring erythrokeratoderma, 19.71
Follicolocentric keratotic disorders, 19.72
Keratosis pilaris, 19.72
Keratosis follicularis spinulosa decalvans, 19.74
Other folliculocentric disorders, 19.75
Pityriasis rubra pilaris, 19.76
Darier's disease and related disorders, 19.81
Darier's disease, 19.81
Transient and persistent acantholytic dermatosis, 19.86
Acrokeratosis verruciformis, 19.88
Other focal disorders, 19.88
Perforating keratotic disorders, 19.88
Porokeratoses, 19.90
Minute and filiform keratoses, 19.92
Miscellaneous circumscribed keratotic disorders, 19.93
Palmoplantar keratodermas, 19.93
Diffuse keratodermas, 19.95
Transgredient keratodermas, 19.98
Focal keratodermas, 19.102
Striate keratoderma, 19.105
Hidrotic ectodermal dysplasia, 19.106
Keratodermas with extracutaneous features, 19.106
Punctate and porokeratotic keratodermas, 19.112
Filiform keratodermas, 19.114
Marginal papular keratodermas, 19.114
Miscellaneous keratoderma syndromes, 19.115
Keratoderma and cancer, 19.116
Other acquired keratodermas, 19.117
Acanthosis nigricans, 19.119
Confluent and reticulate papillomatosis, 19.121

The molecular genetics of keratinizing disorders

Classification of keratinizing disorders

The term 'disorders of keratinization' refers to a broad spectrum of skin disorders where there is abnormal differentiation of the epidermis and/or appendages, often with aberrant formation of the cornified envelope [1]. These disorders may have associated epidermal fragility, and there is clinical and pathological overlap with inherited and acquired blistering disorders (see Chapters 39 and 40). Epidermal and/or adnexal defects may exist in isolation or can also be associated with additional extracutaneous features.

The pathogenesis of many of the acquired disorders included in this chapter is poorly understood and may prove to encompass a variety of infective, inflammatory or other causes. However, many disorders of keratinization are inherited as single-gene Mendelian traits, and understanding their aetiology has permitted re-evaluation of their classification. Traditionally, this group of diseases has been classified according to clinical, histological and ultrastructural findings. As the majority of the genetically determined disorders are uncommon in the population, the morphological approach has been beneficial to the practising clinician and offers a logical pathway to diagnosis when confronted with a patient with an unknown disorder. Remarkable advances have been made in molecular genetic technology during the past decade or so, stemming from the development of the polymerase chain reaction (PCR) technology and related techniques from the late 1980s onwards [2]. This technology facilitates rapid amplification and

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

DNA sequencing (decoding) of genes and parts thereof, using minute amounts of a patient's DNA as the starting material. This, coupled with the recent advances in the mapping and near-complete sequencing of the entire human genome, have led to a rapid increase in understanding the basic molecular defects responsible for inherited disorders of keratinization, and these advances have made possible a new, molecular mechanism-based approach to their classification, which complements the pre-existing morphological classification system (Table 19.1). These molecular genetic and biological insights have in many cases confirmed the accuracy of the original clinical distinctions. As knowledge increases, however, the association of mutations in one gene with a distinct phenotype has become more complicated, as illustrated below.

Genotype–phenotype correlation

A good example of phenotypic heterogeneity arising from mutations in a single gene is that of keratin K1. Heterozygous dominant negative mutations in suprabasal keratins K1 and K10 were initially reported to be the genetic basis of bullous ichthyosiform erythroderma of Brocq (BIE) [3,4]. These mutations were strongly clustered in parts of the keratin molecule that are known to be critical for keratin assembly and function (see Intermediate Filament Mutation database; http://www.interfil.org). In an early genetic study of a family with a quite typical BIE mutation in K1, there were mildly and severely affected persons within one family, all of whom had inherited the same mutation [5]. Later, in a family originally diagnosed by Brocq himself as having a consistently milder BIE phenotype, a mutation was found in a region of the K1 protein, linker L12, where mutations in other keratins produced milder phenotypes [6]. Later still, larger deletion and insertion mutations have been identified in K1 that produce primarily palmoplantar keratoderma [7,8]. The latter phenotype is easily confused with the Vörner form of epidermolytic palmoplantar keratoderma (EPPK) resulting from K9 mutations [9]. Certain mutations have also been associated with mild annular [10] and polycyclic erythematous forms of BIE [11]. More recently, a frameshift mutation affecting only the V2 domain of K1 was shown to consistently produce a phenotype closely resembling ichthyosis hystrix of Curth–Macklin in an African American kindred [12]. In contrast, an almost identical frameshift in K1 produced a very much milder, striate keratoderma phenotype in a British Caucasian kindred [13]. In each of the phenotypes associated with these K1 mutations, there is histological evidence of epidermolytic hyperkeratosis (EHK) and ultrastructural evidence of suprabasal tonofilament disruption; however, the tissue distribution and severity of EHK is quite variable. Similar complexity of genotype–phenotype correlation has been identified in disorders caused by mutations in desmosomal proteins and connexins.

There are a number of lessons from these studies. First, mutations affecting different parts of a gene (and thus specific protein domains) can lead to radically different phenotypes. Secondly, there can be phenotypic variation between families carrying similar mutations, and even within one family where all affected persons have the same mutation. The source of phenotypic variation is presumed to be a result of a combination of unknown genetic modifying factors and environmental influences. Thirdly, there can in some instances be ethnic variation in phenotypes resulting from similar or identical mutations. In this case, there is possibly a greater scope for variation in both genetic background and environmental factors. As time goes on and more cases are studied at the molecular level in close consultation with experienced clinicians, greater insights will be gained into the molecular basis and classification of these diseases, as well as the subtle functions not just of proteins but of individual protein domains in epithelial biology.

The biology of keratinization revealed through genetics

Over the last decade, a great deal has been learned about the basic cell biology of epidermal differentiation and keratinization through the study of genetic disorders of this biological system. The various classes of molecules shown to be involved in this system, along with their respective genetic diseases, are listed in Table 19.1. Some of the defective molecules have a mainly structural role in maintaining the mechanical integrity of the epidermis and its appendages in the face of persistent physical trauma. The keratin intermediate filament cytoskeleton has been shown to be a major player in providing mechanical strength for epithelial cells. To date, mutations in 18 keratin genes are linked to cell fragility syndromes affecting the epidermis, adnexae and other epithelia [14]. Similarly, mutations in keratin-associated proteins, such as desmosomal proteins and molecules involved in the cross-linking of keratins during cornification, such as loricrin, have been linked to other keratinizing disorders [15]. Defects in molecules involved in regulating the movement of ions and other small molecules between cells of the epidermis have also been linked to a range of keratinizing disorders, including gap junction proteins [16] and calcium pump molecules [17]. Calcium metabolism plays an important part in the control of epidermal differentiation [18], as evidenced by the phenotype of Darier's disease. Similarly, a range of enzymes is involved in lipid metabolism, which generates the epidermal lipid barrier and is integral to the production of the cornified cell envelope (a highly cross-linked protein–lipid barrier structure), during the terminal differentiation of the epidermis. These include transglutaminase-1, which cross-links keratins and other structural proteins [19], SPINK5, a protease inhibitor [20], and enzymes of lipid peroxidation [21]. Some unexpected molecules have been turned up by positional cloning, such as SLURP-1, a novel secreted protein whose absence leads to mal de Meleda [22]. The finding that deficiency of the cornified envelope protein filaggrin predisposes to atopic disease indicates the wider importance of integrity of the epidermal barrier [23].

In conclusion, the field of keratinizing disorders as it stands today represents a close marriage between clinical and morphological observations and molecular and cell biology. This union of medicine and science has led to improved classification and diagnosis, including first trimester prenatal genetic testing, accurate genetic counselling and, hopefully in the future, an informed mechanistic approach to the design of new therapeutic agents for this group of diseases.

References

1 Irvine AD, Paller AS. Inherited disorders of keratinization. *Curr Probl Dermatol* 2002; **14**: 71–116.

Table 19.1 Gene defects in disorders of keratinization.

Disorder	Genes affected	Further information
Keratin disorders		
Annular epidermolytic ichthyosis variant of BCIE and cyclic ichthyosis	*KRT10, KRT1*	Suprabasal keratin 10 (chr 17q12–q21) for annular variant; keratin 1 for cyclic ichthyosis (chr 12q11–q13)
Bullous congenital ichthyosiform erythroderma (BCIE)	*KRT1, KRT10*	Suprabasal keratins 1 and 10 (chr 12q11–q13 and 17q12–q21)
Diffuse non-epidermolytic palmoplantar keratoderma	*KRT1*	Keratin 1 (chr 12q11–q13)
Epidermolytic palmoplantar keratoderma	*KRT9*	Keratin 9 (type I keratin; chr 17q12–q21). Keratin specific for palm and sole skin
Focal non-epidermolytic palmoplantar keratoderma	*KRT16*	Keratin 16 (chr 17q12–q21). Constitutive expression in palm and sole epidermis and other sites
Pachyonychia congenita type 1 (PC-1; Jadassohn–Lewandowsky form)	*KRT6A, KRT16*	Dominant-negative mutations in differentiation-specific keratins K6a (chr 12q11–q13) or K16 (chr 17q12–q21)
Pachyonychia congenita type 2 (PC-2; Jackson–Lawler form)	*KRT6B, KRT17A*	Dominant-negative mutations in differentiation-specific keratins K6b (chr 12q11–q13) or K17 (chr 17q12–q21). Some cases are isolated steatocystoma multiplex
Ichthyosis bullosa of Siemens (IBS)	*KRT2E*	Epidermal keratin 2 (chr 12q11–q13). Expressed in late suprabasal cells of epidermis
Ichthyosis hystrix (Curth–Macklin)	*KRT1*	Frameshift mutation in V2 domain of keratin 1 (chr 12q11–q13)
Striate palmoplantar keratoderma	*KRT1*	Frameshift mutation in V2 domain of keratin 1, almost identical to IHCM defect, above (chr 12q11–q13)
Desmosome proteins		
Dilated cardiomyopathy with woolly hair and keratoderma	*DSP*	Desmoplakin 1 (chr 6p2)
Ectodermal dysplasia with skin fragility	*PKP1*	Plakophilin 1 (chr 1q)
Naxos disease	*JUP*	Plakoglobin, component of desmosome and adherens junction (chr 17q21)
Striate palmoplantar keratoderma	*DSG1, DSP, KRT1*	Desmoglein 1, a desmosomal cadherin (chr 18q12.1) Desmoplakin 1, role in attachment of intermediate filaments to the desmosome (chr 6p2)
Stratum corneum proteins		
Ichthyosis vulgaris	*FLG*	Filaggrin (1q21) crosslinks intermediate filaments
Loricrin keratoderma	*LOR*	Loricrin, component of cornified cell envelope (chr 1q21)
Gap junction proteins		
Clouston's syndrome (hidrotic ectodermal dysplasia 2)	*GJB6*	Connexin 30 (chr 13q12)
Erythrokeratoderma variabilis (EKV)	*GJB3*	Connexin 31 (chr 1p35.1)
EKV with erythema gyratum repens	*GJB4*	Connexin 30.3 (chr 1p35.1)
Keratitis, ichthyosis and deafness	*GJB2*	Connexin 26 (chr 13q11–q12)
Palmoplantar keratoderma and deafness (various)	*GJB2*	Connexin 26 (chr 13q11–q12)
Calcium pump defects		
Darier's disease	*ATP2A2*	Sarcoplasmic/endoplasmic reticulum calcium ATPase (SERCA2) (chr 12q24.1)
Hailey–Hailey disease	*ATP2C1*	Calcium transporting ATPase (chr 3q21–q24)
Metabolic and enzyme defects		
Autosomal recessive ichthyosiform erythroderma (Lamellar ichthyosis, Non-bullous ichthyosiform erythroderma)	*TGM1*	Transglutaminase (chr 14q 11.2), cross-linking enzyme in cornified envelope formation (mainly lamellar ichthyosis)
	ALOX12B	Arachidonate lipoxygenase (chr 17p13.1)
	ALOXE3	Arachidonate lipoxygenase (chr 17p13.1)
	ICHYN	Ichthyin (chr 5q33) possibly a receptor for peroxisomal lipids
	CYP4F22	Cytochrome P450 4F22 (chr 19p13.12)
	ABCA12	see Harlequin ichthyosis
Chanarin–Dorfman syndrome	*CGI-58*	CGI-58 (chr 3), CGI protein of the esterase/lipase/thioesterase subfamily
CHILD syndrome (congenital hemidysplasia, ichthyosis and limb defects)	*NSDHL, EBP*	3β-hydroxysteroid dehydrogenase, an enzyme in cholesterol biosynthesis (chr Xq28). Mouse mutant, bare patches Mutations also reported in 3β-hydroxysteroid-δ8, δ7 isomerase
Harlequin ichthyosis	*ABCA12*	ABCA12 (chr 2q35) is a membrane based lipid transporter
IBIDS/Trichothiodystrophy	*ERCC2/XPD; ERCC3/XPB*	DNA excision repair complex (chr 19q13.2–q13.3; 2q21)
Ichthyosis Prematurity syndrome	*SLC27A4*	Fatty acid transport protein 4 (chr 9q34)
Netherton's syndrome	*SPINK5*	Serine protease inhibitor LEKTI (chr 5q32)
Papillon–Léfèvre and Haim-Munk syndromes	*CTSC*	Cathepsin C, a lysosomal protease (chr 11q14.1–14.3)
Refsum's disease	*PAHX*	Phytanoyl-CoA hydroxylase (chr 10pter–p11.2), a PTS2 protein
Rhizomelic chondrodysplasia punctata type I	*PEX7*	Peroxisomal matrix protein with type 2 peroxisome targeting signal receptor (chr 6q22–q24)
Richner–Hanhart (tyrosine transaminase deficiency)	*TAT*	Tyrosine aminotransferase (chr 16q22)
Sjögren–Larsson syndrome	*FALDH (ALDH3A2)*	Fatty aldehyde dehydrogenase (chr 17p11.2). Catalyses medium and long-chain aliphatic aldehyde oxidation
X-linked ichthyosis (steroid sulphatase deficiency)	*STS*	Arylsulphatase C gene (chr Xp22.32)
X-linked recessive chondrodysplasia punctata	*ARSE*	Arylsulphatase E gene (chr Xp22.3) resulting in steroid sulphatase deficiency
X-linked dominant chondrodysplasia punctata (CDPX2) or Conradi–Hünermann syndrome	*EBP*	Emopamil binding protein, 3β-hydroxysteroid-δ8, δ7 isomerase. Role in cholesterol biosynthesis (chr Xp11.22–p11.23). Mouse model, tattered
Secreted protein		
Mal de Meleda	*ARSB*	Encodes SLURP-1 (chr 8q24.3)

2 Irvine AD, McLean WH. The molecular genetics of the genodermatoses: progress to date and future directions. *Br J Dermatol* 2003; **148**: 1–13.
3 Cheng J, Syder AJ, Yu Q-C *et al.* The genetic basis of epidermolytic hyperkeratosis: a disorder of differentiation—specific epidermal keratin genes. *Cell* 1992; **70**: 811–9.
4 Chipev CC, Korge BP, Markova N *et al.* A leucine–proline mutation in the H1 subdomain of keratin 1 causes epidermolytic hyperkeratosis. *Cell* 1992; **70**: 821–8.
5 McLean WHI, Eady RAJ, Leigh IM *et al.* A point mutation in helix 1A of keratin 1 creates a Mae III RFLP and causes BCIE/EHK. *J Invest Dermatol* 1993; **100**: 516.
6 Kremer H, Lavrijsen AP, McLean WHI *et al.* An atypical form of bullous congenital ichthyosiform erythroderma is caused by a mutation in the L12 linker region of keratin 1. *J Invest Dermatol* 1998; **111**: 1224–6.
7 Terron-Kwiatkowski A, Paller AS, Compton J *et al.* Two cases of primarily palmoplantar keratoderma associated with novel mutations in keratin 1. *J Invest Dermatol* 2002; **119**: 966–71.
8 Hatsell SJ, Eady RA, Wennerstrand L *et al.* Novel splice site mutation in keratin 1 underlies mild epidermolytic palmoplantar keratoderma in three kindreds. *J Invest Dermatol* 2001; **116**: 606–9.
9 Reis A, Hennies H-C, Langbein L *et al.* Keratin 9 gene mutations in epidermolytic palmoplantar keratoderma (EPPK). *Nat Genet* 1994; **6**: 174–9.
10 Joh GY, Traupe H, Metze D *et al.* A novel dinucleotide mutation in keratin 10 in the annular epidermolytic ichthyosis variant of bullous congenital ichthyosiform erythroderma. *J Invest Dermatol* 1997; **108**: 357–61.
11 Sybert VP, Francis JS, Corden LD *et al.* Cyclic ichthyosis with epidermolytic hyperkeratosis: a phenotype conferred by mutations in the 2B domain of keratin 1. *Am J Hum Genet* 1999; **64**: 732–8.
12 Sprecher E, Ishida-Yamamoto A, Becker OM *et al.* Evidence for novel functions of the keratin tail emerging from a mutation causing ichthyosis hystrix. *J Invest Dermatol* 2001; **116**: 511–9.
13 Whittock NV, Smith FJ, Wan H *et al.* Frameshift mutation in the V2 domain of human keratin 1 results in striate palmoplantar keratoderma. *J Invest Dermatol* 2002; **118**: 838–44.
14 Irvine AD, McLean WHI. Human keratin diseases: increasing spectrum of disease and subtlety of phenotype–genotype correlation. *Br J Dermatol* 1999; **140**: 815–28.
15 Irvine AD, Paller AS. Molecular genetics of the inherited disorders of cornification: an update. *Adv Dermatol* 2002; **18**: 111–49.
16 Richard G. Human connexin disorders of the skin. *Cell Commun Adhes* 2001; **8**: 401–7.
17 Kimyai-Asadi A, Kotcher LB, Jih MH. The molecular basis of hereditary palmoplantar keratodermas. *J Am Acad Dermatol* 2002; **47**: 327–43; quiz 344–6.
18 Presland RB, Dale BA. Epithelial structural proteins of the skin and oral cavity: function in health and disease. *Crit Rev Oral Biol Med* 2000; **11**: 383–408.
19 Huber M, Rettler I, Bernasconi K *et al.* Mutations of keratinocyte transglutaminase in lamellar ichthyosis. *Science* 1995; **267**: 525–8.
20 Chavanas S, Bodemer C, Rochat A *et al.* Mutations in SPINK5, encoding a serine protease inhibitor, cause Netherton syndrome. *Nat Genet* 2000; **25**: 141–2.
21 Fischer J. Autosomal recessive congenital ichthyosis. *J Invest Dermatol*, 2009; **129**: 1319–21.
22 Fischer J, Bouadjar B, Heilig R *et al.* Mutations in the gene encoding SLURP-1 in mal de Meleda. *Hum Mol Genet* 2001; **10**: 875–80.
23 Palmer CNA, Irvine AD, Terron-Kwiatkowski A *et al.* Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet* 2006; **38**: 441–6.

Ichthyosis

Definition

Ichthyosis describes dry, rough skin with scaling over much of the body (Greek *ichthys/ikhthus*, fish -osis). The ichthyoses are a clinically and genetically heterogeneous group of skin disorders, characterized by a diffuse, generally uniform and persistent pattern of scaling without mucosal or extracutaneous (except in ichthyosiform syndromes) involvement. They are classified as disorders of keratinization or cornification. There are several congenital or genetic ichthyoses (with distinctive morphological features), a number of well-defined ichthyosiform or ichthyotic syndromes, rare cases that do not fit into either category, and acquired ichthyosis which is a complication of several systemic and malignant diseases (Table 19.2). They range in severity from mild ichthyosis vulgaris, to inflammatory and syndromic types and the often lethal harlequin ichthyosis.

Table 19.2 Congenital and acquired ichthyoses.

Congenital ichthyoses
Ichthyosis vulgaris (syn. autosomal dominant ichthyosis)
X-linked recessive ichthyosis (steroid sulphatase deficiency)
Non-bullous ichthyosiform erythroderma
Lamellar ichthyosis
Harlequin ichthyosis
Bullous ichthyosiform erythroderma (syn. epidermolytic hyperkeratosis)
Ichthyosis bullosa of Siemens
Ichthyosis hystrix
Ichthyosiform syndromes
Netherton's syndrome (syn. ichthyosis linearis circumflexa)
Sjögren–Larsson syndrome
Neutral lipid storage disease (syn. Chanarin–Dorfman syndrome)
Refsum's disease
Kallmann's syndrome
Multiple sulphatase deficiency syndrome
X-linked dominant ichthyosis (syn. Conradi–Hünermann-Happle syndrome)
IBIDS (syn. Tay syndrome, trichothiodystrophy, PIBIDS)
KID syndrome (keratitis, ichthyosis, deafness)
CHILD syndrome (congenital hemidysplasia, ichthyosiform erythroderma, unilateral limb defects)
Ichthyosis follicularis with alopecia and photophobia (IFAP)
Neu–Laxova syndrome
Congenital ichthyosis variants
Isolated genetic syndromes with ichthyosis (case reports)
Acquired ichthyosis
Drugs (e.g. nicotinic acid, hypocholesterolaemic agents, maprotiline)
Chronic hepatic disease, renal failure, thyroid and parathyroid disease
Malabsorption states
Sarcoidosis, leprosy
Acquired immune deficiency syndrome (AIDS)
Lymphoma and other malignancies

Ichthyoses result from abnormal epidermal differentiation or metabolism. Defective epidermal desquamation (retention) is a feature of some ichthyoses while a prominent inflammatory component occurs in others, usually associated with epidermal hyperproliferation. Epidermal fragility is a feature of some keratin mutations, while pruritus may complicate others.

History and classification

The first historic reference to ichthyosis appears in an Indian text in 250 BC, where there is mention of 'Ekakushtha, skin disease like scales of a fish' [1]. Detailed reports of 'Porcupine men' in the 1730s highlighted the severity and familial occurrence of hystrix-type ichthyosis [2]. The first account of a harlequin fetus

(ichthyosis) was in 1750 [3]. Willan, in his treatise *On Cutaneous Diseases*, classified ichthyosis as a 'squamous disease' [4] and attempts at genetic classifications followed. Brocq first used the label 'congenital ichthyosiform erythroderma', and distinguished between bullous and non-bullous ichthyosiform erythroderma [5]. The characteristic histological features of bullous ichthyosiform erythroderma were described by Lapiere [6], and subsequently termed epidermolytic hyperkeratosis [7]. Cockayne regarded sex-linked ichthyosis as a separate entity, and lamellar ichthyosis as a recessive condition [8]. Wells differentiated X-linked and autosomal dominant ichthyosis vulgaris in an epidemiological survey [9]. Recognition of ichthyosiform syndromes such as Refsum's disease, Netherton's and Sjögren–Larsson syndromes has come through astute clinical observation.

Early classifications depended on descriptive analogies, such as ichthyosis larvata, tarda, mitis and inversa. Wells and Kerr [9] defined groups of ichthyoses with autosomal recessive, sex-linked and autosomal dominant inheritance patterns, and clearly established X-linked recessive ichthyosis as a separate entity. Esterly [10] identified four categories of ichthyosis; major primary forms (ichthyosis vulgaris, recessive X-linked ichthyosis, bullous ichthyosis and congenital ichthyosiform erythroderma), ichthyosiform syndromes, related disorders of cornification and acquired ichthyoses.

Frost and van Scott [7] used epidermal kinetic data to characterize hyperproliferative (erythrodermic) and retention ichthyoses (ichthyosis vulgaris, X-linked ichthyosis). A numerical approach to 'disorders of cornification', lists 24 conditions (DOC 1–24), including the congenital ichthyoses and diverse diseases such as Darier's disease, peeling skin syndrome and the erythrokeratodermas [11]. Anton-Lamprecht and Schnyder [12] detailed subtle ultrastructural features of congenital ichthyosiform erythrodermas, and subdivided them into types 1–5. Traupe [13] identified four main categories: isolated vulgar ichthyoses, including ichthyosis vulgaris and X-linked recessive ichthyosis; associated ichthyoses of the vulgar type, such as Refsum's disease; isolated congenital ichthyoses, such as harlequin fetus, non-bullous ichthyosis and epidermolytic ichthyoses; and associated congenital ichthyoses, such as Sjögren–Larsson and Netherton's syndromes, IBIDS and X-linked dominant ichthyosis.

Elucidation of the underlying molecular abnormalities in many of these conditions now provides a more logical and mechanistic classification (Table 19.1) and reveals previously unsuspected heterogeneity.

References

1 Menon IA, Hoberman HF. Dermatological writings of ancient India. *Med Hist* 1969; **13**: 387–92.

2 Machin J. An uncommon case of distempered skin. *Philos Trans* 1733; **37**: 299–300.

3 Waring JJ. Early mention of a harlequin fetus in America. *Am J Dis Child* 1932; **43**: 442.

4 Willan R. *On Cutaneous Diseases*, Vol. 1. London: Barnard (J. Johnson), 1808: 197–212.

5 Brocq L. Erythrodermie congenitale ichthyosiforme avec hyperepidermotrophie. *Ann Dermatol Syphiligr* 1902; **4**: 1–31.

6 Lapiere S. Epidermolyse ichthyosiforme congenitale. *Ann Dermatol Syphiligr* 1932; **3**: 401.

7 Frost P, van Scott EJ. Ichthyosiform dermatoses: classification based on anatomic and biometric observations. *Arch Dermatol* 1966; **94**: 113–26.

8 Cockayne EA. *Inherited Abnormalities of the Skin and its Appendages*. London: Oxford University Press, 1933.

9 Wells RS, Kerr CB. Genetic classification of ichthyosis. *Arch Dermatol* 1966; **92**: 1–5.

10 Esterly NB. The ichthyosiform dermatoses. *Pediatrics* 1968; **42**: 990–1004.

11 Williams ML, Elias PM. Genetically transmitted, generalized disorders of cornification. *Dermatol Clin* 1987; **5**: 155–78.

12 Anton-Lamprecht I, Schnyder UW. Ultrastructure of inborn errors of keratinization. VI. Inherited ichthyoses: a model system for heterogeneities in keratinization disturbances. *Arch Dermatol Forsch* 1974; **250**: 207–27.

13 Traupe H. *The Ichthyoses: a Guide to Clinical Diagnosis, Genetic Counselling and Therapy*. Heidelberg: Springer-Verlag, 1989.

The epidermis in health and ichthyosis

Epidermal differentiation is characterized by the synthesis and post-translational modification of many structural proteins, in particular, the proteins constituting the cornified cell envelope and enclosed aggregated keratin filaments, which are the major components of the stratum corneum. Envelope precursors, such as involucrin, loricrin, small proline-rich proteins and envoplakin, are synthesized late in stratification and then cross-linked by the action of transglutaminase enzymes, which are synthesized in the granular layer. The corneocyte protein envelope is linked covalently to an outer ceramide layer, the lipid envelope, which also contains a variety of membrane-associated glycoproteins such as the integrins. Desmosomes are modified in the stratum corneum to form an electron-dense plug, the corneosome. In normal skin, desmosome density and cohesion lessens in transit from the lower to upper stratum corneum, but in hyperkeratotic states this does not occur [1]. Keratin macrofibrils are aggregated by interaction with filaggrin (filament aggregating protein), a basic histidine-rich protein stored as profilaggrin in keratohyaline granules. Keratin intermediate filaments are the major stress-bearing cytoskeletal proteins of mammalian epithelial cells, the product of two gene families encoding type I (acidic) and type II (neutral-basic) polypeptides, which are co-expressed in particular pairs in a tissue-specific and differentiation-related manner.

The intercellular spaces of the stratum corneum contain lipid-rich multilayered lamellae, which are secreted by lamellar or Odland bodies, present in large numbers in the cytoplasm of granular layer keratinocytes. At the granular–corneal junction, the lamellar body gravitates to the apex of the granular cell, and secretes its disc-like contents into the intercellular spaces [2]. The lipid-rich layers are redistributed into multilayered lamellae, composed of alternating electron-dense and electron-lucent lipid bands. Evidence suggests that these structures are formed by the condensation of liposomes under the influence of ceramides (sphingolipids that contain the n6 essential fatty acid, linoleic acid), which span the layers acting as rivets. They are also rich in non-polar lipids, free sterols including cholesterol sulphate, free fatty acids and triglycerides, and contain hydrolytic enzymes [3,4]. Conversion to cholesterol by cholesterol sulphatase, present on the cell membrane surface, leads to breakdown of the intercellular lipid lamellae and resultant desquamation [5]. Stratum corneum barrier function is dependent on the intercellular lipid lamellae, and increased transepidermal water loss is a characteristic feature of ichthyosis [6].

The importance of lipid metabolism in epidermal structure and function was first noted in 1929, when an animal model

deprived of dietary essential fatty acids developed hyperkeratosis, abnormal desquamation and increased transepidermal water loss [7]. In the 1950s, the lipid-lowering drugs nicotinic acid and triparanol caused a reversible ichthyosis in some patients [8]. An inherited enzyme deficiency was identified in the 1960s as the cause of Refsum's disease [9] and cholesterol sulphatase deficiency in patients with X-linked recessive ichthyosis was reported in 1976 [10]. Sjögren–Larsson syndrome, another ichthyosiform disorder with neurological disease, is associated with fatty alcohol defects [11], while peroxisomal dysfunction, specifically abnormal sterol biosynthesis, has been identified in patients with Conradi–Hünermann and CHILD syndromes [12,13].

Disordered keratinization also results from alterations in structural proteins, including individual keratins, cornified envelope proteins and keratin-associated proteins (Table 19.1). Enzyme and metabolic defects (e.g. loss of transglutaminase activity in lamellar ichthyosis) and abnormalities in gap junction proteins (connexin mutations in the keratitis–ichthyosis–deafness (KID) syndrome) have been identified in diverse ichthyoses [14]. Several ichthyoses are associated with hyperproliferative and inflammatory features. Chronic barrier damage induces keratinocyte DNA synthesis and results in epidermal hyperplasia [15], with knock-on effects on the activity of cytokines, growth factors, calcium gradients, adhesion molecules and lytic enzymes. The identification of a serine protease inhibitor mutation in Netherton's syndrome and defects in lipoxygenase activity in an erythrodermic ichthyosis provide further insights into the occurrence of inflammatory changes [16].

References

1 Chapman SJ, Walsh A. Desmosomes, corneosomes and desquamation: an ultrastructural study of adult pig epidermis. *Arch Dermatol Res* 1990; **282**: 304–10.
2 Wertz PW, Swartzendruber DC, Abraham W *et al.* Essential fatty acids and epidermal integrity. *Arch Dermatol* 1987; **123**: 1381–4.
3 Lampe MA, Williams ML, Elias PM. Human epidermal lipids: characterization and modulations during differentiation. *J Lipid Res* 1983; **24**: 131–40.
4 Menon GK, Grayson S, Elias PM. Cytochemical and biochemical localization of lipase and sphingomyelinase activity in mammalian epidermis. *J Invest Dermatol* 1986; **86**: 591–7.
5 Elias PM, Williams ML, Maloney ME *et al.* Stratum corneum lipids in disorders of cornification: steroid sulphatase and cholesterol sulphate in normal desquamation and the pathogenesis of recessive X-linked ichthyosis. *J Clin Invest* 1984; **74**: 1414–21.
6 Elias PM. Epidermal lipids, barrier function and desquamation. *J Invest Dermatol* 1983; **80**: 44–9.
7 Burr GO, Burr MM. A new deficiency disease produced by the rigid exclusion of fat from the diet. *J Biol Chem* 1929; **82**: 345–67.
8 Winklemann RK, Perry HO, Achor RWP, Kirby TJ. Cutaneous syndromes produced as side-effects of triparanol therapy. *Arch Dermatol* 1963; **87**: 372–7.
9 Kahlke W, Riterich R. Refsum's disease: an inborn error of lipid metabolism with storage of 3,5,11,15-tetramethyl hexadecanoic acid. Isolation and identification of the storage product. *Am J Med* 1965; **39**: 237–41.
10 Jobsis AC, van Duuren Chr Y, van de Vries GP *et al.* Trophoblast sulphatase deficiency associated with X-chromosomal ichthyosis. *Ned Tijdschr Geneeskd* 1976; **120**: 180.
11 Rizzo WB, Dammann AL, Craft DA. Sjögren–Larsson syndrome: impaired fatty alcohol oxidation in cultured fibroblasts due to deficient fatty alcohol: NAD oxidoreductase activity. *J Clin Invest* 1988; **81**: 738–44.
12 Holmes RD, Wilson GN, Hajra AK. Peroxisomal enzyme deficiency in the Conradi–Hünermann type of chondrodysplasia punctata. *N Engl J Med* 1987; **316**: 1608.
13 Emami S, Rizzo WB, Hanley KP *et al.* Peroxisomal abnormality in fibroblasts from involved skin of CHILD syndrome. *Arch Dermatol* 1992; **128**: 1213–22.
14 Kelsell DPW, Houseman MJ. Connexin mutations in skin disease and hearing loss. *Am J Hum Genet* 2001; **68**: 559–68.
15 Proksch E, Holleran WM, Menon GK *et al.* Barrier function regulates epidermal lipid and DNA synthesis. *Br J Dermatol* 1993; **128**: 473–82.
16 Chavanas S, Bodemer C, Rochat A *et al.* Mutations in SPINK5, encoding a serine protease inhibitor, cause Netherton syndrome. *Nat Genet* 2000; **25**: T41–2.

Congenital ichthyoses

Ichthyosis vulgaris (MIM 146700)

Synonym
- Autosomal dominant ichthyosis

Ichthyosis vulgaris (IV) is the most common of the inherited ichthyoses, with a reported incidence of 1 in 250 in an English population study of 6051 healthy schoolchildren [1]. It is regarded as an autosomal dominant condition with variable penetrance. The majority of affected individuals have mild scaling which may clear in the summer months. It is more common in temperate climates and Caucasian populations and has an equal sex distribution. There is a close association between IV and atopic diseases; 37–50% of people who have ichthyosis vulgaris show features of atopic disease [1–3]. However, the difficulty in distinguishing IV from the xerosis of atopic eczema on clinical grounds may result in an overestimate of both its frequency and its correlation with atopic eczema [4].

Histopathology. Histology of affected skin shows a mild hyperkeratosis and, usually, a diminished or absent granular layer in the epidermis. The dermis is normal. Features of keratosis pilaris may be seen. Electron microscopy reveals scanty and fragmented keratohyaline granules in granular layer cells, whereas the keratin filaments appear normal [5]. The association between IV and atopic eczema has been questioned on histological grounds, as eczematous features are found in biopsies of atopic xerosis [6]. Furthermore, ultrastructural study of xerotic lesions in 49 patients with atopic eczema and dry skin showed typical features of ichthyosis vulgaris in only two [4].

Aetiology and pathogenesis. In the 1980s, biochemical studies on ichthyosis vulgaris skin showed that, in lesional skin only, uptake of radiolabelled histidine by the granular layer was reduced [7]. Histidine is necessary for the synthesis of profilaggrin, the high-molecular-weight, 400-kD precursor of filaggrin. Profilaggrin was virtually absent from the epidermis and cultured keratinocytes (in those IV patients with absent granular layer and keratohyaline granules) and filaggrin synthesis was defective [7]. Filaggrin (from *fil*ament *aggr*egating prote*in*) is a 37-kD peptide which is a major component of the keratohyaline granule in the granular layer. Filaggrin binds to keratin filaments causing their aggregation and leading to flattening of the stratum corneum keratinocytes (corneocytes). Their intracellular proteins are cross-linked by transglutaminases, forming the cornified envelope which contributes to epidermal barrier function. Cultured keratinocytes from unaffected skin formed thickened layers, with small keratohyaline bodies, which failed to react with monoclonal anti-

body to filaggrin [8]. Expression of filaggrin mRNA was reduced [9], keratin expression and markers were normal [10] and proliferative activity was reduced [11]. A mouse mutant, flaky tail mouse, lacking profilaggrin expression provides an animal model for IV [12].

In 2002, genetic studies confirmed linkage between IV (with absent granular layer) and the epidermal differentiation complex (EDC) of genes on chromosome 1q21 [13]. The EDC contains the genes for filaggrin and several other proteins integral to late epidermal maturation and barrier function. Identification of mutations in the filaggrin gene was delayed because of its complexity, but Smith *et al.* finally sequenced the critical terminal exon [14]. They went on to prove in a large genetic study of affected families that two common filaggrin loss-of-function mutations, R501X and 2282del4, cause ichthyosis vulgaris [14]. These same filaggrin mutations also predispose to atopic eczema [15,16], atopic asthma and possibly psoriasis. Even in patients with homozygous mutations, some filaggrin fragments may be produced which might account for phenotypic variation in IV.

Additional factors that may contribute to the severity of scaling in IV are a deficiency of the water-retentive amino-acid breakdown products of filaggrin (including urocanic acid and pyrrolidone carobxylic acids) in the outer stratum corneum [17] and a defect in serine proteases involved in the degradation of desmoglein 1, a transmembrane desmosomal protein [18].

Clinical features. The skin may appear dry and scaly in the neonatal period, but more usually scaling is obvious from 2 months onwards and may be further delayed. The scale is white or grey, small, flaky or branny, and semi-adherent with turned-up edges (Fig. 19.1). It is most pronounced on the extensor surfaces of the arms and lower legs, and characteristically spares the flexural creases. The trunk, especially the abdominal wall, is often mildly affected and the nappy (diaper) area is spared. Facial scaling, generally forehead and perioral, mild dandruff and involvement of the pinnae are seen in some patients. The palms and soles are usually free of scale, but palmoplantar hyperlinearity (linear grooves crossing perpendicularly to the thenar and hypothenar eminences), a reflection of mild hyperkeratosis, is a helpful feature in many ichthyosis vulgaris patients, whether they have coexistent eczema or not [19]. It also occurs in atopic eczema without ichthyosis [4,20]. Keratosis pilaris is a common associated feature of both atopic eczema and IV, and favours the extensor aspects of the upper arms and thighs.



Fig. 19.1 Ichthyosis vulgaris.

Symptoms of IV are few, mainly dryness or roughness of the skin and the cosmetic effect. In isolated IV, pruritus is not a problem, but in patients who also have eczema, pruritus, excoriation and lichenification are additional features. In these patients, atopic xerosis may mimic IV but the ichthyosis has a characteristic histology and persists after the eczema has settled.

There is a marked seasonal variation in most patients, with improvement in warm and sunny weather, with a degree of ambient humidity. Many sufferers (38% of 169 patients) report a gradual improvement in adolescence [1], although a small number worsen with age. Reports of ocular manifestations and testicular cancer in ichthyosis vulgaris have not been verified, and may have arisen from inclusion of X-linked ichthyosis cases [21,22].

Diagnosis. Ichthyosis vulgaris may be mistaken for atopic xerosis, irritant dermatitis, eczéma craquelé, acquired ichthyosis, Refsum's disease and a mild autosomal recessive ichthyosis variant reported in five of eight siblings [23].

Genetics. Ichthyosis vulgaris is regarded as an autosomal dominant disease with variable penetrance, such that disease severity can vary between generations, and affected siblings. Following the success in sequencing the filaggrin gene, recent extensive genetic studies, including IV families with linkage to the epidermal differentiation complex on chromosome 1, have uncovered two common filaggrin mutations, R501X and 2282del4, which result in loss-of-function, stop codons in the gene and absence of filaggrin in keratinocytes [14,24]. The carrier rate for filaggrin mutations in populations of European descent is around 10% (heterozygotes, clinically mildly affected), with 1% who are compound heterozygous or homozygous (moderate to severe IV). The combined allele frequency was estimated to be 4% [14]. This is referred to as semi-dominant inheritance and the common heterozygote state may confer a biological advantage. A recent Scottish study of the clinical effects of filaggrin mutations showed even higher rates of carriage with 1:8 heterozygous and 1:80 compound heterozygous or homozygous [25]. Different filaggrin mutations have been found in Japanese IV and atopic dermatitis patients [26].

Treatment. As a general measure, avoidance of low humidity environments and extremes of temperature is of benefit to all ichthyosis patients. Regular emollient application is recommended for those with ichthyosis vulgaris, and if provided with samples of a variety of suitable preparations, patients can make their own choice as to the most acceptable and appropriate for them in a given situation. Many do not require treatment in the summer as they spontaneously improve. In drier, colder seasons, mild and moderately affected individuals may opt to use a light emollient, such as aqueous cream, which can also be used as a soap substitute. More severe ichthyosis warrants concentrated paraffin containing (50/50 mixtures of white soft and liquid paraffin) or

cetostearyl alcohol-containing emollients, of which there are many proprietary brands. Glycerol may be added to improve lubrication. It should be borne in mind that greasy emollients such as emulsifying ointment have adverse effects on certain fabrics, the rubber seals of washing machines and drains. Open pots may become contaminated with bacteria as ointments do not contain preservatives.

Emollients need to be applied at regular intervals, but while morning and evening treatments are convenient for most patients, application during the day may not be possible for people with a busy work or school routine or shift workers. Assistance from carers and at school should be arranged for severely affected children. Emollient bath oils and a variety of soap substitutes are available. Cetomacrogol additives may enhance the antipruritic effect of bath oils. Bubble bath, astringent and other irritant products should be avoided.

Keratolytic agents, such as 1–5% salicylic acid, may be added to emollient cream bases, to encourage shedding of scale, but in practice they tend to be too irritant for regular usage. The risk of systemic toxicity (salicylism) precludes widespread application of salicylic acid-containing compounds, especially in young children who have a high surface area relative to body size. Alpha-hydroxy acids, such as lactic, glycollic, malic, mandelic, citric, pyruvic, gluconic and tartaric acids, 5–10% in an oil, lotion, cream or hydrophilic ointment base are said to enhance corneocyte shedding by virtue of their effect in breaking intercellular bonds [27]. They have become popular additives in many commercial skin-care products ('fruit acids') in recent years, and may be less irritant although more expensive than salicylic acid compounds. Toxicity has also been reported with topical lactic acid [28]. Beneficial effects from topical 12% ammonium lactate lotion have been reported [29]. Urea-containing (5–10%) emollients improve epidermal hydration, lyse keratin and are bacterostatic [30,31]. Topical retinoids are generally too irritant. The activity of keratolytic and urea treatments can be enhanced by occlusion under tubular dressings, sleep suits or bandages. In practice, they can be applied as tolerated to localized areas of the limbs for 1–2 weeks at a time to produce a mild exfoliation, which can then be maintained with less frequent application. Mechanical exfoliation can be achieved with a loofah while bathing. Dandruff is not a problem for most ichthyosis vulgaris sufferers, but if present can be controlled with a tar- or salicylic acid-containing shampoo.

Patients with both ichthyosis vulgaris and atopic eczema will need appropriate eczema therapy with the addition of topical anti-inflammatory or immunomodulatory preparations as required. Topical steroids and immunosuppressive agents do not benefit IV but oral evening primrose oil, which contains essential n6 fatty acids, produced a slight improvement in some [32]. Systemic retinoid therapy is not necessary or appropriate for IV, and in patients with associated atopic eczema would be likely to exacerbate the eczema.

References

1 Wells RS, Kerr CB. Clinical features of autosomal dominant and sex-linked ichthyosis in an English population. *BMJ* 1966; **1**: 947–50.

2 Kuokkanen K. Ichthyosis vulgaris: a clinical and histopathological study of patients and their close relatives in the autosomal dominant and sex-linked forms of the disease. *Acta Derm Venereol (Stockh)* 1969; **62**: 1–72.

3 Traupe H. *The Ichthyoses: a Guide to Clinical Diagnosis, Genetic Counselling and Therapy*. Heidelberg: Springer-Verlag, 1989.

4 Fartasch M, Diepgen TL, Hornstein OP. Atopic dermatitis, ichthyosis vulgaris, hyperlinear palms: an ultrastructural study. *Dermatologica* 1989; **178**: 202–5.

5 Anton-Lamprecht I, Hofbauer M. Ultrastructural distinction of autosomal dominant ichthyosis vulgaris and X-linked ichthyosis. *Humangenetik* 1972; **15**: 261–4.

6 Finlay AY, Nicholl S, King C, Marks R. The dry non-eczematous skin associated with atopic eczema. *Br J Dermatol* 1980; **103**: 249–56.

7 Sybert VP, Dale BA, Holbrook KA. Ichthyosis vulgaris: identification of a defect in the synthesis of filaggrin correlated with an absence of keratohyaline granules. *J Invest Dermatol* 1985; **84**: 191–4.

8 Fleckman P, Holbrook KA, Dale BA, Sybert VP. Keratinocytes cultured from subjects with ichthyosis vulgaris are phenotypically abnormal. *J Invest Dermatol* 1987; **88**: 640–5.

9 Nirunsuksiri W, Presland RB, Brumbaugh SG *et al.* Decreased profilaggrin expression in ichthyosis vulgaris is a result of selectively impaired posttranscriptional control. *J Biol Chem* 1995; **270**: 871–6.

10 Weiss RA, Guillet GYA, Freedberg IM *et al.* The use of monoclonal antibody to keratin in human epidermal diseases: alterations in immunohistochemical staining pattern. *J Invest Dermatol* 1983; **81**: 224–30.

11 Kanitakis J, Hoyo E, Chouvet B *et al.* Keratinocyte proliferation in epidermal keratinocyte disorders evaluated through PCNA/cyclin immunolabelling and AgNOR counting. *Acta Derm Venereol (Stockh)* 1993; **73**: 370–5.

12 Presland RB, Boggess D, Lewis SP *et al.* Loss of normal profilaggrin and filaggrin in flaky tail (ft/ft) mice: an animal model for the filaggrin-deficient skin disease ichthyosis vulgaris. *J Invest Dermatol* 2000; **115**: 1072–81.

13 Compton JG, DiGiovanna JJ, Johnston KA *et al.* Mapping of the associated phenotype of an absent granular layer in ichthyosis vulgaris to the epidermal differentiation complex on chromosome 1. *Exp Dermatol* 2002; **11**: 518–26.

14 Smith FJ, Irvine AD, Terron-Kwaitkowski A, Sandilands A *et al.* Loss-of-function mutations in the gene encoding filaggrin cause ichthyosis vulgaris. *Nat Genet* 2006; **38**: 337–42.

15 Palmer CN, Irvine AD, Terron-Kwaitkowski A *et al.* Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet* 2006; **38**: 441–6.

16 Morar N, Cookson WO, Harper JI *et al.* Filaggrin mutations in children with severe atopic dermatitis. *J Invest Dermatol* 2007; **127**: 1667–72.

17 Scott IR, Harding CR, Barrett JG. Histidine rich protein of keratohyaline granules: source of the free amino acids, urocanic acid and pyrrolidone carobxylic acids in stratum corneum. *Biochim Biophys Acta* 1982; **719**: 110–7.

18 Suzuki Y, Koyama J, Moro O *et al.* The role of two endogenous proteases of the stratum corneum in the degradation of desmoglein 1 and their reduced activity in the skin of ichthyotic patients. *Br J Dermatol* 1996; **134**: 460–4.

19 Mevorah B, Marazzi A, Frenk E. The prevalence of accentuated palmoplantar markings and keratosis pilaris in atopic dermatitis, autosomal dominant ichthyosis and control dermatological patients. *Br J Dermatol* 1985; **112**: 679–85.

20 Uehara M, Hayashi S. Hyperlinear palms. *Arch Dermatol* 1981; **117**: 490–1.

21 Sever RJ, Frost P, Weinstein G. Eye changes in ichthyosis. *JAMA* 1968; **206**: 2283–6.

22 Lykkesfeldt G, Bennett P, Lykkesfeldt AE *et al.* Testis cancer: ichthyosis constitutes a significant risk factor. *Cancer* 1991; **67**: 730–4.

23 Bernhardt M, Baden HP. Report of a family with an unusual expression of recessive ichthyosis. *Arch Dermatol* 1986; **122**: 428–33.

24 Segre JA. Epidermal differentiation complex yields a secret: mutations in the cornification protein filaggrin underlie ichthyosis vulgaris. *J Invest Dermatol* 2006; **126**: 1202–4.

25 Sergeant A, Campbell LE, Hull PR *et al.* Heterozygous null alleles in filaggrin contribute to clinical dry skin in young adults and the elderly. *J Invest Dermatol* 2009; **129**: 1042–5.

26 Nomura T, Sandilands A, Akiyama M *et al.* Unique mutations in the filaggrin gene in Japanese patients with ichthyosis vulgaris and atopic dermatitis. *J Allergy Clin Immunol* 2007; **119**: 434–40.

27 Van Scott EJ, Yu RJ. Hyperkeratinization, corneocyte cohesion and alpha-hydroxy acids. *J Am Acad Dermatol* 1984; **11**: 867–79.

28 Ramirez M, Youseef W, Romero R *et al.* Acute percutaneous lactic acid poisoning in a child. *Paediatr Dermatol* 2006; **23**: 282–5.

29 Buxman M, Hickman J, Ragsdale W *et al.* Therapeutic activity of lactate 12% lotion in the treatment of ichthyosis. *J Am Acad Dermatol* 1986; **15**: 1253–8.

30 Swanbeck G. The effect of urea on the skin with special reference to the treatment of ichthyosis. In: Marks R, Dykes PJ, eds. *The Ichthyoses*. Lancaster: MTP Press, 1978: 173–6.
31 Kuster W, Bohnsack K, Rippke F *et al*. Efficacy of urea therapy in children with ichthyosis. *Dermatology* 1998; **196**: 217–22.
32 Chalmers RJG, Shuster S. Evening primrose seed oil in ichthyosis vulgaris. *Lancet* 1983; **1**: 236–7.

X-linked recessive ichthyosis (MIM 308100)

Typically, X-linked recessive ichthyosis (XLRI) affects male offspring who inherit an X chromosome bearing a mutated steroid sulphatase gene from their asymptomatic carrier mother. Although the ichthyosis is rarely a significant problem, XLRI is an important disease for many reasons. It may be associated with extracutaneous manifestations and obstetric complications. The underlying lipid metabolic defect and the pathogenesis of the ichthyosis have been elucidated. The gene for steroid sulphatase (*STS*) is located at the distal end of the short arm of the X chromosome.

Incidence. Wells and Kerr [1], in a large epidemiological study in 1966, differentiated XLRI from ichthyosis vulgaris and defined clinical and genetic features. They estimated its incidence in the UK at 1 in 6190 males. A not dissimilar incidence has been reported in other countries, based on clinical diagnostic criteria. In a Danish population study of placental *STS* deficiency, a predicted incidence of XLRI of 1 in 2000 males was derived [2]. XLRI has a worldwide distribution in all ethnic groups.

Aetiology and pathogenesis. In the 1970s, *STS* deficiency was identified as the cause both of XLRI and placental sulphatase deficiency, confirming them as a single disease entity [3,4]. Fibroblasts, epidermal cells, leukocytes, nail, hair bulbs, amniocytes and testicular tissue can all be assayed for a functional and immunological enzyme deficiency. The enzyme substrate, cholesterol sulphate, is elevated in many tissues, including serum, red blood cell membranes, stratum corneum and nail matrix, but serum cholesterol levels are normal, as its main synthetic enzyme is hydroxymethylglutamyl-CoA reductase. Lipid analysis of normal epidermis shows a gradual decline in cholesterol sulphate (which stabilizes lipid bilayers) from 6% in the granular layer to 3% in the stratum corneum. A concomitant rise in epidermal cholesterol, which triggers stratum corneum intercellular lipid bilayer disintegration and desquamation, reflects the increasing activity of membrane-based steroid sulphatase at the corneal–granular layer junction. In XLRI, cholesterol sulphate accounts for 12–30% of stratum corneum lipids [5,6]. Calorimetric studies identified a failure of the normal liquid–crystalline transition phase of stratum corneum intercellular lipids in XLRI, presumably because of the polar subgroups of cholesterol sulphate [7]. The raised level of cholesterol sulphate in the stratum corneum also reduces the activity of serine proteases responsible for cleaving desmosomes [8].

Steroid or cholesterol sulphatase is one of the two isomers of aryl sulphatase C, a membrane-bound microsomal enzyme, and is responsible for hydrolysing sulphate groups from cholesterol sulphate and certain other steroids. The sulphated forms of some steroid sex hormones, such as 17-hydroxyprogesterone, oestrone and dehydroepiandosterone, are also increased in patients with XLRI [9]. Androstenedione and testosterone sulphate are reduced, but testosterone and dihydrotestosterone levels are normal, as synthesis can be mediated by a desaturase enzyme system. Pituitary gonadotrophins (with the possible exception of LH), prolactin and sex steroid binding globulin are normal. The altered sex hormone profile may, in part, explain the abnormal testicular development in some XLRI patients.

Evidence of a direct causal link between elevated cholesterol sulphate levels and scaling is compelling. Topical application of cholesterol sulphate in the hairless mouse induced a reversible retention ichthyosis, and a threefold increase in stratum corneum thickness after 1 week [10]. The scaling cleared within 3 days of stopping the treatment, and did not occur if other sulphated substrates of the enzyme were applied. Topical cholesterol prevented this effect, and also temporarily reduced the scaling of XLRI but not of other ichthyoses. Many cholesterol-lowering drugs have caused ichthyosis as a side effect [11].

Histopathology. Affected skin in XLRI shows an expanded stratum corneum without parakeratosis or acanthosis. The granular cell layer is usually normal, but may be mildly thickened or, rarely, diminished, making histological differentiation from ichthyosis vulgaris difficult. Ultrastructurally, the keratohyaline granules are normal or small, in contrast to ichthyosis vulgaris, and are numerous. Desmosomes are more persistent than normal, and corneal melanosomes more prominent [12,13]. Kinetic studies have shown normal rates of cell turnover.

Clinical features. In 75% of cases, scaling is evident within the first week of life [14], but 6% develop scaling after the age of 1 year [15]. A Danish study of 76 patients revealed onset of light, flaky scaling before 1 month of age, with more typical scale by 6 months in all but two children [16]. A prominent peeling episode at this stage was characteristic. The scaling tends to increase throughout childhood, often spreading up from the lower legs to the trunk. It stabilizes in the teens with little subsequent change, and in most patients scaling diminishes in the summer months. There is considerable variation in the severity of scaling between families, and even in some instances within affected kindred. Pruritus is unusual.

Scaling in XLRI is most prominent on the extensor surfaces of the upper arms, the abdomen, outer thighs and around the lower legs (Fig. 19.2). Typically, the scale is medium to large, polygonal, adherent, dull and light to dark brown, depending on skin type. The posterior and lateral neck, upper and lateral abdominal wall and pre-auricular facial skin are commonly affected with semi-adherent, grey scale and, in contrast to ichthyosis vulgaris, the flexures may be involved. The face, scalp, axillae, flexor aspects of the limbs and dorsal hands and feet may show light grey scaling but the palms and soles are spared. Rarely, a fine white or brown scaling is the predominant sign, and leads to a delay in diagnosis (Fig. 19.3). In one study the average age of diagnosis was 10.3 years [14].

Extracutaneous features of XLRI. Various extracutaneous abnormalities have been noted in some patients with an increased incidence of testicular maldescent, abnormalities of sperm count or



(a)

(b)

(c)

Fig. 19.2 X-linked recessive ichthyosis. (a) Scaling on the arm, (b) on the legs and (c) on the trunk.



Fig. 19.3 Mild X-linked recessive ichthyosis in a 3-year-old boy.

motility, and testicular cancer have been reported [16–19]. Of a group of 76 patients, nine had testicular maldescent and three developed testicular cancer in normally descended testes (one had bilateral cancer) [16,19]. Inguinal hernia appears to be more common, and unilateral renal agenesis was reported in half of those with cryptorchidism, all of whom had features of Kallmann's syndrome [14]. Male pattern baldness does occur in XLRI.

Corneal dot, thread-like or comma-shaped opacities, detected with the slit-lamp microscope, occur in 24–100% of adult patients [15,16,20,21], and to a lesser degree in 24% or more of female carriers [21]. They are usually of no functional significance but a minority suffer from mild keratitis. Corneal opacities in XLRI are thought to be a result of stromal deposits on the posterior surface of Desçemet's membrane [21].

Perinatal manifestations of steroid sulphatase deficiency. It was noted, in the 1970s, that low maternal urinary oestriol excretion in the third trimester of pregnancy was not invariably associated with intrauterine growth retardation. These pregnancies often ended in a prolonged labour, and the underlying defect, placental

STS deficiency, was identified. Coincidentally, *STS* deficiency was noted in boys with XLRI [2,3].

Prolonged labour may affect up to one-third of patients with XLRI, with a consequent risk of perinatal complications. In a group of 33 patients, four had a spastic paraplegia or paraparesis, apparently as a result of prolonged labour, requiring obstetric intervention [14]. In each case, a younger male sibling with XLRI was neurologically normal.

XLRI and contiguous gene defects. Kallmann's syndrome describes the association of XLRI with hypogonadotropic hypogonadism, anosmia and a variety of neurological defects, including nystagmus and mirror movements of the hands and feet (synkinesis) [22]. It is estimated to affect 1 in 60 000 of the population, and may be misdiagnosed as XLRI until adult life because of delayed recognition of hypogonadism. Adult patients develop obesity and osteoporosis. Renal anomalies and cleft palate have also been reported in Kallmann's syndrome. Developmental delay and spastic paraplegia appear to be more common in Kallmann's syndrome than in isolated XLRI. Kallmann's syndrome is caused by a large deletion of the short arm of the X chromosome proximal to and including the *STS* gene. The features of Rud's syndrome (X-linked ichthyosis, obesity, hypogonadism, mental retardation, epilepsy and endocrinopathies) can, in large part, be attributed to Kallmann's syndrome or to perinatal complications in patients with XLRI [23].

Larger X chromosome deletions distal to and including the *STS* gene may lead to XLRI associated with mild mental retardation, mild chondrodysplasia punctata and short stature [24]. Epiphyseal stippling of long bones, larynx and vertebrae can occur transiently in early childhood in the chondrodysplasia variant, while dysplastic features may be detected on X-rays later in life. Hypoplasia of cartilage and distal phalanges has been noted in affected males, and carrier females may also be of short stature. Sparse, brittle hair occurred in two patients with large X chromosome deletions [14].

Diagnosis. Raised serum cholesterol sulphate in patients with XLRI can be detected on serum lipoprotein electrophoresis [25]. Cholesterol sulphate carries a stronger electronegative charge than cholesterol, resulting in increased mobility of the β low-density lipoprotein fraction (a 'fast' band 2 mm or so beyond that of controls) towards the anode (Fig. 19.4). This simple screening test is not widely available. Equivocal results (1 mm difference) should be followed up with the definitive test, *STS* assay, which is available in regional laboratories. Enzyme activity can be measured in leukocytes (EDTA blood sample) or skin fibroblasts, and is much reduced or absent in XLRI [26]. Serum cholesterol levels are normal in XLRI.

Chromosomal analysis using high-resolution G-banding will detect and quantify significant Xp deletions where clinical evidence of contiguous gene defects exists. DNA-based techniques include fluorescent *in situ* hybridization (FISH) analysis which detects deletion of the *STS* gene, the most common cause of XLRI [27], and Southern blot analysis to identify specific gene deletions, or point mutations at and distal to the *STS* gene locus [28]. PCR amplified testing for exons in Kallmann's syndrome genes is the most sensitive test for this condition

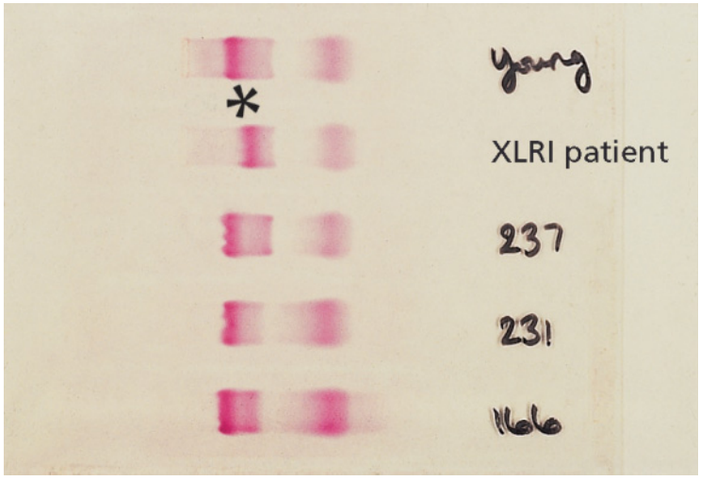


Fig. 19.4 Serum electrophoresis, showing 'fast' band in XLRI patient (compared to controls).

Clinically, XLRI may resemble ichthyosis vulgaris or mild lamellar ichthyosis. A Sardinian kindred with a phenotype suggestive of XLRI but normal *STS* activity has been reported [29]. XLRI has been reported in a female [30].

Genetics. Linkage of XLRI and the Xg red blood cell group in the 1960s was an early example of chromosome localization identified by tracking linked traits in family studies [31]. The association of XLRI with stunted growth, hypogonadism and anosmia has enabled mapping of the relevant genes on the short arm of the X chromosome (Xp). Gene mapping in families with X to Y translocations placed the *STS* gene at the Xp 22.3 locus [32]. The Kallmann's syndrome gene is proximal to this, while deletions distal to the *STS* gene (towards the pseudoautosomal region at the tip of the X chromosome) may cause mental retardation, chondrodysplasia punctata and short stature [24,33].

The virtual absence of immunoreactive *STS* in XLRI patients is matched by a complete deletion of the *STS* gene on Southern blot analysis of genomic DNA in up to 90% of cases [14,34]. Point mutations of the gene have also been identified [28,35]. There is considerable genetic heterogeneity in XLRI and contiguous gene syndromes, with sizeable DNA loss (3.4%, up to 2 megabases) detected by flow cytometry in some [36] and in others evidence of X–Y translocations [37].

Isolated XLRI is generally a mild disease and few families are interested in prenatal diagnosis. However, placental *STS* deficiency is a risk factor in affected pregnancies, and knowledge of their carrier status could reduce perinatal risk for mother and baby. Kallmann's and other contiguous gene defects are more serious conditions and affected families seeking genetic counselling and/or prenatal diagnosis first need genetic and molecular investigation, including heterozygote detection. Prenatal diagnosis of XLRI and associated conditions, previously suggested by low maternal urinary oestriol levels, can be confirmed by steroid sulphatase assay of a chorionic villus/amniocyte biopsy.

Southern blot analysis with PCR will detect *STS* gene deletion and mutations or contiguous gene defects while high-resolution G-banding identifies large Xp deletions. FISH analysis can also rapidly identify female carriers [2,27,28].

Carrier detection. Obligate carriers show no consistent cutaneous features but corneal stromal deposits are detected on slit-lamp examination in a proportion [20,21]. Lipoprotein electrophoresis is normal in obligatory female carriers. *STS* levels in leukocytes, fibroblasts or hair roots are higher in normal females than in normal males, because the Lyon effect (random inactivation of one X chromosome in normal female cells) does not apply to the *STS* gene [38]. Therefore, female carriers would be expected to have 50% of the *STS* values of non-carrier females. Indeed, 30 of 31 obligate carriers had a leukocyte *STS* level below the 2.5 percentile of normal females, indicating enzyme heterozygosity [38]. However, partial X inactivation was evident in other studies; enzyme values in the range of 40–86% in known carriers were obtained. Leukocyte *STS* assay, using oestrone sulphate as substrate, proved the most reliable biochemical test for heterozygote detection [39]. Visual assessment of stained hair roots to detect *STS* has also been used. Southern blot hybridization of leukocyte DNA provides an accurate measure of the anticipated 50% *STS* gene dosage in carriers, but is applicable only to the 90% of XLRI families with complete gene deletion [40]. FISH analysis, a technically less demanding diagnostic technique, is currently the method of choice for carrier detection in XLRI families where a gene deletion is the underlying defect [27]. In the remaining 10% of carriers without gene deletions, PCR and direct DNA sequencing is necessary. Somatic and germinal mosaicism for the *STS* gene deletion in a carrier has been reported [41].

Treatment. The same principles apply to treatment of XLRI as have been outlined for ichthyosis vulgaris. Most patients achieve an acceptable level of control of their scaling and dryness with daily emollient application, and may improve sufficiently in the increased humidity of temperate summers to forgo any therapy. Keratolytic and urea-containing preparations are generally less irritating than in ichthyosis vulgaris. In severe XLRI, short or intermittent courses of oral retinoid therapy may be considered. A topical receptor-selective retinoid, tazarotene, showed promising results in a small number of patients [42]. Topical application of cholesterol reversed the effect of cholesterol sulphate in hairless mice [10], and a 10% cholesterol cream improved scaling in 18 of 20 patients after 3–5 weeks [43]. Abnormalities of genital or secondary sexual development should be investigated by an endocrinologist and appropriate treatment planned. Short stature warrants early investigation, including a radiological check of long-bone epiphyses. Neurological and developmental assessments will detect those patients with neurological damage or Kallmann's syndrome and help identify special educational needs.

References

1 Wells RS, Kerr CB. Clinical features of autosomal dominant and sex-linked ichthyosis in an English population. *BMJ* 1966; **1**: 947–50.

2 Lykkesfeldt G, Nielsen MD, Lykkesfeldt AE. Placental steroid sulphatase deficiency: biochemical diagnosis and clinical review. *Obstet Gynecol* 1984; **64**: 49–54.

3 Jobsis AC, van Duuren ChrY, van de Vries GP *et al.* Trophoblast sulphatase deficiency associated with X-chromosomal ichthyosis. *Ned Tijdschr Geneeskd* 1976; **120**: 1980.

4 Webster D, France JT, Shapiro LJ, Weiss R. X-linked ichthyosis due to steroid sulphatase deficiency. *Lancet* 1978; **1**: 70–2.

5 Elias PM, Williams ML, Maloney ME *et al.* Stratum corneum lipids in disorders of cornification: steroid sulphatase and cholesterol sulphate in normal desquamation and the pathogenesis of recessive X-linked ichthyosis. *J Clin Invest* 1984; **74**: 1414–21.

6 Jetten AM, George MA, Nervi C *et al.* Increased cholesterol sulphate and cholesterol sulphotransferase activity in relation to the multistep process of differentiation in human epidermal keratinocytes. *J Invest Dermatol* 1989; **92**: 203–9.

7 Rehfeld SJ, Plachy WZ, Williams ML, Elias PM. Calorimetric and electron spin resonance examination of lipid phase transitions in human stratum corneum: molecular basis for normal cohesion and abnormal desquamation in recessive X-linked ichthyosis. *J Invest Dermatol* 1988; **91**: 499–505.

8 Elias PM, Crumrine D, Rossner U *et al.* Basis for abnormal desquamation and permeability barrier dysfunction in RXLI. *J Invest Dermatol* 2004; **122**: 314–9.

9 Lykkesfeldt G, Bennett P, Lykkesfeldt AE *et al.* Abnormal androgen and oestrogen metabolism in men with X-linked recessive ichthyosis. *Clin Endocrinol* 1985; **23**: 385–93.

10 Maloney ME, Williams ML, Epstein EH *et al.* Lipids in the pathogenesis of ichthyosis: topical cholesterol sulphate-induced scaling in hairless mice. *J Invest Dermatol* 1984; **83**: 253–6.

11 Winklemann RK, Perry HO, Achor RWP, Kirby TJ. Cutaneous syndromes produced as side-effects of triparanol therapy. *Arch Dermatol* 1963; **87**: 372–7.

12 Anton-Lamprecht I, Hofbauer M. Ultrastructural distinction of autosomal dominant ichthyosis vulgaris and X-linked recessive ichthyosis. *Hum Genet* 1972; **15**: 261–4.

13 Mesquita-Guimaraes J. X-linked ichthyosis: ultrastructural study of 4 cases. *Dermatologica* 1981; **162**: 157–66.

14 Paige DG, Emilion GG, Bouloux PMG, Harper JI. A clinical and genetic study of X-linked recessive ichthyosis and contiguous gene defects. *Br J Dermatol* 1994; **131**: 622–9.

15 Okano M, Kitano Y, Yoshikawa K *et al.* X-linked ichthyosis and ichthyosis vulgaris: comparison of their clinical features based on biochemical analysis. *Br J Dermatol* 1988; **119**: 777–83.

16 Lykkesfeldt G, Hoyer H, Ibsen HH, Brandrup F. Steroid sulphatase deficiency disease. *Clin Genet* 1985; **28**: 231–7.

17 Sigg C, Meyer JC, Bruchner-Tuderman L, Gilardi S. Andrologische Untersuchungen bei Patienten mit X-Chromosomal rezessiver Ichthyose. *Hautartz* 1988; **39**: 97–101.

18 Traupe H, Happle R. Clinical spectrum of steroid sulphatase deficiency: X-linked ichthyosis, birth complications and cryptorchidism. *Eur J Pediatr* 1983; **140**: 19–21.

19 Lykkesfeldt G, Lykkesfeldt AE, Hoyer H, Skakkebaek NE. Steroid sulphatase deficiency associated with testis cancer. *Lancet* 1983; **2**: 1456.

20 Sever RJ, Frost P, Weinstein G. Eye changes in ichthyosis. *JAMA* 1968; **206**: 2283–6.

21 Costagliola C, Fabbrocini G, Illiano GM *et al.* Ocular findings in X-linked ichthyosis: a survey of 38 cases. *Ophthalmologica* 1991; **202**: 152–5.

22 Kallmann FJ, Schonfeld WA, Berrera SE. The genetic aspects of primary eunuchoidism. *Am J Ment Defic* 1944; **48**: 203–36.

23 Traupe H, ed. Ichthyosis and hypogonadism: reflections on the so-called Rud's syndrome. In: *The Ichthyoses*. Berlin: Springer-Verlag, 1989: 91–7.

24 Ballabio A, Parenti G, Carrozzo R *et al.* X–Y translocation in a family with X-linked ichthyosis, chondrodysplasia punctata and mental retardation: DNA analysis reveals deletion of the steroid sulphatase gene and translocation of its Y pseudogene. *Clin Genet* 1988; **34**: 31–7.

25 Epstein EH, Krauss RM, Schackleton CHL. X-linked ichthyosis: increased blood cholesterol sulfate and electrophoretic mobility of low density lipoprotein. *Science* 1981; **214**: 659–60.

26 Epstein EH, Levanthal ME. Steroid sulphatase of human leukocytes and epidermis in the diagnosis of recessive X-linked ichthyosis. *J Clin Invest* 1981; **67**: 1257–67.

27 Valdes-Flores M, Kofman-Alfaro SH, Jimenez Vaca AL *et al.* Deletion of exons 1–5 of the *STS* gene causing X-linked ichthyosis. *J Invest Dermatol* 2001; **116**: 456–8.
28 Gonzalez-Huerta L, Messina-Bass O, Toral-Lopez J *et al.* Point mutation in the STS gene in a severely affected patient with X-linked recessive ichthyosis. *Acta Derm Venereol* 2006; **86**: 78–9.
29 Robledo R, Melis P, Schillinger E *et al.* X-linked ichthyosis without *STS* deficiency. *Am J Med Genet* 1995; **59**: 143–8.
30 Thauvin-Robbinet C, Lanbert D, Vaillant G *et al.* X-linked recessive ichthyosis in a girl: strategy for identifying the causal mechanism. *Br J Dermatol* 2005: **152**: 1912–3.
31 Adam A, Ziprokowski L, Feinstein A *et al.* Linkage relations of X-borne ichthyosis to the Xg blood group. *Ann Hum Genet* 1969; **32**: 323–32.
32 Tiepolo L, Zuffardi O, Fraccaro M *et al.* Assignment by deletion mapping of the steroid sulphatase X-linked ichthyosis locus to Xp 223. *Hum Genet* 1980; **54**: 205–6.
33 Agemetsu K, Koike K, Morosawa H *et al.* Chondrodysplasia punctata with X–Y translocation. *Hum Genet* 1988; **80**: 105–7.
34 Yen PH, Allen E, Marsh B *et al.* Cloning and expression of steroid sulphatase cDNA and frequent occurrence of deletions in *STS* deficiency: implications for X–Y interchange. *Cell* 1987; **49**: 443–54.
35 Basler E, Grompe M, Parenti G *et al.* Identification of point mutations in the steroid sulphatase gene of three patients with X-linked ichthyosis. *Am J Hum Genet* 1992; **50**: 483–91.
36 Cooke A, Gillard EF, Yates JRW *et al.* X-chromosome deletions detectable by flow cytometry in some patients with steroid sulphatase deficiency (X-linked ichthyosis). *Hum Genet* 1988; **79**: 49–52.
37 Ballabio A, Carrozzo R, Parenti G *et al.* Molecular heterogeneity of steroid sulphatase deficiency. *Genomics* 1989; **4**: 36–40.
38 Shapiro LJ. Steroid sulphatase deficiency and the genetics of the short arm of the X chromosome. *Adv Hum Genet* 1985; **14**: 331–81.
39 Lykkesfeldt G, Lykkesfeldt AE. Carrier identification in steroid sulphatase deficiency and recessive X-linked ichthyosis. *Acta Derm Venereol (Stockh)* 1986; **66**: 134–8.
40 Bonifas JM, Epstein EH. Detection of carriers for X-linked ichthyosis by Southern blot analysis and identification of one family with a *de novo* mutation. *J Invest Dermatol* 1990; **95**: 16–9.
41 Cuevas-Covarrubias S, Jimenez-Vaca AL, Gonzalez-Huerta LM *et al.* Somatic and germinal mosaicism for the steroid sulphatase gene deletion in a steroid sulphatase deficiency carrier. *J Invest Dermatol* 2002; **119**: 972–5.
42 Hofmann B, Stege H, Ruzicka T *et al.* Effect of topical tazarotene in the treatment of congenital ichthyoses. *Br J Dermatol* 1999; **141**: 642–6.
43 Lykkesfeldt G, Hoyer H. Topical cholesterol treatment of recessive X-linked ichthyosis. *Lancet* 1983; **2**: 1357–8.

Multiple sulphatase deficiency (MIM 272200)

This is an exceedingly rare, autosomal recessive disorder caused by deficiency of two or more of the nine lysosomal and microsomal sulphatase enzymes, usually including aryl sulphatases A, B and C. This leads, in infancy, to a combination of features of mucopolysaccharidosis type 2 (aryl sulphatase B deficiency), metachromatic leukodystrophy (aryl sulphatase A deficiency) and XLRI [1]. Multiple sulphatase deficiency is due to mutations in *SUMF1* (sulphatase-modifying-factor 1 gene), which encodes lysosomal C-α-formylglycine generating enzyme (FGE) [2]. FGE produces peptides which are necessary for sulphatase activity.

Developmental delay and failure to thrive occur from early infancy with features of Hurler's syndrome (coarse facies, stunted growth, hepatomegaly and skeletal defects) becoming evident in the first year of life. A positive urine spot test for glycosaminoglycans (GAGs) suggests a lysosomal storage disorder. A mild ichthyosis and progressive neurological degeneration evolve in the second or third year but the phenotype varies according to the degree of reduction of each enzyme [3,4]. The neurological disease is often fatal in childhood.

Multiple sulphatase deficiency is confirmed by enzyme assays on fibroblasts, fresh leukocytes or serum, and fibroblast iduronate sulphatase activity is reduced. Urinary sulphatides and GAGs (heparan and dermatan sulphate) are elevated. Prenatal diagnosis by enzyme assay of amniocytes is possible. Mutational analysis on chorionic villus biopsy should allow early prenatal diagnosis.

References

1 Burch M, Fensom AH, Jackson M *et al.* Multiple sulphatase deficiency presenting at birth. *Clin Genet* 1986; **30**: 409–15.
2 Dierks T, Schmidt B, Borissenko LV *et al.* Multiple sulphatase deficiency is caused by mutations in the gene encoding the human C-alpha-formylglycine generating enzyme. *Cell* 2003; **113**: 435–44.
3 Burk RD, Valle D, Thomas GH *et al.* Early manifestations of multiple sulphatase deficiency. *J Pediatr* 1984; **104**: 574–8.
4 Loffeld A, Gray RGF, Green SH *et al.* Mild ichthyosis in a 4-year-old boy with multiple sulphatase deficiency. *Br J Dermatol* 2002; **147**: 353–5.

Collodion baby

This accurate, if outdated, term is used to describe the transient appearance at birth and in the neonatal period of a baby who, in general, subsequently develops congenital ichthyosiform erythroderma [1]. It was reported sporadically in the 19th century [2], and familial, self-healing cases and localized forms have been noted [3,4]. There are no reliable figures on incidence and it may be overlooked or misdiagnosed in some cases. Collodion is a syrupy solution of pyroxylin (nitrocellulose) in ether and alcohol which has medicinal and commercial uses.

Aetiology and pathogenesis. The collodion membrane is thought to develop during the third trimester, although the author has seen a 24-week gestation female neonate with a typical collodion membrane (self-healing). At birth the defective stratum corneum barrier, associated with the collodion membrane, moves from an aquatic to a dry environment, and the membrane desiccates and peels off. The association between fetal periderm, which evolves in the second month of gestation and dissolves with the onset of epidermal differentiation in the sixth month, and the neonatal collodion membrane, is unknown. Periderm does not express profilaggrin nor contain keratohyalin granules, which are present in the collodion membrane. In fetal skin biopsies of lamellar ichthyosis and harlequin ichthyosis, the periderm was normal in appearance [5].

The collodion membrane shares the same aethiopathogenesis as the subsequent ichthyosiform erythroderma, which evolves in the majority of collodion babies. Functional mutations in transglutaminase 1, *ALOX* genes, *ABCA12*, *ichthyin*, *ABHD5* and other genes involved in epidermal lipid and protein homeostasis have been identified in ichthyosiform erythrodermas preceded by collodion baby presentation. Self-healing collodion baby is caused by compound heterozygous transglutaminase 1 mutations which *in utero* render the enzyme inactive in its *cis* form. In the extrauterine environment the enzyme isomerizes back to its partially active *trans* form, allowing a normal phenotype [6]. The rare type 2 variant of the lysosomal (sphingolipid) storage disorder, Gaucher disease is due to β-glucocerebroside mutations. It presents with collodion membrane and evolves to ichthyosis. Ultrastructural

abnormalities in lamellar body and membrane formation and defects in ceramide production underlie the epidermal dysfunction [7]. Transglutaminase deficiency, keratin-associated-protein defects (e.g. loricrin mutations) and other lipid metabolic disorders also cause collodion membrane and ichthyosis by disrupting epidermal differentiation and function.

Histopathology. Light microscopy of skin in the early neonatal phase of a collodion membrane shows a compact hyperkeratosis with a thick eosinophilic periodic acid–Schiff stain (PAS)-positive stratum corneum. However, the epidermis is attenuated because of a reduced granular layer. The mid- and lower epidermis and the dermis are usually unremarkable.

Electron microscopy features in the early neonatal phase vary. In one case, cells of the upper two-thirds of the stratum corneum were convoluted and irregular in shape, with prominent nuclear debris and dense intracytoplasmic granules. Lamellar bodies were numerous in the intercellular spaces and desmosomes were well preserved [8]. Repeat skin biopsy at 16 months showed that, in spite of apparent 'self-healing', the ultrastructural changes persisted. However, in a further two cases, the ultrastructural features on the 15th day of life were predictive of the outcome, with a self-healing case showing relatively normal epidermal ultrastructure, while an infant who developed erythrodermic ichthyosis showed continuing dysplastic changes [9].

Clinical features and prognosis. Premature delivery is more common but not usually a significant problem. At birth, the typical collodion baby presents a striking and characteristic clinical picture with a generalized glistening, taut, yellowish film stretched over the skin (Figs 19.5a, 19.6a & 19.9a). It resembles a Clingfilm wrap or sausage skin, although it may variously be described as 'plastic skin', 'parchment-like' or 'as if dipped in hot wax'. Normal skin markings are obliterated, the eyelids and sometimes the lips are tethered and everted (ectropion and eclabion), the pinnae may be flattened and the nostrils obstructed (Figs 19.5b & 19.9a). Sausage-shaped swelling of digits may result from acral extension of the membrane and, rarely, constricting bands encircle the limbs or digits. General examination is usually normal and movement is minimally restricted.

The collodion membrane desiccates and cracks around flexures during the first days of life (Fig. 19.5c), and is usually completely shed within the first few weeks of life. It may be incomplete or localized in some infants; it may peel away only to partially reform, this pattern being repeated over a period of up to 12 weeks. In most cases, shedding reveals an erythrodermic ichthyosis (Fig. 19.5d).

Previously common and potentially lethal complications of a collodion membrane, especially when associated with erythroderma, were renal failure and neurological sequelae of hypernatraemic dehydration [10], hypothermia and bacterial sepsis. Affected infants require intensive nursing care in humidified incubators to control body temperature, prevent infection and combat electrolyte upset and dehydration. Increased absorption of topical agents through the skin may lead to systemic toxicity, and topical steroids should be avoided. Improved neonatal care has resulted in a reduction in neonatal mortality from 33% in the 1970s to less than 11% in one review [11], and in uncomplicated cases, mortality is now negligible [12].

Sequelae and genetics. In 60–80% of these infants, the features of non-bullous ichthyosiform erythroderma or lamellar ichthyosis become apparent as the collodion membrane is shed [11,12]. The severity of the subsequent ichthyosis cannot be predicted from the duration or complications of the collodion membrane. The rare autosomal dominant form of lamellar ichthyosis also presented with collodion membrane [13]. A minority of patients with lamellar ichthyosis or non-bullous ichthyosiform erythroderma appear not to have a collodion membrane at birth.

Certain ichthyosiform syndromes, including trichothiodystrophy (IBIDS), neutral lipid storage disease, Sjögren–Larsson syndrome, Conradi–Hünermann disease and CHIME syndrome [14], and the non-syndromic autosomal dominant loricrin keratoderma [15] may present with collodion membrane. Up to 20% of collodion babies subsequently have normal or near-normal skin (Fig. 19.6), so-called self-healing collodion baby or 'lamellar ichthyosis of the newborn' [16]. This autosomal recessive condition has been attributed to compound heterozygous transglutaminase 1 mutations which *in utero* render the enzyme inactive in its *cis* form, while post partum it isomerizes back to its partially active *trans* form [6]. Mutation of the *ALOX12B* and *ALOXE3* genes underlie most of the Scandanavian cases of 'self-improving collodion ichthyosis' [17]. An acral self-healing collodion baby phenotype has also been reported [18].

Collodion membrane presentation has also been reported in anhidrotic ectodermal dysplasia [19], Gaucher disease type 2 [20,21] and Neu–Laxova syndrome [22]. An adult with isolated palmoplantar keratoderma who was a collodion baby, was observed by the author and a similar case was included in a review of 10 collodion babies in the Thai literature [23]. A further case of evolution of collodion baby to palmoplantar keratoderma also had anogenital leukokeratosis [24].

Differential diagnosis. A collodion baby is generally easily distinguished from the more severe harlequin fetus or harlequin ichthyosis presentation, but occasional cases with intermediate features have been recorded. These cases have been referred to as 'chrysalis babies'. Restrictive dermopathy, or the 'stiff baby syndrome', produces a generalized taut, thick, tethered and unyielding skin at birth, which does not desiccate in the neonatal period. Its persistence causes respiratory failure and early neonatal death. Collodion-like presentations have been described in Gaucher type 2 and Neu–Laxova syndromes [20–22]. Infective causes of desquamation such as staphylococcal scalded skin should be included.

Management. Skin biopsy is not usually performed at this stage, but hair analysis, blood film microscopy and hearing tests should be arranged. Collodion babies should be nursed in the neonatal intensive care unit (NICU) in a humidified incubator. Cleansing with warm water and sterile aqueous cream or antiseptics daily, and barrier nursing, reduces the risk of infection (which is associated with skin barrier dysfunction, emollient use and high humidity). An emollient, such as sterile white soft paraffin in single-dose containers, is usually applied 4-hourly to keep the membrane



(a)



(b)



(c)



(d)

Fig. 19.5 (a) Collodion baby, day 2. (b) Facial features, collodion baby. (c) Shedding of membrane. (d) Same patient aged 3, with ichthyosiform erythroderma and patchy fungal infection.



(a)



(b)

Fig. 19.6 (a) Collodion baby, born before 25 weeks' gestation. (b) Same baby aged 6 months.

pliable and reduce transepidermal water loss. Analgesics may be required before handling. Intravenous lines should be avoided and regular skin swabs carried out. Signs of skin or systemic sepsis (including *Candida* and *Pseudomonas*) require investigation and prompt treatment, but prophylactic antibiotics are unnecessary. Poor sucking and weight loss may necessitate nasogastric tube feeding, and a higher than normal fluid and calorie requirement can be anticipated. The risk of exposure keratitis due to ectropion can be reduced by the regular use of lubricating drops and ointments, and antibiotic if necessary. Early ophthalmological advice should be sought. Nasal obstruction can be improved by gentle probing, and constricting bands on the limbs should be divided if causing acral pressure effects. Systemic retinoids have been used in severe cases. Every effort must be made to allow the parents to nurse and bond with their baby and their involvement from the beginning will enhance their confidence in managing at home.

The need for continuing intensive care, once the membrane is shed, depends on the baby's condition, but most can be discharged within the first 4 weeks with a skin care plan (including ample emollient supplies) and home nursing support. Accurate information on the condition, its management and prognosis should be made available to family and carers and contact with a patient support group is often appreciated. The details and outcome of an individual case, along with appropriate investigations, are important for genetic counselling of the family, which should be arranged soon after discharge.

References

1 Lentz CL, Altman J. Lamellar ichthyosis: the natural clinical course of collodion baby. *Arch Dermatol* 1968; **97**: 3–13.

2 Fox GH. The 'alligator boy': a case of ichthyosis. *J Cutan Venereol Dis* 1884; **2**: 97–9.

3 Frenk E, de-Techtermann F. Self-healing collodion baby: evidence for autosomal recessive inheritance. *Pediatr Dermatol* 1992; **9**: 95–7.

4 Finlay HVL, Bound JP. Collodion skin in the neonate due to lamellar ichthyosis. *Arch Dis Child* 1952; **27**: 438–41.

5 Holbrook K. Structure and function of developing human skin. In: Goldsmith LA, ed. *Physiology, Biochemistry and Molecular Biology of the Skin*, 2nd edn. Oxford: Oxford University Press, 1991: 63–110.

6 Raghunath M, Hennies HC, Ahvazi B *et al.* Self healing collodion baby: a dynamic phenotype explained by a particular transglutaminase 1 mutation. *J Invest Dermatol* 2003; **120**: 224–8.

7 Sidransky E, Fartasch M, Lee RE *et al.* Epidermal abnormalities may distinguish type 2 from type 1 and type 3 of Gaucher disease. *Pediatr Res* 1996; **39**: 134–41.

8 De Dobbeleer G, Heenen M, Song M, Achten G. Collodion baby skin: ultrastructural and autoradiographic study. *J Cutan Pathol* 1982; **9**: 196–202.

9 Frenk E. A spontaneously healing collodion baby: a light and electron microscopical study. *Acta Derm Venereol (Stockh)* 1981; **61**: 168–71.

10 Buyse L, Graves C, Marks R *et al.* Collodion baby dehydration: the danger of high transepidermal water loss. *Br J Dermatol* 1993; **129**: 86–8.

11 Larregue M, Ottavy N, Bressieux JM, Lorette J. Bébé collodion: trente-deux nouvelles observations. *Ann Dermatol Vénéréol* 1986; **113**: 773–85.

12 Van Gysel D, Lijnen R, Moekti P *et al.* Collodion baby: a follow-up study of 17 cases. *J Eur Acad Dermatol Venereol* 2002; **16**: 472–5.

13 Traupe H, Kolde G, Happle R. Autosomal dominant lamellar ichthyosis: a new skin disorder. *Clin Genet* 1984; **26**: 457–61.

14 Shashi V, Zunich J, Kelly TE *et al.* Neuroectodermal (CHIME) syndrome: an additional case with long term follow up of all reported cases. *J Med Genet* 1995; **32**: 465–9.

15 Matsumoto K, Muto M, Seki S *et al.* Loricrin keratoderma: a cause of congenital ichthyosiform erythroderma and collodion baby. *Br J Dermatol* 2001; **145**: 657–60.

16 Reed WB, Herwick RP, Harville D *et al.* Lamellar ichthyosis of the newborn. *Arch Dermatol* 1972; **105**: 394–9.

17 Vahlquist A, Bygum A, Ganemo A *et al.* Genotypic and clinical spectrum of self-improving collodion ichthyosis. *J Invest Dermatol* advance online publication November 2009; doi:10.1038/jid 2009: 346.

18 Mazereeuw-Hautier J, Aufenvenne K, Deraison C *et al.* Acral self-healing collodion baby: report of a new clinical phenotype caused by a novel *TGM1* mutation. *Br J Dermatol* 2009; **161**: 456–63.

19 Plantin P, Gavanou J, Jouan N *et al*. Collodion skin, a misdiagnosed but frequent clinical aspect of anhidrotic ectodermal dysplasia in the neonatal period. *Ann Dermatol Vénéréol* 1992; **119**: B21–3.
20 Lui K, Commens C, Choong R, Jaworski R. Collodion babies with Gaucher's disease. *Arch Dis Child* 1988; **63**: 854–6.
21 Stone DL, Carey WF, Christodoulou J *et al*. Type 2 Gaucher disease: the collodion baby phenotype revisited. *Arch Dis Child Fetal Neonatal Ed* 2000; **82**: F163–6.
22 Hickey P, Piantenida E, Lentz-Kapua S *et al*. Neu–Laxova syndrome: a case report. *Ped Dermatol* 2003; **20**: 25–7, 78–80.
23 Pongprasit P. Collodion baby: the outcome of long-term follow-up. *J Med Assoc Thai* 1993; **76**: 17–22.
24 Itin PH, Rufli T. Collodion baby with evolution to palmoplantar keratoderma and leucokeratosis anogenitalis. *Eur J Dermatol* 1994; **4**: 589–92.

Non-bullous ichthyosiform erythroderma (MIM 242100)

Non-bullous ichthyosiform erythroderma (NBIE) is a rare and usually severe autosomal recessive inflammatory ichthyosis. There are little data on incidence, but an English population study suggestion of 1 in 300 000 is likely to be an underestimate [1]. It occurs in all races, more so when consanguineous marriage is common. NBIE is probably more common than lamellar ichthyosis, but they were regarded as a single disorder (congenital ichthyosiform erythroderma, CIE) until the 1980s, when clinical, histological and biochemical features helped to differentiate them. However, there are intermediate phenotypes and a lack of disease specificity of the gene mutations that have been found in each disorder points to genotype-phenotype variability [2,3]. NBIE is sometimes referred to as erythrodermic lamellar ichthyosis.

Aetiology and pathogenesis. NBIE is characterized by epidermal hyperplasia with increased mitoses and expression of hyperproliferative keratins K6/K16/K17. *In vitro* studies of NBIE keratinocytes showed hyperkeratosis, and more marked parakeratosis, than control keratinocytes [4]. No consistent changes in epidermal lipids in NBIE have been found, including the alkanes, a saturated hydrocarbon group [5]. Variations in the stratum corneum enzymes, β-glucosidase and butyrase, highlighted differences between the autosomal recessive ichthyoses [6].

Abnormal intracellular cytoplasmic accumulation of keratinocyte transglutaminase 1 (TGase1) was reported in a subset of patients with NBIE [7]. Whereas TGase1 activity in some patients with lamellar ichthyosis was entirely absent, partial deficiency was found in the NBIE patients [8]. Further reports of *TGM1* gene mutations in NBIE followed [9,10] and 38 of 80 patients with NBIE/lamellar ichthyosis (LI) spectrum, who were included in a Swedish national survey of congenital ichthyosis, also proved to have *TGM* mutations [3]. In fact, the same *TGM1* mutation can give rise to either the NBIE or LI phenotype [8,10]. Transglutaminases are Ca^{++} dependent enzymes involved in the assembly of the cornified cell envelope, which is just beneath the corneocyte cell membrane. TGase1 specifically binds ceramide lipids to envelope proteins, such as involucrin. The *TGM1* gene has 15 exons and is sited at chromosome 14q11.2. Several different mutations have been identified and TGase1 deficiency correlates with certain ultrastructural features, even corneocyte collapse seen on light microscopy of epidermal scales [11].

Mutations in two lipoxygenase enzymes, lipoxygenase-3 (ALOXE3) and 12-lipoxygenase (ALOX12B) were identified in six Mediterranean families affected by NBIE, known to be linked to chromosome 17p13.1 [12]. One deletion and six novel missense mutations in the *ALOX12B* gene were found in six of 11 families in France [13]. These two lipoxygenases are mainly expressed in epithelial cells including suprabasal keratinocytes, and are involved in the maintenance of the cutaneous permeability barrier and possibly in terminal differentiation. Lipoxygenases are involved in essential fatty acid, phospholipids and triglyceride metabolism, and deficiency affects lamellar body-derived lipid lamellae and membranes responsible for the epidermal permeability barrier [14]. A mouse model with an *ALOX12B* mutation provides a laboratory model for epidermal barrier function [15].

Mutations in ichthyin, a transmembrane receptor in the 12-lipoxygenase pathway, were found in several families with NBIE in different countries [16]. They all had palmoplantar keratoderma and some were not collodion babies. Three patients with typical NBIE phenotype had missense mutations in *ABCA12* (an epidermal lipid transporter protein), which usually lead to harlequin ichthyosis [17,18]. Two had multiple skin malignancy (squamous carcinoma, melanoma and cutaneous lymphoma), not usually seen in NBIE [17].

Histopathology. Light microscopy of skin sections reveals compact hyperkeratosis and moderate increase in stratum corneum thickness. There is variable mild parakeratosis, acanthosis, a normal or prominent granular layer, increased mitoses and an accentuated broad rete ridge pattern. A mild upper dermal lymphocytic infiltrate and prominent dermal blood vessels may be present. Lipid vacuoles in the stratum corneum were noted in a family with autosomal dominant NBIE, and sweat glands were normal [3].

PAS staining of frozen sections showed positivity in cell membranes of the stratum corneum and granular layer and in the basement membrane, which is absent in normal skin and in other ichthyoses, with the possible exception of Netherton's syndrome [19]. Kinetic studies, using labelled thymidine, confirmed an increased epidermal turnover rate in NBIE, similar to that seen in psoriasis, and in contrast to the relatively normal epidermal kinetics of lamellar ichthyosis [20]. This was unaffected by retinoid therapy [21].

Electron microscopy reveals abnormal lamellar bodies, which are retained in the corneal layer. In the so-called autosomal dominant variant (see below), reduced keratohyalin and tonofilaments, normal lamellar bodies and lipid vacuolation in the stratum corneum were noted [3]. Ultrastructural features more typical of harlequin ichthyosis have been found in several patients with severe NBIE [22]. Classification of autosomal recessive congenital ichthyosis into four subtypes, based on ultrastructural findings, shows some correlation to clinical and genetic subtypes of the NBIE/LI spectrum [23–25]. Type I correlates to NBIE, type II and III to LI and type IV to a mild NBIE variant.

Clinical features. NBIE, in approximately 90% of cases, presents at birth with a collodion baby appearance (Fig. 19.5). The rest are erythrodermic from birth, and some are premature. After shed-



(a)



(b)

Fig. 19.7 Non-bullous ichthyosiform erythroderma: (a) in a 4-year-old-boy; and (b) same child.

ding of the collodion membrane, generalized scaly erythroderma is apparent and persistent (Fig. 19.7). Erythroderma may lessen while scaling increases in early childhood, but there is considerable heterogeneity and even intrafamilial variation. Congenital ichthyosiform erythroderma should be regarded as a clinical spectrum with NBIE at one end and lamellar ichthyosis at the other, with many patients in the centre ground.

Typically, scaling affects all areas including the scalp, ears, face, flexures, palms and soles. The scale of NBIE is white or grey, thin, superficial and semi-adherent. It appears feathery on the face, arms and trunk but may become lamellar or plate-like on the lower legs. Scaling may be cyclical, with build-up and shedding over periods of 2–4 weeks and, rarely, clinically normal skin may evolve on limited sites. Palmoplantar hyperkeratosis/keratoderma occurs in up to 70% of patients, and can cause recurrent painful fissures, digital contractures and sclerodactyly. Scalp involvement may lead to tinea amiantacea and patchy cicatricial alopecia, especially on the temporal scalp.

Ectropion improves during infancy, but persists into adult life in 30% or so and, if untreated, may lead to exposure keratitis and even blindness [26]. Loss of eyebrows and lashes in severe cases accentuates the ocular problem. Hypoplasia of the nasal and aural cartilages may result from compression and scarring, increasing the cosmetic burden.

A mild nail dystrophy consisting of ridging, subungual hyperkeratosis or hypoplasia occurs in up to 50% of patients, but hair, teeth and mucosal surfaces are normal. Nail growth and skin healing are accelerated. In most patients, sweating is absent or markedly reduced in childhood, and care is needed to avoid hyperpyrexia during intercurrent illness, leisure pursuits or in hot climates. Sweat gland function improves in adolescence, and in patients treated with retinoids. Hypohidrosis is therefore thought to be a result of sweat duct obstruction by the hyperkeratotic stratum corneum. Pruritus is not uncommon in NBIE and coexistent atopic eczema can be difficult to diagnose. Cutaneous bacterial and viral infections are rare, but patchy or widespread fungal infection of skin and nails is a common complication (Fig. 19.5d) [27,28]. Mildly affected patients may present with an intertrigo-like pattern, mild palmar hyperkeratosis and subtle facial tightness.

Many severely affected children are of short stature, with a delayed growth spurt in adolescence. They are at increased risk of rickets due to vitamin D deficiency [29]. NBIE may limit a child's ability to take part in sports, but swimming and less vigorous activities should be encouraged. Psychological problems often arise at school because of insensitive comments and reactions of others. However, in general, children with NBIE seem to cope well with their disability, and many achieve academically, on a par with their peers.

Congenital reticular ichthyosiform erythroderma. Three cases of a variant of NBIE were described [30]. In childhood they developed enlarging areas of normal skin on a background of ichthyosiform erythroderma (with hypertrichosis), which accounts for the alternative names, 'ichthyosis en confetti' and 'ichthyosis variegata' [31]. An orange-tinted palmoplantar keratoderma occurred. Specific ultrastructural changes were reported, including perinuclear vacuolation and binuclear cells, and autosomal dominant inheritance was suspected.

Ichthyosis prematurity syndrome (MIM 608649) (IPS; congenital ichthyosis with fine/focal scaling, CIFS). A mild NBIE variant, typified by premature (with polyhydramnios) delivery of a red neonate with striking areas of caseous hyperkeratosis has been reported, especially in Scandinavian populations and encountered once by the author [32]. Neonatal respiratory distress and blood

eosinophilia have been noted in some cases. Fine follicular scaling may persist though most resolve. Electron microscopic features, categorized as type IV, are helpful in diagnosis [21]. A mutation in the fatty acid transport protein 4 gene, which results in reduced incorporation of very long chain fatty acids into cellular lipids, has been reported [33].

KLICK syndrome (keratosis linearis, ichthyosis congenita, keratoderma). The characteristic feature of this rare but mild CIE is linear or striate keratoses in flexural areas [34].

Loricrin keratoderma with ichthyosis (MIM 604117). This is a variant of Vohwinkel's syndrome (constrictive palmoplantar keratoderma) but with a collodion baby presentation and normal hearing. A mild generalized erythrodermic ichthyosis and progressive keratoderma with pseudoainhum ensues [35]. The sixth affected family included two Japanese siblings and their father [36]. Skin biopsy shows characteristic ultrastructural features and loricrin mutations have been identified [37]. Vohwinkel's syndrome is associated with deafness and is due to connexin 26 mutations.

Diagnosis. Classic NBIE presents a characteristic clinical picture enabling differentiation from lamellar ichthyosis. Other causes of congenital erythroderma and collodion membrane presentation need to be considered in the neonatal period. Collodion presentation of loricrin keratoderma is mentioned above. Congenital infections including candidiasis, congenital psoriasis, Netherton's syndrome, immunodeficiency disorders, trichothiodystrophy (IBIDS) and neutral lipid storage disease may mimic the cutaneous signs of NBIE in the neonate. There have been sporadic cases of coexistent congenital ichthyosiform erythroderma and psoriasis [38,39].

Genetics. Classical NBIE is an autosomal recessive condition and therefore more likely to occur in societies where consanguineous marriage is common. In a personal series of 25 patients with NBIE, there were five sibling pairs and also seven patients, including three Caucasians, with consanguineous parents. The risk of further affected children for the parents of the proband is 25% for each child. Affected individuals should not have affected children (unless their partner is a heterozygote carrier of the same allele), and their offspring have a 50% risk of carrier status.

A non-consanguineous Swedish kindred, with typical features of NBIE in a mother and her two daughters, was thought to have an autosomal dominant variant [40]. However, it transpired that the father and presumably the mother's parents were heterozygous for the disease allele, an example of genetic pseudodominance [32]. The incidence of heterozygosity was estimated at 1.8–3.2 per 1000 population.

Prenatal diagnosis may be attempted on fetal skin biopsy using ultrasound guidance at 19–22 weeks (amniocyte pellets have also been used) to detect premature or abnormal keratinization or abnormal ultrastructural inclusions [41,42], but it is far from satisfactory for two reasons [43,44]. First, phenotypic heterogeneity can exist between members of the same family, so that the severity of the proband may not reflect that of the affected fetus. Secondly, normal interfollicular keratinization is established only at 24 weeks' gestation and shows a regional pattern of evolution. To avoid errors, multiple skin biopsies from different sites including the scalp are recommended. The identification of a specific genetic mutation in the proband will allow first trimester DNA-based prenatal diagnosis on chorionic villus samples taken at 10–12 weeks' gestation.

Treatment. The principles of emollient and keratolytic treatments for patients with NBIE are much the same as those outlined for treatment of ichthyosis vulgaris. Because of the inflammatory nature of the condition, the potential for irritation with topical treatment is high, and keratolytics and topical retinoids are rarely used. Topical steroids are ineffective and readily absorbed, and they may even cause systemic steroid toxicity, particularly in infants. Topical and/or systemic antifungal therapy is indicated when tinea infection has been confirmed. Hypohidrosis with the attendant risk of hyperpyrexia may be aggravated by the occlusive action of ointments. Prevention of sunburn and sunstroke in children is important.

Systemic retinoids are effective in many disorders of keratinization, and have been shown to be helpful in reducing scaling, pruritus and erythema in most patients with severe congenital ichthyosis, including NBIE [45]. For many patients, this may allow a more active role in daily activities, such as schooling, sport and socializing. The recommended starting dose of acitretin is 0.5–0.75 mg/kg/day, tending to higher doses in younger children. A response is apparent within 2–3 weeks, and the maintenance dose is titrated down to the lowest effective level between 0.1 and 0.5 mg/kg/day. Effective doses tend to be lower than in the treatment of other disorders of keratinization. Because of potential toxicity and the chronicity of the disease, intermittent therapy is preferred (e.g. 3 months on, 3 months off). Patients with ectropion or corneal damage may not be able to tolerate the side effects of retinoids. Peeling of palmar skin may induce an unpleasant hypersensitivity and increased skin fragility delays healing (see Fig. 19.8b). Rare cases of skeletal toxicity have been reported with retinoid therapy [46], but long-term use of etretinate in 42 children, 14 with NBIE, did not cause significant skeletal abnormalities [47]. Pretreatment baseline selective skeletal survey was recommended for all patients, with follow-up studies restricted to those with pretreatment lesions or who develop musculoskeletal symptoms. Long-term retinoid therapy in two siblings with NBIE, 21 years uninterrupted treatment in one and 20 years in the other, did not cause any obvious cardiovascular or skeletal toxicity [48]. Older children and adults must be (repeatedly) advised of the teratogenicity of retinoids and, where appropriate, contraceptive measures undertaken. The period of mandatory contraception is less with isotretinoin than with acitretin but it is less effective.

A small, open trial of 4 weeks' treatment with oral ciclosporin in congenital ichthyosis (three cases with NBIE and two with lamellar ichthyosis) showed no benefit [49]. Topical tacrolimus ointment 0.1% was associated with dramatic improvement in one case but increased absorption led to potentially toxic blood levels with daily application [50]. Evening primrose oil orally has been helpful in occasional cases.

Patients and families may benefit from contact with other affected people and patient support groups exist in several countries. Advice to carers and teachers, careers advice and ongoing support assists children and young adults in coping with the educational, occupational and social problems resulting from their chronic skin disease.

References

1 Wells RS, Kerr CB. Clinical features of autosomal dominant and sex-linked ichthyosis in an English population. *BMJ* 1966; **1**: 947–50.

2 Akiyama M, Sawamura D, Shimizu H. The clinical spectrum of nonbullous ichthyosiform erythroderma and lamellar ichthyosis. *Clin Exp Dermatol* 2003; **28**: 235–40.

3 Vahlquist A, Ganemo A, Pigg M *et al.* The clinical spectrum of congenital ichthyosis in Sweden: a review of 127 cases. *Acta Derm Venereol* 2003; **83** (Suppl. 213): 34–47.

4 Amsellem C, Haftek M, Hoyo E *et al.* Evidence of increased keratinocyte proliferation in air–liquid interface cultures of non-bullous congenital ichthyosiform erythroderma. *Acta Derm Venereol (Stockh)* 1993; **73**: 262–9.

5 Judge MR, Fisher N, Manku M, Harper JI. Quantification of n-alkanes in hereditary ichthyosis. *Br J Dermatol* 1992; **127**: 91–7.

6 Bergers M, Traupe H, Dunnwald SC *et al.* Enzymatic distinction between two subgroups of autosomal recessive lamellar ichthyosis. *J Invest Dermatol* 1990; **94**: 407–12.

7 Choate KA, Williams ML, Khavari PA. Abnormal transglutaminase 1 expression pattern in a subset of patients with erythrodermic autosomal recessive ichthyosis. *J Invest Dermatol* 1998; **110**: 8–12.

8 Laiho E, Niemi KM, Ignatius J *et al.* Clinical and morphological correlations for transglutaminase 1 mutations in autosomal recessive congenital ichthyosis. *Eur J Hum Genet* 1999; **7**: 625–32.

9 Akiyama M, Takizawa Y, Kokaji T *et al.* Novel mutations of TGM1 in a child with congenital ichthyosiform erythroderma**.** *Br J Dermatol* 2001; **144**: 401–7.

10 Pigg M, Gedde-Dahl T, Cox D *et al.* Strong founder effect for a transglutaminase 1 gene mutation in lamellar ichthyosis and congenital ichthyosiform erythroderma from Norway. *Eur J Hum Genet* 1998; **6**: 589–96.

11 Esposito G, Tadini G, Paparo F *et al.* Transglutaminase 1 deficiency and corneocyte collapse: an indication for targeted molecular screening in autosomal recessive congenital ichthyosis. *Br J Dermatol* 2007; **157**: 799–846.

12 Jobard F, Lefevre C, Karaduman A *et al.* Lipoxygenase-3 (ALOXE3) and 12 (R)-lipoxygenase (ALOX12B) are mutated in non-bullous congenital ichthyosiform erythroderma (NCIE) linked to chromosome 17p13.1. *Hum Mol Genet* 2002; **11**: 107–13.

13 Lesueur F, Bouadjar B, Lefevre C *et al.* Novel mutations in ALOX12B in patients with autosomal recessive congenital ichthyosis and evidence for genetic heterogeneity on chromosome 17p13. *J Invest Dermatol* 2007; **127**: 829–36.

14 Eckl KM, Krieg P, Kuster W *et al.* Mutation spectrum and functional analysis of epidermis-type lipoxygenases in patients with autosomal recessive congenital ichthyosis. *Hum Mutat* 2005; **26**: 351–61.

15 Moran JL, Haiyan Q, Annick TD *et al.* A mouse mutation in the 12R-lipoxygenase, Alox 12b, disrupts formation of the epidermal permeability barrier. *J Invest Dermatol* 2007; **127**: 1893–7.

16 Lefevre C, Bouadjar B, Karaduman A *et al.* Mutations in ichthyin: a new gene on chromosome 5q33 in a new form of autosomal recessive congenital ichthyosis. *Hum Mol Genet* 2004; **13**: 2473–82.

17 Natsuga K, Akiyama M, Kato N *et al.* Novel ABCA12 mutations identified in two cases of non-bullous congenital ichthyosiform erythroderma associated with multiple skin malignant neooplasia. *J Invest Dermatol* 2007; **127**: 2669–73.

18 Akiyama M, Sakai K, Hatamochi A *et al.* Novel compound heterozygous nonsense and missense ABCA12 mutations lead to non-bullous congenital ichthyosiform erythroderma. *J Invest Dermatol* 2008: **158**: 864–7.

19 Williams ML, Elias PM. Heterogeneity in autosomal recessive ichthyosis. *Arch Dermatol* 1985; **121**: 477–88.

20 Hazell M, Marks R. Clinical, histologic and cell kinetic discriminants between lamellar ichthyosis and non-bullous congenital ichthyosiform erythroderma. *Arch Dermatol* 1985; **121**: 489–93.

21 Dover R, Burge S, Ralfs I, Ryan TJ. Congenital non-bullous ichthyosiform erythroderma: cell kinetics before and after treatment with etretinate. *Clin Exp Dermatol* 1986; **11**: 431–5.

22 Virolainen E, Niemi KM, Ganemo A *et al.* Ultrastructural features resembling those of harlequin ichthyosis in patients with severe congenital ichthyosiform erythroderma. *Br J Dermatol* 2001; **145**: 480–3.

23 Anton-Lamprecht I. Ultrastructural identification of basic abnormalities as clues to genetic disorders of the epidermis. *J Invest Dermatol* 1994; **103**: 6s–12s.

24 Niemi KM, Kanerva L, Kuokanen K, Ignatius J. Clinical, light and electron microscopic features of recessive congenital ichthyosis type 1. *Br J Dermatol* 1994; **130**: 626–33.

25 Niemi KM, Kuokkanen K, Kanerva L, Ignatius J. Recessive ichthyosis congenita type IV. *Am J Dermatopathol* 1993; **15**: 224–8.

26 Murdoch ME, Judge MR, Dowd P. Non-bullous ichthyosiform erythroderma: response to etretinate therapy. *Br J Dermatol* 1991; **125**: 62–4.

27 Shelley ED, Shelley WB. Generalized *Trichophyton rubrum* infection in congenital ichthyosiform erythroderma. *J Am Acad Dermatol* 1989; **20**: 1133–4.

28 Ludwig RJ, Woodfolk JA, Grundmann-Kollmann M *et al.* Chronic dermatophytosis in lamellar ichthyosis: relevance of a T-helper 2-type immune response to *Trichophyton rubrum*. *Br J Dermatol* 2001; **145**: 518–21.

29 Thacher TD, Fischer PR, Pettifor JM *et al.* Nutritional rickets in ichthyosis and response to calcipotriene. *Pediatrics* 2004; **114**: 119–23.

30 Brusasco A, Tadini G, Cambiaghi S *et al.* A case of congenital reticular ichthyosiform erythroderma: ichthyosis 'en confettis'. *Dermatology* 1994; **188**: 40–5.

31 Krunic AL, Palcesky D, Busbey S *et al.* Congenital reticular ichthyosiform erythroderma-ichthyosis variegata: a case report and review of the literature. *Acta Derm Venereol* 2003; **83**: 36–9.

32 Ganemo A, Pigg M, Virtanen M *et al.* Autosomal recessive congenital ichthyosis in Sweden and Estonia: clinical, genetic and ultrastructural findings in 83 patients. *Acta Derm Venereol* 2003; **83**: 24–30.

33 Klar J, Schweiger M, Zimmerman R *et al.* Mutations in the fatty acid transport protein 4 gene cause the ichthyosis prematurity syndrome. *Am J Hum Genet* 2009; **85**: 248–53.

34 Vahlquist A, Ponten F, Pettersson A. Keratosis linearis with ichthyosis congenita and sclerosing keratoderma (KLICK syndrome): a rare autosomal recessive disorder of keratohyaline formation? *Acta Derm Venereol* 1997; **77**: 225–7.

35 Camisa C, Rossana C. Variant of keratoderma hereditaria mutilans (Vohwinkel's syndrome): treatment with orally administered isotretinoin. *Arch Dermatol* 1984; **120**: 1323–8.

36 Matsumoto K, Muto M, Seki S *et al.* Loricrin keratoderma: a cause of congenital ichthyosiform erythroderma and collodion baby. *Br J Dermatol* 2001; **145**: 657–60.

37 Korge BP, Ishida-Yamamoto A, Punter C *et al.* Loricrin mutation in Vohwinkel's keratoderma is unique to the variant with ichthyosis. *J Invest Dermatol* 1997; **109**: 604–10.

38 Kahn D, Altman J, Hutchinson E. Lamellar ichthyosis with episodic psoriasiform reaction pattern. *Cutis* 1986; **37**: 162–4.

39 Ingen-Housz-Oro S, Vignon-Pennamen M, Blanchet-Bardon C. Bullous and non-bullous ichthyosiform erythroderma associated with generalized pustular psoriasis of von Zumbusch type. *Br J Dermatol* 2001; **145**: 823–5.

40 Rossmann-Ringdahl I, Anton-Lamprecht I, Swanbeck G. A mother and two children with non-bullous congenital ichthyosiform erythroderma. *Arch Dermatol* 1986; **122**: 559–64.

41 Holbrook KA, Dale BA, Williams ML *et al.* The expression of congenital ichthyosiform erythroderma in second trimester fetuses of the same family: morphologic and biochemical studies. *J Invest Dermatol* 1988; **91**: 521–31.

42 Fassihi H, Eady RAJ, Mellerio JE *et al.* Prenatal diagnosis for severe inherited skin disorders: 25 years experience. *Br J Dermatol* 2006; **154**: 106–13.

43 Arnold ML, Anton-Lamprecht I. Problems in prenatal diagnosis of the ichthyosis congenita group. *Hum Genet* 1985; **71**: 301–11.

44 Akiyama M, Holbrook KA. Analysis of skin-derived amniotic fluid cells in the second trimester: detection of severe genodermatoses expressed in the fetal period. *J Invest Dermatol* 1994; **103**: 674–7.

45 Blanchet-Bardon C, Nazarro V, Rognin C *et al.* Acitretin in the treatment of severe disorders of keratinization. *J Am Acad Dermatol* 1991; **24**: 982–6.

46 Kilcoyne RF. Effects of retinoids on bone. *J Am Acad Dermatol* 1988; **19**: 212–6.

47 Paige DG, Judge MR, Shaw DJ *et al*. Bone changes and their significance in children with ichthyosis on long-term etretinate therapy. *Br J Dermatol* 1992; **127**: 387–91.
48 Macbeth AE, Johnston GA. Twenty one years of oral retinoid therapy in siblings with non-bullous ichthyosiform erythroderma. *Clin Exp Dermatol* 2008; **33**: 190–1.
49 Ho VC, Gupta AK, Ellis CN *et al*. Cyclosporine in lamellar ichthyosis. *Arch Dermatol* 1989; **125**: 511–4.
50 Allen DM, Esterly NB. Significant systemic absorption of tacrolimus after topical application in a patient with lamellar ichthyosis. *Arch Dermatol* 2002; **138**: 1259–60.

Lamellar ichthyosis (MIM 242300, 601277, 146750)

Of the two major autosomal recessive ichthyoses, lamellar ichthyosis (LI) is probably less common than NBIE, with an incidence of less than 1 in 300 000. It has a worldwide distribution. In its severe form it is easily recognized, but phenotypic heterogeneity exists and it may be confused with other ichthyoses. It is likely that the so-called 'alligator boy' reported by Fox in 1884 suffered from LI [1].

The term 'lamellar ichthyosis' (Latin *lamella*, plate) was, in the early 20th century, used for any congenital ichthyosis excluding harlequin fetus and, until the 1960s, it also referred to the collodion baby phenotype. In the European literature, the prefixes erythrodermic or non-erythrodermic LI correspond to NBIE and LI [2]. Evidence for clinical, histological and biochemical heterogeneity in autosomal recessive ichthyosis helped distinguish between NBIE and LI [3,4] and specific genetic mutations have been found in a proportion of LI patients. An autosomal dominant pattern of inheritance of LI has also been described [5].

Aetiology and pathogenesis. The salient histological features point to a disorder of cornification or terminal epidermal differentiation. Reduced skin barrier function was evident in studies of transepidermal water loss, and paralleled stratum corneum lipid defects [6]. Scale lipid analysis in severe LI showed a mild but significant rise in sphingolipids (ceramides) and free sterols, a pattern similar to that of normal palmoplantar skin [3].

Cornification involves the construction of the cornified envelope from intracellular protein precursors including loricrin and involucrin. These are cross-linked to lipid ceramides in the granular layer by the action of transglutaminase 1 (TGase1; see above). Defects in this pathway were first detected on immunohistochemistry and reported in 1993 [7]. There was increased expression of abnormally distributed loricrin and involucrin in keratinocyte cytoplasm, and diminished cytoplasmic TGase1 staining in three patients with autosomal recessive LI [7]. Several reports of transglutaminase 1 gene (*TGM1*) mutations followed [8–10] and *TGM1* mutations were found in 38 of 80 patients with NBIE/LI spectrum in a Swedish national survey of congenital ichthyosis [11]. Many had complete loss of TGase1 activity but a compound heterozygous *TGM1* mutation was associated with mild LI [12]. TGase1 deficiency correlates with certain ultrastructural features, but also corneocyte collapse seen on light microscopy of epidermal scales, and this cytology screen can be used to identify patients likely to have *TGM1* mutations [13]. Patients with CIE, but without *TGM1* mutations, may have increased expression of TGase1.

Some patients with LI experience partial resolution of scaling which clears from the face and limbs. This is called bathing suit



Fig. 19.8 Lamellar ichthyosis, severe (a) in a 10-year-old girl, before and (b) on retinoid therapy.



(a) (b)

Fig. 19.9 Lamellar ichthyosis, severe (a) as a collodion baby, (b) aged 18 months and (c) below 6 years.

ichthyosis and is due to temperature-sensitive TGase1, which was demonstrated to have reduced activity with a rise in temperature from 25° to 37°C [14,15]. Classical LI (designated type II) with palmoplantar keratoderma can also result from missense mutations in the *ABCA12* gene (which codes for a keratinocyte lipid transporter), the same gene implicated in Harlequin ichthyosis (HI) and occasional cases of NBIE [16]. Mutations in the ichthyin gene have been reported in NBIE but are also implicated in mild LI (designated type III) [17]. Mutations in a P450 gene have been reported in 12 Mediterranean families with mild LI who were not collodion babies [18].

Histopathology. Light microscopy of the skin in LI shows striking, compact ortho-hyperkeratosis with variable mild focal parakeratosis, and a stratum corneum thickness at least twice that of NBIE. The granular layer appears normal or increased, the lower epidermis is normal, and overall epidermal thickness is slightly increased. There may be mild papillomatosis, extension and blunting of rete ridges, and dilatation of dermal capillaries reminiscent of psoriasis.

Kinetic studies surprisingly revealed a near-normal transit time, in contrast to the hyperproliferative epidermis of NBIE and psoriasis, and LI is therefore classified as a retention ichthyosis [4].

Electron microscopy features in LI are variable. Niemi *et al.* reported prominent cholesterol clefts or crystals in the stratum corneum, lipid droplets in corneocytes and a thin or absent cornified envelope in nine Finnish patients with clinical features of LI [19]. These ultrastructural signs led to the subclassification of ichthyosis congenita type II and correlated closely with TGase1 deficiency. Other changes including abnormal membrane structures and vesicles within lamellar bodies were noted in patients with a reticulated form of LI, also called ichthyosis congenita type III [20].

Clinical features. At birth, most affected infants present as collodion babies, and after shedding the membrane, show a less intense erythroderma than infants with NBIE—an important and persistent distinguishing feature. Scaling occurs within the first month of life and may affect the whole skin surface, or localize to the scalp, abdomen and lower legs.

The scale in LI is typically large, dark brown or grey and firmly adherent (Figs 19.8 & 19.9). In severely affected individuals, the thick, rigid scale is intermittently shed or splits, causing erythematous patches and deep, painful fissures, especially around flexures and on the digits, palms and soles. Limitation of joint movement, flexion contractures and digital sclerodactyly may result. Additional features in severely affected patients are palmoplantar keratoderma, scarring alopecia, persistent ectropion, and congenital hypoplasia of aural and nasal cartilages. Erythema is mild in LI, pruritus rarely occurs, but sweating is severely impaired. The nails may be small but the hair shaft, teeth and mucous membranes are not affected. Growth is delayed in severe LI and both nutritional and vitamin D deficiency rickets have been reported in children [21,22]. Intellectual ability is normal, unless there have



(c)

Fig. 19.9 *Continued*

been serious perinatal complications. Extracutaneous manifestations have not been reported. Severe LI does not improve with age, and psychological problems resulting from the cosmetic effects, discomfort and limited mobility can lead to isolation, depression and poor school performance.

In mild LI (Fig. 19.10), the typical plate-like scale may only occur on the lower legs, upper arms, and rarely the forehead and trunk [12,20]. These patients usually have fine grey scales on the flexures and neck and mild erythema. They have focal hypohidrosis, hyperlinear palms and soles, and tend to improve in summer months. Cyclical shedding or peeling may occur.

Autosomal dominant lamellar ichthyosis (MIM 146750). Traupe outlined the clinical, ultrastructural and biochemical features of an ichthyosis that clinically resembled LI, but that showed an autosomal dominant transmission in four members, two male and two female, through three generations of a German family [23]. These patients had non-erythrodermic, lamellar-type, generalized scaling from birth, palmoplantar hyperkeratosis and lichenification of the dorsa of the hands and feet and major flexures. They did not have a collodion membrane at birth, and pruritus was a problem in one child. The light microscopy features were similar to those of classical LI. The electron microscopy findings in two of them differed from those of autosomal recessive LI, and included normal tonofilaments and keratohyaline granules, a prominent transforming zone at the granular–corneal junction and sparse corneocyte lipid inclusions.

Since then, reports of a similar disorder in separate families (French and Swedish) have appeared, although in these cases, a collodion baby phenotype and subsequent mild erythroderma were notable features [24,25]. Of the 32 collodion babies reviewed by Larregue [24], 10% were said to have developed autosomal dominant LI, but the disease phenotype is not clearly defined. Lipid analysis of plantar scale from two patients with autosomal



(a)



(b)



(c)

Fig. 19.10 Lamellar ichthyosis, (a) and (b) mild in a child, shown with his brother, and (c) an adult.

dominant LI revealed a different profile to that of classical LI [26].

Bathing suit ichthyosis. A rare variant of LI, which is characterized by scaling confined to the warmer areas of skin, has been reported [27]. It presents with collodion membrane and is due to TGase1 temperature sensitivity, resulting from an autosomal recessive, missense transglutaminase mutation (p.R315L) [14,15].

Diagnosis. Differential diagnosis of LI includes XLRI and ichthyosiform erythrodermas with collodion presentation. It is now accepted that there is considerable clinical and genetic heterogeneity in CIE, ranging from NBIE at one end to classical LI at the other, with intermediate 'mild' phenotypes which lack the erythroderma or lamellar scaling of the more typical forms. Ichthyosiform syndromes, such as Sjögren–Larsson syndrome and trichothiodystrophy, may be mistaken for LI but the associated neurological problems serve to distinguish them.

Light microscopy alone does not help to distinguish between the phenotypic variants of CIE and the disease spectrum includes many different ultrastructural patterns. The TGase1 deficient subtype is detected by electron microscopy (intercorneosomal, electron-lucent rod shaped vacuoles) and phase contrast light microscopy changes of scale scrapings. TGase1 deficiency can be confirmed on TGase1 immunoassay of cryostat sections of a skin biopsy [9,13]. Mutational analysis of the *TGM1* gene, to identify known or novel mutations, is performed on PCR-amplified and sequenced leucocyte DNA, from a blood sample.

Genetics. Genetic studies of families with severe LI revealed genetic linkage, compatible with recessive inheritance, to the region on chromosome 14q11 containing the transglutaminase 1 gene, *TGM1*. This was followed by the identification of several homozygous or compound heterozygote mutations in the *TGM1*, associated with reduced or absent transglutaminase activity [9–13,28]. A minority of patients with LI show partial resolution of scaling which clears from the face and limbs. This is called bathing suit ichthyosis and is due to a temperature-sensitive TGase1 [14,15]. There is biological heterogeneity; 13 of 23 families with a clinically similar phenotype had no evidence of linkage to the *TGM1* gene locus [29]. Linkage of classical LI to chromosome 2q33–35 revealed missense mutations in the *ABCA12* gene (also responsible for harlequin ichthyosis) [16], while other genes related to a mild LI phenotype include ichthyin on chromosome

5q33 [17] and a cytochrome P450 gene on chromosome 19p12–q12 [18]. There is close genotype–phenotype correlation in those families with linkage to these three sites. An autosomal dominant keratoderma with ichthyosiform erythroderma in a kindred reported by Camisa *et al.* [30] is a result of a loricrin mutation [31] (Vohwinkel's syndrome variant).

Classical LI is an autosomal recessive disorder, and the same principles apply in the counselling of families as outlined for NBIE. Because of the rare occurrence of autosomal dominant LI, examination of any relatives with skin disease is indicated, and in non-consanguineous families with an affected parent and child the possibility of dominant or pseudodominant transmission should be borne in mind.

Treatment. Mild LI can be controlled with regular emollients and keratolytics as outlined for the treatment of ichthyosis vulgaris. Topical calcipotriol has been efficacious in LI [21,32] and beneficial effects of a 10% urea lotion and topical *N*-acetylcysteine have been reported [33,34]. A trial of oral retinoid therapy is indicated in severe LI (Fig. 19.8). Of six patients with typical severe LI, five had a marked improvement, while the sixth had a moderate response with reduction of scaling, pruritus and skin tenderness [35]. The main side effects were cheilitis, epistaxis and hair loss in one. In three of these patients, low-dose therapy was effective. The management of systemic retinoid therapy is detailed in the section on the treatment of NBIE, p. 19.19. A topical receptor-selective retinoid, tazarotene 0.05% gel, has also produced good results [36].

References

1 Fox GH. The 'alligator boy': a case of ichthyosis. *J Cutan Venereol Dis* 1884; **2**: 97–9.
2 Traupe H. *The Ichthyoses: a Guide to Clinical Diagnosis, Genetic Counselling and Therapy*. Heidelberg: Springer-Verlag, 1989.
3 Williams ML, Elias PM. Heterogeneity in autosomal recessive ichthyosis. *Arch Dermatol* 1985; **121**: 477–88.
4 Hazell M, Marks R. Clinical, histologic and cell kinetic discriminants between lamellar ichthyosis and non-bullous congenital ichthyosiform erythroderma. *Arch Dermatol* 1985; **121**: 489–93.
5 Traupe H, Kolde G, Happle R. Autosomal dominant lamellar ichthyosis: a new skin disorder. *Clin Genet* 1984; **26**: 457–61.
6 Lavrijsen APM, Bouwstra JA, Gooris GS *et al.* Reduced skin barrier function parallels abnormal stratum corneum lipid organization in patients with lamellar ichthyosis. *J Invest Dermatol* 1995; **105**: 619–24.
7 Hohl D, Huber M, Frenk E. Analysis of the cornified cell envelope in lamellar ichthyosis. *Arch Dermatol* 1993; **129**: 618–24.
8 Huber M, Rettler I, Bernasconi K *et al.* Mutations of keratinocyte transglutaminase in lamellar ichthyosis. *Science* 1995; **267**: 525–8.
9 Pigg M., Gedde-Dahl T, Cox D *et al.* Strong founder effect for a transglutaminase 1 gene mutation in lamellar ichthyosis and congenital ichthyosiform erythroderma from Norway. *Eur J Hum Genet* 1998; **6**: 589–96.
10 Yang JM, Ahn KS, Cho MO *et al.* Novel mutations of the transglutaminase 1 gene in lamellar ichthyosis. *J Invest Dermatol* 2001; **117**: 214–8.
11 Vahlquist A, Ganemo A, Pigg M *et al.* The clinical spectrum of congenital ichthyosis in Sweden: A review of 127 cases. *Acta Derm Venereol* 2003; **83** (Suppl. 213): 34–47.
12 Akiyama M, Takizawa Y, Suzuki Y *et al.* Compound heterozygous TGM1 mutations including a novel missense mutation L204Q in a mild form of lamellar ichthyosis. *J Invest Dermatol* 2001; **116**: 992–5.
13 Esposito G, Tadini G, Paparo F *et al.* Transglutaminase 1 deficiency and corneocyte collapse: an indication for targeted molecular screening in autosomal recessive congenital ichthyosis. *Br J Dermatol* 2007; **157**: 799–846.
14 Oji V, Mazereeuw Hautier J, Ahvazi B *et al.* Bathing suit ichthyosis is caused by transglutaminase 1 deficiency: evidence for a temperature-sensitive phenotype. *Hum Mol Genet* 2006; **15**: 3083–97.
15 Arita K, Jacyk WK, Wessagowit V *et al.* The South African 'bathing suit ichthyosis' is a form of lamellar ichtyosis caused by a homozygous missense mutation, p.R315L, in transglutaminase 1. *J Invest Dermatol* 2007; **127**: 490–3.
16 Lefevre C, Audebert S, Jobard F *et al.* Mutations in the transporter ABCA12 are associated with lamellar ichthyosis type 2. *Hum Mol Genet* 2003; **12**: 2369–78.
17 Dahlqvist J, Klar J, Hauser I *et al.* Congenital ichthyosis: mutations in ichthyin are associated with specific structural abnormalities in the granular layer of the epidermis. *J Med Genet* 2007; **44**: 615–20.
18 Lefevre C, Bouadjar B, Ferrand V *et al.* Mutations in a new cytochrome P450 gene in lamellar ichthyosis type 3. *Hum Mol Genet* 2006; **15**: 767–76.
19 Niemi KM, Kanerva L, Kuokanen K. Recessive ichthyosis congenita, type II. *Arch Dermatol Res* 1991; **283**: 211–8.
20 De Wolf K, Gourdain JM, De Dobbeleer G, Song M. A particular subtype of ichthyosis congenita type III. *Am J Dermatopathol* 1995; **17**: 606–11.
21 Thacher TD, Fischer PR, Pettifor JM *et al.* Nutritional rickets in ichthyosis and response to calcipotriene. *Pediatrics* 2004; **114**: 119–23.
22 Sethuraman G, Khaitan BK, Dash SS *et al.* Ichthyosiform erythroderma with rickets: report of 5 cases. *Br J Dermatol* 2008; **158**: 603–6.
23 Kolde G, Happle R, Traupe H. Ultrastructural characteristics of a new type of congenital ichthyosis. *Arch Dermatol Res* 1985; **278**: 1–5.
24 Larregue M, Ottavy N, Bressieux JM, Lorette J *et al.* Bébé collodion: trente-deux nouvelles observations. *Ann Dermatol Vénéréol* 1986; **113**: 773–85.
25 Toribio J, Redondo VF, Peteiro C *et al.* Autosomal dominant lamellar ichthyosis. *Clin Genet* 1986; **30**: 122–6.
26 Melnik B, Kuster W, Hollman J *et al.* Autosomal dominant lamellar ichthyosis exhibits abnormal scale lipid pattern. *Clin Genet* 1989; **35**: 152–6.
27 Jacyk WK. Bathing-suit ichthyosis: a peculiar phenotype of lamellar ichthyosis in South African blacks. *Eur J Dermatol* 2005; **15**: 433–6.
28 Laiho E, Niemi KM, Ignatius J *et al.* Clinical and morphological correlations for transglutaminase 1 mutations in autosomal recessive congenital ichthyosis. *Eur J Hum Genet* 1999; **7**: 625–32.
29 Parmentier L, Blanchet-Bardon C, Nguyen S *et al.* Autosomal recessive lamellar ichthyosis: identification of a new mutation in transglutaminase 1 and evidence for genetic heterogeneity. *Hum Mol Genet* 1995; **4**: 1391–5.
30 Camisa C, Hessel A, Rossana C, Parks A. Autosomal dominant keratoderma, ichthyosiform dermatosis and elevated serum beta-glucuronidase. *Dermatologica* 1988; **177**: 341–7.
31 Korge BP, Ishida-Yamamoto A, Punter C *et al.* Loricrin mutation in Vohwinkel's keratoderma is unique to the variant with ichthyosis. *J Invest Dermatol* 1997; **109**: 604–10.
32 Lucker GPH, van de Kerkhof PCM, van Dijk MR, Steijlen PM. Effect of topical calcipotriol on congenital ichthyoses. *Br J Dermatol* 1994; **131**: 546–50.
33 Kuster W, Bohnsack K, Rippke F *et al.* Efficacy of urea therapy in children with ichthyosis. *Dermatology* 1998; **196**: 217–22.
34 Redondo P, Bauza A. Topical *N*-acetylcysteine for lamellar ichthyosis. *Lancet* 1999; **354**: 1880.
35 Steijlen PM, van Dooren-Greebe RJ, van de Kerkhof PCM. Acitretin in the treatment of lamellar ichthyosis. *Br J Dermatol* 1994; **130**: 211–4.
36 Hofmann B, Stege H, Ruzicka T *et al.* Effect of topical tazarotene in the treatment of congenital ichthyoses. *Br J Dermatol* 1999; **141**: 642–6.

Harlequin ichthyosis (MIM 242500)

Harlequin ichthyosis (HI) describes a severe erythrodermic ichthyosis that causes a distinctive and alarming appearance at birth. The skin patterning and associated high mortality prompted the label of 'harlequin fetus' but, as survival is possible, the term HI is more appropriate. This was one of the first genodermatoses to be recorded. An affected baby, who survived for 2 days, was described by Oliver Hart, a Charleston pastor, in his diary of 1750, published in 1896 [1]. HI is presumed to be a very rare occurrence (estimated five cases in the UK annually) but, as there is no national genodermatoses register, this may be an underestimate. HI was

invariably associated with stillbirth or early neonatal death until Lawlor's report of a survivor in 1985 [2,3]. Several survivors have been reported since, with the majority eventuating in a severe erythrodermic ichthyosis [4–9]. Most cases are sporadic with autosomal recessive inheritance, but some kindred have had several affected children [2,8–10].

Aetiology and pathogenesis. Defects in keratin expression and epidermal lipid deposition were reported in the 1970s [11,12]. HI cultured keratinocytes show excessive cornification and failure of desquamation. A study of 10 HI cases revealed defective lamellar bodies and intercellular lipid lamellae in all, but variable keratin and filaggrin expression suggested genetic heterogeneity [13,14]. Three subtypes were identified based on keratin and profilaggrin staining; filaggrin was absent in all types [14]. In types 1 and 2 HI, abnormal expression of protein phosphatase 2Ac was found [15]. Reduced calpain 1, a calcium-dependent neutral protease, was also reported in HI epidermis but not in other epidermal disorders [16]. Calpain 1 plays an important role in epidermal differentiation, as a regulator of signal transduction and of profilaggrin, transglutaminase and cytoplasmic protease activity.

In 2003, missense mutations in the epidermal lipid transporter gene for ABCA12, were reported in several patients with lamellar ichthyosis [17]. Two separate research groups identified deletions of the *ABCA12* gene in several families with HI [18,19]. ABCA proteins bind ATP and actively transport lipids across cell membranes against a concentration gradient. ABCA12 is responsible for the formation of the lamellar granules/bodies which contain Golgi-body derived polar lipids, lipid-processing enzymes, proteases and their inhibitors. It is therefore pivotal in the development of epidermal barrier function (which is dependent on lamellar body-derived intercellular lipid lamellae) and desquamation. Akiyama's group further demonstrated localization of ABCA12 staining to lamellar granules in normal epidermis, abnormal lipid secretion in cultured HI keratinocytes and recovery of lamellar body function after corrective *ABCA12* gene transfer into cultured patient keratinocytes [19]. The *ABCA12* gene is large and encoded by 53 exons. Different *ABCA12* mutations have been reported in patients with HI, and a minority of those with NBIE and LI. The closely related ABCA3 protein is responsible for the production of alveolar surfactant and between them, ABCA3 and ABCA12 were essential in the evolutionary progression from aquatic to terrestrial life.

Histopathology. Skin biopsy shows marked, compact orthohyperkeratosis extending down into dilated hair follicles and pilosebaceous units. Parakeratosis is marked in type 3 HI and may occur in types 1 and 2 [13]. Usually, no other specific changes are noted on light microscopy, and the basal and spinous layers appear relatively normal. In some cases, vacuoles are seen in the stratum corneum and the granular layer is reduced in thickness. Rarely, papillomatosis and a dermal inflammatory infiltrate are present. Pilosebaceous and sweat glands are preserved and non-keratinizing mucous membranes are normal.

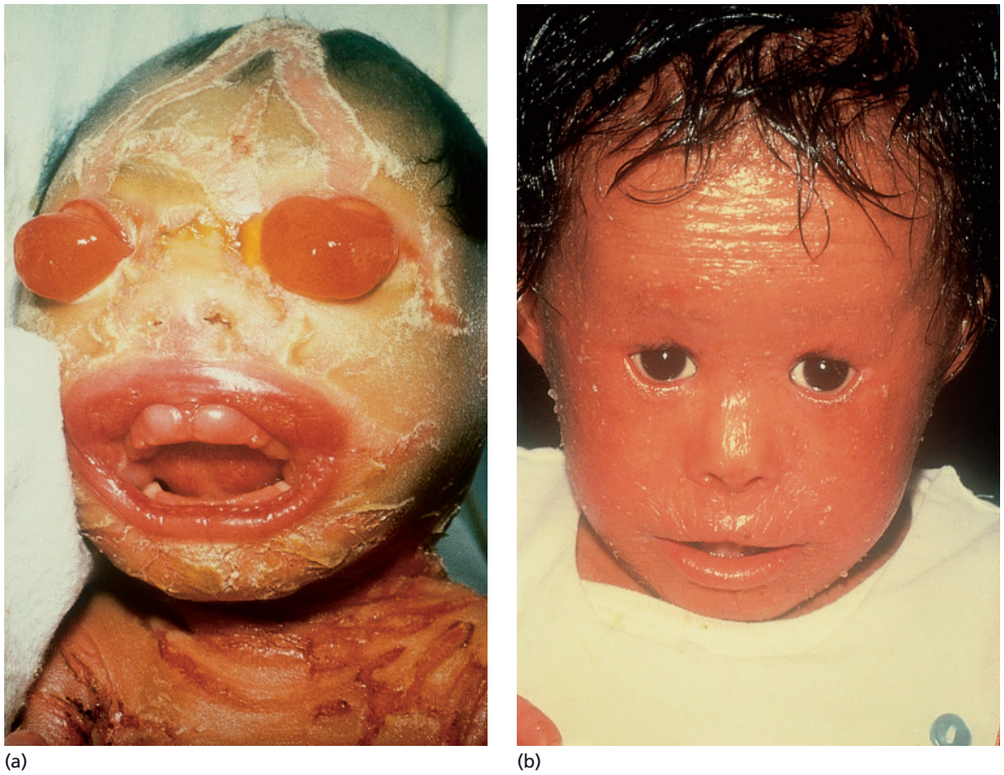
Electron microscopy of 10 cases, including one fetal skin biopsy, revealed multiple vacuoles, lipid droplets and cellular remnants in corneocytes in all cases [13]. Keratohyaline granules were abnormal in types 2 and 3. Lamellar bodies in spinous and granular layer cells are either absent or abnormal, and the intercellular lipid lamellae at the granular–corneal junction are absent or poorly formed [20]. Immunohistochemical staining of the cytoplasmic vesicles seen in granular layer cells suggested that they were abnormal lamellar granules. In fetal biopsies, large abnormal mitochondria in keratinocytes were noted at 16 weeks' gestation, prior to keratinization [21]. Adnexal keratin plugging at 18–20 weeks preceded interfollicular changes, and a thickened cornified envelope was also evident.

A skin biopsy from a 2-year-old survivor showed histological and ultrastructural features similar to those of severe NBIE with more pronounced lamellar body defects [10].

Clinical features. The affected infant, usually premature, sometimes stillborn, is encased in a rigid, taut, yellow-brown, adherent thick skin, a hyperkeratotic 'coat of armour', covering the whole body surface. Deep fissures occur prenatally over the scalp and soon after birth, the inflexible 'cast' splits at sites of stress, producing further red fissures and a skin pattern resembling a harlequin's costume. The head may appear microcephalic, and facial features are distorted because of severe ectropion, conjunctival oedema, which obscures the eyes, and eclabium (everted lips) (Fig. 19.11a and Fig. 19.12a). The scalp feels boggy, and the nose and external ears are tethered and appear rudimentary. Oedematous hands and feet may either be encased in hard mitten-like casts, or covered with a mucoid membrane, but the digits are well formed underneath. Additional congenital defects have been found in some cases.

Movement is restricted, and respiratory insufficiency results from limited chest expansion and sometimes coexistent skeletal deformity. Absence of effective sucking causes feeding difficulties which may lead to hypoglycaemia, dehydration and renal failure. Temperature instability and infection commonly supervene, and may lead to rapid demise. However, several survivors have been reported in recent years [2–10]. In these cases, intensive nursing and medical care prolonged survival until the plate-like scale was shed over several weeks (Fig. 19.12b,c). Early retinoid therapy was instituted in some cases and in all but one a severe ichthyosis resembling NBIE was the eventual outcome. One survivor was reported to be well grown and of normal intelligence and had discontinued retinoid therapy [4]. Another, now in her early twenties, has severe ichthyosiform erythroderma, short stature and mild limb contractures following osteomalacia but had attended mainstream school (Fig. 19.11b) (F. Lawlor, personal communication, 2007) [2,3]. Vitamin D deficiency leading to rickets is a high-risk complication [22].

Genetics and prenatal diagnosis. HI is an autosomal recessive disorder. The relatively uniform HI phenotype is now known to result from loss-of-function mutations in the *ABCA12* gene, which codes for a membrane-based lipid transporter protein responsible for the formation and function of the lamellar granules. One group, using homozygosity mapping, identified the *ABCA12* containing region of chromosome 2q35 and found large intragenic and frameshift mutations in 11 of 12 HI patients [18]. The 12th patient was later shown to have a heterozygous intragenic dele-



(a) (b)

Fig. 19.11 Harlequin ichthyosis: (a) neonate, (b) aged 18 months.

tion in exon 8 of the *ABCA12* gene [23]. A second group found five different compound heterozygous or homozygous *ABCA12* mutations, which caused truncation or deletion of the highly conserved regions of the ABCA12 protein [19]. In a further report of 14 HI patients, all had *ABCA12* mutations but in three only one affected allele could be identified [23]. Therefore affected families possess a range of different *ABCA12* mutations resulting in variable protein truncation, but within families disease expression is consistent. Certain mutations which affect functionally less critical *ABCA12* sites cause milder HI phenotypes. The mutation dataset suggests ethnic-specific founder mutations in the *ABCA12* gene [24]. The most common mutation in HI patients of Pakistani and Indian origin (occurring in 80% of this group) is 7322delC in exon 49 of *ABCA12* [23]. Homozygous mutations suggest parental consanguinity. Awareness of founder mutations will facilitate screening and prenatal diagnosis by targeting specific mutations known to occur more often in ethnic groups.

Detailed genetic counselling is required for affected families, and prenatal diagnostic testing should be offered in any future pregnancies. Previously, this depended on identifying premature keratinization at 20 plus weeks' gestation [25] or ultrastructural abnormalities from 18 weeks in fetal skin biopsy [26]. Amniocentesis at 17 weeks revealed intracellular lipid vesicles in shed keratinocytes [27] and ultrasound detection of amniotic fluid debris was noted [28]. The identification of a specific *ABCA12* mutation in an affected family opens the way to early DNA-based prenatal diagnosis on chorionic villus biopsy [19] or amniocytes, as in the case of a successful prenatal diagnosis of an affected fetus at 17 weeks' gestation [29]. Preimplantation genetic testing is also now possible [24].

HI has been reported in one non-identical twin [30] and in two twin pairs [10,31].

Differential diagnosis. The distinctive clinical features of HI are unlikely to be confused with the less severe presentation of the collodion baby, but some neonates have an intermediate phenotype, which has been termed 'chrysalis baby'. The multiple, different *ABCA12* mutations (and their occasional absence) help to consolidate genotype–phenotype correlation. The early neonatal appearance of HI may resemble that of restrictive dermopathy, but in the latter the tight, thick skin persists and skeletal and facial abnormalities are evident. A variant of infantile systemic hyalinosis and the 'stiff skin syndrome' (congenital fascial dystrophy) also present with tight skin. The Neu–Laxova syndrome has some similarities in its neonatal presentation [32] and Gaucher type 2 lysosomal disease may also present with a restrictive collodion membrane [33].

Treatment. Up to the 1980s, the outcome was uniformly bleak with death resulting in the first days or weeks of life. Since then there have been several long-term survivors, most with severe ichthyosiform erythroderma. The potential for survival of HI babies presents families and carers with the dilemma of providing intensive neonatal care while accepting the outcome of severe, lifelong ichthyosis. The family should be informed of the implications of the condition, encouraged to consider all options and



Fig. 19.12 Harlequin ichthyosis: (a) neonate, (b) aged 6 weeks, on retinoid therapy and (c) 6 months.

supported in the part they wish to play. Staff unfamiliar with the startling and distressing deformity also need to be enlightened about the features, evolution and practical problems associated with HI. If survival seems possible and intensive care is available, a care plan should be drawn up within the first day of life and support provided for staff in their difficult role. The facilities of a neonatal intensive care unit are required to cope with the predictable problems of hypothermia, feeding and respiratory difficulties, and dehydration, with possible electrolyte and renal complications and sepsis.

Regular (3–4 hourly) paraffin-based emollient, such as emulsifying ointment or 50/50 paraffin mix, and skin cleansing with antiseptic washing lotion are required from day 1 onwards. Nursing in a humidified incubator or on a heated cot help maintain body temperature. Early feeding problems (which improve with lessening of eclabium) can be overcome with nasogastric tube feeding but aspiration is a potential risk. A higher fluid requirement can be expected and needs are monitored by daily weighing and renal function assessment (though blood testing is challenging). The apparent benefit of early retinoid therapy is difficult to assess and not all survivors have received it [8]. Early introduction of acitretin probably accelerates shedding of hyperkeratotic plates within the first few weeks without influencing the eventual outcome (Figs 19.11 & 19.12). Whether or not to continue retinoid therapy depends on the severity of the ichthyosis, the degree of improvement in disability and the risk–benefit assessment. An oil-based liquid form of acitretin can be formulated and administered via a nasogastric tube. It should be stored in the dark and treated as a teratogenic agent. HI survivors are at risk of osteopenia, vitamin D deficiency and short stature, in addition to chronic ectropion (with possible exposure keratitis) and constrictive deformities of ears, hands and feet. Later, staged plastic surgery may improve the cosmetic burden. Some HI survivors follow a daily routine of vigorous exfoliation.

The demonstration that ABCA12 deficiency could be corrected by gene transfer in cultured keratinocytes offers the hope that corrective therapy (by administration of ABCA12-like peptides or *ABCA12* gene delivery pre- or postnatally) may eventually be possible [19].

References

1 Waring JI. Early mention of a harlequin fetus in America. *Am J Dis Child* 1932; **43**: 442.

2 Lawlor F, Peiris S. Harlequin fetus successfully treated with etretinate. *Br J Dermatol* 1985; **112**: 585.

3 Lawlor F. Progress of a harlequin fetus to non-bullous ichthyosiform erythroderma. *Paediatrics* 1989; **82**: 870–3.

4 Roberts LJ. Long-term survival of a harlequin fetus. *J Am Acad Dermatol* 1989; **212**: 335–9.

5 Rogers M, Scarf C. Harlequin baby treated with etretinate. *Pediatr Dermatol* 1989; **6**: 216–21.

6 Ward PS, Jones RD. Successful treatment of a harlequin fetus. *Arch Dis Child* 1989; **64**: 1309–11.

7 Nayar M, Chin GY. Harlequin fetus treated with etretinate. *Pediatr Dermatol* 1992; **9**: 311–4.

8 Prasad RS, Pejaver RK, Hassan A *et al*. Management and follow-up of harlequin siblings. *Br J Dermatol* 1994; **130**: 650–3.

9 Haftek M, Cambazard F, Dhouailly D *et al.* A longitudinal study of a harlequin infant presenting clinically as non-bullous congenital ichthyosiform erythroderma. *Br J Dermatol* 1996; **135**: 448–53.

10 Unamuno P, Pierola JM, Fernandez E *et al.* Harlequin fetus in four siblings. *Br J Dermatol* 1987; **116**: 569–72.

11 Craig JM, Goldsmith LA, Baden HP. An abnormality of keratin in the harlequin fetus. *Pediatrics* 1970; **46**: 437–40.

12 Buxman MM, Goodkin PE, Fahrenback WH, Dimond RL. Harlequin ichthyosis with an epidermal lipid abnormality. *Arch Dermatol* 1979; **115**: 189–93.

13 Dale BA, Holbrook KA, Fleckman P *et al.* Heterogeneity in harlequin ichthyosis, an inborn error of epidermal keratinization: variable morphology and structural protein expression and a defect in lamellar granules. *J Invest Dermatol* 1990; **94**: 6–18.

14 Dale BA, Kam E. Harlequin ichthyosis: variability in expression and hypothesis for disease mechanism. *Arch Dermatol* 1993; **129**: 1471–7.

15 Haugen-Schofield J, Resing K, Dale BA. Characterization of an epidermal phosphatase specific for filaggrin phosphorylated by casein kinase II. *J Invest Dermatol* 1988; **91**: 553–9.

16 Michel M, Fleckman P, Smith LT, Dale BA. The calcium-activated neutral protease calpain 1 is present in normal foetal skin and is decreased in neonatal harlequin ichthyosis. *Br J Dermatol* 1999; **141**: 1017–26.

17 Lefevre C, Audebert S, Jobard F *et al.* Mutations in the transporter ABCA12 are associated with lamellar ichthyosis type 2. *Hum Mol Genet* 2003; **12**: 2369–78.

18 Kelsell DP, Norgett EE, Unsworth H *et al.* Mutations in ABCA12 underlie the severe congenital skin disease harlequin ichthyosis. *Am J Hum Genet* 2005; **76**: 794–803.

19 Akiyama M, Sugiyama-Nakagiri Y, Sakai K *et al.* Mutations in lipid transporter ABCA12 in harlequin ichthyosis and functional recovery by corrective gene transfer. *J Clin Invest* 2005; **115**: 1777–84.

20 Milner ME, O'Guin WM, Holbrook KA *et al.* Abnormal lamellar granules in harlequin ichthyosis. *J Invest Dermatol* 1992; **99**: 824–9.

21 Hashimoto K, De Dobbeleer G, Kanzaki T. Electron microscopic studies of harlequin fetus. *Pediatr Dermatol* 1993; **10**: 214–23.

22 Sethuraman G, Khaitan BK, Dash SS *et al.* Ichthyosiform erythroderma with rickets: report of five cases. *Br J Dermatol* 2008; **158**: 603–6.

23 Thomas AC, Cullup T, Norgett EE *et al.* ABCA12 is the major harlequin ichthyosis gene. *J Invest Dermatol* 2006; **126**: 2408–13.

24 Thomas AC, Sinclair C, Mahmud N *et al.* Novel and recurring ABCA12 mutations associated with harlequin ichthyosis: implications for prenatal diagnosis. *Br J Dermatol* 2008; **158**: 611–3.

25 Blanchet-Bardon C, Dumez Y. Prenatal diagnosis of a harlequin fetus. *Semin Dermatol* 1984; **3**: 225–8.

26 Eady RAJ, Blanchet-Bardon C, Gunner DB *et al.* Atypical intraepidermal vesicles serve as a marker for the prenatal diagnosis of harlequin ichthyosis (Abstract). *J Invest Dermatol* 1990; **95**: 468.

27 Akiyama M, Kim DK, Main DM *et al.* Characteristic morphologic abnormality of harlequin ichthyosis detected in amniotic fluid cells. *J Invest Dermatol* 1994; **102**: 210–3.

28 Mihalko M, Lindfors KK, Grix AW *et al.* Prenatal sonographic diagnosis of harlequin ichthyosis. *Am J Roentgenol* 1989; **153**: 827–8.

29 Akiyama M, Titeux M, Sakai K *et al.* DNA-based prenatal diagnosis of harlequin ichthyosis and characterization of ABCA12 mutation consequences. *J Invest Dermatol* 2007; **127**: 568–73.

30 Abramson A, Sperling R, Moshirpur J. Harlequin fetus in twins. *Mt Sinai J Med* 1984; **51**: 290–1.

31 Anstey A, Judge M, Salisbury J, Meadows N. Harlequin ichthyosis twins. *Br J Dermatol* 1991; **125** (Suppl.): 22.

32 Manning MA, Cunniff CM, Colby CE *et al.* Neu-Laxova syndrome: detailed prenatal diagnostic and post-mortem findings and literature review. *Am J Med Genet* 2004; **15**: 240–9.

33 Stone DL, Carey WF, Christodoulou J *et al.* Type 2 Gaucher disease: the collodion baby phenotype revisited. *Arch Dis Child Fetal Neonatal Ed* 2000; **82**: F163–6.

Bullous ichthyosiform erythroderma (MIM 113800)

Bullous ichthyosiform erythroderma (BIE) is a rare autosomal dominant disorder of keratinization that, in its early phase, is associated with blistering. It was first described by Brocq in 1902 [1]. The incidence is thought to be approximately 1 in 100 000 births, although it is likely that some mild cases go unrecognized. The characteristic histological features of BIE, hyperkeratosis with lysis and tonofilament clumping in granular layer keratinocytes, are termed 'epidermolytic hyperkeratosis' and in some countries this term is also used to define the clinical picture. To date, all investigated cases of BIE have been shown to result from mutations in particular keratin genes, with good correlation of phenotype and genotype as skin lesions occur in sites where the affected keratin is expressed.

Aetiology and pathogenesis. The aggregation of tonofilaments in suprabasal keratinocytes in BIE is suggestive of an underlying genetic defect of keratin synthesis or degradation, involving keratins K1 and/or K10, as they are distributed only in the suprabasal compartment in normal epidermis [2]. Immunoelectron microscopy, using highly specific keratin monoclonal antibodies, showed selective involvement of K1/K10 in the aggregated tonofilaments suprabasally, while the non-aggregated filaments seen in basal cells consisted of K5 and K14 [3]. These data pointed to a primary genetic defect in K1 or K10. Increased filaggrin reactivity was also evident on immunohistochemistry and protein blotting, but was preceded by keratin filament aggregation, suggesting that the aggregation was independent of the action of profilaggrin. Affected fetuses have been shown to develop suprabasal tonofilament clumps at a stage of skin development where keratohyalin granules are not yet expressed, implying that filaggrin changes are secondary [4]. There are also alterations in the staining pattern and electron density of cornified envelope proteins, thought to be secondary to the keratin defects [5]. Loricrin staining was prematurely expressed and associated with keratin aggregates. Trichohyalin reactivity, not normally found in epidermis, was found in granular cells. However, the abnormal barrier function in epidermolytic hyperkeratosis has been attributed to defective lamellar body lipid secretion rather than problems in the corneocytes [6].

Genetic linkage studies confirmed autosomal dominant inheritance, and revealed linkage to either of the keratin gene clusters on chromosomes 12q and 17q [7–9]. Transgenic mice carrying mutant K10 developed skin abnormalities similar to BIE [10] and transgenic mice expressing a severely truncated K10 protein displayed a BIE-like phenotype in heterozygotes and a more severe phenotype in homozygotes [11]. Several groups have described heterozygous mutations in the highly conserved regions of K1 (47 different mutations) and K10, predominantly involving point mutations resulting in amino acid substitutions within the specialized sequences of the ends of the rod domains ([12–19], see also Human Intermediate Filament Mutation Database, http://www.interfil.org). These conserved regions are critical for filament integrity and assembly, and the mutations disrupt higher filament assembly in a dominant-negative fashion, leading to collapse of the network and filament aggregation around the nucleus. Most mutations occur within the conserved sequence motif at the beginning of the helical rod domain, with a particular arginine codon in K10 being most vulnerable, the 'hotspot arginine' [14,16]. Specific mutations involving different amino acid substitution within the 2B rod domain of K1 have been associated with the rare annular migratory variant of BIE [20].

Identification of the gene abnormality in a parent can permit prenatal diagnosis by direct gene sequencing from a chorionic villus sample earlier than by prenatal skin biopsy [16]. In a genetic study of 21 American families, the presence or absence of palmoplantar keratoderma (PPK) was used to subset the patients [21]. Of the six families with PPK, four had K1 mutations whereas eight of the 15 families without PPK had K10 mutations.

Histopathology. Skin biopsy shows marked epidermal acanthosis and hyperkeratosis. In the cells of the prominent and degenerate granular layer, and in the upper spinous layers, there are multiple perinuclear vacuoles and large clumped keratohyaline granules. Inter- and intracellular spaces form as a result of suprabasal cytolysis or cell rupture (epidermolysis), and a split with oedema in the granular layer marks the site of a blister (Fig. 19.13). These features together describe 'epidermolytic hyperkeratosis' (EHK). In mild forms of the disease, these changes may be subtle. The basal keratinoyctes are normal and there is a mild upper dermal lymphocytic infiltrate. The epidermis is hyperproliferative and the number of basal keratinocyte mitoses approaches that of psoriatic erythroderma [22].

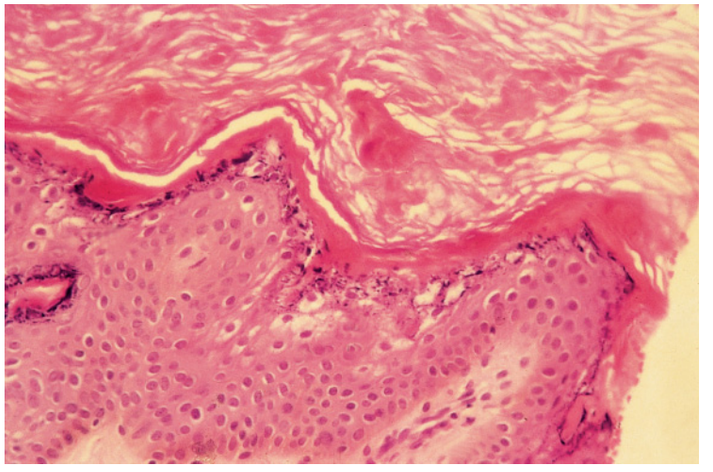


Fig. 19.13 Bullous ichthyosiform erythroderma; histological features of epidermolytic hyperkeratosis.

Electron microscopy reveals clumped keratin tonofilaments dispersed around the keratinocyte nucleus. Desmosomes are disrupted to a variable degree, and clefts between keratinocytes are associated with oedema and acantholysis. The ultrastructural tonofilament changes precede the vacuolation in spinous and granular cell layers [2,23]. There is no defect in the cornified envelope but intercellular lipid bilayers may be abnormal [6]. EHK is not unique to BIE but is seen in ichthyosis bullosa of Siemens, some cases of ichthyosis hystrix, Vorner's palmoplantar keratoderma, a subgroup of epidermal naevi, and as an incidental finding in a variety of unrelated lesions such as solitary acanthoma, dermatofibroma, melanocytic, actinic and inflammatory lesions, in the walls of epidermal cysts and even occasionally in normal oral mucosa [24,25].

Clinical features. BIE typically presents with fragile skin (epidermolysis), which gives way to progressive hyperkeratosis. A mild, generalized erythroderma is present at birth. Flaccid blisters, peeling and superficial erosions at sites of minor trauma or friction are apparent within the first few hours of life (Fig. 19.14). Frequent misdiagnoses at this stage include staphylococcal scalded skin syndrome and epidermolysis bullosa. However, the baby is generally apyrexic and stable, and focal hyperkeratosis may hint at the diagnosis. In the past, many of these infants developed severe infection, dehydration and malnutrition leading to a considerable mortality, but with intensive neonatal care their prognosis has greatly improved. The superficial erosions heal rapidly without



Fig. 19.14 Bullous ichthyosiform erythroderma, neonate.

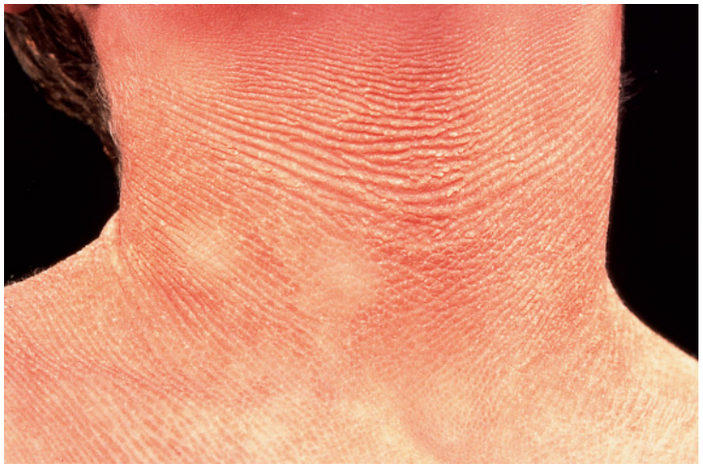


Fig. 19.15 Bullous ichthyosiform erythroderma, neck.

scarring, and easy blistering ceases in the first few months of life. Localized blistering at sites of trauma (the nappy/diaper area, thighs, knees) or infection continues through childhood. Erythroderma fades while the characteristic grey, waxy scale evolves.

Increasing hyperkeratosis is obvious from early childhood and is most prominent around the anterior neck, flexures, abdominal wall, infragluteal folds and scalp (Figs 19.15 & 19.16). Yellow–brown, waxy, ridged or corrugated scale builds up in skin creases, sometimes forming spiny (hystrix) outgrowths. Cobblestone-like keratoses occur at other sites such as the dorsal hands and feet, and over the trunk. Keratotic plaques may coat bony prominences, scalp and areolae, and chunks are easily dislodged, leaving tender erosions where scale slowly accumulates again. Skin colonization by *Staphylococcus*, brevibacterium and possibly yeasts produces a distinctive and embarrassing body odour. Repeated skin infections, causing blisters, pustules or cellulitis, especially in macerated flexural areas, are a troublesome complication in some children. The central face is mildly affected but scalp involvement can be severe and cause patchy alopecia. Spontaneous blistering virtually disappears by adolescence and only a mild erythema persists. Some mildly affected individuals have transient blistering in infancy with focal hyperkeratosis thereafter.

Palmoplantar hyperkeratosis develops in approximately 60% of patients with BIE and may result in recurrent painful fissures, contractures, sclerodactyly and foot deformity with impaired function. It does not relate to disease severity but is usually associated with keratin 1 mutations [21,26]. Nail dystrophy is rare, although curvature may result. Severely affected children may be of short stature, although many catch up in adolescence. Rickets due to vitamin D deficiency has been reported [27].

Evolution of BIE is variable, but in common with other autosomal dominant skin disorders it tends to improve with age. BIE sufferers may have significant physical and psychological morbidity. Visible scaling, skin fragility, keratoderma and odour can lead to social isolation and occupational problems. Mild learning difficulties in some patients may be related to perinatal complications.

Annular epidermolytic ichthyosis (MM 607602). This unusual variant of BIE, characterized by recurring, migrating, truncal annular and polycyclic plaques in association with more typical flexural lesions has been reported under a variety of titles (including annular epidermolytic hyperkeratosis and cyclic ichthyosis with epidermolytic hyperkeratosis) [28]. Histological features of EHK and keratin K10 or K1 mutations (including a 2B domain keratin 1mutation), similar to those of BIE, have been identified [20,28,29].

Naevoid BIE. There have been several reports of individuals with an asymmetrical linear, focal or naevoid lesion (including epidermal naevus with EHK, comedo and systematized naevi) showing histological features of EHK, who have had a child with generalized BIE [30–32]. The limited or naevoid disease expression in the parent (sometimes overlooked), distributed in Blaschko's lines, is suggestive of a post-conceptional somatic mutation of keratin K1 or K10. This produces phenotypic and, in some cases, gonadal mosaicism which in turn may lead to an affected child with generalized disease [31]. K10 gene mutations have been reported in lesional, but not normal skin or peripheral blood, of patients with naevoid BIE [33,34]. A keratin 1 mutation has recently been reported [35]. A palmoplantar epidermal naevus with EHK was found to be due to a keratin 16, V1 domain mutation [36].

Differential diagnosis. In the neonatal period, other blistering and exfoliative disorders such as epidermolysis bullosa, cutaneous mastocytosis, zinc deficiency, staphylococcal scalded skin syndrome, herpetic infection and incontinentia pigmenti must be excluded by clinical, histopathological and microbiological assessment. In older patients, ichthyosis hystrix, ichthyosis bullosa of Siemens and non-epidermolytic epidermal naevi may resemble BIE or its variants.

Genetics. At least half of cases of BIE have no family history of the disease and are presumed to have a new, spontaneous keratin 1 or 10 gene mutation. However, both parents of an affected child should be carefully examined for focal keratotic lesions suggestive of somatic and gonadal mosaicism (naevoid BIE, see above). In the



Fig. 19.16 Bullous ichthyosiform erythroderma: (a) arms, (b) legs and (c) palms.

absence of suspicious parental lesions, further siblings should not be at risk, but an affected parent will transmit the condition in an autosomal dominant fashion to their offspring, who will have generalized disease. The occurrence of inter- and intrafamilial variation in disease severity further complicates genetic assessment. A mildly affected parent may have a severely affected child, either because they have improved with age or because they have a mosaic expression. The reverse can also happen with an attenuated form of familial BIE appearing in the next generation, or variation in severity among affected offspring. It is postulated that a benign simultaneous polymorphism in keratin or keratin-associated protein genes has a modifying effect on the phenotypic expression of the disease in these families [15]. It is also evident that the same keratin 1 mutation has resulted in differing phenotypes/severity of lesions. A number of cases of autosomal recessive BIE, caused by *KRT10* mutations, have been reported [37].

Prenatal diagnosis, based on identification of the characteristic ultrastructural changes on fetal skin biopsy, has traditionally been performed at around 20 weeks' gestation, with ultrasound-guided fetoscopy [38]. Tonofilament clumping is the earliest

morphological abnormality, occurring during the second trimester, and precedes the formation of keratohyalin granules and stratum corneum [39]. First trimester prenatal diagnosis is based on DNA screening by direct gene sequencing to identify specific K1 and K10 gene mutations in chorionic villus samples (following informative direct gene sequencing of the index case) [16,40].

Treatment. Emollients are of limited value in BIE as the scale is often waxy and macerated. Keratolytic preparations (salicylic acid, α-hydroxy acid or propylene glycol compounds) reduce hyperkeratosis on exposed sites but their irritancy limits patients' tolerance. Patients are best placed to decide which, if any, they wish to use and their needs will change over time. Regular use of antiseptic washes and cleansing lotions may improve skin colonization and body odour and reduce the risk of bacterial and fungal infection. Systemic antibiotics are indicated for widespread cutaneous or soft tissue infections; regular sensitivity testing of *Staphylococcus aureus* isolates informs treatment. Long-term antibiotics are rarely justified. Topical calcipotriol produces a slight reduction in scaling at the cost of skin irritation [41]. Retinoid therapy is beneficial in some patients, but significant reduction in scaling is often associated with unacceptable skin fragility, blistering and tenderness [26,42] (for details of acitretin dosage and surveillance, see treatment of NBIE, p. 19.19). It has been noted that patients with K10 mutations (who usually do not have palmoplantar keratoderma) respond better to retinoid therapy than those with K1 defects [26]. UVB phototherapy has proved useful in a few adolescent and adult patients.

References

1 Brocq L. Erythrodermie congenitale ichthyosiforme avec hyperepidermotrophie. *Ann Dermatol Syphiligr* 1902; **4**: 1–31.

2 Anton-Lamprecht I. Disturbances of tonofilament and keratohyaline structure and arrangement in inborn errors of keratinization. In: Marks R, Christophers E, eds. *The Epidermis in Disease*, 1st edn. Lancaster: MTP Press, 1981: 61–77.

3 Ishida-Yamamoto A, McGrath JA, Judge MR *et al.* Selective involvement of keratin 1 and 10 in the cytoskeletal abnormality of epidermolytic hyperkeratosis. *J Invest Dermatol* 1992; **99**: 19–26.

4 Ishida-Yamamoto A, Eady RAJ, Underwood RA *et al.* Filaggrin expression in epidermolytic ichthyosis (epidermolytic hyperkeratosis). *Br J Dermatol* 1994; **131**: 767–9.

5 Ishida-Yamamoto A, Tizuka H, Manabe M *et al.* Altered distribution of keratinization markers in epidermolytic hyperkeratosis. *Arch Dermatol Res* 1995; **287**: 705–11.

6 Schmuth M, Yosipovitch G, Williams ML *et al.* Pathogenesis of the permeability barrier abnormality in epidermolytic hyperkeratosis. *J Invest Dermatol* 2001; **117**: 837–47.

7 Bonifas JM, Bare JW, Chen MA *et al.* Linkage of the epidermolytic hyperkeratosis phenotype and the region of the type II keratin cluster on chromosome 12. *J Invest Dermatol* 1992; **99**: 524–7.

8 Compton JG, Di Giovanna JJ, Santucci SK *et al.* Linkage of epidermolytic hyperkeratosis to the type II keratin gene cluster on chromosome 12q. *Nature Genet* 1992; **1**: 301–5.

9 Rothnagel JA, Dominey AM, Dempsey MD *et al.* Mutations in the rod domains of keratins 1 and 10 in epidermolytic hyperkeratosis. *Science* 1992; **257**: 1128–30.

10 Fuchs E, Esteves RA, Coulombe PA. Transgenic mice expressing a mutant keratin 10 gene reveal the likely genetic basis for epidermolytic hyperkeratosis. *Proc Natl Acad Sci USA* 1992; **89**: 6906–10.

11 Pulkkinen L, Christiano AM, Knowlton RG, Uitto J. Epidermolytic hyperkeratosis (bullous congenital ichthyosiform erythroderma): genetic linkage to chromosome 12q in the region of the type II keratin gene cluster. *J Clin Invest* 1993; **91**: 357–61.

12 Cheng J, Syder AJ, Yu Q-C *et al.* The genetic basis for epidermolytic hyperkeratosis: a disorder of differentiation specific epidermal keratin genes. *Cell* 1992; **70**: 811–9.

13 Chipev CC, Korge BP, Markova N *et al.* A leucine to proline mutation in the H1 subdomain of keratin 1 causes epidermolytic hyperkeratosis. *Cell* 1992; **70**: 821–8.

14 Chipev CC, Yang JM, DiGiovanna JJ *et al.* Preferential sites in keratin 10 mutated in epidermolytic hyperkeratosis. *Am J Human Genet* 1994; **54**: 179–90.

15 McLean WHI, Eady RAJ, Dopping-Hepenstal PJC *et al.* Mutations in the rod 1a domain of keratins 1 and 10 in bullous congenital ichthyosiform erythroderma. *J Invest Dermatol* 1994; **102**: 24–30.

16 Rothnagel JA, Longley MA, Holder RA *et al.* Prenatal diagnosis of epidermolytic hyperkeratosis by direct gene sequencing. *J Invest Dermatol* 1994; **102**: 13–6.

17 Traupe H. The epidermolytic (acantholytic) ichthyoses. In: Traupe H, ed. *The Ichthyoses: a Guide to Diagnosis, Genetic Counselling and Therapy*. Berlin: Springer-Verlag, 1989: 139–53.

18 Lane EB, Mclean WHI. Keratins and skin disorders. *J Pathol* 2004; **204**: 355–66.

19 Ishiko A, Akiyama M, Takizawa Y *et al.* A novel leucine to valine mutation in residue 7 of the helix initiation motif of keratin 10 leads to bullous ichthyosiform erythroderma. *J Invest Dermatol* 2001; **116**: 991–2.

20 Sybert VP, Francis JS, Corden LD *et al.* Cyclic ichthyosis with epidermolytic hyperkeratosis: a phenotype conferred by mutation in the 2B domain of keratin 1. *Am J Hum Genet* 1999; **64**: 732–8.

21 DiGiovanna JJ, Bale SJ. Clinical heterogeneity in epidermolytic hyperkeratosis. *Arch Dermatol* 1994; **130**: 1026–35.

22 Frost P, van Scott EJ. Ichthyosiform dermatoses: classification based on anatomic and biometric observations. *Arch Dermatol* 1966; **94**: 113–26.

23 Anton-Lamprecht I. Genetically induced abnormalities of epidermal differentiation and ultrastructure in ichthyoses and epidermolyses: pathogenesis, heterogeneity, fetal manifestation and prenatal diagnosis. *J Invest Dermatol* 1983; **81**: 149–56.

24 Ackerman AB. Histopathologic concept of epidermolytic hyperkeratosis. *Arch Dermatol* 1970; **102**: 253–9.

25 Mahaisavariya P, Cohen PR, Rapini RP. Incidental epidermolytic hyperkeratosis. *Am J Dermatopathol* 1995; **17**: 23–8.

26 Virtanen M, Gedde-Dahl T, Mork N-J *et al.* Phenotypic-genotypic correlations in patients with epidermolytic hyperkeratosis and the effects of retinoid therapy on keratin expression. *Acta Derm Venereol* 2001; **81**: 163–70.

27 Perosa A, Sardella L, Acquafredda A *et al.* Epidermolytic ichthyosis and rickets. *Eur J Ped Dermatol* 2004; **14**: 13–6.

28 Sahn EE, Weimer CE, Garen PD. Annular epidermolytic ichthyosis: a unique phenotype. *J Am Acad Dermatol* 1992; **27**: 348–55.

29 Yoneda K, Morita E, Akiyama M *et al.* Annular epidermolytic hyperkeratosis. *Br J Dermatol* 1999; **141**: 747–50.

30 Happle R. Lethal genes surviving by mosaicism: a possible explanation for sporadic birth defects involving the skin. *J Am Acad Dermatol* 1987; **16**: 899–906.

31 Lookingbill DP, Ladda RL, Cohen C. Generalized epidermolytic hyperkeratosis in the child of a parent with nevus comedonicus. *Arch Dermatol* 1984; **120**: 223–6.

32 Nazzaro V, Ermacora E, Santucci B, Caputo R. Epidermolytic hyperkeratosis: generalized form in children from parents with systematized linear form. *Br J Dermatol* 1990; **122**: 417–22.

33 Paller AS, Syder AJ, Chan YM *et al.* Genetic and clinical mosaicism in a type of epidermal nevus. *N Engl J Med* 1994; **331**: 1408–15.

34 Moss C, Jones DO, Blight A *et al.* Birthmark due to cutaneous mosaicism for keratin 10 mutation. *Lancet* 1995; **345**: 596.

35 Tsubota A, Akiyama M, Sakai K *et al.* Keratin 1 gene mutation detected in epidermal naevus with epidermolytic hyperkeratosis. *J Invest Dermatol* 2007; **127**: 1371–4.

36 Terrinoni A, Puddu P, Didona B *et al.* A mutation in the V1 domain of keratin 16 is responsible for unilateral palmoplantar verrucous naevus. *J Invest Dermatol* 2000; **114**: 1136–40.

37 Muller FB, Huber M, Kinaciyan T *et al.* A human keratin 10 knockout causes recessive epidermolytic hyperkeratosis. *Hum Mol Genet* 2006; **15**: 1133–41.

38 Holbrook KA, Dale BA, Sybert VP, Sagebiel RW. Epidermolytic hyperkeratosis: ultrastructure and biochemistry of skin and amniotic fluid cells from two affected fetuses and a newborn infant. *J Invest Dermatol* 1983; **80**: 222–7.
39 Eady RAJ, Gunner DB, Carbonne LDL *et al.* Prenatal diagnosis of bullous ichthyosiform erythroderma: detection of tonofilament clumps in fetal epidermis and amniotic fluid cells. *J Med Genet* 1986; **23**: 46–51.
40 Tsuji-Abe Y, Akiyama M, Nakamura H *et al.* DNA-based prenatal exclusion of bullous congenital ichthyosiform erythroderma at the early stage, 10–11 weeks of pregnancy in two consequent siblings. *J Am Acad Dermatol* 2004; **51**: 1008–11.
41 Lucker GPH, van de Kerkhof PCM, van Dijk MR, Steijlen PM. Effect of topical calcipotriol on congenital ichthyoses. *Br J Dermatol* 1994; **131**: 546–50.
42 Blanchet-Bardon C, Nazarro V, Rognin C *et al.* Acitretin in the treatment of severe disorders of keratinization. *J Am Acad Dermatol* 1991; **24**: 982–6.

Ichthyosis bullosa of Siemens (MIM 146800)

A mild variant of BIE affecting a large Dutch kindred was described by Siemens, a Dutch dermatologist, in 1937 [1]. The concept was revived by Traupe who confirmed autosomal dominant inheritance [2] and the phenotype was described in detail in additional Dutch kindreds [3]. Ichthyosis bullosa of Siemens (IBS) is probably less common than BIE, but some milder cases may escape detection.

Aetiology and pathogenesis. In addition to keratins K1 and K10, suprabasal keratinocytes in the upper stratum spinosum and stratum granulosum express a further type II keratin, K2e (now K2), a protein of molecular weight 65.8 kDa encoded by a 2.6 kb mRNA species [4,5]. It is an accessory, unpaired keratin, expressed in skin (K2e) and hard palate (K2p), coded for by the *KRT2* gene which has nine exons and 7634 bp. As epidermolytic hyperkeratosis in IBS correlates with expression of K2e, it was recognized as a likely target gene [6]. Linkage analysis of two affected Dutch families showed linkage with the type II gene cluster on chromosome 12 [7]. Direct sequencing of PCR products of keratin K2e showed a point mutation in the highly conserved helix termination motif in a five-generation kindred and a sporadic UK case [8]. The same mutation was found in two unrelated Dutch families, including the descendants of Siemens' original kindred [9]. Up to 30 missense *KRT2* rod domain mutations have been reported in IBS patients, all except one in the helix initiation or termination motifs [10–15]. A common mutation, E487K (E493K in some reports) at codon 487 in exon 7 of *KRT2* is detected in a majority of IBS cases, including sporadic cases (Intermediate Filament Mutation Database, http://www.interfil.org), indicating a mutation hotspot [8–10,13,14]. This causes a G to A change in nucleotide 1477, leading to a substitution of a glutamic acid codon with a lysine, that is a protein sequence change of E to K. The exception is E178K, a glutamic acid to lysine substitution at codon 178 in exon 1 of the H1 domain of K2e [16].

Histopathology and pathogenesis. On histological examination, features of EHK are confined to the prominent granular layer and the upper spinous layer. Basal and lower spinous layer keratinocytes appear normal. Sites of 'mauserung' (moulting) reveal intracorneal blistering with orthohyperkeratosis above and below the split. Electron microscopy shows granular cell oedema with disrupted keratin filament network and clumped tonofilaments [2].

Clinical features. IBS is phenotypically milder than BIE and typically lacks erythroderma. The characteristic features are mild neonatal disease, or delayed onset in the first year of life, with episodes of superficial blistering persisting through childhood and sometimes into adult life. These occur predominantly on the flexures, shins and abdomen, and quickly rupture to produce annular peeling. There is variable, grey, rippled hyperkeratosis on the limbs, dorsal hands and lower trunk and buttocks, with flexural accentuation and mild hypertrichosis in some (Fig. 19.17). Circumscribed, patchy scaling occurs elsewhere, and focal desquamation or moulting of scale, which Siemens called 'mauserung', is seen at hyperkeratotic flexures and acral sites, especially the dorsal hands and feet (Fig. 19.17). Palmoplantar blistering, associated with hyperhidrosis, occurs in some patients and is more severe in summer, but PPK and skin odour are absent. Children with IBS are also prone to bacterial infection and sudden widespread erythema and peeling due to staphylococcal infection has been observed.

A similar ichthyosis, also caused by K2e mutations, has been reported under the title of ichthyosis exfoliativa [17,18]. This and IBS are now regarded as a single entity [7]. An autosomal recessive form of exfoliative ichthyosis (without epidermolytic hyperkeratosis) in an inbred Bedouin family has been documented [19].

Diagnosis. This condition may be mistaken for other autosomal dominant ichthyoses, ichthyosis vulgaris, the dominant variant of lamellar ichthyosis and mild BIE. In certain phases, epidermolysis bullosa simplex, peeling skin syndrome, infected atopic eczema or staphylococcal scalded skin syndrome may be suspected.

Molecular diagnosis can be performed using whole blood to sequence genomic DNA. Prenatal diagnosis is theoretically possible.

Treatment. Emollients and mild keratolytic preparations suffice in most, and often appear to induce an impressive remission. A beneficial effect from 12% lotion of ammonium lactate has been reported in IBS [20]. Avoidance of friction and measures to reduce hyperhidrosis are indicated. Appropriate antibiotics should be used to treat skin infection or episodic blistering. Some patients responded well to low-dose retinoid therapy [21].

References

1 Siemens HW. Dichtung und Wahrheit über die 'Ichthyosis bullosa', mit Bemerkungen zür Systematik der Epidermolysen. *Arch Dermatol Syphilol* 1937; **175**: 590–680.
2 Traupe H, Kolde G, Hamm H, Happle R. Ichthyosis bullosa of Siemens: a unique type of epidermolytic hyperkeratosis. *J Am Acad Dermatol* 1986; **14**: 1000–5.
3 Steijlen PM, Perret CM, Schuurmans Stekhoven JH *et al.* Ichthyosis bullosa of Siemens: further delineation of phenotype. *Arch Dermatol Res* 1990; **282**: 1–5.
4 Collin C, Moll R, Kubicka S *et al.* Characterization of human cytokeratin 2, an epidermal cytoskeleton protein synthesized late during differentiation. *Exp Cell Res* 1992; **202**: 132–41.
5 Collin C, Ouhayoun J-P, Grund C *et al.* Suprabasal marker proteins distinguishing keratinizing squamous epithelia: cytokeratin 2 polypeptides of oral masticatory epithelium and epidermis are different. *Differentiation* 1992; **51**: 137–48.
6 Smith LT, Underwood RA, McLean WHI. Ontogeny and regional variability of keratin 2e (K2e) in developing human fetal skin: a unique spatial and temporal pattern of keratin expression in development. *Br J Dermatol* 1999; **140**: 582–91.



Fig. 19.17 Ichthyosis bullosa of Siemens, (a) in a 3-year-old boy and (b) with his affected father.

7 Steijlen PM, Kremer H, Vakilzadeh F *et al.* Genetic linkage of the keratin type II gene cluster with ichthyosis bullosa of Siemens and with autosomal dominant ichthyosis exfoliativa. *J Invest Dermatol* 1994; **103**: 282–5.
8 McLean WHI, Morley SM, Lane EB *et al.* Ichthyosis bullosa of Siemens: a disease involving keratin 2e. *J Invest Dermatol* 1994; **103**: 277–82.
9 Kremer H, Zeeuwen P, McLean WHI *et al.* Ichthyosis bullosa of Siemens is caused by mutations in the keratin 2e gene. *J Invest Dermatol* 1994; **103**: 286–9.
10 Rothnagel JA, Traupe H, Wojcik S *et al.* Mutations in the rod domain of keratin 2e in patients with ichthyosis bullosa of Siemens. *Nature Genet* 1994; **7**: 485–90.
11 Whittock N, Ashton G, Griffiths WAD *et al.* New mutations in keratin 1 that cause bullous ichthyosiform erythroderma and keratin 2e that cause ichthyosis bullosa of Siemens. *Br J Dermatol* 2001; **145**: 330–5.
12 Smith FJD, Maingi C, Covello SP *et al.* Genomic organization and fine mapping of the keratin 2e gene (*KRT2E*): K2e V1 domain polymorphism and novel mutations in ichthyosis bullosa of Siemens. *J Invest Dermatol* 1998; **111**: 817–21.
13 Basarab T, Smith FJD, Jolliffe VML *et al.* Ichthyosis bullosa of Siemens: report of a family with evidence of a keratin 2e mutation, and a review of the literature. *Br J Dermatol* 1999; **140**: 689–95.
14 Akiyama M, Tsuji Y, Yanagihara M *et al.* Ichthyosis bullosa of Siemens: its correct diagnosis facilitated by molecular genetic testing. *Br J Dermatol* 2005; **152**: 1353–6.
15 Takizawa Y, Akiyama M, Nagashima M *et al.* A novel asparagine to aspartic acid mutation in the rod 1A domain in keratin 2e in a Japanese family with ichthyosis bullosa of Siemens. *J Invest Dermatol* 2000; **114**: 193–5.
16 Nishizawa A, Toyomaki Y, Nakano A *et al.* A novel H1 domain mutation in the keratin 2 gene in a Japanese family with ichthyosis bullosa of Siemens. *Br J Dermatol* 2007; **156**: 1042–4.
17 Vakilzadeh F, Kolde G. Autosomal dominant ichthyosis exfoliativa. *Br J Dermatol* 1991; **124**: 191–4.
18 de Waard-van der Spek FB, Oranje AP, Vuzevski VD *et al.* Ichthyosis exfoliativa. *Br J Dermatol* 1994; **131**: 725–6.
19 Zvulunov A, Cagnano E, Kachko L *et al.* A new variant of autosomal recessive exfoliative ichthyosis. *Pediatr Dermatol* 2002; **19**: 382–7.
20 Sanclemente G, Falabella R. Ichthyosis bullosa of Siemens: a topical therapy option. *Arch Dermatol* 1999; **135**: 217–8.
21 Steijlen PM, van Dooren-Greebe RJ, Happle R *et al.* Ichthyosis bullosa of Siemens responds well to low-dosage oral retinoids. *Br J Dermatol* 1991; **125**: 469–71.

Ichthyosis hystrix (MIM 146590)

The subgroup, ichthyosis hystrix (IH), encompasses a number of rare conditions, characterized by spiny hyperkeratotic scale similar to that of BIE. IH differs from BIE in that blistering does not occur, erythroderma is mild or absent and localized or naevoid forms are more common. In addition, IH has specific histological and ultrastructural features.

History and nomenclature. The first documented kindred with IH was the Lambert family of Suffolk, which between 1731 and 1851 had 11 affected members in four generations [1]. The first, Edward Lambert, attended the Royal Society of Medicine in 1731 and some of his affected descendants, known as the 'porcupine men', appeared in circuses as 'a new species of man'. A review in the 1950s showed that, contrary to reports, females were also affected and the ichthyosis was autosomal dominant [2]. Their skin, normal at birth, developed dark warty scaling after 7 weeks of age. There was no blistering, and the face, palms and soles were spared. The severity of the ichthyosis varied among family members and lessened in later generations.

Similar cases of ichthyosis were reported during the 19th century, and in 1954 Ollendorff-Curth and Macklin described two teenage brothers who had congenital verrucous scale on the scalp, neck and limbs, palmoplantar keratoderma and keratoses on the lips, ears, nipples and buttocks [3,4]. Skin histology showed acanthosis, hyperkeratosis and swollen hydropic granular layer keratinocytes. Affected relatives spanning five generations had a variable phenotype and it was regarded as an autosomal dominant condition.

Other variants include an isolated case reported by Bafverstedt with striking hystrix scaling on the face [5] and IH gravior of

Rheydt (two patients with ichthyosiform erythroderma, palmoplantar keratoderma and deafness) now known as HID (hystrix ichthyosis and deafness) syndrome [6,7]. HID syndrome is allelic with KID syndrome and caused by the same connexin 26 mutation [8]. Zeligman proposed that, on histological grounds, many cases of IH were variant BIE [9]. A single case of a biphasic ichthyosis (typical IH followed by centrifugal scaly lesions in middle age) was described [10]. IH shows considerable phenotypic heterogeneity [11].

Aetiology and pathogenesis. Features suggestive of abnormal keratin expression in spinous layer keratinocytes, from affected and unaffected skin, were reported [12]. However, other groups found normal epidermal keratin labelling and absence of linkage to the keratin gene clusters [13]. The ultrastructural features are suggestive of a disorganized keratin intermediate filament network [14] while epidermal proliferation rates are normal. In 2001, a novel keratin mutation affecting the carboxy-terminal of the non-helical variable tail domain (V2 domain) of keratin 1 was found in an African American family with severe mutilating palmoplantar keratoderma diagnosed as IH of Curth–Macklin (IHCM) [15]. They had a distinctive cytoskeletal abnormality (unlike that of BIE), with failure of intermediate filament bundling, retraction of the cytoskeleton from the nucleus and failure to translocate loricrin to the desmosomal plaques at the cell periphery. Interestingly, a British Caucasian family with an almost identical frame-shift mutation in K1 had a striate keratoderma of the palms and focal keratoderma of the soles, a phenotype much milder than and quite distinct from that seen in the IHCM [16]. Desmosomal structures were normal in IHCM but altered in striate palmoplantar keratoderma. This feature along with changes in other type II keratins and local mechanical factors may explain the phenotypic disparity [17]. A further, new heterozygous mutation in the V2 region of keratin 1 (in addition to a K1 polymorphism common in African Americans) in a familial IHCM case confirms the influence of changes in the tail domain of keratin molecules [18].

Histopathology. Light microscopy shows orthohyperkeratosis, patchy parakeratosis, acanthosis and papillomatosis. Scattered vacuolated and binucleate keratinocytes in the upper epidermis are characteristic. The granular layer is reduced and contains rounded and some vacuolated cells. Electron microscopic studies of Curth–Macklin type IH highlighted a characteristic thick, continuous perinuclear keratin tonofilament shell (in contrast to the clumped intermediate filaments in EHK) in the upper spinous and granular layers, resulting in three distinct cytoplasmic compartments [12,14,19,20]. That inside the tonofilament shell contained ribosomes, mitochondria and deformed lamellar bodies, while the band outside had normal tonofilament structure terminating on desmosomes. Conspicuous perinuclear vacuoles (some of which contained lipid material) were present in 30%, and double nuclei in 10% of spinous and granular keratinocytes. Similar changes were seen in clinically uninvolved skin, and persisted with retinoid therapy [20]. An unusual histological finding in eight affected members in one family was the presence of cornoid lamellae [21].



(a)



(b)

Fig. 19.18 Ichthyosis hystrix: (a) adult male; and (b) naevoid acral lesions in Blaschko's lines in a child.

Clinical features. Patients may present at birth with a generalized or naevoid, scaly, erythema without blistering or skin fragility. However, delayed onset in infancy or childhood has been noted. Symmetrical hystrix ('porcupine spine') scaling, of dull brown or grey colour, accumulates during childhood and affects extensor aspects of the limbs (Fig. 19.18a), truncal areas, to a variable degree, and flexures, but to a lesser extent than in BIE. Mild scaling may occur at other sites including the scalp. Palmoplantar keratoderma (PPK), diffuse or striate, affects most patients and may extend to the dorsal hands. Severe PPK leads to fissures, contractures, nail dystrophy and functional impairment. Scaling stabilizes or improves slightly in adulthood. Naevoid lesions follow

the lines of Blaschko (Fig. 19.18b) and are accentuated by sun-induced tanning of unaffected skin. There is little seasonal variation, and disturbance of sweating is rare.

IH of Rheydt was reported in two unrelated sporadic cases [6,7]. Generalized scaling, more pronounced on the face and limbs, developed from birth and was associated with profound deafness and palmoplantar keratoderma. This is now known as HID syndrome.

The development of multiple keratoses and squamous cell cutaneous carcinoma in two patients may have been linked to prior carcinogenic treatments, but a cancer proneness related to IH cannot be excluded [22,23].

Genetics. Where a positive family history is evident, IH has been inherited as an autosomal dominant trait [2,4,12]. There is considerable inter- and intrafamilial variation, and the occurrence of naevoid forms also complicates genetic counselling.

Treatment. Non-greasy emollients are used by some patients, while others prefer keratolytic preparations such as salicylic acid, propylene glycol or urea-containing compounds to reduce hystrix scaling and keratoderma [18]. Their use is not influenced by the fragility or malodour that occurs in patients with BIE. Topical calcipotriol or retinoid may be helpful. Systemic retinoid therapy, intermittent or continuous, is beneficial in some [18,20] but not in others [21] (for details of acitretin dosage and surveillance, see treatment section of NBIE, p. 19.19).

References

1 Machin J. An uncommon case of distempered skin. *Philos Trans* 1733; **37**: 299–300.
2 Penrose LS, Stern C. Reconsideration of the Lambert pedigree (ichthyosis hystrix gravior). *Ann Hum Genet* 1957; **22**: 258–83.
3 Ollendorff-Curth H, Macklin MT. The genetic basis of various types of ichthyosis in a family group. *Am J Hum Genet* 1954; **6**: 371–82.
4 Ollendorff-Curth H, Allen FH, Schnyder UW, Anton-Lamprecht I. Follow-up of a family suffering from ichthyosis hystrix, type Curth Macklin. *Hum Genet* 1972; **17**: 37–48.
5 Bafverstedt B. Fall von genereller, naevusartiger Hyperkeratose, Imbecillität, Epilepsie. *Acta Derm Venereol (Stockh)* 1941; **22**: 207–12.
6 Schnyder UW. Ichthyosis hystrix typus Rheydt (ichthyosis hystrix gravior mit praktischer Taubheit). *Z Hautkr* 1977; **52**: 763–6.
7 Traupe H. *The Ichthyoses: a Guide to Clinical Diagnosis, Genetic Counselling and Therapy*. Berlin: Springer-Verlag, 1989.
8 van Geel M, van Steensel M, Kuster W *et al.* HID and KID syndromes are associated with the same connexin 26 mutation. *Br J Dermatol* 2002; **146**: 938–42.
9 Zeligman I, Pomeranz J. Variations of congenital ichthyosiform erythroderma. *Arch Dermatol* 1965; **91**: 120–5.
10 Pinkus H, Nagao S. A case of biphasic ichthyosiform dermatosis: light and electron microscopic study. *Arch Klin Exp Dermatol* 1970; **237**: 737–48.
11 Judge MR, Griffiths WAD. Review of ichthyosis hystrix. *Retinoids* 1993; **33**: 13–5.
12 Niemi KM, Virtanen I, Kanerva L, Muttilainen M. Altered keratin expression in ichthyosis hystrix Curth Macklin. *Arch Dermatol Res* 1990; **282**: 227–33.
13 Brusasco A, Cavalli R, Cambiaghi S *et al.* Ichthyosis hystrix Curth Macklin: a new sporadic case with immunohistochemical study of keratin expression. *Arch Dermatol* 1994; **130**: 1077–9.
14 Anton-Lamprecht I, Kern B, Goerz G, Marghescu S. Perinuclear shell formation in uncommon ichthyoses. *J Cutan Pathol* 1981; **8**: 447–8.
15 Sprecher E, Ishida-Yamamoto A, Becker OM *et al.* Evidence for novel functions of the keratin tail emerging from a mutation causing ichthyosis hystrix. *J Invest Dermatol* 2001; **116**: 511–9.
16 Whittock NV, Smith FJ, Wan H *et al.* Frameshift mutation in the V2 domain of human keratin 1 results in striate palmoplantar keratoderma. *J Invest Dermatol* 2002; **118**: 838–44.
17 Ishida-Yamamoto A, Richard G, Takahashi H *et al.* In vivo studies of mutant keratin 1 in ichthyosis hystrix of Curth-Macklin. *J Invest Dermatol* 2003; **120**: 498–500.
18 Richardson ES, Lee JB, Hyde PH *et al.* A novel mutation and large size polymorphism affecting the V2 domain of keratin 1 in an African American family with severe diffuse palmoplantar keratoderma of the ichthyosis hystrix Curth–Macklin type. *J Invest Dermatol* 2006; **126**: 79–84.
19 Anton-Lamprecht I, Curth HO, Schnyder UW. Zur Ultrastruktur hereditarer Verhornungsstorungen. *Arch Derm Forsch* 1973; **246**: 77–91.
20 Kanerva L, Karvonem J, Oikarinem A *et al.* Ichthyosis hystrix (Curth–Macklin). Light and electron microscopic studies performed before and after etretinate treatment. *Arch Dermatol* 1984; **120**: 1218–23.
21 Braun-Falco O, Schurig V, Meurer M, Klepzig K. Ichthyosis hystrix mit Parakeratose nach Art der kornoiden Lamelle. *Hautarzt* 1985; **36**: 132–41.
22 Judge MR, McGibbon DH. Ichthyosis hystrix and skin cancer. *Clin Exp Dermatol* 1994; **19**: 240–3.
23 Edwards JM, Cooper MACS, Bannerjee S. Congenital epidermolytic hyperkeratosis associated with multiple malignancies. *Br J Dermatol* 1989; **120**: 141–4.

Netherton's syndrome (MIM 256500)

Netherton's syndrome (NS) is the most common of the multisystem ichthyosiform syndromes. It comprises an inflammatory, scaly dermatosis (primarily episodic peeling) with a variable erythroderma, hair shaft defects and atopic features. It is an autosomal recessive condition with a worldwide distribution, and an incidence similar to NBIE, in the order of 1 in 200 000. Diagnosis is often delayed and missed diagnosis, combined with previously high neonatal mortality, have contributed to an underestimate of its incidence.

Netherton's original patient, reported in 1958, was a young girl with a generalized, scaly, erythematous 'dermatitis', paroxysmal pruritus and a hair shaft defect, now known as trichorrhexis invaginata (TI) [1]. Later reports noted the association of TI with migratory double-edged scaly lesions termed ichthyosis linearis circumflexa (ILC) [2]. ILC had been described by Comel in 1949, but there was no comment on the patient's hair [3]. TI is a pathognomonic finding in NS, while the skin manifestations are variable and fluctuate.

Aetiology and pathogenesis. Although various mutations in the serine protease inhibitor Kazal type 5 (*SPINK5*) gene have been identified in NS patients [4–6], the pathogenetic mechanisms are not fully elucidated. Clinicopathological features suggest an intermittent disruption of epidermal and hair shaft maturation and keratinization. Electron microscopy shows premature lamellar body secretion and abnormal lipid processing in the intercellular space, which accounts for the severe impairment of the stratum corneum permeability barrier in NS [7]. This leads to an increase in epidermal DNA synthesis and turnover, further disrupting lipid metabolism. In the hair follicle, the TI lesion coincides with a bulge of external root sheath cells, which invaginate the hair shaft at the level of the keratogenous zone [8]. Failure to convert sulphydryl groups to disulphide bonds in the cortical cells of the hair at this level may contribute to the focal softening [9]. The intermittent nature of the hair shaft defect and the migratory skin lesions are, as yet, unexplained. Retinoid therapy induces deterioration in most patients with NS, and a parallel exists in a

transgenic mouse model with negative retinoic acid receptors, which develops erythroderma and poor skin barrier function. Impaired transcription of retinoic acid receptor genes in NS has been suggested [10].

Certain features of NS are reminiscent of atopic eczema and the skin permeability barrier is disrupted in both. Histological changes in NS include spongiosis and exocytosis as seen in atopic eczema, but immunohistochemical markers differed [11]. Raised total and specific IgE levels are characteristic of both [12,13]. Other immune function tests have usually shown only minor and inconsistent abnormalities. The *SPINK5* gene is located adjacent to a cytokine gene cluster and research efforts are also focusing on the genetic mechanisms of atopy and IgE responses [14].

The *SPINK5* gene is composed of 33 exons spanning over 61 kb on the distal long arm of chromosome 5q32 [4]. It encodes a serine protease inhibitor proprotein called LEKTI (lympho-epithelial Kazal-type inhibitor), which is thought to be necessary for epidermal cell growth and differentiation. LEKTI has 15 different protease inhibitory domains and each *SPINK5* mutation results in truncated LEKTI of different lengths, which correlate with the severity of the clinical features. *SPINK5* transcripts are expressed in the upper stratum spinosum, the stratum granulosum and in hair follicle and sebaceous gland epithelium. The peptides derived from LEKTI proteolysis exert an inhibitory effect, *in vitro*, on epidermal serine proteases, such as trypsin, chymotrypsin, plasmin, subtilisin, cathepsin, elastase, mast cell tryptase and kallikreins [4], which control corneocyte desquamation and help to maintain the epidermal permeability barrier [15]. Elevated epidermal trypsin-like proteolytic activity in NS is associated with reduced desmoglein 1 and desmocollin 1 cadherin activity and premature corneodesmosome degradation, which helps to explain the inflammation and barrier disruption [16]. In NS patients with severe erythroderma, the trypsin levels were higher than in those with a mild phenotype. Phenotypic variation may also relate to the activity of other protease inhibitors and variations in transglutaminase and related protein expression. Specific protease inhibitors may prove useful in the treatment of NS [17].

Histopathology. The histological features vary with the type and phase of the lesion sampled. Hyperkeratosis is mild in contrast to other ichthyoses, but parakeratosis and a reduced or absent granular layer occur at the spreading border of a lesion. Eosinophilic material may collect within the corneal and granular layers in ILC lesions. An intracorneal split at the site of degenerative parakeratotic corneocytes was noted by Comel [3] and others. Psoriasiform epidermal hyperplasia, papillomatosis and a mixed perivascular inflammatory infiltrate occur in older ILC lesions and in the more diffuse, scaly erythroderma. Acute erythroderma in NS is accompanied by pronounced inflammatory changes with spongiosis, exocytosis, intraepidermal microabscesses and upper epidermal eosinophilic necrolysis, which may lead to a subcorneal split. Features of a non-specific dermatitis may be reported.

Ultrastructural studies in NS have identified inclusion bodies (possibly lysosomes) containing finely granular material in suprabasal keratinocytes, reduced numbers of tonofilament–keratohyalin structures and desmosomes and abnormal lamellar bodies [7,10]. Intercellular lipid lamellae in the stratum corneum were disorganized and even absent in places. Lesions of ILC and erythroderma may show similar epidermal changes of retarded keratinization and eosinophilic granular material between and within cells [10].



Fig. 19.19 Trichorrhexis invaginata.

Microscopy of the scalp and eyebrow hair in NS shows, in a variable proportion of intact hairs, the 'bamboo' nodal dilatation consisting of a bulbous distal hair end invaginating a concave dilated proximal hair terminal (Fig. 19.19). The proportion of scalp hair affected varies from 5 to 50%, and the only clue to its presence may be ragged cupped proximal hair ends, where the fragile node has fractured, so-called 'golf tee hairs' [18]. Hair sampling may have to be repeated several times, and clipped hairs, especially eyebrows, may be the most informative. Pili torti and trichorrhexis nodosa also occur. Scalp biopsies have shown early nodal deformity occurring at the keratogenous zone within the hair follicle and variable perifollicular inflammatory changes [8–10].

Clinical features. Generalized (congenital) erythroderma of variable intensity is usually evident at or shortly after birth, and desquamation and scaling quickly develop (Fig. 19.20). In a French study of 51 patients with neonatal and infantile erythroderma, nine (18%) were eventually diagnosed as NS [19]. A minority of neonates is mildly affected. Collodion membrane is not a feature, and the infant is usually born at term with average birth weight. Common complications in the neonatal period and infancy, resulting from epidermal barrier disruption, are temperature instability, skin and systemic infection including fungal sepsis and hypernatraemic dehydration. Hypernatraemia in infancy is more common in NS than in other congenital erythrodermas and can lead to renal failure and neurological complications [20,21]. Severely affected infants often suffer from marked failure to thrive in the first year or so, and may have mild diarrhoea. This occurs even with dietary supplementation and, although malabsorption is a recognized though rare complication of other types of erythroderma ('dermopathic enteropathy'), it is more pronounced in NS. Jejunal villous atrophy was found in one of three NS infants who had biopsies (non-gluten sensitive and resolving spontaneously at 10 months old) [13] and in three of five patients in another report [22]. In fact, most of these infants begin to put on weight in their second year, although they generally remain below the 25th centile for height and weight. The defective barrier function of NS skin predisposes infants, in particular, to systemic toxicity from topically-applied



(a) (b)

Fig. 19.20 Netherton's syndrome, erythrodermic neonates with (a) severe failure to thrive and (b) sparse, spiky 'Mohican' hair; she required gastrostomy feeding for 8 years.

agents, including steroids and iodine-containing cleansers which caused hypothyroidism in one reported case [23]. The erythroderma tends to improve also, but can recur unpredictably. Infant mortality in NS was, in the past, significant and often attributed to 'Leiner's syndrome' or other congenital erythroderma. Complications in the first few months increase the risk of developmental and neurological problems.

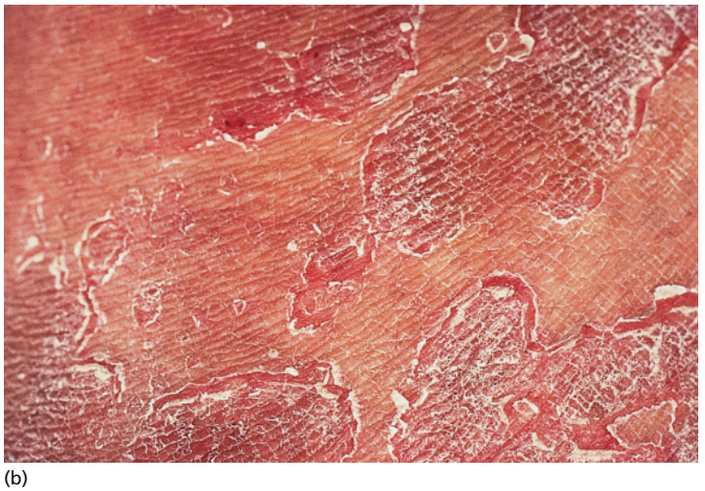
During childhood, approximately half of NS patients develop lesions of ILC on the trunk and limbs, but they may still be at risk of acute erythroderma. A typical ILC lesion is an erythematous, exfoliating or scaly, annular or polycyclic, patch with an incomplete advancing double edge of peeling scale (Fig. 19.21). ILC is episodic, with migrating lesions, often in a cephalocaudal pattern, lasting several days. Lesions without the double-edged scaly margin are commonly seen. While many patients have recurrent ILC every few months, some have infrequent lesions. In severe NS, a fluctuating erythroderma persists, which may be triggered by intercurrent illness, and rarely pustular lesions are superimposed. Between acute attacks, the skin may look surprisingly normal. In a literature review of 43 cases, ILC was recorded in 30, while ichthyosiform erythroderma was predominant in 13 [12]. Many patients are distressed by prominent facial, particularly perioral, erythema and peeling. Palmoplantar peeling and mild keratoderma are noted in severely affected patients while peeling at the margins of the palms and soles is common. Pruritus or burning irritation may be troublesome, and also reminiscent of atopic eczema is flexural lichenification. Impaired sweating can lead to hyperpyrexia. Bacterial and yeast colonization of the skin and human papilloma virus (HPV) viral warts (in older patients) are common in NS. Chronic blepharitis and ectropion can cause a keratitis. Short stature is common in severe NS. Vitamin D deficiency may occur in any chronic erythrodermic condition. A rare, late complication is dilated cardiomyopathy [24].

A modest improvement with age is noted in most patients, but those with chronic erythroderma may develop persistent, painful flexural oedema, maceration and papillomatosis of the axillae, groin, vulva and lower legs [12,13]. This is a premalignant lesion with pseudoepitheliomatous histology; carcinoma of the vulva has been reported in a 63-year-old woman [25]. There are several reports of squamous cell skin cancer in adults with NS [26–30]. In one of these patients, multiple skin cancers (including basal cell carcinoma) occurred on photoexposed sites over 21 years of follow-up [28]. He had a history of widespread, chronic viral warts and oncogenic HPV types were isolated from skin lesions. The other patient, an outdoor worker, developed eight skin cancers, the first on the scalp at age 27. A 29-year-old female patient with two squamous carcinomas on the hand and arm, had a history of multiple infections throughout her life [29]. A 28-year-old female patient had plane warts on the face and arms (from which oncogenic HPV16 was isolated) and papillomatous groin tumours which yielded HPV 51 and 52 subtypes [31].

Hair defects. A pathognomic feature of NS is the hair shaft defect known as trichorrhexis invaginata (TI) or ball and socket defect (Fig. 19.19). TI is detected on light or scanning microscopy and may be picked up on dermatoscopy [32]. It is often missed in infancy, as scalp hair growth is sparse and attributed to erythroderma. In childhood, scalp, eyebrow, eyelash and body hair



(a)



(b)

Fig. 19.21 Ichthyosis linearis circumflexa: (a) in a 12-year-old boy; (b) a young girl. See also Fig. 19.20a.

remains sparse, slow growing, lustreless and brittle (due to fractures at trichorrhexis nodes). Scalp hair growth improves with age, but in many remains unruly or spiky, and some patients opt to wear a wig. A few older patients have clinically normal, but microscopically defective hair. Brittle hair produces a peppered appearance, especially on the limbs. Rarely, a nail dystrophy, ranging from thickening to pterygium, is seen.

Atopic features. Many patients with NS have a personal or family history of atopic asthma or hay fever. The pruritus, flexural accentuation, periods of remission and raised IgE are suggestive of atopic eczema; however, the skin lesions are not clinically eczematous, histological features are not consistent and they do not respond to appropriate eczema therapy. Recurrent urticaria and facial angioedema, triggered by certain foods, are common complications, although the incidence varies [12,13]. The most common food allergens are nuts and fish, and it can manifest in childhood or even in infancy.

Diagnosis. The diagnosis of NS was suspected prenatally in one case because of ultrasound detection of amniotic fluid debris [33]. The triad of congenital erythroderma, poor hair growth and failure to thrive in infancy, or the detection of ILC suggests the diagnosis. In milder cases without a family history, diagnosis is delayed until the specific hair shaft defect of TI is detected. Atopic features in childhood are associated with positive skin prick tests, eosinophilia and high specific serum IgE tests to common airborne and food allergens. Total IgE levels peak, often at very high values, in early childhood and then may fall towards the normal range [5,12,13]. Mild IgG subclass deficiencies have been noted. Lymphocyte subpopulations were normal, though evidence of T- or B-cell activation, altered cytokine profile and reduced natural killer cell numbers have been found in a few [13,34]. Impaired lymphocyte mitogen responses were reported in one case [26]. Transient aminoaciduria and neutrophil function defects were identified in one patient [12]. C1 esterase inhibitor levels were normal in eight patients studied, and complement C3 or C4 were raised in three of them [13]. Skin and hair microscopy are discussed above. Immunohistochemical stains for epidermal and hair root LEKTI antigen reveals absent LEKTI protein (and fragments) in severely affected patients and reduced positivity in those with a milder phenotype [35].

In infancy, the differential diagnoses include erythrodermic atopic or seborrhoeic eczema, staphylococcal or candidal infection, non-bullous ichthyosiform erythroderma (NBIE), psoriasis, hyper-IgE syndrome, immunodeficiency states, zinc or biotin deficiency, cystic fibrosis and protein metabolic disorders. In older children and adults, NBIE is the usual misdiagnosis, but atopic eczema, familial peeling skin syndrome, pemphigus foliaceus and erythrokeratoderma variabilis have been considered.

Genetics. NS is an autosomal recessive disorder with several reports of affected siblings and a proportion of patients coming from consanguineous families. There is significant phenotypic variation and clinical manifestations may also vary between siblings. Several *SPINK5* mutations have been identified in NS [4–6,15,16,35–37]. Close genotype–phenotype correlation has been reported by three groups [5,15,37] but not by another [6]. Komatsu's group used recombinant techniques to show that the length of residual LEKTI, which determines the number of active protease inhibitory domains, correlated with the severity of skin disease (including palmoplantar peeling), risk of skin infections and growth retardation (but not with atopic features, pruritus or hair defects) [37]. Growth retardation may, in part, be due to proteolytic destruction of growth hormone by the overactive proteases (*SPINK5* is expressed in the pituitary) [37].

Molecular diagnosis, using primers to sequence all coding exons and intronic regions of the *SPINK5* gene, is available for patient and heterozygote identification [6]. Homozygous frameshift and splicing *SPINK5* mutations were associated with more severe disease than downstream nonsense mutations which allow for longer LEKTI and more inhibitory domains, resulting in milder ILC-type lesions [5]. Prenatal diagnosis has been carried out by mutational analysis of *SPINK5* gene on a chorionic villus sample

in one case [5] and amniotic fluid in another [36], successfully predicting an unaffected fetus in both.

Treatment. In the neonatal period, intensive medical, nursing and nutritional care will be required to manage erythroderma and its complications and, specifically, to prevent hypernatraemic dehydration and failure to thrive. Frequent paraffin-based ointments, such as 50/50 white soft and liquid paraffin, provide a partial skin barrier, which reduces insensible water loss that contributes to hypernatraemia. Regular skin and eye swabs and stool culture will guide decisions on antimicrobial therapy; staphylococcal, Gram-negative and candidal isolates are common. Supplementary nasogastric tube feeding is often required and a gastrostomy is occasionally necessary. Topical steroids are ineffective, and should be avoided as the erythroderma and high surface area at this age quickly lead to systemic steroid toxicity.

The day-to-day treatment of older patients with NS is similar to that of other ichthyosiform erythrodermas. Regular emollients are helpful, and patients tend towards greasy paraffin-based products. Excessive use in one patient led to a granulomatous lymphadenopathy [38]. Ammonium lactate lotion 12% has been recommended [39]. Keratolytics, such as salicyclic and lactic acids, are poorly tolerated, but intermittent mild topical steroid therapy may help to lessen facial erythema and antifungal compounds improve intertrigo. Tar shampoos are useful in reducing scalp scaling. Topical or systemic antibiotics may be required for skin and respiratory infections. Antipruritics are only partially effective. Significant improvement in the cutaneous features was reported with both topical tacrolimus (0.1% and 0.03%) and pimecrolimus 1% [39,40]. However, blood levels of tacrolimus in patients treated with standard formulations showed that there was significant percutaneous absorption which could cause toxicity [41,42]. Even very dilute 0.005% tacrolimus gave raised blood levels, though below the toxic range [43]. Tachyphylaxis was noted at all concentrations and short-term treatment with topical immunomodulators was advocated. Pimecrolimus 1%, applied to 99% of the skin surface, did not produce detectable blood levels in one patient [41].

A notable feature of NS is the deterioration induced by systemic retinoid therapy (in standard doses), which is usually beneficial in other erythrodermic ichthyoses [9,12,13,28]. Retinoids are known to aggravate atopic eczema. Some patients with ILC do benefit from low-dose therapy [44]. Psoralen with ultraviolet A (PUVA) therapy has produced variable results [26,45]. UVA1 at medium doses was helpful in one adult patient [46] and balneophototherapy cleared ILC [47]. Methotrexate and ciclosporin A were ineffective [28,48]. Dermabrasion and subsequent excision of papillomatosis lesions on the lower leg, with split-skin grafting, was performed in an adult patient [13]. Grenz ray therapy has been used in the past, and laser ablation of hypertrophic areas has been suggested. A trial of topical protease inhibitors in NS patients was suggested in 2002 [15] but topical α_1-antitrypsin did not improve five treated patients [17].

References

1 Netherton EW. A unique case of trichorrhexis nodosa: 'bamboo hairs'. *Arch Dermatol* 1958; **78**: 483–7.

2 Mevorah B, Frenck E, Brooke EM. Ichthyosis linearis circumflexa of Comel: a clinicostatistical approach to its relationship with Netherton's syndrome. *Dermatologia* 1974; **149**: 201–9.

3 Comel M. Ichthyosis linearis circumflexa. *Dermatologica* 1949; **98**: 133–6.

4 Chavanas S, Bodemer C, Rochat A *et al.* Mutations in *SPINK5*, encoding a serine protease inhibitor, cause Netherton syndrome. *Nat Genet* 2000; **25**: 141–2.

5 Sprecher E, Chavanas S, DiGiovanna JJ *et al.* The spectrum of pathogenic mutations in *SPINK5* in 19 families with Netherton syndrome: implications for mutation detection and the first case of prenatal diagnosis. *J Invest Dermatol* 2001; **117**: 179–87.

6 Bitoun E, Chavanas S, Irvine A *et al.* Netherton's syndrome: disease expression and spectrum of *SPINK5* mutations in 21 families. *J Invest Dermatol* 2002; **118**: 352–61.

7 Fartasch M, Williams ML, Elias PM. Altered lamellar body secretion and stratum corneum membrane structure in Netherton syndrome: differentiation from other infantile erythrodermas and pathogenic implications. *Arch Dermatol* 1999; **135**: 823–32.

8 Ito M, Ito K, Hashimoto K. Pathogenesis of trichorrhexis invaginata (bamboo hair). *J Invest Dermatol* 1984; **83**: 1–6.

9 Traupe H. *The Ichthyoses: a Guide to Clinical Diagnosis, Genetic Counselling and Therapy*. Heidelberg: Springer-Verlag, 1989: 175.

10 Hausser I, Anton-Lamprecht I. Severe congenital generalized exfoliative erythroderma in newborns and infants: a possible sign of Netherton's syndrome. *Pediatr Dermatol* 1996; **13**: 183–99.

11 Arico M, Di Leonardo S, Pravata G *et al.* Netherton's syndrome in a male: an immunohistochemical study. *Pediatr Dermatol News* 1987; **6**: 267–71.

12 Greene SL, Muller SA. Netherton's syndrome: a report of a case and review of the literature. *J Am Acad Dermatol* 1985; **13**: 329–37.

13 Judge MR, Morgan G, Harper JI. A clinical and immunological study of Netherton's syndrome. *Br J Dermatol* 1994; **131**: 615–21.

14 Kato A, Fukai K, Oiso N *et al.* Association of *SPINK5* gene polymorphisms with atopic dermatitis in the Japanese population. *Br J Dermatol* 2003; **148**: 665–9.

15 Komatsu N, Takata M, Otsuki N *et al.* Elevated stratum corneum hydrolytic activity in Netherton syndrome suggests an inhibitory regulation of desquamation by *SPINK5*-derived peptides. *J Invest Dermatol* 2002; **118**: 436–43.

16 Descargues P, Deraison C, Prost C *et al.* Corneodesmosomal cadherins are preferential targets of stratum corneum trypsin and chymotrypsin-like hyperactivity in Netherton syndrome. *J Invest Dermatol* 2006; **126**: 1622–32.

17 Mazereeuw-Hautier J, Cope J, Ong C *et al.* Topical recombinant alpha$_1$-antitrypsin: a potential treatment for Netherton syndrome? *Arch Dermatol* 2006; **142**: 396–8.

18 de Berker DAR, Paige DG, Ferguson DJP, Dawber RPR. Golf tee hairs in Netherton disease. *Pediatr Dermatol* 1995; **12**: 7–11.

19 Pruszkowski A, Bodemer C, Fraitag S *et al.* Neonatal and infantile erythrodermas: a retrospective study of 51 patients. *Arch Dermatol* 2000; **136**: 875–80.

20 Jones SK, Thomson LM, Surbrugg SK, Weston WL. Neonatal hypernatraemia in two siblings with Netherton's syndrome. *Br J Dermatol* 1986; **114**: 741–3.

21 Plantin P, Delaire P, Guillet M *et al.* Netherton's syndrome: current aspects a propos 9 cases. *Ann Dermatol Vénéréol* 1991; **118**: 525–30.

22 Pradeaux L, Olives JP, Bonafe JL *et al.* Digestive and nutritional manifestations of Netherton syndrome. *Arch Fr Pediatr* 1991; **48**: 95–8.

23 Garty BZ, Nimri R. Hypothyroidism in Netherton syndrome. *Ped Dermatol* 2008; **25**: 134–5.

24 Hoeger PH, Adwani SS, Whitehead BF *et al.* Ichthyosiform erythroderma and cardiomyopathy: report of two cases and review of the literature. *Br J Dermatol* 1998; **139**: 1055–9.

25 Kubler HC, Kuhn W, Rummel HH *et al.* Zur Karzino-Mentstehung (Vulvakarzinom) beim Netherton-syndrom. *Geburtshilfe-Frauenheilkd* 1987; **47**: 742–4.

26 Hintner H, Jaschke E, Fritsch P. Netherton-syndrom: abwehrschwache, generalisierte verrukose und karzinogenese. *Hautarzt* 1980; **31**: 428–32.

27 Elbaum DJ, Kurz G, MacDuff M. Increased incidence of cutaneous carcinomas in patients with congenital ichthyosis. *J Am Acad Dermatol* 1995; **33**: 884–6.

28 Weber F, Fuchs PG, Pfister HJ *et al.* Human papillomavirus infection in Netherton's syndrome. *Br J Dermatol* 2001; **144**: 1044–9.

29 Saghari S, Wollery-Lloyd H, Nouri K. Squamous cell carcinoma in a patient with Netherton's syndrome. *Int J Dermatol* 2002; **41**: 415–6.

30 Krasagakis K, Ioannidou DJ, Stephanidou M *et al.* Early development of multiple epithelial neoplasms in Netherton syndrome. *Dermatology* 2003; **207**: 182–4.

31 Folster-Holst R, Swennson O, Stockfleth E *et al.* Comel-Netherton syndrome complicated by papillomatous skin lesions containing human papillomaviruses 51 and 52 and plane warts containing human papillomavirus 16. *Br J Dermatol* 1999; **140**: 1139–43.
32 Burk C, Hu S, Lee C *et al.* Netherton syndrome and trichorrhexis invaginata—a novel diagnostic approach. *Ped Dermatol* 2008; **25**: 287–8.
33 Ansai S, Mitsuhashi Y, Sasaki K. Netherton's syndrome in siblings. *Br J Dermatol* 1999; **141**: 1097–100.
34 Van Gysel D, Koning H, Baert MR *et al.* Clinico-immunological heterogeneity in Comel-Netherton symdrome. *Dermatology* 2001; **202**: 99–107.
35 Raghunath M, Tontsidou L. Oji V *et al.* SPINK5 and Netherton syndrome; novel mutations, demonstration of missing LEKTI and differential expression of transglutaminases. *J Invest Dermatol* 2004; **123**: 474–83.
36 Muller FB, Hauber I, Berg D *et al.* Genetic analysis of a severe case of Netherton syndrome and application for prenatal testing. *Br J Dermatol* 2002; **146**: 495–9.
37 Komatsu N, Saijoh K, Jayakumar A *et al.* Correlation between SPINK5 gene mutations and clinical manifestations in Netherton syndrome patients. *J Invest Dermatol* 2008; **128**: 1148–59.
38 Cockayne SE, Lee JA, Harrington CI. Oleogranulomatous response in lymph nodes associated with emollient use in Netherton's syndrome. *Br J Dermatol* 1999; **141**: 562–4.
39 Wehr RF, Hickman JG, Krochmal L. Effective treatment of Netherton's syndrome with 12% lactate lotion. *J Am Acad Dermatol* 1988; **19**: 140–2.
40 Suga Y, Tsuboi R, Hashimoto Y *et al.* A case of ichthyosis linearis circumflexa successfully treated with topical tacrolimus. *J Am Acad Dermatol* 2000; **42**: 520–2.
41 Oji V, Beljan G, Beier K *et al.* Topical pimecrolimus: a novel therapeutic option for Netherton syndrome. *Br J Dermatol* 2005; **153**: 1067–8.
42 Allen A, Siegfried E, Silverman R *et al.* Significant absorption of topical tacrolimus in three patients with Netherton syndrome. *Arch Dermatol* 2001; **137**: 747–50.
43 Shah KN, Yan AC. Low but detectable serum levels of tacrolimus seen with the use of very dilute, extemporaneously compounded formulations of tacrolimus ointment in the treatment of patients with Netherton syndrome. *Arch Dermatol* 2006; **142**: 1362–3.
44 Hartschuh W, Hausser I, Petzoldt D. Successful retinoid therapy of Netherton syndrome. *Hautarz* 1989; **40**: 430–3.
45 Nagata T. Netherton's syndrome which responded to photochemotherapy. *Dermatologica* 1980; **161**: 51–6.
46 Capezzera R, Venturini M, Bianchi D *et al.* UVA1 phototherapy of Netherton syndrome. *Acta Derm Venereol* 2004; **84**: 69–70.
47 Gamblickler T, Senger E, Altmeyer P *et al.* Clearance of ichthyosis linearis circumflexa with balneophototherapy. *J Eur Acad Dermato Venereol* 2000; **14**: 397–9.
48 Braun RP, Ramelet AA. Failure of cyclosporine in Netherton syndrome. *Dermatology* 1997; **195**: 75.

Sjögren–Larsson syndrome (MIM 270200)

Sjögren–Larsson syndrome (SLS) is a rare autosomal recessive condition comprising a congenital ichthyotic hyperkeratosis, spastic diplegia and mild to moderate mental retardation. In addition, a characteristic retinopathy has been noted. Although this syndrome may have been described some years before, Sjögren and Larsson, Swedish psychiatrists, published a detailed monograph in 1957 of the syndrome that bears their name. They reported a clinical and epidemiological study of 28 institutionalized patients from 13 families, many of them consanguineous, in an area of north-west Sweden where there is a relatively high incidence [1]. Common ancestry for most of these was traced back to the 17th century, and a founder mutation introduced to the area in the 13th century has been proposed [2]. Over 200 cases worldwide have been reported, and it occurs in all races. The incidence in Sweden has been estimated at 1 in 100 000 rising to 1 in 10 000 in the northwest region of Vasterbotten [2]. In the UK, the estimated incidence of 1 in 300 000 may be an underestimate [3].

Aetiology and pathogenesis. A defect in essential fatty acid metabolism in plasma phospholipids, involving δ6-desaturase deficiency, was reported in the 1980s [4,5]. Rizzo's group demonstrated elevated plasma hexadecanol (C16) and octadecanol (C18) long-chain fatty alcohols, due to a deficiency of microsomal fatty alcohol:NAD oxidoreductase (FAO) in leukocytes and cultured skin fibroblasts [6,7]. The fatty aldehyde dehydrogenase component (FALDH) of FAO, a two-part enzyme, is predominantly affected. Reduced enzyme levels in the absence of clinical signs were found in obligate carriers [7,8]. FAO activity combines an alcohol dehydrogenase, converting fatty alcohols to fatty aldehydes, and microsomal FALDH, oxidizing medium- and long-chain fatty aldehydes to fatty acids. FALDH is also involved in the metabolism of leukotriene B_4. The histochemical demonstration of absent alcohol–hexanol dehydrogenase in the epidermis (Fig. 19.22) and jejunal mucosa in SLS, but not in other ichthyoses, provided further evidence of the importance of abnormal fatty

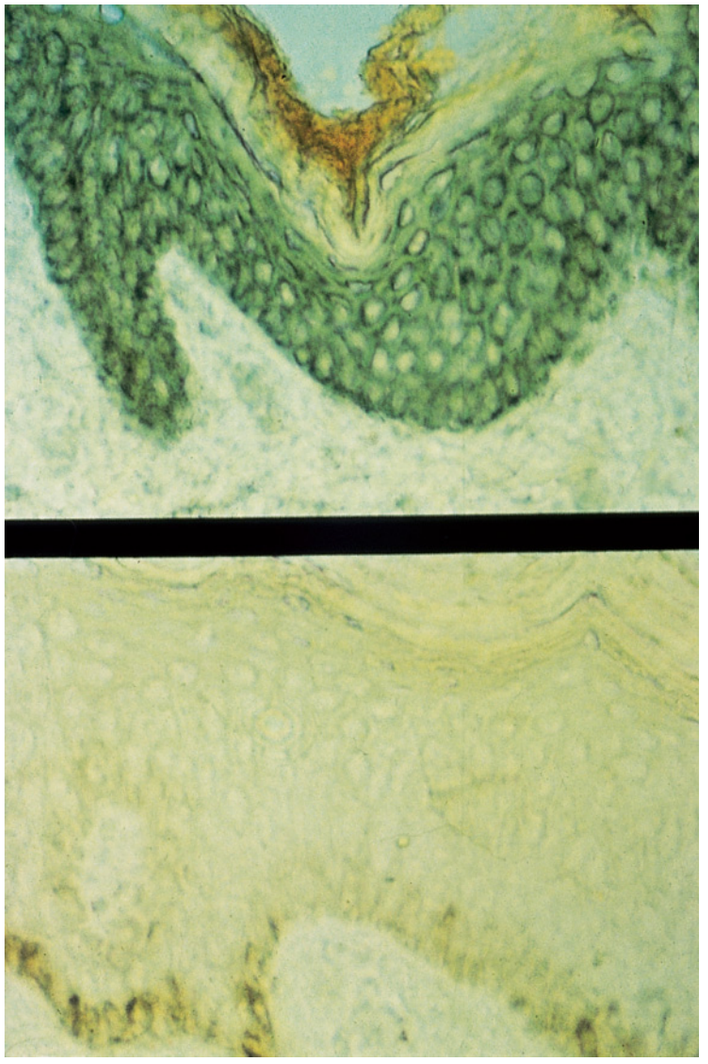


Fig. 19.22 Sjögren–Larsson syndrome, negative staining for alcohol dehydrogenase in skin, lower panel. (Courtesy of Dr B. Lake, Institute of Child Health, London, UK.)



(a) (b) (c)

Fig. 19.23 (a), (b) and (c). Sjögren–Larsson syndrome: a 3-year-old girl with spastic diplegia.

alcohol metabolism in SLS [8]. Skin changes in SLS (abnormal barrier function and inflammation) are due to disturbed epidermal lipid metabolism and overexpression of leukotriene B_4 in fibroblasts and keratinocytes [9,10]. The neurological defects result from abnormal lipid development in myelin, specifically in the glycerol ether pathway, a side arm of the fatty alcohol cycle, in sphingolipids and plasmalogens [11].

The 31-kb FALDH gene (*ALDH3A2*) is located on chromosome 17p11.2, close to the neurofibromatosis-1 gene [12]. Several different mutations have been reported [11–14]. FALDH is a 485 amino acid membrane-bound protein with a hydrophobic carboxy-terminus, which is necessary for microsomal membrane anchoring.

Histopathology. Skin sections show orthohyperkeratosis, acanthosis and papillomatosis. The granular cell layer is normal or increased, and there may be mild upper dermal inflammatory change. Kinetic studies in one patient indicated a hyperproliferative epidermis [15]. Ultrastructurally, atypical membranous structures have been reported in spinous and granular layer cells, associated with numerous, large lamellar bodies some of which were irregular or disc-shaped. A proportion contained granular material in addition to lipid lamellae [16]. Membranous inclusions persisted into the corneal layer and the intercellular spaces were widened. Increased numbers of mitochondria were present in the basal epidermal cells.

Clinical features. Preterm birth is common and has been attributed to abnormal leukotriene B_4 inactivation [9]. Collodion baby presentation has been reported [17,18], but usually the skin is dry and mildly erythematous at birth, and scaling develops within the first 3 months of life. Thereafter, a mild erythroderma persists and a variable degree of scaling evolves, consisting of diffuse peeling on the trunk and more pigmented, lamellar-type ichthyosis on the lower limbs. Scaling tends to follow a cyclical pattern of accumulation and shedding, and predominantly affects the limbs and face (Fig. 19.23). A velvety orange or brown lichenification, often with verrucous hyperkeratosis, is most obvious in and around the flexures, neck and mid-abdomen (Fig. 19.23b). This characteristic feature may even be noted during the first year of life, and is helpful in diagnosis. Lichenification slowly progresses and is embarrassing to older children, in whom it may also restrict the mobility of already hypertonic limbs. Severe and persistent pruritus is a notable feature of SLS; scratch marks and dermographism are often seen on the trunk but skin infections are rare.

Neuro-ocular features. Variable neurological dysfunction is obvious in early infancy, with delayed motor milestones and evolution of upper motor neurone signs (a non-progressive, spastic paraparesis) in the legs and rarely the arms also [13,19]. With early physiotherapy, most patients learn to walk unaided or with crutches in childhood. Increased muscle tone leads to altered posture and movement which predispose to contractures (ankles, knees, hips), kyphoscoliosis, dislocated hips and short stature. Development of speech is delayed and seizures are a rare complication. Mild to moderate learning disability is the rule and all 17 patients in a Dutch study attended special schools [19]. However, there is phenotypic variation among families [13,20] and even between affected siblings [21]. They are notable for their cheerful, friendly disposition. Although many SLS patients were institutionalized in the past, most can achieve a degree of independence if appropriate education, training, physiotherapy and rehabilitation are available to them. The neurological features are non-progressive but contractures due to spasticity may adversely affect gait and mobility in older children. Patchy leukodystrophy and myelination defects have been reported on CT and MR scanning and in post-mortem studies in SLS [13,22].

Ocular signs were reported in 1980, and consist of glistening dots on the fovea and parafovea of the retina, which develop during childhood [23]. They are detected in up to 80% of patients and may fade with advancing age. They may be caused by deposition of lipofuscin pigment granules in the specialized retinal epithelium [24] and can be detected subclinically by optical tomography [25]. Visual acuity is normal or mildly impaired but some patients are photophobic.

Diagnosis. The cutaneous and retinal features are characteristic and quite unlike those of other ichthyosiform syndromes. Biochemical assay of cultured fibroblasts from a skin biopsy or of leukocytes to identify reduced FAO activity, in particular FALDH, confirms the diagnosis. Histochemical analysis of hexanol dehydrogenase in skin is also diagnostic. Assays of plasma C16 and C18 fatty alcohols and urinary leukotriene B_4 metabolites have been used as screening tests and to assess the effect of dietary interventions. Mutational analysis of *ALDH3A2* provides genetic confirmation of SLS, identification of carrier status and the opportunity to do prenatal diagnosis.

The main differential diagnoses are congenital ichthyosiform erythrodermas with neurological signs and neurocutaneous disorders such as neutral lipid storage disease, multiple sulphatase deficiency, hystrix-like ichthyosis and deafness (HID) syndrome. A neuroichthyotic condition resembling SLS but with absent laboratory markers was described in one patient [26].

Genetics. Although rare outside northern Sweden, SLS is a severe autosomal recessive disorder and fully penetrant [2]. Many families seek prenatal diagnosis in subsequent pregnancies, and relations of affected consanguineous families may also request an assessment of their risk. Although FAO is reduced in most obligate carriers, this assay does not allow accurate identification of carrier status. In contrast, the fibroblast FALDH component of FAO was significantly reduced in 10 of 11 heterozygotes [27], and combination of the two enzyme assays was deemed useful in carrier detection. Prenatal diagnosis by fetal skin biopsy was successful in detecting premature keratinization at 20–22 weeks [28]. Accurate first and early second trimester diagnosis based on FALDH and FAO deficiency in cultured chorionic villus cells and amniocytes has been reported [29,30].

SLS is caused by mutations in *ALDH3A2* which catalyses the oxidation of fatty aldehydes to fatty acids. More than 70 different mutations, including amino acid substitutions, deletions (25%), insertions, splicing errors and point missense mutations (38%) have been reported [11–14]. Many of these are unique to individual families but common mutations, as in north-west Sweden, reflect a founder effect and high levels of consanguinity. Successful prenatal diagnosis using PCR-based mutational analysis of the *ALDH3A2* gene confirmed homozygous mutation in the affected fetus [31].

Treatment. The abnormal fatty acid profile in plasma phospholipids in three SLS patients prompted treatment with a 6-month course of essential fatty acid supplements, but there was minimal improvement in the skin or neurologic features [5]. A report of beneficial effects of a diet rich in medium-chain triglycerides on the skin manifestations in SLS [32] has been followed by further small trials with mixed results. Reduction of total fatty intake (to 30% of total calorie intake) with essential fatty acid supplements resulted in significant improvement in the skin and neurological features (and in plasma fatty alcohol levels) in two infants after some months but was less effective in older children [18,33]. This approach failed in another study [34].

Regular emollient and keratolytic therapy may help but does not alleviate the pruritus. Topical calcipotriol ointment for 3 months in two patients produced improvement [35]. Retinoid (etretinate, acitretin) therapy has proven effective in relieving scaling and disabling lichenification in several patients [18,36]. Retinoids are less successful in controlling itching and tolerance may develop after some months; intermittent therapy may be a preferred option. Intensive physiotherapy and skills learning in early childhood clearly improve motor and social development in SLS, and orthopaedic treatment of skeletal deformities of the legs is beneficial in some cases [37]. The discovery of a role for leukotrienes in SLS led to a 3-month trial of a 5-lipoxygenase inhibitor, zileuton, in five patients [9,38,39]. There was a reduction in pruritus and improved well-being associated with a reduced urinary leukotriene B_4 excretion but no change in neuropsychological performance [39]. A single report of reduced pruritus with montelukast therapy, also a leukotriene antagonist, is encouraging [40]. Bezafibrate, a lipid lowering agent, was shown to induce FALDH levels in fibroblasts from SLS patients with some residual enzyme activity and milder phenotype but clinical studies have not been reported [41].

New therapies using viral vectors to restore FALDH activity or to correct the genetic defect are being developed in the laboratory [11,42].

References

1 Sjögren T, Larsson T. Oligophrenia in association with congenital ichthyosis and spastic disorders. *Acta Psychiatr Scand* 1957; **32** (Suppl. 113): 1–112.

2 Jagell S, Gustavson JH, Holmgren G. Sjögren–Larsson syndrome in Sweden: a clinical, genetic and epidemiological study. *Clin Genet* 1981; **19**: 233–56.

3 Richards BW, Rundle A, Wilding A. Congenital ichthyosis, spastic diplegia and mental deficiency. *J Ment Defic Res* 1957; **1**: 118–29.
4 Hernell O, Holmgren G, Jagell SF, Holman RT. Suspected faulty fatty acid metabolism in Sjögren–Larsson syndrome. *Paediatr Res* 1982; **16**: 45–9.
5 Harper JI. Analysis of essential fatty acid metabolism in Sjögren–Larsson syndrome. *Pediatr Dermatol News* 1987; **6**: 7–9.
6 Rizzo WB, Dammann AL, Craft DA. Sjögren–Larsson syndrome: impaired fatty alcohol oxidation in cultured fibroblasts due to deficient fatty alcohol : NAD oxidoreductase activity. *J Clin Invest* 1988; **81**: 738–44.
7 Rizzo WB, Craft DA. Sjögren–Larsson syndrome: deficient activity of the fatty aldehyde dehydrogenase component of fatty alcohol : NAD oxidoreductase in cultured fibroblasts. *J Clin Invest* 1991; **88**: 1643–8.
8 Judge MR, Lake BD, Smith VV *et al.* Depletion of alcohol dehydrogenase activity in the epidermis and jejunal mucosa in Sjögren–Larsson syndrome. *J Invest Dermatol* 1990; **95**: 632–4.
9 Willemsen MA, de Jong JG, van Domburg PH *et al*. Defective inactivation of leukotriene B_4 in patients with Sjögren–Larsson syndrome. *J Pediatr* 2000; **136**: 258–60.
10 Rizzo WB, Craft DA, Somer T *et al*. Abnormal fatty alcohol metabolism in cultured keratinocytes from patients with Sjögren–Larsson syndrome. *J Lipid Res* 2008; **49**: 410–9.
11 Rizzo WB. Sjögren–Larsson syndrome: Molecular genetics and biochemical pathogenesis of fatty aldehyde dehydrogenase deficiency. *Mol Genet Metab* 2007; **90**: 1–9.
12 De Laurenzi V, Rogers GR, Hamrock DJ *et al.* Sjögren–Larsson syndrome is caused by mutations in the fatty aldehyde dehydrogenase gene. *Nat Genet* 1996; **12**: 52–7.
13 Willemsen MA, Ijlst L, Steijlen PM *et al.* Clinical, biochemical and molecular genetic characteristics of 19 patients with the Sjögren–Larsson syndrome. *Brain* 2001; **124**: 1426–37.
14 Di Laurenzi V, Rogers GR, Tarcsa E *et al.* Sjögren–Larsson syndrome is caused by a common mutation in Northern European and Swedish patients. *J Invest Dermatol* 1997; **109**: 79–83.
15 Liden S, Jagell S. The Sjögren–Larsson syndrome. *Int J Dermatol* 1984; **23**: 247–53.
16 Ito M, Oguro K, Sato Y. Ultrastructural study of the skin in Sjögren–Larsson syndrome. *Arch Dermatol Res* 1991; **283**: 141–8.
17 Larregue M, Ottavy N, Bressieux JM, Lorette J. Bébé collodion: trente-deux nouvelles observations. *Ann Dermatol Vénéréol* 1986; **113**: 773–85.
18 Taube B, Billeaud C, Labreze C *et al.* Sjögren–Larsson syndrome: early diagnosis, dietary management and biochemical studies in two cases. *Dermatology* 1999; **198**: 340–5.
19 Verhoog J, Fuijkschot J, Willemsen M *et al.* Sjögren–Larsson syndrome: motor performance and everyday functioning in 17 patients. *Dev Med Child Neurol* 2008; **50**: 38–43.
20 Kawakami T, Saito R, Fujikawa Y *et al*. Incomplete Sjögren–Larsson syndrome in two Japanese siblings. *Dermatol* 1999; **198**: 93–6.
21 Lossos A, Khoury M, Rizzo WB *et al*. Phenotypic variability among adult siblings with Sjögren–Larsson syndrome. *Arch Neurol* 2006; **63**: 278–80.
22 van Domburg PH, Willemsen MA, Rottveel JJ *et al.* Sjögren–Larsson syndrome: clinical and MTI/ MRS findings in FALDH-deficient patients. *Neurology* 1999; **52**: 1307–8.
23 Jagell S, Polland W, Sansgren O. Specific changes in the fundus typical for the Sjögren–Larsson syndrome: an ophthalmological study. *Acta Ophthalmol Scand* 1980; **58**: 321–30.
24 Nilsson SEG, Jagell S. Lipofuscin and melanin content of the retinal pigment epithelium in a case of Sjögren–Larsson syndrome. *Br J Ophthalmol* 1987; **71**: 224–6.
25 Fujikschot J, Cruysberg JR, Willemsen MA *et al*. Subclinical changes in the juvenile crystalline macular dystrophy in Sjögren–Larsson syndrome detected by optical coherence tomography. *Ophthalmol* 2008; **115**: 870–5.
26 Koone MD, Rizzo WB, Elias PM *et al.* Ichthyosis, mental retardation and asymptomatic spasticity: a new neurocutaneous syndrome with normal fatty alcohol NAD oxidoreductase activity. *Arch Dermatol* 1990; **126**: 1485–90.
27 Kelson TL, Craft DA, Rizzo WB. Carrier detection for Sjögren–Larsson syndrome. *J Inherit Metab Dis* 1992; **15**: 105–11.
28 Kouseff BG, Matsuoka LY, Stenn KS *et al.* Prenatal diagnosis of Sjögren–Larsson syndrome. *J Pediatr* 1982; **101**: 998–1001.
29 Rizzo WB, Craft DA, Kelson TL *et al.* Prenatal diagnosis of Sjögren–Larsson syndrome using enzymatic methods. *Prenat Diagn* 1994; **14**: 577–81.
30 van den Brink DM, van Miert JM, Wanders RJA. A novel assay for the prenatal diagnosis of Sjögren–Larsson syndrome. *J Inher Met Dis* 2005; **28**: 965–9.
31 Sillén A, Holmgren G, Wadelius C. First prenatal diagnosis by mutation analysis in a family with Sjögren–Larsson syndrome. *Prenatal Diagnosis* 1997; **17**: 1147–9.
32 Hooft C, Kreikemans J, van Acker K *et al.* Sjögren–Larsson syndrome with exudative enteropathy: influence of medium chain triglycerides on symptomatology. *Helv Paediatr Acta* 1967; **5**: 447–58.
33 Auada MP, Taube P, Collares EF *et al.* Sjögren–Larsson syndrome: biochemical defects and follow-up in three cases. *Eur J Dermatol* 2002; **12**: 263–6.
34 Maaswinkel-Mooij PD, Brouwer OF, Rizzo WB. Unsuccessful dietary treatment of Sjögren–Larsson syndrome. *J Pediatr* 1994; **124**: 748–50.
35 Lucker GP, van de Kerkhof PC, Cruysberg JR *et al*. Topical treatment of Sjögren–Larsson syndrome with calcipotriol. *Dermatology* 1995; **190**: 292–4.
36 Jagell S, Liden S. Treatment of the ichthyosis of the Sjögren–Larsson syndrome with etretinate. *Acta Derm Venereol (Stockh)* 1983; **63**: 89–91.
37 Haddad FS, Lacour M, Harper JI, Fixsen JA. The orthopaedic presentation and management of Sjögren–Larsson syndrome. *J Ped Ortho* 1999; **19**: 617–9.
38 Willemsen MA, Rottveel JJ, Steijlen PM *et al*. 5-Lipoxygenase inhibition: a new treatment strategy for Sjögren–Larsson syndrome. *Neuropediatrics* 2000; **31**: 1–3.
39 Willemsen MA, Lutt MA, Steijlen PM *et al*. Clinical and biochemical effects of zileuton in patients with the Sjögren–Larsson syndrome. *Eur J Pediatr* 2001; **160**: 711–7.
40 Pirgon O, Aydin K, Atabek ME. Proton magnetic resonance spectroscopy findings and clinical effects of montelukast in a case with Sjögren–Larsson syndrome. *J Chil Neurol* 2006; **21**: 1092–5.
41 Gloerich J, Ijlst L, Wanders RJ *et al*. Bezafibrate induces FALDH in human fibroblasts: implications for Sjögren–Larsson syndrome. *Mol Genet Metabol* 2006; **89**: 111–5.
42 Haug S, Braun-Falco M. Adeno-associated virus vectors are able to restore fatty aldehyde dehydrogenase deficiency. Implications for gene therapy in Sjögren–Larsson syndrome. *Arch Dermatol Res* 2005; **296**: 568–72.

Refsum's disease (MIM 266500)

Refsum's disease (RD) is a very rare autosomal recessive neurocutaneous disorder, caused by defective fatty acid metabolism. Sigvald Refsum, a Norwegian neurologist, first defined it as a clinical entity in 1946, in a monograph titled *Heredopathia atactica polyneuritiformis* [1]. Clinical manifestations, primarily neuropathy, ataxia, deteriorating vision and hearing and a mild ichthyosis, develop insidiously in early adult life.

Aetiology and pathogenesis. In the early 1960s, accumulation of a storage product identified as a branched-chain 20-carbon fatty acid in plasma and tissues of patients with RD was reported [2]. Some years later, impaired oxidation of phytanic acid, a long-chain, 20-carbon branched fatty acid (3,7,11,15-tetramethylhexadecanoic acid), in cultured skin fibroblasts, was demonstrated in 11 patients with RD [3]. Asymptomatic heterozygote carriers possessed 50% phytanic acid oxidase levels, pointing to autosomal recessive inheritance.

Phytanic acid is derived from plant chlorophyll and, to a lesser extent, animal sources (phytol) in the diet, and cannot be synthesized by human tissues. In health, it is barely detected in serum (1 mg/100 mL or <30 μMol/L) but in RD it accounts for 5–30% of serum lipids, and levels rise to over 60 mg/100 mL or >200 μMol/L. In lipid-rich tissues and body fluids, it replaces other fatty acids and binds to sterols, thus interfering with membrane structure and function. Storage of phytanic acid results in lipid vacuoles in the basal epidermis. Phytanic acid is a unique branched fatty acid

(it has a methyl group at the 3 carbon position) whose breakdown requires α-oxidation by phytanoyl-CoA hydroxylase, a peroxisomal enzyme, which removes a carbon to produce pristanic acid [4]. Phytanoyl-CoA hydroxylase function depends on accessing the peroxisome via the PTS2 (peroxisome-targeting signal type 2) receptor, encoded by the *PEX7* gene [5]. The genes for both the enzyme and receptor have been cloned and their products localized to peroxisomes [6]. Mutations in the phytanoyl-CoA hydroxylase gene (*PAHX or PHYH* located on chromosome 10p13), are responsible for 90% of cases of RD while the remainder are deficient in the PTS2 receptor, encoded by *PEX7*.

Histopathology. Light microscopy changes are similar to those of ichthyosis vulgaris (acanthosis and hyperkeratosis) but with hypergranulosis. An important feature is the presence of lipid droplets in the basal and suprabasal layers of the epidermis (also seen in neutral lipid storage disease). Their significance may only be appreciated with special lipid stains. Kinetic studies in one patient with advanced disease showed a hyperproliferative pattern [7]. Electron microscopy reveals non-membrane bound vacuoles and enlarged, distorted mitochondria [8].

Clinical features. Age of onset of symptoms ranges from infancy to over 50 years. Due to the insidious and variable development of clinical symptoms, diagnosis is often delayed until late childhood or early adult life [9,10]. Progressive retinitis pigmentosa initially causes night blindness and, later, failing vision and constricted visual fields; cataracts may also develop. Electroretinography reveals reduced rod and cone response in subclinical cases. Neurological features develop in adolescence or the early twenties, and progress slowly over a period of months or years. Anosmia occurs in the majority in the early stages and impaired taste may be noted [11]. Sensorineural deafness with tinnitus develops in more than 50%. A mixed sensorimotor polyneuropathy (type IV) with hypertrophied peripheral nerves and an elevated cerebrospinal fluid (CSF) protein are characteristic findings. Progressive weakness, foot drop and loss of balance due to cerebellar ataxia cause increasing disability. In the early stages, the neurological symptoms and signs of RD may fluctuate, and patients may be labelled as clumsy and neurotic. Delayed diagnosis may result in severe neurological impairment, wasting and depression, and a high mortality has occurred in the past. Some patients develop a cardiomyopathy with serious conduction defects [12]. Skeletal defects have been noted in 35%, usually shortening of the fourth metacarpals and metatarsals.

Ichthyosis occurs in 25% of RD patients and either coincides with or postdates the onset of neurological signs. It resembles ichthyosis vulgaris with a fine white scaling, most noticeable over the lower trunk but also affecting the limbs. In late untreated cases, lamellar scaling develops.

Variability in the clinical features between family members reflects different dietary phytanic acid content. Accelerated or acute RD may develop secondary to sudden weight loss and fasting which mobilize stored fatty acids. Hypokalaemia is reported in acute RD [13].

Infantile Refsum's disease (MIM 260510). This is an autosomal recessive peroxisomal disorder with several enzyme abnormalities including phytanic acid oxidase deficiency. It manifests in early infancy with neurodegenerative disease and signs similar to those seen in adult RD, but ichthyosis is an unusual feature.

Genetics. Diagnosis of a new case of RD should prompt family screening for presymptomatic cases [14]. Heterozygote carriers may have marginally elevated phytanic acid levels and intermediate values for phytanic acid oxidase but biochemical testing is unreliable. Prenatal testing can be performed on cultured amniocytes, obtained by amniocentesis at 15–18 weeks' gestation, to assay phytanic acid oxidase activity. Molecular DNA-based diagnosis may be carried out on amniocytes or a chorionic villus sample taken at 10–12 weeks, but the possibility of early diagnosis and effective dietary therapy may reduce the demand for this approach [15]. It has been suggested that all families with retinitis pigmentosa should be screened for RD [14].

Treatment. Exclusion of sources of chlorophyll in the diet is mandatory in the treatment of RD. The major dietary exclusions are green vegetables (phytanic acid) and animal fat (phytol), and the aim of dietary treatment is to reduce daily intake from the usual level of 50 mg/day to less than 5 mg/day [16]. Rapid weight loss should be avoided, as it mobilizes tissue phytanic acid, which can lead to acute clinical manifestations [13,17]. A high carbohydrate intake ensures adequate calories and, when instituted in the early stages of the disease, blood levels of phytanic acid fall rapidly, followed by clearance of the ichthyosis and, to a variable extent, reversal of recent neurological signs. Retention of vision and hearing is less certain but has been reported [18]. Lifelong strict adherence to the diet is necessary, and recurrence of scaling is an obvious marker of rising phytanic acid levels. Plasmapheresis has been used to reduce phytanic acid levels rapidly in acutely ill patients at diagnosis and as a maintenance therapy once or twice monthly when diet alone is insufficient [17,19–21]. Lipapheresis or cascade filtration which saves albumin and IgG has also been reported in the treatment of RD [22].

References

1 Refsum S. Heredopathia atactica polyneuritiformis. *Acta Psychiatr Scand (Suppl)* 1946; **38**: 1–303.

2 Kahlke W, Riterich R. Refsum's disease: an inborn error of lipid metabolism with storage of 3,5,11,15-tetramethyl hexadecanoic acid—isolation and identification of the storage product. *Am J Med* 1965; **39**: 237–41.

3 Herndon JH, Steinberg D, Uhlendorf BW. Refsum's disease: defective oxidation of phytanic acid in tissue cultures derived from homozygotes and heterozygotes. *N Engl J Med* 1969; **281**: 1034–8.

4 Jansen GA, Ofman R, Ferdinandusse S *et al*. Refsum disease is caused by mutations in the phytanoyl-CoA hydroxylase gene. *Nat Genet* 1997; **17**: 190–3.

5 Jansen GA, Waterham HR, Wanders RJ. Molecular basis of Refsum disease: sequence variations in phytanoyl-CoA hydroxylase (PHYH) and the PTS2 receptor (PEX7). *Hum Mutat* 2004; **23**: 209–18.

6 Wierzbicki AS, Lloyd MD, Schofield CZ *et al*. Refsum's disease: a peroxisomal disorder affecting phytanic acid alpha-oxidation. *J Neurochem* 2002; **80**: 725–35.

7 Dykes PJ, Marks R, Davies MG, Reynolds DJ. Epidermal metabolism in heredopathia atactica polyneuritiformis (Refsum's disease). *J Invest Dermatol* 1978; **70**: 126–9.

8 Blanchet-Bardon CL, Anton-Lamprecht I, Puissant A, Schnyder UW. Ultrastructural features in ichthyotic skin in Refsum's disease. In: Marks R, Dykes PJ, eds. *The Ichthyoses*. Lancaster: MTP Press, 1978: 65–9.
9 Skjeldal OH, Stokke O, Refsum S *et al*. Clinical and biochemical heterogeneity in conditions with phytanic acid accumulation. *J Neurol Sci* 1987; **77**: 87–96.
10 Fertl E, Foldy D, Vass K *et al*. Refsum's disease in an Arabian family. *J Neurol Neurosurg Psychiatry* 2001; **70**: 564–5.
11 Gibberd F, Feher M, Sidey M *et al*. Smell testing: an additional tool for identification of adult Refsum's disease. *J Neurol Neurosurg Psychiatry* 2004; **75**: 1334–6.
12 Leys D, Petit H, Bonte-Adnet C *et al*. Refsum's disease revealed by cardiac disorders. *Lancet* 1989; **1**: 621.
13 Dick JP, Meeran K, Gibberd FB *et al*. Hypokalaemia in acute Refsum's disease. *J Roy Soc Med* 1993; **86**: 171–2.
14 Britton TC, Gibberd FB. A family with heredopathia atactica polyneuritiformis (Refsum's disease). *J R Soc Med* 1988; **81**: 602–3.
15 Poll-The BT, Poulos A, Sharp P *et al*. Antenatal diagnosis of infantile Refsum's disease. *Clin Genet* 1985; **27**: 524–6.
16 Brown PJ, Mei G, Gibberd FB *et al*. Diet and Refsum's disease. The determination of phytanic acid and phytol in certain foods and the application of this knowledge to the choice of suitable convenience foods for patients with Refsum's disease. *J Hum Nutrit Dietet* 1993; **6**: 295–305.
17 Ramsey BC, Meeran K, Woodrow D *et al*. Cutaneous aspects of Refsum's disease. *J R Soc Med* 1991; **84**: 559–60.
18 Djupesland G, Flottorp G, Refsum S. Phytanic acid storage disease: hearing maintained after 15 years of dietary treatment. *Neurology* 1983; **33**: 237–40.
19 Gibberd FB, Page NGR, Billimoria JD, Retsas J. Heredopathia atactica polyneuritiformis (Refsum's disease) treated by diet and plasma exchange. *Lancet* 1979; **i**: 575–8.
20 Harari D, Gibberd FB, Dick JP *et al*. Plasma exchange in the treatment of Refsum's disease. *J Neurol Neurosurg Psychiatry* 1991; **54**: 614–7.
21 Lou J-S, Snyder R, Griggs RC. Refsum's disease: long term treatment preserves sensory nerve action potentials and motor function. *J Neurol Neurosurg Psychiatry* 1997; **62**: 671–2.
22 Gutsche HU, Siegmund JB, Hoppmann I. Lipapheresis: an immunoglobulin-sparing treatment for Refsum's disease. *Acta Neurol Scand* 1996; **94**: 190–3.

IBIDS/PIBIDS syndrome (MIM 601675)

Synonyms
- Tay's syndrome
- Trichothiodystrophy E, F, A

This rare and heterogeneous genodermatosis belongs to a group of disorders that has in common a hair defect termed trichothiodystrophy (TTD) or sulphur-deficient, brittle hair. The trichothiodystrophies are classified into subtypes A–H, three of which (IBIDS, PIBIDS, TTD-A) feature skin lesions. They are grouped within the ectodermal dysplasias. The acronym (P)IBIDS describes *p*hotosensitivity, *i*chthyosis, *b*rittle hair, *i*mpaired intelligence, *d*ecreased fertility and short *s*tature. In 1968, a sibling pair with brittle hair, intellectual impairment, short stature and trichorrhexis nodosa was reported [1]. Reduction of sulphur-containing amino acids in the hair (Greek *thio*, sulphur) was a central feature of the disorder [1,2]. In 1971, Tay reported three Chinese siblings (of consanguineous parents) who also had a generalized ichthyosiform erythroderma and progeric facies [3]. Decreased fertility (in an affected Amish kindred) was added to the list of features of the syndrome [4]. Other rare genetic disorders such as the Marinesco–Sjögren syndrome are variants (BIDS), and misreporting of IBIDS cases has occurred [5]. Photosensitivity was added to the clinical spectrum in 1980 [6] and the acronyms coined soon after [7,8]. IBIDS (TTD type E) and PIBIDS (TTD type F) are autosomal recessive syndromes and occur worldwide. A review of the DNA-repair diagnostic testing services in Western Europe revealed an incidence of 1.2 per million for native and immigrant populations [9]. UV-induced DNA repair defects have been demonstrated in subgroups of patients and several different mutations described [10].

Aetiology and pathogenesis. Reduced levels (approximately 50% of normal) of hair sulphur and sulphur-containing amino acids, cysteine, methionine and proline, are the hallmark of trichothiodystrophy syndromes but circulating amino acid levels are normal. The cornified envelope of stratum corneum cells is cysteine-rich, and sulphur-rich amino acids form hair-specific matrix proteins that cross-link keratin fibres in the hair shaft. The specific reduction in cysteine-rich matrix proteins in the hair indicates a defect in terminal keratinocyte differentiation and this also contributes to the nail dystrophy and ichthyosis.

UV-induced DNA damage is normally corrected by nucleotide excision repair (NER). NER assays on cultured fibroblasts from patients with typical IBIDS revealed three patterns: one with a normal UV response (for which no gene mutation has been identified); one showing a xeroderma pigmentosum (XP) complementation group D response pattern; and a third with reduced clearance of 6–4 photoproducts, reduced DNA repair synthesis and normal cell survival [11,12]. Fibroblasts and lymphocytes from IBIDS patients without and with photosensitivity (PIBIDS) revealed markedly reduced levels of duplicative and unscheduled DNA synthesis on UV exposure [10,13–15]. The response pattern of transcription-coupled repair defects was similar to that seen in XP group D and some cases of Cockayne's syndrome (a neurodevelopmental disorder) [16]. In contrast to classical XP (with more critical mutations), PIBIDS and XP group D patients rarely develop skin malignancies. The DNA repair helicase gene *ERCC2/XPD*, located on chromosome 19q13.2–13.3, corrected the photosensitivity of both (P)IBIDS (the transcriptional function) and XP group D (the repair role of *ERCC2*) and different mutations within *ERCC2*, specific to each disorder (PIBIDS, XPD and Cockayne syndrome) were identified [15,16]. The causative mutations in PIBIDS patients are found in DNA/RNA helicase at the C-terminus while in XPD patients they occur in a highly conserved domain [10]. *XPD* mutations account for 95% of PIBIDS. Mutations in *ERCC3/XPB* helicase (chromosome 2q21) were found in a small number of PIBIDS cases [17]. The *ERCC2* and *ERCC3* gene products are subunits of the DNA repair and RNA transcription superfactor known as TFIIH. A third, rare subgroup of PIBIDS known as TTD-A [18] has been attributed to mutations in a newly recognized subunit of the TFIIH complex [19]. This helps to explain the DNA repair defect, which complemented all XP types, noted in a TTD-A patient who developed photosensitivity [7,18]. Mutations in TFIIH or other transcription factors which affect basal transcription function rather than repair function may explain the absence of photosensitivity in IBIDS patients [20]. DNA repair-deficient transgenic and knock-out mouse models have been produced, including one that mimics PIBIDS [21]. Correction of the DNA repair defect *in vitro* using recombinant adenovirus transfection of wild type *XPD* has been reported [22].

The growth defects, brittle hair and nails and neurological abnormalities of IBIDS/PIBIDS are not related to NER defects, and

may be caused by defective gene transcription of RNA and cellular proteins due to altered function of TFIIH [10,16]. The differences in the incidence of UV-related cancers between IBIDS/PIBIDS and XPD (low risk) and classical XP (high risk) are thought to be due to additional defects in XP, including UV-induced apoptosis, catalase activity and natural killer cell function [16,20,23].

Histopathology. In most cases, skin biopsy has shown changes similar to those of ichthyosiform erythroderma, with hyperkeratosis, focal parakeratosis, acanthosis and a normal or reduced granular layer. Ultrastructural features include perinuclear vacuoles and abnormal tonofilaments. Hair microscopy shows wavy hair shafts with pili torti, trichorrhexis nodosa, trichoschisis (clean transverse fractures) and distal 'brush breaks'. Polarizing light reveals characteristic alternating zig-zag light and dark bands, which give rise to the term 'tiger tail' hair. This defect may also occur in inherited amino acid and zinc deficiencies, as a complication of malnutrition and occasionally in healthy children [24]. Amino acid analysis of hair will identify true trichothiodystrophy [24]. Scanning electron microscopy highlights flattening and irregular ridging of and grooves in the shaft. The cuticle cells are degenerate or missing, leading to weathering and fragile hair.

Clinical features. IBIDS typically presents with a collodion membrane or congenital erythroderma in a low-birth-weight, premature infant. Ichthyosis develops during childhood but skin manifestations vary widely from generalized fine scaling to an erythrodermic hypohidrotic ichthyosis. Additional features in some patients are eczema, palmoplantar hyperkeratosis, pulp atrophy, digital flexion contractures, fragile small nails and hypoplastic aural cartilage [7]. An elfin-like and aged (progeric) face, resulting from fat atrophy, prominent ears and chin recession, is typical (Fig. 19.24).

Scalp and eyebrow hair is fragile, sparse, short and unruly, but its growth may improve with age. Mild to moderate intellectual impairment is the rule, and hypogonadism leads to delayed puberty and infertility in most adult patients. Moderate to severe growth failure is usual and skeletal defects including osteosclerosis have been reported [25,26]. Cataracts, otosclerosis, dental anomalies, cardiac defects and neurological signs (microcephaly, spasticity, cerebellar dysfunction, seizures, nerve deafness, autism) also occur [6,26,27]. Abnormal myelination due to reduced oligodendrocyte-specific structural proteins may account for the wide range of neurodevelopmental problems [20,27]. An increased incidence of asthma has been noted and bronchiectasis developed in one patient, although no immune defect was found [7]. A temperature-dependent deterioration in hair, skin and neurological features has been recorded in several patients at the time of febrile illnesses and attributed to an increased instability in the TFIIH transcription complex which fails to deliver cysteine-rich amino acids during terminal differentiation [28–30]. Early death from sepsis or cachexia may occur and recurrent infections with chronic neutropenia and monocytosis have been reported [10,31]. A friendly disposition is characteristic.

Photosensitivity and photophobia occur in 50% or more of IBIDS patients. Severe photosensitivity was noted in a review of 15 patients with features of IBIDS [10]. In this group, neurological disease and cataracts were more common and hypogonadism less common than expected. Although an increased risk of malignancy is not regarded as a feature of IBIDS or PIBIDS, two cases of cutaneous squamous cell cancer have been reported [32,33].



Fig. 19.24 IBIDS/trichothiodystrophy, in an 18-year-old male. (Courtesy of Professor J.I. Harper, Great Ormond Street Hospital for Children, London, UK.)

Diagnosis. Light and scanning electron microscopy of hair, and cross polarization microscopy are the first step but hair amino acid analysis by ion exchange chromatography is essential in confirming trichothiodystrophy. Skin biopsy shows non-specific features. Phototesting and DNA repair studies may be indicated but immune studies and growth hormone assay are generally normal. The main differential diagnoses are Netherton's syndrome, Sjögren–Larsson syndrome, non-bullous ichthyosiform erythroderma, Cockayne and other progeric syndromes, other ectodermal dysplasias and XPD-TTD variant (which has normal cysteine levels).

Genetics. The clinical heterogeneity of IBIDS and PIBIDS appears to result from the variety of DNA repair gene mutations within the critical functional areas of the transcription complex TFIIH. The majority are caused by mutations of the *ERCC2/XPD* gene (chromosome 19q13.2–13.3) which codes for a helicase subunit of TFIIH [15,17]. A minority are due to mutations in the *ERCC3/XPB* gene (chromosome 2q21) and the rare variant, TTD-A, is caused by mutations in the tenth subunit of the TFIIH complex which affects overall TFIIH function [19].

IBIDS and its variants are autosomal recessive disorders. Successful prenatal diagnosis has been reported in two families by identifying defective UV-induced DNA repair in amniocytes taken at 21 weeks' gestation and trophoblasts (chorionic villus biopsy)

at 9 weeks' gestation, as well as on fetal hair analysis [29,34–36]. Prenatal DNA studies are relevant only to the 70% or so of families with DNA repair defects.

Treatment. Emollients are helpful in improving skin comfort and suppleness. The influence of retinoid therapy and keratolytics on the ichthyosis has been disappointing. However, retinoid therapy was used in an effort to reduce the incidence of further skin cancers in a single patient [32]. Strict sun avoidance, protective measures and sunscreens are necessary for photosensitive patients. Advice on avoidance of physical hair treatments is helpful in reducing further hair damage and loss. Growth hormone treatment failed in one patient, and the effect of sex hormone therapy in hypogonadal patients is unknown. Physiotherapy, splinting and surgical release may reduce the severity of digital contractures [33].

References

1 Pollitt RJ, Jenner FA, Davies M. Sibs with mental and physical retardation and trichorrhexis nodosa with abnormal amino acid composition of the hair. *Arch Dis Child* 1968; **43**: 211–6.

2 Brown AC, Belser RB, Crounse RG, Wehr BF. A congenital hair defect: trichoschisis with alternating birefringence and low sulfur content. *J Invest Dermatol* 1970; **54**: 496–509.

3 Tay CH. Ichthyosiform erythroderma, hair shaft abnormalities and mental and growth retardation: a new recessive disorder. *Arch Dermatol* 1971; **104**: 4–13.

4 Jackson CE, Weiss L, Watson JH. Brittle hair with short stature, intellectual impairment and decreased fertility: an autosomal recessive syndrome in an Amish kindred. *Pediatrics* 1974; **54**: 201–7.

5 Braun-Falco O, Ring J, Butenandt O *et al.* Ichthyosis vulgaris, Minderwuchs, Haardysplasie, Zahnanomalien, Immundefekte, psychomotorische Retardation und Resorptionsstorungen. *Hautarzt* 1981; **32**: 67–74.

6 Price VH, Odom RB, Ward WH *et al*. Trichothiodystrophy. Sulfur-deficient brittle hair as a marker for a neuroectodermal symptom complex. *Arch Dermatol* 1980; **116**: 1375–84.

7 Jorizzo JL, Atherton DJ, Crounse RG, Wells RS. Ichthyosis, brittle hair, impaired intelligence, decreased fertility and short stature (IBIDS). *Br J Dermatol* 1982; **106**: 705–10.

8 Crovato F, Borrone C, Rebora A. Trichothiodystrophy: BIDS, IBIDS and PIBIDS? *Br J Dermatol* 1983; **108**: 247 (letter).

9 Kleijer WJ, Laugel V, Berneburg M *et al*. Incidence of DNA repair deficiency disorders in western Europe: xeroderma pigmentosum, Cockayne syndrome and trichothiodystrophy. *DNA Repair* 2008; **7**: 744–50.

10 Itin PH, Sarasin A, Pittelkow MR. Trichothiodystrophy: update on the sulfur-deficient brittle hair syndromes. *J Am Acad Dermatol* 2001; **44**: 891–920.

11 Lehmann AR, Arlett CF, Broughton BC *et al*. Trichothiodystrophy, a human DNA repair disorder with heterogeneity in the cellular response to ultraviolet light. *Cancer Res* 1988; **48**: 6090–6.

12 Broughton BC, Lehmann AR, Harcourt SA *et al.* Relationship between pyrimidine dimers, 6–4 photoproducts, repair synthesis and cell survival: studies using cells from patients with trichothiodystrophy. *Mutat Res* 1990; **235**: 33–40.

13 Van Neste D, Caulier B, Thomas P, Vasseur F. PIBIDS, Tay's syndrome and xeroderma pigmentosum (Letter). *J Am Acad Dermatol* 1985; **12**: 372–3.

14 Rebora A, Crovato F. PIBI(D)S syndrome: trichothiodystrophy with xeroderma pigmentosum (group D) mutation. *J Am Acad Dermatol* 1987; **16**: 940–7.

15 Takayama K, Salazar EP, Broughton BC *et al*. Defects in the DNA repair and transcription gene *ERCC2* (*XPD*) in trichothiodystrophy. *Am J Hum Genet* 1996; **58**: 263–70.

16 Lehmann AR. The xeroderma pigmentosum group D (XPD) gene: one gene, two functions, three diseases. *Genes Dev* 2001; **15**: 15–23.

17 Weeda G, Eveno E, Donker I *et al.* A mutation in the *XPB/ERCC3* DNA repair transcription gene, associated with trichothiodystrophy. *Am J Hum Genet* 1997; **60**: 320–9.

18 Stefanini M, Vermeulen W, Weeda G *et al.* A new nucleotide-excision-repair gene associated with the disorder trichothiodystrophy. *Am J Hum Genet* 1993; **53**: 817–21.

19 Giglia-Mari G, Coin F, Ranish JA *et al*. A new tenth subunit of TFIIH is responsible for the DNA repair syndrome trichothiodystrophy group A. *Nature Genet* 2004; **36**: 714–9.

20 de Boer J, Hoeijmakers JH. Nucleotide excision repair and human syndromes. *Carcinogenesis* 2000; **21**: 453–60.

21 de Boer J, de Wit J, Van Steeg H *et al*. A mouse model for the basal transcription/DNA repair syndrome trichothiodystrophy. *Mol Cell* 1998; **1**: 981–90.

22 Armelini MG, Muotri AR, Marchetto MC *et al*. Restoring DNA repair capacity of cells from three distinct diseases by XPD gene-recombinant adenovirus. *Cancer Gene Therapy* 2005; **12**: 389–96.

23 Queille S, Drougard C, Sarasin A. Effects of XPD mutations on UV-induced apoptosis in relation to skin cancer-proneness in repair deficient syndromes. *J Invest Dermatol* 2001; **117**: 1162–70.

24 de Berker D. 'Tiger tail' pattern on polarized hair microscopic examination is found in healthy infants. *Arch Dermatol* 1997; **133**: 1313–4.

25 McCuaig C, Marcoux D, Rasmussen JE *et al*. Trichothiodystrophy associated with photosensitivity, gonadal failure and striking osteosclerosis. *J Amer Acad Dermatol* 1993; **28**: 820–6.

26 Toelle SP, Valsangiacomo E, Boltshauser E. Trichothiodystrophy with severe cardiac and neurological involvement in two sisters. *Eur J Ped* 2001; **160**: 728–31.

27 Battistella PA, Peserico A. Central nervous system demyelination in PIBI(D)S syndrome: a further case. *Child Nerv Syst* 1996; **12**: 110–3.

28 Vermeulen W, Rademakers S, Jaspers NG *et al*. A temperature-sensitive disorder in basal transcription and DNA repair in humans. *Nature Genet* 2001; **27**: 299–303.

29 Kleijer WJ, Beemer FA, Boom BW. Intermittent hair loss in a child with PIBIDS syndrome and trichothiodystrophy with defective DNA repair-xeroderma pigmentosum group D. *Am J Med Genet* 1994; **52**: 227–30.

30 Wetzburger CL, Van Regemorter N, Szliwowski HB *et al*. Gray matter heterotopia and acute necrotizing encephalopathy in trichothiodystrophy. *Ped Neurol* 1998; **19**: 392–4.

31 Petrin JH, Meckler KA, Sybert VP. A new variant of trichothiodystrophy with recurrent infections, failure to thrive and death. *Pediatr Dermatol* 1998; **15**: 31–4.

32 Dahbi-Skali H, Benamar L, Benchikhi H *et al*. PIBIDS syndrome (trichothiodystrophy type F) and skin cancer: an exceptional association. *Photodermatol Photoimmunol Photomed* 2004; **20**: 157–8.

33 Charles CA, Connelly EA, Aber CG *et al*. A rare presentation of squamous cell carcinoma in a patient with PIBIDS-type trichothiodystrophy. *Br J Dermatol* 2008; **25**: 264–7.

34 Sarasin A, Blanchet-Bardon C, Renault G *et al.* Prenatal diagnosis in a subset of trichothiodystrophy patients defective in DNA repair. *Br J Dermatol* 1992; **127**: 485–91.

35 Alapetite C, Benoit A, Moustacchi E *et al*. The comet assay as a repair test for prenatal diagnosis of xeroderma pigmentosum and trichothiodystrophy. *J Invest Dermatol* 1997; **108**: 134–9.

36 Kleijer WJ, van der Sterre ML, Garritsen VH *et al*. Prenatal diagnosis of xeroderma pigmentosum and trichothiodystrophy in 76 pregnancies at risk. *Prenat Diagn* 2007; **27**: 1133–7.

Conradi–Hünermann–Happle syndrome (MIM 302960)

Synonyms

- Happle's syndrome
- X-linked dominant chondrodysplasia punctata type II/ichthyosis/cataract syndrome
- X-linked dominant ichthyosis

Conradi–Hünermann–Happle syndrome (CHHS) is a distinctive skin disorder occurring in a mosaic pattern in females, often associated with skeletal and ocular defects. It is usually lethal *in utero*

in affected males. It is considerably rarer than congenital ichthyosiform erythrodermas. The characteristic features were described by Happle in 1979, and, though originally labelled Conradi–Hünermann syndrome (CHS) or X-linked dominant ichthyosis (XLDI), it is now referred to as Happle's syndrome or Conradi–Hünermann–Happle syndrome [1]. It is one of the variants of chondrodysplasia punctata (variant CDPX2), a group of genetic disorders that have in common a congenital punctate epiphyseal and skeletal calcification which affects growth. CDP was first described by Conradi in 1914. There are three other subgroups of CDP: an autosomal recessive rhizomelic type 1; an autosomal dominant form without cutaneous disease, now referred to as Conradi–Hünermann syndrome [2]; and an X-linked recessive variant. CDP also occurs in Down's syndrome, Smith–Lemli–Opitz syndrome, CHILD syndrome and as an acquired defect in congenital hypothyroidism, and fetal warfarin or phenytoin toxicity.

Aetiology and pathogenesis. A deficiency of a peroxisomal enzyme, dihydroxyacetone phosphate acyltransferase (DHAPAT), was identified in cultured fibroblasts from patients with both rhizomelic chondrodysplasia punctata and CHHS [3,4]. DHAPAT is responsible for synthesis of plasmalagen phospholipids and glycolipids. An animal model, the 'bare patches mouse', has an X-linked dominant disorder with a phenotype and peroxisomal defect similar to that of Happle/XLDI syndrome [5]. Accumulation of 8(9)-cholesterol and 8-dehydrocholesterol in tissue samples from seven CHHS/XLDI patients suggested a defect in C8–C7 isomerization, which is catalysed by sterol-Δ8-isomerase, an emopamil-binding membrane protein (EBP) [6]. Functional mutations of the candidate gene, located at Xp11.22–p11.23, were confirmed in these patients and several *EBP* mutations have since been identified [7]. There is poor genotype–phenotype correlation and lyonization of X-linked genes at this site may influence the severity of the clinical phenotype as well as causing functional mosaicism. Similar mutations have been found in the X-linked dominant 'tattered mouse' [8], whereas the 'bare patches mouse' and the CHILD syndrome are due to a mutation of the gene coding 3β-hydroxysteroid dehydrogenase, which maps to Xq28 [9]. Ichthyosis in CHHS may, in part, result from impaired cholesterol biosynthesis and toxic effects of precursors which affect epidermal lamellar body structure and function. Abnormalities of sterol metabolism have also been implicated in other genetic skeletal dysplasias, possibly by interfering with gene transcription (via the hedgehog signalling pathways), growth patterns and steroid hormone metabolism [10]. The Indian hedgehog protein is necessary for vertebrate skeletal development and mutations cause chondrocyte degeneration which affects epiphyseal growth plates, and leads to ectopic calcification. Ectopic epiphyseal, and epidermal, calcification are recognized features of X-linked dominant ichthyosis. Rhizomelic CDP is caused by three different peroxisomal enzyme mutations, including two involved in phospholipid biosynthesis [11].

Histopathology. Neonatal skin biopsy revealed marked orthohyperkeratosis and prominent keratotic follicular plugs containing dystrophic calcification [12]. Biopsy of ichthyotic skin in the child and adult shows changes similar to those of ichthyosis vulgaris, but without the typical ultrastructural features. There is orthohyperkeratosis with a reduced granular layer, mild acanthosis and a light perivascular inflammatory infiltrate in the upper dermis in childhood. Older lesions show prominent perifollicular atrophy. Epidermal calcification, needle-like inclusions in granular keratinocytes and reduced numbers of Langerhans' cells, some of which are degenerate, have been reported [13]. Electron microscopy reveals persistent desmosomal structures in the stratum corneum layer. Abnormal degenerate mitochondria and vacuolated lamellar bodies were seen, and the dilated intercellular spaces contained disordered lipid lamellae and debris [3].



Fig. 19.25 CHHS/X-linked dominant ichthyosis in a 2-year-old girl. (Courtesy of Dr D.J. Atherton, Great Ormond Street Hospital for Children, London, UK.)

Clinical features. Affected babies are typically female, premature and born with either a partial collodion membrane or generalized ichthyosiform erythroderma. Within the first year, generalized linear and swirling patterns of erythroderma and scaling, following the lines of Blaschko, are established (Fig. 19.25). Intervening areas of skin are unaffected. Palmoplantar hyperkeratosis and nail dystrophy may occur. Recurrent infections, especially in the flexures, can be troublesome, and scalp and eyebrow hair growth is sparse and lustreless. The ichthyosis improves in early childhood and the residual signs are often so subtle in adult life that an affected mother may be missed. Signs to be sought in older children and adults include swirls of fine scale, linear pigmentary change, patchy atrophy, follicular atrophoderma mainly on the limbs and dorsal hands, and a striate cicatricial alopecia, all in a Blaschkoid pattern. An adult patient

had persistent ichthyosis and also developed psoriasis in Blaschko's lines [14].

Other variable features include rounded or asymmetrical facies with frontal bossing and hypertelorism, a broad flat nasal bridge, congenital asymmetric cataracts in 60% of patients (mosaic lens involvement), short stature, asymmetrical or, rarely, symmetrical shortening of limbs [15], kyphoscoliosis, supernumerary digits and other skeletal defects. Stippled calcification (asymmetric) of long-bone epiphyses, vertebrae, pelvis, carpus and tarsus, and cartilage, including trachea, is a characteristic but not universal radiological finding in the neonatal period, and usually resolves by adulthood. Patients have normal or mildly impaired intellectual development and neural hearing loss has been reported [14,15]. Renal, cardiac, intestinal and neurological anomalies have also been reported but occasional patients have minimal clinical signs [16,17].

Genetics and diagnosis. The mosaic phenotype of CHHS/XLDI reflects the effects of the two populations of keratinocytes that result from the X chromosome alleles, one normal, the other mutated (functional mosaicism). This X chromosome mutation is compatible with survival in female embryos, because of the Lyon effect of random X inactivation allowing expression of either allele in a given somatic cell. CHHS shows variable penetrance in females and is generally lethal in male embryos. A history of miscarriage and a predominance of female offspring have been noted in affected kindred. However, male patients with cutaneous and skeletal features have been reported, and at least one had the Kleinfelter karyotype [18–20]. The spontaneous improvement with age may reflect progressive elimination of mutant cells by adjacent normal cells, which have a growth advantage. However, clinical severity may worsen in successive generations, so-called anticipation [16,17]. Mutations in the emopamil-binding protein gene, *EBP* which contains five exons, are responsible for CHHS. Up to 50 novel and recurrent disease-causing mutations in the *EBP* gene, mostly in exons 2 and 4, have been reported, including missense, nonsense, deletions, frameshift, splice-site and intronic [6–8,11,16,17,20–22].

Autosomal recessive rhizomelic CDP can cause cataracts but rarely affects skin. An X-linked recessive variant may represent XLRI with contiguous gene defects. Genetic counselling must include assessment of all members of the extended family, looking for dysmorphism, residual skin signs, subclinical cataracts and a history of radiological abnormalities or pregnancy loss. Fetal warfarin or hydantoin toxicity, congenital rubella or varicella and other X-linked dominant genodermatoses (such as Goltz syndrome) can mimic CHHS/XLDI.

The diagnosis is usually clinically suspected in the first weeks of life. Skin biopsy is helpful at this stage [12] and abnormal plasma sterol profile (raised 8(9)-cholesterol and 8-dehydrocholesterol ratio to cholesterol) confirms the metabolic defect [5,6,8,17,21]. Mutational analysis of the *EBP* gene on peripheral blood lymphocytes is available in selected centres.

Prenatal testing, assaying DHAPAT, was successfully used in one family. Sterol assay can be done on amniotic fluid. Ultrasound scans in the second trimester may detect skeletal and other defects. First trimester mutational analysis of the *EBP* gene on chorionic villus biopsy is now widely available [23]. The variability of disease expression and improvement with age make treatment decisions based on prenatal diagnosis difficult.

Treatment. Emollients are helpful in controlling ichthyosis and antimicrobial therapy may be needed for skin infections in infancy. Some adult patients with scarring alopecia may opt to use a wig. Clofibrate, a peroxisome inducer, did not help one patient [24]. The effect of retinoids is unknown and the need for treatment diminishes with age. Continued orthopaedic surveillance and appropriate procedures may be indicated for skeletal anomalies. Cataracts do not usually affect vision. Growth hormone has been tried in one patient [17].

References

1 Happle R. X-linked dominant chondrodysplasia punctata: review of the literature and report of a case. *Hum Genet* 1979; **53**: 65–73.

2 Spranger JW, Opitz JM, Bidder U. Heterogeneity of chondrodysplasia punctata. *Hum Genet* 1971; **11**: 190–212.

3 Heymans HSA, Oorthuys JWE, Nelk G *et al.* Rhizomelic chondrodysplasia punctata: another peroxisomal disorder. *N Engl J Med* 1985; **313**: 187–8.

4 Clayton PT, Kalter DC, Atherton DA *et al.* Peroxisomal enzyme deficiency in X-linked dominant Conradi–Hünermann syndrome. *J Inherit Metab Dis* 1989; **12**: 358–60.

5 Emami S, Hanley KP, Esterly NB *et al.* X-linked dominant ichthyosis with peroxisomal deficiency. *Arch Dermatol* 1994; **130**: 325–36.

6 Braverman N, Lin P, Moebius F *et al.* Mutations in the gene encoding 3β-hydroxysteroid-Δ8,Δ7-isomerase cause X-linked dominant Conradi–Hünermann syndrome. *Nat Genet* 1999; **22**: 291–4.

7 Herman GE, Kelley RI, Pureza V *et al.* Characterization of mutations in 22 females with X-linked dominant chondrodysplasia punctata (Happle syndrome). *Genet Med* 2002; **4**: 434–8.

8 Derry JM, Gormally E, Means GD *et al.* Mutations in a Δ8,Δ7-isomerase in the tattered mouse and X-linked linked dominant chondrodysplasia punctata. *Nat Genet* 1999; **22**: 286–93.

9 Liu XY, Dangel AW, Kelley RI *et al.* The gene mutated in bare patches and striated mice encodes a novel 3β-hydroxysteroid dehydrogenase. *Nat Genet* 1999; **22**: 182–7.

10 Cohen MM. The hedgehog signaling network. *Am J Med Genet* 2003; **123A**: 5–28.

11 Motley AM, Brites P, Gerez L *et al.* Mutational spectrum in the *PEX7* gene and functional analysis of mutant alleles in 78 patients with rhizomelic chondrodysplasia punctata type 1. *Am J Hum Genet* 2002; **70**: 612–24.

12 Hoang MP, Carder KR, Pandya AG *et al.* Ichthyosis and keratotic follicular plugs containing dystrophic calcification in newborns: distinctive histopathologic features of X-linked dominant chondrodysplasia punctata (Conradi–Hünermann–Happle syndrome). *Am J Dermopath* 2004; **26**: 53–8.

13 Kolde G, Happle R. Histologic and ultrastructural features of the ichthyotic skin in X-linked dominant chondrodysplasia punctata. *Acta Derm Venereol (Stockh)* 1984; **64**: 389–94.

14 Bruch D, Megahed M, Majewski F, Ruzicka T. Ichthyotic and psoriasiform skin lesions along Blaschko's lines in a woman with X-linked linked dominant chondrodysplasia punctata. *J Am Acad Dermatol* 1995; **33**: 356–60.

15 Gobello T, Mazzanti C, Fileccia P *et al.* X-linked dominant chondrodysplasia punctata (Happle syndrome) with uncommon symmetrical shortening of the tubular bones. *Dermatology* 1995; **191**: 323–7.

16 Has C, Bruchner-Tuderman L, Muller D *et al.* The Conradi–Hünermann–Happle syndrome (CDPX2) and emopamil binding protein: novel mutations and somatic and gonadal mosaicism. *Hum Mol Genet* 2000; **9**: 1951–5.

17 Feldmeyer L, Mevorah B, Grzeschik KH *et al.* Clinical variation in X-linked dominant chondrodysplasia punctata (X-linked dominant ichthyosis). *Br J Dermatol* 2006; **154**: 766–9.

18 Sutphen R, Amar MJ, Kousseff BG *et al.* XXY male with X-linked chondrodysplasia punctata (Happle syndrome). *Am J Med Genet* 1995; **57**: 489–92.

19 Happle R. X-linked dominant chondrodysplasia punctata, ichthyosis, cataract syndrome in males. *Am J Med Genet* 1995; **57**: 493.
20 Aughton DJ, Kelley RI, Metzenberg A *et al*. X-linked dominant chondrodysplasia punctata (CDPX2) caused by single gene mosaicism in a male. *Am J Med Genet* 2003; **116A**: 255–60.
21 Kolb-Maurer A, Grzeschik KH, Haas D *et al*. Conradi–Hünermann–Happle syndrome (X-linked dominant chondrodysplasia punctata) confirmed by plasma sterol and mutation analysis. *Acta Derm Venereol* 2008; **88**: 47–51.
22 Ikegawa S, Ohashi H, Ogata T *et al*. Novel and recurrent EBP mutations in X-linked dominant chondrodysplasia punctata. *Am J Med Genet* 2000; **94**: 300–5.
23 Tysoe C, Law CJ, Caswell R *et al*. Prenatal testing for a novel EBP missense mutation causing X-linked dominant chondrodysplasia punctata. *Prenat Diagn* 2008; **28**: 384–8.
24 Kalter DC, Atherton DJ, Clayton PT. X-linked dominant Conradi–Hünermann syndrome presenting as congenital erythroderma. *J Am Acad Dermatol* 1989; **21**: 248–56.

Neutral lipid storage disease with ichthyosis (MIM 275630)

Synonym
- Chanarin–Dorfman syndrome

The association of an autosomal recessive congenital ichthyosis and leukocyte lipid vacuolation affecting two sisters was first described in 1966 [1]. Dorfman reported four cases including a follow-up of the two sisters and recognized that this was a specific multisystem lipoidosis [2]. Chanarin, describing a similar case, referred to it as neutral lipid (triglyceride) storage disease (NLSD) [3]. The triglyceride deposition in white blood cells and several organs results in a combination of skin, hepatic, muscle and ocular abnormalities. There are more than 50 reported cases of NLSD, mainly in people of peri-Mediterranean (especially Turkey) or Arabic descent, many from consanguineous families [4,5]. Some families suffer from myopathy but not ichthyosis and the designations NLSDI and NLSDM are used accordingly.

Aetiology and pathogenesis. Cytoplasmic lipid droplets are found in leukocytes, bone marrow, skin, muscle and liver in NLSD. Serum lipid analysis is normal but scale lipids show raised triglyceride content [6]. Histochemical studies on cultured fibroblasts and keratinocytes confirmed that the stored lipid was neutral lipid triacylglycerol or triglyceride [3]. Increased fibroblast triglyceride synthesis with a complete failure of endogenous triglyceride breakdown was demonstrated [6,7]. Exogenous triglyceride metabolism was normal and dietary lipid restriction was unhelpful. A defect in recycling of mono- or diacylglycerols from triglycerides to phospholipids or in long-chain fatty acid oxidation was suspected [8].

Linkage in several families with NLSD to a locus (the *NCIE2* locus) at chromosome 3p21 led to the identification of mutations in the *CGI-58* gene in 13 patients [9]. *CGI-58* (now known as *ABHD5*) is a seven-exon gene which encodes a large family of proteins, many of them enzymes, with a characteristic α/β-hydrolase fold. *ABHD5* is widely expressed in tissues such as skin, muscle, liver and brain, but also lymphocytes [10] and localizes to the surface of cytoplasmic lipid droplets [11]. Families with NLSDM (NLSD with myopathy, without ichthyosis) have mutations in *PNPLA2*, which encodes adipose triglyceride lipase necessary for lipolysis of cellular fat stores [12]. Adipose triglyceride lipase requires the *ABHD5* gene product as a cofactor and it may be that *ABHD5* additionally regulates epidermal function and influences arachidonic acid-mediated inflammation. Basal epidermal and stratum corneum barrier dysfunction are linked to abnormal phase separation of the stored lipid [13].

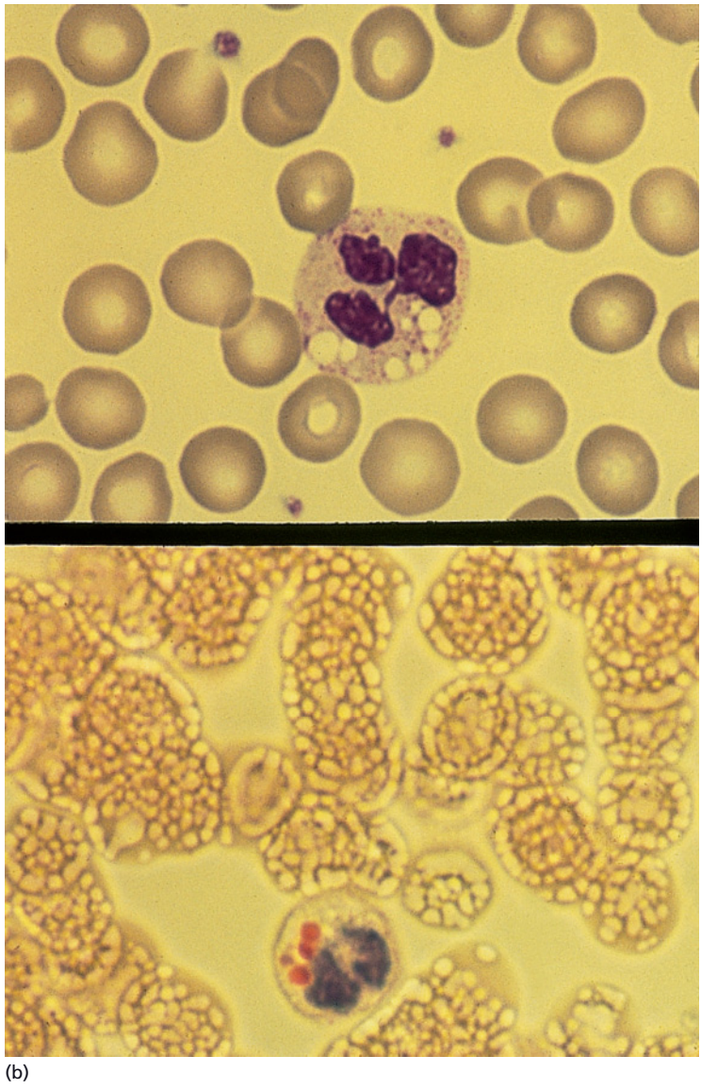
Histopathology. A notable feature of NLSD (seen to a lesser extent in heterozygote carriers) is the presence of lipid droplets, visible on light microscopy, in circulating polymorphs (neutrophils, eosinophils and basophils) and monocytes but not in lymphocytes, red cells or platelets (Fig. 19.26b). The vacuoles are oil red O and Sudan black positive and this feature is termed 'Jordan's anomaly'. Electron microscopy shows non-membrane-bound cytoplasmic lipid droplets. Biopsies of muscle, liver and skin and cultured fibroblasts also reveal numerous cellular lipid droplets. Skin biopsy shows acanthosis and hyperkeratosis, and closely packed lipid droplets of varying size are seen in basal (Fig. 19.26c), granular and adnexal (sweat gland and duct) keratinocytes and in dermal fibroblasts, smooth muscle cells and endothelium. Lipid vacuoles are seen in the epidermis, but not in other tissues, in Refsum's disease. Ultrastructurally, vacuoles may be seen in upper epidermal layers and arrector pili muscles [7]. Epidermal lamellar bodies and intercellular lipid lamellae are disrupted by globular electron lucent inclusions [14]. Lipid vacuoles are present in muscle fibres and marrow. Liver biopsy reveals hepatocyte fatty vacuolation, lobular fibrosis in late-stage disease and normal Kupffer cells.

Clinical features. NLSD is a multisystem disorder but clinical features are variable [4–6,9]. Affected newborns are either collodion babies or erythrodermic. The pattern of skin disease thereafter resembles mild to moderate NBIE with fine white scale on an erythematous background and lamellar scaling on the trunk (Fig. 19.26a) and legs. Scaling may diminish in warm weather and with advancing age. Pruritus is often troublesome and hypohidrosis may occur. Mild ectropion, flexural and neck lichenification and palmoplantar hyperkeratosis are common. Nail dystrophy and scalp alopecia have rarely been reported. Adult twins with late-onset clinical features of NLSD presented with an oily ichthyosis but had negative mutational analysis [15].

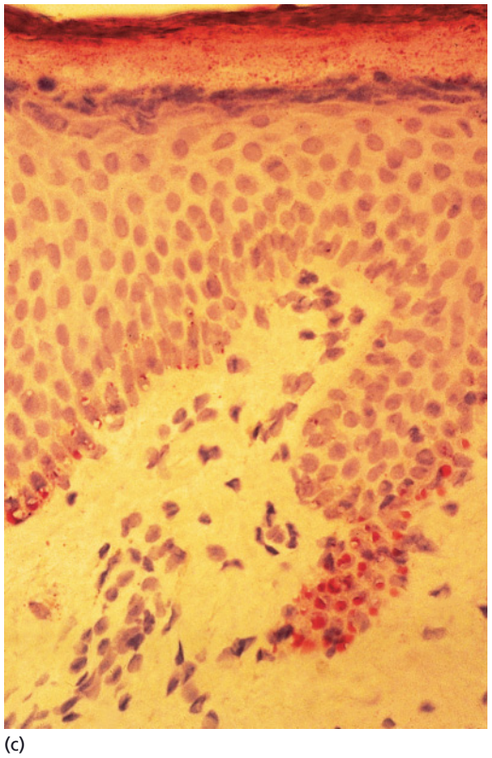
Muscle involvement ranges from an asymptomatic or subclinical myopathy with elevated muscle enzymes in most patients, to marked proximal myopathy in a few late cases. Hepatomegaly, abnormal liver enzymes and fatty infiltration of the liver are common, even in childhood. Cirrhosis may evolve rapidly and in childhood. Liver biopsy is more sensitive than biochemical markers in detecting the degree of involvement. Splenomegaly and malabsorption, resulting from intestinal mucosal lipid deposition, are occasional features. Cataracts of the nuclear type (subcapsular) may be detected from infancy in over 50% of cases but rarely affect vision, though nystagmus may occur. Short stature, retinal disease, nerve deafness, ataxia, microcephaly, spasticity, neuropathy and developmental delay have been reported, but most patients are intellectually normal. Fatal renal complications occurred in an infant with NLSD [16]. Prognosis depends on the pattern and degree of organ involvement.



(a)



(b)



(c)

Fig. 19.26 Neutral lipid storage disease in an infant. (a) In an 18-month-old boy. (b) Lipid vacuoles (lower panel, oil red-O positive) in neutrophils; and (c) in basal keratinocytes.

Diagnosis. The diagnosis is confirmed by direct microscopy of a peripheral blood smear, which shows lipid droplets in approximately 25% of granulocytes (Jordan's anomaly) [1,16]. Careful inspection of a fresh blood film may also be used to detect carriers and should be a routine investigation in all patients with congenital ichthyosis [17]. Moderate elevation of muscle and hepatic enzymes is usual but raised urinary creatine with normal serum muscle enzymes has been noted [5]. Liver biopsy changes are noted above. Muscle biopsy reveals lipid droplets in muscle fibres and EMG/MR signs of myopathy are detected.

Gaucher disease type 2, muscle carnitine deficiency, Wolman's disease, other storage disorders and multiple sulphatase or carboxylase deficiency should be excluded, as they share some of the features of NLSD. Lipid vacuoles are seen in the epidermis, but not in the blood smear, in Refsum's disease. Skin lesions may mimic erythrokeratoderma variabilis [18].

Genetics. The majority of NLSD patients comes from countries bordering the Mediterranean and most are of Arab descent. Many patients have consanguineous parentage reflecting autosomal

recessive inheritance. Asymptomatic heterozygote carriers may be identified by detection of lipid vacuoles in myeloid leukocytes, especially eosinophils on a fresh blood film [19]. This screening test should be offered to members of the extended family. Several different mutations in *ABHD5 (CGI-58)* have been reported [9,10,11,20] and mutational analysis can be performed on peripheral blood lymphocytes, even though lipid storage is not seen in lymphocytes [10]. However, 20% of patients with the classical phenotype have no identifiable *ABHD5* mutations [15,16]. Prenatal diagnosis using fetal blood microscopy, or skin biopsy at 20 weeks' gestation, is possible and identification of the *ABHD5* mutation in an affected family should allow first trimester diagnosis by chorionic villus sampling and mutational analysis.

Treatment. Emollients are helpful and retinoid therapy, either low-dose continuous or intermittent courses, improves the cutaneous features. Dietary manipulation to reduce intake of long-chain fatty acids and increase medium-chain fatty acids has been reported to benefit two patients, but one was also receiving retinoid therapy [5,21]. In another case, dietary treatment was ineffective [7].

References

1 Rozenszajn L, Klazman A, Yaffe D, Efrati P. Jordan's anomaly in white blood cells. *Blood* 1966; **28**: 258–65.
2 Dorfman ML, Hershko C, Eisenberg S, Sagher F. Ichthyosiform dermatosis with systemic lipidosis. *Arch Dermatol* 1974; **110**: 261–6.
3 Chanarin I, Patel A, Slavin G *et al*. Neutral lipid storage disease: a new disorder of lipid metabolism. *BMJ* 1975; **1**: 553–5.
4 Srebrnik A, Tur E, Perluk C *et al*. Dorfman–Chanarin syndrome: case report and review. *J Am Acad Dermatol* 1987; **17**: 801–8.
5 Pena-Penabad C, Almagro M, Martinez W *et al*. Dorfman–Chanarin syndrome (neutral lipid storage disease): new clinical features. *Br J Dermatol* 2001; **144**: 430–2.
6 Radom J, Salvayre R, Maret A *et al*. Metabolism of neutral lipids in cultured fibroblasts from multisystemic (type 3) lipid storage myopathy. *Eur J Biochem* 1987; **164**: 703–8.
7 Judge MR, Hilaire N, Salvayre R *et al*. Neutral lipid storage disease: case report and lipid studies. *Br J Dermatol* 1994; **130**: 507–10.
8 Igal RA, Coleman RA. Acylglycerol recycling from triacylglycerol to phospholipid, not lipase activity, is defective in neutral lipid storage disease fibroblasts. *J Biol Chem* 1996; **271**: 16644–51.
9 Lefevre C, Jobard F, Caux F *et al*. Mutations in *CGI-58*, the gene family encoding a new protein of the esterase–lipase–thioesterase subfamily, in Chanarin–Dorfman syndrome. *Am J Hum Genet* 2001; **69**: 1002–12.
10 Badeloe S, van Geel M, Nagtzaam I *et al*. Chanarin-Dorfman syndrome caused by a novel splice site mutation in *ABHD5*. *Br J Dermatol* 2008; **158**: 1371–401.
11 Akiyama M, Sawamura D, Nomura Y *et al*. Truncation of CGI-58 protein causes malformation of lamellar granules resulting in ichthyosis in Dorfman-Chanarin syndrome. *J Invest Dermatol* 2003; **121**: 1029–37.
12 Fischer J, Lefevre C, Morava E *et al*. The gene encoding adipose triglyceride lipase (PNPLA2) is mutated in neutral lipid storage disease with myopathy. *Nat Genet* 2007; **39**: 28–30.
13 Demerjian M, Crumrine DA, Milstone LM *et al*. Barrier dysfunction and pathogenesis of neutral lipid storage disease with ichthyosis (Chanarin–Dorfman syndrome). *J Invest Dermatol* 2006; **126**: 2032–8.
14 Elias PM, Williams ML. Neutral lipid storage disease: defective lamellar body contents and intracellular dispersion. *Arch Dermatol* 1985; **121**: 1000–8.
15 Solomon C, Bernier L, Germain L *et al*. Severe oily ichthyosis in monozygotic twins mimicking Chanarin-Dorfman syndrome but not associated with a mutation in the *CGI58* gene. *Arch Dermatol* 2006; **142**: 402–3.
16 Aksu G, Kalkan Ucar S, Bulut Y *et al*. Renal involvement as a rare complication of Dorfman–Chanarin syndrome: a case report. *Ped Dermatol* 2008; **25**: 326–31.
17 Wolf R, Zaritzky A, Pollak S. Value of looking at leukocytes in every case of ichthyosis. *Dermatologica* 1988; **177**: 237–40.
18 Pujol RM, Gilaberte M, Toll A *et al*. Erythrokeratoderma variabilis-like ichthyosis in Chanarin-Dorfman syndrome. *Br J Dermatol* 2005; **153**: 838–41.
19 Wollenberg A, Geiger E, Schaller M *et al*. Dorfman–Chanarin syndrome in a Turkish kindred: conductor diagnosis requires analysis of multiple eosinophils. *Acta Dermatol Venereol (Stockh)* 2000; **80**: 39–43.
20 Bruno C, Bertini E, Di Rocco M *et al*. Clinical and genetic characterization of Chanarin–Dorfman syndrome. *Biochem Biophys Res Commun* 2008; **369**: 1125–8.
21 Kakourou T, Drogari E, Christomanou H *et al*. Neutral lipid storage disease: response to dietary intervention. *Arch Dis Child* 1997; **77**: 184.

KID syndrome (MIM 148210) and HID syndrome (MIM 602540)

The condition now known as KID syndrome (*k*eratitis, *i*chthyosis, *d*eafness) was first reported in 1915 as a generalized congenital keratoderma with ocular, aural and mucosal involvement [1]. The acronym KID was coined in 1981 to highlight the main features of the syndrome, which is included in the broad category of ectodermal dysplasias [2]. However, the skin disease combines features of a hystrix-like ichthyosis and an erythrokeratoderma, and keratitis is not present in all cases. Many cases have apparently been sporadic but autosomal dominant inheritance is increasingly reported. It has a worldwide distribution and more than 100 cases have been recorded in the literature. A change in terminology has been suggested but not agreed [3]. HID syndrome describes *h*ystrix-like *i*chthyosis and *d*eafness. It was originally reported in two patients from Germany [4] but is now regarded as an allelic variant of KID.

Aetiology. Mutations in gap junction proteins, namely connexins, have been reported in various epidermal diseases including hidrotic ectodermal dysplasia (connexin 30), erythrokeratoderma variabilis with and without deafness (connexin 31 and 30.3), Vohwinkel's syndrome (connexin 26), Charcot–Marie–Tooth (connexin 32) and non-syndromic hearing loss (connexin 26 and 31). Connexins are universal membrane proteins that form inter- and intracellular channels for ion and molecule transfer, which is the basis of all cellular communications. Mutant connexin expression leads to abnormal cellular and calcium homeostasis and, in some cases, immune responses which cause cell dysfunction, lysis and death. They were considered likely candidate genes for KID and HID and in 2002, two groups reported three different missense mutations of the connexin 26 gene (*GJB2*) in 10 patients [5,6]. KID and HID shared the same connexin 26 mutation [7]. Recurrent and novel *GJB2* mutations have been recorded in 40 patients since [8–11], including the common pAsp50Asn mutation in 12 of 14 patients in one report [11].

Histopathology. Skin biopsy shows marked orthohyperkeratosis and acanthosis, focal parakeratosis and papillomatosis. Fungal and bacterial elements are frequently present within the keratin, and perinuclear vacuolation with keratohyaline clumping are minor features. Proliferating keratoses should be examined for signs of pseudoepitheliomatous hyperplasia and malignancy. There is a mild upper dermal inflammatory infiltrate with plasma cells, and atrophic or plugged hair follicles with scattered folliculitis and foreign body reaction reflect the widespread alopecia.



Fig. 19.27 KID syndrome in an 8-year-old boy. (Courtesy of Dr D.J. Atherton, Great Ormond Street Hospital for Children, London, UK.)

Immunohistochemistry for connexins expression in skin is informative.

Ultrastructural study has shown irregular clumped tonofilaments in lower epidermal layers with perinuclear distribution in the granular layer (similar to changes noted in ichthyosis hystrix) and indented keratinocyte nuclei [12]. Intercellular membrane-bound granules have been noted.

Clinical features. Many affected neonates have generalized erythema and some also have diffuse scaling and a leathery skin. The typical skin changes gradually develop during infancy with linear and spiny hyperkeratosis around the flexures, elbows and knees, and hystrix-like scaling on the limbs [12]. Scattered follicular hyperkeratoses appear on the trunk. Typical features are the evolution of symmetrical, well-demarcated hyperkeratotic and warty plaques on the scalp, ears, face (Fig. 19.27) and occasionally the trunk and limbs. Some patients develop thick perioral rugae, and an aged or leonine facies [13,14]. Keratotic, hyperplastic and inflammatory nodules may develop on the scalp, face, trunk and lower legs, and *in situ* and invasive squamous cell carcinoma arising within these dysplastic lesions have been reported in several KID patients in adult life (Fig. 19.28) [5,11,15–17]. A 37-year-old man died of metastatic squamous carcinoma of the skin; his daughter also has KID syndrome [16]. Squamous cell carcinoma of the tongue has occurred in three young patients [11,18,19] and a 28-year-old had a fatal malignant fibrous histiocytoma [20]. Multiple hair follicle tumours (including malignant progression to tricholemmal tumours) occurred in an adult with KID syndrome [21] and two further adult patients developed metastatic, malignant pilar tumours [22].



Fig. 19.28 KID syndrome: adult with squamous cell carcinoma on the arm. (Courtesy of Dr D.J. Atherton, Great Ormond Street Hospital for Children, London, UK.)

Most patients have extensive scarring alopecia of the scalp and loss of eyebrows, lashes and body hair resulting from follicular hyperkeratosis and atrophy. A reticulate PPK resembling grained leather is a characteristic feature, and progressive nail dystrophy and shedding may occur. Acneiform eruptions and cysts on the upper trunk are common, and chronic deep abscesses and discharging sinuses (follicular occlusion triad) are a distressing late complication in some [22]. Chronic cutaneous, granulomatous fungal and candidal infections may develop and contribute to the alopecia, nail dystrophy and body odour. Scabies was diagnosed in a father and daughter pair [16]. Death in infancy from overwhelming infection (viral, bacterial and mycotic) has been reported in at least four patients with KID syndrome [23–25]. No specific immune defect has been identified. Premature caries, oral leukoplakia, short stature, breast hypoplasia and cryptorchidism are occasional complications.

Congenital, severe sensorineural deafness is evident during infancy in most patients. Conductive hearing loss has also been reported [26,27]. In typical KID syndrome, progressive corneal vascularization occurs in early childhood, often after a febrile illness, and leads to photophobia and blindness by adolescence in 75% of patients [11,28]. Delayed onset of keratitis has been reported [27,28]. A progressive peripheral neuropathy has occurred in several adults with KID [13]. Intellect is unaffected and it is no surprise that the combined disabilities of deafness, blindness and disfigurement impose severe limitations and hardship on the individual.

The cutaneous features of the HID syndrome vary from a diffuse hyperkeratosis with pruritus to a generalized hystrix hyperkeratosis with mild PPK. Multiple squamous cell skin cancers occurred in an adult patient [7]. The deafness runs a similar course to that of KID syndrome and mild punctate keratitis has been noted in some patients (evidence that HID and KID are allelic disorders).

Diagnosis. KID/HID syndromes are clinical diagnoses, supported by audiological and ophthalmological evidence of neurosensory deafness and vascularizing keratitis in early childhood. In spite of

the occurrence of chronic skin infections in most and fatal sepsis in a subgroup of patients, consistent immune defects are not found. The differential diagnosis includes congenital erythrokeratoderma with deafness, ichthyosis hystrix and unusual ectodermal dysplasias. Typical HID syndrome must be differentiated from Sjögren–Larsson syndrome.

Genetics. Most reported cases of KID/HID syndrome have been sporadic, but autosomal dominant inheritance was evident in several families with KID [3,6,11,16,26,29] and one with HID syndrome [7]. A report of two affected sisters with consanguineous ancestors pointed to autosomal recessive transmission [30] but this sibship and half-sibs affected with KID could also be explained by gonadal mosaicism [31]. Germinal mosaicism was also suspected, but could not be verified, in the case of two adult sisters with unaffected parents; one of them also had an affected child [11]. Dizygotic twins with KID syndrome (who died in infancy) each had a heterozygous *GJB2* mutation which again was not detected in their parents [25].

The commonest *GJB2* mutation found in KID syndrome, p.Asp50Asn, occurs in 80% of patients and accounts for most of the familial cases [11,26]. These patients may have less severe skin disease but develop skin cancers [11]. A rare mutation, p.Ser17Phe, causes more extensive skin lesions and infections and one patient died from tongue cancer [11]. A different mutation, p.Gly45Glu, was found in four patients who died in infancy [10,24,25]. First trimester prenatal molecular diagnosis on a chorionic villus sample should be possible where the connexin mutation in the index case in a family has been defined.

Treatment. Early and frequent audiological and ophthalmological assessment of patients with KID and HID syndromes is necessary to enable appropriate treatments such as hearing aids, cochlear implants and speech therapy to be instituted [32]. The ocular lesions are treated topically with lubricants, tears, antibiotics, steroids and ciclosporin drops as indicated. Surgical procedures and corneal transplant for advanced keratitis have usually failed [27,29,33]. Keratolytics, urea and emollients have a limited role. Antiseptic baths and cleansers, intermittent antibiotic and antiviral therapy and prolonged systemic antifungal agents [34] all play an important part in controlling skin infections and odour, and regular bacteriology screening of the skin should guide the choice of antimicrobial treatment. Cleansing, débridement, dressings, excision and grafting of hyperplastic lesions may be needed and may reduce the potential for malignant transformation. Mohs microsurgery is appropriate for invasive malignancies. Systemic retinoids have been tried in several patients with variable success [12,16,29,35]. The potential of acitretin to reduce the skin cancer risk provides further justification for its use. Isotretinoin aggravated the keratitis in one patient [36] and caused headaches in another [12]. PUVA phototherapy was unhelpful in an adult patient [12].

References

1 Burns FS. A case of generalized congenital keratoderma with unusual involvement of eyes, ears and nasal and buccal mucous membranes. *J Cutan Dis* 1915; **33**: 255–60.

2 Skinner BA, Greist MC, Norins AL. The keratitis, ichthyosis and deafness (KID) syndrome. *Arch Dermatol* 1981; **117**: 285–9.

3 Caceres-Rios H, Tamayo-Sanchez L, Duran-Mckinster C *et al*. Keratitis, ichthyosis and deafness (KID syndrome): review of the literature and proposal of a new terminology. *Ped Dermatol* 1996; **13**: 105–13.

4 Schnyder UW. Ichthyosis hystrix typus Rheydt (ichthyosis hystrix gravior mit praktischer Taubheit). *Z Hautkr* 1977; **52**: 763–6.

5 van Steensel M, van Geel M, Nahuys M *et al*. A novel connexin 26 mutation in a patient diagnosed with keratitis–ichthyosis–deafness syndrome. *J Invest Dermatol* 2002; **118**: 724–7.

6 Richard G, Rouan F, Willoughby CE *et al*. Missense mutations in *GJB2* encoding connexin 26 cause the ectodermal dysplasia keratitis–ichthyosis–deafness syndrome. *Am J Hum Genet* 2002; **70**: 1341–8.

7 van Geel M, van Steensel M, Kuster W *et al*. HID and KID syndromes are associated with the same connexin 26 mutation. *Br J Dermatol* 2002; **146**: 938–42.

8 Yotsumoto S, Hashiguchi T, Chen X *et al*. Novel mutations in *GJB2* encoding connexin 26 in Japanese patients with keratitis–ichthyosis–deafness syndrome. *Br J Dermatol* 2003; **148**: 649–53.

9 Alvarez A, del Castillo I, Pera A *et al*. De novo mutation in the gene encoding keratitis–ichthyosis–deafnes syndrome. *Am J Med* 2003; **117**: 89–91.

10 Binder B, Hennies HC, Kraschl R *et al*. Connexin 26 mutation and keratitis–ichthyosis–deafness (KID) syndrome. *J Dtsch Dermatol Ges* 2005; **3**: 105–8.

11 Mazereeuw-Hautier J, Bitoun E, Chevrant-Breton J *et al*. Keratitis-ichthyosis-deafness syndrome: disease expression and spectrum of connexion 26 (*GJB2*) mutations in 14 patients. *Br J Dermatol* 2007; **156**: 1015–9.

12 Langer K, Konrad K, Wolff K. Keratitis, ichthyosis and deafness (KID) syndrome: report of three cases and a review of the literature. *Br J Dermatol* 1990; **122**: 689–97.

13 Rycroft RJG, Moynahan EJ, Wells RS. Atypical ichthyosiform erythroderma, deafness and keratitis: a report of two cases. *Br J Dermatol* 1976; **94**: 211–7.

14 Nousari H, Kimyai-Asadi A, Pinto JL. KID syndrome with features of ichthyosis hystrix. *Pediatr Dermatol* 2000; **17**: 115–7.

15 Madariaga J, Fromowitz F, Phillips M, Hoover HC. Squamous cell carcinoma in congenital ichthyosis with deafness and keratitis. *Cancer* 1986; **57**: 2026–9.

16 Grob JJ, Breton A, Bonafe JL *et al*. Keratitis, ichthyosis and deafness (KID) syndrome: vertical transmission and death from multiple squamous cell carcinomas. *Arch Dermatol* 1987; **123**: 777–82.

17 Hazen PG, Carney P, Lynch WS. Keratitis, ichthyosis and deafness syndrome with development of multiple cutaneous neoplasms. *Cutis* 1989; **28**: 190–1.

18 Lancaster L, Fournet LF. Carcinoma of the tongue in a child. *J Oral Maxillofac Surg* 1969; **27**: 269–70.

19 Baden EP, Alper JC. Ichthyosiform dermatosis, keratitis and deafness. *Arch Dermatol* 1977; **113**: 1701–4.

20 Carey AB, Burke WA, Park HK. Malignant fibrous histiocytoma in keratitis, ichthyosis and deafness syndrome. *J Am Acad Dermatol* 1988; **19**: 1124–6.

21 Kim K-H, Kim J-S, Piao Y-J *et al*. Keratitis ichthyosis and deafness syndrome with development of multiple hair follicle tumours. *Br J Dermatol* 2002; **147**: 139–43.

22 Nyquist GG, Mumm C, Grau R *et al*. Malignant proliferating pilar tumours arising in KID syndrome: a report of two patients. *Am J Med Genet* 2007; **143**: 734–41.

23 Gilliam A, Williams ML. Fatal septicaemia in an infant with keratitis, ichthyosis and deafness syndrome. *Pediatr Dermatol* 2002; **19**: 232–6.

24 Janecke AR, Hennies HC, Gunther B *et al*. *GJB2* mutations in keratitis-ichthyosis-deafness syndrome including its fatal form. *Am J Med Genet* 2005; **133**: 128–31.

25 Jonard L, Feldmann D, Parsy C *et al*. A familial case of Keratitis-Ichthyosis-Deafness (KID) syndrome with the *GJB2* mutation G45E. *Eur J Med Genet* 2008; **51**: 35–43.

26 Kelly B, Lozano A, Altenberg G *et al*. Connexin 26 mutation in keratitis-ichthyosis-deafness (KID) syndrome in mother and daughter with combined conductive and sensorineural hearing loss. *Int J Dermatol* 2008; **47**: 443–7.

27 McGrae JD Jr. Keratitis, ichthyosis and deafness syndrome with adult onset of keratitis component. *Int J Dermatol* 1990; **29**: 145–6.

28 Messmer EM, Kenyon KR, Rittinger O *et al*. Ocular manifestations of keratitis-ichthyosis-deafness (KID) syndrome. *Ophthalmology* 2005; **112**: 1–6.

29 Nazarro V, Blanchet-Bardon C, Lorette G, Civatte J. Familial occurrence of KID (keratitis, ichthyosis, deafness) syndrome: case reports of a mother and daughter. *J Am Acad Dermatol* 1990; **23**: 385–8.

30 Legrand I, Litoux P, Quere M *et al*. Un syndrome rare oculo-auriculo-cutané (syndrome du Burns). *J Fr Ophthalmol* 1982; **5**: 441–5.
31 Restano L, Cambiaghi S, Tadini G. The pattern of inheritance in KID syndrome. *Pediatr Dermatol* 1999; **16**: 164.
32 Choung YH, Shin YR, Kim HJ *et al*. Cochlear implantation and connexin expression in the child with keratitis-ichthyosis-deafness syndrome. *Int J Ped Otorhinolaryngol* 2008; **72**: 911–5.
33 Watanabe D, Zako M, Tamada Y *et al*. A case of keratitis-ichthyosis-deafness (KID) syndrome. *Int J Dermatol* 2007; **46**: 400–2.
34 Shiraishi S, Murakami S, Miki Y. Oral fluconazole treatment of fungating candidiasis in the keratitis-ichthyosis-deafness (KID) syndrome. *Br J Dermatol* 1994; **131**: 904–7.
35 Bondeson ML, Nystrom AM, Gunnarsson U *et al*. Connexin 25 (*GJB2*) mutations in two Swedish patients with atypical Vohwinkel (mutilating keratoderma plus deafness) and KID syndrome both extensively treated with acitretin. *Acta Derm Venereol* 2006; **86**: 503–8.
36 Hazen PG, Carney JM, Langston RH, Meisler DM. Corneal effects of isotretinoin: possible exacerbation of corneal neovascularization in a patient with the keratitis, ichthyosis, deafness syndrome. *J Am Acad Dermatol* 1986; **14**: 141–2.

CHILD syndrome (MIM 308050)

This very rare disorder was reported in 1963, 1968 (in siblings) and 1974 [1–3]. The acronym CHILD, coined by Happle, describes the characteristic *c*ongenital *h*emidysplasia with (lateralizing) *i*chthyosiform erythroderma (or naevus) and unilateral *l*imb *d*efects, mainly skeletal hypoplasia [4]. The skin lesion more often resembles a unilateral inflammatory epidermal naevus, rather than an ichthyosis. Happle suggested that it was a unique inherited naevus determined by an X-linked dominant mutation, as the female : male ratio in the then 20 reported cases was 19 : 1 (indicating lethality in male embryos) and skin involvement may occur in Blaschko's lines [5]. Two male patients are known of, including a 2-year-old Egyptian boy, who had a normal karyotype [6]. Over 40 cases have been reported since the 1960s.

Aetiology. Keratin expression studies indicate a hyperproliferative epidermis [7]. Abnormal differentiation markers in lesional skin normalized in culture whereas abnormal intercellular structures and communication did not [8]. Defective fibroblast activity, increased prostaglandin E_2 synthesis in lesional skin [9] and defective peroxisomal structure and function in lesional skin were reported [10] and similarities to X-linked dominant ichthyosis (Conradi–Hünermann–Happle syndrome) noted. Indeed, abnormal 3β-hydroxysteroid-Δ8,Δ7-isomerase activity was found in one case [11] but the phenotype of each condition is so distinctive that they should not be confused. Reduced NAD(P)H steroid dehydrogenase (NSDHL) due to point mutations in the *NSDHL* gene on chromosome Xq28, has been identified as the cause of CHILD syndrome [12]. *NSDHL* encodes a novel 3β-hydroxysteroid dehydrogenase and the animal model, the 'bare patches' mouse, carries a similar mutation [13]. This enzyme is involved in cholesterol biosynthesis and is the precursor of 3β-hydroxysteroid-Δ8,Δ7-isomerase, which is mutated in Conradi–Hünermann–Happle syndrome. An unusual case of CHILD syndrome with virtually symmetrical lesions was also found to have this mutation [14]. X-linked dominant genodermatoses usually show a pattern of lesions in Blaschko's lines due to the Lyon effect of random X-chromosome inactivation but the lateralizing form of the lesions in CHILD syndrome suggests that the *NSDHL* gene influences the development of body symmetry in the early embryo [12]. The combined effect of random X-inactivation and migration of a clone of organizer stem cells which controls an area of skin and visceral development may explain the unique lateralization of the CHILD naevus and syndrome [15].

Histopathology. Light and electron microscopy of lesional skin in CHILD syndrome shows characteristic features. The epidermis is acanthotic with areas of hyper- and parakeratosis. Neutrophilic collections in the stratum corneum and a dermal lymphocytic inflammatory reaction are suggestive of psoriasis. Hair follicles are plugged, and foamy macrophages may be seen in distended dermal papillae. Foam cells were also seen in a gastric mucosal biopsy in one patient [4]. These changes are similar to those described as verruciform xanthoma [5,16]. Ultrastructural features include lipid vacuoles in granular layer keratinocytes, keratin filament defects, disrupted mitochondria, patchy disruption of lamellar bodies, vacuolated intercellular lamellae and lamellated structures with cytoplasmic lipid-containing vacuoles in fibroblasts and macrophages [7,10,17].

Clinical features. The skin lesions are usually noted in the first days of life as an inflamed, hyperkeratotic, crusted or verrucous plaque covering a large area or most of one side of the body, with sharp demarcation at the edge and midline. Surface scale may have a waxy, yellow appearance. Linear bands of normal skin on the affected side and of ichthyotic scaly red skin on the 'normal' side may occur, and suggest a mosaic somatic mutation [4,7]. The flexures on the affected side are preferentially, and often persistently, involved (ptychotropism), and the head is usually spared. The skin lesions may progress in the first year of life and then improve with time. One patient with almost symmetric but typical skin lesions has been reported [14] and a report of a patient with left-sided skin involvement implies that most are affected on the right side of the body [18]. Unilateral alopecia and nail dystrophy may occur. Various other defects, some of which may prove lethal, include mainly ipsilateral congenital heart and pulmonary disease, spina bifida, brainstem, intestinal and renal defects [3–5,18]. Cataracts do not occur. The most common skeletal defect is ipsilateral limb hypoplasia (phocomelia or amelia) but truncal skeletal hypoplasia and body asymmetry is also characteristic. Occasional patients have minimal or no skeletal defects. Calcific stippling of epiphyses, as seen in chondrodysplasia punctata syndromes including Conradi–Hünermann–Happle syndrome, may be detected on X-rays in affected infants. A sibling of an affected patient had bilateral limited skin disease in the absence of extracutaneous features [19]. Bilateral symmetrical lesions were reported in one patient with a novel *NSDHL* mutation [14]. The lesions, when localized, may be mistaken for an epidermal naevus or inflammatory linear verrucous epidermal naevus (ILVEN), lichen striatus or linear psoriasis. Extracutaneous features may suggest the epidermal naevus syndrome.

Genetics. The theory of X-linked dominant inheritance is convincing and explains the apparent lethality in male embryos [5]. Male patients with CHILD syndrome may have Kleinfelter's syndrome or have suffered a post-zygotic somatic mutation in an X chromosome, which could be passed to a daughter if it were also

in germinal tissue [6]. The predominantly unilateral and mosaic distribution is attributed to the Lyon effect of random X chromosome inactivation and a presumed role for the *NSDHL* gene in determining body symmetry in early embryonic development. Four different nonsense and missense *NSDHL* mutations were found in six patients including a mother–daughter pair [12]. Affected siblings were recorded [2]. An early teratogenic insult and syndromes associated with limb reduction defects must be included in the differential diagnosis.

Treatment. Emollients, urea compounds and keratolytics are helpful. Retinoid therapy and methotrexate have improved the skin lesions in individual patients [5,17]. Surgical excision of skin lesions with grafting with a good result was reported in one patient in Happle's original report [4] but dermabrasion was unsuccessful in another [6]. Orthopaedic procedures may improve limb function [6].

References

1 Rossman RE, Shapiro EM, Freeman RG. Unilateral ichthyosiform erythroderma. *Arch Dermatol* 1963; **88**: 567–71.

2 Falek A, Heath CW Jr, Ebbin A *et al*. Unilateral limb and skin deformities with congenital heart disease in two siblings: a lethal syndrome. *J Pediatr* 1968; **73**: 910–3.

3 Tang TT, McCreadie SR. Congenital hemidysplasia with ichthyosis. *Birth Defects Orig Art Ser* 1974; **10**: 257–61.

4 Happle R, Koch H, Lenz W. The CHILD syndrome: congenital hemidysplasia, ichthyosiform erythroderma and limb defects. *Eur J Pediatr* 1980; **134**: 27–33.

5 Happle R, Mittag H, Kuster W. The CHILD nevus: a distinct skin disorder. *Dermatology* 1995; **191**: 210–6.

6 Happle R, Effendy I, Megahed M *et al*. CHILD syndrome in a boy. *Am J Med Genet* 1996; **62**: 192–4.

7 Hashimoto K, Topper S, Sharata H, Edwards M. CHILD syndrome: analysis of abnormal keratinization and ultrastructure. *Pediatr Dermatol* 1995; **12**: 116–29.

8 Dale BA, Kimball JR, Fleckman P *et al*. CHILD syndrome: lack of expression of epidermal differentiation markers in lesional ichthyotic skin. *J Invest Dermatol* 1992; **98**: 442–9.

9 Goldyne ME, Williams ML. CHILD syndrome: phenotypic dichotomy in eicosanoid metabolism and proliferative rates among cultured dermal fibroblasts. *J Clin Invest* 1989; **84**: 357–60.

10 Emami S, Rizzo WB, Hanley KP *et al.* Peroxisomal abnormality in fibroblasts from involved skin of CHILD syndrome: case study and review of peroxisomal disorders in relation to skin diseases. *Arch Dermatol* 1992; **128**: 1213–22.

11 Braverman N, Lin P, Moebius F *et al.* Mutations in the gene encoding 3β-hydroxysteroid-Δ8,Δ7-isomerase cause X-linked dominant Conradi–Hünermann syndrome. *Nat Genet* 1999; **22**: 291–4.

12 Konig A, Happle R, Bornholdt D *et al.* Mutations in the NSDHL gene, encoding a 3β-hydroxysteroid dehydrogenase, cause CHILD syndrome. *Am J Med Genet* 2000; **90**: 339–46.

13 Liu XY, Dangel AW, Kelley RI *et al.* The gene mutated in bare patches and striated mice encodes a novel 3β-hydroxysteroid dehydrogenase. *Nat Genet* 1999; **22**: 182–7.

14 Konig A, Happle R, Fink-Puches R *et al.* A novel missense mutation of NSDHL in an unusual case of CHILD syndrome showing bilateral, almost symmetrical involvement. *J Am Acad Dermatol* 2002; **46**: 594–6.

15 Happle R. Mosaicism in human skin: understanding the patterns and mechanisms. *Arch Dermatol* 1993; **129**: 1460–70.

16 Palestine RF, Winklemann RK. Verruciform xanthoma in an epidermal nevus. *Arch Dermatol* 1982; **118**: 686–91.

17 Hebert AA, Esterly NB, Holbrook KA *et al*. The CHILD syndrome: histologic and ultrastructural studies. *Arch Dermatol* 1987; **123**: 503–9.

18 Hummel M, Cunningham D, Mullett C *et al*. Left-sided CHILD syndrome caused by a mutation in the *NSDHL* gene. *Am J Med Genet* 2003; **122A**: 246–51.

19 Poiares Baptista A, Cortesao JM. Naevus epidermique inflammatoire variable. *Ann Dermatol Vénéréol* 1979; **106**: 443–50.

Ichthyosis follicularis with alopecia and photophobia (MIM 308205)

Isolated follicular ichthyosis is an ill-defined and controversial entity and may overlap with keratosis pilaris and coexistent ichthyosis vulgaris. On the other hand, the syndrome of *i*chthyosis *f*ollicularis with *a*lopecia and *p*hotophobia (IFAP) is a well-recognized but very rare ectodermal disorder, which was first reported by MacLeod in 1909 [1]. Up to 30 cases have been recorded, the majority in males.

Histopathology. Skin biopsy shows follicular plugging and orthohyperkeratosis with a normal granular layer (which is thickened at the infundibulum), effaced rete ridges and thin dermis. Absence of sebaceous glands, atrophy of hair follicles with perifollicular lymphocytic infiltrates and reduced numbers of sweat glands are characteristic findings [1,2]. No specific ultrastructural features have been noted, although disrupted intercellular connections and reduction in the number and size of desmosomes has been reported [3,4]. Histology of the cornea showed avascular scarring and amyloid deposition [5]. Electron microscopy of the adult cornea revealed desmosome, tonofilament and anchoring fibril anomalies, a thickened basement membrane and absent Bowman's capsule [3,5]. These changes reflect a disturbance in epithelial cell adhesion.

Clinical features. The phenotype is variable, but patients have a striking facial similarity. One presented at birth with a collodion membrane [2]. All have generalized, non-inflammatory follicular keratoses, persistent non-cicatricial scalp, eyebrow, eyelash and body alopecia, and severe photophobia from birth. Alopecia may not develop until childhood [1]. The keratotic papules are most pronounced on the knees, elbows and fingers, and follicular, spiny (filiform) projections develop over extensor surfaces. Generalized xerosis and cheilitis, lamellar scaling, psoriasis-like lesions, skin infections and pruritus are common, and the keratoses may improve in time. Pregnancy-related vulvitis occurred in one patient and her affected daughter developed psoriasiform plaques in early childhood [3]. Teeth, nails and sweating are generally normal, although one infant had natal teeth [6], and nail dystrophy does occur [2,3]. Palmoplantar erythema was present in one case [2]. Severe photophobia, progressive reduction in visual acuity, nystagmus and head tilt are caused by punctate keratitis, which leads to corneal erosions and vascularization. Bilateral cataracts were noted in a 3-year-old girl with IFAP syndrome [4] and retinal vascular tortuosity was regarded as a marker of the heterozygous state in a female carrier of the IFAP mutation [7]. Occasional features include atopy [1,2,6], recurrent chest infections, inguinal hernia, growth and psychomotor retardation [7], hypotonia and seizures [5,8]. Hearing is normal.

The mothers and sister of an affected boy both had linear follicular keratoses with scalp and body alopecia reflecting random X-chromosome inactivation producing a mosaic phenotype, the Lyon effect [9].

Diagnosis. IFAP must be distinguished from the keratosis pilaris variants, keratosis follicularis spinulosa decalvans (KFSD) and

keratosis pilaris rubra atrophicans facei, which are associated with inflammatory scarring alopecia of the scalp and eyebrows. Ocular disease is prominent in KFSD, the KID syndrome and IFAP, but palmoplantar hyperkeratosis is not a feature of IFAP. Skin histology helps to exclude other congenital ichthyoses, such as ichthyosis vulgaris. An autosomal recessive congenital atrichia with papular lesions has been reported [10]. Hereditary mucoepithelial dystrophy/dysplasia shares certain clinical traits with IFAP, but the striking mucosal changes do not occur in IFAP [11]. A syndrome comprising alopecia, contractures, dwarfism, prominent skeletal abnormalities, ectrodactyly, facial dysmorphism and mental retardation (ACD syndrome MIM 203550) has been described in up to seven patients and in one, ichthyosis and photophobia indicated crossover between the two syndromes [12].

Genetics. X-linked recessive inheritance was proposed in the original family with three affected male siblings [1] and in the case of a severely affected boy who reportedly had two affected maternal male relatives [8]. Mosaic features in the mother and sister of a boy with IFAP also points to X-linked transmission [9]. A maternal uncle had died in infancy with the same condition. However, several girls with typical lesions and generalized skin involvement have been reported [4,13,14]; as one had an affected father, autosomal dominant transmission was suggested in that family [13]. This pattern was evident in an affected Japanese mother and daughter [3].

Treatment. Keratolytics, urea preparations and emollients are used. Topical calcipotriol may improve psoriasiform lesions. Oral retinoid therapy produced a partial response (improvement in the ichthyosis and corneal erosions) in two cases [2,15], while topical retinoid proved too irritant [2]. Early and regular ophthalmological assessment is necessary.

References

1 MacLeod JMH. Three cases of ichthyosis follicularis associated with baldness. *Br J Dermatol* 1909; **21**: 165–89.

2 Hamm H, Meinecke P, Traupe H. Further delineation of the ichthyosis follicularis, atrichia and photophobia syndrome. *Eur J Pediatr* 1991; **150**: 627–9.

3 Sato-Matsumura K, Matsumura T, Kumakiri M *et al*. Ichthyosis follicularis with alopecia and photophobia in a mother and daughter. *Br J Dermatol* 2000; **142**: 157–62.

4 Tsolia M, Aroni K, Konstantopoulou I *et al*. Ichthyosis follicularis with alopecia and photophobia in a girl with cataract: histological and electron microscopy findings. *Acta Dermatol Venereol* 2005; **85**: 51–5.

5 Cursiefen C, Schlotzer-Schrehardt U, Holbach LM *et al*. Ocular findings in ichthyosis follicularis, atrichia and photophobia syndrome. *Arch Ophthalmol* 1999; **117**: 681–4.

6 Eramo LR, Esterly NB, Zieserl EJ *et al*. Ichthyosis follicularis with alopecia and photophobia. *Arch Dermatol* 1985; **121**: 1167–74.

7 Traboulsi E, Waked N, Megarbane H *et al*. Ocular findings in ichthyosis follicularis-alopecia-photophobia (IFAP) syndrome. *Ophthal Genet* 2004; **25**: 153–6.

8 Bibas-Bonet H, Fauze R, Boente MC *et al*. IFAP syndrome plus seizures, mental retardation and callosal hypoplasia. *Pediatr Neurol* 2001; **24**: 228–31.

9 Konig A, Happle R. Linear lesions reflecting lyonization in women heterozygous for IFAP syndrome (ichthyosis follicularis with atrichia and photophobia). *Am J Med Genet* 1999; **85**: 365–8.

10 Kanzler MH, Rasmussen JE. Atrichia with papular lesions. *Arch Dermatol* 1986; **122**: 565–7.

11 Rothe MJ, Lucky AW. Are ichthyosis follicularis and hereditary mucoepithelial dystrophy related diseases? (Letter). *Pediatr Dermatol* 1995; **12**: 195.

12 Schell-Apachik C, Hardt M, Ertl-Wagner B *et al*. Expanding the phenotype of alopecia-contractures-dwarfism, mental retardation syndrome (ACD syndrome): description of an additional case and review of the literature. *Eur J Pediatr* 2008; **167**: 1057–62.

13 Rothe MJ, Weiss DS, Dubner BH *et al*. Ichthyosis follicularis in two girls: an autosomal dominant disorder. *Pediatr Dermatol* 1990; **7**: 287–92.

14 Cambiaghi S, Barbareschi M, Tadini G *et al*. Ichthyosis follicularis with atrichia and photophobia in two unrelated female patients. *J Am Acad Dermatol* 2002; **46**: S156–8.

15 Khandpur S, Bhat R, Hamam M. Ichthyosis follicularis with alopecia and photophobia (IFAP) syndrome treated with acitretin. *J Eur Acad Dermatol Venereol* 2005; **19**: 759–62.

Neu–Laxova syndrome (MIM 256520)

A rare and striking ichthyosiform disorder which proves lethal in the neonate was first reported by Neu in 1971 [1] and Laxova in 1972 [2]. They each described three siblings with microcephaly and multiple congenital defects. There have been 60 or more cases reported since [3,4]. It is regarded as a neuroectodermal dysplasia with a variable phenotype.

Clinical features. Affected neonates are usually premature and often stillborn. They are severely growth retarded and microcephalic with a characteristic facial dysmorphism and sloping forehead. A thick, parchment-like membrane covers the baby at birth and restricts movement and breathing. It fissures and sheds within days or weeks, revealing erythematous and ichthyotic skin. Generalized oedema, desquamation and erosions are the predominant findings in some neonates [5]. Flexion deformities of the limbs are common and the hands and feet are swollen. Digital, ocular (proptosis, ectropion), cardiac and genitourinary defects have been recorded [3]. X-rays reveal osteoporosis and brain scans confirm microcephaly with other CNS defects. There are ongoing feeding and respiratory problems requiring intensive neonatal care [6]. All reported cases of Neu–Laxova syndrome have died within weeks from sepsis or respiratory failure; the oldest survivor lived for 134 days [5].

Diagnosis. Second trimester prenatal diagnosis depends on detecting ultrasound and X-ray signs of growth retardation, head and skeletal defects, fetal oedema and, in some pregnancies, polyhydramnios [3,7–9]. Skin biopsy shows epidermal and dermal atrophy and absence of sebaceous glands [5].

Although the neonatal presentation of Neu–Laxova syndrome is distinctive, other conditions to be considered include collodion baby, harlequin ichthyosis, restrictive dermopathy, COFS (cerebro-oculo-facio-skeletal) syndrome and Smith–Lemli–Opitz syndrome [4].

Genetics. Males and females are equally affected and 28% in one review had consanguineous parents, suggesting autosomal recessive inheritance [3]. Many cases come from Turkey and Egypt and several families with multiple affected siblings are recorded [1–4,10]. No chromosomal abnormality has been detected and the cause is unknown.

References

1 Neu RL, Kajii T, Gardner LI *et al*. A lethal syndrome of microcephaly with multiple congenital anomalies in three siblings. *Pediatr* 1971; **47**: 610–2.

2 Laxova R, Ohdra PT, Timothy JAD. A further example of a lethal autosomal recessive syndrome in sibs. *J Ment Defic Res* 1972; **16**: 139–43.
3 Manning MA, Cunniff CM, Colby CE *et al*. Neu–Laxova syndrome: detailed prenatal diagnostic and post-mortem findings and literature review. *Am J Med Genet* 2004; **15**: 240–9.
4 Ugras M, Kocak G, Ozcan H. Neu–Laxova syndrome: a case report and review of the literature. *J Eur Acad Dermatol Venereol* 2006; **20**: 1126–8.
5 Hirota T, Hirota Y, Asagami C *et al*. A Japanese case of Neu–Laxova syndrome. *J Dermatol* 1998; **25**: 163–6.
6 Hickey P, Piantenida E, Lentz-Kapua S *et al*. Neu–Laxova syndrome: a case report. *Ped Dermatol* 2003; **20**: 25–7, 78–80.
7 Shapiro I, Borochowitz Z, Degani S *et al*. Neu–Laxova syndrome: prenatal ultrasonographic diagnosis, clinical and pathological studies and new manifestations. *Am J Med Genet* 1992; **43**: 602–5.
8 Rode ME, Mennuti MT, Giardine RM *et al*. Early ultrasound diagnosis of Neu–Laxova syndrome. *Prenat Diagn* 2001; **21**: 575–80.
9 Driggers RW, Isbister S, McShane C *et al*. Early second trimester prenatal diagnosis of Neu–Laxova syndrome. *Prenat Diagn* 2002; **22**: 118–20.
10 Abdel-Meguid N, Temtamy SA. Neu–Laxova syndrome in two Eygptian families. *Am J Med Genet* 1991; **41**: 30–1.

CHIME syndrome (MIM 280000)

In 1983, Zunich and Kaye [1] reported a child with migratory ichthyosiform erythroderma, retinal colobomas, neurological disease, fine sparse hair and dental abnormalities—the acronym CHIME derives from *c*oloboma, *h*eart disease, *i*chthyosis, *m*ental retardation and *e*ar defects. Further cases have been described [2–4] and occurrence in a sibling pair suggests autosomal recessive inheritance. Generalized pruritus, erythema and scaling develop within the first month, and figurate, red, scaly and itchy patches migrate on the head and body from early childhood. Palms and soles are thickened; the scalp hair is fine, sparse and hypopigmented. Cranial defects, alopecia, hypertelorism, a broad nasal bridge, wide mouth, full lips and wide-spaced teeth combine in a characteristic facial appearance. Neurological features include hearing loss, seizures, severe developmental delay and outbursts of violent behaviour. A 4-year-old with CHIME syndrome and renal anomalies developed leukaemia [5]. CHIME syndrome is regarded as a cancer-prone genodermatosis. Degenerative changes in the myelin sheaths of cutaneous nerves were detected ultrastructurally. Impaired epidermal maturation was associated with a distinctive perinuclear oedema and nuclear pyknosis in upper granular keratinocytes [4]. A similar syndrome of generalized ichthyosis, mental retardation, hypotonia and craniofacial anomalies occurred in a Turkish boy of consanguineous parents [6]. Abnormal myelination also occurred in a patient with ichthyosis associated with congenital sensory neuropathy [7].

References

1 Zunich J, Kaye CI. New syndrome of congenital ichthyosis with neurologic abnormalities. *Am J Med Genet* 1983; **15**: 331–3.
2 Zunich J, Ladda RL. Ichthyosis, coloboma, heart defect, deafness, mental retardation. In: Buyse ML, ed. *Birth Defects Encyclopedia.* Cambridge, MA: Blackwell Scientific Publications, 1990: 945–6.
3 Shashi V, Zunich J, Kelly TE *et al*. Neuroectodermal (CHIME) syndrome: an additional case with long term follow up of all reported cases. *J Med Genet* 1995; **32**: 465–9.
4 Tinschert S, Anton-Lamprecht I, Albrecht-Nebe H *et al*. Zunich neuroectodermal syndrome: migratory ichthyosiform dermatosis, colobomas and other abnormalities. *Pediatr Dermatol* 1996; **13**: 363–71.
5 Schnur RE, Greenbaum BH, Heymann WR *et al*. Acute lymphoblastic leukemia in a child with the CHIME neuroectodermal dysplasia syndrome. *Am J Med Genet* 1997; **72**: 24–9.
6 Devriendt K, van den Oord J, De Vos R *et al*. Ichthyosis, characteristic appearance, mental retardation syndrome with distinct histological skin abnormalities. *Am J Med Genet* 1996; **61**: 127–30.
7 Quinlivan R, Robb S, Hughes RA *et al*. Congenital sensory neuropathy in association with ichthyosis and anterior chamber cleavage syndrome. *Neuromusc Disord* 1993; **3**: 217–21.

Sporadic genetic syndromes with ichthyosis

There are several reports of individuals or small groups with congenital ichthyosis occurring in association with extracutaneous defects that do not fit within the classification of recognized inherited ichthyoses. These are discussed under headings indicating the main non-cutaneous features but some may belong to more than one category.

Ichthyosis associated with neurological and ocular disorders

The rare type 2 variant of the lysosomal storage disorder, Gaucher's disease, is a progressive, multisystem condition with neurologic complications which prove fatal. It presents with collodion membrane and evolves to ichthyosis which may be subclinical [1]. Ultrastructural abnormalities in lamellar body and membrane formation and defects in ceramide production underlie the epidermal dysfunction and are due to glucocerebroside mutations [2,3].

Generalized ichthyosis with mental retardation and spasticity was noted in a patient in whom Sjögren–Larsson syndrome was excluded [4], and a similar syndrome in identical twins was also associated with cortical atrophy, epilepsy and a hearing defect [5]. An inbred Swedish family was reported in which there were two siblings and an aunt and uncle with ichthyosis, mental retardation, alopecia, eclabiun and ectropion [6]. Ichthyosis was noted in a patient with Dubowitz syndrome, which causes microcephaly and growth retardation [7], and in a boy with microcephaly and lentigines, diagnosed as LEOPARD syndrome [8].

A syndrome comprising *a*lopecia, *c*ontractures, *d*warfism, prominent skeletal abnormalities, ectrodactyly, facial dysmorphism and mental retardation, has been described in up to seven patients (ACD mental retardation syndrome, MIM 203550). One patient had follicular ichthyosis and photophobia suggesting a crossover between ACD and IFAP syndromes [9].

Retinitis pigmentosa associated with congenital ichthyosis and other defects was reported in two women [10], and another adult female patient had ocular albinism, Noonan's syndrome and ichthyosiform erythroderma (with collodion baby presentation) [11].

An infant with ichthyosis and deafness may have had KID syndrome but he died of malnutrition brought about by Hirschsprung's disease [12]. A patient with ichthyosis, deafness and mental retardation had, in addition, dental and skeletal defects and developed thyroid cancer [13]. A family with a variable syndrome of unspecified deafness, microphthalmos and ichthyosis is recorded [14]. A syndrome of cerebral dysgenesis, neuropathy, deafness, ichthyosis and keratoderma (CEDNIK syndrome, MIM 609528) was reported in two consanguineous Arab families in Israel and attributed in the *SNAP29* gene mutation [15]. A child with a complex neurodevelopmental disorder has ichthyosis affecting the legs, dorsal feet and hands (Fig. 19.29). The known 'neuroichthyoses' have been excluded.



Fig. 19.29 Congenital ichthyosis in a teenage girl with a complex neurodevelopmental syndrome.

Ichthyosis associated with renal disease

Passwell reported three siblings of consanguineous parents who had ichthyosiform erythroderma with atrophic and pigmentary changes and blisters over the dorsal hands and feet. They had a generalized aminoaciduria, hypergammaglobulinaemia, dental defects, dwarfism, neurological problems and mental retardation [16,17]. Skin biopsy revealed vacuolation in basal keratinocytes, reminiscent of neutral lipid storage disease, and collagen disruption. Hair microscopy was normal, excluding a trichothiodystrophy syndrome.

Congenital ichthyosis has also occurred with renal parenchymal disease, growth and mental retardation and hypogonadism in three siblings of another family [18]. A possibly autosomal dominant syndrome of renal disease, prolinuria, nerve deafness and a poorly-defined ichthyosis affected a third family [19]. Fanconi's syndrome with jaundice occurred in association with congenital ichthyosis [20].

Ichthyosis and skeletal defects

The ICE syndrome, reported in five subjects in four generations of one family, consisted of *i*chthyosis vulgaris, fullness of the *c*heeks and thinning of the *e*yebrows [21]. Other dysmorphic features occurred, and skeletal abnormalities included kyphoscoliosis. Accessory ribs, cortical thickening, arthrogryposis and osteopetrosis have been recorded in individual patients with ichthyosis [13,22–24].

Ichthyosis with immune defects

Patients with ichthyosiform erythroderma associated with defective chemotaxis have been described [25]. Abnormal T cells, hypogammaglobulinaemia, neurological defects, eczema and fungal infection were reported in an infant boy who died at 9 months (cf. Ommen's syndrome) [26]. Three patients with congenital ichthyosiform erythroderma and IgM or IgG deficiencies had recurrent respiratory infections [27].

Ichthyosis and cancer

Apart from the increased incidence of skin and oral cancer in KID and Netherton's syndromes, skin malignancy as a complication of genetic ichthyosis is rare. Two patients with an ill-defined reticular ichthyosis, micropinnae, universal alopecia and ectropion (MAUIE syndrome) developed squamous cell carcinomas in early adult life [28,29]. A 32-year-old man with an autosomal recessive ichthyosisform erythroderma had eight skin cancers, mainly squamous cell carcinomas on the bald scalp [28]. Two adult Japanese patients with congenital ichthyosiform erythroderma due to *ABCA12* mutations developed multiple skin malignancies, including melanoma, squamous cell carcinoma and lymphoma in one [30]. The predisposition to testicular cancer in XLRI is likely to be related to the endocrine dysfunction in that disorder. Non-cutaneous malignancies, including thyroid cancer [13], medulloblastoma [31] and leukaemia [32,33], have been reported in patients with congenital ichthyoses.

Miscellaneous

Ichthyosiform erythroderma from early infancy has been reported in 50% or more of patients with Shwachman's syndrome (MIM 260400). The main features are exocrine pancreatic insufficiency, growth retardation, bone marrow failure and increased risk of leukaemia [33,34]. Granular droplets in keratinocytes and defective lamellar bodies were seen ultrastructurally [34] and it is caused by mutations in the *SBDS* gene on chromosome 7q11 [33]. Migratory ichthyosis and pruritus associated with type 2 diabetes mellitus and acanthosis nigricans occurred in a large

consanguineous family [35]. A sibship with an autosomal recessive ichthyosis, developmental delay, deafness and cirrhosis was reported in 1971 but this syndrome (Desmons' syndrome) was, in later reports, included in the spectrum of KID syndrome [36]. Single cases of ichthyosis, hepatomegaly and cerebellar degeneration [37] and a syndrome of erythrodermic ichthyosis associated with palmoplantar keratoderma, hypogonadism and hepatosplenomegaly have been reported [38]. Dilated cardiomyopathy was reported in association with congenital ichthyosiform erythroderma in an infant (possibly related to malnutrition) and also in an 8-year-old with Netherton's syndrome [39]. Two related inbred Moroccan families with diffuse non-erythrodermic ichthyosis, scarring alopecia, sclerosing cholangitis and eosinophil vacuolation showed linkage to chromosome 3q27–q28 [40]. The NISCH (*n*eonatal *i*chthyosis, *s*clerosing *ch*olangitis) syndrome (MIM 607626) is now known to be due to mutations in claudin 1, a tight junction protein [41]. The autosomal dominant Stormorken's syndrome (MIM 185070), affecting four generations of a family, included ichthyosis, abnormal platelet function, asplenism, migraine, fatigue and dyslexia [42]. It may, however, be an ichthyosis vulgaris variant. Ichthyosis is apparent in some patients with ectodermal dysplasias [43,44]. Two reports of ichthyosis vulgaris-like scaling associated with follicular atrophoderma with pitted scars on the hands and face, hypotrichosis, hypohidrosis (in a sibship of five with consanguineous parents) plus woolly hair in a sixth case (MIM 602400) have been published [45,46]. Three of eight children of first cousin parents had ichthyosis, brittle hair (pili torti), photophobia and dental defects (MIM 610765). A mutation of matriptase, a transmembrane serine protease was identified [47].

References

1 Stone DL, Carey WF, Christodoulou J *et al*. Type 2 Gaucher disease: the collodion baby phenotype revisited. *Arch Dis Child Fetal Neonatal Ed* 2000; **82**: F163–6.

2 Sidransky E, Fartasch M, Lee RE *et al*. Epidermal abnormalities may distinguish type 2 from type 1 and type 3 of Gaucher disease. *Pediatr Res* 1996; **39**: 134–41.

3 Stone DL, Tayebi N, Orvisky E *et al*. Glucocerebrosidase gene mutations in patients with type 2 Gaucher disease. *Hum Mutat* 2000; **15**: 181–8.

4 Koone MD, Rizzo WB, Elias PM *et al*. Ichthyosis, mental retardation and asymptomatic spasticity: a new neurocutaneous syndrome with normal fatty alcohol NAD oxidoreductase activity. *Arch Dermatol* 1990; **126**: 1485–90.

5 Amano R, Ohtsuka Y, Ohtahara S. Monozygotic twin patients with congenital ichthyosis, microcephaly, spastic quadriplegia, myoclonus, EEG abnormalities. *Pediatr Neurol* 1995; **12**: 255–9.

6 Jagell SF, Holmgren G, Hofer PA. Congenital ichthyosis with alopecia, eclabion, ectropion and mental retardation: a new syndrome. *Clin Genet* 1987; **31**: 102–8.

7 Kato T, Komatsu H, Sakakibara A, Tagami H. Ichthyosiform eruption in a patient with Dubowitz syndrome. *Pediatr Dermatol* 1995; **12**: 130–3.

8 Schepis C, Greco D, Siragusa M *et al*. An intriguing case of LEOPARD syndrome. *Pediatr Dermatol* 1998; **15**: 125–8.

9 Schell-Apachik C, Hardt M, Ertl-Wagner B *et al*. Expanding the phenotype of alopecia-contractures-dwarfism, mental retardation syndrome (ACD syndrome): description of an additional case and review of the literature. *Eur J Pediatr* 2008; **167**: 1057–62.

10 Kaufman LM. A syndrome of retinitis pigmentosa, congenital ichthyosis, hypergonadotropic hypogonadism, small stature, mental retardation, cranial dysmorphism and abnormal electrocephalogram. *Ophthal Paediatr Genet* 1998; **19**: 69–79.

11 Hill VA, Griffiths WAD, Kerr-Muir MG *et al*. Non-bullous ichthyosiform erythroderma with ocular albinism and Noonan's syndrome. *Clin Exp Dermatol* 2000; **25**: 611–4.

12 Mallory SB, Haynie LS, Williams ML, Hall W. Ichthyosis, deafness and Hirschsprung's disease. *Pediatr Dermatol* 1989; **6**: 24–7.

13 Ruzicka T, Goerz G, Anton-Lamprecht I. Syndrome of ichthyosis congenita, neurosensory deafness, oligophrenia, dental hypoplasia, brachydactyly, clinodactyly, accessory cervical ribs and carcinoma of the thyroid. *Dermatologica* 1981; **162**: 124–36.

14 Loffredo A, Cennamo G, Cecio A *et al*. Hereditary microphthalmos with ichthyosis. *Ophthalmologica* 1982; **184**: 78–86.

15 Sprecher E, Ishida-Yamamoto A, Mizrahi-Koren M *et al*. A mutation in SNAP29, coding for a SNARE protein involved in intracellular trafficking, causes a novel neurocutaneous syndrome characterized by cerebral dysgenesis and ichthyosis. *Am J Hum Genet* 2005; **77**: 242–51.

16 Passwell J, Zipperkowski L, Katznelson D *et al*. A syndrome characterized by congenital ichthyosis with atrophy, mental retardation, dwarfism and generalized aminoaciduria. *J Pediatrics* 1973; **82**: 466–71.

17 Muhammed K, Safia B. Passwell syndrome. *Ind J Dermatol Venereol Leprol* 2003; **69**: 180–1.

18 Rayner A, Lampert RP, Rennet OM. Familial ichthyosis, dwarfism, mental retardation and renal disease. *J Pediatr* 1978; **92**: 766–8.

19 Goyer RA, Reynolds J, Burke J, Burholder P. Hereditary renal disease with neurosensory hearing loss, prolinuria and ichthyosis. *Am J Med Sci* 1968; **256**: 166–79.

20 Deal JE, Barratt TB, Dillon MJ. Fanconi syndrome, ichthyosis, dysmorphism, jaundice and diarrhoea: a new syndrome. *Pediatr Nephrol* 1990; **4**: 308–13.

21 Sidransky E, Feinstein A, Goodman RM. Ichthyosis–cheek–eyebrow (ICE) syndrome, a new autosomal dominant disorder. *Clin Genet* 1987; **31**: 137–42.

22 Koller E, Maureseth K, Haneberg B, Aarskog D. Familial syndrome of diaphyseal cortical thickening of the long bones, bowed legs, tendency to fracture and ichthyosis. *Pediatr Radiol* 1979; **8**: 179–82.

23 Baraitser M, Burn J, Fixsen J. A recessively inherited windmill-vane camptodactyly/ichthyosis syndrome. *J Med Genet* 1983; **20**: 125–7.

24 Dowd PM, Munro DD. Ichthyosis and osteopetrosis. *J R Soc Med* 1983; **76**: 423–6.

25 Pincus SH, Thomas IT, Clark RA, Ochs HD. Defective neutrophil chemotaxis with variant ichthyosis, hyper IgE and recurrent infections. *J Pediatr* 1975; **87**: 908–11.

26 Hendrickx GF, Zegers BJ, Van Elden L, Stoop JW. Congenital ichthyosis, immunodeficiency and abnormal T cells. *Int J Dermatol* 1979; **18**: 731–42.

27 Kozlowski VJ, Szyszymar B, Wankiewicz R. Immunopathie mit sekundarer Infektionsneigung bei Erythrodermia ichthyosiformis congenita. *Dermatol Monatsschr* 1971; **157**: 525–31.

28 Elbaum DJ, Kurz G, MacDuff M. Increased incidence of cutaneous carcinomas in patients with congenital ichthyosis. *J Am Acad Dermatol* 1995; **33**: 884–6.

29 Hendrix JD, Patterson JW, Greer KE *et al*. Skin cancer associated with ichthyosis; the MAUIE syndrome. *J Am Acad Dermatol* 1997; **37**: 1000–2.

30 Natsuga K, Akiyama M, Kato N *et al*. Novel ABCA12 mutations identified in two cases of non-bullous congenital ichthyosiform erythroderma associated with multiple skin malignant neooplasia. *J Invest Dermatol* 2007; **127**: 2669–73.

31 Walach N. Congenital ichthyosis and medulloblastoma. *Dermatologica* 1977; **154**: 49–52.

32 Schnur RE, Greenbaum BH, Heymann WR *et al*. Acute lymphoblastic leukemia in a child with the CHIME neuroectodermal dysplasia syndrome. *Am J Med Genet* 1997; **72**: 24–9.

33 Hall GW, Dale P, Dodge JA. Shwachman–Diamond syndrome: UK perspective. *Arch Dis Child* 2006; **91**: 521–4.

34 Goeteyn M, Oranje AP, Vuzevski VD. Ichthyosis, exocrine pancreatic insufficiency, impaired neutrophil chemotaxis, growth retardation and metaphyseal dysplasia (Shwachman syndrome). *Arch Dermatol* 1991; **127**: 225–30.

35 Yosipovitch G, Mevorah B, David M *et al*. Migratory ichthyosiform dermatosis with type 2 diabetes mellitus and insulin resistance. *Arch Dermatol* 1999; **135**: 1237–42.

36 Desmons F, Bar J, Chevillard Y. Erythrodermie ichthyosiforme congenitale seche, surdimutite, hépatomegalie, de transmission recessive autosomique: étude d'une famille. *Bull Soc Fr Dermatol Syphilol* 1971; **78**: 585–91.

37 Dykes PJ, Marks R, Harper PS. A syndrome of ichthyosis, hepatosplenomegaly and cerebellar degeneration. *Br J Dermatol* 1979; **100**: 585–90.

38 Arnold ML, Anton-Lamprecht I, Albrecht-Nebe H. Congenital ichthyosis with hypogonadism and growth retardation: a new syndrome with peculiar ultrastructural features. *Arch Dermatol* 1992; **284**: 198–208.
39 Hoeger PH, Adwani SS, Whitehead BF *et al*. Ichthyosiform erythroderma and cardiomyopathy: report of two cases and review of the literature. *Br J Dermatol* 1998; **139**: 1055–9.
40 Baala L, Hadj-Rabia S, Hamel-Teillac D *et al*. Homozygosity mapping of a locus for a novel syndromic ichthyosis to chromosome 3q27–28. *J Invest Dermatol* 2002; **119**: 70–6.
41 Hadj-Rabia S, Baala L, Vabres P *et al*. Claudin-1 gene mutations in neonatal sclerosing cholangitis associated with ichthyosis: a tight junction disease. *Gastroenterol* 2004; **127**: 1386–90.
42 Stormorken H, Sjaastad O, Langslet A *et al*. A new syndrome: thrombocytopathia, muscle fatigue, asplenia, meiosis, migraine, dyslexia and ichthyosis. *Clin Genet* 1985; **28**: 367–74.
43 Baden HP, Imber M. Ichthyosis with an unusual constellation of ectodermal dysplasias. *Clin Genet* 1989; **35**: 455–61.
44 Freire-Maia N, Pinheiro M. *Ectodermal Dysplasias: a Clinical and Genetic Study*. New York: Alan R Liss, 1984.
45 Lestringant GG, Kuster W, Frossard PM *et al*. Congenital ichthyosis, follicular atrophoderma, hypotrichosis and hypohidrosis: a new genodermatosis? *Am J Med Genet* 1998; **75**: 186–9.
46 Tursen U, Kaya TI, Ikizoglu G *et al*. Genetic syndrome with ichthyosis: congenital ichthyosis, follicular atrophoderma, hypotrichosis and wooly hair; a second report. *Br J Dermatol* 2002; **147**: 604–6.
47 Basel-Vanagaite L, Attia R, Ishida-Yamamoto A *et al*. Autosomal recessive ichthyosis with hypotrichosis caused by a mutation in ST14, encoding type II transmembrane serine protease matriptase. *Am J Hum Genet* 2007; **80**: 467–77.

Acquired ichthyoses

Acquired or late-onset ichthyosis is a rare and significant occurrence, as it is generally associated with underlying pathology such as malignancy. It presents with features similar to ichthyosis vulgaris and must be distinguished from xerosis, eczema, ichthyosis vulgaris and Refsum's disease in which scaling develops in early adult life. The scaling is not associated with inflammation and ranges from pityriasiform to lamellar. It is more obvious on the extensor aspects of the limbs and poorly responsive to topical therapy.

Ichthyosis associated with malignancy

The most common ichthyosis-associated malignancy is Hodgkin's disease, and the skin changes may occur simultaneously, postdate or rarely precede the diagnosis [1–3]. The fine scaling affects the trunk and limbs, usually spares the flexures and histologically resembles ichthyosis vulgaris with orthohyperkeratosis and reduced or absent granular layer. It clears with effective anticancer treatment and can be an early marker of subsequent recurrence. It may be associated with pruritus, an independent symptom of lymphoma. Reduced dermal lipogenesis, measured by radiolabelled carbon uptake, paralleled the severity of the ichthyosis and contrasted with results in ichthyosis vulgaris in one study [3]. Increased expression of transforming growth factor-α or epidermal growth factor receptors mediated by the tumour may cause hyperproliferative paraneoplastic cutaneous conditions, including ichthyosis [2].

Acquired ichthyosis has also been reported in association with non-Hodgkin's lymphoma [3–5], cutaneous T-cell lymphoma (Fig. 19.30) [6–9], lymphomatoid papulosis [10], multiple myeloma [11],

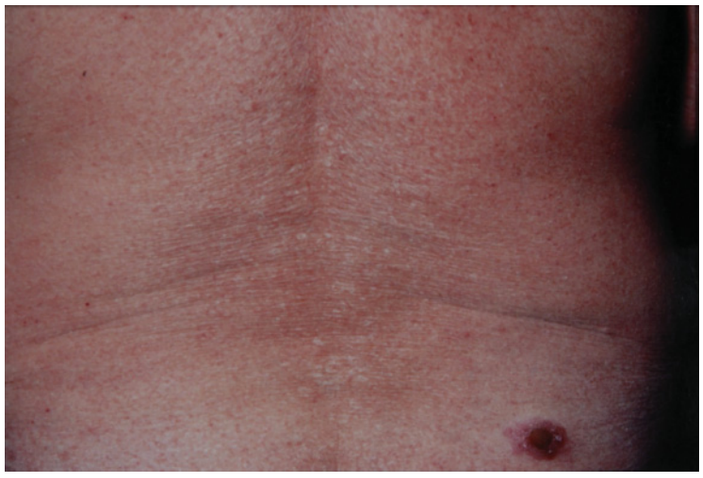


Fig. 19.30 Acquired ichthyosis in a man with cutaneous T-cell lymphoma.

carcinoma of breast, lung, cervix [12] and liver [13], leiomyosarcoma [14], rhabdomyosarcoma [15] and Kaposi's sarcoma [16]. It occurs in patients with acquired immune deficiency syndrome (AIDS), with or without demonstrable malignancy [17,18].

Ichthyosis and non-malignant disease

Ichthyosis may occur with chronic metabolic derangement such as malnutrition [4,7], malabsorption (including coeliac disease and Crohn's disease) [6], essential fatty deficiency [19], and Shwachman syndrome (pancreatic insufficiency) [20]. In these conditions, there is a disturbance of lipid and possibly vitamin absorption; because epidermal structure and integrity are dependent on complex lipid interactions, disordered epidermal maturation and desquamation with permeability barrier dysfunction ensue. Various conditions which apparently cause acquired ichthyosis may do so by virtue of associated malnutrition. Ichthyosis may be a presenting feature of inborn errors of metabolism, such as methylmalonic acidaemia [21], holocarboxylase and biotinidase deficiencies [22]. It may complicate renal failure with or without secondary hyperparathyroidism [6,7,23], primary hyperparathyroidism [24], hypopituitarism [4], hypothyroidism [6] and diabetes, where it affects the shins [25,26]. Ichthyosis may rarely occur with connective tissue diseases such as systemic lupus erythematosus [27], dermatomyositis without associated malignancy [28] and systemic sclerosis/lupus overlap [29]. It has been noted in patients with the granulomatous disorders, sarcoidosis (Fig. 19.31) [30] and leprosy [31], in HIV infection [7,17,18] and HTLV-1-associated myelopathy [32]. Acquired ichthyosis was the presenting sign of myelodysplasia [33], followed on bone marrow transplant [34], occurred with graft-versus-host disease [35] and in association with Haber syndrome [6,36] and eosinophilic fasciitis [37]. A single case of ichthyosiform erythroderma with alopecia and lichenoid features, starting at 10 years old and proving fatal at 28 years old, was reported [38]. No underlying cause was identified.

Drug-induced ichthyosis

The cholesterol-lowering drugs, triparanol and nicotinic acid, induced ichthyosis in a proportion of patients [39,40]. Triparanol

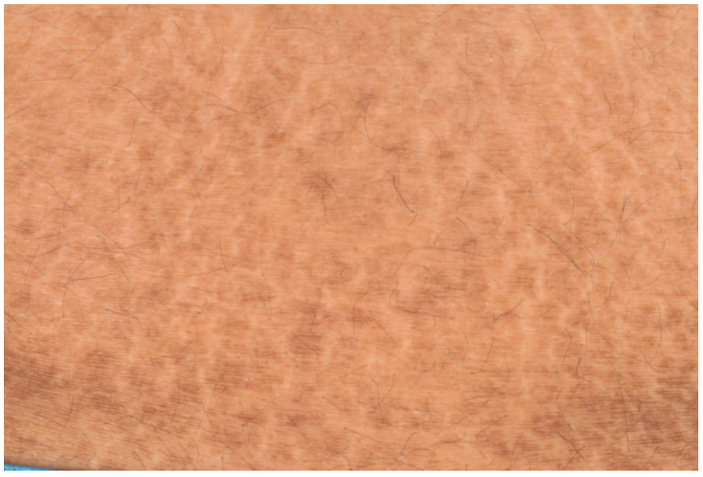


Fig. 19.31 Acquired ichthyosis in an adult Asian man with multisystem sarcoidosis.

also caused poliosis and alopecia. Normal desquamation depends on the conversion of cholesterol sulphate (which maintains the structure of intercellular lipid lamellae in the subcorneal layers) to cholesterol, by cholesterol sulphatase, located on keratinocyte cell membranes. This enzyme is unaffected by hypocholesterolaemic agents but cholesterol constitutes 25% of stratum corneum lipid. Keratinocytes lack low-density lipoprotein receptors, which may explain why so few treated patients show this complication. HMG CoA (hydroxymethylglutaryl coenzyme A) reductase inhibitors are also a rare cause of ichthyosis [41]. Ichthyosis and variable effects on hair have been attributed to certain butyrophenones [40], the phenothiazine dixyrazine [40], maprotiline [42], cimetidine (an antiandrogen) [43], allopurinol, hydroxyurea [44] and clofazamine [45].

References

1 Sneddon IB. Acquired ichthyosis in Hodgkin's disease. *BMJ* 1955; **1**: 763–4.

2 Lucker GP, Steijlen PM. Acrokeratosis paraneoplastica (Bazex syndrome) occurring with acquired ichthyosis in Hodgkin's disease. *Br J Dermatol* 1995; **133**: 322–5.

3 Cooper MF, Wilson PD, Hartop PJ *et al*. Acquired ichthyosis and impaired lipogenesis in Hodgkin's disease. *Br J Dermatol* 1980; **102**: 689–93.

4 Dykes PJ, Marks R. Acquired ichthyosis: multiple causes for an acquired generalized disturbance in desquamation. *Br J Dermatol* 1977; **97**: 327–34.

5 Estines O, Grosieux-Dauger C, Derancourt C *et al*. Paraneoplastic acquired ichthyosis revealing non-Hodgkin's lymphoma. *Ann Dermatol Venereol* 2001; **128**: 31–4.

6 Aram H. Acquired ichthyosis and related conditions. *Int J Dermatol* 1984; **23**: 458–61.

7 Kutting B, Traupe H. Acquired ichthyosis-like skin disease: a challenge for diagnostic evaluation. *Hautarzt* 1995; **46**: 836–40.

8 Kutting B, Metze D, Luger TA, Bonsmann G. Mycosis fungoides presenting as an acquired ichthyosis. *J Am Acad Dermatol* 1996; **34**: 887–9.

9 Eisman S, O'Toole EA, Jones A *et al*. Granulomatous mycosis fungoides presenting as an acquired ichthyosis. *Clin Exp Dermatol* 2003; **28**: 174–6.

10 Yokote R, Iwatsuki K, Hashizume H *et al*. Lymphomatoid papulosis associated with acquired ichthyosis. *J Am Acad Dermatol* 1994; **30**: 889–92.

11 Bluefarb SM. Cutaneous manifestations of multiple myeloma. *Arch Dermatol Syphilol* 1955; **72**: 506–22.

12 Flint GL, Flam M, Soter NA. Acquired ichthyosis: a sign of non-lymphoproliferative malignant disorders. *Arch Dermatol* 1975; **111**: 1446–7.

13 Inuzuka M, Tomita K, Tokura Y *et al*. Acquired ichthyosis associated with dermatomyositis in a patient with hepatocellular carcinoma. *Br J Dermatol* 2001; **144**: 416–7.

14 Majekodunmi AE, Fenii Pearse D. Ichthyosis: early manifestation of intestinal leiomyosarcoma. *BMJ* 1974; **3**: 724.

15 Grattan CE, Williams DM, Raafat F *et al*. Acquired ichthyosis in a child with rhabdomyosarcoma. *Pediatr Dermatol* 1988; **5**: 167–9.

16 Krakowski A, Brenner S, Covo J *et al*. Acquired ichthyosis in Kaposi's sarcoma. *Dermatologica* 1973; **147**: 348–51.

17 Young L, Steinman HK. Acquired ichthyosis in a patient with acquired immunodeficiency syndrome and Kaposi's sarcoma. *J Am Acad Dermatol* 1987; **16**: 395–6.

18 Coldiron BM, Bergstresser PR. Prevalence and clinical spectrum of skin disease in patients infected with the human immunodeficiency virus. *Arch Dermatol* 1989; **125**: 357–61.

19 Elias PM, Brown BE, Ziboh VA. The permeability barrier in essential fatty acid deficiency: evidence for a direct role for linoleic acid in barrier function. *J Invest Dermatol* 1980; **74**: 230–3.

20 Aggett PJ, Cavanagh HP, Matthew DJ *et al*. Shwachman's syndrome: a review of 21 cases. *Arch Dis Child* 1980; **55**: 331–47.

21 Boggia P, Machado MC, De Oliveira Z *et al*. Methylmalonic acidemia presenting with an ichthyosis vulgaris-like aspect. *Pediatr Dermatol* 2007; **24**: 455–6.

22 Arbuckle HA, Morelli J. Holocarboxylase synthetase deficiency presenting as ichthyosis. *Pediatr Dermatol* 2006; **23**: 142–4.

23 London RD, Lebwohl M. Acquired ichthyosis and hyperparathyroidism. *J Am Acad Dermatol* 1989; **21**: 801–2.

24 Dinnen JS, Greenwood RH, Jones JH *et al*. Parathyroid carcinoma in familial hyperparathyroidism. *J Clin Invest* 1977; **30**: 966–75.

25 Yosipovitch G, Mevorah B, David M *et al*. Migratory ichthyosiform dermatosis with type 2 diabetes mellitus and insulin resistance. *Arch Dermatol* 1999; **135**: 1237–42.

26 Scheinfeld N, Libkind M, Freilich S. New-onset ichthyosis and diabetes in a 14-year-old. *Pediatr Dermatol* 2001; **18**: 501–3.

27 Font J, Bosch X, Ingelmo M *et al*. Acquired ichthyosis with systemic lupus erythematosus. *Arch Dermatol* 1990; **126**: 829.

28 Urrutia S, Vazquez F, Requena L *et al*. Acquired ichthyosis associated with dermatomyositis. *J Am Acad Dermatol* 1987; **16**: 627–9.

29 Lee HW, Ahn SJ, Choi JC *et al*. Acquired ichthyosis with an overlap syndrome of systemic sclerosus and systemis lupus erythematosus. *J Dermatol* 2006; **33**: 52–4.

30 Clay Cather J, Cohen PR. Ichthyosiform sarcoidosis. *J Am Acad Dermatol* 1999; **40**: 862–5.

31 Schulz EJ. Ichthyosiform conditions occurring in leprosy. *Br J Dermatol* 1965; **77**: 151–7.

32 Milagres SP, Sanches JA, Milagres ACP *et al*. Histopathological and immunohistochemical assessment of acquired ichthyosis in patients with human T-cell lymphotrophic virus type 1-associated myelopathy. *Br J Dermatol* 2003; **149**: 776–81.

33 Tsochatzis E, Vassilopoulos D, Deutsch M *et al*. Myelodysplastic syndrome presenting as acquired ichthyosis. *Eur J Int Med* 2006; **17/5**: 368–9.

34 Spelman LJ, Strutton GM, Robertson IM *et al*. Acquired ichthyosis in bone marrow transplant recipients. *J Am Acad Dermatol* 1996; **35**: 17–20.

35 Huang J, Pol-Rodriguez M, Silvers D *et al*. Acquired ichthyosis as a manifestation of acute graft-versus-host disease. *Pediatr Dermatol* 2007; **24**: 49–52.

36 Kikuchi J, Saita B, Inoue S. Haber's syndrome: report of a new family. *Arch Dermatol* 1981; **117**: 321–4.

37 de la Cruz-Alvarez J, Allegue F, Oliver J. Acquired ichthyosis associated with eosinophilic fasciitis. *J Am Acad Dermatol* 1996; **34**: 1079–80.

38 Mevorah B, Landau M, Gat A *et al*. Adolescent-onset ichthyosiform-like erythroderma with lichenoid tissue reaction: a new entity? *Br J Dermatol* 2001; **144**: 1063–6.

39 Winklemann RK, Perry HO, Achor RWP, Kirby TJ. Cutaneous syndromes produced as side-effects of triparanol therapy. *Arch Dermatol* 1963; **87**: 372–7.

40 Williams ML, Feingold KR, Grubauer G *et al*. Ichthyosis induced by cholesterol-lowering drugs. *Arch Dermatol* 1987; **123**: 1535–7.

41 Sparsa A, Boulinguez S, Le-Brun V *et al*. Acquired ichthyosis with pravastatin. *J Eur Acad Dermatol Venereol* 2007; **21**: 549–50.

42 Niederaurer HH, Bacharach-Buhles M, Altmeyer P. Ichthyosis and alopecia after maprotiline. *Hautarzt* 1991; **42**: 455–8.
43 Greist MC, Epinette WW. Cimetidine induced xerosis and asteatotic dermatitis. *Arch Dermatol* 1982; **118**: 253–4.
44 Kumar B, Saraswat A, Kaur I. Mucocutaneous adverse effects of hydroxyurea: a prospective study of 30 psoriasis patients. *Clin Exp Dermatol* 2002; **27**: 8–13.
45 Caver CV. Clofazamine induced ichthyosis and its treatment. *Cutis* 1982; **29**: 341–3.

Pityriasis rotunda

Definition. Pityriasis rotunda describes a rare, persistent, sharply defined, circular patch of ichthyosiform scaling with no inflammatory changes. This name is preferred to pityriasis circinata, reported by Toyama in 1906, and to acquired pseudo-ichthyosis [1].

Aetiology. Pityriasis rotunda is relatively common in the Far East, especially Japan, where it accounts for some 0.2% of dermatological cases [1]. It has been reported also in South African Bantus [2], in an Egyptian [3] and in Afro-Caribbeans living in London [4]. It has been described in Caucasians [5] and in two cohorts from Sardinia [6,7]. Its true incidence and geographical distribution are unknown. It is possible that genetic factors are involved and familial occurrence has been observed [6–10]. A familial association with ichthyosis vulgaris has also been noted [1,7,10]. Systemic illnesses, particularly tuberculosis and malnutrition, coexisted in up to 50% of South African patients [1,2,11]. It may rarely be an acquired cutaneous marker of malignancy [12–14]. Pityriasis rotunda was observed in 16% of 63 South African black patients with hepatocellular carcinoma and nearly 5% of those with tuberculosis in one report [15]. However, cases reported from Sardinia had no associated systemic disorders and pityriasis rotunda tended to occur at a younger age [6,7].

Pathology. The histological changes are unimpressive and resemble those of ichthyosis vulgaris, with orthohyperkeratosis and reduced granular layer. There may be pigmentary incontinence and mild perivascular lymphocytic infiltrate. Electron microscopy in one case revealed epidermal lipid vacuoles and other changes [8].

Clinical features. Typical lesions of pityriasis rotunda are circular, sharply defined patches of dry skin with ichthyosiform scaling, usually 2–3 cm in diameter but sometimes much larger, up to 14 cm (Fig. 19.32). Lesions number between four and 200. They rarely itch, slowly enlarge and coalesce and may be hypo- or hyperpigmented. Onset in childhood may have a better prognosis, with remission in later childhood in almost 50% [6,7]. Lesions are commonly situated on the buttocks, thighs, abdomen, back or upper arms, and may be solitary or multiple. They most often develop between the ages of 20 and 45 years (2 and 76 years are the reported extremes) and may remain unchanged throughout life.

Diagnosis. The age of onset, distribution, strikingly circular outline and absence of pruritus and inflammatory change should suggest the diagnosis. Investigations for an underlying cause may be indicated. In prelymphomatous eruptions, the lesions show atrophy and telangiectasia. Dermatophytosis and pityriasis versicolor can be excluded on negative mycology (microscopy and culture).



Fig. 19.32 Pityriasis rotunda.

Treatment. Emollients, urea compounds and topical keratolytics may help, but topical steroid and antifungal agents do not. Where an underlying cause is found, appropriate therapy should clear the lesions.

References

1 Ito M, Tanaka T. Pseudo ichthyose acquise en taches circulaires. *Ann Dermatol Syphiligr* 1960; **87**: 26–37.
2 Findlay GH. Pityriasis rotunda in the South African Bantu. *Br J Dermatol* 1965; **77**: 63–4.
3 El-Hefnawi H, Rasheed A. Pityriasis rotunda: report of study of first case in UAR. *Arch Dermatol* 1966; **93**: 84–6.
4 Sarkany I, Hare PJ. Pityriasis rotunda (pityriasis circinata). *Br J Dermatol* 1964; **76**: 223–8.
5 Segal R, Hodak E, Sandbank M. Pityriasis rotunda in a Caucasian woman from the Mediterranean area. *Clin Exp Dermatol* 1989; **14**: 325–7.
6 Aste N, Pau M, Aste N *et al*. Pityriasis rotunda: a survey of 42 cases observed in Sardinia, Italy. *Dermatol* 1997; **194**: 32–5.
7 Ena P, Cerimele D. Pityriasis rotaunda in childhood. *Pediatr Dermatol* 2002; **19**: 200–3.
8 Grimalt R, Gelmetti C, Brusasco A *et al*. Pityriasis rotunda: report of a familial occurrence and review of the literature. *J Am Acad Dermatol* 1994; **31**: 866–71.
9 Friedmann AC, Ameen M, Swale VJ. Familial pityriasis rotunda in black-skinned patients; a first report. *Br J Dermatol* 2007; **156**: 1362–402.
10 Guberman D, Lichtenstein DA, Gilead L *et al*. Familial pityriasis rotunda. *Acta Derm Venereol* 1997; **77**: 162.
11 Swift PJ, Saxe N. Pityriasis rotunda in South Africa—a skin disease caused by undernutrition. *Clin Exp Dermatol* 1985; **10**: 407–12.
12 Leibowitz MR, Weiss R, Smith EH. Pityriasis rotunda: a cutaneous sign of malignant disease in two patients. *Arch Dermatol* 1983; **119**: 607–9.
13 Griffin LJ, Massa MC. Acquired ichthyosis and pityriasis rotunda. *Clin Dermatol* 1993; **11**: 27–32.
14 Ikada J, Oki M. Concurrent pityriasis rotunda and acquired ichthyosis with IgG myeloma. *Br J Dermatol* 1974; **91**: 585–6.
15 Berkowitz I, Hodkinson HJ, Kew MC *et al*. Pityriasis rotunda as a cutaneous marker of hepatocellular carcinoma: a comparison with its prevalence in other disease. *Br J Dermatol* 1989; **120**: 545–9.



Fig. 19.33 Keratolysis exfoliativa of palms.

Peeling skin syndromes (MIM 270300, 609796)

Periodic or continuous peeling of the superficial layers of the skin resulting from damage to or disruption of the stratum corneum has widely differing aetiologies. Histologically, there is cleavage within the stratum corneum (above the stratum granulosum) and some alteration in histochemical staining. Individual cases and families with either acral peeling or generalized skin peeling (deciduous skin, familial continual skin peeling or shedding) have been reported. In Oudsthoorn disease (erythrokeratolysis hiemalis), the peeling is more pronounced and is associated with erythema.

Acral peeling skin syndromes

Acquired peeling of the palms. The most common peeling skin disorder is *keratolysis exfoliativa.* This affects the palms in young adults, usually in the summer months. It may be related to sweating. Lesions appear as tiny white rings or 'air bubbles', which soon rupture and peel off ('ringed keratolysis') (Fig. 19.33). Attempts to identify a specific fungal or bacterial agent proved negative [1]. Emollients are usually prescribed but are not very effective.

Some patients have non-seasonal, episodic, acral/palmar peeling which may be preceded by a few days by intense itching of the palms. Histologically, there is minimal spongiosis and it may represent a *forme fruste* of hand eczema. The use of degreasing chemicals can produce similar damage to the stratum corneum by affecting intercorneocyte adhesion.

Acral peeling. A congenital, and in one case familial, predominantly acral peeling has been reported in four patients [2–4]. It causes lifelong episodic, painless, non-inflammatory peeling of the dorsal and volar aspects of the hands and feet, especially after immersion in water, which is more severe in summertime. Occasional cases have recurrent painful acral blisters followed by peeling. Electron microscopy showed abnormal lipid lamellae, moth-eaten keratohyaline granules and defective keratin filament aggregation which allowed a mid stratum corneum split. An adult with delayed onset, well-defined palmar erythema and peeling extending to the periungal area was reported as localized peeling skin syndrome [5]. A transglutaminase 5 mutation has been identified in acral peeling skin syndrome [6] but excluded as a cause of generalized skin peeling in four kindred.

References

1 Emmerson RW, Wilson-Jones E. Ringed keratolysis of the palms. *Trans St John's Hosp Dermatol Soc* 1967; **53**: 165–7.

2 Hashimoto K, Hamzavi I, Tanaka K *et al*. Acral peeling skin syndrome. *J Am Acad Dermatol* 2000; **43**: 1112–9.

3 Garcia EG, Carreno RG, Martinez-Gonzalez MA *et al*. Acral peeling skin syndrome: report of two cases. *Ultrastruct Pathol* 2005; **29**: 65–70.

4 Shwayder T, Conn S. Acral peeling skin syndrome. *Arch Dermatol* 1997; **133**: 535–6.

5 Brusasco A, Veraldi S, Tadini G *et al*. Localized peeling skin syndrome: case report with ultrastructural study. *Br J Dermatol* 1998; **139**: 492–5.

6 Cassidy AJ, van Steensel MA, Steijlen PM *et al*. A homozygous missense mutation in TGM5 abolishes epidermal transglutaminase 5 activity and causes acral peeling skin syndrome. *Am J Hum Genet* 2005; **77**: 909–17.

Familial peeling skin syndromes

Variously reported as keratolysis exfoliativa congenita in 1921 [1] or deciduous skin in 1938 [2], the label 'familial continual skin peeling' was suggested in 1969 in a case report of four affected siblings [3]. Two further kindreds and a number of individual cases were reported and the title peeling skin syndrome (PSS) was preferred [4–8]. The peeling was generalized and variations in the salient features among reported cases led to the identification of type A non-inflammatory [2–4,6] and type B inflammatory PSS [5,7,9,10]. Several affected patients were from consanguineous families [3–5] and the occurrence of affected siblings suggested autosomal recessive inheritance. Eleven paediatric cases were seen over a 20-year period in Saudi Arabia, all from Bedouin tribes [11]. Familial occurrence was documented in eight and consanguinity in six cases. Estimation of the frequency of PSS is difficult; it occurs worldwide.

Aetiology. A defect in profilaggrin or a site-specific keratin with resultant abnormal keratin filament aggregation was suggested. Evidence for a desmosomal abnormality and altered vitamin A metabolism has been put forward in one atypical case [12]. Reduced tryptophan with aminoaciduria was reported in at least one case [5]. Some patients with Netherton's syndrome have widespread peeling, which leads some to conclude that deficient protease inhibitor activity in skin may cause PSS type B. This theory was disproven, while the close phenotypic overlap between the two conditions was acknowledged [13,14]. On the other hand, increased levels of kallikrein trypsin-like serine proteases in the stratum corneum (which mediate desquamation) and serum of patients with PSS type B, mimic the increased serine protease activity in the skin of patients with Netherton's syndrome due to *LEKTI* (protease-inhibitor)/*SPINK* mutations [14]. Therefore, upregulated epidermal protease activity, which disrupts intercellular adhesion molecules, is the final common pathway responsible for increased stratum corneum desquamation in both conditions but occurs due to different pathogenetic mechanisms. Both disorders share a disrupted epidermal barrier function and a risk of increased absorption of topical therapy [14].

Histopathology. Mild hyperkeratosis with loose irregular stratification at follicular orifices and a normal granular layer thickness are common findings [4], although psoriasiform acanthosis was noted in two reports [5,9]. Kinetic studies suggested a hyperproliferative disorder [3], but this has been disputed [6]. The split exists at the corneal–granular interface and ultrastructurally inter and intracellular disruption occurs above the lower two layers of stratum corneum, within the stratum lucidum and with intracellular cleavage in the granular cell layer as well [9]. Corneal intercellular lamellae are irregular and fragmented, keratohyalin granules are abnormal and desmosomes may be normal, reduced [4] or disrupted [12]. Lamellar bodies are aggregated in the upper granular layer, but other cytoplasmic structures are normal. A patient with adult-onset disease was found to have intracellular keratinocyte cleavage with globular lipid deposits between corneal cells at all levels [6]. Immunofluorescence studies were normal in three cases [5,15,16].

Clinical features. Generalized superficial peeling starts at birth or in early childhood and is then persistent or periodic in most affected people. Collodion membrane and blisters do not occur in this condition, although vesicles and congenital erythroderma were noted in separate cases [8,14]. Peeling is not preceded by fever or erythema, and can be produced by rubbing intact skin, especially if pre-soaked in water. Exfoliating flakes and peeling sheets of stratum corneum spread across the trunk, limbs and occasionally face, leaving mildly erythematous intact skin. Pruritus is a problem for some patients and patchy hyperpigmentation has been noted. The palms and soles are either spared or mildly thickened without peeling, and hair, nails and teeth are usually normal. However, one atypical patient had severe palmoplantar subcorneal blistering, ichthyosis and keratotic cheilitis (PSS type C) [12]. Two patients had easily plucked hair [5,15], others noted fast-growing hair and nails [7], one shed nails [17], several showed stunted growth [5,14,16,18] and one of these, a woman of 26, had hypogonadism and anosmia [5]. Developmental delay was noted in one case [16]. Some cases are more severely affected in the summer [2,8,15], but generally there is only slight seasonal variation. Shedding occurred in a cephalocaudal pattern for a week once a year in an Indian boy [17]. A Pakistani infant had continuous peeling limited to the face, with two other family members also affected [19].

Diagnosis. Electron microscopy of skin is helpful. Many patients have elevated IgE [5,7,13,14,16,18]. Several unrelated skin disorders eventuate in skin shedding, but differentiation from peeling skin syndrome is generally not a problem. Ichthyosis bullosa of Siemens (autosomal dominant) produces transient blisters and erosions on a background of flexural hyperkeratosis and typical histopathology. An autosomal recessive form of exfoliative ichthyosis (without epidermolytic hyperkeratosis) in an inbred Bedouin family has been documented [20]. It shares some of the clinical features of familial peeling skin syndrome type A. In epidermolysis bullosa simplex superficialis and the Weber–Cockayne variant, subcorneal or basal layer blisters occur with friction but there is no continual peeling. The histology is characteristic and these are autosomal dominant skin fragility disorders [21]. Peeling lesions without double-edged scale occur in Netherton's syndrome and some patients with PSS have stunted growth and atopic features [13,14,18]. However, the absence of typical hair shaft defects and normal LEKTI staining in skin exclude Netherton's syndrome. Acquired keratolysis may complicate tinea (the original definition of keratolysis exfoliativa, an id reaction mainly affecting the palms), staphylococcal or streptococcal infection, atopic eczema and pemphigus foliaceus (where epidermolysis occurs in the superficial layer of the stratum spinosum). It is a common side effect of retinoid therapy and occasionally of azathioprine.

Treatment. Minimizing immersion in water is recommended. Absorbing powders or aluminium antiperspirants may help, especially in the acral variant, by reducing sweating and friction. Keratolytic and urea creams speed up shedding and topical calcipotriol has been reported effective [18]. Topical and oral steroids, emollients and tar, oral retinoids [7,16], methotrexate [8] and UVB phototherapy [5] are among those agents tried without success. Increased absorption of topical agents has been reported [14].

References

1 Fox H. Skin shedding (keratolysis exfoliativa congenita): report of a case. *Ann Dermatol Syphilol* 1921; **3**: 202.
2 Bechet PE. Deciduous skin. *Ann Dermatol Syphilol* 1938; **37**: 267–71.
3 Kurban AK, Azar HA. Familial continual skin peeling. *Br J Dermatol* 1969; **81**: 191–5.
4 Abdel-Hafez K, Safer AM, Selim MM, Rehak A. Familial continual skin peeling. *Dermatologica* 1983; **166**: 23–31.
5 Levy SB, Goldsmith LA. The peeling skin syndrome. *J Am Acad Dermatol* 1982; **7**: 606–13.
6 Silverman AK, Ellis CN, Beals TF *et al*. Continual skin peeling syndrome: an electron microscopic study. *Arch Dermatol* 1986; **122**: 71–5.
7 Mevorah B, Frenk E, Saurat JH *et al*. Peeling skin syndrome: a clinical, ultrastructural and biochemical study. *Br J Dermatol* 1987; **116**: 117–25.
8 Panja SK, Sengupta S. Idiopathic deciduous skin. *Int J Dermatol* 1982; **21**: 262–4.
9 Tsai K, Valente NY, Nico MM. Inflammatory peeling skin syndrome studied with electron microscopy. *Pediatr Dermatol* 2006; **23**: 488–92.
10 Traupe H. *The Ichthyoses: a Guide to Clinical Diagnosis Genetic Counselling and Therapy*. Heidelberg: Springer-Verlag, 1989.
11 Al-Ghamdi F, Al-Raddadi A, Satti M. Peeling skin syndrome: eleven cases from Saudi Arabia. *Ann Saudi Med* 2006; **26**: 352–7.
12 Mevorah B, Salomon D, Siegenthaler G *et al*. Ichthyosiform dermatosis with superficial blister formation and peeling: evidence for a desmosomal anomaly and altered vitamin A metabolism. *J Am Acad Dermatol* 1996; **34**: 379–85.
13 Schneider I, Sebok B, Kosztolanyi G *et al*. Comel-Netherton syndrome: evolution of manifestation in a 20 year follow and phenotypic overlap with peeling skin syndrome type B. *Acta Dermatol Venereol* 2000; **80**: 209–10.
14 Komatsu N, Suga Y, Saijoh K. Elevated human tissue kallikrein levels in the stratum corneum and serum of peeling skin syndrome type B patients suggests an overdesquamation of corneocytes. *J Invest Dermatol* 2006; **126**: 2338–42.
15 Aras N, Sutman K, Tastan HB *et al.* Peeling skin syndrome. *J Am Acad Dermatol* 1994; **30**: 135–6.
16 Dicken CH. Peeling skin syndrome. *J Am Acad Dermatol* 1985; **13**: 158–60
17 Tolat SN, Gharpuray MB. Skin peeling syndrome. *Cutis* 1994; **53**: 255–7.
18 Mizuno Y, Suga Y, Hasegawa T *et al*. A case of peeling skin syndrome successfully treated with topical calcipotriol. *J Dermatol* 2006; **33**: 430–2.
19 Janjua SA, Hussain I, Khachemoune A. Facial skin peeling syndrome: a case report and a brief review. *Int J Dermatol* 2007; **46**: 287–9.
20 Zvulunov A, Cagnano E, Kachko L *et al*. A new variant of autosomal recessive exfoliative ichthyosis. *Pediatr Dermatol* 2002; **19**: 382–7.



(a)



(b)

Fig. 19.34 Oudtshoorn disease: (a) palmar lesions; and (b) truncal lesions.

21 Fine JD, Johnson L, Wright T. Epidermolysis bullosa simplex superficialis: a new variant of epidermolysis bullosa characterized by subcorneal cleavage mimicking peeling skin syndrome. *Arch Dermatol* 1989; **125**: 633–8.

Oudtshoorn disease (MIM 148370)

Synonyms
- Keratolytic winter erythema
- Erythrokeratolysis hiemalis

This rare epidermal disorder, characterized by recurrent skin peeling, palmoplantar erythema and seasonal variation, was originally described as erythrokeratolysis hiemalis in 1977. It has been observed in at least 35 white or mixed-race related South African families of European descent originating from the Oudtshoorn district of Cape Provence [1,2]. The incidence in this population is 1 in 7000. Cases have since been identified in several other countries, and a familial link to the Oudtshoorn cluster is evident in most. It is an autosomal dominant disorder with variable penetrance and linkage to chromosome 8p22–p23 has been reported in five South African and one German kindred [3]. The genetic mutation may have arisen in a French immigrant in the late 1700s. Over 400 descendants are affected. A Norwegian family with four affected members did not show linkage to chromosome 8p22–p23, suggesting genetic heterogeneity [4].

Histopathology. Biopsy of the advancing edge of a lesion shows focal cellular oedema, necrobiosis of the Malpighian layer and absence of the overlying granular layer, through which the Malpighian layer is ejected. It forms a parakeratotic wedge, which becomes sandwiched within the hyperkeratotic stratum corneum and is shed [2]. Hyperproliferative features were evident in the basal layer—so-called basaliosis [2]. Skin histology in the Norwegian family was non-specific [4].

Clinical features. Symmetrical keratolysis of the hands and feet may begin at any age from infancy to early adult life but it is not usually present at birth (Fig. 19.34a). Cyclical centrifugal peeling (sometimes preceded by erythema multiforme-like papules) at several sites on the palms and soles is a constant feature, and may spread to the dorsal hands and feet, and the interdigital spaces. Episodes may be preceded by itch and hyperhidrosis and associated with pustulation. Palmoplantar erythema develops, and is followed by the evolution of painless, superficial opaque dry blebs, which peel or can be pulled away, leaving a red base with intact markings. A second wave may begin at the centre of a lesion, resulting in gyrate and polycyclic annular erythema, which eventually resolves. Cycles repeat every few weeks and the palms and soles appear normal between attacks. Similar rosette lesions may arise on the lower legs, knees and rarely thighs (Fig. 19.34b), upper arms and shoulders. Truncal lesions were reported in one patient [2]. The father of an affected toddler was unaffected but paternal aunts and other family members had similar palmoplantar eruptions and her paternal great-great grandmother came from Oudtshoorn [5].

A frequent precipitant is cold dry weather and, although in South Africa it is most active in winter months, it may be perennial in temperate climates. Other triggers include febrile illness, surgery, stress and menstruation, and it improves in pregnancy and with age.

Diagnosis. The differential diagnosis includes familial peeling skin syndromes, pustular bacterids, annular erythema, erythema multiforme, Hailey–Hailey disease, erythrokeratoderma en cocardes and variabilis, and Weber–Cockayne epidermolysis bullosa simplex. A similar phenotype affecting the palms, more active in summertime, was reported in two siblings (British) who also had atypical, autosomal recessive erythropoietic protoporphyria [6].

Treatment. There is no effective treatment, and topical keratolytics, retinoids and steroids may aggravate the condition. Urea and tar compounds, antiperspirants and oral retinoids have been tried.

References

1 Findlay GH, Nurse GT, Heyl T *et al.* Keratolytic winter erythema or Oudtshoorn disease. *S Afr Med J* 1977; **52**: 871–4.

2 Findlay GH, Morrison JGL. Erythrokeratolysis hiemalis: keratolytic winter erythema or 'Oudtshoorn skin'. *Br J Dermatol* 1978; **98**: 491–5.
3 Starfield M, Hennies HC, Jung M *et al*. Localization of gene causing keratolytic winter erythema to chromosome 8p22-p23 and evidence for a founder effect in South African africaans speakers. *Am J Hum Genet* 1997; **61**: 370–8.
4 Huntington MK, Jassim AD. Genetic heterogeneity in keratolytic winter erythema (Oudtshoorn skin disease). *Arch Dermatol* 2006; **142**: 1073–4.
5 France DM, Xerri S. Erythrokeratolysis hiemalis: Oudtshoorn skin. *Br J Dermatol* 1984; **113** (Suppl. 29): 46.
6 Holme SA, Whatley SD, Roberts AG *et al*. Seasonal palmar keratoderma in erythropoietic protoporphyria indicates autosomal recessive inheritance. *J Invest Dermatol* 2009; **129**: 599–605.

Erythrokeratoderma

Erythrokeratoderma (sometimes erythrokeratodermia) is the association of localized hyperkeratotic plaques with overlapping or distinct areas of circumscribed erythema. Many associations and possible syndromes are reported. There is clinical overlap with KID and transgredient keratoderma syndromes. Identification of underlying genetic defects in gap junction proteins in many cases of erythrokeratoderma variabilis (EKV) (Table 19.1) has led to re-evaluation of their classification [1–3], but the status of clinical variants remains uncertain.

Erythrokeratoderma variabilis (MIM 133200)

Synonym
- Mendes da Costa's syndrome

Mendes da Costa described a mother and daughter with relatively fixed hyperkeratotic plaques and erythematous areas with geographical margins that changed by the hour [4].

Aetiology. Inheritance of EKV is usually autosomal dominant, although recessive pedigrees are reported [3,5–7]. The disease locus is at chromosome 1p34–p35.1, near the rhesus cluster [8], where several genes encode members of the connexin family of gap junction proteins [9]. Dominant negative mutations in gap junction beta3 (*GJB3*), encoding connexin 31 (Cx31), or beta4 (*GJB4*), encoding connexin 30.3 (Cx30.3), are found in many pedigrees of erythrokeratoderma variabilis [7,10–13]; homozygous missense mutations in *GJB3* also cause recessive disease [5,7]. Other mutations in *GJB3* cause autosomal dominant or recessive deafness, in isolation or with peripheral neuropathy [14–16]. EKV associated with erythema gyratum repens [17,18] appears to be specific to mutations in *GJB4* [19,20], but other mutations in this gene cause typical EKV. In some pedigrees of EKV mutations have not been identified in either *GJB3* or *GJB4* [10,21]. Connexins are synthesized in the endoplasmic reticulum and transported to the cell surface via the Golgi apparatus [22,23]. The fact that Cx31 and Cx30.3 both cause EKV may reflect their co-expression to form heteromeric connexons. In an *in vitro* model, co-expression enhances gap junction formation [24]. Trafficking to the cell membrane of Cx31 mutants which cause EKV is defective [22]. In contrast to mutations causing deafness or neuropathy, some EKV mutations increase death amongst cultured cells [22,25], but cell death is not a major feature of EKV lesions [25]. In a transgenic murine model of EKV, mutant Cx31 resulted in hyperproliferation in tail skin but also accelerated wound healing [26].

Pathology. Histology is non-specific: orthohyperkeratosis or parakeratosis, with acanthosis and papillomatosis. Immunohistochemistry shows aberrant staining for basal cytokeratins in the stratum corneum, improved by etretinate [27]. There is an increase of suprabasal staining for involucrin [28]. Connexin 31 is expressed in an abnormal perinuclear distribution, rather than at the cell membrane [22]. Reduced numbers of keratinosomes within the stratum granulosum, restored by isotretinoin, and clumped tonofilaments have been reported [29]; the latter were not confirmed in other cases [30,31].

Clinical features [3,31–35]. Onset is usually in infancy. The manifestations vary within a family and within the individual. There are two types of lesion. Relatively fixed, well-demarcated keratotic and erythematous plaques, often bizarrely shaped, show a predilection for extensor surfaces, lateral trunk and buttocks. They extend and regress in area, thickness and degree of erythema. Secondly, transient erythematous polycyclic or comma-shaped macular lesions occur at any site (Fig. 19.35). These may be triggered by trauma, irritation or temperature change, and evolve in shape over hours. They last days or weeks, fading *in situ* or migrating slowly, leaving a residual fine scale. Improvement may be seen after extended sun exposure. In some cases the erythema is annular or 'en cocarde' (Degos' syndrome) [36,37]; others may show erythema gyratum repens [17,18]. Migratory erythematous plaques resembling EKV are also seen in annular or polycyclic forms of



Fig. 19.35 Erythrokeratoderma variabilis: migrating polycyclic erythematous lesions.

bullous ichthyosiform erythroderma (BIE), due to mutations in keratin 1 or 10 genes (Table 19.1). Palmoplantar involvement in EKV may take the form of mild scaling or peeling [33], but transgredient keratoderma resembling Greither's syndrome is recorded [38]. The condition persists throughout life, but may improve at puberty or worsen during pregnancy or with oral contraceptives [39].

Treatment. Acitretin is now the treatment of choice [40]. Isotretinoin may also be helpful [29]. Successful use of bath PUVA has been reported [41]. Non-sedating antihistamines have been reported to benefit pruritic erythematous lesions [42].

References

1 Hohl D. Towards a better classification of erythrokeratodermias. *Br J Dermatol* 2000; **143**: 1133–7.
2 van Steensel M. Does progressive symmetric erythrokeratoderma exist? *Br J Dermatol* 2004; **150**: 1043–5.
3 Rogers M. Erythrokeratodermas: a classification in a state of flux? *Australas J Dermatol* 2005; **46**: 127–41.
4 Mendes da Costa S. Erythro- et keratodermia variabilis in a mother and daughter. *Acta Derm Venereol (Stockh)* 1925; **6**: 255–61.
5 Armstrong DB, Hutchinson TH, Walsh MY, McMillan JC. Autosomal recessive inheritance of erythrokeratoderma variabilis. *Pediatr Dermatol* 1997; **14**: 355–8.
6 Gottfried I, Landau M, Glaser F *et al.* A mutation in *GJB3* is associated with recessive erythrokeratoderma variabilis (EKV) and leads to defective trafficking of the connexin 31 protein. *Hum Mol Genet* 2002; **11**: 1311–6.
7 Terrinoni A, Leta A, Pedicelli C *et al.* A novel recessive connexin 31 (GJB3) mutation in a case of erythrokeratodermia variabilis. *J Invest Dermatol* 2004; **122**: 837–9.
8 van der Schroeff JG, Njenhuis LE, Meera-Khan P *et al.* Genetic linkage between erythrokeratodermia variabilis and Rh locus. *Hum Genet* 1984; **68**: 165–8.
9 Richard G, Smith LE, Bailey RA *et al.* Mutations in the human connexin gene *GJB3* cause erythrokeratodermia variabilis. *Nat Genet* 1998; **20**: 366–9.
10 Richard G, Brown N, Smith LE *et al.* The spectrum of mutations in erythrokeratodermias: novel and *de novo* mutations in *GJB3*. *Hum Genet* 2000; **106**: 321–9.
11 Richard G, Brown N, Rouan F *et al.* Genetic heterogeneity in erythrokeratodermia variabilis: novel mutations in the connexin gene GJB4 (Cx30.3) and genotype-phenotype correlations. *J Invest Dermatol* 2003; **120**: 601–9.
12 Morley SM, White MI, Rogers M *et al.* A new, recurrent mutation of GJB3 (Cx31) in erythrokeratodermia variabilis. *Br J Dermatol* 2005; **152**: 1143–8.
13 Common JE, O'Toole EA, Leigh IM *et al.* Clinical and genetic heterogeneity of erythrokeratoderma variabilis. *J Invest Dermatol* 2005; **125**: 920–7.
14 Xia J, Liu C, Tang B *et al.* Mutations in the gene encoding gap junction protein beta-3 associated with autosomal dominant hearing impairment. *Nat Genet* 1998; **20**: 370–3.
15 Liu XZ, Xia XJ, Xu LR *et al.* Mutations in connexin 31 underlie recessive as well as dominant non-syndromic hearing loss. *Hum Mol Genet* 2000; **9**: 63–7.
16 Lopez-Bigas N, Olive M, Rabionet R *et al.* Connexin 31 (*GJB3*) is expressed in the peripheral and auditory nerves and causes neuropathy and hearing impairment. *Hum Mol Genet* 2001; **10**: 947–52.
17 Landau M, Cohen BD, Hohl D *et al.* Erythrokeratodermia variabilis with erythema gyratum repens-like lesions. *Pediatr Dermatol* 2002; **19**: 285–92.
18 Cram DL. Erythrokeratoderma variabilis and variable circinate erythrokeratodermas. *Arch Dermatol* 1970; **101**: 68–73.
19 Macari F, Landau M, Cousin P *et al.* Mutation in the gene for connexin 30.3 in a family with erythrokeratodermia variabilis. *Am J Hum Genet* 2000; **67**: 1296–301.
20 Richard G, Brown N, Rouan F *et al.* Genetic heterogeneity in erythrokeratodermia variabilis: novel mutations in the connexin gene *GJB4* (Cx30.3) and genotype–phenotype correlations. *J Invest Dermatol* 2003; **120**: 601–9.
21 Nakamura M. Erythrokeratoderma variabilis without GJB3 or GJB4 mutation: a review of Japanese patients. *Br J Dermatol* 2007; **157**: 410–1.
22 Di W-L, Monypenny J, Common JEA *et al.* Defective trafficking and cell death is characteristic of skin disease-associated connexin 31 mutations. *Hum Mol Genet* 2002; **11**: 2005–14.
23 He LQ, Cai F, Liu Y *et al.* Cx31 is assembled and trafficked to cell surface by ER-Golgi pathway and degraded by proteasomal or lysosomal pathways. *Cell Res* 2005; **15**: 455–64.
24 Plantard L, Huber M, Macari F *et al.* Molecular interaction of connexin 30.3 and connexin 31 suggests a dominant-negative mechanism associated with erythrokeratodermia variabilis. *Hum Mol Genet* 2003; **12**: 3287–94.
25 Diestel S, Richard G, Doring B, Traub O. Expression of a connexin31 mutation causing erythrokeratodermia variabilis is lethal for HeLa cells. *Biochem Biophys Res Commun* 2002; **296**: 721–8.
26 Schnichels M, Worsdorfer P, Dobrowolski R *et al.* The connexin31 F137L mutant mouse as a model for the human skin disease erythrokeratodermia variabilis (EKV). *Hum Mol Genet* 2007; **16**: 1216–24.
27 McFadden N, Oppedal BR, Ree K *et al.* Erythrokeratodermia variabilis: immunohistochemical and ultrastructural studies of the epidermis. *Acta Derm Venereol (Stockh)* 1987; **67**: 284–8.
28 Kanitakis J, Zambruno G, Viac J *et al.* Involucrin expression in keratinization disorders of the skin: a preliminary study. *Br J Dermatol* 1987; **117**: 479–80.
29 Rappaport IP, Goldes JA, Goltz RW. Erythrokeratodermia variabilis treated with isotretinoin: a clinical, histologic and ultrastructural study. *Arch Dermatol* 1986; **122**: 441–5.
30 Belaich S, Homareau S, Blanchet-Bardon C *et al.* Erythrokeratodermie variable (Mendes da Costa): étude ultrastructurale. *Ann Dermatol Vénéréol* 1988; **115**: 1121–3.
31 McFarlane AW, Chapman SJ, Verbov JL. Is erythrokeratoderma one disorder? A clinical and ultrastructural study of two siblings. *Br J Dermatol* 1991; **124**: 487–91.
32 Brown J, Kierland RR. Erythrokeratodermia variabilis. *Arch Dermatol* 1966; **93**: 194–201.
33 Itin P, Levy CA, Sommacal-Schöpf D *et al.* Familienuntersuchung zur Erythrokeratodermia figurata variabilis. *Hautarzt* 1992; **43**: 500–4.
34 Hacham-Zadeh S, Even-Paz Z. Erythrokeratodermia variabilis in a Jewish Kurdish family. *Clin Genet* 1978; **13**: 404–8.
35 Richard G, Lin JP, Smith L *et al.* Linkage studies in erythrokeratodermias: fine mapping, genetic heterogeneity and analysis of candidate genes. *J Invest Dermatol* 1997; **109**: 666–71.
36 Degos R, Delzant O, Morival H. Erytheme desquamatif en plaques, congenital et familial (genodermatose nouvelle?). *Bull Soc Fr Dermatol Syphilol* 1947; **54**: 442.
37 Gougerot H, Grupper C. Geno-dermatose erythemato-squameuse circinée, variable: 'maladie de Degos'. *Bull Derm Soc Fr Dermatol Syphilol* 1948; **55**: 396.
38 Wollina U, Knopf B, Schaaschmidt H *et al.* Familiare Koexistenz von Erythrokeratodermia variabilis und Keratosis palmoplantaris transgrediens et progrediens. *Hautarzt* 1989; **40**: 169–72.
39 Gewirztman GB, Winkler NW, Dobson RL. Erythrokeratodermia variabilis: a family study. *Arch Dermatol* 1978; **114**: 259–61.
40 van de Kerkhof PC, Steijlen PM, van Dooren-Greebe RJ *et al.* Acitretin in the treatment of erythrokeratodermia variabilis. *Dermatologica* 1990; **181**: 330–3.
41 Heinisch S. PUVA bath therapy in erythrokeratodermia figurata variabilis. *Z Hautkrank* 1999; **74**: 445–6.
42 Papadavid E, Koumantaki E, Dawber RP. Erythrokeratoderma variabilis: case report and review of the literature. *J Eur Acad Dermatol Venereol* 1998; **11**: 180–3.

Progressive symmetrical erythrokeratoderma (MIM 602036)

Synonym
- Gottron's syndrome

In progressive symmetrical erythrokeratoderma (PSEK) [1–3], fixed plaques of hyperkeratotic erythema, which gradually extend during childhood, resemble those of EKV, but migratory erythema is not seen. In some pedigrees autosomal dominant inheritance is reported [3,4] but cases are often sporadic. PSEK is probably heterogeneous, and it's existence as an entity has been questioned [5]

since in practice it may be hard to distinguish the static symmetrical lesions of PSEK from the plaques and migratory geographic lesions of EKV.

Aetiology. Connexin or other mutations have not been demonstrated in undisputed cases of PSEK. In an atypical Japanese pedigree, lesions resembling PSEK were associated with honeycomb keratoderma, and an insertional mutation in loricrin of the type found in loricrin keratoderma with ichthyosis was identified [6]. In a Chinese pedigree with an autosomal dominant disorder diagnosed as PSEK, but involving predominantly hands and feet, a locus was identified at 21q11.2–21.2 [4]. In an apparent autosomal recessive case, *GJB3, GJB4* and loricrin mutations were excluded [7].

Pathology [8,9]. The epidermis is acanthotic with a preserved granular layer. The stratum corneum is hyperkeratotic with a basket-weave pattern and foci of parakeratosis. The variable presence of perinuclear vacuolation of keratinocytes further suggests heterogeneity. Ultrastructurally, the granular cells contain swollen mitochondria, and corneocytes show lipid-like vacuoles, both of which are reduced by etretinate therapy. Labelling studies show increased epidermopoiesis with shortening of the interphase [10].

Clinical features [3,11]. The skin is usually normal at birth. Large, geographical but symmetrical fine scaly plaques with an orange–red erythema appear in infancy (Fig. 19.36). There is little pruritus. The shoulder girdle, cheeks and buttocks are most often affected with limited plaques on the ankles and wrists. Keratoderma may be present. Hair and nails are usually normal, but one case showed thickened nails [12]. The plaques extend during childhood but become fixed or occasionally remit. Erythroderma present at birth [13], and onset delayed to 17 years [14], have been recorded. A family with mal de Meleda keratoderma first presenting with inguinal lesions was originally diagnosed as PSEK [15].



Fig. 19.36 Symmetrical progressive erythrokeratoderma: sharply demarcated 'geographical' orange–red plaques. (Courtesy of Dr A.G. Smith, North Staffordshire Hospital, Stoke-on-Trent, UK.)

Treatment. Limited data suggest that etretinate and acitretin are effective [14,16] although etretinate was reported in one patient to cause generalization of the erythema [13]. PUVA treatment has been reported [17].

References

1 Darier J. Erythrokeratodermie verruqueuse en nappes symetrique et progressive. *Bull Soc Fr Dermatol Syphilol* 1911; **2**: 252–64.
2 Gottron H. Congenital angelegte symmetrische progressive Erythrokeratodermie. *Zbl Haut Geschl* 1922; **4**: 493–4.
3 Rogers M. Erythrokeratodermas: a classification in a state of flux? *Australas J Dermatol* 2005; **46**: 127–41.
4 Cui Y, Yang S, Gao M *et al*. Identification of a novel locus for progressive symmetric erythrokeratodermia to a 19.02-cM interval at 21q11.2–21q21.2. *J Invest Dermatol* 2006; **126**: 2136–9.
5 van Steensel M. Does progressive symmetric erythrokeratoderma exist? *Br J Dermatol* 2004; **150**: 1043–5.
6 Ishida-Yamamoto A, McGrath JA, Lam H *et al*. The molecular pathology of progressive symmetric erythrokeratoderma: a frameshift mutation in the loricrin gene and perturbations in the cornified cell envelope. *Am J Hum Genet* 1997; **61**: 581–9.
7 Akhman A, Masse M, Mihci E *et al*. Progressive symmetrical erythrokeratoderma: report of a Turkish family and evaluation for loricrin and connexin gene mutations. *Clin Exp Dermatol* 2008; **33**: 582–4.
8 Niemi KM, Kanerva L. Histological and ultrastructural study of a family with erythrokeratodermia progressiva symmetrica. *J Cutan Pathol* 1993; **20**: 242–9.
9 Nazzaro V, Blanchet-Bardon C. Progressive erythrokeratodermia: histological and ultrastructural study of patient before and after treatment with etretinate. *Arch Dermatol* 1986; **122**: 434–40.
10 Hopsu-Havu VK, Tuohimaa P. Erythrokeratodermia congenitalis progressiva symmetrica (Gottron). II. An analysis of kinetics of epidermal cell proliferation. *Dermatologica* 1971; **142**: 137–44.
11 Ruiz-Maldonado R, Tamayo L, del Castillo V *et al*. Erythrokerato-dermia progressiva symmetrica: report of 10 cases. *Dermatologica* 1982; **164**: 133–41.
12 Kuchmeister B, Schaeg G, Kuhlwein A. Erythrokeratodermia congenitalis progressiva symmetrica Gottron mit atypischem Befall der Nagel im sinne einer Pachyonychie. *Z Hautkr* 1983; **58**: 621–32.
13 Sbano E, Convertini L, Altamura V *et al*. Eritrocheratodermia simmetrica e progressiva. *Ann Ital Dermatol Clin Sper* 1985; **39**: 229–36.
14 Borbujo-Martinez J, Casado-Jimenez M, Jimenez-Acosta F *et al*. Eritroqueratodermia simetrica y progresiva: aportacion de un caso de inicio tardio tratado con etretinato. *Med Cutan Ibero Lat Am* 1988; **16**: 236–8.
15 Fischer J, Bouadjar B, Heilig R *et al*. Mutations in the gene encoding SLURP-1 in mal de Meleda. *Hum Mol Genet* 2001; **10**: 875–80.
16 Tamayo L, Ruiz-Maldonado R. Oral retinoid (Ro-9359) in children with lamellar ichthyosis, epidermolytic hyperkeratosis and symmetrical progressive erythrokeratoderma. *Dermatologica* 1980; **161**: 305–14.
17 Ghetti P, De Padova MP, Bardazzi F *et al*. A case of erythrokeratodermia progressiva symmetrica: PUVA treatment. In: Wilkinson DS, Mascaro M, Orfanos CE, eds. *Clinical Dermatology: CMD Case Collection*. Stuttgart: Schattauer, 1987: 78.

Other syndromes featuring erythrokeratoderma

Erythrokeratoderma with sensorineural deafness [1] may be a form of KID syndrome (see above), now known to be due to mutations in connexin 26 [2,3]. Schnyder's syndrome (asymmetrical erythrokeratoderma with deafness, peripheral neuropathy, muscle

atrophy and mental retardation, and occasionally keratitis) [4–6] and overlapping syndromes may be pathogenetically related. Affected members of three Québécois pedigrees with a recessive disorder of this type were homozygous for a common haplotype at 7q22 but mutations were not found in the gene encoding connexin 31.3 at this locus [7]. In a five-generation Canadian pedigree, erythrokeratoderma appearing in infancy and clearing in later life was associated with late-onset ataxia and neuropathy (Giroux–Barbeau syndrome, MIM 133190) [8]; the defect maps to the connexin gene cluster at 1p34–p35 [9]. A reticulate erythrokeratoderma reported by Itin *et al*. was not due to *GJB3* or *GJB4* mutation [10]. A sporadic case of a boy with atypical erythrokeratoderma involved mainly the periorificial regions but he also had acral involvement and pachyonychia [11]. Vakilzadeh and Rose [12] described a boy with slowly migrating orange–brown plaques over the buttocks and legs from the age of 1 year, without large zones of erythema and without fixed plaques, so distinct from EKV and PSEK. Faninger [13] reported a case of localized hyperkeratosis resembling symmetrical interdigital keratoderma, but with marked underlying erythema.

References

1 Lamprecht A, Goecke T, Anton-Lamprecht I *et al.* Progressive erythrokeratodermia and cochlear hearing impairment: a case report and review of the literature. *Int J Pediatr Otorhinolaryngol* 1988; **15**: 279–89.
2 Richard GA, Rouan F, Willoughby CE *et al.* Mutations in *GJB-2* encoding connexin-26 cause the ectodermal dysplasia keratitis–ichthyosis–deafness syndrome. *Am J Hum Genet* 2002; **70**: 1341–8.
3 van Steensel MAM, van Geel M, Nahuys M *et al*. A novel Cx26 mutation in a patient diagnosed with the keratitis–ichthyosis–deafness syndrome. *J Invest Dermatol* 2002; **118**: 724–7.
4 Schnyder UW. Erythrokeratodermia progressiva (Krankendemonstration). *Arch Klin Exp Dermatol* 1964; **219**: 973–6.
5 Beare JM, Nevin NC, Froggatt P *et al.* Atypical erythrokeratoderma with deafness, physical retardation and peripheral neuropathy. *Br J Dermatol* 1972; **87**: 308–14.
6 Marghescu S, Wolff HH, Braun-Falco O. Kongenitale Erythrokeratodermie mit Taubheit Schnyder. *Hautarzt* 1982; **33**: 416–9.
7 Saba TG, Montpetit A, Verner A *et al.* An atypical form of erythrokeratodermia variabilis maps to chromosome 7q22. *Hum Genet* 2005; **116**: 167–71.
8 Giroux JM, Barbeau A. Erythrokeratodermia with ataxia. *Arch Dermatol* 1972; **106**: 183–8.
9 Richard G, Lin JP, Smith L *et al.* Linkage studies in erythrokeratodermias: fine mapping, genetic heterogeneity and analysis of candidate genes. *J Invest Dermatol* 1997; **109**: 666–71.
10 Itin PH, Moschopulos M, Richard G. Reticular erythrokeratoderma: a new disorder of cornification. *Am J Med Genet A* 2003; **120**: 237–40.
11 Michalowski R. Erythrokeratodermia periorificialis mit Akrenbeteiligung. *Hautarzt* 1983; **34**: 465–7.
12 Vakilzadeh F, Rose I. Erythrokeratodermia anularis migrans: eine neue Genodermatose? *Hautarzt* 1991; **42**: 634–7.
13 Faninger A. Ein kasuistischer Beitrag zur lokalisierten Erythrokeratodermie. *Hautarzt* 1956; **7**: 231.

Folliculocentric keratotic disorders

Keratosis pilaris (MIM 604093)

Keratosis pilaris [1,2] is characterized by keratinous plugs in follicular orifices with varying degrees of perifollicular erythema. Mild forms, appearing in childhood and reaching a peak incidence in adolescence, can be regarded as physiological. Mevorah *et al.* [3] recorded its presence in 44% of 155 normal people, but few were markedly affected. Prevalences of 2.7–4% are recorded in schoolchildren from various countries [4–6]. It is often seen in ichthyosis vulgaris [3]. It was present in 72% of 54 atopic black children with eczema [7], but in a group of white children only 37% of patients with keratosis pilaris had a personal history of atopy [8], and it is a poor discriminator of atopic eczema [9].

Aetiology. Follicular hyperkeratosis is a feature of several inherited disorders (see below) but keratosis pilaris may occur in isolation. Familial keratosis pilaris is seen in ichthyosis vulgaris due to loss of function mutations in filaggrin (*FLG*) [10]. Another locus is suggested by the occurrence of more severe forms with translocations and deletions of chromosome 18p [11–13]. An X-linked dominant form in women has been suggested [14].

Pathology. The follicular orifice is distended by a horny plug which may contain one or more twisted hairs. There may be mild inflammatory changes in the dermis. Lectin staining did not demonstrate abnormal keratinization [15].

Clinical features [9] (Fig. 19.37). Small grey–white plugs of keratin obstruct the mouths of the follicles, entrapping the hair. Extensor surfaces of the upper arms (92%), thighs (59%) and buttocks (30%) are most commonly involved. Occasional cases are generalized; sharply demarcated generalized but unilateral keratosis pilaris has been reported [16]. Uneven involvement of a given area is usual, with some follicles completely spared while adjacent ones are grossly plugged. Individual follicles show a long strand of keratin glinting when examined in side light (antenna sign).



Fig. 19.37 Keratosis pilaris on the extensor aspect of the upper arm.

Perifollicular erythema is often present, and may be psychologically distressing for the patient [17]. The age at onset was in the first decade in 51%, the second decade in 35% and the third decade in 12%. Improvement in the summer months was noticed in 49% [9]. Improvement with age is common, occurring at a mean age of 16 years [9]. The term keratosis rubra pilaris is used when erythema is marked, especially on the cheeks and eyebrows [18]. The erythematous component without plugging is also seen. Severely affected follicles may show a tiny pustule.

Associations. Keratosis pilaris is commoner in obesity and insulin-dependent diabetes [19]. Keratosis pilaris is seen in association with ichthyosis vulgaris including that associated with atopic eczema, rather than atopic eczema *per se* [3]. Keratosis pilaris (or 'follicular ichthyosis') also occurs with Noonan's and cardiofacial-cutaneous syndromes [20–23], renal insufficiency [24], prolidase deficiency [25], Down's syndrome [26] and various mental deficiencies, in which it overlaps with trichostasis spinulosa [27,28], and in Fairbanks' [29] and Olmsted's [30] syndromes. A syndrome with hypotrichosis and leukonychia is recognized [31,32]. Follicular hyperkeratoses occur in monilethrix, pachyonychia congenita and ectodermal dysplasias [33–40]. Follicular hyperkeratosis may be seen during systemic steroid [41] or lithium therapy [42] and with lichenoid disorders such as the Graham-Little syndrome.

Keratosis pilaris with atrophy [43–52]. Keratosis pilaris is sometimes succeeded by atrophy. The nosology is debated [43,44] as only keratosis follicularis spinulosa decalvans can be distinguished genetically at present. *Ulerythema ophryogenes* or *keratosis rubra pilaris faciei atrophicans* shows prominent facial erythema with involvement of the eyebrows and scalp and prominent atrophy, with simple keratosis pilaris on extensor surfaces, and may occur in Noonan's syndrome [22] or with woolly hair alone [40]. The late stage of a previously active case shows fine follicular atrophy. The isolated condition is thought to be inherited as an autosomal dominant [44]. *Atrophoderma vermiculatum* is rare, and affects the cheeks and preauricular regions with a combination of keratotic papules giving way to an atrophic worm-eaten appearance, and may be recessively inherited [44,51,52].

Erythromelanosis follicularis faciei et colli (Fig. 19.38). This is a triad of well-demarcated erythema, hyperpigmentation and follicular plugging on the cheeks [41,53], spreading onto the neck anterior to the angle of the mandible. The majority of cases are in Asian or Middle Eastern men [54–57], but women can be affected [58]. The disorder is probably a variant of keratosis pilaris in pigmented skin, since keratosis pilaris on the arms frequently coexists; overlap with ulerythema ophryogenes is also reported [59]. Juhlin and Alkemade [60] reported a woman with centrifacial erythrosis pigmentosa peribuccalis which moved onto the cheeks, and argued that these entities are also the same. Unilateral cases occur [61,62]. Reported dermal calcium deposition [63] has not been confirmed as a specific histological feature [54].

Follicular ichthyosis. The capacity of this term to describe an entity distinct from keratosis pilaris is doubtful. IFAP is discussed above. A report of follicular hyperkeratosis distinguished from keratosis pilaris may be Noonan's syndrome [64].



Fig. 19.38 Erythromelanosis follicularis faciei in a young Asian man.

Treatment. Simple emollients are rarely effective in keratosis pilaris. One recommended routine is based on initial control of the inflammatory component with a topical steroid, followed by 2% salicylic acid in 20% urea cream and an abrasive sponge [16]. Systemic retinoids are ineffective, and calcipotriol was not effective in nine patients [65], but benefit from topical tazarotene has been claimed [66].

References

1 Brocq L. Notes pour servir à l'histoire de la kératose pilaire. *Ann Dermatol Syphiligr* 1890; **1**: 25–37; 97–133; 238.

2 Touraine A. Essai de classification des keratoses congenitales. *Ann Dermatol* 1958; **85**: 257–66.

3 Mevorah B, Marazzi A, Frenck E. The prevalence of accentuated palmoplantar markings and keratosis pilaris in atopic dermatitis, autosomal dominant ichthyosis and control dermatological patients. *Br J Dermatol* 1985; **112**: 679–85.

4 Bechelli LM, Hadda N, Pimenta WP *et al.* Epidemiological survey of skin diseases in schoolchildren living in the Purus Valley (Acre State, Amazonia, Brazil). *Dermatologica* 1981; **163**: 78–93.

5 Popescu R, Popescu CM, Williams HC, Forsea D. The prevalence of skin conditions in Romanian school children. *Br J Dermatol* 1999; **140**: 891–6.

6 Fung WK, Lo KK. Prevalence of skin disease among school children and adolescents in a Student Health Service Center in Hong Kong. *Pediatr Dermatol* 2000; **17**: 440–6.

7 Macharia WM, Anabwani GM, Owili DM. Clinical presentation of atopic dermatitis in Negroid children. *Afr J Med Sci* 1993; **22**: 41–4.

8 Poskitt L, Wilkinson JD. Natural history of keratosis pilaris. *Br J Dermatol* 1994; **130**: 711–3.

9 Williams HC, Burney PG, Strachan D *et al.* The U.K. Working Party's diagnostic criteria for atopic dermatitis. II. Observer variation of clinical diagnosis and signs of atopic dermatitis. *Br J Dermatol* 1994; **131**: 397–405.

10 Sandilands A, O'Regan GM, Liao H *et al.* Prevalent and rare mutations in the gene encoding filaggrin cause ichthyosis vulgaris and predispose individuals to atopic dermatitis. *J Invest Dermatol* 2006; **126**: 1770–5.

11 Zouboulis CC, Stratakis CA, Rinck G *et al.* Ulerythema ophryogenes and keratosis pilaris in a child with monosomy 18p. *Pediatr Dermatol* 1994; **11**: 172–5.
12 Horsley SW, Knight SJ, Nixon J *et al.* Del (18p) shown to be a cryptic translocation using a multiprobe FISH assay for subtelomeric chromosome rearrangements. *J Med Genet* 1998; **35**: 722–6.
13 Nazarenko SA, Ostroverkhova NV, Vasiljeva EO *et al.* Keratosis pilaris and ulerythema ophryogenes associated with an 18p deletion caused by a Y/18 translocation. *Am J Med Genet* 1999; **85**: 179–82.
14 Voss M. Keratosis follicularis: neue genetische Aspekte. *Hautarzt* 1991; **42**: 319–21.
15 Martinez-Ojeda L, Ramirez-Bosca A, Valcuende-Cavero F *et al.* Marcaje mediante lectinas de trastornos en la queratinization II. *Med Cutan Ibero Lat Am* 1988; **16**: 183–6.
16 Ehsani A, Namazi MR, Barikbin B, Nazemi MJ. Unilaterally generalized keratosis pilaris. *J Eur Acad Dermatol Venereol* 2003; **17**: 361–2.
17 Novick NL. Practical management of widespread, atypical keratosis pilaris. *J Am Acad Dermatol* 1984; **11**: 305–6.
18 Marqueling AL, Gilliam AE, Prendiville J *et al.* Keratosis pilaris rubra: a common but underrecognized condition. *Arch Dermatol* 2006; **142**: 1611–6.
19 Yosipovitch G, DeVore A, Dawn A. Obesity and the skin: skin physiology and skin manifestations of obesity. *J Am Acad Dermatol* 2007; **56**: 901–16.
20 Armour CM, Allanson JE. Further delineation of cardio-facio-cutaneous syndrome: clinical features of 38 individuals with proven mutations. *J Med Genet* 2008: **45**: 249–54.
21 McHenry PM, Nevin NC, Bingham EA. The association of keratosis pilaris atrophicans with hereditary woolly hair. *Pediatr Dermatol* 1990; **7**: 202–4.
22 Occella C, Gargani FF, Rampini E *et al.* Sindrome di Noonan e keratosis pilaris atrophicans faciei. *Minerva Pediatr* 1985; **37**: 181–6.
23 Nield VS, Pegum JS, Wells RS. The association of keratosis pilaris atrophicans and woolly hair, with and without Noonan's syndrome. *Br J Dermatol* 1984; **110**: 357–62.
24 Guillet G, Sanciaume C, Hehunestre JP *et al.* Kératose pilaire generalisée et hypervitaminose A chez une enfant insuffisante rénale. *Ann Dermatol Vénéréol* 1982; **109**: 1061–6.
25 Larregue M, Charpentier C, Laidet B *et al.* Deficit en prolidase et en manganese. *Ann Dermatol Vénéréol* 1982; **109**: 667–8.
26 Finn OA, Grant PW, McCallum DI *et al.* A singular dermatosis of Mongols. *Arch Dermatol* 1978; **114**: 1493–4.
27 Cantu JM, Hernandez A, Larracilla J *et al.* A new X-linked recessive disorder with dwarfism, cerebral atrophy, and generalized keratosis follicularis. *J Pediatr* 1974; **84**: 564–7.
28 Coombs FP, Butterworth T. Atypical keratosis pilaris. *Arch Dermatol Syphilol* 1950; **62**: 305–13.
29 Marks R. Follicular hyperkeratosis and ocular abnormalities associated with Fairbank's syndrome. *Br J Dermatol* 1967; **79**: 118–9.
30 Perry HO, Su WP. Olmsted syndrome. *Semin Dermatol* 1995; **14**: 145–51.
31 Basaran E, Yilmaz E, Alpsoy E *et al.* Keratoderma, hypertrichosis and leukonychia totalis: a new syndrome? *Br J Dermatol* 1995; **133**: 636–8.
32 Galardi I, Mohsen S. Leukonychia totalis associated with keratosis pilaris and hyperhidrosis. *Int J Dermatol* 1993; **32**: 524–5.
33 Carnabuci GJ, Rosenberg PE. Monilethrix and keratosis pilaris. *Arch Dermatol* 1967; **96**: 594.
34 Leachman SA, Kaspar RL, Fleckman P *et al.* Clinical and pathological features of pachyonychia congenita. *J Investig Dermatol Symp Proc* 2005; **10**: 3–17.
35 Thai KE, Sinclair RD. Keratosis pilaris and hereditary koilonychia without monilethrix. *J Am Acad Dermatol* 2001; **45**: 627–9.
36 Abramovitz-Ackerman W, Bustos T, Simosa-Leon V *et al.* Cutaneous findings in a new syndrome of autosomal recessive ectodermal dysplasia with corkscrew hairs. *J Am Acad Dermatol* 1992; **27**: 917–21.
37 Halal F, Setton N, Wang NS. A distinct type of hidrotic ectodermal dysplasia. *Am J Med Genet* 1991; **38**: 552–6.
38 Scheman AJ, Ray DJ, Witkop CJ Jr *et al.* Hereditary mucoepithelial dysplasia: case report and review of the literature. *J Am Acad Dermatol* 1989; **21**: 351–7.
39 Appell ML, Sheretz EF. A kindred with alopecia, keratosis pilaris, cataracts, and psoriasis. *J Am Acad Dermatol* 1987; **16**: 89–95.
40 Chien AJ, Valentine MC, Sybert VP. Hereditary woolly hair and keratosis pilaris. *J Am Acad Dermatol* 2006; **54**: S35–S39.
41 Whittaker SJ, Griffiths WAD. Erythromelanosis follicularis faciei et colli. *Clin Exp Dermatol* 1987; **12**: 33–5.
42 Wakelin SH, Lipscombe T, Orton DI, Marren P. Lithium induced follicular hyperkeratosis. *Clin Exp Derm* 1996; **21**: 296–8.
43 Baden HW, Byers R. Clinical findings, cutaneous pathology, and response to therapy in 21 patients with keratosis pilaris atrophicans. *Arch Dermatol* 1994; **130**: 469–75.
44 Oranje AP, van Osch LDM, Oosterwijk JC. Keratosis pilaris atrophicans: one heterogeneous disease or a symptom in different clinical entities? *Arch Dermatol* 1994; **130**: 500–2.
45 Quinquaud CE. Folliculite épilante et destructive des regions velues. *Bull Mem Soc Med Hop Paris* 1888; **5**: 395.
46 Taenzer P. Uber das Ulerythema ophryogenes. *Monatsh Prakt Dermatol* 1889; **8**: 197–208.
47 McKee GM, Parounagian MB. Folliculitis ulerythematosa reticulata. *J Cutan Dis* 1918; **36**: 339–52.
48 Arnold AW, Buechner SA. Keratosis pilaris and keratosis pilaris atrophicans faciei. *J Dtsch Dermatol Ges* 2006; **4**: 319–23.
49 Pierini DO, Pierini AM. Keratosis pilaris atrophicans faciei (ulerythema ophryogenes): a cutaneous marker in the Noonan syndrome. *Br J Dermatol* 1979; **100**: 409–16.
50 Grob JJ, Laure M, Berge G *et al.* Les signes cutanes du syndrome de Noonan: à propos d'une observation avec ulerytheme ophryogene, kératose pilaire et sudorale disseminée et alopecie progressive. *Ann Dermatol Vénéréol* 1988; **115**: 303–10.
51 Frosch PJ, Brumage MR, Schuster-Pavlovic C *et al.* Atrophoderma vermiculatum. *J Am Acad Dermatol* 1988; **18**: 538–42.
52 Jansen T, Sander CA, Altmeyer P. Atrophodermia vermiculata: case report and review of the literature. *J Eur Acad Dermatol Venereol* 2003; **17**: 70–2.
53 Andersen BL. Erythromelanosis follicularis faciei et colli. *Br J Dermatol* 1980; **102**: 323–5.
54 Min GK, Seok JH, Sook JS *et al.* Quantitative histopathologic findings of erythromelanosis follicularis faciei et colli. *J Cutan Pathol* 2002; **28**: 160–4.
55 Sodaify M. Erythromelanosis follicularis faciei et colli. *Int J Dermatol* 1994; **33**: 643–4.
56 Ermertcan AT, Ozturkcan S, Sahin MT *et al.* Erythromelanosis follicularis faciei et colli associated with keratosis pilaris in two brothers. *Pediatr Dermatol* 2006; **23**: 31–4.
57 Sardana K, Relhan V, Garg V, Khurana N. An observational analysis of erythromelanosis follicularis faciei et colli. *Clin Exp Dermatol* 2008; **33**: 333–6.
58 Warren FM, Davis LS. Erythromelanosis follicularis faciei in women. *J Am Acad Dermatol* 1995; **32**: 863–6.
59 Seki T, Tkahashi S, Morohashi M. A case of erythromelanosis follicularis faciei with a unique distribution. *J Dermatol* 1991; **18**: 167–70.
60 Juhlin L, Alkemade H. Erythrosis pigmentosa mediofacialis (Brocq) and erythromelanosis follicularis faciei et colli in the same patient. *Acta Derm Venereol (Stockh)* 1999; **79**: 65–6.
61 McGillis ST, Tuthill RJ, Ratz JL *et al.* Unilateral erythromelanosis follicularis faciei et colli in a young girl. *J Am Acad Dermatol* 1991; **25**: 430–2.
62 Borkovic SP, Schwartz RA, McNutt NS. Unilateral erythromelanosis follicularis faciei et colli. *Cutis* 1984; **33**: 163–70.
63 Lee CW, Yang IS. Cutaneous calcinosis in erythromelanosis follicularis faciei et colli. *Clin Exp Dermatol* 1987; **12**: 31–2.
64 Hazell M, Marks R. Follicular ichthyosis. *Br J Dermatol* 1984; **111**: 101–9.
65 Kragballe K, Steijlen PM, Ibsen HH *et al.* Efficacy, tolerability, and safety of calcipotriol ointment in disorders of keratinization: results of a randomized, double-blind, vehicle-controlled, right–left comparative study. *Arch Dermatol* 1995; **131**: 556–60.
66 Gergbig AW. Treating keratosis pilaris. *J Am Acad Dermatol* 2002; **47**: 457.

Keratosis follicularis spinulosa decalvans (MIM 308800)

Keratosis follicularis spinulosa decalvans (KFSD) [1,2] is an X-linked recessive disorder mapped to a locus at Xp21.13–p22.2 [3,4]; there may also be an autosomal form [3,5,6]. A child with a complex phenotype including KFSD had a duplication of Xp21.1–



Fig. 19.39 Keratosis follicularis spinulosa decalvans showing atrophy and loss of scalp hair.

p22.12 which included the spermidine/spermine N(1)-acetyltransferase (*SSAT*) gene [7]. It was suggested that because mice overexpressing SSAT develop hair loss [8], mutations resulting in overexpression of this gene might be responsible for KFSD. Keratotic follicular papules develop on the scalp in the first few years of life [9–13] followed by progressive scarring alopecia resembling folliculitis decalvans with variable degrees of inflammatory change (Fig. 19.39). Erythema and plugging of eyebrow follicles, follicular hyperkeratosis and prominent cuticles are seen. Ocular signs include blepharitis, ectropion, corneal dystrophy and photophobia. Variable focal plantar keratoderma may be present [14]. Female heterozygotes may exhibit a mild phenotype [11,13]. The cutaneous and ocular features overlap with ichthyosis follicularis and photophobia in which palmoplantar involvement is absent [15,16]. Other reported associations include Noonan's syndrome [17], deafness [18], cutis laxa, big pinnae and clinodactyly [19], and aminoaciduria high in aspartic acid [20]. Treatment is generally unsatisfactory. *Staphylococcus aureus* is occasionally found in the inflamed lesions but antibiotic therapy does not help. Retinoids, either topically or systemically, produce little improvement [21] but were helpful in one report [12].

References

1 Siemens HW. Keratosis follicularis spinulosa decalvans. *Arch Dermatol Syphilol* 1926; **151**: 384–7.
2 Bogg A. Folliculitis decalvans. *Acta Derm Venereol (Stockh)* 1963; **43**: 14–24.
3 Oosterwijk JC, Richard G, van der Wielen MJ *et al.* Molecular genetic analysis of two families with keratosis follicularis spinulosa decalvans: refinement of gene localization and evidence for genetic heterogeneity. *Hum Genet* 1997; **100**: 520–4.
4 Porteous ME, Strain L, Logie LJ, Herd RM, Benton EC. Keratosis follicularis spinulosa decalvans: confirmation of linkage to Xp22.13-p22.2. *J Med Genet* 1998; **35**: 336–7.
5 Khumalo NP, Loo WJ, Hollowood K *et al*. Keratosis pilaris atrophicans in mother and daughter. *J Eur Acad Dermatol Venereol* 2002; **16**: 397–400.
6 Helbig D, Grabbe S, Jansen T. Keratosis follicularis spinulosa decalvans. *Hautarzt* 2008; **59**: 46–9.
7 Gimelli G, Giglio S, Zuffardi O *et al.* Gene dosage of the spermidine/spermine N(1)-acetyltransferase (SSAT) gene with putrescine accumulation in a patient with a Xp21.1p22.12 duplication and keratosis follicularis spinulosa decalvans (KFSD). *Hum Genet* 2002; **111**: 235–41.
8 Pietilä M, Parkkinen JJ, Alhonen L, Jänne J. Relation of skin polyamines to the hairless phenotype in transgenic mice overexpressing spermidine/spermine N-acetyltransferase. *J Invest Dermatol* 2001; **116**: 801–5.
9 Rand R, Baden HP. Keratosis follicularis spinulosa decalvans: report of two cases and literature review. *Arch Dermatol* 1983; **119**: 22–6.
10 Baden HW, Byers R. Clinical findings, cutaneous pathology, and response to therapy in 21 patients with keratosis pilaris atrophicans. *Arch Dermatol* 1994; **130**: 469–75.
11 van Osch LD, Oranje AP, Keukens FM *et al.* Keratosis follicularis spinulosa decalvans: a family study of seven male cases and six female carriers. *J Med Genet* 1992; **29**: 36–40.
12 Richard G, Harth W. Keratosis follicularis spinulosa decalvans: therapie mit isotretinoin und etretinat im entzundlichen stadium. *Hautarzt* 1993; **44**: 529–34.
13 Herd RM, Benton EC. Keratosis follicularis spinulosa decalvans: report of a new pedigree. *Br J Dermatol* 1996; **134**: 138–42.
14 Stevanovic DV. Keratosis follicularis spinulosa decalvans with birefringent hairs: an association with variable keratoderma. *Dermatol Monatsschr* 1988; **174**: 736–40.
15 Eramo LR, Esterly NB, Zieserl EJ *et al.* Ichthyosis follicularis with alopecia and photophobia. *Arch Dermatol* 1985; **121**: 1167–74.
16 Appell ML, Sherertz EF. A kindred with alopecia, keratosis pilaris, cataracts, and psoriasis. *J Am Acad Dermatol* 1987; **16**: 89–95.
17 Grob JJ, Laure M, Berge G *et al.* Les signes cutanes du syndrome de Noonan: à propos d'une observation avec ulerytheme ophryogene, kératose pilaire et sudorale disseminée et alopecie progressive. *Ann Dermatol Vénéréol* 1988; **115**: 303–10.
18 Britton H, Lustig J, Thompson BJ *et al.* Keratosis follicularis spinulosa decalvans: an infant with failure to thrive, deafness, and recurrent infections. *Arch Dermatol* 1978; **114**: 761–4.
19 Domenech P, Ferrando J, Corretger M *et al.* Queratosis folicular espinulosa decalvante (sindrome de Siemens) asociada a otras anomalias. *Med Cutan Ibero Lat Am* 1985; **13**: 175–81.
20 Grosshans E, Heid E, Stoll C. Keratosis follicularis spinulosa decalvans et aminoacidurie. *Ann Dermatol Vénéréol* 1978; **105**: 433–8.
21 Puppin D, Aractingi S, Dubertret L *et al.* Keratosis follicularis spinulosa decalvans: report of a case with ultrastructural study and unsuccessful trial of retinoids. *Dermatology* 1992; **184**: 133–6.

Other folliculocentric disorders

Lichen spinulosus (syn. keratosis spinulosa). Typical grouped lesions appear predominantly in childhood as crops of minute follicular papules, each with a projecting keratinous spine [1,2] and without erythema, chiefly about the neck, buttocks, trochanteric regions, abdomen, thighs, popliteal spaces and extensor aspects of the arms (Fig. 19.40). The face, hands and feet are usually spared. The isolated disorder is rare, but similar appearances may arise in lichen planus, seborrhoeic dermatitis and reactions to dermatophytes, syphilis and tuberculosis. Friedman [2] studied 35 cases and concluded that it was probably a reaction pattern to several pathogenic processes. Many older reported cases show follicular atrophy and loss of scalp hair, and might be ulerythema ophryogenes. One case was associated with Crohn's disease [3] and another was considered to be a reaction to omeprazole [4]. In human immunodeficiency virus (HIV) associated follicular syndrome, lesions termed 'PRP-like' or 'lichen spinulosus-like' appear to be more filiform and florid [5].

Phrynoderma. This condition, rare in developed countries, is a distinctive form of follicular keratosis associated with nutritional deficiency first reported among prisoners in Beijing province [6]. Horny plugs with perifollicular papules are seen on the elbows, knees, neck and posterior axillary fold. The lesions are 2–3 mm in



Fig. 19.40 Lichen spinulosus: even flesh-coloured grouped keratotic papules.

diameter and easily distinguished from keratosis pilaris. Adjacent skin may be pigmented and scaly. Hypovitaminosis A, although implicated, is not always present, and complex nutritional problems may be involved [7].

Keratosis follicularis squamosa (Dohi). This is an acquired disorder of follicular hyperkeratosis with a surrounding scale 'like lotus leaves on the water', well-recognized in Japan, but apparently unusual elsewhere [8]. The condition responds to antibiotics or tacalcitol [9].

Disseminate and recurrent infundibulofolliculitis. This striking eruption of unknown cause has been reported almost exclusively in young black male adults [10,11]. Recent reports are few. Profuse, monomorphic, tiny follicular papules with a variable degree of follicular plugging occur mainly over the trunk and back. There is no erythema. The epithelium of the upper follicle is oedematous and in parts spongiotic, and is surrounded by a predominantly lymphocytic infiltrate. Immunofluorescence was negative [11]. Both recurrent and chronic cases have been described. It has been suggested that it is a reaction pattern of atopic eczema in black people. The condition may respond to oral vitamin A [12], isotretinoin [12,13] or photochemotherapy [14].

Familial dyskeratotic comedones [15–18]. This is an autosomal dominant condition characterized by scattered comedo-like lesions. The lesions appear around puberty, showing a predilection for the trunk, arms, legs, face and the shaft of the penis. The glans, and palms and soles are spared. The comedones can be picked out without producing bleeding. The lesions reform over a few weeks, and the condition gradually worsens with time. The lesions usually lack any inflammatory signs, but around puberty approximately 50% may show concomitant acne. Histologically, there is a lamellar keratin plug with patchy parakeratosis; there may be acantholysis and scattered but not universal evidence of dyskeratosis. A naevus comedonicus is usually unilateral and the lesions are more closely packed [19]. Retinoid therapy has proved unrewarding.

References

1 Adamson HG. On a form of chronic superficial dermatitis in circumscribed patches with symmetrical distribution occurring in children. *Br J Dermatol* 1908; **20**: 109–22.
2 Friedman SJ. Lichen spinulosus: clinicopathologic review of thirty-five cases. *J Am Acad Dermatol* 1990; **22**: 261–4.
3 Kano Y, Orihara M, Yagita A *et al.* Lichen spinulosus in a patient with Crohn's disease. *Int J Dermatol* 1995; **34**: 670–1.
4 Lee ML, Piper DW, Fischer GO *et al.* Lichen spinulosus after the ingestion of omeprazole. *Med J Aust* 1989; **150**: 410.
5 Resnick SD, Murrell DF, Woosley J. Acne conglobata and a generalized lichen spinulosus-like eruption in a man seropositive for human immunodeficiency virus. *J Am Acad Dermatol* 1992; **26**: 1013–4.
6 Frazier CN, Chuan-kuei Hu. Nature and distribution according to age of cutaneous manifestations of vitamin A deficiency: a study of 207 cases. *Arch Dermatol* 1936; **33**: 825–52.
7 Maronn M, Allen DM, Esterly NB. Phrynoderma: a manifestation of vitamin A deficiency? . . . The rest of the story. *Pediatr Dermatol* 2005; **22**: 60–3.
8 Shimizu S, Shimizu T, Tateishi Y, Shimizu H. Keratosis follicularis squamosa (Dohi): a follicular keratotic disorder well known in Japan. *Br J Dermatol* 2000; **144**: 1070–2.
9 Sadahira C, Yoneda K, Moriue T *et al*. Successful treatment of keratosis follicularis squamosa with topical tacalcitol. *Br J Dermatol* 2006; **154**: 1010–2.
10 Hitch JM, Raleigh NC, Lund HZ. Disseminate and recurrent infundibulo-folliculitis. *Arch Dermatol* 1968; **97**: 432–5.
11 Owen WR, Wood C. Disseminate and recurrent infundibulofolliculitis. *Arch Dermatol* 1979; **115**: 174–5.
12 Calka O, Metin A, Ozen S. A case of disseminated and recurrent infundibulofolliculitis responsive to treatment with systemic isotretinoin. *J Dermatol* 2002; **29**: 431–4.
13 Aroni K, Grapsa A, Agapitos E. Disseminate and recurrent infundibulofolliculitis: response to isotretinoin. *J Drugs Dermatol* 2004; **3**: 434–5.
14 Ravikumar BC, Balachandran C, Shenoi SD *et al*. Disseminate and recurrent infundibulofolliculitis: response to psoralen plus UVA therapy. *Int J Dermatol* 1999; **38**: 75–6.
15 Cantu DJM, Gomez-Bustamente MO, Gonzalez-Mendoza A *et al*. Familial comedones. *Arch Dermatol* 1978; **114**: 1807–9.
16 Hall JR, Holder W, Knox J *et al*. Familial dyskeratotic comedones. *J Am Acad Dermatol* 1987; **17**: 808–14.
17 Leppard BJ. Familial dyskeratotic comedones. *Clin Exp Dermatol* 1982; **7**: 329–32.
18 Price M, Russell-Jones R. Familial dyskeratotic comedones. *Clin Exp Dermatol* 1985; **10**: 147–53.
19 Giam YK, Ong BH, Rajan VS. Naevus comedonicus in homozygous twins. *Dermatologica* 1981; **162**: 249–53.

Pityriasis rubra pilaris

Pityriasis rubra pilaris (PRP) is a group of rare disorders that have in common circumscribed follicular keratoses, branny scale and an orange-red erythema, and palmoplantar keratoderma [1–5]. Incidence was approximately 1 in 5000 among patients presenting to a specialist dermatology centre. Of several classifications [6–8] that of Griffiths [6] has been most widely used. There is a bimodal age of onset [9,10]. Juvenile and adult forms of PRP, particularly atypical forms, may be unrelated disorders although transition between types is recognized.

Aetiology. The causes are unknown. Rarely, the disorder is familial (MIM 173200) [11,12], but remitting congenital PRP in two daughters of a chronically affected mother may indicate transplacental transmission rather than inheritance [13]. An infective aetiology is suggested, especially in the juvenile form [14–18], and a

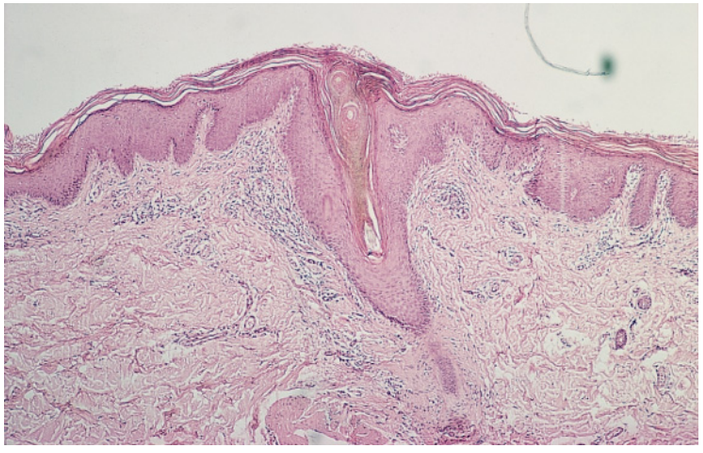


Fig. 19.41 Histopathology of pityriasis rubra pilaris: follicular plugging, acanthosis with exaggerated follicular shoulders, spotty parakeratosis and mild upper dermal inflammatory infiltrate.

Table 19.3 Some differences between pityriasis rubra pilaris and psoriasis.

	Pityriasis rubra pilaris	Psoriasis
Age at onset	Bimodal	Second decade
Scalp scaling	Furfuraceous	Adherent
Keratoderma	Constant	Less common
'Islands' of pale skin	Constant	Less common
Nail changes	No salmon patches	Present
Nail growth rate	Moderate increase	Marked increase
Epidermal kinetics	Moderate increase	Marked increase
Munro microabscesses	Absent	Common
Response to UVB	Poor	Good
Response to corticosteroids	Poor	Positive
Response to methotrexate	Variable	Good
Seronegative arthropathy	Rare	Common

PRP-like eruption is seen in patients with HIV [19]. Human leukocyte antigen (HLA) phenotype frequencies in 31 Finnish PRP patients did not differ significantly from those in a control population [17]. Epidermal thymidine labelling is increased [20–22] from an average normal 3% to 27%, and nail growth is accelerated (although less so than in psoriasis).

Pathology [23,24]. The histology of classical adult PRP is distinctive, but varies with the stage of the process, and may differ from site to site. Affected follicles are filled with dense horny plugs and there are foci of parakeratosis in the perifollicular shoulder and interfollicular epidermis (Fig. 19.41). At other sites, basket-weave hyperkeratosis overlies a prominent granular layer and there is little parakeratosis, but there may also be attenuation of granular and horny layers. Dermal capillaries are dilated, but not tortuous, and there is a lymphohistiocytic dermal infiltrate. Unlike psoriasis, the acanthotic epidermis is not thinned above the dermal papillae, and there is no neutrophil infiltration. In discriminating PRP from psoriasis, follicular plugging and an increased granular layer in PRP may be valuable signs [24], but focal acantholysis also occurs. In one study there was increased staining of keratinocytes for β-D-galactose [25]. Expression of keratins K6/K16, a marker of epidermal proliferation, was present in affected epidermis in familial cases [12]. Circumscribed juvenile PRP shows dense lamellated hyperkeratosis with a normal or increased granular layer and little acanthosis. There is little capillary dilatation, and a sparse histiocytic dermal infiltrate. The pattern of keratin components seen by protein gel electrophoresis indicated a rapid epidermal turnover, as in normal skin, following adhesive-tape stripping of the stratum corneum, which contrasts markedly with that found in psoriasis [26]. Ultrastructural changes of uncertain significance have been reported [14,27].

Clinical features. In view of the clinical and histological heterogeneity, confident diagnosis of PRP necessitates strict criteria, and in the early or late stages of disease distinctive findings may be lacking. Repeated observation and multiple biopsies may be necessary. Psoriasis, notably follicular psoriasis in children [28], may present difficulties, but these are resolved by the clinical course or histology of psoriasis. Some differences between psoriasis and PRP are indicated in Table 19.3. Atypical forms of PRP must be regarded as provisional diagnostic categories.

Type I: Adult onset, classical. The most common and recognizable form, classical adult PRP, affects the sexes equally with highest incidence between 40 and 60 years of age. The eruption usually starts without obvious precipitating factors as an erythematous, slightly scaly macule on the head, neck or upper trunk. Further macules appear within a few weeks, then a profusion of erythematous perifollicular papules with a central keratotic acuminate plug. Follicular lesions appear singly at first, and then coalesce to form groups of two, three or more (Fig. 19.42). Irritation is initially absent, but may be pronounced as the disease spreads. Interfollicular erythema appears, and the follicular lesions are gradually submerged in sheets of erythema with a slight orange colour, which typically spreads from head to feet [6]. The face becomes uniformly erythematous and mild ectropion may follow. Prolonged erythema may give rise to peripheral oedema, and in the elderly precipitate high-output cardiac failure. The scalp shows diffuse bran-like scaling. The palms and soles become hyperkeratotic and yellow (PRP 'sandal'; Fig. 19.43). Erythroderma frequently develops within 2–3 months. In most cases, sharply demarcated islands of unaffected skin 1 cm in diameter remain as a helpful diagnostic sign (island of sparing). Islands of deeper erythema are also sometimes seen. The nails are thickened and discoloured distally, showing splinter haemorrhages, but unlike psoriasis there is no dystrophy of the nail plate and pitting is minimal [29] (Fig. 19.44). Spontaneous resolution occurs in 60–80% of patients in 1–3 years, but the condition may persist indefinitely [9,10]. The eruption resembles seborrhoeic dermatitis as it resolves. Relapses are rare [30].

Type II: Adult-onset, atypical. This uncommon variety affects some 5% of patients. Follicular hyperkeratosis is prominent in some areas, while more lamellar scaling may be seen elsewhere, especially on the legs. Many patients show areas of eczematous



(a)



(b)

Fig. 19.42 Pityriasis rubra pilaris type I: (a) cephalocaudal spread of follicular papules; and (b) follicular papules beginning to coalesce.



Fig. 19.43 Pityriasis rubra pilaris (PRP) type I: the PRP 'sandal'.



Fig. 19.44 Pityriasis rubra pilaris type I: thickening of the nails, subungual hyperkeratosis and splinter haemorrhages.

change. The orderly caudal progression seen in type I does not occur and there is less tendency for the disease to become erythrodermic.

Type III: Juvenile-onset, classical [31] (Fig. 19.45). The onset is between the ages of 5 and 18 [31]. It resembles type I PRP, but may rapidly follow acute infection [15–18], and spontaneous clearing is usual within 1–2 years [7,31]. Evolution from type III to type IV and *vice versa* may occur [31,32]. A case of childhood PRP recurring 15 years later in adulthood is recorded [33]. The atypical varieties described below are less exanthematic and have a poorer prognosis.

Type IV: Juvenile-onset, circumscribed. This usually occurs below the age of 12 years [31]. Well-demarcated plaques of follicular plugging with variable degrees of erythema appear on the knees and elbows (Fig. 19.46). A few scattered scaly erythematous macules are often found on the trunk or in the scalp. Some cases also show marked keratoderma. The histological changes are more reminiscent of psoriasis, but lack neutrophil microabscesses, and evolution to psoriasis is not reported. *Keratosis circumscripta*—prominent follicular papules on the knees, elbows, nape of the neck, and posterior axillary folds—reported in African patients may be the same disorder [34–36]. Circumscribed juvenile PRP must also be differentiated from the erythrokeratodermas. The prognosis is uncertain but some cases clear in the late teens.

Type V: Juvenile-onset, atypical. Familial PRP is often of this type, which overlaps clinically with ichthyoses and erythrokeratoderma [12]. Patients show erythema and hyperkeratosis at birth or in the first few years of life. Follicular plugging and erythema suggest a diagnosis of PRP, but keratoderma is common and several patients have shown a scleroderma-like change of the digits. The disorder is chronic, but in two girls with congenital type V PRP born to a mother with type 1 disease appeared self-limiting [13].



Fig. 19.45 Pityriasis rubra pilaris type III: orange-red erythema with cephalocaudal spread.



Fig. 19.46 Pityriasis rubra pilaris type IV (circumscribed juvenile PRP) showing well-demarcated plaques of follicular plugging.

PRP and immunodeficiency. A PRP-like eruption associated with HIV infection and responding to antiretroviral therapy is recognized [37,38]. Some cases resemble classical PRP, but others show a filiform pattern of keratoses on the face and upper trunk and often have marked acne conglobata [39–41]. The term *type VI PRP* has been proposed [40] but HIV-associated follicular syndrome seems preferable. Hypogammaglobulinaemia [42] has been reported in an isolated case.

Investigation. There are no diagnostic laboratory tests for PRP. Plasma vitamin A and carotenoid levels are normal [43] and reduced serum retinol-binding protein has been disputed [44,45]. Elevated cellular retinol-binding protein (CRBP) and cellular retinoic acid-binding protein (CRABP) levels similar to those found in plaques of psoriasis are reported [46]. Elevation of parathyroid hormone level [47] was not confirmed in five patients (W.A.D. Griffiths, unpublished data). Takematsu *et al.* [48,49] reported a normal level of leukotriene B_4 (LTB_4) and low levels of anaphylotoxins in scale extracts from PRP, within the range found for normal and non-inflamed skin, and differing from psoriatic scale. Shvili *et al.* [50] reported activated suppressor T cells and impairment of helper T-cell function.

Associated disorders. Many associations of uncertain significance have been reported. PRP has been associated with leukaemia [51], Sézary syndrome [52], or other malignancy [53,54]. Conversely, Sézary syndrome and chronic T-cell lymphomas can mimic PRP [55,56]. PRP-like eruptions may also be seen with arthropathies [57–60] and in 'Wong type' dermatomyositis [61,62]. A patient with type I PRP had lichen planus, alopecia universalis, vitiligo and chronic viral hepatitis C [63]. Another developed Kaposi's varicelliform eruption from herpes simplex virus [64]. Photosensitivity and worsening with UVB and UVA have been noted [65,66]. Other reported associations have been reviewed [3].

Treatment. Intensive topical and supportive treatment is needed for the erythrodermic state. Rest and emollient applications reduce exfoliation, and help to restore the skin barrier. Topical and systemic corticosteroids are ineffective. Topical vitamin D analogues are reported to be beneficial [67]. Oral retinoids are widely used [68–74], but no systematic trials have been conducted, and results are unpredictable, with some patients showing dramatic clearing while others appear to be resistant. In children, isotretinoin produced the best response [31]. In the erythrodermic phase, acitretin or isotretinoin are used [73,74]. Methotrexate has been effective as an alternative or adjunct to oral retinoids [69,73,74], but may be less efficacious in PRP than in psoriasis [3,31]. Success [75–78] and failure [69,79] with ciclosporin are reported. Single reports have claimed effectiveness for fumaric acid esters in atypical juvenile PRP [80], intravenous immunoglobulin in adult type II PRP [81], and thyroid replacement therapy in a patient with hypothyroidism [82]. Biological agents such as infliximab, etanercept and efalizumab, sometimes with acetretin, were thought to be effective in some but not all cases [83–91]. Phototherapy may also exacerbate the condition, but narrow-band UVB, UVA1, PUVA, bath PUVA and extracorporeal photopheresis have all been reported as beneficial [73,92–95]. Phototherapy may be combined with acitretin

[96,97], and capsaicin was used to relieve phototherapy pruritus [98]. Antiretroviral therapy, of value in the PRP-like eruption of HIV disease [99], did not help three non-HIV cases [100].

References

1 Davidson CL Jr, Winkelmann RK, Kierland RR. Pityriasis rubra pilaris: a follow-up study of 57 patients. *Arch Dermatol* 1969; **100**: 175–8.
2 Griffiths WA. Pityriasis rubra pilaris: an historical approach. *Trans St John's Hosp Dermatol Soc* 1975; **61**: 58–69.
3 Griffiths WA. Pityriasis rubra pilaris: an historical approach. II. Clinical features. *Clin Exp Dermatol* 1976; **1**: 37–50.
4 Cohen PR, Prystowsky JH. Pityriasis rubra pilaris: a review of diagnosis and treatment. *J Am Acad Dermatol* 1989; **20**: 801–7.
5 Albert MR, Mackool BT. Pityriasis rubra pilaris. *Int J Dermatol* 1999; **38**: 1–11.
6 Griffiths WA. Pityriasis rubra pilaris. *Clin Exp Dermatol* 1980; **5**: 105–12.
7 Gelmetti C, Schiuma AA, Cerri D *et al.* Pityriasis rubra pilaris in childhood: a long-term study of 29 cases. *Pediatr Dermatol* 1986; **3**: 446–51.
8 Piamphongsant T, Akaraphant R. Pityriasis rubra pilaris: a new proposed classification. *Clin Exp Dermatol* 1994; **19**: 134–8.
9 Sanchez-Regana M, Creus L, Umbert P. Pityriasis rubra pilaris: a long-term study of 25 cases. *Eur J Dermatol* 1994; **4**: 593–7.
10 Sorensen KB, Thestrup-Pedersen K. Pityriasis rubra pilaris. A retrospective analysis of 43 patients. *Acta Derm Venereol (Stockh)* 1999; **79**: 405–6.
11 Kuster W, Happle R. Genetics of pityriasis rubra pilaris: autosomal dominant or polygenic inheritance? *Aktuelle Dermatol* 1985; **11**: 25–8.
12 Vanderhooft SL, Francis JS, Holbrook KA *et al*. Familial pityriasis rubra pilaris. *Arch Dermatol* 1995; **131**: 448–53.
13 Thomson MA, Moss C. Pityriasis rubra pilaris in a mother and two daughters. *Br J Dermatol* 2007; **157**: 202–4.
14 Larregue M, Champion R, Bressieux J-M *et al.* Le pityriasis rubra pilaire aigu de l'enfant. *Ann Dermatol Vénéréol* 1983; **110**: 221–8.
15 Varma S, Logan RA. Exanthematic pityriasis rubra pilaris. *Br J Dermatol* 1999; **141**: 769–71.
16 Betlloch I, Ramo Silvestre J-F *et al.* Acute juvenile pityriasis rubra pilaris: a superantigen mediated disease? *Pediatr Dermatol* 2001; **18**: 411–4.
17 Niemi KM, Kousa M, Storgards K, Karvonen J. Pityriasis rubra pilaris: a clinicopathological study with a special reference to autoradiography and histocompatibility antigens. *Dermatologica* 1976; **152**: 109–18.
18 Möhrenschlager M, Abeck D. Further clinical evidence for involvement of bacterial superantigens in juvenile pityriasis rubra pilaris (PRP): report of two new cases. *Pediatr Dermatol* 2002; **19**: 569.
19 Sanchez-Regana M, Fuentes CG, Creus L *et al.* Pityriasis rubra pilaris and HIV infection: a part of associated follicular syndrome. *Br J Dermatol* 1995; **133**: 814–21.
20 Braun Falco O, Ryckmanns F, Schmoeckel C *et al.* Pityriasis rubra pilaris: a clinico-pathological and therapeutic study with special reference to histochemistry, autoradiography and electron microscopy. *Arch Dermatol Res* 1983; **275**: 287–95.
21 Harper RA, Rispler J. Pityriasis rubra pilaris epidermal cells *in vitro*: a comparison with normal and psoriatic cells. *Arch Derm Res* 1977; **260**: 253–5.
22 Ralfs IG, Dawber RPR, Ryan TJ *et al.* Pityriasis rubra pilaris: epidermal cell kinetics. *Br J Dermatol* 1981; **104**: 249–52.
23 Soeprono FF. Histologic criteria for the diagnosis of pityriasis rubra pilaris. *Am J Dermatopathol* 1986; **8**: 277–83.
24 Magro CM, Crowson AN. The clinical and histomorphological features of pityriasis rubra pilaris: a comparative analysis with psoriasis. *J Cutan Pathol* 1997; **24**: 416–24.
25 Ojeda LM, Bosca AR, Cavero AV *et al.* Marcaje mediante lectinas de trastornos en la queratinacion. II. Queratois pilaris, liquen espinuloso, poroqueratosis, liquen estriado y pitiriasis rubra pilaris. *Med Cut Iber Lat Am* 1988; **16**: 183–6.
26 Hunter I, Skerrow D. The effect of increased tissue turnover on the keratinization of human epidermis. *Biochim Biophys Acta* 1981; **674**: 155–9.
27 Kanerva L, Lauharanta J, Niemi K-M *et al.* Ultrastructure of pityriasis rubra pilaris with observations during retinoid (etretinate) treatment. *Br J Dermatol* 1983; **108**: 653–63.
28 Griffiths WAD. The diagnosis of pityriasis rubra pilaris in children. *Eur J Pediatr Dermatol* 1991; **1**: 103–5.
29 Sonnex TS, Dawber RPR, Zachary CB *et al.* The nails in adult type I pityriasis rubra pilaris: a comparison with Sézary syndrome and psoriasis. *J Am Acad Dermatol* 1986; **15**: 956–60.
30 Griffiths WAD, Hall-Smith P. Pityriasis rubra pilaris with relapses. *Br J Dermatol* 1981; **105** (Suppl. 19): 59.
31 Allison DS, el-Hazary RA, Calobrisi SD, Dicken CH. Pityriasis rubra pilaris in children. *J Am Acad Dermatol* 2002; **47**: 386–9.
32 Shahidullah H, Aldridge RD. Changing forms of juvenile pityriasis rubra pilaris: a case report. *Clin Exp Dermatol* 1994; **19**: 254–6.
33 Hong JB, Chiu HC, Wang SH, Tsai TF. Recurrence of classical juvenile pityriasis rubra pilaris in adulthood: report of a case. *Br J Dermatol* 2007; **157**: 842–4.
34 Shrank AB. Keratosis circumscripta. *Arch Dermatol* 1966; **93**: 408–10.
35 Verhagen AR. Keratosis circumscripta. *Dermatologica* 1980; **159**: 182–3.
36 Jacyk WK. Pityriasis rubra pilaris in black South Africans. *Clin Exp Derm* 1999; **24**: 160–3.
37 Cockerell CJ. Non-infectious inflammatory skin diseases in HIV-infected individuals. *Dermatol Clin* 1991; **9**: 531–41.
38 Blauvelt A, Nahass GT, Pardo RJ *et al.* Pityriasis rubra pilaris and HIV infection. *J Am Acad Dermatol* 1991; **24**: 703–5.
39 Resnick SD, Murrell DF, Woosley JT *et al.* Pityriasis rubra pilaris, acne conglobata, and elongated follicular spines: an HIV-associated follicular syndrome? *J Am Acad Dermatol* 1992; **27**: 260–1.
40 Miralles ES, Nunez M, De La Heras ME *et al.* Pityriasis rubra pilaris and human immunodeficiency virus infection. *Br J Dermatol* 1995; **133**: 990–3.
41 Blasdale C, Turner RJ, Leonard N *et al*. Spontaneous clinical improvement in HIV-associated follicular syndrome. *Clin Exp Dermatol* 2004; **29**: 480–2.
42 Castanet J, Lacour JP, Perrin C *et al.* Juvenile pityriasis rubra pilaris associated with hypogammaglobulinaemia and furunculosis. *Br J Dermatol* 1994; **131**: 717–9.
43 Griffiths WAD. Retinol binding protein and pityriasis rubra pilaris. *Br J Dermatol* 1982; **107**: 125.
44 Finzi AF, Altomare G, Bergamaschini L *et al.* Pityriasis rubra pilaris and retinol-binding protein. *Br J Dermatol* 1981; **104**: 253–6.
45 Vahlquist A. Retinol binding protein and pityriasis rubra pilaris. *Br J Dermatol* 1982; **107**: 125–6.
46 Siegenthaler G, Saurat J-H, Salomon D *et al.* Skin cellular retinoid-binding proteins and retinoid-responsive dermatoses. *Dermatologica* 1986; **173**: 163–73.
47 Milstone LM, Ellison AF, Insogna KL. Serum parathyroid hormone level is elevated in some patients with disorders of keratinization. *Arch Dermatol* 1992; **128**: 926–30.
48 Takematsu H, Ohkohchi K, Tagami H. Demonstration of anaphylatoxins C3a, C4a and C5a in the scales of psoriasis and inflammatory pustular dermatoses. *Br J Dermatol* 1986; **114**: 1–6.
49 Takematsu H, Terui T, Tagami H. Demonstration of leukotriene B4 in the scale extracts of psoriasis and inflammatory pustular dermatoses. *Acta Derm Venereol (Stockh)* 1986; **66**: 6–10.
50 Shvili D, David M, Mimouni M. Childhood-onset pityriasis rubra pilaris with immunologic abnormalities. *Pediatr Dermatol* 1987; **4**: 121–3.
51 Reinhardt LA, Rosen T. Pityriasis rubra pilaris as the initial manifestation of leukemia. *Cutis* 1983; **31**: 100–2.
52 Roger J, Burg G, Miller K *et al.* Pityriasis rubra pilaris-artiges Vorstadium eines Sézary-Syndroms. *Z Hautkr* 1991; **66**: 1046–50.
53 Sanchez-Regana M, Lopez-Gil F, Salleras M *et al.* Pityriasis rubra pilaris as the initial manifestation of internal neoplasia. *Clin Exp Dermatol* 1995; **20**: 436–8.
54 Kurzydlo AM, Gillespie R. Paraneoplastic pityriasis rubra pilaris in association with bronchogenic carcinoma. *Australas J Dermatol* 2004; **45**: 130–2.
55 Westfried M, Rosenthal JC, Coppola A *et al*. Sézary syndrome presenting as a follicular dermatosis. *Cutis* 1982; **29**: 390–6.
56 Holmes RCM, McGibbon DH, Black MM. Mycosis fungoides: progression towards Sézary syndrome reversed with chlorambucil. *Clin Exp Dermatol* 1983; **8**: 429–35.
57 Requena L, Grilli R, Soriano L *et al.* Dermatomyositis with a pityriasis rubra pilaris-like eruption: a little-known distinctive cutaneous manifestation of dermatomyositis. *Br J Dermatol* 1997; **136**: 768–71.
58 Lister RK, Perry JD, Cerio R. Pityriasis rubra pilaris and a seronegative polyarthritis. *Br J Dermatol* 1997; **137**: 318–9.
59 Fiallo P, Tagliapietra A-G, Santoro G. Arthropathic pityriasis rubra pilaris. *Br J Dermatol* 1996; **134**: 1154–5.

60 Chan H, Liu FT, Naguwa S. A review of pityriasis rubra pilaris and rheumatologic associations. *Clin Dev Immunol* 2004; **11**: 57–60.
61 Conaghan PG, Sommer S, McGonagle D *et al.* The relationship between pityriasis rubra pilaris and inflammatory arthritis: case report and response of the arthritis to anti-tumor necrosis factor immunotherapy. *Arthr Rheum* 1999; **42**: 1998–2001.
62 Polat M, Lenk N, Ustun H *et al.* Dermatomyositis with a pityriasis rubra pilaris-like eruption: an uncommon cutaneous manifestation in dermatomyositis. *Pediatr Dermatol* 2007; **24**: 151–4.
63 Cecchi R, Giomi A, Tuci F *et al.* Pityriasis rubra pilaris, lichen planus, alopecia universalis and vitiligo in a patient with chronic viral hepatitis C. *Dermatology* 1994; **188**: 239–40.
64 Ng SK, Ang CB, Tham A. Kaposi's varicelliform eruption in a patient with pityriasis rubra pilaris. *J Am Acad Dermatol* 1992; **27**: 263.
65 Marguery MC, Durand-Malgouyres C, Bayle-Lebey P *et al.* Photosensitive and phototriggered pityriasis rubra pilaris. *Photodermatol Photoimmunol Photomed* 1994; **10**: 42–5.
66 Yaniv R. Pityriasis rubra pilaris exacerbated by ultraviolet B phototherapy. *Dermatology* 1994; **189**: 313.
67 van de Kerkhof PM, Wittenhorst M, Gerritsen MP *et al.* Possible indications for vitamin D3 analogues in conditions other than psoriasis vulgaris. *J Dermatol Treat* 1996; **7**: 195–8.
68 Blanchet-Bardon C, Nazzaro V, Rognin C *et al.* Acitretin in the treatment of severe disorders of keratinization. *J Am Acad Dermatol* 1991; **24**: 982–6.
69 Dicken CH. Treatment of classic pityriasis rubra pilaris. *J Am Acad Dermatol* 1994; **31**: 997–9.
70 Basta-Juzbasic A, Dobric I, Schonwald D *et al.* Acitretin in the treatment of pityriasis rubra pilaris. *Retinoids Today Tomorrow* 1994; **35**: 7–10.
71 Goldsmith LA, Weinrich AE, Shupack J. Pityriasis rubra pilaris response to 13-*cis*-retinoic acid (isotretinoin). *J Am Acad Dermatol* 1982; **6**: 710–5.
72 Tabibian P, Lowe NJ. Pityriasis rubra pilaris: etretinate shortens duration of disease. *J Dermatol Treat* 1993; **4**: 9–11.
73 Chapalain V, Beylot-Barry M, Doutre MS, Beylot C. Treatment of pityriasis rubra pilaris: a retrospective study of 14 patients. *J Dermatol Treat* 1999; **10**: 113–7.
74 Clayton BD, Jorizzo JL, Hitchcock MG *et al.* Adult pityriasis rubra pilaris: a 10-year case series. *J Am Acad Dermatol* 1997; **36**: 959–64.
75 Rosenbach A, Lowe NJ. Pityriasis rubra pilaris and cyclosporine. *Arch Dermatol* 1993; **129**: 1346–8.
76 Mukawa R, Yamamoto M, Osuna H *et al.* A case of successful treatment of pityriasis rubura pilaris with cyclosporine. *Skin Res* 1999; **41**: 561–5.
77 Usuki K, Sekiyama M, Shimada T *et al.* Three cases of pityriasis rubra pilaris successfully treated with cyclosporin A. *Dermatology* 2000; **200**: 324–7.
78 Wetzig T, Sticherling M. Juvenile pityriasis rubra pilaris: successful treatment with ciclosporin. *Br J Dermatol* 2003; **149**: 202–3.
79 Meyer P, van Voorst PC. Lack of effect of cyclosporin A in pityriasis rubra pilaris. *Acta Derm Venereol (Stockh)* 1989; **69**: 272.
80 Coras B, Vogt TH, Ulrich H *et al.* Fumaric acid esters therapy: a new treatment modality in pityriasis rubra pilaris? *Br J Dermatol* 2005; **152**: 388–9.
81 Kerr AC, Ferguson J. Type II adult-onset pityriasis rubra pilaris successfully treated with intravenous immunoglobulin. *Br J Dermatol* 2007; **156**: 1055–6.
82 Orlandini V, Cogrel O, Doutre MS *et al.* Pityriasis rubra pilaris and hypothyroidism. Efficacy of thyroid hormone replacement therapy in skin recovery. *Br J Dermatol* 2007; **156**: 606–7.
83 Drosou A, Kirsner RS, Welsh E *et al.* Use of infliximab, an anti-tumor necrosis alpha antibody, for inflammatory dermatoses. *J Cutan Med Surg* 2003; **7**: 382–6.
84 Liao WC, Mutasim DF. Infliximab for the treatment of adult-onset pityriasis rubra pilaris. *Arch Dermatol* 2005; **141**: 423–5.
85 Ruiz-Genao DP, Lopez-Estebaranz JL, Naz-Villalba E *et al.* Pityriasis rubra pilaris successfully treated with infliximab. *Acta Derm Venereol* 2007; **87**: 552–3.
86 Ruzzetti M, Saraceno R, Carboni I *et al.* Type III juvenile pityriasis rubra pilaris: a successful treatment with infliximab. *J Eur Acad Dermatol Venereol* 2008; **22**: 117–8.
87 Davis KF, Wu JJ, Murase JE *et al.* Clinical improvement of pityriasis rubra pilaris with combination etanercept and acitretin therapy. *Arch Dermatol* 2007; **143**: 1597–9.
88 Seckin D, Tula E, Ergun T. Successful use of etanercept in type I pityriasis rubra pilaris. *Br J Dermatol* 2008; **158**: 642–4.
89 Lu R, George SJ, Hsu S. Pityriasis rubra pilaris: failure of combination treatment with acitretin and infliximab. *Dermatol Online J* 2006; **12**: 18.
90 Gomez M, Ruelas ME, Welsh O *et al.* Clinical improvement of pityriasis rubra pilaris with efalizumab in a pediatric patient. *J Drugs Dermatol* 2007; **6**: 337–9.
91 Klein A, Szeimies RM, Landthaler M, Karrer S. Exacerbation of pityriasis rubra pilaris under efalizumab therapy. *Dermatology* 2007; **215**: 72–5.
92 Brenner W, Gschnait F, Honigsmann H *et al.* The testing of photo-chemotherapy in various dermatoses. *Hautarzt* 1978; **29**: 541–4.
93 Kaskel P, Grundmann-Kollmann M, Schiller PI *et al.* Bath-PUVA as a treatment for pityriasis rubra pilaris provoked by ultraviolet B. *Br J Dermatol* 1999; **140**: 769–70.
94 Hofer A, Mullegger R, Kerl H, Wolf P. Extracorporeal photochemotherapy for the treatment of erythrodermic pityriasis rubra pilaris. *Arch Dermatol* 1999; **135**: 475–6.
95 Kaskel P, Peter RU, Kerscher M. Phototesting and phototherapy in pityriasis rubra pilaris. *Br J Dermatol* 2001; **144**: 430.
96 Kirby B, Watson R. Pityriasis rubra pilaris treated with acitretin and narrow-band ultraviolet B (Re-TL-01). *Br J Dermatol* 2000; **142**: 376–7.
97 Herbst RA, Vogelbruch M, Ehnis A *et al.* Combined ultraviolet A1 radiation and acitretin therapy as a treatment option for pityriasis rubra pilaris. *Br J Dermatol* 2000; **142**: 574–5.
98 Nees CM, Hinrichs R, Dissimond J *et al.* Treatment of pruritus by capsaicin in a patient with pityriasis rubura pilaris receiving RE-PUVA therapy. *Clin Exp Dermatol* 2000; **25**: 205–11.
99 Gonzalez-Lopez A, Velasco E, Pozo T, Del Villar A. HIV-associated pityriasis rubra pilaris responsive to triple antiretroviral therapy. *Br J Dermatol* 1999; **140**: 931–4.
100 Griffiths WAD, Hill V. Zidovudine in HIV-negative pityriasis rubra pilaris. *J Dermatol Treat* 1997; **8**: 127–31.

Darier's disease and related disorders

Darier's disease (MIM 124200)

Synonyms
- Keratosis follicularis
- Darier–White disease

Darier's disease, described independently by White and Darier in 1889, is an autosomal dominant condition characterized by a persistent eruption of hyperkeratotic papules, histological examination of which shows suprabasal acantholysis with a distinctive overlying dyskeratosis [1,2]. Expressivity is variable but penetrance complete in adults [3]. Sporadic cases are common. It has a worldwide distribution. Reported prevalence varies from 1 in 100 000 in Denmark [4] to 1 in 30–35 000 in Northern England and Scotland [3,5].

Aetiology. Darier's disease is due to mutations in the *ATP2A2* gene at chromosome 12q24.1, which encodes the sarco/endoplasmic reticulum calcium ATPase type 2 (SERCA2) [6–10]. SERCA2 is a member of a family of ion pumps which maintain high calcium concentration in the endoplasmic reticulum [11–13]. It has two main isoforms; SERCA2a is expressed in cardiac and smooth muscle, whereas SERCA2b is more widely expressed, including in epidermis. A less common third isoform, SERCA2c, has been identified [14]. Many mutations have now been identified. Darier's disease is caused by both nonsense and insertion/deletion mutations likely to produce haploinsufficiency, and hence

reduction in SERCA2b function [6–9,15,16], although some missense mutations may interfere with the normal SERCA2 [15]. The relationship of these defects to clinical and histological features is yet to be fully elucidated. One hypothesis proposes a failure in compensatory mechanisms when the endoplasmic reticulum is stressed [14], and consequent reduced calcium concentrations mean that the folding of secreted or membrane proteins is disrupted. Darier's disease keratinocytes exhibit reduced trafficking of desmosomal proteins to the cell membrane, underlying the failure of adhesion [17]. An impaired stress response may also predispose to apoptosis, which could explain the dyskeratotic cells [18]. There is evidence of reduced expression of Bcl-2 and related antiapoptotic proteins in lesional skin [19,20]. Localization to skin and late-onset of Darier's disease may be explained by an age-related critical dependence on SERCA pumps in the epidermis. Alternatively it may be due to lack of redundancy in calcium pumps; the SERCA3 isoform is co-expressed with SERCA2b in many tissues, but not epidermis [21]. The focal nature of the lesions is intriguing, and recent evidence suggests that defects in SERCA2 may encourage the accumulation of mutations [22,23].

Pathology. In the earliest papular lesions, lacunae appear above the basal layer [1,2], and extend irregularly throughout the Malpighian layer. Small groups of cells around the lacunae become separated from their neighbours, enlarge and present a darkly staining nucleus surrounded by clear cytoplasm and a glistening ring simulating a membrane. These 'corps ronds' show premature partial keratinization (dyskeratosis); they give rise to the grains, small cells with shrunken cytoplasm, seen in the upper layers of the epidermis. This dyskeratosis may or may not be a form of apoptosis [18,24]. Lesions are not exclusively follicular [25], as acantholysis and dyskeratosis appear to occur preferentially around sweat ducts and mucous and salivary glands as frequently as around follicular openings. With the electron microscope, the lacunae can be seen to result from changes in the tonofilaments, which become separated from the desmosomes [26]. Immunocytochemical studies confirm that desmomosal proteins of affected cells are not localized to the membranes but diffusely distributed in the cytoplasm [27–29] and their intra- and extracellular domains are dissociated [30].

Focal acantholytic dyskeratosis also occurs in other conditions, such as solitary dyskeratoma, and transient and persistent acantholytic dermatoses. Hailey–Hailey disease (chronic familial benign pemphigus) may overlap clinically and histologically, although there is more suprabasal clefting and acantholysis and grains and corps ronds are less evident in Hailey–Hailey disease.

Clinical features [1,3]. The distinctive lesion of Darier's disease is a firm, rough papule, which is skin coloured, yellow–brown or brown. Seborrhoeic areas of the trunk (Fig. 19.47) and face, particularly the scalp margins, temples, ears and scalp, are most often involved. Many lesions are subtle; the occurrence of multiple minute acanthomas is easily overlooked. Flat and freckle-like lesions may appear as pale macules (guttate leukoderma) in pigmented skin [31,32], and while thought to be rare, are probably under-recognized in paler skins. Limb involvement usually consists of scattered papules but confluent lesions on lower legs and arms may be a problem [33]. Coalescent papules form irregular warty fissured plaques or papillomatous masses, which may become vegetating and malodorous [1] especially in the flexures, notably the anogenital region, the groins and the natal cleft. On the scalp, the heavy crusting simulates seborrhoea, but has a characteristic spiny feel to palpation. Loss of hair is exceptional. The external auditory meatus may be blocked by keratotic debris [34]. On the dorsa of the hands and feet, discrete papules are clinically indistinguishable from acrokeratosis verruciformis of Hopf [35,36]. These may be the earliest manifestations of the disease [3] (Fig. 19.48). In Darier's disease, characteristic nail changes include red or white longitudinal bands of varying width, often ending in a pathognomic notch at the free margin of the nail (Fig. 19.49). The nails are often brittle. Palms and soles show minute pits or, in older subjects, punctate or filiform keratoses [37] (Fig. 19.50). In severe cases, palmoplantar hyperkeratosis may occur. Lesions of the mucous membranes are uncommon, but white umbilicate or cobblestone papules on the palate resembling nicotinic stomatitis may be seen [38,39]. Lesions of the tongue, buccal mucosa, epiglottis, pharyngeal wall, vulva, oesophagus or rectum may occur, as may gingival hypertrophy [39–43]. Confluent buccal lesions may simulate leukoplakia. Vaginal involvement may result in abnormal cervical cytology [44,45].



Fig. 19.47 Darier's disease: profuse keratotic papules in the seborrhoeic region of the back.

The majority of patients first become aware of lesions in the second decade [1], although minor lesions or nail or palmar changes may be detected earlier [3]. Spontaneous remissions do occur, but the disease usually runs a chronic relapsing course, without affecting general health. The rash is typically exacerbated

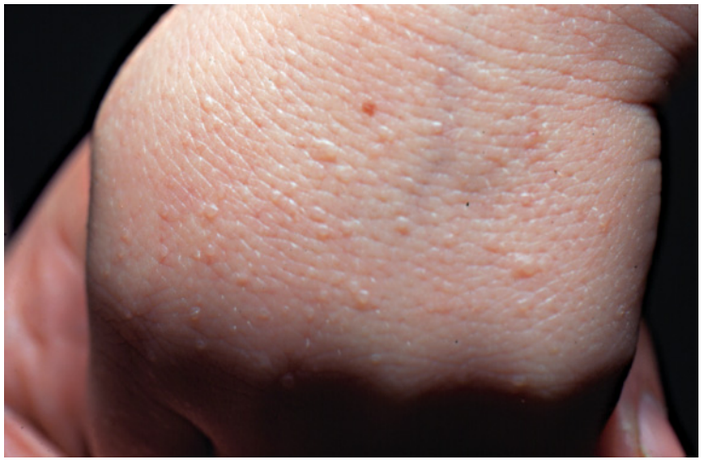


Fig. 19.48 Acrokeratosis verruciformis is a sometimes subtle feature of Darier's disease.



Fig. 19.49 The typical nail dystrophy of Darier's disease.

by heat and light, especially sunburn, and lesions can be experimentally induced by UVB exposure [46]. Lithium therapy precipitates and exacerbates the rash. Exacerbations have also been reported following steroids in naevoid disease [47].

Clinical variants. Most patients have the classical seborrhoeic distribution of papules, but there is considerable variation in severity, from isolated nail or palmar changes to universal and grossly disfiguring involvement. A minority of patients have predominantly vesicobullous [48], flexural or erosive disease or hyperkeratotic lesions, particularly of the distal limbs [33]. The most malodorous cases occur in these patients. Some patients present with multiple comedones or nodulocystic acne with deep pitted scars, and typical histology of Darier's disease may be found in these lesions [49]. Haemorrhagic macules occasionally seen on the hands and feet (Fig. 19.51) represent a true genetic variant, as they occur consistently within families [50], and may be due to specific mutations [8,51]. Atypical or unusually severe Darier's disease is usually due to missense mutations rather than haploinsufficiency [7,8], consistent with evidence of the complex molecular effects of missense mutations [15,16] *in vitro*.



(a)



(b)

Fig. 19.50 (a) Palm prints show focal interruption of dermatoglyphics; (b) palmar pits and keratoses in Darier's disease.

Acantholytic dyskeratotic epidermal naevi following the lines of Blaschko are commonly of late onset and display photoaggravation, suggesting they are naevoid forms of Darier's disease [47,52,53]. *ATP2A2* mutations have been identified in some such naevi [54,55], a finding which implies the potential for transmission of the disorder if the gonads are affected by somatic mosaicism. Somatic mosaicism may also explain cases with linear exacerbation—or amelioration—of generalized disease [56].

Associated features. Despite the wide expression of SERCA2, the phenotype of Darier's disease is largely confined to the skin. Patients do have an increased susceptibility to herpes simplex [40]. Kaposi's varicelliform eruption (Fig. 19.52) is common [57,58], and poxvirus infection is reported [59]. There may also be an increased incidence of chronic pyogenic infection [60]. There is conflicting evidence regarding a defect in cell-mediated immunity [61–64]. Salivary duct narrowing can cause recurrent salivary gland swell-



Fig. 19.51 Haemorrhage into palmoplantar lesions of Darier's disease is found with specific *ATP2A2* mutations. (Ruiz-Perez V.L. *et al. Hum Mol Genet* 1999; **8**: 1621–30, by permission of Oxford University Press.)

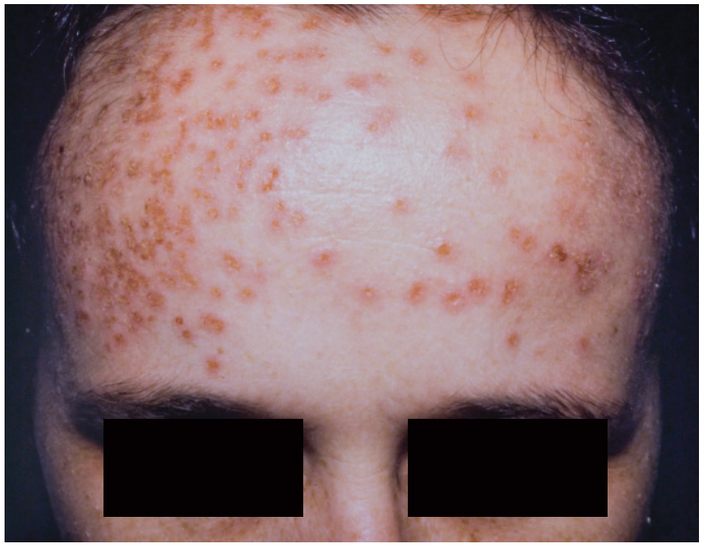


Fig. 19.52 Disseminated herpes simplex virus infection in a patient with Darier's disease.

Table 19.4 Focal and follicular keratoses.

	Age of onset	Distribution	Morphology	Associated features
Keratosis pilaris				
Physiological	Childhood or adolescence	Extensor limbs	Horny follicular plugs	None or erythrocyanosis
Ichthyotic	Early childhood	Extensor limbs	Horny follicular plugs	Ichthyosis—autosomal dominant type
Keratosis pilaris atrophicans (including atrophoderma vermiculatum)	Childhood	Eyebrows, cheeks	Erythema, follicular plugs, alopecia	Miliary cysts
Keratosis pilaris spinulosa decalvans	Childhood	Face, scalp, trunk	Follicular plugs, scarring alopecia	
Phrynoderma	Any age; usually childhood	Elbows, thighs, buttocks	Horny follicular plugs	Skin dry, pigmented
Pityriasis rubra pilaris	Childhood or middle life	Especially dorsa of fingers, knees, elbows; may be widespread	Fine, red papules with central horny plug	Plaques of erythema and scaling; palmoplantar keratoderma
Darier's disease	Usually above 10 years	Seborrhoeic areas	Yellow-brown, greasy papules	Nail and palmoplantar lesions
Kyrle's disease	50–70 years	Mainly arms and legs	Large irregular horny plugs	

ing, and subclinical narrowing may be common [39,65,66]. Most patients are of normal intellect, but clinical experience suggests that mild degrees of learning difficulty are common. There are numerous reports of cases of Darier's disease with a range of neuropsychiatric disorders, including a high prevalence of epilepsy [1,4]. Families in whom Darier's disease is associated with bipolar disorder may be explained by cosegregation of closely linked loci [67–70]. Transgenic mice haploinsufficient for SERCA2 display impaired cardiac contractility [71] and an increased incidence of gastro-oesophageal and other squamous cancers [72,73]. However, SERCA2 haploinsufficiency in human hearts appears to be compensated by other mechanisms, and there is no evidence of a general cardiac dysfunction in Darier's disease [74,75]. Although individual reports document cases of squamous carcinoma of skin, nailbed, mouth, oesophagus and vagina, an increase in the overall incidence of skin or mucosal cancer has not been documented.

Differential diagnosis. In mild forms, acne and seborrhoeic dermatitis may be confused, unless the warty papules are carefully sought. Confluent lesions resemble discoid eczema and may respond to treatment for this. Flexural Darier's disease may overlap clinically and histologically with benign familial pemphigus (Hailey–Hailey disease) but patients with intertriginous Darier's disease have changes typical of Darier's disease elsewhere, and the age of onset is usually earlier. In Dowling Degos disease or acanthosis nigricans, lesions are flexural and pigmented. In confluent reticulate papillomatosis (see below) the lesions are flat and largely confined to the upper trunk. Other follicular keratoses are listed in Table 19.4. The harshness on palpation distinguishes

the disorder from many visually similar disorders such as the reticular erythematous mucinosis syndrome and prurigo pigmentosa [76].

Treatment [77]. Many patients with mild disease require no treatment other than emollients, simple hygiene and advice to avoid sunburn. Topical tretinoin and isotretinoin, adapalene and tazarotene have been reported as effective [78–81]. In practice, irritancy limits the value of most topical preparations and extra emollients are needed. Antiseptics may help with infected plaques, which may respond to topical steroid/antibiotic combinations. For those with more severe disease, oral retinoids are usually effective; both acitretin and isotretinoin are used [82,83]. Severe inflammatory exacerbations of Darier's disease occur in some patients, and may respond to ciclosporin [84,85]; the use of biological agents has not been reported. Dermabrasion [86] or laser treatment [87–89] may prove useful, usually in limited areas. Benefit from photodynamic therapy [90], and with topical 5-fluorouracil in two patients has been reported [91,92].

References

1 Burge SM, Wilkinson JD. Darier–White disease: a review of the clinical features in 163 patients. *J Am Acad Dermatol* 1992; **27**: 40–50.
2 Burge S. Darier's disease—the clinical features and pathogenesis. *Clin Dermatol* 1994; **19**: 193–205.
3 Munro CS. The phenotype of Darier's disease: penetrance and expressivity in adults and children. *Br J Dermatol* 1992; **127**: 126–30.
4 Svendsen IB, Albrectsen B. The prevalence of dyskeratosis follicularis (Darier's disease) in Denmark: an investigation of the heredity in 22 families. *Acta Derm Venereol (Stockh)* 1959; **39**: 256–69.
5 Tavadia S, Mortimer E, Munro CS. Genetic epidemiology of Darier's disease: a population study in the West of Scotland. *Br J Dermatol* 2002; **146**: 107–9.
6 Sakuntabhai A, Ruiz-Perez V, Carter S *et al.* Mutations in ATP2A2, encoding a Ca^{2+} pump, cause Darier disease. *Nature Genet* 1999; **21**: 271–7.
7 Sakuntabhai A, Burge S, Monk S, Hovnanian A. Spectrum of novel ATP2A2 mutations in patients with Darier's disease. *Hum Mol Genet* 1999; **8**: 1611–9.
8 Ruiz-Perez VL, Carter SA, Healy E *et al.* ATP2A2 mutations in Darier's disease: variant cutaneous phenotypes are associated with missense mutations, but neuropsychiatric features are independent of mutation class. *Hum Mol Genet* 1999; **8**: 1621–30.
9 Jacobsen NJ, Lyons I, Hoogendoorn B *et al.* ATP2A2 mutations in Darier's disease and their relationship to neuropsychiatric phenotypes. *Hum Mol Genet* 1999; **8**: 1631–6.
10 Ringpfeil F, Raus A, DiGiovanna JJ *et al.* Darier disease–novel mutations in ATP2A2 and genotype-phenotype correlation. *Exp Dermatol* 2001; **10**: 19–27.
11 Carafoli E, Brini M. Calcium pumps: Structural basis for and mechanism of calcium transmembrane transport. *Curr Opin Chem Biol* 2000; **4**: 152–61.
12 Maclennan, DH. Calcium signalling and muscle disease. *Eur J Biochem* 2000; **267**: 5291–7.
13 Shull GE. Gene knockout studies of calcium-transporting ATPases. *Eur J Biochem* 2000; **267**: 5284–90.
14 Foggia L, Hovnanian A. Calcium pump disorders of the skin. *Am J Med Genet C Semin Med Genet* 2004; **131C**: 20–31.
15 Dode L, Andersen JP, Leslie N *et al.* Dissection of the functional differences between sarco(endo)plasmic reticulum Ca^{2+}-ATPase (SERCA) 1 and 2 isoforms and characterization of Darier disease (SERCA2) mutants by steady-state and transient kinetic analyses. *J Biol Chem* 2003; **278**: 47877–89.
16 Miyauchi Y, Daiho T, Yamasaki K *et al.* Comprehensive analysis of expression and function of 51 sarco(endo)plasmic reticulum Ca^{2+}-ATPase mutants associated with Darier disease. *J Biol Chem* 2006; **281**: 22882–95.
17 Dhitavat J, Cobbold C, Leslie N *et al.* Impaired trafficking of the desmoplakins in cultured Darier's disease keratinocytes. *J Invest Dermatol* 2003; **121**: 1349–55.
18 Gniadecki R, Jemec GB, Thomsen BM, Hansen M. Relationship between keratinocyte adhesion and death: anoikis in acantholytic diseases. *Arch Dermatol Res* 1998; **290**: 528–32.
19 Bongiorno MR, Arico M. The behaviour of Bcl-2, Bax and Bcl-x in Darier's disease. *Br J Dermatol* 2002; **147**: 696–700.
20 Pasmatzi E, Badavanis G, Monastirli A, Tsambaos D. Reduced expression of the antiapoptotic proteins of Bcl-2 gene family in the lesional epidermis of patients with Darier's disease. *J Cutan Pathol* 2007; **34**: 234–8.
21 Tavadia S, Authi KS, Hodgins MB, Munro CS. Expression of the sarco/endoplasmic reticulum calcium ATPase type 2 and 3 isoforms in normal skin and Darier's disease. *Br J Dermatol* 2004; **151**: 440–5.
22 Muller EJ, Caldelari R, Kolly C *et al.* Consequences of depleted SERCA2-gated calcium stores in the skin. *J Invest Dermatol* 2006; **126**: 721–31.
23 Byrne CR. The focal nature of Darier's disease lesions: calcium pumps, stress, and mutation? *J Invest Dermatol* 2006; **126**: 702–3.
24 Gandarillas A, Goldsmith LA, Gschmeissner S *et al.* Evidence that apoptosis and terminal differentiation of epidermal keratinocytes are distinct processes. *Exp Dermatol* 1999; **8**: 71–9.
25 Ellis RA. Keratosis follicularis is not primarily a follicular disease. *Arch Dermatol Syphilol* 1944; **50**: 27–30.
26 Caufield JB, Wilgram GF. An electron-microscopic study of dyskeratosis and acantholysis in Darier's disease. *J Invest Dermatol* 1963; **41**: 57–65.
27 Burge SM, Garrod DR. An immunohistological study of desmosomes in Darier's disease and Hailey–Hailey disease. *Br J Dermatol* 1991; **124**: 242–51.
28 Burge SM, Schomberg KH. Adhesion molecules and related proteins in Darier's disease and Hailey–Hailey disease. *Br J Dermatol* 1992; **127**: 335–43.
29 Hashimoto K, Fujiwara K, Tada J *et al.* Desmosomal dissolution in Grover's disease, Hailey–Hailey's disease and Darier's disease. *J Cutan Pathol* 1995; **22**: 488–501.
30 Hakuno M, Shimizu H, Akiyama M *et al.* Dissociation of intra- and extracellular domains of desmosomal cadherins and E-cadherin in Hailey–Hailey disease and Darier's disease. *Br J Dermatol* 2000; **142**: 702–11.
31 Jacyk WK, Visser AJ. Leukodermic macules in keratosis follicularis (Darier's disease). *Int J Dermatol* 1992; **31**: 715–7.
32 Goh BK, Kumarasinghe SP, Ng SK. Two Singaporean cases of guttate leucoderma in Darier's disease. *Clin Exp Dermatol* 2004; **29**: 313–4.
33 Rongioletti F, Cestari R, Rebora A. Verrucous and malodorous vegetations on the legs. Darier's disease, cornifying type. *Arch Dermatol* 1992; **128**: 399.
34 Thompson AC, Shall L, Moralee SJ. Darier's disease of the external ear. *J Laryngol Otol* 1992; **106**: 725–6.
35 Waisman M. Verruciform manifestations of keratosis follicularis. *Arch Dermatol* 1960; **81**: 39–52.
36 Blanchet-Bardon C, Durand-Delorme M, Nazzaro V *et al.* Acrokeratose verruciforme de Hopf ou maladie de Darier acrale. *Ann Dermatol Vénéréol* 1988; **115**: 1229–32.
37 Zarour H, Grob JJ, Andrac L *et al.* Palmoplantar orthokeratotic filiform hyperkeratosis in a patient with associated Darier's disease. Classification of filiform hyperkeratosis. *Dermatology* 1992; **185**: 205–9.
38 Ferris T, Lamey PJ, Rennie JS. Darier's disease: oral features and genetic aspects. *Br Dental J* 1990; **168**: 71–3.
39 Frezzini C, Cedro M, Leao JC, Porter S. Darier disease affecting the gingival and oral mucosal surfaces. *Oral Surg Oral Med Oral Pathol* 2006; **102**: e29–e33.
40 Macleod RI, Munro CS. The incidence and distribution of oral lesions in patients with Darier's disease. *Br Dent J* 1991; **171**: 133–6.
41 Salopek TG, Krol A, Jimbow K. Case report of Darier disease localized to the vulva in a 5-year old girl. *Pediatr Dermatol* 1993; **10**: 146–8.
42 Ridley CM, Buckley CH. Darier's disease localized to the vulva. *Br J Obstet Gynaecol* 1989; **96**: 997–9.
43 Al Robaee A, Hamadah IR, Khuroo S, Alfadley A. Extensive Darier's disease with esophageal involvement. *Int J Dermatol* 2004; **43**: 835–9.
44 Adam AE. Ectopic Darier's disease of the cervix: an extraordinary cause of an abnormal smear. *Cytopathology* 1996; **7**: 414–21.
45 Suarez-Penaranda JM, Antunez JR, Del Rio E *et al.* Vaginal involvement in a woman with Darier's disease: a case report. *Acta Cytol* 200; **49**: 530–2.
46 Hedblad MA, Nakatani T, Beitner H. Ultrastructural changes in Darier's disease induced by ultraviolet irradiation. *Acta Derm Venereol (Stockh)* 1991; **71**: 108–12.

47 Starink THM, Woerdeman MJ. Unilateral systematized keratosis follicularis. A variant of Darier's disease or an epidermal naevus (acantholytic dyskeratotic epidermal naevus)? *Br J Dermatol* 1981; **105**: 207–14.
48 Telfer NR, Burge SM, Ryan TJ. Vesiculo-bullous Darier's disease. *Br J Dermatol* 1990; **122**: 831–4.
49 Derrick EK, Darley CR, Burge S. Comedonal Darier's disease. *Br J Dermatol* 1995; **132**: 453–5.
50 Foresman PL, Goldsmith LA, Ginn L *et al.* Hemorrhagic Darier's disease. *Arch Dermatol* 1993; **129**: 511–2.
51 Hamada T, Yasumoto S, Karashima T *et al.* Recurrent p.N767S mutation in the ATP2A2 gene in a Japanese family with haemorrhagic Darier disease clinically mimicking epidermolysis bullosa simplex with mottled pigmentation. *Br J Dermatol* 2007; **157**: 605–8.
52 Munro CS, Cox NH. An acantholytic dyskeratotic epidermal naevus with other features of Darier's disease on the same side of the body. *Br J Dermatol* 1992; **127**: 168–71.
53 Plantin P, Le Noac HE, Leroy JP *et al.* Maladie de Darier, localisée, récidivante et photo-induite suivant les lignes de Blaschko. *Ann Dermatol Vénéréol* 1994; **121**: 393–5.
54 Sakuntabhai A, Dhitavat J, Burge S, Hovnanian A. Mosaicism for ATP2A2 mutations causes segmental Darier's disease. *J Invest Dermatol* 2000; **115**: 1144–7.
55 Wada T, Shirakata Y, Takahashi H *et al.* A Japanese case of segmental Darier's disease caused by mosaicism for the ATP2A2 mutation. *Br J Dermatol* 2003; **149**: 185–8.
56 Itin PH, Happle R. Darier disease with paired segmental manifestation of either excessive or absent involvement: a further step in the concept of twin spotting. *Dermatology* 2002; **205**: 344–7.
57 Parham DM, Gawkroger DJ, Vestey JP *et al.* Disseminated herpes simplex infection complicating Darier's disease. *J Infect Dis* 1985; **10**: 77–8.
58 Parslew R, Verbov JL. Kaposi's varicelliform eruption due to herpes simplex in Darier's disease. *Clin Exp Dermatol* 1994; **19**: 428–9.
59 Claudy AL, Gaudin OG, Granouillet R. Pox virus infection in Darier's disease. *Clin Exp Dermatol* 1982; **7**: 261–5.
60 Marks JG, Thor DE, Lowe RS. Darier's disease: an immunologic study. *Arch Dermatol* 1978; **114**: 1336–9.
61 Jegasothy BV, Humeniuk JM. Darier's disease: a partially immunodeficient state. *J Invest Dermatol* 1981; **76**: 129–32.
62 Soppi AM, Soppi E, Eskola J *et al.* Cell-mediated immunity in Darier's disease; effect of systemic retinoid therapy. *Br J Dermatol* 1982; **106**: 141–52.
63 Halevy S, Weltfriend S, Pick AI *et al.* Immunologic studies in Darier's disease. *Int J Dermatol* 1988; **27**: 101–5.
64 Patrizi A, Ricci G, Neri I *et al.* Immunological parameters in Darier's disease. *Dermatologica* 1989; **178**: 138–40.
65 Graham-Brown RAC, Mann BS, Downton D *et al.* Darier's disease with salivary gland obstruction. *J R Soc Med* 1983; **76**: 609–11.
66 Adams AM, Macleod RI, Munro CS. Symptomatic and asymptomatic salivary duct abnormalities in Darier's disease: a sialographic study. *Dentomaxillofac Radiol* 1994; **23**: 25–8.
67 Ewald H, Mors O, Flint T *et al.* Linkage analysis between manic depressive illness and the region on chromosome 12q involved in Darier's disease. *Psychiatr Genet* 1994; **4**: 195–200.
68 Sidenberg DG, Berg D, Bassett AS *et al.* Genetic linkage evaluation of twenty-four loci in an eastern Canadian family segregating Darier's disease (keratosis follicularis). *J Am Acad Dermatol* 1994; **31**: 27–30.
69 Craddock N, Owen M, Burge S *et al.* Familial cosegregation of major affective disorder and Darier's disease (keratosis follicularis). *Br J Psychiatry* 1994; **164**: 355–8.
70 Green E, Elvidge G, Jacobsen N *et al.* Localization of bipolar susceptibility locus by molecular genetic analysis of the chromosome 12q23–q24 region in two pedigrees with bipolar disorder and Darier's disease. *Am J Psychiatry* 2005; **162**: 35–42.
71 Periasamy M, Reed T, Liu L *et al.* Impaired cardiac performance in heterozygous mice with a null mutation in the sarco(endo)plasmic reticulum Ca^{2+}-ATPase isoform 2 (SERCA2) gene. *J Biol Chem* 1999; **274**: 2556–62.
72 Liu LH, Boivin GP, Prasad V *et al.* Squamous cell tumors in mice heterozygous for a null allele of Atp2a2, encoding the sarco(endo)plasmic reticulum Ca^{2+}-ATPase isoform 2 Ca^{2+} pump. *J Biol Chem* 2001; **276**: 26737–40.
73 Prasad V, Boivin GP, Miller ML *et al.* Haploinsufficiency of Atp2a2, encoding the sarco(endo)plasmic reticulum Ca^{2+}-ATPase isoform 2 Ca^{2+} pump, predisposes mice to squamous cell tumors via a novel mode of cancer susceptibility. *Cancer Res* 2005; **65**: 8655–61.
74 Tavadia S, Tait RC, McDonagh TA, Munro CS. Platelet and cardiac function in Darier's disease. *Clin Exp Derm* 2002; **26**: 696–9.
75 Mayosi BM, Kardos A, Davies CH *et al.* Heterozygous disruption of SERCA2a is not associated with impairment of cardiac performance in humans: implications for SERCA2a as a therapeutic target in heart failure. *Heart* 2006; **92**: 105–9.
76 Cotterill JA, Ryatt KS, Greenwood R. Prurigo pigmentosa. *Br J Dermatol* 1981; **105**: 707–10.
77 Burge S. Management of Darier's disease. *Clin Exp Derm* 1999; **24**: 53–6.
78 Steiljen PM, Happle R, van-Muijen GN *et al.* Topical treatment with 13-*cis*-retinoic acid improves Darier's disease and induces the expression of a unique keratin pattern. *Dermatologica* 1991; **182**: 178–83.
79 Burge SM, Buxton PK. Topical isotretinoin in Darier's disease. *Br J Dermatol* 1995; **133**: 924–8.
80 English JC, Browne J, Halbach DP. Effective treatment of localized Darier's disease with adapalene 0.1% gel. *Cutis* 1999; **63**: 227–30.
81 Oster-Schmidt C. The treatment of Darier's disease with topical tazarotene. *Br J Dermatol* 1999; **141**: 603–4.
82 Dicken CH, Bauer EA, Hazen PG. Isotretinoin treatment of Darier's disease. *J Am Acad Dermatol* 1982; **6**: 721–6.
83 Christopherson J, Geiger J-M, Danneskiol-Samsoe P *et al.* A double-blind comparison of acitretin and etretinate in the treatment of Darier's disease. *Acta Derm Venereol (Stockh)* 1992; **72**: 150–2.
84 Shahidulla H, Humphreys F, Beveridge GW. Darier's disease: severe eczematization successfully treated with cyclosporin. *Br J Dermatol* 1994; **131**: 713–6.
85 Larbre B, Nicolas JF, Frappaz A *et al.* Cyclosporine et maladie de Darier. *Ann Dermatol Vénéréol* 1993; **120**: 310–1.
86 Zachariae H. Dermabrasion of Hailey–Hailey disease and Darier's disease. *J Am Acad Dermatol* 1992; **27**: 136.
87 McElroy JA, Mehregan DA, Roenigk RK. Carbon dioxide laser vaporization of recalcitrant symptomatic plaques of Hailey–Hailey disease and Darier's disease. *J Am Acad Dermatol* 1990; **23**: 893–7.
88 Beier C, Kaufmann R. Efficacy of erbium : YAG laser ablation in Darier disease and Hailey–Hailey disease. *Arch Dermatol* 1999; **135**: 423–7.
89 Brown V, Burge SM, Kelly SE, Walker NPJ. Darier's disease successfully treated with laser ablation. *Br J Dermatol* 2007; **157** (Suppl. 1): 21.
90 Exadaktylou D, Kurwa HA, Calonje E, Barlow RJ. Treatment of Darier's disease with photodynamic therapy. *Br J Dermatol* 2003; **149**: 606–10.
91 Knulst AC, De La Faille HB, van Vloten WA. Topical 5-fluorouracil in the treatment of Darier's disease. *Br J Dermatol* 1995; **133**: 463–6.
92 Yoon TY, Kim JW, Kim MK. Successful treatment of Darier disease with topical 5-fluorouracil. *Br J Dermatol* 2006; **154**: 1210–2.

Transient and persistent acantholytic dermatosis

Synonyms
- Grover's disease
- Papular acantholytic dermatosis

These papular acantholytic dermatoses mainly affect the trunk in middle-aged or elderly people, and typically present as an eruption of pruritic papules or papulovesicles with focal acantholysis with or without dyskeratosis on histology [1–5]. Distinction between transient and persistent forms of disease may be artificial [2,4].

Aetiology. The cause is unknown. Heat and sweating are predisposing factors [6,7] and it is suggested that the disorder results from leakage from blocked acrosyringeal ducts. Scheinfeld *et al.* [8] found an increased incidence in winter in non-hospitalized

subjects, and suggested that winter xerosis was contributory. The condition has been regarded by some as a minimal expression of Darier's disease [9] but mutations in the *ATP2A2* gene were not found in four patients [10].

Pathology. Many conditions show histology of focal acantholytic dyskeratosis [11]. In transient acantholytic dermatosis, the histology mimics Darier's disease, pemphigus and Hailey–Hailey disease, and there is also a spongiotic form in which acantholytic cells are contained within spongiotic foci in the epidermis [2,5,12]. Acantholysis is confined to the acrosyringium in a subset of cases [13,14]. Darier-type [2] or pemphigus-type histology [6] appears to predominate in the more persistent type of lesion. Dermal eosinophilia and degranulation is sometimes seen [12]. Immunofluorescence studies are negative [15]. Electron-microscopic studies have shown intra-desmosomal separation, diminution in the number of desmosomes and perinuclear aggregation of tonofilaments [16]. Cells with the electron-microscopic features of corps ronds have also been seen [17]. In a study of the focal acantholytic dermatoses, Hashimoto *et al.* [18] reported that the attachment plaque proteins dissolved and diffused into the acantholytic cells. Internalized desmosomal structures were seldom found in acantholytic cells of non-immune diseases.

Clinical features. Transient acantholytic dermatosis presents as an acute eruption of pruritic, discrete, greyish pink papules or papulovesicles. Lesions most commonly occur on the trunk, and mostly affect middle-aged or elderly men, especially those with a fair skin. The initial lesion may be mistaken for a solar keratosis. The disease may occur on a background of pre-existing skin disease [19]. It is common in hospitalized patients [20]. The rash is usually transient, lasting from 2 weeks to several months. Exposure to sun [1,2], ionizing radiation [21] and 2-chlorodeoxyadenosine [22] and the epidermal growth factor receptor antagonist cetuximab [23] have been noted as precipitating factors. An association with internal malignancy has led to the suggestion that it may be paraneoplastic, but many other medical conditions are associated [5].

The prognosis is variable, and the disease may run a chronic relapsing course. Most patients with persistent disease are men with significant solar damage.

Differential diagnosis. Darier's disease and Hailey–Hailey disease are distinguished by the late onset of scattered truncal lesions without a tendency to confluence, and the absence of family history. Pemphigus is clinically distinct and is also excluded by negative immunofluorescence, although coexistence with pemphigus foliaceus has been recorded [24]. Other conditions in which focal acantholysis can occur include actinic keratoses or pityriasis rubra pilaris [25], and these may need to be differentiated.

Treatment. In mild cases symptomatic treatment of pruritus and topically applied steroids may be all that is required. Success with calcipotriol is recorded [26]. In more troublesome cases, etretinate [2,27], isotretinoin [28], systemic steroids [6], PUVA [29] and UVA1 [30] have been successfully used. A recent report notes clearance during treatment of follicular lymphoma with rituximab [31].

References

1 Grover RW. Transient acantholytic dermatosis. *Arch Dermatol* 1970; **101**: 426–34.
2 Chalet M, Grover R, Ackerman AB. Transient acantholytic dermatosis. A reevaluation. *Arch Dermatol* 1977; **113**: 431–5.
3 Fawcett HA, Miller JA. Persistent acantholytic dermatosis related to actinic damage. *Br J Dermatol* 1983; **109**: 349–54.
4 Simon RS, Bloom D, Ackerman AB. Persistent acantholytic dermatosis: a variant of transient acantholytic dermatosis (Grover disease). *Arch Dermatol* 1976; **112**: 1429–31.
5 Parsons JM. Transient acantholytic dermatosis (Grover's disease): a global perspective. *J Am Acad Dermatol* 1996; **35**: 653–60.
6 Heenan PJ, Quirk CJ. Transient acantholytic dermatosis. *Br J Dermatol* 1980; **102**: 515–20.
7 Hu CH, Michel B, Farber EM. Transient acantholytic dermatosis (Grover's disease). A skin disorder related to heat and sweating. *Arch Dermatol* 1985; **121**: 1439–41.
8 Scheinfeld N, Mones J. Seasonal variation of transient acantholytic dyskeratosis (Grover's disease). *J Am Acad Dermatol* 2006; **55**: 263–8.
9 Carapeto FJ, Armijo M. Maladie de Darier à minimes lesions ou varieté Darier-like de la maladie de Grover. *Ann Dermatol Vénéréol* 1979; **106**: 279–82.
10 Powell J, Sakuntabhai A, James M *et al.* Grover's disease, despite histological similarity to Darier's disease, does not share an abnormality in the ATP2A2 gene. *Br J Dermatol* 2000; **143**: 658.
11 Ackerman AB. Focal acantholytic dyskeratosis. *Arch Dermatol* 1972; **106**: 702–6.
12 Davis MD, Dinneen AM, Landa N, Gibson LE. Grover's disease: clinicopathologic review of 72 cases. *Mayo Clinic Proceedings* 1999; **74**: 229–34.
13 Hashimoto K, Moiin A, Chang MW, Tada J. Sudoriferous acrosyringeal acantholytic disease. A subset of Grover's disease. *J Cutan Pathol* 1996; **23**: 151–64.
14 Antley CM, Carrington PR, Mrak RE, Smoller BR. Grover's disease (transient acantholytic dermatosis): relationship of acantholysis to acrosyringia. *J Cutan Pathol* 1998; **25**: 545–9.
15 Bystryn JC. Immunofluorescence studies in transient acantholytic dermatosis (Grover's disease). *Am J Dermatopathol* 1979; **1**: 325–7.
16 Grover RW. Transient acantholytic dermatosis. Electron microscope study. *Arch Dermatol* 1971; **104**: 26–37.
17 Wolff HH. Transient acantholytic dermatosis (Grover). *Hautarzt* 1977; **28**: 78–82.
18 Hashimoto K, Fujiwara K, Harada M *et al.* Junctional proteins of keratinocytes in Grover's disease, Hailey–Hailey's disease and Darier's disease. *J Dermatol* 1995; **22**: 159–70.
19 Grover RW, Rosenbaum R. The association of transient acantholytic dermatosis with other skin diseases. *J Am Acad Dermatol* 1984; **11**: 253–6.
20 French LE, Piletta PA, Etienne A *et al.* Incidence of transient acantholytic dermatosis (Grover's disease) in a hospital setting. *Dermatology* 1999; **198**: 410–1.
21 Held JL, Bank D, Grossman ME. Grover's disease provoked by ionizing radiation. *J Am Acad Dermatol* 1988; **19**: 137–8.
22 Cohen PR, Kurzrock R. 2-chlorodeoxyadenosine-associated transient acantholytic dermatosis in hairy cell leukemia patients. *Am J Dermatopathol* 1999; **21**: 106–8.
23 Tscharner GG, Buhler S, Borner M, Hunziker T. Grover's disease induced by cetuximab. *Dermatology* 1907; **213**: 37–9.
24 Lang I, Lindmaier A, Hönigsmann H. Das Spektrum der transienten akantholytischen Dermatosen. *Hautarzt* 1986; **37**: 485–93.
25 Magro CM, Crowson AN. The clinical and histomorphological features of pityriasis rubra pilaris. A comparative analysis with psoriasis. *J Cutan Pathol* 1997; **24**: 416–24.
26 Keohane SG, Cork MJ. Treatment of Grover's disease with calcipotriol (Dovonex). *Br J Dermatol* 1995; **132**: 832–3.
27 Golnick H. New indications and new retinoids. *Dermatologica* 1987; **175** (Suppl. 1): 182–95.
28 Helfman RJ. Grover's disease treated with isotretinoin. *J Am Acad Dermatol* 1985; **12**: 981–4.
29 Paul BS, Arndt KA. Response of transient acantholytic dermatosis to photochemotherapy. *Arch Dermatol* 1984; **120**: 121–2.
30 Breuckmann F, Appelhans C, Altmeyer P, Kreuter A. Medium-dose ultraviolet A1 phototherapy in transient acantholytic dermatosis (Grover's disease). *J Am Acad Dermatol* 2005; **52**: 169–70.

31 Ishibashi M, Nagasaka T, Chen KR. Remission of transient acantholytic dermatosis after the treatment with rituximab for follicular lymphoma. *Clin Exp Dermatol* 2008; **33**: 206–7.

Acrokeratosis verruciformis

Acrokeratosis verruciformis of Hopf [1] is characterized by multiple flesh coloured or lightly pigmented papules on the dorsa of the hands and feet and other sites. Its existence as an independent entity has been debated [2–4].

Aetiology. The lesions are typical of acral lesions in Darier's disease, but may occur as an isolated autosomal dominant trait. Causative mutations in *ATP2A2*, the gene implicated in Darier's disease, have been found in a pedigree of acrokeratosis verruciformis [5], but this was not confirmed in three other pedigrees [6] in one of which linkage to the *ATP2A2* locus was excluded. The occurrence of these lesions with other associations (see below) suggests that there could be multiple causes.

Pathology. Hyperkeratosis, acanthosis and a prominent granular layer may be accompanied by papillomatosis and discrete pointed epidermal upgrowths said to resemble church spires. It has been claimed that the absence of subprabasal clefts distinguish this entity from Darier's disease [2], but in practice lesions from the latter do not show always show clefting [4].

Clinical features. Flat or convex, skin-coloured, warty papules are present on the dorsa of the hands and feet, on the knees and elbows, and on the forearms [7]. Small groups or isolated papules may develop in other sites. Friction of the lesions may cause blister formation. The eruption affects both sexes and is usually present at birth or appears in early childhood; however, the onset may be delayed until the fifth decade [8]. Transformation to squamous cell carcinoma has been reported [2,9]. Nail or palmar lesions may suggest the diagnosis of Darier's disease, even in the absence of the rash [5,6]. Lesions consistent with AKV have also been recorded in association with Hailey–Hailey disease [10], naevoid basal cell carcinoma syndrome [11], multiple keratoacanthomas [12], congenital poikiloderma [13], and steatocystoma multiplex and hypertrophic lichen planus [14]. The condition resembles extensive plane warts but in more severe cases epidermodysplasia verruciformis can be differentiated by histopathology and virological studies.

Treatment. Systemic treatment of isolated acrokeratoses is not usually justified. Oral retinoid treatment has variable results [15,16].

References

1 Hopf G. Über eine nicht beschriebene disseminierte Keratose (Acrokeratosis verruciformis). *Dermatol Zeitschr* 1931; **60**: 227–50.
2 Panja RK. Acrokeratosis verruciformis (Hopf)—a clinical entity? *Br J Dermatol* 1977; **96**: 643–52.
3 Blanchet-Bardon C, Durand-Delorme M, Nazzaro V *et al.* Acrokeratose verruciforme de Hopf ou maladie de Darier acrale. *Ann Dermatol Vénéréol* 1988; **115**: 1229–32.
4 Braun-Falco M, Fesq H, Ring J, Abeck D. Acrokeratosis verruciformis Hopf as a minimal manifestation of Darier's disease. *Z Hautkrank* 2001; **76**: 449–52.
5 Dhitavat J, Macfarlane S, Dode L *et al.* Acrokeratosis verruciformis of Hopf is caused by mutation in ATP2A2: evidence that it is allelic to Darier's disease. *J Invest Dermatol* 2003; **120**: 229–32.
6 Wang PG, Gao M, Lin GS *et al.* Genetic heterogeneity in acrokeratosis verruciformis of Hopf. *Clin Exp Dermatol* 2006; **31**: 558–63.
7 Niedelmann ML, McKusick VA. Acrokeratosis verruciformis (Hopf). A follow-up study. *Arch Dermatol* 1962; **86**: 779–82.
8 Schueller WA. Acrokeratosis verruciformis of Hopf. *Arch Dermatol* 1972; **106**: 81–3.
9 Dogliotti M, Schmaman A. Acrokeratosis verruciformis: malignant transformation. *Dermatologica* 1971; **143**: 95–9.
10 Vakis G, Csato M, Kemeny L *et al.* Hailey–Hailey disease with acrokeratosis verruciformis Hopf. *Acta Derm Venereol* 1996; **76**: 157.
11 Humbert P, Laurent R, Faivre B *et al.* Nevoid basal cell carcinoma syndrome and acrokeratosis verruciformis. Occurrence of two rare inherited autosomal dominant conditions in the same patient. *Dermatologica* 1990; **180**: 169–70.
12 Farro P, Zalaudek I, Ferrara G *et al.* Unusual association between acrokeratosis verruciformis of Hopf and multiple keratoacanthomas. Successful therapy with acitretin. *J Dtsch Dermatol Ges* 2004; **2**: 440–2.
13 Marill FG, Vodov I. Association d'acrokeratose verruciforme à la poikilodermie congenitale en tant qu'entité dermatologique. *Dermatologica* 1978; **156**: 351–7.
14 Verbov J. Acrokeratosis verruciformis of Hopf with steatocystoma multiplex and hypertrophic lichen planus. *Br J Dermatol* 1972; **85**: 91–4.
15 Torne-Escasany R, Lopez-Gil F, Umbert-Millet P. Acroqueratosis verruciforme de Hopf Comunicacion de un caso no familiar. *Med Cutan Ibero Lat Am* 1987; **15**: 441–3.
16 Serarslan G, Balci DD, Homan S. Acitretin treatment in acrokeratosis verruciformis of Hopf. *J Dermatolog Treat* 2007; **18**: 123–5.

Other focal disorders

Perforating keratotic disorders [1]

The nature and number of perforating (epidermal elimination) disorders is uncertain. They present as keratotic papules, but as epidermal involvement may be secondary to dermal disease they are probably not true disorders of keratinization. A case has been made for unifying some or all disorders because, with the exception of elastosis perforans serpiginosa, all have been reported in association with diabetes mellitus or renal failure [2]. The unifying term 'acquired perforating dermatosis' has been proposed.

Acquired perforating dermatosis. Kyrle's case was a young diabetic female in whom keratotic nodules appeared around the axillae and later became generalized [3], and Kyrle's disease (hyperkeratosis follicularis et parafollicularis in cutem penetrans) is probably synonymous with acquired perforating dermatosis [4–6]. Keratinous 1-cm nodules are seen mainly on the limbs (Fig. 19.53).

Trauma from scratching is thought to initiate the lesions. It is most often seen with diabetes or before, during or after dialysis for renal failure [7]. Eleven per cent of 72 British patients on renal dialysis developed a perforating dermatosis [8]. Many individual reports of association with malignancy, infection or inflammatory conditions have been published, but often also with renal failure or diabetes [9]. A patient who developed a perforating folliculitis with each of two anti-TNF agents, improving on withdrawal, has been reported [10]. Familial occurrence, with ocular involvement, is reported (MIM 149500) [11,12]. Histology of acquired perforating dermatoses [9] may show follicular and non-follicular lesions

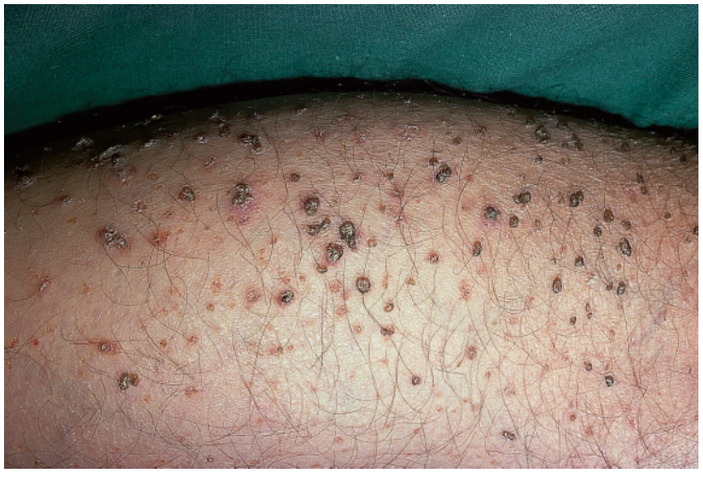


Fig. 19.53 Kyrle's disease/acquired perforating dermatosis: large keratinous plugs on the thigh.

with broad or narrow ulcer craters, and evidence of perforation of both collagen and elastic fibres [13]. Degenerate collagen, elastic tissue and keratin are seen mixed with an unidentified clear material, which has been regarded by some as an accumulation of a metabolite [2]. Changes diagnosed as perforating folliculitis, reactive perforating collagenosis or Kyrle's disease may all be found [9,13] and may depend on the age of the lesions, or sampling. In most cases of acquired perforating dermatosis, lesions could be cleared by treatment with potent topical or intralesional steroids. Success with conventional or narrow-band UVB phototherapy [14–16] has also been recorded. Topical tretinoin may reduce the lesions. Other agents reported to be effective include allopurinol [17] and doxycycline [18].

Necrotizing infundibular crystalline folliculitis. Lucke *et al.* [19] reported two cases of a disorder characterized by transepidermal elimination of negatively birefringent needle-shaped crystals similar to monosodium urate. Kossard *et al.* [20] reported a similar case and suggested that the disorder was due to initiation of crystal formation around microorganisms from follicular lipids at critical concentrations.

Elastosis perforans serpiginosa (see Chapter 45). This presents as grouped arcuate or serpiginous keratotic papules and is associated with Down's syndrome, disorders of connective tissue and penicillamine treatment. Histologically, amorphous masses that bind elastic tissue stains can be seen traversing the epidermis.

Reactive perforating collagenosis (see Chapter 45). This affects children, with the formation of 2 to 5-mm papules, usually on the limbs. Lesions in all stages of eruption and resolution are present at one time [21].

References

1 Seghal VN, Jain S, Thappa DM *et al.* Perforating dermatoses: a review and report of four cases. *J Dermatol* 1993; **20**: 329–40.

2 Rapini RP, Hebert AS, Drucker CR. Acquired perforating dermatosis: evidence for combined transepidermal elimination of both collagen and elastic fibers. *Arch Dermatol* 1989; **125**: 1074–8.

3 Kyrle J. Uber einen ungewohnilichen Fall von universeller follikularer und parafollikularer Hyperkeratose (Hyperkeratosis follicularis et parafollicularis in Cutem penetrans). *Arch Dermatol Syphilol* 1916; **123**: 466–93.

4 Carter VH, Constantine VS. Kyrle's disease. I. Clinical findings in five cases and review of literature. *Arch Dermatol* 1968; **97**: 624–32.

5 Constantine VS, Carter VH. Kyrles disease. II. Histopathologic findings in five cases and review of the literature. *Arch Dermatol* 1968; **97**: 633–9.

6 Price ML, Wilson Jones E, Macdonald DM. Flegel's disease not Kyrle's disease. *J Am Acad Dermatol* 1988; **18**: 1366–7.

7 De Mare S, Koopman RJJ, Steiljen PM. Acquired perforating dermatosis (Kyrle's disease). *Br J Dermatol* 1993; **129**: 211.

8 Morton CA, Henderson IS, Jones MC *et al.* Acquired perforating dermatosis in a British dialysis population. *Br J Dermatol* 1996; **135**: 671–7.

9 Saray Y, Seckin D, Bilezikci B. Acquired perforating dermatosis: clinicopathological features in twenty-two cases. *J Eur Acad Dermatol Venereol* 2006; **20**: 679–88.

10 Gilaberte Y, Coscojuela C, Vazquez C *et al.* Perforating folliculitis associated with tumour necrosis factor-alpha inhibitors administered for rheumatoid arthritis. *Br J Dermatol* 2007; **156**: 368–71.

11 Tessler HH, Apple DJ, Goldberg MF. Ocular findings in a kindred with Kyrle disease. Hyperkeratosis follicularis et parafollicularis in cutem penetrans. *Arch Ophthalmol* 1973; **146**: 101–6.

12 Shivakumar V, Okade R, Rajkumar V, Prathima KM. Familial Kyrle's disease: a case report. *Int J Dermatol* 2007; **46**: 770–1.

13 Rapini RP, Herbert AA, Drucker CR. Acquired perforating dermatosis. Evidence for combined transepidermal elimination of both collagen and elastic fibers. *Arch Dermatol* 1989; **125**: 1074–8.

14 Faver IR, Daoud MS, Su WP. Acquired reactive perforating collagenosis. Report of six cases and review of the literature. *J Am Acad Dermatol* 1994; **30**: 575–80.

15 Bayramgurler D, Apaydin R, Cetiner D, Zincirci C. Narrow-band ultraviolet B phototherapy for acquired perforating dermatosis. *Australas J Dermatol* 2003; **44**: 76–8.

16 Gambichler T, Altmeyer P, Kreuter A. Treatment of acquired perforating dermatosis with narrowband ultraviolet B. *J Am Acad Dermatol* 2005; **52**: 363–4.

17 Kruger K, Tebbe B, Krengel S *et al.* Acquired reactive perforating dermatosis: successful treatment of two cases with allopurinol. *Hautarzt* 1999; **50**: 115–20.

18 Brinkmeier T, Schaller J, Herbst RA, Frosch PJ. Successful treatment of acquired reactive perforating collagenosis with doxycycline. *Acta Derm Venereol* 2002; **82**: 393–5.

19 Lucke TW, Fallowfield ME, Evans A *et al.* Transepidermal elimination of urate-like crystals: a new perforating disorder? *Br J Dermatol* 1999; **141**: 310–4.

20 Kossard S, Scurry J, Killingsworth M. Necrotizing infundibular crystalline folliculitis. *Br J Dermatol* 2001; **145**: 165–8.

21 Mehregan AH, Schwartz OD, Livingood CS. Reactive perforating collagenosis. *Arch Dermatol* 1967; **96**: 277–82.

Flegel's disease (hyperkeratosis lenticularis perstans)

This is inherited as an autosomal dominant condition (MIM 144150). Lesions differ markedly from Kyrle's disease [1]. In the third or fourth decade, 2–3 mm keratotic papules with discrete irregular margins ('cornflake sign', Rowland–Payne) appear over the calves and extensor surfaces of the ankles (Fig. 19.54). Lesions may spread to the arms and the concha of the ears. The keratotic scale separates from many lesions, leaving a non-exudative red base. Irritation may be severe. Histologically, there is hyperkeratosis, sometimes with foci of parakeratosis. The underlying epidermis alternates between atrophy and acanthosis, and there is a dermal infiltrate of mononuclear cells [1,2]. Despite the strong genetic component in the disorder, no reports identifying a candidate gene have appeared to date. The profusion of lesions and poor response to cryotherapy, topical and systemic retinoids, and to 5-fluorouracil make management difficult.



Fig. 19.54 Flegel's disease: polygonal keratotic lesions on legs.

References

1 Flegel H. Hyperkeratosis lenticularis perstans. *Hautarzt* 1958; **9**: 362–4.

2 Price ML, Wilson Jones E, MacDonald DM. A clinicopathological study of Flegel's disease (hyperkeratosis lenticularis perstans). *Br J Dermatol* 1987; **116**: 681–91.

Porokeratoses

Porokeratoses are characterized by marginate scaling lesions, histologically showing a column of parakeratotic keratinocytes (the coronoid lamella). Various forms are recognized, but terminology and classification are debated [1,2]. Some forms appear to be premalignant [3].

Aetiology. In Chinese pedigrees of disseminated superficial (actinic) porokeratosis (DSAP) loci at chromosomes 12q (MIM 175900) [4], 15q (MIM 607728) [5], and 18p [6] have been reported. Loss of heterozygosity at 12q and sequence variations in genes at this locus are reported, but the significance of these findings is uncertain [7–11]. The centrifugal progress of individual lesions is thought to reflect the migration of a clone of abnormal cells [12]. There is keratinocyte dysplasia and Otsuka *et al.* [13,14] have reported aneuploidy and chromosomal abnormalities in lesional keratinocytes. The tumour suppressor protein p53 is overexpressed in the coronoid lamella [15–18], but D'Errico *et al.* [18] found no evidence of p53 mutations or radiation hypersensitivity in DSAP-derived keratinocytes and fibroblasts. Cytogenetic anomalies in fibroblasts, particularly chromosome 3, are also recorded [19]. An association with immunosuppression [1] suggests impaired immunity is permissive, perhaps by reduced immune surveillance of dysplasia, but the possibility of an infective aetiology [20] remains. Esser *et al.* [21] found evidence of HPV types 66 and x14 respectively in two patients with porokeratosis of Mibelli.



Fig. 19.55 Disseminated superficial actinic porokeratoses: annular keratotic lesions with a raised margin.

Pathology [22]. Lesions may or may not involve the eccrine sweat duct. The characteristic histopathology is seen in the edge of the lesion. The stratum corneum is hyperkeratotic, and at the raised border a column of poorly staining parakeratotic stratum corneum cells, the cornoid lamella, is seen running through the surrounding normal-staining cells. The underlying keratinocytes are oedematous with spongiosis, shrunken nuclei and a moderate dermal lymphocytic infiltrate under the lamella [22]; a lichenoid reaction pattern, and the presence of amyloid material may be detected [23]. The central area of a lesion is usually atrophic, but may occasionally show gross hyperkeratosis [24]. Cornoid lamellae may also be found in other conditions, such as viral warts, some ichthyoses and naevoid hyperkeratoses.

Clinical features

Disseminated forms. Clinical distinction between the various forms of disseminated porokeratosis may not be justified [25]. *Disseminated superficial actinic porokeratosis* (DSAP) is the most common presentation, with very many lesions of up to 10 mm predominantly in sun-exposed sites in middle-aged individuals, especially those with sun-sensitive skin (Fig. 19.55). They are easily mistaken for actinic keratoses, with which they may coexist. Lesions were not induced by artificial light exposure [26], but have been provoked by photochemotherapy [27]. No evidence that skin cancer arises in the porokeratotic lesions was found in a study of 29 patients [28]. *Disseminated superficial porokeratoses of immunosuppression* are recognized after renal, hepatic, cardiac and bone marrow transplantation, and in AIDS [1]. The distribution is similar to DSAP, but a history of sun exposure is less likely [29]. *Disseminated superficial porokeratosis of childhood* may be inherited as an autosomal dominant condition, but sporadic cases are seen. Widely disseminated, flat lesions usually begin in childhood, the majority between the ages of 5 and 10 years, but may be present at birth or may first appear at puberty or later. Palmoplantar lesions may be associated (porokeratosis palmaris et plantaris dis-



Fig. 19.56 Porokeratosis of Mibelli.

seminata) [30]. Widespread lesions appeared first at the age of 1 month in a male infant with craniosynostosis and other congenital abnormalities [31].

Porokeratosis of Mibelli [32,33]. The eponym Mibelli is sometimes used generically for porokeratoses, but usually refers only to the form with single or scanty and larger lesions. These develop as annular dry plaques (Fig. 19.56) surrounded by a raised, fine keratotic wall and sometimes also a furrow. Lesions are most common on the limbs and by centrifugal spread may achieve several centimetres in diameter. The centre is usually atrophic but may be hyperkeratotic [34]. The face, genitalia, oral mucosa and cornea may also be affected. The condition may be familial, inherited as an autosomal dominant with onset in childhood (MIM 175800), or sporadic and of later onset.

Giant porokeratoses (up to 20 cm in diameter with a surrounding wall of 1 cm). These are very rare [34], and are most often found on the foot. Large lesions are said to have the highest malignant potential [3,35,36].

Palmoplantar porokeratosis (of Mantoux). Parakeratotic hyperkeratosis histologically reminiscent of the cornoid lamella occurs in some punctate keratodermas, but the absence of marginate lesions distinguishes from true porokeratosis [37]. Nonetheless, annular lesions of palms and soles with a cornoid lamella are recognized [30,38].

Linear porokeratosis [36,39,40]. Linear porokeratoses showing typical cornoid lamellae and following the lines of Blaschko usually appear in childhood. These lesions probably result from a predisposition to porokeratosis in an abnormal clone of epidermal precursors. Malignant degeneration and metastasis has been reported in this variety [37,41]. Linear accentuation of disseminated actinic porokeratosis is reported [42–44].

Treatment. Treatment of disseminated superficial porokeratoses is usually unnecessary, but cryotherapy, carbon dioxide and pulsed dye laser therapy, and photodynamic treatment have all been used [45–47]. Keratolytics offer little relief. Topical tacalcitol [48], 5-fluorouracil ointment [49,50], imiquimod cream [51] and oral etretinate [52] have been effective. Diclofenac gel was disappointing [53].

References

1 Kanitakis J, Euvrard S, Faure M, Claudy A. Porokeratosis and immunosuppression. *Eur J Dermatol* 1998; **8**: 459–65.
2 Schamroth JM, Zlotogorski A, Gilead L. Porokeratosis of Mibelli. *Acta Derm Venereol* 1997; **77**: 207–13.
3 Sasson M, Krain AD. Porokeratosis and cutaneous malignancy: a review. *Dermatol Surg* 1996; **22**: 339–42.
4 Xia JH, Yang YF, Deng H *et al.* Identification of a locus for disseminated superficial actinic porokeratosis at chromosome 12q23.2–24.1. *J Invest Dermatol* 2000; **114**: 1071–4.
5 Xia K, Deng H, Xia JH *et al.* A novel locus (DSAP2) for disseminated superficial actinic porokeratosis maps to chromosome 15q25.1–26.1. *Br J Dermatol* 2000; **147**: 650–4.
6 Wei S, Yang S, Lin D, Li M *et al.* A novel locus for disseminated superficial porokeratosis maps to chromosome 18p11.3. *J Invest Dermatol* 2004; **123**: 872–5.
7 Zhang ZH, Huang W, Niu ZM *et al.* Two closely linked variations in actin cytoskeleton pathway in a Chinese pedigree with disseminated superficial actinic porokeratosis. *J Am Acad Dermatol* 2005; **52**: 972–6.
8 Zhang ZH, Niu ZM, Yuan WT *et al.* A mutation in SART3 gene in a Chinese pedigree with disseminated superficial actinic porokeratosis. *Br J Dermatol* 2005; **152**: 658–63.
9 Zhang ZH, Niu ZM, Huang W *et al.* Loss of heterozygosity analysis on chromosome 12q in disseminated superficial actinic porokeratosis. *J Invest Dermatol* 2007; **127**: 482–5.
10 Frank J, van Steensel MA, Van Geel M. Lack of SSH1 mutations in Dutch patients with disseminated superficial actinic porokeratosis: is there really an association? *Hum Mutat* 2007; **28**: 1241–2.
11 Zhang Z, Niu Z, Wang Y, Huang W. Association of SSH1 mutations with disseminated superficial actinic porokeratosis in Chinese pedigrees (response to Frank *et al.*). *Hum Mutat* 2007; **28**: 1243–4.
12 Reed RJ, Leone P. Porokeratosis: a mutant clonal keratosis of the epidermis. I. Histogenesis. *Arch Dermatol* 1970; **101**: 340–7.
13 Otsuka F, Shima A, Ishibashi Y. Porokeratosis has neoplastic clones in the epidermis. Microfluorometric analysis of DNA content of epidermal cell nuclei. *J Invest Dermatol* 1989; **92**: 231S–3S.
14 Otsuka F, Nashiro K, Kobayashi K, Ishibashi Y. Chromosome abnormalities of porokeratosis-cultured epidermal keratinocytes: comparison with those of cultured dermal fibroblasts. *Cancer Genet Cytogen* 1991; **56**: 163–9.
15 Magee JW, McCalmont TH, LeBoit PE. Overexpression of p53 tumor suppressor protein in porokeratosis. *Arch Dermatol* 1994; **130**: 187–90.
16 Urano Y, Sasaki S, Ninomiya Y *et al.* Immunohistochemical detection of p53 tumor suppressor protein in porokeratosis. *J Dermatol* 1996; **23**: 365–8.
17 Nelson C, Cowper S, Morgan M. p53, mdm-2, and p21 waf-1 in the porokeratoses. *Am J Dermatopathol* 1999; **21**: 420–5.
18 D'Errico M, Teson M, Calcagnile A *et al.* Characterization of the ultraviolet B and X-ray response of primary cultured epidermal cells from patients with disseminated superficial actinic porokeratosis. *Br J Dermatol* 2004; **150**: 47–55.
19 Scappaticci S, Lambiase S, Orecchia G *et al.* Clonal chromosome abnormalities with preferential involvement of chromosome 3 in patients with porokeratosis of Mibelli. *Cancer Genet Cytogenet* 1989; **43**: 89–94.
20 Mizukawa Y, Shiohara T. Onset of porokeratosis of Mibelli in organ transplant recipients: lack of a search for transmissible agents in these patients. *J Am Acad Dermatol* 2001; **44**: 143–4.
21 Esser AC, Pittelkow MR, Randle HW. Human papillomavirus isolated from transplant-associated porokeratoses of mibelli responsive to topical 5% imiquimod cream. *Dermatol Surg* 2006; **32**: 858–61.
22 Ginarte M, Leon A, Toribio J. Disseminated superficial porokeratosis with amyloid deposits. *Eur J Dermatol* 2005; **15**: 298–300.
23 Shumack S, Commens C, Kossard S. Disseminated superficial actinic porokeratosis: a histological review of 61 cases with particular reference to lymphocytic inflammation. *Am J Dermatopathol* 1991; **13**: 26–31.

24 Jacyk W, Esplin L. Hyperkeratotic form of porokeratosis of Mibelli. *Int J Dermatol* 1993; **32**: 902–3.
25 Kanitakis J, Euvrard S, Claudy A. Porokeratosis in organ transplant recipients. *J Am Acad Dermatol* 2001; **44**: 144–6.
26 Ibbotson SH. Disseminated superficial porokeratosis: what is the association with ultraviolet radiation? *Clin Exp Dermatol* 1996; **21**: 48–50.
27 Allen AL, Glaser DA. Disseminated superficial actinic porokeratosis associated with topical PUVA. *J Am Acad Dermatol* 2000; **43**: 720–2.
28 Shumack SP, Commens CA. Disseminated superficial actinic porokeratosis: a clinical study. *J Am Acad Dermatol* 1989; **20**: 1015–22.
29 Bencini PL, Tarantino A, Grimalt R. Porokeratosis and immunosuppression. *Br J Dermatol* 1995; **132**: 74–8.
30 Patrizi A, Passarini B, Minghetti G *et al.* Porokeratosis palmaris et plantaris disseminata: an unusual clinical presentation. *J Am Acad Dermatol* 1989; **21**: 415–8.
31 Judge MR, Michaels M, Sams VR *et al.* Disseminated porokeratosis in an infant with craniosynostosis. *Br J Dermatol* 1996; **123**: 249–54.
32 Allegra F. The man behind the eponym: Vittorio Mibelli and the tale of porokeratosis. *Am J Dermatopathol* 1986; **11**: 79–83.
33 Virgili A, Strumia R. Annular hyperkeratosis: porokeratosis of Mibelli. *Arch Dermatol* 1986; **122**: 586–7.
34 Bacharach-Buhles M, Weindorf N, Altmeyer P. Porokeratosis Mibelli gigantea. *Hautarzt* 1990; **41**: 633–5.
35 Otsuka F, Someya T, Ishibashi Y. Porokeratosis and malignant skin tumors. *J Cancer Res Clin Oncol* 1991; **117**: 55–60.
36 Lucker GP, Steiljen PM. The coexistence of linear and giant porokeratosis associated with Bowen's disease. *Dermatology* 1994; **189**: 78–80.
37 Friedman SJ, Herman PS, Pittelkow MR. Punctate porokeratotic keratoderma. *Arch Dermatol* 1988; **124**: 1678–82.
38 Neumann RA, Knobler RM, Gebhart W. Unusual presentation of porokeratosis palmaris, plantaris et disseminata. *J Am Acad Dermatol* 1989; **21**: 1131–3.
39 Karadaglic DL, Berger S, Jankovic D *et al.* Zosteriform porokeratosis of Mibelli. *Int J Dermatol* 1988; **27**: 589–90.
40 Veraldi S, Bocor M, Gasparini G. Zosteriform porokeratosis: a report of two cases. *Cutis* 1989; **44**: 216–9.
41 Lozinski AZ, Fisher BK, Walter JB *et al.* Metastatic squamous cell carcinoma in linear porokeratosis of Mibelli. *J Am Acad Dermatol* 1987; **16**: 448–51.
42 Dover JS, Miller JA, Levene GM. Linear porokeratosis of Mibelli and DSAP. *Clin Exp Dermatol* 1986; **11**: 79–83.
43 Gautam RK, Bedi GK, Sehgal VN. Simultaneous occurrence of disseminated superficial actinic porokeratosis (DSAP), linear and punctate porokeratosis. *Int J Dermatol* 1995; **34**: 71–2.
44 Boente MC, Lopez-Baro AM, Frontini MV, Asial RA. Linear porokeratosis associated with disseminated superficial actinic porokeratosis: a new example of type II segmental involvement. *Pediatr Dermatol* 2003; **20**: 514–8.
45 Barnett JH. Linear porokeratosis: treatment with the carbon dioxide laser. *J Am Acad Dermatol* 1986; **14**: 902–4.
46 Alster TS, Nanni CA. Successful treatment of porokeratosis with 585 nm pulsed dye laser irradiation. *Cutis* 1999; **63**: 265–6.
47 Cavicchini S, Tourlaki A. Successful treatment of disseminated superficial actinic porokeratosis with methyl aminolevulinate-photodynamic therapy. *J Dermatolog Treat* 2006; **17**: 190–1.
48 Bohm M, Luger TA, Bonsmann G. Disseminated superficial actinic porokeratosis: treatment with topical tacalcitol. *J Am Acad Dermatol* 1999; **40**: 479–80.
49 Hubler WR, Michaelson JD, Knox JM. Linear porokeratosis. *Cutis* 1974; **14**: 61–4.
50 McDonald SG, Peterka ES. Porokeratosis (Mibelli): treatment with topical 5-fluorouracil. *J Am Acad Dermatol* 1983; **8**: 107–10.
51 Agarwal S, Berth-Jones J. Porokeratosis of Mibelli: successful treatment with 5% imiquimod cream. *Br J Dermatol* 2002; **146**: 338–9.
52 Danno K, Yamamoto M, Yokoo T. Etretinate treatment in disseminated porokeratosis. *J Dermatol* 1988; **15**: 440–4.
53 Vlachou C, Kanelleas A, Martin-Clavijo A, Berth-Jones J. Treatment of disseminated superficial actinic porokeratosis with topical diclofenac gel: a case series. *J Eur Acad Dermatol Venereol* 2008; **22**: 1343–5.

Minute and filiform keratoses

A number of entities have been described using names including filiform keratoses, minute aggregate keratosis, and multiple minute digitate hyperkeratosis [1–4] (Fig. 19.57). Ramselaar and Toonstra propose an inclusive approach to classification [5], under the name multiple minute digitate hyperkeratosis. Filiform or spiny palmoplantar keratoses are also recognized [6,7].



Fig. 19.57 Digitate hyperkeratosis. (Courtesy of Dr F.A. Ive, Dryburn Hospital, Durham, UK.)

Cases may be sporadic [3] or familial with probable autosomal dominant inheritance [2,8,9], early or late onset, transient or persistent, follicular or non-follicular. Reported associations include drugs, malignancy, especially haematological, and X-irradiation [4,5,9–13]. One case associated with carcinoma of the larynx cleared following surgery [14]. Filiform keratoses occur with a PRP-like eruption and acne conglobata in association with HIV infection [15]. Histologically, there are focal areas of compact orthohyperkeratosis with few dermal changes and keratohyalin granules thought to be smaller than normal are reported [16]. Parakeratosis may be present [17] but the use of the term porokeratosis is probably misleading [5,6].

References

1 Folster-Holst R, Christophers E. Filiforme keratose. *Hautarzt* 1994; **45**: 484–8.
2 Frenk E, Mevorah B, Leu F. Disseminated spiked hyperkeratosis: an unusual discrete non-follicular keratinization disorder. *Arch Dermatol* 1981; **117**: 412–4.
3 Judd LE, Wood KP. Disseminated spiked hyperkeratosis. *Int J Dermatol* 1993; **32**: 446–7.
4 Carmichael AJ, Tan CY. Digitate keratoses: a complication of etretinate used in the treatment of disseminated superficial actinic porokeratosis. *Clin Exp Dermatol* 1990; **15**: 370–1.
5 Ramselaar C, Toonstra J. Multiple minute digitate hyperkeratoses report of two cases with an updated review and proposal for a new classification. *Eur J Dermatol* 1999; **9**: 460–5.
6 McGovern TW, Gentry RH. Spiny keratoderma: case report, classification, and treatment of music box spine dermatoses. *Cutis* 1994; **54**: 389–94.
7 Torres G, Behshad R, Han A *et al.* 'I forgot to shave my hands': a case of spiny keratoderma. *J Am Acad Dermatol* 2008; **58**: 344–8.
8 Goldstein N. Multiple minute digitate hyperkeratoses. *Arch Dermatol* 1967; **96**: 692–3.
9 Balus L, Donati P, Amantea A *et al.* Multiple minute digitate hyperkeratosis. *J Am Acad Dermatol* 1988; **18**: 431–6.
10 Izakovic J, Stanislaw A, Buchner M *et al.* Haarartige Hyperkeratosen bei einem Nierentransplantierten: eine neue Cyclosporin-nebenwirkung. *Hautarzt* 1995; **46**: 841–6.
11 Paul C, Fermand J-P, Flageul B *et al.* Hyperkeratotic spicules and monoclonal gammopathy. *J Am Acad Dermatol* 1995; **33**: 346–51.

12 Lukitsch O, Gebhardt K-P, Kovary PM. Follicular hyperkeratosis and cryocrystalglobulinemia syndrome: occurrence in a patient with multiple myeloma. *Arch Dermatol* 1985; **121**: 795–8.
13 Wilkinson SM, Wilkinson N, Chalmers RJ. Multiple minute digitate keratoses: a transient, sporadic variant. *J Am Acad Dermatol* 1994; **31**: 802–3.
14 Ferandiz C, Savall R, Baumann E. Hiperqueratosis multiple minuta y digitata (un sintoma paraneoplasico?). *Med Cutan Ibero Lat Am* 1978; **6**: 279–83.
15 Miralles ES, Nunez M, De La Heras ME *et al.* Pityriasis rubra pilaris and human immunodeficiency virus infection. *Br J Dermatol* 1995; **133**: 990–3.
16 Feldmann R, Harms M. Multiple filiform hyperkeratosen. *Hautarzt* 1993; **44**: 658–61.
17 Pujol RM, Perez-Losada E, Matias-Guiu X *et al.* Postirradiation multiple minute digitate porokeratosis: review. *J Cutan Med Surg* 2001; **5**: 126–30.

Miscellaneous circumscribed keratotic disorders

Waxy keratoses of childhood. Three children in two families were reported with a disorder consisting of generalized discrete domed keratotic papules, which were flesh-coloured or yellowish [1]; two young patients reported earlier with 'disseminated hypopigmented keratoses', appear to be identical [2]. The disorder has been reported in a linear form [3] and as linear exacerbation in generalized disease [4], further supporting the notion that this is a genodermatosis. Histological findings were marked orthokeratotic hyperkeratosis, tenting of the epidermis and mild acanthosis. Differential diagnosis includes the leukodermic macules in Darier's disease in dark skin [5].

Facial Afro-Caribbean childhood eruption. A monomorphic, mildly hyperkeratotic, papular facial eruption in black children was reported by Marten *et al.* [6] in 1976. Further cases in children were termed granulomatous perioral dermatitis [7]. Williams *et al.* [8] suggested the name and acronym FACE. The eruption shows a predilection for the perioral and periorbital regions and nose. The condition is of unknown cause, and does not appear to be a rebound phenomenon from the use of topical steroids. A relationship to sarcoid was suggested in one case [9]. Histology shows peri-follicular inflammation with foci of granuloma formation. It does not respond to topical steroids, but resolution within a year without scarring was usual.

Florid cutaneous papillomatosis [10,11]. This term was used to describe the appearance of multiple acuminate keratotic papules in association with an underlying gastric adenocarcinoma. The first patient also had acanthosis nigricans and eruptive seborrhoeic warts (Léser–Trelat sign). Worret's case also had acquired hypertrichosis lanuginosa from metastatic bronchial carcinoma.

Hyperkeratosis of the nipple [12]. Marked hypertrophy of the nipple and areola was noted in association with a T-cell lymphoma, which resolved following chemotherapy.

Knuckle pads [13,14]. These are classified with the fibromatoses (see Chapter 45). Nevertheless, it appears that the dry, rather fleshy lesions occurring over the knuckles and interphalangeal joints differ from the acanthotic grossly hyperkeratotic lesions seen in association with some keratodermas. In Morginson's series of 30 patients [13], seven showed hyperkeratosis, keratodermas and fissuring of varying degree involving the palms and soles. Confusion sometimes occurs with pachydermodactyly (see Chapter 45). Knuckle pads may be seen in keratodermas such as the Papillon–Léfèvre syndrome, epidermolytic keratoderma resulting from keratin 9 mutation [15] and Bart–Pumphrey syndrome [16].

References

1 Coleman R, Malone M, Handfield-Jones S *et al.* Waxy keratoses of childhood. *Clin Exp Dermatol* 1994; **19**: 173–6.
2 Morison WL, Kerker BJ, Tunnessen WW *et al.* Disseminated hypopigmented keratoses. *Arch Dermatol* 1991; **127**: 848–50.
3 Mehrabi D, Thomas JE, Selim MA, Prose NS. Waxy keratoses of childhood in a segmental distribution. *Pediatr Dermatol* 2001; **18**: 415–6.
4 Happle R, Fleiner J, Loskamp U. Kerinokeratosis papulosa with a type 2 segmental manifestation. *J Am Acad Dermatol* 2004; **50**: S84–5.
5 Jacyk WK, Visser AJ. Leukodermic macules in keratosis follicularis (Darier's disease). *Int J Dermatol* 1992; **31**: 715–7.
6 Marten RH, Presbury DGC, Adamson JE *et al.* An unusual papular and acneiform facial eruption in the negro child. *Br J Dermatol* 1976; **91**: 435–8.
7 Frieden IJ, Prose NS, Fletcher V *et al.* Granulomatous perioral dermatitis in children. *Arch Dermatol* 1989; **125**: 369–73.
8 Williams HC, Ashworth J, Pembroke AC, Breathnach SM. FACE: facial Afro-Caribbean childhood eruption. *Clin Exp Dermatol* 1990; **15**: 163–6.
9 Antony FC, Buckley DA, Russell-Jones R. Childhood granulomatous periorificial dermatitis in an Asian girl—a variant of sarcoid? *Clin Exp Dermatol* 2002; **27**: 275–6.
10 Schwartz RA, Burgess GH. Florid cutaneous papillomatosis. *Arch Dermatol* 1978; **114**: 1803–6.
11 Worret W-IF, Mayerhausen W, Emslander HP. Hypertrichosis lanuginosa acquisita associated with florid cutaneous papillomatosis. *Int J Dermatol* 1993; **32**: 56–8.
12 Ahn SK, Chung J, Lee WS *et al.* Hyperkeratosis of the nipple and areola simultaneously developing with cutaneous T-cell lymphoma. *J Am Acad Dermatol* 1995; **32**: 124–5.
13 Morginson WJ. Discrete keratodermas over the knuckle and finger articulations. *Arch Dermatol* 1955; **71**: 349–53.
14 Mackey SL, Cobb MW. Knuckle pads. *Cutis* 1994; **54**: 159–60.
15 Kuster W, Zehender D, Mensing H *et al.* Vörner keratosis palmoplantaris difusa: clinical, formal genetic and molecular biology studies of 22 families. *Hautarzt* 1995; **46**: 705–10.
16 Bart RS, Pumphrey RE. Knuckle pads, leukoncyhia and deafness. *N Engl J Med* 1967; **276**: 202–7.

Palmoplantar keratodermas

Classification of palmoplantar keratodermas

Palmoplantar keratodermas (PPKs) are a diverse group of hereditary and acquired disorders defined by excessive epidermal thickening of palms and soles. Many keratoderma syndromes are restricted to palms and soles but marked palmoplantar hyperkeratosis may also be seen in generalized disorders of keratinization such as ichthyosis vulgaris, epidermolysis bullosa or EHK, in ectodermal dysplasias, dysmorphic syndromes or metabolic disorders, and in inflammatory disease, notably psoriasis, eczema and lichen planus. This section deals mainly with conditions in which keratoderma is the primary or presenting feature, or a major clinical problem. Many such cases are genetic in origin. The molecular basis has been elucidated in the majority of well-defined syndromes (Table 19.5), but clinically homogeneous entities may have distinct molecular pathogenesis, and different mutations in one gene can give rise to distinct syndromes. Consequently, although a number of classifications of keratodermas have been published [1–7], none unite satisfactorily clinical presentation, pathology and

Table 19.5 Principal hereditary palmoplantar keratodermas (fuller descriptions and references are given in the text).

Type	Eponym(s)	Inheritance (presumed)	Gene or locus	Onset (years)	Transgredient/ cicatrizing	Comments/special features
Keratodermas and ectodermal dysplasias						
Diffuse group						
Epidermolytic keratoderma	Vörner	AD	Keratin 9	0–3	N	Most common but histology needed to confirm
Diffuse non-epidermolytic keratoderma*	Thost–Unna	AD	some 12q11–q13 Keratin 1	2–5 or later	N	Likely to be heterogeneous
Loricrin keratoderma	Camisa; variant Vohwinkel	AD	Loricrin	2–5	Y	Mild ichthyosis; honeycomb pattern keratoderma
Autosomal dominant transgredient keratoderma*	Greither; Sybert	AD	some 1p; Keratin 1	3–8	Y	Likely to be heterogeneous
Keratoderma with scleroatrophy	Huriez	AD	4q23		Y	Squamous carcinomas
Mal de Meleda		AR	*SLURP-1*	0–3	Y	Dermatophyte infection common
Autosomal recessive transgredient keratoderma*	Gamborg–Neilsen	AR	—	8–10	Y	Likely to be heterogeneous
Palmoplantar and periorificial keratoderma	Olmsted	?AR	—	0–1	Y	Periorificial and flexural erythema and hyperkeratosis
Focal or areate group						
Focal/areate/nummular keratoderma	Wachters	AD	—			Includes painful hereditary callosities Likely to be heterogeneous
Focal keratoderma with oral leukokeratosis		AD	Keratin 16	3–5	N	Oral leukokeratosis
Pachyonychia congenita type 1	Jadassohn–Lewadowsky	AD	Keratins 6a, 16	3–5	N	Oral lesions, follicular keratoses
Pachyonychia congenita type 2	Jackson–Lawler	AD	Keratins 6b, 17	3–5	N	Natal teeth, multiple cyst, follicular keratoses
Striate keratoderma	Brunauer–Fuhs–Siemens	AD	Desmoplakin Desmoglein Keratin 1		N	
Hidrotic ectodermal dysplasia	Clouston	AD	Connexin 30		Y	Nail and hair dystrophy
Keratodermas with extracutaneous features						
Keratoderma with oesophageal carcinoma	Howel–Evans	AD	17q23		N	Focal PPK with oral lesions
Striate keratoderma, woolly hair and arrhythmogenic cardiomyopathy	Naxos disease	AR	Plakoglobin		N	
Striate keratoderma, woolly hair and dilated cardiomyopathy	Carvajal	AR	Desmoplakin		N	
Cicatrizing keratoderma with hearing loss	Vohwinkel	AD	Connexin 26	5–10	Y	Papular lesions becoming confluent, starfish keratoses. Mild hearing impairment
Keratoderma with prelingual deafness		AD	Connexin 26	0–5	Y	Mild diffuse PPK but profound deafness
Mitochondrial hearing loss with keratoderma		Matrilineal	*A7445G*		N	Variable mild focal PPK
Keratoderma with neuropathy*		Varies	(SNAP29)		N	Peripheral neuropathy; spastic paralysis
Keratoderma with periodontitis	Papillon–Léfèvre	AR	Cathepsin G		N	Severe periodontal and other pyogenic infections

(Continued)

Table 19.5 *Continued*

Type	Eponym(s)	Inheritance (presumed)	Gene or locus	Onset (years)	Transgredient/ cicatrizing	Comments/special features
Keratoderma with eyelid cysts	Schöpf–Schulz–Passarge	AR	—		N	Diffuse keratoderma, hypotrichosis, nail fragility, loss of deciduous teeth, adnexal tumours
Oculocutaneous tyrosinaemia	Richner–Hanhart	AR	Tyrosine aminotransferase		N	Corneal ulcers, painful keratoses, progressive mental impairment
Punctate group						
Punctate keratoderma*	Brauer–Buschke–Fischer	AD	8q24; 15q22	10–40	N	Possible association with malignancy in some families
Punctate keratoderma of palmar creases		AD	—	10–40	N	Palmar creases, sometimes marginal lesions
Marginal papular keratoderma	Costa/Dowd	AD	—	Childhood	N	Marginal crateriform papules with or without elastorrhexis
Papuloverrucous keratoderma	Touraine; Jakac–Wolf	AR	—	2–6	N	Follicular keratoses; dysplastic teeth

* These are pragmatic clinical groupings likely to encompass a variety of genetically distinct syndromes.
AD, autosomal dominant; AR, autosomal recessive.

molecular pathogenesis. Inherited keratodermas described in this chapter are outlined in Table 19.5, but many isolated reports of unusual or unique associations are necessarily excluded.

Keratodermas are often grouped by clinical pattern as diffuse, focal (areate), striate or punctate, but there are no absolute boundaries between these groupings. The presentation of a single disease may vary with site, age, gender or occupation. Plantar skin tends to be more severely or diffusely affected than palmar skin. In assessing an isolated case of keratoderma, it may be unwise to limit the differential diagnosis on the basis of distribution. However, the following definitions may offer some guidance. In *diffuse keratodermas*, the whole of the palmar or plantar epidermis, usually including the centripalmar skin and the instep, is abnormally but uniformly thickened. In *focal (or areate or nummular) keratoderma*, the areas of palmoplantar skin under most pressure are disproportionately thickened, for example at either end of the metatarsal arch, sides or tips of the toes, or margins of the heel. Focal lesions may be painful. *Striate keratoderma* overlaps clinically with focal keratoderma, but the lesions are conspicuously longitudinal, particularly on the fingers, where keratoderma overlies flexor tendons. *Punctate (papular or disseminated) keratoderma* consists of multiple scattered discrete round lesions, not bearing a consistent relationship to pressure points.

Transgredient keratoderma extends beyond palmoplantar skin, contiguously or as callosities on pressure points on the fingers or knuckles, or elsewhere. Confluent hyperkeratosis may extend round whole digits. *Cicatrizing keratodermas* (the term 'cicatrizing' is suggested in preference to the more emotive 'mutilating') are those in which constricting bands appear around digits, usually distal to proximal interphalangeal joints. Such constrictions ('pseudo-ainhum') are found in many severe transgredient keratodermas, and are not diagnostic of any one syndrome. *Hyperhidrosis* is also a commonly used descriptor, as many keratodermas, particularly on the feet, are spongy and malodorous. There may be a real increase in sweat excretion, but water retention by abnormally keratotic and porous stratum corneum also contributes to maceration and microbial overgrowth.

References

1 Greither A. Erbliche Palmoplantarkeratosen. *Hautarzt* 1977; **28**: 395–403.
2 Salamon T. An attempt at classification of inherited disorders of keratinization localized mainly, not exclusively on the palms and soles. *Dermatol Monatsschr* 1986; **172**: 601–5.
3 Zemstov A, Veitschegger M. Keratodermas. *Int J Dermatol* 1993; **32**: 493–8.
4 Lucker GPH, Van de Kerkhof PCM, Steiljen PM. The hereditary palmoplantar keratoses: an updated review and classification. *Br J Dermatol* 1994; **131**: 1–14.
5 Itin PH, Lautenschlager S. Palmoplantar keratoderma and associated syndromes. *Semin Dermatol* 1995; **14**: 152–61.
6 Stevens HHP, Kelsell DP, Bryant SP *et al.* Linkage of an American pedigree with palmoplantar keratoderma and malignancy (palmoplantar ectodermal dysplasia type III) to 17q24. *Arch Dermatol* 1996; **132**: 640–51.
7 Ratnavel RC, Griffiths WAD. The inherited palmoplantar keratodermas. *Br J Dermatol* 1997; **137**: 485–90.

Diffuse keratodermas

Epidermolytic palmoplantar keratoderma (EPPK) (MIM 144200)

Synonym
- Vörner's keratoderma

Vörner described diffuse palmoplantar keratoderma with autosomal dominant inheritance, clinically indistinguishable from that

described by Thost and Unna but with histological features of EHK in affected palms and soles [1]. Thost's original family in fact had epidermolytic histology; indeed Vörner's is probably the most common form of diffuse keratoderma [2,3]. A prevalence of 4.4 per 100 000 was found in Northern Ireland [4].

Aetiology. Epidermolysis with tonofilament clumping suggested an intermediate filament defect, and the type I epithelial keratin 9 (K9), preferentially expressed in palmoplantar skin, was a strong candidate [5,6]. Linkage to the type I keratin gene cluster on chromosome 17 and many causative mutations in highly conserved regions of K9 have been demonstrated, including in Vörner's original pedigree [7–11]. Most mutations are in the helix initiation peptide, but a 3-bp insertion in the helix termination motif has also been identified [12]. Cases with transgredient lesions may be localized forms of epidermolytic hyperkeratosis due to mutation in keratin 1 (see Greither's syndrome, below). However, keratin 1 is a candidate even in localized EPPK [13]. EPPK resembling Vörner PPK but with unusual 'tonotubular' filaments on electron microscopy [14] is due to mutation in the 1B rod domain of keratin 1 [15]. In a pedigree with subconfluent diffuse keratoderma and only mild epidermolysis, a splice-site mutation causing insertion of 18 amino acids into the 2b domain of keratin 1 was identified [16]. Disruption of intermediate filament integrity consequent on these mutations is predicted to reduce the resilience of the cytoskeleton to minor external trauma, leading to blistering and hyperkeratosis. Possible autosomal recessive inheritance was reported in two children born to consanguineous parents [17].

Pathology. Histologically, Vörner's PPK shows epidermolytic change in suprabasal keratinocytes. Round or ovoid eosinophilic inclusions may be detected [18], with large tonofilament aggregates visible on electron microscopy. The morphological appearance of keratin filament bundles in palmoplantar epidermis is different from other epidermis, with thicker bundles in a distinct orientation, so care must be undertaken in the assessment of filament aggregation [8]. There are secondary changes in the expression of markers of cornified envelope formation [19].

Clinical features [1,20]. Diffuse keratoderma develops in infancy. In adults, there is confluent keratoderma, sparing dorsal surfaces, with a sharp demarcation and erythematous edge (Fig. 19.58). Blistering is not a major feature, but a history of blisters or fissuring of the palms may hint at reduced structural strength. Hair, teeth and nails are normal, but knuckle pads and nail changes were found in Vörner's original families [1], many of whom have K9 mutations. Families with associated cancer [21–22] are exceptional and probably coincidental.

Treatment. Response to oral retinoids is good, but excessive peeling may be a problem [23]. Topical calcipotriol has reportedly been helpful [24].



Fig. 19.58 Diffuse epidermolytic keratoderma (Vörner) caused by keratin 9 mutation.

References

1 Vörner H. Zur Kenntnis des keratome hereditarium palmare et plantare. *Arch Derm Syph (Berlin)* 1901; **56**: 3–31.

2 Hamm H, Happle R, Butterfass T *et al.* Epidermolytic palmoplantar keratoderma of Vörner: is it the most frequent type of hereditary palmoplantar keratoderma? *Dermatologica* 1988; **177**: 138–45.

3 Kuster W, Becker A. Indication for the identity of palmoplantar keratoderma type Unna–Thost with type Vörner. *Acta Derm Venereol (Stockh)* 1992; **72**: 120–2.

4 Covello SP, Irvine AD, McKenna KE *et al.* Mutations in keratin K9 in kindreds with epidermolytic palmoplantar keratoderma and epidemiology in Northern Ireland. *J Invest Dermatol* 1998; **111**: 1207–9.

5 Knapp AC, Franke WW, Heid H *et al.* Cytokeratin 9, an epidermal type 1 keratin, characteristic of a special programme of keratinocyte differentiation displaying body site specificity. *J Cell Biol* 1986; **103**: 657–67.

6 Langbein L, Heid H, Moll I, Franke WW. Molecular characterisation of the body site specific human epidermal cytokeratin 9, cDNA cloning, amino acid sequence, and tissue specificity of gene expression. *Differentiation* 1994; **55**: 57–72.

7 Reis A, Kuster W, Eckhardt R, Sperling K. Mapping of a gene for epidermolytic palmoplantar keratoderma to the region of the acidic keratin gene cluster at 17q12–q21. *Hum Genet* 1992; **90**: 113–6.

8 Torchard D, Blanchet-Bardon C, Serrova D *et al.* Epidermolytic palmoplantar keratoderma cosegregates with a keratin 9 mutation in a pedigree with breast and ovarian cancer. *Nat Genet* 1994; **8**: 106–10.

9 Reis A, Hennies H-C, Langbein L *et al.* Keratin 9 gene mutations in epidermolytic palmoplantar keratoderma (EPPK). *Nat Genet* 1994; **8**: 174–9.

10 Irvine AD, McLean WH. Human keratin diseases: the increasing spectrum of disease and subtlety of the phenotype–genotype correlation. *Br J Dermatol* 1999; **140**: 815–28.

11 Kuster W, Reis A, Hennies HC. Epidermolytic palmoplantar keratoderma of Vorner: re-evaluation of Vorner's original family and identification of a novel keratin 9 mutation. *Arch Derm Res* 2002; **294**: 268–72.

12 Coleman CM, Munro CS, Smith FJ *et al.* Epidermolytic palmoplantar keratoderma due to a novel type of keratin mutation, a 3-bp insertion in the keratin 9 helix termination motif. *Br J Dermatol* 1999; **140**: 486–90.

13 Tal O, Bergman R, Alcalay J *et al.* Epidermolytic hyperkeratosis type PS-1 caused by aberrant splicing of KRT1. *Clin Exp Dermatol* 2005; **30**: 64–7.

14 Wevers A, Kuhn A, Mahrle G. Palmoplantar keratoderma with tonotubular keratin. *J Am Acad Dermatol* 1991; **24**: 638–42.

15 Terron-Kwiatkowski A, van Steensel MA, Van Geel M *et al.* Mutation S233L in the 1B domain of keratin 1 causes epidermolytic palmoplantar keratoderma with "tonotubular" keratin. *J Invest Dermatol* 2006; **126**: 607–13.

16 Hatsell SJ, Eady RA, Wennerstrand L *et al.* Novel splice site mutation in keratin 1 underlies mild epidermolytic palmoplantar keratoderma in three kindreds. *J Invest Dermatol* 2001; **116**: 606–9.

17 Alsaleh QA, Teebi AS. Autosomal recessive epidermolytic palmoplantar keratoderma. *J Med Genet* 1990; **27**: 519–22.

18 Bergman R, Khamaysi Z, Sprecher E. A unique pattern of dyskeratosis characterizes epidermolytic hyperkeratosis and epidermolytic palmoplantar keratoderma. *Am J Dermatopathol* 2008; **30**: 101–5.

19 Hashimoto K, Mizuguchi R, Tanaka K, Dorman M. Palmoplantar keratoderma (Vörner) with composite keratohyalin granules: studies on keratinization parameters and ultrastructures. *J Dermatol* 2000; **27**: 1–9.

20 Kuster W, Zehender D, Mensing H *et al.* Vörner keratosis palmoplantaris difusa: clinical, formal genetic and molecular biology studies of 22 families. *Hautarzt* 1995; **46**: 705–10.
21 Chevrant-Breton J, Kerbrat P, Le Marec B *et al.* Keratodermie palmoplantaire epidermolytique, autosomique dominante et adenocarcinomes familiaux. *Ann Dermatol Vénéréol* 1985; **112**: 841–4.
22 Blanchet-Bardon C, Nazzaro V, Chevrant-Breton J *et al.* Hereditary epidermolytic palmoplantar keratoderma associated with breast and ovarian cancer in a large kindred. *Br J Dermatol* 1987; **117**: 363–70.
23 Larregue M, Bardy-Decrion I, Bonvalet D *et al.* Keratodermie palmoplantaire de type epidermolytique. *Ann Dermatol Vénéréol* 1987; **114**: 1420–3.
24 Lucker GPH, van de Kerkhof PCM, Steiljen PM. Topical calcipotriol in the treatment of epidermolytic palmoplantar keratoderma of Vörner. *Br J Dermatol* 1994; **130**: 543–6.

Non-epidermolytic palmoplantar keratoderma

Synonym
- Thost–Unna keratoderma

Thost and Unna separately described keratoderma characterized by even, thick, yellow hyperkeratosis over the whole palm and sole [1,2]. The eponym refers specifically to non-epidermolytic keratoderma, although the original Thost family is now known to have epidermolytic keratoderma [3]. It is inherited as an autosomal dominant disorder but may be genetically heterogeneous.

Aetiology. Studies of a family from Bothnia in northern Sweden and three English pedigrees showed linkage centromeric to the type 2 keratin gene cluster on chromosome 12 [4–6], but the cluster itself was excluded. In another family with diffuse PPK, a mutation occurred in a highly conserved lysine residue in the V1 domain of keratin 1 [7]. This residue is thought to be important in cross-linking in the cornified envelope formation [8].

Pathology. The histological changes are non-specific: orthokeratotic hyperkeratosis, hypergranulosis or normogranulosis and moderate acanthosis [2]. There is usually a mild perivascular infiltrate. A biopsy serves mainly to exclude epidermolytic keratoderma. Although vesiculation secondary to dermatophyte infection may be a confounding factor, the large Bothnian pedigree of diffuse PPK showed no evidence of true epidermolysis in 91 biopsies [9].

Clinical features [10,11]. The condition may present in the first few months of life and is usually obvious by the age of 4 years. It rarely appears in the third decade. An even, very thick, yellow hyperkeratosis occurs over the whole of the foot, starting on the heel and anterior arch, spreading later to the palms (Fig. 19.59). There is a sharp cut-off at the wrist, and no tendency to spread to the extensor surfaces. The margins show a livid red border, which can be seen also to underlie the hyperkeratosis. Hyperhidrosis is usual, and dermatophyte infections and pitted keratolysis are frequent. The nails are usually normal, but may be thickened without evidence of dystrophy. Hair and teeth are normal.

Treatment. Keratolytic therapy, such as 6% salicylic acid in white soft paraffin, or a gel of 6% salicylic acid in 70% propylene glycol may be used. Occlusion with polythene for a few nights enhanced the efficacy of these preparations. Benzoic acid compound ointment is mildly keratolytic, and is useful in reducing fungal and bacterial overgrowth. Topical retinoids have little effect. Acitretin may be effective for patients with marked functional impairment, but response is unpredictable and in some patients the loss of the thick keratin leaves the foot markedly hypersensitive. Response to erythromycin has been described in the Bothnian type [12].



Fig. 19.59 'Thost–Unna' keratoderma: even yellow hyperkeratosis of sole with red border.

References

1 Thost A. *Über Erbliche Ichthyosis Palmaris et Plantaris Cornea*. Heidelberg: Inaug diss, 1880.
2 Unna PG. Über das Keratoma palmare et plantare hereditarum: eine Studie zur Kerato-Nosologie. *Arch Derm Syph (Berlin)* 1883; **15**: 231–70.
3 Kuster W, Becker A. Indication for the identity of palmoplantar keratoderma Unna Thost with type Vörner. *Acta Derm Venereol (Stockh)* 1992; **72**: 120–2.
4 Lind L, Lundstrom A, Hofer PA, Holmgren G. The gene for diffuse palmoplantar keratoderma of the type found in northern Sweden is localized to chromosome 12q11–q13. *Hum Mol Genet* 1994; **3**: 1789–93.
5 Kelsell DP, Stevens HP, Ratnavel R *et al.* Genetic linkage studies in non-epidermolytic palmoplantar keratoderma: evidence for heterogeneity. *Hum Mol Genet* 1995; **4**: 1021–5.
6 Kelsell DP, Stevens HP, Purkis PE *et al.* Fine genetic mapping of diffuse non-epidermolytic palmoplantar keratoderma to chromosome 12q11–q13: exclusion of the mapped type II keratins. *Exp Dermatol* 1999; **8**: 388–91.
7 Kimonis V, DiGiovanna JJ, Yang J-M *et al.* A mutation in the V1 and domain of keratin 1 causes non-epidermolytic palmar plantar keratoderma. *J Invest Dermatol* 1994; **103**: 764–9.
8 Candi E, Tarcsa E, DiGiovanna JJ *et al.* A highly conserved lysine residue on the head domain of type II keratins is essential for the attachment of keratin intermediate filaments to the cornified cell envelope through isopeptide crosslinking by transglutaminases. *Proc Natl Acad Sci USA* 1998; **95**: 2067–72.
9 Gamborg Nielsen P, Hofer PA, Lagerholm B. The dominant form of hereditary palmoplantar keratoderma in the northernmost county of Sweden (Norrbotten). *Dermatology* 1994; **188**: 188–93.
10 Kansky A, Durinovic-Belló I, de Jongh BM *et al.* HLA antigens in Yugoslav patients with palmoplantar keratoderma, type Unna–Thost: a family study. *Acta Derm Venereol (Stockh)* 1982; **62**: 313–6.
11 Gamborg-Nielsen P. Two different clinical and genetic forms of hereditary palmoplantar keratoderma in the northernmost county of Sweden. *Clin Genet* 1985; **28**: 361–6.
12 Wennerstrand LM, Lind LK, Hofer PA, Lundstrom A. Homozygous palmoplantar keratoderma type bothnia improved by erythromycin: a case report. *Acta Derm Venereol* 2004; **84**: 405–6.



Fig. 19.60 Loricrin keratoderma.

Transgredient keratodermas

Loricrin keratoderma (MIM 604117)

Synonyms
- Variant Vohwinkel's syndrome
- Mutilating keratoderma with ichthyosis
- Camisa's syndrome

In two related pedigrees, Camisa and Rossana delineated a diffuse transgredient honeycomb keratoderma with annular constrictions around digits, accompanied by a mild ichthyosis (Fig. 19.60) [1–3]. In true Vohwinkel's syndrome, there is impaired hearing but no generalized ichthyosis [4].

Aetiology. The disorder is caused by mutations in the gene encoding loricrin, a glycine-rich cornified envelope protein [3–7]. Several different single nucleotide insertions have been identified in this gene, but all shift the reading frame and lead to expression of an abnormal protein with a foreign, arginine-rich C-terminal peptide containing nuclear recognition signals [4]. The mutant protein is transported to the nucleus, where it can be identified from the upper spinous layer upwards, and is thought to interfere with regulation of cornification [8]. Direct or indirect consequences of causative mutations include an alteration on the cornified envelope scaffold, and defective barrier function [9]. Transgenic mice in whom loricrin has been knocked out are largely asymptomatic [10], but mice expressing a pathogenic loricrin mutation showed generalized scaling, thickened footpads and a constricting band causing autoamputation of the tail [11,12]. In one Japanese father and son, an insertion mutation in loricrin analogous to these producing keratoderma in other human pedigrees gave a phenotype resembling progressive symmetrical erythrokeratoderma [13].

Pathology. In addition to hyperkeratosis, nuclei may be retained in the stratum corneum [1]. Immunoelectron microscopy shows the presence of loricrin in these nuclei [3,4]. Camisa noted elevated serum levels of the lysosomal enzyme β-glucuronidase [2].

Clinical features [1–6]. The combination of honeycomb keratoderma with mild ichthyosis is typical [7]. Generalized desquamation may be noted at birth, and collodion babies are reported [6,7]. However, the ichthyosis is generally mild and may pass unnoticed. A rugose keratoderma develops during childhood, gradually extending to the confluent 'honeycomb' pattern. The edges of the keratoderma are diffuse (in contrast to true Vohwinkel's syndrome) and cicatricial bands (pseudo-ainhum) may develop around digits. Knuckle pads and warty keratoses have been reported, but are not a prominent feature. There are no consistent extracutaneous features.

Treatment. The successful use of isotretinoin has been reported [1] and acitretin also promotes desquamation.

References

1 Camisa C, Rossana C. Variant of keratoderma hereditaria mutilans (Vohwinkel's syndrome): treatment with orally administered isotretinoin. *Arch Dermatol* 1984; **120**: 1323–8.

2 Camisa C, Hessel A, Rossana C, Parks A. Autosomal dominant keratoderma, ichthyosiform dermatosis and elevated serum β-glucuronidase. *Dermatologica* 1988; **177**: 341–7.

3 Maestrini E, Monaco AP, McGrath JA *et al.* A molecular defect in loricrin, the major component of the cornified cell envelope underlies Vohwinkel's syndrome. *Nat Genet* 1996; **13**: 70–7.

4 Korge BP, Ishida-Yamamoto A, Punter C *et al.* Loricrin mutation in Vohwinkel's keratoderma is unique to the variant with ichthyosis. *J Invest Dermatol* 1997; **109**: 604–10.

5 Armstrong DK, McKenna KE, Hughes AE. A novel insertional mutation in loricrin in Vohwinkel's keratoderma. *J Invest Dermatol* 1998; **111**: 702–4.

6 Matsumoto K, Muto M, Seki S *et al.* Loricrin keratoderma: a cause of congenital ichthyosiform erythroderma and collodion baby. *Br J Dermatol* 2001; **145**: 657–60.

7 Gedicke MM, Traupe H, Fischer B *et al.* Towards characterization of palmoplantar keratoderma caused by gain-of-function mutation in loricrin: analysis of a family and review of the literature. *Br J Dermatol* 2006; **154**: 167–71.

8 Ishida-Yamamoto A, Kato H, Kiyama H *et al.* Mutant loricrin is not crosslinked into the cornified cell envelope but is translocated into the nucleus in loricrin keratoderma. *J Invest Dermatol* 2000; **115**: 1088–94.

9 Schmuth M, Fluhr JW, Crumrine DC *et al.* Structural and functional consequences of loricrin mutations in human loricrin keratoderma (Vohwinkel syndrome with ichthyosis). *J Invest Dermatol* 2004; **122**: 909–22.

10 Jarnik M, De Viragh PA, Schärer E *et al.* Quasi-normal cornified cell envelopes in loricrin knockout mice imply the existence of a loricrin backup system. *J Invest Dermatol* 2002; **118**: 102–9.

11 Koch PJ, De Viragh PA, Schärer E *et al.* Lessons from loricrin-deficient mice: compensatory mechanisms maintaining skin barrier function in the absence of a major cornified envelope protein. *J Cell Biol* 2000; **151**: 389–400.

12 Suga Y, Jarnik M, Attar PS *et al.* Transgenic mice expressing a mutant form of loricrin reveal the molecular basis of the skin diseases, Vohwinkel syndrome and progressive symmetric erythrokeratoderma. *J Cell Biol* 2000; **151**: 401–12.

13 Ishida-Yamamoto A, McGrath JA, Lam H *et al.* The molecular pathology of progressive symmetric erythrokeratoderma: a frameshift mutation in the loricrin gene and perturbations in the cornified cell envelope. *Am J Hum Genet* 1997; **61**: 581–9.

Autosomal dominant transgredient keratoderma

Transgredient autosomal dominant keratodermas are distinguished by involvement of the extensor surfaces of hands, knees and elbows, including overlying the Achilles tendon.

Greither's syndrome (palmoplantar keratoderma transgrediens et progrediens). Greither described a syndrome with gradual onset

and a tendency to improve in the fifth decade [1], but cases reported under this eponym are likely to be genetically heterogeneous [2]. There is clinical overlap with erythrokeratoderma [3]. One pedigree mapped to chromosome 1p [4], but this was not confirmed in another family [5]. The changes on light microscopy are non-specific [6] but Beylot-Barry *et al.* [7] found tonofilament aggregates, numerous desmosomes and abnormal cell–cell junctions on electron microscopy. Two unrelated British pedigrees had an identical keratin 1 mutation, N188S [8], and represent a localized form of epidermolytic hyperkeratosis.

Clinical features. Onset of Greither's syndrome is at 8–10 years old, and it may improve with age. There is diffuse but transgredient hyperkeratosis with patchy lesions of knees and elbows. Erythema at the margins and hyperhidrosis may be present. Some patients experience Raynaud-like vasomotor disturbances.

Sybert's keratoderma. A more severe transgredient keratoderma reported by Sybert *et al.* [9] resembled mal de Meleda but had dominant inheritance. Onset was earlier than in Greither's syndrome. Glove and stocking hyperkeratosis, including autoamputation of toes, extended also to the elbows, knees, posterior aspects of the forearms, shins, groins and natal cleft. Histologically, excessive accumulation of lipid-laden cells was seen in stratum corneum. Electron microscopy showed keratohyalin granules that were abnormal in distribution and structure. Abnormal filaggrin staining suggested that the association of filaggrin and keratin filaments in the stratum corneum was disturbed. Isotretinoin was used with benefit.

Other transgredient keratodermas. Magro *et al.* [10] reported several cases with a milder phenotype clinically resembling that of Sybert, but characterized ultrastructurally by perinuclear accumulations of ribosomes and abnormal keratohyaline granules. In one case, a father and child were affected. The histological features were felt to resemble ichthyosis hystrix (IH) of the Curth–Macklin type. Sprecher *et al.* [11] described an African American family with a more severe, dominant disorder of keratinization diagnosed as Curth–Macklin IH. The main feature was a gross palmoplantar hyperkeratosis, with cobbled papular hyperkeratoses mainly over extensor surfaces. Ultrastructural studies showed retraction of the cytoskeleton to the nucleus and failure of loricrin transport to the cell membrane. They identified a causative frameshift mutation in the V2 domain of Keratin 1 [11]. Linkage to keratin gene clusters was excluded in another family with IH Curth–Macklin [12].

References

1 Greither A. Keratosis extremitatum hereditaria progrediens mit dominatem Erbgang. *Hautarzt* 1952; **3**: 198–203.
2 Kansky A, Arzensek J. Is palmoplantar keratoderma of Greither's type a separate nosologic entity? *Dermatologica* 1979; **158**: 244–8.
3 Wollina U, Knopf B, Schaaschmidt H *et al.* Familiare Koexistenz von Erythrokeratodermia variabilis und Keratosis palmoplantaris transgrediens et progrediens. *Hautarzt* 1989; **40**: 169–72.
4 Gedde-Dahl TJ, Rodge S, Helsing P *et al.* Olaisen Greither's disease and erythrokeratoderma variabilis (EKV) caused by the same mutation on chromosome 1. *Hum Genome Mapp* 1993; **1**: 93.
5 Richard G, Lin JP, Smith L *et al.* Linkage studies in erythrokeratodermias: fine mapping, genetic heterogeneity and analysis of candidate genes. *J Invest Dermatol* 1997; **109**: 666–71.
6 Fluckiger R, Itin PH. Keratosis extremitatum (Greither's disease): clinical features, histology, ultrastructure. *Dermatology* 1993; **187**: 309–11.
7 Beylot-Barry M, Taieb A, Surleve-Bazeille JE *et al.* Inflammatory familial palmoplantar keratoderma: Greither's disease? *Dermatology* 1992; **185**: 210–4.
8 Gach JE, Munro CS, Lane EB *et al.* Two families with Greither's syndrome caused by a keratin 1 mutation. *J Am Acad Dermatol* 2005; **53**: S225–S230.
9 Sybert VP, Dale BA, Holbrook KA. Palmar–plantar keratoderma: a clinical, ultrastructural, and biochemical study. *J Am Acad Dermatol* 1988; **18**: 75–86.
10 Magro CM, Baden LA, Crowson AN *et al.* A novel non-epidermolytic palmoplantar keratoderma: a clinical and histopathologic study of six cases. *J Am Acad Dermatol* 1997; **37**: 27–33.
11 Sprecher E, Ishida-Yamamoto A, Becker OM *et al.* Evidence for novel functions of the keratin tail emerging from a mutation causing ichthyosis hystrix. *J Invest Dermatol* 2001; **116**: 511–9.
12 Bonifas JM, Bare JW, Chen MA *et al.* Evidence against keratin gene mutations in a family with ichthyosis hystrix Curth Macklin. *J Invest Dermatol* 1993; **101**: 890–1.

Keratoderma with scleroatrophy (MIM 181600)

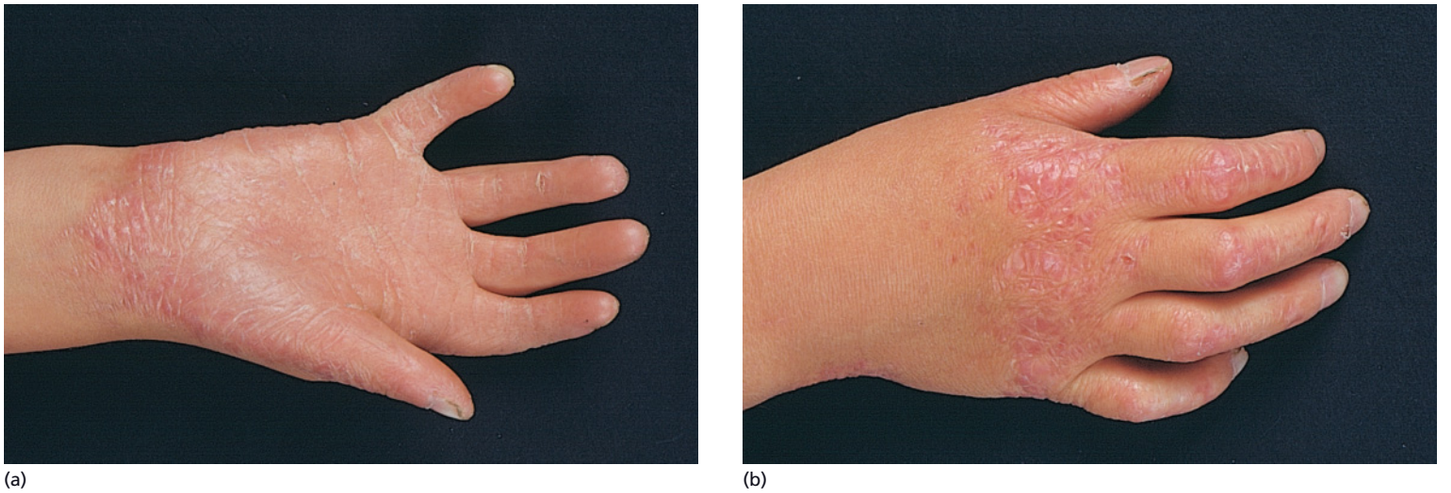
Synonym
- Huriez syndrome

This rare autosomal dominant transgredient keratoderma, first reported in three Franco-Belgian families, is characterized by scleroatrophy of the fingers and a high frequency of squamous carcinomas in affected skin [1–4]. The causative gene maps to chromosome 4q23, but has not been identified [5]. Excision repair of UV damage to lymphocytes was normal [6].

Pathology [6]. Acanthosis with an accentuated granular layer and orthohyperkeratosis were seen in thickened skin. On electron microscopy, dense bundles of tonofilaments were seen in all epidermal layers. The granular layer showed large, coarse, clumped keratohyalin. In the scleroatrophic area, similar changes were seen, with the addition of thinning of the elastic fibres, which on electron microscopy had irregular borders and looked non-homogeneous. There is a reduction in Langerhans' cells in affected palmar epidermis [3,7].

Clinical features [1–4,6,7]. Palms are more often affected than the soles, the keratoderma lacks an underlying erythema, and dermatoglyphics are often absent (Fig. 19.61a). Atrophic parchment-like skin over the dorsal surface of the hands, associated with diffuse keratoderma, is present from birth (Fig. 19.61b). Dense hyperkeratosis gives a pseudosclerodermatous appearance with nail atrophy. Nail changes include hypercurvature, longitudinal ridging, onychorrhexis and koilonychia. Squamous cell carcinomas of the affected skin developed in six cases, and internal malignancy was the cause of death in six out of 33 deaths in the original report. One of the original families was re-examined and reported in 1995 [6]. Only two of the 23 deaths in the family resulted from internal malignancy.

Other scleroatrophic keratodermas. Pujol *et al.* [8] and Vahlquist *et al.* [9] reported cases of sclerosing keratoderma associated with ichthyosis, and bizarre striate keratoses of the flexures. Inheritance



(a) (b)

Fig. 19.61 Huriez syndrome: (a) keratoderma; and (b) atrophy skin over dorsa of hand and sclerodactyly. (Courtesy of Dr M. van Steensel, Department of Dermatology, University of Maastricht, the Netherlands.)

appears to be autosomal recessive. A scleroatrophic keratoderma has been reported in association with sex reversal in a 46,XX subject with a male phenotype [10].

References

1 Huriez C, Deminatti M, Agache P *et al*. Une genodysplasie non encore individualisée: la genodermatose sclerotrophiante et kerato-dermique des extremités frequemment degenerative. *Sem Hôp Paris* 1968; **44**: 481–8.
2 Huriez C, Deminatti M, Agache P. Genodermatose sclero-atrophiante et kerato-dermique des extremités. *Ann Dermatol Syphiligr* 1969; **96**: 135–46.
3 Hamm H, Traupe H, Brocker EB *et al*. The scleroatrophic syndrome of Huriez: a cancer-prone genodermatosis. *Br J Dermatol* 1996; **134**: 512–8.
4 Lucker GH, Zeedijk N, Steijlen PM. The Huriez syndrome: scleroatrophic palmoplantar keratoderma. *Eur J Dermatol* 1997; **7**: 155–7.
5 Lee YA, Stevens HP, Delaporte E *et al*. A gene for an autosomal dominant scleroatrophic syndrome predisposing to skin cancer (Huriez syndrome) maps to chromosome 4q23. *Am J Hum Genet* 2000; **66**: 326–30.
6 Delaporte E, N'Guyen-Mailfer C, Janin A *et al*. Keratoderma with scleroatrophy of the extremities or sclerotylosis (Huriez syndrome): a reappraisal. *Br J Dermatol* 1995; **133**: 409–16.
7 Guerriero C, Albanesi C, Girolomoni G *et al*. Huriez syndrome: case report with a detailed analysis of skin dendritic cells. *Br J Dermatol* 2000; **143**: 1091–6.
8 Pujol RM, Moreno A, Alomar A, de Moragas JM. Congenital ichthyosiform dermatosis with linear keratotic flexural papules and sclerosing palmoplantar keratoderma. *Arch Dermatol* 1989; **125**: 103–6.
9 Vahlquist A, Ponten F, Pettersson A. Keratosis linearis with ichthyosis congenita and sclerosing keratoderma (KLICK syndrome): a rare, autosomal recessive disorder of keratohyaline formation? *Acta Derm Venereol (Stockh)* 1997; **77**: 225–7.
10 Vernole P, Terrinoni A, Didona B *et al*. An SRY-negative XX male with Huriez syndrome. *Clin Genet* 2000; **57**: 61–6.

Mal de Meleda (MIM 248300)

Synonyms
- Keratoderma palmoplantaris transgrediens
- Acroerythrokeratoderma

Mal de Meleda is a rare autosomal recessive transgredient keratoderma named after the Croatian island of Meleda (Mljet) where it was first identified [1,2], but it has been reported widely in the Mediterranean littoral. Maritime dissemination is inferred.

Aetiology. Mal de Meleda is caused by homozygous mutation in the *ARS* (component B) gene, encoding SLURP-1 (secreted Ly-6/uPAR related protein 1) [3–6]. Almost all cases occur in consanguineous pedigrees and families from Croatia (including Meleda), Algeria and Tunisia share very few ancestral haplotypes [3,6,7], indicating founder mutations. SLURP-1 is a member of a superfamily of secreted and receptor proteins implicated in transmembrane signal transduction, cell activation and cell adhesion, which has homologues to reptilian and amphibian toxins. The gene is expressed late in epidermal differentiation, in the granular layer, and particularly in association with the acrosyringium [8]. SLURP-1 modulates the effects of acetylcholine on the keratinocyte α7 nicotinic ACh receptor [9], and regulates keratinocyte differentiation and apoptosis [10].

Pathology. There is a greatly thickened corneal layer, increased stratum lucidum, with marked acanthosis, pseudospongiosis, and a prominent perivascular lymphohistiocytic infiltrate. Sweat glands are enlarged. Electron microscopy showed a less abrupt than normal transition from stratum granulosum to stratum corneum [11].

Clinical features [2,12–14]. Onset is in early childhood, and the development of hyperkeratosis is preceded by erythema. Patches of waxy ivory–yellow hyperkeratosis (Fig. 19.62) extend across the whole palms and soles, and on to the dorsal surfaces of hands and feet. Similar lesions of knees and elbows may develop. The erythematous component often persists in central palms and soles, with hyperhidrotic maceration and malodour. Fungal superinfection is common and should be excluded [13]. Circumferential hyperkeratosis of fingers may lead to sclerodactyly and digital constrictions; nail changes include hypercurvature, thickening and koilonychia [13–14]. Angular cheilitis is common. Melanoma arising within affected skin has been reported (reviewed in [15]). There is clinical overlap with Olmsted's syndrome, keratosis lichenoides chronica striata and progressive symmetrical erythro-



Fig. 19.62 Mal de Meleda.

keratoderma [3,12]. Heterozygous female carriers may have a mild clinical phenotype [16].

Treatment. Oral retinoids are effective but the hyperkeratosis may respond better than the erythema [17–21].

Other autosomal recessive transgredient keratodermas. Other pedigrees of autosomal recessive transgredient PPKs, such as the mutilating keratoderma with knuckle pads identified by Gamborg-Nielsen [22,23], and the transgredient PPK in Japan first reported by Nakajima [24]. Some such cases may prove to be related to mal de Meleda, but multiple disease entities are likely and linkage to the *SLURP-1* locus, or mutations of the ARS coding sequence, have not been found in pedigrees with this phenotype [24–27]. In Japanese siblings with a severe recessive transgredient keratoderma Akiyama *et al.* [28] excluded linkage to the epidermal differentiation complex.

References

1 Stulli L. De una varieta cuanea. *Antologia di Firenzi* 1826: fasc. 71–2.
2 Salamon T, Berberovic L, Topic B *et al.* Mal de Meleda: data and remarks on a series. *G Ital Dermatol Venereol* 1988; **123**: 649–55.
3 Fischer J, Bouadjar B, Heilig R *et al.* Mutations in the gene encoding SLURP-1 in mal de Meleda. *Hum Mol Genet* 2001; **10**: 875–80.
4 Eckl KM, Stevens HP, Lestringant GG *et al.* Mal de Meleda (MDM) caused by mutations in the gene for SLURP-1 in patients from Germany, Turkey, Palestine, and the United Arab Emirates. *Hum Genet* 2003; **112**: 50–6.
5 Ward KM, Yerebakan Ö, Yilmaz E, Çelebi JT. Identification of recurrent mutations in the ARS (component B) gene encoding SLURP-1 in two families with mal de Meleda. *J Invest Dermatol* 2003; **120**: 96–8.
6 Marrakchi S, Audebert S, Bouadjar B *et al.* Novel mutations in the gene encoding secreted lymphocyte antigen-6/urokinase-type plasminogen activator receptor-related protein-1 (SLURP-1) and description of five ancestral haplotypes in patients with mal de Meleda. *J Invest Dermatol* 2003; **120**: 351–5.
7 Bakija-Konsuo A, Basta-Juzbasic A, Rudan I *et al.* Mal de Meleda: genetic haplotype analysis and clinicopathological findings in cases originating from the island of Mljet (Meleda), Croatia. *Dermatology* 2002; **205**: 32–9.
8 Favre B, Plantard L, Aeschbach L *et al.* SLURP1 is a late marker of epidermal differentiation and is absent in Mal de Meleda. *J Invest Dermatol* 2007; **127**: 301–8.
9 Chimienti F, Hogg RC, Plantard L *et al.* Identification of SLURP-1 as an epidermal neuromodulator explains the clinical phenotype of Mal de Meleda. *Hum Mol Genet* 2003; **12**: 3017–24.
10 Arredondo J, Chernyavsky AI, Webber RJ, Grando SA. Biological effects of SLURP-1 on human keratinocytes. *J Invest Dermatol* 2005; **125**: 1236–41.
11 Frenk E, Guggisberg D, Mevorah B, Hohl D. Meleda disease: report of two cases investigated by electron microscopy. *Dermatology* 1996; **193**: 358–61.
12 Niles HD, Klump M. Mal de Meleda: review of the literature and report of four cases. *Arch Derm Syph* 1939; **39**: 409–21.
13 Bouadjar B, Benmazouzia S, Prud'homme JF *et al*. Clinical and genetic studies of three large, consanguineous, Algerian families with mal de Meleda. *Arch Dermatol* 2000; **136**: 1247–52.
14 Lestringant GG, Hadi SM, Qayed KI *et al*. Mal de Meleda: recessive transgressive palmoplantar keratoderma with three unusual facultative features. *Dermatology* 1992; **184**: 78–82.
15 Mozzillo N, Nunziata CA, Caraco C *et al*. Malignant melanoma developing in an area of hereditary palmoplantar keratoderma (Mal de Meleda). *J Surg Oncol* 2003; **84**: 229–33.
16 Mokni M, Charfeddine C, Ben Mously R *et al*. Heterozygous manifestations in female carriers of Mal de Meleda. *Clin Genet* 2004; **65**: 244–6.
17 Brambilla L, Pigatto PD, Boneschi V. Unusual cases of Meleda keratoderma treated with aromatic retinoid, etretinate. *Dermatologica* 1984; **168**: 283–6.
18 Reed ML, Stanley J, Stengel F *et al*. Mal de Meleda treated with isotretinoin. *Arch Dermatol* 1979; **115**: 605–8.
19 Jee S-H, Lee Y-Y, Wu Y-C *et al*. Report of a family with mal de Meleda in Taiwan: a clinical, histopathological and immunological study. *Dermatologica* 1985; **171**: 30–7.
20 van de Kerkhof PC, van Dooren-Greebe RJ, Steijlen PM. Acitretin in the treatment of mal de Meleda. *Br J Dermatol* 1992; **127**: 191–2.
21 Bergman R, Bitterman-Deutsch O, Fartsach M *et al*. Mal de Meleda keratoderma with pseudoainhum. *Br J Dermatol* 1993; **128**: 207–12.
22 Gamborg-Nielsen P. Two different clinical and genetic forms of hereditary palmoplantar keratoderma in the northernmost county of Sweden. *Clin Genet* 1985; **28**: 361–6.
23 Kastl I, Anton-Lamprecht I, Gamborg NP. Hereditary palmoplantar keratosis of the Gamborg-Nielsen type: clinical and ultrastructural characteristics of a new type of autosomal recessive palmoplantar keratosis. *Arch Dermatol Res* 1990; **282**: 363–70.
24 Kabashima K, Sakabe J, Yamada Y, Tokura Y. 'Nagashima-type' keratosis as a novel entity in the palmoplantar keratoderma category. *Arch Dermatol* 2008; **144**: 375–9.
25 Lestringant GG, Frossard PM, Eckl KM *et al*. Genetic and clinical heterogeneity in transgressive palmoplantar keratoderma. *J Invest Dermatol* 2001; **116**: 825–7.
26 van Steensel MA, van Geel MV, Steijlen PM. Mal de Meleda without mutations in the ARS coding sequence. *Eur J Dermatol* 2002; **12**: 129–32.
27 Charfeddine C, Mokni M, Kassar S *et al*. Further evidence of the clinical and genetic heterogeneity of recessive transgressive PPK in the Mediterranean region. *J Hum Genet* 2006; **51**: 841–5.
28 Akiyama M, Christiano AM, Yoneda K, Shimizu H. Abnormal cornified cell envelope formation in mutilating palmoplantar keratoderma unrelated to epidermal differentiation complex. *J Invest Dermatol* 1998; **111**: 133.

Congenital palmoplantar and perioral keratoderma

Synonym
- Olmsted's syndrome

This rare and severe cicatrizing transgredient keratoderma associated with periorificial lesions [1–5] has been reviewed [6,7]. Most cases are sporadic, but there is occasional familial occurrence. Pathogenesis is unknown, but there is cytochemical evidence of hyperproliferation of the epidermis [8,9]. Onset is in the first year of life, with symmetrical, sharply defined palmar and plantar keratoderma surrounded by erythema, and flexion deformities, constriction or spontaneous amputation of the digits (Fig. 19.63a). Other abnormalities include periorificial erythema and warty hyperkeratosis (Fig. 19.63b) and linear keratoses on the flexor forearms [3,4]. Alopecia, nail and tooth anomalies and joint laxity



(a) (b)

Fig. 19.63 Olmsted's syndrome: (a) gross keratoderma with striate features; and (b) periorificial hyperkeratosis. (Courtesy of Professor R.K. Winkelmann, Mayo Clinic, Scottsdale, AZ, USA.)

and corneal dystrophy have been reported [10], and squamous carcinoma is reported. The condition can be confused with acrodermatitis enteropathica, hidrotic ectodermal dysplasia of the Clouston type, mal de Meleda and Vohwinkel's keratoderma. Etretinate has been used in several cases with variable effect [11,12]. Topical tretinoin slightly improved the keratosis but proved irritant in one case [13].

References

1 Olmsted HC. Keratoderma palmaris et plantaris congenitalis: report of a case showing associated lesions of unusual location. *Am J Dis Child* 1927; **33**: 757–64.
2 Perry HO, Su WP. Olmsted syndrome. *Semin Dermatol* 1995; **14**: 145–51.
3 Larregue M, Callot V, Kanitakis J *et al*. Olmsted syndrome: report of two new cases and literature review. *J Dermatol* 2000; **27**: 557–68.
4 Cambiaghi S, Tadini G, Barbareschi M *et al*. Olmsted syndrome in twins. *Arch Dermatol* 1995; **131**: 738–9.
5 Atherton DJ, Sutton C, Jones BM. Mutilating palmoplantar keratoderma with periorificial keratotic plaques (Olmsted's syndrome). *Br J Dermatol* 1990; **120**: 245–52.
6 Mevorah B, Goldberg I, Sprecher E *et al*. Olmsted syndrome: mutilating palmoplantar keratoderma with periorificial keratotic plaques. *J Am Acad Dermatol* 2005; **53**: S266–72.
7 Tao J, Huang CZ, Yu NW *et al*. Olmsted syndrome: a case report and review of literature. *Int J Dermatol* 2008; **47**: 432–7.
8 Requena L, Manzarbeitia F, Moreno C *et al*. Olmsted syndrome: report of a case with study of the cellular proliferation in keratoderma. *Am J Dermatopathol* 2001; **23**: 514–20.
9 Fonseca E, Pena C, Del Pozo J *et al*. Olmsted syndrome. *J Cutan Pathol* 2001; **28**: 271–5.
10 Judge MR, Misch K, Wright P *et al*. Palmoplantar and perioroficial keratoderma with corneal epithelial dysplasia: a new syndrome. *Br J Dermatol* 1991; **125**: 186–8.
11 Ueda M, Nakagawa K, Hayashi K *et al*. Partial improvement of Olmsted syndrome with etretinate. *Pediatr Dermatol* 1993; **10**: 376–81.
12 Hausser I, Frantzmann Y, Anton-Lamprecht I *et al*. Olmsted-Syndrom Erfolgreiche Therapie durch Behandlung mit Etretinat. *Hautarzt* 1993; **44**: 394–400.
13 Poulin Y, Perry HO, Muller SA. Olmsted syndrome: congenital palmoplantar and periorificial keratoderma. *J Am Acad Dermatol* 1984; **10**: 600–10.

Focal keratodermas

Synonyms
- Wachters' keratoderma
- Palmoplantar keratoderma varians

Focal, areate or nummular, and linear or striate keratodermas have been distinguished. The occurrence of both areate and striate forms within a family led Wachters [1] to suggest a single entity, keratoderma varians. Although focal and striate may coexist (Fig. 19.64), several distinct disorders can now be discriminated clinically and genetically. The pattern and severity depends on both the underlying defect and environmental factors, such as the stresses on the tissue. Blisters may be a feature [2]. Striate forms are particularly but not uniquely associated with desmosomal defects (see below). Focal keratoderma may also be associated with other cutaneous or ectodermal disorders, including Dowling–Meara epidermolysis bullosa simplex, or with disease in other systems. Focal keratoderma with oesophageal carcinoma (Howel-Evans' syndrome) and keratodermas with deafness are described separately.

Painful hereditary callosities [2–5]. Plantar callosities of sufficient size are inevitably painful, and the term is probably non-specific. Painful callosities are a feature of conditions corresponding to keratoderma nummularis of Brunauer and Fuhs and keratoderma areata of Siemens, but also pachyonychia congenita and type II oculocutaneous tyrosinaemia (Richner–Hanhart syndrome); reported cases with blisters and tonofilament clumping [2] are likely be an epidermolytic disorder.

References

1 Wachters DHJ. *Over de Verschillende Morphologische Vormen van de Keratosis Palmoplantaris*. Thesis, Leyden: 1963.
2 Baden HP, Bronstein BR, Rand RE. Hereditary callosities with blisters: report of a family and review. *J Am Acad Dermatol* 1984; **11**: 409–15.



Fig. 19.64 Focal keratoderma (keratoderma areata/striata): (a) focal masses of keratin predominantly on pressure points; and (b) striate keratotic lesions on palms in the same patient.

3 Roth W, Penneys NS, Fawcett N. Hereditary painful callosities. *Arch Dermatol* 1978; **114**: 591–2.
4 Wachters DHJ, Frensdorf EL, Hausman R *et al*. Keratosis palmoplantaris nummularis ('hereditary painful callosities'). *J Am Acad Dermatol* 1983; **9**: 204–9.
5 Cambiaghi S, Morel P. Hereditary painful callosities with associated features. *Dermatology* 1996; **193**: 47–9.

Focal keratoderma with oral leukokeratosis (MIM 600962)

Focal non-epidermolytic keratoderma, inherited as an autosomal dominant trait, may be associated with white plaques on the sides of the tongue and buccal mucosa. This syndrome is clinically and genetically a mild variant of pachyonychia congenita; subtle associated nail changes include splinter haemorrhages and a widening of the onychocorneal band, and causative mutations in the helix initiation motif region of keratin 16 have been identified [1]. Kolde *et al*. reported a family with focal epidermolytic PPK and gingival keratoses not mapping to keratin or TOC loci [2]. An isolated patient with leukoplakia and florid oral papillomatosis, and keratoderma without nail changes has been recorded [3]. Oral lesions without nail changes are also seen in Howel-Evans' syndrome [4].

References

1 Shamsher MK, Navsaria HA, Stevens HP *et al*. Novel mutations in keratin 16 gene underly focal non-epidermolytic palmoplantar keratoderma (NEPPK) in two families. *Hum Mol Genet* 1995; **4**: 1875–81.
2 Kolde G, Hennies HC, Bethke G, Reichart PA. Focal palmoplantar and gingival keratosis: a distinct palmoplantar ectodermal dysplasia with epidermolytic alterations but lack of mutations in known keratins. *J Am Acad Dermatol* 2005; **52**: 403–9.
3 Ishii Y, Sayama K, Ohtsuka H *et al*. Oral florid papillomatosis and leukoplakia of the esophagus associated with keratoderma and showing transepidermal elimination. *J Dermatol* 1994; **21**: 974–8.
4 Stevens HP, Kelsall DP, Bryant SP *et al*. Linkage of an American pedigree with palmoplantar keratoderma and malignancy (palmoplantar ectodermal dysplasia type III) to 17q24. *Arch Dermatol* 1996; **132**: 1–12.

Pachyonychia congenita

Synonyms
- Jadassohn–Lewandowsky syndrome
- Jackson–Lawler syndrome

Pachyonychia congenita (PC) is characterized by subungual hyperkeratosis of the distal nails and focal palmoplantar hyperkeratosis. A large number of associations have been reported [1], but only the simplest clinical classification into PC-1 (Jadassohn–Lewandowsky) and PC-2 (Jackson–Lawler) syndromes is borne out genetically [2].

Aetiology. Autosomal dominant inheritance is usual, but a recessive form is reported [3]. Tonofilament aggregates seen on electron microscopy suggest an intermediate filament disorder [4,5]. The distribution of lesions in PC-1 corresponds to the expression patterns of keratins K6a and K16, and a wide variety of causative mutations have been found in these genes [5–10]. By contrast, K17 is constitutively expressed in the pilosebaceous unit and basal appendage keratinocytes, with lesser basal expression in palmoplantar skin and a number of other minor epithelial populations, but not in mucosae [11–13]. Point mutations in the K17 gene and occasionally in K6b isoform of keratin 6 have been found in many families with PC-2 [2,9,10,13]. Identical mutations may also present as isolated steatocystoma multiplex with or without mild nail changes [14]. The prominent nail involvement of pachyonychia

reflects the expression of these keratins in the ventral nail [15,16].

Pathology. Palmoplantar epidermis shows gross hyperkeratosis with alternating ortho- and parakeratosis. Acanthosis is present with patchy hypergranulosis, in which large and misformed keratohyalin granules are present, but there is no gross epidermolysis [4]. In PC-2, the cysts may be keratinous epidermoid cysts, eruptive vellus hair cysts or true steatocysts. Different histologies may be seen within a family, an individual, or even a single cyst.

Clinical features [1,17–19]. A comprehensive analysis of clinical features is given by Leachman [19]. Hyperkeratosis of the nail bed appears in the first year or two of life, followed by focal thickening of palms and soles. Late onset PC has been termed pachyonychia congenita tarda [20,21]. Frictional blisters may occur on the feet, especially in hot weather in childhood. In adults, focal hyperkeratosis may produce marked pain on walking. Severity varies, even within families. The mildest nail changes are similar to those seen in focal keratoderma with oral leukokeratosis, with which PC-1 is allelic.

PC-1 (Jadassohn–Lewandowsky type; MIM 167200). Thick yellow keratoses are found on sites of pressure (Fig. 19.65a), associated with wedge-like thickening of distal finger- and toenails (Fig. 19.65b), keratosis pilaris and follicular keratoses on the knees and elbows. Patchy white thickened areas are seen on the tongue and oral mucosa (oral leukokeratosis). Severe oral lesions resemble candidiasis [22]. Laryngeal involvement may produce hoarseness and in infancy even fatal respiratory obstruction [23]. Squamous carcinoma has been reported in a persistently ulcerated area [17].

PC-2 (Jackson–Lawler type; MIM 167210). Findings are similar to PC-1 but palmoplantar keratoses are possibly less severe. Despite the absence of mucosal lesions, hoarseness is a feature. This variant was first described by Murray, who noted a history of teeth present at birth in many cases [24]; in this family, adult dentition is also affected [25]. Unruly hair and milia may be seen in infancy, and adults have protuberant eyebrows. Multiple epidermal cysts appearing after puberty include both epidermoid and steatocysts. Axillary cysts may mimic hidradenitis suppurativa [26]; extensive and infected vulval, scrotal or scalp cysts also cause significant disability for some patients. Within families, some patients may have only nail changes and some only cysts.

Other clinical variants. Feinstein *et al.* [1] reviewed the many reported associations, although many are coincidental. Thickening of the nails may occur in a variety of ectodermal dystrophies and some suggested PC variants may merit further genetic study. Involvement of the nails alone has been reported [27,28]. Heterozygous missense mutations in the connexin 30 gene, normally associated with Clouston's syndrome (see below), have been identified in a number of families with pachyonychia-like nail changes and no other phenotype [29]. Schafer [30] reported corneal leukokeratosis; Buckley and Cassuto [31] and Tidman *et al.* [32] flexural pigmentation and amyloid.



(a)



(b)

Fig. 19.65 Pachyonychia congenita: (a) keratoderma on weight-bearing areas; and (b) typical wedge-shaped nail.

Treatment [33]. Emollients and keratolytics may help keratoderma in milder cases, and attention to footwear may reduce blistering and callosities. Mechanical reduction of hyperkeratosis and of nails produces symptomatic benefit. Acitretin 25–35 mg/day make the keratin more flexible and less pronounced without complete clearing [34,35], but treatment is often unsatisfactory due to increased tenderness [4]. Retinoids produce a degree of flattening of the nails if given for prolonged periods. Treatment of hyperhidrosis may reduce blistering [36] and the use of botulinum toxin under regional analgesia provided pain relief for several months in three patients with PC [37]. The use of small interfering RNAs (siRNA) to regulate keratin expression is being explored [38].

References

1 Feinstein A, Friedman J, Schewach-Millet M. Pachyonychia congenita. *J Am Acad Dermatol* 1988; **19**: 705–11.

2 Munro CS. Pachyonychia congenita: mutations and clinical presentations. *Br J Dermatol* 2001; **144**: 929–31.
3 Haber RM, Rose TH. Autosomal recessive pachyonychia congenita. *Arch Dermatol* 1986; **122**: 919–23.
4 Thomas DR, Jorizzo JL, Brysk MM *et al.* Pachyonychia congenita: electron microscopic and epidermal glycoprotein assessment before and during isotretinoin treatment. *Arch Dermatol* 1984; **120**: 1475–9.
5 McLean WHI, Rugg EL, Lunny DP *et al.* Keratin 16 and keratin 17 mutations cause pachyonychia congenita. *Nat Genet* 1995; **9**: 273–8.
6 Bowden PE, Haley JL, Kansky A *et al.* Mutation of a type II keratin gene (KBa) in pachyonychia congenita. *Nat Genet* 1995; **10**: 363–5.
7 Smith FJ, McKenna KE, Irvine AD *et al.* A mutation detection strategy for the human keratin 6A gene and novel missense mutations in two cases of pachyonychia congenita type 1. *Exp Dermatol* 1999; **8**: 109–14.
8 Irvine AD, McLean WH. Human keratin diseases: the increasing spectrum of disease and subtlety of the phenotype–genotype correlation. *Br J Dermatol* 1999; **140**: 815–28.
9 Smith FJ, Liao H, Cassidy AJ *et al.* The genetic basis of pachyonychia congenita. *J Investig Dermatol Symp Proc* 2005; **10**: 21–30.
10 Liao H, Sayers JM, Wilson NJ *et al.* A spectrum of mutations in keratins K6a, K16 and K17 causing pachyonychia congenita. *J Dermatol Sci* 2007; **48**: 199–205.
11 Leigh IM, Navsaria HA, Purkis PE *et al.* Keratins (K16 and K17) as markers of keratinocyte hyperproliferation in psoriasis *in vivo* and *in vitro*. *Br J Dermatol* 1995; **133**: 501–11.
12 Wilson CL, Dean D, Lane EB *et al.* Keratinocyte differentiation in psoriatic scalp: morphology and expression of epithelial keratins. *Br J Dermatol* 1994; **131**: 191–200.
13 Smith FJD, Corden LD, Rugg EL *et al.* Missense mutations in keratin 17 cause either pachyonychia congenita type 2 or a phenotype resembling steatocystoma multiplex. *J Invest Dermatol* 1997; **108**: 220–3.
14 Smith FJD, Jonkman MF, van Goor H *et al.* A mutation in human keratin K6b produces a phenocopy of the K17 disorder pachyonychia congenita type 2. *Hum Molec Genet* 1998; **7**: 1143–8.
15 McGowan KM, Coulombe PA. Keratin 17 expression in the hard epithelial context of the hair and nail, and its relevance for the pachyonychia congenita phenotype. *J Invest Dermatol* 2000; **114**: 1101–7.
16 De Berker D, Wojnarowska F, Sviland L *et al.* Keratin expression in the normal nail unit: markers of regional differentiation. *Br J Dermatol* 2000; **142**: 89–96.
17 Su WP, Chun SI, Hammond DE *et al.* Pachyonychia congenita: a clinical study of 12 cases and review of the literature. *Pediatr Dermatol* 1990; **7**: 33–8.
18 Kansky A, Basta-Juzbasic A, Videnic N *et al.* Pachyonychia congenita (Jadassohn–Lewandowsky syndrome): evaluation of symptoms in 36 patients. *Arch Dermatol Res* 1993; **285**: 36–7.
19 Leachman SA, Kaspar RL, Fleckman P *et al.* Clinical and pathological features of pachyonychia congenita. *J Investig Dermatol Symp Proc* 2005; **10**: 3–17.
20 Paller AS, Moore JA, Scher R. Pachyonychia congenita tarda: a late-onset form of pachyonychia congenita. *Arch Dermatol* 1991; **127**: 701–3.
21 Lucker GPH, Steiljen PM. Pachyonychia congenita tarda. *Clin Exp Dermatol* 1995; **20**: 226–9.
22 Mawhinney H, Creswell S, Beare JM. Pachyonychia congenita with candidiasis. *Clin Exp Dermatol* 1981; **6**: 145–9.
23 Stieglitz JB, Centerwall JW. Pachyonychia congenita (Jadassohn–Lewandowsky syndrome): a seventeen-member, four-generation pedigree with unusual respiratory and dental involvment. *Am J Med Genet* 1983; **14**: 21–8.
24 Murray FA. Congenital anomalies of the nails: four cases of hereditary hypertrophy of the nail-bed associated with a history of erupted teeth at birth. *Br J Dermatol Syph* 1991; **23**: 409–11.
25 Zamiri M, McLean WHI, Hodgins MC, Munro CS. Pachyonychia congenital: abnormal dentition extending into adulthood. *Br J Dermatol* 2008; **159**: 500–1.
26 Todd P, Garioch J, Rademaker M *et al.* Pachyonychia congenita complicated by hidradenitis suppurativa: a family study. *Br J Dermatol* 1990; **123**: 663–6.
27 Chang A, Lucker GPH, van de Kerkhof PCM *et al.* Pachyonychia congenita in the absence of other syndrome abnormalities. *J Am Acad Dermatol* 1994; **30**: 1017–8.
28 Pryce DW, Verbov JL. A family with pachyonychia congenita affecting the nails only. *Clin Exp Dermatol* 1994; **19**: 521–2.
29 van Steensel MAM, Jonkman MF, van Geel M *et al.* Clouston syndrome can mimic pachyonychia congenita. *J Invest Dermatol* 2003; **121**: 1035–8.
30 Schafer E. Congenital dyskeratosis. *Arch Derm Syph* 1924; **148**: 425–32.
31 Buckley WR, Cassuto J. Pachyonychia congenita. *Arch Dermatol* 1962; **85**: 397–402.
32 Tidman MJ, Wells RS, MacDonald DM. Pachyonychia congenita with cutaneous amyloidosis and hyperpigmentation: a distinct variant. *J Am Acad Dermatol* 1987; **16**: 935–40.
33 Milstone LM, Fleckman P, Leachman SA *et al.* Treatment of pachyonychia congenita. *J Investig Dermatol Symp Proc* 2005; **10**: 18–20.
34 Dupre A, Christol B, Bonafe JL *et al.* Pachyonychia congenita: three familial cases—effects of the treatment by aromatic retinoid (Ro 10.9395). *Ann Dermatol Vénéréol* 1981; **108**: 145–9.
35 Hoting E, Wassilew SW. Systemic retinoid therapy with etretinate in pachyonychia congenita. *Hautarzt* 1985; **36**: 526–8.
36 Tidman MJ, Wells RS. Control of plantar blisters in pachyonychia congenita with topical aluminium chloride. *Br J Dermatol* 1988; **118**: 451–2.
37 Swartling C, Vahlquist A. Treatment of pachyonychia congenita with plantar injections of botulinum toxin. *Br J Dermatol* 2006; **154**: 763–5.
38 Smith FJ, Hickerson RP, Sayers JM *et al.* Development of therapeutic siRNAs for pachyonychia congenita. *J Invest Dermatol* 2008; **128**: 50–8.

Striate keratoderma (MIM 148700)

Synonym
- Brunauer–Fuhs–Siemens

Striate keratoderma in isolation, usually inherited as an autosomal dominant trait, can be caused by defects in at least three different genes [1].

Aetiology. Autosomal dominant striate keratoderma was mapped to the desmosomal cadherin cluster on 18q12.1 [2]. Mutations causing haploinsufficiency have been identified in the desmoglein 1 gene (*Dsg1*) [3,4]. In another pedigree Armstrong *et al.* [5] had found linkage to 6p21 and identified a heterozygous nonsense mutation in the desmoplakin (*Dp*) gene. Other nonsense mutations in desmoplakin also produce the phenotype, again due to haploinsufficiency [6]. Compound heterozygosity for nonsense and missense mutations in desmoplakin were found in two patients with keratoderma, skin fragility and woolly hair [7]. Other mutations in desmoplakin cause recessive and dominant cardiomyopathy with or without keratoderma (see p. 19.107). The majority of mutations in striate keratoderma are in *Dsg1* or *Dp1* [1], but two pedigrees had frameshift mutations in the V2 tail domain of keratin 1 which may be important in cross-linking to cornified envelope proteins [8].

Pathology. Electron microscopy of involved skin in patients with keratoderma associated with Dp mutations showed abnormal bunching of keratin filaments and reduction in the peripheral keratin network, with loss of connections with desmosomes [5]. Wan and colleagues [9] found differences between lesions of *Dsg1*- and *Dp*-associated PPKs. Desmosome number was reduced in both but desmosome size was reduced only in the former, and reduced expression of other plaque components and keratins K5, K14 and K10 was more marked. Perinuclear aggregation of keratin filaments was more marked in *Dp*-associated disease [9].

Clinical features. As the name implies, there is a linear pattern of skin thickening on the palms and flexor aspects of the fingers (Fig. 19.64b). However, lesions on the soles may be more areate or

confluent, and striate lesions can be seen in affected members of pedigrees in which other patterns of keratoderma predominate. The presence of other features, especially woolly hair, should be specifically sought, and the possibility of cardiac disease considered.

References

1 Barber AG, Wajid M, Columbo M, Lubetkin J, Christiano AM. Striate palmoplantar keratoderma resulting from a frameshift mutation in the desmoglein 1 gene. *J Dermatol Sci* 2007; **45**: 161–6.
2 Hennies HC, Kuster W, Mischke D, Reis A. Localization of a locus for the striated form of palmoplantar keratoderma to chromosome 18q near the desmosomal cadherin gene cluster. *Hum Mol Genet* 1995; **4**: 1015–20.
3 Rickman L, Simrak D, Stevens HP *et al.* N-terminal deletion in a desmosomal cadherin causes the autosomal dominant skin disease striate palmoplantar keratoderma. *Hum Mol Genet* 1999; **8**: 971–6.
4 Hunt DM, Rickman L, Whittock NV *et al.* Spectrum of dominant mutations in the desmosomal cadherin desmoglein 1, causing the skin disease striate palmoplantar keratoderma. *Eur J Hum Genet* 2001; **9**: 197–203.
5 Armstrong DK, McKenna KE, Purkis PE *et al.* Haploinsufficiency of desmoplakin causes a striate subtype of palmoplantar keratoderma. *Hum Mol Genet* 1999; **8**: 143–8.
6 Whittock NV, Ashton GH, Dopping-Hepenstal PJ *et al.* Striate palmoplantar keratoderma resulting from desmoplakin haploinsufficiency. *J Invest Dermatol* 1999; **113**: 940–6.
7 Whittock NV, Wan H, Morley SM *et al.* Compound heterozygosity for non-sense and mis-sense mutations in desmoplakin underlies skin fragility/woolly hair syndrome. *J Invest Dermatol* 2002; **118**: 232–8.
8 Whittock NV, Smith FJ, Wan H *et al.* Frameshift mutation in the V2 domain of human keratin 1 results in striate palmoplantar keratoderma. *J Invest Dermatol* 2002; **118**: 838–44.
9 Wan H, Dopping-Hepenstal PJ, Gratian MJ *et al.* Striate palmoplantar keratoderma arising from desmoplakin and desmoglein 1 mutations is associated with contrasting perturbations of desmosomes and the keratin filament network. *Br J Dermatol* 2004; **150**: 878–91.

Hidrotic ectodermal dysplasia (MIM 129500) [1]

Synonym
- Clouston's syndrome

This autosomal dominant ectodermal dysplasia, characterized by dystrophic nails and sparse hair, and caused by mutations in the gap junction beta-6 gene encoding connexin 30 [2–4], is described in Chapter 15. It is mentioned here because a papillomatous and fissured transgredient keratoderma is a significant feature, and the presentation may resemble pachyonychia congenita [2].

References

1 Clouston HR. A hereditary ectodermal dystrophy. *Can Med Assoc J* 1921; **21**: 18–31.
2 van Steensel MAM, Jonkman MF, van Geel M *et al.* Clouston syndrome can mimic pachyonychia congenita. *J Invest Dermatol* 2003; **121**: 1035–8.
3 Lamartine J, Essenfelder GM, Kibar Z *et al.* Mutations in *GJB6* cause hidrotic ectodermal dysplasia. *Nat Genet* 2000; **26**: 142–4.
4 Smith FJD, Morley SM, McLean WHI. A novel connexin 30 mutation in Clouston syndrome. *J Invest Dermatol* 2002; **118**: 530–2.

Keratodermas with extracutaneous features

Extracutaneous features in cases of hereditary keratoderma are often reported. Unusual associations with well-recognized syndromes may be coincidental, and in isolated cases it is rarely possible to establish their significance. Readily recognizable or clinically important syndromes are described below.

Keratoderma with oesophageal carcinoma (MIM 148700)

Synonyms
- Howel-Evans' syndrome
- Tylosis with oesophageal cancer

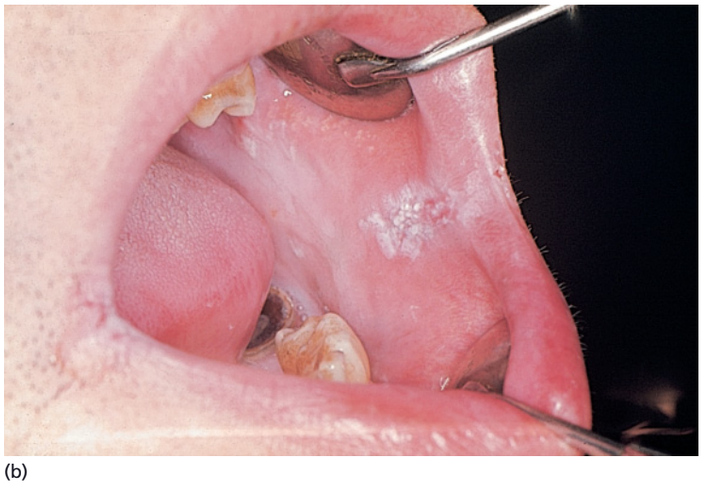
Howel-Evans described two families of autosomal dominant keratoderma associated with later development of oesophageal cancer [1]. The term tylosis, originally synonymous with (diffuse) keratoderma, is now particularly associated with this syndrome, and to avoid unnecessary anxiety is probably better avoided for other keratodermas. Clinical reappraisal has shown that TOC (tylosis with oesophageal cancer) should be considered a focal PPK, as the lesions predominantly affect pressure points of the sole (Fig. 19.66a), and less so the palm [2,3]. There is variable oral leukokeratosis (Fig. 19.66b) and follicular prominence, but the disorder can be distinguished from PC type 1 by the absence of even mild nail changes [3]. Thirty-seven per cent of the original affected family members developed oesophageal cancer 30–40 years later. A further, extensive German American family has been reported, also with an increased (38-fold) risk of oesophageal cancer [3]. The disorder maps to a 42.5-kB segment of chromosome 17q23 [3–7]. The region is commonly deleted in oesophageal carcinomas [8], implying a tumour suppressor gene. Only three genes are present in the minimal region, amongst which both alleles of the cytoglobin gene were downregulated in oesophageal biopsies from the disorder by an undetermined mechanism [9,10].

References

1 Howel-Evans W, McGonnell RB, Clarke GA, Sheppard PM. Carcinoma of the oesophagus with keratosis palmaris et plantaris (tylosis): a study of two families. *QJM* 1950; **27**: 415–29.
2 Ellis A, Field EA, Field JK *et al.* Tylosis associated with carcinoma of the oesophagus and oral leukoplakia in a large Liverpool family: a review of six generations. *Eur J Cancer Oral Oncol* 1994; **30**: 102–12.
3 Stevens HP, Kelsall DP, Bryant SP *et al.* Linkage of an American pedigree with palmoplantar keratoderma and malignancy (palmoplantar ectodermal dysplasia type III) to 17q24. *Arch Dermatol* 1996; **132**: 1–12.
4 Risk JM, Field EA, Field JK *et al.* Tylosis oesophageal cancer mapped. *Nat Genet* 1994; **8**: 319–21.
5 Langan JE, Cole CG, Huckle EJ *et al.* Novel microsatellite markers and single nucleotide polymorphisms refine the tylosis with oesophageal cancer (TOC) minimal region on 17q25 to 42.5 kb: sequencing does not identify the causative gene. *Hum Genet* 2004; **114**: 534–40.
6 Ruhrberg C, Williamson JA, Sheer D, Watt FM. Chromosomal localisation of the human envoplakin gene (*EVPL*) to the region of the tylosis oesophageal cancer gene (*TOCG*) on 17q25. *Genomics* 1996; **37**: 381–5.
7 Risk JM, Ruhrberg C, Hennies H *et al.* Envoplakin, a possible candidate gene for focal NEPPK/esophageal cancer (TOC): the integration of genetic and physical maps of the TOC region on 17q25. *Genomics* 1999; **59**: 234–42.
8 Iwaya T, Maesawa C, Ogasawara S, Tamura G. Tylosis esophageal cancer locus on chromosome 17q25.1 is commonly deleted in sporadic human esophageal cancer. *Gastroenterology* 1998; **114**: 1206–10.
9 Risk JM, Evans KE, Jones J *et al.* Characterization of a 500 kb region on 17q25 and the exclusion of candidate genes as the familial tylosis oesophageal cancer (TOC) locus. *Oncogene* 2002; **21**: 6395–402.
10 McRonald FE, Liloglou T, Xinarianos G *et al.* Down-regulation of the cytoglobin gene, located on 17q25, in tylosis oesophageal cancer (TOC): evidence for trans-allele repression. *Hum Mol Genet* 2006; **15**: 1271–7.



(a)



(b)

Fig. 19.66 Howel-Evans' syndrome: (a) keratoderma; and (b) oral mucosal lesions. (Courtesy of Professor W.R. Tyldesley, Liverpool University School of Dentistry, Liverpool, UK and Dr M.S. Lewis-Jones, Ninewells Hospital, Dundee, UK.)

Keratoderma, woolly hair and cardiac disease

The occurrence of congenital heart disease in patients with keratoderma has been reviewed [1]. The possibility of cardiomyopathy or conduction disorders should be particularly considered in patients with keratoderma and woolly hair. Defects in proteins of the desmosomal plaque are common to the two clearly identified genetic syndromes.

Naxos disease (MIM 601214). An autosomal recessive syndrome of arrhythmogenic right ventricular cardiomyopathy, keratoderma and woolly hair was reported in seven pedigrees from the Greek island of Naxos [2,3]. These families have been found to share a 2-bp deletion causing premature termination in the gene encoding plakoglobin [4], a cell junction protein found in association with desmosomes in the epidermis and in striated and cardiac muscle. Homozygous but not heterozygous individuals show an increased incidence of arrhythmias, cardiac failure or sudden death [5]. A similar autosomal dominant syndrome has been reported [6]. The association may be genetically heterogeneous [7].

Keratoderma, woolly hair and dilated cardiomyopathy (Carvajal syndrome; MIM 605676). Three Equadorian pedigrees displayed recessive inheritance of a striate keratoderma and woolly hair associated with dilated left ventricular cardiomyopathy developing in teenage years. Histology of keratoderma showed wide intercellular spaces, clustering of desmosomes and a collapsed intermediate filament network [8]. Affected cases were all homozygous for a deletion mutation producing a premature stop codon in the tail of the desmoplakin gene [9].

Dominant mutations in desmoplakin have also been reported, causing woolly hair, striate PPK and biventricular cardiomyopathy [10] or arrhythmogenic right ventricular cardiomyopathy without cutaneous phenotype [11]. Skin fragility and woolly hair resulting from compound heterozygosity for nonsense and missense mutations in desmoplakin are also reported [12]. Compound heterozygosity causing loss of the tail domain of desmoplakin presented as lethal acantholytic epidermolysis bullosa [13].

References

1 Hoeger PH, Yates RW, Harper JI. Palmoplantar keratoderma associated with congenital heart disease. *Br J Dermatol* 1998; **138**: 506–9.

2 Barker JNWN, Protonatorios N, Tsatsopoulou A *et al.* Palmoplantar keratoderma, curly hair and endomyocardial fibrodysplasia: a new syndrome. *Br J Dermatol* 1983; **119** (Suppl. 33): 13–4.

3 Protonotarios N, Tsatsopoulou A, Fontaine G. Naxos disease: keratoderma, scalp modifications, and cardiomyopathy. *J Am Acad Dermatol* 2001; **44**: 309–11.

4 McKoy G, Protonotarios N, Crosby A *et al.* Identification of a deletion in plakoglobin in arrhythmogenic right ventricular cardiomyopathy with palmoplantar keratoderma and woolly hair (Naxos disease). *Lancet* 2000; **355**: 2119–24.

5 Protonotarios N, Tsatsopoulou A, Anastasakis A *et al.* Genotype–phenotype assessment in autosomal recessive arrhythmogenic right ventricular cardiomyopathy (Naxos disease) caused by a deletion in plakoglobin. *J Am Coll Cardiol* 2001; **38**: 1477–84.

6 Tosti A, Misciali C, Piraccini BA *et al.* Woolly hair palmoplantar keratoderma and cardiac abnormalities: report of a family. *Arch Dermatol* 1994; **130**: 522–4.

7 Djabali K, Martinez-Mir A, Horev L *et al.* Evidence for extensive locus heterogeneity in Naxos disease. *J Invest Dermatol* 2002; **118**: 557–60.

8 Carvajal-Huerta L. Epidermolytic palmoplantar keratoderma with woolly hair and dilated cardiomyopathy. *J Am Acad Dermatol* 1998; **39**: 418–21.

9 Norgett EE, Hatsell SJ, Carvajal-Huerta L *et al.* Recessive mutation in desmoplakin disrupts desmoplakin–intermediate filament interactions and causes dilated cardiomyopathy, woolly hair and keratoderma. *Hum Mol Genet* 2000; **9**: 2761–6.

10 Norgett EE, Lucke TW, Bowers B *et al.* Early death from cardiomyopathy in a family with autosomal dominant striate palmoplantar keratoderma and woolly hair associated with a novel insertion mutation in desmoplakin. *J Invest Dermatol* 2006; **126**: 1651–4.

11 Rampazzo A, Nava A, Malacrida S *et al.* Mutation in human desmoplakin domain binding to plakoglobin causes a dominant form of arrhythmogenic right ventricular cardiomyopathy. *Am J Hum Genet* 2002; **71**: 1200–6.

12 Whittock NV, Wan H, Morley SM *et al.* Compound heterozygosity for non-sense and mis-sense mutations in desmoplakin underlies skin fragility/woolly hair syndrome. *J Invest Dermatol* 2002; **118**: 232–8.

13 Jonkman MF, Pasmooij AM, Pasmans SG *et al.* Loss of desmoplakin tail causes lethal acantholytic epidermolysis. *Am J Hum Genet* 2005; **77**: 653–60.

Keratoderma and hearing impairment (MIM 148350)

The association of disordered keratinization with impaired hearing is most commonly caused by defects in genes encoding members of the connexin family of gap junction proteins [1], but mitochondrial defects may also be responsible [2].

Keratoderma and prelingual deafness. Premature termination codons in connexin 26 are the single most common cause of non-syndromic autosomal recessive deafness [1,3–5]. Connexin 26 is expressed in the cochlea where it may permit the recycling of potassium to endolymph [5]. In skin, connexin 26 is found in palmoplantar epidermis and sweat glands, and is up-regulated in conditions such as psoriasis [6,7], but patients homozygous for mutations preventing any expression of connexin 26 have no discernible cutaneous phenotype. However, in several pedigrees with diffuse or transgredient autosomal dominant keratoderma and varying degrees of prelingual deafness, missense mutations in connexin 26 have been found [8–12]. Other mutations in connexin 26 cause cicatrizing keratoderma with impaired hearing (Vohwinkel's syndrome; see below), keratoderma with knuckle pads (Bart–Pumphrey syndrome; see below) and KID syndrome [13,14]. Mutations that cause skin disease may exert a transdominant effect, disrupting gap junction communication by interfering with the function of other epidermal connexins [10].

References

1 Kelsell DP, Dunlop J, Hodgins MB. Human diseases: clues to cracking the connexin code. *Trends Cell Biol* 2001; **11**: 2–6.
2 Sevior KB, Hatamochi A, Stewart IA *et al.* Mitochondrial A7445G mutation in two pedigrees with palmoplantar keratoderma and deafness. *Am J Med Genet* 1998; **75**: 179–85.
3 Kelsell DP, Dunlop J, Stevens HP *et al.* Connexin 26 mutations in hereditary non-syndromic sensorineural deafness. *Nature* 1997; **387**: 80–3.
4 Kelley PM, Harris DJ, Comer BC *et al.* Novel mutations in the connexin 26 gene (*GJB2*) that cause autosomal recessive (DFNB1) hearing loss. *Am J Hum Genet* 1998; **62**: 792–9.
5 White TW. Functional analysis of human Cx26 mutations associated with deafness. *Brain Res Rev* 2000; **32**: 181–3.
6 Labarthe MP, Bosco D, Saurat JH *et al.* Upregulation of connexin 26 between keratinocytes of psoriatic lesions. *J Invest Dermatol* 1998; **111**: 72–6.
7 Lucke T, Choudhry R, Thom R *et al.* Upregulation of connexin 26 is a feature of keratinocyte differentiation in hyperproliferative epidermis, vaginal epithelium, and buccal epithelium. *J Invest Dermatol* 1999; **112**: 354–61.
8 Richard G, White TW, Smith LE *et al.* Functional defects of Cx26 resulting from a heterozygous missense mutation in a family with dominant deaf-mutism and palmoplantar keratoderma. *Hum Genet* 1998; **103**: 393–9.
9 Heathcote K, Syrris P, Carter ND, Patton MA. A connexin 26 mutation causes a syndrome of sensorineural hearing loss and palmoplantar hyperkeratosis (MIM 148350). *J Med Genet* 2000; **37**: 50–1.
10 Rouan F, White TW, Brown N *et al.* Trans-dominant inhibition of connexin-43 by mutant connexin-26: implications for dominant connexin disorders affecting epidermal differentiation. *J Cell Sci* 2001; **114**: 2105–13.
11 Uyguner O, Tukel T, Baykal C *et al.* The novel R75Q mutation in the *GJB2* gene causes autosomal dominant hearing loss and palmoplantar keratoderma in a Turkish family. *Clin Genet* 2002; **62**: 306–9.
12 de Zwart-Storm EA, Hamm H, Stoevesandt J *et al.* A novel missense mutation in GJB2 disturbs gap junction protein transport and causes focal palmoplantar keratoderma with deafness. *J Med Genet* 2008; **45**: 161–6.
13 Richard GA, Rouan F, Willoughby CE *et al.* Mutations in *GJB-2* encoding connexin-26 cause the ectodermal dysplasia keratitis–ichthyosis–deafness syndrome. *Am J Hum Genet* 2002; **70**: 1341–8.
14 van Steensel MAM, van Geel M, Nahuys M *et al.* A novel Cx26 mutation in a patient diagnosed with the keratitis–ichthyosis–deafness syndrome. *J Invest Dermatol* 2002; **118**: 724–7.

Cicatrizing keratoderma with hearing impairment (MIM 124500)

Synonyms
- Keratoma hereditarum mutilans
- Vohwinkel's syndrome

Vohwinkel [1] and Wigley [2] independently reported honeycomb-like keratoderma associated with stellate keratoses on the knuckles and the formation of circumferential bands around digits ('pseudo-ainhum'). Vohwinkel's family also had moderate sensorineural deafness [3], and subsequent cases have confirmed autosomal dominant inheritance [4–7].

Aetiology. In three unrelated English, Spanish and Italian pedigrees with true Vohwinkel's syndrome, Maestrini *et al.* [8] found the same mutation, D66H, in the gap junction beta-2 gene encoding connexin 26. This mutation was also found in another English family [9]. Other mutations in the same gene cause KID syndrome or keratoderma with prelingual deafness (see above). The probable mechanism, transdominant inhibition of gap junction function, can be reproduced *in vitro* [10], but expression of mutant Cx26 in transgenic mice resulted in cytoplasmic accumulation of Cx26 and Cx30, with reduced expression at intercellular junctions [11]. The reason for the less profound deafness but more severe cutaneous phenotype with this specific mutation is not understood.

Clinical features [1–8,12]. PPK begins in childhood as shiny or translucent papular hyperkeratosis, gradually becoming confluent on hands and feet. Striate lesions may be seen in some individuals. Warty papules on the knuckles and other extensor sites coalesce into the pathognomonic 'starfish' keratoses (Fig. 19.67a). The edge of the keratoderma at the wrists and Achilles tendon consists of spiky digitate hyperkeratotic projections onto normal skin, sometimes showing koebnerization. This contrasts with the diffuse edge seen in loricrin keratoderma [12]. Multiple keratoses on digits produce circumferential hyperkeratosis, which predisposes to the formation of cicatricial bands (Fig. 19.67b) and autoamputation. The little finger and fifth toe are most commonly affected. A high-tone sensorineural hearing loss [6] is probably present from birth, but is relatively subtle and may escape detection in childhood unless specifically sought. It does not appear to be progressive. A reported association with craniofacial anomalies [13] proved coincidental [8].

Treatment. Vohwinkel's syndrome has been successfully treated by etretinate [7] and the cicatricial bands released surgically [14].

Bart–Pumphrey syndrome (MIM 149200). This is an autosomal dominant condition associating knuckle pads (similar to the focal keratoses of Vohwinkel's syndrome), keratoderma, leukonychia



(a) (b)

Fig. 19.67 Cicatrizing keratoderma with deafness: (a) 'starfish' lesions; and (b) pseudo-ainhum.

and mixed sensorineural and conductive deafness [15] due to specific mutations in connexin 26 [16,17].

References

1 Vohwinkel KH. Keratom hereditarium mutilans. *Arch Dermatol Syphilol* 1929; **158**: 354–64.
2 Wigley JEM. A case of hyperkeratosis palmaris et plantaris associated with ainhum-like constriction of the fingers. *Br J Dermatol* 1929; **41**: 188–91.
3 Nockemann PE. Erbliche Hornhautverdickung mit Schnürfurchen an Fingern und Zehen mit Innenohrschwerhörigkeit. *Med Welt* 1961; **37**: 1894–900.
4 Gibbs RC, Frank SB. Keratoma hereditaria mutilans (Vohwinkel): differentiating features of conditions with constriction of digits. *Arch Dermatol* 1966; **94**: 619–25.
5 Ocaña-Sierra J, Blesa G, Montero E. Syndrome de Vohwinkel. *Ann Derm Syph* 1975; **102**: 41–5.
6 McGibbon DH, Watson RT. Vohwinkel's syndrome and deafness. *J Laryngol Otol* 1977; **91**: 853–7.
7 Wereide K. Mutilating palmoplantar keratoderma successfully treated with etretinate. *Acta Derm Venereol Scand* 1984; **64**: 566–9.
8 Maestrini E, Korge BP, Ocana-Sierra J *et al.* A missense mutation in connexin 26, D66H, causes mutilating keratoderma with sensorineural deafness (Vohwinkel's syndrome) in three unrelated families. *Hum Mol Genet* 1999; **8**: 1237–43.
9 Kelsell DP, Wilgoss AL, Richard G *et al.* Connexin mutations associated with palmoplantar keratoderma and profound deafness in a single family. *Eur J Hum Genet* 2000; **8**: 141–4.
10 Rouan F, White TW, Brown N *et al.* Trans-dominant inhibition of connexin-43 by mutant connexin-26: implications for dominant connexin disorders affecting epidermal differentiation. *J Cell Sci* 2001; **114**: 2105–13.
11 Bakirtzis G, Jamieson S, Aasen T *et al.* The effects of a mutant connexin 26 on epidermal differentiation. *Cell Commun Adhes* 2003; **10**: 359–64.
12 Korge BP, Ishida-Yamamoto A, Punter C *et al.* Loricrin mutation in Vohwinkel's keratoderma is unique to the variant with ichthyosis. *J Invest Dermatol* 1997; **109**: 604–10.
13 Sensi A, Bettoli V, Zampino MR *et al.* Vohwinkel's syndrome (mutilating keratoderma) associated with craniofacial anomalies. *Am J Med Genet* 1994; **50**: 201–3.
14 Pisoh T, Bhatia A, Oberlin C. Surgical correction of pseudo-ainhum in Vohwinkel's syndrome. *J Hand Surg* 1995; **20B**: 338–41.
15 Bart RS, Pumphrey RE. Knuckle pads, leukonychia and deafness. A dominantly inherited syndrome. *N Engl J Med* 1967; **276**: 202–7.
16 Richard G, Brown N, Ishida-Yamamoto A, Krol A. Expanding the phenotypic spectrum of Cx26 disorders: Bart-Pumphrey syndrome is caused by a novel missense mutation in GJB2. *J Invest Dermatol* 2004; **123**: 856–63.



Fig. 19.68 Mitochondrial keratoderma with deafness.

17 Alexandrino F, Sartorato EL, Marques-de-Faria AP, Steiner CE. G59S mutation in the GJB2 (connexin 26) gene in a patient with Bart-Pumphrey syndrome. *Am J Med Genet A* 2005; **136**: 282–4.

Keratoderma with hearing impairment caused by mitochondrial mutation (MIM 590080)

In a Scottish family, Reid *et al.* [1] reported familial progressive post-lingual deafness caused by specific mutation in mitochondrial DNA, encoding both a serine transfer RNA and the first subunit of cytochrome oxidase [2]. The same point mutation (A7445G) was identified in a New Zealand family who also had keratoderma, and in a previously reported Japanese pedigree of keratoderma and deafness [3,4]. The original Scottish family also has a variable plantar keratoderma (Fig. 19.68). Further pedigrees of this association have been reported [2,5–6].

References

1 Reid FM, Vernham GA, Jacobs HT. A novel mitochondrial point mutation in a maternal pedigree with sensorineural deafness. *Hum Mutat* 1994; **3**: 243–7.

2 Maasz A, Komlosi K, Hadzsiev K *et al.* Phenotypic variants of the deafness-associated mitochondrial DNA A7445G mutation. *Curr Med Chem* 2008; **15**: 1257–62.
3 Hatamochi A, Nakagawa S, Ueki H *et al.* Diffuse palmoplantar keratoderma with deafness. *Arch Dermatol* 1982; **118**: 605–7.
4 Sevior KB, Hatamochi A, Stewart IA *et al.* Mitochondrial A7445G mutation in two pedigrees with palmoplantar keratoderma and deafness. *Am J Med Genet* 1998; **75**: 179–85.
5 Martin L, Toutain A, Guillen C *et al.* Inherited palmoplantar keratoderma and sensorineural deafness associated with A7445G point mutation in the mitochondrial genome. *Br J Dermatol* 2000; **143**: 876–83.
6 Caria H, Matos T, Oliveira-Soares R *et al.* A7445G mtDNA mutation present in a Portuguese family exhibiting hereditary deafness and palmoplantar keratoderma. *J Eur Acad Dermatol Venereol* 2005; **19**: 455–8.

Keratoderma with neuropathy

Various reports associate neuropathy or spastic paralysis with keratoderma. These include striate keratoderma with spastic paraplegia, pes cavus and mental retardation in four brothers [1]; autosomal dominant punctate keratoderma and spastic paralysis [2]; autosomal dominant focal keratoderma with nail dystrophy and motor and sensory neuropathy [3]; and Charcot–Marie–Tooth disease [4]. Atypical erythrokeratoderma with deafness has also been associated with peripheral neuropathy [5]. Connexin genes seem good candidates for causative mutations [6]. In two families with a complex recessive disorder including cerebral dysgenesis and neuropathy as well as ichthyosis and keratoderma, Sprecher *et al.* identified deletions in *SNAP29*, encoding a protein involved in membrane fusion [7].

References

1 Fitzsimmons JS, Fitzsimmons EM, McLachlan JI *et al.* Four brothers with mental retardation, spastic paraplegia and palmoplantar hyperkeratosis: a new syndrome? *Clin Genet* 1983; **23**: 329–35.
2 Powell FC, Venencie PY, Gordon H, Winkelmann RK. Keratoderma and spastic paralysis. *Br J Dermatol* 1983; **109**: 589–96.
3 Tolmie JL, Wilcox DE, McWilliam R *et al.* Palmoplantar keratoderma, nail dystrophy, and hereditary motor and sensory neuropathy: an autosomal dominant trait. *J Med Genet* 1988; **25**: 754–7.
4 Rabbiosi G, Borroni G, Pinelli P, Cosi V. Palmoplantar keratoderma and Charcot–Marie–Tooth disease. *Arch Dermatol* 1980; **116**: 789–90.
5 Beare JM, Nevin NC, Froggatt P *et al.* Atypical erythrokeratoderma with deafness, physical retardation and peripheral neuropathy. *Br J Dermatol* 1972; **87**: 308–14.
6 Richard G. Connexins: a connection with the skin. *Exp Dermatol* 2000; **9**: 77–96.
7 Sprecher E, Ishida-Yamamoto A, Mizrahi-Koren M *et al.* A mutation in SNAP29, coding for a SNARE protein involved in intracellular trafficking, causes a novel neurocutaneous syndrome characterized by cerebral dysgenesis, neuropathy, ichthyosis, and palmoplantar keratoderma. *Am J Hum Genet* 2005; **77**: 242–51.

Keratoderma with periodontitis (MIM 245000)

Synonym
- Papillon–Léfèvre syndrome

In this syndrome, redness and thickening of the palms and soles is associated with periodontosis and frequent pyogenic skin infections. The prevalence has been estimated as 1–4 in 1 million [1].

Aetiology. Neutrophil phagocytosis and reactivity to T- and B-cell mitogens are impaired [2–4]. Inheritance is recessive, and the condition is caused by homozygous mutations in the gene encoding the lysosomal protease cathepsin C [5]. This finding explains the predisposition to pyogenic infection, but the mechanism of keratoderma is not established.

Pathology. Histopathological changes are non-specific, but show hyperkeratosis with irregular parakeratosis and a moderate perivascular infiltrate [6]. Electron microscopic findings include lipid-like vacuoles in the corneocytes and granulocytes, reduction in tonofilaments and irregular keratohyalin granules. These changes improve during retinoid therapy [7].

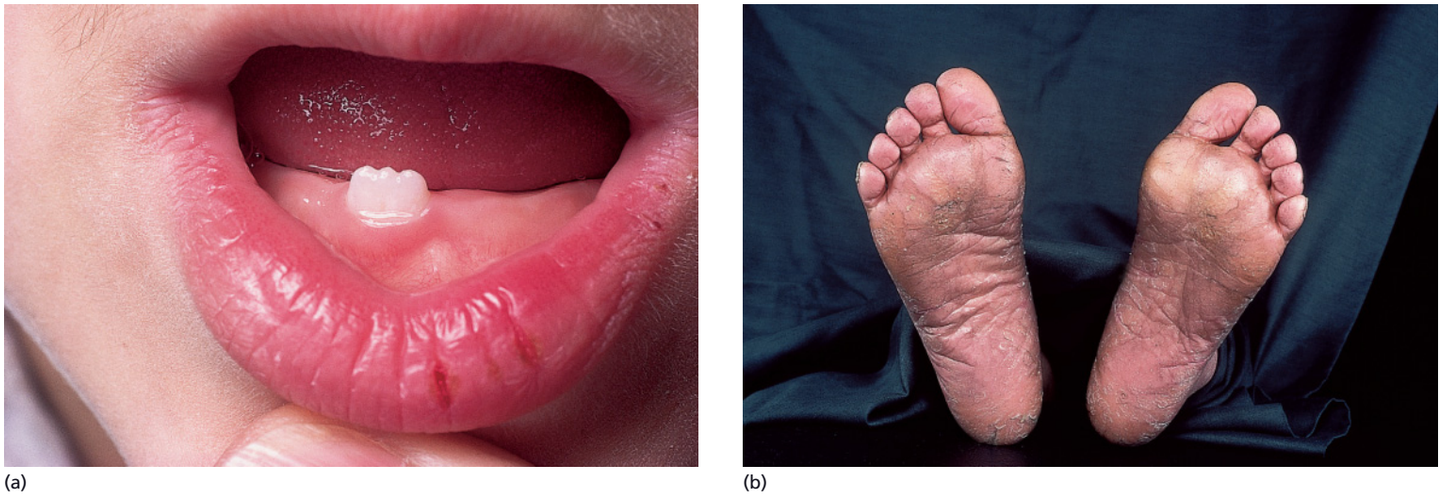
Clinical features [8,9]. Periodontosis resulting in severe gingivitis (Fig. 19.69a) in children leads to the loss of deciduous teeth by the age of 4–5 years unless treated; permanent teeth may be lost in the same fashion. Transgredient palmoplantar keratoderma, preceded by erythema, appears in the first year of life (Fig. 19.69b), and spreads to dorsal surfaces and up the Achilles tendon. Psoriasiform plaques on the knees and elbows may be present, but in a survey of 47 patients cutaneous involvement was not related to the severity of periodontal disease and did not correlate with age [9]. Virulent Gram-negative organisms invade the alveolar socket, usually including *Actinobacillus actinomycetemcomitans* [10–12]. Frequent pyogenic infections of the skin and internal organs occur. Associated hyperhidrosis causes an unpleasant odour [13]. The hair is usually normal but may be sparse [14]. Dural calcification, especially in the attachment of the tentorium and choroid, has been noted in some cases. Malignant melanoma has been reported as a complication [15].

Haim–Munk syndrome (MIM 245010). This variant syndrome combines the features of Papillon–Léfèvre syndrome with onychogryphosis, arachnodactyly and acro-osteolysis [16,17]. The syndrome is allelic with Papillon–Léfèvre syndrome, and all reported cases may be members of a single family of Cochin Jews [18]. Van Steensel *et al.* [19] reported a mother and daughter with a syndrome resembling Haim–Munk syndrome, but with hypotrichosis and an unusual linear and reticulate keratoderma, apparently not caused by mutations in cathepsin C.

Treatment. Etretinate [14,20,21], isotretinoin [22] and acitretin [7] have all been successful in improving the keratoderma, in combination with antibiotics and dental care lessening the gingival inflammation and saving the teeth [23,24].

References

1 Haneke E. The Papillon–Léfèvre syndrome: keratosis palmoplantaris with periodontopathy. *Hum Genet* 1979; **51**: 1–35.
2 Djawari D. Deficient phagocytic function in Papillon–Léfèvre syndrome. *Clin Exp Immunol* 1980; **40**: 407–10.
3 Levo Y, Wollnier S, Hacham-Zadeh S. Immunological study of patients with the Papillon–Léfèvre syndrome. *Clin Exp Immunol* 1980; **40**: 407–10.
4 Van Dyke T, Taubman M, Ebersole J. The Papillon–Léfèvre syndrome: neutrophil dysfunction with severe periodontal disease. *Clin Immunol Immunopathol* 1984; **31**: 419–29.
5 Toomes C, James J, Wood AJ *et al.* Loss-of-function mutations in the cathepsin C gene result in periodontal disease and palmoplantar keratosis. *Nat Genet* 1999; **23**: 421–4.
6 Vrahopoulos TP, Barber P, Kiakoni H *et al.* Ultrastructure of the periodontal lesion in a case of Papillon–Léfèvre syndrome (PLS). *J Clin Periodontol* 1988; **15**: 17–26.



(a) (b)

Fig. 19.69 Papillon–Léfèvre syndrome: (a) loss of dentition; and (b) diffuse plantar hyperkeratosis.

7 Nazzaro V, Blanchet-Bardon C, Mimoz C. Papillon–Léfèvre syndrome: ultrastructural study and successful treatment with acitretin. *Arch Dermatol* 1988; **124**: 533–9.
8 Hattab F, Rawashdeh MA, Yassin OM *et al.* Papillon–Léfèvre syndrome: a review of the literature and report of four cases. *J Periodontol* 1995; **66**: 413–20.
9 Ullbro C, Crossner CG, Nederfors T *et al.* Dermatologic and oral findings in a cohort of 47 patients with Papillon–Léfèvre syndrome. *J Am Acad Dermatol* 2003; **48**: 345–51.
10 Stabholz A, Taichman NS, Soskolne WA. Occurrence of *Actinobacillus actinomycetemcomitans* and anti-leukotoxin antibodies in some members of an extended family affected by Papillon–Léfèvre syndrome. *J Periodontol* 1995; **66**: 653–7.
11 Eickholz P, Kugel B, Pohl S *et al.* Combined mechanical and antibiotic periodontal therapy in a case of Papillon–Léfèvre syndrome. *J Periodontol* 2001; **72**: 542–9.
12 Robertson KL, Drucker DB, James J *et al.* A microbiological study of Papillon–Léfèvre syndrome in two patients. *J Clin Path* 2001; **54**: 371–6.
13 Bach JN, Levan NE. Papillon–Léfèvre syndrome. *Arch Dermatol* 1968; **97**: 154–8.
14 Bergman R, Friedman-Birnbaum R. Papillon–Léfèvre syndrome: a study of the long-term clinical course of recurrent pyogenic infections and the effects of etretinate treatment. *Br J Dermatol* 1988; **119**: 731–6.
15 Nakajima K, Nakano H, Takiyoshi N *et al.* Papillon–Lefevre syndrome and malignant melanoma. A high incidence of melanoma development in Japanese palmoplantar keratoderma patients. *Dermatology* 2008; **217**: 58–62.
16 Haim S, Munk J. Keratosis palmo-plantaris congenita, with periodontosis, arachnodactyly and a peculiar deformity of the terminal phalanges. *Br J Dermatol* 1965; **77**: 42–54.
17 Puliyel JM, Iyer KSS. A syndrome of keratosis palmoplantaris congenita, pes planus, onychogryphosis, periodontosis, arachnodactyly and a peculiar acro-osteolysis. *Br J Dermatol* 1986; **115**: 243–8.
18 Hart TC, Hart PS, Michalec MD *et al.* Haim–Munk syndrome and Papillon–Léfèvre syndrome are allelic mutations in cathepsin C. *J Med Genet* 2000; **37**: 88–94.
19 van Steensel MAM, van Geel M, Steijlen PM. New syndrome of hypotrichosis, striate palmoplantar keratoderma, acro-osteolysis and periodontitis not due to mutation in cathepsin C. *Br J Dermatol* 2002; **147**: 575–81.
20 Driban NE, Jung JR. Treatment of Papillon–Léfèvre syndrome with etretinate. *J Am Acad Dermatol* 1988; **18**: 583–4.
21 Gelmetti C, Nazzaro V, Cerri D *et al.* Long-term preservation of permanent teeth in a patient with Papillon–Léfèvre syndrome treated with etretinate. *Pediatr Dermatol* 1989; **6**: 222–5.
22 Nguyen TQ, Greer KE, Fisher GB *et al.* Papillon–Léfèvre syndrome: report of two patients treated successfully with isotretinoin. *J Am Acad Dermatol* 1986; **15**: 46–9.
23 Ahuja V, Shin RH, Mudgil A *et al.* Papillon-Lefevre syndrome: a successful outcome. *J Periodontol* 2005; **76**: 1996–2001.
24 Sethuraman G, Malhotra AK, Khaitan BK, Sharma VK. Effectiveness of isotretinoin in Papillon–Lefevre syndrome. *Pediatr Dermatol* 2005; **22**: 378–9.

Schöpf–Schulz–Passarge syndrome (MIM 224750)

Synonyms
- Keratoderma with eyelid cysts
- Hypodontia and hypotrichosis

In this rare autosomal recessive syndrome, diffuse palmoplantar keratoderma is associated with hypotrichosis, nail fragility and early loss of deciduous teeth [1,2]. Hydrocystomas of the eyelids but also follicular and other adnexal tumours occur in older patients [3–5].

References

1 Schöpf E, Schulz HJ, Passarge E. Syndrome of cystic eyelids, palmo-plantar keratosis, hypodontia and hypotrichosis as a possible autosomal recessive trait. *Birth Defects* 1971; **7**: 219–21.
2 Monk BE, Pieris S, Soni V. Schöpf–Schulz–Passarge syndrome. *Br J Dermatol* 1992; **127**: 33–5.
3 Burket JM, Burket BJ, Burket D. Eyelid cysts, hypodontia, and hypotrichosis. *J Am Acad Dermatol* 1984; **10**: 922–5.
4 Verplancke P, Driessen L, Wynants P, Naeyaert JM. The Schöpf–Schulz–Passarge syndrome. *Dermatology* 1998; **196**: 463–6.
5 Hampton PJ, Angus B, Carmichael AJ. A case of Schopf–Schulz–Passarge syndrome. *Clin Exp Dermatol* 2005; **30**: 528–30.

Oculocutaneous tyrosinaemia (MIM 276600) [1–5]

Synonyms
- Tyrosinaemia type II
- Tyrosine transaminase deficiency
- Richner–Hanhart syndrome

Tyrosine aminotransferase deficiency causes palmoplantar keratoderma, dendritic corneal ulcers and progressive mental impairment.

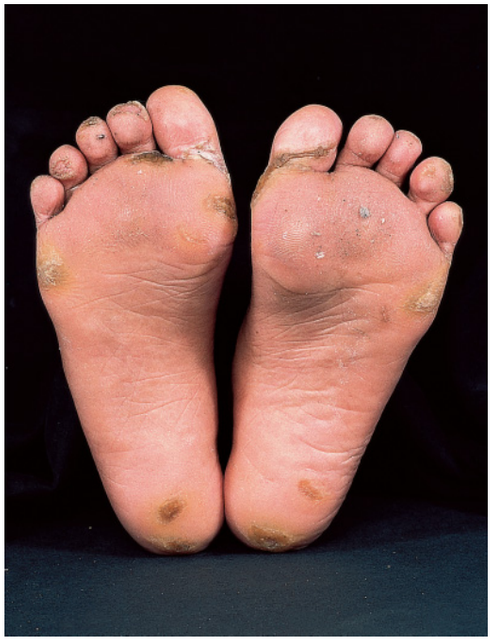


Fig. 19.70 Oculocutaneous tyrosinaemia (Richner–Hanhart syndrome). Callosity-like hyperkeratoses.

Aetiology. This autosomal recessive condition is caused by homozygous defects of the tyrosine aminotransferase gene at 16q21.1–q22.3 [6]. Deficiency of the enzyme leads to increased levels of serum tyrosine and aminoaciduria [6–8].

Pathology. Biopsy shows acanthosis with hyperkeratosis and hypergranulosis. At ultrastructural level, the keratinocytes contain clumped tonofilaments with adherent globoid keratohyalin granules resembling 'dew drops on a blade of grass' [9].

Clinical features (Fig. 19.70). In the first year of life, photophobia and corneal ulcers occur, and the diagnosis may be made by slit-lamp examination showing tyrosine crystals in ocular lesions [10]. Corneal lesions may be misdiagnosed as herpes simplex keratitis [11]. A year or two later, erythematous areas appear on the pressure-bearing areas of the soles, followed by painful circumscribed hyperkeratoses, making the child walk on the toes. In incomplete forms keratoderma may be the presenting feature [12] although conversely keratoderma may be delayed until the second decade [13]. The keratoses vary from gross keratoderma to dry lamellar patches. Bullous lesions and hyperhidrosis are sometimes seen. Unless correctly treated, behavioural problems arise within a few years and progressively worsen, ending in inanition or death. Chitayat *et al.* [14] reported two siblings with tyrosinaemia, only one of whom showed signs of the Richner–Hanhart syndrome.

Treatment. Early institution of a diet low in phenylalanine and tyrosine causes prompt resolution of the ocular and cutaneous symptoms and prevents the development of mental disorder [4,8,15–17].

References

1 Fraser NG, MacDonald J, Griffiths WAD *et al.* Tyrosinaemia type II (Richner–Hanhart syndrome): report of two cases treated with etretinate. *Clin Exp Dermatol* 1987; **12**: 440–3.

2 Goldsmith LA. Tyrosinaemia type II: lessons in molecular pathophysiology. *Pediatr Dermatol* 1983; **1**: 25–34.

3 von Hanhart E. Neue sonderformen von Keratosis palmo-plantaris, u.a. einge regelmassig-dominante mit systematisierten Lipomen, ferner 2 einfach-rezessive mit Schwachsinn und z. T. mit Hornhautveranderungen des Auges (Edtodermalsyndrom). *Dermatologica* 1947; **94**: 286–308.

4 Hunziker N. Richner–Hanhart syndrome and tyrosinemia type II. *Dermatologica* 1980; **160**: 180–9.

5 Richner H. Hornhautaffektion bei Keratoma palmare et plantare hereditarium. *Klin Monatsbl Augenheilkd* 1938; **100**: 580–8.

6 Fellman JH, Vanbellinghen PJ, Jones RT *et al.* Soluble and mitochondrial forms of tyrosine aminotransferase: relationship to human tyrosinaemia. *Biochemistry* 1969; **8**: 615–22.

7 Goldsmith LA, Thorpe JM, Roe CR. Hepatic enzymes of tyrosine metabolism in tyrosinemia. II. *J Invest Dermatol* 1979; **73**: 530–2.

8 Zaleski WA, Hill A, Krushniruk W. Skin lesions in tyrosinosis: response to dietary treatment. *Br J Dermatol* 1973; **88**: 335–40.

9 Bohnert A, Anton-Lamprecht I. Richner–Hanhart's syndrome: ultrastructural abnormalities of epidermal keratinization indicating a causal relationship to high intracellular tyrosine levels. *J Invest Dermatol* 1982; **79**: 68–74.

10 Gipson IK, Burns RP, Wolfe-Lande JD. Crystals in corneal epithelial lesions of tyrosine-fed rats. *Invest Ophthalmol* 1975; **14**: 937–41.

11 al-Hemidan AI, al-Hazzaa SA. Richner–Hanhart syndrome (tyrosinemia type II): case report and literature review. *Ophthal Genet* 1995; **16**: 21–6.

12 Viglizzo GM, Occella C, Bleidl D, Rongioletti F. Richner–Hanhart syndrome (tyrosinemia II): early diagnosis of an incomplete presentation with unusual findings. *Pediatr Dermatol* 2006; **23**: 259–61.

13 Podglajen-Wecxsteen O, Delaporte E, Piette F *et al.* Tyrosinose oculo-cutanée de type II. *Ann Dermatol Vénéréol* 1993; **120**: 139–42.

14 Chitayat D, Balbut A, Hani V *et al.* Hereditary tyrosinaemia type II in a consanguineous Ashkenazi Jewish family: intrafamilial variation in phenotype; absence of parental phenotype effects on the fetus. *J Inherit Metab Dis* 1992; **15**: 198–203.

15 Paige DG, Clayton P, Bowron A *et al.* Richner–Hanhart syndrome (oculo-cutaneous tyrosinaemia, tyrosinaemia type II). *J R Soc Med* 1992; **85**: 759–60.

16 Danks DM, Callan NJ. Palmoplantar keratoderma with normal intelligence in tyrosinaemia II. *J Dermatol* 1988; **29**: 107–9.

17 Ney D, Bay C, Schneider JA. Dietary management of oculocutaneous tyrosinaemia in an 11-year-old child. *Am J Dis Child* 1983; **137**: 995–1000.

Punctate and porokeratotic keratodermas (MIM 148600)

Synonym

- Brauer–Buschke–Fischer keratoderma

Punctate keratodermas differ from focal ones in showing a random distribution of small rounded papular lesions, but clinical differentiation is not always possible. The various terms used for morphological patterns of punctate keratoderma—keratoma dissipatum; keratoderma punctata, papulosa; disseminated clavus; papulotranslucent acrokeratoderma—probably do not justify distinction [1]. Excepting pedigrees with parakeratotic histology, the delineation of entities is uncertain.

Punctate keratoderma [1–4]. This autosomal dominant condition has a much later onset than other hereditary keratodermas, with lesions appearing in the second or third decades or later. Loci at 15q22–15q22.31 [5,6] and 8q24.13–8q24.21 [7] are reported. Occasional reports of punctate PPK with macular pigmentation [8,9]

suggest a mechanistic relationship with chronic arsenicism. Pinpoint, hard keratotic papules, initially translucent but later opaque and warty, appear on the palms and soles (Fig. 19.71). In many families, small and large lesions coexist, including broader focal plantar callosities. Lesions are more florid in manual workers. There is no hyperhidrosis. In most cases, punctate lesions are orthokeratotic on histology. Multiple associations of punctate keratoderma have been described, including association with diverse Lynch type II malignancies [10–12]. Topical retinoids and calcipotriol have only a slight effect on softening the keratoses but may be tried. Results with systemic retinoids are better but variable. Etretinate 0.5–1 mg/kg/day produced good results in three patients, moderate in four and no effect in two patients [13]; acitretin was rapidly effective in another case [14]. Intravenous infusion of 5-fluorouracil produced sustained benefit in a father and son with punctate PPK [15].

The terms punctate PPK type II (MIM 175860) or porokeratosis of Mantoux have been used for cases with parakeratotic histology, but the parakeratosis is columnar rather than lamellar and the suggestion of a relationship to porokeratosis [16] is probably misleading. It has been reported that these lesions fluoresce under Wood's light [17]. Some pedigrees show crateriform lesions or keratoses that can be picked out; histology of these lesions shows parakeratosis [10,16]. A linear distribution of punctate lesions is seen in porokeratotic eccrine ostial and dermal duct naevus (see Chapter 18).

Punctate keratoses of the palmar creases [18–20] is characterized by hard warty lesions of the finger and palmar creases (Fig. 19.72a), often with a clavus-like lesion at the medial border of the distal palmar crease. The absence of marginal lesions distinguishes this entity from marginal papular acrokeratodermas. It is inherited as an autosomal dominant trait and has been reported mainly in patients of African origin. Lesions may coexist with punctate or nummular keratoderma (Fig. 19.72b) [21].



Fig. 19.71 Punctate keratoderma: small even keratotic papules on the palms.

References

1 Stanimirovic A, Kansky A, Basta-Juzbasic A *et al*. Hereditary palmoplantar keratoderma, type papulosa, in Croatia. *J Am Acad Dermatol* 1993; **29**: 435–7.

2 Heierli-Forrer E. Zur Klinik un Genetik der hereditaren papulosen Palmoplantarkeratosen. *Dermatologica* 1959; **119**: 309–27.

3 Hesse S, Berbis P, Privat Y. Keratodermia palmo-plantaris papulosa (Buschke–Fischer's disease): efficacy of acitretin. *Br J Dermatol* 1993; **128**: 104–5.

4 Emmert S, Kuster W, Hennies HC *et al*. 47 patients in 14 families with the rare genodermatosis keratosis punctata palmoplantaris Buschke-Fischer-Brauer. *Eur J Dermatol* 2003; **13**: 16–20.

5 Martinez-Mir A, Zlotogorski A, Londono D *et al*. Identification of a locus for type I punctate palmoplantar keratoderma on chromosome 15q22–q24. *J Med Genet* 2003; **40**: 872–8.

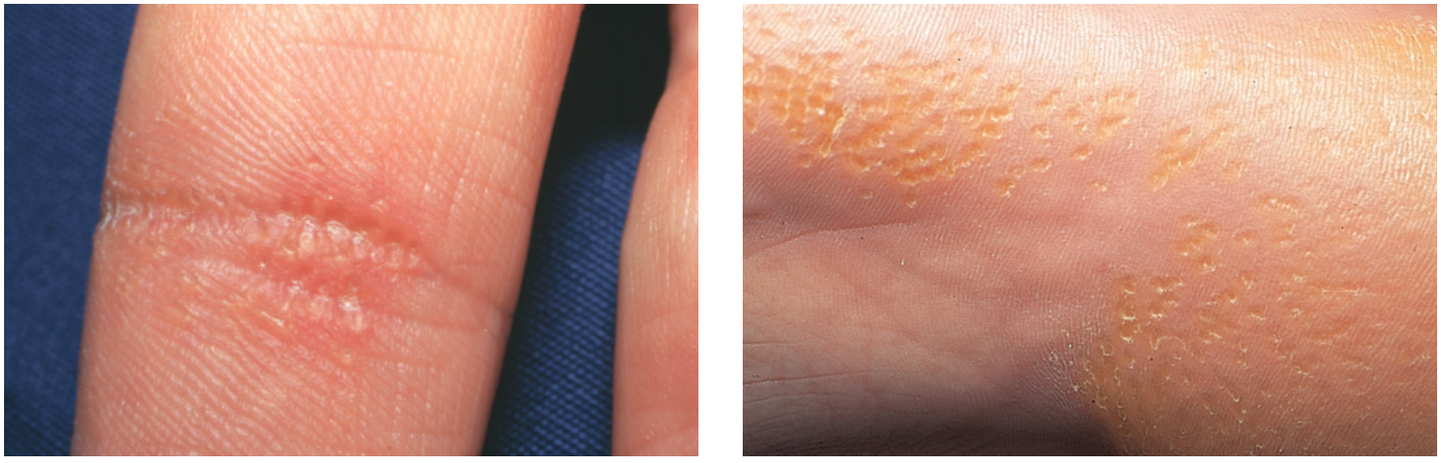
6 Gao M, Yang S, Li M *et al*. Refined localization of a punctate palmoplantar keratoderma gene to a 5.06-cM region at 15q22.2–15q22.31. *Br J Dermatol* 2005; **152**: 874–8.

7 Zhang XJ, Li M, Gao TW *et al*. Identification of a locus for punctate palmoplantar keratodermas at chromosome 8q24.13–8q24.21. *J Invest Dermatol* 2004; **122**: 1121–5.

8 Horikoshi M, Kuroda K, Tajima S. Punctate palmoplantar keratoderma with pigmentary lesions on the dorsa of feet and ankles: successful treatment with a combination of low-dose oral etretinate and topical calcipotriol. *J Dermatol* 2004; **31**: 469–72.

9 Erkek E, Erdogan S, Tuncez F *et al*. Type I hereditary punctate keratoderma associated with widespread lentigo simplex and successfully treated with low-dose oral acitretin. *Arch Dermatol* 2006; **142**: 1076–7.

10 Bianchi L, Orlandi A, Iraci S. Punctate porokeratotic keratoderma: its occurrence with internal neoplasia. *Clin Exp Dermatol* 1994; **19**: 139–41.



(a) (b)

Fig. 19.72 (a) Punctate keratoderma of the palmar creases; and (b) plantar lesions in the same patient.

11 Bennion SD, Patterson JW. Keratosis punctata palmaris et plantaris and adenocarcinoma of the colon. *J Am Acad Dermatol* 1984; **10**: 587–91.
12 Stevens HP, Kelsall DP, Leigh IM *et al.* Punctate palmoplantar keratoderma and malignancy in a four generation family. *Br J Dermatol* 1996; **134**: 720–6.
13 Christiansen JV. Keratodermia punctata hereditaria treated with etretinate (Tigason). *Acta Derm Venereol (Stockh)* 1983; **63**: 181–2.
14 Smith EB, Jetton RL. Punctate pits and keratoses of the palmar creases. *South Med J* 1970; **63**: 1291–3.
15 Lienemann AO, Colucci VJ, Jones MS, Trauscht JM. Treatment of palmoplantar keratoderma with continuous infusion 5-fluorouracil. *Cutis* 2004; **73**: 303–8.
16 Friedman SJ, Herman PS, Pittelkow MR. Punctate porokeratotic keratoderma. *Arch Dermatol* 1988; **124**: 1678–82.
17 Erkek E, Ayva S. Wood's light excites white fluorescence of type I hereditary punctate keratoderma. *J Eur Acad Dermatol Venereol* 2007; **21**: 993–4.
18 Weiss RM, Rasmussen JE. Dermatosis punctata of the palmar creases. *Arch Dermatol* 1980; **116**: 669–71.
19 Del Rio E, Vazquez-Vega H, Aguilar A *et al.* Keratosis punctata of the palmar creases: a report on three generations, demonstrating an association with ichthyosis vulgaris and evidence of involvement of the acrosyringium. *Clin Exp Dermatol* 1994; **19**: 165–7.
20 Penas PF, Rios-Buceta L, Sanchez-Perez J *et al.* Keratosis punctata of the palmar creases: case report and prevalence study in Caucasians. *Dermatology* 1994; **188**: 200–2.
21 Lucker GP, Steijlen PM. Keratosis palmoplantaris varians et punctata: clinical variability of an single genetic defect? *Hautarzt* 1996; **47**: 858–9.

Filiform keratodermas

Synonym
- Music box spine keratoderma

Fine keratotic lesions that project a millimetre or so from the palmoplantar surface are variously described as filiform, spiked, spiculate, spiny, minute digitate, minute aggregate and music box spine keratodermas (Fig. 19.73). Like disseminated filiform keratoses, large morphological differences within this group probably reflect distinct aetiologies. Lesions may be inherited as an autosomal dominant trait, when they appear in the second or third decade [1]. They may be sporadic, and may involve other parts of the skin or palms and soles alone. Histology may show compact orthohyperkeratosis or parakeratosis resembling porokeratosis [2]. Attempts have been made to provide a unifying clinical classification based on histological features and distribution [3–5]. Tosti *et al.* [6] found dyskeratotic foci in the nail matrix. Hashimoto *et al.* [7] demonstrated the presence of hair-type keratin immunostaining in the lesions, suggesting that spiny keratoderma may represent ectopic hair formation. Reported associations include polycystic kidneys and liver [8], Darier's disease [3,9], epidermodysplasia verruciformis [10], renal failure [11], tuberculosis [12], hyperlipidaemia [13] and malignancy [5,14–16]. Profuse filiform keratoses are also associated with multiple myeloma and with HIV-associated PRP.



Fig. 19.73 Filiform keratoderma. Present since age 20 on palms and soles. Son and daughter also affected.

Treatment. Keratolytics are usually prescribed but are rarely successful. Etretinate gave variable slight improvement [10] or good results [6]. Topical 5-fluorouracil ointment cleared the lesions temporarily in one patient [2] but failed in another [8].

References

1 Lestringant GG, Berge T. Porokeratosis punctata palmaris et plantaris: a new entity? *Arch Dermatol* 1989; **125**: 816–9.
2 Osman Y, Daly TJ, Don PC. Spiny keratoderma of the palms and soles. *J Am Acad Dermatol* 1992; **26**: 879–81.
3 Zarour H, Grob JJ, Andrac L *et al.* Palmoplantar orthokeratotic filiform hyperkeratosis in a patient with associated Darier's disease: classification of filiform hyperkeratosis. *Dermatology* 1992; **185**: 205–9.
4 McGovern TW, Gentry RH. Spiny keratoderma: case report, classification, and treatment of music box spine dermatoses. *Cutis* 1994; **54**: 389–94.
5 Kaddu S, Soyer P, Kerl H. Palmar filiform hyperkeratosis: a new paraneoplastic syndrome? *J Am Acad Dermatol* 1995; **33**: 337–40.
6 Tosti A, Morelli R, Fanti PA *et al.* Nail changes of punctate keratoderma: a clinical and pathological study of two patients. *Acta Derm Venereol (Stockh)* 1993; **73**: 66–8.
7 Hashimoto K, Toi Y, Horton S, Sun TT. Spiny keratoderma: a demonstration of hair keratin and hair type keratinization. *J Cutan Pathol* 1999; **26**: 25–30.
8 Anderson D, Cohen DE, Lee HS *et al.* Spiny keratoderma in association with autosomal dominant polycystic kidney disease with liver cysts. *J Am Acad Dermatol* 1996; **34**: 935–6.
9 Salmon-Ehr V, Grosieux C, Derancourt C *et al.* Palmoplantar filiform hyperkeratosis with Darier's disease: association or coincidence? *Eur J Dermatol* 1998; **8**: 519–20.
10 Caputo R, Cavicchini S, Brezzi A, Grimalt R. Spiny hyperkeratosis of the fingers as an unusual sign of epidermodysplasia verruciformis. *J Am Acad Dermatol* 1995; **32**: 523–4.
11 Feldmann R, Harms M. Multiple filiforme Hyperkeratosen. *Hautarzt* 1993; **44**: 658–61.
12 Gimenez-Arnau A, Camarasa JG. Palmar filiform or spiny hyperkeratosis associated with pulmonary tuberculosis. *J Eur Acad Derm Venereol* 1994; **3**: 400–6.
13 Urbani CE, Moneghini L. Palmar spiny keratoderma associated with type IV hyperlipoproteinemia. *J Eur Acad Dermatol Venereol* 1998; **10**: 262–6.
14 Handa Y, Sakakibara A, Araki M, Yamanaka N. Spiny keratoderma of the palms and soles: report of two cases. *Eur J Dermatol* 2000; **10**: 542–5.
15 Bernal AI, Gonzalez A, Aragoneses H *et al.* A patient with spiny keratoderma of the palms and a lymphoproliferative syndrome: an unrelated paraneoplastic condition? *Dermatology* 2000; **201**: 379–80.
16 Mehta RK, Mallett RB, Green C, Rytina E. Palmar filiform hyperkeratosis (FH) associated with underlying malignancy. *Clin Exp Dermatol* 2002; **27**: 216–9.

Marginal papular keratodermas [1,2]

Costa [3,4] reported 13 cases with cornified and umbilicated papules distributed along the borders of the hands and feet (Fig. 19.74). He noted fragmentation and rarefaction of elastic fibres in the dermis, and introduced the term acrokeratoelastoidosis. Fiallo *et al.* [5] argued that the primary defect is in the elastic tissue. However, Dowd *et al.* [6] reported 15 cases, several familial, with



Fig. 19.74 Marginal papular keratoderma: crateriform punctate keratoses at the margin of the sole (Wallace's line).



Fig. 19.75 Aquagenic syringeal acrokeratoderma showing whitish maceration of palmar skin following immersion. (Courtesy of Dr G. Kavanagh, Royal Infirmary of Edinburgh.)

similar oval or polygonal crateriform papules along the borders of the hands and feet in whom there was no solar damage or elastorrhexis. To distinguish this entity, it was termed focal acral hyperkeratosis. However, eight of Costa's 13 patients [3] appear identical. One patient illustrated by Dowd *et al.* [6] also had marked punctate keratoses of the palmar creases. Many patients with these disorders are of Afro-Caribbean origin, but a Filipino patient with focal acral hyperkeratosis and hearing loss has been reported [7].

Rongioletti *et al.* [1] suggest unifying the marginal papular keratodermas with a pragmatic division into the hereditary type with elastorrhexis (acrokeratoelastoidosis), or without it (focal acral hyperkeratosis), and an acquired type, degenerative collagenous plaques [8–11]. The latter are firm plaques, sometimes concave, forming a linear band principally around the web of the thumb and index finger at the margin of the volar and dorsal surfaces. There is marked clinical and histological evidence of solar damage. Pathogenesis and a possible relationship with knuckle pads is discussed by Abulafia and Vignale [11].

Mosaic acral keratosis. Jacyk and Smith [12] reported African patients with widespread polygonal papular lesions over the ankles and shins under the title mosaic acral keratosis. It is not a marginal keratoderma [13] but is included here for convenience, as Costa's case 13 [3] had similar features.

References

1 Rongioletti F, Betti R, Crosti C, Rebora A. Marginal papular acrokeratodermas: a unified nosography for focal acral hyperkeratosis, acrokeratoelastoidosis and related disorders. *Dermatology* 1994; **188**: 28–31.
2 Hafner O, Gerstel C, Schroder B. Focal acral hyperkeratosis. *Hautarzt* 1999; **50**: 586–9.
3 Costa OG. *Acroceratoses* [thesis]. University of Minas Gerais, Brazil, 1964.
4 Costa OG. Acrokeratoelastoidosis. *Arch Dermatol* 1954; **70**: 228–31.
5 Fiallo P, Pesce C, Brusasco A, Nunzi E. Acrokeratoelastoidosis of Costa: a primary disease of the elastic tissue? *J Cutan Pathol* 1998; **25**: 580–2.
6 Dowd PM, Harman RRM, Black MM. Focal acral hyperkeratosis. *Br J Dermatol* 1983; **109**: 97–103.
7 Lambiris AG, Newman PL. Marginal papular acrokeratodermas: no racial limitations for a clinical spectrum that responds to acitretin. *Dermatology* 2001; **203**: 63–5.
8 Burks JW, Wise LJ, Clark WH. Degenerative collagenous plaques of the hands. *Arch Dermatol* 1960; **82**: 362–6.
9 Kocsard E. Keratoelastoidosis marginalis of the hands. *Dermatologica* 1964; **131**: 169–75.
10 Ritchie EB, Williams HM. Degenerative collagenous plaques of the hands. *Arch Dermatol* 1966; **93**: 202–3.
11 Abulafia J, Vignale RA. Degenerative collagenous plaques of the hands and acrokeratoelastoidosis: pathogenesis and relationship with knuckle pads. *Int J Dermatol* 2000; **39**: 424–32.
12 Jacyk WK, Smith A. Mosaic acral keratosis. *Clin Exp Dermatol* 1990; **15**: 361–2.
13 Jacyk WK. Marginal papular acrokeratodermas: classification. *Dermatology* 1995; **190**: 178.

Miscellaneous keratoderma syndromes

Aquagenic syringeal acrokeratoderma. Several patients are reported in whom a subtle keratoderma is revealed by sweating or immersion (Fig. 19.75) [1–4]. Patients typically bring a vessel in order to immerse the hand in water and demonstrate the signs [3]. The painful, whitish papular lesions are associated with dilated acrosyringeal ostia; Kabashima *et al.* found altered expression of the water channel protein, aquaporin 5 [5]. Botulinum toxin has been successfully used to treat this condition [6].

Acro-osteolysis with keratoderma (Bureau–Barrière syndrome) [7,8]. Marked diffuse keratoderma is associated with osteolysis in the forefoot area, polyneuropathy of the lower legs and painless ulcers of the feet. Finger clubbing is a feature of this syndrome [9–11].

Papillomatoverrucous palmoplantar keratoderma. The association of a florid warty keratoderma, dysplastic teeth and follicular keratoses was reported by Jacak and Wolf in four siblings in one family, with a possible autosomal recessive mode of inheritance [12]. Baran and Juhlin [13] reported a similar case, which responded to etretinate.

Symmetrical interdigital keratoderma. This is a sporadic condition of the hands, in which thickening of the interdigital spaces occurs from the second decade. The absence of occupational or

other factors and the poor response to corticosteroids or keratolytics were said to be features supporting the diagnosis [14,15].

Circumscribed hypokeratosis of the palms and soles [16,17]. This occurs in middle aged women and is characterized by solitary atrophic lesions with reduced stratum corneum and granular cell layer, and intraepidermal vacuolation [18]. It may respond to topical calcipotriol [19], cryotherapy [20], or photodynamic therapy [21].

References

1 English JC, McCollough ML. Transient reactive papulotranslucent acrokeratoderma. *J Am Acad Dermatol* 1996; **34**: 686–7.
2 Lowes MA, Khaira GS, Holt D. Transient reactive papulotranslucent acrokeratoderma associated with cystic fibrosis. *Australas J Dermatol* 2000; **41**: 172–4.
3 Itin PH, Lautenschlager S. Aquagenic syringeal acrokeratoderma (transient reactive papulotranslucent acrokeratoderma). *Dermatology* 2001; **204**: 8–11.
4 Yan AC, Aasi SZ, Alms WJ *et al.* Aquagenic palmoplantar keratoderma. *J Am Acad Dermatol* 2001; **44**: 696–9.
5 Kabashima K, Shimauchi T, Kobayashi M *et al.* Aberrant aquaporin 5 expression in the sweat gland in aquagenic wrinkling of the palms. *J Am Acad Dermatol* 2008; **59**: S28–32.
6 Diba VC, Cormack GC, Burrows NP. Botulinum toxin is helpful in aquagenic palmoplantar keratoderma. *Br J Dermatol* 2005; **152**: 394–5.
7 Rauch H-J, Neumayer K. Bureau–Barriere–Thomas-Syndrom eine seltene hereditare Palmoplantarkeratose mit assoziierten Symptomen. *Z Hautkr* 1980; **56**: 102–8.
8 Thoma E, Ruzicka T, Donhauser G *et al.* Klinik und therapie des Bureau–Barriere-Syndroms: Beobachtungen an 17 Fallen mit Literaturubersicht. *Hautarzt* 1993; **44**: 5–13.
9 Hedstrand H, Berglund G, Werner I. Keratoderma palmaris et plantaris with clubbing and skeletal deformity of the terminal phalanges of the hands and feet: report of findings in two sisters. *Acta Derm Venereol (Stockh)* 1972; **52**: 278–80.
10 Koch HJ, Hubner U, Schaarschmidt E, Thiel W. Keratosis palmoplantaris with clubbed fingers, hypotrichosis, hypohidrosis and dental dysplasia. *Hautarzt* 1991; **42**: 399–401.
11 Barraud-Klenovsek MM, Lubbe J, Burg G. Primary digital clubbing associated with palmoplantar keratoderma. *Dermatology* 1997; **194**: 302–5.
12 Jacak D, Wolf A. Papillomatos-verrukose Form der palmo-plantaren Keratodermie kombiniert mit anderen Anomalien der Verhornung sowie dysplastischen Zahnveranderungen. *Hautarzt* 1975; **26**: 25–9.
13 Baran R, Juhlin L. Keratodermia palmoplantare papuloverrucoides progressiva: successful treatment with etretinate. *J Am Acad Dermatol* 1983; **8**: 700–2.
14 Patrizi A, Neri I, Di Lernia V *et al.* Symmetrical interdigital hyperkeratosis of the hands: a new case. *Acta Derm Venereol (Stockh)* 1993; **73**: 459–60.
15 Di Lernia V, Cavazza A, Bisighini G. Symmetrical interdigital keratoderma of the hands. *Clin Exp Dermatol* 1995; **20**: 240–1.
16 Pérez A, Rütten A, Gold R *et al.* Circumscribed palmar or plantar hypokeratosis: a distinctive epidermal malformation of the palms or soles. *J Am Acad Dermatol* 2002; **47**: 21–7.
17 Lee SE, Kim YC, Kim SC. Circumscribed palmar or plantar hypokeratosis: report of a Korean case published work review. *J Dermatol* 2006; **33**: 403–5.
18 Ishiko A, Dekio I, Fujimoto A *et al.* Abnormal keratin expression in circumscribed palmar hypokeratosis. *J Am Acad Dermatol* 2007; **57**: 285–91.
19 Urbina F, Misad C, Gonzalez S. Circumscribed palmar hypokeratosis: clinical evolution and ultrastructural study after prolonged treatment with topical calcipotriol. *J Eur Acad Dermatol Venereol* 2005; **19**: 491–4.
20 Boffa MJ, Degaetano JS. Circumscribed palmar hypokeratosis: successful treatment with cryotherapy. *J Eur Acad Dermatol Venereol* 2007; **21**: 420–1.
21 Benoit S, Seitz CS, Hamm H *et al.* Circumscribed palmar hypokeratosis: partial remission by photodynamic therapy. *Br J Dermatol* 2007; **157**: 804–6.

Keratoderma and cancer

Cancers may arise in keratodermatous skin. Squamous and verrucous carcinomas are common in Huriez syndrome [1]. Isolated cases are reported in mutilating keratoderma [2], porokeratosis [3] and Clouston's syndrome [4] or with non-syndromic focal or diffuse PPKs [5,6]. Melanoma of affected skin is reported in various keratodermas [7–12]. Nakajima *et al.* suggest that it may be more common in Japanese keratoderma patients because of the increased incidence of acral melanoma in this population [13]. Predisposition to internal cancer may be part of a keratoderma syndrome, of which the Howel-Evans' syndrome (see p. 19.106) is best known. A reported association between epidermolytic keratoderma caused by keratin 9 mutation and breast and ovarian cancer [14–16] is not a general feature of this syndrome. Familial punctate keratoderma has been reported with a variety of malignancies [17–20].

Acquired keratoderma may be paraneoplastic. In addition to 'tripe palms' (see p. 19.120), and Bazex's acrokeratosis paraneoplastica (see Chapter 62), reports include acquired diffuse PPK with cancer of the bronchus [21,22], and filiform PPK with cancer of the breast, colon and kidney [23–25].

Carcinogens, of which the best documented example is arsenic, may produce both keratoderma and internal malignancy [26,27]. One survey showed that palmar keratoses occur four to five times more frequently in patients with cancer than in controls [28]. An increased incidence of keratoses in patients with lung or bladder cancer has been debated [29–31]. Smoking [29] and papillomavirus infection [30] are suggested culprits. Keratoses associated with cancer are histologically distinct from arsenical keratoses [32].

Agents used in cancer treatment commonly cause palmoplantar erythema (the hand–foot syndrome) and may cause keratoderma [32–35].

References

1 Delaporte E, N'guyen-Mailfer C, Janin A *et al.* Keratoderma with scleroatrophy of the extremities or sclerotylosis (Huriez syndrome): a reappraisal. *Br J Dermatol* 1995; **133**: 409–16.
2 Barnett JH, Estes SA. Multiple epitheliomata cuniculata occurring in a mutilating keratoderma. *Cutis* 1985; **35**: 345–7.
3 Abadir R, Zurowski S. Case report: squamous cell carcinoma of the skin in both palms, axillary node, donor skin graft site and both soles—associated hyperkeratosis and porokeratosis. *Br J Radiol* 1994; **67**: 507–10.
4 Ena P, Mazzarello V. Hydrotic ectodermal dysplasia (Clouston syndrome) with deafness, strabismus, nystagmus, cutaneous squamous cell carcinoma, oral leukoplakia and other anomalies: report of a previously undescribed case. *G Ital Dermatol Venereol* 1998; **133**: 285–9.
5 Rogozinski TT, Schwartz RA, Towpik E. Verrucous carcinoma in Unna-Thost hyperkeratosis of the palms and soles. *J Am Acad Dermatol* 1994; **31**: 1061–2.
6 Affleck AG, Leach IH, Littlewood SM. Carcinoma cuniculatum arising in focal plantar keratoderma. *Dermatol Surg* 2007; **33**: 745–8.
7 Hacham-Zadeh S, Goldberg L. Malignant melanoma and Papillon–Léfèvre syndrome. *Arch Dermatol* 1982; **118**: 2.
8 Seike T, Nakanishi H, Urano Y, Arase S. Malignant melanoma developing in an area of palmoplantar keratoderma (Greither's disease). *J Dermatol* 1995; **22**: 55–61.
9 Aygit AC, Baycin HN, Demiralay A. Malignant melanoma in association with palmoplantar keratoderma. *Eur J Plast Surg* 1999; **22**: 49–50.
10 Rubegni P, Poggiali S, Cuccia A *et al.* Acral malignant melanoma and striated palmoplantar keratoderma (Brunauer-Fohs-Siemens syndrome): a fortuitous association? *Dermatol Surg* 2004; **30**: 1539–42.
11 Dessureault J, Poulin Y, Bourcier M, Gagne E. Olmsted syndrome-palmoplantar and periorificial keratodermas: association with malignant melanoma. *J Cutan Med Surg* 2003; **7**: 236–42.
12 Mozzillo N, Nunziata CA, Caraco C *et al.* Malignant melanoma developing in an area of hereditary palmoplantar keratoderma (Mal de Meleda). *J Surg Oncol* 2003; **84**: 229–33.

13 Nakajima K, Nakano H, Takiyoshi N *et al.* Papillon–Lefevre syndrome and malignant melanoma. A high incidence of melanoma development in Japanese palmoplantar keratoderma patients. *Dermatology* 2008; **217**: 58–62.
14 Chevrant-Breton J, Kerbrat P, Le-Marec B *et al.* Keratodermie palmoplantaire epidermolytique, autosomique dominante et adenocarcinomes familiaux (etude de 4 generations). *Ann Dermatol Vénéréol* 1985; **112**: 841–4.
15 Blanchet-Bardon C, Nazzaro V, Chevrant-Breton J *et al.* Hereditary epidermolytic palmoplantar keratoderma associated with breast and ovarian cancer in a large kindred. *Br J Dermatol* 1987; **117**: 363–70.
16 Torchard D, Blanchet-Bardon C, Serova O *et al.* Epidermolytic palmo-plantar keratoderma cosegregates with a keratin 9 mutation in a pedigree with breast and ovarian cancer. *Nat Genet* 1994; **6**: 106–10.
17 Ena P, Cottoni F, Cerimele D *et al.* Associazione della cheratodermia palmoplantare punctata con altre condizioni morbose (canizie precoce, carcinoma del colon): studio su tre famiglie. *G Ital Dermatol Venereol* 1986; **121**: 45–54.
18 Bennion SD, Patterson JW. Keratosis punctata palmaris et plantaris and adenocarcinoma of the colon: a possible familial association of punctate keratoderma and gastrointestinal malignancy. *J Am Acad Dermatol* 1984; **10**: 587–91.
19 Stevens HP, Kelsell DP, Leigh IM *et al.* Punctate palmoplantar keratoderma and malignancy in a four-generation family. *Br J Dermatol* 1996; **134**: 720–6.
20 Kerdel FA, MacDonald DM. Palmo-plantar keratoderma associated with carcinoma of the bronchus. *Acta Derm Venereol (Stockh)* 1982; **62**: 178–80.
21 Murata Y, Kumano K, Tani M *et al.* Acquired diffuse keratoderma of the palms and soles with bronchial carcinoma: report of a case and review of the literature. *Arch Dermatol* 1988; **124**: 497–8.
22 Khanna SK, Agnone FA, Leibowitz AI *et al.* Non-familial diffuse palmoplantar keratoderma associated with bronchial carcinoma. *J Am Acad Dermatol* 1993; **28**: 295–7.
23 Hillion B, Le-Bozec P, Moulonguet-Michaut I *et al.* Hyperkeratose palmo-plantaire filiforme et cancer du sein. *Ann Dermatol Vénéréol* 1990; **117**: 834–6.
24 Fegueux S, Bilet S, Crickx B *et al.* Hyperkeratose palmo-plantaire filiforme et cancer recto-sigmoidien. *Ann Dermatol Vénéréol* 1988; **115**: 1145–6.
25 Beylot C, Taieb A, Bioulac P *et al.* Hyperkeratose palmo-plantaire filiforme et neoplasie viscerale. *Ann Dermatol Vénéréol* 1982; **109**: 747–8.
26 Junge J, Moll I. Multiple palmoplantarkeratosen, basaliome und porokarzinome nach Arsen-therapie. *Hautarzt* 1995; **46**: 198–201.
27 Jackson R, Grainge JW. Arsenic and cancer. *Can Med Assoc J* 1975; **113**: 396–401.
28 Dobson RL, Young MR, Pinto JS. Palmar keratoses and cancer. *Arch Dermatol* 1965; **92**: 553–6.
29 Cuzick J, Harris R, Mortimer PS. Palmar keratoses and cancers of the bladder and lung. *Lancet* 1984; **i**: 530–3.
30 Cartwright RA, Glashan RW. Palmar keratoses and bladder cancer. *Lancet* 1984; **i**: 563.
31 Rhodes EL. Palmar and plantar seed keratoses and internal malignancy. *Br J Dermatol* 1970; **82**: 361–3.
32 Woodside JR, Dobson RL. Histopathology of palmar keratoses associated with cancer. *Arch Dermatol* 1968; **98**: 648–51.
33 Jucglà A, Sais G, Navarro M *et al.* Palmoplantar keratoderma secondary to chronic acral erythema due to tegafur. *Arch Dermatol* 1995; **131**: 364–5.
34 Do JE, Kim YC. Capecitabine-induced diffuse palmoplantar keratoderma: is it a sequential event of hand–foot syndrome? *Clin Exp Dermatol* 2007; **32**: 519–21.
35 Lountzis NI, Maroon MS. Sorafenib-induced palmoplantar hyperkeratosis. *J Drugs Dermatol* 2008; **7**: 588–9.

Other acquired keratodermas

Callosities or more extensive thickening of plantar epidermis is a common concomitant of obesity [1], and symptomatic plantar hyperkeratosis is common with increasing age or orthopaedic problems.

Keratodermas caused by other dermatoses. Palmar or plantar lesions occur in a wide range of dermatoses [2]. In psoriasis, both diffuse gross and centripalmar hyperkeratosis are seen. A scalloped margin (*Festonné*), Caro–Senear lesions (depressed plaques) on the sides of the fingers and involvement of the knuckles may suggest the diagnosis. The lesions of Reiter's disease are compact, heaped up and resemble the heads of nails (keratoderma blenorrhagica). The even yellow hyperkeratosis of PRP is associated with an acute follicular eruption in adults and by lesions on the knees and elbows in children. Extensive hyperkeratotic eczema may be difficult to distinguish on clinical and histological grounds from keratoderma but marked itching may indicate eczema. Trichophytosis, especially resulting from *Trichophyton rubrum*, may be unilateral and lacking in inflammatory signs. Keratoderma may be seen in crusted scabies (Fig. 19.76). The tendency of secondary syphilis lesions to involve the palms is well known, and hyperkeratotic late syphilides may be warty or focal [3]. In late yaws, keratoderma may induce a peculiar crab-like gait in those affected. In immunocompromised patients, viral warts may be confluent on the palms or soles. Lupus erythematosus may show dry and atrophic [4], hypertrophic (Fig. 19.77) [5] or ulcerative [6] palmar lesions. Antidesmocollin 3 antibodies were found in a patient with an immunobullous disorder and acquired diffuse PPK [7]. In lichen planus, warty lesions may be mistaken for viral warts, and it and lichen nitidus may mimic punctate keratoderma [8]. Keratoderma may be seen as a result of hypersensitivity to drugs such as iodine. Keratoderma may result from tegafur, glucan, lithium and halogenated weed-killers, and dioxin intoxication [9–13]. Arsenical induced irregular warty keratoses, or more even glassy lesions, are still occasionally seen [14].



Fig. 19.76 Norwegian scabies causing keratoderma. (Courtesy of Dr N. Walker, Oxford Radcliffe Hospital, Oxford, UK.)

Keratoderma climactericum (Haxthausen's disease) [15,16]. The specificity of this syndrome described in women over the age of 45 is uncertain, as many patients are obese. Pressure areas of the heel and the forefoot are involved first (Fig. 19.78). Erythema and heavy hyperkeratosis with fissuring make walking painful. The condition slowly extends to become confluent. Later, the central palms may be affected. Symptoms may be worse in winter. Deschamps *et al.* [16] excluded endocrine dysfunction, contact dermatitis and fungal infection, and found normal serum vitamin A levels. However, Wachtel [17] described three young women in whom an identical condition arising following bilateral oophorectomy was reversed by oestrogen replacement. Laurent *et al.* [18]



Fig. 19.77 Keratoderma produced by lupus erythematosus. (Courtesy of Dr I. Sarkany, Royal Free Hospital, London, UK.)



Fig. 19.78 Keratoderma climactericum.

implicated keratinization of the acrosyringium by the finding of composite keratohyaline granules in the granular cells of the interductal granular cells, believed to serve as a marker for acrosyringeal differentiation [19]. Low-dose etretinate produces improvement in several weeks. In this age group, hypertension, cardiovascular disease or lipid abnormalities may prove contraindications. In one report, topical 0.05% oestradiol in a water-in-oil base was successful where keratolytics and emollients had failed [20].

Myxoedema. Palmoplantar hyperkeratosis with myxoedema, improving with treatment, has been reported on several occasions [21,22].

Lymphoedema and other circulatory disorders. In chronic lymphoedema, the skin overlying the lymphoedematous area first becomes diffusely thickened, and then develops a velvety papillomatous surface, which is ultimately covered by large irregular warty projections (lymphostatic verrucosis; mossy foot) [23–25]. The condition may simulate chromoblastomycosis. Lymphoedematous keratoderma occurs most characteristically in filariasis, but may develop in chronic lymphoedema of any origin. Histologically, there is hyperkeratosis, acanthosis and papillomatosis. The dermis is oedematous with dilated lymphatics, conspicuous new-vessel formation, some sclerosis and a variable infiltrate of inflammatory cells. Both the hyperkeratotic component and the lymphoedema improved in three cases given etretinate 0.6 mg/kg/day [23]. Keratoderma is also reported in association with acrocyanosis and livedo reticularis [26].

References

1 Garcia-Hidalgo L, Orozco-Topete R, Gonzalez-Barranco J *et al.* Dermatoses in 156 obese adults. *Obesity Res* 1999; **7**: 299–302.

2 Saywell C, Griffiths WAD. Acquired keratodermas. *Retinoids Today Tomorrow* 1994; **34**: 15–9.

3 Caumes E, Janier M, Janssen F *et al.* Syphilis acquise au cours de l'infection par le virus de l'immunodeficience humaine. Six cas. *Presse Med* 1990; **19**: 369–71.

4 Ashinoff R, Werth VP, Franks AG. Resistant discoid lupus erythematosus of palms and soles: successful treatment with azathioprine. *J Am Acad Dermatol* 1988; **19**: 961–5.

5 Buck DC, Dodd HJ, Sarkany I. Hypertrophic lupus erythematosus. *Br J Dermatol* 1988; **119** (Suppl. 33): 72–4.

6 Grossberg EB, Scherschun L, Fivenson DP. Ulcerating plantar keratoderma in association with systemic lupus erythematosus. *Lupus* 2001; **10**: 650–2.

7 Bolling MC, Mekkes JR, Goldschmidt WF *et al.* Acquired palmoplantar keratoderma and immunobullous disease associated with antibodies to desmocollin 3. *Br J Dermatol* 2007; **157**: 168–73.

8 Munro CS, Cox NH, Marks JM *et al.* Lichen nitidus presenting as palmo-plantar hyperkeratosis and nail dystrophy. *Clin Exp Dermatol* 1993; **18**: 381–3.

9 Jucglà A, Sais G, Navarro M *et al.* Palmoplantar keratoderma secondary to chronic acral erythema due to tegafur. *Arch Dermatol* 1995; **131**: 364–5.

10 Duvic M, Reisman M, Finley V *et al.* Glucan-induced keratoderma in acquired immunodeficiency syndrome. *Arch Dermatol* 1987; **123**: 751–6.

11 Labelle A, Lapierre YD. Keratodermia: side-effects of lithium. *J Clin Psychopharmacol* 1991; **11**: 149–50.

12 Poskitt LB, Duffill MB, Rademaker M. Chloracne, palmoplantar keratoderma and localized scleroderma in a weed sprayer. *Clin Exp Dermatol* 1994; **19**: 264–7.

13 Geusau A, Jurecka W, Nahavandi H *et al.* Punctate keratoderma-like lesions on the palms and soles in a patient with chloracne: a new clinical manifestation of dioxin intoxication? *Br J Dermatol* 2000; **143**: 1067–71.

14 Sass V, Grosshans E, Simonart JM. Chronic arsenism: criminal poisoning or drug intoxication?—report of two cases. *Dermatology* 1993; **186**: 303–5.

15 Haxthausen H. Keratoderma climactericum. *Br J Dermatol* 1934; **46**: 161–7.

16 Deschamps P, Leroy D, Pedailles S *et al.* Keratoderma climactericum (Haxthausen's disease): clinical signs, laboratory findings and etretinate treatment in 10 patients. *Dermatologica* 1986; **172**: 258–62.
17 Wachtel TJ. Plantar and palmar hyperkeratosis in young castrated women. *Int J Dermatol* 1981; **20**: 270–1.
18 Laurent R, Prost O, Nicollier M *et al.* Composite keratohyaline granules in palmoplantar keratoderma: an ultrastructural study. *Arch Dermatol Res* 1985; **277**: 384–94.
19 Ishida-Yamamoto A, Iizuka A, Eady RAJ. Filaggrin immunoreactive composite keratohyalin granules specific to acrosyringia and related tumours. *Acta Derm Venereol (Stockh)* 1994; **74**: 37–42.
20 Zultak M, Bedeaux C, Blanc D. Keratoderma climactericum treatment with topical estrogen. *Dermatologica* 1988; **176**: 151–2.
21 Tan OT, Sarkany I. Severe palmar keratoderma with myxoedema. *Clin Exp Dermatol* 1977; **2**: 287–8.
22 Hodak E, David M, Feuerman EJ. Palmoplantar keratoderma in association with myxoedema. *Acta Derm Venereol (Stockh)* 1986; **66**: 243–5.
23 Zouboulis CC, Biczo S, Gollnick H *et al.* Elephantiasis nostras verrucosa: beneficial effect of oral etretinate therapy. *Br J Dermatol* 1992; **127**: 411–6.
24 Richards RN. Verrucous and elephantoid lymphedema: morphologic spectrum and terminology. *Int J Dermatol* 1981; **20**: 177–87.
25 Mortimer PS. Lymphatics. In: Champion RH, Pye RJ, eds. *Recent Advances in Dermatology*. Edinburgh: Churchill Livingstone, 1990: 175–92.
26 Ohtake N, Sou K, Tsukamoto K *et al.* Diffuse palmoplantar keratoderma associated with acrocyanosis and livedo reticularis: two sporadic cases. *Acta Derm Venereol (Stockh)* 1995; **75**: 331.

Acanthosis nigricans [1–3]

Skin affected by acanthosis nigricans (AN) is hyperpigmented, with papillomatous hyperkeratosis giving a velvety texture. Neck and flexures are most severely affected. Palms may be involved by papillomatous hypertrophy ('tripe palms').

Aetiology. Acanthosis nigricans has a variety of causes whose likely common mechanism is stimulation of tyrosine kinase growth factor receptor signalling pathways in epidermis [4]. In insulin resistance syndromes, high levels of circulating insulin directly or indirectly activate the insulin-like growth factor 1 receptor (IGF1R) [5,6]. IGF1R is a transmembrane protein related to the insulin receptor, present in many tissues including keratinocytes and some ovarian compartments. Specific activating mutations of fibroblast growth factor receptors (FGFRs), also tyrosine kinase receptors, are associated with acanthosis nigricans in Beare–Stevenson syndrome (FGFR2), Crouzon's syndrome with acanthosis nigricans (FGFR3), and thanatophoric dwarfism (FGFR3) [7]. Verrucous epidermal naevi may resemble AN [8] and somatic mosaicism for specific FGFR3 mutations is common in these; acquired mutations of the same type also occur in seborrhoeic keratoses [9,10]. Transgenic mice bearing activating mutations of FGFR3 also display cutaneous papillomatosis [11]. In malignant acanthosis nigricans, tumour-derived growth factors, in particular transforming growth factor-α, acting through the epidermal growth factor receptor (EGFR) are presumed [12–15], although anti-insulin receptor antibodies have also been implicated [16]. Transient AN has been reported in a woman receiving recombinant keratinocyte growth factor [17].

Pathology. Hyperkeratosis and irregular spiky papillomatosis alternating with areas of attenuation are seen [3,18].



Fig. 19.79 Benign acanthosis nigricans: velvety thickening with skin tags.

Clinical features [1,3,18]. The essential clinical features are common to all forms of the disease, but vary in distribution and degree. In congenital forms, skin lesions may be present at birth, but usually develop during childhood or puberty. The earliest changes in affected sites are grey–brown or black pigmentation and dryness and roughness of the skin, which is palpably thickened and covered by small papillomatous elevations, giving it a velvety texture (Fig. 19.79). As the thickening increases, the skin lines are further accentuated and the surface becomes mammillated or rugose, and larger warty excrescences develop. The sites most commonly involved are the axillae, the back and sides of the neck, the anogenital region and the groins, but the other flexures, the submammary region, the umbilicus and, in some cases, almost the entire skin may be affected. Distal extremities are usually spared. Involvement of the mucous membranes is uncommon, but oral mucous membrane may show delicate velvety furrows [19]. Hyperpigmented plaques over elbows, knuckles, knees, and dorsal feet, but sparing the flexures, in dark-skinned individuals has been suggested as an acral variant of AN; a role for elevated leptin levels has been mooted [20,21].

Inherited forms of acanthosis nigricans. Acanthosis nigricans has been reported in many genetic syndromes [1]. Acanthosis nigricans in isolation may be inherited as a Mendelian dominant trait (MIM 100600) [22,23] and may be due to FGFR3 mutation [24]. Activating mutations of FGFR3 are also found in the dysmorphic syndromes with AN, as noted above. Other known causes include insulin resistance due to insulin receptor defects (type A insulin resistance) such as Leprechaunism, Rabson–Mendenhall syndrome, lipodystrophies and other causes of hyperinsulinaemia [4]. Lelis syndrome is the association of widespread AN with hypotrichosis, hypohidrosis, loss of dentition and other ectodermal features [25].

Benign acquired acanthosis nigricans. The term 'pseudo'-acanthosis nigricans is obsolete, as this condition differs only in degree from other forms. As a complication of obesity, it is seen most often in adults [26,27], but also occurs in childhood [27], and with

increasing obesity in prosperous countries is likely to become commoner. Small patches of pigmentation and velvety thickening, often with multiple skin tags, are present in body folds especially axillae (Fig. 19.79), groins and natal cleft. Stuart [28] examined 1412 unselected American high school children and found acanthosis nigricans in 7%, which correlated well with severe obesity. In a study of native Americans, subjects affected by acanthosis nigricans had two-fold higher fasting insulin levels than weight-matched controls [27]. With weight reduction, the skin changes may slowly regress, although the pigmentation often persists.

HAIR-AN syndrome. The triad of *h*yper*a*ndrogenism, *i*nsulin *r*esistance and *a*canthosis *n*igricans in women is known as the HAIR-AN syndrome [2,6], and may be seen with insulin resistance of various causes. Chronic hyperinsulinism is thought to induce ovarian hyperandrogenism [6], and *in vitro* ovarian tissue from hyperinsulinaemic diabetic women responds to supraphysiological insulin concentrations by enhanced steroidogenesis [29]. The finding of pubic hair before the age of 8 years (premature adrenarche) with acanthosis nigricans was associated with insulin resistance [30].

Autoimmune acanthosis nigricans. Acanthosis nigricans disorder may occur in autoimmune disease, including SLE, due to antibodies to the insulin receptor [2,31], so called type B insulin resistance. Fareau *et al.* [32] report a case of a woman whose acanthosis nigricans remitted, together with refractory hyperglycaemia and insulin receptor antibody titre, following cyclophosphamide chemotherapy.

Drug-induced acanthosis nigricans. Reported causes include nicotinic acid [33,34], fusidic acid [35], stilboestrol in young males [36], triazinate, a folic acid antagonist [37], and antiretroviral agents [38,39].

Malignancy-associated acanthosis nigricans. This is comparatively rare, and lesions are more severe and extensive. Pigmentation is conspicuous and is not confined to hyperkeratotic areas. The nails may be brittle or ridged, and the hair may be shed. Irritation is common. The mucous membranes and mucocutaneous junctions are involved in at least 50% of the cases, and warty papillomatous thickening around the lips and eyes may be a presenting symptom (Fig. 19.80). It may be accompanied by eruptive keratoses (Leser–Trélat). The sexes are equally affected. There is usually an underlying adenocarcinoma, especially of stomach, but other tumours are sometimes found, including those of oesophagus, rectum, bronchus, urinary tract, ovary, bile-duct and thyroid [1]. Acanthosis nigricans occasionally precedes other symptoms by some years. The clinical signs may regress following removal of the tumour, but relapses are common. Rendon *et al.* [40] provide a practical algorithm for investigating these patients. Malignant acanthosis nigricans is very rare in childhood—rapidly progressing lesions and mucous membrane involvement are useful warning signs. Malignant acanthosis nigricans may have to be differentiated from tumour-associated hypertrophic osteoarthropathy simulating pachydermoperiostosis.



Fig. 19.80 Malignant acanthosis nigricans: warty thickening of the oral margins in a patient with carcinoma of the breast.

Tripe palms. Velvety, rugose thickening of the palms, resembling tripe (the villous lining of ruminant stomach), is almost always associated with internal malignancy [41,42]. Acquired diffuse keratoderma may also occur with malignancy, but this and familial keratoderma associated with malignancy (as in Howel-Evans' syndrome) is compact and not rugose. Elevated serum epidermal growth factor was described in a patient with tripe palms and carcinoma of the bronchus [43]. Tripe palms with malignancy may occur alone (25%) or associated with acanthosis nigricans [44].

Treatment. Treatment is of the underlying cause, or is otherwise symptomatic and of little help. Removal of the tumour in the malignant form may allow partial improvement. A case of hereditary benign acanthosis nigricans improved dramatically with etretinate [45]. Rosenbach [46] reported successful use of the alexandrite laser.

References

1 Schwartz RA. Acanthosis nigricans. *J Am Acad Dermatol* 1994; **31**: 1–19.

2 Kahn CR, Flier JS, Bar RS *et al.* The syndromes of insulin resistance and acanthosis nigricans. Insulin-receptor disorders in man. *N Engl J Med* 1976; **294**: 739–45.

3 Matsuoka LY, Wortsman J, Goldman J. Acanthosis nigricans. *Clin Dermatol* 1993; **11**: 21–5.

4 Torley D, Bellus GA, Munro CS. Genes, growth factors and acanthosis nigricans. *Br J Dermatol* 2002; **147**: 1096–101.

5 Cruz PDJ, Hud JA. Excess insulin binding to insulin-like growth factor receptors: proposed mechanism for acanthosis nigricans. *J Invest Dermatol* 1992; **98**: 82S–5S.

6 Barbieri RL. Hyperandrogenism, insulin resistance and acanthosis nigricans. 10 years of progress. *J Reprod Med* 1994; **39**: 327–36.

7 McIntosh I, Bellus GA, Jabs EW. The pleiotropic effects of fibroblast growth factor receptors in mammalian development. *Cell Struct Funct* 2000; **25**: 85–96.

8 Ersoy-Evans S, Sahin S, Mancini AJ *et al.* The acanthosis nigricans form of epidermal nevus. *J Am Acad Dermatol* 2006; **55**: 696–8.

9 Hafner C, van Oers JM, Vogt T *et al.* Mosaicism of activating FGFR3 mutations in human skin causes epidermal nevi. *J Clin Invest* 2006; **116**: 2201–7.

10 Hafner C, van Oers JM, Hartmann A *et al.* High frequency of FGFR3 mutations in adenoid seborrheic keratoses. *J Invest Dermatol* 2006; **126**: 2404–7.

11 Logie A, Dunois-Larde C, Rosty C *et al.* Activating mutations of the tyrosine kinase receptor FGFR3 are associated with benign skin tumors in mice and humans. *Hum Mol Genet* 2005; **14**: 1153–60.

12 Ellis DL, Kafka SP, Chow JC *et al.* Melanoma, growth factors, acanthosis nigricans, the sign of Leser-Trelat, and multiple acrochordons: a possible role for alpha-transforming growth factor in cutaneous paraneoplastic syndromes. *New Eng J Med* 1987; **317**: 1582–7.
13 Wilgenbus K, Lentner A, Kuckelkorn R *et al.* Further evidence that acanthosis nigricans maligna is linked to enhanced secretion by the tumour of transforming growth factor alpha. *Arch Dermatol Res* 1992; **284**: 266–70.
14 Koyama S, Ikeda K, Sato M *et al.* Transforming growth factor-alpha (TGF alpha)-producing gastric carcinoma with acanthosis nigricans: an endocrine effect of TGF alpha in the pathogenesis of cutaneous paraneoplastic syndrome and epithelial hyperplasia of the esophagus. *J Gastroenterol* 1997; **32**: 71–7.
15 Haase I, Hunzelmann N. Activation of epidermal growth factor receptor/ERK signaling correlates with suppressed differentiation in malignant acanthosis nigricans. *J Invest Dermatol* 2002; **118**: 891–3.
16 Matsuoka LY, Goldman J, Wortsman J *et al.* Antibodies against the insulin receptor in paraneoplastic acanthosis nigricans. *Am J Med* 1987; **82**: 1253–6.
17 Lane SW, Manoharan S, Mollee PN. Palifermin-induced acanthosis nigricans. *Intern Med J* 2007; **37**: 417–8.
18 Brown J, Winkelmann RK. Acanthosis nigricans: a study of 90 cases. *Medicine* 1968; **47**: 33–51.
19 Pindborg JJ, Gorlin RJ. Oral changes in acanthosis nigricans (juvenile type). *Acta Derm Venereol (Stockh)* 1961; **42**: 63.
20 Yazici AC, Tursen U, Ikizoglu G *et al.* Atypical localization of acanthosis nigricans in an obese patient with leptin level: is there an association? *J Am Acad Dermatol* 2006; **55**: S55–6.
21 Schwartz RA. Acral acanthosis nigricans (acral acanthotic anomaly). *J Am Acad Dermatol* 2007; **56**: 349–50.
22 Curth HO, Aschner BM. Genetic studies on acanthosis nigricans. *Arch Dermatol* 1959; **79**: 55–66.
23 Dhar S, Dawn G, Kanwar AJ *et al.* Familial acanthosis nigricans. *Int J Dermatol* 1996; **35**: 126–7.
24 Berk DR, Spector EB, Bayliss SJ. Familial acanthosis nigricans due to K650T FGFR3 mutation. *Arch Dermatol* 2007; **143**: 1153–6.
25 Steiner CE, Cintra ML, Marques-de-Faria AP. Ectodermal dysplasia with acanthosis nigricans (Lelis syndrome). *Am J Med Genet* 2002; **113**: 381–4.
26 Hud JAJ, Cohen JB, Wagner JM, Cruz PD Jr. Prevalence and significance of acanthosis nigricans in an adult obese population. *Arch Dermatol* 1992; **128**: 941–4.
27 Stuart CA, Smith MM, Gilkinson CR *et al.* Acanthosis nigricans among Native Americans: an indicator of high diabetes risk. *Am J Public Health* 1994; **84**: 1839–42.
28 Stuart CA, Pate CJ, Peters EJ. Prevalence of acanthosis nigricans in an unselected population. *Am J Med* 1989; **87**: 269–72.
29 Geffner ME, Golde DW. Selective insulin action on skin, ovary and heart in insulin resistant states. *Diabetes Care* 1988; **11**: 500–5.
30 Oppenheimer E, Linder B, DiMarino-Nardi J. Decreased insulin sensitivity in prepubertal girls with premature adrenarche and acanthosis nigricans. *J Clin Endocrinol Metab* 1995; **80**: 614–8.
31 Rosenstein ED, Advani S, Reitz RE, Kramer N. The prevalence of insulin receptor antibodies in patients with systemic lupus erythematosus and related conditions. *J Clin Rheumatol* 2002; **7**: 371–3.
32 Fareau GG, Maldonado M, Oral E, Balasubramanyam A. Regression of acanthosis nigricans correlates with disappearance of receptor autoantibodies and achievement of euglycemia in type B insulin resistance syndrome. *Metabolism* 2007; **56**: 670–5.
33 Stals H, Vercammen C, Peeters C *et al.* Acanthosis nigricans caused by nicotinic acid: case report and review of the literature. *Dermatology* 1994; **189**: 203–6.
34 Coates P, Shuttleworth D, Rees A. Resolution of nicotinic acid-induced acanthosis nigricans by substitution of an analogue (acipimox) in a patient with type V hyperlipidaemia. *Br J Dermatol* 1992; **126**: 412–14.
35 Teknetis A, Lefaki I, Joannides D *et al.* Acanthosis nigricans-like lesions after local application of fusidic acid. *J Am Acad Dermatol* 1993; **28**: 501–2.
36 Banuchi SR, Cohen L, Lorinez AL. Acanthosis nigricans following diethylstilboestrol therapy: occurrence in patients with childhood muscular dystrophy. *Arch Dermatol* 1974; **109**: 545–6.
37 Greenspan AH, Shupack JL, Foo S-H *et al.* Acanthosis nigricans hyperpigmentation secondary to triazinate therapy. *Arch Dermatol* 1985; **121**: 232–6.
38 Mellor-Pita S, Yebra-Bango M, Alfaro-Martinez J, Suarez E. Acanthosis nigricans: a new manifestation of insulin resistance in patients receiving treatment with protease inhibitors. *Clin Infect Dis* 2002; **34**: 716–7.
39 Mur A, Seidel V, Lopez-Vilchez MA *et al.* Acanthosis nigricans as an adverse effect of highly active in an adolescent girl with human immunodeficiency virus infection. *Pediatr Infect Dis J* 2005; **24**: 742–3.
40 Rendon MI, Cruz PD, Sontheimer RD *et al.* Acanthosis nigricans: a cutaneous marker of tissue resistance to insulin. *J Am Acad Dermatol* 1989; **21**: 461–9.
41 Lo WL, Wong CK. Tripe palms: a significant cutaneous sign of internal malignancy. *Dermatology* 1992; **185**: 151–3.
42 Breathnach SM, Wells GC. Acanthosis nigricans: tripe palms. A distinctive pattern of palmar keratoderma frequently associated with internal malignancy. *Clin Exp Dermatol* 1980; **5**: 181–9.
43 Douglas F, McHenry PM, Dagg JH *et al.* Elevated levels of epidermal growth factor in a patient with tripe palms. *Br J Dermatol* 1994; **130**: 686–7.
44 Cohen PR, Kurzrock R. Malignancy-associated tripe palms. *J Am Acad Dermatol* 1992; **27**: 271–2.
45 Akovbyan VA, Talanin NY, Arifov SS *et al.* Successful treatment of acanthosis nigricans with etretinate. *J Am Acad Dermatol* 1994; **31**: 118–20.
46 Rosenbach A, Ram R. Treatment of acanthosis nigricans of the axillae using a long-pulsed (5-alexandrite laser. *Dermatol Surg* 2004; **30**: 1158–60.

Confluent and reticulate papillomatosis [1–3]

Synonym
- Gougerot–Carteaud syndrome

This syndrome of mild truncal hyperkeratosis is included here in view of the suggestion that it is a keratinizing disorder, but there is strong evidence of an infective component in its aetiology.

Aetiology. Most cases are sporadic, although occasional familial cases could suggest an abnormal response to microbial products [4]. *Pityrosporum orbiculare* has been implicated [5], but fungal elements are found in only a minority of cases and antiyeast therapy is unreliable. Response to several antibiotics supports a bacterial contribution [2,3,6]. Natarajan *et al.* [7] isolated a novel Actinomycete, for which they propose the name *Dietzia papillomatosis* [8], but this finding is yet to be reproduced [9].

Pathology. Histologically, hyperkeratosis and papillomatosis are present without acanthosis; increased transitional cells on electron microscopy [10] and increased keratin 16 and Ki67 expression [11] indicate hyperproliferation. Amyloid has been reported [12].

Clinical features [1–3]. The condition is commonly seen in teenagers and young adults, beginning around puberty. Both sexes were equally affected among 39 cases attending the Mayo clinic [2]. Flat, dry papules up to 5 mm in diameter commonly appear on the neck, upper chest, between the breasts or in the interscapular area and the axillae. Neighbouring papules become confluent in the centre of the affected areas, but only partially so at their periphery to form an irregular network (Fig. 19.81).

The lesions gradually extend. They cause few symptoms and little disfigurement. The age of onset and the distribution of lesions differentiate the condition from acanthosis nigricans, although coexistence in childhood has been noted [13]. Darier's disease and reticulate pigmentary disorders [14] must also be considered.



Fig. 19.81 Confluent and reticulate papillomatosis: red–brown reticulate papules with a fine scale in the central area of the chest. (Courtesy of Professor R.J. Hay, St John's Institute of Dermatology, London, UK.)

Treatment. A variety of antibiotics have been found to be effective [15]; minocycline has been most used [2] but azithromycin is also recommended [3]. The response to antifungal agents is variable, even if yeasts are demonstrated [16,17]. Systemic or topical retinoids, or topical vitamin D analogues may also be effective [18–20].

References

1 Gougerot H, Carteaud A. Neue formen der Papillomatose. *Arch Dermatol* 1932; **165**: 232–67.

2 Davis MD, Weenig RH, Camilleri MJ. Confluent and reticulate papillomatosis (Gougerot–Carteaud syndrome): a minocycline-responsive dermatosis without evidence for yeast in pathogenesis. A study of 39 patients and a proposal of diagnostic criteria. *Br J Dermatol* 2006; **154**; 287–93.

3 Scheinfeld N. Confluent and reticulated papillomatosis: a review of the literature. *Am J Clin Dermatol* 2006; **7**: 305–13.

4 Yesudian P, Kamalam S, Razack A. Confluent and reticulated papillomatosis (Gougerot–Carteaud). An abnormal host reaction to Malassezzia furfur. *Acta Derm Venereol* 1973; **53**: 381–4.

5 Roberts SO, Lachapelle JM. Confluent and reticulate papillomatosis (Gougerot–Carteaud) and *Pityrosporum orbiculare*. *Br J Dermatol* 1969; **81**: 841–5.

6 Jang HS, Oh CK, Cha JH *et al*. Six cases of confluent and reticulated papillomatosis alleviated by various antibiotics. *J Am Acad Dermatol* 2001; **44**: 652–5.

7 Natarajan S, Milne D, Jones AL *et al*. Dietzia strain X: a newly described Actinomycete isolated from confluent and reticulated papillomatosis. *Br J Dermatol* 2005; **153**: 825–7.

8 Jones AL, Koerner RJ, Natarajan S *et al*. *Dietzia papillomatosis* sp. nov., a novel actinomycete isolated from the skin of an immunocompetent patient with confluent and reticulated papillomatosis. *Int J Syst Evol Microbiol* 2008; **58**: 68–72.

9 Davis RF, Harman KE. Confluent and reticulated papillomatosis successfully treated with amoxicillin. *Br J Dermatol* 2007; **156**: 583–4.

10 Lee SH, Choi EH, Lee WS *et al*. Confluent and reticulated papillomatosis: a clinical, histopathological, and electron microscopic study. *J Dermatol* 1991; **18**: 725–30.

11 Inaloz HS, Patel GK, Knight AG. Familial confluent and reticulated papillomatosis. *Arch Dermatol* 2002; **138**: 276–7.

12 Groh V, Sigg C, Schnyder UW. New histochemical and ultrastructural findings in three cases of 'papillomatose papuleuse confluente et reticulee' (Gougerot–Carteaud). *Dermatologica* 1982; **165**: 145–57.

13 Inaloz HS, Patel G, Lewis-Jones MS. Coexistence of confluent and reticulated papillomatosis and acanthosis nigricans. *Eur J Ped Dermatol* 1999; **9**: 73–6.

14 Schnur RE, Heymann WR. Reticulate hyperpigmentation. *Sem Cutan Med Surg* 1997; **16**: 72–80.

15 Carteaud A. A case of Gougerot and Carteaud's confluent and reticulated papulous papillomatosis, completely cleared up by antibiotics. *Bull Soc Franc Dermatol Syphilig* 1965; **72**: 396–7.

16 Veglio S, Norat F, Gualco F, Norat GM. Confluent and reticulated papillomatosis: three cases responsive to topical tioconazole. *G Ital Dermatol Venereol* 2002; **136**: 165–8.

17 Thomsen K. Confluent and reticulated papillomatosis (Gougerot–Carteaud). *Acta Derm Venereol* 1979; **59** (Suppl.): 185–7.

18 Bruynzeel-Koomen CA, de Wit RF. Confluent and reticulated papillomatosis successfully treated with the aromatic etretinate. *Arch Dermatol* 1984; **120**: 1236–7.

19 Lee MP, Stiller MJ, McClain SA *et al*. Confluent and reticulated papillomatosis: response to high-dose oral isotretinoin therapy and reassessment of epidemiologic data. *J Am Acad Dermatol* 1994; **31**: 327–31.

20 Kurkcuoglu N, Celebi CR. Confluent and reticulated papillomatosis: response to topical calcipotriol. *Dermatology* 1995; **191**: 341–2.

CHAPTER 20

Psoriasis

C.E.M. Griffiths[1] *& J.N.W.N. Barker*[2]

[1]Dermatology Centre, University of Manchester, Salford Royal Hospital, Salford, Manchester, UK
[2]St John's Institute of Dermatology, King's College London, Guy's Hospital, London, UK

Epidemiological aspects, 20.1
Incidence and prevalence, 20.1
Aetiology and pathogenesis, 20.2
Genetic epidemiology, 20.2
Environmental risk factors, 20.3
Pathogenetic mechanisms, 20.5
Histopathology, 20.9
Early changes, 20.9
Changes in fully developed plaques, 20.9
Clinical features, 20.9
Modes of onset, 20.9
Morphology of common chronic stable plaque psoriasis (psoriasis vulgaris), 20.10
Clinical variants, 20.11
Modification by site, 20.14
Psoriasis in children, 20.16
Atypical forms, 20.16
Disease associations, 20.17
Complications, 20.18
Biomarkers, 20.19
Differential diagnosis, 20.19
Course and prognosis, 20.20
Management, 20.21
Local therapy, 20.21
UV phototherapy, 20.28
Systemic therapy, 20.33
Miscellaneous therapies, 20.42
Pustular forms of psoriasis, 20.44
Localized pustular psoriasis, 20.44
Generalized pustular psoriasis, 20.48
Psoriatic arthritis, 20.54

Definition. A common, chronic, disfiguring, inflammatory and proliferative condition of the skin, in which both genetic and environmental influences have a critical role. The most characteristic lesions consist of red, scaly, sharply demarcated, indurated plaques, present particularly over extensor surfaces and scalp. The disease is enormously variable in duration, periodicity of flares and extent. Morphological variants are common.

Epidemiological aspects

Incidence and prevalence

Accurate figures concerning epidemiology and morbidity of psoriasis are difficult to obtain given that diagnostic criteria have never been validated, different methodologies have been employed and patient ascertainment techniques have varied. Nevertheless, it is clear that psoriasis is a very common disease. Most robust prevalence data come from Northern Europe and Scandinavia where studies of Caucasians indicate population prevalence between 1.5% and 3% (Table 20.1) [1–9], although prevalence as high as 4.8% has been reported [10]. There are, however, considerable racial variations with most other populations having a lower prevalence of disease. In China, psoriasis is estimated to affect 0.3% of the population [7], while the disease is very rare or non-existent in Inuits [11], Latin American Indians [9] or Samoans [8]. It appears to be more common in East than West Africa. Climate also appears to affect psoriasis prevalence, with higher rates recorded in single countries at greater latitudes from the Equator [12].

The incidence of the disease, that is the number of new cases occurring in a given population in a defined time, has been estimated to be 60 individuals per 100 000 per year [13]. This study also provided support for seasonal variation, with 68% of cases first diagnosed in winter and spring months. A recent US study has suggested that the annual incidence of psoriasis has doubled in the 30 years between 1970 and 2000 [14], although whether this reflects a true change in incidence or changes in diagnosis patterns is unclear.

All figures quoted above relate primarily to psoriasis vulgaris (chronic plaque psoriasis). Estimates of disease variants are much less robust. They probably account for approximately 10% of all cases.

Age of onset

Considerable variation exists between studies in age of onset, perhaps in part reflecting the lack of strict criteria used. Lomholt [1] reported average age of onset as 12 years in his study in the Faroe Islands. In a large US survey [5], the average age of onset was 28 years, while in the largest study reported in China, average age of onset was 36 years [7]. It has been reported that 35% of cases have disease onset before age 20 years and 58% before age 30 [8]. In a UK study [4] of a defined population, mean age of onset was 33 years with the mode in the second decade; 75% had disease onset before the age of 46 years.

These studies, however, hide the fact that it appears that psoriasis has a bimodal distribution of age of onset. In a German study, two peaks were identified: the larger, early peak between 16 and 22 years and the later one at 57–60 years [15]. Several other studies,

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

Table 20.1 Worldwide studies on prevalence of psoriasis.

Place and reference	Sample size	Percentage with psoriasis
Faeroes [1]	10984	2.84
Sweden [2]	159200	2.3
UK [3]	2180	1.56
UK [4]	5395	1.48
USA [5]	20749	1.4
USA [6]	7514	1.4
China [7]	670000	0.3
Samoa [8]	12569	0
South America [9]	25000	0

including from the UK [16], broadly support this observation. Those individuals with early onset appear, in general, to have more severe disease and are much more likely to have an affected first-degree relative with psoriasis (see below) [1,5,17].

Sex effects

Males and females are equally affected by psoriasis vulgaris. Many studies indicate that age of onset is younger in females. Thus, one German study demonstrated a peak age of onset of 22 years in males and 16 years in females in early-onset disease [15]. However, results of studies are highly dependent on sampling techniques used and are variable in their results. There is no evidence that the disease is phenotypically different between the sexes.

References

1 Lomholt G. *Psoriasis: Prevalence, Spontaneous Course and Genetics. A Census Study on the Prevalence of Skin Diseases on the Faroe Islands*. Copenhagen: GEC Gad, 1963: 31–3.

2 Hellgren L. *Psoriasis: The Prevalence in Sex, Age and Occupational Groups in Total Populations in Sweden. Morphology, Inheritance and Association with Other Skin and Rheumatic Diseases*. Stockholm: Almqvist & Wiksell, 1967: 19–53.

3 Rea JN, Newhouse ML, Halil T. Skin disease in Lambeth. *Br J Prevent Social Med* 1976; **30**: 107–14.

4 Nevitt GJ, Hutchinson PE. Psoriasis in the community: prevalence, severity and patients' beliefs and attitudes towards the disease. *Br J Dermatol* 1996; **135**: 533–7.

5 Farber EM, Nall ML. The natural history of psoriasis in 5600 patients. *Dermatologica* 1974; **148**: 1–18.

6 US National Health Survey 1971–74. *Vital and Health Statistics*. Series II, No. 212.

7 Yui Yip S. The prevalence of psoriasis in the mongoloid race. *J Am Acad Dermatol* 1984; **10**: 965–8.

8 Farber EM, Nall ML. Epidemiology: natural history and genetics. In: Roenigk HH, Maibach HI, eds. *Psoriasis*. New York: Marcel Dekker, 1985: 141–86.

9 Convit J. Investigation of the incidence of psoriasis among Latin American Indians. In: *Proceedings of the XIIth Congress on Dermatology*. Amsterdam: Exerpta Medica, 1962: 196.

10 Kavli G, Færde OH, Arnesen E *et al*. Psoriasis: familial predisposition and environmental factors. *BMJ* 1985; **291**: 999–1000.

11 Harvald B. Genetic epidemiology of Greenland. *Clin Genet* 1989; **36**: 364–7.

12 Braathen LR, Botten G, Bjerkedal T. Prevalence of psoriasis in Norway. *Acta Derm Venereol (Stockh)* 1989; **142** (Suppl.): 5–8.

13 Bell LM, Sedlack R, Beard CM *et al*. Incidence of psoriasis in Rochester, Minnesota, 1980–83. *Arch Dermatol* 1991; **127**: 1184–7.

14 Icen M, Crowson CS, McEvoy MT *et al*. Trends in incidence of adult-onset psoriasis over three decades: a population-based study. *J Am Acad Dermatol* 2009; **6**: 394–401.

15 Henseler T, Christophers E. Psoriasis of early and late onset: characterization of two types of psoriasis vulgaris. *J Am Acad Dermatol* 1985; **13**: 450–6.

16 Smith AE, Kassab JY, Rowland Payne CME, Beer WE. Bimodality in age of onset of psoriasis in both patients and their relatives. *Dermatology* 1993; **186**: 181–6.

17 Stuart P, Malick F, Nair RP *et al*. Analysis of phenotypic variation in psoriasis as a function of age at onset and family history. *Arch Dermatol Res* 2002; **294**: 207–13.

Aetiology and pathogenesis

Genetic epidemiology

There is overwhelming evidence that psoriasis has an important genetic component. Lomholt's classic epidemiological study of psoriasis in the Faroe Islands (1963), in which he examined more than 10000 inhabitants [1], made the key observation that the incidence of psoriasis was much greater amongst first- and second-degree relatives of sufferers than unaffected control subjects.

A further large-scale study performed in Sweden supported these data showing the prevalence of psoriasis to be 7.8% in first-degree relatives compared with a prevalence of 3.14% in matched controls, and 1.97% in the overall population [2]. Based on population data, several investigators have calculated the risk for a child to develop psoriasis. In a German study, the risk was 14% if one parent was affected, 41% if both parents affected, and 6% if one sibling affected, compared to 2% when no parent or sibling was affected [3]. Henseler and Christophers [4] demonstrated that the bimodal peak in disease onset (see above) could be taken as evidence for the existence of two pathogenetically distinct forms of the disease, similar to the model for diabetes mellitus. Thus, type 1 is hereditary, strongly HLA associated (particularly HLA-Cw6), early onset and more likely to be severe. Type II is sporadic, HLA unrelated, of late onset and usually mild. A study in Iceland has confirmed much of these data [5]. Others, however, have suggested that the true situation is more complex [6], and certainly there are many individuals in extended family pedigrees with late-onset disease.

Support for these population studies comes from analysis of various family pedigrees in which psoriasis appears throughout multiple generations [7]. While some authors have argued that the data are most consistent with an autosomal dominant pattern of inheritance with reduced penetrance and others that the best fit is a double recessive model, most regard the data as consistent with a polygenic or multifactorial pattern (see below). Interestingly, the development and severity of psoriasis may be influenced by the sex of the contributing parent. Thus several studies have noted evidence for a preferential paternal effect, while one Scottish study further showed earlier age of onset when the disease was inherited from the father, consistent with 'genetic anticipation' [8].

Perhaps the most robust data supporting a genetic basis to psoriasis come from studies examining concordance for the disease in twins. Examination of individuals from the Danish Twin Registry has shown concordance for psoriasis in 64% of monozygotic (identical) twins compared to 15% for dizygotic twins, corresponding to an estimated heritability of 91% [9]. Very similar figures (73% and 20% respectively) were found in the retrospective study of Farber *et al*. [10], although in an Australian study lower concord-

ance rates were observed; 35% in monozygotic twins compared to 12% in dizygotic twins [11]. Of interest when monozygotic twins are concordant for psoriasis the age of onset, distribution of the disease and severity are very similar suggesting that genetic factors play a role in these parameters. However, it is self-evident from the data that concordance rates do not reach 100%, even when older twins are examined, indicating that the environment plays a key role in disease expression. Based on the variable extent and pattern in which it is inherited through families, it is suggested that psoriasis represents a spectrum of genetic diseases. At one end are the rare families in which changes in a single gene may be sufficient to cause the disease. At the opposite end of the spectrum is the more common form in which an obvious family history may be lacking. In these individuals, it is likely that changes in multiple genes, interacting both with each other and the environment are required for disease expression [12].

All the above studies have concentrated upon chronic plaque psoriasis, the most common variant. Little is known of the epidemiology of other forms. Guttate psoriasis (see below) is almost invariably HLA associated [13,14] and thought to be closely linked pathogenetically to type 1 plaque psoriasis.

References

1 Lomholt G, ed. *Psoriasis: Prevalence, Spontaneous Course and Genetics. A Census Study on the Prevalence of Skin Diseases on the Faroe Islands*. Copenhagen: GEC Gad, 1963.

2 Hellgren L. *Psoriasis: The Prevalence in Sex, Age and Occupational Groups in Total Populations in Sweden. Morphology, Inheritance and Association with Other Skin and Rheumatic Diseases*. Stockholm: Almqvist & Wiksell, 1967.

3 Andressen C, Henseler T. Inheritance of psoriasis: analysis of 2035 family histories. *Hautarzt* 1982; **33**: 214–7.

4 Henseler T, Christophers E. Psoriasis of early and late onset: characterization of two types of psoriasis vulgaris. *J Am Acad Dermatol* 1985; **13**: 450–6.

5 Gudjonsson JE, Karason A, Antonsdottir AA *et al*. HLA-Cw6-positive and HLA-Cw6-negative patients with psoriasis vulgaris have distinct clinical features. *J Invest Dermatol* 2002; **118**: 362–5.

6 Swanbeck G, Inerot A, Martinsson T *et al*. Age at onset and different types of psoriasis. *Br J Dermatol* 1995; **133**: 768–73.

7 Elder JT, Henseler T, Christophers E *et al*. Of genes and antigens: the inheritance of psoriasis. *J Invest Dermatol* 1994; **103**: 150S–3S.

8 Burden AD, Javed S, Bailey M *et al*. Genetics of psoriasis: paternal inheritance and a locus on chromosome 6p. *J Invest Dermatol* 1998; **110**: 958–60.

9 Brandrup F, Holm N, Grunnet N *et al*. Psoriasis in monozygotic twins. *Acta Derm Venereol (Stockh)* 1982; **62**: 229–34.

10 Farber EM, Nall ML, Watson W. Natural history of psoriasis in 61 twin pairs. *Arch Dermatol* 1974; **109**: 207–11.

11 Duffy DL, Spelman LS, Martin NG. Psoriasis in Australian twins. *J Am Acad Dermatol* 1993; **29**: 428–34.

12 Barker JNWN. Genetic aspects of psoriasis. *Clin Exp Dermatol* 2001; **26**: 321–5.

13 Mallon E, Bunce M, Savoie H *et al*. HLA-C and guttate psoriasis. *Br J Dermatol* 2000; **143**: 1177–82.

14 Asumalahti K, Ameen M, Suomela S *et al*. Genetic analysis of psoriasis distinguishes guttate psoriasis and palmoplantar pustulosis. *J Invest Dermatol* 2003; **120**: 627–32.

Environmental risk factors

Present evidence indicates that interactions between genes and the environment are important in disease causation. Many environmental factors have been linked to psoriasis, and have been implicated in, for example, initiation of the disease process and exacerbation of pre-existing disease. However, conclusive evidence is so far lacking.

Trauma

Psoriasis at the site of an injury is well known (Koebner phenomenon; see below). A wide range of injurious local stimuli, including physical, chemical, electrical, surgical, infective and inflammatory insults, has been recognized to elicit psoriatic lesions [1].

Infection

Acute guttate psoriasis is strongly associated with preceding or concurrent streptococcal infection, particularly of the throat [2]. There is evidence that streptococcal infection may be important in chronic plaque psoriasis [3], and that treatment with rifampicin and penicillin may lead to clearance of skin lesions. Further, acute episodes of guttate psoriasis are much more common in individuals with a family history of plaque psoriasis [4] and one-third of cases of guttate psoriasis progress to the chronic plaque form [5]. As mentioned earlier, guttate and chronic plaque psoriasis share strong HLA associations, particularly with HLA-Cw6. HIV infection has also been associated with psoriasis (see below).

Drugs

There are many drugs reported to be responsible for the onset or exacerbation of psoriasis [6]. Chief amongst these are lithium salts, antimalarials, beta-adrenergic blocking agents, non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme (ACE) inhibitors and the withdrawal of corticosteroids. Their risk, however, has never been formally assessed in controlled epidemiological studies. The adverse effect of beta-blockers is based on early experiences with practolol [7], although data implicating those in current usage are lacking. Likewise, the risk of withdrawal of systemic or potent topical corticosteroids requires careful re-evaluation.

Anecdotal personal experience of the authors and questioning of colleagues have suggested that beta-blockers and NSAIDs have little, if any, adverse effects on psoriasis but that the effect of lithium salts or antimalarials may be severe. Patients with unstable psoriasis should receive appropriate advice before travelling to countries where antimalarial prophylaxis is required.

Sunlight

Although sunlight is generally beneficial, in a small minority of patients, psoriasis may be provoked by strong sunlight (Fig. 20.1) and cause summer exacerbations in exposed skin. In a questionnaire study of 2000 patients in Sweden, the prevalence of photosensitivity in psoriasis was estimated at 5.5% [8,9]. Approximately 40% of these patients gave a history of polymorphic light eruption (PLE) with psoriasis appearing as a secondary phenomenon with PLE lesions. Recent work has indicated that severely photosensitive psoriasis is predominantly female, distinct from PLE, and strongly associated with HLA-Cw6, family history and very early age of onset [10]. Photochemotherapy (PUVA) can be helpful in these patients.

Metabolic factors

The early onset of psoriasis in women, with a peak around puberty, changes during pregnancy and provocation of psoriasis by high-dose oestrogen therapy potentially indicates a role for hormonal



Fig. 20.1 Psoriasis exacerbated by sun exposure. (Courtesy of St John's Institute of Dermatology, London, UK.)

factors in the disease. A questionnaire study has provided data from 65 females who had one or more pregnancies after the diagnosis was made. Psoriasis remained unaltered in approximately 40% of pregnancies, improved in 40% and worsened in 14% [11]. In contrast, in the 3-month postpartum period, 30% remain unchanged, 10% improved and 50% deteriorated. Thus, if psoriasis changes in pregnancy, it is more likely to improve than worsen, while in the postpartum period it is more likely to deteriorate. These results have been broadly supported in other studies [12]. Although rare, generalized pustular psoriasis precipitated by pregnancy has repeatedly been reported [13].

Hypocalcaemia, for example following accidental parathyroidectomy, has been reported to occur in severe forms of psoriasis, particularly generalized pustular psoriasis [14,15] and may be a predictor of poor outcome.

Importantly, it has also been reported that psoriasis *per se* may have an adverse effect on pregnancy outcomes with one study showing increased recurrent abortions, hypertension and need for caesarean delivery [16].

Psychogenic factors

Considerable clinical evidence exists for the role of stress in onset and exacerbation of psoriasis. Seville [17] reported consistent links between major stressful life events and disease manifestation. In a UK study, over 60% of a sample of psoriasis patients believed stress was a principal factor in the cause of their psoriasis [18]. Gupta *et al.* [19] reported that several psychocutaneous characteristics, including increased exacerbations and worse disease, correlated with stress reactivity. Not all studies have supported these observations and prospective epidemiological studies, using appropriate psychometric instruments, are required to answer these important issues.

It is without doubt, however, that psoriasis has a detrimental effect on the psychosocial quality of life of patients and that stress management programmes significantly shorten the time to clearance with standard therapies [20]. Furthermore, psoriasis in patients who are categorized as being high or pathological worriers is less likely to clear with photochemotherapy (PUVA) than in those patients with low worry [21].

Without doubt, the emotional and physical disability that psoriasis may cause is underestimated. One study showed the impact of psoriasis on physical and mental components of the health related quality of life index is very similar to that of many other major diseases, including heart disease and arthritis [22].

Alcohol and smoking

It has long been suspected that both cigarettes and alcohol have a detrimental effect on psoriasis. While recent large epidemiological studies are not conclusive, support for an association is observed [23]. When controlled for confounding variables, studies suggest that alcohol may exacerbate pre-existing disease but does not appear to induce psoriasis [24]. This effect seems greater in men than in women. Heavy drinkers tend to have more extensive and inflamed disease [25,26]. Increased alcohol consumption is a recognized stress response. Excess drinking is undoubtedly also a consequence of the disease and leads to treatment resistance and reduced therapeutic compliance. Abstinence has been reported to induce remission [27].

In the Rochester incidence study [28], female patients at first diagnosis smoked more than a random sample of the population, in contrast to male patients who were comparable. These data were confirmed by Naldi *et al.* [29] in a case–control study. In women who smoked more than 15 cigarettes per day, the odds ratio for association with psoriasis was 3.9 (men = 1.4). Most striking is the link between smoking and pustular forms of psoriasis, particularly palmoplantar pustulosis, a disease most frequently observed in females (see later). Individuals smoking more than 15 cigarettes per day had an odds ratio of 10.5 for association with palmoplantar pustulosis.

HIV and acquired immune deficiency syndrome

The association between severe psoriasis, psoriatic arthropathy and human immunodeficiency virus (HIV) infection is well recognized [30–33]. In a study of 13 HIV-positive psoriasis patients followed over 2.5 years, psoriasis was found to flare severely or to appear *de novo* in explosive form as features of HIV infection developed. The prognosis of acquired immune deficiency syndrome (AIDS) in patients with psoriasis also appeared poor, nine out of 13 patients having died during the course of the above 2.5-year study [30]. The mechanism of worsening of psoriasis in these circumstances is unclear. Furthermore, the knowledge that psoriasis may be aggravated by AIDS, a disease in which the helper T cell is the major target, and the evidence that psoriasis may be greatly improved by ciclosporin, which inhibits helper T-cell function, create a paradox that remains to be fully explained.

References

1 Eyre RW, Krueger GG. The Koebner response in psoriasis. In: Roenigk HH, Maibach HI, eds. *Psoriasis*. New York: Marcel Dekker, 1984: 105–16.
2 Telfer NR, Chalmers RJ, Whale K, Colman G. The role of streptococcal infection in the initiation of guttate psoriasis. *Arch Dermatol* 1992; **128**: 39–42.
3 Tervaert WCC, Esseveld H. A study of the incidence of haemolytic streptococci in the throat in patients with psoriasis vulgaris, with reference to their role in the pathogenesis of this disease. *Dermatologica* 1970; **140**: 282–90.

4 Naldi L, Peli L, Parazzini F, Carrel CF, Psoriasis Study Group of the Italian Group for Epidemiological Research in Dermatology. Family history of psoriasis, stressful life events, and recent infectious disease are risk factors for a first episode of acute guttate psoriasis: results of a case–control study. *J Am Acad Dermatol* 2001; **44**: 433–8.
5 Martin BA, Chalmers RJ, Telfer NR. How great is the risk of further psoriasis following a single episode of acute guttate psoriasis? *Arch Dermatol* 1996; **132**: 717–8.
6 Abel EA, DiCicco LM, Orenberg EK *et al.* Drugs in exacerbation of psoriasis. *J Am Acad Dermatol* 1986; **15**: 1007–22.
7 Ridley CM. Skin reactions to practolol. *BMJ* 1974; **4**: 719.
8 Ros A-M, Eklund G. Photosensitive psoriasis. *J Am Acad Dermatol* 1987; **17**: 752–8.
9 Dawe RS, Arseculeratne G, Ferguson J. Chronic actinic dermatitis recognized on minimal erythema dose testing prior to narrow-band UVB treatment for psoriasis. *Photodermatol Photoimmunol Photomed* 2005; **21**: 112–3.
10 Rutter KJ, Watson REB, Cottrell LF *et al*. Severely photosensitive psoriasis: a phenotypically defined patient subset. *J Invest Dermatol* 2009; Epub ahead of publication.
11 Dunna SF, Finlay AY. Psoriasis: improvement during and worsening after pregnancy. *Br J Dermatol* 1989; **120**: 584.
12 Boyd AS, Morris LF, Phillips CM, Menter MA. Psoriasis and pregnancy: hormone and immune system interaction. *Int J Dermatol* 1996; **35**: 169–72.
13 Murphy FR, Stolman LP. Generalized pustular psoriasis. *Arch Dermatol* 1979; **115**: 1215–6.
14 Zelickson BD, Muller SA. Generalized pustular psoriasis: a review of 63 cases. *Arch Dermatol* 1991; **127**: 1339–45.
15 Stewart AF, Battaglini-Sabetta J, Millstone L. Hypocalcemia induced pustular psoriasis of von Zumbusch. *Ann Intern Med* 1984; **100**: 677–80.
16 Ben-David G, Sheiner E, Hallak M, Levy A. Pregnancy outcome in women with psoriasis. *J Reprod Med* 2008; **53**: 183–7.
17 Seville RH. Psoriasis and stress. *Br J Dermatol* 1977; **97**: 279–302.
18 Fortune DG, Richards HL, Main CJ, Griffiths CEM. What patients with psoriasis believe about their condition. *J Am Acad Dermatol* 1998; **39**: 196–201.
19 Gupta MA, Gupta AK, Kirkby S *et al.* A psychocutaneous profile of psoriasis patients who are stress reactors: a study of 127 patients. *Gen Hosp Psychiatry* 1989; **11**: 166–73.
20 Fortune DG, Richards HL, Kirby B *et al.* A cognitive–behavioural symptom management programme as an adjunct in psoriasis therapy. *Br J Dermatol* 2002; **46**: 458–65.
21 Fortune DG, Richards HL, Kirby B *et al.* Psychological distress impairs clearance of psoriasis in patients treated with photochemotherapy. *Arch Dermatol* 2003; **139**: 752–6.
22 Rapp SR, Feldman SR, Exum ML *et al*. Psoriasis causes as much disability as other major medical diseases. *J Am Acad Dermatol* 1999; **41**: 401–7.
23 Higgins E. Alcohol, smoking and psoriasis. *Clin Exp Dermatol* 2000; **25**: 107–10.
24 Rosset M, Oki G. Diseases in alcoholics. *Q J Stud Alcohol* 1971; **32**: 1017–24.
25 Poikolainen K, Reunala T, Karvonen J *et al.* Alcohol intake: a risk factor for psoriasis in young and middle aged men. *BMJ* 1990; **300**: 780–3.
26 Gupta MA, Schork NJ, Gupta AK, Ellis CN. Alcohol intake and treatment responsiveness of psoriasis: a prospective study. *J Am Acad Dermatol* 1993; **28**: 730–2.
27 Vincenti GE, Blunden SM. Psoriasis and alcohol abuse. *J R Army Med Corps* 1987; **133**: 77–8.
28 Bell LM, Sedlack R, Beard CM *et al.* Incidence of psoriasis in Rochester, Minnesota, 1980–83. *Arch Dermatol* 1991; **127**: 1184–7.
29 Naldi L, Peli L, Parazzini F. Association of early-stage psoriasis with smoking and male alcohol consumption: evidence from an Italian case–control study. *Arch Dermatol* 1999; **135**: 1479–84.
30 Duvic M, Johnson TM, Rapini RP *et al.* Acquired immunodeficiency syndrome-associated psoriasis and Reiter's syndrome. *Arch Dermatol* 1987; **123**: 1622–32.
31 Johnson TM, Duvic M, Rapini RP *et al.* AIDS exacerbates psoriasis (Letter). *N Engl J Med* 1985; **313**: 1415.
32 Lazar AP, Roenigk HH. Acquired immunodeficiency syndrome (AIDS) can exacerbate psoriasis. *J Am Acad Dermatol* 1988; **18**: 144.
33 Reveille JD, Conant MA, Duvic M. Human immunodeficiency virus associated psoriasis, psoriatic arthritis, and Reiter's syndrome; a disease continuum? *Arthritis Rheum* 1990; **33**: 1574–8.

The cardinal features of lesional psoriatic skin are: (i) epidermal hyperproliferation with loss of differentiation; (ii) dilatation and proliferation of dermal blood vessels; and (iii) accumulation of inflammatory cells, particularly neutrophils and T lymphocytes. A vast array of growth factors, cytokines, inflammatory mediators and other biological markers have been shown to be altered in lesional psoriatic skin [1]. Significant progress has been made in understanding the basic pathogenetic mechanism which increasingly underscore the role of interplay between epidermal aberration and innate and acquired immunity (see below) [2,3].

Pathogenetic mechanisms

Epidermal proliferation

A variety of techniques have demonstrated that the increased keratinocyte proliferation observed in psoriasis is a consequence of an increase in the proliferating cell compartment in the basal and supra basal levels of the epidermis, and not due to shortened cell cycle time. The number of cycling cells is increased approximately sevenfold [4]. These changes are not specific for psoriasis as, for example, increased numbers of proliferating keratinocytes are also seen in wound healing and atopic dermatitis. Multiple growth factors, which experimentally have been shown to modulate keratinocyte proliferation, are present in lesional skin [5]. In particular, transforming growth factor-α (TGF-α) appears to be an important autocrine mediator of these events [6].

Vascular changes

Vertical dermal capillary loops in lesional skin are dilated, elongated and twisted. Image analysis quantification of immunostained microvessels has demonstrated a fourfold increase in endothelium of superficial but not deep microvasculature, indicating that these changes are confined to the upper plexus [7]. Autoradiographical and immunohistochemical studies have demonstrated proliferating endothelial cells in pustular and plaque forms of psoriasis, with a proliferation index of approximately 3% [7], indicating that vascular growth, or angiogenesis, is an important component of this process.

Using various *in vivo* models of angiogenesis, it has been demonstrated that epidermal keratinocytes are the primary source of angiogenic activity [8]. These cells produce an array of soluble mediators with angiogenic activity including vascular endothelial growth factor (VEGF). It is over-expressed in psoriatic epidermis as are its receptors on lesional psoriatic microvasculature [9]. Transgenic mice, which over-express VEGF in basal epidermis, have an expanded superficial dermal vasculature similar to that observed in psoriasis [10]. Interestingly, it has been shown in an animal model that cutaneous inflammation can be prevented by an inhibitor of VEGF pathways [11]. Some patients with erythrodermic or severe plaque psoriasis have evidence of systemic capillary leak such as proteinuria. In such patients, circulating VEGF is detectable and correlates with proteinuria [12]. While most studies suggest a primary role for the immune system in psoriasis pathogenesis (see below), it has been argued that vascular change precedes the immune response [13] and some evidence suggests a genetic link [14].

Table 20.2 Replicated genetic loci.

Gene/locus	Chromosomal location	Odds ratio	Putative function	Other disease association	Reference
PSORS1	6p	6.4	–	None	[26]
					[20]
PSORS2	17q	–	–	None	[27]
IL12B	5q	1.4	T-cell differentiation	Crohn's	[28]
					[29]
IL23A	12	1.34	T-cell differentiation	None	[30]
IL23R	1p	2.0	T-cell differentiation	Crohn's	[31]
				Ankylosing spondylitis	[29]
TNIP1	5	1.59	TNF-α pathway	None	[30]
LCE	1q	1.4	Stratum corneum	None	[32]
					[33]
ZNF313	20q	1.25	Ubiquitin pathway	None	[34]
PTPN22	18p	1.3	T-cell development	Type I DM	[35]
				JIA	[36]
				SLE	
				RA	
				Autoimmune thyroid disease	
CDKAL1	6p	1.26	Unknown	Crohn's + Type II DM	[31]

DM, diabetes mellitus; JIA, juvenile idiopathic arthritis; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis.

In addition to vascular growth, dermal capillaries contribute to the inflammatory process actively through surface expression of molecules involved in leukocyte homing, induced by inflammatory mediators such as histamine, neuropeptides, interleukin-1 (IL-1) and tumour necrosis factor-alpha (TNF-α). Importantly, E-selectin is induced and intercellular adhesion molecule-1 (ICAM-1) up-regulated on dermal vessels in lesional tissue, thus providing a mechanism for skin homing T lymphocytes to accumulate within lesional dermis and epidermis [2,15].

Molecular genetics

Classical, genome-wide linkage analysis has identified at least nine chromosomal loci with statistically significant evidence for linkage to psoriasis (nomenclature *PSORS1–9*) [16]. Of particular interest are *PSORS2*, a replicated locus on chromosome 17q, at which a polymorphism causing loss of binding to the RUNX1 transcription factor has been identified associated with psoriasis with low relative risk [17]; *PSORS4* [18], which is located within the epidermal differentiation complex on chromosome 1q and *PSORS8* [19], which overlaps with the Crohn's disease locus on chromosome 16q. The latter is of note because psoriasis and Crohn's disease are observed together more frequently than expected by chance (see below), although several studies have failed to find association of psoriasis with the *CARD15/NOD2* mutation linked to Crohn's disease.

However, by far the major psoriasis genetic determinant is *PSORS1*, which probably accounts for 35–50% of the heritability of the disease [20], and has been replicated in virtually all linkage studies [21]. *PSORS1* is located within the major histocompatibility complex (MHC) on chromosome 6p, spanning an approximate 300-kb segment within the class I region telomeric of HLA-B. The region contains fewer than 10 genes, of which three have been the major focus of attention for investigators, based on the strong association of polymorphic coding sequence variants with psoriasis vulgaris. HLA-C (associated variant = HLA-Cw6) encodes a class I MHC protein. *CCHCR1* (variant *WWCC*) encodes the coiled-coil x-helical rod protein 1, a ubiquitously expressed protein that is over-expressed in psoriatic epidermis [22]. *CDSN* (variant = allele 5) encodes corneodesmosin, a protein which is uniquely expressed in the granular and cornified layers of the epidermis and which is upregulated specifically in psoriasis [23]. Absolute identification of the causative gene at this locus has been hampered by the extensive linkage disequilibrium observed within the MHC.

Investigations have clearly shown that the phenotypic variants of psoriasis are genetically heterogeneous at least at the level of *PSORS1*. Thus guttate psoriasis is strongly *PSORS1* associated [24], whereas palmoplantar pustulosis and late-onset (>50 years of age) psoriasis vulgaris are not associated [25].

The availability of large, well-characterized cohorts of psoriasis patients together with advances in high-throughput genotyping at the genomic level have combined to permit disease case–control association studies producing robust replicated data on associated genes. Several genome-wide association (GWA) scans have now been reported which provide evidence for a multitude of genes involved in disease causation. These include genes involved in immune responses and epidermal function as well as those of (at present) unknown function (Table 20.2) [26–36]. Although the relative risk of associated polymorphisms in these genes is low, the importance of these genetic observations is that they highlight key biological pathways involved in psoriasis pathogenesis and point to potential therapeutic targets. Thus, these studies provide genetic support for the role of Th17 T cells in disease pathogenesis (see below) and provide a scientific rationale for the use of antibodies to p40 in disease management (see below) [37,38].

Immunology and inflammation

There is considerable evidence that T lymphocytes play an important role in development of plaques of psoriasis. This includes: (i) early influx of T cells into expanding lesions [39,40]; (ii) strong association with the MHC, particularly HLA-Cw6 [41]; (iii) ablative (albeit temporary) effect of anti-T-cell therapy [42]; (iv) increased antigen presentation in psoriatic plaques [43]; (v) anecdotal evidence of development of psoriasis after syngeneic bone marrow transplant [44]; and (vi) change in phenotype to lesional psoriatic skin in non-lesional psoriatic skin transplanted on to severe combined immunodeficient mice and injected with autologous T cells [45]. Those T cells involved in psoriasis pathogenesis express markers of memory, activation and skin homing (CLA) [46].

However, it is increasingly clear that the innate immune system, which provides an early response against harm to the host, is dysregulated in psoriasis [47]. Further, in psoriatic stratum corneum, there is an abundance of antimicrobial peptides such as defensins and cathelicidins, which have the capacity to activate innate immunity.

Innate immune mechanisms in turn lead to antigen driven T-cell expansion and activation. The key question remains as to the nature of the antigen involved. To date this is unresolved but evidence of an antigen-specific response includes: (i) limited clonality of infiltrating T cells; (ii) persistence of T-cell clones in plaques over several years; and (iii) identical T-cell clones in tonsils and skin of patients with *Streptococcus*-associated psoriasis [48].

Historically, evidence has suggested a primary role for Th1-type response in disease pathogenesis. However, it has recently been established that a more recently described subset of T cell, thought to play a key role in autoimmunity, termed Th17, is the primary pathogenic subset. Evidence includes genetic association (see above), with IL-23 being a key cytokine in generation of Th17 cells, abundance of IL-23 in psoriatic tissue [49] and induction of a psoriatic phenotype by IL-23 in animal models [50]. Other cytokines downstream of IL-23 in Th17 pathways, including IL-17 and IL-22, have similar functional effects.

Based on the above information, a pathogenic model has been suggested in which aberrations in the stratum corneum trigger activation of innate immune mechanisms, which in turn lead to recruitment and activation of Th17 cells, which provide effector cytokines leading to epidermal hyperproliferation and a pro-inflammatory state [3]. Such mechanisms provide a scientific rationale for the use of biological therapies (see Chapter 74).

References

1 Nickoloff BJ, Nestle FO. Recent insights into the immunopathogenesis of psoriasis provide new therapeutic opportunities. *J Clin Invest* 2004; **113**: 1664–75.
2 Griffiths CEM, Barker JNWN. Pathogenesis and clinical features of psoriasis. *Lancet* 2007; **370**: 263–71.
3 Nestle, F, Kaylan DH, Barker J. Psoriasis. *N Engl J Med* 2009; **361**: 496–509.
4 van de Kerkhof PCM. Pathogenesis. In: van de Kerkhof PCM, ed. *Textbook of Psoriasis*. Blackwell Science, 1999: 79–105.
5 Nickoloff BJ. The immunologic and genetic basis of psoriasis. *Arch Dermatol* 1999; **135**: 1104–10.
6 Elder JT, Fisher GJ, Lindquist PB *et al.* Overexpression of transforming growth factor-α in psoriatic epidermis. *Science* 1989; **243**: 811–4.
7 Creamer D, Allen MH, Sousa A *et al*. Localization of endothelial proliferation and microvascular expansion in active plaque psoriasis. *Br J Dermatol* 1997; **136**: 859–65.
8 Nickoloff BJ, Mitra RS, Varani J *et al*. Aberrant production of interleukin-8 and thrombospondin-1 by psoriatic keratinocytes mediates angiogenesis. *Am J Pathol* 1994; **144**: 820–8.
9 Detmar M, Brown LF, Claffey KP *et al.* Overexpression of vascular permeability factor/vascular endothelial growth factor and its receptors in psoriasis. *J Exp Med* 1994; **180**: 1141–6.
10 Detmar M, Brown LF, Schon MP *et al.* Increased microvascular density and enhanced leukocyte rolling and adhesion in the skin of VEGF transgenic mice. *J Invest Dermatol* 1998; **111**: 1–6.
11 Halin C, Fahrngruber H, Meingassner JG *et al*. Inhibition of chronic and acute skin inflammation by treatment with a vascular endothelial growth factor receptor tyrosine kinase inhibitor. *Am J Pathol* 2008; **173**: 265–77.
12 Creamer D, Allen M, Jaggar R *et al.* Mediation of systemic vascular hyperpermeability in severe psoriasis by circulating vascular endothelial growth factor. *Arch Dermatol* 2002; **138**: 791–6.
13 Goodfield M, Hull SM, Holland D *et al.* Investigations of the 'active' edge of plaque psoriasis: vascular proliferation precedes changes in epidermal keratin. *Br J Dermatol* 1994; **131**: 808–13.
14 Young HS, Summers AM, Bhushan M *et al*. Single-nucleotide polymorphisms of vascular endothelial growth factor in psoriasis of early onset. *J Invest Dermatol* 2004; **122**: 209–15.
15 Barker JNWN. The pathophysiology of psoriasis. *Lancet* 1993; **338**: 227–30.
16 Lowes MA, Bowcock AM *et al*. Pathogenesis and therapy of psoriasis. *Nature* 2007; **445**: 866–73.
17 Helms, C, Cao L *et al*. A putative RUNX1 binding site variant between SLC9A3R1 and NAT9 is associated with susceptibility to psoriasis. *Nat Genet* 2003; **35**: 349–56.
18 Capon F, Novelli G *et al*. Searching for psoriasis susceptibility genes in Italy: genome scan and evidence for a new locus on chromosome 1. *J Invest Dermatol* 1999; **112**: 32–5.
19 Karason AJ, Gudjonsson E *et al*. A susceptibility gene for psoriatic arthritis maps to chromosome 16q: evidence for imprinting. *Am J Hum Genet* 2003; **72**: 125–31.
20 Trembath RC, Clough RL *et al*. Identification of a major susceptibility locus on chromosome 6p and evidence for further disease loci revealed by a two stage genome-wide search in psoriasis. *Hum Mol Genet* 1997; **6**: 813–20.
21 Capon F, Munro M *et al*. Searching for the major histocompatibility complex psoriasis susceptibility gene. *J Invest Dermatol* 2002; **118**: 745–51.
22 Asumalahti K, Laitinen T *et al*. A candidate gene for psoriasis near HLA-C, HCR (Pg8), is highly polymorphic with a disease-associated susceptibility allele. *Hum Mol Genet* 2000; **9**: 1533–42.
23 Allen MH, Veal C *et al*. A non-HLA gene within the MHC in psoriasis. *Lancet* 1999; **353**: 1589–90.
24 Asumalahti K, Ameen M *et al*. Genetic analysis of PSORS1 distinguishes guttate psoriasis and palmoplantar pustulosis. *J Invest Dermatol* 2003; **120**: 627–32.
25 Allen MH, Ameen M *et al*. The major psoriasis susceptibility locus PSORS1 is not a risk factor for late-onset psoriasis. *J Invest Dermatol* 2005; **124**: 103–6.
26 Nair RP, Henseler T, Jenisch S *et al.* Evidence for two psoriasis susceptibility loci (HLA and 17q) and two novel candidate regions (16q and 20p) by genome-wide scan. *Hum Mol Genet* 1997; **6**: 1349–56.
27 Tomfohrde J, Silverman A, Barnes R *et al*. Gene for familial psoriasis susceptibility mapped to the distal end of human chromosome 17q. *Science* 1994; **264**: 1141–5.
28 Tsunemi Y, Saeki H *et al*. Interleukin-12 p40 gene (IL12B) 3'-untranslated region polymorphism is associated with susceptibility to atopic dermatitis and psoriasis vulgaris. *J Dermatol Sci* 2002; **30**: 161–6.
29 Cargill M, Schrodi SJ *et al*. A large-scale genetic association study confirms IL12B and leads to the identification of IL23R as psoriasis-risk genes. *Am J Hum Genet* 2007; **80**: 273–90.
30 Nair RP, Duffin KC *et al*. Genome-wide scan reveals association of psoriasis with IL-23 and NF-kappaB pathways. *Nat Genet* 2009; **41**: 199–204.
31 Wolf N, Quaranta M *et al*. Psoriasis is associated with pleiotropic susceptibility loci identified in type II diabetes and Crohn disease. *J Med Genet* 2008; **45**: 114–6.
32 Zhang XJ, Huang W *et al*. Psoriasis genome-wide association study identifies susceptibility variants within LCE gene cluster at 1q21. *Nat Genet* 2009; **41**: 205–10.



(a) (b)

Fig. 20.2 (a,b) Psoriasis: Koebner phenomenon. (Courtesy of St John's Institute of Dermatology, London, UK.)

33 de Cid R, Riveira-Munoz E *et al*. Deletion of the late cornified envelope LCE3B and LCE3C genes as a susceptibility factor for psoriasis. *Nat Genet* 2009; **41**: 211–5.

34 Capon F, Bijlmakers MJ *et al*. Identification of ZNF313/RNF114 as a novel psoriasis susceptibility gene. *Hum Mol Genet* 2008; **17**: 1938–45.

35 Hüffmeier U, Steffens M *et al*. Evidence for susceptibility determinant(s) to psoriasis vulgaris in or near PTPN22 in German patients. *J Med Genet* 2006; **43**: 517–22.

36 Smith RL, Warren RB *et al*. Polymorphisms in the PTPN22 region are associated with psoriasis of early onset. *Br J Dermatol* 2008; **158**: 962–8.

37 Krueger GG, Langley RG *et al*. A human interleukin-12/23 monoclonal antibody for the treatment of psoriasis. *N Engl J Med* 2007; **356**: 580–92.

38 Kimball AB, Gordon KB *et al*. Safety and efficacy of ABT-874, a fully human interleukin 12/23 monoclonal antibody, in the treatment of moderate to severe chronic plaque psoriasis: results of a randomized, placebo-controlled, phase 2 trial. *Arch Dermatol* 2008; **144**: 200–7.

39 Bos JD, Hulsebosch HJ, Krieg SR. Immunocompetent cells in psoriasis: *in situ* immunophenotyping by monoclonal antibodies. *Arch Dermatol Res* 1983; **275**: 181–9.

40 Baker BS, Swain AF, Fry L, Valdimarsson H. Epidermal T lymphocytes and HLA-DR expression in psoriasis. *Br J Dermatol* 1984; **110**: 555–64.

41 Tiilikainen A, Lassus A, Karvonen J *et al*. Psoriasis and HLA-Cw6. *Br J Dermatol* 1980; **102**: 179–84.

42 Kirby B, Griffiths CEM. Novel immune-based therapies for psoriasis. *Br J Dermatol* 2002; **146**: 546–51.

43 Baadsgaard O, Gupta AK, Taylor RS *et al*. Psoriatic epidermal cells demonstrate increased numbers and function of non-Langerhans' antigen-presenting cells. *J Invest Dermatol* 1989; **92**: 190–5.

44 Snowden JA, Heaton DC. Development of psoriasis after syngeneic bone marrow transplant from psoriatic donor: further evidence for adoptive autoimmunity. *Br J Dermatol* 1997; **137**: 130–2.

45 Wrone-Smith T, Nickoloff BJ. Dermal injection of immunocytes induces psoriasis. *J Clin Invest* 1996; **98**: 1878–87.

46 Bos JD, De Rie MA. The pathogenesis of psoriasis: immunological facts and speculations. *Immunol Today* 1999; **20**: 40–6.

47 Nickoloff BJ. Skin innate immune system in psoriasis: friend or foe? *J Clin Invest* 1999; **104**: 1161–4.

48 Diluvio L, Vollmer S, Besgen G *et al*. Identical TCR beta-chain rearrangements in streptococcal angina and skin lesions of patients with psoriasis vulgaris. *J Immunol* 2006; **176**: 7104–11.

49 Lee E, Treppichio WL, Ostreicher JL *et al*. Increased expression of interleukin 23 p19 and p40 in lesional skin of patients with psoriasis vulgaris. *J Exp Med* 2004; **199**: 125–30.

50 Chan JR, Blumenschein W, Murphy E *et al*. IL-23 stimulates epidermal hyperplasia via TNF and IL-20R2–dependent mechanisms with implications for psoriasis pathogenesis. *J Exp Med* 2006; **203**: 2577–87.

Koebner and reverse Koebner phenomena [1]

Psoriasis is one of several conditions in which various types of trauma may elicit the disease in previously uninvolved skin [2] (Koebner reaction; Fig. 20.2). The Koebner reaction usually occurs 7–14 days after injury [3], and the reported incidence has varied between 38 and 76% of patients with psoriasis [4]. In a given patient, an all-or-none phenomenon occurs at multiple sites of injury, that is if psoriasis occurs at one site of injury it does so at all sites of injury [5,6]. Clearing of existing psoriasis following injury has been observed and termed the reverse Koebner reaction [5]. This reaction also obeys an all-or-none rule, and the Koebner and reverse Koebner reactions are mutually exclusive [5]. Using a standardized injury, one study found that 25% of patients gave a Koebner reaction and 67% a reverse Koebner reaction [5].

The Koebner reaction is often thought to be more frequent in actively spreading, severe psoriasis. Although this may be true, it has yet to be established by prospective studies [1]. The reaction does, however, appear to be a marker for a subgroup of patients

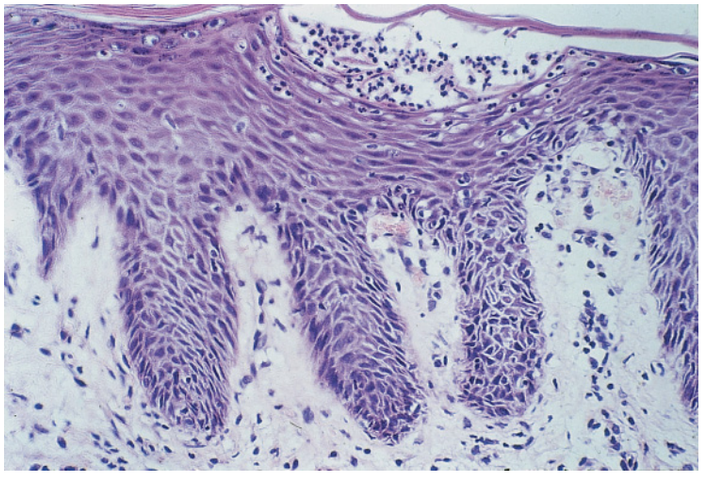


Fig. 20.3 Psoriasis: intraepidermal spongiform pustule. H&E, × 100. (Courtesy of St John's Institute of Dermatology, London, UK.)

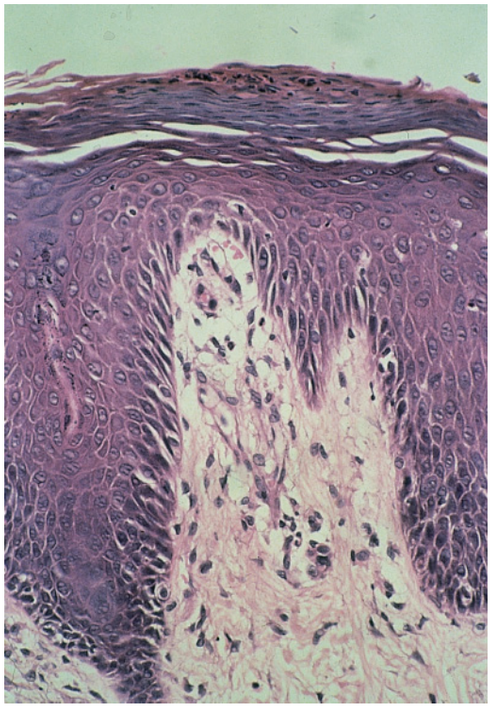


Fig. 20.4 Psoriasis: Munro microabscess formation in lesional stratum corneum. H&E, × 200. (Courtesy of St John's Institute of Dermatology, London, UK.)

with a tendency to early onset and early relapse after various forms of therapy [7].

References

1 Eyre RW, Krueger GG. The Koebner response in psoriasis. In: Roenigk HH, Maibach HI, eds. *Psoriasis*. New York: Marcel Dekker, 1985: 105–16.
2 Koebner H. Klinische, experimentelle und therapeutische Mitteilungen uber Psoriasis. *Berlin Klin Wochenschr* 1878; **21**: 631–2.
3 Illig L, Holz U. Die Blutgefässreaktion bei der Psoriasis vulgaris; das experimentelle Koebner Phänomen. *Arch Klin Exp Dermatol* 1966; **226**: 239–64.
4 Farber EM, Nall LM. The natural history of psoriasis in 5600 patients. *Dermatologica* 1974; **148**: 1–18.
5 Eyre RW, Krueger GG. Response to injury of skin involved and uninvolved with psoriasis and its relation to disease activity. *Br J Dermatol* 1982; **106**: 153–9.
6 Pedace FJ, Muller SA, Winkelmann RK. The biology of psoriasis: an experimental study of the Koebner phenomenon. *Acta Derm Venereol* 1969; **49**: 390–400.
7 Melski JW, Bernhard JD, Stern RS. The Koebner (isomorphic) response in psoriasis. *Arch Dermatol* 1983; **119**: 655–9.

Histopathology

Early changes

Vasodilatation, papillary oedema and leukocyte infiltrates appear to precede epidermal changes in early developing lesions [1]. Compact hyperkeratosis, disappearance of the granular layer and slight epidermal hyperplasia follow. Mitotic figures in keratinocytes, and leukocytic infiltration in spongiotic foci, are seen in the lower half of the epidermis. Scattered mounds of parakeratosis, set in a still predominantly orthokeratotic stratum corneum, appear, with or without neutrophils. In the Malpighian layer, neutrophils may accumulate to form the characteristic spongiform pustules of Kogoj [2] (Fig. 20.3). Epidermal hyperplasia with rete ridges of even length and prominently dilated, tortuous papillary capillaries associated with mixed mononuclear and neutrophil infiltrates are seen [1,3].

Changes in fully developed plaques

There is parakeratosis associated with focal orthokeratosis and Munro microabscess formation (Fig. 20.4), near absence of the granular layer, spongiform pustules in the Malpighian layer [2], hyperplasia with elongation of rete ridges and suprapapillary epidermal thinning (Fig. 20.5). The rete ridges are often clubbed, branched or fused at their bases, with mononuclear leukocyte infiltrates in the lower half of the epidermis. Dilated, tortuous papillary blood vessels almost touch the undersurface of the thinning suprapapillary epidermis and are surrounded by a mixed mononuclear and neutrophil infiltrate, as well as extravasated erythrocytes. Invasion of the epidermis with leukocytes takes place particularly in the suprapapillary region [1,3,4].

References

1 Ragaz A, Ackerman AB. Evolution, maturation and regression of lesions of psoriasis. *Am J Dermatopathol* 1979; **1**: 199–214.
2 Kogoj F. Un cas de maladie de Hallopeau. *Acta Derm Venereol (Stockh)* 1927; **8**: 1–12.
3 Lever WF, Lever GS, eds. *Histopathology of the Skin*, 8th edn. Philadelphia: Lippincott, 1997.
4 Helwig EB. Pathology of psoriasis. *Ann NY Acad Sci* 1958; **73**: 924–35.

Clinical features

Modes of onset

The first manifestation of psoriasis may occur at any age. The common ages of onset, and the tendency for females to develop psoriasis earlier than males, are described above. Its duration may

vary from a few weeks to a whole lifetime. The course is unpredictable and the variations numerous. Certain patterns are, however, more common than others.

The patterns of onset in childhood, including congenital psoriasis, are discussed below [1]. Acute guttate attacks characteristically occur in this age group. Nail changes may herald the development of psoriasis elsewhere, or remain localized for several years. Most forms of psoriasis present before the fourth decade.

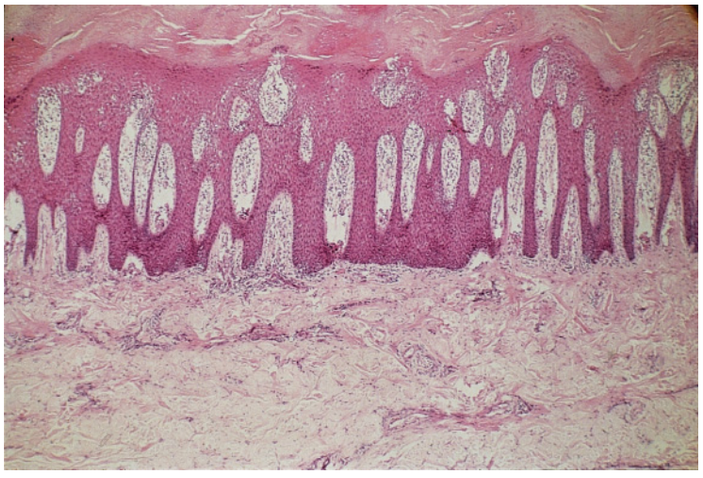


Fig. 20.5 Psoriasis: irregular epidermal hyperplasia with suprapapillary thinning. H&E, × 50. (Courtesy of St John's Institute of Dermatology, London, UK.)

Post-traumatic psoriasis is not uncommon in young, athletic men, who develop psoriasis initially at the site of injury, and later elsewhere. Minor lacerations of the legs during shaving are believed to precipitate psoriasis in some women. Flexural varieties make their appearance either alone or following a pre-existing intertrigo from other causes. Flexural lesions become increasingly common in obese, middle-aged subjects. Psoriasis entirely limited to the groins, perineal and perianal regions may develop insidiously and often remains undiagnosed for several years.

In old age, psoriasis may appear unexpectedly for the first time, either spontaneously or following a pre-existing skin disease. Onset at the age of 108 years has been reported [2].

References

1 Lerner MR, Lerner AB. Congenital psoriasis: report of three cases. *Arch Dermatol* 1972; **105**: 598–601.

2 Buntin DM, Skinner RB, Rosenberg EW. Onset of psoriasis at age 108 (Letter). *J Am Acad Dermatol* 1983; **9**: 276–7.

Morphology of common chronic stable plaque psoriasis (psoriasis vulgaris) [1–3]

The appearance of a typical lesion is characteristic (Fig. 20.6). The diagnostic features may not all be present at the same time or in every case, and are sometimes obscured or evanescent.

The colour, a full rich red (often referred to as 'salmon pink'; Fig. 20.7), has a particular depth of hue not normally seen in eczema, seborrhoeic dermatitis or lichen simplex. This quality of colour is of special diagnostic value in lesions on the palms, soles and scalp. On the legs, a bluish tint is often present, but this differs from the violaceous hue of lichen planus. In the fair-skinned indi-



(a)



(b)

Fig. 20.6 (a,b) Extensive chronic plaque psoriasis. (Courtesy of St John's Institute of Dermatology, London, UK.)

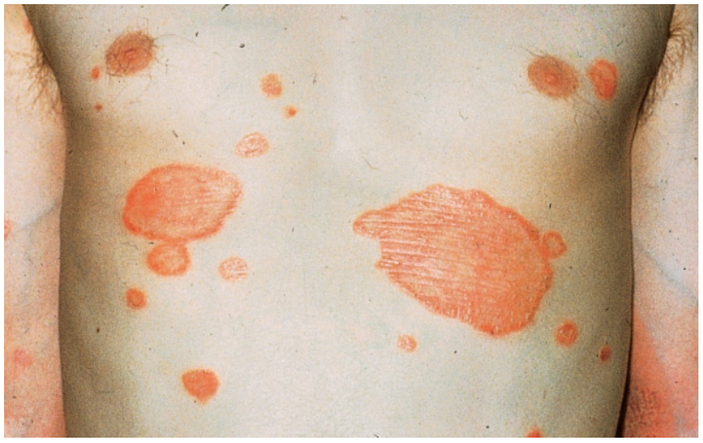


Fig. 20.7 The 'salmon pink' colour of psoriatic lesions. (Courtesy of St John's Institute of Dermatology, London, UK.)



Fig. 20.8 Psoriasis: in the darker-skinned individual, the characteristic red colour is lost, although silvery scaling is readily seen. (Courtesy of St John's Institute of Dermatology, London, UK.)

vidual, the colour is less rich and almost magenta pink. In dark-skinned races, the quality of the colour is lost (Fig. 20.8).

The amount of scaling is variable. It may, as in rupioid forms, be waxy yellow or orange–brown. A similar colour occurs in nails ('oil drop sign'), but most psoriatic lesions are surmounted by the very characteristic silvery white scaling, which varies considerably in thickness (Fig. 20.8). The successive removal of psoriatic scales usually reveals an underlying smooth, glossy red membrane with small bleeding points where the thin suprapapillary

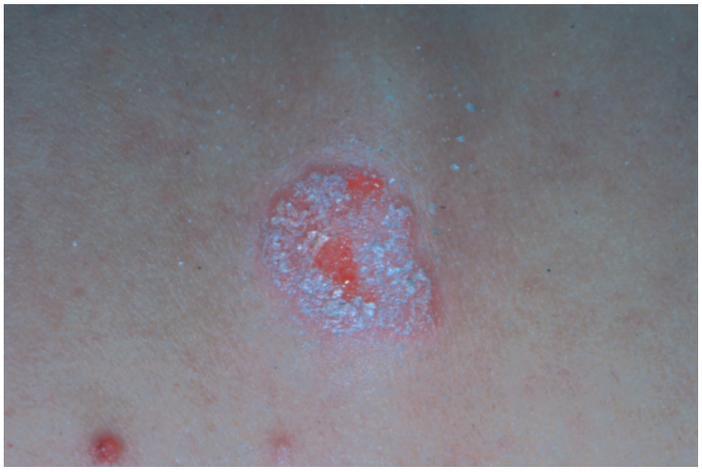


Fig. 20.9 Auspitz's sign: removal of the thinned suprapillary epidermis, by gentle scraping, reveals vascular bleeding points.

epithelium is torn off (Auspitz's sign) (Fig. 20.9). When scaling is not evident, it may often be induced by light scratching, a useful sign in diagnostically uncertain lesions.

Psoriatic lesions exhibit a considerable degree of uniformity, modified little by site except on the palms and soles. The colour remains consistent, although the scaling varies in degree.

The lesions are well defined, with a sharply delineated edge. When they merge, annular and gyrate figures may be produced. This definition is of special diagnostic value on the scalp and penis, when other evidence of psoriasis is absent, and in the flexures.

The epidermal thickening characteristic of the psoriatic process causes the lesions to be raised from the adjoining skin, and easily palpable. When the hyperkeratosis is removed by thorough washing or treatment, this character may sometimes be lost temporarily.

Discs and plaques of varying sizes are often found on the trunk and limbs. They vary in diameter from one to several centimetres and are oval or irregular in shape. There may be any number of lesions or only a single one and, when multiple, may be symmetrically distributed. Large plaques form by their coalescence and are commonly seen on the legs and sacral region. When plaques occur across the line of joint movement, fissuring may occur.

The psoriatic plaque may be encircled by a clear peripheral zone, the halo or ring of Woronoff (Fig. 20.10) [4]. The variety of morphologies of chronic plaque psoriasis has led some authors to attempt a reclassification according to phenotype and to speculate that 'psoriasis' may in fact be several distinct diseases [3,5].

Clinical variants

Guttate psoriasis

This describes the shower of small lesions, appearing more or less generally over the body, particularly in children and young adults, and after acute streptococcal infections (Fig. 20.11). In the early stages, there may be little scaling. The lesions are from 2 or 3 mm to 1 cm in diameter, round or slightly oval. They are scattered more or less evenly over the body, particularly on the trunk and



Fig. 20.10 Woronoff's ring: vasoconstriction around active plaques of psoriasis.



Fig. 20.11 Guttate psoriasis. (Courtesy of St John's Institute of Dermatology, London, UK.)

proximal part of the limbs, rarely on the soles but not infrequently on the face, ears and scalp. The lesions on the face are often sparse, difficult to see and disappear quickly. Although guttate lesions are normally profuse, there are occasionally no more than half a dozen present on the body, and in the early stages the colour is not specific. The diagnosis is made chiefly on the nature of the scaling, the general distribution and evidence for preceding infection. In one series, only 1.9% of all affected psoriatics showed this form [2].

Rupioid, elephantine and ostraceous psoriasis

These terms describe plaques associated with gross hyperkeratosis. Rupioid psoriasis refers to limpet-like cone-shaped lesions.



Fig. 20.12 Elephantine psoriasis: large plaques with gross hyperkeratosis. (Courtesy of St John's Institute of Dermatology, London, UK.)

The term elephantine psoriasis might be used to describe unusual but very persistent, thickly scaling, large plaques that sometimes occur on the back, limbs, hips or elsewhere (Fig. 20.12). Ostraceous psoriasis, an infrequently used term, refers to a ring-like hyperkeratotic lesion with a concave surface, resembling an oyster shell.

'Unstable' psoriasis

This term, which has no aetiological connotation, may be usefully employed to describe phases of the disease in which activity is marked and the course and immediate outcome unpredictable; for example, in stages when a previously stable and chronic form is exacerbated by inappropriate management and threatens to become erythrodermic or pustular, or when localized pustular or ill-defined erythematous lesions appear spontaneously for the first time. Patients may develop such unstable phases repeatedly, settling back again into the classical forms of the disease. Withdrawal of intensive systemic or topical corticosteroid therapy, hypocalcaemia, acute infection, overtreatment with tar, dithranol or UV irradiation, and perhaps severe emotional upset, may precipitate this condition.

Pustular psoriasis

See below.

References

1 Hellgren L, ed. *Psoriasis: The Prevalence in Sex, Age and Occupational Groups in Total Populations in Sweden. Morphology, Inheritance and Association with Other Skin and Rheumatic Diseases.* Stockholm: Almqvist & Wiksell, 1967: 55–63.

2 Ingram JT. The significance and management of psoriasis. *BMJ* 1954; **ii**: 823–8.

3 Griffiths CEM, Christophers E, Barker JNWN *et al.* A classification of psoriasis according to phenotype. *Br J Dermatol* 2007; **156**: 258–62.

4 Penneys NS, Ziboh V, Simon P *et al.* Pathogenesis of Woronoff ring in psoriasis. *Arch Dermatol* 1976; **112**: 955–7.

5 Rakkhit T, Panko JM, Christensen TE *et al.* Plaque thickness and morphology in psoriasis vulgaris associated with therapeutic response. *Br J Dermatol* 2009; **160**: 1083–9.

Erythrodermic psoriasis [1–3]

Two forms exist [4]. In the first form, chronic lesions may evolve gradually into an exfoliative phase, and can be regarded as extensive plaque psoriasis involving all, or almost all, the cutaneous surface (Fig. 20.13). There are usually some areas of uninvolved



Fig. 20.13 Extensive chronic plaque psoriasis with coalescence of lesions and the potential to evolve into an erythrodermic form. (Courtesy of St John's Institute of Dermatology, London, UK.)



Fig. 20.14 Acute unstable erythrodermic psoriasis. (Courtesy of St John's Institute of Dermatology, London, UK.)

skin. The psoriatic characteristics are retained, mild treatment is well-tolerated and the prognosis is good.

The second form is part of the spectrum of 'unstable' psoriasis (Fig. 20.14) [5]. It may occur at any time, either presenting suddenly and unexpectedly, or be ushered in by a period of increasing intolerance to local applications, UV therapy and of loss of control over the disease. It is more frequent in arthropathic psoriasis [6]. Generalized pustular psoriasis may revert to an erythrodermic state. It can be precipitated by infections, hypocalcaemia, antimalarials, tar [7] and classically by withdrawal of corticosteroids [8]. The characteristics of the disease are often lost, the whole skin is involved, the patient may be febrile and ill, the course is often prolonged, relapses are frequent and there is an appreciable mortality. In contrast to the stable form, itching is often severe.

Metabolic complications of erythroderma [2]

Persistent, universal inflammation of the skin may have important consequences for thermoregulation, haemodynamics, intestinal absorption, protein, water and other metabolism.

Under normal environmental conditions, radiant and convective heat loss from the body surface is increased, occasionally leading to dangerous hypothermia [9]. An increase in metabolic activity provides compensatory increases in body heat production, but at the expense of tissue catabolism and muscle wasting if prolonged. At the same time, the psoriatic or erythrodermic skin is hypohidrotic or anhidrotic [9], because of intraepidermal occlusion of the sweat duct [10]. Hyperthermia is a hazard in very high (e.g. tropical) ambient temperatures.

Skin blood flow, blood volume and cardiac output may all be increased, and if these changes persist, they may lead to failure of a cardiovascular system already compromised by hypertension, myocardial or valvular heart disease, or anaemia (particularly in old people). A healthy cardiovascular system will tolerate the increased metabolic demand for years. Malabsorption (dermatogenic enteropathy) may occur, reverting as the psoriasis remits, but earlier reports of structural small bowel changes have not been confirmed [11].

The principal loss in the profuse scaling of exfoliative psoriasis is of protein (keratin) but some iron is also lost. In fulminating psoriasis, further protein loss may be attributable to enteropathy, as well as leakage from the circulation into the skin [12]. Eventually, hypoalbuminaemia may contribute to the oedema caused by the skin inflammation itself, or cardiac failure. Mild anaemia is prone to develop, because of a combination of iron loss and possibly impaired absorption and utilization of iron. Serum and red cell folate and serum B_{12} may also be low.

The barrier efficiency of the skin in psoriatic erythroderma is impaired, the chief effect being increased transepidermal water loss. The urine output tends to drop and, if water intake is inadequate for any reason, dehydration results.

References

1 Goeckerman WH, O'Leary PA. Erythroderma psoriaticum. *JAMA* 1932; **99**: 2102–5.

2 Marks J. Erythroderma and its management. *Clin Exp Dermatol* 1982; **7**: 415–22.

3 Reed WB, Becker SW, Rohde R *et al.* Psoriasis and arthritis. *Arch Dermatol* 1961; **83**: 541–8.

4 Cornbleet T. Action of synthetic antimalarial drugs on psoriasis. *J Invest Dermatol* 1956; **26**: 435–6.

5 Griffiths CEM, Christophers E, Barker JNWN *et al.* A classification of psoriasis according to phenotype. *Br J Dermatol* 2007; **156**: 258–62.

6 Wright V, Reed WB. The link between Reiter's syndrome and psoriatic arthritis. *Ann Rheum Dis* 1964; **23**: 12–21.

7 Starke JC, Jillson OF. Photosensitization to coal tar. *Arch Dermatol* 1961; **84**: 935–6.



Fig. 20.15 Pityriasis amiantacea in a patient with psoriasis. (Courtesy of St John's Institute of Dermatology, London, UK.)

8 Baker H. Corticosteroids and pustular psoriasis. *Br J Dermatol* 1976; **94** (Suppl. 12): 83–8.

9 Grice K, Blendis LM, Keir MI *et al.* Accidental hypothermia in erythroderma from generalized psoriasis. *Arch Dermatol* 1968; **98**: 263–7.

10 Johnson C, Shuster S. Eccrine sweating in psoriasis. *Br J Dermatol* 1969; **81**: 119–24.

11 Feibleman CE, Dobson RL. Disturbances of sweating in psoriasis. In: Farber EM, Cox AJ, eds. *Psoriasis. Proceedings of the 1st International Symposium*. Stanford: Stanford University Press, 1971: 105–9.

12 Preger L, Maibach HI, Osborne RB *et al.* On the question of psoriatic enteropathy. *Arch Dermatol* 1970; **102**: 151–3.

Modification by site

Scalp

Often, very thick plaques develop, especially at the occiput. The whole scalp may be diffusely involved, or multiple discrete plaques of varying size may be seen [1]. A morphological entity consisting of plaques of asbestos-like scaling, firmly adherent to the scalp and associated hair, has been termed pityriasis (tinea) amiantacea [2] (Fig. 20.15). It is most common in children and young adults, and is best regarded as a non-specific reaction pattern, which may be seen in other scaling scalp conditions. It may be an early manifestation occurring before the other stigmata of psoriasis. Hair loss, sometimes cicatricial, is seen in pityriasis amiantacea. Otherwise, common scalp psoriasis is not a frequent cause of alopecia, although it may occur [3]. Psoriatic erythroderma is associated with severe hair loss, as is vigorous local treatment. Hair-shaft abnormalities have been described on electron microscopy [3], but the rate of hair growth is normal [4].

Penis (Fig. 20.16)

A solitary patch on the glans of the uncircumcised male lacks scales, but its colour and well-defined edge are usually distinctive. Where confirmatory signs elsewhere are absent, a diagnostic biopsy may be necessary, as it may resemble erythroplasia or Zoon's plasma cell balanitis (see Chapter 71).



Fig. 20.16 Psoriasis: circumcised penis. (Courtesy of St John's Institute of Dermatology, London, UK.)



Fig. 20.17 Psoriasis: vulval region. (Courtesy of St John's Institute of Dermatology, London, UK.)

Flexural (inverse) psoriasis

Psoriasis involving the groins, vulva (Fig. 20.17), axillae, submammary folds, gluteal cleft and other body folds is more common in older adults than children. The frequency with which the genital area alone is involved appears to be low, but this area is not uncommonly involved together with other areas [5].

Scaling is greatly reduced or absent, and an assured diagnosis may therefore be difficult. Flexural psoriasis may occur as a primary disorder or as a Koebner phenomenon on top of infective or seborrhoeic intertriginous dermatoses. Failure to respond to antibacterial or antifungal preparations should arouse suspicion.



Fig. 20.18 Psoriasis of soles. (Courtesy of St John's Institute of Dermatology, London, UK.)



Fig. 20.19 Psoriasis of palms and fingers with sharply demarcated edge on forearms. (Courtesy of St John's Institute of Dermatology, London, UK.)

Although the lesions are themselves anhidrotic [6], the effect of hyperhidrosis of the surrounding skin, maceration and friction alter the appearance of the psoriasis, which retains its characteristic colour. The surface has a glazed hue and fissuring at the depth of the fold is common, especially in the gluteal cleft. The edges of the lesions are usually well-defined, unless secondary infection or medicament dermatitis, both quite common events, have occurred. Psoriasis of the retroauricular fold or the external auditory meatus may be particularly difficult to distinguish from infective or seborrhoeic dermatitis.

Hands and feet [7]

On the palms and soles (Fig. 20.18), psoriasis may present as typical scaly patches on which a fine silvery scale can be evoked by scratching; as less well-defined plaques resembling lichen simplex or hyperkeratotic eczema; or as a pustulosis. Mixed forms occasionally occur. It may often be difficult to distinguish the psoriasis from eczema, with which it may sometimes alternate. A sharply defined edge at the wrist or forearm (Fig. 20.19) and absence of vesiculation are helpful. On the dorsal surface, the knuckles frequently show a dull red thickening of the skin. Elsewhere on the hands and feet, psoriasis retains its typical character. There may be a relationship to trauma or occupational irritants.

Nail involvement [8,9]

This is seen in association with all types of psoriasis of the skin, and is frequently present with psoriatic arthropathy [10,11]. Figures for its incidence vary considerably. Minor degrees of involvement (e.g. pitting) are difficult to define and may occur in apparently normal subjects. If looked for carefully, nail changes are present in 25–50% of all cases [12]. There is no sex predilection, but patients over 40 years of age are affected twice as often as those under 20 years. Nail disease is more likely to be severe if psoriasis is early onset and familial [13].



Fig. 20.20 Fingernail pitting in psoriasis. (Courtesy of St John's Institute of Dermatology, London, UK.)

Although pitting (Fig. 20.20) is the most frequent change seen, discoloration, subungual hyperkeratosis (Fig. 20.21) and onycholysis are common, and splinter haemorrhages occur. Longitudinal biopsy of the nail bed and matrix has clarified understanding of these changes [14,15]. Pits, ridges and grooves are a result of



Fig. 20.21 Subungual hyperkeratosis in psoriasis. (Courtesy of St John's Institute of Dermatology, London, UK.)

psoriasis of the nail matrix, whereas onycholysis, subungual hyperkeratosis and splinter haemorrhages are attributable to disease of the nail bed or hyponychium [16]. Circular areas of discoloration of the nail bed and hyponychium may resemble an 'oil drop' below the nail. Histologically, these are areas of psoriatic change in the hyponychium [14]. *Candida* species frequently contaminate the psoriatic nail and bed, but dermatophytes are rare. In one series, 19 of 105 patients with candidal paronychia were found to have psoriasis [17].

References

1 Farber EM, Bright RD, Nall LM. Psoriasis. *Arch Dermatol* 1968; **98**: 248–59.
2 Knight AG. Pityriasis amiantacea: a clinical and histopathological investigation. *Clin Exp Dermatol* 1977; **2**: 137–43.
3 Shuster S. Psoriatic alopecia. *Br J Dermatol* 1972; **87**: 73–7.
4 Comaish S. Autoradiographic studies of hair growth in various dermatoses: investigation into a possible circadian rhythm in human hair growth. *Br J Dermatol* 1969; **81**: 283–8.
5 Lomholt G, ed. *Psoriasis: Prevalence, Spontaneous Course and Genetics*. Copenhagen: GEC Gad, 1963: 54–6.
6 Mitchell JC, Forstner J. Eccrine function in psoriasis inversus. *Can Med Assoc J* 1962; **87**: 1093–5.
7 Samitz MH, Albom JJ. Palmar psoriasis. *Arch Dermatol Syphilol* 1951; **64**: 199–204.
8 Pardo-Castello V, Pardo OA, eds. *Diseases of the Nails*. Springfield: Thomas, 1960.
9 Samman PD, ed. *The Nails in Disease*, 3rd edn. London: Heinemann, 1978.
10 Baker H, Golding DN, Thompson N. The nails in psoriatic arthritis. *Br J Dermatol* 1964; **76**: 549–54.
11 Lewin K, DeWit S, Ferrington RA. Pathology of the fingernail in psoriasis. *Br J Dermatol* 1972; **86**: 555–63.
12 Buchner A, Begleiter A. Oral lesions in psoriatic patients. *Oral Surg Oral Med Oral Pathol* 1976; **41**: 327–32.
13 Stuart P, Malick F, Nair RP *et al.* Analysis of phenotypic variation in psoriasis as a function of age at onset and family history. *Arch Dermatol Res* 2002; **294**: 207–13.
14 Kouskoukis CE, Scher RK, Ackerman AB. The 'oil drop' sign of psoriatic nails: a clinical finding specific for psoriasis. *Am J Dermatopathol* 1983; **5**: 259–62.
15 Zaias N. Psoriasis of the nail. *Arch Dermatol* 1969; **99**: 567–79.
16 Robbins TO, Kouskoukis CE, Ackerman AB. Onycholysis in psoriatic nails. *Am J Dermatopathol* 1983; **5**: 39–41.
17 Ganor S. Diseases sometimes associated with psoriasis. *Dermatologica* 1977; **154**: 268–72.

Psoriasis in children [1–4]

Psoriasis is quite common in children; in approximately one-third of patients psoriasis begins in the first two decades of life [5]. Congenital psoriasis is very rare [6]. Guttate psoriasis is discussed below. Apart from the common forms, several other patterns of psoriasis occur in childhood. Interdigital tinea is uncommon in children and a toe cleft intertrigo may be psoriatic. Other flexural forms also occur (Fig. 20.17). The disease may mimic chronic blepharitis or perleche, usually unilaterally, with a small plaque of psoriasis on one eyelid extending to the lid margin, or on the cheek at the angle of the mouth. Psoriasis involving the face appears more common in children than adults [7]. In an Australian study of 1261 children with psoriasis, 26% had a psoriatic rash in the napkin area and facial involvement occurred in 38% [8]. The disease often first appears in the scalp [4], where it may present as pityriasis amiantacea (Fig. 20.15). An indolent pustular acrodermatitis, sometimes of only one digit, usually eventually proves to be psoriatic. More extensive, chronic lesions of the hands and feet may occur with persistent dryness, hyperkeratosis and fissuring. Pitting of the fingernails may be the only manifestation for months or even years. Follicular psoriasis occurs on the extensor prominences of elbows and knees. A child with apparently true psoriasis in a unilateral linear distribution has been reported [9].

All the more serious forms of the disease occur in childhood but are rare. Erythrodermic psoriasis [10] may be intractable for years and may or may not become pustular. Generalized pustular psoriasis is well documented in childhood [11,12]. Arthropathic psoriasis is rare but has been reported.

References

1 Beylot C, Puissant A, Bioulac P *et al.* Particular clinical features of psoriasis in infants and children. *Acta Derm Venereol (Stockh)* 1979; **59** (Suppl. 87): 95–7.
2 Farber EM, Mullen RH, Jacobs AH *et al.* Childhood psoriasis. *Pediatr Dermatol* 1986; **3**: 237–43.
3 Hutton KP, Orenberg EK, Jacobs AH. Childhood psoriasis. *Cutis* 1987; **39**: 26–7.
4 Nyfors A. Psoriasis in children. *Acta Derm Venereol (Stockh)* 1981; **61** (Suppl. 95): 47–53.
5 Benoit S, Hamm H. Childhood psoriasis. *Clin Dermatol* 2007; **25**: 555–62.
6 Lerner MR, Lerner AB. Congenital psoriasis. *Arch Dermatol* 1972; **105**: 598–601.
7 Bernhard JE. Clinical differences in juvenile versus adult-onset psoriasis (Letter). *Br J Dermatol* 1996; **135**: 501.
8 Morris A, Rogers M, Fischer G, Williams K. Childhood psoriasis: a clinical review of 1262 cases. *Pediatr Dermatol* 2001; **18**: 188–98.
9 Atherton DJ, Kahana M, Russell-Jones R. Naevoid psoriasis. *Br J Dermatol* 1989; **120**: 837–41.
10 Pascher F, Wood WS. Erythrodermic psoriasis in children. *Arch Dermatol* 1956; **74**: 173–6.
11 Beylot C, Bioulac P, Grupper C *et al.* Generalized pustular psoriasis in infants and children: report of 27 cases. In: Farber EM, Cox AJ, Jacobs PH, Nall LM, eds. *Psoriasis. Proceedings of the 2nd International Symposium*. New York: Yorke Medical, 1977: 171–9.
12 McGibbon DH. Infantile pustular psoriasis. *Clin Exp Dermatol* 1979; **4**: 115–8.

Atypical forms [1,2]

In a disease as common and variable as psoriasis, atypical forms are frequent. Many unusual localizations have been recorded,

including digital and interdigital forms. Verrucous lesions particularly affect the legs. A follicular form, especially in children, may be confused with pityriasis rubra pilaris but this form seems to be more common in the elderly [3,4]. A lichenoid variety has been reported to involve the flexures or the extremities in a 'glove and stocking' distribution [5].

Linear and zonal lesions

Linear psoriasis may occur in the presence of other typical lesions, as part of the Koebner phenomenon. Zonal lesions may represent a Koebner reaction at a site of herpes zoster. True linear psoriasis in the absence of lesions elsewhere is extremely unusual. It may be confused with inflammatory linear verrucous epidermal naevus (ILVEN) or may occur as a Koebner response on verrucous epidermal naevi of the non-inflammatory type [5]. True psoriasis arranged in linear bands unilaterally has also been described [6].

'Seborrhoeic psoriasis'

There is no reason why a genetically constituted psoriatic should not develop seborrhoeic dermatitis. Lesions involving the scalp, eyebrows and the region of the ears are often of this type, having features of both diseases or changing during the course of observation. Difficulties also occur in the flexures as in the 'napkin psoriasis' of infants [7] and in obese, middle-aged or elderly patients.

Mucosal lesions

True mucosal involvement by psoriasis appears to be rare, but has been associated with cutaneous involvement by pustular, erythrodermic and plaque forms [8–12]. Various lesions have been described, including grey, yellowish, white or translucent plaques or annular forms, diffuse areas of erythema and the geographic tongue [8,10,12]. The association of both psoriasis and geographic tongue (benign migratory glossitis) with HLA-Cw6 provides further evidence that the two disorders are related [13].

Ocular lesions

Blepharitis, conjunctivitis, keratitis, xerosis, symblepharon and trichiasis have been recorded. Chronic uveitis has been found, particularly in patients with psoriatic arthritis [14]. Uveitis was also reported in patients with generalized pustular psoriasis or psoriatic arthritis, who were receiving treatment with methotrexate. It was unclear whether methotrexate contributed to the ocular lesions [15].

References

1 Kerl H, Pachinger W. Psoriasis: odd varieties in the adult. *Acta Derm Venereol (Stockh)* 1979; **59** (Suppl. 87): 90–4.
2 Stevanovich DV. Rarities in the clinical picture of psoriasis. *Acta Derm Venereol (Stockh)* 1979; **59** (Suppl. 87): 98.
3 Stankler L, Ewen SWB. Follicular psoriasis. *Br J Dermatol* 1981; **104**: 153–6.
4 Ploysangam T, Mutasim DF. Follicular psoriasis: an under-reported entity—a report of five cases. *Br J Dermatol* 1997; **137**: 988–91.
5 Ingram JT. The significance and management of psoriasis. *BMJ* 1954; **ii**: 823–8.
6 Atherton DJ, Kahana M, Russell-Jones R. Naevoid psoriasis. *Br J Dermatol* 1989; **120**: 837–41.
7 Warin RP, Faulkner KE. Napkin psoriasis. *Br J Dermatol* 1961; **773**: 445–7.
8 Wagner G, Luckasen JR, Goltz RW. Mucous membrane involvement in generalized pustular psoriasis. *Arch Dermatol* 1976; **12**: 1010–4.
9 Buchner A, Begleiter A. Oral lesions in psoriatic patients. *Oral Surg Oral Med Oral Pathol* 1976; **41**: 327–32.
10 O'Keefe E, Braverman IM, Cohen I. Annulus migrans. *Arch Dermatol* 1973; **107**: 240–4.
11 Sklavounou A, Laskaris G. Oral psoriasis: report of case and review of the literature. *Dermatologica* 1990; **180**: 157–9.
12 Robinson CM, Di Biase AT, Leigh IM *et al*. Oral psoriasis. *Br J Dermatol* 1996; **134**: 347–9.
13 Gonzaga HFS, Torres EA, Alchorne MMA, Gerbase-Delima M. Both psoriasis and benign migratory glossitis are associated with HLA-Cw6. *Br J Dermatol* 1996; **135**: 368–70.
14 Catsarou-Catsari A, Katsambos A, Theodoropoulus P *et al*. Ophthalmological manifestations in patients with psoriasis. *Acta Derm Venereol (Stockh)* 1984; **64**: 557–9.
15 Yamamoto T, Yokozeki H, Katayama I, Nushioka K. Uveitis in patients with generalized pustular psoriasis (Letter). *Br J Dermatol* 1995; **132**: 1023–4.

Disease associations

Studies have reported association between psoriasis and many other diseases, both cutaneous and systemic. Psoriatic arthritis, a seronegative arthritis, is a frequent and classical association and will be discussed elsewhere. Crohn's disease is also more frequently observed [1], an observation that has led to considerable advances in our understanding of genetic mechanisms particularly with respect to key T-cell differentiation pathways. Skin diseases associated with psoriasis include acquired bullous disorders most notably, bullous pemphigoid [2], and vitiligo [3] with psoriasis sometimes reported to be confined to vitiliginous areas.

Intriguingly, Henseler and Christophers [4] reported, in a series of 40 000 patients seen in a dermatology clinic in North Germany, the under-representation of several cutaneous disorders including infections (bacterial, fungal, viral) and atopic dermatitis. Proper community-based epidemiological investigations are required to confirm these findings.

Patients with psoriasis are at an increased risk of developing malignancy, particularly non-melanoma skin cancer and lymphoproliferative cancers. The risk is greatest for those with severe disease and probably reflects those treated with systemic agents and phototherapy [5]. A recent study of 67 761 patients on the UK general practice research database confirms this observation, particularly with respect to lymphohaematopoietic and solid tumours, and provides evidence that risk remains after controlling for systemic therapy [6], although the excess risk is low.

Psoriasis has been reported rarely to occur more frequently in certain metabolic disorders. These include gout [7], although whether it is a true association requires formal epidemiological study. It has been suggested that gout may be precipitated by systemic antipsoriatic therapy [8]. Hypocalcaemia has been reported in association with severe and pustular forms of psoriasis, including certain syndromes [9] and following thyroidectomy [10].

Chronic, recurrent, multifocal osteomyelitis is an unusual, sterile, inflammatory entity of unknown cause characterized by pain and swelling in affected bones. Association with pustular and non-pustular forms of psoriasis has been reported [11,12]. Closely related to this entity is the SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, osteitis) most frequently described in the radiological and rheumatological literature [13].

An association of psoriasis and cardiovascular disease (CVD) has long been recognized. CVD risk is highest in those with more severe disease, with standarized mortality rates reaching 2.6 [14], particularly in younger patients. Much of this risk is due to coexistence of known CVD risk factors, including type II diabetes mellitus, dyslipidaemia, hypertension and obesity [15,16], increasingly referred together as the 'metabolic syndrome'. However, emerging evidence suggests that the risk may in part remain even after controlling for known risk factors [17]. Taken together, these studies indicate that treating patients with moderate or severe psoriasis requires attention to these important general medical issues.

References

1 Lee FI, Bellary SV, Francis C. Increased occurrence of psoriasis in patients with Crohn's disease and their relatives. *Am J Gastroenterol* 1990; **85**: 962–3.
2 Wilczek A, Sticherling M. Concomitant psoriasis and bullous pemphigoid: coincidence or pathogenic relationship? *Int J Dermatol* 2006; **45**: 1353–7.
3 Percivalle S, Piccinno R, Caccialanza M. Concurrence of vitiligo and psoriasis: a simple coincidence? *Clin Exp Dermatol* 2009; **34**: 90–1.
4 Henseler T, Christophers E. Disease concomitance in psoriasis. *J Am Acad Dermatol* 1995; **32**: 982–6.
5 Margolis D, Bilker W, Hennessy S *et al*. The risk of malignancy associated with psoriasis. *Arch Dermatol* 2001; **137**: 778–83.
6 Brauchli YB, Jick SS, Miret M, Meier CR. Psoriasis and risk of incident cancer: an inception cohort study with a nested case–control analysis. *J Invest Dermatol* 2009; in press.
7 Bosmansky K, Trnavsky K. Psoriasis and gout: report of four cases. *Clin Rheumatol* 1983; **2**: 423–6.
8 Martin JH, Gordon M, Wallace R. Methotrexate in psoriasis: precipitation of gout. *Arch Dermatol* 1967; **96**: 431–3.
9 Garrets M. Psoriasiform dermatosis associated with bizarre metabolic abnormalities. *Proc R Soc Med* 1961; **54**: 220–3.
10 Vickers HR, Sneddon IB. Psoriasis and hypoparathyroidism. *Br J Dermatol* 1963; **75**: 419–21.
11 Bjorksten B, Gustavson KH, Eriksson B *et al*. Recurrent multifocal osteomyelitis and pustulosis palmoplantaris. *J Pediatr* 1978; **93**: 227–31.
12 Laxer RM, Shore AD, Manson D *et al*. Chronic recurrent multifocal osteomyelitis and psoriasis: a report of a new association and review of related disorders. *Semin Arthritis Rheum* 1988; **17**: 260–70.
13 Kahn MF, Chamot AM. SAPHO syndrome. *Rheum Dis Clin North Am* 1992; **18**: 225–46.
14 Mallbris L, Akre O, Granath F *et al*. Increased risk for cardiovascular mortality in psoriasis inpatients but not in outpatients. *Eur J Epidemiol*. 2004; **19**: 225–30.
15 Sommer DM, Jenisch S, Suchan M *et al*. Increased prevalence of the metabolic syndrome in patients with moderate to severe psoriasis. *Arch Dermatol Res* 2006; **298**: 321–8.
16 Gisondi P, Tessari G, Conti A *et al*. Prevalence of metabolic syndrome in patients with psoriasis: a hospital-based case-control study. *Br J Dermatol* 2007; **157**: 68–73.
17 Gelfand JM, Neimann AL, Shin DB *et al*. Risk of myocardial infarction in patients with psoriasis. *JAMA* 2006; **296**: 1735–41.

Complications

These are uncommon.

Infection

Secondary infection of psoriatic lesions is rarely a problem except during topical steroid therapy under occlusive dressings, when folliculitis and furunculosis are a hazard. However, staphylococci are carried by 50% of psoriatics, especially on the lesions [1]. This relative 'resistance' of psoriatic skin to infection despite the carriage of staphylococci is probably in part caused by the presence of endogenous antimicrobial peptides—cathelicidins and β-defensins—in the skin of patients with psoriasis [2]. Furthermore, psoriasis is associated with increased β-defensin genomic copy number [3]. Carriage of staphylococci may prove to be a problem if a surgical procedure is to be carried out through a psoriatic plaque. Because of exfoliation, these patients may disseminate infections in hospital wards. A series of postoperative deaths resulting from sepsis was caused by an anaesthetist with psoriasis carrying *Staphylococcus aureus* [4]. Rarely, flexural psoriasis may become clinically infected, especially if fissuring occurs (e.g. in the natal cleft).

Itching

This is very variable in psoriasis, ranging from complete absence to severe pruritus in a minority of patients. It is more common in unstable forms. One study from Poland reported that 80% of patients complain of itching [5]. Pustular and erythrodermic patterns are more usually accompanied by sensations of burning or tightness. Often, the degree of itching reflects the emotional state of the patient and, if severe, may be a symptom of anxiety or depression.

Arthritis

See below.

Alcoholism

Heavy drinking was found significantly more commonly in male patients with severe psoriasis than in other groups with the disease, and could be a symptom of stress caused by severe skin disease [6,7]. The prevalence of psoriasis in patients with alcoholic liver disease (15%) is significantly higher than in the normal population [8].

Nephritis and renal failure

The role of streptococcal infection, especially in the throat, in provoking acute guttate psoriasis is discussed above. It is exceptionally rare for post-streptococcal guttate psoriasis to be associated with glomerulonephritis. One such case has been reported [9], as well as a case of concomitant onset of diffuse psoriasis and mesangiocapillary glomerulonephritis [10]. Renal failure brought about by acute tubular necrosis may rarely result from the oligaemia after loss of albumin into and from the skin in acute pustular psoriasis [11].

Hepatic failure

Severe abnormalities of liver function may occur in erythrodermic or pustular psoriasis, and are likely to be related to drugs, alcohol intake and oligaemia [6,7,12,13].

Apical pulmonary fibrosis

This has been established as a non-articular complication of ankylosing spondylitis, and has been reported in association with a case of psoriatic spondylitis [14]. Two further patients with chronic plaque psoriasis, one with peripheral arthropathy and one free of joint disease, have been reported with apical pulmonary fibrosis typical of that found in association with ankylosing spondylitis. Extensive investigations and follow-up observation showed no evidence of other disease [15].

Amyloidosis

Amyloidosis of the secondary type is a rare sequel of arthropathic, generalized pustular and severe non-pustular psoriasis [16–19]. It is an additional cause of renal failure in association with psoriasis, and may follow an aggressive, fatal course [18].

References

1 Marples RR, Heaton CL, Kligman AM. *Staphylococcus aureus* in psoriasis. *Arch Dermatol* 1973; **107**: 568–70.
2 Ong PY, Ohtake T, Brandt C *et al.* Endogenous antimicrobial peptides and skin infections in atopic dermatitis. *N Engl J Med* 2002; **347**: 1151–60.
3 Hollox EJ, Huffmeier U, Zeeuwen PL *et al.* Psoriasis is associated with increased beta-defensin genomic copy number. *Nat Genet* 2008; **40**: 5–6.
4 Payne RW. Severe outbreak of surgical sepsis due to *Staphylococcus aureus* of unusual type and origin. *Br Med J* 1967; **iv**: 17–20.
5 Szepietowski JC, Reich A, Wisnicka B. Itching in patients suffering from psoriasis. *Acta Dermatovenerol Croat* 2002; **10**: 221–6.
6 Monk BE, Neill SM. Alcohol consumption and psoriasis. *Dermatologica* 1986; **173**: 57–60.
7 Poikolainen K, Reunala T, Karvonen J *et al.* Alcohol intake: a risk factor for psoriasis in young and middle aged men. *BMJ* 1990; **300**: 780–3.
8 Tobin AM, Higgins EM, Norris S, Kirby B. Prevalence of psoriasis in patients with alcoholic liver disease. *Clin Exp Dermatol* 2009; **34**: 698–701.
9 Chalmers RJG, Ive FA. Is acute guttate psoriasis with renal disease a rarity? (Letter). *Arch Dermatol* 1982; **118**: 141.
10 Kida H, Asamoto T, Abe T *et al.* Psoriasis vulgaris associated with mesangiocapillary glomerulonephritis. *Clin Nephrol* 1985; **23**: 255–7.
11 Warren DJ, Winney RJ, Beveridge G. Oligaemia, renal failure, and jaundice associated with acute pustular psoriasis. *BMJ* 1974; **ii**: 406–8.
12 Craig JA. Jaundice in acute pustular psoriasis (Letter). *BMJ* 1974; **iii**: 43.
13 Ryan TJ, Baker H. Systemic corticosteroids and folic acid antagonists in the treatment of generalized pustular psoriasis. *Br J Dermatol* 1969; **81**: 134–45.
14 Guzman LP, Gall EP, Pitt M *et al.* Psoriatic spondylitis, association with advanced non-granulomatous upper lobe pulmonary fibrosis. *JAMA* 1978; **239**: 1416–7.
15 Bourke S, Campbell J, Henderson AF *et al.* Apical pulmonary fibrosis in psoriasis. *Br J Dis Chest* 1988; **82**: 444–6.
16 Berger PA. Amyloidosis: a complication of pustular psoriasis. *BMJ* 1969; **ii**: 351–3.
17 Mackie RM, Burton J. Pustular psoriasis in association with renal amyloidosis. *Br J Dermatol* 1974; **90**: 567–71.
18 Wittenberg GP, Oursler JR, Peters MS. Secondary amyloidosis complicating psoriasis. *J Am Acad Dermatol* 1995; **32**: 465–8.
19 Ujfalassy I, Bely M, Koo E, Sesztak M. Systemic, secondary amyloidosis in a patient with psoriatic arthritis. *Clin Exp Rhematol* 2001; **19**: 225.

Biomarkers

There is no constantly present laboratory abnormality in uncomplicated psoriasis. Erythrocyte sedimentation rate (ESR) and C-reactive protein are unaffected or inconsistently elevated. Modest hyperuricaemia may be found and has been attributed to enhanced epidermopoiesis. The occasional finding of low folate levels can be similarly explained [1]. The laboratory abnormalities associated with erythrodermic psoriasis and arthropathic psoriasis are described in the relevant sections. Immunoglobulins are generally normal, but selective IgA deficiency [2] and monoclonal IgG gammopathy [3] are documented in association with psoriasis.

Studies have reported elevation in many serum immunological markers, including soluble IL-2 receptor, soluble ICAM-1, IL-6 and TNF-α [4,5], consistent with psoriasis being a systemic immunological disease. Indeed more recent studies have further expanded the range of upregulated markers to include those relating to angiogenesis [6] and others derived from adipose cells [7], thus linking obesity and inflammation. However, the presence of these markers is inconsistent both in absolute terms and in their response to therapy, indicating that at present they have no clinical role. Identification of valid biomarkers of disease severity, type and response to therapy would represent a major advance.

References

1 Touraine R, Revuz J, Zittoun J *et al.* Study of folate in psoriasis: blood levels, intestinal absorption and cutaneous loss. *Br J Dermatol* 1973; **89**: 335–41.
2 Sagransky DM, Greenwald RA. Psoriasis associated with selective IgA deficiency. *Arch Dermatol* 1980; **116**: 750.
3 San Miguel J, Corrales A, Lopez-Borrasca A. Monoclonal gammopathy (IgG1) in psoriasis (Letter). *Dermatologica* 1982; **164**: 289.
4 Bonifati C, Carducci M, Cordiali FP *et al*. Correlated increases of tumour necrosis factor-alpha, interleukin-6 and granulocyte monocyte-colony stimulating factor levels in suction blister fluids and sera of psoriatic patients–relationships with disease severity. *Clin Exp Dermatol* 1994; **19**: 383–7.
5 De Rie MA, Zonneveld IM, Witkamp L *et al*. Soluble interleukin-2 receptor (sIL-2R) is a marker of disease activity in psoriasis: a comparison of sIL-2R, sCD27, sCD4, sCD8 and sICAM-1. *Acta Derm Venereol* 1996; **76**: 357–60.
6 Creamer D, Allen M, Jaggar R *et al*. Mediation of systemic vascular hyperpermeability in severe psoriasis by circulating vascular endothelial growth factor. *Arch Dermatol* 2002; **138**: 791–6.
7 Johnston A, Arnadottir S. Obesity in psoriasis: leptin and resistin as mediators of cutaneous inflammation. *Br J Dermatol* 2008; **159**: 342–50.

Differential diagnosis

The characteristics already defined are usually sufficient to enable the diagnosis to be made, but doubt may arise in atypical cases, in particular sites, and when psoriasis is complicated by or alternates with other diseases. In seborrhoeic dermatitis, the lesions are lighter in colour, less well-defined and covered with a dull or branny scale. Eczema at times develops a psoriasiform appearance, especially on the legs. Hyperkeratotic eczema of the palms is a common cause of misdiagnosis. Colour, scratch-evoked scaling and well-defined margins are suggestive of psoriasis, and nail changes may be diagnostic. Lichen planus should give rise to difficulty only when the two diseases alternate or coexist, especially when present as hypertrophic lesions on the legs, as penile lesions and on the palms. The violaceous colour, glistening surface and presence of oral changes are usually decisive. Lichen simplex can resemble psoriasis closely, particularly on the scalp and near the elbow. The intensified skin markings, rather ill-defined edge and the marked itching are characteristic, and the point of the elbow tends to be avoided. Pityriasis lichenoides chronica can closely resemble guttate psoriasis, but the lesions are usually less evenly scattered, have a brownish red or orange–brown colour and are capped by an opaque soft 'mica-like' scale. Candidiasis shows a glistening deep red colour suggestive of psoriasis, particularly in the flexures, but scaling tends to be confined to the edge, and small satellite pustules and papules are usually evident outside the main area. Tinea cruris has a well-defined, often polycyclic edge, but *Trichophyton rubrum* infections, especially of the palm, cause difficulty. If corticosteroids have been applied, scaling may be absent and the diagnosis must be made by microscopy and culture.

Less common causes of confusion are pityriasis rubra pilaris and secondary syphilis. The resemblance to pityriasis rubra pilaris

may be close, especially in the erythrodermic phase. The colour is generally less distinct, and dark red follicular lesions are apparent, and the acquired palmar and plantar keratoderma has a yellow–orange tinge. The psoriasiform lesions of syphilis may cause difficulty to the inexperienced; condylomas, mucosal lesions and other signs of the disease are usually found, if sought. Porokeratosis of Mibelli on the palms and soles, patches of Bowen's and Paget's disease and penile erythroplasia may resemble psoriasis, but the lesions are usually solitary except in chronic arsenical poisoning. A biopsy may be necessary. The rare recurrent circinate erythematous type of psoriasis of Bloch and Lapiere may pose considerable diagnostic difficulties. It is to be distinguished from erythema annulare centrifugum, and from the annular migratory necrolytic erythema associated with carcinoma of the pancreas [1], and sometimes with subcorneal pustular dermatosis. The distribution, course and histology will usually be sufficiently decisive to distinguish these. Psoriasiform drug eruptions must be distinguished from psoriasis.

Parakeratosis pustulosa is an eczematoid eruption seen in young children and commonly mistaken for psoriasis, atopic dermatitis or tinea. It affects the skin around one or more fingernails or toenails, causing subungual hyperkeratosis and thickening of the free edges of the nail. Scaling is more marked than pustulation, the course is often protracted and recurrences are the rule, whatever the treatment. A large series has been reported [2]. Histology shows hyper- and parakeratosis, acanthosis, papillomatosis and a marked infiltrate around dilated capillary loops [3].

References

1 Church RE, Crane WAJ. A cutaneous syndrome associated with islet-cell carcinoma of the pancreas. *Br J Dermatol* 1967; **79**: 284–6.
2 Hjorth N, Thomsen K. Parakeratosis pustulosa. *Br J Dermatol* 1967; **79**: 527–32.
3 Dulanto F, Armijo-Moreno M, Camacho-Martinez F. Histological findings in parakeratosis pustulosa. *Acta Derm Venereol (Stockh)* 1974; **54**: 365–7.

Course and prognosis [1–5]

This remains as unpredictable as it was 150 years ago. 'Psoriasis is at all times and under all forms a very troublesome and, often, an intractable disease, but it is rarely dangerous to life' [6]. 'It is impossible to say, in any particular case, how long the disease will last, whether a relapse will occur, or for what period of time the patient will remain free from psoriasis' [7]. Guttate attacks carry a better prognosis than those of a slower and more diffuse onset, and have longer remissions after treatment [3]. Few studies have assessed the long-term prognosis for first episodes of guttate psoriasis. In one study, only five (33%) of 15 patients followed up 10 years after an initial episode of guttate psoriasis had developed chronic plaque disease [8]. At the other extreme, erythrodermic and pustular forms carry an appreciable mortality and arthropathic forms a considerable morbidity. Early onset and a family history of the disease appear to worsen the prognosis [2].

Among environmental factors, sunlight and hot weather are favourable [1,2,4]; pregnancy had no effect in approximately half of patients [2,4], but improvement was more common than worsening. The influence of stress or 'worry' is more difficult to determine. Patients' beliefs on the importance of stress are probably dependent on cultural and linguistic differences. Sixty per cent of patients studied in Manchester, UK, believed that stress was an important trigger of their psoriasis [9]. In one series [10], 50% reported worsening with 'worry', in others 33–42% reported worsening [1,4]. Common experience suggests that stress is of considerable importance in some patients, but may be too easily accepted as a general cause of variations in this disease.

Complete remissions of psoriasis over 1–54 years were reported by 39% of patients in a large series [4], often without treatment. An even higher figure applied to Japan [11], but lower figures are also quoted [12].

In one follow-up study of 'napkin psoriasis', two out of 67 had developed true psoriasis in 5.4 years [13]; four developed seborrhoeic dermatitis. In another study [14], 123 infants were reviewed 5–13 years later. Of 71 who had shown psoriasiform napkin eruptions, 12 had developed psoriasis; of 40 who had a predominantly seborrhoeic pattern of flare, none had shown later signs of psoriasis but 15 (37%) had atopic eczema. Most of the psoriatic cases occurred within the first 3 months of life.

Relapse

Relapse is the rule, however completely the lesions are treated and by whatever method. Only three of 260 patients in one series [2] were clear for 5 years or more and most of the rest for only 6 months. In another series [15], only three out of 95 were clear for 5 years or more and 11.5% relapsed rapidly. A 7-year follow-up of 142 patients [3] indicated that intensive outpatient treatment gave longer remissions than those treated at home, or the presumably more severe cases admitted to hospital. Guttate lesions had the best prognosis.

There is little doubt that even severe cases can be maintained in prolonged remission by the use of systemic therapies, including the biologics (Chapter 74).

References

1 Braun-Falco O, Burg G, Farber EM. Psoriasis: Line Fragebogenstudie bei 536 Patienten. *Münch Med Wochenschr* 1972; **114**: 1–15.
2 Church R. The prospect of psoriasis. *Br J Dermatol* 1958; **70**: 139–45.
3 Durham GA, Morgan JK. A 7-year follow-up study of ninety patients with psoriasis. *Br J Dermatol* 1974; **91**: 7–11.
4 Farber EM, Nall LM. The natural history of psoriasis in 5600 patients. *Dermatologica* 1974; **148**: 1–18.
5 Lomholt G. *Psoriasis: Prevalence, Spontaneous Course and Genetics*. Copenhagen: GEC Gad, 1963: 78–189.
6 Wilson E. *Diseases of the Skin*. London: Churchill, 1842: 229.
7 Hebra F, ed. *On Diseases of the Skin*, Vol. II. London: New Sydenham Society, 1868: 11.
8 Martin BA, Chalmers RJ, Telfer NR. How great is the risk of further psoriasis following a single episode of acute guttate psoriasis? *Arch Dermatol* 1996; **132**: 717–8.
9 Fortune DG, Richards HL, Main CJ, Griffiths CEM. What patients with psoriasis believe about their condition. *J Am Acad Dermatol* 1998; **39**: 196–201.
10 Savin JA. Patients' belief about psoriasis. *Trans St John's Hosp Dermatol Soc* 1970; **56**: 139–42.
11 Yashuda T, Ishikawa E, Mori S. Psoriasis in the Japanese. In: Farber EM, Cox AJ, eds. *Psoriasis. Proceedings of the 1st International Symposium*. Stanford: Stanford University Press, 1971: 25–34.
12 Janula J, Novotny F. Zur statistischen Erforschung der Psoriasis. *Hautarzt* 1965; **16**: 241–6.
13 Anderson S, La C, Thomsen K. Psoriasiform napkin dermatitis. *Br J Dermatol* 1971; **84**: 316–9.

14 Neville EA, Finn OA. Psoriasiform napkin dermatitis: a follow-up study. *Br J Dermatol* 1975; **92**: 279–85.
15 MacLennan A, Hellier FF. The treatment time in psoriasis. *Br J Dermatol* 1961; **73**: 439–44.

Management

Every patient with psoriasis presents an individual problem. Treatment depends upon age, sex, occupation, personality, general health, intelligence and resources, as well as the type, extent, duration and natural history of the disease. Extensive psoriasis may be ignored by the phlegmatic, yet trivial lesions on exposed areas can be ruinous for the sales executive or artiste. With this in mind, an assessment tool for psoriasis severity has been developed—the Salford Psoriasis Index—which takes into account physical extent of disease, psychosocial difficulty and previous therapy as a means of measuring difficulty in treatment [1]. Reassurance and emotional support are invaluable, stressing the non-contagious and benign nature of psoriasis, the possibility of spontaneous remission, and the availability of a wide range of therapeutic weapons for all psoriatic seasons. Fears for the future of children need to be allayed. The physician must take a long-term view. Treatment must always be appropriate to its severity and importance in that individual. It should never be more unpleasant, intolerable or dangerous than the disease itself. Its details must be commensurate with the patient's intelligence, physical capacity, time and socioeconomic circumstances.

General and non-specific measures

Attention to the patient's general, physical and psychological health is always worthwhile. Mild anaemia, minor but untreated arthritis, an anxiety state or depression, especially in the elderly patient, may all critically lower the patient's tolerance of his or her disability. Physical extent of psoriasis and psychosocial disability produced by the disease do not correlate [2]. Rest, mild sedation, removal from a troublesome environment, a holiday or a short stay in hospital may all help to turn the therapeutic tide. The importance of talking to patients, trying to allay their concerns, coupled with advice on how to handle negative beliefs about their disease cannot be overestimated. A study of cognitive–behavioural therapy (CBT) as an adjunct to pharmaceutical therapies in patients with psoriasis showed a significantly greater reduction in psoriasis severity in the CBT group as compared to pharmaceutical therapy alone, both at the end of 6 weeks' intervention and 6 months later [3]. Indeed, high worry appears to have a significant detrimental effect on response to PUVA therapy and is the best predictor of outcome [4]. Harmless placebos may give comfort and should not be despised.

Diet is unimportant. Diets rich in zinc [5] and turkey meat [6] or low in tryptophan [7], protein [8] or calories [9] do not influence the disease. Spa treatment, involving rest and relaxation in an area where high sunlight exposure is possible, such as the Israeli Dead Sea coast, can undoubtedly induce remissions [10].

General approach

Most stable plaque psoriasis should first be approached with outpatient topical therapy, which disrupts the patient's routine as little as possible. Written guidelines on the management of psoriasis in primary care are effective and help to ensure appropriate referral to secondary care [11].Tar preparations and vitamin D analogues are appropriate, but corticosteroids can be used for localized psoriasis. If necessary, dithranol can be introduced later but is more difficult to handle. If sunlight or UVB phototherapy are available, light can be added at this stage or earlier. Special routines may be necessary for the scalp. If the psoriasis is severe and extensive and the above initial measures have failed, more intensive tar or dithranol therapy should be considered, in a day-care unit or a hospital if such facilities exist, with or without UV phototherapy. The indications for phototherapy, photochemotherapy, systemic therapies and biologics are discussed in Chapters 74 and 78. Intralesional corticosteroid injections, PUVA therapy, retinoids, cytotoxic drugs and ciclosporin are discussed in the appropriate sections below but, in general, the more hazardous measures should be restricted to those patients whose psoriasis is physically, socially, economically or emotionally disabling, and in whom conventional and conscientious topical therapy has failed. Each of the available modalities is discussed in detail below.

References

1 Kirby B, Fortune DG, Bhushan M, Chalmers RJ, Griffiths CEM. The Salford Psoriasis Index: an holistic measure of psoriasis severity. *Br J Dermatol* 2000; **142**: 728–32.
2 Kirby B, Richards HL, Woo P *et al.* Physical and psychological measure are necessary to assess overall psoriasis severity. *J Am Acad Dermatol* 2001; **45**: 72–6.
3 Fortune DG, Richards HL, Kirby B *et al.* A cognitive–behavioural symptom management programme as an adjunct in psoriasis therapy. *Br J Dermatol* 2002; **145**: 458–65.
4 Fortune DG, Richards HL, Kirby B *et al.* Psychological distress impairs clearance of psoriasis in patients treated with photochemotherapy. *Arch Dermatol* 2003; **139**: 752–6.
5 Voorhees JJ, Chakrabarti SG, Botero F *et al.* Zinc therapy and distribution in psoriasis. *Arch Dermatol* 1969; **100**: 669–73.
6 Ellis JP, Sanderson KV, Savin JA. The turkey diet in psoriasis (Letter). *Lancet* 1968; **i**: 1429–30.
7 Farber EM, Zackheim H. Turkey, tryptophan, and psoriasis (Letter). *Lancet* 1967; **ii**: 944.
8 Zackheim HS, Farber EM. Low-protein diet and psoriasis. *Arch Dermatol* 1969; **99**: 580–6.
9 Zackheim HS, Farber EM. Rapid weight reduction and psoriasis. *Arch Dermatol* 1971; **103**: 136–40.
10 Even-Pas Z, Gumon R, Hipnis V. Dead Sea sun vs. Dead Sea water in the treatment of psoriasis. *J Dermatol Treat* 1996; **7**: 83–6.
11 Griffiths CEM, Taylor H, Collins SI *et al.* The impact of psoriasis guidelines on appropriateness of referral from primary to secondary care: a randomized controlled trial. *Br J Dermatol* 2006; **155**: 393–400.

Local therapy

Tar [1,2]

Coal tar is a complex mixture of thousands of substances produced by primary condensation during the carbonization of coal [3]. Some 400 known substances comprise 55% of tar by weight [2,3]. Standardization is impossible and, because great variation in biological activity of various samples of tar has been demonstrated [4], therapeutic results achieved in different centres may not be comparable.

Tar has been used in topical therapy for more than a century. It is assumed to have an antimitotic effect but this is not proven [5]. Its use in psoriasis was popularized by Goeckerman [6] and, for more than half a century since, his regimen of daily application of 2–5% crude coal tar, combined with a tar bath and UV light, has been a mainstay of in-patient treatment [7]. In skilled hands, substantial clearing of stable discoid psoriasis can be achieved in 3–6 weeks in 80% of patients [7]. Many modifications of Goeckerman's regimen have been advocated, utilizing alcoholic extracts of tar (e.g. coal-tar solution) in cream or ointment bases, tar gels [8], etc., which are 'cleaner' and easier to handle, but it seems that the cruder the tar extract, the more effective it is [2]. Concentrations of coal-tar solution up to 10% can be incorporated in various vehicles for outpatient therapy, and many commercial creams, lotions, ointments, gels and shampoos containing tar extracts are available throughout the world.

Controversies surrounding the roles of tar and UV light have not yet been fully resolved [2]. Tar alone is certainly active in psoriasis [9], as is UVB alone [10]. Coal tar seems to sensitize the skin to UVA but not to UVB [11] and phototoxicity is of photodynamic type [12,13]. Nevertheless, UVB is more valuable than UVA in conjunction with tar [14] and probably UVB erythema thresholds prevent UVA exposure sufficient to cause photosensitization in the Goeckerman regimen [15].

Despite a huge literature, it is remarkably difficult to quantify success rates with tar regimens in terms of percentage of patients cleared, the number of days of treatment needed to achieve clearance or the length of remission [2,7]. Only one placebo-controlled trial of coal tar was found in a recent systematic review [16]. This short 4-week trial showed that 5% liquor carbonis detergens was more effective than emollient vehicle [17]. Exorex®, a new formulation of 1% coal tar in esterified fatty acids, was no more effective than crude coal tar in a head-to-head comparative study [18]. Recent attempts at short-contact crude coal-tar treatment have shown that daily 1-h applications of 30% crude coal tar in yellow soft paraffin are effective in improving psoriasis, but less so than daily 23-h treatment with 5% crude coal tar in yellow soft paraffin. It was concluded that the former has no place in in-patient management, but that it may have a limited role in certain outpatients [19]. A combination of 5% crude coal tar and dithranol was found to be as effective as dithranol alone when used in short contact treatment of psoriasis, but was recommended in preference to the latter, as less irritancy was encountered [20]. Others have found that tar and dithranol combination regimens do not enhance the clearance rate of psoriasis and that they offer little benefit over dithranol alone [21,22].

The safety of tar has been regarded as one of its great virtues. In spite of the evidence that increased levels of 1-hydroxypyrene, polycyclic aromatic hydrocarbons and mutagenic activity (as determined by the Ames plate assay) may be detected in the urine of patients following 3 days of therapeutic exposure to coal tar [23], systemic toxicity is unknown. Primary irritation is uncommon except in unstable psoriasis, and on the face, genitalia and in the flexures. Allergic contact dermatitis does occur, but is rare. Folliculitis is the most common side effect. Notwithstanding the undoubted carcinogenicity of coal tar in the skin of experimental animals [24] and human workers chronically exposed to tar, long experience dictates that the risk from therapeutic tar products is small [1,24]. There are certainly case reports of various scattered skin tumours developing in patients treated previously with tar [25–27], but some of these patients had been exposed to other known carcinogens. Reports of carcinoma at the site of local coal-tar treatment are few but significant [28–31]. It may, therefore, be wise to avoid prolonged application of coal tar to the anogenital area, including the scrotum, sites that have been involved in at least two case reports. In spite of negative results in several other series [32–34], a case–control study has shown that there was a significantly greater risk of skin cancer in psoriatic patients treated with high-exposure coal tar and UV light therapy, than in matched patients treated with smaller dosage therapy [35]. This association was confirmed by further epidemiological studies in which patients receiving multiple Goeckerman regimens were compared with age- and sex-matched controls [34]. Another study involved 719 psoriatic patients in the west of Scotland, all of whom had received intermittent topical coal-tar therapy over a 10-year period, but no cytotoxic drugs, ionizing radiation or prescribed UV radiation. No increase in malignancy of skin, bladder or any other organ was found in the psoriasis patients over that in the general population [35]. The increased incidence of malignancy [36,37] may, therefore, depend on exposure to high-dose UVB. It would therefore appear prudent to place patients who have received repeated intensive Goeckerman regimens under careful surveillance. The benefits of repeated Goeckerman regimens in patients with difficult psoriasis may, however, outweigh the risk of skin malignancy, which should be easy to detect and treat.

Other contraindications to tar therapy do exist. Erythrodermic or generalized pustular psoriasis will infrequently tolerate even the weakest tars. Pre-existing folliculitis or severe acne are also possible contraindications.

References

1 Bickers DR. The carcinogenicity and mutagenicity of therapeutic coal tar: a perspective. *J Invest Dermatol* 1981; **77**: 173–4.

2 Comaish JS. Tar and related compounds in the therapy of psoriasis. *Clin Exp Dermatol* 1981; **6**: 639–45.

3 Gruber M, Klein R, Foxx M. Chemical standardization and quality assurance of whole crude coal tar USP utilizing GLC procedures. *J Pharmaceut Sci* 1970; **59**: 830–4.

4 Lowe NJ, Breeding J, Wortzman MS. The pharmacological variability of crude coal tar. *Br J Dermatol* 1982; **107**: 475–9.

5 Fisher LB, Maibach HI. Topical antipsoriatic agents and epidermal mitosis in man. *Arch Dermatol* 1973; **108**: 374–7.

6 Goeckerman WH. Treatment of psoriasis. *Arch Dermatol Syphilol* 1931; **24**: 446–50.

7 Perry HO, Soderstrom CW, Schulze RW. The Goeckerman treatment of psoriasis. *Arch Dermatol* 1968; **98**: 178–82.

8 Frost P, Horwitz SN, Caputo RV *et al.* Tar gel-phototherapy for psoriasis. *Arch Dermatol* 1979; **115**: 840–6.

9 Young E. The external treatment of psoriasis. *Br J Dermatol* 1970; **82**: 510–5.

10 Belsito DV, Kechijian P. The role of tar in Goeckerman therapy. *Arch Dermatol* 1982; **118**: 319–21.

11 Tanenbaum L, Parrish JA, Pathak MA *et al.* Tar phototoxicity and phototherapy for psoriasis. *Arch Dermatol* 1975; **111**: 467–70.

12 Crow KD, Alexander E, Buck WHL *et al.* Photo-sensitivity due to pitch. *Br J Dermatol* 1961; **73**: 220–32.

13 Kaidbey KH, Kligman AM. Clinical and histological study of coal tar phototoxicity in humans. *Arch Dermatol* 1977; **113**: 592–5.

14 Petrozzi JW, Barton JO, Kaidbey K *et al.* Updating the Goeckerman regimen for psoriasis. *Br J Dermatol* 1978; **98**: 437–44.

15 Parrish JA, Morison WL, Gonzalez E *et al.* Therapy of psoriasis by tar photosensitization. *J Invest Dermatol* 1978; **70**: 111–2.
16 Mason J, Mason AR, Cork MJ. Topical preparations for the treatment of psoriasis: a systematic review. *Br J Dermatol* 2002; **146**: 351–64.
17 Kanzler MH, Gorsulowsky DC. Efficacy of topical 5% liquor carbonis detergens versus its emollient base in the treatment of psoriasis. *Br J Dermatol* 1993; **129**: 310–4.
18 Smith CH, Jackson K, Chinn S *et al.* A double-blind, randomized, controlled clinical trial to assess the effect of a new coal tar therapy (Exorex) in the treatment of chronic plaque psoriasis. *Clin Exp Dermatol* 2000; **25**: 580–3.
19 Finlay AY, Young DW. Short contact crude coal tar therapy for psoriasis. *Clin Exp Dermatol* 1985; **10**: 371–4.
20 Schulze H-J, Schauder S, Mahrle G *et al.* Combined tar–anthralin versus anthralin treatment lowers irritancy with unchanged antipsoriatic efficacy. *J Am Acad Dermatol* 1987; **17**: 19–24.
21 Downey DJ, Finlay AY. Combined short contact crude coal tar and dithranol therapy for psoriasis. *Clin Exp Dermatol* 1986; **11**: 498–501.
22 Duhra P, Ryatt KS. Lack of additive effect of coal tar combined with dithranol for psoriasis. *Clin Exp Dermatol* 1988; **13**: 72–3.
23 Clonfero E, Zordan M, Venier P *et al.* Biological monitoring of human exposure to coal tar: urinary excretion of total polycyclic aromatic hydrocarbons, 1-hydroxypyrene and mutagens in psoriatic patients. *Int Arch Occup Environ Health* 1989; **61**: 363–8.
24 Henry SA. Occupational cutaneous cancer attributable to certain chemicals in industry. *Br Med Bull* 1946–47; **4**: 389–401.
25 Alexander J, Macrossen KI. Squamous epithelioma probably due to tar ointment in a case with psoriasis. *BMJ* 1954; **2**: 1089.
26 Annamalai R, Vasantha M, Umaselvam M *et al.* Multiple keratoacanthoma and squamous cell carcinoma in psoriasis. *Int J Dermatol* 1981; **20**: 606–7.
27 Schillinger B, Brody N. Acanthoma induction in psoriasis patients after short-term high potency Goeckerman treatment. *Cutis* 1981; **28**: 568–70.
28 Gotz H. The relationship between UV sensitization and tar exposure to the skin. *Australas J Dermatol* 1976; **17**: 57–60.
29 Hodgson G. Epithelioma following the local treatment of pruritus ani with liquor picis carbonis. *Br J Dermatol Syphilis* 1948; **60**: 282.
30 Moy LS, Chalet M, Lowe NJ. Scrotal squamous cell carcinoma in a psoriatic patient treated with coal tar. *J Am Acad Dermatol* 1986; **14**: 518–9.
31 Rook AJ, Gresham GA, Davis RA. Squamous epithelioma possibly induced by the therapeutic application of tar. *Br J Cancer* 1956; **10**: 17–23.
32 Götz H, Deichmann B, Zobel M. Zur Frage der iatrogenen Karzinomprovokation durch teeranwendung in der Dermatologie. *Z Hautkr* 1978; **53**: 751–5.
33 Muller SA, Perry HO, Pittelkow MR *et al.* Coal tar, ultraviolet light, and cancer. *J Am Acad Dermatol* 1981; **4**: 234–5.
34 Pittelkow MR, Perry HO, Muller SA *et al.* Skin cancer in patients with psoriasis treated with coal tar. *Arch Dermatol* 1981; **117**: 465–8.
35 Jones SK, Mackie RM, Hole DJ *et al.* Further evidence of the safety of tar in the management of psoriasis. *Br J Dermatol* 1985; **113**: 97–101.
36 Stern RS, Zierler S, Parrish JA. Skin carcinoma in patients with psoriasis treated with topical tar and artificial ultraviolet radiation. *Lancet* 1980; **i**: 732–5.
37 Stern RS, Scotto J, Fears TR. Psoriasis and susceptibility to non-melanoma skin cancer. *J Am Acad Dermatol* 1985; **12**: 67–73.

Dithranol (anthralin) [1,2]

The value of chrysarobin, a tree-bark extract, in psoriasis was discovered accidentally [3] a century ago. A synthetic derivative, dithranol (1,8-dihydroxy-9-anthrone), was introduced by Unna in 1916 [4] but is unstable. The role of salicylic acid in stabilizing dithranol formulations was also an accidental discovery, and led to the development of the Ingram regimen [5], which has played a central part in psoriasis management since, especially in Europe. After a tar bath in which scales and the previous applications are removed, suberythema UVB is given, and the lesions then precisely covered with dithranol paste. The initial concentration is 0.05 or 0.1%, increasing cautiously up to 4% according to response, and aiming to avoid irritation of the normal or psoriatic skin [5–7].



Fig. 20.22 Psoriasis partially treated with dithranol, showing brownish staining. (Courtesy of St John's Institute of Dermatology, London, UK.)

The paste is kept in position with tubular gauze or stockingette. After 18–22 h, the cycle is repeated and can be on an in-patient or day-care basis. In skilled hands, most patients with discoid psoriasis can be cleared in 3 weeks, leaving deep brown staining (Fig. 20.22) of the treated skin, which soon disappears after treatment is stopped. Dithranol paste is not suitable for the head and neck, flexures or genitalia, where it is liable to spread and is too irritant; it is highly irritant if accidentally introduced into the eyes. It also stains bed linen and clothing irreversibly.

In the early 1980s, disenchantment with the side effects of cytotoxic and PUVA therapy stimulated a resurgence of interest in dithranol [2], its chemistry and pharmacology [8–10], pharmacokinetics and percutaneous absorption [11,12], and mode of action [2,13,14]. Attempts were made to modify its formulation [15] to allow easier application and removal, and relatively stable cream formulations introduced that are effective, although less so than the classical paste [16–18]. Low-strength formulations may also be active yet less irritating and staining [19–21]. Kinetic studies showing penetration of the full epidermis in 100 min or less [11,22] encouraged the notion that 'short-contact' therapy may be effective and less irritant, while being easier and more convenient for the patient. Dithranol application periods as short as 10 min/day [22–27] have been effective. One study has even shown that immediate removal of dithranol is as effective as removal at 20 min [28]. Another study showed that a 2-h short-contact regimen using dithranol in Lassar's paste was as effective as a standard 24-h Ingram regimen, but that both of these were more effective than 10–20 min contact periods using dithranol in soft paraffin base. Higher concentrations (up to 12%) applied twice daily for 30 min were surprisingly well-tolerated, but provided no advantage over 2% dithranol in Lassar's paste applied for 2 h once daily. The latter schedule was therefore recommended as optimal for home use in well-motivated patients [29]. A randomized controlled trial from the UK [30] showed that dithranol in Lassar's paste applied once daily as per the Ingram regimen was as effective as twice daily applications in clearing psoriasis in in-patients, although nursing time was longer for the twice daily group. A comparative study of short-contact dithranol versus in-patient treatment or UVB

phototherapy reported that short-contact dithranol was the most cost-effective option [31].

Combination of short-contact dithranol with broad-band UVB appears to have little advantage over short-contact dithranol alone [27,32] or broad-band UVB alone [33,34]. However, dithranol or calcitriol in combination with narrow-band UVB (311 nm) were equally effective [35] and short-contact dithranol had a cumulative UVB sparing effect when used in combination with 311 nm narrow-band UVB [36].

Attempts to address the two main side effects of dithranol usage—local staining and irritation—have led to the development of combination therapy and new formulations of dithranol.

Dithranol in 0.0125% clobetasol propionate (quarter-strength Dermovate) ointment was reported to produce more rapid clearing than dithranol in Lassar's paste. The relapse period was similar in the two groups, although folliculitis was an important side effect in the steroid group [37]. In contrast, a combination of dithranol and fluocinonide in Lassar's paste, although causing more rapid initial clearing and reducing irritancy, did not reduce total clearance time when compared with dithranol in Lassar's paste alone. In this study, the steroid combination was also associated with a more rapid relapse rate [38]. Swinkels *et al.* [39] combined short-contact dithranol with clobetasol-17 propionate, each used once daily, and found that this accelerated the improvement of psoriasis produced by dithranol alone. Micanol is a microcrystalline formulation of 1% dithranol that releases the active medication at skin surface temperature [40]. This formulation reduces staining of fabrics significantly, but skin staining can still occur. A novel aqueous gel-based liposome entrapped formulation of dithranol appears, in an open study at least, to produce no irritation and minimal staining [41].

Notwithstanding these developments, any form of dithranol therapy requires careful control and explanation if the patient is not to become quickly disenchanted. The drug has the great virtue of lacking systemic toxicity, although if very high concentrations become general, continued vigilance will be necessary. Allergic contact dermatitis is extremely rare but has been documented [42]. Overall, the relative impracticality of dithranol therapy as compared to topical vitamin D analogues indicates that use of this effective and safe therapy is in decline, particularly for outpatient use.

References

1 Runne U, Kunze J. Psoriasis: the practical use of the 'minutes' therapy with dithranol (anthralin). *Z Hautkr* 1983; **58**: 219–29.
2 Symposium on anthralin. *Br J Dermatol* 1981; **105** (Suppl. 20): 1–114.
3 Behçet PE. Psoriasis. *Arch Dermatol Syphilol* 1936; **33**: 327–34.
4 Unna PG. Cignolin als Heilmittel der Psoriasis. *Dermatol Wochenschr* 1916; **62**: 116–37.
5 Ingram JT. The approach to psoriasis. *BMJ* 1953; **ii**: 591–4.
6 Seville RH. Dithranol paste for psoriasis. *Br J Dermatol* 1966; **78**: 269–72.
7 Vella-Briffa D, Rogers S, Greaves MW *et al.* A randomized, controlled clinical trial comparing photochemotherapy with dithranol in the initial treatment of chronic plaque psoriasis. *Clin Exp Dermatol* 1978; **3**: 339–47.
8 Ippen H. Basic questions on toxicology and pharmacology of anthralin. *Br J Dermatol* 1981; **105** (Suppl. 20): 72–6.
9 Krebs A, Schaltegger H, Schaltegger A. Structure specificity of the antipsoriatic anthrones. *Br J Dermatol* 1981; **105** (Suppl. 20): 6–11.
10 Shroot B, Schaefer H, Juhlin L *et al.* Editorial. Anthralin: the challenge. *Br J Dermatol* 1981; **105** (Suppl. 20): 3–5.
11 Schalla W, Bauer E, Schaefer H. Skin permeability of anthralin. *Br J Dermatol* 1981; **105** (Suppl. 20): 104–8.
12 Selim MM, Goldberg LH, Schaefer H *et al.* Penetration studies on topical anthralin. *Br J Dermatol* 1981; **105** (Suppl. 20): 101–3.
13 Pullman H, Enderer K, Steigleder GK. Cytokinetic effects of anthralin on psoriatic keratinocytes. *Br J Dermatol* 1981; **105** (Suppl. 20): 55–6.
14 Saihan EM, Albano J, Burton JL. The effect of steroid and dithranol therapy on cyclic nucleotides in psoriatic epidermis. *Br J Dermatol* 1980; **102**: 565–9.
15 Whitefield M. Pharmaceutical formulations of anthralin. *Br J Dermatol* 1981; **105** (Suppl. 20): 28–32.
16 Peachey RDG, Burton JL. A double-blind comparison of 0.1% dithranol and 17% urea (Psoradrate cream) and 0.25%-dithranol in vanishing cream (Dithrocream) in the treatment of psoriasis. *Clin Exp Dermatol* 1982; **7**: 625–8.
17 Portnoy B, Beck MH. The treatment of active chronic psoriasis. *Acta Derm Venereol (Stockh)* 1981; **61**: 459–61.
18 Wilson PD, Ive FA. Dithrocream in psoriasis. *Br J Dermatol* 1980; **103**: 105–6.
19 Brody I, Johansson A. A topical treatment programme for psoriasis with low anthralin concentrations. *J Cutan Pathol* 1977; **4**: 233–43.
20 Marley WM, Hernandez AD, Josephs JA *et al.* The effectiveness of low-strength anthralin in psoriasis. *Arch Dermatol* 1982; **118**: 906–8.
21 Montes LF, Wilborn WH, Brody I. Low strength anthralin in psoriasis. *J Cutan Pathol* 1979; **6**: 445–56.
22 Schaefer H, Farber EM, Goldberg L *et al.* Limited application period for dithranol in psoriasis. *Br J Dermatol* 1980; **102**: 571–3.
23 Bielha U, Heller G, Barth J. Erfahrungen mit zwei Anthralin-kurzzeittherapieschemata. *Dermatol Monatsschr* 1983; **169**: 42–5.
24 Lowe NJ, Ashton RE, Koudsi H *et al.* Anthralin for psoriasis: short-contact anthralin therapy compared with topical steroid and conventional anthralin. *J Am Acad Dermatol* 1984; **10**: 69–72.
25 Marsden JR, Coburn PR, Marks J *et al.* Measurement of the response of psoriasis to short-term application of anthralin. *Br J Dermatol* 1983; **109**: 209–18.
26 Runne U, Kunze J. Short-duration ('minutes') therapy with dithranol for psoriasis. *Br J Dermatol* 1982; **106**: 135–9.
27 Schauder S, Mahrle G. Kombinierte Einstundentherapie der Psoriasis mit Anthralin und UV-licht. *Hautarzt* 1982; **33**: 206–9.
28 Macdonald KJS, Marks J. Short contact anthralin in the treatment of psoriasis: a study of different contact times. *Br J Dermatol* 1986; **114**: 235–9.
29 Statham BN, Rowell NR. Short contact dithranol therapy: twice daily and high concentration regimes. *Br J Dermatol* 1985; **113**: 245–6.
30 Kirkup ME, Sabroe RA, Kavanagh GM *et al.* Twice daily versus once daily in-patient dithranol for psoriasis. *Clin Exp Dermatol* 2002; **27**: 695–9.
31 Hartman M, Prins M, Swinkels OQ *et al.* Cost-effectiveness analysis of a psoriasis care instruction programme with dithranol compared with UVB phototherapy and in-patient dithranol treatment. *Br J Dermatol* 2002; **147**: 538–44.
32 Brun J, Juhlin L, Schalla W. Short-contact anthralin therapy of psoriasis with and without UV-irradiation and maintenance schedule to prevent relapses. *Acta Derm Venereol (Stockh)* 1984; **64**: 174–7.
33 Boer J, Smeenk G. Effect of short-contact anthralin therapy on ultraviolet B irradiation of psoriasis. *J Am Acad Dermatol* 1986; **15**: 198–204.
34 Lebwohl M, Berman B, France DS. Addition of short contact anthralin therapy to an ultraviolet B phototherapy regimen: assessment of efficacy. *J Am Acad Dermatol* 1985; **13**: 780–4.
35 Hofmann UB, Eggert AA, Brocke EB, Goebeler M. Calcitriol versus dithranol in combination with narrow-band UVB (9311 nm) in psoriasis. *Br J Dermatol* 2003; **148**: 779–83.
36 Carrozza P, Hausermann P, Nestle FO *et al.* Clinical efficacy of narrow-band UVB (311 nm) combined with dithranol in psoriasis: an open pilot study. *Dermatology* 2000; **200**: 35–9.
37 Monk BE, Hehir ME, Clement MI *et al.* Anthralin-corticosteroid combination therapy in the treatment of chronic plaque psoriasis. *Arch Dermatol* 1988; **124**: 548–50.
38 Grattan CEH, Christopher AP, Robinson M *et al.* Double-blind comparison of a dithranol and steroid mixture with a conventional dithranol regimen for chronic psoriasis. *Br J Dermatol* 1988; **119**: 623–6.
39 Swinkels OQ, Kucharekova M, Prins M *et al.* The effects of topical corticosteroids and a coal tar preparation on dithranol-induced irritation in patients with psoriasis. *Skin Pharmacol Appl Skin Physiol* 2003; **16**: 12–7.

40 Volden G, Bjornberg A, Tegner E *et al.* Short-contact treatment at home with Micanol. *Acta Derm Venereol Suppl (Stockh)* 1992; **172**: 20–2.
41 Agarwal R, Saraswat A, Kaur I *et al.* A novel liposomal formulation of dithranol for psoriasis: preliminary results. *J Dermatol* 2002; **29**: 529–32.
42 Lawlor EF, Hindson JC. Allergy to dithranol. *Contact Dermatitis* 1982; **8**: 137–8.

Topical corticosteroids

Topically applied corticosteroids are of established value in psoriasis [1,2]; in the USA, they are still the mainstay of topical therapy [3]. In appropriate concentrations, they are still the treatment of choice on the face and neck, flexures and genitalia, however topical calcineurin inhibitors are becoming widely used at these sites. Diluted topical steroids are also used in unstable, erythrodermic and generalized pustular psoriasis, in preference to tar or dithranol, although bland emollients may be more suitable. On the scalp and other parts of the body, they can be tried if tar has failed and dithranol is inappropriate or unsuccessful. Corticosteroids have the merits of ease of application and removal, lack of irritancy and the absence of staining of skin or linen. The hazards of therapy are now well known, and enhancement by polythene occlusion will magnify and hasten side effects. Topical steroids under occlusion do have a limited place in the management of recalcitrant psoriasis of the scalp, hands, feet and other areas. Superior results have been claimed with topical steroids occluded by a hydrocolloid dressing as opposed to plastic film [4]. Apart from the cutaneous adverse effects, plasma cortisol levels are easily suppressed by the most potent preparations or high doses [5,6]. As little as 7 g/day of 0.05% clobetasol propionate or 0.05% betamethasone dipropionate was sufficient to suppress morning plasma cortisol levels in 20% of patients [7]. These unwanted effects, and evidence of tolerance [8] induced by intensive therapy, have stimulated use of less frequent applications [2,3,5,9,10]. Thus, once daily applications of 0.1% halcinonide cream were as effective as thrice daily applications [2], and 0.05% clobetasol propionate used on alternate days, or even less frequently, induced and maintained remissions for up to 5 months [9]. A novel regimen of topical high-potency corticosteroid—betamethasone dipropionate—is to apply the agent three times over a 24-h period each week [10]. This so-called 'weekend therapy' was shown to maintain improvement in psoriasis in up to 60% of patients so treated. Another regimen [3] using fluticasone propionate ointment once daily for two consecutive days per week maintained control of psoriasis for up to 10 weeks.

Newer formulations of corticosteroids, particularly foams, are easier to apply than traditional creams or ointments and can be used for scalp, truncal or limb psoriasis [11]. There is evidence that intensive treatment of discoid psoriasis with the most potent preparations can induce generalized pustular psoriasis [12–14]. With less potent or diluted preparations, the volume can be increased *pro rata*. Potent preparations are likely to be needed on the scalp and knuckles particularly; conversely, the flexures and inner thighs need much weaker products, if striae formation is to be avoided. Hydrocortisone (except as the butyrate ester) [15] is too weak to be of value, except perhaps in combination with tar for facial lesions.

Intralesional corticosteroid therapy

Triamcinolone hexacetonide (5 mg/mL) or triamcinolone acetonide (10 mg/mL) can be infiltrated intradermally into localized psoriatic lesions by needle injection. This is a valuable technique in troublesome, small, resistant lesions on the backs of hands, especially the knuckles, intensely pruritic small plaques or lichenoid lesions. The effect is long-lasting and repetition of the injection may be unnecessary for several months. In treatment of psoriasis of fingernails, the nail fold can be injected, but results are disappointing and the procedure may be painful.

References

1 Corbett MF. The response of psoriasis to betamethasone valerate and clobetasol propionate. *Br J Dermatol* 1976; **94** (Suppl. 12): 89–93.
2 Fredriksson T, Lassus A, Bleeker J. Treatment of psoriasis and atopic dermatitis with halcinonide cream applied once and three times daily. *Br J Dermatol* 1980; **102**: 575–7.
3 Lebwohl M, Ali S. Treatment of psoriasis. I. Topical therapy and phototherapy. *J Am Acad Dermatol* 2001; **45**: 487–98.
4 David M, Lowe NJ. Psoriasis therapy: comparative studies with a hydrocolloid dressing, plastic film occlusion, and trimacinolone acetonide cream. *J Am Acad Dermatol* 1989; **21**: 511–4.
5 Hehir M, du Vivier A, Eilon L *et al.* Investigation of the pharmacokinetics of clobetasol propionate and clobetasone butyrate after a single application of ointment. *Clin Exp Dermatol* 1983; **8**: 143–51.
6 Nilsson JE, Gip LJ. Systemic effects of local treatment with high doses of potent corticosteroids in psoriatics. *Acta Derm Venereol (Stockh)* 1979; **59**: 245–8.
7 Katz HI, Hien NT, Prawer SE *et al.* Superpotent topical steroid treatment of psoriasis vulgaris: clinical efficacy and adrenal function. *J Am Acad Dermatol* 1987; **16**: 804–11.
8 Du Vivier A, Stoughton RB. Tachyphylaxis to the action of topically applied corticosteroid. *Arch Dermatol* 1975; **111**: 581–3.
9 Hradil E, Lindström C, Möller H. Intermittent treatment of psoriasis with clobetasol propionate. *Acta Derm Venereol (Stockh)* 1978; **58**: 375–7.
10 Katz HI, Prawer SE, Medansky RS *et al.* Intermittent corticosteroid maintenance treatment of psoriasis: a double-blind, multicenter trial of augmented betamethasone dipropionate ointment in a pulse dose treatment regimen. *Dermatologica* 1991; **183**: 269–74.
11 Franz TJ, Parsell DA, Halualani RM *et al.* Betamethasone valerate foam 0.12%: a novel vehicle with enhanced delivery and efficacy. *Int J Dermatol* 1999; **38**: 628–32.
12 Baker H. Corticosteroids and pustular psoriasis. *Br J Dermatol* 1976; **94** (Suppl. 12): 83–8.
13 Boxley JD, Dawber RPR, Summerly R. Generalized pustular psoriasis on withdrawal of clobetasol propionate ointment. *Br Med J* 1975; **ii**: 255–6.
14 Carruthers JA, August PJ, Staughton RCD. Observations on the systemic effect of topical clobetasol propionate (Dermovate). *Br Med J* 1975; **iv**: 203–4.
15 Polano MK, Suurmond D, Warnaar P. A clinical trial with hydrocortisone butyrate cream in psoriasis. *Br J Dermatol* 1970; **83**: 93–7.

Topical calcineurin inhibitors

The topical calcineurin inhibitors tacrolimus and pimecrolimus were initially developed for the treatment of atopic dermatitis in childhood. Both preparations have been shown to be effective for psoriasis affecting the face, neck, flexures and genitalia [1–3]. Their advantage is that unlike topical corticosteroids they are selective, unlikely to be absorbed systemically and do not produce skin atrophy making them suitable for long-term use.

References

1 Menter A, Korman NJ, Elmetts CA *et al.* Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 3, Guidelines of care for the management and treatment of psoriasis with topical therapies. *J Am Acad Dermatol* 2009; **60**: 643–59.

2 Kalb RE, Bagel J, Korman NJ *et al*. Treatment of intertriginous psoriasis: from the medical board of the National Psoriasis Foundation. *J Am Acad Dermatol* 2009; **60**: 120–4.
3 Jacobi A, Braeutigam M, Mahler V, Schultz E, Hertl M. Pimecrolimus 1% cream in the treatment of facial psoriasis. *Dermatology* 2008; **216**: 133–6.

Vitamin D analogues

The naturally occurring, active metabolite of vitamin D_3, 1,25-dihydroxyvitamin D_3 (calcitriol) [1], and three synthetic analogues, calcipotriol [2–4], 1,24-dihydroxyvitamin D_3 (tacalcitol) [5,6] and 1,25-dihydroxyvitamin D_3 (maxacalcitol) [7], have all been shown to be effective when applied topically in psoriasis. The mechanism of action of these agents is via vitamin D receptor-mediated effects on the proliferation and differentiation of epidermal keratinocytes [1,8] and on the immunological features of psoriasis, including shifting the Th1 cytokine profile of plaques towards a Th2 cytokine profile [9]. The introduction of topical vitamin D analogues into clinical practice in the early 1990s [10] undoubtedly transformed first-line management of psoriasis. Topical formulations of calcipotriol and other vitamin D analogues are probably the most widely prescribed active topical therapy for plaque psoriasis. Systematic reviews [11,12] of calcipotriol therapy for psoriasis attest to its equivalence or superiority to other available topical therapies apart from potent topical corticosteroids [11]. The most widely prescribed analogue in current use, calcipotriol (50 μg/g) ointment, has been reported to be at least as effective as 0.1% betamethasone valerate ointment [13,14] and more effective than short-contact dithranol therapy [15] in plaque psoriasis. Calcipotriol (50 μg/g) ointment has also been shown to be effective and safe in children when administered in amounts up to 45 g/week/m^2 [16]. Side effects of calcipotriol include local irritation, which may affect up to 20% of patients, and can be particularly troublesome on the face, leading to the need for withdrawal of treatment [14–16]. Vitamin D and its analogues all have the potential to affect systemic calcium homeostasis with hypercalciuria and hypercalcaemia [17]. Calcipotriol (50 μg/g) ointment was found to cause no significant changes in serum total adjusted calcium when used in amounts up to 100 g/week [18,19] or 50 g/week/m^2 [18] in adults, and up to 45 g/week/m^2 in children [16]. However, subsequent work showed significant rises in 24-h urinary calcium levels with calcipotriol ointment 100 g/week [19]. Significant rises in both serum and urinary calcium levels were also seen with high doses of calcipotriol ointment of up to 300 g/week [20,21]. It would therefore be prudent to restrict the amount of calcipotriol (50 μg/g) ointment used per week to less than 100 g or 50 g/m^2, and to monitor serum and urinary calcium levels carefully should these doses be exceeded.

New vehicles for calcipotriol have been introduced and calcipotriol cream appears to be slightly less effective than the ointment formulation [22] but cosmetically more appealing. Combining calcipotriol monotherapy applied in the morning with a super-potent topical corticosteroid such as halobetasol ointment applied in the evening for 2 weeks was superior to either drug used twice daily [23]. Based on this observation, a stable ointment formulation of calcipotriol 50 μg/g and betamethasone dipropionate 0.5 mg/g has been investigated and licensed for therapy. Used twice daily, this combination shows superior efficacy to either calcipotriol or betamethasone alone [24] with better clearance and faster onset of action. Once daily application of the combination appears no less effective than twice daily applications [25]. Whether withdrawal of the combination following treatment leads to an increase in rebound or pustular relapse remains to be ascertained.

Long-term treatment of chronic plaque psoriasis with calcitriol (3 μg/g) ointment confirmed previous shorter-term studies indicating the efficacy of this natural vitamin D_3 metabolite [1]. The relative efficacy of this agent compared with topical calcipotriol, corticosteroids or dithranol is currently unclear, although the relapse rate following withdrawal of calcitriol ointment appeared lower than that after topical corticosteroid therapy [1]. No statistically significant changes in serum or urinary calcium levels were found, even in patients using large quantities of the ointment to treat up to 35% of the body surface area for 3 months [26]. Transient local skin irritation, occasionally necessitating withdrawal of treatment, may occur, but calcitriol 3 μg/g ointment is better tolerated than calcipotriol ointment for treatment of face and flexures [27].

Tacalcitol 4 μg/g ointment applied once daily is effective for the treatment of chronic plaque psoriasis [6]. A systematic review [12] indicated that it was probably inferior in efficacy to calcipotriol 50 μg/g ointment. A long-term 18-month study in 197 patients using tacalcitol once daily demonstrated efficacy and safety with no evidence of effect on calcium homeostasis [28], although 5.9% of patients discontinued therapy because of skin irritation. Maxacalcitol 25 μg/g ointment applied once daily for 8 weeks is an effective treatment for chronic plaque psoriasis and may be more effective than once daily application of calcipotriol 50 μg/g ointment [7].

Calcipotriol and tacalcitol have been combined with other therapies. Calcipotriol ointment enhances the efficacy of PUVA and UVB phototherapy [29,30]. As UVA partly inactivates calcipotriol [31] and UVB is absorbed by calcipotriol [32], it is recommended that calcipotriol is not applied until after phototherapy sessions. Tacalcitol ointment when combined with PUVA is UVA-sparing [33] and calcitriol is UVB-sparing in combination [34]. Calcipotriol 50 μg/g ointment used in combination with methotrexate enables lower cumulative doses of methotrexate to be used [35].

References

1 Langer A, Ashton P, van de Kerkhof PCM *et al*. A long-term multicentre assessment of the safety and tolerability of calcitriol ointment in the treatment of chronic plaque psoriasis. *Br J Dermatol* 1996; **135**: 385–9.
2 Kragballe K, Beck HI, Søgaard H. Improvement of psoriasis by a topical vitamin D_3 analogue (MC903) in a double-blind study. *Br J Dermatol* 1988; **119**: 223–30.
3 Staberg B, Roed-Petersen J, Menné T. Efficacy of topical treatment in psoriasis with MC903, a new vitamin D analogue. *Acta Derm Venereol (Stockh)* 1989; **69**: 147–50.
4 Kragballe K. Treatment of psoriasis by the topical application of the novel vitamin D_3 analogue MC903. *Arch Dermatol* 1989; **125**: 1647–52.
5 Baadsgaard O, Traulsen J, Roed-Petersen J, Jakobsen HB. Optimal concentration of tacalcitol in once-daily treatment of psoriasis. *J Dermatol Treat* 1995; **6**: 145–50.
6 van de Kerkhof PCM, Werfel T, Haustein UF *et al*. Tacalcitol ointment in the treatment of psoriasis vulgaris: a multicentre, placebo-controlled, double-blind study on efficacy and safety. *Br J Dermatol* 1996; **135**: 758–65.
7 Barker JNWN, Ashton RE, Marks R *et al*. Topical maxacalcitol for the treatment of psoriasis vulgaris: a placebo-controlled, double-blind, dose-finding study with active comparator. *Br J Dermatol* 1999; **141**: 274–8.

8 Binderup L, Bramm E. Effects of a novel vitamin D analogue MC903 on cell proliferation and differentiation *in vitro* and on calcium metabolism *in vivo*. *Biochem Biopharmacol* 1998; **37**: 889–95.
9 Kang S, Yi S, Griffiths CEM *et al*. Calcipotriene-induced improvement in psoriasis is associated with reduced interleukin-8 and increased interleukin-10 levels within lesions. *Br J Dermatol* 1998; **138**: 77–83.
10 Berth-Jones J. The emergence of vitamin D as a first-line treatment for psoriasis. *J Dermatol Treat* 1998; **9** (Suppl. 3): 13–8.
11 Ashcroft DM, Li Wan Po A, Williams HC, Griffiths CEM. Systematic review of comparative efficacy and tolerability of calcipotriol in treating chronic plaque psoriasis. *BMJ* 2000; **320**: 963–7.
12 Mason J, Mason AR, Cork MJ. Topical preparations for the treatment of psoriasis: a systematic review. *Br J Dermatol* 2002; **146**: 351–64.
13 Kragballe K, Gjertsen BT, de Hoop D *et al.* Double blind, right/left comparison of calcipotriol and betamethasone valerate in treatment of psoriasis vulgaris. *Lancet* 1991; **337**: 393–6.
14 Cunliffe WJ, Berth-Jones J, Claudy A *et al.* Comparative study of calcipotriol (MC903) ointment and betamethasone-17-valerate ointment in patients with psoriasis vulgaris. *J Am Acad Dermatol* 1992; **26**: 736–43.
15 Berth-Jones J, Chu AC, Dodd WAH *et al.* A multicentre, parallel group comparison of calcipotriol ointment and short-contact dithranol therapy in chronic plaque psoriasis. *Br J Dermatol* 1992; **127**: 266–71.
16 Darley CR, Cunliffe WJ, Green CM *et al.* Safety and efficacy of calcipotriol ointment (Dovonex®) in treating children with psoriasis vulgaris. *Br J Dermatol* 1996; **135**: 390–3.
17 Bourke JF, Iqbal SJ, Hutchinson PE. Vitamin D analogues in psoriasis: effects on systemic calcium homeostasis. *Br J Dermatol* 1996; **135**: 347–54.
18 Mortensen L, Kragballe K, Wegmann E *et al.* Treatment of psoriasis vulgaris with topical calcipotriol has no short-term effects on calcium or bone metabolism. *Acta Derm Venereol (Stockh)* 1993; **73**: 300–4.
19 Berth-Jones J, Bourke JF, Hutchinson PE. Urine calcium excretion during treatment of psoriasis with topical calcipotriol. *Br J Dermatol* 1993; **129**: 411–4.
20 Bourke JF, Berth-Jones J, Iqbal SJ, Hutchinson PE. High-dose topical calcipotriol in the treatment of extensive psoriasis vulgaris. *Br J Dermatol* 1993; **129**: 74–6.
21 Bourke JF, Berth-Jones J, Mumford R *et al*. High-dose topical calcipotriol consistently reduces serum parathyroid hormone levels. *Clin Endocrinol* 1994; **41**: 295–7.
22 Molin L, Cutler TP, Helander I *et al*. Comparative efficacy of calcipotriol (MC903) cream and betamethasone 17-valerate cream in the treatment of chronic plaque psoriasis: a randomized, double-blind, parallel group multicenter study. *Br J Dermatol* 1997; **136**: 89–93.
23 Lebwohl M, Siskin SB, Epinette W *et al.* A multicenter trial of calcipotriene ointment and halobetasol ointment compared to either agent alone for the treatment of psoriasis. *J Am Acad Dermatol* 1996; **32**: 268–9.
24 Douglas WG, Poulin Y, Decroix J *et al.* A new calcipotriol/betamethasone formulation with rapid onset of action was superior to monotherapy with betamethasone diproprionate or calcipotriol in psoriasis vulgaris. *Acta Derma Venereol* 2002; **82**: 131–5.
25 Guenther L, van de Kerkhof PCM, Snellman E *et al.* Efficacy and safety of a new combination of calcipotriol and betamethasone dipropionate (one or twice daily) compared to calcipotriol (twice daily) in the treatment of psoriasis vulgaris: a randomized, double-blind, vehicle-controlled clinical trial. *Br J Dermatol* 2002; **147**: 316–23.
26 Barker JNWN, Berth-Jones J, Groves R *et al.* Calcium homoeostasis remains unaffected after 12 weeks' therapy with calcitriol 3 μg/g ointment; no correlation with extent of psoriasis. *J Derm Treat* 2003; **14**: 14–21.
27 Zhu X, Wang B, Zhao G *et al.* An investigator-masked comparison of the efficacy and safety of twice daily applications of calcitriol 3μg/g ointment versus calcipotriol 50 μg/g ointment in subjects with moderate chronic plaque type psoriasis *J Eur Acad Dermatol Venereol* 2007; **21**: 466–72.
28 van de Kerkhof PCM, Berth-Jones J, Griffiths CEM *et al.* Long-term efficacy and safety of tacalcitol ointment in patients with chronic plaque psoriasis. *Br J Dermatol* 2002; **146**: 414–22.
29 Speight EL, Farr PM. Calcipotriol ointment improves the response of psoriasis to PUVA. *Br J Dermatol* 1994; **130**: 79–82.
30 Molin L. Topical calcipotriol combined with phototherapy for psoriasis: the results of two randomized trials and a review of the literature. Calcipotriol–UVB Study Group. *Dermatology* 1999; **198**: 375–81.
31 Lebwohl M, Hecker D, Martinez J *et al*. Interactions between calcipotriene and ultraviolet light. *J Am Acad Dermatol* 1997; **37**: 93–5.
32 Kornreich C, Zheng ZS, Xue GZ, Prystowsky JH. A simple method to predict whether topical agents will interefere with phototherapy. *Cutis* 1996; **57**: 113–8.
33 Tzaneva S, Honingsmann H, Tanew A, Seeber A. A comparison of psoralen plus ultraviolet A (PUVA) monotherapy, tacalcitol plus PUVA and tazarotene plus PUVA in patients with chronic plaque type psoriasis. *Br J Dermatol* 2002; **147**: 748–53.
34 Ring J, Kowalzick L, Christophers E *et al.* Calcitriol 3 μg/g ointment in combination with UVB phototherapy for the treatment of plaque psoriasis: results of a comparative study. *Br J Dermatol* 2001; **144**: 493–9.
35 de Jong EM, Mork NJ, Seijger MM *et al.* The combination of calcipotriol and methotrexate coupled with methotrexate and vehicle in psoriasis: results of a multicentre, placebo-controlled, randomized trial. *Br J Dermatol* 2003; **148**: 318–25.

Vitamin A analogues

Retinoids, with their pleiotropic effects on cellular proliferation and differentiation, would appear to be an ideal topical preparation for psoriasis. Early studies were performed with topical all-*trans*-retinoic acid (tretinoin). Efficacy was reported but local irritation was a major problem [1,2]. The development of retinoic acid receptor (RAR) selective retinoids facilitated a revisitation of the role of topical retinoids. Tazarotene is a synthetic retinoid, whose main metabolite, tazarotenic acid, binds to RARs β and γ [3]. Tazarotene in a 0.05 or 0.1% gel applied once daily for 3 months is significantly more effective than vehicle in the treatment of chronic plaque psoriasis [4,5]. The main drawback of tazarotene is local irritation at the site of application, so much so that various strategies have been devised using once daily application of a potent topical corticosteroid, such as mometasone furoate or clobetasol propionate to alleviate this problem [6,7]. More recently, a cream formulation (0.05 and 0.1%) of tazarotene has been developed. A study [8] involving 1303 patients treated once daily with tazarotene cream reported significant reduction in clinical severity of psoriasis—the 0.1% formulation was more effective but less well-tolerated. Tazarotene is probably best reserved for thick, recalcitrant plaques of psoriasis.

References

1 Fry L, Macdonald A, McMinn RM. Effect of retinoic acid in psoriasis. *Br J Dermatol* 1970; **83**: 391–6.
2 Macdonald A, McMinn RM, Fry L. Retinoic acid in the treatment of psoriasis. *Br J Dermatol* 1972; **86**: 524–7.
3 Chandraratna RAS. Tazarotene: first of a new generation of receptor-selective retinoids. *Br J Dermatol* 1996; **135** (Suppl. 49): 18–25.
4 Weinstein GD. Tazarotene gel: efficacy and safety in plaque psoriasis. *J Am Acad Dermatol* 1997; **37** (Suppl.): S33–8.
5 Krueger GG, Drake LA, Elias PM *et al.* The safety and efficacy of tazarotene gel, a topical acetylenic retinoid, in the treatment of psoriasis. *Arch Dermatol* 1998; **134**: 57–60.
6 Lebwohl MG, Breneman DL, Goffe BS *et al.* Tazarotene 0.1% gel plus corticosteroid cream in the treatment of plaque psoriasis. *J Am Acad Dermatol* 1998; **39**: 590–6.
7 Lebwohl M. Strategies to optimize efficacy, duration of remission and safety in the treatment of plaque psoriasis by using tazarotene in combination with a corticosteroid. *J Am Acad Dermatol* 2000; **43** (Suppl.): S43–6.
8 Weinsten GD, Koo JYM, Krueger GG *et al.* Tazarotene cream in the treatment of psoriasis: two multicenter, double-blind, randomized, vehicle-controlled studies of the safety and efficacy of tazarotene creams 0.05% and 0.1% applied once daily for 12 weeks. *J Am Acad Dermatol* 2003; **48**: 760–7.

Occlusive dressings alone

Improvement or clearing of psoriasis lesions has been described following prolonged occlusion with various tape products, including sticking plasters, although different tapes varied markedly in their effectiveness [1,2]. These findings have been confirmed in a prospective bilateral comparison study in which prolonged application of an adhesive hydrocolloid occlusive dressing was found to be superior to twice daily applications of a potent topical corticosteroid, and as effective as erythemogenic UVB treatment. Side effects included hyperpigmentation, pain on removal of dressings resulting from hair traction and, in a minority, a Koebner response or offensive odour [3]. Further evidence came from a 3-week study when occlusion alone was as effective as the potent topical corticosteroid—fluocinonide ointment [4]. Mechanism of action may relate to normalization of the permeability barrier [5]. This treatment appears to have potential in the management of limited psoriasis.

References

1 Shore RN. Clearing of psoriasis lesions after the application of tape (Letter). *N Engl J Med* 1985; **312**: 246.

2 Shore RN. Treatment of psoriasis with prolonged application of tape (Letter). *J Am Acad Dermatol* 1986; **15**: 540–2.

3 Friedman ST. Management of psoriasis vulgaris with a hydrocolloid occlusive dressing. *Arch Dermatol* 1987; **123**: 1046–52.

4 Griffiths CEM, Tranfaglia MG, Kang S. Prolonged occlusion in the treatment of psoriasis: a clinical and immunohistologic study. *J Am Acad Dermatol* 1995; **32**: 618–22.

5 Hwang SM, Ahn SK, Menon GK *et al*. Basis of occlusive therapy in psoriasis: correcting defects in permeability barrier and calcium gradient. *Int J Dermatol* 2001; **40**: 223–31.

Treatment of the scalp

Psoriasis of the scalp can be intractable and resistant to therapy. Tar-containing shampoos should be the first approach, carried out daily if necessary. Tar lotions or gels may be added, rubbed in at night and shampooed out the following morning. A coconut oil-based tar and salicylic acid pomade applied at bedtime, sometimes occluded overnight with a polythene shower cap, and shampooed off in the morning, is commonly used in the UK [1]. Cream formulations of dithranol can be useful, but care should be taken to avoid irritation of the ears and eyes. Dithranol may also cause unacceptable staining of fair hair. Calcipotriol scalp application may also be of value [1,2].

If these measures fail, corticosteroid scalp lotions, gels or foams should be tried, but even the most potent (e.g. clobetasol propionate 0.05% alcoholic solution) is ineffective if painted on the surface of thick plaques of psoriasis. In these circumstances, the scalp should be copiously drenched overnight (or throughout 24 h if possible) with the coconut oil-based tar and salicylic acid pomade or similar preparation, which is shampooed out once or even twice a day. Two or three days of such treatment generally brings about marked improvement. A clobetasol propionate-containing shampoo is an innovative approach and has been shown to be more effective than the traditional tar shampoo [3]. A recent development is a combination gel containing betamethasone dipropionate and calcipotriol; this is more effective than calcipotriol scalp solution [4].

References

1 Warren RB, Brown BC, Griffiths CEM. Topical treatments for scalp psoriasis. *Drugs* 2008; **68**: 2293–302.

2 Chan CS, van Voorhees AS, Lebwohl MG *et al*. Treatment of severe scalp psoriasis: from the Medical Board of the National Psoriasis Foundation. *J Am Acad Dermatol* 2009; **60**: 962–71.

3 Griffiths CEM, Finlay AY, Fleming CJ *et al*. A randomized investigator-masked evaluation of the efficacy and safety of clobetasol propionate 0.05% shampoo and tar blend 1% shampoo in the treatment of moderate and severe scalp psoriasis. *J Dermatolog Treat* 2006; **17**: 90–5.

4 Kragballe K, Hoffman V, Ortonne JP *et al*. Efficacy and safety of calcipotriol and betamethasone dipropionate scalp formulation compared with calcipotriol scalp solution in the treatment of scalp psoriasis.: a randomized controlled trial. *Br J Dermatol* 2009; **161**: 159–66.

UV phototherapy

UVB

Goeckerman [1] first thoroughly documented the ability of crude coal-tar applications followed by exposure to UV radiation to clear psoriasis. Much later, it became clear that broad-band (290–320 nm) UV radiation (BBUVB) alone, if given in mildly erythemogenic dosage, was capable of clearing psoriasis [2–5] and can be as effective as PUVA [6]. In addition, continued maintenance BBUVB therapy after initial clearance with BBUVB significantly increased the duration of disease control, even though maintenance treatment was given at modest frequency (an average of six treatments per month) [7].

UVB therapy three times weekly is sufficient [2], and twice daily treatment is of no extra value over once daily treatment [8]. The benefit of additional tar therapy is accepted [8,9], but doubt has been cast on the value of adding topical steroid therapy [10,11] or short-contact dithranol to a UV regimen. The known carcinogenicity of BBUVB limits enthusiasm for phototherapy. While some studies have not shown an increased skin cancer risk in UVB-treated psoriasis patients [12–14], one study suggested that high levels of exposure to BBUVB are associated with an approximately fourfold increase in the risk of genital tumours in men [15]. Protection of the genital area from BBUVB exposure would therefore be prudent in these patients.

Philips TL-01 fluorescent lamps emit a narrow-band UVB (NBUVB) at 311 nm. Irradiation with this source has been found to be superior to conventional BBUVB in psoriasis, producing longer remissions, a lower incidence of burning and possibly a lower risk of UV carcinogenesis [16–22]. The effectiveness of NBUVB appears to be similar to that of PUVA, but it is more convenient and also probably less carcinogenic [20,21]. The use of higher intensity (100 W) TL-01 lamps has confirmed the superiority of narrow-band over conventional broad-band therapy, and has allowed shorter, more convenient exposure times [23]. In a randomized controlled trial, 100 patients with psoriasis were allocated to either twice weekly PUVA or NBUVB. Clearance of psoriasis occurred in a significantly greater proportion of patients on PUVA (84%) than with NBUVB (63%) and with significantly fewer treatments (16.7 versus 25.3, respectively) [24]. However, another trial of NBUVB three times weekly was of equivalent efficacy to PUVA and is more effective than bath PUVA [25,26]. Several studies have examined the optimal number of NBUVB treatment sessions per week. Twice-weekly treatment produced equivalent

improvement in psoriasis to four times weekly, but with only 16 as compared to 32 exposures [27]. Three times weekly appears to be the optimum regimen for efficacy in that two NBUVB sessions weekly took 50% longer to clear psoriasis compared to three times weekly (88 versus 58 days, respectively) [28]. An interesting development is home NBUVB treatment based on patient training—all patients who took part in the study preferred home- over hospital-based treatment [29]. Application of dithranol also provided a substantial additional benefit [23]. The combination of NBUVB with etretinate decreased the number of treatments and the UV exposure required for clearing, but was associated with a more rapid relapse than seen in NBUVB monotherapy [29,30]. NBUVB radiation is emerging as the UV therapy of choice in psoriasis, although its long-term safety remains to be confirmed by objective clinical studies. Unlike BBUVB, TL-01 therapy has been reported to cause asymptomatic or painful blistering at the sites of psoriatic lesions towards the middle of a treatment course. This side effect appears to be very unusual, and usually resolves with continued narrow-band treatment, although this may need to be briefly interrupted or restricted [31].

A retrospective study of 1488 psoriasis patients treated for 4 weeks at the Dead Sea Clinic from 1983 to 1986 by sun exposure and bathing in mineral-rich sea has been carried out. Nearly three-quarters improved by 90% or more, results consistent with those of a prior prospective study of 110 patients. The treatment is said to be cost-effective and pleasant, the combined costs of travel, accommodation and nominal medical fees usually being less than that of in-patient treatment for the clearing of psoriasis [32].

In general, UVB therapy is valuable for plaque psoriasis and may be especially valuable in guttate and 'seborrhoeic' patterns. It is usually of little value in psoriatic erythroderma and generalized pustular psoriasis, and may aggravate these forms of the disease.

References

1 Goeckerman WH. Treatment of psoriasis. *Arch Dermatol Syphilol* 1931; **24**: 446–50.
2 Adrian RM, Parrish JA, Momtaz TK *et al.* Outpatient phototherapy for psoriasis. *Arch Dermatol* 1981; **117**: 623–6.
3 Larkö O, Swanbeck G. Home solarium treatment of psoriasis. *Br J Dermatol* 1979; **101**: 13–6.
4 LeVine MJ, White HAD, Parrish JA. Components of the Goeckerman regimen. *J Invest Dermatol* 1979; **73**: 170–3.
5 LeVine MJ, Parrish JA. Outpatient phototherapy of psoriasis. *Arch Dermatol* 1980; **116**: 552–4.
6 Van Weelden H, Young E, van Der Leun JC. Therapy of psoriasis: comparison of photo-chemotherapy and several variants of phototherapy. *Br J Dermatol* 1980; **103**: 1–9.
7 Stern RS, Armstrong RB, Anderson TF *et al.* Effect of continued ultraviolet B phototherapy on the duration of remission in psoriasis: a randomized study. *J Am Acad Dermatol* 1986; **15**: 546–52.
8 Petrozzi JW. Comparison of once-daily and twice-daily ultraviolet radiation treatment in psoriasis. *Arch Dermatol* 1981; **117**: 695–7.
9 Frost P, Horwitz SN, Caputo RV *et al.* Tar gel-phototherapy for psoriasis. *Arch Dermatol* 1979; **115**: 840–6.
10 LeVine MJ, Parrish JA. The effect of topical fluocinonide ointment on phototherapy of psoriasis. *J Invest Dermatol* 1982; **78**: 157–9.
11 Petrozzi JW. Topical steroids and UV radiation in psoriasis. *Arch Dermatol* 1983; **119**: 207–10.
12 Larkö O, Swanbeck G. Is UVB therapy of psoriasis safe? *Acta Derm Venereol (Stockh)* 1982; **62**: 507–12.
13 Lynfield Y, O'Donohue MN. Tar, UVL, PUVA and cancer (Letter). *J Am Acad Dermatol* 1981; **4**: 612–3.
14 Stern RS, Laird N. The carcinogenic risk of treatments for severe psoriasis. *Cancer* 1994; **73**: 2759–64.
15 Stern RS. Members of the Photochemotherapy Follow-up Study. Genital tumors among men with psoriasis exposed to psoralens and ultraviolet A radiation (PUVA) and ultraviolet B radiation. *N Engl J Med* 1990; **322**: 1093–7.
16 van Weelden H, Baart de la Faille H, Young E, van der Leun JC. A new development in UVB phototherapy of psoriasis. *Br J Dermatol* 1988; **119**: 11–9.
17 Green C, Ferguson J, Lakshmipathi T, Johnson BE. 311 nm UVB phototherapy: an effective treatment for psoriasis. *Br J Dermatol* 1988; **119**: 691–6.
18 Karvonen J, Kokkonen E, Ruotsalainen E. 311 nm UVB lamps in the treatment of psoriasis with the Ingram regime. *Acta Derm Venereol (Stockh)* 1989; **69**: 82–5.
19 Larkö O. Treatment of psoriasis with a new UVB lamp. *Acta Derm Venereol (Stockh)* 1989; **69**: 357–9.
20 Man I, Crombie IK, Dawe RS, Ibbotson SH, Ferguson J. The photocarcinogenic risk of narrowband UVB (TL-01) phototherapy: early follow-up data. *Br J Dermatol* 2005; **152**: 755–7.
21 van Weelden H, Baart de la Faille H, Young E, van der Leun JC. Comparison of narrow-band UVB phototherapy and PUVA photochemotherapy in the treatment of psoriasis. *Acta Derm Venereol (Stockh)* 1990; **70**: 212–5.
22 Picot E, Meunier L, Picot-Debeze MC *et al.* Treatment of psoriasis with a 311-nm UVB lamp. *Br J Dermatol* 1992; **127**: 509–12.
23 Storbeck K, Hölzle E, Schürer N *et al.* Narrow-band UVB (311 nm) versus conventional broad-band UVB with and without dithranol in phototherapy for psoriasis. *J Am Acad Dermatol* 1993; **28**: 227–31.
24 Gordon PM, Diffey BL, Matthews JNS, Farr PM. A randomized comparison of narrow-band TL-01 phototherapy and PUVA photochemotherapy for psoriasis. *J Am Acad Dermatol* 1999; **41**: 728–32.
25 Tanew A, Radakovic-Fijan S, Schemper M, Honigsmann H. Narrow-band UVB phototherapy versus photochemotherapy in the treatment of chronic plaque type psoriasis: a paired comparison study. *Arch Dermatol* 1999; **135**: 519–24.
26 Dawe RS, Cameron H, Yule S *et al*. A randomized controlled trial of narrowband ultraviolet B vs bath-psoralen plus ultraviolet A photochemotherapy for psoriasis. *Br J Dermatol* 2003; **148**: 1194–204.
27 Leenataphung V, Nimkulrat P, Sudtim S. Comparison of phototherapy two times and four times a week with low doses of narrow-band ultraviolet B in Asian patients with psoriasis. *Photodermatol Photoimmunol Photomed* 2000; **16**: 202–6.
28 Cameron H, Dawe RS, Yale S *et al.* A randomized, observe blinded trial of twice versus three times weekly narrow-band ultraviolet B phototherapy for chronic plaque psoriasis. *Br J Dermatol* 2002; **147**: 973–8.
29 Cameron H, Yule S, Moseley H *et al.* Taking treatment to the patient, development of a home TL-01 ultraviolet B phototherapy service. *Br J Dermatol* 2002; **147**: 957–65.
30 Green C, Lakshmipathi T, Johnson BE, Ferguson J. A comparison of the efficacy and relapse rates of narrow-band UVB (TL-01) monotherapy versus etretinate (re-TL-01) versus etretinate–PUVA (re-PUVA) in the treatment of psoriasis patients. *Br J Dermatol* 1992; **127**: 5–9.
31 George SA, Ferguson J. Lesional blistering following narrow-band (TL-01) UVB phototherapy for psoriasis: a report of four cases (Letter). *Br J Dermatol* 1992; **127**: 445–6.
32 Abel EA, Barnes S, Le Vine MJ *et al.* Psoriasis treatment at the Dead Sea: second international study tour (Letter). *J Am Acad Dermatol* 1988; **19**: 362–4.

Psoralen photochemotherapy

History. Experience with coal-tar and UV therapy of psoriasis, and psoralen photochemotherapy of vitiligo, led to the suggestion that psoriasis might benefit from the same approach [1]. The first report of successful treatment of psoriasis was ignored [2] but a decade later the effectiveness of topical psoralens followed by long-wave UV radiation (UVA) in resolving plaque psoriasis was confirmed [3,4]. Within 2 years, the first report of successful use of oral 8-methoxypsoralen (8-MOP) and UVA [5] led to intense interest and the coining of the terms 'photochemotherapy' and

'PUVA' [2,6–9]. Multiple studies soon confirmed the efficacy of oral [10–18] and topical [12,19–21] PUVA therapy in various patterns of psoriasis. In the USA, Food and Drug Administration approval of PUVA therapy for severe psoriasis was granted in May 1982. In the UK, official approval is still withheld, and no psoralen preparation has a product licence. Nevertheless, PUVA is widely used in the UK. With the introduction of narrow-band UVB phototherapy and the risk-averse practice of medicine prevalent in the USA, there is a significant reduction in the number of patients receiving PUVA per annum. The National Ambulatory Medical Care Survey revealed an 85% reduction in PUVA use from 1993 to 1998 [22].

Methodology. The methodology for using PUVA is described in detail in Chapter 29 and for the most part is the same as is used for the treatment of psoriasis. Dosage of 8-MOP is arbitrary, as is the time interval before irradiation. Different pharmaceutical preparations of 8-MOP differ markedly in bioavailability [23,24], and there are patient variations in the rate and extent of absorption [25]. In addition, there is no simple correlation between achieved plasma levels and therapeutic response [26], although patients responding unsatisfactorily are more likely to have deviant blood levels [27,28]. Liquid formulations of 8-MOP have been reported to produce higher, earlier peak levels of drug in the plasma and more reproducible plasma concentrations [29,30].

Dietary influences may be important [31], absorption being delayed and reduced by a fat-rich meal. Other photoactive drugs should be avoided. Standard oral dosage using 8-MOP tablets is 0.6 mg/kg [9], given 2 h before irradiation. High-intensity fluorescent UVA tubes are used, and initial UVA dosage is based on skin type. Some clinicians start with somewhat smaller doses. Treatment is given two to four times weekly. UVA dosage is increased by increments of 0.5–1.5 J/cm^2 according to response. Persistent tenderness or erythema of uninvolved skin may call for temporary reduction of UVA dosage, or cessation of treatment for a few days. Once substantial clearance has been achieved, the frequency of treatment can be reduced, so that maintenance treatment (usually the last UVA dose in the clearance phase) is given once every 1–4 weeks. Alternatively, the treatment may be stopped in many cases if the psoriasis remains clear. In either case, clearance schedules may have to be resumed to control relapses. A cost-effective modified UVA dosage schedule leading to an increased clearance rate and reduced cumulative UVA dose, and therefore possibly a lower incidence of long-term cutaneous side effects, has been proposed [32]. In this study, initial and incremental UVA doses were maximized to near erythemogenic levels by weekly testing for the minimal phototoxic dose, by using an automated skin testing UVA irradiation unit. However, the value of repeated minimum UVA phototoxicity dose testing in reducing the cumulative dose of UVA and improving the clearance rate has been questioned [33].

Patient selection [6,23]. In many departments, only vertical UVA irradiation units are available as they occupy less floor space than horizontal units, and they save time, as the entire skin is irradiated simultaneously. Some elderly or infirm patients may encounter difficulty standing in a vertical unit for a prolonged period. A history of previous summer exacerbation of psoriasis involving exposed areas is not necessarily a contraindication; some such patients do well with cautious PUVA treatment [34]. Previous exposure to inorganic arsenic or radiotherapy or a history of cutaneous malignancy are relative contraindications. The treatment should not be given in pregnancy nor to children under 18 years, except in the most compelling circumstances. Because the long-term carcinogenic hazard is uncertain, PUVA should only be considered as a primary treatment in those patients over 55 years of age where psoriasis covers at least 20% of the body surface, and who cannot be controlled by conventional topical therapy. In patients under 55 years or with less widespread psoriasis, other considerations may justify therapy according to individual circumstances. PUVA is of no value for psoriasis in areas where UVA access is impossible, such as the scalp (except in the bald) or certain body flexures.

Results. Therapeutic results have been uniformly good to excellent in psoriasis vulgaris. Clearance rates of up to 90% have been reported [11,13,16–18], substantial clearance being achieved by 15–25 treatments to a total of 100–200 J/cm^2. Less spectacular success rates have probably reflected selection of severe resistant cases [10,15,35] or use of lower 8-MOP or UVA doses [12,36]. The use of four treatments weekly in a European cooperative trial achieved complete clearing in 65%, and substantial improvement in another 29% in approximately 3200 patients, with a mean of 20 exposures in 5–6 weeks, a mean UVA clearance dose of 7 J/cm^2 and a cumulative UVA dose to clearance of about 100 J [18]. Although success was comparable in large US cooperative studies [13,16] in which three treatments weekly were given, higher clearance UVA doses (13–14 J/cm^2), higher cumulative doses (up to 200 J) and 10–12 weeks were needed. The European regimen of four treatments weekly possibly achieved its antipsoriatic action before increasing pigmentation necessitated higher UVA doses.

PUVA is also of value in generalized pustular psoriasis, erythrodermic psoriasis, palmoplantar pustulosis and nail psoriasis [37], but success rates are much lower in these atypical patterns of disease. The value of maintenance therapy is disputed, being thought to be of value by some authors [13,38–40] but not by others [18]. A useful compromise is to give maintenance treatment for 2 months. If the psoriasis remains clear, PUVA is stopped. Low-dose PUVA maintenance is possible after clearance has been achieved by some other modality (e.g. dithranol) [41].

Combined therapy. The simultaneous use of etretinate or acitretin and PUVA is discussed below. Dithranol and PUVA have been used together [37] and sequentially [41]. In extremely severe erythrodermic or generalized pustular psoriasis, a cytotoxic drug may be given concurrently. Methotrexate in combination with PUVA is effective; however, there is an inevitable increased risk of skin cancer [42,43]. Topical corticosteroids may be used concurrently, especially on areas inaccessible to UVA. However, it is unresolved whether this combination results in shorter remission times [44,45]. Calcipotriol combined with PUVA is more effective than PUVA alone and results in less UVA exposure [46]. Although rarely used, PUVA and UVB used together has been reported

effective in patients unresponsive to either PUVA or UVB alone [47].

References

1 Lerner AB, Denton CR, Fitzpatrick TB. Clinical and experimental studies with 8-methoxypsoralen in vitiligo. *J Invest Dermatol* 1953; **20**: 299–314.
2 Anderson TF, Voorhees JJ. Psoralen photochemotherapy of cutaneous disorders. *Ann Rev Pharmacol Toxicol* 1980; **20**: 235–57.
3 Tronnier H, Schüle D. Zur dermatologischen Therapie von Dermatosen mit langwelligem UV nach Photosensibilisierung der Haut mit Methoxsalen. Erste Ergebnisse bei der Psoriasis vulgaris. *Z Haut-Geschl Kr* 1973; **48**: 385–93.
4 Walter JF, Voorhees JJ, Kelsey WH *et al.* Psoralen plus black light inhibits epidermal DNA synthesis. *Arch Dermatol* 1973; **107**: 861–5.
5 Parrish JA, Fitzpatrick TB, Tanenbaum L *et al.* Photochemotherapy of psoriasis with oral methoxsalen and long-wave ultraviolet light. *N Engl J Med* 1974; **291**: 1207–11.
6 Epstein JH, Farber EM, Nall L *et al.* Current status of oral PUVA therapy for psoriasis. *J Am Acad Dermatol* 1979; **1**: 106–17.
7 Harber LC. PUVA therapy status. *J Am Acad Dermatol* 1979; **1**: 150–1.
8 Vella Briffa D, Warin AP. Photochemotherapy in psoriasis. *J R Soc Med* 1979; **72**: 440–6.
9 Parrish JA, LeVine MJ, Fitzpatrick TB. Oral methoxsalen photochemotherapy of psoriasis and mycosis fungoides. *Int J Dermatol* 1980; **19**: 379–86.
10 Swanbeck G, Thyresson-Hök M, Bredberg A *et al.* Treatment of psoriasis with oral psoralens and long-wave ultraviolet light. *Acta Derm Venereol (Stockh)* 1975; **55**: 367–76.
11 Wolff K, Fitzpatrick TB, Parrish JA *et al.* Photochemotherapy for psoriasis with orally administered methoxsalen. *Arch Dermatol* 1976; **112**: 943–50.
12 Lakshmipathi T, Gould PW, MacKenzie LA *et al.* Photochemotherapy in the treatment of psoriasis. *Br J Dermatol* 1977; **96**: 587–94.
13 Melski JW, Tanenbaum L, Parrish JA *et al.* Oral methoxsalen photochemotherapy for the treatment of psoriasis. *J Invest Dermatol* 1977; **68**: 328–35.
14 Hell E, Hodgson C, Manna V. Psoralen photochemotherapy of psoriasis. *Br J Dermatol* 1979; **101**: 293–8.
15 Klaber M, Baker H, Johnson-Smith J *et al.* Photochemotherapy of psoriasis in a general hospital. *Br J Dermatol* 1979; **101** (Suppl. 17): 12–3.
16 Roenigk HH, Farber EM, Storrs F *et al.* Photochemotherapy for psoriasis. *Arch Dermatol* 1979; **115**: 576–9.
17 Siddiqui AH, Cormane RH. Initial photochemotherapy of psoriasis with orally administered 8-methoxypsoralen and long-wave ultraviolet light (PUVA). *Br J Dermatol* 1979; **100**: 247–50.
18 Henseler T, Wolff K, Hönigsman H *et al.* Oral 8-methoxypsoralen photochemotherapy of psoriasis. *Lancet* 1981; **i**: 853–7.
19 Weber G. Combined 8-methoxypsoralen and black light therapy of psoriasis. *Br J Dermatol* 1974; **90**: 317–23.
20 Fischer T, Alsins J. Treatment of psoriasis with trioxsalen baths and dysprosium lamps. *Acta Derm Venereol (Stockh)* 1976; **56**: 383–90.
21 Danno K, Horio T, Ozaki M *et al.* Topical 8-methoxypsoralen photochemotherapy of psoriasis. *Br J Dermatol* 1983; **108**: 519–24.
22 Housman TS, Rohrbeck JM, Fleischer AB Jr, Feldman SR. Phototherapy utilization for psoriasis is declining in the United States. *J Am Acad Dermatol* 2002; **46**: 57–9.
23 Andrew E, Nilsen A, Thune P *et al.* Photochemotherapy in psoriasis: clinical response and 8-MOP plasma concentrations at two dose levels. *Clin Exp Dermatol* 1981; **6**: 591–600.
24 Menne T, Andersen KE, Larsen E *et al.* Pharmacokinetic comparison of seven 8-methoxypsoralen brands. *Acta Derm Venereol (Stockh)* 1981; **61**: 137–40.
25 Roelandts R, van Boven M, Adriaens P. Methoxsalen serum level variations in psoralen and ultraviolet-A (PUVA) therapy (Letter). *Arch Dermatol* 1981; **117**: 758.
26 Thune P. Plasma levels of 8-methoxypsoralen and phototoxicity studies during PUVA treatment of psoriasis with meladinin tablets. *Acta Derm Venereol (Stockh)* 1978; **58**: 149–51.
27 Wagner G, Hofmann C, Busch U *et al.* 8-MOP plasma levels in PUVA problem cases with psoriasis. *Br J Dermatol* 1979; **101**: 285–92.
28 Stevenson IH, Kenicer KJA, Johnson BE *et al.* Plasma 8-methoxypsoralen concentrations in photochemotherapy of psoriasis. *Br J Dermatol* 1981; **104**: 47–51.
29 Stolk L, Kammeyer A, Cormane RH *et al.* Serum levels of 8-methoxypsoralen. *Br J Dermatol* 1980; **103**: 417–20.
30 Hönigsmann H, Jaschke E, Nitsche V *et al.* Serum levels of 8-methoxypsoralen in two different drug prescriptions. *J Invest Dermatol* 1982; **79**: 233–6.
31 Roelandts R, van Boven M, Deheyn T *et al.* Dietary influences on 8-MOP plasma levels in PUVA patients with psoriasis. *Br J Dermatol* 1981; **105**: 569–72.
32 Carabott FM, Hawk JLM. A modified dosage schedule for increased efficiency in PUVA treatment of psoriasis. *Clin Exp Dermatol* 1989; **14**: 337–40.
33 Buckley DA, Healy E, Rogers S. A comparison of twice-weekly MPD-PUVA and three times-weekly skin typing-PUVA regimens for the treatment of psoriasis. *Br J Dermatol* 1995; **133**: 417–22.
34 Ros A-M, Wennersten G. PUVA therapy for photosensitive psoriasis. *Acta Derm Venereol (Stockh)* 1987; **67**: 50–5.
35 Cripps DJ, Lowe NJ. Photochemotherapy for psoriasis remission times: psoralens and UV-A and combined photochemotherapy with anthralin. *Clin Exp Dermatol* 1979; **4**: 477–83.
36 Kenicer KJA, Lakshmipathi T, Addo HA *et al.* An assessment of the effect of photochemotherapy (PUVA) and UV-B phototherapy in the treatment of psoriasis. *Br J Dermatol* 1981; **105**: 629–39.
37 Marx JL, Scher RK. Response of psoriatic nails to oral photochemotherapy. *Arch Dermatol* 1980; **116**: 1023–4.
38 Melski JW, Stern RS. Annual rate of psoralen and ultraviolet-A treatment of psoriasis after initial clearing. *Arch Dermatol* 1982; **118**: 404–8.
39 Stern RS, Melski JW. Long-term continuation of psoralen and ultraviolet-A treatment of psoriasis. *Arch Dermatol* 1982; **118**: 400–3.
40 Vella Briffa D, Greaves MW, Warin AP *et al.* The influence of maintenance photochemotherapy on the relapse of plaque psoriasis. *Br J Dermatol* 1980; **103** (Suppl. 18): 14–5.
41 van de Kerkhof PCM, Mali JWH. Low-dose PUVA maintenance in psoriasis following Ingram therapy. *Br J Dermatol* 1981; **104**: 681–4.
42 Morison WL, Momtaz K, Parrish JA, Fitzpatrick TB. Combined methotrexate-PUVA therapy in the treatment of psoriasis. *J Am Acad Dermatol* 1982; **6**: 46–51.
43 Stern RS, Laird N. The carcinogenic risk of treatment for severe psoriasis: photochemotherapy follow-up study. *Cancer* 1994; **73**: 2759–64.
44 Schmoll M, Henseler T, Christophers E. Evaluation of PUVA, topical corticosteroids and the combination of both in the treatment of psoriasis. *Br J Dermatol* 1978; **99**: 693–702.
45 Morisson WL, Parish JA, Fitzpatrick TB. Controlled study of PUVA and adjunctive topical therapy in the management of psoriasis. *Br J Dermatol* 1978; **98**: 125–32.
46 Speight EL, Farr PM. Calcipotriol improves the response of psoriasis to PUVA. *Br J Dermatol* 1994; **130**: 79–82.
47 Momtaz K, Parrish JA. Combination of psoralens and ultraviolet A and ultraviolet B in the treatment of psoriasis vulgaris: a bilaterial comparison study. *J Am Acad Dermatol* 1984; **10**: 481–6.

The carcinogenic hazard. It is undisputed that solar UV radiation is a major aetiological factor in squamous and basal cell carcinoma and malignant melanoma in humans. Tumours have been induced in the skin of hairless albino mice by PUVA exposure using both 8-MOP and 5-MOP [1]. An early report suggested that PUVA therapy accelerated the development of skin tumours in patients with xeroderma pigmentosum [2], and it appeared to have an obvious promoter effect in a patient previously exposed to X-irradiation, arsenic and several cytotoxic drugs, who developed 25 basal or squamous cell carcinomas, the first within 21 months of onset of PUVA therapy [3].

There is now substantial literature dealing with the incidence of skin tumours in groups of PUVA-treated patients and this is dealt with in detail in Chapter 29. Although certain studies have failed to show a clear relationship between PUVA and tumour development [4–6], long-term follow-up of a large US cohort has provided conclusive evidence for the carcinogenicity of PUVA [7].

The carcinogenic risk of PUVA is compounded by subsequent systemic immunosuppressive therapies particularly ciclosporin which significantly enhances the risk of developing squamous cell carcinomas (SCC) [8].

References

1 Young AR, Magnus IA, Davies AC *et al.* A comparison of the phototumorigenic potential of 8-MOP and 5-MOP in hairless albino mice exposed to solar simulated radiation. *Br J Dermatol* 1983; **108**: 507–18.
2 Reed WB. Treatment of psoriasis with oral psoralens and long-wave ultraviolet light (Letter). *Acta Derm Venereol (Stockh)* 1976; **56**: 315.
3 Baker H, Darley CR, Johnson-Smith J *et al.* Skin neoplasia associated with PUVA therapy. *Br J Dermatol* 1981; **105** (Suppl. 19): 65–6.
4 Roenigk HH, Caro WA. Skin cancer in the PUVA-48 cooperative study. *J Am Acad Dermatol* 1981; **4**: 319–24.
5 Ros A-M, Wennersten G, Lagerholm B. Long-term photochemotherapy for psoriasis. *Acta Derm Venereol (Stockh)* 1983; **63**: 215–21.
6 Henseler T, Christophers E, Hönigsmann H *et al.* Skin tumours in the European PUVA study. *J Am Acad Dermatol* 1987; **16**: 108–16.
7 Stern RS, Laird N. The carcinogenic risk of treatments for severe psoriasis. *Cancer* 1994; **73**: 2759–64.
8 Paul CF, Ho VC, McGeown C *et al.* Risk of malignancies in psoriasis patients treated with cysclosporine: a 5 year cohort study. *J Invest Dermatol* 2003; **120**: 211–6.

PUVA using other psoralens

There has been interest in 5-MOP as a substitute for the standard 8-MOP in PUVA therapy. The two forms have been compared [1], and it has been reported that 0.6 mg/kg 5-MOP is as effective as the same dose of 8-MOP [2]. Higher doses of 1.2 mg/kg were more effective, but produced more erythema [2]. The main advantage of 5-MOP lies in better gastrointestinal tolerance, nausea occurring only rarely [1,2]. It has also been shown that therapeutic doses of 5-MOP are associated with a lower incidence of phototoxic reactions than 8-MOP [3]. It may therefore be preferable to 8-MOP in PUVA therapy, particularly in light-sensitive patients and subjects with 8-MOP intolerance. There is no evidence that 5-MOP is less photocarcinogenic than 8-MOP [4].

Trimethylpsoralen has been used to good effect in PUVA baths (see below). Use of 3-carbethoxypsoralen has been advocated because it is non-carcinogenic in mice [5].

References

1 Langner A, Wolska H, Kowalski J *et al.* Photochemotherapy (PUVA) and psoriasis: comparison of 8-MOP and 8-MOP/5-MOP. *Int J Dermatol* 1976; **15**: 688–9.
2 Hönigsmann H, Jaschke E, Gschnait F *et al.* 5-methoxypsoralen (Bergapten) in photochemotherapy of psoriasis. *Br J Dermatol* 1979; **101**: 369–78.
3 Tanew A, Ortel B, Rappersberger K *et al.* 5-Methylpsoralen (Bergapten) for photochemotherapy. *J Am Acad Dermatol* 1988; **18**: 333–8.
4 Young AR, Magnus IA, Davies AC *et al.* A comparison of the phototumorigenic potential of 8-MOP and 5-MOP in hairless albino mice exposed to solar simulated radiation. *Br J Dermatol* 1983; **108**: 507–18.
5 Dubertret L, Averbeck D, Zajdela F *et al.* Photochemotherapy (PUVA) of psoriasis using 3-carbethoxypsoralen, a non-carcinogenic compound in mice. *Br J Dermatol* 1979; **101**: 379–89.

PUVA therapy with topically applied psoralens

A desire to avoid some of the side effects of oral treatment, especially in patients with localized forms of psoriasis, reactivated interest in the use of 8-MOP topically. A lotion or emulsion containing 0.1–1% 8-MOP has been used, and the time interval before UV irradiation seems to be relatively unimportant, periods as short as 5 min giving results as good as those with a delay of up to 2 h [1]. If extensive areas of skin are treated with topical 8-MOP in an oil-in-water emulsion, blood levels comparable to those achieved during oral therapy are found [2], so that the usual precautions to protect the eyes must be taken and little advantage is incurred. Local treatment can be given two to five times weekly, the dose of UVA being slowly increased according to response.

Trimethylpsoralen (TMP) has also been used topically to the whole body in a bath, combined with UVA, initially mainly in Finland and Sweden [3–5]. TMP is used at a concentration of 0.33 mg/L [6]. Comparisons of TMP baths with oral 8-MOP PUVA have shown that the response and relapse rates are similar. Nausea and headache occurred in the group using systemic treatment but not in the bath group, but short-term, local cutaneous side effects, such as pruritus, were more common in the bath group [7,8]. Benefits have also been claimed for a combination of TMP bath PUVA with oral etretinate [9] and acitretin [10]. One report has suggested that TMP bath PUVA carries a lower risk for skin cancer than oral 8-MOP PUVA, possibly because the doses of UVA are 15–20 times lower with bath PUVA [11]. However, the data are preliminary and may be confounded by the fact that there were fewer high-dose PUVA patients among the bath group, that maintenance treatment was not given and that the face (an important site of SCC in the oral PUVA group) was not treated in the bath PUVA patients. It is prudent to conclude that, as yet, there is insufficient evidence that bath PUVA is safer. While no excess risk of skin cancer has been reported with bath PUVA, both keratoses and lentigines are common [12].

Bath PUVA with 8-MOP, at a concentration of 2.6–3.7 mg/L, has been successful [8,13]. A comparison of 8-MOP bath PUVA and oral PUVA found no difference in efficacy between the two, but bath delivery required 50% less UVA [13]. Although plasma levels of psoralen have been reported as either undetectable or very low after bath PUVA, a relationship between plasma 8-MOP levels and severity of psoriasis has been found, raising the possibility of adverse systemic reactions in patients with extensive disease [14]. The practice of not using UVA-screening spectacles following bath PUVA [13] may therefore need to be reassessed in such patients. Bath temperature should remain constant from treatment to treatment, 37°C seems optimal with a bath time of 15 min—followed immediately by UVA; local head and foot treatment may require up to 40 min before UVA. Guidelines issued by the British Photodermatology Group provide protocols for delivery of bath PUVA [6].

Psoriasis of the fingernails has been successfully treated with topical 1% 8-MOP solution and UVA two to three times weekly [15].

References

1 Danno K, Horio T, Ozaki M *et al.* Topical 8-methoxypsoralen photochemotherapy of psoriasis: a clinical study. *Br J Dermatol* 1983; **108**: 519–24.
2 Neild VS, Scott LV. Plasma levels of 8-methoxypsoralen in psoriatic patients receiving topical 8-methoxypsoralen. *Br J Dermatol* 1982; **106**: 199–203.
3 Fischer T, Alsins J. Treatment of psoriasis with trioxsalen baths and dysprosium lamps. *Acta Derm Venereol (Stockh)* 1976; **56**: 383–90.
4 Hannuksela M, Karvonen J. Trioxsalen bath plus UVA effective and safe in the treatment of psoriasis. *Br J Dermatol* 1978; **99**: 703–7.
5 Salo OP, Lassus A, Taskinen J. Trioxsalen bath plus UVA treatment of psoriasis. *Acta Derm Venereol (Stockh)* 1981; **61**: 551–4.

6 Halpern SM, Anstey A, Dawe RS *et al.* Guidlelines for topical PUVA: a report of a workshop of the British Photodermatology Group. *Br J Dermatol* 2000; **142**: 22–31.
7 Turjanmaa K, Salo H, Reunala T. Comparison of trioxsalen bath and oral methoxsalen PUVA in psoriasis. *Acta Derm Venereol (Stockh)* 1985; **65**: 86–8.
8 Lowe NJ, Weingarten D, Bourget T *et al.* PUVA therapy for psoriasis: comparison of oral and bath-water delivery of 8-methoxypsoralen. *J Am Acad Dermatol* 1986; **14**: 754–60.
9 Väätäinen N, Hollmen A, Fräki JE. Trimethylpsoralen bath plus ultraviolet A combined with oral retinoid (etretinate) in the treatment of severe psoriasis. *J Am Acad Dermatol* 1985; **12**: 52–5.
10 Lauharanta J, Geiger J-M. A double-blind comparison of acitretin and etretinate in combination with bath PUVA in the treatment of extensive psoriasis. *Br J Dermatol* 1989; **121**: 107–12.
11 Lindelöf B, Sigurgeirsson B, Tegner E *et al.* Comparison of the carcinogenic potential of trioxsalen bath PUVA and oral methoxsalen PUVA. *Arch Dermatol* 1992; **128**: 1341–4.
12 Takashima A, Sunohara A, Matsunami E, Mizuno N. Comparison of therapeutic efficacy of topical PUVA, oral etretinate and combined PUVA and etretinate for the treatment of psoriasis and development of PUVA lentigines and antinuclear antibodies. *J Dermatol* 1988; **15**: 471–9.
13 Collins P, Rogers S. Bath-water compared with oral delivery of 8-methoxypsoralen PUVA therapy for chronic plaque psoriasis. *Br J Dermatol* 1992; **127**: 392–5.
14 Gómez MI, Azaña JM, Arranz I *et al.* Plasma levels of 8-methoxypsoralen after bath-PUVA for psoriasis: relationship to disease severity. *Br J Dermatol* 1995; **133**: 37–40.
15 Handfield-Jones SE, Boyle J, Harman RRM. Local PUVA treatment for nail psoriasis. *Br J Dermatol* 1987; **116**: 280–1.

Systemic therapy

For practical purposes, the alternatives are corticosteroids, methotrexate, retinoids, ciclosporin and the new biologic therapies. Photochemotherapy is discussed above.

Methotrexate

The beneficial effect of aminopterin on psoriasis was first observed in 1951 [1]. Safe regimens were soon developed [2], and aminopterin was replaced by its more stable analogue, methotrexate, which may be given orally, intramuscularly, subcutaneously or intravenously. In cancer patients, absorption of an oral dose was found to be complete [3], but variable degrees of malabsorption are found in psoriatics even with small doses, 32–98% of the oral dose being absorbed, and the degree of absorption correlating well with D-xylose absorption [4]. Excretion is largely (95%) by the kidney, but there is extensive enterohepatic cycling [5,6]. The drug is 50–70% bound to plasma albumin [3,7]. Methotrexate inhibits DNA synthesis by competitive inhibition of dihydrofolate reductase [8], and may thus exert an antimitotic action on the epidermis. Recently, *in vitro* studies showed that methotrexate was 10–100 times more effective at inhibiting the proliferation of lymphoid cell lines than cultured keratinocytes, suggesting that lymphoid cells may be a more important cellular target than epithelial cells in psoriasis [9]. In regimens for psoriasis, methotrexate also inhibits polymorphonuclear leukocyte chemotaxis [10]. These actions may explain its clinical effects.

Controlled trials have suggested that topical methotrexate is ineffective in psoriasis [11,12] in spite of evidence for local absorption [13]. In contrast, significant improvement was subsequently noted following the use of a topical methotrexate gel containing the penetration enhancer, laurocapram. It was therefore suggested that topical methotrexate may be effective in psoriasis if adequate percutaneous absorption is provided for a sufficient period [14].

Oral therapy is given once weekly, occasionally fortnightly. Daily regimens are dangerous and have been abandoned. For a 70 kg adult, an initial test dose of 5–10 mg is given to avoid early toxicity. Maintenance doses should be achieved by gradual increases of 2.5–5 mg/week, and usually range between 7.5 and 30 mg/week. Methotrexate may be given as a single weekly oral dose, or divided into three parts given 12 h apart over 24 h [15]. Parenteral therapy is equally safe, similar doses being given intramuscularly, subcutaneously or intravenously every 7–14 days. The subcutaneous route is becoming popular with the advent of this form of administration as the norm for patients on biologic therapies. In the elderly, the effective dosage of methotrexate is below the above range, and toxicity may be more readily encountered with higher dosage, probably owing to reduced renal clearance. Patients over 80 years of age have been adequately treated with as little methotrexate as 2.5 mg/week [16].

Before treatment, renal, hepatic and marrow function must be shown to be normal. If renal function is impaired, a reduced dosage of methotrexate may be given with extreme care and regular monitoring. Routine liver-function tests should be supplemented by a liver biopsy, which may be delayed for 2–4 months until it is established that methotrexate is effective and tolerated, and that long-term treatment will be carried out. Many centres are now starting to use an assay of serum levels of the aminopropeptide of type III procollagen (PIIINP) as an alternative to liver biopsy (see below) [17,18]. Anaemia, thrombocytopenia and leukopenia are contraindications to therapy, as are active infection, peptic ulceration, ulcerative colitis past or present, alcoholism, immunodeficiency, pregnancy, lactation and an unreliable patient [15].

Initial dosage should always be cautious (at the lower end of the therapeutic range). Note should always be taken of concurrent therapy with drugs that may displace methotrexate from plasma albumin, such as aspirin, NSAIDs and sulphonamides, including co-trimoxazole [19], as has been reviewed [15]. In addition to the drugs reviewed, furosemide (frusemide) has induced severe toxicity in one patient [20] and a profound fatal leukopenia in another (D.H. Jones, personal communication), probably by interfering with tubular secretion of the drug. Diuretic therapy should be avoided if possible, and used only with great caution if cardiac failure threatens. Special caution is needed if corticosteroids are being given orally, because the toxic effects of the two drugs on the intestinal tract and defence against infection may be additive [21].

Clinical response is usually evident in 7–14 days, but maximal response may take 4–8 weeks. Generalized pustular psoriasis (if acute) may respond within 48 h. As soon as acceptable control is achieved it may be possible to lower the dosage or to extend the interval between doses. It is prudent to accept less than 100% control; quite small doses (e.g. 7.5–10 mg or less weekly) may afford adequate control, especially in the elderly patient. Subsequent minor fluctuation in activity can be treated by other means. In the treatment of erythrodermic or pustular psoriasis where gross oedema, especially of the legs, is common, the temptation to use diuretics, especially furosemide (frusemide) [20] should be

resisted. As the psoriatic inflammation is controlled, a spontaneous diuresis will follow.

Laboratory control of treatment is essential. Initially, the haemoglobin, leukocyte and platelet counts should be shown to be within normal limits; weekly, but later less frequent counts, say monthly or even less often, are adequate. Maximal myelosuppression occurs 7–10 days after an oral dose. The liver enzymes give the simplest guide to hepatic function, and serum albumin, liver-function tests and blood urea or creatinine levels should be checked every 3–4 months during maintenance therapy, although the value of liver enzyme measurements in predicting significant hepatotoxicity is controversial [22]. Liver biopsy should usually be undertaken not less frequently than after every 1.5 g of cumulative methotrexate dosage [15,22]. However, the need for repeated follow-up liver biopsies in carefully selected and monitored patients who have no other risk factors for hepatotoxicity has been questioned, especially in view of the morbidity and cost associated with liver biopsy, and the low yield of pathological findings leading to discontinuation of methotrexate [23].

Numerous toxic effects of methotrexate therapy are recognized. In one long-term study, 73% of patients had side effects, most frequently abnormal liver-function tests, nausea and upper gastrointestinal symptoms [24]. Oral regimens commonly provoke transient anorexia, nausea and dyspeptic pain. Many patients feel slightly unwell for 24 h or so after each dose. Bursting headaches, lasting a day or so, may follow large parenteral doses. Burning sensations in the psoriatic plaques, lasting several days, are not uncommon after full doses, and herald rapid resolution of lesions. Toxic effects on the marrow include leukopenia, thrombocytopenia and, rarely, folate-deficient megaloblastic anaemia. Folic acid given regularly during treatment with methotrexate can prevent nausea and reduce the chances of bone marrow suppression. A UK audit [25] of folic acid prescribing during methotrexate therapy indicated the preferred regimen to be 5 mg/day every day including the day of methotrexate dosing. Modest thrombocytopenia ($100–125 \times 10^9$/L) and low to normal white cell counts ($3.5–4.5 \times 10^9$/L) do not necessarily preclude safe long-term treatment if the counts remain stable.

It is now established beyond all doubt that methotrexate is hepatotoxic, causing fibrosis and cirrhosis, the incidence of which has varied in different series [15,26,27]. One report described cirrhosis and liver failure leading to liver transplantation in three patients receiving largely unsupervised methotrexate treatment for psoriasis, although no information was given about other potential aetiological factors [28]. In general, the incidence of cirrhosis is low with total dosage of less than 1.5 g. Higher incidences of fibrosis and cirrhosis have been reported by Danish authors in patients receiving higher cumulative dosage or longer exposure, findings that have conflicted with the data of others [15]. These higher incidences in Denmark may possibly be explained by a higher average age and previous intake of hepatotoxins, such as arsenic, vitamin A and alcohol [29].

Pre-existing liver disease adds to the risk from the drug, and both functional and structural abnormalities have been demonstrated frequently in severe psoriatics being assessed prior to methotrexate therapy. In one series, premethotrexate liver biopsies showed that steatosis, periportal inflammation and focal necrosis were all found with a statistically significant higher grading among psoriatic patients than controls [26]. Other risk factors include impaired renal function, diabetes, obesity and increasing age [11,15,29–31]. The presence of chronic hepatitis B or C infection is also likely to be a risk, and should be excluded prior to methotrexate therapy.

The clinical course of cirrhosis induced by methotrexate may, however, not be aggressive, some patients being able to continue on the drug without worsening of liver biopsy findings [27,32]. Generally, it is an indolent, slowly developing process that will be detected by serial liver biopsies, when the hazards of stopping and continuing therapy can be weighed against each other. Fatty change and mild inflammatory infiltrate can be ignored, as can the mildest stage of fibrosis if the need for methotrexate is compelling. Progressively more severe damage in serial biopsies demands withdrawal of the drug, as do the findings of advanced fibrosis or cirrhosis, but the serial biopsies may show apparent reversibility or fluctuation of changes [23]. At present, liver biopsy remains the gold standard for the exclusion of significant hepatotoxicity, as indicated in the guidelines of Roenigk *et al.* [15]. However, there is now compelling evidence that 3-monthly monitoring of serum levels of PIIINP may permit dispensing with liver biopsy altogether in approximately 70% of patients. Careful work by researchers in Manchester, UK, and Aarhus, Denmark, [17,18,33] has established that serum levels of PIIINP accurately reflect liver pathology. If serum levels of PIIINP remain within the normal range liver histology is normal; there are occasions when high serum levels of PIIINP occur with a normal liver biopsy—in such circumstances patients can continue on methotrexate but hepatotoxicity is monitored by regular (1.5 g cumulative dosage of methotrexate) liver biopsy.

Another focus of anxiety has concerned the possible hazard of the development of malignant disease. Metastasizing SCC of the skin has been described in a patient on long-term methotrexate [34]. Furthermore, long-term follow-up of a large cohort of patients on PUVA, and other treatments for psoriasis, has suggested a relative risk of 2:1 for SCC of the skin in those who have had high-dose methotrexate exposure (a probable cumulative dosage of more than 3 g over 4 years or more) versus low or no exposure. This risk was independent of PUVA therapy [35]. Careful examination of the skin at intervals would therefore be prudent in any patient on high cumulative dosage of methotrexate.

Anagen alopecia, cutaneous erosions, ulceration and bleeding are rare with weekly dose regimens [36]. Other uncommon side effects include epidermal necrolysis [36], candidiasis [36], folliculitis, ataxia [37], keratoconjunctivitis [38], depression and other psychotic symptoms [21], reactivation of tuberculosis [39] and other pulmonary illnesses [40]. Gastrointestinal bleeding has been reported. Fatal complications of therapy [21] have included rapidly progressive renal failure [41] and septicaemia, as well as the consequences of irreversible marrow or hepatic failure. Death has followed a single intravenous injection in a patient with severe renal failure. The majority of the published deaths are attributable to absolute or relative overdosage [21]. Renal damage is not a recognized hazard of conventional antipsoriatic dosage [41]. Oligospermia is an important hazard in men [42] and may persist long after the drug is withdrawn. Methotrexate osteopathy is a

little-recognized complication of long-term low-dose treatment, affected patients presenting with the triad of severe pain localized to the distal tibia, osteoporosis and compression fractures of the distal tibia. The condition is readily confused with psoriatic arthropathy and, as the only treatment is said to be withdrawal of methotrexate, it is important that it should be recognized [43].

Despite these dangers, methotrexate has a secure place in the treatment of severe psoriasis that is physically or socially disabling, and which is resistant to conventional topical therapy and photochemotherapy. It is particularly valuable in the chronic erythrodermic and generalized pustular forms, where it may be life-saving, and for weaning such patients off systemic steroids. It is useful in intractable non-pustular forms of psoriasis of the hands and feet. Nevertheless, it has long-term hazards and it should never be used as an easy substitute for topical therapy. It should rarely be used in the first half of life, but this is sometimes inevitable, and the use of methotrexate (0.2–0.4 mg/kg/week) in children with severe psoriasis has been reported [44]. It is abortifacient and teratogenic in early pregnancy [45] and fertile patients should take contraceptive precautions. Conception should not be allowed within 3 months of stopping treatment, but is probably safe after that time [46].

In the event of accidental overdosage or unexpected acute toxicity, folinic acid should be given intramuscularly in full dosage (10 mg/m^2) and repeated every 6 h orally or parenterally as tolerated by the patient [15]. After the first dose, subsequent administration of folinic acid should ideally be governed by the serum methotrexate level [15]. Its effectiveness in counteracting the haematological toxicity of methotrexate diminishes with increasing delay.

Methotrexate has been combined successfully with various other therapies such as UVB phototherapy [47–49], PUVA [50] and etretinate [51], in the hope of reducing dosage and therefore toxicity of each modality, while maintaining efficacy. Methotrexate and acitretin should only be used with caution because of the risk of hepatitis. Combining methotrexate with ciclosporin [52] appears to be effective in patients (particularly those with psoriatic arthritis) in whom either drug as monotherapy is poorly tolerated and/or ineffective. This combination approach is analogous to that practised by rheumatologists. Reactivation of UV-induced erythema by methotrexate [47–49] ('erythema recall') may be a problem. Colchicine and methotrexate together have been used in generalized pustular psoriasis [53], and methotrexate can be used to maintain clearance induced by PUVA or a dithranol regimen [54]. However, in view of a report of possible cancer induction, care should be exercised in using PUVA and methotrexate concomitantly [55].

Head-to-head trial of methotrexate compared to ciclosporin revealed that efficacy is similar in the short term [56] but a controlled trial against the TNF-α antagonist adalimumab over 16 weeks demonstrated inferiority of effect [57].

Developments in the understanding of methotrexate pharmacology and the identification of single nucleotide polymorphisms in the enzymes responsible for methotrexate action indicate that pharmacogenetics may have an important role to play in predicting efficacy and side effects of the drug for management of psoriasis [58,59].

References

1 Gubner R. Effect of 'aminopterin' on epithelial tissues. *Arch Dermatol* 1983; **119**: 513–24.
2 Weinstein GD. Commentary: three decades of folic acid antagonist in dermatology. *Arch Dermatol* 1983; **119**: 525–7.
3 Wan SH, Huffman DH, Azarnoff DL *et al.* Effect of route of administration and effusions on methotrexate pharmacokinetics. *Cancer Res* 1974; **34**: 3487–91.
4 Hendel L, Hendel J, Johnsen A *et al.* Intestinal functional and methotrexate absorption in psoriatic patients. *Clin Exp Dermatol* 1982; **7**: 491–8.
5 Baird GM, Dossetor JFB. Methotrexate enteropathy (Letter). *Lancet* 1981; **i**: 164.
6 Calvert AH, Bondy PK, Harrap KR. Some observations on the human pharmacology of methotrexate. *Cancer Treat Rep* 1977; **61**: 1647–56.
7 Taylor JR, Halprin KM. Effect of sodium salicylate and indomethacin on methotrexate-serum albumin binding. *Arch Dermatol* 1977; **113**: 588–91.
8 Taylor JR, Halprin KM, Levine V *et al.* Effects of methotrexate *in vitro* on epidermal cell proliferation. *Br J Dermatol* 1983; **108**: 45–61.
9 Jeffes EWB, McCullough JL, Pittelkow MR *et al.* Methotrexate therapy of psoriasis: differential sensitivity of proliferating lymphoid and epithelial cells to the cytotoxic and growth-inhibitory effects of methotrexate. *J Invest Dermatol* 1995; **104**: 183–8.
10 Walsdorfer U, Christophers E, Schröder J-M. Methotrexate inhibits polymorphonuclear leukocyte chemotaxis in psoriasis. *Br J Dermatol* 1983; **108**: 451–6.
11 Comaish S, Juhlin L. Site of action of methotrexate in psoriasis. *Arch Dermatol* 1969; **100**: 99–105.
12 Steward WD, Wallace SM, Runikis JO. Absorption and local action of methotrexate in human and mouse skin. *Arch Dermatol* 1972; **106**: 357–61.
13 Bjerring P, Beck H-I, Zachariae H *et al.* Topical treatment of psoriatic skin with methotrexate cream: a clinical, pharmacokinetic, and histological study. *Acta Derm Venereol (Stockh)* 1986; **66**: 515–9.
14 Weinstein GD, McCullough JL. Topical methotrexate therapy for psoriasis. *Arch Dermatol* 1989; **125**: 227–30.
15 Roenigk HH, Auerbach R, Maibach HI *et al.* Methotrexate in psoriasis: revised guidelines. *J Am Acad Dermatol* 1988; **19**: 145–6.
16 Fairris GM, Dewhurst AG, White JE *et al.* Methotrexate dosage in patients aged over 50 with psoriasis. *BMJ* 1989; **298**: 801–2.
17 Zachariae H, Søgaard H, Heickendorff L. Serum aminoterminal propeptide of type III procollagen. *Acta Derm Venereol (Stockh)* 1989; **69**: 241–4.
18 Chalmers RJG, Kirby B, Smith A *et al.* Replacement of routine liver biopsy by procollagen III aminopeptide for monitoring patients with psoriasis receiving long-term methotrexate: a multicentre audit and health economic analysis. *Br J Dermatol* 2005; **152**: 444–50.
19 Thomas DR, Dover JS, Camp RDR. Pancytopenia induced by the interaction between methotrexate and trimethoprim-sulfamethoxazole. *J Am Acad Dermatol* 1987; **17**: 1005–6.
20 Nierenberg DW, Mamelok RD. Toxic reaction to methotrexate in a patient receiving penicillin and furosemide (Letter). *Arch Dermatol* 1983; **119**: 449–50.
21 Baker H. Some hazards of methotrexate treatment of psoriasis. *Trans St John's Hosp Dermatol Soc* 1970; **56**: 111–6.
22 Petrazzuoli M, Rothe MJ, Grin-Jorgensen C *et al.* Monitoring patients taking methotrexate for hepatoxicity: does the standard of care match published guidelines? *J Am Acad Dermatol* 1994; **31**: 969–77.
23 Boffa MJ, Chalmers RJG, Haboubi NY *et al.* Sequential liver biopsies during long-term methotrexate treatment for psoriasis: a reappraisal. *Br J Dermatol* 1995; **133**: 774–8.
24 van Dooren-Greebe RJ, Kuijpers ALA, Mulder J *et al.* Methotrexate revisited: effects of long-term treatment in psoriasis. *Br J Dermatol* 1994; **130**: 204–10.
25 Kirby B, Lyon CC, Griffiths CEM, Chalmers RJG. The use of folic acid supplementation in psoriasis patients receiving methotrexate: a survey in the United Kingdom. *Clin Dermatol* 2000; **25**: 265–8.
26 Zachariae H. Psoriasis and the liver. In: Roenigk HH, Maibach HI, eds. *Psoriasis*. New York: Marcel Dekker, 1985: 47–64.
27 Zachariae H, Kragballe K, Sogaard H. Methotrexate-induced liver cirrhosis. *Br J Dermatol* 1980; **102**: 407–12.
28 Gilbert SC, Klintmalm G, Menter A *et al.* Methotrexate-induced cirrhosis requiring liver transplantation in three patients with psoriasis. *Arch Intern Med* 1990; **150**: 889–91.
29 van de Kerkhof PCM, Hoefnagels WHL, van Haelst UJGM *et al.* Methotrexate maintenance therapy and liver damage. *Clin Exp Dermatol* 1985; **10**: 194–200.

30 Miller JA, Dodd H, Rustin MHA *et al.* Ultrasound as a screening procedure for methotrexate-induced hepatic damage in severe psoriasis. *Br J Dermatol* 1985; **113**: 699–705.
31 Newman M, Auerbach R, Feiner H *et al.* The role of liver biopsies in psoriatic patients receiving long-term methotrexate treatment. *Arch Dermatol* 1989; **125**: 1218–24.
32 Zachariae H, Søgaard H. Methotrexate-induced liver cirrhosis: a follow-up. *Dermatologica* 1987; **175**: 178–82.
33 Zachariae H, Heickendorff L, Søgaard H. The value of amino-terminal propeptide of type III procollagen in routine screening for methotrexate-induced liver fibrosis: a 10 year follow-up. *Br J Dermatol* 2001; **144**: 100–3.
34 Jensen DB, Albrektsen SB, Krag C. Development of metastatic skin cancer during methotrexate therapy for psoriasis. *Acta Derm Venereol (Stockh)* 1989; **69**: 274–5.
35 Stern RS, Laird N. The carcinogenic risk of treatments for severe psoriasis. *Cancer* 1994; **73**: 2759–64.
36 Kaplan DL, Olsen EA. Erosion of psoriatic plaques after chronic methotrexate administration. *Int J Dermatol* 1988; **27**: 59–62.
37 Baker H. Intermittent high dose oral methotrexate therapy in psoriasis. *Br J Dermatol* 1970; **82**: 65–9.
38 Lischka G. Auffallend rasche Wirkung des Methotrexats® bei Psoriasis eines 82 jährigen Patienten mit gleichzeitigen Nebenwirkungen am Auge. *Hautarzt* 1968; **19**: 473.
39 Smith JD, Knox JM. Psoriasis, methotrexate and tuberculosis. *Br J Dermatol* 1971; **84**: 590–3.
40 Verdich J, Christensen AL. Pulmonary disease complicating intermittent methotrexate therapy of psoriasis. *Acta Derm Venereol (Stockh)* 1979; **59**: 471–3.
41 Kennedy C, Baker H. Renal function in methotrexate treated psoriatics. *Br J Dermatol* 1976; **94**: 702–3.
42 Sussman A, Leonard JM. Psoriasis, methotrexate, and oligospermia. *Arch Dermatol* 1980; **116**: 215–7.
43 Zonneveld IM, Bakker WI, Dijkstra PF *et al.* Methotrexate osteopathy in long-term, low-dose methotrexate treatment for psoriasis and rheumatoid arthritis. *Arch Dermatol* 1996; **132**: 184–7.
44 Kumar B, Dhar S, Handa S, Kaur I. Methotrexate in childhood psoriasis. *Pediatr Dermatol* 1994; **11**: 271–3.
45 Milunsky A, Graef JW, Gaynor MF. Methotrexate-induced congenital malformations. *J Pediatr* 1968; **72**: 790–5.
46 Baker H. Methotrexate: the conservative treatment for psoriasis. In: Farber EM, Cox AJ, eds. *Psoriasis. Proceedings of the 2nd International Symposium*. New York: Yorke Medical, 1977: 235–42.
47 Armstrong RB, Poh-Fitzpatrick MB. Methotrexate and ultraviolet radiation. *Arch Dermatol* 1982; **118**: 177–8.
48 LeVine MJ. Erythema resulting from suberythemogenic doses of ultraviolet radiation and methotrexate. *Arch Dermatol* 1981; **117**: 656–8.
49 Paul BS, Momtaz K, Stern RS *et al.* Combined methotrexate: ultraviolet B therapy in the treatment of psoriasis. *J Am Acad Dermatol* 1982; **7**: 758–62.
50 Morison WL, Momtaz K, Parrish JA *et al.* Combined methotrexate-PUVA therapy in the treatment of psoriasis. *J Am Acad Dermatol* 1982; **6**: 46–51.
51 Vanderveen EE, Ellis CN, Campbell JP *et al.* Methotrexate and etretinate as concurrent therapies in severe psoriasis. *Arch Dermatol* 1982; **118**: 660–2.
52 Clark CM, Kirby B, Morris AD *et al.* Combination treatment with methotrexate and cyclosporin for severe recalcitrant psoriasis. *Br J Dermatol* 1999; **141**: 279–82.
53 Horiguchi M, Takigawa M, Imamura S. Treatment of generalized pustular psoriasis with methotrexate and colchicine (Letter). *Arch Dermatol* 1981; **117**: 760.
54 Van de Kerkhof PCM, Mali JWH. Methotrexate maintenance following Ingram therapy in 'difficult' psoriasis. *Br J Dermatol* 1982; **106**: 623–7.
55 Fitzsimons CP, Long J, Mackie RM. Synergistic carcinogenic potential of methotrexate and in psoriasis (Letter). *Lancet* 1983; **i**: 235–6.
56 Heydendael VM, Spuls PI, Opmeer BC *et al.* Methotrexate versus cyclosporine in moderate-to-severe chronic plaque psoriasis. *N Engl J Med* 2003; **349**: 658–65.
57 Saurat JH, Stingl G, Dubertret L *et al.* Efficacy and safety results from the randomized controlled comparative study of adalimumab vs methotrexate vs placebo in patients with psoriasis (CHAMPION). *Br J Dermatol* 2008; **158**: 558–66.
58 Campalani E, Arenas M, Aranaki AM *et al.* Polymorphisms in folate, pyrimidine and purine metabolism are associated with efficacy and toxicity of methotrexate in psoriasis. *J Invest Dermatol* 2007; **127**: 1860–7.
59 Warren RB, Smith RL, Campalani E *et al.* Genetic variation in efflux transporters influences outcome to methotrexate therapy in patients with psoriasis. *J Invest Dermatol* 2008; **128**: 1925–9.

Hydroxycarbamide

Hydroxycarbamide (hydroxyurea) is an antimetabolite that has been used principally for the treatment of malignant disease, particularly chronic myeloid leukaemia. The active drug, which is converted *in vivo* from its parent, blocks the conversion of ribonucleotides to deoxyribonucleotides by interfering with the enzyme ribonucleoside diphosphate reductase, thereby inhibiting DNA synthesis in proliferating cells [1,2]. Hydroxyurea was first recommended for psoriasis by Yarbro in 1969 [3,4]. It is quickly and well absorbed and excreted by the kidney. Bone marrow suppression is a common side effect of treatment with hydroxyurea, leukopenia is seen in most treated patients. Profound anaemia and thrombocytopenia occur less frequently, although a fall in haemoglobin to 110 g/dL is common [5–8]. Macrocytosis is almost universal. Irreversible bone marrow failure and death have not been reported. Because it is teratogenic, hydroxyurea must be avoided during pregnancy. Compared with methotrexate, it has the virtue of being a less frequent cause of anorexia, nausea and hepatotoxicity. In the three largest case series of patients with psoriasis treated with hydroxyurea [1,9,10], the reported satisfactory response rates have ranged from 45 to 80%. Clinical response is slow, and may become evident only over several weeks [4]. A therapeutic trial should therefore last at least 2 months. It is only modestly effective in palmoplantar pustulosis [11], and is less effective than methotrexate overall. That it may be a valuable reserve drug for patients needing systemic treatment and who are resistant to methotrexate or develop side effects, has been confirmed by a report of its use in 85 patients [1]. Hydroxyurea may be effective when other systemic drugs have failed, but is a less potent antipsoriatic agent. Its use has been advocated in combination with methotrexate [12], ciclosporin [13] and acitretin [14].

Regimens should rarely exceed 0.5 g three times daily, and sometimes 0.5 g once or twice daily long-term suffices for therapy [1,2]. A cutaneous vasculitis resulting from the drug has been reported [9,15]. Other recently recorded side effects include diffuse hyperpigmentation, actinic psoriasis, alopecia and psychological effects [1].

References

1 Layton AM, Sheehan-Dare RA, Goodfield MJD *et al.* Hydroxyurea in the management of therapy-resistant psoriasis. *Br J Dermatol* 1989; **121**: 647–53.
2 Smith CH. Use of hydroxyurea in psoriasis. *Clin Exp Dermatol* 1999; **24**: 2–6.
3 Yarbro JW. Hydroxyurea in the treatment of refractory psoriasis. *Lancet* 1969; **2**: 846–7.
4 Leavell UW, Yarbro JW. Hydroxyurea. *Arch Dermatol* 1970; **102**: 144–50.
5 Hunter GA, Simmons IJ, Thomas BM. A clinical trial of hydroxyurea for psoriasis. *Australas J Dermatol* 1972; **13**: 93–9.
6 Rosten M. Hydroxyurea: a new antimetabolite in the treatment of psoriasis. *Br J Dermatol* 1971; **85**: 177–81.
7 Spier S, Solomon LM, Esterly NB *et al.* Hydroxyurea and macrocytosis (Letter). *Arch Dermatol* 1971; **104**: 564.
8 Touraine R, Revuz J, Tulliez M. Psoriasis and hydroxyurea. *Br J Dermatol* 1972; **86**: 102.

9 Moschella SL, Greenwald MA. Psoriasis with hydroxyurea. *Arch Dermatol* 1973; **107**: 363–8.
10 Baker H. Antimitotic drugs in psoriasis. In: Farber EM, Cox AJ, eds. *Psoriasis. Proceedings of the 3rd International Symposium*. New York: Marcel Dekker, 1985: 451–5.
11 Hattel T, Sondergaard J. Pustulosis palmaris et plantaris treated with hydroxyurea. *Acta Derm Venereol (Stockh)* 1974; **54**: 152–4.
12 Sauer GC. Combined methotrexate and hydroxyurea therapy for psoriasis. *Arch Dermatol* 1973; **107**: 369–70.
13 Kirby B, Harrison PV. Combination low-dose cyclosporin (Neoral) and hydroxyurea for severe recalcitrant psoriasis. *Br J Dermatol* 1999; **140**: 186–7.
14 Choo D, McHenry P. Combination therapy with acitretin and hydroxyurea for severe psoriasis. *J Dermatolog Treat* 1999; **10**: 71–2.
15 Roe LD, Wilson JW. Hydroxyurea therapy (Letter). *Arch Dermatol* 1973; **108**: 426–7.

Retinoids

Vitamin A has long been recognized to have profound effects on epithelial differentiation, and the toxicity of hypervitaminosis A is well known. Deficiency causes cutaneous hyperkeratosis and squamous metaplasia of mucous membranes. This knowledge stimulated development of synthetic derivatives, and the term 'retinoid' has been applied to a family of natural and synthetic analogues of vitamin A [1,2].

Etretinate [3–6]

This analogue was first reported in 1975 by Ott and Bollag [7] to have antipsoriatic efficacy, and many subsequent reports have confirmed this [8–13]. In a dosage of 1 mg/kg/day, resolution of psoriasis vulgaris [9,10], pustular [10,14] and erythrodermic psoriasis [14] has been demonstrated. Etretinate is little used for the treatment of psoriasis nowadays as it has been superseded in many countries by acitretin, which has a shorter half-life.

References

1 Bollag W. From vitamin A to retinoids: chemical and pharmacological aspects. In: Orfanos CE, Braun Falco O, Farber EM *et al.*, eds. *Retinoids: Advances in Basic Research and Therapy*. Berlin: Springer-Verlag, 1981: 5–11.
2 Bollag W. Chemistry and pharmacology of retinoids. In: Farber EM, Cox AJ, eds. *Psoriasis. Proceedings of the 3rd International Symposium*. New York: Grune & Stratton, 1982: 175–83.
3 Lowe NJ, Lazarus V, Matt L. Systemic retinoid for psoriasis. *J Am Acad Dermatol* 1988; **19**: 186–91.
4 Lowe NJ, Roenigk H, Hoorhees JJ. Etretinate: appropriate use in severe psoriasis. *Arch Dermatol* 1988; **124**: 527–8.
5 Morison WL. Etretinate and psoriasis. *Arch Dermatol* 1987; **123**: 879–81.
6 Gollnick HPM. Oral retinoids: efficacy and toxicity in psoriasis. *Br J Dermatol* 1996; **135** (Suppl. 49): 6–17.
7 Ott F, Bollag W. Therapie der Psoriasis mit einem oral wirksamen neuen Vitamin-A-säure-derivat. *Schweiz Med Wochenschr* 1975; **105**: 439–41.
8 Guilhou J-J, Malbos S, Meynadier J. Traitement oral des psoriasis graves par un nouveau rétinoide aromatique (RO 10-9359). *Ann Dermatol Vénéréol* 1978; **105**: 813–8.
9 Lassus A. Systemic treatment of psoriasis with an oral retinoic acid derivative (RO 10-9359). *Br J Dermatol* 1980; **102**: 195–202.
10 Mahrle G, Meyer-Hamme S, Ippen H. Oral treatment of keratinizing disorders of skin and mucous membranes with etretinate. *Arch Dermatol* 1982; **118**: 97–100.
11 Orfanos CE, Steigleder GK, Pullmann H *et al.* Oral retinoid and UVB radiation. *Acta Derm Venereol* 1979; **59**: 241–4.
12 Ott F. Behandlung der Psoriasis mit einem oral wirksamen aromatischen Retinoid. *Schweiz Med Wochenschr* 1977; **107**: 144–7.
13 Van Der Rhee HJ, Polano MK. Treatment of psoriasis vulgaris with low-dosage RO 10-9359 (Tigason) orally combined with corticosteroids topically. In: Orfanos CE, Braun Falco O, Farber EM *et al.*, eds. *Retinoids: Advances in Basic Research and Therapy*. Berlin: Springer-Verlag, 1981: 193–9.
14 Orfanos CE, Runne U. Systemic use of a new retinoid with and without local dithranol treatment in generalized psoriasis. *Br J Dermatol* 1976; **95**: 101–3.

Isotretinoin (13-cis-retinoic acid)

Isotretinoin was reported to improve generalized pustular psoriasis, but additional therapy was required to produce satisfactory control during maintenance treatment. Isotretinoin was also found to be less effective than etretinate in the treatment of chronic plaque psoriasis [1]. However, it may have a place in the management of psoriasis in fertile females who urgently need treatment, in view of its short half-life [2], and has been advocated in combination with PUVA in this patient group [3].

Acitretin

This is the main active metabolite of etretinate. Being a free acid as opposed to an ester as in the case of etretinate, acitretin has the great advantage of decreased lipophilicity. It is therefore not sequestered in the adipose tissue, and has an elimination half-life of approximately 50 h compared to more than 80 days for etretinate [4,5]. Several clinical trials showed that the clinical efficacy and side effects of acitretin are similar to those of etretinate [6–11]. The greatly reduced half-life of acitretin compared with etretinate suggested that it would have clinical advantages over the latter, especially for women of child-bearing potential. Accordingly, marketing of etretinate ceased in the UK in 1993 and acitretin took its place. However, in an unpredictable number of patients, reversed metabolism of acitretin to etretinate has been found to occur [12]. It has therefore been essential for women on acitretin to avoid pregnancy during and for 2 years after the course, as in the case of etretinate. A further comparative study [13] confirmed the equal efficacy of etretinate and acitretin in psoriasis, but in this study etretinate was better tolerated both objectively and subjectively, and to an extent that was statistically significant. Limited recent experience also indicates that the occasional patient previously controlled on etretinate may not do well on acitretin but benefits from transfer back to etretinate once again [14]. Thus, the great advantages initially perceived for acitretin have not been realized in practice. If reversed metabolism to etretinate only occurs in 50% of subjects, albeit unpredictably [12], and the levels of etretinate thus obtained are low, this may confer a theoretically lower risk of fetal abnormalities in women becoming pregnant inadvertently before expiry of the 2-year period. The use of acitretin in fertile women therefore has a theoretical advantage, but it seems to have no major advantages over etretinate in other patients. In combination with PUVA, acitretin has been shown to be therapeutically superior to PUVA with placebo. Acitretin in a regimen of 50 mg/day for 2 weeks followed by up to 10 weeks of 25 mg/day combined with PUVA significantly reduced the number of PUVA treatments required for clearance and the cumulative dosage of UVA (by 40%) [15]. These results were confirmed by Tanew *et al.* [16], in that acitretin at 1 mg/kg/day in addition to PUVA reduced the total UVA dosage and time to clearance. Similarly, acitretin enhances the efficacy of broad-band UVB in that the number of subjects who improve or clear with the combination therapy is significantly greater than with UVB alone: 60%

versus 24% in one study [17] and 74 and 35%, respectively, in another [18]. Acitretin may also reduce the photo-ageing effects of phototherapy and act as a chemopreventive against the development of cutaneous malignancy. This benefit has not been proven, but extrapolates from the known effects of retinoids on photo-aged skin and as chemopreventive agents in kidney transplant recipients [19,20]. Acitretin can be combined with UVB or PUVA [21].

The side-effect profile of acitretin is generally similar to that of etretinate [5–10,22–24] and is detailed in Chapter 74. Side-effects are usually inevitable, but are often a nuisance rather than a real danger.

Although apparently 1.5% of patients on acitretin may develop a toxic hepatitis, there is no histological evidence of hepatotoxicity on liver biopsy [25]. The starting daily dosage in adults is usually 25 mg, the optimum being about 50 mg (0.66 mg/kg/day) depending on therapeutic response and side effects.

To summarize, despite the high incidence of nuisance side effects, acitretin has been a valuable addition to the antipsoriatic weaponry, especially in generalized pustular psoriasis. The drug should not be used in children except in compelling circumstances nor in young women unless essential. Active liver disease and pre-existing hyperlipidaemia are contraindications to treatment.

References

1 Moy RL, Kingston TP, Lowe NJ. Isotretinoin versus etretinate therapy in generalized pustular and chronic psoriasis. *Arch Dermatol* 1985; **121**: 1297–301.

2 Gollnick HPM. Oral retinoids: efficacy and toxicity in psoriasis. *Br J Dermatol* 1996; **135** (Suppl. 49): 6–17.

3 Anstey A, Hawk JL. Isotretinoin: PUVA in women with psoriasis. *Br J Dermatol* 1997; **136**: 798–9.

4 Pilkington T, Brogden RN. Acitretin: a review of its pharmacological properties and therapeutic use. *Drugs* 1992; **43**: 597–627.

5 Larsen GF, Nielsen-Kudsk F, Jakobsen P *et al.* Pharmacokinetics and therapeutic efficacy of retinoids in skin diseases. *Clin Pharmacokinet* 1992; **23**: 42–61.

6 Kingston TP, Matt LH, Lowe NJ. Etretin therapy for severe psoriasis: evaluation of clinical responses. *Arch Dermatol* 1987; **123**: 55–8.

7 Lassus A, Geiger J-M, Nyblom M *et al.* Treatment of severe psoriasis with etretin (RO 10-1670). *Br J Dermatol* 1987; **117**: 333–41.

8 Goldfarb MT, Ellis CN, Gupta AK *et al.* Acitretin improves psoriasis in a dose-dependent fashion. *J Am Acad Dermatol* 1988; **18**: 655–62.

9 Gollnick H, Bauer R, Brindley C *et al.* Acitretin versus etretinate in psoriasis. *J Am Acad Dermatol* 1988; **19**: 458–69.

10 Gupta AK, Goldfarb MT, Ellis CN *et al.* Side-effect profile of acitretin therapy in psoriasis. *J Am Acad Dermatol* 1989; **20**: 1088–93.

11 Ledo A, Martin M, Geiger J-M *et al.* Acitretin (RO 10-1670) in the treatment of severe psoriasis: a randomized double-blind parallel study comparing acitretin and etretinate. *Int J Dermatol* 1988; **27**: 656–60.

12 Lambert WE, Meyer E, De Leenheer AP *et al.* Pharmacokinetics and drug interactions of etretinate and acitretin. *J Am Acad Dermatol* 1992; **27**: S19–S22.

13 Kragballe K, Jansén CT, Geiger J-M *et al.* A double blind comparison of acitretin and etretinate in the treatment of severe psoriasis: results of a Nordic multicentre study. *Acta Derm Venereol (Stockh)* 1989; **69**: 35–40.

14 Bleiker TO, Bourke JF, Graham-Brown RAC, Hutchinson PE. Etretinate may work where acitretin fails. *Br J Dermatol* 1997; **136**: 368–70.

15 Saurat J-H, Geiger J-M, Amblard P *et al.* Randomized double-blind multicentre study comparing acitretin–PUVA, etretinate–PUVA and placebo–PUVA in the treatment of severe psoriasis. *Dermatologica* 1988; **177**: 218–24.

16 Tanew A, Guggenbichler A, Honigsmann H *et al.* Photochemotherapy for severe psoriasis without or in combination with acitretin: a randomized, double-blind comparison study. *J Am Acad Dermatol* 1991; **25**: 682–4.

17 Ruzicka T, Sommerburg C, Fraun-Falco O *et al.* Efficacy of acitretin in combination with UVB in the treatment of severe psoriasis. *Arch Dermatol* 1990; **126**: 482–6.

18 Lowe N, Prystowsky JH, Bourget T *et al.* Acitretin plus UVB therapy for psoriasis: comparisons with placebo plus UVB and acitretin alone. *J Am Acad Dermatol* 1991; **24**: 591–4.

19 Fisher GJ, Talwar HS, Lin J *et al.* Retinoic acid inhibits induction of c-Jun protein by ultraviolet radiation that occurs subsequent to activation of mitogen-activated protein kinase pathways in human skin *in vivo*. *J Clin Invest* 1998; **101**: 1432–40.

20 Bavinck JN, Teiben LM, Van der Woude FJ *et al.* Prevention of skin cancer and reduction of keratotic skin lesions during acitretin therapy in renal transplant recipients: a double-blind, placebo controlled study. *J Clin Oncol* 1995; **13**: 1933–8.

21 Lebwohl M, Drake L, Menter A *et al.* Consensus conference: acitretin in combination with UVB or PUVA in the treatment of psoriasis. *J Am Acad Dermatol* 2001; **45**: 544–53.

22 Gupta AK, Goldfarb MT, Ellis CN, Voorhees JJ. Side-effect profile of acitretin therapy in psoriasis. *J Am Acad Dermatol* 1989; **20**: 1088–93.

23 Kilcoyne RF. Effects of retinoids in bone. *J Am Acad Dermatol* 1988; **19**: 212–6.

24 Olsen EA, Weed WW, Meyer CJ, Cobo LM. A double-blind, placebo controlled trial of acitretin for the treatment of psoriasis. *J Am Acad Dermatol* 1989; **21**: 681–6.

25 Roenigk HH Jr, Callen JP, Guzzo CA *et al.* Effects of acitretin on the liver. *J Am Acad Dermatol* 1999; **41**: 584–8.

Ciclosporin

The antilymphocytic effects of ciclosporin, a cyclic undecapeptide derived from the fungus *Tolypocladium inflatum* Gams, were first described in 1976 [1]. The ability of ciclosporin to clear the skin lesions of psoriasis was first noted in four patients in 1979, as an incidental finding during a trial of this drug in inflammatory arthritis [2].

This information appears to have been somewhat disregarded until 1984, when the dramatic therapeutic effect of ciclosporin was again noted in a single patient with otherwise unresponsive psoriasis [3]. Subsequently, several case reports appeared [4–10], followed by unequivocal evidence for therapeutic efficacy in the form of double-blind placebo-controlled trials with both high [11] and lower [12,13] dosage. The mechanism of action of ciclosporin in psoriasis is not entirely certain, but is likely to be related to its inhibitory effects on T-cell activation [14], a possibility that has substantially affected attitudes towards pathogenic mechanisms in psoriasis.

Ciclosporin is highly lipophilic, but is active orally and metabolized in the liver by the cytochrome P-450 system. A series of consensus conferences on its use in psoriasis have been held and the proceedings published [15–17]. Briefly, a twice daily oral regimen is recommended. The side effects associated with ciclosporin (see below) demand that it should be given only to patients with sufficiently severe disease, in whom less toxic forms of treatment have been unsuccessful. Such treatment should include conventional topical therapy, if possible carried out in an inpatient department or day-treatment centre on at least one occasion, UVB, PUVA and possibly a retinoid. However, the prolonged use of high-dose PUVA may predispose certain patients to skin malignancy, and constitute a relative contraindication to ciclosporin. The choice between ciclosporin and methotrexate is not straightforward, the latter being thoroughly tried, relatively safe in the right hands and much cheaper, but currently requiring repeated invasive investigation in the form of liver biopsies. There has, to

date, been no published head-to-head comparison of the two drugs in the treatment of psoriasis. Ciclosporin should not be given to unreliable patients or if regular monitoring for side effects is not possible. Other major exclusion criteria include renal dysfunction, uncontrolled hypertension, past or present malignancy, history of epilepsy, acute infections, other immunosuppressive therapy, concomitant therapy with nephrotoxins, previous serious side effects from ciclosporin and known hypersensitivity. Minor exclusion criteria include abnormal liver function, previous therapy that may predispose to skin malignancy, malabsorption, drug or alcohol abuse, and concomitant treatment with drugs that affect the metabolism of ciclosporin. NSAIDs are often used by patients with psoriatic arthropathy, and may enhance the nephrotoxicity of ciclosporin (see below). Other drugs interacting with ciclosporin are described in a consensus report [17] and elsewhere [14], and include anticonvulsants which induce hepatic cytochrome P-450 and thus enhance metabolism of ciclosporin, which may never reach therapeutic blood levels [18].

An initial daily oral regimen of 2.5 mg/kg equally divided in two doses has been recommended. Improvement may be seen within days, but if this does not occur within 2 weeks, the dosage may be increased gradually to a maximum of 5 mg/kg/day [14,17]. Maintenance dosage should be reduced to the minimum that allows adequate control and, as for methotrexate, the aim should not be to achieve complete clearance. Withdrawal of ciclosporin in patients with severe psoriasis is usually associated with relapse within weeks but, with few exceptions [19], has not been associated with the severe rebound phenomenon seen following withdrawal of systemic steroids. In patients with moderately severe chronic psoriasis, the relapse rate (41% at 6 months) following cessation of ciclosporin therapy (5 mg/kg/day) was no greater than that seen with dithranol or PUVA [20]. A systematic review of therapies for severe psoriasis [21] concluded that 'ciclosporin is a well-tested treatment for severe psoriasis and in the short term is probably more effective than other forms of systemic therapy'. Ideally, ciclosporin should be used for short courses of 3–4 months' maximum duration [22,23]. Only in exceptional circumstances should ciclosporin be used as continuous therapy for periods exceeding 6 months. The accepted modern regimen (intermittent short courses of ciclosporin) is effective for at least 2 years—most patients require less than four courses of treatment over this time with good control of the disease and no significant side effects [23]. A Japanese study that compared intermittent with continuous ciclosporin for psoriasis showed that an intermittent regimen was probably safer [24].

The most important side effects associated with ciclosporin are dose-related hypertension and nephrotoxicity. The blood pressure may rise sharply within weeks of starting treatment, and plasma creatinine levels may increase or glomerular filtration rates decrease within the same period [14]. Immunosuppression associated with the long-term use of ciclosporin may increase the risk of cutaneous malignancy, especially in patients who have previously had high-dose UV irradiation, PUVA, Goeckerman regimens or arsenic. SCCs of the skin have been reported in patients receiving ciclosporin for psoriasis [14]. A prospective 5-year survey of 1252 European patients with psoriasis who had on average received ciclosporin for 1.9 years [25] found that ciclosporin produced a sixfold increase in risk for developing non-melanoma skin cancer (mainly SCC). The risk was compounded by contributions from PUVA and other immunosuppressants such as methotrexate. There was no increase in non-cutaneous malignancies. Lymphoproliferative disorders are an important risk of high-dose immunosuppressive treatment in transplant recipients, although these diseases were not more common in transplant recipients receiving ciclosporin than in those not receiving it [14]. Eight malignant lymphomas developed in more than 6000 patients receiving ciclosporin for autoimmune disorders, although a causal relationship was not proved [14]. Overall, there is no clear association between ciclosporin treatment and a risk of other internal malignancies, although cases have been reported [26,27] and vigilance is essential. The finding of cervical intraepithelial neoplasia associated with possible human papillomavirus infection underlines the need for cervical smears in female patients on ciclosporin, perhaps every 6 months [14,27]. Human papillomavirus-associated penile carcinoma has also been reported [28]. Other side effects include elevated serum potassium and uric acid levels, decreased serum magnesium, mild normochromic normocytic anaemia, gum hyperplasia, hypertrichosis, acral paraesthesia or hyperaesthesia, tremor, altered liver-function tests and gastrointestinal intolerance [14]. Gum hyperplasia is associated with poor dental hygiene and regular dental check-ups are recommended. The hyperplasia may respond to treatment with azithromycin [29].

Regular monitoring is therefore essential during ciclosporin therapy, and has been reviewed [14,17]. Further details can be found in Chapter 74. There is no evidence that monitoring of serum trough levels of ciclosporin is indicated during treatment of psoriasis unless there is doubt about compliance and/or absorption of the drug [30].

References

1 Borel JF, Feurer C, Gubler HU *et al.* Biological effects of cyclosporin A: a new antilymphocytic agent. *Agents Actions* 1976; **6**: 468.
2 Mueller W, Herrman B. Cyclosporin A for psoriasis (Letter). *N Engl J Med* 1979; **301**: 555.
3 Harper JI, Keat ACS, Stoughton RCD. Cyclosporin for psoriasis (Letter). *Lancet* 1984; **ii**: 981–2.
4 Van Hooff JP, Leunissen KML, vd Staak W. Cyclosporin and psoriasis (Letter). *Lancet* 1985; **i**: 335.
5 Griffiths CEM, Powles AV, Leonard JN *et al.* Clearance of psoriasis with low-dose cyclosporin. *BMJ* 1986; **293**: 731–2.
6 Marks JM. Cyclosporin A treatment of severe psoriasis (Letter). *Br J Dermatol* 1986; **115**: 745–6.
7 Van Joost T, Heule F, Stolz E *et al.* Short-term use of cyclosporin A in severe psoriasis. *Br J Dermatol* 1986; **114**: 615–20.
8 Meinardi MMHM, Westerhof W, Bos JD. Generalized pustular psoriasis (von Zumbusch) responding to cyclosporin A. *Br J Dermatol* 1987; **116**: 269–70.
9 Picascia DD, Garden JM, Freinkel RK *et al.* Treatment of resistant severe psoriasis with systemic cyclosporine. *J Am Acad Dermatol* 1987; **17**: 408–14.
10 Wentzell JM, Baughman RD, O'Connor GT *et al.* Cyclosporin in the treatment of psoriasis (Letter). *Arch Dermatol* 1987; **123**: 163–5.
11 Ellis CN, Gorsulowski DC, Hamilton TA. Cyclosporine improves psoriasis in a double-blind study. *JAMA* 1986; **256**: 3110–6.
12 Van Joost T, Bos JD, Heule F *et al.* Low-dose cyclosporin A in severe psoriasis: a double-blind study. *Br J Dermatol* 1988; **118**: 183–90.
13 Ellis CN, Fradin MS, Messana JM *et al.* Cyclosporine for plaque-type psoriasis: results of a multidose, double-blind trial. *N Engl J Med* 1991; **324**: 277–84.

14 Bos JD, Meinardi MMHM, van Joost T *et al.* Use of cyclosporin in psoriasis. *Lancet* 1989; **ii**: 1500–2.
15 Mihatsch MJ, Wolff K. Consensus conference on cyclosporin A for psoriasis. *Br J Dermatol* 1992; **126**: 621–3.
16 Berth-Jones J, Voorhees JJ. Consensus conference on cyclosporin A microemulsion for psoriasis. *Br J Dermatol* 1996; **135**: 775–7.
17 Griffiths CEM Dubertret L, Ellis CN *et al.* Ciclosporin in psoriasis clinical practice: an international consensus statement. *Br J Dermatol* 2004; **150**: 11–23.
18 Schofield OMV, Camp RDR, Levene GM. Cyclosporin A in psoriasis: interaction with carbamazepine (Letter). *Br J Dermatol* 1990; **122**: 425–6.
19 Cacoub P, Artru L, Canesi M *et al.* Life-threatening psoriasis relapse on withdrawal of cyclosporin (Letter). *Lancet* 1988; **ii**: 219–20.
20 Higgins E, Munro C, Marks J *et al.* Relapse rates in moderately severe chronic psoriasis treated with cyclosporin A. *Br J Dermatol* 1989; **121**: 71–4.
21 Griffiths CEM, Clark CM, Chalmers RJG *et al.* A systematic review of treatments for severe psoriasis. *Health Technol Assess* 2000; **4**: 1–125.
22 Berth-Jones J, Henderson CA, Munro CS *et al.* Treatment of psoriasis with intermittent short course cyclosporin (Neoral): a multicentre study. *Br J Dermatol* 1997; **136**: 527–30.
23 Ho VC, Griffiths CEM, Berth-Jones J *et al.* Intermittent short courses of cyclosporine microemulsion for long-term management of psoriasis: a 2 year cohort study. *J Am Acad Dermatol* 2001; **44**: 643–51.
24 Ohtsuki M, Nakagawa H, Sugai J *et al.* Long-term continuous versus intermittent cyclosporin: therapy for psoriasis. *J Dermatol* 2003; **30**: 290–8.
25 Paul C, Ho VC, McGeown C *et al.* Risk of malignancies in psoriasis patients treated with cyclosporine: a 5 year cohort study. *J Invest Dermatol* 2003; **120**: 211–6.
26 Mrowietz U, Färber L, Henneicke-von Zepelin H-H *et al.* Long-term maintenance therapy with cyclosporine and post-treatment survey in severe psoriasis: results of a multicenter study. *J Am Acad Dermatol* 1995; **33**: 470–5.
27 Grossman RM, Maugée E, Dubertrel L. Cervical intraepithelial neoplasia in a patient receiving long-term cyclosporin for the treatment of severe plaque psoriasis (Letter). *Br J Dermatol* 1996; **135**: 147–8.
28 Noel JC, de Dobbeleer G. Development of human papillomavirus-associated Buschke–Löwenstein penile carcinoma during cyclosporine therapy for generalized pustular psoriasis. *J Am Acad Dermatol* 1994; **31**: 299–300.
29 Nash MM, Zaltzman JS. Efficacy of azithromycin in the treatment of cyclosporine-induced gingival hyperplasia in renal transplant recipients. *Transplantation* 1998; **65**: 1611–5.
30 Heyendael VM, Spuls PI, Tenberge IJ *et al.* Cyclosporine trough levels: is monitoring necessary during short-term treatment in psoriasis? A systematic review and clinical data on trough levels. *Br J Dermatol* 2002; **147**: 122–9.

Systemic glucocorticosteroids [1]

The glucocorticosteroids (steroids) have shown themselves to be double-edged weapons. The fluorinated forms such as triamcinolone and betamethasone have more effect on psoriasis than prednisolone [2,3]. When triamcinolone, 12–20 mg/day, is given for the first time, clearance of the psoriasis is rapid but the disease usually eventually 'breaks through', necessitating progressive increases in dosage and incidence of side effects [4]. If withdrawal is attempted, the psoriasis tends to relapse often promptly [4] and may 'rebound'. 'Rebound' may take the form of widespread, small-patterned, eruptive psoriasis, often involving the face and backs of hands. Erythrodermic or generalized pustular phases may be precipitated [1,5]. Systemic steroids should not be used in the routine care of psoriasis. They do have a role in the management of persistent, otherwise uncontrollable erythroderma that is causing metabolic complications and in fulminating generalized pustular psoriasis of the von Zumbusch type [6] if other drugs are contraindicated or ineffective. Associated psoriatic arthropathy is not an indication *per se*, but steroids may occasionally be needed, and in high dosage (prednisolone 40 mg/day initially), to control hyperacute polyarthritis that is threatening severe irreversible joint damage. Patients with psoriasis who have concomitant psoriatic arthritis controlled with low-dose steroids often have active labile skin disease that is difficult to control [7].

Psoriasis may remain labile and treatment resistant for many months after the withdrawal of systemic corticosteroids [8].

6-Thioguanine

6-Thioguanine is closely related to 6-mercaptopurine. The observations of one group [9] led to studies confirming that thioguanine appears to be effective in psoriasis [10]. Further experience in 81 patients was reported [11]. This drug may prove to be a useful alternative when other forms of treatment have failed. In 21 patients with severe psoriasis that had failed to respond to other systemic therapies, 14 of 18 had greater than 90% improvement in psoriasis [12]. Treatment was for an average of 15 months and regimens ranged from 20 mg twice weekly to 120 mg/day. Bone marrow toxicity is common, and is usually inevitable if an effect on psoriasis is to be seen. Increased liver enzymes are also seen and veno-occlusive disease of the liver may be a consequence of therapy [13], but preliminary evidence suggests that 6-thioguanine does not induce hepatic fibrosis [11]. Clearance of psoriasis correlates with depletion of T cells in the skin [14].

Fumaric acid esters (fumarates)

For more than 20 years fumarates have been used extensively in northern Europe, particularly German-speaking countries, for the treatment of moderate to severe psoriasis [15,16]. The commercially available preparation of fumarates, Fumaderm, comprises a mixture of dimethylfumarate and the calcium, magnesium and zinc salts of monoethylfumaric acid. After ingestion, dimethylfumarate is hydrolysed to monomethylfumarate—the main active metabolite. Clinical trials [17–19] attest to the efficacy of fumarates. The drug is introduced gradually, starting at 30 mg/day, building up over several weeks to a maximum dosage of 240 mg three times daily. It is estimated that if they tolerate the drug then approximately 57% of patients will achieve a 70% reduction in severity of psoriasis. Two-thirds of treated patients develop gastrointestinal symptoms such as dyspepsia and diarrhoea; one-third of patients develop flushing. In most patients these side effects settle down over time. Lymphocyte counts fall in nearly all treated patients, sometimes by 50% [17,19–21]. Renal function and liver function should be monitored but impairment is unusual. The mechanism of action of fumarates appears to be mediated at least in part by an ability to inhibit nuclear binding of nuclear factor kappa B and promoting the secretion of Th2 cytokines such as IL-10, which are beneficial in psoriasis [22,23].

References

1 Baker H. Corticosteroids and pustular psoriasis. *Br J Dermatol* 1976; **94** (Suppl. 12): 83–8.
2 Cohen HJ, Baer RL. Triamcinolone and methyl prednisolone in psoriasis: comparison of their intralesional and systemic effects. *J Invest Dermatol* 1960; **34**: 71–5.
3 Marsden CW. Oral steroid therapy in psoriasis vulgaris. *Br J Dermatol* 1961; **73**: 103–6.
4 Hollander JL, Brown EM, Jassar RA *et al.* The effect of triamcinolone on psoriatic arthritis. *Arthritis Rheum* 1959; **2**: 513–25.
5 Baker H, Ryan TJ. Generalized pustular psoriasis. *Br J Dermatol* 1968; **80**: 771–93.

6 Ryan TJ, Baker H. Systemic corticosteroids and folic antagonists in the treatment of generalized pustular psoriasis. *Br J Dermatol* 1969; **81**: 134–45.
7 Griffiths CEM. Therapy for psoriatic arthritis: sometimes a conflict for psoriasis. *Br J Rheumatol* 1997; **36**: 409–10.
8 Champion RH. Treatment of psoriasis. *BMJ* 1966; **ii**: 993–6.
9 Zackheim HS, Maibach HI, Grekin DA. Thioguanine for psoriasis. In: Farber EM, Cox AJ, Nall L, eds. *Psoriasis. Proceedings of the 3rd International Symposium*. New York: Grune & Stratton, 1982: 405.
10 Molin L, Thomsen K. Thioguanine treatment in psoriasis. *Acta Derm Venereol (Stockh)* 1987; **67**: 85–8.
11 Zackheim HS, Glogau RG, Fisher DA, Maibach HI. 6-Thioguanine treatment of psoriasis: experience in 81 patients. *J Am Acad Dermatol* 1994; **30**: 452–8.
12 Mason C, Krueger GG. Thioguanine for refractory psoriasis: a 4-year experience. *J Am Acad Dermatol* 2001; **44**: 67–72.
13 Ramagosa R, Kerdel F, Shah N. Treatment of psoriasis with 6-thioguanine and hepatic veno-occlusive disease. *J Am Acad Dermatol* 2002; **47**: 970–2.
14 Murphy FP, Coven TR, Burack LH *et al.* Clinical clearing of psoriasis by 6-thioguanine correlates with cutaneous T-cell depletion via apoptosis: evidence for selective effects on activated T lymphocytes. *Arch Dermatol* 1999; **135**: 1495–502.
15 Schweckendiek W. Heilung von Psoriasis. *Med Monutschr* 1959; **13**: 103–4.
16 Mrowietz U, Christophers E, Altmeyer P. The German Fumaric Acid Ester Consensus Conference: treatment of severe psoriasis with fumaric acid ester, scientific background and guidelines for therapeutic use. *Br J Dermatol* 1999; **141**: 424–9.
17 Altmeyer PJ, Matthes U, Pawlak F *et al.* Antipsoriatic effects of fumaric acid derivatives: results of a multicenter double-blind study in 100 patients. *J Am Acad Dermatol* 1994; **30**: 977–81.
18 Nugteren-Huying WM, van der Schroeff JG, Hermans J, Saarmond D. Fumaric acid therapy for psoriasis: a randomized, double-blind, placebo-controlled study. *J Am Acad Dermatol* 1990; **22**: 311–2.
19 Mrowietz U, Christophers E, Altmeyer P. Treatment of psoriasis with fumaric acid esters: results of a prospective multicentre study. German Multicentre Study. *Br J Dermatol* 1998; **138**: 456–60.
20 Harries MJ, Chalmers RJG, Griffiths CEM. Fumaric acid esters for psoriasis: a retrospective review of 58 cases. *Br J Dermatol* 2005; **153**: 549–51.
21 Yazdi MR, Mrowietz U. Fumaric acid esters. *Clin Dermatol* 2008; **26**: 522–56.
22 Gerdes S, Shakey K, Mrowietz U. Dimethylfumarate inhibits nuclear binding of nuclear factor of kappaB but not of nuclear factor of activated T cells and CCAAT/enhancer binding protein beta in activated human T cells. *Br J Dermatol* 2007; **156**: 838–42.
23 Ockenfels HM, Schaltewolter T, Ockenfels G *et al.* The antipsoriatic agent dimethylfumarate immunomodulates T-cell cytokine secretion and inhibits cytokines of the psoriatic cytokine network. *Br J Dermatol* 1998; **139**: 390–5.

Biological therapies

Biological therapies (biologics) directed at selected targets integral to the pathogenesis of psoriasis are the logical progression of the biotechnological revolution as applied to a more detailed knowledge of the roles of T cells, their differentiation pathways and pro-inflammatory cytokines in psoriasis. Several of these therapies are now in widespread clinical use for moderate and severe psoriasis [1]. In general these treatments are highly effective, including in patients in whom standard systemics are either ineffective or contraindicated. However, the recent withdrawal of one agent, efalizumab, on safety grounds, coupled with their high cost illustrates the need for careful patient selection.

Biological agents. The introduction of biological therapies into the management of moderate and severe psoriasis has made a dramatic impact on practice and on patient outcomes, for example in one of the author's practice, admission rates have dropped by 90%. These drugs are extensively reviewed in Chapter 74 so comments below refer specifically to use in psoriasis.

The British Association of Dermatologists has recently prepared guidelines [2] for their usage incorporating all licensed biologics up to mid-2009. In keeping with the licensed indications for each of these drugs, their use should be restricted to: (i) patients with severe disease defined by a psoriasis area severity index (PASI) score of 10 or more (or a body surface area (BSA) of 10% or greater where PASI is not applicable) and dermatology life quality index (DLQI) of greater than 10; and (ii) who have failed to respond to, or who have a contraindication to, or who are intolerant to other systemic therapies such as ciclosporin and methotrexate.

Importantly, there are some key exceptions. Firstly, some patients will have disease affecting high impact sites such as face, hands and feet that will cause considerable psychological or functional morbidity. Secondly, given the beneficial effect of these drugs on psoriatic arthritis, patients with both skin and joint involvement should be considered earlier for intervention with a biological therapy, particularly the TNF-α antagonists. Thirdly, there is increasing evidence that forms of psoriasis other than plaque type respond to biological agents and the patient with resistant disease should be considered.

When using these agents it is essential that appropriate safety screening and monitoring measures are implemented as discussed elsewhere and information provided to national registries where appropriate. Further, validated measures of treatment outcome such as PASI and DLQI should be recorded at appropriate intervals to provide evidence of effectiveness and justification for continuation of therapy. These include values at baseline and at 10–16 weeks, depending upon the intervention.

At present, there are five biological agents licensed for the treatment of psoriasis vulgaris. They are: (i) etanercept, a fully human soluble p75 TNF-α receptor fusion protein; (ii) infliximab, a chimeric human-immune antibody to TNF-α; (iii) adalimumab, a fully human recombinant antibody to TNF-α; (iv) ustekinumab, a fully human recombinant antibody to the p40 component of IL-12/IL-23: and (v) alefacept, a fusion protein of lymphocyte function associated antigen-3 and IgG that inhibits T-cell activation—this is not licensed in the UK. Infliximab is administered by intravenous infusion while the others are administered by subcutaneous injection.

The lack of head-to-head studies coupled with a paucity of data concerning these drugs in various clinical scenarios makes recommendations concerning their individual use difficult. Thus, the choice of which of the three TNF-α antagonists to use first should be based on clinical need and requires a careful assessment of risks and benefits of each agent in the context of the individual patient [2]. For stable disease, particularly if not too severe (e.g. PASI >10 but <20), etanercept or adalimumab are often first options. For patients requiring rapid disease control, adalimumab or infliximab may be considered first choice due to early onset of action. For patients with unstable or generalized pustular psoriasis, limited evidence indicates that infliximab is effective and may be considered first choice amongst the biologics. Equally, it appears to be the most active agent for severe nail disease [3] including acropustulosis of Hallopeau.

For patients who do not respond to a TNF-α antagonist (either primary or secondary failure), a second TNF-α antagonist may be considered.

The role and place of ustekinumab in the management of psoriasis is complicated by the lack of patient years' exposure and long-term safety data limited to 1 year (at time of writing). The British guidelines suggest it should therefore be reserved for use as a second-line biological agent [2].

References

1 Menter A, Griffiths CEM. Current and future management of psoriasis. *Lancet* 2007; **370**: 272–84.

2 Smith CH, Anstey AV, Barker JNWN *et al*. British Association of Dermatologists' guidelines for biologic interventions for psoriasis 2009. *Br J Dermatol* 2009; **161**: 987–1019.

3 Reich K, Nestle FO, Papp K *et al*. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. *Lancet* 2005; **366**: 1367–74.

Miscellaneous therapies

Sulfasalazine

Sulfasalazine (sulphasalazine) is an anti-inflammatory agent, 5-{[*p*-(2-pyridylsulfamoyl)phenyl]azo}salicylic acid, commonly used in the treatment of inflammatory bowel disease. One open study and one randomized controlled trial provide evidence that sulfasalazine for 8 weeks at 3–4 g/day can produce marked improvement in about one-third of patients [1,2]. Approximately 25% of patients find the side effects of headache, nausea and vomiting disabling. Oligospermia, pruritus and haemolytic anaemia may occur. Sulfasalazine is a useful alternative systemic therapy for psoriasis.

Azathioprine

This is a synthetic purine analogue synthesized by attaching 6-mercaptopurine to an imidazole ring—*in vivo* it is converted to its active metabolite 6-mercaptopurine by hepatic xanthine oxidase. Several uncontrolled or case studies [3–5] describe efficacy in psoriasis but, in the absence of data from controlled trials, it is best to conclude that there is no good evidence that azathioprine is an effective treatment for psoriasis. The most important side effect is bone marrow suppression.

Mycophenolate mofetil

Following ingestion, mycophenolate mofetil (MMF) is hydrolysed to its active metabolite—mycophenolic acid. Mycophenolic acid inhibits inosine monophosphate dehydrogenase, a key enzyme in *de novo* purine synthesis—this results in blockade of T- and B-cell proliferation. Dosage is 1–2 g/day increased to a maximum of 4 g/day. MMF is only moderately effective as monotherapy for psoriasis [6–8], but its place in the therapy of severe psoriasis is probably in combination with ciclosporin as a ciclosporin-sparing agent [9,10], used at an average dosage of 1–2 g/day. Side-effects include gastrointestinal symptoms and bone marrow suppression.

Tacrolimus and pimecrolimus

Despite the undoubted efficacy of ciclosporin in the treatment of psoriasis, its long-term use is limited by nephrotoxicity and hypertension. In an effort to find drugs that have a similar mechanism of action, namely blockade of calcineurin phosphatase and consequent inhibition of T-cell activation, a number of drugs structurally dissimilar to ciclosporin, but with a similar mechanism of action, have been investigated.

Tacrolimus and pimecrolimus, both of which are derived from species of the soil fungus *Streptomyces*, have been trialled for the treatment of severe psoriasis. Oral tacrolimus at a dosage of 0.05–0.15 mg/kg/day can significantly improve severe psoriasis in the short term (10 weeks) [11,12]. Side effects include paraesthesia, headache and minor elevations in serum creatinine and blood pressure. Tacrolimus is rarely used for the treatment of psoriasis, but is a useful alternative.

Oral pimecrolimus showed highly promising results in severe psoriasis in a placebo-controlled, 12-week trial but has not been developed further for this indication [13]. Side effects were minimal, with no effect on either blood pressure or serum creatinine. A novel calcineurin inhibitor, ASA247, has recently proven safe and effective for plaque psoriasis in a 24-week study [14].

Cytokines

Plaques of psoriasis contain a predominance of Th1 cytokines such as IL-2, IL-12 and IFN-γ. Systemic administration of Th2 cytokines such as IL-4 or IL-10 appears to neutralize the Th1 bias and improve psoriasis. IL-10 was the first Th2 cytokine to be used for treatment of psoriasis. Phase II trials show that subcutaneous injections of recombinant IL-10 given either daily or three times weekly produce a mean reduction in psoriasis severity of 50% [15,16]. This response is associated with a Th2 cytokine shift and, when used as maintenance therapy, length of remission correlates with T-cell production of IL-4 [17]. Systemic administration of IL-4, in an open study, has demonstrated very significant reduction in clinical severity of psoriasis [18].

Protein kinase C inhibitor

The orally administered novel protein kinase C inhibitor, AEB071, demonstrated efficacy in moderate-severe plaque psoriasis in an early phase 2-week study. It was well tolerated and its mechanism of action is believed to reside in inhibition of T-cell activation [19].

Zidovudine (azidothymidine, AZT)

The skin lesions of patients with therapy-resistant AIDS-associated psoriasis have been reported to clear with oral zidovudine [20,21]. This drug may be the treatment of choice for retinoid-resistant AIDS-associated psoriasis, as therapies such as methotrexate, ciclosporin and PUVA may be contraindicated.

Somatostatin

Following uncontrolled reports of the efficacy of somatostatin in psoriasis, a double-blind placebo-controlled study of intravenous somatostatin suggested benefit in recalcitrant psoriasis [22].

Liarozole

Liarozole, a member of the imidazole family and an inhibitor of retinoic acid 4-hydroxylase, belongs to a new class of drugs, the retinoic acid metabolism blockers. It delivers a retinoid-like effect

by increasing endogenous levels of naturally occurring all-*trans*-retinoic acid and other retinoids upstream of retinoic acid 4-hydroxylase. The advantage of liarozole over acitretin is that the raised levels of retinoic acid return to normal within a few days of cessation of therapy. Trials [23,24] indicate that liarozole is effective for chronic plaque psoriasis. Side effects are 'retinoid' in nature (teratogenicity, hyperlipidaemia and mucocutaneous symptoms).

Gluten-free diet

Studies, primarily from Sweden [25,26], have established that approximately 16% of patients with psoriasis have IgA and IgG antibodies to gliadin. In a further study [27], 33 psoriasis patients with IgA antibodies to gliadin (15 of whom had evidence of a lymphocytic infiltrate in the duodenal epithelium) were placed on a gluten-free diet for 3 months. All 33 patients had significant improvement in psoriasis severity while on the diet. These fascinating results indicate that in a very few patients a gluten-free diet may be worth trying if antigliadin antibodies are present.

Photodynamic therapy

Photodynamic therapy has been investigated for the treatment of small plaques of psoriasis. Using 5-aminolaevulinic acid as the topical photosensitizer has produced improvement in the treated plaques, but use is limited by local pain at the site of treatment [28,29]. Further work is required to ascertain the value of photodynamic therapy for treatment of psoriasis—if larger plaques could be treated in a relatively painless manner then this would be an advance.

Lasers

Recalcitrant plaques of psoriasis have been treated with lasers. Local destruction of psoriatic epidermis using carbon dioxide laser resurfacing gave mixed results [30,31]; further investigation is required. Pulsed dye laser (585 nm) therapy appears to be more effective than the carbon dioxide laser; indeed some plaques treated with pulsed dye laser remain in remission for a year or more [32,33].

Excimer laser-generated 308-nm UVB radiation is the laser source most likely to be used for routine management of psoriasis. The UVB source is handheld and delivers high-intensity UVB selectively directed to plaques, thereby sparing uninvolved skin. Controlled trials show it to be safe and effective for localized plaques, and it requires fewer treatments than conventional phototherapy [34,35].

References

1 Gupta AK, Ellis CN, Siegel MT *et al.* Sulfasalazine: a potential psoriasis therapy? *J Am Acad Dermatol* 1989; **20**: 797–800.
2 Gupta AK, Ellis CN, Siegel MT *et al.* Sulfasalazine improves psoriasis: a double-blind analysis. *Arch Dermatol* 1990; **126**: 487–93.
3 du Vivier A, Munro DD, Verbov J. Treatment of psoriasis with azathioprine. *BMJ* 1974; **1**: 49–51.
4 Greaves MW, Dawber R. Azathioprine in psoriasis. *BMJ* 1970; **2**: 237–8.
5 Hacker SM, Ramos-Caro FA, Ford MJ, Flowers FP. Azathioprine: a forgotten alternative for treatment of severe psoriasis. *Int J Dermatol* 1992; **31**: 873–4.
6 Haufs MG, Beissert S, Grabbe S *et al.* Psoriasis vulgaris treated successfully with mycophenolate mofetil. *Br J Dermatol* 1998; **138**: 179–81.
7 Grundmann-Kollmann M, Mooser G, Schraeder P *et al.* Treatment of chronic plaque-stage psoriasis and psoriatic arthritis with mycophenolate mofetil. *J Am Acad Dermatol* 2000; **45**: 835–7.
8 Geilen CC, Arnold M, Orfanos CE. Mycophenolate mofetil as a systemic antipsoriatic agent: positive experience in 11 patients. *Br J Dermatol* 2001; **144**: 583–6.
9 Davison SC, Morris-Jones R, Powles AV, Fry L. Change of treatment from ciclosporin to mycophenolate mofetil in severe psoriasis. *Br J Dermatol* 2000; **143**: 405–7.
10 Ameen M, Smith HR, Barker JNWN. Combined mycophenolate mofetil and ciclosporin therapy for severe recalcitrant psoriasis. *Clin Exp Dermatol* 2001; **26**: 480–3.
11 Jegasothy BV, Ackerman CD, Todo S *et al.* Tacrolimus (FK506): a new therapeutic agent for severe recalcitrant psoriasis. *Arch Dermatol* 1992; **128**: 781–5.
12 European FK506 Multicenter Psoriasis Study Group. Systemic tacrolimus (FK506) is effective for the treatment of psoriasis in a double-blind, placebo controlled study. *Arch Dermatol* 1996; **132**: 419–23.
13 Gottlieb AB, Griffiths CEM, Ho VC *et al.* Oral pimecrolimus in the treatment of moderate to severe plaque-type psoriasis: a double-blind, multicentre, randomized, dose-finding study. *Br J Dermatol* 2005; **152**: 1219–27.
14 Papp K, Bissonnette R, Rosoph L *et al.* Efficacy of ASA247 in plaque psoriasis: a randomized, multicentre, double-blind, placebo-controlled phase III study. *Lancet* 2008; **371**: 1337–42.
15 Asadullah K, Docke WD, Ebeling M *et al.* Interleukin-10 treatment of psoriasis: clinical results of a phase 2 trial. *Arch Dermatol* 1999; **135**: 187–92.
16 Kimball AB, Kawamura T, Tejura K *et al.* Clinical and immunologic assessment of patients with psoriasis in a randomized, double-blind, placebo-controlled trial using recombinant human interleukin-10. *Arch Dermatol* 2002; **138**: 1341–6.
17 Friedrich M, Docke WD, Klein A *et al.* Immunomodulation by interleukin-10 therapy decreases the incidence of relapse and prolongs the relapse-free interval in psoriasis. *J Invest Dermatol* 2002; **118**: 672–7.
18 Ghureschi K, Thomas P, Breit S *et al.* Interleukin-4 therapy of psoriasis induces Th2 responses and improves human autoimmune disease. *Nat Med* 2003; **9**: 40–6.
19 Skvara H, Dawid M, Kleyn E *et al.* The PKC inhibitor AEB071 may be a therapeutic option for psoriasis. *J Clin Invest* 2008; **118**: 3151–9.
20 Duvic M, Rios A, Brewton GW. Remission of AIDS-associated psoriasis with zidovudine (Letter). *Lancet* 1987; **ii**: 627.
21 Duvic M, Crane MM, Conant M *et al.* Zidovudine improves psoriasis in human immunodeficiency virus-positive males. *Arch Dermatol* 1994; **130**: 447–51.
22 Matt LH, Kingston TP, Lowe NJ. Treatment of severe psoriasis with intravenous somatostatin. *J Dermatolog Treat* 1989; **1**: 3–4.
23 Dockx P, Decree J, Degreef H. Inhibitor of the metabolism of endogenous retinoic acid as treatment for severe psoriasis: an open study with oral liarozole. *Br J Dermatol* 1995; **133**: 426–32.
24 Berth-Jones J, Todd G, Hutchinson PE *et al.* Treatment of psoriasis with oral liarozole: a dose-ranging study. *Br J Dermatol* 2000; **143**: 1170–6.
25 Michaelsson G, Gerden B, Ottosson M *et al.* Patients with psoriasis often have increased serum levels of IgA antibodies to gliadin. *Br J Dermatol* 1993; **129**: 667–73.
26 Michaelsson G, Kraaz W, Gerden B *et al.* Increased lymphocytic infiltration in duodenal mucosa from patients with psoriasis and serum IgA antibodies to gliadin. *Br J Dermatol* 1995; **133**: 896–904.
27 Michaelsson G, Gerden B, Hagforsen E *et al.* Psoriasis patients with antibodies to gliadin can be improved by a gluten-free diet. *Br J Dermatol* 2000; **142**: 44–51.
28 Collins P, Robinson DJ, Stringer MR *et al.* The variable response of plaque psoriasis after a single treatment with topical 5-amino/aevulinic acid photodynamic therapy. *Br J Dermatol* 1997; **137**: 743–9.
29 Robinson DJ, Collins P, Stringer M *et al.* Improved response of plaque psoriasis after multiple treatments with topical 5-amino/aevulinic acid photodynamic therapy. *Acta Derm Venereol* 1999; **79**: 451–5.
30 Bekassy Z, Astedt B. Carbon dioxide laser vaporization of plaque psoriasis. *Br J Dermatol* 1986; **114**: 489–92.
31 Alora MB, Anderson RR, Quinn TR, Taylor CR. CO_2 laser resurfacing of psoriatic plaques: a pilot study. *Lasers Surg Med* 1998; **22**: 165–70.
32 Katugampola GA, Rees AM, Lanigan SW. Laser treatment of psoriasis. *Br J Dermatol* 1995; **133**: 909–13.

33 Zelickson BD, Mehregan DA, Wendelschter-Crabb G *et al.* Clinical and histologic evaluation of psoriatic plaques treated with flashlamp dye laser. *J Am Acad Dermatol* 1996; **35**: 64–8.
34 Asawanonda P, Anderson RR, Chang Y, Taylor CR. 308-nm excimer laser for the treatment of psoriasis: a dose–response study. *Arch Dermatol* 2000; **137**: 95–6.
35 Feldman SR, Mellen BG, Housman TS *et al.* Efficacy of the 308-nm excimer laser for treatment of psoriasis: results of a multicenter study. *J Am Acad Dermatol* 2002; **46**: 900–6.

Dialysis and related therapies [1,2]

The clearing of incidental psoriasis during haemodialysis for uraemia was reported in 1976 [3]. Others then recorded similar experiences with both haemodialysis and peritoneal dialysis [4–6]. It soon became clear that dialysis could favourably influence psoriasis in patients with normal renal function [1,6–9] and that peritoneal dialysis is more effective than haemodialysis [1,9,10], possibly because substances of higher molecular weight can be removed in larger quantities [2].

Success rates with dialysis have been variable. Although some patients clear completely, others do not improve, and successfully treated patients may relapse quickly afterwards [4,8]. Not all have achieved success [11] and, confusingly, there are several reports of psoriasis worsening or appearing *de novo* during chronic haemodialysis for renal disease [12–14].

Plasmapheresis and leukapheresis were ineffective, findings that led to the suggestion that there is no pathogenic circulating factor or leukocyte abnormality in psoriasis [15,16].

References

1 Anderson PC. Dialysis treatment of psoriasis. *Arch Dermatol* 1981; **117**: 67–8.
2 Steck WD, Nakamoto S, Bailin PL *et al.* Haemofiltration treatment of psoriasis. *J Am Acad Dermatol* 1982; **6**: 346–9.
3 McEvoy J, Kelly AMT. Psoriatic clearance during haemodialysis. *Ulster Med J* 1976; **45**: 76–8.
4 Buselmeier TJ, Cantieri JS. Dialysis and psoriasis (Letter). *Arch Dermatol* 1979; **115**: 370.
5 Muston HL, Conceicao S. Remission of psoriasis during haemodialysis. *BMJ* 1978; **i**: 480–1.
6 Twardowski ZJ, Nolph KD, Rubin J *et al.* Peritoneal dialysis for psoriasis. *Ann Intern Med* 1978; **88**: 349–51.
7 Binazzi M, Buoncristiani U, Lisi P. Sperimentazione del trattamento dialitico della psoriasis eritrodermico-artropatica. *Ann Ital Derm Clin Sper* 1979; **33**: 369–77.
8 Glinski W, Zarebska Z, Jablonska S *et al.* The activity of polymorphonuclear leukocyte neutral proteinases. *J Invest Dermatol* 1980; **75**: 481–7.
9 Halevy S, Halevy J, Boner G *et al.* Dialysis therapy for psoriasis. *Arch Dermatol* 1981; **117**: 69–72.
10 Nissenson AR, Rapaport M, Gordon A *et al.* Haemodialysis in the treatment of psoriasis. *Ann Intern Med* 1979; **91**: 218–20.
11 Miller LH. NIH psoriasis/dialysis workshop highlights. *J Invest Dermatol* 1980; **74**: 242–3.
12 Breathnach SM, Boon NA, Black MM *et al.* Psoriasis developing during dialysis. *BMJ* 1979; **i**: 236.
13 Graf H, Wolf A, Stummvoll HK. Dialysis and psoriasis (Letter). *Ann Intern Med* 1979; **90**: 994–5.
14 Llewellyn M, Nethercott JR, Bear RA. Peritoneal dialysis in the treatment of psoriasis (Letter). *Can Med Assoc J* 1980; **122**: 13–4.
15 Lieden G, Skogh M. Plasma exchange and leukapheresis in psoriasis: no effect? *Arch Dermatol Res* 1986; **278**: 437–40.
16 Schuster R, Lenzhofer R, Raff M. Plasmapheresis in the management of psoriasis. *Arch Dermatol Res* 1985; **277**: 330–1.

Pustular forms of psoriasis

Neutrophilic accumulation in the epidermis is a characteristic histological feature of all types and patterns of psoriasis, but in clinical practice the term 'pustular psoriasis' is reserved for those forms of the disease in which macroscopic pustules appear.

It is convenient to separate two main types of pustular psoriasis: localized and generalized. In the localized forms, the disease is confined to the hands and feet and tends to be chronic. There is a rapidly developing and widely held opinion that palmoplantar pustulosis is a disease distinct from psoriasis and as such should not be included in a chapter on psoriasis save as a comorbidity. In the generalized forms, the whole body may be involved and the course is subacute, acute or even fulminating and life-threatening.

A convenient classification is as follows.

1 Localized pustular psoriasis:
  (a) palmoplantar pustulosis
  (b) acrodermatitis continua
2 Generalized pustular psoriasis:
  (a) acute
  (b) of pregnancy
  (c) infantile and juvenile
  (d) circinate
  (e) localized (not hands and feet).

Localized pustular psoriasis

Palmoplantar pustulosis

Synonyms
- Chronic palmoplantar pustular psoriasis
- Pustulosis palmaris et plantaris
- Persistent palmoplantar pustulosis

Definition. A common condition in which erythematous and scaly plaques studded with sterile pustules persist on the palms or soles. The disease is chronic, very resistant to treatment and probably a separate disease to psoriasis.

Pathogenesis. The relationship of palmoplantar pustulosis (PPP) to psoriasis vulgaris is controversial [1,2]. Sometimes the presence of typical psoriasis elsewhere, or a personal or strong family history of psoriasis, or the future development of psoriasis vulgaris, establishes the relationship. However, typical PPP often occurs in the absence of such evidence [1–3]. This, and the absence of immunogenetic associations characteristic of psoriasis (see below) in such patients, indicate that PPP may represent a separate and distinct entity. Furthermore, PPP is more common in females, unlike psoriasis vulgaris there is no seasonal variation, and it tends to start at a later age [2].

HLA antigens. Three potential candidate genes for psoriasis susceptibility reside within *PSORS1* locus on chromosome 6, HLA-Cw6, *HCR WWCC* and the *CD5N5*. A recent immunogenetic study demonstrated categorically that PPP is not associated with any of

the three candidate genes—indicating that it is a distinct disorder [4]. Combining the results of these and other studies, it may be concluded that there is no predominant HLA locus associated with PPP [2].

Provocative factors. PPP usually starts without obvious provocation. Septic foci have been blamed [1,5,6] but their removal may not cure the eruption. The disease has appeared for the first time after several months of treatment with lithium [7]. Japanese otolaryngologists remain interested in the tonsils as a site of relevant focal infection [8]. Smoking has also been reported as a possible provoking factor [9]. With the advent of TNF-antagonist biologic therapies for rheumatoid arthritis and psoriasis has come a series of reports of *de novo* occurrence of PPP or exacerbation of the condition [10–11]. An immunohistochemical study of biopsies of palmar skin revealed an altered staining pattern for nicotinic acetylcholine receptors in PPP—the authors suggested that an abnormal response to nicotine in patients with PPP resulted in inflammation [12].

References

1 Ashurst PJC. Relapsing pustular eruptions of the hands and feet. *Br J Dermatol* 1964; **76**: 169–80.
2 Reitamo S, Erkko P, Remitz A. Palmoplantar pustulosis. *Eur J Dermatol* 1992; **2**: 311–4.
3 Hellgren L, Mobacken H. Pustulosis palmaris et plantaris: prevalence, clinical observations and prognosis. *Acta Derm Venereol (Stockh)* 1971; **51**: 284–8.
4 Asumalahti K, Ameen M, Suomela S *et al.* Genetic analysis of *PSORS1* distinguishes guttate psoriasis and palmoplantar psoriasis. *J Invest Dermatol* 2003; **120**: 627–32.
5 Enfors W, Molin L. Pustulosis palmaris et plantaris: a follow-up study of a 10-year material. *Acta Derm Venereol (Stockh)* 1971; **51**: 289–94.
6 Yamanaka N, Sambe S, Kataura A. Conceptual understanding of pustulosis palmaris et plantaris as an immune complex disease due to focal tonsillar infections. *Acta Otolaryngol Suppl* 1981; **401**: 31–5.
7 White SW. Palmoplantar pustular psoriasis provoked by lithium therapy. *J Am Acad Dermatol* 1982; **7**: 660–2.
8 Yamazaki Y, Saito S, Ogawa H. Tonsil and pustulosis palmaris et plantaris. *Acta Otolaryngol Suppl* 1981; **401**: 43–50.
9 O'Doherty CJ, MacIntyre C. Palmoplantar pustulosis and smoking. *Br Med J* 1985; **291**: 861–4.
10 Rallis E, Korfitis C, Stavropoulou E, Papaconstantis M. Onset of palmoplantar pustular psoriasis white on adalimumab for psoriatic arthritis: A 'class effect' of TNF-alpha antagonists or simply an anti-psoriatic treatment adverse reaction? *J Dermatology Treat* 2009; **1**: 1–3.
11 Cohen JD, Bournerias I, Buffard V *et al.* Psoriasis induced by tumor necrosis factor-alpha antagonist therapy: a case series. *J Rheumatol* 2007; **34**: 390–5.
12 Hagforsen E, Edvinsson M, Nordlink K, Michaelsson G. Expression of nicotinic receptors in the skin of patients with palmoplantar pustulosis. *Br J Dermatol* 2002; **146**: 383–91.

Clinical features [1–3]. PPP is a disease of adults and is rare in children. It usually starts in the fifth or sixth decade, although sometimes earlier. In most series, there has been a preponderance of women [4]. The disease presents with one or more well-defined plaques. On the hands, the thenar eminence is the most common site. Less commonly, the hypothenar eminence or the central palm or the distal palm are involved. On the feet, the instep, the medial or lateral border of the foot at the level of the instep, or the sides or back of the heel are involved. Less frequently, the distal sole or the whole sole is implicated. Digital lesions are uncommon. A striking symmetry of the lesions on the hands or feet is common, but sometimes a solitary lesion persists for weeks or months before others appear.

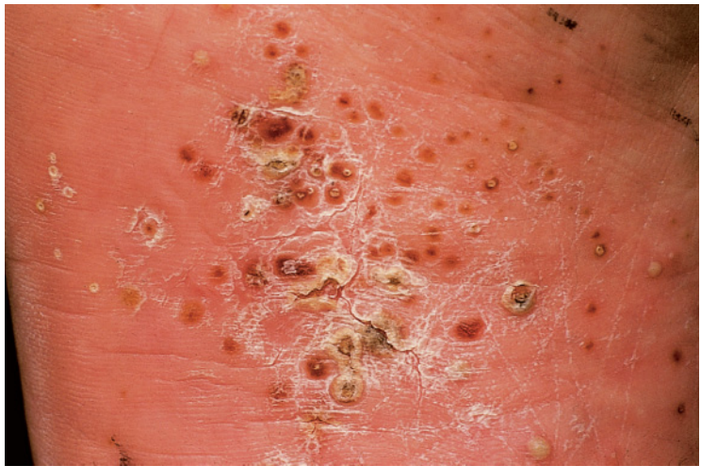


Fig. 20.23 Palmoplantar pustulosis. Note pustules in different stages of evolution. (Courtesy of St John's Institute of Dermatology, London, UK.)

The affected area is dusky red and often scaly. Removal of scale (e.g. by treatment) leaves a glazed dull-red surface. Within this plaque, numerous pustules are present, usually 2–5 mm in diameter. Fresh pustules are yellow; older ones are yellow-brown or dark brown as the pustule dries. Eventually, the desiccated pustule is exfoliated. Normally, pustules in all stages of evolution are seen (Fig. 20.23). Itching is variable; more often the patient complains of 'burning' discomfort in the lesions.

Associations. A significant incidence of hyper- and hypothyroidism and the presence of thyroid antibodies has been found in association with PPP [5–7]. A greater tendency to develop diabetes was found in a Japanese study [8]. Various arthropathies are also associated [9], including chronic recurrent multifocal osteomyelitis [10,11], sternoclavicular involvement [12,13], pustular arthro-osteitis, axial and peripheral arthritis [9,14]. The association of some of these conditions with PPP may represent part of the spectrum of SAPHO syndrome [15]. More than 90% of patients with PPP are current or previous smokers [5,16]. Some patients have anti-gliadin antibodies [5].

Differential diagnosis. Tinea and eczema are the most common alternatives. Tinea is usually asymmetrical or unilateral. The toe clefts may be involved. Acute vesiculopustular tinea is more common in hot weather. Microscopy and culture confirm the diagnosis. Secondary infection of eczema may be pustular but is more painful, and Gram stains and culture of pustule contents will establish the diagnosis. Chronic allergic contact dermatitis caused by rubber in footwear should not cause difficulties. Typically, the insteps are spared. The chronic acropustulosis seen in black infants does not occur in adults, and affects the digits and dorsal aspects of the extremities as well as the palms and soles [17,18].

Prognosis. The usual course is prolonged. Sometimes spontaneous remission does occur but is more often temporary than



Fig. 20.24 Acute palmoplantar pustulosis. (Courtesy of St John's Institute of Dermatology, London, UK.)

permanent. Slow spread or extension may be refractory to all treatment.

Pustular bacterid

This term was first used [19] to describe an acute monomorphic eruption of sterile pustules occurring on the hands and feet (Fig. 20.24). Whether it is a distinct entity or merely an acute variant of PPP is unclear. The term 'bacterid' implies that the eruption is provoked by a remote bacterial infection.

References

1 Baker H. Pustular psoriasis. *Dermatol Clin* 1984; **2**: 455–70.
2 Baker H. Generalized pustular psoriasis. In: Roenigk HH, Maibach HI, eds. *Psoriasis*. New York: Marcel Dekker, 1985: 35.
3 Reitamo S, Erkko P, Remitz A. Palmoplantar pustulosis. *Eur J Dermatol* 1992; **2**: 311–4.
4 Thomsen K, Osterbye P. Pustulosis palmaris et plantaris. *Br J Dermatol* 1973; **89**: 293–6.
5 Eriksson MO, Hagfursen E, Lundin TP, Michaelsson G. Palmoplantar pustulosis: a clinical and immunohistological study. *Br J Dermatol* 1998; **138**: 390–8.
6 Rosén K, Lindstedt G, Mobacken H, Nyström E. Thyroid function in patients with pustulosis palmoplantaris. *J Am Acad Dermatol* 1988; **19**: 1009–16.
7 Agner T, Sindrup JH, Hoier-Madsen M, Hegedüs L. Thyroid disease in pustulosis palmoplantaris. *Br J Dermatol* 1989; **121**: 487–91.
8 Uehara M, Fujigaki T, Hayashi S. Glucose tolerance in pustulosis palmaris et plantaris. *Arch Dermatol* 1980; **116**: 1275–6.
9 Jurik AG, Ternowitz T. Frequency of skeletal disease, arthro-osteitis, in patients with pustulosis palmoplantaris. *J Am Acad Dermatol* 1988; **18**: 666–71.
10 Bergdahl K, Björkstén B, Gustavson KH *et al*. Pustulosis palmoplantaris and its relation to chronic recurrent multifocal osteomyelitis. *Dermatologica* 1979; **159**: 37–45.
11 Paller AS, Pachman L, Rich K *et al*. Pustulosis palmaris et plantaris: its association with chronic recurrent multifocal osteomyelitis. *J Am Acad Dermatol* 1985; **12**: 927–30.
12 Chigira M, Maehara S, Nagase M *et al*. Sternocostoclavicular hyperostosis. *J Bone Joint Surg Am* 1986; **68**: 103–12.
13 Hradil E, Gentz CF, Matilainen T *et al*. Skeletal involvement in pustulosis palmoplantaris with special reference to sterno-costo-clavicular joint. *Acta Derm Venereol (Stockh)* 1988; **68**: 65–73.
14 Sonozaki H, Mitsui H, Miyanaga Y *et al*. Clinical features of 53 cases with pustulotic arthro-osteitis. *Ann Rheum Dis* 1981; **40**: 547–53.
15 Maugars Y, Berthelot J-M, Ducloux J-M, Prost A. SAPHO syndrome: a follow-up study of 19 cases with special emphasis on enthesis involvement. *J Rheumatol* 1995; **22**: 2135–41.
16 O'Doherty CJ, MacIntyre C. Palmoplanator pustulosis and smoking. *BMJ* 1985; **291**: 861–4.
17 Jarratt M, Ramsdell W. Infantile acropustulosis. *Arch Dermatol* 1979; **115**: 834–6.
18 Kahn G, Rywlin AM. Acropustulosis of infancy. *Arch Dermatol* 1979; **115**: 831–3.
19 Andrews GC, Machacek GF. Pustular bacterids of the hands and feet. *Arch Dermatol Syphilol* 1935; **32**: 837–47.

Acrodermatitis continua

Synonyms
- Acropustulosis
- Pustular acrodermatitis
- Acrodermatitis perstans
- Dermatitis repens
- Acrodermatitis continua of hallopeau

Definition. A chronic, sterile, pustular eruption affecting initially the tips of fingers or toes that tends slowly to extend locally but which, in adults, may evolve into generalized pustular psoriasis.

Clinical features. Whereas PPP is a disease of middle life, acrodermatitis may be seen in children. It is rare in young adults and, unlike PPP, not infrequently begins in old age. It is more common in females.

The first lesion starts on a finger or thumb more often than on a toe. Onset is often related by the patient to minor trauma, or infection at the tip of the digit. The skin over the distal phalanx becomes red and scaly, and pustules develop. The nail folds and nail bed may be involved, leading to nail dystrophy. The proximal edge of the lesion is bordered by a fringe of undermined epidermis, irregular, often sodden and sometimes preceded by a line of vesiculopustules. Removal of scale or desiccation of pustules may leave a brighter red, glazed, very sore and painful digit. Slow proximal extension is the rule but this may be spread over years. Eventually, other digits may be involved. The nail plate may be completely destroyed (Fig. 20.25). Bony changes can occur with osteolysis of the tuft of the distal phalanx [1]. The free end of the digit may become wasted and tapered, mimicking scleroderma. In such digits, the circulation may be secondarily affected so that discomfort is greatest in cold weather.

Acrodermatitis continua may evolve into generalized pustular psoriasis, especially in the elderly [2]. The tongue may become involved with fissuring or the annulus migrans of pustular psoriasis [3].

Differential diagnosis. In the earliest stage, staphylococcal infection, pulp infection, herpetic whitlow, tinea or contact dermatitis may be suspected. Candidiasis is only likely to be a problem in



Fig. 20.25 Acrodermatitis continua with destruction of nail plate. (Courtesy of St John's Institute of Dermatology, London, UK.)

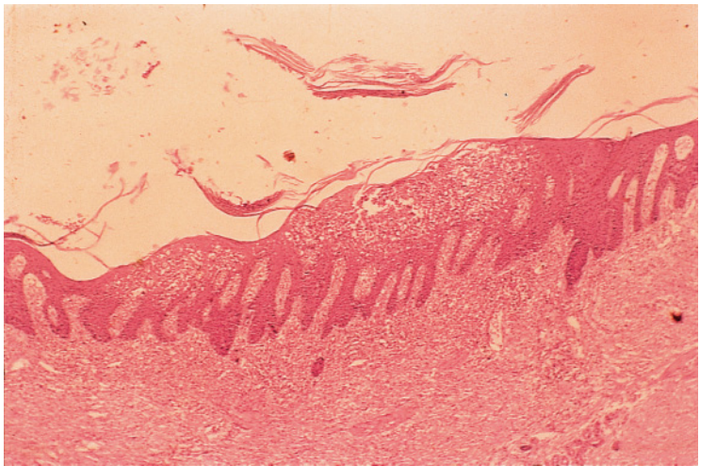


Fig. 20.26 Pustular psoriasis: intraepidermal pustule packed with neutrophils. (Courtesy of St John's Institute of Dermatology, London, UK.)

the immunocompromised. Parakeratosis pustulosa [4] should be considered in children.

References

1 Mahowald ML, Parrish RM. Severe osteolytic arthritis mutilans in pustular psoriasis. *Arch Dermatol* 1982; **118**: 434–7.

2 Baker H, Ryan TJ. Generalized pustular psoriasis. *Br J Dermatol* 1968; **80**: 771–93.

3 O'Keefe E, Braverman IM, Cohen I. Annulus migrans. *Arch Dermatol* 1973; **107**: 240–4.

4 Hjorth N, Thomsen K. Parakeratosis pustulosa. *Br J Dermatol* 1967; **79**: 527–32.

Histopathology. The changes are essentially psoriatic, but the central feature is a fully developed, large pustule within the epidermis, unilocular and full of neutrophils (Fig. 20.26). Spongiform pustules may be found in the wall of the larger unilocular pustule. There is some overlying parakeratosis. The acrosyringium is involved in the inflammation, and there are at times large numbers of eosinophils and mast cells present [1].

Management. Effective therapy is elusive and treatment is often as disappointing for the physician as for the patient. In view of the finding that PPP is an immunogenetically distinct disease from psoriasis vulgaris [2], it is perhaps unsurprising that using traditional therapies for the treatment of PPP is not ideal. The choice of treatment is influenced by its side effect profile. It is usual to start with topical therapy but topical treatments alone tend to be ineffective for PPP [3]. Superpotent topical corticosteroids may be beneficial in the short term. Hydrocolloid gel occlusion can enhance efficacy of moderate potency steroid cream, which is applied every third day up to a maximum of 4 weeks [4,5]. Atrophy, particularly of the skin around the medial longitudinal arch, is a significant risk. There are no published controlled trials to support efficacy of coal tar or dithranol [3]. Tar-impregnated occlusive bandages may be helpful for acrodermatitis continua. Neither calcipotriol nor tazarotene have been formally evaluated for the treatment of PPP. Studies of topical psoralens in either soak, paint or gel form have failed to demonstrate superiority over placebo [6]. Open studies, particularly for 8-MOP soaks, indicate efficacy; in one study the majority of patients achieved remission [7].

Systemic therapies offer the best opportunity for remission. Oral retinoids either alone or in combination with oral PUVA are the best of the second-line therapies [8–11]. Acitretin produces objective improvement in PPP [10]. Liarozole—an imidazole derivative that blocks metabolism of all-*trans*-retinoic acid and thus boosts endogenous levels of retinoids—may be effective, as shown in a small, placebo-controlled study [12]. Oral PUVA is effective [9,13] and the response is enhanced by combination with retinoid (Re–PUVA) [13–15]. Various other forms of oral therapy have been used. Placebo-controlled trials of clomocycline 170 mg three times daily [16] or tetracycline 250 mg twice daily [17] have demonstrated efficacy in PPP. Ciclosporin at the low dosage of 2.5 mg/kg/day significantly improved PPP in most patients [18]—this placebo-controlled trial confirmed observations made in earlier open trials [19,20]. Dosage as low as 1 mg/kg/day may be effective [21]. Biologic, TNF antagonists are more likely to exacerbate than improve PPP [22]. Methotrexate is occasionally beneficial, but an open study refutes this claim [23]. Anecdotal evidence exists for dapsone [24] and clofazimine [25], and grenz ray therapy may be a useful adjunct [26]. Oral corticosteroids should be used with extreme caution; triamcinolone in a dosage of 6 mg/day or less initially and 2–4 mg as maintenance may be effective.

Oral tetracycline and topical betamethasone valerate [27], and a combination of oral propylthiouracil and methotrexate [28], have been advocated for treatment of acrodermatitis continua, as has low-dose ciclosporin [29]. Narrow-band UVB and 8-MOP [30] and the TNF antatagonists [31,32] have all been reported as beneficial for acrodermatitis continua.

Remission of pustulosis in three obese patients after jejunoileal shunt operations leading to marked weight reduction awaits confirmation [33].

References

1 Eriksson MO, Hagforsen E, Lundin IP, Michaelsson G. Palmoplantar pustulosis: a clinical and immunohistological study. *Br J Dermatol* 1998; **138**: 390–8.
2 Asumalahti K, Ameen A, Suomela S *et al*. Genetic analysis of *PSORS1* distinguishes guttate psoriasis and palmoplantar pustular psoriasis. *J Invest Dermatol* 2003; **120**: 627–32.
3 Marsland AM, Chalmers RJG, Griffiths CEM. Treatments for chronic palmoplantar pustular psoriasis. *Skin Therapy Lett* 2001; **6**: 3–5.
4 Kragballe K, Larsen FG. A hydrocolloid occlusive dressing plus triamcinolone acetonide cream is superior to clobetasol cream in palmoplantar pustulosis. *Acta Derm Venereol (Stockh)* 1991; **71**: 540–2.
5 Nielsen PG, Madsen SM. Occlusive treatment of palmoplantar pustular psoriasis with clobetasol proprionate ointment succeeded by short-term PUVA. *J Dermatol Treat* 1995; **6**: 77–9.
6 Layton AM, Sheehan-Dare R, Cunliffe WJ. A double-blind placebo controlled trial of topical PUVA in persistent palmoplantar pustulosis. *Br J Dermatol* 1991; **124**: 581–4.
7 Behrens G, von Kobyletzki G, Gruss C *et al*. PUVA–bath photochemotherapy (PUVA–soak therapy) of recalcitrant dermatoses of the palms and soles. *Photodermatol Photoimmunol Photomed* 1999; **15**: 47–51.
8 White SI, Marks JM, Shuster S. Etretinate in pustular psoriasis of palms and soles. *Br J Dermatol* 1985; **113**: 581–5.
9 Rosen K, Mobacken H, Swanbeck G. PUVA, etretinate and PUVA–etretinate therapy for pustulosis palmoplantaris. *Arch Dermatol* 1987; **123**: 885–9.
10 Lassus A, Geiger JM. Acitretin and etretinate in the treatment of palmoplantar pustulosis: a double-blind comparative trial. *Br J Dermatol* 1988; **119**: 755–9.
11 Lassus A, Leukorantis J, Juvakoski T *et al*. Efficacy of etretinate in clearing and prevention of relapse of palmoplantar pustulosis. *Dermatologica* 1983; **166**: 215–29.
12 Bhushan M, Burden AD, McElhone K *et al*. Oral liarozole in the treatment of palmoplantar pustular psoriasis: a randomized, double-blind, placebo-controlled study. *Br J Dermatol* 2001; **145**: 546–53.
13 Morison WL, Parrish JA, Fitzpatrick TB. Oral methoxsalen photochemotherapy of recalcitrant dermatoses of the palms and soles. *Br J Dermatol* 1978; **99**: 297–302.
14 Lassus A, Lauharanta J, Eskelinen A. The effect of etretinate compared with different regimes of PUVA in the treatment of persistent palmoplantar pustulosis. *Br J Dermatol* 1985; **112**: 455–9.
15 Lawrence CM, Marks J, Parker S, Shuster S. A comparison of PUVA–etretinate and PUVA–placebo for palmoplantar pustular psoriasis. *Br J Dermatol* 1984; **110**: 221–6.
16 Ward JM, Corbett MF, Hanna MJ. A double-blind trial of clomocycline in the treatment of persistent palmoplantar pustulosis. *Br J Dermatol* 1976; **95**: 317–22.
17 Thomsen K, Osterbye P. Pusutlosis palmaris et plantaris. *Br J Dermatol* 1973; **89**: 293–6.
18 Reitamo S, Erkko P, Remitz A *et al*. Cyclosporin in the treatment of palmoplantar pustulosis: a randomized, double-blind, placebo-controlled study. *Arch Dermatol* 1993; **129**: 1273–9.
19 Reitamo S, Puska P, Lassus A. Cyclosporin in the treatment of palmoplantar pustulosis (Letter). *Br J Dermatol* 1989; **120**: 857.
20 Meinardi MMHM, de Rie MA, Bos JD. Oral cyclosporin is effective in clearing persistent pustuloses palmaris et plantaris. *Acta Derm Venereol (Stockh)* 1990; **70**: 77–9.
21 Erkko P, Granlund H, Remitz A *et al*. Double-blind, placebo-controlled trial of long-term, low-dose cyclosporine in the treatment of palmoplantar pustulosis. *Br J Dermatol* 1998; **139**: 997–1004.
22 Imai N, Tatanabe R, Fujiwara H *et al*. Successful treatment of impetigo herpetiformis with oral cyclosporine during pregnancy. *Arch Dermatol* 2002; **138**: 128–9.
23 Thomsen K. Pustulosis palmaris et plantaris treated with methotrexate. *Arch Derm Venereol (Stockh)* 1971; **51**: 397–400.
24 Ridley M. Pustular psoriasis. *Br J Dermatol* 1981; **105** (Suppl. 19): 39–40.
25 Molin L. Clofazimine-enhanced phagocytosis in pustulosis palmaris et plantaris. *Acta Derm Venereol (Stockh)* 1975; **55**: 151–3.
26 Lindelof B, Beitner H. The effect of grenz ray therapy on pustulosis palmoplantaris: a double-blind bilateral trial. *Acta Derm Venereol (Stockh)* 1990; **70**: 529–31.
27 Piquero-Casals J, Forseca de Mello AP, Dolcoleto C *et al*. Using oral tetracycline and topical betamethasone valerate to treat acrodermatitis of Hallopeau. *Cutis* 2002; **70**: 106–8.
28 Chowdhury MM, Motley RJ. Treatment of acrodermatitis continua of Hallopeau. *Clin Exp Dermatol* 2001; **26**: 657–60.
29 Peter RU, Ruzicka T, Donhauser G, Braun-Falco O. Acrodermatitis continua type of pustular psoriasis responds to low-dose cyclosporin. *J Am Acad Dermatol* 1990; **23**: 515–6.
30 Durmazlar SP, Akpinar H, Eren C *et al*. Treatment of acrodermatitis continua with topical 8-methoxypsoralen plus local narrowband UVB phototherapy. *Eur J Dermatol* 2009; **19**: 478–80.
31 Rubio C, Martin MA, Arranz-Sanchez DM *et al*. Excellent and prolonged response to infliximab in a case of recalcitrant acrodermatitis of Hallopeau. *J Eur Acad Dermatol* 2009; **160**: 203–5.
32 Nikkels AF, Pierard GE. Etanercept and recalcitrant acrodermatitis continua of Hallopeau. *J Drugs Dermatol* 2006; **5**: 705–6.
33 Hallberg D, Molin L. Remission of pustulosis palmaris et plantaris after intestinal shunt operation. *Acta Derm Venereol (Stockh)* 1974; **54**: 155–6.

Generalized pustular psoriasis

Definition. Generalized pustular psoriasis (GPP) is an uncommon variant of psoriasis in which an acute, subacute or occasionally chronic eruption has sterile pustulosis as its central feature.

Relationship to psoriasis vulgaris. GPP is an extreme form of psoriasis in which all the main pathological features of the disease are accentuated. Its relationship to psoriasis vulgaris is clear, because patients may have phases of ordinary psoriasis before or after the GPP [1]. Family data are similar to those found in psoriasis vulgaris [2,3]. In addition, methotrexate, etretinate, PUVA and ciclosporin A are effective in both psoriasis vulgaris and GPP.

Provocative factors. Provocation is most obvious in the acute forms. Von Zumbusch's original patient [4] was provoked by irritating topical therapy. Coal tar [5] and dithranol [2] may provoke pustulation if injudiciously continued when the psoriasis is intolerant. Other documented factors have been infection [2,6], pregnancy (see below) and hypocalcaemia associated with hypoparathyroidism [7–9]. Drugs implicated have included salicylates [10], iodide [11], lithium [12], phenylbutazone and oxyphenbutazone [13] and progesterone [14], terbinafine [15–17] and amfebutamone (bupropion) prescribed to assist with cessation of smoking [18]. The most important drug provocation is by corticosteroids. There is substantial evidence that withdrawal of systemic steroid therapy can precipitate GPP [1,2]. Intensive topical therapy with strong corticosteroids under occlusion has also been implicated [2,19,20]. Withdrawal of ciclosporin therapy has also been documented to induce GPP [21,22]. Chronic, previously stable acrodermatitis continua has been converted to GPP by high-dose oral prednisolone followed by sudden withdrawal [23].

References

1 Baker H. Corticosteroids and pustular psoriasis. *Br J Dermatol* 1976; **94** (Suppl. 12): 83–8.
2 Baker H, Ryan TJ. Generalized pustular psoriasis. *Br J Dermatol* 1968; **80**: 771–93.

3 Karvonen J, Tiilikainen A, Lassus A. HLA antigens in psoriasis. In: Farber EM, Cox AJ, eds. *Psoriasis. Proceedings of the 2nd International Symposium*. New York: Yorke Medical, 1977: 405–8.
4 von Zumbusch LR. Psoriasis und pustulöses Exanthem. *Arch Dermatol Syphilol* 1910; **99**: 335–46.
5 Ogawa M, Baughman RD, Clendenning WE. Generalized pustular psoriasis. *Arch Dermatol* 1969; **99**: 671–3.
6 Maguire A. Dermatitis herpetiformis presenting as impetigo herpetiformis. *Br J Dermatol* 1966; **78**: 360–1.
7 Feiwel M, Ferriman D. Impetigo herpetiformis. *Proc R Soc Med* 1957; **50**: 392–4.
8 Risum G. Psoriasis exacerbated by hypoparathyroidism with hypocalcaemia. *Br J Dermatol* 1973; **89**: 309–12.
9 Kawamura A, Kinoshita MT, Suzuki H. Generalized pustular psoriasis with hypoparathyroidism. *Eur J Dermatol* 1999; **9**: 574–6.
10 Shelley WB. Birch pollen and aspirin psoriasis. *JAMA* 1964; **189**: 985–8.
11 Shelley WB. Generalized pustular psoriasis induced by potassium iodide. *JAMA* 1967; **201**: 1009–14.
12 Lowe NJ, Ridgway HB. Generalized pustular psoriasis precipitated by lithium carbonate. *Arch Dermatol* 1978; **114**: 1788–9.
13 Reshad H, Hargreaves GK, Vickers CFH. Generalized pustular psoriasis precipitated by phenylbutazone and oxyphenbutazone. *Br J Dermatol* 1983; **109**: 111–3.
14 Yasuda T, Ito M, Mizuno A *et al.* Internal factors and pustular psoriasis. In: Farber EM, Cox AJ, eds. *Psoriasis. Proceedings of the 2nd International Symposium*. New York: Yorke Medical, 1977: 140–5.
15 Gupta AK, Sibbald RG, Knowles SR *et al*. Terbinafine therapy may be associated with the development of psoriasis *de novo* or its exacerbation: four case reports and a review of the literature. *J Am Acad Dermatol* 1997; **36**: 858–62.
16 Wilson NJ, Evans S. Severe pustular psoriasis provoked by oral terbinafine. *Br J Dermatol* 1998; **139**: 168.
17 Papa CA, Miller OF. Pustular psoriasiform eruption with leukocytosis associated with terbinafine. *J Am Acad Dermatol* 1998; **39**: 115–7.
18 Cox NH, Gordon PM, Dodd H. Generalized pustular and erythrodermic psoriasis associated with bupropion treatment. *Br J Dermatol* 2002; **146**: 1061–3.
19 Boxley JD, Dawber RPR, Summerly R. Generalized pustular psoriasis on withdrawal of clobetasol propionate ointment. *BMJ* 1975; **ii**: 255–6.
20 Carruthers JA, August PJ, Staughton RCD. Observations on the systemic effect of topical clobetasol propionate (Dermovate). *BMJ* 1975; **iv**: 203–4.
21 Mahendran R, Grech C. Generalized pustular psoriasis following a short course of ciclosporin A. *Br J Dermatol* 1998; **139**: 934.
22 Georgala S, Koumantaki E, Rallis E, Papadavid E. Generalized pustular psoriasis developing during withdrawal of short-term ciclosporin therapy. *Br J Dermatol* 2002; **146**: 1361–3.
23 Calkins E, Reznick L, Bauer W. Clinical and metabolic effects of prednisone, prednisolone and cortisone in a patient with acrodermatitis continua (Hallopeau). *N Engl J Med* 1957; **256**: 245–50.

HLA antigens. There is a strong positive correlation of GPP with HLA-B27 [1,2]. The association of GPP with polyarthritis [1,2] may partly explain this finding. A Japanese study has reported an association between HLA CW1 and HLADQβ*0303 and GPP [3].

Histopathology [2,4]. In acute GPP, there is intense inflammation. The earliest infiltrate is lymphocytic. Intense papillary and epidermal oedema cause spongiosis. The arrival of masses of neutrophils leads to spongiform pustule formation (Kogoj) and abscesses that quickly become macroscopic. There is acanthosis with elongation of rete ridges [2]. The stratum corneum soon becomes parakeratotic and the subcorneal pustule is shed as epidermal turnover is accelerated. Essentially, the same features are seen in subacute as in chronic patterns but in a less intense form.

References

1 Karvonen J, Tiilikainen A, Lassus A. HLA antigens in psoriasis. In: Farber EM, Cox AJ, eds. *Psoriasis. Proceedings of the 2nd International Symposium*. New York: Yorke Medical, 1977: 405–8.
2 Zachariae H. Significance of the pustular reaction in psoriasis. In: Farber EM, Cox AJ, eds. *Psoriasis. Proceedings of the 2nd International Symposium*. New York: Yorke Medical, 1977: 163–70.
3 Ozawa A, Mighara M, Sugai J *et al.* HLA class I and II alleles and susceptibility to generalized pustular psoriasis is associated with HLA-CW1 and HLADQB1*0303. *Br J Dermatol* 1998; **25**: 573–81.
4 Uehara M, Ofuji S. The morphogenesis of pustulosis palmaris et plantaris. *Arch Dermatol* 1974; **109**: 518–20.

Acute generalized pustular psoriasis (von Zumbusch)

Clinical features [1–3]. Two main groups have been distinguished [1]. In the first, typical psoriasis of early onset develops into pustular psoriasis after some years, often after provocation by steroid withdrawal or other extraneous factors. In the second, the onset of psoriasis is later in life and usually atypical, acral [4] or flexural [2,4] in distribution. A rapid and apparently spontaneous progression to the generalized pustular form follows.

The eruption may be ushered in by a sensation of burning. The skin becomes dry and tender. These warning signs—not always present—are followed by an abrupt onset of high fever and severe malaise. Pre-existing lesions become fiery and develop pinpoint pustules (Fig. 20.27). Sheets of erythema and pustulation spread to involve previously unaffected skin, the flexures and genital regions being particularly involved. Any configuration or variety of pustular exanthems may occur—isolated pustules, lakes of pus, circinate lesions, plaques of erythema with pustular collarettes or a generalized erythroderma. Waves of pustulation may succeed each other, subsiding into exfoliation of the dried pustules.



Fig. 20.27 Acute generalized pustular psoriasis. (Courtesy of St John's Dermatology Centre, London, UK.)

The nails become thickened or separated by subungual lakes of pus. The buccal mucosa and tongue may be involved, the lesions on the latter being clinically and histologically indistinguishable from 'geographic' tongue [1,5,6]. Persistent fissured tongue has also been associated with GPP and geographic tongue [7]. If the patient does not die of exhaustion, toxicity or infection, a remission may occur within days or weeks, the psoriasis returning to its normal state, or erythroderma develops. Relapses are common.

Complications. In the absence of effective treatment, death can occur in the acute stage. Hypoalbuminaemia may be profound, perhaps because of a sudden loss of plasma protein into the tissues [8]. In one patient, albumin half-life was shortened to 4 days (normal 11–12 days) [8]. Hypocalcaemia may be a consequence of the hypoalbuminaemia [1,9]. The consequent oligaemia can cause acute and fatal renal tubular necrosis [10]. There may be evidence of liver damage or even jaundice, perhaps caused by a combination of oligaemia, general toxicity and drugs [10,11]. Cholestatic jaundice of uncertain pathogenesis, closely related to acute episodes of GPP, has been described [12]. Deep-vein thrombosis in a leg can cause fatal pulmonary embolism. Staphylococcal infection may complicate GPP, usually because of hospital ward cross-infection. *Staphylococcus aureus* may be grown from pustules and rarely from blood cultures. However, claims that most GPP is caused by staphylococcal bacteraemia [13] were not substantiated [14].

Inflammatory polyarthritis is common. In one large series, one-third of patients were eventually affected [1]. Malabsorption may be a feature of the acute episode [9,15] and may further contribute to hypocalcaemia [9]. The absorption of therapeutic drugs may be impaired. Amyloidosis is a rare complication [16,17]. The obstetric complications of GPP in pregnancy are discussed below.

If GPP lasts more than a few days, gross hair loss may follow from all areas of the body. Occasionally, a telogen effluvium follows 2–3 months after the height of the illness.

Laboratory findings. There may be an absolute lymphopenia at the onset of GPP [18]. A polymorphonuclear leukocytosis quickly follows [1,18]. Plasma albumin, zinc [19] and calcium may be abnormally low. The ESR is usually raised. Malabsorption partially explains these findings. Hyperlactataemia is probably secondary to hyperproliferation [20].

References

1 Baker H, Ryan TJ. Generalized pustular psoriasis. *Br J Dermatol* 1968; **80**: 771–93.
2 Baker H. Pustular psoriasis. *Dermatol Clin* 1984; **2**: 455–70.
3 Baker H. Generalized pustular psoriasis. In: Roenigk HH, Maibach HI, eds. *Psoriasis*. New York: Marcel Dekker, 1985: 15.
4 Ridley M. Pustular psoriasis. *Br J Dermatol* 1981; **105** (Suppl. 19): 39–40.
5 O'Keefe E, Braverman IM, Cohen I. Annulus migrans. *Arch Dermatol* 1973; **107**: 240–4.
6 Dawson TAJ. Tongue lesions in generalized pustular psoriasis. *Br J Dermatol* 1974; **91**: 419–24.
7 Hubler WR. Lingual lesions of generalized pustular psoriasis. *J Am Acad Dermatol* 1984; **11**: 1069–76.
8 Braverman IM, Cohen I, O'Keefe E. Metabolic and ultrastructural studies in a patient with pustular psoriasis (von Zumbusch). *Arch Dermatol* 1972; **105**: 189–96.
9 Copeman PWM, Bold AM. Generalized pustular psoriasis (von Zumbusch) with episodic hypocalcaemia. *Proc R Soc Med* 1965; **58**: 425–7.
10 Warren DJ, Winney RJ, Beveridge GW. Oligaemia, renal failure, and jaundice associated with acute pustular psoriasis. *BMJ* 1974; **ii**: 406–8.
11 Ryan TJ, Baker H. Systemic corticosteroids and folic acid antagonists in the treatment of generalized pustular psoriasis. *Br J Dermatol* 1969; **81**: 134–45.
12 Aronsson A, Nilsson A. Pustular psoriasis of von Zumbusch type associated with recurring cholestatic jaundice. *Acta Derm Venereol (Stockh)* 1986; **66**: 164–7.
13 McFadyen T, Lyell A. Successful treatment of generalized pustular psoriasis (von Zumbusch) by systemic antibiotics controlled by blood culture. *Br J Dermatol* 1971; **85**: 274–6.
14 Matta M. Blood and pustule culture in pustular psoriasis. *Br J Dermatol* 1974; **90**: 309–12.
15 Ott F, Krakowski A, Tur E *et al*. Impetigo herpetiformis with lowered serum level of vitamin D and its diminished intestinal absorption. *Dermatologica* 1982; **164**: 360–5.
16 Berger PA. Amyloidosis: a complication of pustular psoriasis. *BMJ* 1969; **ii**: 351–3.
17 Mackie RM, Burton J. Pustular psoriasis in association with renal amyloidosis. *Br J Dermatol* 1974; **90**: 567–71.
18 Sauder DN, Steck WD, Bailin PB *et al*. Lymphocyte kinetics in pustular psoriasis. *J Am Acad Dermatol* 1981; **4**: 458–60.
19 Thune P. Abnormally low plasma zinc levels in pustular psoriasis. *Dermatologica* 1980; **161**: 179–82.
20 Yung CW, Ell SR, Soltani K, Lorinez AL. Hyperlactataemia associated with pustular psoriasis and leukocytosis. *Arch Dermatol* 1982; **118**: 432–3.

Generalized pustular psoriasis of pregnancy [1–4]

Synonym
- Impetigo herpetiformis

Definition. A rare eruption, occurring especially in pregnancy, with the features of generalized pustular psoriasis, but with a tendency to be symmetrical and grouped, and often starting in the flexures. Constitutional disturbance may be severe.

Pathogenesis. The worsening of pustular psoriasis just before menstruation is well recognized [5,6] and challenge with progesterone [7] or clomifene (clomiphene) [5] has produced pustular exacerbations in such patients. The syndrome was first described by Hebra [8] and an endocrine cause is suspected. The claims that impetigo herpetiformis stands as an entity separate from GPP have been restated [3,9].

Clinical features. The disease is rare; by 1982 less than 200 cases were documented [2]. Onset is usually in the last trimester of pregnancy, but may be earlier, and has been recorded in the first month of pregnancy [6] and in the first day of the puerperium [10]. The disease tends to persist until the child is born, and occasionally long afterwards [6]. There is one report of familial disease [11]. Essentially, the features are of a GPP, usually of flexural onset and with a marked tendency to symmetry, and sometimes grouping of areas of pustulation. Constitutional disturbance is characteristically severe with fever, and death may occur, attributable to cardiac or renal failure. Delirium, diarrhoea, vomiting and tetany have been described. The eruption usually starts in the inguinogenital region and other flexures, with minute pustules arising on an acutely inflamed area of skin. These extend centrifugally, drying in the centre, or form plaques in which eroded greenish yellow pustules become fetid, crusted or vegetating. Condyloma-

like lesions may form in the flexures [12]. The eruptions may become widespread. As individual areas heal, they leave a reddish brown pigmentation. The tongue, buccal mucosa and even the oesophagus may be involved, with circinate or erosive lesions following short-lived pustules.

The more severe and long-standing the disease, the greater are the risks of placental insufficiency leading to stillbirth, neonatal death or fetal abnormalities [3,9,13].

Prognosis. Characteristically, the disease recurs in subsequent pregnancies [2,14]. Recurrence has been described in up to nine pregnancies, and on subsequent use of oral contraceptives [2,3]. In one case, the disease continued unabated despite termination of the pregnancy [6].

Laboratory findings. Hypocalcaemia has often been reported [1,6]. Lowered levels of serum vitamin D have been found, probably attributable to its malabsorption [2].

Treatment. This is discussed with that of other forms of GPP (see below). In one case, where termination failed to halt the disease, a mestranol–ethynodiol combination orally was effective when other measures had failed [6].

References

1 Baker H, Ryan TJ. Generalized pustular psoriasis. *Br J Dermatol* 1968; **80**: 771–93.
2 Ott F, Krakowski A, Tur E *et al.* Impetigo herpetiformis with lowered serum level of vitamin D and its diminished intestinal absorption. *Dermatologica* 1982; **164**: 360–5.
3 Oumeish OY, Farraj SE, Bataineh AS. Some aspects of impetigo herpetiformis. *Arch Dermatol* 1982; **118**: 103–5.
4 Pierard GE, Pierard-Franchimont C, de la Brassine M. Impetigo herpetiformis and pustular psoriasis during pregnancy. *Am J Dermatopathol* 1983; **5**: 215–20.
5 Yasuda T, Ito M, Mizuno A *et al.* Internal factors are pustular psoriasis. In: Farber EM, Cox AJ, eds. *Psoriasis. Proceedings of the 2nd International Symposium*. New York: Yorke Medical, 1977: 140–5.
6 Gligora M, Kolacio Z. Hormonal treatment of impetigo herpetiformis. *Br J Dermatol* 1982; **107**: 253.
7 Shelley WB. Generalized pustular psoriasis induced by potassium iodide. *JAMA* 1967; **201**: 1009–14.
8 Hebra F. Ueber einzelne während der Schwangerschaft, dem Wochenbette und bei Uterinalkrankheiten der Frauen zu beobachtende Hautkrankheiten. *Wien Med Wochenschr* 1872; **22**: 1197–202.
9 Lotem M, Katzenelson V, Rotem A *et al.* Impetigo herpetiformis: a variant of pustular psoriasis or a separate entity? *J Am Acad Dermatol* 1989; **20**: 338–41.
10 Katsambas A, Stavropoulus PG, Katsiboulas V *et al.* Impetigo herpetiformis during the puerperium. *Dermatology* 1999; **198**: 400–2.
11 Ebagei Z, Erkilic S. A case of recurrent inpetigo herpetiformis with a positive family history. *Int J Clin Pract* 2000; **54**: 619–20.
12 Sauer GC, Geha BJ. Impetigo herpetiformis. *Arch Dermatol* 1961; **83**: 119–26.
13 Beveridge GW, Harkness RA, Livingstone JRB. Impetigo herpetiformis in two successive pregnancies. *Br J Dermatol* 1966; **78**: 106–12.
14 Sahin HG, Sahin HA, Metin A *et al.* Recurrent impetigo herpetiformis in a pregnant adolescent: a report. *Eur J Obstet Gynecol Reprod Biol* 2002; **101**: 201–3.

Infantile and juvenile pustular psoriasis

All forms of pustular psoriasis are rare in childhood. Five cases were seen in one series of 479 children with psoriasis [1], and one case of GPP in another series of 112 [2]. In a series of 104 cases of GPP in patients of all ages, there were only five children [3]. Although GPP can begin at any age in childhood, in over 25% of certain series onset has been in the first year [4,5]. The disease may begin in the first few weeks of life and two cases of congenital GPP have been described [5].



Fig. 20.28 Juvenile pustular psoriasis. (Courtesy of St John's Institute of Dermatology, London, UK.)

In contrast to psoriasis vulgaris in childhood [6] and GPP in adults [3], a male preponderance is seen in GPP of childhood (about 3:2) [4,5]. Infantile cases are usually benign. Systemic symptoms are often absent and spontaneous remissions occur [4,5]. In at least one-third of infantile cases, a history of an eruption diagnosed as seborrhoeic dermatitis [7], napkin dermatitis or sudden-onset napkin psoriasis [8] is obtained [4,9]. More severe forms with fever and toxicity do occur, necessitating active treatment. Rarely, pustulosis has supervened on a congenital erythroderma [4,10].

The majority of children are aged 2–10 years at onset. The disease may be of Zumbusch pattern, but annular and circinate forms are the most common [4,9,11]. Onset of Zumbusch-type psoriasis may be abrupt with toxicity, and an erythrodermic background can become generalized rapidly (Fig. 20.28). Attacks often settle within a few days, but repeated waves of inflammation may follow [4]. Systemic steroid therapy carries the hazard of disseminated infections with varicella and other viruses [9]. In older children, the disease resembles that in the adult and may be of any of the recognized patterns.

The prognosis may be variable [3] but has been generally good in two series [9,12]. Treatment is discussed below.

References

1 Marill FG, Vodov I. Psoriasis pustuleux chez des enfants: remarques à propos de cinq cas. *Bull Soc Fr Dermatol Syphiligr* 1974; **81**: 590–2.

2 Kumar B, Dhar S, Handa S, Kaur I. Methotrexate in childhood psoriasis. *Pediatr Dermatol* 1994; **11**: 271–3.
3 Baker H, Ryan TJ. Generalized pustular psoriasis. *Br J Dermatol* 1968; **80**: 771–93.
4 Beylot C, Bioulac P, Grupper C *et al.* Generalized pustular psoriasis in infants and children: report of 27 cases. In: Farber EM, Cox AJ, eds. *Psoriasis. Proceedings of the 2nd International Symposium*. New York: Yorke Medical, 1977: 171–9.
5 Beylot C, Puissant A, Bioulac P *et al.* Particular clinical features of psoriasis in infants and children. *Acta Derm Venereol (Stockh)* 1979; **59** (Suppl. 87): 95–7.
6 Nyfors A. Psoriasis in children. *Acta Derm Venereol (Stockh)* 1981; **61** (Suppl. 95): 47–53.
7 Nayek K, Dasgupta MK. Infantile pustular psoriasis: may mimic seborrhoeic dermatitis. *Indian Pediatr* 2002; **38**: 1059.
8 Watanabe M, Tabata N, Tagami H. Explosive diaper pustular psoriasis. *Pediatr Dermatol* 2002; **19**: 564–5.
9 Khan SA, Peterkin GAG, Mitchell PC. Juvenile generalized pustular psoriasis: a report of five cases and a review of the literature. *Arch Dermatol* 1972; **105**: 67–72.
10 Henriksen L, Zachariae H. Pustular psoriasis and arthritis in congenital psoriasiform erythroderma. *Dermatologica* 1972; **144**: 12–8.
11 Liao PB, Robinson R, Howard R *et al*. Annular pustular psoriasis: most common form of psoriasis in children—a report of three cases and review of the literature. *Pediatr Dermatol* 2002; **19**: 19–25.
12 Zelickson BD, Muller SA. Generalized pustular psoriasis in childhood: report of 13 cases. *J Am Acad Dermatol* 1991; **24**: 186–94.

Circinate, annular and linear pustular psoriasis

Annular and other patterned lesions may be seen in acute GPP, but are more characteristic of the subacute or chronic forms of widespread pustular psoriasis [1,2]. Lesions begin as discrete areas of erythema, which become raised and oedematous. Slow centrifugal spread may mimic erythema annulare centrifugum [3,4]. Pustules appear peripherally on the crest of the advancing edge, become desiccated and leave a trailing fringe of scale as the lesion slowly advances.

Some authors have separated a related pattern, well described by Lapière as recurrent circinate erythematous psoriasis [5,6]. It was originally described in 1907 as 'recurrent circinate erythema'. It may occur alone (in the complete absence at any stage of recognizable psoriasis) or as a phase in what is clearly generalized pustular psoriasis.

Linear forms of pustular psoriasis are occasionally observed within the context of more generalized pustulosis [7,8].

Localized forms of GPP

These must be distinguished from PPP or acropustulosis. The term 'psoriasis with pustules' is perhaps more appropriate. One or more plaques of psoriasis vulgaris may develop pustules (e.g. after excessively irritant topical therapy).

References

1 Degos R, Civatte J, Arrouy M. Psoriasis et psoriasis pustuleux à type d'érythème annulaire centrifuge (3 cas). *Bull Soc Fr Dermatol Syphiligr* 1966; **73**: 356–8.
2 Milian G, Katchoura V. Psoriasis pustuleux généralisé. *Bull Soc Fr Dermatol Syphiligr* 1933; **40**: 851–3.
3 Rajka G, Thune PO. An erythema annulare centrifugum-type of psoriasis. *Acta Derm Venereol* 1979; **59** (Suppl. 85): 143–5.
4 Vocks E, Worrett WI, Ring J. Erythema annulare centrifugum type psoriasis: a pustular variant of acute eruptive psoriasis. *J Eur Acad Dermatol Venereol* 2003; **17**: 446–8.
5 Bazex A, Dupré A, Christol B *et al.* Psoriasis à type d'érytheme circiné récidivant de Bloch. *Bull Soc Fr Dermatol Syphiligr* 1967; **74**: 689–95.
6 Lapière S. Deux cas de psoriasis recidivants à elements evoluant de façon anormalement rapide en quelques jours. *Arch Belges Dermatol* 1959; **15**: 7–12.
7 Kanoh H, Ichihashi N, Kamiga H. Linear pustular psoriasis that developed in a patient with generalized pustular psoriasis. *J Am Acad Dermatol* 1998; **39**: 635–7.
8 Ozkaya-Bayazit E, Akaasya E, Buyukbabani N, Baykal C. Pustular psoriasis with a striking linear pattern. *J Am Acad Dermatol* 2000; **42**: 329–31.

Differential diagnosis. Subcorneal pustular dermatosis of Sneddon and Wilkinson remains a controversial entity [1,2]. Acute generalized exanthematous pustulosis (AGEP) is perhaps the most important differential, occurring as an acute, spontaneously healing reaction to drugs, usually antibiotics [3]. It is probable that some cases previously reported as drug-induced GPP (see above) may in fact have been AGEP. In infantile acropustulosis, the process does not become generalized and is not associated with constitutional disturbance [4,5]. The distinction between GPP and pustular lesions in Reiter's disease is probably academic. Acute pemphigus foliaceus can mimic subacute GPP, but histological and immunofluorescence testing will distinguish the two. The wasting, glossitis and anaemia associated with the migratory necrolytic eruption of glucagonoma should allow easy differentiation. Occasionally, the bowel bypass syndrome [6,7], Sweet's syndrome [8] and Behçet's syndrome will cause difficulty. Staphyloderma, rampant impetigo or candidiasis in the immunosuppressed or pustular drug eruption (e.g. caused by halides) should be remembered.

References

1 Chimenti S, Ackerman B. Is subcorneal pustular dermatosis of Sneddon and Wilkinson an entity sui generis? *Am J Dermatopathol* 1981; **3**: 363–76.
2 Moschella SL. Review of so-called aseptic neutrophilic dermatoses. *Australas J Dermatol* 1983; **24**: 55–62.
3 Roujeau J-C, Bioulac-Sage P, Bourseau C *et al.* Acute generalized exanthematous pustulosis: analysis of 63 cases. *Arch Dermatol* 1991; **127**: 1333–8.
4 Jarratt M, Ramsdell W. Infantile acropustulosis. *Arch Dermatol* 1979; **115**: 834–6.
5 Kahn G, Rywlin AM. Acropustolosis of infancy. *Arch Dermatol* 1979; **115**: 831–3.
6 Dicken CH, Seehafer JR. Bowel bypass syndrome. *Arch Dermatol* 1979; **115**: 837–9.
7 Fagan EA, Elkon KB, Griffin GF *et al.* Systemic inflammatory complications following jejuno-ileal bypass. *QJM* 1982; **51**: 445–60.
8 Sweet RD. An acute febrile neutrophilic dermatosis. *Br J Dermatol* 1964; **76**: 349–56.

Management [1]. The treatment of acute GPP requires admission to hospital, removal of possible provocative factors, general support measures and topical and usually systemic drug therapy.

Withdrawal of provocative factors. Tar or dithranol can be withdrawn abruptly, but massive overdosage with potent topical corticosteroids requires more care. The application of serially diluted topical steroids over several days may be the safest course, and is preferable to substitution of oral or parenteral corticosteroid, however temporary. Infection, where present, should be treated rigorously with the appropriate antibiotic, usually erythromycin or flucloxacillin. Rarely, when GPP in pregnancy is threatening maternal life, termination or early delivery may be indicated.

General measures. If there is no immediate metabolic threat in acute GPP, and generally in subacute forms, initial treatment

should be conservative [2]. This is particularly so in infancy and childhood [3]. Bed rest in hospital, mild sedation, bland local applications with fluid and protein replacement may promote spontaneous reversion to a quieter erythrodermic psoriasis or even psoriasis vulgaris [2]. This approach is particularly apt if a provocative factor has been at play [2]. However, such a course has to be weighed against the risk of repeated waves of pustulation that may exhaust the patient, and the hypostatic and thrombotic hazards of prolonged bed rest, particularly in the elderly patient. Excessive heat loss must be prevented by maintaining an adequate ambient temperature, avoiding cool draughts of air. A low-reading thermometer is essential. Fluid intake should be increased so that the daily urine volume remains adequate.

Topical therapy. Often, completely bland creams or lotions are best. Weak corticosteroid creams may be helpful in subacute forms. Tar [4] and dithranol are contraindicated.

Systemic therapy. Most cases of GPP require systemic therapy. Retinoids are probably the treatment of choice. A recent survey of 385 Japanese patients with GPP [5] reported that acitretin was effective in more than 80% of cases. Response to high doses of acitretin (1 mg/kg/day) may be rapid [6] and lower doses of 0.5–0.75 mg/kg/day may be sufficient to maintain control [7]. Disease control can sometimes be achieved with intermittent therapy [8]. Combination of etretinate with PUVA is beneficial [9].

PUVA therapy is effective in acute and subacute GPP [9–12]. Very ill patients may have to be treated in the horizontal position. Small doses of UVA should be given initially three or four times weekly; the dose of UVA is slowly increased.

Methotrexate is probably as effective as acitretin but no comparative studies are available [2]. In fulminating GPP, small (7.5–10.0 mg) intravenous doses, repeated every 5–7 days may be safest. The intramuscular route can be used, but the intravenous or intramuscular dosage should rarely exceed 0.3 mg/kg/week. Oral therapy is less predictable, because of variable absorption. Sudden unexpected toxicity from repeated methotrexate doses may follow, because of improved absorption of the drug as the GPP subsides. Orally, dosage of 0.2–0.4 mg/kg/week should suffice, starting at the lower end of the range. If the patient is very ill, renal function may have to be monitored daily if methotrexate overdosage is to be avoided. Methotrexate has been used with success in children with GPP [13].

Control of GPP has been achieved with very high dosage of ciclosporin alone (9–12 mg/kg/day), but toxicity prevented prolonged treatment at these dose levels. With lower dosage, the addition of topical steroids allowed adequate control [14]. However, ciclosporin (5–7 mg/kg/day) failed to alleviate GPP in a renal transplant recipient during periods of prednisolone withdrawal [15]. In contrast, a case of GPP was reported to respond rapidly to ciclosporin 7.5 mg/kg/day, and was successfully maintained in remission at 3.5 mg/kg/day [16]. Three patients, including two children, were successfully treated with low-dose (1–2 mg/kg/day) ciclosporin; the lesions cleared within 4 weeks of starting therapy [17].

Razoxane has been effective in acute GPP [18] but is rarely used now. Hydroxyurea is less effective [19]. Colchicine has been used either alone [20,21] or in combination [22] with methotrexate. 6-Thioguanine has also been used successfully [23].

In the subacute and chronic forms of GPP, the use of dapsone (50–200 mg/day) [24–26] can be considered, and may be particularly valuable in atypical variants and children [2,27]. Oral or parenteral corticosteroid should be used only when urgent control of metabolic complications is needed [2]. The short-term effects of prednisolone (30–40 mg/day) are excellent [2,28], but serious relapses are liable to occur as the dosage is reduced unless another form of therapy (e.g. methotrexate or acitretin) is given simultaneously [2].

Biologic agents have been used occasionally and to excellent effect. It appears that these therapies are perhaps well-suited to rapid control of GPP. The TNF-antagonists, and basiliximab, an antibody directed at the IL-2 receptor, have all been reported to rapidly control acute GPP [29–32]. It is likely that TNF-antagonists will become the treatment of choice in cases of fulminant disease, however there are cases of paradoxical exacerbation of PPP by these agents [33].

Acitretin, methotrexate and PUVA cannot be used in GPP of pregnancy unless termination has become inevitable. Fulminating disease in pregnancy is best treated with prednisolone, the drug that carries the least hazard for the fetus, but ciclosporin has been used safely for treatment of impetigo herpetiformis [34]. Methotrexate, retinoids, PUVA or combination therapy may be needed after delivery to allow weaning off the steroid or ciclosporin [35].

References

1 Baker H. Generalized pustular psoriasis. In: Roenigk HH, Maibach HI, eds. *Psoriasis*. New York: Marcel Dekker, 1985: 15.

2 Ryan TJ, Baker H. Systemic corticosteroids and folic acid antagonists in the treatment of generalized pustular psoriasis. *Br J Dermatol* 1969; **81**: 134–45.

3 Khan SA, Peterkin GAG, Mitchell PC. Juvenile generalized pustular psoriasis. *Arch Dermatol* 1972; **105**: 67–72.

4 Ogawa M, Baughman RD, Clendenning WE. Generalized pustular psoriasis. *Arch Dermatol* 1969; **99**: 671–3.

5 Ozawa A, Ohkido M, Haraki Y. Treatment of generalized pustular psoriasis: a multicentre study in Japan. *J Dermatol* 1999; **26**: 141–9.

6 Orfanos CE. Oral retinoid in psoriasis: current clinical experiences and possible mechanisms of action. In: Farber EM, Cox AJ, eds. *Psoriasis. Proceedings of the 3rd International Symposium*. New York: Grune & Stratton, 1982: 197–209.

7 Lowe NJ, Lazarus V, Matt L. Systemic retinoid therapy for psoriasis. *J Am Acad Dermatol* 1988; **19**: 186–91.

8 Wolska H, Jablonska S, Langner A *et al.* Etretinate therapy in generalized pustular psoriasis (Zumbusch type): immediate and long-term results. *Dermatologica* 1985; **171**: 297–304.

9 Piamphongsant T, Nimsuwan P, Gritiyarangsan P. Treatment of generalized pustular psoriasis: clinical trials using different therapeutic modalities. *Clin Exp Dermatol* 1985; **10**: 552–61.

10 Hönigsmann H, Gschnait F, Konrad K *et al.* Photochemotherapy for pustular psoriasis (von Zumbusch). *Br J Dermatol* 1977; **97**: 199–226.

11 Henseler T, Wolff K, Hönigsmann H *et al.* Oral 8-methoxypsoralen photo-chemotherapy of psoriasis. *Lancet* 1981; **i**: 853–7.

12 Wolff K, Fritsch PO. Retinoid PUVA chemophototherapy. In: Farber EM, Cox AJ, eds. *Psoriasis. Proceedings of the 3rd International Symposium*. New York: Grune & Stratton, 1982: 211–9.

13 Kumar B, Dhar S, Handa S, Kaur I. Methotrexate in childhood psoriasis. *Pediatr Dermatol* 1994; **11**: 271–3.

14 Meinardi MMHM, Westerhof W, Bos JD. Generalized pustular psoriasis (von Zumbusch) responding to cyclosporin A. *Br J Dermatol* 1987; **116**: 269–70.

15 Coulson IH, Evans CD, Holden CA. Generalized pustular psoriasis after renal transplantation: failure to suppress with cyclosporin A. *Clin Exp Dermatol* 1988; **13**: 416–7.
16 Fradin MS, Ellis CN, Voorhees JJ. Rapid response of von Zumbusch psoriasis to cyclosporine. *J Am Acad Dermatol* 1990; **23**: 925–6.
17 Kilic SS, Hacimustafaoglu M, Celebi S *et al*. Low-dose cyclosporin A treatment in generalized pustular psoriasis. *Pediatr Dermatol* 2001; **18**: 246–8.
18 Horton JJ, Wells RS. Razoxane: a review of 6 years' therapy in psoriasis. *Br J Dermatol* 1983; **109**: 669–73.
19 Stein KM, Shelley WB, Weinberg RA. Hydroxyurea in the treatment of pustular psoriasis. *Br J Dermatol* 1971; **85**: 81–5.
20 Wahba A, Cohen H. Therapeutic trials with colchicine in psoriasis. *Acta Derm Venereol (Stockh)* 1980; **60**: 515–20.
21 Zachariae H, Kragballe K, Herlin T. Colchicine in generalized pustular psoriasis: clinical response and antibody-dependent cytoxicity by monocytes and neutrophils. *Arch Dermatol Res* 1982; **274**: 327–33.
22 Horiguchi M, Tagikawa M, Imamura S. Treatment of generalized pustular psoriasis with methotrexate and colchicine (Letter). *Arch Dermatol* 1981; **117**: 760.
23 Sherer DW, Lebwohl MG. 6-Thioguanine in the treatment of psoriasis: a case report and literature review. *J Cutan Med Surg* 2002; **6**: 546–50.
24 Peachey RDG. Atypical pustular psoriasis treated with dapsone. *Br J Dermatol* 1977; **97** (Suppl. 15): 64–6.
25 Ridley M. Pustular psoriasis. *Br J Dermatol* 1981; **105** (Suppl. 19): 39–40.
26 MacMillan AL, Champion RH. Generalized pustular psoriasis treated with dapsone. *Br J Dermatol* 1973; **88**: 183–5.
27 Yu HJ, Park JW, Park JM *et al*. A case of childhood generalized pustular psoriasis treated with dapsone. *J Dermatol* 2001; **28**: 316–9.
28 Baker H. Corticosteroids and pustular psoriasis. *Br J Dermatol* 1976; **94** (Suppl. 12): 83–8.
29 Elewski BE. Infliximab for the treatment of severe pustular psoriasis. *J Am Acad Dermatol* 2002; **47**: 796–7.
30 Callen JP, Jackson JH. Adalimumab effectively controlled recalcitrant generalized pustular psoriasis in an adolescent. *J Dermatolog Treat* 2005; **16**: 350–2.
31 Eposito M, Mazzotta A, Casciello C, Chimenti S. Etanercept at different dosages in the treatment of generalized pustular psoriasis: a case series. *Dermatology* 2008; **216**: 355–60.
32 Salim A, Emerson RM, Dalziel KL. Successful treatment of severe generalized pustular psoriasis with basiliximab (interleukin-2 receptor blocker). *Br J Dermatol* 2000; **143**: 1121–2.
33 Ko JM, Gottlieb AB, Kerbleski JF. Induction and exacerbation of psoriasis with TNF-blockade therapy: a review and analysis of 127 cases. *J Dermatolog Treat* 2009; **20**: 100–8.
34 Imai N, Tatanabe R, Fujiwara H *et al*. Successful treatment of impetigo herpetiformis with oral cyclosporine during pregnancy. *Arch Dermatol* 2002; **138**: 128–9.
35 Breier-Maly J, Ortel B, Breier F *et al*. Generalized pustular psoriasis of pregnancy (impetigo herpetiformis). *Dermatology* 1999; **198**: 61–4.

Prognosis. There is a paucity of data on the long-term prognosis of GPP. Von Zumbusch's patient [1] survived many acute episodes over a number of years, and perhaps had the good fortune to live before potent (and dangerous) remedies were available. Ryan and Baker [2,3] reported on the prognosis in 155 patients with all types of GPP. Thirty-four of 106 patients followed up had died, and 26 of these deaths were attributable to the disease or its treatment. GPP developing from acropustulosis (acrodermatitis continua) had the worst prognosis, seven out of 11 patients having died and a further one remaining severely disabled. To some extent, this particularly poor outlook reflected the age at onset of these patients, who were predominantly elderly. However, death was a direct result of GPP in all of these cases, resulting from cardiac failure or respiratory infection during uncontrolled pustular psoriasis. In general, patients with preceding ordinary psoriasis had a better prognosis than those with atypical prepustular psoriasis [2,3].

The better prognosis of GPP of pregnancy reflects the abrupt removal of the main provocative factor by childbirth or, *in extremis*, termination of the pregnancy [4,5]. GPP of childhood also carries a more benign prognosis [6], providing oral corticosteroids and methotrexate can be avoided [7]. Khan *et al.* [7] stressed the hazard of fatal virus infections in corticosteroid-treated children and advocated bland topical therapy, if necessary in hospital, for up to 3 months in anticipation of spontaneous remission. In their patients, where oral corticosteroids were avoided, growth and development progressed unimpaired despite GPP [7].

References

1 von Zumbusch LR. Psoriasis und pustulöses Exanthem. *Arch Dermatol Syphilis (Berlin)* 1910; **99**: 335–46.
2 Ryan TJ, Baker H. Systemic corticosteroids and folic acid antagonists in the treatment of generalized pustular psoriasis. *Br J Dermatol* 1969; **81**: 134–45.
3 Ryan TJ, Baker H. The prognosis of generalized pustular psoriasis. *Br J Dermatol* 1971; **85**: 407–11.
4 Ott F, Krakowski A, Tur E *et al*. Impetigo herpetiformis with lowered serum level of vitamin D and its diminished intestinal absorption. *Dermatologica* 1982; **164**: 360–5.
5 Oumeish OY, Farraj SE, Bataineh AS. Some aspects of impetigo herpetiformis. *Arch Dermatol* 1982; **118**: 103–5.
6 Beylot C, Puissant A, Bioulac P *et al*. Particular clinical features of psoriasis in infants and children. *Acta Derm Venereol (Stockh)* 1979; **59** (Suppl. 87): 95–7.
7 Khan SA, Peterkin GAG, Mitchell PC. Juvenile generalized pustular psoriasis. *Arch Dermatol* 1972; **105**: 67–72.

Psoriatic arthritis

Definition. An inflammatory arthritis associated with psoriasis of the skin and/or nails, with usually a negative serological test for rheumatoid factor and the absence of rheumatoid nodules [1].

Epidemiology. Like psoriasis of the skin, good population studies remain to be performed and thus estimation of population prevalence is difficult and highly variable, depending on the study. Historically, arthritis prevalence amongst psoriasis patients has been estimated at 2.6–7% [2,3]. However, more recent, large questionnaire-based studies have indicated that the real prevalence may be much higher. Thus, a Scandinavian study revealed arthritis in 30% [4] of psoriatics and in the USA, 23% (http://www.psoriasis.org). In general, it appears that there is no direct relationship between the extent and severity of psoriasis and of psoriatic arthritis [5,6]. Further, nail disease is more frequent in cases with arthritis. A review of population-based studies estimated the population prevalence of psoriatic arthritis at 0.02–0.1% [7]. There appears to be a stronger association with generalized pustular psoriasis [8] or erythrodermic psoriasis [9] and arthritis.

The age of onset for psoriatic arthritis is, in general, later than for the skin disease, with peak age of onset being the fourth decade. Biodi-Oriente *et al.* [10] reported psoriasis predating arthritis in 68% of cases occurring at the same time in 11%, and following it in 21%. There is a rare but well-recognized juvenile-onset form of psoriatic arthritis [11], with age of onset between

9 and 12 years. Psoriatic arthritis appears more common in individuals with type 1 early-onset psoriasis vulgaris.

In contrast to rheumatoid arthritis, where females predominate 3:1, in psoriatic arthritis the sexes appear equally affected.

References

1 Moll JMH, Wright V. Psoriatic arthritis. *Semin Arthritis Rheum* 1973; **3**: 55–78.
2 Baker H. Epidemiological aspects of psoriasis and arthritis. *Br J Dermatol* 1966; **78**: 249–61.
3 Leczinsky CG. The incidence of arthropathy in a 10 year series of psoriasis cases. *Acta Derm Venereol (Stockh)* 1948; **28**: 483–7.
4 Zachariae H, Zachariae R, Blomqvist K *et al.* Quality of life and prevalence of arthritis reported by 5795 members of the Nordic Psoriasis Associations. Data from the Nordic Quality of Life Study. *Acta Derm Venereol* 2002; **82**: 108–13.
5 Jones SM, Armas JB, Cohen MG *et al*. Psoriatic arthritis: outcome of disease subsets and relationship of joint disease to nail and skin disease. *Br J Rheumatol* 1994; **33**: 834–9.
6 Elkayam O, Ophir J, Yaron M, Caspi D. Psoriatic arthritis: interrelationships between skin and joint manifestations related to onset, course and distribution. *Clin Rheumatol* 2000; **19**: 301–5.
7 O'Neill T, Silman AJ. Psoriatic arthritis: historical background and epidemiology. *Baillière's Clin Rheumatol* 1994; **8**: 245–61.
8 Baker H, Ryan TJ. Generalized pustular psoriasis: a clinical and epidemiological study of 104 cases. *Br J Dermatol* 1968; **80**: 771–93.
9 Baker H, Golding DN, Thompson M. Psoriasis and arthritis. *Ann Intern Med* 1963; **58**: 909–25.
10 Biodi-Oriente C, Scarpa R, Pucino A, Oriente P. Psoriasis and psoriatic arthritis: dermatological and rheumatological co-operative report. *Acta Derm Venereol Suppl* 1989; **146**: 69–71.
11 Shore A, Ansell BM. Juvenile psoriatic arthritis: an analysis of 60 cases. *J Pediatr* 1982; **100**: 529–35.

Aetiology and pathogenesis.

Genetics. Familial clustering of psoriatic arthritis has been reported [2] although much less frequently than for cutaneous psoriasis. There is no evidence that psoriatic arthritis follows Mendelian patterns of inheritance. A large number of HLA association studies have been performed [3]. In general, results concur with studies of cutaneous disease, with HLA Cw6, B13, B17 and DR3 occurring most frequently. A specific association with psoriatic arthritis, not seen in the cutaneous form, is HLA-B27, seen particularly in spondyloarthritis (see below). Genome scans have recently been reported with evidence for a susceptibility locus on chromosome 16q [4]. CARD15, a molecule involved in macrophage–monocyte cell signalling, has been implicated as a candidate gene, at least in some patients [5]. This molecule has also been implicated in Crohn's disease but not in cutaneous psoriasis.

Environmental factors. Studies of families in which psoriatic arthritis aggregates suggest an important environmental component to disease pathogenesis [6]. Increased immunoreactivity to streptococcal antigens has been reported in sera of patients [7], but establishing a pathogenic link has proved elusive and appears much more tenuous than for the skin disease. An increased prevalence of psoriatic arthritis has been reported in HIV [8] and hepatitis C infection [9], and antibodies to enterobacterial antigens are also recorded [10].

Trauma as a precipitating event has also been noted. Interestingly, trauma appears to be more important in psoriatic compared to rheumatoid and other inflammatory forms of arthritis [11]. Neuropeptides and the nervous system have been implicated in these events [12].

Pathogenetic mechanisms. As for cutaneous psoriasis, T cells probably have a key role in arthritis pathogenesis. Those implicated possess activation and memory surface markers but, unlike skin, do not express the skin homing molecule CLA [13]. Thus, when skin and joint manifestations coexist, different populations of T cells mediate disease at different sites. Intra-articular clonal expansion of CD8-expressing T cells have been observed, but putative antigens remain elusive. As observed in the skin, the morphology of blood vessels in psoriatic arthritis is altered with the presence of dilated tortuous vessels and evidence of angiogenesis [14]. Interestingly, these features are different from that seen in rheumatoid arthritis.

References

1 Hellgren L. Association between rheumatoid arthritis and psoriasis in total populations. *Acta Rheumatol Scand* 1969; **15**: 316–26.
2 Chandran V, Schentag CT, Brockbank J *et al*. Familial aggregation of psoriatic arthritis. *Ann Rheum Dis* 2009; **68**: 664–7.
3 Eastmond CJ. Genetics and HLA antigens in psoriatic arthritis. *Baillière's Clin Rheumatol* 1994; **8**: 245–61.
4 Karason A, Gudjonsson JE, Upmanyu R *et al*. A susceptibility gene for psoriatic arthritis maps to chromosome 16q: evidence for imprinting. *Am J Hum Genet* 2003; **72**: 125–31.
5 Rahman P, Bartlett S, Siannis F *et al. CARD15*: a pleiotropic autoimmune gene that confers susceptibility to psoriatic arthritis. *Am J Hum Genet* 2003; **73**: 677–81.
6 Moll JMH, Wright V. Familial occurrence of psoriatic arthritis. *Ann Rheum Dis* 1973; **22**: 181–201.
7 Vasey FB, Deitz C, Fenske NA *et al*. Possible involvement of group A streptococci in the pathogenesis of psoriatic arthritis. *J Rheumatol* 1982; **9**: 719–22.
8 Espinoza LR, Berman A, Vasey FB *et al.* Psoriatic arthritis and acquired immunodeficiency syndrome. *Arthritis Rheum* 1988; **31**: 1034–40.
9 Taglione E, Vatteroni ML, Martini P *et al.* Hepatitis C virus infection: prevalence in psoriasis and psoriatic arthritis. *J Rheumatol* 1999; **26**: 370–2.
10 Lapadula G, Iannone F, Covelli M *et al*. Anti-*Enterobacteria* antibodies in psoriatic arthritis. *Clin Exp Rheumatol* 1992; **10**: 461–6.
11 Punzi L, Pianon M, Bertazzolo N *et al.* Clinical, laboratory and immunogenetic aspects of post-traumatic psoriatic arthritis: a study of 25 patients. *Clin Exp Rheumatol* 1998; **16**: 277–81.
12 Fearon U, Veale DJ. Pathogenesis of psoriatic arthritis. *Clin Exp Dermatol* 2001; **26**: 333–7.
13 Pitzalis C, Cauli A, Pipitone N *et al.* Cutaneous lymphocyte antigen-positive T lymphocytes preferentially migrate to the skin but not to the joint in psoriatic arthritis. *Arthritis Rheum* 1996; **39**: 137–45.
14 Reece RJ, Canete JD, Parsons WJ *et al*. Distinct vascular patterns of early synovitis in psoriatic, reactive, and rheumatoid arthritis. *Arthritis Rheum* 1999; **42**: 1481–4.

Clinical features.

In one series of 180 patients, the mode of onset was studied, and skin lesions were found to precede arthritis in 65%, arthritis antedated skin lesions in 19%, and in 16% skin and joint involvement occurred almost simultaneously. The peak age of onset of arthritis in this series was 40–60 years [1].

Clinical subgroups. Psoriatic arthritis is not accompanied by rheumatoid-type nodules. The Moll and Wright classification includes five clinical groups, which often overlap [2,3].

1 Predominantly peripheral mono- or asymmetrical oligoarthritis is the most common form, and often overlooked. An appearance



Fig. 20.29 Psoriatic arthritis, showing peripheral oligoarthropathy with sausage-like digital swelling. (Courtesy of St John's Institute of Dermatology, London, UK.)

similar to low-grade gout, as well as sausage-like swelling of one or more digits (dactylitis) resulting from terminal and proximal interphalangeal joint involvement and flexor sheath synovitis are recognized (Fig. 20.29). Enthesitis—inflammation at the site of tendon insertion into the bone—is common.

2 Predominantly distal interphalangeal arthritis, the well-recognized classical form, but less common than previously emphasized.

3 Predominantly symmetrical, rheumatoid-like, rheumatoid factor-negative polyarthritis, usually less severe than rheumatoid arthritis.

4 'Arthritis mutilans', a relatively uncommon, severely deforming arthritis involving fingers and toes predominantly. Gross osteolysis may cause digital foreshortening and ankylosis (Figs 20.30–20.32).

5 Predominantly axial arthritis: psoriatic spondylitis and/or sacroiliitis, with or without variable peripheral arthropathy. Spinal involvement may be clinically silent, but radiological examination suggests that it may affect about one-third of all cases of psoriatic arthritis. Clinically, this form may involve: (i) both spine and sacroiliac joints, as in idiopathic ankylosing spondylitis; (ii) sacroiliac joints alone; and (iii) spine alone. It may be less disabling than the idiopathic form [3,4].

Several more recent clinical studies have indicated a need to reclassify psoriatic arthritis. In two studies, each involving 100 patients, three subgroups were proposed, any of which may include the classical features of psoriatic arthritis, such as distal interphalangeal joint involvement, dactylitis or spondylitis [5,6].



Fig. 20.30 Arthritis mutilans showing gross digital foreshortening. (Courtesy of St John's Institute of Dermatology, London, UK.)



Fig. 20.31 Arthritis mutilans: osteolysis and bony ankylosis. (Courtesy of Royal London Hospital, London, UK.)

1 Asymmetrical arthritis usually, but not always, involving a small number of joints with few erosions, infrequent deformity and good preservation of function

2 Symmetrical polyarthritis, frequently erosive, deforming and functionally disabling, but distinguished from rheumatoid arthritis by association with distal interphalangeal joint involvement, spondylitis and negative rheumatoid factor (titre less than 1:80)



Fig. 20.32 Arthritis mutilans: gross osteolysis of metatarsal heads and phalanges. Note pencil-in-cup changes at metatarsophalangeal joints. (Courtesy of Royal London Hospital, London, UK.)

3 Predominant spondylitis, similar to ankylosing spondylitis, possibly accompanied by peripheral arthritis but behaving independently of it [6].

Cervical spinal involvement. This is well recognized [7,8] and may be primarily ankylosing in nature or inflammatory and rheumatoid-like [9]. Both forms may be associated with cord or nerve-root compression related to intervertebral subluxation and/or fusion, and neurological deterioration may require surgical stabilization [8,10–13].

Temporomandibular joint involvement. This may manifest as local pain, often aggravated by eating [14,15] and may progress to ankylosis requiring surgical management [16]. Orthopan-tomographical examination showed that 31% of patients with psoriatic arthritis had radiographical changes in the condyle of the temporomandibular joint, as compared with 13% of controls [17]. Computed tomography may reveal changes not visible on conventional radiography [18].

Sternal joint involvement. This is becoming increasingly recognized but is unusual as an initial manifestation [19,20].

Nail involvement. Psoriasis of the nails occurs in about three-quarters of psoriatic patients with arthritis, but only in about one-third of those with skin lesions alone [1,21,22]. The distal and mutilating forms of arthritis are particularly associated with severe nail dystrophy, and the distal joints and nails affected are often but not necessarily correlated in the same digits [22]. All types of nail involvement may occur [23].

Extra-articular features. These occur less frequently than in rheumatoid arthritis. Subcutaneous nodules are not seen, and tendon sheath effusions are uncommon. In contrast, inflammatory eye lesions are common, conjunctivitis being reported to occur in 20%, uveitis in 10%, and episcleritis and keratoconjunctivitis sicca in about 2 and 3%, respectively [24]. Cardiac involvement similar to that seen in ankylosing spondylitis has been reported [25].

References

1 Scarpa R, Oriente P, Pucino A *et al*. Psoriatic arthritis in psoriatic patients. *Br J Rheumatol* 1984; **23**: 246–50.
2 Moll JMH, Wright V. Psoriatic arthritis. *Semin Arthritis Rheum* 1973; **3**: 55–78.
3 Moll JMH. Psoriatic arthropathy. In: Mier PD, van de Kerkhof PCM, eds. *Textbook of Psoriasis*. Edinburgh: Churchill Livingstone, 1986: 55–83.
4 Scarpa R, Oriente P, Pucino A *et al*. The clinical spectrum of psoriatic spondylitis. *Br J Rheumatol* 1988; **27**: 133–7.
5 Kammer GM, Soter NA, Gibson DJ, Schur PH. Psoriatic arthritis: a clinical immunologic and HLA study of 100 patients. *Semin Arthritis Rheum* 1979; **9**: 75–97.
6 Veale D, Rogers S, Fitzgerald O. Classification of clinical subsets in psoriatic arthritis. *Br J Rheumatol* 1994; **33**: 133–8.
7 Kaplan D, Plotz CM, Nathanson L *et al*. Cervical spine in psoriasis and in psoriatic arthropathy. *Ann Rheum Dis* 1964; **23**: 50–6.
8 Daunt SO, Robinson JC. Spontaneous fusion of atlanto-axial dislocation in psoriatic spondylitis. *Clin Rheumatol* 1985; **4**: 465–9.
9 Blau RH, Kaufman RL. Erosive and subluxing cervical spine disease in patients with psoriatic arthritis. *J Rheumatol* 1987; **14**: 111–7.
10 Dzioba RB. Spontaneous atlantoaxial fusion in psoriatic arthritis. *Spine* 1985; **10**: 102–3.
11 Lee S-T, Lui T-N. Psoriatic arthritis with C-1–C-2 subluxation as a neurosurgical complication. *Surg Neurol* 1986; **26**: 428–30.
12 Pease CT, Pozo JL. Atlantoaxial subluxation and spinal cord compression in psoriatic arthropathy (Letter). *Ann Rheum Dis* 1987; **46**: 717–8.
13 Santavirta S, Slätis P, Sandelin J *et al*. Atlantoaxial subluxation in patients with seronegative spondyloarthritis. *Rheumatol Int* 1987; **7**: 43–6.
14 Lundberg M, Ericson S. Changes in the temporomandibular joint in psoriasis arthropathica. *Acta Derm Venereol (Stockh)* 1967; **47**: 354–8.
15 Könönen M. Craniomandibular disorders in psoriatic arthritis: correlations between subjective symptoms, clinical signs, and radiographic changes. *Acta Odontol Scand* 1986; **44**: 369–75.
16 Kudryk WH, Baker GL, Percy JS. Ankylosis of the temporomandibular joint from psoriatic arthritis. *J Otolaryngol* 1985; **14**: 336–8.
17 Könönen M. Radiographic changes in the condyle of the temporomandibular joint in psoriatic arthritis. *Acta Radiol* 1987; **28**: 185–8.
18 Avrahami E, Garti A, Weiss-Peretz J *et al*. Computerized tomographic findings in the temporomandibular joint in patients with psoriatic arthritis. *J Rheumatol* 1986; **13**: 1096–8.
19 Becker NJ, de Smet AA, Cathcart-Rake W *et al*. Psoriatic arthritis affecting the manubriosternal joint. *Arthritis Rheum* 1986; **29**: 1029–31.
20 Nicolas JF, Larbre JP, Faure M *et al*. Psoriatic arthritis affecting the sternoxiphoid joint. *J Am Acad Dermatol* 1988; **4**: 752–4.
21 Wright V. Psoriasis and arthritis. *Br J Dermatol* 1957; **69**: 1–10.
22 Baker H, Golding DN, Thompson M. The nails in psoriatic arthritis. *Br J Dermatol* 1964; **76**: 549–54.
23 Eastmond CJ, Wright V. The nail dystrophy of psoriatic arthritis. *Ann Rheum Dis* 1979; **38**: 226–8.
24 Lambert JR, Wright V. Eye inflammation in psoriatic arthritis. *Ann Rheum Dis* 1976; **35**: 354–6.
25 Reed WB. Psoriatic arthritis: a complete clinical study of 86 patients. *Acta Derm Venereol (Stockh)* 1961; **41**: 396–403.

Laboratory findings. The most important serological feature is the negative test for rheumatoid factor, particularly in patients with distal and mutilating arthritis. In patients with psoriatic arthritis of the rheumatoid type, about one-quarter had a positive test or a test that fluctuated between positive and negative [1]. Some of these patients probably represent the coincidental association of psoriasis and rheumatoid arthritis, but a weakly or intermittently positive rheumatoid factor occurs in approximately

5% of the normal population [2] and should not necessarily lead to the diagnosis of rheumatoid arthritis. Other reported laboratory abnormalities, such as anaemia, raised ESR and C-reactive protein, transient leukocytosis, and raised immunoglobulin levels, most consistently IgA, have been reviewed [3,4]. It has been concluded that none of these is sufficiently specific to contribute to diagnosis, management or prognostic evaluation [4]. The conflicting reports of the association between hyperuricaemia and psoriasis are outlined above. Antinuclear antibodies have been reported as both positive and negative [3], but in an American study of 1285 patients they were found to have little predictive value [5].

Histopathology. The histopathologies of psoriatic and rheumatoid arthritis appear to be similar, except that characteristic rheumatoid granulomas have not been found and there may be more fibrosis [6,7] and vascular changes [8] in the psoriatics. In spite of these possible differences, synovial biopsy usually has no place in the routine clinical management of psoriatic arthritis [4].

References

1 Roberts MET, Wright V, Hill AGS *et al*. Psoriatic arthritis: follow-up study. *Ann Rheum Dis* 1976; **35**: 206–12.
2 Waller M, Toone EC. Normal individuals with positive tests for rheumatoid factor. *Arthritis Rheum* 1968; **11**: 50–5.
3 Laurent MR. Psoriatic arthritis. *Clin Rheum Dis* 1985; **11**: 61–85.
4 Moll JMH. Psoriatic arthropathy. In: Mier PD, van de Kerkhof PCM, eds. *Textbook of Psoriasis*. Edinburgh: Churchill Livingstone, 1986: 55–83.
5 Stern RS. The epidemiology of joint complaints in patients with psoriasis. *J Rheumatol* 1985; **12**: 315–20.
6 Bauer W, Bennett GA, Zeller JW. Pathology of joint lesions in patients with psoriasis and arthritis. *Trans Assoc Am Phys* 1941; **56**: 349–52.
7 Sherman M. Psoriatic arthritis: observations on the clinical, roentgenographic and pathological changes. *J Bone Joint Surg Am* 1952; **34**: 831–52.
8 Espinosa LR, Vasey FB, Espinoza CG *et al*. Vascular changes in psoriatic synovium. *Arthritis Rheum* 1982; **25**: 677–84.

Radiological changes [1–3]. The changes may be indistinguishable from those of rheumatoid arthritis: local demineralization, narrowing of joint spaces, articular erosion of varying degree and soft-tissue swellings. Atypical features include destructive changes in the terminal interphalangeal joints, a tendency to hypertrophic changes and absence of generalized demineralization.

In the distal type of psoriatic arthropathy, early changes may consist only of minimal 'fluffiness' and osteoporosis of the distal phalanx, but gross destruction eventually occurs. Four characteristic signs of psoriatic arthropathy, seen in one controlled series [1], were:

1 A destructive distal interphalangeal arthropathy—bony ankylosis of the interphalangeal joints
2 Destruction of the interphalangeal joints with abnormally wide joint spaces and sharply demarcated adjacent bony surfaces
3 Destruction of the interphalangeal joint of the great toe with bony proliferation of the distal phalanx
4 Resorption of tufts of the distal phalanges of hands and feet (uncommon).

In arthritis mutilans, the joint changes are widespread. The 'opera-glass hand', in which the fingers can be pulled in and out, results from gross destruction and absorption of the bones. The heads of metacarpals and metatarsals may completely disappear, leaving a tapered bone looking like a sharpened pencil. Such gross osteolysis may be followed by bony fusion (Figs 20.31 & 20.32).

Intermittent hydrarthrosis may occur. Sacroiliac changes similar to those of ankylosing spondylitis are common [4–6]. Syndesmophytes and calcification of the interspinous ligaments are also seen [6]. Cervical changes including apophyseal sclerosis or joint narrowing, and calcification of the anterior ligament, are common [7], and there is a tendency to posterior fusion of the cervical vertebrae [3]. Paravertebral ossification of the lumbar and thoracic regions may occur more laterally in psoriasis than in spondylitis [8].

Magnetic resonance imaging has enhanced the ability to identify early changes of psoriatic arthritis and to visualize enthesitis [9,10].

References

1 Avila R, Pugh DG, Slocumb CH *et al*. Psoriatic arthritis: a roentgenologic study. *Radiology* 1960; **75**: 691–702.
2 Lassus A, Mustakallio KK, Laine V. Psoriasis arthropathy and rheumatoid arthritis. *Acta Rheum Scand* 1964; **10**: 62–8.
3 Moll JMH, Wright V. Psoriatic arthritis. *Semin Arthritis Rheum* 1973; **3**: 55–78.
4 Dixon AJ, Lience E. Sacro-iliac joint in adult rheumatoid arthritis and psoriatic arthropathy. *Ann Rheum Dis* 1961; **20**: 247–57.
5 Golding DN, Baker H, Thompson M. Arthritis mutilans and psoriasis. *Ann Phys Med* 1963; **7**: 133–9.
6 Jajic I. Radiological changes in the sacro-iliac joints and spine of patients with psoriatic arthritis and psoriasis. *Ann Rheum Dis* 1968; **27**: 1–6.
7 Kaplan D, Plotz CM, Nathanson L *et al*. Cervical spine in psoriasis and in psoriatic arthritis. *Ann Rheum Dis* 1964; **23**: 50–6.
8 Bywaters EGL, St Dixon AJ. Paravertebral ossification in psoriatic arthritis. *Ann Rheum Dis* 1965; **24**: 313–31.
9 Tan AL, Benjamin M, Toumi H *et al*. The relationship between the extensor tendon enthesis and the nail in distal interphalangeal joint disease in psoriatic arthritis—a high-resolution MRI and histological study. *Rheumatol* 2007; **46**: 253–6.
10 Marzo-Ortega H, Tanner SF, Rhodes LA *et al*. Magnetic resonance imaging in the assessment of metacarpophalangeal joint disease in early psoriatic and rheumatoid arthritis. *Scan J Rheumatol* 2009; **38**: 79–83.

Differential diagnosis. This has been reviewed in detail elsewhere [1]. One of the subgroups of psoriatic arthritis may be clinically indistinguishable from rheumatoid arthritis. As a weakly or intermittently positive rheumatoid factor occurs in 5% of the normal population [2], this should not necessarily lead to the diagnosis of rheumatoid arthritis. Gout may be simulated, especially if the onset is acute and monoarticular, or if widespread psoriasis is associated with hyperuricaemia. Ankylosing spondylitis may be similar, but the onset tends to be later, peripheral involvement is more common, and the arthritis does not necessarily begin in the spine. The acute Heberden's node of osteoarthritis may cause confusion, and distinction from Reiter's disease may be difficult or impossible.

Treatment. Treatment follows the general lines of management of inflammatory polyarthritis, and is best supervised by a rheumatologist. Assessment of efficacy of therapies for psoriatic arthritis is hindered by inexact definition of the condition, the variable clinical presentation and lack of validated outcome measures. The treatment of psoriatic arthritis has been recently reviewed [1].

Symptomatic treatment. Mild arthritis can usually be controlled with NSAIDs. There is concern that NSAIDs may exacerbate the

skin lesions of psoriasis [2,3], although a randomized controlled trial showed no worsening of psoriasis in patients treated with the NSAID nimesulide [4]. Cyclo-oxygenase-2 (COX-2) selective inhibitors are effective but, as with traditional NSAIDs, caution should be exercised in the elderly and those with impaired renal function.

Systemic glucocorticosteroids are not recommended for the long-term treatment of psoriatic arthritis not only because of the well-recognized side effects but also because chronic glucocorticosteroid use can make psoriasis more labile and withdrawal can on occasion lead to a rebound pustular flare [2,5]. Intra-articular injections of glucocorticosteroid are used to treat monoarthritis [6].

Disease-modifying antirheumatic drugs (DMARDs). Ascertaining effectiveness of DMARDs in the management of psoriatic arthritis is complex [1]. The clinical subgroups respond differently, for instance axal involvement associated with HLA-B27 has a relatively poor response to treatment [7]. The most commonly used DMARDs for psoriatic arthritis are methotrexate, ciclosporin and sulfasalazine although there are few randomized controlled trials.

Methotrexate is the most widely used of the DMARDs for psoriatic arthritis—particularly as it is effective for the skin lesions, and is amenable to combination with other DMARDs to enhance efficacy. Only two randomized controlled trials provide evidence [8,9], one [8] used parenteral injections of high-dose methotrexate (1–3 mg/kg)—a dose probably too toxic. A second study [9] showed that methotrexate 7.5–15 mg/week was superior to placebo only in physician assessment of arthritis. Thus, the data imply that methotrexate is beneficial for synovitis but there is no evidence of benefit for axial disease.

Ciclosporin is probably less effective than methotrexate for the treatment of psoriatic arthritis but evidence is mainly accrued from open studies. In an 18-week open study [10], ciclosporin 4.8 mg/kg/day benefited psoriatic arthritis but the effect was less marked than for the skin lesions. In a trial comparing methotrexate to ciclosporin [11], ciclosporin 3–5 mg/kg/day produced significant improvement in clinical and serological measures of severity of psoriatic arthritis. An Italian study [12] found that ciclosporin was more effective than either sulfasalazine or placebo in reducing a variety of clinical measures of severity. Long-term use of ciclosporin may control progression of radiological damage in peripheral joints [13].

Sulfasalazine has been subject to more open trials and randomized controlled trials than either methotrexate or ciclosporin for the treatment of psoriatic arthritis. Despite encouraging results from open studies and one short (8-week) study [14], this promise has not been substantiated by most randomized controlled trials [1,15,16]. Overall, the evidence suggests that sulfasalazine has a small beneficial effect on peripheral synovitis, particularly pain [17], but whether efficacy is enhanced by increasing the daily dosage above 3 g is unclear [1,18]. Axial disease is not benefited [1].

Gold salts (oral auranofin) and intramuscular sodium thiomalate are used to treat psoriatic arthritis [19,20]—on the evidence sodium thiomalate appears to be the better of the two, but less effective than methotrexate [21,22]. Occasional exacerbation of the skin lesions of psoriasis by gold salts can occur [23].

A variety of other DMARDs have been investigated and advocated for the treatment of psoriatic arthritis, none of which has been subject to good randomized controlled trials. Leflunomide (a pyrimidine synthesis inhibitor effective for rheumatoid arthritis) appeared to have some benefit in psoriatic arthritis in both the short term (3 months) and long term (2 years) in a longitudinal study of eight patients [24].

A limited randomized controlled trial of azathioprine versus placebo showed benefit [25].

Biological therapies. The most significant advance in the management of psoriatic arthritis has been the introduction of the TNF-antagonist biologics therapies. Not only are TNF-antagonists capable of producing significant improvement in joint disease, there is good evidence that they can prevent joint destruction. These data hold firm for infliximab, adalimumab, etanercept and golimumab [26–29]. The T-cell antagonist alefacept is modestly effective [31]. The anti-IL12/IL23p40 ustekinumab is also effective for psoriatic arthritis but whether this is comparable to the TNF-antagonists remains to be determined [31].

Surgery. The place of surgery has been reviewed [32,33]. In spite of past reluctance to perform elective surgical procedures in view of perceived risks of infection, a review of 41 orthopaedic operative procedures and 54 other surgical procedures in patients with psoriasis and arthritis revealed a low prevalence of wound sepsis and other complications. It was therefore suggested that elective surgery should not be withheld from these patients [32]. Such procedures might include joint prosthesis and cervical spine stabilization, and the use of digital distraction lengthening and bone grafting for severe arthritis mutilans has also been described [33].

Prognosis. A 10-year follow-up study suggested that psoriatic arthritis produced less pain and disability than rheumatoid disease [34]. Excluding the arthritis mutilans group, in this study 30% lost no time off work, only 3% had more than a total of 1 year off work in 10 years, and many patients showed little or no radiological deterioration. Thus, it is usually perceived that psoriatic arthritis may be a mild disease, and that the descriptions of mutilating digital disease and occasional severe spondylitis may give a false impression of the usual prognosis in these patients. However, in a Canadian study of 220 patients with psoriatic arthritis, deforming erosive arthropathy was found in 40% of cases. The concept that psoriatic arthritis is often a benign arthropathy was therefore challenged [35]. Indicators of poor prognosis include younger age at onset, extensive skin involvement, polyarticular synovitis, HIV infection, high ESR at presentation, large numbers of effusions and association with HLA B27, B39 and DLW3 [1,36].

References

1 Gladman DD. Psoriatic arthritis. *Dermatol Ther* 2009; **22**: 40–55.

2 Griffiths CEM. Therapy for psoriatic arthritis: sometimes a conflict for psoriasis. *Br J Rheumatol* 1997; **36**: 409–10.

3 Powles AV, Griffiths CEM, Seifert MH, Fry L. Exacerbation of psoriasis by indomethacin. *Br J Dermatol* 1987; **117**: 799–800.

4 Sarzi-Puttini P, Santandrea S, Boccassini L *et al*. The role of NSAIDs in psoriatic arthritis: evidence from a controlled study with nimesulide. *Clin Exp Rheumatol* 2001; **19**: S17–S20.
5 Baker H, Ryan TJ. Generalized pusutular psoriasis: a clinical and epidemiological study of 104 cases. *Br J Dermatol* 1968; **80**: 771–8.
6 Wright V. Psoriatic arthritis. In: Kelly WN, Harris ED, Ruddy S, Sledge CB, eds. *Textbook of Rheumatology*, Philadelphia: Saunders, 1989: 1021–31.
7 Scarpa R. Psoriatic arthritis: is something changing? *Adv Exp Med Biol* 1999; **455**: 207–14.
8 Black RL, O'Brien WM, Van Scott EJ *et al.* Methotrexate therapy in psoriatic arthritis. *JAMA* 1964; **189**: 743–7.
9 Willkens RF, Williams HJ, Ward JR *et al.* Randomized, double-blind, placebo-controlled trial of low-dose pulse methotrexate in psoriatic arthritis. *Arthritis Rheum* 1984; **27**: 376–81.
10 Raffayova H, Rovensky J, Malis F. Treatment with cyclosporin in patients with psoriatic arthritis: results of clinical assessment. *Int J Clin Pharmacol Res* 2000; **20**: 1–11.
11 Spadaro A, Riccieri V, Sili-Scavalli A *et al.* Comparison of cyclosporin A and methotrexate in the treatment of psoriatic arthritis: a 1 year prospective study. *Clin Exp Rheumatol* 1995; **13**: 589–93.
12 Salvarani C, Macchioni P, Olivieri I *et al.* A comparison of ciclosporin, sulphasalazine and symptomatic therapy in the treatment of psoriatic arthritis. *J Rheumatol* 2001; **28**: 2274–82.
13 Macchioni P, Buicardi L, Cremonesi T *et al.* The relationship between serum-soluble interleukin-2 receptor and radiological evolution in psoriatic arthritis patients treated with cyclosporin-A. *Rheumatol Int* 1998; **18**: 27–33.
14 Gupta AK, Grober PS, Hamilton TA *et al.* Sulfasalazine therapy for psoriatic arthritis: a double-blind, placebo-controlled trial. *J Rheumatol* 1995; **22**: 894–8.
15 Combe B, Goupille P, Kuntz JL *et al.* Sulphasalazine in psoriatic arthritis: a randomized, multicentre, placebo-controlled study. *Br J Dermatol* 1996; **35**: 664–8.
16 Clegg DO, Reda DJ, Mejias E *et al.* Comparison of sulfasalazine and placebo in the treatment of psoriatic arthritis. A Department of Veterans Affairs Cooperative Study. *Arthritis Rheum* 1996; **39**: 2013–20.
17 Dougados M, van der Linden S, Leirisalo-Repo M *et al.* Sulfasalazine in the treatment of spondyloarthropathy: a randomized, multicenter, double-blind, placebo-controlled study. *Arthritis Rheum* 1995; **35**: 618–27.
18 Pitzalis C, Pitpitone N. Psoriatic arthritis. *J R Soc Med* 2000; **93**: 412–5.
19 Bruckle W, Dexel T, Grasedyck K, Schaffenkirchner M. Treatment of psoriatic arthritis with auranofin and gold sodium thiomalate. *Clin Rheumatol* 1994; **13**: 209–16.
20 Palit J, Hill J, Capell HA *et al.* A multicentre, double-blind comparison of auranofin, intramuscular gold, thiomalate and placebo in patients with psoriatic arthritis. *Br J Rheumatol* 1990; **29**: 280–3.
21 Carette S, Calin A, McCafferty JP *et al.* A double-blind placebo controlled study of auranofin in patients with psoriatic arthritis. *Arthritis Rheum* 1989; **32**: 158–65.
22 La Caille D, Steing HB, Raboud J, Klinkhoff AV. Long-term therapy of psoriatic arthritis: intramuscular gold or methotrexate? *J Rheumatol* 2000; **27**: 1922–7.
23 Smith DL, Wernick R. Exacerbation of psoriasis by chrysotherapy. *Arch Dermatol* 1991; **127**: 268–70.
24 Liang GC, Barr WG. Long-term follow-up of the use of leflunomide in recalcitrant psoriatic arthritis and psoriasis. *Arthritis Rheum* 2001; **44** (9S): S121.
25 Levy J, Paulus HE, Barrett EV *et al.* A double-blind controlled evaluation of azathioprine treatment in rheumatoid arthritis and psoriatic arthritis (Abstract). *Arthritis Rheum* 1972; **15**: 116–7.
26 Mease PJ, Goffe BS, Metz J *et al.* Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomized trial. *Lancet* 2000; **356**: 385–90.
27 Marzo-Ortega H, McGonagle D, O'Connor P, Emery P. Efficacy of etanercept in the treatment of the entheseal pathology in resistance spondylarthropathy: a clinical and magnetic resonance imaging study. *Arthritis Rheum* 2001; **44**: 2112–7.
28 Antoni CE, Kavanaugh A, Kirkham B *et al.* Sustained benefits of infliximab therapy for dermatologic and articular manifestations of Psoriatic Arthritis: results from the infliximab multinational Psoriatic Arthritis Controlled Trial (IMPACT). *Arthritis Rheum* 2005; **52**: 1227–36.
29 Hutas G. Golimumab, a fully human monoclonal antibody against TNFalpha. *Curr Opin Mol Ther* 2008: **10**: 393–406.
30 Kraan MC, van Kujk AW, Dinant HJ *et al*. Alefacept treatment in psoriatic arthritis: reduction of the effector T-cell population in peripheral blood and synovial tissue is associated with improvement of clinical signs of arthritis. *Arthritis Rheum* 2002; **46**: 2776–84.
31 Gottlieb AB, Menter A, Mendelsohn A *et al*. Ustekinumab, a human interleukin 12/23 monoclonal antibody for psoriatic arthritis: randomized, double-blind placebo-controlled, crossover trial. *Lancet* 2009; **373**: 633–40.
32 Lambert JR, Wright V. Surgery in patients with psoriasis and arthritis. *Rheumatol Rehabil* 1979; **18**: 35–7.
33 Walton RL, Brown RE, Giansiracusa DF. Psoriatic arthritis mutilans: digital distraction lengthening—pathophysiologic and current therapeutic review. *J Hand Surg* 1988; **13A**: 510–5.
34 Roberts MET, Wright V, Hill AGS *et al.* Psoriatic arthritis: follow-up study. *Ann Rheum Dis* 1976; **35**: 206–12.
35 Gladman DD, Shuckett R, Russell ML *et al.* Psoriatic arthritis (PSA): an analysis of 220 cases. *QJM* 1987; **62**: 127–41.
36 Gladman DD, Farewell VT. The role of HLA antigens as indicators of disease progression in psoriatic arthritis: multivariate relative risk model. *Arthritis Rheum* 1995; **38**: 845–50.

CHAPTER 21
Pruritus

M.W. Greaves
St John's Institute of Dermatology, St Thomas' Hospital, London, UK

Introduction and classification, 21.1
Epidemiology, 21.1
Measurement, 21.2
Pathophysiology, 21.2
Central itch, 21.3
Peripheral mediators of itching in skin diseases, 21.3
Histamine and its receptors, 21.3
Acetyl choline, 21.4
Substance P, 21.4
Calcitonin gene-related peptide (CGRP), 21.4
Opioid peptides, 21.4
Proteases, 21.4
Cytokines, 21.5
Prostaglandins and other eicosanoids, 21.5
Neurotrophins, 21.5
Scratching, 21.5
Itching in non-inflamed skin, 21.5
Itching in systemic disease, 21.7
Chronic renal disease, 21.7
Cholestasis, 21.9
Iron deficiency, 21.10
Polycythaemia vera, 21.10
Endocrine disease, 21.11
Malignancy, 21.11
Aquagenic pruritus, 21.11
Pruritus of senescence, 21.12
Psychogenic pruritus, 21.12
Postmenopausal pruritus, 21.13
Pruritus of atopic dermatitis, 21.13
Acquired immune deficiency syndrome, 21.14
Pruritus in pregnancy, 21.14
Pruritus ani and pruritus vulvae, 21.15
Important miscellaneous causes of intense itching, 21.15
Hydroxyethyl starch, 21.15
Pemphigoid nodularis, 21.15
Notalgia paraesthetica, 21.15
Brachioradial pruritus, 21.15
Anorexia nervosa, 21.16
Clinical and laboratory investigation of generalized pruritus, 21.16
Management of itching, 21.16
Ultraviolet phototherapy for generalized pruritus, 21.18

Introduction and classification

Pruritus (itching), the predominant symptom of skin disease and an important symptom of systemic disease, is now, after years of comparative neglect, the subject of active investigation. Itch can be defined subjectively as a poorly localized, non-adapting, usually unpleasant sensation which elicits an immediate desire to scratch. Itch has recently been classified by Twycross *et al*. [1] as *pruritoceptive* (cutaneous, e.g. scabies, urticaria), *neuropathic* (due to lesions of afferent pathways of the nervous system, e.g. peripheral neuritis, nerve entrapment, brain tumours), *neurogenic* (due to centrally acting mediators which do not damage the central nervous system, e.g. morphine, opioid peptides of cholestasis) and *psychogenic*, including delusional parasitosis.

Itch and pain can readily be dissociated since the former elicits the scratch reflex, but the latter causes withdrawal and since morphine relieves pain but aggravates itch. Although they broadly share similar overall molecular mechanisms and neurophysiological pathways, new evidence indicates the existence of separate dedicated neurones for itch in both the peripheral and central pathways [2,3].

When itching is caused by a low-intensity mechanical stimulation moving across the skin involving weak activation of mechanoreceptors, the itch sensation is immediate, often provokes uncontrollable laughter, persists for no longer than the stimulus and is interpreted as a 'tickle' [4]. Chronic itch is multidimensional, the sensation being variably modified by emotional and cognitive components. In dry skin and skin of some atopics, mechanical stimulation may trigger a more persistent itching sensation (alloknesis) [5]. Prurigo is a term frequently incorrectly used to describe chronic itching of any cause. As originally defined by Hebra [6], prurigo denotes papules induced by scratching. On this basis, prurigo would include 'scratch prurigo', a rarely used synonym for symptomatic dermographism and, at the other end of the spectrum, chronic inflammatory and pigmented papules due to long-continued or repeated scratching (prurigo nodularis of Hyde) [7].

When itching is a symptom of skin disease it is generally independent of external stimulation. The quality of itch varies greatly, ranging from burning, through pricking, to sensations of insects crawling over the skin. The psychophysiological basis of these differences remains unclear. Teleologically, itching, with resultant scratching, is of possible biological value in combating parasitic infestation. Although often publicly perceived as a trivial—even humorous—disability or even, with its associated scratching, as a pleasurable personal indulgence, it is more often socially disabling and a cause of serious impairment of quality of life.

Epidemiology

We all itch from time to time, but the prevalence of chronic pruritus is unknown. One study in a UK urban community indicated a prevalence of 20% [8] but the prevalence in a Norwegian city setting is reported as about 8% [9]. In one recent retrospective study of patients with chronic pruritus [10], 35.6% of patients with

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

generalized pruritus had an underlying systemic disease and in 7.6% the cause was unknown. The remainder had skin disease-associated pruritus.

Measurement

Results from animal models of pruritus need to be interpreted with caution. Hind limb scratching in response to intradermal injection of a pruritogen has been widely used [11], but whether the scratching is in response to pain or itch is unclear [12]. Methods used in humans include visual analogue scales (VAS) and recording of scratch movements [13] using limb movement meters. The 'Symtrack' computerized continuous itch-rating system, which is based on the VAS, or a variant of it, is the most widely used [14]. However, results obtained with a new method for quantifying scratching, in which a piezoelectrical device is attached to the middle fingernail, have been impressive [15].

Pathophysiology

Significant progress has recently been made in elucidating the neurophysiological pathways for itch. Although specialized nerve endings have been identified for a wide range of stimuli [16], no specific receptor structure has been identified for itch. It is generally agreed that itch (and pain) are received by unspecialized free nerve endings [17], identified immunohistochemically by protein gene product (PGP) 9.5 or by neurone-specific enolase [18] and located close to the dermal–epidermal junction. Itch nerve endings are unmyelinated, confined to the skin and cornea, and are members of the polymodal nociceptor class. That itching is alleviated by cooling and menthol but aggravated by warmth is a common experience now explained by the close association of temperature-sensitive transient receptor potential (TRP) ion channels [19] with afferent itch transmitting nociceptor neurone terminals. Interestingly, other members of this same class of receptors (TRPV1; vanilloid receptors) are activated and desensitized by capsaicin (the active principle of chilli), now widely used topically to alleviate localized pruritus [20]. Keratinocytes also express TRPV1 and these receptors are greatly up-regulated in prurigo nodularis [21]. The co-localization of cannabinoid receptors (CB1) with TRPV1 in sensory neurones and the ability of endocannabinoids to activate TRPV1 [22] raises the possibility of functional interactions between cannabinoids and TRP channels in the modulation of itch.

Apart from TRPV1 ion channels, keratinocytes also express voltage-gated ATP channels, adenosine receptors, cannabinoid receptors, opioid receptors and PAR-2 (proteinase activated receptors-2) [23]. They also express several itch-modulating mediators, prompting the provocative notion that the epidermis itself may constitute the hitherto elusive 'itch receptor'.

Itch-transmitting, polymodal, unmyelinated C fibres enter the dorsal horn of the grey matter of the spinal cord, synapse there with secondary neurones, which cross over to the contralateral spinothalamic tract and ascend to the thalamus. There, tertiary neurones relay itch to the level of conscious perception in the cerebral cortex.

There is now convincing evidence that dedicated itch-transmitting neurones exist in both peripheral and central afferent pathways [2,3]. Microneurographic technology using ultra-fine glass electrodes, which can be inserted into individual afferent nociceptor neurones, has enabled electrical recordings to be made from individual polymodal C fibres in peripheral cutaneous nerve fascicles. Stimulation of these neurones using histamine iontophoresis to cause itching has resulted in identification of a small (less than 5% of the total) subset of slowly conducting C fibres distinct from, and with a larger receptor field than, mechanosensitive polymodal neurones. However, it is unlikely that these mechanoinsensitive neurones represent the only afferents involved in itch transmission. Itch due to electrical stimulation seems to involve a different subset of afferent neurones stimulation, which causes itch but no axon reflex flare [24]. Using the microneurography technique, dedicated histamine-sensitive secondary transmission neurones have also been demonstrated in the lateral spinothalamic tract of the cat [3]. It is evident that specialized itch-specific afferent pathways project this sensation from the skin to the thalamus.

Recent studies, using functional positron-emission tomography and functional magnetic resonance imaging to record activation of cortical responses to itching and associated scratching, suggest the involvement of the anterior cingulate and insular cortex in the recognition of itch sensation at conscious levels [25–27], whilst the premotor cortical areas participate in intention to scratch.

The relief obtained by scratching an itch is centrally mediated. Pain induced by noxious heat or scratching diminishes itch by a central, probably gated, mechanism [28,29]. The effect of scratching is short lived but a more prolonged relief may be obtained by cutaneous electric field stimulation, which can be used therapeutically [30]. There is also evidence that itch may be modulated by descending pathways originating in the periacqueductal grey [25]. Ascending and descending pathways are represented in a simplified form in Fig. 21.1.

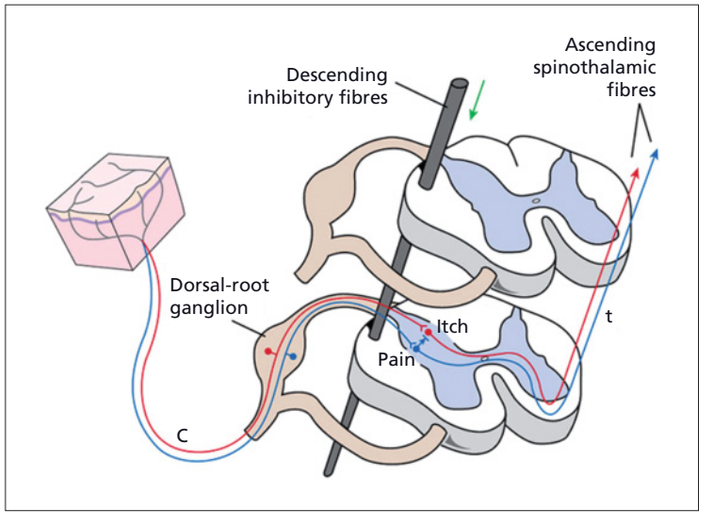


Fig. 21.1 Ascending and descending pathways modulating itch. C, unmyelinated slow-conducting C fibres; t, transmission neurone. (Reproduced with permission from Elsevier Science Ltd, *Lancet* 2003; **361**: 690–4.)

Central itch

Psychoneurophysiological aspects of itching are complex and poorly understood. They have led to the important concept of 'central itch', that is itching which is perceived as occurring in the skin but which actually originates in the central nervous system due to dysfunctional processing of sensory information in the central pathways. Melzack and Wall [28] proposed the involvement of large, fast-conducting, myelinated sensory fibres in modulation of the discharge of the unmyelinated itch- or pain-transmitting fibres via the substantia gelatinosa ('gate' control of pain). According to this proposal, itch is due to a combination of peripheral excitation and central disinhibition. Scratching, by activating inhibitory fast-conducting myelinated fibres, closes the 'gate' by activation of suppressor neurones of the substantia gelatinosa and reduces the itch. Alloknesis (slight mechanical stimulation of skin causing intense itching) characteristically occurs in some patients with atopic eczema. It is thought to be due to excitation of central itch-transmission neurones due to reduced gating [5,28]. Chronic pruritus may also cause 'sensitization' of central itch pathways so that scratching can enhance itching rather than allaying it [31].

Opioid peptides have important peripheral actions, but also have an even more crucial central role. Morphine, administered spinally or epidurally, as well as alleviating pain, frequently causes intense itching [32–34], especially of the face, without visible inflammatory changes, and this symptom is rapidly relieved by intravenous naloxone or other opioid peptide μ-receptor antagonists [33–35]. Thus, the presence of opioid peptides and their μ-specific receptors, which modulate function of calcium channels specifically on unmyelinated C fibres in the central nervous system [36], provides a central itch- and pain-regulatory mechanism which is capable of therapeutic manipulation. Although μ-opioid receptor ligation causes central pruritus, κ-opioids are antipruritic so that central pruritus may result from an imbalance of the two systems [37].

Peripheral mediators of itching in skin diseases

Itch can be evoked or augmented by a variety of mediators (Table 21.1). That peripheral pharmacological mediators play a key role in the production of itching in inflammatory skin disease, originally proposed by Lewis as his 'H-substances' [38], is supported by several lines of evidence. These include the ability of a wide range of naturally occurring pharmacological agents, including histamine and proteases, to reproduce the sensation of itch on injection into skin, the ability of antagonists of these agents to reduce itching and the regular experimental recovery of mediators known to be capable of causing or enhancing itching from inflamed pruritic skin. However, it must be appreciated that not all forms of itching involve release of peripheral mediators. Low-grade mechanical and electrical stimuli and the 'dry itch' of senescent skin may not involve peripheral mediators, although in these cases pruritus is likely to be peripheral rather than central. Nevertheless, it is a reasonable assumption that peripheral mediators cause itching in the majority of inflammatory dermatoses.

Table 21.1 Important mediators and receptors for itch.

Mediator	Receptor(s) involved in itch	Function in itch
Histamine	H_1; possibly H_4	Pruritus of urticaria, controversial role in atopic eczema
Acetyl choline	Muscarinic acetyl choline receptors	Possibly in itch of atopic dermatitis
Substance P	Neurokinin (NK)	Prime mast cells for release of histamine and other mediators
Calcitonin gene-related peptide (CGRP)	CGRP receptors	Sensitization of itch-receptive neurone terminals
Opioid peptides	μ-opioid (κ-opioid receptors are anti-itch)	Cause central itch, especially in cholestasis
Proteases	Proteinase-activated receptor-2 (PAR-2)	Evokes itch by neurogenic mechanism involving release of substance P
Neurotrophins	Trk a, b, c; NT3, NT4	Neurotrophin levels elevated in atopic eczema, sensitizes itch-receptive neurones
Prostaglandin E	PGE receptors	Sensitize itch receptors to pruritogenic action of histamine
Cytokines	Receptor mediated?	Indirect via other mediators?

Histamine and its receptors

Histamine causes severe itching if injected or iontophoresed into skin, or if it is applied to superficially abraded skin, although it produces pain if injected more deeply into skin. At present, four subclasses of histamine receptors are recognized. The recently described histamine H_3 subclass behave as autoreceptors, regulating release and biosynthesis of histamine in brain slices and certain other tissues, but they have yet to be positively identified in skin [39]. Both H_1 and H_2 receptors have been characterized in human skin using specific H_1- and H_2-receptor agonists and antagonists, and these studies have consistently implicated histamine H_1 but not H_2 receptors in histamine-induced itching [40]. Thus, there is no theoretical basis for the use of H_2 antagonists (cimetidine, ranitidine) in the suppression of itching caused by histamine. In the mouse, ligation of H_4 receptors induces intense scratching [41] but whether these receptors are important in human skin is unclear.

Cutaneous responses to histamine may not be due solely to the direct actions of histamine. Recent work on the kinetics of the inflammatory responses of skin to histamine raises the possibility that some of these may be mediated indirectly by hitherto unrecognized substances whose release or formation is evoked by histamine [42]. The majority of histamine released in skin as a consequence of injury originates from the dermal mast cells. Evoked release of histamine and other mast-cell mediators is a consequence of an energy-dependent signal-transduction process. That alternative sources of histamine-evoked itching may exist in skin cannot be ruled out. A recent immunohistochemical study in

rat skin [43] has clearly demonstrated immunoreactive histaminergic nerves, although this phenomenon has yet to be reported in human skin.

Histamine has been recovered directly from involved skin in a number of inflammatory dermatoses. In cold urticaria, release of histamine into the venous blood effluent from the cold-challenged limb consistently reflects the onset, development and regression of itching and other local changes occurring following cold exposure. Suppression of evoked histamine release by oral doxantrazole treatment also suppressed itching, but not wealing, in patients with cold urticaria [44]. Histamine has also been recovered from affected skin in ultraviolet-induced inflammation [45] and atopic eczema [46]. Further evidence of the involvement of histamine in inflammatory dermatoses derives from the well-known symptomatic relief obtained in some of these by systemic H_1 antihistamine treatment, although the sedative effect of the traditional H_1 antihistamines has been claimed to be at least as important as the antihistaminic action in atopic eczema [47].

Acetyl choline

Acetyl choline behaves as a pruritic in atopic eczema via muscarinic receptors, although it does not cause pruritus in healthy subjects [48]. This may explain the pruritus commonly experienced by atopic eczema patients when they sweat.

Substance P

In view of their location in unmyelinated afferent nerve fibres in skin, neuropeptides are candidate mediators of itching in inflammatory dermatoses. Substance P, an 11-amino-acid neuropeptide, causes redness, wealing and itching [49,50], mainly via NK1 receptors. Immunoreactive substance P is present in normal skin and in increased amounts in inflamed, itchy skin [51]. Of special interest is the fact that—unlike anti-IgE, compound 48/80 and other mast-cell degranulators—substance P selectively and rapidly releases histamine but little or no prostaglandin D_2 or other cutaneous mast cell products from human, isolated, cutaneous mast cells *in vitro* [52]. It seems likely that this neuropeptide has a priming function on histamine release evoked by other mast cell activators, including specific antigen–IgE interaction [53]. Recent work has shed further light on links between dermal mast cells and afferent C neurones (Fig. 21.2). It is now recognized that substance-P-expressing neurones are in close and functional proximity to mast cells in the skin [54]. Tryptase released by activated mast cells acts on PAR-2 (proteinase activated receptor-2) located on C neurone terminals [55]. This results in release of vasoactive peptides, including substance P. As already indicated, substance P can activate mast cells, thus closing the loop. Topical capsaicin application, which is known to deplete substance P from sensory nerve endings, abolishes pain and itch [56]. Substance P is co-localized with other neuropeptides, including calcitonin gene-related peptide (CGRP) and vasoactive intestinal peptide (VIP), in cutaneous human sensory nerve endings, but the involvement of CGRP and VIP in itch has not been fully explored. Substance P is synthesized in the dorsal root ganglion of nociceptor C fibres and transmitted peripherally in granules.

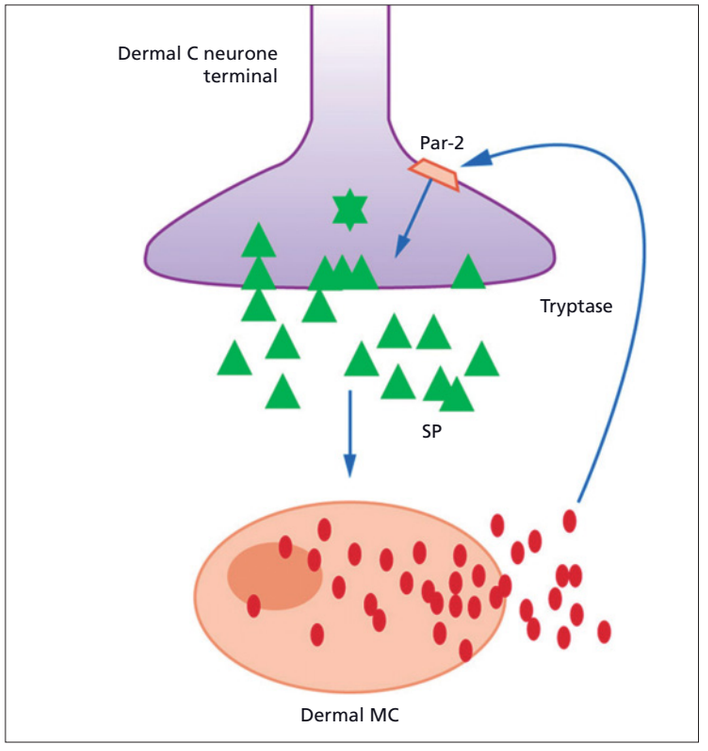


Fig. 21.2 Functional links between C neurone terminals and dermal mast cells: role of proteinase-activated receptor-2 (PAR-2). SP, substance P; MC, mast cell.

Calcitonin gene-related peptide (CGRP)

This 37 amino acid peptide is the most highly expressed neuropeptide in human skin and is probably the principle mediator of capsaicin erythema [57]. Like substance P, CGRP appears to act as a modulator of itch rather than as a pruritogen. It also up-regulates secretion of pro-inflammatory cytokines including TNF-α, IL-1 and IL-8 and it is found in abundant amounts in involved skin of prurigo nodularis [58].

Opioid peptides

Opioid peptides are classified into three groups: endorphins, enkephalins and dynorphins. The opioid receptors also consist of three classes: μ, δ and κ. The pruritic action of opioids is antagonized by naloxone and therefore belongs to the μ category. However, ligation of the κ-receptor has an antipruritic action. Opioid peptides are believed to cause pruritus by a central rather than a peripheral action [59]. Although opioid peptides degranulate mast cells *in vitro*, insufficient concentrations are present in skin for this to be a relevant action *in vivo* [60].

Proteases

The use of the fine spicules of *Mucuna pruriens* (cowage) as probes enabled Shelley and Arthur [61] to carry out simple pathophysiological studies of itching in human volunteers, which led them to propose the involvement of peptide products of proteases as mediators of itching. The protease of cowage (mucunain) proved to be more active than histamine on a molar basis in inducing itching. However, no potent itch-producing peptide released by

protease activity *in situ* has yet been recovered from human skin.

As mentioned above [55], dermal mast cell-derived tryptase acts on the PAR-2 receptors localized on cutaneous nociceptor afferent neurones, leading to release of substance P and other neuropeptides.

The protease kallikrein is pruritogenic in human skin [62], but bradykinin produced by the action of kallikrein has little or no pruritic activity, although it causes pain [62]. In the rat, bradykinin type 2 receptor antagonists and kallikrein inhibitors suppressed experimentally evoked itch suggesting a role for kallikrein in this model [63]. Other proteases besides kallikrein cause itching, including chymotrypsin [64].

Cytokines

Cytokines are low-molecular-weight proteins produced by almost all eukaryotic cells, and they act on specific cell-surface receptors. They include the interleukins, chemokines, interferons and colony-stimulating factors. The first to be studied, interleukin-1 (IL-1), although powerfully pro-inflammatory in human skin [65], does not cause itching. Few others have been systematically studied from this standpoint. However, human recombinant interleukin-2 (IL-2) given intravenously to cancer patients for therapeutic reasons was noted regularly to cause intense itching, associated with redness and a blood eosinophilia [66]. Human recombinant IL-2 injected intradermally caused intense itching in skin of atopic and non-atopic human volunteers alike [67]. Since activated T lymphocytes, an important source of IL-2, are a feature of the dermal infiltrate of atopic dermatitis, a role for IL-2 in the characteristic itching of this disorder has been proposed. That ciclosporin, a potent inhibitor of IL-2 production by T lymphocytes, causes relief of itching in atopic dermatitis lends further support to a proposed role for IL-2 in the itching of atopic dermatitis [68].

There has been considerable recent interest in the role of interleukin-31 (IL-31) in the itch of atopic eczema. Over-expression of IL-31, produced by T-helper lymphocyte type 2 (TH2) cells, in a transgenic mouse caused intense scratching behaviour and eczematous changes [69]. Subsequently, new evidence has emerged that IL-31 is involved in the pruritus of atopic dermatitis in man [70]. Targeting IL-31 may be a promising approach to improved drug treatment of atopic eczema.

Prostaglandins and other eicosanoids

Increased cutaneous levels of arachidonate metabolites are found in a wide range of inflammatory skin diseases, including physical urticarias, ultraviolet inflammation, psoriasis and eczema [71]. The lipoxygenase metabolites most frequently identified in these conditions—leukotrienes B_4, C_4, D_4 and E_4, and 12- and 15-hydroxyeicosatetraenoic acid—cause little or no pruritus, despite being potent pro-inflammatory agents in human skin. Prostaglandin E also shows little or no pruritic activity in human skin, even when applied in a wide range of doses. However, it has the striking property of potentiating itching due to other mediators in concentrations which, by themselves, have no visible pro-inflammatory activity [72]. Similar results were subsequently reported by others who have also shown potentiation by prostaglandin E_2 of itch due to other substances [73], and a study in which the H_1 antihistamine clemastine failed to antagonize the prostaglandin E enhancement of itching [74] suggests that this prostaglandin enhances itching due to other mediators. Increased skin concentrations of E prostaglandins have been reported in eczema and ultraviolet B inflammation, both of which are associated with pruritus [45]. Although aspirin, a prostaglandin synthetase inhibitor, has little or no effect as an antipruritic when administered orally [75], topical application effectively reduces pruritus in patients with localized itch [76]. Non-steroid anti-inflammatory drugs have also been demonstrated to reduce pruritus associated with morphine-induced spinal analgesia [77]. Recent work in mice suggests that the eicosanoid thromboxane A2 may cause itching via neural TP receptors in skin [78].

Neurotrophins

Nerve growth factor (NGF) and neurotrophin-4 induce nerve terminal proliferation, increased expression of neuropeptides and sensitization, associated with enhanced responsiveness to neuropeptides. Serum levels of NGF are increased in atopic dermatitis patients causing increased secretion of tryptase by mast cells [79]. Furthermore, neurotrophin-4 serum levels, probably derived from keratinocytes, are elevated in atopic dermatitis [80]. Thus neurotrophins seem likely to be involved in the pathophysiology of atopic dermatitis.

Scratching

Scratching is a reflex functioning at a spinal level, although modified greatly by higher centres. Scratching relieves itching for several minutes after scratching has ceased. Since the sensation of itching is reinforced by facilitating circuits in the relay synapses of the spinal cord, the prolonged scratch-induced relief could be due to temporary suppression of these circuits [28]. Stimulation of fast-conducting myelinated afferents inhibits these circuits via pre- and postsynaptic mechanisms. These afferents could be activated by vibration, transepidermal electrical nerve stimulation (used therapeutically to allay itching) [30], or more simply by scratching. Alternatively, scratching could simply damage sensory nerve endings, repair occupying several minutes. Why some itches evoke scratching and excoriation (as in scabies) whereas others prompt rubbing (as in lichen planus) is unknown. Scratching has been ingeniously utilized as an indirect, objective method of quantifying itch and as such has been utilized in the evaluation of treatment of itching [13,14].

Itching in non-inflamed skin

The molecular and physiological basis of pruritus associated with clinically normal skin in the absence of underlying systemic disease is in most instances uncertain, although clues are beginning to emerge. The problem of itch in ostensibly healthy skin is likely to become more pressing, with the increasing emergence of pruritus in senescent but visibly normal skin as a challenging therapeutic problem. Initially, careful examination of the skin must be made to exclude visible signs of skin disease. Patients

with symptomatic dermographism who have the will to forbear scratching may have a normal-looking skin at the time of examination. It is also conceivable that localized or widespread itching without physical signs may be a manifestation of mild urticaria ('weal-less urticaria'). In such cases, levels of histamine and other mediators could be subthreshold with regard to vascular, but not sensory, effects. This phenomenon is recognized in aquagenic pruritus, contact urticaria, dermographic pruritus and cholinergic urticaria [81–84].

A detailed history is of paramount importance, including the quality, distribution and periodicity of itching. Itching, likened by the patient to insects crawling over the skin, is often psychoneurotic in origin. Itch that is migratory in timing and distribution may be secondary to internal malignancy. Most patients with itching are especially uncomfortable in bed, probably because of warmth and little to distract their attention. Localized, fixed itching may be due to organic neurological disease—for example, in nerve entrapment or segmental neurofibromatosis [85].

References

1 Twycross R, Greaves MW, Handwerker H *et al.* Itch: scratching more than the surface. *QJM* 2003; **96**: 7–26.

2 Schmelz M, Schmidt R, Bickel A *et al.* Specific C receptors for itch in human skin. *J Neurosci* 1997; **17**: 8003–8.

3 Andrew D, Craig AD. Spinothalamic lamina 1 neurons selectively sensitive to histamine: a central neural pathway for itch. *Nature Neuroscience* 2001; **4**: 72–7.

4 Selden ST. Tickle. *J Am Acad Dermatol* 2004; **50**: 93–7.

5 Heyer G, Ulmer FJ, Schmitz J, Handwerker HO. Histamine-induced itch and alloknesis (itchy skin) in atopic eczema patients and controls. *Acta Derm-Venereol (Stockh)* 1995; **75**: 348–52.

6 Hebra FV. *On Diseases of the Skin*, Vol. 2. London: New Sydenham Society translation, 1868: 257.

7 Hyde JN, Montgomery FHA. *Practical Treatise on Diseases of the Skin for Use of Students and Practitioners*. Philadelphia: Lea & Febiger, 1909.

8 Rea JN, Newhouse ML, Halil T. Skin disease in Lambeth. A community study of prevalence and use of medical care. *Br J Prev Soc Med* 1976; **30**: 107–14.

9 Dalgard F, Svensson A, Holm JO, Sunby J. Self reported skin morbidity in Oslo. Associations with sociodemographic factors among adults in a cross sectional study. *Br J Dermatol* 2004; **151**: 452–7.

10 Weisshaar E, Apfelbacher C, Jager G *et al.* Pruritus as a leading symptom: clinical characteristics and quality of life in German and Ugandan patients. *Br J Dermatol* 2006; **155**: 957–64.

11 Kuraishi Y, Nagasawa T, Hayashi K, Satoh M. Scratching behaviour induced by pruritogenic but not algesiogenic agents in mice. *Eur J Pharmacol* 1995; **275**: 229–33.

12 De Castro Costa M, Gybels J, Kupers R, Van Hees J. Scratching behaviour in arthritic rats: a sign of chronic pain or itch? *Pain* 1987; **29**: 123–31.

13 Ebata T, Iwasaki S, Kamide R, Niimura M. Use of a wrist activity monitor for the measurement of nocturnal scratching in patients with atopic dermatitis. *Br J Dermatol* 2001; **144**: 305–9.

14 Hagermark O, Wahlgren CF. Some methods for evaluating clinical itch and their application for studying pathophysiological mechanisms. *J Dermatol Sci* 1992; **4**: 55–62.

15 Molenaar HAJ, Oosting J, Jones EA. Improved device for measuring pruritus. *Med Biol Eng Comput* 1998; **36**: 220–4.

16 Frey M. Zur Physiologie der Juckempfinding. *Arch Neerl Physiol* 1922; **7**: 142–5.

17 Woollard HH, Harpman JA. Itch and pain receptors consists of unspecialised cutaneous sensory nerve endings. *J Anat* 1940; **74**: 413–40.

18 Johansson O, Hilliges M, Stahle-Backdahl M. Intra epidermal neurone-specific enolase (NSE) immunoreactive nerve fibres: evidence for sprouting in uremic patients on maintenance hemodialysis. *Neurosci Lett* 1989; **99**: 281–6.

19 Clapham DE. TRP channels as cellular sensors. *Nature* 2003; **426**: 517–24.

20 Szallasi A, Blumberg PM. Vanilloid (capsaicin) receptors and mechanisms. *Pharmacol Rev* 1999; **51**: 159–212.

21 Stander S, Moormann C, Schumacher M *et al*. Expression of vanilloid receptor subtype 1 in cutaneous sensory nerve fibres, mast cells and epithelial cells of appendage structures. *Exp Dermatol* 2004; **13**: 129–39.

22 De Petrocellis L, Cascio MG, Di Marzo V. The endocannabinoid system: a general view and latest additions. *Br J Pharmacol* 2004; **141**: 765–74.

23 Steinhoff M, Bienestock J, Schmelz M *et al*. Neurophysiological and neuroendocrine basis of pruritus. *J Invest Dermatol* 2006; **126**: 1705–18.

24 Ikoma A, Handwerker H, Myachi Y, Schmelz M. Electrically evoked itch in humans. *Pain* 2005; **113**: 148–54.

25 Mochizuki H, Tashiro M, Kano M *et al.* Imaging of central itch modulation in the human brain using positron emission tomography. *Pain* 2003; **105**: 339–46.

26 Hsieh JC, Hagermark O, Stahle-Backdahl M *et al.* Urge to scratch represented in human cerebral cortex during itch. *J Neurophysiol* 1994; **72**: 3004–8.

27 Walter B, Sadlo MN, Kupfer J *et al*. Brain activation by histamine prick test-induced itch. *J Invest Dermatol* 2005; **125**: 380–2.

28 Melzack R, Wall PD. Pain mechanisms: a new theory. *Science* 1965; **150**: 971–9.

29 Yosipovitch G, Fast K, Bernhard JD. Noxious heat and scratching decrease histamine—induced itch and blood flow. *J Invest Dermatol* 2005; **125**: 1268–72.

30 Nilsson HJ, Levinsson A, Schouenborg J. Cutaneous field stimulation (CFS): a new powerful method to combat itch. *Pain* 1997; **71**: 49–55.

31 Ikoma A, Rukweid R, Stander S *et al*. Neuronal sensitization for histamine induced itch in lesional skin of patients with atopic dermatitis. *Arch Dermatol* 2003; **139**: 1455–8.

32 Ballantyne JC, Loach AB, Carr DB. Itching after epidural and spinal opiates. *Pain* 1988; **33**: 149–60.

33 Bernstein JE, Swift R. Relief of intractable pruritus with naloxone. *Arch Dermatol* 1979; **115**: 1366–7.

34 Thomas DA, Williams GM, Iwata K *et al*. The medullary dorsal horn, a site for action of morphine in producing facial scratching in monkeys. *Anesthesiology* 1993; **79**: 548–54.

35 Dunteman E, Karanikolas M, Filos KS. Transnasal butorphanol for the treatment of opioid-induced pruritus unresponsive to antihistamines. *J Pain Symptom Manag* 1996; **12**: 255–60.

36 Chen Y. Molecular cloning and functional expression of a mu-opioid receptor from rat brain. *Mol Pharmacol* 1993; **44**: 8–12.

37 Umeuchi H, Togashi Y, Honda T *et al.* Involvement of the central mu-opioid system in the scratching behaviour in mice, and suppression of it by the activation of the kappa-opioid system. *Eur J Pharmacol* 2003; **477**: 29–35.

38 Lewis T. *The Blood Vessels of the Human Skin and their Responses*. London: Shaw and sons, 1927.

39 Arrang JM, Garbarg M, Lancelot JC *et al.* Highly potent and selective ligands for histamine H_3 receptors. *Nature* 1987; **327**: 117–23.

40 Davies MG, Greaves MW. Sensory responses of human skin to synthetic histamine analogues and histamine. *Br J Clin Pharmacol* 1980; **9**: 461–5.

41 Bell JK, McQueen DS, Rees JL. Involvement of histamine H_1 and H_4 receptors in scratching induced by histamine receptor agonists in Balb C mice. *Br J Pharmacol* 2004; 142: 374–80.

42 Cook J, Shuster S. Histamine weal formation and absorption in man. *Br J Pharmacol* 1980; **69**: 579–85.

43 Johansson O, Virtanen M, Hilliges M. Histaminergic nerves demonstrated in the skin: a new direct mode of neurogenic inflammation? *Exp Dermatol* 1995; **4**: 93–6.

44 Bentley-Phillips CB, Eady RAJ, Greaves MW. Cold urticaria: inhibition of cold-evoked histamine release by doxantrazole. *J Invest Dermatol* 1978; **71**: 266–8.

45 Greaves MW, Sondergaard JS. Pharmacologic agents released in ultraviolet inflammation studied by continuous skin perfusion. *J Invest Dermatol* 1970; **54**: 365–7.

46 Johnson HH, De Oreo GA, Lascheid WP *et al.* Skin histamine levels in chronic atopic dermatitis. *J Invest Dermatol* 1960; **34**: 237–8.

47 Krause L, Shuster S. Mechanism of action of antipruritic drugs. *BMJ* 1983; **287**: 1119–200.

48 Vogelsang M, Heyer G, Hornstein OP. Acetyl choline induces different sensations in atopic and in non-atopic subjects. *Acta Derm-Venereol* 1995; **75**: 434–6.

49 Jorizzo JL, Coutts A, Greaves MW. Vascular responses of human skin to injection of substance P and mechanism of action. *Eur J Pharmacol* 1983; **87**: 67–76.

50 Hägermark Ö, Hokfelt T, Pernow B. Flare and itch induced by substance P in human skin. *J Invest Dermatol* 1978; **71**: 233–5.

51 Polak JM, Bloom SR. The peripheral substance P-ergic systems. *Peptides* 1981; **2** (Suppl. 2): 133–48.
52 Lowman MA, Benyon RC, Church MK. Substance P causes selective histamine release from human skin. *Br J Pharmacol* 1988; **95**: 121–30.
53 Shanahan F, Denburg JA, Fox J *et al*. Mast cell heterogeneity: effects of neuroenteric peptides on histamine release. *J Immunol* 1985; **135**: 1331–7.
54 Suzuki R, Furuno T, McKay DM *et al*. Direct neurite–mast cell communication in vitro occurs via the neuropeptide substance P. *J Immunol* 1999; **163**: 2410–5.
55 Steinhoff M, Vergnolle N, Young SH *et al*. Agonists of proteinase-activated receptor 2 induce inflammation by a neurogenic mechanism. *Nat Med* 2000; **6**: 151–8.
56 Lynn B. Capsaicin: actions on C fibre afferents that may be involved in itch. *Skin Pharmacol* 1992; **5**: 9–13.
57 Sann H, Pierau FK. Efferent functions of C fiber nociceptors. *Z Rheumatol* 1998; **57** (Suppl. 2): 8–13.
58 Abadia Molina F, Burrows NP, Russell Jones R *et al*. Increased sensory neuropeptides in nodular prurigo: a quantitiative histochemical analysis. *Br J Dermatol* 1992; **127**: 344–51.
59 Steinhoff M, Bienenstock J, Schmelz M *et al*. Neurophysiological, neuroimmunological and neuroendocrine basis of pruritus. *J Invest Dermatol* 2006; **126**: 1705–18.
60 Blunk JA, Schmelz M, Zeck S *et al*. Opioid–induced mast cell activation and vascular responses is not mediated by mu–opioid receptors: an in vivo microdialysis study in human skin. *Anesth Analg* 2004; **98**: 364–70.
61 Shelley WB, Arthur RP. Studies on cowhage (*Mucuna pruriens*) and its pruritogenic proteinase mucunain. *Arch Dermatol* 1955; **72**: 399–406.
62 Cormia FE, Dougherty JW. Proteolytic activity in development of pain and itching: Cutaneous reactions to bradykinin and kallikrein. *J Invest Dermatol* 1960; **35**: 21–6.
63 Hayashi K, Majima M. Reduction of sodium deoxycholic acid-induced scratching behaviour by bradykinin B2 receptor antagonists. *Br J Pharmacol* 1999; **126**: 197–204.
64 Hägermark Ö, Rajka G, Bergqvist U. Experimental itch in human skin elicited by rat mast cell chymase. *Acta Derm-Venereol (Stockh)* 1972; **52**: 125–8.
65 Dowd PM, Camp RDR, Greaves MW. Human recombinant interleukin-1 alpha is proinflammatory in normal human skin. *Skin Pharmacol* 1988; **1**: 30–7.
66 Gaspari AA, Lotze MT, Rosenberg SA *et al*. Dermatological changes associated with interleukin-2 administration. *JAMA* 1987; **258**: 1624–9.
67 Wahlgren CF, Tengvall Linder M, Hagermark O, Scheynius A. Itch and inflammation induced by intradermally injected interleukin-2 in atopic dermatitis patients and healthy subjects. *Arch Dermatol Res* 1995; **287**: 572–80.
68 Wahlgren CF, Scheynius A, Hagermark O. Antipruritic effect of oral cyclosporin A in atopic dermatitis. *Acta Derm-Venereol (Stockh)* 1990; **70**: 323–9.
69 Dillon SR, Sprecher C, Hammond A *et al*. Interleukin 31, a cytokine produced by activated T cells, induces dermatitis in mice. *Nat Immunol* 2004; **5**: 752–60.
70 Sonkoly E, Muller A, Kauerma AI *et al*. IL-31: a new link between T cells and pruritus in atopic skin inflammation. *J Allergy Clin Immunol* 2006; **117**: 411–7.
71 Greaves MW, Camp RDR. Prostaglandins, leukotrienes, phospholipase, platelet activating factor and cytokines: an integrated approach to inflammation of human skin. *Arch Dermatol Res* 1988; **280** (Suppl.): S33–41.
72 Greaves MW, McDonald-Gibson W. Itch: the role of prostaglandins. *BMJ* 1973; **3**: 608–9.
73 Hägermark Ö, Strandberg K, Hamberg M. Potentiation of itch and flare responses in human skin by prostaglandins E_2 and H_2 and a prostaglandin endoperoxide analogue. *J Invest Dermatol* 1977; **69**: 527–30.
74 Boss M, Burton JL. Lack of effect of the antihistamine drug clemastine on the potentiation of itch by prostaglandin E. *Arch Dermatol* 1981; **117**: 208–9.
75 Daly BM, Shuster S. Effect of aspirin on pruritus. *BMJ* 1986; **293**: 907.
76 Yosipovitch G, Sugeng MW, Chan YH *et al*. The effect of topically applied aspirin on localized circumscribed neurodermatitis. *J Am Acad Dermatol* 2001; **45**: 910–3.
77 Colbert S, O'Hanlon DM, Galvin S *et al*. The effect of rectal diclofenac on pruritus in patients receiving intrathecal morphine. *Anaesthesia* 1999; **54**: 948–52.
78 Anhoh T, Nishikawa Y, Yamaguchi-Myamoto T *et al*. Thromboxane A2 induces itch-associated responses through TP receptors in the skin in mice. *J Invest Dermatol* 2007; **127**: 2042–7.
79 Groneberg DA, Serowka F, Peckenschneider N *et al*. Gene expression and regulation of nerve growth factor in atopic dermatitis mast cells and in the human mast cell line-1. *J Neuroimmunol* 2005; **161**: 87–92.
80 Grewe M, Vogelsang K, Ruzicka T *et al*. Neurotrophin-4 production by human epidermal keratinocytes: increased expression in atopic dermatitis. *J Invest Dermatol* 2000; **114**: 1108–12.
81 Kligman AM, Greaves MW, Steinman H. Water induced itching without cutaneous signs: aquagenic pruritus. *Arch Dermatol* 1986; **122**: 183–6.
82 Berth-Jones J, Graham-Brown RAC. Cholinergic pruritus, erythema and urticaria: a disease spectrum responding to danazol. *Br J Dermatol* 1989; **121**: 235–7.
83 Bernhard JD, Kligman AM, Shelley WB. Dermographic pruritus: invisible dermographism. *J Am Acad Dermatol* 1995; **33**: 322.
84 Kligman AM. The spectrum of contact urticaria: wheals, erythema and pruritus. *Dermatol Clin* 1990; **8**: 57–60.
85 McFadden JP, Logan R, Griffiths WAD. Segmental neurofibromatosis and pruritus. *Clin Exp Dermatol* 1988; **13**: 265–8.

Itching in systemic disease

Except for the itch of atopic dermatitis, the subject of recent intense research, pruritus associated with primary skin disease (pruritoceptive pruritus) is discussed in the chapters dealing with each of the diseases and will not be considered further here. This section deals with itch in skin devoid of primary skin disease, and occurring in response to systemic or internal disease (neurogenic pruritus), any signs in the skin being secondary to scratching or rubbing. The more important conditions are listed in Table 21.2.

Chronic renal disease

Persistent itching is a major cause of impairment of quality of life in patients with chronic renal failure [1]. It is becoming less prevalent due to more efficient dialysis techniques, but still occurs in around 20% of patients [2]. It is rarely a feature in children, or in patients with acute renal failure [3] but the reasons for this are unknown. It is more common in patients receiving haemodialysis than in patients on continuous ambulatory peritoneal dialysis (CAPD) [4]. The clinical features have been comprehensively described [1]. Although the skin of some patients may appear dry, frequently it is essentially normal in appearance. Itching may be persistent, extensive and intractable, but in other patients it may

Table 21.2 Itch in response to systemic/internal disease (neurogenic itch).

Uraemia
Cholestasis and liver disease
Haematological disease
Iron deficiency
Polycythaemia vera
Malignant disease
Solid tumours
Lymphomas
Endocrine disease
Thyroid disease
Diabetes mellitus (localized itch only)
HIV infection
Adverse drug reaction
Pruritus due to morphine and related drugs

be transitory and localized [1,3]. Secondary skin changes due to scratching and rubbing are very common. These include pigmentation, prurigo nodules and eczematization, often secondarily infected. Histologically, the clinically normal skin may show attenuation of sweat and sebaceous glands, and increased population densities of cutaneous mast cells have been described [5]. However, no correlation between mast cell population densities and pruritus has been established. There may be a microangiopathy [6]. Abnormal sprouting of neurone-specific enolase-positive unmyelinated nerve fibres in skin of uraemic patients has also been reported [7]. Other suggested factors in the pathogenesis include raised serum parathyroid hormone levels due to secondary hyperparathyroidism [8], and it is of interest that parathyroid hormone is known to cause increased populations of tissue mast cells [9].

However, although parathyroidectomy has relieved pruritus in some patients [10], no convincing correlation between parathormone levels and pruritus has been demonstrated in renal failure patients [8]. Renal pruritus has been proposed to be related to aluminium overload during haemodialysis [11] treatable by administration of desferrioxamine mesylate, but this has not been confirmed. Pharmacological mediators have been proposed to be responsible for renal pruritus. Histamine is an improbable candidate, since treatment by antihistamines is ineffective. Skin biopsies from patients with chronic renal failure show increased numbers of intraepidermal $CD1^+$ T cells, raising the possibility that T-cell-derived cytokines could be implicated in pruritus [12,13]. Interestingly, uraemic pruritus in haemodialysis patients has been associated with elevated proportions of Th1 lymphocytes and elevated C reactive protein and interleukin-6 serum levels compared with levels in non-pruritic haemodialysis patients termed 'microinflammation' [14]. However, the topical calcineurin inhibitor tacrolimus 0.1% proved ineffective in a double-blind, randomized placebo-controlled study in haemodialysis-related pruritus [15].

Opioid peptides have also recently been implicated, elevated plasma met-enkephalin levels having been reported in haemodialysis patients [16], although a correlation has yet to be established [17]. A recent report claims that pruritus of renal failure responds to a κ-opioid agonist [18], suggesting a role for opioid peptides although this needs to be confirmed. The pathophysiology of uraemic itching has been usefully reviewed by Murphy and Carmichael [19].

Important general therapeutic measures include emollients for xerosis. Secondary eczematization and its accompanying secondary infection should be treated vigorously. Dialysis itself has little beneficial effect on uraemic pruritus, although its frequency and severity has lessened since the advent of dialysis membranes with better biocompatibility. The only curative and reliably effective treatment for renal pruritus is renal transplantation. Parathyroidectomy may be followed by remission of pruritus in patients with secondary hyperparathyroidism [10]. Phototherapy with ultraviolet B (UVB) is frequently effective and may act systemically as well as locally (Table 21.3). Its value has been supported by a recent meta-analysis [20]. That ultraviolet therapy depletes the vitamin A content of the skin has been proposed as a mode of action [21]. Only UVB phototherapy and activated charcoal have an established track record for this indication [22,23].

Table 21.3 Treatments for pruritus of chronic renal failure.

Treatment	Level of preference	Level of effectiveness
Broad-band UVB phototherapy	1	high
Activated charcoal	1	high
Gabapentin	2	medium
Erythropoietin	2	medium
Naltrexone	2	medium
Antihistamine	3	low
Corticosteroids (topical, systemic)	3	low

1 = high; 2 = moderate; 3 = low.

A double-blind placebo-controlled crossover trial in 25 patients indicated that gabapentin is effective in treatment of pruritus of renal failure [24]. Other treatments, including heparin, mexiletine, ion-exchange resin and intravenous lidocaine (lignocaine) have been advocated, but are of uncertain effectiveness and usually impractical to use. A 1996 report of a placebo-controlled trial of an orally administered opioid antagonist, naltrexone, attracted much attention, but the apparent effectiveness of this treatment remains to be independently confirmed [25]. The possible value of a κ-opioid agonist for this indication has been alluded to above, but these compounds are as yet unavailable. Antihistamines and topical steroids are generally unhelpful in uraemic itching, but emollients may provide relief in those with a dry skin.

Since itching may be restricted to certain areas, topical capsaicin 0.025% has been reported to be effective in localized uraemic pruritus [26]. In the longer term, only expansion of the renal transplant programme is likely to bring sustained relief to these greatly distressed patients.

References

1 Gilchrest BA, Stern RS, Steinman TI *et al*. Clinical features of pruritus among patients undergoing maintenance haemodialysis. *Arch Dermatol* 1982; **118**: 154–60.

2 Mettang T, Pauli-Magnus C, Alscher DM. Uraemic pruritus—new perspectives from recent trials. *Nephrol Dial Transplant* 2002; **17**: 1558–63.

3 Szepietowski JC, Schwarz RA. Uraemic pruritus. *Int J Dermatol* 1998; **37**: 247–53.

4 Mettang T, Fritz P, Weber J *et al*. Uremic pruritus in patients on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD). The role of plasma histamine and skin mast cells. *Clin Nephrol* 1990; **34**: 136–41.

5 Szepietowski J, Thepen T, Van Vloten WA *et al*. Pruritus and mast cell proliferation in the skin of haemodialysis patients. *Inflamm Res* 1995; **44** (Suppl. 1): S84–5.

6 Gilchrest BA, Rowe JW, Mihm MC. Clinical and histological cutaneous clinical findings in chronic renal failure: evidence for a dialysis resistant transplant responsive microangiopathy. *Lancet* 1980; **ii**: 1271–5.

7 Johansson O, Hilliges M, Stahle-Backdahl M. Intraepidermal neurone specific enolase (NSE)—immunoreactive nerve fibres: evidence for sprouting in uremic patients on maintenance hemodialysis. *Neurosci Lett* 1989; **99**: 281–6.

8 Cho YL, Liu HN, Huang TP *et al*. Uraemic pruritus: roles of parathormone and substance P. *J Am Acad Dermatol* 1997; **36**: 538–41.

9 Rockoff SD, Armstrong JD. Parathyroid hormone as a stimulus to mast cell accumulation in bone. *Calcif Tissue Res* 1970; **5**: 49–55.

10 Massry SG, Popovtzer MM, Coburn JW *et al*. Intractable pruritus as a manifestation of secondary hyperparathyroidism in uraemia: disappearance of itching after subtotal parathyroidectomy. *N Engl J Med* 1968; **279**: 697–700.

11 Brown MA, George CR, Dunstan CR *et al*. Prurigo nodularis and aluminium overload in maintenance haemodialysis. *Lancet* 1992; **340**: 48.

12 Szepietowski J, Thepen T, Szepietowski T *et al*. Phenotypic analysis of cell infiltrate in normal looking skin of haemodialysis patients. *Acta Dermatovenerol Croat* 1996; **4**: 3–6.
13 Pereira BJG, Dinarello CA. Production of cytokines and cytokine inhibitory proteins in patients on dialysis. *Nephrol Dial Transplant* 1994; **9** (Suppl. 2): 60–71.
14 Kimmel, M, Alscher DM, Dunst R *et al*. The role of microinflammation in the pathogenesis of uraemic pruritus in haemodialysis patients. *Nephrol Dial Transplant* 2006; **21**: 749–55.
15 Duque MI, Yosipovitch G, Fleischer AB *et al*. Lack of efficacy of tacrolimus ointment 0.1% for treatment of haemodialysis-related pruritus: a randomized double-blind vehicle-controlled study. *J Am Acad Dermatol* 2005; **52**: 519–21.
16 Danno K, Nishiura K, Tanaka M. Increased met-enkephalin plasma levels in hemodialysis patients with or without pruritus. *J Dermatol Sci* 1995; **10**: 238–40.
17 Mettang T, Fischer FP, Dollenbacher U *et al*. Uraemic pruritus is not related to beta-endorphin serum levels in haemodialysis patients. *Nephrol Dial Transplant* 1998; **13**: 232–3.
18 Wikstrom B, Gellert R, Ladefoged SD *et al*. Kappa-opioid system in uremic pruritus: multicentre randomized double-blind placebo controlled clinical studies. *J Am Soc Nephrol* 2005; **16**: 3447–8.
19 Murphy M, Carmichael AJ. Renal itch. *Clin Exp Dermatol* 1999; **25**: 103–6.
20 Tan JK, Haberman HF, Coldman AJ. Identifying effective treatments for uremic pruritus. *J Am Acad Dermatol* 1991; **25**: 811–8.
21 Berne B, Vahlquist A, Fisher T *et al*. UV treatment of uraemic pruritus reduces the vitamin A content of the skin. *Eur J Clin Invest* 1984; **14**: 203–6.
22 Gilchrest BA, Rowe JW, Brown RS. Relief of uraemic pruritus with ultraviolet phototherapy. *N Engl J Med* 1977; **297**: 136–8.
23 Pederson JA, Matter BJ, Czerwinski AW. Relief of idiopathic generalized pruritus in dialysis patients treated with activated oral charcoal. *Ann Intern Med* 1980; **93**: 446–8.
24 Gunal AI, Yoldas TK, Kirciman E, Celiker H. Gabapentin therapy for pruritus in haemodialysis patients: a randomized, placebo-controlled double-blind trial. *Nephrol Dial Transplant* 2004; **19**: 3137–9.
25 Peer G, Kivity S, Agami O *et al*. Randomised crossover trial of naltrexone in uraemic pruritus. *Lancet* 1996; **348**: 1552–4.
26 Breneman DL, Cardone JS, Blumsack RF *et al*. Topical capsaicin for treatment of hemodialysis-related pruritus. *J Am Acad Dermatol* 1992; **26**: 91–4.

Cholestasis

Pruritus may be generalized or localized, for example to the hands and feet, and can be an early symptom of hepatobiliary disease. It is associated with rubbing rather than scratching so secondary excoriation, eczematization and infection are less common than in renal pruritus. It is a frequent and distressing symptom of cholestasis, and its molecular basis is still debated. Hepatitis C is an important cause of intense cholestatic pruritus, occurring in 15% of infected patients [1]. That it should be considered as part of the routine work-up of patients with pruritus is questionable since a case-controlled study failed to show a higher frequency of hepatitis C infection in patients with pruritus compared with the general population [2].

Cholestatic pruritus is associated with elevated plasma levels of bile salts [3], but evidence of a direct correlation has been lacking. Measurements of skin-tissue levels of bile salts and their relationship to serum levels, and to intensity of itching, gave inconclusive results and the bile-salt levels did not differ from corresponding values in control subjects [4]. Bile salts applied to blister bases in human skin, although causing pruritus, do so at minimal effective concentrations far exceeding those achieved in cholestatic jaundice [5]. Analysis of individual bile acids in skin and serum, including quantitatively minor components of the bile-acid family, also failed to show a quantitative relationship with pruritus [4]. Lack of demonstrable quantitative relationships has not, however, discouraged a number of investigators from exploring methods for lowering serum and skin bile-salt levels in the management of itching due to cholestasis. For example, plasma perfusion through charcoal-coated glass beads was associated with a marked improvement in cholestatic pruritus, although a relationship between clinical response and fall in bile-salt level was not demonstrated. Similar results have been achieved with ion-exchange resins, including cholestyramine [6,7], and with a newer bile acid sequestrant, colesevalem hydrochloride [8]. These reports raise the possibility that observed clinical improvements may be a consequence of removal of pruritogenic factors other than bile salts following such procedures.

Table 21.4 Treatments for hepatobiliary pruritus.

Treatment	Level of preference	Level of effectiveness
Cholestyramine*	1	high
Opioid antagonists	1	high
Rifampicin	2	high
Ursodeoxycholic acid	3	low
UVB phototherapy	3	low
Antihistamines	3	low

* Ineffective in total biliary obstruction.
1 = high; 2 = moderate; 3 = low.

Treatments for pruritus of cholestasis are summarized in Table 21.4. In a randomized cross-over trial comparing cholestyramine, terfenadine (a low-sedation H_1 antihistamine now withdrawn by the manufacturer owing to cardiac side effects) and chlorpheniramine with placebo in pruritus due to obstructive liver disease, only terfenadine and cholestyramine showed evidence of significant suppression of pruritus, but cholestyramine was associated with a high incidence of side effects [6]. Other methods advocated for the relief of itching of cholestasis include rifampicin [9,10], extracorporeal albumin dialysis [11] and phototherapy [7]. Rifampicin is effective, but is associated with hepatotoxicity [12]. Ursodeoxycholic acid has proved disappointing in a recent meta-analysis [13]. Effective treatments of hepatobiliary pruritus have been reviewed [14].

Earlier work highlighted the importance of dysregulation of central opioid peptides in patients with cholestatic pruritus [15]. The evidence can be summarized as follows. Plasma levels of opioid peptides are elevated in human [15] and rat [16] cholestasis. Furthermore, plasma from patients suffering from pruritus of cholestasis induces facial scratching, reversed by naloxone, when injected into the medullary dorsal horn of the monkey [17]. Most importantly, carefully controlled trials established the effectiveness of parenteral and oral opioid antagonists in the treatment of cholestatic pruritus [18,19]. Thus, the conclusion that opioid antagonists are of value in treatment of the pruritus of cholestasis is based upon evidence of increased opioidergic tone in chronic cholestasis patients, and the impressive response to naloxone or naltrexone (specific opioid μ-receptor antagonists). This response can be associated with opioid withdrawal symptoms [20].

Apart from biliary disease, cholestatic pruritus may also occur in pregnancy [21] and premenstrually [22]. However, the role of opioid peptides in these contexts has yet to be established.

References

1 Cacoub P, Poynard T, Ghillan P *et al*. Extrahepatic manifestations of chronic hepatitis C. *Arthritis Rheum* 1999; **42**: 2204–12.
2 Cribier B, Santinelli F, Schmitt C *et al*. Should patients with pruritus be tested for hepatitis C infection? A case-controlled study. *Br J Dermatol* 2000; **142**: 1234–5.
3 Ghent CN, Bloomer JR, Klastskin G. Elevations of skin tissue levels of bile acids in human cholestasis: relation to serum levels and to pruritus. *Gastroenterology* 1977; **73**: 1125–30.
4 Bartholomew TC, Summerfield JA, Billing BH *et al.* Bile acid profiles of human serum and skin interstitial fluid and their relationship to pruritus studied by gas chromatography mass spectrometry. *Clin Sci (Lond)* 1982; **63**: 65–73.
5 Kirby J, Heater KW, Burton JL. Pruritic effects of bile salts. *BMJ* 1974; **4**: 693–5.
6 Van Itallie TB, Hashim SA, Crampton RS, Tennent DM. The treatment of pruritus and hypercholesteremia of primary biliary cirrhosis with cholestyramine. *N Engl J Med* 1961; **265**: 469–74.
7 Cerio R, Murphy GM, Salden GE *et al.* A combination of phototherapy and cholestyramine for the relief of pruritus in primary biliary cirrhosis. *Br J Dermatol* 1987; **116**: 265–7.
8 Berg CI. Use of colesevalem hydrochloride (Welchtol) as a novel therapeutic agent for the management of refractory pruritus in chronic liver disease. *Hepatology* 2001; **34**: 541.
9 Bachs L, Pares A, Elena M *et al.* Comparison of rifampicin with phenobarbitone for treatment of pruritus in biliary cirrhosis. *Lancet* 1989; **i**: 574–6.
10 Duncan JS, Kennedy HJ, Triger DR. Treatment of pruritus due to chronic obstructive liver disease. *BMJ* 1984; **289**: 22.
11 Pares A, Cisneros L, Salmeron JM *et al.* Extracorporeal albumin dialysis: a procedure for prolonged relief of intractable pruritus in patients with primary biliary cirrhosis. *Am J Gastroenterol* 2004; **99**: 1105–10.
12 Prince MI, Burt AD, Jones DEJ. Hepatitis and liver dysfunction with rifampicin therapy for pruritus in primary biliary cirrhosis. *Gut* 2002; **50**: 436–9.
13 Goulis J, Leandro G, Burroughs AK. Randomised controlled trials of ursodeoxycholic acid therapy for primary biliary cirrhosis: a meta-analysis. *Lancet* 1999; **355**: 657–8.
14 Bergasa NV. Treatment of hepatobiliary pruritus. *Curr Gastroenterol Rep* 2004; **6**: 10–6.
15 Thornton JR, Losowsky MS. Opioid peptides and primary biliary cirrhosis. *BMJ* 1988; **297**: 1501–4.
16 Swain MG, Rothman RG, Xu H *et al.* Endogenous opioids accumulate in plasma in a rat model of acute cholestasis. *Gastroenterology* 1992; **103**: 630–5.
17 Bergasa NV, Thomas DA, Vergalla J *et al.* Plasma from patients with pruritus of cholestasis induces opioid peptide receptor mediated scratching in monkeys. *Life Sci* 1993; **53**: 1253–7.
18 Bergasa NV, Alling DW, Talbot TL *et al*. Effects of naloxone infusions in patients with the pruritus of cholestasis: a double-blind, randomized, controlled trial. *Ann Intern Med* 1995; **123**: 161–7.
19 Terg R, Coronel E, Sordá J *et al*. Efficacy and safety of oral naltrexone treatment for pruritus of cholestasis, a crossover, double-blind, placebo-controlled study. *J Hepatol* 2002; **37**: 717–22.
20 Jones EA, Bergasa NV. Pruritus of cholestasis and the opioid system. *JAMA* 1992; **268**: 3359–62.
21 Fagan EA. Intrahepatic cholestasis of pregnancy. *BMJ* 1994; **309**: 1243–4.
22 Dahl MGC. Premenstrual pruritus due to recurrent cholestasis. *Trans St John's Hosp Dermatol Soc* 1970; **56**: 11–3.

Iron deficiency

Iron deficiency has been implicated as a cause of intractable pruritus in the absence of visible skin disease, or even in the absence of anaemia [1]. Of special interest is a report by Salem *et al*. [2] of pruritus and severe iron deficiency in polycythaemia vera. In these patients, correction of iron deficiency apparently correlated with improvement in pruritus. A study of iatrogenic venesection-induced iron deficiency over a 60-month period revealed no instance of pruritus in 21 patients [3]; however, iron deficiency is a factor in pruritus of polycythaemia in some patients [4].

References

1 Lewiecki EM, Rahman F. Pruritus: a manifestation of iron deficiency. *JAMA* 1976; **236**: 2319–20.
2 Salem HH, Van der Weyden MB, Young IF, Wiley JS. Pruritus and severe iron deficiency in polycythaemia vera. *BMJ* 1982; **285**: 91–2.
3 Tucker WFG, Briggs C, Challoner T. Absence of pruritus in iron deficiency following venesection. *Clin Exp Dermatol* 1984; **9**: 186–9.
4 Diehn F, Tefferi A. Pruritus in polycythaemia vera: prevalence laboratory correlates and management. *Br J Haematol* 2001; **115**: 619–21.

Polycythaemia vera

Pruritus is a common symptom in polycythaemic patients [1]. As many as 50% of untreated patients with polycythaemia develop a severe, prickly and distressing discomfort within minutes of water contact, lasting 15–60 min [2]. As it frequently occurs after the patient emerges from bathing, it is often referred to as 'bath itch'. No visible changes are present in the skin, and the symptom may be associated with elevated serum and urinary histamine levels [2]. Platelet aggregation has been suggested as a possible mechanism and source of pruritogenic factors, including histamine [3]. Water-induced itching may precede development of polycythaemia vera by several years [4]. Bathing by regional sponging may mitigate the itch. Successful treatment of the underlying polycythaemia may not relieve the itching and although correction of venesection-induced iron deficiency may give relief, it may be at the expense of exacerbating the polycythaemia [5]. Antihistamines are generally ineffective. Psoralen ultraviolet A (PUVA) photochemotherapy, with 8-methoxypsoralen and UVA, has been successful in some patients [6]. Success has been claimed for narrow-band UVB phototherapy [7]. One report cites the use of long-term treatment with interferon-α 2b for severe pruritus of polycythaemia vera [8]. Another advocates use of serotonin reuptake inhibitors such as paroxetine [9]. Some patients may respond to aspirin [3].

Intense, widespread pruritus is also a major feature of the Sézary syndrome (T-cell leukaemia) and occurs in cutaneous mastocytosis (urticaria pigmentosa) if the skin is rubbed to provoke a weal (Darier's sign). In mycosis fungoides, pruritus may be the presenting symptom without skin signs ('invisible mycosis fungoides') [10].

References

1 Diehn F, Tefferi A. Pruritus in polycythaemia vera: prevalence laboratory correlates and management. *Br J Haematol* 2001; **115**: 619–21.
2 Gilbert HS, Warner RP, Wassermann LR. A study of histamine in myeloproliferative disease. *Blood* 1966; **28**: 795–806.
3 Fjellner B, Hagermark O. Pruritus in polycythaemia vera: treatment with aspirin and possibility of platelet involvement. *Acta Derm-Venereol (Stockh)* 1979; **59**: 505–12.
4 Archer CB, Camp RDR, Greaves MW. Polycythaemia vera can present with aquagenic pruritus [letter]. *Lancet* 1988; **i**: 1451.
5 Salem HH, Van der Weyden MB, Young IF, Wiley JS. Pruritus and severe iron deficiency in polycythaemia vera. *BMJ* 1982; **285**: 91–2.
6 Menagé HP, Norris PG, Hawk JLM, Greaves MW. The efficacy of psoralen photochemotherapy in the treatment of aquagenic pruritus. *Br J Dermatol* 1993; **129**: 163–5.
7 Baldo A, Sammarco E, Plaitano R *et al*. Narrow band (TL-01) ultraviolet B phototherapy for pruritus in polycythaemia vera. *Br J Dermatol* 2002; **147**: 979–81.
8 Muller EW, De Wolf TM, Egger PW *et al.* Long term treatment with interferon-a2b for severe pruritus in patients with polycythaemia vera. *Br J Haematol* 1995; **89**: 313–8.
9 Tefferi A, Fonesca R. Selective serotonin reuptake inhibitors are effective in the treatment of polycythaemia vera-associated pruritus. *Blood* 2002; **99**: 262–7.

10 Pujol RM, Gallardo F, Listosella E *et al*. Invisible mycosis fungoides: a diagnostic challenge. *J Am Acad Dermatol* 2000; **42**: 324–8.

Endocrine disease

Thyrotoxicosis

Intractable itching, associated with a warm, moist skin, is a recognized accompaniment of thyrotoxicosis and may be the presenting symptom [1]. The cause is uncertain. Localized pruritus may result from mucocutaneous candidiasis. Cutaneous vasodilatation, a regular feature of the disease, leads to increased skin surface temperature, which lowers the itch threshold [2]. Myxoedema may also cause troublesome itching, but in this case the cause is usually excessive drying of the skin, which feels cool, and which responds to application of moisturizing creams.

Diabetes mellitus

Contrary to popular wisdom, generalized pruritus is not a manifestation of diabetic mellitus, the erroneous belief having originated from a 1927 report of a 3% prevalence in 500 patients [3], which coincides with the expected frequency in the general population. A more recent study [4] reported generalized pruritus in eight of 300 diabetic patients, which was not more common than in non-diabetic patients. However, intractable anogenital itching may occur due to mucocutaneous candidiasis. Localized pruritus of the scalp is also a recognized manifestation of diabetes and is usually resistant to antipruritic measures [5].

Malignancy

The problem of pruritus as a manifestation of malignant diseases has been the subject of numerous publications reviewed by Lober [6] and Paul *et al.* [7]. Paul *et al*. followed up 125 patients with generalized pruritus for 6 years [7]. Of these, 66% still had pruritus at the end of the study. Although four proved to have a malignant condition at the onset of the study, only four others developed malignancy during the follow-up period. This is no different from the expected frequency in the general population. However, pruritus, often induced by contact with water, is a recognized presenting symptom of polycythaemia vera [8]. Pruritus is intense in Sézary syndrome, but the skin is inflamed in this malignancy. The practical issue of the extent to which patients with generalized pruritus in the presence of a normal skin should be investigated cannot be separated from economic considerations [9]. Pruritus may be an early B symptom of Hodgkin's disease [10].

References

1 Caravati CM Jr, Richardson DR, Wood BT, Cawley EP. Cutaneous manifestations of hyperthyroidism. *South Med J* 1969; **62**: 1127–30.
2 Fruhstorfer H, Hermanns M, Latzke L. The effects of thermal stimulation on clinical and experimental itch. *Pain* 1986; **24**: 259–69.
3 Greenwood AM. A study of the skin in 500 cases of diabetes. *JAMA* 1927; **89**: 774–6.
4 Neilly JB, Martin A, Simpson N, MacCuish AC. Pruritus in diabetes mellitus: investigation of prevalence and correlation with diabetes control. *Diabetes Care* 1986; **9**: 273–5.
5 Scribner M. Diabetes and pruritus of the scalp [letter]. *JAMA* 1977; **237**: 1559.
6 Lober CW. Should the patient with generalized pruritus be evaluated for malignancy? *J Am Acad Dermatol* 1988; **19**: 350–2.
7 Paul R, Paul R, Jansen CT. Itch and malignancy prognosis in generalized pruritus: a six year follow up of 125 patients. *J Am Acad Dermatol* 1987; **16**: 1179–82.
8 Gilbert HS, Warner RP, Wassermann LR. A study of histamine in myeloproliferative disease. *Blood* 1966; **28**: 795–806.
9 Kantor GR, Lookingbill DP. Generalized pruritus and systemic disease. *J Am Acad Dermatol* 1983; **9**: 375–82.
10 Stefanato CM, Reyes-Mugica M. Masked Hodgkin's disease: the pruriginous disguise. *Ped Hematol Oncol* 1996; **13**: 293–4.

Aquagenic pruritus

This term was first used by Shelley [1] to describe what was considered to be a variant of aquagenic urticaria. Three cases of aquagenic pruritus were subsequently reported in detail and shown to be distinct from aquagenic urticaria [2]. The condition was subsequently extensively reviewed [3,4]. Typically, contact with water at any temperature leads to an intense pricking itch in the exposed skin, without visible change in the appearance of the skin. The same symptoms may be evoked by a sudden drop in temperature of the skin. The condition is very chronic and intractable, and sufferers frequently are wrongly considered to be psychoneurotic. The condition, which closely resembles the pruritus of polycythaemia vera, responds poorly to antihistamine treatment but may respond to UVB phototherapy or PUVA [5–7]. It may be a premonitory symptom of polycythaemia vera [8]. Other underlying causes recently reported include metastatic carcinoma of the cervix [9], hypereosinophilic syndrome [10], juvenile xanthogranuloma [11] and the myelodysplastic syndrome [12]. Aquagenic pruritus may also be a manifestation of an adverse drug reaction [13].

The molecular basis of the pruritus is uncertain. Investigation of affected skin has shown elevated histamine concentrations and increased cutaneous mast cell degranulation, and the serum histamine concentration has also been shown to be raised [2]. The lack of visible evidence of histamine release can be explained by its slow rate of release, leading to skin concentrations sufficient to cause itching but below the threshold for visible vascular changes. However, histamine is unlikely to be the sole mediator, since antihistamine treatment is generally ineffective, and there is also evidence of the involvement of acetylcholine, since topical hyoscine treatment rendered skin unresponsive to water contact [2]. Further evidence for acetyl choline as a mediator derives from a report of increased acetyl cholinesterase activity localized to nerve fibres investing eccrine sweat glands in patients with aquagenic pruritus [14]. There has also been a report of increased tissue fibrinolytic activity in affected skin of patients with aquagenic pruritus [15], which could be a response to increased local concentrations of histamine or acetyl choline.

References

1 Shelley WB. Questions and answers. *JAMA* 1970; **212**: 1385.
2 Greaves MW, Black AK, Eady RAJ, Coutts A. Aquagenic pruritus. *BMJ* 1981; **282**: 2008–10.
3 Steinman HK, Greaves MW. Aquagenic pruritus. *J Am Acad Dermatol* 1985; **13**: 91–6.
4 Kligman AM, Greaves MW, Steinman H. Water induced itching without cutaneous signs: aquagenic pruritus. *Arch Dermatol* 1986; **122**: 183–6.
5 Menagé HP, Norris PG, Hawk JLM, Greaves MW. The efficacy of psoralen photochemotherapy in the treatment of aquagenic pruritus. *Br J Dermatol* 1993; **129**: 163–5.
6 du Peloux Menage H, Greaves MW. Aquagenic pruritus. *Semin Dermatol* 1995; **14**: 313–6.

7 Holme SA, Anstey AV. Aquagenic pruritus responding to intermittent photochemotherapy. *Clin Exp Dermatol* 2002; **27**: 164–5.
8 Archer CB, Camp RDR, Greaves MW. Polycythaemia vera can present with aquagenic pruritus [letter]. *Lancet* 1988; **i**: 1451.
9 Ferguson JE, August PJ, Guy AJ. Aquagenic pruritus associated with metastatic squamous cell carcinoma of the cervix. *Clin Exp Dermatol* 1994; **19**: 257–8.
10 Newton JA, Singh AK, Greaves MW, Spry CJF. Aquagenic pruritus associated with the idiopathic hypereosinophilic syndrome. *Br J Dermatol* 1990; **122**: 103–6.
11 Handfield-Jones SE, Hills RJ, Ive FA, Greaves MW. Aquagenic pruritus associated with juvenile xanthogranuloma. *Clin Exp Dermatol* 1993; **18**: 253–5.
12 McGrath JA, Greaves MW, Warin AP. Aquagenic pruritus and myelodysplastic syndrome. *Am J Hematol* 1991; **37**: 63.
13 Jimenez-Alonso J, Tercedor J, Jaimez, L, Garcia-Lora E. Antimalarial drug-induced aquagenic-type pruritus in patients with lupus. *Arthritis Rheum* 1998; **41**: 744–5.
14 Bircher AJ, Meier-Ruge W. Aquagenic pruritus: water induced activation of acetyl cholinesterase. *Arch Dermatol* 1988; **124**: 84–9.
15 Lotti T, Cappigi P, Lattari P, Panconesi E. Increased cutaneous fibrinolytic activity in a case of aquagenic pruritus. *Int J Dermatol* 1984; **23**: 61–2.

Pruritus of senescence

Persistent and widespread itching, often associated with extensive excoriation, is experienced by at least 50% of people in the seventh decade of life or beyond. Because of the gradually increasing proportion of elderly persons in the population, it is also a burgeoning problem. In women, itching may be a manifestation of the postmenopausal syndrome. Pruritus of elderly people may be a symptom of subtle skin disease such as scabies, especially in institutionalized elderly persons, a manifestation of underlying systemic disorder, including renal, hepatic or malignant disease, a skin manifestation of an adverse drug reaction or symptomatic of depression and loneliness. However, in most instances, itching is a result of excessive dryness (xerosis) of the skin. In a study of 149 elderly men and women, 39% had pruritus due to xerosis [1]. There is evidence of slow reduction of sebum production by skin in association with ageing, and its composition also alters [2,3]; however, this is not thought to be a major factor in xerosis of the elderly. Senescence in the skin is frequently associated with failure of the skin to retain water. The resulting dryness and fine cracking of the skin is associated with troublesome itching, which in most instances responds to emollient treatment. Water-induced itching in elderly people [4] is a variant of senescent pruritus, being particularly common in institutionalized elderly people who may be exposed to an overheated, dry environment, resulting in skin desiccation, and both it and the common spontaneous variety respond to emollient treatment. Analysis of senescent stratum corneum has shown a greatly reduced water content [5]. Recently dystrophic changes in afferent nerve terminals have been identified in pruritic senescent skin and may have a pathogenetic role [6,7].

It is usually most expedient to prescribe several different emollients and encourage the patient to experiment with these, since it is not possible to predict with confidence individual responses. Soft white paraffin ointment is cheap, occlusive and has been shown to accelerate recovery of barrier function in damaged skin [8]. The patient must be encouraged to apply emollients at least four times daily and, if necessary, ambient temperature and humidity should be modified. Doxepin 10–20 mg at night is useful in patients in whom there is a significant element of depression. Corticosteroids, antihistamines and cooling lotions are not indicated in itching due to xerosis.

References

1 Thaipisuttikul Y. Pruritic diseases of the elderly. *J Dermatol* 1998; **25**: 153–7.
2 Jacobsen E, Billings JK, Frantz RA *et al*. Age related changes in sebaceous wax ester secretion rates in men and women. *J Invest Dermatol* 1985; **85**: 483–5.
3 Yamamoto A, Serizawa S, Ito M, Sato Y. Effect of ageing on sebaceous gland activity and on fatty acid composition of wax esters. *J Invest Dermatol* 1987; **89**: 507–12.
4 Kligman AM, Greaves MW, Steinman H. Water induced itching without cutaneous signs: aquagenic pruritus. *Arch Dermatol* 1986; **122**: 183–6.
5 Hara M, Kikuchi K *et al*. Senile xerosis, functional morphological and biochemical studies. *J Geriatr Dermatol* 1993; **1**: 111–20.
6 Nusbaum J. Aging and sensory senescence. *South Med J* 1999; **92**: 135–9.
7 Ward JR, Bernhard JD. Willan's itch and other causes of pruritus in the elderly. *Int J Dermatol* 2005; **44**: 267–73.
8 Ghiadially R, Halkier-Sorensen L, Elias PM. Effects of petrolatum on stratum corneum structure and function. *J Am Acad Dermatol* 1992; **26**: 387–96.

Psychogenic pruritus

Itching, either localized or generalized, can be a skin manifestation of psychological disturbance. There are no satisfactory 'rule in, rule out' diagnostic paradigms; therefore, in practice the conclusion that local or generalized itch is psychogenic in origin is arrived at by a process of exclusion of cutaneous or systemic causes.

Perianal and, in women, vulval itching are recognized manifestations of local psychogenic pruritus and are in some cases stress related, although this cause is probably over-rated and care must be taken to rule out occult remediable causes, including threadworms (pinworms), dermatitis medicamentosa, diabetes-induced candidiasis and local inflammatory or neoplastic disease. Attacks of nocturnal pruritus, associated with a sensation of heat and accompanied by sweating, are often due to anxiety. Such episodes of pruritus were recently reported in patients awaiting transplant surgery [1]. Widespread psychogenic pruritus may result in extensive and disfiguring excoriations and even scarring to the extent of self-mutilation. Parasitophobia (delusions of parasitic infestation of the skin) is normally readily recognizable, because of the patient's description of the itch and even the presentation by the patient of particulate material considered by the sufferer to represent the supposed insects or their products. Of two recent patients of the author, one brought along a small portable microscope to aid viewing of the 'insects', and the other brought textbooks of dermatology and parasitology to the clinic to support her case! Although rarely successful, psychiatric advice should be sought, and antidepressant and anxiolytic drugs, including doxepin and hydroxyzine, should be tried. Treatment options for these patients have been well reviewed [2]. Pimozide (phenylbutylpiperidine), a phenothiazine, has been used for treatment of delusions of parasitosis [3] and paroxetine, a selective serotonin reuptake inhibitor, has also been advocated [4]. It is also self-evident that patients experiencing severe, persistent pruritus become secondarily depressed, and that this may itself lower the threshold for pruritus, thus completing a 'vicious circle' of itch, depression and more itch [5].

References

1 Gabriel GM, Crone CC. Nocturnal pruritus in a cardiac pretransplant patient. *Psychosomatics* 2001; **42**: 344–6.
2 Fried RG. Evaluation and treatment of 'psychogenic' pruritus and self-excoriation. *J Am Acad Dermatol* 1994; **30**: 993–9.
3 Newbold PCH. Antidepressants and skin disease. *BMJ* 1988; **298**: 379.
4 Biondi M, Arcangeli T, Pertucci RM. Paroxetine in a case of psychogenic pruritus and neurotic excoriations. *Psychother Psychosom* 2000; **69**: 165–6.
5 Gupta MA, Gupta AK, Schork NJ, Ellis CN. Depression modulates pruritus perception: a study of pruritus in psoriasis, atopic dermatitis and chronic idiopathic urticaria. *Psychosom Med* 1994; **56**: 36–40.

Postmenopausal pruritus

The commonest presentation of postmenopausal pruritus is pruritus vulvae, often a manifestation of oestrogen deficiency and associated with mucocutaneous candidiasis and diabetes. It should respond to corrective hormone therapy, combined if necessary with nystatin or other anti-*Candida* therapy.

Persistent or episodic widespread itching is occasionally associated with the postmenopausal syndrome. The itching characteristically evokes rubbing, rather than heavy excoriation, and is frequently associated with hot flushes. It is especially troublesome at night, and is usually associated with raised plasma levels of pituitary follicular and luteal stimulating hormones. These hormones are unlikely, however, to be the direct cause of the itching and associated flushing, which are probably attributable to local tissue mediators. Hormone-replacement therapy with ethinyl oestradiol is usually sufficient to control postmenopausal pruritus due to this cause [1], but since systemic oestrogen therapy can be hazardous, expert endocrinological advice should be sought.

Reference

1 Tzingounis VA, Aksu MF, Greenblatt RB. Estriol in the management of the menopause. *JAMA* 1978; **239**: 1638–41.

Pruritus of atopic dermatitis

The itch of atopic dermatitis is aggravated by scratch damage, which causes enhanced inflammation (itch–scratch cycle). Itching is usually worse at night, and is aggravated by contact with wool, sweat, spicy foods and alcohol. Considerable sleep loss and incapacity ensues. No aspect of pruritus has provoked more debate than the pathophysiology of itching in atopic dermatitis and its management. The itching of atopic dermatitis is multifactorial, being due to dryness, almost invariable in atopic dermatitis sufferers, inflammation and probably to disturbed regulation of itch traffic in the central nervous system. In this context, alloknesis (itchy skin; see p. 21.5) forms a major component of the itch suffered by the atopic dermatitis patient—explaining, for example, the paroxysms of itching experienced by patients in response to sweating, sudden changes of temperature, humidity, undressing or dressing, etc. These multiple and distinct mechanisms may explain seemingly conflicting views on the nature and causation of pruritus in atopic dermatitis. Pruritus in atopic dermatitis involves pruritoceptive neurogenic, and probably psychogenic, mechanisms. Several studies, reviewed by Rajka [1], have reported an enhanced and abnormally prolonged response to application of pruritic pharmacological stimuli in unaffected skin in atopic patients. Studies of the itching response of atopic dermatitis patients to histamine iontophoresis suggest a decreased response of afferent cutaneous fibres to high doses, but an increased sensitivity to low concentrations—possibly because of increased permeability of clinically normal-looking skin of these atopic patients [2]. There is also an increased population density of sensory nerve fibres in the affected lichenified pruriginous skin [3], although this is probably non-specific. It is important to distinguish itching associated with inflammatory changes or chronic lichenification from that simply due to excessive drying of the skin in patients with atopic dermatitis. Emollients, which should always be prescribed and which in many cases may be all that is required, will be inadequate alone where inflammatory changes are responsible for the itching. Recent dermal microdialysis studies have demonstrated the involvement of mast-cell mediators other than histamine in lesional skin of atopic dermatitis patients [4]. An evidence-based review [5] of the effectiveness of H_1 antihistamines concluded that they are of little value in relieving pruritus. However, it is self-evident that most patients with itchy atopic dermatitis receive antihistamines, mainly of the sedative type, and usually find them of some value—presumably due to their central action. On the basis of a comparison of itching in atopic dermatitis patients receiving successively terfenadine (now withdrawn by the manufacturers due to adverse cardiac side effects) or astemizole (low-sedation antihistamines), trimeprazine (sedative antihistamine) and nitrazepam (non-antihistamine sedative), one study [6] concluded that sedation was a required component of successful systemic treatment of itching in atopics, and that, moreover, itching in atopic dermatitis involved a central component. However, numbers of patients were small and subsequent studies have yielded conflicting results.

Systemic antibiotics frequently bring about relief from pruritus. *Staphylococcus aureus* behaves as a superantigen leading to T-cell activation, and also activates dermal mast cells via toll-like receptors [7].

Topical steroids are frequently effective in suppressing itching in the atopic dermatitis patient. Corticosteroids are not inherently antipruritic, but suppress the inflammatory component of the dermatosis thereby alleviating the itching indirectly. They are especially effective in highly pruritic children with atopic dermatitis applied by the 'wet wrap' technique [8]. Phototherapy is widely used for the pruritus of atopic dermatitis in older children and adults, especially when it is intractable and widespread. Both broad-band and narrow-band ultraviolet B are used, the latter being deemed superior [9]. Immunosuppressives—including systemic azathioprine and ciclosporin—are highly effective in relieving the itching (and other signs and symptoms) of chronic atopic dermatitis in selected patients [10,11], probably due to an action on activated $CD4^+$ T-helper lymphocytes. The recent introduction of topical calcineurin inhibitors, tacrolimus and pimecrolimus, provides an effective new measure for amelioration of pruritus of atopic dermatitis [12,13]. These agents owe their action to down-regulation of activated T cells. Recent work [14] has highlighted the role of interleukin-31 (IL-31) in the itch of atopic dermatitis

Table 21.5 Treatments for pruritus of atopic dermatitis.

Treatment	Level of preference	Level of effectiveness
Emollients	1	high
Topical steroids	2	high
Sedative antihistamines	2	medium
Topical calcineurin inhibitors	2	high
Narrow-band UVB phototherapy	1	high
Azathioprine	3	high
Ciclosporin	3	high

1 = high; 2 = moderate; 3 = low

and this cytokine is likely to be a target for future antipruritic therapeutic intervention (see section Cytokines, above).

Opioid antagonists such as oral naltrexone may be of value in patients with intensely pruritic atopic dermatitis [15]. Aspirin given systemically is ineffective in the suppression of itching in atopic dermatitis but may be effective in a topical formulation [16]. Treatment approaches to itching in atopic dermatitis are summarized in Table 21.5.

References

1 Rajka G. *Atopic Dermatitis,* Vol. 3, Major Problems in Dermatology. London: Saunders, 1975: 38–41.
2 Hieger G, Hornstein OP, Handwerker HO. Skin reactions and itch sensation induced by epicutaneous histamine application in atopic dermatitis and controls. *J Invest Dermatol* 1960; **34**: 237–8.
3 Runne U, Orfanos CE. Cutaneous neural proliferation in highly pruritic lesions of chronic prurigo. *Arch Dermatol* 1977; **113**: 787–91.
4 Rukwied R, Lischetzki G, McGlone F *et al.* Mast cell mediators other than histamine induce pruritus in atopic dermatitis patients: a dermal microdialysis study. *Br J Dermatol* 2000; **142**: 1114–20.
5 Klein PA, Clarke RAF. An evidence-based review of the efficacy of antihistamine in relieving pruritus in atopic dermatitis. *Arch Dermatol* 1999; **135**: 1522–5.
6 Krause L, Shuster S. Mechanism of action of antipruritic drugs. *BMJ* 1983; **287**: 1119–2000.
7 Supajatura V, Hiroko U, Nakao A *et al.* Differential responses of mast cell Toll-like receptors 2 and 4 in allergy and innate immunity. *J Clin Invest* 2002; **109**: 1351–9.
8 Devillers A, Oranje AP. Efficacy and safety of wet-wrap dressings in the treatment of children with atopic dermatitis: a review of the literature. *Br J Dermatol* 2006; **154**: 579–85.
9 Reynolds NJ, Franklin V, Gray JC *et al*. Narrow band ultraviolet B and broad band ultraviolet A phototherapy in adult atopic eczema: a randomized controlled trial. *Lancet* 2001; **357**: 2012–6.
10 Wahlgren CF, Scheynius A, Hagermark O. Antipruritic effect of oral cyclosporin A in atopic dermatitis. *Acta Derm-Venereol (Stockh)* 1990; **70**: 323–9.
11 Megitt SJ, Gray JC, Reynolds N. Azathioprine dosed by thiopurine methyltransferase activity for moderate-to-severe atopic eczema: a double-blind randomised controlled trial. *Lancet* 2006; **367**: 839–46.
12 Ruzicka T, Bieber T, Schopf E *et al.* A short-term trial of tacrolimus ointment for atopic dermatitis. *N Engl J Med* 1997; **337**: 816–21.
13 Stander S, Luger TA. Antipruritische Wirkung von Pimecrolimus und Tacrolimus. *Hautartz* 2003; **54**: 413–7.
14 Sonkoly E, Muller A, Lauerman AI. IL-31: a new link between T cells and pruritus in atopic skin inflammation. *J Allergy Clin Immunol* 2006; **117**: 411–7.
15 Heyer G, Groene D, Martens P. Efficacy of natrexone on acetyl choline-induced alloknesis in atopic eczema. *Exp Dermatol* 2002; **11**: 448–55.
16 Yosipovitch G, Sugeng MW, Chan YH *et al*. The effect of topically applied aspirin on localized circumscribed neurodermatitis. *J Am Acad Dermatol* 2001; **45**: 910–3.

Acquired immune deficiency syndrome

Itching is an important symptom of acquired immune deficiency syndrome (AIDS) [1]. It may be associated with underlying systemic disease (cholestasis, hepatitis B or C, renal failure, lymphoreticular malignancy) as well as numerous skin diseases including seborrhoeic dermatitis, psoriasis, scabies, candidiasis, ringworm, staphylococcal skin infections, eosinophilic folliculitis [2], lichenoid dermatitis and prurigo nodularis. In some patients, intractable itching occurs in the absence of any obvious primary skin or systemic cause apart from the HIV infection itself [3]. Patients with intense pruritus tend to have high IgE levels, a rapid decline in CD4 lymphocyte counts, hypereosinophilia and a high viral load [4]. Pruritus as a presenting feature of adverse drug reactions in HIV-positive patients must not be overlooked, and these reactions may be associated with photosensitivity. Thalidomide can be useful in the treatment of HIV-positive patients with intractable pruritus and prurigo nodularis [5]. Other treatments reported to be effective include dapsone, pentoxifylline, UVB phototherapy and PUVA [6–8].

References

1 Rodwell GEL, Berger EG. Pruritus and cutaneous inflammatory conditions in HIV disease. *Clin Dermatol* 2000; **18**: 479–84.
2 Hevia O, Jimenez-Acostera F, Ceballos PI *et al.* Pruritic papular eruption of acquired immunodeficiency syndrome: a clinicopathologic study. *J Am Acad Dermatol* 1991; **24**: 231–5.
3 Gelfand JM, Rudikoff D. Evaluation and treatment of itching in HIV-infected patients. *Mount Sinai J Med* 2001; **68**: 298–308.
4 Milazzo F, Piconi S, Trabattoni D *et al.* Intractable pruritus in HIV infection: immunologic characterization. *Allergy* 2000; **54**: 266–72.
5 Calibrese L, Fleischer AB. Thalidomide: current and potential clinical applications. *Am J Med* 2000; **108**: 487–95.
6 Bason MM, Berger TG, Nesbitt LT Jr. Pruritic papular eruption of HIV-disease. *Int J Dermatol* 1993; **32**: 784–9.
7 Lim H, Vallurupalli S, Meola T, Soter NA. UVB phototherapy is an effective treatment for pruritus in patients infected with HIV. *J Am Acad Dermatol* 1997; **37**: 414–7.
8 Burke B, Flores F, Burke G. Efficacy of pentoxifylline in the treatment of papular eruption of HIV infected persons. *J Am Acad Dermatol* 1998; **38**: 955–9.

Pruritus in pregnancy

Pruritus occurs in about 20% of pregnant women. In the majority of these the itching is localized to the anogenital area, often secondary to vulvovaginitis due to candidosis, bacterial causes or to pre-existing dermatoses such as psoriasis and endogenous eczema. However, more widespread pruritus is also frequent. Important possible causes include scabies and exacerbation of pre-existing atopic dermatitis or psoriasis. The specific dermatoses of pregnancy may also present with pruritus. The commonest is pruritic urticated papules of pregnancy (PUPP; polymorphous eruption of pregnancy), but the less common pemphigoid gestationis and cholestasis of pregnancy are also intensely pruritic; these have been reviewed [1].

No treatment for itching is absolutely safe in pregnancy, but it is a reasonable assumption that persistent, intense pruritus is itself prejudicial to healthy pregnancy. The following are deemed the least unsafe measures in the pruritic pregnant patient: (i) topical—

1–2% menthol cream or lotion; 5% urea cream (for dry skin); benzyl benzoate application (for scabies); topical steroids (low–moderate potency only); (ii) systemic—chlorpheniramine; diphenhydramine; hydroxyzine; (iii) other—UVB phototherapy.

Reference

1 Al-Fares SI, Vaughan SA, Black MM. The specific dermatoses of pregnancy: a reappraisal. *J Eur Acad Derm Vener* 2001; **15**: 197–206.

Pruritus ani and pruritus vulvae

Pruritus ani occurs in 1–5% of the adult population, and is more common in males than females [1]. The frequency of pruritus vulvae is unknown, but it is evident that most women suffer from it at some time in their lives, most commonly postmenopausally. Anogenital pruritus in both sexes is a cause of severe distress and sleep disturbance due to persistent treatment-resistant itch–scratch–itch cycle. It may be a manifestation of skin or systemic disease. Common dermatoses involving the anogenital area include psoriasis, atopic dermatitis, lichen sclerosus, lichen planus, seborrhoeic dermatitis, scabies and allergic contact dermatitis—especially to perfumed soaps. In one study, 18 of 40 patients with pruritus ani had positive patch tests [2]. Common culprits include topical antihistamines and local anaesthetics (dermatitis medicamentosa) [3]. There are also several important local causes of anogenital pruritus including threadworms (pinworms), viral warts, haemorrhoids, lichen simplex chronicus, squamous cell carcinoma, exposure to detergents, bubble baths and urinary or faecal incontinence. In both sexes, but especially in the female, candidosis is an important cause and should always prompt screening for diabetes mellitus. In a large study of 1104 patients with pruritus vulvae, 85% were found to have vaginitis due to *Candida*, *Trichomonas* or bacterial causes [4]. Oestrogen deficiency is also an important cause in postmenopausal females. 'Stress' is often cited as a psychogenic cause but in reality is probably over-diagnosed [4]. Treatment includes avoidance of overenthusiastic use of cleansers, foam baths, perfumed soaps. Sitz baths (warm water hip baths) yield immediate relief. Ointments rather than creams, including silicone or zinc ointments, are helpful. The priority must be to remove or treat any underlying cause and a rectal and/or vaginal examination should always be performed. However, no cause may be identified or, even if identified and treated, itching may persist and in these cases topical corticosteroids are normally prescribed. However, in one comparative study of idiopathic perianal pruritus, topical methyl prednisolone cream applied for 2 weeks in 28 patients and application of a liquid cleanser in 32 patients were equally effective, with a good response in 90% of patients in each group [5]. Topical capsaicin is also effective. In one double-blind cross-over study comparing capsaicin 0.006% cream with menthol 1% cream in 44 patients with idiopathic intractable pruritus ani, capsaicin was effective in 31, menthol being invariably ineffective [6].

References

1 Daniel GL, Longo WE, Vernava AM. Pruritus ani: causes and concern. *Dis Colon Rectum* 1994; **37**: 670–4.

2 Dasan S, Neill SM, Donaldson NDR *et al.* Treatment of persistent pruritus ani in a combined colorectal and dermatological clinic. *Br J Surgery* 1999; **86**: 1337–40.

3 Bauer A, Geier J, Elsner P. Allergic contact dermatitis in patients with anogenital complaints. *J Reprod Med* 2000; **45**: 649–54.

4 Rumpianske R, Shiskin J. Pruritus vulvae: a five year survey. *Dermatologica* 1965; **131**: 446–51.

5 Oztas MO, Oztas P, Onder M. Idiopathic perianal pruritus: washing compared with topical steroids. *Postgrad Med J* 2004; **80**: 295–7.

6 Lysy J, Sistiery-Ittah M, Israelit Y *et al.* Topical capsaicin—a novel and effective treatment for idiopathic pruritus ani: a randomized placebo-controlled cross-over study. *Gut* 2003; **52**: 1323–6.

Important miscellaneous causes of intense itching

Hydroxyethyl starch [1]

Hydroxyethyl starch (HES) is used widely as a plasma substitute, especially on the continent of Europe. It is also used to improve the function of the microcirculation. Generalized pruritus has been reported as a well-recognized complication, occurring in 15–42% of patients [2]. It results from deposits of HES in macrophages and peripheral nerves in the skin, and may be associated with erythema [1,3]. It is poorly responsive to antihistamines, but may respond to topical capsaicin [4].

Pemphigoid nodularis

Bullous pemphigoid can present with non-specific pruritus. There have also been reports from several centres [5–7] of patients presenting with a chronic prurigo nodularis-like eruption who subsequently proved—by histological examination, direct immunofluorescence and clinical follow-up—to have bullous pemphigoid; blisters eventually developed in most cases reported. It is important to carry out a skin biopsy for histological examination and direct immunofluorescence for immunoreactants on all patients with what appears to be prurigo nodularis.

Notalgia paraesthetica

This is a fairly common cause of localized persistent pruritus. Characteristically, patients complain of persistent burning pruritus localized to the mid-scapular area, but often extending from there to a more widespread distribution, including the scalp. Apart from mild lichenification and pigmentation with or without macular amyloidosis, there is usually little to see. Reports of increased cutaneous innervation are probably correct, but may represent a non-specific change [8]. Recent reports stress the importance of nerve root entrapment (neuropathic pruritus) [8–10]. Capsaicin cream appears to be effective in some patients, and the current view is that it is a type of localized sensory neuropathy [11].

Brachioradial pruritus

This increasingly common sunlight-induced chronic pruritus is localized to the outer aspect of the elbow, and adjacent lower and upper arms [12]. The increased popularity of prolonged and frequent outdoor holidays in areas of high insolation amongst middle-aged and elderly fair-skinned people probably accounts

for its increased frequency. A typical patient of the author with this diagnosis had spent much of the year sailing and golfing in the Caribbean region. She responded to treatment with capsaicin cream [13]. However, brachioradial pruritus can be unresponsive to treatment. Gabapentin has been reported to be effective in such cases [14]. Pruritus and prurigo due to chronic sun exposure may occasionally be much more widespread and has been termed 'solar pruritus'. They are probably identical to brachioradial pruritus [15]. Bilateral cases should prompt investigation for a spinal tumour [16].

Anorexia nervosa

That generalized pruritus is one of several skin manifestations of anorexia nervosa is well recognized [17]. Itching is associated with low body weight and resolves with weight restoration. The itching is independent of underlying disease, including endocrine factors, renal or hepatic complications, or excessive washing. The skin may be excoriated and present a prurigo-like appearance. The itching could be central (neurogenic) in origin, but further evidence is awaited [18].

References

1 Cox NH, Popple AW. Persistent erythema and pruritus, with a confluent histiocytic skin infiltrate, following the use of a hydroxyethyl starch plasma expander. *Br J Dermatol* 1996; **134**: 353–7.

2 Metze D, Reimann S, Szepfalusi Z *et al*. Persistent pruritus after hydroxyethyl starch infusion therapy: a result of long-term storage in cutaneous nerves. *Br J Dermatol* 1997; **136**: 553–9.

3 Jurecka W, Szepfalusi Z, Parth E *et al*. Hydroxyethyl starch deposits in human skin: a model for pruritus? *Arch Dermatol Res* 1993; **285**: 13–9.

4 Szeimies RM, Stolz W, Wlotzke U *et al*. Successful treatment of hydroxyethyl starch-induced pruritus with topical capsaicin. *Br J Dermatol* 1994; **131**: 380–2.

5 Bourke JF, Berth-Jones J, Gawkrodger DJ, Burns DA. Pemphigoid nodularis: a report of 2 cases. *Clin Exp Dermatol* 1994; **19**: 496–9.

6 Roenigk RK, Dahl MV. Bullous pemphigoid and prurigo nodularis. *J Am Acad Dermatol* 1986; **14**: 944–7.

7 Ross JS, McKee PH, Smith NP *et al.* Unusual variants of pemphigoid: from pruritus to pemphigoid nodularis. *J Cutan Pathol* 1992; **19**: 212–6.

8 Springall DR, Karanth SS, Kirkham N *et al.* Symptoms of notalgia paresthetica may be explained by increased dermal innervation. *J Invest Dermatol* 1991; **97**: 555–61.

9 Massey EW, Fleet AB. Electromyographic evaluation of notalgia paraesthetica. *Neurology* 1981; **31**: 642.

10 Eisenberg E, Barmeir E, Bergman R. Notalgia paraesthetica associated with nerve root impingement. *J Am Acad Dermatol* 1997; **37**: 998–2000.

11 Wallengren J, Klinker M. Successful treatment of notalgia paraesthetica with topical capsaicin: vehicle controlled, double blind, crossover study. *J Am Acad Dermatol* 1995; **32**: 287–9.

12 Walcyk PJ, Elpern DJ. Brachio-radial pruritus: a tropical dermopathy. *Br J Dermatol* 1986; **115**: 177–80.

13 Knight TE, Hayashi T. Solar (brachioradial) pruritus: response to capsaicin cream. *Int J Dermatol* 1994; **33**: 206–9.

14 Bueller HA, Bernhard JD, Dubroff LM. Gabapentin treatment for brachioradial pruritus. *J Eur Acad Dermatol* 1999; **12**: 227–30.

15 Bech-Thomsen N, Thomsen K. Solar pruritus. *Acta Derm-Venereol (Stockh)* 1995; **75**: 488–9.

16 Kavak, A, Dosoglu M. Can a spinal tumour cause brachioradial pruritus? *J Am Acad Dermatol* 2002; **46**: 437–40.

17 Taniguchi S, Yamamoto N, Kono T *et al.* Generalised pruritus in anorexia nervosa. *Br J Dermatol* 1996; **134**: 510–1.

18 Morgan JF, Lacey JH. Scratching and fasting: a study of pruritus and anorexia nervosa. *Br J Dermatol* 1999; **140**: 453–6.

Clinical and laboratory investigation of generalized pruritus

Pruritus is a highly subjective symptom and careful history taking is crucial. The onset, quality, severity and timing of the itching should be established. Quantification of itch frequency is best achieved by using categoric scales (e.g. never, rarely, occasionally, frequently, always). For severity, a continuous visual analogue scale [1] is usually employed. Other more sophisticated methods for measuring itch, including scratch behaviour measurement devices, are discussed above (p. 21.2) and are primarily useful for research applications.

The location and fixed or ephemeral nature of bouts of itching should be determined, together with relationship to activities, provoking factors, medications, recreational, social and ablutional habits. It is always worth listening to the patient's own views on causation. Sufferers from aquagenic pruritus were rarely believed until the disease became recognized as an entity in the 1970s. Use of a questionnaire, for example the Eppendorf Itch Questionnaire [2], enables elicitation of standardized historical information.

To distinguish secondary eczematization due to persistent scratching from primary skin disease as a cause of pruritus is a common diagnostic challenge, especially in the elderly. In the absence of obvious causative primary skin disease or symptoms or signs indicating systemic disease, it is essential to carry out a full physical examination, including lymph node, rectal and pelvic examination. This should be followed by full blood count urine examination for sugar protein and blood, erythrocyte sedimentation rate, chest X-ray and thyroid, renal and liver-screening tests. Other routine imaging investigations and endoscopy are probably not justified in the absence of localizing symptoms or signs, although examination of the stool for occult blood is a useful and cheap investigation. The possibility that persistent, generalized pruritus in the absence of skin signs can be an adverse reaction to a systemic drug should never be overlooked.

In the absence of clinical evidence of primary skin disease, histological examination of a skin biopsy is rarely helpful and is not recommended as part of the routine work-up. All patients with generalized pruritus of unrecognized cause should be followed up regularly as long as the symptom persists.

References

1 Wahlgren CF, Ekblom A, Hagermark Ö. Some aspects of the experimental induction and measurement of itch. *Acta Derm-Venereol* 1989; **69**: 185–9.

2 Darsow U, Scharein E, Simon D *et al.* New aspects of itch pathophysiology: component analysis of atopic itch using the Eppendorf Itch Questionnaire. *Int Arch Allergy Immunol* 2001; **124**: 326–31.

Management of itching

Obviously, the most important step is to identify and treat the fundamental cause of the itch, whether it is primarily in the skin or of a systemic origin. At the same time, patients require symptomatic relief. At the time of writing there are no specific anti-itch medications. Pruritus is temperature dependent [1], and therefore wearing light clothes, keeping the bedroom cool, using light

Table 21.6 Topical treatments for itchy dry skin.

Medication	Mode of action	Comment
Emollients	Form water-impervious barrier, reduce transepidermal water loss	
Aqueous cream		Short lived action, needs to be applied frequently
Emulsifying ointment White soft paraffin Hydrous wool fat		More greasy and substantive
Hydrating creams	Attract and bind water within stratum corneum	
Creams containing 5–10% urea		For dry very scaly skin, can be irritant in some patients

Table 21.7 Topical antipruritic medications.

Topical antipruritic	Mode of action	Comment on usage
Calamine	Cooling as a shake-lotion	Short lived relief, use as a cream in itch associated with dry skin
Menthol	Acts on TRP temperature-sensitive neural channels	Of proven but short-lived value
Capsaicin	Depletes neuropeptides of afferent nerve terminals, acts on TRPV1 vanilloid neural channels	Proven effect in some localized recalcitrant itches (see text), but compliance poor due to burning sensation in early stages of treatment
Doxepin	Tricyclic, also potent H_1 antihistamine	Effective in allaying itch of eczematous dermatitis, but may cause drowsiness, contact allergic sensitization
Corticosteroids	Anti-inflammatory, indirectly antipruritic	Ineffective in itching of clinically normal skin
Calcineurin inhibitors	Down-regulate activated T cells in skin, indirectly antipruritic in eczematous skin	Ineffective in itching of clinically normal skin; relieve itch of atopic dermatitis
Local anaesthetics	Cause temporary loss of all skin sensation at site of application	Suitable for short-term relief only, due to risk of contact allergic sensitization

bedclothes and keeping the working environment as cool as possible are all helpful measures. A cool shower before retiring may allow sleep. Pruritus due to dry skin, especially prevalent in elderly people, will respond to emollients such as soft yellow paraffin and aqueous cream as well as creams containing 5–10% urea (Table 21.6). Water-induced itching in elderly people, which is distinguished from aquagenic pruritus by the presence of clinical evidence of dry skin, is especially responsive to treatment by moisturizing preparations.

Topical phenol and crotamiton [2], though widely used as antipruritics, are of unproven value. A carefully controlled study suggested that topical 1% menthol in 90% ethanol is of significant value in the symptomatic relief of histamine-induced pruritus [3], probably due to activation of cold-sensitive TRP channels on afferent nerve terminals. Topical H_1 antihistamines and topical corticosteroids should not be used in the absence of visible inflammatory changes in the skin. Antihistamine creams and ointments carry a significant risk of contact sensitization. The topical tricyclic compound 5% doxepin cream has been shown to be effective for treatment of itch due to eczema [4] but can cause sedation due to percutaneous absorption and occasionally causes contact sensitization. Local anaesthetic creams are occasionally justifiable for short-term relief, but carry a risk of evoking contact sensitization following prolonged use. Capsaicin, the active alkaloid principle of chilli pepper is being used topically in several localized chronic pruritic disorders. Controlled clinical trials have verified its effectiveness in post-herpetic dysaesthesia [5] and diabetic neuropathy [6]. Its effectiveness in the localized pruritus of nostalgia paraesthetica and brachioradial pruritus has already been alluded to above and has been supported by controlled trials [7,8]. Its main drawback is the burning discomfort associated with its application in the initial stages of treatment, which leads to poor compliance.

Effective antipruritic topical medications are listed in Table 21.7.

Systemic treatments of proven effectiveness for itching are few in number and usually cause some degree of sedation. H_1 antihistamines, mainly the first generation sedative compounds, are widely used for this purpose. Proof of efficacy is often hard to acquire as placebo effects in itching are substantial [9]. H_1 antihistamines are the treatment of choice for the itch of urticaria [10]. In the itch of atopic dermatitis the role of H_1 antihistamines is controversial, there being no clear evidence of effectiveness [11]. Nevertheless, first-generation H_1 antihistamines are widely prescribed to allay itching in atopic dermatitis, any effectiveness for this or other causes of pruritus being probably attributable to their sedative properties. Systemic tricyclic antidepressants such as doxepin 10–25 mg at night may be of help in some patients with intractable itching [12]. Other suggested measures of uncertain efficacy include transcutaneous nerve stimulation [13] and acupuncture [14]. Opioid μ-receptor antagonists, including naloxone, show promise in the management of otherwise intractable pruritus [15] but other than in pruritus of cholestasis, firm evidence of effectiveness is lacking. Paroxetine, a selective serotonin reuptake inhibitor, may have a place in the treatment of intractable pruritus, including the pruritus of advanced cancer according to a recent placebo-controlled double-blind trial [16]. Recently mirtazapine, a dual serotonergic and noradrenergic antidepressant, has been advocated for intractable pruritus including the itch of cutaneous T-cell lymphoma [17,18].

Gabapentin, an anticonvulsant, has also been advocated recently for treatment of pruritus of unknown origin [19]. It is also reported effective in uraemic pruritus in a controlled study [20]. Systemic treatments for pruritus are listed in Table 21.8.

Table 21.8 Systemic antipruritic medications.

Systemic antipruritic	Mode of action	Comment on usage
H_1 antihistamines	Inverse agonists at the H_1 receptor	Proven efficacy in urticaria; controversial in atopic dermatitis and other pruritic dermatoses in which efficacy may be due to sedative action of 1st generation compounds
Doxepin	Tricyclic, and potent H_1 antihistamine	Avoid in presence of cardiac disease, do not prescribe concurrently with other anti-depressants, do not withdraw abruptly
Naltrexone	μ-opioid receptor antagonist	Only of proven efficacy in pruritus of cholestasis; worth trying in other cases of intractable itch
Paroxetine	Selective serotonin reuptake inhibitor	Advocated on the basis of controlled trial data for management of intractable pruritus, especially that associated with internal malignancy; avoid in patients with heart disease
Mirtazapine	Serotonergic and noradrenergic antidepressant	Advocated anecdotally for intractable nocturnal pruritus
Gabapentin	Prevents release of neurotransmitters from pre-synaptic nerve terminals by action on voltage-dependent calcium channels	Effective in uraemic pruritus according to results of a controlled trial

Ultraviolet phototherapy for generalized pruritus

Broad-band or narrow-band ultraviolet B phototherapy (UVB) is used extensively for symptomatic treatment of generalized pruritus whether due to underlying systemic disease, primary skin disease or idiopathic [21]. It has largely superseded UVA photochemotherapy (PUVA). However, randomized controlled trial data are hard to come by. UVB has a good track record in the treatment of pruritus of renal failure and in the treatment of pruritus of polycythaemia vera (see p. 21.10). Its mode of action is unknown, however it may have a systemic rather than an exclusively local action. Other conditions reported to be responsive to UVB phototherapy include Hodgkin's disease, pruritus of HIV infection, prurigo nodularis and aquagenic pruritus.

References

1 Fruhstorfer H, Hermanns M, Latzke L. The effects of thermal stimulation on clinical and experimental itch. *Pain* 1986; **24**: 259–69.
2 Smith EB, King CA, Baker MD. Crotamiton lotion in pruritus. *Int J Dermatol* 1984; **23**: 684–5.
3 Bromm B, Scharein E, Darsow U, Ring J. Effects of menthol and cold on histamine-induced skin reactions in man. *Neurosci Lett* 1995; **187**: 157–60.
4 Breneman DL, Dunlap FE, Monroe EW. Doxepin cream relieves eczema associated pruritus within 15 minutes and is not accompanied by a risk of rebound upon discontinuation. *J Dermatol Treat* 1997; **8**: 161–8.
5 Watson CPN, Tyler KL, Bichers SDR *et al*. A randomised vehicle controlled trial of topical capsaicin in the treatment of post-herpetic neuralgia. *Clin Ther* 1993; **15**: 510–26.
6 Capsaicin Study Group. Treatment of painful diabetic neuropathy with topical capsaicin. *Arch Intern Med* 1991; **151**: 2225–9.
7 Wallengren J. Brachioradial pruritus: a recurrent solar dermopathy. *J Am Acad Dermatol* 1998; **39**: 803–6.
8 Wallengren J, Klinker M. Successful treatment of notalgia paraesthetica with topical capsaicin: vehicle controlled, double blind, crossover study. *J Am Acad Dermatol* 1995; **32**: 287–9.
9 Epstein E, Pinkus JB. A blind study. *Arch Dermatol* 1964; **89**: 548–9.
10 Simons FER. Antihistamines. In: Adkinson NF, Yunginger JW, Busse WW, Simons FER, eds. *Middleton's Allergy: Principles and Practice*, 6th edn. St Louis: Mosby 2003: 834–69.
11 Hoare C, Li Wan Po A, Williams H. Systematic reviews of treatments for atopic eczema. *Health Technol Assess* 2000; **4**: 1–191.
12 Tennyson H, Levine N. Neurotropic and psychotropic drugs in dermatology. *Derm Clinics* 2001; **19**: 179–97.
13 Ekblom B, Fjellner B, Hansson P. The influence of mechanical stimulation and transcutaneous nerve stimulation on the experimental pruritus induced by histamine. *J Physiol Scand* 1984; **122**: 361–7.
14 Lundeberg T, Bondesson K, Thomas M. Effect of acupuncture on experimentally induced itch. *Br J Dermatol* 1987; **117**: 771–7.
15 Taddese A, Nah SY, McCleskey EW. Selective opioid inhibition of small nociceptive neurones. *Science* 1995; **270**: 1366–9.
16 Zylicz Z, Krajnik M, Van Sorge AA, Constantini M. Paroxetine in the treatment of severe non-dermatological pruritus: a randomised controlled trial. *J Pain Symptom Manag* 2003; **26**: 1105–12.
17 Hundley JL, Yosipovitch G. Mirtazapine for reducing nocturnal itch in patients with chronic pruritus: a pilot study. *J Am Acad Dermatol* 2004; **50**: 889–91.
18 Demierre M-F, Taverna J. Mirtazapine and gabapentin for reducing pruritus in cutaneous T cell lymphoma. *J Am Acad Dermatol* 2006; **55**: 542–3.
19 Yesudian PD, Wilson NJE. Efficacy of gabapentin in the management of pruritus of unknown origin. *Arch Dermatol* 2005; **141**: 1507–10.
20 Gunal AI, Yoldas TK, Kirciman E, Celiker H. Gabapentin therapy for pruritus in haemodialysis patients: a randomized, placebo-controlled double-blind trial. *Nephrol Dial Transplant* 2004; **19**: 3137–9.
21 Rivard J, Lim HW. Ultraviolet phototherapy for pruritus. *Dermatol Ther* 2005; **18**: 344–54.

CHAPTER 22

Urticaria and Mastocytosis

C.E.H. Grattan[1] *& A. Kobza Black*[2]

[1]Department of Dermatology, Norfolk and Norwich University Hospital, Norwich, UK
[2]St John's Institute of Dermatology, St Thomas' Hospital, London, UK

Urticaria, 22.1
Introduction, 22.1
Definitions, 22.1
Historical background, 22.2
Classification, 22.2
Associations, 22.2
Prevalence, 22.3
Genetics, 22.3
Histology, 22.3
Pathophysiology, 22.4
Ordinary urticaria, 22.5
Clinical features, 22.5
Urticaria in childhood, 22.6
Aetiology of ordinary urticaria, 22.7
Acute urticaria, 22.7
Chronic urticaria, 22.9
Physical and cholinergic urticarias, 22.12
Urticaria due to mechanical forces, 22.12
Temperature-dependent urticaria, 22.15
Solar urticaria, 22.16
Aquagenic urticaria, 22.17
Urticarial vasculitis, 22.18
Contact urticaria, 22.19
Angio-oedema (without weals), 22.20
Idiopathic angio-oedema, 22.20
ACEI-induced angio-oedema, 22.21
Hereditary angio-oedema, 22.21
Acquired C1 esterase inhibitor deficiency angio-oedema, 22.22
Episodic angio-oedema with eosinophilia, 22.23
Other syndromes resembling urticaria or angio-oedema, or with urticaria as one component, 22.23
Papular urticaria, 22.23
Schnitzler's syndrome, 22.23
Hereditary periodic fever syndromes, 22.24
Clinical history taking and diagnosis, 22.25
Differential diagnosis, 22.25
Investigation of urticaria, 22.26
Natural history, 22.27
Management, 22.27
Mastocytosis, 22.30
Introduction, 22.30
Classification, 22.30
Aetiopathogenesis, 22.31
Clinical presentation, 22.31
Histopathology, 22.34
Investigations, 22.34
Management, 22.35

Urticaria

Introduction

Urticaria is a common disease with many different clinical presentations. Dermatologists, allergists, accident and emergency specialists, general physicians, paediatricians and general practitioners may see a quite different selection of cases, and this may cause confusion. The literature is large, and there are several monographs that can be consulted for a detailed bibliography [1–5].

References

1 Champion RH, Greaves MW, Kobza Black A, Pye RJ, eds. *The Urticarias*. Edinburgh: Churchill Livingstone, 1985.
2 Schocket AL, ed. *Clinical Management of Urticaria and Anaphylaxis*. New York: Dekker, 1993.
3 Henz BM, Zuberbier T, Grabbe J, Monroe E, eds. *Urticaria: Clinical, Diagnostic and Therapeutic Aspects*. Berlin: Springer, 1998.
4 Dreskin SC, ed. Urticaria [special issue]. *Immunol Allergy Clin N Am* 2004; **24** (2).
5 Greaves MW, Kaplan AP, eds. *Urticaria and Angioedema*. New York: Decker, 2004.

Definitions

The urticarias are characterized by short-lived swellings of the skin and mucosa due to plasma leakage. Urticaria is commonly used to describe an eruption of weals, as distinct from angio-oedema, although this does lead to confusion with classification of the physical urticarias. The term 'urticaria' is increasingly being used to describe a disease that may present with weals, angio-oedema or both [1]. Weals and angio-oedema often occur together and for practical purposes are similar processes resulting from superficial and deep swellings, respectively. However, angio-oedema that is caused by C1 esterase inhibitor deficiency shows some differences clinically and in response to treatment.

Weals (synonym 'nettle rash', hives) is the descriptive term for transient, well-demarcated, superficial erythematous or pale swellings of the dermis, which are usually very itchy and are associated with a surrounding red flare initially.

Angio-oedema (synonym angioneurotic oedema, Quincke's oedema) swellings affect the deeper dermal, subcutaneous and submucosal tissues. They are usually painful rather than itchy, poorly defined, and pale or normal in colour.

Anaphylaxis, in the strict sense, is an acute, severe, life-threatening, generalized or systemic hypersensitivity reaction. It consists of a combination of symptoms and signs, including diffuse erythema, pruritus, urticaria and angio-oedema, hypotension and difficulty in breathing. A similar clinical picture from non-allergic causes used to be called an anaphylactoid reaction but the term 'non-allergic anaphylaxis' is now preferred [2]. 'Anaphylaxis' is frequently used to describe the clinical picture whatever the cause (see Chapter 13).

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

References

1 Grattan CEH. Towards rationalizing the nomenclature and classification of urticaria: some guidance on guidelines. *Clin Exp Allergy* 2007; **37**: 623–6.

2 Johansson SGO, Bieber T, Dahl R *et al*. A revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization. *J Allergy Clin Immunol* 2004; **113**: 832–6.

Historical background

Urticaria has been recognized since the days of Hippocrates. The term dates back to the 18th century, when the stinging and burning was likened to the sting of a nettle (*Urtica dioica*). The changing opinions on the pathogenesis and management of urticaria provide a fascinating reflection of the changing fashions in medical thought [1,2].

References

1 Rook AJ. The historical background. In: Warin RP, Champion RH, eds. *Urticaria*. London: Saunders, 1974: 1–2.

2 Czarnetzki BM. The history of urticaria. *Int J Dermatol* 1989; **28**: 52–7.

Classification (Table 22.1)

Urticaria is a heterogeneous group of disorders that may be broadly classified by duration of disease and clinical features.

Urticaria is traditionally classified into acute and chronic, with a time division arbitrarily chosen between 6 weeks and 3 months. When urticaria is present daily or almost daily for less than 6 weeks it is called acute. If urticaria occurs continuously on most days for longer than this, it is called chronic. This applies to all patterns of urticaria, but is most relevant to the ordinary presentation of urticaria, because physical urticarias and urticarial vasculitis nearly always have a chronic course. Contact urticaria usually presents with brief episodes. Repeated episodes of continuous urticaria over a period of time are acute or chronic intermittent depending on their usual duration. This classification by disease duration is of limited value, but an exogenous cause is more likely to be found in acute urticaria than in chronic urticaria.

A classification based on clinical features and trigger factors is convenient (Table 22.1), but has inherent inconsistencies. Several types of urticaria may coexist in the same person—for example, ordinary urticaria and various forms of physical urticarias, including delayed pressure urticaria. The term 'ordinary urticaria' can be used when other patterns of urticaria have been excluded. It refers to the usual presentation of continuous urticaria with no implication about the aetiology, duration or severity of the illness. The new terminology is preferred because it is now evident that around 50% of patients previously diagnosed with chronic 'idiopathic' urticaria have an autoimmune basis for their disorder. The criteria for 'idiopathic' will vary between clinicians depending on whether or not non-specific aggravating factors (such as aspirin and food additives) are regarded as causes [1]. It is useful to separate patients who have angio-oedema *without* weals from the majority who have angio-oedema *with* weals. Some patients presenting with the former will have C1 esterase inhibitor deficiency, some will be due to angiotensin-converting enzyme inhibitors (ACEIs) or non-steroidal anti-inflammatory drugs (NSAIDs), but many will remain 'idiopathic' after full evaluation.

Table 22.1 Clinical classification of urticaria.

1 Ordinary urticaria
Acute
Episodic (acute and chronic intermittent)
Chronic (previously qualified as 'idiopathic' prior to recognition of the autoimmune subtype)
2 Physical and cholinergic urticarias
3 Urticarial vasculitis
4 Contact urticaria
5 Angio-oedema without weals
6 Other syndromes resembling urticaria or angio-oedema, or with urticaria as a component

Reference

1 Champion RH, Roberts SOB, Carpenter RG, Roger JH. Urticaria and angio-oedema: a review of 554 patients. *Br J Dermatol* 1969; **81**: 588–97.

Associations (Table 22.2)

There have been many reports of an association between chronic ordinary urticaria and autoimmune thyroid disease, which was reported initially by Leznoff [1]. There also appears to be a higher frequency of autoimmune diseases in patients with autoimmune urticaria [2]. An association between chronic urticaria and coeliac disease in children has been proposed [3]. The older literature suggests that chronic 'idiopathic' urticaria may be associated with chronic infections, especially dental, and *Candida* infections of the bowel, but in the authors' experience this occurs rarely, if at all. A meta-analysis of therapeutic trials for patients with active *Helicobacter pylori* infection and chronic urticaria showed that those who responded to eradication treatment were more likely to go into remission of urticaria than those who did not [4]. Bowel helminth infection as a cause of chronic urticaria is rare in developed countries but should be considered in countries where it is endemic. The evidence linking chronic urticaria and infections has been reviewed [5]. These authors describe a link between *H. pylori* and a positive autologous serum skin test (ASST), also known as autoreactivity. They draw attention to the relatively high frequency of upper respiratory tract viral infections (47%) with acute urticaria and conclude that the evidence base to link viral, bacterial, parasitic and fungal infection with chronic urticaria is lacking. Although there have been anecdotal reports of urticaria occurring with systemic malignancies, including lymphoma, no overall association was found in a large epidemiological study [6].

Table 22.2 Associations with chronic ordinary urticaria.

Autoimmune disease
Thyroiditis
Other organ-specific autoimmunity (e.g. vitiligo, pernicious anaemia)
Systemic lupus erythematosus
? Coeliac disease
Infection
Helicobacter pylori gastritis
? Malignancy
Anecdotes only

References

1 Leznoff A, Sussman GL. Syndrome of idiopathic chronic urticaria and angio-edema with thyroid autoimmunity: a study of 90 patients. *J Allergy Clin Immunol* 1989; **84**: 66–71.

2 O'Donnell BF, Swana GT, Kobza Black A *et al*. Organ and nonorgan specific autoimmunity in chronic urticaria. *Br J Dermatol* 1995; **133** (Suppl. 45): 42A.

3 Caminiti L, Passalacqua G, Magazzu G *et al*. Chronic urticaria and associated coeliac disease in children: a case–control study. *Pediatr Allergy Immunol* 2005; **16**: 428–32.

4 Federman DG, Kirsner RS, Moriarty JP, Concato J. The effect of antibiotic therapy for patients infected with *Helicobacter pylori* who have chronic urticaria. *J Am Acad Dermatol* 2003; **49**: 861–4.

5 Wedi B, Raap U, Kapp A. Chronic urticaria and infections. *Curr Opin Allergy and Clin Immunol* 2004; **4**: 387–96.

6 Lindelöf B, Sigurgeirsson B, Wahlgren CF, Eklund G. Chronic urticaria and cancer: an epidemiological study of 1155 patients. *Br J Dermatol* 1990; **123**: 453–6.

Prevalence

Urticaria is a common problem, with a point prevalence of 0.1% in one survey [1]. Estimates of the cumulative lifetime prevalence of chronic urticaria have varied from 0.05% to 23.6% in the general population, but a range of 1–5% seems more realistic [2].

References

1 Hellgren L. The prevalence of urticaria in the total population. *Acta Allergol* 1972; **27**: 236–40.

2 Schäfer T, Ring J. Epidemiology of urticaria. *Monogr Allergy* 1993; **31**: 49–60.

Genetics

Hereditary angio-oedema, the autoinflammatory syndromes (now known collectively as the cryopyrin-associated autoinflammatory syndrome) and a few other rare physical urticarias are inherited as autosomal dominant traits. There is a highly significant linkage of human leukocyte antigen (HLA) DRB1*04 (DR4) and its associated allele DQB1*0302 (DR8) with histamine-releasing autoantibody-positive chronic ordinary urticaria [1]. Polymorphisms of the FcεRIα promoter [2] and leukotriene C_4 synthetase genes [3] have been associated with aspirin-sensitive urticaria and associations with other allelic variants have been reported.

References

1 O'Donnell BF, Neill CM, Francis DM *et al*. Human leucocyte antigen class II associations in chronic urticaria. *Br J Dermatol* 1999; **140**: 853–8.

2 Bae J-S, Kim S-H, Ye Y-M *et al*. Significant association of FcεRIα promoter polymorphisms with aspirin-intolerant chronic urticaria. *J Allergy Clin Immunol* 2007; **119**: 449–56.

3 Mastalerz L, Setkowicz M, Sanak M *et al*. Familial aggregation of aspirin-induced urticaria and leukotriene C_4 synthetase allelic variant. *Br J Dermatol* 2006; **154**: 256–60.

Histology

The histology of urticarial weals is usually non-specific, with vascular and lymphatic dilatation, oedema and a variable perivascular cellular dermal infiltrate consisting of lymphocytes, neutrophils and eosinophils (Fig. 22.1). On electron microscopy, dermal mast cells show signs of degranulation. In one study, dermal mast cells in weals of chronic urticaria were increased by 10 times [1] compared with non-urticated skin, using conventional histochemical stains, but this increase was not confirmed in a study using tryptase and chymase as markers [2]. In the majority of weals, there is a sparse perivascular infiltrate, predominantly of helper T lymphocytes [3,4] with a TH_0 cytokine profile expressing mRNA for interleukin (IL)-4, IL-5 and interferon-γ (IFN-γ) [5]. In a minority of weals, neutrophils are a conspicuous feature, within the vessel walls or scattered in the dermis [6]. Eosinophils may play a more important role than their sparse numbers seen on light microscopy would suggest, as extracellular eosinophil major basic protein is frequently deposited in spontaneous weals [7] and they stain for activation markers [8]. The spectrum of cellular changes may depend on the age of weals and their underlying cause. Biopsies are generally performed if individual weals are persistent, and they may show features of delayed pressure urticaria or urticarial vasculitis. In delayed pressure urticaria, the infiltrate is denser, with neutrophils often present in early weals, and eosinophils extending deep into the fat in early and late weals. These cellular changes correlated with moderate up-regulation of the vascular endothelial adhesion molecules E-selectin, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) on perivascular cells [9]. Urticaria with histological evidence of vasculitis (venulitis) is defined as urticarial vasculitis.

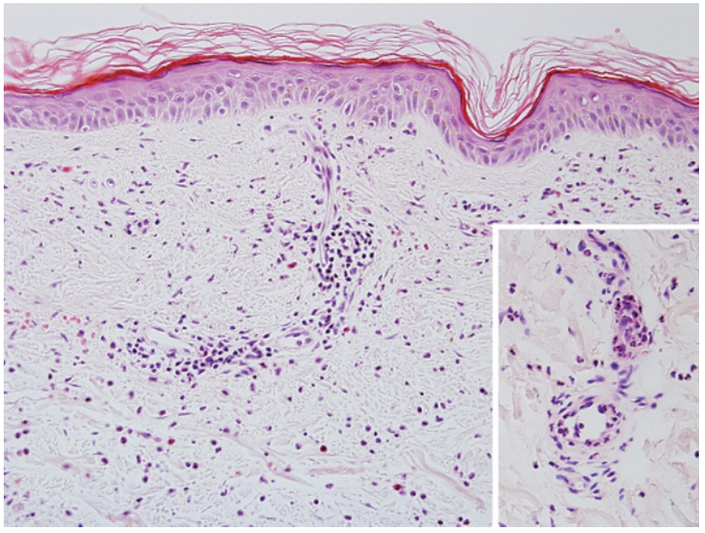


Fig. 22.1 Histology of a spontaneous weal from a patient with chronic ordinary urticaria showing dermal oedema with a moderate perivascular and interstitial mixed inflammatory infiltrate, including intravascular neutrophils (inset) but no vasculitis. (Photomicrograph courtesy of Dr Alistair Robson, St John's Institute of Dermatology, London.)

References

1 Natbony SF, Phillips ME, Elias JM *et al*. Histologic studies of chronic idiopathic urticaria. *J Allergy Clin Immunol* 1983; **71**: 177–83.

2 Smith CH, Kepley C, Schwartz LB, Lee TH. Mast cell number and phenotype in chronic idiopathic urticaria. *J Allergy Clin Immunol* 1995; **96**: 360–4.

3 Mekori YA, Giorno RC, Anderson P, Kohler PF. Lymphocyte subpopulations in the skin of patients with chronic urticaria. *J Allergy Clin Immunol* 1983; **72**: 681–4.

4 Rosentreich DL. Chronic urticaria, activated T-cells and mast cells. *J Allergy Clin Immunol* 1986; **78**: 1099–102.

5 Ying S, Kikuchi Y, Meng Q, Kay B, Kaplan AP. TH1/TH2 cytokines and inflammatory cells in skin biopsy specimens from patients with chronic idiopathic urticaria: comparison with the allergen-induced late-phase cutaneous reactions. *J Allergy Clin Immunol* 2002; **109**: 694–700.

6 Winkelmann RK, Reizner GT. Diffuse dermal neutrophilia in urticaria. *Hum Pathol* 1988; **19**: 389–93.
7 Peters MS, Schroeter AL, Kephart GM, Gleich GJ. Localization of eosinophil major basic protein in chronic urticaria. *J Invest Dermatol* 1983; **81**: 39–43.
8 Sabroe RA, Poon E, Orchard GE *et al.* Cutaneous inflammatory cell infiltrate in chronic idiopathic urticaria: comparison of patients with and without anti-FcεRI or anti-IgE autoantibodies. *J Allergy Clin Immunol* 1999; **103**: 484–93.
9 Barlow RJ, Ross EL, MacDonald D *et al.* Adhesion molecule expression and the inflammatory cell infiltrate in delayed pressure urticaria. *Br J Dermatol* 1994; **131**: 341–7.

Pathophysiology [1] (Table 22.3)

Mast cell mediators

Urticaria is due to a local increase in permeability of capillaries and venules. These changes are dependent on activation of cutaneous mast cells in nearly all types of urticaria except C1 esterase inhibitor deficiency and ACEI-induced angio-oedema, where kinins are primarily responsible for the increased vasopermeability, and the autoinflammatory syndromes in which interleukin (IL)-1 and -18 are activated by caspase 1. Mast cells contain a range of pro-inflammatory mediators, but predominantly histamine. Increased concentrations of histamine have been recovered in tissue fluid from lesions of chronic idiopathic urticaria [1] and from venous effluent draining the urticated areas in most physical urticarias. The clinical improvement on treatment with H_1 antihistamines underlines the role of mast cell-derived histamine as a major mediator in urticarias. Activation of H_1 receptors in the skin induces itching, flare, erythema and wealing. Activation of H_2 receptors contributes to erythema and wealing, but not itch or flare. So far, H_3 receptors—identified in the nervous system as inhibitory autoreceptors, in that their activation leads to reduced biosynthesis and release of histamine—have not been identified in human skin. H_4 receptor activation leads to scratching behaviour in mice [2] but a human equivalent has not been confirmed. Other vasoactive and chemoattractant mast cell-derived mediators, and secondary release of non-mast cell mediators from inflammatory cells, may amplify and prolong the weal. Little is known of the process of weal resolution.

Table 22.3 Pathophysiology of urticaria.

Mast cell mediated urticaria
Mediators
Histamine
Cysteinyl leukotrienes (C_4 D_4 E_4)
Prostaglandin D_2
Platelet activating factor
Cytokines
Interleukin-3, -4, -5
Granulocyte macrophage colony stimulating factor
Tumour necrosis factor-α
Releasing stimuli (*in vivo*)
Allergen cross-linking of specific IgE on FcεRI
Anti-FcεRI and anti-IgE autoantibodies
IgG1 and 3 subclasses for functionality
Complement dependence
Immune complex deposition (serum sickness and urticarial vasculitis)
Neuropeptides (*in vitro* only)
Cellular response
Basophil, eosinophil, neutrophil and lymphocytes
Non-mast cell mediated urticaria (angio-oedema without weals)
Kallikrein-kininogen-kinin-kininase system
C1 esterase inhibitor deficiency
Angiotensin converting enzyme inhibitors

Compared with normal controls, the cutaneous mast cells from chronic urticaria also release more histamine spontaneously and in response to non-specific degranulating agents such as codeine and morphine [3]. There is no evidence for decreased skin histamine metabolism in the skin of chronic urticaria subjects. However, their cutaneous vasculature is more responsive to histamine than skin of normal controls [4]. Tryptase and chymase are released in conjunction with histamine. Potentially, they could play a part in the pathogenesis of urticaria, as chymase can induce mast cell degranulation and tryptase and chymase cleave C3 to C3a and C3b. C3a can activate mast cells, and C3b can activate the alternative complement pathway. The example of hereditary angio-oedema has encouraged a search for other inhibitor deficiencies as a cause for other types of urticaria. A decrease of α_1-antitrypsin has been reported in cold urticaria [5]. Low levels have only sometimes been found in other types of urticaria, including chronic idiopathic urticaria [6]. Usually there is a poor correlation between the levels found and the clinical activity.

There is no direct evidence that prostaglandin D_2 (PGD_2) and leukotriene C_4 (LTC_4) released from cutaneous mast cells play a significant role in spontaneous urticaria but the response of some patients with aspirin-sensitive urticaria to leukotriene receptor antagonists suggests that release of cysteinyl leukotrienes may be clinically important in certain clinical situations. Whilst TNF-α upregulates vascular endothelial adhesion molecules, IL-8 stimulates neutrophil activation and accumulation, and IL-4 influences T-lymphocyte differentiation towards a Th2 phenotype, a direct role for these cytokines in urticaria has not been proven.

Mast cell activation

Mast cell activation may be non-immunological or immunological. Non-immunological mast cell activation occurs with a variety of substances including: neuropeptides, such as substance P; drugs, including opiate derivatives such as morphine and codeine, vancomycin and polymyxin; some radiocontrast media; and some foods, such as strawberries. Neuropeptides elicit histamine but not PGD_2 or LTC_4 release *in vitro*.

Immunological mast cell activation (Chapter 12) occurs as a result of linkage of two adjacent α-subunits of high-affinity IgE receptors (FcεRIα) of a mast cell. Preformed histamine, proteases and newly generated mediators, including PGD_2 and cytokines—IL-3, -4, -5, -6, -8, -13 and tumour necrosis factor-α (TNF-α)—are released from mast cells. In classic immediate allergic reactions, receptor cross-linking occurs indirectly when an allergen (such as latex, nuts, etc.) reacts with two or more allergen-specific IgE antibodies, each bound to FcεRIα. Activation also occurs by cross-linking autoantibodies directed against IgE bound to FcεRIα or against the α-subunit of FcεRI itself. Complement C3a and C5a can release histamine directly and appear to be necessary for some autoantibody-induced degranulation [7]. Basophils also express FcεRIα and release histamine, IL-4, IL-13 and LTC_4 on activation.

Neuropeptides

Some mast cells are positioned close to nerve endings. Histamine can stimulate sensory afferent nerves to release substance P. Neuropeptides appear to be responsible for the neurogenic axon flare after intradermal histamine injection [8], but there is no direct evidence for neuropeptide involvement in weal formation.

Cellular involvement

The dermal leukocyte cellular infiltrate in chronic ordinary urticaria, consisting of lymphocytes, neutrophils and eosinophils, releases a variety of cytokines with pro-inflammatory properties. Blood basophils may be involved in the pathogenesis of chronic ordinary urticaria, as their numbers are substantially reduced in the presence of histamine-releasing factors in serum [9], and they also release less histamine in response to anti-IgE stimulation [10]. They may contribute to prolongation of urticarial weals by active recruitment from the circulation [11]. The observation that the cellular infiltrates in weals of patients with chronic autoimmune and idiopathic ordinary urticaria are similar [12] suggests that the inflammatory response is determined by the event of mast cell degranulation rather than its stimulus.

In physical urticarias, there is no evidence for increased mast cell numbers. Infiltrates tend to be mild and mixed in dermographism [13]. In addition to histamine release, ill-defined eosinophil and neutrophil chemotactic factors have been demonstrated in venous effluent from cold, cholinergic and solar urticarial lesions. The mode of activation of mast cells in physical urticaria is poorly understood, but in some patients with dermographism, cholinergic, cold and solar urticaria, a transferable IgE-like factor has been identified. It has been speculated that the physical stimulus in these patients may induce a neo-antigen that could stimulate IgE production directed specifically against it. On rechallenge, this neo-antigen would react with its specific IgE bound to mast cells and activate mediator release. Increased substance P and vasoactive intestinal peptide (VIP) have been recovered from dermographic and cold urticarial lesions, while clinical lesions of cold and localized heat urticaria were diminished by prior application of topical capsaicin, a depletor of neuropeptides.

Kinins and complement

Plasma-derived kinins do not appear to have a significant role in chronic urticaria, but it is thought that production of bradykinin by the action of kallikrein on kininogen and kinin-like peptides derived from the early components of complement are important in the pathogenesis of angio-oedema associated with C1 esterase inhibitor deficiency. The angio-oedema seen with ACEI is believed to be due to inhibition of breakdown of bradykinin by ACE, also known as kininase II. Complement activation, with production of the anaphylatoxins C3a and C5a, occurs in urticarial vasculitis.

References

1 Kaplan AP, Horakova Z, Katz SI. Assessment of tissue fluid histamine levels in patients with urticaria. *J Allergy Clin Immunol* 1978; **61**: 350–4.

2 Dunford PJ, Williams KN, Desai PJ *et al.* Histamine H4 receptor antagonists are superior to traditional antihistamines in the attenuation of experimental pruritus. *J Allergy Clin Immunol* 2007; **119**: 176–83.

3 Cohen RW, Rosentreich DL. Discrimination between urticaria-prone and other allergic patients by intradermal testing with codeine. *J Allergy Clin Immunol* 1986; **77**: 802–7.

4 Juhlin L, Michaelsson G. Cutaneous reactions to kallikrein, bradykinin and histamine in healthy subjects and in patients with urticaria. *Acta Derm Venereol (Stockh)* 1969; **49**: 26–36.

5 Doeglas HMG, Bleumink E. Plasma inhibitors in the plasma of patients with chronic urticaria. *Arch Dermatol* 1975; **11**: 979–85.

6 Imai S. Serum a_1-protease inhibitor levels in patients with chronic idiopathic urticaria. *Acta Derm Venereol (Stockh)* 1993; **73**: 10–1.

7 Ferrer M, Nakazawa K, Kaplan AP. Complement dependence of histamine release in chronic urticaria. *J Allergy Clin Immunol* 1999; **104**: 169–72.

8 Petersen LJ, Church MK, Stahl Skov P. Histamine is released in the wheal but not the flare following challenge of human skin *in vivo*: a microdialysis study. *Clin Exp Allergy* 1997; **27**: 284–95.

9 Grattan CEH, Walpole DA, Francis DM *et al.* Flow cytometric analysis of basophil numbers in chronic urticaria: basopenia is related to serum histamine releasing activity. *Clin Exp Allergy* 1997; **27**: 1417–24.

10 Greaves MW, Plummer VM, McLaughlan P, Stanworth DR. Serum and cell bound IgE in chronic urticaria. *Clin Allergy* 1974; **4**: 265–71.

11 Grattan CEH, Dawn G, Gibbs S, Francis DM. Blood basophil numbers in chronic ordinary urticaria and healthy controls: diurnal variation, influence of loratadine and prednisolone and relationship to disease activity. *Clin Exp Allergy* 2003; **33**: 337–41.

12 Sabroe RA, Poon E, Orchard GE *et al.* Cutaneous inflammatory cell infiltrate in chronic idiopathic urticaria: comparison of patients with and without anti-FcεRI or anti-IgE autoantibodies. *J Allergy Clin Immunol* 1999; **103**: 484–93.

13 Winkelmann RK. The history and immunopathology of dermographism. *J Cutan Pathol* 1985; **12**: 486–92.

Ordinary urticaria

Clinical features

Itching erythematous macules develop into weals consisting of pale to pink, oedematous, raised areas of the skin often with a surrounding red flare. They occur anywhere on the body, including scalp, palms and soles, in variable numbers and sizes, ranging from a few millimetres to lesions covering large areas, and of varying shapes including rounded, annular, serpiginous and bizarre patterns due to confluence of adjacent lesions (Fig. 22.2). Very rarely, bullae may form when oedema is intense. Weals generally last a few hours and resolve within 24 h, passing through a macular erythematous phase, leaving the skin with a normal appearance. They are generally very itchy, especially superficial weals and particularly at night. Patients tend to rub rather than scratch, so excoriation marks are unusual, but occasionally bruising may result, which may be seen particularly on thighs. Weals may be more pronounced in the evenings or premenstrually.

There may be associated angio-oedema in 50% of patients with ordinary urticaria. These deep swellings, which may be the same colour as normal skin, occur most frequently on the face, affecting the eyelids and lips, but any other area of the body may be affected, such as ears, neck, hands, feet and genitalia. Mucosal swellings may also occur inside the oral cavity on the buccal mucosa, tongue and pharynx but laryngeal involvement is fortunately rare. Angio-oedema may be preceded by an itching or tingling sensation, but it is not always itchy and may be painful. The lesions may last for several days.

Urticaria may be preceded by vomiting [1] and be associated with systemic symptoms of malaise, loss of concentration, low mood, feeling hot and cold, headache, abdominal pain, diarrhoea,



Fig. 22.2 Different morphology of urticarial weals. (Courtesy of Addenbrooke's Hospital, Cambridge, UK (a); courtesy of St John's Institute of Dermatology, London, UK (b–d).)

arthralgia, dizziness and syncope and, in its most severe acute form, with anaphylaxis.

Reference

1 Champion RH. Acute and chronic urticaria. *Semin Dermatol* 1987; **6**: 286–91.

Urticaria in childhood

The same multiplicity of factors is found as in the adult [1], with a tendency to more cases of acute disease. Cow's-milk allergy is the commonest cause of urticaria in infants under 6 months old [2]. In infants, there may be less itching and a greater tendency for



Fig. 22.3 Acute haemorrhagic oedema of infancy or cocarde purpura of childhood. (Courtesy of Addenbrooke's Hospital, Cambridge, UK.)

weals to become purpuric. A not uncommon pattern is one of bizarrely shaped weals, not seen as frequently in adults. No specific aetiology or natural history has emerged in such cases. Acute haemorrhagic oedema of infancy (purpura en cocarde) occurs in very young children and is borderline between urticaria and vasculitis (Fig. 22.3).

References

1 Hannuksela M. Urticaria in children. *Semin Dermatol* 1987; **6**: 321–5.

2 Legrain V, Taieb A, Sage T, Maleville J. Urticaria in infants: a study of forty patients. *Pediatr Dermatol* 1990; **7**: 101–7.

Aetiology of ordinary urticaria (Table 22.4)

Although some cases of acute urticaria can be ascribed to allergy, non-allergic causes or infections and around 50% of chronic urticaria may be attributed to autoimmunity, other cases will remain idiopathic after evaluation.

Acute urticaria

Most acute urticaria is ordinary and some will become chronic. Serum sickness due to injection of therapeutic animal antisera (e.g. to snake venoms) is now rare. Physical urticarias will go through an acute phase but most will last more than 6 weeks. Contact urticaria does not usually present as acute urticaria because it tends to be localized, intermittent and short-lived. The incidence in the community is not well defined. Many cases will not present to secondary care.

Idiopathic

This form of acute urticaria, in which no cause can be identified, was found in more than 50% of patients with acute urticaria presenting to a city 'walk-in' dermatology centre [1]. In the others, the most common preceding event was an upper respiratory tract infection, followed by drug ingestion, but allergy or intolerance to food was rare [1,2].

Allergic

This is commoner in the community than in dermatological practice, where it is rare. Allergic urticaria is due to interaction of an allergen with specific preformed IgE bound to the mast cell. It is commoner in people who are atopic and have elevated IgE levels. Although it is unusual to find an allergic cause for acute urticaria [1], any drug, food, foreign substance from blood transfusion, injection, implant, contactant and inhalant should be considered as a potential allergen (Table 22.5). In an IgE-mediated reaction, there will have been a previous exposure and the reaction may occur in minutes and no longer than 60 min. Patients will usually recognize this and avoid the offending substance. Acute urticarial

Table 22.4 Aetiology of ordinary urticaria.

Acute urticaria
Idiopathic
Infectious
Upper respiratory tract infection (NOS)
Streptococcal infection
Hepatitis B infection
Anisakiasis
Allergy (immediate hypersensitivity)
Foods
Drugs
(Inhalants)
Non-allergic
Histamine liberators (e.g. codeine, atracurium)
Pseudoallergens
Aspirin and other non-steroidal anti-inflammatories
? Dietary (food additives, natural salicylates)
Radiocontrast media
Chronic urticaria
Idiopathic
Autoimmunity
Functional autoantibodies
Pseudoallergy
Salicylates
Food colours, preservatives, antioxidants and flavour enhancers
Infection
Bowel parasites
? *Helicobacter pylori*
? Candidiasis of the bowel
? Chronic sepsis (e.g. dental abscess)

Table 22.5 Some substances reported to cause urticaria and anaphylaxis due to an immunoglobulin E-dependent mechanism, although other mechanisms may also be involved.

Latex	Tree and groundnuts
Hymenoptera (bee and wasp) stings	Celery, parsley
Penicillins	Carrots
Vaccines	Spices
Blood products	Apples
Crustaceans (lobsters, shrimp, crab)	Peaches
Fish	
Milk	

reactions from drugs are common [3] (Table 22.6), usually occurring within 36 h of drug administration although it should be noted that *urticarial* drug reactions (i.e. reactions with an urticarial component) are not synonymous with acute urticaria due to a drug. It is unusual for urticaria to develop from a drug taken continuously for months. Sometimes, it is uncertain if a drug-induced urticaria is allergic and, if it is, whether the reaction is IgE-mediated or IgG-mediated via immune complexes [4]. Antibiotics, especially penicillins and cephalosporins, are common causes. Increased risk factors include previous exposure and reaction to the drug or a chemically related drug, intermittent and multiple drug therapy, and a familial predisposition.

Acute urticarial reactions to food are believed to be common and many go unreported [5]. Urticarial reactions may not be to the basic nutrient but to other ingredients, such as seeds or spices. Reactions typically occur within minutes and no more than 30 min. Rarely, allergic reactions to food occur only if intake is followed by exercise, with neither food nor exercise alone inducing weals (food-dependent exercise-induced anaphylaxis) [6]. Substances reported to cause this include wheat, hazelnuts and shellfish.

Stinging insects are members of the order Hymenoptera, of which bees and wasps are its two major subgroups. Allergic reactions to injected sting venom are not uncommon and occasionally are fatal [7]. Development of bee-sting allergy usually requires multiple exposures, and is commonly seen in beekeepers. Development of allergy to wasp stings and the pattern of severity of reactions to any subsequent stings are unpredictable. Hypersensitivity to insect stings is unrelated to an atopic background.

Reactions to some substances may be dramatically severe and may proceed rapidly to systemic anaphylaxis [8–10]. Here, prodromal symptoms include itching or tingling of the mouth, palms, soles and genital area. Subsequent signs include widespread erythema, urticaria, lacrimation, nasal stuffiness, bronchospasm, laryngeal oedema, nausea, diarrhoea, vomiting, hypotension or cardiac arrhythmias and can rarely lead to death. This is a medical emergency, and first-line treatment is with epinephrine (adrenaline) [10] given by intramuscular injection.

Some substances more readily evoking IgE-mediated anaphylactic reactions include penicillins, sesame seeds, peanuts, latex and Hymenoptera stings. The need to label food with individual constituents is increasingly recognized. In some patients, despite all efforts, no cause for anaphylactic symptoms can be identified [11].

Table 22.6 Some substances implicated in causing non-allergic urticaria and anaphylaxis.

Drugs
Acetylsalicylic acid (aspirin)
Other non-steroidal anti-inflammatory drugs
Polymyxin
General anaesthetic agents (especially muscle relaxants and opioids)
Radiocontrast media (especially ionic)
Plasma expanders (especially dextrans)

Non-allergic

Acute urticarias from ingested substances may be non-allergic (see Table 22.6). They are then referred to as intolerance reactions. These may be due to direct histamine release from mast cells (histamine liberators) or due to other mechanisms (pseudoallergic). If they are very severe, resembling anaphylaxis, they are known as non-allergic anaphylaxis [12].

Histamine liberators

Here, mast cell histamine release is not immunological and may occur after first exposure to a substance. Examples include morphine, codeine, atracurium and antibiotics, such as polymyxin and vancomycin. Iodine-based radiocontrast dyes may cause non-allergic anaphylaxis. Exactly how radiocontrast media, low- and high-molecular dextran plasma expanders cause these reactions is not known. Complement activation is thought to play a role in serious dextran reactions.

Pseudoallergic reactions

The reaction is not substance-specific, and similar reactions may occur to unrelated compounds in the same individual. The severity of reaction is usually related to the dose of the offending substance. Common offending substances include aspirin and other non-steroidal anti-inflammatory agents. These cause the reactions by pharmacological mechanisms thought to be related to their activity in inhibiting the cyclo-oxygenase (COX-1) pathway of arachidonic acid metabolism, diverting it to the pro-inflammatory lipoxygenase pathway products LTC_4,D_4,E_4 and by reducing PGE_2, which is inhibitory for immunological mast cell degranulation [13].

Alcohol-induced urticaria is rare; the mechanism of causation is unknown, but appears not to be allergic [14]. Alcoholic beverages can aggravate urticaria non-specifically. White wines are often treated with sulphites, which have rarely been reported to cause urticaria and anaphylaxis [15,16]. Some red wines contain measurable concentrations of vasoactive amines including histamine [17] which could aggravate urticaria, but cutaneous symptoms relate poorly to histamine content [18].

Food may also contain vasoactive amines including histamine (such as cheese, fish, meat, tomatoes, pineapple and avocados) or histamine-releasing substances (such as in strawberries). Histamine generated in scombroid fish (underprocessed tuna, mackerel) by histidine decarboxylase from bacteria can cause acute urticaria, vomiting and diarrhoea, and high levels of histamine can usually be found in affected fish [19].

Infections

Urticaria may follow non-specific viral infections [1,2], Epstein–Barr [20] or acute hepatitis B viral infections, anisakiasis (infection by a fish parasite in pre-sensitized individuals) [21], streptococcal throat infections in children and, rarely, *Campylobacter jejuni* infections [22].

References

1 Zuberbier T, Iffländer J, Semmler C, Henz BM. Acute urticaria: clinical aspects and therapeutic responsiveness. *Acta Derm Venereol (Stockh)* 1996; **76**: 295–7.

2 Aoki T, Kojima M, Horiko T. Acute urticaria: history and natural course of 50 cases. *J Dermatol* 1994; **21**: 73–7.

3 Weber EA, Knight A. Testing for allergy to antibiotics. *Semin Dermatol* 1989; **8**: 204–12.
4 Van Arsdel PP. Classification and risk factors for drug allergy. *Immunol Allergy Clin N Am* 1991; **11**: 475–92.
5 Young E, Stoneham MD, Petruckevitch A *et al.* A population study of food intolerance. *Lancet* 1994; **343**: 1127–30.
6 Kidd JM, Cohen SH, Sosman AJ *et al.* Food-dependent exercise induced anaphylaxis. *J Allergy Clin Immunol* 1983; **71**: 407–11.
7 Reisman RE. Insect stings. *N Engl Med J* 1994; **331**: 523–7.
8 Kemp SF, Lockey RF, Wolf BL *et al.* Anaphylaxis: a review of 266 cases. *Arch Intern Med* 1995; **155**: 1749–54.
9 Bochner BS, Lichtenstein LM. Anaphylaxis. *N Engl J Med* 1991; **324**: 1785–90.
10 Atkinson TP, Kaliner MA. Anaphylaxis. *Med Clin North Am* 1992; **76**: 841–55.
11 Wiggins CA, Dykewicz MS, Patterson R. Idiopathic anaphylaxis; classification, evaluation and treatment of 123 patients. *J Allergy Clin Immunol* 1988; **82**: 849–55.
12 Wilkinson JRW, Lee TH. General anaphylaxis. In: Lachmann PJ, Peters DK, Rosen FS, Walport MS, eds. *Clinical Aspects of Immunology*, 5th edn. Oxford: Blackwell Scientific Publications, 1993: 999–1014.
13 Grattan C. Aspirin-sensitive urticaria. *Clin Exp Dermatol* 2003; **28**: 123–7.
14 Sticherling M, Brasch J, Bruning H, Christophers E. Urticarial and anaphylactoid reactions following alcohol intake. *Br J Dermatol* 1995; **132**: 464–7.
15 Clayton DE, Busse W. Anaphylaxis to wine. *Clin Allergy* 1980; **10**: 341–3.
16 Twarog FJ, Leung DYM. Anaphylaxis to a component of isoetharine (sodium bisulphite). *JAMA* 1982; **248**: 2030–1.
17 Malone MH, Metcalfe DD. Histamine in foods: its possible role in nonallergic adverse reactions to ingestants. *N Engl Reg Allergy Proc* 1986; **7**: 241–6.
18 Kanny G, Gerbaux V, Olszewski A *et al.* No correlation between wine intolerance and histamine content of wine. *J Allergy Clin Immunol* 2001; **107**: 375–8.
19 Gilbert RJ, Hobbs G, Murray CK *et al.* Scrombotic fish poisoning: features of the first 50 incidents to be reported in Britain (1976–9). *BMJ* 1980; **281**: 71–2.
20 Cowdrey SC, Reynolds JS. Acute urticaria in infectious mononucleosis. *Ann Allergy* 1969; **27**: 182–7.
21 Daschner A, Alonso-Gómez A, Caballero T *et al.* Gastric anisakiasis: an underestimated cause of acute urticaria and angio-oedema? *Br J Dermatol* 1998; **139**: 822–8.
22 Bretag AH, Archer RS, Atkinson HM, Woods WH. Circadian urticaria: another *Campylobacter* association. *Lancet* 1984; **i**: 954.

Inhalants

Grass pollens, mould spores, animal danders and house dust mite [1] have been implicated as triggers of acute or chronic urticaria, with or without respiratory symptoms, but this must be very rare. If pollen allergy is proven, desensitization may exceptionally be successful [2].

References

1 Numata T, Yamamoto S, Yamura T. The role of mite allergen in chronic urticaria. *Ann Allergy* 1979; **43**: 356–8.
2 August PJ, O'Driscoll J. Urticaria successfully treated by desensitization with grass pollen extract. *Br J Dermatol* 1987; **120**: 409–10.

Chronic urticaria

Chronic urticaria of at least 6 weeks' duration may be ordinary, physical or vasculitic but the term is often considered to be synonymous with the ordinary presentation of chronic urticaria.

Idiopathic

Most patients were considered to have 'idiopathic' urticaria before autoimmunity was recognized as a cause. It is still not possible to ascribe a specific aetiology to around 50% of patients presenting with the ordinary presentation of chronic urticaria even after looking for autoreactivity with the ASST or testing for functional autoantibodies with the basophil histamine release assay. The reasons for this are not clear but may be due to relative insensitivity of the assay for low concentrations of functional autoantibodies that could, in theory, degranulate hyper-releasable mast cells in chronic urticaria but not the normal basophils of healthy donors. Clinical experience suggests that chronic urticaria is often a multifactorial disease and that its day-to-day activity is determined by exogenous aggravating factors (see below) acting in conjunction with an endogenous cause.

Autoimmune

There is increasing acceptance that histamine releasing autoantibodies define an autoimmune aetiology in an important subset of patients. Sera of approximately 60% of patients with chronic ordinary urticaria have been shown to cause a pink weal when injected intradermally into the patient's own skin (the autologous serum skin test) [1]. Approximately half of these patients' sera (30% of total chronic ordinary urticaria patients) released histamine *in vitro* from basophils and skin slices obtained from healthy people, in one series [2]. The proportion of chronic urticaria sera releasing histamine has been up to 50% in others [3]. Almost 100% of sera from chronic urticaria patients with a positive ASST were histamine releasers from a panel of basophils and mast cells from different donors [4]. This histamine releasing activity is due to functional IgG autoantibodies directed against the α-subunit of FcεRI or, less frequently, against receptor-bound IgE [5,6]. These functional autoantibodies are predominantly of IgG1 and 3 complement-fixing subclasses [7]. Complement dependence of autoantibody-induced mast cell degranulation has been shown [8]. In a few patients with a positive skin test but negative basophil histamine releasing activity, there was evidence of an unidentified non-IgG factor reacting with mast cells [9]. Autoantibodies against FcεRIα, of predominantly IgG2 and 4 subclasses (unable to fix complement), have been detected by western blot and enzyme-linked immunoassay (ELISA) in the sera of patients with other conditions, such as systemic lupus erythematosus (SLE), dermatomyositis, bullous pemphigoid and pemphigus vulgaris [7], and even in healthy subjects [10], but appear to be non-functional and therefore unlikely to be of pathogenic importance.

Immune-modulating treatment of severely affected chronic urticaria patients with a positive skin test, using plasmapheresis [11] and intravenous immunoglobulin [12], was associated with clinical remission in some. Thus, in some patients, chronic urticaria appears to be a manifestation of a specific autoimmune disorder. In the remaining 50% of patients, no histamine-releasing factor can be identified *in vitro* or *in vivo* and the reasons for this have not yet been clarified. It is possible that other non-antibody factors are involved. Histamine releasing autoantibodies have not been demonstrated in the physical or cholinergic urticarias.

Even now, the cause can rarely be identified with certainty, since there are no routinely available tests for histamine-releasing autoantibodies. The ASST is used in some centres as a non-specific screening test for histamine releasing factors in blood of patients with chronic urticaria but the results need to be interpreted with caution and should not be regarded as proof of an autoimmune aetiology.

Pseudoallergy

Although 30% of chronic urticaria patients were considered to have intolerance reactions to dietary pseudoallergens as causing or aggravating their urticaria in a quality of life study [13], it is the authors' experience that exposure to dietary and drug pseudoallergens is a rare cause of chronic urticaria. However, dietary additives and salicylates may be one of many factors that aggravate existing chronic urticaria and this should be explored in the medical history (see Aggravating factors, Table 22.7).

Infections and infestations

The incidence of bacterial infections, such as dental sepsis, sinusitis, urinary tract and gallbladder infections, in chronic urticaria varies in different series. If present, treatment of the infection usually does not improve urticaria and, overall, infections are a rare cause of chronic urticaria. *H. pylori* infection of the stomach has been associated with chronic urticaria [14] but appears uncommon in the UK. *Candida* infections, although described [15], are found extremely rarely to be a cause of urticaria. Intestinal parasites are a rare cause in developed and developing countries [16], but should be looked for if there is a blood eosinophilia or a history of recent travel to subtropical or tropical areas [17]. Rarely, protozoa or helminthic infection in the tissue may be a cause. Linear weals may follow migration of *Ancylostoma* and *Strongyloides* worms. *Toxocara canis* antibodies have been associated with chronic urticaria, but a causal relationship is not proven [18].

References

1 Grattan CEH, Wallington TB, Warin RP *et al*. A serological mediator in chronic idiopathic urticaria: a clinical, immunological and histological evaluation. *Br J Dermatol* 1986; **114**: 583–90.

2 Niimi N, Francis DM, Kermani F *et al*. Dermal mast cell activation by autoantibodies against the high affinity IgE receptor in chronic urticaria. *J Invest Dermatol* 1996; **106**: 1001–6.

3 Tong LJ, Balakrishnan G, Kochan JP, *et al*. Assessment of autoimmunity in patients with chronic urticaria. *J Allergy Clin Immunol* 1997; **99**: 461–5.

4 Asero R, Lorini M, Chong SU *et al*. Assessment of histamine releasing activity of sera from patients with chronic urticaria showing positive autologous skin test on human basophils and mast cells. *Clin Exp Allergy* 2004; **34**: 1111–4.

5 Hide M, Francis DM, Barr RM, Greaves MW. Skin mast cell activation by autoantibodies in urticaria and therapeutic implications. In: Kitamura Y, Yamamoto S, Galli SJ, Greaves MW, eds. *Biological and Molecular Aspects of Mast Cell and Basophil Differentiation and Function*. New York: Raven Press, 1995: 183–92.

6 Fiebiger E, Maurer D, Holub H *et al*. Serum IgG autoantibodies directed against the α chain of FcεRI: a selective marker and pathogenetic factor for a distinct subset of chronic urticaria patients? *J Clin Invest* 1995; **96**: 2606–12.

7 Fiebiger E, Hammerschmid F, Stingl G, Maurer D. Anti-FcεRIα autoantibodies in autoimmune-mediated diseases. *J Clin Invest* 1998; **101**: 243–51.

8 Ferrer M, Nakazawa K, Kaplan AP. Complement dependence of histamine release in chronic urticaria. *J Allergy Clin Immunol* 1999; **104**: 169–72.

9 Sabroe RA, Fiebiger E, Francis DM *et al*. Classification of anti-FcεRI and anti-IgE autoantibodies in chronic idiopathic urticaria and correlation with disease severity. *J Allergy Clin Immunol* 2002; **110**: 492–9.

10 Horn MP, Pachlopnik JM, Vogel M *et al*. Conditional autoimmunity mediated by human natural anti-FcεRIα autoantibodies? *FASEB J* 2001; **15**: 2268–74.

11 Grattan CEH, Francis DM, Slater NGP *et al*. Plasmapheresis for severe unremitting chronic urticaria. *Lancet* 1992; **339**: 1078–80.

12 O'Donnell BF, Barr RM, Kobza Black A *et al*. Intravenous immunoglobulin in autoimmune chronic urticaria. *Br J Dermatol* 1998; **130**: 101–6.

13 Staubach P, Eckhardt-Henn A, Dechene M *et al*. Quality of life in patients with chronic urticaria is differentially impaired and determined by psychiatric comorbidity. *Br J Dermatol* 2006; **154**: 294–8.

14 Tebbe B, Geilen CC, Schulzke JD *et al*. *Helicobacter pylori* infection in chronic urticaria. *J Am Acad Dermatol* 1996; **34**: 685–6.

15 James J, Warin RP. An assessment of the role of *Candida albicans* and food yeasts in chronic urticaria. *Br J Dermatol* 1971; **84**: 227–37.

16 Gosh S, Kanwar AJ, Dhar S *et al*. Role of gastrointestinal parasites in urticaria. *Indian J Dermatol Venereol Leprol* 1993; **59**: 117–9.

17 Mehta RK, Shah N, Scott DGI, Grattan CEH. Clinicopathological cases: case 4. *Clin Exp Dermatol* 2002; **27**: 84–5.

18 Wolfrom E, Chene G, Boisseau H *et al*. Chronic urticaria and *Toxocara canis*. *Lancet* 1995; **345**: 196.

Aggravating factors (Table 22.7)

Even though a specific cause of urticaria may not be identified in individual patients it is often possible to identify non-specific aggravating factors in chronic urticaria, such as heat and clothing pressure in ordinary urticaria, avoidance of which can help to minimize exacerbations.

Drugs

Salicylates and other related NSAIDs, such as diclofenac, can aggravate urticaria and asthma by non-allergic mechanisms. Patients usually react with either urticaria or asthma, but not both [1]. The percentage of patients whose urticaria is exacerbated by aspirin (acetylsalicylic acid) varied from 20% to 30% in different studies [2,3]. Many medicines and proprietary preparations contain aspirin, but the small amounts of salicylates present in food are unlikely to be significant [4]. Although aspirin may exacerbate chronic urticaria, these reactions are usually not life-threatening. ACEIs can provoke angio-oedema and may, perhaps, aggravate urticaria. The relationship between penicillin and chronic urticaria is a complex one, but the amount present in dairy products seems unlikely to perpetuate chronic urticaria except in people with extreme penicillin sensitivity, or if penicillin is present in food above permitted levels [5].

Foods and food additives

Numerous foods have been blamed as a cause of urticaria [6]. However, an allergic cause was found in fewer than 3.5% of cases [1,7]. The general population blamed foods for their adverse clinical reactions, including urticaria, more often than could be reproduced on double-blind challenge [8].

There are many reports that food additives aggravate chronic urticaria, but the high incidence of 33% [9] has not been confirmed in some double-blind studies [10]. The discrepancies in incidence in different studies could arise from the differing populations and test methods used. Other variables during testing include antihistamine therapy, basic diet, hospitalization and whether testing

Table 22.7 Aggravating factors in chronic ordinary urticaria (often more than one).

Aspirin and other non-steroidal anti-inflammatories
Dietary pseudoallergens
Upper respiratory tract infections (NOS)
Pressure
Overheating
Premenstrual period in women
Alcohol
Stress
Unrelated viral infections

Table 22.8 Substances used in single blind-challenge testing of food additives at St John's Institute of Dermatology (adults only).

Colouring agents
Tartrazine (E102) 10 mg
Quinoline yellow (E104) 10 mg
Erythrosine (E127) 5 mg
Preservatives
Sorbic acid (E200) 100 mg
Sodium benzoate (E211) 1000 mg
4-hydroxybenzoic acid (E214–219) 1000 mg
Sodium metabisulphite (E223) 50 mg
Sodium nitrate (E251) 100 mg
Antioxidants
Butylhydroxyanisole (E320) 50 mg
Butylhydroxytoluene (E321) 50 mg
Flavour enhancer
Monosodium glutamate (E621) 200 mg
Aspirin 75 mg
Aspirin 300 mg*

* Not to be given if there is a history of asthma or severe aspirin reactions.

was placebo-controlled and double-blind, with confirmation of positive results on retesting [11]. The exact percentage of reactions to additives is not known, but is considered to be important in fewer than 10% of patients with chronic ordinary urticaria. The most frequently implicated food additives are tartrazine (E102) and other azo dyes, including sunset yellow (E110). Reactions to benzoate preservatives (E210–219) and antioxidants, such as butylated hydroxytoluene (E321) and butylated hydroxyanisole (E320), are reported less often. Sulphites (E223–228), monosodium glutamate (E621) and aspartate are very rare causes of urticaria, which is usually of the acute type. The sensitivity to additives gradually lessens as the urticaria resolves. Dyes and preservatives can be found in medicinal products, but usually in smaller doses than in food [12]. Oral challenge testing may be performed if desired by physician or patient but tends to be most rewarding in episodic than chronic urticaria (see St John's challenge test, Table 22.8).

References

1 Ameisen JC, Capron A. Aspirin-sensitive asthma. *Clin Exp Allergy* 1990; **20**: 127–9.
2 Stevenson DD. Diagnosis, prevention and treatment of adverse reactions to aspirin and nonsteroidal anti-inflammatory drugs. *J Allergy Clin Immunol* 1984; **74**: 617–22.
3 Grattan C. Aspirin-sensitive urticaria. *Clin Exp Dermatol* 2003; **28**: 123–7.
4 Swain AR, Dutton SP, Truswell AS. Salicylates in foods. *J Am Dietetic Assoc* 1985; **85**: 950–60.
5 Ormerod AD, Reid TMS, Main RA. Penicillin in milk: its importance in urticaria. *Clin Allergy* 1987; **17**: 229–34.
6 Champion RH, Muhlemann MF. A list of potential causes of urticaria. In: Champion RH, Greaves MW, Kobza Black A *et al*., eds. *The Urticarias*. Edinburgh: Churchill Livingstone, 1985: 123–9.
7 Atkins FM. Food induced urticaria. In: Metcalfe DD, Sampson HA, Simon RA, eds. *Food Allergy: Adverse Reactions to Foods and Food Additives*. Oxford: Blackwell Scientific Publications, 1991: 129–38.
8 Young E, Stoneham MD, Petruckevitch A *et al*. A population study of food intolerance. *Lancet* 1994; **343**: 1127–30.
9 Juhlin L. Recurrent urticaria: clinical investigation of 330 patients. *Br J Dermatol* 1981; **104**: 369–81.
10 Hannuksela M, Lahti A. Peroral challenge tests with food additives in urticaria and atopic dermatitis. *Int J Dermatol* 1986; **25**: 178–80.
11 Young E. Food additives, food and dermatology. In: Champion RH, Pye RJ, eds. *Recent Advances in Dermatology*, Vol. 9. Edinburgh: Churchill Livingstone, 1992: 133–45.
12 Pollock I, Young E, Stoneham M *et al*. Survey of colourings and preservatives in drugs. *BMJ* 1989; **299**: 649–51.

Infections

Chronic urticaria is frequently exacerbated by intercurrent viral infections. This may be a non-specific effect of circulating pro-inflammatory cytokines or chemokines.

Menstrual cycle and pregnancy

Urticaria may occur in pregnancy, but it is difficult to evaluate any causal relationship. It should be distinguished from pruritic urticarial papules and plaques of pregnancy (PUPPP, synonym polymorphic eruption of pregnancy), which is the most common specific dermatosis of pregnancy and occurs during the third trimester. Urticaria may worsen premenstrually, but if urticaria occurs predominantly or only premenstrually, it has been attributed to progesterone sensitivity [1] or more rarely oestrogen sensitivity [2], usually on an autoimmune basis. A non-immune mechanism has been suggested for 'autoimmune' progesterone urticaria [3].

References

1 Stephens CJM, Black MM. Premenstrual eruptions: autoimmune progesterone dermatitis. *Semin Dermatol* 1989; **8**: 26–9.
2 Shelley WB, Shelley ED, Talanin NY, Santoso-Pham J. Estrogen dermatitis. *J Am Acad Dermatol* 1995; **32**: 25–31.
3 Wilkinson SM, Beck MH, Kingston TP. Progesterone-induced urticaria: need it be autoimmune? *Br J Dermatol* 1995; **133**: 792–4.

Implants and nickel allergy

Urticaria has been linked anecdotally with a metal pin in the femur [1], a metal dental prosthesis [2] and with dental amalgams [3], but an apparent association in these cases may have been fortuitous. A role for contact sensitization in chronic urticaria has been proposed [4]. The authors reported positive patch tests in 41% of their series. All nickel allergic patients went into remission within 8 weeks of a nickel-free diet, but these results have not yet been confirmed by other centres or subjected to a randomized controlled study.

References

1 McKenzie AW. Urticaria after insertion of Smith–Petersen vitallium nail. *BMJ* 1967; **iv**: 36.
2 Espana A, Alonso ML, Soria C *et al*. Chronic urticaria after implantation of two nickel-containing dental prostheses in a metal allergic patient. *Contact Dermatitis* 1989; **21**: 204–5.
3 Markow H. Urticaria following a dental silver filling. *N Y State J Med* 1943; **43**: 1648–52.
4 Guerra L, Rogkakou A, Massacane P *et al*. Role of contact sensitization in chronic urticaria. *J Am Acad Dermatol* 2007; **56**: 88–90.

Stress

Psychological factors appear to play a contributory role in a proportion of patients, and flare-ups of urticaria do occur at times of psychological stress [1]. Psychological factors are often wrongly

thought to contribute to angio-oedema because of the old name 'angioneurotic oedema', which implied something very different when it was first introduced. The importance of psychological factors is difficult to evaluate scientifically and can be over-emphasized. Depression and anxiety were found more frequently in chronic urticaria in two studies [2,3], but not in another [4]; however, depression may reduce the threshold for pruritus [5], and the effect of chronic urticaria on quality of life should not be underestimated [6].

References

1 Koblenzer C. Psychosomatic concepts in dermatology: a dermatologist–psychoanalyst's viewpoint. *Arch Dermatol* 1983; **119**: 501–12.

2 Hashiro M, Okumura M. Anxiety, depression, psychomotor symptoms and autonomic nervous function in patients with chronic urticaria. *J Dermatol Sci* 1990; **123**: 129–35.

3 Hein UR, Henz BM, Haustein UW *et al*. Zur Beziehung zwischen chronischer Urtikaria und Depression/Somatisierungsstörung. *Hautarzt* 1996; **47**: 20–3.

4 Sheehan-Dare RA, Henderson MJ, Cotterill JA. Anxiety and depression in patients with chronic urticaria and generalized pruritus. *Br J Dermatol* 1990; **123**: 769–74.

5 Gupta MA, Gupta AK, Schork NJ, Ellis CN. Depression modulates pruritus perception: a study of pruritus in psoriasis, atopic dermatitis and chronic idiopathic urticaria. *Psychosom Med* 1994; **56**: 36–40.

6 O'Donnell BF, Lawlor F, Simpson J *et al*. The impact of chronic urticaria on the quality of life. *Br J Dermatol* 1997; **136**: 197–201.

Physical and cholinergic urticarias [1,2]

The physical urticarias are a distinct subgroup of urticarias in which a specific physical stimulus induces reproducible wealing. This feature is the basis of diagnosis and classification (Table 22.9). Cholinergic urticaria occurs in response to sweating caused by an increase in core temperature, so it is frequently included in the physical urticaria group, but it may also be triggered by emotional and gustatory sweating. The currently accepted challenge procedures for the diagnosis of physical urticarias are summarized in Table 22.10.

The frequency of physical urticarias in the general population is unknown, but they accounted for 19% of urticaria cases in a dermatology clinic [3], with dermographism making up 9% and cholinergic urticaria 4%. However, mixtures of various types of physical urticaria or of a physical urticaria with ordinary urticaria are common—for example, a component of delayed pressure urticaria occurs in 37% of people with ordinary chronic urticaria.

Wealing caused by physical stimuli usually occurs within minutes at the site of contact with the skin and persists for less than 30–60 min (immediate contact type—for example, dermographism and most cold urticarias). However, sometimes a generalized stimulus affecting the whole body is necessary (reflex type—for example, cooling body core temperature to induce reflex cold urticaria and a rise in core temperature to induce cholinergic urticaria). In a few forms of physical urticaria, a delay of several hours from the physical stimulus occurs before weals appear—for example, delayed dermographism, delayed pressure urticaria and the rare delayed cold urticaria.

In many forms of physical urticaria, if the stimulus is sufficiently great or the patient is very sensitive, angio-oedema and systemic reactions may occur from mediator release.

Table 22.9 A classification of physical urticarias and their prevalence.

	Prevalence
Due to mechanical force	
Dermographism	
Immediate	
Symptomatic dermographism	+
Simple dermographism	+ +
Red dermographism	+ –
Cholinergic dermographism	+
Delayed dermographism	+ –
Associated with mastocytosis (Darier's sign)	+
Delayed pressure urticaria	+ +
Vibratory angio-oedema	+ –
Due to heat	
Generalized heating	
Cholinergic urticaria	+ +
Variants	
Cholinergic pruritus	+
Persistent cholinergic erythema	+
Cholinergic dermographism	+
Exercise-induced anaphylaxis	+
Localized heating	
Heat contact urticaria	+ –
Due to cold	
Acquired	
Primary (idiopathic)	
Localized cooling	
Cold erythema	+
Immediate cold contact urticaria	+ + +
Delayed cold contact urticaria	+ –
Localized cold contact urticaria	+ –
Generalized	
Generalized reflex cold urticaria	+ –
Cold-dependent cholinergic urticaria	+ –
Secondary (to serum cryoproteins)	+
Inherited	+ –
Others	
Solar urticaria	+
Aquagenic urticaria	+

Combinations of different types are common.
+ –, rare; +, uncommon; + +, moderately common; + + +, very common.

Urticaria due to mechanical forces

Dermographism

Immediate symptomatic dermographism (factitious urticaria)

This involves the triple response which may arise from firm stroking of the skin [4]. This response consists of *local erythema* due to capillary vasodilatation, followed by *oedema* and a *surrounding flare* due to axon reflex-induced dilatation of arterioles. This reaction is normal, but in 5% of normal people this physiological response is sufficiently exaggerated to warrant the term simple dermographism. In a minority of these people, it is accompanied symptomatically by itching (symptomatic dermographism). Symptomatic dermographism may have an immunological basis.

Table 22.10 Challenge tests for the diagnosis of physical and cholinergic urticarias. All should be medically supervised.

Physical urticaria	Testing
Dermographism	Itching weals occur in minutes lasting less than 1 hour after: a. Firm stroking of the skin with a smooth blunt object (back preferable) b. A calibrated dermographometer set at 36 g/mm^2 or less
Delayed pressure urticaria	Sustained pressure is applied to the back, shoulder or thigh: a. 4.5 kg weighted rods with a 1.5 cm diameter applied for 15 min b. Dermographometer set at 100 g/mm^2 pressed against the back of the shoulder for 70 s, read after 2–6 h and next day c. Hanging a weight 15 lbs (7 kg) by a broad strap from a shoulder results in a weal, often painful, at the application site 4–6 h later, lasting from several hours up to 24 h
Cholinergic urticaria	Raising the core body temperature by 0.7–1.0°C by: a. Exercise in a hot environment until sweating b. Hot bath (42°C) for 15 min induces itching within minutes, with widespread small weals In an individual patient, either method may be more successful In exercise-induced anaphylaxis, only the exercised-induced challenge will be positive
Cold urticaria	
Idiopathic contact	Application of a melting ice cube in a thin plastic bag for up to 20 min results in an itching weal at the site within minutes of removal; if mild may take up to 10 min to develop after removal; induced weals last less than 1 h
Generalized reflex	Placing the patient (with supervision) in a cold room at 4°C for 30 min induces widespread small weals; the ice cube test is negative
Solar urticaria	Exposure to sunlight or solar simulator induces redness, itching weals at site of exposure within a few minutes lasting less than 1 h Exposure to a monochromator can determine the individual wavelengths that induce wealing
Aquagenic urticaria	a. Exposure of skin to water at body temperature in a bath for 15 min induces small itching weals on the immersed site within minutes b. Application of water soaked towels at body temperature for 30 min at sites where aquagenic urticaria occurs, e.g. back or upper chest, induces small itching weals at the site of application within minutes lasting less than 1 h (NB other physical urticarias should be excluded)
Heat contact urticaria	Wealing occurs in minutes localized to the site of application of heated objects at 39–45°C for 2–5 min lasting less than 1 h
Vibratory angio-oedema	Application of a laboratory vortex resting on the forearm or finger for 1–5 min results, within minutes, in a red swelling of the vibrated area, lasting less than 1 h

Dermographism has been successfully transferred when IgE (and occasionally IgM) in patients' sera has been injected into normal recipients [5,6]. It has been proposed that mast cells sensitized with immunoglobulins (especially IgE) react to a neoantigen induced by mechanical stimulation of the skin and release their mediators. Neuropeptides may contribute to the reaction [7].

Symptomatic dermographism can occur at any age, but the greatest incidence is in young adults. Patients complain of wealing and itching at sites of trauma, friction with clothing or scratching the skin. The itching is often disproportionately severe compared with wealing and is often most severe at night. The eliciting stimulus determines the shape of the weals (Fig. 22.4), but they are often linear from scratching or stroking (Fig. 22.5). Dermographism may be present but is not increased in chronic ordinary urticaria, nor is there any correlation with systemic disease or food allergy [7]. Dermographism is usually idiopathic, but sometimes may follow a drug reaction—for example, penicillin reaction [8] or an infestation, including scabies. Dermographism may last for months or years, or be present intermittently.

Symptomatic dermographism is most easily diagnosed by using a calibrated instrument, the dermographometer [9], which has a spring-loaded stylus, the pressure of which can be adjusted to a predetermined setting. Stroking the skin at a tip pressure of less than 36 g/mm^2 [7] induces a linear, itching weal within 10 min.

Other forms of dermographism

Rarer forms of dermographism exist, including *red dermographism*, where repeated rubbing is necessary to induce small, punctate weals [10]. *Cholinergic dermographism* is seen in some patients with cholinergic urticaria, whose dermographic response consists of an erythematous line studded with punctate weals characteristic of cholinergic weals [11]. *Delayed dermographism* is rare. After a normal fading of the triple response or an immediate dermographic response, a weal returns in the same site, but is usually tender and persists up to 48 h [12]. The mechanism is unknown, but it is closely related to pressure urticaria [13], in which a delayed dermographic response is not unusual.



Fig. 22.4 Dermographism, meaning 'skin writing'. (Courtesy of St John's Institute of Dermatology, London, UK.)



Fig. 22.5 Linear lesions of immediate dermographism induced by stroking back skin with a calibrated dermographometer. (Courtesy of St John's Institute of Dermatology, London, UK.)



Fig. 22.6 Extensive delayed pressure urticaria over the back after sitting against a hard surface. Induced delayed dermographism is also seen on the upper back. (Courtesy of St John's Institute of Dermatology, London, UK.)

The presence of wealing following friction (Darier's sign) is characteristic of the lesions of urticaria pigmentosa as a presentation of mastocytosis, in which the number of skin mast cells is increased.

Treatment of symptomatic immediate dermographism with low-sedating H_1 antihistamines is often effective, sometimes in low doses. For the more severely affected, there is probably no clinical benefit from combining H_1 with H_2 antihistamines [14]. However, some improvement may be obtained with narrow-band ultraviolet B (NB-UVB) or psoralen and ultraviolet A (PUVA) therapy [15].

It should be noted that not all forms of dermographism are urticarial. *White dermographism* (due to capillary vasoconstriction following light stroking of the skin) occurs normally and is particularly pronounced in atopic subjects. *Black dermographism* is discolouration of the skin after pressure from a metallic object.

Delayed pressure urticaria

Delayed pressure urticaria [16] in its predominant form is uncommon (2% of urticarias) but it occurs to some degree in about a third of patients with chronic ordinary urticaria, although they may be unaware of this unless directly questioned [17]. Patients with predominantly delayed pressure urticaria nearly always have a component of chronic ordinary urticaria. Wealing occurs at sites of sustained pressure applied to the skin after a delay of 30 min to 9 h, but usually 4–8 h, and lasts 12–72 h [16].

Weals occur frequently under tight clothing, on the hands after manual work, on the buttocks and lower back after sitting (Fig. 22.6) and on the feet after walking. Lesions may be itchy, but are often tender or painful, particularly on the soles and scalp. The severity is variable, but it may be accompanied by systemic symptoms of malaise, flu-like symptoms, arthralgia, myalgia and leukocytosis. The condition may be mistaken for urticarial vasculitis.

The diagnosis can usually be made by careful questioning and confirmed by testing. Objective testing is performed by using a dermographometer set at 100 g/mm^2 pressed perpendicularly on the upper back for 70 s [18], or rods with a convex end diameter of 1.5 cm weighted with 2.5 kg for 20 min or 4.5 kg for 15 min on the back or thighs [17]. A positive response is when indurated lesions are present at test sites at 6 h. Areas of delayed pressure urticaria may be refractory to further pressure-induced lesions for up to 48 h.

Delayed pressure urticaria responds poorly to H_1 antihistamines but higher than licensed doses of cetirizine (10 mg three times a day) have been used, as it also inhibits eosinophil migration. Although NSAIDs may be helpful for pressure-induced lesions, they may aggravate the ordinary component of chronic urticaria. Montelukast has been reported to help [19] but is not usually effective for the more severe patterns of the disease. Drugs that inhibit granulocyte infiltration (including colchicine, dapsone and sulphasalazine) may be helpful although supporting clinical studies are lacking. The use of very potent topical steroids under occlusion for the hands and feet may be effective [20] and wearing comfortable shoes or insoles can be useful.

The prognosis is variable. The symptoms fluctuate in severity; they may show spontaneous improvement, or last for many years.

Vibratory angio-oedema

Vibratory urticaria is a very rare form of urticaria, which was first described in its familial form [21]. Any vibratory stimulus such as jogging, vigorous towelling or using lawnmowers induces a localized, red, itchy swelling within minutes and lasting less than a few hours, but if the stimulus is severe, generalized erythema and headache may occur. Avoidance of the precipitating stimuli enables patients to lead normal lives. Occasionally, vibratory angio-oedema may occur in an acquired form [22,23].

Temperature-dependent urticaria

Heat urticaria

Cholinergic urticaria

Cholinergic urticaria is a very distinctive type in which characteristic small weals appear in association with sweating. It accounts for about 5% of urticaria, and lesser degrees are common in adolescents. Wealing occurs on stimulation of sweating, whether induced by a rise in core temperature, emotion or gustatory stimuli.

The pathogenesis is still not clear. It is thought to be related to stimulation of the cholinergic postganglionic sympathetic nerve supply to the sweat glands. Increased histamine levels have been detected in the blood of patients with cholinergic urticaria. It was originally proposed that acetyl choline can release histamine, perhaps in an indirect way, but such a mechanism is conjectural [24]. Passive transfer tests with serum of affected individuals are sometimes positive, probably due to an immunoglobulin [25]. Such an antibody may prime the mast cell for activation. An allergy to sweat itself has been proposed [26]. It has also been proposed that cholinergic urticaria should be classified into two subtypes based on intradermal skin test reactions to autologous sweat and serum [27]. Decreased levels of the protease inhibitor antichymotrypsin have been detected in the serum of some patients [28]. There is no generalized disturbance of autonomic function [29].

The disease typically occurs in adolescents of either sex and may be worse in the winter months [30]. It has been reported to occur in families [31] and often occurs in atopics. The patient complains of itching weals that appear within minutes of exertion, when hot, or after emotional disturbances or even eating spicy food. The weals characteristically are small, 1–3 mm across, with or without a well-marked flare (Fig. 22.7). Sometimes, the erythematous component is more pronounced, especially in the 'blush areas', and is confluent and studded with weals. Oblique lighting is helpful for observing the weals, especially in dark skin. The lesions persist for a few minutes to an hour or two. Ordinary urticaria not precipitated by heat may be associated with cholinergic urticaria in some patients. Although micropapular weals resembling those of cholinergic urticaria can occur in ordinary urticaria, these usually last for hours. Cholinergic angio-oedema has been recorded [32]. In persistent cholinergic erythema, multiple small erythematous macules are distributed symmetrically on trunk and limbs, increasing in number after exercise. Individual



Fig. 22.7 Close-up of small monomorphic lesions of cholinergic urticaria on the trunk. (Courtesy of Norfolk and Norwich University Hospital, UK.)

macules are short-lived, but appear at different sites over a prolonged period, giving the overall impression of a persisting rash [33]. Cholinergic itching without weals has been described [34].

In some patients with cholinergic urticaria, systemic symptoms of flushing, faintness or asthma may occur [35,36]. Exercise-induced anaphylaxis may occur as part of the cholinergic urticaria spectrum after severe exercise [37]. However, exercise-induced anaphylaxis in others does not appear to be associated with cholinergic urticaria and can not be reproduced by hot bathing. It often occurs in patients sporadically and unpredictably, and appears to be a distinct entity [38]. It is possible that some are examples of unrecognized food and exercise-induced anaphylaxis.

Rarely, a generalized eruption resembling cholinergic urticaria may be provoked by systemic chilling [39].

The diagnosis of cholinergic urticaria is best confirmed by provocation, with the appearance of typical weals after warming—for example in a hot bath at 42°C for 15 min, to raise the core temperature by 0.7 to 1°C—or exercise in a hot environment [40]. Intradermal injections of cholinergic drugs such as methacholine produce local axon reflex sweating and sometimes the appearance of satellite weals. However, this test is unreliable and not specific enough to be useful [40]. A few patients find that if they can bring on a severe attack by suitable exertion they can achieve freedom for up to 24 h afterwards, analogous to temporary desensitization.

Heat contact urticaria [41,42]

This is one of the rarest forms of physical urticaria. Localized warming of skin at temperatures varying from 38 to 50°C for 2–

5 min induces wealing at the test site lasting 1 h. Treatment with antihistamines or induction of tolerance by repeated heat exposure may be helpful [43].

Cold urticaria [44,45]

Cold urticaria encompasses a variety of syndromes in which cold induces urticaria (see Table 22.9). Idiopathic cold contact urticaria is the most common, comprising 96% of a series of cold urticaria patients [46], while others are rare. In some patients with idiopathic cold contact urticaria, the serum can passively transfer the cold urticarial response to normal recipients. This autoantibody is usually IgE-like [47], but IgM has been recorded. It is important to warn against cold-water bathing due to the risk of anaphylaxis and drowning. Treatment with low-sedation antihistamine is helpful. Induction of tolerance by repeated graduated exposures to cold can be helpful for selected patients [48,49], but it is time consuming and not always effective.

Idiopathic cold urticaria

Immediate cold contact urticaria. This is by far the commonest form, occurring at any age but most frequently in young adults. It may be preceded by non-specific upper respiratory viral infections, infectious mononucleosis or insect bites. Itching and wealing of the skin occur on cold exposure within minutes and last up to 1 h. Cold winds and cold rain are particularly effective stimuli. Sometimes, the mouth and pharynx may swell after drinking cold liquids. Systemic symptoms include flushing, palpitations, headache, wheezing and loss of consciousness, and drowning has occurred after cold-water bathing.

Dermographism and cholinergic urticaria are frequently associated with cold urticaria. The average duration of cold urticaria was 6 years in one series [46], but it may persist for many years.

Diagnosis is made by application of an ice cube in a thin plastic bag for up to 20 min onto the skin, and wealing occurs within 15 min, usually during rewarming [45] (Fig. 22.8). Sometimes a more extensive local challenge, such as immersion of a forearm in iced cold water, is necessary. A temperature testing device has recently been described (TempTest®, Berlin) which allows temperature thresholds to be established for individual patients as well as cold stimulation time as a measure of severity [50].

Delayed cold contact urticaria. This form, where wealing occurs after a delay of hours after cold contact, is very rare [51]. A familial form has been reported [52].

Localized cold contact urticaria. This is very rare [53].

Familial cold urticaria. This rare form is inherited as an autosomal-dominant trait and is now known to be caused by the same gene mutation as Muckle–Wells syndrome [54] (p. 22.24). The ice cube test is negative.

Acquired cold contact erythema. Painful erythema without wealing occurs in response to cold [55], but in other patients it may be a forme fruste of immediate cold contact urticaria.



Fig. 22.8 Wealing following an ice-pack application for 20 min. (Courtesy of St John's Institute of Dermatology, London, UK.)

Cold urticaria secondary to serum cryoproteins

This is rare and was found in only 1% of one series [46]. It is usually associated with other manifestations such as Raynaud's phenomenon, purpura or skin necrosis. Cryogobulinaemia may be idiopathic or occur in collagen vascular disease, chronic lymphatic leukaemia, myeloma and in infectious disease, including infectious mononucleosis. Cold urticaria is said to occur in only 3% of people with cryoglobulinaemia [56]. Blood samples for cryoprotein estimation must be kept warm until laboratory testing. Treatment is directed against the underlying condition. Cryofibrinogen occurred in the blood of 3.4% of a large hospital population [57], and in 3% of patients in cold urticaria [58]. Its significance in relationship to cold urticaria remains to be determined. Cold agglutinins are not usually associated with cold urticaria [59]. Cold haemolysins have not been detected.

Systemic cold urticaria

In generalized reflex cold urticaria, widespread wealing occurs in response to cooling of core body temperature, but a local ice-cube test is negative [60]. Testing is performed by placing the patient in a cold room at 4°C for 30 min in lightweight clothes. In cold-induced cholinergic urticaria, additional exercise is necessary in the cold room to induce weals.

Solar urticaria [61–63]

Weals develop at the site of exposure within minutes of visible, long- or short-wave ultraviolet radiation [63] and usually fade within 2 h, in contrast to polymorphic light eruption, in which urticated lesions appear hours later and last days. A rare delayed



Fig. 22.9 Aquagenic urticaria on the back after swimming, showing a few small papular weals surrounded by wide flares. (Courtesy of Norfolk and Norwich University Hospital, UK.)

form has been described [64]. The cause of solar urticaria is usually unknown (idiopathic) but may be secondary to porphyrias [65]. The pathogenesis is discussed in Chapter 29.

Aquagenic urticaria [66,67]

Contact with water at any temperature induces an eruption resembling cholinergic urticaria, although the weals are few in number and are surrounded by a wide flare (Fig. 22.9). Other urticarias that can also be induced by water, such as cold urticaria, cholinergic urticaria and dermographism, must be excluded. This is a different entity from aquagenic pruritus, in which there is water-induced itching but no wealing [68,69].

References

1 Illig L. Physical urticaria: its diagnosis and treatment. In: Mali JWH, ed. *Current Problems in Dermatology*, Vol. 5. Basle: Karger, 1973: 79–116.
2 Kobza Black A. The physical urticarias. In: Champion RH, Greaves MW, Kobza Black A *et al.*, eds. *The Urticarias*. Edinburgh: Churchill Livingstone, 1985: 168–90.
3 Champion RH. Urticaria then and now. *Br J Dermatol* 1988; **119**: 588–97.
4 Lewis T. Vascular reactions of the skin to injury, 1: reaction to stroking—urticaria factitia. *Heart* 1924; **2**: 119–29.
5 Newcomb RW, Nelson H. Dermographia mediated by immunoglobulin E. *Am J Med* 1973; **54**: 174–80.
6 Horiko T, Aoki T. Dermographism (mechanical urticaria) mediated by IgM. *Br J Dermatol* 1984; **114**: 545–50.
7 Breathnach SM, Allen R, Milford Ward A, Greaves MW. Symptomatic dermographism: natural history, clinical features, laboratory investigations and response to therapy. *Clin Exp Dermatol* 1983; **8**: 463–76.
8 Smith JA, Mansfield LE, Fokakis A *et al.* Dermographia caused by IgE mediated penicillin allergy. *Ann Allergy* 1983; **51**: 30–3.
9 James J, Warin RP. Factitious wealing at the site of previous cutaneous response. *Br J Dermatol* 1969; **81**: 882–4.
10 Warin RP. Factitious urticaria: red dermographism. *Br J Dermatol* 1981; **104**: 285–8.
11 Mayou SC, Kobza Black A, Greaves MW. Cholinergic dermographism. *Br J Dermatol* 1986; **115**: 371–7.
12 Baughman RD, Jillson OF. Seven specific types of urticaria, with a special reference to delayed persistent dermographism. *Ann Allergy* 1963; **21**: 248–55.
13 Warin RP. Clinical observations on delayed pressure urticaria. *Br J Dermatol* 1989; **121**: 225–8.
14 Sharpe GR, Shuster S. In dermographic urticaria H_2 receptor antagonists have a small but therapeutically irrelevant additional effect compared with H_1 antagonists alone. *Br J Dermatol* 1993; **129**: 575–9.
15 Logan RA, O'Brien TJ, Greaves MW. The effect of psoralen photo-chemotherapy (PUVA) on symptomatic dermographism. *Br J Dermatol* 1989; **14**: 25–8.
16 Dover JS, Kobza Black A, Milford Ward A, Greaves MW. Delayed pressure urticaria: clinical features, laboratory investigations and response to therapy of 44 patients. *J Am Acad Dermatol* 1988; **18**: 1289–98.
17 Barlow RJ, Warburton F, Watson K *et al.* Diagnosis and incidence of delayed pressure urticaria in patients with chronic urticaria. *J Am Acad Dermatol* 1993; **29**: 954–8.
18 Lawlor F, Kobza Black A, Milford Ward A *et al.* Delayed pressure urticaria, objective evaluation of a variable disease using a dermographometer and assessment of treatment using colchicine. *Br J Dermatol* 1989; **120**: 403–8.
19 Nettis E, Colanardi AL, Soccio A *et al*. Desloratadine in combination with montelukast suppresses the dermographometer challenge test papule, and is effective in the treatment of delayed pressure urticaria: a randomized, double-blind, placebo-controlled study. *Br J Dermatol* 2006; **155**: 1279–82.
20 Vena GA, Cassano N, D'Argento V, Milani M. Clobetasol propionate 0.05% in a novel foam formulation is safe and effective in the short-term treatment of patients with delayed pressure urticaria: a randomized, double-blind, placebo-controlled study. *Br J Dermatol* 2006; **154**: 353–6.
21 Patterson R, Mellies CJ, Blakenship ML, Pruzansky JJ. Vibratory angioedema: a hereditary type of physical hypersensitivity. *J Allergy Clin Immunol* 1972; **50**: 175–82.
22 Ting S, Reimann BEF, Nat R *et al.* Nonfamilial, vibration-induced angioedema. *J Allergy Clin Immunol* 1983; **71**: 546–51.
23 Lawlor F, Kobza Black A, Breathnach AS, Greaves MW. Vibratory angioedema: lesion induction, clinical features, laboratory and ultrastructural findings, and response to therapy. *Br J Dermatol* 1989; **120**: 93–9.
24 Grant RT, Bruce Pearson RS, Comeau WJ. Observations on urticaria provoked by emotion, by exercise and by warming the body. *Clin Sci* 1936; **2**: 253–72.
25 Illig L, Heinicke A. Zur Pathogenese der cholinergischen Urticaria, 4: Zur Frage einer echten Antigen-Antikorper-Reaktion. *Arch Klin Exp Dermatol* 1967; **229**: 360–71.
26 Adachi J, Aoki T, Yamatodani A. Demonstration of sweat allergy in cholinergic urticaria. *J Dermatol Sci* 1994; **142**: 142–9.
27 Fukunaga A, Bito T, Tsuru K *et al*. Responsiveness to autologous sweat and serum in cholinergic urticaria classifies its clinical subtype. *J Allergy Clin Immunol* 2005; **116**: 397–402.
28 Wong E, Eftekhari N, Greaves MW, Milford Ward A. Beneficial aspects of danazol on symptoms and laboratory changes in cholinergic urticaria. *Br J Dermatol* 1987; **116**: 553–6.
29 Murphy GM, Smith SE, Smith SA, Greaves MW. Autonomic function in cholinergic urticaria and atopic eczema. *Br J Dermatol* 1984; **110**: 581–6.
30 Udassin R, Harari Z, Shoenfeld Y, Keren G. Cholinergic urticaria: a seasonal disease. *Arch Intern Med* 1981; **141**: 1029–30.
31 Onn A, Levo Y, Kivity S. Familial cholinergic urticaria. *J Allergy Clin Immunol* 1996; **98**: 847–9.
32 Lawrence CM, Jorrizo JL, Kobza Black A *et al.* Cholinergic urticaria associated with angio-oedema. *Br J Dermatol* 1981; **105**: 543–50.
33 Murphy GM, Kobza Black A, Greaves MW. Persistent cholinergic erythema: a variant of cholinergic urticaria. *Br J Dermatol* 1983; **109**: 343–8.
34 Berth-Jones J, Graham Brown AC. Cholinergic pruritus, erythema and urticaria: a disease spectrum responding to danazol. *Br J Dermatol* 1989; **121**: 235–7.
35 Czarnetzki BM, Galinski C, Meister R. Cutaneous and pulmonary reactivity in cholinergic urticaria. *Br J Dermatol* 1984; **110**: 587–91.

36 Soter NA, Wasserman SI, Austen KF, McFadden ER. Release of mast cell mediators and alterations in lung function in patients with cholinergic urticaria. *N Engl J Med* 1980; **302**: 604–8.
37 Kaplan AP, Natbony SF, Taiwil AP *et al.* Exercise-induced anaphylaxis as a manifestation of cholinergic urticaria. *J Allergy Clin Immunol* 1981; **88**: 319–24.
38 Sheffer AL, Soter NA, McFadden ER, Austen KF. Exercise-induced anaphylaxis: a distinct form of physical allergy. *J Allergy Clin Immunol* 1983; **73**: 311–6.
39 Kaplan AP, Garofalo J. Identification of a new physically induced urticaria: cold induced cholinergic urticaria. *J Allergy Clin Immunol* 1981; **68**: 438–41.
40 Commens CA, Greaves MW. Tests to establish the diagnosis in cholinergic urticaria. *Br J Dermatol* 1978; **98**: 47–51.
41 Delorme P. Localized heat urticaria. *J Allergy* 1969; **43**: 284–91.
42 Greaves MW, Sneddon IB, Smith AK, Stanworth DR. Heat urticaria. *Br J Dermatol* 1974; **90**: 289–92.
43 Leigh IM, Ramsay CA. Localized heat urticaria treated by inducing tolerance to heat. *Br J Dermatol* 1975; **92**: 191–4.
44 Black AK. Cold urticaria. *Semin Dermatol* 1987; **6**: 292–301.
45 Wanderer AA. Cold urticaria syndromes: historical background, diagnostic classification, clinical and laboratory characteristics, pathogenesis, and management. *J Allergy Clin Immunol* 1990; **85**: 965–81.
46 Neittaanmaki H. Cold urticaria: clinical findings in 220 patients. *J Am Acad Dermatol* 1985; **13**: 636–44.
47 Wanderer AA, Maselli R, Ellis EF *et al.* Immunological characterization of serum factors responsible for cold urticaria. *J Allergy Clin Immunol* 1971; **48**: 13–8.
48 Bentley-Phillips CB, Kobza Black A, Greaves MW. Induced tolerance in cold urticaria caused by cold-evoked histamine release. *Lancet* 1976; **ii**: 63–6.
49 Henquet CJM, Martens BPM, Van Vloten WA. Cold urticaria: a clinicotherapeutic study in 30 patients, with special emphasis on cold desensitization. *Eur J Dermatol* 1992; **2**: 75–7.
50 Siebenhaar F, Weller K, Mlynek *et al*. Acquired cold urticaria: clinical picture and update on diagnosis and treatment. *Clin Exp Dermatol* 2007; **32**: 241–5.
51 Sarkany I, Turk JL. Delayed hypersensitivity to cold. *Proc R Soc Med* 1965; **58**: 622–3.
52 Soter NA, Joshi NP, Twarog FJ *et al.* Delayed cold induced urticaria. *J Allergy Clin Immunol* 1977; **59**: 294–7.
53 Kurtz AS, Kaplan AP. Regional expression of cold urticaria. *J Allergy Clin Immunol* 1990; **86**: 272–3.
54 Hoffman HM, Mueller JL, Broide DH *et al*. Mutation of a new gene encoding a putative pyrin-like protein causes familial cold autoinflammatory syndrome and Muckle–Wells syndrome. *Nat Genet* 2001; **29**: 301–5.
55 Shelley WB, Caro WA. Cold erythema: a new hypersensitivity syndrome. *JAMA* 1962; **180**: 639–42.
56 Constanzi JJ, Coltman CA. Kappa chain cold precipitable immunoglobulin G (IgG) associated with cold urticaria, 1: clinical observations. *Clin Exp Immunol* 1967; **2**: 167–78.
57 Smith SB, Arkin C. Cryofibrinogenemia: incidence, clinical correlations and a review of the literature. *Am J Clin Pathol* 1972; **58**: 524–30.
58 Houser DD, Arbesman CE, Ito K *et al.* Cold urticaria: immunologic studies. *Am J Med* 1970; **49**: 23–33.
59 Pruzanski W, Shumak KH. Biological activity of cold-reacting autoantibodies, 2. *N Engl J Med* 1977; **297**: 583–9.
60 Kivity S, Schwartz Y, Wolf R, Topilsky M. Systemic cold-induced urticaria: clinical and laboratory classification. *J Allergy Clin Immunol* 1990; **85**: 52–4.
61 Leenutaphong V, Holzle E, Plewig G. Pathogenesis and classification of solar urticaria: a new concept. *J Am Acad Dermatol* 1989; **210**: 237–40.
62 Beattie PE, Dawe RS, Ibbetson SH, Ferguson J. Characteristics and prognosis of idiopathic solar urticaria. A cohort of 87 cases. *Arch Dermatol* 2003; **139**: 1149–54.
63 Uetso N, Miyauchi-Hashimoto H, Okamoto H, Horio T. The clinical and photobiological characteristics of solar urticaria in 40 patients. *Br J Dermatol* 2000; **142**: 32–8.
64 Monfrecola G, Nappa P, Pini D. Solar urticaria with delayed onset. A case report. *Photodermatol* 1988; **5**: 103–4.
65 Magnus IA, Jarrett A, Prankerd TAJ, Rimington C. Erythropoietic protoporphyic syndrome with solar urticaria due to protophyrinaemia. *Lancet* 1961; **ii**: 448–51.
66 Shelley WB, Rawnsley HM. Aquagenic urticaria. *JAMA* 1964; **189**: 895–8.
67 Panconesi E, Lotti T. Aquagenic urticaria. *Clin Dermatol* 1987; **5**: 49–51.
68 Greaves MW, Black AK, Eady RAJ, Coutts A. Aquagenic pruritus. *BMJ* 1981; **282**: 2007–10.
69 Steinman H, Greaves MW. Aquagenic pruritus. *J Am Acad Dermatol* 1985; **13**: 91–6.

Urticarial vasculitis [1–3]

Some urticarias are considered to be due to a type III hypersensitivity immune reaction, with deposition of immune complexes in blood vessels and other tissues and are often associated with systemic symptoms. The archetypal reaction is serum sickness [4], which presents as an acute illness. Some acute drug allergies give rise to a serum-sickness response. Classically, serum sickness follows parenteral injections of therapeutic sera, the immune complexes consisting of antigen and IgG, usually with antigen excess (type III reaction). The immune complexes activate complement and are deposited in tissues, including skin. It was a prevalent illness in the pre-antibiotic era—when heterologous antisera were used extensively to treat diphtheria, scarlet fever and pneumococcal pneumonia—but is now uncommon. Other causes of serum sickness-like syndrome include drugs, especially penicillin, radiocontrast media, hepatitis B infections and, rarely, foods. Onset is after 1–3 weeks, or more quickly if there has been previous exposure. Urticarial lesions are persistent, lasting a few days, and are sometimes tender or painful with bruising. Systemic features include fever, arthropathy, lymphadenopathy, cough, gastrointestinal disturbances and nephritis. The illness usually lasts for 5–28 days.

Urticarial vasculitis is essentially the same condition, but is frequently chronic, although it may be intermittent. The cutaneous lesions resemble urticaria in appearance, but histologically demonstrate vasculitis (venulitis). Characteristic histological changes include endothelial swelling, extravasation of red cells and a perivenular cellular infiltrate rich in neutrophils, with leukocytoclasia and fibrinoid deposits in and around blood vessels [1] (Fig. 22.10). Occasionally, a lymphocytic or eosinophilic infiltrate may be prominent. The minimum criteria for vasculitis are evidence of vessel damage and/or leukocytoclasia.

Serum hypocomplementaemia may be present in a minority of patients. When it is, serum $C1_q$ levels are reduced and $C1_q$ precipitins, which are IgG autoantibodies against the collagen-like region of $C1_q$, are increased. These anti-$C1_q$ autoantibodies are also present in SLE, suggesting a relationship between the two conditions. However, no cause can be found in most cases of urticarial vasculitis. Only a minority are associated with infections (from hepatitis B and C, Epstein–Barr virus and *Borrelia burgdorferi*), serum sickness, collagen vascular disease (including lupus erythematosus and Sjögren's syndrome) or hypergammaglobulinaemia (including Schnitzler's syndrome, where IgM gammopathy is associated with fever, lymphadenopathy and bone pain). Drugs, such as cimetidine and diltiazem, and haematological diseases [1] are very rare causes.

Compared with lesions of ordinary urticaria, lesions of urticarial vasculitis usually persist for more than 24 h and may burn as well as itch, be tender or painful and sometimes resolve with

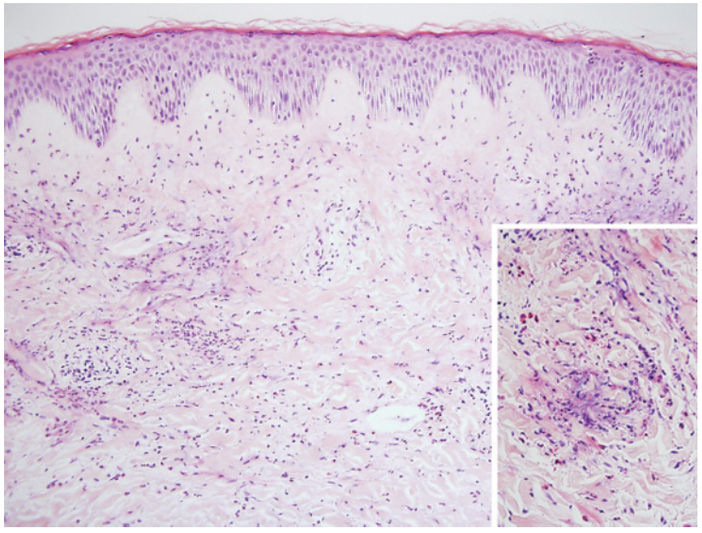


Fig. 22.10 Histology of a spontaneous lesion from a patient with urticarial vasculitis showing a heavy perivascular and interstitial inflammatory infiltrate with leukocytoclasia, eosininophils and damage to the blood vessel wall (inset).



Fig. 22.11 Lesions of urticarial vasculitis which had been present for 2 days. (Courtesy of St John's Institute of Dermatology, London, UK.)

residual bruising or staining (Fig. 22.11). Angio-oedema is present in up to 40% of cases [1]. However, it is often not possible to distinguish urticarial vasculitis from urticaria by the clinical appearance of the lesions. Systemic involvement is common; the most frequent symptom, affecting more than 50% of cases, is arthralgia, which is usually flitting and migratory, but frank arthritis is rare. Gastrointestinal involvement, with abdominal pain, nausea and vomiting, occurs in approximately 20%. A similar percentage are affected with pulmonary disease, characteristically pulmonary obstructive disease found in smokers, especially in hypocomplementaemic urticarial vasculitis (HUVS). Microscopic proteinuria and haematuria occur in 5–10% of patients, but in the absence of connective tissue disease, progression to severe renal disease is unlikely. Rarer manifestations include Raynaud's phenomenon, lymphadenopathy and splenomegaly, conjunctivitis, episcleritis, uveitis, pseudotumour cerebri, myositis, pericardial and pleural involvement.

The diagnosis is established on lesional skin biopsy. Laboratory abnormalities are common, with a raised ESR being the most frequent. Hypocomplementaemia probably occurs in fewer than 50% of cases, but often correlates with the severity of systemic involvement. Other abnormalities sometimes found include circulating immune complexes, a positive antinuclear and rheumatoid factor (usually in low titre) and presence of cryoglobulins and anti-$C1_q$.

Investigations should include a search for the occasional associated disease, and for any systemic involvement. They should include a full blood count and ESR, urinalysis, renal and liver function, serum complement and immunoglobulins, and chest radiograph. Further testing depends on other suspected clinical involvement.

Overall, the disease has a relatively benign course lasting an average of 3 years [1], although it can persist for many years.

References

1 Mehregan DR, Hall MJ, Gibson LE. Urticarial vasculitis: a histopathologic and clinical review of 72 cases. *J Am Acad Dermatol* 1992; **26**: 441–8.
2 O'Donnell B, Kobza Black A. Urticarial vasculitis. *Int Angiol* 1995; **14**: 166–74.
3 Wisnieski JJ. Urticarial vasculitis. *Curr Opin Rheumatol* 2000; **12**: 24–31.
4 Buhner D, Grant JA. Serum sickness. *Dermatol Clin* 1985; **3**: 107–17.

Contact urticaria [1]

Contact urticaria is quite common, but is not usually a cause of hospital referral unless there is an occupational problem, for instance latex allergy due to glove use. The term simply means urticaria resulting from skin or mucosal contact with the provoking substance. It may be allergic or non-allergic (also called immunological and non-immunological). The range of chemical, plant, animal and food exposures causing contact urticaria is very wide [2] (Table 22.11).

Allergic

Percutaneous or mucosal penetration of an allergen to which the individual has already developed specific IgE will result in a type I hypersensitivity response involving mast cell degranulation with histamine release. This may result in an immediate, localized weal and flare resolving within 2 h, an acute episode of generalized urticaria, or even anaphylaxis if the individual is extremely hypersensitive. It is easily missed when it is responsible for exacerbations of a pre-existing eczema, for example in atopic children. Weals occur at sites of contact with the allergen, usually therefore on the hands and face. The commonest causes are foods (for example, nuts, fish, fruits) or latex. Diagnosis can be confirmed by CAP fluoroimmunassay (previously the radioallergosorbent test, RAST) if there is a history of anaphylaxis, or by skin-prick testing.

Table 22.11 Some causes of contact urticaria.

Allergic (immunological)
Cow's milk
Cod
Kiwi fruit
Peanuts
Sesame seeds
Spices
Celery
Non-allergic (non-immunological)
Balsam of Peru
Cinnamic aldehyde
Methyl salicylate
Benzoic acid
Sorbic acid
Witch hazel
Jellyfish
Nettles

Management is largely directed at avoidance of the allergen, although taking an antihistamine prophylactically reduced the number of episodes of urticaria in atopic children [3].

Oral allergy syndrome [4]

This is a form of allergic contact urticaria involving the mouth, characterized by immediate itching, swelling and burning after eating a wide range of fresh fruits, including apples, pears, cherries, plums, celery, spices and hazelnuts. Eating cooked, dried, peeled or bottled fruit often does not cause symptoms. The symptoms are due to cross-reactions between profilins (ubiquitous panallergens in plants, including grass and mugwort in north Europe) and Bet v.1 (the major allergen in silver birch pollen) and homologous proteins in plants, especially fruits. Oral allergy syndrome therefore occurs in patients with respiratory allergies to common pollens (pollinosis). Diagnosis is by skin-prick testing with the fresh fruit. CAP and skin-prick testing with commercial standardized solutions may be negative. Fortunately, the condition only rarely progresses to angio-oedema, and treatment with antihistamines is not usually necessary.

Non-allergic

This form of contact urticaria may be caused by direct injection of vasoactive chemicals by plants (e.g. nettles) or animals (e.g. caterpillars, jellyfish). A more common form, though, is from exposure to cosmetics (e.g. cinnamic aldehyde, balsam of Peru) or food additives (e.g. sorbic acid or benzoic acid). Occupational exposures include ammonium persulphate in hairdressers. The reaction may take up to 45 min to develop and is thought to be due to PGD_2 formation rather than histamine release, since it can be blocked by NSAIDs. The relevant investigation is either a prick test or patch test, read at 15–45 min rather than 48 h.

References

1 Wakelin S. Contact urticaria. *Clin Exp Dermatol* 2000; **26**: 132–6.
2 Champion RH, Muhlemann MF. A list of the potential causes of urticaria. In: Champion RH, Greaves MW, Kobza Black A, Pye RJ, eds. *The Urticarias*. Edinburgh: Churchill Livingstone, 1985: 123–9.
3 Simons FER. Prevention of acute urticaria in young children with atopic dermatitis. *J Allergy Clin Immunol* 2001; **107**: 703–6.
4 Konstantinou GN, Grattan CEH. Food contact hypersensitivity syndrome: the mucosal contact urticaria paradigm. *Clin Exp Dermatol* 2008; **33**: 383–9.

Angio-oedema (without weals) [1]

It is useful to separate angio-oedema without weals from angio-oedema with weals, as may occur in ordinary, physical and vasculitic urticarias, since the aetiology, investigation and management may be different. The same multiple aetiologies for angio-oedema and frequent lack of precise diagnosis are found as in chronic ordinary urticaria [2]. Several clinical subtypes are recognized (Table 22.12). The most common identifiable causes of angio-oedema without weals are ACEI-induced angio-oedema and C1 esterase inhibitor deficiency.

Idiopathic angio-oedema

Synonyms
- Angioneurotic oedema
- Quincke's oedema

This is a variant of urticaria in which the subcutaneous tissues, rather than the dermis, are mainly involved. The term 'angioneurotic oedema' is somewhat misleading. It was originally considered to be an abnormality of the nerve supply of the small blood vessels, without the implication of emotional disturbance that the word now suggests. Almost any part of the body may be involved, but the commonest sites are the lips (Fig. 22.12), eyelids and genitalia. The tongue and pharynx may also be affected. Individual lesions may be single or multiple and may appear with dramatic suddenness. Itching is often absent. The lesions last for a few

Table 22.12 Classification of angio-oedema without weals.

Acquired
Idiopathic
Drug-related, especially:
Angiotensin converting enzyme inhibitors
Non-steroidal anti-inflammatory drugs
Physical
Exercise-induced angio-oedema
Vibratory angio-oedema
Acquired C1 esterase inhibitor deficiency
Lymphoproliferative disease
C1 inhibitor autoantibody
Others (including systemic lupus erythematosus)
Episodic angio-oedema with eosinophilia (Gleich's syndrome)
Hereditary
Hereditary angio-oedema
C1 esterase inhibitor deficiency
Type I (reduced absolute level of C1 esterase inhibitor)
Type II (reduced functional inhibitor but normal or increased level)
Normal C1 esterase inhibitor
Type III (oestrogen-dependent)



(a)

(b)

Fig. 22.12 Angio-oedema of the lip (a) during and (b) 3 days after an attack. (Courtesy of St John's Institute of Dermatology, London, UK.)

hours, or occasionally persist for 2–3 days. Differential diagnosis includes eczema especially of the eyelids, cellulitis, lymphoedema, idiopathic oedema, idiopathic scrotal oedema and the Melkersson–Rosenthal syndrome.

The management of idiopathic angio-oedema is essentially the same as that for acute urticaria, except that mucosal lesions may occur and cause great distress. Emergency treatment of mucosal lesions is discussed along with anaphylaxis in Chapter 74. However, in contrast to hereditary angio-oedema and ACEI-induced angio-oedema, described below, life-threatening swellings are very rare. The treatment of non-histaminergic angioedema due to C1 esterase inhibitor deficiency is completely different and is discussed below.

References

1 Greaves MW, Lawlor F. Angioedema: manifestations and management. *J Am Acad Dermatol* 1991; **25**: 155–61.

2 Champion RH, Roberts SOB, Carpenter RG, Roger JH. Urticaria and angio-oedema: a review of 554 cases. *Br J Dermatol* 1969; **81**: 588–97.

ACEI-induced angio-oedema

ACEIs have a special ability to cause angio-oedema, nearly always without associated weals [1]. The mechanism is thought to relate to the ability of ACEIs to prolong bradykinin survival and potentiate its effects by inhibiting ACE, also known as kininase II [2]. Most cases develop within 3 weeks of commencing treatment, but can occur at any time during treatment, even years after starting. Angio-oedema affects the face and oral mucosa predominantly. Symptoms may be severe, and laryngeal involvement may be life-threatening. Intravenous antihistamines and corticosteroids have been used, sometimes repeatedly, and epinephrine injections should be given if swelling involves the airway [1], although the development of a bradykinin receptor antagonist, icatibant, is likely to be more effective and may well become the treatment of choice. Reactions are more likely to occur if the patient has had previous episodes of angio-oedema, is Afro-Caribbean, has ACEI-induced cough or has hereditary angio-oedema [3]. If such reactions do occur, it is not safe to change to one of the other ACEIs, which should be used with great care (or avoided) with angio-oedema of any cause. The angiotensin II receptor antagonists ('sartans') should also be prescribed with caution since angio-oedema has also been described in a few patients previously intolerant of ACEI, but probably by another mechanism that has been proposed to involve nitric oxide release with potentiation of the effects of bradykinin [2].

References

1 Sabroe RA, Kobza Black A. Angiotensin-converting enzyme (ACE) inhibitors and angio-oedema. *Br J Dermatol* 1997; **136**: 153–8.

2 Tan E, Grattan CEH. Drug-induced urticaria. *Expert Opin Drug Saf* 2004; **3**: 471–84.

3 Borzova E, Grattan CEH. Angioedema. In: Zuberbier T, Grattan CEH, Maurer M, eds. *The Urticarias*. Berlin: Springer, in press.

Hereditary angio-oedema [1]

This is a rare disorder, accounting for less than 5% of all cases of angio-oedema without weals. It has an estimated prevalence of 1:50 000. It is transmitted as an autosomal-dominant trait on chromosome 11. At a molecular level, several different mutations have been identified. A family history is usually, but not invariably, apparent. However, it must be remembered that a family history is not infrequent in the ordinary presentation of urticaria with angio-oedema. The clinical picture usually allows the diagnosis to be made before laboratory confirmation. Over 75% of cases present before puberty [1], but the onset may be delayed even into late adult life. There are recurrent swellings of the skin and mucous membranes throughout life, often associated with nausea, vomiting, colic and urinary symptoms. These attacks may occur regularly every few weeks, or may be less frequent. Between the attacks, the patient is well. Abdominal symptoms may occur in the absence of skin changes and cause great diagnostic difficulty. In one large series [2], 34% of patients had undergone abdominal surgery. Pharyngeal, laryngeal and even bronchial involvement, are especially significant and dominate the prognosis. The skin and mucosal lesions are often solitary and may be painful. They seldom itch. They may appear spontaneously or after trauma; dental trauma and intubation being especially hazardous. Weals do not occur, but there may be a rather distinctive reticulate erythema, perhaps with minimal oedema, which occurs prodromally [3] (Fig. 22.13) in some families. Some patients have a relatively minor disability and may improve over many years. In other families, before the advent of modern therapy, over 20% of cases used to die of respiratory obstruction before early middle age, and fatalities are still at risk of occurring.

The blood of these patients is deficient in a natural inhibitor of C1 esterase, which is made in the liver under genetic control. It seems to require the activity of both alleles to maintain normal levels. The inhibitor is present either in reduced amounts (type I) or, in 15% of affected families, in an inactive form, although it can be detected in normal amounts immunologically (type II).

A third type of hereditary angio-oedema has been proposed that is mainly restricted to women with a family history of recurrent angio-oedema, including swellings of the upper airway, but with normal levels of plasma C1 esterase inhibitor and C_4 [4]. The



Fig. 22.13 The prodromal eruption of hereditary angio-oedema. 'Chicken-wire' reticulate erythema/urticaria, non-pruritic, on the trunk of a woman aged 38 years who had had numerous episodes over many years, each one lasting many hours or even days. Many attacks, but not all, were followed within 24 h by classical attacks of hereditary angio-oedema, confirmed by history and laboratory confirmation of C1 esterase deficiency. (Courtesy of Dr A.P. Warin, Royal Devon and Exeter Hospital, UK.)

term hereditary oestrogen-dependent angio-oedema has been proposed to distinguish this entity from hereditary C1 esterase inhibitor deficiency [5]. Mutations in the Hageman factor XII have been identified in some affected families [6].

C1 esterase inhibitor is a natural inhibitor of the activated first component of complement, kallikrein and the fibrinolytic and coagulation systems. It may be that attacks are triggered by stimuli that normally activate Hageman factor and hence consume the deficient inhibitor. This C1 esterase inhibitor deficiency may be detected antigenically, but functional assays are necessary to detect type II hereditary angio-oedema. The components of complement (C_2, C_4 and CH50) are low during, after and to some extent even between attacks, or in symptomless carriers. Complement C_4 is nearly always low, and its measurement may be used as an initial screening test. There is no clear correlation between the clinical severity and laboratory abnormalities. There is a weak association with autoimmune diseases, including Sjögren's syndrome and SLE [7].

The response of hereditary angio-oedema to conventional treatment for urticaria is generally poor. Antihistamines, steroids and even epinephrine are said to be of little or no help. Not all patients need treatment. It may be considered as long-term prophylaxis, short-term prophylaxis and the emergency management of an established attack. Oestrogen therapies, such as the oral contraceptive pill, may induce or exacerbate hereditary angio-oedema [8] and should be avoided if possible.

Androgens have been used prophylactically for many years with some success, but more recently the lives of many of these patients have been revolutionized by the use of attenuated androgen/anabolic drugs such as danazol and stanozolol. They stimulate the production of the deficient inhibitor. Long-term treatment is often required and may cause androgenic problems in women and children. The usual starting doses are danazol 200–600 mg daily or stanozolol 1.0–5.0 mg daily. However, considerably smaller doses given intermittently on several days of a week may suffice. The dose is assessed on the clinical response, rather than any changes in the laboratory tests, as improvement may occur even when the C1 esterase inhibitor levels remain low. Liver function tests and blood lipids should be monitored during long-term treatment, and benign hepatic adenomas have been reported. Such therapy may also be used for short-term prophylaxis, for example 48 h before and after dental surgery, at the higher dose ranges [1]. Some, but not all, cases of the acquired variant of the disease (see below) also respond to this therapy. Epsilon amino caproic acid (not available in the UK), 12–18 g daily, or the related tranexamic acid 2.0–4.5 g daily, has been found to help some patients, but these drugs are contraindicated with thrombosis. They are less effective than danazol or stanozolol, but are useful where androgens are contraindicated, especially for short-term prophylaxis. Replacement therapy with fresh frozen plasma has been used for short-term prophylaxis and appears to work as well as purified C1 inhibitor [9], which is now widely available. It is the treatment of choice for severe attacks, especially laryngeal oedema and abdominal colic, or it can be used for short-term prophylaxis [10] prior to procedures placing the patient at risk of laryngeal swelling, including dental extraction, endoscopy or intubation. Symptoms usually subside in 30–90 min [2]. Development of a bradykinin receptor 2 antagonist, icatibant [11], a kallikrein inhibitor, DX-88 [12], and a recombinant C1 esterase inhibitor [13] offer the promise of more specific and targeted therapies for patients in the near future.

Acquired C1 esterase inhibitor deficiency angio-oedema [14–18]

An acquired deficiency of the inhibitor may also give rise to a picture very similar to the hereditary form but with later onset. This may be associated with:

1. B-cell lymphoma in which anti-idiotypic antibodies against the monoclonal antibody expressed on the surface of the abnormal cells activate complement with consumption of $C1_q$ and of its inhibitor
2. SLE [19]
3. An antibody directed against the inhibitor, but without any evidence of lymphoma

The laboratory changes are similar to those of hereditary angio-oedema, except that the C1 levels are also decreased. Danazol is helpful in some cases, but not the autoantibody type, which also fails to respond to replacement therapy but may be helped by tranexamic acid and corticosteroids. Rituximab has been reported to give long-lasting improvement in one patient [20].

References

1 Gompels MM, Lock RJ, Abinun M *et al*. C1 inhibitor deficiency: consensus document. *Clin Exp Immunol* 2005; **139**: 379–94.

2 Agostoni A, Cicardi M. Hereditary and acquired C_1-inhibitor deficiency: biological and clinical characteristics in 235 patients. *Medicine* 1992; **71**: 206–15.

3 Williamson DM. Reticulate erythema: a prodrome in hereditary angio-oedema. *Br J Dermatol* 1979; **101**: 549–52.

4 Bork K, Barnstedt SE, Koch P, Traupe H. Hereditary angioedema with normal C1-inhibitor activity in women. *Lancet* 2000; **356**: 213–7.

5 Binkley KE, Davis A. Clinical, biochemical, and genetic characterization of a novel estrogen-dependent inherited form of angioedema. *J Allergy Clin Immunol* 2000; **106**: 546–50.

6 Bork K. Hereditary angioedema with normal C1 inhibitor activity including hereditary angioedema with coagulation factor XII gene mutations. *Immunol Allergy Clin North Am* 2006; **26**: 709–24.
7 Brickman CM, Tsokos GC, Balow JE *et al.* Immunoregulatory disorders associated with hereditary angioedema, 1: clinical manifestations of autoimmune disease. *J Allergy Clin Immunol* 1986; **77**: 749–57.
8 Bork K, Fischer B, Dewald G. Recurrent episodes of skin angioedema and severe attacks of abdominal pain induced by oral contraceptives or hormone replacement therapy. *Am J Med* 2003; **114**: 294–8.
9 Prematta M, Gibbs JG, Pratt EL *et al.* Fresh frozen plasma for the treatment of hereditary angioedema. *Ann Allergy Asthma Immunol* 2007; **98**: 383–8.
10 Bork K, Witzke G. Long term prophylaxis with C_1-inhibitor (C_1 INH) concentrate in patients with recurrent angioedema caused by hereditary and acquired C_1-inhibitor deficiency. *J Allergy Clin Immunol* 1989; **83**: 677–82.
11 Bork K, Frank J, Grundt B *et al.* Treatment of acute edema attacks in hereditary angioedema with a bradykinin receptor-2 antagonist (Icatibant). *J Allergy Clin Immunol* 2007; **119**: 1497–503.
12 Schneider L, Lumry W, Vegh A *et al.* Critical role of kallikrein in hereditary angioedema pathogenesis: a clinical trial of ecallantide, a novel kallikrein inhibitor. *J Allergy Clin Immunol* 2007; **120**: 416–22.
13 Choi G, Soeters MR, Farkas H *et al.* Recombinant human C1-inhibitor in the treatment of acute angioedema attacks. *Transfusion* 2007; **47**: 1028–32.
14 Alsenz J, Bork K, Loos M. Autoantibody-mediated acquired deficiency of C1 inhibitor. *N Engl J Med* 1987; **316**: 1360–6.
15 Geha RS, Quinti I, Austen KF *et al.* Acquired C_1-inhibitor deficiency associated with anti-idiotypic antibody to monoclonal immunoglobulins. *N Engl J Med* 1987; **312**: 534–40.
16 Zingale LC, Castelli R, Zanichelli A, Cicardi M. Acquired deficiency of the inhibitor of the first complement component: presentation, diagnosis, course, and conventional management. *Immunol Allergy Clin North Am* 2006; **26**: 669–90.
17 Cicardi M, Bisiani G, Cugno M *et al.* Autoimmune C_1 inhibitor deficiency: report of eight patients. *Am J Med* 1993; **95**: 169–75.
18 Chevaller A, Arlaud G, Ponard D *et al.* C1-inhibitor binding monoclonal immunoglobulins in three patients with acquired angioneurotic edema. *J Allergy Clin Immunol* 1996; **97**: 998–1008.
19 Massa MC, Connolly SM. An association between C1 esterase inhibitor deficiency and lupus erythematosus: report of two cases and review of literature. *J Am Acad Dermatol* 1982; **7**: 255–64.
20 Levi M, Hach CE, van Oers MH. Rituximab-induced elimination of acquired angioedema. *Am J Med* 2006; **119**: e3–e5.

Episodic angio-oedema with eosinophilia [1,2]

Recurrent episodes of angio-oedema and weals associated with pyrexia, blood eosinophilia and infiltration of the dermis with eosinophils have been described. There is no evidence of systemic involvement or progression to a cardiomyopathy. Each episode resolves with prednisolone treatment. During an attack, elevated serum levels of IL-5 have been demonstrated in some cases [3], IL-6 in others [4] and a subsequent increase in TNF-α in others with a more transient variant [5].

References

1 Gleich GJ, Schroeter AL, Marcoux JP *et al.* Episodic angioedema associated with eosinophilia. *N Engl J Med* 1984; **310**: 1621–6.
2 Banerji A, Weller PF, Sheikh J. Cytokine-associated angioedema syndromes including episodic angioedema with eosinophilia (Gleich's syndrome). *Immunol Allergy Clin N Am* 2006; **26**: 769–81.
3 Obuko Y, Sato E, Hossain M *et al.* Periodic angioedema with eosinophilia: increased serum level of interleukin 5. *Intern Med* 1995; **34**: 108–11.
4 Tillie-Leblond I, Gosset P, Janin A *et al.* Increased interleukin-6 production during the acute phase of the syndrome of episodic angioedema and hypereosinophilia. *Clin Exp Allergy* 1998; **28**: 491–6.
5 Mizukawa Y, Shioara T. The cytokine profile in a transient variant of angioedema with eosinophilia. *Br J Dermatol* 2001; **144**: 169–74.

Other syndromes resembling urticaria or angio-oedema, or with urticaria as one component

Papular urticaria [1]

The term is misleading since lesions last for days or weeks rather than hours and should not therefore be regarded as urticaria. Injection of foreign protein by biting insects into skin of the most sensitive subjects may cause an immediate IgE-mediated reaction consisting of weals. A punctum is often visible on the weal, which may blister. This reaction sometimes evolves into a delayed hypersensitivity reaction, leading to intensely itchy, indurated papules lasting weeks or months. It is most commonly seen on the legs of children after flea and mosquito bites.

Reference

1 Millikan LE. Papular urticaria. *Semin Dermatol* 1993; **12**: 53–6.

Systemic capillary leak syndrome [1–3]

Synonym
- Clarkson's syndrome

This is a rare syndrome in which there are dramatic, recurrent attacks of exudation of fluid into various organs and may involve the skin. Attacks of angio-oedema have been reported. A severe shock-like state may ensue and the eventual mortality is high. There is an IgG paraproteinaemia. The response to treatment has been poor, although patients have been helped by a combination of aminophylline and terbutaline [4]. A similar syndrome may follow therapy for metastatic cancer with IL-2 [3].

References

1 Clarkson B, Thompson D, Horwith M *et al.* Cyclical edema and shock due to increased capillary permeability. *Am J Med* 1960; **29**: 193–216.
2 Barnadas MA, Cisteró A, Sitjas D *et al.* Systemic capillary leak syndrome. *J Am Acad Dermatol* 1995; **32**: 364–6.
3 Cicardi M, Gardinali M, Biasini G *et al.* The systemic capillary leak syndrome: appearance of interleukin-2-receptor-positive cells during attacks. *Ann Intern Med* 1990; **113**: 475–7.
4 Droder RM, Kyle RA, Greipp PR. Control of systemic capillary leak syndrome with aminophylline and terbutaline. *Am J Med* 1992; **92**: 523–6.

Schnitzler's syndrome [1–5]

Synonym
- Urticarial vasculitis with monoclonal gammopathy

This syndrome was first reported in 1974 [1]. There is chronic urticaria, often with rather persistent, non-itchy weals suggesting an urticarial vasculitis, which is sometimes confirmed by histology but more usually shows a neutrophilic urticaria [6]. Bone pains, with associated radiological bone changes, are present in half the cases. Malaise, fever and lymphadenopathy may occur. The characteristic finding is a monoclonal gammopathy—usually IgM, but perhaps IgG [7]. An IgG autoantibody against IL-1α was found in the sera of patients with Schnitzler's syndrome more frequently than controls [8], although the significance of this in the pathogenesis is not certain. The overall prognosis is often, but

not always, benign. Long-term follow-up is required, because evolution to Waldenström's macroglobulinaemia may occur [9]. Symptomatic treatment has included NSAIDs, thalidomide, colchicine, dapsone and IFN-α but sometimes prednisolone is required. Antihistamines are unhelpful. There have been recent encouraging reports of complete responses to anakinra and pefloxacin. A review of the response to treatments and prognosis of 94 patients in the world literature summarizes the range and success of different therapies to date [10]. The clinical behaviour of Schnitzler's syndrome and response to anakinra suggest that it may be regarded as an acquired periodic fever syndrome.

References

1 Schnitzler L, Schubert B, Boasson L *et al.* Urticaire chronique, lésions osseuses, macroglobulinémie IgM: maladie de Waldenström? 2e présentation. *Bull Soc Fr Dermatol Syphilol* 1974; **81**: 363.

2 Janier M, Bonvalet D, Blanc MF *et al.* Chronic urticaria and macroglobulinemia (Schnitzler's syndrome): report of two cases. *J Am Acad Dermatol* 1989; **20**: 206–11.

3 Borradori L, Rybojad M, Puissant A *et al.* Urticarial vasculitis associated with a monoclonal IgM gammopathy: Schnitzler's syndrome. *Br J Dermatol* 1990; **123**: 113–8.

4 Machet L, Vaillant L, Machet MC *et al.* Schnitzler's syndrome (urticaria and immunoglobulinaemia) associated with pseudoxanthoma elasticum. *Acta Derm Venereol (Stockh)* 1992; **72**: 22–44.

5 Verret JL, Leclech C, Rousselet MC *et al.* Syndrome de Schnitzler et maladie de Waldenström. Evolution terminale du cas princep. *Ann Dermatol Vénéréol* 1993; **120**: 459–60.

6 de Castro FR, Maysoue I, Winkelmann RK *et al.* Urticarial pathology in Schnitzler's (hyper–IgM) syndrome. *Dermatology* 1996; **193**: 94–9.

7 Nashan D, Sunderkötter C, Bonsmann G *et al.* Chronic urticaria, arthralgia, raised erythrocyte sedimentation rate and IgG paraproteinaemia: a variant of Schnitzler's syndrome? *Br J Dermatol* 1995; **133**: 132–4.

8 Saurat JH, Schifferli J, Steiger G *et al.* Anti-interleukin-1α autoantibodies in humans: characterization, isotype distribution, and receptor-binding inhibition—higher frequency in Schnitzler's syndrome (urticaria and macroglobulinemia). *J Allergy Clin Immunol* 1991; **88**: 244–56.

9 Machet L, Vaillant L, Machet MC *et al.* Schnitzler's syndrome (urticaria and macroglobulinaemia): evolution to Waldenström's disease is not uncommon. *Acta Derm Venereol* 1996; **76**: 413.

10 de Koning H, Bodar EJ, Jos WM *et al*. Schnitzler syndrome: beyond the case reports: review and follow-up of 94 patients with an emphasis on prognosis and treatment. *Semin Arth Rheum*, in press doi:10.1016/j.semarthrit.2007.04.001.

Hereditary periodic fever syndromes

Cryopyrin-associated periodic syndrome

Synonyms
- Muckle–Wells syndrome
- Familial cold urticaria
- NOMID

Urticaria is a common feature of these rare, autosomal-dominant, autoinflammatory syndromes, which are due to mutations in a common gene called *CIAS1* on chromosome 1q.44, encoding a protein with a pyrin domain [1]. They nevertheless have distinctive phenotypes. The term cryopyrin-associated periodic syndrome (CAPS) has been proposed to embrace a common pathogenesis [2].

During childhood and adolescence, patients with Muckle–Wells syndrome [3–5] suffer recurrent bouts of urticaria with chills, fever and malaise, lasting 24 h. The urticaria may start from birth and may occur daily throughout life. There may be actual weals or sometimes only macular erythema (Fig. 22.14). Conjunctival erythema may occur. Over the next two to four decades, sensory deafness appears, and in some cases progressive nephropathy due to amyloidosis. Amyloidosis is present in other parts of the body in the prereticulin pattern of deposition. C-reactive protein is persistently high and serum amyloidosis A protein levels are raised considerably.

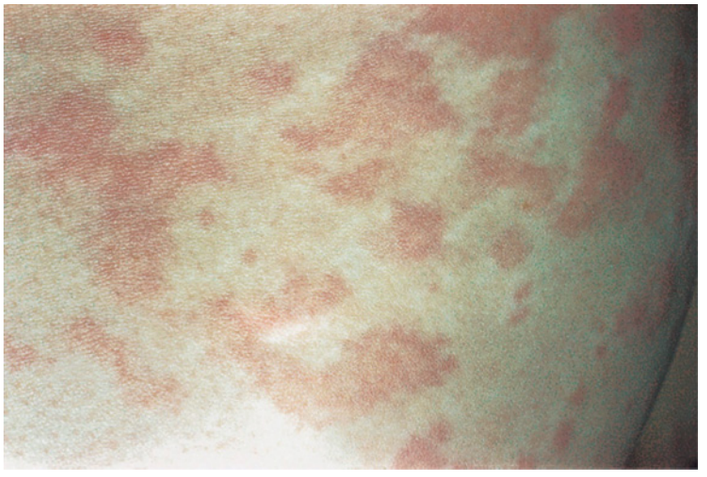


Fig. 22.14 Muckle–Wells syndrome. The characteristic, often rather faint, transient, sometimes erythematous, sometimes urticarial eruption. (Courtesy of Addenbrooke's Hospital, Cambridge, UK.)

The condition, which is inherited as an autosomal dominant trait, must be distinguished from familial Mediterranean fever, which has autosomal-recessive inheritance, and other forms of renal amyloidosis. The onset of familial cold urticaria is also noted in infancy and persists for life [6–8]. Non-itchy weals occur in response to a drop in body temperature and can persist for 48 h but may be short-lived. Fever, headache and a leukocytosis may accompany the rash. An ice-cube test is negative. Neonatal onset multisystem disease (NOMID) has a more severe phenotype than Muckle–Wells syndrome or familial cold urticaria, including arthritis, neurological and developmental impairment. All patients with CAPS treated to date have made a dramatic clinical and biochemical response to anakinra [9] and trials of a novel long-standing interleukin-1 beta antagonist are on-going.

References

1 Hoffman HM, Mueller JL, Broide DH *et al*. Mutation of a new gene encoding a putative pyrin-like protein causes familial cold autoinflammatory syndrome and Muckle–Wells syndrome. *Nat Genet* 2001; **29**: 301–5.

2 Shitiko K, Leslie K. Cryopyrin-associated periodic syndrome (CAPS) and autoinflammation. *Clin Exp Dermatol*, in press.

3 Muckle TJ, Wells MV. Urticaria, deafness and amyloidosis: a new heredo-familial syndrome. *QJM* 1961; **32**: 235–48.

4 Muckle TJ. The 'Muckle–Wells' syndrome. *Br J Dermatol* 1979; **100**: 87–92.

5 Alexander F, Atkins EL. Familial neural amyloidosis. *Am J Med* 1975; **59**: 121–8.

6 Tindall JP, Beeker SK, Rosse WF. Familial cold urticaria: a generalized reaction involving leukocytosis. *Arch Intern Med* 1974; **124**: 129–43.

7 Doeglas HM, Bleumink E. Familial cold urticaria: clinical findings. *Arch Dermatol* 1974; **110**: 382–8.

8 Zip CM, Ross JB, Greaves MW *et al*. Familial cold urticaria. *Clin Exp Dermatol* 1993; **18**: 338–41.

9 Leslie KS, Lachmann HJ, Bruning E *et al*. Phenotype, genotype, and sustained response to anakinra in 22 patients with autoinflammatory disease associated with *C1AS-1/NALP-3* mutations. *Arch Dermatol* 2006; **142**: 1591–7.

Familial Mediterranean fever [1,2]

Familial Mediterranean fever usually has autosomal-recessive inheritance and a striking predilection for Sephardic Jews, Armenians and Arabs. The gene responsible *MEVR1* is carried on the short arm of chromosome 16. Many patients present with recurrent, self-limiting attacks of fever and a tendency to peritonitis, pleurisy and synovitis. Skin lesions include rather distinctive, erysipelas-like lesions on the lower leg, but urticarial and vasculitic lesions may occur rarely [3,4]. About one-quarter of patients develop or even present with renal amyloidosis, which is often fatal. Some symptoms are controlled by colchicine.

References

1 Sohar E, Gafni J, Pras M *et al.* Familial Mediterranean fever. *Am J Med* 1967; **43**: 227–53.
2 Cook GC. Recurrent hereditary polyserositis. *BMJ* 1990; **301**: 1110–1.
3 Azizi E, Fisher BK. Cutaneous manifestations of familial Mediterranean fever. *Arch Dermatol* 1976; **112**: 364–6.
4 Majeed HA, Quabazard Z, Hijazi Z *et al.* The cutaneous manifestations in children with familial Mediterranean fever (recurrent hereditary polyserositis): a six-year study. *QJM* 1990; **75**: 607–16.

Hyper-IgD syndrome [1–4]

A few cases have been recognized since its first description in 1984 [1]. It has some features in common with familial Mediterranean fever and Muckle–Wells syndrome, but appears to be a distinct entity. The clinical features include periodic fever and skin lesions, among which are erythematous macules, urticaria, annular erythema and nodules. Other findings include joint pains, abdominal pain, cervical lymphadenopathy, leukocytosis and raised ESR. The special finding is a raised IgD level in the blood, although it is uncertain how this is related to the other findings. There is no tendency to amyloid deposition. The response to treatment is unsatisfactory.

References

1 Van der Meer JWM, Vossen JM, Radl J *et al.* Hyperimmunoglobulinaemia D and periodic fever; a new syndrome. *Lancet* 1984; **i**: 1087–96.
2 Drenth JPH, Haagsma CJ, Van der Meer JWM. Hyperimmunoglobulinemia D and periodic fever syndrome. *Medicine* 1994; **73**: 133–4.
3 Drenth JPH, Boom BW, Toonstra J *et al.* Cutaneous manifestations and histologic findings in the hyperimmunoglobulinemia D syndrome. *Arch Dermatol* 1994; **130**: 59–65.
4 Bader-Meunier B, Venecie PY, Villeford A *et al.* Hyperimmunoglobulinémie D et urticaire familiale de l'enfant. *Ann Dermatol Vénéréol* 1996; **123**: 398–400.

TNF-receptor-associated periodic syndrome (TRAPS)

Synonym
- Familial hibernian fever [1,2]

This multisystem disorder comprises a recurrent migratory erythematous rash, fever, arthralgia, synovitis, conjunctivitis, pleurisy and amyloidosis of the kidneys and liver due to mutations in the TNF receptor I gene on chromosome 12. Levels of soluble TNF receptor are reduced in the blood during disease activity because the receptor is not shed from monocytes and neutrophils. Although the rash is typically migratory and macular rather than urticarial, oedematous plaques lasting up to 21 days may occur [2]. The condition should be considered in the differential diagnosis of the periodic fever syndromes.

References

1 Toro JR, Aksentijevich I, Hull K *et al*. Tumour necrosis factor receptor-associated periodic syndrome: a novel syndrome with cutaneous manifestations. *Arch Dermatol* 2000; **136**: 1487–94.
2 Galon J, Aksentijevich I, McDermott MF *et al*. TNFRSFIA mutations and autoinflammatory syndromes. *Curr Opin Immunol* 2000; **12**: 479–86.

Clinical history taking and diagnosis

The clinical diagnostic process is the same for all urticarias. A comprehensive history is essential for diagnosis and elucidation of any causative factors, as weals are often not present at the time of consultation. Performing an extensive panel of investigations in addition to a standardized questionnaire added little to making a final diagnosis [1]. Information should be obtained regarding the onset, duration and course of the disease. The duration of individual weals and presence of purpura are important. Weals lasting more than 24–48 h, particularly if painful or tender, suggest the possibility of urticarial vasculitis or delayed pressure urticaria, but can occur in ordinary urticaria. Purpura, although rarely seen, suggests urticarial vasculitis, but can occur in ordinary urticaria. The location, numbers and shapes of weals vary and are usually not helpful in differentiating most urticarias, except for the typical small, monomorphic, short-lasting weals of cholinergic urticaria and the linear weals of dermographism. The occurrence of angio-oedema should be noted, particularly if it has affected the oropharynx with difficulty in swallowing or breathing. Enquiry should be made for systemic symptoms sometimes associated with cutaneous lesions, including malaise, headache, abdominal pain, arthralgia, wheezing and syncope. Possible precipitating or aggravating factors—including physical factors such as heat, cold, localized pressure on the skin, friction and sunlight—should be sought directly. It is important to ask about any association with recent acute infection, drugs, non-prescription medicines and foods, although the latter are rarely a cause for chronic urticaria. A family history of atopy, autoimmunity or angio-oedema may be useful information.

Reference

1 Kozel MMA, Mekkes JR, Bossuyt PMM, Bos JD. The effectiveness of a history-based diagnostic approach in chronic urticaria and angioedema. *Arch Dermatol* 1998; **134**: 1575–80.

Differential diagnosis

The diagnosis of urticaria is rarely a problem. Weals are distinguished by their evanescent nature and normal overlying epidermis. Papular urticaria, erythema multiforme and prebullous eruptions must be distinguished from urticaria. Acute contact dermatitis, lymphoedema and collagen vascular disease (such as dermatomyositis) may mimic angio-oedema, but these conditions last longer than 24–48 h. The part played by urticarial reactions in atopic dermatitis is discussed in Chapter 24.

Investigation of urticaria (Table 22.13)

Acute urticaria

In patients with potentially life-threatening reactions to an allergen, confirmation is by CAP fluoroimmunoassay that measures serum allergen-specific IgE to the allergen or skin-prick testing (SPT), for example for peanut sensitization. In most cases of acute urticaria in which no cause is suggested in the history, investigation rarely provides an answer. Prick testing is potentially dangerous if there is a background of anaphylaxis. Epinephrine administration for severe reactions may be less effective in patients on β-blocking drugs. The clinical relevance of the results of skin-prick and CAP tests needs careful evaluation. Routine prick testing in chronic urticaria is unhelpful [1].

Chronic urticaria

A thorough history of the rash and any associated systemic symptoms is essential. Attention should be paid to medication, especially NSAIDs. It is important to identify an associated physical urticaria, especially delayed pressure urticaria, by appropriate testing (see Physical urticarias). If weals persist and are painful, with systemic symptoms of fever or arthralgia, urticarial vasculitis should be considered, and a skin biopsy performed of a spontaneous lesion, preferably one that is 12–15 hours old. Patients frequently suspect allergy to foods, but this is rarely if ever found in adults with chronic ordinary urticaria. A food diary may be helpful, especially in episodic urticaria, but it should be remembered that the time interval may vary from a few seconds with allergy and up to 24 h with dietary pseudoallergens, and the substance may have been consumed regularly for years. If the patient suspects food additives, or if they have improved substantially on elimination of the substance or on a diet free of food additives, challenge testing can be carried out on a placebo-controlled basis. This is performed when the patient is in relative remission, and antihistamine therapy need not be stopped, although this is desirable. Daily coded test substances (see Table 22.10) are given orally in a gelatin capsule, with placebo capsules preceding different types of additives [2]. The most important test substances are tartrazine (E102), aspirin, sodium benzoate (E211) and 4-hydroxybenzoate (E214–219). The patient records any urticarial response, and if present the suspected substance and placebos should be re-administered on at least one occasion for confirmation of the results. When the provocation tests are positive, a tartrazine-free, salicylate-free or other appropriate diet can be suggested and is usually only necessary for a few months [3]. It is usually inappropriate to carry out provocation tests in patients who respond well to antihistamines. A low-pseudoallergen diet may be helpful for some patients [4], especially if antihistamines have failed or are not accepted.

Skin-prick or intradermal tests are even less helpful, and there were no relevant unsuspected positive tests in a group of urticaria patients [1]. In addition, a positive skin test is difficult to interpret, as an atopic patient with urticaria will show many irrelevant positive results, and false-negative results may also occur. Although a few patients with chronic urticaria and a positive intradermal test to *Candida albicans* were helped by an anti-*Candida*/antiyeast regimen (nystatin orally and vaginal pessaries, amphotericin lozenges and a yeast-free diet for 2–4 weeks) [5], this has not been our experience.

Other investigations are aimed at finding any associated disease, but it is uncommon for a cause of urticaria to be found in the absence of some lead from the general history. A full blood count and erythrocyte sedimentation rate (ESR) should be performed routinely. An elevated ESR suggests the possibility of an underlying systemic disease (lupus erythematosus, urticarial vasculitis, macroglobulinaemia), and an eosinophilia would prompt a search for parasitic disease. Thyroid function tests and thyroid autoantibodies may be worthwhile, as around 14% of patients with chronic ordinary urticaria may have thyroid autoimmunity [6]. Clinical experience indicates that the proportion of severe chronic urticaria patients with thyroid autoimmunity is considerably higher than this, possibly up to 40% and this may be a surrogate marker for histamine releasing autoantibodies [7]. Initial reports suggest that treatment with thyroxine to suppress thyroid activity may resolve the urticaria [8]. Further tests depend on the history. Routine biochemistry, complement levels, serum proteins and electrophoresis, serum immunoglobulins, non-organ-specific and organ-specific autoantibodies, total and specific IgE, skin tests and fastidious searching for evidence of infection are not indicated [9]. There is currently no simple clinical test for serum histamine-releasing autoantibodies, although the ASST appears to be a reasonably sensitive and specific marker for them [10]. If angio-oedema is a major component of the disease, measuring plasma C4 complement should be performed as a screening test for hereditary or acquired C1 esterase inhibitor deficiency. It is reduced and rarely, if ever, reaches normal values even between attacks of C1 esterase deficiency angio-oedema. Functional C1 esterase inhibitor is reduced in hereditary and acquired disease. A skin biopsy may be helpful if the weals persist for more than 48 h and do not respond to antihistamines. Urticarial vasculitis or delayed pressure urticaria is then suspected.

Table 22.13 Investigation of urticaria.

Acute urticaria
Usually none, except where suggested by the history
Specific IgE (CAP fluoroimmunassay or skin-prick tests)
Tests for upper respiratory viral or bacterial infection
Episodic urticaria
Pseudoallergy challenge capsules (if available)
Food additives
Non-steroidal anti-inflammatory drugs
Chronic urticaria
Physical challenge provocation tests (where suggested by the history)
Blood tests (ordinary urticaria, if unresponsive to H1-antihistamines)
FBC, ESR, thyroid antibodies, thyroid function tests
C4 complement (angio-oedema without weals and urticaria vasculitis)
Autologous serum skin test (where facilities are available)
Basophil histamine release assay (if available)
Others: as determined by the history and physical examination
Skin biopsy (12–16 h old lesions, if urticarial vasculitis suspected)
Stool examination for parasites (if infection suspected)
Testing for *Helicobacter pylori* infection (if peptic ulcer symptoms)
Testing for coeliac disease (primarily symptomatic children)
Imaging: none routinely

References

1 Champion RH, Roberts SOB, Carpenter RG, Roger JH. Urticaria and angio-oedema: a review of 554 cases. *Br J Dermatol* 1969; **81**: 588–97.
2 Warin RP, Smith RJ. Challenge test battery in chronic urticaria. *Br J Dermatol* 1976; **94**: 401–6.
3 Noid HE, Schulze TW, Winkelmann RK. Diet plan for patients with salicylate-induced urticaria. *Arch Dermatol* 1974; **109**: 866–9.
4 Zuberbier T, Chantraine-Hess S, Hartmann K, Czarnetzki BM. Pseudoallergen-free diet in the treatment of chronic urticaria: a prospective study. *Acta Derm Venereol (Stockh)* 1995; **75**: 484–7.
5 James J, Warin RP. An assessment of the role of *Candida albicans* and food yeasts in chronic urticaria. *Br J Dermatol* 1971; **84**: 227–37.
6 Leznoff A, Sussman GL. Syndrome of idiopathic chronic urticaria and angio-edema with thyroid autoimmunity: a study of 90 patients. *J Allergy Clin Immunol* 1989; **84**: 66–71.
7 O'Donnell BF, Francis DM, Swana GT *et al*. Thyroid autoimmunity in chronic urticaria. *Br J Dermatol* 2005; **153**: 331–5.
8 Ruberyt JS, Katz JL, Schocket AL. Resolution of chronic urticaria in patients with thyroid autoimmunity. *J Allergy Clin Immunol* 1995; **96**: 901–5.
9 Sibbald RG, Cheema AS, Lozinski A, Taro S. Chronic urticaria: evaluation of the role of physical, immunologic, and other contributory factors. *Int J Dermatol* 1991; **30**: 381–6.
10 Sabroe RA, Grattan CEH, Francis DM *et al*. The autologous serum skin test: a screening test for autoantibodies in chronic idiopathic urticaria. *Br J Dermatol* 1999; **140**: 446–52.

Natural history

Acute attacks may last a few hours or days and be of great severity. There is no way of predicting the duration of an initial attack. Chronic cases where no diagnosis is established may last for weeks, months or even years, or be intermittent with repeated episodes occurring over decades. The severity is often greatest at the onset, with subsequent waning. New lesions appear daily or at irregular intervals, and there may be periodic exacerbations, sometimes associated with intercurrent infections or NSAID intake. In general, spontaneous improvement occurs even in the absence of diagnosis or treatment. Fifty per cent of cases of those with weals alone attending a specialist clinic can be expected to clear within 6 months of onset, but 50% of those with associated angio-oedema can still be expected to have their condition 10 years later [1] (Fig. 22.15). A more recent survey of the prognosis of patients attending a tertiary referral clinic in the Netherlands confirms the poor outlook for many patients with chronic urticaria, especially those with cold urticaria [2].

References

1 Champion RH, Roberts SOB, Carpenter RG, Roger JH. Urticaria and angio-oedema: a review of 554 cases. *Br J Dermatol* 1969; **81**: 588–97.
2 van der Valk PGM, Moret G, Kiemeney LALM. The natural history of chronic urticaria and angioedema in patients visiting a tertiary referral centre. *Br J Dermatol* 2002; **146**: 110–3.

Management

Explanation and non-specific measures may be helpful. Patients should minimize overheating, stress and alcohol. Aspirin and

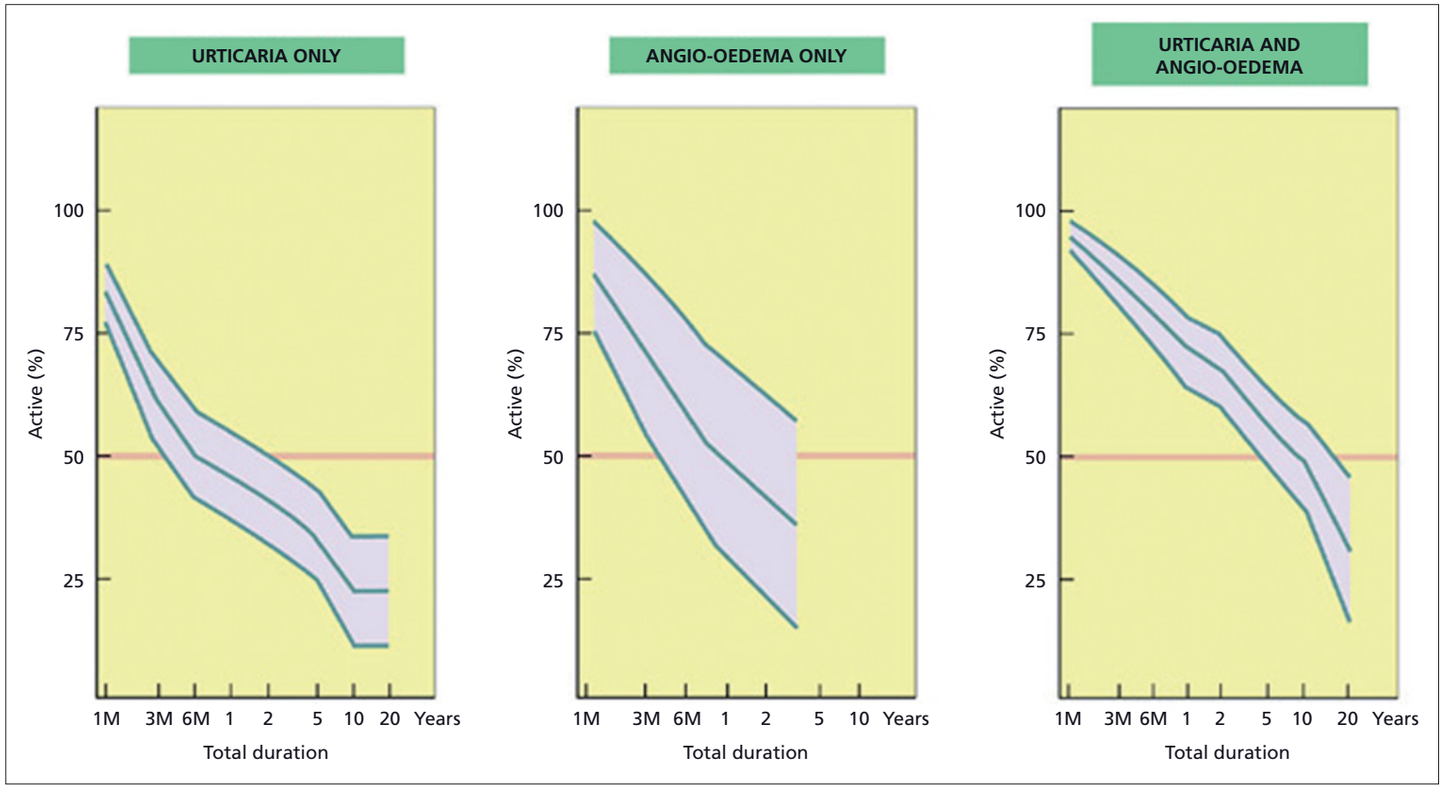


Fig. 22.15 The natural history of urticaria in 554 hospital patients. The expected percentage of patients with active urticaria, with 95% confidence limits, by the total duration of disease (log scale). M, months.

aspirin-containing compounds, other NSAIDs, and also opiates, should be avoided if possible. Paracetamol is usually a satisfactory alternative. Selective COX-2 inhibitors may be tolerated by aspirin-sensitive patients if an anti-inflammatory drug is essential. If food additives, colourings or preservatives have been proven to be a problem, diets excluding these substances may be of value to a limited number of patients. Drug therapies can be first-, second-, or third-line, the choice of treatment depending upon the response to previous measures [1] and the degree of impairment in quality of life for the patient (Fig. 22.16).

First-line therapies (antihistamines)

Histamine is the main mediator of urticaria, with H_1-receptor activation causing itch, wealing and flare, while H_2 activation plays a smaller role in weal formation. Thus, H_1 antihistamines are the first-line treatment of urticaria. Generally H_1 antihistamines are rapidly absorbed, reaching peak serum concentrations in 1–3 h.

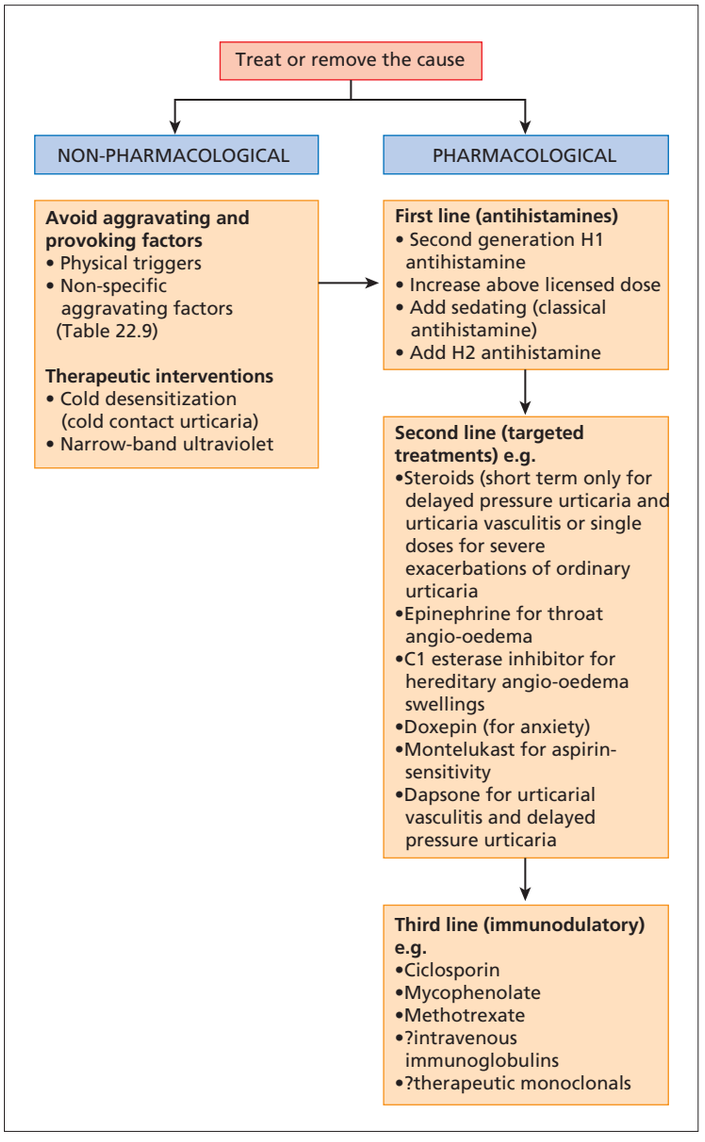


Fig. 22.16 Management of urticaria.

However, many are metabolized in the liver, and some active metabolites have a longer half-life than the parent compound and determine the activity profile of the medication. The main properties of second generation antihistamines, currently licensed in the UK, are summarized in Table 22.14.

Antihistamines for urticaria

The use of classical antihistamines is limited by their side effects, including sedation, anticholinergic properties and paradoxical excitation in children. There may be carry-over effects of sedation in the morning and patients should be warned of this. Hydroxyzine is the most potent of the classical antihistamines. Twenty five mg of hydroxyzine is equivalent to 10 mg of cetirizine.

The second generation of potent, specific, low-sedation H_1 antihistamines is now the treatment of choice [2]. Their main advantage is low sedation at doses recommended by the manufacturer and minimal anticholinergic side effects, although an occasional individual may develop sedation with any of them. They are at least as effective as hydroxyzine and generally as effective as each other. There is no clear evidence that tolerance occurs after continued use. Very rarely, antihistamines appear to make urticaria worse. This has been reported anecdotally with cetirizine but clinical experience suggests that most or all antihistamines may be implicated in those who are affected.

Acrivastine (adult dose 8 mg three times a day) has a rapid onset and duration of action and is excreted predominantly in the urine.

Cetirizine (adult dose 10 mg/day) is poorly metabolized in the liver and is excreted, predominantly in the urine, unchanged. It is also rapidly absorbed. It is more sedative than placebo in some studies and is best taken at night. Cetirizine reduces dermal eosinophil cell accumulation *in vitro* and *in vivo*. However, the clinical importance of this effect in the treatment of delayed pressure urticaria and urticarial vasculitis, where eosinophils may be an important component of the inflammatory cell infiltrate, is uncertain. There are no studies to show that its active enantiomer, levocetirizine, has an advantage in the treatment of chronic urticaria.

Fexofenadine is the metabolite of terfenadine but appears to be devoid of cardiotoxicity at clinically relevant doses and has the widest therapeutic window of the second generation antihistamines.

Loratadine (adult dose 10 mg daily) is a derivative of azatadine. Although loratadine is also metabolized in the liver by cytochrome P450 to some extent, so far no clinically proven, relevant drug interactions have been reported. It is not yet clear whether its metabolite, desloratadine, offers a clinical advantage in urticaria or any subsets of it.

Low-sedation antihistamines are used to reduce urticarial activity, with minimal side effects. Individual response is variable, but adequate dose and timing in relationship to maximal urticarial activity is important. Alternative low-sedation antihistamines can be tried, and sedating ones added at night. A combination of an H_1 antihistamine with an H_2 antagonist may be more effective than H_1 antihistamines alone in some patients. Use of ranitidine (adults 150 mg twice a day) is preferable to cimetidine, which has more antiandrogenic side effects and potential drug interactions.

Table 22.14 Properties of second generation H_1 antihistamines currently available in the UK.

Name	T_{max} (h)	T½ (h)		5 × T½ (h)	5 × T½ (days)	Principal elimination	Severe renal impairment†
		Adults	Children				
Acrivastine	1.5	1.5		7.5	<1	Renal	Avoid
Cetirizine	0.5–1	10	6	50	2	Renal	Half dose
Levocetirizine	0.9	8		40	2	Renal	Reduced dose
Loratadine	1 (2 h after food)	(8.4)*		(42)	(2)	Hepatic (CYP 3A4)	Caution
Desloratadine*	3	27		135	6	Hepatic	Caution
Fexofenadine	1–3	11–15		65	3	Biliary	Same dose
Mizolastine	1.5	13		65	3	Hepatic	Same dose

* Active metabolite is descarboethoxyloratadine (desloratadine).

† Glomerular filtration rate <10 ml/min or creatinine >700 μg/l.

T_{max} = time to maximum blood concentration after a single dose; T½ = plasma half life.

Adverse effects of antihistamines

Concerns about the potential cardiotoxity of antihistamines have receded since terfenadine and astemizole have been withdrawn from the market. Elucidation of the *HERG1* gene encoding the major K^+ cardiac repolarization channels offers a molecular understanding of the cardiotoxic properties of terfenadine and astemizole, which block the channels at clinically relevant concentrations [3] and have been withdrawn from the market. Mizolastine, which also undergoes limited conversion by hepatic CYP 3A4, is able to block HERG1 channels to some degree. Its use with drugs that prolong the Q–T interval—such as amiodarone, quinidine and neuroleptic drugs and tricyclic antidepressants—and with electrolyte disturbance should be avoided. The classical antihistamines hydroxyzine and diphenhydramine also have the ability to induce Q–T prolongation [3], emphasizing that higher than recommended doses of these antihistamines should be used only with caution.

Antihistamines in pregnancy

Antihistamines cross the placenta. There is no reliable evidence that they are teratogenic, but they should be avoided in pregnancy and particularly in the first trimester if possible. If it is not possible, then chlorphenamine appears to be the least risky to use based on its long availability and safety record. Current guidelines on urticaria support the use of cetirizine and loratadine beyond the first trimester of pregnancy if the benefits of an antihistamine are considered to outweigh any risks of administration for an individual patient [4,5].

Second-line therapies (targeted therapy)

Oral systemic corticosteroids are effective in severe urticaria when started at high doses, such as 0.5–1.0 mg prednisolone/kg/day. Although short courses are useful for acute exacerbations, prolonged use should be avoided because of the risk of side effects. Oral corticosteroids are often required for disease control in severe delayed pressure urticaria and urticarial vasculitis, but every attempt should be made to minimize the dose and duration.

The emergency treatment for histaminergic non-hereditary angio-oedema causing respiratory embarrassment from oropharyngeal–laryngeal angio-oedema is intramuscular epinephrine. It acts rapidly by vasoconstriction and stabilizing mast cells through β-adrenoceptor stimulation. For moderately severe reactions it can be inhaled for its local effect, but for severe reactions, particularly of the anaphylactic type, epinephrine must be injected intramuscularly. Treatment should be repeated if there is no improvement after 10–15 min. Patients who have had a severe reaction should be shown how to self-administer epinephrine and should keep two unexpired 'pens' available.

The choice of other second-line therapies will be influenced by the clinical situation. Perhaps the most promising new class of drugs is the leukotriene receptor antagonists, which have been shown to benefit aspirin-sensitive urticaria and may be of value in delayed pressure urticaria and autoimmune urticaria [6]. Doxepin, a tricyclic antidepressant with potent antihistaminic activity, may be useful at night in a starting dose of 10–30 mg, but as it also reacts with α-adrenergic receptors it should not be taken with monoamine oxidase inhibitors. It is especially useful for night-time itching and anxious patients but is probably not effective as an antidepressant at the dose used for urticaria. Danazol may be beneficial for patients with refractory cholinergic urticaria [7]. Thyroxine appears to reduce urticarial activity in some clinically euthyroid patients with thyroid autoimmunity [8]. Sulphasalazine [9] and dapsone [10] may be useful for delayed pressure urticaria, especially when oral corticosteroids are otherwise required for disease control although the literature on these useful agents remains surprisingly small. Tranexamic acid may suppress antihistamine-unresponsive non-hereditary angio-oedema without weals [11]. Narrow-band phototherapy may help some patients [12] especially those with symptomatic dermographism, although controlled studies are needed. Cold desensitization has been shown to be effective for well-motivated patients with cold contact urticaria [13]. There is a small literature on 'curative' antibiotic therapy for the same group [14].

Third-line therapies (immunomodulatory)

For patients with severe, unremitting urticaria not responding to conventional therapy, immunomodulatory strategies have been tested in small, uncontrolled trials. Plasmapheresis improved six out of eight such patients with autoimmune urticaria for 3–8

weeks only [15], illustrating the relevance of functional autoantibodies to disease activity. Intravenous immunoglobulin (IVIG) infusions, at 0.4 g/kg/day for 5 days (total 2 g), improved nine out of 10 patients, two of whom remained clear for 2 years [16], but subsequent clinical experience has been disappointing. Placebo-controlled studies of IVIG for urticaria are required. Ciclosporin at 2.5–3.5 mg/kg/day for 1–3 months improved or temporarily cleared the majority of patients with severe urticaria [17,18] and its efficacy has been confirmed in a randomized, placebo-controlled study at 4 mg/kg/day for 4 weeks [19]. Fewer therapeutic failures occurred with a reducing dose of ciclosporin over 4 months than over 8 weeks [20], although the optimal dose and duration of treatment has yet to be defined. Open studies of tacrolimus [21] and mycophenolate mofetil [22] suggest that they may have similar efficacy in severe chronic ordinary urticaria. There is an anecdotal literature on methotrexate [23], cyclophosphamide [24] and early reports suggest a potential benefit from omalizumab (anti-IgE) [25].

References

1 Grattan CEH, Sabroe RA, Greaves MW. Chronic urticaria. *J Am Acad Dermatol* 2002; **46**: 645–60.
2 Simons FER, Simons KJ. The pharmacology and use of H_1-receptor antagonist drugs. *N Engl J Med* 1994; **330**: 1663–70.
3 Leurs R, Church MK, Taglialatela M. H_1-antihistamines: inverse agonism, anti-inflammatory actions and cardiac effects. *Clin Exp Allergy* 2002; **32**: 489–98.
4 Grattan CEH, Humphreys F. Guidelines for the evaluation and management of urticaria in adults and children. *Br J Dermatol* 2007: **157**: 1116–23.
5 Powell RJ, Du Toit GL, Siddique N *et al*. BSACI guidelines for the management of chronic urticaria and angio-oedema. *Clin Exp Allergy* 2007; **37**: 631–50.
6 Di Lorenzo G, Pacor ML, Mansueto M *et al*. Is there a role for antileukotrienes in urticaria? *Clin Exp Dermatol* 2006; **31**: 327–4.
7 Wong E, Eftekhari N, Greaves MW, Milford Ward A. Beneficial effects of Danazol on symptoms and laboratory changes in cholinergic urticaria. *Br J Dermatol* 1987; **116**: 553–6.
8 Rumbyrt JS, Katz JL, Schoket AL. Resolution of chronic urticaria in patients with thyroid autoimmunity. *J Allergy Clin Immunol* 1995; **96**: 901–5.
9 Engler RJM, Squire E, Benson P. Chronic sulphasalazine therapy in the treatment of delayed pressure urticaria and angioedema. *Ann Allergy Asthma Immunol* 1995; **74**: 155–9.
10 Fox RW, Lockey RF. Treatment of severe chronic urticaria with dapsone. *J Allergy Clinc Immunol* 1988; **81**: 260.
11 Munch EP, Weeks B. Non-hereditary angioedema treated with tranexamic acid. *Allergy* 1985; **40**: 92–7.
12 Berroeta L, Clark C, Ibbetson SH *et al*. Narrow-band (TL01) ultraviolet B phototherapy for chronic urticaria. *Clin Exp Dermatol* 2004; **29**: 91–9.
13 Henquet CJM, Martens BPM, van Vloten WA. Cold urticaria: a clinico-therapeutic study in 30 patients; with special emphasis on cold desensitisation. *European J Dermatol* 1992; **2**: 75–7.
14 Siebenhaar F, Weller K, Mlynek A *et al*. Acquired cold urticaria: clinical picture and update on diagnosis and treatment. *Clin Exp Dermatol* 2007; **32**: 241–5.
15 Grattan CEH, Francis DM, Slater NGP *et al*. Plasmapheresis for severe, unremitting, chronic urticaria. *Lancet* 1992; **339**: 1078–80.
16 O'Donnell BF, Barr RM, Kobza Black A *et al*. Intravenous immunoglobulin in autoimmune chronic urticaria. *Br J Dermatol* 1998; **138**: 101–6.
17 Barlow RJ, Kobza Black A, Greaves MW. Treatment of severe chronic urticaria with cyclosporin. *Eur J Dermatol* 1993; **3**: 273–5.
18 Toubi E, Blant A, Kessel A *et al*. Low-dose cyclosporin A in the treatment of severe chronic idiopathic urticaria. *Allergy* 1997; **52**: 312–6.
19 Grattan CEH, O'Donnell BF, Francis DM *et al*. Randomised double-blind study of cyclosporin in chronic 'idiopathic' urticaria. *Br J Dermatol* 2000; **143**: 365–72.
20 Vena Ga, Cassano N, Colombo D *et al*. Cyclosporine in chronic idiopathic urticaria: a double-blind, randomised, placebo-controlled trial. *J Am Acad Dermatol* 2006; **55**: 705–9.
21 Kessel A, Bamberger E, Toubi E. Tacrolimus in the treatment of severe chonic idiopathic urticaria: an open-label prospective study. *J Am Acad Dermatol* 2005; **52**: 145–8.
22 Shahar E, Bergman R, Gutman-Yassky E, Pollack S. Treatment of severe chonic idiopathic urticaria with oral mycophenolate mofetil in patients not responding to antihistamines and/or corticosteroids. *Int J Dermatol* 2006; **45**: 1224–7.
23 Gach JE, Sabroe RA, Greaves MW, Kobza Black A. Methotrexate-responsive chronic idiopathic urticaria: a report of two cases. *Br J Dermatol* 2001; **145**: 340–3.
24 Bernstein JA, Garramone SM, Lower EG. Successful treatment of autoimmune chronic idiopathic urticaria with intravenous cyclophosphamide. *Ann Allergy Asthma Immunol* 2002; **89**: 212–4.
25 Kaplan AP, Joseph K, Maykut RJ *et al*. Treatment of chronic autoimmune urticaria with omalizumab. *J Allergy Clin Immunol* 2008; **122**: 569–73.

Mastocytosis

Introduction

Mastocytosis is a rare condition characterized by too many mast cells, associated with an altered immunophenotype which may express somatic mutations of the receptor for stem cell factor. It usually presents in the skin, but may affect other tissues, especially the bone marrow and gastrointestinal tract. The distinction between cutaneous mastocytosis and systemic mastocytosis (as defined by demonstrating excess mast cells outside the skin) will depend to an extent on how hard they are sought, and it is therefore of less value to the practising clinician than some classifications would suggest. The first description of mastocytosis was made by Nettleship and Tay in 1869 [1]. The term urticaria pigmentosa was used by Sangster to describe the skin lesions in 1878 [2], but it was not until 1936 that the term 'mastocytosis' was offered by Sézary to describe skin and systemic involvement occurring together [3].

There have been considerable gains in the understanding of its aetiopathogenesis and classification over the last decade, with the recognition of specific gene mutations in the proto-oncogene *KIT*, which encodes a transmembrane tyrosine kinase receptor on mast cells (KIT). The relationship between mastocytosis presenting primarily in the skin and primarily as a haematological disorder continues to be clarified. Two in-depth reviews are recommended reading [4,5].

References

1 Nettleship E, Tay W. Rare forms of urticaria. *BMJ* 1869; **ii**: 323–30.
2 Sangster A. An anomalous mottled rash, accompanied by pruritus, factitious urticaria and pigmentation, 'urticaria pigmentosa (?)'. *Trans Clin Soc London* 1878; **11**: 161–3.
3 Parr MM, Sézary A, Lévy-Coblentz G, Chauvillon P. Dermographisme et mastocytose. *Bull Soc Fr Dermatol Syphilol* 1936; **43**: 359–61.
4 Metcalfe DD, Soter NA, eds. Special issue: Mast cell disorders. *Hematol Clin N Am* 2000; **14**: 497–701.
5 Hartmann K, Henz BM. Mastocytosis: recent advances in defining the disease. *Br J Dermatol* 2001; **144**: 682–95.

Classification

A modification of the clinical classification embracing dermatological and haematological presentations of mastocytosis by Metcalfe [1] is shown in Table 22.15. It should be emphasized, though, that the great majority of cases presenting to dermatology clinics will be cutaneous or systemic indolent and that progression to an

Table 22.15 Clinical classification of mastocytosis.

A Cutaneous
Urticaria pigmentosa
Mastocytoma
Telangiectasia macularis eruptiva perstans (TMEP)
Diffuse cutaneous mastocytosis
B Systemic (extracutaneous mast cells in at least one organ)
I *Indolent systemic mastocytosis*
II *Mastocytosis with an associated haematological disorder (AHNMD)*
A Myeloproliferative disorders
B Myelodysplastic disorders
III *Aggressive mastocytosis*
IV *Mast cell leukaemia*

associated haematological non-mast cell disorder (AHNMD) is uncommon. Both type III (aggressive mastocytosis) and type IV (mast cell leukaemia) are rare. Classifications based on aetiopathogenesis encompassing *KIT* mutational analysis are currently of no practical value in the dermatology clinic, although it is possible that identifying subsets of disease using molecular genetics may lead to more accurate prognosis and better management in the future.

Reference

1 Metcalfe DD. Classification and diagnosis of mastocytosis: current status. *J Invest Dermatol* 1991; **96**: 2S–4S.

Aetiopathogenesis

That the release of mast cell mediators causes symptoms of flushing, itching and gastrointestinal disturbance in mastocytosis is not in doubt, but the reason for mast cell accumulation in tissues in the first place is not yet clear. Interest has been focused on activating mutations of *KIT* which were first found on a growth factor-independent mast cell line from a patient with mast cell leukaemia (HMC-1) and subsequently in adults with mastocytosis [1]. Several amino acid substitution mutations have been described in *KIT*, leading to autoactivation of the receptor, the commonest being D816V. However, the story is not straightforward, because activating mutations have not been found in some children with typical urticaria pigmentosa. Three of six children were found to have a novel dominant *in*activating mutation in codon 839 [2]. Furthermore, mutations in *KIT* have not been identified in familial mastocytosis or in the germ line of affected adults, indicating that they are somatic. *KIT* is also expressed on haemopoietic stem cells and melanocytes, which might be relevant to the occasional occurrence of myeloproliferative and myelodysplastic disorders in mastocytosis and the hyperpigmentation usually seen in urticaria pigmentosa lesions.

Clinical presentation

Nearly all mastocytosis with bone marrow abnormalities will show skin lesions, but few patients with skin lesions will have an associated non-mast cell haematological disease.

Prevalence

Mastocytosis is uncommon. Reliable population-based prevalence data are not available, but only two new patients were seen each year in one dermatology centre from a catchment population of 300 000 [3]. There is no sex difference or increase in atopy [4].

Genetics

Over 50 families with familial mastocytosis have been reported to date. Most of these had urticaria pigmentosa, but four cases of telangiectasia macularis eruptiva perstans (TMEP) occurred in three generations of one family, with an autosomal-dominant pattern of inheritance [5].

Cutaneous mastocytosis

Urticaria pigmentosa

This is the commonest pattern of cutaneous mastocytosis. Urticaria pigmentosa developed in the first year of life in 84% of 67 children [6]. The most common age of onset for adult urticaria pigmentosa is 20–40 years [7]. Numerous reddish-brown or pale, monomorphic maculopapules, plaques or nodules appear in a symmetrical distribution anywhere on the body except the face, head, palms and soles, with the highest concentration usually being on the trunk (Fig. 22.17) and thighs (Fig. 22.18). The edges of the lesions are not completely sharp. They urticate within a few minutes of gentle rubbing (Darier's sign) (Fig. 22.19) causing localized itch, redness and wealing, which subsides within an hour. Stroking may also produce wealing in clinically unaffected skin. Darier's sign is not always demonstrable, especially in those with



Fig. 22.17 Urticaria pigmentosa in a child, showing multiple pigmented lesions on the trunk. (Courtesy of St John's Institute of Dermatology, London, UK.)

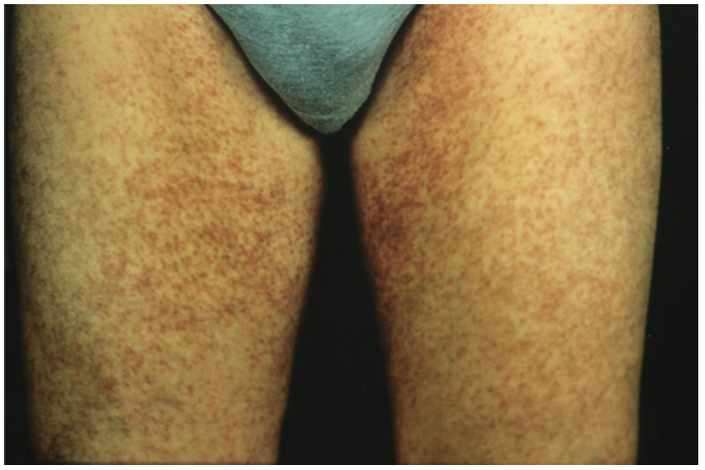


Fig. 22.18 Adult urticaria pigmentosa on the thighs, showing numerous reddish-brown lesions. (Courtesy of St John's Institute of Dermatology, London, UK.)



Fig. 22.20 Solitary mastocytoma, which urticates and blisters on rubbing. (Courtesy of St John's Institute of Dermatology, London, UK.)

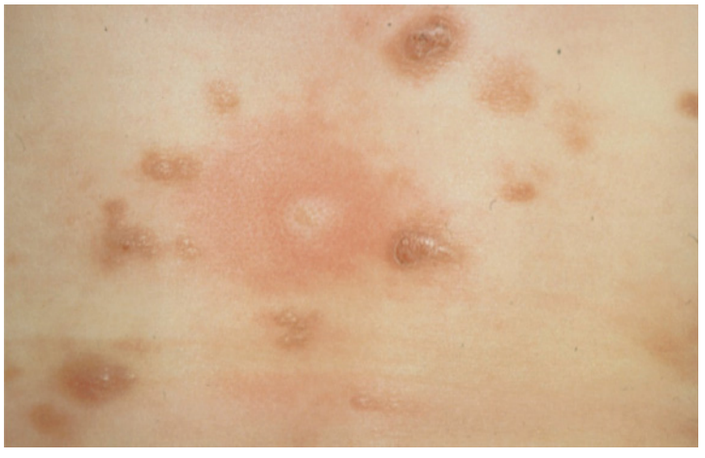


Fig. 22.19 Intense wealing and flare reaction (Darier's sign) induced by gentle rubbing of urticaria pigmentosa lesions on the back of an infant. (Courtesy of Norfolk and Norwich University Hospital, UK.)



Fig. 22.21 Telangiectasia macularis eruptiva perstans after gentle rubbing on the thigh of an adult. (Courtesy of St John's Institute of Dermatology, London, UK.)

a long history of the disorder, and is not 100% specific for mastocytosis, since it has also been described rarely in juvenile xanthogranuloma [8] and acute lymphoblastic leukaemia of neonates [9]. Lesions may blister in infancy or childhood and may be the presenting feature, but heal without scarring. Bullous mastocytosis is not a specific clinical pattern. It is most often seen with mastocytomas and diffuse cutaneous mastocytosis.

Flushing occurs in about 50% of patients, alcohol intolerance and pruritus in slightly less [10]. Other symptoms may include heat or cold intolerance, recurrent diarrhoea and headache. Wheezing is often quoted, but is extremely rare. Studies have shown that up to 60% of adult patients have bone marrow involvement [10–12], but there is no obvious relationship between finding this on biopsy and symptomatology or prognosis [10]. Clearance or fading of urticaria pigmentosa was observed in 12 of 106 adult patients with confirmed bone marrow involvement who were followed for 12–20 years, with a parallel overall improvement in the patients' well-being [13].

Mastocytoma

Cutaneous mastocytosis may present with red, pink or yellowish nodules or plaques in infancy or early childhood, measuring up to 3–4 cm in diameter (Fig. 22.20). They are usually solitary. About 15% of young children will present with localized lesions [14]. If multiple, the lesions can overlap in appearance with urticaria pigmentosa. They tend to blister if rubbed, especially in the nappy area, and occasionally attacks of flushing can be induced by rubbing a solitary mastocytoma [15]. Nearly all mastocytomas involute over the first few years of childhood.

Telangiectasia macularis eruptiva perstans

Telangiectasia may rarely be the predominant clinical feature of cutaneous mastocytosis. Patients are usually adults presenting with red, telangiectatic macules, especially on the trunk, which tend not to urticate on rubbing (Fig. 22.21). Finding excess mast cells on skin biopsy will confirm the clinical suspicion, although they may not be numerous. Historically, TMEP is a cutaneous

pattern of mastocytosis but overlaps with widespread urticaria pigmentosa (including those with systemic disease) are not uncommon and may be difficult to classify. TMEP tends to be very persistent and unresponsive to treatment.

Diffuse cutaneous mastocytosis

This is a very rare form of mastocytosis in which mast cells infiltrate the entire skin diffusely, and it usually presents in the neonatal period. The skin tends to be thickened and doughy in consistency, but may be smooth. Blistering after minor trauma or scratching is common (Fig. 22.22) and pruritus intense. Pigmentation is usually absent. Patients with this type of mastocytosis are at risk of systemic disease and severe complications including anaphylaxis and diarrhoea [16], but it may resolve spontaneously, as in other types.

Systemic mastocytosis

The WHO criteria for diagnosis of systemic mastocytosis are shown in Table 22.16. Patients must meet at least one major and one minor, or three minor criteria [17]. Not all patients with proven bone marrow involvement will be symptomatic, but in those who are, nausea, vomiting, diarrhoea, palpitations, hypotension, syncope, headache, dyspnoea, wheezing and sometimes fatigue and 'fogginess' may feature dominantly as symptoms. This is partly due to cutaneous mast cell mediator release having distant effects and partly to direct local effects of infiltration in other tissues, such as the gastrointestinal tract. Bone pain, bone cysts, premature osteoporosis, osteopetrosis or spontaneous fractures should prompt further investigation.



Fig. 22.22 Diffuse cutaneous mastocytosis in an infant, showing blistering and crusting on the face. (Courtesy of Dr C.T.C. Kennedy, Department of Dermatology, Bristol Royal Infirmary, Bristol, UK.)

Table 22.16 WHO criteria for diagnosis of systemic mastocytosis (2001).

Major
Multifocal dense aggregates of mast cells (≥15) in bone marrow or other tissues (not skin)
Minor
(a) On biopsy of bone marrow or other extracutaneous tissue ≥25% of mast cells in the infiltrate are spindle-shaped or have atypical morphology OR ≥25% of mast cells on bone marrow aspirate are immature or atypical
(b) Detection of a *KIT* point mutation at codon 816 in bone marrow, blood or other organs (not skin)
(c) Mast cells in bone marrow, blood or other extracutaneous organs that co-express CD117 with CD2 and/or CD25
(d) Total blood tryptase persistently ≥20 ng/ml (unless there is an associated clonal myeloid disorder in which case this parameter is not valid)

Diagnosis of systemic mastocytosis may be made if one major and one minor criteria OR three minor criteria are fulfilled.

As over half of adult patients investigated for urticaria pigmentosa will have bone marrow involvement and therefore, by definition, indolent systemic mastocytosis, making a distinction between them is more academic than practical. Blood tryptase and urinary methylhistamine may be useful markers for bone marrow involvement. A persistent blood tryptase of 20 ng/ml or greater is one of the WHO minor criteria for the diagnosis of systemic mastocytosis [17]. Although there is a theoretical risk of progression of systemic indolent mastocytosis to type II (associated myeloproliferative or myelodysplastic disorders) or type III disease, the literature indicates that this is unusual and that there are no markers to identify subgroups of patients at greatest risk of this. The occasional presentation of type III disease (aggressive systemic mastocytosis) or type IV disease (mast cell leukaemia) is more likely to be to a haematologist than to a dermatologist, with the patient showing changes in the peripheral blood against a background of being unwell with lymphadenopathy.

References

1 Büttner C, Henz BM, Welker P *et al*. Identification of activating c-*kit* mutations in adult-, but not in childhood onset indolent mastocytosis: a possible explanation for divergent clinical behaviour. *J Invest Dermatol* 1998; **111**: 1227–31.

2 Longley BJ, Metcalfe DD, Tharp M *et al*. Activating and dominant inactivating c-*kit* catalytic domain mutations in distinct clinical forms of human mastocytosis. *Proc Natl Acad Sci USA* 1999; **96**: 1609–14.

3 Rosbotham JL, Malik NM, Syrris P *et al*. Lack of c-*kit* mutation in familial urticaria pigmentosa. *Br J Dermatol* 1999; **140**: 849–52.

4 Müller U, Helbling A, Hunziker T *et al*. Mastocytosis and atopy: a study of 33 patients with urticaria pigmentosa. *Allergy* 1990; **45**: 597–603.

5 Chang A, Tung RC, Schlesinger T *et al*. Familial cutaneous mastocytosis. *Pediatr Dermatol* 2001; **18**: 271–6.

6 Azaña JM, Torrelo A, Mediero IG, Zambrano A. Urticaria pigmentosa: a review of 67 pediatric cases. *Pediatr Dermatol* 1994; **11**: 102–6.

7 Soter NA. The skin in mastocytosis. *J Invest Dermatol* 1991; **96**: 32S–39S.

8 Nagayo K, Sakai M, Mizuno N. Juvenile xanthogranuloma with Darier's sign. *J Dermatol* 1983; **10**: 283–5.

9 Yen A, Sanchez R, Oblender M, Raimer S. Leukemia cutis: Darier's sign in a neonate with acute lymphoblastic leukaemia. *J Am Acad Dermatol* 1996; **34**: 375–8.

10 Topar G, Staudacher C, Geisen F *et al*. Urticaria pigmentosa: a clinical, haematopathological and serologic study of 30 adults. *Am J Clin Pathol* 1998; **109**: 279–85.

11 Czarnetzki BM, Kolde G, Schoemann A *et al*. Bone marrow findings in adult patients with urticaria pigmentosa. *J Am Acad Dermatol* 1988; **18**: 45–51.
12 Tebbe B, Stavropoulos PG, Krasagakis K, Orfanos CE. Cutaneous mastocytosis in adults: evaluation of 14 patients with respect to systemic disease manifestations. *Dermatology* 1998; **197**: 101–8.
13 Brockow K, Scott LM, Worobec AS *et al.* Regression of urticaria pigmentosa in adult patients with systemic mastocytosis. *Arch Dermatol* 2002; **138**: 785–90.
14 Johnson EC, Helwig EB. Solitary mastocytosis (urticaria pigmentosa). *Arch Dermatol* 1961; **84**: 806–15.
15 Birt AR, Nickerson M. Generalized flushing of the skin with urticaria pigmentosa. *Arch Dermatol* 1959; **80**: 311–7.
16 Stein DH. Mastocytosis: a review. *Pediatr Dermatol* 1986; **3**: 365–75.
17 Valent P, Horny H-P, Li CY *et al*. Mastocytosis. In *World Health Organization Classification of Tumours. Pathology and genetics of tumours of haematopoietic and lymphoid tissues*. Lyon: IARC Press, 2001: 293–7.

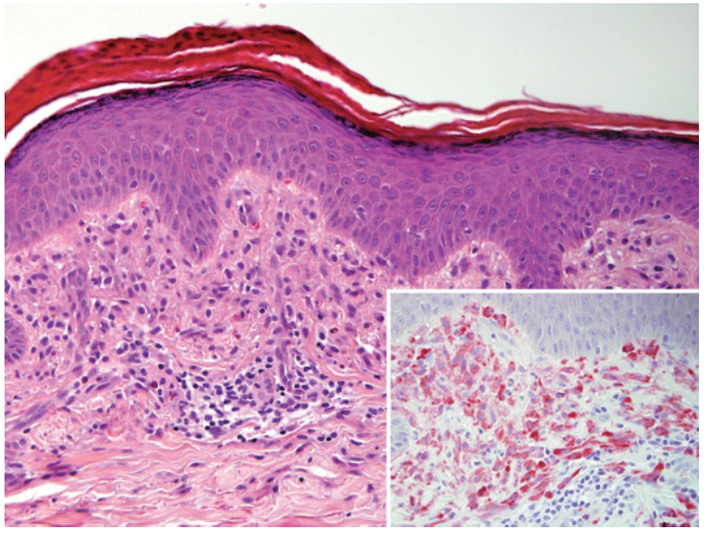
Histopathology

Skin

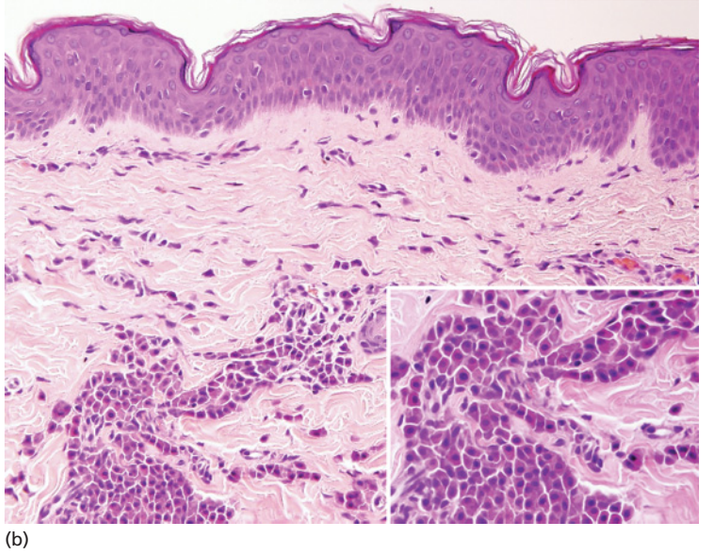
There are increased numbers of mast cells in the dermis of all types of mastocytosis. The epidermis is normal apart from an increase in melanin. The mast cells are usually oval or spindle-shaped and have granules that stain metachromatically with toluidine blue. They are also well demonstrated by Giemsa or chloroacetate esterase stains in formalin-fixed biopsies. Mast cell infiltrates are predominantly found around blood vessels and skin appendages in the papillary dermis (Fig. 22.23). In urticaria pigmentosa, they are increased up to 15-fold above normal [1], but may be less numerous. Careful technique when taking the skin biopsy, to minimize traumatic degranulation, is important. Injecting local anaesthetic around the lesion to be sampled and avoiding epinephrine may yield a higher number of stainable mast cells. A small increase in numbers of mast cells has been found in non-lesional skin of urticaria pigmentosa [2]. Full-thickness infiltration of skin or a band-like involvement of the upper dermis are seen in mastocytomas and diffuse cutaneous mastocytosis. By contrast, mast cells are confined to superficial capillaries and dilated venules in TMEP.

Bone marrow

Bone marrow involvement typically presents with focal aggregates of mast cells on biopsy, although infiltration may be diffuse and spindle-shaped. Mast cell infiltration of the marrow is often accompanied by increased numbers of immature neutrophils, phagocytosing macrophages, eosinophils and lymphocytes and sometimes by fibrosis [3,4].



(a)



(b)

Fig. 22.23 Lesional skin biopsies (a) of an adult with urticaria pigmentosa H&E × 100, inset stained with chloroacetate esterase × 400 to reveal numerous mast cells in the upper dermis; and (b) of a child with multiple mastocytomas showing large numbers of well defined dermal mast cells in clusters H&E × 100; inset with detail H&E × 200. (Photomicrographs courtesy of Dr Alistair Robson, St John's Institute of Dermatology, London.)

References

1 Garriga MM, Friedman MM, Metcalfe DD. A survey of the number and distribution of mast cells in the skin of patients with mast cell disorders. *J Allergy Clin Immunol* 1988; **82**: 425–32.
2 Olafsson JH, Roupe G, Enerbäck L. Dermal mast cells in mastocytosis: fixation, distribution and quantitation. *Acta Derm Venereol (Stockh)* 1986; **66**: 16–22.
3 Czarnetzki BM, Kolde G, Schoemann A *et al.* Bone marrow findings in adult patients with urticaria pigmentosa. *J Am Acad Dermatol* 1988; **18**: 45–51.
4 Topar G, Staudacher C, Geisen F *et al*. Urticaria pigmentosa: a clinical, hematopathologic and serologic study of 30 adults. *Am J Clin Pathol* 1998; **109**: 279–85.

Investigations

A skin biopsy is desirable to confirm a clinical diagnosis in most patients, although observation alone may be appropriate in very young children, especially those with a solitary mastocytoma, in whom systemic disease is very unlikely. A full blood count should be performed at presentation and at yearly intervals when systemic disease is suspected or proven to detect the onset of significant bone marrow disease. Other investigations should be guided by the clinical presentation. Routine bone marrow examination is not essential in the absence of other features, such as an anaemia, persistent leukocytosis, unexplained eosinophilia, bone pain, hepatosplenomegaly or lymphadenopathy. Blood tryptase is a useful surrogate marker for bone marrow involvement but not diagnostic of systemic disease without other features being present [1]. A basal tryptase of >20 ng/ml is considered to be a useful threshold in adults, although the significance of a raised tryptase in very young children is less certain [2]. An abdominal ultrasound scan may be helpful initially if there is a suspicion of systemic disease,

Table 22.17 Work-up of mastocytosis in adults.

Initial assessment

History: to include enquiry about allergic reactions, bowel symptoms and bone pain

Investigations:

Standard

- Skin biopsy
- FBC, blood chemistry profile and tryptase

Conditional

- IF FBC abnormal, e.g. eosinophilia, or tryptase >20 ng/ml for haematology opinion re: bone marrow and *KIT* mutational analysis on bone marrow aspirate
- IF systemic mastocytosis suspected or confirmed, bone densitometry, abdominal ultrasound or other imaging
- IF allergic disease suspected on the history, appropriate allergy assessment
- IF peptic ulceration suspected, for gastroscopy

Follow-up assessment

IF no evidence of systemic disease, discharge to primary care for annual FBC and blood chemistry

IF indolent systemic mastocytosis, at least annual review in secondary or tertiary care centres

- FBC, blood chemistry and tryptase
- 3-yearly bone densitometry
- other investigations guided by disease progression

IF AHNMD or aggressive systemic disease for follow-up in haematology or oncology clinics

and perhaps bone densitometry, especially if there is bone pain. A suggested protocol for the initial diagnostic work-up and review is summarized in Table 22.17.

References

1 Valent P, Horny H-P, Li CY *et al*. Mastocytosis. In *World Health Organization Classification of Tumours. Pathology and genetics of tumours of haematopoietic and lymphoid tissues*. IARC Press: Lyon, 2001: 293–7.

2 Webber NK, Ponnampalam J, Grattan CEH. How reliable is blood tryptase as a marker of systemic disease in an infant with cutaneous mastocytomas? *Clin Exp Dermatol* 2008; **33**: 198–9.

Management

Most patients presenting to dermatology clinics with cutaneous or indolent systemic mastocytosis will have an excellent prognosis, particularly children, so it is important to provide reassurance about the nature and outlook of the condition. Management hinges on avoidance of trigger factors for mast cell degranulation, symptomatic relief and detection of significant systemic disease. No cures are currently available, and there are no predictors for the onset of haematological complications or occurrence of familial disease.

Avoidance measures and management of anaphylactic emergencies

The flushing and itching experienced by many patients with cutaneous mastocytosis are due to release of mast cell mediators. This can be exaggerated by physical stimuli, such as temperature extremes, towelling, massage or alcohol. Potential triggers of mast cell degranulation include known allergens, NSAIDs, opiates, Hymenoptera venoms (even in the absence of allergy), iodinated contrast media, dextrans and some muscle relaxants (Table 22.18).

Table 22.18 Potential mast cell degranulating stimuli.

Physical triggers (especially rubbing)

Alcohol

Non-steroidal anti-inflammatory drugs (including aspirin, diclofenac)

Allergens (confirmed IgE-mediated reactions, e.g. latex allergy)

Insect and snake venoms (allergic and/or toxic effects)

Radiocontrast media (especially if iodinated)

Plasma expanders (especially dextran)

Opiates (including codeine and morphine)

General anaesthetic agents

- Non-depolarizing muscle relaxants (especially benzylisoquinolinium group, e.g. atracurium, gallamine)
- Anticholinergic drugs (e.g. hyoscine)

IgE, immunoglobulin E

Patients should be advised about the possibility of an anaphylactic emergency. Consideration should be given to carrying an epinephrine pen for self-administration, especially when there is a background of allergy. Epinephrine injectors should always be carried by mastocytosis patients with a previous history of anaphylaxis. Oral antihistamines may be helpful for milder attacks not involving respiratory difficulty or hypotension. Venom immunotherapy for patients with anaphylaxis has been reported to reduce the risk of non-allergic reactions to Hymenoptera stings, when there is no evidence of specific IgE [1], but this remains to be confirmed in larger studies. Fatal cardiovascular collapse during general anaesthesia has been reported [2]. Prophylactic administration of corticosteroids (e.g. 1 mg/kg prednisolone or equivalent) and antihistamines 30 min prior to general anaesthesia [3] is not necessarily protective.

Therapies

Antihistamines

Antihistamines are the mainstay of therapy, as for urticaria. Itching and flushing can be controlled by antihistamines in many patients, but can be refractory to treatment. Taking a classical sedating antihistamine at night, with or without a non-sedating antihistamine by day, may be beneficial, although there are no controlled studies of antihistamines in mastocytosis. Doxepin may also be used for its antihistaminic properties. H_2 antihistamines and proton pump inhibitors are used for gastrointestinal symptoms, including indigestion and diarrhoea.

Mast cell stabilizing and anti-inflammatory drugs

Abdominal pain, nausea and diarrhoea also respond to sodium cromoglycate which, however, has no value for other systemic symptoms because it is not absorbed from the gut [4]. Aspirin and other NSAIDs have been reported to ameliorate prostaglandin-mediated flushing in some patients, but must be introduced with caution if there is any history of intolerance, under cover of antihistamines and with initial observation.

Photochemotherapy and phototherapy

Although oral PUVA may help itch and wealing and improve the appearance of urticaria pigmentosa [5], the benefits are only temporary, so the risks of long-term treatment need to be considered



Fig. 22.24 Considerable improvement, but not complete resolution, of urticaria pigmentosa by the age of 5 years. (Courtesy of St John's Institute of Dermatology, London, UK.)

carefully. The mechanism for improvement is not certain, but probably involves a reduction of mast cell numbers in the papillary dermis only and total histamine content in lesional skin [6], with some cosmetic improvement due to tanning. Narrow-band UVB therapy may be effective for pruritus when PUVA is not tolerated.

Corticosteroids

Use of potent or very potent topical steroids applied under polythene occlusion, or intralesional injection of individual mastocytomas, can lead to clearance of mast cells and reduction of pigmentation for at least a year [7], but steroid atrophy is an important limitation. Restriction of treatment to limited cosmetically sensitive areas, such as the forearms and lower legs, will minimize the risk of significant adrenocortical suppression. Oral corticosteroids at high doses can offer temporary symptomatic improvement for patients with aggressive systemic mastocytosis.

Others

IFN-α-2a and -2b have been reported anecdotally to ameliorate some features of systemic mastocytosis [8,9], but not the number or appearance of skin lesions. Chemotherapies do not alter the course of the mast cell disease, are given for associated haematological disorders. There has been considerable interest in the tyrosine kinase inhibitors, especially imatinib, although unfortunately this is not effective for patients with the D816V mutation. Other inhibitors with promising *in vitro* properties include PKC412 and dasatinib but clinical experience and controlled studies are lacking. Several novel therapies for the treatment of mastocytosis are under development [10].

Prognosis

Most mastocytomas resolve in childhood. Around 50% of children with urticaria pigmentosa clear by adolescence. In a review of 67 paediatric cases, five resolved over 2 years of follow-up and 20 improved but did not clear over a mean period of 6 years [11] (Fig. 22.24). The outlook for paediatric cases that do not remit is the same as for adults with indolent disease. The prognosis for this group is difficult to ascertain due to the obvious limitations of not having information on lifelong follow-up, but it does appear from the experiences of clinics with large numbers of patients under review that progression to significant haematological disorders is rare, even with proven bone marrow involvement with mastocytosis [3,12]. Spontaneous resolution of cutaneous mastocytosis was observed in about 10% of adults [13]. The main problems likely to be experienced by patients relate to the risks of anaphylaxis and peptic ulceration. Prognosis of aggressive mastocytosis will relate to the associated haematological disorder, and management will be directed primarily towards this.

References

1 Fricker M, Helbling A, Schwartz L, Müller U. Hymenoptera sting anaphylaxis and urticaria pigmentosa: clinical findings and the results of immunotherapy in ten patients. *J Allergy Clin Immunol* 1997; **100**: 11–5.

2 Vaughan STA, Jones GN. Systemic mastocytosis presenting as profound cardiovascular collapse during anaesthesia. *Anaesthesia* 1998; **53**: 804–7.

3 Hartmann K, Henz BM. Mastocytosis: recent advances in defining the disease. *Br J Dermatol* 2001; **144**: 682–95.

4 Horan RF, Sheffer AL, Austen KF. Cromolyn sodium in the management of systemic mastocytosis. *J Allergy Clin Immunol* 1990; **85**: 852–5.

5 Vella Briffa D, Eady RAJ, James MP *et al.* Photochemotherapy (PUVA) in the treatment of urticaria pigmentosa. *Br J Dermatol* 1983; **109**: 67–75.

6 Kolde G, Frosch PJ, Czarnetzki BM. Response of cutaneous mast cells to PUVA in patients with urticaria pigmentosa: histomorphometric, ultrastructural and biochemical investigations. *J Invest Dermatol* 1984; **83**: 175–8.

7 Barton J, Lavker RM, Schechter NM, Lazarus GS. Treatment of urticaria pigmentosa with corticosteroids. *Arch Dermatol* 1985; **121**: 1516–23.

8 Czarnetzki BM, Algermissen B, Jeep S *et al.* Interferon treatment of patients with chronic urticaria and mastocytosis. *J Am Acad Dermatol* 1994; **30**: 500–1.

9 Hübner C, Wedding U, Sträter J *et al.* Clinical stable systemic mastocytosis treated with interferon alpha-2b therapy. *J Intern Med* 1997; **241**: 529–33.

10 Quintas-Cardama A, Aribi A, Cortes J *et al.* Novel approaches in the treatment of systemic mastocytosis. *Cancer* 2006; **107**: 1429–39.

11 Azãna JM, Torrelo A, Mediero IG, Zambrano A. Urticaria pigmentosa: a review of 67 pediatric cases. *Pediatr Dermatol* 1994; **11**: 102–6.

12 Topar G, Staudacher C, Geisen F *et al.* Urticaria pigmentosa: a clinical, hematopathologic and serologic study of 30 adults. *Am J Clin Pathol* 1998; **109**: 279–85.

13 Brockow K, Scott LM, Worobec AS *et al.* Regression of urticaria pigmentosa in adult patients with systemic mastocytosis. Correlation with clinical patterns of disease. *Arch Dermatol* 2002; **138**: 785–90.

CHAPTER 23

Eczema, Lichenification, Prurigo and Erythroderma

J. Berth-Jones

Department of Dermatology, University Hospitals Coventry and Warwickshire, Coventry, UK

Eczema, 23.1
Asteatotic eczema, 23.6
Chronic superficial scaly dermatitis, 23.7
Dermatophytide, 23.8
Discoid eczema, 23.9
Eczematous drug eruptions, 23.11
Eyelid eczema, 23.11
Exudative discoid and lichenoid chronic dermatosis, 23.11
Halo dermatitis, 23.12
Hand eczema, 23.13
Infective dermatitis, 23.23
Juvenile plantar dermatosis, 23.26
'Metabolic' eczema and eczema associated with systemic disease, 23.27
Pityriasis alba, 23.27
Post-traumatic eczema, 23.28
Seborrhoeic dermatitis, 23.29
Venous eczema, 23.35
The management of eczema, 23.36
Murray Williams' warts, 23.39
Lichenification, 23.39
Lichen simplex, 23.39
Lichen striatus, 23.41
Notalgia paraesthetica, 23.42
Prurigo, 23.42
Nodular prurigo, 23.42
Chronic prurigo of adults, 23.44
Prurigo pigmentosa, 23.44
Prurigo of pregnancy, 23.45
Dermographic prurigo, 23.45
Actinic prurigo, 23.45
Neurotic excoriation, 23.46
Erythroderma, 23.46
Papuloerythroderma of Ofuji, 23.50

Eczema

Definition. Eczema, a term derived from the Greek word έκζεμα meaning 'to boil', is a clinical and histological pattern of inflammation of the skin seen in a variety of dermatoses with widely diverse aetiologies. Clinically, eczematous dermatoses are characterized by variable intensity of itching and soreness, and, in variable degrees, a range of signs including dryness, erythema, excoriation, exudation, fissuring, hyperkeratosis, lichenification, papulation, scaling and vesiculation. Histologically, the clinical signs are reflected by a range of epidermal changes including spongiosis (epidermal oedema) with varying degrees of acanthosis and hyperkeratosis, accompanied by a lymphohistiocytic infiltrate in the dermis.

The terms 'dermatitis' and 'eczema' are generally regarded as synonymous, although some authors still use the term 'dermatitis' to include all types of cutaneous inflammation, so that all eczema is dermatitis, but not all dermatitis is eczema. Some caution is required when using the term 'dermatitis', as some patients regard it as implying an occupational cause. Unfortunately, there is still no international agreement on the use of these terms [1,2]. Ackerman has argued that, as the term eczema cannot be defined in a way that meets with universal approval, it should be dropped from dermatological parlance [1], but there seems to be a consensus that the term still serves a useful purpose for the clinician.

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

Classification. The classification of eczematous dermatoses is based on aetiology when this is understood, for example contact allergic or irritant dermatitis. When the aetiology is not so well clarified, classification is based largely on clinical features, such as the age of onset, distribution and the predominance of various signs and symptoms. For example, 'pompholyx', a term derived from the Greek word for blister, is used to define a pattern of eczema characterized by the acute eruption of blisters on the hands and feet, and 'discoid' is a descriptive term referring to eczema comprising scattered 'discs' or circular lesions on the trunk and limbs. This dual approach to classification can lead to confusion, because a clinical pattern such as pompholyx can have a range of different aetiologies, some of which are understood whereas others are not.

A useful approach to classification is the division of the various forms of eczema into exogenous and endogenous. The former are those which have a clearly recognized, exogenous trigger and the latter those which are mediated by processes originating within the body. The particular value of this dichotomy for the clinician is that it implies an approach to management. Whereas the key strategy for exogenous eczema is to remove the cause, endogenous eczema more often requires pharmacological intervention. Table 23.1 provides a list of the commonest recognized varieties of endogenous and exogenous eczematous dermatoses. All of these are defined and described in further detail in this and subsequent chapters. Some disorders in which the predominant feature is lichenification (e.g. lichen simplex) or prurigo (e.g. nodular prurigo) are also generally regarded as eczematous dermatoses. These are also described in this chapter.

Although this classification is a useful starting point, individual patients often do not fall neatly into these categories. Multiple factors may be implicated, and two or more forms of eczema may be present in the same patient simultaneously or consecutively. Although exogenous eczemas are related to clearly defined external trigger factors, inherited predisposition can also play a part. In some conditions there are both external and internal precipitating factors. Hand eczema, for example, even when primarily endogenous, is often aggravated by contact with irritants such as detergents or solvents. Discoid, atopic and asteatotic eczemas (regarded as endogenous) can be adversely affected, if not caused, by excessive dehydration of the stratum corneum by low ambient humidity.

Some forms of eczema are altered by regional variations in structure and function of the skin, and these may modify its appearance in regions such as the hands and the lower leg.

There remain cases of eczema that do not fit any of the described patterns [3]. These are not uncommon and have been termed 'unclassified eczema' [4]. These patients may have a poor prognosis, with a tendency for the disease to become chronic. It is not uncommon to see generalized, apparently endogenous, but otherwise unclassified eczema in the elderly [5].

Table 23.1 Classification of the principal forms of eczema.

Exogenous eczemas
Irritant eczema (Chapter 25)
Allergic contact eczema (Chapter 26)
Photoallergic contact eczema (Chapter 26 & 29)
Eczematous polymorphic light eruption (Chapter 29)
Infective eczema*
Dermatophytide*
Post-traumatic eczema*
Endogenous eczemas
Atopic eczema (Chapter 24)
Seborrhoeic eczema*
Asteatotic eczema*
Discoid eczema*
Eyelid eczema*
Exudative discoid and lichenoid chronic dermatosis*
Chronic superficial scaly dermatitis*
Pityriasis alba*
Hand eczema*
Venous eczema*
Juvenile plantar dermatosis*
Metabolic eczema or eczema associated with systemic disease*
Eczematous drug eruptions*

* Discussed in this chapter.

Acute versus chronic eczema. In certain types of eczema, of which a good example is atopic eczema, lesions are seen to change in morphology over time. Newly developed 'acute' lesions of eczema, seen at times when the disease is flaring, tend to be papular, oedematous, exudative (Fig. 23.1a) and, especially on the hands and feet, vesicobullous. More longstanding or 'chronic' lesions tend to have a different morphology, in which the predominant features are dryness, hyperkeratosis and 'lichenification' (Fig. 23.1b) (see below).

Other types of eczema tend to be more consistent in morphology; thus, pompholyx and acute episodes of contact allergic eczema, or phytophotodermatitis, are typified by an acute morphology. In contrast, lichen simplex and nodular prurigo tend to consistently demonstrate the features of chronic eczema.

These clinical features are reflected in a range of different histological features, as described below.

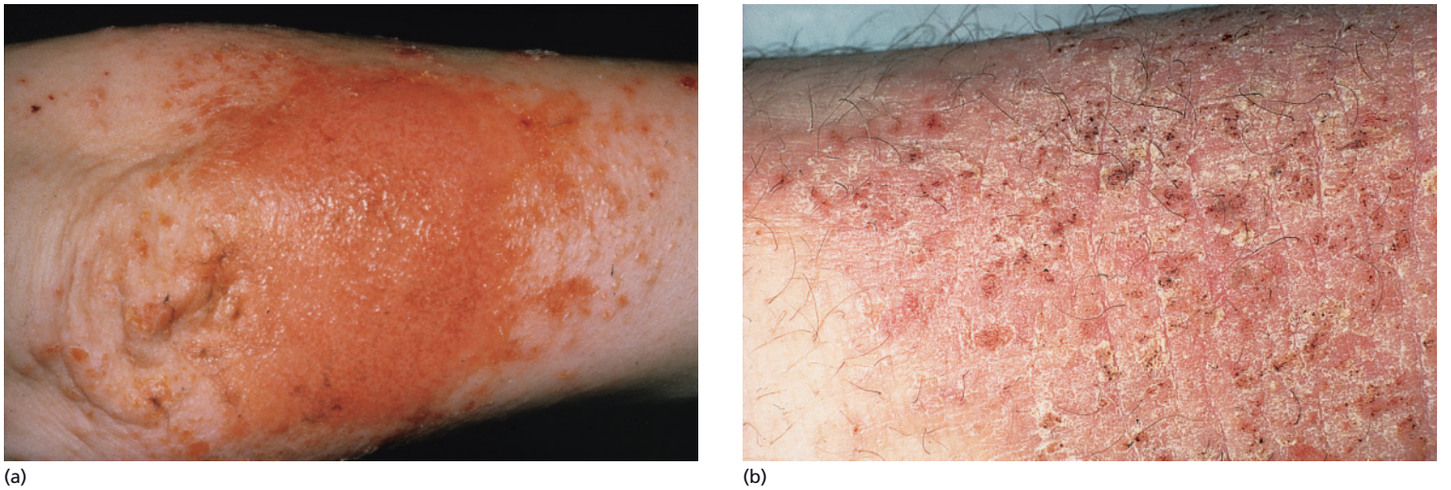
References

1 Altekrueger I, Ackerman AB. 'Eczema' revisited. A status report based on current textbooks of dermatology. *Am J Dermatopathol* 1994; **16**: 517–22.

2 Burton JL. Response of J.L. Burton. *Am J Dermatopathol* 1994; **16**: 529–30.

3 MacKenzie-Wood AR, Freeman S. Unclassified endogenous eczema. *Contact Dermatitis* 1999; **41**: 18–21.

4 Li LF, Liu G, Wang J. Prognosis of unclassified eczema. *Arch Dermatol* 2008; **144**: 160–4.



(a) (b)

Fig. 23.1 (a) Acute eczema of the arm, with erythema and marked exudation. (b) Chronic eczema of the arm.

5 Shaffrali FC, Colver GB, Messenger AG, Gawkrodger DJ. Experience with low-dose methotrexate for the treatment of eczema in the elderly. *J Am Acad Dermatol* 2003; **48**: 417–9.

Prevalence. Eczematous dermatoses account for a large proportion of all skin disease. There have been numerous studies of the prevalence of atopic dermatitis (Chapter 24), but fewer in other types of eczema. An important survey of the prevalence of skin disease was carried out in the USA on a sample of over 20 000 people who were representative of the whole population, and who were examined meticulously for skin disease by trained observers [1]. Nearly one-third had some significant skin pathology. The prevalence of all forms of eczema was 18 per 1000, seven of whom had atopic dermatitis. Hand eczema, dyshidrotic eczema and nummular eczema each accounted for about two per 1000. In a population-based survey of public health issues in Stockholm, Sweden, a postal questionnaire was sent to 15 000 adult inhabitants. Fifteen percent of respondents reported a history of childhood eczema. The 1-year prevalence of hand eczema was 8%, skin symptoms on the face were present in 14% and allergy to nickel was reported in 15% of females [2]. Population-based studies of contact allergic dermatitis suggest 40% of subjects demonstrate at least one contact allergic reaction [3].

Consultations for eczema are a major part of the workload in primary care. A survey of records in a general practice in Leicester, England, revealed that 32% of children aged 1–4 years had been diagnosed as suffering from eczema [4]. Horn [5] recorded the details of 6819 dermatological consultations in a UK general practice of 3000–4000 patients from 1958 to 1985. Eczema patients formed the largest group (19% of the consultations; see Table 23.2 for details). In a general practice in Belfast, 8% of patients seen during an 8-week period had a dermatological condition. Eczema accounted for 25% of these, of which 63% were considered to be exogenous in origin [6].

In addition, many cases are referred to hospital. These may represent 17% of all new dermatological cases [7]. A national tertiary referral centre in Singapore has described the profile of eczema referred between 1989 and 1990 [8]; 25 448 new cases were analysed. These represented 34% of new cases seen at the centre. Sixty-seven percent of eczema cases were classified as endogenous and 13.7% were contact dermatitis. Exfoliative dermatitis comprised 0.5% of all eczemas. The authors commented on the increase in the proportion of endogenous eczema seen in 1989–90 compared with that reported in 1973.

Table 23.2 Incidence of various types of eczema seen in a single general practice over 27 years in Ipswich, UK. From Horn [5].

Eczema type	Incidence (%)
Hand eczema	15
Contact dermatitis	12
Seborrhoeic	11
Discoid	7
Lichen simplex	6
Atopic	5
Gravitational	4
Other (mainly unspecified)	40

The uncertainty and variation in the nomenclature of endogenous eczema makes interpretation of statistics tentative, especially when examining changes over time. Atopic eczema is reasonably well defined, and there have been several recent studies suggesting an increased prevalence of atopic dermatitis (see Chapter 24), but prevalence of other forms of eczema may actually be decreasing [9].

Certain patterns of eczema can be seen more commonly in particular age groups. Most cases of eczema in infants and young children are atopic. In the HANES epidemiological survey in the USA [10], atopic dermatitis was by far the most common form found up to the age of 11 years; discoid and 'dyshidrotic' eczema were recorded, but were far less frequent. Perioral eczema or lick eczema around the mouth is common in children with atopic eczema (see Chapter 24), but it can also occur in non-atopic children. Hand eczema is common in atopic children, but uncommon in non-atopic children. Other specific patterns of eczematous change are almost restricted to children; for example, lichen striatus (p. 23.41), juvenile plantar dermatosis (p. 23.26), seborrhoeic dermatitis of infancy and napkin dermatitis (Chapter 17).

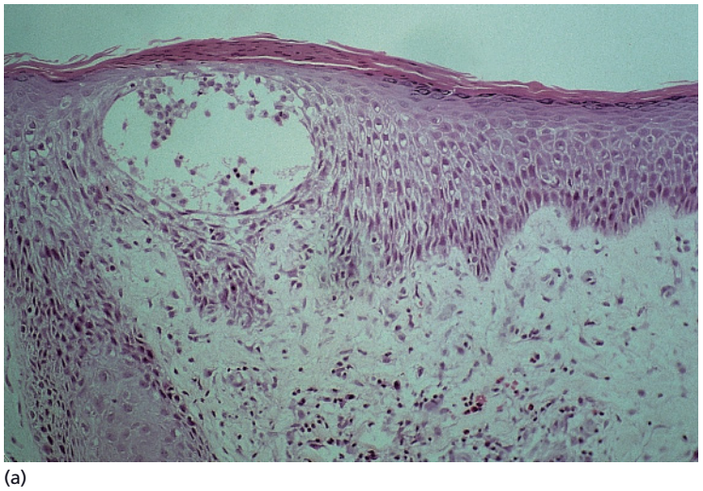
Pompholyx and atopic eczema are less common in elderly people, but other forms of eczema assume greater importance. Discoid eczema occurs particularly in elderly males in winter, and asteatotic eczema of the legs is also common. In elderly factory workers, irritant hand eczema can be very troublesome, although contact dermatitis becomes less common with advancing age. The subject is discussed more fully in Chapter 8.

References

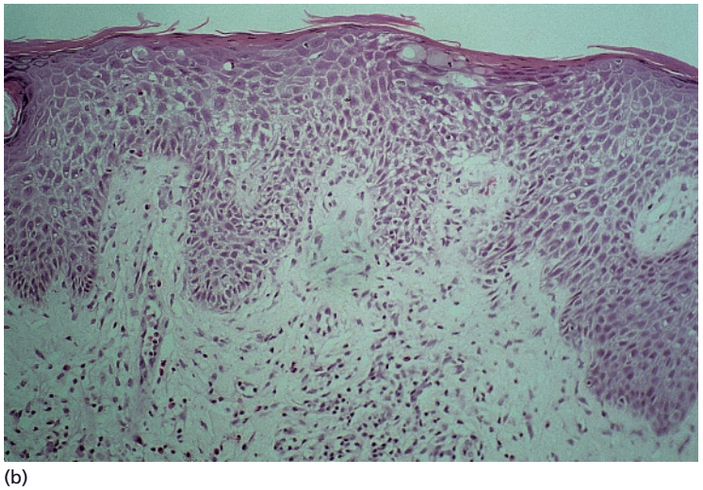
1 Johnson M-LT, Roberts J. *Prevalence of Dermatological Disease Among Persons 1–74 Years of Age*. Washington DC: US Department of Health Education, National Center for Health Statistics, 1978: PHS 79–1660.
2 Meding B, Liden C, Berglind N. Self-diagnosed dermatitis in adults. Results from a population survey in Stockholm. *Contact Dermatitis* 2001; **45**: 341–5.
3 Schafer T, Böhler S, Ruhdorfer S *et al*. Epidemiology of contact allergy in adults. *Allergy* 2001; **56**: 1192–6.
4 Neame RL, Berth-Jones J, Kurinczuk JJ, Graham-Brown RAC. Prevalence of atopic dermatitis in Leicester: a study of methodology and examination of possible ethnic variation. *Br J Dermatol* 1995; **132**: 772–7.
5 Horn R. The pattern of skin disease in general practice. *Dermatol Pract* 1986; **Dec**: 14–9.
6 Steele K. Primary dermatological care in general practice. *J R Coll Gen Pract* 1984; **34**: 22–4.
7 Bowker NV, Cross KW, Fairburn EA *et al*. Sociological implications of an epidemiological study of eczema in the city of Birmingham. *Br J Dermatol* 1976; **95**: 137–44.
8 Goh CL, Chua-Ty C, Koh SL. A descriptive profile of eczema in a tertiary referral centre in Singapore. *Ann Acad Med Singapore* 1993; **22**: 307–15.
9 Meding B, Järvholm B. Hand eczema in Swedish adults—changes in prevalence between 1983 and 1996. *J Invest Dermatol* 2002; **118**: 719–23.
10 Johnson MLT, Roberts R. *Skin Conditions and Related Need for Medical Care Among Persons 1–74 Years of Age*. Washington DC: US Department of Health Education, National Center for Health Statistics 1978; Series II, No. 212.

Histopathology [1–4]. The histopathological features of eczema, in common with the clinical features, are variable, and depend particularly on whether the disease is acute or chronic.

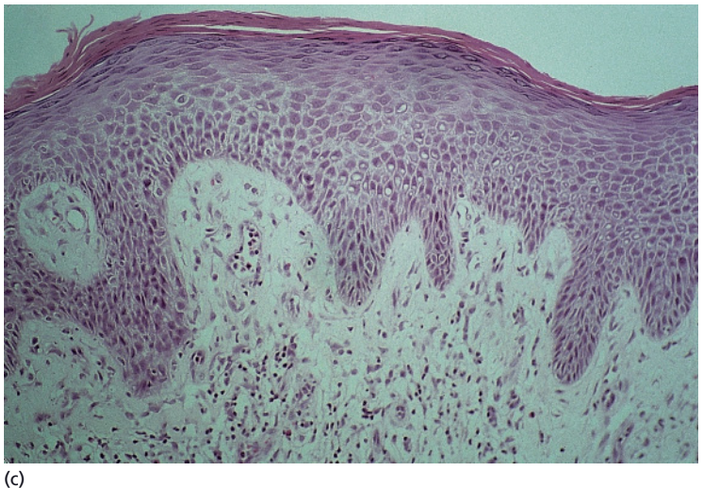
In the acute phase (Fig. 23.2a), the histological picture is dominated by spongiosis, an intercellular epidermal oedema which



(a)



(b)



(c)

Fig. 23.2 (a) Acute eczema. The epidermis shows distinct vesicle formation. The vesicle contains serum, and a moderate number of inflammatory cells. H&E, ×100. (b) Subacute eczema. There is irregular acanthosis and patchy spongiosis, with the formation of incipient microvesicles. A few lymphocytes are migrating up from the dermis into the epidermis. H&E, ×100. (c) Chronic lichenified eczema. There is compact hyperkeratosis, some patchy parakeratosis and irregular acanthosis. Mild spongiosis is seen throughout much of the epidermis, and there is a lymphocytic infiltrate in the upper dermis. H&E, ×100. (All courtesy of Dr M.J. Cook, Guildford, Surrey, UK.)

leads to stretching and eventual rupture of the intercellular attachments, with the formation of vesicles. The epidermal vesicles commonly occur in discrete foci, but on the palms and soles they tend to become large by coalescence. There is variable infiltration of the epidermis by lymphocytes. Increased epidermal mitotic activity leads to acanthosis, but if spongiosis is intense, disintegration of the suprapapillary epidermis may cause clefts to form. The intercellular oedema may be diffuse, but is commonly most intense in the mid-epidermal region. Loosening and disruption of the individual cells occur, and some intracellular vacuolation may be found, with displacement of the nucleus from the centre of the cell. Loose, shrunken epidermal cells may resemble histiocytes. Vesicles and the oedematous epidermis may be permeated by mononuclear cells, chiefly monocytes.

In the subacute stage (Fig. 23.2b), spongiosis and vesiculation diminish, and increasing acanthosis is associated with formation of a parakeratotic horny layer. This often contains layers of coagulated plasma and pyknotic nuclei of inflammatory cells.

In chronic eczema (Fig. 23.2c), hyperkeratosis gradually replaces parakeratosis. Acanthosis is more prominent than spongiosis. Inflammatory cells are less evident in the epidermis, but dermal changes become more prominent. The rete ridges become elongated and broadened. The changes are then those of lichenification.

Vascular dilatation in the dermis is marked in all stages. The papillary vessels are particularly involved, and in lichenification they may become tortuous. The infiltrate is predominantly lymphohistiocytic, although polymorphs and eosinophils may be present in very acute eczema, and eosinophils are particularly common in eczematous drug eruptions. In the presence of infection, polymorphs may invade the epidermis. In grossly lichenified eczema, prurigo and exfoliative dermatitis, the infiltrate is mixed, and may be so dense that it simulates a granuloma.

The trauma of rubbing or scratching may cause superficial erosions, haemorrhage or subepidermal fibrinoid changes. Although some degree of lichenification is always present during a prolonged attack of eczema, it is particularly prominent in atopic dermatitis. At times, extreme hyperkeratosis and papillomatosis develop.

With secondary infection, the formation of follicular or subcorneal pustules can simulate the appearance of impetigo, although typical eczematous changes are still visible at the edges of the lesion. Other modifications of the histopathological pattern are mentioned below in relation to different clinical varieties of eczema.

Although spongiosis and a dermal lymphohistiocytic infiltrate are always present at some stage in eczema, the dynamic nature of the changes and their modification by secondary events may make histological diagnosis difficult. All the changes mentioned, with the exception of the spongiotic vesicle, may also be found in burns or simple traumatic lesions of the skin.

The distinction between eczema and psoriasis can be especially difficult, particularly on the palms and soles. Seborrhoeic dermatitis (p. 23.29) is particularly difficult to distinguish from psoriasis, but the finding of Munro microabscesses is suggestive of the latter. It is generally true that cases which cause diagnostic difficulty clinically often have equivocal histological appearance.

The histological features of pityriasis rosea are those of eczema, but the clinical features, particularly the distribution, are characteristic.

Pathogenesis. There has been considerable research on the pathogenesis of some types of eczema, particularly allergic contact dermatitis, primary irritant dermatitis and atopic dermatitis (see Chapter 24). A difficulty in the research has been distinguishing non-specific common pathways from specific mechanisms. The interaction of trigger factors, keratinocytes and T lymphocytes seems particularly important in most eczema types.

Allergic contact dermatitis represents a reproducible model of eczema development [5]. The condition is an immune reaction to small molecules (haptens). On first exposure to the hapten, Langerhans' cells and dermal dendritic cells bearing the antigen migrate to the regional lymph nodes and encounter naïve T cells. Interaction with the antigen-bearing dendritic cells causes T lymphocyte differentiation into a variety of subtypes secreting different cytokine patterns (Th1 and Th2) and specialized $CD4^+$ T lymphocytes with regulatory functions to modulate allergic contact dermatitis. The T cells also acquire tissue homing antigens such as cutaneous lymphocyte-associated antigen (CLA) along with receptors permitting adhesion to skin endothelium and response to cytokines promoting specific binding to keratinocytes.

On subsequent exposure to the contact allergen, $CD8^+$ T cells display a Th1 cytokine profile that is interferon-γ (IFN-γ) predominant. The hapten in the skin may be presented to the T cells by Langerhans' cells, keratinocytes or other T cells. T-cell activation ensues, with cytokine release and upregulation of killer molecules such as perforin, granzyme-B and Fas ligand. IFN-γ promotes expression of MHC class II, the intercellular adhesion molecule ICAM 1, and increases Fas expression on the keratinocytes. In addition, IFN-γ stimulates keratinocyte production of cytokines and chemokines which attract the epidermal influx of lymphocytes. Chemokine release from infiltrating cells also modifies the reaction.

Epidermal damage and the characteristic feature of spongiosis seem to result from T-cell-mediated cytotoxicity, in particular Fas-induced keratinocyte apoptosis, which may be a final common pathway in many types of eczema [6].

Eczema may also be provoked in a non-allergic manner, as in irritant contact dermatitis. Three predominant processes occurring in irritant dermatitis are disturbed barrier function, epidermal cell change and release of inflammatory mediators and cytokines.

Certain irritants may provoke a chronic reaction in which an effect on epidermal cell turnover predominates, leading to lichenification, whereas in acute irritant reactions inflammatory mediator and cytokine release is similar to that seen in acute allergic contact dermatitis [7]. There is debate whether the cytokine profiles of the two reactions differ [7–9]. Indeed, it has been proposed that irritant reactions to haptens may be required to facilitate contact sensitization [10].

Following activation of the immune pathway by cytokine release, the accumulation of inflammatory cells progresses, leading to the morphological changes apparent histologically and clinically. In allergic contact dermatitis, the earliest changes seen by light microscopy occur some 3–6 h after the application of the allergen to the skin. Vasodilatation occurs, with extravasation of monocytes into the upper dermis [1]. After 8 h, the mononuclear cells enter the epidermis and spongiosis is seen, and by 72 h vesicles are present. The histological changes of primary irritant dermatitis are similar, but they appear to proceed more quickly, depending on the concentration of the irritant used. Both intracellular and intercellular oedema are visible throughout the epidermis at 3–6 h, and within 24 h there may be epidermal necrosis, with cellular vacuolation and nuclear pyknosis. In severe forms, the primary epidermal damage may progress to subepidermal blister formation.

Electron microscopy has shown that the earliest epidermal changes in allergic dermatitis start in the basal and Malpighian layers, where cytoplasmic vacuoles and dilated endoplasmic reticulum are seen. The keratinocytes then lose contact by breakage of their microvilli and retraction of desmosomes [11,12].

References

1 Baer RL, Rosenthal SA, Sims CF. The allergic eczema-like reaction and the primary irritant reaction. *Arch Dermatol* 1957; **76**: 549–60.

2 Komura J, Ofuji S. Ultrastructural studies of allergic contact dermatitis in man. *Arch Dermatol Res* 1980; **267**: 275–82.

3 Russell Jones R. The histogenesis of eczema. *Clin Exp Dermatol* 1983; **8**: 213–25.

4 Russell Jones R, MacDonald DM. Eczema: immunopathogenesis and histogenesis. *Am J Dermatopathol* 1982; **4**: 335–6.

5 Girolomoni G, Sebastiani S, Albanesi C, Cavani A. T-cell populations in the development of atopic and contact allergy. *Curr Opin Immunol* 2001; **13**: 733–7.

6 Trautmann A, Akdis M, Kleeman D *et al*. T cell-mediated Fas-induced apoptosis plays a key pathogenic role in eczematous dermatitis. *J Clin Invest* 2000; **106**: 25–35.

7 Berardesca E, Distante F. The modulation of skin irritation. *Contact Dermatitis* 1994; **31**: 281–7.

8 Corsini E, Galli CL. Cytokines and irritant contact dermatitis. *Toxicol Lett* 1998; **102–103**: 277–82.

9 Effendy I, Loffler H, Maibach HI. Epidermal cytokines in murine irritant responses. *J Appl Toxicol* 2000; **20**: 335–41.

10 Smith HR, Basketter DA, McFadden JP. Irritant dermatitis, irritancy and its role in allergic contact dermatitis. *Clin Exp Dermatol* 2002; **27**: 138–46.

11 Forslind B, Wahlberg JE. Assessment of chromium allergy; features of patch test reactions at electron microscopic resolution. *Acta Derm Venereol (Stockh)* 1977; **57**: 29.

12 Lindberg M. Studies on the cellular and subcellular reactions in the epidermis of irritant and allergic dermatitis. *Acta Derm Venereol (Stockh)* 1982; **105** (Suppl.).

Secondary dissemination. A very characteristic feature of eczematous inflammation is its tendency to spread far from its point of origin and to become generalized [1]. This phenomenon is often termed autosensitization or, more specifically, autoeczematization [2]. Generalized spread is especially likely when the primary site of the eczema is on the legs or the feet. There is also a particular tendency for an eruption beginning on the feet to extend to the hands and vice versa. The eczema may have been present for only a few days, or for many years before dissemination occurs. The dissemination, which is often preceded by an exacerbation at the primary site, often occurs explosively. The secondary eruption may at first consist of small oedematous papules, but these soon become obviously eczematous, and grouped papulovesicles may become confluent in small plaques. Occasionally, the lesions take the form of red macules, or weals. The distribution is usually symmetrical.

The course of the secondary eruption depends largely on the progress of the primary lesion. If the primary lesion remains acutely inflamed, the eruption increases in severity and may become generalized. If the patient is rested and the local lesion allowed to settle, the secondary eruption will subside, but will often recur very readily if the local lesion relapses. In a small proportion of patients, the generalized secondary eruption evolves into erythroderma, which may become self-perpetuating.

Conditioned hyperirritability is probably closely related to dissemination of eczema. This refers to the phenomenon whereby an area of inflamed skin on one part of the body results in a generalized hyperirritability of the skin at distant sites. There is considerable evidence that eczematous patients are more vulnerable to mild primary irritants than normal people. Conditioned hyperirritability seems to be associated with any focal inflammation of the skin, and it may explain some clinical phenomena such as the tendency for patients suffering from eczema, especially acute eczema, to have a higher proportion of false positive 'irritant' reactions to patch tests. The 'angry back' syndrome, in which a strongly positive patch test response can increase the percentage of false-positive reactions on the back at the same time, is an example of this.

There may be several mechanisms underlying the dissemination of eczema and conditioned hyperirritability. Circulating activated T lymphocytes are increased in number [3,4]. In addition, peripheral blood mononuclear cells show increased proliferation in the presence of an autologous skin homogenate compared with control subjects. This suggests that an abnormal cell-mediated immune response against autologous skin antigens could be occurring [5,6]. In some cases the presence of infection may lead to a phenomenon related to infective eczema (see below). The possibility of a non-immune process such as a neurological mechanism has not been completely excluded.

References

1 Calnan CD. Eczema for me. *Trans St John's Hosp Dermatol Soc* 1968; **54**: 54–64.
2 Young AW. Dynamics of autosensitisation dermatitis. A clinical and microscopic concept of autoeczematisation. *Arch Dermatol* 1958; **77**: 495–9.
3 Cunningham MJ, Zone JJ, Petersen MJ *et al*. Circulating activated (DR-positive) T lymphocytes in a patient with auto-eczematisation. *J Am Acad Dermatol* 1986; **13**: 1039–41.
4 Kasteler JS, Peterson MJ, Vance JE, Zone JJ. Circulating activated T lymphocytes in autoeczematization. *Arch Dermatol* 1992; **128**: 795–8.
5 Gonzalez-Amaro R, Baranda L, Abud-Mendoza C *et al*. Auto-eczematization is associated with abnormal immune recognition of autologous skin antigens. *J Am Acad Dermatol* 1993; **28**: 56–60.
6 Fehr BS, Takashima A, Bergstresser PR, Cruz PD Jr. T cells reactive to keratinocyte antigens are generated during induction of contact hypersensitivity in mice. A model for autoeczematization in humans? *Am J Contact Dermatitis* 2000; **11**: 145–54.

Eczematous dermatoses

Some of the commonest types of eczema are discussed in separate chapters (see Table 23.1). Others are described below.

Asteatotic eczema

Synonyms
- Winter eczema
- Eczéma craquelé

Definition. Eczema developing in very dry skin, usually in the elderly.

Aetiology. Although the condition is thought to be due to a decrease in skin-surface lipid, the exact pathogenesis of the skin changes is obscure. The amino-acid content of the skin is lower in the more severe cases [1]. A decrease in the keratohyaline-derived natural moisturizers may also be important [2].

Hyposteatosis occurs in many conditions of maldevelopment, malnutrition and atrophy of the skin, but does not necessarily lead to eczema. The part played by loss of fluid from the skin has been underrated in the past. The relationship between the transpiration rate and the lipid layer has been the subject of many studies [3]. Using excised skin it was shown that removal of these lipids increased water loss by 75 times, and that this returned to normal when they were restored. The implications for treatment are obvious. At present, the relevant factors in the production of asteatotic eczema can be considered to be: a naturally 'dry' skin and a lifelong tendency to chapping; a further reduction in lipid with age, illness, malnutrition or hormonal decline; increased transpiration relative to the environmental water content; loss of integrity of the water reservoir of the horny layer; chapping and degreasing (and perhaps cell damage) by industrial or domestic cleansers or solvents; low environmental humidity and dry, cold winds increasing convection loss; and repeated minor trauma leading to inflammation and further disorganization of the surface aqueous/lipid balance. Percutaneous absorption through the degreased and damaged epidermis is increased, and contact irritants and sensitizers may further damage and irritate the skin.

A patient will often ascribe the onset to an event or change in life that is quite trivial, for example the installation of central heating or a particularly cold, dry winter [4]. In industry, years of contact with degreasing agents may be tolerated until, usually in the 50–60 age group, some small, additional hazard precipitates a disabling dermatitis.

Diuretics sometimes appear to be an important contributory factor in elderly people [5]. Asteatotic eczema may be a presenting sign of myxoedema [6]. It can also be due to zinc deficiency [7]. Cimetidine has also been reported to cause asteatotic dermatitis [8], as have topical corticosteroids [9].

Histopathology. The features are those of a mild, subacute eczema, with a varying amount of dermal infiltrate. When vesicular or nummular eczema supervenes, the changes are more marked, and are as seen in the latter disease.

Clinical features (Fig. 23.3). The condition occurs particularly on the legs, arms and hands. It tends to be more marked in the winter and in elderly people. The asteatotic skin is dry and slightly scaly. The surface of the backs of the hands is marked in a criss-cross fashion, as though the continuity and flexibility of the keratin had been disturbed. The finger pulps are dry and cracked, producing distorted prints and retaining a prolonged depression after pressure ('parchment pulps'). On the legs the pattern of superficial markings is more marked and deeper ('crazy-paving' pattern or eczéma craquelé). In some patients the fissures may become haem-

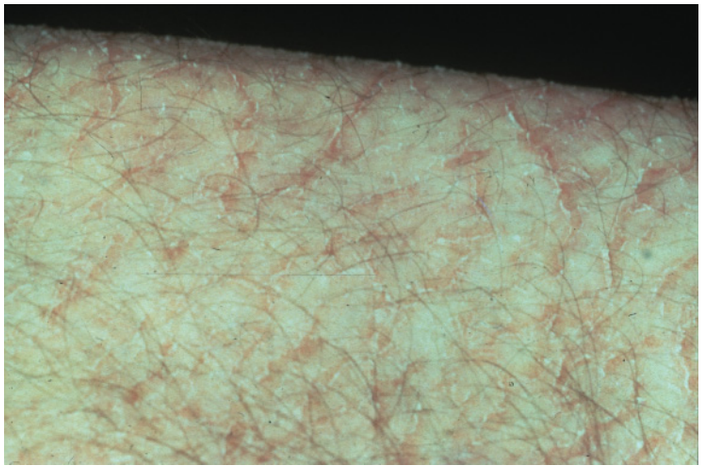


Fig. 23.3 Asteatotic eczema (eczéma craquelé, winter eczema).

orrhagic. The borders of this irregular reticulation become erythematous and slightly raised, and frank eczematous changes finally develop. Similarly, on the hands, localized areas become 'chapped' or itchy, and eventually form eczematous patches.

The condition can remain in this state for months, relapsing each winter and clearing in the summer, but eventually becoming permanent. Scratching, rubbing or contact irritants and sensitizers cause further eczematous changes or spread; or a more diffuse vesiculosquamous eruption occurs.

Nummular eczema can also occur on this background, although the relationship between the two conditions is uncertain.

Irritation in this form of eczema is often intense, and worse with changes of temperature, particularly on undressing at night.

Treatment. The patient's immediate environment may need to be adjusted. Central heating should be humidified where possible, and abrupt temperature changes should be avoided. Wool is usually poorly tolerated and possibly damaging by irritation. Baths are best restricted and should not be hot. Bath oils or oatmeal packs may be helpful, although it is important to remember that bath oils are potentially hazardous in the elderly as the bath may be made slippery. Emollients should be used after bathing or daily. Emollient creams such as those based on lanolin or paraffins are generally helpful.

Weak topical corticosteroids are often prescribed, and those contained in a urea base (Chapter 73) are very appropriate in this situation as urea encourages hydration. Among the older remedies, ichthammol is of value.

This is one of the forms of eczema in which soaps and detergent cleansers can be seen by the physician, and felt by the patient, to be deleterious. Emulsifying ointment BP, aqueous cream BP, or similar proprietary formulations should be substituted.

References

1 Horri I, Nakayama Y, Obata M *et al*. Stratum corneum hydration and amino-acid content in xerotic skin. *Br J Dermatol* 1989; **121**: 587–92.

2 Tezuka T. Electron microscopic changes in xerosis senilis epidermis. *Dermatologica* 1983; **166**: 59–61.

3 Onken HD, Moyer CA. The water barrier in human epidermis. *Arch Dermatol* 1963; **87**: 584–90.

4 Anonymous. Winter skin. *Lancet* 1990; **335**: 226.

5 Caplan RM. Superficial haemorrhagic fissures of the skin. *Arch Dermatol* 1970; **101**: 442–51.

6 Warin AP. Eczéma craquelé as the presenting feature of myxoedema. *Br J Dermatol* 1973; **89**: 289–91.

7 Weismann K, Wadskov S, Mikkelson HI. Acquired zinc deficiency dermatosis in man. *Arch Dermatol* 1978; **114**: 1509–11.

8 Greist MC, Epinette WW. Cimetidine-induced xerosis and asteatotic dermatitis. *Arch Dermatol* 1982; **118**: 253–4.

9 Björnberg J. Erythema craquelé provoked by corticosteroids on normal skin. *Acta Derm Venereol (Stockh)* 1982; **62**: 147–51.

Generalized eczéma craquelé. Extensive or generalized forms involving the trunk as well as the legs are rare but should raise the suspicion of malignancy. Cases have been reported in association with malignant lymphoma [1], angioimmunoblastic lymphadenopathy [2], anaplastic gastric adenocarcinoma [3] and spheroidal cell carcinoma of the breast [4].

References

1 Barker DJ, Cotterill JA. Generalised eczéma craquelé as a presenting feature of lymphoma. *Br J Dermatol* 1977; **97**: 323–6.

2 Van Voorst Vader PC, Folkers E, van Rhenen DJ. Craquelé-like eruption in angioimmunoblastic lymphadenopathy. *Arch Dermatol* 1979; **115**: 370.

3 Greenwood R. Generalised eczéma craquelé as a presenting feature of adenocarcinoma. *Br J Dermatol* 1983; **109**: 277–8.

4 Ridley CM. Eczéma craquelé and systemic carcinoma. *Br J Dermatol* 1984; **110**: 246.

Chronic superficial scaly dermatitis

Synonyms

- Benign form of parapsoriasis-en-plaques
- Chronic superficial dermatitis
- Digitate dermatosis
- Persistent superficial dermatitis
- Small plaque parapsoriasis
- Xanthoerythroderma perstans of Radcliffe–Crocker

Definition. A chronic condition characterized by the presence of round or oval erythematous, slightly scaly patches on the limbs and trunk, which histologically show mild eczematous changes with little or no dermal infiltrate.

The condition is clinically benign by definition [1]. However, in some cases clonality of the lymphocytic infiltrate can be demonstrated [2], a feature suggesting that this may be regarded as an abortive form of cutaneous T-cell lymphoma [3]. Ackerman has taken this argument further and expressed the view that even an abortive T-cell lymphoma is still a T-cell lymphoma, so this condition is a clinical presentation of mycosis fungoides [4].

Nomenclature. This condition was formerly included with various potentially prelymphomatous eruptions under the general term of 'parapsoriasis' [5–7]. The term chronic superficial scaly dermatitis was introduced by Calnan and Meara [1] to distinguish a subgroup of patients who did not progress to frank lymphoma, and the features which they used to distinguish this subgroup are shown in Table 23.3. The nomenclature has been discussed in detail by Lambert and Everett [6].

Table 23.3 Features which distinguish between prelymphomatous (prereticulotic) eruption and persistent superficial scaly dermatitis.

Prelymphomatous eruption	Persistent superficial dermatitis
Bizarre or angulated shape	Regular, round or oval shape
Fine scale	Coarser scale
May be irritable	Little or no irritation
Progresses to cutaneous lymphoma	Does not become malignant
Histology	
Absence of epidermal eczema	May be eczematous changes
Dermal infiltrate	Little or no dermal infiltrate



Fig. 23.4 Chronic superficial scaly dermatitis.

Aetiology. The cause is unknown.

Histopathology. The histology is not characteristic. It usually shows the changes of a very mild eczematous eruption, consisting of patchy parakeratosis, mild spongiosis, and a slight, mainly perivascular, infiltrate in the dermis, chiefly composed of lymphocytes [7].

Clinical features. The disease occurs in all races, although it is probably rare in dark-skinned people. Its geographical distribution varies considerably; for example, it is commoner in the south than in the north of England, and appears to be uncommon in America. In most cases the onset is in middle life, and the disease persists indefinitely, with or without remission. It is much commoner in men than in women.

The disease begins insidiously with one or more erythematous, slightly scaly patches. The legs, trunk and arms are most often affected (Fig. 23.4). It seldom involves the face, palms or soles. The patches are generally round or oval, but finger-like processes are also common, especially on the trunk, giving rise to the alternative name 'digitate dermatosis'. The patches are usually about 2.5 cm across, although much larger areas occur at times, especially on the legs. The colour is pink, brown or slightly yellow. The individual patches are often slightly wrinkled and appear like cigarette paper.

Symptoms are usually minimal, but some itching may occur. The patches are more prominent in winter than in summer, and may clear temporarily with natural or artificial sunlight. They will also clear for a time with suitable topical medications, but recur in the same—or adjacent—areas when treatment is stopped. After extending for a time, in most cases they then remain static and, with minor fluctuations, persist throughout life. In a few patients the condition clears permanently.

Some cases originally diagnosed as chronic superficial scaly dermatitis later develop reticulate pigmentation or atrophy, and these cases may then need to be reclassified as prelymphomatous poikiloderma.

Differential diagnosis. The main diagnostic problems are discoid eczema, eczematides, poikiloderma in its early phase, and the early stages of the classical (Alibert) form of mycosis fungoides (Chapter 57 and Table 23.3).

The history, clinical appearance, response to treatment and histology will usually establish the diagnosis.

Treatment. Only symptomatic treatment is required to allay irritation. Mild steroid ointments are generally beneficial. Natural sunlight, broad-band UVB and PUVA can be helpful when required, but relapse often occurs soon. Narrow-band UVB may also be effective in inducing remission, which can last from a few weeks to many months [8].

References

1 Calnan CD, Meara RH. Chronic superficial scaly dermatitis. *Trans St John's Hosp Dermatol Soc* 1956; **37**: 12–3.

2 Haeffner AC, Smoller BR, Zepter K, Wood GS. Differentiation and clonality of lesional lymphocytes in small plaque parapsoriasis. *Arch Dermatol* 1995; **131**: 321–4.

3 Burg G, Dummer R. Small plaque (digitate) parapsoriasis is an 'abortive cutaneous T-cell lymphoma' and is not mycosis fungoides. *Arch Dermatol* 1995; **131**: 336–8.

4 Ackerman AB. If small plaque (digitate) parapsoriasis is a cutaneous T-cell lymphoma, even an 'abortive' one, it must be mycosis fungoides. *Arch Dermatol* 1996; **132**: 562–6.

5 Hu CH, Winklemann RK. Digitate dermatosis. A new look at symmetrical small plaque parapsoriasis. *Arch Dermatol* 1973; **107**: 65–9.

6 Lambert WE, Everett MA. The nosology of parapsoriasis. *J Am Acad Dermatol* 1981; **5**: 731–45.

7 Samman PD. The natural history of parapsoriasis en plaques (chronic superficial dermatitis) and prereticulotic poikiloderma. *Br J Dermatol* 1972; **87**: 405–11.

8 Hofer A, Cerroni L, Kerl H, Wolf P. Narrowband (311 nm) UV-B therapy for small plaque parapsoriasis and early-stage mycosis fungoides. *Arch Dermatol* 1999; **135**: 1377–80.

Dermatophytide

Definition. A reaction, at a remote site, to a dermatophyte infection [1–3]. This diagnosis should be suspected when the presence of a dermatophyte infection has been established and no fungus can be demonstrated in the dermatophytide lesions. The diagnosis is supported further by clearing of the dermatophytide after the dermatophyte has been eradicated. A dermatophytide is thus a secondary, distant, aseptic skin lesion. The terminology implies analogy to the cutaneous tuberculides associated with tuberculosis [1], although the pathomechanisms involved may be different.

Prevalence. One study indicated that this condition is rare, as only 10 cases were confirmed in 1500 dermatophyte infections [2]. Others have suggested that dermatophytide may be more common. In one retrospective review of cases of dermatophytide, 37 cases were seen in a dermatology department in a 2-year period [4].

Clinical features. Various clinical patterns of dermatophytide can occur. Eczematous vesicles on the hands or feet are the commonest pattern. On the hands, the lesions occur symmetrically on the sides of the fingers, usually as a reaction to tinea pedis. An eczematous dermatophytide can also mimic pityriasis rosea [1].

Other dermatophytides have been described, often as single-case reports, including erysipelas-like dermatitis, erythema nodosum, erythema annulare centrifugum, urticaria and erythroderma.

A dermatophytide is probably more likely to develop with inflammatory dermatophytes, such as *Trichophyton mentagrophytes* of the zoophilic type [2].

A similar allergic reaction to a yeast infection may be termed a candidide (levuride). In this case the eczematous reaction may be localized to the hands or groin [1].

A dermatophytide can be mimicked by bacterial infection. In one study, *Staphylococcus aureus* and β-haemolytic streptococci were commonly isolated from lesions that were clinically thought to be examples of a dermatophytide [2].

References

1 Jillson OF. Dermatophytids and candidids. *Semin Dermatol* 1983; **2**: 60.

2 Kaaman T, Torssander J. Dermatophytide—a misdiagnosed entity. *Acta Derm Venereol (Stockh)* 1983; **63**: 404–8.

3 Peck SM. Fungus antigens and their importance as sensitizers in the general population. *Ann NY Acad Sci* 1950; **50**: 1362–75.

4 Veien NK, Hattel T, Laurberg G. Plantar *Trichophyton rubrum* infections may cause dermatophytids on the hands. *Acta Derm Venereol (Stockh)* 1994; **74**: 403–4.

Discoid eczema

Synonym

- Nummular eczema

Definition. Discoid eczema is characterized by a single, non-specific morphological feature, namely circular or oval plaques of eczema with a clearly demarcated edge. It is to be distinguished from an irregular patchy form of eczema in which the lesions do not have recognizable, clear margins. The condition is poorly defined, however, because many eczema patients have one or two circular or oval lesions and few patients with discoid eczema have only circular lesions [1,2].

Aetiology. In many cases the cause is unknown and this can then be regarded as a distinctive primary endogenous form of eczema. Some authors have found a high incidence of atopy in such patients [3], but others have not [4], and levels of IgE are often within the normal range [5]. However, lesions of similar morphology may undoubtedly occur as part of atopic eczema.

Some have stressed the role of infection [6,7]. As in other forms of eczema, heavy colonization of the lesions by staphylococci may increase their severity, even in the absence of clinical evidence of infection [6,7]. However, allergic sensitivity to staphylococci or micrococci may be responsible at least for secondary dissemination [8].

Local physical or chemical trauma plays a part in some cases, and discoid eczema sometimes develops at the site of an old injury or scar.

Specific allergy is uncommon, but may be overlooked in severe or persistent cases if patch tests are not performed [9,10].

Dry skin due to low environmental humidity is sometimes associated with discoid eczema [2,11], particularly in the elderly [12]. An association between excessive alcohol intake and discoid eczema has been reported [13].

Discoid eczema has occurred rarely as a result of sensitivity to aloe [14], depilating creams [15], mercury [16], and in patients taking methyldopa [17] or gold [18].

Emotional stress may play a role in some cases, but it is unlikely to be the primary cause.

Discoid eczema is relatively rare in children [19], except as a manifestation of atopy.

Histopathology [20,21]. There is a subacute dermatitis indistinguishable from other forms of eczema, with spongiotic vesicles and a predominantly lymphohistiocytic infiltrate. Eosinophils may also be present in the upper dermis.

Electron microscopic studies have shown that the intense intercellular oedema leads to a reduction in the number of desmosomes between the cells of the basal layer, whereas those in the stratum spinosum are mostly preserved.

Clinical features. The diagnostic lesion of discoid eczema is a coin-shaped plaque of closely set, thin-walled vesicles on an erythematous base. This arises, quite rapidly, from the confluence of tiny papules and papulovesicles. These may occur, in the phase of very acute dissemination, as individual lesions on the trunk or limbs at the same time as localized plaques are being formed. In the acute phase the lesions are dull red, very exudative or crusted and highly pruritic (Fig. 23.5). They progress towards a less



Fig. 23.5 Discoid eczema of the lower leg. (Courtesy of Dr W.A.D. Griffiths, Epsom Hospital, Surrey, UK.)

Table 23.4 Diagnosis of some discoid lesions.

Disease	Distribution	Features	Histology	Course and evolution
Prelymphomatous eruption	Flank, trunk, proximal limbs	Angular, bizarre, infiltrated, itchy	Dermal infiltrate	Persistent, may change to lymphoma
Chronic superficial dermatitis	Limbs more than trunk	Oval or round, no infiltration	Epidermal eczematous	Very chronic, benign, no fluctuations
Pityriasis alba	Face, proximal limbs	Depigmentation	Very mild eczema	Spontaneous remission after 1 or more years
Discoid (nummular) eczema	Limbs more than trunk	Oval or round, very itchy	Eczema, often intense changes	Variable, fluctuant or intermittent
Tinea corporis	Limbs or trunk	Oval or round, itchy Scraping produces scale for mycology	PAS stain shows fungus	Progresses and spreads steadily until treated

vesicular and more scaly stage, often with central clearing, and peripheral extension, causing ring-shaped or annular lesions. As they fade, they leave dry, scaly patches.

After any period between 10 days and several months, secondary lesions occur, often in a mirror-image configuration on the opposite side of the body. It is very characteristic of this disease that patches which have apparently become dormant may become active again, particularly if treatment is discontinued prematurely.

It may be convenient to recognize the following patterns:

1 Discoid eczema of the hands and forearms
2 Discoid eczema of the limbs and trunk
3 'Dry' discoid eczema.

Discoid eczema of the hands affects the dorsa of the hands or the backs or sides of individual fingers. It often develops as a single plaque, which may occur at the site of a burn or a local chemical or irritant reaction. Secondary lesions may occur on the hands, fingers or forearms, but generalized spread is uncommon. It is a not uncommon form of irritant occupational dermatitis, but may also occur in housewives or secretaries in whom the provoking factors are less clear. An atopic history appears to be more frequent in young women with discoid hand eczema than in other forms of the disease.

The more usual form of discoid eczema affects the limbs and trunk. It appears to be particularly prevalent among managerial or professional classes. It is also seen in elderly people, often with dry skin exacerbated by low humidity, central heating, car heating, etc. The initial patch usually occurs on the lower leg, and secondary lesions spread to the other leg, the arms, and often the trunk. In the course of their evolution, the lesions may become increasingly oedematous and crusted, possibly because of secondary infection. Extension then becomes rapid and, in severe cases, much of the trunk and limbs will be involved. Scattered papulovesicles may then be interspersed with large and small plaques.

All forms of discoid eczema are chronic, with partial remission during which plaques tend to clear in their centres. Most forms tend to relapse at long or short intervals, and most are worse during the colder months of the year. A review of 325 cases showed that most either cleared within a year or persisted for many years [22].

'Dry' discoid eczema is an uncommon variant, consisting of multiple, dry, scaly, round or oval discs on the arms or legs, but also with scattered microvesicles on an erythematous base on the palms and soles [23]. Itching is minimal, in contrast with other forms of discoid eczema, and the condition persists for several years, with fluctuation or remission. It is notably resistant to treatment.

Diagnosis (Table 23.4). Discoid eczema may simulate ringworm when lesions clear in the centre. If there is any doubt, scrapings should be examined for the presence of mycelia.

Exogenous contact dermatitis should be suspected if the condition is unusually severe and persistent or if patches are few, asymmetrical, or of unusual configuration. Irritants and, occasionally, sensitizers, may provoke this discoid type of response. When the history suggests this, patch tests should be performed. In one series 33% of patients were considered to have clinically relevant positive results, reacting to rubber chemicals, formaldehyde, neomycin, chrome and nickel [9]. In a series reported from India [10], positive patch tests were detected in 56% of patients, of which the commonest were to chromate, nickel, cobalt or fragrance.

In psoriasis, the lesions are dry, the scaling is more prominent, and the irritation milder. Pityriasis rosea may transiently resemble discoid eczema, but usually presents with the history of a herald patch and the characteristic oval patches with long axes parallel to the ribs (often fancifully likened to the shape of a Christmas tree). The features of exudative discoid and lichenoid chronic dermatitis and chronic superficial scaly dermatitis are discussed below.

Treatment. General considerations such as the avoidance of irritants apply, as with other forms of eczema. Bed rest and removal from a stressful environment can be helpful. Ambient conditions of low humidity should be corrected.

Emollients and topical corticosteroids, perhaps with added antibiotic or antiseptics such as clioquinol, are useful. In the early stages, a potent or very potent steroid may be needed. Traditionally, a range of coal-tar pastes or ointments were used in the less acute stages, and sometimes a combination of tar and dilute corticosteroid proved useful in long-term management.

A course of a broad-spectrum systemic antibiotic, such as oxytetracycline or erythromycin, is often helpful in severe exudative cases.

Potentially useful treatments in severe and refractory cases include topical immunosuppressants, oral steroids and immunosuppressants, PUVA and broad- or narrow-band UVB.

References

1 Bendl BJ. Nummular eczema of stasis origin: a morphological pattern of diverse etiology. *Int J Dermatol* 1979; **18**: 129–35.
2 Shelley WB, ed. *Consultations in Dermatology*, Vol II. Philadelphia: WB Saunders, 1974; 172–5.
3 Carr R, Berke M, Becker SW. Incidence of atopy in patients with various neurodermatoses. *Arch Dermatol* 1964; **89**: 20–6.
4 Hellgren L, Mobacken H. Nummular eczema. Clinical and statistical data. *Acta Derm Venereol (Stockh)* 1969; **49**: 189–96.
5 Kreuger GG. IgE levels in nummular eczema and ichthyosis. *Arch Dermatol* 1973; **107**: 56–8.
6 Leyden JJ, Kligman AM. The case for steroid–antibiotic combinations. *Br J Dermatol* 1977; **96**: 179–87.
7 Wachs GN, Maibach H. Co-operative double blind trial of an antibiotic-corticoid combination in impetiginized atopic dermatitis. *Br J Dermatol* 1976; **95**: 323–8.
8 Parish WE, Welbourn E, Champion RH. Hypersensitivity to bacteria in eczema. IV: Cytotoxic effect of antibacterial antibody on skin cells acquiring bacterial antigens. *Br J Dermatol* 1976; **95**: 493–500.
9 Fleming C, Parry E, Forsyth A, Kemmett D. Patch testing in discoid eczema. *Contact Dermatitis* 1997; **36**: 261–4.
10 Khurana S, Jain VK, Aggarwal K, Gupta S. Patch testing in discoid eczema. *J Dermatol* 2002; **29**: 763–7.
11 Rollins TG. From xerosis to nummular dermatitis. *JAMA* 1968; **206**: 637.
12 Aoyama H, Tanaka M, Hara M *et al*. Nummular eczema: an addition of senile xerosis and unique cutaneous reactivities to enviromental aeroallergens. *Dermatology* 1999; **199**: 135–9.
13 Higgins EM, DuVivier AW. Cutaneous disease and alcohol misuse. *Br Med Bull* 1994; **50**: 85–98.
14 Morrow DM, Rapaport MJ, Strick RA. Hypersensitivity to aloe. *Arch Dermatol* 1980; **116**: 1064–5.
15 Le Coz CJ. Contact nummular (discoid) eczema from depilating cream. *Contact Dermatitis* 2002; **42**: 111–2.
16 Adachi A, Horikawa T, Takashima T, Ichihashi M. Mercury-induced nummular dermatitis. *J Am Acad Dermatol* 2000; **43**: 383–5.
17 Church R. Eczema provoked by methyldopa. *Br J Dermatol* 1974; **91**: 373–8.
18 Wilkinson SM, Smith AG, Davis MJ *et al*. Pityriasis rosea and discoid eczema: dose related reactions to treatment with gold. *Ann Rheum Dis* 1992; **51**: 881–4.
19 Hambly EM, Wilkinson DS. Sur quelques formes atypiques d'eczéma chez l'enfant. *Ann Dermatol Vénéréol* 1978; **105**: 369–71.
20 Ackerman AB, ed. *Histologic Diagnosis of Inflammatory Skin Diseases*. Philadelphia: Lea & Febiger, 1978: 499–506.
21 Elder D, ed. *Lever's Histopathology of the Skin*, 8th edn. Philadelphia: Lippincott, 1997: 209–16.
22 Cowan MA. Nummular eczema—a review, follow-up and analysis of 325 cases. *Acta Derm Venereol (Stockh)* 1961; **41**: 453–60.
23 Calnan CD, Meara RH. Discoid eczema—dry type. *Trans St John's Hosp Dermatol Soc* 1956; **37**: 26–8.

Eczematous drug eruptions

Eczematous drug reactions may be localized, resembling, for example, seborrhoeic or discoid eczema, or generalized. Carbamazepine is a well recognized cause of eczematous reactions, which may initially involve the flexures, resembling atopic dermatitis [1]. Eczematous eruptions, including cheiropompholyx, may follow infusion of human immunoglobulin [2]. Severe reactions can rapidly progress to erythroderma.

Drug reactions are more fully described in Chapter 75.

References

1 Ozkaya-Bayazit E, Gungor H. Carbamazepine induced eczematous eruption—clinically resembling atopic dermatitis. *J Eur Acad Dermatol Venereol* 1999; **12**: 182–3.
2 Whittam LR, Hay RJ, Highes RAC. Eczematous reactions to human immune globulin. *Br J Dermatol* 1997; **137**: 481–2.

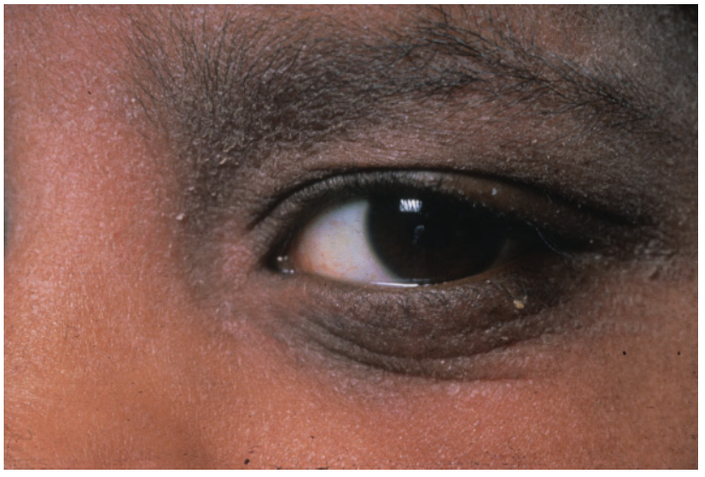


Fig. 23.6 Eyelid dermatitis (atopic, note Dennie–Morgan fold).

Eyelid eczema

Definition. Eczema affecting predominantly the eyelids.

Aetiology [1,2]. This is a common clinical presentation. Eyelid involvement is a very common feature of atopic dermatitis (Fig. 23.6) and it is therefore likely that many cases represent mild atopic dermatitis without other manifestations. Others are due to seborrhoeic dermatitis. Contact allergy to various components of eye makeup, nail varnish, fragrance, rubber [3] or ophthalmic medicaments [4] are responsible for some cases. Allergy to nickel in spectacle frames often causes eczema near the lower eyelids, originating at a site of contact with a metal frame. In some cases the cause remains obscure.

Treatment. When the condition is not amenable to removal of the cause, treatment with hydrocortisone cream is often effective. Topical immunosuppressants (tacrolimus, pimecrolimus) can also be particularly useful in this setting, and avoid the risks of inducing atrophy, rosacea or raised intraocular pressure associated with prolonged use of steroids.

References

1 Guin JD. Eyelid dermatitis: a report of 215 patients. *Contact Dermatitis* 2004; **50**: 87–90.
2 Amin KA, Belsito DV. The aetiology of eyelid dermatitis: a 10-year retrospective analysis. *Contact Dermatitis* 2006; **55**: 280–5.
3 Guin JD. Clinical presentations of patients sensitive to natural rubber latex. *Dermatitis* 2004; **15**: 192–6.
4 Dewachter P, Mouton-Faivre C. Anaesthetists should be aware of delayed hypersensitivity to phenylephrine. *Acta Anaesthesiol Scand* 2007; **51**: 637–9.

Exudative discoid and lichenoid chronic dermatosis [1]

Synonym
- Sulzberger–Garbe disease

Definition. This disease has no rigid criteria, but it is a widespread, extremely pruritic eruption, characterized by discoid



Fig. 23.7 Sulzberger–Garbe disease. (Courtesy of Dr A. Warin, Royal Devon and Exeter Hospital, Exeter, UK.)

lesions with 'lichenoid' and exudative phases, which either coexist or alternate rapidly with each other. After a chronic course of months or years the condition ends in spontaneous cure. It occurs predominantly in adult male Jews, usually between the ages of 40 and 60. More than 100 cases have been reported [2], but some authors deny its existence as a distinct entity [3], and the scarcity of reports of this entity over the last two decades lends support to this contention [4,5].

Aetiology. The cause is unknown.

Histopathology. The histology is non-specific, and can mimic discoid eczema, allergic contact dermatitis or lichen simplex. There may be a characteristic swelling of the endothelial cells of the small vessels, which are surrounded by a 'cloudy' oedema. An infiltrate of mixed cells, including plasma cells and eosinophils, may form a mantle around the arterioles.

Clinical features. The eruption, which is exceedingly pruritic, comprises discoid lesions with lichenified and exudative phases, present together or alternately. The plaques are widely distributed (Fig. 23.7). In addition, there may be showers of round, urticated lesions which appear as the discoid eczematous lesions wane.

Penile and scrotal lesions are common, and are almost pathognomonic. They are also the most persistent feature. Gynaecomastia is present in some patients [2], and blood eosinophilia is frequent.

Differential diagnosis. The differential diagnosis is wide, and includes mycosis fungoides, contact dermatitis, dermatitis herpetiformis, discoid eczema and lichen planus.

Treatment. Treatment is with systemic steroids, which may have to be continued until spontaneous resolution occurs. A rapid response to azathioprine was observed in two cases [5].

References

1 Sulzberger MB, Garbe W. Nine cases of distinctive exudative discoid and lichenoid chronic dermatosis. *Arch Dermatol Syphilol* 1937; **36**: 247–72.



Fig. 23.8 Halo dermatitis: eczema around a mole.

2 Sulzberger MB. Distinctive exudative discoid and lichenoid chronic dermatosis (Sulzberger and Garbe) re-examined—1978. *Br J Dermatol* 1979; **100**: 13–20.
3 Rongioletti F, Corbella L, Rebora A. Exudative discoid and lichenoid chronic dermatosis (Sulzberger–Garbe). A fictional disease? *Int J Dermatol* 1989; **28**: 40–3.
4 Trueb RM. Exudative discoid and lichenoid chronic dermatosis (Sulzberger–Garbe): presentation with a puzzling penile plaque. Report of two cases of Sulzberger–Garbe dermatosis with typical penile lesions. *J Eur Acad Dermatol Venereol* 1994; **3**: 411–7.
5 Freeman K, Hewitt M, Warin AP. Two cases of distinctive exudative discoid and lichenoid chronic dermatosis of Sulzberger and Garbe responding to azathioprine. *Br J Dermatol* 1984; **111**: 215–20.

Halo dermatitis

Synonyms
- Meyerson's naevus
- Meyerson phenomenon

Meyerson [1] described two patients with multiple pruritic, papulosquamous lesions surrounding melanocytic naevi (Fig. 23.8). More than 20 similar cases have since been described [2–4], mainly in young adults. Histology shows a benign naevus surrounded by a dermal lymphocytic and eosinophilic infiltrate, with overlying acanthosis, spongiosis and parakeratosis. One case developed during treatment with interferon α-2b in a patient with dysplastic naevus syndrome and Behçet's disease [5]. The condition usually resolves spontaneously within a few months, without involution of the naevus. It differs from Sutton's halo depigmentation, although the two conditions have been reported to coexist in the same patient, and in one case progression to Sutton's naevus occurred [6]. Similar changes are not infrequently seen around seborrhoeic warts [7] and other elevated skin lesions [8], and are termed the 'Meyerson phenomenon'.

References

1 Meyerson LB. A peculiar papulosquamous eruption involving pigmented naevi. *Arch Dermatol* 1971; **103**: 510–2.
2 Brenan J, Kossard S, Krivanek J. Halo eczema around melanocytic naevi. *Int J Dermatol* 1985; **24**: 226–9.
3 Nicholls DSH, Mason GH. Halo dermatitis around a melanocytic naevus: Meyerson's naevus. *Br J Dermatol* 1988; **118**: 125–9.

4 Weedon D, Farnsworth J. Spongiotic changes in melanocytic naevi. *Am J Dermatopathol* 1984; **6**: 257–9.
5 Krischer J, Pechere M, Salomon D *et al*. Interferon alfa-2b-induced Meyerson's nevi in a patient with dysplastic nevus syndrome. *J Am Acad Dermatol* 1999; **40**: 105–6.
6 Ramon R, Silvestre JF, Betlloch I *et al*. Progression of Meyerson's naevus to Sutton's naevus. *Dermatology* 2000; **200**: 337–8.
7 Rosen R, Paver K, Kossard S. Halo eczema surrounding seborrheic keratosis: an example of perilesional dermatitis. *Australas J Dermatol* 1990; **31**: 73–6.
8 Gallais V, Lacour JP, Perrin C *et al*. Halo eczema around a histiocytofibroma: the Meyerson phenomenon. *Ann Dermatol Venereol* 1993; **120**: 617–20.

Hand eczema

Hand eczema is such a common and distressing condition, and poses such difficult problems for the dermatologist, that it deserves separate consideration [1]. Up to 30% of occupational medical practice relates to hand eczema, with important issues regarding medical litigation, worker's compensation and disability. A quarter of the patients referred to a specialized contact dermatitis clinic suffered from hand dermatitis [2].

Definition. The term hand eczema implies that the dermatitis is largely confined to the hands, with only minor involvement of other areas. If the eczema is widespread and the hands appear to be involved only coincidentally, it is preferable to speak of hand involvement.

Classification. No single classification of hand eczema is completely satisfactory. As with eczematous dermatoses in general, classification is based partly on aetiology and partly on morphology. Several different morphological forms are seen clinically as fairly consistent entities, but some of these entities can have several different causes. Conversely, a single cause can sometimes produce several different morphological patterns.

Morphological variants of hand eczema are described below, and an aetiological classification is shown in Table 23.5. This may be useful to the clinician as a checklist in an individual case, although the list does not exhaust the aetiological possibilities. Other rare causes have been reported, for example venous eczema secondary to arteriovenous shunts in the forearm. There are probably other causative agents which have yet to be identified.

Most cases of hand eczema have a multifactorial aetiology. This not only makes treatment difficult, but it can cause considerable problems in medicolegal cases (e.g. occupational dermatitis in which negligence is alleged against an employer).

Atopy, a naturally dry skin, a tendency to seborrhoeic dermatitis, a superadded contact allergic or irritant dermatitis, or even the effect of rubbing or scratching may all obscure or potentiate the original cause. Even the daily, mild trauma of normal life and climatic influences may play some part [3], and litigation itself may cause an exacerbation of the condition.

The role of stress in aggravating hand eczema is difficult to evaluate, and the disease itself is very stressful [4]. Many patients give a convincing account of exacerbations at times of acute anxiety, frustration or grief.

The role of hormonal factors is also difficult to assess. Occasionally, there is a history of premenstrual exacerbation, or deterioration during pregnancy.

Table 23.5 Hand eczema: aetiological possibilities to be considered.

Exogenous
Contact irritants
Chemical (e.g. soap, detergents, solvents)
Physical (e.g. friction, minor trauma, cold dry air)
Contact allergens
Delayed hypersensitivity (type IV) (e.g. chromium, rubber)
Immediate hypersensitivity (type I) (e.g. seafood)
Ingested allergens (e.g. drugs, possibly nickel, chromium)
Infection (e.g. following bacterial infection of hand wounds)
Secondary dissemination (e.g. dermatophytide reaction to tinea pedis)
Endogenous
Idiopathic (e.g. discoid, hyperkeratotic palmar eczema)
Immunological or metabolic defect (e.g. atopic)
Psychosomatic: stress aggravates, but may not be causative
Dyshidrosis: increased sweating aggravates, but may not be causative



Fig. 23.9 Bullous eczema due to contact allergy to rubber gloves.

Exogenous causes. Contact irritants are the commonest exogenous cause of hand eczema [5], but contact allergens such as chromate, epoxy glues, rubber, etc. are also important (Chapter 26). All patterns of hand eczema are possible in contact allergy. Rubber dermatitis usually affects the dorsa of the hands (Fig. 23.9), but so can contact irritant and atopic dermatitis [6]. Certain occupations are particularly likely to provoke hand eczema. The problem of occupational eczema in hairdressers, fish industry workers, farmers, construction workers, dental and medical personnel, metal workers and caterers has provoked many studies to determine its prevalence and to develop programmes for prevention of hand dermatitis [7–9]. This topic is discussed in more detail in specialized textbooks such as that of Menné and Maibach [1].

Mention must also be made of the possibility of type 1 allergic reactions to certain proteins. In mild cases they provoke a vesicular eczema of the fingers in certain individuals, particularly those who prepare seafood. In one Scandinavian study, no less than one-third of restaurant food handlers with hand dermatitis had such a contact urticaria [10]. Greater concern has arisen in recent

Table 23.6 Morphological patterns of hand eczema.

Apron eczema
Chronic acral dermatitis
Discoid eczema
Fingertip eczema
'Gut' eczema
Hyperkeratotic palmar eczema
Pompholyx
Recurrent focal palmar peeling
Ring eczema
'Wear and tear' dermatitis (dry palmar eczema)
Other patterns (e.g. patchy vesiculosquamous)

years because of the increasing frequency of reactions to natural rubber latex protein found in latex gloves. The reactions range from contact urticaria to rhinitis, asthma and anaphylaxis [11]. There has been particular attention paid to hospital employees, and 7% of staff reported symptoms suggestive of latex sensitivity in a study conducted in the northwest of England [12].

Oral ingestion of allergens such as nickel, chromium or balsam of Peru has been reported to provoke or aggravate hand eczema in sensitized subjects [13–17], although the importance of this phenomenon is controversial [18].

Endogenous causes. Twin studies suggest hereditary factors play a role in the development of hand eczema [19], with the atopic diathesis as the commonest endogenous cause [20]. Hand eczema is more common in people with a previous history of atopic dermatitis elsewhere [21]. The most common site of atopic dermatitis in the adult is the hands, and in some patients the hands alone may be involved. Indeed, the atopic state may first become apparent with the development of hand eczema in an adolescent or young adult when they are exposed to school, hobby or occupational irritants. The eruption is often patchy and always very irritable. There is no specific topographic pattern, although the feet may also be involved [22,23]. Lichenification may be evident at an early stage, and pompholyx may or may not be present. The atopic diathesis may also predispose to a discoid pattern of hand eczema in young adults. Atopic hand eczema probably has the worst prognosis of all types of hand eczema [5].

A morphological classification of hand eczema is often suggested. Although most cases are of a patchy vesiculosquamous nature without any special characteristics, about one-third of cases present particular patterns that deserve recognition (Table 23.6). The various patterns are discussed below. However, there are no hard and fast divisions; the morphology frequently changes in an individual case, so that a diagnosis based on morphology may have to be revised.

Histopathology. In general, the differences between the various forms of hand eczema are clinical rather than histological, but the considerably thickened horny layer and the presence of numerous sweat glands modify the histological features of eczema on the hands.

Prevalence. Minor degrees of hand eczema are very common, and virtually everyone suffers from mild dryness and chapping at some time or another. The perception of whether these changes amount to hand dermatitis can influence the findings of epidemiological studies [24].

In most surveys, hand eczema is commoner in females, in a ratio of about two to one [5], and in adolescents with hand eczema the prevalence increases in girls as they age, whereas boys tend to improve [25]. Agrup [26] found that about 2% of people in a county in southern Sweden had active hand eczema, but only 25% of them had consulted their doctor about it in the previous year, and 25% had never sought medical advice. A study of prevalence in Sweden in 1984–8, by questionnaire of 16584 individuals, showed that 11% had suffered from hand eczema within the year, with a point prevalence of 5% [27].

In high-risk groups the figures are even higher. In Finland, 44% of 617 hospital personnel engaged in 'wet work' (nurses, cleaners, kitchen staff, etc.) had a past or present history of hand eczema, and 28% had at least two attacks [28]. This is confirmed by a study demonstrating significantly greater risk of hand dermatitis among hairdressers compared with office workers [29].

Eczema of the hands accounted for 34% of cases of eczema attending a contact dermatitis clinic in Singapore [30].

References

1 Menné T, Maibach HI. *Hand Eczema*, 2nd edn. Boca Raton: CRC Press, 2000.
2 Smith HR, Armstrong DK, Wakelin SH *et al*. Descriptive epidemiology of hand dermatitis at the St John's contact dermatitis clinic 1983–97. *Br J Dermatol* 2000; **142**: 284–7.
3 Uter W, Gefeller O, Schwanitz HJ. An epidemiological study of the influence of season (cold and dry air) on the occurrence of irritant skin changes of the hands. *Br J Dermatol* 1998; **138**: 266–72.
4 Miller RM, Coger RW. Skin conductance conditioning with dyshidrotic eczema patients. *Br J Dermatol* 1979; **101**: 435–40.
5 Meding B, Swanbeck G. Epidemiology of different types of hand eczema in an industrial city. *Acta Derm Venereol (Stockh)* 1989; **69**: 227–33.
6 Duarte I, Terumi Nakano J, Lazzarini R. Hand eczema: evaluation of 250 patients. *Am J Contact Dermatitis* 1998; **9**: 216–23.
7 Lonnroth E, Shahnavaz H. Atopic dermatitis, conjunctivitis, and hand dermatitis among Swedish dental personnel, including use of personal protective devices. *Swed Dent J* 1998; **22**: 105–15.
8 Funke U, Fartasch M, Diepgen TL. Incidence of work-related hand eczema during apprenticeship: first results of a prospective cohort study in the car industry. *Contact Dermatitis* 2001; **44**: 166–72.
9 Uter W, Pfahlberg A, Gefeller O, Schwanitz HJ. Hand dermatitis in a prospectively-followed cohort of hairdressing apprentices: final results of the POSH study. Prevention of occupational skin disease in hairdressers. *Contact Dermatitis* 1999; **41**: 280–6.
10 Hjorth N, Roed Petersen J. Occupational protein contact dermatitis in food handlers. *Contact Dermatitis* 1976; **2**: 28–42.
11 Hamann C P. Natural rubber latex protein sensitivity: a review. *Am J Contact Dermatitis* 1993; **4**: 4–21.
12 Sinha A, Harrison PV. Latex glove allergy among hospital employees: a study in the north-west of England. *Occup Med (Oxf)* 1998; **48**: 405–10.
13 Christensen OB, Möller H. External and internal exposure to the antigen in the hand eczema of nickel allergy. *Contact Dermatitis* 1975; **1**: 136–41.
14 Cronin E. Oral challenge in nickel hypersensitive women with hand eczema. In: Brown SS, Sundermann FW, eds. *Nickel Toxicology*. New York: Academic Press, 1980: 149–55.
15 Kaaber K, Veien NK. Chromate ingestion in chronic dermatitis. *Contact Dermatitis* 1978; **4**: 119–20.
16 Menné T, Hjorth N. Reactions from systemic exposure to contact allergens. *Semin Dermatol* 1982; **1**: 15–24.



Fig. 23.10 'Apron' eczema, showing the characteristic distribution.

17 Veien NK. Systemically induced eczema in adults. *Acta Derm Venereol (Stockh)* 1989; **147**: 1–58.
18 Fisher AA. Possible role of diet in pompholyx and nickel dermatitis—a critical survey. *Cutis* 1978; **22**: 412–4.
19 Bryld LE, Agner T, Kyvik KO *et al*. Hand eczema in twins: a questionnaire investigation. *Br J Dermatol* 2000; **142**: 298–305.
20 Forsbeck M, Skog E, Asbrink E. Atopic hand dermatitis. *Acta Derm Venereol (Stockh)* 1983; **63**: 9–143.
21 Coenraads PJ, Diepgen TL. Risk for hand eczema in employees with past or present atopic dermatitis. *Int Arch Occup Environ Med* 1998; **71**: 7–13.
22 Cronin E. Clinical patterns of hand eczema in women. *Contact Dermatitis* 1985; **13**: 153–61.
23 Lee HJ, Ha SJ, Ahn WK *et al*. Clinical evaluation of atopic hand dermatitis. *Pediatric Dermatol* 2001; **18**: 102–6.
24 Vermeulen R, Kromhout H, Bruynzeel DP, de Boer EM. Ascertainment of hand dermatitis using a symptom-based questionnaire; applicability in an industrial population. *Contact Dermatitis* 2000; **42**: 202–6.
25 Yngveson M, Svensson A, Johannisson A, Isacsson A. Hand dermatosis in upper secondary school pupils: 2-year comparison and follow-up. *Br J Dermatol* 2000; **142**: 485–9.
26 Agrup G. Hand eczema with other dermatoses in South Sweden. *Acta Derm Venereol (Stockh)* 1969; **49** (Suppl. 61).
27 Meding B, Swanbeck G. Prevalence of hand eczema in an industrial city. *Br J Dermatol* 1987; **116**: 627–34.
28 Lammintausta T, Kalimo K, Havu VK. Occurrence of contact allergy and hand eczema in hospital 'wet work'. *Contact Dermatitis* 1982; **8**: 84–90.
29 Uter W, Pfhalberg A, Gefeller O, Schwanitz HJ. Risk of hand dermatitis among hairdressers versus office workers. *Scand J Work Environ Health* 1999; **25**: 450–6.
30 Goh CL. An epidemiological comparison between hand eczema and non-hand eczema. *Br J Dermatol* 1988; **118**: 797–83.

Morphological types of hand eczema

Apron eczema

This condition is a type of hand eczema which involves the proximal palmar aspect of two or more adjacent fingers and the contiguous palmar skin over the metacarpophalangeal joints, thus resembling an apron [1] (Fig. 23.10). This pattern of hand eczema can be irritant or allergic, but is often considered endogenous.

Chronic acral dermatitis

This is a distinctive syndrome affecting patients in middle age. A chronic, hyperkeratotic, papulovesicular eczema of the hands and feet, intensely pruritic, is associated with grossly elevated IgE levels in subjects with no personal or family history of atopy. The condition responds to oral corticosteroids, but the response to topical therapy is poor [2].



Fig. 23.11 Fingertip eczema resulting from allergy to plant bulbs. (Courtesy of Dr F.A. Ive, Durham, UK.)

Discoid eczema

See p. 23.9.

Fingertip eczema

This condition also presents a very characteristic pattern, involving the palmar surface of the tips of some or all the fingers. The skin is dry, cracked and sometimes breaks down into painful fissures. Usually remaining localized, it may occasionally extend along the palmar surfaces of the fingers to merge with palmar eczema (Fig. 23.11).

Two patterns may be distinguished. The first and most common involves most or all of the fingers, mainly those of the dominant hand, and particularly the thumb and forefinger. The condition is usually worse in the winter and generally improves on holiday. Patch tests are negative or not relevant; it is a cumulative irritant dermatitis in which degreasing agents combine with trauma as causative factors. The second pattern involves preferentially the thumb, forefinger and third finger of one hand. This is usually occupational (whether in factory, market garden or house). It may be either irritant (e.g. in newspaper-delivery employees) or allergic (e.g. to colophony in polish, or to tulip bulbs or stems [3,4]). The condition usually involves the dominant hand, but there may be allergy to onions, garlic [5] and other kitchen products held in the non-dominant hand when being cut. In these cases, patch testing (and 20-min contact tests) may be rewarding.

References
1 Cronin E. Clinical patterns of hand eczema in women. *Contact Dermatitis* 1985; **13**: 153–61.
2 Winkelman RK, Gleich GJ. Chronic acral dermatitis—association with extreme elevations of IgE. *JAMA* 1973; **225**: 378–81.
3 Gette MT, Marks JE. Tulip fingers. *Arch Dermatol* 1990; **126**: 203–5.
4 Guin JD, Franks H. Finger tip dermatitis in a retail florist. *Cutis* 2001; **67**: 328–30.
5 Bleumink KE. Contact dermatitis to garlic. *Arch Dermatol Forsch* 1973; **247**: 117–24.

'Gut' eczema

Synonym
- Slaughterhouse eczema

Workers who eviscerate and clean pig carcasses are at risk of developing vesicular eczema which starts in the finger-webs and spreads to the sides of the fingers. This is a mild, self-limiting condition, which clears in a week or two, even if the patient remains at work, but it can recur at intervals. Workers in Danish bacon factories call this 'fat eczema', although there is little evidence that it is due to fat, and prick tests to pig fat extracts are negative [1]. The pathogenesis is unknown, but some slaughtermen have developed contact urticaria from exposure to animal blood [2].

References
1 Hjorth N. Gut eczema in slaughterhouse workers. *Contact Dermatitis* 1978; **4**: 49–52.
2 Goransson K. Occupational contact urticaria to fresh cow and pig blood in slaughtermen. *Contact Dermatitis* 1982; **7**: 281–2.

Hyperkeratotic palmar eczema

Synonym
- Tylotic eczema

This condition is a distinct form of hand eczema which is characterized by highly irritable, scaly, fissured, hyperkeratotic patches on the palms and palmar surfaces of the fingers [1,2] (Fig. 23.12). It is a common condition, and 2–5% of all applications for permanent disability pensions in some western European countries are due to hyperkeratotic hand eczema.

The aetiology is unknown. Patch tests are usually negative, and the incidence of atopy and psoriasis is no greater than in a normal control population. The distinction from localized psoriasis of the hands can, however, be very difficult. It is most frequent in men of middle age or over, and is extremely refractory to treatment, although PUVA may be helpful [3]. Steroid ointments, crude coal tar, salicylic acid and Grenz rays may be tried. A review of 32 patients re-examined 10 years after initial presentation showed that in 29 the condition had remained more or less unchanged [1,3]. Oral retinoid tablets such as alitretinoin and etretinate may be helpful [4,5].

References
1 Hersle K, Mobacken H. Hyperkeratotic dermatitis of the palms. *Br J Dermatol* 1982; **107**: 195–202.
2 Schwanitz HJ, ed. *Atopic Palmoplantar Eczema*. Berlin: Springer-Verlag, 1988.



Fig. 23.12 Hyperkeratotic palmar eczema.

3 Mobacken H, Rosen K, Swanbeck G. Oral psoralen photochemotherapy (PUVA) of hyperkeratotic dermatitis of the palms. *Br J Dermatol* 1983; **109**: 205–8.
4 Ruzicka T, Lynde CW, Jemec GBE *et al*. Efficacy and safety of oral alitretinoin (9-cis retinoic acid) in patients with severe chronic hand eczema refractory to topical corticosteroids: results of a randomized, double-blind, placebo-controlled, multicentre trial. *Br J Dermatol* 2008; **158**: 808–17.
5 Menné T, Maibach HI. *Hand Eczema*, 2nd edn. Boca Raton: CRC Press, 2000: 165–8.

Patchy vesiculosquamous eczema

In a large group of cases, a mixture of irregular, patchy, vesiculosquamous lesions occur on both hands, usually asymmetrically. In contrast to the lesions of discoid hand eczema, the degree of activity and distribution of the lesions vary, appearing now at one site, now at another. Nail changes are common if the nail folds are affected.

Pompholyx

Synonyms
- Vesicular eczema of palms and soles
- Dyshidrotic eczema

Definition and nomenclature. Pompholyx is a form of eczema of the palms and soles, in which oedema fluid accumulates to form visible vesicles or bullae. Because of the thick epidermis in these sites, the blisters tend to become larger than in other body areas before they burst. When pompholyx occurs on the palms, it may be called cheiropompholyx, and when on the soles, podopompholyx. The alternative name, dyshidrotic eczema, refers to a sup-

posed connection with sweat-gland activity, as the condition is worse in hot weather. However, most authors feel that this term should be abandoned, as no causal relationship with the sweat glands or sweating has been demonstrated.

Incidence. Few figures are available, but pompholyx probably accounts for about 5–20% of all cases of hand eczema [1,2].

Aetiology. The cause remains obscure. In most cases no exogenous cause is found. Monozygotic twins have been affected simultaneously [3], suggesting that hereditary predisposition may be important, but in a study of nickel allergy in twins, only one pair out of 14 was concordant with pompholyx. In seven other pairs, pompholyx occurred only in the nickel-sensitive twin [4].

The role of the sweat glands has been disputed. Although the distribution of the lesions corresponds to that of emotionally activated palmoplantar sweating and the condition is worse in hot weather, hyperhidrosis is by no means a constant feature. Indeed, eczematous changes have been both induced and relieved by sympathectomy reducing hyperhidrosis [5,6]. A thorough examination of serial sections of pompholyx vesicles [7] showed that sweat ducts were often pushed aside by the tense vesicles or passed between them. The contents and pH of the vesicular fluid suggested that vesicles ruptured the sweat ducts rather than the reverse. In one study, biofeedback training aimed at reducing sweating produced slight improvement [8].

The role of atopy is also difficult to assess, partly because of the paucity of controlled studies [9]. In one study, a family or personal history of atopy was obtained in 54 out of 131 patients with pompholyx [10]. Lodi *et al.* [11] found personal and family atopy in 50% of their patients with pompholyx compared with 12% of control patients, but other studies have found no correlation between atopy and pompholyx [12,13]. Schwanitz [9] reviewed the evidence relating to the causes of pompholyx in some detail, and concluded that atopy is probably the most important factor and the role of dyshidrosis has been overemphasized in the past.

Primary irritants can cause pompholyx, for example in metal workers exposed to soluble oils [12].

Direct-contact allergens may sometimes evoke a palmar vesicular reaction instead of the more common dorsal pattern [14]. Responsible allergens include primin, isopropyl paraphenylenediamine, benzoisothiazolones and dichromates [15]. Perfumes, fragrances and balsam ingredients must also be considered as potential allergens [16]. Patch tests of nickel sulphate applied to the palms or fingers of nickel-sensitive subjects may produce a vesicular pompholyx-like reaction, but contact sensitivities found on patch testing may be secondary phenomena [17].

The role of ingested metals in provoking exacerbations of vesicular palmar hand eczema has been studied. Some authors [17–20] found that many nickel-sensitive patients have this pattern of hand eczema, and produced flares by giving oral nickel sulphate—although usually in doses far greater than the natural daily intake. Others have been unable to confirm this [21,22]. Chromium and cobalt allergy may also occasionally be implicated [16,23]. Oral neomycin provoked pompholyx in three of 10 neomycin-sensitive patients with leg ulcers [24].

Other haptens may give rise to pompholyx. These are difficult to detect, but a careful history, supplemented by 'feed-back' tests may occasionally pinpoint an offending allergen. Patch tests, although producing a low yield of positive results, should be performed in all cases of pompholyx.

Fungal infection elsewhere on the body, usually the feet, can provoke eczema of the palms. In the past this pompholyx *dermatophytide* [16] was diagnosed more frequently than it is now, and it has been regarded as a rare association in other studies [15,25]. Confirmation depends on disappearance of the pompholyx when the focus is treated and its relapse if fungus recurs. It is necessary, of course, to prove the presence of the fungus—coexistence of pompholyx on the hands and feet is not uncommon.

Irritant or allergic dermatitis resulting from treatment of a fungal infection of the foot may also precipitate a palmar pompholyx. Primary allergic contact dermatitis of the feet, for example from rubber shoe chemicals, may induce a sympathetic palmar eruption.

The role of *bacterial foci* cannot be dismissed. Some reported cases may have been examples of a true pustular bacteride affecting the palms or soles.

The role of *stress* is, as usual, difficult to define. In some patients, recurrences can convincingly be related to stressful episodes, but in many others there is no such correlation. It has been suggested that patients with pompholyx are unduly susceptible to stress, but it should be remembered that pompholyx itself causes stress, particularly if there are financial problems due to loss of work.

Pompholyx may rarely follow a *drug eruption*. Aspirin ingestion, oral contraceptives and cigarette smoking also increase the risk of pompholyx [13].

Histopathology. The early features have not been sufficiently well studied. Fully formed lesions show the changes of acute eczema modified by the thick, overlying epidermis. The subsequent course is that of a subsiding eczema, with hyperkeratosis and epidermal shedding.

Clinical features (Fig. 23.13). Pompholyx may occur at any age, but it is more common before the age of 40 years. Onset before 10 years is unusual. An attack of pompholyx is characterized by the sudden onset of crops of clear vesicles, which appear deeply seated and 'sago-like'. There is no erythema, but a sensation of heat and prickling of the palms may precede attacks. Vesicles may become confluent and present as large bullae, especially on the feet. Itching may be severe, preceding the eruption of vesicles. The attack subsides spontaneously, and resolution with desquamation occurs in 2–3 weeks in most cases, but recurrent attacks in this period may cause a wave-like continuation of symptoms in a minority of cases. In mild cases, only the sides of the fingers may be affected, but in a typical case the vesicles develop symmetrically on the palms and/or soles. Unilateral or asymmetrical patterns occur, but this should alert the dermatologist to look for contact causes of the eruption. In 80% of patients only the hands are involved. The hands and feet, and the feet alone each account for about 10% of patients. Secondary infection with pustule formation and lymphangitis is not uncommon, and may complicate each attack in certain patients. Rubbing and inappropriate treatment



Fig. 23.13 Pompholyx, showing confluent vesicles of the palm.

may produce secondary eczematous changes extending beyond the volar surfaces. After recurrent attacks spreading to the dorsa of the fingers, the nails may develop dystrophic changes, irregular transverse ridging and pitting, thickening and discoloration. Such changes may follow even mild attacks, and may be the patient's presenting complaint.

In cases in which no cause can be demonstrated (i.e. the majority) recurrences are usual. They may occur at intervals of 3 or 4 weeks for months or years, or at long irregular intervals. Pompholyx is more common in warm weather, and in some patients attacks occur annually each summer.

Diagnosis. There is some debate whether the term pompholyx should be reserved for typical cases in which the attacks resolve and recur. Chronic, recurrent vesiculation without periods of remission may be termed chronic vesicular dermatitis.

A circumscribed and asymmetrical area of scaling and vesiculation of the palm or sole should suggest the possibility of dermatophytosis, and scrapings should be examined for fungus. If the erythema is limited to one or two interdigital clefts, or is asymmetrical, or involves the dorsal skin to any extent, the possibility of a contact dermatitis must be considered, and excluded by a careful history and by patch testing. In pustular psoriasis of the palms and soles there are usually no clear vesicles, although this is not invariably so [26]. The pustules are sterile on culture, and leave characteristic brown marks as they resolve. Occasionally, secondary bacterial infection of pompholyx may occur, with pustule formation, but in these cases the lesions tend to be painful, with surrounding erythema, and culture of the pus yields the causative organism. A pustular bacteride secondary to bacterial infection elsewhere in the body may also lead to confusion.

Repeated attacks of pompholyx may produce hyperkeratotic lesions that mimic psoriasis vulgaris.

Pemphigoid, linear IgA disease and pemphigoid gestationis occasionally present with blisters on the palms that mimic pompholyx [27,28].

Treatment. Any obvious cause of the eruption should be eliminated, but in most cases one will have to rely on non-specific measures. In the acute phase, rest and bland applications are indicated. Involvement of the feet may require the patient to be treated in bed. The hands or feet should be soaked three or four times a day in either Burow's solution (aluminium acetate 1%) or potassium permanganate solution (diluted 1:8000). Large bullae may be aspirated using a sterile syringe. Systemic antibiotics will be required if secondary bacterial infection develops. This is most likely to be staphylococcal, and flucloxacillin is usually effective.

As the eruption subsides the soaks should be discontinued, and zinc cream or oily calamine lotion can be substituted. Topical steroids are useful in the subacute and chronic phases. In a few severe cases, a course of oral steroids may be justified.

For chronic pompholyx which has entered the hyperkeratotic phase, tar preparations such as 2–5% crude coal tar may be used, or a steroid preparation may be combined with a coal-tar solution. Low-dose methotrexate and radiation therapy have both been used with success in refractory cases [29–30].

References

1 Agrup G. Hand eczema and other dermatoses in southern Sweden. *Acta Derm Venereol (Stockh)* 1969; **49** (Suppl. 61).
2 Meding B, Swanbeck G. Epidemiology of different types of hand eczema in an industrial city. *Acta Derm Venereol (Stockh)* 1989; **69**: 227–33.
3 Lorincz AL, Grauer FH. Simultaneous dyshidrosis in monozygotic twins during their separation. *Arch Dermatol* 1956; **74**: 245–52.
4 Menné T, Holm NV. Nickel allergy in a female twin population. *Int J Dermatol* 1983; **22**: 22–8.
5 Hofbauer GF, Nestle FO. Irritant contact dermatitis of the hands following thoracic sympathectomy. *Contact Dermatitis* 2000; **42**: 119–20.
6 Chowdrey MM, Hedges R, Lanigan SW. Unilateral resolution of palmar eczema and hyperhidrosis complicated by Horner's syndrome following ipsilateral endoscopic cervical sympathectomy. *Br J Dermatol* 2000; **143**: 653–4.
7 Simons RDGP, ed. *Eczema of the Hands*, 2nd edn. Basel: Karger, 1966.
8 Miller RM, Coger RW. Skin conductance conditioning with dyshidrotic eczema patients. *Br J Dermatol* 1979; **101**: 435–40.
9 Schwanitz HJ, ed. *Atopic Palmoplantar Eczema*. Berlin: Springer-Verlag, 1988.
10 Oddoze L, Témime P. Dyshidrosis and atopy. *Bull Soc Fr Dermatol Syphiligr* 1968; **75**: 378.
11 Lodi A, Betti R, Chianelli G *et al*. Epidemiological, clinical and allergological observations on pompholyx. *Contact Dermatitis* 1992; **26**: 17–21.
12 de Boer EM, Bruynzeel DP, Van Ketel WG. Dyshidrotic eczema as an occupational dermatitis in metal workers. *Contact Dermatitis* 1988; **19**: 184–8.
13 Edman B. Palmar eczema: a pathogenic role for acetylsalicylic acid, contraceptives and smoking? *Acta Derm Venereol (Stockh)* 1988; **68**: 402–7.
14 Lehucher-Michel MP, Koeppel MC, Lanteaume A, Sayag J. Dyshidrotic eczema and occupation: a descriptive study. *Contact Dermatitis* 2000; **43**: 200–5.
15 Meneghini CL, Angelini G. Contact and microbial allergy in pompholyx. *Contact Dermatitis* 1974; **5**: 46.
16 Menné T, Hjorth N. Pompholyx-dyshidrotic eczema. *Semin Dermatol* 1983; **2**: 75–80.
17 Christensen OB, Möller H. Nickel allergy and hand eczema. *Contact Dermatitis* 1975; **1**: 129–35.
18 Christensen OB, Möller H. External and internal exposure to antigen in hand eczema of nickel allergy. *Contact Dermatitis* 1975; **1**: 136–42.
19 Cronin E. Oral challenge in nickel hypersensitive women with hand eczema. In: Brown SS, Sunderman FW Jr, eds. *Nickel Toxicology*. New York: Academic Press, 1980: 149–55.
20 Kaaber K, Veien NK, Tjell JC. Low nickel diet in the treatment of patients with chronic nickel dermatitis. *Br J Dermatol* 1978; **98**: 197–201.
21 Burrows D, Creswell S, Merrett JD. Nickel, hands and hip prostheses. *Br J Dermatol* 1981; **105**: 437–44.
22 Jordan WP, King SE. Nickel feeding in nickel-sensitive patients with hand eczema. *J Am Acad Dermatol* 1979; **1**: 506–8.

23 Kaaber K, Veien NK. Antabuse treatment of nickel dermatitis: chelation—a new principle in the treatment of nickel dermatitis. *Contact Dermatitis* 1979; **5**: 221–8.
24 Ekelund AG, Möller H. Oral provocation in eczematous contact allergy to neomycin and hydroxyquinolones. *Acta Derm Venereol (Stockh)* 1969; **49**: 422–6.
25 Tagami H, Watanabe S, Ofuji S. *Trichophyton* contact sensitivity in patients with dermatophytosis. *Arch Dermatol* 1977; **113**: 1409–14.
26 Uehara M. Pustulosis palmaris et plantaris. Evolutionary sequence from vesicular to pustular lesions. *Semin Dermatol* 1983; **2**: 51–6.
27 Barth JH, Venning VA, Wojnarowska F. Palmoplantar involvement in autoimmune blistering disorders: pemphigoid, linear IgA disease, and herpes gestationis. *Clin Exp Dermatol* 1988; **13**: 85–6.
28 Duhra P, Ryatt KS. Haemorrhagic pompholyx in bullous pemphigoid. *Clin Exp Dermatol* 1988; **13**: 342–3.
29 Egan CA, Rallis TM, Meadows KP, Krueger GG. Low dose oral methotrexate treatment for recalcitrant palmoplantar pompholyx. *J Am Acad Dermatol* 1999; **40**: 612–4.
30 Stambaugh MD, DeNittis AS, Wallner PE, Heymann WR. Complete remission of refractory dyshidrotic eczema with the use of radiation therapy. *Cutis* 2000; **65**: 211–4.

Recurrent focal palmar peeling

Synonyms
- Desquamation en aires
- Keratolysis exfoliativa
- Ringed keratolysis of the palms

The condition is sometimes a mild form of pompholyx. During the summer months, small areas of superficial, white desquamation develop on the sides of the fingers and on the palms or on the feet (Fig. 23.14). They appear abruptly, and expand before peeling off. There is little or no irritation, and vesicles as such are not seen. The condition is probably not rare, but because it is relatively asymptomatic it often does not reach the dermatologist. Some patients subsequently develop true pompholyx.

The differential diagnosis includes the generalized peeling skin syndromes discussed in Chapter 19.

Ring eczema

This characteristic pattern particularly affects young women, rarely men. The condition usually starts soon after marriage or childbirth. An irritable patch of eczema begins under a ring—usually a broad wedding ring—and typically spreads to involve the adjacent side of the middle finger and the adjacent area of the palm. It may remain confined to these sites, but is occasionally followed by the appearance of discoid patches elsewhere; or a more diffuse vesicular eczema may develop. Despite the clearly defined demarcation of the initial eruption, these patients cannot be shown to be sensitive to gold or copper although, curiously, nickel, cobalt and even chromium sensitivity are more commonly found on patch testing than might be expected; only rarely can 'white gold' alloys be implicated. Ring dermatitis has been described as the clinical presentation of fragrance sensitization [1]. Transference of the ring to the other hand is often rapidly followed by the appearance of eczema at the new site and, once affected, patients may aver that wearing of the ring for only a few minutes, even without washing, causes irritation. This type of hand eczema is probably due primarily to concentrations of soap and detergent beneath rings (which may tighten on fingers immersed in hot water), but microtrauma, especially friction, may also play a role.

Very rarely, radioactive gold in a ring may cause radiation dermatitis which mimics this type of wedding ring eczema [2].


(a) (b)

Fig. 23.14 Recurrent focal palmar peeling. Well-established lesions on: (a) hands (courtesy of Dr A. Marsden, St George's Hospital, London, UK) and (b) feet.

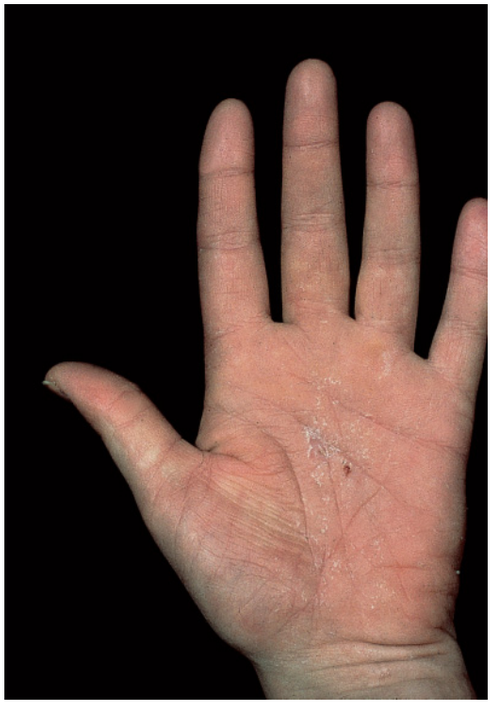


Fig. 23.15 Dry palmar eczema.

References

1 Cordoba S, Sanchez-Perez J, Garcia-Diez A. Ring dermatitis as a clinical presentation of fragrance sensitization. *Contact Dermatitis* 2000; **42**: 242.

2 Gerwig T, Winer MN. Radioactive jewelry as a cause of cutaneous tumor. *JAMA* 1968; **205**: 595–6.

'Wear and tear' dermatitis

Synonyms
- Asteatotic hand eczema
- Housewives' dermatitis
- Dry palmar eczema
- Dermatitis palmaris sicca

This pattern of exogenous dermatitis affects housewives and cleaners who frequently immerse their hands in water and detergents, and is presumably due to a combination of asteatosis, exposure to mild irritants such as soaps and detergents, and mild trauma, for example from wringing out dishcloths. The skin feels dry, it becomes criss-crossed with superficial cracks associated with a damaged horny layer, and it is unable to respond with its normal pliability to hand and finger movement (Fig. 23.15). These cracks often stand out white against an erythematous background. In addition to palmar involvement there may be dryness and chapping of the skin over the dorsa of the knuckle joints. The condition may also be associated with fingertip eczema (Fig. 23.16) or with ring dermatitis.

Some patients with juvenile plantar dermatosis also have hand involvement, and some patients have the distinctive palmar dermatitis alone. This is a dry, glazed, erythematous, fissured and only mildly pruritic condition, which has been called dermatitis palmaris sicca [1]. Exudation and weeping do not occur in this condition. There seems to be little or no clear morphological distinction between this condition and 'wear and tear' dermatitis.



Fig. 23.16 Fingertip eczema in a patient with wear and tear eczema. (Courtesy of Dr D.A. Burns, Leicester Royal Infirmary, Leicester, UK.)

Reference

1 Lim KB, Tan T, Rajan VS. Dermatitis palmaris sicca—a distinctive pattern of hand dermatitis. *Clin Exp Dermatol* 1986; **11**: 553–9.

The above list by no means exhausts the possible morphological patterns of hand eczema. Some patients, for example, have dry, scaly eczema confined to a small area on the thenar or hypothenar eminence, and this is almost always endogenous. Others may have vesicular eczema confined to the edge of the hand in a very persistent form, and so on.

Differential diagnosis. The diagnosis of hand eczema is usually self-evident, but the distinction from psoriasis can be very difficult. Most experienced dermatologists have seen cases they have confidently labelled as hand eczema, which have later developed typical psoriasis in other areas [1]. In some cases even biopsy does not allow a clear distinction to be made. In most cases of psoriasis on the hands, however, the silvery nature of the scale, involvement of the knuckles, sharply demarcated 'scalloped' edges to the erythema along the borders of the hands and fingers, and the relative absence of pruritus, are helpful pointers. A family history of psoriasis and the presence of nail pits in the absence of nail-fold lesions are also suggestive.

Tinea can also be missed, especially when it is extensive and irritable (Fig. 23.17), or secondarily infected. Unilateral scaling of the palm should always suggest a possible *Trichophyton* infection, and a discoid plaque due to *T. verrucosum* is sometimes seen in farmers.

The special characteristics of palmar pustulosis are usually evident. Lichen planus (Fig. 23.18) and pityriasis rubra pilaris may resemble eczema on the hands, but usually present with typical lesions at other sites.

It must be emphasized that the whole skin should be examined in any case of hand eczema in which the diagnosis is in doubt. There may, for example, be evidence of nickel allergy or tinea pedis, or small patches of psoriasis of which the patient is unaware.



Fig. 23.17 *Trichophyton* infection of the hands, which had failed to respond to topical steroids. Note the nail involvement.



Fig. 23.18 Lichen planus mimicking hyperkeratotic hand eczema, but the margins are well demarcated, and the lesions on the left wrist are characteristic of lichen planus.

Prognosis. Unless a responsible allergen can be identified and removed, the prognosis of hand eczema is always uncertain. Some allergens, such as nickel, rubber, chemicals and fragrances, are ubiquitous, however, and complete avoidance in the home environment is difficult to achieve [2–5]. In general, eczema on the dorsa of the hands clears more readily, and is less likely to recur than palmar eczema. Acute attacks of pompholyx will usually settle down and in one-third of the cases will not recur. In another third, recurrences will take place, and in the remainder the condition will pass into a chronic, possibly hyperkeratotic stage. Those forms of hand eczema that are due in part or wholly to the effects of irritants carry a particularly poor prognosis unless these irritants can be completely removed. Interdigital dermatitis has been shown to be a potential precursor to more severe hand dermatitis in hairdressers. Recognition of this sign by the patient may allow early intervention to prevent progression of the disease [6].

A prolonged period of rest for the skin is usually necessary for complete restoration of the protective function of the stratum corneum [7]. Patients who have suffered from severe hand eczema will often remain vulnerable to mild irritants for several months after the eczema has apparently cleared.

There are few figures available for assessing the prognosis of non-occupational hand eczema. Many patients learn to 'live with' their condition, and cease to attend doctors—a poor reflection of our capabilities in this field. The prognosis is worse in patients with atopic eczema [8,9].

In one study, one-quarter of patients were symptom-free, and a further half had improved after a follow-up period of 6–22 months [10]. In a longer follow-up of 213 cases, less than one-third had entered complete remission [11]. Change of occupation did not affect the prognosis.

The behaviour of hand eczema in pregnancy is variable.

Treatment. Treatment of *acute* hand eczema is as for pompholyx (p. 23.18). For *chronic* eczema particular attention must be paid to possible causative factors, and a full occupational and social history, with details of hobbies and spare time activities, is essential. Patients must be asked exactly what their job involves, and how they protect their hands. Patch tests are advisable (Chapter 26).

The same general principles of treatment apply as for chronic eczema on other parts of the body (p. 23.38). The three most useful measures are:

1 Avoidance of irritants
2 Frequent application of emollients
3 Topical steroids.

Avoidance of irritants is particularly difficult for patients with hand eczema, as irritants are so ubiquitous. Education of the patient to the possible dangers is of paramount importance, and printed advice sheets are useful, as patients often have a poor recollection of oral instructions. Examples of suitable instruction sheets have been provided by Epstein [12].

Cleanliness is important, but too much soap and water can be harmful. A wide variety of soap substitutes are now available. Older remedies, such as a tablespoon of emulsifying ointment mixed in a cup of hot water, are often helpful. Very brief exposure to soap followed by immediate application of a topical lipid is unlikely to be harmful, and may be beneficial by removing bacteria and debris [13].

Barrier creams are usually ineffective for hand eczema of occupational origin, although new products are frequently being reported as showing some promise [14,15]. In practice they may not be applied effectively [16], and the debate continues about their actual benefit [17]. Gloves usually provide the best protection, and time should be spent discussing with the patient the details of the material, size and weight of the gloves to be used, so that they can be tailored to the individual's particular need.

Gloves with holes in them may be worse than no gloves at all, but gloves that are too thick may make it impossible to perform a particular task. It should also be remembered that some allergens, such as acrylates and epoxy resins, can penetrate vinyl or rubber gloves [18]. Rubber gloves generally give good protection for housework. In patients with rubber allergy, polyvinyl chloride household gloves should be worn instead. If sweating makes the condition worse, it may be helpful to wear cotton gloves beneath the protective gloves. Gloves should also be used for dry work, to prevent soiling and trauma, especially for gardening in cold, dry air. Thin leather is usually better than cotton for this purpose.

Emollients should be applied frequently as a thin smear rubbed gently into the skin, and several jars should be left at convenient locations near sinks, etc., so that they are readily available. The choice of emollient will vary with the patient. Some people will benefit from a greasy preparation such as emulsifying ointment, and others will prefer a more cosmetically acceptable cream such as aqueous cream, which sinks into the skin more readily, and is less likely to stain paper, etc. Numerous commercial preparations are now available. Patients should be warned that some topical preparations sold over the counter by pharmacists as antipruritics or emollients can contain irritants such as alcohol or propylene glycol, and they should use only what the dermatologist recommends.

Topical steroids are used in all but the mildest cases, but as always they should be used sparingly, and in the weakest potency that is effective. Hydrocortisone in a concentration of 1% is perfectly safe, but stronger steroids will often be required and these can cause atrophy. Even though the palms are thick, the epidermis can be rendered thin and fragile by potent topical steroids. This is not a major problem in hyperkeratotic eczema, but in these cases steroids are relatively ineffective. If bacterial infection is present, a systemic antibiotic may be needed, and the use of a combined steroid–antiseptic or antibiotic preparation may help to lessen the risk of infection and improve the response. The risk of bacterial overgrowth due to steroids, however, is probably less than one might expect. It has been shown that a potent steroid used alone can reduce or even eliminate *Staphylococcus aureus* colonization in hand eczema [19].

In difficult, unresponsive cases the use of a potent steroid under occlusion may be considered. The steroid is applied at bedtime, and polythene gloves are worn overnight, sealed at the wrist with sticky tape. This is an effective treatment, but it greatly increases the risk of atrophy and secondary bacterial infection, and should be discontinued as soon as the eczema shows satisfactory improvement.

If hand eczema does not respond to topical steroid therapy, the diagnosis should be reviewed, particularly with regard to the possibility of tinea. The patient should be quizzed again about exposure to irritants or allergens, and the possibility of sensitization to medicament bases or preservatives or even the corticosteroid itself should also be considered, with patch tests if necessary.

After improvement of the dermatitis with daily corticosteroid use, the intermittent use of a potent corticosteroid cream may safely prevent relapse [20].

Intradermal injection of triamcinolone (10 mg/ml) into recalcitrant, localized patches of hand eczema has been found helpful [12].

Topical immunosuppressants provide a further option for treating hand eczema. In a left/right comparative trial with 16 subjects, topical tacrolimus 0.1% proved similar in efficacy to mometasone furoate [21]. The response to tacrolimus was better on palms than soles.

Other measures: tar pastes are often useful for chronic unresponsive cases. Generally speaking, the messier preparations such as 5% crude coal tar tend to be more effective than the cosmetically more pleasant preparations.

Salicylic acid ointment is also sometimes helpful for hyperkeratosis and persistent scaling [22]. Various combinations of tar, steroids and salicylic acid may be tried, and Baden [23] has recommended the application of a keratolytic gel of salicylic acid and propylene glycol under occlusion for 2–4 h before the application of steroid ointments at night.

Oral psoralen phototherapy (PUVA) and UVB therapy have proved useful for several types of hand eczema, including allergic contact dermatitis, dyshidrotic eczema and hyperkeratotic palmar eczema [3,24–30]. Topical hand PUVA soaks have also been shown to be effective and safe, although patient compliance is crucial to the treatment's success [31]. A PUVA-cream approach may be more useful [32].

Radiotherapy is also effective for stubborn hand eczema. Grenz rays were widely used in the past, as these were thought to be safer than X-rays. Fairris *et al*. [33] have shown that superficial X-rays give a better result, and they advise that patients can safely receive three courses of 300 Rad (3 Gy) of superficial X-ray therapy during a lifetime.

Alitretinoin (9-cis-retinoic acid) is a retinoid which interacts with both RXR and RAR receptors. It has been shown to improve chronic hand eczema in a large placebo-controlled trial with over 1000 subjects [34]. These included patients with any morphology of hand eczema. Although patients with pompholyx improved as well as those with hyperkeratotic eczema, it remains unclear whether this drug is working as an anti-inflammatory agent or just by reducing hyperkeratosis. The side effect profile of alitretinoin is that of an RXR agonist (rexinoid). Reduction in thyroid hormone and TSH levels may occur. Cholesterol and triglyceride levels are raised. The mucocutaneous side effects associated with RAR agonists such as acitretin are much less pronounced. Acitretin and etretinate can be effective for hyperkeratotic eczema, but there is a high incidence of side effects [35]. It is probable that retinoids may work synergistically with topical therapies, as reduction of hyperkeratosis may enhance penetration. Combining retinoids with PUVA may also prove useful.

Ciclosporin has been reported to be useful in recalcitrant cases of chronic vesicular hand eczema and appears to be equivalent in efficacy to a potent topical corticosteroid, although side effects may be a concern [36,37].

Ranitidine was shown to have adjuvant benefits to topical steroid treatment of atopic hand dermatitis, without any side effects [38].

Painful fissures of the fingertips are a particular therapeutic problem. The main requirement is to keep the keratin as pliable as possible, by the use of greasy preparations, and it often helps to use polythene occlusion at night, with thin leather gloves during the day. Once formed, fissures are slow to heal, but they can some-

times be rendered painless by sealing them with a product such as compound benzoin tincture. Recurrent infection of fissured hand eczema can give rise to lymphoedema and long-term, low-dose antibiotic prophylaxis with penicillin may be required [39].

In indolent cases in which metal allergy of dietary origin is thought to be playing a part [40], the use of an oral chelating agent may be considered. Disulfiram 200 mg daily for 8 weeks produced a good result in an open study, but this treatment carries the risk of liver dysfunction [41].

References

1 Maibach HI, Epstein E. Eczematous psoriasis. *Semin Dermatol* 1983; **2**: 45–50.
2 Fregert S, Hjorth N. Epidemiology of contact dermatitis. *Trans St John's Hosp Dermatol Soc* 1969; **55**: 17–35.
3 Menné T, Holm NV. Nickel allergy and hand dermatitis in a stratified sample of the Danish female population. *Acta Derm Venereol (Stockh)* 1982; **62**: 35–41.
4 Wilkinson DS. The role of contact allergy in hand eczema. *Trans St John's Hosp Dermatol Soc* 1970; **56**: 19–21.
5 Wilkinson DS. Contact dermatitis of the hands. *Trans St John's Hosp Dermatol Soc* 1972; **58**: 163–72.
6 Schwanitz HJ, Uter W. Interdigital dermatitis: sentinel skin damage in hair dressers. *Br J Dermatol* 2000; **142**: 1011–2.
7 Malten KE. Thoughts on irritant contact dermatitis. *Contact Dermatitis* 1981; **7**: 238–47.
8 Lammintausta K, Kalimo K. Atopy and hand dermatitis in hospital wet work. *Contact Dermatitis* 1981; **7**: 301.
9 Meding B, Swanbeck G. Epidemiology of different types of hand eczema in an industrial city. *Acta Derm Venereol (Stockh)* 1989; **69**: 227–33.
10 Agrup G. Hand eczema and other hand dermatoses in South Sweden. *Acta Derm Venereol (Stockh)* 1969; **49** (Suppl. 61).
11 Keczkes K, Bhate SM, Wyatt EH. The outcome of primary hand dermatitis. *Br J Dermatol* 1983; **109**: 665–9.
12 Epstein E. Hand dermatitis: practical management and current concepts. *J Am Acad Dermatol* 1984; **10**: 395–424.
13 Uehara M, Takada K. Use of soap in the management of atopic dermatitis. *Clin Exp Dermatol* 1985; **10**: 419–25.
14 McCormick RD, Buchman TL, Maki DG. Double-blind, randomised trial of scheduled use of a novel barrier cream and an oil-containing lotion for the protection of the hands of health care workers. *Am J Infection Control* 2000; **28**: 302–10.
15 Fowler JF Jr. A skin moisturising cream containing Quaternium-18-Bentonite effectively improves chronic hand dermatitis. *J Cutan Med Surg* 2001; **5**: 201–5.
16 Wigger-Alberti W, Maraffio B, Wernli M, Elsner P. Self-application of a protective cream. Pitfalls of occupational skin protection. *Arch Dermatol* 1997; **133**: 861–4.
17 Wigger-Alberti W, Elsner P. Do barrier creams and gloves prevent or provoke contact dermatitis. *Am J Contact Dermatitis* 1998; **9**: 100–6.
18 Mourisden HIT, Faber O. Penetration of protective gloves by allergens and irritants. *Trans St John's Hosp Dermatol Soc* 1973; **57**: 230.
19 Nilsson E. Density of the microflora in hand eczema before and after topical treatment with a potent corticosteroid. *J Am Acad Dermatol* 1986; **15**: 192–7.
20 Veien NK, Olholm Larsen P, Thestrup-Pederson K, Schou G. Long term intermittent treatment of chronic hand eczema with mometasone furoate. *Br J Dermatol* 1999; **140**: 882–6.
21 Schnopp C, Remling R, Mohrenschlager M *et al*. Topical tacrolimus (FK506) and mometasone furoate in treatment of dyshidrotic palmar eczema: a randomized, observer-blinded trial. *J Am Acad Dermatol* 2002; **46**: 73–7.
22 Hersle K, Mobacken H. Hyperkeratotic dermatitis of the palms. *Br J Dermatol* 1982; **107**: 145–202.
23 Baden HP. Treatment of hyperkeratotic dermatitis of the palms. Sequential treatment with a keratolytic gel and corticosteroid ointment. *Arch Dermatol* 1974; **110**: 737–8.
24 Bruynzeel DP. Oral psoralen photochemotherapy of allergic contact dermatitis of the hands. *Dermatosen* 1982; **30**: 16–20.
25 Le Vine MJ, Parrish JA, Fitzpatrick TB. Oral methoxalen photochemotherapy (PUVA) of dyshidrotic eczema. *Acta Derm Venereol (Stockh)* 1981; **61**: 570–1.
26 Mobacken H, Rosen K, Swanbeck G. Oral psoralen photochemotherapy (PUVA) of hyperkeratotic dermatitis of the palms. *Br J Dermatol* 1983; **109**: 205–8.
27 Morison WL, Parish JA, Fitzpatrick TB. Oral methoxalen photochemotherapy of recalcitrant dermatoses of the palms and soles. *Br J Dermatol* 1978; **99**: 297–302.
28 Mork N-J, Austad J. Short wave ultraviolet light (UVB) treatment of allergic contact dermatitis of the hands. *Acta Derm Venereol (Stockh)* 1983; **63**: 87–9.
29 Rosen K, Mobacken H, Swanbeck G. Chronic eczematous dermatitis of the hands; a comparison of PUVA and UVB treatment. *Acta Derm Venereol (Stockh)* 1987; **67**: 48–54.
30 Tegner E. PUVA treatment of chronic eczematous dermatitis of the palms and soles. *Acta Derm Venereol (Stockh)* 1985; **65**: 451–3.
31 Taylor CR, Baron ED. Hand and foot PUVA soaks: an audit of the Massachusetts General Hospital's experience from 1994 to 1998. *Photodermatol Photoimmunol Photomed* 1999; **15**: 188–92.
32 Grundmann-Kollmann M, Behrens S, Peter RU, Kerscher M. Treatment of severe recalcitrant dermatoses of the palms and soles with PUVA-bath versus PUVA-cream therapy. *Photodermatol Photoimmunol Photomed* 1999; **15**: 87–9.
33 Fairris GM, Jones DH, Mack PD *et al*. Conventional superficial X-ray versus Grenz ray therapy in the treatment of constitutional eczema of the hands. *Br J Dermatol* 1985; **112**: 339–41.
34 Ruzicka T, Lynde CW, Jemec GBE *et al*. Efficacy and safety of oral alitretinoin (9-*cis* retinoic acid) in patients with severe chronic hand eczema refractory to topical corticosteroids: results of a randomized, double-blind, placebo-controlled, multi-centre trial. *Br J Dermatol* 2008; **158**: 808–17.
35 Reymann F. Two years experience with Tigason treatment of pustulosis palmoplantaris and eczema keratoticum manuum. *Dermatologica* 1982; **164**: 209–16.
36 Peterson CS, Menné T. Cyclosporin A responsive chronic vesicular hand eczema. *Acta Derm Venereol (Stockh)* 1992; **72**: 436–7.
37 Granlund H, Erkko P, Reitamo S. Comparison of the influence of cyclosporine and topical betamethasone-17, 21-dipropionate treatment on quality of life in chronic hand eczema. *Act Derm Venereol (Stockh)* 1997; **77**: 54–8.
38 Veien NK, Kaaber K, Larsen PO *et al*. Ranitidine treatment of hand eczema in patients with atopic dermatitis: a double-blind placebo-controlled trial. *J Am Acad Dermatol* 1995; **32**: 1056–7.
39 Proske S, Uter W, Schwanitz HJ. Lymphedema of the hand following recurrent erysipelas secondary to fissured irritant contact dermatitis. *Contact Dermatitis* 2000; **42**: 368–9.
40 Christensen OB, Möller H. External and internal exposure to the antigen in the hand eczema of nickel allergy. *Contact Dermatitis* 1975; **1**: 136–41.
41 Christensen OB, Kristensen M. Treatment with disulfiram in chronic nickel hand dermatitis. *Contact Dermatitis* 1982; **8**: 59–63.

Infective dermatitis

Synonym
- Microbial eczema

Definition. Infective eczema (Fig. 23.19) is eczema that is caused by microorganisms or their products, and that clears when the organisms are eradicated. This should be distinguished from infected eczema (Fig. 23.20) in which eczema due to some other cause is complicated by secondary bacterial or viral invasion of the broken skin. In practice, however, the two conditions can coexist, and the distinction can be difficult. Moreover, the bacterial flora of an eczematous lesion differs quantitatively from that of normal skin [1], and the demonstration that organisms are present does not establish that they are modifying the lesion. The distinction between colonization and infection can be very difficult, but the presence of an increased level of C-reactive protein in the blood may offer a useful clue [2].

Infective dermatitis, therefore, is a controversial entity, and some dermatologists never make this diagnosis. Nevertheless, cases are seen occasionally in which bacterial or viral invasion of



Fig. 23.19 Infective eczema in a non-atopic man. Histology of this localized rash showed eczema, and *Staphylococcus aureus* was repeatedly isolated. There was no response to topical steroid therapy, but the condition cleared rapidly with oral flucloxacillin.



Fig. 23.20 Infected dermatitis. This man had a patch of discoid eczema which became secondarily infected with *Staphylococcus aureus*.

the skin seems to occur as the primary event, and is followed by secondary eczematization which can spread for some centimetres beyond the obvious infection. The patches of eczema that occasionally develop around lesions of molluscum contagiosum provide a good example (Fig. 23.21), because the pearly papules are the initiating event, and eczema can develop in the surrounding skin some days later, even when the lesions have not been scratched or traumatized. The eczema generally clears when the



Fig. 23.21 An area of eczematization developing around lesions of molluscum contagiosum. The skin had previously appeared normal, and it returned to normal when the molluscum infection cleared. (Courtesy of Dr D.A. Burns, Leicester Royal Infirmary, Leicester, UK.)

molluscum lesions subside. Similarly, one occasionally sees eczematous skin around infected wounds, and the eczema clears with antibiotic treatment alone.

Some experts would include seborrhoeic dermatitis as a form of infective dermatitis, on the grounds that the levels of *Malassezia* yeasts in the skin are increased, and the eczema may clear following antiyeast therapy. However, the exact role of these yeasts in the pathogenesis of seborrhoeic dermatitis is still uncertain, and some authorities do not accept seborrhoeic dermatitis as infective.

Pityriasis rosea is not usually considered to be a form of eczema, although the histology may show spongiosis (see Chapter 33).

Histopathology. The histological picture of infective eczema is in general that of subacute or chronic eczema, in which spongiosis is combined with acanthosis, hyperkeratosis and patchy parakeratosis. The dermis shows inflammatory changes, with polymorphonuclear and lymphocytic infiltration which invades the epidermis to a variable extent. In some stages, subcorneal pustulation may be conspicuous.

Pathogenesis. The mechanism by which microorganisms cause eczema is not understood. Bacterial antigens can promote a cytotoxic reaction in the skin, but such a reaction is perhaps more likely to aggravate or perpetuate than to initiate the eczematous process [3–6]. Bacterial superantigens such as staphylococcal protein A

and enterotoxin B [7] may be profound immune stimulants and may aggravate atopic dermatitis (see Chapter 24). Bacterial antigens may play this role in a variety of syndromes, including discoid eczema, and not merely in infective dermatitis. Cultured staphylococci applied topically can also provoke an eczematous delayed hypersensitivity reaction [7,8].

The possibility that bacterial antigens from systemic foci of infection may cause eczema has not been fully established. It does seem to be accepted, however, that eczematous reactions can occur as an allergic reaction to a fungal infection elsewhere in the skin (see Dermatophytide section above, p. 23.8).

Clinical features. As mentioned above, the distinction between infective and infected eczema can be difficult.

Infected eczema. Infected eczema shows erythema, exudation and crusting. The exudation may be profuse with crusting, or slight, with the accumulation of layers of somewhat greasy, moist scale, beneath which the surface is raw and red. The margin is characteristically sharply defined, and the horny layer is often split to form an encircling collarette. There may be small pustules in the advancing edge and, where a flexure is involved, it is often the site of a deep and persistent fissure.

Infective eczema. Infective eczema usually presents as an area of advancing erythema, sometimes with microvesicles. It is seen predominantly around discharging wounds or ulcers, or moist skin lesions of other types. Infective dermatitis is relatively common in patients with venous leg ulcers, but care must be taken to distinguish it from contact dermatitis due to the application of topical medicaments.

Microbial eczema of the feet is a distinctive pattern of eczema which mainly affects the interdigital spaces on the dorsum of the medial toes. Staphylococci or streptococci can be cultured, and the lesions respond to antiseptic or antibiotic therapy [9]. This condition seems to occur particularly in patients with poor standards of hygiene, and it is favoured by hyperhidrosis and heavy footwear. In children, the condition must be distinguished from juvenile plantar dermatosis.

Tinea pedis may also become eczematous due to the overgrowth of Gram-negative organisms [10]. Infective dermatitis may also complicate chronic threadworm infestation, pediculosis or scabies. It is not always clear how much of the eczematous change is due to repeated scratching, how much is due to secondary impetigo and how much, if any, is a direct response to the infestation.

Treatment. Factors predisposing to infection should be sought, and when possible eliminated. Although topical antibacterial agents are effective in mild forms of infective eczema due to bacteria, systemic antibiotics should not be withheld, especially in severe or widespread infections. In acute exudative lesions, potassium permanganate soaks are helpful for the first 2 or 3 days, in combination with a systemic antibiotic.

References

1 Nilsson E, Henning C, Hjoreitsson M-L. Density of the microflora in hand eczema before and after topical treatment with a potent corticosteroid. *J Am Acad Dermatol* 1986; **15**: 192–7.

2 Goodfield M. C-reactive protein levels in venous ulceration: an indication of infection? *J Am Acad Dermatol* 1988; **18**: 1048–52.

3 Parish WE, Welbourn E, Champion RH. Hypersensitivity to bacteria in eczema. Titre and immunoglobulin class of antibodies to staphylococci and micrococci. *Br J Dermatol* 1976; **95**: 285–93.

4 Parish WE, Welbourn E, Champion RH. Hypersensitivity to bacteria in eczema. IV: cytotoxic effect of antibacterial antibody on skin cells acquiring bacterial antigens. *Br J Dermatol* 1976; **95**: 493–506.

5 Welbourn E, Champion RH, Parish WE. Hypersensitivity to bacteria in generalized eczema. I: bacterial culture, skin tests, and immunofluorescent detection of immunoglobulins and bacterial antigens. *Br J Dermatol* 1976; **94**: 619–25.

6 Welbourn E, Champion RH, Parish WE. Hypersensitivity to bacteria in eczema. III: Arthus-like responses in bacterial antigens in the absence of specific antibody. *Br J Dermatol* 1976; **95**: 379–87.

7 Skov L, Olsen JV, Giornd R *et al*. Application of Staphylococcal enterotoxin B on normal and atopic skin induces upregulation of T cells by a superantigen-mediated mechanism. *J Allergy Clin Immunol* 2000; **105**: 820–6.

8 Rockl H. Mikrobiele Genese von Ekzemen. *Hautarzt* 1964; **15**: 398–9.

9 Weismann K, Hjorth N. Microbial eczema of the feet. *Br J Dermatol* 1982; **107**: 330–7.

10 Leyden JJ, Kligman AM. Interdigital athlete's foot. The interaction of dermatophytes and resident bacteria. *Arch Dermatol* 1978; **114**: 1466–9.

Infective dermatitis of children associated with human T-cell leukaemia virus 1 (HTLV-1) infection

Synonym

- Infective dermatitis of Jamaican children

Sweet, in 1966 [1], used the term infective dermatitis to describe a pattern of dermatitis observed in Jamaican children. Subsequently, Walshe documented the clinical features in 25 Jamaican children [2]. They included severe, exudative eczema with crusting involving the scalp, eyelid margins, perinasal skin, retroauricular areas, axillae and groins. There was a generalized, fine papular rash, a chronic nasal discharge and positive cultures for *Staphylococcus aureus* or β-haemolytic streptococci from nose and/or skin. The rash responded to oral antibiotic therapy, but relapsed on its cessation.

LaGrenade *et al*. [3], in 1990, found HTLV-1 infection in all of 14 children with this pattern of dermatitis. A later case report identified one of the children originally described by Sweet and Walshe who, 17 years later, had developed adult T-cell leukaemia [4]. Some of these children may also go on to develop tropical spastic paraparesis [5]. This pattern of dermatitis may be an important early marker of HTLV-1 infection [6].

References

1 Sweet RD. A pattern of eczema in Jamaica. *Br J Dermatol* 1966; **78**: 93–100.

2 Walshe M. Infective dermatitis in Jamaican children. *Br J Dermatol* 1967; **79**: 229–36.

3 LaGrenade L, Hanchard B, Fletcher V *et al*. Infective dermatitis of Jamaican children: a marker for HTLV-1 infection. *Lancet* 1990; **336**: 1345–7.

4 Hanchard B, LaGrenade L, Carberry C *et al*. Childhood infective dermatitis evolving into adult T-cell leukaemia after 17 years. *Lancet* 1991; **338**: 1593–4.

5 LaGrenade L. HTLV-1, infective dermatitis, and tropical spastic paraparesis. *Mol Neurobiol* 1994; **8**: 147–53.

6 LaGrenade L, Manns A, Fletcher V *et al*. Clinical pathologic and immunologic features of human T-lymphotrophic virus type-1 associated infective dermatitis in children. *Arch Dermatol* 1998; **134**: 439–44.

Juvenile plantar dermatosis

Synonyms
- Forefoot eczema
- Peridigital dermatosis
- Dermatitis plantaris sicca
- Atopic winter feet

Definition. This condition is characterized by shiny, dry, fissured dermatitis of the plantar surface of the forefoot. It occurs mainly in children aged 3–14 years.

Nomenclature. The first record of this condition appeared in 1968, and since then it has been described under a variety of names depending on the author's beliefs concerning pathogenesis and the possible association with atopy. The name 'juvenile plantar dermatosis' has the merit of making no presumptions about cause.

Aetiology [1–6]. It seems likely that changes in fashion, and the resulting changes in the composition of children's socks and shoes, may have been responsible for the emergence of this disease. In the author's experience the condition has become much less common in the UK over the last decade, suggesting that more recent changes in the composition of footwear may have proved beneficial. Waxing and waning fashions for the use of natural materials such as cotton, wool and leather, and various synthetic materials such as nylon and plastics, which are less porous, may have been responsible, although the exact pathogenesis of the disease remains uncertain [3]. This is not the whole story, for occasional cases have occurred in children wearing open leather sandals and cotton socks. Many of the affected children are keen on dancing or sports, and this suggests that friction and enhanced sweating may be playing some part.

An association with atopy has been proposed but the evidence for this is not convincing. In a controlled study, a personal or family history of eczema or other atopic illness was not more common in cases than in controls [1].

Juvenile plantar dermatosis has been seen in identical twins [7].

Histopathology [2,8]. The histology shows a mild, non-specific eczema. Blockage of sweat ducts can sometimes be identified.

Clinical features. Only occasional cases are seen in adults or infants. There is a slight preponderance of male children. The presenting features are redness and soreness on the plantar surface of the forefoot, which assumes a shiny, 'glazed' and cracked appearance (Fig. 23.22). The condition is most severe on the ball of the foot and toe pads, and tends to spare the non-weight-bearing instep. The toe clefts are normal, and this helps to distinguish the condition from tinea pedis. The symmetry of the lesions is a striking feature. Occasionally, the disease can affect the hands, resulting in sore, shiny, fissured palms or fingertips. This is more likely in atopic subjects [9].



Fig. 23.22 Juvenile plantar dermatosis, showing the characteristic glazed appearance of the forefoot skin.

Diagnosis. This is a clinical diagnosis, although skin scrapings to exclude fungus and patch tests to exclude footwear allergy may be helpful if there is any doubt. Consultation with the manufacturer of the shoes may help to identify potential allergens.

Treatment. Most cases will clear spontaneously during childhood or adolescence, but the condition may persist into adulthood [10]. Patients are usually advised to change from non-porous footwear to 100% cotton socks, and leather shoes or sandals, although the majority report that these changes in footwear do not help significantly [1,6,10,11].

In severe cases, with cracking and exudation, bed rest may be needed. A variety of topical preparations may help, including urea preparations, Lassar's paste, white soft paraffin or tar, but no single preparation is always effective [2,12,13].

References

1 Ashton RE, Griffiths WA. Juvenile plantar dermatosis—atopy or footwear? *Clin Exp Dermatol* 1986; **11**: 529–34.
2 Mackie RM. Juvenile plantar dermatosis. *Semin Dermatol* 1982; **1**: 67–75.
3 Shrank AB. Aetiology of juvenile plantar dermatosis. *Br J Dermatol* 1979; **100**: 641–6.
4 Young E. Forefoot eczema—further studies and a review. *Clin Exp Dermatol* 1986; **11**: 523–8.
5 Schultz H, Zachariae H. The Trafuril test in recurrent juvenile eczema of hands and feet. *Acta Derm Venereol (Stockh)* 1972; **52**: 398–400.
6 Graham RM, Verbov JL, Vickers CFH. Juvenile plantar dermatosis. *Clin Exp Dermatol* 1987; **12**: 468.
7 Stankler L. Juvenile plantar dermatosis in identical twins. *Br J Dermatol* 1978; **99**: 585–6.
8 Neering H, Van Dijk E. Juvenile plantar dermatosis. *Acta Derm Venereol (Stockh)* 1978; **58**: 531.
9 Lim KB, Tan T, Rajan VS. Dermatitis palmaris sicca—a distinctive pattern of hand eczema. *Clin Exp Dermatol* 1986; **11**: 553–9.
10 Jones SK, English JSC, Forsyth A *et al*. Juvenile plantar dermatosis—an eight year follow-up of 102 patients. *Clin Exp Dermatol* 1987; **12**: 5–7.
11 Kint A. Dermatitis plantaris sicca. *Dermatologica* 1982; **165**: 500–9.
12 Millard LG, Gould DG. Juvenile plantar dermatosis. *Clin Exp Dermatol* 1977; **2**: 186–7.
13 Möller H. Atopic winter feet in children. *Acta Derm Venereol (Stockh)* 1972; **52**: 401–5.

'Metabolic' eczema and eczema associated with systemic disease

Eczema associated with malabsorption

The possible interrelation of eczema and disordered intestinal absorption is not fully understood, but it seems that widespread eczema can occasionally be either the cause or the result of intestinal malabsorption [1,2].

Severe, inflammatory skin disease often seems to cause a degree of malabsorption—a condition known as dermatogenic enteropathy [1,3]. This is usually asymptomatic. The mechanism is not known, but the malabsorption improves rapidly as the skin is treated.

Many of the cases of eczema reportedly caused by malabsorption may, in reality, have been dermatitis herpetiformis as they mostly predate the establishment of modern histological and immunological criteria for this disease [4,5]. However, the response of the eczema in some cases to correction of the serum calcium suggests that there may be other mechanisms involved [6]. A case of dermatitis associated with lactose intolerance and apparently improving in response to a lactose-free diet, is also difficult to explain [7].

References

1 Shuster S, Marks J. Dermatogenic enteropathy. A new cause of steatorrhoea. *Lancet* 1965; **i**: 1367–8.
2 Wells GC. Skin disorders in relation to malabsorption. *BMJ* 1962; **ii**: 937–43.
3 Marks J, Shuster S. Small intestinal mucosal abnormalities in various skin diseases—fact or fancy. *Gut* 1970; **11**: 281.
4 Cooke WT, Peeney ALP, Hawkins CF. Symptoms, signs and diagnostic features of idiopathic steatorrhoea. *QJM* 1953; **22** (New series): 59–79.
5 Badenoch DM. Steatorrhoea in the adult. *BMJ* 1960; **ii**: 879–87.
6 Dent CE, Garretts M. Skin changes in hypocalcaemia. *Lancet* 1960; **i**: 142.
7 Grimbacher B, Peters T, Peter HH. Lactose-intolerance may induce severe chronic eczema. *Int Arch Allergy Immunol* 1997; **113**: 516–8.

Wiskott–Aldrich syndrome

This syndrome is fully described in Chapter 17.

Hypogammaglobulinaemia

A form of eczema, clinically very similar to atopic eczema, has been described in boys with hypogammaglobulinaemia [1,2].

References

1 Peterson RDA, Page AR, Good RA. Wheal and erythema allergy in patients with agammaglobulinaemia. *J Allergy* 1962; **33**: 406–11.
2 Webster AD, Wood CBS. Skin diseases in immunodeficiency. In: Verbov J, ed. *Modern Topics in Paediatric Dermatology*. London: Heinemann, 1979: 179–200.

Hyper-IgE recurrent infection syndrome

Synonym
- Job's syndrome

This rare disorder is characterized by recurrent bacterial infections of the skin, nasal sinuses and respiratory tract, commencing in early childhood, in the presence of serum levels of IgE which are around 10 times normal (greater than 2000 i.u./mL). Chronic eczema, often impetiginized, is a common feature (Chapter 17).

Pyoderma, folliculitis and atopy, with defective leukocyte and lymphocyte function

Synonym
- Jung's disease

A familial immunodeficiency disease characterized by atopic dermatitis, recurrent and persistent pyoderma and folliculitis has been described in a father and son [1]. It was accompanied by abnormalities of lymphocyte function and defective leukocyte chemiluminescence responses, which were associated with defective intracellular killing of microbial organisms. The abnormalities of lymphocyte and leukocyte function and the clinical manifestations responded dramatically to treatment with the H1 antagonist chlorpheniramine, suggesting that the underlying defect in this disease may be related to defective histamine metabolism or abnormal expression of histamine receptors on lymphocytes and leukocytes.

Reference

1 Jung LKL, Kapoor N, Englehard D *et al*. Pyoderma, eczema and folliculitis, with defective leucocyte and lymphocyte function. *Lancet* 1983; **ii**: 185–7.

Pellagra

Photosensitive dermatitis is a feature of pellagra, the syndrome which results from niacin and tryptophan deficiency (see Chapter 59). Hartnup disease, with massive aminoaciduria, may also be associated with a pellagra-like rash after exposure to the sun, presumably because nicotinamide synthesis from tryptophan is decreased. A similar phenomenon may occur during isoniazid therapy and as part of the carcinoid syndrome.

Phenylketonuria

Eczema occurs in 25% of untreated patients with phenylketonuria in the early years of life. It responds to dietary treatment by exclusion of phenylalanine and recurs when the treatment is stopped [1–3].

References

1 Armstrong MD. Further observations on the effect of phenylalanine-restricted diet on patients with phenylketonuria. *Am J Clin Nutr* 1957; **5**: 543–54.
2 Kang ES, Kennedy JL, Gates L *et al*. Clinical observations in phenylketonuria. *Pediatrics* 1965; **35**: 932–43.
3 Tourian A. In: Stanbury J *et al*., eds. *Metabolic Basis of Inherited Disease*, 5th edn. New York: McGraw-Hill, 1983: 279.

Pityriasis alba

Definition. This is a pattern of dermatitis in which hypopigmentation is the most conspicuous feature. Some erythema and scaling usually precede the development of hypopigmentation but these are often relatively mild.

Aetiology. Pityriasis alba is often a manifestation of atopic dermatitis but it is not confined to atopic individuals.

Histopathology. The histological changes are unimpressive—acanthosis and mild spongiosis, with moderate hyperkeratosis



Fig. 23.23 Pityriasis alba: the failure of the affected patches to tan may first bring them to the patient's notice. (Courtesy of Dr A. Marsden, St George's Hospital, London, UK.)

and patchy parakeratosis. There may be follicular plugging, spongiosis and sebaceous gland atrophy [1–4]. On electron microscopy, there are reduced numbers of active melanocytes and a decrease in number and size of melanosomes in affected skin [3]. Although pigment is reduced, melanocyte numbers are not, and may even be increased relative to healthy skin [5].

Clinical features [2,5–7]. Pityriasis alba occurs predominantly in children between the ages of 3 and 16 years. The sexes are equally susceptible. The individual lesion is a rounded, oval or irregular hypopigmented patch which is usually not well marginated. Lesions are often slightly erythematous and have fine scaling. Initially, the erythema may be conspicuous and there may even be minimal serous crusting. Later, the erythema subsides completely, and at the stage at which the lesions are commonly seen by a physician they show only persistent fine scaling and hypopigmentation. It is this that commonly induces the patient to seek advice. The hypopigmentation is most conspicuous in pigmented skin, and in lighter skins may become more evident after sun-tanning (Fig. 23.23).

There are usually several patches ranging from 0.5 to 2 cm in diameter, but they may be larger, especially on the trunk. In children the lesions are often confined to the face, and are most common on the cheeks and around the mouth and chin. In 20% of affected children the neck, arms and shoulders are involved as well as the face. Less commonly the face is spared and there are scattered lesions on the trunk and limbs.

The course is extremely variable. Most cases persist for some months, and some may still show hypopigmentation for a year or more after all scaling subsides. Recurrent crops of new lesions may develop at intervals. The average duration of the common facial form in childhood is a year or more.

Diagnosis. The age incidence, the fine scaling and the distribution of the lesions usually suggest the diagnosis. Conspicuous hypopigmentation may lead to a misdiagnosis of vitiligo. Naevus depigmentosus most commonly presents at birth or before 3 years of age, and most often causes single, well-marginated lesions on the trunk [8]. However, this condition may be difficult to distinguish from pityriasis alba when it occurs on the face and in cases of later onset. Discoid eczema in an atopic child is intensely pruritic, and the lesions are larger and more oedematous.

In older children and adults, the lesions on the trunk, during their early erythematous phase, may be mistaken for psoriasis but the distribution and the relatively mild scaling should exclude this diagnosis. Mycosis fungoides, although relatively rare, may present with lesions clinically resembling pityriasis alba [9]. This condition may also be difficult to distinguish histologically, so follow-up and repeat biopsy are sometimes required.

Treatment. Response to treatment is often disappointing, mainly because the pigmentation takes a long time to recover. The scaling may be reduced by a bland emollient cream, and for chronic lesions on the trunk a mild tar paste may be helpful. Mild topical corticosteroids are helpful if inflammation persists. Topical tacrolimus and pimecrolimus are effective in facial atopic eczema and seem likely to prove helpful, if required, in pityriasis alba [10].

References

1 O'Farrell N. Pityriasis alba. *Arch Dermatol* 1956; **73**: 376–7.
2 Wells BT, Whyte BT, Kierland R. Pityriasis alba. A ten-year survey and review of the literature. *Arch Dermatol* 1960; **82**: 183–9.
3 Zaynoun ST, Aftimos BG, Tenekjian KK. Extensive pityriasis alba: a histological, histochemical and ultrastructural study. *Br J Dermatol* 1983; **108**: 83–90.
4 Vargos-Ocampo F. Pityriasis alba: a histologic study. *Int J Dermatol* 1993; **32**: 870–3.
5 In S-I, Yi SW, Kang HY *et al*. Clinical and histopathologic characteristics of pityriasis alba. *Clin Exp Dermatol* 2009: in press.
6 Adamson HG. On a form of chronic superficial dermatitis in circumscribed patches with symmetrical distribution occurring in children. *Br J Dermatol* 1908; **120**: 109–22.
7 Bassaly M, Miale A, Prasad AS. Studies on pityriasis alba. *Arch Dermatol* 1963; **88**: 272–3.
8 Kim SK, Kang HY, Lee ES *et al*. Clinical and histopathologic characteristics of nevus depigmentosus. *J Am Acad Dermatol* 2006; **55**: 423–8.
9 Whitmore SE, Simmons-O'Brien E, Rotter FS. Hypopigmented mycosis fungoides. *Arch Dermatol* 1994; **130**: 476–80.
10 Fujita WH, McCormick CL, Parneix-Spake A. An exploratory study to evaluate the efficacy of pimecrolimus cream 1% for the treatment of pityriasis alba. *Int J Dermatol* 2007; **46**: 700–5.

Post-traumatic eczema [1]

It is rare for eczematous dermatoses to demonstrate the Koebner (isomorphic) phenomenon. However, this may occasionally occur, and eczema may also develop at sites of trauma in individuals who have no past history of eczematous dermatosis. Eczema can also occur in burn scars.

There have been several case reports of dermatitis occurring in the saphenous vein graft donor site for coronary artery bypass surgery [2,3]. The rash comprises reddish brown, slightly crusted and scaly patches, with occasional papulovesicles. Histology shows subacute spongiotic dermatitis. The condition responds to topical corticosteroids, but tends to relapse when the treatment is

stopped. Initially, postoperative venous stasis was suggested as the cause. Subsequently, two cases have been reported associated with sensory neuropathy in the distribution of the saphenous nerve [4]. The dermatitis was located in the same area. Otherwise, the cases were identical to those previously reported. The dermatitis and the sensory neuropathy resolved in tandem over a 2-year period.

References

1 Mathias CG. Post-traumatic eczema. *Dermatol Clin* 1988; **6**: 35–42.
2 Carr RD, Rau RC. Dermatitis at vein graft site in coronary artery bypass patients. *Arch Dermatol* 1981; **117**: 814–5.
3 Bart RS. Dermatitis at vein graft site. *Arch Dermatol* 1983; **119**: 97.
4 Hruza LL, Hruza GJ. Saphenous vein graft donor site dermatitis: case reports and literature review. *Arch Dermatol* 1993; **129**: 609–12.

Seborrhoeic dermatitis

Synonyms
- Pityrosporal dermatitis
- Dermatitis of the sebaceous areas

Definition. This is a chronic dermatitis which is difficult to define exactly, but it has a distinctive morphology (red, sharply marginated lesions covered with greasy-looking scales) and a distinctive distribution in areas with a rich supply of sebaceous glands, namely the scalp, face and upper trunk. In some cases the flexures are also involved, but this is not an essential diagnostic criterion.

Dandruff (visible desquamation from the scalp surface) appears to be the precursor of seborrhoeic dermatitis, and this may gradually progress through redness, irritation and increasing scaling of the scalp to true seborrhoeic dermatitis.

Incidence. The prevalence of seborrhoeic dermatitis is around 1–3% in the general population of the USA, and 3–5% in young adults, although mild degrees of dandruff are of course much commoner [1]. The figure is much higher, however, in patients with early human immunodeficiency virus (HIV) infection. Of 155 patients in the WR1A-2A stage of infection (with normal helper T-cell count and delayed hypersensitivity), 36% had seborrhoeic dermatitis [2].

Aetiology [3,4]. Yeast of the genus *Malassezia* is increased in the scaly epidermis of dandruff and seborrhoeic dermatitis [5,6]. Although it has been suggested that this is secondary to the increase in size of the habitat provided by the scaling [7], it is generally accepted that the presence of yeast of the genus *Malassezia* causes the condition [3,4,8].

The way in which *Malassezia* spp. induce inflammation and desquamation is not clear. Although patients with dandruff have high antibody titres to *Malassezia* compared with control subjects, and patients with seborrhoeic dermatitis have altered cell-mediated responses, the immunological reaction is variable [9–10]. Some of the histological features of seborrhoeic dermatitis can be reproduced by inoculating animal skin with killed yeasts [11], and the wide variety of cytokines expressed in the inflammation are similar to those seen in other yeast infections [12]. However, the principal evidence of the role of *Malassezia* spp. remains the response of the condition to treatments that reduce the yeast numbers [4].

The sebaceous glands are active at birth, but when stimulation by maternal androgen ceases they become inactive for 9–12 years. This observation has been regarded as significant in relation to the age incidence of seborrhoeic dermatitis. The condition known as seborrhoeic dermatitis of infancy (Chapter 17) is normally confined to the first months of life, but it is not established that it is the same condition as seborrhoeic dermatitis of adolescence and adult life. The latter is rare before puberty, and reaches its peak between 18 and 40 years of age; occasional cases are seen in old age. At all ages seborrhoeic dermatitis is more common in males than in females.

Although maturation of the sebaceous glands may be a permissive factor for the development of seborrhoeic dermatitis, the role of seborrhoea in the pathogenesis of the condition is debatable. Many young adults with the condition appear to have a greasy skin, but when the sebum excretion rate from forehead skin was measured in patients with classical seborrhoeic dermatitis, the rate was normal in male patients and significantly reduced in female patients [13]. On the basis of this finding, it was suggested that 'dermatitis of the sebaceous areas' might be a more accurate term than 'seborrhoeic dermatitis'. Some clinicians believe that there is an increased prevalence of seborrhoeic dermatitis among patients with acne vulgaris and rosacea, but there are no data to support this.

Seborrhoeic dermatitis may also be a complication of parkinsonism, which is associated with seborrhoea. Treatment of parkinsonism with levodopa reduced sebum excretion when seborrhoea was initially present, but had no effect on the normal sebum excretion rate [14]. Treatment of parkinsonism with levodopa can also sometimes improve seborrhoeic dermatitis in these patients [15]. Seborrhoeic dermatitis has also been reported in a patient in whom unilateral seborrhoea and seborrhoeic dermatitis developed on the face after facial nerve paralysis [16], and also in patients with paralysis of the trunk [17]. The increase in the pool of sebum in immobile skin may be important in these cases, and in parkinsonism [18].

Qualitative abnormalities in the composition of sebum have not been demonstrated. Mild abnormalities in the surface lipids [19,20] could well result from the ineffective keratinization which is often demonstrable histologically.

The heightened susceptibility of the seborrhoeic skin to bacterial infection and to physical and chemical injury results in a high incidence of contact dermatitis and skin infection. Some authors confuse exogenous dermatitis in a seborrhoeic subject with the morphologically distinctive seborrhoeic dermatitis.

Seborrhoeic dermatitis is now established as a possible marker of early HIV infection [2,21], and exacerbations may be seen with progression of the HIV infection, presumably due to the enhanced growth of yeasts secondary to immunosuppression [22]. It is also suggested that local cutaneous immunosuppression may increase the prevalence of seborrhoeic dermatitis [23].

It has also been claimed that seborrhoeic dermatitis is more common in a variety of general medical disorders, including myocardial ischaemia [24], malabsorption, epilepsy, obesity and

alcoholism, especially alcoholic pancreatitis [25]. However, the evidence is far from convincing, and poor hygiene associated with hospitalization and severe illness may play a part in some of these cases.

Seborrhoeic dermatitis involving the usual sites on the face was observed to occur in 28 of 402 patients undergoing psoralen and UVA (PUVA) therapy for psoriasis, but not in 55 patients being treated for other conditions [26]. Spongiosis was present in the three patients biopsied.

Histopathology. The histology is not diagnostic, but generally shows features of both psoriasis and chronic dermatitis. Much of the stratum corneum is often lost in the process of fixation, and most of its cells are parakeratotic. There is slight to moderate acanthosis, with slight spongiosis. Spongiosis is the major feature which distinguishes it from psoriasis. The dermis shows a mild, chronic inflammatory infiltrate.

It seems likely that the initial event is the 'squirting papilla' described by Pinkus and Mehregan [27]. Capillary dilatation in the papillae is followed by migration of inflammatory cells through the vessel walls and into the epidermis, where they incite spongiosis. This is similar to the burst of inflammation which sometimes occurs in psoriasis.

As the inflammation subsides there is an increase in production of keratinocytes. Epidermal proliferation, as measured by the mitotic and labelling indices, is increased, and desquamation is increased [28].

Ultrastructural studies show a closer resemblance to discoid eczema than to allergic or irritant contact dermatitis.

The histology of seborrhoeic dermatitis in patients with AIDS tends to show more follicular involvement, and more plasma cells. Neutrophils and nuclear dust may be present focally among the epidermal parakeratotic cells [21]. *Malassezia* yeasts are prominent in the skin of AIDS patients with seborrhoeic dermatitis compared with seborrhoeic dermatitis patients without AIDS [29].

Clinical features. Most forms of seborrhoeic dermatitis share certain distinctive characteristics. They commonly originate in hairy skin, and involve the scalp, face, presternal and interscapular regions, and the flexures. The lesions tend to be dull or yellowish red in colour and covered with greasy scales.

Morphological variants. There are several morphological variants of seborrhoeic dermatitis, which in the adult form occur in various combinations and degrees of severity (Table 23.7).

Scalp. Dandruff is usually the earliest manifestation of seborrhoeic dermatitis. At a later stage perifollicular redness and scaling gradually extend to form sharply marginated patches which may remain discrete, or coalesce to involve the greater part of the scalp and extend beyond the frontal hairline as the 'corona seborrhoeica'.

In chronic cases there may be some degree of hair loss, which is reversible when the inflammation is suppressed. It has not been established whether seborrhoeic dermatitis of the scalp accelerates the onset of male-pattern (androgenic) alopecia.

Table 23.7 Clinical patterns of seborrhoeic dermatitis.

Infantile (Chapter 17)
Scalp (cradle cap)
Trunk (including flexures and napkin area)
Leiner's disease
Non-familial
Familial C5 dysfunction
Adult
Scalp
Dandruff
Inflammatory—may extend onto non-hairy areas (e.g. postauricular)
Face (may include blepharitis and conjunctivitis)
Trunk
Petaloid
Pityriasiform
Flexural
Eczematous plaques
Follicular
Generalized (may be erythroderma)



Fig. 23.24 This type of seborrhoeic dermatitis around the ears readily develops secondary bacterial infection.

Behind the ears there may be redness and greasy scaling, and a crusted fissure often develops in the fold (Fig. 23.24). Adherent masses of sticky scale and crusts may extend into the adjacent scalp. Both sides of the pinna, the periauricular region, and the sides of the neck may be involved. Otitis externa, irritable and intractable, may accompany seborrhoeic dermatitis in other sites, or may occur alone.



(a)



(b)

Fig. 23.25 (a) Seborrhoeic dermatitis of the forehead. (b) Severe seborrhoeic dermatitis of the face with prominent involvement of the nasolabial groove.

Face. On the face, seborrhoeic dermatitis characteristically involves the medial part of the eyebrows, the glabella and the nasolabial folds (Fig. 23.25). Areas of erythema and scaling occur, usually in association with involvement of the scalp.

Blepharitis is common. The margins of the lids are red and covered by small, white scales. Yellow crusts may form, and separate to leave small ulcers, healing to form scars, with destruction of lash follicles.

Episodic variation in intensity is common, often being precipitated by tiredness or stress. Exposure to sunlight produces a temporary exacerbation, followed by improvement as the tan develops.



Fig. 23.26 Seborrhoeic dermatitis of the presternal region. (Courtesy of Dr D.A. Burns, Leicester Royal Infirmary, Leicester, UK.)

A superficial form of seborrhoeic dermatitis of the chin is common in men in the early stages of growing a beard, but is cured when the beard is shaved off.

Young women sometimes have paranasal erythema associated with a tendency to flushing. It is not always clear whether this is rosacea or mild seborrhoeic dermatitis, but overtreatment with strong topical corticosteroids may convert this into perioral dermatitis.

Trunk. On the trunk, several forms of seborrhoeic dermatitis occur. Commonest is the petaloid form (so-called because the lesions are petal-shaped). This is often seen in men on the front of the chest and in the interscapular region (Fig. 23.26). The initial lesion is a small, red–brown follicular papule, covered by a greasy scale. Some patients have a widespread eruption of lesions which do not progress beyond this stage. More often, extension and confluence of the follicular papules gives rise to a figured eruption, consisting of multiple circinate patches, with a fine branny scaling in their centres, and with dark-red papules with larger greasy scales at their margins.

A rarer form, involving the trunk and limbs, is the so-called pityriasiform type. This is a generalized erythematosquamous eruption, somewhat similar to, but more extensive than, pityriasis rosea. In particular it involves the neck up to the hair margin. It is not particularly pruritic, and it resolves spontaneously, although somewhat more slowly than does pityriasis rosea. In some patients the lesions may become psoriasiform.

Flexures. In the flexures, notably in the axillae (Fig. 23.27), the groins, the anogenital and submammary regions, and the umbilicus, seborrhoeic dermatitis presents as an intertrigo, with diffuse, sharply marginated erythema and greasy scaling. Crusted fissures develop in the folds, and with sweating, secondary infection and inappropriate treatment, a weeping dermatitis may extend far beyond them. The genitalia of both sexes may be involved, and the lesions show the usual range from minimal erythema and scaling to severe crusted dermatitis. In this site, and occasionally elsewhere, the chronic, thickened, dull-red, scaly patches of the psoriasiform variety of seborrhoeic dermatitis may develop.



Fig. 23.27 Seborrhoeic dermatitis of the axilla: flexural areas often become secondarily infected.



Fig. 23.28 Redness and scaling at the medial ends of the eyebrows may provide a diagnostic pointer to seborrhoeic dermatitis.

The severity and course of seborrhoeic eruptions are very variable. All show a tendency to chronicity and recurrence.

Severe and extensive forms may be complicated by eczematous reactions remote from the sites initially involved, especially by pompholyx and discoid eczema. Such eruptions are discussed separately below. The pattern and course of the disease may also be modified by contact dermatitis and provoked by medicaments, or by an infective bacterial dermatitis.

Occasionally, seborrhoeic dermatitis may become generalized, resulting in erythroderma.

Modifications in the clinical features and course may be seen when seborrhoeic dermatitis occurs in association with atopy, or with psoriasis, and in the latter case the diagnosis can be extremely difficult, because both the clinical and histological features can be equivocal. Some dermatologists use the term *sebopsoriasis* for this overlap condition.

Diagnosis (Fig. 23.28). In a classical case the diagnosis is easy, but in some cases the diagnosis can be difficult, partly because of the lack of well-defined diagnostic criteria. The diagnosis is often made too freely.

Nowadays it is very important to consider the possibility of HIV infection in any patient with severe seborrhoeic dermatitis, particularly in a patient involved in high-risk activities.

The differential diagnosis covers an enormous range of conditions. Psoriasis, when confined to the scalp, may be confused with seborrhoeic dermatitis. The lesions are often more circumscribed and usually palpably thickened in psoriasis, with a brighter pink colour and silvery scale. The rest of the body must be examined, especially the nails, and there may be a family history of psoriasis.

Lichen simplex of the nape of the neck occurs in females, and can mimic seborrhoeic dermatitis. The thickened plaques in this condition are, however, intensely irritable.

Infective dermatitis complicating pediculosis can also be confused with seborrhoeic dermatitis.

Contact allergy [30] and *Trichophyton tonsurans* infection [31] may mimic seborrhoeic dermatitis of the scalp.

Pityriasis rosea must be distinguished from the pityriasiform type of seborrhoeic dermatitis, in which the lesions are more widely distributed, and in which there is no herald patch. In the flexures, microscopic examination of scrapings from the advancing margin, and examination under Wood's light will exclude ringworm infections, candidiasis and erythrasma. Acute flexural dermatitis may also suggest the possibility of allergic sensitization to a chemical in clothing, and patch tests may be needed. Moist crusting of the face or of the midline of the chest or back occurs in pemphigus erythematosus, and in pemphigus foliaceus. Biopsy is required if these conditions are suspected. Axillary and sometimes interscapular crusting, tending to relapse in the warmer weather, occurs in benign familial pemphigus.

The brown scaly lesions of pityriasis versicolor are flatter, more extensive, and less symmetrical than the lesions of petaloid seborrhoeic dermatitis of the trunk. Microscopy of scrapings quickly establishes the diagnosis.

Follicular seborrhoeic dermatitis of the trunk must be differentiated from Darier's disease, in which the papules are brown, greasy and dome-shaped, and tend to be clustered. Biopsy is diagnostic. Lesions resembling seborrhoeic dermatitis can occur in zinc deficiency and acrodermatitis enteropathica [32].

Drug eruptions, particularly those due to methyl dopa, chlorpromazine or cimetidine may mimic seborrhoeic dermatitis.

Despite the non-specific nature of the histological appearances of seborrhoeic dermatitis, biopsy will often reliably differentiate it from many of the conditions with which it may be confused.

Treatment. It should be emphasized to the patient at the outset that, although seborrhoeic dermatitis can generally be suppressed, there is no permanent cure. The condition may require regular treatment for many years.

Dandruff is usually treated by the frequent and regular use of medicated shampoos which act against *Malassezia* yeasts, including selenium sulphide, zinc pyrithione, ketoconazole [33] and various tar shampoos; 1% terbinafine solution has also been shown to be effective [34]. Alcohol-based preparations and hair tonics should be avoided. For severe dandruff with persistent scaling or

crusting, 5% salicyclic acid ointment may be useful. If secondary bacterial infection is present or suspected, oral erythromycin or flucloxacillin may be used.

Acute forms of seborrhoeic dermatitis on the face and trunk are generally sensitive to mild steroid ointments. Hydrocortisone ointment (0.5%) is often effective, particularly if combined with sulphur (0.5%). Ketoconazole cream (2%) is possibly a more logical therapy, which has been shown to be equally effective [35–39]. In many situations, the acute inflammatory changes can be suppressed with mild topical corticosteroid creams or steroid and imidazole combination creams, which can then be changed to ketoconazole cream for long-term control.

Topical immunosuppressants (tacrolimus, pimecrolimus) are also an effective treatment [40,41], and are particularly useful for facial seborrhoeic dermatitis, when there is concern about overuse of topical steroids.

Topical metronidazole, ciclopiroxolamine and tacalcitol have also been reported to be helpful [42–44]. Frequent washing with soap and water is helpful, possibly because removal of lipid removes the substrate for the yeasts. Other topical preparations which have been shown to be effective include benzoyl peroxide [45] and 5% lithium succinate ointment [46].

For unresponsive cases, a course of UVB therapy may be helpful [47]. Oral itraconazole (100 mg daily for up to 21 days) is also effective, as is oral terbinafine [48].

Generalized seborrhoeic dermatitis usually responds to the medications listed above, but in recalcitrant cases systemic steroids may be required. Prednisolone 30 mg daily usually produces a rapid response. Isotretinoin may also be helpful [18].

Flexural seborrhoeic dermatitis is treated in the same way as intertrigo (Chapter 71).

References

1 Johnson M-LT, Roberts J. *Prevalence of Dermatological Diseases Among Persons 1–74 Years of Age*. Washington DC: US Department of Health Education, National Center for Health Statistics, 1978: *PHS* 79–1660.

2 Berger RS. Cutaneous manifestations of early human immunodeficiency virus exposure. *J Am Acad Dermatol* 1988; **19**: 298–303.

3 Shuster S. The aetiology of dandruff and mode of action of therapeutic agents. *Br J Dermatol* 1984; **111**: 235–42.

4 Hay RJ, Graham-Brown RA. Dandruff and seborrhoeic dermatitis: causes and management. *Clin Exp Dermatol* 1997; **22**: 3–6.

5 Pechere M, Krischer J, Remondat C *et al*. *Malassezia* species carriage in patients with seborrhoeic dermatitis. *J Dermatol* 1999; **26**: 558–61.

6 Nakabayashi A, Sei Y, Guillot J. Identification of *Malassezia* species isolated from patients with seborrhoeic dermatitis, atopic dermatitis, pityriasis versicolor and normal subjects. *Med Mycol* 2000; **38**: 337–41.

7 McGinley KJ, Leyden JJ, Marples RR, Kligman AM. Quantitative microbiology of the scalp in non-dandruff, dandruff and seborrhoeic dermatitis. *J Invest Dermatol* 1975; **64**: 401.

8 Shuster S, Blatchford N. Seborrhoeic dermatitis and dandruff—a fungal disease. *Royal Soc Med Services* 1988; Series **132**: 1–54.

9 Bergbrant IM, Andersson B, Faergemann J. Cell-mediated immunity to Malassezia furfur in patients with seborrhoeic dermatitis and pityriasis versicolor. *Clin Exp Dermatol* 1999; **24**: 402–6.

10 Parry ME, Sharpe GR. Seborrhoeic dermatitis is not caused by an altered immune response to Malassezia yeast. *Br J Dermatol* 1998; **139**: 254–63.

11 Rosenberg EW. Effect of topical applications of heavy suspensions of killed *Malassezia ovalis* on rabbit skin. *Mycopathologia* 1980; **72**: 147–52.

12 Faergemann J, Bergbrant IM, Dohse M *et al*. Seborrhoeic dermatitis and *Pityrosporum* (*Malassezia*) folliculitis: characterization of inflammatory cells and mediators in the skin by immunohistochemistry. *Br J Dermatol* 2001; **144**: 549–56.

13 Burton JL, Pye RJ. Seborrhoea is not a feature of seborrhoeic dermatitis. *BMJ* 1983; **286**: 1169–71.

14 Burton JL, Cartilidge M, Shuster S. Effect of L-dopa on the seborrhoea of Parkinsonism. *Br J Dermatol* 1973; **88**: 475–9.

15 Parish LC. L-dopa for seborrhoeic dermatitis. *N Engl J Med* 1970; **283**: 879.

16 Bettley FR, Marten RH. Unilateral seborrhoeic dermatitis following a nerve lesion. *Arch Dermatol* 1956; **73**: 110–5.

17 Wilson CL, Walshe M. Incidence of seborrhoeic dermatitis in spinal injury patients. *Br J Dermatol* 1988; **119**: 48S.

18 Cowley NC, Farr PM, Shuster S. The permissive effect of sebum in seborrhoeic dermatitis: an explanation of the rash in neurological disorders. *Br J Dermatol* 1990; **122**: 71–6.

19 Hodgson-Jones IS, McKenna RMB, Wheatley VR. The surface skin fat in seborrhoeic dermatitis. *Br J Dermatol* 1953; **65**: 246–51.

20 Pye RJ, Meyrick G, Burton JL. Skin surface lipids in seborrhoeic dermatitis. *Br J Dermatol* 1977; **97** (Suppl. 15): 12.

21 Alessi E, Cusini M, Zerboni R. Mucocutaneous manifestations of patients infected with AIDS. *J Am Acad Dermatol* 1988; **19**: 290–7.

22 Smith KJ, Skelton HG, Yeager J *et al*. Cutaneous findings in HIV-1 positive patients: a 42-month prospective study. *J Am Acad Dermatol* 1994; **31**: 746–54.

23 Moehrle M, Dennenmoser B, Schlagenhauff B *et al*. High prevalence of seborrhoeic dermatitis on the face and scalp in mountain guides. *Dermatology* 2000; **201**: 146–7.

24 Tager A. Seborrhoeic dermatitis in acute cardiac disease. *Br J Dermatol* 1964; **76**: 367–9.

25 Barba A, Piubello W, Vantini I *et al*. Skin lesions in chronic alcoholic pancreatitis. *Dermatologica* 1982; **164**: 322–6.

26 Tegner E. Seborrhoeic dermatitis of the face induced by PUVA treatment. *Acta Derm Venereol (Stockh)* 1983; **63**: 335–9.

27 Pinkus H, Mehregan AM. The squirting papilla. *J Invest Dermatol* 1966; **49**: 109–15.

28 Kligman AM. Dandruff, its causes and treatment. In: Orfanos C, ed. *Haar und Haarkrankheiten*. Stuttgart: Fischer, 1979: 663–9.

29 Groisser D, Bottone EJ, Lebwohl M. Association of *Pityrosporum orbiculare (Malassezia furfur)* with seborrhoeic dermatitis in patients with acquired immunodeficiency syndrome (AIDS). *J Am Acad Dermatol* 1989; **20**: 770–3.

30 Armstrong DK, Smith HR, Rycroft RJ. Contact allergy to methyldibromo glutaronitrile presenting as severe scalp seborrhoeic eczema. *Contact Dermatitis* 1999; **40**: 335.

31 Pandya AG. Seborrhoeic dermatitis or tinea capitis: don't be fooled. *Int J Dermatol* 1998; **37**: 827–8.

32 Weismann NK, Hjorth N, Fischer A. Zinc depletion syndrome with acrodermatitis enteropathica during long term intravenous feeding. *Clin Exp Dermatol* 1976; **1**: 237–42.

33 Pierard-Franchimont C, Pierard GE, Arrese JE, De Doncker P. Effect of ketoconazole 1% and 2% shampoos on severe dandruff and seborrhoeic dermatitis: clinical, squamometric and mycological assessments. *Dermatology* 2001; **202**: 171–6.

34 Faergemann J, Jones TC, Hettler D, Loria Y. *Pityrosporum ovale (Malassezia furfur)* as the causative agent of seborrhoeic dermatitis: new treatment options. *Br J Dermatol* 1996; **134** (Suppl. 46): 12–5.

35 Farr PM, Shuster S. Treatment of seborrhoeic dermatitis with topical ketoconazole. *Lancet* 1984; **ii**: 1271–2.

36 Ford GP, Farr P, Ive FA, Shuster S. The response of seborrhoeic dermatitis to ketoconazole. *Br J Dermatol* 1984; **111**: 603–7.

37 Green CA, Farr P, Shuster S. Treatment of seborrhoeic dermatitis with ketoconazole. II. Response of seborrhoeic dermatitis of face, scalp and trunk to topical ketoconazole. *Br J Dermatol* 1987; **116**: 217–21.

38 Skinner RB. Double blind treatment of seborrhoeic dermatitis with 2% ketoconazole cream. *J Am Acad Dermatol* 1985; **12**: 852–6.

39 Stratigos JD, Antoniou C, Katsambas A *et al*. Ketoconazole 2% cream versus hydrocortisone cream in the treatment of seborrhoeic dermatitis. *J Am Acad Dermatol* 1988; **19**: 850–3.

40 Warshaw EM, Wohlhuter RJ, Liu A *et al*. Results of a randomized, double-blind, vehicle-controlled efficacy trial of pimecrolimus cream 1% for the treatment of moderate to severe facial seborrheic dermatitis. *J Am Acad Dermatol* 2007; **57**: 257–64.

41 Meshkinpour A, Sun J, Weinstein G. An open pilot study using tacrolimus ointment in the treatment of seborrheic dermatitis. *J Am Acad Dermatol* 2003; **49**: 145–7.
42 Parsad D, Pandhi R, Negi KS, Kumar B. Topical metronidazole in seborrhoeic dermatitis—a double blind study. *Dermatology* 2001; **202**: 35–7.
43 Dupuy P, Maurette C, Amoric JC, Chosidow O. Study Investigator Group. Randomised placebo-controlled, double-blind study on clinical efficacy of ciclopiroxolamine 1% cream in facial seborrhoeic dermatitis. *Br J Dermatol* 2001; **144**: 1033–7.
44 Nakayama J. Four cases of sebopsoriasis or seborrhoeic dermatitis of the face and scalp successfully treated with 1a-24 (R)-dihydroxycholecalciferol (tacalcitol) cream. *Eur J Dermatol* 2000; **10**: 528–32.
45 Bonnetblanc JM, Bernard P. Benzoyl peroxide in seborrhoeic dermatitis. *Arch Dermatol* 1986; **122**: 752.
46 Boyle J, Burton JL, Faergemann J. Use of topical lithium succinate for seborrhoeic dermatitis. *BMJ* 1986; **292**: 28.
47 Pirkhammer D, Seeber A, Honigsmann H, Tanew A. Narrow-band ultraviolet B (ATL-01) phototherapy is an effective and safe treatment option for patients with severe seborrhoeic dermatitis. *Br J Dermatol* 2000; **143**: 964–8.
48 Scaparro E, Quadri G, Virno G *et al*. Evaluation of the efficacy and tolerability of oral terbinifine (Daskil) in patients with seborrhoeic dermatitis. A multicentre, randomised, investigator-blinded, placebo-controlled trial. *Br J Dermatol* 2001; **144**: 854–7.

Infantile seborrhoeic dermatitis

There is still some debate as to whether this condition occurs as a separate entity, or is merely a variant of atopic dermatitis (see Chapter 17 for discussion).

Malassezia folliculitis

Synonyms
- Seborrhoeic folliculitis
- Pityrosporal folliculitis

Definition. Folliculitis caused by *Malassezia* yeasts (e.g. *Malassezia furfur*). Although not an eczema, *Malassezia* folliculitis is included here because of its association with seborrhoeic dermatitis.

Aetiology. *Malassezia* yeasts can hydrolyse triglycerides into free fatty acids, and it has been postulated that an overgrowth of the yeast in a follicle produces folliculitis by a combination of fatty acid production and blockage of the follicular ostium by scale [1,2]. The ability of the yeasts to activate the alternative complement pathway may also be implicated in the inflammatory process.

Pathology. There is folliculitis, with a perifollicular mononuclear infiltrate, predominantly around the infundibular region of the follicle. Sparse *Malassezia* yeasts can be identified in the affected follicles, but mycelial forms are usually absent. *Malassezia* yeasts can also be identified in skin scrapings.

Clinical features [3–4]. The condition most commonly affects adult males, and is associated with a tendency to seborrhoeic dermatitis or severe dandruff. It has been reported in 12 of 42 patients with Down's syndrome [5]. The rash is dimorphic, with erythematous follicular papules and follicular pustules. Lesions occur mainly on the upper trunk and shoulders, and are usually pruritic (Fig. 23.29).



Fig. 23.29 *Malassezia* folliculitis. (Courtesy of Dr F.A. Ive, Durham, UK.)

Differential diagnosis. Acne vulgaris may be distinguished by the presence of comedones, cysts and scars, which do not occur in *Malassezia* folliculitis. Similar lesions can occur in immunocompromised individuals such as AIDS sufferers and organ transplant recipients [6]. The condition should be considered in the differential diagnosis of steroid-induced folliculitis [7]. Transmission of the condition between individuals has been suggested [8].

Treatment. Patients should be advised to avoid occlusive clothing, and broad-spectrum antibiotic therapy should be stopped whenever possible. The condition responds well to 2% ketoconazole cream [9]. However, the eruption will often relapse, and intermittent prophylactic treatment once or twice weekly may be indicated [10]. Systemic treatment with oral itraconazole may occasionally be helpful. In the Down's syndrome patients the condition improved with oral itraconazole but relapsed when the medication was stopped [5].

References

1 Goodfield MJD, Saihan EM, Crowley J. Experimental folliculitis with *Pityrosporum orbiculare*: the influence of host response. *Acta Derm Venereol (Stockh)* 1987; **67**: 445–7.
2 Hill MK, Goodfield MJ, Rodgers FG *et al*. Skin surface electron microscopy in *Pityrosporum* folliculitis. *Arch Dermatol* 1990; **126**: 181–4.
3 Back O, Faergemann J. *Pityrosporum* folliculitis: a common disease of the young and middle-aged. *J Am Acad Dermatol* 1985; **12**: 56–61.
4 Potter BS, Burgoon CF, Johnson WC. *Pityrosporum* folliculitis. Report of 7 cases and review of the *Pityrosporum* organism relative to cutaneous disease. *Arch Dermatol* 1973; **107**: 388–91.
5 Kavanagh GM, Leeming JP, Marshman GM, Burton JL. Folliculitis in Down's syndrome. *Br J Dermatol* 1993; **129**: 696–9.
6 Rhie S, Turcios R, Buckley H, Suh B. Clinical features and treatment of Malassezia folliculitis with fluconazole in orthotopic heart recipients. *J Heart Lung Transplant* 2000; **19**: 215–9.
7 Yu HJ, Lee SK, Son SJ *et al*. Steroid acne vs. Pityrosporum folliculitis: the incidence of Pityrosporum ovale and the effect of antifungal drugs in steroid acne. *Int J Dermatol* 1998; **37**: 72–7.
8 Archer-Dubon C, Icaza-Chivez ME, Orozco-Topete R *et al*. An epidemic outbreak of Malassezia folliculitis in three adult patients in an intensive care unit: a previously unrecognised nosocomial infection. *Int J Dermatol* 1999; **38**: 453–6.
9 Ford GP, Ive FA, Midgley G. *Pityrosporum* folliculitis and ketoconazole. *Br J Dermatol* 1982; **109**: 691–5.
10 Faergemann J. *Pityrosporum* infections. *J Am Acad Dermatol* 1994; **31**: s18–s20.

Venous eczema

Synonym
- Gravitational eczema

Definition. Eczema secondary to venous hypertension.

Nomenclature. This condition is also called stasis eczema or varicose eczema. It is increased venous pressure rather than stasis which seems to be the prerequisite. Although it is often associated with varicose veins these are not always present.

Pathogenesis [1–4]. The oxygen content in the femoral venous blood of the leg affected by venous hypertension is increased, and the venous blood in such limbs has a faster circulation time than normal [5,6]. These observations could be explained by the development of arteriovenous shunts in the affected areas, but the use of radioactively labelled macroaggregates or microspheres has failed to provide any evidence for such shunts.

An alternative explanation for these findings has been provided by Browse and Burnand [2], who suggested that the high ambulatory venous pressure within the calf muscle pump is transmitted to the capillary circulation in the skin and subcutaneous tissues of the calf. This distends the local capillary bed and widens the endothelial pores, thus allowing fibrinogen molecules to escape into the interstitial fluid, where they form a fibrin sheath around the capillaries. This layer of fibrin presumably forms a pericapillary barrier to the diffusion of oxygen and other nutrients which are essential for the normal vitality of the skin. The hypothesis that pericapillary fibrin impedes oxygen diffusion has been supported by a study using positron-emission tomography [7].

It has also been suggested that cutaneous inflammation in venous hypertension may result from increased sequestration of white cells in the venules, with consequent release of proteolytic enzymes and free radicals which produce tissue damage [3]. In normal subjects, white cells are sequestered in the limb when venous pressure is elevated, and in patients with venous insufficiency the effect is enhanced, with increased endothelial contact and adhesion of white cells [8]. This effect may be related to an increase in expression of adhesion molecules ICAM-1 and VCAM-1 on the vascular endothelium in affected skin [9].

Clinical features. Venous eczema is an erythematous, scaly and often exudative eruption usually seen around the ankle and lower leg (Fig. 23.30). It often occurs as a late result of deep vein thrombosis. Occasionally, similar changes occur at other sites of venous hypertension such as the pendulous skin over an obese abdomen or in association with an ateriovenous fistula in the upper limb [10]. The eczema may develop suddenly or insidiously. The patients are usually middle-aged or elderly and most often female. The increased incidence in females is presumably due to hormonal effects and the tendency for venous thrombosis to occur during pregnancy.

The eczema is often accompanied by other manifestations of venous hypertension, including dilatation or varicosity of the superficial veins, oedema, purpura, haemosiderosis, ulceration, or small patches of white, atrophic, telangiectatic scarring ('atrophie blanche'). These changes, which occur in various combinations, are discussed in more detail in Chapter 47. Leashes of dilated venules around the dorsum of the foot or the ankle are particularly common. There may be a subepidermal vascular proliferation producing purple papules around the ankle, which may resemble Kaposi's sarcoma [11]. Secondary patches of eczema may develop on the other leg, even when it is not affected by obvious venous insufficiency. Generalized secondary dissemination may occur, and occasionally this can progress to erythroderma.



Fig. 23.30 Venous (gravitational) eczema.

These changes are often modified by secondary contact dermatitis, infection and rubbing. Allergic contact dermatitis is a common complication of gravitational eczema, possibly because of the large number of antigen-presenting cells in the inflamed skin [12].

Differential diagnosis. Although most cases of eczema of the lower leg are secondary to venous hypertension, it must be remembered that many other types of eczema may affect this region, and in many cases there are multiple causative factors. In children or young adults, atopic dermatitis may manifest as lichenified patches around the ankle or behind the knees. Allergic contact dermatitis of the lower legs is usually due to topical medicaments (Fig. 23.31). Patch testing is often indicated. An infected ulcer may be complicated by infective eczema spreading from the edge of the ulcer, with response to appropriate antibiotic therapy (p. 23.23). Discoid eczema is common on the lower leg, usually on the anterior or anterolateral aspect. Asteatotic eczema commonly affects the legs of elderly patients.

Although the exact cause of eczema on the lower legs can be difficult to elucidate, other conditions can usually be readily identified. Psoriasis may present as a single, irritable plaque on the leg, but is usually more scaly and clearly marginated. Hypertrophic lichen planus of the lower leg may occasionally be mistaken for eczema if there are no characteristic lesions elsewhere. Dermatophyte infection may present as diffuse erythema and scaling and may be difficult to recognize, particularly if it has been treated with topical steroids. Profuse actinic keratoses may cause red,



Fig. 23.31 Contact eczema of the lower legs due to allergy to paste bandages.

irritable patches on the lower legs in sunny climates. In the late stage of borreliosis the leg can feel heavy, with thick cyanotic itchy skin which may mimic the changes of venous hypertension [13].

Treatment. The underlying venous hypertension should be controlled. Obese patients should be urged to lose weight. Well-fitted support stockings or firm bandages can be helpful if worn regularly and care is taken to avoid the formation of a band at the top of the leg. The legs should be elevated as effectively as possible.

Mild topical steroids may be used to relieve irritation, but the use of potent steroids should be limited to short periods of a few days as they may cause cutaneous atrophy and increase the risk of ulceration. Topical tacrolimus has been reported to be effective [14]. Bacterial infection must be treated where appropriate, but the risk of sensitization to topical antibiotics and antiseptics should be borne in mind, and systemic antibiotics may be preferable. Bacteria cultured from a swab are not necessarily playing a pathogenic role. If trauma is thought to be playing a part, and the patient cannot resist scratching, a paste bandage may be helpful.

References

1 Burton JL. Venous hypertension, fibrin and leg ulcers. *Br J Dermatol* 1983; **109**: 229–31.

2 Browse NL, Burnand KC. The cause of venous ulceration. *Lancet* 1982; **ii**: 243–5.

3 Coleridge Smith PD, Thomas P, Scurr JH *et al*. Causes of venous ulceration: a new hypothesis. *BMJ* 1988; **296**: 1726–7.

4 Heng MC. The post-phlebitic syndrome. *Int J Dermatol* 1987; **26**: 14–20.

5 Fontaine R. Remarks concerning venous thrombosis and its sequelae. *Surgery* 1957; **41**: 6–25.

6 Piulachs P, Vidal-Barraquerr F. Pathogenic study of varicose veins. *Angiology* 1953; **4**: 59–100.

7 Hopkins NFG. Positron emission tomography in venous ulceration and liposclerosis: a study of regional tissue function. *BMJ* 1983; **286**: 333–6.

8 Thomas PRS, Nash GB, Dormandy JA. White cell accumulation in dependent legs of patients with venous hypertension: a possible mechanism for trophic changes in the skin. *BMJ* 1988; **296**: 1693–5.

9 Peschen M, Lahaye T, Henning B *et al*. Expression of the adhesion molecules ICAM-1, VCAM-1, LFA-1 and VLA-4 in the skin is modulated in progressing stages of chronic venous insufficiency. *Acta Derm Venereol (Stockh)* 1999; **79**: 27–32.

10 Bilen N, Apaydin R, Harova G *et al*. Stasis dermatitis of the hand associated with an iatrogenic arteriovenous fistula. *Clin Exp Dermatol* 1998; **23**: 208–10.

11 Boyle J, Burton JL. Pseudo-Kaposi sarcoma. *Lancet* 1986; **ii**: 921.

12 Bahmer FZ. Immunohistologische Charakterisierung stauungsdermatotisch veränderter Unterschenkelhaut. *Z Hautkr* 1987; **62**: 1056–63.

13 Fagrell B, Steirnstedt G, Ostergen J. Acrodermatitis chronica atrophicans (Herxheimer) can often mimic a peripheral vascular disorder. *Acta Med Scand* 1986; **220**: 485–8.

14 Dissemond J, Knab J, Lehnen M *et al*. Successful treatment of stasis dermatitis with topical tacrolimus. *Vasa* 2004; **33**: 260–2.

The management of eczema

A wide range of dermatoses are encompassed by the term eczema. Specific aspects of their treatment are described under their respective headings. Some fundamental principles of management shared by all eczematous dermatoses are described here.

In order to establish the underlying diagnosis a careful history and examination is required. This will also help to identify additional aggravating factors (such as exposure to irritants) or complicating factors (such as infections or allergies to medications) which are playing a role in the pathogenesis. In order to optimize management, the dermatologist needs to be familiar with the patient's occupation, domestic circumstances and personality. It is also important to determine how the patient is affected by the disease. Which symptoms are most troublesome? How much embarrassment is experienced? Which aspects of the patient's work and social life are disrupted?

Previous treatment experience must be explored. It is necessary to assess how much time and effort a patient (or parent) is willing and able to devote to the care of their (or their child's) skin. An additional issue which must be addressed is the attitude of the patient to the risks and side effects associated with any treatment that may be required. A particularly common problem is an inappropriate level of anxiety about the use of topical corticosteroids. Only when all this information is available can the optimal treatment strategy be determined.

Diagnostic tests for eczema

Most cases of eczema can be diagnosed clinically. It can sometimes be helpful to measure the total IgE level in order to determine whether an individual is atopic, particularly when the distribution of eczema is atypical and there is no background of other atopic illness. Secondary infection can be confirmed by taking swabs for culture and sensitivity to identify any bacterial resistance, such as methicillin-resistant staphylococci. When dermatophyte infection is suspected, a potassium hydroxide preparation should be examined or scrapings sent to a laboratory for microscopy and culture. Microscopy can also be invaluable to confirm a diagnosis of scabies, which is easy to miss in a patient with pre-existing eczema. Biopsy

can occasionally be helpful in confirming the eczematous nature of the eruption, and immunofluorescence can help identify less common conditions such as dermatitis herpetiformis or, in older patients, a non-bullous presentation of bullous pemphigoid.

Patch testing in eczema [1–3]

Routine use of patch testing is not indicated for typical presentations of endogenous eczema such as atopic dermatitis, pityriasis alba and seborrhoeic eczema. This investigation is much more important in atypical or asymmetrical eruptions, and especially in dermatitis affecting the face, hands and feet [3].

In apparently endogenous eczema the threshold for patch testing should still be low. Sensitization commonly develops to topical medicaments, prescribed or self-administered, and this may exacerbate the eruption. Sometimes, topical remedies are concealed or forgotten by the patient, or the reaction they cause is partially suppressed by the concomitant use of topical corticosteroids. Sometimes, an unexpected positive test points to a 'hidden' or obscure cause, for example fragrances, preservatives, vehicles, epoxy or rubber chemicals. Such substances are commonly encountered in the environment and in topical medication.

When a strong suspicion of a contact-allergic cause for the eczema exists, it may be important to test with other potential allergens in addition to the routine battery—household plants, material extracted from footwear, phosphorus sesquisulphide, acrylates, etc. The observer must be wary of false-positive, irritant reactions, especially in an 'excited' eczematous skin [4]. For this reason it is always wise to allow the acute phase of an eczema to subside before patch testing is carried out, or to repeat any positive tests when it has done so. If a contact urticaria is thought to be occurring, the patch tests should be read 1 h after application [5].

Even if a positive patch test is judged to be relevant (i.e. the patient comes into contact with that substance), it does not necessarily follow that the exclusion of that substance from the environment of the patient will result in a cure. The allergen may be only one of several contributory factors.

Although patch tests are designed to detect allergens, many substances give an irritant reaction when tested, and it is often difficult to be sure of the relevance of such a reaction to the patient's eczema. It must also be borne in mind that many topical medicaments can produce an irritant reaction, for example alcohol-based preparations and propylene glycol. The choice of concentration of test substance and suitable vehicle are vitally important [2] (see also Chapter 26 for details of patch testing).

It is important to remember that patch testing performed in a setting of any poorly controlled eczematous dermatosis may yield false-positive results due to conditioned hyperirritability (as discussed above).

The 'atopy patch test' comprises patch testing with allergens such as pollens, animal danders and dust mite allergens, and frequently yields positive results in atopic individuals. This may be a further method of confirming the atopic status of a patient [6], but has yet to find a more useful role in routine management.

References

1 Cronin E. Contact dermatitis. VII: Reactions to contact allergens given orally and systemically. *Br J Dermatol* 1972; **86**: 104–7.

2 de Groot AC, ed. *Patch Testing. Test Concentrations and Vehicles for 2800 Allergens.* Amsterdam: Elsevier, 1986.

3 Wilkinson DS. The role of contact allergy in hand eczema. *Trans St John's Hosp Dermatol Soc* 1970; **56**: 19–27.

4 Bruynzeel DP, Maibach HI. Excited skin syndrome (angry back). *Arch Dermatol* 1986; **122**: 323–8.

5 Hjorth N, Roed-Peterson J. Occupational protein contact dermatitis in food handlers. *Contact Dermatitis* 1976; **2**: 28–42.

6 Samochocki Z, Owczarek W, Zabielski S. Can atopy patch tests with aeroallergens be an additional diagnostic criterion for atopic dermatitis? *Eur J Dermatol* 2006; **16**: 151–4.

Table 23.8 Indications for therapeutic agents in eczema.

Therapeutic agent	Acute	Subacute	Chronic
Rest, sedation	++	+	±
Wet dressings and soaks	++	±	–
Wet wrap bandaging	++	+	±
Paste bandages	±	+	++
Sedative antihistamines	++	++	+
Emollients	++	++	++
Corticosteroids, local	+	++	+
Pimecrolimus (topical)	+	++	++
Tacrolimus (topical)	+	++	++
Tar, ichthammol, etc.	±	+	++
Polythene occlusion	±	+	+
Intralesional steroids	–	±	+
Habit reversal therapy	–	±	+
X-ray therapy	–	–	±
Systemic corticosteroids	+	+	±
Ciclosporin	+	+	±
Azathioprine	–	+	+

Treatment of eczema

A considerable variety of effective treatment modalities is available. These range from conservative and extremely safe approaches such as rest and the application of emollients, to 'aggressive', more hazardous treatments such as phototherapy, systemic immunosuppressants or radiotherapy. Some frequently used treatments are listed in Table 23.8. When an extrinsic cause is identified or suspected this should be removed. In all cases, exposure to irritants should be carefully avoided and the skin should be protected using emollients and appropriate dressings. Psychological support is an important aspect of management at all stages.

Acute eczema

Acute eruptions and exacerbations of eczema cause great alarm and anxiety, and the stress of the situation is usually aggravated by loss of sleep caused by intense pruritus and soreness. Patients need to be reassured that the eruption will be brought under control. Adequate rest is essential, and on occasions this is best provided in a hospital bed. An affected leg should be elevated or well supported, and affected hands should be used as little as is practicable. In extremely acute hand eczema a sling is useful.

Highly oedematous, vesicular and exudative eruptions such as pompholyx benefit from soaks in an astringent such as a 1:10 000 solution of potassium permanganate. An alternative is Burow's solution BP, which contains the astringent aluminium acetate and

is less messy than potassium permanganate. Liberal applications of aqueous cream and other bland emollients are soothing. Moderate or potent topical steroids are generally used, at least for a few days, to speed resolution of acute episodes. Topical immunomodulators such as tacrolimus and pimecrolimus seem likely to be beneficial in most forms of eczema, and especially in atopic dermatitis [1]. Tacrolimus ointment 0.1% seems to be equivalent in potency to potent topical corticosteroids such as betamethasone valerate [2] and hydrocortisone butyrate [3]. When practical, tubular bandaging can be used to help keep topical medications in place. The wet wrapping technique, in which a layer of wet tubular bandage (e.g. Tubifast®) is covered with a dry layer, can be particularly useful. Hazards include a risk of hypothermia, although, in moderation, the cooling effect is highly beneficial. Emollients and other medications can be applied under the bandaging as required. Penetration of topical corticosteroids can be significantly increased by this form of occlusion, enhancing both beneficial and adverse effects. Mild or moderate corticosteroids should be used for the face and genital areas. Potent or very potent steroids are required, at least initially, for acute pompholyx on the hands or feet.

When secondary infection is present, or staphylococcal contamination of the skin is thought to be an aggravating factor, oral antibiotics are often used. Topical preparations containing antibiotics or antiseptics in combination with steroids can also be helpful. These compound formulations should only be used when there is an indication for each constituent, in order to avoid unnecessary exposure to the risks of sensitization and emergence of bacterial resistance.

Excoriation can be reduced further by a sedative antihistamine such as hydroxyzine or trimeprazine, and additional hypnotics may be needed for a few days to ensure sleep.

Subacute eczema

If an acute eczema has failed to clear almost completely in 3–4 weeks, the perpetuating factors should be carefully sought. Has exposure to a sensitizing agent been overlooked? Has the patient become intolerant of the treatment prescribed? Has the treatment been effectively carried out?

Admission to hospital can often be helpful in these circumstances, to ensure that the aetiological factors have been fully explored and that treatment will be regularly and effectively applied. Rapid resolution usually follows admission and a period of rest. A prompt relapse on discharge may indicate photosensitivity or an allergic cause in the patient's home environment. Rapid deterioration after the arrival at the bedside of a generous bunch of flowers sometimes helps to establish the diagnosis of chrysanthemum sensitivity.

Paste bandages are of special value in occluding areas that are frequently excoriated, as in many lower leg eczemas. These must be applied skilfully to ensure that they are firm but not tight enough to cause discomfort or to restrict arterial or venous blood flow. Corticosteroids under polythene occlusion may be helpful at this stage, if only for a few days, to lessen itching. Topical immunomodulators such as tacrolimus and pimecrolimus are effective. Cleaning and bathing need not be routinely forbidden, and may be comforting, but long hot soaks and the use of soap should be discouraged. In some cases of asteatotic and discoid eczema, baths may be poorly tolerated and should be restricted. Liberal applications of emollients after bathing are helpful. Bath oils can be beneficial, but are best avoided for elderly patients as they make the bath more slippery.

Chronic eczema

In chronic eczema, oedema, vesiculation and exudation give way to a more stable picture of erythema, scaling, excoriation and lichenification. Pruritus often remains troublesome, especially in atopic dermatitis. It is important to regularly reconsider whether complications such as sensitization to medicaments or superinfection are playing a role.

Emollients should be applied frequently. Soaps and other potential irritants and sensitizers such as perfumes should be avoided. Mild, moderate or potent topical corticosteroids and topical immunomodulators [1–3] are helpful. In seborrhoeic dermatitis, and most cases of discoid eczema and atopic dermatitis, mild or moderate steroids are usually adequate. In severe atopic dermatitis and endogenous hand eczema, more potent steroids may be required. Long-term use of potent corticosteroids requires particular caution to minimize atrophy of the treated skin. For patients prone to frequent flares of eczema a strategy which may prove useful to limit steroid requirement is to induce remission with once or twice daily application of a potent topical steroid and then apply the steroid only for 2 days each week to maintain remission [4]. The use of topical immunomodulators such as tacrolimus and pimecrolimus provides a useful alternative, and these will also help in reducing cumulative exposure to steroids. This is particularly beneficial when prolonged treatment is required for eczema involving the face—a common situation in atopic dermatitis. Coal tar or shale tar (ichthammol), usually applied as creams containing tar extracts or bandages impregnated with tar paste, can be soothing and reduce pruritus. Occlusive dressings and bandages may be useful.

In the most severe cases, systemic steroids may be required. These act rapidly, improving symptoms within a day or two, but they should be discontinued as soon as possible. Alternatives to steroids include ciclosporin, which also acts rapidly [5], and azathioprine, which has a more gradual onset of action [6]. Cytotoxic immunosuppressants such as mycophenolate mofetil, methotrexate and cyclophosphamide have also occasionally been used. All these systemic modalities require careful monitoring. Various modalities of phototherapy have been successfully used in chronic eczema, especially in atopic dermatitis. These include UVB and, more recently, narrow-band UVB [7,8], PUVA [9] and UVA1 [10]. PUVA is also used for hand and foot eczema, often with topical application of 8-methoxypsoralen. However, phototherapy is potentially carcinogenic. In carefully selected cases of severe hand or foot eczema, superficial radiotherapy (Grenz rays) is effective. This is also carcinogenic and is probably best reserved for older patients.

References

1 Ruzicka T, Bieber T, Schopf E *et al*. A short-term trial of tacrolimus ointment for atopic dermatitis. *New Engl J Med* 1997; **337**: 816–21.

2 Nakagawa H. Phase III comparative study of FK506 ointment. Parallel-group comparison study with betamethasone valerate in atopic dermatitis of the trunk and limbs. *Nishihinon J Dermatol* 1997; **58**: 870–9.

3 Reitamo S, Rustin M, Ruzicka T *et al*. Efficacy and safety of tacrolimus ointment compared with hydrocortisone butyrate ointment in adult patients with atopic dermatitis. *J Allergy Clin Immunol* 2002; **109**: 547–55.
4 Berth-Jones J, Damstra R, Golsch S *et al*. Fluticasone propionate (FP) reduces risk of relapse in patients with atopic dermatitis. *J Eur Acad Dermatol Venereol* 2000; **14** (Suppl. 1): 125.
5 Berth-Jones J, Graham-Brown RAC, Marks R *et al*. Long-term efficacy and safety of cyclosporin in severe adult atopic dermatitis. *Br J Dermatol* 1997; **136**: 76–81.
6 Berth-Jones J, Takwale A, Tan E *et al*. Azathioprine in severe adult atopic dermatitis: a double-blind, placebo-controlled, crossover trial. *Br J Dermatol* 2002; **147**: 324–30.
7 George SA, Bilsland DJ, Johnson BE, Ferguson J. Narrow-band (TL-01) UVB air-conditioned phototherapy for chronic severe adult atopic dermatitis. *Br J Dermatol* 1993; **128**: 49–56.
8 Reynolds NJ, Franklin V, Gray JC. Narrow-band ultraviolet B and broad-band ultraviolet A phototherapy in adult atopic eczema: a randomised controlled trial. *Lancet* 2001; **357**: 2012–6.
9 Sheehen MP, Atherton DJ, Norris P, Hawk J. Oral psoralen photochemotherapy in severe childhood atopic eczema: an update. *Br J Dermatol* 1993; **129**: 431–6.
10 Krutmann J, Czech W, Diepgen T *et al*. High dose UVA1 therapy in the treatment of patients with atopic dermatitis. *J Am Acad Dermatol* 1992; **26**: 225–30.

Murray Williams' warts

Multiple seborrhoeic warts occurring in areas of resolved eczema have only occasionally been reported since the phenomenon was described by Williams in 1956 [1,2]. Multiple warts arise in the few months following resolution of the eczema and tend to gradually resolve by 5–6 months.

References

1 Williams MG. Acanthomata appearing after eczema. *Br J Dermatol* 1956; **68**: 268–71.
2 Horiuchi Y. Multiple seborrhoeic verrucae following eczema. *J Dermatol* 1989; **16**: 505–7.

Lichenification

Definition. Lichenification is a change in appearance and texture of the skin associated particularly with pruritic dermatoses.

Clinical features. Mild or early lichenification presents as a rather subtle coarsening of the skin surface markings on a background of dry and usually erythematous skin. As the condition progresses, the skin becomes markedly thickened and hyperkeratotic (Fig. 23.32). The borderline between lichenification and some prurigos is tenuous, both in nomenclature and in practice. Prurigo nodularis could also be called nodular lichenification.

Histopathology. The variable clinical severity of lichenification is reflected histologically in variable degrees of acanthosis and hyperkeratosis. Additional features specific to lichenified dermatoses are discussed further below.

Aetiology. The features of lichenification are sometimes regarded as developing secondary to excoriation. This may not be entirely accurate, and it seems likely that inflammation associated with the underlying dermatosis often plays an independent role. Lichenification can occur to some degree in all pruritic, and especially eczematous, dermatoses.



Fig. 23.32 Lichenification of the arm in a patient with atopic eczema.

Lichenified dermatoses

In lichen simplex, lichen striatus and notalgia paraesthetica, lichenification is usually the predominant clinical feature.

Lichen simplex

Synonym
- Circumscribed neurodermatitis

Definition. Lichen simplex is an eczematous dermatosis characterized by a small number of heavily lichenified plaques or, very often, a single lesion.

Not all individuals are capable of developing lichenification. Patients with lichen simplex are more readily conditioned to scratch following an itch stimulus than control subjects [1]. Lichen simplex may occur as a manifestation of the atopic state [2], but not all atopics lichenify, and lichen simplex is seen in many individuals who show no stigmata of atopy. There appears to be well-marked racial variation in the capacity of the skin to lichenify; the high incidence of lichenification in oriental people has often been emphasized.

In the predisposed subject, emotional tensions play an important role in favouring the development of lichen simplex and ensuring its perpetuation [3].

Histopathology [4,5]. The histological changes of lichen simplex vary with site and duration. Acanthosis and variable degrees of hyperkeratosis are usually observed. The rete ridges are lengthened. Spongiosis is sometimes present, and small areas of parakeratosis are occasionally seen. There is hyperplasia of all components of the epidermis [6]. The labelling index has been shown autoradiographically to be over 25%, but the transit time is longer than in psoriasis [7].

The dermis contains a chronic inflammatory infiltrate, and in very chronic lesions there may be some fibrosis. Silver impregnation techniques show proliferation of the Schwann cells, which may make up an appreciable proportion of the cellular infiltrate.



Fig. 23.33 Follicular papules of lichenification adjacent to the elbow.

In very chronic lesions, especially in giant lichenification, the acanthosis and hyperkeratosis are gross, and the rete ridges are irregularly but strikingly elongated and widened.

Clinical features [5]. As in all forms of lichenification, pruritus is a prominent symptom, and is often out of proportion to the extent of the objective changes. It may develop in paroxysms of great intensity. Scratching tends to give great satisfaction initially, but is then continued with violence until the skin is sore. There is then a refractory period of some hours until the itch recurs. During the early stages the skin is reddened and slightly oedematous, and the normal markings are exaggerated. The redness and oedema subside, and the central area becomes scaly and thickened, and sometimes pigmented. Surrounding this central plaque is a zone of lichenoid papules, and beyond this an indefinite zone of slight thickening and pigmentation merges with normal skin. These features may be greatly modified by the site and duration of the lesion. In mild cases, follicular eczematous papules may be seen, particularly on the forearms and elbow regions of children (Fig. 23.33).

Lichen simplex is uncommon in childhood. The peak incidence is between 30 and 50 years of age, but it is seen at any age from adolescence onwards. Women are affected more often than men. Single and multiple sites are involved with about equal frequency. Almost any area may be affected, but the commonest sites are those that are conveniently reached. The usual sites are the nape of the neck, the lower legs (Fig. 23.34) and ankles, the sides of the neck, the scalp, the upper thighs, the vulva, pubis or scrotum, and the extensor forearms.

Lichen simplex of the nape of the neck (lichen nuchae) is almost confined to women. The plaque may be limited to a small area around the midline of the nape or may extend some distance into the scalp and over the neck. Scaling is often profuse and psoriasiform, and episodes of secondary infection are frequent. The fold behind the ear may also be involved. Scaling, crusting and fissuring are more evident than the usual changes of lichenification. Other regions of the scalp are less often affected. The presenting manifestation is an area of scaling, with twisted, broken hairs. The epidermal thickening may be great enough to form a nodule.



Fig. 23.34 Lichen simplex. (Courtesy of Dr D.A. Burns, Leicester Royal Infirmary, Leicester, UK.)

In other sites the typical features of lichenification are usually retained, but if the subcutaneous tissues are lax, and excoriation continues for many years, solid, tumour-like plaques may be formed, with a warty, cribriform surface. This, the so-called *giant lichenification of Pautrier* [8], occurs mainly in the genitocrural region.

The descriptive term *pebbly lichenification* has been applied to a distinctive clinical variant, consisting of discrete, smooth nodules, seen occasionally in atopic and seborrhoeic subjects, and in photodermatitis. Clinically it may simulate lichen planus.

A dermatomal pattern of lichen simplex chronicus has been described as the initial presentation of an intramedullary neoplasm with syringomyelia [9].

Diagnosis. The morphological diagnosis of lichenification is not usually difficult—lichen planus, lichen amyloidosus and psoriasis have to be excluded, and typical lesions should be sought in other sites. Sometimes, however, no conclusive diagnosis is possible on either clinical or histological grounds. A patient with psoriasis may develop lichen simplex which combines the histological features of both conditions.

Once the diagnosis of lichenification has been established its causation must be carefully investigated. Secondary lichenification complicates persistent skin lesions of many types. It occurs on the lower leg in the presence of venous insufficiency, in atopic dermatitis, in asteatotic eczema, in low-grade chronic contact dermatitis, and in some chronic infections with *Trichophyton rubrum*. Symmetrical lesions in particular should suggest secondary lichenification of a contact dermatitis. More than one woman with formalin dermatitis of the base of the neck has been referred to a

psychiatrist, when she should have been patch tested and advised merely to discard the offending article of clothing. Similarly, a chronic *T. rubrum* infection of the thighs or feet, with secondary lichenification, responds better to griseofulvin than to tranquillizers.

Treatment. A careful psychological history should be taken, and the patient given some assistance in reducing their tensions. The nature of lichen simplex and the need to break the scratching habit must be explained. Sedation is often needed, and sedative antihistamines may be helpful. A topical antibiotic may be prescribed for a few days if secondary infection is present. A potent or very potent topical corticosteroid can be very helpful in some cases, but seems to have no effect in others.

On an arm or leg it is useful to apply an occlusive bandage which prevents scratching. For very chronic lesions, tar paste medicated bandages can be very helpful. They should be renewed at intervals of 5–7 days. Self-adhesive, steroid-impregnated tape (e.g. Haelan® tape) can often be effective. Alternatively, a potent steroid ointment under polythene occlusion, for short periods, may also be useful. Modest improvement has also been shown with 5% doxepin cream [10].

Circumscribed, chronic lesions can often be effectively treated by dermal infiltration with triamcinolone (10 mg/ml).

Response has been reported to capsaicin cream [11].

References

1 Robertson IM, Jordan JM, Whitlock FA. Emotions and skin (III)—the conditioning of scratch responses in cases of lichen simplex. *Br J Dermatol* 1975; **92**: 407–12.
2 Singh G. Atopy in lichen simplex (neurodermatitis circumscripta). *Br J Dermatol* 1973; **88**: 625–7.
3 Cormia FE. Basic concepts in the production and management of the psychosomatic dermatoses—II. *Br J Dermatol* 1951; **63**: 129–51.
4 Cowan MA. Neurohistological changes in lichen simplex chronicus. *Arch Dermatol* 1964; **89**: 562–8.
5 Shaffer B, Beerman H. Lichen simplex chronica and its variants. A discussion of certain psychodynamic mechanisms and clinical and histopathologic correlation. *Arch Dermatol Syphilol* 1951; **64**: 340–51.
6 Marks R, Wells GC. Lichen simplex: morphodynamic correlates. *Br J Dermatol* 1973; **88**: 249–56.
7 Marks R, Wells GC. A histochemical profile of lichen simplex. *Br J Dermatol* 1973; **88**: 557–62.
8 Berlin C. Lichenificatio gigantea. (Lichenification géante of Brocq and Pautrier). *Arch Dermatol Syphilol* 1939; **39**: 1012–20.
9 Kinsella LJ, Carney-Godley K, Feldman E. Lichen simplex chronicus as the initial manifestation of intramedullary neoplasm and syringomyelia. *Neurosurgery* 1992; **30**: 418–21.
10 Drake LA, Millikan LE. The antipruritic effect of 5% doxepin cream in patients with eczematous dermatitis. *Arch Dermatol* 1995; **131**: 1403–8.
11 Tupker RA, Coenraads PJ, van der Meer JB. Treatment of prurigo nodularis, chronic prurigo and neurodermatitis circumscripta with topical capsaicin. *Acta Derm Venereol (Stockh)* 1992; **72**: 463.

Lichen striatus

Synonym
- Linear lichenoid dermatosis

Definition and aetiology. Lichen striatus is a self-limiting, inflammatory, linear dermatitis of unknown origin. The factors determining the linear distribution are unknown, as none of the proposed embryological, neurological and vascular hypotheses is applicable to all cases. It has been suggested that the lesions develop in the lines of Blaschko [1], which are thought to be due to a form of human 'mosaicism' in which different groups of cells behave differently for reasons which are not yet clear. In a series of 26 patients, 80% were atopic [2].

Histopathology [3–5]. The histological appearances are variable, but may be distinctive. They often resemble lichen planus, with a band-like infiltrate in the dermis, and overlying epidermal changes. The earliest change is intercellular oedema, stretching the tonofilament–desmosome complexes and separating the epidermal cells. Like the spongiosis, acanthosis is variable in degree. Dyskeratotic keratinocytes, like the 'corps ronds' of Darier's disease, are seen in about 50% of cases. There is focal liquefactive degeneration of the basal layer. The dermis is oedematous, and the vessels and appendages are surrounded by an infiltrate of lymphocytes and histiocytes, which may be quite dense and extend deeply. Scattered cells often penetrate the epidermis.

Clinical features [2,6]. Over 50% of cases occur in children, usually between the ages of 5 and 15 years, but onset in early infancy and in old age has been reported. Females are affected two or three times as frequently as males. Small, pink, lichenoid papules, discrete at first but rapidly coalescing, appear suddenly and extend over the course of a week or more to form a dull-red, slightly scaly, linear band, usually 2 mm to 2 cm in width, and often irregular. Occasionally, the bands broaden into plaques, especially on the buttocks. The lesion may be only a few centimetres in length or may extend the entire length of the limb, and may be continuous or interrupted (Fig. 23.35). Parallel linear bands or zosteriform patterns have been recorded.

The initial lichenoid papules are pink and not violaceous, and show no umbilication or Wickham's striae. The papules may be hypopigmented in dark-skinned people.

The lesions occur most commonly on one arm or leg, or on the neck, but may develop on the trunk. The abdomen, buttocks and thighs may be involved in single extensive lesions, but multiple lesions are rare, and bilateral involvement is exceptional. Involvement of the nails may result in longitudinal ridging, splitting, onycholysis or nail loss [7–8].

There are usually no symptoms, but pruritus may occasionally occur. The course is variable. The lesion usually reaches its maximum extent within 2 or 3 weeks, but gradual extension can continue for several months. Spontaneous resolution can be expected within 3–6 months in most cases, but some lesions may persist for over a year. Resolution may be followed by temporary hypopigmentation.

Diagnosis. Epidermal naevi, linear or zosteriform, may first appear in childhood or later, and the inflammatory linear epidermal naevus (Chapter 18) in particular has many clinical and histological features in common with lichen striatus, but the naevi persist indefinitely. Linear forms of lichen planus and psoriasis can usually be differentiated clinically, even in the absence of typical lesions in other sites, which should always be sought.



Fig. 23.35 Lichen striatus of the inner thigh in a girl aged 16 years. The histological changes were those of chronic eczema. (Courtesy of Dr R.A. Marsden, St George's Hospital, London, UK.)

Linear porokeratosis must also be considered [9]. Biopsy may be helpful.

Treatment. Usually none is necessary. In the unusual persistent case, infiltration with steroids may be effective. Nail involvement may respond to potent steroid cream under occlusion.

References

1 Jackson R. The lines of Blaschko: a review and consideration. Observations of the cause of certain unusual linear conditions of the skin. *Br J Dermatol* 1976; **95**: 349–60.
2 Toda K, Okamoto H, Horio T. Lichen striatus. *Int J Dermatol* 1986; **25**: 584–5.
3 Reed RJ. Lichen striatus. A model for the histologic spectrum of lichenoid reactions. *J Cutan Pathol* 1975; **2**: 1–18.
4 Staricco RG. Lichen striatus. *Arch Dermatol* 1959; **79**: 311.
5 Stewart WM, Lauret P, Dietrini P. Lichen striatus: critères histologiques. *Ann Dermatol Vénéréol* 1977; **104**: 132–5.
6 Charles CR. Lichen striatus. A clinical, histologic and electron microscopic study of an unusual case. *J Cutan Pathol* 1974; **1**: 265–74.
7 Baran R, Dupré A, Lauret P *et al*. Le lichen striatus onychodystrophique. *Ann Dermatol Vénéréol* 1979; **106**: 885–91.
8 Kaufman JP. Lichen striatus with nail involvement. *Cutis* 1974; **14**: 232–4.
9 Rahbari H, Cordero AA, Mehregan AH. Linear porokeratosis. A distinctive clinical variant of porokeratosis of Mibelli. *Arch Dermatol* 1974; **109**: 526–8.

Notalgia paraesthetica

Definition. A localized, pruritic patch of lichenified and often hyperpigmented skin at or near the inferior tip of the scapula. This distinctive pruritic condition seen in adults is thought to result from entrapment of the dorsal nerve root.

Treatment. Capsaicin 0.025% cream applied three to five times daily for 4 weeks proved effective in a placebo-controlled trial [1].

Reference

1 Wallengren J, Klinker M. Successful treatment of notalgia paresthetica with topical capsaicin: vehicle-controlled, double-blind, crossover study. *J Am Acad Dermatol* 1995; **32**: 287–9.

Prurigo [1]

Definition. This term is best used to denote a group of skin diseases characterized by intensely pruritic papules or nodules.

The definition has been the subject of much debate. Some authors have stressed the intense pruritus, others have emphasized visible excoriations, and yet others have suggested that there should be no identifiable local cause for the scratched lesions.

The term was originally introduced by Hebra [1] to denote papules induced by scratching. This definition allows the inclusion of entities such as the papular urticaria caused by insect bites, where dermographism may also be present. Many of the original cases of Hebra's prurigo, described in Vienna in the 19th century, were probably atopic patients in poor social conditions. Flea bites may well have played a part in producing the papular lesions.

The archaic term Besnier's prurigo has been applied to the chronic lichenified flexural form of atopic eczema.

Reference

1 Hebra F. *On Diseases of the Skin*. London: New Sydenham Society, 1868: 257.

Pruriginous dermatoses

Pruriginous lesions are the characteristic feature of nodular prurigo, chronic prurigo, prurigo pigmentosa, prurigo of pregnancy and actinic prurigo. Dermographic prurigo and neurotic excoriation can present with a similar appearance and are therefore also described here.

Nodular prurigo

Synonym
- Hyde's prurigo

Definition. Nodular prurigo is characterized clinically by chronic, intensely itchy nodules and histologically by marked hyperkeratosis and acanthosis, with downward projections of the epidermis. It is generally regarded as a variety of eczema. In many cases there is a history of atopic dermatitis or another form of eczema.

Aetiology [1]. The cause is unknown. Emotional stress seems to be a contributory factor in some cases, and it can be difficult to determine whether this is the cause or a result of the prurigo. Around 65–80% of patients are atopic. In these patients the age of onset may be earlier [2], even if no eczematous eruption is present. In 20% the condition starts after an insect bite [3].

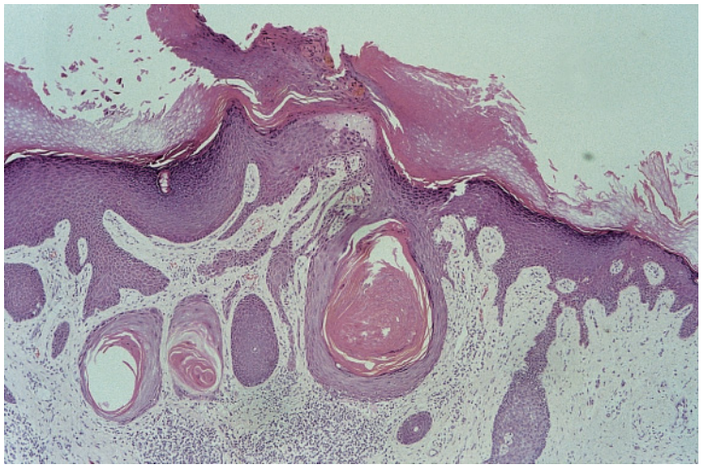


Fig. 23.36 Nodular prurigo. This shows gross accentuation of the changes found in lichenification. The epidermal downgrowth is pseudoepitheliomatous in extent. There is a mixed inflammatory cell infiltrate in the dermis and some sclerosis of the dermal collagen. H&E, ×40. (Courtesy of Dr M.J. Cook, Royal Surrey County Hospital, Guildford, Surrey, UK.)



Fig. 23.37 Nodular prurigo of the arm. (Courtesy of Dr D.A. Burns, Leicester Royal Infirmary, Leicester, UK.)

Histopathology [4,5]. The changes somewhat resemble those of lichen simplex, but the hyperkeratosis may be even greater, and the downward projections of the epidermis so marked as to suggest pseudoepitheliomatous hyperplasia (Fig. 23.36). The dermal infiltrate is dense, and there may be neural and vascular hyperplasia. These changes may arise, in part, as a non-specific reaction to repeated scratching [6]. In some cases the histology is that of chronic eczema. Mast cells are prominent, and there may be striking extracellular deposits of eosinophilic granule proteins such as major basic protein and eosinophil-derived neurotoxin [7], suggesting that mast cells and eosinophils may play a major role.

In the early literature, Pautrier described 'neuromas' in this condition, but these have not been seen in large series of patients [3,8]. There are, however, increased numbers of calcitonin gene-related peptide and substance P immunoreactive nerve fibre bundles in the skin of the nodular lesions, and neuropeptides may play a part in causing the intense itching [9,10]. In 75% of cases an increase in the number of Merkel cells is also seen [11]. Such changes do not occur in the lesions of lichen simplex.

Clinical features. Cases occur at all ages, but mainly from 20 to 60 years. Both sexes are equally affected. The individual lesions range from small papules to hard globular nodules, 1–3 cm in diameter, with a raised, warty surface. The early lesion is red, and may show a variable urticarial component. Pigmentary changes are common. Crust and scale may cover recently excoriated lesions. The intervening skin often shows slight xeroderma, and there is often an irregular ring of hyperpigmentation immediately around the nodules. The number of lesions varies greatly and may be very large. The nodules may be arranged in groups. They usually develop initially on the distal parts of the limbs, and are worse on the extensor surfaces (Fig. 23.37). The trunk, face and even the palms can be affected.

The patient is tormented by crises of intense pruritus. New nodules develop from time to time, and existing nodules may remain pruritic indefinitely, although some may regress spontaneously to leave scars. The disease runs a very protracted course.

Diagnosis. The large, more-or-less symmetrical nodules, and the intense, often distressing pruritus, are the key clinical features. These may also arise as a secondary event in a wide range of cutaneous and systemic diseases, which must be considered carefully before arriving at a diagnosis of idiopathic nodular prurigo.

Skin diseases that may mimic nodular prurigo include hypertrophic lichen planus, especially on the lower legs. The lesions are usually violaceous, and may be associated with more typical lichen planus lesions elsewhere. A variant of bullous pemphigoid called pemphigoid nodularis may present as nodular prurigo for some time before the typical urticated plaques and blisters supervene [12,13]. Immunofluorescence findings are those of pemphigoid, and the disease can be treated as pemphigoid with immunosuppressive therapy. Most cases occur in elderly women, but a juvenile form has been reported [14]. An unusual case of porokeratosis has been described in which some lesions, histologically demonstrating features of porokeratosis, clinically resembled prurigo nodules [15]. Cases are also described in association with oncocerciasis, leech bites, reactive perforating collagenosis and multiple granular cell tumours [1]. Allergic contact dermatitis may also result in a papulonodular eruption, and patch testing can sometimes be helpful [16].

Systemic causes of pruritus which can give rise to lesions resembling nodular prurigo include renal failure [17], liver disease [18], lymphoma [19] and HIV infection [20]. Gluten-sensitive enteropathy has been found in some patients [21,22], but is not present in the majority [3,23].

Treatment. Measures used to reduce excoriation include cutting the nails very short, wearing gloves at night and occlusion of the involved regions of skin with bandages, dressings or steroid-impregnated tape. Sedative antihistamines are often used, and are most helpful at night. Emollients may be helpful when xerosis is present. Topical steroids are not usually effective, but intralesional injection of triamcinolone can be beneficial. Topical capsaicin [24]

has been used with success in some cases. Cryotherapy can be helpful, but may result in pigmentary changes, especially in pigmented skin. Application of the sensitizer DNCB improved nodular prurigo in one case [25].

Systemic agents that can be highly effective include thalidomide, although this is hazardous in fertile female patients due to teratogenicity. This drug can also induce a painful peripheral neuropathy [26,27]. Ciclosporin [28] and azathioprine [29] can also be highly effective, although the disease tends to relapse after the drugs are discontinued. Interestingly, ciclosporin also proved effective in a case associated with uraemia [30].

Nodular prurigo can respond well to PUVA, using local application of psoralen [31]. Oral PUVA is also used on occasions. A pleasing response has been reported to UVB [32], and narrowband UVB may be effective alone and in combination with thalidomide [33].

Assessment of the patient's emotional state is desirable; antidepressants and tranquillizers can prove useful in selected cases [34].

References

1 Rowland-Payne CME. Prurigo nodularis. In: Bernhard J, ed. *Itch: Mechanisms and Management of Pruritus.* New York: McGraw Hill, 1994: 102–19.

2 Tanaka M, Aiba S, Matsumura N *et al*. Prurigo nodularis consists of two distinct forms: early-onset atopic and late-onset non-atopic. *Dermatology* 1995; **190**: 269–76.

3 Rowland-Payne CME, Wilkinson JD, McKee PH. Nodular prurigo: a clinicopathological study of 46 patients. *Br J Dermatol* 1985; **113**: 431–9.

4 Cowan MA. Neurohistological changes in prurigo nodularis. *Arch Dermatol* 1964; **89**: 754–8.

5 Feuerman EJ, Sandbank M. Prurigo nodularis. Histological and microscopical study. *Arch Dermatol* 1975; **111**: 1472–7.

6 Runne V, Orfanos EC. Cutaneous neural proliferation in highly pruritic lesions of chronic prurigo. *Arch Dermatol* 1977; **114**: 787–91.

7 Perez GL, Peters MS, Reda AM *et al*. Mast cells, neutrophils and eosinophils in prurigo nodularis. *Arch Dermatol* 1993; **129**: 861–6.

8 Doyle JA, Connolly SM, Hunziker N *et al*. Prurigo nodularis: a reappraisal of the clinical and histological features. *J Cutan Pathol* 1979; **6**: 392–403.

9 Molina FA, Burrows NP, Russell Jones R *et al*. Increased sensory neuropeptides in nodular prurigo: a qualitative immunohistochemical study. *Br J Dermatol* 1992; **127**: 344–51.

10 Vaalasti A, Suomalainen H, Rechardt L. Calcitonin-gene related peptide immunoreactivity in prurigo nodularis: a comparative study with neurodermatitis circumscripta. *Br J Dermatol* 1989; **120**: 619–23.

11 Nahass GT, Penneys NS. Merkel cells and nodular prurigo. *J Am Acad Dermatol* 1994; **31**: 86–8.

12 Bourke JF, Berth-Jones J, Gawkrodger DJ, Burns DA. Pemphigoid nodularis: a report of two cases. *Clin Exp Dermatol* 1994; **19**: 496–9.

13 Massa MC, Connolly SM. Bullous pemphigoid with features of prurigo nodularis. *Arch Dermatol* 1982; **118**: 937–9.

14 Ratnavel RC, Shranks AS, Grant JW, Norris PG. Juvenile pemphigoid nodularis. *Br J Dermatol* 1994; **130**: 125–6.

15 Kang BD, Kye YC, Kim SN. Disseminated superficial actinic porokeratosis with both typical and prurigo nodularis-like lesions. *J Dermatol* 2001; **28**: 81–5.

16 Zelickson BD, McEvoy MT, Fransway AF. Patch testing in prurigo nodularis. *Contact Dermatitis* 1989; **20**: 321–5.

17 Murphy M, Carmichael AJ. Renal itch. *Clin Exp Dermatol* 2000; **25**: 103–6.

18 Baykal C, Ozkaya-Bayazit E, Gokdemir G, Diz Kucukkaya R. The combined occurrence of macular amyloidosis and prurigo nodularis. *Eur J Dermatol* 2000; **10**: 297–9.

19 Fina L, Grimalt R, Berti E. Nodular prurigo associated with Hodgkin's disease. *Dermatologica* 1991; **182**: 243–6.

20 Matthews SN, Cockerell CJ. Prurigo nodularis in HIV-infected individuals. *Int J Dermatol* 1998; **37**: 401–9.

21 McKenzie AW, Stubbing DG, Elvy BL. Prurigo nodularis and gluten enteropathy. *Br J Dermatol* 1976; **95**: 89–92.

22 Wells GC. Skin disorders in relation to malabsorption. *BMJ* 1962; **ii**: 937–43.

23 Hudson PM, Black MM, Whimster IW. Nodular prurigo—a clinical, biochemical and histological study. *Br J Dermatol* 1978; **99** (Suppl. 16): 12.

24 Tupker RA, Coenraads PJ, van de Meer JB. Treatment of prurigo nodularis, chronic prurigo and neurodermatitis circumscripta with topical capsaicin. *Acta Derm Venereol (Stockh)* 1992; **72**: 463.

25 Yoshizawa Y, Kitamura K, Maibach HI. Successful immunotherapy of chronic nodular prurigo with topical dinitrochlorobenzene. *Br J Dermatol* 1999; **141**: 387–9.

26 Van der Broek H. Treatment of prurigo nodularis with thalidomide. *Arch Dermatol* 1980; **116**: 571–2.

27 Winkelmann RK. Thalidomide treatment of prurigo nodularis. *Acta Derm Venereol (Stockh)* 1984; **64**: 412–7.

28 Berth-Jones J, Smith SG, Graham-Brown RAC. Nodular prurigo responds to cyclosporin. *Br J Dermatol* 1995; **132**: 795–9.

29 Lear JT, English JSC, Smith AG. Nodular prurigo responsive to azathioprine. *Br J Dermatol* 1996; **134**: 1151.

30 Ahmed E, McMillan MA. Cyclosporin treatment of nodular prurigo in a dialysis patient. *Br J Dermatol* 1997; **136**: 805–6.

31 Vaatainen N, Hannuksela M, Karvonen J. Local photochemotherapy in nodular prurigo. *Acta Derm Venereol (Stockh)* 1979; **59**: 544–7.

32 Hans SK, Cho MY, Park YK. UV treatment of generalised prurigo nodularis. *J Am Acad Dermatol* 1990; **29**: 436–7.

33 Ferrandiz C, Carrasocsa JM, Just M *et al*. Sequential combined therapy with thalidomide and narrowband (TL01) UVB in the treatment of prurigo nodularis. *Dermatology* 1997; **195**: 359–61.

34 Koblenzer CS. Treatment of nodular prurigo with cyclosporin (treat the disease, not just the symptoms). *Br J Dermatol* 1996; **135**: 330–1.

Chronic prurigo of adults

Synonyms

- Chronic papular urticaria
- Subacute prurigo
- Papular dermatitis

These terms are used to denote pruritic papular eruptions, which often appear rather similar to nodular prurigo except that the lesions are smaller and less elevated. Chronic prurigo is regarded as eczematous in nature although, as in the case of nodular prurigo, a similar clinical picture can arise in patients with systemic causes of pruritus. Another similarity with nodular prurigo is the association with stress and other psychological factors in some cases. Neurotic excoriation has previously been included as synonymous with subacute prurigo (see below).

Biopsy shows a non-specific dermatitis.

Treatment is similar to that of nodular prurigo and tends to be difficult. Soothing topical applications such as crotamiton or 0.5% menthol in aqueous cream are often used. Some patients respond well to a course of UVB or PUVA [1].

Reference

1 Clark AR, Jorizzo JL, Fleischer AB. Papular dermatitis (subacute prurigo, 'itchy red bump' disease): Pilot study of phototherapy. *J Am Acad Dermatol* 1998; **38**: 929–33.

Prurigo pigmentosa [1–6]

Definition. Irritable, red papules on the trunk and neck which fade to leave reticular hyperpigmentation.



(a) (b)

Fig. 23.38 (a) Prurigo pigmentosa. (Courtesy of Dr M. Aso, Tottori University School of Medicine, Japan.) (b) Prurigo pigmentosa. (Courtesy of Dr L. Chiam, National Skin Centre, Singapore. Published with permission from *Clinical and Experimental Dermatology*.)

Aetiology. The cause is unknown. Some cases have occurred in patients who were diabetic, dieting or anorexic, and it has been suggested that the associated metabolic changes, including ketosis, may play a role [7].

Histopathology. The histology is non-specific, but often somewhat lichenoid. Immunofluorescence is negative. Occasional blood eosinophilia occurs.

Clinical features. The condition is rare in the Western world, but many cases have been described in Japan. The disorder is more common in adult females, with an onset in the spring and summer months. The characteristic lesions are found on the trunk and neck, and present as itchy, red papules, sometimes with vesicles, which coalesce to produce a reticular pattern (Fig. 23.38). Later they are replaced by a reticular hyperpigmentation.

Diagnosis. This is based on the clinical and histological features. Patch testing may be helpful in excluding allergic contact dermatitis.

Treatment. Minocycline 200 mg daily appears to be the treatment of choice [1], as the pruritus and rash disappear within a week in most cases. About one-third of patients will respond dramatically to dapsone. A prompt response to macrolide antibiotics has been reported [8]. Neither the rash nor the itching respond to oral antihistamines or topical steroids.

References

1 Aso M, Miyamato T, Morimura T *et al*. Prurigo pigmentosa successfully treated with minocycline. *Br J Dermatol* 1989; **120**: 705–8.
2 Cotterill JA, Ryatt KS, Greenwood R. Prurigo pigmentosa. *Br J Dermatol* 1981; **105**: 707–10.
3 Cox NH. Prurigo pigmentosa. *Br J Dermatol* 1987; **117**: 121–4.
4 Jorizzo J, Gath S, Smith EB. Prurigo—a clinical review. *J Am Acad Dermatol* 1981; **4**: 723–9.
5 Joyce AP, Horn TD, Anholt GJ. Prurigo pigmentosa—review of the literature. *Arch Dermatol* 1989; **125**: 1551–4.
6 Nagashima M. Prurigo pigmentosa—clinical observations in 14 cases. *J Dermatol* 1978; **5**: 61–7.
7 Nakada T, Sueki H, Iijima M. Prurigo pigmentosa (Nagashima) associated with anorexia. *Clin Exp Dermatol* 1998; **23**: 25–7.
8 Yazawa N, Ihn H, Yamane K *et al*. The successful treatment of prurigo pigmentosa with macrolide antibiotics. *Dermatology* 2001; **202**: 67–9.

Prurigo of pregnancy [1,2]

This is regarded as a specific dermatosis of pregnancy (see Chapter 8). It occurs in about one in 300 pregnancies. In some cases it appears to be a manifestation of atopy. Pruritic papules and nodules develop on the abdomen and/or limbs, usually at 25–30 weeks of gestation. These may persist for several weeks after delivery. Skin biopsy reveals non-specific epidermal thickening, parakeratosis and a lymphocytic infiltrate in the upper dermis. Immunofluorescence is negative. The itch is usually improved by potent topical steroids and sedative antihistamines. The condition is not associated with any risk to the pregnancy.

References

1 Nurse DS. Prurigo of pregnancy. *Australas J Dermatol* 1968; **9**: 258–67.
2 Holmes RC, Black MM. The specific dermatoses of pregnancy. *J Am Acad Dermatol* 1983; **8**: 405–12.

Dermographic prurigo

This is a severe form of symptomatic dermographism in which urticarial weals and excoriations occur at sites of clothing pressure, especially around the edges of a brassière or belt. There may eventually be some pigmentation.

Actinic prurigo

Synonym
- Hutchinson's summer prurigo

This is an uncommon photodermatosis (see Chapter 29).

Neurotic excoriation

This disorder, which predominantly affects middle-aged women who appear to be under emotional stress, has also been called subacute prurigo. This latter term is now more appropriately used synonymously with chronic prurigo of adults. It is not a satisfactory description of neurotic excoriation, as the lesions are excoriated erosions or ulcers rather than papules. This term should be reserved for cases where psychological factors are the primary cause of repeated excoriation. Neurotic excoriation is described further in Chapter 64.

Erythroderma

Definition. Erythroderma is the term applied to any inflammatory skin disease that affects more than 90% of the body surface. The term exfoliative dermatitis is used synonymously, although the degree of exfoliation is sometimes quite mild.

Incidence. A study from the Netherlands estimated the annual incidence at 0.9 per 100 000 population [1].

Aetiology [2–6]. The main causes of erythroderma in adults are listed in Table 23.9 and are discussed below. The figures vary somewhat with the age of the population, and are based on several published studies. In younger people, for example military personnel, there will be a larger proportion due to drug allergies [6]. Drugs commonly causing erythroderma are listed in Chapter 75. In some communities, the incidence of erythroderma may be higher because of self-medication and use of traditional remedies [7]. The use of herbal remedies, such as St John's wort [8], may trigger this reaction.

The causes of erythroderma in the newborn are considered in Chapter 17.

Other, rare causes of erythroderma include sarcoidosis [9], Hailey–Hailey disease [10], pemphigoid [11], toxic shock syndrome [12], lupus erythematosus [13], angioimmunoblastic lymphadenopathy [14] and dermatomyositis [15]. Graft-versus-host disease may progress to erythroderma in some cases. A related disorder was reported in Japan, where cases of fatal erythroderma occurred following major surgery. It was suggested that these cases were examples of post-transfusion graft-versus-host disease [16].

Erythroderma has occasionally been reported with seroconversion following HIV infection [17]. In established AIDS, erythroderma may arise from a variety of causes. Some are examples of severe seborrhoeic dermatitis, others are associated with lymphoma, and some are of unknown cause [18]. However, it should be noted that $CD4^+$ T lymphocytopenia has been caused by erythroderma in the absence of HIV infection [19].

Males are affected between two and three times more frequently than females and, if the hereditary disorders and atopic dermatitis are excluded, most are over 45 years old.

Table 23.9 Causes of erythroderma and relative prevalence in adults.

Condition	Prevalence (%)
Hereditary disorders	1.0
Ichthyosiform erythroderma	
Pityriasis rubra pilaris	
Psoriasis	25.0
Eczema of various types	40.0
Drugs	10.0
Especially organic arsenic, gold, mercury	
Occasionally penicillin, barbiturates, etc.	
Pemphigus foliaceus	0.5
Lymphoma and leukaemias	15.0
Other skin diseases	0.5
Lichen planus	
Dermatophytosis	
Crusted scabies	
Dermatomyositis	
Unknown	8.0

Histopathology. Histopathology can help identify the cause of erythroderma in up to 50% of cases, particularly if multiple skin biopsies are examined [20]. The histological appearances vary depending upon the severity and duration of the inflammatory process. In the acute stage, spongiosis and parakeratosis are prominent, and a non-specific inflammatory infiltrate permeates, to a variable depth, a grossly oedematous dermis. In the chronic stage, acanthosis and elongation of the rete ridges become more prominent.

In erythroderma due to lymphoma, the infiltrate may become increasingly pleomorphic, and it may eventually acquire specific diagnostic features, such as a band-like lymphoid infiltrate at the dermoepidermal junction, with atypical cerebriform mononuclear cells and Pautrier microabscesses [21]. In other cases, however, it remains non-specific throughout its course, and the distinction can be difficult. Patients with Sézary syndrome often show some features of chronic dermatitis, and benign erythroderma may occasionally show some features suggestive of lymphoma.

Immunophenotyping of the lymphoid infiltrate may not solve the problem, as it generally shows features of mature T cells in both benign and malignant erythroderma [22].

In psoriasis, papillomatosis and clubbing of the papillary zones may be seen, and in pemphigus foliaceus, superficial acantholysis will be present. In ichthyosiform erythroderma and pityriasis rubra pilaris, repeated biopsies from carefully selected sites may reveal their characteristic features.

Clinical features. Erythroderma developing in primary eczema or associated with a lymphoma is often of sudden onset. Patchy erythema, which rapidly generalizes, may be accompanied by fever, shivering and malaise. Hypothermia may develop.

The erythema extends rapidly, and may be universal in 12–48 h. Scaling appears after 2–6 days, often first in the flexures, but it varies greatly in degree and character from case to case. The scales may be large, or fine and bran-like. At this stage the skin is bright red, hot and dry, and palpably thickened. The intensity of the erythema may fluctuate over periods of a few days or even a few hours. Irritation is sometimes severe, but a sensation of tightness

is more characteristic. Many patients complain of feeling cold, especially when the erythema is increasing.

When the erythroderma has been present for some weeks, the scalp and body hair may be shed and the nails become ridged and thickened, and may also be shed. The periorbital skin is inflamed and oedematous, resulting in ectropion, with consequent epiphora. In very chronic cases there may be pigmentary disturbances, especially in black people, in whom patchy or widespread loss of pigment is often seen.

The degree of enlargement of the lymph nodes in the absence of an underlying malignant lymphoma is variable. They are usually slightly or moderately enlarged and of rubbery consistency, but in some cases the enlargement may be gross. It is important that this dermatopathic lymphadenopathy is not mistaken for lymphoma. In difficult cases, lymph node biopsy may be advisable, but the pathologist must be told that the patient is erythrodermic for a reliable histological interpretation to be made.

The general picture is modified according to the nature of any underlying disease, and the patient's age and general physical condition.



Fig. 23.39 Erythrodermic psoriasis.



Fig. 23.40 Widespread drug rash. This will rapidly progress to erythroderma if the drug is continued.

Eczematous dermatoses

Generalization of an eczema occurs most frequently in the sixth and seventh decades when venous eczema is a common precedent. However, atopic erythroderma may occur at any age. Exacerbation of existing lesions usually precedes the generalization, which follows the usual pattern. Pruritus is often intense. Some elderly patients have increased serum IgE and lactic dehydrogenase levels, with eosinophilia [23].

Psoriasis

In erythrodermic psoriasis (Fig. 23.39) the clinical picture may be highly desquamative but when the erythroderma is fully developed the specific features of psoriasis are often lost. In some cases, crops of miliary pustules may develop at intervals, and transition to generalized pustular psoriasis may occur, especially in cases treated with potent topical steroids, or systemic steroids [24]. Emotional stress, intercurrent illness and phototherapy overdosage may also precipitate erythroderma.

Drugs

A wide range of drugs can cause erythroderma. Among the more commonly implicated are pyrazalone derivatives such as phenylbutazone, hydantoin derivatives, carbamazepine, cimetidine, gold salts and lithium [25]. The eruption may start as a generalized eczema, or scarlatiniform or morbilliform erythema, often accompanied by some irritation, which increases steadily in severity. Erythema may first appear in the flexures, or over the whole skin (Fig. 23.40). This group has the best prognosis of all the causes of erythroderma [2,26], often resolving in 2–6 weeks [27]. However, it is important to remember that the cutaneous manifestations of drug hypersensitivity may be accompanied by involvement of other organs, for example haematological abnormalities, hepatitis or nephritis. An example is the syndrome known as DRESS (drug reaction with eosinophilia and systemic symptoms). This term is used for a group of severe, multisystem drug reactions characterized by later onset than most manifestations of drug hypersensitivity. Exposure to the causative drug may last for 2 weeks to several months before the reaction emerges. DRESS may also persist for a long time and even worsen after withdrawal of the causative agent. Multisystem involvement may include fever, eosinophilia, lymphadenopathy, hepatitis, renal dysfunction and pneumonitis.



Fig. 23.41 Erythroderma in Sézary syndrome. (Courtesy of Dr B. Dharma, University Hospitals Coventry and Warwickshire, UK.)

Lymphoma, leukaemia and other malignancy

Cutaneous T-cell lymphoma (Fig. 23.41) is the commonest malignancy to cause erythroderma, followed by Hodgkin's disease. Non-Hodgkin's lymphoma, leukaemias and myelodysplasia have also been reported as causes. Association with other internal malignancies has been observed less often [5].

The clinical picture follows the pattern already described, but the accentuation of certain features should arouse suspicion that a lymphoma is associated, even if repeated investigations over a period of months fail to provide convincing confirmatory evidence. In many such cases the underlying disease will eventually be detected. Pruritus is often very severe. The erythroderma is universal, and the infiltration of the skin may be so severe that the patient's features are deformed. Rubbing and scratching may produce secondary lichenification. Enlargement of the lymph nodes may be considerable, even if they are histologically not involved by the lymphoma.

Biopsy of involved skin may show only non-specific features initially, and may need to be repeated several times before infiltration with atypical lymphocytes becomes evident. The use of a skin biopsy for analysis of T-cell receptor gene rearrangement, to determine whether clonality is present in the infiltrate, may prove to be a useful investigation in these circumstances [28,29]. Lymph-node biopsy may be diagnostic of lymphoma, but often shows only the features of dermatopathic lymphadenopathy. There may be hepatosplenomegaly. A differential white blood cell count should be performed, and the blood examined for abnormal cells. Eosinophilia may suggest Hodgkin's disease. Atypical lymphocytes with cerebriform nuclei (Sézary cells) are often observed in erythroderma regardless of cause. When they constitute more than 20% of the circulating peripheral blood mononuclear cells they become diagnostic of the leukaemic variant of cutaneous T-cell lymphoma known as the Sézary syndrome. Large Sézary cells (15–20 μm in diameter) are diagnostic even in small numbers [30]. The demonstration of a clonal T-cell population in the peripheral blood by analysis of T-cell receptor genes, using PCR, appears to offer high diagnostic specificity for Sézary syndrome. The sensitivity also appears high, but on occasions the test may need to be repeated if initial results are negative and this diagnosis is still suspected [30].

Pemphigus foliaceus

Moist, crusted lesions on the face and upper trunk often precede the development of the erythroderma. Scaling is conspicuous, moist and adherent. Crops of thin-walled bullae may erupt, especially on the limbs.

Ichthyosiform erythroderma

This condition is usually present from birth or early infancy.

Pityriasis rubra pilaris

The erythrodermic forms may begin in childhood or adult life. The presence of follicular, horny plugs on the knees and elbows, and on the backs of the fingers and toes, is distinctive. In many cases, islands of normal skin persist in the erythrodermic regions, and horny plugs may be evident around their margins. These normal pale 'islands' are very suggestive of the diagnosis, and the skin on the palms and soles often has an orange discoloration.

Lichen planus

Erythrodermic lichen planus is very rare, but lichenoid reactions to gold, quinine and other drugs are not uncommon. As the initial erythema and oedema subside, individual violaceous papules may be revealed. The buccal mucous membrane may show typical lacy, bluish-white streaks.

Dermatophytosis

Generalized erythroderma has very rarely resulted from chronic infection with organisms such as *Trichophyton violaceum*.

Norwegian scabies

The heavily crusted hands and feet, with thickened nails, so characteristic of Norwegian scabies, may occasionally be accompanied by generalized erythema and scaling. The condition is often mistaken for erythrodermic psoriasis. The occurrence of scabies in others in the same environment, or in the medical or nursing staff caring for the patient, will soon make the diagnosis clear.

Erythroderma of unknown origin

The percentage of cases in which no underlying disease is demonstrable diminishes with the thoroughness of investigation and the duration of observation, but in any series of cases it is rarely below 10% [3,4,27]. The cutaneous changes may precede any other evidence of a lymphoma by many months or years. If these cases are excluded, the hard core of chronic erythrodermas of unknown origin consists mainly of elderly men, in whom the condition runs a very long course with partial and temporary remissions. These have been labelled the 'red-man syndrome'. It is characterized by marked palmoplantar keratoderma, dermatopathic lymphadenopathy and a raised serum IgE [23,31]. It is important to note that

this condition is not established erythrodermic cutaneous T-cell lymphoma, which is occasionally referred to as 'l'homme rouge'.

The three commonest causes of idiopathic protracted erythroderma are probably atopic eczema of the elderly, intake of drugs overlooked by the patient and pre-lymphomatous eruptions [3].

Secondary haemodynamic and metabolic disturbances. Chronic, generalized erythroderma is associated with profound metabolic disturbances [11,32–34]. The blood flow through the skin is markedly increased, and this can result in high-output cardiac failure, especially in elderly patients [35,36]. The increased skin perfusion may lead to hypothermia [37]. When the body temperature is raised, heat loss is further increased. The regulation of temperature is grossly disturbed, and the patient behaves like a poikilothermic animal, tending to adopt the environmental temperature. The excessive loss of heat leads to compensatory hypermetabolism and a raised basal metabolic rate.

Fluid loss by transpiration is much increased and is roughly proportional to the basal metabolic rate. The loss of exfoliated scale may reach 9 g/m^2 of body surface or more each day [38].

Hypoalbuminaemia is common, and probably has several causes. Dilution by increased plasma volume may be one cause [39], but is likely to be less important than a lowered total albumin mass due either to a decrease in synthesis or an increase in metabolism [40,41]. There is also, of course, an increased protein loss via scaling and exudation. Oedema is common. Occasionally, the increased capillary permeability is severe enough to justify plasma infusions as well as parenteral steroids.

Immune responses may become altered, reflected by an increase in gammaglobulins; occasional patients have been described with very high levels of serum IgE [42], and $CD4^+$ T lymphocytopenia may occur in the absence of HIV infection [19].

Elderly patients living alone may already be malnourished prior to developing erythroderma. Any exudative or extensive scaling condition will intensify this.

Diagnosis. The recognition of erythroderma is easy, but the diagnosis of the underlying cause may be very difficult. The difficulty of exact classification of some of these cases is illustrated by the report of seven patients with erythroderma who were followed for 3–16 years before they developed the Sézary syndrome (cutaneous T-cell lymphoma). Four of these patients had multiple contact allergies or drug reactions, and one had severe atopic dermatitis [43].

The history is often helpful in identifying the hereditary disorders, drug reactions, psoriasis, etc., but in some cases the erythroderma is of sudden onset and the history may not be helpful. Multiple biopsies are usually, but not invariably, helpful [44], and the eczematous erythrodermas and those associated with lymphoma may not show any distinctive histological features.

Treatment. Treatment in hospital is frequently necessary, especially in acute and fulminant cases, because some patients may develop serious general medical problems. In these cases the protein and electrolyte balance, circulatory status and body temperature require continual surveillance. The environmental temperature must be carefully regulated. Cooling and overheating must both be avoided by the use of extra blankets or fans, respectively.

Urea and electrolyte levels and fluid balance should be monitored. Adequate fluid intake must be maintained, but if there is oedema, diuretics and/or plasma infusion should be considered. Cardiac failure must be treated if it develops.

The possibility that the erythroderma is due to a drug reaction should be considered in every case, and all non-essential drugs should be withdrawn.

The cutaneous inflammation should be treated in the first instance with soothing emollient creams, or a mild topical steroid. The majority of patients will improve over a week or two on this regimen, during which time the diagnosis of the underlying condition will probably be established.

If active topical medication is applied it must be remembered that the barrier function of erythrodermic skin is greatly reduced. This is potentially hazardous because topical application of medications, such as salicylic acid, corticosteroids or vitamin D analogues, will result in much higher systemic exposure than might be expected in other circumstances.

Many dermatologists prefer to avoid systemic steroids if possible, because of the dangers of fluid retention, secondary infection, diabetes, etc., but in severe persistent cases they may become necessary. There is some evidence that the use of systemic steroids or potent topical steroids in psoriatic erythroderma may provoke the development of pustule formation [24]. In such cases, low-dose methotrexate, acitretin or ciclosporin [33] may be safer alternatives. Topical tar and UV therapy should also be avoided on erythrodermic psoriasis.

Antibiotics will be required to control secondary infection. Heng [45] has suggested that colonization of the skin by *Staphylococcus aureus* may actually cause erythroderma, which will clear with appropriate antibiotic therapy.

The optimum treatment of erythrodermic cutaneous lymphoma is still debated. Options include systemic steroids, PUVA, total body electron-beam irradiation, topical nitrogen mustard and systemic chemotherapy [46]. The use of methotrexate has appeared beneficial in a retrospective study on 29 patients [47]. However, diagnostic histology was only obtained in 13 of these cases, so they may have been a somewhat heterogeneous group. Extracorporeal photopheresis has been advocated [48] but it is not yet clear whether this prolongs survival.

Prognosis and complications. Erythroderma is a serious condition in itself, quite apart from hazards associated with the underlying disease, and is sometimes fatal despite skilled management. It is particularly dangerous in elderly people. Reported death rates have varied from 18 to 64% [2,4,6], but with modern therapy the rate is probably lower.

The commoner forms of erythroderma—eczematous, psoriatic or of unknown origin—may continue for months or years, and tend readily to relapse [24]. As the patients are often elderly, the prognosis must always be guarded. The metabolic disturbances involve a serious risk of hypothermia, cardiac decompensation, peripheral circulatory failure and thrombophlebitis. Cutaneous, subcutaneous and respiratory infections are common, and the majority of patients who die do so from pneumonia [24].

The treatment can also be hazardous, especially when systemic steroids and immunosuppressants are required.

References

1 Sigurdsson V, Steegmans PHA, van Vloten WA. The incidence of erythroderma: a survey among all dermatologists in The Netherlands. *J Am Acad Dermatol* 2001; **45**: 675–8.
2 Abrahams I, McCarthy JT, Sanders SL. 101 cases of exfoliative dermatitis. *Arch Dermatol* 1963; **87**: 96–101.
3 Botella-Estrada R, Sanmartin O, Oliver V *et al*. Erythroderma: a clinico-pathological study of 56 cases. *Arch Dermatol* 1994; **130**: 1503–7.
4 Hasan T, Jansen CT. Erythroderma: a follow-up of 50 cases. *J Am Acad Dermatol* 1983; **8**: 836–40.
5 Rosen T, Chappell R, Drucker C. Exfoliative dermatitis: presenting sign of internal malignancy. *South Med J* 1979; **72**: 652–3.
6 Nicolis GD, Helwig WB. Exfoliative dermatitis. A clinicopathological study of 135 cases. *Arch Dermatol* 1973; **108**: 788–97.
7 Wong KS, Wong SN, Tham SN *et al*. Generalised exfoliative dermatitis: a clinical study of 108 patients. *Ann Acad Med Singapore* 1988; **17**: 520–3.
8 Holme SA, Roberts DL. Erythroderma associated with St John's wort. *Br J Dermatol* 2000; **143**: 1127–8.
9 Morrison JG. Sarcoidosis in a child presenting as erythroderma with keratotic spines. *Br J Dermatol* 1976; **95**: 93–7.
10 Marsch WC, Stuttgen G. Generalized Hailey–Hailey disease. *Br J Dermatol* 1978; **99**: 553.
11 Tappeiner G, Konrad K, Holubar K. Erythrodermic bullous pemphigoid. *J Am Acad Dermatol* 1982; **6**: 489–92.
12 Bach M. Dermatological signs in the toxic shock syndrome. *J Am Acad Dermatol* 1983; **8**: 343–7.
13 De Spain J, Clark DP. Subacute cutaneous lupus erythematosus presenting as erythroderma. *J Am Acad Dermatol* 1988; **19**: 388–92.
14 Bernengo MG, Levi L, Zina G. Skin lesions in angio-immunoblastic lymphadenopathy. *Br J Dermatol* 1981; **104**: 131–9.
15 Pierson JC, Taylor JS. Erythrodermic dermatomyositis. *J Am Acad Dermatol* 1993; **28**: 136.
16 Sakakibara T, Ida T, Mannouji E *et al*. Post-transfusion graft-versus-host disease following open heart surgery: report of six cases. *J Cardiovasc Surg* 1989; **30**: 687–91.
17 Janniger CK, Gascon P, Schwartz RA *et al*. Erythroderma as the initial presentation of the acquired immunodeficiency syndrome. *Dermatologica* 1991; **183**: 143–5.
18 Sadick NS, McNutt NS, Kaplan MH. Papulosquamous dermatoses of AIDS. *J Am Acad Dermatol* 1990; **22**: 1270–7.
19 Griffiths TW, Stevens SR, Cooper KD. Acute erythroderma as an exclusion criterion for idiopathic $CD4^+$ T lymphocytopenia. *Arch Dermatol* 1994; **130**: 1530–3.
20 Walsh NMG, Prokopetz R, Tron VA *et al*. Histopathology in erythroderma: review of a series of cases by multiple observers. *J Cutan Pathol* 1994; **21**: 419–23.
21 Sentis HJ, Willemze R, Scheffer E. Histopathologic studies of Sézary syndrome and erythrodermic mycosis fungoides: a comparison with benign forms of erythroderma. *J Am Acad Dermatol* 1986; **15**: 1217–26.
22 Abel EA, Lindae ML, Hoppe TR *et al*. Benign and malignant forms of cutaneous erythroderma: cutaneous immunophenotypic characteristics. *J Am Acad Dermatol* 1988; **19**: 1089–95.
23 Asai T, Horiuchi Y. Senile erythroderma with serum hyper-IgE. *Int J Dermatol* 1989; **28**: 225–8.
24 Boyd AS, Menter A. Erythrodermic psoriasis. *J Am Acad Dermatol* 1989; **21**: 985–91.
25 Wilson DC, Jester JD, King LE. Erythroderma and exfoliative dermatitis. *Clin Dermatol* 1993; **11**: 67–72.
26 King LE. Erythroderma. Who, where, when, why and how? *Arch Dermatol* 1994; **130**: 1545–7.
27 King LE, Dufresne RG, Lovett G, Rosin MA. Erythroderma: review of 82 cases. *South Med J* 1986; **79**: 1210–5.
28 Cherny S, Mraz S, Su L *et al*. Heteroduplex analysis of T-cell receptor gamma gene rearrangement as an adjuvant diagnostic tool in skin biopsies for erythroderma. *J Cutan Pathol* 2001; **28**: 351–5.
29 Cordel N, Lenormand B, Courville P *et al*. Detection of clonal T-cell receptor gamma gene rearrangement with the use of PCR-DGGE for diagnosis of erythroderma. *Ann Dermatol Venereol* 2001; **128**: 220–3.
30 Russell-Jones R, Whittaker S. T-cell receptor gene analysis in the diagnosis of Sézary syndrome. *J Am Acad Dermatol* 1999; **41**: 254–9.
31 Thestrup-Pederson K, Halkier-Sorenson L, Sogaard H, Zacharie H. The red man syndrome: exfoliative dermatitis of unknown aetiology. A description and follow-up of 38 patients. *J Am Acad Dermatol* 1988; **18**: 1307–12.
32 Shuster S, Wilkinson P. Protein metabolism in exfoliative dermatitis and erythroderma. *Br J Dermatol* 1963; **75**: 344–53.
33 Studio Italiano Multicentrico Nella Psoriasi. Management of erythrodermic psoriasis with low-dose cyclosporin. *Dermatology* 1993; **187** (Suppl. 1): 30–7.
34 Zoon JJ, Mali JWH. The influence of erythroderma on the body. *Arch Dermatol* 1957; **75**: 573–8.
35 Fox RH. Temperature regulation in erythroderma. *J R Coll Physicians Lond* 1967; **1**: 372–9.
36 Leading Article. Haemodynamics of extensive skin disease. *Lancet* 1983; **i**: 1144.
37 Krook G. Hypothermia in patients with exfoliative dermatitis. *Acta Derm Venereol (Stockh)* 1960; **40**: 142.
38 Freedberg IM, Baden HP. The metabolic response to exfoliation. *J Invest Dermatol* 1962; **38**: 277–84.
39 Marks J, Shuster S. Method for measuring capillary permeability and its use in patients with skin disease. *BMJ* 1966; **ii**: 88–90.
40 Shuster S. Systemic effects of skin disease. *J R Coll Physicians Lond* 1967; **1**: 345–55.
41 Worm AM, Taaning E, Rossing N. Distribution and degradation of albumin in extensive skin disease. *Br J Dermatol* 1981; **104**: 389–96.
42 Frenk E, Guiessaz F, Vion B. Senile erythroderma with serum hyper-IgE. *Dermatologica* 1991; **183**: 72–3.
43 Beuchner SA, Winkelmann RK. Pre-Sézary erythroderma evolving into Sézary syndrome. *Arch Dermatol* 1983; **119**: 285–91.
44 Zip C, Murray S, Walsh NMG. The specificity of histopathology in erythroderma. *J Cutan Pathol* 1993; **20**: 393–8.
45 Heng MCV. Erythroderma associated with mixed lymphoendothelial cell interactions and *Staph. aureus* infections. *Br J Dermatol* 1986; **115**: 693–705.
46 Marsden JR. Cutaneous T-cell lymphomas. In: Lebwohl M, Heymann WR, Berth-Jones J, Coulson I, eds. *Treatment of Skin Disease: Comprehensive Therapeutic Strategies*. London: Mosby, 2002: 131–7.
47 Zackheim HS, Kashani-Sabet M, Hwang ST. Low dose methotrexate to treat erythrodermic cutaneous T-cell lymphoma: results in 29 patients. *J Am Acad Dermatol* 1996; **34**: 626–31.
48 Heald P, Rook A, Perez M *et al*. Treatment of erythrodermic cutaneous T-cell lymphoma with extracorporeal photochemotherapy. *J Am Acad Dermatol* 1992; **27**: 427–33.

Papuloerythroderma of Ofuji [1–5]

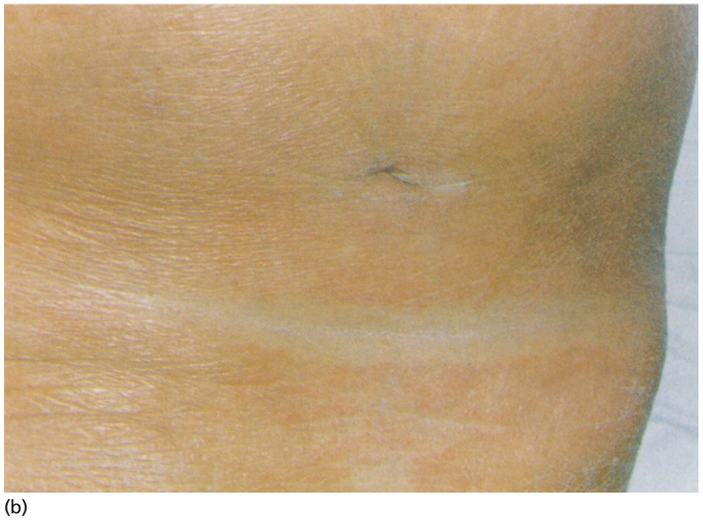
This distinctive pattern of erythroderma was described by Ofuji in 1984 [1]. It differs from ordinary erythroderma in that papulation is prominent, it tends to spare the face and flexures, and it is consistently and, often intensely, pruritic.

It is not yet clear whether this represents a distinct disease or a reaction pattern. Although most cases have been seemingly 'idiopathic', several have been reported in association with other diseases.

Pathology. Histological features are usually non-specific. In the epidermis there are variable, but most often mild, degrees of acanthosis, spongiosis, hyperkeratosis and focal parakeratosis. There is marked lymphohistiocytic infiltration of the dermis, predominantly perivascular in distribution, with a variable, and often conspicuous, number of eosinophils. A mild degree of epidermotropism has occasionally been observed and, rarely, plasma cells and multinucleate giant cells. Immunofluorescence is negative.



(a)



(b)

Fig. 23.42 Papuloerythroderma of Ofuji. (a) The papules. (b) The 'deck-chair' sign (sparing of the body folds). (Courtesy of Dr M.J. Tidman, Edinburgh Royal Infirmary, Edinburgh, UK.)

Clinical features. Papuloerythroderma has been observed entirely in an elderly population, with ages at diagnosis ranging from 57 to 100. Many cases occur in the eighth or ninth decades. Males are predominantly affected, the male : female ratio being estimated at 4.7 : 1 [2].

The erythroderma typically begins with an eruption of brownish-red, flat-topped papules which become confluent (Fig. 23.42a). The limbs and trunk are affected, but the face and flexures, especially axillary and inguinal regions, tend to be spared. A characteristic and distinctive pattern of sparing of the abdominal flexures has been termed the 'deck chair sign' [3], indicating the similarity to the distribution of sunburn in one who has been sitting out in a deck chair for too long (Fig. 23.42b). The lesions sometimes develop along scratch marks. Pruritus is a consistent feature and ranges from moderate to extremely severe. Additional features often observed include hyperkeratosis and fissuring of the palms and soles, and benign lymphadenopathy.

There is usually circulating eosinophilia and a raised IgE. There is often a mild degree of absolute or relative lymphocytopenia.

Reports of papuloerythroderma occurring in association with malignancies, which have included T-cell [4,5] and B-cell lymphomas [5], gastric [5], lung [5], colon [6], prostate [2] and hepatocellular carcinomas [7], would suggest that this eruption may sometimes occur as a paraneoplastic phenomenon. There are also several reports that papuloerythroderma may progress into mycosis fungoides [2,8,9], in one case 11 years after the onset of symptoms [10]. In some cases, papuloerythroderma therefore seems to be a presentation of cutaneous T-cell lymphoma. One case developed into psoriasis [2]. Papuloerythroderma has also been reported in association with HIV infection [11,12], and, in one case, biliary sepsis [13].

Treatment. Emollients, topical corticosteroids and antihistamines have produced a slow response in some cases. The condition can respond well to oral prednisolone, although high doses are sometimes required. PUVA, including bath PUVA, has proved effective in several reports. Azathioprine [14], ciclosporin [15] and etretinate [16] may be effective. In view of the possible associations with malignancy and HIV infection, and as some cases progress to cutaneous T-cell lymphoma, the use of retinoids or PUVA would seem preferable to immunosuppressant drugs. However, papuloerythroderma is sometimes very refractory to treatment. It typically persists for many years, but some cases have remitted.

References

1 Ofuji S, Furukawa F, Miyachi Y *et al*. Papuloerythroderma. *Dermatologica* 1984; **16**: 125–30.

2 Bech-Thomsen N, Thomsen K. Ofuji's papuloerythroderma: a study of 17 cases. *Clin Exp Dermatol* 1998; **23**: 79–83.

3 Farthing CF, Staughton RCD, Harper JI *et al*. *Dermatologica* 1986; **172**: 65–6.

4 Grobb JJ, Collet-Villette AM, Horchowski N *et al*. Ofuji papuloerythroderma. Report of a case with T-cell skin lymphoma and discussion of the nature of this disease. *J Am Acad Dermatol* 1989; **20**: 927–31.

5 Ofuji S. Papuloerythroderma. *J Am Acad Dermatol* 1990; **22**: 697.

6 Schepers C, Malvehy J, Azon-Masoliver A *et al*. Papuloerythroderma of Ofuji: a report of two cases including the first European case associated with visceral carcinoma. *Dermatology* 1996; **193**: 131–5.

7 Nishijima S. Papuloerythroderma associated with hepatocellular carcinoma. *Br J Dermatol* 1998; **139**: 1115–6.

8 Dwer CM, Chapman RS, Smith GD. Papuloerythroderma and cutaneous T-cell lymphoma. *Dermatology* 1994; **188**: 326–8.

9 Shah M, Reid WA, Layton AM. Cutaneous T-cell lymphoma presenting as papuloerythroderma—a case and review of the literature. *Clin Exp Dermatol* 1995; **20**: 161–3.

10 Tan YK, Tan KC, Ong BH. Papuloerythroderma of Ofuji and cutaneous T-cell lymphoma. *Br J Dermatol* 1997; **137**: 160–1.

11 Garcia-Patos V, Repiso T, Rodriguez-Cano L, Castells A. Ofuji papuloerythroderma in a patient with the acquired immunodeficiency syndrome. *Dermatology* 1996; **192**: 164–6.

12 Lonnee ER, Toonstra J, van der Putte SCJ *et al*. Papuloerythroderma of Ofuji in a HIV-infected patient. *Br J Dermatol* 1996; **135**: 489–504.

13 Azon-Masoliver A, Casado J, Brunet J *et al*. Ofuji's papuloerythroderma following choledocholithiasis with secondary sepsis: complete resolution with surgery. *Clin Exp Dermatol* 1998: **23**: 84–6.

14 Quemeneur T, Ghislain PD, Morant C *et al*. Ofuji's papuloerythroderma: two cases treated with azathioprine. *Ann Dermatol Venereol* 2002; **129**: 213–5.

15 Sommer S, Henderson CA. Papuloerythroderma of Ofuji responding to treatment with cyclosporin. *Clin Exp Dermatol* 2000; **25**: 293–5.

16 Fujii K, Kanno Y, Ohgo N. Etretinate therapy for papuloerythroderma. *Eur J Dermatol* 1999; **9**: 610–3.

CHAPTER 24

Atopic Dermatitis

P.S. Friedmann[1], M.R. Ardern-Jones[1] & C.A. Holden[2]

[1]Dermatopharmacology, Southampton General Hospital, Southampton, UK
[2]Department of Dermatology, Epsom & St Helier NHS Trust, St Helier Hospital, Carshalton, UK

Definition, 24.1
Diagnostic criteria, 24.2
Prevalence, 24.2
Aetiology, 24.3
Genetic influence, 24.3
Environmental factors, 24.5
Immune dysregulation, 24.6
Pathogenesis of eczema, 24.10
The role of allergy, 24.10
The role of infection, 24.12
Altered immune function, 24.13
Pharmacological and vascular abnormalities, 24.15
Pruritus, 24.17
Sweating, 24.18
Psychological factors, 24.19
Clinical features, 24.19
Infantile phase, 24.19
Childhood phase, 24.20
Adult phase, 24.21
Atopic hand eczema, 24.21
Associated disorders, 24.22
Other manifestations of atopy, 24.22
Dry skin, 24.22
Other patterns of eczema, 24.22
Drug sensitivity, 24.23
Food allergy, 24.23
Alopecia areata, 24.23
Urticaria, 24.23
Complications, 24.23
Psychosocial aspects, 24.23
Growth delay, 24.24
Bacterial infections, 24.24
Viral infections, 24.24
Ocular abnormalities, 24.24
Miscellaneous, 24.25
Natural history and prognosis, 24.25
Diagnosis, 24.26
Differential diagnosis, 24.26
Hyper-IgE syndrome, 24.26
Hypereosinophilic syndrome, 24.27
Pachydermatous eosinophilic dermatitis, 24.27
Investigations, 24.27
Treatment, 24.28
Initial treatment, 24.28
Topical therapy, 24.29
Oral therapy, 24.29
Maintaining control, 24.30
Unresponsive disease, 24.30
Allergy management, 24.30
Phototherapy, 24.31
Systemic therapies, 24.31
Other approaches, 24.31
Disease prevention and occupational advice, 24.33

Definition

Atopic dermatitis is a difficult condition to define because it lacks a diagnostic test and shows variable clinical features. The following definition seems to be in accord with most consensus groups. Atopic dermatitis (which is synonymous with atopic eczema) is an itchy, chronic, or chronically relapsing, inflammatory skin condition. The rash is characterized by itchy papules (occasionally vesicles in infants) which become excoriated and lichenified, and typically have a flexural distribution. The eruption is frequently associated with other atopic conditions in the individual or other family members [1–3].

Atopic and non-atopic dermatitis

One of the difficulties in defining atopic dermatitis arises from the impreciseness of its association with atopy and the nature of atopy itself. Atopic dermatitis and disorders resulting from anaphylaxis, for example those resulting from insect stings and food allergies, may be associated with IgE antibodies and therefore grouped with the atopic diseases. Such grouping is not completely acceptable, as 20–40% of individuals with atopic dermatitis can have a normal total or specific IgE level [4], and it is rarely attributable to a specific allergic reaction; the IgE antibodies present in the blood often appear to be incidental to the condition.

It is still a matter of debate whether the group with dermatitis and normal IgE levels, termed intrinsic atopic dermatitis or non-atopic dermatitis, can be distinguished clinically, immunologically, and prognostically from extrinsic or atopic dermatitis [5]. Up to 50% of infants have been reported to have intrinsic dermatitis [6], but with time atopic features become more prevalent and the intrinsic form may be found in only 5.4% of adult patients [7].

Terminology

Debate has added to the already wide variety of historical names for the condition. Currently, atopic dermatitis and atopic eczema are the most widely used. The World Allergy Organization has suggested that 'eczema' should be used as an umbrella term, and subdivided it into atopic eczema and non-atopic eczema [8]. Historical terms such as Besnier's prurigo, disseminated neurodermatitis, Spatexudativ Ekzem and prurigo diathesique are now

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

little used. We continue to use the term atopic dermatitis until the clinical relevance of dividing the disease into subgroups is confirmed.

References

1 Darsow U, Lubbe J, Taïeb A *et al*., for the European Task Force on Atopic Dermatitis. Position paper on the diagnosis and treatment of atopic dermatitis. *J Eur Acad Dermatol Venereol* 2005; **19**: 286–95.
2 Williams H. Atopic dermatitis. *N Engl J Med* 2005; **352**: 2314–24.
3 Brown S, Reynolds NJ. Atopic and non-atopic eczema. *BMJ* 2006; **332**: 584–8.
4 Juhlin L, Johanson SGO, Bennich H *et al*. Immunoglobulin E in dermatoses. *Arch Dermatol* 1969; **100**: 12–6.
5 Schmid-Grendelmeier P, Simon D, Simon HU *et al*. Epidemiology, clinical features, and immunology of the intrinsic (non-IgE-mediated) type of atopic dermatitis (constitutional dermatitis). *Allergy* 2001; **56**: 841–9.
6 Park J-H, Choi Y-L, Namkung J-H *et al*. Characteristics of extrinsic vs. intrinsic atopic dermatitis in infancy: correlations with laboratory variables. *Br J Dermatol* 2006; **155**: 778–83.
7 Fölster-Holst R, Pape M, Buss YL *et al*. Low prevalence of the intrinsic form of atopic dermatitis among adult patients. *Allergy* 2006; **61**: 629–32.
8 Johannson SGO, Bieber T, Dahl R *et al*. Revised nomenclature for allergy for global use: report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol* 2004; **113**: 832–6.

Diagnostic criteria

Hanifin and Rajka [1] proposed major and minor diagnostic criteria based on their clinical experience. These criteria allow a uniformity of diagnosis for hospital-based and experimental studies but were considered not helpful for population-based studies [2]. Consequently, Williams coordinated a UK working party to attempt to refine the criteria of Hanifin and Rajka into a repeatable and validated set of diagnostic criteria for atopic dermatitis [3,4] (Table 24.1).

These diagnostic guidelines appear to be valid for adults, children and non-white ethnic groups suffering from atopic dermatitis [3], and have been validated in a population setting [4]. They were primarily developed for epidemiological studies and, of necessity, exclude some signs that could be useful for diagnosis in individuals but are not common enough for use when assessing large populations.

More recently, other modifications of the diagnostic criteria have been proposed, but these have been less rigorously validated [5,6].

Table 24.1 The UK refinement of Hanifin and Rajka's diagnostic criteria for atopic dermatitis. (From Williams *et al*. [4].) Scabies should be excluded.

In order to qualify as a case of atopic dermatitis with the UK diagnostic criteria, the child must have:

- An itchy skin condition (or parental report of scratching or rubbing in a child)

Plus three or more of the following:

1 Onset below age 2 years (not used if child is under 4 years)
2 History of skin crease involvement (including cheeks in children under 10 years)
3 History of a generally dry skin
4 Personal history of other atopic disease (or history of any atopic disease in a first-degree relative in children under 4 years)
5 Visible flexural dermatitis (or dermatitis of cheeks/forehead and outer limbs in children under 4 years)

References

1 Hanifin JM, Rajka RG. Diagnostic features of atopic dermatitis. *Acta Derm Venereol (Stockh)* 1980; **92** (Suppl. 144): 44–7.
2 Schultz-Larsen F, Hanifin JM. Secular changes in the occurrence of atopic dermatitis. *Acta Derm Venereol Suppl (Stockh)* 1992; **176**: 7–12.
3 Williams HC, Burney PGJ, Pembroke AC, Hay RJ. The U.K. working party's diagnostic criteria for atopic dermatitis. III. Independent hospital validation. *Br J Dermatol* 1994; **131**: 406–16.
4 Williams HC, Burney PGJ, Pembroke AC, Hay RJ. Validation of the U.K. diagnostic criteria for atopic dermatitis in a population setting. *Br J Dermatol* 1996; **135**: 12–17.
5 Bos JD, Van Leent EJ, Sillevis Smitt JH. The millennium criteria for the diagnosis of atopic dermatitis. *Exp Dermatol* 1998; **7**: 132–8.
6 Eichenfield LF, Hanifin JM, Luger TA *et al*. Consensus conference on pediatric atopic dermatitis. *J Am Acad Dermatol* 2003; **49**: 1088–95.

Prevalence

Although it is accepted that atopic dermatitis is a common disease, precise measurement of its frequency is difficult because different methods of assessment have been used. For example, some studies have based information purely on questionnaire results without objective validation of the quality of responses. Other studies have used clinical examination by dermatologists to supplement and confirm data from interview and questionnaire. Detailed reviews of the prevalence studies are to be found in McNally and Phillips [1] and Williams [2]. The international study of asthma and allergies in childhood (ISAAC) used cross-sectional questionnaires to sample school children of 6–7 years and 13–14 years in 56 centres throughout the world [3]. A history of an itchy relapsing rash affecting skin creases in the previous 12 months was a main outcome measure.

Overall, from the ISAAC study data and many other studies, a pattern emerges that atopic eczema is most prevalent in the most developed Westernized countries, and least prevalent in the most non-Westernized and underdeveloped countries. Thus, in Norwegian children from 7 to 13 years of age, the cross-sectional prevalence was 19.7% [4]. In Danish children up to 7 years of age, the lifetime prevalence was 22.9%, whereas in Germany and Sweden 13.1% and 15.5%, respectively, were reported [5]. In England, the point prevalence in 3- to 11-year-old children was found to be 11.5–14% [6] and the 1-year period prevalence was reported as 11.5% [7]. In Japan, figures of 9.5 and 20% have been reported for elementary school children and 3 year olds, respectively [8,9]. In contrast, in Tanzania, a point prevalence in 7–8 year olds was found to be only 0.7% [10].

Studies of migrants show some interesting patterns. There are reports comparing the frequencies of atopic eczema in particular ethnic/genetic groups in their homeland with those in their adopted new homeland. For example, children who migrated to New Zealand from Tokelau have a much greater prevalence of atopic eczema than those in their country of origin [11]. Immigrant populations appear to develop a prevalence of atopic eczema even greater than that of the indigenous population of their adopted homeland. Thus, black Afro-Caribbean children residing in London were shown to have twice the prevalence (16.3%) of atopic eczema of their Caucasian counterparts (8.7%) [6]. A study from Sweden showed that immigrant Turkish children had a signifi-

cantly higher prevalence of atopic disease (32.4%) than Swedish children (6%) [12].

These observations clearly reflect the fact that environmental factors play a large part in determining the expression of atopic diseases. The tantalizing question is whether the Westernized countries have an environment that actively promotes the atopic phenotype or whether the underdeveloped world has factors that actively suppress the expression of the atopic phenotype.

There is accumulating evidence that the prevalence of atopic diseases in general, and atopic eczema in particular, have been increasing over the last three to four decades. Among the epidemiological experts, there is concern that changing methods of assessment and methodological errors may have distorted the true picture [13]. However, a composite picture from many studies suggests that the cumulative incidence in children up to 7 years of age was less than 3% if they were born before 1960, 4–8% for those born between 1960 and 1970, and 8–12% for those born after 1970.

In the elegant twin studies by Shultz Larsen the cumulative incidence was shown to rise progressively from about 3% for twins born between 1960 and 1964, to 12% for those born between 1975 and 1979 [14,15]. Selnes surveyed large numbers of Norwegian children (7–13 years of age) in 1985 and 1995, and found the cumulative incidence of atopic eczema had risen from 13.2% to 19.7% over the intervening 10 years [4]. The reason for this steady rise in the prevalence of atopic diseases is not clear, but there are a number of possible environmental candidates (see below).

The consequence of the rising prevalence of atopic eczema is a heavy burden on medical services and budgets. In Britain, the annual cost of atopic dermatitis was estimated as about £465 million [16], and in the USA, insurance payouts to cover the costs of atopic eczema have been estimated at between $0.9 and $3.8 billion [17].

References

1 McNally N, Phillips D. Geographical studies of atopic dermatitis. In: Williams HC, ed. *Atopic Dermatitis: The Epidemiology, Causes and Prevention of Atopic Dermatitus*. Cambridge: Cambridge University Press, 2000: 71–84.

2 Williams HC. Epidemiology of atopic dermatitis: recent advances and future predictions. *Curr Probl Dermatol* 1999; **28**: 9–17.

3 The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. *Lancet* 1998; **351**: 1225–32.

4 Selnes A, Bolle R, Lund E, Holt J. Cumulative incidence of asthma and allergy in north-Norwegian schoolchildren in 1985 and 1995. *Pediatr Allergy Immunol* 2002; **13**: 58–63.

5 Schultz Larsen FV, Diepgen T, Svensson A. The occurrence of atopic dermatitis in north Europe: an international questionnaire study. *J Am Acad Dermatol* 1996; **34**: 760–4.

6 Williams HC, Pembroke AC, Forsdyke H *et al*. London-born black Caribbean children are at increased risk of atopic dermatitis. *J Am Acad Dermatol* 1995; **32**: 212–7.

7 Kay J, Gawkrodger DJ, Mortimer MJ, Jaron AG. The prevalence of childhood atopic eczema in a general population. *J Am Acad Dermatol* 1994; **30**: 35–9.

8 Okuma M. [Prevalence rate of allergic diseases among school children in Okinawa]. *Arerugi* 1994; **43**: 492–500.

9 Sugiura H, Uchiyama M, Omoto M *et al*. Prevalence of infantile and early childhood eczema in a Japanese population: comparison with the disease frequency examined 20 years ago. *Acta Derm Venereol* 1997; **77**: 52–3.

10 Henderson CA. The prevalence of atopic eczema in two different villages in rural Tanzania. *Br J Dermatol* 1995; **133** (Suppl. 45): 50.

11 Waite DA, Eyles EF, Tonkin SL, O'Donnell TV. Asthma prevalence in Tokelauan children in two environments. *Clin Allergy* 1980; **10**: 71–5.

12 Kalyoncu AF, Stalenheim G. Survey on the allergic status in a Turkish population in Sweden. *Allergol Immunopathol (Madr)* 1993; **21**: 11–4.

13 Diepgen T. Is the prevalence of atopic dermatitis increasing? In: Williams HC, ed. *Atopic Dermatitis: The Epidemiology, Causes and Prevention of Atopic Dermatitis*. Cambridge: Cambridge University Press, 2000: 96–109.

14 Schultz Larsen FV, Holm NV, Henningsen K. Atopic dermatitis: a genetic-epidemiologic study in a population-based twin sample. *J Am Acad Dermatol* 1986; **15**: 487–94.

15 Schultz Larsen FV. Atopic dermatitis: a genetic-epidemiologic study in a population-based twin sample. *J Am Acad Dermatol* 1993; **28**: 719–23.

16 Herd RM, Tidman MJ, Prescott RJ, Hunter JA. The cost of atopic eczema. *Br J Dermatol* 1996; **135**: 20–3.

17 Ellis CN, Drake LA, Prendergast MM *et al*. Cost of atopic dermatitis and eczema in the United States. *J Am Acad Dermatol* 2002; **46**: 361–70.

Aetiology

Recently, there has been a growing realization that the atopic state and the syndromes of atopic eczema and asthma involve abnormalities not only of immune regulation but also a range of primary functions of the epidermis and bronchial epithelium. It is not clear whether these are independent or whether there is an interplay in which the epithelia and the immune system regulate each other.

Genetic influence

The importance of genetic factors in determining the expression of the atopic phenotype is reflected in data from twin studies. Thus, monozygotic twins have a concordance rate of 0.72, whereas dizygotic twins have a concordance rate of only 0.23 [1–3].

Four genome screens have been reported from German/Scandinavian (n = 839) [4], British (n = 383) [5], Swedish (n = 470) [6] and Danish (n = 424) [7] populations. These have identified susceptibility loci on 1q21 [5], 3p24–22 [6], 3q21 [4] and 17q25 [5] in association with atopic dermatitis. A number of other associated loci have also been reported by further association with disease severity, or IgE, or concurrent asthma: 3p26–24 [7], 3q14 [6], 4p15–14 [7], 13q14 [6], 15q14–15 [6], 17q21 [6], 18q11–12 [7], 18q21 [6], 20p [5]. Genome screens for asthma report some overlapping loci: 13q [8] and 20p [5]. Interestingly, many loci associated with atopic dermatitis overlap with known psoriasis loci (1q, 3q, 17q and 20p [5]), which is unexpected because the two conditions are almost mutually exclusive in clinical practice. This information suggests that genetic influences on these two conditions may overlap in the targeting of the epidermis. Clearly, overlapping loci of association do not imply the same causative genetic factors, but even if the same gene were to be implicated by such a study, it would be important to investigate the effects on gene expression and protein function in that setting, which could be very different for the two diseases.

Recently, studies of genetic linkage have identified a number of genes related to the expression of different atopic syndromes, IgE levels and cytokines relevant to the regulation of IgE levels. A polymorphism in the gene encoding the β chain of the high affinity IgE receptor FCεR1β has demonstrated a highly significant association with atopic dermatitis [9]. Genes on chromosome 5q encoding the cytokine gene cluster have been linked to atopic mucosal

syndromes [10] and include associations with polymorphisms in the IL-4 gene with atopic dermatitis [11–14]. A gene at 16p11.2–12 encoding the α chain of the IL-4 receptor has been linked to atopy [15–17]. The gene encoding mast cell chymase has been linked to atopic eczema [18,19], but this association has not been confirmed [20,21]. Variants in the RANTES gene promoter region have also been reported to be associated with atopic eczema [22], and further studies have demonstrated this variant to be associated with enhanced RANTES production [23].

Abnormal epidermal barrier function is a well recognized clinical association of atopic eczema, and until recently it was not clear whether the dry skin was only a consequence of the underlying immune inflammatory process. However, loss-of-function mutations have been described in the filaggrin gene, which is part of the so-called epidermal differentiation complex on chromosome 1q21 [24–26]. These genetic defects predict early onset of atopic eczema, a worse prognosis and persistence of the disease into adulthood [26]. It is very interesting that, even though filaggrin is not expressed in bronchial epithelium, filaggrin gene mutations are also associated with atopic asthma, being linked to asthma severity independently of eczema [27]. Another genetic influence contributing to abnormal barrier function is *SPINK5* which encodes LEKTI, a serine protease inhibitor expressed at epithelial and mucosal surfaces. Although mutations in this gene determine Netherton's syndrome, variants in the gene have also been associated with atopic eczema [28–30].

References

1 Schultz Larsen FV, Holm NV. Atopic dermatitis in a population based twin series. Concordance rates and heritability estimation. *Acta Derm Venereol Suppl (Stockh)* 1985; **114**: 159–63.

2 Schultz Larsen FV, Holm NV, Henningsen K. Atopic dermatitis: a genetic-epidemiologic study in a population-based twin sample. *J Am Acad Dermatol* 1986; **15**: 487–94.

3 Schultz Larsen FV. The epidemiology of atopic dermatitis. *Monogr Allergy* 1993; **31**: 9–28.

4 Lee YA, Wahn U, Kehrt R *et al*. A major susceptibility locus for atopic dermatitis maps to chromosome 3q21. *Nat Genet* 2000; **26**: 470–3.

5 Cookson WO, Ubhi B, Lawrence R *et al*. Genetic linkage of childhood atopic dermatitis to psoriasis susceptibility loci. *Nat Genet* 2001; **27**: 372–3.

6 Bradley M, Soderhall C, Luthman H *et al*. Susceptibility loci for atopic dermatitis on chromosomes 3, 13, 15, 17 and 18 in a Swedish population. *Hum Mol Genet* 2002; **11**: 1539–48.

7 Haagerup A, Bjerke T, Schiotz PO *et al*. Atopic dermatitis—a total genome-scan for susceptibility genes. *Acta Derm Venereol* 2004; **84**: 346–52.

8 Zhang Y, Leaves NI, Anderson GG *et al*. Positional cloning of a quantitative trait locus on chromosome 13q14 that influences immunoglobulin E levels and asthma. *Nat Genet* 2003; **34**: 181–6.

9 Sandford AJ, Shirakawa T, Moffatt MF *et al*. Localisation of atopy and beta subunit of high-affinity IgE receptor (Fc epsilon RI) on chromosome 11q [see comments]. *Lancet* 1993; **341**: 332–4.

10 Doull IJ, Lawrence S, Watson M *et al*. Allelic association of gene markers on chromosomes 5q and 11q with atopy and bronchial hyperresponsiveness. *Am J Respir Crit Care Med* 1996; **153**: 1280–4.

11 He JQ, Chan-Yeung M, Becker AB *et al*. Genetic variants of the IL13 and IL4 genes and atopic diseases in at-risk children. *Genes Immun* 2003; **4**: 385–9.

12 Kawashima T, Noguchi E, Arinami T *et al*. Linkage and association of an interleukin 4 gene polymorphism with atopic dermatitis in Japanese families. *J Med Genet* 1998; **35**: 502–4.

13 Hosomi N, Fukai K, Oiso N *et al*. Polymorphisms in the promoter of the interleukin-4 receptor alpha chain gene are associated with atopic dermatitis in Japan. *J Invest Dermatol* 2004; **122**: 843–5.

14 Oiso N, Fukai K, Ishii M. Interleukin 4 receptor alpha chain polymorphism Gln551Arg is associated with adult atopic dermatitis in Japan. *Br J Dermatol* 2000; **142**: 1003–6.

15 Deichmann KA, Heinzmann A, Forster J *et al*. Linkage and allelic association of atopy and markers flanking the IL4-receptor gene. *Clin Exp Allergy* 1998; **28**: 151–5.

16 Hershey GK, Friedrich MF, Esswein LA *et al*. The association of atopy with a gain-of-function mutation in the alpha subunit of the interleukin-4 receptor. *N Engl J Med* 1997; **337**: 1720–5.

17 Kruse S, Japha T, Tedner M *et al*. The polymorphisms S503P and Q576R in the interleukin-4 receptor alpha gene are associated with atopy and influence the signal transduction. *Immunology* 1999; **96**: 365–71.

18 Mao XQ, Shirakawa T, Yoshikawa T *et al*. Association between genetic variants of mast-cell chymase and eczema. *Lancet* 1996; **348**: 581–3.

19 Tanaka K, Sugiura H, Uehara M *et al*. Association between mast cell chymase genotype and atopic eczema: comparison between patients with atopic eczema alone and those with atopic eczema and atopic respiratory disease. *Clin Exp Allergy* 1999; **29**: 800–3.

20 Kawashima T, Noguchi E, Arinami T *et al*. No evidence for an association between a variant of the mast cell chymase gene and atopic dermatitis based on case-control and haplotype-relative-risk analyses. *Hum Hered* 1998; **48**: 271–4.

21 Pascale E, Tarani L, Meglio P *et al*. Absence of association between a variant of the mast cell chymase gene and atopic dermatitis in an Italian population. *Hum Hered* 2001; **51**: 177–9.

22 Nickel RG, Casolaro V, Wahn U *et al*. Atopic dermatitis is associated with a functional mutation in the promoter of the C-C chemokine RANTES. *J Immunol* 2000; **164**: 1612–6.

23 Bai B, Tanaka K, Tazawa T *et al*. Association between RANTES promoter polymorphism-401A and enhanced RANTES production in atopic dermatitis patients. *J Dermatol Sci* 2005; **39**: 189–91.

24 Palmer CN, Irvine AD, Terron-Kwiatkowski A *et al*. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet* 2006; **38**: 441–6.

25 Stemmler S, Parwez Q, Petrasch-Parwez E *et al*. Two common loss-of-function mutations within the filaggrin gene predispose for early onset of atopic dermatitis. *J Invest Dermatol* 2007; **127**: 722–4.

26 Barker JN, Palmer CN, Zhao Y *et al*. Null mutations in the filaggrin gene (FLG) determine major susceptibility to early-onset atopic dermatitis that persists into adulthood. *J Invest Dermatol* 2007; **127**: 564–7.

27 Palmer CN, Ismail T, Lee SP *et al*. Filaggrin null mutations are associated with increased asthma severity in children and young adults. *J Allergy Clin Immunol* 2007; **120**: 64–8.

28 Walley AJ, Chavanas S, Moffatt MF *et al*. Gene polymorphism in Netherton and common atopic disease. *Nat Genet* 2001; **29**: 175–8.

29 Kato A, Fukai K, Oiso N *et al*. Association of SPINK5 gene polymorphisms with atopic dermatitis in the Japanese population. *Br J Dermatol* 2003; **148**: 665–9.

30 Nishio Y, Noguchi E, Shibasaki M *et al*. Association between polymorphisms in the SPINK5 gene and atopic dermatitis in the Japanese. *Genes Immun* 2003; **4**: 515–7.

Maternal factors and inheritance

There is accumulating evidence that atopic disorders are more frequently transmitted by mothers than by fathers. A number of population–based surveys have shown that the risk of children developing atopy is significantly higher when the mother is atopic than when the father is [1,2]. Cord blood IgE is high in babies whose mothers are atopic or have high IgE, whereas paternal atopy or raised IgE are not associated with raised cord blood IgE.

Genes encoding IgE responsiveness, located on chromosome 11q13, are more frequently inherited from the maternal side [3,4]. Thus, of 203 sib pairs analysed, 62% shared the maternal allele whereas 38% did not. Of the alleles that were paternal, the proportion shared with the offspring was close to 50%.

Pregnancy/intrauterine factors

The question arises of how maternal factors can modify the expression of atopy. One possible mechanism is through so-called genetic imprinting—in which paternal genomic effects are suppressed. Another possible mechanism is intrauterine programming—a major factor of which is the balance between fetal nutrition and growth rate. A number of non-dermatological conditions are programmed in fetal life. For example, death rates from coronary heart disease fell progressively between those who were less than 5.5 lb (2.5 kg) at birth and those who were more than 9.5 lb (4.3 kg) [5]. For atopy, there is a positive correlation between increasing birth weight and prevalence of atopic eczema [6–8]. A third possible factor is the onset of immunological sensitization through intrauterine exposure to food and environmental allergens. Cord blood IgE levels and the presence of antigen-specific T lymphocytes in cord blood indicate that immune sensitization occurs in fetal life. The concentration of IgE in cord blood is a predictor for subsequent development of atopy [9]. Maternal exposure to a number of agents, including antigens, alcohol, cigarettes and other pollutants, has attracted attention, but none has emerged as a major regulatory factor.

References

1 Dold S, Wjst M, von Mutius E *et al*. Genetic risk for asthma, allergic rhinitis, and atopic dermatitis. *Arch Dis Child* 1992; **67**: 1018–22.

2 Ruiz RG, Kemeny DM, Price JF. Higher risk of infantile atopic dermatitis from maternal atopy than from paternal atopy. *Clin Exp Allergy* 1992; **22**: 762–6.

3 Cookson WO, Young RP, Sandford AJ *et al*. Maternal inheritance of atopic IgE responsiveness on chromosome 11q [published erratum appears in *Lancet* 1992 Oct 31; **340**(8827): 1110]. *Lancet* 1992; **340**: 381–4.

4 Selnes A, Bolle R, Lund E *et al*. Cumulative incidence of asthma and allergy in north-Norwegian schoolchildren in 1985 and 1995. *Pediatr Allergy Immunol* 2002; **13**: 58–63.

5 Barker DJ. Fetal origins of coronary heart disease. *BMJ* 1995; **311**: 171–4.

6 Peters TJ, Golding J. The epidemiology of childhood eczema: II. Statistical analyses to identify independent early predictors. *Paediatr Perinat Epidemiol* 1987; **1**: 80–94.

7 Olesen AB, Ellingsen AR, Olesen H *et al*. Atopic dermatitis and birth factors: historical follow up by record linkage. *BMJ* 1997; **314**: 1003–8.

8 Godfrey K. Fetal and perinatal origins of atopic dermatitis. In: Williams HC, ed. *Atopic Dermatitis: The Epidemiology, Causes and Prevention of Atopic Dermatitis*. Cambridge: Cambridge University Press, 2000: 125–38.

9 Tariq SM, Arshad SH, Matthews SM *et al*. Elevated cord serum IgE increases the risk of aeroallergen sensitization without increasing respiratory allergic symptoms in early childhood. *Clin Exp Allergy* 1999; **29**: 1042–8.

Environmental factors

The rate of increase in the prevalence of atopic eczema is too rapid to be accounted for by change in population genetics. Therefore, environmental factors are the most likely modulating influences. The two principal aspects that have attracted attention are 'pollution' and microbes.

A different prevalence in populations of the same genetic background separated only by geographical factors is well documented in developed countries. The fall of the Berlin wall separating East and West Germany provided an opportunity to examine the role of industrial pollution by comparing the 'dirty' East with the 'clean' West. Cohorts of pre-school children from comparable cities in the East (Halle) and West (Duisberg) and a rural area (Borken) were recruited. Questionnaires assessed the personal and family history of atopic disease as well as many of the relevant factors such as socio-economic status. All the children were examined by dermatologists. The levels of airborne pollutants were compared, and sulphur dioxide was fourfold higher in Halle, whereas dust and nitrogen oxides were comparable between the cities. The prevalence of atopic eczema was 17.5% in Halle but only 5.7–7.3% in Duisberg [1]. However, conflicting findings emerged in the study comparing the prevalence of atopic disease in Leipzig (East Germany) and Munich (West Germany). A slightly lower prevalence was observed in Leipzig compared with Munich [2]. For comparison, prevalence in rural Ethiopia was estimated to be 0.3% [3], yet this was significantly lower than the urban population of the same country (1.5%).

The identification of relevant pollutants that might contribute to the expression of the atopic phenotype is still confused. Indoor pollution levels from cigarette smoke or nitrogen oxides in the gas exhaust from cookers and heaters are difficult to quantify.

Environmental microbes—the hygiene hypothesis [4,5]

Interaction with environmental microbes may be important in the causation of atopic eczema in a number of ways. First, early life exposure may condition the maturation of the immune system so that the apparent dysregulation associated with production of IgE antibody and formation of allergies does not occur. Secondly, in individuals with the atopic phenotype, eczema may be induced or exacerbated by staphylococcal toxins or by the presence on the skin of *Malassezia* yeasts. The possible role of microbes in the early maturation of the immune system may be the major factor that could explain the differences between the Western world and the developing world regarding the incidence of atopy and allergic diseases. This idea was initially proposed as the 'hygiene hypothesis' [5] and remains controversial [6]. Indirect support for this hypothesis derives from the observations that allergic sensitization is greatest in first-born children and is less frequent in children from large families [5]. However, numerous epidemiological studies have failed to demonstrate a reduced infection rate in children who go on to develop atopic dermatitis [7–15].

Many studies have examined the effects of particular organisms or routes of infection, and a preponderance of findings suggest that microbes entering via the faecal–oral route have a greater protective effect against the development of atopic allergic diseases than those entering via respiratory routes. Thus, early exposure to hepatitis A virus, *Helicobacter pylori* or *Toxoplasma gondii* is reported to reduce the risk of atopy by more than 60% [16]. In contrast, it seems that exposure to respiratory pathogens is not associated with this effect [16].

Significant differences have been observed in the prevalence of allergies between rural and urban areas within one country, which could also reflect different levels of exposure to microbes. Moreover, there are differences in the prevalence of allergic diseases among children living on farms and in those living in the same rural environment, but not on farms [17–20]. This difference suggests that contact with livestock and poultry is a key factor and, although the levels of aero-allergens are likely to be higher in the farm environment, the levels of bacterial endotoxin are also much higher in the household dust from farms [19,21]. However, it is of

considerable interest that the reported differences only apply to respiratory diseases and not to eczema.

The potential importance of endotoxins lies in the powerful effects they can have in regulating the responses developed by the immune system (see below). The possibility that microbial endotoxins play a major role in driving the immune system towards productive/protective responses and away from non-productive/nuisance responses associated with allergy, suggests that what matters is the immunological outcome following exposure to stimulatory microbial factors, rather than particular infections themselves. The effects of bacterial endotoxins on immune function will be discussed in the following section on immune dysregulation.

References

1 Schafer T, Vieluf D, Behrendt H *et al*. Atopic eczema and other manifestations of atopy: results of a study in East and West Germany. *Allergy* 1996; **51**: 532–9.

2 von Mutius E, Fritzsch C, Weiland SK *et al*. Prevalence of asthma and allergic disorders among children in united Germany: a descriptive comparison. *BMJ* 1992; **305**: 1395–9.

3 Yemaneberhan H, Flohr C, Lewis SA *et al*. Prevalence and associated factors of atopic dermatitis symptoms in rural and urban Ethiopia. *Clin Exp Allergy* 2004; **34**: 779–85.

4 Strachan DP. Family size, infection and atopy: the first decade of the 'hygiene hypothesis'. *Thorax* 2000; **55** (Suppl. 1): S2–10.

5 Strachan DP. Hay fever, hygiene, and household size. *BMJ* 1989; **299**: 1259–60.

6 Bach JF. Infections and autoimmune diseases. *J Autoimmun* 2005; **25** (Suppl.): 74–80.

7 Benn CS, Melbye M, Wohlfahrt J *et al*. Cohort study of sibling effect, infectious diseases, and risk of atopic dermatitis during first 18 months of life. *BMJ* 2004; **328**: 1223.

8 McKeever TM, Lewis SA, Smith C *et al*. Early exposure to infections and antibiotics and the incidence of allergic disease: a birth cohort study with the West Midlands General Practice Research Database. *J Allergy Clin Immunol* 2002; **109**: 43–50.

9 Bodner C, Godden D, Seaton A. Family size, childhood infections and atopic diseases. The Aberdeen WHEASE Group. *Thorax* 1998; **53**: 28–32.

10 Linneberg A, Ostergaard C, Tvede M *et al*. IgG antibodies against microorganisms and atopic disease in Danish adults: the Copenhagen Allergy Study. *J Allergy Clin Immunol* 2003; **111**: 847–53.

11 Wickens KL, Crane J, Kemp TJ *et al*. Family size, infections, and asthma prevalence in New Zealand children. *Epidemiology* 1999; **10**: 699–705.

12 Forastiere F, Agabiti N, Corbo GM *et al*. Socioeconomic status, number of siblings, and respiratory infections in early life as determinants of atopy in children. *Epidemiology* 1997; **8**: 566–70.

13 Nafstad P, Magnus P, Jaakkola JJ. Early respiratory infections and childhood asthma. *Pediatrics* 2000; **106**: E38.

14 Matricardi PM, Rosmini F, Ferrigno L *et al*. Cross-sectional retrospective study of prevalence of atopy among Italian military students with antibodies against hepatitis A virus. *BMJ* 1997; **314**: 999–1003.

15 Ponsonby AL, Couper D, Dwyer T *et al*. Relationship between early life respiratory illness, family size over time, and the development of asthma and hay fever: a seven year follow-up study. *Thorax* 1999; **54**: 664–9.

16 Matricardi PM, Rosmini F, Riondino S *et al*. Exposure to foodborne and orofecal microbes versus airborne viruses in relation to atopy and allergic asthma: epidemiological study. *BMJ* 2000; **320**: 412–7.

17 von Ehrenstein OS, von Mutius E, Illi S *et al*. Reduced risk of hay fever and asthma among children of farmers. *Clin Exp Allergy* 2000; **30**: 187–93.

18 Braun-Fahrlander C. The role of the farm environment and animal contact for the development of asthma and allergies. *Clin Exp Allergy* 2001; **31**: 1799–803.

19 Braun-Fahrlander C, Riedler J, Herz U *et al*. Environmental exposure to endotoxin and its relation to asthma in school-age children. *N Engl J Med* 2002; **347**: 869–77.

20 Riedler J, Eder W, Oberfeld G *et al*. Austrian children living on a farm have less hay fever, asthma and allergic sensitization. *Clin Exp Allergy* 2000; **30**: 194–200.

21 von Mutius E, Braun-Fahrlander C, Schierl R *et al*. Exposure to endotoxin or other bacterial components might protect against the development of atopy. *Clin Exp Allergy* 2000; **30**: 1230–4.

Immune dysregulation

T lymphocytes

The fetal immune system is normally weighted towards generating Th2 responses, which is necessary to reduce the chance of the fetus and mother reacting against each other, with subsequent spontaneous abortion. This is reflected in the production of low basal levels of interferon-γ. In the post-natal period the immune system appears to mature and production of interferon-γ increases. However, in infants destined to develop infantile atopic eczema, the basal production of interferon-γ is particularly low [1] and Th2 dominant responses persist [2]. This could reflect an intrinsic defect in T-cell function.

Biopsy of developing lesions of atopic dermatitis reveals that T cells infiltrate the skin early in the disease process [3,4]. The cellular infiltrate in atopic dermatitis is predominantly T lymphocytes ($CD4^+$:$CD8^+$ ratio 7:1) but eosinophils are also present, albeit at lower frequencies [5,6]. A large fraction of lesional T cells are CLA^+ (skin homing receptor) and predominantly $CD45RO^+$, suggesting previous encounter with antigen [7,8]. Markers of activation, such as IL-2Rα (CD25) and HLA-DR, are also prominent [9].

In situ hybridization experiments reveal an increased number of cells expressing IL-4 and IL-13, but not IL-5 or IFN-γ mRNA, in non-lesional atopic dermatitis skin than in normal control skin [10,11]. The same authors demonstrated significantly greater numbers of IL-4, IL-5 and IL-13 mRNA-expressing cells in lesional skin than in non-lesional or control skin. IFN-γ mRNA expression was not detected in acute atopic dermatitis but only in chronic skin lesions in which there were significantly fewer IL-4 and IL-13 mRNA-expressing cells. In chronic as opposed to acute lesions, IL-5, GM-CSF, IL-12 and IFN-γ mRNA-expressing cells predominate. Both IL-5 and GM-CSF production are important in promoting the growth and survival of eosinophils and macrophages, whereas IL-12 and IFN-γ promote the Th1 polarization of T lymphocytes. These data, suggesting a role for both classical Th1 and Th2 cytokines, have been supported by serial investigations using application of allergen to the skin of atopics in an atopy patch test model. Investigation using this method and serial biopsies reveal a biphasic pattern of cytokine release [3,4]: IL-4 expression is predominant early in the process and begins to decline after 24 h, whereas IFN-γ expression peaks at 48–72 h. Thus, although development of acute lesions of atopic dermatitis is characterized by Th2 cytokines, persistence to chronic disease is associated with Th1 production as well.

Further evidence of the role of Th2 cells is derived from demonstration that allergens evoke Th2 responses in atopic subjects [12,13]. Furthermore, Th2 cell numbers increase in target organs of allergic disease [14–16], modulating Th2 responses towards Th1 can be associated with disease improvement [17–20], and transfer and correction of atopy may be achieved by bone marrow transplantation [21–23].

There is evidence that activation signalling in T cells may be different in atopic individuals (see below). Thus, constitutional

over-activity of cyclic AMP phosphodiesterase is associated with blunted or attenuated cAMP-mediated signalling. This has been shown to tie up with differentiation of atopic T cells towards a Th2 phenotype [24]. In addition, T cells from atopic donors respond to allergens such as Der p1 from dust mites with an increased production of Th2-type cytokines, and IL-13 in particular [25]. This could be blocked with an inhibitor of adenylate cyclase—the kinase that transduces cAMP-induced signals to more downstream targets. Paradoxically, it was also blocked by rolipram, an inhibitor of type IV cAMP phosphodiesterase which, by inhibiting breakdown of cAMP, augments intracellular cAMP levels and therefore has the exact opposite effect of inhibiting cAMP breakdown.

Chemokines are cytokine-like molecules which are essential for cellular recruitment to tissues in response to injury or infection. Chemokine–receptor interactions have been implicated in atopic dermatitis by demonstration of a significant role in skin homing of T cells. Demonstration of raised lesional mRNA levels correlating with atopic dermatitis severity include eotaxin (CCL11) and CTACK (CCL27).

The reasons why the atopic immune system responds with ready generation of Th2 lymphocytes are not clear, but a hypothesis attracting much attention is the so-called hygiene hypothesis (see above). This proposes that exposure in early life to microbes of various types, but especially those possessing lipopolysaccharide (LPS) endotoxin such as *E. coli* and other enteropathogens, is critical in pushing immune responses towards a Th1 type. The LPS activates production of IL-12 by DCs, which promotes production of interferon-γ and hence can deviate T-cell activation induced by any other antigen present at the same time towards a Th1 response.

Regulatory T cells in atopic disease. Over-active Th2 responses are critical to the manifestation of allergic disease. The mechanisms whereby similar responses do not occur in allergen-exposed, unaffected individuals are not clear. Interest in the role of regulatory cells in atopic dermatitis and allergy stems from two observations: firstly, that murine models of autoimmune disease can be prevented by adoptive transfer of regulatory T cells (Tregs) [26–28] and, secondly, that genetic disorders with resultant lack of regulatory T cells (immune dysregulation polyendocrinopathy enteropathy X-linked syndrome (IPEX syndrome) due to mutations in the forkhead box protein P3 (FoxP3) gene [29]) are associated with spontaneous dermatitis, hyper-IgE and food allergy, amongst other defects.

Evidence exists for the role of Tregs in inhibiting antigen-specific Th2 responses in various clinical allergy settings: allergen-specific immunotherapy (SIT) of hymenoptera venom [30]; aeroallergen sensitivity [31–33]; cow's milk allergy [34]; and allergic contact dermatitis to nickel [35]. Glucocorticoids have been reported to increase the Treg cell population [36,37], and staphylococcal-derived superantigens, which are detected in and correlate with disease severity in atopic dermatitis, can subvert Treg cell function [38]. Furthermore, the role of the epithelium in controlling Treg function has been recently highlighted by demonstration of keratinocyte expression of RANKL, which appears to have a critical role in modulating dendritic cell control of Treg populations [39].

Despite these reports, investigations of peripheral blood Treg number and suppressive function have found them to be normal in individuals with atopic dermatitis [40,41]. Verhagen *et al.* [42] reported that the number of $FoxP3^+$ cells in atopic dermatitis lesional skin was low, yet IL-10 and TGF-β cytokines and their receptors were found to be expressed, suggesting that Tr1 cells may be present in lesions of atopic dermatitis.

Apart from alterations in immune regulatory mechanisms, the allergens themselves seem to evoke different responses in atopic individuals. Thus, both atopic and non-atopic people make IgG antibodies against *Candida albicans*, whereas house dust mite antigen Der p1 evokes IgE antibodies in atopics but IgG antibodies in non-atopics [12,13]. It has been suggested that this property is related to the natural function of many allergens as proteases.

References

1 Warner JO, Warner JA, Miles EA *et al*. Reduced interferon-gamma secretion in neonates and subsequent atopy. *Lancet* 1994; **344**: 1516.

2 Lange J, Ngoumou G, Berkenheide S *et al*. High interleukin-13 production by phytohaemagglutinin- and Der p 1-stimulated cord blood mononuclear cells is associated with the subsequent development of atopic dermatitis at the age of 3 years. *Clin Exp Allergy* 2003; **33**: 1537–43.

3 Grewe M, Walther S, Gyufko K *et al*. Analysis of the cytokine pattern expressed in situ in inhalant allergen patch test reactions of atopic dermatitis patients. *J Invest Dermatol* 1995; **105**: 407–10.

4 Thepen T, Langeveld-Wildschut EG, Bihari IC *et al*. Biphasic response against aeroallergen in atopic dermatitis showing a switch from an initial TH2 response to a TH1 response in situ: an immunocytochemical study. *J Allergy Clin Immunol* 1996; **97**: 828–37.

5 Zachary CB, Allen MH, MacDonald DM. In situ quantification of T-lymphocyte subsets and Langerhans cells in the inflammatory infiltrate of atopic eczema. *Br J Dermatol* 1985; **112**: 149–56.

6 Lever R, Turbitt M, Sanderson A *et al*. Immunophenotyping of the cutaneous infiltrate and of the mononuclear cells in the peripheral blood in patients with atopic dermatitis. *J Invest Dermatol* 1987; **89**: 4–7.

7 Bos JD, Hagenaars C, Das PK *et al*. Predominance of 'memory' T cells (CD4+, CDw29+) over 'naive' T cells (CD4+, CD45R+) in both normal and diseased human skin. *Arch Dermatol Res* 1989; **281**: 24–30.

8 Leung DY, Bhan AK, Schneeberger EE *et al*. Characterization of the mononuclear cell infiltrate in atopic dermatitis using monoclonal antibodies. *J Allergy Clin Immunol* 1983; **71**: 47–56.

9 Piletta PA, Wirth S, Hommel L *et al*. Circulating skin-homing T cells in atopic dermatitis. Selective up-regulation of HLA-DR, interleukin-2R, and CD30 and decrease after combined UV-A and UV-B phototherapy. *Arch Dermatol* 1996; **132**: 1171–6.

10 Hamid Q, Boguniewicz M, Leung DY. Differential in situ cytokine gene expression in acute versus chronic atopic dermatitis. *J Clin Invest* 1994; **94**: 870–6.

11 Hamid Q, Naseer T, Minshall EM *et al*. In vivo expression of IL-12 and IL-13 in atopic dermatitis. *J Allergy Clin Immunol* 1996; **98**: 225–31.

12 Wierenga EA, Snoek M, de Groot C *et al*. Evidence for compartmentalization of functional subsets of CD2+ T lymphocytes in atopic patients. *J Immunol* 1990; **144**: 4651–6.

13 Parronchi P, Macchia D, Piccinni MP *et al*. Allergen- and bacterial antigen-specific T-cell clones established from atopic donors show a different profile of cytokine production. *Proc Natl Acad Sci USA* 1991; **88**: 4538–42.

14 Hamid Q, Azzawi M, Ying S *et al*. Interleukin-5 mRNA in mucosal bronchial biopsies from asthmatic subjects. *Int Arch Allergy Appl Immunol* 1991; **94**: 169–70.

15 van der Heijden FL, Wierenga EA, Bos JD *et al*. High frequency of IL-4-producing CD4+ allergen-specific T lymphocytes in atopic dermatitis lesional skin. *J Invest Dermatol* 1991; **97**: 389–94.

16 Del Prete GF, de Carli M, D'Elios MM *et al*. Allergen exposure induces the activation of allergen-specific Th2 cells in the airway mucosa of patients with allergic respiratory disorders. *Eur J Immunol* 1993; **23**: 1445–9.

17 Secrist H, Chelen CJ, Wen Y *et al*. Allergen immunotherapy decreases interleukin 4 production in CD4+ T cells from allergic individuals. *J Exp Med* 1993; **178**: 2123–30.
18 Varney VA, Hamid QA, Gaga M *et al*. Influence of grass pollen immunotherapy on cellular infiltration and cytokine mRNA expression during allergen-induced late-phase cutaneous responses. *J Clin Invest* 1993; **92**: 644–51.
19 McHugh SM, Deighton J, Stewart AG *et al*. Bee venom immunotherapy induces a shift in cytokine responses from a TH-2 to a TH-1 dominant pattern: comparison of rush and conventional immunotherapy. *Clin Exp Allergy* 1995; **25**: 828–38.
20 Jutel M, Pichler WJ, Skrbic D *et al*. Bee venom immunotherapy results in decrease of IL-4 and IL-5 and increase of IFN-gamma secretion in specific allergen-stimulated T cell cultures. *J Immunol* 1995; **154**: 4187–94.
21 Agosti JM, Sprenger JD, Lum LG *et al*. Transfer of allergen-specific IgE-mediated hypersensitivity with allogeneic bone marrow transplantation. *N Engl J Med* 1988; **319**: 1623–8.
22 Saurat JH. Eczema in primary immune-deficiencies. Clues to the pathogenesis of atopic dermatitis with special reference to the Wiskott-Aldrich syndrome. *Acta Derm Venereol Suppl (Stockh)* 1985; **114**: 125–8.
23 Koharazawa H, Kanamori H, Takabayashi M *et al*. Resolution of atopic dermatitis following allogeneic bone marrow transplantation for chronic myelogenous leukemia. *Bone Marrow Transpl* 2005; **35**: 1223–4.
24 Hanifin JM, Chan SC. Monocyte phosphodiesterase abnormalities and dysregulation of lymphocyte function in atopic-dermatitis. *J Invest Dermatol* 1995; **105**: S84–S88.
25 Kanda N, Watanabe S. Intracellular 3′,5′-adenosine cyclic monophosphate level regulates house dust mite-induced interleukin-13 production by T cells from mite-sensitive patients with atopic dermatitis. *J Invest Dermatol* 2001; **116**: 3–11.
26 Chen Y, Kuchroo VK, Inobe J *et al*. Regulatory T cell clones induced by oral tolerance: suppression of autoimmune encephalomyelitis. *Science* 1994; **265**: 1237–40.
27 Powrie F, Correa-Oliveira R, Mauze S *et al*. Regulatory interactions between CD45RBhigh and CD45RBlow CD4+ T cells are important for the balance between protective and pathogenic cell-mediated immunity. *J Exp Med* 1994; **179**: 589–600.
28 Groux H, O'Garra A, Bigler M *et al*. A CD4+ T-cell subset inhibits antigen-specific T-cell responses and prevents colitis. *Nature* 1997; **389**: 737–42.
29 Bacchetta R, Passerini L, Gambineri E *et al*. Defective regulatory and effector T cell functions in patients with FOXP3 mutations. *J Clin Invest* 2006; **116**: 1713–22.
30 Akdis CA, Blesken T, Akdis M *et al*. Role of interleukin 10 in specific immunotherapy. *J Clin Invest* 1998; **102**: 98–106.
31 Jutel M, Akdis M, Budak F *et al*. IL-10 and TGF-beta cooperate in the regulatory T cell response to mucosal allergens in normal immunity and specific immunotherapy. *Eur J Immunol* 2003; **33**: 1205–14.
32 Bellinghausen I, Konig B, Bottcher I *et al*. Regulatory activity of human CD4 CD25 T cells depends on allergen concentration, type of allergen and atopy status of the donor. *Immunology* 2005; **116**: 103–11.
33 Ling EM, Smith T, Nguyen XD *et al*. Relation of CD4+CD25+ regulatory T-cell suppression of allergen-driven T-cell activation to atopic status and expression of allergic disease. *Lancet* 2004; **363**: 608–15.
34 Karlsson MR, Rugtveit J, Brandtzaeg P. Allergen-responsive CD4+CD25+ regulatory T cells in children who have outgrown cow's milk allergy. *J Exp Med* 2004; **199**: 1679–88.
35 Cavani A, Nasorri F, Ottaviani C *et al*. Human CD25+ regulatory T cells maintain immune tolerance to nickel in healthy, nonallergic individuals. *J Immunol* 2003; **171**: 5760–8.
36 Karagiannidis C, Akdis M, Holopainen P *et al*. Glucocorticoids upregulate FOXP3 expression and regulatory T cells in asthma. *J Allergy Clin Immunol* 2004; **114**: 1425–33.
37 Peek EJ, Richards DF, Faith A *et al*. Interleukin-10-secreting 'regulatory' T cells induced by glucocorticoids and beta2-agonists. *Am J Respir Cell Mol Biol* 2005; **33**: 105–11.
38 Ou LS, Goleva E, Hall C *et al*. T regulatory cells in atopic dermatitis and subversion of their activity by superantigens. *J Allergy Clin Immunol* 2004; **113**: 756–63.
39 Loser K, Mehling A, Loeser S *et al*. Epidermal RANKL controls regulatory T-cell numbers via activation of dendritic cells. *Nat Med* 2006; **12**: 1372–9.
40 Maggi L, Santarlasci V, Liotta F *et al*. Demonstration of circulating allergen-specific CD4+CD25highFoxp3+ T-regulatory cells in both nonatopic and atopic individuals. *J Allergy Clin Immunol* 2007; **120**: 429–36.
41 Vukmanovic-Stejic M, McQuaid A, Birch KE *et al*. Relative impact of CD4+CD25+ regulatory T cells and tacrolimus on inhibition of T-cell proliferation in patients with atopic dermatitis. *Br J Dermatol* 2005; **153**: 750–7.
42 Verhagen J, Akdis M, Traidl-Hoffmann C *et al*. Absence of T-regulatory cell expression and function in atopic dermatitis skin. *J Allergy Clin Immunol* 2006; **117**: 176–83.

Immunoglobulins

IgE. The main immunoglobulin abnormality is increased production of IgE. This results in the presence of many antigen-specific IgE species to ingested or inhaled antigens and, frequently, an increase in total serum IgE. About 80% of patients with atopic dermatitis have increased amounts of total IgE. If dermatitis is the only clinical manifestation of atopy, the amounts of total IgE may be little above the normal range [1–3] and the patients show no anaphylactic sensitivity to environmental antigens [4,5]. However, even though total IgE levels may be normal, there are almost always specific IgEs directed at environmental aero- and/or food allergens [6–10]. If there is concomitant asthma or allergic rhinitis the concentrations of IgE may be very much above normal [1,3]. Surface-bound IgE on epithelial dendritic cells (DC) by the high affinity IgE receptor (Fc epsilon RI) is an important mechanism of allergen capture and internalization by the DC, which enhances processing and presentation of antigenic epitopes to the adaptive immune system [11,12]. Epithelial DC expression of Fc epsilon R1 is significantly increased in individuals with atopic dermatitis. IgE also increases in amount with increasing severity and extent of the dermatitis, even without respiratory allergy, and patients with high levels are likely to have a poorer prognosis. The converse has also been demonstrated, in that persons who were free of classical signs of atopic dermatitis for a year had normal amounts of IgE, even if they had persistent or recurrent eczema of the hands, or discoid eczema [13].

The production of very large amounts of IgE, equivalent to levels encountered in the hyper-IgE syndrome, may be induced by *Staphylococcus aureus* antigens [14]. Some staphylococcal exotoxins are superantigens [15], which activate a greater number of lymphocytes than those stimulated by specific antigen, resulting in a 'superstimulation' (Chapter 13). One manifestation is an excessive synthesis of IgE. Staphylococci colonize the skin of atopic dermatitis patients, and exotoxins with superantigen properties have been isolated from them [16,17]. One such exotoxin, the toxic shock syndrome toxin I, although inhibiting *in vitro* IgE synthesis by blood mononuclear cells at high concentration, was found to stimulate synthesis of IgE by the mononuclear cells of atopic dermatitis patients at low concentration. This pathway may have contributed to the increased IgE synthesis in this disorder [17].

IgE is involved in autoimmune reactivity in two ways. Firstly, it is an antigenic target for IgG anti-IgE antibodies and, secondly, it can also be autoreactive, with specificity for self proteins. IgE occurs in serum in the form of immune complexes with IgG and C3, but the amounts of precipitable complexes are not related to the concentrations of serum IgE or to the severity of the skin condition [18,19]. As much as 32% of the serum IgE may be in the

high-molecular-weight complexes [20], which should therefore influence the interpretation of serum IgE assays. IgE–anti-IgE complexes also occur, with antibody specificity to the CH_3 and the CH_4 IgE epitopes [19]. The ability of the free IgG anti-IgE antibodies to release histamine and other mediators from mast cells and basophils *in vitro* varies. In some tests no histamine was released [21,22], whereas in others histamine release occurred [23,24]. Similar autoantibody complexes occur in other atopic disorders.

Autoreactive IgE antibodies have been reported to be directed against self-proteins, some of which may be skin-derived [25,26]. This autoreactivity probably develops secondary to the chronic exposure to skin-derived antigens. However, it is thought that once present, the autoreactivity may contribute to the chronicity and severity of the dermatitis.

References

1 Ohman S, Johansson SG. Allergen-specific IgE in atopic dermatitis. *Acta Derm Venereol* 1974; **54**: 283–90.
2 Ohman S, Johansson SG. Immunoglobulins in atopic dermatitis with special reference to IgE. *Acta Derm Venereol* 1974; **54**: 193–202.
3 Jones HE, Inouye JC, McGerity JL *et al*. Atopic disease and serum immunoglobulin-E. *Br J Dermatol* 1975; **92**: 17–25.
4 Uehara M, Sawai T. Familial background of respiratory atopy. A factor of type I allergy to house dust mite in patients with atopic dermatitis. *Arch Dermatol* 1989; **125**: 939–43.
5 Wuthrich B, Schnyder UW. Haufigkeit genetische Aspekte und Prognose der Neurodermatitis atopica. *Allergologie* 1991; **14**: 284–90.
6 Sampson HA, McCaskill CC. Food hypersensitivity and atopic dermatitis: evaluation of 113 patients. *J Paediatr* 1985; **107**: 669–75.
7 Guillet G, Guillet MH. Food allergy in dermatological disease in children. *Revue Francaise D Allergologie Et D Immunologie Clinique* 1997; **37**: 602–12.
8 Uehara M, Kimura C, Uenishi T. Type I allergy to foods in atopic dermatitis. Comparison between RAST-positive and RAST-negative cases. *Acta Derm Venereol Suppl (Stockh)* 1992; **176**: 38–40.
9 Adinoff AD, Tellez P, Clark RA. Atopic dermatitis and aeroallergen contact sensitivity. *J Allergy Clin Immunol* 1988; **81**: 736–42.
10 Beck HI, Korsgaard J. Atopic dermatitis and house dust mites. *Br J Dermatol* 1989; **120**: 245–51.
11 van der Heijden FL, Joost van Neerven RJ, van Katwijk M *et al*. Serum-IgE-facilitated allergen presentation in atopic disease. *J Immunol* 1993; **150**: 3643–50.
12 Bieber T. Fc epsilon RI on human epidermal Langerhans cells: an old receptor with new structure and functions. *Int Arch Allergy Immunol* 1997; **113**: 30–4.
13 Johansson SG, Juhlin L. Immunoglobulin E in 'healed' atopic dermatitis and after treatment with corticosteroids and azathioprine. *Br J Dermatol* 1970; **82**: 10–3.
14 Nordvall SL, Lindgren L, Johansson SG *et al*. IgE antibodies to *Pityrosporum orbiculare* and *Staphylococcus aureus* in patients with very high serum total IgE. *Clin Exp Allergy* 1992; **22**: 756–61.
15 Marrack P, Kappler J. The staphylococcal enterotoxins and their relatives. *Science* 1990; **248**: 705–11.
16 McFadden JP, Noble WC, Camp RD. Superantigenic exotoxin-secreting potential of staphylococci isolated from atopic eczematous skin. *Br J Dermatol* 1993; **128**: 631–2.
17 Hofer MF, Lester MR, Schlievert PM *et al*. Upregulation of IgE synthesis by staphylococcal toxic shock syndrome toxin-1 in peripheral blood mononuclear cells from patients with atopic dermatitis. *Clin Exp Allergy* 1995; **25**: 1218–27.
18 Kapp A, Kemper A, Schopf E *et al*. Detection of circulating immune complexes in patients with atopic dermatitis and psoriasis. *Acta Derm Venereol* 1986; **66**: 121–6.
19 Czech W, Stadler BM, Schopf E *et al*. IgE autoantibodies in atopic dermatitis—occurrence of different antibodies against the CH3 and the CH4 epitopes of IgE. *Allergy* 1995; **50**: 243–8.
20 Swainson JA, Wilson PB, Dore P *et al*. Evidence for circulating complexes containing IgE in patients with atopic dermatitis. *Int Arch Allergy Appl Immunol* 1985; **76**: 237–42.
21 Johansson SG. Anti-IgE antibodies in human serum. *J Allergy Clin Immunol* 1986; **77**: 555–7.
22 Williams RC Jr, Griffiths RW, Emmons JD *et al*. Naturally occurring human antiglobulins with specificity for E. *J Clin Invest* 1972; **51**: 955–63.
23 Marone G, Casolaro V, Paganelli R *et al*. IgG anti-IgE from atopic dermatitis induces mediator release from basophils and mast cells. *J Invest Dermatol* 1989; **93**: 246–52.
24 Paganelli R, Quinti I. Pathological significance of circulating IgG anti-IgE complexes. *Monogr Allergy* 1989; **26**: 184–97.
25 Valenta R, Maurer D, Steiner R *et al*. Immunoglobulin E response to human proteins in atopic patients. *J Invest Dermatol* 1996; **107**: 203–8.
26 Valenta R, Natter S, Seiberler S *et al*. Molecular characterization of an autoallergen, Hom s 1, identified by serum IgE from atopic dermatitis patients. *J Invest Dermatol* 1998; **111**: 1178–83.

Other immunoglobulins. The amounts of IgG, IgA and IgM in atopic dermatitis are usually normal but increases have been reported, particularly in severely affected persons. However, in patients with severe eczema complicated by cutaneous infection, an increase in IgG appears to be due to antibodies to bacteria. In other cases the increase is due to antibodies to food antigens. Any change in total IgG is considered to be a secondary or unrelated phenomenon, and not contributory. Furthermore, *in vitro* synthesis of IgG by blood mononuclear leukocytes was less than in cells from normal persons, and attributed to decreased responsiveness of atopic B cells [1].

Although total IgG usually remains within normal limits, some patients show an increase in the subclass IgG4 [2,3]. However, because this subclass is quantitatively the smallest of the four subclasses the increase in IgG4 is unlikely to make a significant difference to the total IgG. IgG4 antibodies were specific for β-lactoglobulin [4] and for egg [5]. No clinical relevance was found on comparison of the amounts of IgG4 antibody with those of IgE, or with skin-test results [5]. In children with eczema complicated by asthma, IgG4 was much increased, usually with increases in total IgE [6,7]. Those who had an increase only in IgE or IgG4 did not have eczema, but asthma alone [6]. There is no clear evidence that IgG4 is anaphylactic, that is mediating mast-cell responses on challenge with antigens, or that it contributes to the clinical changes of atopic dermatitis. It may be protective, because it has been shown *in vitro* that IgG4 will impede sensitization of basophils by IgE [8]; a conclusion supported by the finding of increased amounts of IgG4 and relatively small amounts of IgE antiovalbumin in children with atopic dermatitis [9].

It has been proposed that atopic subjects have an IgA deficiency which permits excessive absorption of allergen through mucosae, resulting in increased production of IgE. A modification of this theory is that the IgA deficiency may be transient, occurring for a few months early in infancy, and that the increased allergen absorption primes the individual to excessive production of IgE later in life.

The contention that a transient IgA deficiency in infants, particularly those born of atopic parents, predisposes the infants to increased production of IgE antibodies and atopic eczema later in life, led to the proposition that the atopic state could be avoided if the infants were not exposed to potent allergens during the susceptible period. The most common allergens are foods, for example milk and eggs, and elimination of potent food allergens

for the first 6 months of life in high-risk infants is reported to reduce the incidence of eczema. However, allergen avoidance by breastfeeding and soya preparations has not been associated consistently with a decreased incidence of atopy, although in these reports complete avoidance is not evidenced during the critical period. Likewise, allergen avoidance by the mother during pregnancy and during breastfeeding has led to modest or equivocal benefit.

References

1 Cooper KD, Kazmierowski JA, Wuepper KD. Immunoregulation in atopic dermatitis. Functional analysis of T–B cell interactions and enumeration of Fc receptor-bearing T-cells. *J Invest Dermatol* 1983; **80**: 139–45.

2 Barnetson R StC, Merrett TC. Food allergy and atopic eczema. *Proc Nutr Soc* 1983; **42**: 247–56.

3 Merrett J, Barnetson R StC, Burr ML. Total and specific IgG4 antibody levels in atopic eczema. *Clin Exp Immunol* 1984; **56**: 645–52.

4 Husby S, Larsen FS, Ahlstedt S. Humoral immunity to dietary antigens in atopic dermatitis. II. Analysis of IgE and IgG subclass antibodies. *Allergy* 1986; **41**: 386–91.

5 Rowntree S, Platts-Mills TAB, Cogswell JJ. A subclass IgG4-specific antigen binding radioimmunoassay (RIA): comparison between IgG and IgG4 antibodies to food and inhaled antigens in adult atopic dermatitis after desensitization treatment and during development of antibody responses in children. *J Allergy Clin Immunol* 1987; **80**: 622–30.

6 Gwynn CM, Morrison Smith J, Leon GL. Role of IgG4 subclass in childhood allergy. *Lancet* 1978; **i**: 910–1.

7 Gwynn CM, Morrison Smith J, Leon GL. IgE and IgG4 subclass in atopic families. *Clin Allergy* 1979; **9**: 119–23.

8 Parish WE. The clinical relevance of heat-stable, short-term sensitizing anaphylactic IgG antibodies (IgG S-TS) and of related activities of IgG4 and IgG2. *Br J Dermatol* 1981; **105**: 225–31.

9 Gondo A, Saeki N, Tokuda Y. IgG4 antibodies in patients with atopic dermatitis. *Br J Dermatol* 1987; **117**: 301–10.

Pathogenesis of eczema

The role of allergy

There are many factors, including allergies, infections, emotional, climatic and other environmental influences, that contribute to the causation of atopic dermatitis. In early life, atopic infants develop eczema as the first of the possible atopic syndromes, which include eczema, asthma and rhinitis. There is uncertainty as to whether this is the result of allergic sensitization or the consequence of pro-inflammatory effects of staphylococci and their superantigens.

The epithelia of atopic individuals have significant impairments of innate antimicrobial defences. Thus, in the bronchial epithelium of asthmatics, viral infections do not evoke normal production of interferon-α [1,2]. Epidermal keratinocytes in atopic eczema produce reduced levels of the anti-bacterial peptides human beta defensins (HBD)-1, -2 and -3, and cathelicidin [3,4]. This is apparently not a constitutive deficiency but is the result of the cytokine milieu (high levels of IL-10 in particular) causing downregulation of the production of the antimicrobial peptides [5]. The consequence is reduced defence against *Staphylococcus aureus*, *M. furfur* and probably the herpesvirus family. Colonization of the skin by *S. aureus* exacerbates eczema in two ways. Firstly, the staphylococci often produce superantigens which have the property of driving an inflammatory response and eliciting an eczematous inflammatory reaction. Secondly, invasive infection by staphylococci produces acute, infected flares of eczema.

There is evidence that immune sensitization occurs to food-derived allergens as well as aeroallergens [6–8]. The infantile intestine shows increased permeability to macromolecules and this is greater in atopic infants. This may be due to inherent 'leakiness' and also, because of the transient deficiency of IgA, the IgA-mediated clearance mechanisms are less effective, allowing greater entry of food-derived macromolecules into the systemic circulation where they may induce immunological sensitization. The increased permeability of the intestine may also reflect a general reduction in barrier function that is also seen in the bronchial and epidermal epithelia [9,10]. It is unclear why circulating T cells reactive with food antigens should home to the skin and generate an eczematous process rather than a gut-centred pathology. It may be hypothesized either that food-derived antigens somehow activate immature T cells to become skin-homing or that skin-homing lymphocytes are stimulated as a result of their target antigens reaching the skin via the circulation. Perhaps because the epidermal permeability barrier is disrupted by the eczema, allowing penetration of environmental aeroallergens, during the first few years of life there is progressive development of immune reactivity to aeroallergens, reflected by the presence of specific IgE and T-cell responses [11].

The role of airborne environmental allergens, both in the initial sensitization of atopic individuals and the subsequent elicitation of the clinical features, is becoming clear. Environmental allergen levels are probably the major determinant of whether sensitization of genetically predisposed individuals occurs. Thus, children born just before the birch pollen season in Scandinavia have a higher risk of sensitization to birch pollen than those born after the season [12]. Babies born in autumn, when house-dust mite (HDM) numbers are highest, have a greater risk of sensitization by HDM [13], and avoidance of exposure to HDM and food allergens for the first year of life was associated with significant diminution in the proportions of clinically detectable eczema and asthma [14]. A recent Japanese study showed that if atopic babies (with detectable IgE antibodies to various foods but not HDM) were protected from contact with HDM by encasing their bedding in dust-proof bags, there was significantly less sensitization to HDM, reflected by IgE and prick test response [15]. However, it was not followed through to see whether there was a reduction in associated clinical problems. It has been proposed that the risk of becoming sensitized to HDM is greatly increased by exposure to dust containing 10 μg/g of Der p1, and that even 2 μg/g confers a significant risk [16]. It appears that in some individuals, priming of immune responses to a range of allergens may happen during intrauterine development [17,18]. In others, the induction of sensitization appears to occur postnatally and during childhood. The sensitization is reflected by the presence of antigen-specific helper T lymphocytes and specific antibodies of IgE class.

The role of aeroallergens such as HDM in provoking or maintaining atopic dermatitis has been the subject of controversy and uncertainty. The presence of immune sensitization and allergic reactivity, reflected by the presence of positive responses to skin challenge administered in different ways, can be detected in the large majority of patients with atopic dermatitis. Prick testing with

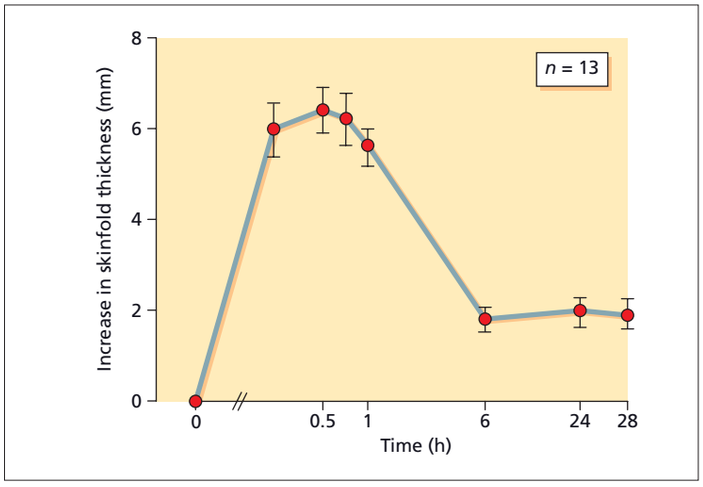


Fig. 24.1 Response elicited by intradermal inoculation of allergen (house-dust mite extract) in individuals with atopic dermatitis. A triphasic allergic response is seen, consisting of an immediate (15-min) weal and flare, a 6-h late-phase response and a 24- to 48-h delayed-type response. (Reproduced with permission from [19].)

aeroallergens, such as Der p1 or extracts of animal fur or pollens, elicits a weal and flare response after 10 to 15 min. This is mediated by specific IgE antibodies on the surface of skin mast cells. When the IgE binds antigen the mast cells are triggered to degranulate, releasing histamine and other mediators. Intradermal or epicutaneous patch challenge on tape-stripped skin elicits a triphasic allergic response [19,20] (Fig. 24.1). There is a 15 min immediate weal and flare due to histamine release from skin mast cells. There is a late-phase response comprising erythema and a deeper oedematous reaction between 6 and 24 h, and there is a delayed response at 48 h. After intradermal challenge, there is an erythematous papular reaction similar to a tuberculin test, but after patch challenge a classical eczematous reaction develops. The proportion of positive responses can be varied by more or less aggressive tape-stripping to disrupt the stratum corneum permeability barrier and by using higher concentrations of allergen [21]. This author (PSF) detected positive patch tests to HDM extract in up to 88% of adults and 60% of children older than 5 years. Others have used the so-called atopy patch test without tape stripping and obtained positive responses to aeroallergens in about one-third of atopic eczema sufferers [22].

Patch test responses can be elicited in atopic eczema sufferers with a range of other allergens, including foods [23] and the ubiquitous skin surface *Malassezia* yeasts [24–26].

The eczematous response developing in allergen-induced patch test reactions has been used to model naturally occurring eczema for investigation of the role of T lymphocytes. From 8 h onwards there is infiltration of $CD4^+$ T cells, 10–20% of which express $CD25^+$, the p55 chain of the IL-2 receptor, indicating that they have been activated through the T-cell receptor by contact with specific antigen. A number of workers have cloned the T cells in the first 12–24 h of such reactions and shown that they are predominantly of the Th2 type, producing IL-4 and IL-5 [27–29]. Also, up to 24 h after intradermal challenge with HDM, IL-4 and IL-5 production has been detected after amplification by polymerase chain reaction (PCR), but at later time points Th1 cells and their cytokines predominate [30–32]. In addition to the lymphocyte infiltration, there is heavy infiltration with eosinophils during the first 6–24 h of patch test challenge in atopic eczema sufferers.

The crucial question is whether allergic reactions induced by any allergen—aero or food—are of pathogenic importance in the causation of lesions of atopic eczema. The strongest evidence that this can be the case derives from studies of the effects of avoidance of house-dust allergens in the domestic environment. A placebo-controlled, double-blind study by Tan *et al*. [33] examined a combination of dust-mite eradication measures (sealed containment bags for the mattress, pillows and bedding top covers, a high power vacuum cleaner and a spray containing agents to kill mites and denature their allergens). It was shown that highly significant reductions in Der p1 load in carpets and beds occurred. This was associated with great clinical benefits in both adults and children (over 6 years old) with severe atopic eczema. These findings were not reproduced in a German study which used an essentially similar design but omitted the acaricidal and allergen-denaturing spray [34], or a Dutch study which used only bedding encasements [35].

The clinical relevance of allergy to *Malassezia* yeast is indicated by studies showing that treatment with itraconazole to eradicate the yeast resulted in improvement of the eczema comparable with that obtained with betamethasone valerate [26]. Hence, there is some compelling evidence that allergic reactions to common allergens may play an important part in the pathogenesis of atopic eczema in many people. However, such reactions do not appear to account for the entire process, and the whole approach suffers from a lack of robustness in the tests to identify those individuals who would benefit from avoiding any particular allergen.

References

1 Contoli M, Message SD, Laza-Stanca V *et al*. Role of deficient type III interferon-lambda production in asthma exacerbations. *Nat Med* 2006; **12**: 1023–6.

2 Wark PA, Johnston SL, Bucchieri F *et al*. Asthmatic bronchial epithelial cells have a deficient innate immune response to infection with rhinovirus. *J Exp Med* 2005; **201**: 937–47.

3 Ong PY, Ohtake T, Brandt C *et al*. Endogenous antimicrobial peptides and skin infections in atopic dermatitis. *N Engl J Med* 2002; **347**: 1151–60.

4 Nomura I, Goleva E, Howell MD *et al*. Cytokine milieu of atopic dermatitis, as compared to psoriasis, skin prevents induction of innate immune response genes. *J Immunol* 2003; **171**: 3262–9.

5 Howell MD, Boguniewicz M, Pastore S *et al*. Mechanism of HBD-3 deficiency in atopic dermatitis. *Clin Immunol* 2006; **121**: 332–8.

6 Isolauri E, Turjanmaa K. Combined skin prick and patch testing enhances identification of food allergy in infants with atopic dermatitis. *J Allergy Clin Immunol* 1996; **97**: 9–15.

7 Majamaa H, Seppala U, Palosuo T *et al*. Positive skin and oral challenge responses to potato and occurrence of immunoglobulin E antibodies to patatin (Sol t 1) in infants with atopic dermatitis. *Pediatr Allergy Immunol* 2001; **12**: 283–8.

8 Miles EA, Warner JA, Jones AC *et al*. Peripheral blood mononuclear cell proliferative responses in the first year of life in babies born to allergic parents. *Clin Exp Allergy* 1996; **26**: 780–8.

9 Weidinger S, Illig T, Baurecht H *et al*. Loss-of-function variations within the filaggrin gene predispose for atopic dermatitis with allergic sensitizations. *J Allergy Clin Immunol* 2006; **118**: 214–9.

10 Palmer CN, Ismail T, Lee SP *et al*. Filaggrin null mutations are associated with increased asthma severity in children and young adults. *J Allergy Clin Immunol* 2007; **120**: 64–8.

11 Ng TW, Holt PG, Prescott SL. Cellular immune responses to ovalbumin and house dust mite in egg-allergic children. *Allergy* 2002; **57**: 207–14.

12 Bjorksten F, Suoniemi I, Koski V. Neo-natal birch pollen contact and subsequent allergy to birch pollen. *Clin Allergy* 1980; **10**: 585–91.
13 Warner JO, Price JF. House dust mite sensitivity in childhood asthma. *Arch Dis Child* 1978; **53**: 710–3.
14 Arshad SH, Matthews S, Gant C *et al*. Effect of allergen avoidance on development of allergic disorders in infancy. *Lancet* 1992; **339**: 1493–7.
15 Nishioka K, Yasueda H, Saito H. Preventive effect of bedding encasement with microfine fibers on mite sensitization. *J Allergy Clin Immunol* 1998; **101**: 28–32.
16 Smith TF, Kelly LB, Heymann PW *et al*. Natural exposure and serum antibodies to house dust mite of mite allergic children with asthma in Atlanta. *J Allergy Clin Immunol* 1985; **76**: 782–8.
17 Prescott SL, Macaubas C, Holt BJ *et al*. Transplacental priming of the human immune system to environmental allergens: universal skewing of initial T cell responses toward the Th2 cytokine profile. *J Immunol* 1998; **160**: 4730–7.
18 Prescott SL, Macaubas C, Smallacombe T *et al*. Development of allergen-specific T-cell memory in atopic and normal children. *Lancet* 1999; **353**: 196–200.
19 Munro CS, Higgins EM, Marks JM *et al*. Cyclosporin A in atopic dermatitis: therapeutic response is dissociated from effects on allergic reactions. *Br J Dermatol* 1991; **124**: 43–8.
20 Friedmann PS, Tan BB, Musaba E *et al*. Pathogenesis and management of atopic dermatitis. *Clin Exp Allergy* 1995; **25**: 799–806.
21 van Voorst Vader PC, Lier JG, Woest TE *et al*. Patch tests with house dust mite antigens in atopic dermatitis patients: methodological problems. *Acta Derm Venereol (Stockh)* 1991; **71**: 301–5.
22 Ring J, Darsow U, Gfesser M *et al*. The 'atopy patch test' in evaluating the role of aeroallergens in atopic eczema. *Int Arch Allergy Immunol* 1997; **113**: 379–83.
23 Turjanmaa K. 'Atopy patch tests' in the diagnosis of delayed food hypersensitivity. *Allerg Immunol (Paris)* 2002; **34**: 95–7.
24 Rokugo M, Tagami H, Usuba Y *et al*. Contact sensitivity to *Pityrosporum ovale* in patients with atopic dermatitis. *Arch Dermatol* 1990; **126**: 627–32.
25 Tengvall LM, Johansson C, Scheynius A *et al*. Positive atopy patch test reactions to *Pityrosporum orbiculare* in atopic dermatitis patients. *Clin Exp Allergy* 2000; **30**: 122–31.
26 Back O, Bartosik J. Systemic ketoconazole for yeast allergic patients with atopic dermatitis. *J Eur Acad Dermatol Venereol* 2001; **15**: 34–8.
27 van der Heijden FL, Wierenga EA, Bos JD *et al*. High frequency of IL-4-producing CD4+ allergen-specific T lymphocytes in atopic dermatitis lesional skin. *J Invest Dermatol* 1991; **97**: 389–94.
28 Bos JD, Wierenga EA, Sillevis Smitt JH *et al*. Immune dysregulation in atopic eczema. *Arch Dermatol* 1992; **128**: 1509–12.
29 van Reijsen FC, Bruijnzeel-Koomen CA, Kalthoff FS *et al*. Skin-derived aeroallergen-specific T-cell clones of Th2 phenotype in patients with atopic dermatitis. *J Allergy Clin Immunol* 1992; **90**: 184–93.
30 Kay AB, Ying S, Varney V *et al*. Messenger RNA expression of the cytokine gene cluster, interleukin 3 (IL-3), IL-4, IL-5, and granulocyte/macrophage colony-stimulating factor, in allergen-induced late-phase cutaneous reactions in atopic subjects. *J Exp Med* 1991; **173**: 775–8.
31 Grewe M, Gyufko K, Schopf E *et al*. Lesional expression of interferon-gamma in atopic eczema. *Lancet* 1994; **343**: 25–6.
32 Hamid Q, Boguniewicz M, Leung DYM. Differential in situ cytokine gene expression in acute versus chronic atopic dermatitis. *J Clin Invest* 1994; **94**: 870–6.
33 Tan BB, Weald D, Strickland I *et al*. Double-blind controlled trial of effect of housedust-mite allergen avoidance on atopic dermatitis. *Lancet* 1996; **347**: 15–8.
34 Gutgesell C, Heise S, Seubert S *et al*. Double-blind placebo-controlled house dust mite control measures in adult patients with atopic dermatitis. *Br J Dermatol* 2001; **145**: 70–4.
35 Terreehorst I, Duivenvoorden HJ, Tempels-Pavlica Z *et al*. The effect of encasings on quality of life in adult house dust mite allergic patients with rhinitis, asthma and/or atopic dermatitis. *Allergy* 2005; **60**: 888–93.

The role of infection

Patients with atopic dermatitis are particularly susceptible to certain cutaneous infections [1]. The most common skin infection is with *Staphylococcus aureus*. However, human papillomavirus-induced warts, fungal infections, viruses (such as HSV1 and 2, vaccinia, coxsackie A and the pox virus of molluscum contagiosum) are also frequent pathogens causing, in some cases, severe complications.

Innate immunity is compromised in atopic dermatitis, as demonstrated by reductions in keratinocyte-derived antimicrobial peptides (cathelicidin LL-37, β-defensin 2 and β-defensin 3) [2,3], neutrophil chemoattractant IL-8 [3], and inducible nitric oxide synthetase (iNOS) [3] which mediates pathogen death through release of NO [4]. Further antimicrobial compromise occurs as a result of defective dermcidin-derived antimicrobial peptides, produced by eccrine glands [5]. Production of IgA, a key epithelial antimicrobial immunoglobulin, is also reduced in the sweat and tears of atopic dermatitis patients [6,7], which may help to explain the concordance between staphylococcal growth on both mucosal and skin surfaces in these patients.

Most individuals with atopic dermatitis have *S. aureus* identifiable on skin swabs, often at very high density, and more often present on lesional than non-lesional skin [8]. Furthermore, *S. aureus* present on the skin of atopics is significantly more likely to express superantigen than in non-atopics, and indeed the levels correlate with disease severity [9–11]. Direct exposure of skin to staphylococcal superantigen in an allergen patch test model has been demonstrated to enhance allergen-specific responses *in vivo* [12]. Further work has demonstrated that keratinocytes show enhanced allergen presentation to T cells following exposure to staphylococcal enterotoxin B (SEB)-stimulated peripheral blood mononucular cells (PBMC) *in vitro* through up-regulation of HLA class II and ICAM-1 expression [13], providing evidence of a potent adjuvant effect of staphylococcal products for human allergen-specific Th2 responses. Furthermore, staphylococcal superantigen has been documented to reduce regulatory T-cell activity in humans [14] and to confer T-cell steroid resistance [15], both of which may contribute to the association with more severe atopic dermatitis.

References

1 Baker BS. The role of microorganisms in atopic dermatitis. *Clin Exp Immunol* 2006; **144**: 1–9.
2 Ong PY, Ohtake T, Brandt C *et al*. Endogenous antimicrobial peptides and skin infections in atopic dermatitis. *N Engl J Med* 2002; **347**: 1151–60.
3 Nomura I, Goleva E, Howell MD *et al*. Cytokine milieu of atopic dermatitis, as compared to psoriasis, skin prevents induction of innate immune response genes. *J Immunol* 2003; **171**: 3262–9.
4 Bruch-Gerharz D, Fehsel K, Suschek C *et al*. A proinflammatory activity of interleukin 8 in human skin: expression of the inducible nitric oxide synthase in psoriatic lesions and cultured keratinocytes. *J Exp Med* 1996; **184**: 2007–12.
5 Rieg S, Steffen H, Seeber S *et al*. Deficiency of dermcidin-derived antimicrobial peptides in sweat of patients with atopic dermatitis correlates with an impaired innate defense of human skin in vivo. *J Immunol* 2005; **174**: 8003–10.
6 Imayama S, Shimozono Y, Hoashi M *et al*. Reduced secretion of IgA to skin surface of patients with atopic dermatitis. *J Allergy Clin Immunol* 1994; **94**: 195–200.
7 Toshitani A, Imayama S, Shimozono Y *et al*. Reduced amount of secretory component of IgA secretion in tears of patients with atopic dermatitis. *J Dermatol Sci* 1999; **19**: 134–8.
8 Guzik TJ, Bzowska M, Kasprowicz A *et al*. Persistent skin colonization with *Staphylococcus aureus* in atopic dermatitis: relationship to clinical and immunological parameters. *Clin Exp Allergy* 2005; **35**: 448–55.
9 Zollner TM, Munk ME, Keller T *et al*. The superantigen exfoliative toxin induces cutaneous lymphocyte-associated antigen expression in peripheral human T lymphocytes. *Immunol Lett* 1996; **49**: 111–6.

10 Bunikowski R, Mielke ME, Skarabis H *et al*. Evidence for a disease-promoting effect of *Staphylococcus aureus*-derived exotoxins in atopic dermatitis. *J Allergy Clin Immunol* 2000; **105**: 814–9.
11 Zollner TM, Wichelhaus TA, Hartung A *et al*. Colonization with superantigen-producing *Staphylococcus aureus* is associated with increased severity of atopic dermatitis. *Clin Exp Allergy* 2000; **30**: 994–1000.
12 Langer K, Breuer K, Kapp A *et al*. *Staphylococcus aureus*-derived enterotoxins enhance house dust mite-induced patch test reactions in atopic dermatitis. *Exp Dermatol* 2007; **16**: 124–9.
13 Ardern-Jones MR, Black AP, Bateman EA *et al*. Bacterial superantigen facilitates epithelial presentation of allergen to T helper 2 cells. *Proc Natl Acad Sci U S A* 2007; **104**: 5557–62.
14 Ou LS, Goleva E, Hall C *et al*. T regulatory cells in atopic dermatitis and subversion of their activity by superantigens. *J Allergy Clin Immunol* 2004; **113**: 756–63.
15 Li LB, Goleva E, Hall CF *et al*. Superantigen-induced corticosteroid resistance of human T cells occurs through activation of the mitogen-activated protein kinase kinase/extracellular signal-regulated kinase (MEK-ERK) pathway. *J Allergy Clin Immunol* 2004; **114**: 1059–69.

Altered immune function

The defining characteristic of the atopic immune system is the capacity to generate IgE antibodies in response to allergens. The key disturbance to immune regulation that results in this IgE production appears to be the differentiation pathway followed by $CD4^+$ helper T lymphocytes. Naïve precursor Th0 cells are induced to differentiate into Th2 cells, characterized by the production of interleukins (IL) -4, -5 and -13. Th2 cells 'help' or control the type of immunoglobulin (Ig) that B lymphocytes make, inducing synthesis of IgE.

Cellular mechanisms

The regulatory mechanisms that underlie the preferential development of Th2 cells appear to involve the interaction between dendritic antigen-presenting cells and $CD4^+$ helper T lymphocytes. The question arises of whether there is something different about the dendritic cells (DCs) of atopic individuals and the signals they give to T cells, or whether there is a defect in the T cells themselves.

Dendritic cells. Much work has gone into examining the mechanisms by which DCs regulate the differentiation of Th cells, and there is accumulating evidence that DCs may also subdivide into DC1 that preferentially induce Th1 cells and DC2 that induce Th2 cells [1]. The critical stimulus, signal 1, is given during the presentation of antigenic peptides held in the groove of MHC class II molecules (Fig. 24.2). Secondary signals (signal 2) come via interactions of co-stimulatory surface molecules such as CD 80 and 86 on the DCs, with their counter receptors CD28 and CTLA4 on the T cells. In murine systems, signalling via CD80 can preferentially induce Th1 differentiation, and CD86 can induce Th2 differentiation [2]. There is evidence that signalling through CD28 gives a positive activation signal, whereas signalling through CTLA4 may either give an inhibitory signal or activate T regulatory cells which have inhibitory (suppressor) activities [3]. In addition, binding of CD40 on T cells interacting with CD40 ligand on the DC is one of the strongest signals for the T cell to produce interferon-γ and to differentiate towards a Th1 phenotype [4,5]. Cytokines released from the DCs give 'signal 3' which is also important in determining the final differentiation into Th1 or Th2 cells. IL-12 drives a Th1 response and IL-4 drives a Th2 response (Figs 24.2 & 24.3) [4,6,7].

There is little direct evidence that DC function is altered in atopic individuals. However, it has been observed that monocytes from atopic donors produce greater quantities of prostaglandin E_2 (PGE_2) and IL-10 than cells from non-atopic individuals [8,9]. PGE_2 can suppress production of interferon-γ, a cytokine which is not

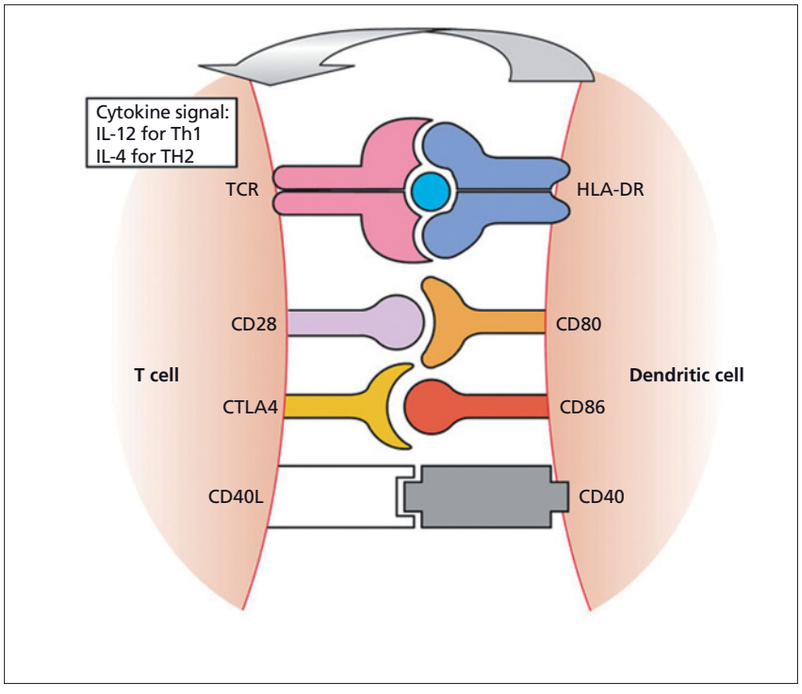


Fig. 24.2 Activation of naïve T lymphocyte by interaction with dendritic antigen-presenting cell. Signal 1 comes from interaction of the T-cell receptor (TCR) with the complex of MHC class II and the antigenic peptide (blue circle) lying within its groove, on the surface of the dendritic cell. Signal 2 results from the interaction of co-stimulatory molecules (CD80, 86 and 40) on the dendritic cell with their counter receptors. CD28 is thought to give positive signals whereas CTLA-4 appears to give negative or inhibitory signals. Signal 3 is given by soluble cytokines including IL-1β and IL-12 which drive T-cell differentiation towards a Th1 phenotype, and IL-4 which favours differentiation towards the Th2 type. Th17 cells are a recently described CD-4 subset, which are characterized by IL-17 production and require IL-23 for expansion and survival. Further Th subdivision arises with differentiation of regulatory T cells, full discussion of which is beyond the scope of this chapter.

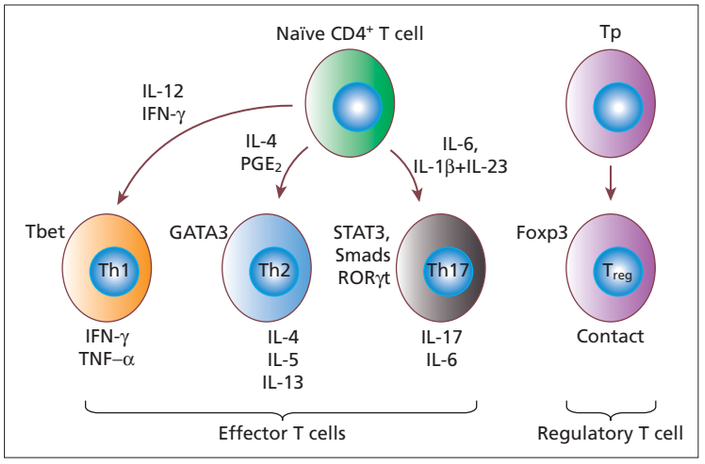


Fig. 24.3 Differentiation of CD4+ T lymphocytes. Precursor naïve T cells have the potential to differentiate into either Th1, Th2 or Th17 cells, depending upon the signals they receive during the interaction with dendritic antigen-presenting cells (APC) (see also Fig. 24.2). Depending upon the cell surface co-stimulatory molecule interactions and the presence of particular cytokines, the differentiation is directed. IL-12 is the critical determinant of Th1 generation, which acts via the transcription factor T-bet, IL-4 drives Th2 formation via GATA-3 and IL-6 and TGFβ drive Th17 cells via STAT3, Smads and RORγt. Atopic monocytes (and hence possible dendritic cells) produce increased amounts of prostaglandin E_2 (PGE_2), which helps drive T-cell differentiation towards the Th2 phenotype. Thymic precursor T cells (Tp) can develop into natural regulatory T cells, which inhibit the actions of effector T cells in a contact-dependent fashion.

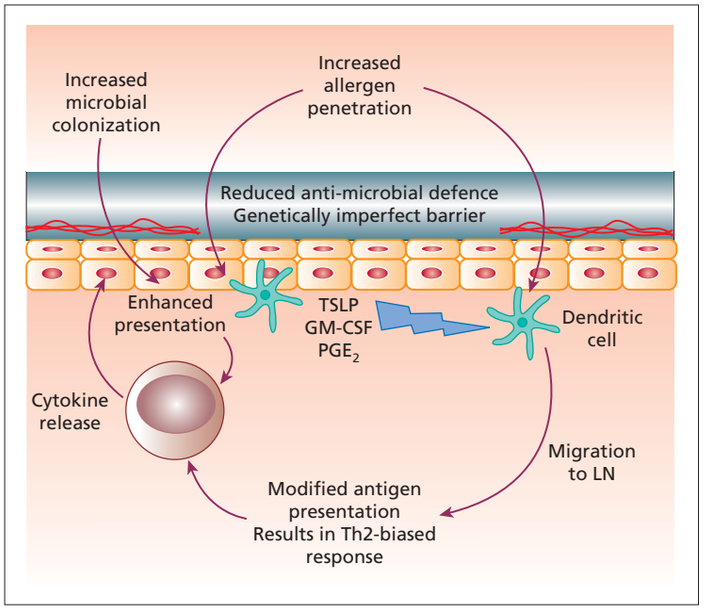


Fig. 24.4 Interaction between epidermis and immune system in atopic dermatitis. The epidermis has increased permeability (genetic abnormalities of filaggrin) and reduced innate antimicrobial defences. In addition, production of thymic stromal lymphoprotein (TSLP) and prostaglandin E_2 conditions dendritic cells to induce Th2 differentiation. Th2-cell re-encounter with antigen in the skin is enhanced by local inflammation induced by factors such as microbial products, and activation results in inflammatory Th2 cytokine release and induces further down-regulation of genes involved in both antimicrobial defence and skin barrier formation.

only produced by Th1 lymphocytes but which also favours the differentiation of naïve Th0 cells towards the Th1 phenotype. Similarly, IL-10 is both a suppressive/regulatory cytokine and also drives Th0 cells towards a Th2 phenotype [10]. Dendritic cells from atopic individuals have yet to be shown to behave similarly.

A property of DCs in atopic individuals that has attracted much interest is the finding that they bear antigen-specific IgE on their surface [11,12]. The IgE is bound to the high affinity receptor for IgE, FcεR1, normally found on mast cells and basophils [13–15]. There is controversy as to whether FcεR1 is expressed exclusively on DCs from people with atopic eczema or whether it can be expressed in atopic individuals without eczema but with active 'allergic' disease such as asthma [15,16]. FcεR1 on DCs differs from that on mast cells and basophils in that it comprises the alpha and gamma chains, but lacks the beta chain [17]. This may alter its capacity either for expression on the cell surface or for activating intracellular signals [17]. FcεR1 is induced on DCs by IL-4 and possibly also by high levels of IgE. The surface-bound IgE on DCs has been shown *in vitro* to perform the function of 'antigen focusing' to allow DCs to present antigens to T cells much more efficiently. Thus, T cells can be activated to respond to one-hundredth to one-thousandth the amount of antigen [18]. However, it is not clear whether or how this is important in the pathogenesis of atopic eczema.

Epidermal modulation of dendritic cell function. Recent findings have produced evidence indicating that the epidermal environment is critically involved in programming dendritic cells to direct the differentiation of Th0 cells towards a Th2 phenotype (Fig. 24.4). Epidermal keratinocytes in atopic eczema produce a cytokine with similarities to interleukin-7 called thymic stromal lymphopoietin (TSLP). This cytokine is also produced by atopic bronchial epithelium, Hassall's corpuscles in the thymus and mast cells that have been activated by cross-linking of the IgE receptors (FcεR1) [19]. Mice that have TSLP over-expressed in the epidermis spontaneously develop an inflammatory skin condition that resembles atopic eczema. The crucial finding is that TSLP conditions dendritic cells so that when they interact with naïve T cells they drive them to differentiate into Th2 cells. Of special relevance is the fact that TSLP-conditioned dendritic cells induce the Th2 cells to produce not only the classical Th2 cytokines IL-4, -5 and -13 but also TNF-α—hence they are called 'inflammatory Th2 cells' [19–21]. So it appears that the immune dysregulation and the epidermal dysfunction may be functionally connected and that the epidermis may actually play an important role in programming the immune system.

References

1 Reid SD, Penna G, Adorini L. The control of T cell responses by dendritic cell subsets. *Curr Opin Immunol* 2000; **12**; 114–21.
2 Swain SL. Helper T cell differentiation. *Curr Opin Immunol* 1999; **11**: 180–5.
3 Walunas TL, Lenschow DJ, Bakker CY *et al*. CTLA-4 can function as a negative regulator of T cell activation. *Immunity* 1994; **1**: 405–13.
4 Macatonia SE, Hosken NA, Litton M *et al*. Dendritic cells produce IL-12 and direct the development of Th1 cells from naive CD4+ T cells. *J Immunol* 1995; **154**: 5071–9.

5 Langenkamp A, Messi M, Lanzavecchia A *et al*. Kinetics of dendritic cell activation: impact on priming of TH1, TH2 and nonpolarized T cells. *Nature Immunol* 2000; **1**: 311–6.
6 Heufler C, Koch F, Stanzl U *et al*. Interleukin-12 is produced by dendritic cells and mediates T helper 1 development as well as interferon-gamma production by T helper 1 cells. *Eur J Immunol* 1996; **26**: 659–68.
7 O'Garra A, Murphy K. Role of cytokines in development of Th1 and Th2 cells. *Chem Immunol* 1996; **63**: 1–13.
8 Betz M, Fox BS. Prostaglandin E2 inhibits production of Th1 lymphokines but not of Th2 lymphokines. *J Immunol* 1991; **146**: 108–13.
9 Ohmen JD, Hanifin JM, Nickoloff BJ *et al*. Overexpression of IL-l0 in atopic-dermatitis—contrasting cytokine patterns with delayed-type hypersensitivity reactions. *J Immunol* 1995; **154**: 1956–63.
10 D'Andrea A, Aste Amezaga M, Valiante NM *et al*. Interleukin 10 (IL-10) inhibits human lymphocyte interferon gamma-production by suppressing natural killer cell stimulatory factor/IL-12 synthesis in accessory cells. *J Exp Med* 1993; **178**: 1041–8.
11 Bruijnzeel-Koomen CA, van Wichen DF, Toonstra J *et al*. The presence of IgE molecules on epidermal Langerhans cells in patients with atopic dermatitis. *Arch Dermatol Res* 1986; **278**: 199–205.
12 Mudde GC, van Reijsen FC, Bruijnzeel-Koomen CA. IgE-positive Langerhans cells and Th2 allergen-specific T cells in atopic dermatitis. *J Invest Dermatol* 1992; **99**: 103S.
13 Bieber T, de la Salle H, Wollenberg A *et al*. Human epidermal Langerhans cells express the high affinity receptor for immunoglobulin E (Fc epsilon RI). *J Exp Med* 1992; **175**: 1285–90.
14 Wang B, Rieger A, Kilgus O *et al*. Epidermal Langerhans cells from normal human skin bind monomeric IgE via Fc epsilon RI. *J Exp Med* 1992; **175**: 1353–65.
15 Bieber T, Kraft S, Jurgens M *et al*. New insights in the structure and biology of the high affinity receptor for IgE (Fc epsilon RI) on human epidermal Langerhans cells. *J Dermatol Sci* 1996; **13**: 71–5.
16 Semper AE, Heron K, Woollard ACS *et al*. Surface expression of FcεRI on Langerhans' cells of clinically uninvolved skin is associated with disease activity in atopic dermatitis, allergic asthma, and rhinitis. *J Allergy Clin Immunol* 2003; **112**: 411–9.
17 Jurgens M, Wollenberg A, Hanau D *et al*. Activation of human epidermal Langerhans cells by engagement of the high affinity receptor for IgE, Fc epsilon RI. *J Immunol* 1995; **155**: 5184–9.
18 Mudde GC, van Reijsen FC, Boland GJ *et al*. Allergen presentation by epidermal Langerhans' cells from patients with atopic dermatitis is mediated by IgE. *Immunol* 1990; **69**: 335–41.
19 Liu YJ, Soumelis V, Watanabe N *et al*. TSLP: an epithelial cell cytokine that regulates T cell differentiation by conditioning dendritic cell maturation. *Annu Rev Immunol* 2007; **25**: 193–219.
20 Liu YJ. Thymic stromal lymphopoietin: master switch for allergic inflammation. *J Exp Med* 2006; **203**: 269–73.
21 Ebner S, Nguyen VA, Forstner M *et al*. Thymic stromal lymphopoietin converts human epidermal Langerhans cells into antigen-presenting cells that induce proallergic T cells. *J Allergy Clin Immunol* 2007; **119**: 982–90.

Pharmacological and vascular abnormalities

The small blood vessels in atopic dermatitis show a tendency to vasoconstriction responses:

1 Pallor of the skin after stroking – white dermographism
2 Delayed blanch with acetylcholine
3 White reaction to nicotinic acid esters
4 Abnormal reactions to histamine in affected skin
5 Low finger temperature
6 Pronounced vasoconstriction on exposure to cold.

None of these findings is pathognomonic. The delayed blanch phenomenon with acetylcholine [1–3] and related drugs is characteristic for atopic dermatitis, and occurs less regularly with other atopic disorders. Whether these pharmacological changes in atopic dermatitis are secondary to cutaneous inflammation, or the deranged pharmacology and the immune abnormalities are both secondary to a common defect, is not known. However, these patterns in vascular responses led to the so-called β-adrenergic blockade theory proposed by Szentivanyi [4]. Although this theory no longer remains tenable, it has led to observations of abnormalities in a range of intracellular second messenger signalling pathways. In atopic individuals, attenuated cAMP signalling results from overactive cAMP-phosphodiesterase which is associated with several of the phenotypic features. The principal observations, summarized by Hanifin and Chan [5], follow from the well-known increased IgE synthesis that characterizes atopic individuals. *In vitro* this appears linked to reduced IFN-γ production by mixed peripheral blood mononuclear cells (PBMCs) from patients with atopic dermatitis. However, atopic T cells actually show increased production of IFN-γ *in vitro*; hence, it was concluded that the monocytes produce an inhibitor of IFN-γ synthesis. Atopic PBMCs produce increased amounts of PGE_2 and it is the monocytes that are the source [6]. It had been shown by Betz and Fox that PGE_2 inhibits IFN-γ production [7] and Chan *et al*. [6] showed that inhibition of PGE_2 with indometacin results in increased IFN-γ production by atopic PBMC. Atopic monocytes also produce increased amounts of IL-10, which also inhibits production of IFN-γ [8].

Hanifin had previously shown that PBMCs from atopic subjects have blunted cAMP responses to agents acting on adenylyl cyclase such as histamine, isoprenaline or prostaglandins [9]. This was found to be a result of elevated cAMP-phosphodiesterase (PDE) activity [10], so the cAMP was hydrolysed more completely. These abnormalities were also present in people with respiratory atopic disease. Sawai *et al*. [11] showed that there was no correlation between cAMP-PDE activity and severity of eczema. The abnormality has also been shown to be present in cord blood from babies with atopic parents [12,13].

The elevated cAMP-PDE activity was shown to be located predominantly in monocytes [14]. Chan and colleagues went on to type the PDEs in atopic leukocytes [15]. They found three isoforms were common to both monocytes and lymphocytes and all were more active than in cells from non-atopics. However, the atopic monocytes had an additional isoform which was specific for cAMP and was calcium/calmodulin-dependent. Also, the PDE was more susceptible than control PDE to inhibition by Ro20-1724—an inhibitor of PDE type 4 [15,16]. It should be noted that Gantner *et al*. [17] found no differences between PDE expression and activity in cells from healthy and atopic blood donors.

One aspect which makes interpretation of data about levels of PDE activity difficult is that PDE activity is subject to modulation by various factors. Thus, PDE activity is induced by stimuli that increase cAMP, such as long-term administration of β-adrenergic agonists. This has clouded the question of whether elevated PDE is found in atopic asthma, as most patients receive chronic therapy with these agents. In monocytes from healthy subjects PDE activity is increased by cytokines IL-4 and IFN-γ [18]. However, in monocytes from atopic dermatitis patients, IFN-γ at low concentrations was without effect and at higher concentrations it reduced PDE activity [18]. This difference may be because in atopic cells PDE activity is already maximally induced.

The PDEs form a family of at least seven groups [19]. The different types vary in their affinity for cAMP or cGMP, their

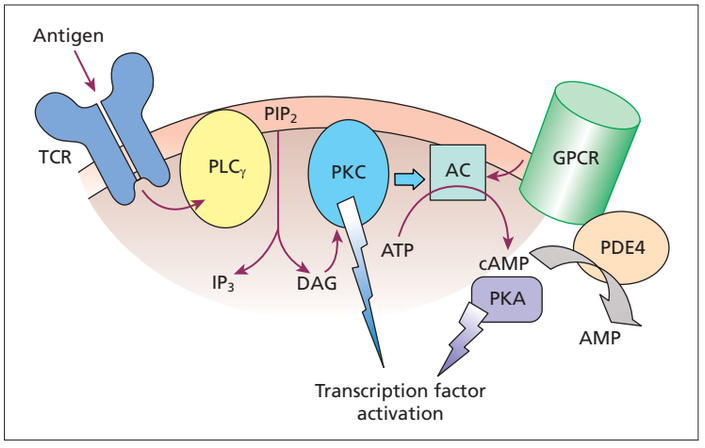


Fig. 24.5 Intracellular signalling that interacts with cAMP in T cells. The T-cell receptor (TCR) receives activating signals from the dendritic antigen-presenting cell. It activates phospholipase Cγ (PLCγ), which cleaves membrane phosphatidyl inositol bisphosphate (PIP_2) to diacylglycerol (DAG) and inositol trisphosphate (IP_3). The DAG activates protein kinase C (PKC), which activates a variety of targets including transcription factors. It can also activate adenylate cyclase (AC), which generates cAMP. Membrane receptors that are coupled to G proteins (G protein-coupled receptors, GPCR) activated by their ligands signal via generation of cAMP, which in turn activates protein kinase A (PKA). cAMP is degraded by the actions of cAMP phosphodiesterase type 4 (PDE4), which is constitutively overactive in atopic cells. This attenuates or switches off cAMP signalling, which may alter the balance of 'cross-talk' between different signalling pathways.

susceptibility to different inhibitors and, in some cases, in their cell/tissue distribution. Type 4 PDE (PDE4) is cAMP-specific and was characterized by inhibition by rolipram and Ro20-1724. PDE type 4 is present in inflammatory cells—mast cells, eosinophils, monocytes, macrophages and lymphocytes.

Several activities of mononuclear cells are mediated via cAMP and can be reduced by inhibitors of PDE4: increased PGE_2 production [8]; spontaneous IgE production by B cells [20] and release of histamine from basophils [8]; increased spontaneous production of IL-10 is reduced as is the anti-CD3-induced increase in IL-4 production [8,21]; migration of eosinophils [22]; *in vitro* transmigration of lymphocytes but not monocytes through a monolayer of endothelial cells [23]; and allergen-induced release of IL-5 [24].

cAMP is a second messenger that lies in the midst of a network of pathways (Fig. 24.5). Different signalling mechanisms are involved depending on which cell surface receptors are activated. The T-cell receptor activates phospholipase Cγ, which in turn cleaves phosphatidyl inositol bisphosphate to release diacyl glycerol (DAG) and inositol trisphosphate (IP_3). These moieties can both act as further signals in different directions; IP_3 activates release of calcium from intracellular stores and DAG activates protein kinase C (PKC). PKC can activate adenylate cyclase, generating cAMP which activates protein kinase A (PKA). The intensity of the effects of cAMP are blunted through the overactivity of PDE4 (see above). The inositol pathway of peripheral blood mononuclear cells shows evidence of chronic activation and hyporesponsiveness to subsequent stimulation [25,26]. Apart from the clear evidence of the effects of the altered second messenger signalling in T lymphocyte differentiation towards a Th2 type (see above and [27]) the further importance of these processes in the wide range of vascular, neural and immune alterations in atopic eczema has yet to be elucidated.

References

1 Lobitz WC, Campbell CJ. Physiologic studies in atopic dermatitis (disseminated neurodermatitis). I. Local cutaneous response to intradermally injected acetylcholine and epinephrine. *Arch Dermatol Syphilol* 1953; **67**: 575–89.

2 West JR, Johnson LA, Winkelmann RK. Delayed blanch phenomenon in atopic individuals without dermatitis. *Arch Dermatol* 1962; **85**: 227–31.

3 Champion RA. Abnormal vascular reactions in atopic eczema. *Br J Dermatol* 1963; **75**: 12–5.

4 Szentivanyi A. The beta adrenergic theory of the atopic abnormality in bronchial asthma. *J Allergy Clin Immunol* 1968; **42**: 203–32.

5 Hanifin JM, Chan SC. Monocyte phosphodiesterase abnormalities and dysregulation of lymphocyte function in atopic-dermatitis. *J Invest Dermatol* 1995; **105**: S84–8.

6 Chan SC, Kim JW, Henderson WR Jr *et al*. Altered prostaglandin E2 regulation of cytokine production in atopic dermatitis. *J Immunol* 1993; **151**: 3345–52.

7 Betz M, Fox BS. Prostaglandin E2 inhibits production of Th1 lymphokines but not of Th2 lymphokines. *J Immunol* 1991; **146**: 108–13.

8 Hanifin JM, Chan SC, Cheng JB *et al*. Type 4 phosphodiesterase inhibitors have clinical and in vitro anti-inflammatory effects in atopic dermatitis. *J Invest Dermatol* 1996; **107**: 51–6.

9 Safko MJ, Chan SC, Cooper KD *et al*. Heterologous desensitisation of leukocytes: a possible mechanism for beta adrenergic blockade in atopic dermatitis. *J Allergy Clin Immunol* 1981; **68**: 218–25.

10 Grewe SR, Chan SC, Hanifin JM. Elevated leukocyte cyclic AMP-phosphodiesterase in atopic disease: a possible mechanism for cyclic AMP-agonist hyporesponsiveness. *J Allergy Clin Immunol* 1982; **70**: 452–7.

11 Sawai T, Ikai K, Uehara M. Cyclic adenosine monophosphate phosphodiesterase activity in peripheral blood mononuclear leucocytes from patients with atopic dermatitis: correlation with respiratory atopy. *Br J Dermatol* 1998; **138**: 846–8.

12 Heskel NS, Chan SC, Thiel ML *et al*. Elevated umbilical-cord blood leukocyte cyclic adenosine-monophosphate phosphodiesterase activity in children with atopic parents. *J Am Acad Dermatol* 1984; **11**: 422–6.

13 McMillan JC, Heskel NS, Hanifin JM. Cyclic AMP-phosphodiesterase activity and histamine-release in cord blood leukocyte preparations. *Acta Derm Venereol (Stockh)* 1985; **114**: 24–32.

14 Holden CA, Chan SC, Hanifin JM. Monocyte localization of elevated cAMP phosphodiesterase activity in atopic dermatitis. *J Invest Dermatol* 1986; **87**: 372–6.

15 Chan SC, Reifsnyder D, Beavo JA *et al*. Immunochemical characterization of the distinct monocyte cyclic amp-phosphodiesterase from patients with atopic dermatitis. *J Allergy Clin Immunol* 1993; **91**: 1179–88.

16 Crocker IC, Ohia SE, Church MK. Phosphodiesterase type 4 inhibitors, but not glucocorticoids, are more potent in suppression of cytokine secretion by mononuclear cells from atopic than nonatopic donors. *J Allergy Clin Immunol* 1998; **102**: 797–804.

17 Gantner F, Tenor H, Gekeler V *et al*. Phosphodiesterase profiles of highly purified human peripheral blood leukocyte populations from normal and atopic individuals: a comparative study. *J Allergy Clin Immunol* 1997; **100**: 527–35.

18 Li SH, Chan SC, Kramer SM *et al*. Modulation of leukocyte cyclic AMP phosphodiesterase activity by recombinant interferon-gamma: evidence for a differential effect on atopic monocytes. *J Interferon Res* 1993; **13**: 197–202.

19 Spina D, Landells LJ, Page CP. The role of theophylline and phosphodiesterase 4 isoenzyme inhibitors as anti-inflammatory drugs. *Clin Exp Allergy* 1998; **28**: 24–34.

20 Cooper KD, Kang K, Chan SC *et al*. Phosphodiesterase inhibition by Ro20-1724 reduces hyper-IgE synthesis by atopic dermatitis cells *in vitro*. *J Invest Dermatol* 1985; **84**: 477–82.

21 Chan SC, Li SH, Hanifin JM. Increased interleukin-4 production by atopic mononuclear leukocytes correlates with increased cyclic adenosine monophosphate-phosphodiesterase activity and is reversible by phosphodiesterase inhibition. *J Invest Dermatol* 1993; **100**: 681–4.

22 Tenor H, Hatzelmann A, Church MK *et al*. Effects of theophylline and rolipram on leukotriene C-4 (LTC(4)) synthesis and chemotaxis of human eosinophils from normal and atopic subjects. *Br J Pharmacol* 1996; **118**: 1727–35.
23 Lidington E, Nohammer C, Dominguez M *et al*. Inhibition of the transendothelial migration of human lymphocytes but not monocytes by phosphodiesterase inhibitors. *Clin Exp Immunol* 1996; **104**: 66–71.
24 Essayan DM, Huang SK, Kageysobotka A *et al*. Effects of nonselective and isozyme-selective cyclic-nucleotide phosphodiesterase inhibitors on antigen-induced cytokine gene-expression in peripheral-blood mononuclear-cells. *Am J Resp Cell Mol Biol* 1995; **13**: 692–702.
25 Coulson IH, Hurt GR, Holden CA. Inositol metabolism in mononuclear leucocytes from patients with atopic dermatitis. *Br J Dermatol* 1991; **124**: 124–9.
26 Mallett RB, Myint S, Holden CA. Measurement of phosphoinositide-specific phospholipase C activity in mononuclear leucocytes from atopic and normal subjects. *Br J Dermatol* 1992; **127**: 97–102.
27 Kanda N, Watanabe S. Intracellular 3′,5′-adenosine cyclic monophosphate level regulates house dust mite-induced interleukin-13 production by T cells from mite-sensitive patients with atopic dermatitis. *J Invest Dermatol* 2001; **116**: 3–11.

Neuropeptides

Neuropeptides mediate vasodilatation, oedema, itch and pain, the axon-reflex flare, sweat-gland secretion, and have some, probably minor, ability to regulate T-cell activation [1]. Vasoactive and pro-inflammatory neuropeptides mediate tissue change and sensory stimuli in perturbed skin (Chapter 12). Theoretically, neuropeptides could have a significant role in many of the features of atopic dermatitis, including vascular changes, itch, symptoms associated with sweating and leukocyte infiltration. The neuropeptides that have been studied in the lesions are substance P (SP) and calcitonin gene-related peptide (CGRP), often present together in unmyelinated C sensory fibres, somatostatin (SOM), vasoactive intestinal polypeptide (VIP), which coexists with acetylcholine in postganglionic sympathetic fibres, and neuropeptide Y (NPY) in adrenergic fibres. Assays of skin extracts have shown greatly increased amounts of VIP in atopic lesions [2–4], and reduced amounts of SP [3,5], although SP has also been reported to be unchanged in comparison with normal controls in one study [2].

Immunohistochemical examination has revealed NPY-positive dendritic epidermal cells in lichenified atopic dermatitis lesions, but no somatostatin fibres. Healthy, normal control skin showed the opposite—no NPY dendritic cells but a normal network of somatostatin fibrils [6]. Elsewhere, it has been reported that NPY fibres (adrenergic) are fewer than normal, but CGRP and SP (sensory) fibres are increased in number [7].

The skin of atopic dermatitis patients shows altered reactivity to injections of neuropeptides. Intradermal injection of SP induces a weal and flare response—at low doses this is the result of direct effects on vasculature whereas at higher doses SP induces degranulation of mast cells with histamine-mediated weal and flare. Contradictory findings have been reported regarding cutaneous responses to injection of SP in atopic individuals. Coulson and Holden observed greater weal volumes in atopics than in non-atopics, with no difference in the area of flare [8]. In another study, although injection of SP elicited weals of similar size, there was less flare in atopic dermatitis skin than in controls [9]. Injection of neuropeptides was also reported to induce less than normal weal and flare responses [10].

Apart from effects on vascular reactivity and pruritus, neuropeptides can play a part in recruitment of granulocytes by up-regulating expression of adhesion molecules, including VCAM-1 on endothelial cells [11]. They can also modulate lymphocyte function *in vitro*. Thus, SP augments production of interferon-γ and IL-4 by lymphocytes from atopic donors but has little effect on cells from non-atopic donors [1,12]. VIP had no effect on lymphocyte cytokine production [12]. Thus, neuropeptides may contribute to the complex mix of factors regulating lymphocytes in atopic dermatitis.

References

1 Gordon DJ, Ostlere LS, Holden CA. Neuropeptide modulation of Th1 and Th2 cytokines in peripheral blood mononuclear leucocytes in atopic dermatitis and non-atopic controls. *Br J Dermatol* 1997; **137**: 921–7.
2 Anand P, Springall DR, Blank MA *et al*. Neuropeptides in skin disease: increased VIP in eczema and psoriasis but not axillary hyperhidrosis. *Br J Dermatol* 1991; **124**: 547–9.
3 Giannetti A, Fantini F, Cimitan A *et al*. Vasoactive intestinal polypeptide and substance P in the pathogenesis of atopic dermatitis. *Acta Derm Venereol Suppl (Stockh)* 1992; **176**: 90–2.
4 Pincelli C, Fantini F, Romualdi P *et al*. Skin levels of vasoactive intestinal polypeptide in atopic dermatitis. *Arch Dermatol Res* 1991; **283**: 230–2.
5 Fantini F, Pincelli C, Romualdi P *et al*. Substance P levels are decreased in lesional skin of atopic dermatitis. *Exp Dermatol* 1992; **1**: 127–8.
6 Pincelli C, Fantini F, Massimi P *et al*. Neuropeptides in skin from patients with atopic dermatitis: an immunohistochemical study. *Br J Dermatol* 1990; **122**: 745–50.
7 Tobin D, Nabarro G, de la Faille HB *et al*. Increased number of immunoreactive nerve fibers in atopic dermatitis. *J Allergy Clin Immunol* 1992; **90**: 613–22.
8 Coulson IH, Holden CA. Cutaneous reactions to substance P and histamine in atopic dermatitis. *Br J Dermatol* 1990; **122**: 343–9.
9 Heyer G, Hornstein OP, Handwerker HO. Reactions to intradermally injected substance P and topically applied mustard oil in atopic dermatitis patients. *Acta Derm Venereol* 1991; **71**: 291–5.
10 Giannetti A, Girolomoni G. Skin reactivity to neuropeptides in atopic dermatitis. *Br J Dermatol* 1989; **121**: 681–8.
11 Smith CH, Barker JN, Morris RW *et al*. Neuropeptides induce rapid expression of endothelial cell adhesion molecules and elicit granulocytic infiltration in human skin. *J Immunol* 1993; **151**: 3274–82.
12 Kang H, Byun DG, Kim JW. Effects of substance P and vasoactive intestinal peptide on interferon-gamma and interleukin-4 production in severe atopic dermatitis. *Ann Allergy Asthma Immunol* 2000; **85**: 227–32.

Pruritus

The major symptom that accompanies the rash of atopic eczema is pruritus. The mediators and mechanisms responsible for this symptom are still totally obscure. Symptoms of itching are induced in patients with atopic eczema by stimuli that induce sweating, both thermal and emotional, as well as contact with fibres, especially wool. Clues regarding mediators come from the effects of therapeutic agents with defined mechanisms of action. Thus, despite the general presumption that mast cell degranulation via IgE-mediated allergen-specific mechanisms is important in atopic eczema, antihistamines are generally of little effect against the pruritus of atopic eczema [1]. The older, sedating H1 antagonists may improve the subjective comfort through sedation and deeper sleep. Ciclosporin causes very rapid cessation of the pruritus—which might indicate the involvement of T-lymphocyte products such as cytokines. However, ciclosporin has effects on cells other than lymphocytes and, for example, may inhibit formation of prostaglandins [2]. As described above, responses to neuropeptides appear altered in atopic eczema. Neuropeptides such as substance P (SP), VIP, somatostatin and neurotensin provoke itch,

together with neurogenic inflammation in the form of erythema and weal and flare [3]. Capsaicin depletes nociceptive nerve endings of CGRP and SP and is reported to reduce pruritus in atopic eczema [4]. Acetylcholine (ACh), the archetypal neurotransmitter, activates both vasodilatation and sweating. ACh is also produced *in vitro* by keratinocytes [5]. ACh levels are raised in lesional skin of atopic eczema, and intradermal injection of ACh elicits pruritus rather than pain in patients with atopic eczema [6]. However, use of anticholinergic agents for treatment of the pruritus of atopic eczema has not become a useful therapeutic measure.

It has been suggested that opioids may play a part in the pruritus of atopic eczema; indirect evidence for this comes from the observation that opioid receptor antagonists such as naloxone or nalmefene can reduce pruritus [7]. However, others have failed to reproduce this observation [8].

Proteases, including tryptase and chymotryptase are released by mast cells, and it has been proposed that they play a part in causing pruritus. Intradermal injection of mast cell tryptase elicits pruritus, erythema, leukocyte infiltration and oedema [9]. Proteases exert a range of effects through activation of protease-activated receptors (PARs) including PAR-2 in particular [10]. PAR-2 receptors are found on endothelial cells, sensory nerves and keratinocytes, and play a part in the inflammatory process resulting from mast cell degranulation. With greater availability of PAR-2 antagonists for use in clinical situations, it will be easier to assess the functional importance of these receptors.

There has been speculation that cytokines may contribute to the pruritus of atopic eczema. Cytokine-rich supernatants from mitogen-stimulated lymphocytes can induce pruritus when injected into atopic eczema sufferers but not healthy controls [11,12]. A wide range of cytokines are released in atopic eczema. They include IL-2, 4, 5, 6, 8, 10, 13, IFN-γ and TNF-α. Most of these have been injected into human skin without producing significant pruritus. The exception is IL-2, which can produce redness and itching when used in the therapy of malignancy [13]. A possibility that has not been explored is that of synergism between some of the above mediators–say cytokines and neuropeptides.

A recently described cytokine, interleukin-31, was overexpressed in the epidermis of transgenic mice. This was accompanied by a progressively worsening itch, excoriation and dermatitis [14–16]. Moreover, IL-31 is strongly expressed by skin-homing, CLA-positive T cells in atopic eczema epidermis [17]. The receptor for IL-31 is expressed by keratinocytes and infiltrating macrophages in atopic eczema [17]. The most potent inducer of increased expression of IL-31 identified so far is staphylococcal superantigen [18].

References

1 Wahlgren CF. Itch and atopic dermatitis: clinical and experimental studies. *Acta Derm Venereol Suppl (Stockh)* 1991; **165**: 1–53.

2 Hernandez GL, Volpert OV, Iniguez MA *et al*. Selective inhibition of vascular endothelial growth factor-mediated angiogenesis by cyclosporin A: roles of the nuclear factor of activated T cells and cyclooxygenase 2. *J Exp Med* 2001; **193**: 607–20.

3 Stander S, Steinhoff M. Pathophysiology of pruritus in atopic dermatitis: an overview. *Exp Dermatol* 2002; **11**: 12–24.

4 Stander S, Luger T, Metze D. Treatment of prurigo nodularis with topical capsaicin. *J Am Acad Dermatol* 2001; **44**: 471–8.

5 Grando SA, Kist DA, Qi M *et al*. Human keratinocytes synthesize, secrete, and degrade acetylcholine. *J Invest Dermatol* 1993; **101**: 32–6.

6 Heyer G, Vogelgsang M, Hornstein OP. Acetylcholine is an inducer of itching in patients with atopic eczema. *J Dermatol* 1997; **24**: 621–5.

7 Monroe EW. Efficacy and safety of nalmefene in patients with severe pruritis caused by chronic urticaria and atopic dermatitis. *J Am Acad Dermatol* 1989; **21**: 135–6.

8 Metze D, Reimann S, Beissert S *et al*. Efficacy and safety of naltrexone, an oral opiate receptor antagonist, in the treatment of pruritus in internal and dermatological diseases. *J Am Acad Dermatol* 1999; **41**: 533–9.

9 Bernstein JE. Capsaicin in dermatologic disease. *Semin Dermatol* 1988; **7**: 304–9.

10 Steinhoff M, Vergnolle N, Young SH *et al*. Agonists of proteinase-activated receptor 2 induce inflammation by a neurogenic mechanism. *Nat Med* 2000; **6**: 151–8.

11 Cremer B, Heimann A, Dippel E *et al*. Pruritogenic effects of mitogen-stimulated peripheral blood mononuclear cells in atopic eczema. *Acta Derm Venereol* 1995; **75**: 426–8.

12 Grothe C, Heese K, Meisinger C *et al*. Expression of interleukin-6 and its receptor in the sciatic nerve and cultured Schwann cells: relation to 18-kD fibroblast growth factor-2. *Brain Res* 2000; **885**: 172–81.

13 Gaspari AA, Lotze MT, Rosenberg SA *et al*. Dermatologic changes associated with interleukin 2 administration. *JAMA* 1987; **258**: 1624–9.

14 Dillon SR, Sprecher C, Hammond A *et al*. Interleukin 31, a cytokine produced by activated T cells, induces dermatitis in mice. *Nat Immunol* 2004; **5**: 752–60.

15 Takaoka A, Arai I, Sugimoto M *et al*. Expression of IL-31 gene transcripts in NC/Nga mice with atopic dermatitis. *Eur J Pharmacol* 2005; **516**: 180–1.

16 Takaoka A, Arai I, Sugimoto M *et al*. Involvement of IL-31 on scratching behavior in NC/Nga mice with atopic-like dermatitis. *Exp Dermatol* 2006; **15**: 161–7.

17 Bilsborough J, Leung DY, Maurer M *et al*. IL-31 is associated with cutaneous lymphocyte antigen-positive skin homing T cells in patients with atopic dermatitis. *J Allergy Clin Immunol* 2006; **117**: 418–25.

18 Sonkoly E, Muller A, Lauerma AI *et al*. IL-31: a new link between T cells and pruritus in atopic skin inflammation. *J Allergy Clin Immunol* 2006; **117**: 411–7.

Sweating

Many patients are aware that sweating induces itching and aggravates their condition. This may reflect altered sensations associated with the neuropeptides released in the neurogenic control of sweat glands. Altered inflammatory responses to acetylcholine are described above, and increased numbers of nerve fibres have been described around the sweat glands in atopic non-lesional skin compared with lesional and healthy control skin [1]. Sweating responses to neurogenic stimuli are altered in atopic eczema sufferers, although there is some lack of agreement between findings, and diverse methods have been used to quantify sweat production. Sweating in response to cholinergic stimulation was found to be reduced in volume by one group [2,3] but normal in volume, although of more prolonged duration, by another group [4]. A possible explanation for differences comes from the study of Eishi *et al*. [5], who measured both direct cholinergic effects on sweat glands and distant effects mediated via the axon reflex. They found that directly induced sweat production hardly differed from that in healthy controls, whereas axon reflex-induced sweating was of lower volume with a longer latency. In a study of the response to adrenergic stimulation, sweating was similar between atopic eczema patients and non-atopic controls at low concentrations of adrenaline, but at higher concentrations sweating in non-atopic individuals was increased, whereas in atopic eczema patients it was decreased [6]. Sweating in response to the thermal stress of sitting in a heated room was found to be reduced

in atopic eczema patients [7]. However, there was no difference in sweating responses induced by hard cycling on a bicycle ergometer between atopic eczema sufferers and healthy controls [8].

Another way in which sweating may induce itching and aggravate eczema is related to the observation that there seems to be an IgE-mediated allergic reactivity to components of sweat [9]. Thus, skin challenges with autologous sweat induced positive responses in 56 of 66 (84%) patients compared with three of 27 (11%) healthy controls. Also, basophils were induced to release histamine in an IgE-dependent process [9]. The nature of the reaction-inducing substances is completely obscure.

References

1 Ostlere LS, Cowen T, Rustin MH. Neuropeptides in the skin of patients with atopic dermatitis. *Clin Exp Dermatol* 1995; **20**: 462–7.
2 Kiistala R, Kiistala U, Parkkinen MU. Local cholinergic sweat stimulation in atopic dermatitis: an evaporimetric study. *Acta Derm Venereol* 1991; **71**: 219–23.
3 Kiistala R. Cholinergic and adrenergic sweating in atopic dermatitis. *Acta Derm Venereol* 1992; **72**: 106–8.
4 Kato F, Saga K, Morimoto Y *et al*. Pilocarpine-induced cholinergic sweat secretion compared with emotional sweat secretion in atopic dermatitis. *Br J Dermatol* 1999; **140**: 1110–3.
5 Eishi K, Lee JB, Bae SJ *et al*. Impaired sweating function in adult atopic dermatitis: results of the quantitative sudomotor axon reflex test. *Br J Dermatol* 2002; **147**: 683–8.
6 Kiistala R. Adrenaline-induced local sweating and vasoconstrictive responses in atopic skin. *Br J Dermatol* 1992; **126**: 246–9.
7 Parkkinen MU, Kiistala R, Kiistala U. Sweating response to moderate thermal stress in atopic dermatitis. *Br J Dermatol* 1992; **126**: 346–50.
8 Bothorel B, Heller A, Grosshans E *et al*. Thermal and sweating responses in normal and atopic subjects under internal and moderate external heat stress. *Arch Dermatol Res* 1992; **284**: 135–40.
9 Hide M, Tanaka T, Yamamura Y *et al*. IgE-mediated hypersensitivity against human sweat antigen in patients with atopic dermatitis. *Acta Derm Venereol* 2002; **82**: 335–40.

Psychological factors

Patients with atopic dermatitis commonly complain that their condition is exacerbated by episodes of psychological stress, a situation that is also found in many inflammatory dermatological conditions. Buske-Kirschbaum *et al.* [1] showed that formal stressing of people who experience recurrent herpes simplex lesions could significantly increase the recurrence rate of cold sores, and that there was also a rise in plasma levels of TNF-α. The role and mechanisms of psychosocial stress on the clinical course of atopic dermatitis still remain to be elucidated. When volunteers are subjected to formal stress tests in the form of public speaking and performance of mental arithmetic, a wide range of endocrinological changes occur. These include increased production of adrenaline, ACTH, corticotrophin releasing factor (CRF) and cortisol, and reduced production of growth hormone, prolactin and progesterone [2]. The stress-induced rise in free cortisol is reportedly lower in patients with atopic dermatitis [3]. White blood cells and various cytokines also change in response to stress tests: increases in lymphocyte, monocyte, neutrophil and basophil numbers were seen 10 min after the stress provocation test and were equal in atopic individuals and healthy controls [4]. Also, although IFN-γincreased and IL-4 decreased in both control and atopic groups, atopic individuals showed a significant increase in eosinophils and IgE in response to stress [4]. Fjellner *et al*. [5] examined itch in response to intradermal inoculation of histamine, but found there was no demonstrable effect of stress.

Another humoral influence that appears to modulate atopic dermatitis is mediated by the sex steroids. One-third of 133 patients questioned claimed there was a significant pre-menstrual flare of atopic eczema [6]. Pregnancy exacerbated eczema in 52% of women, whereas it ameliorated eczema in 24% [6]. It has been proposed that a possible mechanism by which sex steroids alter susceptibility to inflammatory skin diseases is by modification of sensitivity to anti-inflammatory effects of glucocorticoids (GC). In a comparison of differences in susceptibility between men and women, Rohleder *et al*. [7] stressed volunteers as above; women were tested in the luteal phase of the menstrual cycle. Sensitivity to GC was assessed *in vitro* by measurement of dexamethasone inhibition of lipopolysaccharide-stimulated production of IL-6 and TNF-α. Salivary cortisol levels increased equally between the sexes. However, in men, GC sensitivity was markedly increased 1 h after stress, whereas GC sensitivity decreased significantly in women. Similarly, lipopolysaccharide-induced cytokine production decreased in response to stress in men but increased in women. It is not clear whether this is the result of the increased cortisol production suppressing cytokine production in men or of a change in responsiveness to lipopolysaccharide itself. Hence, the premenstrual flares of atopic eczema could reflect the reduced sensitivity to the anti-inflammatory effects of endogenous cortisol.

References

1 Buske-Kirschbaum A, Geiben A, Wermke C *et al*. Preliminary evidence for Herpes labialis recurrence following experimentally induced disgust. *Psychother Psychosom* 2001; **70**: 86–91.
2 Arnetz BB, Fjellner B, Eneroth P *et al*. Stress and psoriasis: psychoendocrine and metabolic reactions in psoriatic patients during standardized stressor exposure. *Psychosom Med* 1985; **47**: 528–41.
3 Buske-Kirschbaum A, Jobst S, Psych D *et al*. Attenuated free cortisol response to psychosocial stress in children with atopic dermatitis. *Psychosom Med* 1997; **59**: 419–26.
4 Buske-Kirschbaum A, Gierens A, Hollig H *et al*. Stress-induced immunomodulation is altered in patients with atopic dermatitis. *J Neuroimmunol* 2002; **129**: 161–7.
5 Fjellner B, Arnetz BB, Eneroth P *et al*. Pruritus during standardized mental stress. Relationship to psychoneuroendocrine and metabolic parameters. *Acta Derm Venereol* 1985; **65**: 199–205.
6 Kemmett D, Tidman MJ. The influence of the menstrual cycle and pregnancy on atopic dermatitis. *Br J Dermatol* 1991; **125**: 59–61.
7 Rohleder N, Schommer NC, Hellhammer DH *et al*. Sex differences in glucocorticoid sensitivity of proinflammatory cytokine production after psychosocial stress. *Psychosom Med* 2001; **63**: 966–72.

Clinical features

Atopic dermatitis is an itchy, chronic, fluctuating disease that is slightly more common in boys than girls, with a range of clinical features (Table 24.2). The age of onset is between 2 and 6 months in the majority of cases, but it may start at any age, even before the age of 2 months in some cases. The distribution of the eruption varies with age, as described below.

Infantile phase

The lesions most frequently start on the face (Fig. 24.6), but may occur anywhere on the skin surface. Often, the napkin area

Table 24.2 Clinical features of atopic dermatitis.

Itching
Macular erythema
Papules or papulovesicles
Eczematous areas with crusting
Lichenification and excoriation
Dryness of the skin
Secondary infection



Fig. 24.6 Atopic dermatitis: infantile phase.

is relatively spared. When the child begins to crawl, the exposed surfaces, especially the extensor aspect of the knees, are most involved. The lesions consist of erythema and discrete or confluent oedematous papules. The papules are intensely itchy, and may become exudative and crusted as a result of rubbing. Secondary infection and lymphadenopathy are common. The disease runs a chronic, fluctuating course, varying with such factors as teething, respiratory infections, emotional upsets and climatic changes.

Childhood phase

From 18 to 24 months onwards, the sites most characteristically involved are the elbow and knee flexures, sides of the neck, wrists and ankles [1] (Fig. 24.7). The sides of the neck may show a striking reticulate pigmentation, sometimes referred to as 'atopic dirty neck' [2,3] (Fig. 24.8). The anatomical basis for this distribution is unknown. Sometimes only one site is involved. The erythematous and oedematous papules tend to be replaced by lichenification. Some patients with atopic dermatitis are apparently unable to lichenify, even after prolonged rubbing (Fig. 24.9), and they may be very difficult to treat. Patients with an extensor distribution of



Fig. 24.7 Flexural atopic dermatitis of the wrist in a child.



Fig. 24.8 Atopic 'dirty neck'; reticulate pigmentation on the neck of a patient with long-standing atopic dermatitis.

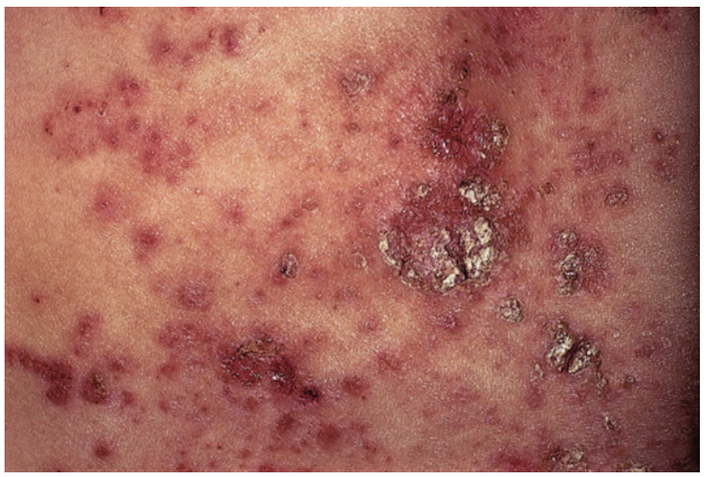


Fig. 24.9 Atopic dermatitis: erythema, papules, excoriations, crusting and secondary infection but, in this case, little lichenification.



Fig. 24.10 Marked lichenification on the knees of an African child. The popliteal fossae were spared.



Fig. 24.12 Nail involvement in atopic dermatitis in childhood.



Fig. 24.11 Atopic eczema of the fingers of a child.



Fig. 24.13 Adult flexural dermatitis.

eczema in later childhood are uncommon, and may take longer to remit. This distribution is said to be commoner in Asian or black children (Fig. 24.10), but frequently they show the typical distribution [4]. As well as the typical mixture of papules and lichenification, true eczematous lesions with vesiculation may occur, often in discoid patches. Involvement of the hands, often with exudative lesions, and sometimes with nail changes, is common (Figs 24.11 & 24.12). Acute generalized or localized vesiculation should always suggest the possibility of secondary bacterial or viral infection (p. 24.24).

Adult phase (Fig. 24.13)

The picture is essentially similar to that in later childhood [5], with lichenification, especially of the flexures and hands. Localized patches of atopic dermatitis can occur on the nipples, especially in adolescent and young women. Involvement of the vermilion of the lips and the adjacent skin is commonly an atopic manifestation. Follicular lichenified papules are a frequent feature in black people and the Japanese. A distribution on the face, upper arms and back may correlate with areas of maximal thermal sweating or *Malassezia* sensitivity [6]. Photosensitivity is not uncommon, especially in adults with atopic dermatitis. The mechanisms involved are several and complex. Many such cases do not show sensitivity when tested with the monochromator. Rajka [7] has suggested that infrared and UV radiation may both contribute. Management of such cases requires a combination of approaches used for ordinary atopic dermatitis and for photosensitivity, neither alone sufficing.

Atopic hand eczema (Chapter 23)

The prevalence of hand eczema in patients with active atopic dermatitis was 58.9% in a recent study, and the prevalence rises with increasing age [8]. A patchy, somewhat vesicular and lichenified eczema is a common manifestation of atopic dermatitis in childhood. The nails are often involved, resulting in coarse pitting and ridging. A more diffuse, chronic lichenified eczema of the

hands is frequently found in cases of extensive atopic dermatitis which persist into adult life, and atopic dermatitis is frequently a contributory factor in many cases of what usually has to be called constitutional hand eczema [9]. A previous history of atopic dermatitis, and more particularly hand involvement, is a highly significant risk factor for the development of occupational dermatitis [10]. Involvement of the feet is also common and almost half the patients with atopic hand eczema will have eczema on the feet [11].

References

1 Aoki T, Fukuzumi J, Adachi K *et al*. Re-evaluation of skin lesion distribution in atopic dermatitis. *Acta Derm Venereol Suppl (Stockh)* 1992; **176**: 19–23.
2 Colver GB, Mortimer PS, Millard PR *et al*. The 'dirty neck'—a reticulate pigmentation in atopics. *Clin Exp Dermatol* 1987; **12**: 1–4.
3 Humphreys F, Spencer J, Mclaren K, Tidman MJ. An histological and ultrastructural study of the 'dirty neck' appearance in atopic eczema. *Clin Exp Dermatol* 1996; **21**: 17–9.
4 Macharia WM, Anabwani GM, Owili DM. Clinical presentation of atopic dermatitis in Negroid children. *Afr J Med Sci* 1993; **22**: 41–4.
5 Bannister MJ, Freeman S. Adult-onset atopic dermatitis. *Australas J Dermatol* 2000; **41**: 225–8.
6 Waersted A, Hjorth N. *Pityrosporum orbiculare*—a pathogenetic factor in atopic dermatitis of the face, scalp and neck. *Acta Derm Venereol Suppl (Stockh)* 1985; **114**: 46–8.
7 Rajka G. *Essential Aspects of Atopic Dermatitis*. Berlin: Springer-Verlag, 1989.
8 Simpson EL, Thompson MM, Hanifin JM. Prevalence and morphology of hand eczema in patients with atopic dermatitis. *Dermatitis* 2006; **17**: 123–7.
9 Rystedt I. Atopy, hand eczema and contact dermatitis. *Semin Dermatol* 1986; **5**: 290–300.
10 Diepgen T. Epidemiology and job-related problems for the eczema patient. *Acta Derm Venereol* 2005; **85** (Suppl.): 41–4.
11 Lee HJ, Ha SJ, Ahn WK *et al*. Clinical evaluation of atopic hand dermatitis. *Pediatr Dermatol* 2001; **18**: 102–6.

Associated disorders

Other manifestations of atopy (Fig. 24.14)

Allergic rhinitis (hay fever) and asthma are beyond the scope of this book. They occur in 30–50% of cases of atopic dermatitis [1,2]. Atopic dermatitis is a risk factor for the future development of allergic airways disease, possibly by percutaneous sensitization to protein antigen [2,3]. The age of onset is later than that of the eczema. Latent asthma may be detected by bronchial inhalation tests in a proportion of patients with atopic dermatitis without clinical asthma.

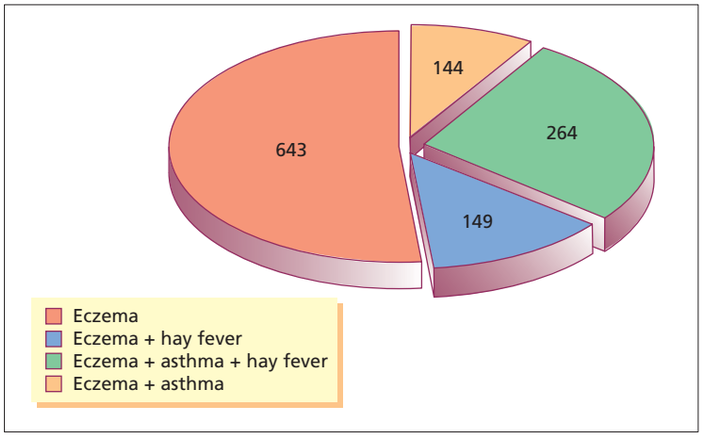


Fig. 24.14 The incidence of atopic respiratory symptoms in 1200 patients with atopic dermatitis. (From Rajka G. Prurigo Besnier (atopic dermatitis) with special reference to the role of allergic factors. *Acta Derm Venereol (Stockh)* 1960–1; **40**: 285; **41**: 363.)

Dry skin

This is a common feature of atopic dermatitis and figures prominently in its management. It is likely that it occurs because of increased transepidermal water loss through an abnormal stratum corneum [4,5], which may also correlate with disease activity [6]. The dry skin may be a consequence of abnormal ceramide synthesis and have an important role in the development of inflammation. Ceramide-containing emollients may be helpful in managing the condition [7]. Ichthyosis vulgaris and keratosis pilaris may also be seen in association with the condition and loss-of-function variants of the barrier protein filaggrin may be the link between these conditions and atopic dermatitis [8].

Other patterns of eczema

Infantile seborrhoeic dermatitis

This condition is discussed in Chapter 17. It normally starts earlier than atopic dermatitis, and it may be possible to distinguish between the two conditions clinically [9]. However, there are a number of children who present with what appears to be seborrhoeic dermatitis and then progress to typical atopic dermatitis [10].

Allergic contact dermatitis

It is clear that atopic dermatitis patients are at greater risk of developing irritant contact dermatitis than non-atopic patients [11]. However, there is a dispute about whether they are at greater risk of developing allergic contact dermatitis [12]. Nonetheless, patients can develop sensitivity to a variety of contact allergens such as topical medicaments, including topical corticosteroids [13,14]. There is also a risk of protein contact sensitivity, such as that associated with latex in rubber gloves [15,16]. The development of contact allergic dermatitis does not seem to adversely affect the prognosis for the atopic dermatitis [17].

Lip-lick cheilitis

Synonyms
- Perioral eczema
- 'Lick eczema'

Moist or fissured eczema around the mouth is common in children with atopic dermatitis. It can also occur as a result of food allergy, and in children with no known atopy or allergy. Frequently spreading some distance around the mouth, it may become secondarily infected and crusted (Fig. 24.15). Its persistence, and perhaps its origin, is attributable to habits of lip licking, thumb sucking, dribbling or chapping. It is easily transformed into true perioral dermatitis by the application of potent corticosteroids (Chapter 43). The regular application of 1% hydrocortisone ointment is usually most helpful. Contact sensitivity, for example to toothpaste ingredients, can occasionally be demonstrated.



Fig. 24.15 Lip-lick cheilitis.

Several other patterns of eczema are seen in individuals with atopy, but they are also seen in non-atopic individuals. These include eczema with a predominantly follicular accentuation, and discoid eczema. Certain well-defined conditions appear more common in atopic individuals; pityriasis alba and juvenile plantar dermatosis are discussed in Chapter 23. Nodular prurigo can quite frequently complicate the atopic diathesis (Chapter 23).

Infra-auricular dermatitis is quite frequently seen in atopic dermatitis patients, and infra-auricular fissures appear to be quite specific to atopic dermatitis [18].

Drug sensitivity

IgE-mediated drug reactions of the anaphylactic type are more common in atopic persons, but anaphylactic reactions to injected antigens can occur in persons with no other atopic manifestations. Anaphylactic reactions to topically applied drugs have been reported [19]. Other types of drug reaction with different immunological mechanisms occur with equal frequency in atopic and non-atopic individuals.

Food allergy

Abdominal symptoms due to food allergy are more frequent in patients with atopic disorders, but are not restricted to them. The role of food allergy in asthma and allergic rhinitis is probably minor. The role of food intolerance in the management of atopic dermatitis is discussed on p. 24.30.

Alopecia areata

There is a statistically significant association between alopecia areata and atopy.

Urticaria

The majority of cases of urticaria cannot be shown to be due to IgE or any other allergic sensitivity. Those cases in which an allergic basis is found occur more often in atopic individuals (Chapter 22). Contact urticaria, for example on the hands, occurs not infrequently in atopic dermatitis, and may present as an acute exacerbation of the dermatitis [20]. It occurs particularly in food handlers and slaughterhouse workers [21], and has been reported in health carers because of latex protein sensitivity [15].

References

1 Gustasson D, Sjoberg O, Foucard T. Development of allergies and asthma in infants and young children with atopic dermatitis—a prospective follow-up to 7 years of age. *Allergy* 2000; **55**: 240–5.

2 Ricci G, Patrizi A, Baldi E *et al*. Long-term follow up of atopic dermatitis: retrospective analysis of related risk factors and association with concomitant allergic diseases. *J Am Acad Dermatol* 2006; **55**: 765–71.

3 Spergel JM, Mizoguchi E, Brewer JP *et al*. Epicutaneous sensitization with protein antigen induces localised allergic dermatitis and hyperresponsiveness to methacholine after single exposure to aerosolized antigen in mice. *J Clin Invest* 1998; **101**: 1614–22.

4 Finlay AY, Nicholls S, King CS, Marks R. The dry non-eczematous skin associated with atopic eczema. *Br J Dermatol* 1980; **102**: 249–56.

5 Uehara M. Clinical and histological features of dry skin in atopic dermatitis. *Acta Derm Venereol Suppl (Stockh)* 1985; **114**: 82–6.

6 Kim DW, Park JY, Na GY *et al*. Correlation of clinical features and skin barrier function in adolescent and adult patients with atopic dermatitis. *Int J Dermatol* 2006; **45**: 698–701.

7 Chamlin SL, Frieden IJ, Fowler A *et al*. Ceramide-dominant barrier-repair lipids improve childhood atopic dermatitis. *Arch Dermatol* 2001; **137**: 1110–2.

8 Palmer CNA, Irvine DA, Terron-Kwiatkoski A *et al*. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet* 2006; **38**: 441–6.

9 Yates VN, Kerr RA, MacKie RM. Early diagnosis of infantile seborrhoeic dermatitis and atopic dermatitis—clinical features. *Br J Dermatol* 1983; **108**: 633–8.

10 Podmore P, Burrows D, Eedy DJ *et al*. Seborrhoeic eczema—a disease entity or a clinical variant of atopic eczema? *Br J Dermatol* 1986; **115**: 341–50.

11 Rysted I. Contact sensitivity in adults with atopic dermatitis in childhood. *Contact Dermatitis* 1985; **13**: 1–8.

12 Heine G, Schnuch A, Uter W, Worm M. Type-IV sensitization profile of individuals with atopic eczema: results from the Information Network of Departments of Dermatology (IVDK) and the German Contact Dermatitis Research Group (DKG). *Allergy* 2006; **61**: 611–6.

13 Cronin E, McFadden JP. Patients with atopic eczema do become sensitised to contact allergens. *Contact Dermatitis* 1993; **28**: 225–8.

14 Dooms-Goosens A, Morren M. Results of routine patch testing with corticosteroid series in 2073 patients. *Contact Dermatitis* 1992; **26**: 182–91.

15 Hamann CP. Natural rubber latex protein sensitivity in review. *Am J Contact Dermatitis* 1993; **4**: 4–21.

16 Holme SA, Lever RS. Latex allergy in atopic children. *Br J Dermatol* 1999; **140**: 919–21.

17 Mäkelä L, Lammintausta K, Kalimo K. Contact sensitivity and atopic dermatitis: association with prognosis, a follow-up study in 801 atopic patients. *Contact Dermatitis* 2007; **56**: 76–80.

18 Tada J, Toi Y, Akiyama H, Arata J. Infra-auricular fissures in atopic dermatitis. *Acta Derm Venereol (Stockh)* 1994; **74**: 129–31.

19 Roupe G, Stannegard O. Anaphylactic shock elicited by topical administration of bacitracin. *Arch Dermatol* 1969; **100**: 450–2.

20 Hansen KS, Petersen HO. Protein contact dermatitis in slaughterhouse workers. *Contact Dermatitis* 1989; **21**: 221–4.

21 Hjorth N, Roed-Petersen J. Occupational protein contact dermatitis in food handlers. *Contact Dermatitis* 1976; **2**: 28–42.

Complications

Psychosocial aspects

Atopic dermatitis has a profound effect, equal to or greater than that of asthma and diabetes, on many aspects of patients' lives and the lives of their families [1–4]. In children, the most troublesome symptoms are itching, distress at bath time and difficulty going to sleep. This can lead to behavioural difficulties in severely affected children [5,6]. The patient's dermatitis promotes family

dysfunction, causing exhaustion, sleep deprivation and emotional distress [7]. Increasingly, a demonstration of improvement in the quality of life of patients forms part of the assessment of new therapies [8] and reveals that advice from experienced teams can improve well-being [7].

Growth delay

Growth delay can be associated with atopic dermatitis [9]. It used to be seen in severe cases before the advent of corticosteroid therapy, and can therefore be attributed to the disease. However, suspicion must also clearly rest on both oral and topical steroid therapy, which can cause growth stunting in any child on long-term therapy [10]. Prepubertal children with atopic dermatitis show features consistent with constitutional growth delay [11].

Bacterial infections

Secondary bacterial infection with staphylococci or streptococci is virtually an integral part of the clinical picture [12]. It contributes to many exacerbations of the disease, even without grossly visible purulent exudate. Widespread impetigo may sometimes closely mimic Kaposi's varicelliform eruption. Indeed, any acute vesicular eruption in an atopic should suggest the diagnosis of secondary bacterial or viral infection.

Viral infections

Patients with atopic dermatitis, both active and quiescent, are liable to develop acute generalized infections with herpes simplex virus (eczema herpeticum), to produce the clinical picture of Kaposi's varicelliform eruption (Fig. 24.16) [13] (see Chapter 33).



Fig. 24.16 Kaposi's varicelliform eruption: eczema herpeticum.

Such episodes may present as a severe systemic illness with high fever and a widespread eruption. However, there may be no systemic disturbance, and at times the eruption may be quite localized, often to areas of pre-existing atopic dermatitis. The individual lesions start as the characteristic viral papulovesicles, but not necessarily with an herpetiform grouping. There may then be rapid evolution to a state in which extensive purulent exudate masks the initial papulovesicles, or superficial scattered erosions may be the only clue to the cause of a rapid deterioration of the dermatitis. The differential diagnosis includes bacterial impetigo and chickenpox. Herpes zoster and chickenpox apparently behave as in normal persons.

There is a lack of agreement about whether viral warts are more prevalent in atopic dermatitis. An initial uncontrolled study suggested an increased frequency of viral wart infections [14], but a more recent epidemiological study has cast doubt on this observation [15].

Similarly, the frequency of molluscum contagiosum in such patients is not clear. However, the clinical impression is that widespread molluscum contagiosum is more common in the atopic child.

An abnormal response to a Coxsackie infection in an atopic has been described [16]. AIDS may aggravate atopic dermatitis, and 'recall' atopic dermatitis has been described in AIDS patients [17]. A condition resembling atopic dermatitis has been seen in association with HTLV-1 infection, although this may be coincidental [18].

Ocular abnormalities (see also Chapter 67)

A number of ocular changes can occur in atopic dermatitis [19]. The Dennie–Morgan fold is often present as a fold of skin under the lower eyelids [20]. However, this change is not specific to atopic dermatitis, and is commonly seen in non-atopic black children [21].

Conjunctival irritation is a common syndrome in atopic persons. As in hay fever it may represent a true allergic reaction, or it may be due to a non-allergic irritability such as occurs in the nose or skin. Keratoconjunctivitis has been recorded [22].

Keratoconus [23,24], or conical cornea, is a rare condition. It may occur in the absence of any other disease or in association with atopic dermatitis. It is due to a degenerative change in the cornea, which is forced outwards by the intraocular pressure, to give rise to marked visual disturbances. Onset is in childhood, and after some years progress of the disease becomes arrested. Contact lenses may be helpful.

Cataract associated with atopic dermatitis (Fig. 24.17) has certain peculiarities which distinguish it from other types of cataract [25]. It occurs in up to 10% of the more severe adolescent and adult cases, but overall it is uncommon. It is associated with atopic dermatitis rather than with other atopic diseases perhaps because of a genetic risk factor [26]. It may start in early childhood or up to the age of 30 years, but the peak incidence is between 15 and 25 years. It is almost always bilateral. The appearances on slit-lamp examination are characteristic but not diagnostic. In the early stages translucent globules and small opacities appear at the pole in front of the posterior capsule and also in the anterior subcapsular zone. Progression may be slow, or alarmingly rapid over a

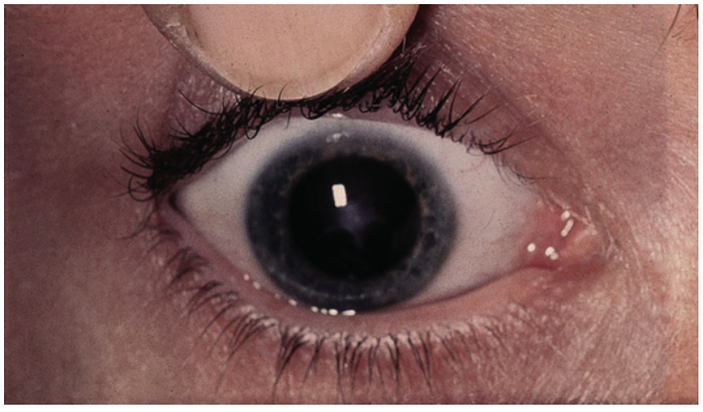


Fig. 24.17 Atopic cataract.

few days, and seems to be related to severe facial involvement [26]. The final appearance may resemble a mature, cortical, senile cataract.

Atopic cataracts may resemble those induced by topical or systemic steroids. The potential for cataract formation is an important reason for examining the eyes of any patient with atopic dermatitis when psoralen and UVA (PUVA) therapy is being contemplated.

Retinal detachment has been reported, particularly in Japanese patients [27], and appears to be identical to the retinal detachment seen following trauma [28].

Miscellaneous

Cartilaginous pseudocyst of the external auricle may be more common in children with atopic dermatitis [29], as may olecranon and pretibial bursitis [30]. A case of Sézary syndrome has been described in a patient with severe atopic dermatitis [31], and lymphomatoid papulosis in a patient receiving ciclosporin for their dermatitis [32]. However, the overall risk of cancer may be reduced in patients with atopic dermatitis [33].

References

1 Finlay AY. Quality of life in atopic dermatitis. *J Am Acad Dermatol* 2001; **45** (Suppl. 1): S67–8.
2 Lundberg L, Johannesson M, Silverdahl M *et al*. Health related quality of life in patients with psoriasis and atopic dermatitis measured with SF-36, DLQI and a subjective measure of disease activity. *Acta Derm Venereol (Stockh)* 2000; **80**: 430–4.
3 Holm EA, Esmann S, Jemec JBE. The handicap caused by atopic dermatitis—sick leave and job avoidance. *J Eur Acad Dermatol Venereol* 2006; **20**: 255–9.
4 Lawson V, Lewis-Jones MS, Finlay AY *et al*. The family impact of childhood atopic dermatitis: the dermatitis family impact questionnaire. *Br J Dermatol* 1998; **138**: 107–13.
5 Reid P, Lewis-Jones MS. Sleep difficulties and their management in pre-schoolers with atopic eczema. *Clin Exp Dermatol* 1995; **20**: 38–41.
6 Dahl RE, Bernhisel-Broadbent J, Scanlon-Holdford S *et al*. Sleep disturbances in children with atopic dermatitis. *Arch Paediatr Adolesc Med* 1995; **149**: 856–60.
7 Beattie PE, Lewis-Jones MS. An audit of the impact of a consultation with a paediatric dermatology team on quality of life in infants with atopic eczema and their families: further validation of the Infants' Dermatitis Quality of Life Index and Dermatitis Family Impact score. *Br J Dermatol* 2006; **155**: 1249–55.
8 Drake L, Prendergast M, Maher R *et al*. The impact of tacrolimus ointment on health-related quality of life of adult and paediatric patients with atopic dermatitis. *J Am Acad Dermatol* 2001; **44** (Suppl. 1): S65–72.
9 Ellison JA, Patel L, Kecojevic T *et al*. Pattern of growth and adiposity from infancy to adulthood in atopic dermatitis. *Br J Dermatol* 2006; **155**: 532–8.
10 Bode HH. Dwarfism following long-term corticosteroid therapy. *JAMA* 1980; **244**: 813–4.
11 Patel L, Clayton PE, Addison GM *et al*. Linear growth in prepubertal children with atopic dermatitis. *Arch Dis Child* 1998; **79**: 169–72.
12 Williams JV, Vowels B, Honig P, Leyden JJ. *Staphylococcus aureus* isolation from the lesions, the hands, and anterior nares of patients with atopic dermatitis. *J Emerg Med* 1999; **17**: 207–11.
13 Rysted I, Stranegard IL, Stranegard O. Recurrent viral infections in patients with past or present atopic dermatitis. *Br J Dermatol* 1986; **114**: 575–82.
14 Currie JM, Wright RC, Miller OG. The frequency of warts in atopic patients. *Cutis* 1971; **8**: 243–5.
15 Williams H, Pottier A, Strachan D. Are viral warts seen more commonly in children with eczema? *Arch Dermatol* 1993; **129**: 717–21.
16 Nahmia AJ, Foreschle JE, Feomino PM *et al*. Generalised eruption in a child with eczema due to Coxsackie virus A16. *Arch Dermatol* 1968; **97**: 147–8.
17 Parkin JM, Eales LJ, Galazka AR *et al*. Atopic manifestation in the acquired immune deficiency syndrome: response to recombinant interferon-γ. *BMJ* 1987; **294**: 1185–6.
18 Shohat M, Ben Amitai D, Shohat B *et al*. Atopic dermatitis and HTLV-1-associated myelopathy: associated or coincidental disorders? *Dermatology* 1999; **199**: 356–60.
19 Sehgal VN, Jain S. Atopic dermatitis: ocular changes. *Int J Dermatol* 1994; **33**: 11–4.
20 Uehara MAD. Infra-orbital fold in atopic dermatitis. *Arch Dermatol* 1981; **117**: 627.
21 Williams HC, Pembroke AC. Infraorbital crease, ethnic group, and atopic dermatitis. *Arch Dermatol* 1996; **132**: 51–4.
22 Karel I, Myska V, Koicalova E. Ophthalmological changes in atopic dermatitis. *Acta Derm Venereol (Stockh)* 1965; **45**: 381–6.
23 Brunsting LA, Reed WB, Bair HL. Occurrence of cataracts and keratoconus with atopic dermatitis. *Arch Dermatol* 1955; **72**: 237–41.
24 Copeman PWM. Eczema and keratoconus. *BMJ* 1966; **ii**: 977–9.
25 Nagaki Y, Hayasaka S, Kadoi C. Cataract progression in patients with atopic dermatitis. *J Cataract Refract Surg* 1999; **25**: 96–9.
26 Matsuda A, Ebihara N, Kumagai N *et al*. Genetic polymorphisms in the promoter of the interferon gamma receptor 1 gene are associated with atopic cataracts. *Ophthalmol Vis Sci* 2007; **48**: 583–9.
27 Yoneda K, Okamoto H, Wada Y *et al*. Atopic retinal detachment. Report of four cases and review of the literature. *Br J Dermatol* 1995; **133**: 586–91.
28 Hida T, Tano Y, Okinami N *et al*. Multicenter retrospective study of retinal detachment associated with atopic dermatitis. *Jpn J Ophthalmol* 2000; **44**: 407–18.
29 Devlin J, Harrison CJ, Whitby DJ *et al*. Cartilaginous pseudo-cyst of the external auricle in children with atopic eczema. *Br J Dermatol* 1990; **122**: 699–704.
30 Nassif A, Smith DL, Hanifin JM. Olecranon and pretibial bursitis in atopic dermatitis: coincidence or association? *J Am Acad Dermatol* 1994; **30**: 737–42.
31 Van Haselen CW, Toonstra J, Preesman AH *et al*. Sezary syndrome in a young man with severe atopic dermatitis. *Br J Dermatol* 1999; **140**: 704–7.
32 Laube S, Stephens M, Smith AG *et al*. Lymphomatoid papulosis in a patient with atopic eczema on long-term ciclosporin therapy. *Br J Dermatol* 2005; **152**: 1346–8.
33 Wang H, Diepgen TL. Atopic dermatitis and cancer risk. *Br J Dermatol* 2006; **154**: 205–10.

Natural history and prognosis [1–5]

Hospital-based studies suggest the age of onset is less than 6 months in 75% of cases and before the age of 5 years in 80–90%. However, community-ascertained cases may have a later age of onset than that reported in hospital-based studies [6]. The reported prognosis differs considerably according to how the cases are selected, the criteria for diagnosis and many other variables. There is a general tendency towards spontaneous improvement

throughout childhood and often some slight relapse during adolescence. Relatively few typical cases persist over the age of 30 years; perhaps half of all cases clear by the age of 13 years. The reported clearance rates range from 40 to 60% within 10–20 years [2,6]; 84% within 5–20 years [5]; and 50% at 10 years [3].

It is difficult to predict the prognosis in an individual case. However, children with severe disease, starting early, who also have asthma, hay fever and a family history of atopic dermatitis are likely to have more persistent disease [6]. Children with raised IgE antibodies to foods and inhalant antigens at 2 years of age may also have a poorer prognosis [7].

Recently, it has been suggested that involvement of the head and neck of adults implies further prolonged disease [8]. In addition, the atopic patient remains particularly at risk from occupational irritant hand dermatitis as an adult [9].

References

1 Musgrove K, Morgan JK. Infantile eczema. A long-term follow-up study. *Br J Dermatol* 1976; **95**: 365–72.
2 Rajka G. *Essential Aspects of Atopic Dermatitis*. Berlin: Springer-Verlag, 1989.
3 Rystedt I. Prognostic factors in atopic dermatitis. *Acta Derm Venereol (Stockh)* 1985; **65**: 206–13.
4 Sedlis E. Natural history of infantile eczema. Its incidence and course. *J Pediatr* 1965; **66**: 158–63.
5 Vickers CFH. The natural history of atopic eczema. *Acta Derm Venereol Suppl (Stockh)* 1980; **92**: 113–5.
6 Williams HC, Wüthrich B. The natural history of atopic dermatitis. In: Williams HC, ed. *Atopic Dermatitis: The Epidemiology, Causes, and Prevention of Atopic Eczema*. Cambridge: Cambridge University Press, 2000: 41–59.
7 Illi S, von Mutius E, Lau S *et al*.The natural course of atopic dermatitis from birth to age 7 years and the association with asthma. *J Allergy Clin Immunol* 2004; **113**: 925–31.
8 Sandström Falk MH, Faergemann J. Atopic dermatitis in adults: does it disappear with age? *Acta Derm Venereol* 2006; **86**: 135–9.
9 Diepgen T. Epidemiology and job-related problems for the eczema patient. *Acta Derm Venereol* 2005; **85** (Suppl. 215): 41–4.

Diagnosis

The diagnosis of atopic dermatitis is usually based on clinical criteria. The UK refinements of Hanifin and Rajka's diagnostic criteria (see Table 24.1) appear to be valid for both adults and children of white and non-white groups. However, these criteria were developed primarily for epidemiological use and were considered less reliable under 1 year of age.

Differential diagnosis

In the individual patient, one must consider a number of other conditions. Scabies should always be excluded, and can cause confusion when superimposed on pre-existing atopic dermatitis. In the first few months of life the differentiation of infantile seborrhoeic dermatitis from atopic dermatitis can be difficult [1], although with time the distinction becomes apparent. Immunodeficiency states should also be considered in infants in whom the disease is unusually severe, when there are recurrent systemic or ear infections, and if there is failure to thrive, malabsorption or petechiae. Recurrent infected eczema in Jamaican children may be associated with HTLV-1 infection (Chapter 23). An eruption resembling atopic dermatitis, with or without other atopic disorders, and sometimes with raised IgE levels, may be found in several genetic and metabolic disorders (Table 24.3).

Table 24.3 Genetic and metabolic disorders.

Agammaglobulinaemia
Anhidrotic ectodermal defect
Ataxia telangiectasia
Coeliac disease [2]
Cystic fibrosis heterozygote [3]
Experimental histidine depletion [4]
Hearing loss (genetic) [5]
Hurler's syndrome
Jung's disease (Chapter 23)
Nephrotic syndrome [6]
Netherton's syndrome (ichthyosis, bamboo hairs) [7]
Phenylketonuria
Wiskott–Aldrich syndrome (infections and thrombocytopenia)

In adults, flexural eczema may be a consequence of secondary dissemination of other types of eczema, for example in nickel allergy and occupational contact dermatitis [8].

References

1 Yates VM, Kerr REI, MacKie RM. Early diagnosis of infantile seborrhoeic dermatitis and atopic dermatitis I. Clinical features; 'total' and specific IgE levels. *Br J Dermatol* 1983; **108**: 633–9.
2 Hodgson HJF, Davies RJ, Gent AE *et al*. Atopic disorders and adult coeliac disease. *Lancet* 1976; **i**: 115–7.
3 Warner JO, Norman AP, Soothill JF. Cystic fibrosis heterozygosity in the pathogenesis of allergy. *Lancet* 1976; **i**: 990–1.
4 Snyderman SE, Boyer A, Roitman E *et al*. The histidine requirement of the infant. *Pediatrics* 1963; **31**: 786–801.
5 Frentz G, Everberg G, Wulf HC. Congenital perceptive hearing loss and atopic dermatitis. *Acta Otolaryngol* 1976; **82**: 242.
6 Sandberg DH, McIntosh RM, Berstein CW. Severe steroid responsive nephrosis associated with hypersensitivity. *Lancet* 1977; **i**: 388–90.
7 Walley AJ, Chavanas S, Moffatt MF *et al*. Gene polymorphisms in Netherton and common atopic disease. *Nat Genet* 2001; **29**: 175–8.
8 Williams J, Cahill J, Nixon R. Occupational autoeczematization or atopic eczema precipitated by occupational contact dermatitis? *Contact Derm* 2007; **56**: 21–6.

Hyper-IgE syndrome [1–3]

Synonyms
- Job's syndrome
- Buckley's syndrome

This is a syndrome that develops in infants or children. It resembles atopic dermatitis, but tends to involve particularly the scalp, axillae and groins. It may be inherited in an autosomal dominant or autosomal recessive form. In the dominant inheritance the associated features include persistent secondary bacterial infection, fluctuant cold abscesses, contact urticaria, bronchitis and more severe lung damage [1]. The recessive disease has a broader range of bacterial infections along with severe chronic molluscum contagiosum and herpes infections [2]. The key laboratory finding is the great elevation of serum IgE levels (greater than 200 i.u./mL),

often with some eosinophilia. Other immunoglobulins are often normal in the dominant form but elevated in the recessive variant.

References

1 Grimbacher B, Holland SM, Puck JM. Hyper-IgE syndromes. *Immunol Rev* 2005; **203**: 244–50.
2 Grimbacher B, Holland SM, Gallin JL *et al*. Hyper-IgE syndrome with recurrent infections—an autosomal dominant multisystem disorder. *N Engl J Med* 1999; **340**: 692–702.
3 Renner ED, Puck JM, Holland SM *et al*. Autosomal recessive hyperimmunoglobulin E syndrome: a distinct disease entity. *J Pediatr* 2004; **144**: 93–9.

Hypereosinophilic syndrome [1–4]

Eosinophilia is a common feature of many diseases, including several skin diseases. In this situation the eosinophilia is reactive and induced as a response to eosinophilopoietic cytokines. However, clonal eosinophilia may present with skin signs, including: a non-specific, itchy, maculopapular eruption; urticaria or angio-oedema; an eruption resembling atopic dermatitis; or erythroderma [3–5]. Only a few such cases can be attributed to an eosinophil leukaemia. The clinical manifestations appear to be attributable to the eosinophilia itself, and include cardiac involvement, and involvement of the nervous system, liver, lungs and gut.

References

1 Fletcher S, Bain B. Diagnosis and treatment of hypereosinophilic syndromes. *Curr Opin Hematol* 2007; **14**: 37–42.
2 Dagmar S, Hans-Uwe S. Eosinophilic disorders. *J Allergy Clin Immunol* 2007; **119**: 1291–9.
3 Kazmieruwski JA, Chusie MJ, Parrillo JE *et al*. Dermatologic manifestations of the hypereosinophilia syndrome. *Arch Dermatol* 1978; **114**: 531–5.
4 Leiferman KM. Hypereosinophilic syndrome. *Semin Dermatol* 1995; **14**: 122–8.
5 Offidani A, Bernadini ML, Simonetti O *et al*. Hypereosinophilic dermatosis: skin lesions as the only manifestation of the idiopathic hypereosinophilic syndrome. *Br J Dermatol* 2000; **143**: 675–7.

Pachydermatous eosinophilic dermatitis

Nir and Westfried described a generalized rash associated with marked blood and skin eosinophilia, and called it hypereosinophilic dermatitis [1]. More recently, a variant of this disorder has been described in three black South African teenage girls, and designated pachydermatous eosinophilic dermatitis [2]. This condition is thought to resemble severe atopic dermatitis or onchodermatitis. However, the three patients had peculiar hypertrophic genital lesions, peripheral blood eosinophilia and an eosinophil-rich lymphohistiocytic cutaneous infiltrate.

References

1 Nir MA, Westfried M. Hypereosinophilic dermatitis. A distinct manifestation of the hypereosinophilic syndrome with response to dapsone. *Dermatologica* 1981; **162**: 444–50.
2 Jacyk WK, Simson IW, Slater DN, Leiferman KM. Pachydermatous eosinophilic dermatitis. *Br J Dermatol* 1996; **134**: 469–74.

Investigations

The diagnosis of atopic dermatitis is rarely aided by investigations. Estimation of total serum IgE, specific radioallergosorbent tests (RASTs) and prick tests usually serve only to confirm the atopic nature of the individual. It is possible that such confirmation may be of value occasionally in adult-onset dermatitis. However, one must remember that 20% of patients with atopic dermatitis have normal total IgE levels and negative RASTs, whereas 15% of apparently healthy individuals have a raised IgE [1].

The value of investigations in identifying trigger factors in atopic dermatitis is disputed. How helpful specific RASTs to foods or aeroallergens are for disease management is unclear [2–4], although it is suggested that if they are negative allergy is unlikely [5]. It may be that skin prick test positivity to food allergens in young children with severe atopic dermatitis and a high serum IgE indicates a high risk of developing later allergic respiratory disease [6]. Adults with head and neck dermatitis and positive RASTs to *Malassezia* species may benefit from treatment with oral anti-yeast therapies [7].

If one suspects immunodeficiency with atopic dermatitis, then the appropriate investigations should be performed, for example immunoglobulin levels and subclasses, IgE levels, white-cell count, platelets, complement levels and function, and T, B and phagocyte cell numbers and functions. If clinically appropriate, one may also consider testing for HTLV-1 and HIV.

Bacteriology and virology swabs may be helpful in identifying causes for deterioration of atopic dermatitis. Although atopic dermatitis skin is often colonized by *Staphylococcus aureus*, bacterial culture can identify antibiotic resistance and detect β-haemolytic *streptococci*. Herpes simplex is usually readily cultured, but a Tzanck smear, an immunofluorescence slide test or electron microscopy can also be helpful, and will provide more rapid confirmation of infection.

Patch testing may also help to identify a contact allergen responsible for deterioration of the skin condition, particularly in adults [8,9]. The 'atopy patch test' for aeroallergens [4] and foods [10] in atopic dermatitis, and the skin-application food test (SAFT) in the management of the IgE-mediated contact urticaria syndrome in children with atopic dermatitis [11], are recommended by some authorities.

References

1 Juhlin L, Johansson SGO, Bennick H *et al*. Immunoglobulin E in dermatoses. *Arch Dermatol* 1969; **100**: 12–16.
2 David TJ. Conventional allergy tests. *Arch Dis Child* 1991; **66**: 281–2.
3 Pryzbilla B, Ring J. Food allergy and atopic eczema. *Semin Dermatol* 1990; **9**: 220–5.
4 Darsow U, Ring J. Airborne and dietary allergens in atopic eczema: a comprehensive review of diagnostic tests. *Clin Exp Dermatol* 2000; **25**: 544–51.
5 Hanifin JM. Atopic dermatitis in infants and children. *Pediatr Clin North Am* 1991; **38**: 763–89.
6 Patrizi A, Guerrini V, Ricci G *et al*. The natural history of sensitizations to food and aeroallergens in atopic dermatitis: a 4-year follow-up. *Pediatr Dermatol* 2000; **17**: 261–5.
7 Sandström Falk MH, Tengvall Linder M, Johansson C *et al*. The prevalence of *Malassezia* yeasts in patients with atopic dermatitis, seborrhoeic dermatitis and healthy controls. *Acta Derm Venereol* 2005; **85**: 17–23.
8 Cronin E, McFadden JP. Patients with atopic eczema do become sensitised to contact allergens. *Contact Dermatitis* 1993; **28**: 225–8.
9 Lever R, Forsyth A. Allergic contact dermatitis in atopic dermatitis. *Acta Derm Venereol Suppl (Stockh)* 1992; **76**: 95–8.

10 Niggemann B. The role of the atopy patch test (APT) in diagnosis of food allergy in infants and children with atopic dermatitis. *Pediatr Allergy Immunol* 2001; **12**: 37–40.
11 Oranje AP, Vangysez D, Mulder PGH, Dieges PH. Food-induced contact urticaria syndrome (CUS) in atopic dermatitis: reproducibility of repeated and duplicate testing with a skin provocation test, the skin application food test (SAFT). *Contact Dermatitis* 1994; **31**: 314–8.

Treatment [1–5]

Atopic dermatitis is a chronic condition that is variable in severity and age of onset. Many current therapies are based on small studies or even anecdotal evidence [1]. Nevertheless, treatment should be tailored to an individual's needs, bearing in mind age, sex, social conditions, sites of involvement and severity. A treatment strategy based on consistent advice and cooperation between health carers and the patient should be developed. It is clear that these aspirations are frequently not realized in practice [6]. However, recent years have seen the emergence of several new treatment approaches that hold promise for the near future (see below).

Initial treatment

In most settings initial treatment comprises advice and education, reduction of trigger factors, use of bathing with emollients and suppression of inflammation with a topical corticosteroid. Sometimes oral sedating antihistamines and antibiotics may be added for short periods. Studies reveal this approach is both effective and safe [7,8], although adherence to the regimen can be difficult [9].

General advice and education

In order to develop a strategy, the patient's specific requirements (in the discussion below the term patient refers either to the individual or the carers in the case of a baby or child) should be discussed and achievable aims agreed. These may include improvement in a range of factors, such as decreasing itch, improving sleep, reducing absenteeism from school/work or improving family interactions.

It is the clinician's responsibility to determine a balance between effective control of the condition and improved quality of life, and safe long-term therapy.

Educational programmes clearly improve outcomes and this has led to the development of educational schools about atopic dermatitis in some communities [10]. Clear and consistent advice from doctors, nurses, pharmacists, self-help groups and national support groups is also very helpful in achieving these aims. As part of the discussion, patients should be taught current knowledge of the disease, the types of trigger factors, the treatment options and their likely benefits and risks. Demonstration of the use of topically applied medications, bandages or wet wraps will improve compliance and disease control.

Reduction of trigger factors

Atopic dermatitis can be aggravated by a variety of trigger factors acting in concert (Fig. 24.18). These will vary between patients, and may differ at various times in an individual patient.

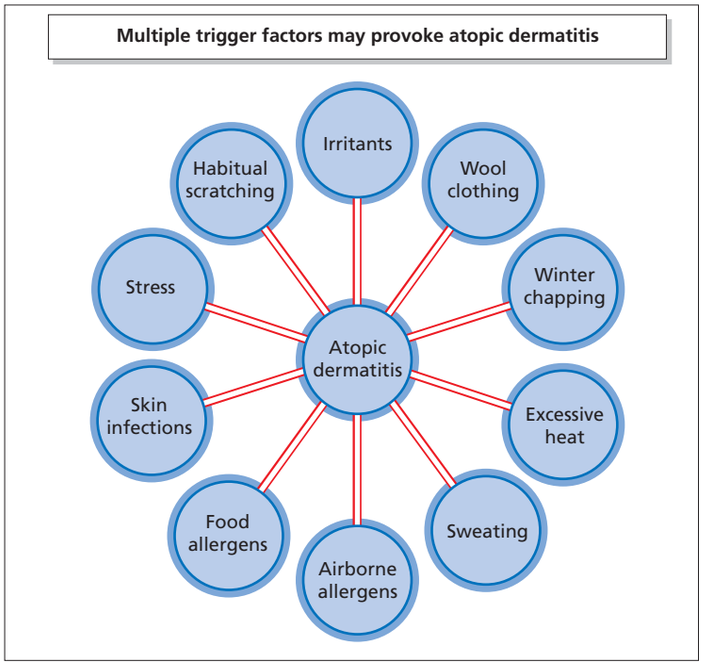


Fig. 24.18 Trigger factors for atopic dermatitis.

Most patients have dry skin, will suffer winter exacerbations, and soaps and detergents can irritate the dermatitis [11]. A dispersible cream can be used as a soap substitute to cleanse the skin. Simple measures such as turning down the central heating, not heating the bedroom, avoiding contact of wool with the skin and wearing cotton clothing may make life more comfortable for the patient.

Formal dietary manipulation is rarely necessary but should be discussed. Many patients have already started a restricted diet before seeing a doctor, so dietary assessment is important to confirm adequate nutrition. If the patient clearly identifies aggravating foods then avoidance can be tried. Airborne allergens are also aggravating factors, but again formal manipulation of the environment is not required for most patients. Regular cleaning of the bedroom in particular, with hoovering and damp dusting, may be helpful. Animal dander can aggravate atopic dermatitis and contribute to house-dust mite antigen levels, and so the keeping of household pets should be discouraged. Spring and summer flare, often in association with hay fever, can be related to exposure to grass and tree pollens. Flares of the dermatitis may be associated with the introduction of a new trigger factor into the environment or even a new environment such as moving house or change of childminder, and so the trigger factor history should be reviewed frequently.

Not only can stress aggravate atopic dermatitis, but the severely affected child is also a source of stress to the whole family [12,13]. The doctor's role in giving simple reassurance and listening to family problems should not be underestimated. Stress can respond to treatment, and the dermatitis can be improved by using a variety of cognitive behavioural techniques and group therapy [14].

Atopic dermatitis is not a contraindication to routine childhood vaccinations. Although egg protein is present in some vaccines the amount is so small that it should not be a problem in practice, unless the child has documented severe systemic reactions to egg protein; if in doubt, vaccination should be supervised in an environment where resuscitation equipment is available.

Parents should be advised about the risk of herpes simplex infection in a child with atopic dermatitis, and told to avoid contact of active cold sores with the child's skin.

Topical therapy

Bathing and emollients

Bathing is soothing for the majority of patients, and is helpful as long as the skin is moisturized immediately afterwards. Foaming detergents and soaps should be avoided and a soap substitute used for cleansing [11]. Dispersible bath oils are helpful, but do not maintain skin hydration as long as emollients applied immediately after the bath.

The regular use of emollients may even protect against inflammation provoked by irritants such as detergent [15], and increase the benefit obtained from topical corticosteroid therapy [16]. Indeed, ceramide-rich emollients may lead to improvements in childhood atopic dermatitis through a specific barrier repair mechanism [17].

In general, in chronic lesions of atopic dermatitis ointments are to be preferred, particularly when lichenification is prominent. In certain individuals ointments can cause irritation, and less oily preparations may be required. If lesions are exudative then creams or lotions may be required for a short time until ointments become more appropriate. In order to identify the emollient that best suits an individual it may be useful to provide small quantities of several agents, so that they may choose which they prefer. Then a generous quantity should be prescribed to encourage their frequent use throughout the day.

Topical suppression of inflammation

Topical steroids are the predominant treatment for the inflammation of atopic dermatitis, and if not abused are very safe. Anxiety among both the general public and family doctors about potential adverse effects of topical steroids has led to undertreatment of the skin in many sufferers [18].

The strength and mode of application of the topical steroids depends on the severity of the dermatitis, the sites to be treated and the age of the patient. Less potent topical steroids should be used on the eyelids, the face, the axillae, and the groins and inner thighs. Less potent topical steroids are also usually employed in children who are less than 1 year old, because systemic absorption occurs, even with 1% hydrocortisone ointment. Once daily treatment in the evening, with morning application of emollients, may be as effective as twice daily corticosteroid treatment. There appear to be no differences in efficacy or side effects between pulsed potent corticosteroid creams and the continuous use of mild topical corticosteroids in patients with mild to moderate disease [19].

A general principle is to use a topical steroid strong enough to settle severe dermatitis by twice daily application for 3–7 days, and then to reduce either the frequency of application or the steroid potency for maintenance therapy. In adults, a sequence of a potent steroid followed by a moderately potent steroid would be appropriate, whereas in children moderately potent and mild topical steroids may be successful.

Corticosteroid-resistant or infected or crusted dermatitis may respond better to steroid/antibiotic or steroid/antiseptic combinations. However, in young children there is some concern about the potential systemic toxicity of some antiseptics, such as clioquinol, if large surface areas are to be treated.

Monitoring corticosteroid use. Topical steroids can cause side effects if abused. Complications related to systemic absorption are rare. It is advisable to educate patients about the quantities to apply, for example the fingertip unit [20], and to be aware of the quantity used. Height and weight should be monitored in young children if they have severe dermatitis requiring moderately potent or potent steroids. Local side effects, such as permanent telangiectasis on the cheeks in babies and striae of the breasts, abdomen and thighs in adolescents, may be minimized if appropriate steroid strengths are used. Particular care is required around the eyes, as glaucoma may be induced by topical steroids [21]. When there are concerns about side effects the topical calcineurin inhibitors, pimecrolimus and tacrolimus may prove to be helpful (see below).

Oral therapy

Antihistamines

Itch is the most difficult symptom of atopic dermatitis to treat, and currently there is no specific antipruritic treatment [22]. The use of anti-inflammatory preparations, emollients and reduction of trigger factors is still the initial approach.

H1-receptor antagonists are used predominantly for their sedative effect [23]. Agents such as promethazine or trimeprazine given 1 h before bedtime can be useful when there is severe nocturnal itching. However, they can cause drowsiness and lack of concentration the next morning. In infants, these preparations may occasionally cause paradoxical excitation. They are best used in short courses, for example 10–14 days, as tachyphylaxis can occur with prolonged use [24]. Most studies conclude that nonsedating antihistamines are of little value for the pruritus of atopic dermatitis [23,25], but in some cases with an allergic component, for example contact urticaria, they may be of value.

Antibiotics

Exudation and pustule formation often implies staphylococcal infection of the skin, and oral antibiotics such as flucloxacillin or erythromycin are usually prescribed. Colonization of the skin by these bacteria may exacerbate the dermatitis, although *Staphylococcus aureus* colonization is effectively reduced by anti-inflammatory therapies [26]. In patients with recurrent flares of atopic dermatitis associated with infection, long-term antibiotic treatment, topical steroid/antibiotic combination creams, and measures to reduce staphylococcal colonization of the nose and perineum, could be considered [27].

Herpes simplex infection should be treated with oral antiherpetic medications. If the patient is febrile or toxic, intravenous therapy should be considered.

Maintaining control

The majority of patients will respond to initial treatment regimens. At follow-up the importance of continuing to reduce exposure to trigger factors, as far as is practical, should be discussed. Particularly in children, one needs to strike a balance between social and physical development and avoidance of trigger factors.

The continuous use of emollients should be emphasized, and often in mild disease prolonged control can be obtained with very intermittent use of topical corticosteroids. In more problematic patients the addition of twice-weekly application of mid-potency topical steroids to the healed areas (the 'weekender approach') can safely and significantly reduce relapses of atopic dermatitis [28,29]. If relapse occurs then topical corticosteroids should be used daily again for a week and the weekender approach resumed.

The calcineurin inhibitors have also been used to maintain control. Topical pimecrolimus applied to the first signs of inflammation can reduce the number of flares and amount of topical steroid required [30]. Adding mid-week use of tacrolimus ointment to the weekender approach can improve control of severe atopic dermatitis [31].

Unresponsive disease

Patients who fail to respond should be reviewed to check compliance, important triggers that have been missed, to exclude recurrent or antibiotic-resistant infection and to consider more intensive treatment.

Intensive topical treatment

The strength of topical steroid treatment can be increased for a short period as an out-patient. If this is ineffective, in-patient treatment will often control severe exacerbations of dermatitis [32], and the skin frequently improves using the same treatment that was unsuccessful as an out-patient.

Wet-wrap technique

This can be a useful technique for the control of severe atopic dermatitis in younger children. Two layers of absorbent tubular bandage are applied to the skin. The inner layer is presoaked in warm water and the outer layer is dry. A generous quantity of a low potency topical corticosteroid is applied to the skin before the dressings. The dressings can be used overnight or changed every 12 h. This regimen can be used in hospital or for short-term out-patient treatment. Close supervision should be maintained because suppression of the hypothalamopituitary axis can occur when topical steroids are employed. Regimens using emollient only under the wet dressings have become popular but are somewhat less effective [33].

Topical calcineurin inhibitors

The use of tacrolimus and pimecrolimus ointments has been licensed in the UK since 2001 subject to National Institute of Health and Clinical Excellence guidance. Tacrolimus ointment is restricted to use in adults (0.1%) and children over 2 years of age (0.03%) with moderate to severe atopic dermatitis not controlled by topical corticosteroids. Pimecrolimus cream is for use in corticosteroid-resistant facial dermatitis. Generally, worldwide they are perceived as second-line agents, but conditions of use vary. Many studies have demonstrated their efficacy, and their attraction is the absence of the cutaneous side effects of skin atrophy, striae, telangiectasia and bruising that may been seen with prolonged or inappropriate corticosteroid use [34].

Tacrolimus 0.1% ointment seems similar in strength to potent topical corticosteroids whereas pimecrolimus cream is significantly weaker [35]. Both preparations can cause stinging and burning on application to the skin. They would seem to be of value for resistant eczema, particularly in areas at high risk of skin thinning.

The US Food and Drug Administration issued an alert in 2005 concerning potential risk of lymphoma and skin cancer from topical use. This alert, which was based on theoretical considerations arising from systemic use of high concentration of the drugs in animals, means that these concerns must be discussed with patients. However, topical use seems to be associated with a good safety profile to date, and an increased risk of lymphoma has not been observed [36–38].

Allergy management

Eighty percent of patients with atopic dermatitis show IgE hyper-reactivity to common allergens. Some authorities argue that the intrinsic type (with no demonstrable IgE hyper-reactivity) is important to identify because it will never progress to allergic respiratory disease and such patients will not benefit from allergy management [39]. Although it is clear that reactivity can be demonstrated *in vivo* and *in vitro* it is less clear how well such reactivity correlates with clinical improvement following allergen avoidance. This has led to clear variations of recommendations for practice from different authorities [3,40]. However, the patients or carers will expect advice on at least the following issues.

Foods

Dietary factors may aggravate the dermatitis of 15–35% of children with atopic dermatitis [41], but in older children and adults this is far less common. Approaches to dietary management range from intensive investigation using double-blind food challenges [42] to empirical diets [43]. The clinical benefit of dietary management is still debated because there are few controlled studies of its value [41]. Even so, because some children, usually with severe dermatitis, benefit who have failed to respond to general and topical therapy, a 3- to 4-week trial of a modified elimination diet may be considered. Increased suspicion may be aroused by a history of urticarial reactions or gastrointestinal reactions to foods. A positive specific raised IgE, particularly the specific circulating titres (IgE cap), may have a predictive value in young children [44,45]. Commonly, dairy produce, beef, eggs, chicken, fish, wheat, citrus and berry fruits, food additives, chocolate and nuts may be excluded. Decreased itch and improvement of the dermatitis show the benefits of a relevant exclusion diet. It is important that the diet is appropriately supervised by a paediatric dietician. If such measures do not reveal an obvious dietary culprit, a normal diet can be resumed, with the suspected foods reintroduced every 3 to 4 days.

It must be remembered that there have been occasional severe anaphylactic reactions when a food to which an atopic is very sensitive has been reintroduced [46]. Frequently, in children, an

inadequate unbalanced diet is given before medical advice has been sought, and malnutrition may be present, usually because of cow's milk avoidance. It is important to thoroughly review the child's diet with the help of a dietician in these circumstances. Extensively hydrolysed cow's milk formulates can be used as a cow's milk substitute, and recently an amino acid-based formula has been found to be an effective substitute in children with dermatitis [47].

Breastfeeding for at least 6 months in infants with atopic dermatitis is usually suggested [41]. However, the protective effect of breastfeeding against the development of atopic dermatitis remains controversial [48].

In older children and young adults dietary management is rarely helpful [45,49], and screening tests are not helpful in this age group (roughly over 6 years) because of false-positive reactions. However, occasionally patients benefit from a diet free from food additives [50].

Inhalants

Although a variety of inhalants have been implicated in exacerbations of atopic dermatitis [51], HDM allergen appears to be the most important [52]. Clinical improvement in children's dermatitis has been noted following intensive eradication of mite allergens from the bedroom [53,54]. However, the benefit of HDM eradication on adults with atopic dermatitis is less convincing [55]. There is some suggestion that early avoidance of airborne allergens, along with common dietary allergens, may reduce the chances of later developing atopic conditions [56].

Contact allergy

Contact urticaria is usually quickly recognized from the history, and avoidance of the responsible foods is advised. Tests to identify such foods are not usually required (see Investigations, above).

Delayed hypersensitivity to medicaments, including hydrocortisone, tacrolimus and pimecrolimus [57], and fragrances may be responsible for treatment failure, particularly in adults and in periorbital eczema [58], and patch tests are useful if this is suspected. However, because of irritancy interpretation of patch tests can be difficult in atopics. It may be necessary to admit the patient to hospital to settle the eczema before performing patch tests. Contact allergy may be found in children and this possibility must not be forgotten [59].

Phototherapy

Numerous types of phototherapy have undergone trials for the treatment of severe atopic dermatitis and seem to be effective. These include UVB, narrow-band UVB, medium- and high-dose UVA1 and PUVA [60–64]. Some studies suggest that air-conditioned treatment cabinets improve patients' tolerance of phototherapy [65]. A practical consideration is the relative timing of the use of phototherapy and immunosuppressant therapy because of the concerns about skin cancer development in later life.

Systemic therapies

A number of systemic therapies are available for recalcitrant cases. Limited effectiveness or concerns over toxicity may restrict their long-term usefulness.

Low-dose ciclosporin therapy is effective in the control of adult [66] and childhood atopic dermatitis [67,68]. Occasionally, permanent remission appears to be induced [69]. Renal toxicity, hypertension and the risk of skin cancer are limiting factors.

Oral corticosteroids have a limited but definite role in the management of severe exacerbations of atopic dermatitis, but long-term treatment often requires doses that may produce significant adverse effects.

Azathioprine may be less toxic than other oral immunosuppressives, particularly when low thiopurinemethyltransferase (TPMT) activity is identified by pretreatment screening, but the onset of its effect can be slow and improvement was modest in a recent double-blind, placebo-controlled study [70,71]. Methotrexate also shows promise for the treatment of atopic dermatitis, but randomized, controlled trials are still awaited [72,73]. Mycophenolate mofetil is also showing promise for severe atopic dermatitis unresponsive to other therapies [74,75]. Recent case reports using biological agents as therapy show variable results, but this is likely to be a rapidly advancing therapeutic area [76–78].

Other approaches

Over the years, a wide variety of therapies have been tried in atopic dermatitis. Recent studies have shown that specific textiles used in clothing are associated with clinical improvement [79,80]. Dietary supplementation with probiotics, prebiotics and their combinations (synbiotics) for treating atopic dermatitis still remains to be established [81,82], and oral konjac ceramide was associated with clinical and immunological improvement in a small controlled study [83].

Oral evening primrose oil was used for patients with atopic dermatitis, and a meta-analysis of placebo-controlled studies suggested a slight benefit [84], but this is strongly disputed [85].

Clinical trials of Chinese herbal medicines have been performed, and decoctions of a standard formulation appear to be helpful in adults and children [86,87]. Concern has been expressed about their potential for hepatotoxicity [88].

Many other drugs have been reported to be effective in atopic dermatitis but are rarely used, including high-dose oral sodium cromoglycate [89], topical sodium cromoglycate solution [90], interferon-gamma [91], thymopentin [92], type 4 phosphodiesterase inhibitors [93], intravenous immunoglobulins [94], oral ketoconazole [95] and monteleukast [96]. Extracorporeal photopheresis has also been shown to be of benefit [97].

Desensitization

Desensitization plays a very limited part in the management of patients with atopic dermatitis, even when an allergic factor has been firmly established clinically [98]. Allergen-specific immunotherapy may reduce the need for topical corticosteroids [99], but more studies are required [100].

References

1 Hoare C, Li Wan Po A, Williams H. Systematic review of treatments for atopic eczema. *Health Technol Assess* 2000; **4**: 1–191.

2 Darsow U, Lubbe J, Taïeb A *et al*. for the European Task Force on Atopic Dermatitis. Position paper on the diagnosis and treatment of atopic dermatitis. *J Eur Acad Dermatol Venereol* 2005; **19**: 286–95.

3 National Institute for Health and Clinical Excellence. *Atopic Eczema in Children: management of atopic eczema in children from birth up to the age of 12 years*, 2007. http://www.nice.org.uk/Guidance/CG57
4 Brown S, Reynolds NJ. Atopic and non-atopic eczema. *BMJ* 2006; **332**: 584–8.
5 Hanifin JM, Cooper KD, Ho VC *et al*. Guidelines of care for atopic dermatitis, developed in accordance with the American Academy of Dermatology (AAD)/American Academy of Dermatology Association. Administrative regulations for evidence based clinical practice guidelines. *J Am Acad Dermatol* 2004; **50**: 391–404.
6 Shum KW, Lawton S, Williams HC *et al*. The British Association of Dermatologists audit of atopic eczema management in secondary care. Phase 3: audit of service outcome. *Br J Dermatol* 2000; **142**: 721–7.
7 Kawashima M, Harada S. Effect of standard medication on quality of life of patients with atopic dermatitis. *J Dermatol* 2007; **34**: 9–16.
8 Callen J, Chamlin S, Eichenfield LF *et al*. A systematic review of the safety of topical therapies for atopic dermatitis. *Br J Dermatol* 2007; **156**: 203–21.
9 Krejci Manwaring J, Tusa MG, Carrol C *et al*. Stealth monitoring of adherence to topical medication: adherence is very poor in children with atopic dermatitis. *J Am Acad Dermatol* 2007; **56**: 211–6.
10 Staab D, Diepgen TL, Fartasch M *et al*. Age related, structured educational programmes for the management of atopic dermatitis in children and adolescents: multicentre, randomized controlled trial. *BMJ* 2006; **332**: 933–8.
11 Holden CA, English J, Hoare C *et al*. Advised best practice for the use of emollients in eczema and other dry skin conditions. *J Dermatol Treat* 2002; **13**: 103–6.
12 Buske-Kirschbaum A, Geiben A, Hellhammer D. Psychobiological aspects of atopic dermatitis: an overview. *Psychother Psychosom* 2001; **70**: 6–16.
13 Linnet J, Jemec GB. The assessment of anxiety and dermatological life quality in patients with atopic dematitis. *Br J Dermatol* 1999; **140**: 268–72.
14 Staughton R. Psychologic approach to atopic skin disease. *J Am Acad Dermatol* 2001; **45** (Suppl. 1): S53–4.
15 Loden M, Andersson A-C. Effect of topically applied lipids on surfactant irritated skin. *Br J Dermatol* 1996; **134**: 215–20.
16 Grimalt R, Mengeaud V, Cambazard F. The steroid sparing effect of an emollient therapy in infants with atopic dermatitis: a randomized controlled study. *Dermatology (Basel)* 2007; **214**: 61–7.
17 Chamlin SL, Frieden IJ, Fowler A *et al*. Ceramide-dominant, barrier-repair lipids improve childhood atopic dermatitis. *Arch Dermatol* 2001; **137**: 1110–2.
18 Charman CR, Morris AD, Williams HC. Topical corticosteroid phobia in patients with atopic eczema. *Br J Dermatol* 2000; **142**: 931–6.
19 Thomas KS, Armstrong S, Avery A *et al*. Randomised controlled trial of short bursts of a potent topical corticosteroid versus prolonged use of a mild preparation for children with mild to moderate atopic eczema. *BMJ* 2002; **324**: 768–71.
20 Long CC, Finlay AY. The finger tip unit—a new practical measure. *Clin Exp Dermatol* 1991; **16**: 444–7.
21 Cubey RB. Glaucoma following the application of corticosteroids to the skin of the eyelids. *Br J Dermatol* 1976; **95**: 207–8.
22 Wahlgren CF. Itch and atopic dermatitis: an overview. *J Dermatol* 1999; **26**: 770–9.
23 Klein PA, Clark RA. An evidence-based review of the efficacy of antihistamines in relieving pruritus in atopic dermatitis. *Arch Dermatol* 1999; **135**: 1522–5.
24 Kemp JP. Tolerance to antihistamines: is it a problem? *Ann Allergy* 1989; **63**: 621–3.
25 Diepgen TL. Early treatment of the Atopic Child Study Group. Long-term treatment with cetirizine of infants with atopic dermatitis: a multi-country, double–blind, placebo-controlled trial (the ETAC trial) over 18 months. *Paediatr Allergy Immunol* 2002; **13**: 278–86.
26 Hung SH, Lin YT, Chu CY *et al*. Staphylococcus colonisation in atopic dermatitis treated with fluticasone or tacrolimus with or without antibiotics. *Ann Allergy Asthma Immunol* 2007; **98**: 51–6.
27 Breneman DL, Hanifin JM, Berge CA *et al*. The effect of antibacterial soap with 1.5% triclocarban on *Staphylococcus aureus* in patients with atopic dermatitis. *Cutis* 2000; **66**: 296–300.
28 Hanifin J, Gupta AK, Rajagopalan R. Intermittent dosing of fluticasone propionate cream for reducing the risk of relapse in atopic dermatitis patients. *Br J Dermatol* 2002; **147**: 528–37.
29 Berth-Jones J, Damstra RJ, Golsch S *et al*. Twice weekly fluticasone proprionate added to emollient maintenance treatment to reduce risk of relapse in atopic dermatitis patients: randomized, double-blind, parallel group study. *BMJ* 2003; **326**: 1367.
30 Wahn U, Bos JD, Goodfield M *et al*. Flare reduction in eczema with Elidel. (Children) Multicenter Investigator Study Group. Efficacy and safety of pimecrolimus cream in the long-term management of atopic dermatitis in children. *Pediatrics* 2002; **110**: e2.
31 Nakahara T, Koga T, Fukagawa S *et al*. Intermittent topical corticosteroid/tacrolimus sequential therapy improves lichenification and chronic papules more efficiently than intermittent topical corticosteroid/emollient sequential therapy in patients with atopic dermatitis. *J Dermatol* 2004; **31**: 524–8.
32 Schmitt J, Heese E, Wozel G, Meurer M. Effectiveness of inpatient treatment on quality of life and clinical disease severity in atopic dermatitis and psoriasis vulgaris. *Dermatology (Basel)* 2007; **214**: 68–76.
33 Devillers ACA, Oranje AP. Efficacy and safety of 'wet wrap' dressings as an intervention treatment in children with severe and/or refractory atopic dermatitis: a critical review of the literature. *Br J Dermatol* 2006; **154**: 579–85.
34 Ashcroft DM, Dimmock P, Garside R *et al*. Efficacy and tolerability of topical pimecrolimus and tacrolimus in the treatment of atopic dermatitis: meta-analysis of randomized controlled trials. *BMJ* 2005; **330**: 516–22.
35 Luger TA, Lahfa M, Folster-Holst R *et al*. Long–term safety and tolerability of pimecrolimus cream 1% and topical corticosteroids in adults with moderate to severe atopic dermatitis. *J Dermatol Treat* 2004; **15**: 169.
36 Shainhouse T, Eichenfield LF. Long-term safety of tacrolimus ointment in children treated for atopic dermatitis. *Expert Opin Drug Saf* 2003; **2**: 457–65.
37 Arellano FM, Wentworth CE, Arana A *et al*. Risk of lymphoma following exposure to calcineurin inhibitors and topical steroids in patients with atopic dermatitis. *J Invest Dermatol* 2007; **127**: 808–16.
38 Spergel JM, Leung DYM. Safety of topical calcineurin inhibitors in atopic dermatitis: evaluation of the evidence. *Curr Allergy Asthma Rep* 2006; **6**: 270–4.
39 Schmidt-Grendelmeier P, Simon D, Simon H-U *et al*. Epidemiology, clinical features, and immunology of the 'intrinsic' type (non-IgE-mediated) of atopic dermatitis (constitutional dermatitis). *Allergy* 2001; **56**: 841–9.
40 Société Francaise de Dermatolgie. Consensus conference; management of atopic dermatitis in children. Recommendations (short version). *Eur J Dermatol* 2005; **15**: 215–23.
41 Lever R. The role of food in atopic eczema. *J Am Acad Dermatol* 2001; **45** (Suppl. 1): S57–60.
42 Sampson HA, McCaskill CC. Food hypersensitivity and atopic dermatitis: evaluation of 113 patients. *J Pediatr* 1985; **107**: 669–75.
43 Atherton DJ, Sewell M, Soothill JF *et al*. A double-blind controlled crossover trial of an antigenic avoidance diet in atopic eczema. *Lancet* 1978; **i**: 401–3.
44 Lever R, MacDonald C, Waugh P, Aitchison T. Randomised controlled trial of advice on an egg exclusion diet in young children with atopic eczema and sensitivity to eggs. *Pediatr Allergy Immunol* 1998; **9**: 13–9.
45 Sampson H. The evaluation and management of food allergy in atopic dermatitis. *Clin Dermatol* 2003; **21**: 183–92.
46 David T. Anaphylactic shock during elimination diets for severe atopic eczema. *Arch Dis Child* 1984; **59**: 983–6.
47 Niggemann B, Binder C, Dupont C *et al*. Prospective, controlled, multi-center study on the effect of an amino-acid-based formula in infants with cows milk allergy/intolerance and atopic dermatitis. *Pediatr Allergy Immunol* 2001; **12**: 78–82.
48 Gdalevich M, Mimouni D, David M, Mimouni M. Breast-feeding and the onset of atopic dermatitis in childhood: a systematic review and meta-analysis of prospective studies. *J Am Acad Dermatol* 2001; **45**: 520–7.
49 Neild VS, Marsden RA, Bailes JA, Bland JM. Egg and milk exclusion diets in atopic eczema. *Br J Dermatol* 1986; **114**: 117–23.
50 Worm M, Ehlers I, Sterry W, Zuberbier T. Clinical relevence of food additives in adult patients with atopic dermatitis. *Clin Exp Allergy* 2000; **30**: 407–14.
51 Rajka G. *Essential Aspects of Atopic Dermatitis*. Berlin: Springer-Verlag, 1989: 80.
52 Friedmann PS. Dust mite avoidance in atopic dermatitis. *Clin Exp Dermatol* 1999; **24**: 433–7.
53 Tan BB, Weald D, Strickland I, Friedmann PS. Double-blind controlled trial of effect of house dust mite allergen avoidance in atopic dermatitis. *Lancet* 1996; **347**: 15–8.

54 Ricci G, Patrizi A, Specchia F *et al*. Effect of house dust mite avoidance measures in children with atopic dermatitis. *Br J Dermatol* 2000; **143**: 379–84.
55 Gutgesell C, Heise S, Seubert S *et al*. Double-blind placebo-controlled house dust mite control measures in adult patients with atopic dermatitis. *Br J Dermatol* 2001; **145**: 70–4.
56 Hide DW, Matthews S, Tariq S, Arshad SH. Allergen avoidence in infancy and allergy at four years of age. *Allergy* 1996; **51**: 89–93.
57 Shaw DW, Maibach HI, Eichenfield LF. Allergic contact dermatitis from pimecrolimus in a patient with tacrolimus allergy. *J Am Acad Dermatol* 2007; **56**: 342–5.
58 Ockenfels HM, Seemann U, Goos M. Contact allergy in patients with periorbital eczema: an analysis of allergens. Data recorded by the information network of the Departments of Dermatology. *Dermatology* 1997; **195**: 119–24.
59 Roul S, Ducombs G, Taieb A. Usefulness of the European standard series for patch testing in children. A 3-year single-centre study of 337 patients. *Contact Dermatitis* 1999; **40**: 232–5.
60 Krutmann J. Phototherapy for atopic dermatitis. *Clin Exp Dermatol* 2000; **25**: 552–8.
61 Reynolds NJ, Franklin V, Gray JC *et al*. Narrow-band ultraviolet B and broad-band ultraviolet A phototherapy in adult atopic eczema: a randomised controlled trial. *Lancet* 2001; **357**: 2012–6.
62 Tzaneva S, Seeber A, Schwaiger M *et al*. High-dose versus medium-dose UVA1 phototherapy for patients with severe generalized atopic dermatitis. *J Am Acad Dermatol* 2001; **45**: 503–7.
63 Der-Petrossian M, Seeber A, Honigsmann H, Tanew A. Half-side comparison study on the efficacy of 8-methoxypsoralen bath-PUVA versus narrow-band ultraviolet B phototherapy in patients with severe chronic atopic dermatitis. *Br J Dermatol* 2000; **142**: 39–43.
64 Clayton TH, Clark SM, Turner D, Goulden V. The treatment of severe atopic dermatitis in childhood with narrowband ultraviolet B phototherapy. *Clin Exp Dermatol* 2007; **32**: 28–33.
65 George S, Bilsand D, Johnson BE *et al*. Narrow-band UVB (TL-01) air-conditioned therapy for chronic severe adult atopic eczema. *Acta Derm Venereol Suppl (Stockh)* 1992; **176**: 137–8.
66 Berth-Jones J, Graham-Brown RAC, Marks R *et al*. Long term efficacy and safety of cyclosporin in severe adult atopic dermatitis. *Br J Dermatol* 1997; **136**: 76–81.
67 Harper JI, Ahmed I, Barclay G *et al*. Cyclosporin for severe childhood atopic dermatitis: short course versus continuous therapy. *Br J Dermatol* 2000; **142**: 52–8.
68 Harper JI, Berth-Jones J, Camp RD *et al*. Cyclosporin for atopic dermatitis in children. *Dermatology* 2001; **203**: 3–6.
69 Sepp N, Fritsch PO. Can cyclosporin A induce permanent remission of atopic dermatitis? *Br J Dermatol* 1993; **128**: 213–6.
70 Murphy LA, Atherton D. A retrospective evaluation of azathioprine in severe childhood atopic eczema, using thiopurine methyltransferase levels to exclude patients at high risk of myelosuppression. *Br J Dermatol* 2002; **147**: 308–15.
71 Meggitt SJ, Gray JC, Reynolds NJ. Azathioprine dosed by thiopurine methyltransferase activity for moderate-to-severe atopic eczema: a double-blind, randomized controlled trial. *Lancet* 2006; **367**: 839–46.
72 Weatherhead SC, Wahie S, Reynolds NJ, Meggitt SJ. An open-label, dose-ranging study of methotrexate for moderate-to-severe adult atopic dermatitis. *Br J Dermatol* 2007; **156**: 346–51.
73 Goujon C, Bérard F, Dahel K *et al*. Methotrexate for the treatment of adult atopic dermatitis. *Eur J Dermatol* 2006; **16**: 155–8.
74 Grundmann-Kollmann M, Podda M, Ochsendorf F *et al*. Mycophenolate mofetil is effective in the treatment of atopic dermatitis. *Arch Dermatol* 2001; **137**: 870–3.
75 Murray ML, Cohen JB. Mycophenolate mofetil therapy for moderate to severe atopic dermatitis. *Clin Exp Dermatol* 2007; **32**: 23–7.
76 Weinberg JM, Siegfried EC. Successful treatment of severe atopic dermatitis in a child and an adult with the T-cell modulator efalizumab. *Arch Dermatol* 2006; **142**: 555–8.
77 Lane JE, Cheyney JM, Lane TN *et al*. Treatment of recalcitrant atopic dermatitis with omalizumab. *J Am Acad Dermatol* 2006; **54**: 68–72.
78 Buka RL, Resh B, Roberts B *et al*. Etanercept is minimally effective in 2 children with atopic dermatitis. *J Am Acad Dermatol* 2005; **53**: 358–9.
79 Ricci G, Patrizi A, Bellini F, Medri M. Use of textiles in atopic dermatitis: care of atopic dermatitis. *Curr Probl Dermatol* 2006; **33**: 127–43.
80 Senti G, Steinmann LS, Fischer B *et al*. Antimicrobial silk clothing in the treatment of atopic dermatitis proves comparable to topical corticosteroid treatment. *Dermatology* 2006; **213**: 228–33.
81 Passeron T, Lacour JP, Fontas E, Ortonne JP. Prebiotics and synbiotics: two promising approaches for the treatment of atopic dermatitis in children above 2 years. *Allergy* 2006; **61**: 431–7.
82 Fölster HR, Müller F, Schnopp N *et al*. Prospective, randomised controlled trial on *Lactobacillus rhamnosus* in infants with moderate to severe atopic dermatitis. *Br J Dermatol* 2006; **155**: 1256–61.
83 Kimata H. Improvement of atopic dermatitis and reduction of skin allergic responses by oral intake of konjac ceramide. *Pediatr Dermatol* 2006; **23**: 386–9.
84 Morse PF, Horrobin DF, Manku MS *et al*. Meta-analysis of placebo-controlled studies of the efficacy of Epogam in the treatment of atopic eczema: relationship between plasma essential fatty acid changes and clinical response. *Br J Dermatol* 1989; **121**: 75–90.
85 Williams HC. Evening primrose oil for atopic dermatitis—time to say good-night. *BMJ* 2003; **327**: 1358–9.
86 Sheehan M, Atherton DJ. A controlled trial of traditional Chinese medicinal plants in widespread non-exudative atopic eczema. *Br J Dermatol* 1992; **126**: 179–84.
87 Sheehan M, Rustin MHA, Atherton DJ *et al*. Efficacy of traditional Chinese herbal therapy in adult atopic dermatitis: results of a double-blind placebo-controlled study. *Lancet* 1992; **340**: 13–7.
88 Graham-Brown R. Toxicity of Chinese herbal remedies. *Lancet* 1992; **340**: 673.
89 Businco L, Cantani A. Mast cell blockers and atopic eczema. In: Ruzicka T, Ring J, Pryzbilla B, eds. *Handbook of Atopic Eczema*. Berlin: Springer-Verlag, 1991: 407–14.
90 Kimata H, Hirasuka S. Effect of topical cromoglycate solution on atopic dermatitis: combined treatment of sodium cromoglycate solution with the oral anti-allergic medication oxotamide. *Eur J Pediatr* 1994; **153**: 66–71.
91 Boguniewicz M, Jaffe HS, Izu A *et al*. Recombinant gamma-interferon in treatment of patients with atopic dermatitis and elevated IgE levels. *Am J Med* 1990; **88**: 365–70.
92 Leung DY, Hirsch RL, Scheider L *et al*. Thymopentin therapy reduces the clinical severity of atopic dermatitis. *J Allergy Clin Immunol* 1990; **85**: 927–33.
93 Hanifin JM, Chan CS, Cheng JB *et al*. Type 4 phosphodiesterase inhibitors have clinical and *in vitro* anti-inflammatory effects in atopic dermatitis. *J Invest Dermatol* 1996; **107**: 51–6.
94 Jolles S. A review of high-dose intravenous immunoglobulin treatment for atopic dermatitis. *Clin Exp Dermatol* 2002; **27**: 3–7.
95 Lintu P, Savolainen J, Kortekangas-Savolainen O, Kalimo P. Systemic ketoconazole is an effective treatment of atopic dermatitis with IgE-mediated hypersensitivity to yeasts. *Allergy* 2001; **56**: 512–7.
96 Capella GL, Grigerio E, Altomare G. A randomised trial of leukotriene receptor antagonist monteleukast in moderate-to-severe atopic dermatitis of adults. *Eur J Dermatol* 2001; **11**: 209–13.
97 Prinz B, Michelsen S, Pfeiffer C, Plewig G. Long-term application of extracorporeal photochemotherapy in severe atopic dermatitis. *J Am Acad Dermatol* 1999; **40**: 577–82.
98 Glover MT, Atherton DJ. A doubleblind controlled trial of hyposensitization to *Dermatophagoides pteronyssinus* in children with atopic eczema. *Clin Exp Allergy* 1992; **22**: 440–6.
99 Werfel T, Breuer K, Ruéff F *et al*. Usefulness of specific immunotherapy in patients with atopic dermatitis and allergic sensitization to house dust mites: a multicentre, randomised, dose-response study. *Allergy* 2006; **61**: 202–5.
100 Mastrandrea F. Immunotherapy in atopic dermatitis. *Expert Opin Investig Drugs* 2001; **10**: 49–63.

Disease prevention and occupational advice

There is excitement about the possibility that atopic dermatitis and other atopic diseases may be prevented by altering the fetal or the newborn's antigenic exposure. However, precisely what and when changes need to be made is not clear [1].

There are conflicting data about whether maternal avoidance of milk, eggs and other dietary allergens during pregnancy and lactation can reduce the incidence of atopic disorders [2], but a Cochrane review of the evidence concluded that avoidance of such allergens in pregnancy protects the baby against the development of atopic dermatitis, and the same approach during lactation may have a small beneficial effect [3].

The evidence that breastfeeding or diets to avoid potential allergens during the first 6 months of the infant's life will significantly protect against atopy or reduce its manifestations is also contradictory [2]. Although a cohort study of 1265 children followed for 10 years suggests that a diverse solid-food diet during the first 4 months of life roughly doubles the risk of developing atopic dermatitis [4], an American Academy of Dermatology guidelines task force review found that definite evidence for exclusive breastfeeding and dietary allergen avoidance was still lacking [5].

There are suggestions that the use of hydrolysed infant formulas may be helpful, although perhaps not practical, for the prevention of atopic dermatitis in at-risk newborns [6]. The use of probiotics, prebiotics or synbiotics as dietary supplements is also controversial [7].

Atopic dermatitis will often improve about the time of puberty. This is often the time when adolescents are deciding what occupation they should undertake. Exposure of the skin to irritant chemicals and physical trauma should be avoided as far as possible. Adolescents with atopic dermatitis, particularly with hand involvement, would be well advised to avoid occupations involving wet work or exposure to irritants, such as car mechanics, engineering, hairdressing or nursing [8].

References

1 Simpson EL, Hanifin JM. Atopic dermatitis. *Med Clin N Am* 2006; **90**: 149–67.

2 Hoare C, Li Wan Po A, Williams H. Systematic review of treatments of atopic eczema. *Health Technol Assess* 2000; **4**: 16–20.

3 Kramer MS, Kakuma R. Maternal dietary antigen avoidance during pregnancy and/or lactation for preventing or treating atopic disease in the child. *Cochrane Database of Systematic Reviews*, Issue 4, Chichester (UK): John Wiley and Sons, 2004.

4 Fergusson DM, Horwood LJ. Early solid food diet and eczema in childhood: a 10-year longitudinal study. *Pediatr Allergy Immunol* 1994; **5** (Suppl. 1): 44–7.

5 Hanifin JM, Cooper KD, Ho VC *et al*. Guidelines for care for atopic dermatitis. *J Am Acad Dermatol* 2004; **50**: 391–404.

6 Osborn DA, Sinn J. Formulas containing hydrolysed protein for prevention of allergy and food intolerance in infants. *Cochrane Database of Systematic Reviews*, Issue 1, Chichester (UK): John Wiley and Sons, 2004.

7 Taylor AL, Dunstan JA, Prescott SL. Probiotic supplementation for the first 6 months of life fails to reduce the risk of atopic dermatitis and increases the risk of allergen sensitization in high risk children: a randomized controlled trial. *J Allergy Clin Immunol* 2007; **119**: 184–91.

8 Diepgen T. Epidemiology and job-related problems for the eczema patient. *Acta Derm Venereol* 2005; **85** (Suppl.): 41–4.

CHAPTER 25

Contact Dermatitis: Irritant

S.M. Wilkinson[1] *& M.H. Beck*[2]

[1]Department of Dermatology, Leeds General Infirmary, Leeds, UK
[2]Department of Dermatology, Salford Royal Hospital, Salford, UK

History, 25.1
Epidemiology, 25.2
Pathogenesis, 25.2
The skin barrier, 25.2
The mechanism of action of irritants, 25.3
Pathology, 25.3
Histology, 25.4
Immunopathology, 25.5
Differentiation from allergic contact dermatitis, 25.6
Predisposing factors, 25.6
Individual, 25.6
Environmental, 25.8
Chemical and physical, 25.8
Identifying irritants, 25.9
Clinical features, 25.10
Chemical burns, 25.10
Irritant contact dermatitis, 25.11
Non-immune contact urticaria, 25.18
Symptomatic (subjective) irritant responses, 25.18
Specific irritants, 25.19
Investigations, 25.21
Quantifying the irritant response, 25.22
Management, 25.22
Chemical burns, 25.22
Irritant contact dermatitis, 25.23
Non-immune contact urticaria, 25.24
Symptomatic irritant responses, 25.24
Prevention, 25.24
Prognosis, 25.26
Persistent post-irritant dermatitis, 25.26

Introduction

Irritant contact dermatitis in a broad sense represents the cutaneous response to the physical/toxic effects of a wide range of environmental exposures. A burn results when the effect on the skin is irreversible and necrosis occurs. Reversible cellular injury may cause contact urticaria or dermatitis dependent on the nature of the insult. Where there is no apparent cellular injury various sensory symptoms, such as stinging, smarting and burning, may occur. The following types of irritant contact reaction may be distinguished:

1 Burns
2 Irritant contact dermatitis:
  (a) acute (toxic) irritant contact dermatitis
  (b) cumulative irritant/insult contact dermatitis
3 Transient or immediate-type, non-immune, contact urticaria
4 Symptomatic (subjective) irritant responses
5 Other: pigmentary and granulomatous responses and those localized to appendageal structures (Table 25.1).

Table 25.1 Other irritant contact responses of the skin and their causes.

Folliculitis	Tar and oils, arsenic trioxide, fibreglass
Acne	Halogenated aromatic hydrocarbons
Miliaria	Aluminium chloride, occlusion
Pigmentary	
hyperpigmentation	Phototoxic agents, metals (arsenic, silver, gold, mercury, bismuth)
hypopigmentation	Substituted phenols and catechols
Granulomatous	Silica, talc, beryllium
Alopecia	Borax, chloroprene dimers

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

Allergic contact dermatitis and light-related skin reactions are covered in Chapters 26 and 29. Damage to the skin from physical and mechanical factors, thermal injury and ionizing radiation is discussed in Chapters 28 and 79. Pigmentary, follicular and granulomatous responses are covered in Chapters 9 and 61.

History

Contact dermatitis was first described to plants as long ago as 2000 BC, when an extract of the castor oil bean was rubbed into the scalp, as an irritant, to promote hair growth [1]. Whilst presumably recognized, there appears to be little subsequent documentation of irritant contact dermatitis other than in an occupational setting. For example, Agricola documented deep ulcers of the skin among metal workers in 1556. The apparent lack of interest may date back to ancient times and the Greek prejudice against manual labour, as a result of which in some cities it was illegal for a citizen to ply a manual trade. Consequently, medical works tended to concentrate on the afflictions of the citizen rather than of the work force. Increased awareness of occupational disease is noticeable from the 1700s and the Industrial Revolution. Ramazzini (1633–1714) described fissures on the hands of washerwomen and ulcers on the legs of salt miners. In England, during the 19th century, there was a revival of interest in occupational dermatoses, with Willan describing dermatitis from shoemaker's wax and Bateman eruptions due to lime among builders [2].

References

1 Mitchell JC, Rook A. *Botanical Dermatology: Plants Injurious to the Skin*. Vancouver: Greengrass, 1979: 1–25.
2 Rycroft RJG. Occupational diseases of the skin. In: Baxter PJ, Adams PH, Aw T-C, *et al.*, eds. *Hunter's Diseases of Occupations*, 9th edn. London: Arnold, 2000: 725–37.

Epidemiology

Few population studies differentiate between irritant reactions and allergic contact dermatitis, and study populations are also often either selective or poorly defined. A questionnaire study of 20 000 persons in an industrial town in the south of Sweden revealed a point prevalence of hand eczema of 5.4% (with a 1-year period prevalence of 11%). Females were twice as commonly affected as males, and in 35% the hand eczema was thought to be irritant in nature. Atopic hand dermatitis accounted for 22% of cases; the presence of childhood eczema increasing the prevalence of hand dermatitis by three compared with non-atopic individuals. Allergic contact dermatitis accounted for 19%. The most frequent sources of exposure were 'unspecified' chemicals, water, detergents, dust and dirt [1]. Occupationally, soaps (22.0% of cases), wet work (19.8%), petroleum products (8.7%), and cutting oils and coolants (7.8%) are the most frequently cited causes. Individuals involved in mining/manufacturing, hairdressing, agriculture and medical and nursing occupations had the highest frequency of dermatitis [2]. In one large study of adverse reactions to cosmetics [3], 16% were thought to be irritant.

Burns are relatively common, with an American survey showing that 119 hospitals treated 11 759 patients during a 1-year period. The majority of burns involved the upper limb, with most occurring in young adults and infants. Occupational burns are also relatively common, with 29% of burns requiring admission being work-related, with a rate of 26.4 per 10 000 employees. In women burns of the wrist and hand were most frequent, whereas in men eye involvement was more common. Welders, labourers, cooks and mechanics were most at risk [4].

'Sensitive skin' might be considered a marker of a form of skin irritancy. In a questionnaire-based study [5] of 3300 women and 500 men, 51.4% of women and 38.2% of men considered that they were susceptible. Fifty-seven per cent of women and 31.4% of men had had an adverse reaction to a personal care product during their lives. Among women, symptoms of subjective skin irritation (burning, stinging, etc.) occurred more frequently in those who considered that they had a sensitive skin (53%) than in those who did not (17%). Dry skin and a predisposition to blushing/flushing were factors associated with a sensitive skin. An atopic background was a predictive factor for the presence of sensitive skin, as the incidence of atopy was higher among those with sensitive skin (49%) than among those in the non-sensitive group (27%). However, equal numbers of atopics and non-atopics constituted the sensitive skin group, indicating that other variables were involved. In North America, there has been shown to be no ethnic difference in the prevalence of sensitive skin, although there are racial differences in how it is perceived. Euro-Americans experience greater reactivity to wind and less to cosmetics; African Americans have reduced reactivity to most environmental factors; Asians have greater reactivity to spices, change in temperature and wind, and itch more frequently; Hispanics react less to alcohol. Overall, however, there were more similarities than differences [6].

References

1 Meding B, Jarvholm B. Incidence of hand eczema—a population based retrospective study. *J Invest Dermatol* 2004; **122**: 873–7.

2 Meyer JD, Chen Y, Holt DL *et al*. Occupational contact dermatitis in the UK: a surveillance report from EPIDERM and OPRA. *Occup Med* 2000; **50**: 265–73.

3 Eiermann HJ, Larsen W, Maibach HI *et al*. Prospective study of cosmetic reactions: 1977–80. *J Am Acad Dermatol* 1982; **6**: 909–17.

4 Pruitt VM. Work-related burns. *Clin Occup Environ Med* 2006; **5**: 423–33.

5 Willis CM, Shaw S, De Lacharrière O *et al*. Sensitive skin: an epidemiological study. *Br J Dermatol* 2001; **145**: 258–63.

6 Jourdain R, De Lacharrière O, Bastien P, Maibach HI. Ethnic variations in self-perceived sensitive skin: epidemiological survey. *Contact Dermatitis* 2002; **46**: 162–9.

Pathogenesis

The skin barrier

The skin provides the first and most important line of defence against exogenous noxious agents, and this is one of its primary physiological functions [1]. This defence is far from perfect, as many substances penetrate readily into and through the epidermis, even when it is intact.

The principal epidermal barrier resides almost entirely in the stratum corneum. This is normally renewed every 17–27 days, but barrier function can be restored in 2–5 days following stripping or superficial injury. The stratum corneum appears to function as a homogeneous unit, the largest amount of penetrant always being found in the outermost layers. Damage to the stratum corneum is normally followed by an increase in percutaneous absorption and in transepidermal water loss, the increase in transepidermal water loss being proportional to the decrease in thickness of the stratum corneum.

Solvent extraction studies indicate that epidermal lipid is a main contributor to the barrier, consisting of ceramides (45–50%), cholesterol (25%), free fatty acids (10–15%) and other lipids including cholesterol sulphate. The lipids are arranged as stacked membrane sheets in the intercellular space and are produced from lamellar granules in the cells of the granular cell layer of the epidermis (see Chapter 4). It follows that inherited abnormalities of the pathway might result in impaired barrier function usually associated with ichthyosis.

In addition to the lipid barrier, tight junctions between epidermal cells have also been shown to provide a block to water loss. Claudin-1 (an essential protein of tight junctions) knockout mice developed wrinkly skin and greatly increased transepidermal water loss (TEWL). They died within 1 day of birth [2].

For certain materials, there may be a second barrier at or near the dermal–epidermal junction or basement membrane [3] but, for most substances, the horny layer remains the principal barrier.

References

1 Madison KC. Barrier function of the skin: 'La raison d'être' of the epidermis. *J Invest Dermatol* 2003; **121**: 231–41.

2 Furuse M, Hata M, Furuse K *et al*. Claudin-based tight junctions are crucial for the mammalian permeability barrier: a lesson from claudin-1 deficient mice. *J Cell Biol* 2002; **156**: 1099–111.

3 Van der Valk PGM, Maibach HI. A functional study of the skin barrier to evaporative water loss by means of repeated cellophane-tape stripping. *Clin Exp Dermatol* 1990; **15**: 180–2.

The mechanism of action of irritants

An irritant is any agent, physical or chemical, that is capable of producing cellular perturbation if applied for sufficient time and in sufficient concentration. Immunological memory is not involved and dermatitis occurs without prior sensitization. Many chemicals penetrate the skin, and many substances will alter or damage skin cells. Dermatitis arises when the defence or repair capacity of the skin is exhausted, or when the penetration of chemicals excites an inflammatory response. Strong irritants will induce a clinical reaction in almost all individuals, whereas with less potent irritants the response may be physiological rather than apparent, with dermatitis developing only in the most susceptible or in situations where there is repeated contact with irritants [1].

The relationship between physicochemical structure and cytotoxic activity remains to be fully elucidated, but it would appear that hydrophobicity (log *P*) and dissociation constant (pK_a) are among the factors that contribute to irritation potential [2,3] (Table 25.2). For sodium lauryl sulphate, concentration has been shown to be a more important determinant of subsequent dermatitis than exposure time [4]. The nature of the response is in part determined by the irritant [5].

In the laboratory, barrier disruption has been shown to induce interleukin-1α (IL-1α) release from a preformed pool in mouse epidermis [6] and upregulation of tumour necrosis factor α (TNF-α and granulocyte–macrophage colony-stimulating factor (GM-CSF). There is then a rise in Langerhans' cell-derived IL-1α stimulated by GM-CSF and IL-1α production. Concurrently, the loss of the normal extracellular calcium gradient stimulates lamellar body secretion and barrier repair [7]. Oxidative stress also contributes to the development of inflammation with various irritants [8].

Detergents at lower levels of exposure predominantly affect the horny layer, causing dryness and scaling by destroying lysosomal enzymes in the horny layer [9], whereas at higher concentrations they will dissolve cell membranes and damage lysosomes [10]. With repeated exposure, there will be signs of chronic inflammation, with increased DNA synthesis, acanthosis and changes in cellular metabolism.

Table 25.2 Factors influencing irritancy potential of substances on human skin.

Exogenous	Endogenous	Co-factors
Chemical characteristics	Individual susceptibility	Mechanical
Molecular structure	Atopy	Thermal
pH	Race/skin colour/phototype	Climatic
pK_a	Age	
Hydrophobicity (log *P*)	Hormonal	
Inherent toxicity	Barrier function	
Concentration/dose	Repair capacity	
Penetration characteristics	Eczema elsewhere	
Vehicle	Other skin diseases	
Solubility	Other unknown	
Duration of contact	Site of exposure	
Type of contact		

Detergents and other irritants such as croton oil and phenol esters are chemotactic for polymorphonuclear leukocytes at non-toxic concentrations [11], and may cause pustular reactions. Organic solvents such as methanol or chloroform will damage blood vessels, causing hyperaemia [12], and dimethyl sulphoxide (DMSO) is a very effective degranulator of mast cells [13].

Irritants affect everyone, although individual susceptibility with regard to the development of dermatitis varies greatly. The body's immune response is important in generating dermatitis, and this has been shown in the attenuated response to irritants in CD4-deficient mice [14].

References

1 Lisby S, Baadsgaard O. Mechanisms of irritant contact dermatitis. In: Frosch PJ, Menné T, Lepoittevin J-P. *Contact Dermatitis,* 4th edn. Berlin: Springer, 2006: 69–82.

2 Barratt MD. Quantitative structure–activity relationships for skin irritation and corrosivity of neutral and electrophilic organic chemicals. *Toxicol Vitro* 1996; **10**: 247–56.

3 Nangia A, Andersen PH, Berner B, Maibach HI. High dissociation constants (pK_a) of basic permeants are associated with *in vivo* skin irritation in man. *Contact Dermatitis* 1996; **34**: 237–42.

4 Aramaki J, Loffler C, Kawana S *et al.* Irritant patch testing with sodium lauryl sulphate: interrelation between concentration and exposure time. *Br J Dermatol* 2001; **145**: 704–8.

5 Grangsjo A, Leijon-Kuligowski A, Torma H *et al.* Different pathways in irritant contact eczema? Early differences in the epidermal elemental content and expression of cytokines after application of 2 different irritants. *Contact Dermatitis* 1996; **35**: 355–60.

6 Wood LC, Elias PM, Calhoun C *et al.* Barrier disruption stimulates interleukin-1 alpha expression and release from a preformed pool in murine epidermis. *J Invest Dermatol* 1996; **106**: 397–403.

7 Elias PM, LaDonna C, Feingold KR. Epidermal pathogenesis of inflammatory dermatoses. *Am J Contact Dermatitis* 1999; **10**: 119–26.

8 Willis CM, Reiche L, Wilkinson JD. Immunocytochemical demonstration of reduced Cu,Zn-superoxide dismutase levels following topical application of dithranol and sodium lauryl sulphate: an indication of the role of oxidative stress in acute irritant dermatitis. *Eur J Dermatol* 1998; **8**: 8–12.

9 Prottey C, Oliver D, Coxon AC. Prediction and measurement of surfactant action upon human skin under realistic conditions. *Int J Cosmet Sci* 1984; **6**: 263–73.

10 Fulmer AW, Kramer GJ. Stratum corneum lipid abnormalities in surfactant induced dry scaly skin. *J Invest Dermatol* 1986; **86**: 598–602.

11 Frosch P, Czarnetzki BM. Surfactants cause *in vitro* chemotaxis and chemokinesis of human neutrophils. *J Invest Dermatol* 1987; **88**: 52s–55s.

12 Steele RH, Wilhelm DL. The inflammatory reaction in chemical injury, 3: leucocytosis and other histological changes induced by superficial injury. *Br J Exp Pathol* 1970; **51**: 265–79.

13 Sjogren F, Anderson C. The spectrum of inflammatory cell response to dimethyl sulfoxide. *Contact Dermatitis* 2000; **42**: 216–21.

14 Kondo S, Beissert S, Wang B *et al.* Hyporesponsiveness in contact hypersensitivity and irritant contact dermatitis in CD4 gene targeted mouse. *J Invest Dermatol* 1997; **108**: 811–12.

Pathology

Whereas allergic contact dermatitis reactions are histologically almost always eczematous and rather monomorphic, those elicited by irritants show much greater pleomorphism. Histological changes vary according to the chemical nature and concentration of the irritant, the type and duration of exposure, the severity of the response and the time of sampling. Some irritant reactions may be histologically indistinguishable from allergic contact

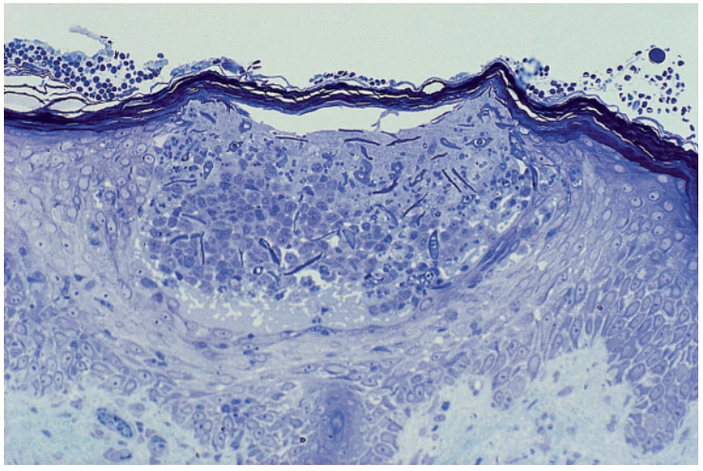


Fig. 25.1 Pustular reaction induced by 48-h patch testing with croton oil (0.08%). Toluidine blue stained, 1-μm resin section; original magnification ×200. (Courtesy of J.D. Wilkinson and C.M. Willis, Amersham General Hospital, Amersham, UK.)

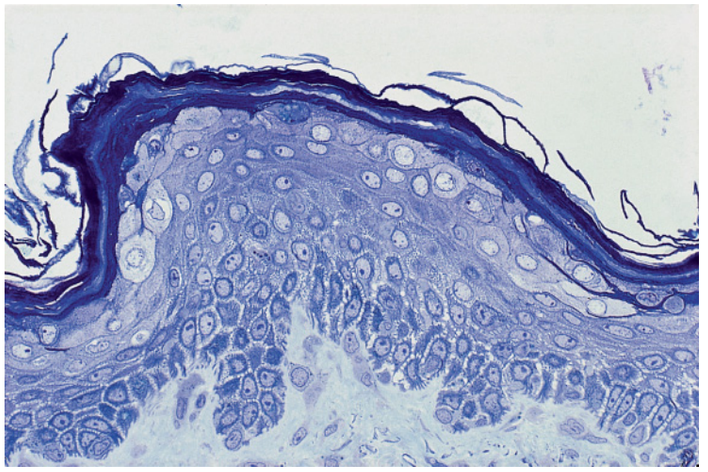


Fig. 25.3 Hydropic swelling of keratinocytes within the upper epidermis following 48-h patch testing with dithranol (0.02%). Toluidine blue stained, 1-μm resin section; original magnification ×400. (Courtesy of J.D. Wilkinson and C.M. Willis, Amersham General Hospital, Amersham, UK.)

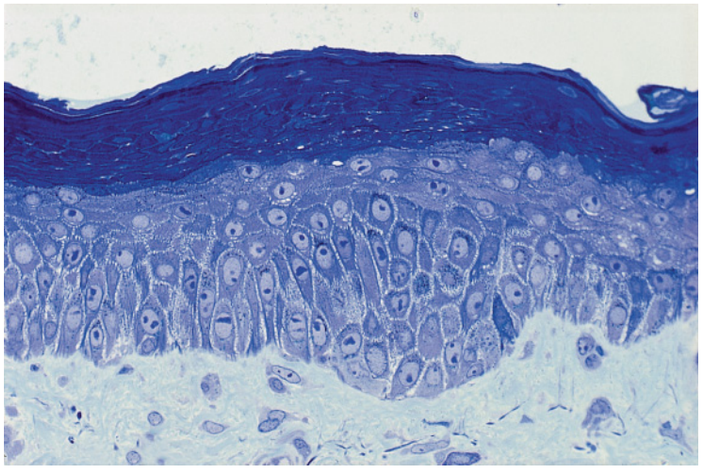


Fig. 25.2 Deeply stained parakeratotic layer induced in the epidermis by 48-h patch testing with sodium lauryl sulphate (5%). Such an appearance is characteristic of this irritant, and is probably related to increased epidermal cell division. Toluidine blue stained, 1-μm resin section; original magnification ×400. (Courtesy of J.D. Wilkinson and C.M. Willis, Amersham General Hospital, Amersham, UK.)

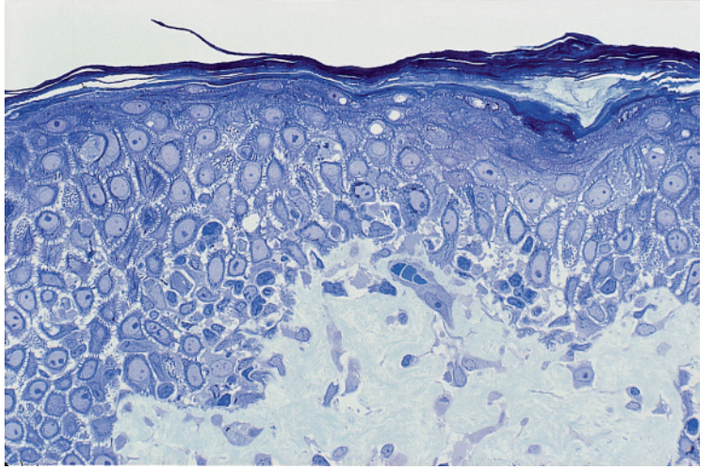


Fig. 25.4 Forty-eight-hour patch-test reaction to benzalkonium chloride (0.5%), exhibiting similar histopathological features (i.e. spongiosis and exocytosis) to those of allergic contact dermatitis. Toluidine blue stained, 1-μm resin section; original magnification ×400. (Courtesy of J.D. Wilkinson and C.M. Willis, Amersham General Hospital, Amersham, UK.)

dermatitis, whereas others may possess morphological features characteristic of a certain type of chemical. More than one pattern of response may be induced by the same irritant.

Histology

Mild-to-moderate acute reactions to most irritants are characterized by predominantly superficial epidermal changes with spongiosis, intracytoplasmic vacuolation and nuclear pyknosis. In general, spongiosis is less marked than that seen in allergic contact dermatitis, although more highly vesicular changes may be induced by such irritants as croton oil. With more severe irritation, necrolysis or cytolysis of epidermal cells occurs, leading to intra- or subepidermal vesicles and bullae. Such changes are seen particularly with cantharidin and trichloroethylene. A neutrophilic infiltrate may result in the formation of subcorneal or intraepidermal pustules. With some chemicals this change may be limited to the follicles, resulting in the follicular pustules typically seen as an irritant reaction when patch testing with metal salts. Parakeratosis is a common feature of acute reactions to one of the most widely studied irritants, sodium lauryl sulphate (SLS), possibly arising from enhanced keratinocyte proliferation [1] (Figs 25.1–25.4).

Electron microscopy has provided additional information on the nature of the cellular damage following acute exposure to various irritants. In the stratum corneum irritants may variably impair synthesis of new lipids, as is the case with sodium lauryl

sulphate, or disrupt the existing lamellar structure (acetone and water). Ultrastructural changes are irritant-dependent, but in general indicate autolysis or cytolysis of epidermal keratinocytes. Changes include condensation of chromatin and cytoplasm, tonofilament clumping and loss of membrane-bound cell fragments [2].

Chronic or cumulative irritant contact dermatitis differs from acute reactions in that the histological picture is predominantly one of hyperkeratosis with areas of parakeratosis, moderate-to-marked acanthosis and elongation of rete ridges.

The role of Langerhans' (CD1a+) cells in the induction and elicitation of allergic contact dermatitis is well established, but it remains unclear whether these cells also actively respond to irritants. Studies of acute irritant contact dermatitis have demonstrated histological changes in Langerhans' cells, ranging from signs of cytotoxicity, such as reduced dendrite length, condensed nuclear chromatin and loss of integrity of organelles and membranes, to indications of cellular activation, including widened rough endoplasmic reticulum and increased numbers of Birbeck granules. Some indication that Langerhans' cells may have functional significance in irritant contact dermatitis has emerged in that increased numbers of Langerhans' cells can be detected in regional lymph nodes, concomitant with increased lymph-cell antigen-presenting capacity [3]. It seems probable that they are involved in the provision of accessory signals in the sensitization process should the individual be co-exposed to an allergen.

Disruption and/or degeneration of collagen is commonly seen in irritant reactions together with oedema. A number of irritants induce more specific changes in dermal cells, examples being DMSO, which acts as an effective mast cell degranulator, and organic solvents, which affect principally the vasculature, leading to capillary dilatation and hyperaemia.

Quantitatively and, to a limited extent, qualitatively, the cellular response to irritant-induced skin damage is dependent upon the nature and concentration of the irritant, the severity of the reaction, the time of sampling and the species under investigation. In mild-to-moderate reactions, the infiltrating cells are predominantly mononuclear, consisting mainly of helper-inducer T lymphocytes (CD4+) with an accompanying admixture of suppressor/cytotoxic T cells (CD8+), macrophages and CD1a+ cells. B cells, natural killer (NK) cells and follicular dendritic cells are absent or rare [4]. The majority of infiltrating inflammatory cells express human leukocyte antigen (HLA)-DR, with significant numbers of T lymphocytes also expressing the receptor for IL-2 (CD25).

Polymorphonuclear leukocytes, which play a significant role in guinea-pig responses, are generally only seen in substantial numbers in human reactions where there is severe epidermal damage with necrosis and the formation of subcorneal and intraepidermal bullae, or where infection has occurred. Follicular pustules tend to develop, particularly in individuals with atopy, following exposure to such irritants as croton oil and metal salts. However, the presence of follicular spongiosis is said to be more typical of an allergic contact dermatitis [5].

Immunopathology

Identification of the inflammatory mediators involved in irritant contact dermatitis is valuable both as a possible means to distinguish irritant from allergic reactions and as an indicator of potential therapeutic avenues. Substances derived from arachidonic acid, in particular leukotrienes and prostaglandins, are present in the reactions to at least some irritants [6], in particular elevated levels of prostaglandins E_1 and E_2, as well as 12-hydroxyeicosatetraenoic acid (12-HETE). The pattern of release is determined by the nature of the irritant [7]. Elevation of prostaglandins and leukotriene-B4 correlate with the degree of inflammation, which is not the case for IL-1α.

Cytokines are hormone-like, secreted proteins that regulate the growth and differentiation of many cells, including those of the immune system. Keratinocytes produce a number of these cytokines and play an active role in the inflammatory process. Among the pro-inflammatory cytokines that have been found to be released from epidermal cells following exposure to some irritants are TNF-α, IL-1, IL-6 and IL-8 [8]. GM-CSF and T-cell-derived cytokines, including IL-2 and interferon-γ (IFN-γ), have also been observed subsequent to irritant application or tape stripping. Cytokines exhibiting anti-inflammatory characteristics, such as IL-10, are likely to play an important role in the regulation of irritant reactions, but have, as yet, only been studied in the tape-stripping model of barrier function impairment [9].

Keratinocyte involvement in irritant contact dermatitis is not confined to the production and release of cytokines, but extends to the up-regulation and expression of immune-associated adhesion molecules, both in response to cytokine release and as a result of direct irritant induction. These molecules include intercellular adhesion molecule 1 (ICAM-1), which acts as ligand for the leukocyte function-associated antigen 1 (LFA-1) constitutively expressed by leukocytes [10], and certain integrins that are involved in a variety of cell–cell and cell–matrix adhesion interactions [11]. Expression of the class II major histocompatibility complex (MHC) molecule HLA-DR by keratinocytes has been described, but appears not to be a predominant feature of the majority of irritant reactions.

Activation of protein kinase C-mediated events, leading to cell proliferation and differentiation, has been shown [12,13].

References

1 Lachapelle J-M, Marot L. Histopathological and immunohistopathological features of irritant and allergic contact dermatitis. In: Frosch PJ, Menné T, Lepoittevin J-P, eds. *Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 107–116.

2 Willis CM. Ultrastructure of irritant and allergic contact dermatitis. In: Frosch PJ, Menné T, Lepoittevin J-P, eds. *Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 117–126.

3 Brand CU, Hunziker T, Limat A, Braathen LR. Large increase of Langerhans cells in human skin lymph derived from irritant contact dermatitis. *Br J Dermatol* 1993; **128**: 184–8.

4 Willis CM, Stephens CJM, Wilkinson JD. Differential patterns of epidermal leukocyte infiltration in patch test reactions to structurally unrelated chemical irritants. *J Invest Dermatol* 1993; **101**: 364–70.

5 Vestergaard L, Clemmensen OJ, Sorensen FB, Andersen KE. Histological distinction between early allergic and irritant patch test reactions: follicular spongiosis may be characteristic of early allergic contact dermatitis. *Contact Dermatitis* 1999; **41**: 207–10.

6 Reilly DM, Green MR. Eicosanoid and cytokine levels in acute skin irritation in response to tape stripping and capsaicin. *Acta Derm Venereol (Stockh)* 1999; **79**: 187–90.

7 Muller-Decker K, Heinzelmann T, Furstenberger G *et al*. Arachidonic acid metabolism in primary irritant dermatitis produced by patch testing of human skin with surfactants. *Toxicol Appl Pharmacol* 1998; **153**: 59–67.

8 Wilmer JL, Burleson PG, Kayama F *et al.* Cytokine induction in human epidermal keratinocytes exposed to contact irritants and its relation to chemical-induced inflammation in mouse skin. *J Invest Dermatol* 1994; **102**: 915–22.
9 Nickoloff BJ, Naidu Y. Perturbation of epidermal barrier function correlates with initiation of cytokine cascade in human skin. *J Am Acad Dermatol* 1994; **30**: 535–46.
10 Willis CM, Stephens CJM, Wilkinson JD. Selective expression of immune-associated surface antigens by keratinocytes in irritant contact dermatitis. *J Invest Dermatol* 1991; **96**: 505–11.
11 von der Driesch P, Kammerer U, Ponec M *et al.* Modulation of integrins on epidermal keratinocytes *in vivo* and on *in vitro* reconstructed epidermis. In: Elsner P, Maibach HI, eds. *Current Problems in Dermatology*, Vol. 23*: Irritant Dermatitis: New Clinical and Experimental Aspects*. Basel: Karger, 1995: 114–20.
12 Li LF, Fiedler VC, Kumar R. Down-regulation of protein kinase C isoforms in irritant contact dermatitis. *Contact Dermatitis* 1998; **38**: 319–24.
13 Le TK, Schalkwijk J, van de Kerkhof PC *et al.* A histological and immunohistochemical study on chronic irritant contact dermatitis. *Am J Contact Dermatitis* 1998; **9**: 23–8.

Differentiation from allergic contact dermatitis

With some irritants, the histopathological changes are obvious and sometimes even characteristic, whereas with others the epidermal and dermal appearances are indistinguishable from allergic contact dermatitis. In general, however, spongiosis is more marked in allergic reactions, whereas epidermal necrosis, acantholysis and pustulation are normally seen only with irritants.

Despite considerable effort, immunocytochemical analysis of the cellular infiltrate has so far failed to reveal any significant differential diagnostic features [1]. The problem is compounded by the fact that many allergens are also potentially irritant. Avnstorp *et al*. [2] found a histological diagnostic specificity of 87% and sensitivity of 81% for allergic reactions, with 100% specificity and 46% sensitivity for irritant reactions.

Early studies in man showed little evidence of differential cytokine release between allergic and irritant contact dermatitis, suggesting that, although their initiating events vary fundamentally, the cascade mechanisms responsible for the induction and release of regulatory mediators are similar [3,4]. Subsequently, quantitative differences have become apparent, with absent production of IL-4 in irritant compared with allergic dermatitis [5].

In mice, the chemokine IP-10, along with IL-1, was shown to be induced in allergic but not irritant contact dermatitis [6]. Subsequently, expression of IP-10 in man has been shown to mimic this pattern within the first 3 days, using sodium lauryl sulphate (SLS) as the irritant. IP-9, IP-10 and monokine induced by interferon γ (Mig) are all induced by IFN-γ and interact with the CXCR3 receptor that is almost exclusively expressed on activated T cells. Examination of the cellular infiltrate revealed that 50% of the T cells expressed CXCR3 in allergic compared with 30% in irritant contact dermatitis [7]. It was assumed that the differences reflected the presence of IFN-γ, which also mediates keratinocyte expression of ICAM-1 and HLA-DR. Other qualitative differences were noted, including increased expression of IL-8 in irritant contact dermatitis, which attracts neutrophils by binding to either CXCR1 or CXCR2 expressed on neutrophils.

Protective mechanisms have been shown to be important in preventing sensitization when the irritant is also an allergen, specifically, glutathione and related thiols detoxify exogenous electrophilic compounds such as dinitrochlorobenzene [8].

References
1 Lachapelle J-M, Marot L. Histopathological and immunohistopathological features of irritant and allergic contact dermatitis. In: Frosch PJ, Menné T, Lepoittevin J-P, eds. *Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 107–16.
2 Avnstorp C, Balslev E, Thomsen HK. The occurrence of different morphological parameters in allergic and irritant patch test reactions. In: Frosch PJ, Dooms-Goossens A, Lachapelle JM *et al*., eds. *Current Topics in Contact Dermatitis*. Berlin: Springer, 1989: 38–41.
3 Hoefakker S, Caubo M, Van't Erve EH *et al*. In vivo cytokine profiles in allergic and irritant contact dermatitis. *Contact Dermatitis* 1995; **33**: 258–66.
4 Ulfgren AK, Klareskog L, Lindberg M. An immunohistochemical analysis of cytokine expression in allergic and irritant contact dermatitis. *Acta Derm Venereol (Stockh)* 2000; **80**: 167–70.
5 Morhenn VB, Chang EY, Rheins LA. A noninvasive method for quantifying and distinguishing inflammatory skin reactions. *J Am Acad Dermatol* 1999; **41**: 687–92.
6 Enk AH, Katz SI. Early molecular events in the induction phase of contact sensitivity. *Proc Natl Acad Sci USA* 1992; **89**: 1398–42.
7 Flier J, Boorsma DM, Bruynzeel DP *et al*. The CXCR3 activating chemokines IP-10, Mig, and IP-9 are expressed in allergic but not in irritant patch test reactions. *J Invest Dermatol* 1999; **113**: 574–8.
8 Hirai A, Minamiyama Y, Hamada T *et al.* Glutathione metabolism in mice is enhanced more with hapten-induced allergic contact dermatitis than with irritant contact dermatitis. *J Invest Dermatol* 1997; **109**: 314–18.

Predisposing factors (Table 25.2)

Individual

Age, skin colour, race, phenotype and presence of eczema elsewhere may all affect the skin's response to marginal irritants. There is also significant individual variation in the patch test result with the same irritant on retesting [1,2]. It is particularly important, therefore, when using techniques such as SLS exposure tests [3] or tape stripping [4] to measure individual susceptibility, that the method is standardized.

Genetic/ racial background. Twin studies suggest that genetic factors independent of atopy may influence susceptibility to irritants and the development of hand eczema [5]. A TNF-α gene polymorphism has been demonstrated as a marker for susceptibility to irritant contact dermatitis [6].

A high baseline transepidermal water loss (TEWL) value points to an increased susceptibility to irritants in short-term exposure models [7], but in practice a correlation between baseline TEWL and the risk of developing subsequent hand dermatitis has not been proven [8]. Traditionally, Afro-Caribbean, Asian or Hispanic skin was thought to be more resistant than that of Celtic origin, but some studies measuring TEWL after SLS exposure have cast doubt on this. Although statistical differences can be shown between populations, dose–response relationships are similar [9].

Age. Although the skin of the very young is usually regarded as being more vulnerable, there is very little evidence to substantiate this, except perhaps in the neonate or premature infant. It is thought that the stratum corneum is not functionally mature until about 32 weeks' gestation, and that it may take up to 4 weeks for the barrier to develop irrespective of the gestational age prior to this [10].

Older individuals react less strongly to some irritants. There is often a reduced inflammatory response and TEWL is reduced, which may represent a reduced potential for percutaneous penetration. This is true of repeated irritation as well as a single insult. Onset of the reaction and subsequent recovery are also delayed [11]. *In vitro*, keratinocytes from older individuals demonstrate comparatively reduced secretion of IL-1 in response to SLS and, in an elderly age group, higher secretion in photo-aged skin than in intrinsically aged skin [12].

Sex. Women more frequently report skin disease than men, and epidemiological studies of hand eczema show that they are more often affected. This is particularly true of the younger age group, where many female-dominated occupations involve exposure to wet work. They do not appear to be any more susceptible to skin irritation than men, and these differences presumably relate to differences in exposure between the sexes [13]. Female skin, however, may be more reactive in the premenstrual phase of the cycle [14]. In a large group of individuals, use of the 4-h patch test has shown men to be more sensitive than women [1].

Neurological factors. Experimentally, sleep deprivation and the stress of an interview, but not exercise, resulted in delayed barrier recovery following tape stripping. Simultaneous increases in plasma cortisol, noradrenaline, IL-1α, IL-10, TNF-α and NK cell number and activity were measured. Cytokine responses to the interview stress were inversely correlated with barrier function recovery [15].

Site. The effect of irritant contact varies from region to region on the body. This partially reflects differences in thickness or type of stratum corneum and subsequent rate of chemical penetration [16]. Other factors might include the density of transepidermal shunts (hair follicles, sweat ducts), as well as potential for occlusion by body folds.

The skin of the face, scrotum and back of the hands is more permeable than skin elsewhere [17], and therefore more vulnerable to the effects of irritants and, in the case of exposed skin, more prone to chapping. The skin of the palms and soles is, in comparison, so thick that it is almost impermeable to everything except water and caustic substances. In addition, there are probably inherent differences in keratinization and in composition of the intercellular lipids [18] that may account for some of the site differences and also for some of the changes in barrier function following damage to the skin or associated with abnormal keratinization [19].

Fat-soluble chemicals can be absorbed through the sebaceous glands and epithelium of the follicular root sheath, and may cause both allergic and non-specific inflammation in the deeper parts of the skin, even when there is an undamaged horny layer. In general, however, except for ions and large polar molecules, the appendageal route is an insignificant one so far as the penetration of most irritants and allergens is concerned [20].

As a consequence of the above factors, the intensity of an irritant response varies according to body site with, for example, the strongest reactions to DMSO occurring on the face and upper back, and the weakest reactions on distal parts of the limbs. Barrier recovery also varies according to body site, with the face and back healing most rapidly [21].

Skin disease and atopy. Percutaneous absorption is facilitated by inflammatory changes in the epidermis. Tape stripping of the skin and exposure to irritants can significantly reduce barrier function and it may take up to 2 or more weeks for barrier function to be restored completely [22]. The presence of eczema or recently healed disease may therefore predispose to further dermatitis.

Atopic individuals, particularly those with atopic dermatitis or a past history of hand dermatitis, seem to have more easily irritated skins [23]. In a study using serial dilutions of SLS, individuals with active and healed atopic dermatitis and with respiratory atopy alone had a lower threshold for irritation than normal controls [24]. This was most severe in those with current skin disease. Other studies do not show this predisposition, which may reflect patient selection and complexity of the processes involved [25]. In an occupational setting, it has been estimated that 21.6% of skin disease can be attributed to this risk factor (95% confidence interval 19.4–23.7%) [26].

References

1 Robinson MK. Population differences in acute skin irritation responses: race, sex, age, sensitive skin and repeat subject comparisons. *Contact Dermatitis* 2002; **46**: 86–93.

2 Robinson MK. Intra-individual variations in acute and cumulative skin irritation responses. *Contact Dermatitis* 2001; **45**: 75–83.

3 Tupker RA, Willis C, Berardesca E *et al*. Guidelines on sodium lauryl sulphate (SLS) exposure tests. *Contact Dermatitis* 1997; **37**: 53–69.

4 Breternitz M, Flach M, Prassler *et al*. Acute barrier disruption by adhesive tapes is influenced by pressure, time and anatomical location: integrity and cohesion assessed by sequential tape stripping. A randomised, controlled study. *Br J Dermatol* 2007; **156**: 231–40.

5 Bryld LE, Hindsberger C, Kyvik KO *et al*. Risk factors influencing the development of hand eczema in a population-based twin sample. *Br J Dermatol* 2003; **149**: 1214–20.

6 Allen MH, Wakelin SH, Holloway D *et al*. Association of TNFA gene polymorphism at position-308 with susceptibility to irritant contact dermatitis. *Immunogenetics* 2000; **51**: 201–5.

7 Tupker RA. Prediction of irritancy in the human skin irritancy model and occupational setting. *Contact Dermatitis* 2003; **49**: 61–9.

8 Schmid K, Broding HC, Uter W, Drexler H. Transepidermal water loss and incidence of hand dermatitis in a prospectively followed cohort of apprentice nurses. *Contact Dermatitis* 2005; **52**: 247–53.

9 Peters L, Marriott M, Mukerji B *et al*. The effect of population diversity on skin irritation. *Contact Dermatitis* 2006; **55**: 357–63.

10 Kali YN, Nonato LB, Lund CH, Guy RH. Development of skin barrier function in premature infants. *J Invest Dermatol* 1998; **111**: 320–6.

11 Schwindt DA, Wilhelm KP, Miller DL, Maibach HI. Cumulative irritation in older and younger skin: a comparison. *Acta Derm Venereol (Stockh)* 1998; **78**: 279–83.

12 Suh DH, Youn JI, Eun HC. Effect of 12-O-tetradecanoyl-phorbol-13-acetate and sodium lauryl sulfate on the production and expression of cytokines and proto-oncogenes in photoaged and intrinsically aged human keratinocytes. *J Invest Dermatol* 2001; **117**: 1225–33.

13 Meding B. Differences between the sexes with regard to work-related skin disease. *Contact Dermatitis* 2000; **43**: 65–71.

14 Agner T, Damm P, Skouby SO. Menstrual cycle and skin reactivity. *J Am Acad Dermatol* 1991; **24**: 566–70.

15 Altemus M, Rao B, Dhabhar FS *et al*. Stress-induced changes in skin barrier function in healthy women. *J Invest Dermatol* 2001; **117**: 309–17.

16 de Jongh CM, Jakasa I, Verberk MM, Kezic S. Variation in barrier impairment and inflammation of human skin as determined by sodium lauryl sulphate penetration rate. *Br J Dermatol* 2006; **154**: 651–7.

17 Feldmann RJ, Maibach HI. Regional variation in percutaneous penetration of ^{14}C cortisol in man. *J Invest Dermatol* 1967; **48**: 181–3.
18 Elias PM, Cooper ER, Korc A *et al.* Percutaneous transport in relation to stratum corneum structure and lipid composition. *J Invest Dermatol* 1981; **76**: 297–301.
19 Solomon AE, Lowe NJ. Percutaneous absorption in experimental epidermal disease. *Br J Dermatol* 1979; **100**: 717–22.
20 Dugard PH. Skin permeability theory in relation to measurements of percutaneous absorption in toxicology. *Adv Mod Toxicol* 1977; **4**: 525–50.
21 Fluhr JW, Dickel H, Kuss O *et al.* Impact of anatomical location on barrier recovery, surface pH and stratum corneum hydration after acute barrier disruption. *Br J Dermatol* 2002; **146**: 770–6.
22 Koopman DG, Kezic S, Verberk MM. Skin reaction and recovery: a repeated sodium lauryl sulphate patch test vs a 24-h patch test and tape stripping. *Br J Dermatol* 2004; **150**: 493–9.
23 Cork MJ, Robinson DA, Vasilopoulos Y *et al*. New perspectives on epidermal barrier dysfunction in atopic dermatitis: gene-environment interactions. *J Allergy Clin Immunol* 2006; **118**: 3–21.
24 Nassif A, Chan SC, Storrs FJ, Hanifin JM. Abnormal skin irritancy in atopic dermatitis and in atopy without dermatitis. *Arch Dermatol* 1994; **130**: 1402–7.
25 Gallacher G, Maibach HI. Is atopic dermatitis a predisposing factor for experimental acute irritant contact dermatitis? *Contact Dermatitis* 1998; **38**: 1–4.
26 Dickel H, Bruckner TM, Schmidt A, Diepgen TL. Impact of atopic skin diathesis on occupational skin disease incidence in a working population. *J Invest Dermatol* 2003; **121**: 37–40.

Environmental

Although toxic chemicals are the principal cause of irritant reactions, there are often significant contributory factors, including the potentiating effects of temperature, climate, occlusion and mechanical irritation.

Temperature. The development of irritant dermatitis is partially temperature-dependent. Higher temperature leads to a reduction in barrier function and increases the penetration of SLS detergent through the skin [1]. Exposure to hot detergent appears to be more irritant than cold [2]. There is also an influence of temperature on barrier recovery, with most rapid healing occurring at physiological temperatures and delayed recovery above 42°C or below 34°C [3].

Air flow. Wind empirically results in chapping of the skin. Experimentally, air flow alone did not affect TEWL, but in combination with exposure to SLS it enhanced the irritant effect of the chemical [4].

Low humidity. Low ambient humidity is the single most important factor with regard to the water content of the stratum corneum; a change to a low dew point can occur suddenly during winter, and can cause chapping even in normal persons. Experimentally, low humidity has been shown to stimulate epidermal DNA synthesis and amplify the proliferative response to barrier disruption [5]. Susceptibility to SLS irritation is greatest during the winter in the northern hemisphere [6] when stratum corneum hydration is reduced. Chapping, and atopic and hyperkeratotic forms of hand eczema, are often worse in temperate climates during the winter.

Low-humidity dermatosis has occurred in factories where the ambient humidity was too low [7]. Although the effects of temperature and humidity are to some degree interrelated, cold alone will reduce the water content and plasticity of the stratum corneum and lead to cracking. Simultaneous exposure to these and other factors may maintain a dermatosis or cause transition from simple chapping or low-humidity dermatoses to a more 'eczematous' dermatitis. In mice, epidermal IL-1 is constitutively expressed and released in greater amounts following tape stripping in a low humidity environment [8].

Occlusion. Occlusion promotes percutaneous absorption and may facilitate skin irritation and enhance the effect of irritants to which an individual has already been exposed [9]. Water is imbibed by the keratin, which swells, producing wrinkling, as is seen after prolonged immersion in water. Increasing the water content of the stratum corneum by occlusion can enhance percutaneous absorption of certain substances many times. It is of practical importance that rubber and plastic gloves, wristwatch straps, rings, waterproof adhesives, shoes, boots, clothes and the natural folds of the skin provide such occlusion.

References

1 Ohlenschlaeger J, Friberg J, Ramsing D, Agner T. Temperature dependency of skin susceptibility to water and detergents. *Acta Derm Venereol (Stockh)* 1996; **76**: 274–6.
2 Clarys P, Manou I, Barel AO. Influence of temperature on irritation in the hand/forearm immersion test. *Contact Dermatitis* 1997; **36**: 240–3.
3 Denda M, Sokabe T, Fukumi-Tominaga T, Tominaga M. Effects of skin surface temperature on epidermal permeability barrier homeostasis. *J Invest Dermatol* 2007; **127**: 654–9.
4 Fluhr JW, Praessler J, Akengin A *et al*. Air flow at different temperatures increases sodium lauryl sulphate-induced barrier disruption and irritation in vivo. *Br J Dermatol* 2005; **152**: 1228–34.
5 Denda M, Sato J, Tsuchiya T *et al*. Low humidity stimulates epidermal DNA synthesis and amplifies the hyperproliferative response to barrier disruption: implication for seasonal exacerbations of inflammatory dermatoses. *J Invest Dermatol* 1998; **111**: 873–8.
6 Agner T, Serup J. Seasonal variation in skin resistance to irritants. *Br J Dermatol* 1989; **121**: 323–8.
7 Rycroft RJG, Smith WDL. Low humidity occupational dermatoses. *Contact Dermatitis* 1980; **6**: 488–93.
8 Ashida Y, Ogo M, Denda M. Epidermal interleukin-1 alpha generation is amplified at low humidity. Implications for the pathogenesis of inflammatory dermatoses. *J Invest Dermatol* 2001; **144**: 238–43.
9 Van der Valk PGM, Maibach HI. Post-application occlusion substantially increases the irritant response of the skin to repeated short-term sodium lauryl sulfate (SLS) exposure. *Contact Dermatitis* 1989; **21**: 335–8.

Chemical and physical

Different groups of chemicals show significant differences in absorption and diffusion characteristics. Results obtained from hydrocortisone, for example, cannot be presumed to reflect the situation for water or other molecules [1].

The main barrier to water transport through the skin is attributed to stratum corneum lipids and to high molecular-weight proteins of the corneocyte [2]. The stratum corneum, having a predominantly lipid intercellular composition, is more susceptible to lipid-soluble irritants [3], and modifying factors in respect of barrier function may be quite different for hydrophilic and hydrophobic substances [4]. When the lipids of the stratum corneum are removed by solvents, water transport rates through the skin increase. Subsequent immersion in water for 2 min will remove as many of the water-soluble substances from the keratin layer as a 2-h immersion in water not preceded by defatting [5]. A detergent effects the combined removal of both lipids and water-holding

substances and thus predisposes to chapping and dermatitis. Combined exposure to both solvent and detergent has been shown to have an additive effect on inducing dermatitis [6].

Alkaline solutions have a deleterious action on the horny layer and promote percutaneous absorption. Cross-links in the keratin are broken, and water can penetrate into the fibrils and cause swelling of the horny layer. If reducing substances are present in alkaline solution the disulphide links are also broken, which leads to greater damage. However, change in pH was found not to influence irritancy of alkaline detergents between pH 7.4 and 10.8 [7].

Physical injury often plays a role in dermatitis; *in vivo* mechanical irritation has been shown experimentally to aggravate the irritant effect of SLS [8].

References

1 Barry BW. *Dermatological Formulations: Percutaneous Absorption*. New York: Marcel Dekker, 1983.
2 Friberg SE, Kayali I. Water evaporation rates from a model of stratum corneum lipids. *J Pharm Sci* 1989; **78**: 639–43.
3 Elias PM, Cooper ER, Korc A *et al.* Percutaneous transport in relation to stratum corneum structure and lipid composition. *J Invest Dermatol* 1981; **76**: 297–301.
4 Boman A, Wahlberg JE. Percutaneous absorption of 3 organic solvents in the guinea pig, 1: effects of physical and chemical injuries on the skin. *Contact Dermatitis* 1989; **21**: 36–45.
5 Fulmer AW, Kramer GJ. Stratum corneum lipid abnormalities in surfactant-induced dry scaly skin. *J Invest Dermatol* 1986; **86**: 598–602.
6 Wigger-Alberti W, Krebs A, Elsner P. Experimental irritant contact dermatitis due to cumulative epicutaneous exposure to sodium lauryl sulphate and toluene single and concurrent application. *Br J Dermatol* 2000; **143**: 551–6.
7 Park KS, Kim YS, Cho YH *et al.* Effects of alkalinity of household dishwashing liquids on hand skin. *Contact Dermatitis* 2001; **45**: 95–8.
8 Fluhr JW, Akengin A, Bornkessel A *et al.* Additive impairment of the barrier function by mechanical irritation, occlusion and sodium lauryl sulphate in vivo. *Br J Dermatol* 2005; **153**: 125–31.

Identifying irritants

The need to reduce the use of animals for irritant testing has increased the amount of research directed towards the development of *in vitro* tests. None of these can as yet replace human or animal testing entirely, but they do allow a staged process of toxicological evaluation. Initially, this involves a literature search, and a search for any unpublished toxicological data. To this can be added an assessment based on chemical structure. Subsequently, *in vitro* testing methods can be used to assess both corrosion and irritation, although finally animal/ human test methods may be needed to assess acute or cumulative irritant potential *in vivo* [1].

Traditionally, the rabbit Draize test was used to classify the irritant potential of chemicals. A 4-h semiocclusive treatment with undiluted chemical, followed by assessments of erythema and oedema for up to 72 h in three rabbits was used to separate substances into the following groups for regulatory purposes:

- Causes severe burns
- Causes burns
- Irritant
- Mild irritant
- Not classified

Set against this background various *in vitro* tests have been developed in an attempt to predict irritancy [2].

Corrosion. Several methods have been validated and accepted into international legislation. The rat skin transcutaneous electrical resistance test uses discs of rat epidermis to which the chemical is applied. A dye is then used to see if any increase in ionic permeability is due to destruction of the epidermis. Human skin models (EpiSkin™, EpiDerm™) use reconstructed *in vitro* skin equivalents to induce cell destruction that is then measured by staining with a vital dye—the dimethylthiazoldiphenyl tetrazolium bromide (MTT) assay. A further method assays the penetration of chemical through a collagen membrane (Corrositex™).

Irritation. *In vitro* tests for irritation are varied and none is yet sufficiently well validated for regulatory purposes. Lines of research being pursued include Prediskin™ (measuring cytotoxicity to *ex vivo* human skin cultures), the non-perfused pig ear model (measuring transepidermal water loss from the skin surface), and the *in vitro* mouse skin integrity function test (SIFT) which uses TEWL and electrical resistance as the end points. The currently most promising methods involve the use of EpiDerm™ and EpiSkin™. Chemical is applied for 15 min, followed by a 42-h recovery period before cytotoxicity measurement with an MTT assay. Chemicals are predicted as irritant if they reduce mean culture viability to <50% of untreated controls. A further method assays the release of the cytokine IL-1 from epidermal cells in the skin equivalent. Correlation with *in vivo* tests is not absolute and results should always be interpreted critically, as the epidermal barrier does not exist in cell culture models [3].

Phototoxicity. An essential requirement for phototoxicity is the absorption of light by the chemical. An initial screen therefore involves the measurement of the absorption spectrum of the suspect chemical. If this indicates the chemical may be photoreactive then the 3T3 NRU PT can be performed, which has been validated and accepted into legislation. This test compares the cytotoxicity of a chemical when tested with and without exposure to a non-cytotoxic dose of simulated solar light (UVA/visible spectrum). Mouse 3T3 fibroblasts are incubated with the chemical and the concentration-dependent reduction of the uptake of the vital dye Neutral Red is measured 24 h after treatment. Substances identified are likely to be phototoxic following systemic administration and distribution to the skin or following topical application. The test has been found to detect photoallergens in addition to irritants, and the use of further photobinding studies to human albumin may distinguish between the two. In general, photoallergy requires protein binding as a prelude to antigen presentation.

The use of ethical tests in human volunteers is likely to prove the way forward where testing *in vivo* is considered essential [4]. Strong irritants may cause dermatitis on first exposure, whereas weak irritants may be detected only by repeated application [5]. Internal standards are necessary to allow comparison with other established irritants [6].

Acute irritation. A protocol for human testing is the 4-h irritant patch test measured against standard internal controls [7]. Closed 48-h patch tests on the intact skin of eczema-prone subjects may be used as a simple screen of irritancy for products intended for

use on the skin. Assessment is often made visually, but barrier function tests and other bioengineering techniques [8] can be applied to increase sensitivity and reduce morbidity, as the differences in irritant potential may be detected earlier.

Chronic irritation. In practice, the results of acute irritation tests may not translate directly into how a product will perform in the marketplace. To overcome this, various use tests are employed to simulate or exaggerate how a product is used in reality, and to better inform how a product will perform when the public are exposed [4]. The control used is often an already marketed product that has an acceptable safety profile.

However, not all irritant reactions are erythematous or impair barrier function. The immediate-type, non-immunological, contact reactions, and immediate and delayed symptomatic contact reactions encountered when applying some substances to the skin, produce principally subjective responses, such as stinging and smarting, and require a different approach [9] such as the lactic acid stinging test.

People with symptomatic contact reactions often view themselves as having sensitive skin. Formulating products for use on sensitive skin is fraught with difficulties as no single definition exists. A variety of evaluations may need to be used to cover the variety of sensations described [10]:

- Stinging—sensation that occurs when alcohol is applied to a cut, following a pin-prick or insect bite.
- Itching—a desire to scratch.
- Tingle—a 'pins and needles' sensation.
- Prickle—sensation caused by movement of rough fabric over the skin.
- Burning—painful sensation caused by extremes of temperature or corrosive chemicals.
- Numbness—diffuse sensation produced during the on/off set of local anaesthetic.

Different chemicals may be used to assess an individual's sensitivity to particular sensations—lactic acid causes stinging, chloroform : methanol 20 : 80 burning, and histamine causes itching. In practice, sensitive skin panels are often used to compare a new formulation with a known product.

References

1 Robinson MK, Perkins MA. A strategy for skin irritation testing. *Am J Contact Dermatitis* 2002; **13**: 21–9.

2 Jones PA, Basketter DA. *In vitro* approaches to the assessment of skin irritation and phototoxicity of topically applied materials. In: Zhai H, Maibach HI, eds. *Dermatotoxicology*, 7th edn. Boca Raton, FL: CRC Taylor & Francis, 2008. In press.

3 Wilhelm KP, Bottjer B, Siegers CP. Quantitative assessment of primary skin irritants *in vitro* in a cytotoxicity model: comparison with *in vivo* human irritation tests. *Br J Dermatol* 2001; **145**: 709–15.

4 Cooper K, Marriott M, Peters L, Basketter DA. Stinging and irritating substances: their identification and assessment. In: Lóden M, Maibach HI, eds. *Dry Skin and Moisturisers*, 2nd edn. Boca Raton, FL: CRC Taylor & Francis, 2005: 501–14.

5 Kligman AM, Wooding WM. A method for the measurement and evaluation of irritants on human skin. *J Invest Dermatol* 1967; **49**: 78–94.

6 Basketter DA, Griffiths HA, Wang XM *et al.* Individual, ethnic and seasonal variability in irritant susceptibility of skin: the implications for a predictive human patch test. *Contact Dermatitis* 1996; **35**: 208–13.

7 Robinson MK, McFadden JP, Basketter DA. Validity and ethics of the human 4-h patch test as an alternative method to assess acute skin irritation potential. *Contact Dermatitis* 2001; **45**: 1–12.

8 Agner T, Serup J. Skin reactions to irritants assessed by non-invasive bioengineering methods. *Contact Dermatitis* 1989; **20**: 352–9.

9 Frosch PJ, Kligman AM. A method for appraising the stinging capacity of topically applied substances. *J Soc Cosmet Chem* 1977; **28**: 197–209.

10 Marriott M, Peters L, Cooper K, Basketter DA. Identification of a sensitive skin panel. In: Berardesca E, Fluhr J, Maibach HI, eds. *Sensitive Skin Syndrome*. Boca Raton, FL: CRC Taylor & Francis, 2006: 107–19.

Clinical features

Irritant contact reactions are inflammatory reactions of the skin to an external agent or agents in which, although inflammatory and immunological mediators may be activated, no antigen-specific reaction is involved.

Irritants produce a wide range of responses on the skin which are not necessarily eczematous. These may range from purely subjective sensations, such as stinging, smarting, burning, or sensations of dryness and tightness, through delayed stinging or transient urticarial reactions to more persistent irritant reactions or irritant contact dermatitis. Irritant contact dermatitis has a spectrum of clinical features, ranging from a little dryness, redness or chapping through various types of eczematous dermatitis to an acute caustic burn. Irritants may also penetrate skin via appendageal structures and cause folliculitis and other types of reaction (see Table 25.1).

The same chemical may cause different irritant reactions depending on concentration; DMSO, for instance, is able to induce both conventional irritant dermatitis and immediate, non-immunological, contact urticarial reactions. Reaction patterns vary between species, mast cells providing an important component of the cellular response in guinea pigs but being generally less evident in humans. The response may also vary according to site and mode of application, vehicle and between individuals.

Although the nature, concentration and duration of contact with the irritant chemical are of primary importance, mechanical, thermal, climatic and constitutional factors are important modifying and/or enhancing factors in many irritant responses (Table 25.2).

Chemical burns

A chemical burn (Fig. 25.5) results when there is irreversible cell damage, and necrosis occurs. There is usually rapid onset of painful erythema, often within minutes, at the site of exposure. This is followed by blistering and the development of necrotic ulcers. Weals may be seen as a result of toxic degranulation of mast cells. Symptoms coincide with the exposure, but with some chemicals, including phenols and weak hydrofluoric acid, the onset may be delayed [1,2]. With ethylene oxide gas, used to sterilize medical instruments, textiles and plastic materials, the chemical can remain on items for several days if not allowed to evaporate. The possibility of exposure may therefore not be obvious. Damage continues to occur until all of the agent has chemically reacted or has been neutralized as a result of treatment.

Burns are classified according to the depth of cutaneous involvement:

1 Superficial partial-thickness burns extend to the level of the dermal papillae. As the papillary blood vessels remain intact the



Fig. 25.5 Caustic 'burns' from wet cement. (Courtesy of J.D. Wilkinson and C.M. Willis, Amersham General Hospital, Amersham, UK.)

skin blanches on pressure and vasodilatation of the vessels results in the skin appearing shiny pink to red and wet as a result of capillary leakage. Blisters may be present, and sensation is preserved. The burn typically heals within 10–14 days without scarring.

2 Deep partial-thickness burns extend into the dermis but the appendages are spared. The burn appears white or pale pink and oedematous. Some sensation may be retained but often only that of deep pressure. Re-epithelialization begins from the residual adnexal structures, taking up to 6 weeks to occur, with scarring.

3 Full-thickness burns extend into the subcutaneous tissue. The burn appears brown/black or pale white, with a leathery eschar. Sensation is completely lost and healing occurs slowly from the margins. Healing occurs with scarring and a risk of contracture.

4 Fourth-degree burns extend into tendon, muscle, bone or joint.

Most acids (e.g. sulphuric, nitric, hydrochloric, chromic) coagulate skin proteins, and as a result form a barrier that impedes further penetration. Some acids can discolour (e.g. nitric acid turns the skin yellow). Ulceration of the skin and nasal passages 'chrome ulcers' used to occur, prior to modern safety precautions, in tanners, textile workers, smelters and electroplaters, due to corrosion by chromate fumes. Hydrofluoric acid [3] differs in that it causes a liquefactive necrosis, and penetration can continue for several days after exposure, even down to bone. Pain, which can last several days, is typical of burns due to hydrofluoric acid and other fluorides. It is related to the ability of the fluoride ion to bind calcium and disrupt neural function. If more than 1% of the body surface area is affected, systemic toxicity can develop.

Alkalis (e.g. sodium, calcium, potassium hydroxides; wet concrete [4]; sodium and potassium cyanides) degrade lipids, and saponification of the resulting fatty acids forms soaps which aid penetration deeper into the skin. As a consequence, damage is more severe than with most acids, and pain is also a feature. The dead skin turns brown and later black, usually without blistering, and forms a hard eschar.



Fig. 25.6 Acute irritant contact dermatitis following immersion in concentrated bleach. (Courtesy of A. Yung, Leeds General Infirmary, Leeds, UK.)

Phenols [5] and unhardened phenolic resins penetrate the skin easily and rarely can cause nerve damage in the absence of visible skin change. Vasoconstriction may contribute to the necrosis that develops, and in the case of systemic absorption can lead to shock and renal damage.

References

1 Bruze M, Fregert S, Gruvberger B. Chemical skin burns. In: Kanerva L, Elsner P, Wahlberg JE, Maibach HI, eds. *Handbook of Occupational Dermatology*. Berlin: Springer, 2000: 325–32.

2 Pruitt VM. Work-related burns. *Clin Occup Environ Med* 2006; **5**: 423–33.

3 Kirkpatrick JJ, Enion DS, Burd DA. Hydrofluoric acid burns: a review. *Burns* 1995; **21**: 483–93.

4 Spoo J, Elsner P. Cement burns: a review 1960–2000. *Contact Dermatitis* 2001; **45**: 68–71.

5 Horch R, Spilker G, Stark GB. Phenol burns and intoxications. *Burns* 1994; **20**: 45–50.

Irritant contact dermatitis

The clinical appearance of irritant dermatitis (eczema) is essentially no different from that due to other causes: allergic or endogenous. Diagnosis therefore is essentially clinical after exclusion of contact allergy.

Acute irritant contact dermatitis

Acute irritant contact dermatitis is often the result of a single overwhelming exposure to an irritant or caustic chemical (Fig. 25.6), or a series of brief chemical or physical contacts. This results in acute inflammation of the skin, and is usually associated with an immediate sensation of burning or stinging. Differentiation

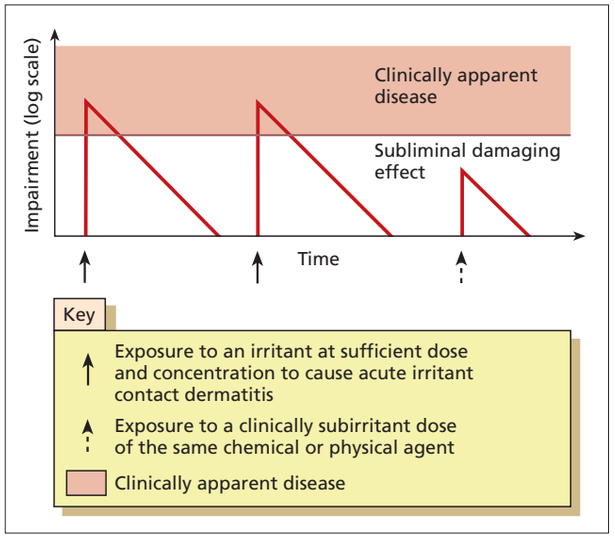


Fig. 25.7 Acute irritant contact dermatitis. The damaging effects on the skin of acute (non-cumulative) exposure to irritants. (From Malten [2].)

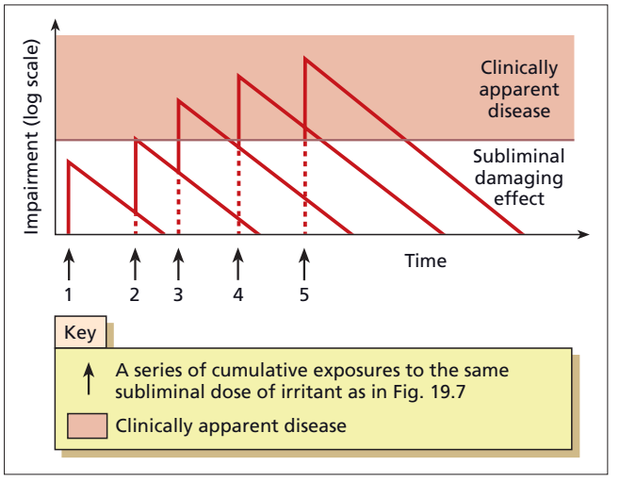


Fig. 25.8 Cumulative irritant contact dermatitis. The damaging effect on the skin of cumulative doses of a subliminal irritant. (From Malten [2].)

between an acute (toxic) contact dermatitis and a primary chemical burn is not always possible. The initial reaction is usually strictly limited to the site of application or contact, the concentration of the substance diffusing outside the area of contact almost immediately falling below the critical threshold necessary to provoke a reaction.

Irritant effects may be considerably enhanced by occlusion, and care must always be taken to ensure that irritants do not penetrate gloves or protective clothing. Most cases of acute irritant dermatitis occur as a result of accidents at work. Some substances—for example, gentian violet and dequalinium chloride—are toxic only under certain conditions, such as under occlusion, on mucosal surfaces or when the stratum corneum barrier is breached.

The rapidity of an acute irritant response usually makes the cause obvious, especially with strong alkalis or acids, which will produce a toxic reaction within a few minutes. The duration of application necessary to provoke a reaction with less potent irritants will vary considerably. The clinical spectrum of acute irritant dermatitis may range from a mild irritant reaction with transient erythema or chapping to a much more florid dermatitis with oedema, inflammation, pain and vesiculation. In more severe cases there may be exudation, bullae formation and tissue necrosis indistinguishable from a chemical burn. Caustic burns from lime or cement may cause extensive tissue damage. In patients with accidental or sporadic exposure, the dermatitis usually heals quickly, unless there is skin necrosis. In mild cases, the skin may revert to normal within a few days, but in more severe cases several weeks may be required for complete resolution.

Delayed irritancy

Delayed irritancy—or, rather, a delayed time course of irritation—has been reported in respect of several substances, including SLS, propylene glycol and certain diacrylates. This may sometimes cause problems in the interpretation of patch-test reactions because the inflammatory response occurs late (at 48 h), and may therefore simulate an allergic contact reaction.

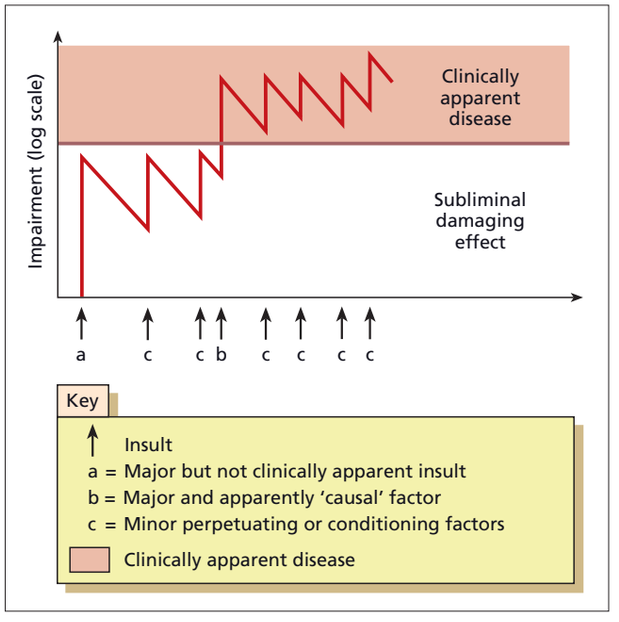


Fig. 25.9 Cumulative irritant contact dermatitis—mixed causation. (From Malten [2].)

Cumulative irritant contact dermatitis [2]

Synonyms
- Chronic irritant dermatitis
- 'Wear and tear dermatitis'
- Traumiterative dermatitis



Fig. 25.10 Dry palmar or 'extended fingertip' dermatitis. Often associated with wet work. (Courtesy of J.D. Wilkinson and C.M. Willis, Amersham General Hospital, Amersham, UK.)



Fig. 25.12 Facial (eyelid) dermatitis from a volatile irritant. (Courtesy of J.D. Wilkinson and C.M. Willis, Amersham General Hospital, Amersham, UK.)



Fig. 25.11 An irritant pattern of 'finger web' eczema. (Courtesy of J.D. Wilkinson and C.M. Willis, Amersham General Hospital, Amersham, UK.)

This type of dermatitis develops as a result of a series of repeated and damaging insults to the skin. These insults may include both chemical irritants and a variety of harmful physical factors, such as friction, microtrauma, low humidity, the desiccant effects of powder, soil or water and temperature.

Once the stratum corneum barrier has been breached, a great number of normally innocuous substances can perpetuate an irritant contact dermatitis. Scratching, rubbing and even topical treatment may on occasion become causes of persistence. Chronic irritant dermatitis may therefore be due to the summation of various adverse factors, many of which would not in themselves be strong enough to cause irritant dermatitis but which, taken together, are enough to weaken the skin and lead to the development of cumulative irritant contact dermatitis. These minor irritants may also act as perpetuating factors once the dermatitis has become established. Among this great variety of causative factors, there may be some that are overlooked by the patient because they do not appear to be related to the onset of the dermatitis (Figs 25.7–25.9).

Cumulative irritant dermatitis most commonly affects thin or exposed skin—for example, the dorsa of the hands, fingertips and the webs of the fingers (Figs 25.10 & 25.11), or the face and eyelids in those with cosmetic intolerance or low-humidity dermatosis. The face, eyes and upper respiratory tract are often affected by volatile types of irritant (Fig. 25.12) especially in those exposed industrially.

Irritant contact dermatitis often begins with a few localized patches of dry, slightly inflamed or chapped skin (Figs 25.13 & 25.14), and the tendency to disseminate is normally less than with constitutional or contact allergic forms of eczema. Irritant contact dermatitis tends to be more static and monomorphic than other forms of eczema, but constitutional and allergic factors frequently coexist (Figs 25.15 & 25.16).

Occupations with a high incidence of cumulative insult dermatitis are listed in Table 25.3 (see also Chapter 27). Most workers, however, even those working in high-risk occupations, usually develop only minor degrees of dermatitis, and constitutional factors are therefore probably important in those who develop more severe forms of dermatitis. Nearly 80% of those with chronic disability dermatitis have been found to be atopic. Other factors are also important, such as additional exposure to irritants at home or in the pursuit of hobbies, for example car maintenance or gardening, accidental exposure to strong caustics or irritants, adverse climatic and environmental conditions, lack of attention to industrial hygiene and poor working technique. Excessive use of abrasive or solvent cleansers may be more damaging to the skin than some of the substances that they are designed to remove. Common irritants are listed in Table 25.4.



Fig. 25.13 Dry irritant reaction. (Courtesy of J.D. Wilkinson and C.M. Willis, Amersham General Hospital, Amersham, UK.)



Fig. 25.14 Erythematous irritant reaction. (Courtesy of J.D. Wilkinson and C.M. Willis, Amersham General Hospital, Amersham, UK.)

Table 25.3 Occupations associated with irritant contact dermatitis.

Hairdressing
Medical, dental, veterinary
Cleaning
Agriculture, horticulture, forestry
Food preparation and catering
Printing and painting
Metal work
Mechanical engineering
Construction
Fishing



Fig. 25.15 A patchy 'discoid' eczema affecting the back of the hand in a hairdresser. Irritant, constitutional and allergic factors frequently coexist. (Courtesy of J.D. Wilkinson and C.M. Willis, Amersham General Hospital, Amersham, UK.)

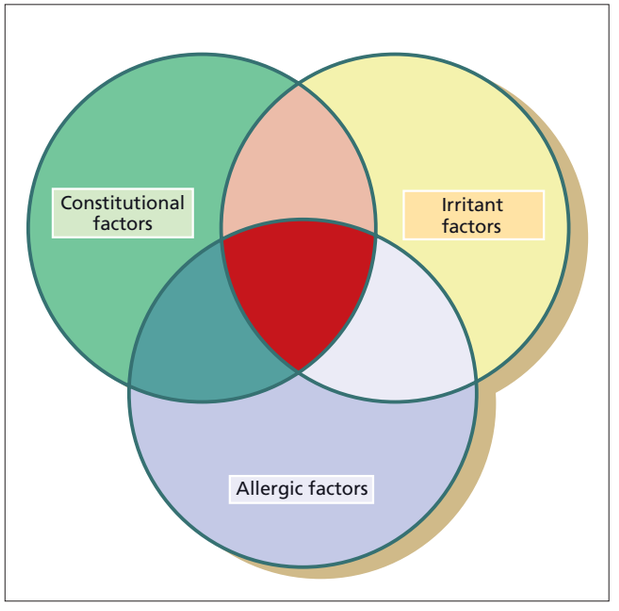


Fig. 25.16 A multifactorial view of dermatitis.

Table 25.4 Common irritants.

Water and wet work: sweating under occlusion
Household cleaners: detergent, soap, shampoo, disinfectant
Industrial cleaning agents: including solvents and abrasives
Alkalis, including cement
Acids
Cutting oils
Organic solvents
Oxidizing agents, including sodium hypochlorite
Reducing agents, including phenols, hydrazine, aldehydes, thiophosphates
Certain plants, e.g. spurge, Boracinaceae, Ranunculaceae
Pesticides
Raw food, animal enzymes and secretions
Desiccant powders, dust, soil
Miscellaneous chemicals

References

1 Frosch PJ, John SM. Clinical aspects of irritant contact dermatitis. In: Frosch PJ, Menné TM, Lepoittevin JP, eds. *Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 255–94.

2 Malten KE. Thoughts on irritant contact dermatitis. *Contact Dermatitis* 1981; **7**: 238–48.

Hand dermatitis

The pathogenesis of hand eczema is often complex. Constitutional, irritant and allergic factors frequently coexist. Although hand eczema is more common in women [1], this seems to be the result of increased irritant exposure rather than an inherent susceptibility [2]. Allergy can never be completely excluded, nor is any pattern of hand dermatitis pathognomonic for a single causation. In spite of this, there are certain types of hand dermatitis that are at least suggestive of irritant contact dermatitis. These include a patchy 'housewife'-type eczema affecting principally the dorsa, sides and webs of the fingers, or a 'ring' eczema—both are patterns associated with wet work and exposure to detergent. What may start as dryness can develop into patchy or diffuse erythema with scaling, fissuring and even vesiculation.

However, vesicles are less commonly seen in irritant than allergic or constitutional eczema, and the principal clinical features are usually dryness or chapping. The wrists and distal arms may also be affected. With increased mechanization in the house and more widespread use of protective gloves and hand creams, this pattern of hand eczema is less common than in the past.

Another common pattern of irritant hand eczema is the 'apron' or extended fingertip eczema, with dryness, redness and fissuring affecting principally the palmar aspects of fingers and distal palm. This pattern of dermatitis commonly occurs in those who frequently hold wet cloths containing detergent or household chemicals in the unprotected hand. Friction, irritants and repetitive wetting/desiccation all play a part. A similar pattern may be seen in occupations where employees are repeatedly exposed to solvents, friction or irritating food components. Discoid or nummular hand eczema is another rarer pattern of irritant contact dermatitis, affecting especially the dorsa of hands or fingers.

The differential diagnosis of hand dermatitis includes fungal infection, which simulates a unilateral palmar dermatitis (Fig. 25.17) and can resemble eczema on the dorsum of the hand (Fig. 25.18). Skin scrapings are important to exclude tinea as the cause of a hard to treat 'dermatitis'. Psoriasis frequently affects the palms, resulting in a hyperkeratotic appearance. This can be difficult to distinguish from dermatitis when there are no lesions elsewhere. Further, there may be a history of exacerbation when the disease leads to the Koebner phenomenon on the hands as a result of manual work. The presence of scaling erythema over the interphalangeal joints is often a helpful clue to the diagnosis (Fig. 25.19). Scabies in the interdigital spaces can simulate an irritant dermatitis (Fig. 25.20). Rarely, the presence of milia may lead to a diagnosis of porphyria cutanea tarda (Fig 25.21).

Cosmetic dermatitis

Cosmetics, toiletries and skin-care products, including sunscreens, quite frequently cause adverse reactions [3]. In most cases, these are only mild or transient, and most consumers simply change to an alternative product. In a minority, reactions may be more severe, with redness, oedema, dryness and scaling. The eyelids are particularly susceptible to irritants [4], as are atopic individuals and those with very fair, rosaceous or seborrhoeic skins. It is of interest that irritant reactions are commoner in younger (premenopausal) women. Those using many products are at risk of 'cosmetic exhaustion', a form of cumulative cosmetic irritant contact dermatitis. Allergy is excluded only by comprehensive patch testing including both products and ingredients.



Fig. 25.17 A unilateral dry palm is characteristic of *Trichophyton rubrum* infection.



Fig. 25.18 Tinea incognito on the dorsum of the hand.

Volatile/airborne irritant contact dermatitis

Irritants, as well as allergens, may cause volatile contact dermatitis [5]. Volatile irritants are a not infrequent cause of eyelid dermatitis. In any exposed-site dermatitis, one should consider the possibility of irritant volatile fumes or airborne particles. The fumes can be from acids, alkalis, solvents, resins or any other irritant chemical, such as ammonia or formaldehyde. Irritant dusts include those of some (mostly tropical) woods, cement, fibreglass or rockwool, some metals and metal salts, and powdered chemicals.



Fig. 25.19 Erythema and scale over the interphalangeal joints is a clue to the diagnosis of psoriasis.



Fig. 25.20 Scabies affecting the finger web spaces. (Courtesy of A. Yung, Leeds General Infirmary, Leeds, UK.)

Cheilitis

Cheilitis is a common problem, often of multifactorial aetiology. Atopic eczema frequently predisposes to its development [6]. The most common identifiable causes of cheilitis are irritant dermatitis, due to lip licking, cosmetics and medication, and allergic contact dermatitis, particularly from ricinoleic acid and the patient's own lip preparations [7].

Napkin (diaper), peristomal and perianal dermatitis

Irritant dermatitis will develop in situations of prolonged or too frequent contact with degraded urine or faeces/faecal residues [8].



Fig 25.21 Milia over the dorsa of the hands should prompt exclusion of porphyria in an individual with a presumed dermatitis.

Sweat, occlusion, irritant cleansers, secondary infection and secondary medicament allergy are all additional complicating factors. It occurs most frequently in very young, or in elderly individuals in situations of urinary or faecal incontinence. Measures to improve continence in the elderly and sufficiently frequent changes of absorbent [9] napkins in infants are important, as are mild cleansers and protective pastes or silicone-based creams. Any dermatitis or secondary infection should be controlled with appropriate-strength topical steroids or steroid–antimicrobial combinations. In napkin dermatitis, secondary candidal infection is sufficiently common that routine treatment with an imidazole antifungal is of benefit [10].

A similar situation appertains to perianal dermatitis, where mucus or faecal leakage may occur in association with haemorrhoids and/or poor sphincter function. A bidet, or 'wet' cleansing routine using aqueous cream or equivalent, is of benefit.

With peristomal dermatitis, there is the additional complication of the need to maintain a protective seal between the stoma bag and skin. The use of corticosteroid-containing lotions, either aqueous or alcoholic, has been shown to be effective without interfering with stoma adhesion [11]. Dermatitis, as well as being caused by leakage, may also be due to continuous occlusion and repeated stripping of the skin. Where there is erosive disease, the use of topical sucralfate has been shown to promote healing in peristomal disease but not erosions from other causes [12]. The sucralfate acts as both a physical barrier and, it is suggested, by binding to basic fibroblast growth factor preventing its degradation, as a stimulus to healing.

Computer-related irritation

Various problems have been reported. Keyboard wrist pads have developed on the ulnar side of the wrist as a consequence of repeated minor frictional trauma. Computer palms are described as well-demarcated blanchable erythema and telangiectasia, thought to be a reactive hyperaemia induced by the ischaemia of applying pressure to the hands when stretching to relieve back strain. Most frequently a rosacea-like dermatosis has been

described associated with subjective symptoms. The cause is uncertain, although a low-humidity dermatosis has been postulated. There is an association with atopy and facial stinging predicted by a lactic acid test, but psychosocial factors and high levels of stress are also predictors [13].

Other sites

Irritant dermatitis at other sites occurs less frequently, but may develop on the feet from spillage under shoes or on the thigh from the habit of keeping an oily rag in a pocket.

References

1 Lantinga H, Nater JP, Coenraads PJ. Prevalence, incidence and course of eczema on the hand and forearm in a sample of the general population. *Contact Dermatitis* 1984; **18**: 135–9.
2 Lammintausta K, Maibach HI, Wilson D. Irritant reactivity in males and females. *Contact Dermatitis* 1987; **17**: 276–80.
3 Foley P, Nixon R, Marks R *et al.* The frequency of reactions to sunscreens: results of a longitudinal population based study on the regular use of sunscreen in Australia. *Br J Dermatol* 1993; **128**: 512–8.
4 Valsecchi R, Imberti G, Martino D *et al.* Eyelid dermatitis: an evaluation of 150 patients. *Contact Dermatitis* 1992; **27**: 143–7.
5 Dooms Gossens A, Debusschere KM, Gevers DM *et al.* Contact dermatitis caused by airborne agents. *J Am Acad Dermatol* 1986; **15**: 1–10.
6 Freeman S, Stephens R. Cheilitis: an analysis of 75 cases referred to a contact dermatitis clinic. *Am J Contact Dermatitis* 1999; **10**: 198–200.
7 Lim SW, Goh CL. Epidemiology of eczematous cheilitis at a tertiary dermatological referral centre in Singapore. *Contact Dermatitis* 2000; **43**: 322–6.
8 Scardillo J, Aronovitch SA. Successfully managing incontinence-related irritant dermatitis across the lifespan. *Ostomy Wound Manage* 1999; **45**: 36–40.
9 Akin F, Spraker M, Aly R *et al.* Effects of breathable disposable diapers: reduced prevalence of *Candida* and common diaper dermatitis. *Pediatr Dermatol* 2001; **18**: 282–90.
10 Concannon P, Gisoldi E, Phillips S, Grossman R. Diaper dermatitis—a therapeutic dilemma: results of a double-blind placebo-controlled trial of miconazole nitrate 0.25%. *Pediatr Dermatol* 2001; **18**: 149–55.
11 Lyon CC, Smith AJ, Griffiths CE, Beck MH. Peristomal dermatoses: a novel indication for topical steroid lotions. *J Am Acad Dermatol* 2000; **43**: 679–82.
12 Lyon CC, Stapleton M, Smith AJ *et al.* Topical sucralfate in the management of peristomal skin disease: an open study. *Clin Exp Dermatol* 2000; **25**: 584–8.
13 Wintzen M, van Zuuren EJ. Computer-related skin diseases. *Contact Dermatitis* 2003; **48**: 241–43.

Phototoxicity [1]

A number of chemicals cause irritation only after absorption of photons; the photoactivated chemical has altered properties which are directly tissue damaging. They include psoralens, porphyrins, tetracyclines, non-steroidal anti-inflammatory drugs, phenothiazines and amiodarone. This is discussed in greater detail in Chapter 29.

Reference

1 Mang R, Stege K, Krutmann J. Mechanisms of phototoxic and photoallergic reactions. In: Frosch PJ, Menné T, Lepoittevin J-P, eds. *Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 97–106.

Mechanical irritation

In an experimental setting, distortion of the skin at the edge of adhesive tape (Fig. 25.22) has been shown to be directly related to the development of irritant dermatitis [1]. Koebnerization of eczema as both primary and secondary events following injury has been reported [2]. Friction is reported to cause nipple dermatitis in association with jogging [3] and ill-fitting bras [4]. Dermatitis has similarly been reported under other items of clothing at sites of friction. The presence of a rash, particularly in the summer months, suggested that damp clothing/skin from sweating was implicated in the pathogenesis in 15 patients reported by Ramam *et al*. [5] (Fig. 25.23). Localized dermatitis from prosthetic limbs is also frequently trauma induced [6]. In a retrospective review of physical irritant contact dermatitis [7], 35.3% of cases were induced by friction, 32.7% by drying and 11% by heat. The majority of cases had an occupational origin, with 36.3% of cases affecting the hands and 26.4% the face.

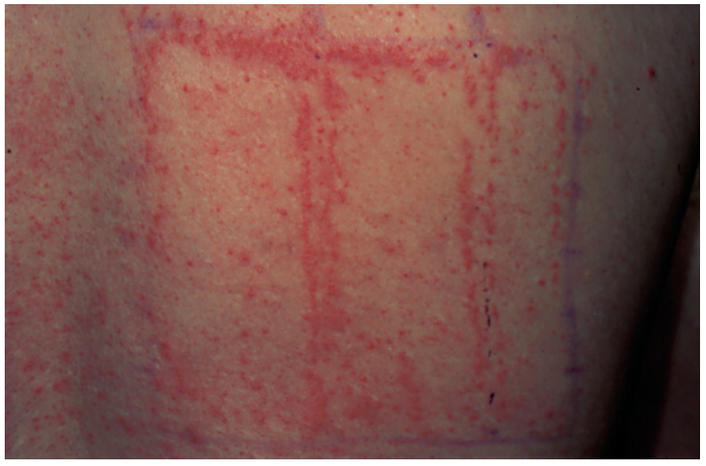


Fig. 25.22 Dermatitis developing at the edge of Scanpor tape after patch testing.



Fig. 25.23 In the same patient, frictional dermatitis under a bra strap (contact allergy excluded).

Fibreglass dermatitis [8] is usually irritant in nature, and is the result of skin injury by direct penetration of fibre particles. It is directly proportional to the diameter (greater than 3.5 µm) and inversely proportional to the length of the fibres. Pathologically, the changes are eczematous, with spongiosis. This is also discussed in Chapter 27.

Mechanical injury by plants is also common [9]. Most injuries to the skin by thorns or spines are purely mechanical. However, glandular hairs of some plant species inoculate pharmacologically

active substances, and certain spines and thorns give rise to distinctive reactions, which suggest that the mechanical effects may be enhanced or modified by as yet unidentified toxic agents. The small bristles, or glochidia, of some species of cactus are retained in the skin and produce an eruption of very persistent, small, irritable papules. Similarly, trichomes of other plants have caused an irritating eruption of the interdigital spaces simulating eczema or tinea. The sharp-tipped leaves of palms or yuccas and the thorns of roses may become deeply embedded in or near bones or in joints, especially in children's hands. They may then cause a chronic septic arthritis or intense periosteal reaction, which may mimic bone tumours. Small thorns may induce foreign-body granulomas. The persistent nodules are usually on the wrists and fingers.

References

1 Tokumura F, Ohyama K, Fujisawa H *et al.* Conformability and irritancy of adhesive tapes on skin. *Contact Dermatitis* 1997; **37**: 173–8.
2 Mathias CGT. Post-traumatic eczema. *Dermatol Clin* 1988; **6**: 35–42.
3 Levit F. Joggers' nipples. *N Engl J Med* 1977; **297**: 1127.
4 Kapur N, Goldsmith PC. Nipple dermatitis: not all what it 'seams'. *Contact Dermatitis* 2001; **45**: 44–5.
5 Ramam M, Khaitan BK, Singh MK, Gupta SD. Frictional sweat dermatitis. *Contact Dermatitis* 1998; **38**: 49.
6 Lyon CC, Kulkarni J, Zimmerman E *et al.* Skin disorders in amputees. *J Am Acad Dermatol* 2000; **42**: 501–7.
7 Morris-Jones R, Robertson SJ, Ross JS *et al.* Dermatitis caused by physical irritants. *Br J Dermatol* 2002; **147**: 270–5.
8 Björnberg A. Glass fiber dermatitis. *Am J Ind Med* 1985; **8**: 395–400.
9 Lovell C. *Plants and the Skin*. Oxford: Blackwell Scientific Publications, 1993.

Non-immune contact urticaria

Immediate contact reactions may be either allergic or toxic. They are transient, developing within minutes, and fade quickly (usually within hours). They may appear on both normal and damaged/eczematous skin, and may present as only a transient, symptomatic erythema or as a contact urticaria.

For some agents that cause immediate-type reactions, it is still unclear as to whether or not the mechanism is immunological. Non-immunological, immediate contact reactions occur without prior sensitization. The reactions remain localized, and may present as a transient erythema or as an urticarial weal and flare, depending on concentration, area of contact, mode of exposure and agent involved [1,2]. Substances reported to cause non-immunological contact urticaria are listed in Table 25.5. The most potent of these, such as benzoic acid, sorbic acid, cinnamic acid, cinnamic aldehyde and nicotine acid esters, may induce a local reaction within 45 min in more than 50% of those tested. Reactions may occur at concentrations as low as 0.1% for benzoic acid, sorbic acid and sodium benzoate, and as low as 0.01% for cinnamic aldehyde. Reactions are not enhanced by occlusion, but may affect mucosal surfaces; low concentrations of cinnamic aldehyde are sometimes added to toothpaste and mouthwashes to impart a sensation of 'freshness'. Studies on an unselected population have shown that reactions to urticants are not predictable; an individual who reacted strongly to one urticant did not necessarily react to another. In addition, there was no significant correlation between age or sex and urticant response [3].

Table 25.5 Agents reported to cause non-immunological contact reactions. (From Lahti and Basketter [2].)

Animals	*Plants*
Arthropods	Nettles
Caterpillars	Seaweed
Coral	*Preservatives*
Jellyfish	Benzoic acid
Moths	Chlorocresol
Sea anemones	Formaldehyde
Foods	Sodium benzoate
Cayenne pepper	Sorbic acid
Fish	*Miscellaneous*
Mustard	Butyric acid
Fragrances and flavourings	Cobalt
Balsam of Peru	Dimethyl fumarate
Benzaldehyde	Histamine
Cinnamic acid	Pine oil
Cinnamic aldehyde	Pyridine carbo-aldehyde
Cinnamon oil	
Thyme	
Medicaments	
Alcohols	
Benzocaine	
Camphor	
Cantharidin	
Capsaicin	
Chloroform	
Dimethyl sulphoxide	
Friars' balsam (compound benzoin tincture)	

References

1 Wakelin SH. Contact urticaria. *Clin Exp Dermatol* 2000; **26**: 132–6.
2 Lahti A, Basketter D. Immediate contact reactions. In: Frosch PJ, Menné T, Lepoittevin J-P, eds. *Contact Dermatitis*, 4th edn Berlin: Springer, 2006: 83–96.
3 Basketter DA, Wilhelm KP. Studies on non-immune immediate contact reactions in an unselected population. *Contact Dermatitis* 1996; **35**: 237–40.

Symptomatic (subjective) irritant responses

With some irritants there is little or nothing to see, but individuals complain of a subjective sensation of stinging, burning or smarting. These sensations most commonly affect the head and neck, may present as one form of cosmetic intolerance, and are frequently termed 'sensitive skin' [1]. Although stinging potential is often assessed by the application of lactic acid to the nasolabial fold the results do not necessarily correlate with the sensation perceived at other facial sites [2]. With soaps and detergents, the perceived sensory symptoms correlate with and predict the development of clinical signs of irritant dermatitis [3], although more typically the sensation does not correlate with a predisposition to irritant dermatitis or non-immune contact urticaria.

Little is known of the mechanisms involved in subjective irritant reactions [1]. It is presumed that penetration of the irritant is primarily via sweat ducts and hair follicles, is not related to pH, and that the reaction involves stimulation of sensory nerve endings.

The reaction is substantially reduced in the absence of sweating and is commoner in the summer. Factors thought to predispose to sensitive skin include female sex and hormonal status, young age, fair skin, susceptibility to blushing/flushing, thin stratum corneum, increased number of sweat glands, innervation and impairment of epidermal barrier function. The presence of sensitive skin also affects quality-of-life scores, with affected individuals having an impaired psychological component, although there was no significant relationship to depressive symptoms [4].

Triggers are not necessarily chemical, and include environmental factors such as wind. Sensory irritation from woollen garments is also well known among patients with atopic eczema. Experimental studies have shown this to be due to stimulation of nerve fibres which transmit pain. It required a 100-mg force on the end of a 40-μm diameter textile fibre to trigger the nerve receptor. Thus, garments that induce the sensation will have protruding fibre ends that can withstand 100 mg pressure without buckling. Prickle was not experienced if the fabric was rubbed over the skin, if the skin was cold or if the area of contact was less than 1 cm^2. Moisture increased the severity of the sensation [5].

Immediate-type stinging

Some chemicals will cause painful sensations within seconds of contact [6]. These include acids, where the stinging may be a prodrome to the development of more severe cutaneous damage. Other chemicals, however, will cause stinging without any significant cutaneous damage. The best known of these are chloroform and methanol (1:1), and 95% ethanol. Responses vary according to site and individual susceptibility, and probably relate indirectly to stratum corneum thickness. The sensation abates quickly following removal of the irritant substance.

Delayed-type stinging

Delayed-type stinging [6] may occur following contact with a number of substances (Table 25.6). Typically, there is no immediate stinging, but discomfort develops within 1–2 min, reaches a maximum in 5–10 min, and fades slowly over the next half hour. The reaction normally affects only the face, especially in association with heat and humidity or sweating. The sensation is not alleviated by washing off the offending chemical. It is an idiosyncratic response, and only a proportion of the population will be affected.

Individuals can be screened to ascertain whether they are stingers or not by the application of 5% aqueous lactic acid to the nasolabial fold after induction of sweating. Preparations can be screened for stinging potential by testing a predetermined panel of 'stingers and smarters'.

Table 25.6 Substances known to cause delayed stinging or burning. (From Frosch and John [6].)

Weak
Aluminium chloride 30% aq.
Benzene 1% alc.
Phenol 1% alc.
Phosphoric acid 1% aq.
Resorcinol 5% aq.
Salicylic acid 5% alc.
Zirconium hydroxychloride 30% aq.
Moderate
Benzoyl peroxide 5% aq.
Dimethyl acetamide 100%
Dimethyl formamide 100%
Dimethyl sulphoxide 100%
Diethyl toluamide 50% alc.
Dimethyl phthalate 50% alc.
2-ethyl-1,3-hexanediol 50% alc.
Propylene glycol 100%
Propylene carbonate 100%
Propylene glycol diacetate 100%
Sodium carbonate 15% aq.
Trisodium phosphate 5% aq.
Severe
Amyldimethyl-*p*-aminobenzoic acid (Escalol 506) 5% alc.
2-ethoxyethyl-*p*-methoxy-cinnamate (Giv-Tan FR) 2% alc.
Hydrochloric acid 1.2% aq.
Lactic acid 5% aq.
Phosphoric acid 3.3% aq.
Sodium hydroxide 1.3% aq.

References

1 Farage M, Katsarou A, Maibach HI. Sensory, clinical and physiological factors in sensitive skin: a review. *Contact Dermatitis* 2006; **55**: 1–14.

2 Marriott M, Whittle E, Basketter DA. Facial variations in sensory responses. *Contact Dermatitis* 2003; **49**: 227–31.

3 Simion FA, Rhein LD, Morrison BM *et al*. Self-perceived sensory responses to soap and synthetic detergent bars correlate with clinical signs of irritation. *J Am Acad Dermatol* 1995; **32**: 205–11.

4 Misery L, Myon E, Martin N *et al*. Sensitive skin: psychological effects and seasonal changes. *J Eur Acad Dermatol* 2007; **21**: 620–8.

5 Hatch KL, Maibach HI. Textile dermatitis: an update, 1: resins, additives and fibers. *Contact Dermatitis* 1995; **32**: 319–26.

6 Frosch PJ, John SM. Clinical aspects of irritant contact dermatitis. In: Frosch PJ, Menné T, Lepoittevin J-P, eds. *Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 255–94.

Specific irritants [1]

Substances that commonly cause irritant contact dermatitis are listed in Table 25.4. Certain, mostly 'wet', occupations, have an increased risk of irritant contact dermatitis; these are listed in Table 25.3.

Water [2]. Wet work occurs in a wide range of occupations. Water is hypotonic and acts as a cytotoxic agent on eroded skin. If the surface lipid layer has been removed previously by suitable solvents, including detergents, water may dissolve the hygroscopic substances needed to keep the skin pliable. Hard water is more irritant than soft [3]. Lime, magnesium and iron from hard water deposited in skin fissures may cause mechanical irritation. Irritation of the skin may arise from poorly controlled chlorination or bromination of swimming and spa pools [4].

Skin cleansers [5]. Soap, detergents and waterless cleansers containing organic solvents are the commonest irritants. They raise the pH and dissolve lipids. Added silica or sand tends to damage by mechanical abrasion. It is difficult to evaluate the role of soap in the causation of cumulative insult dermatitis and difficult to prove that it is, in fact, a perpetuating factor. In many occupations, for example the metal industries, the procedures used for hand cleansing may be more harmful to the skin than the work itself. Aromatics in the solvents in 'waterless cleansers' are particularly hazardous [6].

Detergents, surface-active agents, sulphonated oils, wetting agents, emulsifiers. These are used for domestic and industrial cleaning, skin cleansing, and as wetting and emulsifying agents in many industries. Washing powders contain detergents, perborates, phosphates, optical bleaches and perfume. Some also have added soap and, to prevent precipitation of calcium soap, chelating agents. The irritant effect is different, being dependent on the chemistry of the detergent [7]. Most are alkaline, but even at neutral pH they remove the surface lipid film and the water-holding substances in the horny layer as well as the vital lipids from the semipermeable membrane of stratum corneum. They denature protein and damage the cell membranes. Oxidation has been shown to increase the irritant potential of some surfactants [8]. Enzymes used in detergents may or may not [9] act as irritants.

Preservatives. Most quaternary ammonium compounds have an irritant effect, particularly in superficial cracks in dry skin. Other preservatives, as well as being potentially allergenic, can be irritant [10].

References

1 Basketter DA, Holland G, York M. Corrosive materials. In: Chew A-L, Maibach HI, eds. *Handbook of Irritant Dermatitis*. Boca Raton, FL: CRC Press, 2006: 239–48.
2 Tsai TF, Maibach HI. How irritant is water? An overview. *Contact Dermatitis* 1999; **41**: 311–14.
3 Warren R, Ertel KD, Bartolo RG *et al.* The influence of hard water (calcium) and surfactants on irritant contact dermatitis. *Contact Dermatitis* 1996; **35**: 337–43.
4 Fitzgerald DA, Wilkinson SM, Bhaggoe R *et al.* Spa pool dermatitis. *Contact Dermatitis* 1995; **33**: 53.
5 English JS, Ratcliffe J, Williams HC. Irritancy of industrial hand cleansers tested by repeated open application on human skin. *Contact Dermatitis* 1999; **40**: 84–8.
6 Dobson RL. Evaluation of hand cleansers. *Contact Dermatitis* 1979; **5**: 305–7.
7 Tupker RA, Bunte EE, Fidler V *et al*. Irritancy ranking of anionic detergents using one-time occlusive, repeated occlusive and repeated open tests. *Contact Dermatitis* 1999; **40**: 316–22.
8 Bodin A, Fischer T, Bergh M *et al.* Skin irritation from air-oxidized ethoxylated surfactants. *Contact Dermatitis* 2000; **43**: 82–9.
9 White IR, Lewis J, El Alami A. Possible adverse reactions to an enzyme-containing washing powder. *Contact Dermatitis* 1985; **13**: 175–9.
10 Ng CK, Tay P. Two case reports of delayed skin burns from methylisothiazolines used in water treatment. *Singapore Med J* 1996; **37**: 577–8.

Alkalis. Alkaline solutions saponify the surface lipids and dissolve water-holding substances, break the cross-linkages of keratin and cause swelling of cells. Soap, soda, ammonia, potassium and sodium hydroxides, cement, chalk, sodium silicate, trisodium phosphate and amines (e.g. in epoxy hardeners or as an antistatic agent [1]) are the commonest irritants.

It should be noted that soda ash (anhydrous sodium carbonate) is three times stronger than washing soda. Stearyl amine is used as an emulsifier in mixtures of oil and gravel. Alkalis are used in many industries (dyeing, tanning, rubber, plastic, glass, etc.). Copying papers based on the diazo process are developed by ammonia gas, which sometimes causes irritant dermatitis of the face.

Acids. Acids are widely used in industry, for example chromic acid for rust-proofing iron and hydrofluoric acid for glass etching, rust stain removal, and in the electronics and petroleum industries. Sulphuric, hydrochloric and nitric acids are other common inorganic acids. Hydrochloric acid is used by masons for the cleaning of building stones, but sometimes also for cleaning their hands. Acetic and oxalic acids are the most often used organic acids. Acid anhydrides such as phthalic anhydride are stronger irritants than the corresponding acids. Weaker acids may be used as preservatives and have caused dermatitis due to their presence in animal feed [1].

Oils. The major offenders are metalworking fluids [2], which may be neat oils, oil-in-water emulsions ('soluble oils'), semisynthetic or synthetic, in roughly increasing order of irritancy. The less viscous a neat oil, the more irritant it tends to be, although chlorination or sulphonation may make viscous oils more irritant. Oil acne/folliculitis is a localized form of irritancy (Chapter 27). In water-based metalworking fluids, the principal irritant is the emulsifier or wetting agent, although other factors, still poorly understood, may increase irritancy.

Organic solvents [3]. These include aliphatic petroleum solvents such as white spirit. Commonly, they contain 18–20% of aromatics. Prime-grade kerosene contains about 2% of aromatics and is less irritant. The much more irritating diesel oil and fuel oil are used, for example, as solvents for oil in casting moulds.

Other organic solvents include the following: aromatic hydrocarbons such as benzene, toluene and aromatic petroleum solvents; chlorinated hydrocarbons such as trichloroethylene, perchloroethylene, methylene chloride and chlorobenzene; alcohols such as methanol, ethanol, isopropanol and propylene glycol; esters such as ethyl acetate; ketones such as acetone and methylethylketone; ether alcohols such as ethylene glycol monomethylether; nitroparaffins such as nitroethane; turpentine; carbon disulphide.

Thinner is commonly a mixture of alcohols, ketones and esters, but sometimes also toluene, turpentine and dipentene (limonene). These are used in many industrial processes, including cleaning textiles and metals, the graphics industries, floor laying (where glue is used), wood-finishing, dyeing, painting, etc. They also act as solvents for many technical products, for example polishes and disinfectants. Sometimes, they are used as hand cleansers in dirty work, as in the rubber, plastics and metal industries. They remove the lipid film and water-holding substances, and damage cell membranes. Their irritating capacity depends on their chemical structure, and commonly the following range is valid: aromatic > aliphatic > chlorinated > turpentine > alcohols > esters > ketones.

Oxidizing agents. Organic peroxides such as benzoyl peroxide and cyclohexanone peroxide are used in hardening polyester resins. Some are used in hair bleaching and some for bleaching textiles, oils and flour. They are strong cytotoxic agents and may cause unusual urticarial reactions. The cytotoxicity of persulphates may also cause irritation during their manufacture [4].

Sodium hypochlorite (bleach) is used, as well as for cleaning, by printers and dyers to remove staining from their hands. Its cytotoxicity makes its medical use in Dakin's solution (Eusol) unsuitable for clean wounds and ulcers.

Ethylene oxide is used as a sterilizing agent and may remain on instruments or rubber articles [5].

Reducing agents. Phenols [6], hydrazines, aldehydes, sulphurated hydrogen and thioglycolates are common in industry. Penta-, tetra- and trichlorophenols are used as wood preservatives; thioglycolates for cold waving (Chapter 27). Thioglycolates break cross-linkages, including the strong disulphide bonds in keratin, in an alkaline environment. Keratin fibrils take up water, and percutaneous absorption is thereby increased.

Other organic and inorganic substances. Some other substances may also act as strong cytotoxic agents. Examples are as follows: formaldehyde, industrial processing of polyethylene with formation of acrolein, crotonaldehyde, thiomersal, allyl alcohol, cresol in pesticides (dog collars prepared with a flea repellent have caused irritant dermatitis) and halogenated acetophenones; alkyl bromides and chlorides in paint removers or fumigation; bromine and chlorine derivatives in chemical synthesis; styrene; organic silicones can cause blepharitis; acrylic monomer, diallylglycol carbonate monomer and epichlorohydrin in plastic processes; arsenic in wine culture. Metal polishes, fertilizers and rust-preventive products often contain irritant agents. Alkyl tin compounds are used as preservatives, and as antifoulants in marine paints. Mercuric salts, cobalt, zinc chloride, etc., have an irritant effect.

Unsaturated aliphatic chains give compounds a more irritating effect—for example, allyl alcohol, diallylphthalate (in polyester resins), cinnamaldehyde compared with hydrocinnamaldehyde (in perfumes) and acrolein.

References

1 Henschel R, Agathos M, Breit R. Acute irritant contact dermatitis from propionic acid used in animal feed preservation. *Contact Dermatitis* 1999; **40**: 328.

2 Goh CL. Cutting fluid dermatitis: epidemiology and an appraisal of some preventive measures. *Environ Dermatol* 1994; **1**: 3–11.

3 Boman A. Factors influencing the percutaneous absorption of organic solvents: an experimental study in the guinea pig. *Arbete Och Hälsa* 1989; **11**: 1–51.

4 White IR, Catchpole HE, Rycroft RJG. Rashes among persulphate workers. *Contact Dermatitis* 1982; **8**: 168–72.

5 Bryant HE, Visser ND, Yoshida K. Ethylene oxide sterilizer use and short-term symptoms amongst workers. *J Soc Occup Med* 1989; **30**: 101–6.

6 Bruze M, Almgren G. Occupational dermatoses in workers exposed to resins based on phenol and formaldehyde. *Contact Dermatitis* 1988; **19**: 272–7.

Plants and woods [1]. Citrus peel, flower bulbs, garlic, flour, wood dust, spices, corn, onion, pineapple, pelargonium, iris, stinking mayweed, buttercup, daffodil and the mustard family can act as irritants, and some can cause bullous reactions even without ultraviolet irradiation (Table 25.7). Spines can cause mechanical damage. Thus, barley awns are sharp and may cause papular eruptions and severe pruritus all over the body.

Table 25.7 Irritating plants.

Ranunculaceae
Ranunculus (many species of buttercup)
Anemone
Clematis
Helleborus
Araceae
Dieffenbachia (ornamental plant in tropics and house plant in Europe)
Euphorbiaceae (spurge; the milky latex of many species is intensely irritating)
Hippomane manchinella (the manzanillo tree of the Caribbean contains a powerful irritant)
Cruciferae
Brassica nigra and other 'mustards'
Compositae
Achillea (milfoil and related species)
Anthemis (mayweeds)
Matricaria

Animal products. Vesicular or papular dermatitis may be caused by caterpillars, carpet beetles and moths. Wet work with fish, shrimps, meat and herring in canning industries or restaurants may cause an irritant effect. Herring brine contains trimethylamine. Separating the pancreas from the intestines involves contact with enzymes which can give rise to loosening of the nails in butchers. Irritation also arises from proteolytic enzymes in pineapple and papaya, and in baking.

Topical medicaments. Tar, dithranol, potassium permanganate, gentian violet, mercury, hexachlorophane, etc. can, in susceptible persons, even in low concentrations, cause overtreatment dermatitis, which also occurs after prolonged use of wet dressings, particularly under occlusive bandaging. Occlusive transdermal drug delivery systems can also cause irritation.

Physical and mechanical factors. These include the following: heat, steam, cold, high or low humidity, electricity, sunlight, UV light and other rays; friction, pressure, trauma, rubbing, scratching and scrubbing; metal particles, metal dust, adhesive plaster, fibreglass and rockwool, textile particles, jute, wood dust, sand, asbestos, silica, cement, plaster, hot-metal particles from welding, and glass spicules.

References

1 Lovell C. *Plants and the Skin*. Oxford: Blackwell Scientific Publications, 1993.

Investigations

Irritant contact dermatitis is essentially a clinical diagnosis based on knowledge of the nature and conditions of an individual's

exposure in the context of their dermatitis. A complicating allergic contact dermatitis always should be excluded by patch testing, but patch tests do not aid in the diagnosis. Investigations are most frequently used in the context of scientific studies but may also predict an individual's susceptibility. None can be reliably used clinically on a large scale.

Quantifying the irritant response

Although visual appraisal of skin erythema and surface changes is still widely used to assess irritant reactions, a number of non-invasive techniques have been developed in recent years that permit objective evaluation of key changes to the skin. The optimal method to be used varies with the nature of the irritant [1].

Erythema. Among the most overt clinical features of irritant reactions is erythema, which may be quantified using a number of different approaches. Laser Doppler flowmetry (LDF) provides a measure of superficial blood flow by transmitting monochromatic light from a helium–neon laser through optical fibres to the skin surface. The light is Doppler-shifted by moving blood cells in the upper dermis, remaining unchanged in the surrounding stationary tissue. By means of a differential signal detector and signal processing arrangement, the back-scattered or reflected light is interpreted. The final output, which is linearly related to the product of the number of blood cells and their average velocity in the measured volume, is expressed in relative and dimensionless units. Studies by a number of investigators have shown that LDF generally correlates well with visually-assessed erythema, and is capable of discriminating between negative and weakly-positive irritant reactions [2].

Alternative methods for objectively quantifying erythema rely upon the generalized increase in red blood cells resulting from both increased blood flow and blood vessel dilatation. Those which are based upon remittance spectroscopy emit red and green light from a tungsten halogen lamp or LED source. Oxyhaemoglobin in the blood vessels absorbs a proportion of the green light, and largely reflects the red light. Changes in the quantity of oxyhaemoglobin significantly alter the amount of green light absorbed, but have very little influence on the red light. An erythema index can therefore be calculated from the ratio between the reflected green and red light, such that the greater the erythema, the higher the value of the erythema index [3].

Erythema may also be quantified using tristimulus colorimeters, virtually all of which employ a system for colour definition known as the Commission Internationale de l'Eclairage (CIE) L*a*b* colour system. This provides a three-dimensional coordinate system where L* represents an axis for brightness, a* represents a green–red axis and b* represents a yellow–blue axis.

Transepidermal water loss. In addition to inducing erythema, irritants commonly affect barrier function, leading to alterations in TEWL. Measuring instruments employ open chambers, through which, when applied to the surface of the skin, water vapour evaporates, creating a water-pressure gradient from which the evaporative TEWL, expressed in $g/m^2/h$, is calculated. Many variables influence TEWL measurements. Some relate to the environment and to instrument operation, necessitating a careful adherence to 'good laboratory practice', as outlined in a report from the Standardization Group of the European Society of Contact Dermatitis [4]. Others relate directly to the individual; age and anatomical site are among the most important variables. Measurements of TEWL have proved valuable in predicting susceptibility to skin irritation, assessing the protective effects of barrier creams, and evaluating the irritancy potential of different chemicals.

Hydration. Changes in the hydration state of the skin also commonly occur in irritant contact dermatitis and, again, this parameter may be objectively measured. Several different devices are available, based on differing biophysical approaches. Using the principle of capacitance, hydration of the stratum corneum can be measured to a depth of approximately 0.1 mm. In contrast, skin conductance has also been used as a measure of hydration. Studies suggest that capacitance may be more effective in the assessment of dry skin, whereas conductance is better suited for studies of water accumulation in the stratum corneum [5]. A third method uses the principle of impedance-based capacitance to assess hydration levels.

Skin thickness. Although not extensively applied, high-frequency ultrasound has also proved valuable for the assessment of another aspect of the irritant response, namely changes in skin thickness [6].

References

1 Fluhr JW, Kuss O, Diepgen T *et al.* Testing for irritation with a multifactorial approach: comparison of eight non-invasive measuring techniques on five different irritation types. *Br J Dermatol* 2001; **145**: 696–703.

2 Willis CM, Stephens CJM, Wilkinson JD. Assessment of erythema in irritant contact dermatitis: comparison between visual scoring and laser Doppler flowmetry. *Contact Dermatitis* 1988; **18**: 138–42.

3 Babulak SW, Rhein LD, Scala DD *et al.* Quantification of erythema in a soap chamber test using the Minolta Chroma (reflectance) meter: comparison of instrumental results with visual assessments. *J Soc Cosmet Chem* 1986; **37**: 475–7.

4 Pinnagoda J, Tupker RA, Agner T, Serup J. Guidelines for transepidermal water loss (TEWL) measurement: a report from the Standardization Group of the European Society of Contact Dermatitis. *Contact Dermatitis* 1990; **22**: 164–78.

5 Agner T, Serup J. Comparison of two electrical methods for measurement of skin hydration: an experimental study on irritant patch test reactions. *Bioeng Skin* 1988; **4**: 263–9.

6 Seidenari S, Di Nardo A. B scanning evaluation of irritant reactions with binary transformation and image analysis. *Acta Derm Venereol Suppl (Stockh)* 1992; **175**: 3–7.

Management

Chemical burns

Initial treatment of chemical burns [1,2] requires irrigation with large volumes of lukewarm water and removal of contaminated clothing. Where the chemical is insoluble in water a soap solution or solvent may be used instead. High pressures should not be used, to avoid splashing other areas of the body or bystanders with the corrosive material.

Although neutralizing solutions offer an alternative to irrigation, theoretically an exothermic reaction and potential delay in obtaining the treatment might result in increased tissue damage, and they are not generally recommended [3]. Specific antidotes that have

been suggested include the use of milk or egg whites for oxidizing agents such as chromic acid and potassium permanganate. Reducing agents such as hydrochloric and nitric acids can be neutralized with soap, or sodium and magnesium hydroxides.

Consideration should be given to referral to a burns unit in the following circumstances:

1 Partial-thickness burns with >10% surface area involvement
2 Burns of the face, hands, feet, genitalia or over joints where contractures may affect function
3 Full-thickness burns
4 Chemical and inhalational injury where there is a risk of systemic involvement
5 Burns in individuals with co-morbidities that may complicate management.

On arrival in hospital, initial assessment involves providing systemic support and fluid replacement. The fluid requirement varies depending on body weight and surface area involved. Jewellery should be removed to prevent it acting as a tourniquet as oedema develops, and tetanus status reviewed.

For some chemicals such as hydrofluoric acid, specific antidotes should be used subsequently, for example 2.5% calcium gluconate gel. Application should be repeated 4-hourly and disappearance of pain is a sign of successful treatment [4]. If the pain fails to resolve, infiltration or regional infusion have been used. If treatment is delayed the fluoride ion disassociates and complexes with calcium and magnesium forming insoluble salts in the tissues, with destruction of soft and bony tissue. Hypocalcaemia leads to cardiac arrhythmia. When there is a risk of toxicity from systemic absorption, as with chromic acid [5], early debridement of necrotic areas reduces blood levels, and consideration should be given to the use of dialysis to remove circulating chromium. Ulcerated areas should be managed with antibacterial creams to prevent secondary infection whilst re-epithelialization occurs. If there is a surrounding inflammatory reaction a moderately potent topical corticosteroid can be applied. Vapour-permeable dressings are recommended in view of the role of TEWL in stimulating barrier repair [6].

Frequent review is required because the ulcers can progress over several days. Subsequent management with excision/debridement and/or grafting may speed the healing process. Where the ulcer extends into the dermis healing frequently results in a scar, and pigmentary change is common. Several chemicals (e.g. hydrofluoric acid, phenolic compounds, chromic acid, gasoline) carry a significant risk of systemic toxicity even when cutaneous involvement is small (~1%). In these instances, regular monitoring of blood, liver and kidney function, with appropriate supportive treatment, is required [7].

When the chemical is a sensitizer, allergic contact dermatitis may subsequently occur on re-exposure to non-irritant concentrations, as burns and irritant dermatitis appear to promote sensitization [8].

References

1 Bruze M, Fregert S, Gruvberger B. Chemical skin burns. In: Kanerva L, Elsner P, Wahlberg JE, Maibach HI, eds. *Handbook of Occupational Dermatology*. Berlin: Springer, 2000: 325–32.
2 Pruitt VM. Work-related burns. *Clin Occup Environ Med* 2006; **5**: 423–33.
3 Flamminger A, Maibach HI. Sulfuric acid burns (corrosion and acute irritation): evidence based overview to management. *Cutan Ocular Toxicol* 2006; **25**: 55–61.
4 Matsuno K. The treatment of hydrofluoric acid burns. *Occup Med* 1996; **46**: 313–7.
5 Matey P, Allison KP, Sheehan TMT *et al*. Chromic acid burns: early aggressive excision is the best method to prevent systemic toxicity. *J Burn Care Rehabil* 2000; **21**: 241–5.
6 Grubauer G, Elias PM, Feingold KR. Transepidermal water loss: the signal for recovery of barrier structure and function. *J Lipid Res* 1989; **30**: 323–33.
7 Chan TC, Williams SR, Clark RF. Formic acid skin burns resulting in systemic toxicity. *Ann Emerg Med* 1995; **26**: 383–6.
8 McFadden JP, Basketter DA. Contact allergy, irritancy and danger. *Contact Dermatitis* 2000; **42**: 123–7.

Irritant contact dermatitis

The successful management [1] of irritant contact dermatitis requires both prevention and subsequently treatment if dermatitis develops.

The most important aspect of treatment is avoidance of the cause (Table 25.8). In an occupational setting, automation of the production process may avoid exposure but can be expensive. A cost-effective compromise is the use of personal protective equipment and/or substitution of a chemical. It should be remembered that natural rubber latex gloves provide protection against water-miscible substances but may be inappropriate for other exposures (Table 25.9). With organic solvents and chemicals the choice of glove material may vary [2]; advice may be found on the material safety data sheet.

Once present, dermatitis requires palliation of symptoms with topical steroids and emollients. The efficacy of topical corticosteroids in irritant contact dermatitis has been questioned [3,4], although another study has shown benefit [5]. Retinoids and vitamin D analogues are not of any value [3].

Experimentally, an emollient alone has been shown to improve barrier repair. The choice of emollient may be important, with lipid-rich preparations being more effective. Studies have shown that barrier repair may be impaired or accelerated according to the constituents of a physiological lipid mixture [6]. It has been suggested that conditions in which the lamellar body secretory system is impaired or immature (radiation dermatitis, sunburn, irritant dermatitis due to some surfactants and retinoids, and premature infants of less than 33 weeks' gestation) should be treated with non-physiological lipids, e.g. petrolatum, whereas most other causes of irritant dermatitis, where lipid metabolism has not been deranged (e.g. diaper dermatitis), should be treated with a mixture of cholesterol : ceramides : free fatty acids, in a 3 : 1 : 1 ratio, to achieve most rapid return to normal barrier function [7].

In severe cases, phototherapy or systemic drugs such as azathioprine and ciclosporin (cyclosporin) may be required. Where there is secondary infection, topical or systemic antimicrobial agents may be necessary.

References

1 Saary J, Qureshi R, Palda V *et al*. A systematic review of contact dermatitis treatment and prevention. *J Am Acad Dermatol* 2005; **53**: 845–55.
2 Berardinelli SP. Prevention of occupational skin disease through use of chemical protective gloves. *Dermatol Clin* 1988; **6**: 115–9.
3 Le TK, de Mon P, Schalkwijk J, van der Valk PG. Effect of a topical steroid, a retinoid, and a vitamin D3 derivative on sodium dodecyl sulphate induced skin irritation. *Contact Dermatitis* 1997; **37**: 19–26.

Table 25.8 Advice to patients with hand eczema.

To speed healing and prevent your dermatitis from returning, you must now take great care of your hands and allow your skin to heal and recover its natural resilience/strength (this may take many months, even though the skin may look normal before then)

1 Use a hand cream many times a day so that the skin does not become dry

2 Use the steroid creams/ointments prescribed by the doctor

3 Hand washing. Use lukewarm water and soap substitute (e.g. aqueous cream). If soap is used, find a soap with no fragrance, tar or sulphur, use it sparingly, rinse thoroughly and then dry thoroughly (especially finger webs and wrists)

4 If wet work cannot be avoided wear gloves; use plastic rather than rubber, preferably with a cotton lining
- Avoid contact with detergents and other cleaning agents. Always dilute them according to manufacturers' instructions. Keep outside of container clean or you will contaminate your hands with the neat product
- When washing up, use running water and a pot brush rather than a cloth
- Washing machines and dishwashers are a great help, but avoid contact with detergent powder or liquid—use a measure with a handle
- Water softeners are helpful, but too expensive unless you are not contemplating moving house for a long time. Try adding water softener, e.g. Calgon, to dish water, washing water, baths, etc.; less soap/detergent is then required
- Avoid contact with polish, e.g. metal, shoe, floor, car, furniture, window and wax polishes. NB: Spray polish carries a long way
- Avoid contact with shampoo. Either use plastic gloves or get someone else to wash your own and your children's hair
- Do not apply hair products with bare hands, e.g. setting mousse/gel/lotions, colourants, creams, brilliantine. Some of these are irritant, but the friction of running hands through hair is considerable
- Avoid contact with solvents, e.g. white spirit and brush cleaners, petrol, trichlorethylene, xylene, carbon tetrachloride, e.g. dry cleaning and stain-removal agents. Solvents pass through rubber gloves. Buy vinyl for these jobs
- Do not peel citrus fruits with bare hands, e.g. oranges, lemons, satsumas

5 Wear gloves in cold weather

6 If the skin becomes inflamed and throbs, it is likely to be infected. Visit your doctor, who may take a skin swab and prescribe antibiotic treatment
- Individuals with hand eczema are at increased risk of contracting infection through damaged skin and should wear gloves when in contact with blood or potentially infectious biological secretions, e.g. when handling soiled linen, cleaning lavatories, etc.
- Patients with hand eczema should not be involved in commercial food preparation because the bacteria that cause infection may also cause food poisoning

Your hand eczema should improve if you follow all these suggestions. Once the skin appears to have healed, you should always continue to take care of your hands

4 Levin C, Zhai H, Bashir S *et al*. Efficacy of corticosteroids in acute experimental irritant contact dermatitis? *Skin Res Technol* 2001; **7**: 214–8.
5 Ramsing DW, Agner T. Efficacy of topical corticosteroids on irritant skin reactions. *Contact Dermatitis* 1995; **32**: 293–7.
6 Yokota M, Maibach HI. Moisturizer effect on irritant dermatitis: an overview. *Contact Dermatitis* 2006; **55**: 65–72.
7 Elias PM, Feingold KR. Does the tail wag the dog? Role of the barrier in the pathogenesis of inflammatory dermatoses and therapeutic implications. *Arch Dermatol* 2001; **137**: 1079–81.

Non-immune contact urticaria

The mechanism of action of non-immunological contact reactions is not known, but is presumed to be via direct release of inflammatory mediators, including prostaglandins and leukotrienes [1]; the reaction is blocked by non-steroidal anti-inflammatory drugs and ultraviolet light, or by pretreatment with capsaicin, but not by antihistamines [2–4].

References

1 Lahti A, Maibach HI. Immediate contact reactions: contact urticarial syndrome. *Semin Dermatol* 1987; **6**: 313–20.
2 Johansson J, Lahti A. Topical non-steroidal anti-inflammatory drugs inhibit non-immunologic immediate contact reactions. *Contact Dermatitis* 1988; **19**: 161–5.
3 Larmi E, Lahti A, Hannuksela M. Ultraviolet light inhibits non-immunologic contact reactions to benzoic acid. *Arch Dermatol Res* 1988; **280**: 420–3.
4 Lahti A, Vaaneucu A, Kokkoneu EL, Hannuksela M. Effects of capsaicin and topical anesthesia on non-immunologic immediate contact reactions to benzoic acid and methyl nicotinate. In: Frosch PJ, Dooms-Goossens A, La Chapelle JM *et al*., eds. *Current Topics in Contact Dermatitis*. Berlin: Springer, 1989: 441–7.

Symptomatic irritant responses

Treatment is largely that of avoidance, although strontium salts have been shown to inhibit the sensation [1]. Currently this seems of little practical value.

Reference

1 Zhai H, Hannon W, Hahn GS *et al*. Strontium nitrate suppresses chemically-induced sensory irritation in humans. *Contact Dermatitis* 2000; **42**: 98–100.

Prevention

Identification of the susceptible individual and appropriate career advice prior to employment may reduce an individual's risk of

Table 25.9 Recommended glove materials for chemical protection. (From Berardinelli [2].)

Glove materials	Nitrile	Butyl	Neoprene	Fluorocarbon	PVC	PVA	Notes
Aliphatic hydrocarbons	+			+		+*	Except cyclohexane*
Aromatic hydrocarbons	+			+		+*	Except ethylbenzene*
Halogenated hydrocarbons			+		+*		Except methyl chloride* and halothane*
Aldehydes, amines, amides	+*						Except butylamine* and triethylamine*
Esters			+*			+†	Except butylacrylate* and octylphthalate†
Alkalis		+		+		+	
Organic acids	+*	+	+†				Except acrylic*†, methacrylic*† and acetic* acids
Inorganic acids	+*		+†		+‡		Except chromic†, hydrofluoric*, nitric*‡ and sulphuric*‡ acids

PVA, polyvinyl alcohol; PVC, polyvinyl chloride.

developing dermatitis. Skin irritation thresholds to SLS have been shown to correlate with the subsequent development of dermatitis in hairdressers [1]. Education of an individual or workforce is a prerequisite. Although preventive measures may be available, individuals may not make use of them if they do not understand the rationale for so doing. In health-care workers, those in an intervention group had a 3-year prevalence of visible skin change of 66.7% compared with 89.3% in the control population. The odds ratio for developing skin changes was 4.8 (confidence interval 2.9–7.8) in controls compared with those who underwent an education programme [2].

Mechanization

In general, increased use of mechanization for wet or irritant work, thus avoiding exposure, will help to reduce the incidence of irritant contact dermatitis.

Personal protective equipment/clothing

Prolonged use of gloves may increase TEWL, but in general their protective effects outweigh any potential to induce dermatitis. Use of gloves with a cotton liner has been shown to result in less impairment of skin barrier function [3]. In a study of hairdressers, unprotected wet work for greater than 2 h per day was the most significant risk factor for the development of dermatitis [4]. Gloves should be carefully chosen for the specific chemical exposure (see above). The properties of a specific glove can be delineated as the breakthrough time and the rate of penetration for any specific chemical. In general, the thicker the glove the longer the breakthrough time. The rate of penetration then determines the flow through the material. For a specific timed exposure, a glove with a short penetration time may be preferable to one with a longer penetration time if the flow through the glove is low, whereas the other results in significant chemical exposure once penetration has occurred. Help in choosing a glove can often be found on the website of commercial suppliers (e.g. www.ansell-edmont.com). Chemical degradation occurs when a substance reacts with the glove material, impairing its physical properties. Other conditions of use should also be borne in mind; for example use of gloves in metal machining runs the risk of tears and, if the glove is caught in machinery, trauma to the hand.

For the domestic environment, the use of fabric softener has been shown to result in clothing being better tolerated on irritated and sensitive but otherwise normal skin [5].

References

1 Smith HR, Armstrong DKB, Holloway D *et al*. Skin irritation thresholds in hairdressers: implications for the development of hand dermatitis. *Br J Dermatol* 2002; **146**: 849–52.

2 Löffler H, Bruckner T, Diepgen T, Effendy I. Primary prevention in health care employees: a prospective intervention study with a 3 year training period. *Contact Dermatitis* 2006; **54**: 202–9.

3 Ramsing DW, Agner T. Effect of glove occlusion on human skin (II): long-term experimental exposure. *Contact Dermatitis* 1996; **34**: 258–62.

4 Uter W, Pfahlberg A, Gefeller O, Schwanitz HJ. Hand dermatitis in a prospectively-followed cohort of hairdressing apprentices: final results of the POSH study. Prevention of occupational skin disease in hairdressers. *Contact Dermatitis* 1999; **41**: 280–6.

5 Pierard GE, Arrese JE, Rodrigues C, Daskaleros PA. Effects of softened and unsoftened fabrics on sensitive skin. *Contact Dermatitis* 1994; **30**: 286–91.

Topical preparations

Barrier creams are designed to reduce the penetration of hazardous materials into the skin. Some are specifically formulated for individual chemical exposure. It is said that water-in-oil emulsions protect against aqueous irritants and oil-in-water ones against lipophilic materials [1]. At best they have only a marginal effect [2], and inappropriate use may exacerbate dermatitis. Most claim to give 4 h protection, although others suggest applying 'as necessary'. They are, in general, more effective as a means of preventing excessive soiling of the hands, and therefore may help to avoid the need for strong cleaners which are often more damaging than agents causing the soiling. They may be effective against airborne irritants on the face. The use of barrier creams should not be over-promoted as this may engender a false sense of security rather than a reliance on more effective measures. If they are used, instruction in their application is essential if areas of skin are not to be missed [3].

Emollients or hand creams will help to prevent dryness or chapping of the skin, and may also help to prevent subsequent development of dermatitis [4]. They are promoted as after-work creams, and controlled trials have shown their effectiveness. Conversely, prolonged use of emollient has been shown to increase susceptibility to irritant dermatitis in an experimental setting. The relative risk/benefit may therefore depend on the circumstances of use or the constituents of the product, with high lipid content products generally performing better [5]. The term 'anti-irritant' has been used to describe the use of an ingredient in a product that minimizes the irritant effect of another. Experimentally, only glycerol has been shown to have some benefit in this respect [6]. The contents of a suggested skin protection programme are summarized in Table 25.10 [7].

Soap substitutes have been shown to be effective in preventing dermatitis when compared with soaps and detergent-based products [8]. Other practices associated with hand washing should also be critically evaluated. In medicine, the habit of using a brush when scrubbing for a surgical procedure has been shown to increase TEWL without any additional benefit in reducing bacterial contamination [9].

References

1 Zhai H, Anigbogu A, Maibach HI. The treatment of irritant and allergic contact dermatitis. In: Kanerva L, Elsner P, Wahlberg JE, Maibach HI, eds. *Handbook of Occupational Dermatology*. Berlin: Springer, 2000: 402–11.

2 Berndt U, Wigger-Alberti W, Gabard W *et al*. Efficacy of a barrier cream and its vehicle as protective measures against occupational irritant contact dermatitis. *Contact Dermatitis* 2000; **42**: 77–80.

3 Wigger-Alberti W, Maraffio B, Wernli M, Elsner P. Self-application of a protective cream: pitfalls of occupational skin protection. *Arch Dermatol* 1997; **133**: 861–4.

4 Saary J, Qureshi R, Palda V *et al*. A systematic review of contact dermatitis treatment and prevention. *J Am Acad Dermatol* 2005; **53**: 845–55.

5 Buraczewska I, Berne B, Lindberg M *et al*. Changes in skin barrier function following long term treatment with moisturizers: a randomised controlled trial. *Br J Dermatol* 2007; **156**: 492–8.

6 Andersen F, Hedegaard K, Petersen TK *et al*. Anti-irritants I: dose-response in acute irritation. *Contact Dermatitis* 2006; **55**: 148–54.

7 Agner T, Held E. Skin protection programmes. *Contact Dermatitis* 2002; **46**: 253–6.

8 Lauharanta J, Ojajarvi J, Sarna S, Makela P. Prevention of dryness and eczema of the hands of hospital staff by emulsion cleansing instead of washing with soap. *J Hosp Infect* 1991; **42**: 77–80.

Table 25.10 Recommended occupational skin protection programme [7].

Washing
Wash in lukewarm water—the damage caused by detergent is temperature dependent
Rinse and dry thoroughly—dermatitis often develops in web spaces and other areas frequently missed
Do not wear rings—soap and other irritants accumulate underneath
Disinfection
Do not use unless a job requirement—disinfectants are more irritant than ordinary washing
Alcohol gel may be preferable—detergent-based disinfectants are more irritant [10]
Gloves
Wear gloves—unprotected wet work is a major cause of irritant dermatitis
Wear for as short a time as possible—prolonged usage impairs barrier function
Wear with a cotton liner—prevents the irritation induced by glove occlusion
Change them frequently—occlusion enhances the effect of irritants that are contaminating or penetrate gloves
Emollients
Apply during and after work—to prevent and treat dermatitis if it develops
Apply to all of the hand—areas are often missed
Use a lipid-rich product—more effective than the alternatives
At home
Follow the same measures—domestic exposures are additive
Wear warm gloves in winter—the skin is more susceptible to irritants in winter

9 Kikuchi-Numagami K, Saishu T, Fukaya M *et al*. Irritancy of scrubbing up for surgery with or without a brush. *Acta Derm Venereol (Stockh)* 1999; **79**: 230–2.
10 Pedersen LK, Held E, Johansen JD, Agner T. Less skin irritation from alcohol-based disinfectant than from detergent used for hand disinfection. *Br J Dermatol* 2005; **153**:1142–6.

Prognosis

Following experimental induction of contact dermatitis with 1% SLS, the response to further irritant exposure on previously irritated skin returned to normal after 4 weeks [1]. As the duration of the initial stimulus extends, recovery time is prolonged, with the skin remaining abnormal 10 weeks after a 3-week induction [2].

Clinically, assessment of the prognosis of irritant contact dermatitis is mostly based on occupational studies in which exposure to irritants has been prolonged. In a Danish study of 758 workers with occupational hand dermatitis 25% had persistent severe disease, 41% were improved and 34% had mild-to-moderate disease 1 year later. Individuals older than 40 and with an atopic background had a worse prognosis. Age greater than 40 and severe impairment of quality of life at baseline were predictors of long-term sick leave and unemployment. Those with a lower socioeconomic status also had greater risk of prolonged sick leave, change and loss of job. There was no influence of sex on prognosis, although other studies have variably agreed and disagreed with this finding [3]. An American study found that 47% of claims for workers' compensation came from individuals with less than 1 year's job tenure, with the average case costing US$3552 with 23.9 days of disability [4]. A change of job may be helpful if undertaken early, but is of less benefit in those with established and chronic dermatitis [5]. Some individuals simply exchange one inappropriate job for another [6], with continued exposure to irritants. Delay in diagnosis and assessment worsens prognosis. Lack of knowledge as to the cause of their dermatitis [7] will also affect a patient's overall prognosis and outcome. In a population-based study of hand dermatitis, after 15 years 44% still experienced symptoms, with 36% experiencing sleep disturbance and 72% disturbance of leisure activities. Five per cent of individuals experienced prolonged sick leave, early retirement or change in occupation [8].

Although too frequent or too extreme exposure to irritants will normally lead to dermatitis, some workers exposed to irritants seem to develop hardening. Experimentally, following repetitive irritation with SLS for 3 weeks the skin returned to normal reactivity after 3 weeks, but subsequently became hyporesponsive up to 9 weeks after the initial insult [9].

Persistent post-irritant dermatitis

Some hand eczemas that start as irritant or allergic contact dermatitis subsequently persist when the original cause has been eliminated. Whether, in these individuals, there is some inherent constitutional factor that leads to persistence, or whether some eczemas simply become self-perpetuating, remains unclear. In the occupational setting this has been labelled 'persistent post-occupational dermatitis' [6], and affected 11% of individuals in the absence of any other contributory factor or known constitutional tendency. It seems probable that a similar situation would appertain following non-occupational exposures. In circumstances where an individual is receiving compensation, the failure to recognize the entity may result in termination of their income [10].

References

1 Lee JY, Effendy I, Maibach HI. Acute irritant dermatitis: recovery time in man. *Contact Dermatitis* 1997; **36**: 285–90.
2 Choi JM, Lee JY, Cho BK. Chronic irritant dermatitis: recovery time in man. *Contact Dermatitis* 2000; **42**: 264–9.
3 Cvetkovski RS, Zachariae R, Jensen H *et al*. Prognosis of occupational hand eczema: a follow-up study. *Arch Dermatol* 2006; **142**: 305–11.
4 McCall BP, Horwitz IB, Feldman SR, Balkrishnam R. Incidence rates, costs, severity and work-related factors of occupational dermatitis. *Arch Dermatol* 2005; **141**: 713–8.
5 Hogan DJ, Dannaker CJ, Maibach HI. The prognosis of contact dermatitis. *J Am Acad Dermatol* 1990; **23**: 300–7.
6 Wall L, Gebauer K. A follow-up study of occupational skin disease in Western Australia. *Contact Dermatitis* 1991; **24**: 241–3.
7 Holness DL, Nethercott JR. Is a worker's understanding of their diagnosis an important determinant of outcome in occupational contact dermatitis? *Contact Dermatitis* 1991; **25**: 296–301.
8 Meding B, Wrangso K, Jarvholm B. Fifteen-year follow-up of hand eczema: persistence and consequences. *Br J Dermatol* 2005; **152**: 975–80.
9 Widmer J, Elsner P, Burg G. Skin irritant reactivity following experimental cumulative irritant contact dermatitis. *Contact Dermatitis* 1994; **30**: 35–9.
10 Cahill J, Keegel T, Dharmage S *et al*. Persistent post-occupational dermatitis. *Contact Dermatitis* 2004; **51**: 278–83.

CHAPTER 26

Contact Dermatitis: Allergic

M.H. Beck[1] *& S.M. Wilkinson*[2]

[1]Dermatology Centre, University of Manchester, Salford Royal Hospital, Salford, Manchester, UK
[2]Department of Dermatology, Leeds General Infirmary, Leeds, UK

History, 26.1
Epidemiology, 26.2
Methodologies, 26.2
Prevalence, 26.3
Pathogenesis, 26.5
Sensitization, 26.5
Elicitation, 26.6
Predisposing factors, 26.6
Individual, 26.6
Environmental, 26.10
Chemical, 26.11
Pathology, 26.13
Clinical features, 26.13
History, 26.13
Clinical examination, 26.14
Systemically reactivated contact dermatitis, 26.22
Cutaneous reactions to implanted metals, 26.23
Photoallergic contact dermatitis, 26.23
The allergens, 26.23
Clinical features, 26.24
Avoidance, 26.24
Investigation, 26.24
Non-eczematous responses, 26.25
Contact urticaria, 26.25
Erythema multiforme-like reactions, 26.25
Purpuric reactions, 26.26
Lichen planus and lichenoid reactions, 26.26
Lymphomatoid eruptions, 26.26
Pigmented dermatitis, 26.26
Depigmentation, 26.26
Granulomatous reactions, 26.26
Onycholysis, 26.27
Systemic non-eczematous, 26.27
Differential diagnosis, 26.28
Allergic contact dermatitis to specific allergens, 26.30
Metals, 26.30
Fragrances, balsams, flavouring agents and spices, 26.40
Applied medicaments, 26.43
Cosmetics, 26.47
Antimicrobial agents and preservatives, 26.49
Vehicles and other cosmetic and medicament excipients, 26.58
p-Phenylenediamine and related dyes, 26.60
UV filters, 26.62
Rubber, 26.63
Clothing, 26.65
Shoes, 26.68
Resins and plastics, 26.69
Plants, 26.74
Woods, colophony, turpentine and propolis, 26.79
Patch testing, 26.84
Background, 26.84
Indications, 26.84
Methods, 26.84
Exposure time, 26.86
Readings and interpretation, 26.87
Relevance of patch tests, 26.88
Non-invasive measurement techniques, 26.88
Sources of error, 26.88
Selection of test substances, 26.91
Concentrations and vehicles for patch testing, 26.92
Photopatch testing, 26.93
Complications of patch and photopatch tests, 26.94
Multiple patch-test reactions, 26.95
Other tests, 26.97
In vitro tests, 26.98
Spot tests, 26.99
Prevention, 26.99
Management, 26.101
Prognosis, 26.103
Immune contact urticaria, 26.104
Pathogenesis, 26.104
Clinical features, 26.104
Investigations, 26.106
Management, 26.106

History [1]

The term 'allergie' was first coined by the scientist von Pirquet in 1906 [2]. The word was derived from the Greek *allos* and *ergon*, meaning other or different work [3]. However, idiosyncratic reactions to various substances had been recognized since the 17th century [2]. In 1829, Dakin observed the selectivity of *Rhus* dermatitis [4] and Fuchs suggested that 'dermatitis venenata' was an expression of constitutional idiosyncrasy in 1840 [5]. The word 'idiosyncrasy' was again applied by Neisser in his descriptions of iodoform dermatitis in 1884 [6].

Allergic sensitization of the skin was first proved experimentally by Bloch and Steiner-Woerlich using *Primula* extract on humans [7]. Thereafter, research on the pathogenesis of allergic dermatitis has largely involved animal experiments using guinea pigs. Landsteiner and Jacobs [8] performed the basic experiment, which showed that a simple chemical capable of causing contact dermatitis must be combined with proteins in order to sensitize. Up to 1940 it was not known whether sensitization depended on a factor localized in the skin, but in 1942 Landsteiner and Chase [9] succeeded in transmitting sensitivity from one guinea pig to another by the use of a mainly mononuclear peritoneal exudate from sensitized guinea pigs. In the same year, Haxthausen's transplantation experiments [10] finally proved that allergy was due to a factor supplied to the skin from within.

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

Patch testing is the diagnostic tool for allergic dermatitis and it is Josef Jadassohn who is generally accepted as the founder of this technique in 1895 while working at Breslau University, publication taking place the following year [11]. Nevertheless, anecdotal observations of a similar nature had been made prior to this, usually by applying the suspected causative agent to intact skin [12]. By 1847 Stadeler had developed a rudimentary patch test using blotting paper to reproduce lesions provoked by *Anacardium occidentale* [13].

Bruno Bloch was a dermatological pioneer who was able to expand and enhance Jadassohn's technique while working in Basel in 1911, when he also produced a grading system for patch-test reactions [14]. He then moved to Zurich where he introduced the concept of a standard series of allergens [15]. He furthermore conceived important ideas about both cross-sensitization and systemic allergic contact dermatitis [1]. Marion Sulzberger had been an assistant to both Bloch and Jadassohn before returning to New York where he introduced the patch-test technique and was a strong advocate and promoter of its use in the New World. Another former assistant of Bloch's, Paul Bonnevie, Professor of Occupational Medicine in Copenhagen, expanded the standard series to what could be considered the prototype of our present-day series.

By the early 1960s, Scandinavian dermatologists were developing a standardized protocol for patch testing and their group was expanded to involve, initially, other European members before it finally evolved into the International Contact Dermatitis Research Group (ICDRG) [1]. Further national and international research groups have proliferated in the last 20 years, a fitting recognition of the significance of the findings and researches of these earlier pioneers.

References

1 Lachapelle J-M. Historical aspects. In: Frosch PJ, Menné T, Lepoittevin J-P, eds. *Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 1–7.

2 Adams RM. Diagnostic patch testing. In: *Occupational Skin Disease*. New York: Grune & Stratton, 1983: 136.

3 Ayto J. *Dictionary of Word Origins*. London: Bloomsbury, 1990: 18.

4 Dakin R. Remarks on a cutaneous affection produced by certain poisonous vegetables. *Am J Med Sci* 1829; **4**: 98–100.

5 Fuchs CH. *Die Krankhaften Veränderungen der Haut—und ihre Anhänge*. Göttingen: Dieterichs'sche Buch-handlung, 1840.

6 Neisser A. Ueber Iodoform-Exantheme. *Dtsch Med Wochenschr* 1884; **10**: 467–8.

7 Bloch B, Steiner-Woerlich A. Die willkürliche Erzeugung der Primelüberempfindlichkeit bein Menschen und ihre Bedeutung für das Idiosynkrasieproblem. *Arch Dermatol Syphilol* 1926; **152**: 283–303.

8 Landsteiner K, Jacobs J. Studies on the sensitization of animals with simple chemical compounds. *J Exp Med* 1936; **64**: 629–39.

9 Landsteiner K, Chase MW. Experiments on transfer of cutaneous sensitivity to simple compounds. *Proc Soc Exp Biol Med* 1942; **49**: 688–90.

10 Haxthausen H. The pathogenesis of allergic eczema elucidated by transplantation experiments on identical twins. *Acta Derm Venereol (Stockh)* 1942; **23**: 438–57.

11 Jadassohn J. Zur Kenntnis der medikamentosen Dermatosen. In: *Verhandlungen der Deutsch Dermatoligischen Gesellschaft, V Congress, Graz (1895)*. Vienna: Braumuller, 1896: 103–29.

12 Foussereau J. History of epicutaneous testing: the blotting-paper and other methods. *Contact Dermatitis* 1984; **11**: 219–23.

13 Stadeler J. Uber die eigenthumthumlichen Bestandteile der Anacardium Fruchte. *Ann Chemie Pharmacie* 1847; **63**: 117–65.

14 Bloch B. Experimentelle Studien über das Wesen der Iodoformidiosynkrasie. *Z Exp Pathol Ther* 1911; **9**: 509–38.

15 Bloch B. The role of idiosyncrasy and allergy in dermatology. *Arch Dermatol Syphilis* 1929; **19**: 175–97.

Epidemiology [1]

Prevalence and incidence (definition). Definition of these terms is important as they mean two different things. Prevalence relates to the number or proportion of individuals who are identified with the condition being studied (e.g. contact dermatitis, nickel allergy) at a given *point* in time, or over a certain *period* of time. Incidence relates to the number of new cases developing over a defined period of time and is expressed as number of cases per unit of time. Knowledge of the sample size is also essential to give an indication of the reliability of the data.

Methodologies

Epidemiological studies may be undertaken on the general population or on selected groups, for example those referred for patch testing or those with a specific occupation.

Follow-up studies select individuals on the basis of the presence or absence of a defined risk factor such as 'wet work'. The relative risk of developing hand dermatitis can then be calculated as the ratio of those developing dermatitis in the exposed to unexposed population. The attributable risk is the difference in incidence rates between the two populations.

Case–control studies select individuals based on the presence or absence of a particular disease. By comparing the frequency of exposure to a factor such as 'wet work' in the two populations an odds ratio can be calculated that expresses the relative contribution of the exposure to the development of the disease. In such studies the choice of controls is critical if the results are not to be biased.

In cross-sectional studies, all individuals are studied irrespective of exposure or disease status (in contrast with the above).

Data collection. The method of data collection in studies on the general population, which need to be large to gain useful information and are challenging to perform, can significantly influence the results. For reasons of expediency, questionnaires have been used, but when performed alone underestimate those suffering from dermatitis because accuracy of recall fades with time. The validity of the results also depends on the extent to which those who respond to the questionnaire differ from those who do not. As a rough guide, studies in which the response rate is below 70% may be unrepresentative.

Population assessments made on individuals attending a general practitioner or referred to a dermatologist may be unreliable, particularly in the UK where prompt access to a dermatologist is achieved only by the fortunate few. In a UK survey, only 21% of those with skin disease thought to justify medical care had seen their general practitioner about it in the previous 6 months [2]. In another large-scale study of a Swedish population of over 107 000, only 50% of the patients with dermatitis had seen a doctor within the previous year [3].

Table 26.1 Occupational skin disease: estimated rate per 100 000 workers reported to EPIDERM (Occupational Dermatoses Surveillance Scheme, University of Manchester) [4].

Dermatologists	
Hairdressers and barbers	116.3
Printers	85.8
Beauticians	76.8
Other chemical operatives	69.1
Window dressers, floral arrangers	68.1
Occupational physicians	
Other chemical operatives	183.8
Glass product and ceramic makers	101.2
Vehicle and metal assemblers	94.8
Engineering labourers	82.4
Machine tool operatives	67.9

The reporting of contact dermatitis also varies according to the method of collection and the type of person collecting the data. Results from the UK EPIDERM occupational dermatoses surveillance study show how reports of occupational dermatoses differ according to whether the returns are made by dermatologists or by occupational health physicians [4] (Table 26.1). The differences probably reflect the different types of occupational population accessed by the two groups. Occupational physicians will relate to large industries and collective working groups, whereas dermatologists will mainly receive individual referrals, accounting for the comparatively high representation of, for example, hairdressers, florists and beauticians seen by them.

Case definition. Studies of the epidemiology of dermatitis may be further confounded by the fact that it is commonly multifactorial in origin. It is therefore difficult to analyse the relative prevalence of irritant versus allergic contact dermatitis because the two commonly coexist, and constitutional eczema may also be involved. Ideally, all those studied should be examined and patch tested, but this is not always a practical proposition when large numbers of an unselected group are being assessed.

Standardization. Apparent differences in overall sensitization frequencies may be due to differences in population structure, especially in relation to age and sex. This can be compensated for either by using standardized populations or by reporting results within specified age bands, and by reporting results for each sex separately.

However, in a particular clinic the incidence of allergic contact dermatitis is reflected not only by the sex and age of the patients but also by the industrial development in the area and the degree of interest dermatologists take in the various facets of contact dermatitis (e.g. occupational dermatitis, medicament allergy or leg ulcers). Furthermore, local prescribing habits can influence patch-test results. It has been suggested that all comparative patch-test data should include an analysis of patient details, the MOAHL index, where M is percentage of males tested, O is percentage occupational, A is percentage of atopics, H is percentage of patients with hand eczema, and L is percentage of patients with leg ulcers or stasis eczema. The percentage of atopics is important, particularly in relation to irritant contact dermatitis. Certain body sites, especially the lower legs in those with stasis eczema or leg ulcers and the ears, eyelids and perineum, have a particularly high level of allergic contact dermatitis from medicaments. Inclusion of a significant number of any such cases in a patch-test series will affect the overall sensitivity rates for various allergens. Further enhancement to the index has been suggested by adding F, the proportion of those with facial dermatitis, and A, those above the age of 40, to generate the MOAHLFA index [5]. Guidelines for the presentation of contact allergy data have been produced [6].

References

1 Coenraads P-J, Diepgen T, Uter W *et al*. Epidemiology. In: Frosch PJ, Menné T, Lepoittevin J-P, eds. *Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 135–63.

2 Rea JN, Newhouse ML, Halil T. Skin disease in Lambeth. A community study of prevalence and use of medical care. *Br J Prev Soc Med* 1976; **30**: 107–14.

3 Agrup G. Hand eczema and other hand dermatoses in South Sweden. *Acta Derm Venereol Suppl (Stockh)* 1969; **61**.

4 Cherry N, Meyer JD, Adisesh A *et al*. Surveillance of occupational skin disease: EPIDERM and OPRA. *Br J Dermatol* 2000; **142**: 1128–34.

5 Schnuch A, Geier J, Uter W *et al*. National rates and regional differences in sensitization to allergens of the standard series. Population-adjusted frequencies of sensitization (PAFS) in 40,000 patients from a multicenter study (IVDK). *Contact Dermatitis* 1997; **37**: 200–9.

6 Uter W, Schnuch A, Gefeller O. Guidelines for the descriptive presentation and statistical analysis of contact allergy data. *Contact Dermatitis* 2004; **51**: 47–56.

Prevalence [1]

General population studies

Contact dermatitis accounts for 4–7% of all dermatological consultations. Skin disease, chiefly dermatitis, accounts for almost half of all reported cases of occupational disease. Over 20% of females will suffer from hand eczema at some stage in their lives. In one population study in southern Sweden, hand eczema was shown to affect 11.8% of the population aged 20–65 years over a 12-month period. A recent follow-up study indicates that this frequency has dropped to 9.8% despite a rise in the level of childhood atopic eczema [2].

A number of other studies on the prevalence of contact dermatitis in the unselected general population have been undertaken, but those that include clinical assessments and patch tests are rare, making it more difficult to ascertain the prevalence of allergic contact dermatitis. A study of 1500 children aged 12–16 years in Denmark, which involved an initial questionnaire followed by interview, clinical examination and patch testing, found a lifetime prevalence of hand dermatitis of 9.2%, with a 1-year prevalence of 7.3% and point prevalence of 3.2%. Patch testing showed a point prevalence of contact sensitivity of 15.2%. There was a clear sex difference, with 19.4% of girls and 10.3% of boys being patch-test positive. Following interview and examination, a lifetime prevalence of allergic contact dermatitis of 7.2% and point prevalence of 0.7% was demonstrated. Of the girls, 11.3% gave a history of relevant contact allergy, compared with 2.5% of boys. Allergens responsible included nickel 8.6%, fragrance 1.8%, colophony 1% and PTBP formaldehyde resin 0.9%. The study showed a significant association between contact allergy and hand eczema but no relation between contact allergy and either atopic eczema or inhalant allergy [3]. A smaller study in adults, with participation rates of 69% in 1990 and 51% in 1998, showed a point prevalence of

contact sensitivity of 15.9% in 1990 rising to 18.6% in 1998. Risk factors for nickel allergy included female sex, young age and ear piercing (before 1990). With the introduction of controls on nickel release from jewellery the association of ear piercing with nickel allergy was lost [4]. A recent Norwegian study with a response rate of 60%, that included 1236 adults patch tested to the TRUE test, found contact sensitivity in 35.4% of women and 14.8% of men. Positive allergens included nickel 17.6%, cobalt 2.8%, thiomersal 1.9%, fragrance mix 1.8% and colophony 1.2%. Smoking and atopic eczema were thought to be risk factors [5].

Selected population studies

Most other epidemiological studies have been based on patients already attending dermatology clinics, or have involved either specific occupational or other population groups.

The selective nature of patients patch tested in dermatological clinics for investigation of contact allergy is not necessarily representative of the general population; nevertheless, the findings may reflect the relative frequency of the causes of allergic contact dermatitis in that population. Patch testing can be used to generate information on individuals, groups of patients and allergens, and also to assess risk factors in groups of workers and particular subgroups of the population.

Dermatology patients

The percentage of patients with positive reactions to many standard test substances remains largely constant [6], and although some allergens such as colophony, methylchloroisothiazolinone and methylisothiazolinone (MCI/MI), thiuram mix and nickel in women have become less common, this has been balanced by an increase in other sensitizers such as *Myroxylon pereirae*, and paraphenylenediamine in women. The prevalence of allergy to specific allergens in patch-tested patients is discussed later in the chapter. It should be remembered that the presence of sensitization does not imply the presence of dermatitis. In addition, variations in the reading or interpretation of patch-test results will affect the perceived prevalence of contact dermatitis.

In general, the commoner allergens are similar from one country to another, although there are differences in rank order [7–10]. Some environmental allergens are widely dispersed and the level of sensitivity remains fairly constant, but cosmetics and fragrance materials are becoming increasingly important sources of sensitivity. Medicament allergens, such as benzocaine, neomycin and lanolin, are common in all countries. However, there may be differences in prescribing habits even within the same country, which can be reflected by the pattern of medicament sensitization. Corticosteroid allergy has been shown to have a very different profile in Oxford compared with Manchester, UK, by virtue of differences in prescribing habits leading to greater usage of non-fluorinated corticosteroids in the latter catchment [11].

Young females tend to have more cosmetic and occupational sensitivities; in older people, many sensitivities will be of past relevance only, and there will be a higher prevalence of medicament sensitivity. Nickel sensitivity is common in women and, unless allowance is made for this, false occupational associations may be inferred. Allergens can come and go [12], and the prevalence of sensitivity to an individual substance will depend on many variables, including the selection of individuals to be tested, exposure levels, fashion, environment, introduction of new materials and loss of others, maximum permitted concentrations and usage.

The incidence and prevalence of allergic reactions will therefore parallel the extent of such exposure, and occasionally this may lead to localized 'epidemics' of sensitivity to a particular allergen. Cosmetic and preservative exposure varies from country to country and from region to region, according to the degree of usage. This principle may extend to other allergenic sources, so there is a rationale for each centre and country developing its own epidemiological base.

Patterns also change with fashion, as shown by the virtual disappearance of suspender dermatitis from nickel, to be replaced by an increase in dermatitis from earrings, watches and jeans studs. The sensitizers found vary with the patients' social backgrounds, and they may change over the years.

Differences in environmental exposure influence the nature of sensitizers; for instance *Toxicodendron* spp. dermatitis is extremely common in the USA but virtually absent in Europe, whereas *Primula* dermatitis is well recognized in the UK but practically non-existent in many other countries. The introduction of new potential sensitizers, such as methyl dibromoglutaronitrile, will increase the incidence of contact dermatitis due to them in the exposed population [13]; at the same time, allergens that were previously common may disappear.

Technological advances have led to new and more widespread exposures to allergens, such as epoxy and acrylic resins in the occupational setting [14], although the potential for contact allergy may be reduced by improved personal protective equipment, better containment of sensitizing chemicals and allergen substitution. Similarly, in the domestic environment, phosphorus sesquisulphide allergy in the UK is disappearing because production of 'strike-anywhere' matches has diminished in this country.

Occupational studies

The incidence of occupational dermatitis in most western European countries is in the range of 0.5–1.9 cases per 1000 workers per year; skin diseases account for 13–34% of all occupational diseases and contact dermatitis constitutes 90–95% of this [1]. Risk reflects both constitutional susceptibility (atopy) and exposure. Skin disease (contact dermatitis) is a significant occupational problem, accounting for 5.73 claims per 100 000 workers, with 47% having less than 1 year job tenure. The average disability time in this American study was 23.9 days at a cost of US$3552 [15]. Twenty-two per cent of occupational skin disease may be attributable to atopy [16].

Occupational disease surveillance and compensation registries identify occupations at high risk of dermatitis (see Table 26.1). Most are unable to distinguish between irritant and allergic dermatitis. Some countries have mandatory reporting. In the UK, EPIDERM is a scheme accepting reports made on a voluntary basis from dermatologists and occupational physicians [17]; in a recent study covering the years 1993–99, 52% of dermatitis cases reported by dermatologists and 30% of those reported by occupational physicians had allergic contact dermatitis as the primary cause or as a contributory factor [14]. The higher rate reported by

dermatologists might be a reflection of their more frequent use of patch testing. The commonest allergens were rubber chemicals (including those in gloves), nickel and resins. The numbers and proportions of cases of contact dermatitis within occupations remained fairly constant over the 6-year reporting period, although nursing personnel showed an increase, perhaps as a result of increased exposure to agents required to reduce infectious disease transmission. In northern Bavaria there is a mandatory reporting and follow-up investigation scheme [18]. In a survey of occupations at higher risk of dermatitis, positive patch tests of occupational and clinical relevance occurred in 52% of those with occupational skin disease, including 73% of construction workers, 72% of hairdressers and barbers, but only 20% of food industry workers.

The pattern of employment has a significant effect on the incidence of skin disease, but most common allergens are widely dispersed and, except within small occupational groups, the pattern of sensitivity in a population mainly reflects environmental rather than occupational allergens. Chromate, however, remains a predominantly occupational allergen, the incidence of sensitivity in the normal population being low.

References

1 Coenraads P-J, Diepgen T, Uter W *et al*. Epidemiology. In: Frosch PJ, Menné T, Lepoittevin J-P, eds. *Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 135–63.

2 Meding B, Jarvholm B. Hand eczema in Swedish adults: changes in prevalence between 1983 and 1996. *J Invest Dermatol* 2002; **118**: 719–23.

3 Mortz CG, Lauritsen JM, Bindslev-Jensen C, Andersen KE. Prevalence of atopic dermatitis, asthma, allergic rhinitis, and hand and contact dermatitis in adolescents. *Br J Dermatol* 2001; **144**: 523–32.

4 Nielsen NM, Linneberg A, Menné T *et al*. Incidence of allergic contact sensitization in Danish adults between 1990 and 1998; the Copenhagen Allergy Study, Denmark. *Br J Dermatol* 2002; **147**: 487–92.

5 Dotterud LK, Smith-Sivertsen T. Allergic contact sensitization in the general adult population: a population-based study from Northern Norway. *Contact Dermatitis* 2007; **56**: 10–5.

6 Lindberg M, Edman B, Fischer T, Stenberg B. Time trends in Swedish patch test data from 1992 to 2000. A multi-centre study based on age- and sex-adjusted results of the Swedish standard series. *Contact Dermatitis* 2007; **56**: 205–10.

7 Pratt M, Belsito DV, DeLeo VA *et al*. North American Contact Dermatitis Group patch-test results, 2001–2002 study period. *Dermatitis* 2004; **15**: 176–83.

8 Uter W, Hegewald J, Aberer W *et al*. The European standard series in 9 European countries, 2002/3—first results of the European surveillance system on contact allergies. *Contact Dermatitis* 2005; **53**: 136–45.

9 Britton JER, Wilkinson SM, English JSC *et al*. The British Standard series of contact allergens: validation in clinical practice and value for clinical governance. *Br J Dermatol* 2003; **148**: 259–64.

10 Lim JTE, Goh CL, Ng SK *et al*. Changing trends in the epidemiology of contact dermatitis in Singapore. *Contact Dermatitis* 1992; **26**: 321–6.

11 Thomson KF, Wilkinson SM, Powell S, Beck MH. The prevalence of corticosteroid allergy in two UK centres: prescribing implications. *Br J Dermatol* 1999; **141**: 863–6.

12 Ayala F, Balato N, Lembo G *et al*. Statistical evaluation of the persistence of acquired hypersensitivity by standardized patch tests. *Contact Dermatitis* 1996; **34**: 354–8.

13 Wilkinson JD, Shaw S, Andersen KE *et al*. Monitoring levels of preservative sensitivity in Europe. A 10-year overview (1991–2000). *Contact Dermatitis* 2002; **46**: 207–10.

14 Meyer JD, Chen Y, Holt DL *et al*. Occupational contact dermatitis in the UK: a surveillance report from EPIDERM and OPRA. *Occup Med* 2000; **50**: 265–73.

15 McCall BP, Horwitz IB, Feldman SR, Balkrishnan R. Incidence rates, costs, severity, and work-related factors of occupational dermatitis: a workers' compensation analysis of Oregon, 1990–1997. *Arch Dermatol* 2005; **141**: 713–8.

16 Dickel H, Bruckner TM, Schmidt A, Diepgen TL. Impact of atopic skin diathesis on occupational skin disease incidence in a working population. *J Invest Dermatol* 2003; **121**: 37–40.

17 Cherry N, Meyer JD, Adisesh A *et al*. Surveillance of occupational skin disease: EPIDERM and OPRA. *Br J Dermatol* 2000; **142**: 1128–34.

18 Dickel H, Kuss O, Blesius CR *et al*. Occupational skin diseases in Northern Bavaria between 1990 and 1999: a population-based study. *Br J Dermatol* 2001; **145**: 453–62.

Pathogenesis

The immunology of skin disease is discussed in detail in Chapter 13. There are two main processes involved in allergic contact dermatitis: (i) sensitization (induction, or afferent limb, of sensitivity); and (ii) elicitation (or efferent limb) of contact dermatitis. Four different types of delayed-type hypersensitivity reactions to exogenous chemicals, of which allergic contact dermatitis is a form, have been proposed [1]:

- Th1-mediated—with release of IFN-γ and TNF-α, and activation of monocytes and macrophages in allergic contact dermatitis, bullous exanthema and the tuberculin skin test
- Th2-mediated—with release of IL-5, IL-4, IL-13 and eotaxin, resulting in eosinophilic inflammation seen in maculopapular and bullous exanthema
- Mediated by cytotoxic $CD4^+$ and $CD8^+$ T cells, with release of perforin, granzyme and Fas-ligand, resulting in allergic contact dermatitis, maculopapular, pustular and bullous exanthema
- Release of CXCL-8 and GM-CSF by T cells, resulting in recruitment of neutrophils in pustular exanthema

Sensitization

The induction of sensitivity is the primary event, which has to take place before clinical expression of dermatitis can occur. The main events are described below.

Binding of allergen to skin components. Broadly speaking, the chemicals which result in allergic contact dermatitis are too small to be recognized by the immune system. Allergens penetrating the skin may be sufficiently chemically reactive that they bind covalently with skin peptides directly or, alternatively, metabolism may result in a reaction product that is able to bind. The products formed associate with major histocompatibility complex (MHC) class II molecules [2]. Interference in the process of protein binding to thiol and amino groups in cysteine and lysine residues has been shown to interfere with the process of sensitization [3]. Chemicals may also bind directly to MHC class II molecules inducing a sensitization reaction. MHC class II molecules are coded on the human leukocyte antigen (HLA)-D region genes, and are present on epidermal dendritic cells and Langerhans' cells. Epicutaneously applied allergen associates with these antigen-presenting cells within 6 hours.

Recognition of 'complete' or conjugated antigen. The 'danger model' supposes that sensitization to MHC-bound antigen does not occur unless other co-stimulatory factors are also present and produced as a consequence of cell 'stress'. IL-1β, TNF-α and

GM-CSF are all required for the activation, maturation and migration of Langerhans' cells [4]. Production by injured keratinocytes may lead to Langerhans' cell migration and subsequent sensitization. The danger hypothesis has been adapted to contact hypersensitivity, and evidence produced to support a role for irritant dermatitis in the generation of contact hypersensitivity [5]. In the absence of these co-factors it is assumed that tolerance would develop.

Sensitization is possible only if the connection to the regional lymph nodes is intact [6]. The allergen-carrying Langerhans' cells travel via the afferent lymphatics to the paracortical areas of the regional lymph nodes, where they become apposed to T lymphocytes. The binding is assisted not only by physical factors—the ruffled membrane and dendritic nature of the Langerhans' cells and the intricate structure of the paracortical areas—but also by specialist cellular adhesion molecules (CAMs). These CAMs act at different loci to encourage binding. For example, leukocyte functional antigen-1 (LFA-1) on CD4 helper cells interacts with intercellular adhesion molecule-1 (ICAM-1) on Langerhans' cells, and CD2 on T cells binds to LFA-3 in plasma membranes on most nucleated cells. With recognition of the antigen, many mediators or cytokines are released by this apposition, for example IL-1 by antigen-presenting cells and IL-2 by T lymphocytes.

Proliferation and dissemination of sensitized T lymphocytes. The cytokines cause blast formation in the lymph nodes and the proliferation of antigen-specific cytotoxic $CD8^+$ (Tc1) and also $CD4^+$ (Th1) lymphocytes [7]. The type of T-cell response generated is dependent on the pathway by which the antigen is processed: small lipid-soluble molecules such as urushiol enter the cytoplasm and are presented on MHC class I as an endogenous antigen; polar haptens are more likely to be presented on MHC class II [8] as an exogenous antigen.

The T cells disseminate via the efferent lymphatics throughout the body and interact with Langerhans' cells and residual antigen in the skin. Contact hypersensitivity is mediated through a subset of T cells that express cutaneous lymphocyte-associated antigen (CLA). Localization to areas of inflammation occurs via production of the chemokine CCL27 by basal keratinocytes, which binds to dermal glycoprotein; CLA-positive lymphocytes also express CCR10, the receptor for CCL27 [9]. The cytotoxic T cells induce keratinocyte death through release of Fas ligand and perforin-mediated pathways [10].

Elicitation [6]

On first exposure to a strong sensitizer such as dinitrochlorobenzene (DNCB), most subjects develop a local reaction after 5–25 days. During this period, sensitization has been accomplished, and the residues of the allergen in the skin react with the newly formed sensitized T lymphocytes. Such a response has been termed a 'late' reaction. There is evidence to suggest that allergen-specific T lymphocytes persist at the site of original contact for some months following an initial sensitization exposure and this may explain the 'retest' or 'flare-up' reactions following re-exposure at a distant site.

If a sensitized person is re-exposed to a specific allergen in sufficient concentration, the clinical reaction subsequently develops much more quickly, usually within 24–48 h; however, depending on the degree of sensitivity, penetration and other factors, this may vary from a few hours to many days. Antigen may be presented not only by antigen-presenting Langerhans' cells but also by IL-1-secreting keratinocytes that acquire Ia/HLA-DR status, augmenting the cascade of cytokine, immune cell and inflammatory response. This cascade is autoregulating, and although the mechanism of this is not well understood it probably involves $CD4^+$ T cells.

A delayed reaction time (sometimes also referred to as a 'late' reaction) describes a delayed elicitation response following antigenic challenge in persons who are already sensitized. There has been confusion over the use of this term, as it has been used not only to describe reactions that have taken more than the usual 4 days to develop but also acute primary sensitization reactions which, in normal clinical practice, often present as more sudden and florid reactions around 21 days after challenge. A delayed reaction time is found with low degrees of sensitivity (when there are very few memory T cells), following exposures to small amounts of allergen (when it takes longer to augment the T-cell response) and in situations of delayed penetration of allergens (e.g. neomycin in petrolatum).

References

1 Posadas SJ, Pichler WJ. Delayed drug hypersensitivity reactions—new concepts. *Clin Exp Allergy* 2007; **37**: 989–99.

2 Lepoittevin J-P. Molecular aspects of allergic contact dermatitis. In: Frosch PJ, Menné T, Lepoittevin J-P, eds. *Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 45–68.

3 Becker D, Valk E, Zahn S *et al*. Coupling of contact sensitizers to thiol groups is a key event for the activation of monocytes and monocyte-derived dendritic cells. *J Invest Dermatol* 2003; **120**: 233–8.

4 Cumberbatch M, Dearman R, Kimber I. Langerhans cells require signals from both tumour necrosis factor-alpha and interleukin-1 beta for migration. *Immunology* 1997; **92**: 388–95.

5 Smith HR, Basketter DA, McFadden JP. Irritant dermatitis, irritancy and its role in allergic contact dermatitis. *Clin Exp Dermatol* 2002; **27**: 138–46.

6 Rustemeyer T, van Hoogstraten IMW, von Blomberg BME, Scheper R. Mechanisms in allergic contact dermatitis. In: Frosch PJ, Menné T, Lepoittevin J-P, eds. *Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 45–68.

7 Kimber I, Dearman RJ. Allergic contact dermatitis: the cellular effects. *Contact Dermatitis* 2002; **46**: 1–5.

8 Gruchalla RS. Drug metabolism, danger signals, and drug-induced hypersensitivity. *J Allergy Clin Immunol* 2001; **108**: 475–88.

9 Homey B, Alenius H, Müller A *et al*. CCL27–CCR10 interactions regulate T cell-mediated skin inflammation. *Nat Med* 2002; **8**: 157–65.

10 Trautmann A, Akdis M, Kleemann D *et al*. T cell-mediated Fas-induced keratinocyte apoptosis plays a key pathogenetic role in eczematous dermatitis. *J Clin Invest* 2000; **106**: 25–35.

Predisposing factors

Individual

Constitution. Sensitization presupposes individual susceptibility. This has been investigated using epidemiological, family and twin studies [1]. In humans, susceptibility does not seem to follow Mendelian inheritance and, in some cases, may occur by non-antigen-specific amplification of the immune response [2]. Nearly everyone can be sensitized with *Primula* extract, and most with 2,4-DNCB. However, experiments with the latter indicate that

nearly all susceptible subjects will be sensitized after one or two applications of the allergen in a suitable concentration; repeated applications increase the number of persons sensitized only marginally. Some individuals are thus resistant to sensitization. This resistance may have been acquired by repeated exposure to subsensitizing doses of the allergen [3] or as a result of exposure through the oral route with the development of tolerance [4].

The capacity for sensitization varies from person to person, but certain individuals are more prone to developing sensitivity to a particular substance, for example nickel. The 'heritability' of nickel sensitivity has been calculated to be about 60% [5]. This may be a genetically determined trait but, if so, it is not known whether the property inherited is an increased capacity for conjugation to form an effective antigen, for sensitization or for facilitation of percutaneous absorption. In guinea pigs, the capacity for sensitization, both in general and to particular substances, has been shown to be inherited [6,7]. In humans, such studies are less likely to be conclusive because of the difficulty in distinguishing between genetic and environmental factors. One experiment compared the susceptibility of parents and their children to contact sensitization with DNCB and *p*-nitrodimethylaniline. Children whose parents became sensitized were sensitized more commonly than were children whose parents were not sensitized [8]. Siblings and children of patients suffering from allergic contact dermatitis have an increased incidence of positive patch tests, and first-degree relatives of nickel-allergic subjects have increased prevalence of the same disorder [9]. Conversely, studies on twins with hand eczema and nickel allergy indicate environmental rather than genetic factors are the more important [10], and a previous study also failed to show any difference in capacity for sensitization to DNCB between monozygotic and dizygotic twins [11]. Studies of HLA types and blood groups have not proved very helpful to date [12,13]. However, a statistically significant increased proportion of rapid acetylators has been found in contact allergic patients [14]. The authors were unable to say whether this state was contributory or was a genetic marker for the ability to become sensitized. Interleukin 16–295 promoter [15] and TNFA–308 polymorphism in polysensitized subjects suggest that these may also influence susceptibility to contact allergy [16].

The relationship of atopy, particularly atopic eczema, to predisposition to allergic contact dermatitis has prompted much debate. Atopics are known to exhibit down-regulation of Th1 cells [17,18], which should mean a decreased tendency to develop allergic contact dermatitis; indeed, patients with severe atopic dermatitis may have a diminished capacity for DNCB sensitization [19]. However, clinical studies are conflicting, some showing an increase in prevalence of contact allergy, especially to medicaments [20], others the same [21] and others a decrease [22,23]. In a study of 101 sets of twins, no correlation was found between positive patch tests and atopy [11], and the prevalence of allergic contact dermatitis in atopics was found to be similar to that in patients suffering from discoid or seborrhoeic eczema [21]. An increased level of nickel sensitization noted in one study [24] contrasts with another where there was no increase [25]. Confounding factors include the fact that in many cases of chronic atopic eczema there has been considerable exposure, both in extent and time, to medicaments and emollients applied to broken skin, which might explain the increased rate of allergy to medicament components noted in some studies. False-positive patch-test reactions to nickel, chromate and cobalt and probably other marginally irritant allergens, are frequently seen in patients with atopic eczema and can be difficult to interpret. At present no certain conclusion can be made about the relative risk of contact sensitization in atopic patients.

References

1 Menné T, Holm V. Genetic susceptibility in human allergic sensitization. *Semin Dermatol* 1986; **5**: 301–6.
2 Moss C, Friedmann PS, Shuster S *et al*. Susceptibility and amplification of sensitivity in contact dermatitis. *Clin Exp Immunol* 1985; **61**: 232–41.
3 Lowney ED. Attenuation of contact sensitization in man. *J Invest Dermatol* 1968; **50**: 241–9.
4 White JML, Goon A, Jowsey IR *et al*. Oral tolerance to contact allergens: a common occurrence? A review. *Contact Dermatitis* 2007; **56**: 247–54.
5 Menné T, Holm NV. Nickel allergy in a female twin population. *Int J Dermatol* 1983; **22**: 22–8.
6 Parker D, Sommer G, Turk JL. Variations in guinea pig responsiveness. *Cell Immunol* 1975; **18**: 233–8.
7 Polak L, Barnes JM, Turk JL. The genetic control of contact sensitization to inorganic metal compounds in guinea-pigs. *Immunology* 1968; **14**: 707–11.
8 Walker FB, Smith PD, Maibach HI. Genetic factors in human allergic contact dermatitis. *Int Arch Allergy Appl Immunol* 1967; **32**: 453–62.
9 Fleming CJ, Burden AD, Forsyth A. The genetics of allergic contact hypersensitivity to nickel. *Contact Dermatitis* 1999; **41**: 251–3
10 Bryld LE, Hindsberger C, Kyvik KO *et al*. Genetic factors in nickel allergy evaluated in a population-based female twin sample. *J Invest Dermatol* 2004; **123**: 1025–9.
11 Forsbeck M, Skog E, Ytterborn KH. Delayed type of allergy and atopic disease among twins. *Acta Derm Venereol (Stockh)* 1968; **48**: 192–7.
12 Lidén S, Beckman C, Groth O *et al*. Lack of association between allergic contact dermatitis and HLA antigens of the A and B series. *Acta Derm Venereol (Stockh)* 1980; **61**: 155–7.
13 Valsecchi R, Bontempelli M, Vicari O *et al*. HLA antigens and contact sensitivities. *Arch Dermatol* 1982; **118**: 533–4.
14 Schnuch A, Westphal GA, Muller MM *et al*. Genotype and phenotype of *N*-acetyltransferase 2 (NAT2) polymorphism in patients with contact allergy. *Contact Dermatitis* 1998; **38**: 209–11.
15 Reich K, Westphal G, König IR *et al*. Association of allergic contact dermatitis with a promoter polymorphism in the IL16 gene. *J Allergy Clin Immunol* 2003; **112**: 1191–4.
16 Westphal GA, Schnuch A, Mössner R *et al*. Cytokine gene polymorphisms in allergic contact dermatitis. *Contact Dermatitis* 2003; **48**: 93–8.
17 Clark RAF. Cell-mediated and IgE-mediated responses in atopic dermatitis. *Arch Dermatol* 1989; **125**: 413–6.
18 Bos JO, Wierenga EA, Smitt JHS *et al*. Immune dysregulation in atopic eczema. *Arch Dermatol* 1992; **128**: 1509–12.
19 Uehara M, Sawai T. A longitudinal study of contact sensitivity in patients with atopic dermatitis. *Arch Dermatol* 1989; **125**: 366–8.
20 Bandmann H-J, Breit R, Leutgeb C. Kontakallergie und Dermatitis atopica. *Arch Dermatol Forsch* 1972; **244**: 332–4.
21 Cronin E, Bandmann H-J, Calnan CD *et al*. Contact dermatitis in the atopic. *Acta Derm Venereol (Stockh)* 1970; **50**: 183–7.
22 De Groot AC. The frequency of contact allergy in atopic patients with dermatitis. *Contact Dermatitis* 1990; **22**: 273–7.
23 Hanifin JH. Atopic dermatitis. *J Am Acad Dermatol* 1982; **6**: 1–13.
24 Diepgen TL, Fartasch M, Hornstein OP. Evaluation and relevance of atopic basic and minor features in patients with atopic dermatitis and in the general population. *Acta Derm Venereol Suppl (Stockh)* 1989; **144**: 50–4.
25 McDonagh AJ, Wright AL, Cork MJ *et al*. Nickel sensitivity: the influence of ear piercing and atopy. *Br J Dermatol* 1992; **126**: 16–8.

Sex [1]. Women have stronger cell-mediated immune responses than men [2] and yet, at least experimentally, women do not

appear to be more susceptible to sensitization [3]. However, sensitization is accomplished more easily with some allergens, for example lanolin, fragrance and *p*-phenylenediamine, perhaps as a result of prior 'conditioning' exposure and subclinical sensitization [4]. In one study, women were found to have greater reactivity to DNCB than men [5] whereas, in another, men were more susceptible to DNCB sensitization than women [6]. The reason for the female preponderance in clinical patch-test studies is mainly explained by exposure [1]—for instance the large number of metal-sensitive females, largely the result of ear piercing [7], and the greater exposure to fragrances, cosmetics and hair dyes. Multiple allergies are found most frequently in elderly women [8]. It is of interest that nickel sensitivity seems to be less common in men even if they wear earrings [9].

Hormones. Hormones have some effect on contact dermatitis [10]. In one study the response to DNCB was enhanced in women taking an oral contraceptive [11]. Pregnancy and the use of gestagens may, unpredictably, either improve or aggravate contact dermatitis [12,13]. Contact dermatitis may flare premenstrually, and cutaneous reactivity to patch testing may vary according to the stage of the menstrual cycle [14], with patch tests to nickel being less intense during the ovulatory than the progestagenic phase [15]. Premenstrual exacerbation of nickel allergy has been described [16].

References

1 Modjtahedi BS, Modjtahedi SP, Maibach HI. The sex of the individual as a factor in allergic contact dermatitis. *Contact Dermatitis* 2004; **50**: 53–9.

2 Ansar Ahmed S, Penhale WJ, Talat N. Sex hormones, immune responses and autoimmune diseases. *Am J Pathol* 1985; **121**: 531–51.

3 Leyden JJ, Kligman AM. Allergic contact dermatitis. Sex differences. *Contact Dermatitis* 1977; **3**: 333–6.

4 Jordan WP, King SE. Delayed hypersensitivity in females. The development of allergic contact dermatitis in females during the comparison of two predictive patch tests. *Contact Dermatitis* 1977; **3**: 19–26.

5 Rees JL, Friedmann PS, Matthews JNS. Sex difference in susceptibility to development of contact hypersensitivity to dinitrochlorobenzene (DNCB). *Br J Dermatol* 1989; **120**: 371–4.

6 Walker FB, Smitt PD, Maibach HI. Genetic factors in human allergic contact dermatitis. *Int Arch Allergy Appl Immunol* 1987; **32**: 453–62.

7 Peltonen L, Terho P. Nickel sensitivity in schoolchildren in Finland. In: Frosch P, Dooms-Goossens A, LaChapelle J-M *et al*., eds. *Current Topics in Contact Dermatitis*. Heidelberg: Springer, 1989: 184–7.

8 Carlsen BC, Menné T, Johansen JD. 20 years of standard patch testing in an eczema population with focus on patients with multiple contact allergies. *Contact Dermatitis* 2007; **57**: 76–83.

9 Meijer C, Bredberg M, Fischer T *et al*. Ear piercing, and nickel and cobalt sensitization, in 520 young Swedish men doing compulsory military service. *Contact Dermatitis* 1995; **32**: 147–9.

10 Fabris N. Hormones and ageing. In: Makinodan T, Yunis EJ, eds. *Immunology and Ageing*. New York: Plenum Press, 1977.

11 Rea TH. Quantitative enhancement of dinitrochlorobenzene responsivity in women receiving oral contraceptives. *Arch Dermatol* 1979; **115**: 361–2.

12 Denman AM. Pregnancy and immunological disorders. *BMJ* 1982; **284**: 999–1000.

13 Hawes CS, Kemp AS, Jones WR *et al*. A longitudinal study of cell-mediated immunity in human pregnancy. *J Reprod Immunol* 1981; **3**: 165–73.

14 Alexander S. Patch testing and menstruation. *Lancet* 1988; **ii**: 751.

15 Bonamonte D, Foti C, Antelmi AR, Biscozzi AM *et al*. Nickel contact allergy and menstrual cycle. *Contact Dermatitis* 2005; **52**: 309–13.

16 McLelland J, Lawrence CM. Premenstrual exacerbation of nickel allergy. *Br J Dermatol* 1991; **125**: 83.

Race. Racial differences appear to exist, judging from experimental sensitization to poison ivy and DNCB, where Afro-Caribbeans are generally more resistant than white people [1], although weak reactions to the eliciting dose are difficult to discern on Afro-Caribbean skin. Although there are differences in prevalence of sensitization to individual allergens among racial groups, this is felt to be a reflection of exposure rather than predisposition [2,3].

Age. Age has little influence on capacity for sensitization [4]. Children are sensitized as easily as adults, and both infants and elderly people can be sensitized to poison ivy (*Toxicodendron* spp.). *Toxicodendron* dermatitis is very common in American children [5]. This suggests that the paucity of other types of contact dermatitis may be due to the simpler environment of childhood and, being younger, they have had less time to develop sensitivities. Susceptibility to sensitization with DNCB declines after the age of 70 years but is otherwise constant, and sensitivities may fade with time [6]. However, the number of positive patch-test reactions tends to increase with age [7], due to the accumulation of allergies acquired over a lifetime. Young adults are more likely to have occupational or cosmetic allergies whereas elderly people are more liable to medicament [8] and 'historic' sensitivities. Age is an important factor in any patch-test study [9].

Contact dermatitis in children. This seems to be increasing, either because a child's environment is now more complex or dermatologists have been underestimating the frequency of childhood allergic contact dermatitis, possibly because of their reluctance to patch test younger children. There have now been several series of results of patch testing in children, summarized by Goossens and Morren [10]. The increased prevalence of sensitivity in children has been associated with increased exposure to nickel-containing objects and an earlier age of ear piercing [11]. The commonest allergens are nickel (especially in girls), fragrance, thimerosal, medicaments, rubber chemicals, chromate and resins in footwear [10]. The relevance of the unexpectedly high number of reactions to thimerosal remains obscure, but the increased level of reactivity to it has been blamed on vaccines and inoculations [12,13]. The use of *p*-phenylenediamine-contaminated henna tattoos on children is resulting in increasing numbers of cases of contact allergy from this source [14].

Small children pose practical problems with patch testing. There is a limited area to which a series of patch tests can be applied and they may become restless once the tests are applied, creating problems with adhesion. It is advised that more than one session of patch tests should be undertaken if necessary and a stronger adhesive used to keep the test units in place [15]. It has also been suggested that children are more susceptible to irritant patch-test reactions than adults [16]. This is not our experience, except for nickel and cobalt, and although positive patch-test reactions are less common than in adults, most reactions appear to be relevant apart from thimerosal. The use of lower concentrations for certain allergens has been suggested, but most published reports have advocated no change.

Attempts have been made to identify clinical patterns to indicate which children should be patch tested, but recent studies

suggest that any child with persistent eczema should be considered for patch testing [17,18]. Although an abbreviated standard series based on previous published results has been suggested for children [19], we endeavour to perform a full adult standard series, plus relevant extra tests whenever possible.

References

1 Anderson KE, Maibach HI. Black and white human skin differences. *J Am Acad Dermatol* 1979; **1**: 276–82.
2 Goh CL. Prevalence of contact allergy by sex, race and age. *Contact Dermatitis* 1986; **14**: 237–40.
3 Deleo VA, Taylor SC, Belsito DV *et al*. The effect of race and ethnicity on patch test results. *J Am Acad Dermatol* 2002; **46**: S107–S112.
4 Kwangsukstith C, Maibach HI. Effects of age and sex on the induction and elicitation of allergic contact dermatitis. *Contact Dermatitis* 1995; **33**: 289–98.
5 Epstein E. Contact dermatitis in children. *Pediatr Clin North Am* 1971; **18**: 839–52.
6 Schwartz M. Eczematous sensitization in various age groups. *J Allergy* 1953; **24**: 143–8.
7 Berit CC, Menné T, Johansen JD. 20 years of standard patch testing in an eczema population with focus on patients with multiple contact allergies. *Contact Dermatitis* 2007; **57**: 76–83.
8 Green CM, Holden CR, Gawkrodger DJ. Contact allergy to topical medicaments becomes more common with advancing age: an age-stratified study. *Contact Dermatitis* 2007; **56**: 229–31.
9 Christopherson J, Menné T, Tanghof P *et al*. Clinical patch test data evaluated by multivariate analysis. *Contact Dermatitis* 1989; **21**: 291–9.
10 Goossens A, Morren M. Contact allergy in children. In: Frosch PJ, Menné T, Lepoittevin J-P, eds. *Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 811–30.
11 Larsson-Stymne B, Widström L. Ear piercing: a cause of nickel allergy in schoolgirls? *Contact Dermatitis* 1985; **13**: 289–93.
12 Möller H. All these positive tests to thiomersal. *Contact Dermatitis* 1994; **31**: 209–14.
13 Osawa J, Kitamura K, Izekawa Z *et al*. A probable role for vaccines containing thiomersal in thiomersal sensitivity. *Contact Dermatitis* 1991; **24**: 183–7.
14 Sosted H, Johansen JD, Andersen KE *et al.* Severe allergic hair dye reactions in 8 children. *Contact Dermatitis* 2006; **54**: 87–91.
15 Mallory SB. The pediatric patient. In: Guin JD, ed. *Practical Contact Dermatitis*. New York: McGraw-Hill, 1995: 603–16.
16 Marcussen PV. Primary irritant patch test reactions in children. *Arch Dermatol* 1963; **87**: 378–82.
17 Clayton TH, Wilkinson SM, Rawcliffe C *et al.* Allergic contact dermatitis in children: should pattern of dermatitis determine referral? A retrospective study of 500 children tested between 1995 and 2004 in one U.K. centre. *Br J Dermatol* 2006; **154**: 114–7.
18 Beattie PE, Green C, Lowe G, Lewis-Jones MS. Which children should we patch test? *Clin Exp Dermatol* 2007; **32**: 6–11.
19 Vigan M, Sauvage C, Adessi B *et al.* Pourquoi et comment réaliser une batterie standard chez les enfants? *Nouv Dermatol* 1994; **13**: 12–5.

Medication. Drug influences on skin-test reactivity have been reviewed by Schopf [1]. Antihistamines and sodium cromoglicate (disodium cromoglycate) appear to have little effect, whereas both prednisolone (dose >15 mg/day) [2] and potent topical steroids [3] suppress allergic patch-test reactions. Similarly, other immunomodulators such as ciclosporin and azathioprine may reduce the intensity of allergic contact reactions [4]. Therapeutic UVB or psoralen UVA (PUVA) therapy may also temporarily reduce contact allergic reactions [5,6]. Experimentally, in rats, opiates have been found to enhance allergic, but not irritant, contact dermatitis. This effect was greater in female rats, and was found to be mediated through central mechanisms enhanced by peripheral hormonal effects [7].

References

1 Schopf E. Drug influences upon skin test reactivity. In: Ring J, Burg G, eds. *New Trends in Allergy*. Berlin: Springer, 1981: 108–14.
2 Feuerman E, Levy A. A study of the effect of prednisolone and an antihistamine on patch test reactions. *Br J Dermatol* 1972; **86**: 68–71.
3 Moed H, Stoof TJ, Boorsma DM *et al*. Identification of anti-inflammatory drugs according to their capacity to suppress type-1 and type-2 T cell profiles. *Clin Exp Allergy* 2004; **34**: 1868–75.
4 Sukanto H, Nater JP, Bleumink E. Influence of topically applied corticosteroids on patch test reactions. *Contact Dermatitis* 1981; **7**: 180–5.
5 Thorvaldsen J, Volden G. PUVA-induced diminution of contact allergic and irritant skin reactions. *Clin Exp Dermatol* 1980; **5**: 43–6.
6 Skov L, Hansen H, Barker JN *et al*. Contrasting effects of ultraviolet-A and ultraviolet-B exposure on induction of contact sensitivity in human skin. *Clin Exp Immunol* 1997; **107**: 585–8.
7 Elliott JC, Picker MJ, Nelson CJ *et al*. Sex differences in opioid induced enhancement of contact hypersensitivity. *J Invest Dermatol* 2003; **121**: 1053–9.

Coincidental diseases. Patients with acute or debilitating diseases, such as cancer, Hodgkin's disease and mycosis fungoides, have impaired capacity for contact sensitization [1–3]. This may also apply to patients who for other reasons have impaired T-lymphocyte function.

References

1 Grossman J, Baum J, Gluckman J *et al*. The effect of aging and acute illness on delayed hypersensitivity. *J Allergy Clin Immunol* 1975; **55**: 262–75.
2 Johnson MW, Maibach HI, Salmon SE. Quantitative impairment of primary inflammatory response in patients with cancer. *J Natl Cancer Inst* 1973; **51**: 1075–6.
3 Van der Harst-Oostven CJGR, van Vloten WA. Delayed-type hypersensitivity in patients with mycosis fungoides. *Dermatologica* 1978; **157**: 129–35.

Local factors. It is convenient to categorize eczemas as endogenous or exogenous, and the latter can be divided into contact irritant and allergic. It is common to see combinations of these disorders, particularly on the hands. Pre-existing or concomitant constitutional and/or irritant contact dermatitis damages the skin, affecting its barrier function and producing increased opportunities for allergen absorption and secondary sensitization. It is known that hand eczema predisposes to nickel sensitivity and *vice versa* [1], and that the prevalence of chromate, cobalt and balsam sensitivity is increased in men with hand eczema [2]. The longer the duration of eczema, the greater is the chance of sensitization. Occlusion greatly promotes percutaneous absorption and probably contributes to the high incidence of medicament dermatitis in stasis eczema, otitis externa and perianal dermatitis, and is also a factor in dermatitis from shoes and rubber gloves.

As sensitivity is more easily acquired if an allergen is applied to damaged skin, concomitant irritant contact dermatitis will promote sensitization and lower the threshold for elicitation of an allergic contact dermatitis in those exposed to associated allergens [3]. In experimental sensitization, skin damage may be produced by previous application of sodium lauryl sulphate. The enhanced risk of sensitization may be due to: (i) increased absorption of allergen as a result of skin barrier disruption; (ii) priming of the immunological response with prior recruitment of immunocompetent cells, cytokines, etc.; or (iii) accumulation of mononuclear cells. Furthermore, by adapting Matzinger's 'danger model' concept for sensitization [4], it has been suggested that contact allergy can *only* develop in the presence of cytokine release from

non-immune skin cells (principally keratinocytes) provoked by a coexisting irritant (often the same as the allergen) or trauma [5,6]. If there is no concomitant irritancy, then tolerance rather than allergy will follow.

In guinea pigs, sensitization is facilitated by acanthosis induced by detergents or paraffins, even in the absence of dermatitis [7]. Although the mechanism for this promotion of sensitization by acanthosis is unknown, it may be relevant to burns and other types of skin damage known to increase the chance of sensitization [8].

Once allergy is established, it seems reasonable to suppose that an allergen may be able to reactivate or maintain dermatitis in low concentration. However, even when such exposure seems to have ceased, a hand eczema that started as a contact dermatitis may continue as an apparently 'constitutional' post-insult form of dermatitis [9].

References

1 Menné T, Borgan O, Green A. Nickel allergy and hand dermatitis in a stratified sample of the Danish female population. *Acta Derm Venereol (Stockh)* 1982; **62**: 35–41.
2 Wilkinson DS, Bandmann H-J, Calnan CD *et al*. The role of contact allergy in hand eczema. *Trans St John's Hosp Dermatol Soc* 1970; **56**: 15–9.
3 Pedersen LK, Johansen JD, Held E, Agner T. Augmentation of skin response by exposure to a combination of allergens and irritants—a review. *Contact Dermatitis* 2004; **50**: 265–73.
4 Matzinger P. An innate sense of danger. *Semin Immunol* 1998; **10**: 399–415.
5 McFadden JP, Basketter DA. Contact allergy, irritancy and 'danger'. *Contact Dermatitis* 2000; **42**: 123–7.
6 Smith HR, Basketter DA, McFadden JP. Irritant dermatitis, irritancy and its role in allergic contact dermatitis. *Clin Exp Dermatol* 2002; **27**: 138–46.
7 Hunziker N. *Experimental Studies on Guinea-pig's Eczema*. Berlin: Springer, 1969.
8 Meneghini CL. Sensitization in traumatised skin. *Am J Ind Med* 1985; **8**: 319–21.
9 Sajjachareonpong P, Cahill J, Cahill T *et al*. Persistent post-occupational dermatitis. *Contact Dermatitis* 2004; **51**: 278–83.

Environmental

By definition, the environment will influence exposure to potential allergens, which in turn will affect liability to contact allergy. For the individual, certain immediate environments, including those encountered in the home, at work and during spare-time activities, are particularly relevant. However, more general influences are important, including climatic, geographical, ecological, socio-economic and cultural factors. Some of these may also affect the individual's response to allergen exposure. Climate, geography and ecology are often interrelated.

Climate. Climate, by virtue of varying UV exposure, heat and relative humidity, may play a part in liability to contact allergy. UVB exposure has been shown to diminish the skin's immune response to contact allergens [1,2]. UVA exposure, however, does not appear to have the same effect, and there is evidence that the reduction in immune responsiveness is transient, perhaps due to an adaptive mechanism [2]. UVB exposure from the sun may therefore temporarily reduce contact allergic reactions, although there is conflicting evidence about the effect of sunshine on patch-test reactions [3,4]. Conversely, chapping of the skin during winter predisposes to irritant contact dermatitis and also increases the incidence of false-positive patch-test reactions to substances such as formaldehyde [4] and propylene glycol [5]. Occlusion and increased sweating may increase allergy from shoes and clothing. Exposure to UV-absorbing chemical filters increases where there is a higher exposure to sunshine, with a consequent increase in contact and photocontact allergy from this source during the summer months, when photoallergy from other causes would also be anticipated to be more of a problem. These varying observations indicate that several factors must influence the seasonal liability to contact dermatitis.

Flora and fauna. Plant dermatitis commonly shows a distinct seasonal pattern, the allergenicity of some plants such as *Primula obconica* varying considerably with light and season [6]. Many allergenic plants, especially those belonging to the Compositae (Asteraceae) family, are destroyed by cold and frosty weather but return during the warmer spring and summer months. Global warming is also felt to be an issue, with evidence that *Toxicodendron* spp. may become more abundant and allergenic as a result [7]. Distribution of allergenic plant material will be facilitated by dry and windy climates. Similarly, geographical location is a very important influence. Exposure to *Toxicodendron* spp. is mainly confined to North America. Compositae allergy is seen in many parts of the world but the plants responsible vary: in the USA ragweed is the main cause, in Europe it is chrysanthemums and garden weeds, in India the weed *Parthenium*, and in Australia a number of wild Compositae found in the 'bush'. Occupational contact allergy from plants is often seasonal, for instance in lichen pickers [8] and from plant and vegetable cultivation [9,10].

Fauna are not a major seasonal cause of contact allergy, although European fishermen are liable to contact dermatitis of exposed skin during the summer when handling nets containing marine organisms known as bryozoans. The disorder is known as 'Dogger Bank Itch' in the UK [11]. The allergen has been identified as the (2-hydroxyethyl)dimethylsulfoxonium ion [12].

Socio-economic and cultural. The relationship of contact dermatitis to socio-economic groups has not been studied in detail, but exposure to cheap (nickel-releasing) metals used as jewellery might be expected to be relatively increased in those with less disposable income. Similarly, the pattern of perfume and cosmetic use and exposure might vary according to social class.

Cultural factors are important, and not always fully appreciated as a predisposing cause for contact allergy, particularly the use of sensitizing traditional herbal medicines and balms to treat skin disorders in the Middle and Far East [13,14]. Furthermore, ingested herbal folk remedies containing *Toxicodendron* have caused outbreaks of systemic allergic contact dermatitis in Korea [15].

Hair dyes are used much more commonly by men in the Middle East and the Indian subcontinent, including use on the beard [16]. Indian women may become sensitized to dyes and adhesives used in kumkum and bindi applied to the forehead [17]. Western culture, in contrast, is associated with higher cosmetic use and leisure pursuits, including lying in the sun and seaside holidays requiring the application of sunscreens. The frequency of tattooing and body piercing has increased in recent years, especially amongst young adults, thereby increasing their risk of contact with potential allergens including nickel and *p*-phenylenediamine.

References

1 Skov L, Hansen H, Barker JN *et al*. Contrasting effects of ultraviolet-A and ultraviolet-B exposure on induction of contact sensitivity in human skin. *Clin Exp Immunol* 1997; **107**: 585–8.
2 Damian DL, Barnetson RS, Halliday GM. Low-dose UVA and UVB have different time courses for suppression of contact hypersensitivity to a recall antigen in humans. *J Invest Dermatol* 1999; **112**: 939–44.
3 Dooms-Goossens A, Lesaffre E, Heidbuchel M *et al*. UV sunlight and patch test reactions in humans. *Contact Dermatitis* 1988; **19**: 36–42.
4 Uter W, Geier J, Land M *et al*. Another look at seasonal variation in patch test results. A multifactorial analysis of surveillance data of the IVDK. Information Network of Departments of Dermatology. *Contact Dermatitis* 2001; **44**: 146–52.
5 Hannuksela M, Pirilä V, Salo OP. Skin reactions to propylene glycol. *Contact Dermatitis* 1975; **1**: 112–6.
6 Hjorth N. Seasonal variations in contact dermatitis. *Acta Derm Venereol (Stockh)* 1967; **47**: 409–18.
7 Mohan JE, Ziska LH, Schlesinger WH *et al*. Biomass and toxicity responses of poison ivy *(Toxicodendron radicans)* to elevated atmospheric CO_2. *Proc Natl Acad Sci* 2006; **103**: 9086–9.
8 Salo H, Hannuksela M, Hausen B. Lichen picker's dermatitis (*Cladonia alpestris* (L.) Rab.). *Contact Dermatitis* 1981; **7**: 9–13.
9 Paulsen E, Andersen KE. Compositae dermatitis in a Danish dermatology department in 1 year (II). Clinical features in patients with Compositae contact allergy. *Contact Dermatitis* 1993; **29**: 195–201.
10 Malten KE. Chicory dermatitis from September to April. *Contact Dermatitis* 1983; **9**: 232.
11 Pathmanaban ON, Porter JS, White IR. Dogger Bank itch in the eastern English Channel: a newly described geographical distribution of an old problem. *Clin Exp Dermatol* 2005; **30**: 622–6.
12 Carle JS, Christophersen C. Dogger bank itch. 4. An eczema-causing sulfoxonium ion from the marine animal, *Alcyonidium gelatinosum* [Bryozoa]. *Toxicon* 1982; **20**: 307–10.
13 Li LF. A clinical and patch test study of contact dermatitis from traditional Chinese medicinal materials. *Contact Dermatitis* 1995; **33**: 392–5.
14 Goh CL. The need for epidemiological studies. *Am J Contact Dermatitis* 1997; **8**: 135–6.
15 Park SD, Lee SW, Chun JH *et al*. Clinical features of 31 patients with systemic contact dermatitis due to the ingestion of *Rhus* (lacquer). *Br J Dermatol* 2000; **142**: 937–42.
16 Hsu TS, Davis MD, el-Azhary R *et al*. Beard dermatitis due to paraphenylenediamine use in Arabic men. *J Am Acad Dermatol* 2001; **44**: 867–9.
17 Dwyer CM, Forsyth A. Allergic contact dermatitis from bindi. *Contact Dermatitis* 1994; **30**: 174.

Chemical

Skin cells, especially their nucleic acids and proteins, are composed of molecules that contain nucleophilic atoms, that is negatively charged and electron rich. Most allergens (haptens) are 'simple' chemicals of low molecular weight (less than 500–1000 Da) that contain electrophilic atoms [1,2], that is positively charged and electron deficient. Interaction between these two types of atoms leads to strong covalent bonding to form a hapten–protein complex or 'complete antigen'. Metal and metal salts can bond to electron-rich atoms (ligands) by taking some of the electrons and forming coordinate bonds. Haptens can be grouped according to their chemical reactivity in relation to putative carrier proteins or according to functional groups (Table 26.2).

Some molecules, although themselves not allergenic (pro-haptens), are converted into electrophilic molecules by the skin's detoxification processes, such as hydroxylation systems, monoamine oxidases and peroxidases. Peroxidases can convert electron-rich aromatic derivatives into electrophile quinones, for example poison ivy catechols are changed into highly reactive orthoquinones. Hydrolysis can convert tuliposides into allergenic tulipalins. Other pro-haptens can be transformed into haptens by the effect of atmospheric oxygen or UV irradiation. Cutaneous enzymatic transformation of a chemical into many different metabolites, depending on the pathway taken, makes determination of the allergenicity of the original chemical more difficult. It also explains the difficulty in deciding if multiple sensitivities are cross-reactions or concomitant sensitization.

Enzymatic systems may also play a preventative role, as with glutathione in some drug-induced reactions [4].

Table 26.2 Classification of haptens based on functional grouping. (From Dupuis & Benezra [3].)

Hapten group	Example
1 Acids	Maleic acid
2 Aldehydes	Formaldehyde
3 Amines	Ethylenediamine, *p*-phenylenediamine
4 Diazo compounds	Bismark brown, Congo red
5 Esters	Benzocaine
6 Ethers	Benzyl ether
7 Epoxides	Epoxy resin
8 Halogenated compounds	Dinitrochlorobenzene, picryl chloride
9 Quinones	Primin, hydroquinone
10 Metals	Ni^{2+}, Co^{2+}, Cr^{3+}, Hg^{2+}, etc.
11 Unsaturated compounds	Δ^3-Carene (turpentine)

Assessment of sensitization potential. The sensitization potential is the relative capacity of a given agent to induce sensitization in a group of humans or animals [5]. Both in guinea pigs and humans, an estimate of the sensitizing index requires patch-test exposures modified to increase the sensitizing impact. Such predictive patch tests are used to compare the sensitizing properties of new products or chemicals with those of known substances. Many test procedures have been developed over the last 40 years to evaluate the sensitizing properties of new chemicals. Kligman and Basketter [6] have critically evaluated the various methods of predictive testing. Most previous methods could not reveal even potent sensitizers. Kligman and Epstein have described a 'maximization test', based on the application of a high concentration of the chemical to be studied on a skin area previously irritated by sodium lauryl sulphate. This method was later modified by Marzulli and Maibach, who used repeated patch tests with high concentrations of the allergen to be studied. Jordan and King have shown that some substances giving negative reactions in maximization tests in males sometimes sensitize females. This may reflect previous subliminal exposure to substances such as the ingredients of cosmetics.

Ethical considerations may prevent experimental sensitization in humans. The guinea-pig maximization test described by Magnusson and Kligman gives results that compare favourably with predictive patch tests in humans. To enhance sensitization, the guinea-pig maximization test employs a combination of patch testing and intradermal injection of allergen in a simple solution of Freund's adjuvant. Other tests, such as the Buehler test and the open epicutaneous test, use the epicutaneous route only, whereas

the Draize test and Freund's complete adjuvant test use a purely intradermal method of sensitization. There is, however, no absolute conformity in the sensitizing potential of a substance in mouse, guinea pig and human.

The 6th Amendment of the EC Cosmetic Directive, which came into effect in January 1997, is committed to banning all animal testing. The local lymph node assay is a mouse model that has gained regulatory approval. A logarithmic scale is used to classify the potential of chemicals to induce sensitization, from strong to non-sensitizing, dependent on the dose needed to induce lymphocyte proliferation [7]. The mouse ear swelling test [8] avoids postmortem examination of tested animals.

The theoretical allergenicity [2,9] of a compound may be studied by reference to databases of cases of reported sensitivity and the results of previously performed guinea-pig maximization tests. By comparing the structure of known allergens and reactive groups with that of any new compound, an expert system can be developed to predict a compound's likely sensitization potential. Molecular modelling using structure–activity relationships has been used with sesquiterpene lactones, primin and relative alkylation index for sultones to test such a model.

Sensitization risk. The risk of sensitization depends not only on the sensitization potential of the substance applied. Prior to stimulating the immune system a chemical must penetrate the epidermis [10]. Subsequently, the log dose applied per unit area, where the area of application is above 1 cm^2, appears to be the most important determinant of the risk of sensitization, with the reactivity showing a sigmoid dose–response curve [11]. In practice, the conditions of exposure are also important: the duration of exposure (rinse off or leave on product), if the exposure is repeated [12], and the condition of the skin (the presence of pre-existing dermatitis predisposing to the presence of accessory signals in the sensitization process).

There are also individual factors; studies in individuals already sensitized indicating that those with more contact allergies are more susceptible to become sensitized to other allergens compared with those who do not demonstrate any pre-existing contact allergy. With high concentrations of a strong allergen such as DNCB, individual susceptibility is of little importance; nearly everyone is capable of being sensitized.

In personal care products the concentration of any allergen is adjusted so that the risk of inducing sensitization is small, although there may still be sufficient to induce dermatitis in an individual already sensitized. An approach to sensitization risk assessment for such products has been described [13]. This involves an assessment of both exposure, including knowledge of skin absorption, and sensitization potential, based on literature review and known structure–activity relationships. If *in vivo* testing is needed, various animal tests or human repeat-insult patch tests would then be performed. Legislative measures have been introduced in an attempt to reduce the prevalence of contact dermatitis [14].

Development of dermatitis. Some persons sensitive to a substance may tolerate normal contact with it, and are said to have a latent sensitivity. There is no immunological difference between latent and expressed sensitivity.

Whether sensitivity is manifest or latent is determined partly by the threshold of sensitivity, that is the lowest concentration of allergen giving a positive patch-test response. The dose at induction determines, in part, the strength of response at challenge, higher induction doses resulting in greater reactions at challenge [11]. Persons who are clinically sensitive to poison ivy invariably have a positive reaction to pentadecylcatechol (PDC) 1 : 10 000, but many who react only to 1 : 100 PDC are clinically immune. Patch-test sensitivity and clinical sensitivity are not necessarily proportional. The threshold determined by patch tests depends on a number of technical factors, such as the base used and the region where the tests are applied. It also varies from time to time in the same person. The threshold may fall after repeated contact with an allergen, and positive test reactions in latent allergy may reveal candidates for future allergic contact dermatitis.

Patch testing with a new substance may reveal that some persons are already sensitive to it, either from contact with related substances or from exposure to the compound in other forms. Negative reactions in 200 persons do not exclude the possible occurrence of sensitivity in 1 of 38 consumers (99.5% level). This frequency would immediately preclude any practical use of the substance. It has been calculated that negative patch tests in 5300 subjects indicate that sensitivity would be liable to occur in less than 1 of 1000 consumers.

Immunological tolerance. The sensitization reaction induces effector T cells and suppressor T cells, the latter curtailing the immune response so that the epidermal reaction regresses and does not continue indefinitely [15]. Theoretically, therefore, preferential stimulation of suppressor cells could lead to antigen unresponsiveness. This can be achieved by administering the allergen (in previously unsensitized individuals) by non-cutaneous routes, such as intravenously, orally or peritoneally [16], thereby bypassing epidermal Langerhans' cells. This tolerance is also achieved by applying the allergen to skin with no Langerhans' cells, for example mouse tails, or skin in which Langerhans' cells have been inhibited by UV radiation or depleted by glucocorticoids. Suppressor T cells, or their precursors, are sensitive to cytostatic drugs, so that administration of cyclophosphamide can reverse a tolerant state.

References

1 Basketter D, Dooms-Goossens A, Karlberg AT, LePoittevin J-P. The chemistry of contact allergy: why is a molecule allergenic? *Contact Dermatitis* 1995; **32**: 65–73.

2 Lepoittevin JP. Molecular aspects of allergic contact dermatitis. In: Frosch PJ, Menné T, Lepoittevin J-P, eds. *Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 45–68.

3 Dupuis G, Benezra C. *Allergic Contact Dermatitis to Simple Chemicals: a Molecular Approach*. New York: Marcel Dekker, 1982.

4 Gruchalla RS. Drug metabolism, danger signals, and drug-induced hypersensitivity. *J Allergy Clin Immunol* 2001; **108**: 475–88.

5 Klecak G. Test methods for allergic contact dermatitis in animals. In: Marzulli FN, Maibach HI, eds. *Dermatotoxicology*, 5th edn. Washington, DC: Hemisphere, 1996: 437–59.

6 Kligman AM, Basketter DA. A critical commentary and updating of the guinea pig maximisation test. *Contact Dermatitis* 1995; **32**: 129–34.

7 Basketter DA, Gerberick F, Kimber I. The local lymph node assay and the assessment of relative potency: status of validation. *Contact Dermatitis* 2007; **57**: 70–5.

8 Gad SC, Dunn BJ, Dobbs DW *et al*. Development and validation of an alternative dermal sensitisation test: the mouse ear swelling test (MEST). *Toxicol Appl Pharmacol* 1986; **84**: 93–114.
9 Barratt MD, Basketter DA, Chamberlain M *et al*. Development of an expert system rulebase for identifying contact allergens. *Toxicol In Vitro* 1994; **8**: 1053–60.
10 Schaefer H, Redelmeier TE. Skin penetration. In: Frosch PJ, Menné T, Lepoittevin J-P, eds. *Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 167–78.
11 Friedmann PS. The relationships between exposure dose and response in induction and elicitation of contact hypersensitivity in humans. *Br J Dermatol* 2007; **157**: 1093–102.
12 Basketter DA, Jefferies D, Safford BJ *et al*. The impact of exposure variables on the induction of skin sensitization. *Contact Dermatitis* 2006; **55**: 178–85.
13 Gerberick GF, Robinson MK. A skin sensitization risk assessment for evaluation of new ingredients and products. *Am J Contact Dermatitis* 2000; **11**: 65–73.
14 Lidén C. Legislative and preventive measures related to contact dermatitis. *Contact Dermatitis* 2001; **44**: 65–9.
15 Rustemeyer T, van Hoogstraten IMW, von Blomberg BME, Scheper R. Mechanisms in allergic contact dermatitis. In: Frosch PJ, Menné T, Lepoittevin J-P, eds. *Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 45–68.
16 White JML, Goon A, Jowsey IR *et al*. Oral tolerance to contact allergens: a common occurrence? A review. *Contact Dermatitis* 2007; **56**: 247–54.

Pathology

Biopsies are of limited help in contact dermatitis. Most types of eczema show identical pathological changes, and allergic and primary irritant contact dermatitis cannot be distinguished with certainty; the topic is discussed in more detail in Chapter 25. It would appear that the only sure way to distinguish irritant from allergic contact dermatitis is by study of the very early events of the inflammatory process because the remainder of the inflammatory cascade is similar in the two processes [1].

Reference

1 Meller S, Lauerma AI, Kopp FM *et al*. Chemokine responses distinguish chemical-induced allergic from irritant skin inflammation: memory T cells make the difference. *J Allergy Clin Immunol* 2007; **119**: 1470–80.

Clinical features

Contact dermatitis can mimic or be associated with any type of eczematous eruption. The diagnosis is based on a careful history combined with a sound knowledge of common allergens and irritants in the environment.

History

A comprehensive history is essential to identify contact with allergens, and some knowledge of chemistry and industrial processes is of value. Sensitization and subsequent contact dermatitis may result from a single exposure [1], although usually several or many exposures are necessary before sensitization and dermatitis occur.

Primary site. This must be ascertained by questioning the patient carefully. By definition, contact dermatitis must begin in sites where contact has taken place with the responsible agent(s), and the sites of origin are an important clue to the cause. Patients are frequently assessed at a stage when there has been worsening and secondary spread of the dermatitis, obscuring the original pattern.



Fig. 26.1 Medicament contact dermatitis. (Courtesy of Dr J.D. Wilkinson, Amersham General Hospital, Amersham, UK.)

Duration and behaviour. Once the date of onset and the primary site(s) have been identified, it is necessary to establish the subsequent behaviour of the disorder. In particular, did the condition spread and if so where? Has the problem been persistent or intermittent? Repeated sudden exacerbations may point to an allergic contact dermatitis. Are there any obvious exacerbating factors?

Improvement of dermatitis during weekends or holidays favours an occupational origin. Relapse at weekends suggests a hobby or non-occupational allergen. Seasonal variation (worsening when light intensity is greatest) suggests a plant allergen, perhaps with photoaggravation, or photoallergy. Plant dermatitis may recur in atypical patterns. Dermatitis around a wound, especially leg ulcers, suggests sensitization to medicaments (Fig. 26.1) and exacerbations and recurrences induced by particular medicaments or cosmetics suggest contact allergy from these sources.

Previous history. A history of previous dermatitis may provide a clue to the origin of a relapse. For example, earring dermatitis may precede nickel dermatitis of the hands by several years. Previous dermatitis, especially if localized to the lower legs, may have been caused or complicated by repeated use of applications containing sensitizers. It is useful to ask specifically about skin reactions to cheap metal, perfume and adhesive plasters.

A history of infantile or childhood flexural eczema, asthma, hay fever or conjunctivitis may point to an atopic diathesis. Atopic eczema predisposes to irritant dermatitis of the hands, and in such



Fig. 26.2 Acute allergic contact dermatitis in a patient allergic to acrylates used in the printing industry. (Courtesy of Dr J.D. Wilkinson, Amersham General Hospital, Amersham, UK.)

cases constitutional factors may be the major but not necessarily the sole cause.

Sources of allergy

A search for possible sources of allergic contact dermatitis should include a review of all the patient's activities, but initially should concentrate on: (i) occupation, past and present; (ii) hobbies; (iii) cosmetics, clothing and personal objects; (iv) home environment; and (v) current and previous topically applied medicaments both prescribed and 'over-the-counter'. Most patients believe that newly encountered items are the cause of dermatitis, whereas in fact those that have been in use for a long time are commonly responsible.

Occupational (Fig. 26.2). A precise history backed by a thorough knowledge of the materials handled at work, machinery operated and personal protection employed will be necessary when occupational dermatitis is suspected. However, no dermatologist can rely entirely on his or her knowledge of industrial processes, and a factory visit may be required to become familiar with the process described, especially if it is strange or new. Health and safety data sheets must be examined as these may give the chemical names of materials used, as well as an indication of their irritancy or allergenicity. A telephone number or email address may be given for further enquiries, if required. The presence of other similar cases will alert one to an increased probability of occupational dermatitis. There are increasing reports of allergy to components of cleansers, creams and conditioners supplied at work, and workers must be asked about use of these [2].

Problems associated with housework should not be overlooked. The amount of housework performed and methods employed are extremely variable. The number of children and availability of labour-saving devices should be determined. Few people volunteer information about domestic work outside their own home, and all must be directly questioned about it.

Patients who are unemployed may, in fact, be engaged in casual work, and even employed persons should be asked about second jobs.

Hobbies. Common sensitizers, well known as industrial allergens, are introduced into most homes for do-it-yourself work. Cement, glues, paint, wood and wood preservatives are handled by many householders. Another important source of hobby dermatitis is gardening. Other pursuits, such as car maintenance, sports, cookery and photography, should be considered.

Personal objects. These are items either worn in context with or applied to the skin, and include textiles, footwear, protective clothing and gloves, jewellery, spectacles, hearing aids, medical appliances, cosmetics, toiletries, fragrances and medicaments. Untoward reactions to cosmetics, toiletries and topical applications are among the commonest reasons for hospital referral with allergic contact dermatitis. The number of products used may be large, and some may be used only intermittently. Often, only prescribed therapies are declared, and repeated specific enquiry must be made about over-the-counter preparations, including cosmetics used as moisturizers, herbal treatments and borrowed medicaments. Often patients will not mention 'hypoallergenic' products in the mistaken belief that they could not be responsible. Applied cosmetics may be removed by employing creams, lotions or wipes, the use of which may easily be overlooked. Patients should be specifically asked about the use of nail varnish, false nails and hair dyes. Skin cleansing and hair products, which are 'rinse off' as opposed to 'leave on', may also be responsible. Many patients have a poor recollection of products used, and most forget some items. They should be invited to bring all their topically applied items when they attend for patch testing.

References

1 Kanerva L, Tarvainen K, Pinola A *et al*. A single accidental exposure may result in a chemical burn, primary sensitization and allergic contact dermatitis. *Contact Dermatitis* 1994; **31**: 229–36.

2 Wong CS, Beck MH. Occupational contact allergy to methyldibromoglutaronitrile in abrasive cleansers and work creams. *Contact Dermatitis* 2001; **44**: 311–2.

Clinical examination

Eczematous responses (dermatitis)

The severity of the dermatitis is determined by the intensity of exposure and the level of sensitivity. The clinical picture is also to some extent dependent upon the site of dermatitis and on the causative agent. The distribution of the dermatitis may suggest a cause, for example that due to nickel or textiles.

The primary signs in acute contact dermatitis are erythema, swelling, papules and papulovesicles, which reflect the sequence of inflammatory changes in the dermis and the intracellular and intercellular oedema in the epidermis. In more acute and severe cases this may progress to disruption of the intercellular bridges and the development of larger vesicles or blisters; if they burst, a weeping dermatitis results. The dominant symptom is itching.

If contact dermatitis persists, it may be due to continued or repeated exposure to the allergen or to secondary irritants or allergens. The skin becomes dry, scaly and thicker as a result of acanthosis, hyperkeratosis, oedema, and cellular infiltration in the dermis. Lichenification and fissuring may develop later (Fig. 26.3). These clinical features of chronic allergic contact dermatitis cannot always be distinguished from constitutional (Fig. 26.4) or irritant contact dermatitis, and the aetiology is indeed often mixed.



Fig. 26.3 Dry, scaling, thickened skin with fissuring due to chronic contact dermatitis.

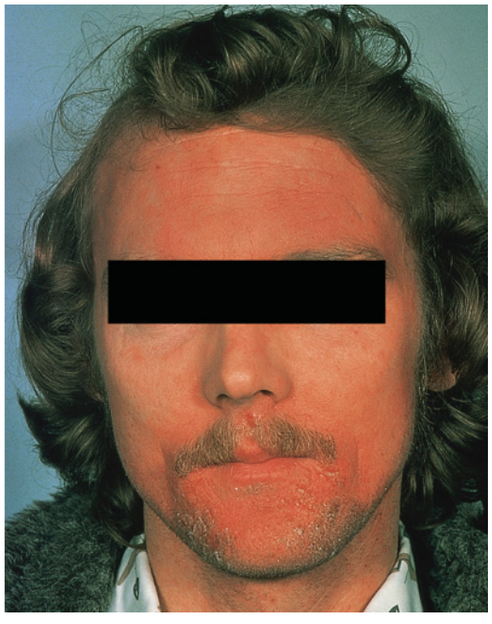


Fig. 26.4 A 'seborrhoeic dermatitis-like' pattern of allergic contact dermatitis due to phosphorus sesquisulphide ('strike anywhere' matches). (Courtesy of Dr J.D. Wilkinson, Amersham General Hospital, Amersham, UK.)

The distribution of the dermatitis is of diagnostic importance but its morphology is usually of no help in tracing the cause, with some exceptions, for example exceptionally strong allergens may provoke a bullous eruption even after brief contact and dermatitis from plant leaves may provoke a linear pattern of dermatitis.



Fig. 26.5 Acute vesicular eczema in a patient allergic to 1,2-benzisothiazolin-3-one mimicking constitutional pompholyx. (Courtesy of Dr J.D. Wilkinson, Amersham General Hospital, Amersham, UK.)

Primary patterns

Anatomical patterns of dermatitis often suggest a specific cause, but in other cases the pattern merely indicates a range of possible allergens, such as in shoe dermatitis.

Sometimes, the dermatitis is sharply limited to the usual site of contact, but because the area of contact with most objects varies, the distribution may be more erratic. Some allergens may be spread locally by the fingers or be carried to distant body regions. Even when there is no eruption on the hands, allergens on the fingertips may cause dermatitis elsewhere, for example the genital area, eyes, or face and neck.

Once the primary site has been established, questioning should focus on those allergens that are particularly frequent causes of dermatitis in that region.

Hands and arms. Hand dermatitis is usually multifactorial. About two-thirds of all cases of contact dermatitis involve the hands, which are the most important site for both irritant and allergic contact dermatitis [1,2]. No pattern of hand eczema is characteristic of a particular aetiology, and it is important to emphasise that allergic contact dermatitis may mimic constitutional patterns. Housewives' dermatitis and most occupational dermatitis remain confined to the hands. Although the majority of cases are of primary irritant nature, the yield of relevant positive reactions to patch tests is high [1]. Allergens may be traced by relating the shape and site of the eczematous patches to items handled. Rubber gloves may induce a clear pattern of dermatitis over the sites where they are worn.

Vesicular palmar contact dermatitis may mimic constitutional eczema and may result not only from contact with but also from ingestion of an allergen to which the person is already sensitized. Chromate in cement, *N*-isopropyl-*N*′-phenyl-*p*-phenylenediamine (IPPD) and 1,2-benzisothiazolin-3-one (Fig. 26.5) are three allergens particularly liable to induce a palmar pattern of allergic dermatitis. Discoid patterns of eczema may be seen with chromate allergy.

Streaky dermatitis on the fingers, dorsa of the hands and forearms is typically caused by plants (Fig. 26.6), and may be allergic



Fig. 26.6 Characteristic 'streaky' contact dermatitis on the wrists in a patient allergic to *Primula obconica*. (Courtesy of Dr J.D. Wilkinson, Amersham General Hospital, Amersham, UK.)

(e.g. *Primula obconica* and poison ivy), irritant (e.g. *Dieffenbachia* and spurge) or phototoxic (e.g. giant hogweed and rue).

Dermatitis of the hands in those involved with agriculture, animals and food preparation may be associated with immediate-type hypersensitivity to animal and plant proteins [3,4]. Allergic contact dermatitis of the fingertips is seen with plant allergens such as tulipalins in horticulturists and florists ('tulip fingers') [5]. Garlic allergy in chefs typically affects the non-dominant thumb, fore and middle fingers [6] (Fig. 26.7).

The arms are affected by the same allergens as the hands, but usually later. If the hands have been protected by gloves at work, the forearms may be the major sites of occupational dermatitis (Fig. 26.8). Allergy to nickel, chromate and *p*-tertiary-butylphenol formaldehyde resin may develop at the wrists from sensitivity to the metal, leather and glue, respectively, in watchstraps containing these allergens. Dust (exotic woods, cement), nickel and textiles produce dermatitis in the elbow flexures, and this must be distinguished from atopic dermatitis.

Face. Dermatitis of the face may occur alone or in association with eczema elsewhere. Facial allergic contact dermatitis from fragrances, hair dyes, preservatives and other constituents of skin-care products and cosmetics, including nail varnish, is common.

Dermatitis due to a cosmetic may start with dryness, tightness and itching. Most women change to another brand at this stage and never reach the dermatologist. They are referred only if symptoms persist or are severe. Some allergens, for example hair dyes and 'strike-anywhere matches', may provoke acute oedema (Fig. 26.9) and intense pruritus, but no manifest eczema, followed by desquamation. Nail varnish allergy often affects the face in well-localized patches, and may be associated with eyelid dermatitis and more



Fig. 26.7 Fingertip pattern of allergic contact dermatitis from garlic affecting the non-dominant thumb, forefinger and middle fingers.



Fig. 26.8 Contact allergy to epoxy resin and hardener affecting unprotected forearms.

extensive involvement of the neck, chest and even further afield [7]. The clinical presentation can suggest artefact because the affected sites are so well demarcated [8]. A similar distribution may be seen from allergy to acrylic nails and rubber sponge applicators [9,10]. The forehead is affected by allergy to anything applied to the hair and also to chromate in leather hatbands. Spectacle frames containing nickel or plastics may cause dermatitis on areas of contact with the cheeks, nose, eyelids and ears.

The patterns of dermatitis caused by airborne or volatile allergens [11] and photosensitizers can often be distinguished by



Fig. 26.9 Contact dermatitis presenting as acute oedema, as seen in patients sensitive to *Primula* and *p*-phenylenediamine-type hair dyes and in those with volatile patterns of contact dermatitis. (Courtesy of Dr J.D. Wilkinson, Amersham General Hospital, Amersham, UK.)

involvement of the eyelids in the former, and by triangles of relatively spared skin below the chin and behind and below the ear lobes in the latter.

Facial allergic contact dermatitis must be distinguished from intolerance, irritant contact dermatitis and constitutional eczemas, but it is sometimes multifactorial.

Eyelids [12,13]. Allergens affecting the face may initially produce eyelid dermatitis, as the skin of the eyelids is thin, sensitive and may be contaminated by the fingers (e.g. nail varnish [7]), airborne droplets (e.g. fragrance sprays) or volatile substances (e.g. epoxy resin). Eye creams, eye shadows, mascara and eye make-up removers may be responsible, often for irritant dermatitis, but patch testing may reveal relevant allergens. Eyelash curlers and make-up applicators may contain nickel and/or rubber and cause contact allergy in this site [14,15].

Primula obconica and poison ivy allergy may involve the eyelids, usually associated with a streaky pattern of dermatitis at contact sites, which may be haemorrhagic.

Dermatitis is frequently caused by remedies for ocular disorders. Common sensitizers in eye drops and ointments are neomycin, framycetin, gentamicin, tobramycin, chloramphenicol, sulphonamides, local anaesthetics, antihistamines, β-blockers, anticholinergics and sympathomimetics. Eye drops and contact lens solutions contain preservatives (benzalkonium chloride, EDTA, mercurials), which may also sensitize.

Lips or perioral area. Sensitivity may occur from lipsticks and salves, nickel, medicaments, flavourings, garlic [16], shellac [17] and cosmetic excipients. Lipstick dermatitis may be limited to the vermilion border, which appears dry, scaling or cracked; but the perioral area may also be affected. Eosin was a common sensitizer in lipsticks before 1960 [18] but since its allergenicity was found to be due to impurities there have been no further reports of adverse effects, and lipstick dermatitis is less common.

Allergy to toothpaste is a recognized cause of cheilitis and perioral eczema. Flavours are the usual cause, such as cinnamic aldehyde [19], spearmint oil, peppermint oil, anethole and L-carvone [20]. Colophony and derivatives may be found in chewing gum and cause allergic contact cheilitis [21]. Allergy to other food additives such as sodium metabisulphite, preservatives, colours and antioxidants may have a potential to cause cheilitis. In Europe, their presence can be determined by identifying the relevant E number on the ingredient label of the foodstuff packaging.

Allergic reactions to dentures and fillings are considered in the section on mucous membranes (see p. 26.20). Angular cheilitis is usually due to badly fitting dentures, but cheilitis may exceptionally be caused by sensitizers habitually carried to the mouth, such as nail varnish or nickel-plated objects [22] (e.g. keys, pins or musical instruments).

Ears. External otitis has a complex aetiology (see Chapter 68) and usually runs a chronic relapsing course. Neurodermatitis (lichen simplex chronicus) is also common, and may be superimposed on seborrhoeic eczema.

Secondary medicament contact dermatitis, which is often unsuspected, is particularly common in the ear [23]. Dermatitis can also be both caused and maintained by habitual scratching with hairpins (nickel), matches (phosphorus sesquisulphide and chromate) [24] or fingertips (nail varnish).

Although dermatitis from hearing-aids occurs it is often a non-specific consequence of occlusion [25]. Hearing-aids may contain acrylates and plasticizing and stabilizing chemicals. Headsets may contain urea and phenol-formaldehyde resins, or rubber in earphones.

Spectacle-frame dermatitis may be of irritant origin, especially behind and over the ears. Metals, particularly nickel and palladium, may cause allergy, and some frames responsible for dermatitis have been wrongly described as being nickel-free or made of titanium [26,27]. Plastic components, including epoxy resins, acrylates, plasticizers, UV inhibitors and dyes, have been identified as the cause of the dermatitis. Earplugs for noise protection may contain antiseptics, dyes, rubber and plastic chemicals, and finishes including formaldehyde resins. Elastic on shower caps and hair dye caps cause dermatitis in the retro-auricular area.

Earrings and clips commonly cause dermatitis on the ear lobes as a result of the presence of nickel or, less commonly, gold. Piercing of the ear lobe may be the sensitizing event in nickel dermatitis, leading to a chronic contact dermatitis. Granulomatous contact allergy to nickel, palladium and gold has been seen after ear piercing [28].

Scalp. The scalp tends to be relatively spared from involvement by allergic contact dermatitis. Dermatitis caused by fragrances, biocides and amphoteric detergents in hair cosmetics is usually limited to the ears, neck and face, but may be preceded by persistent itching of the scalp. Permanent hair dye, *p*-phenylenediamine, and related semi-permanent dyes still remain an important source of dermatitis. Correctly used, permanent hair dyes are applied to the hair and not the scalp, followed by oxidation and rinsing. Bleaches contain ammonium persulphate, which may cause peculiar urticarial eruptions as well as contact dermatitis. Glyceryl monothioglycollate, used for acid or cold perms, is a significant sensitizer in hairdressers but only occasionally causes problems in



Fig. 26.10 A patch of 'lichen simplex-like' eczema on the nape of the neck associated with allergy to tosylamide formaldehyde resin (nail varnish). (Courtesy of Dr J.D. Wilkinson, Amersham General Hospital, Amersham, UK.)

their clients. Hair-styling products such as mousses, gels, waxes and holding sprays often contain fragrances and preservatives that may be allergenic, but they also contain conditioning quaternary ammonium compounds, which are often irritant. Medicated shampoos may contain tar extracts, zinc pyrithione or other agents, and many shampoos contain formaldehyde, formaldehyde releasers or isothiazolinones, added as preservatives. Cocamidopropylbetaine is also found in many shampoos. All these materials may potentially sensitize, although allergic subjects may tolerate them because of the short duration of contact, provided the hair is thoroughly rinsed after washing. Topical minoxidil lotion, prescribed to promote hair growth, will sensitise occasionally [29]. Scalp dermatitis from allergy to azo disperse dyes in a nylon wig has been reported [30].

Neck. Nickel in the clasps of necklaces or zip fasteners produces a small area of dermatitis on the nape of the neck. Nail varnish (Fig. 26.10) or primin from fingertips may be the cause of a patchy allergic dermatitis sometimes simulating lichen simplex.

Textiles (finishes in collars, dyes) and necklaces (nickel, exotic wood) may cause a collar-like dermatitis, or eruptions on the sides of the neck. Dermatitis from airborne allergens and photosensitizers is sharply limited by the collar to the 'V' of the neck if blouses or open-necked shirts are worn.

Perfume may cause both allergic contact dermatitis and phototoxic dermatitis (Berloque dermatitis) on the neck, especially the sides.

Axillae. Many cases of dermatitis are irritant due to sweating, occlusion and the use of antiperspirants, which often contain aluminium salts to block the sweat glands. Allergic sensitivity may occur to fragrances used to mask odour, and to antiseptics intended to reduce the bacterial flora. The dermatitis produced by textiles tends to be periaxillary.

Trunk. The distribution of a clothing dermatitis may provide a clue to the responsible garment. In both sexes, nickel buttons and zip fasteners cause dermatitis localized to where they are worn, but a more widespread secondary spread eruption is often associated. Chromate sensitivity from leather, and rubber allergy from elastic, may present as truncal eczema. Dermatitis from dresses, blouses and sweaters usually predominantly affects the neck and folds of the axilla, and spares areas of skin covered by undergarments. The allergens are usually textile dyes or finishes.

Outdoor workers sensitized to Compositae (Asteraceae) plants may have a diffuse dermatitis or dermatitis of an airborne pattern, which affects all the exposed areas, including the trunk if they remove their clothing to work. Detergents and fabric conditioners are commonly blamed for truncal skin eruptions but objective confirmation is usually lacking [31]. Diffuse papular eczema may be a feature of medicament sensitivity with secondary spread.

Anogenital. The anogenital region is a common site for medicament sensitization. There is often experimentation with a wide range of prescribed and over-the-counter medicaments for pruritus, skin eruptions and haemorrhoids, and many of these contain sensitizers, most commonly perfume, local anaesthetics and balsam of Peru (*Myroxylon pereirae*). Other sensitizers prescribed by the medical profession include neomycin, hydroxyquinolines, ethylenediamine, corticosteroids and topical antifungals. Moist toilet tissues and wipes may contain unnecessarily high levels of preservative, which have been associated with an increased prevalence of allergic sensitivity [32]. Ectopic contact dermatitis from nail varnish may affect this site [33]. Nylon dyes, especially in tights, may also produce allergic contact dermatitis largely confined to this area.

Ingestion of contact allergens may cause pruritus ani, particularly if they are excreted unchanged. Spices and medicaments may occasionally be suspected. Cashew nut oil in butter was found to induce perianal dermatitis in an individual allergic to the cross-sensitizing allergenic urushiol found in poison ivy [34].

Many studies in women have not distinguished an anogenital pattern from dermatitis confined to the perianal or vulval area, but allergic contact dermatitis confined to the vulva appears to be less common [35]. Medicaments used for vaginitis rarely provoke allergic reactions on the mucosa but sometimes produce a rash on the adjacent skin, and may cause connubial dermatitis in sexual partners. Medicament allergy has frequently been associated with vulval dermatitis [36,37], and in another study investigating pruritus vulvae without associated inflammation, 49% had one or more relevant allergic reactions on patch testing, as did seven of 16 patients with lichen sclerosus. In over 50% of these patients, symptoms improved significantly or resolved when avoidance measures were taken [38]. Perfumes or antiseptics in soaps, sprays or sanitary pads are rare causes of genital dermatitis, although



Fig. 26.11 Allergic contact dermatitis due to items kept in trouser pockets. (Courtesy of Dr J.D. Wilkinson, Amersham General Hospital, Amersham, UK.)

feminine hygiene sprays may cause both irritant and allergic reactions. Vulvodynia does not appear to be frequently associated with contact allergy [39].

Rubber accelerators in condoms can also be a cause of genital eczema or pruritus vulvae. Delayed hypersensitivity to semen has been reported [40]. Genital dermatitis from transfer of material carried on the hands may occur in carpenters and cabinet-makers and those who work with resins.

Thighs. Dermatitis from nickel and rubber in suspenders is now rarely seen. Textile dermatitis starts at the edge of the underwear, and is usually more pronounced in the popliteal spaces or gluteal folds. Finishes in the material of the pockets or objects kept in the pockets (e.g. nickel coins or boxes of matches) may provoke a patch of dermatitis on the underlying skin (Fig. 26.11). Allergens may penetrate working clothes.

Lower legs. The lower leg is particularly prone to contact allergy. Allergic contact dermatitis from medicaments and dressings predominates, especially in those with varicose eczema and ulcers. The common medicament allergens are topical antibiotics and components of creams and paste bandages, such as lanolin, cetearyl alcohol and preservatives [41]. Allergy seems to occur readily to materials that are rarely problematic in other sites. Rubber allergy may be associated with compression bandaging and elastic hosiery. Allergy to colophony and derivatives may occur from dressing adhesives, and nylon dye allergy may be seen from hosiery.

Rubber boots provoke dermatitis either at their upper edge or on the calf in areas of greatest friction.

Feet. Dermatitis may result from shoe materials including leather, rubber, glues and nickel, stockings, topical medicaments, antiseptics and antiperspirants.

Generalized. Generalized erythroderma may be the result of a chronic contact dermatitis maintained by continued exposure to a wide range of allergens, including components of topical medicaments. Patch testing is not possible until the skin has cleared.

References

1 Wilkinson DS, Bandmann H-J, Calnan CD *et al*. The role of contact allergy in hand eczema. *Trans St John's Hosp Dermatol Soc* 1970; **56**: 19–25.
2 Agrup G. Hand eczema and other hand dermatoses in South Sweden. *Acta Derm Venereol Suppl (Stockh)* 1969; **61**: 54.
3 Hjorth N, Roed-Petersen J. Occupational protein contact in food handlers dermatitis. *Contact Dermatitis* 1976; **2**: 28–42.
4 Kanerva L, Toikkanen J, Jolanki R, Estlander T. Statistical data on occupational contact urticaria. *Contact Dermatitis* 1996; **35**: 299–33.
5 Bruynzeel DP, De Boer EM, Brouwer EJ *et al*. Dermatitis in bulb growers. *Contact Dermatitis* 1993; **29**: 11–5.
6 Burks JW. Classic aspects of onion and garlic dermatitis in housewives. *Ann Allergy* 1954; **12**: 592–6.
7 Lidén C, Berg M, Farm G *et al*. Nail varnish allergy with far-reaching consequences. *Br J Dermatol* 1993; **128**: 57–62.
8 Calnan CD, Sarkany I. Studies in contact dermatitis. III. Nail varnish. *Trans St John's Hosp Dermatol Soc* 1958; **40**: 1–11.
9 Tucker SC, Beck MH. A 15-year study of patch testing to (meth)acrylates. *Contact Dermatitis* 1999; **40**: 278–9.
10 Helbling I, Beck MH. Rubber sponge applicator responsible for 'cosmetic' facial dermatitis. *Contact Dermatitis* 1998; **39**: 43.
11 Dooms-Goossens AE, Debusschere KM, Cevers DM *et al*. Contact dermatitis caused by airborne agents. *J Am Acad Dermatol* 1986; **15**: 1–10.
12 Valsecchi R, Imberti G, Martino D *et al*. Eyelid dermatitis: an evaluation of 150 patients. *Contact Dermatitis* 1992; **27**: 143–7.
13 Guin JD. Eyelid dermatitis: a report of 215 patients. *Contact Dermatitis* 2004; **50**: 87–90.
14 Brandrup F. Nickel eyelid dermatitis from an eyelash curler. *Contact Dermatitis* 1991; **25**: 77.
15 Vestey JP, Buxton PK, Savin JA. Eyelash curler dermatitis. *Contact Dermatitis* 1985; **13**: 274–5.
16 Ekeowa-Anderson AL, Shergill B, Goldsmith P. Allergic contact cheilitis to garlic. *Contact Dermatitis* 2007; **56**: 174–5.
17 Orton DI, Salim A, Shaw S. Allergic contact cheilitis due to shellac. *Contact Dermatitis* 2001; **44**: 250.
18 Calnan CD, Sarkany I. Studies in contact dermatitis. II. Lipstick cheilitis. *Trans St John's Hosp Dermatol Soc* 1957; **39**: 28–36.
19 Magnusson B, Wilkinson DS. Cinnamic aldehyde in a toothpaste. *Contact Dermatitis* 1975; **1**: 70–6.
20 Andersen KE. Contact allergy to toothpaste flavors. *Contact Dermatitis* 1978; **4**: 195–8.
21 Gupta G, Forsyth A. Allergic contact reactions to colophony presenting as oral disease. *Contact Dermatitis* 1999; **40**: 332–3.
22 Fisher AA. Perlèche (angular cheilitis) due to contactants. *Cutis* 1974; **14**: 499–501.
23 J Millard TP, Orton DI. Changing patterns of contact allergy in chronic inflammatory ear disease. *Contact Dermatitis* 2004; **50**: 83–6.
24 Tucker SC, Lyon CC, Beck MH. Persistent otitis externa due to allergic contact dermatitis to phosphorus sesquisulphide in 'strike-anywhere' matches (Minerva). *BMJ* 1999; **318**: 1566.
25 Lear JT, Sandhu G, English JS. Hearing aid dermatitis: a study in 20 consecutive patients. *Contact Dermatitis* 1998; **38**: 212.
26 Glas B, Egelrud T. Nickel in 'nickel-free' spectacle frames. *Contact Dermatitis* 1999; **40**: 217.
27 Bircher AJ, Stern WB. Allergic contact dermatitis from 'titanium' spectacle frames. *Contact Dermatitis* 2001; **45**: 244–5.
28 Casper C, Groth W, Hunzelmann N. Sarcoidal-type allergic contact granuloma: a rare complication of ear piercing. *Am J Dermatopathol* 2004; **26**: 59–62.
29 Friedman ES, Friedman PM, Cohen DE *et al*. Allergic contact dermatitis to topical minoxidil solution: etiology and treatment. *J Am Acad Dermatol* 2002; **46**: 309–12.
30 Shehade SA, Beck MH. Contact dermatitis from disperse dyes in synthetic wigs. *Contact Dermatitis* 1990; **23**: 124–5.
31 Corea NV, Basketter DA, Clapp C *et al*. Fragrance allergy: assessing the risk from washed fabrics. *Contact Dermatitis* 2006; **55**: 48–53.

32 De Groot AC. Vesicular dermatitis of the hands secondary to perianal allergic contact dermatitis caused by preservatives in moistened toilet tissues. *Contact Dermatitis* 1997; **36**: 173–4.
33 Lazarov A. Perianal contact dermatitis caused by nail lacquer allergy. *Am J Contact Dermatitis* 1999; **10**: 43–4.
34 Rosen T, Fordice DB. Cashew nut dermatitis. *South Med J* 1994; **87**: 543–6.
35 Goldsmith PC, Rycroft RJ, White IR *et al*. Contact sensitivity in women with anogenital dermatoses. *Contact Dermatitis* 1997; **36**: 174–5.
36 Nardelli A, Degreef H, Goossens A. Contact allergic reactions of the vulva: a 14-year review. *Contact Dermatitis* 2004; **15**: 131–6.
37 Batchelor RJ, Young HS, Beck MH. The role of patch testing in perineal disorders affecting women. *Exog Dermatol* 2003; **2**: 178–83.
38 Lewis FM, Shah M, Gawkrodger DJ. Contact sensitivity in pruritus vulvae: patch test results and clinical outcome. *Am J Contact Dermatitis* 1997; **8**: 137–40.
39 Nunns D, Ferguson J, Beck M *et al*. Is patch testing necessary in vulval vestibulitis? *Contact Dermatitis* 1997; **37**: 87–9.
40 Guillet G, Dagregorio G, Guillet MH. Vulvar contact dermatitis due to seminal allergy: 3 cases. *Ann Dermatol Venereol* 2005; **132**: 123–5.
41 Wilson CL, Cameron J, Powell SM *et al*. High incidence of contact dermatitis in leg-ulcer patients: implications for management. *Clin Exp Dermatol* 1991; **16**: 250–3.

Exposed sites [1]

Contact dermatitis from dust, sprays, pollens or volatile chemicals is typically confined to the exposed surfaces of the hands, arms, face and neck. The first attack often originates from direct handling of an allergen, but recurrences may be seen despite avoidance of direct contact. There is great diversity in the nature of airborne reactions, which may be irritant, allergic, phototoxic, photoallergic and contact urticarial. Some agents may cause more than one type of reaction.

Lists of airborne allergens have been published and updated by Goossens *et al*. [1]. Plants, natural resins and woods are among the commoner causes of this distribution of contact allergy. In the USA, the oleoresins of ragweed commonly cause allergic contact dermatitis. A similar pattern in the UK during the summer months is caused by other Compositae (Asteraceae) weeds which, when they occur in other parts of the world, also produce an 'airborne' pattern of dermatitis. In India and Pakistan, *Parthenium* has been associated with widespread epidemics of severe dermatitis and even deaths [2].

Dermatitis from wood dust is common in carpenters and cabinet-makers. It normally starts on the eyelids or the lower half of the face, and is often preceded by a period of itching. Swelling and redness spread to the neck, hands and forearms. By the time the patient attends for treatment, a diffuse dermatitis may have developed, distinctly limited at the margins of the sleeves and collar. Because of the accumulation of dust and sweat, the elbow flexures and the skin under a tight collar are often lichenified. Cabinet-makers frequently develop a genital dermatitis from accumulation of sawdust on the clothes during sawing and planing, and by hand contact. Swelling and redness of the eyelids may be the only signs of recurrence. Exotic woods are more likely to sensitize than fir or spruce, although the latter may cause dermatitis in patients sensitive to colophony and turpentine. Dermatitis in woodworkers may additionally be caused by liverworts and lichens on the bark of trees. Colophony can also give an exposure pattern of dermatitis from its presence in solder fluxes, paper dust, polish and linoleum flooring [3,4].

Resin systems, particularly epoxy resins, including the more volatile amine hardeners, may induce an airborne pattern of allergy, especially in the occupational setting. Other causes of this pattern include perfumes, metals, many industrial and pharmaceutical chemicals, pesticides, fungicides, animal feed additives, textile dyes and matches [1]. Equivalent patterns of airborne dermatitis may be seen with type I allergens, such as house-dust mite antigens in atopics [5].

Photocontact allergy causes a similar distribution, and is discussed on p. 26.33.

References

1 Huygens S, Goossens A. An update on airborne contact dermatitis. *Contact Dermatitis* 2001; **44**: 1–6.
2 Mitchell JC, Calnan CD. Scourge of India: *Parthenium* dermatitis. *Int J Dermatol* 1978; **17**: 303–4.
3 Sadhra S, Foulds IS, Gray CN *et al*. Colophony: uses, health effects, airborne measurement and analysis. *Ann Occup Hyg* 1994; **38**: 385–96.
4 Karlberg AT, Gäfvert E, Meding B *et al*. Airborne contact dermatitis from unexpected exposure to rosin (colophony). Rosin sources revealed with chemical analyses. *Contact Dermatitis* 1996; **35**: 272–8.
5 De Groot AC, Young E. The role of contact allergy to aeroallergens in atopic dermatitis. *Contact Dermatitis* 1989; **21**: 209–14.

Mucous membranes

Application of DNCB to the oral mucosa may, in some cases, induce a low degree of contact sensitivity, but more often an immunological tolerance to later sensitization [1]. Similarly, prior exposure to nickel and chromate in orthodontic appliances seems to reduce the risk of later sensitization [2,3].

Contact inflammation of the mucous membranes is uncommon, and is often secondary to skin sensitization with the same substances. Reactions may be allergic or irritant in nature. Both immune and non-immune immediate-type contact urticarial reactions may occur.

The skin and mucous membranes differ in both anatomy and environment. In the mouth, except on the gums and hard palate, there is no horny layer with a barrier function and storage capacity. There is no lipid secretion, but instead a continuous flow of saliva, which washes away foreign substances. Penetration of water-soluble substances is rapid. It is not known whether these differences are relevant to the paucity of allergic contact reactions in mucous membranes. The oral mucosa of sensitized animals has been shown to have an identical cellular phenotype and cytokine expression as the skin when challenged by an allergen [4].

Allergic reactions in the mouth show erythema and swelling, but vesicles are rarely seen, except on the vermilion border. Intraoral blistering has been seen from cinnamon allergy [5]. The symptoms are soreness and burning, and itching is uncommon. Eczematous reactions of the adjacent skin may occur, and these may be the only signs of an allergic contact dermatitis.

The burning mouth syndrome is an entity in which psychological factors are important. Sometimes, allergens such as metals, rubber, food additives and flavourings have been identified and the symptoms relieved by contact avoidance [6], but the return from investigations is often disappointing [7].

Orofacial granulomatosis has been associated with contact allergy to food additives and some of these individuals may obtain

a favourable response, often only partial, to dietary elimination of the identified allergens [8].

Dentures are frequently incriminated as the cause of oral symptoms and lesions. Allergic reactions to denture materials have been found in some cases [9], due to traces of residual acrylic monomer following wearing of new dental appliances or following their repair with cold-curing resins. Most cases are the result of irritation from ill-fitting dentures. Candidal infection may also play a role [10], and is often present in angular cheilitis. Acrylate allergy has also been seen rarely after dental restorative work [11].

Mercury from amalgam fillings may cause local mucosal [12] or lichenoid [13,14] reactions; perioral dermatitis after dental filling may also occur, as may generalized skin eruptions [15]. Contact reactions to other metals have also been reported, especially gold used in dental restorative materials, and nickel and palladium in orthodontic appliances [16,17]. Gingivitis is reported from eugenol in dental cement [18]. Toothpaste flavours can cause stomatitis, glossitis, gingivitis, cheilitis and perioral eczema [19].

The nasal mucosa may react to medications containing antibacterial agents and antihistamines. Corticosteroid allergy from nasal sprays has been reported, with one case of associated perforation of the nasal septum [20]. In the conjunctivae, various drugs are reported to have elicited allergic contact reactions, for example β-blocking compounds for the treatment of glaucoma, antibiotics, and preservatives in both drugs and contact lens solutions [21].

Genital mucous membranes may be affected by allergens, particularly medicaments, causing dermatitis on the surrounding skin [22].

There remains debate as to whether materials sensitize via the mucosal route or whether there is only elicitation of pre-existing sensitivity (in those already sensitized) and the induction of tolerance (in those who have not already been sensitized) [3,4].

References

1 Lowney ED. Immunologic unresponsiveness to a contact sensitizer in man. *J Invest Dermatol* 1968; **51**: 411–7.

2 Van Hoogstraten MW, Andersen KE, Von Blomberg BME *et al*. Preliminary results of a multicenter study on the incidence of nickel allergy in relationship to previous oral and cutaneous contacts. In: Frosch PJ, Dooms-Goossens A, LaChapelle JM *et al*., eds. *Current Topics in Contact Dermatitis*. Berlin: Springer, 1989: 178–83.

3 Vreeburg KJJ, De Groot K, Von Blomberg BME *et al*. Induction of immunological tolerance by oral administration of nickel and chromium. *J Dent Res* 1984; **63**: 124–8.

4 Ahlfors EE, Lyberg T. Contact sensitivity reactions in the oral mucosa. *Acta Odontol Scand* 2001; **59**: 248–54.

5 Nadiminti H, Ehrlich A, Udey MC. Oral erosions as a manifestation of allergic contact sensitivity to cinnamon mints. *Contact Dermatitis* 2005; **52**: 46–7.

6 Shah M, Lewis F, Gawkrodger DJ. Contact allergy in patients with oral symptoms: a study of 47 patients. *Am J Contact Dermatitis* 1996; **7**: 146–51.

7 Helton J, Storrs F. The burning mouth syndrome: lack of a role for contact urticaria and contact dermatitis. *J Am Acad Dermatol* 1994; **31**: 201–5.

8 Armstrong DK, Biagioni P, Lamey PJ *et al*. Contact hypersensitivity in patients with orofacial granulomatosis. *Am J Contact Dermatitis* 1997; **8**: 35–8.

9 Koutis D, Freeman S. Allergic contact stomatitis caused by acrylic monomer in a denture. *Australas J Dermatol* 2001; **42**: 203–6.

10 Renner RP, Lee M, Andors L *et al*. The role of *C. albicans* in denture stomatitis. *Oral Surg Oral Med Oral Pathol* 1979; **47**: 323–8.

11 Alanko K, Kanerva L, Jolanki R *et al*. Oral mucosal diseases investigated by patch testing with a dental screening series. *Contact Dermatitis* 1996; **34**: 263–7.

12 Jolly M, Moule AJ, Freeman S. Amalgam related chronic ulceration of oral mucosa. *Br Dent J* 1986; **160**: 434–7.

13 Koch P, Bahmer FA. Oral lichenoid lesions, mercury sensitivity and combined hypersensitivity to mercury and other metals: histologically-proven reproduction of the reaction by patch testing with metal salts. *Contact Dermatitis* 1995; **33**: 323–9.

14 Scalf LA, Fowler JF Jr, Morgan KW *et al*. Dental metal allergy in patients with oral, cutaneous, and genital lichenoid reactions. *Am J Contact Dermatitis* 2001; **12**: 146–50.

15 Nakayama H, Niki F, Shono M *et al*. Mercury exanthem. *Contact Dermatitis* 1983; **9**: 411–7.

16 Van Loon Heidelberg LAJ, van Elzas PW, van Joost Th *et al*. Contact stomatitis and dermatitis to nickel and palladium. *Contact Dermatitis* 1984; **11**: 294–7.

17 Laeijendecker R, van Joost Th. Oral manifestations of gold allergy. *J Am Acad Dermatol* 1994; **30**: 205–9.

18 Silvestre JF, Albares MP, Blanes M *et al*. Allergic contact gingivitis due to eugenol present in a restorative dental material. *Contact Dermatitis* 2005; **52**: 341.

19 Sainio E-L, Kanerva L. Contact allergens in toothpastes and a review of their hypersensitivity. *Contact Dermatitis* 1995; **33**: 100–6.

20 Isaksson M, Bruze M, Wihl JA. Contact allergy to budesonide and perforation of the nasal septum. *Contact Dermatitis* 1997; **37**: 133.

21 Herbst RA, Maibach HI. Contact dermatitis caused by allergy to ophthalmic drugs and contact lens solutions. *Contact Dermatitis* 1991; **25**: 305–12.

22 Goldsmith PC, Rycroft RJ, White IR *et al*. Contact sensitivity in women with anogenital dermatoses. *Contact Dermatitis* 1997; **36**: 174–5.

Secondary patterns

Contact dermatitis may start at one site, but commonly other sites are subsequently involved, and sometimes several regions simultaneously. By the time the patient has been sensitized, many body regions may have been in contact with the allergen, some indirectly by contamination from the fingertips. Heavily contaminated areas, or those that were exposed last, tend to be the ones to react first, other sites flaring later. This has been shown experimentally with poison ivy [1], and is an obvious clinical feature in *Primula obconica* dermatitis. Regions close to the primary site of allergic contact dermatitis are easily contaminated by the allergen.

Such a simple explanation cannot account for the frequent spread of dermatitis from feet to hands and *vice versa*. This occurs primarily in constitutional eczema, but may occur in contact dermatitis. Sometimes, a common allergen is found that could explain occurrence at both sites, yet often it is a pattern of secondary spread. Epstein [2] suggested that skin protein might have a regional specificity, identical for fore and hind legs, that is 'four-hoof disease'; autoeczematization was first described by Whitfield in 1921 [3], and Parish *et al*. [4] suggested the term 'auto-allergy'. No precise explanation exists.

Because of the similarity to Darier's trichophytids and eczematids, dissemination to distant regions has been termed an 'id-like' spread. Local aggravation may precede secondary spread by several days.

The pattern of spread is largely determined by the primary site. Dermatitis of the hands commonly spreads to the arms and face; dermatitis of the feet tends to spread to the legs and hands. Many patients with stasis dermatitis have secondary eruptions by the time they are seen by a dermatologist, and are referred because of the alarming dissemination. This may be due to an 'id' reaction or secondary contact dermatitis. Dissemination from leg eczema commonly involves the arms and shoulders in a patchy fashion before becoming generalized, often beginning with pruritus and

sometimes progressing to generalized erythroderma. On the face, diffuse redness and oedema are common. Eyelid dermatitis or a diffuse dry dermatitis of seborrhoeic type may be seen.

Severe nickel allergy may induce extensive patchy eczema, which is slow to respond to treatment, and this will not settle unless strict nickel avoidance measures are undertaken.

Contact allergy to components of topical treatments presents special difficulties. The allergen may be an active ingredient or an excipient. If dermatitis spreads further in spite of treatment, it may wrongly be assumed to be an endogenous process. In contact dermatitis caused by topical steroid preparations, the action of the steroid may partially suppress the local reaction. The sensitivity becomes clinically manifest only as 'failure to heal' of the original eczema, or with the development of a secondary eruption.

Constant alertness is therefore a prerequisite for the diagnosis of allergic contact dermatitis in which dissemination is a dominant feature. Patch tests should be delayed until the acute eruption has settled.

References

1 Kligman AM. Poison ivy (*Rhus*) dermatitis. *Arch Dermatol* 1958; **77**: 149–80.
2 Epstein S. The antigen–antibody reaction in contact dermatitis. A hypothesis and review. *Ann Allergy* 1952; **10**: 633–58.
3 Whitfield A. Some points in the aetiology of skin diseases. *Lancet* 1921; **2**: 122–7.
4 Parish WE, Rook AJ, Champion RN. A study of auto-allergy. *Br J Dermatol* 1965; **77**: 479–526.

Systemically reactivated contact dermatitis [1]

Systemically reactivated allergic contact dermatitis, where ingestion or other systemic exposure to a contact allergen takes place in an already sensitized person, may result in a number of different patterns of skin eruption. The threshold of reaction varies in each individual case and depends on the dose given and the level of sensitivity. Reactions may occur not only after systemic exposure to the primary allergen but also to closely related allergens.

The most frequent types of reaction are focal flares of previous patch tests and sites of previous dermatitis, vesicular hand eczema, or more widespread eczema and erythema, sometimes with additional urticarial features. In severe cases vasculitis [2], erythema multiforme [3] and systemic upset may occur. Involvement of the eyelids, body folds and buttocks induced by oral challenge with nickel in allergic subjects led to this particular reaction being labelled the 'baboon syndrome' [4]. This is often also the pattern seen in patients with a mercury exanthem [5]. In some patients following widespread reactions, and in others following attempts at 'desensitization', the level of patch-test reactivity appears to be reduced [6].

Probably all contact allergens can cause systemic reactions, provided the patient has a sufficient degree of pre-existing sensitivity and the dose administered is sufficiently large. The causes are many, and include medicaments that may have been given not only by mouth but also parenterally, rectally, intravesically or as an inhalant. Dietary causes include metals, plants and spices.

Systemic contact dermatitis from medicaments has decreased as a result of reduced use of topical sensitizers such as the antibiotics streptomycin, sulphonamides and penicillin, and topical antihistamines such as promethazine. Nevertheless, exposure to other topical and systemic medicament sensitizers continues to give problems. Standard allergens responsible for these reactions include neomycin, quinolines, local anaesthetics, ethylenediamine and corticosteroids. In subjects with contact allergy to ethylenediamine, parenteral and oral administration of aminophylline (which contains ethylenediamine) has resulted in widespread eczematous eruptions [7,8]. Ethylenediamine is structurally related to some antihistamines (e.g. hydroxyzine, cetirizine and levocetirizine) and may therefore also trigger a systemic flare [9]. A positive patch test to tixocortol pivalate is an indication of hydrocortisone allergy, and systemic administration of hydrocortisone has induced recurrence and extension of dermatitis [10]. Furthermore, administration of parenteral adrenocorticotrophic hormone (ACTH), thereby raising endogenous hydrocortisone, has resulted in flares in hydrocortisone-allergic individuals [10]. Other systemic steroids have also induced systemic contact dermatitis. Inhalation of budesonide has been associated with reactivation of positive patch tests, and continued exposure to budesonide from this source may therefore maintain dermatitis in sensitized subjects [11]. The reader should consult the more specialized literature for a full list of the many other medicament causes reported.

Persistence of dermatitis, especially vesicular hand eczema in metal-allergic subjects, has been blamed on dietary intake, particularly of nickel [12]. Traces of metal dissolved by cooking acid or salty food in stainless steel may be of consequence in the persistence of dermatitis due to metals, such as chromium, nickel and cobalt [13,14]. In one study, dietary restriction of nickel helped about one-quarter of selected nickel-sensitive patients with resistant dermatitis [14]. However, the role of ingested or dietary nickel in hand dermatitis remains controversial, especially as a percentage of patch-test-negative patients also appear to have flares of vesicular hand eczema following oral metal challenge [15], and the challenge dosage has been artificially high. A recent meta-analysis suggests that 1% of nickel-allergic subjects will develop systemic allergic contact dermatitis from normal daily exposure to nickel in drinking water and the diet [16]. Systemic nickel dermatitis is reported also to have been induced by peripheral intravenous catheters and orthodontic appliances [17,18].

Balsam of Peru, garlic, certain ingested food colours, preservatives and antioxidants have also been reported as causing flares of vesicular hand eczema [19–21].

Flares of dermatitis and perianal pruritus may occur in patients undergoing desensitization to *Toxicodendron* spp., and systemic contact dermatitis may be induced following ingestion of cashew nuts, whose shells contain an oleoresin closely related to that found in poison ivy [22,23]. Similar problems may also result after eating the fruit of the *Ginkgo* tree and using herbal medicines [24,25].

References

1 Veien NK, Menné T. Systemic contact dermatitis. In: Frosch PJ, Menné T, Lepoittevin J-P, eds. *Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 295–307.
2 Hjorth N. Nickel dermatitis. *Contact Dermatitis* 1976; **2**: 356–7.
3 Le Coz CJ, Lepoittevin JP. Occupational erythema-multiforme-like dermatitis from sensitization to costus resinoid, followed by flare-up and systemic contact dermatitis from beta-cyclocostunolide in a chemistry student. *Contact Dermatitis* 2001; **44**: 310–1.

4 Andersen KE, Hjorth N, Menné T. The baboon syndrome. Systemically induced allergic contact dermatitis. *Contact Dermatitis* 1984; **10**: 97–100.
5 Nakayama H, Shono M, Hada S. Mercury exanthem. *J Am Acad Dermatol* 1989; **11**: 137–9.
6 Ekelund AG, Moller H. Oral provocation in eczematous contact allergy to neomycin and hydroxy-quinolines. *Acta Derm Venereol (Stockh)* 1969; **49**: 422–6.
7 Provost TT, Jilson OF. Ethylenediamine contact dermatitis. *Arch Dermatol* 1967; **96**: 231–4.
8 Walker SL, Ferguson JE. Systemic allergic contact dermatitis due to ethylenediamine following administration of oral aminophylline. *Br J Dermatol* 2004; **150**: 594.
9 Cusano F, Ferrara G, Crisman G *et al.* Clinicopathologic features of systemic contact dermatitis from ethylenediamine in cetirizine and levocetirizine. *Dermatology* 2006; **213**: 353–5.
10 Lauerma AI, Reitamo S, Maibach HI. Systemic hydrocortisone/cortisol induces allergic skin reactions in presensitized subjects. *J Am Acad Dermatol* 1991; **24**: 182–5.
11 Isaksson M, Bruze M. Allergic contact dermatitis in response to budesonide reactivated by inhalation of the allergen. *J Am Acad Dermatol* 2002; **46**: 880–5.
12 Christensen OB, Moller H. External and internal exposure to the antigen in the hand eczema of nickel allergy. *Contact Dematitis* 1975; **1**: 136–41.
13 Kaaber K, Veien NK. The significance of chromate ingestion in patients allergic to chromate. *Acta Derm Venereol (Stockh)* 1977; **57**: 321–3.
14 Veien NK, Hattel T, Justensen O *et al*. Oral challenge with nickel and cobalt in patients with positive patch test to nickel and/or cobalt. *Acta Derm Venereol (Stockh)* 1987; **67**: 321–5.
15 Veien NK, Kaaber K. Nickel, cobalt and chromium sensitivity in patients with pompholyx (dishidrotic eczema). *Contact Dermatitis* 1979; **5**: 371–4.
16 Jensen CS, Menné T, Johansen JD. Systemic contact dermatitis after oral exposure to nickel: a review with a modified meta-analysis. *Contact Dermatitis* 2006; **56**: 79–86.
17 Raison-Peyron N, Guillard O, Khalil Z *et al.* Nickel-elicited systemic contact dermatitis from a peripheral intravenous catheter. *Contact Dermatitis* 2005; **53**: 222–5.
18 Pigatto PD, Guzzi G. Systemic contact dermatitis from nickel associated with orthodontic appliances. *Contact Dermatitis* 2004; **50**: 100–1.
19 Veien NK, Hattel T, Justensen O *et al*. Oral challenge with balsam of Peru. *Contact Dermatitis* 1985; **12**: 104–7.
20 Burden AD, Wilkinson SM, Beck MH *et al*. Garlic-induced systemic contact dermatitis. *Contact Dermatitis* 1994; **30**: 299–300.
21 Baer RL, Leider M. The effects of feeding certified food azo dyes in paraphenylenediamine-hypersensitive subjects. *J Invest Dermatol* 1949; **13**: 223–32.
22 Kligman AM. Poison ivy (*Rhus*) dermatitis. *Arch Dermatol* 1958; **77**: 149–80.
23 Marks JG, Demelfi E, McCarthy MA *et al*. Dermatitis from cashew nuts. *J Am Acad Dermatol* 1984; **10**: 627–31.
24 Becker LE, Skipworth GB. Ginkgo-tree dermatitis, stomatitis and proctitis. *JAMA* 1975; **231**: 1162–3.
25 Park SD, Lee SW, Chun JH *et al*. Clinical features of 31 patients with systemic contact dermatitis due to the ingestion of *Rhus* (lacquer). *Br J Dermatol* 2000; **142**: 937–42.

Cutaneous reactions to implanted metals
(see p. 26.37)

Photoallergic contact dermatitis [1]

Certain substances are transformed into irritants or sensitizers (photosensitizers) after irradiation with UV or short-wave visible radiation (280–600 nm). The wavelength required is usually, but not always, the same as the absorption spectrum of the substance [2].

The basic mechanisms of photosensitization have been reviewed by Thune [3]. The initial phase of all photoreactions is dependent upon absorption of photons by light-sensitive chemicals. Following absorption, a higher state of energy (excited state) is induced in the molecule (photoactivation). Some of the energy may be released as fluorescence, that is emission of radiation at a longer wavelength. Alternatively, there may be phosphorescence, heat or other energy transfer to another molecule, or photochemical alteration of the molecule [4].

Photoactivation is a physical phenomenon and may occur *in vitro*. When it occurs *in vivo* the activation may have a phototoxic (non-immunological) or a photoallergic (immunological) action. The photoactivated molecules may be transformed into new substances capable of acting as irritants or haptens. Photoallergic reactions are based on immunological mechanisms, and can be provoked by UV radiation only in a small number of individuals who have been sensitized by previous exposure to the photosensitizer. The reaction to a photoallergen is based on the same immunological mechanism as contact allergic reactions. In guinea pigs the sensitivity can be transferred with mononuclear cells [5]. The action spectrum for photoallergy is generally in the UVA range [1].

Newly formed haptens may, by virtue of the excited state and free-radical formation, be able to combine chemically with other substances, for example protein, to produce a full antigen. The photoallergen tribromosalicylanilide has been shown to change into dibromosalicylanilide and monobromosalicylanilide [6], and with sulphonamides it has been suggested that an oxidation product is formed [7]. Some photosensitizers may, in the presence of UV radiation, produce only short-lived reactive molecules [8].

Several photoallergic substances simultaneously produce phototoxic reactions when applied in high concentrations and with a sufficient amount and type of radiation. Thus, in an individual case, the two reactions may be clinically indistinguishable.

The allergens

The first significant recognized problems from photoallergy were related to the use of chlorinated salicylanilides in germicidal soaps in the early 1960s, with many thousands being affected [9]. Regulatory elimination of these photoallergens resulted in the disappearance of the allergy, but some affected individuals became persistent light reactors [9]. By the mid-1980s the most important photoallergen was the fragrance musk ambrette whose use is now prohibited [10]. In the present era, UV-absorbing chemical filters are virtually the only substances causing clinical photoallergic problems in the UK [11,12]. Exposure to UV filters is becoming more common as a result of their increasing use not only in sun products but also in cosmetics, including hairsprays. Their presence in cosmetics may be not only to prolong shelf-life but also to support 'antiageing' claims for the products. These UV filters can also induce conventional contact allergy. Nevertheless, many photocontact allergens have been identified with varying degrees of confirmatory evidence, and these are summarized below.

1 UV filters, including *p*-aminobenzoic acid and its derivatives, cinnamates, benzophenones and dibenzoylmethanes [13]. Benzophenone 3 (oxybenzone) appears to be the most frequently identified photoallergen since the 1990s [12].
2 Perfumes: musk ambrette [10] and 6-methyl coumarin [14], although now prohibited in Europe and the USA, caused significant problems in the 1980s, but these products have now virtually disappeared.

3 Halogenated salicylanilides: tribromosalicylanilide and tetrachlorsalicylanilide, used as antibacterials in soaps and detergents, caused many outbreaks of photosensitive eczema in the 1960s [9]. Fentichlor (bis(2-hydroxy-5-chlorphenyl)sulphide and bromosalicylchloranilide) is used as a topical antifungal agent in Australia and is used domestically in Sweden. It is a known photosensitizer [15].
4 Topical non-steroidal anti-inflammatory agents, especially ketoprofen, which may cross-sensitize with the UV filter benzophenone 3 (oxybenzone) [16–18].
5 Phenothiazines (tranquillizers causing occupational dermatitis in hospital personnel, topical antihistamines, insecticides) [19].
6 Sulphonamides used for topical treatment [2].
7 Bithionol and hexachlorophene in toilet soaps, shampoos and deodorants [20].
8 *N*-Butyl-4-chlorsalicylamide (Jadit—antifungal) [21].
9 Eosin: used to be present in lipstick [22].
10 Quinines: hair tonic, quinidine, quindoxin and olaquindox used in animal feeds [23].
11 Thiourea (in design paper) [24].
12 Garlic [25].

Clinical features

Photoallergic reactions can resemble sunburn, but usually show the same spectrum of features seen with allergic contact dermatitis. The dermatitis is localized to exposed areas of the skin, usually with well-demarcated margins where the skin is covered by clothing, for example at the collar and 'V' of the neck, below the end of the sleeves and trouser leggings. The area below the chin is usually spared. The most distinctive sign is the exempt 'Wilkinson's triangle' behind the earlobe [9]. There may nevertheless be some spread to covered sites. Asymmetry may result from increased UV exposure to one side of the body, for example those who drive with the vehicle windows open.

Photoallergy to UV filters in cosmetics may be clinically identical to that seen from conventional allergy to cosmetics (see p. 26.47). It may be widespread when related to liberal use of sunscreen agents. Furthermore, it may simulate sunburn and other causes of photosensitivity.

Musk ambrette, used in men's aftershave lotions and colognes, was historically the cause of a distinctive patchy pattern of photosensitivity on the face [10].

In some individuals, photoallergic reactions may progress to produce a light sensitivity that can persist a long time after the elimination of the sensitizer. This is known as persistent light reaction [26]. The phenomenon has been reported with many different substances, including chlorpromazine [27], halogenated salicylanilides [9], musk ambrette [28], promethazine hydrochloride [29], ketoprofen [30], quindoxin [31] and olaquindox [23]. This chronic photosensitive dermatitis presents as chronic eczematous changes on light-exposed areas with or without spread elsewhere; on monochromator testing, the patients have abnormal responses to UV radiation, with a shift to UVB sensitivity [32].

Photoallergy may simulate other photosensitive dermatoses and airborne contact allergy, and *vice versa*. Furthermore, there may be a combination of these disorders in the same person. It is also important to recognize that photoallergy may sometimes fail to follow the typical pattern of sparing of light-protected sites, and airborne contact allergy may paradoxically induce the classical photosensitivity distribution. Combined airborne and photoaggravated contact allergy is seen particularly with Compositae (Asteraceae) [33] and lichens [34]. A similar pattern of dermatitis may also be seen in patients sensitive to Colophonium, pine and spruce. It is therefore important to identify every potential component of these clinical presentations by screening for contact allergy using patch tests (especially to plants), for photoallergy with photopatch tests, and also for photosensitivity using phototesting.

Patients with established photosensitivity who have a flare of their dermatitis may have reacted to an increase in light levels or re-exposure to their primary or a cross-reacting allergen by airborne contact. Alternatively, they may have developed a secondary allergic or photoallergic contact sensitivity to their sunscreen or to one of their other medicaments.

The disorder of chronic actinic dermatitis (see Chapter 29) may be associated with contact allergy, particularly to Compositae. Often there are multiple contact allergies. Phototesting reveals abnormal results but photopatch tests to Compositae and other allergens are generally normal. Nevertheless, persistent light reactivity following photoallergy may progress to chronic actinic dermatitis.

The intensity of response to phototoxic and photoallergic agents depends upon a number of factors:
1 nature and concentration of the substance applied
2 duration of exposure to the substance
3 percutaneous absorption
4 intensity and wavelength of the radiation
5 duration of radiation exposure
6 radiation absorption in the skin, depending on the thickness of stratum corneum as well as the amount and distribution of melanin
7 extraneous matter and secretions on the skin
8 humidity.

Avoidance

Photoallergy in the UK is now only likely to occur to UV filters or very rarely to imported perfumed materials containing musk ambrette, which should be easy to eliminate. Once photoallergy has been demonstrated to a UV filter, the patient should be informed of the INCI (International Nomenclature of Cosmetic Ingredients) name and synonyms of the material to which they are sensitive. UV filters relying totally on opaque/reflectant micronized titanium dioxide and zinc oxide will be free of chemical UV-filtering agents, and can be used for coexistent photodermatoses in those allergic to chemical UV filters. The situation is different on mainland Europe where topical NSAIDs are commonly used but once the photoallergy has been confirmed avoidance should be straightforward.

Investigation

Investigation of photoallergy by photopatch tests is described on p. 26.93.

References

1 Palmer RA, White IR. Phototoxic and photoallergic reactions. In: Frosch PJ, Menné T, Lepoittevin J-P, eds. *Textbook of Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 309–17.
2 Frain-Bell W. Photodermatoses. In: Rook A, ed. *Recent Advances in Dermatology*. Edinburgh: Churchill Livingstone, 1973: 101–33.
3 Thune P. Basic mechanisms of photosensitization. In: Frosch PJ, Dooms-Goossens A, LaChappelle LM *et al*., eds. *Current Topics in Contact Dermatitis*. Berlin: Springer, 1989: 473–9.
4 Kornhauser A, Wamer W, Giles A. Light-induced dermal toxicity: effects on the cellular and molecular level. In: Marzulli FN, Maibach HI, eds. *Dermatoxicology*, 3rd edn. Washington, DC: Hemisphere, 1987: 377–412.
5 Harber LC, Targovnik SE, Baer RL. Studies on contact photosensitivity to hexachlorophene and trichlorocarbanilide in guinea pigs and man. *J Invest Dermatol* 1968; **51**: 373–84.
6 Osmundsen PE. Contact photo-allergy to tribromosalicylanilide. *Br J Dermatol* 1968; **31**: 429–34.
7 Salser H. Photochemische Kupplung des Sulfanilamids und aromatischer Amine an Eiweib und andere hochmolekulare Verbindungen. *Arch Klin Exp Dermatol* 1962; **215**: 266–78.
8 Epling GA, Wells JL, Ungchan Yoon. Photochemical transformations in salicylanilide photoallergy. *Photochem Photobiol* 1988; **47**: 167–71.
9 Wilkinson DS. Patch test reactions to certain halogenated salicylanilides. *Br J Dermatol* 1962; **74**: 302–6.
10 Wojnarowska F, Calnan CD. Allergy to musk ambrette. *Br J Dermatol* 1986; **114**: 667–75.
11 Bryden AM, Mosely H, Ibbotson SH *et al*. Photopatch testing of 1155 patients: results of the U.K. multicentre photopatch study group. *Br J Dermatol* 1997; **155**: 737–47.
12 Darvay A, White IR, Rycroft RJ *et al*. Photoallergic contact dermatitis is uncommon. *Br J Dermatol* 2001; **145**: 597–601.
13 Palmer RA, White IR. Photopatch testing. In: Frosch PJ, Menné T, Lepoittevin J-P, eds. *Textbook of Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 433–40.
14 Jackson RT, Nesbitt LT Jr, DeLeo VA. 6-Methylcoumarin photocontact dermatitis. *J Am Acad Dermatol* 1980; **2**: 124–7.
15 Ramsay CA. Skin responses to ultraviolet radiation in contact photodermatitis due to fentichlor. *J Invest Dermatol* 1979; **72**: 99–102.
16 Mozzanica N, Pucci M, Pigatto PD. Contact and photoallergic dermatitis to topical nonsteroidal anti-inflammatory drugs (propionic acid derivatives): a study of eight cases. In: Frosch PJ, Dooms-Goossens A, LaChapelle LM *et al*., eds. *Current Topics in Contact Dermatitis*. Berlin: Springer, 1989: 488–92.
17 Matthieu CL, Meuleman L, Van Hecke E *et al*. Contact and photocontact allergy to ketoprofen. The Belgian experience. *Contact Dermatitis* 2004; **50**: 238–41.
18 Hindsén M, Zimerson E, Bruze M. Photoallergic contact dermatitis from ketoprofen in southern Sweden. *Contact Dermatitis* 2006; **54**: 150–7.
19 Calnan CD, Frain-Bell W, Cuthbert JW. Occupational dermatitis from chlorpromazine. *Trans St John's Hosp Dermatol Soc* 1962; **48**: 49–74.
20 O'Quinn SE, Kennely CB, Iskell KH. Contact photodermatitis due to bithionol and related compounds. *JAMA* 1967; **199**: 89–92.
21 Jung EG, Hornke J, Hajdu P. Photoallergie durch 4-chlor-2-hydroxy-Benzoesaure-*n*-Butylamid. II. Photochemische Untersuchungen. *Arch Klin Exp Dermatol* 1966; **233**: 287–95.
22 Calnan CD, Sarkany I. Studies in contact dermatitis. II. Lipstick cheilitis. *Trans St John's Hosp Dermatol Soc* 1957; **39**: 28–36.
23 Schauder S, Schroder W, Geier J. Olaquindox-induced airborne photoallergic contact dermatitis followed by transient or persistent light reactions in 15 pig breeders. *Contact Dermatitis* 1996; **35**: 344–54.
24 Dooms-Goossens A, Chrispeels MT, De Veylder H *et al*. Contact and photocontact sensitivity problems associated with thiourea and its derivatives: a review of the literature and case reports. *Br J Dermatol* 1987; **116**: 573–9.
25 Alvarez MS, Jacobs S, Jiang SB *et al*. Photocontact allergy to diallyl disulfide. *Am J Contact Dermatitis* 2003; **14**: 161–5.
26 Thune P, Eeg-Larsen T. Contact and photocontact allergy in persistent light reactivity. *Contact Dermatitis* 1984; **11**: 98–107.
27 Baer RL, Harber LC. Photosensitivity induced by drugs. *JAMA* 1965; **192**: 989–90.
28 Cirue de Castro JL, Pereira MA, Prates Nunes F *et al*. Musk ambrette and chronic actinic dermatitis. *Contact Dermatitis* 1985; **13**: 302–6.
29 Sidi E, Hincky M, Gervais A. Allergic sensitization and photosensitization to Phenergan cream. *J Invest Dermatol* 1955; **24**: 345–52.
30 Albes B, Marguery MC, Schwarze HP *et al*. Prolonged photosensitivity following contact photoallergy to ketoprofen. *Dermatology* 2000; **201**: 171–4.
31 Zaynoun S, Johnson BE, Frain-Bell W. The investigation of quindoxin photosensitivity. *Contact Dermatitis* 1976; **2**: 343–52.
32 Wolf C, Honigsmann H. [The syndrome of chronic actinic dermatitis. Persistent light reaction—actinic reticuloid.] *Hautarzt* 1988; **39**: 635–41.
33 Murphy GH, White IR, Hawk JL. Allergic airborne contact dermatitis to Compositae with photosensitivity: chronic actinic dermatitis in evolution. *Photodermatol Photoimmunol Photomed* 1990; **7**: 38–9.
34 Thune P. Contact allergy due to lichens in patients with a history of photosensitivity. *Contact Dermatitis* 1977; **3**: 267–72.

Non-eczematous responses [1]

Well-recognized non-eczematous responses include contact urticaria, erythema multiforme-like, purpuric, lichen planus and lichenoid, lymphomatoid, pigmented, leukoderma, granulomatous, onycholysis and systemic.

Contact urticaria

Clinically this presents as an immediate wealing eruption at the site of contact, and may in some instances be associated with systemic features. The syndrome of contact urticaria is discussed in detail on p. 26.104.

Erythema multiforme-like reactions

The characteristic presentation is that of a spreading eruption from the primary site, which may also involve distant sites. It has been called 'urticarial papular and plaque eruption' by Goh [2]. The rash has features of erythema multiforme, in that single lesions appear target-like, but the distribution is not necessarily acral as in classic erythema multiforme nor is the histology characteristic. There is sometimes a vasculitic purpuric element to the rash and, although the mechanism is unknown, it appears to represent an immune complex (type III) reaction as well as a delayed hypersensitivity (type IV) reaction. Many of these patients will give a very strong patch-test response to the causative allergen, often accompanied by a flare of their dermatosis.

It is often precipitated by strong allergens, such as quinones in exotic woods [3], and *Primula* [4]. Contact with other plant materials may cause this reaction, including poison ivy (*Toxicodendron* spp.) [5], Compositae (Asteraceae) [6] and tea tree oil [7]. Ingestion of herbal remedies containing *Toxicodendron* [8] and sesquiterpene lactones [9] by sensitized persons has also induced erythema multiforme-like eruptions.

Topical medicaments, especially antimicrobials [10], corticosteroids [11] and anti-inflammatories [12,13], have all caused erythema multiforme-like eruptions. A nitroglycerin patch has also induced erythema multiforme at the applied site, with a secondary spread eruption [14]. Medicaments applied to mucosal surfaces may sensitize and may also be absorbed, causing systemic erythema multiforme-like reactions, for example sulphonamide in vaginal creams [15] and ocular preparations [16].

p-Phenylenediamine in hair dye [17] and temporary tattoos [18], and rubber chemicals [19] and clothing dyes [20] are also recognized causes of this reaction pattern.

Erythema annulare centrifugum of the trunk has been linked to contact allergy to nickel and cobalt in clothing hooks and studs [21].

Purpuric reactions

Originally described in association with khaki uniforms [22], although the precise cause was not established, pigmented purpuric reactions are uncommon and have mostly been described recently from textile azo dyes [23,24] and also textile resins [23]. The presence of the rubber chemical IPPD in footwear, diving suits, bandages and brassières is also reported as a cause of allergic contact purpura [25,26]. Purpuric reactions have also been described with allergy to diphenylthiourea in heat retainers [27], *p*-phenylenediamine in black hats [28], and as a secondary spread eruption from balsam of Peru [29].

Lichen planus and lichenoid reactions

These have been described following contact with colour developers used in the photographic industry [30]. The developers are *p*-phenylenediamine derivatives. New chemicals have been introduced to replace older more sensitizing ones, not always successfully. *p*-Phenylenediamine-induced allergic lichenoid contact reactions from hair dye have been reported from India [31]. We have also seen this pattern from hair dye in Asians in the UK. *Primula obconica* allergy has also produced a lichen planus-like eruption of the hands [32].

Lichen planus-like reactions of the buccal mucosa may represent allergy to metals [33,34], other materials used in dental treatments [35,36], cinnamal and spearmint [37,38]. Some patients have had improvement in their lichen planus following the removal of some or all of their fillings [39,40]. Oral lichen planus is more apparent where there is evidence of corrosion [41,42] and the aetiology of lichenoid lesions is likely to be multifactorial [40]. The histology may show features compatible with lichen planus or a non-specific chronic superficial perivascular dermatitis [42].

Lichenoid reactions to tattoo pigments are discussed in the section on granulomatous reactions below.

Lymphomatoid eruptions [43]

Occasionally, contact dermatitis presents with cutaneous lymphoma-like plaques and histopathology suggestive of mycosis fungoides [43]. These have been seen at the site of ear piercing in those sensitized to gold [44]. The reaction tends to persist for months, even when contact with metallic gold is avoided. The patch-test reaction to gold sodium thiosulphate in these patients is papular and very strongly positive. The histology of both the papular eruption and the patch-test reaction shows a dense T-cell infiltrate [45]. Other reported causes include matches [43], nickel [46], dental amalgam [47], medicament components [48], *p*-phenylenediamine [49], isopropyl-diphenylenediamine [50] and para-tertyl-butyl phenol formaldehyde resin [51].

Pigmented dermatitis [52]

Contact dermatitis may induce post-inflammatory hyperpigmentation, and distinctive patterns of pigmented dermatitis without a lichenoid appearance or histopathology are recognized. These patterns are much more commonly seen in the Far East. The first such cases of pigmented contact dermatitis in Europe were described by Osmundsen [53]. The hyperpigmentation occurred mainly on covered areas, with or without dermatitis, and was traced to an optical whitener in washing powder, Tinopal CH 3566. Another outbreak was described by Ancona-Alayon *et al*. [54] in textile workers and was traced to contact with Naphthol AS, an azo-dye coupling agent. Cases also occurred on covered sites from garments in Japan [55], and this led to a systematic search for other causes of textile dermatitis. Chemicals implicated included the fungicide Biochek 60, an impurity of colour index blue CI Blue 19, and textile finishes [52].

Pigmented cosmetic dermatitis is seen mainly in oriental women. Slight dermatitis may precede or coexist with the hyperpigmentation, which occurs mainly on the cheeks. The allergens associated with this have been found to be fragrances and pigments, especially D and C Red 31 (from an impurity), and Yellow no. 11 in cosmetics and soaps [56,57]. Pigmented cheilitis has occurred from allergy to ricinoleic acid in castor oil used in lipsticks [58]. Components of kumkum, applied as a cosmetic to the forehead in Asian women, commonly cause a pigmented dermatitis [59].

Oral ingestion of flavourings allied to the fragrances, such as cinnamon, may cause not only a focal flare but also diffuse hyperpigmentation on the body [56].

Environmental agents, possibly pesticides and fungicides, have sometimes been thought to be a factor. In one study, a majority of pigmented dermatitis cases were found to have positive patch tests to chlorothalonil used as a fungicide in banana plantations. It is used in other parts of the world as a preservative for wood and paint [60].

Depigmentation [52]

Irritant and allergic contact dermatitis can induce hypopigmentation as a post-inflammatory effect or by koebnerization of vitiligo. This has to be distinguished from the direct melanocytotoxic effect of certain quinones and substituted phenols, which most commonly presents as an occupational vitiligo (Chapter 27). This effect occurs independently of their sensitizing potential.

A number of cases of persistent leukoderma following allergic contact dermatitis have been reported. In some it has been difficult to be certain whether the cause was post-inflammatory or melanocytotoxic. In particular, it is reported from hair dyes [61,62] and is commonly seen from temporary tattoos. Epoxy resin components [63], methacrylates [64], perfumes [65], *Alstroemeria* [66] and chloroxylenol [67] are also reported as causes. *Primula* allergy has resulted in extension of pre-existing vitiligo to the sites affected by the dermatitis (Fig. 26.12). The allergic reaction to primin was followed by vitiligo at the positive patch-test sites [68]. Persistence of hypopigmentation for longer than 2 years has been seen following contact allergy to a temporary tattoo [69].

Granulomatous reactions

Some topically applied metal salts produce non-allergic granulomatous skin reactions, for example zirconium in deodorants. Granulomas occurring at the site of previous immunization with aluminium-adsorbed vaccines, or following the use of parenteral hyposensitization preparations, are often due to aluminium allergy [70]. Patch tests are positive either to aluminium chloride 2%



Fig. 26.12 Koebnerization of vitiligo as a result of previous *Primula obconica* allergy.

aqueous or an empty Finn chamber [70]. Granulomatous reactions have also been found in association with allergy to gold and palladium in earrings [71,72].

Pigments in tattoos may cause allergic granulomatous and lichenoid reactions [42]. Metal salts have been identified as culprits: mercury (red colour), chromium (green colour), cobalt (blue colour) and cadmium (yellow colour) [73]. However, in our experience most reactions are in the red areas, and patch testing with mercurials is negative, suggesting another cause. Unfortunately, tattooists are extremely secretive about the nature of the pigments they use but an analysis has been undertaken of a series of pigments obtained from 20 tattoo parlours [74]. This has shown that a wide range of metallic salts, pigments and dyes may be used, and a suitable patch-test series for tattoo reactions has been suggested as a result of this investigation.

Orofacial granulomatosis has been associated with allergy to gold crowns and mercury fillings [75]. In one study 22% of patients with this condition had allergy to one or more food additives on patch testing, and most of these improved with an elimination diet. The authors concluded that the cause of the disorder was multifactorial and that patch testing had been helpful for a subgroup of those affected [76].

Onycholysis

Onycholysis may be the only presenting feature in contact dermatitis to hairdressing chemicals. We have seen it as an isolated finding in nail varnish allergy, but more commonly it is found in subjects sensitized to multifunctional acrylates in anaerobic sealants [77] and false nails [78], when there may be concomitant dystrophy and persistent paraesthesiae [79].

Systemic non-eczematous

Extensive allergic contact dermatitis is not uncommonly associated with systemic upset from the metabolic effects of the disorder itself and secondary infection, particularly in those who are erythrodermic. Sultones occurring as impurities in lauryl ethyl sulphate have in the past caused several outbreaks of contact dermatitis characterized by intense oedema accompanied by general malaise [80,81].

References

1 Goon A, Goh CL. Non-eczematous contact reactions. In: Frosch PJ, Menné T, Lepoittevin J-P, eds. *Textbook of Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 349–62.

2 Goh CL. Urticarial papular and plaque eruptions. A noneczematous manifestation of allergic contact dermatitis. *Int J Dermatol* 1989; **28**: 172–6.

3 Holst R, Kirby J, Magnusson B. Sensitisation to tropical woods giving erythema multiforme-like eruptions. *Contact Dermatitis* 1976; **2**: 295–6.

4 Lengrand F, Tellart AS, Segard M *et al*. Erythema multiforme-like eruption: an unusual presentation of primula contact allergy. *Contact Dermatitis* 2001; **44**: 35.

5 Bara C, Milpied B, Geraut C, Stalder JF. Poison ivy: an underreported cause of erythema multiforme. *J Am Acad Dermatol* 2004; **51**: S159–60.

6 Jovanović M, Mimica-Dukić N, Poljački M, Boža P. Erythema multiforme due to contact with weeds: a recurrence after patch testing *Contact Dermatitis* 2003; **48**: 17–25.

7 Khanna M, Qasem K, Sasseville D. Allergic contact dermatitis to tea tree oil with erythema multiforme-like id reaction. *Am J Contact Dermatitis* 2000; **11**: 238–42.

8 Park SD, Lee SW, Chun JH *et al*. Clinical features of 31 patients with systemic contact dermatitis due to the ingestion of *Rhus* (lacquer). *Br J Dermatol* 2000; **142**: 937–42.

9 Mateo MP, Velasco M, Miguel FQ, de la Guardia J. Erythema multiforme-like eruptions following allergic contact dermatitis from sesquiterpene lactones in a herbal medicine. *Contact Dermatitis* 1995; **33**: 449.

10 Munoz D, del Pozo MD, Audicana M *et al*. Erythema multiforme-like eruptions from antibiotics of three different classes. *Contact Dermatitis* 1996; **34**: 227–8.

11 Valsecchi R, Reseghetti A, Leghissa P *et al*. Erythema-multiforme-like lesions from triamcinolone acetonide. *Contact Dermatitis* 1998; **38**: 362–3.

12 Koch P, Bahmer FA. Erythema-multiforme-like urticarial papular and plaque eruptions from bufexamac: report of 4 cases. *Contact Dermatitis* 1994; **31**: 97–101.

13 Degreef H, Bonamie A, van Derheyden D *et al*. Mephenesin contact dermatitis with erythema multiforme features. *Contact Dermatitis* 1984; **10**: 220–3.

14 Silvestre JF, Betlloch I, Guijarro J *et al*. Erythema-multiforme-like eruption on the application site of a nitroglycerin patch, followed by widespread erythema multiforme. *Contact Dermatitis* 2001; **45**: 299–300.

15 Goette DK, Odom RB. Vaginal medication as a cause for varied widespread dermatitides. *Cutis* 1980; **26**: 406–9.

16 Gottschalk HR, Stone OJ. Stevens–Johnson syndrome from ophthalmic sulfonamide. *Arch Dermatol* 1976; **112**: 513–4.

17 Tosti A, Bardazzi F, Valeri F *et al*. Erythema multiforme with contact dermatitis to hair dyes. *Contact Dermatitis* 1987; **17**: 321–2.

18 Jappe U, Hausen BM, Petzoldt D. Erythema-multiforme-like eruption and depigmentation following allergic contact dermatitis from a paint-on henna tattoo, due to para-phenylenediamine contact hypersensitivity. *Contact Dermatitis* 2001; **45**: 249–50.

19 Bara C, Milpied B, Geraut C *et al.* Erythema multiforme with occupational rubber contact sensitivity. *Contact Dermatitis* 2003; **49**: 269–70.

20 Baldari U, Alessandrini F, Raccagni AA. Diffuse erythema multiforme-like contact dermatitis caused by disperse blue 124 in a 2-year-old child. *J Eur Acad Dermatol Venereol* 1999; **12**: 180–1.

21 Sambucety PS, Agapito PG, Prieto MA. Contact erythema annulare centrifugum. *Contact Dermatitis* 2006; **55**: 309–10.

22 Hodgson GA, Hellier FF. Dermatitis in shirts in B.L.A. *J R Army Med Corps* 1946; **87**: 110–7.

23 Lazarov A, Cordoba M. Purpuric contact dermatitis in patients with allergic reaction to textile dyes and resins. *J Eur Acad Dermatol Venereol* 2000; **14**: 101–5.

24 Shah SA, Ormerod AD. Pigmented purpuric clothing dermatitis due to disperse dyes. *Contact Dermatitis* 2000; **43**: 360.

25 Roed-Petersen J, Clemmensen OJ, Menné T *et al*. Purpuric contact dermatitis from black rubber chemicals. *Contact Dermatitis* 1988; **18**: 166–8.

26 Verma K, Sharma NL, Mahajan VK *et al.* Purpuric contact dermatitis from footwear. *Contact Dermatitis* 2007; **56**: 362–4.

27 Meding B, Baum H, Bruze M *et al*. Allergic contact dermatitis from diphenylthiourea in Vulkan heat retainers. *Contact Dermatitis* 1990; **22**: 8–12.

28 Shmunes E. Purpuric allergic contact dermatitis to paraphenylenediamine. *Contact Dermatitis* 1978; **4**: 225–9.

29 Bruynzeel DP, Van der Hoogenband HM, Coedjik F. Purpuric vasculitis-like eruption in a patient sensitive to balsam of Peru. *Contact Dermatitis* 1984; **11**: 207–9.
30 Lidén C, Brehmer-Andersson E. Occupational dermatoses from colour developing agents. Clinical and histopathological observations. *Acta Derm Venereol (Stockh)* 1988; **68**: 514–22.
31 Sharma VK, Mandal SK, Sethuraman G *et al*. Para-phenylenediamine-induced lichenoid eruptions. *Contact Dermatitis* 1999; **41**: 40–1.
32 Lapiere K, Matthieu L, Meuleman L *et al*. Primula dermatitis mimicking lichen planus. *Contact Dermatitis* 2001; **44**: 199.
33 Koch P, Baumer FA. Oral lichenoid lesions, mercury hypersensitivity and combined hypersensitivity to mercury and other metals: histologically-proven reproduction of the reaction by patch testing with metal salts. *Contact Dermatitis* 1995; **33**: 323–9.
34 Athavale PN, Shum KW, Yeoman CM, Gawkrodger DJ. Oral lichenoid lesions and contact allergy to dental mercury and gold. *Contact Dermatitis* 2003; **49**: 264–5.
35 Garcia-Bravo B, Pons A, Rodriguez-Pichardo A. Oral lichen planus from colophony. *Contact Dermatitis* 1992; **26**: 279.
36 Auzerie V, Mahe E, Marck Y *et al*. Oral lichenoid eruption due to methacrylate allergy. *Contact Dermatitis* 2001; **45**: 241.
37 Hoskyn J, Guin JD. Contact allergy to cinnamal in a patient with oral lichen planus. *Contact Dermatitis* 2005; **52**: 160–1.
38 Clayton R, Orton D. Contact allergy to spearmint oil in a patient with oral lichen planus. *Contact Dermatitis* 2004; **51**: 314–5.
39 Smart ER, Macleod RI, Lawrence CM. Resolution of lichen planus following removal of amalgam restorations in patients with proven allergy to mercury salts: a pilot study. *Br Dent J* 1995; **178**: 108–12.
40 Ostman PO, Anneroth G, Skoglund A. Amalgam-associated oral lichenoid reactions. Clinical and histologic changes after removal of amalgam fillings. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1996; **81**: 459–65.
41 Lundström IM. Allergy and corrosion of dental materials in patients with oral lichen planus. *Int J Oral Surg* 1984; **13**: 16–24.
42 Martin MD, Broughton S, Drangsholt M. Oral lichen planus and dental materials: a case-control study. *Contact Dermatitis* 2003; **48**: 331–6.
43 Orbaneja JG, Diez LI, Lozano JL *et al*. Lymphomatoid contact dermatitis: a syndrome produced by epicutaneous hypersensitivity with clinical features and a histopathologic picture similar to that of mycosis fungoides. *Contact Dermatitis* 1976; **2**: 139–43.
44 Fleming C, Burden D, Fallowfield M *et al*. Lymphomatoid contact reaction to gold earrings. *Contact Dermatitis* 1997; **37**: 298–9.
45 Iwatsuki K, Yamada M, Takigawa M *et al*. Benign lymphoplasia of the earlobes induced by gold earrings: immunohistologic study on the cellular infiltrates. *J Am Acad Dermatol* 1987; **16**: 83–8.
46 Houck HE, Wirth FA, Kauffman CL. Lymphomatoid contact dermatitis caused by nickel. *Am J Contact Dermatitis* 1997; **8**: 175–6.
47 Zenarola P, Lomuto M, Bisceglia M. Hypertrophic amalgam dermatitis of the tongue simulating carcinoma. *Contact Dermatitis* 1993; **29**: 157–8.
48 Wall LM. Lymphomatoid contact dermatitis due to ethylenediamine dihydrochloride. *Contact Dermatitis* 1982; **8**: 51–4.
49 Veysey EC, Burge S, Cooper S. Consort contact dermatitis to paraphenylenediamine, with an unusual clinical presentation of tumid plaques. *Contact Dermatitis* 2007; **56**: 366–7.
50 Marliere V, Beylot-Barry M, Doutre MS *et al*. Lymphomatoid contact dermatitis caused by isopropyl-diphenylenediamine: two cases. *J Allergy Clin Immunol* 1998; **102**: 152–3.
51 Evans AV, Banerjee P, McFadden JP, Calonje E. Lymphomatoid contact dermatitis to para-tertyl-butyl phenol resin. *Clin Exp Dermatol* 2003; **28**: 272–3.
52 Nakayama H. Pigmented contact dermatitis and chemical depigmentation. In: Frosch PJ, Menné T, Lepoittevin J-P, eds. *Textbook of Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 319–33.
53 Osmundsen PE. Pigmented contact dermatitis. *Br J Dermatol* 1976; **81**: 799–803.
54 Ancona-Alayon AA, Escobar-Marques R, Gonzales-Mendoza A. Occupational pigmented contact dermatitis from Naphthol AS. *Contact Dermatitis* 1976; **2**: 129–34.
55 Hayakawa R, Matsunaga K, Kojima S *et al*. Naphthol AS as a cause of pigmented contact dermatitis. *Contact Dermatitis* 1985; **13**: 20–5.
56 Nakayama H, Matsuo S, Hayakawa K *et al*. Pigmented cosmetic dermatitis. *Int J Dermatol* 1984; **23**: 299–305.
57 Kozuka T, Tashiro M, Sano S *et al*. Brilliant Lake Red R as a cause of pigmented contact dermatitis. *Contact Dermatitis* 1979; **5**: 297–304.
58 Leow YH, Tan SH, Ng SK. Pigmented contact cheilitis from ricinoleic acid in lipsticks. *Contact Dermatitis* 2003; **49**: 48–9.
59 Nath AK, Thappa DM. Kumkum-induced dermatitis: an analysis of 46 cases. *Clin Exp Dermatol* 2007; **32**: 385–7.
60 Penegos H, Jiminez V, Fallas V *et al*. Chlorothalonil, a possible cause of erythema dyschromicum perstans (ashy dermatosis). *Contact Dermatitis* 1996; **35**: 214–8.
61 Bajaj AK, Gupta SC, Chatterjee AK *et al*. Hair dye depigmentation. *Contact Dermatitis* 1996; **35**: 56–7.
62 Mahendran R, Stables GI, Wilkinson SM. Contact leukoderma secondary to occupational toluenediamine sulfate exposure. *Contact Dermatitis* 2002; **47**: 117–8.
63 Jappe U, Geier J, Hausen BM. Contact vitiligo following a strong patch test reaction to triglycidyl-p-aminophenol in an aircraft industry worker: case report and review of the literature. *Contact Dermatitis* 2005; **53**: 89–92.
64 Casse V, Salmon-Ehr V, Mohn C *et al*. Chronic depigmentation due to positive patch tests for methacrylate derivatives. *Ann Dermatol Vénéréol* 1998; **125**: 56–7.
65 Larsen WG. Perfume dermatitis. *J Am Acad Dermatol* 1985; **12**: 1–9.
66 Björkner BE. Contact allergy and depigmentation from *Alstroemeria*. *Contact Dermatitis* 1982; **8**: 178–84.
67 Malakar S, Panda S. Post-inflammatory depigmentation following allergic contact dermatitis to chloroxylenol. *Br J Dermatol* 2001; **144**: 1275–6.
68 Bhushan M, Beck MH. Allergic contact dermatitis from primula presenting as vitiligo. *Contact Dermatitis* 1999; **41**: 292–3.
69 Valsecchi R, Leghissa P, Di Landro A *et al*. Persistent leukoderma after henna tattoo. *Contact Dermatitis* 2007; **56**: 108–9.
70 Kaaber K, Nielsen AO, Veien NK. Vaccination granulomas and aluminium allergy, course and prognostic factors. *Contact Dermatitis* 1992; **26**: 304–6.
71 Armstrong DK, Walsh MY, Dawson JF. Granulomatous contact dermatitis due to gold earrings. *Br J Dermatol* 1997; **136**: 776–8.
72 Goossens A, De Swerdt A, De Coninck K *et al*. Allergic contact granuloma due to palladium following ear piercing. *Contact Dermatitis* 2006; **55**: 338–41.
73 Levy J, Sewell M, Goldstein N. A short history of tattooing. *J Derm Surg Oncol* 1979; **5**: 851–3.
74 Vilaplana J, Chimenos JM, Fernández AI *et al*. Problems in the diagnosis of contact dermatitis by tattooing. *Exog Dermatol* 2002; **1**: 307–12.
75 Lazarov A, Kidron D, Tulchinsky Z, Minkow B. Contact orofacial granulomatosis caused by delayed hypersensitivity to gold and mercury. *J Am Acad Dermatol* 2003; **49**: 1117–20.
76 Armstrong DK, Biagioni P, Lamey PJ *et al*. Contact hypersensitivity in patients with orofacial granulomatosis. *Am J Contact Dermatitis* 1997; **8**: 35–8.
77 Corazza M, Bacilieri S, Virgili A. Anaerobic sealants: still a problem today. *Eur J Dermatol* 2000; **10**: 468–9.
78 Lazarov A. Sensitization to acrylates is a common adverse reaction to artificial fingernails. *J Eur Acad Dermatol Venereol* 2007; **21**: 169–74.
79 Baran R, Schibli H. Permanent paresthesiae to sculptured nails. *Dermatol Clin* 1990; **8**: 139–42.
80 Lindup WE, Nowell PT. Role of sultone contaminants in an outbreak of allergic contact dermatitis caused by alkyl ethoxysulphates: a review. *Food Cosmet Toxicol* 1978; **16**: 59–62.
81 Magnusson B, Gilfe O. Allergic contact dermatitis from a dish washing liquid containing lauryl ether sulphate. *Acta Derm Venereol (Stockh)* 1973; **53**: 136–40.

Differential diagnosis

It should always be remembered that allergic contact dermatitis can mimic or complicate other types of eczema and other dermatoses. Sensitization to topical applications may be a complication of almost any dermatosis that leads to specialist referral. The diagnostic problem differs according to the site of the dermatitis. Patch testing will often be required before confirming the cause in its entirety.

Head. Allergic and photoallergic conditions of the face must be distinguished from a number of disorders.

Atopic eczema may be confined to the face, especially around the eyes and particularly the medial aspects. A previous or family history of infantile or childhood flexural eczema, asthma, allergic conjunctivitis, hay fever or immediate skin reactivity to animals and certain foods may point to the patient's atopic status. Associated flexural eczema, ichthyosis or xeroderma may be features. Multiple positive radioallergosorbent (RAST) or prick tests to common environmental allergens are used by some to confirm an atopic diathesis.

Seborrhoeic eczema, which commonly starts around the alae nasi, is usually accompanied by dandruff or seborrhoeic eczema in the scalp and eyebrows, and by blepharitis; involvement of the presternal region, the external auditory meati and the retro-auricular areas is common. Older patients frequently develop a flexural pattern of seborrhoeic eczema. Allergic contact dermatitis may imitate seborrhoeic eczema [1].

Psoriasis is normally easy to distinguish as there is evidence elsewhere on the body, although psoriasis in and around the ears and scalp margins may mimic a dry scaly contact dermatitis.

Cellulitis and erysipelas may be difficult to distinguish from an acute allergic contact dermatitis, but the former are usually accompanied by pyrexia and systemic symptoms.

Angio-oedema, especially of the eyelids, is notoriously difficult to differentiate from contact allergy. The swelling would be expected to resolve within 24–48 h. Patch tests are helpful in reaching a conclusion.

Dermatomyositis may initially appear identical to allergic contact dermatitis, and we have seen and patch tested such cases. The purple/mauve hue of the eyelids is a major clue, and the hands, fingers and nail folds must be carefully examined. The characteristic associated muscle pains and weakness may not always be present.

Herpes simplex may be simulated by *Primula obconica* dermatitis affecting the face and elsewhere [2]. Haemorrhage into the blisters seems to be more common with the latter.

Photosensitivity, including reactions to ingested drugs, cannot always be distinguished from photoallergic contact dermatitis, and may also simulate contact dermatitis from airborne sensitizers. Lupus erythematosus may be confused both clinically and histologically with contact allergy [3], and basal cell carcinoma has been simulated by nickel allergy from spectacle frames [4].

Hands and arms. Allergic and irritant contact dermatitis and constitutional eczema of the hands may only be distinguishable by a careful history and patch testing. They commonly coexist. Superimposed irritant contact dermatitis from home and work exposures is common.

Indicators of atopic eczema are discussed above. The eczema may be confined to the hands, especially in later life. A nummular pattern of eczema is commonly constitutional but may be a feature of irritant and allergic contact dermatitis, particularly from chromate in cement.

Recurrent vesicular eczema of the palms may indicate constitutional pompholyx, although contact allergy can produce an identical appearance. Some contact allergies, for example from IPPD and 1,2-benzisothiazolin-3-one, seem to induce a palmar pattern of dermatitis preferentially. *Primula* allergy often induces a haemorrhagic vesicular dermatitis of the palmar surfaces and fingertips. The relationship of pompholyx to ingestion of contact allergens, especially nickel, by sensitized subjects is controversial [5–7]. There is evidence that oral intake of balsams and garlic can induce palmar vesicular eczema in patch-test-positive subjects [8,9]. Tinea pedis can induce palmar pompholyx as an id eruption. Papules and vesicles on the hands and fingers are a feature of scabies, and this disorder must always be excluded by a careful history and examination for diagnostic burrows. The condition is normally associated with a more generalized pruritus and rash.

Psoriasis of the palms and hyperkeratotic eczema are often confused. Differentiation is sometimes somewhat arbitrary. Often, hyperkeratotic plaques are localized at points of contact, for example with tools, but not all frictional hyperkeratosis is necessarily an expression of psoriasis. The possibility of psoriasis koebnerizing into areas of contact dermatitis should not be forgotten [10].

Tinea manuum is classically unilateral or asymmetrical. An inflammatory edge may be seen extending on to the dorsum of the hand. Nail dystrophy may be an association. Scaling palms should be scraped for mycology. These appearances may be complicated by a vesicular id eruption.

Lichen planus confined to the palms can be difficult to distinguish from a palmar dermatitis, but usually there are more typical changes elsewhere on the skin or in the mouth. Lichen planus-like contact reactions from colour developers may occur on the hands and forearms [11].

Porphyria cutanea tarda may simulate a bullous contact dermatitis such as plant dermatitis. The formation of bullae after minor trauma and the presence of white atrophic scars and milia suggest the diagnosis, which can be confirmed by porphyrin assays.

Flexures and anogenital region. Seborrhoeic eczema and psoriasis may preferentially involve the flexures and be difficult to distinguish from allergic contact dermatitis, but there is often evidence of these conditions elsewhere.

Tinea is usually asymmetrical or unilateral and has an inflammatory edge. Scrapings for mycology should be taken from inflammatory flexural rashes. The typical coral-pink fluorescence under Wood's light will help to distinguish erythrasma from other flexural rashes.

Legs and feet. Persistent varicose eczema is an indication for patch testing as it is often complicated by sensitivity to topical medicaments and dressings, including rubber in support bandages and stockings.

Vesicular and vesiculobullous areas may occur in tinea pedis, and mycological specimens should be taken if this is suspected. In common with the hands, scabies affecting the feet may induce a papulovesicular eruption and must be considered in the differential diagnosis.

Trunk. Papular drug eruptions or scabies may sometimes be difficult to distinguish from nickel or textile dermatitis.

Dermatomyositis and mycosis fungoides sometimes show eczematous features.

Exposed sites. Photosensitive dermatoses and drug eruptions must be distinguished from contact allergy to volatile and airborne materials. Although not always reliable, sparing in certain sites—behind the ears and under the chin—might indicate a photosensitive eruption. Nevertheless, some patients will require thorough investigation with phototesting, patch and photopatch testing before a diagnosis can be made.

Generalized. Erythroderma is rarely primarily due to contact allergy, and other causes such as drug eruptions, constitutional eczema and psoriasis should be considered; the possibility of secondary contact allergy from topical medicaments must not be forgotten. Skin biopsy may be helpful in these cases.

Scabies can easily be overlooked as a cause of a widespread pruritic rash, especially as skin lesions may look classically eczematous. Careful examination of the hands, feet and genitals for diagnostic lesions is required.

References

1 Kuznetsov AV, Erlenkeuser-Uebelhoer I, Thomas P. Contact allergy to propylene glycol and dodecyl gallate mimicking seborrheic dermatitis. *Contact Dermatitis* 2006; **55**: 307–8.

2 Thomson KF, Charles-Holmes R, Beck MH. Primula dermatitis mimicking herpes simplex. *Contact Dermatitis* 1997; **37**: 185–6.

3 Sánchez-Pérez J, Gala SP, Jiménez YD *et al*. Allergic contact dermatitis to prednicarbate presenting as lupus erythematosus. *Contact Dermatitis* 2006; **55**: 247–9.

4 Hague J, Ilchyshyn A. Nickel allergy mimicking basal cell carcinoma. *Contact Dermatitis* 2006; **54**: 344–5.

5 Veien NK. Systemically induced eczema in adults. *Acta Derm Venereol Suppl (Stockh)* 1989; **147**: 1–58.

6 Gawkrodger DJ, Fell GS, Hunter JAA. Nickel dermatitis: the reaction to oral nickel challenge. *Br J Dermatol* 1985; **113** (Suppl. 29): 22–3.

7 Wilkinson DS, Wilkinson JD. Nickel allergy and hand eczema. In: Maibach HI, Menné T, eds. *Nickel and the Skin. Immunology and Toxicology*. Boca Raton, FL: CRC Press, 1989: 133–63.

8 Veien NK, Hattel T, Justensen O *et al*. Oral challenge with balsam of Peru. *Contact Dermatitis* 1985; **12**: 104–7.

9 Burden AD, Wilkinson SM, Beck MH *et al*. Garlic-induced systemic contact dermatitis. *Contact Dermatitis* 1994; **30**: 299–300.

10 Spiewak R. Köbnerizing occupational contact allergy to thiuram in a farmer with psoriasis. *Contact Dermatitis* 2004; **51**: 214–5.

11 Lidén C, Brehmer-Andersson E. Occupational dermatoses from colour developing agents. Clinical and histopathological observations. *Acta Derm Venereol (Stockh)* 1988; **68**: 514–22.

Allergic contact dermatitis to specific allergens

Metals

Nickel [1–3]

Chemistry. In common with cobalt, but unlike chromium, the metal itself sensitizes and is, in practice, the most frequent source of sensitization [2]. Most salts, for example nickel chloride ($NiCl_2$) and nickel sulphate ($NiSO_4$), are readily soluble in water and sweat and have strong sensitizing properties. Some oxides (e.g. Ni_2O_3) and the hydroxide ($Ni(OH)_2$) can elicit contact dermatitis, but heated NiO does not. This compound is insoluble even in hydrochloric acid.

Incidence and prevalence. Nickel is the most frequent contact allergen, and sensitivity is more common in women than in men. The prevalence of nickel sensitivity recorded in a patch-test clinic is between 15 and 30%, and is influenced by the relative number of females tested. Nickel is the most usual cause of contact dermatitis in women. All age groups are affected, but the prevalence of nickel sensitivity among females tends to rise from 10 years of age onwards [4]. The incidence of nickel dermatitis in Denmark varied with the total imports of nickel during and after the Second World War [5], which suggests that the level of sensitivity is determined by the total nickel exposure in the environment. In Denmark in the early 1990s it was found that the prevalence of nickel dermatitis in the general population was 11.1% in women and 2.2% in men. Sensitization to nickel was found in 14.8% of those with pierced ears and 1.4% of those who had not had their ears pierced, confirming that ear piercing is a significant risk factor for the development of nickel sensitivity [6]. A more recent study from northern Norway showed the prevalence of nickel allergy in women was 27.5% and in men 5.1%, with a clear relationship in women to the number of earlobe piercings [7].

This female predominance is not universal. In Kuwait, nickel allergy was commoner in males [8], and in Nigeria [9] and Japan [10] the prevalence was similar in both sexes in patch-tested patients.

The prevalence may be higher in some occupational groups, for example hairdressers, in whom studies have shown that 27–38% are nickel allergic [11,12].

Legislation was introduced in Denmark in 1990 with the intention of controlling the use of nickel-releasing objects in contact with the skin. In 1994 the European Union passed regulations based on the Danish legislation (Table 26.3). These laws only relate to metallic items in prolonged and direct skin contact, for example jewellery, clothing items and spectacle frames. Other metallic materials with which there is relatively short-term contact (e.g. coins, keys and cutlery) have been excluded from the legislation. The prevalence of allergy to nickel in under-18s attending for patch tests in Denmark has decreased considerably, from 24.8% in 1985–86 to 9.2% in 1997–98 [13], and in Germany there has also been a significant fall in frequency of nickel allergy in those under 30 [14].

Occurrence [15]. The commonest sources of metallic nickel are alloys and plated objects. Sensitization is chiefly the result of frequent skin contact with corroded objects containing nickel. A high

Table 26.3 European Union Nickel Directive (summary).

1 After piercing: posts, rings or other items used during the period of re-epithelialization shall not *contain* more than 0.05% nickel
2 Objects intended to be used in direct and prolonged contact with the skin shall not *release* more than 0.5 μg/cm²/week of nickel. Examples include jewellery, watches, buttons and zips

rate of corrosion has been documented from nickel-plated items, nickel-iron, German silver, coin and several other alloys [16]. Chromium-plated metal is often first nickel-plated, and after long use the nickel may reach the surface, for example on water taps. Stainless steels contain nickel but most are incapable of releasing sufficient quantities to elicit contact dermatitis. Quantitative studies indicate that repeated exposure to occluded metal items releasing nickel at a rate greater than 0.5 $\mu g/cm^2$/week involves a significant risk of nickel sensitization [17], but thereafter very small amounts of nickel are sufficient to elicit dermatitis in sensitized persons.

Jewellery and metal components of clothing are the usual sources of nickel in prolonged contact with the skin. Transient but potentially frequent and repeated exposure may occur from handling coins, keys, scissors, knitting needles, thimbles, scouring pads and other metallic tools and utensils. Most silver coins, including the new 1 and 2 € coins, contain nickel, and there is debate as to whether exposure might be a risk factor in those already sensitized to nickel [18]. Platers and some metal machinists are necessarily at risk of occupational nickel allergy. Other sources include pigments in glass, pottery and enamel, electrocautery plates [19], mobile phones [20], bindi [21], tattoo pigment [22], intravenous cannulae [23], orthodontic appliances [24], metal scouring pads, and even soaps [25] and detergents [15]. Nickel has been identified in some eye cosmetics [26,27].

Systemic exposure may take place from the diet. Certain foods and plants contain much higher concentrations than others, as can particular sources of domestic water [28], and nickel may also be a contaminant in fertilizers [29] and fungicides. Stainless steel saucepans release negligible nickel, but cooking acid fruit in them, particularly when new, has the potential to contribute to dietary intake [30].

Systemic exposure from implanted metals is considered on p. 26.37.

Clinical features. Classical nickel allergy is identified by patches of dermatitis at sites of contact with metal objects, most commonly the ears from earrings, the wrists from watches and bracelets, the neck from necklaces and their clasps, the central back and upper chest from bra components, the central abdomen from studs and zips in trousers, especially jeans (Fig. 26.13), and the dorsa of the feet from shoe buckles. Lesions on the upper cheeks and sides of the nose and face may relate to metal-framed spectacles and on the eyelids from eyelash curlers. A discoid pattern around the lower trunk and thighs from metal studs in clothing is quite frequent, although the involvement of the thighs from metal suspenders has all but disappeared following the advent of tights (pantyhose).

The eruption may be papular, nummular, diffuse or consist only of excoriated papules on almost normal-looking skin. Some patients are referred to dermatologists because of spread of dermatitis to distant regions. These secondary eruptions used to be a characteristic feature of nickel dermatitis [31], but now seem to be less common. The secondary rash normally starts shortly after, or at the same time as, the primary eruption. It affects the neck, face (especially the eyelids; Fig. 26.14), the elbow flexures and the flexor surfaces of the arms; the anogenital area may also be affected,



Fig. 26.13 Allergic contact dermatitis to nickel in metal studs on jeans. (Courtesy of Dr J.D. Wilkinson, Amersham General Hospital, Amersham, UK.)



Fig. 26.14 Secondary eyelid dermatitis in a patient sensitive to nickel. (Courtesy of Dr J.D. Wilkinson, Amersham General Hospital, Amersham, UK.)

and the rash may be generalized. Flexural lesions may resemble textile dermatitis or atopic dermatitis.

The relationship between hand eczema and nickel sensitivity remains complex [32]; however, well-controlled statistical studies do support a connection between hand eczema and nickel allergy [33–35], and nickel-sensitive women do appear to have a predilection for hand eczema [32,36]. However, nickel allergy in childhood did not seem to predispose to hand dermatitis later in life in one study [37]. Hand eczema is often multifactorial, and is particularly common in women who have a heavy burden of housework or

who are employed in occupations that expose the skin regularly to trauma or wet work. There may be a vesicular palmar (dyshidrotic) pattern, but other distributions occur without being diagnostic. Wet work, atopy and nickel sensitivity are associated with an increased risk of hand dermatitis [38], although atopy is probably the most important factor [39]. Analytical data demonstrate that consumer products such as personal care items, detergents and cleaning products do not contain sufficient nickel, cobalt or chromium to pose a risk to those who do wet work [15].

Sometimes, nickel allergy is directly of occupational origin, and in more than half of these cases it starts on the hands. It is normally associated with the metal and nickel-plating industries. The pattern of dermatitis on the hands is rarely diagnostic. Spread occurs to the elbow flexures, eyelids and face in the same manner as described above.

A recurrent vesicular palmar (dyshidrotic) pattern of eczema has been related to dietary intake of nickel. Ingestion of nickel sulphate caused a flare of vesicular hand eczema in nine of 12 patients studied by Christensen and Möller [40]. The significance of this has been disputed, as similar results have been demonstrated in non-sensitized patients and the challenge dose was artificially high [41–44]. However, a subsequent placebo-controlled oral challenge did show a flare of dermatitis, including the original site, in 4/10 nickel allergic subjects receiving nickel equivalent to a normal dietary intake [45]. A further meta-analysis of 17 relevant studies has concluded that 1% of those exposed to a normal dietary nickel intake will develop systemic contact dermatitis [46]. Oral symptoms and systemically reactivated dermatitis have also resulted from nickel in orthodontic appliances, in those already sensitized [24,47,48]. Paradoxically, tolerance to nickel exposure may develop as a result of nickel release from orthodontic appliances in those who are not already sensitized [49,50].

Avoidance. Most people think of their environment in terms of objects rather than materials, and it is important to realize that they find it difficult to identify nickel, unless the possible causes of contact are specifically listed. The importance of minor items, such as eyelash curlers, zip fasteners and jeans studs, may not otherwise be appreciated. Many dermatologists provide all nickel-sensitive patients with a list of possible contact items. A dimethylglyoxime test kit (see p. 26.99) may also be of use in identifying nickel-containing objects among a patient's personal items at work or in the home [16].

Nickel cannot be entirely avoided in daily life, but elimination of nickel from clothing and avoidance of nickel-containing jewellery may be sufficient to clear dermatitis. In our experience, initial compliance with avoidance advice is poor, particularly with clothing, and repeated explanations may be necessary. Waterproof tape and metal lacquer can be used to cover nickel-plated objects that cannot be replaced, although nickel can leach out if the contact site is sweaty and prone to friction. Contact may be difficult to avoid in certain occupations. Protection with rubber gloves may be insufficient, as nickel solutions may penetrate them [51]. Heavy-duty vinyl gloves have been suggested as an alternative.

Prognosis. The prognosis of dermatitis from nickel in jewellery and clothing is excellent if further use of nickel-plated objects is avoided. Once the hands are involved, the eczema may remain chronic, persistent or intermittent. Ingestion of nickel is a possible cause of chronicity [52].

Specific therapies. Barrier creams and cleansers containing chelating agents may have potential benefit, and a number have shown promise under experimental conditions [53–55]. Clioquinol is known to chelate nickel [56], and a topical clioquinol/steroid combination can be considered as a treatment.

Dietary reduction of nickel intake is recommended, by some, for those nickel-allergic subjects with recurrent palmar vesicular eczema. Knowledge of the nickel content of foods is at present imprecise, and the prescription of a low-nickel diet [57] is not always practical [43]. Nevertheless, there are strong advocates for this approach and a trial of dietary reduction may be worthwhile, although this is frequently disappointing in our experience.

Treatment with tetraethylthiuramdisulphide (disulfiram; Antabuse), which chelates nickel, has been reported as helpful [58], but has a significant prevalence of side effects [59]. Liver enzymes should be carefully monitored. An alternative chelating agent, trientine, gave disappointing results in a small, open trial [60].

Patch tests. Nickel sulphate 5% in petrolatum is used for patch tests. False-negative reactions are common with 2.5% nickel in petrolatum or 2% aqueous nickel [61]. False-negative reactions may also occur with 5% nickel sulphate in petrolatum because nickel ions penetrate the skin only very slowly [62]. Testing with nickel sulphate may produce irritant false-positive reactions with a deep erythema and pustulation, especially in atopics. Some follicular reactions are irritant, but those with raised papules are often truly allergic in our experience. In cases of doubt, intracutaneous testing with 1 mol/L nickel sulphate in saline has been used to clarify the situation [63].

References

1 Andersen KE, White IR, Goossens A. Allergens from the standard series. In: Frosch PJ, Menné T, Lepoittevin J-P, eds. *Contact Dermatitis,* 4th edn. Berlin: Springer, 2006: 455–9.

2 Maibach HI, Menné T, eds. *Nickel and the Skin: Immunology and Toxicology*. Boca Raton, FL: CRC Press, 1989.

3 Menné T. *Nickel Allergy*. Copenhagen: Marselis tryk a-s, 1983.

4 Cronin E. *Contact Dermatitis*. Edinburgh: Churchill Livingstone, 1980: 344–5, 353–7.

5 Marcussen PV. The rise in prevalence of nickel sensitivity. *Br J Dermatol* 1959; **71**: 97–101.

6 Nielsen NH, Menné T. Nickel sensitisation and ear piercing in an unselected Danish population. *Contact Dermatitis* 1993; **29**: 16–21.

7 Kåre Dotterud L, Smith-Sivertsen T. Allergic contact sensitization in the general adult population: a population-based study from northern Norway. *Contact Dermatitis* 2007; **56**: 10–5.

8 Kanan MW. Contact dermatitis in Kuwait. *J Kuwait Med Assoc* 1968; **3**: 129–44.

9 Olumide YM. Contact dermatitis in Nigeria. *Contact Dermatitis* 1985; **12**: 241–6.

10 Sugai T, Takagi T, Yamamoto S *et al*. Age distribution of the prevalence of contact sensitivity to standard allergens. *Contact Dermatitis* 1979; **5**: 383–8.

11 Van der Burg CKH, Brunyzeel DP, Vreeburg KHH *et al*. Hand eczema in hairdressers and nurses: a prospective study. I. Evaluation of atopy and nickel hypersensitivity at the start of apprenticeship. *Contact Dermatitis* 1986; **14**: 275–9.

12 Van der Walle HB, Brunsveld VM. Dermatitis in hairdressers. (1). The experience of the last 4 years. *Contact Dermatitis* 1994; **30**: 217–21.

13 Johansen J, Menné T, Christophersen J *et al*. Changes in the pattern of sensitization to common contact allergens in Denmark between 1985–86 and 1997–98, with a special view to the effect of preventive strategies. *Br J Dermatol* 2000; **142**: 490–5.
14 Schnuch A, Uter W. Decrease in nickel allergy in Germany and regulatory interventions. *Contact Dermatitis* 2003; **49**: 107–8.
15 Basketter DA, Briatico-Vangosa G, Kaestner W *et al*. Nickel, cobalt and chromium in consumer products: a role in allergic contact dermatitis? *Contact Dermatitis* 1993; **28**: 15–25.
16 Menné T, Andersen KE, Kaaber K *et al*. Evaluation of the dimethylglyoxime test for detection of nickel. *Berufsdermatosen* 1987; **35**: 128–30.
17 Menné T, Christophersen J, Green A. Epidemiology of nickel dermatitis. In: Maibach HI, Menné T, eds. *Nickel and the Skin: Immunology and Toxicology*. Boca Raton, FL: CRC Press, 1989: 109–15.
18 Jellesen MS, Hilbert LR, Menné T, Möller H. Nickel-containing coins: a health risk for nickel-sensitive individuals? *Br J Dermatol* 2006; **155**: 1301–2.
19 Trevisan G, Kokelj F. Allergic contact dermatitis from nickel in an electrocautery plate. *Contact Dermatitis* 1992; **26**: 267.
20 Wöhrl S, Jandl T, Stingl G, Kinaciyan T. Mobile telephone as new source for nickel dermatitis. *Contact Dermatitis* 2007; **56**: 113.
21 Baxter KF, Wilkinson SM. Contact dermatitis from a nickel-containing bindi. *Contact Dermatitis* 2002; **47**: 55.
22 Raison-Peyron N, Guillard O, Khalil Z *et al* Nickel-elicited systemic contact dermatitis from a peripheral intravenous catheter. *Contact Dermatitis* 2005; **53**: 222–5.
23 Morales-Callaghan AM, Aguilar-Bernier M, Martínez-García G, Miranda-Romero E. Sarcoid granuloma on black tattoo. *J Am Acad Dermatol* 2006; **55**: S71–3.
24 Genelhu MC, Marigo M, Alves-Oliveira LF *et al*. Characterization of nickel-induced allergic contact stomatitis associated with fixed orthodontic appliances. *Am J Orthod Dentofacial Orthop* 2005; **128**: 378–81.
25 Kokelj F, Daris F, Lutmann A *et al*. Nickel, chromate and cobalt in toilet soaps analysed by inductively coupled plasma mass spectrometry. *Contact Dermatitis* 1994; **31**: 270.
26 Van Ketel WG, Bruynzeel DP. Allergic contact dermatitis from nickel in eyeshadow (letter). *Contact Dermatitis* 1989; **21**: 355.
27 Berne B, Boström Å, Grahnén AF, Tammela M. Adverse effects of cosmetics and toiletries reported to the Swedish Medical Protection Agency 1989–94. *Contact Dermatitis* 1996; **34**: 359–62.
28 Lee AY, Lee YS. A case of allergic contact dermatitis due to nickel in underground water. *Contact Dermatitis* 1990; **22**: 141–3.
29 Pecegueiro M. Contact dermatitis due to nickel in fertilizers. *Contact Dermatitis* 1990; **22**: 114–5.
30 Flint GN, Packirisamy S. Systemic nickel: the contribution made by stainless-steel cooking utensils. *Contact Dermatitis* 1995; **32**: 218–24.
31 Marcussen PV. Spread of nickel dermatitis. *Dermatologica* 1957; **115**: 596–607.
32 Wilkinson DS, Wilkinson JD. Nickel allergy and hand eczema. In: Maibach HI, Menné T, eds. *Nickel and the Skin: Immunology and Toxicology*. Boca Raton, FL: CRC Press, 1989: 133–63.
33 Christophersen J, Menné TM, Tanghof P *et al*. Clinical patch test data evaluated by multivariate analysis. *Contact Dermatitis* 1989; **21**: 291–9.
34 Edman B. Sites of contact dermatitis in relationship to particular allergens. *Contact Dermatitis* 1985; **13**: 129–35.
35 Meding B, Swanbeck G. Predictive factors for hand eczema. *Contact Dermatitis* 1990; **23**: 154–62.
36 Menné T, Borgan Ø, Green A. Nickel allergy and hand dermatitis in a stratified sample of the Danish female population. *Acta Derm Venereol (Stockh)* 1982; **62**: 35–41.
37 Josefson A, Färm G, Stymne B, Meding B. Nickel allergy and hand eczema—a 20-year follow up. *Contact Dermatitis* 2006; **55**: 286–90.
38 Nilsson EJ, Bäck O. The importance of anamnestic information of atopy, metal dermatitis and earlier hand eczema for the development of hand dermatitis in women in wet hospital work. *Acta Derm Venereol (Stockh)* 1986; **66**: 45–50.
39 Nilsson EJ, Knutson A. Atopic dermatitis, nickel sensitivity and xerosis as risk factors for hand eczema in women. *Contact Dermatitis* 1995; **33**: 401–6.
40 Christensen OB, Möller H. Nickel allergy and hand eczema. *Contact Dermatitis* 1975; **1**: 129–35.
41 Burrows D. Mischievous metals: chromate, cobalt, nickel and mercury. *Clin Exp Dermatol* 1989; **14**: 266–72.
42 Gawkrodger DJ, Cook SW, Fell GS *et al*. Nickel dermatitis: the reaction to oral nickel challenge. *Br J Dermatol* 1986; **115**: 33–8.
43 Jordan WP, King SE. Nickel feeding in nickel-sensitive patients with hand eczema. *J Am Acad Dermatol* 1979; **1**: 506–8.
44 Roduner J, Haudenschilde-Falb E, Kunz E *et al*. Oral nickel challenge in non-pompholyx and pompholyx-type nickel eczema. *Hautarzt* 1987; **38**: 262–6.
45 Jensen CS, Menné T, Lisby S *et al*. Experimental systemic contact dermatitis from nickel: a dose-response study. *Contact Dermatitis* 2003; **49**: 124–32.
46 Jensen CS, Menné T, Johansen JD. Systemic contact dermatitis after oral exposure to nickel: a review with a modified meta-analysis. *Contact Dermatitis* 2006; **54**: 79–86.
47 Pigatto PD, Guzzi G. Systemic contact dermatitis from nickel associated with orthodontic appliances. *Contact Dermatitis* 2004; **50**: 100–1.
48 Schultz JC, Connelly E, Glesne L, Warshaw EM. Cutaneous and oral eruption from oral exposure to nickel in dental braces. *Dermatitis* 2004; **15**: 154–7.
49 Van Hoogstraten IMW, Andersen KE, Von Blomberg BME *et al*. Preliminary results of a multicentre study on the prevalence of nickel allergy in relationship to previous oral and cutaneous contacts. In: Frosch P, Dooms-Goossens A, LaChapelle J-M *et al*., eds. *Current Topics in Contact Dermatitis*. Berlin: Springer, 1989: 178–83.
50 White JM, Goon AT, Jowsey IR *et al*. Oral tolerance to contact allergens: a common occurrence? A review. *Contact Dermatitis* 2007; **56**: 247–54.
51 Wall LM. Nickel penetration through rubber gloves. *Contact Dermatitis* 1980; **6**: 461–3.
52 Veien NK. Nickel dermatitis: its relationship to food and experimental oral challenge. In: Maibach HI, Menné T, eds. *Nickel and the Skin: Immunology and Toxicology*. Boca Raton, FL: CRC Press, 1989: 165–97.
53 Gawkrodger DJ, Healy J, Howe AM. The prevention of nickel contact dermatitis. A review of the use of binding agents and barrier creams. *Contact Dermatitis* 1995; **32**: 257–65.
54 Wohrl S, Kriechbaumer N, Hemmer W *et al*. A cream containing the chelator DTPA (diethylenetriaminepenta-acetic acid) can prevent contact allergic reactions to metals. *Contact Dermatitis* 2001; **44**: 224–8.
55 Healy J, Johnson S, Little MC *et al*. An in vitro study of the use of chelating agents in cleaning nickel-contaminated human skin: an alternative approach to preventing nickel allergic contact dermatitis. *Contact Dermatitis* 1998; **39**: 171–81.
56 Memon AA, Molokhia MM, Friedmann PS. The inhibitory effects of topical chelating agents and antioxidants on nickel-induced hypersensitivity reactions. *J Am Acad Dermatol* 1994; **30**: 560–5.
57 Kaaber K, Veien NK, Tjell JC. Low nickel diet in the treatment of patients with chronic nickel dermatitis. *Br J Dermatol* 1978; **98**: 197–201.
58 Sharma AD. Disulfiram and low nickel diet in the management of hand eczema: a clinical study. *Indian J Dermatol Venereol Leprol* 2006; **72**: 113–8.
59 Christensen OB, Kristensen M. Treatment with disulfiram in chronic nickel hand dermatitis. *Contact Dermatitis* 1982; **8**: 59–63.
60 Burrows D, Rogers S, Beck M *et al*. Treatment of nickel dermatitis with trientine. *Contact Dermatitis* 1986; **15**: 55–7.
61 Cronin E. Patch testing with nickel. *Contact Dermatitis* 1975; **1**: 56–7.
62 Fullerton A, Anderson JR, Hoelgaard A *et al*. Permeation of nickel salts through human skin *in vitro*. *Contact Dermatitis* 1986; **15**: 173–7.
63 Möller H. Intradermal testing in doubtful cases of contact allergy to metals. *Contact Dermatitis* 1989; **20**: 120–3.

Cobalt [1]

Chemistry. Cobalt metal and its oxides (e.g. Co_2O_3 and CoO) and salts (e.g. $CoCl_2$ and $CoSO_4$) are sensitizers. Also, heated CoO elicits positive patch-test reactions (unlike NiO).

Prevalence. Little is known of the prevalence of allergy in the general population but one study showed that 1.1% of an unselected Danish population of 567 individuals were patch-test positive [2]. A more recent Norwegian study found 4.3% of women

and 0.9% of men to be allergic [3]. Of patients with dermatitis 4.6–9% are patch-test positive, with females predominating [4].

Occurrence. Metallic cobalt is present in 'hard metal' used for metal cutting and drilling. It is used in magnets and jewellery. It is always present as a contaminant in nickel [5]. It occurs in alloys, for example vitallium used in dentures and in nails for pinning fractures.

Cobalt oxides, present as traces in cement, are sensitizers; however, isolated cobalt allergy from cement is much rarer than its occurrence in association with chromium allergy. The cobalt content of cement is about the same as that of chromium [6].

Cobalt compounds are found in paints, glass, china, pottery, ceramics, enamel (blue), coloured crayons and animal feed additives [7], multivitamin pills, textile dyes [8], tattoos [9], soaps [10], cosmetic pigments, hair dye and detergents [11].

The salts are seldom used for plating, unlike nickel salts, although cobalt chloride has sensitized in a metal-etching solution [12].

Organic compounds (e.g. cobalt naphthenate, resinate and stearate) are used as driers in paints and varnishes, bonders of rubber to metal [13] and accelerators for unsaturated polyester resins [14]. They may also be present as additives in lubricating oils.

Clinical features. As cobalt is an invariable contaminant of nickel, the clinical features of cobalt allergy can be identical to those of nickel allergy. Cobalt sensitivity might explain why some women with dermatitis typical of that provoked by nickel have a negative patch-test reaction to the latter. Furthermore, its presence in cement may induce a clinical pattern identical to allergy from chromate in this source. Isolated cobalt allergy is seen in hard-metal workers and in the pottery and glass industries, when it is usually associated with hand dermatitis. Stomatitis has been reported from dentures [15]. Allergic granulomatous reactions to tattoo pigment are recognized, but are rare in our experience. Animal feed may induce contact allergy [16], and photocontact dermatitis has been reported from this source, as well as from cement [17]. Vitamin B_{12} is a cobalt-containing compound and cheilitis has been reported from oral vitamin B_{12} ingestion [15], and dermatitis from its parenteral use [18]. An oral lichenoid eruption to a chrome/cobalt prosthesis has been reported [19]. It can be difficult to identify the source of allergy when there is an isolated positive cobalt patch test.

The relationship of cobalt allergy to metal implants is discussed on p. 26.37.

Avoidance. This will depend on identifying a relevant cause and eliminating contact. In those with a nickel allergic pattern, the advice is the same as for nickel-allergic subjects (see p. 26.32); similarly, for those with cement allergy, the advice is the same as for chromate (see p. 26.35). Reduction of the dietary intake of cobalt (monitoring plasma vitamin B_{12} if prolonged) may benefit some cobalt-sensitive patients [20].

Prognosis. Concomitant cobalt and chromate sensitivity is associated with more troublesome dermatitis than that which occurs with chromate allergy alone [21]. Possibly the same applies to a combined nickel and cobalt sensitivity because of the increased number of contact sources, which may cause recurrence of the dermatitis.

Patch tests. Cobalt chloride 1% in petrolatum is reliable for testing [11]. False-positive, irritant, purpuric reactions are common, especially in atopics.

References

1 Andersen KE, White IR, Goossens A. Allergens from the standard series. In: Frosch PJ, Menné T, Lepoittevin J-P, eds. *Contact Dermatitis,* 4th edn. Berlin: Springer, 2006: 461–2

2 Nielsen NH, Linneberg A, Menné T *et al*. Incidence of allergic contact sensitization in Danish adults between 1990 and 1998; the Copenhagen Allergy Study, Denmark. *Br J Dermatol* 2002; **147**: 487–92.

3 Dotterud LK, Smith-Sivertsen T. Allergic contact sensitization in the general adult population: a population-based study from northern Norway. *Contact Dermatitis* 2007; **56**: 10–5.

4 Rietschel RL, Fowler JF Jr. *Fisher's Contact Dermatitis*, 5th edn. Philadelphia: Lippincott, Williams & Wilkins, 2001: 605–62.

5 Basketter DA, Briatico-Vangosa G, Kaestner W *et al*. Nickel, cobalt and chromium in consumer products: a role in allergic contact dermatitis? *Contact Dermatitis* 1993; **28**: 15–25.

6 Tandon R, Aarts B. Chromium, nickel and cobalt contents of some Australian cements. *Contact Dermatitis* 1993; **28**: 201–5.

7 Tuomi M-L, Räsänen L. Contact allergy to tylosin and cobalt in a pig-farmer. *Contact Dermatitis* 1995; **33**: 285.

8 Laing ME, Hackett CB, Murphy GM. Unusual allergen in nurse uniform trousers. *Contact Dermatitis* 2005; **52**: 293.

9 Björnberg A. Allergic reaction to cobalt in light blue tattoo markings. *Acta Derm Venereol (Stockh)* 1961; **41**: 259–63.

10 Kokelj F, Daris F, Lutmann A *et al*. Nickel, chromate and cobalt in toilet soaps analysed by inductively coupled plasma mass spectrometry. *Contact Dermatitis* 1994; **31**: 270.

11 Allenby CF, Basketter DA. Minimum eliciting patch test concentrations of cobalt. *Contact Dermatitis* 1989; **20**: 185–90.

12 Gawkrodger DJ, Lewis FM. Isolated cobalt sensitivity in an etcher. *Contact Dermatitis* 1993; **29**: 46.

13 Foussereau J, Cavelier C. Allergic contact dermatitis from cobalt in the rubber industry. *Contact Dermatitis* 1988; **19**: 217.

14 Tarvainen K, Jolanki R, Forsman-Grönholm L *et al*. Exposure, skin protection and occupational skin diseases in the glass-fibre-reinforced plastics industry. *Contact Dermatitis* 1993; **29**: 119–27.

15 Price ML, MacDonald DM. Cheilitis and cobalt allergy related to ingestion of vitamin B_{12}. *Contact Dermatitis* 1981; **7**: 352.

16 Ratcliffe J, English JS. Allergic contact dermatitis from cobalt in animal feed. *Contact Dermatitis* 1998; **39**: 201–2.

17 Romaguera C, Lecha M, Grimalt F *et al*. Photocontact dermatitis to cobalt salts. *Contact Dermatitis* 1982; **8**: 383–8.

18 Fisher AA. Contact dermatitis at home and abroad. *Cutis* 1972; **10**: 719–23.

19 Sockanathan S, Setterfield J, Wakelin S. Oral lichenoid reaction due to chromate/cobalt in dental prosthesis. *Contact Dermatitis* 2003; **48**: 342–3.

20 Veien N, Hattel T, Laurberg G. Placebo-controlled oral challenge with cobalt in patients with positive patch tests to cobalt. *Contact Dermatitis* 1995; **33**: 54–5.

21 Förström L, Pirilä V, Huju P. Rehabilitation of workers with cement eczema due to hypersensitivity to bichromate. *Scand J Rehab Med* 1969; **1**: 95–100.

Chromium [1,2]

Chemistry. The metal itself, if not dissolved in oil [3] or acids or as a salt, seems to be non-sensitizing, unlike nickel and cobalt. This is probably due to the insoluble monomolecular layer of chromium (III) oxide (Cr_2O_3) on the surface [4].

Hexavalent chromate (occurring as an anion), for example in chromic acid or chromium (VI) trioxide (CrO_3) and in chromates

and dichromates of potassium, sodium and ammonium, is the commonest sensitizer. It occurs in alkaline solution as chromate (K_2CrO_4) and in acid solution as dichromate ($K_2Cr_2O_7$). The less soluble lead chromate, barium chromate and zinc chromate ($ZnCrO_4$) are also allergenic.

The trivalent chromium compounds (occurring as cations), for example chromium trichloride ($CrCl_3$), are sensitizers but, being less readily absorbed into the skin, they have been considered to be of less clinical importance [5]. However, recent work challenges this view and combined Cr III and Cr VI allergy may be equally important [6].

Incidence and prevalence. In Europe, chromate was for many years a frequent cause of occupational allergic contact dermatitis and chronic incapacity [5]. The prevalence of sensitivity is commoner in men than in women and is higher in clinics where men with occupational dermatitis predominate. A study of construction workers attending occupational contact dermatitis clinics in Germany showed that potassium dichromate was the commonest allergen, at 31.9% [7], whereas chromate sensitivity was found in less than 2% of patients attending the general patch-test clinic. In some countries (including the UK) chromate sensitivity is less common [8]. Nevertheless, nearly 25% of UK-based grouters assessed during the construction of the Channel Tunnel gave a history of occupational dermatitis and 17% were allergic to chromate [9]. Review of EPIDERM data in the UK found that 6% of cases of occupational dermatitis reported by dermatologists were from chromate, often with an onset later in life [10].

In Scandinavian countries, the addition of ferrous sulphate to cement to convert the more sensitizing hexavalent chromate to the less sensitizing trivalent chromate (because it is less easily absorbed) appears to have decreased the risk of sensitization in construction workers [11], although other changes in cement manufacture and increased mechanization may also be contributory factors [12]. In 2005 the EU directed that levels of chromate in cement should be restricted to 2 ppm hexavalent chromium [13], and it is anticipated that the frequency of chromate allergy in construction workers will fall as a result.

Occurrence [1,2]. The main source of hexavalent chromium is cement [9], although the amount varies widely [14,15]. Other important sources are antirust paints (lead chromate and zinc chromate) [16], including dust liberated by drilling, cutting or sandpapering of painted metals which may cause contact dermatitis on the hands, arms and face. Further sources are plating salts, metal alloys, lithography/offset printing materials, anticorrosive oil, cutting oils, cooling water [17], foundry sand, polysulphide sealants [18], matches [19], photographic chemicals, chemicals for fat determination in milk, welding fumes [20], wood preservatives, wood ashes, wood pulp [21], mordant in wool dyeing, green baize, stains in glass, glazing enamels [22], catgut, violin strings [23], coating on zinc-galvanized iron sheets [24], textiles [25], glass polishing [26], flour [27], tyre-fitting solution [28], colour television manufacture [29], soaps and detergents [30], and dental prostheses [31]. Chromate sensitivity in some European women was found to be related to chromate in household bleach [32], which was subsequently removed.

Among trivalent compounds, basic chromium sulphate used as a tanning agent for leather is the most important [5]. Exposure to chromate in leather occurs occupationally in tanners, and in the general population from clothing, especially shoes, and furniture.

Clinical features. Acute weeping dermatitis is unusual in patients allergic to chromate in cement; more commonly there is a dry insidious eruption, which tends to fissure, particularly on the hands. Secondary lichenification is often a feature. There is frequently a concomitant irritant element, because cement is alkaline, hygroscopic and abrasive. Primary irritant dermatitis and discoid and atopic eczema may be mimicked, and a palmar distribution may be difficult to distinguish from chronic tinea manuum. Widespread eruptions may occur from cement dust, with flexural accentuation and involvement of the ankles and dorsa of the feet. Palmar vesicular eruptions have been blamed on traces of chromate in the diet [33]. Contact with leather footwear, gloves, belts and other clothing, or even handbags and purses, may produce dermatitis in those areas in contact with the material. Exposure to leather furniture has induced eczematous flares on the back, calves, arms and feet in sensitized subjects [34]. An oral lichenoid eruption to a chrome/cobalt prosthesis has been reported [35].

Prognosis. Chromate sensitivity tends to persist [36], and the prognosis of occupational dermatitis is poor as a result of its persistence and associated social and financial handicap [37]. Fewer than 20% of cases were clear of dermatitis when reviewed after 10 years [38]. In men, allergy to chromate carries a worse prognosis than does sensitization to other allergens [39]. Chronicity and frequent relapses are the rule; the latter are more frequent than in any other industrial dermatosis [40] and affected individuals have been labelled as 'chrome cripples' [38]. Once established, hand dermatitis tends to continue, and superimposed shoe dermatitis may prevent any improvement unless chromate-free shoes can be acquired. Few of those affected give up their work despite the chronicity of the condition [41], and in one study only 8% of chromate sensitized cement workers were clear of dermatitis 10–13 years after the initial eruption. Changing work to avoid contact with cement does not seem to improve the prognosis [42]. These findings contrast with a Swiss study in which occupational chromate dermatitis resolved in 72% of individuals as a result of strictly enforced avoidance measures and financial support given by their regulatory authorities [43]. Many chromate-sensitized cement workers develop hardening and are able to continue at work, albeit with ongoing but manageable dermatitis. Positive patch tests have been reported in cement workers with no dermatitis [44]. Insufficient knowledge of the occurrence of chromate in the environment may account for the poor prognosis, and it is suggested that tiny amounts and oral ingestion may maintain the dermatitis [45].

Avoidance. Avoidance of contact with sources of chromate, including leather footwear and gloves, will be necessary, although those cement workers with hardening can be encouraged to stay at their work, bearing in mind the poor prognosis. Ferrous sulphate added to cement converts soluble hexavalent chromate to

insoluble trivalent chromate, thus potentially preventing chromium sensitization by cement. Various reducing agents [46], chelating compounds and ion exchangers have been recommended as components of hand creams to prevent dermatitis in chromate-sensitive individuals [47,48], and these may have value; however, long-term studies are lacking. It is not yet known whether reduction of the dietary intake of chromate might benefit chromate-sensitive patients [49]. Dapsone has been suggested as a treatment, but no controlled trial has been undertaken [50].

Patch tests. Sensitivity is demonstrated by a closed patch test with potassium dichromate 0.5% in petrolatum. At this concentration, weak irritant reactions are quite common, especially in atopics, but lower concentrations will miss relevant positives [51]. Nevertheless, in the USA a concentration of 0.25% is recommended because of the potential for false-positive results. A compromise (0.375%) has been suggested, although there may still be a risk of false-positive and false-negative reactions [51]. Dilutions can be tested to assist in distinguishing allergic from irritant reactions.

References

1 Burrows D, ed. *Chromium: Metabolism and Toxicity*. Boca Raton, FL: CRC Press, 1983.

2 Frosch PJ, Menné T, Lepoittevin J-P, eds. *Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 459–61, 548–54.

3 Wahlberg JE, Lindstedt G, Einarsson Ö. Chromium, cobalt and nickel in Swedish cement, detergents, mould and cutting oils. *Berufsdermatosen* 1977; **25**: 220–8.

4 Fregert S. Chromium valencies and cement dermatitis. *Br J Dermatol* 1981; **105** (Suppl. 21): 7–9.

5 Fregert S, Rorsman H. Allergic reactions to trivalent chromium compounds. *Arch Dermatol* 1966; **93**: 711–3.

6 Hansen MB, Johansen JD, Menné T. Chromium allergy: significance of both Cr(III) and Cr(VI). *Contact Dermatitis* 2003; **49**: 206–12.

7 Geier J, Schnuck A. A comparison of contact allergens among construction and non-construction workers attending contact dermatitis clinics in Germany: results of the Information Network of Departments of Dermatology from November 1989 to July 1993. *Am J Contact Dermatitis* 1995; **6**: 86–94.

8 Wilkinson DS, Wilkinson JD. Comparison of patch test results in two adjacent areas of England. I. Industrial allergens. *Acta Derm Venereol Suppl (Stockh)* 1979; **89**: 189–92.

9 Irvine C, Pugh CE, Hansen E, Rycroft RJ. Cement dermatitis in underground workers during construction of the Channel Tunnel. *Occup Med* 1994; **44**: 17–23.

10 Athavale P, Shum KW, Chen Y *et al.* Occupational dermatitis related to chromium and cobalt: experience of dermatologists (EPIDERM) and occupational physicians (OPRA) in the U.K. over an 11-year period (1993–2004). *Br J Dermatol* 2007; **157**: 518–22.

11 Zachariae COC, Agner T, Menné T. Chromium allergy in consecutive patients in a country where ferrous sulphate has been added to cement since 1981. *Contact Dermatitis* 1996; **35**: 83–6.

12 Goh CL, Gan SL. Change in cement manufacturing process, a cause for decline in chromate allergy? *Contact Dermatitis* 1996; **34**: 51–4.

13 Thyssen JP, Johansen JD, Menné T. Contact allergy epidemics and their controls. *Contact Dermatitis* 2007; **56**: 185–95.

14 Fregert S, Gruvberger B. Chemical aspects on chromate in cement. *Dermatosen* 1982; **30**: 76–8.

15 Tandon R, Aarts B. Chromium, nickel and cobalt contents of some Australian cements. *Contact Dermatitis* 1993; **28**: 201–5.

16 Engel HO, Calnan CD. Chromate dermatitis from paint. *Br J Ind Med* 1963; **20**: 192–8.

17 Calnan CD, Harman RRM. Studies in contact dermatitis XIII. Diesel coolant chromate dermatitis. *Trans St John's Hosp Dermatol Soc* 1961; **46**: 13–21.

18 Handley J, Burrows D. Dermatitis from hexavalent chromate in the accelerator of an epoxy sealant (PR1422) used in the aircraft industry. *Contact Dermatitis* 1994; **30**: 193–6.

19 Fregert S. Chromate eczema and matches. *Acta Derm Venereol (Stockh)* 1961; **41**: 433–42.

20 Fregert S, Övrum P. Chromate in welding fumes with special reference to contact dermatitis. *Acta Derm Venereol (Stockh)* 1963; **43**: 119–24.

21 Fregert S, Gruvberger B, Heijer A. Sensitization to chromium and cobalt in processing of sulphate pulp. *Acta Derm Venereol (Stockh)* 1972; **52**: 221–4.

22 Wilkinson SM, Heagerty AHM, English JSC. Hand dermatitis in the pottery industry. *Contact Dermatitis* 1992; **26**: 91–4.

23 Buckley DA, Rogers S. 'Fiddler's fingers': violin-string dermatitis. *Contact Dermatitis* 1995; **32**: 46–7.

24 Fregert S, Gruvberger B. Chromate dermatitis from oil emulsion contaminated from zinc-galvanized sheet. *Contact Dermatitis* 1976; **2**: 121.

25 Fregert S, Gruvberger B, Göransson K *et al*. Allergic contact dermatitis from chromate in military textiles. *Contact Dermatitis* 1978; **4**: 223–4.

26 Richter G, Heidelbach U. Chromatekzem nach Glasmattierung mit einem Korund. *Berufsdermatosen* 1969; **17**: 8–12.

27 Heine A, Fox G. Bäckerekzem durch Chromverbindung in Mehlen. *Dermatosen* 1980; **28**: 113–5.

28 Burrows D. Chromium dermatitis in a tyre fitter. *Contact Dermatitis* 1981; **7**: 55–6.

29 Stevenson CJ, Morgan PR. Investigation and prevention of chromate dermatitis in colour television manufacture. *J Soc Occup Med* 1983; **33**: 19–20.

30 Basketter DA, Briatico-Vangosa G, Kaestner W *et al*. Nickel, cobalt and chromium in consumer products: a role in allergic contact dermatitis? *Contact Dermatitis* 1993; **28**: 15–25.

31 Veien NK, Borchorst E, Hattel T, Laurberg G. Stomatitis or systemically-induced contact dermatitis from metal wire in orthodontic materials. *Contact Dermatitis* 1994; **30**: 210–3.

32 LaChapelle J-M, Lauwerys R, Tennstedt D *et al*. Eau de Javel and chromate allergy in France. *Contact Dermatitis* 1980; **6**: 107–10.

33 Kaaber K, Veien NK. The significance of chromate ingestion in patients allergic to chromate. *Acta Derm Venereol (Stockh)* 1977; **57**: 321–3.

34 Patel TG, Kleyn E, King CM, Wilson NJ. Chromate allergy from contact with leather furnishings. *Contact Dermatitis* 2006; **54**: 171–2.

35 Sockanathan S, Setterfield J, Wakelin S. Oral lichenoid reaction due to chromate/cobalt in dental prosthesis. *Contact Dermatitis* 2003; **48**: 342–3.

36 Thormann J, Jespersen NB, Joensen HD. Persistence of contact allergy to chromium. *Contact Dermatitis* 1979; **5**: 261–4.

37 Breit R, Türk RBM. The medical and social fate of the dichromate allergic patient. *Br J Dermatol* 1976; **94**: 349–51.

38 Burry JN, Kirk J. Environmental dermatitis: chrome cripples. *Med J Aust* 1975; **2**: 720–1.

39 Czarnecki N. Die Persistenz der Chromatallergie beim Zementekze. *Hautartz* 1979; **30**: 80–3.

40 Dooms-Goossens A, Ceuterick A, Vanhaele N *et al*. Follow-up study of patients with contact dermatitis caused by chromates, nickel and cobalt. *Dermatologica* 1980; **160**: 249–60.

41 Fregert S. Occupational dermatitis in 10-year material. *Contact Dermatitis* 1975; **1**: 96–107.

42 Burrows D. Prognosis in industrial dermatitis. *Br J Dermatol* 1972; **87**: 145–8.

43 Lips R, Rast H, Elsner P. Outcome of job change in patients with occupational chromate dermatitis. *Contact Dermatitis* 1996; **34**: 268–71.

44 Burrows D, Calnan CD. Cement dermatitis. II. Clinical aspects. *Trans St John's Hosp Dermatol Soc* 1965; **51**: 27–39.

45 Kaaber K, Veien NK. The significance of chromate ingestion in patients allergic to chromate. *Acta Derm Venereol* 1977; **57**: 321–3.

46 Valsecchi R, Caineti T. Chromium dermatitis and ascorbic acid. *Contact Dermatitis* 1984; **10**: 252–97.

47 Samitz NH, Katz S. A study of the chemical reactions between chromium and skin. *J Invest Dermatol* 1964; **43**: 35–43.

48 Schuppli R. Uber einen neuen Typus von Schutzalben gegen Chromatekzeme. *Berufsdermatosen* 1970; **18**: 350–5.

49 Veien NK, Hattel T, Laurberg G. Chromate-allergic patients challenged orally with potassium dichromate. *Contact Dermatitis* 1994; **31**: 137–9.

50 Miyachi Y, Uchida K, Komura J *et al*. Auto-oxidative damage in cement dermatitis. *Arch Dermatol Res* 1985; **277**: 288–92.

51 Burrows D, Andersen KE, Camarasa JG *et al*. Trial of 0.5% versus 0.375% potassium dichromate. *Contact Dermatitis* 1989; **21**: 351.

Implanted alloys [1,2]

Orthopaedic metallic prosthetic implants are made from a variety of metals, often alloys and especially stainless steel. Stainless steels contain up to 25% nickel, but for orthopaedic use generally contain 13–16% nickel and a minimum of 17% chromium [3]. However, nickel release from stainless steels, apart from those containing sulphur, is very low [4]. Nickel, cobalt and chromate may also be used in wrought and cast alloys. Vitallium, a cast cobalt/chromium alloy, and titanium may also be used for implants.

Orthopaedic implants may be static (e.g. plate and screws) or dynamic (e.g. artificial hips). There are two potential concerns in relation to metal allergy and these implants, namely allergic skin disorders and loosening. There is little doubt that static implants can be associated with localized eczema over the site of implantation and more extensive skin eruptions in sensitized subjects, sometimes only resolving after removal [5]. The delay between insertion of the prosthesis and onset of dermatitis may be days or years. Similar eruptions were reported in the early days of hip replacements when metal heads articulated with metal cups [6]. This problem seemed to have largely disappeared following the introduction of plastic joint surfaces, and prospective studies of hip joint replacements in known metal-allergic subjects are reassuring [1].

There is evidence of increased metal sensitization associated with loosening and failure of joints, particularly when these joints involve metal–metal contact [7,8]. It is suggested that the increased allergy is caused by, rather than being responsible for, loosening [9].

In recent years there has been a return to metal on metal hip prostheses because it is felt that they produce less wear debris. Consequently the issue of metal allergy in relation to these procedures has resurfaced [1,10]. As allergy is common in the general population, prospective controlled studies will be required to assess whether there is genuine risk of dermatitis and loosening as a result.

Titanium allergy is virtually unknown, and thus titanium is an alternative for patients with extreme sensitivity to other metals. The patient may need to be appraised that the metal is not thought to be as long lasting as stainless steel.

Reactions have also been reported to sternotomy wires [11], shrapnel [12], mitral valve prostheses [13], dental prostheses and fillings [14], pacemakers [15], atrial septal occluders [16] and infusion and acupuncture needles [17,18]. The contention that metal allergy is associated with restenosis of coronary artery stents [19] is questionable at this time [20–22] and requires prospective controlled studies. There is evidence of an increased rate of allergy to gold after the stenting procedure [23].

References

1 Gawkrodger DJ. Metal sensitivities and orthopaedic implants revisited: the potential for metal allergy with the new metal-on-metal joint prostheses. *Br J Dermatol* 2003; **148**: 1089–93.

2 Wilkinson JD. Nickel allergy and orthopaedic prostheses. In: Maibach HI, Menné T, eds. *Nickel and the Skin: Immunology and Toxicology*. Boca Raton, FL: CRC Press, 1989: 187–93.

3 Maibach HI, Menné T, eds. *Nickel and the Skin: Immunology and Toxicology*. Boca Raton, FL: CRC Press, 1989: 51.

4 Haudrechy P, Mantout B, Frappaz A *et al*. Nickel release from stainless steels. *Contact Dermatitis* 1997; **37**: 113–7.

5 Gawkrodger DJ. Nickel sensitivity and the implantation of orthopaedic prostheses. *Contact Dermatitis* 1993; **28**: 257–9.

6 Elves MW, Wilson JN, Scales JT, Kemo HB. Prevalence of metal sensitivity in patients with total joint replacements. *BMJ* 1975; **iv**: 376–8.

7 Munro-Ashman D, Miller AJ. Rejection of metal to metal prosthesis and skin sensitivity to cobalt. *Contact Dermatitis* 1976; **2**: 65–7.

8 Evans EM, Freeman MAR, Miller AJ *et al*. Metal sensitivity as a cause of bone necrosis and loosening of the prosthesis in total joint replacement. *J Bone Joint Surg* 1974; **56B**: 626–42.

9 Deutman R, Mulder J, Brian R *et al*. Metal sensitivity before and after total hip arthroplasty. *J Bone Joint Surg* 1977; **59A**: 862–5.

10 Antony W, Holden CA. Metal allergy resurfaces in failed hip endoprostheses. *Contact Dermatitis* 2003; **48**: 45–55.

11 Gordan PM, Buxton PK, McLaren KN *et al*. Sensitivity to sternotomy wires may cause post-operative pruritus. *Ann Thorac Surg* 1966; **61**: 1514–6.

12 Bruynzeel DP. Dermatitis from shell splinters after 43 years. *Contact Dermatitis* 1988; **19**: 233–5.

13 Lyell A, Bain WH. Repeated failure of nickel containing prosthetic heart valves in a patient allergic to nickel. *Lancet* 1978; **ii**: 657–9.

14 Vreeburg KJJ. Exposure to metals. In: *Immunological Consequences of the Use of Metals in Dentistry*. Amsterdam: Free University Press, 1989: 32–65.

15 Peters MS, Schioeter AL, van Hale HM *et al*. Pacemaker contact sensitivity. *Contact Dermatitis* 1984; **11**: 214–8.

16 Wertman B, Azarbal B, Riedl M, Tobis J. Adverse events associated with nickel allergy in patients undergoing percutaneous atrial septal defect or patent foramen ovale closure. *J Am Coll Cardiol* 2006; **47**: 1226–7.

17 Romaguera C, Grimalt F, Viloplana J. Nickel dermatitis from an infusion needle. *Contact Dermatitis* 1985; **12**: 181.

18 Koizumi H, Tomoyori T, Kumahn M *et al*. Acupuncture needle dermatitis. *Contact Dermatitis* 1989; **21**: 352.

19 Koster R, Vieluf D, Kiehn M *et al*. Nickel and molybdenum contact allergies in patients with coronary in-stent restenosis. *Lancet* 2000; **356**: 1895–7.

20 Keane FM, Morris SD, Smith HR, Rycroft RJ. Allergy in coronary in-stent restenosis. *Lancet* 2001; **357**: 1205–6; discussion 6–7.

21 Norgaz T, Hobikoglu G, Serdar ZA *et al*. Is there a link between nickel allergy and coronary stent restenosis? *Tohoku J Exp Med* 2005; **206**: 243–6.

22 Hillen U, Haude M, Erbel R, Goos M. Evaluation of metal allergies in patients with coronary stents. *Contact Dermatitis* 2002; **47**: 353–6.

23 Svedman C, Tillman C, Gustavsson CG *et al*. Contact allergy to gold in patients with gold-plated intracoronary stents. *Contact Dermatitis* 2005; **52**: 192–6.

Palladium [1]

Chemistry. Palladium is a relatively inexpensive metal of the platinum group of elements.

Prevalence. Of patients undergoing routine patch testing to palladium chloride, 3–8% were shown to be allergic [2].The sensitization rate is reported to be increasing [3]. Nearly always there is concomitant sensitivity to nickel, and guinea-pig and clinical studies have suggested this may be a true cross-reaction [4,5]. There are, however, mixed views as to whether this association is concomitant sensitivity, cross-reactivity, or contamination of palladium chloride by nickel sulphate [6–8].

Occurrence. Palladium is increasingly used in dental alloys, prostheses and industry [3]. It can be used as a whitener in white gold. Occupationally, its main uses are in electrical components and as a catalyst.

Clinical features. The clinical relevance of a positive palladium chloride patch-test reaction is questionable in many instances, and

may just be a reflection of nickel allergy. Stomatitis and lichen planus have nevertheless been related to palladium in dental materials [9,10]. Removal of prostheses or dental alloys containing palladium may need to be considered in these instances. A granulomatous reaction after ear piercing has also been seen with palladium allergy [11].

Patch tests. Palladium chloride is normally tested at 1% in petrolatum.

References

1 Lidén C. Metals. In: Frosch PJ, Menné T, Lepoittevin J-P, eds. *Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 566–7.
2 Aberer W, Holub H, Strohal R *et al*. Palladium in dental alloys: the dermatologists' responsibility to warn? *Contact Dermatitis* 1993; **28**: 163–5.
3 Larese Filon F, Uderzo D, Bagnato E. Sensitization to palladium chloride: a 10-year evaluation. *Am J Contact Dermatitis* 2003; **14**: 78–81.
4 Wahlberg JE, Boman AS. Cross-reactivity to palladium and nickel studied in the guinea pig. *Acta Derm Venereol (Stockh)* 1992; **72**: 95–7.
5 Hindsén M, Spirén A, Bruze M. Cross-reactivity between nickel and palladium demonstrated by systemic administration of nickel. *Contact Dermatitis* 2005; **53**: 2–8.
6 Kanerva L, Kerosuo H, Kullaa A *et al*. Allergic patch test reactions to palladium chloride in schoolchildren. *Contact Dermatitis* 1996; **34**: 39–42.
7 Kranke B, Aberer W. Multiple sensitivities to metals. *Contact Dermatitis* 1996; **34**: 225.
8 Todd DJ, Burrows D. Patch testing with pure palladium metal in patients with sensitivity to palladium chloride. *Contact Dermatitis* 1992; **26**: 327–31.
9 Downey D. Contact mucositis due to palladium. *Contact Dermatitis* 1989; **21**: 54.
10 Murao Y, Yamada S, Kameyoshi Y, Yamamoto S. A case of generalized lichen planus due to palladium in dental metals. *Environ Dermatol* 1995; **2**: 197–203.
11 Goossens A, De Swerdt A, De Coninck K *et al.* Allergic contact granuloma due to palladium following ear piercing. *Contact Dermatitis* 2006; **55**: 338–41.

Gold [1]

Chemistry. Metallic gold is soft, malleable and ductile. It is stable and resistant to corrosion. Its strength is increased when alloyed with other metals. Gold salts, such as gold trichloride and potassium dicyanoaurate, are recognized as sensitizing as well as irritant.

Occurrence. Metallic gold is mainly encountered in jewellery, stents and dental materials. Gold salts are used in the plating, electronics, photographic, glass and porcelain industries [1].

Prevalence. Metallic gold has, until recently, been regarded as safe and very unlikely to sensitize. However, when gold sodium thiosulphate was added to the standard patch-test series, positive reactions were obtained in 8.6% of a series of Swedish patients [2], and subsequent surveys of various selected subgroups recorded a frequency of positive reactions ranging from 1 to 23% [1]. There is a relationship between the amount of dental gold and frequency of allergy [3]. There is a female predominance, and where relevance has been found it has usually been in the context of jewellery or gold dental work [4]. However, the allergic mechanism behind the positive patch tests, and their relevance, have been questioned [4,5].

Clinical features. In our experience a relevance for a gold sodium thiosulphate positive patch test is found infrequently, and generally these patients can wear jewellery and have gold dental fillings without problems [2,4]. Nevertheless, analysis of the involved anatomical sites has been undertaken by others who have found that involvement of fingers, ear lobes and eyes by dermatitis predominates [4]. A seborrhoeic eczema pattern has been described [6], as have persistent papules and nodules on the ear lobes, with lymphomatoid or granulomatous histology [7,8]. Reported oral manifestations of allergy have included erythema, burning mouth, erosions, ulceration, orofacial granulomatosis and lichen planus-like lesions [9–12].

The relationship between gold stents and allergy is discussed on p. 26.37.

Sodium aurothiomalate injections for rheumatoid arthritis have induced systemic contact dermatitis and 'fever' in those previously sensitized to gold [13].

Acral dermatitis has been described from allergy to gold salts in the gilding industry [14].

Patch tests. Many gold salts have been used for patch testing, but most centres now use gold sodium thiosulphate 0.5% in petrolatum. Late reactions are common and an additional 7-day or even 2- or 3-week reading has been advised [15]. The appearance of a positive patch test may be 'dermal', with erythema and oedema but no vesiculation, and persistent patch-test reactions are well recognized [15]. The controversy over the debatable relevance has led many to advise against routine standard-series screening for gold allergy [5].

References

1 Lidén C. Metals. In: Frosch PJ, Menné T, Lepoittevin J-P, eds. *Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 563–5.
2 Björkner B, Bruze M, Möller H. High frequency of contact allergy to gold sodium thiosulfate: an indication of gold allergy? *Contact Dermatitis* 1994; **30**: 144–51.
3 Ahlgren C, Ahnlide I, Björkner B *et al*. Contact allergy to gold is correlated to dental gold. *Acta Derm Venereol* 2002; **82**: 41–4.
4 Bruze M, Edman B, Björkner B *et al*. Clinical relevance of contact allergy to gold sodium thiosulfate. *J Am Acad Dermatol* 1994; **31**: 579–83.
5 Bruze M, Andersen KE. Gold: a controversial sensitizer. European Environmental and Contact Dermatitis Research Group. *Contact Dermatitis* 1999; **40**: 295–9.
6 McKenna KE, Dolan O, Walsh MY *et al*. Contact allergy to gold sodium thiosulfate. *Contact Dermatitis* 1995; **32**: 143–6.
7 Fleming C, Burden D, Fallowfield M *et al*. Lymphomatoid contact reaction to gold earrings. *Contact Dermatitis* 1997; **37**: 298–9.
8 Armstrong DK, Walsh MY, Dawson JF. Granulomatous contact dermatitis due to gold earrings. *Br J Dermatol* 1997; **136**: 776–8.
9 Laeijendecker R, van Joost T. Oral manifestations of gold allergy. *J Am Acad Dermatol* 1994; **30**: 205–9.
10 Alanko K, Kanerva L, Jolanki R *et al*. Oral mucosal diseases investigated by patch testing with a dental screening series. *Contact Dermatitis* 1996; **34**: 263–7.
11 Torgerson RR, Davis MD, Bruce AJ *et al.* Contact allergy in oral disease. *J Am Acad Dermatol* 2007; **57**: 315–21.
12 Lazarov A, Kidron D, Tulchinsky Z, Minkow B. Contact orofacial granulomatosis caused by delayed hypersensitivity to gold and mercury. *J Am Acad Dermatol* 2003; **49**: 1117–20.
13 Möller H, Ohlsson K, Linder C *et al*. The flare-up reactions after systemic provocation in contact allergy to nickel and gold. *Contact Dermatitis* 1999; **40**: 200–4.
14 Nava C, Briatico Vangosa G. Allergy to gold salts. *Med Lavoro (Milano)* 1971; **62**: 572–5.

15 Bruze M, Hedman H, Björkner B, Möller H. The development and course of test reactions to gold sodium thiosulfate. *Contact Dermatitis* 1995; **33**: 386–91.

Mercury [1]

Chemistry. The metal and its inorganic salts, for example corrosive sublimate ($HgCl_2$), calomel (HgCl), fulminate ($Hg(CNO)_2$) and ammoniated mercury ($HgCl.2NH_4Cl$), as well as organic compounds (e.g. mercurochrome, thimerosal and phenylmercuric salts; see p. 26.57), may all sensitize.

Occurrence. The metal is used in thermometers, instruments and amalgam (alloy of silver or copper and mercury) for filling teeth. Mercury and inorganic mercurials may be used in disinfectants, fungicides, herbicides, insecticides, detonators, emulsion paints and jewellery, as well as in the production of caustic soda and chlorine. Red mercuric sulphide (cinnabar, HgS) is used in red tattoos and in artists' paints.

Organic mercurials may be found in topical and parenteral medicaments (see p. 26.57). Ammoniated mercury has been used in the topical treatment of psoriasis, although concerns about toxicity have led to its withdrawal in the UK. Mercury and ammoniated mercury have been used in skin lightening creams.

Clinical features. Contact dermatitis is only rarely seen on the skin from mercury and inorganic mercurials in the UK but amalgam fillings in patients already sensitized to mercury have caused local mucosal reactions and stomatitis which settled when they were removed [2]. Hypertrophic amalgam dermatitis simulating carcinoma of the tongue has been described in one patient [3]. Perioral dermatitis after dental filling may also occur [2].

There are many reports of oral lichen planus in association with amalgam fillings [4,5] but the relationship is not consistent [6,7]. Patch tests to mercury are frequently positive when lichen planus is adjacent to amalgam fillings, but less so when there is not a close anatomical relationship [5]. The disorder is more apparent when there is corrosion [8]. In many sensitized subjects the condition will improve or settle when the amalgam is removed [5,9]. The causes of lichen planus are nevertheless likely to be multifactorial [5].

The relationship between oral inflammations, burning mouth syndrome and mercury allergy is contentious [6,10,11], but some individuals with mercury allergy have responded to amalgam removal. Orofacial granulomatosis has also been seen in association with mercury allergy and has resolved after removal of amalgam fillings [6,12].

Generalized exanthems and erythema multiforme have been reported from mercury exposure, including inhalation, dental fillings, following the breakage of thermometers in the mouth and also the use of an antiparasitic powder for the treatment of crab lice [13,14]. Recalcitrant eczemas in mercury-sensitized individuals are recorded as clearing after removal of mercury amalgam fillings [15], although in most cases systemic reactions from amalgam seem to develop a few hours after insertion or removal and settle after 10–14 days [16]. In our view, malaise and general ill health are not related to allergy to mercury in amalgams.

Red mercuric sulphide (cinnabar) in a tattoo may induce granulomatous reactions in allergic subjects [17]. We have seen several granulomatous and lichenoid reactions confined to the red parts of tattoos but none of our patients has been allergic to mercurials.

Patch tests. Mercury is normally tested at 0.5% in petrolatum, mercurochrome 2% in petrolatum or aqueous, mercuric chloride 0.1% in petrolatum and ammoniated mercury 2% in petrolatum. However, mercury compounds can be irritant, and aqueous solutions of mercury salts may react with aluminium in Finn chambers to cause false-positive reactions [2]. Patch testing with both mercury and ammoniated mercury is suggested if allergy is suspected [2].

References

1 Burrows D. Mischievous metals: chrome, cobalt, nickel and mercury. *Clin Exp Dermatol* 1989; **14**: 266–72.
2 Handley J, Todd D, Burrows D. Mercury allergy in a contact dermatitis clinic in Northern Ireland. *Contact Dermatitis* 1993; **29**: 258–61.
3 Zenarola P, Lomuto M, Bisceglia M. Hypertrophic amalgam dermatitis of the tongue simulating carcinoma. *Contact Dermatitis* 1993; **29**: 157–8.
4 Koch P, Baumer FA. Oral lichenoid lesions, mercury hypersensitivity and combined hypersensitivity to mercury and other metals: histologically-proven reproduction of the reaction by patch testing with metal salts. *Contact Dermatitis* 1995; **33**: 323–9.
5 Thornhill MH, Pemberton MN, Simmons RK, Theaker ED. Amalgam-contact hypersensitivity lesions and oral lichen planus. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2003; **95**: 291–9.
6 Khamaysi Z, Bergman R, Weltfriend S. Positive patch test reactions to allergens of the dental series and the relation to the clinical presentations. *Contact Dermatitis* 2006; **55**: 216–8.
7 Hietanen J, Pihlman K, Forstrom L *et al*. No evidence of hypersensitivity to dental restorative metals in oral lichen planus. *Scand J Dent Res* 1987; **95**: 320–7.
8 Martin MD, Broughton S, Drangsholt M. Oral lichen planus and dental materials: a case-control study. *Contact Dermatitis* 2003; **48**: 331–6.
9 Henriksson E, Mattsson U, Håkansson J. Healing of lichenoid reactions following removal of amalgam. A clinical follow-up. *J Clin Periodontol* 1995; **22**: 287–94.
10 Pigatto PD, Guzzi G, Persichini P, Barbadillo S. Recovery from mercury-induced burning mouth syndrome due to mercury allergy. *Dermatitis* 2004; **15**: 75–7.
11 Bergdahl BJ, Anneroth G, Anneroth I. Clinical study of patients with burning mouth. *Scand J Dent Res* 1994; **102**: 299–305.
12 Skoglund A, Egelrud T, Guttman-Yassky E *et al*. Resolution of orofacial granulomatosis with amalgam removal. *J Eur Acad Dermatol Venereol* 2003; **17**: 344–7.
13 Vena GA, Foti C, Grandolfo M, Angelini G. Mercury exanthem. *Contact Dermatitis* 1994; **31**: 214–6.
14 Lerch M, Bircher AJ. Systemically induced allergic exanthem from mercury. *Contact Dermatitis* 2004; **50**: 349–53.
15 Johnson HH, Schonberg IL, Bach NF. Chronic atopic eczema with pronounced mercury sensitivity: partial clearing after extraction of teeth containing mercury amalgam. *Arch Derm Syph* 1951; **63**: 279–80.
16 Thomson J, Russell JA. Dermatitis due to mercury following amalgam dental restorations. *Br J Dermatol* 1970; **82**: 292–7.
17 Levy J, Sewell M, Goldstein N. A short history of tattooing. *J Dermatol Surg Oncol* 1979; **5**: 851–3.

Aluminium

Occurrence and clinical features. Aluminium is widely used but contact allergy is very rare. Most reported cases are from aluminium-adsorbed vaccines and parenteral solutions used for hyposensitization, with granulomatous reactions at the injection site

[1,2]. It is found in antiperspirants, and axillary dermatitis (usually irritant) may occur. Allergy in a child with chronic otitis externa treated with aluminium acetate eardrops has been seen [3].

Patch tests. As Finn chambers are aluminium, a positive patch test, often annular in configuration, may develop under every single test site in sensitized persons. Patch testing is best undertaken with plastic chambers if this diagnosis is suspected. Pure aluminium metal or salts, for example aluminium acetate 10% aqueous or aluminium chloride 2% aqueous, can be used for testing.

References

1 Bergfors E, Björkelund C, Trollfors B. Nineteen cases of persistent pruritic nodules and contact allergy to aluminium after injection of commonly used aluminium-adsorbed vaccines. *Eur J Pediatr* 2005; **164**: 691–7.

2 Hindsén M. Contact allergy to aluminium in patients hyposensitized with aluminium-containing hyposensitizing extracts. *Contact Dermatitis* 2005; **53**: 301–2.

3 O'Driscoll JB, Beck MH, Kesseler ME, Ford G. Contact sensitivity to aluminium acetate eardrops. *Contact Dermatitis* 1991; **24**: 156–7.

Other metals

Copper is a ubiquitous metal found especially in coinage, jewellery, pipes, electrical equipment and wiring. Its salts are used in insecticides, fungicides, wood preservatives, food processing, fertilizer and fur dyes. Contact allergy is very rare. Dermatitis has been reported from copper intrauterine contraceptive devices and proven by patch testing and resolution of the dermatitis after removal [1,2].

Other metals used in dentistry may have the potential to cause contact allergy, including platinum, rhodium, indium and iridium [3–5].

References

1 Barranco VP. Eczematous dermatitis caused by internal exposure to copper. *Arch Dermatol* 1972; **106**: 386–7.

2 Romaguera C, Grimalt F. Contact dermatitis from a copper-containing intrauterine contraceptive device. *Contact Dermatitis* 1981; **7**: 163–4.

3 Koch P, Baum HP. Contact stomatitis due to palladium and platinum in dental alloys. *Contact Dermatitis* 1996; **34**: 253–7.

4 Vilaplana J, Romaguera C, Cornellana F. Contact dermatitis and adverse oral mucous membrane reactions related to the use of dental prostheses. *Contact Dermatitis* 1994; **30**: 80–4.

5 Marcusson JA, Cederbrant K, Heilborn J. Indium and iridium allergy in patients exposed to dental alloys. *Contact Dermatitis* 1998; **38**: 297–8.

Fragrances, balsams, flavouring agents and spices [1,2]

Perfumes are blends of ingredients producing an odour intended to be aesthetically pleasant or to mask other less pleasant odours. The components are either of natural origin or produced synthetically. Natural sources include extracts from plants, trees, lichens and animals (e.g. musk, civet) [1]. Commercially available perfumes are mixtures of essential oils from these sources and synthetic compounds, with usually at least 10, and up to several hundred, ingredients [3]. The scent is determined by the mixture of volatile substances. 'Fixatives' are added to delay evaporation, influencing the quality and persistence of the perfume. Common 'fixatives' are balsams, benzyl benzoate, benzyl salicylate and synthetic musks.

Tree balsams contain many different fragrance and flavouring components. Balsam of Peru is one such material that has been studied in depth [4]. It comes from a tree, *Myroxylon pereirae*, that grows in Central America (not Peru!). The balsam was given its name because it was packed in, and shipped from, Peru to Europe [5]. It was widely used earlier this century for treating wounds, and also for scabies [4]. Its composition is still not completely known, but the balsam does contain benzyl benzoate, benzyl cinnamate, cinnamic acid alcohol and aldehyde, benzoic acid, vanillin, farnesol and nerolidol [6]. It may cross-sensitize with resorcinol monobenzoate used in cellulose ester plastics [7]. Other related balsams include balsam of Tolu, balsam of spruce, gum benzoin and storax.

Flavours may similarly be of natural or synthetic origin. Examples of natural flavours include citrus fruit peel, peppermint oil, spearmint and vanilla. Natural spices include nutmeg, mustard, cinnamon, cloves and oil of juniper. In the modern food industry a large number of synthetic flavouring agents are used. As with perfumes, flavours may be complicated mixtures.

Prevalence. In general, as measured by the frequency of allergic reactions in routinely patch-tested patients, fragrances are the second most common allergen (after nickel). Studies have indicated that fragrance allergy affects in the region of 1% of the adult population [8], whereas children and adolescents have shown rates of 1.8% [9]. In those clinics investigating allergic contact dermatitis the rates have varied between 5.7 and 17.4%, with roughly 10% being an average for European investigation clinics [1]. Sex incidence has generally only shown a slight preponderance of females, and in some instances it has been equal [10]. There is evidence from some centres that perfume allergy is increasing quite significantly [1].

The pattern of allergy may change. In one UK centre, although the level of allergy to the test allergen Fragrance mix I remained stable, a significant reduction of cinnamic aldehyde and cinnamic alcohol allergy occurred when components of the mix were tested [10]. This is thought to reflect a decreasing concentration of these materials in cosmetics in the last 17 years.

Routine patch testing with balsam of Peru as a marker of allergy to perfume and certain flavours has shown a positive rate of allergy of around 4% [11]. It was thought to be a decreasingly relevant marker of perfume allergy but a recent study from Finland has revealed a sharp rise in the frequency of allergy, perhaps in parallel with increased exposure to relevant components [12].

Fragrance labelling regulations have now been extended in the EU. One or more of 26 named fragrance allergens will be found on the ingredient label if present at 10 ppm or more in leave-on products and 100 ppm or more in rinse-off products. This should improve evaluation and surveillance of fragrance allergy within the population in the future.

Occurrence. Fragrances are ubiquitous. Perfumes, cosmetics, moisturizers, deodorants, aftershaves, soaps, bath additives, aromatherapy oils and toilet tissues and wipes are typical sources. Medicaments and work creams and cleansers often contain perfume. In the domestic environment cleansers, fabric conditioners and polishes may all be perfumed. At work some materials



Fig. 26.15 An urticated contact dermatitis in a patient allergic to fragrance. (Courtesy of Dr J.D. Wilkinson, Amersham General Hospital, Amersham, UK.)

(e.g. coolant oils) may contain a masking perfume [13]. Limonene is used in industrial and histology solvents and degreasing agents. D-Limonene and other terpenes have been shown to act as allergens when they become oxidized and may therefore only be allergenic with prolonged exposure to air [14]. Auto-oxidation of terpenes may make a significant contribution to the allergenicity of perfumes [15].

Flavours and spices are to be found in foods, beverages, lipsalves and dental products, including toothpastes.

Clinical features. Analysis of common patterns of perfume dermatitis has shown a tendency to involve the hands, face and neck (Fig. 26.15) in women; hands, face and lower legs in men; and axillae in both sexes [16]. A streaky pattern may be observed. There is evidence that allergy to more than one perfume component may result in a synergistic effect [1].

Connubial (consort) allergy is well recognized [17], and allergy to lavender applied to a pillow has been described [18]. Many affected subjects suspect their allergy, but a substantial number do not. Furthermore, those who are aware of their allergy may continue to suffer dermatitis by failing to take appropriate avoidance measures, for example by unwittingly applying perfumed medicaments and cosmetics to their skin. Aromatherapists and their clients are liable to sensitization in sites where there is contact with the essential oils [19,20].

D-Limonene in its oxidized state may cause allergic occupational hand dermatitis [14], which can also develop in bakers and chefs as a result of contact with sensitizing flavouring agents [21]. Peeling of citrus fruit in the domestic environment may also induce allergic hand dermatitis.

Cheilitis may be a reflection of allergy to flavouring agents in toothpastes [22,23], lipsalves [24], food and drink [25]. Gingivitis has occurred from allergy to eugenol in dental cement [26], and cinnamon has induced oral blisters, erosions and lichen planus [27,28].

Balsam of Peru is still used as a medicament, particularly in haemorrhoid preparations, and allergy is therefore relevant to perianal problems. Sensitizing balsams are also used in medicaments and balms for wounds, sprains and joint pains, particularly in the Far East [29]. Tincture of benzoin is used in a similar way, and may also be used under orthopaedic plaster casts [30]. Vesicular hand dermatitis has been related to dietary intake of flavours related to balsam of Peru [31].

Musk ambrette is a synthetic perfume component responsible for photoallergy, and although its use has been stopped in the Western world it may still be present in perfumed materials from other parts of the world.

Fragrance-allergic subjects appear to be at increased risk of more frequent and more severe eye and respiratory symptoms than would be expected by chance [32].

Avoidance. Perfumes are marketed as concentrated liquids and in more diluted form such as eau de toilette, or as sprays, and all should be avoided. Application of perfume to clothing may still cause problems in allergic subjects, who often believe they will only react if perfume is applied directly to the skin. Occasionally, affected subjects are able to use a specific perfume without any problem. Other perfumed skin products to be avoided include deodorants, aftershaves, talcum powders, soaps and bath additives.

The presence of perfume in a cosmetic or wet wipe will be denoted by the INCI term 'parfum', and the presence of balsam of Peru by the INCI term '*Myroxylon pereirae*', and fragrance-allergic patients should avoid these products. Some cosmetics' labels may suggest they are fragrance-free, yet the products are found to contain perfume when the full ingredient label is studied, reinforcing the need to avoid unlabelled products. Some plant extracts may potentially be a hidden source of fragrance in cosmetics as the INCI nomenclature may use the plant's Linnaean name rather than the word parfum. Some extracts, however, may only contain traces of fragrance chemicals.

Surprisingly, some prescribable moisturizers, emollients, bath additives and corticosteroids, as well as over-the-counter medicaments, contain perfume. Allergic patients with ongoing problems should be counselled carefully about avoidance of these sources.

In the domestic situation, perfume-containing sprays such as air fresheners, insect repellents and hairsprays should be avoided, as should skin contact with perfumed household cleansing products and polishes. Unperfumed soaps or soap substitutes are required for washing the skin. The levels of perfume residues from washing powders and fabric conditioners for clothes are probably too low to cause clinical problems [33], but in those with a clothing pattern of eczema extra rinsing and avoidance of fabric conditioners can be considered. Peeling citrus fruit with bare hands should be avoided by those with hand eczema and allergy to balsam of Peru.

In the occupational environment many cleansers, conditioning creams and barrier creams are perfumed, and similar avoidance measures are needed. Some work materials, including cutting oils and paints, may contain masking perfume and enquiries may be necessary to establish their components.

Dietary measures may be helpful not only for oral and perioral allergy from flavours but also in those with vesicular palmar eczema associated with balsam of Peru allergy; however, the response can be disappointing [34,35].

Table 26.4 Ingredients of Fragrance mix I*.

Substance	Concentration† (%)
Cinnamaldehyde	1
Cinnamyl alcohol	1
Eugenol	1
Amyl cinnamaldehyde	1
Hydroxycitronnellol	1
Geraniol	1
Isoeugenol	1
Oak moss absolute (*Evernia prunastri*)	1

* Fragrance mix allergens contain sorbitan sesquioleate (5% in petrolatum) as an emulsifier.
† All ingredients are diluted in petrolatum.

Table 26.5 Ingredients of Fragrance mix II.

Substance	Concentration* (%)
Alpha-hexyl cinnamldehyde	5
Citral	1
Citronellol	0.5
Farnesol	2.5
Coumarin	2.5
Hydroxymethylpentylcyclohexenecarboxaldehde (Lyral)	2.5

* All ingredients are diluted in petrolatum.

Patch tests. The complexity of perfumes is such that there is not a perfect screening patch test for perfume allergy. Before 1977, the main recommended marker for perfume allergy was balsam of Peru, which is still advised. It is tested at 25% in petrolatum, but was thought to identify only 50% of perfume-allergic subjects [36]. Screening for perfume allergy was significantly advanced by the development of fragrance mix as a result of Larsen's studies [37,38]. He advised a mix of eight substances (Table 26.4). The original mix has been modified so that now each component is present at 1% concentration [39]. The mix now known as Fragrance mix I contains an emulsifier, sorbitan sesquioleate at 5%, which is reported to have improved the return of identified perfume allergies [40]. Fragrance mix I will identify approximately 75% of perfume-allergic subjects, although this figure was reported to increase to 90% if balsam of Peru is also tested [41,42]. However, more recently efforts have been made to improve identification of allergic subjects following studies on a range of fragrances [43,44]. In particular there was evidence from Europe that 4-(4-hydroxy-4-methylpentyl)3-cyclohexine carboxyaldehyde (Lyral®) was a perfume sensitizer that might be missed if reliance was placed on Fragrance mix I and balsam of Peru testing [41,45]. This and five other fragrances (citral, farnesol, coumarin, citronellal and α-hexyl-cinnamicaldehyde) have been combined to make a further mix for patch testing known as Fragrance mix II as a result of these studies (Table 26.5). It is anticipated that by including this in the standard series identification of fragrance allergy will be improved.

Other potentially missed fragrance allergens include jasmine, sandalwood, spearmint oil, lemon grass oil, narcissus and ylang-ylang oil [42,46]. Oxidized terpenes, especially D-limonene, may also be missed, particularly as there is no commercial source from which to obtain these for patch testing. An improved return will be achieved by testing with patients' own perfumed products [47].

Both Fragrance mix I and II may give false-positive irritant reactions, and testing the ingredients separately may help to avoid these. However, when individual materials are mixed they may combine in such a way as to produce compound allergy, or other synergistic effects inducing a true allergic reaction, despite the components themselves being negative. The reverse situation (quenching), that is the mix is negative and one or more components positive, has been reported, but also questioned [48]. Nevertheless, it is worthwhile testing with the breakdown in addition to the fragrance mix when perfume allergy is suspected.

An extended additional flavours series of patch tests can be developed for those with cheilitis or oral problems.

References

1 Johansen JD. Contact allergy to fragrances. Clinical and experimental investigations of the fragrance mix and its ingredients. *Contact Dermatitis* 2002; **46** (Suppl. 3): 1–31.
2 Beck MH. Fragrance allergy. *Br J Dermatol* 2000; **142**: 203–4.
3 Harder U. The art of creating a perfume. In: Frosch PJ, Johansen JD, White IR, eds. *Fragrances: Beneficial and Adverse Effects.* Berlin: Springer, 1998: 3–5.
4 Hjorth N. *Eczematous Allergy to Balsams, Allied Perfumes and Flavouring Agents: with Special Reference to Balsam of Peru* [thesis]. University of Copenhagen, Copenhagen, 1961.
5 Amado A, Taylor JS. Balsam of Peru or Balsam of El Salvador? *Contact Dermatitis* 2006; **55**: 119.
6 Andersen KE, White IR, Goossens A. Allergens from the standard series. In: Frosch PJ, Menné T, Lepoittevin J-P, eds. *Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 462–6.
7 Jordan WP Jr. Resorcinol monobenzoate, steering wheels, Peruvian balsam. *Arch Dermatol* 1973; **108**: 278.
8 Nielsen NH, Menné T. Allergic contact sensitization in an unselected Danish population. The Glostrup Allergy Study, Denmark. *Acta Derm Venereol (Stockh)* 1992; **72**: 456–60.
9 Mørtz CG. *The Prevalence of Atopic Dermatitis, Hand Eczema, Allergic Contact Dermatitis, Type IV and Type I Sensitisation in 8th Grade School Children in Odense* [PhD thesis]. Faculty of Health Sciences, University of Southern Denmark, 1999.
10 Buckley DA, Wakelin SH, Seed PT *et al*. The frequency of fragrance allergy in a patch-test population over a 17-year period. *Br J Dermatol* 2000; **142**: 279–83.
11 Christophersen J, Menné T, Tanghoj P *et al*. Clinical patch test data evaluated by multivariate analysis. Danish Contact Dermatitis Group. *Contact Dermatitis* 1989; **21**: 291–9.
12 Hasan T, Rantanen T, Alanko K *et al*. Patch test reactions to cosmetic allergens in 1995–1997 and 2000–2002 in Finland—a multicentre study. *Contact Dermatitis* 2005; **53**: 40–5.
13 Owen CM, August PJ, Beck MH. Contact allergy to oak moss resin in a soluble oil. *Contact Dermatitis* 2000; **43**: 112.
14 Karlberg AT, Dooms-Goossens A. Contact allergy to oxidized *d*-limonene among dermatitis patients. *Contact Dermatitis* 1997; **36**: 201–6.
15 Matura M, Sköld M, Börje A *et al*. Selected oxidized fragrance terpenes are common contact allergens. *Contact Dermatitis* 2005; **52**: 320–8.
16 Edman B. Sites of contact dermatitis in relationship to particular allergens. *Contact Dermatitis* 1985; **13**: 129–35.
17 Held JL, Ruszkowski AM, Deleo VA. Consort contact dermatitis due to oak moss. *Arch Dermatol* 1988; **124**: 261–2.
18 Coulson IH, Khan AS. Facial 'pillow' dermatitis due to lavender oil allergy. *Contact Dermatitis* 1999; **41**: 111.

19 Keane FM, Smith HR, White IR, Rycroft RJ. Occupational allergic contact dermatitis in two aromatherapists. *Contact Dermatitis* 2000; **43**: 49–51.
20 Boonchai W, Iamtharachai P, Sunthonpalin P. Occupational allergic contact dermatitis from essential oils in aromatherapists. *Contact Dermatitis* 2007; **56**: 181–2.
21 Malten KE. Four bakers showing positive patch-tests to a number of fragrance materials, which can also be used as flavors. *Acta Derm Venereol Suppl (Stockh)* 1979; **59**: 117–21.
22 Sainio EL, Kanerva L. Contact allergens in toothpastes and a review of their hypersensitivity. *Contact Dermatitis* 1995; **33**: 100–5.
23 Francalanci S, Sertoli A, Giorgini S *et al*. Multicentre study of allergic contact cheilitis from toothpastes. *Contact Dermatitis* 2000; **43**: 216–22.
24 Ferguson JE, Beck MH. Contact sensitivity to vanilla in a lip salve. *Contact Dermatitis* 1995; **33**: 352.
25 Guin JD. Rosemary cheilitis: one to remember. *Contact Dermatitis* 2001; **45**: 63.
26 Silvestre JF, Albares MP, Blanes M *et al*. Allergic contact gingivitis due to eugenol present in a restorative dental material. *Contact Dermatitis* 2005; **52**: 341.
27 Hoskyn J, Guin JD. Contact allergy to cinnamal in a patient with oral lichen planus. *Contact Dermatitis* 2005; **52**: 160–1.
28 Nadiminti H, Ehrlich A, Udey MC. Oral erosions as a manifestation of allergic contact sensitivity to cinnamon mints. *Contact Dermatitis* 2005; **52**: 46–7.
29 Leow YH, Ng SK, Wong WK, Goh CL. Contact allergic potential of topical traditional Chinese medicaments in Singapore. *Am J Contact Dermatitis* 1995; **6**: 4–8.
30 James WD, White SW, Yanklowitz B. Allergic contact dermatitis to compound tincture of benzoin. *J Am Acad Dermatol* 1984; **11**: 847–50.
31 Veien NK, Hattel T, Justesen O *et al*. Reduction of intake of balsams in patients sensitive to balsam of Peru. *Contact Dermatitis* 1985; **12**: 270–3.
32 Elberling J, Linneberg A, Mosbech H *et al*. A link between skin and airways regarding sensitivity to fragrance products? *Br J Dermatol* 2004; **151**: 1197–203.
33 Corea NV, Basketter DA, Clapp C *et al*. Fragrance allergy: assessing the risk from washed fabrics. *Contact Dermatitis* 2006; **55**: 48–53.
34 Veien NK, Hattel T, Laurberg G. Can oral challenge with balsam of Peru predict possible benefit from a low-balsam diet? *Am J Contact Dermatitis* 1996; **7**: 84–7.
35 Niinimaki A. Double-blind placebo-controlled peroral challenges in patients with delayed-type allergy to balsam of Peru. *Contact Dermatitis* 1995; **33**: 78–83.
36 Larsen WG. Perfumes. In: Baran R, Maibach HI, eds. *Cosmetic Dermatology*. London: Martin Dunitz, 1994: 21–6.
37 Larsen WG. Perfume dermatitis: a study of 20 patients. *Arch Dermatol* 1977; **113**: 623–6.
38 Larsen WG. Perfume dermatitis. *J Am Acad Dermatol* 1985; **12**: 1–9.
39 Larsen WG. Detection of allergic dermatitis to fragrances. *Acta Derm Venereol Suppl (Stockh)* 1987; **134**: 83–6.
40 Frosch PJ, Pilz B, Burrows D *et al*. Testing with fragrance mix. Is the addition of sorbitan sesquioleate to the constituents useful? *Contact Dermatitis* 1995; **32**: 266–72.
41 Frosch PJ, Pilz B, Andersen KE *et al*. Patch testing with fragrances: results of a multicenter study of the European Environmental and Contact Dermatitis Research Group with 48 frequently used constituents of perfumes. *Contact Dermatitis* 1995; **33**: 333–42.
42 Larsen W, Nakayama H, Lindberg M *et al*. Fragrance contact dermatitis: a worldwide multicenter investigation (Part I). *Am J Contact Dermatitis* 1996; **7**: 77–83.
43 Frosch PJ, Pirker C, Rastogi SC *et al*. Patch testing with a new fragrance mix detects additional patients sensitive to perfumes and missed by the current fragrance mix. *Contact Dermatitis* 2005; **52**: 207–15.
44 Frosch PJ, Rastogi SC, Pirker C *et al*. Patch testing with a new fragrance mix—reactivity to the individual constituents and chemical detection in relevant cosmetic products. *Contact Dermatitis* 2005; **52**: 216–25.
45 Frosch PJ, Johansen JD, Menné T *et al*. Lyral is an important sensitizer in patients sensitive to fragrances. *Br J Dermatol* 1999; **141**: 1076–83.
46 Frosch PJ, Johansen JD, Menné T *et al*. Further important sensitizers in patients sensitive to fragrances. *Contact Dermatitis* 2002; **47**: 279–87.
47 Held E, Johansen JD, Agner T *et al*. Contact allergy to cosmetics: testing with patients' own products. *Contact Dermatitis* 1999; **40**: 310–5.
48 Basketter D. Quenching: fact or fiction? *Contact Dermatitis* 2000; **43**: 253–8.

Applied medicaments [1,2]

Prevalence and incidence. Of all allergic contact dermatitis about 15% is caused, or complicated, by sensitivity to medicaments, although this may be higher in susceptible patient populations. The literature on contact dermatitis abounds with reports of reactions to medicaments, and it is not possible to review all of these. It is doubtful whether the incidence has changed significantly, although the incidence of sensitivity to a particular allergen varies from country to country and from decade to decade, according to both local prescribing habits and the number of patients who are at high risk, for example with leg ulcers and stasis eczema, included in any series. Contact allergy to medicaments is also more common in an elderly population, particularly to fragrance, lanolin, local anaesthetics, neomycin and corticosteroids [3]. Cases are missed unless patch tests are routinely performed and if locally used medicaments are not included in a standard series. Meaningful sensitization indices for the various medicaments can be calculated only if prevalence of sensitivity is correlated with usage.

Clinical features. Certain sites appear to be prone to the development of allergic contact dermatitis from medicaments. This is probably the result of frequent medicament usage at these sites, occlusive skin conditions and pre-existing skin damage. Sensitization to medicaments is particularly common in patients with leg ulcers or eczema of the lower legs (Fig. 26.16), and is



Fig. 26.16 Medicament allergic contact dermatitis superimposed on stasis eczema. Topical antibiotics/antibacterials, preservatives, lanolin and other constituents of the medicament base are often to blame. (Courtesy of Dr J.D. Wilkinson, Amersham General Hospital, Amersham, UK.)



Fig. 26.17 Pruritus ani is often complicated by secondary contact dermatitis to local anaesthetics or other medicaments. (Courtesy of Dr J.D. Wilkinson, Amersham General Hospital, Amersham, UK.)

found in about half of those with chronic stasis eczema. Even weak allergens appear to sensitize if used on the lower leg. Contact dermatitis is also common in patients with chronic perianal inflammatory disorders (Fig. 26.17), including pressure sores, chronic otitis externa [4] and in those who frequently use ocular medicaments [5].

However, dermatitis from applied medicaments can develop anywhere. Sometimes, the sensitivity is obvious but often is occult and easily overlooked, and it will then be detected only by patch testing. In burns, the damaged skin may be incapable of reaction, and dermatitis may be apparent only at the periphery of the burn site.

Sensitivity to a topically applied medicament may result in several types of reaction.

1 Local aggravation, with increased itching and redness.
2 Spread to other regions, in most cases preceded by local aggravation. This is especially common in patients with stasis eczema or leg ulcers.
3 A local reaction may not develop, and dissemination may be the only sign of sensitivity. This typically occurs with creams and ointments containing a potent steroid capable of suppressing the reaction locally, but not in other regions.
4 Sensitization can also manifest merely as failure to respond to treatment. The original condition may worsen or fail to improve, without there being any acute flares or spread to arouse suspicion. This is seen mainly when there is a low degree of sensitivity and low concentration of allergens, typically with parabens and lanolin, or where the contact allergen is a corticosteroid.
5 Persistent generalized erythroderma is a rare manifestation of allergic contact sensitization to medicaments.
6 Contact urticarial reactions have also been reported.

Systemic reactions. Patients sensitized by the topical use of a drug may develop systemic reactions if that drug, or one that is closely related, is then given systemically. A pattern of dermatitis with erythema of the buttocks and flexural involvement elsewhere has been termed the 'baboon syndrome' (see p. 26.22). Widespread dermatitis or generalized exfoliative dermatitis has been reported following challenge with a systemic drug to which the patient already has contact allergy.

Other patients may develop a systemic reaction after topical application of a medicament. Anaphylactic reactions have been reported, for example following the topical use of bacitracin, cephalosporins, rifamycin and chlorhexidine. Erythema multiforme-like reactions to topical medicaments have also been reported. Some patients have positive patch-test reactions to a topically applied drug, having previously been sensitized by its systemic use.

Patients who have been sensitized by the topical use of promethazine hydrochloride may develop serious photosensitivity if the drug is given systemically. Care must always be taken in prescribing an antihistamine systemically if the patient is known to have been exposed to the same or a chemically similar drug topically. Patients who are known to be allergic to ethylenediamine should not be given antazoline hydrochloride, piperazine or several other antihistamines.

References

1 De Groot AC, Weyland JW, Nater JP. *Unwanted Effects of Cosmetics and Drugs Used in Dermatology*, 3rd edn. New York: Elsevier, 1994.
2 Brandao FM, Goossens A, Tosti A. Topical drugs. In: Frosch PJ, Menné T, Lepoittevin J-P, eds. *Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 623–52.
3 Green CM, Holden CR, Gawkrodger DJ. Contact allergy to topical medicaments becomes more common with age: an age-stratified study. *Contact Dermatitis* 2007; **56**: 229–31.
4 Yariktas M, Yildirim M, Doner F *et al*. Allergic contact dermatitis prevalence in patients with eczematous external otitis. *Asian Pac J Allergy Immunol* 2004; **22**: 7–10.
5 Jappe U, Uter W, Menezes de Padua CA *et al*. Allergic contact dermatitis due to beta-blockers in eye drops: a retrospective analysis of multicentre surveillance data 1993–2004. *Acta Derm Venereol* 2006; **86**: 509–14.

Avoidance and prognosis. Sensitization from a single constituent may lead to recurrent dermatitis due to its inclusion in several proprietary formulations. In only a few countries are the contents of a proprietary cream stated on the package or listed on the data sheet and, even then, the information is often insufficient, constituents sometimes being given as trade names or only 'active' ingredients listed. In order to reduce the risk of relapse, the ingredients of all topical medicaments should be established. Ideally, all topical medicaments, whether prescribed or purchased without a prescription, would exhibit full ingredient labelling.

It is also necessary to consider cross-sensitivity to other, untested medicaments. This has received particular study in relation to contact sensitivity to the aminoglycoside group of antibiotics. A

similar situation may develop in patients sensitive to the 'para' group of chemicals, with cross-sensitization between local anaesthetics, dyes, sulphonamides, UV filters, etc.

Patch tests. Patients with suspected contact dermatitis should be tested with all the medicaments they have applied. The information obtained in the history may be incomplete, and commonly used medicaments should also be routinely tested. It is often helpful to have a vehicle and medicament series, or several 'site' series with the ingredients of the most commonly used topical preparations in that geographical location. Testing to the medicament ('as is') may miss allergens, because they may be present in insufficient concentration. Where there is a high index of suspicion, the individual components should be obtained and appropriately diluted for patch testing.

It is important not to forget self-prescription of over-the-counter preparations. Popular habits of self-treatment vary from country to country and region to region. Knowledge of these habits is obtained by experience, but local pharmacists can often supply information. Certain remedies may be popular in one country but almost unknown in another. 'Natural' or herbal treatments are increasing in popularity. Some of these are irritant, and others, such as Chinese herbal remedies [1] and tea tree oil [2], contain allergens.

Various pharmaceutical developments have been associated with successive waves of dermatitis from applied medicaments; for example sulphonamides from 1945 to 1950, then antihistamine creams, and later neomycin and ethylenediamine. Sensitivity to neomycin, gentamicin, lanolin, balsams, mercurials and preservatives is still common today. Newer sensitizers include the imidazoles, topical non-steroidal anti-inflammatory drugs (NSAIDs), transdermal delivery systems and topical steroids. Photosensitivity also occurs with some topical NSAIDs. Less common medicament allergens are listed in Table 26.6.

Sensitivity may be confirmed in some patients exposed to drugs, particularly the penicillins, by *in vitro* lymphocyte transformation tests and, for type I reactions, by specific IgE assay. Skin tests may also sometimes be positive in those who have had eczematous or urticarial reactions to ingested drugs. Care must be taken in re-challenging anyone who has had a type I reaction because anaphylactic reactions may be induced. Guidelines for investigating potential drug reactions have been produced [3].

Medicament allergens included in the European Environmental and Contact Dermatitis Research Group-recommended European standard series include the following [4].

Neomycin 20% in petrolatum

Neomycin has two active components, neomycin B and neomycin C, which are stereoisomers. It cross-reacts with other aminoglycoside antibiotics. The pattern of cross-sensitivity has been studied in guinea pigs. Clinically, neomycin is known to cross-react frequently with kanamycin and framycetin (Soframycin), which would be anticipated with the latter as it consists almost entirely (99%) of neomycin B. Cross-sensitivity also occurs to a varying degree with gentamicin and tobramycin. Neomycin classically produces late reactions.

Clioquinol 3% in petrolatum

In areas where there is high use of chlorquinaldol the retention of the quinoline mix may be of value due to the lack of cross-reactions between it and clioquinol.

Benzocaine 5% in petrolatum

Experience suggests that, in the UK at least, the replacement of benzocaine with a mixture containing cinchocaine (dibucaine) 2.5% and amethocaine (tetracaine) 2.5% will double the yield of allergic positive reactions. Local anaesthetics are either of the ester or amide type, and cross-reactions can occur within groups. Although cinchocaine is an aminoalkylamide and lidocaine (lignocaine) is an aminoacylamide, most individuals do not cross-react. Ideally, any reaction to the mix should be followed up by testing to the constituents and to lidocaine. Not all reactions to local anaesthetic are detected by the mix and patch tests should always be dictated by the particular exposure of the patient.

Corticosteroids (tixocortol pivalate 0.1% in petrolatum and budesonide 0.01% in petrolatum) [5]

When testing with corticosteroids it is not unusual to see reflex vasodilatation following the steroid-induced vasoconstriction and this should not be interpreted as a positive reaction. Conversely, an annular response is frequently allergic, as a result of central suppression of the reaction by the corticosteroid.

A reaction to tixocortol pivalate almost invariably means that the patient is allergic to hydrocortisone. Although tixocortol pivalate is typically tested at 0.1%, if suspicion of allergy is high a 1% dilution should also be tested. In the UK, a reaction to budesonide almost certainly represents a cross-reaction to another corticosteroid, most likely an 'ester' such as hydrocortisone 17-butyrate or an 'acetonide' such as triamcinolone acetonide. A reaction to either of these steroids in the standard series should prompt further testing to an extended steroid series, as 50% of tixocortol pivalate-positive and 90% of budesonide-positive individuals react to other corticosteroids. Our experience suggests that although intradermal testing may have a role, testing other corticosteroids at 1% in ethanol is more sensitive. Together with knowledge of cross-reaction patterns [6], this helps in deciding what topical steroid to use as an alternative. Empirically, fluocinolone acetonide (Synalar) preparations react least frequently, and are available in a range of potencies. In view of the potential cross-reactivity between these two corticosteroids and prednisolone and its derivatives, it seems prudent to advise the use of either betamethasone or dexamethasone if a systemic steroid is needed, in order to reduce the risk of inducing a generalized dermatitis.

Although steroids are also applied topically to mucosal surfaces in the treatment of respiratory diseases, reports of contact allergy are rare. Indeed, individuals challenged with inhaled steroid to which they are sensitized typically develop a cutaneous but not a respiratory response. In contrast, there are reports of both immediate and delayed-type allergic reactions following various other systemic routes of administration.

Table 26.6 Other medicament allergens [7].

Antiandrogens

Spironolactone.

Antiseptic agents

There is a current vogue for the use of topical antiseptics in the domestic environment, and many who work in the health care and food industries are also exposed. Chlorocresol and chloroxylenol are both included in the British standard series [8]. Less common sensitizers are benzoyl peroxide used to treat acne, benzalkonium chloride, chloroacetamide, nitrofurazones in ear drops, benzyl alcohol [9], iodine, chlorhexidine, proflavine, resorcinol, glutaraldehyde as sterilizing agent, 4-aminoquinaldine, triclosan [10] and isopropyl alcohol in medical skin wipes. It should be remembered that many of these substances are irritant and that as a consequence positive patch tests should be interpreted with caution [11].

Antibiotics

Common sensitizers are the aminoglycosides, including gentamicin and framycetin, fusidic acid, minocycline and chloramphenicol. Although neomycin is in many standard series, fusidic acid is more selectively included dependent on use [8]. Less common are penicillins, metronidazole and tetracyclines (e.g. as syrups), bacitracin, azithromycin, vancomycin and clindamycin. Streptomycin is a strong sensitizer, but dermatitis is now rare because of more careful use.

Antimycotic agents

Most antimycotics have sensitizing properties: tolnaftate, nystatin, amorolfine, undecylenic acid and naftifine. Imidazoles are rare but consistent sensitizers and cross-reactions are frequent.

Antiviral agents

Aciclovir, interferons, amantadine, tromantadine, lamivudine, trifluridine and idoxuridine have all been reported as causing contact dermatitis.

Antihistamines

The phenothiazines are the strongest sensitizers, but all can sensitize when used topically, including doxepin.

Cytotoxic drugs

Topical mechlorethamine (nitrogen mustard), carmustine and 5-fluorouracil, as well as intravesical mitomycin, can sensitize. Occupational dermatitis has been seen with diethyl-β-chloroethylamine, and contact urticaria from cisplatin.

Immunosuppressive agents

Occupational contact dermatitis has been described from azathioprine. Topical macrolides are increasingly used in the treatment of eczema and as a potential alternative in individuals sensitized to topical corticosteroids. Allergy to pimecrolimus and tacrolimus has been reported and they may cross-react [12].

Non-steroidal anti-inflammatory drugs [13]

The arylpropionic acid derivatives, particularly ketoprofen but also ibuprofen, ibuproxam and tiaprofenic acid, cause contact and photocontact dermatitis, with cross-reactivity, if used topically. Topical benzydamine is also a contact and photocontact sensitizer, and phenylbutazone is a cause of erythema multiforme-like reaction.

Ophthalmic preparations [14]

Treatments for glaucoma, particularly β-blockers, including timolol and levobunolol, cause problems. Patch tests with the eye drops may give false-negative reactions. Preferably test with higher concentrations or enhance penetration. Other glaucoma treatments reported as causing contact dermatitis include the parasympathomimetic pilocarpine, sympathomimetics apraclonidine, brimonidine and dipivefrine, the carbonic anhydrase inhibitor dorzalamide and the prostaglandins latanoprost and bimatoprost.

Treatment of conjunctivitis with antibiotics may cause allergic reactions, as may sodium cromoglicate and the antihistamine pheniramine used for allergic conjunctivitis. The mucolytic *N*-acetylcysteine used to alleviate dry eyes may sensitize, as may mydriatics, especially phenylephrine, with which false-negative patch tests occur. Reactions to the anaesthetics tropicamide and proparacaine are also reported.

Otolaryngological preparations

Antibiotics are frequent sensitizers, particularly neomycin and polymyxin. Some are peculiar to the ear, such as furaltadone.

Psoriasis drugs

Reactions to both tars and dithranol have been reported (see also vitamins).

Traditional Chinese medicaments [1]

Sensitization, as well as irritation, has been reported from Hong Kong, Japan and Singapore, as well as from China.

Transdermal therapeutic systems [15]

Sensitization has been reported to both active (clonidine, nicotine, nitroglycerin, oestradiol, norethisterone and testosterone, scopolamine, pyridostigmine bromide and fentanyl) and inactive (unspecified adhesives, acrylates, ethanol, menthol, hydroxypropylcellulose, polyisobutylene) ingredients.

Vaccines [16]

Thiomersal is a preservative, frequently of unknown relevance, sensitization to which is thought to occur following exposure to it in vaccinations. Other potential allergens include formaldehyde, neomycin, phenoxyethanol and aluminium which may result in a nodular reaction at the site of injection.

Vitamins

Vitamins A, E and K, the vitamin D_3 derivatives calcipotriol and tacalcitol, and dexpanthenol have all sensitized following use in topical medicaments.

References

1 Leow Y-H, Ng S-K, Wong W-K *et al*. Contact allergic potential of topical traditional Chinese medicaments in Singapore. *Am J Contact Dermatitis* 1995; **6**: 4–8.
2 Simpson EL, Law SV, Storrs FJ. Prevalence of botanical extract allergy in patients with contact dermatitis. *Dermatitis* 2004; **15**: 67–72.
3 Barbaud A, Goncalo M, Bruynzeel D, Bircher A. Guidelines for performing skin tests with drugs in the investigation of cutaneous adverse drug reactions. *Contact Dermatitis* 2001; **45**: 321–8.
4 Andersen KE, White IR, Goossens A. Allergens from the standard series. In: Frosch PJ, Menné T, Lepoittevin J-P, eds. *Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 453–92.
5 English JS. Corticosteroid-induced contact dermatitis: a pragmatic approach. *Clin Exp Dermatol* 2000; **25**: 261–4.
6 Wilkinson SM. Corticosteroid cross-reactions: an alternative view. *Contact Dermatitis* 2000; **42**: 59–63.
7 Brandao FM, Goossens A, Tosti A. Topical drugs. In: Frosch PJ, Menné T, Lepoittevin J-P, eds. *Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 623–52.
8 Britton JER, Wilkinson SM, English JSC *et al*. The British Standard series of contact allergens: validation in clinical practice and value for clinical governance. *Br J Dermatol* 2003; **148**: 259–64.
9 Curry EJ, Warshaw EM. Benzyl alcohol allergy: importance of patch testing with personal products. *Dermatitis* 2005; **16**: 203–8.
10 Campbell L, Zirwas MJ. Triclosan. *Dermatitis* 2006; **17**: 204–7.
11 Basketter DA, Marriott M, Gilmour NJ, White IR. Strong irritants masquerading as skin allergens: the case of benzalkonium chloride. *Contact Dermatitis* 2004; **50**: 213–7.
12 Shaw DW, Maibach HI, Eichenfield LF. Allergic contact dermatitis from pimecrolimus in a patient with tacrolimus allergy. *J Am Acad Dermatol* 2007; **56**: 342–5.
13 Diaz RL, Gardeazabal J, Manrique P *et al*. Greater allergenicity of topical ketoprofen in contact dermatitis confirmed by use. *Contact Dermatitis* 2006; **54**: 239–43.
14 Chaudhari PR, Maibach HI. Allergic contact dermatitis from ophthalmics: 2007. *Contact Dermatitis* 2007; **57**: 11–13.
15 Musel AL, Warshaw EM. Cutaneous reactions to transdermal therapeutic systems. *Dermatitis* 2006; **17**: 109–22.
16 Heidary N, Cohen DE. Reactions to vaccine components. *Dermatitis* 2005; **16**: 115–20.

Cosmetics [1–3]

Cosmetics have been defined as any preparation applied to the skin, mouth, hair or nails for the purpose of cleansing, enhancing appearance, giving a pleasant smell or providing protection [1]. There is consequently a considerable range of products that can be included within this definition, for example perfumes, deodorants, aftershaves, hairsprays, lipsticks, nail varnishes and extensions, moisturizers, emollients, cleansers and wipes, mascara, eye shadow, make-up, make-up removers, sunscreens, hair colours and styling agents, depilatories, soaps, shampoos, shower gels, bath oils and toothpastes.

Good manufacturers aim to eliminate known sensitizers and irritants. However, because all cosmetics and toiletries have to be protected against bacteriological contamination and decomposition, and as most consumers require their cosmetics to have a pleasing smell, there are potentially sensitizing preservatives and fragrances in most cosmetic products. The substitution of one allergen by an alternative component may lead to the introduction of perhaps an even more sensitizing substance [4]. When entirely new products or ingredients are used on a large number of consumers, unexpected allergic or irritant reactions may occur, and it may be some time before the cause is identified.

The range of cosmetic allergens is potentially considerable. The more frequently detected allergens are discussed in the specific sections relating to perfumes (p. 26.40), preservatives (p. 26.49), *p*-phenylenediamine and related dyes (p. 26.60), UV filters (p. 26.62), and vehicles and excipients (p. 26.58).

Allergy to tosylamide formaldehyde resin in nail varnish has been shown to be relatively frequent in those who wear it, and to have important adverse consequences [5,6]. Allergy to acrylates used in artificial nail glues and sculptured nails can produce similar results [7,8].

There is an increasing vogue for including natural plant-based products in cosmetics, for example tea tree oil (*Melaleuca alternifolia*), and these may be potentially allergenic [9–11].

Hairdressers (and their clients) are exposed to a wide range of allergens in dyes, bleaches (ammonium persulphate), permanent wave solutions (thioglycollates), shampoos and hairsprays, etc. [12,13]. Depilatory waxes may contain colophony derivatives which can induce allergic dermatitis [14].

Incidence and prevalence. Contact dermatitis to ingredients of cosmetics and toiletries is common in patients attending patch-test clinics; approximately 10% of patients investigated for contact dermatitis in a multicentre European study were allergic to cosmetic products [15]. The exact incidence and prevalence of sensitivity in the population is difficult to establish. In a UK study of 1022 persons, 8.3% had experienced some sort of adverse reaction to a cosmetic or toiletry in the preceding year; most reactions were irritant rather than allergic in nature [16]. In one American survey comprising 30 000 consumers, 700 reactions had occurred during 1 year [17]. Some reactions are transient, such as stinging and smarting, and contact urticarial. Most people simply change brand and do not report adverse reactions to the manufacturer. It is nevertheless estimated that 1–3% of the population is allergic to a cosmetic or cosmetic ingredient [18], with a female predominance.

The commonest allergens are fragrances and preservatives. Also of importance are *p*-phenylenediamine, UV filters, tosylamide formaldehyde resin in nail varnish, lanolin and derivatives and cocamidopropyl betaine, but there are potentially many others [1]. As many as 6.6% of women habitually wearing nail varnish are allergic to it, and 1.6% of patients routinely tested to the usual allergen, tosylamide formaldehyde resin, are patch-test positive [5,19].

Clinical features [1]. Cosmetic allergy is unsuspected in about half of those in whom it is subsequently diagnosed [20]. Apart from hair dye allergy, acute weeping and oedematous reactions are unusual. More commonly, there are erythematous scaling patches or a more diffuse erythema. Differentiation from atopic and seborrhoeic eczema and lupus erythematosus may be difficult, especially on the face.

Sites of involvement are very varied, and depend on the type of product containing the allergen(s) and where it has been applied. Patterns of perfume allergy are described on p. 26.41, and hair dye allergy on p. 26.60. The eyelids, face (Fig. 26.18) and neck (Fig. 26.15) are sites commonly involved in cosmetic allergy, but hand involvement and more widespread dermatitis are seen. It is not always appreciated how often cosmetics, particularly moisturizers, are applied not only to dry skin but also to pre-existing eczemas, including constitutional forms. Flares may wrongly be blamed on the underlying disorder, and cosmetic allergy may go undetected unless appropriate patch testing is undertaken. In



Fig. 26.18 Facial allergic contact dermatitis, often due to fragrance, preservatives or other ingredients of cosmetics. (Courtesy of Dr J.D. Wilkinson, Amersham General Hospital, Amersham, UK.)

general, 'leave-on' products are more likely to sensitize than wash-off cosmetics, although dermatitis may be maintained from the latter source in allergic subjects [1].

Cheilitis is seen from lipstick, lipsalve and toothpaste allergy. Hair cosmetic allergy may cause a scalp margin pattern as well as periorbital swelling. A similar distribution is seen in hairdressers' clients allergic to permanent wave chemicals (usually glyceryl monothioglycollate).

Nail varnish allergy is often ectopic, with patches and streaks on the face, neck (see Fig. 26.10) and behind the ears, and episodic periorbital swelling. The face and neck are involved in about 80% of cases, the eyes in about 50%, and periungual dermatitis, although often absent or minimal, occurs in 60% [6]. The allergen is usually tosylamide formaldehyde resin, but we and others are increasingly seeing allergy to other agents, for example dibutyl phthalate, methyl acrylate, nitrocellulose and especially copolymers [21–24]. More widespread involvement of, for example, the chest and anogenital regions may be seen [4,25]. Onycholysis may occur [26], but this is more likely with allergy from acrylates in adhesives for false nails and from sculptured nails, which may also cause dystrophy and paronychia [7,27]. A similar, potentially widespread, ectopic pattern of contact allergy may occur from acrylic nail cosmetics [8]. The socio-economic and medical consequences of nail varnish allergy have been investigated and shown to be potentially severe, with sick leave, work loss and even hospitalization resulting [6].

Passive transfer of allergy from cosmetics used by partners (connubial or consort allergy) [28,29] and relatives [30] should not be forgotten.

Occupational allergic hand dermatitis associated with hairdressing materials is described in Chapter 27.

Avoidance. Full ingredient labelling of cosmetics has made a major contribution to avoidance measures. It is important to give the patient the INCI name of the material to which they are allergic, as this is the nomenclature used on cosmetic ingredient labels in Europe. There is still potential for confusion, particularly with plants which, when used in cosmetics, are identified by their Latin name in the Linnaean system. Some plant extracts may potentially contain, or cross-react with, fragrances, and it may be difficult for the patient and the dermatologist to be absolutely sure if a product containing natural plant extracts is safe for fragrance-allergic subjects. Unlabelled products should not be used. The reader is referred to the sections on individual cosmetic allergens for more details. It may be wisest to advise women who are allergic to tosylamide formaldehyde resin to stop wearing all nail varnishes, as some products claiming to be free of the resin have been shown to contain it [31].

An alphabetical list of INCI names has been published, and an up-to-date list can be obtained via the Internet on http://ec.europa.eu/enterprise/cosmetics/inci/inci_2006.pdf

Patch testing. The EEC-DRG standard series contains a number of cosmetic allergens, including Fragrance mix I and II, balsam of Peru (*Myroxylon pereirae*), parabens mix, quaternium-15, methylchloroisothiazolinone/methylisothiazolinone, formaldehyde, *p*-phenylenediamine and Colophonium (colophony). The British Contact Dermatitis Society (BCDS) include others in their recommended standard series: imidazolidinyl urea, diazolidinyl urea, methyldibromo glutaronitrile, chloroxylenol and 2-bromo-2-nitropropane-1,3-diol [32]. However, a wider screen of allergens is advised when investigating cosmetic allergy, in particular, tosylamide formaldehyde resin (10% in petrolatum) and, if relevant, an acrylic nail chemical series when investigating facial and patchy disseminated eczemas and periungual problems. Patch testing with a series of UV filters is also advised. In addition, the main allergen suppliers have a range of other potential allergens, including more preservatives, antioxidants, surfactants, emulsifiers and other cosmetic excipients.

It is also most important to patch test with all the cosmetics used by the patient. As a general rule, 'leave-on' products and perfumes can be tested 'as is' but, because of irritancy, soaps and shampoos should be diluted to 1% aqueous. There is still a risk of false-positive reactions and also, because of the dilution, false-negatives. We test toothpastes at 25% in petrolatum. Mascara and nail varnish are often irritant, and should be applied to a chamber and left to evaporate before applying them as a patch test.

Allergy cannot be totally ruled out unless all ingredients of all cosmetics have been tested individually at appropriate concentration and in a suitable vehicle. In practice, however, most cosmetics are initially tested 'as is', but false-negative reactions and marginal irritant reactions are common. Ideally, each component of a suspect cosmetic should be tested individually and where there is a high index of suspicion the individual components should be obtained if the manufacturer is willing to provide them. Ideally, the raw material should be the same as that used in the suspect product, because batch differences, source and purity may all be important.

Sometimes the allergy is to the substance itself, and sometimes to an impurity. The concentration necessary to test an individual substance is often greater than its concentration in the product. Manufacturers' patch-test kits, which contain ingredients at the concentration in which they are present in the product, are likely to be misleading and should not be used.

Testing with hair dyes is discussed on p. 26.61.

Other tests. If cosmetic allergy is still suspected despite negative patch tests, the possibility of photoallergy should be considered and, if clinically indicated, photopatch tests should be undertaken.

Repeat open application tests (ROAT) (see p. 26.97) may also be worthwhile to try and identify the offending cosmetic, although these will not necessarily differentiate between irritant and allergic reactions. Finally, after discussion with the patient, a usage test can be considered, with reintroduction of the suspected products, one at a time, and using each for up to 3 days.

References

1 White IR, De Groot AC. Cosmetics and skin care products. In: Frosch PJ, Menné T, Lepoittevin J-P, eds. *Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 493–506.
2 Rietschel RL, Fowler JF Jr. *Fisher's Contact Dermatitis*, 5th edn. Baltimore: Lippincott, Williams & Wilkins, 2001: 211–61.
3 De Groot AC, Weyland JW, Nater JP. *Unwanted Effects of Cosmetics and Drugs Used in Dermatology*, 3rd edn. Amsterdam: Elsevier, 1994.
4 Thyssen JP, Johansen JD, Menné T. Contact allergy epidemics and their controls. *Contact Dermatitis* 2007; **56**: 185–95.
5 Tosti A, Guerra L, Vincenzi C *et al*. Contact sensitization caused by toluene sulfonamide-formaldehyde resin in women who use nail cosmetics. *Am J Contact Dermatitis* 1993; **4**: 150–3.
6 Lidén C, Berg M, Farm G *et al*. Nail varnish allergy with far-reaching consequences. *Br J Dermatol* 1993; **128**: 57–62.
7 Freeman S, Lee MS, Gudmundsen K. Adverse contact reactions to sculptured acrylic nails: 4 case reports and a literature review. *Contact Dermatitis* 1995; **33**: 381–5.
8 Fitzgerald DA, English JS. Widespread contact dermatitis from sculptured nails. *Contact Dermatitis* 1994; **30**: 118.
9 Thomson KF, Wilkinson SM. Allergic contact dermatitis to plant extracts in patients with cosmetic dermatitis. *Br J Dermatol* 2000; **142**: 84–8.
10 Rutherford T, Nixon R, Tam M, Tate B. Allergy to tea tree oil: retrospective review of 41 cases with positive patch tests over 4.5 years. *Australas J Dermatol* 2007; **48**: 83–7.
11 Simpson EL, Law SV, Storrs FJ. Prevalence of botanical extract allergy in patients with contact dermatitis. *Dermatitis* 2004; **15**: 67–72.
12 Katugampola RP, Statham BN, English JS *et al*. A multicentre review of the hairdressing allergens tested in the UK. *Contact Dermatitis* 2005; **53**: 130–2.
13 Uter W, Lessmann H, Geier J, Schnuch A. Contact allergy to ingredients of hair cosmetics in female hairdressers and clients—an 8-year analysis of IVDK data. *Contact Dermatitis* 2003; **49**: 236–40.
14 Goossens A, Armingaud P, Avenel-Audran M *et al*. An epidemic of allergic contact dermatitis due to epilating products. *Contact Dermatitis* 2002; **47**: 67–70.
15 De Groot AC. Labelling cosmetics with their ingredients. *BMJ* 1990; **300**: 1636–8.
16 Consumer Association. *Consumer Association Report on Reactions of the Skin to Cosmetics and Toiletries*. London: Consumer Association, 1979.
17 Greif M, Maibach HI. United States cosmetic ingredient labelling. *Contact Dermatitis* 1977; **3**: 94–8.
18 De Groot AC, Beverdam E, Tjong Ayong C *et al*. The role of contact allergy in the spectrum of adverse effects caused by cosmetics and toiletries. *Contact Dermatitis* 1988; **19**: 195–201.
19 Marks JG, Belsito DV, DeLeo VA *et al*. North American Contact Dermatitis Group patch test results for the detection of delayed-type hypersensitivity to topical allergens. *J Am Acad Dermatol* 1998; **38**: 911–8.
20 Adams RM, Maibach HI. A five-year study of cosmetic reactions. *J Am Acad Dermatol* 1985; **13**: 1062–9.
21 Shaw S. A case of contact dermatitis from 'hypoallergenic' nail varnish. *Contact Dermatitis* 1989; **20**: 385.
22 Kanerva L, Lauerma A, Jolanki R *et al*. Methyl acrylate: a new sensitizer in nail lacquer. *Contact Dermatitis* 1995; **33**: 203–4.
23 Castelain M, Veyrat S, Laine G *et al*. Contact dermatitis from nitrocellulose in a nail varnish. *Contact Dermatitis* 1997; **36**: 266–7.
24 Gach JE, Stone NM, Finch TM. A series of four cases of allergic contact dermatitis to phthalic anhydride/trimellitic anhydride/glycols copolymer in nail varnish. *Contact Dermatitis* 2005; **53**: 63–4.
25 Lazarov A. Perianal contact dermatitis caused by nail lacquer allergy. *Am J Contact Dermatitis* 1999; **10**: 43–4.
26 Guin JD, Wilson P. Onycholysis from nail lacquer: a complication of nail enhancement? *Am J Contact Dermatitis* 1999; **10**: 34–6.
27 Kanerva L, Estlander T. Allergic onycholysis and paronychia caused by cyanoacrylate nail glue, but not by photobonded methacrylate nails. *Eur J Dermatol* 2000; **10**: 223–5.
28 Veysey EC, Burge S, Cooper S. Consort contact dermatitis to paraphenylenediamine, with an unusual clinical presentation of tumid plaques. *Contact Dermatitis* 2007; **56**: 366–7.
29 Swinyer LJ. Connubial contact dermatitis from perfumes. *Contact Dermatitis* 1980; **6**: 226.
30 Madan V, Beck MH. Contact allergy to octocrylene in sunscreen with recurrence from passive transfer of a cosmetic. *Contact Dermatitis* 2005; **53**: 241–2.
31 Hausen BM, Milbrodt M, Koenig WA. The allergens of nail polish. (I). Allergenic constituents of common nail polish and toluenesulfonamide-formaldehyde resin (TS-F-R). *Contact Dermatitis* 1995; **33**: 157–64.
32 Bourke J, Coulson I, English J. Guidelines for care of contact dermatitis. *Br J Dermatol* 2001; **145**: 877–85.

Antimicrobial agents and preservatives

Formaldehyde [1]

Chemistry. Formaldehyde (HCHO) is a gas, and formalin is a solution of the gas in water (about 38%). Methylol groups can be combined with other compounds to form formaldehyde releasers, which are widely used as preservatives. Formaldehyde may combine with other chemicals to produce resins, which may sensitize (see p. 26.75).

Prevalence. In individuals routinely patch tested for the investigation of contact dermatitis, the frequency of allergic positive reactions is generally 2–3%, although the North American Contact Dermatitis Group (NACDG) found 8.4% were positive in 2001–2002 [2,3].

Occurrence. Formaldehyde is a ubiquitous allergen and Table 26.7 gives an idea of the wide variety of potential sources. Threshold concentrations for elicitation of contact dermatitis from formaldehyde are as low as 30 ppm in the axillae [4], and as low as 250 ppm under an occluded patch test [5].

It can often be difficult to find relevance for a positive patch test, but more commonly identified causes are cosmetic ingredients [1] and clothing resins. Shampoos may contain formaldehyde, although this is more likely to be of relevance in the context of hairdressers' hand dermatitis than in relation to transient use on the hair. Some textile resins will release formaldehyde, and free formaldehyde may be found in treated cotton clothing and rayons (see p. 26.65). Paints/lacquers, printing inks and cleaning products, filling agents and glues were the most frequently registered products containing formaldehyde marketed in Denmark [6]. Formaldehyde is used for the preservation of anatomical and pathological specimens, and those working with such specimens, for example histopathologists and embalmers, are at risk of allergy

Table 26.7 Formaldehyde exposure.

Cosmetic preservatives	Cotton clothing (wash and wear, crease resistant)
Shampoos and soaps	Household cleaning products
Rayons	Polishes
Industrial biocides	Metalworking fluids
Orthopaedic casts	Wart treatment
Hyperhidrosis treatment	Antiperspirants
Embalming fluids and tissue fixatives	Preservatives
Renal dialysis	Colouring agents
Hardeners	Paints/lacquers
Glues	Water-resistant papers and tissues
Fibreboard/chipboard	Plywood
Tanning agents for leather	Photographic plates and solutions
Fumigators	Printing chemicals
Dry-cleaning materials	Disinfectants and deodorizers
Fertilizers	Insecticide (flypapers)
? Smoke from tobacco, coal and wood	Reusable gloves

Table 26.8 Formaldehyde-releasing preservatives in cosmetics and medicaments.

Substance	Patch-test concentration
Quaternium-15	1% in petrolatum
Imidazolidinyl urea	2% in petrolatum (or 2% aqueous)
Diazolidinyl urea	2% in petrolatum (or 2% aqueous)
2-Bromo-2-nitropropane-1,3-diol	0.25% in petrolatum (or 0.5% in petrolatum)
DMDM hydantoin	2% aqueous

from free formaldehyde. It is used medically in renal dialysis and may be found in orthopaedic casts. It is also used as a treatment for warts and hyperhidrosis, especially of the feet, where powders containing paraformaldehyde may also be used. Formaldehyde has been found in reusable protective gloves [7]. The very widely used surfactant sodium lauryl sulphate may be preserved with formaldehyde at a level of 0.1% [8]. It is used in detergents, shampoos, shower gels and bubble baths.

In addition, formaldehyde-releasing chemicals must be considered, including certain preservatives and biocides widely used in industry (e.g. in cutting oils). Many preservatives used in cosmetics, and to a lesser degree in topical medicaments, may release formaldehyde (Table 26.8). Many of these releasers not only sensitize simultaneously with, but also independently of, formaldehyde [9–12]. It is common practice in Sweden to prescribe corticosteroid ointments in formaldehyde-allergic patients because some cream-based products have been shown to release small quantities of formaldehyde [13].

Clinical features. The presenting dermatitis will depend on the source of contact, for instance a clothing pattern (see p. 26.66), a cosmetic pattern (see p. 26.47) or involvement of the hands in occupational dermatitis. Formaldehyde allergy is often only diagnosed retrospectively by finding a positive patch test, and relating this to the distribution of the problem by identifying formaldehyde or formaldehyde-releasing chemicals that come into contact with the affected site.

Avoidance. Avoidance may be difficult, bearing in mind the wide exposure possibilities, but it is important to recognize that avoidance steps are only required if the individual has skin problems that are relevant to the exposure. For those with a clothing pattern, avoidance advice is given on p. 26.67. If cosmetics, medicaments and moisturizers come into contact with the affected sites, their ingredient labels should be carefully assessed in order that those containing not only formaldehyde but also the formaldehyde-releasing preservatives listed in Table 26.8 are avoided. Some allergic patients may find this difficult [14]. It may also be necessary to contact manufacturers or check the material safety data sheet to establish the presence of formaldehyde in their products, particularly cutting oils. The difficulties faced by patients in identifying formaldehyde in products is highlighted by the fact that in one study of sensitized persons with persistent dermatitis, all were still using at least one product containing formaldehyde. Only by detailed enquiries and access to product databases could the presence of formaldehyde be demonstrated [15].

A number of tests can be used to detect the presence of formaldehyde. The chromotropic acid test may give false-positive reactions, and the alternative acetylacetone method may be more sensitive and specific (see p. 26.99). A closed container diffusion method for quantification of formaldehyde has also been devised [16]. High-performance liquid chromatography is an alternative method that is more accurate than the chromatropic acid test [13].

Prognosis. In a follow-up study of 57 patients with formaldehyde dermatitis, 29 (51%) still had frequent or persistent dermatitis several years later. Formaldehyde was identified in cosmetics, toiletries, household cleaners and other materials still being used by 38 of these patients. The authors concluded that patients who paid attention to their allergy had statistically significantly fewer eruptions than those who did not [17].

Patch tests. Patch testing is now recommended with formaldehyde 1% aqueous. Previously, 2% aqueous was advised but false-positive reactions prompted a change in the recommended concentration, yet with the potential for the occasional false-negative reaction [18]. It is a generally recommended standard allergen.

References

1 Andersen KE, White IR, Goossens A. Allergens from the standard series. In: Frosch PJ, Menné T, Lepoittevin J-P, eds. *Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 473–5.

2 Schnuch A, Geier J, Uter W *et al*. National rates and regional differences in sensitization to allergens of the standard series. Population-adjusted frequencies of sensitization (PAFS) in 40,000 patients from a multicenter study (IVDK). *Contact Dermatitis* 1997; **37**: 200–9.

3 Pratt MD, Belsito DV, DeLeo VA *et al*. North American Contact Dermatitis Group patch-test results, 2001–2002 study period. *Dermatitis* 2004; **15**: 176–83.

4 Jordan WP Jr, Sherman WT, King SE. Threshold responses in formaldehyde-sensitive subjects. *J Am Acad Dermatol* 1979; **1**: 44–8.

5 Flyvholm MA, Hall BM, Agner T *et al*. Threshold for occluded formaldehyde patch test in formaldehyde-sensitive patients. Relationship to repeated open application test with a product containing formaldehyde releaser. *Contact Dermatitis* 1997; **36**: 26–33.

6 Flyvholm MA. Preservatives in registered chemical products. *Contact Dermatitis* 2005; **53**: 27–32.

7 Pontén A. Formaldehyde in reusable protective gloves. *Contact Dermatitis* 2005; **54**: 268–71.
8 Fisher AA. Dermatitis due to the presence of formaldehyde in certain sodium lauryl sulfate (SLS) solutions. *Cutis* 1981; **27**: 360–2.
9 Jacobs MC, White IR, Rycroft RJ *et al*. Patch testing with preservatives at St John's from 1982 to 1993. *Contact Dermatitis* 1995; **33**: 247–54.
10 Ford GP, Beck MH. Reactions to Quaternium 15, Bronopol and Germall 115 in a standard series. *Contact Dermatitis* 1986; **14**: 271–4.
11 Kranke B, Szolar-Platzer C, Aberer W. Reactions to formaldehyde and formaldehyde releasers in a standard series. *Contact Dermatitis* 1996; **35**: 192–3.
12 Anderson BE, Tan TC, Marks JG. Patch-test reactions to formaldehydes, bioban, and other formaldehyde releasers. *Dermatitis* 2007; **18**: 92–5.
13 Goon AT, Gruvberger B, Persson L *et al.* Presence of formaldehyde in topical corticosteroid preparations available on the Swedish market. *Contact Dermatitis* 2003; **48**: 199–203.
14 Noiesen E, Munk MD, Larsen K *et al.* Difficulties in avoiding exposure to allergens in cosmetics. *Contact Dermatitis* 2007; **57**: 105–9.
15 Flyvholm MA, Menné T. Allergic contact dermatitis from formaldehyde. A case study focussing on sources of formaldehyde exposure. *Contact Dermatitis* 1992; **27**: 27–36.
16 Karlberg AT, Skare L, Lindberg I *et al*. A method for quantification of formaldehyde in the presence of formaldehyde donors in skin-care products. *Contact Dermatitis* 1998; **38**: 20–8.
17 Agner T, Flyvholm MA, Menné T. Formaldehyde allergy: a follow-up study. *Am J Contact Dermatitis* 1999; **10**: 12–7.
18 Trattner A, Johansen JD, Menné T. Formaldehyde concentration in diagnostic patch testing: comparison of 1% with 2%. *Contact Dermatitis* 1998; **38**: 9–13.

Formaldehyde-releasing preservatives/biocides [1]

Quaternium-15

Quaternium-15 is also known as Dowicil 75, 100 or 200, chlorallyl methenamine chloride, *N*-(3-chlorallyl)-hexaminium chloride, and 1-(3-chlorallyl)-3,5,7-triaza-1-azoniondamantane. It is water soluble, odourless and colourless. Its broad antimicrobial activity is independent of the pH of the product.

Prevalence. Quaternium-15 can sensitize either independently or via formaldehyde release, or both [2]. The prevalence of positive patch tests in those attending for routine testing in North America is high, with 9.3% positive in a NACDG survey of 4910 patients [3]. Equivalent returns in Europe have generally shown lower levels, although the prevalence is dependent on the amount of usage in a given country. In the UK in 1986, 2.6% were positive, whereas there were no positives in a Dutch survey of the same year [2,4].

Occurrence. Quaternium-15 is found in cosmetic products and hand creams, including barrier and other creams used at work. It is found in a small number of medicaments in the UK [5] and in electroencephalography skin preparation gel [6].

Clinical features. These are discussed in the sections on allergy to cosmetics (p. 26.47) and medicaments (p. 26.43).

Avoidance. The INCI name is quaternium-15. Only ingredient-labelled products should be used, and any product shown to contain it should be avoided. Knowledge of synonyms is helpful, particularly as non-cosmetic products, including medicaments, may not adhere to INCI terminology.

Patch tests. For quaternium-15, 1% in petrolatum is the generally recommended concentration and vehicle. It is recommended as a standard allergen in Europe and North America.

Diazolidinyl urea

Diazolidinyl urea is also known as Germall II. It is a broad-spectrum biocide, soluble in water and effective at various pH levels [1].

Prevalence. Studies in the UK on routinely patch-tested individuals showed that 0.7% of 3062 patients were patch-test positive [7], whereas in North America 3.1% were positive [3]. In one study 81% of those allergic to it were also allergic to formaldehyde [8].

Occurrence. Diazolidinyl urea has been used since 1982, predominantly in cosmetics, shampoos and creams, including barrier and other work creams.

Clinical features. These are discussed in the section on allergy to cosmetics (p. 26.47).

Avoidance. The INCI name is diazolidinyl urea. Only ingredient-labelled cosmetics and creams should be used, and any product shown to contain it should be avoided. ROAT confirms that formaldehyde-allergic subjects should also avoid creams preserved with diazolidinyl urea [9].

Patch tests. Patch testing at 1% and 2% aqueous has been advised [10], but it is generally supplied at 2% in petrolatum, which we have found satisfactory. Although not a frequent sensitizer in the UK, the BCDS has recommended its inclusion in the standard series [11].

Imidazolidinyl urea

Imidazolidinyl urea is also known as Germall 115. It has broad-spectrum antimicrobial activity and is colourless, water-soluble and not pH dependent. It acts synergistically with other preservatives and will kill *Pseudomonas aeruginosa* [1]. It releases only small amounts of formaldehyde, and may therefore possibly be less of a problem than other formaldehyde releasers for formaldehyde-sensitive subjects [12].

Prevalence. It is not a common allergen in most European studies, for example positive reactions occur in 0.7% of routinely patch-tested persons in the UK [2]. In North America the NACDG has reported a figure of 3.0% [3].

Occurrence. Imidazolidinyl urea is used in cosmetics, shampoos and hand creams, including barrier and other work creams. It is found in a cream containing the corticosteroid fluticasone, marketed in the UK as Cutivate®, where its presence is denoted by the word 'imidurea'.

Clinical features. These are discussed in the section on allergy to cosmetics (p. 26.47).

Avoidance. Imidazolidinyl urea is the INCI name. Only ingredient-labelled cosmetics should be used, and any product shown to contain it should be avoided. Cutivate® cream should also be avoided and this also applies to those allergic to formaldehyde [13].

Patch tests. Although patch testing with 2% aqueous has been advised [14], 2% in petrolatum is generally used. Its inclusion in the standard series is recommended by the BCDS in the UK [11].

2-Bromo-2-nitropropane-1,3-diol

2-Bromo-2-nitropropane-1,3-diol is also known as bronopol and BNPD. It has broad-spectrum antimicrobial activity and is particularly effective against *Pseudomonas aeruginosa.* It is soluble in water, alcohols, glycols and, to a lesser degree, oils [1].

Prevalence. The reported prevalence of positive reactions to 2-bromo-2-nitropropane-1,3-diol in routinely patch-tested individuals in North America in 2001–02 was 3.3% [3]. In the UK, 0.8% were positive in a 2003 study [11].

Occurrence. 2-Bromo-2-nitropropane-1,3-diol is present in a wide range of cosmetics, moisturizers, shampoos, medicaments and hand creams. It is used as a preservative when testing milk samples, and outbreaks of dermatitis have been reported from this source [15]. In the USA, allergic problems have arisen from Eucerin® cream [16], and in the UK from metronidazole gel used to treat rosacea [17]. It is also found in a number of chemical products especially paints, lacquers and cleaning agents [18]. We have seen it sensitize printers when used as a biocide with isothiazolinones in fountain solution.

Clinical features. These are discussed in the section on allergy to cosmetics (p. 26.47). In the occupational setting the usual site of involvement is the hands.

Avoidance. The INCI name is 2-bromo-2-nitropropane-1,3-diol. The simpler name of bronopol may be used in other products. Only ingredient-labelled cosmetics should be used, and any product shown to contain it should be avoided.

Patch tests. The two recommended concentrations are 0.5% and 0.25% in petrolatum; 0.5% may occasionally give false-positive reactions. It is recommended by the BCDS for the standard series in the UK [11].

DMDM hydantoin

DMDM hydantoin is also known as Glydant and is a colourless liquid that contains 0.5–2% free formaldehyde and over 17% combined formaldehyde [1].

Prevalence. In the Netherlands, 1.2% of patients routinely patch tested to DMDM hydantoin showed allergic reactions [4], and the NACDG reported 2.8% positivity [3]. Testing with formaldehyde demonstrated concomitant sensitivity in eight of 15 (57%) individuals [19], but a much lower rate was seen in Germany [20].

Occurrence. DMDM hydantoin is used in a wide range of cosmetics. Surprisingly, there are no specific reports in the literature of allergy from this source [12], but we have seen occasional allergies relevant to cosmetics.

Clinical features. These are discussed in the section on allergy to cosmetics (p. 26.47).

Avoidance. DMDM hydantoin is the INCI name, and it can be identified in a product provided this is fully ingredient-labelled. There is evidence from ROATs that formaldehyde-allergic patients should avoid products containing DMDM hydantoin [19].

Patch tests. Patch tests have been undertaken at 1–3% aqueous and 1% in petrolatum. We have found 2% aqueous satisfactory.

Other biocides

The above formaldehyde releasers are encountered particularly in cosmetics, including shampoos and other hair-care products. A much broader series of formaldehyde releasers is to be found in materials such as industrial and household cleaning agents, colouring agents, paints and lacquers, polishes and especially metalworking fluids [21–23]. A number of formaldehyde-releasing biocides in these fluids will sensitize, and a special series of allergens should be used for testing in those exposed, as well as the material itself [24].

References

1 Rietschel RL, Fowler JF Jr. *Fisher's Contact Dermatitis*, 5th edn. Baltimore: Lippincott, Williams & Wilkins, 2001: 211–61.
2 Ford GP, Beck MH. Reactions to Quaternium 15, Bronopol and Germall 115 in a standard series. *Contact Dermatitis* 1986; **14**: 271–4.
3 Pratt MD, Belsito DV, DeLeo VA *et al.* North American Contact Dermatitis Group patch-test results, 2001–2002 study period. *Dermatitis* 2004; **15**: 176–83.
4 De Groot AC, Bos JD, Jagtman BA *et al*. Contact allergy to preservatives II. *Contact Dermatitis* 1986; **15**: 218–22.
5 Boffa MJ, Beck MH. Allergic contact dermatitis from quaternium 15 in Oilatum cream. *Contact Dermatitis* 1996; **35**: 45–6.
6 Finch TM, Prais L, Foulds IS. Occupational allergic contact dermatitis from quaternium-15 in an electroencephalography skin preparation gel. *Contact Dermatitis* 2001; **44**: 44–5.
7 Britton JE, Wilkinson SM, English JS *et al.* The British standard series of contact dermatitis allergens: validation in clinical practice and value for clinical governance. *Br J Dermatol* 2003; **148**: 259–64.
8 Hectorne KJ, Fransway AF. Diazolidinyl urea: incidence of sensitivity, patterns of cross-reactivity and clinical relevance. *Contact Dermatitis* 1994; **30**: 16–9.
9 Zachariae C, Hall B, Cupferman S *et al.* ROAT: morphology of ROAT on arm, neck and face in formaldehyde and diazolidinyl urea sensitive individuals. *Contact Dermatitis* 2006; **54**: 21–4.
10 De Groot AC, Bruynzeel DP, Jagtman BA *et al*. Contact allergy to diazolidinyl urea (Germall II). *Contact Dermatitis* 1988; **18**: 202–5.
11 Bourke J, Coulson I, English J. Guidelines for care of contact dermatitis. *Br J Dermatol* 2001; **145**: 877–85.
12 White IR, De Groot AC. Cosmetics and skin care products. In: Frosch PJ, Menné T, Lepoittevin J-P, eds. *Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 498.
13 Isaksson M, Gruvberger B, Goon AT, Bruze M. Can an imidazolidinyl urea-preserved corticosteroid cream be safely used in individuals hypersensitive to formaldehyde? *Contact Dermatitis* 2006; **54**: 29–34.
14 Van Neer PA, van der Kley AM. Imidazolidinyl urea (Germall 115) should be patch tested in water. *Contact Dermatitis* 1991; **24**: 302.
15 Grattan CE, Harman RR, Tan RS. Milk recorder dermatitis. *Contact Dermatitis* 1986; **14**: 217–20.
16 Storrs FJ, Bell DE. Allergic contact dermatitis to 2-bromo-2-nitropropane-1,3-diol in a hydrophilic ointment. *J Am Acad Dermatol* 1983; **8**: 157–70.
17 Choudry K, Beck MH, Muston HL. Allergic contact dermatitis from 2-bromo-2-nitropropane-1,3-diol in Metrogel. *Contact Dermatitis* 2002; **46**: 60–1.
18 Flyvholm MA. Preservatives in registered chemical products. *Contact Dermatitis* 2005; **53**: 27–32.
19 De Groot AC, van Joost T, Bos JD *et al*. Patch test reactivity to DMDM hydantoin. Relationship to formaldehyde allergy. *Contact Dermatitis* 1988; **18**: 197–201.
20 Uter W, Frosch PJ. Contact allergy from DMDM hydantoin, 1994–2000. *Contact Dermatitis* 2002; **47**: 57–8.

21 Flyvholm M-A. Formaldehyde and formaldehyde releasers. In: Kanerva L, Elsner P, Wahlberg JE, Maibach HI, eds. *Handbook of Occupational Dermatology*. Berlin: Springer, 2000: 474–8.
22 Madan V, Beck MH. Occupational allergic contact dermatitis from N,N-methylene-bis-5-methyl-oxazolidine in coolant oils. *Contact Dermatitis* 2006; **55**: 39–41.
23 Geier J, Lessmann H, Dickel H *et al*. Patch test results with the metalworking fluid series of the German Contact Dermatitis Research Group (DKG). *Contact Dermatitis* 2004; **51**: 118–30.
24 Geier J, Uter W, Lessmann H, Frosch PJ. Patch testing with metalworking fluids from the patient's workplace. *Contact Dermatitis* 2004; **51**: 172–9.

Isothiazolinones [1]

Isothiazolinone preservative systems have effective broad-spectrum activity against both bacteria and fungi. A number of different formulations have been shown to be sensitizing to the skin.

1 A mixture of 5-chloro-2-methyl-4-isothiazolin-3-one and 2-methyl-4-isothiazolin-3-one in a 3:1 ratio by weight. The INCI name is methylchloroisothiazolinone and methylisothiazolinone (MCI/MI). This mixture has various other names, including Kathon CG, Kathon WT, Euxyl K 100 and Acticide. MI by itself has now been introduced as a preservative.
2 1,2-Benzisothiazolin-3-one (BIT), which is used under the commercial name Proxel in a range of biocides.
3 2-*n*-Octyl-4-isothiazolin-3-one, also known as Kathon 893, Kathon LP and Skane M-8.

There seems to be little in the way of cross-sensitization between these compounds [2]. A further isothiazolinone, 2-methyl-4,5-trimethylene-4-isothiazolin-3-one (MTI), has also sensitized, but only in the laboratory setting [3].

Methylchloroisothiazolinone and methylisothiazolinone [4,5]

Prevalence. Since first marketed in 1980, there have been many reports of allergy, particularly from Europe, with a prevalence of positive reactions as high as 8.3% in routinely tested patients in the first few years after its introduction [6]. This level has now stabilized to around 2.5% [7]. However, there has been considerable variability in the prevalence of allergy from country to country. In the USA, rates of 2–3% have generally been the rule [8].

There has been much discussion about the reason for differing prevalence rates worldwide. It has been suggested that in some countries there has been lack of control over the amount of this biocide added to products that come in contact with the skin [8]. Furthermore, patch testing with concentrations as high as 300 ppm in some centres may have produced false-positive reactions, whereas other centres have tested with 100 ppm [8].

Levels below 15 ppm are considered unlikely to induce sensitization [9], and in those already sensitized this concentration has been shown to be insufficient to elicit a dermatitis in many instances [9]. A decrease in, and stabilization of, frequency of allergy is felt to reflect tighter regulation of concentrations used. The maximum allowable concentration in the European Union (EU) for both 'rinse-off' and 'leave-on' cosmetics is 15 ppm, with a lower recommended concentration of 7.5 ppm for 'leave-on' products in the USA [7].

Occurrence. MCI/MI is used in cosmetics mainly in 'rinse-off' products, including liquid soaps and cleansers, shower gels, bubble baths and shampoos. Nevertheless, 'leave-on' cosmetics may contain it. It may be present in medicated wipes and moist toilet paper [10]. In 1990, a study showed its presence in 48% of 'rinse-off' and 31% of 'leave-on' cosmetic products used in Denmark [11]. In 1988, it was reported as being present in 25% of all cosmetic products in the Netherlands [4].

However, this biocide can be found in other situations, most notably soluble cutting oils, paints, wallpaper pastes, glues, spin finishes, military fuel, household cleansers, printing inks and fountain solution, latex emulsions, water cooling systems and as a slimicide in paper mills.

Clinical features. These are discussed in the section on allergy to cosmetics (p. 26.47). Shampoos do not usually cause problems from washing the hair, but allergy may be associated with hairdressers' hand dermatitis. A positive patch test to MCI/MI associated with perianal dermatitis suggests the possibility of moist toilet paper or wipes as a cause [10]. However, this source of MCI/MI can provoke allergic dermatitis of the hands and elsewhere [10,12].

An exposure pattern of dermatitis has been seen in sensitized subjects staying in newly painted rooms, and the source of the problem may easily be overlooked [13].

Hands are the usual sites for occupational allergic dermatitis, although spread to other parts of the body, including an exposure pattern, may occur [14]. A chemical burn from spillage of concentrated MCI/MI on to any part of the skin may be followed by a secondary delayed dermatitis from active sensitization [15,16].

Patch tests. The recommended patch-test concentration and vehicle is now 100 ppm in water, as it has been suggested that 200–300 ppm might be associated with false-positive reactions and active sensitization [17]. However, there is also evidence that 200 ppm may identify sensitized subjects missed by the 100 ppm patch test [18]. MCI/MI is generally recommended as a standard allergen.

1,2-Benzisothiazolin-3-one (BIT)

Occurrence. Sensitization normally occurs from manufacturing or handling the raw material, for example paint manufacture, water treatment or in the laboratory. Painters and decorators may be exposed not only from paints but also wallpaper pastes. Allergy has been reported in the pottery industry from its presence in mould-release agents. Other potential sources include soluble cutting oils, laundry detergents and fabric softeners, varnishes, dyes, printing materials, water softener and air-freshener manufacture. Allergy to PVC gloves has been traced to BIT used in their manufacture [19].

Clinical patterns. Classically, with hand dermatitis, a low-grade palmar psoriasiform or pompholyx pattern occurs (see Fig. 26.5). In more severe cases an exposed-site pattern develops [20]. Sensitized workers involved in manufacture may complain of a burning sensation of the eyes and face within the factory environment without there being observable dermatitis.

Patch tests. A number of patch-test concentrations in petrolatum have been suggested, varying from 0.05 to 1%. False-positive

reactions have been reported with 0.1% in petrolatum [21], and as our experience is that false-positive reactions occur above 0.05% in petrolatum we advocate the use of this concentration.

2-n-Octyl-4-isothiazolin-3-one

Occurrence. 2-*n*-Octyl-4-isothiazolin-3-one may occur in leather, textiles, soluble cutting oils, paints and polishes, adhesives, cleaning agents, wood preservatives and plastic manufacture.

Clinical features. Reports of contact allergy tend to be sporadic and anecdotal, and these include hand dermatitis associated with its presence in paints [22]. Contact allergy to leather in footwear has been reported [23] and we have found a small number of positive reactions in individuals with possible shoe dermatitis, but of unproven relevance.

Patch tests. 2-n-Octyl-4-isothiazolin-3-one is usually patch tested at 0.1% in petrolatum.

References

1 Lepoittevin J-P, Le Coz CJ. Dictionary of occupational allergens. In: Kanerva L, Elsner P, Wahlberg JE, Maibach HI, eds. *Handbook of Occupational Dermatology*. Berlin: Springer, 2000: 1183–5.
2 Geier J, Schnuch A. No cross-sensitization between MCI/MI, benzisothiazolinone and octylisothiazolinone. *Contact Dermatitis* 1996; **34**: 148–9.
3 Burden AD, O'Driscoll JB, Page FC, Beck MH. Contact hypersensitivity to a new isothiazolinone. *Contact Dermatitis* 1994; **30**: 179–80.
4 De Groot AC, Weyland JW. Kathon CG: a review. *J Am Acad Dermatol* 1988; **18**: 350–8.
5 De Groot AC. Methylisothiazolinone/methylchloroisothiazolinone (Kathon CG) allergy: an updated review. *Am J Contact Dermatitis* 1990; **1**: 151–6.
6 De Groot AC, Herxheimer A. Isothiazolinone preservative: cause of a continuing epidemic of cosmetic dermatitis. *Lancet* 1989; **i**: 314–6.
7 Wilkinson JD, Shaw S, Andersen KE *et al*. Monitoring levels of preservative sensitivity in Europe. A 10-year overview (1991–2000). *Contact Dermatitis* 2002; **46**: 207–10.
8 Rietschel RL, Fowler JF Jr. *Fisher's Contact Dermatitis*, 5th edn. Baltimore: Lippincott, Williams & Wilkins, 2001: 220–2.
9 Fewings J, Menné T. An update of the risk assessment for methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) with focus on rinse-off products. *Contact Dermatitis* 1999; **41**: 1–13.
10 De Groot AC. Vesicular dermatitis of the hands secondary to perianal allergic contact dermatitis caused by preservatives in moistened toilet tissues. *Contact Dermatitis* 1997; **36**: 173–4.
11 Rastogi SC. Kathon CG and cosmetic products. *Contact Dermatitis* 1990; **22**: 155–60.
12 Timmermans A, Hertog SD, Gladys K *et al*. 'Dermatologically tested' baby toilet tissues: a cause of allergic contact dermatitis in adults. *Contact Dermatitis* 2007; **57**: 97–9.
13 Bohn S, Niederer M, Brehm K, Bircher AJ. Airborne contact dermatitis from methylchloroisothiazolinone in wall paint. Abolition of symptoms by chemical allergen inactivation. *Contact Dermatitis* 2000; **42**: 196–201.
14 Thyssen JP, Sederberg-Olsen N, Thomsen JF, Menné T. Contact dermatitis from methylisothiazolinone in a paint factory. *Contact Dermatitis* 2006; **54**: 322–4.
15 Kanerva L, Tarvainen K, Pinola A *et al*. A single accidental exposure may result in a chemical burn, primary sensitization and allergic contact dermatitis. *Contact Dermatitis* 1994; **31**: 229–35.
16 Isaksson M, Gruvberger B, Bruze M. Occupational contact allergy and dermatitis from methylisothiazolinone after contact with wallcovering glue and after a chemical burn from a biocide. *Dermatitis* 2004; **15**: 201–5.
17 Marks J, Moss JN, Parno JR *et al*. Methylchloroisothiazolinone/methylisothiazolinone (Kathon CG) biocide: second United States multicenter study of human skin sensitization. *Am J Contact Dermatitis* 1993; **4**: 87–9.
18 Farm G, Wahlberg JE. Isothiazolinones (MCI/MI): 200 ppm versus 100 ppm in the standard series. *Contact Dermatitis* 1991; **25**: 104–7.
19 Aalto-Korte K, Alanko K, Henriks-Eckerman ML, Jolanki R. Antimicrobial allergy from polyvinyl chloride gloves. *Arch Dermatol* 2006; **142**: 1326–30.
20 Hardcastle NJ, Gawkrodger DJ. Occupational contact dermatitis to 1,2-benzisothiazolin-3-one and 5-chloro-2-methylisothiazolin-3-one/2-methylisothiazolin-3-one in paint manufacturers. *Contact Dermatitis* 2005; **53**: 115–6.
21 Chew AL, Maibach HI. 1,2-Benzisothiazolin-3-one (Proxel): irritant or allergen? A clinical study and literature review. *Contact Dermatitis* 1997; **36**: 131–6.
22 Mathias CG, Andersen KE, Hamann K. Allergic contact dermatitis from 2-n-octyl-4-isothiazolin-3-one, a paint mildewcide. *Contact Dermatitis* 1983; **9**: 507–9.
23 Oleaga JM, Aguirre A, Landa N *et al*. Allergic contact dermatitis from Kathon 893. *Contact Dermatitis* 1992; **27**: 345–6.

Parabens (hydroxybenzoates) [1,2]

Parabens are esters of *p*-hydroxybenzoic acid. The four main esters used are methyl-, ethyl-, propyl- and butyl-paraben (hydroxybenzoate). They may have a synergistic effect when used in combination. They are more active against Gram-positive than Gram-negative bacteria (including poor activity against *Pseudomonas*). They are also active against moulds and yeasts. They are stable, colourless, odourless and poorly soluble in water [1].

Prevalence. There is a relatively low prevalence of positive reactions in routinely patch-tested patients, and rates between 0.5 and 1.7% are typical [3–5].

Occurrence. Parabens are very widely used preservatives in topical and parenteral medicaments, paste bandages, cosmetics, ultrasound gels and foods.

Clinical features. The striking feature of allergy to parabens is its relative infrequency compared with the degree of usage and exposure in the general population. Relevant allergies are mainly from sensitization to medicaments (including paste bandages) used on venous ulcers and eczema, but contact allergy may be superimposed on other inflammatory dermatoses, particularly on high-risk sites such as the anogenital region. Relevant problems from parabens in cosmetics are rare [1]. Interestingly, many individuals allergic to parabens in medicaments can use cosmetics containing them on normal skin without any problem, the so-called 'paraben paradox' [6]. However, there are exceptions, and sometimes cosmetics containing parabens have to be abandoned [7]. Flares from parabens in food and medicaments [8] have been reported in sensitized subjects, but a low-paraben diet did not help two patients whose eczema flared with oral challenge [9].

Avoidance. The INCI name for this group of preservatives ends in '-paraben' according to the ester used. In individuals in whom cosmetic allergy may be relevant, the full ingredient label must be examined in order that they may be avoided. Terminology for medicaments may be different, and the name may end in '-hydroxybenzoate'. Furthermore, the commercial names may sometimes be used, in particular Nipagin, Nipsasol and Nipabutyl, but there are many others. Only medicaments and paste bandages whose ingredients are known in full should be used, avoiding those containing parabens or agents whose names

are synonyms of parabens. It is advisable to avoid all parabens even if only one or two are positive in breakdown testing.

Patch tests. Hydroxybenzoates are normally tested as a mix of the four esters, each at 3% in petrolatum. The mix is marginally irritant, and testing with each ester individually will help to confirm whether the patch-test reaction is truly allergic. Often more than one ester will react, which may be a marker of both concomitant sensitization and cross-sensitization. Parabens mix 12% in petrolatum is generally advised for the standard series.

References

1 Rietschel RL, Fowler JF Jr. *Fisher's Contact Dermatitis*, 5th edn. Baltimore: Lippincott, Williams & Wilkins, 2001: 218–20.
2 Cashman AL, Warshaw EM. Parabens: a review of epidemiology, structure, allergenicity, and hormonal properties. *Dermatitis* 2005; **16**: 57–66.
3 Wilkinson JD, Shaw S, Andersen KE *et al*. Monitoring levels of preservative sensitivity in Europe. A 10-year overview (1991–2000). *Contact Dermatitis* 2002; **46**: 207–10.
4 Schnuch A, Geier J, Uter W *et al*. Patch testing with preservatives, antimicrobials and industrial biocides. Results from a multicentre study. *Br J Dermatol* 1998; **138**: 467–76.
5 Marks JG Jr, Belsito DV, DeLeo VA *et al*. North American Contact Dermatitis Group patch-test results, 1996–1998. *Arch Dermatol* 2000; **136**: 272–3.
6 Fisher AA. The paraben paradox. *Cutis* 1973; **12**: 830–2.
7 Simpson JR. Dermatitis due to parabens in cosmetic creams. *Contact Dermatitis* 1978; **4**: 311–2.
8 Sánchez-Pérez J, Diez MB, Pérez AA *et al* Allergic and systemic contact dermatitis to methylparaben. *Contact Dermatitis* 2006; **54**: 117–8.
9 Veien NK, Hattel T, Laurberg G. Oral challenge with parabens in paraben-sensitive patients. *Contact Dermatitis* 1996; **34**: 433.

Methyldibromo glutaronitrile [1]

Methyldibromo glutaronitrile (MDBGN), also known as dibromocyanobutane, is to be found in the preservative system Euxyl K 400 (also called Tektamer 38), which is a mix of MDBGN and phenoxyethanol in a ratio of 1:4. Euxyl K 400 is a broad-spectrum preservative with activity against fungi and bacteria. MDBGN is nearly always the allergen when sensitization to Euxyl K 400 occurs.

Prevalence. Until recently, increasing rates of sensitization were reported throughout Europe and the USA. Of particular significance was the finding of a multicentre European study monitoring rates of preservative allergy, where the frequency of MDBGN allergy between 1991 and 2000 rose from 0.7 to 3.5%, whereas the level of all other cosmetic preservative allergy had remained stable [2]. In consequence, EC countries have banned the use of this preservative, initially in leave-on and later wash-off cosmetics. It is therefore anticipated that sensitization rates will fall very significantly. At the same time, high rates have been reported in the USA, with 11.7% being allergic to MDBGN in one small study [3]. Rates for the NACDG have varied from 2.7 to 7.6% according to the test concentration used [4]. This has caused concern about the correct test concentration [5].

Occurrence. MDBGN was historically widely used in cosmetics, sunscreens, shampoos, liquid soaps, and barrier and moisturizing creams used at work. Other sources include moistened toilet tissues, ultrasound gel, adhesives, soluble cutting oils, latex paints, vaginal examination gel and sanitary pads. The EU ban will reduce these exposures very significantly.

Clinical features. These are discussed in the section on allergy to cosmetics (p. 26.47). However, hand dermatitis is a frequent finding as a result of exposure to hand creams and liquid soaps [6]. Irritant hand dermatitis may be suspected prior to patch testing but demonstration of allergy and withdrawal of the incriminated products has resolved the dermatitis in many instances [7,8].

Allergy to MDBGN in wipes and moistened toilet tissues, vaginal examination gels and sanitary pads is a potential cause of anogenital dermatitis [8–10].

Avoidance. Methyldibromo glutaronitrile is the INCI name that should be sought on the full ingredient label. In some instances its presence may be identified by its synonym dibromcyanobutane or Euxyl K400 (Tektamer 38). Many producers of work cleansers and creams now give a full ingredient list on the health and safety data sheet. Skin products whose ingredients are not known should not be used.

Other potentially allergenic sources may require specific enquiry as to the nature of the biocide/preservative used.

Patch tests. There has been much discussion about the optimal patch-test concentration. We prefer to test MDBGN at 0.3% in petrolatum, although this has been found by some [2] and ourselves to be marginally irritant. Others have advised 0.2% as the optimum concentration [11], and 0.1% has been used, but may give false-negative reactions [12]. Conversely, positive ROAT findings and some relevant allergies have only been confirmed by testing with 0.5 or 1% concentrations [13]. Euxyl K 400 is also available at 0.5% and 1% (containing 0.1% and 0.2% MDBGN) in petrolatum. A 2.5% concentration may increase the return, but with the risk of false-positive reactions [4]. At present it is still recommended for the BCDS standard series at a concentration of 0.3% [14].

References

1 De Groot AC, van Ginkel CJ, Weijland JW. Methyldibromoglutaronitrile (Euxyl K 400): an important 'new' allergen in cosmetics. *J Am Acad Dermatol* 1996; **35**: 743–7.
2 Wilkinson JD, Shaw S, Andersen KE *et al*. Monitoring levels of preservative sensitivity in Europe. *Contact Dermatitis* 2002; **46**: 207–10.
3 Jackson JM, Fowler JF. Methyldibromoglutaronitrile (Euxyl K400): a new and important sensitizer in the United States? *J Am Acad Dermatol* 1998; **38**: 934–7.
4 Marks JG Jr, Belsito DV, DeLeo VA *et al*. North American Contact Dermatitis Group patch-test results, 1996–1998. *Arch Dermatol* 2000; **136**: 272–3.
5 Rietschel RL, Fowler JF Jr. *Fisher's Contact Dermatitis*, 5th edn. Baltimore: Lippincott, Williams & Wilkins, 2001: 222.
6 Tosti A, Guerra L, Bardazzi F *et al*. Euxyl K 400: a new sensitizer in cosmetics. *Contact Dermatitis* 1991; **25**: 89–93.
7 Wong CS, Beck MH. Occupational contact allergy to methyldibromo glutaronitrile in abrasive cleansers and work creams. *Contact Dermatitis* 2001; **44**: 311–2.
8 Zachariae C, Johansen JD, Rastogi SC, Menné T. Allergic contact dermatitis from methyldibromo glutaronitrile—clinical cases from 2003. *Contact Dermatitis* 2005; **52**: 6–8.
9 De Groot AC, de Cock PAJJM, Coenraads PJ *et al*. Methyldibromoglutaronitrile is an important contact allergen in the Netherlands. *Contact Dermatitis* 1996; **34**: 118–20.

10 Williams JD, Frowen KE, Nixon RL. Allergic contact dermatitis from methyldibromo glutaronitrile in a sanitary pad and review of Australian clinic data. *Contact Dermatitis* 2007; **56**: 164–7.
11 Schnuch A, Kelterer D, Bauer A *et al*. Quantitative patch and repeated open application testing in methyldibromo glutaronitrile-sensitive patients. *Contact Dermatitis* 2005; **52**: 197–206.
12 De Groot AC, van Ginkel CJ, Weyland JW. How to detect sensitization to Euxyl K 400. *Contact Dermatitis* 1996; **34**: 373–4.
13 Gruvberger B, Andersen KE, Brandão FM *et al*. Repeated open application test with methyldibromo glutaronitrile, a multicentre study within the EECDRG. *Contact Dermatitis* 2005; **52**: 19–23.
14 Britton JE, Wilkinson SM, English JS *et al*. The British standard series of contact dermatitis allergens: validation in clinical practice and value for clinical governance. *Br J Dermatol* 2003; **148**: 259–64.

Chloroxylenol (parachlorometaxylenol, PCMX) [1]

Chloroxylenol is a halogenated aromatic compound used not only as a preservative but also as an active disinfectant. It is water and oil soluble, and active against Gram-positive and Gram-negative bacteria.

Prevalence. Generally, reports of chloroxylenol allergy have been sporadic, with few large-scale studies. In one UK study 1.8% of 951 routinely-tested persons were patch-test positive, with a high level of current or previous relevance [1]. A more recent British study yielded a lower prevalence rate of 0.4% [2]. Reports from the USA document seven patients sensitized by medicated Vaseline or electrocardiogram paste and two with allergy to soap and hand cream [3,4].

Occurrence. Chloroxylenol is a potential allergen for the UK as it is found in Dettol, a widely used household disinfectant. This may also be used in diluted form as a wound cleanser. However, it is important to know that Dettol is used in many ways that may not always be predictable. Some people use the product to 'decontaminate' themselves or their environment. It is not uncommon for them to add Dettol to bathwater, and if they have a skin disorder that they consider represents an infection, they may add extra in the hope of its eradication. Persons with perineal inflammatory disorders are particularly liable to do this. Some may apply neat Dettol to their skin in the hope of eradicating a genuine or imagined infection; the residual smell may be a helpful diagnostic indicator of use. Clothes and bedding may be washed in Dettol and inadequately rinsed, and then worn or used.

Chloroxylenol may also be found in a number of over-the-counter pharmaceutical preparations for cuts, grazes and infections [1]. Other sources include foot and talcum powders, soaps and cleansers, work creams, coolant oils, electrocardiograph pastes and, rarely, cosmetics.

Clinical features. In many cases there is a localized skin eruption at the site where a product containing chloroxylenol has been applied, or allergy may present as an unexpected exacerbation of pre-existing dermatitis.

Hand dermatitis is a potential problem for cleaners coming in contact with disinfectants when their hands are unprotected, and allergy to chloroxylenol in other work materials (e.g. coolant oils) may give a similar distribution of rash.



Fig. 26.19 Allergy to chloroxylenol from washing with Dettol. (Geoffrey Auckland collection, Hope Hospital, Manchester, UK.)

More widespread eruptions may be associated with its use for washing and bathing (Fig. 26.19), and also when applied to clothing. Recently, widespread hypopigmentation following contact allergy to chloroxylenol added to bathwater has been reported [5].

Often, the source is only identified retrospectively after finding a positive patch test.

Avoidance. Chloroxylenol is the INCI name. Cosmetics and work creams that contain it can usually be identified from the full ingredient label or data sheet. Labels on medicated foot powders and talcs generally acknowledge it as an ingredient, but specific enquiries may be necessary to establish its presence in some topical medicaments and disinfectants.

Patch tests. Chloroxylenol is generally patch tested at 1% in petrolatum. It may cross-sensitize with chlorocresol [6]. It has been recommended as a standard allergen for the UK [1,4].

Chlorocresol (parachlorometacresol, PCMC)

Chlorocresol is identical with chloroxylenol, except for the absence of a methyl group on the benzene ring. It is active against Gram-positive and Gram-negative bacteria, and is water and oil soluble.

Prevalence. Chlorocresol is a rare allergen. A multicentre UK survey of routinely patch-tested patients confirmed a low rate of 0.6% [2].

Occurrence. The major source is corticosteroid creams. In the past, aqueous cream BP was preserved with chlorocresol, but this is generally no longer the case. We have only seen it as a sensitizer from topical medicaments, although it may be used in hand cleaners, metalworking fluids and occasionally cosmetics.

Clinical features. These are discussed in the section on medicament allergy (p. 26.43). Erythroderma has occurred in a diabetic known to be allergic to chlororesol when given insulin preserved

with m-cresol, and this improved on changing to a parabens-preserved insulin [7].

Avoidance. It is helpful to give a sensitized patient a list of corticosteroid creams that indicates their constituents and which are free from chlorocresol. Moisturizers should not be used unless they are fully ingredient-labelled or known to be free from this preservative. The INCI name is chlorocresol.

Patch tests. The recommended test concentration and vehicle is 1% chlorocresol in petrolatum. Although contact allergy is rare, its use in many popular corticosteroid creams available in the UK has prompted the BCDS to recommend its inclusion in the standard series [8]. Cross-sensitivity with chloroxylenol is well recognized [6].

References

1 Myatt AE, Beck MH. Contact sensitivity to parachlorometaxylenol (PCMX). *Clin Exp Dermatol* 1985; **10**: 491–4.
2 Britton JE, Wilkinson SM, English JS *et al*. The British standard series of contact dermatitis allergens: validation in clinical practice and value for clinical governance. *Br J Dermatol* 2003; **148**: 259–64.
3 Storrs FJ. Para-chloro-meta-xylenol allergic contact dermatitis in seven individuals. *Contact Dermatitis* 1975; **1**: 211–3.
4 Berthelot C, Zirwas MJ. Allergic contact dermatitis to chloroxylenol. *Dermatitis* 2006; **17**: 156–9.
5 Malakar S, Panda S. Post-inflammatory depigmentation following allergic contact dermatitis to chloroxylenol. *Br J Dermatol* 2001; **144**: 1275–6.
6 Burry JN, Kirk J, Reid J *et al*. Chlorocresol sensitivity. *Contact Dermatitis* 1975; **1**: 41–2.
7 Rajpar SF, Foulds IS, Abdullah A, Maheshwari M. Severe adverse cutaneous reaction to insulin due to cresol sensitivity. *Contact Dermatitis* 2006; **55**: 119–20.
8 Bourke J, Coulson I, English J. Guidelines for care of contact dermatitis. *Br J Dermatol* 2001; **145**: 877–85.

Organic mercurials

Sensitizing compounds include phenylmercuric salts and thimerosal (thiomersal; merthiolate). Thimerosal is composed of an organic mercurial and thiosalicylate. Allergy may occur to either moiety [1].

Occurrence. Organic mercurials are used as preservatives in vaccines and antigen extracts, eye drops, contact lens solutions, oils, bindi, and eye make-up and remover products. Their use in all other cosmetics is banned by European legislation. Phenylmercuric salts have been used in contraceptive jelly, antifungal treatments, shoe linings and emulsion paints.

Prevalence. Positive reactions occur in 4–5% of individuals routinely patch tested with thimerosal; higher rates have been reported in North America (10.9%) and Japan (9.5%) [2,3]. Even higher levels are found in children and adolescents [4].

Clinical features. Allergy to organic mercurials in eye medicaments and contact lens preservatives will induce a localized dermatitis affecting the eyelids, with periorbital extension. Hand eczema has been reported in a sensitized nurse undertaking vaccinations [5]. Palmar and fingertip dermatitis, isolated conjunctivitis, and even corneal neovascularization from contact lens solutions are described [6–8].

Many people have a positive patch test to thimerosal of no demonstrable relevance [9,10]. Consequently, it was ironically entitled 'contact (non) allergen of the year' in 2002 in North America [11]. A much higher return of relevant allergy, mainly inducing hand dermatitis, was seen in Israel, particularly in mechanics. It was blamed on contact with oil containing thimerosal [12]. Most sensitization is thought to develop from parenteral vaccinations and immunotherapeutic agents preserved with thimerosal [13–15]. Localized reactions from injections are rare but have been observed, and generalized dermatitis is very rare [16,17]. Of 57 patients with demonstrable thimerosal allergy only five reacted with a mild localized erythema following intramuscular challenge, and this led the authors to state that vaccines preserved with thimerosal were relatively safe [18].

Allergy to the thiosalicylic acid component may be associated with photoallergy to piroxicam [19].

Patch tests. Phenylmercuric salts may be tested at 0.01% and 0.05% in petrolatum and water. There is evidence that 0.05% gives frequent false-positive irritant reactions [20]. Thimerosal is normally tested at 0.1% in petrolatum.

References

1 Goncalo M, Figueiredo A, Goncalo S. Hypersensitivity to thimerosal: the sensitizing moiety. *Contact Dermatitis* 1996; **34**: 201–3.
2 Rietschel RL, Fowler JF Jr. *Fisher's Contact Dermatitis*, 5th edn. Baltimore: Lippincott, Williams & Wilkins, 2001.
3 Fransway AF. The problem of preservation in the 1990s. III. Agents with preservative function independent of formaldehyde release. *Am J Contact Dermatitis* 1991; **2**: 145–74.
4 Heine G, Schnuch A, Uter W, Worm M. Frequency of contact allergy in German children and adolescents patch tested between 1995 and 2002: results from the Information Network Departments of Dermatology and the German Contact Dermatitis Research Group. *Contact Dermatitis* 2004; **51**: 111–7.
5 Kiec-Swierczynska M, Krecisz B, Swierczynska-Machura D. Occupational allergic contact dermatitis due to thimerosal. *Contact Dermatitis* 2003; **48**: 337–8.
6 Sertoli A, Di Fonzo E, Spallanzani P *et al*. Allergic contact dermatitis from thimerosol in a soft contact lens wearer. *Contact Dermatitis* 1980; **6**: 292–3.
7 Van Ketel WG, Melzer-van Riemsdijk FA. Conjunctivitis due to soft lens solutions. *Contact Dermatitis* 1980; **6**: 321–4.
8 Pedersen NB. Allergic contact conjunctivitis from merthiolate in soft contact lenses. *Contact Dermatitis* 1978; **4**: 165.
9 Möller H. All these positive tests to thimerosal. *Contact Dermatitis* 1994; **31**: 209–13.
10 Suneja T, Belsito DV. Thimerosal in the detection of clinically relevant allergic contact reactions. *J Am Acad Dermatol* 2001; **45**: 23–7.
11 Belsito DV. Thimerosal: contact (non)allergen of the year. *Am J Contact Dermatitis* 2002; **13**: 1–2.
12 Slodownik D, Ingber A. Thimerosal—is it really irrelevant? *Contact Dermatitis* 2005; **53**: 324–6.
13 Möller H. Merthiolate allergy: a nationwide iatrogenic sensitization. *Acta Derm Venereol (Stockh)* 1977; **57**: 509–17.
14 Tosti A, Guerra L, Bardazzi F. Hyposensitizing therapy with standard antigenic extracts: an important source of thimerosal sensitization. *Contact Dermatitis* 1989; **20**: 173–6.
15 Osawa J, Kitamura K, Ikezawa Z *et al*. A probable role for vaccines containing thimerosal in thimerosal hypersensitivity. *Contact Dermatitis* 1991; **24**: 178–82.
16 Cox NH, Forsyth A. Thiomersal allergy and vaccination reactions. *Contact Dermatitis* 1988; **18**: 229–33.
17 Lee-Wong M, Resnick D, Chong K. A generalized reaction to thimerosal from an influenza vaccine. *Ann Allergy Asthma Immunol* 2005; **94**: 90–4.
18 Audicana MT, Munoz D, del Pozo MD *et al*. Allergic contact dermatitis from mercury antiseptics and derivatives: study protocol of tolerance to intramuscular injections of thimerosal. *Am J Contact Dermatitis* 2002; **13**: 3–9.

19 De Castro JL, Freitas JP, Brandao FM *et al*. Sensitivity to thimerosal and photosensitivity to piroxicam. *Contact Dermatitis* 1991; **24**: 187–92.
20 Geier J, Lessmann H, Uter W, Schnuch A. Patch testing with phenylmercuric acetate. *Contact Dermatitis* 2005; **53**: 117–8.

Other preservatives/biocides

Many other antimicrobial agents have been used as preservatives and biocides, and have been reported to sensitize. These include chloracetamide, triclosan (Irgasan DP300), benzalkonium chloride, glutaraldehyde, sorbic acid, benzyl alcohol, chlorphenesin, glyoxal, captan, chlorhexidine, ethylenediamine tetracetate (EDTA), dichlorophene, iodopropynyl butyl carbamate and many more [1,2]. Sources where antimicrobial protection is required are legion, but include particularly medicaments, cosmetics, cleansing agents, paints and soluble coolant oils. The possibility of allergy to this group of materials must always be considered as a cause of dermatitis.

References

1 Timmer C. Antimicrobials and disinfectants. In: Kanerva L, Elsner P, Wahlberg JE, Maibach HI, eds. *Handbook of Occupational Dermatology*. Berlin: Springer, 2000: 462–73.
2 Rietschel RL, Fowler JF Jr. *Fisher's Contact Dermatitis*, 5th edn. Baltimore: Lippincott, Williams & Wilkins, 2001: 211–59.

Vehicles and other cosmetic and medicament excipients

Lanolin [1]

Lanolin is a natural product obtained from sheep fleece. It is a complex and variable mixture of sterols, fatty alcohols, fatty acids and their esters. Wool wax alcohols (INCI name: lanolin alcohols) are obtained by hydrolysis of the oily wax fraction of the fleece. Although they are not all known, it is thought the allergens are in this fraction [2].

Attempts to reduce allergenicity include modification by acetylation, hydrogenation, ethylenation, transesterification and removal of the allergenic fractions by a purification process [1]. Allergenicity has been shown virtually to disappear by removing detergent residues and reducing the level of alcohols to below 3% (w/w) [3].

Prevalence. Prevalence of lanolin allergy in the general population is thought to be low [4]. Contact allergy is normally detected by patch testing with wool alcohols, and enhanced identification of allergic subjects has been attempted by testing with a wider range of lanolin derivatives and lanolin itself. Most surveys of patients routinely patch tested to wool alcohols report positive reactions in 1.7–3.3% [5–7]. However, other studies, in which patch testing with lanolin derivatives including Amerchol L 101 (mineral oil and lanolin alcohol) was undertaken, have shown a much higher rate of positive reactions than those using wool alcohols alone [8].

The belief that lanolin is a frequent sensitizer has been questioned by Kligman [9], and there are grounds for this because experimental sensitization of animals and humans has not been achieved [10]. Furthermore, patch testing with wool alcohols at 30% in petrolatum (as generally recommended) and with Amerchol L 101, particularly if patch tested at 100%, may give false-positive results [5,9]. In addition, retesting showed that the allergy 'disappeared' in up to 40% of those originally considered to have positive reactions [11]. Nevertheless, there is good evidence of a high prevalence of allergy to lanolin in medicaments applied to varicose eczema [12,13]. The use of lanolin-containing medicaments on other chronic eczemas, particularly in elderly women, may be associated with the development of lanolin sensitivity. However, usage on normal skin rarely seems to be associated with significant problems [14].

Occurrence. Lanolin is most commonly encountered in medicaments, emollients, bath additives and cosmetics. Other sources include polishes, waxes, inks, adhesive tapes and bandages, anticorrosive coatings, sealants and cutting oil emulsions.

Clinical features. These are discussed in the sections on allergy to cosmetics (p. 26.47) and medicaments (p. 26.43).

Avoidance. Lanolin alcohols is the INCI name for lanolin, and its presence in cosmetics can be established by examining the full ingredient label. However, prescribed and over-the-counter medicaments are not always fully ingredient-labelled in the UK, and examination of the data sheet or contacting the manufacturer may be necessary to ascertain whether it is in a medicament. This also applies to other potential domestic and work exposures such as polishes, waxes, coatings and oils.

Patch tests. Many patients state that they are allergic to lanolin but patch testing does not substantiate this. Conversely, allergy may be unsuspected, particularly when there is an associated eczema being treated with a lanolin-containing medicament.

Standard testing with wool alcohols 30% in petrolatum is advised, but where medicament sensitivity is suspected or to be excluded, extra lanolin allergens should be tested. We use Amerchol L 101 50% in petrolatum and lanolin 'as is'. Weak positive reactions may be false-positive, but can be exceedingly difficult to distinguish from weak allergic reactions.

Cetearyl alcohol

Cetearyl alcohol is the INCI name. It has emulsifying and stabilizing properties, and is also known as cetylstearyl alcohol and Lanette O. It is essentially a mixture of two long-chained stereoisomers, cetyl and stearyl alcohol. These alcohols are components of lanolin.

Prevalence. Reports of allergy are often anecdotal, although there is evidence of it being a significant allergen complicating varicose eczema and ulcers, with up to 16% positive reactions in patients with these conditions attending for patch testing [12,15]. In the UK, a level of 0.8% was seen in routinely patch-tested patients [16].

Occurrence. Cetearyl alcohol is widely used in steroid creams, emollients and cosmetics. Sometimes only one of the stereoisomers is used. It is a component of emulsifying wax and therefore found in emulsifying ointment and aqueous cream BP.

Clinical features. These are discussed in the sections on allergy to cosmetics (p. 26.47) and medicaments (p. 26.43).

Avoidance. Cetearyl alcohol is the INCI name, but cosmetics labelled as containing cetyl or stearyl alcohol should also be avoided. Avoidance of medicaments, including emollients, is more difficult, as they are not always fully ingredient-labelled. Even when they are, they may not follow the rules for cosmetics. Emulsifying wax is an ingredient that may be listed without it being clear that the preparation contains cetearyl alcohol. The designations cetylstearyl alcohol or Lanette O may be used instead of the INCI name. It may be preferable to provide a sensitized individual with a list of products free of cetearyl alcohol.

Patch tests. Although it is an uncommon allergen, its ubiquitous presence in dermatological therapies means that identification of allergy is important. The BCDS has therefore recommended its inclusion in the standard series for the UK [17]. Patients suffering from varicose eczema should always be patch tested with it. It is normally tested at 20% in petrolatum.

Ethylenediamine dihydrochloride

Ethylenediamine is a low-molecular-weight aliphatic amine. Some antihistamines are chemically related, which may be of significance to the sensitized patient.

Prevalence. Allergy to ethylenediamine is becoming less common, and sufficiently so for the EECDRG to recommend omitting it from their recommended standard series [18]. In general, the prevalence of allergy reflects the amount of nystatin/neomycin sulphate/gramicidin/triamcinolone acetonide cream (see below) being used in the catchment area of those being tested, as this is the usual source of sensitization. This preparation has been reformulated in the USA, but the original formula may still occur in generic creams. It is still used in the UK. Of routinely patch-tested patients, 1.3% were shown to be allergic, so the BCDS recommend the continued inclusion of ethylenediamine in the standard series [16,17].

Occurrence. Ethylenediamine is used as a stabilizer in a combined preparation that contains nystatin, neomycin sulphate, gramicidin and triamcinolone acetonide, marketed in the UK as Tri-Adcortyl® cream and in the USA and other countries as Mycolog® cream. The equivalent ointment does not contain ethylenediamine. It is a component of oral and parenteral aminophylline preparations, which may also come in contact with the hands. Other systemic and topical medicaments are also related to ethylenediamine, most notably hydroxyzine and probably cetirizine and levocetirizine [19,20], as well as piperazines [21], which include the antihistamines meclozine and cyclizine [22]. Industrial exposure is potentially wide, as it and related amines are used as epoxy hardeners and in coolant oils, wire-drawing lubricants, floor polish remover, antifreeze, synthetic waxes, anticorrosive paints and dye manufacture. It is used as a rubber stabilizer, but we have not seen sensitization occurring from rubber garments.

Clinical features. These are discussed in the sections on medicament (p. 26.43) and systemic contact allergy (p. 26.2).

Occupational patterns will depend on the source of the exposure, but the hands are the most likely site to be affected. In those sensitized to epoxy systems, there is often concomitant sensitization to epoxy resin, with an associated exposed-site pattern of dermatitis.

Avoidance. Avoidance of topical exposure to the creams containing nystatin, neomycin sulphate, gramicidin and triamcinolone acetonide is essential. It may also be necessary to avoid topical antihistamine creams and eye drops. Once sensitized, individuals may be at risk of systemic contact dermatitis. In the UK, avoidance of systemic hydroxyzine, piperazine, cetirizine and levocetirizine is advisable [19,20,23]. Sensitized patients must also avoid oral and parenteral aminophylline [24,25].

Avoidance of occupational exposure depends on identification of the source.

Patch tests. Ethylenediamine is tested at 1% in petrolatum. It is still recommended for standard testing in the UK because of the continued availability of Tri-Adcortyl® cream.

Other excipients

There is potential for virtually any vehicular component of a cosmetic or medicament to cause sensitization. If allergy is suspected, it may be necessary to widen the range of allergens tested. Examples include antioxidants (butylated hydroxyanisole, butylated hydroxytoluene, *t*-butylhydroquinone and gallates), surfactants (e.g. cocamidopropyl betaine), which may cause hand dermatitis in hairdressers from shampoos, Cocamide DEA (coconut diethanolamide) and humectants (e.g. propylene glycol). This list is by no means exhaustive. Many excipient allergens are available from the main allergen suppliers, suitably prepared for patch testing, but others may need to be sought from the material's manufacturer and diluted appropriately for patch testing.

References

1 *The Lanolin Book*. Hamburg: Beiersdorf AG, 1999.
2 Schlossman ML, McCarthy JP. Lanolin and derivatives chemistry: relationship to allergic contact dermatitis. *Contact Dermatitis* 1979; **5**: 65–72.
3 Clark EW, Blondeel A, Cronin E, Oleffe JA. Lanolin of reduced sensitizing potential. *Contact Dermatitis* 1981; **7**: 80–3.
4 Clark EW. Estimation of the general incidence of specific lanolin allergy. *J Soc Cosmet Chem* 1975; **26**: 323–5.
5 Wakelin SH, Smith H, White IR *et al*. A retrospective analysis of contact allergy to lanolin. *Br J Dermatol* 2001; **145**: 28–31.
6 Marks JG, Belsito DV, DeLeo VA *et al*. North American Contact Dermatitis Group patch test results for the detection of delayed-type hypersensitivity to topical allergens. *J Am Acad Dermatol* 1998; **38**: 911–8.
7 Schnuch A, Geier J, Uter W *et al*. National rates and regional differences in sensitization to allergens of the standard series. Population-adjusted frequencies of sensitization (PAFS) in 40,000 patients from a multicenter study (IVDK). *Contact Dermatitis* 1997; **37**: 200–9.
8 Matthieu L, Dockx P. Discrepancy in patch test results with wool wax alcohols and Amerchol L-101. *Contact Dermatitis* 1997; **36**: 150–1.
9 Kligman AM. The myth of lanolin allergy. *Contact Dermatitis* 1998; **39**: 103–7.
10 Kligman AM. Lanolin allergy: crisis or comedy. *Contact Dermatitis* 1983; **9**: 99–107.

11 Carmichael AJ, Foulds IS, Bransbury DS. Loss of lanolin patch test positivity. *Br J Dermatol* 1991; **125**: 573–6.
12 Wilson CL, Cameron J, Powell SM *et al*. High incidence of contact dermatitis in leg-ulcer patients: implications for management. *Clin Exp Dermatol* 1991; **16**: 250–3.
13 Machet L, Couhé C, Perrinaud A *et al*. A high prevalence of sensitization still persists in leg ulcer patients: a retrospective series of 106 patients tested between 2001 and 2002 and a meta-analysis of 1975–2003 data. *Br J Dermatol* 2004; **150**: 929–35.
14 Wolf R. The lanolin paradox. *Dermatology* 1996; **192**: 198–202.
15 Pasche-Koo F, Piletta PA, Hunziker N *et al*. High sensitization rate to emulsifiers in patients with chronic leg ulcers. *Contact Dermatitis* 1994; **31**: 226–8.
16 Britton JE, Wilkinson SM, English JS *et al*. The British standard series of contact dermatitis allergens: validation in clinical practice and value for clinical governance. *Br J Dermatol* 2003; **148**: 259–64.
17 Bourke J, Coulson I, English J. Guidelines for care of contact dermatitis. *Br J Dermatol* 2001; **145**: 877–85.
18 Bruynzeel DP, Andersen KE, Camarasa JG *et al*. The European standard series. European Environmental and Contact Dermatitis Research Group (EECDRG). *Contact Dermatitis* 1995; **33**: 145–8.
19 Ash S, Scheman AJ. Systemic contact dermatitis to hydroxyzine. *Am J Contact Dermatitis* 1997; **8**: 2–5.
20 Cusano F, Ferrara G, Crisman G *et al*. Clinicopathologic features of systemic contact dermatitis from ethylenediamine in cetirizine and levocetirizine. *Dermatology* 2006; **213**: 353–5.
21 Calnan CD. Occupational piperazine dermatitis. *Contact Dermatitis* 1975; **1**: 126.
22 Rietschel RL, Fowler JF Jr. *Fisher's Contact Dermatitis*, 5th edn. Baltimore: Lippincott, Williams & Wilkins, 2001: 186–7.
23 Burry JN. Ethylenediamine sensitivity with a systemic reaction to piperazine citrate. *Contact Dermatitis* 1978; **4**: 380.
24 Walker SL, Ferguson JE. Systemic allergic contact dermatitis due to ethylenediamine following administration of oral aminophylline. *Br J Dermatol* 2004; **150**: 594.
25 Thompson PJ, Gibb WR, Cole P *et al*. Generalised allergic reactions to aminophylline. *Thorax* 1984; **39**: 600–3.

p-Phenylenediamine and related dyes [1,2]

p-Phenylenediamine (PPD) and toluene-2,5-diamine (PTD) are aniline derivatives, whose main use is for dyeing hair. These chemicals are colourless until oxidized by hydrogen peroxide in the presence of ammonia, and polymerized by a coupler, often in the presence of other intermediates, to produce a variety of shades of colour that stay fast within the hair shaft [1]. Once oxidized and polymerized, PPD is no longer allergenic [3]. Semi-permanent hair dyeing may be undertaken with related dyes, for example *o*-nitro-*p*-phenylenediamine (ONPPD).

There is structural similarity to some azo dyes (e.g. *p*-aminoazobenzene). Many disperse dyes used to dye synthetic clothing and fibres are azo dyes and these are discussed on p. 26.65.

Prevalence. Use of hair colours has increased greatly in recent years, with 75% of US and Danish women reported to dye their hair [4]. There is clear evidence of increasing frequency of allergy in the UK, and the frequency of allergy in one clinic almost doubled to 7.1% over a 6-year period [5]. Of those patch tested in the early 2000s by the NACDG, 4.8% were allergic to PPD [6]. Similarly, 4.8% have been shown to be allergic to PPD in Germany and Austria, where there was considerable geographical variation in frequency (2.8–7.1%) [7]. In a large Belgian study of over 5000 routinely tested patients, 7.2% were allergic to PPD, 1.6% were allergic to PTD and 1.8% were allergic to ONPPD [8]. PPD is the second most common allergen of relevance to hairdressers in Europe [9].

Occurrence. PPD and PTD are found in permanent hair dyes, and ONPPD in semi-permanent hair dyes whose colour will persist for 5–10 shampooings. In the EU, PPD is allowed in hair dyes up to a concentration of 6% free base [10]. PPD has been used to dye fur. PPD may be mixed with henna and used on the skin as a temporary tattoo. Application of these is particularly likely during beach holidays. Allergy to PPD is reported from a violin chin-rest and cello bowstring stain [11,12]. PPD derivatives are used as rubber antioxidants, particularly in heavy-duty black rubber. Although reported to be in photographic developers (including those for radiography), photocopiers, petrol, oils, greases and printing inks, sensitization is rare from these sources.

Azo dyes are mainly encountered as disperse dyes for synthetic clothing. Allergy to azo dyes in maggots used for fishing bait has been reported [13].

Clinical features. PPD and related hair dye allergy can result in extremely severe skin reactions. The scalp is often relatively spared, but severe oedema and weeping of the scalp margin, ears and eyes, with more extensive secondary-spread eruptions, may be seen. However, there can be lower grade reactions, usually around the scalp margin. The patient does not always recognize the relationship of the skin eruption to dyeing the hair. Allergic contact dermatitis from hair, including connubial allergy from partner's dyed hair, has been described. This is probably the result of the presence of unoxidized residue when there is poor dyeing technique, which is more likely with self-application of the dye [14,15].

Although banned in the EU, permanent hair dye products are readily available for use on eyelashes and eyebrows. Severe reactions including blindness have been reported [16].

The possibility of contact allergy from the use of permanent hair dyes on the beard, particularly in Arabic or Asian men, should not be overlooked [17]. Lichen planus-like presentations of hair dye allergy have been reported from the Indian subcontinent, and we have seen similar patterns in Asian patients in the UK [18]. Furthermore, in our experience, hair dye allergy is relatively common in both sexes in this ethnic group. An equivalent over-representation has been identified in African-Americans [19]. Lymphomatoid eruptions are also described [13,20].

Hairdressers can become sensitized by the dyeing process, resulting in hand dermatitis. A pre-existing irritant hand dermatitis may predispose to this. Styling of dyed hair should theoretically not present a problem in view of the reported non-allergenicity of the oxidized dye.

Allergy to PPD contaminating henna tattoos has been reported frequently in recent years [21]. Reactions in the site of application of temporary tattoos may be delayed for about 2 weeks while sensitization takes place, but the subsequent reaction can be severe and persistent. Erythema multiforme-like and lichenoid eruptions are described, and both post-inflammatory hypopigmentation and hyperpigmentation can be a feature [21–24]. If affected persons dye their hair at a later date then there may be a major recrudescence of allergic contact dermatitis [25]. Subsequent clothing dye allergy is also possible [26].

Immediate-type hypersensitivity presenting as an urticarial reaction to PPD is also recognized [27], and contact anaphylaxis is described [28].

Clinical presentation of clothing dye allergy is described on p. 26.66.

Avoidance. Permanent hair dyes will be clearly marked 'contains phenylenediamines', and that patch testing is advised on each occasion prior to dyeing the hair. Open testing on retroauricular skin, with a 2-day reading, is thought to be an accurate method of identifying sensitized persons [29], but this is rarely done by the individual or the hairdressing salon. Once PPD allergy is diagnosed, the hair should not be permanently dyed. Semi-permanent dyes might be tolerated, but in the region of 25% of PPD allergic subjects are likely to have problems due to cross-sensitivity [1]. An open patch test with these dyes is also advised before use. Other alternatives include henna and colour rinses with temporary (non-PPD related) dyes.

Disperse azo clothing dye avoidance is discussed on p. 26.67.

Cross-sensitivity. Molecules with a similar structure may cross-sensitize with PPD, for example benzocaine, procaine, sulphonamides, mesalazine, diaminodiphenylmethane, *para*-aminobenzoic acid (PABA) UV filters and certain azo dyes, and patients should be counselled about this possibility [1,2,30].

Patch tests. A significant drop in the frequency of positive allergic reactions was noted when PPD base 1% in petrolatum was changed to PPD dihydrochloride by the allergen suppliers, and relevant positive cases were missed [31]. PPD base is again the preferred standard test allergen.

Concern has arisen over the risk of active sensitization on routine patch testing with PPD [32,33]. Most data on this issue have been reassuring [34,35]. It is our and others' [36] view that it should continue to be tested as a standard allergen, especially as relevant allergy is not always suspected.

In some individuals, close examination of the patch test site is required, as a positive reaction may be obscured by the black colour left by the patch test. Fierce '+++' reactions to PPD are seen on occasions. In those with a recent severe presumed hair dye allergic dermatitis, and particularly those with a temporary tattoo reaction, we generally undertake an initial test concentration of 0.5% in petrolatum, but a more conservative stepwise increase starting at 0.01%, and increasing to 0.1% before progressing to 1% has been advocated [37].

Related hair dye chemicals are also usually tested at 1% in petrolatum. Where permanent hair dye allergy is suspected it is important to test also with toluene-2,5-diamine (PTD), as many dyes contain this and not PPD. It has been shown that about 9% of PTD-allergic subjects were patch-test negative to PPD [38].

Azo dyes will normally be incorporated into a larger series of allergens for the investigation of textile dermatitis (see p. 26.67). They are also tested at 1% in petrolatum.

References

1 Rietschel RL, Fowler JF Jr. *Fisher's Contact Dermatitis*, 5th edn. Baltimore: Lippincott, Williams & Wilkins, 2001: 248–9.

2 Andersen KE, White IR, Goossens A. Allergens from the standard series. In: Frosch PJ, Menné T, Lepoittevin J-P, eds. *Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 478–80.

3 Reiss F, Fisher AA. Is hair dyed with para-phenylenediamine allergenic? *Arch Dermatol* 1974; **109**: 221–2.

4 Thyssen JP, Johansen JD, Menné T. Contact allergy epidemics and their control. *Contact Dermatitis* 2007; **56**: 185–95.

5 Patel S, Basketter DA, Jefferies D *et al*. Patch test frequency to *p*-phenylenediamine: follow up over the last 6 years. *Contact Dermatitis* 2007; **56**: 35–7.

6 Pratt MD, Belsito DV, DeLeo VA *et al*. North American Contact Dermatitis Group patch-test results, 2001–2002 study period. *Dermatitis* 2004; **15**: 176–83.

7 Schnuch A, Geier J, Uter W *et al*. National rates and regional differences in sensitization to allergens of the standard series. Population-adjusted frequencies of sensitization (PAFS) in 40,000 patients from a multicenter study (IVDK). *Contact Dermatitis* 1997; **37**: 200–9.

8 Broeckx W, Blondeel A, Dooms-Goossens A, Achten G. Cosmetic intolerance. *Contact Dermatitis* 1987; **16**: 189–94.

9 Frosch PJ, Burrows D, Camarasa JG *et al*. Allergic reactions to a hairdressers' series: results from 9 European centres. The European Environmental and Contact Dermatitis Research Group (EECDRG). *Contact Dermatitis* 1993; **28**: 180–3.

10 White IR, De Groot AC. Cosmetics and skin care products. In: Frosch PJ, Menné T, Lepoittevin J-P, eds. *Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 499.

11 Bork K. Allergic contact dermatitis on a violinist's neck from para-phenylenediamine in a chin rest stain. *Contact Dermatitis* 1993; **28**: 250–1.

12 O'Hagan AH, Bingham EA. Cellist's finger dermatitis. *Contact Dermatitis* 2001; **45**: 319.

13 Warren LJ, Marren P. Textile dermatitis and dyed maggot exposure. *Contact Dermatitis* 1997; **36**: 106.

14 Veysey C, Burge S, Cooper S. Consort contact dermatitis to paraphenylenediamine, with an unusual clinical presentation of tumid plaques. *Contact Dermatitis* 2007; **56**: 366–7.

15 Rastogi SC, Søsted H, Johansen JD *et al*. Unconsumed precursors and couplers after formation of oxidative hair dyes. *Contact Dermatitis* 2006; **55**: 95–100.

16 Teixeira M, de Wachter L, Ronsyn E, Goossens A. Contact allergy to para-phenylenediamine in a permanent eyelash dye. *Contact Dermatitis* 2006; **55**: 92–4.

17 Hsu TS, Davis MD, el-Azhary R *et al*. Beard dermatitis due to para-phenylenediamine use in Arabic men. *J Am Acad Dermatol* 2001; **44**: 867–9.

18 Sharma VK, Mandal SK, Sethuraman G, Bakshi NA. Para-phenylenediamine-induced lichenoid eruptions. *Contact Dermatitis* 1999; **41**: 40–1.

19 Deleo VA, Taylor SC, Belsito DV *et al*. The effect of race and ethnicity on patch test results. *J Am Acad Dermatol* 2002; **46**: S107–12.

20 Calzavara-Pinton P, Capezzera R, Zane C *et al*. Lymphomatoid allergic contact dermatitis from *para*-phenylenediamine. *Contact Dermatitis* 2002; **47**: 173–4.

21 Wolf R, Wolf D, Matz H, Orion E. Cutaneous reactions to temporary tattoos. *Dermatol Online J* 2003; **9**: 3.

22 Jappe U, Hausen BM, Petzoldt D. Erythema-multiforme-like eruption and depigmentation following allergic contact dermatitis from a paint-on henna tattoo, due to para-phenylenediamine contact hypersensitivity. *Contact Dermatitis* 2001; **45**: 249–50.

23 Rubegni P, Fimiani M, de Aloe G *et al*. Lichenoid reaction to temporary tattoo. *Contact Dermatitis* 2000; **42**: 117–8.

24 Valsecchi R, Leghissa P, Di Landro A *et al*. Persistent leukoderma after henna tattoo. *Contact Dermatitis* 2007; **56**: 108–9.

25 Redlick F, DeKoven J. Allergic contact dermatitis to paraphenylendiamine in hair dye after sensitization from black henna tattoos: a report of 6 cases. *Can Med Assoc J* 2007; **176**: 445–6.

26 Saunders H, O'Brien T, Nixon R. Textile dye allergic contact dermatitis following paraphenylenediamine sensitization from a temporary tattoo. *Australas J Dermatol* 2004; **45**: 229–31.

27 Birnie AJ, English JS. Immediate hypersensitivity to paraphenylenediamine. *Contact Dermatitis* 2007; **56**: 240.

28 Pasche-Koo F, French L, Piletta-Zanin P. Contact urticaria and shock due to hair dye. *Allergy* 1998; **53**: 904–5.

29 Krasteva M, Cristaudo A, Hall B *et al*. Contact sensitivity to hair dyes can be detected by the consumer open test. *Eur J Dermatol* 2002; **12**: 322–6.

30 Charles J, Bourrain JL, Tessier A *et al*. Mesalazine and para-phenylenediamine allergy. *Contact Dermatitis* 2004; **51**: 313–4.

31 Andersen KE, Burrows D, Cronin E *et al*. Recommended changes to standard series. *Contact Dermatitis* 1988; **19**: 389–90.
32 Hillen U, Jappe U, Frosch PJ *et al*. Late reactions to the patch-test preparations para-phenylenediamine and epoxy resin: a prospective multicentre investigation of the German Contact Dermatitis Research Group. *Br J Dermatol* 2006: **154**: 665–70.
33 Devos SA, Van der Valk PGM. The risk of active sensitisation to PPD. *Contact Dermatitis* 2001: **44**: 273–5.
34 Dawe SA, White IR, Rycroft RJ *et al*. Active sensitization to para-phenylenediamine and its relevance: a 10-year review. *Contact Dermatitis* 2004: 51: 96–7.
35 Thyssen JP, Menné T, Nielsen NH, Linneberg A. Is there a risk of active sensitization to PPD by patch testing the general population? *Contact Dermatitis* 2007; **57**: 133–4.
36 Mcfadden JP, White IR, Johansen J, Bruze M. Should para-phenylenediamine (PPD) 1% pet. be part of commercially available standard series? *Contact Dermatitis* 2005; **53**: 183–4.
37 Ho SG, White IR, Rycroft RJ, McFadden JP. A new approach to patch testing patients with para-phenylenediamine allergy secondary to temporary black henna tattoos. *Contact Dermatitis* 2004; **51**: 213–4.
38 Winhoven SM, Rutter KJ, Beck MH. Toluene-2,5-diamine may be an isolated allergy in individuals sensitized by permanent hair dye. *Contact Dermatitis* 2007; **57**: 193.

UV filters [1–3]

UV filters work by absorbing light chemically or by acting as a physical block. The latter agents are usually based on titanium or zinc oxide, which are not sensitizers. However, some chemical UV filters may be contact allergens, photocontact allergens or both. The main groups of light-absorbing chemicals are: PABA and its derivatives, cinnamates and salicylates, which absorb predominantly UVB light; benzophenones, which also absorb some longer wavelength UVA light; and dibenzoylmethanes and camphor derivatives, which tend to absorb the longer wavelength UV light [2,3]. UV filters may be known by many synonyms; the INCI names are used here.

Prevalence. Ordinarily UV filters are not tested in the standard series, and aimed testing is generally the rule. However, many UV filters are included routinely in the photopatch-test series. The pattern of usage of UV filters varies, and prevalence figures will reflect this.

Benzophenone 3 (oxybenzone) is the most frequently reported UV filter allergen [1,3,4]. Benzophenone 10 has also been identified as an allergen and photoallergen but is not commonly used in sunscreen manufacture [5]. Benzophenone 4 has recently been reported as an emerging cosmetic allergen [6].

Isopropyl dibenzoylmethane was a common photosensitizer in the past, and as a result has been withdrawn from the market [7]. Butyl methoxydibenzoylmethane is an occasional sensitizer and photosensitizer [4]. Allergy and photoallergy to PABA and derivatives are now less frequent, but these agents may still be found in cosmetics and sunscreens [4]. Cinnamates are commonly used as UVB filters, and both allergy and photoallergy to them are seen occasionally [4,8]. A high prevalence of allergy to 4-methylbenzilidene camphor was noted in one survey, but other reports have indicated a lesser frequency or have referred to individual cases [4,7]. Small numbers of cases of phenylbenzimidazole sulphonic acid allergy and photoallergy have also been seen [1,5]. Allergy to salicylates has only occasionally been reported [9,10]. Others include drometrizole trisiloxane, and photoallergy to octyl triazone and methylene-bis-benzotriazolyl tetramethylbutylphenol (Tinosorb M®) [11–13].

Occurrence. These chemicals are not confined to sunscreens. They may be added to cosmetics in small quantities to prevent photodegradation and also as an 'antiageing' agent. UV light absorbers may be added to plastics and spandex. Allergy from this source is unusual but has been reported, most notably from 2-(2-hydroxy-5-methylphenyl)-benzotriazole (Tinuvin P) [14,15].

Clinical features. Allergy and photoallergy from UV filters may coexist or occur separately. Clinical features are discussed under photocontact and also cosmetic allergy (see p. 26.47). It is important to appreciate that other photodermatoses can be complicated by photoallergy to UV filters being used in treatment, and this may easily go unrecognized. The possibility of allergy and photoallergy to UV filters must be considered before individuals are diagnosed as having an idiopathic photodermatosis such as polymorphic light eruption.

Avoidance. Once allergy or photoallergy has been demonstrated, patients should be appraised of the need to avoid sunscreens and cosmetics containing the allergen, which will be identified by its INCI name. They should only use fully ingredient-labelled cosmetics (including hairsprays). In addition, a list of synonyms should be given to the patients as they may encounter sunscreens labelled differently in other countries.

Patch tests. UV filters are generally tested at 10% in petrolatum, although 5% has also been advocated. We have found that benzophenone 4 tested at 10% gives many weak reactions which we have interpreted as false positive, particularly as they have been of questionable relevance. A lower concentration may be a better test concentration. Sunscreens and cosmetics containing UV filters should also be patch tested, and if necessary photopatch tested at the same time.

References

1 White IR, De Groot AC. Cosmetics and skin care products. In: Frosch PJ, Menné T, Lepoittevin J-P, eds. *Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 493–506.
2 Rietschel RL, Fowler JF Jr. *Fisher's Contact Dermatitis*, 5th edn. Baltimore: Lippincott, Williams & Wilkins, 2001: 402–4.
3 Palmer RA, White IR. Phototoxic and photoallergic reactions. In: Frosch PJ, Menné T, Lepoittevin J-P, eds. *Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 309–17.
4 Bryden AM, Mosely H, Ibbotson SH *et al*. Photopatch testing of 1155 patients: results of the U.K. multicentre photopatch study group. *Br J Dermatol* 1997; **155**: 737–47.
5 Darvay A, White IR, Rycroft RJ *et al*. Photoallergic contact dermatitis is uncommon. *Br J Dermatol* 2001; **145**: 597–601.
6 Hughes TM, Stone NM. Benzophenone 4: an emerging allergen in cosmetics and toiletries? *Contact Dermatitis* 2007; **56**: 153–6.
7 Schauder S, Ippen H. [Photoallergic and allergic contact eczema caused by dibenzoylmethane compounds and other sunscreening agents.] *Hautarzt* 1988; **39**: 435–40.
8 Delplace D, Blondeel A. Octocrylene: really non-allergenic? *Contact Dermatitis* 2006; **54**: 295.

9 Singh EM, Beck MH. Octyl salicylate: a new contact sensitivity. *Contact Dermatitis* 2007; **56**: 48.
10 Shaw DW. Allergic contact dermatitis from octisalate and cis-3-hexenyl salicylate. *Dermatitis* 2006; **17**: 152–5.
11 Hughes TM, Martin JA, Lewis VJ, Stone NM. Allergic contact dermatitis to drometrizole trisiloxane in a sunscreen with concomitant sensitivities to other sun screens. *Contact Dermatitis* 2005; **52**: 226–7.
12 Sommer S, Wilkinson SM, English JS, Ferguson J. Photoallergic contact dermatitis from the sunscreen octyl triazone. *Contact Dermatitis* 2002; **46**: 304–5.
13 González-Pérez R, Trébol I, García-Río I *et al*. Allergic contact dermatitis from methylene-bis-benzotriazolyl tetramethylbutylphenol (Tinosorb M®). *Contact Dermatitis* 2007; **56**: 121.
14 Niklasson B, Björkner B. Contact allergy to the UV-absorber Tinuvin P in plastics. *Contact Dermatitis* 1989; **21**: 330–4.
15 Arisu K, Hayakawa R, Ogino Y *et al*. Tinuvin P in a spandex tape as a cause of clothing dermatitis. *Contact Dermatitis* 1992; **26**: 311–6.

Rubber

Chemistry. Natural rubber was used by the native South Americans before the voyages of Columbus in 1492. For 200 years Europeans tried to duplicate the water-resistant shoes, coats and capes, but were unsuccessful. In 1791 the first commercial application of rubber began when an English manufacturer patented a method of waterproofing cloth by treating it with a solution of rubber in turpentine. Charles Macintosh, in 1823, established a plant in Glasgow for the manufacture of waterproof cloth and rainproof garments. Initially, the resulting products became brittle in cold weather and tacky and malodorous in summer. In 1839, the American Charles Goodyear discovered that heating rubber with sulphur removed the unfavourable properties, in a process termed vulcanization.

The term 'latex' defines an aqueous dispersion of a rubber. The rubber obtained from latex by drying or coagulation is called latex rubber. Natural latex is derived from the sap of the tree *Hevea brasiliensis*. During the world wars the availability of natural latex was limited and proved a stimulus to the development of various synthetic rubbers.

Rubber dermatitis is usually caused by accelerators, antioxidants and other chemicals used in its manufacture. More than 1000 substances are employed for these purposes [1,2].

Prevalence and incidence. The incidence of sensitivity is of the order of 5–10% of patients tested in most patch-test series [3]. Rubber dermatitis occurs with equal frequency in both sexes, but the actual sensitizers differ, depending on exposure, the antioxidants in black rubber more frequently causing problems in men from occupational exposure.

Occurrence. Potential sources of exposure include the following:
1 Rubber industries and revulcanization shops: both non-vulcanized and vulcanized rubber-containing additives are sensitizers; in rubber-tyre factories, much dermatitis is irritant rather than allergic.
2 Other workplaces: rubber gloves, other protection for hands and fingers, electric cords, tubes, handles (e.g. on hammers), packings, masks, rubber bands, etc.
3 Daily life: shoes, gloves, clothing, condoms and many other articles.

References

1 Saint Cyr DR. Rubber, natural. In: Kirk RE, Othmer DF, eds. *Encyclopedia of Chemical Technology*. Baltimore: Wiley, 1982: 468–91.
2 Kortschak E. Rubber chemicals. *Australas J Dermatol* 1977; **50**: 174–82.
3 Geier J, Gefeller O. Sensitivity of patch test with rubber mixes: results of the information network of departments of dermatology from 1990 to 1993. *Am J Contact Dermatitis* 1995; **6**: 143–9.

Clinical features. Rubber sensitivity may be the primary cause of a dermatitis or it may become superimposed on an existing dermatitis, as sometimes occurs following the use of rubber gloves [1] (Fig. 26.20). It is not always obvious, and many cases will be missed if patients are not routinely patch tested with a series of the more common rubber chemicals. A positive patch-test reaction to a rubber chemical is usually relevant.

Dermatitis from rubber gloves may be diffuse, but is more often localized to the dorsa of the hands, especially over the knuckles and the wrist, where a sharp proximal margin is often evident. The eyelids and face may also be involved from touching the face while wearing gloves. Dermatitis may be caused by objects touched only briefly during a daily routine. A digitate and patchy dermatitis has occurred in previously sensitized patients following examination with surgeons' gloves.

Shoe dermatitis occurs in both adults and children, and in the latter group needs to be differentiated from juvenile plantar dermatosis [2]. Rubber chemicals may occur in almost any part of the shoe [3], and a rubber adhesive is commonly used to glue parts together. The dermatitis may occur on the dorsum of the foot, soles or toes, usually with sparing of the web spaces and instep. A secondary dermatitis, especially of the hands, is not uncommon. The outer soles rarely cause shoe dermatitis. Primary sensitization from all-rubber boots and rubber shoes is common, especially in agricultural workers.

Antioxidants related to PPD are used in car tyres and wear-resistant rubber products. They often impart a dark or black colour to the rubber materials vulcanized with them. Not all cases have an occupational origin. Black rubber flexes or cables, hoses, grips and even scuba masks or squash balls may be responsible. The ensuing dermatitis may sometimes be purpuric, and an erythema multiforme-like presentation has also been reported.



Fig. 26.20 Contact dermatitis from rubber gloves. (Courtesy of Dr J.D. Wilkinson, Amersham General Hospital, Amersham, UK.)



Fig. 26.21 Allergic contact dermatitis to elastic in clothing. (Courtesy of Dr J.D. Wilkinson, Amersham General Hospital, Amersham, UK.)

In some cases, the site of dermatitis may provide a clue as, for instance, when the dermatitis is due to a rubber finger-stall used when counting money or rubber bands under a wrist watch. Rubber dermatitis may also occur at the site of contact with rubber in clothing (Fig. 26.21) or dressings, on the face from swimming goggles, between the thighs or on the abdomen from hot water bottles, and on the knees from kneeling mats. Genital dermatitis or pruritus vulvae may occur following the use of condoms and diaphragms, and may also result from rubber catheters, when the dermatitis also spreads down the thighs. An apparent worsening of venous eczema may be related to allergy to rubber in elastic bandaging, and such patients are prone to develop a secondary generalized eczema. A generalized dermatitis may occur after sleeping on a rubber mattress or using rubber pillows, or the dermatitis may be predominantly on the side on which the patient sleeps.

References

1 Rietschel RL, Fowler JF Jr. *Fisher's Contact Dermatitis*, 5th edn. Baltimore: Lippincott, Williams & Wilkins, 2001.

2 Cockayne SE, Shah M, Messenger AG, Gawkrodger DJ. Foot dermatitis in children: causative allergens and follow-up. *Contact Dermatitis* 1998; **38**: 203–6.

3 Taylor JS, Erkek E, Podmore P. Shoes. In: Frosch PJ, Menné T, Lepoittevin J-P, eds. *Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 623–52.

Avoidance and prognosis. Although it may be impossible to avoid contact with rubber entirely, many patients remain clear of dermatitis, and others may only have intermittent symptoms if they take simple precautions to avoid contact with rubber material. In many cases, hand eczema improves or clears if patients can be persuaded to change from rubber gloves to cotton-lined vinyl gloves.

Patch tests. Most types of rubber contain up to 5% of potentially allergenic additives. Dermatitis from the smoked sheets of rubber used as raw material is rarely reported. The sensitizers in rubber change in accordance with industrial development, technical requirements and market prices. Unless the choice of substances kept for patch testing is constantly supplemented, rubber dermatitis will be missed. A list of potential sensitizers in rubber is shown in Table 26.9.

Table 26.9 Common sensitizers in rubber.

Mercapto mix
Mercaptobenzothiazole (MBT)
Cyclohexylbenzothiazylsulphenamide (CBS)
Dibenzothiazyldisulphide (MBTS)
Morpholinylmercaptobenzothiazole
Patch-test concentration: 0.5% each = total 2% in petrolatum
Thiuram mix
Tetramethylthiuram disulphide (TMTD)
Tetramethylthiuram monosulphide (TMTM)
Tetraethylthiuram disulphide (TETD)
Dipentamethylenethiuram disulphide (PTD)
Patch-test concentration: 0.25% each = total 1% in petrolatum
Black rubber mix
Phenylcyclohexyl-p-phenylenediamine (CPPD)
Phenylisopropyl-p-phenylenediamine (IPPD) (identical to isopropylaminodiphenylamine)
Diphenyl-p-phenylenediamine (DPPD)
Patch-test concentration: 0.25% of CPPD and DPPD, 0.1% of IPPD = total 0.6% in petrolatum
Carba mix
1,3-Diphenylguanidine (DPG)
bis-(Diethyldithiocarbamato) zinc (ZDC)
bis-(Dibutyldithiocarbamato) zinc (ZBC)
Patch-test concentration: 1% each = total 3% in petrolatum

The mixtures mentioned are commercially available.

Most standard series contain rubber chemicals, both mixes and individual chemicals, as a screen for rubber-induced contact hypersensitivity. The mixes of rubber chemicals are useful because they allow allergy to be detected with fewer patch tests [1]. In order to avoid patch-test sensitization, the concentration of the individual chemicals must be reduced, and this involves the risk of false-negative reactions. This is especially so for mercaptobenzothiazole (MBT), and therefore MBT and MBT mix are usually both included in most patch-test series [2]. The concentrations of the individual chemicals in these mixes are therefore selected as a compromise. Too high a concentration will carry the risk of active sensitization, whereas too low a concentration of any of the individual ingredients may lead to false-negative reactions and missed sensitivities. PPD derivatives are sensitizing when tested at 2% in petrolatum, and should be tested at 0.25% and 0.1%. Simultaneous sensitivity to PPD and to the PPD derivatives in rubber is uncommon. Black rubber mix is no longer included in the European standard series, having been replaced by IPPD. Testing with IPPD alone will potentially miss 10% of individuals allergic to this group of antioxidants [3]. Carba mix and the diphenylguanidine in the carba mix often produce marginal irritant reactions. Although carba mix has been deleted from the European standard series, the predominant use of carbamates as accelerators in rubber gloves [4] argues for retention of the mix, as in the North American and British series, rather than relying on a cross-reaction with thiurams to detect the allergy.

Where rubber allergy is suspected, additional testing with the ingredients of the mixes and additional rubber-related allergens may reveal what would otherwise have been a missed contact allergy [5,6]. Cyclohexylthiophthalimide, a common rubber antidegradant, frequently causes reactions, but the relevance is often uncertain, particularly where there is no ingredient labelling [7]. Dithiodimorpholine [8] is also reported as a rubber allergen in footwear; sensitivity to which is potentially missed by not testing with an extended series. It is also essential to test with a sample of the suspect rubber in case sensitization has occurred to a chemical not present in any standard or rubber series. Delayed-type hypersensitivity reactions to natural rubber latex itself have been reported [9].

Synthetic rubbers such as styrene–butadiene, polybutadiene, polychloroprene (neoprene) and polyurethane (spandex) may contain similar accelerators and antioxidants. In particular, neoprene items frequently contain thioureas [10]. Elastane (Lycra) does not contain rubber accelerators.

Sensitivity to a certain rubber chemical does not necessarily indicate any specific source, although sensitivity to carbamates and thiurams suggests rubber gloves, mercapto compounds suggests shoes, and the PPD group is mainly associated with black rubber products such as tyres.

References

1 Geier J, Gefeller O. Sensitivity of patch test with rubber mixes: results of the information network of departments of dermatology from 1990 to 1993. *Am J Contact Dermatitis* 1995; **6**: 143–9.

2 Adams AK, Warshaw EM. Allergic contact dermatitis from mercapto compounds. *Dermatitis* 2006; **17**: 56–70.

3 Andersen KE, White IR, Goossens A. Allergens from the standard series. In: Frosch PJ, Menné T, Lepoittevin J-P, eds. *Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 623–52.

4 Bergendorff O, Persson C, Hansson C. High performance liquid chromatography analysis of rubber allergens in protective gloves used in health care. *Contact Dermatitis* 2006; **55**: 210–5.

5 Holness DL, Nethercott JR. Results of patch testing with a special series of rubber allergens. *Contact Dermatitis* 1997; **36**: 207–11.

6 Sherertz EF, Fransway AF, Belsito DV *et al*. Patch testing discordance alert: false-negative findings with rubber additives and fragrances. *J Am Acad Dermatol* 2001; **45**: 313–4.

7 Huygens S, Barbaud A, Goossens A. Frequency and relevance of positive patch tests to cyclohexylthiophthalimide, a new rubber allergen. *Eur J Dermatol* 2001; **11**: 443–5.

8 Belsito DV. Common shoe allergens undetected by commercial patch-testing kits: dithiodimorpholine and isocyanates. *Am J Contact Dermatitis* 2003; **14**: 95–6.

9 Sommer S, Wilkinson SM, Beck MH *et al*. Type IV hypersensitivity reactions to natural rubber latex: results of a multicentre study. *Br J Dermatol* 2002; **146**: 114–7.

10 Comfere NI, Davis MD, Fett DD. Patch-test reactions to thioureas are frequently relevant. *Dermatitis* 2005; **16**: 121–3.

Clothing [1–5]

Textile fibres may be natural, for example cotton, wool, silk, linen, rubber, or they may be synthetic, for example cellulose derivatives (rayon), polyamides such as nylon, polyesters, acrylics and elastomers. Apart from rubber, they rarely sensitize in their own right.

Commoner allergens in clothing include nickel (p. 26.30), chromate (in leather and as a dyeing mordant) (p. 26.35), rubber (p. 26.63), glues, textile dyes, formaldehyde (p. 26.49) and resins.

Disperse dyes are the class of dye most likely to sensitize, particularly as it is not possible to make them completely fast to the fibres [2]. They are principally anthroquinone and azo dyes. Disperse dyes may contain more than one fraction, as well as impurities, all of which can sensitize [6]. A mixture of several different dyes may be responsible for the final colour [1]. Fibre-reactive dyes are covalently bound to the fibre and unlikely to cause problems from clothing, but may sensitize those handling the dye powder [7]. However, if the clothing is not adequately rinsed during the production process reactive dye residue in new unwashed garments may then cause allergic dermatitis [8]. Clothing dermatitis has also been reported from acid, basic, direct, vat and solvent dyes, as well as coupling agents [1].

Finishes are used on textiles to give 'body' to inexpensive materials, and provide crease-resistant and stain-repellent properties. Urea and melamine formaldehyde resin finishes are now being superseded by others, such as dimethylolalkyl carbamate, dimethylolethylene urea, dihydroxydimethylethylene urea and other similar reactive cyclic urea resins [1,4]. These new resins may be less sensitizing, particularly as they release less formaldehyde and remain relatively fast.

Optical whiteners are frequently added to clothes, and although in the past they were associated with contact dermatitis, there are no recent reports of allergy [2]. Fire retardants in clothing have also been reported to cause sensitivity [9]. Isocyanates in an anti-pill finish have caused dermatitis occupationally [10].

Incidence and prevalence. Since 1970, textile dermatitis has probably become rarer, mainly due to changed methods of production, although accurate information on the incidence and prevalence of clothing allergy is lacking. In those undergoing patch testing, the frequency of allergy to textile dyes has varied from 1.1 to 5.8% and for resins from 1.2 to 2.3%, either from formaldehyde or the resin, or both [11].

Many clothing resins will release formaldehyde, and free formaldehyde may be found on treated garments and will induce dermatitis in its own right. Most, but not all, patients with formaldehyde textile resin dermatitis are also sensitive to formaldehyde [12]. Between 1950 and 1965, formaldehyde resins used for crease-resistant finishes caused numerous cases of textile dermatitis. The most frequently identified resins causing allergy in recent studies are melamine formaldehyde, ethyleneurea melamine formaldehyde, dimethylol dihydroxyethyleneurea, dimethylol propylene urea and urea formaldehyde resins [13–15].

Recent surveys confirm that the most commonly identified azo disperse dye allergens are Disperse Blue 124 and the very closely related Disperse Blue 106, followed by Disperse Orange 3, Red 1, Yellow 3 and Red 17 [16–18]. In particular, Disperse Blue dyes 106 and 124 have been reported as causing frequent problems in Canada, especially from blue/black polyester or acetate garment liners [17]. In southern Sweden, however, Disperse Orange 1 was the most common textile dye allergen [19]. The most frequently reported sensitizing anthroquinone dyes are Disperse Red 11, Blue 3 and Blue 35 [3,16]. Basic Red 46 in acrylic blend socks has caused an outbreak of foot dermatitis, but the problem so far seems to have been confined to Australia [20].

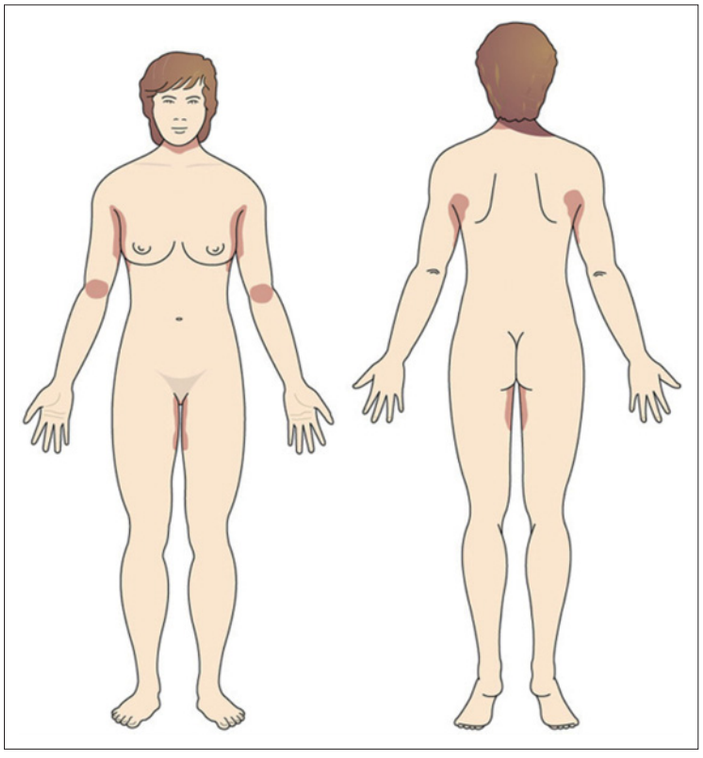


Fig. 26.22 Pattern of textile dermatitis.

Occurrence. Disperse dyes are used to colour artificial fibres such as polyester, acetate, acrylic and nylon. Both azo and anthraquinone dyes may cause dermatitis from modern artificial fibres, and non-disperse azo dyes from natural fibres. Reactive dyes will combine with protein and cellulose in natural fibres and polyamides. Rarely, other chemicals such as Naphthol AS (a coupling agent for cotton dyeing) may sensitize [21]. Textile resins are added to cotton and mixed cotton/polyester fibres as well as rayon and crease-resistant linen.

Clinical features. The distribution of contact dermatitis, in areas of sweating and friction, is the same for dyes and finishes (Fig. 26.22). The eruption typically starts in the axillae, sparing the hairy part of the vault, and forms a crescentic patch on the anterior chest wall sharply limited by the underwear (Fig. 26.23). The anterior and posterior folds are also affected. The dermatitis is often sheeted, and the inner posterior thighs, popliteal fossae and lower leg may be involved when trousers or tights (pantyhose) are the responsible garments. Allergy to dyes in socks, stockings and tights often starts on the dorsa of the feet, where they are occluded by footwear. The typical pattern for allergy to tights and stockings is shown in Fig. 26.24. Long sleeves cause eruptions in the elbow flexures, and collars provoke a rash around the neck. Later in the course of the disease, the chest and upper back may be involved, sparing areas protected by shoulder straps and underwear. In the flexures and round the neck the lesions are diffuse and oedematous; on the shoulders and chest they are usually papular. Papular dermatitis may cover the whole body, and eyelid dermatitis may rarely be a feature.



Fig. 26.23 Axillary dermatitis (sparing the axillary vault). The characteristic pattern of eczema seen in patients allergic to textile dyes and finishes. (Courtesy of Dr J.D. Wilkinson, Amersham General Hospital, Amersham, UK.)

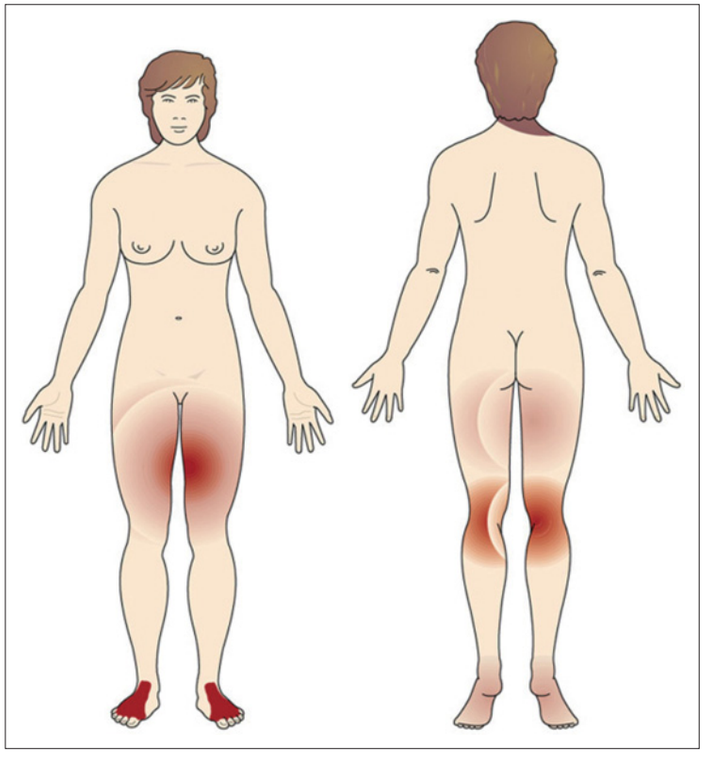


Fig. 26.24 Pattern of dermatitis from nylon stockings.

In the early 1970s permanent-press resins were also the source of an outbreak of follicular dermatitis due to a range of coloured Canadian perma-press sheets [22]. Patients developed a widespread itchy, follicular rash especially affecting the arms and legs, but also with eczema of the face and ears due to contact with pillowcases. Dyes have also been described as sensitizers in perma-press bed linen [23].

Some fabrics provoke a purpuric, sometimes lichenoid dermatitis in areas of contact, as seen with uniforms in the Second World War (khaki dermatitis) [24]. Textile dyes and resins will occasionally cause purpuric eruptions associated with contact allergy

[23–28]. In the early 1970s a pigmented dermatitis was described that was caused by allergy to optical whiteners in detergents. It started on the inner aspects of the upper arms, from where it spread to the trunk, with indistinct coalescing macules as the major lesions [29]. In some cases, the dermatitis left persistent hyperpigmentation.

Hand dermatitis may be a feature of textile allergy from occupational exposure [30].

Patterns of allergy from nickel, chromate (in leather) and rubber are described in the sections discussing these allergens.

Avoidance [2,3]. Patients sensitive to formaldehyde or one of the formaldehyde resins should be advised to avoid treated fabrics, for example drip-dry, crease-resistant or durable-press cotton, cotton-mix and rayon clothes. Satisfactory alternatives include wool, silk and 100% nylon, polyester or acrylic fabric, as these rarely contain significant amounts of formaldehyde or formaldehyde resins. The washing of new clothes at least twice before wearing may also be useful as this will help to remove free formaldehyde [31].

A precise knowledge of the dye responsible for an individual's allergy is not helpful as cross-sensitivity is common and the finished colour is commonly a mix of several dyes. Strongly coloured synthetic clothing should be avoided, but lightly coloured garments may sometimes be tolerated. Pure natural fibres, such as cotton, wool, linen and silk of any colour, can generally be worn.

Patients with disperse dye stocking dermatitis can buy undyed nylon stockings and dye them by soaking in a potassium permanganate solution (0.3–0.6%) for 30–60 min. Stockings and tights (pantyhose) without azo dyes may be commercially available, but manufacturers have to be contacted directly. Grey stockings and tights do not usually contain Disperse Yellow 3 or Orange 3. Lycra products are normally dyed with acid dyes rather than azo dyes.

The wearing of undergarments may protect the skin from allergy to outer clothing, although there is still the possibility that sweating could leach out allergens.

Patch tests. Patch testing with the suspected clothing can be undertaken, although there is a high risk of obtaining a false-negative reaction. Soaking 1 cm^2 of the fabric in water for 10 min before testing might increase the return, and extraction techniques have also been suggested [2,32].

Formaldehyde is a standard-series allergen. A PPD-positive patch test may alert one to clothing dye allergy, but it is an inadequate screen. Standard-series screening with four textile disperse dye allergens has been advocated, and the possibility of using a textile dye mix explored, but further data are required [33].

The commercial allergen suppliers have developed screening series of clothing allergens and these will help detect most cases of textile allergy. As various azo dyes and *p*-phenylenediamine are structurally similar there is a risk of multiple strong positive reactions in allergic patients screened for clothing dye allergy. It has not been possible so far to rationalize testing to prevent this [34]. Patients investigated with a series of textile azo dyes should be warned of the risk, although low, of multiple positive reactions, particularly if there is a previous history of hair dye or temporary tattoo allergy. In such cases consideration for testing for textile allergy separately from standard series patch testing should be considered.

References

1 Le Coz C-J. Clothing. In: Frosch PJ, Menné T, Lepoittevin J-P eds. *Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 679–702.
2 Rietschel RL, Fowler JF Jr. *Fisher's Contact Dermatitis*, 5th edn. Baltimore: Lippincott, Williams & Wilkins, 2001: 279–319.
3 Cronin E. *Contact Dermatitis*. Edinburgh: Churchill Livingstone, 1980: 36–92.
4 Hatch KL, Maibach HI. Textile dermatitis, an update. (1) Resins, additives and fibres. *Contact Dermatitis* 1995; **32**: 319–27.
5 Hatch KL, Maibach HI. Textile dye allergic contact dermatitis prevalence. *Contact Dermatitis* 2000; **42**: 187–95.
6 Foussereau J, Dallara JM. Purity of standardized textile dye allergens: a thin layer chromatography study. *Contact Dermatitis* 1986; **14**: 303–6.
7 Wilkinson SM, McGechaen K. Occupational allergic contact dermatitis from reactive dyes. *Contact Dermatitis* 1996; **35**: 376.
8 Moreau L, Goossens A. Allergic contact dermatitis associated with reactive dyes in a dark garment: a case report. *Contact Dermatitis* 2005; **53**: 150–4.
9 Andersen KE. Sensitivity to flame retardant tris (2,3-dibromopropyl) phosphate (Firemaster LVT 23P). *Contact Dermatitis* 1977; **3**: 297–300.
10 Wilkinson SM, Cartwright PH, Armitage JD, English JS. Allergic contact dermatitis from 1,6-diisocyanatohexane in an anti-pill finish. *Contact Dermatitis* 1991; **25**: 94–6.
11 Hatch KL, Maibach HI. Textiles. In: Kanerva L, Elsner P, Wahlberg JE, Maibach HI, eds. *Handbook of Occupational Dermatology*. Berlin: Springer, 2000: 622–36.
12 Sheretz EF. Clothing dermatitis: practical aspects for the clinician. *Am J Contact Dermatitis* 1992; **3**: 91–6.
13 Carlson RM, Smith MC, Nedorost ST. Diagnosis and treatment of dermatitis due to formaldehyde resins in clothing. *Dermatitis* 2004; **15**: 169–75.
14 Lazarov A. Textile dermatitis in patients with contact sensitization in Israel: a 4-year prospective study. *J Eur Acad Dermatol Venereol* 2004; **18**: 531–7.
15 Metzler-Brenckle L, Rietschel RL. Patch testing for permanent-press allergic contact dermatitis. *Contact Dermatitis* 2002; **46**: 33–7.
16 Seidenari S, Giusti F, Massone F, Mantovani L. Sensitization to disperse dyes in a patch test population over a five-year period. *Am J Contact Dermatitis* 2002; **13**: 101–7.
17 Pratt M, Taraska V. Disperse blue dyes 106 and 124 are common causes of textile dermatitis and should serve as screening allergens for this condition. *Am J Contact Dermatitis* 2000; **11**: 30–41.
18 Lazarov A, Trattner A, David M *et al*. Textile dermatitis in Israel: a retrospective study. *Am J Contact Dermatitis* 2000; **11**: 26–9.
19 Ryberg K, Isaksson M, Gruvberger B *et al*. Contact allergy to textile dyes in southern Sweden. *Contact Dermatitis* 2006; **54**: 313–21.
20 Opie J, Lee A, Frowen K *et al*. Foot dermatitis caused by the textile dye Basic Red 46 in acrylic blend socks. *Contact Dermatitis* 2003; **49**: 297–303.
21 Roed-Petersen J, Batsberg W, Larsen E. Contact dermatitis from Naphthol AS. *Contact Dermatitis* 1990; **22**: 161–3.
22 Rycroft RJG, Cronin E, Calnan CD. Canadian sheet dermatitis. *BMJ* 1976; **ii**: 1175.
23 Brown R. Allergy to dyes in permanent press bed linen. *Contact Dermatitis* 1990; **20**: 303–4.
24 Hodgson GA, Hellier FF. Dermatitis in shirts in B.L.A. *J R Army Med Corps* 1946; **87**: 110–7.
25 Lazarov A, Cordoba M. Purpuric contact dermatitis in patients with allergic reaction to textile dyes and resins. *J Eur Acad Dermatol Venereol* 2000; **14**: 101–5.
26 Shah SA, Ormerod AD. Pigmented purpuric clothing dermatitis due to disperse dyes. *Contact Dermatitis* 2000; **43**: 360.
27 Komericki P, Aberer W, Arbab E *et al*. Pigmented purpuric contact dermatitis from Disperse Blue 106 and 124 dyes. *J Am Acad Dermatol* 2001; **45**: 456–8.
28 van der Veen JP, Neering H, de Haan P *et al*. Pigmented purpuric clothing dermatitis due to Disperse Blue 85. *Contact Dermatitis* 1988; **19**: 222–3.
29 Osmundsen PE, Alani MD. Contact allergy to an optical whitener, 'CPY', in washing powders. *Br J Dermatol* 1971; **85**: 61–6.
30 Giusti F, Mantovani L, Martella A, Seidenari S. Hand dermatitis as an unsuspected presentation of textile dye contact sensitivity. *Contact Dermatitis* 2002; **47**: 91–5.

31 Hatch KL, Maibach HI. Textile chemical finish dermatitis. *Contact Dermatitis* 1986; **14**: 1–13.
32 Fregert S. Extractions of allergens for patch tests. *Acta Derm Venereol (Stockh)* 1964; **44**: 107–9.
33 Sertoli A, Francalanci S, Giorgini S. Sensitization to textile disperse dyes: validity of reduced-concentration patch tests and a new mix. *Contact Dermatitis* 1994; **31**: 47–8.
34 Winhoven SM, Rutter KJ, Beck MH. Multiple positive allergic reactions from patch testing to *p*-phenylenediamine and azo dyes. Is this a frequent risk and can it be reduced? *Contact Dermatitis* 2008; **58**: 182–3.

Shoes [1–4]

The commoner identified allergens in shoes are rubber chemicals, chromate (in leather), nickel in buckles and eyelets, and *p*-tertiary-butylphenol formaldehyde resin (PTBPFR). However, many others have been described, including vegetable tanning agents, dyes, colophony, cobalt, leather preservatives and polyurethane components.

A typical shoe will be formed from an upper, a sole, an insole, and heel and toe counters to stiffen the shoe and give it shape. Adhesives may be required throughout the shoe.

Uppers tend to be leather, rubber or synthetic material. Leather is tanned, usually with chromate, but other tanning agents, including vegetable tans, colophony, formaldehyde and glutaraldehyde, may be used. Formaldehyde is associated with the tanning of white or water-resistant leather and is tightly bound, making sensitization less likely [2]. After tanning, the leather may be oiled, dyed and finished. Biocides such as 2-*n*-octyl-4-isothiazolin-3-one may be added to the oils and finishes [3]. Uppers may be made from, or be lined with, dyed fabric. Polyurethane, rubber and neoprene foams are used in the uppers, particularly of sports footwear. Neoprene is a synthetic rubber to which phenolic resins, most notably PTBPFR, thioureas, carbamates, and other accelerators and additives, may be added [5].

Shoe soles are made from similar materials and more solid forms of rubber. Insoles can also be made of a similar range of materials. Fibreboard used for insoles is a composite of fibres, usually paper but occasionally wood or leather in a glue matrix, which may contain biocides. Insoles may also contain allergenic deodorizers, including formaldehyde and fragrances.

Counters may be made from many different potentially allergenic materials, including natural rubber, formaldehyde resins, biocides and pine oil.

The main adhesives are hot melt, urethane, neoprene and natural rubber. Hot melt adhesives do not tend to cause allergy but the others may, particularly rubber accelerators and PTBPFR. Additives include isocyanates, epoxy resins and biocides. Tackifiers may contain formaldehyde resins and colophony.

Shoe fabrics may become reservoirs for materials applied to the skin of the feet, including athlete's foot remedies, treatments for other inflammatory skin disorders and talc. They may act as a source for continued exposure even though the items are no longer being actively applied to the skin.

Prevalence. The prevalence of shoe allergy has ranged between 3 and 11% in patients referred for routine patch testing [1,4]. The highest frequencies of dermatitis have been reported from hot climates, which will promote sweating and leaching out of allergenic shoe chemicals [4]. A wide age range is seen, with young children prominently represented in many studies. In one study on 55 patients the breakdown of the most frequent positive reactions was as follows: rubber 43.1%, chromate 23.6%, PTBPFR 20.0%, colophony 9.0% and PPD 3.6%. However, a further 14.5% reacted to pieces of their shoes but not to the shoe allergens tested. Most patients were noted to have hyperhidrosis and 43% were atopic. Follow-up (average 3 years) of 48 patients after they had employed a number of strategies to avoid contact with the allergens responsible for their dermatitis revealed that 87.5% were clear or significantly better, 10% the same and only one person was worse [6]. More recent European studies had a similar range of allergens responsible but at a generally lower frequency. Chromate was commoner than rubber allergy in these reports [4,7]. Cobalt was also a common allergen but the source for this is not always clear [4].

Clinical features. Sweating causes allergens in shoes to leach out and migrate, and as a result of this the pattern of dermatitis is often not distinctive. It may be patchy or superimposed on a pre-existing constitutional eczema. Nevertheless, in many instances the distribution will reflect whether the sensitizer is present in the upper or sole of the shoe [4].

Dermatitis from the upper commonly starts over the dorsal surface of the big toes and spreads to the dorsa of the feet and the other toes. Outbreaks of dermatitis from tanning agents (chromate and vegetable), dyes and adhesives have often followed this pattern [4]. The interdigital spaces are normally spared. The heels may be involved, but less frequently than the toes. On the heels, patches of dermatitis may correspond to the heel-cap, and on the dorsum of the foot they may correspond to the tongue of the shoe. Adhesives and rubber components may cause localized areas of dermatitis limited to the toecap [8]. Nickel allergy from shoe buckles and eyelets may cause a localized dermatitis on the adjacent skin. Indian sandal dermatitis has a characteristic pattern, is often severe, and affects mainly the first toe web and adjacent toes and the dorsum of the foot [9].

Rubber chemical allergy has an increased tendency to affect the soles [4]. Involvement of the sole usually affects only the weight-bearing areas—the instep is frequently spared. In sports shoes, the sole is usually moulded to fit into the instep and the dermatitis may affect the whole sole [10]. Sometimes, only the forefoot is involved (Fig. 26.25), and in children the condition must be differentiated from juvenile plantar dermatosis by patch testing.

Surprisingly, not all cases are bilateral [11], but the great majority are. Patients with shoe dermatitis often have evidence of dermatitis elsewhere, especially on the hands.

Boots produce a pattern similar to shoe dermatitis, sometimes with an additional eruption on the calves. An eczematous and purpuric allergic contact dermatitis has been reported in a patient sensitive to thiourea and IPPD [12,13].

Allergy to socks and stockings, agents such as perfumed sprays, talcs and antifungal powders used in shoes, and medicaments applied to the skin may simulate footwear dermatitis [7,14].

Avoidance. Individuals who are allergic to leather tanning agents and additives can be advised to wear synthetic fabric or rubber



Fig. 26.25 Forefoot dermatitis from shoe allergy.

footwear. Some specialized outlets sell 'vegetarian' shoes that should not be leather.

However, with other allergens avoidance is often difficult. Manufacturers and distributors will not generally guarantee their shoes are free of rubber chemicals and PTBPFR in adhesives, and may know even less about other sensitizers. Patients allergic to rubber, PTBPFR and colophony should consider all-leather stitched footwear with no insoles, or injection-moulded plastic shoes, moccasins or wooden shoes. Certain manufacturers will produce bespoke shoes free of the allergen(s) but these are expensive. Sometimes, orthotists advising hospital orthopaedic departments are helpful in making special shoes.

Those allergic to dyes will need to avoid dyed fabric and nylon-lined footwear, as well as coloured nylon socks and stockings. Old socks may act as a reservoir of allergen and should be discarded with the incriminated shoes, medicaments, etc.

Hyperhidrosis is common in shoe dermatitis, and the dermatitis may be helped by treating the sweating with iontophoresis, or by other means, and by wearing cotton socks to absorb the sweat [2].

Patch tests. Many of the commoner shoe allergens are found in the standard series, including dichromate, certain rubber accelerators and antioxidants, PTBPFR, colophony and nickel. In addition, a special shoe series should be used, and commercial allergen suppliers have such a series of allergens. Non-standard allergens of particular importance include nylon dyes, dodecyl mercaptan, 2-thiocyanomethyl benzothiazole (TCMTB), thioureas, dithiomorpholine, isocyanates, dimethylaminoethyl ether, 2-*n*-octyl-4-isothiazolin-3-one and *p-tert*-butylcatechol (PTBC) [4,5,7,15,16]. More extensive series have been advocated as a screen, but even these may miss some shoe allergens, including biocides, vegetable tans, hydroquinone and polyurethane agents [1].

Investigation of possible shoe allergy can be frustrating, as even with special screening series 10–20% of shoe allergies have only been identified by testing with pieces of the shoe itself [2]. Ideally, pieces for patch testing should be taken from the parts of the shoe in contact with the dermatitic area. They should be thin and 1 cm^2 or larger [1]. Some have suggested testing the pieces under a special large Finn chamber, whereas others recommend occlusive tape [1,2]. Further suggestions have been to soak the pieces in water for 15 min before they are applied, and to leave the test pieces in place for 4–5 days [2,17]. False-positive reactions may be seen from pressure, particularly around the edge, and false-negative reactions are common. Furthermore, positive reactions may develop as a result of contamination by a non-shoe allergen, for example a medicament or perfume to which the patient is allergic [14].

References

1 Taylor JS, Erkek E, Podmore P. Shoes. In: Frosch PJ, Menné T, Lepoittevin J-P eds. *Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 703–16.
2 Rietschel RL, Fowler JF Jr. *Fisher's Contact Dermatitis*, 5th edn. Baltimore: Lippincott, Williams & Wilkins, 2001: 279–319.
3 Geier J. Leather and shoes. In: Kanerva L, Elsner P, Wahlberg JE, Maibach HI, eds. *Handbook of Occupational Dermatology*. Berlin: Springer, 2000: 637–43.
4 Nardelli A, Taveirne M, Drieghe J *et al.* The relation between the localization of foot dermatitis and the causative allergens in shoes: a 13-year retrospective study. *Contact Dermatitis* 2005; **53**: 201–6.
5 Woo DK, Militello G, James WD. Neoprene. *Dermatitis* 2004; **15**: 206–9.
6 Freeman S. Shoe dermatitis. *Contact Dermatitis* 1997; **36**: 247–51.
7 Holden CR, Gawkrodger DJ. 10 years' experience of patch testing with a shoe series in 230 patients: which allergens are important? *Contact Dermatitis* 2005; **53**: 37–9.
8 Weston JA, Hawkins K, Weston WL. Foot dermatitis in children. *Pediatrics* 1983; **72**: 824–7.
9 Adams RM. Shoe dermatitis. *Calif Med* 1972; **117**: 12–6.
10 Roberts JL, Hanifin JM. Athletic shoe dermatitis. *JAMA* 1979; **241**: 275–6.
11 Angelini G, Vena GA, Meneghini CL. Shoe contact dermatitis. *Contact Dermatitis* 1980; **6**: 279–83.
12 Romaguera C, Grimalt F, Vilaplana J. Eczematous and purpuric allergic contact dermatitis from boots. *Contact Dermatitis* 1989; **21**: 269.
13 Calnan CD, Peachey RDG. Allergic contact purpura. *Clin Allergy* 1971; **1**: 287–90.
14 Saha M, Srinivas CR, Shenoi SD *et al*. Sensitivity to topical medicaments among suspected cases of footwear dermatitis. *Contact Dermatitis* 1993; **28**: 44–5.
15 Belsito DV. Common shoe allergens undetected by commercial patch-testing kits: dithiodimorpholine and isocyanates. *Am J Contact Dermatitis* 2003; **14**: 95–6.
16 Oleaga JM, Aguirre A, Landa N *et al.* Allergic contact dermatitis from Kathon 893. *Contact Dermatitis* 1992: **27**: 345–6.
17 Jordan WP Jr. Clothing and shoe dermatitis. Recognition and management. *Postgrad Med* 1972; **52**: 143–8.

Resins and plastics

Resins are intermediate synthetic substances that are polymerized, often using a hardener and other additives to produce a plastic end-product. Many low-molecular-weight materials, including the monomers and oligomers used in resins, are allergenic, but a fully polymerized resin should not be sensitizing. Many additives, fillers and hardeners also have allergenic potential. The systems most commonly associated with contact allergy include epoxy, acrylic and formaldehyde resins.

Epoxy resins [1,2]

In terms of usage, 75–90% of epoxy resins comprise diglycidyl ether of bisphenol A (DGEBA) [2]. They are reaction products of epichlorhydrin and bisphenol A. The monomer (molecular weight 340) is the main sensitizer, and oligomers with molecular weights above 900 do not sensitize [3,4]. Higher-molecular-weight resins may contain small amounts of the oligomers or monomer but rarely sufficient for induction of sensitivity [5]. However, they can elicit clinical and patch-test reactions in those already sensitized.

Non-DGEBA epoxy resins, such as cycloaliphatic epoxy resin, diglycidyl ether of bisphenol F (also used in phenol epoxy novolac systems), diglycidyl ether of propylene glycol, triglycidyl isocyanurate (TGIC), tetraglycidyl-4,4′-methylenedianiline (TGMDA), triglycidyl p-aminphenol (TGPAP), *o*-diglycidyl phthalate and 1,6-bis (2,3-epoxypropoxy) naphthalene, are also reported as sensitizers [6–12].

Epoxy resins may be reacted with other resins, for example acrylates and formaldehyde resins, to produce new resins which may have an allergic profile different from their parent resins [13].

Sometimes, 'reactive diluents' in the resins used to reduce viscosity are responsible for their sensitizing capacity. These diluents are usually glycidyl ethers or, occasionally, glycidyl esters, and are thought to be present in over 50% of epoxy resin products. Bisphenol A and epichlorhydrin themselves are seldom responsible for allergy from epoxy resin.

Resins containing latent hardeners are polymerized or cured by heat alone. Two-part resins require hardeners to be added immediately prior to their application. Some of these are cold-curing and some require heat to complete the polymerization. Hardeners are of many types: aliphatic amines, cycloaliphatic amines, aromatic amines, polyaminoamides, amidopolyamines, polymercaptan, anhydrides, isocyanates, polyphenols and adducts. Formaldehyde resins may be used as hardeners.

The commonest sensitizers among the hardeners are amines, for example the aliphatic amines ethylenediamine, diethylenetetramine, triethylenetetramine, dipropylenetriamine and dimethylaminopropylamine. Triethylenetetramine is a particularly strong sensitizer [14]. There are also sensitizing cycloaliphatic amines (e.g. isophoronediamine) and aromatic amines, such as m-xylenediamine, diaminodiphenylmethane (methylene dianiline) and 2,4,6-tris-(dimethylaminomethyl)phenol.

Hardeners of the polyaminoamide type are much less likely to sensitize, and so are anhydrides (e.g. phthalic anhydride). They are used for thermal hardening. Adducts are non-sensitizing, providing they do not contain free amine.

Additives include colours, fillers, UV light absorbers, flame retardants and plasticizers.

Incidence and prevalence. Epoxy resin of the bisphenol A type is a standard allergen. However, figures for the prevalence of allergy in patch-tested patients with dermatitis will reflect the degree of occupational interest of a particular clinic, and also the local industry. Series of relatively unselected patch-tested patients have reported rates of 0.4–3% positive reactions, with a male preponderance [1]. However, higher rates are recorded for occupational referrals. Annually, approximately 1% of exposed workers are believed to develop an epoxy resin allergy [15].

Allergy to other components of epoxy systems is commonly concomitant with resin sensitization but may also occur by itself [16,17]. Detailed analysis of 182 cases in Finland showed that 80% were allergic to DGEBA epoxy resins, 23% to polyamine hardeners, 16% to reactive diluents and 9% to non-DGEBA epoxy resins [1].

A high incidence of allergy among exposed individuals can occur in factory outbreaks, for example 56% in an aircraft construction factory, 45% in marble workers, 27% in ski-factory workers and 21% in paint factory workers [18–20].

Occurrence. The epoxy resins are among the most sensitizing substances that have been introduced to industrial work in recent years. Coatings, including paints, varnishes and metals account for roughly 45% of all epoxy resin use [2]. They are widely used in the construction industry, in cement to make it waterproof, and in floorings, grouts and filling materials, including those for marble and window frames. They are commonly used as binders and coatings for fibreglass and carbon fibre, for example in car body repairs, wind turbine rotor blades and aircraft construction [1,2,21,22]. In the electronics industry they are used for insulation and in printed-circuit boards. They are efficient glues for metals, rubber, polyester resins and ceramics. Cardiac pacemakers and hypodermic needles may contain them. Dental personnel and their patients sensitized by epoxy acrylates in filling materials often also react to epoxy resin [13]. In the laboratory they have been found as sensitizers in microscopy immersion oil [23].

High-molecular-weight resins, which may contain residual low-molecular-weight resin, are used for coating metal or wood [24]. Occasionally, uncured epoxy resins are used as stabilizers and plasticizers in, for example, polyvinyl chloride plastic and spectacle frames. Thus, contact dermatitis may be elicited in consumers [25,26] as well as occupationally.

Non-DGEBA epoxy resins have found increasing use in electron microscopy, electronics and carbon and glass fibre composite materials, especially in the aerospace construction industry [2,21]. Cycloaliphatic epoxy resin has sensitized in hydraulic fluid and neat metalworking oil [27,28]. TGIC is used, mainly as a hardener, in thermosetting one-component polyester powder paints [29].

Clinical features. Dermatitis is predominantly occupational. It usually affects the hands and arms (see Fig. 26.8), and often also the face and eyelids. Facial and periorbital involvement may be indicators of associated or isolated allergy to the more volatile epoxy diluents and hardeners [30]. Partially cured epoxy resin dusts from sanding and drilling may induce dermatitis with a similar distribution.

Severe oedematous and weeping eruptions are not uncommon, and widespread generalized eruptions can develop if exposure continues. Erythema multiforme-like reactions have also been described [31]. Other body sites, especially the genitals, may be affected following hand contact. Hand and fingertip dermatitis was a feature of window-frame restorers' dermatitis [32]. Localized dermatitis can sometimes be attributed to traces of free epoxy monomer found in a wide range of products, such as twist-off

caps, coated door knobs, tool handles [25], microscopy immersion oil [23], stoma bags [26], clothing labels [33], portable infusion pumps [34], spectacle frames, plastic tubing in medical devices and gloves. A flare-up of hand eczema has been reported from an implanted epoxy resin-containing needle [35]. Children have been sensitized by a knee-patch adhesive in jeans [36]. Gingivitis and stomatitis may result from the use of epoxy acrylates in dental materials [13,37].

Contact allergy to epoxy components may rarely cause vitiligo [38].

Avoidance. Redeployment away from contact with epoxy resin is usually required for occupational dermatitis but even so the prognosis is not always favourable [39]. Use of epoxy (usually two-part) adhesives and fillers in domestic and spare-time activities (e.g. car body repairs) should be avoided. Identification of epoxy chemicals in suspect materials by chromatography techniques may be helpful in confirming a suspected source of epoxy resin [26,40].

Prevention. Prevention of epoxy dermatitis is important, and includes education, instructions and warning notices for the workforce, stressing the need for 'good housekeeping'. High-molecular-weight epoxy resins and diluents are less sensitizing and, where possible and appropriate, are to be preferred. Aliphatic and aromatic amines may be replaced by polyaminoamides or amine-epoxy adducts [2]. If feasible, automation or a 'two in one' mixing package [41] is advised or, if not, mixing should be done in disposable containers.

Protective impermeable, preferably disposable, clothing and gloves should be worn. Epoxy resin will nevertheless penetrate plastic and rubber gloves [42]. Heavy-duty vinyl gloves or multilayered gloves of folio type (4H-Glove; Safety 4, Denmark) provide the best protection [43].

Patch tests. Epoxy resin of the bisphenol A type is included in the standard series at 1% in petrolatum. Other components of epoxy resin systems are not, apart from ethylenediamine. Extra patch-test reagents, which incorporate the commoner amine hardeners and reactive diluents, are available from the commercial allergen suppliers, although these are not all-inclusive. Allergy to non-DGEBA epoxy resins and other components may still be missed unless the worker's own materials are tested [16,17,22,44].

A rough guide to patch-test concentrations (all in petrolatum) is 0.5% for non-DGEBA epoxy resins, 0.25% for reactive diluents and 1% for most polyamine hardeners, but a literature search should also be undertaken, and lower concentrations considered initially if in doubt.

References

1 Jolanki R, Kanerva L, Estlander T. Epoxy resins. In: Kanerva L, Elsner P, Wahlberg JE, Maibach HI, eds. *Handbook of Occupational Dermatology*. Berlin: Springer, 2000: 570–90.

2 Björkner B, Pontén A, Zimerson E, Frick M. Plastic materials. In: Frosch PJ, Menné T, Lepoittevin J-P, eds. *Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 595–9.

3 Fregert S, Thorgeirsson A. Patch testing with low molecular oligomers of epoxy resins in humans. *Contact Dermatitis* 1977; **3**: 301–3.

4 Thorgeirsson A, Fregert S. Allergenicity of epoxy resins in the guinea pig. *Acta Derm Venereol (Stockh)* 1977; **57**: 253–6.

5 Bokelund F, Fregert S, Trulsson L. Sensitization from epoxy resin powder of high molecular weight. *Contact Dermatitis* 1980; **6**: 144.

6 Kanerva L, Jolanki R, Estlander T. Allergic contact dermatitis from non-diglycidyl-ether-of-bisphenol-A epoxy resins. *Contact Dermatitis* 1991; **24**: 293–300.

7 Pontén A, Bruze M. Contact allergy to epoxy resin based on diglycidyl ether of bisphenol F. *Contact Dermatitis* 2001; **44**: 98–9.

8 Pontén A, Zimerson E, Bruze M. Contact allergy to the isomers of diglycidyl ether of bisphenol F. *Acta Derm Venereol (Stockh)* 2004; **84**: 12–7.

9 Burrows D, Fregert S, Campbell H *et al*. Contact dermatitis from the epoxy resins tetraglycidyl-4,4′-methylene dianiline and *o*-diglycidyl phthalate in composite material. *Contact Dermatitis* 1984; **11**: 80–2.

10 Yokota K, Michitsuji H. Occupational allergic contact dermatitis from 1,6-bis (2,3-epoxypropoxy) naphthalene in a one-component epoxy coating. *Contact Dermatitis* 2004; **51**: 154–5.

11 Yung A, Wilkinson SM. Allergic contact dermatitis from the epoxy resin plasticizer diglycidyl ether of propylene glycol. *Contact Dermatitis* 2003; **49**: 109–10.

12 Kanerva L, Jolanki R, Estlander T *et al*. Airborne occupational allergic contact dermatitis from triglycidyl-*p*-aminophenol and tetraglycidyl-4,4′-methylene dianiline in preimpregnated epoxy products in the aircraft industry. *Dermatology (Basel)* 2000; **201**: 29–33.

13 Kanerva L, Estlander T, Jolanki R. Allergic contact dermatitis from dental composite resins due to aromatic epoxy acrylates and aliphatic acrylates. *Contact Dermatitis* 1989; **20**: 201–11.

14 Thorgeirsson A. Sensitization capacity of epoxy resin hardeners in the guinea pig. *Acta Derm Venereol (Stockh)* 1978; **58**: 332–6.

15 Holness DL, Nethercott JR. Results of testing with epoxy resin in an occupational health clinic population. *Am J Contact Dermatitis* 1992; **3**: 169–74.

16 Chu CY, Pontén A, Sun CC, Jee SH. Concomitant contact allergy to the resins, reactive diluents and hardener of a bisphenol A/F-based epoxy resin in subway construction workers. *Contact Dermatitis* 2006; **54**: 131–9.

17 Geier J, Lessmann H, Hillen U *et al*. An attempt to improve diagnostics of contact allergy due to epoxy resin systems. First results of the multicentre study EPOX 2002. *Contact Dermatitis* 2004; **51**: 263–72.

18 Angelini G, Rigano L, Foti C *et al*. Occupational sensitization to epoxy resin and reactive diluents in marble workers. *Contact Dermatitis* 1996; **35**: 11–6.

19 Jolanki R, Tarvainen K, Tatar T *et al*. Occupational dermatoses from exposure to epoxy resin compounds in a ski factory. *Contact Dermatitis* 1996; **34**: 390–6.

20 Omer SA, al-Tawil NG. Contact sensitivity among workers in a paint factory. *Contact Dermatitis* 1994; **30**: 55–7.

21 Bruze M, Edenholm M, Engström K *et al*. Occupational dermatoses in a Swedish aircraft plant. *Contact Dermatitis* 1996; **34**: 336–40.

22 Pontén A, Carstensen O, Rasmussen K *et al*. Epoxy-based production of wind turbine rotor blades: occupational contact allergies. *Dermatitis* 2004; **15**: 33–40.

23 Le Coz CJ, Coninx D, Van Rengen A *et al*. An epidemic of occupational contact dermatitis from an immersion oil for microscopy in laboratory personnel. *Contact Dermatitis* 1999; **40**: 77–83.

24 Goulden V, Wilkinson SM. Occupational allergic contact dermatitis from epoxy resin on chipboard. *Contact Dermatitis* 1996; **35**: 262–3.

25 Fregert S, Persson K, Trulsson L. Hidden sources of unhardened epoxy resin of bisphenol A type. *Contact Dermatitis* 1980; **6**: 446–7.

26 Beck MH, Burrows D, Fregert S *et al*. Allergic contact dermatitis to epoxy resin in ostomy bags. *Br J Surg* 1985; **72**: 202–3.

27 Jensen CD, Andersen KE. Two cases of occupational allergic contact dermatitis from a cycloaliphatic epoxy resin in a neat oil: case report. *Environ Health* 2003; **262**: 3.

28 Maibach HI, Mathias CT. Allergic contact dermatitis from cycloaliphatic epoxide in jet aviation hydraulic fluid. *Contact Dermatitis* 2001; **45**: 56.

29 Foulds IS, Koh D. Allergic contact dermatitis from resin hardeners during the manufacture of thermosetting coating paints. *Contact Dermatitis* 1992; **26**: 87–90.

30 Dahlquist I, Fregert S. Allergic contact dermatitis from volatile epoxy hardeners and reactive diluents. *Contact Dermatitis* 1979; **5**: 406–7.

31 Whitfield MJ, Rivers JK. Erythema multiforme after contact dermatitis in response to an epoxy sealant. *J Am Acad Dermatol* 1991; **25**: 386–8.

32 Brooke RC, Beck MH. Occupational allergic contact dermatitis from epoxy resin used to restore window frames. *Contact Dermatitis* 1999; **41**: 227–8.
33 Fregert S, Orsmark K. Allergic contact dermatitis due to epoxy resin in textile labels. *Contact Dermatitis* 1984; **11**: 131–2.
34 Boom BW, van Driel LMJ. Allergic contact dermatitis to epoxy resins in infusion sets of an insulin pump. *Contact Dermatitis* 1985; **12**: 280.
35 Geldof BA, Oranje AP, van Joost Th. Hand eczema associated with continuous subcutaneous insulin infusion. *Contact Dermatitis* 1989; **20**: 384–5.
36 Taylor JS, Bergfeld WF, Guin JD. Contact dermatitis to knee patch adhesive in boy's jeans: a nonoccupational cause of epoxy resin sensitivity. *Cleve Clin Q* 1983; **50**: 123–7.
37 Koch P. Allergic contact stomatitis from BIS-GMA and epoxy resins in dental bonding agents. *Contact Dermatitis* 2003; **49**: 104–5.
38 Silvestre JF, Albares MP, Escutia B *et al*. Contact vitiligo appearing after allergic contact dermatitis from aromatic reactive diluents in an epoxy resin system. *Contact Dermatitis* 2003; **49**: 113–4.
39 Cahill J, Keegel T, Dharmage S *et al*. Prognosis of contact dermatitis in epoxy resin workers. *Contact Dermatitis* 2005; **52**: 147–53.
40 Fregert S. Physicochemical methods for detection of contact allergens. *Dermatol Clin* 1988; **6**: 97–104.
41 Van Putten PB, Coenraads PJ, Nater JP. Hand dermatoses and contact allergic reactions in construction workers exposed to epoxy resins. *Contact Dermatitis* 1984; **10**: 146–50.
42 Pegum JS. Penetration of protective gloves by epoxy resin. *Contact Dermatitis* 1979; **5**: 281–3.
43 Roed-Petersen J. A new glove material protective against epoxy and acrylate monomer. In: Frosch PJ, Dooms-Goossens A, LaChapelle J-M *et al*., eds. *Current Topics in Contact Dermatitis*. Berlin: Springer, 1989: 569–78.
44 Rømyhr O, Nyfors A, Leira HL, Smedbold HT. Allergic contact dermatitis caused by epoxy resin systems in industrial painters. *Contact Dermatitis* 2006; **55**: 167–72.

Acrylic resins [1]

Acrylic resins are formed from acrylic and methacrylic acids and their esters, and cyanoacrylic acid and its esters. These resins show a wide range of sensitizing potential and a complex cross-reaction pattern. Multifunctional acrylates, epoxy acrylates, acrylamides, acrylonitrile and acrylated polyester are other sensitizers. Polymerization may be induced by heat, by adding initiators, accelerators and catalysts, by tiny amounts of water, by anaerobic conditions and by exposure to UV and visible light or electron beams, depending on the nature and function of the acrylate [1]. Sometimes, additives such as dimethyl-*p*-toluidine, benzoyl peroxide, hydroquinone, *p*-methoxyphenol, pyrogallol, resorcinol or pentaerythritol tetrakis 3-mercaptopropionate may elicit contact dermatitis.

Prevalence. Acrylate allergy is not routinely sought, and levels of allergy will reflect the referral pattern to a particular clinic. A UK study examined the records of approximately 14 000 unselected patients, and identified 440 who had been tested for possible (meth)acrylate allergy: 67 had one or more positive reactions; 47 cases were occupational, with dental personnel and printers being the most frequent, followed by gas workers, gearbox fitters and beauty therapists. Sixteen cases were sensitized by wearing acrylic nail cosmetics [2]. A similar survey in the USA on 56 allergic patients showed the commonest sources of allergy were nail cosmetics (25 cases), dental materials (14 cases) and adhesives (seven cases) [3]. Most other series have concentrated on occupational exposure. Dental personnel and printers are confirmed as occupational groups particularly at risk of sensitization.

Occurrence [1]. Monomeric acrylates and methacrylates may be used to produce transparent plastics (e.g. Perspex), dentures, hearing aids, limb prostheses, spectacle frames, nail cosmetics and bone cement for orthopaedic surgery. Other commoner exposures include coatings, varnishes, paints, inks and adhesives (including those for stick-on nails). UV-cured monomers are also encountered in coatings, printing plates, printing inks and dentistry.

Multifunctional acrylates, which have at least two reactive acrylic groupings, are also used in UV-cured resins, as well as printed circuit boards, artificial nails, adhesives, dental materials and anaerobic sealants used in screwlocks and gas pipes. Epoxy acrylates are used in dental restorative materials. Acrylamide and derivatives have sensitized from printing plates and paint manufacture [4].

Cyanoacrylates are known as 'superglues' and are used extensively to bond artificial nails, metal, glass, rubber, plastics and textiles. They are also used by surgeons to bind tissues and seal wounds, and by dermatologists to treat painful fissures of the hands and feet. Sensitization to cyanoacrylates is rare, as a result of almost immediate polymerization [5], but it has been reported [6].

Clinical features. The commonest sites of occupational allergy are the fingertips and hands (see Fig. 26.2), but the face, arms and eyelids may also be involved. Manicurists may develop hand dermatitis, and sometimes a more extensive exposure pattern dermatitis from dust generated by nail filing. Rhinitis has been seen in association [7]. Workers with fingertip dermatitis should always be asked about contact with screwlocks and glues, as this is a typical distribution of allergic dermatitis from this source. A similar distribution may be seen in dentists and dental technicians. Localized dermatitis is seen from limb prostheses, the use of diathermy plates during surgery and incontinence pads [8–10]. We have seen allergic dermatitis with secondary spread eruption from allergy to a cyanoacrylate surgical wound sealant.

Dermatitis from artificial nails may be associated with painful onycholysis, nail dystrophy, periungual dermatitis, paraesthesiae, and an ectopic dermatitis of the face and neck, and sometimes other parts of the body [11,12]. Paraesthesiae can persist for some months after patients stop wearing the nails [13].

Stomatitis has been blamed on incompletely cured acrylate in newly made or repaired dentures [14,15], and gingivo-stomatitis on acrylates in a temporary crown [16]. Oral problems may arise in those previously sensitized to acrylic nails [17]. An extensive skin eruption has been seen from allergy to a dental composite resin used to fix an orthodontic prosthesis [18].

Avoidance. Once identified, avoidance should be possible by removal of the cause, redeployment, adequate protection or altered work practice. Acrylates penetrate latex and vinyl gloves [19,20].

The 4H multilayer folio glove (Safety 4, Denmark) [21] is the best protection, but may be impractical for some activities. In those with finger problems (especially dentists), it may be possible to remove the 4H glove fingers and wear these under another more pliable glove, although ideally dental personnel should use a no-touch technique [22]. Double gloving, polyethylene gloves

and nitrile gloves are possible, but potentially less effective, alternatives.

Education, instructions on handling, printed warning notices and 'good housekeeping' are important preventative measures.

Patch tests. Chemotechnique allergens include three (meth) acrylate series: adhesive, nail and printing. In general, methacrylated monomers are tested at 2% in petrolatum and acrylated monomers at 0.1% in petrolatum. The lower 0.1% concentrations have reduced the incidence of the previously noted problem of active sensitization [23]. Cyanoacrylates are tested at 10% in petrolatum. Multiple positives may be seen if the full series is tested. As a result of retrospective analyses shorter screening series have been suggested [24,25]. Late and persistent patch-test reactions may occur [26].

References

1 Björkner B. Acrylic resins. In: Kanerva L, Elsner P, Wahlberg JE, Maibach HI, eds. *Handbook of Occupational Dermatology*. Berlin: Springer, 2000: 562–9.
2 Tucker SC, Beck MH. A 15-year study of patch testing to (meth)acrylates. *Contact Dermatitis* 1999; **40**: 278–9.
3 Sood A, Taylor JS. Acrylic reactions: a review of 56 cases. *Contact Dermatitis* 2003; **48**: 346–7.
4 Malten KE. Printing plate manufacturing processes. In: Maibach HI, ed. *Occupational and Industrial Dermatology*, 2nd edn. Chicago: Year Book Medical Publishers, 1987: 351–66.
5 Calnan CD. Cyanoacrylate dermatitis. *Contact Dermatitis* 1979; **5**: 165–7.
6 Bruze M, Björkner B, Lepoittevin JP. Occupational allergic contact dermatitis from ethyl cyanoacrylate. *Contact Dermatitis* 1995; **32**: 156–9.
7 Torres MC, Linares T, Hernandez MD. Acrylates induced rhinitis and contact dermatitis. *Contact Dermatitis* 2005; **53**: 114.
8 Lyon CC, Kulkarni J, Zimerson E *et al*. Skin disorders in amputees. *J Am Acad Dermatol* 2000; **42**: 501–7.
9 Sidhu SK, Shaw S. Allergic contact dermatitis to acrylates in disposable blue diathermy pads. *Ann R Coll Surg Engl* 1999; **81**: 187–90.
10 Giroux L, Pratt MD. Contact dermatitis to incontinency pads in a (meth)acrylate allergic patient. *Am J Contact Dermatitis* 2002; **13**: 143–5.
11 Freeman S, Lee MS, Gudmundsen K. Adverse contact reactions to sculptured acrylic nails: 4 case reports and a literature review. *Contact Dermatitis* 1995; **33**: 381–5.
12 Fitzgerald DA, English JS. Widespread contact dermatitis from sculptured nails. *Contact Dermatitis* 1994; **30**: 118.
13 Slodownik D, Williams JD, Tate BJ. Prolonged paresthesia due to sculptured acrylic nails. *Contact Dermatitis* 2007; **56**: 298–9.
14 Kanerva L, Estlander T, Jolanki R. Allergic contact dermatitis from dental composite resins due to aromatic epoxy acrylates and aliphatic acrylates. *Contact Dermatitis* 1989; **20**: 201–11.
15 Koutis D, Freeman S. Allergic contact stomatitis caused by acrylic monomer in a denture. *Australas J Dermatol* 2001; **42**: 203–6.
16 Kanerva L, Alanko K, Estlander T. Allergic contact gingivostomatitis from a temporary crown made of methacrylates and epoxy diacrylates. *Allergy* 1999; **54**: 1316–21.
17 Jung HP, Jarisch R, Hemmer W. Hypersensitivity from dental acrylates in a patient previously sensitized to artificial nails. *Contact Dermatitis* 2005; **53**: 119–20.
18 Menni A, Lodi A, Coassini D *et al*. Unusual widespread vesicular eruption related to dental composite resin sensitization. *Contact Dermatitis* 2003; **48**: 174.
19 Rietschel RL, Huggins R, Levy N *et al*. In vivo and in vitro testing of gloves for protection against UV-curable acrylate resin systems. *Contact Dermatitis* 1984; **11**: 279–82.
20 Munksgaard EC. Permeability of protective gloves to (di)methacrylates in resinous dental materials. *Scand J Dent Res* 1992; **100**: 189–92.
21 Roed-Petersen J. A new glove material protective against epoxy and acrylate monomer. In: Frosch PJ, Dooms-Goossens A, LaChapelle J-M *et al*., eds. *Current Topics in Contact Dermatitis*. Berlin: Springer, 1989: 569–78.
22 Kanerva L. Skin disease from dental materials. In: Kanerva L, Elsner P, Wahlberg JE, Maibach HI, eds. *Handbook of Occupational Dermatology*. Berlin: Springer, 2000: 855.
23 Kanerva L, Estlander T, Jolanki R. Sensitization to patch test acrylates. *Contact Dermatitis* 1988; **18**: 10–5.
24 Goon AT, Bruze M, Zimerson E *et al*. Contact allergy to acrylates/methacrylates in the acrylate and nail acrylics series in southern Sweden: simultaneous positive patch test reaction patterns and possible screening allergens. *Contact Dermatitis* 2007; **57**: 21–7.
25 Constandt L, Hecke EV, Naeyaert JM, Goossens A. Screening for contact allergy to artificial nails. *Contact Dermatitis* 2005; **52**: 73–7.
26 Isaksson M, Lindberg M, Sundberg K *et al*. The development and course of patch-test reactions to 2-hydroxyethyl methacrylate and ethyleneglycol dimethacrylate. *Contact Dermatitis* 2005; **53**: 292–7.

Formaldehyde resins [1–3]

'Phenoplastics' are condensation products of formaldehyde and phenolic compounds, for example phenol, cresol, *p*-tertiary-butylphenol and resorcinol. There are two main types of phenol formaldehyde resin (PFR): resol (phenol reacted with excess formaldehyde in alkaline conditions) and novolac (formaldehyde reacted with excess phenol in acid conditions). Fourteen different sensitizers have been isolated from PFRs [4]. The two types of PFR do not necessarily cross-sensitize and neither of them seems to cross-sensitize to any significant degree with PTBPFR [5,6].

'Amino-plastics' are condensation products of formaldehyde or hexamethylenetetramine, and carbamide (= urea), thiourea, melamine, sulphonamide or anilide. They are often white or transparent. Formaldehyde, hexamethylenetetramine or low-molecular-weight condensation products can sensitize separately or simultaneously.

Usually, sensitization occurs when the resins are handled in 'half-condensed' form. Coexistent formaldehyde sensitivity is rare with PTBPFR and PFRs, but is quite common with urea and melamine formaldehyde resins [5–7].

Prevalence. Apart from allergy associated with clothing (p. 26.65), shoes (p. 26.68) and nail varnish (p. 26.47), formaldehyde resin allergy is uncommon. Many cases of PFR allergy are sporadic. Laminate manufacturers in Sweden were found to have a high frequency of allergy [8]. In a recent review, 17 cases of PFR allergy were seen in one clinic over a 15-year period. Commoner occupational associations were friction material (e.g. brake linings) production, work with fibreglass and contact with foundry sand [5]. Of routinely patch-tested patients, 0.3–2.6% are allergic to PTBPFR [9–11]. In many instances it is difficult to find a relevance for a positive patch test.

Occurrence. PFRs have electrical resistance and binding properties, resulting in their widespread use in electrical appliances, glues, laminated floorboards, plywood, fibreglass (including insulation), brake linings, clutch facings, grinding wheels, foundry sand moulds, abrasive cloths and papers, plastic moulds, telephones and steering wheels. Finished plastics are often brown or black and of the Bakelite type. Cashew nut shell oil has been used to modify the PFRs incorporated into brake linings, and this has sensitized [12].

PTBPFR is used as an adhesive and is found in sealants and neoprene glues. Contact may occur directly following its use as a

glue, particularly in shoemakers and cobblers, or when it is used to attach artificial nails and ECG-monitoring electrodes [13,14], and indirectly from its use in shoes, watch straps, wet suits and limb prostheses. Other sources include furniture and upholstery glue and marking pen ink [15].

Amino formaldehyde resins occur in textiles (p. 26.65), plywood and in waterproof paper. They are also used for finishing parquet floors, gluing wood and in orthopaedic casts. Tosylamide formaldehyde resin is extensively used in nail varnish. Formaldehyde, continuously liberated from formaldehyde resins in floors and walls, may elicit contact dermatitis in very sensitive people (p. 26.70).

Clinical features. Dermatitis from formaldehyde resins in clothing, shoes and nail varnish is discussed on pp. 26.68, 26.65 and 26.48, respectively. In most other cases of PTBPFR allergy, dermatitis is localized under leather watchstraps and limb prostheses, although the hands may be affected by contact with glues in the working and domestic environments.

Most cases of PFR allergy we have seen have had occupational dermatitis of the hands, with occasional manually transmitted spread to the face and genitals.

Patch tests. PTBPFR patch testing is discussed on p. 26.69 (shoes), amine formaldehyde resin on p. 26.67 (clothing) and tosylamide formaldehyde resin on p. 26.48 (cosmetics). PFRs are variable in composition and allergenicity [3]. There are a number of commercially available allergens: PFR-2 1% in petrolatum and monomethylol phenol 1% in petrolatum from Chemotechnique, and a novolac and resol resin, each at 5% in petrolatum, from TROLAB (Hermal). PFR-2 is the most successful in identification of allergic subjects [5,6]. However, testing with the patient's own resin at 1% and 5% in petrolatum, followed by testing controls if positive, is probably the most reliable method.

References

1 Björkner B, Pontén A, Zimerson E, Frick M. Plastic materials. In: Frosch PJ, Menné T, Lepoittevin J-P, eds. *Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 600–3.

2 Zimerson E, Bruze M. Contact allergy to phenol-formaldehyde resins. In: Kanerva L, Elsner P, Wahlberg JE, Maibach HI, eds. *Handbook of Occupational Dermatology*. Berlin: Springer, 2000: 591–6.

3 Bruze M. Contact sensitizers in resins based on phenol and formaldehyde. *Acta Derm Venereol Suppl (Stockh)* 1985; **119**: 1–83.

4 Bruze M, Persson L, Trulsson L *et al*. Demonstration of contact sensitizers in resins and products based on phenol-formaldehyde. *Contact Dermatitis* 1986; **14**: 146–54.

5 Owen CM, Beck MH. Occupational allergic contact dermatitis from phenol-formaldehyde resins. *Contact Dermatitis* 2001; **45**: 294–5.

6 Bruze M, Fregert S, Zimerson E. Contact allergy to phenol-formaldehyde resins. *Contact Dermatitis* 1985; **12**: 81–6.

7 Logan WP, Perry HO. Contact dermatitis due to formaldehyde sensitivity. *Arch Dermatol* 1973; **106**: 717–21.

8 Bruze M, Almgren G. Occupational dermatoses in workers exposed to resins based on phenol and formaldehyde. *Contact Dermatitis* 1988; **19**: 272–7.

9 Handley J, Todd D, Bingham A *et al*. Allergic contact dermatitis from para-tertiary-butylphenol-formaldehyde resin (PTBP-F-R) in Northern Ireland. *Contact Dermatitis* 1993; **29**: 144–6.

10 Schnuch A, Geier J, Uter W *et al*. National rates and regional differences in sensitization to allergens of the standard series. Population-adjusted frequencies of sensitization (PAFS) in 40 000 patients from a multicenter study (IVDK). *Contact Dermatitis* 1997; **37**: 200–9.

11 Tarvainen K. Analysis of patients with allergic patch test reactions to a plastics and glues series. *Contact Dermatitis* 1995; **32**: 346–51.

12 Beck MH. Experiences of contact dermatitis with phenol formaldehyde resins. In: Frosch PJ, Dooms-Goossens A, LaChapelle J-M, Rycroft RJG, Scheper RJ, eds. *Current Topics in Contact Dermatitis*. Berlin: Springer, 1989: 374–6.

13 Rycroft RJG, Wilkinson JD, Holmes R *et al*. Contact sensitization to *p*-tertiary butylphenol (PTBP) resin in plastic nail adhesive. *Clin Exp Dermatol* 1980; **5**: 441–5.

14 Avenel-Audran M, Goossens A, Zimerson E, Bruze M. Contact dermatitis from electrocardiograph-monitoring electrodes: role of *p-tert*-butylphenol-formaldehyde resin. *Contact Dermatitis* 2003; **48**: 108–11.

15 Hagdrup H, Egsgaard H, Carlsen L *et al*. Contact allergy to 2-hydroxy-5-tert-butyl benzylalcohol and 2,6-bis (hydroxymethyl)-4-tert-butylphenol, components of a phenolic resin used in marking pens. *Contact Dermatitis* 1994; **31**: 154–6.

Other plastics

Other plastics are rarely the cause of allergic contact dermatitis outside industry. Other resin systems, most notably unsaturated polyesters and their hardeners, and isocyanates in polyurethanes may sensitize [1–3]. Co-polymers are emerging as sensitizers in cosmetics, sunscreens and nail varnish [4]. Additives in cellulose acetate spectacle frames have caused dermatitis [5]. The literature contains many case reports of allergens traced to specific products, for example spectacle frames [6], hearing-aids, ballpoint pens and other plastic items. Other plastic additives such as plasticizers, antioxidants, UV light absorbers, initiators, cross-linking agents, flame retardants and pigments may sometimes sensitize during the manufacturing process or during use [1].

References

1 Björkner B, Pontén A, Zimerson E, Frick M. Plastic materials. In: Frosch PJ, Menné T, Lepoittevin J-P, eds. *Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 603–13.

2 Kanerva L, Tarvainen K, Estlander T, Jolanki R. Polyester resins. In: Kanerva L, Elsner P, Wahlberg JE, Maibach HI, eds. *Handbook of Occupational Dermatology*. Berlin: Springer, 2000: 591–6.

3 Estlander T, Kanerva L, Jolanki R. Polyurethane resins. In: Kanerva L, Elsner P, Wahlberg JE, Maibach HI, eds. *Handbook of Occupational Dermatology*. Berlin: Springer, 2000: 597–601.

4 Quartier S, Garmyn M, Becart S, Goossens A. Allergic contact dermatitis to copolymers in cosmetics – case report and review of the literature. *Contact Dermatitis* 2006; **55**: 257–67.

5 Jordan WP, Dahl MV. Contact dermatitis from cellulose ester plastics. *Arch Dermatol* 1972; **105**: 880–5.

6 Walsh G, Wilkinson SM. Materials and allergens within spectacle frames: a review. *Contact Dermatitis* 2006; **55**: 130–9.

Plants [1–5]

Plant life is exceedingly diverse, with much geographical and seasonal variation, and consequently the range of reported allergens is huge, with considerable differences worldwide in the incidence and prevalence of allergy. The reader is therefore referred to the standard texts on this subject for in-depth analysis. We propose to concentrate only on those plant families frequently associated with contact allergy.

Incidence and prevalence. Accurate statistics for prevalence and incidence of plant allergy as a whole are not available. These parameters vary from country to country and depend on the local

flora and the population's way of life. Numerous investigations have shown that 25–60% of North Americans are sensitive to poison ivy and other members of the Anacardiaceae family [5]. Occupational dermatitis to plants is common in gardeners, florists and undertakers. English Ivy (*Hedera helix)* is not related but it is becoming increasingly recognized as a cause of plant allergy in the UK [6].

It has been estimated that 5–10% of all cases of contact allergy seen in European dermatology clinics are caused by plants or their products [4]. Primin, found in *Primula obconica*, is recommended as a standard-series allergen in Europe. Of 3075 patients patch tested in Denmark, positive reactions were recorded in 1.8%, about 95% of the positive reactors being female [7]; in the UK, positive reactions were recorded in 1% of 3462 patients routinely tested [8]. There is recent evidence of a statistically significant decreasing frequency of allergy in the UK and Europe [9,10].

Sesquiterpene lactone mix in the standard series is used to identify Compositae (Asteraceae) allergy. A multicentre European study showed varying frequencies of allergy in patch-tested patients, ranging from 0.1 to 2.7% according to the centre, with clinical relevance found in approximately three-quarters of cases [11]. In a large UK review of 7420 patients, 1.8% had positive reactions [12]. However, it has been suggested that the sesquiterpene lactone mix might only detect about one-third of those allergic to Compositae [13].

Garlic allergy is frequent in Spain, with 2% of patients attending for investigation of dermatitis being sensitized, mainly housewives [14]. Other countries where garlic is used frequently in cooking might have a similar prevalence. In the UK, curry chefs are an at-risk group [15].

Tea tree oil (*Melaleuca alternifolia*) is being increasingly used in cosmetics and medicaments and has caused allergic reactions from these sources [16,17].

Anacardiaceae

Plants from this family have caused more contact allergy than all other plants combined [1]. Much of this sensitization relates to poison ivy, sumac and oak, which are species of *Toxicodendron* found extensively in North America. The plants are generally found outdoors and recognized by their three-leafed configuration. Their diverse morphology and various habitats have been described by Guin *et al*. [18].

The main allergens found in the oleoresin (or urushiol) are derivatives of catechol, particularly pentadecylcatechols, phenol, resorcinol and salicylic acid [4]. Cross-reactions occur with cashew nut oil, which may be used industrially in resins, mucilages, printer's inks and electrical insulation [5]. Haitian voodoo dolls and swizzle sticks made from cashew nut shells have also sensitized [5]. Further cross-sensitivity is found with mangoes, gingko tree fruit, indelible laundry marking ink from the marking nut tree in India, furniture lacquer from the Japanese lacquer tree, *Lithraea* trees in South America, and plants and trees from the genus *Grevillea* found in Australia [4,5,19–23]. Although poison ivy is not a native European plant it may be brought back from North America and planted. Isolated cases of contact sensitization have been seen from this source [24,25]. Localized outbreaks of dermatitis from contact with the Japanese lacquer tree have occurred in the UK [26–28].

Clinical features. *Toxicodendron* spp. dermatitis occurs after contact with the sap of the plant. Classically the rash is streaky, with erythema, papules and vesiculo-bullous lesions on exposed sites. The hardened sap may leave a black spot on the skin in the areas of dermatitis and this may be helpful diagnostically [29]. Distant spread is common, particularly facial and genital involvement from contaminated hands. More profound erythema multiforme-like, exanthematous and urticarial eruptions, and even renal damage, may occur from systemic absorption [30]. Stomatitis and proctitis have occurred after chewing the leaves, and with hyposensitization [30]. Contamination of clothing, animals, garden tools, firewood, fishing rods and golf clubs may also act as sources of contact.

Phytophotodermatitis (Chapter 29) and allergy to *Primula* and other plants has to be considered in the differential diagnosis.

Compositae (Asteraceae)

Compositae plants are also known as Asteraceae. There are over 25 000 species found throughout the world and more than 200 have been reported to cause allergic contact dermatitis [31]. They may be decorative plants (e.g. chrysanthemums, dahlias, sunflowers), weeds (e.g. ragweed, dandelion, tansy, marsh elder, feverfew, chamomile, yarrow, arnica, *Parthenium*) or foods (e.g. lettuce, endive, artichoke). Herbal teas, medicines and cosmetics may all contain Compositae plants or extracts.

The allergens are sesquiterpene lactones and more than 1350 have been described, including dehydrocostus lactone, alantolactone, costunolide and parthenolide [4,5]. In lettuce and chicory, lactucin and lactucopicrin have also been identified as sensitizers [32,33]. Monoterpenes may also contribute to Compositae allergy [34].

As might be expected, there is considerable but variable cross-reactivity among Compositae plants. Cross-sensitivity with *Frullania* liverworts has been described and has also occurred with members of other plant families, most notably Lauraceae and Magnoliaceae [35]. Furthermore, there is some evidence of cross-sensitivity to colophonium and a number of essential oils which may be found in fragrances [36].

Clinical features [37]. Six patterns of dermatitis are described, which are generally worse during the summer months in temperate climates.

1 *Pseudophotodermatitis*. Exposed sites are involved, including both eyelids, and photoprotected areas under the chin and behind the ears. In hot regions, during summer months, dry dead plant material contributes to the airborne pattern of dermatitis. In the USA many Compositae weeds, including ragweed (*Ambrosia* spp.), induce this pattern of dermatitis, almost exclusively in males. A similar pattern is seen in Europe from Compositae flowers and weeds, in India [38] from *Parthenium hysterophorus* (see below), and in Australia where it is known as bush dermatitis [39]. Chronic cases may produce a marked thickening of the facial skin—a leonine facies. Photosensitivity quite commonly coexists with Compositae allergy (Fig. 26.26). In one UK study, 22% of the contact-allergic patients were also photosensitive [12]. True photoallergy to Compositae is, however, generally not a feature.



Fig. 26.26 Photosensitive eczema in a patient also allergic to Compositae (sesquiterpene lactones). A similar pattern may be seen in woodcutters sensitive to lichens, and in others with photosensitive eczema, including photocontact allergy. (Courtesy of Dr J.D. Wilkinson, Amersham General Hospital, Amersham, UK.)



Fig. 26.27 Haemorrhagic blisters on the palm from *Primula* allergy.

2 *Atopic eczema-like*. Compositae allergy may mimic late-onset atopic eczema, with a flexural accentuation of involvement, which may include the groins and genital area [40].
3 *Erythrodermatous exfoliative*. This pattern is classically seen from the weed *Parthenium hysterophorus*, which was transported to India from the USA in contaminated seed wheat [41]. Unfortunately, the weed has spread over much of the subcontinent, including urban areas. It has become markedly allergenic in these environmental conditions, which also enhance the spread of dry plant dust and pollen. There is increased opportunity for skin exposure because many of the indigenous male population wear relatively scanty clothing. Severe incapacity and even fatalities have resulted from *Parthenium* dermatitis.
4 *Hand eczema*. This pattern is seen particularly in gardeners after contact with weeds. A palmar distribution often predominates. Dermatitis of the hands is also associated with handling lettuce.
5 *Localized dermatitis*. Dermatitis may be confined to one or more localized areas, although this pattern is unusual in our experience. Facial dermatitis has occurred from steaming chamomile tea, and hand and arm dermatitis from herbal compresses [42,43].
6 *Oral*. Oral swelling and soreness after eating lettuce has been reported in sensitized persons [44].
7 *Erythema multiforme.* This has been reported. It recurred after patch testing [45].
8 *Systemic.* Oral swelling, perianal pruritus and dermatitis of the trunk and arms has been reported after a sensitized subject drank chamomile tea [46].

Primulaceae

Primula obconica is the most important allergenic plant, although other *Primula* species may also cause allergic contact dermatitis [47]. *Primula obconica* is a decorative indoor plant. The major allergen is primin, a quinone found in the tiny breakable hairs on the leaves, stem and flowers of the plant. Another potential allergen is miconidin [48].

Contact occurs particularly when dead leaves and plant heads are removed manually. Primin levels are at their highest between April and August. The allergen content of the plant also varies with sun exposure, temperature and feeding. The pattern of dermatitis is determined by both the allergen content of the plant and the patient's degree of sensitivity and exposure. Primin-free strains have now been developed [49] and, probably as a result, there is evidence of a decreased frequency of allergy [9,10].

Clinical features. The classical appearance of *Primula* allergy is linear papulovesicles, oedema and blisters, which may be haemorrhagic, on the palms, dorsa of the hands and forearms (Figs 26.6 & 26.27). Transfer of the allergen via the fingers to the face, or more widely, is common. In some patients palpebral oedema is the presenting feature, but half of the cases have other patterns, and the diagnosis is easily missed unless the possibility of *Primula* dermatitis is kept in mind. Misdiagnoses include constitutional pompholyx, urticaria or recurrent angio-oedema, and disseminated herpes simplex [50]. Erythema multiforme, a lichen planus-like eruption and toxic erythema as a result of *Primula* allergy can also cause diagnostic difficulty [51–53].

Alstroemeriaceae and Liliaceae

Alstroemeria (Peruvian lily) is a highly decorative plant commonly displayed as a spray with other flowers. The damaged plant's sap is allergenic to florists when the stems are wired and leaves stripped, in preparation for making the spray.

The allergen is tulipalin A, also known as α-methylene-γ-butyrolactone, released from the precursor tuliposide A. This allergen is also found in tulips (especially the bulbs). Tulips are members of the Liliaceae family, and dermatitis is a particular risk for bulb collectors, sorters and packers, as well as florists.

Clinical features. Dermatitis from tulip bulbs may cause a painful, dry, fissured and hyperkeratotic allergic dermatitis, at first underneath the free margins of the nails and then on the fingertips. A similar pattern of dermatitis is seen in florists sensitized to *Alstroemeria*, and this may be followed by depigmentation [54].

Alliaceae

Garlic and onion are both members of this family and may sensitize, but do not seem commonly to cross-sensitize mutually [55]. Diallyl disulphide is the major allergen in garlic. The allergen(s) in onion has not been identified.

Clinical features. Classically there is fingertip involvement in those allergic to garlic (see Fig. 26.7) and onion. This may preferentially affect the non-dominant hand, as this is the one that holds the vegetable while it is being cut with an implement held by the dominant hand. Cheilitis and photoallergic contact dermatitis have also been reported [56,57]. Systemic contact allergy, including pompholyx, caused by ingestion of garlic has been described [58,59].

Lichens and liverworts

Lichens consist of a fungus and an alga. They are found on trees, rocks, roofs and walls [4]. Forestry workers, gardeners, lichen pickers and woodcutters are particularly liable to come in contact with them. Oak moss (*Evernia prunastri*) and other tree mosses are perfume ingredients derived from lichens. Chloroatranol and atranol are the main allergens [60]. They are common components of perfumed materials. Other allergenic components include atranornin, usnic acid and evernic acid [61]. Liverworts (*Frullania*) are small red/brown plants often growing with lichens and mosses. The allergens, in common with Compositae with which they commonly cross-react, are sesquiterpene lactones.

Clinical features. A pattern similar to pseudophotodermatitis from Compositae has been seen in woodcutters' dermatitis caused by sensitivity to lichens and liverworts [62]. Erythroderma may ensue in severe cases. Even walking through a forest may cause an exposed-site pattern of dermatitis in sensitized individuals [35].

Avoidance

Patients who know of their sensitivity may manage to avoid further contact if taught to recognize the plants to which they are allergic. This is fairly straightforward for *Primula obconica*, *Alstroemeria*, tulips, Alliaceae, lichens and liverworts. Tulipalin A, in tulips and *Alstroemeria*, penetrates vinyl gloves. Nitrile gloves are more satisfactory for handling bulbs and the plants [63]. Diallyl disulphide penetrates most glove materials [64].

The recognition of *Toxicodendron* spp. is particularly important. Although the classical three-lobed leaves are a helpful feature, clusters of five or more leaves can occur. As there is considerable regional variability in the morphology of these species, it is preferable that sensitized persons become familiar with the appearance of *Toxicodendron* spp. in their own region.

Toxicodendron oleoresin may remain under the fingernails and on the clothes, resulting in continuing problems. Detergents, soap and water will inactivate the residual unreacted allergen. After exposure, thorough washing of the hands, fingers and the rest of the body should be carried out as soon as possible, ideally within 10 min. Clothes should be changed. Contaminated tools and clothing, including shoes, should be washed in detergent [5].

Specific creams, containing quaternium-18 bentonite and other barriers, have been developed and these may help prophylactically to a varying but incomplete extent [65,66]. Heavy-duty vinyl gloves afford better protection than rubber gloves [5].

Seasonal Compositae exposure may be difficult to avoid. Severe Compositae allergy may necessitate changing occupation (e.g. florists, gardeners) or avoiding pastimes such as flower arranging and gardening. It may be necessary to avoid handling lettuce, chicory, artichokes and endives in food preparation. Those with associated photosensitivity may have significant problems from this, especially over the summer months. A high protection broad-spectrum sunscreen is required for this subgroup. Where contact with *Toxicodendron* spp. and certain Compositae such as ragweed is unavoidable (e.g. outdoor workers), hyposensitization has been attempted, with limited success. There is a risk of unpleasant side effects, including extensive skin eruptions and perianal dermatitis [67–69]. This treatment does not have the approval of the Food and Drug Administration in the USA [5].

Those sensitized to lichens may also be allergic to certain perfumes, particularly those containing oak moss (*Evernia prunastri*). Perfume avoidance advice (see p. 26.41) may also have to be followed.

Patch tests

There are two plant allergens recommended for the standard series: primin is tested at 0.01% in petrolatum; sesquiterpene lactone mix contains alantolactone 0.033%, dehydrocostus lactone 0.033% and costunolide 0.033% emulsified with sorbitan sesquioleate.

Primin is the major allergen in *Primula obconica* but may fail to detect *Primula* allergy occasionally [70]. Other *Primula* species may contain this allergen [47]. The diminishing number of cases of allergy has brought into question the need for its inclusion in the standard series [7].

Sesquiterpene lactone mix does not identify all persons with Compositae allergy [71–73]. An alternative screen consisting of a mix of arnica, yarrow, tansy, German chamomile and feverfew extracts has been developed [74]. In one study, it identified twice the number of sensitized persons detected by sesquiterpene lactone mix, and by testing with both allergens 76% of all allergic subjects were identified [75]. However, this Compositae mix gave frequent false-positive reactions and was felt to be sensitizing [76–78], and consequently it is at present no longer commercially available as a test allergen, as far as we are aware. A lower concentration than 6% has been suggested [79]. Dandelion allergy, in particular, may be missed by the sesquiterpene lactone mix patch test, and supplementary testing with extract has increased the number of Compositae-allergic subjects identified [80,81].

Other commercially available plant allergens comprise a number of Compositae extracts, including dandelion. Diallyl disulphide, the main allergen in garlic, is tested at 1% in petrolatum, and α-methylene-γ-butyrolactone, the allergen in tulips and *Alstroemeria*, is tested at 0.01% in petrolatum. Lichen acid mix consists of atranornin, usnic acid and evernic acid, each at 0.1% in petrolatum. Oxidized tea tree oil is available at 5% but recent work suggests 10% may be the concentration of choice [16].

Plant extracts, preferably of known concentration, can be used for patch testing. Dipping the plant in diethyl ether for 60–90 s, evaporating to dryness and resuspending in petrolatum (1–10%) is a suggested simple method, although there are many alternative approaches [4,5,82]. Patch testing for *Toxicodendron*, if considered necessary, can be undertaken by diluting the oleoresin 1 in 10 in acetone [5].

Patch testing with the plants themselves may be undertaken but carries the risk of false-positive irritant reactions and active sensitization. If multiple tests with plants and plant allergens are carried out, there is a possibility that many strong positives may occur, leading to an 'angry back' and inducing false-positive reactions to other allergens. Ideally, before patch testing with a plant, it should be identified and if it is a known irritant then testing may not be advisable. A textbook on plant dermatitis is a useful reference source. Several parts of one plant may contain the same allergen, and if this is the case 1 cm^2 of leaf bruised gently with an orange stick is sufficient for patch testing. Sometimes, however, the allergen is concentrated in one organ of the plant (orange peel, cinnamon bark) or the concentration of the allergen varies from one part to another. When testing with unknown plants, several parts should be tested. Half of the material should be kept in a refrigerator for later botanical identification. Any plant that has given positive allergic reactions should be properly identified by its Linnaean name.

In order to prevent registration of irritant tests, it is important to employ controls when testing with the plants and their extracts.

References

1 Mitchell JC, Rook A. *Botanical Dermatology*. Philadelphia: Lea & Febiger, 1979.
2 Schmidt RJ. *The Botanical Dermatology Database*. http://bodd.cf.ac.uk/
3 Lovell CR. *Plants and the Skin*. Oxford: Blackwell Scientific Publications, 1993.
4 Le Coz CJ, Ducombs G. Plants and plant products. In: Frosch PJ, Menné T, Lepoittevin J-P, eds. *Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 751–800.
5 Rietschel RL, Fowler JF Jr. *Fisher's Contact Dermatitis*, 5th edn. Baltimore: Lippincott, Williams & Wilkins, 1995: 351–95, 715–21.
6 Hafejee A, Williams J, Lovell C *et al*. Allergic contact dermatitis to English Ivy (*Hedera helix*). *Br J Dermatol* 2007; **157** (Suppl. 1): 88–9.
7 Ingber A, Menné T. Primin standard patch testing: 5 years' experience. *Contact Dermatitis* 1990; **23**: 15–9.
8 Logan RA, White IR. Primula dermatitis: prevalence, detection and outcome. *Contact Dermatitis* 1988; **19**: 68–9.
9 Connolly M, McCune J, Dauncey E, Lovell CR. Primula obconica–is contact allergy on the decline? *Contact Dermatitis* 2004; **51**: 167–71.
10 Zachariae C, Engkilde K, Johansen JD, Menné T. Primin in the European standard patch test series for 20 years. *Contact Dermatitis* 2007; **56**: 344–6.
11 Paulsen E, Andersen KE, Brandao FM *et al*. Routine patch testing with the sesquiterpene lactone mix in Europe: a 2-year experience. A multicentre study of the EECDRG. *Contact Dermatitis* 1999; **40**: 72–6.
12 Ross JS, du Peloux Menage H, Hawk JL *et al*. Sesquiterpene lactone contact sensitivity: clinical patterns of Compositae dermatitis and relationship to chronic actinic dermatitis. *Contact Dermatitis* 1993; **29**: 84–7.
13 Green C, Ferguson J. Sesquiterpene lactone mix is not an adequate screen for Compositae allergy. *Contact Dermatitis* 1994; **31**: 151–3.
14 Cabanillas M, Fernández-Redondo V, Toribio J. Allergic contact dermatitis to plants in a Spanish dermatology department: a 7-year review. *Contact Dermatitis* 2006; **55**: 84–91.
15 Hubbard VG, Goldsmith P. Garlic-fingered chefs. *Contact Dermatitis* 2005; **52**: 165–6.
16 Rutherford T, Nixon R, Tam M, Tate B. Allergy to tea tree oil: retrospective review of 41 cases with positive patch tests over 4.5 years. *Australas J Dermatol* 2007; **48**: 83–7.
17 Hartford O, Zug KA. Tea tree oil. *Cutis* 2005; **76**: 178–80.
18 Guin JD, Gillis WT, Beaman JH. Recognizing the Toxicodendrons (poison ivy, poison oak, and poison sumac). *J Am Acad Dermatol* 1981; **4**: 99–114.
19 Goldstein N. The ubiquitous urushiols: contact dermatitis from mango, poison ivy, and other 'poison' plants. *Cutis* 1968; **6**: 679–85.
20 Tomb RR, Foussereau J, Sell Y. Mini-epidemic of contact dermatitis from ginkgo tree fruit (*Ginkgo biloba* L.). *Contact Dermatitis* 1988; **19**: 281–3.
21 Kullavanijaya P, Ophaswongse S. A study of dermatitis in the lacquerware industry. *Contact Dermatitis* 1997; **36**: 244–6.
22 Ale SI, Ferreira F, Gonzalez G *et al*. Allergic contact dermatitis caused by *Lithraea molleoides* and *Lithraea brasiliensis*: identification and characterization of the responsible allergens. *Am J Contact Dermatitis* 1997; **8**: 144–9.
23 Menz J, Rossi ER, Taylor WC *et al*. Contact dermatitis from *Grevillea* 'Robyn Gordon'. *Contact Dermatitis* 1986; **15**: 126–31.
24 Walker SL, Lear JT, Beck MH. Toxicodendron dermatitis in the UK. *Int J Dermatol* 2006; **45**: 810–3.
25 Leclercq RM. Severe contact-allergy dermatitis due to poison ivy – a plant that is rarely encountered in The Netherlands: a family history. *Ned Tijdschr Geneesk* 2005; **149**: 1697–700.
26 Powell SM, Barrett DK. An outbreak of contact dermatitis from *Rhus verniciflua* (*Toxicodendron vernicifluum*). *Contact Dermatitis* 1986; **14**: 288–9.
27 Roberts DL. An outbreak of contact dermatitis from Japanese lacquer tree. *Contact Dermatitis* 1997; **37**: 237.
28 Gach JE, Tucker W, Hill VA. Three cases of severe Rhus dermatitis in an English primary school. *J Eur Acad Dermatol Venereol* 2006; **20**: 212–3.
29 Guin JD. The black spot test for recognizing poison ivy and related species. *J Am Acad Dermatol* 1980; **2**: 332–3.
30 Cronin E. *Contact Dermatitis*. Edinburgh: Churchill Livingstone, 1980: 480.
31 Andersen K, White I, Goossens A. Allergens from the standard series. In: Frosch PJ, Menné T, Lepoittevin J-P, eds. *Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 488.
32 Hausen BM, Andersen KE, Helander I, Gensch K. Lettuce allergy: sensitizing potency of allergens. *Contact Dermatitis* 1986; **15**: 246–9.
33 Mitchell D, Beck MH, Hausen BM. Contact sensitivity to lettuce in a chef. *Contact Dermatitis* 1989; **20**: 398–9.
34 Paulsen E, Christensen LP, Andersen KE. Do monoterpenes released from feverfew (*Tanacetum parthenium*) plants cause airborne Compositae dermatitis? *Contact Dermatitis* 2002; **47**: 14–8.
35 Foussereau J, Muller JC, Benezra C. Contact allergy to *Frullania* and *Laurus nobilis*: cross-sensitization and chemical structure of the allergens. *Contact Dermatitis* 1975; **1**: 223–30.
36 Paulsen E, Andersen KE. Colophonium and Compositae mix as markers of fragrance allergy: cross-reactivity between fragrance terpenes, Colophonium and Compositae plant extracts. *Contact Dermatitis* 2005; **53**: 285–91.
37 Guin JD. Occupational contact dermatitis to plants. In: Kanerva L, Elsner P, Wahlberg JE, Maibach HI, eds. *Handbook of Occupational Dermatology*. Berlin: Springer, 2000: 730–66.
38 Sharma VK, Sethuraman G, Bhat R. Evolution of clinical pattern of *Parthenium* dermatitis: a study of 74 cases. *Contact Dermatitis* 2005; **53**: 84–8.
39 Burry JN, Reid JG, Kirk J. Australian bush dermatitis. *Contact Dermatitis* 1975; **1**: 263–4.
40 Guin JD, Skidmore G. Compositae dermatitis in childhood. *Arch Dermatol* 1987; **123**: 500–2.
41 Mitchell JC, Calnan CD. Scourge of India: *Parthenium* dermatitis. *Int J Dermatol* 1978; **17**: 303–4.
42 Pereira F, Santos R, Pereira A. Contact dermatitis from chamomile tea. *Contact Dermatitis* 1997; **36**: 307.
43 Rycroft RJ. Recurrent facial dermatitis from chamomile tea. *Contact Dermatitis* 2003; **48**: 229.
44 Oliwiecki S, Beck MH, Hausen BM. Compositae dermatitis aggravated by eating lettuce. *Contact Dermatitis* 1991; **24**: 318–9.
45 Jovanović M, Mimica-Dukić N, Poljacki M, Boza P. Erythema multiforme due to contact with weeds: a recurrence after patch testing. *Contact Dermatitis* 2003; **48**: 17–25.

46 Rodríguez-Serna M, Sánchez-Motilla JM, Ramón R, Aliaga A. Allergic and systemic contact dermatitis from *Matricaria chamomilla* tea. *Contact Dermatitis* 1998; **39**: 192–3.
47 Aplin CG, Lovell CR. Contact dermatitis due to hardy *Primula* species and their cultivars. *Contact Dermatitis* 2001; **44**: 23–9.
48 Krebs M, Christensen LP. 2-Methoxy-6-pentyl-1,4-dihydroxybenzene (miconidin) from *Primula obconica*: a possible allergen? *Contact Dermatitis* 1995; **33**: 90–3.
49 Christensen LP, Larsen E. Primin-free *Primula obconica* plants available. *Contact Dermatitis* 2000; **43**: 45–6.
50 Thomson KF, Charles-Holmes R, Beck MH. Primula dermatitis mimicking herpes simplex. *Contact Dermatitis* 1997; **37**: 185–6.
51 Virgili A, Corazza M. Unusual primin dermatitis. *Contact Dermatitis* 1991; **24**: 63–4.
52 Lengrand F, Tellart AS, Segard M *et al*. Erythema multiforme-like eruption: an unusual presentation of primula contact allergy. *Contact Dermatitis* 2001; **44**: 35.
53 Lapiere K, Matthieu L, Meuleman L *et al*. Primula dermatitis mimicking lichen planus. *Contact Dermatitis* 2001; **44**: 199.
54 Björkner BE. Contact allergy and depigmentation from alstroemeria. *Contact Dermatitis* 1982; **8**: 178–84.
55 Van Ketel WG, de Haan P. Occupational eczema from garlic and onion. *Contact Dermatitis* 1978; **4**: 53–4.
56 Ekeowa-Anderson AL, Shergill B, Goldsmith P. Allergic contact cheilitis to garlic. *Contact Dermatitis* 2007; **56**: 174–5.
57 Alvarez MS, Jacobs S, Jiang SB *et al.* Photocontact allergy to diallyl disulfide. *Am J Contact Dermatitis* 2003; **14**: 161–5.
58 Burden AD, Wilkinson SM, Beck MH *et al*. Garlic-induced systemic contact dermatitis. *Contact Dermatitis* 1994; **30**: 299–300.
59 Pereira F, Hatia M, Cardoso J. Systemic contact dermatitis from diallyl disulfide. *Contact Dermatitis* 2002; **46**: 124.
60 Rastogi SC, Bossi R, Johansen JD *et al.* Content of oak moss allergens atranol and chloroatranol in perfumes and similar products. *Contact Dermatitis* 2004; **50**: 367–70.
61 Thune P, Solberg Y, McFadden N *et al*. Perfume allergy due to oak moss and other lichens. *Contact Dermatitis* 1982; **8**: 396–400.
62 Salo H, Hannuksela M, Hausen B. Lichen pickers dermatitis (*Cladonia alpestris* (L) Rab.). *Contact Dermatitis* 1981; **7**: 9–13.
63 Marks JG Jr. Allergic contact dermatitis to *Alstroemeria*. *Arch Dermatol* 1988; **124**: 914–6.
64 Moyle M, Frowen K, Nixon R. Use of gloves in protection from diallyl disulphide allergy. *Australas J Dermatol* 2004; **45**: 223–5.
65 Marks JG Jr, Fowler JF Jr, Sheretz EF *et al*. Prevention of poison ivy and poison oak allergic contact dermatitis by quaternium-18 bentonite. *J Am Acad Dermatol* 1995; **33**: 212–6.
66 Grevelink SA, Murrell DF, Olsen EA. Effectiveness of various barrier preparations in preventing and/or ameliorating experimentally produced *Toxicodendron* dermatitis. *J Am Acad Dermatol* 1992; **27**: 182–8.
67 Epstein WL, Byers VS, Frankart W. Induction of antigen specific hyposensitization to poison oak in sensitized adults. *Arch Dermatol* 1982; **118**: 630–3.
68 Marks JG Jr, Trautlein JJ, Epstein WL *et al*. Oral hyposensitization to poison ivy and poison oak. *Arch Dermatol* 1987; **123**: 476–8.
69 Watson ES. *Toxicodendron* hyposensitization programs. *Clin Dermatol* 1986; **4**: 160–70.
70 Dooms-Goossens A, Biesemans G, Vandaele M *et al*. Primula dermatitis: more than one allergen? *Contact Dermatitis* 1989; **21**: 122–4.
71 Paulsen E, Andersen KE, Hausen BM. Compositae dermatitis in a Danish dermatology department in one year (I). Results of routine patch testing with the sesquiterpene lactone mix supplemented with aimed patch testing with extracts and sesquiterpene lactones of Compositae plants. *Contact Dermatitis* 1993; **29**: 6–10.
72 Lepoittevin JP, Tomb R. Sesquiterpene lactone mix is not an adequate screen for Compositae allergy. *Contact Dermatitis* 1995; **32**: 254.
73 Shum KW, English JS. Allergic contact dermatitis in food handlers with patch tests positive to Compositae mix but negative to sesquiterpene lactone mix. *Contact Dermatitis* 1998; **39**: 207–8.
74 Hausen BM. A 6-year experience with compositae mix. *Am J Contact Dermatitis* 1996; **7**: 94–9.
75 Paulsen E. Occupational dermatitis in Danish gardeners and greenhouse workers (II). Etiological factors. *Contact Dermatitis* 1998; **38**: 14–9.
76 Von der Werth JM, Ratcliffe J, English JS. Compositae mix is a more sensitive test for Compositae dermatitis than the sesquiterpene lactone mix. *Contact Dermatitis* 1999; **40**: 273–6.
77 Wilkinson SM, Pollock B. Patch test sensitization after use of the Compositae mix. *Contact Dermatitis* 1999; **40**: 277–8.
78 Kanerva L, Estlander T, Alanko K *et al*. Patch test sensitization to Compositae mix, sesquiterpene-lactone mix, Compositae extracts, laurel leaf, Chlorophorin, Mansonone A, and dimethoxydalbergione. *Am J Contact Dermatitis* 2001; **12**: 18–24.
79 Bong JL, English JS, Wilkinson SM. Diluted Compositae mix versus sesquiterpene lactone mix as a screening agent for Compositae dermatitis: a multicentre study. *Contact Dermatitis* 2001; **45**: 26–8.
80 Lovell CR, Rowan M. Dandelion dermatitis. *Contact Dermatitis* 1991; **25**: 185–8.
81 Jovanović M, Poljacki M, Mimica-Dukić N *et al*. Sesquiterpene lactone mix patch testing supplemented with dandelion extract in patients with allergic contact dermatitis, atopic dermatitis and non-allergic chronic inflammatory skin diseases. *Contact Dermatitis* 2004; **51**: 101–10.
82 Guin J. Patch testing to plants: some practical aspects of what has become an esoteric area of contact dermatitis. *Am J Contact Dermatitis* 1995; **6**: 232–5.

Woods, colophony, turpentine and propolis [1–4]

Woods are normally of two types, hard and soft. The same woods may have many different names, and sometimes an incorrect name is mistakenly or deliberately applied [4,5]. The situation is complicated further by the occasional introduction of 'rogue' timbers into batches of hardwoods [6,7]. The commonest allergenic woods are listed in Table 26.10 [4].

Occupational allergic contact dermatitis is more frequently associated with hardwoods, especially among cabinet-makers, carpenters, instrument makers, and so on. Some tropical hardwoods are especially allergenic. In many instances the precise allergens are not known, but some have been identified. Chemically, these include quinones (including dalbergiones and lapachol), phenols, terpenes, stilbenes and anthothecol [1–4]. Softwoods, apart from pines and other conifers, are not commonly associated with contact allergy [4]. Jelutong (*Dyera costulata*) is a South-East Asian tree whose timber has sensitized woodwork teachers [8].

Pine trees are the source of two significant allergenic materials, colophony and turpentine [4]. Turpentine is the balsam from species of *Pinus*. Oil of turpentine is the volatile oil distilled from this balsam. The term 'turpentine' is commonly used to designate oil of turpentine. Colophony is the non-volatile part of the balsam and is known as gum rosin. Swedish and Finnish turpentine is made in the processing of paper pulp from wood. Venice turpentine is the balsam from larch trees.

Colophony is also extracted as a distillate from pine tree stumps, when it is known as wood rosin, and as a by-product of pulping pine wood, when it is called tall oil rosin [9]. The chemical composition varies according to geographical source, production method and storage conditions. It is composed of approximately 90% resin acids and 10% neutral substances [10]. Auto-oxidation products of abietic and dehydroabietic acids, including peroxides, hydroperoxides, epoxides and ketones, have been proposed as allergens [11]. The most potent allergen has been shown to be 15-hydroperoxyabietic acid [12]. Colophony may be modified, thereby altering its allergenicity with the development of new allergens [13]. Maleopimaric acid and glyceryl monoabietate have been

Table 26.10 Principal timbers causing dermatitis.* (Adapted from Hausen [4].)

Botanical name	Common name†	Origin	Uses
Apocynaceae			
Dyera costulata	Jelutong	SE Asia	Modelmaking Woodwork teaching
Boraginaceae			
Cordia goeldiana Huber	Freijo Frei jorge	Brazil	Boat building Furniture Interior construction Joinery
Cordia gerascanthus R. Br.	Canalete	Venezuela	Furniture Interior construction Joinery
Cordia millenii Baker	Cordia	W. Africa	Furniture Interior construction Joinery
Cordia platythyrsa Baker	Cordia	W. Africa	Furniture Interior construction Joinery
Cupressaceae			
Calocedrus decurrens (Torrey) Florin	Incense cedar	USA	Pencils Fence posts Furniture Interior construction
x *Cupressocyparis leylandii*	Leyland cypress	Temperate	Garden shrub Hedges
Thuja plicata Donn ex D. Don	Western red cedar Arbor vitae	USA	Construction Boat building
Ebenaceae			
Diospyros celebica Bakh.	Macassar	Indonesia	Cabinet and inlay work Musical instruments Rulers
Diospyros crassifolia Hiern	African ebony	Africa	Cabinet and inlay work Musical instruments
Diospyros ebenum Koenig	Ceylon ebony East Indian ebony	Sri Lanka, India, Indonesia	Cabinet and inlay work Musical instruments
Diospyros melanoxylon Roxb.	Coromandel	Sri Lanka, India, Indonesia	Cabinet and inlay work Musical instruments
Leguminosae			
Caesalpiniaceae			
Distemonanthus benthamianus Baillon	Ayan Movingui Nigerian satinwood	W. Africa	Coffins Furniture Floors Window frames
Mimosaceae			
Acacia melanoxylon R. Br.	Australian blackwood	W. Australia	Boat building Construction Furniture Musical instruments
Papilionaceae			
Bowdichia nitida Spruce ex Benth.	Sucupira	Brazil	Construction Floors Furniture
Brya ebenus	Cocus Jamaica ebony	W. Indies	Musical instruments Handles Plates
Dalbergia latifolia Roxb.	E. Indian rosewood Bombay blackwood Sissoo	India, Indonesia	Veneers Furniture Musical instruments Handles Wooden jewellery

(Continued)

Table 26.10 *Continued*

Botanical name	Common name†	Origin	Uses
Dalbergia melanoxylon Guillemin & Perrottet	African blackwood Grenadil	Africa	Musical instruments Handles
Dalbergia nigra All.	Brazilian rosewood Rio-Palisander Grenadilla Jacaranda	Brazil	Veneers Furniture Musical instruments Handles Wooden jewellery
Dalbergia retusa Hemsley	Cocobolo	Central America	Handles Scientific instruments Wooden jewellery
Machaerium scleroxylon Tul.	Pao ferro Santos palisander Caviuna vermelha	Brazil	Veneers Furniture Handles
Pterocarpus soyauxii Taub.	Red African padauk	West Africa	Veneers Handles Musical Instruments Furniture
Malvaceae (L.) Sol.			
Thespesia populnea (L.) Sol.	Milowood	USA	Carved utensils Bracelets Furniture
Meliaceae			
Khaya anthotheca C. DC	African mahogany Krala	W. Africa	Furniture
Khaya grandiflora DC	Big leaf mahogany	W. Africa	Furniture
Khaya ivorensis A. Chev.	Khaya mahogany	W. Africa	Furniture
Khaya senegalensis (Desr.) A. Juss.	Dry zone mahogany	W. Africa	Furniture
Moraceae			
Chlorophora excelsa Benth. & Hook.	Iroko Kambala African teak	W. Africa	Construction Shipbuilding Laboratory benches
Pinaceae			
Pinus spp.	Pine	Northern temperate	Construction Furniture General
Picea spp.	Spruce Fir	Northern temperate	Construction Furniture General
Proteaceae			
Grevillea robusta Cunn. ex R. Br.	Australian silky oak	Australia (planted elsewhere)	Floors Furniture Plywood Telegraph poles
Sterculiaceae			
Mansonia altissima A. Chev.	Mansonia African black walnut Bété	W. Africa	Furniture Walnut substitute
Verbenaceae			
Tectona grandis L.	Teak	India, SE Asia	Furniture Floors Construction Shipbuilding

* Lichens on the wood may also sensitize.

† There is no accepted international nomenclature.

identified as allergens in modified rosins [14,15]. Certain other resins are chemically related.

The major sensitizer in turpentine is hydroperoxide of Δ^3-carene [16], which is also an auto-oxidation product. Swedish and Finnish turpentine contains more of this substance than, for example, French and American turpentine. Oxidized limonene (D or L) and pinene (α or β) can also sensitize [17]. The term 'mineral turpentine' is used for the non-sensitizing, but irritant, white spirit, that is a petroleum product.

Propolis is a resinous material collected by bees and used as a glue in beehives. It is derived mainly from poplar resin. It may be found also in beeswax [18,19]. The allergens include caffeates and benzyl isoferulate [20].

Lichens, liverworts and sensitizing plants may cause allergic sensitization by virtue of their coexistence with trees. Additives to wood such as varnishes, dyes, glues or preservatives may also sensitize at work.

Incidence and prevalence. The incidence and prevalence of occupational wood allergy are unknown. Colophony is a standard allergen, with a 2–6% prevalence of allergy in patch-tested populations [13].

Turpentine was removed from the ICDRG's recommended standard series because of infrequent allergy. It has been excluded from many industrial products, especially solvents, and replaced by petroleum products such as white spirit, although a high prevalence of sensitization continues to occur in Spain and Portugal [21,22]. An unexplained rise in frequency of allergy (from 1.7% to 3.1%) was reported in patch-tested patients from Germany in the late 1990s [23].

The frequency of allergy to propolis in patch-tested patients in various centres has ranged from 1.2% to 6.6% [18].

Occurrence. Trees, wood and sawdusts are predictable sources. Colophony, however, is ubiquitous and not only found in pine and spruce trees and wood. The commoner sources of colophony and its modifications are identified in Table 26.11, but this list is not all-inclusive. It is labelled in cosmetics by its INCI name Colophonium. Colophony derivatives (e.g. abietic acid, hydroabietic acid and hydraobietyl alcohol) may also be found in cosmetics.

Table 26.11 Sources of colophony.

Pine trees and wood	Spruce trees and wood
Rosin (grip/antislip materials)	Adhesive plasters and tapes
Adhesive dressings	Insulating and jointing tapes
Ostomy appliances	Dental dressings
Clear and brown soaps	Varnishes and coatings
Metalworking fluids (tall oils)	Solder flux
Glues, adhesives and sealants	Shoe adhesives and counters
Paper size	Flypaper
Shoe and floor polishes	Cosmetics (eye shadow, mascara)
Printing inks	Wood wool
Chewing gum	Linoleum
Balms and salves	Wart treatments
Depilatory strips	Herbal medicaments

Turpentine is present in balsams and sawdust from pine and spruce. It was used as an industrial solvent but has now largely been replaced by petroleum derivatives and D-limonene. It is still used by artists and in ceramic decoration. In certain producing countries such as Spain and Portugal, turpentine is still more widely used than elsewhere, and it remains a common allergen there. In the USA it is still commonly used as a paint remover [24].

Propolis is encountered not only by beekeepers but also in both systemic and topically applied agents used in 'natural' products from health food stores and mainstream cosmetic outlets. Solid propolis can be chewed. Increasing self-medication may mean increased contact allergy from this source. It may also be found in beeswax [25] used in cosmetics and topical medicaments.

Clinical features. Most cases of wood allergy present in the occupational setting and are related to contact with airborne sawdust. The pattern of dermatitis therefore affects the exposed sites, with the scalp of bald men being typically involved. Differentiation from a photosensitive eczema may be difficult, but light-protected sites (e.g. under the chin and behind the ears) are more likely to be equally affected in wood dermatitis. However, sawdust can gain access inside clothing to produce dermatitis predominating in the flexures. Genital involvement is a particular feature, in part from transfer of the allergen during urination [7]. Severe erythema multiforme-like eruptions have been described, particularly from *Machaerium scleroxylon* allergy [7,26].

Localized dermatitis may occur under exotic hardwoods, for example from a violin chin-rest, or wooden adornments and utensils.

Colophony allergy may present in many different ways because colophony is ubiquitous. Over 300 potential allergenic sources have been identified [24]. An exposed-site pattern may be seen after machining pine and cutting down branches when gardening. Sensitivity to x *Cupressocyparis leylandii* trees has been associated with concomitant colophony allergy [27]. Allergy to colophony in solder fumes can give a similar distribution, but dermatitis may be confined to the face [28]. Unsuspected sources for an exposed-site pattern have included linoleum flooring, paper dust and floor polish [29].

Facial and eye dermatitis can develop from contact with colophony-containing cosmetics, particularly mascara [30]. Reactions to sticky tapes and plasters, and colophony-containing medicaments are often confined to the site of application, but secondary spread may be a feature from allergy to both colophony and colophony derivatives (e.g. ester gum resin) used as adhesives for lower leg dressings. This may be confused with varicose eczema and secondary medicament sensitization [31,32]. Adhesive plasters are often used to cover painful fissures on the hands and feet. These may have been caused by a pre-existing eczema or psoriasis, which may consequently be perpetuated or exacerbated by colophony allergy. Adhesive depilatory strips may contain colophony or derivatives and cause localized dermatitis [33], as may topical colophony-containing medicaments, including wart treatments.

Colophony may induce hand dermatitis due to contact with a diverse range of colophony-containing materials such as glues,

polishes, paper, rosin, antislip powders, topical medicaments, waxes, and tall oils in metal machining coolants.

Perioral dermatitis and cheilitis have been related to colophony in chewing gum [34,35]. Dental materials, including floss, fluoride varnish, dressings and impression materials, may contain colophony, but rarely sensitize in the mouth [36–38]. A case of widespread dermatitis has been recorded after dental treatment in an allergic individual [39].

Colophony can also be present in adhesives in footwear. It has also been incorporated, in modified form, in footwear in an impregnated cloth [40].

Turpentine allergy is usually associated with hand dermatitis or a localized pattern of dermatitis.

Allergy to propolis in medicaments is manifest at their sites of application. Sensitized beekeepers may develop problems on the face and around the eyes [18]. Allergy to chewed propolis may induce a perioral distribution of dermatitis [41].

Avoidance. Demonstration of allergy to a wood should be followed by anatomical confirmation of its botanical name and, ideally, by testing with the known allergen(s) for that wood [4]. Subsequent avoidance of the wood and related timbers may be necessary.

Detection of the origin of colophony allergy requires careful appraisal of potential sources. Use of traditional sticking plasters should be replaced by 'hypoallergenic' tapes. Insulating tapes may also contain colophony, as may certain adhesive leg ulcer dressings. Contact with pine and other coniferous trees, and probably x *Cupressocyparis leylandii*, should be avoided; in those with extreme sensitivity, felling and removing the offending trees may be necessary. Occupationally, it may be possible to change the allergenic product to an alternative.

Colophony and derivatives can be identified in fully ingredient-labelled cosmetics. The INCI term Colophonium is used. Derivatives that may be used in cosmetics include abietic acid, hydroabietic acid and hydroabietyl alcohol. Transparent colophony-containing soap should be avoided for washing. Wart paints incorporating collodion should also be avoided, along with colophony-containing topical medicaments and balms.

Colophony allergy from paper has been implicated in hand dermatitis, and the use of cotton gloves is suggested if this is a possibility [42].

However, the list of potential exposures is so extensive that it will often be a case of establishing whether any of the sources identified in Table 26.11 are relevant and tailoring avoidance advice accordingly. For a more comprehensive coverage of sources the reader is referred to *Fisher's Contact Dermatitis* [24].

Turpentine substitutes are now readily available for sensitized subjects. Propolis (and beeswax) found in topical applications can be avoided by using only fully ingredient-labelled cosmetics and medicaments.

Patch tests. Patch testing with freshly made, uncontaminated sawdust 10% in petrolatum is recommended but may carry the risk of false-positive and false-negative patch tests, and active sensitization [4]. Apparent allergic positive reactions should only be confirmed after testing on controls. It is advisable to ask the patient to bring a piece of unmachined wood at the same time as the sawdust. If a positive allergic reaction develops, the piece can be sent to a wood anatomist who will confirm the correct name for the wood. If the allergen for that wood is known, it is sometimes possible to patch test with it at the appropriate concentration. However, this may be difficult as most wood allergens are not commercially available.

Colophony is a standard allergen tested at 20% in petrolatum. A mixture of Chinese and Portuguese gum rosin is presently used in commercially available patch-test allergens [10]. The allergen profile may differ according to the source of the colophony, particularly if it has been modified, and consequently false-negative reactions can occur when patch testing with the unmodified standard series allergen [43]. Where modified colophony allergy is suspected a wider series of patch tests should be considered, for example ester gum resin, Granuflex®, as well as the suspected product [31,44,45].

Propolis is patch tested at 10% in petrolatum.

References

1 Hausen BM. *Woods Injurious to Human Health. A Manual*. Berlin: Walter de Gruyter, 1981.
2 Mitchell JC, Rook AJ. *Botanical Dermatology*. Vancouver: Greengrass, 1979.
3 Woods B, Calnan CD. Toxic woods. *Br J Dermatol* 1976; **94** (Suppl. 13): 1–97.
4 Hausen BM. Woods. In: Kanerva L, Elsner P, Wahlberg JE, Maibach HI, eds. *Handbook of Occupational Dermatology*. Berlin: Springer, 2000: 771–80.
5 Morgan JWW, Orsler RJ, Wilkinson DS. Dermatitis due to wood dusts of *Khaya anthotheca* and *Macherium scleroxylon*. *Br J Ind Med* 1968; **25**: 119–25.
6 Rojas-Hijazo B, Lezaun A, Hausen BM *et al.* Airborne contact dermatitis in gaitas (flageolets) constructors after exposure to sawdust of caviuna. *Contact Dermatitis* 2007; **56**: 274–7.
7 Beck MH, Hausen BM, Dave VK. Allergic contact dermatitis from *Machaerium scleroxylum* Tul. (Pao ferro) in a joinery shop. *Clin Exp Dermatol* 1984; **9**: 159–66.
8 Meding B, Karlberg AT, Ahman M. Wood dust from jelutong (*Dyera costulata*) causes contact allergy. *Contact Dermatitis* 1996; **34**: 349–53.
9 Cronin E. *Contact Dermatitis*. Edinburgh: Churchill Livingstone, 1980: 771–838.
10 Andersen K, White I, Goossens A. Allergens from the standard series. In: Frosch PJ, Menné T, Lepoittevin J-P, eds. *Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 466–8.
11 Karlberg A-T, Gäfvert E. Isolated colophony allergens as screening substances for contact allergy. *Contact Dermatitis* 1996; **35**: 201–7.
12 Karlberg AT, Bråred-Christensson J, Börje A *et al.* Methyl esterification of 15-hydroperoxyabietic acid does not affect the patch-test result in colophonium allergic patients. *Contact Dermatitis* 2007; **56**: 355–6.
13 Karlberg A-T. Colophony. In: Kanerva L, Elsner P, Wahlberg JE, Maibach HI, eds. *Handbook of Occupational Dermatology*. Berlin: Springer, 2000: 509–16.
14 Gäfvert E, Bordalo O, Karlberg A-T. Patch testing with allergens from modified rosin (colophony) discloses additional cases of contact allergy. *Contact Dermatitis* 1996; **35**: 290–8.
15 Hausen BM, Mohnert J. Contact allergy due to colophony (V). Patch test results with different types of colophony and modified-colophony products. *Contact Dermatitis* 1989; **20**: 295–301.
16 Pirilä V, Kilpiö O, Olkkonen A *et al*. On the chemical nature of the eczematogens in oil of turpentine V. Pattern of sensitivity to different terpenes. *Dermatologica* 1969; **139**: 183–94.
17 Romaguera C, Alomar A, Condé Salazar L *et al*. Turpentine sensitization. *Contact Dermatitis* 1986; **14**: 197.
18 Walgrave SE, Warshaw EM, Glesne LA. Allergic contact dermatitis from propolis. *Dermatitis* 2005; **16**: 209–15.
19 Jensen CD, Andersen KE. Allergic contact dermatitis from cera alba (purified propolis) in a lip balm and candy. *Contact Dermatitis* 2006; **55**: 312–3.
20 Hausen BM, Evers P, Stuwe HT *et al*. Propolis allergy (IV). Studies with further sensitizers from propolis and constituents common to propolis, poplar buds and balsam of Peru. *Contact Dermatitis* 1992; **26**: 34–44.

21 Romaguera C, Camarasa JM, Grimalt F *et al*. Turpentine: an attempt to explain sensitization to this allergen in Spain. *Contact Dermatitis* 1983; **9**: 384–6.
22 Cachao P, Menezes Brandao F, Carmo M *et al*. Allergy to oil of turpentine in Portugal. *Contact Dermatitis* 1986; **14**: 205–8.
23 Treudler R, Richter G, Geier J *et al*. Increase in sensitization to oil of turpentine: recent data from a multicenter study on 45 005 patients from the German-Austrian Information Network of Departments of Dermatology (IVDK). *Contact Dermatitis* 2000; **42**: 68–73.
24 Rietschel RL, Fowler JF Jr. *Fisher's Contact Dermatitis*, 5th edn. Baltimore: Lippincott, Williams & Wilkins, 1995: 365, 479.
25 Rothenborg HW. Occupational dermatitis in beekeeper due to poplar resins in beeswax. *Arch Dermatol* 1967; **95**: 381–4.
26 Holst R, Kirby J, Magnusson B. Sensitization to tropical woods giving erythema multiforme-like eruptions. *Contact Dermatitis* 1976; **2**: 295–6.
27 Lovell CR, Dannaker CJ, White IR. Dermatitis from *X Cupressocyparis leylandii* and concomitant sensitivity to colophony. *Contact Dermatitis* 1985; **13**: 344–5.
28 Goh CL, Ng SK. Airborne contact dermatitis to colophony in soldering flux. *Contact Dermatitis* 1987; **17**: 89–91.
29 Karlberg AT, Gäfvert E, Meding B *et al*. Airborne contact dermatitis from unexpected exposure to rosin (colophony). Rosin sources revealed with chemical analyses. *Contact Dermatitis* 1996; **35**: 272–8.
30 Karlberg AT, Lidén C, Ehrin E. Colophony in mascara as a cause of eyelid dermatitis. Chemical analyses and patch testing. *Acta Derm Venereol (Stockh)* 1991; **71**: 445–7.
31 Salim A, Shaw S. Recommendation to include ester gum resin when patch testing patients with leg ulcers. *Contact Dermatitis* 2001; **44**: 34.
32 Machet L, Couhé C, Perrinaud A *et al.* A high prevalence of sensitization still persists in leg ulcer patients: a retrospective series of 106 patients tested between 2001 and 2002 and a meta–analysis of 1975–2003 data. *Br J Dermatol* 2004; **150**: 929–35.
33 Satyawan I, Oranje AP, van Joost T. Perioral dermatitis in a child due to rosin in chewing gum. *Contact Dermatitis* 1990; **22**: 182–3.
34 Goossens A, Armingaud P, Avenel-Audran M *et al*. An epidemic of allergic contact dermatitis due to epilating products. *Contact Dermatitis* 2002; **47**: 67–70.
35 Gupta G, Forsyth A. Allergic contact reactions to colophony presenting as oral disease. *Contact Dermatitis* 1999; **40**: 332–3.
36 Freeman S, Stephens R. Cheilitis: analysis of 75 cases referred to a contact dermatitis clinic. *Am J Contact Dermatitis* 1999; **10**: 198–200.
37 Isaksson M, Bruze M, Björkner B *et al*. Contact allergy to Duraphat. *Scand J Dent Res* 1993; **101**: 49–51.
38 Garcia-Bravo B, Pons A, Rodriguez-Pichardo A. Oral lichen planus from colophony. *Contact Dermatitis* 1992; **26**: 279.
39 Bruze M. Systemically induced contact dermatitis from dental rosin. *Scand J Dent Res* 1994; **102**: 376–8.
40 Lyon CC, Tucker SC, Gäfvert E *et al*. Contact dermatitis from modified rosin in footwear. *Contact Dermatitis* 1999; **41**: 102–3.
41 Wanscher B. Contact dermatitis from propolis. *Br J Dermatol* 1976; **94**: 451–5.
42 Karlberg AT, Lidén C. Colophony (rosin) in newspapers may contribute to hand eczema. *Br J Dermatol* 1992; **126**: 161–5.
43 Gäfvert E, Bordalo O, Karlberg AT. Patch testing with allergens from modified rosin (colophony) discloses additional cases of contact allergy. *Contact Dermatitis* 1996; **35**: 290–8.
44 Pereira TM, Flour M, Goossens A. Allergic contact dermatitis from modified colophonium in wound dressings. *Contact Dermatitis* 2007; **56**: 5–9.
45 Mallon E, Powell SM. Allergic contact dermatitis from Granuflex hydrocolloid dressing. *Contact Dermatitis* 1994; **30**: 110–1.

Patch testing

Background

The diagnosis of allergic contact dermatitis is made by patch testing and of photoallergic contact dermatitis by photopatch testing. The techniques have evolved into a generally standardized methodology worldwide, although there are some variations, particularly with regard to reading times, test units and photopatch-test protocols.

Patch testing relies on the observation that primed antigen-specific T lymphocytes will be present throughout the body, and hence allergen in the patch test can be applied to normal skin, usually on the upper back where the tests are least likely to be disturbed. Other sites may be considered when this is not practicable, for example when there is pre-existing inflammation or other skin changes are on the back.

The test relies on the allergen being absorbed in sufficient quantity to induce a reproducible inflammation of the skin at the site of application in sensitized subjects. A positive reaction to a correctly prepared and applied patch test confirms the person has an allergic contact sensitivity, although this does not necessarily mean that the substance is the cause of the presenting clinical dermatitis, and its relevance should always be carefully considered.

Indications

It is well established that aimed patch testing with a few suspected allergens is suboptimal. The reason is that even experienced dermatologists are poor predictors of the outcome of patch tests; 17% of patients with allergies were missed on a prepatch-test assessment in one large clinic [1]. This parallels our own experience, with 20% of allergic patients regarded as definitely not allergic prior to patch tests and, conversely, 16% of patients thought to have contact allergy who were negative when patch tested.

An audit of patch testing has suggested that the investigation is underused, and consequently important opportunities to improve or resolve potentially disabling and undiagnosed allergic contact dermatitis are lost [2]. It concluded that facilities should be available to patch test at least 142 per 100 000 population annually and that the categories of patient listed in Table 26.12 should be patch tested where practicable [2]. Dermatology-specific quality of life has been shown to improve significantly more in those patients who are patch tested, because of more accurate diagnosis and earlier intervention [3–5]. Furthermore, the investigation has been shown to be cost-effective and to reduce the cost of therapy in patients with severe allergic contact dermatitis [3,6].

Methods

The basis of testing is to elicit an immune response by challenging already sensitized persons to defined amounts of allergen and assessing the degree of response. The amount of allergen is defined by its concentration in the vehicle and the amount applied. By testing the same allergens in parallel, the technique has been confirmed to be generally reproducible [7,8].

Table 26.12 Indications for patch testing. (From Bhushan & Beck [2].)

1	Eczematous disorders where contact allergy is suspected or is to be excluded
2	Eczematous disorders failing to respond to treatment as expected
3	Chronic hand and foot eczema
4	Persistent or intermittent eczema of the face, eyelids, ears and perineum
5	Varicose eczema

Chambers or discs are used to ensure occluded contact with the skin. The fixing tape should be non-occlusive, non-allergenic and non-irritant. If the adhesive tapes peel off, the test should be repeated. Ideally, patch testing should not be carried out in patients with active eczema because it may reduce the threshold of activity and cause non-specific reactions, although in practice this is commonly not possible. The procedure ideally should be delayed until the test site has been clear of eczema for at least a fortnight. Patch testing should be delayed for 4 weeks following sunbathing, and the patches should not be exposed to the sun or other sources of UV light. This information should be given to the patients before they book their appointments. Corticosteroids and other immunosuppressive drugs should be stopped (if this is feasible) before patch testing as they may reduce or extinguish positive patch tests in sensitized subjects. Nevertheless, this is unlikely at doses below 15 mg prednisolone daily [9,10], and we have identified relevant positive patch tests in patients who could only be investigated while they were taking other immunomodulators.

We prefer not to patch test pregnant patients in case an adverse event is blamed on the test, although we are unaware of any proven problem. Young children, even infants, can be patch tested when indicated, but the number of allergens tested may have to be reduced because of lack of space [11].

Test materials

Allergens are obtainable from the following manufacturers: Hermal, D-21462 Reinbeck, Germany (email: Hermalinfo@hermal.de), who market TROLAB allergens; and Chemotechnique Diagnostics AB, Modemgatan 9, S-235 39 Vellinge, Sweden (email: info@chemotechnique.se); or from their local distributors.

The commonest system used to apply allergens is the Finn chamber (Epitest Ltd, Oy., Rannankoukku 22, FIN-04300 Tuusula, Finland) on Scanpor tape (Norgesplaster, Granliveien 21, N-4702 Vennesia, Norway). These are also available from local distributors. The chambers are supplied in strips of five or 10 (two rows of five), and consist of small, occlusive aluminium discs. They are mounted on non-occlusive tape with an acrylic-based adhesive backing that has been chosen for its hypoallergenicity.

Other systems consist of square plastic chambers (Van der Bend chambers), and oval plastic chambers (Epicheck). The older AL Test system (a filter paper disc mounted on aluminized paper) is now rarely used.

There is also a prepackaged, ready-to-use patch-test system, TRUE (thin layer rapid use epicutaneous) test, based on a dispersion of allergen in a hydrophilic polymer [12]. Although this is at present only available as a standard series of 24 allergens, it is anticipated that further test allergens will be developed. It was developed by Torkil Fischer and Pharmacia, and is marketed in the UK by Diagenics Ltd and in the USA by Allerderm. This system has been tested in parallel with the established Finn chamber system and there was close correlation of results [13,14]. It is a consistent, convenient, portable method for those wishing to test only the standard series, but supplementary tests are generally necessary to achieve a comprehensive range of investigations.

Patch-test vehicles

Few substances can be applied to the skin as they are. In order to avoid an irritant effect, they must be mixed or dissolved in a vehicle to achieve a suitable test concentration. The test substance should, if possible, be soluble in the vehicle. If a dispersion of allergen in petrolatum is used, contact with the skin depends on the size of the particles and on their solubility or dispersion in petrolatum. Uniform dispersion and particle size are important [15]. Many substances can also be dissolved in water, alcohol, acetone, methylethylketone (MEK) or olive oil, as appropriate. Irritant solvents such as chloroform and benzene must not be employed. False-positive or false-negative reactions may occur when inappropriate vehicles are used. Petrolatum is generally more reliable, and has the added advantage of being occlusive, which helps to prevent oxidation and prolongs shelf-life. Allergic reactions to petrolatum itself are very rare [16]. In hot climates, petrolatum may not be ideal, as it melts too quickly between preparation and application of the patch test, and a series in modified Plastibase has been devised for the Indian Contact Dermatitis Group [17].

Patch-test concentrations

Choice of a suitable concentration is of fundamental importance. Excessive concentrations result in false-positive reactions, because of their irritant effect, and may even sensitize patients; insufficient concentrations produce false-negative results. The concentration of allergen routinely employed for patch tests may, under some conditions and in some individuals, give rise to false-negative or false-positive reactions. The choice of concentration is thus a compromise, but most have been chosen by long experience with commonly used allergens. The concentrations used for patch testing are usually much higher than those encountered during development of dermatitis. To demonstrate the existence of nickel dermatitis produced by the minute amounts dissolved from nickel-plated objects, a 5% concentration of nickel sulphate in petrolatum is necessary. Chromate 0.25–0.5% is required to prove sensitivity to cement containing 0.0005–0.002% of chromate. Neomycin should be tested at 20% despite only being at 0.5% concentration in many topical medicaments.

Lists of suitable concentrations and vehicles are provided in a number of texts listed on p. 26.93. Metal salts in particular are tested at the margins of irritancy and may give false-positive, irritant patch-test reactions, especially in atopic individuals. Weak reactions may not be allergic. In important cases of doubt the patient can be retested later with serial dilutions. Other standard allergens such as fragrance mix, parabens mix and wool alcohols may also be marginally irritant. On rare occasions, active sensitization may still occur even at the concentrations recommended. Irritant reactions are rarer with other substances used in standard series. They are potentially much more common with materials brought to the clinic for testing. Many industrial or domestic chemicals, if undiluted, will give irritant false-positive reactions which may be severe. No chemical or substance should be applied to the skin until full details of its composition and potential irritancy or toxicity are known.

If work or other materials are brought, a number of factors should be considered before they are used for patch testing. Is it

appropriate to test with the material? Some materials are strong irritants and not allergens (e.g. strong acids and alkalis), and others may be contaminated or of uncertain or mixed composition (e.g. dust or grime from a working environment). The product may be intrinsically dangerous (e.g. explosive or produces toxic fumes) and require special handling. Some patients bring foods in the mistaken belief that the test will diagnose ingested food allergy.

The precise nature of the material should be ascertained by questioning the patient and examining the product label. In the UK, employers are required by law to have Health and Safety data sheets for all materials handled at work. These provide key information and a contact point with the manufacturing company. They must be scrutinized carefully, particularly with regard to irritancy, allergenicity, stability and solubility of the product and its components. Named chemical substances may be recognized as irritants or allergens, and their concentrations documented. Substances can be checked for pH, and neutralized if necessary [18].

An initial patch-test concentration can often be selected either by reference to standard texts or by contacting the manufacturer for details of toxicological testing data. A range of differing test concentrations is advised where there is no literature on the material. It is advisable to start low (0.01% or less), and increase the concentration gradually if there is doubt about the optimum level for testing. It may be advisable to perform open tests before proceeding to closed patch tests because the effect of irritants is enhanced by occlusion [19]. Materials intended to be left on the skin, such as medicaments and cosmetics, can be tested 'as is', 'rinse-off' products at 5%, and soaps, shampoos and detergents at 1% or less. However, the dermatologist administering a patch test will need to refer to standard references for guidance on dilutions and vehicles when testing finished products or specific chemicals. These are discussed on p. 26.93.

If a positive reaction to an unknown substance occurs, it should not be immediately accepted as allergic. Volunteers, who are not suffering from dermatitis related to the same agent, should be tested at the same concentration and using the same methods. If any reaction occurs among 50 controls, the substance should be regarded as a primary irritant at that concentration, and subsequent tests should be performed with decreasing concentrations.

Patch-test dose

If petrolatum is used as the vehicle and disposable syringes are the containers, a length of 5 mm of test substance in vehicle will suffice. For a Finn chamber, 20 mg of allergen as a petrolatum dispersion has been shown to be the optimum dose [20]. If the vehicle is a fluid, a digital pipette should be used to deliver 15 µL to a filter paper in the chamber. Dropper bottles supplied by the allergen manufacturers tend to overfill the chambers. A surplus should be avoided, as it may contaminate neighbouring test sites. With TRUE test, the patches are pre-prepared. The risk of patch-test sensitization increases with the concentration and amount of test substance applied.

Storage of allergens

'Shelf-life' is prolonged if test substances not in daily use are stored in the dark in a refrigerator at 4°C. Many substances are unstable if exposed to light. Commercially available allergens are labelled with an expiry date.

Storage in small jars has the drawbacks of oxidation, drying and evaporation of volatile test substances. Rubber pipette caps contaminate the solutions and may cause false-positive reactions in persons sensitive to rubber. Homogeneity of patch-test allergens may be lost, especially in hot climates, if they are not refrigerated.

Table 26.13 Reactivity of various test sites. (From Magnusson & Hersle [21].)

	Type of reaction	
Test site	**Irritant (%)**	**Allergic (%)**
Upper back	100	100
Lower back	50	95
Upper arm	52	72
Forearm	38	74
Thigh	36	50

Test site

Most dermatologists prefer to apply patch tests to the back. The region used for testing is important with regard to the results of the investigation: both allergic and irritant reactions are most easily provoked on the upper back [21] (Table 26.13). Reactions on the lateral aspect of the upper arm are stronger than on the medial aspect. Sites other than the back and lateral aspect of the upper arm are generally less suitable as test areas, but when necessary we have used the abdomen or even the thighs rather than abandoning the investigation.

Marking

Test sites must be marked with indelible ink or stratum corneum stains (or fluorescent markers on dark skins). Marking materials can be obtained from allergen suppliers. It is necessary to repeat marking before removal of the patches, because their positions cannot be distinguished once the pressure effects have subsided. The patient should be instructed not to bathe or shower for the duration of the tests, and to avoid exercise or other activity likely to dislodge the patches.

Exposure time

The mere touch of a *Primula* leaf may provoke a subsequent bullous response in a sensitive person, but with some materials (e.g. textiles) even 5 days of occlusive patch tests may lead to false-negative reactions. However, few formal studies on the relationship of exposure time, dose and elicitation have been undertaken. Recent work with PPD (*p*-phenylenediamine) and isoeugenol has shown that elicitation is dependent not only on exposure time but also concentration and number of applications of the allergen [22,23].

Well-established allergens, however, are conventionally tested in such concentrations that a 48-h exposure under an occlusive patch will generally allow penetration of an amount sufficient to provoke a reaction. With low sensitivity, low concentration of allergen or poor absorption of a particular agent, there may be a

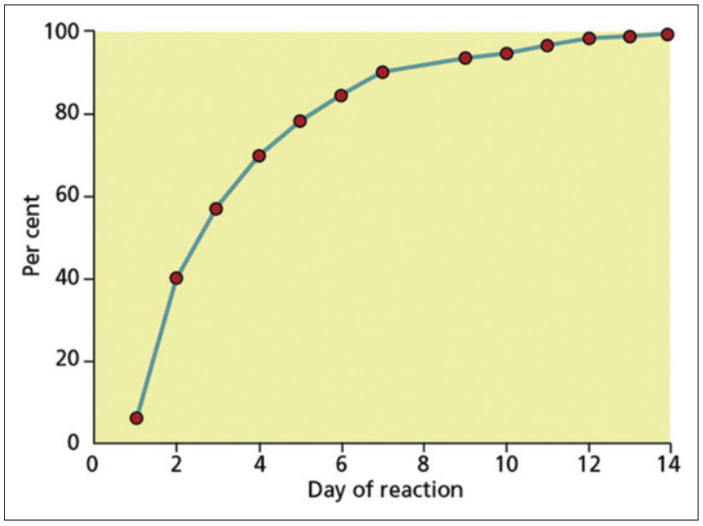


Fig. 26.28 Patch tests with neomycin 20% in petrolatum: positive reaction times after application.

long period of latency. A typical regimen is a 48-h application time, with readings taken 1 h after removal and again 48 h later, that is Day 2 and Day 4, with preferably the same observer performing each reading. Others have suggested that a Day 5 second reading is better [24]. A single Day 2 reading is not advised as it may lead to the labelling of some marginal irritants as allergens, and positive reactions to more poorly absorbed allergens may be missed [25,26]. Variations to this schedule are made for expediency, to fit in with clinic times, and for the convenience of patients travelling long distances. If only one patch-test reading is possible, a Day 4 reading has been recommended [27,28] although, according to some authors, a single Day 4 reading is also associated with the risk of missing some significant positive reactions [29]. A third reading at Day 5–7 seems to identify a small proportion of additional relevant positive allergies where sensitivity is weak or partially 'forgotten', or where there is poor absorption of the allergen [24,28,30]. Neomycin (Fig. 26.28) and corticosteroids are particularly liable to give late reactions.

Immediately after removal of the patch tests, there may be erythema from the stripping action of the tape, especially in dermographic subjects, and this must be allowed to settle. Furthermore, some reactions may take up to 1 h to develop once the pressure of the strips has been released and the infiltration allowed to swell the dermis.

Readings and interpretation

It is important that patch-test readings are scored according to the reactions seen and not according to the interpretation placed on the reaction by the reader. As the strength of a reaction is not always reproducible, an over-detailed quantification should be avoided. The scoring system devised by the ICDRG in 1970 is shown in Table 26.14 [31].

There are drawbacks to the ICDRG system in that it confuses morphology with interpretation. The ideal system is to record what is seen at 2 and 4 days, and then to decide if this represents an allergic or irritant response. This is done by assessing morphology and skin type, combined with knowledge and experience of the substance and the patient's history. Patch-test results should be recorded objectively, and the interpretation of the results should be recorded separately. In this way raw data remain available for re-examination.

Table 26.14 Recording of patch-test reactions according to the International Contact Dermatitis Research Group. (From Wilkinson *et al*. [31].)

–	Negative
?+	Doubtful reaction; faint erythema only
+	Weak positive reaction; palpable erythema, infiltration, possibly papules
++	Strong positive reaction; erythema, infiltration, papules, vesicles
+++	Extreme positive reaction; intense erythema and infiltration and coalescing vesicles
IR	Irritant reaction of different types
NT	Not tested

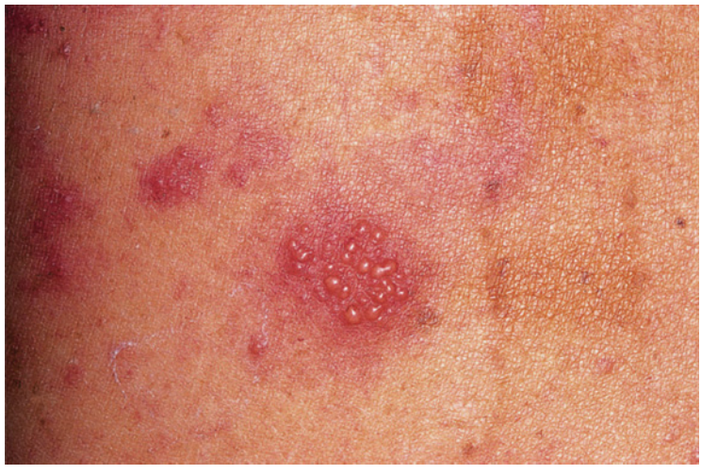


Fig. 26.29 A positive allergic (++) patch-test response in a patient sensitive to neomycin. (Courtesy of Dr J.D. Wilkinson, Amersham General Hospital, Amersham, UK.)

Once they have developed, positive allergic reactions often persist for several days. The strength of the reaction depends on barrier function, the presence or absence of sweating, the atmospheric humidity, test material, technique and the reactivity of the individual.

Strong reactions of an allergic nature are erythematous and infiltrated, commonly with minute papules or vesicles (Fig. 26.29), which in severe reactions coalesce into bullae. The infiltration causes a thickening in the dermis, which is palpable and can be distinguished from surface changes in the epidermis. The reaction may extend beyond the margins of the patch, and there is often some itching. Nevertheless, sometimes true allergic reactions can be weaker than this, making interpretation more difficult.

In most instances there is little difficulty for the experienced clinician in identifying true positive allergic patch-test reactions. Nevertheless, there are occasions when distinguishing an allergic from a false-positive non-allergic irritant reaction can be difficult or even impossible. There may be clues—no infiltration, lack of itching, deep redness or a brown hue, and sharp delineation corresponding to the margins of the patch test (particularly around the edge with solid materials)—these all point to an irritant



Fig. 26.30 Pustular patch-test reactions to metals are common in atopics and are often irritant in type.

reaction. Some irritants provoke a 'soap effect', with a well-localized, glistening, finely wrinkled surface. Patch tests with nickel may cause pustular reactions that are often false-positive (Fig. 26.30), although some progress to more typical allergic reactions. Cobalt also produces a distinctive false-positive purpuric reaction which may result from poor dispersion of the allergen in the petrolatum base. In our experience these tend to occur much more in atopic individuals, and need to be distinguished from allergic follicular reactions consisting of papules without pustules or purpura.

False-positive irritant reactions are liable to induce stronger reactions at 2 days than at 4 days, the so-called crescendo–decrescendo effect. However, this is not always the case and the reverse can happen in our experience. Difficulties in evaluation are particularly common with substances brought in by the patient for testing. It may be necessary to apply several concentrations at the first visit; controls should be performed with any substances giving positive reactions.

There is no substitute for a thorough knowledge and experience of the allergens used for patch testing. Even some standard allergens may be liable to induce weak false-positive reactions (e.g. metal salts, fragrance mix, parabens mix, wool alcohols and carba mix). Repeat patch testing may be helpful, especially with a breakdown of the mixes.

Relevance of patch tests

Once a decision has been reached that a patient has an allergic positive patch test, it is important to establish relevance by carefully re-examining the patient's history, distribution of rash and materials with which there has been contact. In many cases relevance can be clearly established and avoidance advice given. In some instances the relevance may be in the past and no longer apply. In other cases the relevance may be uncertain or impossible to ascertain. Patients will need to be advised on the potential sources of all their allergies for future reference, and if their problem is ongoing it may be necessary to reassess their exposures. A person may react to a patch test but still tolerate contact with the allergen. However, confusion can occur if they are given extensive avoidance advice for materials of no relevance to their dermatitis, and therefore advice should be targeted.

Table 26.15 Causes of false-positive reactions.

Excessive concentration
Impure substance (contaminants)
Irritant vehicle
Excess allergen applied
Uneven dispersion
Current or recent dermatitis at patch-test site
Current dermatitis at distant sites
Pressure effect of hard materials
Adhesive tape reactions
'Angry back' reaction causing intensification of weak irritants
Artefact

Non-invasive measurement techniques [32]

There are several non-invasive techniques that can be used to quantify and delineate the effects of patch tests, including measurements of changes in skin surface, epidermal hydration and water barrier function, and parameters of inflammation. At present, these are more useful to the investigator than to the clinician. They include replica techniques [33], transepidermal water loss [34], skin reflectance [35,36], laser Doppler flowmetry [37,38], thermography [39] and high-frequency ultrasound [40]. Attempts have been made to use some of these techniques to differentiate irritant from allergic patch-test reactions [36,41,42] but they have not superseded the combination of human brain, eye and hand in the assessments of patch tests.

Sources of error

False-positive reactions (Table 26.15). Irritant reactions occur if a chemical is tested at excessive concentration. Incorrectly interpreted false-positive reactions may lead to the wrong conclusions about the cause of a dermatitis, and this may result in inappropriate career or medicolegal advice. Recent or active dermatitis in the test area lowers the threshold for irritant reactions, as does dermatitis in other areas [43], and non-specific reactions can occur.

Secondary non-specific reactions close to genuine positive ones have been termed 'angry back' [44] or the 'excited skin syndrome' [45], and this may be an important cause of false-positive patch-test reactions. The phenomenon has been extensively investigated by Bruynzeel [46]. However, multiple positive reactions to nickel did not cause 'angry back' in a study by Andersen *et al*. [47].

If there is any doubt, the patch tests should be repeated some weeks later, preferably with individual agents and at various dilutions, as false-positive irritant reactions tend to stop abruptly below a certain concentration whereas allergic responses tend to persist, albeit proportionally weaker, at lower concentrations. Testing the same substance on a panel of controls, using the ROAT on the elbow flexure or usage tests, may help to differentiate allergic from irritant responses. Controls should be tested at the lowest concentration of a positive test to avoid interpreting a false-positive irritant reaction as allergic.

Table 26.16 Causes of false-negative reactions.

Insufficient concentration
Insufficient amount applied
Poor adhesion of patches
Patches applied at wrong site
Inappropriate vehicle
Readings performed too early
Substance degraded
Pretreatment of patch-test site with topical corticosteroids
UV irradiation of patch-test site
Systemic treatment with immunosuppressants

False-negative reactions (Table 26.16). Sometimes a patch test fails to provoke a positive reaction in a person who is sensitive to the substance tested. The dermatitis therefore persists because of continued exposure to the allergen. The most common cause of false-negative reactions is insufficient penetration through the skin.

A low degree of sensitivity or poor penetration sometimes results in a long period of latency before a positive reaction develops, so that up to 7.5% of allergic positive patch tests do not become apparent until after 4 days, and may go unnoticed unless read 7–14 days after application. This particularly applies to neomycin and corticosteroids.

The apparent discrepancy between the concentration of allergen needed to elicit clinical dermatitis and the occasional failure of a patch test to elicit a reaction can be explained by many factors. In particular, a single exposure on normal skin is probably not representative of the accumulation of the allergen during repeated exposure conditions and chronic usage on already primed skin.

False-negative reactions are common when testing with textiles, cosmetics, medicaments, leather and rubber, as some ingredients are present in very low concentrations. False-negative reactions also occur when allergens are present in irritant products. Because of irritancy, a product may have to be diluted to such an extent before it can be safely tested that the allergen is present in insufficient concentration to elicit a response. Such products include cutting oils and washing materials. Sensitivity to finished products and topically applied preparations is best confirmed and revealed by testing with the individual components.

An allergy may be missed on patch testing if the test material has been wrongly diluted in a material in which it is immiscible or insoluble. Furthermore, an incorrect diluent may change the allergen into another substance altogether [48]. Partition coefficients are also important, because oil/water solubility may be a significant factor in skin penetration and allergenic potential.

Local treatment with topical corticosteroids, and systemic treatment with immunomodulators including ciclosporin, azathioprine and corticosteroids such as prednisolone (at a dose above 15–20 mg/day), may diminish or abolish reactions [10,49], as does preceding sunbathing [50]. Negative reactions, in spite of clinical sensitivity, also occur in photocontact dermatitis if appropriate allergens are not photopatch tested.

Compound allergy [51,52]. Compound allergy occurs when a positive allergic patch-test reaction is seen to a finished product but tests with the ingredients are negative. Hence, the product and the constituents should be patch tested when allergy is suspected. This was a concept first proposed by Calnan [53] and considered in depth by Dooms-Goossens in her thesis [51].

New compounds may be formed within a product, and their presence can be confirmed by the finding of incongruous peaks on spectrometry. This was elegantly demonstrated in Hirudoid cream, where a new allergen was formed as a reaction product of two preservatives in the medicament [54]. The additive effect of multiple weak sensitizers [55], or the additive effect of weak allergens and irritants, should be considered [56].

There are several possible alternative explanations. The reaction to the finished product may be irritant. A product's irritancy is not merely the sum of the irritancy of the ingredients, but an expression of the hydrophilic–hydrophobic balance of its ingredients. This can change with varying manufacturing techniques, for example changing the temperature or manipulating the proportion of one of the ingredients. A constituent allergen may be an undeclared ingredient or there may be batch/source differences between the original compound and the subsequently provided components. The allergen may be in the container, for example a rubber stopper, and not in the product. The allergen may not have been tested in the correct vehicle or at the correct concentration, and testing it in its own base may reveal the allergy [51].

Quenching. Theoretically, just as there may be potentiation of allergic and irritant responses, so a combination of chemicals may lead to a quenching effect [57]. This phenomenon has been investigated mostly in fragrance material aldehydes. It might be explained by the combined compounds changing available bonding sites for class II molecules or forming a compound that does not follow the same detoxification pathway. However, some authors have been unable to demonstrate any physicochemical interaction [58], and its existence has been questioned [59].

Other observed quenching effects may be due to one of the compounds having anti-inflammatory properties [60], such as triclosan having a 'quenching' effect on nickel allergic contact dermatitis.

Other factors. The interpretation of patch-test reactions can be affected by the presence or absence of impurities or degradation products, hidden additives, batch differences and the fact that some chemicals may undergo reactive metabolic changes in the skin. Natural products vary according to source, season and method of extraction. Storage or 'ageing' of a product may also affect its allergenicity and irritancy; D-limonene has been shown to be allergenic only in its old and oxidized state [61]. Patients should therefore always be tested with their own product. Season may also influence patch-test results, but whether this is due to UV radiation suppression of test reactions in summer or an enhancement of irritant-type reactions in winter remains uncertain [62].

Errors may occur in the registration of the relative sites of the tests. It is therefore advisable to repeat the test if in doubt.

References

1 Podmore P, Burrows D, Bingham EA. Prediction of patch test results. *Contact Dermatitis* 1984; **11**: 283–4.

2 Bhushan M, Beck MH. An audit to identify the optimum referral rate to a contact dermatitis investigation unit. *Br J Dermatol* 1999; **141**: 570–2.
3 Rajagopalan R, Anderson RT, Sarma S *et al*. An economic evaluation of patch testing in the diagnosis and management of allergic contact dermatitis. *Am J Contact Dermatitis* 1998; **9**: 149–54.
4 Thomson KF, Wilkinson SM, Sommer S *et al*. Eczema: quality of life by body site and the effect of patch testing. *Br J Dermatol* 2002; **146**: 627–30.
5 Woo PN, Hay JC, Ormerod AS. An audit of the value of patch testing and its effect on the quality of life. *Contact Dermatitis* 2003; **48**: 244–7.
6 Rietschel RL. Is patch testing cost-effective? *J Am Acad Dermatol* 1989; **21**: 885–7.
7 Belsito DV, Storrs FJ, Taylor SJ *et al*. Reproducibility of patch tests: a United States multicenter study. *Am J Contact Dermatitis* 1992; **3**: 193–200.
8 Brasch J, Henseler T, Aberer W *et al*. Reproducibility of patch tests. A multicenter study of synchronous left- versus right-sided patch tests by the German Contact Dermatitis Research Group. *J Am Acad Dermatol* 1994; **31**: 584–91.
9 O'Quin SE, Isbell KH. Influence of oral prednisolone on eczematous patch test reactions. *Arch Dermatol* 1969; **99**: 380–6.
10 Feuerman E, Levy A. A study of the effect of prednisone and an antihistamine on patch test reactions. *Br J Dermatol* 1972; **86**: 68–71.
11 Vigan M, Sauvage C, Adessi B *et al*. Pourquoi et comment réaliser une batterie standard chez les enfants? *Nouv Dermatol* 1994; **13**: 12–5.
12 Fischer T, Maibach HI. Easier patch testing with True Test. *J Am Acad Dermatol* 1989; **20**: 447–53.
13 LaChapelle JM, Bruynzeel DP, Ducombs G *et al*. European multi-centre study of the True Test. *Contact Dermatitis* 1988; **19**: 91–7.
14 Wilkinson JD, Bruynzeel DP, Ducombs G *et al*. European multicentre study of True Test. Panel 2. *Contact Dermatitis* 1990; **22**: 218–25.
15 Fischer T, Maibach HI. Amount of nickel applied with a standard patch test. *Contact Dermatitis* 1984; **11**: 285–7.
16 Dooms-Goossens A, Degreff H. Contact allergy to petrolatums. I. Sensitizing capacity of different brands of yellow and white petrolatums. *Contact Dermatitis* 1983; **9**: 175–85.
17 Bajaj AK, Gupta SC, Chatterjee A. Suitable bases for patch testing in tropical countries. *Int J Dermatol* 1986; **25**: 379–80.
18 Bruze M. Use of buffer solutions for patch testing. *Contact Dermatitis* 1984; **10**: 267–9.
19 Magnusson B, Hersle K. Patch test methods. III. Influence of adhesive tape on test response. *Acta Derm Venereol (Stockh)* 1966; **46**: 275–8.
20 Bruze M, Isaksson M, Gruvberger B, Frick-Engfeldt M. Recommendation of appropriate amounts of petrolatum preparation to be applied at patch testing. *Contact Dermatitis* 2007; **56**: 281–5.
21 Magnusson B, Hersle K. Patch test methods: II. Regional variations of patch test responses. *Acta Derm Venereol (Stockh)* 1965; **45**: 257–61.
22 Hextall JM, Alagaratnam NJ, Glendinning AK *et al*. Dose-time relationships for elicitation of contact allergy to para-phenylenediamine. *Contact Dermatitis* 2002; **47**: 96–9.
23 Andersen KE, Johansen JD, Bruze M *et al*. The time-dose–response relationship for elicitation of contact dermatitis in isoeugenol allergic individuals. *Toxicol Appl Pharmacol* 2001; **170**: 166–71.
24 Geier J, Gefeller O, Wiechmann K *et al*. Patch test reactions at D4, D5 and D6. *Contact Dermatitis* 1999; **40**: 119–26.
25 Shehade SA, Beck MH, Hiller VF. Epidemiological survey of standard series patch test results on day 2 and day 4 readings. *Contact Dermatitis* 1991; **24**: 119–22.
26 Uter WJ, Geier J, Schnuch A. Good clinical practice in patch testing: readings beyond day 2 are necessary: a confirmatory analysis. Members of the Information Network of Departments of Dermatology. *Am J Contact Dermatitis* 1996; **7**: 231–7.
27 Todd DJ, Handley J, Metwali M *et al*. Day 4 is better than day 3 for a single patch test reading. *Contact Dermatitis* 1996; **34**: 402–4.
28 Macfarlane AW, Curley RK, Graham RM *et al*. Delayed patch test reactions at days 7 and 9. *Contact Dermatitis* 1989; **20**: 127–32.
29 Mathias CG, Maibach HI. When to read the patch test. *Int J Dermatol* 1979; **18**: 127–8.
30 Jonker MJ, Bruynzeel DP. The outcome of an additional patch-test reading on days 6 or 7. *Contact Dermatitis* 2000; **42**: 330–5.
31 Wilkinson DS, Fregert S, Magnusson B *et al*. Terminology of contact dermatitis. *Acta Derm Venereol (Stockh)* 1970; **50**: 287–92.
32 Serup J. Non-invasive techniques for quantification of contact dermatitis. In: Frosch PJ, Menné T, Lepoittevin J-P, eds. *Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 441–50.
33 Peters K, Serup J. Papulo-vesicular count for the rating of allergic patch test ratings. A simple technique based on polysulfide rubber replica. *Acta Derm Venereol (Stockh)* 1987; **67**: 491–5.
34 Pinnagoda J, Tupker RA, Agner T *et al*. Guidelines for transepidermal water loss (TEWL) measurement. *Contact Dermatitis* 1990; **22**: 164–78.
35 Mendelow AY, Forsyth A, Feather JW *et al*. Skin reflectance measurements of patch test responses. *Contact Dermatitis* 1986; **15**: 73–8.
36 Astner S, González S, Gonzalez E. Noninvasive evaluation of allergic and irritant contact dermatitis by in vivo reflectance confocal microscopy. *Dermatitis* 2006; **17**: 182–91.
37 Willis CM, Stephens CJM, Wilkinson JD. Assessment of erythema in irritant contact dermatitis. *Contact Dermatitis* 1988; **18**: 138–42.
38 Staberg B, Serup J. Patch test responses evaluated by cutaneous blood flow measurements. *Arch Dermatol* 1984; **120**: 741–3.
39 Baillie AJ, Biagioni PA, Forsyth A *et al*. Thermographic assessment of patch-test responses. *Br J Dermatol* 1990; **122**: 351–60.
40 Brazier S, Shaw S. High-frequency ultrasound measurement of patch test reactions. *Contact Dermatitis* 1986; **15**: 199–201.
41 Staberg B, Serup J. Allergic and irritant skin reactions evaluated by laser Doppler flowmetry. *Contact Dermatitis* 1988; **18**: 40–5.
42 Goon AT, Leow YH, Chan YH, Goh CL. Correlation between laser Doppler perfusion imaging and visual scoring of patch test sites in subjects with experimentally induced allergic and irritant contact reactions. *Skin Res Technol* 2004; **10**: 64–6.
43 Bjornberg A. *Skin Reactions to Primary Irritants in Patients with Hand Eczema*. Gothenburg: Isaacsons O, Tryckeri AB, 1968.
44 Mitchell JC. The angry back syndrome. Eczema creates eczema. *Contact Dermatitis* 1975; **1**: 193–4.
45 Maibach HI, Fregert S, Magnusson B *et al*. Quantification of the excited skin syndrome (the 'angry back'). Retesting one patch at a time. *Contact Dermatitis* 1982; **8**: 78–9.
46 Bruynzeel DP. *Angry Back or Excited Skin Syndrome* [thesis]. Amsterdam: Free Universiteit te Amsterdam, 1983.
47 Andersen KE, Lidén C, Hansen J, Vølund A. Dose–response testing with nickel sulphate using the TRUE test in nickel sensitive subjects. Multiple nickel sulphate patch test reactions do not cause an 'angry back'. *Br J Dermatol* 1993; **129**: 50–6.
48 O'Driscoll J, Beck M, Taylor S. Occupational allergy to 2,5-dimercapto-1,3,4-thiadiazole. *Contact Dermatitis* 1990; **23**: 268–9.
49 Anveden I, Lindberg, Andersen KE *et al*. Oral prednisone suppresses allergic but not irritant patch test reactions in individuals hypersensitive to nickel. *Contact Dermatitis* 2004; **50**: 298–303.
50 Sjovall P. *Ultraviolet Radiation and Allergic Contact Dermatitis. An Experimental and Clinical Study* [thesis]. University of Lund, Sweden, 1988.
51 Dooms-Goossens A. *Allergic Contact Dermatitis to Ingredients Used in Topically Applied Pharmaceutical Products and Cosmetics* [thesis]. Leuven University, Belgium, 1983.
52 Bashir SJ, Maibach HI. Compound allergy. An overview. *Contact Dermatitis* 1997; **36**: 179–83.
53 Calnan CD. Compound allergy to a cosmetic. *Contact Dermatitis* 1975; **1**: 123.
54 Smeenk G, Kerckhoffs HP, Schreurs PH. Contact allergy to a reaction product in Hirudoid cream: an example of compound allergy. *Br J Dermatol* 1987; **116**: 223–31.
55 McLelland J, Shuster S. Contact dermatitis with negative patch tests: the additive effect of allergens in combination. *Br J Dermatol* 1990; **122**: 623–30.
56 Seidenari S, Motolese A, Bettetti B. Pre-treatment of nickel test areas with sodium lauryl sulphate detects nickel sensitivity in subjects reacting negatively to routinely performed patch tests. *Contact Dermatitis* 1996; **34**: 88–92.
57 Opdyke DLJ. Monographs on fragrance raw materials. *Food Cosmet Toxicol* 1979; **17**: 241–75.
58 Basketter D, Allenby F. Studies of the quenching phenomenon in delayed contact hypersensitivity reactions. *Contact Dermatitis* 1991; **25**: 160–71.
59 Basketter D. Quenching: fact or fiction? *Contact Dermatitis* 2000; **43**: 253–8.

60 Barkroll P, Rolla G. Triclosan reduces the clinical symptoms of the allergic patch test reaction (APR) elicited with 1% nickel sulphate in sensitised patients. *J Clin Periodontol* 1995; **22**: 485.
61 Karlberg AT, Dooms-Goossens A. Contact allergy to oxidized d-limonene among dermatitis patients. *Contact Dermatitis* 1997; **36**: 201–6.
62 Edman B. Seasonal influence on patch test results. *Contact Dermatitis* 1989; **20**: 206.

Selection of test substances

The decision about what to test is dependent on a sound knowledge of the common sensitizers, in conjunction with a thorough history of exposure. Fortunately, a high proportion of cases of contact dermatitis are caused by sensitivity to a small number of contactants, although there are potentially thousands. In relatively few cases of contact dermatitis are the clinical appearances and history so typical that an allergen can be incriminated readily.

It is therefore essential to test with a standard series of common contact allergens. Many investigation clinics have extra allergens and some of these may be grouped into additional special test series (e.g. for certain occupations or affected sites). Furthermore, it may be necessary to test with materials encountered in patients' working and domestic environments, and with any medicaments and cosmetics applied to affected areas.

Standard series

The principle of screening all patients with a series of allergens commonly encountered in their environment is now well established. Aimed patch testing is ill-advised. The decision as to what should be in the standard series has now generally devolved from the ICDRG to other national and international groups. The standard series recommended by the EECDRG contains 27 allergens [1–3]. The BCDS presently has 39 allergens for their standard series (Table 26.17) [Statham BN. Personal communication]. The most recent North American Contact Dermatitis Group's (NACDG) published standard screening results included 65 allergens [4].

As some allergens disappear from a given environment and others attain significance, it is important that a standard series evolves. Two significant standard allergens have emerged since we last wrote this chapter; fragrance mix II and methyldibromo glutaronitrile.

In the past, several common sources of contact dermatitis were overlooked until they were included in a standard series. Nowadays, fragrance materials are familiar contact allergens but were virtually unknown 30 years ago [5]. Conversely, others (e.g. wood tars and turpentine) were removed from the standard series some years ago.

Newer standard allergens recommended for Europe include markers for corticosteroid allergy [2] (tixocortol pivalate and budesonide), methyldibromo glutaronitrile [3] and fragrance mix II. The European standard series identified 75–80% of all allergies diagnosed in one multicentre study [6].

In some studies as many as half of the relevant positive reactions were unexpected. Obviously, if patch testing is carried out for very wide indications, the percentage of negative reactions will increase, but at the same time unexpected positive reactions will correct misdiagnoses of constitutional or irritant dermatitis.

The selection of substances for a standard patch-test series must be based on local experience, but several substances are universally recognized allergens. Unless a permanent record is kept, a number of substances will continue to be included despite a low yield of positive reactions. In general, a substance should be included in the standard battery if it gives positive reactions in more than 1% of those tested, or if without it a significant number of unsuspected allergic reactions would be missed. This is true of ubiquitous allergens such as rubber chemicals, nickel and chromate, fragrance materials and common therapeutic and cosmetic allergens such as lanolin, neomycin and preservatives. However,

Table 26.17 Comparative lists of allergens in European and British standard series.

	EECDRG*	BCDS†
Potassium dichromate	0.5	0.5
Neomycin sulphate (fradiomycin)	20	20
Thiuram mix	1	1
p-Phenylenediamine (PPD) base	1	1
Cobalt chloride ($CoCl_2 \cdot 6H_2O$)	1	1
Benzocaine	5	–
Formaldehyde	1 (aq.)	1 (aq.)
Colophony (Colophonium)	20	20
Clioquinol	5	–
Balsam of Peru (*Myroxylon pereirae*)	25	25
N-isopropyl-*N*′-phenyl-*p*-phenylenediamine	0.1	0.1
Wool (lanolin) alcohols	30	30
Mercapto mix	2	2
Epoxy resin	1	1
Parabens mix	12	12
p-Tertiary-butylphenol formaldehyde resin	1	1
Fragrance mix I	8	8
Quaternium-15	1	1
Nickel sulphate ($NiSO_4 \cdot 6H_2O$)	5	5
Methylchloroisothiazolinone/methylisothiazolinone	0.01 (aq.)	0.01 (aq.)
Mercaptobenzothiazole	2	2
Primin	0.01	0.01
Sesquiterpene lactone mix	0.1	0.1
Tixocortol pivalate	0.1	0.1
Budesonide	0.01	0.1
Methyldibromo glutaronitrile	0.5	0.3
Fragrance mix II	14	14
Quinoline mix	–	6
Imidazolidinyl urea	–	2
Diazolidinyl urea	–	2
2-Bromo-2-nitropropane-1,3-diol	–	0.5
Chloroxylenol	–	1
Carba mix	–	3
Ethylenediamine dihydrochloride	–	1
Caine mix	–	10
Cetearyl alcohol	–	20
Fusidic acid	–	2
Chlorocresol	–	1
Disperse Blue mix	–	1

Concentrations are quoted as percentages in petrolatum except where otherwise stated; aq, aqueous.
* European standard series as recommended by the European Environmental and Contact Dermatitis Research Group 1995 and 2000 [1–3].
† British Contact Dermatitis Society recommended standard series [Statham BN. Personal communication].

Table 26.18 Comparative results of patch-test series (expressed as percentage positive).

	UK (BCDS) [4]	Europe [8]	USA [4]	Japan [7]
	2007	1996–2000	2001–2	1994
Metals				
Nickel sulphate	21.0	17.9	16.7	13.5
Cobalt chloride	6.3	5.9	7.4	17.3
Potassium dichromate	2.5	4.6	4.3	9.2
Rubber chemicals				
Thiuram mix	2.6	3.2	4.5	2.6
Carba mix	2.2	NT	4.9	0.5
Mercapto mix	0.7	1.0	0.7	0.6
IPPD/black rubber mix	0.3	0.9	1.0	1.2
Pharmaceuticals				
Caine mix/Benzocaine	1.1	1.6	1.7	1.8
Neomycin sulphate	2.5	3.0	11.6	4.0
Quinoline mix/Chinoform	0.5	0.8	NT	NT
Ethylenediamine dihydrochloride	1.1	NT	2.8	0.3
Parabens	0.7	0.6	0.6	1.8
Lanolin alcohols	1.8	2.9	2.2	2.8
Tixocortol Pivalate	1.5	1.3	3.0	–
Budesonide	0.7	1.6	1.1	–
Cosmetic ingredients				
Balsam of Peru (*Myroxylon pereirae*)	6.6	6.0	11.6	5.2
Fragrance mix	8.1	9.7	10.4	5.8
Formaldehyde	2.3	2.3	8.4	1.2
Quaternium-15	2.1	1.3	9.3	NT
Methylchloroisothiazolinone/ methylisothiazolinone	1.9	2.2	2.3	1.3
Methyldibrom glutaronitrile	1.2	NT	5.8	–
Plants				
Sesquiterpene lactone mix	1.1	0.7	0.6	NT
Primin	0.2	1.1	NT	0.7
Miscellaneous				
p-Tertiary-butylphenol formaldehyde resin	0.7	1.3	1.9	1.7
Epoxy resin	1.0	1.3	2.3	NT
Colophony	3.8	4.0	2.6	2.3
p-Phenylenediamine	3.8	3.9	4.8	6.1

IPPD, *N*-isopropyl-*N*′-phenyl-*p*-phenylenediamine; NT, not tested.

less common allergens may be included if they are potentially easily overlooked and important. The results of testing to a standard series of allergens vary from one part of a country to another, and from one country to another (Table 26.18) [Statham BN. Personal communication, 4,7,8]. In most countries, additions to the international standards are required. In order to reduce the number of tests, defined groups of substances can be made up as 'mixes'.

Additional series

There are many situations in which additional series of allergens are useful, for example in the investigation of dermatitis occurring in certain sites liable to medicament allergy (eyes, ears, perineum and venous ulcers/eczema) or sensitization from components of shoes or clothing. Some occupational groups, for example hairdressers, florists, dentists and metal machinists, are exposed at work to a variety of potential allergens not found in the standard series. Others may handle a specific group of allergenic chemicals, for example epoxy or acrylic resins. The main patch-test allergen producers now market extra series, although these may have to be further adapted to local habits or occupational exposures. Allergens provided by commercial allergen manufacturers tend to be of pharmaceutical grade, and may be negative when the actual sensitizer is an impurity in a commercial-grade product.

Other materials

Commercially produced patch-test allergens, either singly or in small numbers, may be applied where relevant. Patients may bring a wide variety of materials of their own from home or work for testing and, as mentioned previously, these must be thoroughly assessed and diluted appropriately before being tested. In those units with access to thin layer chromatography there is the opportunity to patch test with extracted components of textiles, plastics, plants and other materials [9].

References

1 Bruynzeel DP, Andersen KE, Camarasa JG *et al*. The European standard series. European Environmental and Contact Dermatitis Research Group (EECDRG). *Contact Dermatitis* 1995; **33**: 145–8.

2 Isaksson M, Brandao FM, Bruze M *et al*. Recommendation to include budesonide and tixocortol pivalate in the European standard series. ESCD and EECDRG. European Society of Contact Dermatitis. *Contact Dermatitis* 2000; **43**: 41–2.

3 Bruze M, Goossens A, Gruvberger B. Recommendation to include methyldibromo glutaronitrile in the European standard patch test series. *Contact Dermatitis* 2005; **52**: 24–8.

4 Pratt M, Belsito DV, DeLeo VA *et al*. North American Contact Dermatitis Group patch-test results, 2001-2002 study period. *Dermatitis* 2004; **15**: 176–83.

5 Magnusson B, Fregert S, Hjorth N *et al*. Routine patch testing: V. Correlations of reactions to the site of dermatitis and the history of the patient. *Acta Derm Venereol (Stockh)* 1969; **49**: 556–63.

6 Menné T, Dooms-Goossens A, Wahlberg JE *et al*. How large a proportion of contact sensitivities are diagnosed with the European standard series? *Contact Dermatitis* 1992; **26**: 201–2.

7 Adachi A. JSCD Research Group study. Results of patch tests with standard allergen series of the Research Group of the Japanese Society for Contact Dermatitis in 1994 and annual variations of patients with pigmented contact dermatitis of lichenoid type in 1993. *Environ Dermatol* 1996; **3**: 140–50.

8 Bruynzeel DP, Diepgen TL, Andersen KE *et al*. Monitoring the European standard series in 10 centres 1996–2000. *Contact Dermatitis* 2005; **53**: 146–9.

9 Bruze M, Frick M, Persson L. Patch testing with thin-layer chromatograms. *Contact Dermatitis* 2003; **48**: 278–9.

Concentrations and vehicles for patch testing

Recommended patch-test concentrations and vehicles for many different materials, including specific chemicals, chemical groups and substances, and finished products, have been collated in a number of standard contact dermatitis references as outlined below. Most (but not necessarily all) of these lists are reliable, in that the stated concentrations do not usually give an irritant effect. Before patch testing with any unfamiliar material, the appropriate vehicle and concentration should be sought from one or more of these databases.

1 General [1–5]
2 Selective:
(a) occupational [6,7]
(b) clothing and footwear [8]
(c) cosmetics [8,9]
(d) medicaments [8,9]
(e) woods [10]
(f) plants [11–13].

References

1 Fregert S. *Manual of Contact Dermatitis*, 2nd edn. Copenhagen: Munksgaard, 1981: 121–8.
2 De Groot AC. *Patch Testing. Test Concentrations and Vehicles for 3700 Chemicals*, 2nd edn. Amsterdam: Elsevier, 1994.
3 Rietschel RL, Fowler JF Jr. *Fisher's Contact Dermatitis*, 5th edn. Philadelphia: Lippincott, Williams & Wilkins, 2000: 735–817.
4 De Groot AC, Frosch PJ. Patch test concentrations and vehicles for testing contact allergens. In: Frosch PJ, Menné T, Lepoittevin J-P, eds. *Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 907–28.
5 Hausen BM, Brinkmann J, Dohn W. *Lexicon der Kontaktallergene*. Landsberg am Lech: Ecomed, 1992.
6 Adams RM. *Occupational Skin Disease*, 2nd edn. Philadelphia: Saunders, 1990.
7 De Groot AC. Patch-test concentrations and vehicles for testing contact allergens. In: Kanerva L, Elsner P, Wahlberg JE, Maibach HI, eds. *Textbook of Occupational Dermatology*. Berlin: Springer, 2000.
8 Foussereau J. *Les Eczémas Allergiques Cosmétologiques, Thérapeutiques et Vestimentaires*. Paris: Masson, 1987.
9 De Groot AC, Weyland JW, Nater JP. *Unwanted Effects of Cosmetics and Drugs Used in Dermatology*, 3rd edn. Amsterdam: Elsevier, 1994.
10 Hausen BM. *Woods Injurious to Human Health. A Manual*. Berlin: de Gruyter, 1981.
11 Benezra C, Ducombs G, Sell Y *et al*. *Plant Contact Dermatitis*. Toronto: BC Decker, 1985.
12 Hausen BM. *Allergiepflanzen–Pflanzenallergene: Handbuch und Atlas der allergieinduzierenden Wild- und Kulturplanzen Kontaktallergene*. Landsberg, Münich: Ecomed, 1988.
13 Lovell CR. *Plants and the Skin*. Oxford: Blackwell Scientific Publications, 1993.

Photopatch testing [1]

Indications

The main clinical indications for photopatch tests include the investigation of patients with eczematous eruptions predominantly affecting light-exposed sites and a history of worsening following sun exposure. A history of a reaction to sunscreens is a further indication. Grounds may be extended to testing anyone with an exposed site distribution of dermatitis. Some patients have coexisting photosensitive disorders, causing practical problems in performing and interpreting the investigation.

Method

A British Photodermatology Group (BPG) workshop has achieved a consensus on the protocol for photopatch testing in the UK and Ireland [1], but the technique may vary slightly in other parts of the world. The BPG stated that photopatch testing is an evolving technique with a need for more research. A European task force has now been set up to look further into a consensus methodology [2].

A UVA source is required, which in most centres will be the UVA lamps used for PUVA therapy, commonly a hand/foot treatment unit. In photobiology centres, the more sophisticated irradiation monochromator may be used as an alternative. Other UVA sources include UVA blacklights, and filtered metal halide and xenon arc lamps. In all cases irradiance should be measured with a calibrated UVA meter. The energy source must be monitored regularly, as the tubes deteriorate with time.

Historically, administered dosages of UVA to the photopatch-test site have generally ranged from 5 to 10 J/cm^2. However, the higher doses have the disadvantage of being more likely to induce false-positive phototoxic responses without increased detection of photoallergic subjects [1], and therefore a dose of 5 J/cm^2 is recommended. Modification of the dose may be necessary in UVA-photosensitive individuals, in which case 50% of the UVA minimal erythema dose is suggested. However, UVA phototesting to establish the minimal erythema dose is not always feasible or practicable, but is nevertheless advised before photopatch testing known photosensitive individuals. Application of the allergens is performed in an identical fashion to conventional patch tests, except that they must be applied in duplicate—one set is irradiated and the other (the control) is not. Usually, the two sets of tests are applied on either side of the vertebral column at the same level. It is suggested that the patient's back is positioned 15 cm from the front panel of the lamps [1]. Steps must be taken to avoid any incidental irradiation by natural light of both the irradiated and the control set of allergens. The control site and the rest of the skin must be covered with opaque material during irradiation of the photopatch-test site. Three protocols have been used and these are described in Table 26.19. There is evidence to show that a 48-hour application is superior to 24 hours [3], and one study has failed to show an improved return with UVB irradiation or with a 7-day reading [4].

Table 26.19 Photopatch-test protocols. (From British Photodermatology Group [1].)

	Day				
	0	1	2	3	4
Protocol 1	Phototest Apply allergens	Read phototest results Remove patches and irradiate allergens		Read results	
Protocol 2	Apply allergens		Remove patches, read results and irradiate allergens		Read results
Protocol 3	Apply allergens	Phototest	Read phototest results Remove patches, read results and irradiate allergens		Read results

Table 26.20 Photopatch-test standard series. (European Taskforce for Photopatch Testing [2].)

Substance*	Concentration (%) in petrolatum
p-Aminobenzoic acid (PABA)	10.0
Octyl dimethyl PABA	10.0
Octyl methoxycinnamate	10.0
Benzophenone 3	10.0
Butyl methoxydibenzoylmethane	10.0
4-methylbenzylidene camphor	10.0
Benzophenone 4	10.0
Isoamyl *p*-methoxycinnamate	10.0
Phenylbenzimidazole sulphonic acid	10.0
Naproxen	5.0
Ibuprofen	5.0
Diclofenac	1.0
Ketoprofen	2.5
Patient's own products	

* A more extensive series of UV filters and photosensitizers may now be appropriate for some centres.

Test materials

The principle of a standard series also applies to photopatch tests. Having considered the available evidence, the BPG recommended just six compounds for a standard photopatch-test series, five UV filters and musk ambrette [1]. The latter, although no longer incorporated into perfumed materials in the western world, was felt to be relevant to imported fragranced materials. However, a more extensive series has been proposed for Europe, particularly as topical NSAIDs are used much more in mainland Europe [2]. This series is listed in Table 26.20. However, for some centres more UV filters and other materials may be advisable as new exposures and photoallergens, for example octocrylene and octyl triazone, are identified.

Readings

A positive reaction on the irradiated side only is an indication of photoallergy. There are occasional difficulties distinguishing a false-positive phototoxic reaction from photoallergy, but this is less likely with a dose of 5 J/cm^2. Readings are scored identically to conventional patch tests, but the positive symbol is preceded by the prefix Ph, for example Ph++ is a strong positive photoallergic reaction. If the same allergen provokes an equally strong reaction on both sides, it is an indication of contact allergy alone; if it is significantly stronger on the irradiated side, then combined allergy and photocontact allergy may be occurring. Doubtful and slight amplification of photoallergic reactions may be the result of phototoxicity.

References

1 British Photodermatology Group. Photopatch testing: methods and indications. *Br J Dermatol* 1997; **136**: 371–6.

2 Bruynzeel DP, Ferguson J, Andersen K *et al*. European Taskforce for Photopatch Testing. Photopatch testing: a consensus methodology for Europe. *J Eur Acad Dermatol Venereol* 2004; **18**: 679–82.

Table 26.21 Potential complications of patch testing.

Pruritus
Folliculitis
Leakage of materials on to clothing, especially dyes
Localized flare of dermatitis and other skin disorders
Flare of dermatitis at previous contact sites
Generalized flare of dermatitis
Irritant reactions from patients' own inappropriately diluted products
Active sensitization
Pigmentation or depigmentation
Scarring
Anaphylaxis (very rare)

3 Batchelor RJ, Wilkinson SM. Photopatch testing – a retrospective review using the 1 day and 2 day irradiation protocols. *Contact Dermatitis* 2006; **54**: 75–8.

4 Pollock B, Wilkinson SM. Photopatch test method: influence of type of irradiation and value of day-7 reading. *Contact Dermatitis* 2001; **44**: 270–2.

Complications of patch and photopatch tests (Table 26.21)

Generally, the risks of patch testing when it is performed correctly are minimal, but there are a number of potential complications outlined below.

Positive reactions may spread locally and cause a flare of contact dermatitis at the original site or more generally. The long strips of adhesive semi-occlusive tape, which preclude bathing for several days, may lead to eczema, itching or folliculitis, especially with high temperature and humidity. In warm weather there may be leakage of the test materials on to clothing, and patients should be advised to wear an old shirt or blouse during the test. Irritants at excessive concentrations may induce caustic burns and scarring, and even a strong allergic reaction might leave a scar on extremely rare occasions. Secondary infection of a positive reaction is virtually never a problem.

Short-term post-inflammatory hypopigmentation does occur occasionally following positive patch tests, but more permanent hypopigmentation may develop, including koebnerization of vitiligo (Fig. 26.31). Post-inflammatory hyperpigmentation may also develop, although this is usually temporary. Phototoxic substances may cause pigmentation if exposed to UV light from photopatch tests or natural sunlight.

Significant epidermal detachment has been seen in patients with both pemphigus foliaceus and Hailey-Hailey disease after removal of the patch-test units [1,2].

Short-lived, non-immunological, urticarial reactions are common, particularly from cinnamates and sorbic acid. More importantly, anaphylactic reactions are a potential risk when patch testing with some materials, especially rubber latex [3] and penicillin. A history of immediate hypersensitivity to rubber should be sought before patch testing with latex.

Active sensitization

Patch testing involves a small risk of sensitization. A reaction appearing 7 or more days after the application may indicate either



Fig. 26.31 Persistent hypopigmentation after patch tests.

delayed expression of a pre-existing sensitivity or sensitization from the patch test. However, some late reactions, occurring up to 14 days after application of patch tests, are weak sensitivities from poorly penetrating allergens. Active sensitization usually presents as a strong positive patch test occurring at around 3 weeks. Few clinics observe their patients long enough to note such reactions, but patients report them. The true incidence of sensitization is therefore difficult to establish, because even re-examination of a random sample of the patients tested cannot differentiate between those sensitized by patch testing and those whose pre-existing subliminal sensitivity has been boosted by further exposure from patch testing. Patch-test sensitization from most routinely tested substances is very uncommon, and occurs more frequently when new substances are being investigated to ascertain the correct patch-test concentration. Sensitization is more common when testing with unrefined wood or plant extracts or with material provided by the patient.

The possibility of active sensitization to *p*-phenylenediamine (PPD) has caused the German Contact Dermatitis Research Group to remove it from their standard series pending further evaluation [4]. However, an in-depth study looking at patients who were repeat patch tested over a 10-year period has shown that the maximal sensitization rate was at the most 0.3% for PPD [5]. The authors therefore support its continued retention in the standard series.

Testing itself may cause a reawakening of sensitivity. However, the practical consequences of this are uncertain. Patients who can be resensitized by patch tests must also be easily resensitized by contact with the allergen under everyday conditions.

Such induced sensitivity tends to fade relatively quickly, and the patient's clinical course does not appear to be adversely affected. These rare adverse events are usually of no long-term consequence and must be balanced against the benefits of finding one or more relevant allergens.

Rarely, persistence of patch-test reactions may continue for several weeks unless treated. This has been especially noted with gold sodium thiosulphate [6].

References

1 Cocklin CL, Shackelford K, Wolverton SE, Fett DD. Pemphigus foliaceus with epidermal detachment: adverse events from patch testing. *Dermatitis* 2006; **17**: 32–5.

2 Walker SL, Beck MH. Undiagnosed Hailey-Hailey disease causing painful erosive skin changes during patch testing. *Br J Dermatol* 2005; **153**: 233–4.

3 Parry EJ, Beck MH. Acute anaphylaxis resulting from routine patch testing with latex. *Contact Dermatitis* 1999; **41**: 236–7.

4 Hillen U, Jappe U, Frosch PJ *et al*. Late reactions to the patch-test preparations para-phenylenediamine and epoxy resin: a prospective multicentre investigation of the German Contact Dermatitis Research Group. *Br J Dermatol* 2006; **154**: 665–70.

5 Dawe SA, White IR, Rycroft RJ *et al*. Active sensitization to para-phenylenediamine and its relevance: a 10-year review. *Contact Dermatitis* 2004; **51**: 96–7.

6 Bruze M, Hedman H, Björkner B, Möller H. The development and course of test reactions to gold sodium thiosulfate. *Contact Dermatitis* 1995; **33**: 386–91.

Multiple patch-test reactions

The finding of multiple positive patch tests is common, and it is important to consider the reasons for this so that the correct advice can be given to the patient. The main explanations are:

1 non-specific hyperreactivity
2 multiple primary hypersensitivities
3 cross-reactions (true and false).

Non-specific hyperreactivity [1]

Ideally, patch tests should be applied at a concentration that always identifies the allergen and never induces false-positive reactions. Unfortunately, some allergens have to be applied at a concentration that is marginally irritant in some subjects in order that allergic positive reactions are not missed. The threshold at which a false-positive irritant reaction develops differs from individual to individual and may even be variable in the same subject [2]. During active dermatitis, uninvolved skin, even at distant body sites, exhibits increased susceptibility to irritant reactions [3]. This 'status eczematicus' may lead to false-positive patch-test results. It has become an established tenet that 'eczema creates eczema' [1], and that a strongly positive patch-test reaction may induce other non-specific false-positive patch-test reactions [4]. Such reactions occur more readily with marginally irritant chemicals. When this affects adjacent patch-test sites it is often referred to as 'spillover' [5], 'excited skin' [6] or 'angry back' [4]. Rietschel [7] has proposed that 'stochastic resonance' may be involved. This suggests that there is signal amplification of immune-mediated events by neurological influence. The incidence has been variously assessed as 8.6% [8] to 63.5% [4,9,10]. In view of these findings, it has been proposed that repeat patch tests should be undertaken in all individuals with three or more strong positive allergic reactions, with exclusion of the strongest reactants. However, some studies [11,12] have not found evidence to support a concept of non-specific hypersensitivity.

The occurrence of weak false-positive patch-test reactions can be reduced by delaying patch testing until all active eczema has settled. As skin hyperirritability may persist for some weeks or months, even when a dermatitis has resolved, this is often impractical.

Multiple primary hypersensitivities

Multiple primary specific (or concomitant) sensitivities to substances that are unrelated chemically are frequent among patients with contact dermatitis. Among 5000 Scandinavian patients, they occurred in 20% of all persons tested. The reason why some patients develop multiple sensitivities and others do not is not clear. Patients with a long history of dermatitis are those most likely to accumulate several primary sensitivities, because of the opportunities to encounter new allergens under conditions favourable for sensitization. Patients with leg ulcers are especially prone to developing multiple allergies, as are patients with chronic actinic dermatitis. One sensitivity may predispose to the acquisition of another, and there may be a genetic or constitutional predisposition to acquire sensitivities.

Sensitization is facilitated if an allergen is applied on injured (e.g. eczematous) skin [13], particularly if it is occluded, and such local factors may be sufficient to explain the frequency of sensitivity to topical medicaments and simultaneous sensitivity to several constituents. In dermatitis from applied medicaments, concomitant sensitivity to both an antibiotic and an unrelated component of the vehicle is quite common. Similarly, in rubber dermatitis, sensitivity to unrelated vulcanizing agents is not unusual. Cobalt and nickel are difficult to separate, and thus cobalt commonly contains traces of nickel, and nickel traces of cobalt. Sensitivity may be caused by either or both. Combined cobalt and chromate allergy is common among cement workers. However, closeness in the periodic table is a hypothesis put forward to explain the finding of palladium sensitivity in a high proportion of individuals with a strong positive reaction to nickel [14].

In dermatitis of the feet, concomitant sensitivity to chromate, rubber and dyes in shoes or stockings presents a particularly difficult clinical problem; one allergen may be primarily responsible but others are important in maintaining the eczematous state. The inflammatory response to allergens has been shown to be additive [15], as has the response to an allergen and an irritant [16].

Cross-reactions [17]

Cross-sensitization is defined as the phenomenon where sensitization engendered by one compound, the primary allergen, extends to one or more other compounds, the secondary allergens, as a result of structural similarity. The proposal is that the primary and secondary allergens are so closely related that sensitized T cells are unable to distinguish between them, and therefore react as if the compounds were identical. Aromatic compounds with a 'para' group, for example *p*-phenylenediamine, benzocaine, procaine, sulphonamides, mesalazine, diaminodiphenylmethane and *para*-aminobenzoic acid (PABA) UV filters, may all cross-sensitize [18,19]. Aminoglycosides may do the same to a varying degree [20]. Other examples include chlorocresol and chloroxylenol [21], as well as corticosteroids of a similar structure [22]. Enantiospecificity or stereospecificity may lead to cross-reactivity with some isomers and not others [23]. Examples include usnic acid, 4-methoxydalbergiones and frullanolides. A computerized resource has been used for the systematic evaluation of structure–activity relationships [24].

Contaminants may cause 'false' cross-sensitivity as one substance may contain traces of another. In studies of cross-sensitivity, absolutely pure test substances must be used. Few investigations in the past have fulfilled these requirements, and most should be repeated using modern methods of separation.

In simultaneous sensitivity to natural products such as perfumes, balsams and wood tars, it is impossible to decide whether reactions to several of the substances may be due to related or identical chemicals. Cinnamic aldehydes, for example, may occur in them all. The same applies to plants such as Compositae (Asteraceae), *Frullania*, and *Toxicodendron* spp.

References

1 Mitchell JC. The angry back syndrome: eczema creates eczema. *Contact Dermatitis* 1975; **1**: 193–4.
2 Hindsen M, Bruze M, Christenson O. Long term individual variation in patch test reactivity. Presented at the Second Congress of the European Society of Contact Dermatitis, Barcelona, October 1994.
3 Bjornberg A. *Skin Reactions to Primary Irritants in Patients with Hand Eczema*. Gothenburg: Isaacsons O, Tryckeri AB, 1968.
4 Bruynzeel DP. *Angry Back or Excited Skin Syndrome* [thesis]. Amsterdam: Vrie Universiteit te Amsterdam, 1983.
5 Paramsothy Y, Collins M, Smith AG. Contact dermatitis in patients with leg ulcers. The prevalence of late positive reactions and the evidence against systemic ampliative allergy. *Contact Dermatitis* 1988; **18**: 3–57.
6 Maibach HI. The ESS: excited skin syndrome (alias the 'angry back'). In: Ring J, Burg G, eds. *New Trends in Allergy*. Berlin: Springer, 1981: 208–21.
7 Rietschel R. Stochastic resonance and angry back syndrome: noisy skin. *Am J Contact Dermatitis* 1996; **7**: 152–4.
8 Bandmann H-J, Agathos M. New results and some remarks on 'angry back syndrome'. *Contact Dermatitis* 1981; **7**: 23–6.
9 Maibach HI, Fregert S, Magnusson B *et al*. Quantification of the excited skin syndrome (the 'angry back'). Retesting one patch at a time. *Contact Dermatitis* 1982; **8**: 78.
10 Duarte I, Almeida FA, Proenca NG. Excited skin syndrome. *Am J Contact Dermatitis* 1996; **7**: 24–34.
11 Memon AA, Friedmann PS. The angry back syndrome: a non-reproducible phenomenon. *Br J Dermatol* 1997; **135**: 924–30.
12 Andersen KE, Lidén C, Hansen J *et al*. Dose–response testing with nickel sulphate using the TRUE test in nickel-sensitive individuals. Multiple nickel sulphate patch-test reactions do not cause an 'angry back'. *Br J Dermatol* 1993; **129**: 50–6.
13 Pedersen LK, Johansen JD, Held E, Agner T. Augmentation of skin response by exposure to a combination of allergens and irritants—a review. *Contact Dermatitis* 2004; **50**: 265–73.
14 Vincenzi C, Tosti A, Guerra L *et al*. Contact dermatitis to palladium: a study of 2300 patients. *J Am Acad Dermatol* 1995; **6**: 110–2.
15 McLelland J, Shuster S. Contact dermatitis with negative patch tests: the additive effect of allergens in combination. *Br J Dermatol* 1990; **122**: 623–30.
16 Seidenari S, Molotese A, Belletti B. Pre-treatment of nickel test areas with sodium lauryl sulfate detects nickel sensitivity in subjects reacting negatively to routinely performed patch tests. *Contact Dermatitis* 1996; **34**: 88–93.
17 Benezra C, Maibach HI. True cross-sensitization, false cross-sensitization and otherwise. *Contact Dermatitis* 1984; **11**: 65–9.
18 Uter W, Lessmann H, Geier J *et al*. The spectrum of allergic (cross-)sensitivity in clinical patch testing with 'para amino' compounds. *J Allergy* 2002; **57**: 319–22.
19 Mackie BS, Mackie LE. Cross sensitization in dermatitis due to hair dyes. *Australas J Dermatol* 1964; **7**: 189–202.
20 Rudzki E, Zakrzewski Z, Rebandel P. Cross reactions between aminoglycoside antibiotics. *Contact Dermatitis* 1988; **18**: 314–6.
21 Burry JN, Kirk J, Reid J *et al*. Chlorocresol sensitivity. *Contact Dermatitis* 1975; **1**: 41–2.
22 Wilkinson SM. Corticosteroid cross-reactions: an alternative view. *Contact Dermatitis* 2000; **42**: 59–63.
23 Benezra C, Stampf JL, Barbier P *et al*. Enantiospecificity in allergic contact dermatitis: a review and new results in *Frullania*-sensitive patients. *Contact Dermatitis* 1985; **13**: 110–4.

24 Benezra C, Sigman CC, Perry LR *et al*. A systematic search for structure–activity relationships of skin contact sensitizers: methodology. *J Invest Dermatol* 1985; **85**: 351–6.

Other tests

Occlusive patch testing has stood the test of time. Although it is an artificial procedure, it has not been superseded. Nevertheless, alternatives continue to be sought and some of these may be useful adjunctive investigations.

Open tests

Patch testing is usually performed with the test site occluded, in order to increase percutaneous absorption. This is an artificial procedure, and clinical exposure might be more closely simulated by simple application of the sensitizer to uninvolved skin. However, few allergens provoke dermatitis with a single exposure on normal skin. It is seen in *Primula* dermatitis, some patients having positive, even bullous, reactions to an open patch test to the leaf [1]. In most cases of clinical contact dermatitis, however, the allergen gradually accumulates in the epidermis, and irritants and mechanical injury promote its absorption. These conditions are not readily reproduced in a test procedure.

In highly sensitive individuals, allergens with good penetration can produce positive reactions in an open test, although the concentrations used for testing must be much higher than those used in a closed test. Thus, potassium dichromate 5% in water and nickel chloride 10–20% in alcohol provoke a positive reaction in many chromate- or nickel-sensitive persons [2]. Positive reactions often develop in a few hours.

The technique is simple. The liquid test substance is dropped on an area of skin measuring about 1 cm in diameter and the solution is allowed to dry. The time for reading and the characteristics of the reaction are the same as for closed patch testing. The reaction can be followed from the start and may develop sooner than with a closed patch-test reaction [2]. It is often weaker, and a positive reaction, especially in the initial phase, may consist of isolated papules only.

One situation where open testing has been widely used and advocated is prior to dyeing hair. Application of the dye to the retro-auricular area and examination of the site 2 days later was shown to be an accurate method of detecting sensitized subjects [3]. However, hairdressers and individual users tend to do this only once and not each time the hair is tinted, and often they mistakenly undertake a 30-min reading. They may therefore miss the allergy if it develops subsequently.

With irritants, the reactions are also usually fewer and weaker in open than in closed patch testing because of reduced absorption. Open tests are therefore sometimes used as a preliminary screening procedure with less well-known substances to reduce the risk of severe reactions. However, experience with open tests is limited and the risk of sensitization cannot always be estimated.

Usage tests

In cases of doubt, when either a closed patch test or open test is negative yet the history suggests a contact dermatitis, the patient can be asked to use the preparation again. This is especially helpful with cosmetic and clothing dermatitis. Because it reproduces all the other factors associated with the original dermatitis, for example sweating, friction and application of allergen on damaged or pre-sensitized skin, it is sometimes positive when conventional patch tests fail to reveal a sensitivity. However, it is not always possible to differentiate between an allergic and a non-specific or irritant response. With cosmetic preparations or medicaments, a repeat 'dab' test may be performed on previously affected skin.

Repeat open application tests [4]

In this test, substances are applied twice daily for up to 4 weeks or until an eczematous reaction develops. The most appropriate site is the upper arm or flexor surface of the forearm, as patients can perform the test and observe any developing reaction. They should be told to discontinue the application if eczema occurs. An area of at least 5 cm^2 should be employed. The test may be used to determine the relevance of doubtful positive patch-test reactions to preparations in which the putative allergen is present in a low concentration, although false-negative results may occur [5]. It may also establish the clinical relevance of such products and confirm the source of the allergy. A scale for recording ROAT reactions has been proposed and advocated [6].

Intradermal tests

Intracutaneous tests, as used in tuberculin sensitivity, have also been performed with simple chemicals, although mainly for investigative purposes. Within 1 day erythema and swelling appear at the site of injection. Later, usually after 2–4 days, papules or vesicles may develop. Sometimes, a flare may be seen shortly after the injection, and this lasts a few hours. Over the next few days, erythema and infiltration are sometimes seen along the lymphatics leading from the test site.

Technical pitfalls with intracutaneous testing are numerous, as is known from extensive studies with tuberculin. Too deep an injection will result in negative reactions. An immediate reaction, which is not a rarity with metal salts, may result in dilution and removal of the test substance. The concentrations employed should be at least 10–100 times lower than those used for epicutaneous testing [7]. In cases of extreme sensitivity, the concentration may need to be 1000–10 000 times lower.

The technique has proved reliable for nickel [2] and may identify allergy in patients with false-negative patch tests [8–10]. It has proven particularly helpful in the investigation of corticosteroid allergy [10].

References

1 Fregert S, Hjorth N, Schulz K-H. Patch testing with synthetic primin in persons sensitive to *Primula obconica*. *Arch Dermatol* 1968; **98**: 144–7.
2 Christensen OB, Wall LM. Open, closed and intradermal testing in nickel allergy. *Contact Dermatitis* 1987; **16**: 21–6.
3 Krasteva M, Cristaudo A, Hall B *et al*. Contact sensitivity to hair dyes can be detected by the consumer open test. *Eur J Dermatol* 2002; **12**: 322–6.
4 Hannuksela M, Salo H. The repeated open application test (ROAT). *Contact Dermatitis* 1986; **14**: 221–7.
5 Flyvholm MA, Hall BM, Agner T *et al*. Threshold for occluded formaldehyde patch test in formaldehyde-sensitive patients. Relationship to repeated open application test with a product containing formaldehyde releaser. *Contact Dermatitis* 1997; **36**: 26–33.

6 Johansen JD, Bruze M, Andersen KE *et al*. The repeated open application test: suggestions for a scale of evaluation. *Contact Dermatitis* 1998; **39**: 95–6.
7 Meneghini C, Angelini G. Intradermal test in contact allergy to metals. *Acta Derm Venereol Suppl (Stockh)* 1979; **85**: 123–4.
8 Botelho C, Rodrigues J, Castel Branco MG. Allergic contact blepharoconjunctivitis with phenylephrine eyedrops –the relevance of late readings of intradermal tests. *Allergol Immunopathol (Madr)* 2007; **35**: 157–8.
9 Wilkinson SM, English JSC. Hydrocortisone sensitivity. An investigation into the nature of the allergen. *Contact Dermatitis* 1991; **25**: 175–81.
10 Seukeran DC, Wilkinson SM, Beck MH. Patch testing to detect corticosteroid allergy: is it adequate? *Contact Dermatitis* 1997; **36**: 127–30.

In vitro tests

The principle of diagnosing contact allergy by *in vitro* testing is attractive, although the use of peripheral blood as a routine investigation for contact dermatitis may not be viable, not only from the budgetary point of view but also for logistical and practical reasons. Nevertheless, attempts continue to be made to achieve this, albeit with single or small numbers of allergens. A number of different techniques have been tried and these are described below.

As yet, none of these tests is a substitute for the *in vivo* system of the challenge patch test. However, they may be helpful in elucidation of the immune cascade as they are based on measurements of products from T-cell activation. They may also have a role in looking at cross-sensitivity patterns.

Migration inhibition test

Migration inhibition factor is a soluble factor released by sensitized lymphocytes following stimulation. It inhibits the migration of monocytes and macrophages but not polymorphonuclear leukocytes [1]. A direct and indirect assay is performed and the results expressed as a migration index. The test has been employed in nickel and chromate allergy, but is not completely reliable as there is overlap between sensitized and non-sensitized patients. Interference may be caused by a cytotoxic action of the allergens, and concentrations have to be optimum at just below non-toxic levels. The technique was not reliable as an investigation for medicament contact allergy [2], but a capillary tube assay has been demonstrated to be of practical clinical value for diagnosing chromium allergy [3]. The method requires further investigation and refinement [4,7].

Lymphocyte transformation tests

Antigens are able to induce specific transformation of lymphocytes to large lymphoblasts, culminating in mitosis. Most work has been carried out on nickel allergy [6,7], although there are conflicting accounts of the optimum stimulatory concentration of nickel and the method of preparation of cells following culture for radioactive thymidine uptake assays. Nickel may induce non-specific transformation in non-allergic subjects [8], but several groups of investigators have reported a significant difference between lymphocyte transformation in nickel-sensitive patients and controls [6,7,9,10]. The assay may be enhanced by adding a combination of cytokines to the culture [11]. Other standard-series allergens investigated, with potentially promising results, include fragrance, chromate, PPD, neomycin sulphate and thiuram [12–14], but testing with a range of medicament allergens failed to reach statistical significance [2].

Furthermore, measurement of cytokine levels after culture may also improve the accuracy of the *in vitro* test and, depending on the study, raised levels of interleukin (IL) -2, IL-4, IL-5, IL-10, IL-13 and interferon-γ have all been noted [11,15,16].

Unfortunately, many haptens are toxic to lymphocytes even in low concentrations [17].

Leukocyte procoagulant activity

When stimulated by an antigen, leukocytes produce a significant level of procoagulant that activates the extrinsic cascade of blood clotting. Its activity is measured as a ratio of the clotting time of plasma incubated with cells, with and without antigen. It has been used in nickel-sensitive patients [18], when the procoagulant activity increased as the stimulatory nickel concentration increased.

References

1 David JR. Lymphocyte mediators and cellular hypersensitivity. *N Engl J Med* 1973; **288**: 143–9.
2 Jovanovic M, Poljacki M, Milakov J *et al*. [Skin and laboratory tests: comparison of the epicutaneous patch test with the TTL and LIF tests in the diagnosis of medicamentous allergic contact dermatitis]. *Med Pregl* 1992; **45**: 365–8.
3 Tio D. A study on the clinical application of a direct leukocyte migration test in chromium contact allergy. *Br J Dermatol* 1976; **94**: 65–70.
4 Mirza AM, Perea MG, Maccia CA *et al*. Leucocyte migration inhibition in nickel dermatitis. *Int Arch Allergy Appl Immunol* 1975; **49**: 782–8.
5 Jordan WP, Dvorak J. Leucocyte migration inhibition assay (LIF) in nickel contact dermatitis. *Arch Dermatol* 1976; **112**: 1741–4.
6 Everness KM, Gawkrodger DJ, Botham PA *et al*. The discrimination between nickel-sensitive and non-nickel-sensitive subjects by an *in vitro* lymphocyte transformation test. *Br J Dermatol* 1990; **122**: 293–8.
7 Kimber I, Quirke S, Beck MH. Attempts to identify the causative allergen in cases of contact dermatitis using an in vitro lymphocyte transformation test. *Toxicol In Vitro* 1990; **4**: 302–6.
8 Lisby S, Hansen LH, Skov L *et al*. Nickel-induced activation of T cells in individuals with negative patch test to nickel sulphate. *Arch Dermatol Res* 1999; **291**: 247–52.
9 Al Tawil NG, Marcusson JA, Moller E. Lymphocyte transformation test in patients with nickel sensitivity: an aid to diagnosis. *Acta Derm Venereol (Stockh)* 1981; **61**: 511–5.
10 Veien NK, Svejgaard E, Menné T. *In vitro* lymphocyte transformation to nickel: a study of nickel sensitive patients before and after oral and epicutaneous challenge with nickel. *Acta Derm Venereol (Stockh)* 1979; **59**: 447–51.
11 Spiewak R, Moed H, von Blomberg BM *et al*. Allergic contact dermatitis to nickel: modified in vitro test protocols for better detection of allergen-specific response. *Contact Dermatitis* 2007; **56**: 63–9.
12 Sieben S, Hertl M, Al Masaoudi T *et al*. Characterization of T cell responses to fragrances. *Toxicol Appl Pharmacol* 2000; **172**: 172–8.
13 Yamada M, Niwa Y, Fujimoto F *et al*. Lymphocyte transformation in allergic contact dermatitis. *Jpn J Dermatol* 1972; **82**: 94–7.
14 Kimber I, Quirke S, Cumberbatch M *et al*. Lymphocyte transformation and thiuram sensitization. *Contact Dermatitis* 1991; **24**: 164–71.
15 Minang JT, Areström I, Troye-Blomberg M *et al*. Nickel, cobalt, chromium, palladium and gold induce a mixed Th1- and Th2-type cytokine response in vitro in subjects with contact allergy to the respective metals. *Clin Exp Immunol* 2006; **146**: 417–26.
16 Cederbrant K, Anderson C, Andersson T *et al*. Cytokine production, lymphocyte proliferation and T-cell receptor Vbeta expression in primary peripheral blood mononuclear cell cultures from nickel-allergic individuals. *Int Arch Allergy Immunol* 2003; **132**: 373–9.
17 Wolf R, Davidovici B, Marcos B, Orion E. Lymphocyte transformation test in patients with allergic contact dermatitis. *Contact Dermatitis* 2005; **53**: 245.
18 Aldridge RD, Milton JI, Thompson AW. Leucocyte procoagulant activity as an *in vitro* index of nickel hypersensitivity. *Int Arch Allergy Appl Immunol* 1985; **76**: 350–3.

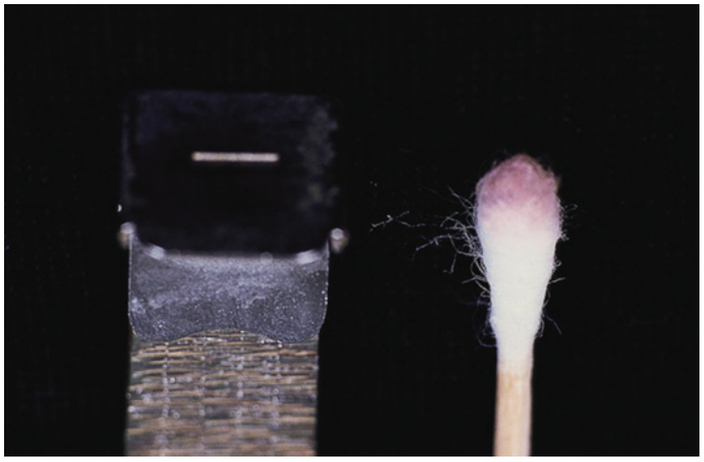


Fig. 26.32 Dimethylglyoxime test: a pink colour is detected when metals release a significant amount of nickel. (Courtesy of Dr J.D. Wilkinson, Amersham General Hospital, Amersham, UK.)

Spot tests [1]

Two spot tests are of particular practical value in the patch-test clinic as the materials are easy to handle and store.

Dimethylglyoxime test for nickel [1–3]

Dimethylglyoxime 1% (alcoholic solution) and ammonium hydroxide (aqueous solution) are stored in separate bottles. A few drops of each are put in separate clean white saucers, a cotton bud is then dipped in each of these and rubbed on the surface of the test object. A pink coloration on the cotton bud denotes the presence of nickel (Fig. 26.32). This test is accurate to 10 ppm of nickel, but the immune system may be able to detect lower levels than this. It is a very useful test, and patients can be given kits to test items in the home and at work.

Acetylacetone method for formaldehyde [4]

The reagent is prepared by dissolving 15 g of ammonium acetate, 0.2 mL of acetylacetone and 0.3 mL of glacial acetic acid in 100 mL of distilled water. It can then be stored in a refrigerator. A sample (1 mL or 1 mg) of the product to be tested is put in a disposable glass test tube and 2.5 mL of the reagent is added. The mixture is shaken and stoppered and then placed in a water bath at 60°C for 10 min. A yellow colour is produced in the presence of formaldehyde, due to the formation of 3,5-diacetyl-1,4-dihydrolutidine. The alternative chromotropic acid method is less specific.

Other analyses

There are other spot tests for chromate [1] and epoxy resin [5], but these are not simple to perform during a clinic. More sophisticated tests such as chromatography, spectrophotometry, mass spectrometry and nuclear magnetic resonance spectroscopy require specialized equipment and expertise.

References

1 Gruvberger B, Bruze M, Fregert S. Spot tests and chemical analyses for allergen evaluation. In: Rycroft RJG, Menné T, Frosch PJ, Lepoittevin J-P, eds. *Textbook of Contact Dermatitis*, 3rd edn. Berlin: Springer, 2001: 497–510.

2 Feigl F. *Spot Tests in Inorganic Analysis*. Amsterdam: Elsevier, 1949.

3 Shore RN. Dimethylglyoxime stick test for easier detection of nickel. *Arch Dermatol* 1977; **113**: 1734.

4 Dahlquist I, Fregert S, Gruvberger B. A simple method for the detection of formaldehyde. *Contact Dermatitis* 1982; **8**: 301–3.

5 Fregert S, Trulsson L. A simple method for the detection of epoxy resins of bisphenol A type. *Contact Dermatitis* 1978; **4**: 111–9.

Prevention [1,2]

Many statutory bodies have a role in the prevention of contact dermatitis, including medical personnel, legislative bodies, central and local government, corporate industry, the media, surveillance and consumer bodies, and patient support groups. Principles of prevention can be related to two categories, individual and collective, and further divided into primary, secondary and tertiary. Primary prevention focuses on the induction of contact sensitization and control of exposure. Secondary prevention relates to elicitation, and tertiary to measures for established and continuing dermatitis. Some of the more important elements of prevention are discussed below; the reader is referred to Lachapelle's overview for more detailed coverage [1].

Allergen containment and replacement [3]

Potent allergens encountered in industry can be kept in closed systems, thereby avoiding the potential for direct skin contact. In other instances products can be kept in special containers, which allow a no-touch technique when using the contents. Replacement and elimination of potential allergenic hazards can be helpful in both the domestic and working environments, for example perfume-free cosmetics and medicaments, non-latex gloves, high-molecular-weight epoxy resins [4], and white spirit instead of turpentine.

Legal and other regulatory measures [5]

Regulatory measures can influence the incidence of dermatitis [6]. They may be legally or voluntarily enforced. The EU has passed a number of directives relating to contact dermatitis, particularly in relation to nickel, chromate and cosmetics.

As most consumers are primarily sensitized to nickel either following ear piercing or by prolonged close contact with nickel-releasing alloys, it was proposed that such items should not release more than 0.5 $\mu g/cm^2$/week of nickel [7,8]. Ten per cent of the female population of Europe and the USA are sensitive to nickel [9], and this has significant implications with regard to hand eczema [10,11] and employment [12]; hence, nickel sensitivity is an issue where legal restraints could prove effective in improving the health of the population. Following the lead of Denmark and Sweden, the Nickel Directive was introduced in 1994 with the aim of primary and secondary prevention of the high levels of nickel allergy in the EU [5]. The recommendations are summarized in Table 26.3. A Danish follow-up study comparing 1985–86 with 1997–98 patterns of nickel sensitization has already shown a decrease in allergy from 24.8% to 9.2% in the tested populations aged under 19 [6], and a significant drop in the frequency of females with nickel allergy under the age of 30 has been seen in Germany since 1994 [13].

Dermatitis accounts for a significant proportion of occupational disease. Allergy to chromate in cement is a significant problem in the construction industry. Since the early 1980s some Scandinavian countries have restricted hexavalent chromium in cement to below 2 ppm, which is achieved by adding ferrous sulphate. Subsequently, there has been a reduction of chromate allergy amongst construction workers [14,15]. In 2005, the EU followed suit by directing that levels of hexavalent chromate in cement should be restricted to this level [2].

The EU Cosmetics Directive lists materials as allowed, not allowed and restricted. For instance, the preservative MCI/MI is not permitted above 15 ppm and formaldehyde above 0.2% in cosmetic products [2]. Methyldibromo glutaronitrile is a preservative which came into prominence in the 1990s when the frequency of allergy amongst patch-tested patients rose by a factor of 5 over the 10-year period [16]. As a result, steps were taken to ban its use, firstly in leave-on cosmetics, but later in wash-off products as well [2]. It is anticipated that the incidence of allergy to it will fall as a result.

Enforced ingredient labelling on the packaging of cosmetics, which is also a requirement in the USA, has been a major factor in enabling avoidance of cosmetic allergens by sensitized customers [17]. Since 2005, in the EU, labelling of certain fragrance substances (26 in all), at levels of >10 ppm for leave-on products and >100 ppm for wash-off products, has also been required.

The Directives on Dangerous Substances and Dangerous Preparations list 360 skin sensitizers and their concentration limits (e.g. formaldehyde 0.2%, acrylates 0.5–2%). A chemical product containing a classified skin sensitizer above 1% concentration must be labelled with the risk phrase 'R43—may cause sensitization by skin contact' [5]. For many substances 1% is above the level of sensitization and elicitation of contact dermatitis. The usefulness of labelling in this unselective quantitative way has been questioned [18].

Some legislation may apply only to one or a few countries. For instance, the use of PPD in hair dyes is forbidden in some countries and controlled in many others. Formaldehyde in clothing is limited in Finland [5]. Prohibition of persulphate improvers in flour in Denmark (1938) and Germany (1956) led to a striking decline in bakers' dermatitis in both countries [19]. In Germany, the use of turpentine for paint is strictly limited [20].

In the UK, the assessment and monitoring of hazards and risks at work has improved following the introduction of Control of Substances Hazardous to Health (COSHH) legislation, but attention to dermatitis checks and risks is still suboptimal [21]. In addition, the HSE have a statutory right to investigate skin problems at work through the Employment and Medical Advisory Service (EMAS), provided they are reported [22].

Corporate responsibility

Although legal measures can influence the incidence of dermatitis, few have been introduced. In many instances governments will not intervene with legislation, relying on self-regulation, and this includes the cosmetic and pharmaceutical industries. The withdrawal of musk ambrette is an example of cosmetic industry self-regulation.

Manufacturers of all goods should ensure that their products are safe to use, including the performance of pre- and post-marketing risk assessments. A risk assessment programme involves hazard identification, dose–response assessment, exposure assessment and risk characterization, including any potential for allergenicity [23,24]. A product must be clearly labelled to ensure that it is handled safely.

Dermatologists and consumers have a pivotal role by alerting authorities to the emergence of both new and existing allergens within communities. National groups, surveillance systems, particularly of occupational dermatitis, or more comprehensive data networks such as the European Surveillance System of Contact Allergens (ESSCA), can feedback their findings to responsible agencies who can then respond to any concerns [25–27]. Rapid computerized analysis of epidemiological information, with feedback to interested parties, can provide early warning of new allergens and sources of work-related dermatoses [28–30].

Work

The preventative aspects of occupational contact dermatitis are discussed in detail in Chapter 27.

Domestic

The availability of modern domestic equipment should significantly reduce skin contact with irritants and potential sensitizers in the home; however, housewives are still one of the greatest 'at-risk' groups as far as the development of hand dermatitis is concerned. Cotton-lined gloves should be worn when the hands are in contact with irritants, including food, cleaning agents and polishes. Plastic gloves are less allergenic than rubber but are less pliable and malleable.

Education

Education of the community and workforces through the media, courses, lectures and wall charts in public places (including medical waiting areas) and at work will help to promote awareness of the problem of contact dermatitis. Skin protection courses and education have been shown to reduce occupational dermatitis [31,32]. Patient support groups have played an increasing role in education of the general public as well as those suffering from dermatitis.

References

1 Lachapelle J-M. Principles of prevention and protection in contact dermatitis. In: Rycroft RJG, Menné T, Frosch PJ, Lepoittevin J-P, eds. *Textbook of Contact Dermatitis*, 3rd edn. Berlin: Springer, 2001: 981–93.

2 Thyssen JP, Johansen JD, Menné T. Contact allergy epidemics and their control. *Contact Dermatitis* 2007; **56**: 185–95.

3 Calnan CD. Studies in contact dermatitis. XXIII. Allergen replacement. *Trans St John's Hosp Dermatol Soc* 1970; **56**: 131–8.

4 Thorgeirsson A, Fregert S, Fammas O. Sensitization capacity of epoxy resin oligomers in the guinea pig. *Acta Derm Venereol (Stockh)* 1978; **58**: 17–21.

5 Lidén C. Legislative and preventative measures related to contact dermatitis. *Contact Dermatitis* 2001; **44**: 65–9.

6 Johansen J, Menné T, Christophersen J *et al*. Changes in the pattern of sensitization to common contact allergens in Denmark between 1985–86 and 1997–98, with a special view to the effect of preventive strategies. *Br J Dermatol* 2000; **142**: 490–5.

7 Emmet AE, Risby TH, Jiang L *et al*. Allergic contact dermatitis to nickel: bioavailability from consumer products and provocation threshold. *J Am Acad Dermatol* 1988; **19**: 314–22.

8 Menné T, Brandrup F, Thestrup-Pedersen K *et al*. Patch test reactivity to nickel alloys. *Contact Dermatitis* 1987; **16**: 255–9.
9 Menné T, Christophersen J, Green A. Epidemiology of nickel dermatitis. In: Maibach HI, Menné T, eds. *Nickel and the Skin: Immunology and Toxicology*. Boca Raton, FL: CRC Press, 1989: 109–17.
10 Christensen OB. Prognosis in nickel allergy and hand eczema. *Contact Dermatitis* 1982; **8**: 7–15.
11 Wilkinson DS, Wilkinson JD. Nickel allergy and hand eczema. In: Maibach HI, Menné T, eds. *Nickel and the Skin: Immunology and Toxicology*. Boca Raton, FL: CRC Press, 1989: 133–63.
12 Menné T, Bachmann E. Permanent disability in females sensitive to nickel, chromium and cobalt. *Berufsdermatosen* 1979; **27**: 129–35.
13 Schnuch A, Uter W. Decrease in nickel allergy in Germany and regulatory interventions. *Contact Dermatitis* 2003; **49**: 107–8.
14 Roto P, Sainio H, Reunala T *et al*. Addition of ferrous sulphate to cement and risk of chromium dermatitis among construction workers. *Contact Dermatitis* 1996; **34**: 43–51.
15 Zachariae COC, Agner T, Menné T. Chromium allergy in consecutive patients in a country where ferrous sulphate has been added to cement since 1981. *Contact Dermatitis* 1996; **35**: 83–6.
16 Wilkinson JD, Shaw S, Andersen KE *et al*. Monitoring levels of preservative sensitivity in Europe. A 10-year overview (1991–2000). *Contact Dermatitis* 2002; **46**: 207–10.
17 De Groot AC. Labelling cosmetics with their ingredients. *BMJ* 1990; **300**: 1636–8.
18 Roggeband R, Basketter DA, De Groot AC *et al*. Labelling of skin sensitizers: the new European Dangerous Preparations Directive. *Contact Dermatitis* 2001; **44**: 321–4.
19 Preyss A. Zur Beurteilung des Bäckerekzems. *Berufsdermatosen* 1960; **8**: 68–80.
20 Behrbohm P. Legislation on prevention of occupational dermatoses. *Contact Dermatitis* 1975; **1**: 207–10.
21 Douglas E, Rushton L, Williams HC. Is occupational dermatitis being taken seriously by UK industries? *Occup Med (Lond)* 1999; **49**: 85–91.
22 Dornan JD. The work of the Employment Medical Advisory Service. *Br J Dermatol* 1981; **105** (Suppl. 21): 79–83.
23 Felter SP, Ryan CA, Basketter DA *et al*. Application of the risk assessment paradigm to the induction of allergic contact dermatitis. *Regul Toxicol Pharmacol* 2003: **37**: 1–10.
24 Jowsey IR. Proactive surveillance of contact allergies: an important component of the risk management strategy for skin sensitizers. *Contact Dermatitis* 2007; **56**: 305–10.
25 Dickel H, Kuss O, Blesius CR *et al*. Report from the register of occupational skin diseases in northern Bavaria (BKH-N). *Contact Dermatitis* 2001; **44**: 258–9.
26 Cherry N, Meyer JD, Adisesh A *et al*. Surveillance of occupational skin disease: EPIDERM and OPRA. *Br J Dermatol* 2000; **142**: 1128–34.
27 Uter W, Hegewald J, Aberer W *et al*. The European standard series in 9 European countries, 2002/2003—first results of the European Surveillance System on Contact Allergies. *Contact Dermatitis* 2005; **53**: 136–45.
28 Dooms-Goossens A, Degreef H, Drieghe J, Dooms M. Computer assisted monitoring of contact dermatitis patients. *Contact Dermatitis* 1980; **6**: 123–7.
29 Edman B. The usefulness of detailed information to patients with contact allergy. *Contact Dermatitis* 1988; **19**: 43–7.
30 Beck MH, Hillier V. Computer analysis of patients undergoing contact dermatitis investigation. *Semin Dermatol* 1989; **8**: 105.
31 Soder S, Diepgen TL, Radulescu M *et al*. Occupational skin diseases in cleaning and kitchen employees: course and quality of life after measures of secondary individual prevention. *J Dtsch Dermatol Ges* 2007; **5**: 670–6.
32 Löffler H, Bruckner T, Diepgen T, Effendy I. Primary prevention in health care employees: a prospective intervention study with a 3-year training period. *Contact Dermatitis* 2006; **54**: 202–9.

Management

Avoidance advice

A diagnosis of allergic contact dermatitis is reached on the basis of a detailed history and examination followed by patch tests, with an assessment of the relevance of any positive reactions. Once a diagnosis has been made, possible sources of exposure to the causative allergen(s) should be identified, and avoidance advice given. In some instances, particularly of work-related problems, appropriate protective clothing or changes in handling technique may be advised. Materials used for protection, especially gloves, should not allow penetration of the allergen responsible for the dermatitis.

The first principle of management is to give advice on avoidance tailored to an individual. Examples of specific avoidance measures include plastic instead of rubber gloves, cosmetics and medicaments free of an identified allergen, and clothing free of nickel-containing studs, zips, etc. More general written information on the allergen sources may be helpful, but may also be confusing if many are not relevant to that person.

Ideally, the result of this advice will be resolution of dermatitis, but this does not always occur, and other factors, such as the possible contribution of irritant or constitutional eczemas to persistence of the problem, should be considered and discussed with the patient. The possibility of non-compliance with avoidance advice should be considered. Factors affecting compliance include social and educational status of the individual and lack of resources [1]. Reassessment and reinforcement of avoidance measures is often required, sometimes repeatedly, in order that patients are fully aware of what action they should take. In some patients continued exposure is unavoidable, but can be reduced to a sufficient degree to keep the dermatitis at an acceptable level. It is advisable to stress that allergy does not disappear when the dermatitis clears but that the risk of relapse after further contact with the allergen persists throughout life.

Active treatment

The mainstay of treatment of allergic contact dermatitis is avoidance of the causative factor(s), although topical corticosteroids will be required in most instances to control the disorder. The manner in which they are used will vary, and optimum regimens have yet to be established [2]. In acute, severe, localized allergic contact dermatitis a potent topical corticosteroid should be used. In more chronic or widespread contact allergies the potency may need to be reduced, and for long-term use in certain sites (face, genitals and flexures) mild topical corticosteroids are indicated. On the palms and soles, the longer-term intermittent use of a potent corticosteroid preparation is usually beneficial and well tolerated [3].

General principles of eczema treatment should be followed, with regular and liberal use of hydrating emollients and soap substitutes. Fissures of the fingers, palms and soles can be covered with hypoallergenic tape. Alternatively, zinc and salicylic acid paste BPC twice daily may be helpful, and cyanoacrylates (superglues) have been used with benefit by some dermatologists [4].

For acute weeping forms of allergic contact dermatitis, wet dressings with saline, aluminium acetate or silver nitrate (0.5%; stains black) may be of benefit. Potassium permanganate 1 in 8000 in warm water is helpful when used four times a day as a soak for vesiculobullous eruptions of the palms and soles. Brown staining of the skin and nails is a problem, and the treatment should be stopped when the affected areas become dry.

Secondary infection will require antibiotics, and a sedative antihistamine is indicated for pruritus, particularly at night. In severe or widespread eruptions, systemic steroids may be necessary.

Topical ascomycin derivatives (tacrolimus and pimecrolimus), which act as immunomodulating agents, have been introduced for the treatment of atopic eczema, and there is now evidence of their benefit in allergic contact dermatitis in animal and human studies [5,6]. These agents are more expensive than topical corticosteroids and have not been shown to be superior to them. They may nevertheless be helpful in recalcitrant cases, and also where corticosteroid use is contraindicated or not tolerated.

Recalcitrant, disabling cases may require consideration of immunosuppressive therapy such as azathioprine [7,8] and ciclosporin. Assessment of thiopurine methyltransferase levels should be performed before undertaking treatment with azathioprine [9]. The investigation will identify a subset of patients potentially at high risk of myelotoxicity from this treatment. There is evidence in animals that ciclosporin suppresses allergic contact dermatitis [10], but most reported clinical studies have been undertaken on chronic hand eczemas of mixed aetiology [11,12].

It has been reported that certain patterns, especially vesicular palmar eczema, have benefited from dietary avoidance or reduction in intake of allergen, most notably nickel and balsams, in sensitized subjects [13–17]. The effects of a low-nickel diet have been disappointing in our experience; nevertheless, there are strong advocates of these measures. Dietary chelation of nickel has also been attempted [18–20], but is not widely used in practice because of side effects [18].

Dietary manoeuvres have also been reported to be helpful for cheilitis and oral symptoms, particularly in those with positive patch tests to balsam of Peru, cinnamates, eugenol, colophony, flavours and antioxidants [21–25], although the relationship between 'burning mouth' and contact allergy is questionable [26,27].

Superficial X-rays and Grenz rays, which have been shown to suppress experimental contact dermatitis [28], can be safely used for localized dermatitis, although facilities for this treatment are gradually dwindling in the UK [29–31]. Phototherapy, both PUVA and UVB, is helpful in some subjects [31–34], including Compositae-allergic individuals with photosensitivity [35]. The use of barrier creams as preventatives in already sensitized persons is generally unsatisfactory. However, there is documented evidence of the value of products containing quaternium-18 bentonite in the prevention of *Toxicodendron* spp. dermatitis [4,36]. Other barrier creams containing active agents (e.g. chelating agents) against specific allergens may have future potential [37–39]. In one study clioquinol was the most effective agent at preventing nickel dermatitis [38].

Hyposensitization [40]

Many attempts have been made to down-regulate the immune response to allergens in an already sensitized individual. This has proved difficult to realize in practice. The degree of hyposensitization achieved by oral doses of allergens is limited and transient, for example DNCB and chromate in guinea pigs [41,42], and poison ivy in humans [43]. Although it has been attempted for *Toxicodendron* spp. allergy [44], oral hyposensitization is not routinely recommended [4]. Some success has nevertheless been claimed in India for hyposensitization against *Parthenium hysterophorus* [45].

References

1 Noiesen E, Larsen K, Agner T. Compliance in contact allergy with focus on cosmetic labelling: a qualitative research project. *Contact Dermatitis* 2004; **51**: 189–95.

2 Levin C, Maibach HI. An overview of the efficacy of topical corticosteroids in experimental human nickel contact dermatitis. *Contact Dermatitis* 2000; **43**: 317–21.

3 Veien NK, Olholm Larsen P, Thestrup-Pedersen K *et al*. Long-term, intermittent treatment of chronic hand eczema with mometasone furoate. *Br J Dermatol* 1999; **140**: 882–6.

4 Rietschel RL, Fowler JF Jr. *Fisher's Contact Dermatitis*, 5th edn. Philadelphia: Lippincott, Williams & Wilkins, 2001: 357, 715–21.

5 Wollina U. The role of topical calcineurin inhibitors for skin diseases other than atopic dermatitis. *Am J Clin Dermatol* 2007; **8**: 157–73.

6 Alomar A, Puig L, Gallardo CM, Valenzuela N. Topical tacrolimus 0.1% ointment (Protopic®) reverses nickel contact dermatitis elicited by allergen challenge to a similar degree to mometasone furoate 0.1% with greater suppression of late erythema. *Contact Dermatitis* 2003; **49**: 185–8.

7 Roed-Petersen J, Thomsen K. Azathioprin in the treatment of airborne contact dermatitis from compositae oleoresins and sensitivity to UVA. *Acta Derm Venereol (Stockh)* 1980; **60**: 275–7.

8 Verma KK, Manchanda Y, Pasricha JS. Azathioprine as a corticosteroid sparing agent for the treatment of dermatitis caused by the weed *Parthenium*. *Acta Derm Venereol (Stockh)* 2000; **80**: 31–2.

9 Meggitt SJ, Reynolds NJ. Azathioprine for atopic dermatitis. *Clin Exp Dermatol* 2001; **26**: 369–75.

10 Anderson C, Groth O. Suppression of the allergic contact reaction in the guinea pig by cyclosporin A. *Int Arch Allergy Appl Immunol* 1985; **78**: 396–400.

11 Reitamo S, Granlund H. Cyclosporin A in the treatment of chronic dermatitis of the hands. *Br J Dermatol* 1994; **130**: 75–8.

12 Granlund H, Erkko P, Reitamo S. Long-term follow-up of eczema patients treated with cyclosporine. *Acta Derm Venereol (Stockh)* 1998; **78**: 40–3.

13 Kaaber K, Veien NK, Tjell JC. Low nickel diet in the treatment of patients with chronic nickel dermatitis. *Br J Dermatol* 1978; **98**: 197–201.

14 Gawkrodger DJ, Shuttler IL, Delves HT. Nickel dermatitis and diet: clinical improvement and a reduction in blood and urine nickel levels with a low-nickel diet. *Acta Derm Venereol (Stockh)* 1988; **68**: 453–5.

15 Veien NK, Hattel T, Laurberg G. Low nickel diet: an open, prospective trial. *J Am Acad Dermatol* 1993; **29**: 1002–7.

16 Veien NK, Hattel T, Justesen O, Norholm A. Reduction of intake of balsams in patients sensitive to balsam of Peru. *Contact Dermatitis* 1985; **12**: 270–3.

17 Veien NK, Hattel T, Laurberg G. Can oral challenge with balsam of Peru predict possible benefit from a low-balsam diet? *Am J Contact Dermatitis* 1996; **7**: 84–7.

18 Menné T, Kaaber K, Tjell JC. Treatment of nickel dermatitis. The influence of tetraethylthiuramdisulfide (Antabuse) on nickel metabolism. *Ann Clin Lab Sci* 1980; **10**: 160–4.

19 Burrows D, Rogers S, Beck M *et al*. Treatment of nickel dermatitis with Trientine. *Contact Dermatitis* 1986; **15**: 55–7.

20 Sharma AD. Disulfiram and low nickel diet in the management of hand eczema: a clinical study. *Indian J Dermatol Venereol Leprol* 2006; **72**: 113–8.

21 Lamey PJ, Lamb AB, Hughes A *et al*. Type 3 burning mouth syndrome: psychological and allergic aspects. *J Oral Pathol Med* 1994; **23**: 216–9.

22 Morton CA, Garioch J, Todd P *et al*. Contact sensitivity to menthol and peppermint in patients with intra-oral symptoms. *Contact Dermatitis* 1995; **32**: 281–4.

23 Shah M, Lewis F, Gawkrodger DJ. Contact allergy in patients with oral symptoms: a study of 47 patients. *Am J Contact Dermatitis* 1996; **7**: 146–51.

24 Armstrong DK, Biagioni P, Lamey PJ *et al*. Contact hypersensitivity in patients with orofacial granulomatosis. *Am J Contact Dermatitis* 1997; **8**: 35–8.

25 Gupta G, Forsyth A. Allergic contact reactions to colophony presenting as oral disease. *Contact Dermatitis* 1999; **40**: 332–3.

26 van Loon LA, Bos JD, Davidson CL. Clinical evaluation of fifty-six patients referred with symptoms tentatively related to allergic contact stomatitis. *Oral Surg Oral Med Oral Pathol* 1992; **74**: 572–5.

27 Helton J, Storrs F. The burning mouth syndrome: lack of a role for contact urticaria and contact dermatitis. *J Am Acad Dermatol* 1994; **31**: 201–5.
28 Lindelof B, Wrangso K, Lidén S. A double-blind study of Grenz ray therapy in chronic eczema of the hands. *Br J Dermatol* 1987; **117**: 77–80.
29 King CM, Chalmers RJ. A double-blind study of superficial radiotherapy in chronic palmar eczema. *Br J Dermatol* 1984; **111**: 451–4.
30 Lindelof B, Lidén S, Lagerholm B. The effect of grenz rays on the expression of allergic contact dermatitis in man. *Scand J Immunol* 1985; **21**: 463–9.
31 Sheehan-Dare RA, Goodfield MJ, Rowell NR. Topical psoralen photochemotherapy (PUVA) and superficial radiotherapy in the treatment of chronic hand eczema. *Br J Dermatol* 1989; **121**: 65–9.
32 Sjovall P, Christensen OB. Treatment of chronic hand eczema with UV-B Handylux in the clinic and at home. *Contact Dermatitis* 1994; **31**: 5–8.
33 Rosen K, Mobacken H, Swanbeck G. Chronic eczematous dermatitis of the hands: a comparison of PUVA with UVB treatment. *Acta Derm Venereol (Stockh)* 1987; **67**: 48–54.
34 Simons JR, Bohnen IJ, van der Valk PG. A left–right comparison of UVB phototherapy and topical photochemotherapy in bilateral chronic hand dermatitis after 6 weeks' treatment. *Clin Exp Dermatol* 1997; **22**: 7–10.
35 Burke DA, Corey G, Storrs FJ. Psoralen plus UVA protocol for Compositae photosensitivity. *Am J Contact Dermatitis* 1996; **7**: 171–6.
36 Fowler JF Jr. A skin moisturizing cream containing quaternium-18-bentonite effectively improves chronic hand dermatitis. *J Cutan Med Surg* 2001; **5**: 201–5.
37 Wohrl S, Kriechbaumer N, Hemmer W *et al*. A cream containing the chelator DTPA (diethylenetriaminepenta-acetic acid) can prevent contact allergic reactions to metals. *Contact Dermatitis* 2001; **44**: 224–8.
38 Memon AA, Molokhia MM, Friedmann PS. The inhibitory effects of topical chelating agents and antioxidants on nickel-induced hypersensitivity reactions. *J Am Acad Dermatol* 1994; **30**: 560–5.
39 Gruvberger B, Bruze M. Can glutathione-containing emollients inactivate methylchloroisothiazolinone/methylisothiazolinone? *Contact Dermatitis* 1998; **38**: 261–5.
40 Sjovall P, Christensen OB. Oral hyposensitization in allergic contact dermatitis. *Semin Dermatol* 1990; **9**: 206–9.
41 Chase MW. Inhibition of experimental drug allergy by prior feeding of the sensitizing agent. *Proc Soc Exp Biol Med* 1946; **61**: 257–9.
42 Polak L, Frey JR. Studies on contact hypersensitivity to chromium in the guinea pig. *Int Arch Allergy Appl Immunol* 1973; **44**: 51–61.
43 Epstein WL. The poison ivy picker of Pennypack Park: the continuing saga of poison ivy. *J Invest Dermatol* 1987; **88** (Suppl. 3): 7S–11S.
44 Watson ES. *Toxicodendron* hyposensitization programs. *Clin Dermatol* 1986; **4**: 160–70.
45 Handa S, Sahoo B, Sharma VK. Oral hyposensitization in patients with contact dermatitis from *Parthenium hysterophorus*. *Contact Dermatitis* 2001; **44**: 279–82.

Prognosis

The prognosis of allergic contact dermatitis depends on its cause and the feasibility of avoiding repeated or continued exposure to the causative allergen. Associated irritant dermatitis and constitutional factors are also important. Some studies suggest age of onset is not important prognostically for occupational dermatitis but others suggest a poorer outlook in older age [1,2]. In the USA, patients with allergic contact dermatitis tended to have a poorer quality of life if they were non-Caucasian, younger or industrial workers, but gender was not important [3]. In Sweden, skin atopy was the factor that carried the worst outlook, followed by contact allergy, especially to nickel, and female sex [2].

The prognosis is generally relatively poor for those allergic to nickel [4] and chromate [5], probably as a result of their ubiquity in the environment, even though most chromate studies have involved those with occupational dermatitis, which is a selective group. It has been suggested that dietary nickel [6] and chromate [7] exposure might be responsible for the chronicity, but this is disputed [8]. There is a better outlook for those allergic to materials that are easy to identify and avoid, and often the dermatitis will resolve within a few weeks if conscientious avoidance measures are taken. This was exemplified by a European joint study where the sources of contact with allergens could be traced in only 35% of those who reacted to colophony, but in 85% of those sensitive to tetramethylthiuram disulphide. The reason for the limited success with colophony was probably lack of knowledge of the sources of this sensitizer [9]. However, in a small Australian study, workers with epoxy resin allergy had a worse outlook than might be expected in spite of avoidance [10]. Greater age, associated atopy, and longer duration and severity of dermatitis, at diagnosis correlated with poorer prognosis in this survey. It is clear from a number of other studies that poor compliance and understanding results in a higher rate of ongoing exposure to the causative allergen, and is associated with a worse prognosis [11–13]. A better knowledge of their condition, and early diagnosis and treatment, are also factors which should improve the prognosis and reduce the costs of occupational dermatitis [1].

As the skin integrity is compromised, there are enhanced opportunities for new sensitivities to medicaments or other substances to develop during the course of dermatitis. Sensitivity to rubber gloves may complicate pre-existing dermatitis of the hands. Such allergies are revealed only by repeat patch tests. During a long course of relapsing dermatitis, sensitivity to various allergens may accumulate, and this increases the risk of recurrence or persistence [14].

Contact dermatitis of the hands is often of mixed origin, with alternating or simultaneous exposure to allergens and irritants. In one study of the prevalence of dermatitis of the hands, half the patients had suffered from their dermatitis for more than 5 years. Follow up after 6–22 months revealed one-quarter had healed completely, half had improved and one-quarter were unchanged or worse. There was no difference in prognosis between irritant and allergic dermatitis [15]. A change of occupation does not necessarily alter the prognosis of occupational hand dermatitis [16–21]. The concept of persistent post-occupational dermatitis despite avoidance of the original cause(s) is now well established, and may occur following both irritant and allergic contact dermatitis [20,22].

Once acquired, contact sensitivity tends to persist [23]. The degree of sensitivity may decline unless boosted by repeated exposure, but with a high initial level of sensitivity it often remains demonstrable even several years later [24]. Sensitivity to ubiquitous allergens, such as nickel and chromate [25], and to strong allergens, such as primin and PPD [26], is reported to persist, whereas sensitivity to other weaker and avoidable allergens may disappear. Patterns of cross-sensitization tend to persist [26].

Relapse or chronicity is due not only to unavoidable or unrecognized re-exposure to allergens and irritants but also to other contributory mechanisms.

1 The barrier function of the skin is impaired for months after an attack of dermatitis. Recovery is prevented by exposure to allergens or irritants in concentrations that might well be tolerated by normal skin.

2 Inappropriate treatment, including the overzealous use of cleansers and antiseptics, and the use of sensitizing popular or herbal remedies may also prolong the course of dermatitis.
3 Ingestion of allergens.
4 Secondary infection, especially with dermatitis of the hands. Microbial allergy may also be a factor in some eczemas [9].
5 Contact sensitivity has been thought in some cases to involve sensitization to the protein moiety ('protigen') of the hapten–protein conjugate. On this assumption, autosensitization might account for chronicity [27].
6 Stress is common in chronic dermatitis and may be both a consequence of and a trigger for eczema.
7 Constitutional factors predispose to chronicity.
8 There appears to be an 'inherent tendency' in almost any eczema to become continuous and chronic, but the factors causing this are unknown [28].

References

1 Cahill J, Keegel T, Nixon R. The prognosis of occupational contact dermatitis in 2004. *Contact Dermatitis* 2004; **51**: 219–26.
2 Meding B, Lantto R, Lindahl G *et al*. Occupational skin disease in Sweden—a 12-year follow-up. *Contact Dermatitis* 2005; **53**: 308–13.
3 Kadyk DL, Hall S, Belsito DV. Quality of life of patients with allergic contact dermatitis: an exploratory analysis by gender, ethnicity, age, and occupation. *Dermatitis* 2004; **15**: 117–24.
4 Christensen OB. Prognosis in nickel allergy and hand eczema. *Contact Dermatitis* 1982; **8**: 7–15.
5 Halbert AR, Gebauer KA, Wall LM. Prognosis of occupational chromate dermatitis. *Contact Dermatitis* 1992; **27**: 214–9.
6 Kaaber K, Veien NK, Tjell JC. Low nickel diet in the treatment of patients with chronic nickel dermatitis. *Br J Dermatol* 1978; **98**: 197–201.
7 Kaaber K, Veien NK. The significance of chromate ingestion in patients allergic to chromate. *Acta Derm Venereol (Stockh)* 1977; **57**: 321–3.
8 Burrows D. Prosser White Oration. Mischievous metals: chromate, cobalt, nickel and mercury. *Clin Exp Dermatol* 1989; **14**: 266–72.
9 Fregert S, Hjorth N, Magnusson B *et al*. Epidemiology of contact dermatitis. *Trans St John's Hosp Dermatol Soc* 1969; **55**: 17–35.
10 Cahill J, Keegel T, Dharmage S. Prognosis of contact dermatitis in epoxy resin workers. *Contact Dermatitis* 2005; **57**: 147–53.
11 Holness DL, Nethercott JR. Is a worker's understanding of their diagnosis an important determinant of outcome in occupational contact dermatitis? *Contact Dermatitis* 1991; **25**: 296–301.
12 Kalimo K, Lammintausta K, Jalava J *et al*. Is it possible to improve the prognosis in nickel contact dermatitis? *Contact Dermatitis* 1997; **37**: 121–4.
13 Agner T, Flyvholm MA, Menné T. Formaldehyde allergy: a follow-up study. *Am J Contact Dermatitis* 1999; **10**: 12–7.
14 Moss C, Friedmann PS, Shuster S, Simson JM. Susceptibility and amplification of sensitivity in contact dermatitis. *Clin Exp Immunol* 1985; **61**: 232–41.
15 Agrup G. Hand eczema and other hand dermatoses in South Sweden. *Acta Derm Venereol Suppl (Stockh)* 1969: **61**.
16 Fregert S. Occupational dermatitis in a 10-year material. *Contact Dermatitis* 1975; **1**: 96–107.
17 Cronin E. Dermatitis of the hands in caterers. *Contact Dermatitis* 1987; **17**: 265–9.
18 Pryce DW, Irvine D, English JS *et al*. Soluble oil dermatitis: a follow-up study. *Contact Dermatitis* 1989; **21**: 28–35.
19 Hogan DJ, Dannaker CJ, Maibach HI. The prognosis of contact dermatitis. *J Am Acad Dermatol* 1990; **23**: 300–7.
20 Wall LM, Gebauer KA. A follow-up study of occupational skin disease in Western Australia. *Contact Dermatitis* 1991; **24**: 241–3.
21 Shah M, Lewis FM, Gawkrodger DJ. Prognosis of occupational hand dermatitis in metalworkers. *Contact Dermatitis* 1996; **34**: 27–30.
22 Sajjachareonpong P, Cahill J, Keegel T. Persistent post-occupational dermatitis. *Contact Dermatitis* 2004; **51**: 278–83.
23 Ayala F, Balato N, Lembo G *et al*. Statistical evaluation of the persistence of acquired hypersensitivity by standardized patch tests. *Contact Dermatitis* 1996; **34**: 354–8.
24 Valsecchi R, Ross A, Bigardi A, Pigatto PD. The loss of contact sensitization in man. *Contact Dermatitis* 1991; **24**: 183–6.
25 Thormann J, Jesperson NB, Joensen HD. Persistence of contact allergy to chromium. *Contact Dermatitis* 1979; **5**: 261–5.
26 Fisher AA, Prelzig A, Kanof NB. The persistence of allergic eczematous sensitivity and the cross-sensitivity pattern to paraphenylenediamine. *J Invest Dermatol* 1958; **30**: 9–12.
27 Williams J, Cahill J, Nixon R. Occupational autoeczematization or atopic eczema precipitated by occupational contact dermatitis? *Contact Dermatitis* 2007; **56**: 21–6.
28 Calnan CD. Studies in contact dermatitis: XXII. Chronicity. *Trans St John's Hosp Dermatol Soc* 1968; **54**: 170–7.

Immune contact urticaria

Contact urticaria may be non-immune, or immune due to IgE antibodies against protein peptides. Rarely, low-molecular-weight chemicals may induce an allergic reaction. Immune contact urticaria is commoner in, but not exclusive to, atopic individuals [1,2].

Pathogenesis

The pathogenesis of urticaria is discussed in more detail in Chapter 22. In a previously sensitized individual, the protein allergens react with IgE molecules on mast-cell membranes, releasing vasoactive substances, including histamine. In addition to atopy, the presence of a pre-existing dermatitis predisposes to the development of allergic contact urticaria due to the presence of 'danger signals' that promote sensitization.

It has been reported that patients with atopic dermatitis and raised IgE levels have IgE on the surface of Langerhans' cells. This does not occur in atopic individuals with normal IgE levels or non-atopic controls [3,4]. This may explain why patients with atopic dermatitis have delayed hypersensitivity on patch testing to aeroallergens and develop a vesicular response to handling food proteins (protein contact dermatitis).

References

1 Wakelin SH. Contact urticaria. *Clin Exp Dermatol* 2001; **26**: 132–6.
2 Lahti A, Basketter D. Immediate contact reactions. In: Frosch PJ, Menné T, Lepoittevin J-P, eds. *Contact Dermatitis*, 4th edn. Berlin: Springer, 2006: 83–96.
3 Reitamo S, Visa K, Kahonen K *et al*. Eczematous reactions in atopic patients caused by epicutaneous testing with inhalant allergens. *Br J Dermatol* 1986; **114**: 303–9.
4 Barker JNWN, Alegre VA, McDonald DM. Surface bound immunoglobulin E on antigen-presenting cells in cutaneous tissue of atopics. *J Invest Dermatol* 1988; **90**: 117–21.

Clinical features

The symptoms usually occur within 1 h and fade by 3 h. The spectrum of associated symptoms is wide. Local symptoms are itching and burning, with the development of erythema and the characteristic weal and flare reaction. Early symptoms are commonly missed by physicians although well recognized by patients.

Exposure to allergens in those who are highly sensitized, topically or via the oral or respiratory route, may result in widespread

Table 26.22 Cross-reactions between foods causing contact urticaria. (From Sicherer [3].)

Food type	Risk (%)	Cross-reaction
Fish, e.g. salmon	5	Other fish, e.g. swordfish, sole
Grain, e.g. wheat	20	Other grains, e.g. barley, rye
Peach	55	Other Rosaceae fruit, e.g. apple, pear, cherry, plum
Melon (cantaloupe)	92	Watermelon, banana, avocado
Fruit (kiwi, avocado, banana)	11	Latex

urticaria and swelling of mucous membranes, resulting in conjunctivitis, rhinitis, oropharyngeal swelling, bronchoconstriction and anaphylaxis.

Contact urticaria to foodstuffs

The commonest causes of contact urticaria are foodstuffs, which can provoke orolaryngeal symptoms (the oral allergy syndrome) from ingestion, or hand symptoms in food handlers. The oral allergy syndrome results from eating raw/uncooked fruit and vegetables. Perioral symptoms are caused by heat-labile proteins that typically cross-react with aeroallergens [1]. In Scandinavia there is a strong association between the incidence of birch-pollen allergy and contact urticaria to fruit and vegetables, which is due to the presence of similar peptides [2]. Birch pollen is a common aeroallergen in Scandinavia, whereas in the UK the commonest aeroallergens are house-dust mite antigen and grass pollen, which may explain why there are fewer reports of contact urticaria in food handlers in the UK. If contact urticaria is confirmed there are recognized cross-reactions between various foodstuffs [3] (Table 26.22).

In an occupational setting contact urticaria frequently develops in those who are exposed to animals, such as agricultural workers, fish processors [4] and slaughterhouse workers, or are involved in food production [5], such as bakers and chefs. In Scandinavia, the commonest cause of occupational contact urticaria is from cow dander in farmers [6]. Of those exposed to contact allergic urticants, bakers, butchers and agricultural workers appear to be most at risk of becoming sensitized, more so than health-care workers.

Contact urticaria to natural rubber latex [7,8]

Allergy to natural rubber latex was first recognized in 1979 by Nutter. It has become a major health-care issue. The allergens are present in the water-soluble protein moiety of the sap collected from the rubber-bearing tree *Hevea braziliensis*, harvested mainly in Malaya and South-East Asia. The problem has been associated primarily with dipped rubber items, that is those made by dipping a mould or former into a latex solution, such as gloves, condoms, balloons, dummies and teats, catheters and medical tubing. These items are vulcanized at a lower temperature than solid rubber products such as tyres, seals and gaskets.

With the advent of acquired immune deficiency syndrome (AIDS) and the huge increase in the use of latex examination gloves among health-care personnel, the production of inexpensive disposable natural rubber latex gloves escalated. During the production process, the natural rubber latex was not left to stand in holding tanks as long, the process was shortened by lower vulcanization temperatures, and there was less thorough washing of the final product [9]. All these measures led to an increase in the protein content of the gloves and this, coupled with their increasing use, resulted in an increase in the incidence of allergy to natural rubber latex.

Natural rubber latex allergens are adsorbed on the maize starch powder on latex rubber gloves, and are released into the air when packets are opened or gloves are pulled out of multipack boxes. The allergens contaminate the air, and in operating theatres with recirculated air systems they can be spread to the whole theatre suite and cause unsuspected problems. The use of powder-free gloves prevents contamination of the environment and the development of symptoms in already sensitized individuals [10].

Anaphylaxis can occur in any sensitized patients, and seems to be particularly prevalent when challenge is via mucosal surfaces, as in dental and vaginal examinations, intraperitoneal operations, catheter changing (especially in spina bifida patients who have frequent surgery and catheter changes) and barium enemas.

The allergenic proteins are multiple. Many of the allergenic peptides in natural rubber latex cross-react with those found in other plants [11], such as banana, lychees, chestnuts and avocado, and patients allergic to latex may exhibit sensitivity to such foods. It is possible that some patients were first sensitized by the fruits and have a secondary allergy to latex.

Protein contact dermatitis [12,13]

Patients who have repeated exposure of the hands, especially the fingertips, to contact urticants, such as food proteins, may develop a vesicular eruption or protein contact dermatitis. Characteristically, the condition involves skin sites that have been affected previously by dermatitis. Damaged skin probably facilitates penetration of the allergens, and inflammatory cells already present in the dermis may explain the accelerated clinical response. Many patients have no other signs of atopy. Protein dermatitis is common in dairy workers and veterinarians, slaughterhouse workers, chefs and sandwich makers, who become sensitized to the proteins they touch during work. A similar situation has also been reported with latex, both with and without contact urticaria [14,15].

References

1 Mari A, Ballmer Webber BK, Vieths S. The oral allergy syndrome: improved diagnostic and treatment methods. *Curr Opin Allergy Clin Immunol* 2005; **5**: 267–73.

2 Halmepuro L, Vuentela K, Kalimo K *et al*. Cross-reactivity of IgE antibodies with allergens in birch pollen, fruits and vegetables. *Int Arch Allergy Appl Immunol* 1984; **74**: 235–40.

3 Sicherer SH. Clinical implications of cross-reactive food allergens. *J Allergy Clin Immunol* 2001; **108**: 881–90.

4 Kanerva L, Susitaival P. Cow dander: the most common cause of occupational contact urticaria in Finland. *Contact Dermatitis* 1996; **35**: 309–10.

5 Jeebhay MF, Robbins TG, Lehrer SB, Lopata AL. Occupational seafood allergy: a review. *Occup Environ Med* 2001; **58**: 553–62.

6 Chan EF, Mowad C. Contact dermatitis to foods and spices. *Am J Contact Dermatitis* 1998; **9**: 71–9.

7 Reunala T, Alenius H, Turjanmaa K, Palosuo T. Latex allergy and skin. *Curr Opin Allergy Clin Immunol* 2004; **4**: 397–401.

8 Bousquet J, Flahault A, Vandenplas O *et al*. Natural rubber latex allergy among health care workers: a systematic review of the evidence. *J Allergy Clin Immunol* 2006; **118**: 447–54.

9 Dalrymple SJ, Audley BG. Allergenic proteins in dipped rubber products: factors influencing extractable protein levels. *Rubber Dev* 1992; **45**: 51–60.
10 Allmers H, Brehler R, Chen Z *et al*. Reduction of latex aeroallergens and latex-specific IgE antibodies in sensitized workers after removal of powdered natural rubber latex gloves in a hospital. *J Allergy Clin Immunol* 1998; **102**: 841–6.
11 Blanco C. Latex-fruit syndrome. *Curr Allergy Asthma Rep* 2003; **3**: 47–53.
12 Doutre MS. Occupational contact urticaria and protein contact dermatitis. *Eur J Dermatol* 2005; **15**: 419–24.
13 Janssens J, Morren M, Dooms-Goossens A, DeGreef H. Protein contact dermatitis: myth or reality? *Br J Dermatol* 1995; **132**: 1–6.
14 Sommer S, Wilkinson SM, Beck MH *et al*. Type IV hypersensitivity reactions to natural rubber latex: results of a multicentre study. *Br J Dermatol* 2002; **146**: 114–7.
15 Gottlober P, Gall H, Peter RU. Allergic contact dermatitis from natural latex. *Am J Contact Dermatitis* 2001; **12**: 135–8.

Investigations

Testing is usually performed by a scratch patch test (or a prick test) to the food in question. A small piece of the substance is applied on a closed patch test to an area of skin. The skin may be lightly scarified with a needle or degreased with 96% alcohol [1]. After 20 min the area is examined for erythema or weal and flare. Sometimes, the patient will state that the symptoms are being reproduced well before the end of the test time. Occasionally, there is no reaction on normal skin and the substance has to be applied to previously affected skin, for example the fingertips. Skin testing should be performed with appropriate positive and negative controls. With an unknown allergen, exposure should be graded with initially an application test (open and subsequently occluded) followed by a prick test and, if appropriate, an intradermal test. Although commercial allergen extracts are available, it should be remembered that unless standardized they may not contain the relevant protein allergens, and the gold standard should always be test and challenge with a sample of fresh material. Skin tests should only be performed where resuscitation facilities are available.

If the patient has experienced an anaphylactic reaction and a specific IgE test is available, the blood test may confirm the diagnosis and thus avoid the risk of anaphylaxis as a result of skin tests.

In the case of latex, the specific IgE test is not sensitive and a negative test does not exclude the diagnosis. Although skin tests with glove extracts have been recommended, many gloves now contain low levels of latex protein and prick testing with home-made extracts frequently gives false-negative results. Prick test solutions for latex are commercially available, some of which claim greater than 98% sensitivity and 100% specificity. The final arbiter is a usage test in which a patient wears the suspect glove on a moistened hand and any reaction is observed.

Localized symptomatic dermographism is a common cause of urticaria to gloves in the absence of latex allergy [2]; contact urticaria to rubber chemicals is extremely rare [3].

References

1 Oranje AP, Van Gysel D, Mulder PGH *et al*. Food-induced contact urticaria syndrome (CUS) in atopic dermatitis: reproducibility of repeated and duplicate testing with a skin provocation test, the skin application food test (SAFT). *Contact Dermatitis* 1994; **31**: 314–8.
2 Thomson KF, Wilkinson SM. Localised dermographism: a differential diagnosis of latex glove allergy. *Contact Dermatitis* 1999; **41**: 103–4.
3 Brehler R, Sedlmayr S. Contact urticaria due to rubber chemicals? *Contact Dermatitis* 1997; **37**: 125–7.

Management

Management is by means of avoidance or the use of appropriate personal protective equipment, as desensitization for the majority of allergens concerned is not available. In the case of latex, immunotherapy is being developed [1], although most studies have yet to show significant improvement in symptoms with minimal side effects. Avoidance measures are required for latex articles, especially rubber gloves, condoms, balloons, pacifiers, catheters and other medical tubing. Treatment of the acute episode includes the use of systemic antihistamines and epinephrine (adrenaline), depending on the severity of the attack.

In the case of latex, the use of a 'Medic-alert' type bracelet will warn health-care workers should a patient be taken to casualty unconscious. The management of the latex-sensitized individual in the hospital environment can be a particular problem due to the widespread use of natural rubber latex products. Most hospitals are now aware of the problem and maintain a latex-free environment when treating such individuals. Examinations and interventional surgical and radiographic procedures should not be undertaken with latex gloves or equipment.

A change to low-protein gloves has been associated with a reduction in the prevalence of latex induced contact urticaria and asthma among health-care workers [2].

References

1 Rolland JM, Drew AC, O'Hehir RE. Advances in development of hypoallergenic latex immunotherapy. *Curr Opin Allergy Clin Immunol* 2005; **5**: 544–51.
2 Allmers H, Schmengler J, John SM. Decreasing incidence of occupational contact urticaria caused by natural rubber latex allergy in German health care workers. *J Allergy Clin Immunol* 2004; **114**: 347–51.

Acknowledgement. The authors wish to acknowledge the contributions of Dr J.D. Wilkinson and Dr S. Shaw who wrote the chapter entitled 'Contact Dermatitis: Allergic', and Dr R.J.G. Rycroft who wrote the chapter entitled 'Principal Irritants and Sensitizers', in the 6th edition of this textbook.

CHAPTER 27
Occupational Dermatoses

J.S.C. English
Queen's Medical Centre, University Hospital, Nottingham, UK

Eczematous dermatoses, 27.1
Epidemiology, 27.1
Diagnosis, 27.4
Occupational contact urticaria, 27.5
Occupational irritant contact dermatitis, 27.5
Occupational physical irritant contact dermatitis, 27.6
Occupational allergic contact dermatitis, 27.7
Investigations, 27.7
Prognosis, 27.9
Prevention, 27.9
Assessment of dermatitic potential, 27.10
Non-eczematous occupational dermatoses, 27.11
Chemical burns, 27.11
Acne of external chemical origin, 27.12
Chemical depigmentation, 27.15
Occupationally-induced skin tumours, 27.15
Scleroderma and related diseases, 27.16
Vibration white finger, 27.17
Medicolegal aspects of occupational dermatoses, 27.17
Specific occupational hazards, 27.18

Eczematous dermatoses

The occupational aspects of dermatology have attracted increasing attention [1–13]. This has been reflected in the establishment in many countries of special departments of occupational dermatology [3,6]. Full-time and part-time appointments in occupational dermatology now exist in many countries [3]. Occupational dermatoses are common enough and sufficiently disabling to demand a wide knowledge from dermatologists of the noxious agents in various occupations, as well as an understanding of the workings of compensation systems.

Epidemiology

In many countries, loss of income due to occupational illness is compensated more fully than economic hardship from other diseases. Because of the public expenditure involved, governmental and legal definitions of an occupational dermatosis do not always agree with medical concepts.

A medical definition adopted by the Committee on Occupational Dermatoses of the American Medical Association (1939) was: 'An occupational dermatosis is a pathological condition of the skin for which occupational exposure can be shown to be a major causal or contributory factor.' This definition, although comprehensive, does not address the question of attributability to occupation rigorously enough for all purposes. Many dermatologists prefer to limit their concept of occupational dermatoses to 'a skin disease, which would not have occurred if the patient had not been doing the work of that occupation' [4].

In practice, lack of knowledge and of diagnostic tests often makes the diagnosis of occupational dermatoses very difficult [4]. Evidence in favour of an occupational origin is [14–17]:

1 Occupational contact with an agent known to have caused similar skin changes in other individuals.
2 Occurrence of similar dermatoses in fellow workers or within the same occupation.
3 Correct time relationship between exposure and dermatitis.
4 Type and site of lesions consistent with information of exposure, and similar to other cases.
5 Attacks of dermatitis appearing after exposure, followed by improvement or clearing after exposure ceases.
6 History and examination corroborated by patch (or sometimes skin-prick) test results.

The legal definitions of occupational dermatosis vary considerably from one country to another [18]. In the UK, the majority of occupational dermatoses are defined by Prescribed Disease D5 of the Department of Social Security as 'non-infective dermatitis of external origin (including chrome ulceration of the skin but excluding dermatitis due to ionizing particles or electromagnetic radiations other than radiant heat)'. The disadvantage of this type of definition is that it may exclude certain newly recognized occupational dermatoses, so that these require their own additional definitions. This was necessary in the UK in the case of occupationally acquired hypomelanosis (Prescribed Disease C25) (Chapter 58).

In the assessment of individual cases, the legal attitude revolves around whether the patient could reasonably have been expected to contract the disease if he or she had not been engaged in that particular occupation and type of work [19,20]. In the UK, the compensation that may be obtainable through a legal action is of a higher order of magnitude than that provided by the state system. Patients therefore will frequently seek both forms of compensation. In other European countries, the equivalent regulations vary [18]. Most include infections such as ringworm. Some traditionally reserve compensation for conditions and causative agents specifically listed. This practice is gradually being abandoned because, in a period of rapid industrial progress, any list of substances proves too restrictive. In some countries, only some employees

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

are covered by the compensation laws, and self-employed persons are excluded. In spite of its frequency and chronicity, housewives' dermatitis receives no legal compensation.

Outside the workplace, the worker is exposed to the same risk of contact dermatitis as anyone else in the community. Contact dermatitis is therefore not necessarily of occupational origin. Dermatologists demur at the popular terminological identification of 'dermatitis' with 'occupational dermatitis'. A dermatitis that primarily originates from occupational exposure is influenced by many other factors. A number of problems cause legal dispute:

1 Constitutional factors [21]. Most manufacturing processes cause dermatitis in certain workers only. If others similarly exposed remain healthy, those whose skin breaks down must have a lower resistance. Such a lowered resistance to contact irritants may be present in patients with previous atopic dermatitis [22] or in those with dry, seborrhoeic or fair skin [21]. Accordingly, any occupational contact dermatitis presupposes a certain constitutional predisposition and usually only occurs in a minority of the workforce. This has to be taken into account in deciding whether, in an attack of dermatitis, an occupational trauma is sufficient to be considered as a major causal factor or only as a contributory factor. A young person with previous atopic dermatitis may do office work with impunity, but if apprenticed as a hairdresser is likely to develop dermatitis. Similarly, a young atopic person runs a great risk of dermatitis if working in a coal mine [23]. It may be beyond dispute that dermatitis would not have developed in occupations suitable for the particular person, but medical and legal opinions are still divided over the justification of compensation to young people with constitutional eczema and occupational dermatitis. Similar constitutional factors may be implicated in the middle-aged group, but as they cannot yet be identified they do not disqualify.
2 Sensitization to medicaments prescribed or self-prescribed for occupational dermatitis inevitably occurs in some cases and fragrance in this situation is considered to be an occupational allergen [24]. This complication must be regarded as a sequel of disease, just as is secondary infection. Problems arise from late relapses due to repeated contact with the same medicaments.
3 Sensitization in private life, with relapse of dermatitis from occupational exposure (e.g. dermatitis of the hands from contact with nickel in patients sensitized by nickel in jewellery [17]; formaldehyde dermatitis in patients sensitized by textiles).
4 Primary occupational dermatitis, with chronicity maintained by private activity [25]. For example, to relieve the strain of inactivity, some workers resort to do-it-yourself work during sick leave (perhaps involving exposure to cement, paint, solvents, etc.), and housework is unavoidable.
5 The contributions of factors broadly grouped under the term 'stress' cannot be dismissed, but are usually difficult to assess [26]. It is accepted by many dermatologists that episodes of stress may be an aggravating factor in both irritant and allergic contact dermatitis and may even contribute to their initial onset.

Incidence

Most available incidence statistics are unsuitable for comparison. Some do not distinguish between occupational accidents and illnesses; others fail to separate dermatitis from other skin conditions. Few give information on short periods of absence from work or on dermatitis without disability, and most are based on compensation paid. However, the ongoing UK EPIDERM and the BKH-S surveillance schemes are addressing the epidemiology of occupational contact skin reactions [27,28]. Dermatitis was the predominant cutaneous reaction (73.5%), compared with urticaria (3.3%), infective conditions (21.7%) and neoplasia (18.0%) [27]. Recent findings show that skin diseases rank second (29%) to musculoskeletal conditions (57%) as causes of occupational disease [27]. The frequency of work-related skin reactions has been looked at in various occupational groups (Table 27.1).

Table 27.1 Occupations with the highest risk (rate/100 000 employed per year)—using labour force survey data as the denominator and cases of contact dermatitis reported to the UK EPIDERM survey as the numerator.

Occupation	Rate/100 000 per year
Hairdressers	120
Printers	71
Machine tool operators	56
Chemical, gas and petroleum plant operatives	45
Car assemblers	35
Machine tool setters	34

The introduction of new chemicals may have increased the incidence of industrial dermatitis, but such a trend is counteracted by preventive and educational measures. The total number affected has increased, as the number of persons employed in industry has risen. In a population sample from an industrial city, the overall 1-year period prevalence of hand eczema was 11.8% [29]. Hand eczema was significantly more common among those reporting potentially harmful skin exposures, cleaners for example having a corresponding prevalence rate of 21.3%.

In a joint European study of consecutive clinic patients with dermatitis, 30% of the men and 12% of the women had occupational dermatitis [30].

Of all occupational diseases, dermatoses comprise from 20 to 70% in different countries, and of the dermatoses between 20 and 90% are contact dermatitis. The relative proportions are determined by the extent and type of industrialization in an area, and certainly also by the skill and interest of dermatologists in contact dermatitis [30].

Age

Occupational dermatitis may occur at any age. The average age of onset varies from one occupation to another [7]. In some studies [31], two peaks appear, one at each end of working life. The young age group includes many patients with irritant and atopic dermatitis of the hands. Others find that the risk increases progressively with age [32].

Occupations

Certain industries and occupational groups contribute the majority of cases: in England and West Germany, hairdressers [26,27], and in Italy, bricklayers [33]. Agriculture, manufacturing and construction consistently head the list in the USA [34,35]. If the number

of persons exposed is taken into account, certain subgroups or departments of large industries have a particularly high risk of dermatitis [12]. A high chromium content in local cement may place building workers at the top of the list. Among 1071 building workers, 6% had occupational cement dermatitis and half of them were sensitized to chromium [36].

Certain high-risk groups may not be identified because the number employed is low. Thus, tilers were found to have a much higher risk than bricklayers when the number of cases seen was correlated with the number employed. Self-employed persons are rarely compensated and are therefore not registered. A high risk of dermatitis among veterinary surgeons thus escaped notice. The most common occupational contact dermatitis is probably housewives' dermatitis. In a Swedish public health examination, this affected approximately 1% of adult women. Thirty-eight per cent of these had allergic contact dermatitis [37].

Period of exposure

Bakers get their dermatitis early, bricklayers later in life [7]. In one study, chromium in primers caused dermatitis after an average exposure of 5–7 months [38]. Hairdressers generally develop dermatitis early in their career [7], but the number who leave hairdressing before the age of 30 years is considerable and many leave for reasons other than dermatitis [39].

No comprehensive statistics have analysed the sum total of factors determining occupational risks. Wagner and Wezel [40] have suggested an approach. They base their calculations of occupational risk on three factors:

1 The number of cases related to the number employed.
2 The average age of onset of occupational dermatitis.
3 The average period of work before onset.

Ideally, the number employed should be divided into age groups. All three factors vary independently. Many workers start a job late in life (e.g. unskilled labour in manufacturing industries) and develop their dermatitis rapidly. In others, dermatitis occurs after decades of work.

Clinical features

Occupational contact dermatitis has the same morphology as any other contact dermatitis, i.e. cumulative irritant, allergic and photocontact dermatitis. The regional distribution, however, differs considerably because occupational contact dermatitis is mainly on exposed parts. The hands are affected, alone or together with other sites, in 80–90% of all cases of occupational contact dermatitis [29]. Irritant contact dermatitis started under finger rings in 12% of women and 2% of men [41]. The arms are also involved, especially if not covered by sleeves. Dusts and vapours affect the face and neck. Cement workers and miners often have dermatitis on the lower legs and feet. Those wearing rubber boots may have dermatitis from footwear.

Irritants and sensitizers

The most important irritants and sensitizers encountered in different occupations are detailed at the end of this chapter. The relative importance of occupational noxious agents varies considerably in different reports. Irritants such as detergents, alkalis and organic solvents head the list [40]. Schwartz *et al*. [42], in an extensive investigation, found petroleum products and alkalis to be the most important. Dermatitis from synthetic resins, such as epoxy resins and acrylates, has become increasingly frequent in the last few decades. In most reports, cumulative irritant dermatitis is more common than the allergic type. Most authorities agree that the commonest sensitizer is chromium, but this should decrease in frequency over the next few years with the recently introduced EU chromium (VI) directive [43]. Because a cumulative irritant contact dermatitis increases the penetration of allergens, it may predispose to the development of a superimposed allergic contact dermatitis. Likewise, an allergic contact dermatitis may render the skin more vulnerable to attack by irritants.

References

1 Kanerva L, Elsner P, Wahlberg JE, Maibach HI. *Handbook of Occupational Dermatology*. Berlin: Springer, 2000.
2 Adams RM. *Occupational Skin Disease*, 3rd edn. Philadelphia: Saunders, 1999.
3 Calnan CD. Dermatology and industry. *Clin Exp Dermatol* 1978; **3**: 1–16.
4 Calnan CD, Rycroft RJG. Rehabilitation in occupational skin disease. *Trans Coll Med S Afr* 1981; **25** (Suppl. on Third Interdisciplinary Symposium: Rehabilitation): 136–42.
5 Foussereau J, Benezra C, Maibach HI. *Occupational Contact Dermatitis: Clinical and Chemical Aspects*. Copenhagen: Munksgaard, 1982.
6 Fregert S. The organization of occupational dermatology in Lund. *Acta Derm Venereol (Stockh)* 1963; **43**: 203–5.
7 Fregert S. Occupational dermatitis in a 10-year material. *Contact Dermatitis* 1975; **1**: 96–107.
8 Griffiths WAD, Wilkinson DS, eds. *Essentials of Industrial Dermatology*. Oxford: Blackwell Scientific Publications, 1984.
9 Stevenson CJ. Occupational diseases of the skin. In: Raffle PAB, Lee WR, McCallum RI, Murray R, eds. *Hunter's Diseases of Occupations*. London: Hodder and Stoughton, 1987: 917–48.
10 Taylor JS, ed. *Occupational Dermatoses*. Philadelphia: Saunders, 1988.
11 Zschunk E. *Grundriss der Arbeitsdermatologie*. Berlin: VEB Verlag Volk und Gesundheit, 1985.
12 Rycroft RJG. Occupational contact dermatitis. In: Rycroft RJG, Menné T, Frosch PJ, Lepoittevin J-P, eds. *Textbook of Contact Dermatitis*, 3rd edn. Berlin: Springer, 2001: 555–80.
13 Davies NF, Rycroft RJG. Dermatology. In: Fox RAF, Edwards FC, McCallum RI, eds. *Fitness for Work: the Medical Aspects*, 2nd edn. Oxford: Oxford University Press, 1995: 102–12.
14 Mathias CGT. Contact dermatitis and workers' compensation: criteria for establishing occupational causation and aggravation. *J Am Acad Dermatol* 1989; **20**: 842–8.
15 van de Walle HB, Piebenga WP. *Skin and Occupation*, 2nd edn. Arnhem: Centre of Skin and Occupation, 1999.
16 Rietschel RL. Patch testing in occupational hand dermatitis. *Dermatol Clin* 1988; **6**: 43–6.
17 Wilkinson DS. Some causes of error in the diagnosis of occupational dermatoses. In: Griffiths WAD, Wilkinson DS, eds. *Essentials of Industrial Dermatology*. Oxford: Blackwell Scientific Publications, 1985: 47–57.
18 Frosch PJ, Rycroft RJG. International legal aspects of contact dermatitis. In: Rycroft RJG, Menné T, Frosch PJ, Lepoittevin J-P, eds. *Textbook of Contact Dermatitis*, 3rd edn. Berlin: Springer, 2001: 995–1014.
19 Adams RM. Medicolegal aspects of occupational skin diseases. *Dermatol Clin* 1988; **6**: 121–9.
20 Bursell R. Principles in dermatitis legislation. In: Griffiths WAD, Wilkinson DS, eds. *Essentials of Industrial Dermatology*. Oxford: Blackwell Scientific Publications, 1985: 136–44.
21 Shmunes E. Predisposing factors in occupational skin diseases. *Dermatol Clin* 1988; **6**: 7–13.
22 Dickel H, Bruckner TM, Schmidt A *et al*. The impact of atopic skin diathesis on occupational skin disease incidence in a working population. *J Invest Dermatol* 2003; **121**: 37–40.

23 Puttick LM. *Skin Disorders in the Coal Mining Industry* [dissertation]. London: University of London, 1989.
24 Buckley DA, Rycroft RJ, White IR *et al*. Fragrance as an occupational allergen. *Occup Med* 2002; **52**: 13–6.
25 Wilkinson DS. Causes of unexpected persistence of an occupational dermatitis. In: Griffiths WAD, Wilkinson DS, eds. *Essentials of Industrial Dermatology*. Oxford: Blackwell Scientific Publications, 1985: 111–24.
26 Fjellner B, Arnetz BB, Eneroth P *et al*. Pruritus during standardized mental stress: relationship to psychoneuroendocrine and metabolic parameters. *Acta Derm Venereol (Stockh)* 1985; **65**: 199–205.
27 Turner S, Carder M, van Tongeren M *et al*. The incidence of occupational skin disease as reported to The Health and Occupation Reporting (THOR) network between 2002 and 2005. *Br J Dermatol* 2007; **157**: 713–22.
28 Dickel H, Bruckner T, Bernhard-Klimt C *et al*. Surveillance scheme for occupational skin disease in Saarland, FRG. First report from BKH-S. *Contact Dermatitis* 2002; **46**: 197–206.
29 Meding B, Swanbeck G. Occupational hand eczema in an industrial city. *Contact Dermatitis* 1990; **22**: 13–23.
30 Malten KE, Fregert S, Bandmann HJ *et al*. Occupational dermatitis in five European dermatology departments. *Berufsdermatosen* 1963; **11**: 181–244.
31 Campion KM, Rycroft RJG. A study of attenders at an occupational dermatology clinic. *Contact Dermatitis* 1993; **28**: 307.
32 Coenraads PJ, Foo SC, Phoon WO *et al*. Dermatitis in small-scale metal industries. *Contact Dermatitis* 1985; **12**: 155–60.
33 Meneghini CL, Rantuccio F, Riboldi A. Klinisch-allergologische Beobachtungen bei beruflichen ekzematösen Kontakt-Dermatosen. *Berufsdermatosen* 1963; **11**: 181–202, 280–93.
34 Mathias CGT, Morrison JH. Occupational skin disease, United States: results from the Bureau of Labor Statistics Annual Survey of Occupational Injuries and Illnesses, 1973 through 1984. *Arch Dermatol* 1988; **124**: 1519–24.
35 O'Malley M, Thun M, Morrison J *et al*. Surveillance of occupational skin disease using the supplementary data system. *Am J Ind Med* 1988; **13**: 291–9.
36 Wahlberg JE. Health-screening for occupational skin diseases in building workers. *Berufsdermatosen* 1969; **17**: 184–98.
37 Agrup G. Hand eczema and other hand dermatoses in South Sweden. *Acta Derm Venereol (Stockh)* 1969; **49** (Suppl. 69): 59.
38 Engel HO, Calnan CD. Chromate dermatitis from paint. *Br J Ind Med* 1963; **20**: 192–8.
39 Rivett J, Merrick C. Prevalence of occupational contact dermatitis in hairdressers. *Contact Dermatitis* 1990; **22**: 304–5.
40 Wagner G, Wezel G. Art und Häufigkeit hautschädigender Berufsnoxen in Schleswig-Holstein. Ergebnisse einer statistischen Analyse der von 1952–62 an der Universitäts-Hautklinik Kiel erstellten Gutachten über Berufsdermatosen. *Berufsdermatosen* 1966; **14**: 1–40.
41 Fregert S, Hjorth N, Magnusson B *et al*. Epidemiology of contact dermatitis. *Trans St John's Hosp Dermatol Soc* 1969; **55**: 17–35.
42 Schwartz L, Tulipan L, Birmingham DJ. *Occupational Diseases of the Skin*, 3rd edn. Philadelphia: Lea & Febiger, 1957.
43 Athavale p, Shum KW, Chen Y *et al*. Occupational dermatitis related to chromium and cobalt: experience of dermatologists (EPIDERM) and occupational physicians (OPRA) in the U.K. over an 11-year period (1993–2004). *Br J Dermatol* 2007; **157**: 518–22.

Diagnosis

The diagnostic approach to a suspected occupational dermatosis needs to be systematic. Most diagnostic difficulties arise from eczematous dermatoses [1]. Great care must be taken in the accurate distinction between contact dermatitis and endogenous eczema, and between irritant and allergic contact dermatitis. Skill is needed, not only in dermatology, but also in taking an occupational history [2,3], and in obtaining as detailed a picture as possible of what the patient actually does at work [4].

The clinical distinction on the hands, forearms or face between endogenous eczema, irritant contact dermatitis and allergic contact dermatitis is beset with pitfalls. Differences in distribution and morphology are useful guides, but dangerous to rely on uncritically. There is a tendency for irritant contact dermatitis to affect the dorsa of the hands (Fig. 27.1) and fingers (Fig. 27.2) and the finger webs, rather than the palms, and to be relatively devoid of vesicles. There is a tendency for vesicular eczema of the palms and sides of the fingers to be endogenous. However, certain irritants and allergens (Fig. 27.3) can produce a vesicular eczema of the palmar aspects of the hands and fingers, and both allergic contact dermatitis and endogenous eczema frequently involve the dorsal aspects of the hands, fingers and webs. Discs of eczema on the dorsa of the hands and forearms are frequently endogenous, but allergic contact dermatitis from chromium and cumulative irritant contact dermatitis can present in a very similar distribution (Fig. 27.1). Gross eyelid swelling usually indicates allergic contact dermatitis, but degrees of eyelid swelling can occur in both irritant contact dermatitis and endogenous eczema.



Fig. 27.1 Discoid pattern of irritant contact dermatitis from soluble oil.

It is difficult to overemphasize the importance of a sound working knowledge of occupational irritants, as well as allergens, and of patch testing, in overcoming these difficulties in clinical differentiation. It should be appreciated that hand eczemas, in particular, are often the joint outcome of endogenous, irritant, allergic and even general climatic factors, and may be partly occupational as well as wholly occupational or non-occupational. In identifying the primary and/or major cause of a contact dermatitis, antecedent and aggravating causes should not be neglected. Diagnosis of secondary bacterial infection in occupational contact dermatitis, for example, may allow significant improvement to be obtained with antibiotic therapy. Guidelines on the management of contact dermatitis have been formulated by the British Association of Dermatologists [5].



Fig. 27.2 Irritant contact dermatitis of the fingers in a printer.



Fig. 27.3 Allergic contact dermatitis from Compositae plants in a florist.

References

1 Freeman S. Diagnosis and differential diagnosis. In: Adams RM, ed. *Occupational Skin Disease*, 3rd edn. Philadelphia: Saunders, 1999: 189–207.

2 Guidotti TL, Cortez JH, Abraham HL *et al*. Taking the occupational history. Occupational and Environmental Health Committee of the American Lung Association of San Diego and Imperial Counties. *Ann Intern Med* 1983; **99**: 641–51.

3 Lee WR, McCallum RI. The occupational history. In: Raffle PAB, Lee WR, McCallum RI, Murray R, eds. *Hunter's Diseases of Occupations*. London: Hodder & Stoughton, 1987: 229–36.

4 Rycroft RJG. Occupational contact dermatitis. In: Rycroft RJG, Menné T, Frosch PJ, Lepoittevin J-P, eds. *Textbook of Contact Dermatitis*, 3rd edn. Berlin: Springer, 2001: 555–80.

5 Bourke J, Coulson I, English J. Guidelines of care for contact dermatitis. *Br J Dermatol* 2001; **145**: 877–85.

Occupational contact urticaria [1,2]

High-molecular-weight antigens such as proteins may induce specific immunoglobulin E (IgE) antibody production [3]. Many of these antigens can penetrate only thin skin or a defective skin surface. If the antigen and specific IgE antibodies bind to Fc receptors on the mast cells, these will release histamine and other mediators. The typical clinical picture is an urticarial reaction with erythema and oedema [1,2]. Contact urticaria can frequently be an occupational dermatosis [4,5]; immediate hypersensitivity to natural rubber latex in rubber gloves is an obvious example [6]. The epidemic of natural rubber latex allergy seen in the 1990s may be declining because of better recognition of the epidemic leading to the use of powder-free, low protein natural rubber gloves in healthcare settings [6,7].

Veterinarians exposed to amniotic fluid, and kitchen staff who have contact with uncooked food items, may develop protein contact dermatitis, a variant of contact urticaria [8].

References

1 Amin S, Lahti A, Maibach HI. *Contact Urticaria Syndrome*. Boca Raton, FL: CRC Press, 1997.

2 Ale SI, Maibach HI. Occupational contact urticaria. In: Kanerva L, Elsner P, Wahlberg JE, Maibach HI, eds. *Handbook of Occupational Dermatology*. Berlin: Springer, 2000: 200–16.

3 Hannuksela M. Mechanisms in contact urticaria. *Clin Dermatol* 1997; **15**: 619–22.

4 Kanerva L, Jolanki R, Estlander T. Occupational contact urticaria in numbers. In: Kanerva L, Elsner P, Wahlberg JE, Maibach HI, eds. *Handbook of Occupational Dermatology*. Berlin: Springer, 2000: 217–20.

5 Kanerva L, Susitaival P. Cow dander: the most common cause of occupational contact urticaria in Finland. *Contact Dermatitis* 1996; **35**: 309–10.

6 Clayton TH, Wilkinson SM. Contact dermatoses in healthcare workers: reduction in type I latex allergy in a U.K. centre. *Clin Exp Dermatol* 2005; **30**: 221–5.

7 Allmers H, Schmengler J, John SM. Decreasing incidence of occupational contact urticaria caused by natural rubber latex allergy in German health care workers. *J Allergy Clin Immunol* 2004; **114**: 347–51.

8 Hjorth N, Roed-Petersen J. Occupational protein contact dermatitis in food handlers. *Contact Dermatitis* 1976; **2**: 28–42.

Occupational irritant contact dermatitis [1–9]

Dermatitis from the type of metal-working fluid or coolant most commonly known in the UK as 'soluble oil' is a prime example of occupational contact dermatitis that is usually primarily, and frequently totally, of cumulative irritant (Chapter 25) rather than allergic causation [9–14]. Soluble oils are oil-in-water emulsions used to cool and lubricate metal-working and certain other industrial manufacturing operations [15]. Synthetic coolants are aqueous chemical solutions and can have similar effects on the skin. Both types of product contain numerous additives, some of which are potential sensitizers (especially biocides [16,17]), but it is the substantial content of surface-active agents as emulsifiers or wetting agents in coolants that appears to underlie their potential for skin irritation [15,18]. Synthetic coolants also contain traces of nitrosamines, formed by triethanolamine or diethanolamine reacting with nitrites. Although currently under evaluation as carcinogens, there is no evidence that nitrosamines in coolants are irritant or sensitizing to the skin.

Soluble oil dermatitis is typical of occupational irritant contact dermatitis in that it is cumulative and has a multifactorial aetiol-

ogy [11,12]. The degree of skin contact [19], individual susceptibility, machine type and control method [20], and biocide additions [21] are all important factors, in addition to the specification and condition of the metal-working fluid itself. Clinically, the dorsa of the hands, finger webs, wrists and forearms are predominantly affected [22] and the dermatitis can have a patchy distribution that mimics nummular eczema [12] (Fig. 27.1). This is also true of several other forms of occupational contact dermatitis, including cement dermatitis [23] and dermatitis from machine oil in hosiery workers [24]. There are two reports [25,26] of soluble oil dermatitis presenting as 'dyshidrotic' eczema; a similar pattern has been described from mechanical irritancy [27]. The prognosis is highly variable but may eventually be good even without a change of work [28].

Irritant contact dermatitis provoked by soluble oils and synthetic coolants is to be distinguished from oil acne, discussed later in relation to neat (or insoluble) non-aqueous cutting oils.

References

1 Fischer T. Prevention of irritant dermatitis. In: Adams RM, eds. *Occupational Skin Disease*. Philadelphia: Hanley and Belfus, 1986: 335–42.
2 Fregert S. *Manual of Contact Dermatitis*, 2nd edn. Copenhagen: Munksgaard, 1981: 55–62.
3 Frosch PJ. Irritant contact dermatitis. In: Frosch PJ, Dooms-Goossens A, Lachapelle J-M *et al*., eds. *Current Topics in Contact Dermatitis*. Berlin: Springer, 1989: 385–98.
4 Griffiths WAD, Wilkinson DS. Primary irritants and solvents. In: Griffiths WAD, Wilkinson DS, eds. *Essentials of Industrial Dermatology*. Oxford: Blackwell Scientific Publications, 1985: 58–72.
5 Goh CL. Irritant contact dermatitis. In: English JSC, ed. *A Colour Handbook of Occupational Dermatology*. London: Manson, 1998: 11–29.
6 Malten KE. Thoughts on irritant contact dermatitis. *Contact Dermatitis* 1981; **7**: 238–47.
7 Jungbauer FH, van der Vleuten P, Groothoff JW *et al*. Irritant hand dermatitis: severity of disease, occupational exposure to skin irritants and preventive measures 5 years after initial diagnosis. *Contact Dermatitis* 2004; **50**: 245–51.
8 Lisby S, Baadsgaard O. Mechanisms of irritant contact dermatitis. In: Rycroft RJG, Menné T, Frosch PJ, Lepoittevin J-P, eds. *Textbook of Contact Dermatitis*, 3rd edn. Berlin: Springer, 2001: 91–110.
9 Rycroft RJG. Occupational contact dermatitis. In: Rycroft RJG, Menné T, Frosch PJ, Lepoittevin J-P, eds. *Textbook of Contact Dermatitis*, 3rd edn. Berlin: Springer, 2001: 555–80.
10 De Boer EM, van Ketel WG, Bruynzeel DP. Dermatoses in metal workers, 1: irritant contact dermatitis. *Contact Dermatitis* 1989; **20**: 212–8.
11 Foulds IS, Koh D. Dermatitis from metalworking fluids. *Clin Exp Dermatol* 1990; **15**: 157–62.
12 Pryce DW, White J, English JSC *et al*. Soluble oil dermatitis: a review. *J Soc Occup Med* 1989; **39**: 93–8.
13 Goh CL. Cutting fluid dermatitis: epidemiology and an appraisal of some preventive measures. *Environ Dermatol* 1994; **1**: 3–11.
14 Zugerman C. Cutting fluids: their use and effects on the skin. In: Adams RM, ed. *Occupational Skin Disease*. Philadelphia: Hanley & Belfus, 1986: 245–58.
15 Kajdas C. Additives for metalworking lubricants: a review. In: *Proceedings of the Sixth International Colloquium on Industrial Lubricants. Properties, Application, Disposal*. Esslingen: Technische Akademie, 1988: 11.2-1–14.
16 Rycroft RJG. Petroleum and petroleum derivatives. In: Adams RM, ed. *Occupational Skin Disease*, 3rd edn. Philadelphia: Saunders, 1999: 553–66.
17 Shennan JL. Selection and evaluation of biocides for aqueous metalworking fluids. *Tribol Int* 1983; **16**: 317–30.
18 Wigger-Alberti W, Hinnen U, Elsner P. Predictive testing of metalworking fluids: a comparison of 2 cumulative human irritation models and correlation with epidemiological data. *Contact Dermatitis* 1997; **36**: 14–20.
19 Rietschel E. Kombinierte Belastung der Haut am Beispiel des Schleifens und Honens als Folge von Rationalisierungsmassnahmen. *Arbeitsmed Sozialmed Präventivmed* 1982; **17**: 272–3.
20 Cookson JO. Machine tool design and use in relation to cutting fluids. *Ann Occup Hyg* 1971; **14**: 181–90.
21 Ernst B, Schmidt O. Bestrahlung von Kühlschmierstoffen mit harter Gamma-Strahlung. Ein Weg zur Reduktion von Hautschäden. *Arbeitsmed Sozialmed Präventivmed* 1983; **18**: 79–82.
22 Wilkinson DS, Budden MG, Hambly EM. A 10-year review of an industrial dermatitis clinic. *Contact Dermatitis* 1980; **6**: 11–7.
23 Burrows D, Calnan CD. Cement dermatitis, 2: clinical aspects. *Trans St John's Hosp Dermatol Soc* 1965; **51**: 27–39.
24 Burrows D. Contact dermatitis to machine oil in hosiery workers. *Contact Dermatitis* 1980; **6**: 10.
25 De Boer EM, Bruynzeel DP, van Ketel WG. Dyshidrotic eczema as an occupational dermatitis in metalworkers. *Contact Dermatitis* 1988; **18**: 184–8.
26 Weidenbach T, Rakoski J. Gehäuftes Auftreten von dyshidrosiformen Handekzemen durch eine Öl-in-Wasser-Emulsion bei Metallarbeitern. *Dermatosen* 1985; **33**: 121–4.
27 Vassileva S, Stransky L. Occupational dyshidrotic dermatitis of the hands following cactus contact. *Dermatosen* 1987; **35**: 204–5.
28 Pryce DW, Irvine D, English JSC *et al*. Soluble oil dermatitis: a follow-up study. *Contact Dermatitis* 1989; **21**: 28–35.

Occupational physical irritant contact dermatitis [1,2]

The skin can react in a variety of ways to excessive friction and microtrauma. The reaction depends upon constitutional factors, such as a tendency to develop psoriasis (Fig. 27.4), or the type of trauma [3]. Various types of reactions can occur: calluses, fissuring, lichenification, blistering, Koebner phenomen on aggravating psoriasis, and granulomas.

Fibreglass dermatitis is a well-known example of a physical irritant contact dermatitis and was first described in 1942 [4]. It consists of sharp glass spicules which are capable of penetrating the superficial part of the horny layer of the skin to cause immediate skin irritation. The acute irritation reaction results in a pruriginous dermatitis; as clothing may trap the fibreglass, this may occur on covered parts of the body.



Fig. 27.4 Psoriasis of the palm caused by frictional forces from repeated use of a screw driver.

References

1 Freeman S. Repeated low-grade frictional trauma. In: Kanerva L, Elsner P, Wahlberg JE, Maibach HI, eds. *Handbook of Occupational Dermatology*. Berlin: Springer, 2000: 111–4.
2 Sertoli A, Francalanci S, Giorgini S. Fibreglass dermatitis. In: Kanerva L, Elsner P, Wahlberg JE, Maibach HI, eds. *Handbook of Occupational Dermatology*. Berlin: Springer, 2000: 122–34.
3 McMullen E, Gawkrodger DJ. Physical friction is under-recognized as an irritant that can cause or contribute to contact dermatitis. *Br J Dermatol* 2006; **154**: 154–6.
4 Sulzberger MB, Baer RL. The effects of fibreglass on animal and human skin. *Ind Med Surg* 1942; **11**: 482–4.

Occupational allergic contact dermatitis [1–4]

Although probably less common than occupational irritant contact dermatitis, occupational allergic contact dermatitis still tends to be underdiagnosed [5]. Better history taking [3], more extensive patch testing, workplace visiting and greater use of chemical investigations [3] significantly increase the proportion of patients found to have contact sensitization relevant to their occupation. Allergic contact dermatitis also frequently complicates irritant contact dermatitis in occupational cases. A prime example of occupational allergic contact dermatitis is that from chromium [6,7] (Chapter 26).

References

1 Rycroft RJG. Occupational contact dermatitis. In: Rycroft RJG, Menné T, Frosch PJ, Lepoittevin J-P, eds. *Textbook of Contact Dermatitis*, 3rd edn. Berlin: Springer, 2001: 555–80.
2 Veien NK. Allergic contact dermatitis: immunological aspects and common occupational causes. In: English JSC, ed. *A Colour Handbook of Occupational Dermatology*. London: Manson, 1998: 31–52.
3 Foussereau J, Benezra C, Maibach HI. *Occupational Contact Dermatitis*. Copenhagen: Munksgaard, 1982.
4 Dickel H. Kuss O, Schmidt A *et al*. Occupational relevance of positive standard patch-test results in employed persons with an initial report of an occupational skin disease. *Int Arch Occup Environ Health* 2002; **75**: 423–34.
5 Fregert S. *Manual of Contact Dermatitis*, 2nd edn. Copenhagen: Munksgaard, 1981: 88.
6 Burrows D, Adams RM, Flint GN. Metals. In: Adams RM, ed. *Occupational Skin Disease*, 3rd edn. Philadelphia: Saunders, 1999: 395–433.
7 Burrows D. *Chromium: Metabolism and Toxicity*. Boca Raton, FL: CRC Press, 1983.

Investigations

Skin prick test/RAST

Although testing for immediate hypersensitivity is not always a part of assessment of contact dermatitis, it can be important, particularly in the situation of hand dermatitis when type 1 hypersensitivity to natural rubber latex (NRL) is suspected [1]. The two tests in common use are the skin prick test and the radioallergosorbent test (RAST). The glove usage or challenge test requires a highly allergenic brand of glove and is potentially dangerous—emergency treatment facilities for the management of anaphylaxis are needed [2]. Skin prick testing involves an intradermal puncture through a drop of allergen or glove. A positive reaction consists of an urticarial weal, which is usually apparent after 15 min, although it may take as long as 45 min to develop. A positive control test of histamine should also be performed to exclude a false-negative reaction due to oral antihistamine ingestion. A negative control prick test with saline should be also be performed to check if the patient is dermographic. There are occasional reports of anaphylaxis following prick testing with NRL extract [3]. With the advent of standardized, commercially available NRL extracts, this risk is probably greatly reduced. Some clinicians may prefer to perform a RAST for NRL allergy, as they may not have adequate facilities or training to deal with anaphylaxis; however, the sensitivity and specificity may be less for RAST compared with prick testing. Skin prick and use tests are also useful when investigating protein contact dermatitis in occupations at risk, such as chefs or veterinarians [4].

References

1 Bourke J, Coulson I, English J. Guidelines of care for contact dermatitis. *Br J Dermatol* 2001; **145**: 877–85.
2 Turjanmaa K, Alenius H, Makinen-Kiljunen T *et al*. Natural-rubber latex allergy. In: Kanerva L, Elsner P, Wahlberg JE, Maibach HI, eds. *Handbook of Occupational Dermatology*. Berlin: Springer, 2000: 719–29.
3 Kelly KJ, Kurup V, Zacharisen M *et al*. Skin and serologic testing in the diagnosis of latex allergy. *J Allergy Clin Immunol* 1993; **91**: 1140–5.
4 Ale SI, Maibach HI. Occupational contact urticaria. In: Kanerva L, Elsner P, Wahlberg JE, Maibach HI, eds. *Handbook of Occupational Dermatology*. Berlin: Springer, 2000: 200–16.

Patch testing [1–5]

Four general problems of patch testing (Chapter 26) are particularly relevant in suspected occupational dermatitis:

1 False-positive reactions
2 False-negative reactions
3 Unexplained positive reactions
4 Missed allergens.

False-positive reactions are commonly obtained if industrial chemicals are applied as patch tests undiluted [3]. Such reactions can be shown to be false-positive irritant reactions if testing in control subjects also demonstrates positive reactions; applying serial dilutions of the chemical to the original patient will often demonstrate an abrupt loss of the reaction. The uncritical use of undiluted chemical samples as patch tests also increases the risk of active sensitization and other complications of patch testing (Chapter 26). When testing an unknown substance, a preliminary open test is often advisable [4].

False-negative reactions can also be obtained with samples acquired from the patient's workplace. This is because the concentration of an allergen in a sample—for example, rubber—may be too low to elicit a positive patch test reaction. This problem also arises when allergens are found in irritant products such as cutting fluids, solvents and soaps. Dilution of these to avoid a false-positive reaction from the irritancy of the sample may over-dilute an allergen initially present in only low concentration (Chapter 26).

Unexplained positive reactions found on standard patch testing in suspected occupational cases should always be pursued for explanation [4,6]. This is particularly so when the allergens concerned are known to have a multiplicity of industrial uses, such as chromium, cobalt and colophony. A factory visit can be invaluable in the detection of previously unsuspected sources of allergens [7–9].

Missed allergens. When clinical assessment points strongly towards an occupational allergic contact dermatitis, the occurrence of negative patch test results should always raise the possibility of the responsible allergen having been omitted from testing

[5,6]. Another major function of a factory visit is to detect such missed allergens.

Routine pre-employment testing with potential sensitizers to be used in the future job should not be carried out [4].

References

1 Adams RM. Patch testing: a recapitulation. *J Am Acad Dermatol* 1981; **5**: 629–43.
2 Wahlberg JE. Patch testing. In: Rycroft RJG, Menné T, Frosch PJ, Lepoittevin JP, eds. *Textbook of Contact Dermatitis*, 3rd edn. Berlin: Springer, 2001: 435–78.
3 Fischer T, Adams RM. Diagnostic patch testing. In: Adams RM, ed. *Occupational Skin Disease*, 3rd edn. Philadelphia: Saunders, 1999: 221–50.
4 Fregert S. *Manual of Contact Dermatitis*, 2nd edn. Copenhagen: Munksgaard, 1981.
5 Dickel H. Kuss O, Schmidt A *et al*. Occupational relevance of positive standard patch-test results in employed persons with an initial report of an occupational skin disease. *Int Arch Occup Environ Health* 2002; **75**: 423–34.
6 Rycroft RJG. Problems in occupational allergy. *Semin Dermatol* 1982; **1**: 43–7.
7 Adams RM. Prevention, treatment, rehabilitation and plant inspection. In: Adams RM, ed. *Occupational Skin Disease*, 3rd edn. Philadelphia: Saunders, 1999: 279–90.
8 Carmichael AJ, Foulds IS. Performing a factory visit. *Clin Exp Dermatol* 1993; **18**: 208–10.
9 Rycroft RJG. Occupational contact dermatitis. In: Rycroft RJG, Menné T, Frosch PJ, Lepoittevin JP, eds. *Textbook of Contact Dermatitis*, 3rd edn. Berlin: Springer, 2001: 555–80.

Chemical investigations

There is an array of qualitative chemical spot tests [1,2], of which four are likely to be of particular use in the investigation of occupational cases. These are the dimethylglyoxime test for nickel [3], the diphenylcarbazide test for chromium [1], the lutidine test for formaldehyde [4] and the filter-paper test for epoxy resin [5]. These are all tests that can be carried out simply and reliably with minimum time and bench space.

Quantitative microanalysis of allergens and physicochemical techniques for the isolation of allergens [6] are likely to be beyond the scope of most dermatologists outside special departments, although they may be available within neighbouring departments. Thin-layer chromatography does, however, offer opportunities for relatively simple separation and identification, such as the detection of the sensitizing low-molecular-weight oligomers of epoxy resin [2,5].

Liquid and gas chromatography, which may be linked to mass spectrometry, colorimetric spectrophotometry, and atomic absorption and emission spectrophotometry all play important parts in current investigations [2].

References

1 Gruvberger B, Bruze M, Fregert S. Spot tests and chemical analyses for allergen evaluation. In: Rycroft RJG, Menné T, Frosch PJ, Lepoittevin J-P, eds. *Textbook of Contact Dermatitis*, 3rd edn. Berlin: Springer, 2001: 495–510.
2 Fregert S. Physicochemical methods for detection of contact allergens. *Dermatol Clin* 1988; **6**: 97–104.
3 Fregert S. *Manual of Contact Dermatitis*, 2nd edn. Copenhagen: Munksgaard, 1981: 31.
4 Flyvholm MA, Tiedemann E, Menné T. Comparison of 2 tests for clinical assessment of formaldehyde exposure. *Contact Dermatitis* 1996; **34**: 35–8.
5 Fregert S, Trulsson L. Simple methods for demonstration of epoxy resins of bisphenol A type. *Contact Dermatitis* 1978; **4**: 69–72.
6 Foussereau J, Benezra C, Maibach HI. *Occupational Contact Dermatitis*. Copenhagen: Munksgaard, 1982: 80–9.

Factory visiting

The diagnostic advantage to the dermatologist of seeing the way in which a patient carries out their work cannot be overestimated (Fig. 27.5). Some general guidance is available [1–5], but it is the experience of making such visits that is the best instructor. The main types of information that are worth establishing during such visits, and recording subsequently, are as follows:

1 *Organizational*. Name, address (including postcode) and telephone number of workplace; names and status of all medical, nursing, employer and employee representatives met.
2 *Demographic*. Numbers employed overall and in patient's work area; current expansion, contraction, turnover; shift system and pay scheme.
3 *Technological*. Broad concept of production as a whole; detailed understanding of work carried out by patient and in patient's work area, including all potential irritants and allergens observed and their degree and extent of skin contact; names and addresses of suppliers of materials requiring further identification.
4 *Preventive*. Broad impression of working conditions (space, lighting, ventilation); more detailed review of protective installations, protective clothing, skin-care products and education; assessment of actual uptake and practical effectiveness of preventive methods.
5 *Miscellaneous*. Industrial relations; psychological, sociological or economic factors; any similar problem in sister factory, etc.
6 *Clinical*. Skin complaints in employees other than the patient, their clinical assessment, and subdivision into occupational and non-occupational (often provisional).



Fig. 27.5 The hygiene in some workplaces leaves a lot to be desired.

7 *Epidemiological*. Prevalence of skin complaints as a proportion of the total exposed; estimate of prevalence of occupational dermatoses.
8 *Aetiological*. Opinions of others, with attribution as to source and estimate of reliability; own opinion, with grounds for it (may be inconclusive).
9 *Operational*. Summary of findings; recommendations for future investigation, management and review; follow-up.

Factory (or other workplace) visits can provide many major benefits [4].

1 Detection of relevance of previously unexplained positive standard patch test reactions.
2 Detection of missed allergen.
3 Substantiation of diagnosis of irritant contact dermatitis.
4 Diagnosis of mild or unfamiliar occupational dermatoses by their occurrence in several members of a workforce.
5 Substantiation that various non-occupational skin conditions have been grouped together as a pseudo-occupational dermatosis [6], and why.
6 Recognition of phenomenon of visible dermatoses, whether occupational or not, causing anxiety and subconsciously imitative symptoms in fellow employees [7].
7 Initiation of research on new occupational dermatoses.
8 Incidental effects, including improved dermatologist–occupational physician [8] and dermatologist–patient relationships.
9 Progressive increase in dermatologist's overall knowledge of the working contactants of his or her patients.

A second-best alternative that can still provide useful information if a factory visit is impossible is to communicate with medical, nursing, employer or employee representatives by letter or telephone.

References

1 Adams RM. Prevention, treatment, rehabilitation and plant inspection. In: Adams RM, ed. *Occupational Skin Disease*, 3rd edn. Philadelphia: Saunders, 1999: 279–90.
2 Calnan CD. Dermatology and industry. *Clin Exp Dermatol* 1978; **3**: 1–16.
3 Carmichael AJ, Foulds IS. Performing a factory visit. *Clin Exp Dermatol* 1993; **18**: 208–10.
4 Rycroft RJG. Plant survey and inspection. In: Kanerva L, Elsner P, Wahlberg JE, Maibach HI, eds. *Handbook of Occupational Dermatology*. Berlin: Springer, 2000: 437–40.
5 Rycroft RJG. Looking at work dermatologically. *Dermatol Clin* 1988; **6**: 1–5.
6 Rycroft RJG. Occupational dermatoses in perspective. *Lancet* 1980; **ii**: 24–6.
7 Maguire A. Psychic possession among industrial workers. *Lancet* 1978; **i**: 376–8.
8 Valsecchi R, Cassina G, Leghissa P *et al*. Cooperation between departments of dermatology and occupational disease: an eighteen months' experience results. *Boll Dermatol Allergol Prof* 1987; **2**: 192–8.

Prognosis [1] (Chapters 25 and 26)

The most important aspect of prognosis in occupational dermatoses is that neither irritant nor allergic contact dermatitis may be as beneficially affected by change of work as some believe [1–6]. This has a profound influence on the management of the established case, as well as underlining the importance of primary prevention.

References

1 Rycroft RJG. Occupational contact dermatitis. In: Rycroft RJG, Menné T, Frosch PJ, Lepoittevin J-P, eds. *Textbook of Contact Dermatitis*, 3rd edn. Berlin: Springer, 2001: 555–80.
2 Fregert S. Occupational dermatitis in a 10-year material. *Contact Dermatitis* 1975; **1**: 96–107.
3 Pryce DW, Irvine D, English JSC *et al*. Soluble oil dermatitis: a follow-up study. *Contact Dermatitis* 1989; **21**: 28–35.
4 Adishesh A, Meyer JD, Cherry NM. Prognosis and work absence due to occupational contact dermatitis: outcome of cases reported to EPIDERM. *Contact Dermatitis* 2002; **46**: 273–9.
5 Sajjachareonpong P, Cahill J, Keegel T *et al*. Persistent post-occupational dermatitis. *Contact Dermatitis* 2004; **51**: 278–83.
6 Cvetkovski RS, Rothman KJ, Olsen J *et al*. Relation between diagnoses on severity, sick leave and loss of job among patients with occupational hand eczema. *Br J Dermatol* 2005; **152**: 93–8.

Prevention [1–4] (Chapters 25 and 26)

Secondary preventive measures can reduce the risk of dermatitis in an established case, although success can be obtained only by close collaboration between the management of the factory and the dermatologist. Changes in the process, when practicable, are always likely to be more successful than personal protection [5]. Some preventive measures that are desirable from a dermatological point of view may be unsafe or impractical in an industrial environment. The wearing of gloves is often ruled out because of these strictures [6].

Materials selected for protective clothing may in practice allow many contactants to penetrate. Various sources provide practical guidance as to the choice of protective material [2,7–11]. There are now multilayered materials that show much greater resistance to allergens such as methyl methacrylate [12] and irritants such as organic solvents [7]. Even when protective clothing is practicable and competent to protect, the way in which it is taken off and put on again may lead to contamination of inside surfaces. Because occlusion increases penetration, wearing a glove that has been contaminated on the inside can be more harmful than wearing no glove at all [4]. Correct procedures must therefore be instituted and maintained.

Automated processes are often far from free of skin contact. Fregert [13] has listed many possible sources of skin contamination. Service engineers are particularly at risk [14].

Allergen replacement [1,14,15] is a useful concept. Extreme care must be taken to ensure as far as possible that the replacement is genuinely safer in all respects.

Some skin-care creams ('barrier' and moisturizing creams) have been demonstrated by various test methods [2,16–19] to have a protective effect against certain irritants. Their effectiveness in actual use remains less securely established [2]. Topical binding agents may have a role in the prevention of nickel dermatitis [20].

The basic principle of prevention of occupational contact dermatitis continues to be that of reduction of contact, or preferably avoidance. If chemicals remain on the skin for 24 h instead of 8 h, sensitization and irritation occur more readily [4]. Evidence-based skin care recommendations have been published [21] (summarized in Table 27.2). If improvements are made to the working conditions by intensified preventive measures, then this is likely to lead to a reduction in cases of occupational contact dermatitis [22,23].

Table 27.2 Basic workplace skin-care principles.

Luke-warm water for washing
Use correct gloves before exposure for the shortest time
Remove rings
Cotton liners underneath protective gloves
Avoid disinfectant hand cleansers
Apply emollient hand creams
Protect hands at home
Workforce education

References

1 Adams RM. Prevention, treatment, rehabilitation and plant inspection. In: Adams RM, ed. *Occupational Skin Disease*, 3rd edn. Philadelphia: Saunders, 1999: 279–90.
2 Rycroft RJG. Occupational contact dermatitis. In: Rycroft RJG, Menné T, Frosch PJ, Lepoittevin J-P, eds. *Textbook of Contact Dermatitis*, 3rd edn. Berlin: Springer, 2001: 555–80.
3 Foussereau J, Benezra C, Maibach HI. *Occupational Contact Dermatitis*. Copenhagen: Munksgaard, 1982: 78–9.
4 Fregert S. *Manual of Contact Dermatitis*, 2nd edn. Copenhagen: Munksgaard, 1981: 105–14.
5 Ellenbecker MJ. Engineering controls as an intervention to reduce worker exposure. *Am J Ind Med* 1996; **29**: 303–7.
6 Church R. Prevention of dermatitis and its medico-legal aspects. *Br J Dermatol* 1981; **105** (Suppl. 21): 85–90.
7 Estlander T, Jolanki R. How to protect the hands. *Dermatol Clin* 1988; **6**: 105–14.
8 Forsberg K, Keith LH. *Chemical Protective Clothing Performance Index Book*. New York: Wiley, 1989.
9 Mellstrom G, Carlsson B. *Second Scandinavian Symposium on Protective Clothing Against Chemicals and Other Health Risks*. Arbete Och Hälsa Vetenskaplig Skriftserie, 1987: 12.
10 Wahlberg JE. Prophylaxis of contact dermatitis. *Semin Dermatol* 1986; **5**: 255–62.
11 Wilkinson DS. Protective gloves. In: Griffiths WAD, Wilkinson DS, eds. *Essentials of Industrial Dermatology*. Oxford: Blackwell Scientific Publications, 1985: 101–5.
12 Darre E, Vedel P, Jensen JS. Skin protection against methyl-methacrylate. *Acta Orthop Scand* 1987; **58**: 236–8.
13 Fregert S. Possibilities of skin contact in automatic processes. *Contact Dermatitis* 1980; **6**: 23.
14 Zschunke E. Management of industrial dermatitis. *Contact Dermatitis* 1980; **6**: 18–9.
15 Calnan CD. Studies in contact dermatitis, 23: allergen replacement. *Trans St John's Hosp Dermatol Soc* 1970; **56**: 131–8.
16 de Fine Olivarius F, Hansen AB, Karlsmark T *et al*. Water protective effect of barrier creams and moisturizing creams: a new *in vivo* test method. *Contact Dermatitis* 1996; **35**: 219–25.
17 Mortz CG, Andersen KE, Halkier-Sorensen L. The efficacy of different moisturizers on barrier recovery in hairless mice evaluated by non-invasive bioengineering methods. *Contact Dermatitis* 1997; **36**: 297–301.
18 Schlüter-Wigger W, Elsner P. Efficacy of 4 commercially available protective creams in the repetitive irritation test (RIT). *Contact Dermatitis* 1996; **34**: 278–83.
19 Grunewald AM, Gloor M, Gehring W *et al*. Barrier creams: commercially available barrier creams versus urea- and glycerol-containing oil-in-water emulsions. *Dermatosen* 1995; **43**: 69–74.
20 Gawkrodger DJ, Healy J, Howe AM. The prevention of nickel contact dermatitis: a review of the use of binding agents and barrier creams. *Contact Dermatitis* 1995; **32**: 257–65.
21 Agner T, Held E. Skin protection programmes. *Contact Dermatitis* 2002; **47**: 253–6.
22 Dickel H, Kuss O, Schmidt A, Diepgen TI. Impact of preventative strategies on trend of occupational skin disease in hairdressers: population based register study. *BMJ* 2002; **324**: 1422–3.
23 Brown TP, Rushton L, Williams HC *et al*. Intervention development in occupational research: an example from the printing industry. *Occup Environ Med* 2006; **63**: 261–6.

Management of the established case [1,2]

As most workers naturally prefer to continue their work, a detailed analysis of causative factors is required. Minor changes of procedure may be helpful once guided by a precise diagnosis. A change of job may be considered in first-year apprentices, in those with uncomplicated allergic contact dermatitis from readily avoidable substances or in atopics who have unavoidable contact with irritants. This should only be decided after full dermatological investigation. In the majority of cases, continuation in the same occupation should be made possible [1,3–5].

References

1 Adams RM. Prevention, treatment, rehabilitation and plant inspection. In: Adams RM, ed. *Occupational Skin Disease*, 3rd edn. Philadelphia: Saunders, 1999: 279–90.
2 Rycroft RJG. Occupational contact dermatitis. In: Rycroft RJG, Menné T, Frosch PJ, Lepoittevin J-P, eds. *Textbook of Contact Dermatitis*, 3rd edn. Berlin: Springer, 2001: 555–80.
3 Calnan CD, Rycroft RJG. Rehabilitation in occupational skin disease. *Trans Coll Med S Afr* 1981; **25** (Suppl.): 136–43.
4 Fregert S. Occupational dermatitis in a 10-year material. *Contact Dermatitis* 1975; **1**: 96–107.
5 Fregert S. *Manual of Contact Dermatitis*, 2nd edn. Copenhagen: Munksgaard, 1981: 110–4, 115–6.

Assessment of dermatitic potential

The potential of chemicals to act as contact irritants [1,2], contact allergens [3–7], photoirritants [8] and photoallergens [7,9,10] can be assessed by test methods in laboratory animals and, to a lesser extent, in human volunteer subjects. These methods assess potential; they do not in themselves predict the incidence of dermatitis. Actual risk depends not only on dermatitic potential but also on other factors, the most important of which concern the conditions of exposure (concentration, frequency and duration) and the normality of skin. Also useful is background knowledge of the structure–activity relationships of chemical groups [11].

Modifications of widely accepted test procedures such as the guinea-pig maximization test [6] tend to occur with experience of their use [12–14], and sufficiently different tests have been developed to justify separate names [7,15–17]. Standardization of test procedures greatly reduces inter- and intralaboratory variation in results—but, as this is never likely to cease to be a problem to some degree [18], the development of new tests that may offer greater ease of standardization (and economy) continues [19]. The use of mouse models for the prediction of sensitizing potential is now well established [20,21].

References

1 Frosch PJ, Kligman AM. The chamber-scarification test for irritancy. *Contact Dermatitis* 1976; **2**: 314–24.
2 Kligman AM, Wooding WM. A method for the measurement and evaluation of irritants on human skin. *J Invest Dermatol* 1967; **49**: 78–94.
3 Schlede E, Eppler R. Testing for skin sensitization according to the notification procedure for new chemicals: the Magnusson and Kligman test. *Contact Dermatitis* 1995; **32**: 1–4.
4 Magnusson B. Identification of contact sensitizers by animal assay. *Contact Dermatitis* 1980; **6**: 46–50.
5 Magnusson B, Fregert S, Wahlberg J. *Determination of Skin Sensitization Potential of Chemicals. Predictive Testing in Guinea Pigs*. Stockholm: Liber Tryck, 1979 (Arbete Och Hälsa, Ventenskaplig Skriftserie, 26 (E)).

6 Magnusson B, Kligman AM. *Allergic Contact Dermatitis in the Guinea Pig: Identification of Contact Allergens*. Springfield: Thomas, 1970.
7 Maurer T. *Contact and Photocontact Allergens: A Manual of Predictive Test Methods*. New York: Dekker, 1983.
8 Kaidbey KH, Kligman AM. Identification of topical photosensitizing agents in humans. *J Invest Dermatol* 1978; **70**: 149–51.
9 Kaidbey KH, Kligman AM. Photomaximization test for identifying photoallergic contact sensitizers. *Contact Dermatitis* 1980; **6**: 161–9.
10 Maurer TH, Weirich EC, Hess R. Predictive animal testing for photocontact allergenicity. *Br J Dermatol* 1980; **103**: 593–605.
11 Dupuis G, Benezra C. *Allergic Contact Dermatitis to Simple Chemicals: A Molecular Approach*. New York: Dekker, 1982.
12 Kligman AM, Basketter DA. A critical commentary and updating of the guinea pig maximization test. *Contact Dermatitis* 1995; **32**: 129–34.
13 Sato Y, Katsumura Y, Ichikawa H *et al*. A modified technique of guinea pig testing to identify delayed hypersensitivity allergens. *Contact Dermatitis* 1981; **7**: 225–37.
14 Shillaker RO, Bell GM, Hodgson JT *et al*. Guinea pig maximisation test for skin sensitisation: the use of fewer test animals. *Arch Toxicol* 1989; **63**: 283–8.
15 Goodwin BFJ, Crevel RWR, Johnson AW. A comparison of three guinea-pig sensitization procedures for the detection of 19 reported human contact sensitizers. *Contact Dermatitis* 1981; **7**: 248–58.
16 Maurer T, Hess R, Weirich EG. Prädiktive tierexperimentelle Kontaktallergenitätsprüfung. Relevanz der Methoden der OECD- und EG-Richtlinien. *Dermatosen* 1985; **33**: 6–11.
17 Ziegler V, Süss E. Methodological problems in detecting new allergens in animal experiments. *Dermatosen* 1980; **28**: 152–7.
18 Weil CS, Scala RA. Study of intra- and interlaboratory variability in the results of rabbit eye and skin irritation tests. *Toxicol Appl Pharmacol* 1971; **19**: 276–360.
19 Roupe G, Ridell B. The cellular infiltrate in contact hypersensitivity to picryl chloride in the mouse. *Acta Derm Venereol (Stockh)* 1979; **59**: 191–5.
20 Maisey J, Purchase R, Robbins MC *et al*. Evaluation of the sensitizing potential of 4 polyamines present in technical triethylenetetramine using 2 animal species. *Contact Dermatitis* 1988; **18**: 133–7.
21 Basketter DA, Kimber I. Olive oil: suitability for use in the local lymph node assay. *Contact Dermatitis* 1996; **35**: 190–1.

Alkali tests

The usefulness of alkali resistance and alkali neutralization tests as predictors of susceptibility to irritants remains controversial. Neither test is sufficiently simple and reliable to achieve widespread clinical use [1–3], and their diagnostic value has been overestimated.

More sophisticated tests with panels of irritants have been used to identify a 14% proportion of the general population with 'hyperirritable skin' [1]. Susceptibility to one irritant, however, does not necessarily imply susceptibility to another irritant in the same individual [1,4]. Skin irritation thresholds have been correlated with the development of dermatitis in hairdressers [5].

References

1 Frosch PJ. Cutaneous irritation. In: Rycroft RJG, Menné T, Frosch PJ, eds. *Textbook of Contact Dermatitis*, 2nd edn. Berlin: Springer, 1995: 28–61.
2 Iliev D, Hinnen U, Elsner P. Reproducibility of a non-invasive skin irritancy test in a cohort of metalworker trainees. *Contact Dermatitis* 1997; **36**: 101–3.
3 Foussereau J, Benezra C, Maibach HI. *Occupational Contact Dermatitis*. Copenhagen: Munksgaard, 1982: 76–7.
4 Björnberg A. *Skin Reactions to Primary Irritants in Patients with Hand Eczema*. Göteborg, Sweden: Isaacsons O, Tryckeri AB, 1968.
5 Smith HR, Armstrong DK, Holloway D *et al*. Skin irritation thresholds in hairdressers: implications for the development of hand dermatitis. *Br J Dermatol* 2002; **146**: 849–52.

Transepidermal water loss

Measurement of the baseline transepidermal water loss (TEWL) may be a useful indicator of reactivity to irritants, although there is variation between studies [1].

Reference

1 Frosch PJ. Cutaneous irritation. In: Rycroft RJG, Menné T, Frosch PJ, eds. *Textbook of Contact Dermatitis*, 2nd edn. Berlin: Springer, 1995: 28–61.

Measurement of skin contamination

Methods of quantifying the degree of skin contamination by substances include skin wiping [1], skin rinsing [2], exposure pads [3,4], and the use of natural fluorescence (oils and tars) [5] or fluorescent tracers [6].

References

1 Klingner TD, McCorkle T. The application and significance of wipe samples. *Am Ind Hyg Assoc J* 1994; **55**: 251–4.
2 Keenan RR, Cole SB. A sampling and analytical procedure for skin contamination evaluation. *Am Ind Hyg Assoc J* 1982; **43**: 473–6.
3 Cohen BSM, Popendorf W. A method for monitoring dermal exposure to volatile chemicals. *Am Ind Hyg Assoc J* 1989; **50**: 216–23.
4 Jongeneelen FJ, Scheepers PTJ, Groenendijk A *et al*. Airborne concentrations, skin contamination, and urinary metabolite excretion of polycyclic aromatic hydrocarbons among paving workers exposed to coal tar derived road tars. *Am Ind Hyg Assoc J* 1988; **49**: 600–7.
5 Hill RH. Ultraviolet detection of synthetic oil contamination of skin. *Am Ind Hyg Assoc J* 1984; **45**: 474–84.
6 Fenske RA. Correlation of fluorescent tracer measurements of dermal exposure and urinary metabolite excretion during occupational exposure to malathion. *Am Ind Hyg Assoc J* 1988; **49**: 438–44.

Non-eczematous occupational dermatoses

These constitute an important minority of occupational dermatoses. Particularly significant examples also described in other chapters are acquired hypomelanosis (see p. 27.15 in this chapter, and Chapter 58), scleroderma (Chapter 51) and carcinoma (Chapter 52). Many other dermatoses can be occupational, including some skin diseases caused by arthropods (Chapter 38), *Candida* paronychia (Chapter 36), onycholysis (Chapter 65) and exogenous pigmentations such as argyria (Chapter 58).

Chemical burns

Many chemicals used in industry and the home are capable not only of causing burns, but also of being absorbed and causing toxic effects leading to acute yellow atrophy of the liver or renal failure. Burns from acids and alkalis may cause acidosis or alkalosis, both requiring treatment.

Certain chemicals cause chemical burns, the first perceptible or visible changes of which can be delayed for several hours. Examples of these are mustard gas, podophyllin, dithranol, hydrofluoric acid, propane sultone, ethylene oxide and epichlorohydrin [1].

The primary—and essential—treatment of all chemical burns is copious washing (except for metallic potassium and sodium, which ignite in water). Specific remedies are available for only a few chemicals. Buffered phosphate solution, when readily

available, is useful for acid and alkali burns, but is only practicable in large units likely to deal with more than the occasional case.

The depth of necrosis depends on the concentration, duration of contact and time before treatment is instituted.

Acids and alkalis

Sulphuric acid and potassium or sodium [2] hydroxide are the most common agents. Strong acids are hygroscopic and cause coagulative necrosis and discoloration of the tissues. Alkalis form proteinates and saponify fats. Copious washing may have to be continued for a long time. Sodium bicarbonate solution can be used for acid burns, and vinegar and ammonium chloride for alkalis.

Cement (lime) [3–6]

Wet cement under occlusion (e.g. due to kneeling in cement, or contamination inside boots) can cause delayed full-skin-thickness burns. Soiled clothing should be removed immediately and the injury bathed copiously with water or, if available, phosphate buffer; excision and grafting of necrotic areas is frequently required [4].

Chromic acid [7]

This produces skin ulceration and necrosis. It may be absorbed and cause renal failure. Deeper burns may require excision and grafting. Superinfection with *Streptococcus pyogenes* may be a missed cause of delayed healing.

Phosphorus

This ignites on exposure to air. Burns should be kept moist until all particles are removed. Dry dressings should not be used. Small residual particles can be detected by phosphorescence in a dark room. Severe metabolic changes may occur, and patients who have suffered phosphorus burns should be carefully monitored. Copper sulphate solutions (in small amounts) have been advocated [8].

Hydrofluoric acid (HF) [9–12]

One of the strongest acids known, HF is widely used in industry and research. It is ionized in solution and penetrates deeply. Burns are characterized by intense pain (often delayed) and deep tissue necrosis, which progresses for several days. Skin contact must be dealt with instantly with copious washing with water for at least 10–15 min. Repeated application of 2.5% calcium gluconate gel is then usually adequate for minor exposure of the skin to less than 20% HF. If this fails to reduce the pain within 30 min–1 h, repeated infiltration with 5–10% calcium gluconate (0.5 mL/cm^2 burned surface area) should be considered [10]. Regional intra-arterial calcium gluconate [10] or chloride [13] infusion also has its expert advocates, but hypercalcaemia is a significant risk. Surgical debridement may be required later, as in all chemical burns. Earlier surgical intervention has been successful in severe burns [14].

Phenol [15]

This is rapidly absorbed through the intact skin. Local necrosis is proportionate to concentration and small amounts of water or alcohol may increase the absorption. Toxic effects are numerous. 'Deluge' washing with large amounts of water or swabbing with polyethylene glycol [15] should be employed.

References

1 Ippen H, Mathies V. Die 'protrahierte Verätzung' (unter besonder Berücksichtigung der Hautschäden durch Epoxide und Propansulton). *Berufsdermatosen* 1970; **18**: 144–65.
2 Frosch PJ. Cutaneous irritation. In: Rycroft RJG, Menné T, Frosch PJ, eds. *Textbook of Contact Dermatitis*, 2nd edn. Berlin: Springer, 1995: 28–61.
3 Early SH, Simpson RL. Caustic burns from contact with wet cement. *JAMA* 1985; **254**: 528–9.
4 Feldberg L, Regan PJ, Roberts AHNR. Cement burns and their treatment. *Burns* 1992; **18**: 51–3.
5 Rycroft RJG. Acute ulcerative contact dermatitis from Portland cement. *Br J Dermatol* 1980; **102**: 487–9.
6 Tosti A, Peluso AM, Varotti C. Skin burns due to transit-mixed Portland cement. *Contact Dermatitis* 1989; **21**: 58.
7 Hippke WE, Barth J. The problem of chromic acid burns. *Dermatosen* 1994; **42**: 156–8.
8 Ben-Hur N, Giladi A, Applebaum J *et al.* Phosphorus burns—the antidote: a new approach. *Br J Plast Surg* 1972; **25**: 245–9.
9 Bracken WM, Cuppage F, McLaury RL *et al.* Comparative effectiveness of topical treatments for hydrofluoric acid burns. *J Occup Med* 1985; **27**: 733–9.
10 Matsuno K. The treatment of hydrofluoric acid burns. *Occup Med* 1996; **46**: 313–7.
11 El Saadi MS, Hall AH, Hall PK *et al.* Hydrofluoric acid dermal exposure. *Vet Hum Toxicol* 1989; **31**: 243–7.
12 Pedersen NB. Edema of fingers from hydrogen fluoride containing aluminium blancher. *Contact Dermatitis* 1980; **6**: 41.
13 Siegel DC, Heard JM. Intra-arterial calcium infusion for hydrofluoric acid burns. *Aviat Space Environ Med* 1992; **63**: 206–11.
14 Buckingham F. Surgery: a radical approach to severe hydrofluoric acid burns—a case report. *J Occup Med* 1988; **30**: 873–4.
15 Pardoe R, Minami RT, Sato RM *et al.* Phenol burns. *Burns* 1976; **3**: 29–41.

Acne of external chemical origin

Synonym
- Acne venenata

Aetiology. Various chemicals possess, to some degree, the capacity to induce acne by external contact [1]. Many are occupational hazards, but some may be encountered in the home. The occupational chloracnes are of outstanding medical importance, because their development provides a valuable indicator of exposure to a toxic hazard. Many of the substances inducing chloracne are also hepatotoxic.

Halogenated aromatic hydrocarbons [2–7] are the most potent acnegenic agents. The chloronaphthalenes, chlorobiphenyls [8] and chlorobiphenyl oxides are used as dielectrics in conductors and insulators. Exposure occurs in those manufacturing these substances or making or handling cables [9,10]. A naphthalene wax used to 'feather proof' a counterpane caused acne on the face and arms of a child [11]. These substances will induce acne at any site [12] and at any age, usually after 1 or 2 months' exposure. The chlorophenols are used as insecticides, fungicides, herbicides and wood preservatives [13]. Their capacity to cause chloracne depends on the degree to which they are contaminated with chlorinated dioxins and the precise chemical structure of the latter, for example 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) (Fig. 27.6) is the most powerful chloracnegenic agent known [14–18].

Similarly, the toxicity of the polychlorinated biphenyls (PCBs) is largely due to contamination with polychlorinated

dibenzofurans (PCDFs). Chloracne has been caused by a weed-killer containing 2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid [19], by sodium tetrachlorophenate used as a wood preservative [2], by the herbicide 2,6-dichlorobenzonitrile [20], by a trifluoromethylpyrazole derivative being developed as an antirheumatic drug [21] and by an intermediate product found in the manufacture of tetrachloroazobenzene [4].

As a consequence of industrial or other accidents, large numbers of individuals may be heavily exposed to such chemicals [22]. In such circumstances, TCDD caused serious systemic symptoms and severe chloracne [23]. After another industrial accident the same chemical caused chloracne in members of the families of affected workers [24]. TCDD-induced chloracne, mainly in children, cleared well within a decade, and systemic effects were absent, following the more recent Seveso accident [25].

The induction of chloracne by the ingestion of PCBs has occurred in two large epidemics caused by the contamination of cooking oil [2,26]: the chloracnegen was shown to have caused transplacental, as well as direct, toxicity [27]. Polybrominated biphenyls became widely distributed in the state of Michigan, following a labelling error that resulted in their introduction into cattle feed [22].

Neat (insoluble) cutting oils, which are impure paraffin–oil mixtures, are the commonest chemical cause of acne, because they are so widely used in the engineering industry, but their acnegenic capacity is inconstant and not necessarily high. Men are more readily affected than women, and those with acne vulgaris are particularly susceptible. The use of moulding oil in the manufacture of precast concrete can cause oil acne [28]. Brilliantines containing impure paraffins may have a similar effect [29]. Comedones and cysts behind the ears have been attributed to paraffin products in shaving soap inadequately rinsed from this region [30].

Crude petroleum is acnegenic in oilfield and refinery workers [7]. Diesel oil can cause acne in motor mechanics [31].

Heavy coal-tar distillates, especially pitch and creosote, are also to some extent acnegenic. Conduit makers and road workers are affected. Under experimental conditions the lesions induced by crude coal tar are more inflammatory in white people than in black people [32].

Cosmetics [33]. Mild comedonal acne with occasional papulopustules occurs in one-third of adult women in the USA. Of 25 facial cosmetic creams tested in rabbits, 50% were comedogenic; so were lanolin, petrolatum and some vegetable oils [34]. Pomades had an even more marked effect in black Americans [29]. Also acnegenic were indigenous vegetable oils in India [35]. The salts of fatty acids in conventional soaps are comedogenic if used excessively [36]. Fatty acid esters, especially isopropyl linoleate, acetylated lanolin alcohol, grape seed and sweet almond oils, have been found to be particularly comedogenic in rabbits [37].

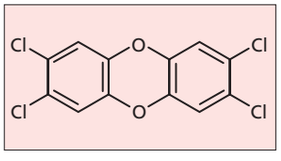


Fig. 27.6 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin—a halogenated aromatic compound—is highly toxic and causes chloracne.

Asbestos. A large percentage of workers in a hardboard factory in Germany developed acne which was attributed to asbestos [38].

Topical corticosteroids. The continued application of topical corticosteroids under occlusive dressings may also induce comedo formation. It does not occur under the age of 10 years and is difficult to induce experimentally in subjects over 50 years of age [39].

Psoralen and UVA therapy. A predominantly perioral acne can appear during psoralen and UVA (PUVA) therapy [1].

Pathology [40]. In chloracne, squamous cell proliferation occurs in sebaceous gland acini and acanthosis in the upper part of the external root sheath. The wall of the comedo is at first acanthotic and tortuous, but later becomes thin.

Clinical features [3] (Table 27.3). Chloracne, or more correctly halogen acne, may be differentiated from chemical acne of other origins. The eruption involves the face predominantly, even if the chemical has been ingested. The nose tends to be spared, and skin of the malar regions, the angles of the jaw and behind the ears is often most severely affected. The typical lesions are small, skin-coloured cysts, 1 mm to 1 cm in diameter, associated with numerous comedones (Fig. 27.7). There may be some itching. If exposure to the causative agent ceases, the lesions very slowly resolve, leaving some scarring. Asymmetrical lesions in any region of the body may be seen when unusual sites are in direct contact with the acnegenic agent. When the poison has been ingested, constitutional symptoms are frequently present; hypertrophy of meibomian glands of the eyelids, a predominantly sensory peripheral neuropathy, and patchy pigmentation of skin, nails and gums have been reported [26]. In acne caused by pitch or tar, comedones of the malar region predominate and there are few or no cysts. There may be a folliculitis of thighs and forearms. There is often

Table 27.3 Clinical features of acne vulgaris vs halogen acne.

Clinical features	Acne vulgaris	Halogen acne
Usual age	Teenage	Any
Comedones	Present	>3 (if absent not chloracne)
Straw-coloured cysts	Rare	Pathognomonic
Temporal comedones	Rare	Diagnostic
Inflammatory papules and cysts	≥3	Present
Retroauricular involvement	Uncommon	Common
Nose involvement	Often spared	Often spared
Associated systemic findings	Rare	Common

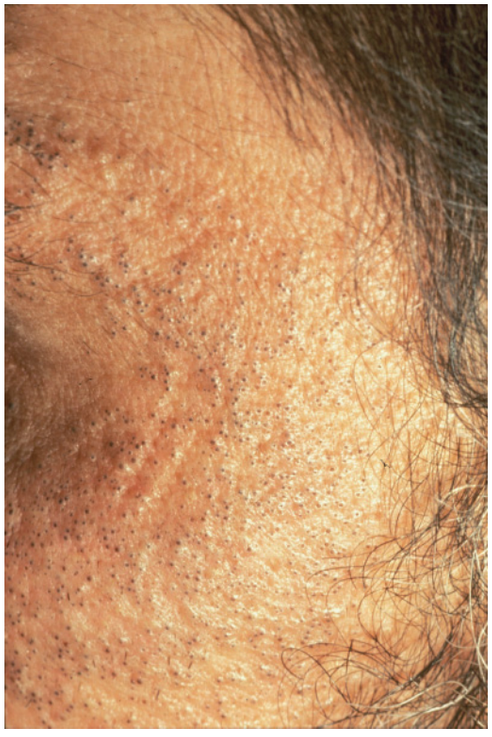


Fig. 27.7 Chloracne. Profuse open comedones in malar crescent.

some melanosis of exposed skin. Although it is doubtful that acne vulgaris predisposes to chloracne, its victims are more susceptible to oil acne. A highly inflammatory folliculitis of the forearms and thighs, with many comedones, is associated with aggravation of existing acne. Comedones induced by brilliantines or pomades [29] occur mainly around the frontal hair line.

Diagnosis (Table 27.4). Acne in the 'wrong' sites and at the 'wrong' age, or with a predominance of comedones, should initiate an enquiry into possible external chemical factors. Mechanical trauma alone can aggravate or even induce acne in predisposed individuals [41], and its possible role as a contributory factor should always be taken into account.

Treatment. Even treatment with isotretinoin [21] or acitretin [19] may fail to prevent chloracne from persisting for many years, despite avoidance of further contact.

Table 27.4 Differential diagnosis of various forms of occupational acne.

	Aetiology	Location	Lesion
Chloracne	Halogenated aromatics	Malar, retroauricular, mandibular	Comedones, straw-coloured cysts (0.1–1.0 cm)
Oil folliculitis	Oil	Arms, thighs, buttocks	Erythematous papules, pustules
Pitch acne	Tar/pitch	Exposed facial areas, especially malar	Open comedones
Tropical acne	Heat/humidity	Back, neck, buttocks, proximal extremities	Nodules, cysts

References

1 Bedane C, Souyri N. Les acnés induites. *Ann Dermatol Vénéréol* 1990; **117**: 53–8.
2 Crow KD. Chloracne: a critical review including a comparison of two series of cases of acne from chlornaphthalene and pitch fumes. *Trans St John's Hosp Dermatol Soc* 1970; **56**: 79–99.
3 Crow KD. Chloracne and its potential clinical implications. *Clin Exp Dermatol* 1981; **6**: 243–57.
4 Taylor JS, Wuthrich RC, Lloyd KM *et al.* Chloracne from manufacture of a new herbicide. *Arch Dermatol* 1977; **113**: 616–9.
5 Tindall JP. Chloracne and chloracnegens. *J Am Acad Dermatol* 1985; **13**: 539–58.
6 Weirich EG. Die Kontaktakne: Beispiel einer Zivilisationsdermatose. *Dermatosen* 1978; **26** (7–21): 45–52.
7 Zugerman C. Chloracne, chloracnegens, and other forms of environmental acne. In: Adams RM, ed. *Occupational Skin Disease*, 2nd edn. Philadelphia: Saunders, 1990: 127–35.
8 Truhaut R. La toxicologie des polychlorobiphényles (P.C.B.). Un problème d'hygiene industrielle d'actualité. *Arch Mal Prof* 1989; **50**: 63–77.
9 Fischbein A, Rizzo JN, Solomon SJ *et al.* Oculodermatological findings in workers with occupational exposure to polychlorinated biphenyls. *Br J Ind Med* 1985; **42**: 426–30.
10 Maroni M, Colombi A, Arbosti A *et al.* Occupational exposure to polychlorinated biphenyls in electrical workers, 2: health effects. *Br J Ind Med* 1981; **38**: 55–60.
11 Höfs W. Ungewöhnliche Entstehungsweise einer kindlichen Halogenwachsakne. *Dermatol Wochenschr* 1957; **135**: 1–6.
12 Shelley WB, Kligman AM. The experimental production of acne by penta- and hexachloronaphthalenes. *Arch Dermatol* 1957; **75**: 689–95.
13 Coenraads PJ, Brouwer A, Olie K *et al.* Chloracne: some recent issues. *Dermatol Clin* 1994; **12**: 569–76.
14 Council on Scientific Affairs. Health effects of Agent Orange and dioxin contaminants. *JAMA* 1982; **248**: 1895–7.
15 O'Malley MA, Carpenter AV, Sweeney MH *et al.* Chloracne associated with employment in the production of pentachlorphenol. *Am J Ind Med* 1990; **17**: 411–21.
16 Moses M, Lilis R, Crow KD *et al.* Health status of workers with past exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in the manufacture of 2,4,5-trichlorophenoxyacetic acid: comparison of findings with and without chloracne. *Am J Ind Med* 1984; **5**: 161–82.
17 Rozman K. A critical view of the mechanism(s) of toxicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin: implications for human safety assessment. *Dermatosen* 1989; **37**: 81–92.
18 Suskind RR, Hertzberg VS. Human health effects of 2,4,5-T and its toxic contaminants. *JAMA* 1984; **251**: 2372–80.
19 Poskitt LB, Duffill MB, Rademaker M. Chloracne, palmoplantar keratoderma and localized scleroderma in a weed sprayer. *Clin Exp Dermatol* 1994; **19**: 264–7.
20 Deeken JH. Chloracne induced by 2,6-dichlorobenzonitrile. *Arch Dermatol* 1974; **109**: 245–6.
21 Scerri L, Zaki I, Millard LG. Severe halogen acne due to a trifluoro-methylpyrazole derivative and its resistance to isotretinoin. *Br J Dermatol* 1995; **132**: 144–8.
22 Chanda JJ, Anderson HA, Glamb RW *et al.* Cutaneous effects of exposure to polybrominated biphenyls (PBBs): the Michigan PBB incident. *Environ Res* 1982; **29**: 97–108.
23 Zober A, Messerer P, Huber P. Thirty-four-year mortality follow-up of BASF employees exposed to 2,3,7,8-TCDD after the 1953 accident. *International Arch Occup Environ Health* 1990; **62**: 139–57.
24 Jensen NE, Sneddon IB, Walker AE. Tetrachlorobenzodioxin and chloracne. *Trans St John's Hosp Dermatol Soc* 1972; **58**: 172–7.
25 Baccarelli A, Pesatori AC, Consonni D *et al.* Health status and plasma dioxin levels in chloracne cases 20 years after the Seveso, Italy accident. *Br J Dermatol* 2005; **152**: 459–65.
26 Kuratsune M, Shapiro RE. PCB poisoning in Japan and Taiwan. *Am J Ind Med* 1984; **5**: 1–155.
27 Gladen BC, Taylor JS, Wu Y-C *et al.* Dermatological findings in children exposed transplacentally to heat-degraded polychlorinated biphenyls in Taiwan. *Br J Dermatol* 1990; **122**: 799–808.
28 Farkas J. Oil acne from mineral oil among workers making prefabricated concrete panels. *Contact Dermatitis* 1982; **8**: 141.

29 Plewig G, Fulton JE, Kligman AM. Pomade acne. *Arch Dermatol* 1970; **101**: 580–4.
30 Wulf K, Fegeler F. Komedonen und Talgcysten hinter den Ohren durch Siefenschaum. *Hautarzt* 1953; **4**: 371–5.
31 Das M, Misra MP. Acne and folliculitis due to diesel oil. *Contact Dermatitis* 1988; **18**: 120–1.
32 Kaidbey KH, Kligman AM. A human model of coal tar acne. *Arch Dermatol* 1974; **109**: 212–5.
33 Durupt G, Montastier C. Etude du pouvoir comédogène des cosmétiques. *J Méd Esth Chir Derm* 1987; **14**: 111–5.
34 Kligman AM, Mills OH. Acne cosmetica. *Arch Dermatol* 1972; **106**: 843–50.
35 Bhutani LK, Malhotra YK, Kandhari KC. Vegetable oils and acneform lesions. *Indian J Dermatol Venereol* 1970; **36**: 119–21.
36 Mills OH, Kligman AM. Acne detergicans. *Arch Dermatol* 1975; **111**: 65–8.
37 Morris WE, Kwan SC. Use of the rabbit ear model in evaluating the comedogenic potential of cosmetic ingredients. *J Soc Cosmet Chem* 1983; **34**: 215–25.
38 Weber G, Brehm G. Zur Kenntnis der Pseudo-Ölakne. *Berufsdermatosen* 1964; **12**: 37–41.
39 Kaidbey KH, Kligman AM. The pathogenesis of topical steroid acne. *J Invest Dermatol* 1974; **62**: 31–6.
40 Plewig G. Zur Kinetik der Comedonen-Bildung bei Chloracne (Halowachsacne). *Arch Klin Exp Dermatol* 1970; **238**: 228–41.
41 Mills OH, Kligman AM. Acne mechanica. *Arch Dermatol* 1975; **111**: 481–3.

Chemical depigmentation [1,2]

Definition. Occupational leukoderma is defined as depigmentation or hypopigmentation of the skin due to industrial exposure to a chemical or chemicals known to have a destructive effect on epidermal melanocytes [1].

Aetiology. Certain chemicals, particularly the substituted phenols, are destructive to functional melanocytes [2]. Many of these compounds cause permanent depigmentation of the skin, resembling vitiligo. The most commonly implicated chemicals are *para*-tertiary butyl phenol, *para*-tertiary butyl catechol, monobenzyl ether of hydroquinone (Fig. 27.8), hydroquinone and related compounds [1,2]. A list of chemicals known to cause occupational leukoderma is shown in Table 27.5.

Diagnosis. The diagnosis of occupational vitiligo should be suspected if a worker who potentially has been exposed to depigmenting chemicals develops leukoderma on the dorsal aspects of the hands or in a more widespread distribution [3]. There should be particular suspicion if more than one worker is involved. The chemicals to which the worker is exposed should be identified and investigation made to see if it or they are known to cause depigmentation. Some occupations known to be at risk of exposure to depigmenting chemicals are shown in Table 27.6.

Treatment. There is no specific treatment for occupational vitiligo. Removal of the offending chemical may result in partial repigmentation, but this process may take years and may not occur at all. Treatment should be aimed at preventing further exposure. Camouflage cosmetics may be used and the depigmented skin protected from ultraviolet irradiation by sunscreens.

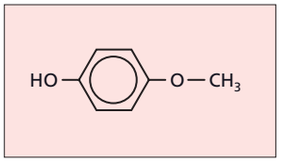


Fig. 27.8 Monomethylether of hydroquinone (4-hydroxyanisole or 4-methoxyphenol) is an intermediate in the manufacture of several chemicals.

Table 27.5 Chemicals capable of causing occupational leukoderma.

Hydroquinone
Monobenzylether of hydroquinone
Monoethylether of hydroquinone (*p*-ethoxyphenol)
Monomethylether of hydroquinone (*p*-methoxyphenol)
p-Cresol
p-Isopropylcatechol
p-Methylcatechol
p-Nonylphenol
p-Octylphenol
p-Phenylphenol
p-*tert*-Amylphenol
p-tertiary-Butylcatechol
p-tertiary-Butylphenol
N,*N*′,*N*″-Triethylenethiophosphoramide (thio-TEPA)
Mercaptoamines, e.g. *N*-2-mercaptoethyl-dimethylamine hydrochloride (MEDA)
Physostigmine

Table 27.6 Occupations with potential exposure to depigmenting chemicals.

Insecticides, paints, plastics and rubber
Lubricating and motor oils
Photographic chemicals
Antimicrobials and disinfectants
Detergents and deodorants
Inks

References

1 Wattanakrai P, Miyamoto L, Taylor JS. Occupational pigmentary disorders. In: Kanerva L, Elsner P, Wahlberg JE, Maibach HI, eds. *Handbook of Occupational Dermatology*. Berlin: Springer, 2000: 280–94.
2 Ortonne JP, Mosher DB, Fitzpatrick TB, eds. Hypomelanosis secondary to irradiation and physical trauma, chemical hypomelanosis, hypomelanosis associated with inflammation. In: *Vitiligo and Hypomelanosis of Hair and Skin*. New York: Plenum, 1983: 475–522.
3 Gawkrodger DJ. Pigmentary changes due to occupation. In: English JSC, ed. *A Colour Handbook of Occupational Dermatology*. London: Manson, 1998: 147–58.

Occupationally-induced skin tumours

Occupational skin cancers are rare and mainly of historical importance, apart from obvious examples such as epitheliomas developing in outdoor workers; however, some occupational exposures will predispose patients to develop skin tumours.

Historical review [1–4]

In 1775, the first cancer of any type to be linked with occupational exposure was scrotal squamous carcinoma in British chimney sweeps, reported by Percivall Pott [1]. In the rest of Europe, the disease was unknown because of wearing protective clothing and the reduced carcinogenicity of wood soot as opposed to coal predominantly burnt in Britain. Soot formed by burning wood has

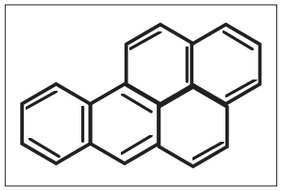


Fig. 27.9 Benzo[*a*]pyrene.

much lower levels of the polycyclic hydrocarbon, benzo[*a*]pyrene (Fig. 27.9), implicated in the aetiology of skin cancer, compared with coal soot. Skin cancer was still reported in chimney sweeps in Britain in the 1950s. By 1945 in Britain, almost 50% of industrial skin cancer was attributable to exposure to pitch and tar in occupations such as cotton mule spinners, jute workers and the engineering industry [2]. Various skin tumours are still seen in the tar refining industry [5].

Definition. Occupational skin cancers are defined as those in which a person's occupation has played a major role in the aetiology of the tumour. Currently, multiple aetiological factors are thought to contribute to the development of skin cancer. In the past, however, there have been several virtual epidemics of skin cancer which were traceable to occupational exposures. The major occupational carcinogens recognized were polycyclic hydrocarbons, ionizing radiation and arsenic. Ultraviolet radiation is now the most important carcinogen in the aetiology of occupational skin cancer.

Aetiology and occupations (Tables 27.7 & 27.8). Polycyclic hydrocarbons are produced by incomplete combustion and distillation of coal, natural gas and oil shale. These chemicals are contained in tar, fuel oils, lubricating oils and greases, oil shale and bitumen.

Table 27.7 Causative agents in occupational skin cancer.

Polycyclic hydrocarbons
soot
tar
pitch
mineral oil
shale oil
crude paraffin
asphalt
Ionizing radiation
Arsenic
Ultraviolet light

Diagnosis. The diagnosis of skin cancer is similar to that of non-occupational skin cancers. Generally, the exposed sites are involved. Previously, the scrotum was involved frequently, because of continuous exposure to carcinogens and the increased likelihood of skin absorption in that site. There may be coexisting signs of exposure prior to or in addition to evidence of skin cancer. These may include oil folliculitis and hyperkeratoses, described in people working with mineral oil, and pitch or tar warts. Oil hyperkeratoses were described as being flat, white, circular, hyperkeratotic smooth plaques, small in diameter and often clustered. In addition, there were verrucose pigmented round or oval irregular raised warts. Tar warts were pigmented small papules, which were often seen around the face on the eyes, eyelids, cheek, forearms and back of the hands.

Table 27.8 Occupations with potential exposure to causative agents in occupational skin cancer.

Causative agent	Occupation
Polycyclic hydrocarbons	Tar distilling Coal gas manufacturing Briquettes manufacturing Shale oil workers Refinery workers
Ultraviolet light	Outdoor workers Welders Laser exposure Printers
Ionizing radiation	Nuclear power plant workers X-ray technicians Uranium mining

Management. Prevention of the development of skin cancers is most important. In the workplace, it is important to consider substitution of carcinogens where possible; an example is the declining exposure to polycyclic hydrocarbons in recent decades. Protection of the skin, with either protective clothing or with engineering control such as machine guarding, is important. Daily washing is essential. Since most of the skin cancers are associated with a very long latency period, it is important to have continued surveillance of older or retired workers. Finally, the skin cancers need to be treated as appropriate.

References

1 Waldron HA. A brief history of scrotal cancer. *Br J Ind Med* 1983; **40**: 390–401.
2 Cruishank C, Squire JR. Skin cancer in the engineering industry from use of mineral oil. *Br J Ind Med* 1950; **7**: 1–11.
3 Emmett EA. Occupational skin cancer: a review. *J Occup Med* 1975; **17**: 44–9.
4 Epstein JH, Ormsby A, Adams RM. Occupational skin cancer. In: Adams RM, ed. *Occupational Skin Disease*, 3rd edn. Philadelphia: Saunders, 1999: 142–64.
5 Voelter-Mahlknecht S, Scheriau R, Zwahr G *et al*. Skin tumours among employees of a tar refinery: the current data and their implications. *Int Arch Occup Environ Health* 2007; **80**: 485–95.

Scleroderma and related diseases [1–4]

Scleroderma and related diseases are dealt with elsewhere, but a summary is shown in Table 27.9.

References

1 Ziegler V, Haustein UF. Die progressive Sklerodermie—eine quarzinduzierte Berufskrankheit? *Dermatol Monatsschr* 1992; **178**: 34–43.
2 Yamakage A, Ishikawa H. Generalised morphea-like scleroderma occurring in people exposed to organic solvents. *Dermatologica* 1992; **165**: 186–93.
3 Black CM, Welsh KI. Occupationally and environmentally induced scleroderma-like illness: etiology, pathogenesis, diagnosis, and treatment. *Intern Med Spec* 1988; **9**: 135–54.
4 Walker AE. Clinical aspects of vinyl chloride disease: skin. *Proc R Soc Med* 1976; **69**: 286–9.

Table 27.9 Scleroderma-like diseases related to occupational and environmental factors.

Inducing factors	Symptoms or disease
Occupational agents	
Vinyl chloride	Raynaud's phenomenon, sclerodactyly, acro-osteolysis, hepatic fibrosis, angiosarcoma, plaque-like fibrotic cutaneous lesions, leukocytopenia and thrombocytopenia
Organic solvents	Skin fibrosis, irritant dermatitis, hepatitis, neurological symptoms
Bis(4-amino-3-methylcyclohexyl) methane (used in epoxy production)	Skin sclerosis, erythema, fatigue, myalgia, arthralgia
Quartz (silicon dioxide, SiO_2)	Systemic sclerosis
Iatrogenic agents	
Bleomycin	Pulmonary fibrosis, scleroderma-like lesions
Pentazocine	Pigmentary changes, panniculitis, ulcerations and sclerotic fibrosis on injection sites
L-Tryptophan	Sclerodermatous induration, peripheral eosinophilia, myalgia, arthralgia
Silicon	Systemic sclerosis, Sjögren's syndrome, arthritis
Other substances	
Toxic oil syndrome	Scleroderma-like changes, neuromuscular atrophy, hypertension, sicca syndrome

Vibration white finger [1] (see also Chapter 28)

Definition. Vibration white finger (VWF) consists of the episodic appearance of white-finger skin patches (Raynaud's phenomenon [2]) in response to environmental cold and is accompanied by secondary loss of sensation caused by vascular ischaemia. It can be part of, but is not synonymous with, the hand–arm vibration syndrome [1].

Aetiology. The pathogenesis of VWF is poorly understood. Chronic vibration exposure may damage endothelial vasoregulatory mechanisms by disturbing the endothelial-derived relaxing factor-mediated vasodilatory function [3].

Clinical features. Operatives using vibrating tools, such as lumberjacks, coalminers and road and construction workers, are at risk of developing VWF. Affected individuals develop symptoms of Raynaud's phenomenon on exposure to cold or vibration, usually after many years of working with vibrating tools [1].

Diagnosis. The diagnosis is usually made by history alone; ice provocation tests are not always reliable in precipitating attacks of VWF [1].

Prevention. With widespread knowledge of the cause of VWF, controls over duration of use of relevant machinery and improved personal protective equipment have led to a reduction in the incidence of VWF [1].

Treatment. The treatment of VWF is the same as for Raynaud's phenomenon. It is generally believed that symptoms of VWF regress some time after cessation of exposure [1].

References

1 Gemne G. Raynaud's phenomena ('white fingers') in workers using hand-held vibrating tools. In: Kanerva L, Elsner P, Wahlberg JE, Maibach HI, eds. *Handbook of Occupational Dermatology*. Berlin: Springer, 2000: 162–6.
2 Raynaud M. *De l'Asphyxie locale et la gangrène symétrique des extrémités* [thesis]. Ringoux, Paris: 1862.
3 Gemne G. Pathophysiology and pathogenesis of disorders in workers using hand-held vibrating tools. In: Pelmear P, Taylor W, Wassermann D, eds. *Hand-Arm Vibration: A Comprehensive Guide for Occupational Health Professionals*. New York: Van Nostrand Reinhold, 1992: 41–76.

Medicolegal aspects of occupational dermatoses [1–4]

A report on a patient seen for compensation purposes should be prepared with much thought and care. Medical terms not of common currency should be explained as they occur. The following items of information should always be considered for inclusion:

1 Sources of information other than the patient (previous case notes; previous medical reports; workplace inspections).
2 Family history of atopy or any other allergies or skin disorders.
3 Previous personal history of atopy or any other allergies or skin disorders.
4 Previous occupations. Job titles, employers, types of contact, dates.
5 Present occupation. Job title, employer's name and full address, dates.
6 Time in contact with suspected causal factors. May be shorter (or longer) than time in present occupation.
7 Description of the working process. In sufficient detail to give accurate assessment of degree of skin contact, as well as the range of skin contactants.
8 Other cases of dermatitis and standard of hygiene at the place of work. Types of skin cleanser, skin creams and protective clothing used at work.
9 Time and site of initial skin complaints. Previous injury at the initial site.
10 Progress, with approximate dates of gradual or sudden aggravation or improvement, and the influence of weekends, holidays, sickness absence.
11 Degree of incapacity during period of illness. Dates of absence from work. Level of earnings: previously, during illness, at present.
12 Changes in occupation since onset of skin complaint. Job titles, dates, details of changes in skin contactants.
13 Medical advice sought, treatment obtained and its effectiveness.
14 Clinical findings. Present state (have the lesions been suppressed by topical steroids?).
15 Special investigations: patch tests, prick or scratch tests, open tests, repeated open application tests (positive and negative

tests, times of readings, vehicles, concentrations, application method, site). Exposure tests. Mycological/bacteriological examination.

16 Intercurrent diseases (fever, light eruptions, mycotic infection).

17 Diagnosis. With the Woolf reforms in the UK, it is necessary to give the full range of the opinions, including the reasons for the opinion given [5].

18 Common knowledge of risk at the occupation in question. Whether the employer could reasonably have been expected to have foreseen any risk to the skin.

19 Conclusions (in terms understandable to non-medical readers):

(a) Probable connection between occupational activity and the present pathological condition; balanced against predisposing factors and contributory factors in spare time.

(b) Possibility of continuing in previous occupation. If change of work is required, what are the chances of rehabilitation?

(c) Probable medical prognosis (state of the dermatitis), probable social prognosis (capacity for work).

References

1 Rycroft RJG. Occupational contact dermatitis. In: Rycroft RJG, Menné T, Frosch PJ, Lepoittevin J-P, eds. *Textbook of Contact Dermatitis*, 3rd edn. Berlin: Springer, 2001: 555–80.

2 Goldstein A. Writing report letters for patients with skin disease resulting from on-the-job exposures. *Dermatol Clin* 1984; **2**: 631–41.

3 McMillan EM, McKenna WB, Milne CM. Guidelines on preparing medical report for compensation purposes. *Br J Dermatol* 1982; **106**: 489–94.

4 Frosch PJ, Rycroft RJG. International legal aspects of contact dermatitis. In: Rycroft RJG, Menné T, Frosch PJ, Lepoittevin J-P, eds. *Textbook of Contact Dermatitis*, 3rd edn. Berlin: Springer, 2001: 995–1014.

5 Friston M. New rules for expert witnesses. *BMJ* 1999; **318**: 1365–6.

Specific occupational hazards [1–4]

The following is offered as an *aide-mémoire*. Many causes of contact urticaria [4] have also been described as causing protein contact dermatitis.

Agriculture [5–15]

Irritants. Artificial fertilizers, disinfectants and cleansers for milking utensils, petrol, diesel oil.

Sensitizers. Rubber (boots, gloves, milking machines), cement, local remedies for veterinary use, wood preservatives, plants, pesticides, antibiotics in animal feeds, penicillin for mastitis, nickel and cobalt in fertilizers, cobalt and vitamin K_3 in animal feeds, ethoxyquin (preservative) in feed, quinoxaline and derivatives (growth factor), dinitolmide (anticoccidiosis), phenothiazine sedatives, soil disinfectants.

Contact urticaria. Animal hair and dander.

Artists [16,17]

Irritants. Solvents, clay, plaster.

Sensitizers. Turpentine, cobalt–nickel pigments and chromium pigments, azo and phthalocyanine dyes, colophony, and epoxy, acrylic and formaldehyde resins.

Automobile, aerospace industries and aircrew [18–20]

Irritants. Solvents, oils, cutting oils, paints, glass fibre, carbon fibre, hand cleansers, low humidity, kerosene.

Sensitizers. Chromate (primers, anticorrosives, oils and cutting oils), nickel, beryllium, cobalt, rubber, epoxy and acrylic resins, dipentene in thinners.

Baking and pastry making [21–25]

Irritants. Flour, detergents.

Sensitizers. Citrus fruits, flour improvers, thiamine, spices (cinnamon, cardamom), essential oils, azo dyes, fat preservatives (lauryl gallate), sodium carboxymethyl cellulose.

Contact urticaria. Flour, spices, essential oils, α-amylase.

Bartenders [26–28]

Irritants. Detergents, citrus fruits.

Sensitizers. Flavouring agents, citrus fruits, antibacterials in detergents, nickel.

Bathing attendants [29,30]

Irritants. Detergents, free or combined chlorine/bromine.

Sensitizers. Antimicrobial agents, sodium hypochlorite, formaldehyde, essential oils.

Contact urticaria. Sodium hypochlorite.

Bookbinders [31,32]

Irritants. Glues, solvents, paper.

Sensitizers. Glues, formaldehyde, plastic monomers, size (colophony, maleopimaric acid).

Building trade [33–36]

Irritants. Cement, chalk, fly ash, hydrochloric and hydrofluoric acids, glass wool, wood preservatives (also phototoxic), organic tin compounds.

Sensitizers. Cement and fly ash (chromate, cobalt), rubber and leather gloves, additives in shale oils, glues (phenol- or urea-formaldehyde resins), wood preservatives, teak, glass wool impregnated with phenol-formaldehyde resin, epoxy resin, polyurethanes, rubber strip seals, jointing materials.

Butchers [24,37–40]

Irritants. Detergents, meat, entrails.

Sensitizers. Nickel, colophony (sawdust), antiseptics, hardwood knife handles, meat.

Contact urticaria. Meat, blood.

Canning industry

Irritants. Brine, syrup, prawns and shrimps.

Sensitizers. Asparagus, carrots, preservatives (hexamethylenetetramine in fish canning), rubber gloves.

Contact urticaria. Fruit, vegetables, prawns, shrimps.

Carpenters, cabinet makers [41–45]

Irritants. French polish, solvents, glues, cleansers, wood preservatives (also phototoxic), glass fibre.

Sensitizers. Exotic woods (teak, mahogany, rosewood, etc.), glues, polishes, turpentine, nickel, rubber (handles), plastics, colophony, and epoxy, acrylic, formaldehyde and isocyanate resins.

Chemical and pharmaceutical industry [46–50]
Irritants and sensitizers are numerous and specific for each workplace. Halogenated chemical intermediates are frequent sensitizers.

Cleaning work [51,52]
Irritants. Detergents, solvents.
Sensitizers. Rubber gloves, nickel, formaldehyde, perfumes.
Contact urticaria. Rubber gloves, perfumes, alcohols.

Coal miners [53–56]
Irritants. Stone dust, coal dust, oil, grease, hydraulic fluid, wood preservatives, cement, powdered limestone and anhydrous calcium sulphate.
Sensitizers. Rubber (boots), facemasks, explosives, chromate and cobalt in cement.

Cooks, catering industry [2,24,57–61]
Irritants. Detergents, dressings, vinegar, fish, meat, fruit and vegetable juices.
Sensitizers. Fruit and vegetables (onions, garlic, lemons, lettuce, artichokes), hardwood knife handles, spices, formaldehyde, rubber gloves.
Contact urticaria. Meat, fish, fruit, vegetables.

Dentists and dental technicians [51,62–64]
Irritants. Soap, detergents, plaster of Paris, acrylic monomer, fluxes.
Sensitizers. Local anaesthetics (tetracaine, procaine), mercury, rubber, UV-curing acrylates, aromatic epoxy acrylates, aliphatic acrylates, melamine-formaldehyde resin, BAC-ester chloride, disinfectants and sterilants (formaldehyde, glutaraldehyde, eugenol), nickel, epoxy resin (filling), periodontal dressing (balsam of Peru, colophony, eugenol), catalysts (methyl-*p*-toluenesulphonate and methyl-1,4-dichlorbenzenesulphonate) in impression and sealant materials.
Contact urticaria. Saliva, rubber gloves.

Dyers [3,34,65–68]
Irritants. Solvents, oxidizing and reducing agents, hypochlorite, hair removers.
Sensitizers. Dyes, chromate, formaldehyde.

Electricians [1,69]
Irritants. Soldering flux.
Sensitizers. Soldering flux, insulating tape (rubber, colophony, tar), rubber, nickel, bitumen, epoxy resins, glues (phenol-formaldehyde), polyurethanes.

Electronics industry [70–72]
Irritants. Soldering flux, organic solvents, HF, fibreglass, antistatic agents.
Allergens. Soldering flux, chromate, cobalt, nickel, epoxy resins, anaerobic acrylic sealants.
Contact urticaria. Soldering flux.

Enamel workers [73]
Irritants. Enamel powder.
Sensitizers. Chromate, nickel, cobalt.

Fishing [57,74–78]
Irritants. Wet work, friction, oils, petrol, redfeed from mackerel, fish juice (polypeptides).
Sensitizers. Tars, organic dyes in nets, rubber boots, rubber gloves, marine organisms (Dogger Bank itch) and plants.
Contact urticaria. Fish, marine organisms and plants.

Floor layers [1,79]
Irritants. Solvents, detergents, cement (can be ulcerative).
Sensitizers. Chromate (cement), epoxy resin, glues (phenol- and urea-formaldehyde), exotic woods, acrylates, varnish (urea-formaldehyde), polyurethanes.

Florists, gardeners, plant growers [80–84]
Irritants. Manure, bulbs, fertilizers, pesticides.
Sensitizers. Plants (*Primula obconica*, chrysanthemum, Asteraceae (Compositae), weeds, tulips, narcissus, daffodils, *Alstroemeria*), formaldehyde, pesticides, lichens.

Food industry [24,25,57,59,61]
Irritants. Detergents, vegetables.
Sensitizers. Rubber gloves, spices, vegetables, fruits, preservatives.
Contact urticaria. Vegetables, fruits, meats, fish.

Foundry work [1,34,85]
Irritants. Oils, phenol-formaldehyde resins.
Sensitizers. Phenol- and urea-formaldehyde resins, furan and epoxy resins, chromate (cement, gloves, bricks).

Glaziers [1]
Sensitizers. Rubber, epoxy resin, hardwoods.

Hairdressers and barbers [2,51,86–90]
Irritants. Shampoos, soaps, permanent-wave liquids, bleaching agents.
Sensitizers. Hair dyes, rubber, nickel, perfumes, lanolin, thioglycolates, cocamidopropylbetaine.
Contact urticaria. Ammonium persulphate, henna, rubber gloves.

Histology technicians [1,91,92]
Irritants. Solvents, formaldehyde.
Sensitizers. Formaldehyde, glutaraldehyde, organic dyes, epoxy resin, acrylates, D-limonene.

Hospital workers [51,52,93–96]
Irritants. Disinfectants, quaternary ammonium compounds, hand creams, soaps, detergents.

Sensitizers. Rubber gloves, formaldehyde, chloroxylenol, penicillin, cephalosporins, streptomycin, neomycin, piperazine, phenothiazines, hand creams, nickel, glutaraldehyde, acrylic monomer, nitrogen mustard, local anaesthetics, propacetamol.
Contact urticaria. Rubber gloves, cisplatin.

Housework [59,61,97]
Irritants. Detergents, solvents, polishes, wet work, vegetables.
Sensitizers. Rubber (gloves), nickel, chromate, flowers and plants, hand creams and lotions, handles of knives and irons, oranges, balsams, spices, pyrethrum.
Contact urticaria. Vegetables, fruits, meats, fish, spices, rubber gloves.

Jewellers [1,98,99]
Irritants. Solvents, fluxes.
Sensitizers. Nickel, epoxy resins, enamels (chromate, nickel, cobalt), precious metals.

Masons [33,100]
Irritants. Cement, chalk, bricks, acids.
Sensitizers. Chromate and cobalt in cement, rubber and leather gloves, epoxy resin, hardwoods.

Mechanics [1,18,101,102]
Irritants. Solvents, detergents, degreasers, lubricants, oils, cooling system fluids, battery acid, soldering flux.
Sensitizers. Rubber, chromate, nickel, epoxy resin, polyester resin, D-limonene.

Metal workers [1,34,103,104]
Irritants. Cutting and drilling oils, hand cleansers, solvents.
Sensitizers. Nickel, chromate (antirust agents and dyes, welding fumes), cobalt, colophony (tall oil), antibacterial agents and antioxidants in cutting oils, and chromate, cobalt and nickel in used cutting oils.

Office workers [1,105–109]
Irritants. Photocopy paper, fibreglass, indoor climate.
Sensitizers. Rubber (erasing rubber, mats, cords, finger stalls), nickel (clips, scissors, typewriters), copying papers, glue, felt-tip pen dyes.

Painters and handymen [1,99,110–113]
Irritants. Solvents, turpentine, thinner, emulsion paints, wallpaper adhesive, organic tin compounds.
Sensitizers. Turpentine, dipentene, D-limonene, cobalt (dyes, driers), chromate (green, yellow), polyurethane, epoxy and acrylic resins, triglycidyl isocyanurate, glues (urea- and phenol-formaldehyde), varnish (colophony, urea-formaldehyde), preservatives in water-based paints and glues (methylol-chloracetamide, chloracetamide), polyester paint pigments.

Performing artists [114–117]
Irritants. Mechanical, sweating.
Sensitizers. Cosmetics, colophony, nickel, hardwoods.

Photography [1,118,119]
Irritants. Alkalis, reducing and oxidizing agents, solvents.
Sensitizers. Metol (*p*-aminophenol), colour developers (azo compounds), chromate, formaldehyde, PBA-1.

Plastics industry [120,121]
Irritants. Solvents, styrene, oxidizing agents, acids.
Sensitizers. Low-molecular-weight raw materials, hardeners, additives, dyes, styrene.

Plating–electroplating (and electroforming) [1,34,122–126]
Irritants. Metal cleaners, alkalis, acids, detergents, heat, dust from metal blasting.
Sensitizers. Nickel, chromate, cobalt, mercury, gold, rhodium, rubber gloves.

Plumbers [1,127,128]
Irritants. Oils, soldering flux, hand cleansers.
Sensitizers. Rubber (gloves, packing, hoses), nickel, chromate (cement, antirust paint), epoxy resin, hydrazine, epichlor-hydrin (solvent cement).

Printers [1,34,129,130]
Irritants. Solvents, acrylates in radiation-curing printing inks and lacquers.
Sensitizers. Nickel, chromate, cobalt, formaldehyde, isothiazolinones, colophony, paper finishes, glues, turpentine, azo dyes, acrylates, etc., in radiation-curing printing inks, lacquers and printing plates, rubber gloves.

Radio and television repair [1,34]
Irritants. Soldering flux, solvents.
Sensitizers. Soldering flux (hydrazine, colophony), epoxy resin, nickel, chromate.

Restaurant personnel [59,61]
Irritants. Detergents, vegetables, citrus fruits, shrimps, herring.
Sensitizers. Nickel, spices, vegetables, hardwoods (knife handles).
Contact urticaria. Vegetables, fruit, meat, fish.

Road workers [1]
Irritants. Sand–oil mix, asphalt (phototoxic), hand cleansers.
Sensitizers. Cement, gloves (leather, rubber), epoxy resin, tar, chromate in antirust paint.

Rubber workers [131–134]
Irritants. Talc, zinc stearate, solvents.
Sensitizers. Rubber chemicals, organic dyes, tars, colophony, chromate, cobalt, phenol-formaldehyde resin.

Sheet metal workers [34,135,136]
Irritants. Solvents, paints.
Sensitizers. Chromium in paints and on zinc-galvanized sheets, glues.

Shoemakers [1,137–139]
Irritants. Solvents.
Sensitizers. Glues (PTBPF resin), leather (formaldehyde, chloroacetamide, chromate, dyes), turpentine, rubber, colophony, bisphenol A.

Shop assistants [140]
Irritants. Detergents, vegetables, fruit, meats, fish.
Sensitizers. Nickel, colophony (price labels).
Contact urticaria. Vegetables, fruit.

Tanners [1,34,141–143]
Irritants. Acids, alkalis, reducing and oxidizing agents.
Sensitizers. Chromium, formaldehyde, glutaraldehyde, vegetable tanning agents, finishes, anti-mildew agents, dyes, resins.
Contact urticaria. Formaldehyde.

Textile workers [1,67,142,144,145]
Irritants. Solvents, bleaching agents, fibres, formaldehyde.
Sensitizers. Finishes (formaldehyde resins), dyes, mordants, caprolactam, nickel, diazo paper.
Contact urticaria. Formaldehyde.

Veterinarians [51,146–149]
Irritants. Hypochlorite, quaternary ammonium compounds, cresol, rectal and vaginal examinations of cattle.
Sensitizers. Rubber gloves, antibiotics (penicillin, streptomycin, neomycin, tylosin tartrate, virginiamycin), antimycotic agents, mercaptobenzothiazole (MBT) in medicaments, glutaraldehyde, preservatives in rectal lubricants.
Contact urticaria. Animal hair and dander, obstetric fluids, animal tissues, rubber gloves.

Welders [1,34]
Irritants. Oil.
Sensitizers. Chromium (welding fumes, gloves), nickel, cobalt.

Woodworkers [41–43,150–153]
Irritants. Woods, wood preservatives, solvents, detergents, fibreboard (urea-formaldehyde resin).
Sensitizers. Woods, wood preservatives, colophony, turpentine, balsams, tars, lacquers, glues (urea, phenol- and PTBP-formaldehyde resins), *Frullania*, lichens.
Contact urticaria. Woods.

References

1 Adams RM. *Occupational Skin Disease*, 3rd edn. Philadelphia: Saunders, 1999: 578–691.
2 Rycroft RJG. Occupational contact dermatitis. In: Rycroft RJG, Menné T, Frosch PJ, Lepoittevin J-P, eds. *Textbook of Contact Dermatitis*, 3rd edn. Berlin: Springer, 2001: 555–80.
3 Foussereau J, Benezra C, Maibach HI. *Occupational Contact Dermatitis*. Copenhagen: Munksgaard, 1982.
4 Kanerva L, Elsner P, Wahlberg JE, Maibach HI. *Handbook of Occupational Dermatology*. Berlin: Springer, 2000.
5 Kanerva L, Susitaival P. Cow dander: the most common cause of occupational contact urticaria in Finland. *Contact Dermatitis* 1996; **35**: 309–10.
6 Schauder S, Schröder W, Geier J. Olaquindox-induced airborne photo-allergic contact dermatitis followed by transient or persistent light reactions in 15 pig breeders. *Contact Dermatitis* 1996; **35**: 344–54.
7 Gauchía R, Rodríguez-Serna M, Silvestre JR *et al*. Allergic contact dermatitis from streptomycin in a cattle breeder. *Contact Dermatitis* 1996; **35**: 374–5.
8 Timmer C, Coenraads PJ. Allergic contact dermatitis from cow hair and dander. *Contact Dermatitis* 1996; **34**: 292–3.
9 Koch P. Occupational allergic contact dermatitis and airborne contact dermatitis from 5 fungicides in a vineyard worker. *Contact Dermatitis* 1996; **34**: 324–9.
10 De Groot AC, Conemans JMH. Contact allergy to furazolidone. *Contact Dermatitis* 1990; **22**: 202–5.
11 Dinis A, Brandão M, Faria A. Occupational contact dermatitis from vitamin K_3 sodium bisulphite. *Contact Dermatitis* 1988; **18**: 170–1.
12 Ertle T. Beruflich bedingte Kontakt- und Photokontaktallergie bei einem Landwirt durch Chlorpromazin. *Dermatosen* 1982; **30**: 120–2.
13 Pecegueiro M. Contact dermatitis due to nickel in fertilizers. *Contact Dermatitis* 1990; **22**: 114–5.
14 Richter G. Allergic contact dermatitis from methylisothiocyanate in soil disinfectants. *Contact Dermatitis* 1980; **6**: 183–6.
15 Savini C, Morelli R, Piancastelli E *et al*. Contact dermatitis due to ethoxyquin. *Contact Dermatitis* 1989; **21**: 342–3.
16 Raccagni AA, Baldari U, Righini MG. Airborne dermatitis in a painter. *Contact Dermatitis* 1996; **35**: 119–20.
17 Fregert S, Gruvberger B. Blue and black pottery as a potential source of cobalt. *Contact Dermatitis* 1984; **10**: 50.
18 Leggat PA, Smith DR. Dermatitis and aircrew. *Contact Dermatitis* 2006; **54**: 1–4.
19 Eedy D. Carbon-fibre-induced airborne irritant contact dermatitis. *Contact Dermatitis* 1996; **35**: 362–3.
20 Condé-Salazar L, Guimaraens D, Romero LV. Occupational allergic contact dermatitis from anaerobic acrylic sealants. *Contact Dermatitis* 1988; **18**: 129–32.
21 Kanerva L, Vanhanen M, Tupasela O. Occupational allergic contact urticaria from fungal but not bacterial alpha-amylase. *Contact Dermatitis* 1997; **36**: 306–7.
22 Vincenzi C, Stinchi C, Ricci C *et al*. Contact dermatitis due to an emulsifying agent in a baker. *Contact Dermatitis* 1995; **32**: 57.
23 Hamada T, Horiguchi S. A case of allergic contact dermatitis due to sodium carboxymethyl cellulose. *Jpn J Ind Health* 1978; **20**: 207–11.
24 Bauer A, Geier J, Elsner P. Type IV allergy in the food processing industry: sensitization profiles in bakers, cooks and butchers. *Contact Dermatitis* 2002; **46**: 228–35.
25 Veien NK, Hattel T, Justesen O *et al*. Causes of eczema in the food industry. *Dermatosen* 1983; **31**: 84–6.
26 Kanerva L, Estlander T, Jolanki R. Occupational allergic contact dermatitis from nickel in bartender's metallic measuring cup. *Am J Contact Dermatitis* 1993; **4**: 39–41.
27 Sonnex TS, Rycroft RJG. Allergic contact dermatitis from orthobenzyl parachlorophenol in a drinking glass cleaner. *Contact Dermatitis* 1986; **14**: 247–8.
28 Cardullo AC, Ruszkowski AM, DeLeo VA. Allergic contact dermatitis resulting from sensitivity to citrus peel, geraniol, and citral. *J Am Acad Dermatol* 1989; **21**: 395–7.
29 Hostynek JJ, Patrick E, Younger B *et al*. Hypochlorite sensitivity in man. *Contact Dermatitis* 1989; **20**: 32–7.
30 Rycroft RJG, Penny PT. Dermatoses associated with brominated swimming pools. *BMJ* 1983; **287**: 462.
31 Karlberg AT, Gäfvert E, Hagelthorn G *et al*. Maleopimatic acid: a potent sensitizer in modified rosin. *Contact Dermatitis* 1990; **22**: 193–201.
32 English JSC, Lovell CR, Rycroft RJG. Contact dermatitis from dibutyl maleate. *Contact Dermatitis* 1985; **13**: 337–8.
33 Avnstorp C. Risk factors for cement eczema. *Contact Dermatitis* 1991; **25**: 81–8.
34 Burrows D. Adverse chromate reactions on the skin. In: Burrows D, ed. *Chromium: Metabolism and Toxicity*. Boca Raton, FL: CRC Press, 1983: 137–63.
35 Garcia J, Armisen A. Cement dermatitis with isolated cobalt sensitivity. *Contact Dermatitis* 1985; **12**: 52.
36 Bock M, Schmidt A, Bruckner T *et al*. Occupational skin disease in the construction industry. *Br J Dermatol* 2003; **149**: 1165–71.
37 Beck HI, Nissen BK. Type I and type IV allergy to specific chicken organs. *Contact Dermatitis* 1982; **8**: 217–8.

38 Francalanci S, Giorgini S, Gola M *et al.* Occupational dermatitis in a butcher. *Contact Dermatitis* 1984; **11**: 320–1.
39 Göransson K. Occupational contact urticaria to fresh cow and pig blood in slaughtermen. *Contact Dermatitis* 1981; **7**: 281–2.
40 Lachapelle JM. Occupational allergic contact dermatitis to povidone–iodine. *Contact Dermatitis* 1984; **11**: 189–90.
41 Estlander T, Jolanki R, Alanko K *et al*. Occupational allergic contact dermatitis caused by wood dusts. *Contact Dermatitis* 2001; **44**: 213–7.
42 Beck MH, Hausen BM, Dave VK. Allergic contact dermatitis from *Machaerium scleroxylum* Tul. (Pao ferro) in a joinery shop. *Clin Exp Dermatol* 1984; **9**: 159–66.
43 Hausen BM. *Woods Injurious to Human Health: A Manual*. Berlin: de Gruyter, 1981.
44 Irvine C, Reynolds A, Finlay AY. Erythema multiforme-like reaction to 'rosewood'. *Contact Dermatitis* 1988; **19**: 224–5.
45 Tilsley DA. Australian blackwood dermatitis. *Contact Dermatitis* 1990; **23**: 40–61.
46 Jolanki R, Alanko K, Pfäffli P *et al.* Occupational allergic contact dermatitis from 5-chloro-1-methyl-4-nitroimidazole. *Contact Dermatitis* 1997; **36**: 53–4.
47 Sherertz EF. Occupational skin disease in the pharmaceutical industry. *Dermatol Clin* 1994; **12**: 533–6.
48 Kleine-Natrop HE, Richter G. Arbeitsdermatosen in der pharmazeutischen Industrie. *Dermatosen* 1980; **28**: 8–10.
49 Niklasson B, Björkner B, Hansen L. Occupational contact dermatitis from antitumor agent intermediates. *Contact Dermatitis* 1990; **22**: 233–5.
50 Pedersen NB, Thormann J, Senning A. Occupational contact allergy to *bis*-(4-chlorophenyl)-methyl chloride. *Contact Dermatitis* 1980; **6**: 56.
51 Turjanmaa K, Mäkinen-Kiljunen S, Reunala T *et al.* Natural rubber latex allergy: the European experience. *Immunol Allergy Clin North Am* 1995; **15**: 71–88.
52 Nilsson E. Contact sensitivity and urticaria in 'wet' work. *Contact Dermatitis* 1985; **13**: 321–8.
53 Lachapelle JM, Mahmoud G, Vanherle R. Anhydrite dermatitis in coal mines: an airborne irritant reaction assessed by laser Doppler flowmetry. *Contact Dermatitis* 1984; **11**: 188–9.
54 Matthews BF. Dermatitis in the South Wales mining industry: a report of a survey of two collieries. *Br J Ind Med* 1959; **16**: 200–7.
55 Puttick LM. *Skin Disorders in the Coal Mining Industry* [dissertation]. London: University of London, 1989.
56 Rook A, Hodgson G. Dermatitis in coal miners. *Br J Ind Med* 1956; **13**: 281–6.
57 Halkier-Sørensen L, Heickendorff L, Dalsgaard I *et al.* Skin symptoms among workers in the fish processing industry are caused by high molecular weight compounds. *Contact Dermatitis* 1991; **24**: 94–100.
58 Cronin E. Dermatitis of the hands in caterers. *Contact Dermatitis* 1987; **17**: 265–9.
59 Cronin E. Dermatitis in food handlers. In: Callen JP, Dahl MV, Golitz LE *et al.*, eds. *Advances in Dermatology*, Vol. 4. Chicago: Year Book, 1989: 113–23.
60 Dooms-Goossens A, Dubelloy R, Degreef H. Contact and systemic contact-type dermatitis to spices. *Dermatol Clin* 1990; **8**: 89–93.
61 Hausen BM, Hjorth N. Skin reactions to topical food exposure. *Dermatol Clin* 1984; **2**: 567–78.
62 Wallenhammar LM, Ortengren U, Andreasson H *et al*. Contact allergy and hand eczema in Swedish dentists. *Contact Dermatitis* 2000; **43**: 192–9.
63 Rustemeyer T, Frosch PJ. Occupational skin diseases in dental laboratory technicians, 1: clinical picture and causative factors. *Contact Dermatitis* 1996; **34**: 125–33.
64 Straube M, Szliska C, Peiler D *et al.* Occupational allergic contact dermatitis from BAC-esterchloride (beta-phenylethyl-dibutylacetic acid-ethylester-ammonium chloride). *Contact Dermatitis* 1996; **35**: 103–4.
65 Wilkinson SM, McGechaen K. Occupational allergic contact dermatitis from reactive dyes. *Contact Dermatitis* 1996; **35**: 376.
66 Fujimoto K, Hashimoto S, Kozuka T *et al.* Occupational pigmented contact dermatitis from azo-dyes. *Contact Dermatitis* 1985; **12**: 15–7.
67 Kiec-Swierczynska M. Occupational contact dermatitis in the workers employed in production of Texas textiles. *Dermatosen* 1982; **30**: 41–3.
68 Sadhra S, Duhra P, Foulds IS. Occupational dermatitis from Synacril Red 3B liquid (CI Basic Red 22). *Contact Dermatitis* 1989; **21**: 316–20.
69 Kanerva L, Estlander T, Jolanki R. Allergic patch test reactions caused by the rubber chemical cyclohexyl thiophthalimide. *Contact Dermatitis* 1996; **34**: 23–6.
70 Bennett DE, Mathias CGT, Susten AS *et al.* Dermatitis from plastic tote boxes impregnated with an antistatic agent. *J Occup Med* 1988; **30**: 252–5.
71 Koh D, Foulds IS, Aw TC. Dermatological hazards in the electronics industry. *Contact Dermatitis* 1990; **22**: 1–7.
72 Stevenson CJ, Morgan PR. Investigation and prevention of chromate dermatitis in colour television manufacture. *J Soc Occup Med* 1983; **33**: 19–20.
73 Motolese A, Truzzi M, Giannini A *et al.* Contact dermatitis and contact sensitization among enamellers and decorators in the ceramics industry. *Contact Dermatitis* 1993; **28**: 59–62.
74 Ashworth J, Curry FM, White IR *et al.* Occupational allergic contact dermatitis in east coast of England fishermen: newly described hypersensitivities to marine organisms. *Contact Dermatitis* 1990; **22**: 185–6.
75 Bonnevie P. Fishermen's 'Dogger Bank itch', an allergic contact eczema due to the *Alcyonidium hirsutum*, the 'sea chervil'. *Acta Allergy* 1948; **1**: 40–6.
76 Carlé JS, Thybo H, Christophersen C. Dogger Bank itch, 3: isolation, structure determination and synthesis of a hapten. *Contact Dermatitis* 1982; **8**: 43–7.
77 Newhouse ML. Dogger Bank itch: survey of trawlermen. *BMJ* 1966; **1**: 1142–5.
78 Van der Willigen AH, Habets JMW, van Joost T *et al.* Contact allergy to iodine in Japanese sargassum. *Contact Dermatitis* 1988; **18**: 250–2.
79 Wahlberg JE, Hogberg M. Health screening for occupational dermatoses in flooring installers. *Boll Dermatol Allergol Prof* 1987; **2**: 95–102.
80 Bruynzeel DP, Tafelkruijer J, Wilks MF. Contact dermatitis due to a new fungicide used in the tulip bulb industry. *Contact Dermatitis* 1995; **33**: 8–11.
81 Lovell CR. *Plants and the Skin*. Oxford: Blackwell Scientific Publications, 1993.
82 Benezra C, Ducombs G, Sell Y *et al. Plant Contact Dermatitis*. Toronto: Decker, 1985.
83 Mitchell JC, Rook A. *Botanical Dermatology*. Philadelphia: Lea & Febiger, 1979.
84 Zug KA, Marks JG. Plants and woods. In: Adams RM, ed. *Occupational Skin Disease*, 3rd edn. Philadelphia: Saunders, 1999: 567–96.
85 Bruze M. Allergic contact dermatitis from cured and used casting sand. *Contact Dermatitis* 1994; **31**: 128–9.
86 Majoie IM, Bruynzeel DP. Occupational immediate-type hypersensitivity to henna in a hairdresser. *Am J Contact Dermatitis* 1996; **7**: 38–40.
87 Van der Walle HB, Brunsveld VM. Dermatitis in hairdressers, 1: the experience of the past 4 years; 2: management and prevention. *Contact Dermatitis* 1994; **30**: 217–21, 265–70.
88 Peters KP, Frosch PJ, Uter W *et al*. Occupational contact dermatitis in hairdressers: results of a multicenter study in eight centers of the 'Information Network of Dermatological Clinics' in Germany. *Dermatosen* 1994; **42**: 50–7.
89 Cronin E, Kullavanijaya P. Hand dermatitis in hairdressers. *Acta Derm Venereol Suppl (Stockh)* 1979; **85**: 47–50.
90 Holness DL, Nethercott JR. Dermatitis in hairdressers. *Dermatol Clin* 1990; **8**: 119–26.
91 Mathias CGT, Caldwell TM, Maibach HI. Contact dermatitis and gastrointestinal symptoms from hydroxyethylmethacrylate. *Br J Dermatol* 1979; **100**: 447–9.
92 Karlberg AT, Dooms-Goossens A. Contact allergy to oxidized D-limonene among dermatitis patients. *Contact Dermatitis* 1997; **36**: 201–6.
93 Mathelier-Fusade P, Mansouri S, Aïssaoui M *et al.* Airborne contact dermatitis from propacetamol. *Contact Dermatitis* 1997; **36**: 267–8.
94 Filipe P, Silva R, Soares Almeida L *et al.* Occupational allergic contact dermatitis from cephalosporins. *Contact Dermatitis* 1996; **34**: 226.
95 Schena D, Barba A, Costa G. Occupational contact urticaria due to cisplatin. *Contact Dermatitis* 1996; **34**: 220–1.
96 Lammintausta K. Hand dermatitis in different hospital workers who perform wet work. *Dermatosen* 1983; **31**: 14–9.
97 Calnan CD, Bandmann H-J, Cronin E *et al.* Hand dermatitis in housewives. *Br J Dermatol* 1970; **82**: 543–8.
98 Bedello PG, Goitre M, Roncarolo G *et al.* Contact dermatitis to rhodium. *Contact Dermatitis* 1987; **17**: 111–12.
99 McCunney RJ. Diverse manifestations of trichloroethylene. *Br J Ind Med* 1988; **45**: 122–6.
100 Van Putten PB, Coenraads PJ, Nater JP. Hand dermatoses and contact allergic reactions in construction workers exposed to epoxy resins. *Contact Dermatitis* 1984; **10**: 146–50.
101 Meding B, Barregärd L, Marcus K. Hand eczema in car mechanics. *Contact Dermatitis* 1994; **30**: 129–34.
102 Burrows D. Chromium dermatitis in a tyre fitter. *Contact Dermatitis* 1981; **7**: 55–6.

103 Foulds IS, Koh D. Dermatitis from metalworking fluids. *Clin Exp Dermatol* 1990; **15**: 157–62.
104 Pryce DW, White J, English JSC *et al*. Soluble oil dermatitis: a review. *J Soc Occup Med* 1989; **39**: 93–8.
105 Marks JG. Dermatologic problems of office workers. *Dermatol Clin* 1988; **6**: 75–9.
106 Rycroft RJG. Low-humidity occupational dermatoses. In: Gardner AW, ed. *Current Approaches to Occupational Health*, Vol. 3. Bristol: Wright, 1987, 1–13.
107 Skov P, Valbjørn O, Pedersen BV. Influence of personal characteristics, job-related factors and psychosocial factors on the sick building syndrome. *Scand J Work Environ Health* 1989; **15**: 286–95.
108 Thestrup-Pedersen K, Bach B, Petersen R. Allergic investigations in patients with the sick building syndrome. *Contact Dermatitis* 1990; **23**: 53–5.
109 Verbeck SJA, Buise-van Unnik EMM, Malten KE. Itching in office workers from glass fibres. *Contact Dermatitis* 1981; **7**: 354.
110 Wigger-Alberti W, Hofmann M, Elsner P. Contact dermatitis caused by triglycidyl isocyanurate. *Am J Contact Dermatitis* 1997; **8**: 106–7.
111 Cofield BG, Storrs FJ, Strawn CB. Contact allergy to aziridine paint hardener. *Arch Dermatol* 1985; **121**: 373–6.
112 Högberg M, Wahlberg JE. Health screening for occupational dermatoses in house painters. *Contact Dermatitis* 1980; **6**: 100–6.
113 Mathias CGT. Dermatitis from paints and coatings. *Dermatol Clin* 1984; **2**: 585–602.
114 Färm G, Karlberg AT, Lidén C. Are opera-house artistes afflicted with contact allergy to colophony and cosmetics? *Contact Dermatitis* 1995; **32**: 273–80.
115 Rimmer S, Spielvogel RL. Dermatological problems of musicians. *J Am Acad Dermatol* 1990; **22**: 657–63.
116 Bork K. Stigmas, symptoms and diseases of the skin in musicians. *Hautarzt* 1993; **44**: 574–80.
117 Helm TN, Taylor JS, Adams RM *et al*. Skin problems of performing artists. *Am J Contact Dermatitis* 1993; **4**: 27–32.
118 Lidén C. Persulfate bleach accelerator—a potent contact allergen in film laboratories: chemical identification, purity studies, and patch testing. *Am J Contact Dermatitis* 1990; **1**: 21–4.
119 Rustemeyer T, Frosch PJ. Allergic contact dermatitis from colour developers. *Contact Dermatitis* 1995; **32**: 59–60.
120 Björkner B. Plastic materials. In: Rycroft RJG, Menné T, Frosch PJ, Lepoittevin J-P, eds. *Textbook of Contact Dermatitis*, 3rd edn. Berlin: Springer, 2001: 783–824.
121 Sjöborg S, Dahlquist I, Fregert S *et al*. Contact allergy to styrene with cross reaction to vinyltoluene. *Contact Dermatitis* 1982; **8**: 207–8.
122 Goh CL. Occupational dermatitis from gold plating. *Contact Dermatitis* 1988; **18**: 122–3.
123 Lee HS, Goh CL. Occupational dermatosis among chrome platers. *Contact Dermatitis* 1988; **18**: 89–93.
124 Mathias CGT. Contact dermatitis from cyanide plating solutions. *Arch Dermatol* 1982; **118**: 420–2.
125 Rudzki E, Rebandel P, Stroinski J *et al*. Reactions to cadmium. *Contact Dermatitis* 1988; **18**: 183–4.
126 De la Cuadra J, Grau-Massanés M. Occupational contact dermatitis from rhodium and cobalt. *Contact Dermatitis* 1991; **25**: 182–4.
127 Beck MH, King CM. Allergic contact dermatitis to epichlorhydrin in a solvent cement. *Contact Dermatitis* 1983; **9**: 315.
128 Condé-Salazar L, Gorospe M, Guimaraens D. A new source of sensitivity to epoxy resin. *Contact Dermatitis* 1993; **28**: 292.
129 Andrews LS, Clary JJ. Review of the toxicity of multifunctional acrylates. *J Toxicol Environ Health* 1986; **19**: 149–64.
130 Livesley EJ, Rushton L, English JS *et al*. The prevalence of occupational dermatitis in the UK printing industry. *Occup Environ Med* 2002; **59**: 487–92.
131 Hansson C. Allergic contact dermatitis from *N*-(1,3-dimethylbutyl)-*N*′-phenyl-*p*-phenylenediamine and from compounds in polymerized 2,2,4-trimethyl-1,2-dihydroquinoline. *Contact Dermatitis* 1994; **30**: 114–5.
132 Kilpikari I. Occupational contact dermatitis among rubber workers. *Contact Dermatitis* 1982; **8**: 359–62.
133 Guin JD, Hamann C, Sullivan KM. Natural and synthetic rubber. In: Adams RM, ed. *Occupational Skin Disease*, 3rd edn. Philadelphia: Saunders, 1999: 501–52.
134 White IR. Dermatitis in rubber manufacturing industries. *Dermatol Clin* 1988; **6**: 53–9.
135 Fregert S, Gruvberger B. Chromate dermatitis from oil emulsion contaminated from zinc-galvanized iron plate. *Contact Dermatitis* 1976; **2**: 121.
136 Fregert S, Gruvberger B, Heijer A. Chromium dermatitis from galvanized sheets. *Berufsdermatosen* 1970; **18**: 254–60.
137 Foussereau J, Cavelier C, Selig D. Occupational eczema from paratertiary-butylphenol formaldehyde resins: a review of the sensitizing resins. *Contact Dermatitis* 1976; **2**: 254–8.
138 Jelen G, Cavelier C, Protois JP *et al*. A new allergen responsible for shoe allergy: chloroacetamide. *Contact Dermatitis* 1989; **21**: 110–11.
139 Srinivas CR, Devadiga R, Aroor AR. Footwear dermatitis due to bisphenol A. *Contact Dermatitis* 1989; **20**: 150–1.
140 Hausen BM, Kuhlwein A, Schulz KH. Kolophonium-Allergie. Ein Beitrag zur Herkunft, Chemie und Verwendung von Kolophonium und Kolophonium-modifizierten Produkten. *Dermatosen* 1982; **30**: 107–15, 145–52.
141 Calnan CD, Cronin E. Vegetable tans in leather. *Contact Dermatitis* 1978; **4**: 295–6.
142 Estlander T, Kanerva L, Jolanki R. Occupational allergic dermatoses from textile, leather and fur dyes. *Am J Contact Dermatitis* 1990; **1**: 13–20.
143 Helander I. Contact urticaria from leather containing formaldehyde. *Arch Dermatol* 1977; **113**: 1443.
144 Aguirre A, González Pérez R, Zubizarreta J. Allergic contact dermatitis from epsilon-caprolactam. *Contact Dermatitis* 1995; **32**: 174–5.
145 Sengel D, Khelladi A, Foussereau J. Allergie professionnelle au papier diazo dans l'industrie textile. *Dermatosen* 1979; **27**: 178–9.
146 Wilson CL, Powell SM. An unusual case of allergic contact dermatitis in a veterinary surgeon. *Contact Dermatitis* 1990; **23**: 42–3.
147 Falk ES, Hektoen H, Thune PO. Skin and respiratory tract symptoms in veterinary surgeons. *Contact Dermatitis* 1985; **12**: 274–8.
148 Hjorth N, Roed-Petersen J. Allergic contact dermatitis in veterinary surgeons. *Contact Dermatitis* 1980; **6**: 27–9.
149 Rudzki E, Rebandel P, Grzywa Z *et al*. Occupational dermatitis in veterinarians. *Contact Dermatitis* 1982; **8**: 72–3.
150 Jagels R. Health hazards of natural and introduced chemical components of boatbuilding woods. *Am J Ind Med* 1985; **8**: 241–51.
151 Vale PT, Rycroft RJG. Occupational irritant contact dermatitis from fibreboard containing urea-formaldehyde resin. *Contact Dermatitis* 1988; **19**: 62.
152 Wilkinson DS. Timber preservatives. *Contact Dermatitis* 1979; **5**: 278–9.
153 Woods B, Calnan CD. Toxic woods. *Br J Dermatol* 1976; **94** (Suppl. 13): 1–97.

CHAPTER 28
Mechanical and Thermal Injury

C.T.C. Kennedy[1], *D.A.R. Burd*[2] *& D. Creamer*[3]

[1]Bristol Dermatology Centre, Bristol Royal Infirmary, Bristol, UK
[2]Department of Surgery, Prince of Wales Hospital, Shatin, New Territories, Hong Kong
[3]Department of Dermatology, King's College Hospital, London, UK

Overview of skin injury, 28.1
Determinants of the response to injury, 28.2
Isomorphic (Koebner) response, 28.2
Nikolsky sign, 28.4
Utilization of mechanical stimuli, 28.4
Biomechanical considerations, 28.4
Mechanical properties of the skin, 28.5
Physiological variation, 28.7
Pathological variation, 28.8
Effects of friction, 28.9
Callosities, corns and calluses, 28.10
Friction blisters, 28.12
Friction and dermatitis, 28.13
Friction and other dermatoses, 28.15
Black heel and palm, 28.16
Pressure ulcer, 28.16
Effects of suction, 28.23
Neonatal suction blisters, 28.24
Therapeutic cupping, 28.24
Suction purpura in children, 28.24
Penile suction injuries, 28.24
Other examples of suction purpura, 28.24
Miscellaneous reactions to mechanical trauma, 28.25
Coin-rubbing injuries, 28.25
Reactions to musical instruments, 28.25
Hypothenar hammer syndrome, 28.26
Achenbach's syndrome, 28.27
Trauma and subcutaneous fat, 28.27
Computer palms and mouse fingers, 28.27
Dermatological problems of the amputee, 28.27
Spectacle-frame acanthoma, 28.29
Acne mechanica, 28.30
Traumatic effects of sports, 28.30
Skin signs of torture, 28.32
Skin signs of child abuse, 28.34
Traumatic lesions during intensive care, 28.39
Cutaneous injuries in the newborn, 28.39
Penile injuries, 28.39
Foreign bodies, 28.39
Some distinctive foreign-body reactions, 28.43
Fibreglass dermatitis, 28.47
Complications of tattoos, 28.48
Hair as a foreign body, 28.49
Other penetrating injuries, 28.51
Reactions to ornamental metal piercing, 28.51
Titanium implants, 28.52
Skin lesions in drug addicts, 28.52
Skin hazards of swimming and diving, 28.53
General hazards, 28.53
Swimming pools and whirlpools, 28.54
Outdoor swimming, 28.55
Professional deep-sea diving, 28.55
Vibration, 28.56
Hand–arm vibration syndrome, 28.57
Other vasomotor symptoms, 28.58
Vibratory angio-oedema, 28.58
Reactions to internal mechanical stress, 28.60
Tissue expansion, 28.60
Piezogenic pedal papules, 28.61
Muscle herniation of the limbs, 28.61
Mechanical trauma and skin neoplasia, 28.62
Reactions to cold, 28.63
Physiological reactions to cold, 28.63
Diseases caused or aggravated by cold, 28.63
Diseases of cold exposure, 28.63
Diseases of abnormal sensitivity to cold, 28.65
Effects of heat and infrared radiation, 28.71
Experimental effects, 28.72
Erythema ab igne, 28.72
Heat-associated carcinomas, 28.73
Burns, 28.74
Clinical aspects, 28.75
Cutaneous sequelae of burns, 28.88
Electrical burns, 28.88
Laser burns, 28.90
Microwave radiation burns, 28.90
Burns and skin neoplasia, 28.90
Abuse by burning, 28.91
Miscellaneous reactions, 28.92
Blackening of the skin by metals, 28.92
Rusting, 28.93
Finger wrinkling, 28.93
Carbon monoxide poisoning, 28.93

Overview of skin injury

C.T.C. Kennedy and D. Creamer, pp. 28.1–28.63

The skin is constantly subjected to both internal and external mechanical forces, so that for experimental purposes it may be impossible to determine what constitutes the normal resting state. These forces are likely to be as important in the maintenance of the structural integrity of the connective tissues of the dermis [1–3] and the keratin intermediate filament network of the epidermis [4] as they are with bone, which becomes demineralized during the protracted absence of normal gravitational force during space travel [5]. Mechanical stretching of keratinocytes induces a hyperproliferative response via activation of extracellular-signal related kinase [6]. In contrast to events in the whole organism, isolated human dermal fibroblasts in culture make more collagen when subjected to reduced gravity [7]. Many normal biochemical functions of the skin are dependent on appropriate mechanical forces, and when these become excessive, as in lymphoedema,

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

protease inhibitors are released with many deleterious consequences [8].

Healthy skin is well adapted to resist the adverse effects of a wide range of mechanical injuries [9]. These include friction, pressure, contusion, laceration, suction and vibration. The clinical consequence of injury will depend on characteristics of the noxious stimulus, such as its intensity and duration. Factors related to the skin also influence the response; thus, the same degree of friction may produce a blister in one person but no visible change in another. Time is required for adaptive responses, such as callus formation and lichenification, to occur.

When skin is subjected to mechanical stress its properties may be altered, and these changes may make disease more likely. For example stretched skin can have a higher transepidermal water loss [10].

Determinants of the response to injury

It is likely that racial and genetic factors have a major role in determining the responses to mechanical forces. At extremes of age, the skin has a reduced ability to withstand shear and other forces. Body site can determine how the skin responds, for example friction blisters do not occur on loose skin. The presence and degree of subcutaneous fat will influence the effect of pressure on the skin.

The physiological status of the skin that is being subjected to injury can have a major effect; for example, a moderate degree of sweating hydrates the stratum corneum and increases the coefficient of friction, whereas higher levels of sweating sufficient to produce free fluid on the surface markedly reduce the coefficient of friction. Environmental temperature is also important, as is humidity, the stratum corneum becoming brittle and inelastic when humidity is reduced. The withdrawal response to noxious stimuli is impaired by neurological disorders, such as syringomyelia, and as a result burns and other injuries are common in patients with neurological deficits. Some systemic diseases can result in a qualitatively different response to injury, for example the dermopathy of diabetes, and debilitating disease will increase susceptibility to pressure. The defective organization of the dermal–epidermal junction or of the superficial dermis seen in the mechanobullous disorders predisposes to blister formation with trivial trauma, and individuals with disorders of the connective tissue, such as Ehlers–Danlos syndrome and Marfan's syndrome, show abnormal fragility to mechanical injury. Some drugs, notably corticosteroids and d-penicillamine, can modify the structural integrity of the skin. Occasionally, structural changes in the skin protect patients from mechanical injury. In amyotrophic lateral sclerosis, pressure ulcers occur less than in comparably bedridden patients, probably because of more dense packing of collagen fibrils [11]. Finally, there seem to be reproducible differences in response between individuals that are poorly understood.

The discussion of mechanical and thermal injury to the skin in this chapter is limited to those effects that may concern the dermatologist. Some conditions are discussed elsewhere; for example, self-inflicted trauma (see Chapter 64). The therapeutic uses of pressure applied to the skin for venous hypertension (see Chapter 47), lymphoedema (see Chapter 48) and hypertrophic scars (see Chapter 45) are discussed in other chapters.

References

1 Smith DW. Mechanical factors in the normal and abnormal development of the skin and its derivatives. *Birth Defects* 1981; **17**: 61–6.
2 Evans G, Egan JM. Catching up the orthopods: mechanical forces matter in tissues other than bone. *BMJ* 1988; **297**: 936.
3 Eckes B, Krieg T. Regulation of connective tissue homeostasis in the skin by mechanical forces. *Clin Exp Rheumatol* 2004; **22** (3 Suppl. 33): S73–6.
4 Russell D, Andrews PD, James J, Lane EB. Mechanical stress induces profound remodelling of keratin filaments and cell junctions in epidermolysis bullosa simplex keratinocytes. *J Cell Sci* 2004; **117**: 5233–43.
5 Toback AC, Kohn SR. Manifesto of space medicine: the next dermatologic frontier. *J Am Acad Dermatol* 1989; **20**: 489–95.
6 Yano S, Komine M, Fujimoto M *et al*. Mechanical stretching in vitro regulates signal transduction pathways and cellular proliferation in human epidermal keratinocytes. *J Invest Dermatol* 2004; **122**: 783–90.
7 Seitzer U, Bodo M, Müller PK *et al*. Microgravity and hypergravity effects on collagen biosynthesis of human dermal fibroblasts. *Cell Tissue Res* 1995; **282**: 513–7.
8 Ryan TJ. Biochemical consequences of mechanical forces generated by distension and distortion. *J Am Acad Dermatol* 1989; **21**: 116–30.
9 Suskind RR. Environment and the skin. *Med Clin North Am* 1990; **74**: 307–24.
10 Pedersen L, Jemec GB. Mechanical properties and barrier function of healthy human skin. *Acta Derm Venereol* 2006; **86**: 308–11.
11 Ono S, Nagao K, Yamauchi M. Amorphous material of skin in amyotrophic lateral sclerosis: a morphologic and biochemical study. *Neurology* 1994; **44**: 537–40.

Isomorphic (Koebner) response

Definition. The development of lesions in previously normal skin that has been subjected to trauma [1,2]. The response should be reproducible and not limited to one type of trauma. The term Koebner response is best not used when a dermatosis occurs resulting from the spread of an infective agent (e.g. molluscum contagiosum or warts); for this phenomenon, the term *pseudo-Koebner* could be used. In the 'reverse' Koebner response, trauma to a lesion results in it resolving. It differs from the *isotopic response* [3,4], in which a dermatosis occurs at the site of a previous healed and unrelated dermatosis; this is not within the scope of this chapter.

History. Koebner originally described the localization of psoriasis to skin injured by a wide range of stimuli [1] but the term has been used for a similar phenomenon in other diseases [2].

Aetiology. Many forms of physical trauma, including friction, pressure, incision and laceration, skin grafting, bites, vaccination skin tests, burns, freezing, and ultraviolet (UV) and ionizing radiation have been implicated; in addition, many infections of the skin and dermatoses have been associated with the Koebner response.

Pathogenesis. Underlying mechanisms have been most intensively studied in psoriasis (Fig. 28.1) [5], in which it seems that the epidermis and dermis both contribute [6] but that epidermal damage is probably a critical event [7]. There is an increased influx of CD4 lymphocytes [8] and local production of cytokines and adhesion molecules are likely to be important. Little is known about the pathogenesis in other conditions in which the Koebner phenomenon occurs.



Fig. 28.1 Histologically proven psoriasis appearing in a split-skin donor site. (Courtesy of Southmead Hospital, Bristol, UK.)

Table 28.1 Diseases showing the Koebner response.

Disease	Reference
Carcinomas	Fisher *et al*. [14]
Darier's disease	Penrod *et al*. [15]
Erythema multiforme	Huff & Weston [16]
Granuloma annulare	Borgia *et al.* [17]
Hailey–Hailey disease	Morales *et al*. [18]
Leukaemia	Koizumi *et al*. [19]
Lichen planus	(see Chapter 41)
Lichen sclerosus	Todd *et al*. [20]
Lupus erythematosus	Ueki [21]
Scleromyxoedema	Durani *et al*. [25]
Multicentric reticulohistiocytosis	Aldridge *et al*. [29]
Necrobiosis lipoidica	Gebauer & Armstrong [23]
Pemphigus foliaceus	Rotunda *et al.* [26]
Perforating collagenosis and folliculitis	Jelinek [24]
Psoriasis	Farber *et al*. [9]
Myxoedema, pretibial	Missner *et al*. [22]
Vasculitis	Green & Narajan [27]
Vitiligo	Sweet [10]
Xanthoma	Miwa & Kanzaki [28]

Clinical features. A dermatosis develops at a site of trauma. In psoriasis, the Koebner response occurs in about 20% of patients, but reported series vary widely [5]; the latency is about 10–14 days, and a Koebner response is more likely to occur when the disease is active. As well as in psoriasis [9], the Koebner response is often seen in lichen planus [2] and vitiligo [10–13]. It has been well recorded in many other diseases, some of which are shown in Table 28.1 [14–29].

It is controversial whether it is appropriate to use the term Koebner phenomenon for the pustular response to injury in Behçet's disease and pyoderma gangrenosum; this is usually termed pathergy (see Chapter 50). Kaposi's sarcoma is still sometimes included, although some cases could be an example of pseudo-Koebner response caused by Kaposi's sarcoma-related herpesvirus [30] and others are examples of the isotopic response [31].

References

1 Köbner H. Zur aetiologie der psoriasis. *Viertel jahresschrift fur Dermatologie und Syphilis* 1876; **3**: 559–61.
2 Boyd AS, Neldner KH. The isomorphic response of Köbner. *Int J Dermatol* 1990; **29**: 401–10.
3 Wolf R, Brenner S, Ruocco V, Filioli FG. Isotopic response. *Int J Dermatol* 1995; **34**: 341–8.
4 Ruocco V, Ruocco E, Ghersetich I *et al*. Isotopic response after herpesvirus infection: an update. *J Am Acad Dermatol* 2002; **46**: 90–4.
5 Mohla G, Brodell RT. The Köbner phenomenon in psoriasis: a common response to skin trauma. *Postgrad Med* 1999; **106**: 39–40.
6 Miller RAW. The Köbner phenomenon. *Int J Dermatol* 1982; **21**: 192–7.
7 Powles AV, Baker BS, Rutman AJ *et al*. Epidermal rupture is the initiating factor for the Köbner response in psoriasis. *Acta Derm Venereol (Stockh)* 1990; **70**: 35–8.
8 Baker BS, Powles AV, Lambert S *et al*. A prospective study of the Köbner reaction and T lymphocytes in uninvolved psoriatic skin. *Acta Derm Venereol (Stockh)* 1988; **68**: 430–4.
9 Farber EM, Roth RJ, Aschheim E *et al*. Role of trauma in isomorphic response in psoriasis. *Arch Dermatol* 1965; **91**: 246–51.
10 Sweet RD. Vitiligo as a Köbner phenomenon. *Br J Dermatol* 1978; **99**: 223–4.
11 Hatchome N, Kato T, Tagami H. Therapeutic success of epidermal grafting in generalized vitiligo is limited by the Köbner phenomenon. *J Am Acad Dermatol* 1990; **22**: 87–91.
12 Levine EL, Ribeiro GG. Vitiligo and radiotherapy: the Köbner phenomenon demonstrated in patients with vitiligo undergoing radiotherapy for carcinoma of the breast. *Clin Oncol* 1994; **6**: 133–4.
13 Njoo MD, Das PK, Bos JD, Westerhof W. Association of the Köbner phenomenon with disease activity and therapeutic responsiveness in vitiligo vulgaris. *Arch Dermatol* 1999; **135**: 407–13.
14 Fisher B, Fisher ER, Feduska N. Trauma and the localisation of tumor cells. *Cancer* 1967; **20**: 23–30.
15 Penrod JN, Everett MA, McCreight WG. Observations on keratosis follicularis. *Arch Dermatol* 1960; **82**: 367–70.
16 Huff JC, Weston WL. Isomorphic phenomenon in erythema multiforme. *Clin Exp Dermatol* 1983; **8**: 409–13.
17 Borgia F, Cannavo SP, Guarneri F *et al*. Isomorphic response after saphenectomy in a patient with granuloma annulare. *J Am Acad Dermatol* 2004; **50** (2 Suppl.): S31–3.
18 Morales A, Livingood CS, Hu F. Familial benign chronic pemphigus. *Arch Dermatol* 1966; **93**: 324–8.
19 Koizumi H, Kumakiti M, Ishizuka M *et al*. Leukemia cutis in acute myelomonocytic leukemia: infiltration to minor traumas and scars. *J Dermatol* 1991; **18**: 281–5.
20 Todd P, Halpern S, Kirby J, Pembroke A. Lichen sclerosus and the Köbner phenomenon. *Clin Exp Dermatol* 1994; **19**: 262–3.
21 Ueki H. Koebner phenomenon in lupus erythematosus with special consideration of clinical findings. *Autoimmun Rev* 2005; **4**: 219–23.
22 Missner SC, Ramsay EW, Houck HE, Kauffman CL. Graves' disease presenting as localized myxedema in a thigh donor graft site. *J Am Acad Dermatol* 1998; **39**: 846–9.
23 Gebauer K, Armstrong M. Köbner phenomenon with necrobiosis lipoidica diabeticorum. *Int J Dermatol* 1993; **32**: 895–6.
24 Jelinek JE. Dermatoses reported to be more frequent in diabetes. In: Jelinek JE, ed. *The Skin in Diabetes*. Philadelphia: Lea & Febiger, 1986: 175–202.
25 Durani BK, Kurzen H, Hartschuh W, Naeher H. Köbner phenomenon due to scratch test in scleromyxoedema. *Br J Dermatol* 2001; **145**: 306–8.
26 Rotunda AM, Bhupathy AR, Dye R, Soriano TT. Pemphigus foliaceus masquerading as postoperative wound infection: report of a case and review of the Koebner and related phenomenon following surgical procedures. *Dermatol Surg* 2005; **31**: 226–31.
27 Green ST, Narajan S. The Köbner phenomenon in anaphylactoid purpura. *Cutis* 1986; **38**: 56–7.
28 Miwa N, Kanzaki T. The Köbner phenomenon in eruptive xanthoma. *J Dermatol* 1992; **19**: 48–50.

29 Aldridge RD, Main RA, Daly BM. The Köbner's response in multicentric reticulohistiocytosis. *Cutis* 1984; **34**: 78–80.
30 Seckin D, Ozcan G, Demirag A *et al*. The Köbner phenomenon in Kaposi's sarcoma in a renal transplant recipient. *Br J Dermatol* 1998; **139**: 340–61.
31 Niedt GW, Prioleau PG. Kaposi's sarcoma occurring in a dermatome previously involved by herpes zoster. *J Am Acad Dermatol* 1988; **18**: 448–51.

Nikolsky sign

This well-known effect of shearing trauma was originally described as evoking lesions of pemphigus foliaceus but may be positive in other bullous diseases (see Chapter 40).

Utilization of mechanical stimuli [1]

Selective use may be made of mechanical stimuli to confirm the diagnosis or to allow for biopsy of early lesions in conditions in which dynamic changes and secondary effects occur rapidly. Simple frictional trauma, such as that caused by twisting a rubber-tipped pencil on the skin, can be used to facilitate accurate diagnosis of mechanobullous diseases.

The Nikolsky and Koebner phenomena may be used to study the early changes in diseases in which they are characteristic and can be of value in the diagnosis of pemphigus when patients are already on treatment and immunofluorescent techniques are not available [2]. The pustular reaction to skin puncture (including venesection) is evidence of an active stage of Behçet's syndrome. Suction [3,4] evokes bullous diseases and may produce petechiae in scurvy, etc. It has also been used to study vasculitis [5,6].

Firm stroking of the skin may elicit purpura in amyloidosis, is routinely used to diagnose dermographism, and has also been used to study the early lesions of vasculitis [7] and to confirm a diagnosis of delayed pressure urticaria [8].

References

1 Shelley WB. Experimental disease in the skin of man. *Acta Derm Venereol Suppl (Stockh)* 1983; **108**: 5–32.
2 Hameed A, Khan AA. Microscopic Nikolsky's sign. *Clin Exp Dermatol* 1999; **24**: 312–4.
3 Kiistala U, Mustakallio KK. Dermo-epidermal separation with suction: electron microscopic and histochemical study of initial events of blistering on human skin. *J Invest Dermatol* 1967; **48**: 466–77.
4 Comaish S, McVittie E. Suction blisters in bullous pemphigoid and other dermatoses. *Br J Dermatol* 1973; **89**: 127–32.
5 Copeman PWM, Ryan TJ. Cutaneous angiitis: patterns of rashes explained by (1) Flow properties of blood (2) Anatomical disposition of vessels. *Br J Dermatol* 1971; **85**: 205–14.
6 Braverman IM, Yen A. Demonstration of immune complexes in spontaneous and histamine-induced lesions and in normal skin of patients with leucocytoclastic angiitis. *J Invest Dermatol* 1975; **64**: 105–12.
7 Soter NA, Mihm MC, Dvorak HF, Austen KF. Cutaneous necrotising venulitis: a sequential analysis of the morphological reactions occurring after mast cell degranulation in a patient with a unique syndrome. *Clin Exp Dermatol* 1978; **32**: 46–58.
8 Estes SA, Young CW. Delayed pressure urticaria: an investigation of some parameters of lesion induction. *J Am Acad Dermatol* 1981; **5**: 25–31.

Biomechanical considerations [1–4]

Resistance to various mechanical stimuli, both external and arising within the body, is a fundamental property of the skin. External forces include friction, stretching, compression, vibration and penetration. The major mechanical properties of skin are stiffness (resistance to change of shape), elasticity (ability to recover the initial shape after deformation) and viscoelasticity (see below). Quantification of the behaviour of skin subjected to mechanical forces is complicated by many factors. The skin is composed of not one but multiple and interrelated functional components, and its behaviour is subject to the confounding effects of physiological phenomena, such as the previous experience of the tissue, nutritional status, sweating and sebum excretion. Other variables of practical relevance [5] are related to body site, age, sex and disease—not only cutaneous disease but also systemic (e.g. diabetes). In addition, the mechanical properties of the skin may be profoundly influenced by environmental factors such as UV and heat radiation.

The generation of mechanical forces within the skin and subcutis has long been of interest to surgeons, with early contributions by Langer on the oval shapes produced when round punctures are made in the skin, and the recognition of relaxed skin tension lines [6]. The mechanical qualities of skin, especially creep, are critical to understanding expansion techniques used in dermatological surgery [7]. The effects of mechanical forces have also been studied extensively in relation to wound healing and the consequences of excess fluid in tissues [8].

In vitro studies have shown that application of mechanical stress results in increased DNA synthesis [9], production of collagen and proteoglycans [10], non-collagenous proteins [11] and cytoskeleton formation. Application of mechanical force intermittently results in more cellular activity than a constant force [12]. Wounds that heal under some stress have greater strength than those where there is no stress [13].

The importance of weight bearing on bones for their normal structural integrity was recognized long ago, and the stress imposed by gravitational forces is also important for the maintenance of dermal constituents [14].

A quantitative analysis of mechanical properties of skin and subjacent tissues must begin from engineering principles [1,15]. Most studies involve the measurement over time of deformation produced by a given constant force. The force is standardized as force per unit area or 'stress'. Stresses perpendicular to the surface are termed normal, whereas those in other directions are termed shearing stresses. The change in dimensions may be expressed as 'strain' and is the ratio between the deformation and the original length. Many elastic materials show a linear relationship between stress and strain, for example:

$$\text{Stress} = \text{Young's modulus} \times \text{strain}$$

Similarly, linear viscous liquids obey Newton's law in which stress is directly proportional to the rate of strain but independent of the strain itself. Many biological materials combine the characteristics of elastic solids and viscous liquids and are termed viscoelastic. Skin, in common with other viscoelastic materials, has non-linear stress–strain properties and has time-dependent behaviour even with low loads [16]. The best known of these are the properties of hysteresis (in which the stress–strain relationships are different between loading and unloading), stress relaxation (the stress resulting from a constant strain decreases with time) and 'creep' (increasing strain or length of the material when a

constant stress is maintained). These time-dependent properties are thought in part to be a function of the ground substance. Furthermore, skin shows anisotropic properties; there is a systematic and regular directional variation in its mechanical and viscoelastic properties. The elastic component is broadly analogous to a linear spring and the viscous component to a dashpot shock absorber.

Much of the earlier work on the mechanical properties of the skin was carried out on tissues or their components (collagen, elastin, etc.) *in vitro* [1,17]. Strength-related values such as breaking strain, time-dependent creep and non-time-dependent parameters, such as elasticity and viscosity, have been measured, but these studies can be unhelpful in predicting the behaviour of whole skin *in vivo*.

The principal source of mechanical strength in the skin and subcutis is the reticular dermis; the papillary and periadnexal dermis (often known as adventitial dermis) and the connective tissue running between fat lobules to deeper structures have somewhat similar and lesser capacity to resist deformation [18], and it is likely that the epidermal components are only relevant in resisting relatively minor forces [2]. At a molecular level, it is the properties of collagen, usually of types I and III and its relationship with elastic fibres and ground substance, that determine the mechanical responses of skin.

References

1 Tregear RT. *The Physical Functions of Skin*. New York: Academic Press, 1966.
2 Piérard GE. A critical approach to *in vivo* mechanical testing of the skin. In: Lévêque J-L, ed. *Cutaneous Investigation in Health and Disease*. New York: Marcel Dekker, 1989: 215–40.
3 Elsner P, Berardesca E, Wilhelm K-P, Maibach HI, eds. *Bioengineering of the Skin: Skin Biomechanics*. Boca Raton, FL: CRC Press, 2001.
4 Serup J, Jemec GBE, Grove GL, eds. *Handbook of Non-Invasive Methods and the Skin*, 2nd edn. Boca Raton, USA: CRC Press, 2006.
5 Kligman AM. The chronic effects of repeated mechanical trauma to the skin. *Am J Ind Med* 1985; **8**: 257–64.
6 Cox HT. The cleavage lines of the skin. *Br J Surg* 1941; **29**: 234–40.
7 Wilhelmi BJ, Blackwell SJ, Mancoli JS, Philips LG. Creep vs. stretch: a review of the viscoelastic properties of skin. *Ann Plast Surg* 1998; **41**: 215–9.
8 Ryan TJ. Biochemical consequences of mechanical forces generated by distention and distortion. *J Am Acad Dermatol* 1989; **21**: 116–30.
9 Brunette DM. Mechanical stretching increases the number of epithelial cells synthesizing DNA in culture. *J Cell Sci* 1984; **69**: 35–45.
10 Leung DYM, Glagov S, Mathews MD. Cyclic stretching stimulates synthesis of matrix components by arterial smooth muscle cells *in vitro*. *Science* 1976; **191**: 475–7.
11 Meikle MC, Reynolds JJ, Sellers A *et al.* Rabbit cranial sutures *in vitro*: a new experimental model for studying the response of fibrous joints to mechanical stress. *Calcif Tissue Int* 1979; **28**: 137–44.
12 Takei T, Rivas-Gotz C, Delling CA *et al.* Effect of strain on human keratinocytes *in vitro*. *J Cell Physiol* 1997; **173**: 64–72.
13 Urschel JD, Scott PG, Williams HTG. The effect of mechanical stress on soft and hard tissues. *Br J Plast Surg* 1988; **412**: 182–6.
14 Gillard GC, Reilly HC, Bell-Booth PG *et al.* A comparison of the glycosaminoglycans of weight-bearing and non-weight-bearing human epidermis. *J Invest Dermatol* 1977; **69**: 257–61.
15 Fung YCB. Elasticity of soft tissues in simple elongation. *Am J Physiol* 1967; **213**: 1532–44.
16 Wan Abas WAB. Stress stabilisation behaviour in skin under small tensile loads *in vitro*. *Biomed Mater Eng* 1995; **5**: 59–63.
17 Vogel HG. Mechanical properties of human skin: animal models. In: Elsner P, Berardesca E, Wilhelm K-P, Maibach HI, eds. *Bioengineering of the Skin: Skin Biomechanics*. Boca Raton, FL: CRC Press, 2001: 17–39.
18 Piérard G, Lapière CM. Physiopathological variations in the mechanical properties of skin. *Arch Dermatol Res* 1977; **260**: 231–9.

Mechanical properties of the skin

Methods of evaluation [1–4]

Many methods have been used to derive information about mechanical properties of the skin. Some have included subcutaneous tissue [5,6]. Most methods measure properties of the dermis, although some give information predominantly about the stratum corneum [7,8], and all have limitations.

1 Tensile tests, in which the skin is extended by applying a force parallel to the surface [9–17]
2 Torsional tests, in which force is used to rotate a disc glued to the skin [3,18–20]
3 Vertical traction [7,21–23]
4 Indentation [8,24–26] and nano-indentation [27]
5 Suction within a cup pressed on the skin [28–34]
6 Vibration, for example using the hammer of a ballistometer [35–38]
7 Elastic wave propagation [39]
8 Hardness, using a durometer [40,41].

Because of problems with standardization of methods, results are usually not comparable between investigators. Details of methodology, such as the area of skin subjected to suction, are of great importance in understanding which zone of the skin is being evaluated. Results should always be standardized for skin thickness [42,43]. One of the few studies that directly compared different methods concluded that the suction cup device mainly measures elasticity, whereas the ballistometer predominantly measures stiffness [44].

Some of the measurements that can be derived from *in vivo* methods such as torsion [42] and suction [43] can be expressed as ratios, obviating the dependence on skin thickness, and give useful information about the elastic and viscoelastic properties of skin (Fig. 28.2). Despite their shortcomings, the various methods used have led to a general understanding of the mechanical properties

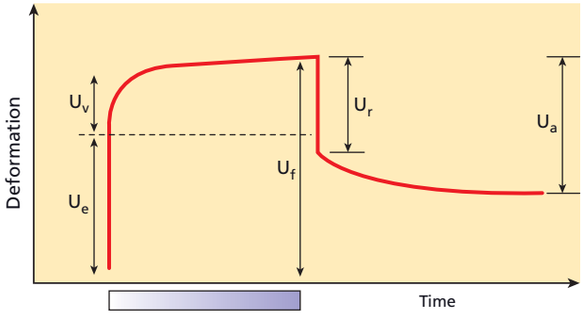


Fig. 28.2 Deformation of skin by an applied force showing how elastic and viscoelastic properties can be deduced from ratios of measurements.

of the skin, and quantification of some of these properties has proved useful in the recognition of pathological changes in connective tissues before they have become clinically apparent.

References

1 Piérard GE. A critical approach to *in vivo* mechanical testing of the skin. In: Lévêque JL, ed. *Cutaneous Investigation in Health and Disease*. New York: Marcel Dekker, 1989: 215–40.
2 Vogel HG. Mechanical measurements of skin. *Acta Derm Venereol Suppl (Stockh)* 1994; **185**: 39–43.
3 Elsner P, Berardesca E, Wilhelm K-P, Maibach HI, eds. *Bioengineering of the Skin: Skin Biomechanics*. Boca Raton, FL: CRC Press, 2001.
4 Serup J, Jemec GBE, Grove GL, eds. *Handbook of Non-Invasive Methods and the Skin*, 2nd edn. Boca Raton, USA: CRC Press, 2006.
5 Wu KS, van Osdol WW, Dauskardt RH. Mechanical properties of human stratum corneum: effects of temperature, hydration, and chemical treatment. *Biomaterials* 2006; **27**: 785–95.
6 Wu JZ, Cutlip RG, Andrew ME, Dong RG. Simultaneous determination of the nonlinear-elastic properties of skin and subcutaneous tissue in unconfined compression tests. *Skin Res Technol* 2007; **13**: 34–42.
7 Matts PJ. Hardware and measurement principles: the gas-bearing electrodynamometer and linear skin rheometer. In: Elsner P, Berardesca E, Wilhelm K-P, Maibach HI, eds. *Bioengineering of the Skin: Skin Biomechanics*. Boca Raton, FL: CRC Press, 2001: 99–109.
8 Graves CJ, Edwards C. Hardware and measuring principles: the micro-indentometer. In: Elsner P, Berardesca E, Wilhelm K-P, Maibach HI, eds. *Bioengineering of the Skin: Skin Biomechanics*. Boca Raton, FL: CRC Press, 2001: 161–78.
9 Ridge MD, Wright V. The rheology of skin: a bioengineering study of the mechanical properties of human skin in relation to its structure. *Br J Dermatol* 1965; **77**: 639–49.
10 Burton JL, Shuster S. A rapid increase in skin extensibility due to prednisolone. *Br J Dermatol* 1973; **89**: 491–5.
11 Lanir Y, Fung YCB. Two-dimensional mechanical properties of rabbit skin. I. Experimental model. *J Biomech* 1974; **7**: 29–34.
12 Burlin TE, Hutton WC, Ranu HS. A method of *in vivo* measurements of the elastic properties of skin. *J Invest Dermatol* 1977; **69**: 321–3.
13 Christensen MS, Hargens CW, Nacht S *et al*. Viscoelastic properties of intact human skin, instrumentation, hydration effects and the contribution of the stratum corneum. *J Invest Dermatol* 1977; **69**: 282–6.
14 Cook T, Alexander H, Cohen ML. An experimental method for determining the two-dimensional mechanical properties of living human skin. *Med Biol Eng Comput* 1977; **15**: 381–9.
15 Fung YC, ed. *Biomechanics: Mechanical Properties of Living Tissue*. New York: Springer, 1981: 22–61.
16 Vescovo P, Varchon D, Humbert P. *In vivo* tensile tests on human skin; the extensometers. In: Elsner P, Berardesca E, Wilhelm K-P, Maibach HI, eds. *Bioengineering of the Skin: Skin Biomechanics*. Boca Raton, FL: CRC Press, 2001: 77–90.
17 Khatyr F, Imberdis C, Vescovo P *et al*. Model of the viscoelastic behaviour of skin in vivo and study of anisotropy. *Skin Res Technol* 2004; **10**: 96–103.
18 Wan Abas WAB. Stress stabilisation behaviour in skin under small tensile loads *in vitro*. *Biomed Mater Eng* 1995; **5**: 59–63.
19 Piérard G, Lapière CM. Physiopathological variations in the mechanical properties of skin. *Arch Dermatol Res* 1977; **260**: 231–9.
20 de Rigal J. Hardware and basic principles of the dermal torque meter. In: Elsner P, Berardesca E, Wilhelm K-P, Maibach HI, eds. *Bioengineering of the Skin: Skin Biomechanics*. Boca Raton, FL: CRC Press, 2001: 63–76.
21 Piérard G, Lapière CM. Physiopathological variations in the mechanical properties of skin. *Arch Dermatol Res* 1977; **260**: 231–9.
22 Dikstein S, Hartzshtark A. *In vivo* measurement of some elastic properties of human skin. In: Marks R, Payne PA, eds. *Bioengineering and the Skin*. Lancaster: MTP Press, 1988: 45–53.
23 Hargens CW. The gas-bearing electrodynamometer applied to measuring mechanical changes in the skin and other tissues. In: Marks R, Payne PA, eds. *Bioengineering and the Skin*. Lancaster: MTP Press, 1981: 113–22.
24 Kirk JE, Chieffi M. Variation with age in elasticity of skin and subcutaneous tissue in human individuals. *J Gerontol* 1962; **17**: 373–80.
25 Parot S, Bourlière F. A new technique for measuring compressibility of skin and subcutaneous tissue: influences of sex, age and body area. *Gerontol* 1967; **13**: 95–110.
26 Delalleau A, Josse G, Lagarde JM *et al*. Characterization of the mechanical properties of skin by inverse analysis combined with the indentation test. *J Biomech* 2006; **39**: 1603–10.
27 Yuan Y, Verma R. Measuring microelastic properties of stratum corneum. *Colloids Surf B Biointerfaces* 2006; **48**: 6–12.
28 Piérard GE. Evaluation des proprietes mechaniques de la peau par les methodes d'indentation et de compression. *Dermatologica* 1984; **168**: 61–6.
29 Lowe LB, van Der Leun JC. Suction blisters and dermal–epidermal adherence. *J Invest Dermatol* 1968; **50**: 308–14.
30 Grahame R. Elasticity of human skin *in vivo*. *Biomed Eng* 1971; **6**: 567–73.
31 Berdt U, Elsner P. Hardware and measuring principles: the Cutometer®. In: Elsner P, Berardesca E, Wilhelm K-P, Maibach HI, eds. *Bioengineering of the Skin: Skin Biomechanics*. Boca Raton, FL: CRC Press, 2001: 91–7.
32 Serup J. Hardware and measuring principles: the Dermaflex A®. In: Elsner P, Berardesca E, Wilhelm K-P, Maibach HI, eds. *Bioengineering of the Skin: Skin Biomechanics*. Boca Raton, FL: CRC Press, 2001: 111–5.
33 Häuselmann HJ, Huber K, Seifert B, Michel B. Hardware and measuring principles: the Dermagraph in patients with systemic sclerosis and in healthy volunteers. In: Elsner P, Berardesca E, Wilhelm K-P, Maibach HI, eds. *Bioengineering of the Skin: Skin Biomechanics*. Boca Raton, FL: CRC Press, 2001: 123–38.
34 Khatyr F, Imberdis C, Varchon D *et al*. Measurement of the mechanical properties of the skin using the suction test. *Skin Res Technol* 2006; **12**: 24–31.
35 Tronnier H, Wagener HH. Über die Frequenz-Leitf higkiet der Menschlichen Haut. *Dermatologica* 1952; **104**: 135–51.
36 Tosti A, Campagno G, Fazzini MC *et al*. A ballistometer for the study of the plasto-elastic properties. *J Invest Dermatol* 1977; **69**: 315–7.
37 Bjerring P. Skin elasticity measured by dynamic admittance: a new technique for mechanical measurements in patients with scleroderma. *Acta Derm Venereol Suppl (Stockh)* 1985; **120**: 83–7.
38 Pugliese PT, Potts JR. Hardware and measuring principles: the Ballistometer. In: Elsner P, Berardesca E, Wilhelm K-P, Maibach HI, eds. *Bioengineering of the Skin: Skin Biomechanics*. Boca Raton, FL: CRC Press, 2001: 147–59.
39 Potts RD. Chrisman DA, Buras M. The dynamic mechanical properties of human skin *in vivo*. *J Biomech* 1983; **16**: 365–72.
40 Falanga V, Bucalo B. Use of a durometer to assess skin hardness. *J Am Acad Dermatol* 1993; **29**: 47–51.
41 Romanelli M, Falanga V. Hardware and measuring principles: the Durometer. In: Elsner P, Berardesca E, Wilhelm K-P, Maibach HI, eds. *Bioengineering of the Skin: Skin Biomechanics*. Boca Raton, FL: CRC Press, 2001: 139–45.
42 Lévêque JL, de Rigal J, Agache PG *et al*. Influence of ageing on the *in vivo* extensibility of human skin at low stress. *Arch Dermatol Res* 1980; **269**: 127–35.
43 Elsner P, Wilhelm D, Maibach HI. Mechanical properties of human forearm and vulvar skin. *Br J Dermatol* 1990; **122**: 607–14.
44 Jemec GBE, Selvaag E, Ågren M, Wulf HC. Measurement of the mechanical properties of skin with ballistometer and suction cup. *Skin Res Technol* 2001; **7**: 122–6.

Determinants

Stratum corneum

The main function of the stratum corneum is to provide a limited barrier across which exchanges occur with the environment. It consists of dead corneocytes embedded in an extracellular lipid matrix. *In vivo* it is criss-crossed by a series of depressions outlining polygonal zones. This pattern is anisotropic and related to the anisotropy of the underlying dermis. When subjected to stretch it is only slightly extensible [1], deformation occurring by flattening out or redistribution of these depressions [2]. These changes cause secondary alterations in shape of the cells in the Malpighian layer and the underlying papillary dermis [2]. The elastic modulus of the individual corneocyte is far higher than of the complete stratum corneum, suggesting that the biomechanical properties of the latter are largely a function of the substances binding the cells

to each other [3,4]. Direct measurements of the biomechanical properties of the stratum corneum using nano-technology methods have recently been published [5].

The extensibility of the stratum corneum is greatly influenced by the relative humidity and its state of hydration [4,6–9].

Frictional contact with the stratum corneum is an essential prerequisite for tactile sensation and many physical activities. It is also a cause of a variety of acute and chronic injuries to the skin. The stratum corneum behaves as a viscoelastic membrane when subjected to frictional force. The major component producing friction is a tendency to adhesion at the surface. In general, frictional resistance increases with the state of hydration, although free water or sebum on the surface reduces resistance. The contribution of the stratum corneum towards skin biomechanics can be seen in studies evaluating the effect of moisturizers and emollients. Extensibility and creep were both rapidly increased by water and paraffin oil, and more slowly by glycerine; water only had a very short-term effect [10]. Chemical modification of stratum corneum proteins (e.g. by glutaraldehyde) can also reduce frictional resistance [11].

The important property of the stratum corneum to resist forces that would tend to separate its layers, as occurs with Sellotape stripping, has been studied in various ways [12].

Basement-membrane region

This has been evaluated mainly by suction devices, which can split the skin in this region. It is likely that the basement-membrane region has a relatively minor role in the overall mechanical integrity of the skin [13], although abnormalities of structural components such as laminin 5 in the lamina lucida cause marked weakening of the skin in some types of junctional epidermolysis bullosa.

Dermis

The dermal collagen bundles are an intermeshing network of undulating fibres (see Chapter 3). Although electron-microscopic studies show the bundles running in all directions, in the reticular dermis the predominant direction is parallel with the skin surface, and in the adventitial dermis and subcutis the alignment is perpendicular to the surface. The initial response to deformation is a straightening of the collagen bundles and realignment of the straightened fibres in the direction of the applied force; beyond this, extension may occur through slip between fibrils, a process opposed by the closely associated glycosaminoglycans (see Chapter 3). Elastic fibres are responsible for returning the collagen to its predeformation state, particularly with low levels of load [14]. Elastin is the only mammalian protein with truly elastic properties. The interdependence of elastic tissue and collagen has been demonstrated in experiments using selective removal [15]. In addition to collagen, elastin and glycosaminoglycans, α and β integrins are essential for mechanical integrity, and contribute to fibroblast homeostasis [16].

References

1 Park AC, Baddiel CB. Rheology of stratum corneum: a molecular interpretation of the stress–strain curve. *J Soc Cosmet Chem* 1972; **23**: 3–12.

2 Schellander FA, Headington JT. The stratum corneum: some structural and functional correlates. *Br J Dermatol* 1974; **91**: 507–15.

3 Lévêque JL, Poelman MC, de Rigal J, Kligman AM. Are corneocytes elastic? *Dermatologica* 1988; **176**: 65–9.

4 Lévêque JL, Rasseneur L. Mechanical properties of stratum corneum: influence of water and lipids. In: Marks RM, Barton SP, Edwards C, eds. *The Physical Nature of the Skin*. Lancaster: MTP Press, 1988: 155–61.

5 Yuan Y, Verma R. Measuring microelastic properties of stratum corneum. *Colloids Surf B Biointerfaces* 2006; **48**: 6–12.

6 Blank IM. Factors which influence the water content of the stratum corneum. *J Invest Dermatol* 1952; **18**: 433–40.

7 Christensen MS, Hargens CW, Nacht S *et al*. Viscoelastic properties of intact human skin, instrumentation, hydration effects and the contribution of the stratum corneum. *J Invest Dermatol* 1977; **69**: 282–6.

8 de Rigal J, Lévêque JL. *In vivo* measurement of the stratum corneum elasticity. *Bioeng Skin* 1985; **1**: 13–23.

9 Larsen TH, Jemec GBE. Skin mechanics and hydration In: Elsner P, Berardesca E, Wilhelm K-P, Maibach HI, eds. *Bioengineering of the Skin: Skin Biomechanics*. Boca Raton, FL: CRC Press, 2001: 199–205.

10 Olsen LO, Jemec GBE. The influence of water, glycerin, paraffin oil and ethanol on skin mechanics. *Acta Derm Venereol (Stockh)* 1993; **73**: 404–6.

11 Comaish S. Glutaraldehyde lowers skin friction and enhances its resistance to friction injury. *Acta Derm Venereol (Stockh)* 1973; **53**: 455–9.

12 Marks R, Nicholls S, Fitzgeorge D. Measurement of intracorneal cohesion in man using in vivo techniques. *J Invest Dermatol* 1977; **69**: 299–302.

13 Lapière CM, Nusgens BV, Piérard GE. The architectural organisation and function of the macromolecules in the dermis. In: Marks RM, Barton SP, Edwards C, eds. *The Physical Nature of the Skin*. Lancaster: MTP Press, 1988: 163–76.

14 Oxlund H, Manschot J, Vhdik A. The role of elastin in the mechanical properties of skin. *J Biomech* 1988; **21**: 213–8.

15 Oxlund H. Relationships between the biomechanical properties, composition and molecular structure of the connective tissues. *Connect Tissue Res* 1986; **15**: 65–72.

16 Fujimura T, Moriwaki S, Imokawa G, Takema Y. Crucial role of fibroblast integrins alpha2 and beta1 in maintaining the structural and mechanical properties of the skin. *J Dermatol Sci* 2007; **45**: 45–53.

Physiological variation

Age

From about the age of 35 years in women and 45 years in men, the thickness of skin decreases with ageing on light-protected sites and the dermal–epidermal junction becomes flatter [1–4]. Many studies, using a variety of techniques, have evaluated the skin at different ages (reviewed in [5]). Although there are some conflicting results, overall there is agreement that there is a decrease in elastic properties with age. It seems likely that there is increasing resistance by the dermis to traction parallel to the skin surface, at least until the age of 60 years, but vertical resistances at the dermal–epidermal junction and within the dermis and subcutis progressively fall. Using a device for propagation of low amplitude shear disturbances it has been shown that there is a progressive increase in viscosity of the skin with age [6].

Sex

Again, no clear answer emerges as to whether there is a difference between sexes, except for a decrease in skin thickness and elasticity after menopause. Some methods have shown that female skin is more extensible [7–9], although others have failed to confirm this [1,10,11]. The increase in extensibility from hydration of the stratum corneum may be greater in women than men [12]. Hormone replacement therapy appears to alleviate the loss of elasticity associated with the menopause [13,14].

Body site

There are great differences between body sites, mainly because of differences in skin thickness [3,15]. When this is corrected for, skin distensibility and elasticity are lower in the acral areas than centrally, and are subject to diurnal variation, with elasticity increasing in the evening [16]. Elasticity is greater across the epidermal ridges of the fingerpads, a feature that may contribute to their specialized sensory function [17]. These properties contribute resistance to gravitational oedema formation, and are diminished in the elderly.

Using a small suction device, the ratio between viscous deformation and elastic deformation and the biological elasticity (i.e. the ratio between immediate recovery and total deformation) was lower in vulval than in forearm skin [18].

Light exposure

Chronic sun exposure produces a decrease in extensibility, elastic recovery and elastic modulus. The higher the melanin content, the lower the differences between sun-exposed compared with sun-protected sites [19]. Sun-exposed facial dermis has both increased thickness and decreased parameters of elasticity [20].

Pathological variation

Various *in vivo* techniques have been used to measure mechanical properties of the skin in disease states over a period of time. In some situations, the abnormalities have predated the clinical changes (as in Raynaud's phenomenon, when preceding scleroderma [21]). Such measurements clearly have application for monitoring therapy [22]. Examples include: scleroderma [23–27] and its treatment by d-penicillamine [28,29]; the decreased distensibility but unaltered elasticity of scleroderma of Buschke [30,31]; the consequences of corticosteroid atrophy [32,33]; the waxy skin of diabetics [34]; the increased elasticity in acromegaly, broadly related to IGF-1 levels [35]; the reduced extensibility (photosclerosis) resulting from psoralen and UVA (PUVA) therapy [36–38]; and an acute increase in elasticity during radiotherapy [39] and in the gravitational syndrome [40]. In neurofibromatosis the skin is hyperextensible, to some extent even the clinically normal skin [41]. In lymphoedema there is reduced viscoelasticity [42]. Chronic haemodialysis produces some impairment of the viscous properties of the skin similar to those of ageing [43]. Useful correlations have emerged between biomechanical and genetic differences in diseases of connective tissue such as pseudoxanthoma elasticum [44] and Ehlers–Danlos syndrome [45–47]. Smoking can cause facial wrinkling [48] but the biomechanical correlates have not been defined.

Piérard *et al*. [36] have studied the ability of skin to be elongated (skin extensibility) and its capacity to regain the initial position after deformation (biological elasticity) in a number of disease states: their findings are used in Fig. 28.3 to illustrate the principles outlined in this section.

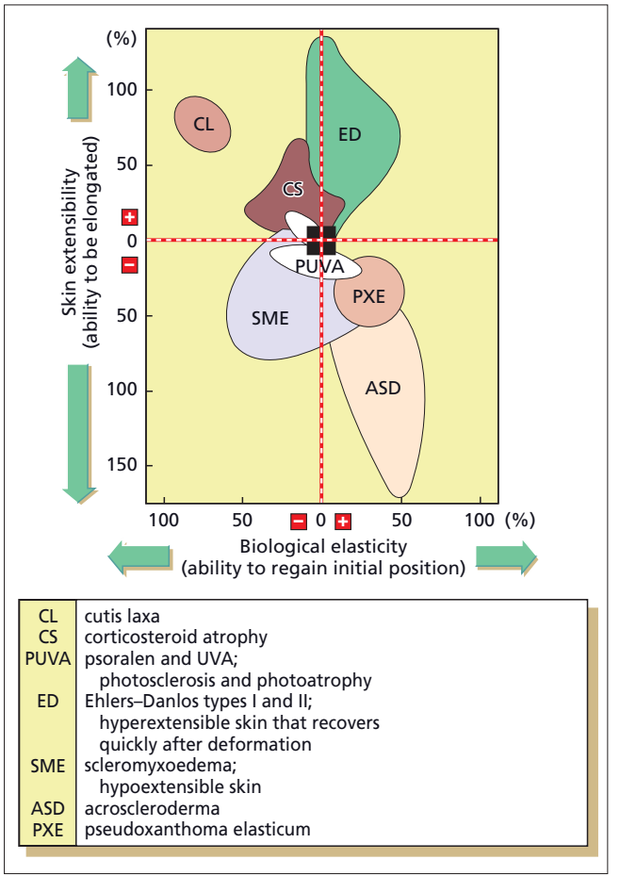


Fig. 28.3 Rheological properties of some conditions affecting the dermis. Each area represents data from several patients. (From Piérard *et al*. [38].)

References

1 Lévêque JL, de Rigal J, Agache PG *et al*. Influence of ageing on the *in vivo* extensibility of human skin at low stress. *Arch Dermatol Res* 1980; **269**: 127–35.

2 Escoffier C, Rigal J, Rochefort A, Vasselet R. Age-related mechanical properties of human skin: an *in vivo* study. *J Invest Dermatol* 1989; **93**: 353–7.

3 Cua AB, Wilhelm KP, Maibach HI. Elastic properties of human skin: relation to age, sex and anatomical region. *Arch Dermatol Res* 1990; **282**: 283–8.

4 Lévêque JL, Agache PG. *Ageing Skin: Properties and Functional Changes*. New York: Marcel Dekker, 1993.

5 Piérard GE. A critical approach to *in vivo* mechanical testing of the skin. In: Lévêque JL, ed. *Cutaneous Investigation in Health and Disease*. New York: Marcel Dekker, 1989: 215–40.

6 Davis BR, Bahnjuk E, Young JK *et al*. Age-dependent changes in the shear wave propagation through human skin. *Exp Gerontol* 1989; **24**: 201–10.

7 Ridge MD, Wright V. The rheology of skin, a bioengineering study of the mechanical properties of human skin in relation to its structure. *Br J Dermatol* 1965; **77**: 639–49.

8 Kiistala V. Dermal epidermal separation. I. The influence of age, sex and body region on suction blister formation in human skin. *Ann Clin Res* 1972; **4**: 10–22.

9 Piérard G, Lapière CM. Physiopathological variations in the mechanical properties of skin. *Arch Dermatol Res* 1977; **260**: 231–9.

10 Grahame R. Elasticity of human skin *in vivo*. *Ann Phys Med* 1968; **10**: 130–41.

11 Finlay B. The torsional characteristics of human skin *in vivo*. *Biomed Eng* 1971; **6**: 567–73.

12 Auriol F, Vaulant L, Machet L *et al*. Effects of short-term hydration on skin extensibility. *Acta Derm Venereol (Stockh)* 1993; **73**: 344–7.

13 Piérard GE, Letawe C, Dowlati A *et al*. Effect of hormone replacement therapy for menopause on the mechanical properties of skin. *J Am Geriatr Soc* 1995; **43**: 662–5.

14 Sumino H, Ichikawa S, Abe M *et al*. Effects of aging, menopause, and hormone replacement therapy on forearm skin elasticity in women. *J Am Geriatr Soc* 2004; **52**: 945–9.

15 Wilhelm KP, Maibach HI. Mapping mechanic properties of human skin. In: Elsner P, Berardesca E, Wilhelm K-P, Maibach HI, eds. *Bioengineering of the Skin: Skin Biomechanics*. Boca Raton, FL: CRC Press, 2001: 187–97.
16 Gniadecka M, Gniadecki R, Serup J, Sondergaard J. Skin mechanical properties present adaptation to man's upright position. *Acta Derm Venereol (Stockh)* 1994; **74**: 188–90.
17 Wang Q, Hayward V. In vivo biomechanics of the fingerpad skin under local tangential traction. *J Biomech* 2007; **40**: 851–60.
18 Elsner P, Wilhelm D, Maibach HI. Frictional properties of human forearm and vulvar skin: influence of age and correlation with transepidermal water loss and capacitance. *Dermatologica* 1990; **181**: 88–91.
19 Berardesca E. Racial differences in skin function. *Acta Derm Venereol Suppl (Stockh)* 1994; **185**: 44–6.
20 Takema Y, Yorimoto Y, Kawai M, Imokawa G. Age-related changes in the elastic properties and thickness of human facial skin. *Br J Dermatol* 1994; **131**: 641–8.
21 Dobrev H. In vivo study of skin mechanical properties in Raynaud's phenomenon. *Skin Res Technol* 2007; **13**: 91–4.
22 Dobrev HP. Mechanical properties in other dermatological diseases. In: Elsner P, Berardesca E, Wilhelm K-P, Maibach HI, eds. *Bioengineering of the Skin: Skin Biomechanics*. Boca Raton, FL: CRC Press, 2001: 215–27.
23 Bjerring P. Skin elasticity measured by dynamic admittance: a new technique for mechanical measurements in patients with scleroderma. *Acta Derm Venereol Suppl (Stockh)* 1985; **120**: 83–7.
24 Aghassi D, Monoson T, Braverman I. Reproducible measurements to quantify cutaneous involvement in scleroderma. *Arch Dermatol* 1995; **131**: 1160–6.
25 Dobrev HP. *In vivo* study of skin mechanical properties in patients with systemic sclerosis. *J Am Acad Dermatol* 1999; **40**: 436–42.
26 Piérard GE *et al*. Skin tensile strength in scleroderma. In: Elsner P, Berardesca E, Wilhelm K-P, Maibach HI, eds. *Bioengineering of the Skin: Skin Biomechanics*. Boca Raton, FL: CRC Press, 2001: 207–13.
27 Balbir-Gurman A, Denton CP, Nichols B *et al*. Non-invasive measurement of biomechanical skin properties in systemic sclerosis. *Ann Rheum Dis* 2002; **61**: 237–41.
28 Bluestone R, Grahame R, Holoway V *et al.* Treatment of systemic sclerosis with d-penicillamine: a new method of observing the effects of treatment. *Ann Rheum Dis* 1970; **29**: 153–8.
29 Piérard GE, Franchimont C, Lapière CM. Les compartiments conjonctifs dans les sclerodermies: etude de la structure et des propriétes biomechaniques. *Dermatologica* 1985; **170**: 105–13.
30 Dobrev HP. *In vivo* study of skin mechanical properties in scleredema of Buschke. *Aca Derm Venereol* 1998; **78**: 103–6.
31 Grudeva-Popova J, Dobrev HP. Biomechanical measurement of skin distensibility in scleroderma of Buschke associated with multiple myeloma. *Clin Exp Dermatol* 2000; **25**: 247–9.
32 Burton JL, Shuster S. A rapid increase in skin extensibility due to prednisolone. *Br J Dermatol* 1973; **89**: 491–5.
33 Piérard GE. Iatrogenic alterations of the biomechanical properties of human skin. *Br J Dermatol* 1978; **98**: 113–4.
34 Nikkels-Tassoudji M, Henry F, Letcuve C *et al*. Mechanical properties of the diabetic waxy skin. *Dermatology* 1996; **192**: 11–22.
35 Braham C, Betea D, Pierard-Franchimont C *et al*. Skin tensile properties in patients treated for acromegaly. *Dermatology* 2002; **204**: 325–9.
36 Piérard GE, de la Brassine M, Lapière CM. Effects of long term photochemotherapy on the dermis. *J Invest Dermatol* 1977; **68**: 249–50.
37 Adoute H, de Rigal J, Popoff B *et al.* Influence of PUVA treatment on the thickness and elastic properties of the skin. *Bioeng Skin* 1985; **1**: 245–51.
38 Piérard GE, Franchimont C, de la Brassine M, Lapière CM. Photosclerosis induced by long-wave ultraviolet light and psoralens. In: Marks R, Payne PA, eds. *Bioengineering of the Skin*. Lancaster: MTP Press, 1981: 75–82.
39 Burlin TE, Hutton WC, Ranu HS. A method of *in vivo* measurements of the elastic properties of skin. *J Invest Dermatol* 1977; **69**: 321–3.
40 Piérard-Franchimont C, Letawe C, Fumal I *et al*. Gravitational syndrome and tensile properties of skin in the elderly. *Dermatology* 1998; **197**: 317–20.
41 Mimoun N, Razzouq N, Wolkenstein P *et al*. Evaluation of skin viscoelasticity in type 1 neurofibromatosis patients. *Skin Pharmacol Physiol* 2006; **19**: 22–7.
42 Mridha M, Odman S, Oberg PA. Mechanical pulse propogation in gel, normal and oedematous tissues. *J Biomech* 1992; **25**: 1213–8.
43 Deleixhe-Mauhin F, Piérard-Franchimont C, Rorive G, Piérard GE. Influence of chronic haemodialysis on the mechanical properties of skin. *Clin Exp Dermatol* 1994; **19**: 130–3.
44 Harvey W, Pope FM, Grahame R. Cutaneous extensibility in pseudoxanthoma elasticum. *Br J Dermatol* 1975; **92**: 679–83.
45 Grahame R, Beighton P. Physical properties of the skin in Ehlers–Danlos syndrome. *Ann Rheum Dis* 1969; **28**: 246–55.
46 Piérard GE, Franchimont C, Lapiere CH. Histopathological aid to the diagnosis of the Ehlers–Danlos syndrome, gravis and mitis types. *Int J Dermatol* 1983; **22**: 300–4.
47 Henry F, Goffin V, Piérard-Franchimont C, Piérard GE. Mechanical properties of skin in Ehlers–Danlos syndrome, types I, II and III. *Pediatr Dermatol* 1996; **13**: 464–7.
48 Smith JB, Fenske NA. Cutaneous manifestations and consequences of smoking. *J Am Acad Dermatol* 1996; **34**: 717–32.

Effects of friction

Friction is defined as the resistance that any body meets in moving over another. Humans cannot function without friction between themselves and the environment, although even mild degrees of friction can cause distress, as in the unpleasant sensation that wool can induce for an atopic subject. Excessive frictional forces will cause injury, which may be acute, occurring in seconds or minutes, or chronic, as a result of repeated, lesser degrees of friction. The response of the skin will depend on the magnitude and duration of the frictional force applied and properties of the skin itself. Abrasions and friction blisters are examples of acute frictional trauma, but blisters can only form if the stratum corneum is tough and thick enough to form a blister roof. Friction blisters are therefore difficult to produce except on the palms and soles [1]. The chronic effects of friction are dependent on adaptive responses, in particular a steady rate of increase in epidermal turnover, and perhaps the laying down of thickened, vertically orientated collagen bundles in the papillary dermis, as seen in lichenification. The best defined clinical consequences of chronic frictional injury are calluses and corns, but various forms of dermatitis are perpetuated and perhaps initiated by friction (see below).

The scientific study of friction-induced injury has largely been directed towards understanding friction blister formation. The laws of static friction state that frictional resistance is: (i) directly proportional to load; and (ii) independent of the area of contact between the surfaces [2]. The ratio between the force necessary to move one surface over the other and the load between the two surfaces is thus a constant, called the coefficient of friction. The static coefficient of friction is the force required to start one object in motion past another and the dynamic coefficient is the force required to sustain the motion of one object past another. Because of its viscoelastic properties, skin deviates from Amonton's laws. Several different techniques have been used to measure friction [1–13]. Coefficients of static and dynamic friction have been determined for a number of materials in contact with human skin, with and without lubricants, but there is great individual variation [1,2,14,15]. Of the various anatomical sites measured, the palm of the hand has the highest coefficient of friction [16]. A number of machines to simulate repetitive rubbing have been devised, but there is no entirely satisfactory model for chronic frictional injury [6].

Physiological changes, such as the degree of hydration, have a large effect—very dry or wet skin having a much lower frictional resistance than moderately hydrated skin [17] for most sites but not for the dorsal forearm or lower back [18]. Skin surface lipids have relatively little effect [19]. Petrolatum initially decreases the coefficient of friction because of its lubricating property but then increases it because of its occluding effect on skin, causing increased hydration [15]. Age and sex have no significant effect on frictional properties of the skin, but body site is important; the forehead and behind the ear have the highest dynamic coefficient of friction and the abdomen the lowest [18]. The rough skin in atopics has a lower coefficient of friction than normal [10].

References

1 Sulzberger MB, Cortese TA, Fishman L *et al.* Studies on blisters produced by friction. I. Results of linear rubbing and twisting techniques. *J Invest Dermatol* 1966; **47**: 456–65.
2 Comaish S, Bottoms E. Skin and friction: deviations from Amonton's laws, and the effects of hydration and lubrication. *Br J Dermatol* 1971; **84**: 37–43.
3 Comaish JS, Harborow PRH, Hofman DA. A hand-held friction meter. *Br J Dermatol* 1973; **89**: 33–5.
4 El Shimi AF. *In vivo* skin friction measurements. *J Soc Cosmet Chem* 1977; **28**: 37–51.
5 Armstrong TJ. Mechanical considerations of skin at work. *Am J Ind Med* 1985; **8**: 463–72.
6 Akers WA. Measurements of friction injuries in man. *Am J Ind Med* 1985; **8**: 473–81.
7 Wilkinson DS. Dermatitis from repeated trauma to the skin. *Am J Ind Med* 1985; **8**: 307–17.
8 Zimmerer RE, Lawson KD, Culvert CJ. The effects of wearing diapers on the skin. *Pediatr Dermatol* 1986; **3**: 95–101.
9 Buchholz B, Frederick LJ, Armstrong TJ. An investigation of human skin friction and the effects of materials, prick force and moisture. *Ergonomics* 1988; **31**: 317–25.
10 Loden M, Olsson H, Axell T, Linde YW. Friction, capacitance and transepidermal water loss (TEWL) in dry atopic and normal skin. *Br J Dermatol* 1992; **126**: 137–41.
11 Hills RJ, Unsworth A, Ive A. A comparative study of the frictional properties of emollient bath additives using porcine skin. *Br J Dermatol* 1994; **130**: 37–41.
12 Elsnau WH. Skin friction measurement. In: Berardesca E, Elsner P, Wilhelm K-P, Maibach HI, eds. *Bioengineering of the Skin: Methods and Instrumentation*. Boca Raton, FL: CRC Press, 1995: 120–3.
13 Sivamani RK, Goodman J, Gitis NV, Maibach HI. Friction coefficient of skin in real-time. *Skin Res Technol* 2003; **9**: 235–9.
14 Highley DR, Coomey M, Den Beste M *et al.* Frictional properties of skin. *J Invest Dermatol* 1977; **69**: 303–5.
15 Nacht S, Close J, Yeung D *et al.* Skin friction coefficient: changes induced by hydration and emollient application and correlation with perceived skin feel. *J Soc Cosmet Chem* 1981; **32**: 55–65.
16 Zhang M, Mak AFT. *In vivo* friction properties of human skin. *Prosthet Orthot Int* 1999; **23**: 135–41.
17 Naylor PFD. The skin surface and friction. *Br J Dermatol* 1955; **67**: 239–48.
18 Cua AB, Wilhelm K-P, Maibach HI. Frictional properties of human skin: relation to age, sex and anatomical region, stratum corneum hydration and transepidermal water loss. *Br J Dermatol* 1990; **123**: 473–9.
19 Cua AB, Wilhelm K-P, Maibach HI. Skin surface lipid and skin friction: relation to age, sex and anatomical region. *Skin Pharmacol* 1995; **8**: 246–51.

Callosities, corns and calluses

Definition [1]. A callosity is a plaque of hyperkeratosis caused by repeated friction and/or pressure. A corn is a sharply demarcated callosity occurring over a bony prominence, usually on the hand or foot, and is painful. A soft corn occurs between the toes.



Fig. 28.4 Calluses of the forefoot.

Podiatrists often refer to a corn as a heloma (Greek *helus*, a stone wedge). A callus is a broad-based diffuse area of hyperkeratosis of *relatively* even thickness, usually under the metatarsal heads.

Aetiology. Calluses (Fig. 28.4) and corns on the feet are usually the result of deformity, sometimes associated with dynamic changes in the function of the foot. They are more common in the elderly, in particular in those with high pressures exerted on the plantar skin [2]. They are often made worse or even caused by unsuitable footwear. Perhaps the most extreme example of footwear causing gross abnormalities is the Chinese foot-binding syndrome, although some Western shoe fashions, such as 'winkle-pickers' and high-heeled shoes, can be similarly damaging albeit on a lesser scale [3]. Various intrinsic abnormalities of the foot predispose to callosities. These include bony prominences such as occur with hallux valgus, a prominent condylar projection or malunion of a fracture. In some rheumatic diseases (e.g. rheumatoid arthritis) there are distinctive patterns of callosity formation which can be predicted from the joints involved [4]. Diabetic subjects, especially those with neuropathy, are prone to callus formation, and high pressure is strongly associated with ulceration [5]. Faulty foot mechanics can occur when there is a toe deformity (e.g. claw, hammer or mallet toe), a short first metatarsal or hallux rigidus. The dermatologist should be aware of the effects of deformity throughout the foot. In the hindfoot, a varus or valgus position of the heel as an anatomical abnormality will lead to a failure of the foot to absorb loads applied to it during the stance phase of gait. The net result is that excessive loads are applied to the plantar skin, leading to callosities. The pattern of these changes can be very distinctive. With the hindfoot anomaly, there is often an associated forefoot deformity with excessive pronation or supina-

tion of the metatarsals, hallux valgus and fixed deformities of the lesser toes. Calluses on the edges of the weight-bearing area of the sole are often caused by shoes that are too loose.

The biomechanics of the foot that lead to callosities have been investigated in detail [6–8]. A variety of measuring devices are available to document the abnormal forces and assist design of appropriate orthoses [9].

On the dorsum of the foot, factors provoking callosities include footwear and a habit of sitting with the foot tucked under the body [10,11], with or without a prominent underlying talus.

The soft corn usually occurs when tight shoes press the condyle of a metatarsal or phalanx against the base of a phalanx on the adjacent toe.

On the hand and at other sites, callosities generally reflect repeated frictional injury which will be apparent from the history.

An inherited disposition to callosities has been described, with an autosomal dominant inheritance [12,13].

Pathology. In a callus, there is epidermal hyperplasia. The stratum corneum is thickened and compact, sometimes with parakeratosis over the dermal papillae, and there may be expansion of the granular layer. The underlying dermis may show an increase in dermal collagen and fibrosis around neurovascular bundles.

A corn differs in that there is a thick parakeratotic plug set in a cup-shaped depression of the epidermis, usually with loss of the granular cell layer.

Clinical features. These are as follows.

Feet [1,5,10–12]. On the plantar surface, the most common site for corns and callosities is over the metatarsal heads (Fig. 28.4), although the sides of the arches and heel can be involved. A callus is an ill-defined area of waxy, often yellowish thickening over which the dermatoglyphic markings may become indistinct. A corn is smaller, usually very painful, and may have a glassy centre. Corns can occur within an area of callus. On the dorsum of the foot, corns and calluses are particularly found over the interphalangeal joints and tips of the toes. A distinctive variety of callus occurs over the talus, anteromedial to the lateral malleolus [12]. Calluses and corns can be painful, interfere with mobility, and can damage deeper tissues, even causing ulceration.

In the autosomal dominant 'hereditary callosities', blisters occur at the periphery of hyperkeratotic skin [12]. This is distinct from epidermolysis bullosa, epidermolytic hyperkeratosis and blistering sometimes associated with palmoplantar keratodermas (see Chapter 19).

The soft corn is usually between the fourth and fifth toes, is typically very painful and exhibits hyperkeratosis that becomes white from maceration. A small sinus may be present, and secondary bacterial infection can then present as cellulitis.

Hands. Callosities on the hands most commonly occur as distinctive occupational stigmata in many trades and professions [14,15]. Areas of thickening most commonly occur on the palmar surface and over the metacarpophalangeal joints. The site of the callosity may be highly specific [16]. They are rarely complained of, as was shown in a survey of solid-waste handlers in whom there was a 75% prevalence of palmar calluses [17]. Unless they become fissured or infected, they should be considered as an adaptation rather than a disability.

The habit of biting or chewing the side or knuckle of the finger is not uncommon in children ('gnaw warts'). Larger callosities are sometimes seen in the mentally retarded.

Callosities on the hands caused by frictional injury against the teeth have been described in patients with bulimia nervosa as a result of repeated manual stimulation of the gag reflex [18,19]. A distinctive hyperkeratosis on the side of the thumb can occur with use of a cigarette lighter [20].

Prayer nodules [21–24]. These are seen on the forehead of Muslims from repeatedly touching the forehead on a prayer stone. They may also occur on the knees, ankles and dorsa of feet from the squatting position adopted by worshippers. A similar pattern has been described on the ankles from sitting cross-legged [10].

Callosities from clothing and appliances. Trusses, especially if ill-fitting, may cause circumscribed patches of hyperkeratosis and pigmentation. Pressure from callipers or reinforced shoes may cause calluses in the disabled. The effects of friction and pressure on the amputee are discussed on p. 28.27.

Diagnosis. Corns on the feet can be difficult to distinguish from viral warts, particularly when the latter have a zone of reactive hyperkeratosis around them. Corns are generally more painful when pressed vertical to the skin surface, whereas warts are more tender when squeezed laterally between the finger and thumb. Paring down a wart usually reveals the circumscribed abnormal surface markings and thrombosed vessels. Granuloma annulare occasionally resembles callosity, but can be distinguished by biopsy. Various forms of keratoderma can resemble callosities, but do not occur selectively over sites of excessive compression.

Management. The major difficulties with diagnosis lie with foot callosities. The patient's footwear and any orthoses, the gait and the alignment of the feet should all be examined. Palpation may reveal abnormal bony prominences. There may be a past history of surgery. Radiography can be helpful. Pressure studies (pedobarographs) can be helpful in evaluating foot biomechanics (reviewed in [9,25]).

The aims of treatment are to:

1 Provide symptomatic relief
2 Determine the source of abnormal mechanical stress
3 Relieve the cause by conservative means
4 Consider surgery if these fail.

Relief of symptoms caused by corns and calluses can usually be achieved by careful and regular paring. Regular paring reduces the pressure induced by corns [26]. The initial procedure is often best done with a scalpel and subsequent treatment with an abrasive device. For soft corns, the use of a toe separator (felt, foam or silicone) can provide rapid relief. Salicylic acid (10–20%) keratolytic preparations can be of some help, but care is needed to avoid irritancy.

The role of the patient's shoes in producing callosities should be carefully assessed, and appropriate corrective steps taken. Extra width may be needed, especially with the toebox. A softer upper may be needed. With marginal calluses, the shoe is likely to be too loose. The shoe may need to be adapted to receive an orthosis—a cushioning device designed to redistribute the mechanical forces causing the callosity. Examples are the metatarsal pad for localized plantar callus, and a medial wedge for the cavovarus foot. Customized shoe inlays can be moved from shoe to shoe. Another useful orthosis is the silicone sleeve that can be used on deformed toes that have corns on them.

Sometimes, conservative measures are insufficient or fail. Surgical correction of toe deformities and resection of prominent condyles causing soft corns can be rewarding. Surgery for other bony causes should only be undertaken after careful study of radiographs and pedobarographs by an orthopaedic surgeon with expertise in the field [27,28]; results can be encouraging [29,30], but can also be disappointing [31]. When there is loss of subcutaneous fat, silicone injections are sometimes used [32].

The principles outlined above can be applied to symptomatic callosities elsewhere, for example at sites of abnormal pressure from a limb prosthesis. Occasionally, excision is justified on cosmetic grounds, for example for athlete's nodules [33].

References

1 Singh D, Bentley G, Trevino SG. Callosities, corns and calluses. *BMJ* 1996; **312**: 1403–6.
2 Menz HB, Zammit GV, Munteanu SE. Plantar pressures are higher under callused regions of the foot in older people. *Clin Exp Dermatol* 2007; **32**: 375–80.
3 Jackson R. The Chinese foot-binding syndrome: observations on the history and sequelae of wearing ill-fitting shoes. *Int J Dermatol* 1990; **29**: 322–8.
4 Woodburn J, Helliwell PS. Relation between heel position and the distribution of forefoot plantar pressures and skin callosities in rheumatoid arthritis. *Ann Rheum Dis* 1996; **55**: 806–10.
5 Murray HJ, Young MJ, Hollis S, Boulton AJM. The association between callus formation, high pressures and neuropathy in diabetic foot ulceration. *Diabet Med* 1996; **13**: 979–82.
6 Duckworth T, Betts RP, Franks CI, Burke J. The measurement of pressures under the foot. *Foot Ankle* 1982; **3**: 130–41.
7 Gibbs RC, Boxer MC. Abnormal biomechanics of feet and their cause of hyperkeratoses. *J Am Acad Dermatol* 1982; **6**: 1061–9.
8 Condie DN. Biomechanics. In: Helal B, Rowley DI, Crachiolo A III, Myerson M, eds. *Surgery of Disorders of the Foot and Ankle*. London: Martin Dunitz, 1996: 37–46.
9 Orlin MN, McPoil TG. Plantar pressure assessment. *Phys Ther* 2000; **80**: 399–409.
10 Cox NH, Finlay AY. Crossed-leg callosities. *Acta Derm Venereol (Stockh)* 1985; **65**: 559–61.
11 Verbov JL, Monk CJE. Talar callosity: a little-recognised common entity. *Clin Exp Dermatol* 1991; **16**: 118–20.
12 Baden HP, Bronstein BR, Rand RE. Hereditary callosities with blisters. *J Am Acad Dermatol* 1984; **11**: 409–15.
13 Cambiaghi S, Morel P. Hereditary painful callosities with associated features. *Dermatology* 1996; **193**: 47–9.
14 Ronchese F, ed. *Occupational Marks and Other Physical Signs: a Guide to Personal Identification*. New York: Grune & Stratton, 1968.
15 Ronchese F. Occupation marks. *Practitioner* 1973; **210**: 507–12.
16 Koh D, Jeyaratnam J. An occupational mark of screwdriver operators. *Contact Dermatitis* 1995; **32**: 46.
17 Gellin GA. Dermatoses acquired by solid-waste handlers. *Am J Ind Med* 1985; **8**: 363–70.
18 Joseph AB, Herr B. Finger calluses in bulimia. *Am J Psychiatry* 1985; **5**: 655.
19 Russell G. Bulimia nervosa: an ominous variant of anorexia nervosa. *Psychol Med* 1979; **9**: 429–48.
20 Maharaj D, Naraynsingh V. Cigarette lighter thumb. *Am J Med* 2001; **110**: 506.
21 Harahap M. Peculiar forehead mark from praying. *Int J Dermatol* 1981; **20**: 133.
22 Vollum DI, Azadeh B. Prayer nodules. *Clin Exp Dermatol* 1979; **4**: 39–47.
23 Kahana M, Cohen M, Ronnen M *et al*. Prayer nodules in Muslim men. *Cutis* 1986; **38**: 281–6.
24 Abanmi AA, Al Zouman AY, Al Hussaini H, Al-Asmari A. Prayer marks. *Int J Dermatol* 2002; **41**: 411–4.
25 Abboud RJ, Rowley DI. Foot pressure measurement: history and development. In: Helal B, Rowley DI, Crachiolo A III, Myerson M, eds. *Surgery and Disorders of the Foot and Ankle*. London: Martin Dunitz, 1996: 123–38.
26 Pitei DL, Foster A, Edmonds M. The effect of regular callus removal on foot pressures. *J Foot Ankle Surg* 1999; **38**: 251–5.
27 Regnauld B, ed. *The Foot*. Berlin: Springer-Verlag, 1986.
28 Helal B, Rowley DI, Crachiolo A III, Myerson MS. *Surgery and Disorders of the Foot and Ankle*. London: Martin Dunitz, 1996.
29 Kiviniemi VJ, Leppilahti J, Jalovaara PI. Study of straight metatarsal osteotomy for the treatment of plantar callosities. *Ann Chir Gynaecol* 2000; **89**: 309–12.
30 Okuda R, Kinoshita M, Morikawa J *et al*. Surgical treatment for hallux valgus with painful plantar callosities. *Foot Ankle Int* 2001; **22**: 203–8.
31 Idusuyi OB, Kitaoka HB, Patzker GL. Oblique metatarsal osteotomy for intractable plantar keratosis: 10-year follow-up. *Foot Ankle Int* 1998; **19**: 351–5.
32 Balkin SW. Injectable silicone and the foot: a 41-year clinical and histologic history. *Dermatol Surg* 2005; **31**: 1555–9.
33 Cohen PR, Eliezri YD, Silvers DN. Athlete's nodules: treatment by excision. *Sports Med* 1990; **10**: 198–203.

Friction blisters

For friction blisters to occur, the stratum corneum must be strong enough not to be rubbed away. Usually, friction blisters do not form on lax or thin skin but are common on the palm (Fig. 28.5), sole, heel or dorsum of the fingers. Frictional force and the number of times an object moves across the skin determine the likelihood of blister development; the greater the force, the fewer the number of cycles of movement needed.

Pathology [1]. The blister usually forms in the spinous layer, just beneath the stratum granulosum. The keratinocytes in the base of the blister show variable oedema and perhaps degenerative changes. Mitotic activity commences in the base within 30 h [2].



Fig. 28.5 Friction blister on the palm mimicking a target lesion of erythema multiforme. This patient had generalized pruritus caused by biliary cirrhosis, and he repeatedly rubbed his thenar eminence on his skin to relieve the itch.

Clinical features. These are usually self-evident and seldom present diagnostic problems when the cause is known. However, a patient may seek advice when a bulla appears unexpectedly or under inappropriate circumstances. It then becomes important for the dermatologist to consider whether the trauma was merely a localizing factor in a hitherto undiagnosed congenital or acquired disease (Fig. 28.5). As well as blister formation, there may be other consequences of the inciting trauma such as callus formation, petechiae, etc.

Prognosis. Uncomplicated blisters heal rapidly.

Diagnosis. A careful history of appropriate frictional trauma will usually enable the diagnosis to be made. There are often specific aspects of the circumstances in which blisters occur that are relevant to occupational causes [3] and other situations such as sporting activities. Trauma may induce lesions in both acquired and hereditary epidermolysis bullosa. Skin fragility can occasionally be a presenting feature of systemic amyloidosis, and the blisters seen in patients comatose from neurological lesions or drug overdose can clinically resemble those caused by friction; however, they differ histologically. Occasionally, bullous insect-bite reactions and other bullous diseases can be confused with friction blisters.

Management. Preventive measures include antiperspirants [4]; some case studies have shown that these may reduce blistering in epidermolysis bullosa simplex (Weber–Cockayne) [5] and in pachyonychia congenita [6]. Although most controlled trials have not shown convincing evidence of benefit [7,8], 20% aluminium chloride hexahydrate in anhydrous ethyl alcohol used for 3 days before hiking can reduce blistering [9]; but such preparations may cause irritant dermatitis. Foot powders with the aim of absorbing moisture are another traditional approach [10], but again controlled trials show lack of efficacy [11–13].

By contrast, certain types of synthetic insole can absorb frictional force and reduce blistering, for example Spenco, a closed-cell neoprene material [14,15], and the polyurethane product Poron [16]. Acrylic socks [17] and the use of a thin polyester sock under a thick, dense outer sock [18] can reduce blistering. It is likely that subthreshold exposure of the feet to friction reduces the likelihood of blistering [19].

When blistering has occurred, drainage so as to allow the roof to adhere to the base provides relief of symptoms and optimizes healing [20]. If the blister has burst and the roof has torn away, the wound should be treated with a non-adherent dressing and protective padding. Hydrocolloid dressings have been used with success [21,22]. There is no evidence that cyanoacrylate glue helps [23].

References

1 Brehmer-Andersson E, Goransson K. Friction blisters as a manifestation of pathomimia. *Acta Derm Venereol (Stockh)* 1975; **55**: 65–71.
2 Epstein WL, Fukuyama K, Cortese TA. Autoradiographic study of friction blisters. *Arch Dermatol* 1969; **99**: 94–106.
3 Pigatto PD, Legori A, Bigardi AS. Occupational dermatitis from physical causes. *Clin Dermatol* 1992; **10**: 231–43.
4 Darrigrand A, Reynolds K, Jackson R *et al.* Efficacy of antiperspirants on feet. *Mil Med* 1992; **157**: 256–9.
5 Tkach JR. Treatment of recurrent bullous eruption of the hands and feet (Weber–Cockayne disease) with topical aluminium chloride. *J Am Acad Dermatol* 1982; **6**: 1095–6.
6 Tidman MJ, Wells RS. Control of plantar blisters in pachyonychia congenita with topical aluminium chloride. *Br J Dermatol* 1988; **118**: 451–2.
7 Younger IR, Priestley GC, Tidman MJ. Aluminium chloride hexahydrate and blistering in epidermolysis bullosa simplex. *J Am Acad Dermatol* 1990; **23**: 930–1.
8 Reynolds KL, Darrigrand A, Roberts D *et al.* Effects of an antiperspirant with emollients on foot-sweat accumulation and blister formation while walking in the heat. *J Am Acad Dermatol* 1995; **33**: 626–30.
9 Knapik JJ, Reynolds K, Barson J. Influence of an antiperspirant on foot blister incidence during cross-country hiking. *J Am Acad Dermatol* 1998; **39**: 202–6.
10 Levine N. Friction blisters. *Physician Sports Med* 1982; **10**: 84–92.
11 Allan JR, Macmillan AL. *The Immediate Effects of Heat on Unacclimatized Paratroops. Exercise 'Tiger Brew II'*. UK: Army Operational Research Establishment, Memorandum no. 16/62, 1963.
12 Allan JR. *A Study of Foot Blisters*. UK: Army Operational Research Establishment, Memorandum no. 16/64, 1964.
13 Quinn J. *The Effects of Two New Foot Powders on the Incidence of Foot Infection and Blisters in Recruits During Basic Training*. Farnborough, UK: Army Personnel Research Establishment, Memorandum no. P/6, 1967.
14 Spence WR, Shields MN. Insole to reduce shear forces on the sole of the feet. *Arch Phys Med Rehabil* 1968; **49**: 476–9.
15 Spence WR, Shields MN. New insole for prevention of athletic blisters. *J Sports Med* 1968; **8**: 177–80.
16 Smith W, Walter J, Bailey M. Effects of insoles in coastguard basic training footwear. *J Am Podiatr Med Assoc* 1985; **75**: 644–7.
17 Herring KM, Richie DH. Friction blisters and sock fiber composition. *J Am Podiatr Med Assoc* 1990; **80**: 63–71.
18 Knapik JJ, Hamlet MP, Thompson KJ *et al.* Influence of boot-sock systems on frequency and severity of foot blisters. *Mil Med* 1995; **161**: 594–8.
19 Patterson HS, Woolley TW, Lednar WM. Foot blister risk factors in an ROTC summer camp population. *Mil Med* 1994; **159**: 130–5.
20 Cortese TA, Fukuyama K, Epstein W *et al.* Treatment of friction blisters: an experimental study. *Arch Dermatol* 1968; **97**: 717–21.
21 Alvarez OM, Mertz PM, Eaglstein WH. The effect of occlusive dressings on collagen synthesis and re-epithelialization in superficial wounds. *J Surg Res* 1983; **35**: 142–8.
22 Yarkony GM, Lukane C, Carle TV. Pressure sore management efficacy of a moisture reactive occlusive dressing. *Arch Phys Med Rehabil* 1984; **65**: 567–600.
23 Levy PD, Hile DC, Hile LM, Miller MA. A prospective analysis of the treatment of friction blisters with 2-octylcyanoacrylate. *J Am Podiatr Med Assoc* 2006; **96**: 232–7.

Friction and dermatitis

The inflammatory changes that characterize eczematous dermatitis have been reported as a result of friction, and there are a number of eczematous conditions in which mild repetitive frictional injury has an important initiating, localizing or perpetuating role [1]. The importance of friction was recognized long ago [2], but has often been underestimated since. An experimental model has been devised [3].

Friction as a direct cause of dermatitis

Physical irritant contact dermatitis accounted for just over 1% of all patients attending a large contact dermatitis clinic in London, and of these about one-third were attributable to friction; low humidity was a common accompanying factor, especially for office workers [4]. A similar prevalence was found in a series from Sheffield [5].

Menné and Hjorth [6] described two workers repeatedly handling NCR (No Carbon Required) paper, and a third whose contact was with bus tickets, in whom scaling, vesicles and occasional pustules developed on the areas of maximal contact; patch tests were negative. Three cases of nipple dermatitis were attributed to friction from poorly fitting brassieres [7].

Friction treatment for acne can lead to dermatitis [8].

Airbag dermatitis [9]

Although dermatitis was not proven in the histological sense, a symptomatic red rash has been described from injury from deployment of the airbag in automobiles. It is possible that talc used in the packaging plays a part as well as frictional injury. The bizarre shapes produced by the impact of the airbag can give the appearance of dermatitis artefacta [10].

Juvenile plantar dermatosis [11]

In this distinctive condition, there is a glazed, erythematous, hyperkeratotic and often fissured change on the contact areas of the anterior third of the plantar aspect of the feet (see Chapter 23).

Friction from footwear and barefoot sporting activities may be important causes, but are clearly not the only factors involved. In some series, there is a pronounced worsening in winter [12,13], whereas in others there is exacerbation in summer [14–16]. Certain types of occlusive footwear, such as the trainer shoe and rubber boots, often combined with relatively non-absorbent synthetic fibre socks, have been thought to contribute [16,17] and in some cases this may explain the seasonal effect. However, in a controlled study, children without juvenile plantar dermatosis had a similar use of trainer-type shoes as those with the disorder [18]. Up to 10% of cases have relevant contact allergy to shoe materials [11,18,19] and are clinically indistinguishable from the majority of cases, which are not caused by an allergic reaction.

Atopic dermatitis

Friction is probably one of many factors that account for the localization of atopic dermatitis, for example on the backs of the thighs in school children [20] and on the feet.

An eruption of follicular papules on the chin brought about by repeated contact with the knee has been described in Japanese children. It can resemble naevus sebaceous [21].

Contact dermatitis

Frictional injury presumably enhances percutaneous penetration of irritants and allergens. In the clinical setting, friction has been shown to have an adjuvant role in irritant dermatitis to soaps and detergents [22,23] and to cement [24], and is probably important in many other circumstances [5].

The induction of contact allergy is also more likely when there is concurrent mechanical trauma. In a series of 8230 patients patch tested for eczematous disorders, those who had sustained cuts, abrasions and other mechanical injuries had a much higher incidence of positive results than other groups [25]. In a number of industries, friction has been regarded as contributory to the high rate of allergic as well as irritant reactions, for example cobalt allergy in hard-metal workers [26].

Friction and nummular dermatitis

Patients sometimes attribute localization of nummular (discoid) dermatitis to repeated mild chronic frictional injury. Shin pad dermatitis may be more commonly due to friction and sweating than allergy [27]. An unusual example has been described as shower-jet dermatitis, in which eczematous lesions were localized to an area on the front of the chest subjected to a high-pressure jet for 10–15 min/day [28].

Hyperkeratotic palmar and plantar dermatitis

Hyperkeratotic palmar dermatitis (see Chapter 23) has been described mainly in middle-aged or elderly men, and less commonly in women [29]. It may be difficult to distinguish from psoriasis, and some authors dispute its existence [30]. Chronic mechanical trauma and friction from hard manual work has been thought to be a contributory factor in some cases [1,29].

Frictional dermatitis of children

Although first described in 1956 [31], the exact status of this condition remains obscure and its prevalence undetermined. In a more recent series of cases, nearly half were atopic [32].

Aetiology. Friction from surfaces such as sand and rough carpets [33] and from activities such as tobogganing [34] have been held responsible. Other authors have attributed the condition to sunlight [35] and similar cases have been described in which neither friction nor sunlight were considered to have a role [32].

Pathology. The histology shows mild non-specific changes with acanthosis, hyperkeratosis, small foci of spongiosis and a lymphohistiocytic infiltrate in the upper dermis [32].

Clinical features. An eruption of pinhead-sized pale or white papules or warty lesions occurs on the elbows, knees or backs of the hands, spreading to the adjacent areas, in children and occasionally in adolescence. Pruritus is mild. The condition may be more common in spring and summer.

Prognosis. The condition often recurs during childhood. Long-term studies have not been performed.

Treatment. A mild topical steroid or tar ointment is usually helpful.

Frictional sweat dermatitis

A spongiotic dermatitis occurring beneath undergarments during the hottest months of the year has been described from New Delhi and attributed to friction, heat and contact with sweat [35].

Pool palms

This term has been used for an erythema on the contact areas of the palmar surfaces due to repeated contact with the rough surface of a swimming pool. It is typically found in children learning to swim or dive [36,37]. Similar changes can be seen on the soles.

Pretibial pruritic papular dermatitis

A distinctive itchy papular eruption on the shins attributed to rubbing has been described in 44 cases from Italy. The lesions are roundish and smooth; histologically there is no amyloid deposition, and a lack of the vertically orientated coarse collagen bundles characteristic of lichen simplex chronicus [38].

References

1 Wilkinson DS. Dermatitis from repeated trauma to the skin. *Am J Ind Med* 1985; **8**: 307–17.
2 Prosser White R. *The Dermatergoses or Occupational Affections of the Skin*, 4th edn. London: Lewis, 1934: 82–121.
3 Graves CJ, Edwards C, Marks R. A model of measured percussive mechanical trauma and its effects on the skin. *Br J Dermatol* 1993; **129**: 558–62.
4 Morris-Jones R, Robertson SJ, Ross JS *et al*. Dermatitis caused by physical irritants. *Br J Dermatol* 2002; **147**: 270–5.
5 McMullen E, Gawkrodger DJ. Physical friction is under-recognized as an irritant that can cause or contribute to contact dermatitis. *Br J Dermatol* 2006; **154**: 154–6.
6 Menné T, Hjorth N. Frictional contact dermatitis. *Am J Ind Med* 1985; **8**: 401–2.
7 Kapur N, Goldsmith PC. Nipple dermatitis: not all what it 'seams'. *Contact Dermatitis* 2001; **45**: 44–5.
8 Ayres S Jr, Mehan R. Facial dermatitis following friction treatment of acne. *Cutis* 1979; **24**: 610–1.
9 Foley S, Mallory SB. Airbag dermatitis. *J Am Acad Dermatol* 1995; **33**: 824–5.
10 Burton JL. Airbag injury. *J Accident Emerg Med* 1994; **11**: 60.
11 Mackie RM, Husain SL. Juvenile plantar dermatosis: a new entity. *Clin Exp Dermatol* 1976; **1**: 253–60.
12 Lachapelle JM, Tennstedt D. Juvenile plantar dermatosis: a report of 80 cases. *Am J Ind Med* 1985; **8**: 291–5.
13 Schultz H, Zachariae H. The Trafuril test in juvenile eczema of hands and feet. *Acta Derm Venereol (Stockh)* 1972; **52**: 398–400.
14 Hambly EM, Wilkinson DS. Sur quelques formes atypiques d'eczéma chez l'enfant. *Ann Dermatol Vénéréol* 1978; **105**: 369–71.
15 Kint A, Van Hecke E, Leys G. Dermatitis plantaris sicca. *Dermatologica* 1982; **165**: 500–9.
16 Millard LG, Gould DJ. Juvenile plantar dermatosis. *Clin Exp Dermatol* 1977; **2**: 186–7.
17 Shrank A. The aetiology of juvenile plantar dermatosis. *Br J Dermatol* 1979; **100**: 641–8.
18 Ashton RE, Griffiths WAD. Juvenile plantar dermatosis: atopy or footwear? *Clin Exp Dermatol* 1986; **11**: 529–34.
19 Young E. Forefoot eczema: further studies and review. *Clin Exp Dermatol* 1986; **11**: 523–8.
20 Naylor PFD. The reaction to friction of patients with flexural eczema. *Br J Dermatol* 1955; **67**: 365–91.
21 Kanzaki T, Morita A, Takashima A. Follicular keratosis of the chin. *J Am Acad Dermatol* 1992; **26**: 134–5.
22 Wilkinson DS. Contact dermatitis of the hands. *Trans Rep St John's Hosp Derm Soc Lond* 1972; **58**: 261–8.
23 Matthias CGT. Contact dermatitis from use or misuse of soap, detergents and cleansers in the workplace: state of the art review. *Occup Med* 1986; **1**: 205–18.
24 Cronin E. *Contact Dermatitis*. Edinburgh: Churchill Livingstone, 1980: 277.
25 Meneghini CL. Sensitization in traumatised skin. *Am J Ind Med* 1985; **8**: 319–21.
26 Fisher T, Rystedt I. Cobalt allergy in hard metal workers. *Contact Dermatitis* 1983; **9**: 115–21.
27 Weston WL, Morelli JG. Dermatitis under soccer shin guards: allergy or contact irritant reaction? *Pediatr Dermatol* 2006; **23**: 19–20.
28 Forgie JC, Highet AS. Shower jet dermatitis. *Clin Exp Dermatol* 1992; **17**: 141–2.
29 Hersle K, Mobacken H. Hyperkeratotic dermatitis of the palms. *Br J Dermatol* 1982; **107**: 195–202.
30 Menne T, Bachman E. Permanent disabilities from skin diseases. *Dermatosen* 1979; **27**: 37–42.
31 Sutton RL Jr. Summertime pityriasis of the elbow and knee. In: Sutton RL Jr, ed. *Diseases of the Skin*, 2nd edn. St Louis: CV Mosby, 1956: 898.
32 Patrizi A, Di Lernia V, Ricci G *et al*. Atopic background of a recurrent papular eruption of childhood (frictional lichenoid eruption). *Paediatr Dermatol* 1990; **7**: 111–5.
33 Waisman M, Sutton RL Jr. Frictional lichenoid eruption in children. *Arch Dermatol* 1966; **94**: 592–3.
34 Dupre A, Christol B, Bonafe JL *et al*. La dermite du toboggan. *Bull Soc Fr Dermatol Syph* 1974; **81**: 203–4.
35 Ramam M, Kaitan BK, Singh MK, Gupta SD. Frictional sweat dermatitis. *Contact Dermatitis* 1998; **38**: 49.
36 Blauvelt A, Duarte AM, Pruksachatkunakorn C *et al*. Human papillomavirus type 6 infection involving cutaneous nongenital sites. *J Am Acad Dermatol* 1992; **27**: 876–9.
37 Wong LC, Rogers M. Pool palms. *Pediatr Dermatol* 2007; **24**: 95.
38 Annessi G, Petresca M, Petresca A. Pretibial pruritic papular dermatitis: a distinctive cutaneous manifestation in response to chronic rubbing. *Am J Dermatopathol* 2006; **28**: 117–21.

Friction and other dermatoses

Frictional trauma can localize skin diseases by means of the Koebner phenomenon (p. 28.2).

Psoriasis on the palms can be difficult to distinguish from hyperkeratotic eczema, and may be localized by repetitive exposure to friction. A relationship to occupation is not always obvious [1].

Mechanical forces, including friction, are aetiological factors in acne mechanica (Chapter 42) and in dermographism and deep pressure urticaria (see Chapter 22).

Hyperpigmentation following repetitive rubbing occurs in predisposed, usually dark-skinned individuals and has been termed frictional melanosis. It is often localized over bony prominences of the trunk and limbs [2,3]. Frictional melanosis may occur *de novo*, or may accompany or follow dermatitis [4]. A distinctive rippled pattern, which overlaps with macular amyloidosis, has been described following the use of vigorous washing practices [5,6]. In some of these subjects, superficial amyloid deposits have been found on biopsy.

Pachydermodactyly, a distinctive digital fibromatosis (see Chapter 45), has been attributed to repetitive mechanical trauma such as repeated clasping of the hands and rubbing of crossed fingers [7]. Diffuse swelling of the digits, involving dermis as well as epidermis, clearly differs from calluses, knuckle pads, etc.

Bos and de Koning [8] described a distinctive frictional dermatosis on the upper gluteal region of elderly people, characterized by skin colour or slightly red patches with a rough surface and hyperkeratotic ridges running parallel to the natal cleft. These lesions occur particularly in those who spend most of the day sitting, and superficial ulceration may be a complication. Skin biopsies showed hyperkeratosis, psoriasiform hyperplasia, 'meandering' superficial vessels and some degenerative changes in the connective tissue.

References

1 Moroni P, Cazzaniga R, Pierini F *et al*. Occupational contact psoriasis. *Dermatosen* 1988; **36**: 163–4.
2 Hidano A, Mizuguchi M, Higaki Y. Friction melanosis. *Ann Dermatol Vénéréol* 1984; **111**: 1063–71.
3 Naimer SA, Trattner A, Biton A *et al*. Davener's dermatosis: a variant of friction hypermelanosis. *J Am Acad Dermatol* 2000; **42**: 442–5.
4 Dominguez-Soto L, Hojyo-Tomoka T, Vega-Memije E *et al*. Pigmentary problems in the tropics. *Dermatol Clin* 1994; **12**: 777–84.

5 Sharquie KE, Al-Dorky MK. Frictional dermal melanosis (Lifa disease) over bony prominences. *J Dermatol* 2001; **28**: 12–5.
6 Siragusa M, Ferri R, Cavallari V, Schepis C. Friction melanosis, friction amyloidosis, macular amyloidosis, towel melanosis: many names for the same clinical entity. *Eur J Dermatol* 2001; **11**: 545–8.
7 Itin PH, Lautenschlager S. Pachydermodactyly: a psychocutaneous disorder. *Dermatology* 1995; **190**: 1–3.
8 Bos WH, de Koning J. A senile gluteal dermatosis caused by friction. *Eur J Dermatol* 1992; **2**: 157–9.

Black heel and palm

Synonyms
- Talon noir
- Calcaneal petechiae

Definition. Pigmentation of the heel (or palm) secondary to extravasation of red blood cells.

Aetiology. The condition results from shear–stress rupture of the papillary capillaries, for example during violent sport, particularly where repeated jumping and sudden stopping or twisting of the heel occurs. Similar circumstances explain the occurrence on the palm.

Pathology. Extravasated erythrocytes may be found in the dermal papillae [1], but often the histological changes are limited to the stratum corneum, where amorphous yellow–brown material may be found in rounded collections having undergone transepidermal elimination. This material is often negative with Perls' stain (which stains haemosiderin) but gives a positive benzidine reaction, showing that it is derived from haemoglobin [2,3].

Clinical features. Closely aggregated groups of bluish black specks occur suddenly at the back or side of the heel (Fig. 28.6), just above the hyperkeratotic edge of the foot. The metatarsal area has, rarely, been involved. The lesion may resemble a tattoo [4] or even a melanoma [2,5]. Either sex may be affected [2], but the condition is virtually confined to athletic adolescents [6]. Football, basketball, lacrosse and, less often, tennis and squash players are mainly affected. The condition can occur on the hands of weightlifters [7].



Fig. 28.6 Black heel. Stippled pigmentation within the stratum corneum.

Diagnosis. When there is a history of sudden appearance of the pigmented lesions at a typical site, diagnosis is rarely in doubt. Viral warts can also produce a black stippled appearance because of extravasation of red cells, but the skin surface is generally abnormal. Occasionally, melanoma or atypical melanocytic hyperplasia [8] will need to be excluded. With black heel, the patient and physician can usually be reassured by carefully paring the affected area, thereby completely removing the abnormality. By epiluminescence microscopy, black heel has highly specific features [9].

Treatment. The condition is usually asymptomatic, and its importance lies in its resemblance to malignant melanoma. When in doubt as to the diagnosis, carefully paring away the stratum corneum is generally sufficient to remove the pigment.

References

1 Crissey JT, Peachey JC. Calcaneal petechiae. *Arch Dermatol* 1961; **83**: 501.
2 Kirton V, Wheatley-Price M. Black heel. *Trans St John's Hosp Derm Soc Lond* 1965; **51**: 80–4.
3 Hafner J, Haenseler E, Ossent P *et al*. Benzidine stain for the histochemical detection of hemoglobin in splinter hemorrhage (subungual hematoma) and black heel. *Am J Dermatopathol* 1995; **17**: 362–7.
4 Degos R, Civatte J. Pseudo-chromidrose eccrine intra-cornée. *Bull Soc Fr Dermatol Syph* 1963; **70**: 402–3.
5 Juhlin L, Pontén B. Plantar pseudochromidrosis simulating malignant melanoma. *Acta Dermatol Venereol* 1967; **47**: 255–8.
6 Wilkinson DS. Black heel: a minor hazard of sport. *Cutis* 1977; **20**: 393–6.
7 Izumi AK. Pigmented palmar petechiae. *Arch Dermatol* 1974; **109**: 261.
8 Cho KH, Kim YE, Seo KI, Suh DH. Black heel with atypical melanocytic hyperplasia. *Clin Exp Dermatol* 1993; **18**: 437–40.
9 Saida T, Oguchi S, Ishihara Y. In vivo observations of magnified features of pigmented lesions on volar skin using video microscope. *Arch Dermatol* 1995; **131**: 248–304.

Pressure ulcer

Synonyms
- Decubitus ulcer
- Bedsore
- Pressure sore

Definition. A localized area of necrosis caused by ischaemia, resulting from compression of soft tissue between a bony prominence and an external surface. Although formerly terms such as bedsore and decubitus ulcer (from the Latin 'to lie down') have been used, pressure ulcers can occur at any body site and in any situation where there has been prolonged pressure.

Epidemiology. Although estimates of incidence and prevalence vary greatly between studies it is clear that some groups, in par-

ticular hospital inpatients, are especially prone to pressure ulcers. There is no recent published dataset; however, in a study from 1991, new pressure ulcers were estimated to occur in 4–10% of patients admitted to acute hospitals in the UK [1]. A study in a US teaching hospital found that the overall prevalence of pressure ulcers was approximately 10% [2]. The risk rises further in certain disease groups; patients with hip fractures have an enhanced risk but the reported prevalence of pressure ulcers in this group varies between 2–3% [3] and 50% [4], depending on inclusion criteria. The incidence of pressure ulcers is high in patients with spinal cord injuries [5]. The elderly population also have an increased risk [6] which applies in the community as well as in hospital; an Italian study reported a pressure ulcer prevalence of 18% in nursing home residents [7]. In the UK it has been estimated that approximately 412 000 patients will develop a new pressure ulcer each year [8].

References

1 Clark M, Watts S. The incidence of pressure sores within a National Health Service Trust Hospital during 1991. *J Adv Nurs* 1994; **20**: 33–6.
2 Perneger TV, Heliot C, Rae A-C *et al*. Hospital-acquired pressure ulcers. *Arch Intern Med* 1998; **158**: 1940–5.
3 Keong N, Ricketts D, Alakeson N, Rust P. Pressure sores following elective total hip arthroplasty: pitfalls of misinterpretation. *Ann R Coll Surg Engl* 2004; **86**: 174–6.
4 Houwing R, Rozendaal M, Wouters-Wesseling W *et al*. Pressure ulcer risk in hip fracture patients. *Acta Orthop Scand* 2004; **75**: 390–3.
5 Haisma JA, van der Wonde LH, Stam HJ *et al*. Complications following spinal cord injury. *J Rehabil Med* 2007; **39**: 393–8.
6 Young JB, Dobrzanski S. Pressure sores: epidemiology and current management concepts. *Drugs Aging* 1992; **2**: 42–57.
7 Landi F, Onder G, Russo A, Bernabei R. Pressure ulcer and mortality in frail elderly people living in the community. *Arch Gerontol Geriatr* 2007; **44**: 217–23.
8 Bennett G, Dealey C, Posnett J. The cost of pressure ulcers in the UK. *Age Ageing* 2004; **33**: 230–5.

Pathogenesis and pathophysiology. Pressure ulcers develop due to the cellular and biochemical changes triggered by mechanical deformation and ischaemia occurring during the compression of skin and subcutaneous tissues.

Pressure, shear and friction. Sustained high pressure is ultimately responsible for necrosis of muscle, subcutaneous tissue, dermis and epidermis, and consequent formation of an ulcer. Fat and muscle are more susceptible to pressure than skin and may show evidence of damage earlier [1]. Experiments using an *in vitro* muscle model demonstrated that compression caused much more rapid cell death compared to that produced by hypoxia [2]. Kosiak showed a parabolic relationship between pressure and time, indicating that higher pressures require a shorter time period to cause ulceration than lower pressures [3,4]. Tissue damage is thought to occur when pressures over 9.3 kPa are sustained for more than 2–3 h. This is readily achieved when lying on a standard hospital mattress. Shear force is generated by the relative motion between the skin, which is restrained by frictional forces, and the subcutaneous tissues. Shear reduces the pressure needed to occlude the blood vessels [5], and is particularly damaging in elderly patients when there is a reduced amount of elastin in the skin. Frictional forces themselves may lead to the formation of intraepidermal blisters, which in turn induce superficial skin erosions, initiating or accelerating pressure ulceration.

Microvascular damage. Compression of microvasculature by pressures in excess of the mean capillary pressure leads to the exclusion of blood from the skin, with consequent tissue ischaemia. Trauma-induced endothelial cell damage initiates haemostatic mechanisms which further increase microvascular occlusion [6]. There is also an accumulation of fibrin, both within and outside microvessels, and defective fibrinolysis which contributes to the slow rate of pressure ulcer healing [7]. Pressure-induced vasodilatation is a homeostatic mechanism whereby cutaneous blood flow increases in response to locally applied pressure. Experiments in an animal model demonstrated that acute pain induces a loss of pressure-induced vasodilatation, a change that was reversed by morphine [8]. Modulation of this protective vasodilatory response by pain suggests the involvement of neurovascular pathways in pressure injury.

Neural dysfunction. Spinal cord injury confers an increased susceptibility to pressure ulceration. This is part caused by sensory and motor deficit and disuse atrophy, but other factors have been recognized. Following damage to the upper spinal cord, there is a large and immediate increase in the degradation of collagen in both skin and bone [9]. As a measure of defective collagen synthesis, it has been shown that the cross-linking enzyme lysyl hydroxylase has reduced activity in the insensitive compared with the sensitive skin in paraplegics [10]. Spinal cord injury, particularly above the T6 level, is associated with a progressive decrease in α-adrenergic receptors after the injury and is therefore liable to impair autonomic control of the cutaneous vasculature [11].

References

1 Nola GT, Vistnes LM. Differential response of skin and muscle in the experimental production of pressure sores. *Plast Reconstr Surg* 1980; **66**: 728–33.
2 Gawlitta D, Li W, Oomans CW *et al*. The relative contributions of compression and hypoxia to development of muscle tissue damage: an in vitro study. *Ann Biomed Eng* 2007; **35**: 273–84.
3 Kosiak M, Kubicek WG, Olson M *et al*. Evaluation of pressure as factor in production of ischial ulcer. *Arch Phys Med Rehab* 1958; **36**: 623–9.
4 Kosiak M. Etiology of decubitus ulcers. *Arch Phys Med Rehab* 1961; **42**: 19–29.
5 Bennett L, Kavner D, Lee BY, Trainer FA. Shear pressure as a causative factor in skin blood occlusion. *Arch Phys Med Rehab* 1979; **60**: 309–14.
6 Barton A, Barton M, eds. *The Management and Prevention of Bedsores.* London: Faber and Faber, 1978.
7 Seiler WO, Huser B, Marbet G *et al*. Verminderte fibrinolytische Aktivitat in Raudzonen von Dekubitaluzere. *Schweiz Med Wochenschr* 1980; **110**: 685–9.
8 Fromy B, Siqaudo-Roussel D, Baron C *et al*. Neuroendocrine pathway involvement in the loss of the cutaneous pressure-induced vasodilatation during acute pain in rats. *J Physiol* 2007; **579**: 247–54.
9 Claus-Walker J. The urinary excretion of collagen degradation products by quadriplegic patients and during weightlessness. *J Bone Joint Surg* 1977; **59**: 209–12.
10 Rodriguez GP, Claus-Walker J. Biochemical changes in skin composition in spinal cord injury: a possible contribution to decubitus ulcers. *Paraplegia* 1988; **26**: 302–9.
11 Rodriguez GP, Claus-Walker J, Kent MC *et al*. Adrenergic receptors in insensitive skin of spinal and injured patients. *Arch Phys Med Rehab* 1986; **67**: 177–80.

Risk factors. Identification of characteristics which increase a patient's susceptibility to pressure damage has led to the develop-

ment of quantitative tools for assessing risk. There are schemes proposed by Norton [1], Waterlow [2,3] and Braden and Bergstrom [4]. The Waterlow score is for general use, while that devised by Braden and Bergstrom is for use in nursing homes. Risk assessment tools should be used in conjunction with clinical judgement to determine pressure ulcer risk.

Immobilization. Any circumstance that results in prolonged immobilization or reduced spontaneous movement will increase the risk for pressure ulceration. Examples include coma, neurological illness (including spinal cord injuries and sensory impairment), rheumatological problems and uncontrolled pain. Other situations where there is a reduced ability to relieve pressure include lengthy operations, high dependency or critical care states, poor cognitive function, severe depression with apathy, and immobility as a result of plaster cast, body brace or prosthesis.

Reduced oxygen perfusion. Hypotension [5], whether caused by cardiac failure or drugs, anaemia, blood dyscrasias, arterial insufficiency and situations producing interstitial oedema such as nephrotic syndrome, can all increase the likelihood of pressure-induced ischaemia or may delay healing. Extracorporeal circulation is an important risk factor [6]. Scar tissue is avascular and therefore more prone to pressure damage.

Malnutrition. Studies using a variety of nutritional status parameters, including serum albumin, total lymphocyte count and body weight, have suggested a correlation between inadequate nutrition and pressure ulcers [7]. Comparison of biochemical nutritional indices in a group of elderly, acutely ill patients demonstrated significantly lower values in those with pressure ulcers compared to those without [8]. Postulated mechanisms include reduction of subcutaneous fat and delayed wound healing.

Age and other risk factors. Old age is associated with an increased risk, but it is unclear whether this is an independent variable. Neonates may also be at increased risk. Some surveys have suggested that diabetes mellitus, cancer, sepsis, prolonged pyrexia, prior corticosteroid therapy, dehydration, incontinence, smoking and excessive alcohol intake are additional systemic risk factors. Warming blankets used during surgery [9], compression stockings for prevention of venous thrombosis [10] and compression bandaging treatment of venous ulcers [11] have been identified as risk factors.

References

1 Norton D, McLaren R, Exton-Smith AN eds. *An Investigation of Geriatric Nursing Problems in Hospital.* Edinburgh: Churchill Livingstone, 1975.
2 Waterlow J. Pressure sores: a risk assessment card. *Nurs Times* 1985; **81**: 49–55.
3 Waterlow J. From costly treatment to cost-effective prevention: using Waterlow. *Br J Community Nurs* 2005; **10**: S25–6.
4 Braden BJ, Bergstrom N. Predictive validity of the Braden Scale for pressure sore risk in a nursing home population. *Res Nurs Health* 1994; **17**: 459–70.
5 Schubert V. Hypotension as a risk factor for the development of pressure sores in elderly subjects. *Age Aging* 1991; **20**: 255–61.
6 Kemp MG, Keithley JK, Smith DW, Morreale B. Factors that contribute to pressure sores in surgical patients. *Res Nurs Health* 1990; **13**: 293–301.
7 Langer G, Schloemer G, Knerr A *et al*. Nutritional interventions for preventing and treating pressure ulcers. *Cochrane Database Syst Rev* 2003; **4**: CD003216.
8 Gengenbacher M, Stahelin HB, Scholer A, Seiler WO. Low biochemical nutritional parameters in acutely ill hospitalised elderly patients with and without stage III and IV pressure ulcers. *Aging Clin Exp Res* 2002; **14**: 420–3.
9 Radcliffe CR, Rodehaever GT. Prospective study of the incidence of OR-induced pressure ulcers in elderly patients undergoing lengthy surgical procedures. *Adv Wound Care* 1998; **11** (suppl): 10.
10 Bliss MR. Pressure injuries: cause and prevention. *Hosp Med* 1998; **59**: 841–4.
11 Chan CLH, Meyer FJ, Hay RJ, Burnand KG. Toe ulceration associated with compression bandaging: observational study. *BMJ* 2001; **323**: 1099.

Pathology. The most complete study of the histopathology of pressure ulcer and its antecedents in humans is given by Witkowski and Parish [1]. In the earliest clinically recognizable stage of blanchable erythema, there is dilatation of superficial dermal venules and papillary capillaries with a mild perivascular inflammatory infiltrate and degenerative changes in occasional sweat coils and ducts. At the stage of non-blanchable erythema, there is marked red cell engorgement of superficial vessels, platelet thrombi in many of them, and extravasation of red cells. More eccrine units are degenerate and there is evident fat necrosis. Before ulceration occurs, various additional changes are recognized, including epidermal atrophy, subepidermal blister formation, tissue eosinophilia and necrosis of hair follicles. Some other studies have emphasized the presence of intra- and extravascular fibrin [2,3]. In early ulceration, there is loss of the epidermis, and at the stage of a black eschar there is full thickness destruction of the skin. The antecedent for black eschar formation was not seen in the biopsies studied, but was presumed to be vascular disruption at a deeper plane. In a chronic ulcer, there was fibrosis with isolated collections of capillaries and no residual appendages.

References

1 Witkowski JA, Parish LC. Histopathology of the decubitus ulcer. *J Am Acad Dermatol* 1982; **6**: 1014–21.
2 Seiler WO, Stahelin HB. Recent findings on decubitus ulcer pathology: implications for care. *Geriatrics* 1986; **41**: 47–60.
3 Vande Berg JS, Rudolph R. Pressure (decubitus) ulcer: variation in histopathology—a light and electron microscope study. *Hum Pathol* 1995; **26**: 195–200.

Clinical features and classification. Most pressure ulcers develop over bony prominences on the lower part of the body: 65% in the pelvic area (the sacral bone, ischial tuberosities and greater trochanters); and 30% on the lower limbs, usually the heels and lateral malleoli. On the upper part of the body the most common sites are the shoulder and elbow.

Pressure-induced damage varies in appearance from blanchable erythema to necrosis of all tissues down to and including bone and joints. In order to classify the severity of injury, pressure ulcers are graded according to the depth of skin damage and the extent of subcutaneous tissue involvement. A number of different grading methods have been proposed and, although there is no ideal system, the one developed by the European Pressure Ulcer Advisory Panel (EPUAP) uses a simple, four-grade classification [1]. In a grade 1 lesion there is non-blanchable erythema of intact skin (Fig. 28.7a). Discoloration of the skin, warmth, oedema, induration or hardness may also be used as indicators, particularly on individuals with darker skin. In a grade 2 ulcer there is partial-thickness skin loss involving epidermis, dermis or both (Fig.



(a)



(b)



(c)



(d)

Fig. 28.7 (a) A grade 1 lesion on the buttocks consisting of areas of erythema with, in general, an intact epidermis. (b) A grade 2 pressure ulcer on the right buttock with loss of epidermis and slough overlying the dermis. (c) Grade 2/3 pressure ulcers overlying the sacrum. Most of the ulcers show erosion into the dermis (grade 2). At one end of the large ulcer there is penetration into the subcutaneous tissue (grade 3). (d) A large grade 4 pressure ulcer overlying the sacrum with extensive destruction of subcutaneous tissues, including muscle.

28.7b). The ulcer is superficial and presents clinically as an abrasion or blister. Grade 3 ulceration is characterized by full-thickness skin loss involving necrosis of subcutaneous tissue which may extend down to, but not through, underlying fascia (Fig. 28.7c). In a grade 4 ulcer there is extensive destruction, tissue necrosis, or damage to muscle, bone or supporting structures with or without full-thickness skin loss (Fig. 28.7d). This latter feature reflects subcutaneous damage, which may far exceed surface change. This phenomenon occurs as a consequence of skin's greater resistance to ischaemia than underlying fat and muscle.

In America, a similar classification system has been devised by the National Pressure Ulcer Advisory Panel [2].

References

1 European Pressure Ulcer Advisory Panel. Guide to pressure ulcer grading. *EPUAP Review* 2001; **3**: 75.

2 Black J, Baharestani MM, Cuddigan J *et al*. National Pressure Ulcer Advisory Panel. National Pressure Ulcer Advisory Panel's updated pressure ulcer staging system. *Adv Skin Wound Care* 2007; **20**: 269–74.

Complications. There are several important complications of pressure ulceration. The development of a pressure ulcer in a hospitalized patient will interfere with recovery and may prolong the period of in-patient stay. Pressure ulcers are a marker of poor prognosis and may contribute to premature mortality [1]. Specific complications include the following.

Infections and osteomyelitis. It is important to distinguish between predictable colonization of a pressure ulcer and clinically relevant infection [2]. Colonization with one or more of a wide range of aerobic and anaerobic bacteria is very common, but wound healing is not necessarily impaired [3]. True infection of adjacent healthy tissue may result in cellulitis, abscess, necrotizing fasciitis, osteomyelitis or systemic sepsis. More subtle signs of infection include erythema, warmth, tenderness and increased purulent discharge. However, these features may not occur in the debilitated; the so-called 'inapparent' infection may be difficult to distinguish from colonization [4]. When taking a swab, surface contamination (pus etc.) should be removed with a non-bacteriostatic liquid such as normal saline, and tissue fluid should be sampled; needle aspiration or even biopsy material are better for obtaining relevant microbiology [5]. In practice, inapparent infection may only be recognized when an ulcer does not heal

despite pressure relief, correctional of nutritional needs, etc. An empirical course of antibiotic therapy may be justified in such circumstances [6].

Diagnosing osteomyelitis in patients with pressure ulcers is complicated by overlying soft tissue inflammation and reactive bone formation. All imaging techniques have shortcomings. A bone scan is usually abnormal and, if so, bone biopsy and culture will enable the appropriate antibiotic therapy to be determined [7]. A study of patients with grade 4 ulcers compared indium leukocyte scintigraphy (white cell scan) with bone biopsy analysis in the diagnosis of osteomyelitis [8]. Radioimaging was 100% sensitive but only 50% specific and therefore is useful to rule out osteomyelitis but should not be relied upon as a primary diagnostic tool.

Sinus tracts. These can extend deep into joint spaces, causing osteomyelitis, septic arthritis and, occasionally, communicate with viscera. A sinogram will assist surgical management [9].

Squamous cell carcinoma. Although rare, squamous cell carcinoma can arise in long-standing pressure ulcers. Generally, a squamous cell carcinoma developing from a chronic pressure ulcer (Marjolin's ulcer) is aggressive and carries a high risk for metastasis [10].

References

1 Thomas DR, Goode PS, Terquine PH, Allman RM. Hospital-acquired pressure ulcers and risk of death. *J Am Geriatr Soc* 1996; **44**: 1435–40.

2 Ebright JR. Microbiology of chronic leg and pressure ulcers: clinical significance and implications for treatment. *Nurs Clin North Am* 2005; **40**: 207–16.

3 Daltrey DC, Rhodes B, Chattwood JG. Investigations into the microbial flora of healing and non-healing decubitus ulcers. *J Clin Pathol* 1981; **34**: 701–5.

4 Parish LC, Witkowski JA, Crissey JT, eds. *Bacteriology: the Decubitus Ulcer*. New York: Masson, 1983: 31–5.

5 Stotts NA, Hunt TK. Managing bacterial colonization and infection. *Clin Geriatr Med* 1997; **13**: 3.

6 Thomas DR. Issues and dilemmas in the prevention and treatment of pressure ulcers: a review. *J Gerontol A Biol Sci Med* 2001; **56**: 328–40.

7 Lewis VL, Bailey MH, Pulawski G *et al.* The diagnosis of osteomyelitis in patients with pressure sores. *Plast Reconstr Surg* 1988; **81**: 229–323.

8 Melkun ET, Lewis VL. Evaluation of (111) indium-labelled autologous leucocyte scintigraphy for the diagnosis of chronic osteomyelitis in patients with grade 4 pressure ulcers, as compared with a standard diagnostic protocol. *Ann Plast Surg* 2005; **54**: 633–6.

9 Putnam T, Calenoff L, Betts HB *et al.* Sinography in management of decubitus ulcers. *Arch Phys Med Rehab* 1978; **59**: 243–5.

10 Chraibi H, Dereure O, Teot L, Guillot B. The diagnosis and treatment of carcinomas occurring at the sites of chronic pressure ulcers. *J Wound Care* 2004; **13**: 447–8.

Prevention. Pressure ulcers can usually be avoided if the at-risk patient is identified early and a programme of preventative measures instituted [1]. Effective prophylaxis will limit unnecessary patient suffering and will be ultimately less costly than treatment of established ulcers. The prevention of pressure ulceration is a multidisciplinary responsibility and to this end the UK National Institute for Health and Clinical Excellence (NICE) has published guidelines detailing the measures that should be taken to avoid pressure ulcers [2].

Recognition of the at-risk patient. A number of risk assessment scales have been devised so that nursing staff and other carers can maximize their application of preventative measures. With the Norton scale, a score of 14 or below indicates risk; with the Braden scale, 12 or less indicates high risk, 13–15 moderate risk and 16–17 mild risk. A systematic review of the commonly used risk assessment scales indicated that the Braden system (Table 28.2) offers the best balance between sensitivity and specificity and best risk estimate [3].

General nursing measures. Standard nursing practices to prevent pressure ulcer formation in those most at risk include:

1. A skin inspection at least once daily, especially over bony prominences.
2. Prevention of moisture accumulation from perspiration, wound drainage, urinary and faecal incontinence. Patients who are incontinent should be cleaned with water alone; soap is astringent and increases the potential for skin damage.
3. Minimizing shearing forces by maintaining the head of the bed at less than 30° and lifting rather than dragging the patient.
4. Pressure relief by turning the patient at least every 2 h. Patients should be turned successively from the back to the right side, then to the left side; when on the side, the patient should be positioned at an angle to avoid pressure on the trochanter and lateral malleolus.
5. Use of soft pillows or foam wedges to prevent direct ('kissing') contact of bony prominences such as the knees and ankles. Excess heel pressure on the bed should be avoided using pressure-relieving techniques, such as pillows under the lower leg.
6. Pressure relief on the ischial tuberosities, for those in wheelchairs, by ensuring that there is a shift of weight every 20–30 min.

Specialized beds, mattresses and cushions. Specialized support surfaces, such as mattresses, beds and cushions, reduce or relieve the pressure that the patient's body weight exerts on the skin and subcutaneous tissues as it presses against the surface of a bed or chair. A systematic review of such appliances is available from the Cochrane database [4]. Pressure-reducing surfaces may be either static support surfaces (such as overlays that are applied to the top of a mattress and filled with air, water, gel or foam) or dynamic support surfaces (which mechanically vary the pressure beneath the patient and thereby reduce the duration of the applied pressure). Static surfaces mould around the shape of the patient to redistribute pressure over a greater surface area, whereas dynamic surfaces mechanically vary the pressure beneath the individual in a cyclical fashion, so reducing the duration of the applied pressure. The latter include alternating-pressure mattresses, low air-loss beds and air-fluidized mattresses. In alternating pressure support surfaces, air-filled cells are sequentially inflated and deflated—the inflated cells support the body while the deflated cells provide pressure relief. Air-fluidized mattresses contain silicone-coated beads that liquefy when air is pumped through them.

A study of 446 patients undergoing elective major surgery demonstrated that specialized foam mattress overlays on operating tables decreased the incidence of postoperative pressure ulcers [5].

Table 28.2 Braden scale for predicting pressure sore risk.

Patient's name _____ Evaluator's name _____ Date of assessment _____

SENSORY PERCEPTION (Ability to respond meaningfully to pressure-related discomfort)			Score
1 Completely limited Unresponsive to painful stimuli (does not moan, flinch, grasp) due to unconsciousness or sedation. *OR* Limited ability to feel pain over most of body surface.	**2** Very limited Responds only to painful stimuli. Cannot communicate discomfort except by moaning or restlessness. *OR* Has a sensory impairment that limits the ability to feel pain or discomfort over half the body.	**3** Slightly limited Responds to verbal commands, but can't always communicate discomfort or need to be turned. *OR* Has some sensory impairment that limits ability to feel pain or discomfort in 1 or 2 extremities.	**4** No impairment Responds to verbal commands. Has no sensory deficit that would limit ability to feel or voice pain or discomfort.
ACTIVITY (Degree of physical activity)			
1 Bedfast Confined to bed.	**2** Chairfast Severely limited or non-existent ability to walk. Cannot bear own weight and/or must be helped into chair or wheelchair.	**3** Walks occasionally Walks sometimes but for very short distances, with or without assistance. Spends most of each shift in bed or chair.	**4** Walks often Walks outside the room at least once every 2 h during waking hours.
MOBILITY (Ability to change and control body position)			
1 Completely immobile Does not make even slight changes in body or extremity position without assistance.	**2** Very limited Makes occasional slight changes in body or extremity position but cannot make frequent or significant changes independently.	**3** Slightly limited Makes frequent though slight changes in body or extremity position independently.	**4** No limitations Makes major and frequent changes in position with no assistance.
MOISTURE (Degree to which skin is exposed to moisture)			
1 Constantly moist Skin is kept moist almost constantly by perspiration, urine, etc. Dampness is found every time the patient is moved or turned.	**2** Very moist Skin is often, but not always moist. Linen must be changed at least once a shift.	**3** Occasionally moist Skin is sometimes moist, requiring an extra linen change about once a day.	**4** Rarely moist Skin is usually dry, linen needs changing at routine intervals.
NUTRITION (Usual food intake pattern)			
1 Very poor Never eats a complete meal. Rarely eats more than a third of any food offered. Eats 2 servings or less of protein (meat or dairy products) per day. Takes fluids poorly. Does not take a dietary supplement.	**2** Probably inadequate Rarely eats a complete meal and generally eats only about half of any food offered. Protein intake includes only 3 servings a day. Will occasionally take a dietary supplement. *OR* Receives less than optimum amount of liquid diet or tube feeding.	**3** Adequate Eats more than half of most meals. Eats 4 servings of protein each day. Will sometimes refuse a meal, but usually takes a supplement if offered. *OR* Is on a tube feeding or TPN regimen that probably meets most nutritional needs.	**4** Excellent Eats most of every meal. Never refuses a meal. Usually eats 4 or more servings of meat and dairy products. Sometimes eats between meals. Does not require supplementation.
FRICTION AND SHEAR			
1 Problem Requires moderate to maximum assistance in moving. Complete lifting without sliding against sheets is impossible. Often slides down in bed or chair requiring repositioning with maximum assistance. Spasticity, agitation or contractions lead to almost constant friction.	**2** Potential problem Moves feebly or needs minimum assistance. During a move, skin probably slides to some extent against sheets, chair, restraints or other devices. Usually maintains relatively good position in chair or bed, but occasionally slides down.	**3** No apparent problem Moves in bed and in chair independently and has sufficient muscle strength to sit up completely during move. Maintains good position in bed or chair at all times.	Total score ☐

Copyright 1988, Barbara Braden and Nancy Bergstrom. Used with permission.

A trial comparing dynamic and support surfaces in a large number of patients found no difference in pressure ulcer incidence between dynamic and support surfaces [6]. A study comparing a mechanical bed which turns the patient with a standard hospital bed demonstrated no advantage in automized turning in reducing pressure ulcer incidence [7].

Nutrition. A relationship between nutritional intake and prevention of pressure ulcers is based on limited evidence. However, two randomized trials have demonstrated a reduced pressure ulcer risk in critically ill patients who received dietary supplements: in the first, the intervention group was given additional nutritional supplements containing 400 kcal per day [8]; in the second, the treated group received oral supplementary eicosapentanoic acid, gamma-linolenic acid and antioxidants [9].

References

1 Reddy M, Gill SS, Rochon PA. Preventing pressure ulcers: a systematic review. *JAMA* 2006; **296**: 974–84.

2 NICE. *Pressure Ulcers: the Management of Pressure Ulcers in Primary and Secondary Care: a Clinical Guidline*. CG029. National Institute for Health and Clinical Excellence, London, 2005.

3 Pancorbo-Hidalgo PL, Garcia-Fernandez FP, Lopez-Medina IM, Alvarez-Nieto C. Risk assesment scales for pressure ulcer prevention; a systematic review. *J Adv Nurs* 2006; **54**: 94–100.

4 Callum N, McInnes E, Bell-Syer SE, Legood R. Support surfaces for pressure ulcer prevention. *Cochrane Database Syst Rev* 2004; **3**: CD001735.

5 Nixon J, McElvenny D, Mason S *et al*. A sequential randomised controlled trial comparing a dry visco-elastic polymer pad and standard operating table mattress in the prevention of postoperative pressure sores. *Int J Nurs Stud* 1998; **35**: 193–203.

6 Vanderwee K, Grypdonck MH, DeFloor T. Effectiveness of an alternating pressure air mattress for the prevention of pressure ulcers. *Age Ageing* 2005; **34**: 261–7.

7 Keogh A, Dealey C. Profiling beds versus standard hospital beds: effects on pressure ulcer incidence outcomes. *J Wound Care* 2001; **10**: 15–9.

8 Bourdel-Marchasson I, Barateau M, Rondeau V *et al*: GAGE Group. A multicenter trial of the effects of oral nutritional supplementation in critically ill older inpatients. *Nutrition* 2000; **16**: 1–5.

9 Theilla M, Singer P, Cohen J, Dekeyser F. A diet enriched in eicosapentanoic acid, gamma-linolenic acid and antioxidants in the prevention of new pressure ulcer formation in critically ill patients with acute lung injury: a randomised, prospective, controlled study. *Clin Nutr* 2007; **26**: 752–7.

Management. The principles outlined above for prevention also apply to management of an established ulcer. Once the early reversible signs of pressure-induced injury are evident, action should be prompt [1].

Relief of pressure. Pressure relief is essential, all other treatment modalities are of secondary importance. Nursing in a prone position may be required and is acceptable for all patients except, perhaps, quadriplegic subjects. The lateral position must be avoided, as it frequently causes pressure sores over the greater trochanters and malleoli. Pillows positioned correctly are used to protect the knees and iliac spines. Pressure-relieving support surfaces, outlined in detail above, reduce the interface pressure and may also minimize friction and shear, thus permitting an optimum environment for ulcer healing. Although there is, in general, a paucity of good-quality evidence, two studies have reported enhanced pressure ulcer healing of air-fluidized beds when compared to conventional therapies [2,3].

Wound care. It is important to assess the nature and progress of a pressure ulcer. Regular inspections should be carried out at least once weekly, and observations of ulcer size documented using tracing and/or photographs. Signs of infection, sinus tract formation, offensive discharge, new necrotic tissue, undermining, etc. may determine the need for a change in management. Irrigation with normal saline is generally sufficient to keep the ulcer clean. Although it is desirable to minimize growth of bacteria, the many antiseptics and antibiotics used on pressure ulcers are mostly of unproven benefit [4]; some can cause local and systemic toxicity, may select resistant bacteria and can result in irritant or allergic contact dermatitis.

In many cases, when pressure is relieved, the necrotic tissue separates naturally after 1–2 weeks. However, persistent slough or an adherent eschar will act as a barrier to healing and should be removed by débridement. There are a number of techniques and products available which aim to assist removal of adherent devitalized tissue or slough [5]. In autolytic débridement, rehydration of the eschar by hydrogel or hydrocolloid products allows separation of necrotic tissue from the wound bed. Preparations which contain enzymes, such as streptokinase, streptodornase, trypsin and collagenase, can be used to digest slough and necrotic tissue. These agents should be used with care since irritant or allergic contact dermatitis is a recognized complication. Although there is a lack of convincing controlled data, débriding agents probably have a role in the management of necrotic tissue in pressure ulcers [5]. Surgery is the most efficient method of débridement; devitalized tissue can be removed with a scalpel under local anaesthetic in small, superficial wounds. More extensive surgical débridement may be necessary for grade 3 or 4 ulcers, however this will necessitate a general anaesthetic which in itself carries certain risks. Larval therapy uses the feeding behaviour of maggots of the common green bottle fly (*Lucilia sericata*) to remove wound slough [6]. When placed in a wound the larvae selectively ingest necrotic debris but leave the healthy tissue intact. In practice there is no consensus on which débriding agent or technique is the most appropriate; the clinician should decide which method is most appropriate to each case.

Dressings available for covering pressure ulcers can be divided into groups according to their primary function. Contact layers are applied to the wound surface but are non-adherent and allow drainage of exudate (for example paraffin gauze). Interactive dressings form a gel when in contact with exudate, a change which is claimed to enhance healing (for example alginates, hydrocolloids, carboxymethylcellulose). Passive dressings control the wound environment but do not alter their physical state (for example films and foams). Active dressings, such as skin grafts and products containing growth factors, aim to influence the pathophysiology of wound healing.

The choice of dressing will be dictated by the stage of pressure ulcer, the amount of exudate and the presence of slough or eschar. Table 28.3 offers a guide to suitable dressing type according to ulcer grade and exudation status.

Table 28.3 Types of dressing for pressure ulcers according to ulcer grade and exudation status

Exudation/grade	Dressing type
Minimally exuding grade 2 or grade 1	Semipermeable film
Low–moderately exuding grade 2–3	Foams
Low–moderately exuding grade 3–4	Hydrogels/hydrocolloids
Moderate–highly exuding grade 2–4	Alginates/hydrofibres

Adapted from: Grey *et al.* [7].

Surgery. Only a small percentage of patients with pressure ulcers are candidates for surgical management. Deep ulcers, grade 3 or 4, may require surgical intervention; techniques used include local sensate flaps and skin grafts [8]. Despite the use of musculocutaneous flaps, recurrence is a significant problem [9]. Tissue expansion may have a role to provide skin for a flap [10].

Topical negative pressure therapy. Topical negative pressure therapy has emerged as an important adjunct in the treatment of many wound types [11]. The technique involves the application of a vacuum force across the wound surface using a pump, tubing and foam dressing. The negative (sub-atmospheric) pressure generated by the vacuum leads to a change in the wound environment which positively enhances healing. Studies have reported the successful use of topical negative pressure, known commercially as vacuum-assisted closure (VAC™), in the management of pressure ulcers (reviewed in [12]). Various mechanisms have been proposed to explain the effectiveness of topical negative pressure: the removal of excessive interstitial fluid, increased local blood flow, decreased bacterial colonization and induction of cellular proliferation and angiogenesis [13]. In the management of grade 3 or 4 pressure ulcers, VAC therapy can be used either as a definitive therapy or to optimize the wound bed prior to surgical closure. If there is undermining at the wound margin, or a high volume of exudate, VAC therapy can be used with a drainage pouch instead of the usual foam dressing [14]. VAC therapy is not a débriding tool and is contraindicated if there is necrotic tissue or eschar present in the wound. Other contraindications to the use of VAC therapy include the presence of exposed blood vessels, unexplored fistulae or untreated osteomyelitis within the wound.

Growth factors. Several growth factors have been evaluated for the treatment of pressure ulcers, however the data for accelerated healing is generally not convincing. Nonetheless, one trial assessing the effects of 2.5S murine growth factor compared to placebo found that active treatment significantly reduced ulcer area and improved the rate of complete healing [15].

General treatment. It is essential to treat the whole patient. Pressure ulcers can be extremely painful and adequate analgesia is essential. Nutrition should receive special attention and a positive nitrogen balance should be achieved. The blood urea and serum albumin should be checked regularly. Studies investigating the role of nutrition in ulcer healing are few and generally of poor methodological quality. One randomized trial showed an enhanced rate of ulcer healing in a small group of patients receiving a diet with supplementary arginine, vitamin C and zinc compared to a control group [16]. Zinc and ascorbic acid deficiency must be corrected and for those with poor appetite, or unable to take sufficient solid food by mouth, frequent sip feeds of protein supplement or, occasionally, nasogastric tubal feeding may be required. Anaemia should also be corrected, with a blood transfusion if necessary. Any serious underlying disease should be assessed and treated appropriately. Whenever possible the advice of a physician conversant with the problem of pressure ulcers (commonly a geriatrician) should be sought if first-line measures do not induce healing. In UK hospitals, tissue viability nurses provide a pressure ulcer management service and liaise with physicians, surgeons and ward nurses.

References

1 Brem H, Lyder C. Protocol for the successful treatment of pressure ulcers. *Am J Surg* 2004; **188** (S1A): 9–17.
2 Allman RM, Walker JM, Hart MK *et al*. Air-fluidized beds or conventional therapy for pressure sores: a randomised trial. *Ann Intern Med* 1987; **107**: 641–8.
3 Munro BH, Brown L, Heitman BB. Pressure ulcers: one bed or another. *Ger Nurs* 1989; **10**: 190–2.
4 NICE. *Pressure Ulcers: the Management of Pressure Ulcers in Primary and Secondary Care: a Clinical Guideline*. CG029. National Institute for Health and Clinical Excellence, London, 2005.
5 Stephen-Haynes J, Thompson G. The different methods of wound debridement. *Br J Community Nurs* 2007; **12**: S6–16.
6 Parnes A, Lagan KM. Larval therapy in wound management: a review. *Int J Clin Pract* 2007; **61**: 488–93.
7 Grey JE, Enoch S, Harding KG. Pressure ulcers. *BMJ* 2006; **332**: 472–5.
8 Sorensen JL, Jorquensen B, Gottrup F. Surgical treatment of pressure ulcers. *Am J Surg* 2004; 1**88 S1A**: 42–51.
9 Relander M, Palmer B. Recurrence of surgically treated pressure sores. *Scand J Plast Reconstr Surg* 1988; **22**: 88–92.
10 Neves RI, Kahler SH, Banducci DR, Manders EK. Tissue expansion of sensate skin for pressure sores. *Ann Plast Surg* 1992; **29**: 433–7.
11 Evans D, Land L. Topical negative pressure for treating chronic wounds: a systematic review. *Br J Plast Surg* 2001; **54**: 238.
12 Mandal A. Role of topical negative pressure in pressure ulcer management. *J Wound Care* 2007; **16**: 33–5.
13 Morykwas MJ, Argenta LC, Shelton-Brown EI, McGuirt W. Vacuum-assisted closure: a new method for wound control and treatment: animal studies and basic foundation. *Ann Plast Surg* 1997; **38**: 553–62.
14 Tachi M, Hirabayashi S, Yonehara Y *et al*. TNP using a drainage pouch without foam dressing for the treatment of undermined pressure ulcers. *Ann Plast Surg* 2004; **53**: 338–42.
15 Landi F, Aloe L, Russo A *et al*. Topical treatment of pressure ulcers with nerve growth factor: a randomized clinical trial. *Ann Int Med* 2003; **139**: 41.
16 Desneves KJ, Todorovic BE, Cassar A, Crowe TC. Treatment with supplementary arginine, vitamin C and zinc in patients with pressure ulcers, a randomised controlled trial. *Clin Nutr* 2006; **24**: 979–87.

Effects of suction

Localized suction to the skin usually produces either blisters, which can rupture to form erosions, or purpura. Early work evaluated the inverse relationship between the degree of negative pressure and time taken for blistering to occur [1,2] and demonstrated that the time taken to blister could be shortened if the temperature at the suction site was raised to 40°C [3]. Suction blisters are often used in experimental dermatology (e.g. to yield fluids for analysis

of inflammatory mediators) and to generate pieces of epidermis for grafting as used in the treatment of vitiligo [4]. Blisters induced by suction are subepidermal in type, in contrast to friction blisters, which develop within the epidermis. The dermal papillae are usually well preserved, producing the effect known as festooning [5]. When the force of suction is sufficient to produce purpura, this may either take the form of petechiae or, if the injury is over a larger surface area, an ecchymosis will result. At the outset, such lesions are red, but they then undergo the usual changes associated with extravasation of red cells into the skin, producing purplish and then yellow staining.

Suction is also used therapeutically as a modality for healing wounds, for example pressure ulcer [6], as discussed above.

Neonatal suction blisters

These present as one or a small number of blisters or erosions, typically on the fingers, lips or forearms. They heal quickly after birth [7]. (For further discussion see Chapter 17.)

Therapeutic cupping

This is a widespread folk medicine practice, particularly in Oriental countries [8] and in some parts of eastern Europe, although it has been used in the West and may increase because of migration of populations [9,10]. Cupping is performed on patients with various diseases, particularly febrile illnesses, by warming the edge of a cup and applying it to the patient's back. Suction is produced when the cup cools. The visible effect is a round area of ecchymosis often with petechiae at the border (Fig. 28.8). Cupping is often combined with acupuncture, and a number of complications have been associated (e.g. panniculitis) [11]. The skin changes caused by cupping can simulate child abuse [12,13].



Fig. 28.8 Purpura caused by therapeutic cupping. (Courtesy of Dr M. Rustin, Royal Free Hospital, London, UK, and the Editor of the *British Medical Journal*.)

Suction purpura in children

Vacuum extraction to assist in parturition can cause a characteristic, rounded, purpuric lesion on the forehead of the infant. Ecchymoses have been induced by suction cups attached to babies' rattles [14]. The habit of sucking on a cup and aspirating the air trapped within it can produce a distinctive zone of petechiae on a child's chin [15]. As a habit or neurotic activity, children sometimes suck on their arms, and this can produce small areas of purpura, typically arranged in lines [15]. The sucker-shaped rubber ends on toy arrows have also been recorded as producing purpura by a suction effect [15]. Distinctive, rounded, purpuric lesions on the forehead (purpura cyclops) from the rubber suckers on their children's toys can occur on fathers—the 'sucker-daddy' syndrome [16,17]. A U-shaped distribution of purpura has been described on the back due to a suction effect in the bath [18].

When the cause of unusual purpura in children is not apparent, non-accidental injury may have to be considered.

Penile suction injuries

Penile injuries resulting from sexual experimentation may be bizarre. Vacuum cleaner injuries can cause ecchymosis if the suction is mild, and extensive lacerations when severe [19].

Other examples of suction purpura

Other recorded examples include the so-called 'love bite', a consequence of sucking while kissing; the use of suction devices on electrocardiograph leads; and gas masks, for example used during the Gulf War [15]; suction from cup-shaped indentations on a bath mat [20] and from getting stuck in the bath [21].

Suction pads

Hyperkeratotic lesions on the thumbs of a child attributed to repetitive suction have been described, but chewing was also taking place and may have been a contributory factor [22].

References

1 Blank H, Miller OG. A method for separating the epidermis from dermis. *J Invest Dermatol* 1950; **15**: 9–12.
2 Lowe LB, Van der Laun JC. Suction blisters and dermal–epidermal adherence. *J Invest Dermatol* 1958; **50**: 308–14.
3 Peachey RDG. Skin temperature and blood flow in relation to the speed of suction blister formation. *Br J Dermatol* 1971; **84**: 447–52.
4 Falabella R. Suction blistering as a research and therapeutic tool in dermatology. *Int J Dermatol* 2000; **39**: 670–1.
5 Hunter JAA, McVittie E, Comaish JS. Light and electron microscopic studies of physical injury to the skin. I. Suction. *Br J Dermatol* 1974; **90**: 481–90.
6 Mendonca DA, Papini R, Price PE. Negative-pressure wound therapy: a snapshot of the evidence. *Int Wound J* 2006; **3**: 261–71.
7 Murphy WE, Langly AL. Common bullous lesions, presumably self inflicted, occurring *in utero* in the newborn infant. *Pediatrics* 1963; **32**: 1099–2001.
8 Green A. Scarification, cupping and other traditional measures, with reference to folk medicine in Greece and elsewhere. *Aust J Dermatol* 1971; **12**: 89–96.
9 Stoeckle DB, Carter RD. Cupping in New York State—1978. *NY State J Med* 1980; **80**: 117–20.
10 Kaptchuk TJ. Consequences of cupping. *N Engl J Med* 1997; **336**: 15.

11 Lee JS, Ahn SK, Lee SH. Factitial panniculitis induced by cupping and acupuncture. *Cutis* 1995; **55**: 217–8.
12 Asnes RS, Wisotsky DH. Cupping lesions simulating child abuse. *J Pediatr* 1981; **99**: 267–8.
13 Look KM, Look RM. Skin scraping, cupping, and moxibustion that may mimic physical abuse. *J Forensic Sci* 1997; **42**: 103–5.
14 Cipollaro VA. Suction cup ecchymosis of the forehead. *Cutis* 1976; **18**: 216.
15 Metsker A, Merlob P. Suction purpura. *Arch Dermatol* 1992; **128**: 822–4.
16 Tunstall-Pedoe H, Lightman S. An unreported syndrome. *Lancet* 1981; **2**: 1429.
17 Tunstall-Pedoe H, Lightman S. Sucker-daddy (purpura cyclops). *Lancet* 1982; **1**: 632.
18 Landers MC, Schroeder TL. Bathtub suction-induced purpura. *Pediatr Dermatol* 2004; **21**: 146–9.
19 Citron ND, Wade PJ. Penile injuries from vacuum cleaners. *BMJ* 1980; **281**: 26.
20 Yates VM. Factitious purpura. *Clin Exp Dermatol* 1992; **17**: 238–9.
21 Urkin J, Katz M. Suction purpura. *Isr Med Assoc J* 2000; **2**: 711.
22 Ciambiani S, Pistritto G. Suction pads related to thumb sucking and chewing. *Br J Dermatol* 1998; **138**: 1096–7.

Miscellaneous reactions to mechanical trauma

Coin-rubbing injuries

Coin rubbing or *kua'sha* originated in China and has spread to many other countries in South East Asia. It is often known by the Portuguese term *cao gio*. As a form of folk medicine, it is used to treat many complaints. The coin (usually copper or silver), or sometimes a silver spoon or other object, is dipped in wine, water or an aromatic oil and then scraped over the skin surface until a visible change—redness or purpura—is observed. The technique is often accompanied by pinch-pulling (*t'i-sha* or various synonyms) in which the index and middle fingers are used to pluck the skin. Common sites include the intercostal spaces, bridge of the nose, the space between the eyebrows, the occipital depression over the neck, either side of the larynx, and the elbow and knee flexures.

Clinical features. There are symmetrical bands and ovoid patterns of bruising. Occasionally, the lesions can be misinterpreted as representing foul play [1].

Reference

1 Hulewicz B. Coin rubbing injuries. *Am J Forensic Med Pathol* 1994; **15**: 257–60.

Reactions to musical instruments

These have been reviewed by type of instrument [1–3], and by type of causative injury [4,5]. One study has been prospective [6]. Mechanical injuries can be acute (e.g. erythema, blisters and erosions) but are more commonly chronic, resulting from repetitive friction and/or pressure between the musician and the instrument, in some situations aggravated by sweating, faulty techniques or excessive hours of playing. Not only the skin but also bony and soft tissues can be affected, and in younger wind instrument players there can be permanent distortion of dentition and palatal morphology. Trauma to fingers can also quite often damage nails and associated tissues. Contact allergies in musicians are usually to rosin (various string instruments), exotic woods (e.g. used for chin rests), nickel, cane reeds (saxophones and clarinets) or to propolis (violin varnish) [3,7].



Fig. 28.9 'Fiddler's neck'. Lichenification and cysts on the neck of a violinist. (Courtesy of Dr R.D.G. Peachey, Bristol Royal Infirmary, Bristol, UK.)

Violin and viola players may develop 'fiddler's neck' [8], characterized by localized plaques of lichenification, often with hyperpigmentation, erythema, inflammatory papules and pustules and sometimes cysts. Marked oedema may be associated in some cases [9]. The condition occurs at the site where the chin rest of the instrument presses against the skin over the angle of the jaw (Fig. 28.9). The mode of grip on the instrument and the fitting of the chin rest are likely causative factors and a soft cloth may ameliorate a poor fit in the short term [10]. Violinists are also subject to developing thickened pads over the interphalangeal joints (Garrod's pads or fiddler's fingers). These are areas of thickening over the dorsal aspect of the left second and third proximal interphalangeal joints. They may result from the intermittent relaxation and contraction of the extensor tendon over an interphalangeal joint that is held in extreme flexion [11]. Thrombosis of the axillary and subclavian veins has occurred from pressure from a viola [12]. Pizzicato paronychia is another hazard for string players.

Finger callosities occur on the pulps of the fingers of many musical instrument players. A typical example is 'harpist's fingers', which usually show paronychia and calluses on the sides and tips of the fingers, often together with onycholysis and subungual haemorrhage [13].

Piano paronychia is associated with long hours of piano playing, and nails can be loosened by repetitive glissando (gliding of fingers over the keys).

'Guitar nipple' is usually found in young girls and presents as an inflamed cystic swelling at the base of the nipple [14]. Deep-vein thrombosis has been described in guitarists as a result of a combination of flexion of the left leg with pressure from the belly of the guitar on the medial aspect of the thigh [15]. Acro-osteolysis has been described in the digits of the left hand, the only symptom being tenderness in relation to pressure on the nails [16].

Cellists can develop a lesion known as 'cellist's chest' [17] from pressure, producing erythema, oedema and pigmentation over

the sternal area. There may be changes similar to those of 'fiddler's neck'. 'Cellist's knee' and even 'cello scrotum' have been described, although the validity of the latter has been questioned [18].

'Clarinettist's cheilitis' [19,20] is an eczematous condition, not caused by contact allergy, that affects the middle of the lower lip (see Chapter 69).

'Flautist's chin' [21] is probably similar to fiddler's neck.

Wind instrument players can develop permanent laxity of the cheeks, and forceful blowing of the trumpet can rupture the orbicularis oris (Satchmo's syndrome) [22].

'Drummer's digit' is an erosion or blister on the left ring finger [23].

Black dermographism of the lip has been described in a flute player using a lotion containing zinc oxide, titanium dioxide, iron oxides and talc [24] (for further details on black dermographism see p. 28.92).

Treatment. Modification of technique can usually result in resolution of trauma-related problems in musicians. Callosities can be helped by keratolytics and a pumice.

References

1 Rimmer S, Spielvogel RL. Dermatologic problems of musicians. *J Am Acad Dermatol* 1990; **22**: 657–63.
2 Fisher AA. Dermatitis in a musician. Part III. Injuries caused by specific musical instruments. *Cutis* 1998; **62**: 261–2.
3 Gambichler T, Boms S, Freitag M. Contact dermatitis and other skin conditions in instrumental musicians. *BMC Dermatol* 2004; **4**: 3.
4 Fisher AA. Dermatitis in a musician. Part I. Allergic contact dermatitis. *Cutis* 1998; **62**: 167–8.
5 Fisher AA. Dermatitis in a musician. Part II. Injuries to skin, soft tissue, and bone from musical instruments. *Cutis* 1998; **62**: 214–5.
6 Baccouche D, Mokni M, Ben Abdelaziz A, Ben Osman-Dhahri A. Dermatological problems of musicians: a prospective study in musical students. *Ann Dermatol Venereol* 2007; **134**: 445–9.
7 Lombardi C, Bottello M, Caruso A *et al*. Allergy and skin diseases in musicians. *Allerg Immunol (Paris)* 2003; **35**: 52–5.
8 Peachey RDG, Matthews CNA. Fiddler's neck. *Br J Dermatol* 1978; **98**: 669–74.
9 Stern JB. The edema of fiddler's neck. *J Am Acad Dermatol* 1979; **1**: 538–40.
10 Kaufman BH, Hoffman AD, Zimmerman D. Fiddler's neck in a child. *J Pediatr* 1988; **113**: 89–90.
11 Bird HA. Development of Garrod's pads in the fingers of a professional violinist. *Ann Rheum Dis* 1987; **46**: 169–70.
12 Reina NJ, Honet JC, Brown OW *et al*. Paget–Schrotter syndrome in a viola player. *Med Probl Perform Art* 1988; **3**: 24–5.
13 Adams RM. *Occupational Skin Disease*. New York: Grune & Stratton, 1983: 421–2.
14 Curtis P. Guitar nipple (Letter). *BMJ* 1974; **2**: 226.
15 Semple R, Gillingham J. Musical bumps. *BMJ* 1974; **2**: 504.
16 Baran R, Tosti A. Occupational acro-osteolysis in a guitar player. *Acta Derm Venéréol (Stockh)* 1993; **73**: 64–5.
17 Mandel HN. Cellist's chest. *N Engl J Med* 1962; **266**: 348.
18 Shapiro PE. 'Cello scrotum' questioned (Letter). *J Am Acad Dermatol* 1991; **24**: 665.
19 Hindson TC. Clarinettist's cheilitis. *BMJ* 1978; **2**: 1295.
20 Friedman SC, Connolly SM. Clarinettist's cheilitis. *Cutis* 1986; **38**: 183–4.
21 Dahl MGC. Flautist's chin (Letter). *BMJ* 1978; **2**: 1023.
22 Planus J. Rupture of the orbicularis oris in trumpet players (Satchmo's syndrome). *Plast Reconstr Surg* 1982; **69**: 690–3.
23 Signore RJ. Dermatologic problems of musicians. *J Am Acad Dermatol* 1991; **24**: 321.
24 Koransky JS. Dermatologic problems of musicians: iatrogenic black dermographism. *J Am Acad Dermatol* 1994; **31**: 519.

Hypothenar hammer syndrome

This condition is brought about by the effects on the ulnar artery and associated soft tissues of repetitive trauma to the hypothenar eminence [1]. It is typically associated with actions that use the hand to hammer, push or squeeze. It is mainly found among individuals in certain craft occupations, such as mechanics and carpenters, but can also occur as a sporting injury (e.g. in golf and badminton) [2] and may present in those using a vibrating tool [3].

The proposed pathogenesis is that the superficial palmar branch of the ulnar artery is compressed against the hook of the hamate and this can lead to stenosis, occlusion or aneurysm, with thrombosis or emboli ensuing. Although the condition typically presents unilaterally, the presence of bilateral abnormalities when patients are investigated suggests that there is an underlying predisposition [4].

Among manual workers, most patients are middle-aged men and present with pain or paraesthesia and variable degrees of ischaemic change including blackened eschar formation on the ends of the second, third, fourth or fifth digits of the dominant hand. There may be surrounding hyperkeratotic changes [5]. Fingers affected by the underlying vascular pathology are cooler, and may show other signs of chronic ischaemia. Allen's test is often positive. Some patients have comorbidity factors such as smoking and cold exposure.

The condition is often misdiagnosed as hand–arm vibration syndrome [6] (see p. 28.57), a collagen vascular disease, or some other vaso-occlusive disorder.

Investigations should include arteriography, which can demonstrate stenosis, occlusion, aneurysm, etc. and provide essential information for vascular surgical repair. Magnetic resonance angiography is proving to be a highly informative minimally invasive method of evaluation [7,8].

Management includes counselling to avoid repetitive trauma, minimize exposure to the cold and stop smoking. Aspirin and calcium-channel blockers may be helpful. Vascular surgical expertise will generally be required for thrombolytic measures or resection of the abnormal vasculature and appropriate reconstruction.

References

1 Conn J, Bergan JJ, Bell JL. Hypothenar hammer syndrome: post-traumatic digital ischaemia. *Surgery* 1970; **68**: 1122–8.
2 De Monaco D, Fritsche E, Rigonia G *et al*. Hypothenar hammer syndrome. *J Hand Surg* 1999; **24**: 731–4.
3 Kaji H, Honma H, Usui M *et al*. Hypothena hammer syndrome in workers occupationally exposed to vibrating tools. *J Hand Surg* 1993; **18**: 761–6.
4 Ferris BL, Taylor LM Jr, Oyama K *et al*. Hypothenar hammer syndrome: proposed etiology. *J Vasc Surg* 2000; **31**: 104–13.
5 Duncan WC. Hypothenar hammer syndrome: an uncommon cause of digital ischemia. *J Am Acad Dermatol* 1996; **34**: 880–3.
6 Cooke RA. Hypothenar hammer syndrome: a discrete syndrome to be distinguished from hand-arm vibration syndrome. *Occup Med* (Lond) 2003; **53**: 320–4.
7 Winterer JT, Ghanem N, Roth M *et al*. Diagnosis of the hypothenar hammer syndrome by high-resolution contrast-enhanced MR angiography. *Eur Radiol* 2002; **12**: 2457–62.
8 Winterer JT, Ghanem N, Roth M *et al*. Diagnosis of the hypothenar hammer syndrome by high-resolution contrast-enhanced MR angiography. *Eur Radiol* 2002; **12**: 2457–62.

Achenbach's syndrome

This disorder is characterized by sudden, painful blue discoloration and swelling of a finger or fingers (or sometimes the palm of the hand), often after physical effort of gripping or twisting [1]. It is probably caused by rupture of a small vein. Its importance is that it may be confused with Raynaud's phenomenon (see also Chapter 49). There may be angiographic abnormalities [2].

References

1 Layton AM, Cotterill JA. A case of Achenbach's syndrome. *Clin Exp Dermatol* 1993; **18**: 60–1.

2 Robertson A, Liddington MI, Kay SP. Paroxysmal finger haematomas (Achenbach's syndrome) with angiographic abnormalities. *J Hand Surg (Br)* 2002; **27**: 391–3.

Trauma and subcutaneous fat

Acute panniculitis is considered in detail in Chapter 46. It should be noted here that mechanical injury to the subcutaneous fat, especially on the lower legs, can be a primary cause of fat injury, although more often it is a localizing factor [1,2]. It is often followed by atrophic changes.

Semicircular lipoatrophy

This distinctive condition, also known as lipoatrophia semicircularis, is characterized by one or more partial, horizontal, band-like depressions, usually on the anterolateral thigh or thighs. It mainly occurs in women. Since the initial report [3], relatively few cases have been reported, but it is asymptomatic so may be underreported; several authors have commented that it may well not be rare [4].

Repetitive mild trauma has been suggested as causative in most cases. In one series, seven women of different heights and body mass index working in the same office all developed the condition at the same vertical distance from the floor, corresponding to the height of the edge of their desks; pressure against this edge was postulated to have caused the semicircular lipoatrophy [5]. Pressure from folds in trousers has also been implicated [6].

When a cause is identified and remedial action taken, spontaneous resolution generally occurs [5], in most cases after 9 months to 4 years.

Semicircular lipoatrophy on the thighs can also occur following therapeutic injections [7]. A similar appearance can occur for no apparent reason; the topic is considered further in Chapter 46.

References

1 Forstrom L, Winkelmann RK. Acute panniculitis: a clinical and histopathologic study of 34 cases. *Arch Dermatol* 1977; **113**: 909–17.

2 Diaz-Cascajo C, Borghi S. Subcutaneous pseudomembranous fat necrosis: new observations. *J Cutan Pathol* 2002; **29**: 5–10.

3 Gschwandtner WR, Munzberger H. Ein Beitrag zur band Formig circularen Atrophien del subcutanen Fettgewebes in Extremitatenbereich. *Hautzart* 1974; **25**: 222–7.

4 Nagore E, Sanchez-Motilla JM, Rodriguez-Serna M *et al*. Lipoatrophia semicircularis: a traumatic panniculitis—report of cases and review of literature. *J Am Acad Dermatol* 1998; **39**: 879–81.

5 Gruber PC, Fuller LC. Lipoatrophy semicircularis induced by trauma. *Clin Exp Dermatol* 2001; **26**: 269–71.

6 Herane MI, Urbina F, Sudy E. Lipoatrophia semicircularis: a compressive lipoatrophy consecutive to persistent mechanical pressure. *J Dermatol* 2007; **34**: 390–3.

7 Haas N, Henz BM, Bunikowski R, Keitzer R. Semicircular lipoatrophy in a child with systemic lupus erythematosus after subcutaneous injections with methotrexate. *Pediatr Dermatol* 2002; **19**: 432–5.

Computer palms and mouse fingers

It has long been recognized that manual occupations can leave characteristic changes on the skin, some of which are discussed elsewhere in this chapter.

Computer palms

Two cases of a distinctive, non-blanchable erythema with telangiectasia on the ulnar side of the palms has been described in two healthy computer programmers who had spent 10 or more hours a day, 7 days a week, leaning forward and thereby putting pressure on the hands [1]. The authors speculated that there were similar causative factors to those producing pressure ulcers (pressure, shear, moisture and friction).

The differential diagnosis includes liver disease, connective tissue disease, exposure to chemotherapeutic agents, internal neoplasia and erythema ab igne.

Mouse fingers

A single case has been described of erythema, scaling and peeling of the thumb and fifth finger tip of the right hand, attributed to friction, pressure and sheer exerted on these digits while holding a computer mouse for long periods at a time [2].

References

1 Lewis AT, Hsu S, Phillips M, Lee JA. Computer palms. *J Am Acad Dermatol* 2000; **42**: 1073–5.

2 Vermeer MH, Bruynzeel DP. Mouse fingers, a new computer-related skin disorder. *J Am Acad Dermatol* 2001; **45**: 477.

Dermatological problems of the amputee [1–4]

Skin problems arising from amputation are seen much more on the weight-bearing lower limb than on the upper limb. The main factors are pressure, shear friction and overhydration of the stratum corneum. Lesions that might be trivial elsewhere on the skin, such as minor calluses or fissures, can have a major impact when they occur on a weight-bearing amputation stump. Factors relating to the stump, the prosthesis and other systemic or cutaneous disease all contribute to the likelihood of dermatological complications.

Ideally, the skin on the stump should be well vascularized, freely mobile and with no redundant folds, tension or adhesions to the bone. Scars should be away from weight-bearing areas and bony prominences. The muscles should be fixed so that movements are balanced and no muscle groups are left free to undergo atrophy. Sockets should be designed to provide a close but comfortable fit, with weight-bearing areas designed onto the inner wall and outer rim, and the greatest pressure should be exerted onto those regions most able to receive it. These ideal circumstances may be impossible to achieve, for example after a traumatic amputation the stump may be too short, and often in cases of vascular disease there is reduced blood supply.

Above-knee amputation prostheses are of two basic types: the conventional prosthesis, which is suspended from a belt; and the suction-socket type, which is held in place by negative pressure

and therefore must be a very accurate fit to the stump. Because of the dearth of soft tissues, the prostheses for below-knee stumps are usually suspended, although recently suction-socket types have become more frequently used. Nowadays, there is usually a socket liner made of silicone gel between the stump and the socket, and this is tethered to the socket by a quick-release shuttle lock [5]. The silicone gel roll-on liner is advantageous for some amputees but creates additional problems for others, notably skin problems resulting from heat retention and friction injury from the edge of the liner [6,7]. Dermatological problems in the first weeks after an amputation are unusual; if they occur, they are usually the consequence of secondary infection of the wound or of reaction to topical medicaments. The frequency of skin problems has been reviewed in a retrospective study of 828 lower limb amputations; in this study 40% of limbs had at least one diagnosis, the commonest was ulceration, and problems were more common in those with higher levels of physical activity [4].

Management of the conditions that present in the amputee requires a multidisciplinary approach [2,8].

Common mechanical injuries

Constant rubbing over pressure points readily produces a burning sensation, associated initially with erythema and desquamation. If there are folds in the stump skin, intertrigo can occur, particularly in hot humid weather. With chronicity, painful fissures and secondary eczematization can occur. Friction blisters and erosions usually occur around the brim of the socket and the distal end of amputation stumps. On below-knee stumps, the pretibial area is also a common site for friction blisters. Friction-related injuries, including blistering, can be a problem with the cut edge of silicone gel sleeves. Erosions can progress to ulceration (Fig. 28.10), especially when there is underlying arterial insufficiency, oedema, scars adherent to bone or neurological impairment. Sometimes, quite soon after the prosthesis has been fitted, there is some reduction in size of the stump, such that the limb wedges into the prosthesis. This can cause oedema and also ulceration.



Fig. 28.10 Pressure-induced lichenification, inflammation and ulceration on an amputation stump. (Courtesy of Dr N. Purry, Disablement Services, Southmead Hospital, Bristol, UK.)

Skin thickening can also occur in response to injury. Lichenification, often with hyperpigmentation [9] may be seen, sometimes as part of an eczematous response. Callosities and corns may occur at focal pressure points, especially in below-knee amputees. The 'lenticular button' hyperkeratosis [10] is often painful. Pressure and friction can induce follicular hyperkeratoses [11], sometimes containing entrapped hairs, which can then develop into sterile abscesses. Acne mechanica has been described, responding to isotretinoin [12]. Trauma to the stump can occasionally produce purpura.

Treatment. It is important to recognize injuries resulting from mechanical factors, as they are likely to require adjustments to the prosthesis.

Epidermoid cysts

These are common, usually occurring a few months or more after the prosthesis has been in use. In one series of 67 amputees with epidermoid cysts, the cysts interfered with the wearing of a prosthesis in 23 [13]. Predisposing factors include the previous occurrence of acne, hairy skin and a poor prosthetic fit so as to cause a roll of flesh above the socket brim. Common sites are the adductor, ischial, inguinal and popliteal areas. It seems likely that the cysts originate from shearing forces invaginating fragments of the epidermis into the dermis. Cysts can rupture to produce granulomatous inflammation and discharging sinuses.

Treatment. Adjustment of the prosthesis is necessary, but is sometimes not sufficient to cure the difficult problem of cyst formation. This may require incision and drainage, or excision. It is often necessary for the patient to do without the prosthesis if such measures are undertaken. For the inflammation associated with rupture of the cysts, intralesional steroid may be helpful. If there is true secondary infection, this will require appropriate treatment.

Circulatory disorders

Both venous and lymphatic return are readily impaired by unsatisfactory pressure gradients and inadequate muscle activity in the amputation stump, and these problems are aggravated if there was a pre-existing venous disorder in the limb. The clinical features are oedema, often accompanied by eczema, and sometimes with purpura leading to haemosiderin staining. Stump oedema is very common and can occur even without circulatory insufficiency. Obesity, lack of exercise and poor fit are among the most common contributory factors. As well as correcting underlying causes, application of a graduated pressure bandage at night is useful, and counter-pressure can be produced by modifications to the prosthesis.

A distinctive verrucous hyperplasia can occur with the combination of venous impairment and poor fit [14] and is associated with below-knee amputation [15]. Kaposi-like acroangiodermatitis can present as bluish plaques [16,17].

Treatment. It is important to exclude abnormal pressure or lack of support as a cause of oedema, and to make appropriate adjustments. The garment worn over the prosthesis can provide some useful support, as can wind-on elasticated bandaging when the prosthesis is not in use.

Other problems

Infection. Bacterial colonization and both primary and secondary infections are more common on amputation stumps than on normal skin, probably because of the increased humidity and tendency to frictional injury of the stratum corneum. Folliculitis is one of the more common problems that occur with the silicone gel socket liner. Antiseptic cleansers, such as chlorhexidine, have an important role in prevention. Fungal infection was more common than cellulitis in one large series [4].

Miliaria. In warm weather, miliaria of the stump is often seen. The papules, papulovesicles or pustules may cause no symptoms, but can be intensely irritating. Problems resulting from heat retention with silicone gel socket liners can sometimes be relieved by careful, more frequent washing [7].

Contact dermatitis. This can be caused by a metal, plastic or leather component of the prosthesis, or to medicaments, talcs, oils, etc., and may be overlooked or may be falsely attributed to infection or friction. In a cross-sectional study of 210 amputees, 71 had a related skin disorder and, of these, 12 had relevant patch-test reactions [3]. Patch tests [18,19] should include azo dyes, methacrylates and acrylates, epoxy resins, polyester resin, chrome, nickel, paraphenylenediamine (PPD), *para*-tertiary butylphenol, formaldehyde resin, *para*-tertiary butyl catechol and when suction-socket prostheses are used, appropriate rubber additives and neoprene [3,18–21].

Bullous pemphigoid. This has been reported localized to the amputation stump [22,23].

Neoplasms. Most tumours occurring in stump skin are coincidental or related to the disease necessitating the amputation. A traumatic neuroma can result from amputation, usually appearing on the end of a nerve that has been cut and, when painful, excision may be needed. Squamous carcinoma can rarely arise from a persistent stump ulcer [24] or from verrucous hyperplasia [25].

Incidental reactions

Dermatoses localized by trauma (Koebner response; p. 28.2) are liable to occur on the amputation stump, especially psoriasis or lichen planus. Troublesome psoriasis has also been noted on the palms through the use of crutches as a result of amputation. Patients with atopic dermatitis often have exacerbations on prosthesis-bearing stumps because of the effects of increased temperature, humidity, friction and, perhaps, oedema and bacterial infection. Mechanical forces and increased hydration in amputees can localize acne vulgaris and can aggravate hidradenitis suppurativa. Particularly when sympathy or compensation are sought, the amputation stump may become the site for dermatitis artefacta.

References

1 Levy SW, ed. *Skin Problems of the Amputee*. St Louis, MO: Warren H. Green, 1983.
2 Levy SW. Amputees: skin problems and a prosthesis. *Cutis* 1995; **55**: 297–301.
3 Lyon CC, Kulkarni J, Zimerson E *et al.* Skin disorders in amputees. *J Am Acad Dermatol* 2000; **42**: 501–7.
4 Dudek NL, Marks MB, Marshall SC, Chardon JP. Dermatologic conditions associated with use of a lower-extremity prosthesis. *Arch Phys Med Rehabil* 2005; **86**: 659–63.
5 Marks LJ, Michael JW. Artificial limbs. *BMJ* 2001; **323**: 731–5.
6 McCurdie T, Hanspal R, Nieveen R. ICEROSS: a consensus view. A questionnaire survey of the use of ICEROSS in the United Kingdom. *Prosthet Orthot Int* 1997; **21**: 124–8.
7 Hachisuka K, Nakamura T, Ohmine S. Hygiene problems of residual limb and silicone liners. *Arch Phys Med Rehabil* 2001; **4**: 82.
8 Chadwick SJD, Wolfe JHN. Rehabilitation of the amputee. *BMJ* 1992; **304**: 373–6.
9 Bendl BJ. Painful pigmented prosthesis pressure papules. *Cutis* 1976; **17**: 954–7.
10 Larrégue M, Babin P, Gallet P *et al.* Hyperkératose pénétrante sur moignon d'amputation. *Bull Soc Fr Dermatol Syphiligr* 1975; **82**: 462–4.
11 Ibbotson SH, Simpson NB, Fyfe NCM, Lawrence CM. Follicular keratoses at amputation sites. *Br J Dermatol* 1994; **130**: 770–2.
12 Strauss RM, Harrington CI. Stump acne: a new variant of acne mechanica and a cause of immobility. *Br J Dermatol* 2001; **144**: 647.
13 Allende MF, Levy SW, Barnes GH. Epidermoid cysts in amputees. *Acta Derm Venereol (Stockh)* 1963; **43**: 56–67.
14 Levy SW, Barnes GH. Verrucous hyperplasia of amputation stump. *Arch Dermatol* 1956; **74**: 448–9.
15 Suarez EC, Olivo CZ, Lopez-Rios F *et al.* Circulatory disorders in amputation stumps. *J Am Acad Dermatol* 2001; **44**: 723–4.
16 Badell A, Marcoval J, Graells J *et al.* Kaposi-like acroangiodermatitis induced by a suction socket prosthesis (Letter). *Br J Dermatol* 1994; **131**: 915–7.
17 Gucluer H, Gurbuz O, Kotiloglu E. Kaposi-like acroangiodermatitis in an amputee. *Br J Dermatol* 1999; **141**: 350–92.
18 Suurmond D, Verspijk Mijnssen GAW. Allergic dermatitis due to shoes and a leather prosthesis. *Dermatologica* 1967; **134**: 371–7.
19 Balato N, Costa L, Lembo G *et al.* Allergic contact dermatitis from orthopaedic devices. *Contact Dermatitis* 1995; **32**: 314–5.
20 Conde-Salazar Llinas Volpe MG, Guimaraens D, Romero L. Allergic contact dermatitis from a suction socket prosthesis. *Contact Dermatitis* 1988; **19**: 305–6.
21 Komamura H, Doi T, Inui S, Yoshikawa K. A case of contact dermatitis due to impurities of cetyl alcohol. *Contact Dermatitis* 1997; **36**: 44–6.
22 Reilly GD, Boulton AJM, Harrington CI. Stump pemphigoid: a new complication of the amputee. *BMJ* 1983; **287**: 875–6.
23 Brodell RT, Norman NJ. Stump pemphigoid. *Cutis* 1996; **57**: 245–6.
24 Mahaisavariya B, Mahaisavariya P. Marjolin's ulcer complicating a poorly fabricated prosthesis. *Br J Accident Surg* 1991; **22**: 423–4.
25 Schwartz RA, Bagley MP, Janniger CK, Lambert WC. Verrucous carcinoma of a leg amputation stump. *Dermatologica* 1991; **182**: 193–5.

Spectacle-frame acanthoma

This is the preferred term for a condition initially described as *granuloma fissuratum of the ear* [1] and also known as *acanthoma fissuratum*.

Factors that contribute to the pathogenesis include the weight of the spectacles, minor derangement in local anatomy and maceration.

Histology shows acanthosis and hyperkeratosis of the epidermis, with a central depression and occasionally ulceration. In the dermis, there is often hyalinization of the collagen and a mild mixed inflammatory infiltrate [2]. Granulomatous change is not usually present.



Fig. 28.11 Acanthoma fissuratum. A soft plaque, which may mimic basal cell carcinoma, caused by pressure and friction from the spectacle frame.

The typical lesion occurs behind the ear or on the side of the nose [3–5] as a soft flesh-coloured papule, nodule or plaque, often with a groove at the site where there is contact with the spectacle frame (Fig. 28.11). In a review of 27 published cases, males predominated [2]. Cases with bilateral involvement are uncommon [6].

Spectacle-frame acanthoma usually resolves after a few weeks or months if the patient discontinues wearing spectacles or changes are made to obviate the mechanical trauma.

The main importance of the condition is that it can mimic basal cell carcinoma, which can also be bilateral behind the ears. If necessary, the condition can be treated by surgical excision, electrosurgery and curettage, or intralesional corticosteroids.

References

1 Epstein EE. Granuloma fissuratum of the ear. *Arch Dermatol* 1965; **94**: 621–2.
2 Benedetto AV, Bergfeld WF. Acanthoma fissuratum: histopathology and review of the literature. *Cutis* 1979; **24**: 225–9.
3 Farrel WL, Wilson JW. Granuloma fissuratum of the nose. *Arch Dermatol* 1968; **97**: 34–7.
4 Barnes HM, Calnan CD, Sarkany I. Spectacle frame acanthoma. *Trans St John's Hosp Dermatol Soc* 1974; **60**: 99–102.
5 MacDonald DM, Martin SJ. Acanthoma fissuratum: spectacle frame acanthoma. *Acta Derm Venereol (Stockh)* 1975; **55**: 485–8.
6 Betti R, Inselvini E, Pozzi G, Grosti C. Bilateral spectacle frame acanthoma. *Clin Exp Dermatol* 1994; **19**: 503–4.

Acne mechanica [1]

Pressure of tight clothing or friction, often with heat and increased humidity causing maceration, may exacerbate acne vulgaris or cause its appearance in unusual sites in susceptible subjects. Right-handed students may have predominantly left-handed facial acne from pressure of the left hand. High-necked jerseys, shoulder pads, seat backs in trucks or even adhesive plasters may produce the required mechanical stress. Some athletes are prone to this condition [2]. Acne mechanica has also been described in other circumstances (e.g. on the backs of young patients lying in hospital beds for several weeks, and on the face following jaw splinting [3] and with the use of orthopaedic crutches [4]). The resultant acne can be severe (e.g. acne conglobata occurred on the buttocks in a transatlantic rower) [5].

References

1 Mills DH, Kligman AM. Acne mechanica. *Arch Dermatol* 1975; **111**: 481–3.
2 Basler RS. Acne mechanica in athletes. *Cutis* 1992; **50**: 125–8.
3 Tan SG, Cunliffe WJ, MacGregor AJ. Acne mechanica. *BMJ* 1976; **i**: 130.
4 Kang YC, Choi EH, Hwang SM *et al*. Cane mechanica due to an orthopedic crutch. *Cutis* 1999; **64**: 97–8.
5 Darley CR. Acne conglobata of the buttocks aggravated by mechanical and environmental factors. *Clin Exp Dermatol* 1990; **15**: 462–3.

Traumatic effects of sports

Skin conditions related to sport include mechanical injuries and other direct consequences of the sporting activity, conditions initiated by the environment and infections. They have been usefully reviewed in terms of disease processes [1] and the causative sports [2,3]. While the professional sportsperson and trainer may be well aware of these skin conditions, the amateur may not recognize any connection and even the dermatologist may at times be puzzled. Some of the clinical entities are highly characteristic. The skin adapts to training, developing a higher degree of 'elastic efficiency', but this requires time and continuity in the chosen sport. Many traumatic effects occur in the 'weekend jogger' or the summer holiday activist. The wheelchair athlete is particularly prone to blisters and pressure injury [4,5].

Many conditions affecting those engaged in sports are an indirect consequence of trauma. These include infections commonly transmitted by contact [6,7], such as herpes simplex [8], molluscum contagiosum [9] and tinea corporis [10,11]. Other infections that appear to be more common include viral warts [12], impetigo and furunculosis [13]. The sport of mud-wrestling has been associated with Gram-negative folliculitis [14]. Tinea pedis, often in a mixed infection with Gram-negative bacteria, is a common problem particularly in those using swimming pools. Otitis externa is also an important problem for the swimmer (see Chapter 68). Trauma to nails and trauma-related paronychia is considered in Chapter 65.

Trauma together with heat and moisture are likely contributory factors to contact dermatitis acquired during various sporting activities [15,16].

The sports enthusiast is often at significant risk from sunburn and skin cancer or cold injury. In hot conditions, miliaria and hyperhidrosis can be problems. There are many circumstances in which contact dermatitis can occur; from sports equipment, environmental allergens, etc. [3,16,17]. Sporting activities can exacerbate pre-existing skin disease, such as atopic dermatitis, psoriasis, acne and other skin diseases. The spectrum of sports-related skin disorders also includes the consequences of anabolic steroid misuse, the physical urticarias, exercise-induced anaphylaxis [18] and leukocytoclastic vasculitis [19].

Blisters

These usually result from violent or unaccustomed localized friction, and are most common on weight-bearing surfaces; in the

wheelchair athlete, this includes the back [5]. Heat and humidity favours the development of blisters. Preventive measures and the management of friction blisters are discussed above (p. 28.12).

Haemorrhagic effects

Calcaneal petechiae ('black heel') [20] is described above (p. 28.16). It is particularly common after sports where there are sudden stops such as basketball. A similar condition, 'black palm', can occur in weightlifters [21] and is occasionally seen in golf and tennis players. Petechiae around the ankle in a long-distance runner have been described [22]. Annular purpura can occur when the skin is struck by a table tennis ball ('ping-pong patch') [23]. Annular purpura of a different type has been described in association with step aerobics; annular purpuric lesions developed on the legs [24]. Subungual haematoma, sometimes preceded by erythema, oedema and a throbbing pain, is common among racket-sport enthusiasts ('tennis toe') [25] and runners ('jogger's toe') [26]. Splinter haemorrhages have been seen in golfers [27]. Tennis toe most often affects the first or second toe, whichever is the longer, and the symptoms and signs may mimic a fracture. Jogger's toe tends to involve the third, fourth or fifth toe. Hyperpigmentation resulting from small ecchymoses of the skin on either side of the upper portion of the gluteal cleft is a distinctive finding in long-distance runners, and has been called 'runner's rump'. It is caused by contact between the buttocks while running [28].

Abrasions

These are common in many sports but are particularly associated with contact with wrestling mats [29,30] and artificial turf, which can also produce 'turf toe' (see below). Abrasions from use of skateboards are also common [31].

Acute inflammation

'Turf toe', a painful condition in which there is oedema and erythema over the dorsal aspect of the great toe with acute tendonitis of the flexor and extensor tendons, frequently occurs in athletes playing on artificial turf [32,33]. 'Jogger's nipples' was described in women who run without brassieres [34], but also occurs in men who wear shirts consisting of coarse fibres. It may be more prevalent when ambient conditions are cool, making the nipples erect, and when the skin is moist from sweating, increasing frictional resistance. A similar condition can be seen in competitive cyclists, but it has been suggested that the injury is thermal rather than the result of friction [35].

Corns and calluses

Many sporting activities result in calluses and corns. Some special examples include 'pulling boat hands' [36] in which there is an additional effect of cold injury, and 'rower's rump' [37]. When calluses or corns are a problem on the feet in runners, it is important to consider basic biomechanical principles of the foot, which may require specialist orthopaedic intervention.

Athlete's nodules

An entity sometimes known as surfer's or athlete's nodules can present on the anterior tibial prominence [38], dorsa of the feet or knuckles [39]. These asymptomatic nodules show dermal fibrosis as well as epidermal hyperplasia. Knuckle pads can occur at this site but these fail to resolve when the athletic activity is discontinued [40]. A similar ovoid, largely dermal nodule occurring in the sacrococcygeal area of Japanese students has been attributed to pressure from the bicycle saddle over a distinctive abnormally posteriorly projecting sacrum [41,42].

Other frictional effects

Acne mechanica is common in many participants in sports [43] and may precede acne keloidalis nuchae in football players [44].

'Swimmer's shoulder' is a transient erythematous plaque caused by friction from an unshaven face during freestyle swimming [45].

Intertrigo of the groins is a frequent problem in the heavily muscled athlete. 'Judo jogger's itch' [46] occurred while jogging following vigorous judo but may be a manifestation of a dry skin subjected to abnormal physical and climatic trauma. A distinctive eruption of symmetrical erythematous linear plaques on the palms has been described in children, resulting from grabbing the floor and walls of the pool while swimming underwater [47].

'Mogul skier's palm' consists of hypothenar ecchymoses from repetitive planting of ski poles [48]. 'Hooking thumb' is unique to competitive weightlifters and consists of abrasions, haematomas and calluses on the distal third of the thumb [49].

Miscellaneous

Striae distensae have been associated with weightlifting [50,51]. The areas of skin most frequently involved are the anterior shoulders, lower back and thighs. Painful piezogenic pedal papules and muscle herniation, both described later in this chapter (pp. 28.61–2) have been ascribed to sporting activities [52,53]. 'Bicyclist's vulva' is a unilateral lymphoedema resulting from repeated chafing and folliculitis; investigations showed previously unrecognized abdominopelvic lymphatic abnormalities [1].

References

1 Adams BB. Dermatologic disorders of the athlete. *Sports Med* 2002; **32**: 309–21.
2 Metelitsa A, Barankin B, Lin AN. Diagnosis of sports-related dermatoses. *Int J Dermatol* 2004; **43**: 113–9.
3 Mailler-Savage EA, Adams BB. Skin manifestations of running. *J Am Acad Dermatol* 2006; **55**: 290–301.
4 Curtis KA, Dillon D. Survey of wheelchair athletic injuries: common patterns and prevention. *Paraplegia* 1985; **23**: 170–5.
5 Schaeffer RS, Proffer DS. Sports medicine for wheelchair athletes. *Am Fam Physician* 1989; **39**: 239–45.
6 Beck CK. Infectious diseases in sports. *Med Sci Sports Exerc* 2000; **32**: 431–8.
7 Adams BB. Transmission of cutaneous infections in athletes. *Br J Sports Med* 2000; **34**: 413–4.
8 Becker T, Kodsi R, Bailey P *et al.* Grappling with herpes: herpes gladiatorum. *Am J Sports Med* 1988; **16**: 665–9.
9 Mobacken H, Nordin P. Molluscum contagiosum among cross-country runners. *J Am Acad Dermatol* 1987; **17**: 519–20.
10 Beller M, Gessner BD. An outbreak of tinea corporis gladiatorum on a high school wrestling team. *J Am Acad Dermatol* 1994; **31**: 197–201.
11 Kohl TD, Lisney M. Tinea gladiatorum. *Sports Med* 2000; **29**: 439–47.
12 Roach MC, Chrétien JH. Common hand warts in athletes: association with trauma to the hand. *J Am Coll Health* 1995; **44**: 125–6.
13 Sosin DM, Gunn RA, Ford WL, Skaggs JN. An outbreak of furunculosis among high school athletes. *Am J Sports Med* 1989; **17**: 828–32.

14 Adler A, Altman J. An outbreak of mud-wrestling-induced pustular dermatitis in college students. *JAMA* 1993; **269**: 502–4.
15 Fisher AA. Sports-related cutaneous reactions. II. Allergic contact dermatitis to sports equipment. *Cutis* 1999; **63**: 203.
16 Kockentiet B, Adams BB. Contact dermatitis in athletes. *J Am Acad Dermatol* 2007; **56**: 1048–55.
17 Brooks C, Kujawska A, Patel D. Cutaneous allergic reactions induced by sporting activities. *Sports Med* 2003; **33**: 699–708.
18 Pharis DB, Teller C, Wolf JE. Cutaneous manifestations of sports participation. *J Am Acad Dermatol* 1997; **36**: 448–59.
19 Prins M, Veraart JCJM, Vermeulen AHM *et al.* Leucocytoclastic vasculitis induced by prolonged exercise. *Br J Dermatol* 1996; **134**: 915–8.
20 Wilkinson DS. Black heel: a minor hazard of sport. *Cutis* 1977; **20**: 393–6.
21 Izumi AK. Pigmented palmar petechiae (black palm). *Arch Dermatol* 1974; **109**: 261.
22 Cohen HJ. Jogger's petechiae. *N Engl J Med* 1968; **279**: 109.
23 Scott MJ Jr, Scott MJ III. Pingpong patches. *Cutis* 1989; **43**: 363–5.
24 Allan SJR, Humphreys F, Buxton PK. Annular purpura and step aerobics. *Clin Exp Dermatol* 1994; **19**: 418.
25 Gibbs RC. Tennis shoe. *Arch Dermatol* 1973; **107**: 918.
26 Sher RK. Jogger's toe. *Int J Dermatol* 1978; **17**: 719–20.
27 Ryan A, Goldsmith LA. Golfer's nails. *Arch Dermatol* 1995; **131**: 857–8.
28 Basler RSW. Skin injuries in sports medicine. *J Am Acad Dermatol* 1989; **21**: 1257–62.
29 Freeman MJ, Bergfeld WF. Skin diseases of football and wrestling participants. *Cutis* 1977; **20**: 333–41.
30 Birrer RB, Halbrook SP. Martial arts injuries: the results of a 5 year national survey. *Am J Sports Med* 1988; **16**: 408–10.
31 Illingworth C, Jay A, Parkin R *et al.* Skateboard injuries: a preliminary report. *BMJ* 1977; **ii**: 1636.
32 Clanton TO, Ford JJ. Turf toe injury. *Clin Sports Med* 1994; **13**: 731–41.
33 Doller J, Strother S. Turf toe: an acute inflammatory response to athletic activity on artificial playing surfaces. *J Am Podiatr Med* 1978; **68**: 512–4.
34 Levit F. Jogger's nipples. *N Engl J Med* 1977; **297**: 1127.
35 Powell B. Bicyclist's nipples. *JAMA* 1983; **249**: 2457.
36 Toback A, Korson R, Krusincki P. Pulling boat hands: a unique dermatosis from coastal New England. *J Am Acad Dermatol* 1985; **12**: 649–55.
37 Tomecki K, Mikesell J. Rower's rump. *J Am Acad Dermatol* 1987; **16**: 890–1.
38 Erickson JG, von Gemmingen GR. Surfer's nodules and other complications of surf-boarding. *JAMA* 1977; **167**: 134–6.
39 Cohen PR, Eliezri YD, Silvers DN. Athlete's nodules: sport-related connective tissue nevi of the collagen type (collagenomas). *Cutis* 1992; **50**: 131–5.
40 Dickens R, Adams BB, Mutasim DF. Sports-related pads. *Int J Dermatol* 2002; **41**: 291–3.
41 Nakamura A *et al.* Acquired coccygeal nodule due to repeated stimulation by a bicycle saddle. *Dermatology* 1995; **22**: 365–9.
42 Kawaura K, Yano K, Takama H *et al.* Nodular lesion on the sacrococcygeal area in a bicycle rider. *Br J Dermatol* 2000; **143**: 1124–5.
43 Basler RSW. Acne mechanica in athletes. *Cutis* 1992; **50**: 125–8.
44 Knable AL, Hanke CW, Gonin R. Prevalence of acne keloidalis nuchae in football players. *J Am Acad Dermatol* 1997; **37**: 570–4.
45 Koehn GG. Skin injuries in sports medicine (Letter). *J Am Acad Dermatol* 1991; **24**: 152.
46 Sullivan SN. Judo-jogger's itch. *N Engl J Med* 1979; **300**: 866.
47 Blauvelt A, Duarte AM, Schachner LA. Pool palms. *J Am Acad Dermatol* 1992; **27**: 111.
48 Swinehart JM. Mogul skier's palm: traumatic hypothenar ecchymosis. *Cutis* 1992; **50**: 117.
49 Scott MJ Jr, Scott NI, Scott LM. Dermatologic stigmata in sports: weight lifting. *Cutis* 1992; **50**: 141–5.
50 Levine N. Dermatologic aspects of sports medicine. *J Am Acad Dermatol* 1980; **3**: 415–24.
51 Souminen H, Heikkinen E, Moisio H *et al.* Physical and chemical properties of skin in habitually trained and sedentary men. *Br J Dermatol* 1978; **99**: 147–54.
52 Shelley WB, Rawnsley HM. Painful feet due to herniations of fat. *JAMA* 1968; **205**: 308–9.
53 Berglund HT, Stocks GW. Muscle hernia in a recreational athlete. *Orthop Rev* 1993; **22**: 1246.

Skin signs of torture [1]

Definition. In its Tokyo declaration, the World Medical Association in 1975 defined torture thus: 'Deliberate, systematic or wanton infliction of physical or mental suffering by one or more persons acting alone or on the orders of any authority, to force another person to yield information, to make a confession, or for any other reason'.

Prevalence. Amnesty International has listed 144 countries known for some form of human rights violation [2].

Clinical features. Dermatologists may be involved in caring for victims of torture immediately after it has been inflicted, but are far more likely to see individuals as patients or for legal purposes when the acute injury has settled and the signs are those of previous tissue damage [3,4]. The immediate signs of torture (e.g. abrasions, skin defects and haematomas) are dealt with in depth by Rasmussen [5].

It is important to recognize that, in some societies, the torturer takes great effort to minimize or avoid visible external signs from the injuries inflicted. Another characteristic is that beneath the normal or near-normal skin, there may be long-term or permanent injury (e.g. fractured bones, fibrosis of muscles, damage to nerves and tendons).

Examination of the victim of torture should take account of the potential legal implications as well as the emotional welfare of the victim [6]. The wider aspects of the psychological consequences for the victim, and aspects of rehabilitation, should also be considered by the physician caring for the victim of torture [7].

Specific injuries

The accounts from victims have revealed a wide variety of physical methods are used by torturers including blunt and sharp trauma, electrical and thermal burns etc. Acute injuries in the form of bruising, oedema, abrasions and lacerations may be evident from their pattern as being consistent with some form of assault. As with child abuse, the weapon may have left a distinctive imprint, such as petechial haemorrhages produced by a hand, or parallel lines from a truncheon or stick. Usually, the dermatologist will be presented with scars, and it is important that a careful history is taken to support the diagnosis. There are a number of close mimics of the sequelae of torture.

Beating or whipping

These often produce parallel or criss-cross lines on the back or buttocks. Over bony points the residual marks tend to be circular. If the victim has been able to use his or her arms to protect the face, scars may be found on the backs of the forearms and hands rather than the face.

Beating on the soles of the feet

Synonyms
- Falanga
- Bastinado

This form of torture is used throughout the Middle East, in India and Sri Lanka. As well as damage to the skin and soft tissues, falanga can produce alterations in the plantar aponeurosis, tendons and joints in the feet. Immediately after the beating has been carried out, there is gross swelling and exquisite pain on walking. Late falanga symptoms include pain in the legs and feet, which tends to increase during the day and with exercise. The springiness of the subcutaneous tissue of the forefoot area and heels can be permanently damaged, producing so-called 'smashed' balls of the feet [8,9]. The loss of elastic resistance in the soft tissue of the balls of the feet is best tested when the patient is standing. Not all observers of falanga victims have found these characteristic changes [6]. Magnetic resonance imaging shows a distinctive thickening of the plantar aponeurosis in most cases [10].

The after-effects of falanga can be greatly helped by appropriate physiotherapy and supportive footwear.

Kicks

Injury from kicking tends to produce more or less circular scars over areas where there is bone close to the skin such as the patellae, shins and ankles.

Electrical burns

Electrical burns rarely leave permanent scars, but there may be fine, white, linear or puckered circular scars or groups of red punctate marks. If electricity is passed through clips applied to the skin, there is a greater likelihood of scarring. If seen early after electrical torture, there may be brown scales at the site of application of electrodes [5]; there are vesicular changes in the nuclei of cells in the epidermis, vessel walls and sweat glands [11], and a distinctive pattern of calcification is seen [12]. These changes can be helpful in distinguishing electrical and thermal injury. Scars may be grouped around a target area such as the nipples, lips, ear lobes or helices [13]. In a type of electrical torture known as Picona, an electrically charged needle is used repeatedly on a sensitive site, and may leave clusters of scars [14,15]. Scars on the genitalia, a frequent site of electrical torture, are rare because the skin of the penis or vulva does not scar easily. The pubic skin nearby, however, is very easily scarred.

Cigarette burns

Burns from cigarettes or heated circular instruments tend to be distinctive (Fig. 28.12). Brief contact with a cigarette tends to leave little scarring, but if there has been prolonged contact, there may be a deep, puckered, circular scar with a thin, silvery surface. Deliberately inflicted cigarette burns are often applied to a part of the body that is readily accessible to the interrogator, for example the front of the thigh, or back of the forearm or hand, if the victim was seated. Such injuries are often inflicted in a regular pattern.

Stab wounds

Stabbing with a knife usually leaves a regular 1–2 cm linear scar. A bayonet, however, has one sharp edge and one blunt one and this may leave a teardrop-shaped scar. If a metal implement sharpened to a point is used to prod the victim it leaves a circular scar somewhat like a deep cigarette burn.



Fig. 28.12 Torture. Circular lesions on the dorsum of the left hand presenting a thin, atrophic and wrinkled centre (thin arrow) and a narrow hyperpigmented zone in the periphery (thick arrow). (Courtesy of Amnesty International.)

Inflicted injury to finger- and toenails

Finger- and toenails may be crushed or removed, or implements pushed beneath them. The end result is usually thickening and distortion of nail growth, but this can be difficult to distinguish from other forms of trauma.

Mimics of torture

Scars may have an innocent origin, for example from accidents, sporting injuries, etc. These are often on the most exposed parts of the body. Common dermatoses, such as acne and insect bites, particularly if the latter are infected, can leave prominent scarring. Tribal markings and traditional healing practices, involving injuries inflicted by knives, burning, etc., can be problematic in differential diagnosis. Scars from such practices are often parallel and in groups. Some Islamic fundamental sects ritually flog themselves with whips or chains and this can also result in parallel linear scarring. Vaccination may be a cause of prominent scarring, but the site is usually characteristic. Occasionally, operation scars can cause confusion.

References

1 Danielsen L, Rasmussen OV. Dermatological findings after alleged torture. *Torture* 2006; **16**: 108–27.
2 *Amnesty International 1990 Report*. London: Amnesty International, 1990.
3 Gordon E, Mant AK. Clinical evidence of torture. *Lancet* 1984; **i**: 213–4.
4 Forrest D, Knight B, Hinshelwood G *et al*. A guide to writing reports on survivors of torture. *Forensic Sci Int* 1995; **76**: 69–75.
5 Rasmussen OV. Medical aspects of torture. *Danish Med Bull* 1990; **37** (Suppl. 1): 1–88.
6 Forrest D. The physical after-effects of torture. *Forensic Sci Int* 1995; **76**: 77–84.
7 Basoglu M, ed. *Torture and its Consequences: Current Treatment Approaches*. Cambridge: Cambridge University Press, 1992.
8 Rasmussen OV, Skylv G. Signs of falanga torture. *Lancet* 1992; **340**: 725.

9 Skylv G. The physical sequelae of torture. In: Basoglu M, ed. *Torture and its Consequences: Current Approach to Treatment*. Cambridge: Cambridge University Press, 1992: 38–55.
10 Savnik A, Amris K, Rogind H *et al*. MRI of the plantar structures of the foot after falanga torture. *Eur Radiol* 2000; **10**: 1655–9.
11 Thomsen HK, Danielsen L, Nielson O *et al*. Early epidermal changes in heat, and electrically injured pig skin. *Forensic Sci Int* 1981; **17**: 133–43.
12 Karlsmark T, Thomsen HK, Danielsen L *et al*. The morphogenesis of electrically and heat-induced dermal changes in pig skin. *Forensic Sci Int* 1988; **39**: 175–88.
13 Bork K, Nagel C. Long-standing pigmented keloid of the ears induced by electrical torture. *J Am Acad Dermatol* 1997; **36**: 490–1.
14 Danielsen L, Aalund O. Torture sequelae in the skin (Hutforandring ereffer tortur). *Manedsskerift Praktisk Laegegerning* 1982; **60**: 193–209.
15 Kjaersgaard A, Genefke IK. Victims of torture in Uruguay and Argentina: case studies. In: *Evidence of Torture: Studies by the Amnesty International Danish Medical Group*. London: Amnesty International, 1977: 20–6.

Skin signs of child abuse

Child abuse is usually a clandestine activity denied by the perpetrator. The diagnosis can be very difficult to establish and may require the analytical observational skills of a dermatologist. There is often a differential diagnosis—physical abuse, accidental injury and various naturally occurring conditions can closely resemble one another and may coexist. Four circumstances may arouse suspicion of child abuse: suggestive physical findings, the past and present medical history, behavioural abnormalities exhibited by the child and the psychosocial conditions that are unearthed during the consultation. Suspected child abuse is best managed by a team including a paediatrician and social worker, following a framework of guidelines. Over the past two decades several reviews have detailed the features that should be understood by the dermatologist [1–8].

Definition. Child abuse is treatment of a child by an adult in a way that is unacceptable in a given culture at a given time [9]. Commonly, there is subdivision into four categories:

1 *Physical abuse* (syn. non-accidental injury): bodily injury is deliberately inflicted or the child is forced to engage in a harmful activity
2 *Sexual abuse*: inappropriate exposure to sexual acts or materials
3 *Emotional abuse*: coercive, demeaning or overly distant behaviour so as to interfere with normal psychological or social development
4 *Neglect*: the failure to provide the basic needs of life [10].

There are many difficulties with these definitions. For example, physicians (and others) do not agree among themselves as to what constitutes an 'acceptable' level of physical punishment for a child [11]. Society itself may have a high level of violence, and may tolerate widespread use of corporal punishment in its schools [12]. It can be difficult to categorize physical damage caused by healing practices used by some cultures and faiths, for example coin-rubbing (p. 28.25) and moxibustion, although members of satanic cults who subject children to physical and sexual abuse are generally regarded as transgressing the law.

Epidemiology. In the USA, a national survey indicated a prevalence of 16 in 1000 for child abuse [13]. The actual prevalence may be much higher—in the UK, 4% of children up to the age of 12 years are brought to the notice of professional agencies because of suspicions about possible abuse, and approximately 1 in 1000 children under 4 years suffer severe physical abuse [9]. In the USA, at least 1300 children die each year as a result of child abuse and neglect [14]; Meadow gives an estimate of 1 in 10 000 for the UK [9]. There is evidence that child abuse is becoming more common [9,12]. Although child sexual abuse occurs across the social strata, physical abuse and neglect are correlated with poverty [15].

Most child abuse is perpetrated by a family member, usually a parent or a cohabitant, for example the mother's boyfriend. Abuse is about 20 times more likely if one of the parents was abused as a child. Young parents seem more prone to abusing than older ones.

The different forms of child abuse may be concurrent, so the dermatologist must be vigilant to examine for forms of injury beyond that presenting in the skin (e.g. fractures, ruptured viscera, brain damage) and to evaluate for emotional abuse and neglect.

Physical abuse

Clinical features. The many manifestations of deliberate harm to children are illustrated in great depth in the monograph by Hobbs and Wynne [5]. The most common lesions that may present to a dermatologist are bruises and abrasions, followed by lacerations, scratches (Fig. 28.13), soft-tissue swellings, strap marks, haematomas, burns and bites [12]. Accidental bruises are most common over the fronts of the lower legs, knees, forearms and over other bony prominences such as the forehead, hips and spine. Non-accidental injury should be considered for bruises over relatively protected sites such as the medial and posterior thighs, upper arms, buttocks and particularly the ears and genitalia. There may be a distinctive shape to the bruise from the object used to inflict the injury, for example linear from a rod or rope, or finger marks from slapping or grabbing. Bites can be recognized as human by measuring the intercanine distance (greater than 3 cm implicates a perpetrator with secondary dentition) and recording the pattern of the puncture marks. Cigarette burns can often be suspected when there are one or multiple, rounded, crater-like ulcers or erosions. Acutely, there may be singed vellus hairs. Immersion burns tend to be sharply demarcated and uniform in degree [16] and there are often no splash marks (for further discussion of deliberately inflicted burns see p. 28.33). Needle injuries are a rare cause [17].

In general, one or more of several clues may point towards physical abuse:

1 Unconvincing delay in seeking medical help. With genuine injury there is a speedy request for help in most cases.
2 Details of the history appear implausible, change over time and/or are inconsistent with the developmental capabilities of the child.
3 Lack of concern by the person bringing the child.
4 Abnormal reactions, for example hostility to medical staff.
5 Abnormal demeanour by the child.
6 Disclosure by the child that the injury was inflicted.
7 Lesions have a shape or pattern recognizable as being caused by the means that inflicted them. Examples include bruises in



(a)



(b)

Fig. 28.13 Non-accidental injury. Scratches inflicted by the child's mother. (Courtesy of Dr B.K. Sandhu, Bristol Royal Children's Hospital, Bristol, UK.)

the shape of a hand or pressure from fingers, linear lesions from being struck by a cord or coat hanger, the imprint from the buckle of a belt, and burns from metal utensils such as spoons (Fig. 28.14).

8 Location of lesions. Bruises from accidental trauma are usually over the bony prominences [18], such as knees, forearms, elbows, shins and forehead. Those resulting from abuse are often on the soft parts of the thighs, abdomen, buttocks, cheeks, neck and anogenital regions. Bruising in the mouth, and tears of the frenulum of the tongue, should arouse suspicion.

9 Multiple injuries over many body sites in different stages of healing.

10 The presence of other signs that suggest physical abuse. These may include bilateral periorbital ecchymoses, retinal haemorrhages, rib fractures and traumatic hair loss. The latter may be suspected when the scalp is bruised or tender.

Management. It is essential that the child is examined in a comfortable, supportive environment and that meticulous details are recorded in any case of suspected child abuse. It is important that the examination includes the mouth and anogenital areas. It is often necessary for permission to be granted. If possible, photographs should be taken. There is usually a statutory procedure to be followed when child abuse is suspected, which will necessitate the involvement of those with expertise in paediatric examination and assessment of the social setting of the child.



Fig. 28.14 Non-accidental injury. Superficial burns.

When bruising is present, the colour and location of each lesion should be documented. Bruises can be aged according to colour: red, 0–1 day; blue/purple, 1–4 days; green/yellow, 5–7 days; yellow/brown, 8–10 days; cleared 1–3 weeks [19], although more recent work has cast doubt on the reliability of these conclusions [20–22]. Faint bruises can be seen more readily with the Wood's light [23].

Investigations may be needed. When bruising is present, it is prudent to request a full blood count and clotting screen. Swabs should be taken from fresh bite marks. If there are reasons to suspect bony injury, a skeletal survey may be appropriate, as may an abdominal ultrasound for evaluation of the viscera.

References

1 Raimer BG, Raimer SS, Hebeler JR. Cutaneous signs of child abuse. *J Am Acad Dermatol* 1981; **5**: 203–12.

2 Reece RM, Grodin MA. Recognition of non-accidental injury. *Pediatr Clin North Am* 1985; **32**: 41–60.

3 Schuchner LA, Hankin D. Assessing child abuse in the dermatologist's office. *Adv Dermatol* 1988; **3**: 61–74.

4 Reece RM. Child abuse. *Medical Diagnosis and Management*. Philadelphia: Lea & Febiger, 1994.

5 Hobbs CJ, Wynne JM. *Physical Signs of Child Abuse*, 2nd edn. London: Saunders, 2001.

6 Pride HB. Child abuse and mimickers of child abuse. *Adv Dermatol* 1999; **14**: 417–55.

7 Kos L, Shwayder T. Cutaneous manifestations of child abuse. *Pediatr Dermatol* 2006; **23**: 311–20.

8 Swerdlin A, Berkowitz C, Craft N. Cutaneous signs of child abuse. *J Am Acad Dermatol* 2007; **57**: 371–92.

9 Meadow R. ABC of child abuse: epidemiology. *BMJ* 1989; **298**: 727–30.
10 Wissow LS. Child abuse and neglect. *N Engl J Med* 1995; **332**: 1425–31.
11 Morris JL, Johnson CF, Clasen M. To report or not to report: physicians' attitudes towards discipline and child abuse. *Am J Dis Child* 1985; **139**: 194–7.
12 Johnson CF. Inflicted injury versus accidental injury. *Pediatr Clin North Am* 1990; **37**: 791–814.
13 US Department of Health and Human Services. *Study Findings: Study of National Incidence and Prevalence of Child Abuse and Neglect*. Washington, DC: Children's Bureau, National Center on Child Abuse, 1988.
14 *National Clearinghouse on Child Abuse and Neglect Information: Child Abuse and Neglect Fatalities: Statistics and Interventions*. Washington, DC: US Department of Health and Human Sevices, 2003.
15 Moy JA, Sanchez MR. The cutaneous manifestation of violence and poverty. *Arch Dermatol* 1992; **128**: 829–39.
16 Stratman E, Melski J. Scald abuse. *Arch Dermatol* 2002; **138**: 318–20.
17 Fearne C, Kelly J, Habel J, Drake DP. Needle injuries as a cause of non-accidental injury. *Arch Dis Child* 1997; **77**: 187.
18 Carpenter RF. The prevalence and distribution of bruising in babies. *Arch Dis Child* 1999; **80**: 363–6.
19 Wilson EF. Estimation of the age of cutaneous contusions in child abuse. *Pediatrics* 1977; **60**: 750–2.
20 Langlois NEI, Gresham GA. The ageing of bruises: a review and study of the colour changes with time. *Forensic Sci Int* 1991; **50**: 227–38.
21 Stephenson T, Bialas Y. Estimation of the age of bruising. *Arch Dis Child* 1996; **74**: 53–5.
22 Stephenson T. Ageing of bruising in children. *J R Soc Med* 1997; **90**: 312–4.
23 Vogeley E, Pierce MC, Bertocci G. Experience with wood lamp illumination and digital photography in the documentation of bruises on human skin. *Arch Pediatr Adolesc Med* 2002; **156**: 265–8.

Differential diagnosis. As well as being called on to recognize the varied physical signs of deliberate damage to the skin, the dermatologist may have to diagnose a wide variety of simulants of inflicted injury. These include purpuric and vascular disorders, some other causes of hyperpigmentation, blisters that can mimic burns and unusual scars. Establishing the dermatological diagnosis will require a full and careful history with all appropriate investigations. Animal bites can usually be distinguished by the narrower punctures and different spacings. Some examples of mimics of physical child abuse are summarized in Table 28.4 [1–38].

Table 28.4 Some dermatological mimics of physical abuse.

Mimics of bruising caused by physical abuse
Purpura, vascular and pigmentary problems
Disorders of coagulation [1,2]
Valsalva petechiae (vomiting and coughing) [3]
Sports injuries
Vasculitis [4]
Acute haemorrhagic oedema [5,6]
Erythema multiforme [7]
Leukaemia
Perniosis [8]
Vascular malformations [9]
Haematoma from hair combing [10]
Ehlers–Danlos syndrome [11]
Topical steroid misuse
Incontinentia pigmenti [12]
Phytophotodermatitis [13,14]
Medication-induced hyperpigmentation (e.g. fixed drug eruption)
Maculae cerulae (pediculosis) [15]
Coin rubbing (*cao gio*) [16] and spooning [17]
Cupping [18]
Hair-thread tourniquet syndrome [19]
Mongolian spots [20]
Urticaria pigmentosa [21]
Subcutaneous fat necrosis
Morphoea
Neuroblastoma [22]
Ink or dye stains [23]
Mimics of burns caused by physical abuse
'Therapeutic' burn [24]
Moxibustion [25]
Car seat burns [26]
Impetigo [27]
Staphylococcal scalded skin syndrome [28]
Eczema [29]
Immunobullous diseases
Photodermatoses, phytophotodermatitis
Enuresis blanket [30]
Chemicals [31]
Accidental laxative ingestion [32]
Mimics of scarring caused by physical abuse
Ehlers–Danlos syndrome [33]
Striae [34–36]
Miscellaneous disorders that have mimicked physical abuse
Congenital indifference to pain [37]
Angio-oedema [38]

References

1 Wheeler DM, Hobbs CJ. Mistakes in diagnosing non-accidental injury: 10 years' experience. *BMJ* 1988; **296**: 1233–6.
2 Wetzel RC, Slater AJ, Dover GJ. Fatal intramuscular bleeding diagnosed as suspected non-accidental injury. *Pediatrics* 1995; **95**: 771–3.
3 Mokrohisky ST, Kesselman NE. Valsalva effect may mimic child abuse. *Pediatrics* 1991; **85**: 420.
4 Waskerwitz S, Christoffel KK, Hanger S. Hypersensitivity vasculitis presenting as suspected child abuse. *Pediatrics* 1981; **67**: 283–4.
5 Legrain V. Infantile acute haemorrhagic edema of the skin: study of 10 cases. *J Am Acad Dermatol* 1991; **24**: 17–22.
6 Pride HB, Maroon MS, Tyler WB. Ecchymoses and edema in a 4-month old boy. *Pediatr Dermatol* 1995; **12**: 373–5.
7 Adler R, Kane-Nussen B. Erythema multiforme: confusion with child battering syndrome. *Pediatrics* 1983; **72**: 718–20.
8 Goette DK. Chilblains (perniosis). *J Am Acad Dermatol* 1990; **23**: 257–62.
9 Williams CM, Spector R, Braun M. Cervical bruises: a battered child? Cystic lymphangionia. *Arch Dermatol* 1986; **122**: 1066–7; 1069–70.
10 Falvo CE, San Filippo JA, Vartany A, Osborn EH. Subgaleal hematoma from hair combing. *Pediatrics* 1981; **68**: 583–4.
11 Roberts DL, Pope FM, Nicholls AC, Narcisi P. Ehlers–Danlos syndrome type IV mimicking non-accidental injury in a child. *Br J Dermatol* 1984; **111**: 341–5.
12 Ciarallo L, Paller AS. Two cases of incontinentia pigmenti simulating child abuse. *Pediatrics* 1997; **100**: 6.
13 Coffman K, Boyce WT, Hansen RC. Phytophotodermatitis simulating child abuse. *Am J Dis Child* 1985; **139**: 239–40.
14 Barradell R, Addo A, McDonagh AJG *et al*. Phytophotodermatitis mimicking child abuse. *Eur J Pediatr* 1993; **152**: 291–2.
15 Ragosta K. Pediculosis masquerades as child abuse. *Pediatr Emerg Care* 1989; **5**: 253–4.
16 Amshel CE, Caruso DM. Vietnamese 'coining': a burn case report and literature review. *J Burn Care Rehabil* 2000; **21**: 112–4.
17 Leung AKC. Ecchymoses from spoon scratching simulating child abuse. *Clin Pediatr (Phila)* 1986; **25**: 98.

18 Asnes RS, Wisotsky DH. Cupping lesions simulating child abuse. *J Pediatr* 1981; **99**: 267–8.
19 Barton DJ, Sloan GM, Nichter LS *et al*. Hair-thread tourniquet syndrome. *Pediatrics* 1988; **82**: 925–8.
20 Dungy CI. Mongolian spots, day care centers and child abuse. *Pediatrics* 1982; **69**: 672.
21 Gordon EM, Bernat JR, Ramos-Caros K. Urticaria pigmentosa mistaken for child abuse. *Pediatr Dermatol* 1998; **15**: 484–5.
22 Bohdiewicx PJ, Gallegos E, Fink-Bennett D. Raccoon eyes and the MIBG super scan: scintigraphic signs of neuroblastoma in a case of suspected child abuse. *Pediatr Radiol* 1995; **25**: 90S–92S.
23 Tunnessen WW. The girl with blue hands. *Contemp Pediatr* 1985; **2**: 55–6.
24 Rosenberg L. Maqua (therapeutic burn) as an indicator of underlying disease. *Plast Reconstr Surg* 1988; **82**: 277–80.
25 Feldman KW. Pseudoabusive burns in Asian refugees. *Am J Dis Child* 1984; **138**: 768–9.
26 Schmitt BD, Gray JD, Britton HL. Car seat burns in infants: avoiding confusion with inflicted burns. *Pediatrics* 1978; **62**: 607–9.
27 Oates RK. Overturning the diagnosis of child abuse. *Arch Dis Child* 1984; **59**: 665–6.
28 Porzionato A, Aprile A. Staphylococcal scalded skin syndrome mimicking child abuse by burning. *Forensic Sci Int* 2007; **168**: e1–4.
29 Heider TR, Priolo D, Hultman CS, Peck MD, Cairns BA. Eczema mimicking child abuse: a case of mistaken identity. *J Burn Care Rehabil* 2002; **23**: 357–9.
30 Diez F, Berger TG. Scarring due to an enuresis blanket. *Pediatr Dermatol* 1988; **5**: 58–61.
31 Nunez AE, Taff ML. A chemical burn simulating child abuse. *Am J Forensic Med Pathol* 1985; **6**: 181.
32 Leventhal JM, Griffin D, Duncan KO *et al*. Laxative-induced dermatitis of the buttocks incorrectly suspected to be abusive burns. *Pediatrics* 2001; **107**: 178–9.
33 Owen SM, Durst RD. Ehlers–Danlos syndrome simulating child abuse. *Arch Dermatol* 1984; **120**: 97–101.
34 Robinson AL, Koester GA, Kaufman A. Striae vs. scars of ritual abuse, in a male adolescent. *Arch Fam Med* 1994; **3**: 398–9.
35 Heller D. Lumbar physiological striae in adolescence suspected to be non-accidental injury. *BMJ* 1995; **311**: 738.
36 Cohen HA, Matalon A, Mezger A *et al*. Striae in adolescents mistaken for physical abuse. *J Fam Pract* 1997; **45**: 84–5.
37 Spencer JA, Grieve DK. Congenital indifference to pain mistaken for non-accidental injury. *Br J Radiol* 1990; **63**: 308–10.
38 Thakur BK, Kaplan AP. Recurrent 'unexplained' scalp swelling in an eighteen-month-old child: an atypical presentation of angioedema causing confusion with child abuse. *J Pediatr* 1996; **129**: 163–5.

Sexual abuse

Sexual abuse has been defined as: 'Each and every sexual act that injures the self-determination of any person, who has either not reached a certain age, or who stands in a particular relation to the perpetrator, or who is unable to defend him/herself as a result of their physical or mental condition' [1]. It may occasionally have to be considered when there are physical signs suggestive of acute injury to the vulva, penis, anus and oral cavity in adults with learning difficulties, but the dermatologist is much more likely to see cases suspected of child abuse.

Reference

1 Harth W, Linse R. Dermatological symptoms and sexual abuse: a review and case reports. *J Eur Acad Dermatol Venereol* 2000; **14**: 489–94.

Child sexual abuse

Child sexual abuse has been defined as: 'Any use of children for the sexual gratification of adults' [1]. The dermatological features have been reviewed [2–4] and are illustrated extensively in Hobbs and Wynne's monograph [5].

Acutely, child sexual abuse presents with one or more of four types of complaint:

1 Symptoms caused by local trauma or infection, such as perineal soreness, bleeding, vaginal discharge and anal pain
2 Those caused by emotional effects of the abuse (e.g. enuresis, encopresis and anorexia)
3 Sexualized conduct
4 Sexually transmitted disease.

When a child presents with perianal warts or molluscum contagiosum, the possibility of sexual abuse will need to be considered even though there may be an innocent explanation.

As with the examination for physical abuse, it is important that the conditions for the examination are conducive and that appropriately skilled personnel are involved [1,6]. For anal and genital examination, colposcopy is very useful [5]. An assessment of the vulva should include: the size, shape and any irregularities of the hymenal orifice, especially tears, and whether there are any swellings within the hymenal membrane; any erythema, swelling or bruising of the labia; and any vaginal discharge. Digital penetration tends to produce tears anteriorly, whereas penile penetration is associated with tears of the posterior fourchette. The examiner should be aware of normal variants of paediatric genital anatomy [5,7]. Bruises or scratching in areas adjacent to the anogenital region should raise suspicion. Perianal signs that may cause concern include multiple fissures, swelling or thickening, and purpura. It is important to examine the mouth for signs of oral sex (e.g. palatal petechiae). There are specialized techniques for detection of semen [8].

With the exception of finding semen, lubricants or hairs, or genital infection with *Neisseria gonorrhoeae*, it can be impossible to prove sexual abuse on the basis of physical signs and investigations alone. Nevertheless, appropriate swabs should be taken to culture the full range of sexually transmitted pathogens and other likely infective agents. Pregnancy testing may be necessary.

For most cases where there is some suspicion (e.g. from sexually precocious conduct by the child), evident emotional disturbance or a disclosure of sexual abuse, it is essential for the dermatologist to involve the appropriate paediatrician and support team. The dermatologist should be aware that child sexual abuse often has long-term psychological consequences that can underlie dermatitis artefacta, 'neurotic excoriations', various manifestations of body dysmorphic disorder, compulsive washing practices and vulvodynia [4]. If previous child sexual abuse is recognized as a causative factor, psychotherapy can prove helpful.

References

1 Bamford F, Roberts R. ABC of child abuse: child sexual abuse I & II. *BMJ* 1989; **299**: 312–3, 377–81.
2 Berth Jones J, Graham-Brown RAC. Childhood sexual abuse: a dermatological perspective. *Clin Exp Dermatol* 1990; **15**: 321–30.
3 Finkel MA, De Jong AR. Medical findings in child sexual abuse. In: Reece RM, ed. *Child Abuse: Medical Diagnosis and Management*. Philadelphia: Lea & Febiger, 1994: 185–247.
4 Harth W, Linse R. Dermatological symptoms and sexual abuse: a review and case reports. *J Eur Acad Dermatol Venereol* 2000; **14**: 489–94.
5 Hobbs CJ, Wynne JM. *Physical Signs of Child* Abuse, 2nd edn. London: Saunders, 2001.
6 Ceci SJ, Bruck M. Suggestibility of the child witness: a historical review and synthesis. *Psychol Bull* 1993; **113**: 403–39.

7 McCann J. Genital findings in prepubertal girls selected for nonabuse: a descriptive study. *Pediatrics* 1990; **86**: 428–39.
8 Gabby T, Winkleby MA, Boyce T *et al.* Sexual abuse of children. *Am J Dis Child* 1992; **146**: 700–3.

Differential diagnosis. Almost any condition that can cause inflammation or bruising in the anogenital region may cause concern if there are social or other circumstances pointing towards sexual abuse, as may infection that is not inevitably sexually transmitted. Accidental trauma can also present difficulties [1]. Probably the most common dermatosis mistaken for child sexual abuse is lichen sclerosus, especially when there is subepidermal haemorrhage or when fissures are present [2,3]. If necessary, a biopsy can confirm the diagnosis. The dermatologist should, however, be aware that lichen sclerosus and sexual abuse are not mutually exclusive, not uncommonly coexist, and it has been suggested that trauma is a contributory factor in the aetiology [4].

As with physical abuse, other causes of bruising may need to be considered. These include idiopathic thrombocytopenic purpura, other bleeding diatheses and Ehlers–Danlos syndrome [5]. Haemolytic uraemia syndrome has presented with rectal bleeding thought to be caused by sexual abuse [6]. Conditions that mimic bruising include Mongolian spot, phytophotodermatitis (e.g. from prior handling of psoralen-containing plants or innocent transfer of lime juice onto the buttocks and thighs followed by sun exposure) [7,8] and dyes on the skin from clothing. Bleeding from vulvar haemangioma has been mistaken for sexual abuse [9], as have various congenital anomalies of the genitalia, such as hymenal tags and clefts [10]. Urethral disorders, particularly those that bleed, have led to suspicion of abuse (e.g. caruncle [5] and urethral prolapse [11]). Many blistering disorders have been mistaken for child sexual abuse (e.g. vulvar pemphigoid [12] and chronic bullous disease of childhood [13]).

Perianal Crohn's disease [14], abscesses and fistulae may resemble the fissures and scarring that can occur from anal abuse. Similar changes can cause confusion when Crohn's disease involves the vulva [15].

Strangulation of the penis or clitoris is usually accidental [16–18].

The reliability of anal dilatation as a sign of abuse has been questioned [19,20]. However, gross examples are more likely to be significant. It is worth noting therefore that severe constipation [21] and neurological disorders [22] can cause marked anal dilatation. Accidental trauma (e.g. from the crossbar of a bicycle) can cause contusion of the external genitalia, including the clitoris and anterior parts of the labia, but is not likely to damage the hymen; in contrast, penetrative vulval abuse tends to damage the posterior parts of the vulva [16,17,23].

Much trauma is done by the act of female circumcision, which may not be admitted. Infectious diseases that may be wrongly attributed to sexual abuse include yaws, in which syphilis serology will be positive [24], and streptococcal infection of the anus, vagina, urethra and penis.

Some infections that can be sexually transmitted, but are not necessarily so, include herpesvirus type 2, anogenital warts (even the human papillomavirus types most associated with the genital tract) [25] and molluscum contagiosum.

Occasionally, common dermatoses that produce erythema, such as irritant dermatitis, seborrhoeic dermatitis, atopic dermatitis, napkin dermatitis, psoriasis, candidal infection or threadworm infestation, may require correct diagnosis in the context of suspicion of abuse.

Some of the conditions discussed above are included in Table 28.4.

References

1 Bays J. Conditions mistaken for child sexual abuse. In: Reece RM, ed. *Child Abuse: Medical Diagnosis and Management*. Philadelphia: Lea & Febiger, 1994: 386–403.
2 Handfield Jones SE, Hinde FRJ, Kennedy CTC. Lichen sclerosus et atrophicus in children misdiagnosed as sexual abuse. *BMJ* 1987; **294**: 1404–5.
3 Jenny C, Kirby P, Fuquay D. Genital lichen sclerosus mistaken for child sexual abuse. *Pediatrics* 1989; **83**: 597–9.
4 Warrington SA, de San Lazaro C. Lichen sclerosus et atrophicus and sexual abuse. *Arch Dis Child* 1996; **75**: 512–6.
5 Bays J, Jenny C. Genital and anal conditions confused with child sexual abuse trauma. *Am J Dis Child* 1990; **144**: 1319–22.
6 Vickers D, Morris K, Coulthard MG, Eastham EJ. Anal signs in haemolytic uraemic syndrome (Letter). *Lancet* 1988; **1**: 998.
7 Coffman K, Boyce WT, Hansen RC. Phytophotodermatitis simulating child abuse. *Am J Dis Child* 1985; **139**: 239–40.
8 Barradell R, Addo A, McDonagh AJG *et al.* Phytophoto dermatitis mimicking child abuse. *Eur J Pediatr* 1993; **152**: 291–2.
9 Levin AV, Selbst SM. Vulvar hemangioma simulating child abuse. *Clin Pediatr* 1988; **27**: 213–5.
10 McCann J, Voris J, Simon M, Wells R. Perianal findings in prepubertal children selected for non-abuse: a descriptive study. *Child Abuse Negl* 1989; **13**: 179–93.
11 Johnson CF. Prolapse of the urethra: confusion of clinical and anatomic characteristics with sexual abuse. *Pediatrics* 1991; **87**: 722–5.
12 Levine V, Sanchez M, Nestow M. Localised vulvar pemphigoid in a child misdiagnosed as sexual abuse. *Arch Dermatol* 1992; **128**: 804–6.
13 Coleman H, Shrubb VA. Chronic bullous disease of childhood: another cause for potential misdiagnosis of sexual abuse? *Br J Gen Pract* 1997; **47**: 507–8.
14 Stratakis CA, Graham W, Di Palma J, Leibowitz I. Misdiagnosis of perianal manifestation of Crohn's disease. *Clin Pediatr* 1994; **33**: 631–3.
15 Porzionato A, Alaggio R, Aprile A. Perianal and vulvar Crohn's disease presenting as suspected abuse. *Forensic Sci Int* 2005; **155**: 24–7.
16 West R, Davies A, Fenton T. Accidental vulval injuries in childhood. *BMJ* 1989; **298**: 1002–3.
17 Jones LW, Bass DH. Perineal injuries in children. *Br J Surg* 1991; **78**: 1105–7.
18 Press S, Schachner L, Paul P. Clitoris tourniquet syndrome. *Pediatrics* 1980; **66**: 781–2.
19 Bamford F, Roberts R. An ABC of child abuse: child sexual abuse II. *BMJ* 1989; **299**: 377–82.
20 Bays J, Chadwick D. Medical diagnosis of the sexually abused child. *Child Abuse Negl* 1993; **17**: 91–110.
21 Clayden GS. Reflex anal dilatation associated with severe chronic constipation. *Arch Dis Child* 1988; **63**: 832–6.
22 Reardon W, Hughes HE, Green SH *et al.* Anal abnormalities in childhood myotonic dystrophy: a possible source of confusion in child sexual abuse. *Arch Dis Child* 1992; **67**: 527–8.
23 Muram D. Genital tract injuries in the prepubertal child. *Pediatr Ann* 1986; **15**: 616–20.
24 Engelkens HJ, Judanarso J, van der Sluis JJ *et al.* Disseminated early yaws: report of a child with a remarkable genital lesion mimicking venereal syphilis. *Pediatr Dermatol* 1990; **7**: 60–2.
25 Gibbs NF. Anogenital papillomavirus infections in children. *Curr Opin Pediatr* 1998; **10**: 393–7.

Signs of emotional abuse and neglect

Neglect may be evident from malnutrition, an uncared-for dirty appearance, exaggerations of common dermatoses or lack of appropriate immunizations for the child's age [1]. Some examples

of burn and scald are a result of neglect rather than deliberate physical abuse [2]. Both physical neglect and 'emotional abuse' can result in failure to thrive with depressed gain in height and weight. Cold, swollen, blue or red hands and feet have been described in cases of emotional neglect [3,4]. Some would consider the failure to administer treatments (e.g. to a child with eczema) as a form of child abuse.

References

1 Fontana VJ. The maltreatment of children. *Pediatr Ann* 1984; **13**: 736–44.
2 Hobbs CJ. ABC of child abuse: burns and scalds. *BMJ* 1989; **298**: 1302–5.
3 Glover S, Nicholl A, Pullan C. Deprivation hands and feet. *Arch Dis Child* 1985; **60**: 976–7.
4 Feehan CJ. Cold hands and feet as a sign of abusive neglect in infants and children. *Psychiatry* 1992; **55**: 303–9.

Munchausen syndrome by proxy

This term is used to denote the situation in which the parent or caretaker falsely attributes symptoms in order to gain medical care or some other benefit. Such behaviour can result in multiple unnecessary surgical interventions [1].

Reference

1 Weston WL, Morelli JG. 'Painful and disabling granuloma annulare': a case of Munchausen by proxy. *Pediatr Dermatol* 1997; **14**: 363–4.

Traumatic lesions during intensive care

The complex technology now involved in intensive care includes a number of invasive procedures and other devices that can cause cutaneous lesions [1–3], and for convenience these are summarized here. Continuous arterial catheterization may lead to bruising, haematomas and even local or peripheral skin necrosis [4–6]. Other sites of necrosis may be caused by pressure of headbands or other attachments. Phlebitis may occur from infection or irritant intravenous agents. Blisters can arise resulting from heat generated beneath oxygen transducers, perhaps more so in children than in adults [7]. When conducting gel is smeared across the chest wall, electrical burns can result from arcing between the paddle electrodes used for defibrillation or cardioversion; in most centres this is avoided nowadays by using prepackaged conducting gel pads [7]. Erythema ab igne has been described following malfunction of an adjustable temperature blanket [8]. Even though preventive measures are widely used, pressure ulcers do occur (p. 28.16).

References

1 Peerless JR, Davies A, Klein D, Yu D. Skin complications in the intensive care unit. *Clin Chest Med* 1999; **20**: 453–67.
2 Johnston IDA. Hazards of intravenous feeding. *Adv Drug React Bull* 1979; **77**: 276–9.
3 Ryan DW. Morbidity of intensive care. *Hosp Update* 1982; **8**: 1287–97.
4 Bedford RF, Wollman H. Complications of percutaneous radial artery cannulation. *Anesthesiology* 1973; **38**: 228–36.
5 Wyatt R, Glaves I, Cooper DJ. Proximal skin necrosis after radial artery cannulation. *Lancet* 1974; **i**: 1135–8.
6 Downs JB, Chapman RL, Hawkins IF. Prolonged radial artery catheterization. *Arch Surg* 1984; **108**: 671–3.
7 Green T, Manara AR, Park GR. Dermatological conditions in the intensive care unit. *Hosp Update* 1989; **15**: 367–76.
8 Dellavalle RP, Gillum P. Erythema ab igne following heating/cooling blanket use in the intensive care unit. *Cutis* 2000; **66**: 136–8.

Cutaneous injuries in the newborn

In the neonatal period, iatrogenic injury can be caused by trauma before, during or after delivery [1]. The skin of the newborn, especially if premature, is especially vulnerable to various noxious insults. Examples of prenatal injury include amniocentesis or fetal skin biopsy, leaving a dimpled scar. Common intrapartum injuries include that caused by the heart-monitoring scalp electrode, laceration from episiotomy or amniotomy, and ecchymosis and variable oedema from vacuum extraction or delayed delivery. Post-natal mechanical trauma can be caused by the identification tag, blood sampling by heel prick, intravenous cannulae, and pressure from the prone position to the nose, toes and knees. Heating pads and monitoring devices can cause second- or even third-degree burns.

Neonatal injuries are considered further in Chapter 17.

Reference

1 Metzher A, Brenner S, Merlob P. Iatrogenic cutaneous injuries in the neonate. *Arch Dermatol* 1999; **135**: 697–703.

Penile injuries

A variety of constrictive bands at the base of the penis are used by some individuals to increase sexual gratification. Sometimes these can become incarcerated and cause secondary ischaemic injury [1].

Human hair accidentally wrapped round the penis has caused penile oedema [2].

Petechiae may result from squeezing the glans to prevent premature ejaculation [3]. Zip-fastener tears are less common than previously, possibly because of the popularity of Y-front briefs. Lesions resulting from sexual experimentation may be bizarre. Vacuum cleaners can cause various injuries to the skin and urethra [4,5] and a meatal stricture may result.

References

1 Wasadikar PP. Incarceration of the penis by a metallic ring. *Postgrad Med J* 1997; **73**: 255.
2 Garty BZ, Mimouni M, Varsano I. Penile tourniquet syndrome. *Cutis* 1983; **31**: 431–2.
3 Handler HL. Penile petechiae. *Arch Dermatol* 1976; **112**: 121–2.
4 Rossi M, Cacini F, Torcigliani S. Lesione del pene da masturbazione con aspirapolvere. *Minerva Urol Nefrol* 1992; **44**: 43–5.
5 Citron ND, Wade PJ. Penile injuries from vacuum cleaners. *BMJ* 1980; **281**: 26.

Foreign bodies

Definition. Some extraneous materials (e.g. silica and zirconium) incite a characteristic pattern of granulomatous reaction in which a distinctive type of multinucleate giant cell, the foreign-body giant cell, is prominent. The term foreign-body reaction is used for this tissue response but may also be used for other patterns of pathological response to extraneous materials that become deposited in the skin or deeper tissues, usually as a result of direct penetration of the skin by the material itself, during surgery or by injection. Epidermis, hair and nail can induce a 'foreign-body' response if implanted in or beneath the dermis. Cutaneous reactions to medicaments introduced at a distant site (e.g. the

pigmentation caused by minocycline) and some local adverse reactions to drugs are considered in Chapter 75.

Aetiology. Some examples of the types of foreign body and routes of entry are shown in Table 28.5 [1–48].

References

1 Young PC, Smack DP, Sau P *et al.* Golf club granuloma. *J Am Acad Dermatol* 1995; **32**: 1047–8.
2 Mehregan AH, Faghri B. Implantation dermatoses. *Acta Derm Venereol (Stockh)* 1974; **54**: 61–4.
3 Hirsh BC, Johnson WC. Pathology of granulomatous diseases: epithelioid granulomas. II. *Int J Dermatol* 1984; **23**: 306–13.
4 Winer LH, Zeilenga RH. Cactus granulomas of the skin. *Arch Dermatol* 1955; **72**: 566–9.
5 Snyder RA, Schwartz RA. Cactus bristle implantation: report of an unusual case initially seen with rows of yellow hairs. *Arch Dermatol* 1983; **119**: 152–4.
6 Lindsey D, Lindsey WE. Cactus spine injuries. *Am J Emerg Med* 1988; **6**: 362–9.
7 Iwatsu T, Miyaji M. Phaeomycotic cyst: a case with a lesion containing a wooden splinter. *Arch Dermatol* 1984; **120**: 1209–11.
8 Connor DH, Gibson DW. Association of splinters with chromomycosis and phaeomycotic cyst (Letter). *Arch Dermatol* 1985; **121**: 168.
9 Kinmont PDC. Sea-urchin sarcoidal granuloma. *Br J Dermatol* 1965; **77**: 335–43.
10 Allen AC. Persistent 'insect bites' (dermal eosinophilic granulomas) simulating lymphoblastomas, histiocytoses, and squamous cell carcinomas. *Am J Pathol* 1948; **24**: 367–75.
11 Schon MJ, Scott FA, Boswick JA. High pressure injection injuries of the hand. *J Trauma* 1980; **20**: 229–38.
12 Mesquita-Guimaraes J, Azevedo F, Aguiar S. Silica granulomas secondary to explosion of a land mine. *Cutis* 1987; **40**: 41–3.
13 Hanke CW, Connor AC, Probst EL, Fondak AA. Blast tattoos resulting from black powder firearms. *J Am Acad Dermatol* 1987; **17**: 819–25.
14 Hatch CL, Terezhalmy GT, Krolls SO. Amalgam tattoos of the oral soft tissue. *Ear Nose Throat J* 1984; **63**: 416–22.
15 Hartman LC, Natiella JR, Meenaghan MA. The use of elemental microanalysis in verification of the composition of presumptive amalgam tattoo. *J Oral Maxillofac Surg* 1986; **44**: 628–33.
16 Cortez Pimentel J. Sarcoid granulomas of the skin produced by acrylic and nylon fibres. *Br J Dermatol* 1977; **96**: 673–7.
17 Centeno JA, Kalasinsky VF, Johnson FB *et al.* Fourier transform infrared microscopic identification of foreign materials in time sections. *Lab Invest* 1992; **66**: 123–30.
18 Stein F. Foreign body injuries of the hand. *Emerg Med Clin North Am* 1985; **3**: 383–90.
19 Hogan DJ. Subungual trichogranuloma in a hairdresser. *Cutis* 1988; **42**: 105–6.
20 Brown CK, Wooten SL, Fair LK. Retained foreign body: a fingernail fragment? *J Emerg Med* 1993; **11**: 259–64.
21 Jones Williams W. Beryllium disease. *Postgrad Med J* 1988; **64**: 511–6.
22 Mowry GM, Sams MW, Caulfield JB. Cutaneous silica granuloma. *Arch Dermatol* 1991; **127**: 692–4.
23 Travis WD, Balogh K, Abraham JL. Silicone granulomas: report of three cases and review of the literature. *Hum Pathol* 1985; **16**: 19–27.
24 Swanson NA, Stoner JG, Siegle RJ, Solomon AR. Treatment site reactions to Zyderm collagen implantation. *J Dermatol Surg Oncol* 1983; **9**: 377–80.
25 Kligman AM. Histologic responses to collagen implants in human volunteers: comparison of Zyderm collagen with Zyplant implant. *J Dermatol Surg Oncol* 1988; **14** (Suppl. 1): 35–8.
26 Morgan AM. Localized reactions to injected therapeutic materials. I. Medical agents. *J Cutan Pathol* 1995; **22**: 193–214.
27 Oertel VC, Johnson FB. Sclerosing lipogranuloma of the male genitalia. *Arch Pathol* 1977; **101**: 321–6.
28 Alagaratnam TT, Ong GB. Paraffinomas of the breast. *J R Coll Surg Edin* 1983; **28**: 260–3.
29 Nakamura M, Saekrai T, Yoskida K *et al.* Sclerosing lipogranuloma of the penis: chemical analysis of lipid from lesional tissue. *J Urol* 1985; **133**: 1046–8.
30 Hirsh BC, Johnson WC. Pathology of granulomatous diseases: foreign body granulomas. *Int J Dermatol* 1984; **23**: 531–8.
31 Postlethwaite RW, Willigan DA, Ulin AW. Human tissue reaction to sutures. *Ann Surg* 1975; **181**: 144–50.
32 Terzakis JA, Shustak SR, Stock EG. Talc granuloma identified by X-ray microanalysis. *JAMA* 1978; **239**: 2371–2.
33 Leonard DD. Starch granulomas. *Arch Dermatol* 1973; **107**: 101–3.
34 Jaworsky C. Analysis of cutaneous foreign bodies. *Clin Dermatol* 1991; **9**: 149–56.
35 Jordaan HF, Sandler M. Zinc-induced granuloma: a unique complication of insulin therapy. *Clin Exp Dermatol* 1989; **14**: 227–9.
36 Slater DN, Underwood JCE, Durrant TE *et al.* Aluminium hydroxide granulomas: light and electron microscopic studies and X-ray microanalysis. *Br J Dermatol* 1982; **107**: 103–8.
37 Garcia-Patos V, Pujol RM, Alomar A *et al.* Persistent subcutaneous nodules in patients hyposensitized with aluminium-containing allergen extracts. *Arch Dermatol* 1995; **131**: 1421–4.
38 Morgan AM. Localized reactions to injected therapeutic materials. II. Surgical agents. *J Cutan Pathol* 1995; **22**: 289–303.
39 Goldman L. Reactions following intralesional and sublesional injections of corticosteroids. *JAMA* 1962; **182**: 613–6.
40 Weedon D, Gutteridge BH, Hockly RG, Emmett AJJ. Unusual cutaneous reactions to injections of corticosteroids. *Am J Dermatopathol* 1982; **4**: 199–203.
41 Bhawan J. Steroid-induced 'granulomas' in hypertrophic scar. *Acta Derm Venereol (Stockh)* 1983; **63**: 560–3.
42 Kossard S, Ecker RI, Dicken CH. Povidone panniculitis. *Arch Dermatol* 1980; **116**: 704–6.
43 Morgan AM, Johnson FB, Lupton GP. Cutaneous and subcutaneous polyvinylpyrrolidone (PVP) storage disease (Abstract). *J Cutan Pathol* 1989; **16**: 318.
44 Texier L. Hypodermite sclerodermiforme lombo-fessiere induite par injection de vitamin K. *Bull Soc Fr Dermatol Syphiligr* 1975; **82**: 448–9.
45 Padilla AS, Becker LE, Hoffman H. Cutaneous and venous complications of pentazocine abuse. *Arch Dermatol* 1979; **115**: 975–7.
46 Posner DI, Guill MA. Cutaneous foreign body granulomas associated with intravenous drug abuse. *J Am Acad Dermatol* 1985; **13**: 869–72.
47 Hirsch CS. Dermatopathology of narcotic addiction. *Hum Pathol* 1972; **3**: 37–53.
48 Sullivan M. Multiple subcutaneous abscesses produced by the hypodermic injection of feces. *South Med J* 1949; **42**: 402–4.

Pathogenesis. The biological response to a foreign body will depend on its composition, how it enters the body, the body site, the quantity of material and its physical form. In some instances (e.g. mercury and some animal and vegetable matter), a toxic or allergic reaction can occur as well as a later foreign-body reaction. Some reactions are complicated by infection, especially traumatic inoculation of wooden splinters and vegetation spines, which can introduce sporotrichosis and deep mycotic organisms as well as more common pyogenic infections. Infection may also localize to sites of inert foreign bodies during bacteraemia [1].

Pathology. When material has penetrated the skin there is usually a phase of acute inflammation in response to the injury. This may be necrotizing if there is significant trauma, toxin release or bacterial infection. Persistence of foreign material results in accumulation of monocytes, evolution of these into tissue macrophages, epithelioid histiocytes and giant cells (Langhans' and foreign-body type) and a fibroblastic reaction with laying down of new connective tissue around the area of foreign-body deposition.

Penetration injury can also result in implantation cysts mixed with granulomatous response.

Polarizable foreign bodies can be seen in biopsies of otherwise typical sarcoidosis, and if adequate criteria are met for a diagnosis of sarcoidosis, such foreign body material does not alter the diagnosis [2].

Table 28.5 Foreign bodies: their source and investigation.

Source	Material	References	Pathological features
Traumatic	Metals		H, EDXA as appropriate, e.g. Hg
	Glass		P, EDXA (Si)
	Graphite, e.g. carbon fibre	Young *et al*. [1]	P, characteristic heat resistance up to 600°C
	Thorns, wood splinters	Mehregan & Faghri [2]	
	Other vegetation	Hirsh & Johnson [3]	P, H&E; rectangular cell walls
	Cactus spines	Winer & Zeilenga [4]	PAS (may be concurrent) bacterial?
		Snyder & Schwartz [5]	and/or fungal infection [7]
		Lindsey & Lindsey [6]	
		Connor & Gibson [8]	
	Sea-urchin spines	Kinmont [9]	
	Arthropod mouth parts	Allen [10]	
	Grease gun injury	Schon *et al*. [11]	H&E; extensive necrosis and thrombosis
	Blast injury	Mesquita-Guimaraes *et al*. [12]	EDXA (Si)
		Hanke *et al*. [13]	
	Amalgam tattoo	Hatch *et al*. [14]	EDXA (usually Hg, Ag, Sn)
		Hartman *et al*. [15]	
	Synthetics:		
	Plastics	Cortez Pimentel [16]	
	Fibres	Centeno *et al*. [17]	P, H, FTIRM
	Epidermis	Stein [18]	
	Hair	Hogan [19]	P, H&E appearance
	Nail	Brown *et al*. [20]	
Occupational	Beryllium	Jones Williams [21]	EELS
	Silica	Mowry *et al*. [22]	P, EDXA (Si)
	Hair	Hogan [19]	P, H&E appearance
	Fibreglass	See p. 28.47	P
Cosmetic	Tattoos	See p. 28.48	H&E appearance, EDXA (appropriate elements)
	Silicone	Travis *et al*. [23]	
	Collagen	Swanson *et al*. [24]	IRS or EDXA (Si), H&E; vacuoles
		Kligman [25]	Immunoperoxidase using antibovine type I collagen antibody
		Morgan [26]	
	Paraffins	Oertel & Johnson [27]	
	Vegetable oils	Alagaratnam & Ong [28]	H&E; 'Swiss cheese' cavities
		Nakamura *et al*. [29]	FDMS
	Zirconium	Hirsh & Johnson [30]	EDXA (Zr)
Surgically implanted	Suture materials	Postlethwaite *et al*. [31]	P, H&E
	Talc	Terzakis *et al*. [32]	P, EDXA
	Starch	Leonard [33]	?P, PAS crystals with Maltese cross appearance on polaroscopy
	Absorbable gelatine	Jaworsky [34]	
Injected drugs	Insulin	Jordaan & Sandler [35]	H&E appearance of acellular sponge material
	Vaccines	Slater *et al*. [36]	
		Garcia-Patos *et al*. [37]	EDXA (Zn)
		Morgan [38]	EDXA (Al)
	Calcium salts		H, EDXA (Ca)
	Intralesional corticosteroid	Goldman [39]	
		Weedon *et al*. [40]	H&E; granular, amorphous, acellular material
		Bhawan [41]	
		Morgan [38]	
	Polyvinylpyrrolidone	Kossard *et al*. [42]	
		Morgan *et al*. [43]	
	Vitamin K	Texier [44]	
Self-inflicted	Narcotic and analgesic abuse, e.g. pentazocine (Fig. 28.16), meperidine	Padilla *et al*. [45]	H&E (P if talc from tablets is used); thrombosis and fibrosis
		Posner & Guill [46]	
	Talc in fillers used by intravenous drug abusers	Hirsch [47]	EDXA
	Dermatitis artefacta using injections of faeces, milk, etc.	Sullivan [48]	H&E; necrosis, abscesses

Key to techniques: EDXA, electron dispersive X-ray analysis; EELS, electron energy loss spectroscopy; FDMS, field desorption mass spectroscopy; FTIRM, Fourier transform infrared microscopy; H, histochemical reaction available; H&E, haematoxylin and eosin; IRS, infrared spectrophotometry; LAMMA, laser microprobe mass analysis; P, birefringence by polarization microscopy; PAS, periodic acid–Schiff stain.

Clinical features. The clinical presentation will depend on the mode of entry and nature of the foreign body, the tissue response to it and whether there is associated infection. In some instances, there may be characteristic toxic effects (e.g. absorption of mercury from a broken thermometer) [3], pharmacological effects (e.g. resulting from alkaloids in blackthorn) [4] or allergic responses (e.g. to oils and resins in some woods).

Retained foreign bodies are commonly associated with bacterial infection, which tends to be resistant to antibiotic therapy. Vegetative foreign bodies may be associated with fungal infection. Soft tissue infections may manifest as cellulitis, an abscess or a draining sinus. A wound that fails to heal or continues to cause pain with movement may suggest the presence of a foreign body, as can the persistence of a purulent discharge.

Many types of foreign body elicit a granulomatous response, seen clinically as erythematous brown or purple papules, nodules or plaques. The lesions often become harder over time because of fibrosis. Some materials result in discharge even when there is no infection (e.g. paraffins and other oils).

The implanted material may produce pigmentary change (e.g. carbon and metals result in a tattoo-like, black or bluish-black colour). A metallic foreign body rich in iron can present as a black skin lesion and be mistaken for a melanoma [5].

Clinical presentation can be modified by epidermal cyst formation, resulting from pieces of epidermis being carried in by a penetrating foreign body. It is important to recognize that even small external signs of entry of a foreign body can denote significant damage to deeper structures, such as tendons, joints and bones. This is especially true of high-pressure injection (grease, paint, water and some firearm injuries).

Diagnosis. A careful history surrounding any suspected penetrating injury is essential, taking into account the timing and the type of material involved. Patients with a foreign body implanted into the skin may have discomfort at the wound site. Lacerations should be carefully examined for foreign bodies, using instruments rather than the gloved finger if there might be a sharp object in the wound. Palpation of a mass may justify extending the wound so as to explore it adequately.

When there is strong suspicion that all or part of a foreign body is in or beneath the skin, imaging techniques should be considered.

Plain radiography. A plain X-ray will often detect a foreign body, but visualization depends on the object's density, configuration, size and orientation. Metal, bone, teeth, pencil graphite, some plastics, glass and gravel are radio-opaque but may not be visible if located over a radiologically dense background such as bone. Some materials that are less dense than tissue can be seen as filling defects (e.g. white pine) [6], but very often organic foreign bodies are not visible on plain radiographs, especially 48 h or more after entry [7]. Plain films, using multiple projections, can enhance localization.

Ultrasonography. Ultrasound imaging is often helpful for vegetative foreign bodies that are not visible on plain X-ray. However, there are a number of pitfalls in interpretation, especially in the hand where tendons produce their own echogenic images [8,9]. Wooden splinters can be obscured by surrounding granulomatous tissue [10], and old scar tissue, small bones, fresh bleeding and sutures can produce false-positive echo patterns [11].

Computed tomography. Computed tomography (CT) scanning, which can visualize wooden material, has the advantage of producing images in multiple planes, which can aid localization and can relate a foreign body accurately to nearby structures. However, there is a greater radiation dose than plain radiography, so CT is best avoided as a screening procedure.

Magnetic resonance imaging. Magnetic resonance imaging (MRI) is comparable to CT for materials of similar density to soft tissue (Fig. 28.15) and may be superior for the detection of plastics [12], but must not be used for metal fragments. Gravel produces a severe artefact.

Histopathological techniques [13]. For foreign bodies below the limits of detectability by imaging techniques, it may be possible to make a diagnosis on material taken at biopsy by microscopic or ultrastructural techniques.

Some foreign materials have a distinctive microscopic structure, for example the regular arrays of plant cells in some vegetative material, such as wooden splinters and thorns. The presence of particulate material in phagocytic cells can often be seen on routine haematoxylin and eosin-stained sections. The periodic acid–Schiff (PAS) stain often shows up splinters, talc, starch and fungi. Dark-field illumination can help visualize some metallic materials. Polarization microscopy can demonstrate silica, talc, suture material, wood and plant matter [14]. In suitably processed material, the elements present can be ascertained by electron dispersive X-ray analysis (EDXA) and for lower-molecular-weight substances electron energy loss spectroscopy (EELS) may be appropriate [15].

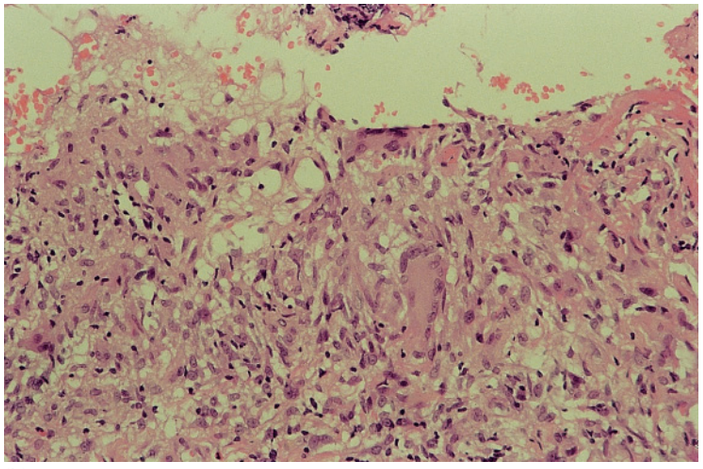
The application of different methods is indicated in Table 28.6.

Treatment [16]. It can be a difficult judgement as to whether or not to remove a foreign body. Some indications for removal of a foreign body are shown in Table 28.6. Reactive material, especially if organic in nature (thorns, spines), should be removed so as to prevent infection and inflammation. Non-reactivity, small size and inaccessibility may weigh in favour of leaving a foreign body. All wounds should be clean and tetanus immunization provided if necessary.

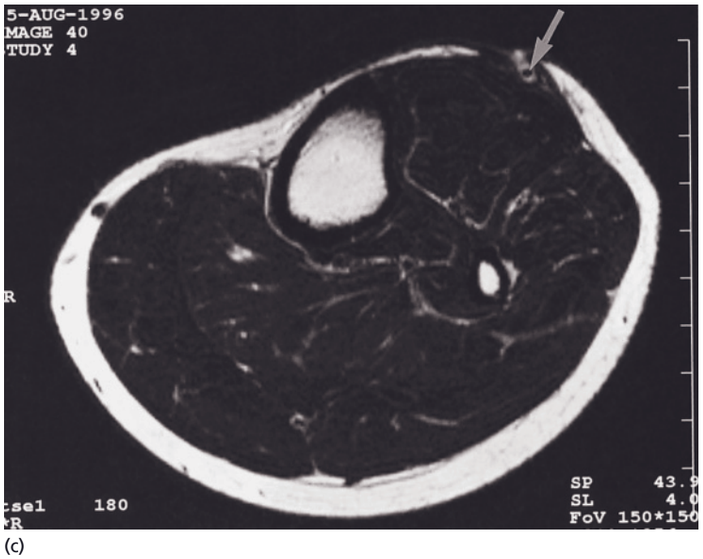
The best approach to remove a foreign body will depend on the size, location and nature of the material, and length of time it has been there. A simple method for locating a radio-opaque foreign body is to insert two or three needles of different sizes angled at 90° to each other. Using radiographs in multiple projections, ultrasound or CT, the needle closest to the foreign body is identified, and tissue dissected along its path [17]. It may be possible to pull out the foreign body intact, or slide out a long pointed object along the axis it entered. Material likely to be dealt with by the dermatologist may often be excised as a block of tissue.



(a)



(b)



(c)

Fig. 28.15 Foreign-body reaction caused by deeply embedded thorn. The patient presented with a chronic leg ulcer. (a) Thorn that eventually emerged spontaneously. (b) Mixed inflammatory and granulomatous reaction from the ulcer bed. (c) Magnetic resonance imaging scan showing sinus tract containing the thorn (in cross-section, at tip of arrow).

Table 28.6 Indications for removal of a foreign body. (Adapted from Lammers and Magill [16].)

Reactivity of the material (e.g. thorns, spines, clothing)
Heavy bacterial contamination (e.g. teeth, soil)
Toxicity (e.g. spines with venom, heavy metals)
Proximity to tendons, vessels, nerves or fractured bone
Impairment of mechanical function (e.g. abnormal gait from foreign body in foot)
Intra-articular location
Potential for migration towards an important anatomical structure
Intravascular location
Persistent pain
Established infection or inflammation
Allergic reaction
Cosmetic or psychological considerations

After removal, the wound should be irrigated and débrided if necessary. If the foreign body was radio-opaque, and there is any doubt about completeness of removal, a post-operative film can be carried out.

References

1 Zimmerli W, Zak O, Vosbeck K. Experimental haematogenous infection of subcutaneously implanted foreign bodies. *Scand J Infect Dis* 1985; **17**: 303–10.
2 Kim YC, Triffet MK, Gibson LE. Foreign bodies in sarcoidosis. *Am J Dermatopathol* 2000; **22**: 408–12.
3 Saw P, Solivan G, Johnson FB. Cutaneous reaction from a broken thermometer. *J Am Acad Dermatol* 1991; **25**: 915–9.
4 Kelly JJ. Blackthorn inflammation. *J Bone Joint Surg* 1966; **48B**: 474–7.
5 Paproski SM, Smith SL, Crawford RI. Ferruginous foreign body. A clinical stimulant of melanoma with distinctive histologic features. *Am J Dermatopathol* 2002; **24**: 396–8.
6 Mucci B, Stenhouse G. Soft tissue radiography for wooden foreign bodies: a worthwhile exercise? *Injury* 1985; **16**: 402–4.
7 Lammers RL. Soft tissue foreign bodies. *Ann Emerg Med* 1988; **17**: 1336–46.
8 Gilbert FJ, Campbell RSD, Bayliss AP. The role of ultrasound in the detection of non-radio-opaque foreign bodies. *Clin Radiol* 1990; **41**: 109–12.
9 Donaldson JS. Radiographic imaging of foreign bodies in the hand. *Hand Clin North Am* 1991; **7**: 125–34.
10 Suramo I, Pamil M. Ultrasound examination of foreign bodies: an *in vitro* investigation. *Acta Radiol Diagn* 1986; **27**: 463–6.
11 De Flaviis Scaglione P, Del Bo P *et al*. Detection of foreign bodies in soft tissues: experimental comparison of ultrasonography and xeroradiography. *J Trauma* 1988; **28**: 400–4.
12 Russell RC, Williamson DA, Sullivan JW *et al*. Detection of foreign bodies in the hand. *J Hand Surg* 1991; **16**: 2–11.
13 Jaworsky C. Analysis of cutaneous foreign bodies. *Clin Dermatol* 1991; **9**: 157–78.
14 Bloom W, Fawcett DW. *A Textbook of Histology*, 10th edn. Philadelphia: Saunders, 1975: 21–30.
15 Baker D, Kupke KC, Ingram P *et al*. Microprobe analysis in human pathology. *Scan Electron Microsc* 1985; **2**: 659–80.
16 Lammers RL, Magill T. Detection and management of foreign bodies in soft tissues. *Emerg Med Clin North Am* 1992; **4**: 767–81.
17 Rickoff SE, Bauder T, Kerman BL *et al*. Foreign body localization and retrieval in the foot. *J Foot Surg* 1981; **20**: 33–4.

Some distinctive foreign-body reactions

Paraffinoma

Synonym
- Sclerosing lipogranuloma

Some vegetable oils containing triglyceride can be digested by lipases, but others, and mineral oils, greases and wax, cannot be broken down, and elicit a foreign-body reaction. Most instances of paraffinoma nowadays are caused by misguided attempts at tissue augmentation, often self-administered. The male genitalia is the most common site [1]; other sites include the male breast [2], gluteal regions and extremities. Paraffin gauze that was used to pack the nasal passages and sinuses has caused chronic inflammatory paraffinoma of the periorbital tissues [3,4]. A study of 11 patients with periocular deposition of petrolatum-based material demonstrated a range of iatrogenic causes, including ointment being applied to the eyelid skin, to the canaliculi and to the ethmoid cavities following surgery [5].

The pathology of paraffinoma shows rounded clear spaces of varying sizes surrounded by fibrous tissue and a mixed inflammatory reaction, including foamy macrophages and multinucleated giant cells—the 'Swiss cheese' appearance. A study of paraffinomas of the female breast has reported magnetic resonance imaging appearances which can reliably distinguish a mass caused by paraffin injection from a breast cancer [6].

Treatment is by excision.

References

1 Claudy A, Garcier F, Schmitt D. Sclerosing lipogranuloma of the male genitalia: ultrastructural study. *Br J Dermatol* 1981; **105**: 451–6.

2 Basse P, Alsbjorn B. Paraffinoma of the male breast. *Acta Chir Plast* 1991; **33**: 163–5.

3 Feldman R, Harms M, Chavaz P *et al*. Orbital and palpebral paraffinoma. *J Am Acad Dermatol* 1992; **26**: 833–5.

4 Hintschich CR, Beyer-Machule CK, Stefani FH. Paraffinoma of the periorbit: a challenge for the oculoplastic surgeon. *Ophthalm Plast Reconstr Surg* 1995; **11**: 39–43.

5 Merkur AB, Jardeleza MS, Illiff NT *et al*. Periocular petrolatum. *Ophthal Plast Reconstr Surg* 2005; **21**: 23–30.

6 Khong PL, Ho LWC, Chan JHM, Leong LLY. MR imaging of breast paraffinomas. *Am J Radiol* 1999; **173**: 929–32.

Polyvinyl pyrrolidone

This hydrophilic polymer, formerly used as a plasma expander, is still used as a slow-release agent in a few injectable medications. Occasionally, it can produce a soft-tissue mass, often after a long latent period [1]. The material appears as a distinctive blue-grey deposit in macrophages with little or no inflammation or fibrosis. Using Congo red, polyvinyl pyrrolidone (PVP) stains a cherry-red colour [2].

References

1 Kossard S, Ecker RI, Dicken CH. Povidone panniculitis. *Arch Dermatol* 1980; **116**: 704–6.

2 Feiman DG, Gall EA. A staining method for the detection of poly-vinylpyrrolidone (PVP) in tissue sections. *Am J Clin Pathol* 1955; **25**: 1427–9.

Hydroxyethyl starch pruritus

Hydroxyethyl starch (HES) is a plasma expander. It is widely used in intensive care units, and to improve the microcirculation in some otological and peripheral vascular diseases. Pruritus is a well-recognized complication, with a frequency of more than 30% in some European retrospective series [1,2] and 13% in a UK questionnaire survey [3], although in a large prospective study the incidence was only 1% [4]. HES is deposited in the skin.

The pruritus usually begins between a few days and several months (typically within a few weeks) after the infusion. It is usually generalized, although can be localized (e.g. to the trunk or anogenital regions). Bouts of itching can be triggered by friction, bathing in warm water and physical exertions. HES pruritus is often severe and can last years. Usually there are no visible signs, but a single case has been described of diffuse erythematous skin infiltration [5].

HES is degraded in the plasma, taken up by histiocytes in many tissues including skin, and cleared through the kidneys. In the skin, HES accumulates in vacuoles within macrophages, which if abundant can resemble a storage disorder [5]. The vacuoles may also be seen in endothelial cells and basal epithelial cells. The identity of HES can be confirmed using specific immunostaining [6]. Only in patients who develop pruritus, the characteristic vacuoles are also seen in the various components of peripheral nerve cells, and resolution of itching is associated with eventual loss of the vacuoles [7].

It is not clear why only some patients given HES develop pruritus. In several series there is a threshold cumulative dose of approximately 200 g, although there is no close relationship to the volume given [3]. Patients with otological disease may be more susceptible than other groups [4]. Tissue storage is greater in those who develop pruritus [8].

The mechanism for pruritus is uncertain, although direct stimulation of cutaneous nerves by the deposits of HES has been proposed [9].

Treatment is unsatisfactory. The pruritus is unresponsive to oral antihistamines, topical or systemic corticosteroids and phototherapy, although topical capsaicin has some therapeutic value [9]. In most cases the pruritus resolves after 6–18 months.

References

1 Schneeberger R, Albegger K, Oberascher G, Miller K. Pruritus: a side effect of hydroxyethyl starch? First report. *HNO* 1990; **38**: 298–303.

2 Gall H, Kaufmann R, von Ehr M *et al.* Persistierender pruritus nach hydroxyathylstarke-infusionen. Retrospektive langzeitstudie an 266 Fellen. *Hautarzt* 1993; **44**: 713–6.

3 Murphy M, Carmichael AJ, Lawlor PG, White M, Cox NH. The incidence of hydroxyethyl starch-associated pruritus. *Br J Dermatol* 2001; **144**: 973–6.

4 Grochenig E, Albegger K, Dieterich HJ *et al.* Hydroxyethyl starch-related pruritus: a prospective multicentre investigation of 544 patients. *Perfusion* 1998; **11**: 62–9.

5 Cox NH, Popple AW. Persistent erythema and pruritus, with a confluent histiocytic skin infiltrate, following the use of a hydroxyethyl starch plasma expander. *Br J Dermatol* 1996; **134**: 353–7.

6 Stander S, Szepfalusi Z, Bohle B *et al.* Differential storage of hydroxyethyl starch (HES) in the skin: an immunoelectron-microscopical long-term study. *Cell Tissue Res* 2001; **304**: 261–9.

7 Metze D, Reimann S, Szepfalusi Z *et al.* Persistent pruritus after hydroxyethyl starch infusion therapy: a result of long-term storage in cutaneous nerves. *Br J Dermatol* 1997; **136**: 553–9.

8 Sirtl C, Laubenthal H, Zumtobel V *et al.* Tissue deposits of hydroxyethyl starch (HES): dose-dependent and time-related. *Br J Anaesth* 1999; **82**: 510–5.

9 Szeimes RM, Stolz Wlotzke U *et al.* Successful treatment of hydroxyethyl starch-induced pruritus with topical capsaicin. *Br J Dermatol* 1994; **131**: 380–2.

Sclerodermiform reaction to vitamin K and vitamin B_{12} injections

The intramuscular injection of preparations of vitamin K has been followed by an erythematous plaque in the lumbosacral area,

which takes on a dusky colour and becomes infiltrated and itchy after 10–15 days. After some months, it resembles a patch of scleroderma, ivory-white in colour with a surrounding lilac ring. Confluence of plaques in the trochanteric and lumbosacral area produces the so-called 'cowboy's belt' appearance, complete with holsters. The distribution of these changes reflects the sites of vitamin K injections. A case has been reported of similar changes occurring on the upper arms, where intramuscular injections of vitamin K had been administered [1]. Histopathology demonstrated dermal and pannicular sclerosis [1]. A case resembling eosinophilic fasciitis has also been described [2]. All the nine cases studied by Texier [3] had received other vitamins, liver extract or iron injections and no case resulted from vitamin K alone, but this ingredient was a common factor. There is a tendency for sclerotic reactions to resolve slowly following withdrawal of vitamin K injections [1,4]. Intradermal testing with vitamin K produced erythema and induration at 2 days in one reported case [4].

Localized sclerodermoid skin reactions have also been reported occurring at the site of intramuscular injections of vitamin B_{12} [5,6].

References

1 Alonso-Llamazares J, Ahmed I. Vitamin K-induced localised scleroderma (morphea) with linear deposition of IgA in the basement membrane zone. *J Am Acad Dermatol* 1998; **38**: 322–4.
2 Janin-Mercier A, Mosser C, Souteyrand P. Subcutaneous sclerosis with fasciitis and eosinophilia after phytonadione injection. *Arch Dermatol* 1985; **121**: 1421–3.
3 Texier L. Hypodermite sclérodermiforme lombo-fessière induite par injection de vitamin K1. *Bull Soc Fr Dermatol Syphiligr* 1975; **82**: 448–9.
4 Guidetta MS, Vincenzi C, Papi M, Tosti A. Sclerodermatous skin reaction after vitamin K injections. *Contact Dermatitis* 1994; **31**: 45–6.
5 Manduit G, Cambazard F, Faure M, Thivolet J. Pseudoscleroderma and sclerodermiform states. *Ann Intern Med* 1984; **135**: 615–23.
6 Ho J, Rothchild YH, Sengelmann R. Vitamin B12-associated localized scleroderma and its treatment. *Dermatol Surg* 2004; **30**: 1252–5.

Pentazocine ulcers (Fig. 28.16)

A distinctive woody induration with overlying ulceration is characteristic of repeated intramuscular or subcutaneous use of the analgesic pentazocine (Table 28.5) [1]. Such reactions are usually found in narcotic abusers. Longstanding changes occurring around major joints can lead to myofibrosis with contractures [2].



Fig. 28.16 Pentazocine ulcers.

References

1 Prasad HRY, Khaitan BK, Ramam M *et al*. Diagnostic clinical features of pentazocine-induced ulcers. *Int J Dermatol* 2005; **44**: 910–5.
2 Jain A, Bhattacharya SN, Singal A *et al*. Pentazocine induced widespread cutaneous and myo-fibrosis. *J Dermatol* 1999; **26**: 368–70.

Immunization granulomas

Temporary nodule formation at the site of immunization procedures may occur and usually subsides quickly. A more persistent granulomatous reaction resulting from the aluminium hydroxide component has been described [1] and may have an allergic basis in some cases [2,3]. This reaction has been found after administration of tetanus–diphtheria–pertussis [2,3], influenza [4,5] or hepatitis B [6] vaccines and after desensitization therapy with allergen extracts. A pure histiocytic foreign-body reaction is often observed in early lesions, whereas a delayed hypersensitivity granulomatous reaction is seen in older lesions. Although patch tests may be positive to aluminium [2], there is no relationship between patch-test results and the histopathological pattern [6]. A study of 14 cases of persistent injection reactions revealed a range of pathological changes including fibrosis, fat necrosis, non-specific panniculitis and a pseudolymphomatous infiltrate, in which lesional tissue contained lymphoid follicles with germinal centres [7]. Other cases demonstrated features suggestive of deep granuloma annulare with necrobiosis and pallisaded histiocytes [7]. X-ray microanalysis has shown the presence of abundant aluminium in the histiocytes [7,8]. In a series of 21 cases followed for up to 8 years, five cleared, improvement occurred in 11 and five were unchanged [3]. Patients known to have such reactions should in future receive non-adsorbed vaccines or toxoids [9].

References

1 Garcia-Patos V, Pujol RM, Alomar A *et al*. Persistent subcutaneous nodules in patients hyposensitized with aluminium-containing allergen extracts. *Arch Dermatol* 1995; **131**: 1421–4.
2 Cox NH, Moss C, Forsyth A. Allergy to non-toxoid constituents of vaccines and implications for patch testing. *Contact Dermatitis* 1988; **18**: 143–6.
3 Kaaber K, Nielsen AO, Veien NK. Vaccination granulomas and aluminium allergy: course and prognostic factors. *Contact Dermatitis* 1992; **26**: 304–6.
4 Fawcett HA, Smith NP. Injection-site granuloma due to aluminium. *Arch Dermatol* 1984; **120**: 1318–22.
5 Orell AR. Subcutaneous granulomata following inoculation of influenza vaccine. *Acta Pathol Microbiol Immunol Scand* 1962; **56**: 127–34.
6 Cosnes A, Flechet ML, Revuz J. Inflammatory nodular reaction after hepatitis B vaccination due to aluminium sensitization. *Contact Dermatitis* 1990; **23**: 65–7.
7 Chong H, Brady K, Metze D, Calonje E. Persistent nodules at injection sites (aluminium granuloma)—clinicopathological study of 14 cases with a diverse range of histological reaction patterns. *Histopath* 2006; **48**: 182–8.
8 Slater DN, Underwood JCE, Durrant TE *et al*. Aluminium hydroxide granulomas: light and electron microscopic studies and X-ray microanalysis. *Br J Dermatol* 1982; **107**: 103–8.
9 Cox NH, Moss C, Forsyth A. Cutaneous reactions to aluminium in vaccines: an avoidable problem. *Lancet* 1988; **ii**: 43.

Angiolymphoid hyperplasia with eosinophilia

(see Chapter 56)

This has also been associated with tetanus toxoid inoculation [1].

Reference

1 Akosa AB, Ali MH, Khoo CTK, Evans DM. Angiolymphoid hyperplasia with eosinophilia associated with tetanus toxoid vaccination. *Histopathology* 1990; **16**: 589–93.

Zinc-induced insulin granuloma

A distinctive granulomatous response to zinc-insulin has been described [1] in which there is an acute neutrophilic response before granuloma formation. Other cutaneous and subcutaneous adverse effects of insulin preparations are discussed in Chapter 75. Use of a non-zinc insulin usually results in resolution.

Reference

1 Jordaan HF, Sandler M. Zinc-induced granuloma: a unique complication of insulin therapy. *Clin Exp Dermatol* 1989; **14**: 227–9.

Intralesional corticosteroids

Occasionally, deposits of injected insoluble corticosteroids have been associated with a granulomatous response [1,2] and in one instance a reaction resembling rheumatoid nodule has been described [2]. Other adverse effects of intralesional corticosteroids are discussed in Chapter 45.

References

1 Goldman L. Reactions following intralesional and sublesional injections of corticosteroids. *JAMA* 1962; **182**: 613–6.

2 Weedon D, Gutteridge BH, Hockly RG, Emmett AJJ. Unusual cutaneous reactions to injections of corticosteroids. *Am J Dermatopathol* 1982; **4**: 199–203.

Silicone

Silicone (polydimethyl siloxane) is used medically in three forms: liquid for soft-tissue augmentation, bag-gel implants for augmentation mammoplasty, and as a solid elastomer in joint prostheses. In tissues, it has a characteristic of tending to migrate both locally and via lymphatics. Many of the reported adverse effects are likely to have been a result of adulterants, although even medical grade silicone can produce a granulomatous reaction [1,2]. The possible role of silicones in the aetiology of scleroderma and other connective tissue diseases is discussed in Chapter 51.

When silicone bag-gel material ruptures, it can migrate along fascial planes and gravitate into the skin, producing indurated inflammatory subcutaneous masses [3].

Following liquid or gel silicone injections, the histological appearance is of varying sized vacuoles similar to paraffinoma, but with less fibrosis and usually an absence of granulomatous response if medical grade silicone was used [4]. Sometimes, however, granulomatous reactions do occur [5], including cases of multiple silicone-containing granulomas at the site of entry of acupuncture needles coated in silicone oil [6,7]. A case has been reported of widespread granulomatous papules developing many years after liquid silicone injection into the face [8]. In the facial lesions, silicone was demonstrated by EDXA, while extra-facial lesions did not contain foreign material but were histologically consistent with sarcoidosis [8]. It was suggested that the granulomatous response to silicone in this case occurred as a manifestation of sarcoidosis [9].

If adulterants are present, a more inflammatory reaction is described. Particles of rubbery silicone elastomer can elicit a vigorous foreign-body granulomatous response.

The Si–C chemical bond, characteristic of silicone and not found in nature, can be detected by infrared spectroscopy, and silicon can be demonstrated by EDXA.

Silicone reactions can only be eliminated by appropriate surgery, although amelioration of the inflammatory response by treatment with minocycline has been reported [10].

References

1 Ellenbogen R, Ellenbogen R, Rubin L. Injectable fluid silicone therapy: human morbidity and mortality. *JAMA* 1975; **234**: 308–9.

2 Morgan AM. Localized reaction to injected therapeutic materials. *J Cutan Pathol* 1995; **22**: 289–303.

3 Teuber SS, Feilly DA, Howell L *et al*. Severe migratory granulomatous reactions to silicone gel in three patients. *J Rheumatol* 1999; **26**: 699–704.

4 Selmanovitz VJ, Orentreich N. Medical-grade fluid silicone: a monographic review. *J Dermatol Surg Oncol* 1977; **3**: 597–611.

5 Brown SL, Silverman BG, Berg WA. Rupture of silicone-gel breast implants: causes, sequelae, and diagnosis. *Lancet* 1997; **350**: 1531–7.

6 Yanagihara M, Fujii T, Wakamatu N *et al.* Silicone granuloma on the entry points of acupuncture, venepuncture and surgical needles. *J Cutan Pathol* 2000; **27**: 301–5.

7 Alani RM, Busam K. Acupuncture granulomas. *J Am Acad Dermatol* 2001; **45**: 225–6.

8 Andrews TR, Calamia KT, Waldorf JC, Walsh JS. Subcutaneous nodules on the face. *Arch Dermatol* 2005; **141**: 93–8.

9 Marcoval J, Mana J. Silicone granulomas and sarcoidosis. *Arch Dermatol* 2005; **141**: 904.

10 Senet P, Bachelez H, Ollivaud L *et al.* Minocycline for the treatment of cutaneous silicone granulomas. *Br J Dermatol* 1999; **140**: 985–7.

Collagen implants and dermal fillers

Soft tissue augmentation uses a range of substances for both reconstructive and cosmetic purposes. Injectable filling agents are used cosmetically in an attempt to achieve facial rejuvenation without recourse to surgery. Certain fillers are also used to improve the contour defects caused by lipoatrophy, particularly in patients with HIV infection undergoing highly active antiretroviral therapy. The number of different fillers available is increasing continually and this is matched by a rise in the number of individuals seeking such interventions. Several studies and case reports have highlighted the side effects associated with injectable filling agents and it is crucial that dermatologists are aware of the risks associated with these products.

The agents used in tissue augmentation can be broadly divided into permanent, semi-permanent and temporary substances. Injectable temporary products, such as bovine collagen and pure hyaluronic acid, are rapidly absorbed and have a relatively short-term effect. Transient side effects to injected bovine collagen have been reported in 1.3% of patients [1], and skin testing prior to use on the face is therefore recommended. A study has demonstrated a positive skin test response in 3–3.5% of patients [2]. Of those who do not react to the test site, 1–3% will subsequently develop induration, which may progress to nodule formation [3]. When deposited in the dermis, bovine collagen appears microscopically as an amorphous eosinophilic material, less birefringent than normal collagen. When hypersensitivity reactions occur, there is a diffuse granulomatous reaction in the early stages and later the

response tends to be a palisaded granuloma, with an admixture of lymphocytes, plasma cells, eosinophils and neutrophils [4,5]. This can produce a superficial similarity to necrobiotic granulomas such as granuloma annulare. Special stains can be useful, for example colloidal iron, which stains the bovine collagen a strong magenta colour compared with the pink of normal collagen [3].

More recently, injectable hyaluronic acid derivatives have been developed for volume expansion and are now the most commonly used reabsorbable dermal fillers. Modified hyaluronic acid forming cross-linked polymer molecules generates a substance which is more insoluble and has a longer duration within the tissues. Restylane® is a partially cross-linked hyaluronic acid produced by bacterial fermentation, Hylaform® is a cross-linked hyaluronic acid processed from rooster combs, while Dermalive® is composed of 60% cross-linked hyaluronic acid vector and 40% acrylic hydrogel particles. New-Fill® is a semi-permanent filler composed of polylactic acid microspheres suspended in a mannitol and carbomethoxycellulose solution.

Local cutaneous adverse events have been reported with all the semi-permanent hyaluronic acid injectable fillers. Transient inflammatory reactions such as redness, swelling and pain have been reported by 3–5% of patients within 14 days following the first treatment and which disappear within 2–3 days [6,7].

A large study of Restylane® and Hylaform® identified delayed inflammatory skin reactions occurring with a prevalence of 0.42% [8]. The most commonly reported long-term adverse effect to Restylane® is indurated, inflammatory nodules at injection sites occurring 2–5 months after treatment [9–11]. Generally, histology of Restylane® lesions shows a foreign body granulomatous reaction [12]. In one case, scleromyxoedematous papules developed on the trunk and limbs after the initial local granulomatous response on the face [13]. There are a number of case reports of late granulomatous reactions to Dermalive® in which firm red lines and nodules occur at treatment sites 4–19 months after injection [14–17]. Granulomatous reactions are also seen with Hylaform® [18] and New-Fill® [19]. Permanent fillers include Artecoll®, which is made from polymethylmethacrylate microspheres in a solution of bovine collagen. Side effects to Artecoll® are thought to be rare, but patients may develop allergy to the bovine collagen and foreign body-type granulomatous reactions to the microspheres [20].

References

1 Watson W, Kaye RL, Klein AW *et al*. Injectable collagen: a clinical overview. *Cutis* 1983; **31**: 543–6.
2 Klein AW. Skin filling. Collagen and other injectables of the skin. *Dermatol Clin* 2001; **19**: 491–508.
3 Swanson NA, Stoner JG, Siegle RJ, Solomon AR. Treatment site reactions to Zyderm collagen implantation. *J Dermatol Surg Oncol* 1983; **9**: 377–80.
4 Stegman SJ, Chu S, Armstrong RA. Adverse reactions to bovine collagen implant: clinical and histologic features. *J Dermatol Surg Oncol* 1988; **14** (S): 39–48.
5 Barr RJ. Delayed skin test reaction to injectable collagen implant (Zyderm). *J Am Acad Dermatol* 1984; **10**: 652–8.
6 Duranti F, Salti G, Bovani B *et al*. Injectable hyaluronic acid gel for soft tissue augmentation. A clinical and histological study. *Dermatol Surg* 1998; **24**: 1317–25.
7 Manna F, Dentini M, Desideri P *et al*. Comparative chemical evaluation of two commercially available derivatives of hyaluronic acid used for soft tissue augmentation. *J Eur Acad Dermatol Venereol* 1999; **13**: 183–92.
8 Lowe NJ, Maxwell CA, Lowe P *et al*. Hyaluronic acid skin fillers: adverse reactions and skin testing. *J Am Acad Dermatol* 2001; **45**: 930–3.
9 Shafir R, Amir A, Gur E. Long-term complications of facial injections with Restylane (injectable hyaluronic acid). *Plast Reconstructr Surg* 2000; **106**: 1215–6.
10 Micheels P. Human anti-hyaluronic acid antibodies: is it possible? *Dermatol Surg* 2001; **27**: 185–91.
11 Honig JF, Brink U, Korabiowska M. Severe granulomatous allergic tissue reaction after hyaluronic acid injection in the treatment of facial lines and its surgical correction. *J Craniof Surg* 2003; **14**: 197–200.
12 Ghislanzoni M, Bianchi F, Barbareschi M, Alassi E. Cutaneous granulomatous reaction to injectable hyaluronic acid gel. *Br J Dermatol* 2006; **154**: 755–8.
13 Rongioletti F, Cattarini G, Sottofattori E, Rebora A. Granulomatous reaction after intradermal injections of hyaluronic acid gel. *Arch Dermatol* 2003; **139**: 815–6.
14 Sidwell RU, Dhillon AP, Butler PEM, Rustin MHA. Localized granulomatous reaction to a semi-permanent hyaluronic acid and acrylic hydrogel cosmetic filler. *Clin Exp Dermatol* 2004; **29**: 630–2.
15 Requena C, Izquierdo MJ, Navarro M *et al*. Adverse reactions to injectable aesthetic microimplants. *Am J Dermatopathol* 2001; **45**: 197–202.
16 Angus JE, Affleck AG, Leach IH, Millard LG. Two cases of delayed granulomatous reactions to the cosmetic filler Dermalive (R), a hyaluronic acid and acrylic hydrogel. *Br J Dermatol* 2006; **154**: 1077–9.
17 Vargas-Machuca I, Gonzalez-Guerra E, Anqulo J *et al*. Facial granulomas secondary to Dermalive microimplants. *Am J Dermatopathol* 2006; **28**: 173–7.
18 Raulin C, Greve B, Hartschuh W, Soegding K. Exudative granulomatous reaction to hyaluronic acid (Hyalaform). *Contact Dermatitis* 2000; **43**: 178–9.
19 Lombardi T, Samson J, Plantier F *et al*. Orofacial granulomas after injection of cosmetic fillers. Histopathologic and clinical study of 11 cases. *J Oral Pathol Med* 2004; **33**: 115–20.
20 Kim K-J, Lee H-W, Lee M-W *et al*. Artecoll granuloma: a rare adverse reaction induced by microimplant in the treatment of neck wrinkles. *Dermatol Surg* 2004; **30**: 545–7.

Fibreglass dermatitis

Reactions to glass fibre are usually caused by physical injury, although allergic contact dermatitis resulting from residual epoxy resin on the fibres has been described [1]. The fibres that cause reactions are generally greater than 4 μm in diameter [2]. Pruritus is very common and may occur with or without skin lesions, which, if present, usually consist of transient erythematous papules that are often follicular. The forearms, hands, face, neck and flexural folds are common sites. Covered sites can be affected because the fibres can penetrate clothing. Fair-skinned blue-eyed individuals seem to be more susceptible [3]. The fibres only penetrate the more superficial epidermis, yet the histopathological changes include subcorneal pustules, spongiosis and a mixed upper dermal infiltrate [4]. The mechanisms underlying these changes remain speculative. Glass fibres are often difficult to see in biopsy specimens but can be recovered by Scotch tape stripping and this may be of use in diagnosis [5].

With prolonged exposure, a form of hardening can occur, with the pruritus, but not the visible signs of dermatitis, reducing in intensity [3].

References

1 Dahlquist J, Fregert S, Trulsson L. Allergic contact dermatitis from epoxy resin finished glass fibre. *Contact Dermatitis* 1979; **5**: 190.
2 Possick PA, Gellin GA, Key MM. Fibreglass dermatitis. *Am Ind Hyg Assoc J* 1970; **31**: 12–5.
3 Bjornberg A. Fiberglass dermatitis. *Am J Ind Med* 1985; **8**: 395–400.
4 Bjornberg A, Lowhagen GB. Patch testing with mineral wool (rock-wool). *Acta Derm Venereol (Stockh)* 1977; **57**: 257–60.

5 Cuypers JMC, Hoedmaker J, Nater JP. The histopathology of fibre-glass dermatitis in relation to von Hebra's concept of eczema. *Contact Dermatitis* 1975; **1**: 88–95.

Complications of tattoos

The term tattoo, derived from the Tahitian *tatau* [1], is used for both the deliberate introduction of permanent colours into the skin through punctures, and for accidental entry of pigmented material [2]. The latter is common after abrasion injuries, for instance in cyclists and coal miners. Cases have been described of tattooing from close exposure to black gunpowder, as used in replica firearms [3]. Accidental tattooing from Monsel's solution or ferric chloride [4,5] provides rare iatrogenic causes. Tattooing can occur from contact with jewellery (e.g. earrings) [6]. The placement of tattoos for cosmetic reasons has increased in recent years; a US survey from 2004 showed that 24% of adults aged 18–50 years had at least one tattoo [7].

For body art, the most common method of tattooing uses an electric tattoo machine, in which a group of oscillating needles injects ink into the skin 80 to 150 times a second. Since tattoo instruments come in contact with blood, infectious diseases may be transmitted if appropriate precautions are ignored. A properly equipped tattoo studio will have a sharps container for used needles, biohazard containers and an autoclave for sterilizing equipment. In certain states in the USA, tattoo artists are required to pass a test of health and safety understanding to gain a licence. The potential infection risk has led to the prohibition of blood donation for 12 months after receiving a tattoo in the US (unless the procedure was done in a state-regulated and licensed studio) and for 6 months in the UK.

Modern tattooing inks are carbon-based pigments and have uses outside tattoo applications. Many of the brighter tattoo pigments available are derived from the plastic acrylonitrile butadiene styrene (ABS). ABS is ground down to particles less than 1 μm in diameter and these are introduced into tattoo inks to produce vivid colours which are less likely to fade. The traditional pigments are carmine, indigo, vermilion, India ink, chrome green, cobalt blue, cinnabar (red) and cadmium sulphide (yellow). Ferrous oxide is used to pigment the eyebrow area [8]. A study using energy-dispersive spectrometry analysed the constituents of 30 tattoo inks and found that the most commonly identified elements were aluminium, oxygen, titanium and carbon [9]. Histologically, tattoo pigments are refractile and found in macrophages and fibroblasts clustered around vessels in the upper and mid dermis [10]. Deposits of pigment can also be visualized between collagen bundles [10].

Immediately after tattooing there is a local traumatic response with formation of a scab. Although pyogenic infection as a post-procedure complication is generally uncommon, one US study identified unlicensed tattooists as the source of six unlinked clusters of community-acquired MRSA skin infection [11]. The tattooists were found to be using non-sterile equipment and poor infection-control procedures [11]. Hepatitis infection has been attributed to tattooing [12], however a US study was unable to identify an increased risk for hepatitis B or hepatitis C virus infection in low-risk adults who had received a tattoo [13]. In a study of 345 Brazilian subjects, a positive association between tattooing and hepatitis C infection was demonstrated but no relationship with respect to hepatitis B, HIV or syphilis [14]. Transmission of molluscum contagiosum [15] and of viral warts [16] by tattoos has been reported.

Aside from infectious complications, other adverse effects of tattoos include the induction of skin diseases via the Koebner phenomenon, such as lichen planus, psoriasis, Darier's disease and discoid lupus erythematosus. Sarcoidal granulomatous inflammation can also develop in tattoos and may occur in conjunction with systemic sarcoidosis [17–20]. Hypersensitivity reactions to the tattoo inks are most commonly seen with the red pigment cinnabar (mercuric sulphide) [21,22], but also with inks containing cobalt, chrome, manganese [23] and aluminium (purple) [24]. Histologically, there is a diffuse lymphohistiocytic infiltrate in the dermis with an admixture of plasma cells and eosinophils [9]. Other histological patterns reported include lichenoid reactions [25,26] and a pseudolymphomatous infiltrate [27,28]. B-cell lymphoma has been recorded as evolving from a tattoo-induced pseudolymphoma [29]. Abnormal photosensitivity in tattoos has been observed and is considered to be triggered by photoreaction to pigment containing cadmium yellow [30,31]. Perforating granuloma annulare can also complicate tattooing [32].

Traumatic tattooing (e.g. from an explosion) is amenable to laser treatment (e.g. with the erbium–YAG) [33]. The treatment of decorative tattoos is discussed in Chapters 77 and 78.

References

1 Mercer NSG, Davies DM. Tattoos: marked for life. *BMJ* 1991; **303**: 380.
2 Scutt R, Gotch C, eds. *Skin Deep*. London: Davies, 1974.
3 Hanke CW, Connor AC, Probst EL *et al.* Blast tattoos resulting from black powder firearms. *J Am Acad Dermatol* 1987; **17**: 819–25.
4 Camisa C, Roberts W. Monsel solution tattooing. *J Am Acad Dermatol* 1983; **8**: 753–4; *J Am Acad Dermatol* 1987; **17**: 819–25.
5 Olmstead PM, Lund HZ, Leonard DD. Monsel's solution: a histologic nuisance. *J Am Acad Dermatol* 1980; **3**: 492–8.
6 Kurban RS, Goldstein JA, Bhawan J. Earring-induced localised iron tattoo. *J Am Acad Dermatol* 1991; **24**: 788–9.
7 Laumann AE, Derick AJ. Tattoos and body piercings in the United States: a national data set. *J Am Acad Dermatol* 2006; **55**: 413–21.
8 Angres CG. Angres permalid-liner method: a new surgical procedure. *Ann Ophthalmol* 1984; **16**: 145–6.
9 Timko AL, Miller CH, Johnson FB, Ross E. In vitro quantitative chemical analysis of tattoo pigments. *Arch Dermatol* 2001; **137**: 143–7.
10 Goldstein AP. Histologic reactions in tattoos. *J Dermatol Surg Oncol* 1979; **5**: 896–900.
11 Centers for Disease Control and Prevention. Methicillin-resistant *Staphylococcus aureus* skin infections among tattoo recipients—Ohio, Kentucky and Vermont, 2004–2005. *Morb Mortal Wkly Rep* 2006; **55**: 677–9.
12 Limentani AE, Elliott LM, Noah ND *et al*. An outbreak of hepatitis B from tattooing. *Lancet* 1979; **ii**: 86–8.
13 Hwang LY, Kramer JR, Troisi C *et al*. Relationship of cosmetic procedures and drug use to hepatitis C and hepatitis B virus infection in a low-risk population. *Hepatology* 2006; **44**: 341–51.
14 de Nichioka SA, Gyorkos TW, Joseph L *et al*. Tattooing and transfusion-transmitted diseases in Brazil: a hospital-based cross-sectional matched study. *Eur J Epidemiol* 2003; **18**: 441–9.
15 Foulds I. Molluscum contagiosum, an unusual complication of tattooing. *BMJ* 1982; **285**: 607.
16 Ragland HP, Hubbell C, Steward KR, Nesbitt LT. Verruca vulgaris inoculated during tattoo placement. *Int J Dermatol* 1994; **33**: 796–7.
17 Kennedy C. Sarcoidosis presenting in tattoos. *Clin Exp Dermatol* 1976; **1**: 395–9.
18 Sowden JM, Cartwright PH, Smith AG *et al*. Sarcoidosis presenting with a granulomatous reaction confined to red tattoos. *Clin Exp Dermatol* 1992; **17**: 446–8.

19 McElvanney AM, Sherriff SMM. Uveitis and skin tattoos. *Eye* 1994; **8**: 602–3.
20 Landers MC, Skokan M, Law S, Storrs FJ. Cutaneous and pulmonary sarcoidosis in association with tattoos. *Cutis* 2005; **75**: 44–8.
21 Sowden JM, Byrne JPH, Smith AG *et al.* Red tattoo reactions: X-ray microanalysis and patch test studies. *Br J Dermatol* 1991; **124**: 576–80.
22 Mortimer NJ, Chave TA, Johnson GA. Red tattoo reactions. *Clin Exp Dermatol* 2003; **28**: 508–10.
23 Nguyen LQ, Allen HB. Reactions to manganese and cadmium in tattoos. *Cutis* 1979; **23**: 71–2.
24 McFadden N, Lyberg T, Hensten-Pettersen A. Aluminium-induced granulomas in a tattoo. *J Am Acad Dermatol* 1989; **20**: 903–8.
25 Clarke J, Black MM. Lichenoid tattoo reactions. *Br J Dermatol* 1979; **100**: 451–4.
26 Winkelman RK, Harris RB. Lichenoid delayed hypersensitivity reactions in tattoos. *J Cutan Pathol* 1979; **6**: 59–65.
27 Blumenthal G, Okun MD, Poritch JA. Pseudolymphomatous reactions to tattoos. *J Am Acad Dermatol* 1982; **6**: 485–8.
28 Rijlarsdam JU, Bruynzeel DP, Vos W *et al.* Immunohistochemical studies of lymphadenosis benigna cutis occurring in a tattoo. *Am J Dermatopathol* 1988; **6**: 518–23.
29 Sangueza OP, Yadav S, White CR, Braziel RM. Evolution of B-cell lymphoma from pseudolymphoma. *Am J Dermatopathol* 1992; **14**: 408–13.
30 Bjornberg A. Reactions to light in yellow tattoos from cadmium sulphide. *Arch Dermatol* 1963; **88**: 267–71.
31 Golstein N. Mercury-cadmium sensitivity in tattoos. A photoallergic reaction in red pigment. *Ann Inten Med* 1967; **67**: 984–9.
32 Gradwell E, Evans S. Perforating granuloma annulare complicating tattoos. *Br J Dermatol* 1998; **139**: 926–7.
33 Kunzi-Rapp K, Krahn GM, Wortmann S, Peter RU. Early treatment of traumatic tattoo by erbium-YAG laser. *Br J Dermatol* 2001; **144**: 219–21.

Hair as a foreign body

Fragments of hair may penetrate the skin and cause a variety of reactions, according to the site and depth of penetration, ranging from slight erythema to the formation of abscesses and sinuses. Chronic reactions take the form of foreign-body granulomas, which may present as subcutaneous nodules or with hypertrophy of the overlying epidermis. The clinical syndromes encountered are very diverse and their cause is often unsuspected.

Barbers' hair sinus

Interdigital sinuses are common in men's barbers, presumably because of the short sharp hair fragments generated from cutting men's hair [1,2]. They also occur in female hairdressers [3] and those who cut animal hair [1]. The sinuses usually affect the first or third left or second right finger web. The lesions—tender nodules with a central sinus or intermittently discharging papules—are relatively inconspicuous and are often disregarded. Hair can also cause inflammation when implanted into the finger pulp [4] and beneath fingernails [5], probably when there is an abnormality of the nail or a pre-existing dermatosis [6].

Hair sinuses of the feet

Hair fragments may penetrate the skin of the feet. Long, curved hairs embedded in the toes or ankles have been recorded in ladies' hairdressers [7]. Deeper penetration may provoke tender nodules or abscesses.

A distinctive syndrome, seldom recognized, may follow the penetration by a hair of the toe-cleft skin, usually the fourth. The patient complains of pain and tenderness, which is usually attributed to other causes. There is oedema of the dorsum of the foot above the involved cleft. A pinhole sinus is found beneath the accumulated interdigital debris. Surgical excision may be necessary. The hair-thread tourniquet syndrome may also involve the feet (see below).

Creeping hair

Loose, individual hairs can penetrate the skin and migrate superficially, producing a wave-like linear erythema with the hair at the leading end. This eruption has been called 'creeping hair' and clinically resembles cutaneous larva migrans. Two reported cases have involved pubic hairs penetrating lower abdominal or pubic skin and migrating along Langer's lines to the iliac region [8,9]. The hair can be easily removed by extracting through a shallow incision.

Milker's sinuses

Milker's sinuses are now uncommon but are more disabling. Fragments of cow hair may penetrate deeply, involving even the tendon sheaths. Secondary infection often follows, sometimes by dermatophytes [10]. Most lesions involve the second or third web of the right hand, forming tender nodules and discharging sinuses [11]. Recurrent episodes of cellulitis follow. Spontaneous cure may eventually take place, but may be so long delayed that surgical intervention is advisable.

Anogenital pilonidal sinus

Anogenital pilonidal sinus is discussed more fully in Chapter 71. Some cases are of developmental origin but many follow the penetration of the skin by hair(s) by the root-end, through the action of the cuticular cells. The sinus itself does not have hair follicles. The penetrating hair(s) may cause a foreign-body giant cell reaction, sometimes with secondary bacterial infection, which can cause a sudden onset of pilonidal abscess. In addition to the primary track resulting from the initiating hair(s), there may be secondary tracks opening from the cavity. Presentation is usually as a midline opening or series of openings in the natal cleft about 5 cm from the anus. Pilonidal disease usually starts at the onset of puberty. Males are affected much more commonly than females. The peak age of onset is 15–24 years and it is rare over the age of 45 [12]. It occurs more commonly in individuals with stiff dark or auburn hair.

Half of affected patients present as emergencies with an acute pilonidal abscess; the remainder have chronic fluctuating discomfort associated with a foul-smelling discharge from one or more sinus openings [12]. Examination reveals the characteristic opening in the natal cleft (Fig. 28.17) through which a tuft of hair is often seen emerging.

There is no uniform approach to management. A small sinus can sometimes be treated by removal of the hairs and regular shaving of the surrounding skin. A phenol injection technique has been used, either alone, with curettage or combined with excision [12]. Most patients are treated either by excision and primary closure [13], or by laying open and healing by secondary intention or repair with skin flaps [14]. Primary closure or flap repair produces more rapid healing and shorter time off work [14,15]; wound breakdown after suturing may be lessened by prophylactic use of clindamycin [16]. Modifications of direct closure can be used to flatten the natal cleft and thereby reduce the risk of recurrence

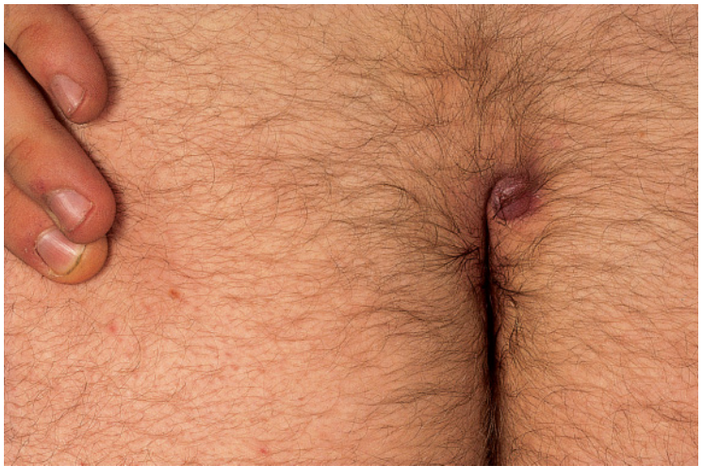


Fig. 28.17 Pilonidal sinus.

[17], but there may be greater morbidity if such techniques fail [12].

A pilonidal abscess is probably best treated by incision, drainage, curettage of hair and granulation tissue, and leaving open for secondary intention healing.

Squamous cell carcinoma has been described as a rare complication of pilonidal sinus [18,19]. The high rate of metastasis and mortality in reported cases indicates that pilonidal sinus-related squamous cell carcinoma tends to be aggressive [20,21].

Miscellaneous hair-filled sinuses

The penis can occasionally be the site for a pilonidal sinus-like lesion [22]. Pain, tenderness and discharge in the umbilicus has been associated with the presence of hair, perhaps in association with a hirsute abdomen and poor umbilical hygiene [23]. A hair sinus originating on the chin has resulted in loss of a tooth resulting from penetration of the sinus through into the incisor tooth socket [24]. Trauma was reported to account for a hair sinus over the mandible [25]. Hair sinuses of the areola of the breast [26–28] are discussed further in Chapter 70.

Hair-thread tourniquet syndrome

A foreign-body reaction to hair and hair-like fibres has been described following the encirclement of fingers, toes and the penis, usually as an accidental event [29] but also as an instance of child abuse. The affected area presents as a dusky swelling, sometimes with focal discharge, and the hair may be completely buried and only evident after surgery [30]. Removal of the constricting fibre is usually sufficient to solve the problem [29,31].

Pseudofolliculitis barbae

This foreign-body reaction to the ingrowth of obliquely cut, often tightly curled hair causes an eruption of erythematous papules in the beard area [32,33]. It is especially common in dark-skinned races. Stretching of the skin and shaving against the 'lie' of the hair increases the tendency. The pubic hair has also been involved. A similar condition has been described in Iraqi women who pluck the hairs of their legs, leaving some broken stumps which curl back into the follicle [34]; 'pseudofolliculitis vibrissae' [35] represents a variant caused by close cutting of nasal hairs, that may be confused with perforating folliculitis of the nose.

Preventive measures include discontinuing shaving and the use of a clipper to maintain a beard hair length of 1 mm.

Treatment is generally unsatisfactory; reported symptomatic remedies include topical retinoids, α-hydroxyacids and antibiotics. Depilation techniques modify the physical trigger in pseudofolliculitis barbae, and laser hair removal may offer the best approach thus far [36,37].

Complications of artificial hair implantation

Although the use of synthetic fibres implanted in the scalp has been known for many years to produce severe foreign-body reactions [38–40], baldness sufferers continue to undergo implantation procedures with synthetic materials. Although some fibres, such as polyester, have been promoted as less liable to produce reactions [41], chronic purulent foreign-body reactions remain a typical consequence [42,43].

References

1 Price SM, Popkin GL. Barbers' interdigital hair sinus. *Arch Dermatol* 1976; **112**: 523–4.
2 Donahue JR, Donahue JK Jr, Surmay JN *et al*. Interdigital sinuses of barber's hands. *J Med Soc New Jersey* 1978; **75**: 598–600.
3 Adams CI, Petrie PWR, Hooper G. Interdigital pilonidal sinus in the hand. *J Hand Surg* 2001; **26B**: 53–5.
4 Grant I, Mahaffey PJ. Pilonidal sinus of the finger pulp. *J Hand Surg* 2001; **26**: 490–1.
5 Hogan DJ. Subungual trichogranuloma in a hairdresser. *Cutis* 1988; **42**: 105–6.
6 de Berker D, Dawber R, Wojnarowska F. Subungual hair implantation in hairdressers. *Br J Dermatol* 1994; **130**: 400–1.
7 Schroder CM, Merk HF, Frank J. Barber's hair sinus in a female hairdresser: uncommon manifestion of an occupational dermatosis. *J Eur Acad Dermatol Venereol* 2006; **20**: 209–11.
8 Sakai R, Higashi K, Ohta M *et al*. Creeping hair: an isolated hair burrowing in the uppermost dermis resembling larva migrans. *Dermatol* 2006; **213**: 242–4.
9 Lehmuskallio EA. Hair fragments in the skin resembling larva migrans. *Br J Dermatol* 1975; **93**: 349–51.
10 Meneghini CL, Gianotti F. Granulomatosis fistulosa of milkers' hands. *Dermatologica* 1964; **128**: 38–50.
11 Stolp A. Interdigitale pilonidale Sinus an beiden Händen. *Dermatol Monat* 1970; **156**: 16–22.
12 Jones D. Pilonidal sinus. *BMJ* 1992; **305**: 409–12.
13 Akinci OF, Coskun A, Ozgonul A, Terzi A. Surgical treatment of complicated pilonidal disease: limited separate elliptical excision with primary closure. *Colorectal Dis* 2006; **8**: 704–9.
14 Khawaja HT, Bryan S, Weaver PC. Treatment of natal cleft sinus: a prospective clinical and economic evaluation. *BMJ* 1992; **304**: 1282–3.
15 Aydede H, Erhan Y, Sakarya A, Kumkumoglu Y. Comparison of three methods in surgical treatment of pilonidal disease. *J Surg* 2001; **71**: 362–4.
16 Kronberg U, Christensen KI, Zimmermann-Nielson O. Chronic pilonidal disease: a randomised trial with complete 3-year follow-up. *Br J Surg* 1986; **72**: 303–4.
17 Akinci F. Simple and effective surgical treatment of pilonidal sinus. *Dis Colon Rectum* 2000; **43**: 701–7.
18 Bark T. Squamous-cell carcinoma in a pilonidal sinus. *Acta Chir Scand* 1986; **152**: 703–4.
19 Borges VF, Keating JT, Nasser IA *et al*. Clinicopathologic characterization of squamous-cell carcinoma arising from pilonidal disease in association with condylomata acuminatum in HIV-infected patients. *Dis Colon Rectum* 2001; **44**: 1873–7.
20 De Bree E, Zoctmulder FA, Christodoulakis M *et al*. Treatment of malignancy arising in pilonidal disease. *Ann Surg Oncol* 2001; **8**: 60–4.

21 Matsushita S, Ohtake N, Mochitomi Y *et al*. A case of squamous cell carcinoma arising in a pilonidal sinus. *J Dermatol* 2002; **29**: 757–8.
22 Lingam MK, Hayes M, Mackay C. Pilonidal sinus of the penis. *Br Urol* 1996; **78**: 642–58.
23 Botelho RJ. Acute umbilical sepsis. *J Fam Pract* 1989; **29**: 205–9.
24 Mitchell DA. A bizarre facial sinus. *Dent Update* 1994; **21**: 303–4.
25 O'Sullivan MJ, Kirwan WO. Post-traumatic pilonidal sinus of the face. *Br J Dermatol* 2000; **143**: 1319–59.
26 Bowers PW. Roustabouts and barbers' breasts. *Clin Exp Dermatol* 1982; **7**: 445–8.
27 Gannon MX, Crowson MC, Fielding JWL. Periareolar pilonidal abscesses in a hairdresser. *BMJ* 1988; **297**: 1641–2.
28 Ferdinand RD, Sciott DJ, McLean NR. Pilonidal cyst of the breast. *Br J Surg* 1996; **84**: 781–4.
29 Barton DJ, Sloan GM, Nichter LS, Reinisch JF. Hair-thread tourniquet syndrome. *Pediatrics* 1988; **83**: 1007–8.
30 Collins AG. Hair-thread syndrome. *Australas J Dermatol* 1990; **31**: 117–8.
31 Liow RYL, Budny P, Regan PJ. Hair thread touniquet syndrome. *J Accid Emerg* 1996; **13**: 138–9.
32 Alexander AM, Delph WI. Pseudofolliculitis barbae in the miltary: a medical, administrative and social problem. *J Natl Med Assoc* 1974; **66**: 459–64.
33 Perry PK, Cook-Bolden FE, Rahman Z *et al.* Defining pseudofolliculitis barbae in 2001: a review of the literature and current trends. *Am Acad Dermatol* 2002; **46**: 113–9.
34 Dilaimy M. Pseudofolliculitis of the legs. *Arch Dermatol* 1976; **112**: 507–8.
35 White SW, Rodman OG. Pseudofolliculitis vibrissa. *Arch Dermatol* 1981; **117**: 368–9.
36 Weaver SM, Sagaral EC. Treatment of pseudofolliculitis barbae using the long-pulse Nd:Yag laser on skin types V and VI. *Dermatol Surg* 2003; **29**: 187–91.
37 Ross EV, Cooke LM, Timko AL *et al*. Treatment of pseudofollicultis barbae in skin types IV, V, VI with long-pulsed Neodymium:yttrium aluminium garnet laser. *J Am Acad Dermatol* 2002; **47**: 263–70.
38 Hanke GW, Bergfeld WF. Fiber implantation for pattern baldness. *JAMA* 1979; **241**: 146–8.
39 Lepaw I. Therapy and histopathology of complications from synthetic fiber implants for hair replacement. *J Am Acad Dermatol* 1980; **3**: 195–204.
40 Hanke CW, Bergfeld WF. Fiber implantation for pattern baldness: a review of complications in 41 patients. *J Am Acad Dermatol* 1981; **4**: 278–83.
41 Taniguchi S. A histopathological study of the percutaneous implantation of polyester fibers. *Aesthetic Plast Surg* 1984; **8**: 67–74.
42 Sheill RC, Kossard S. Problems associated with synthetic fibre implants for hair replacement ('NIDO' process) (Letter). *Med J Aust* 1990; **152**: 560.
43 Kelly RI, Marsden RA. Complications of artificial hair implantation. *J R Soc Med* 1994; **87**: 291–2.

Other penetrating injuries

Reactions to ornamental metal piercing

Piercing of body parts with metal ornaments and jewellery is a tradition in many societies, and may have originated in the Hindu religion. In Western societies piercing has predominantly been confined to the earlobes but in recent decades piercing of other sites, notably the nose, tongue, lips, nipples, navel and genitalia, has become commonplace. A variety of genital piercings are encountered, for example the 'Prince Albert' or 'dressing ring' which penetrates the urethra and was said to be used to secure the penis inside tight fitting trousers in Victorian times [1].

In general, complications are frequent but, unless serious, do not come to the attention of specialists. They include redness and swelling, exudation, minor infection, bleeding and, less often, cyst formation, significant tears and scars. A survey of students in a US university found a prevalence of body piercing of 51%, with medical complications in 17% and 58/315 (18%) of piercings having been removed (although the survey had less than 15% response) [2]; navel piercings were particularly prone to infection. Allergic contact dermatitis, usually to nickel, is also common.

Much of the data on complications from piercing in relation to ears is discussed in Chapter 68. A large survey from the USA demonstrated that 14% of adults aged 18–50 years had a non-earlobe body piercing [2]. Mild, local infective or inflammatory complications, including metal allergy, occurred in 23% [3]. A survey of individuals with mouth jewellery identified a number of common problems, especially tooth chipping with tongue piercing and traumatic gingival recession with lip piercing [4].

Serious infective complications of body piercings can be life-threatening. Bacterial endocarditis has been reported with nose [5] and tongue [6] piercing in patients with normal valves; there may be an increased incidence of endocarditis in individuals with abnormal cardiac valves [7]. *Pseudomonas aeruginosa* causing necrotizing chondritis has been reported as a complication of high ear piercing [8]. Intraoral cellulitis requiring ventilation and surgical intervention has occurred following tongue piercing [9] and Fournier's gangrene after genital piercing [10]. An adolescent developed fatal staphylococcal-mediated toxic shock syndrome 2 weeks after nipple piercing performed by a friend [11]. Lack of attention to sterility may also lead to transmission of hepatitis and HIV [12].

Granulomatous reactions as a result of ear piercing with gold jewellery are recognized [13]. In one report of granulomatous inflammation in a lobe piercing investigators were able to identify the component metal particles (titanium, aluminium, vanadium) in macrophages using environmental scanning electron microscopy with energy dispersive spectroscopy [14].

Unlike ear piercing, nose boring does not seem to be particularly associated with hypertrophic scar or keloid formation but is often followed by a self-limiting type of pyogenic granuloma-like capillary proliferation [15]. The nose piercing clasp can become embedded in a mass of granulation tissue, necessitating surgical intervention [16].

Significant trauma is particularly a feature of body piercing through genitalia (e.g. urethral rupture after insertion of a Prince Albert ring) [17].

It is sometimes necessary to remove a body piercing, for example because of infection, local tissue damage or the need for a radiological investigation. Removal depends on the design of the piercing. There are three basic designs: the barbell stud in which a straight bar has a threaded ball on each end; the labret stud in which the threaded ball is on one end only, and the captive bead ring, which consists of a bead held 'captive' by tension from both sides of an incomplete ring. Removal is usually straightforward once the design is appreciated [18].

References

1 Koenig LM, Carnes M. Body piercing: medical concerns with cutting edge fashion. *J Gen Intern Med* 1999; **14**: 379–85.
2 Mayers LB, Judelson DA, Moriarty BW, Rundell KW. Prevalence of body art (body piercing and tattooing) in university undergraduates and incidence of medical complications. *Mayo Clin Proc* 2002; **77**: 29–34.
3 Laumann AE, Derick AJ. Tattoos and body piercings in the United States: a national data set. *J Am Acad Dermatol* 2006; **55**: 413–21.

4 De Moor RJ, De Witte AM, Delme KI *et al*. Dental and oral complications of lip and tongue piercings. *Br Den J* 2005; **199**: 506–9.
5 Ramage IJ, Wilson N, Thomson RB. Fashion victim: infective endocarditis after nasal piercing. *Arch Dis Child* 1997; **77**: 187.
6 Lick SD, Edozic SN, Woodside KJ, Conti VR. Streptococcus viridans endocarditis from tongue piercing. *J Emerg Med* 2005; **29**: 57–9.
7 Ochsenfahrt C, Friedl R, Hannekum A *et al*. Endocarditis after nipple piercing in a patient with a bicuspid valve. *Ann Thorac Surg* 2001; **71**: 1365–6.
8 Sandhu A, Gross M, Wylie J *et al*. Pseudomonas aeruginosa necrotising chondritis complicating high helical ear piercing. *Can J Public Health* 2007; **98**: 74–7.
9 Perkins CS, Meissner J, Harrison JM. A complication of tongue piercing. *Br Dent J* 1997; **182**: 147–8.
10 Ekelius L, Bjorkman H, Kalin M, Fohlman J. Fournier's gangrene after genital piercing. *Scand J Infect Dis* 2004; **36**: 610–2.
11 Bader MS, Hamodat M, Hutchinson J. A fatal case of *Staphylococcus aureus*: associated toxic shock syndrome following nipple piercing. *Scand J Infect Dis* 2007; **39**: 741–3.
12 Pugatch D, Milerno M, Rich JD. Possible transmission of human immunodeficiency virus type 1 from body piercing. *Clin Infect Dis* 1998; **26**: 767–78.
13 Armstrong DK, Walsh MY, Dawson JF. Granulomatous contact dermatitis due to gold earrings. *Br J Dermatol* 1997; **136**: 776–8.
14 High, WA, Ayers RA, Adams JR *et al*. Granulomatous reaction to titanium alloy: an unusual reaction to ear piercing. *J Am Acad Dermatol* 2006; **55**: 716–20.
15 Premulatha S, Thambiah AS. Pyogenic granuloma following the trauma of nose boring. *Br J Dermatol* 1979; **100**: 455–8.
16 Watson MG, Campbell JB, Pahor AL. Complications of nose piercing. *BMJ* 1987; **294**: 1262.
17 Higgins SP, Estcourt CS, Bhattacharvya MN. Urethral rupture in a homosexual male following avulsion of a Prince Albert penile ring. *Int J STD AIDS* 1995; **6**: 54–5.
18 Khanna R, Kumar SS, Raju BS, Kumar AV. Body piercing in the accident and emergency department. *J Accid Emerg Med* 1999; **16**: 418–21.

Titanium implants

Bone-anchored skin-penetrating titanium implants are now a well-established method for securing auricular and other facial prostheses and hearing aids. There can be secondary infection with *Staphylococcus aureus* [1], and occasionally untreated reactions at the skin interface can lead to loss of osteo-integration [2]. Although most patients have no adverse cutaneous reaction to this procedure, inflammation does occur in about 10% [3]. Even in clinically normal skin around such implants, there is an increase in B lymphocytes, presumably because of the breach of skin barrier function by virtue of the passage through it of the titanium to the bone beneath [4], and the cellular components for a T-cell-mediated hypersensitivity response may be present to the same degree as happens with stainless steel implants, even though a clinically evident allergic event does not take place [5].

References

1 Gitto CA, Plata WG, Schaaf NG. Evaluation of the peri-implant epithelial tissue of percutaneous implant abutments supporting maxillofacial prostheses. *Int J Oral Maxillofac Implants* 1994; **9**: 197–206.
2 Reyes RA, Tjellstrom A, Granstrom G. Evaluation of implant losses and skin reactions around extraoral bone-anchored implants: a 0–8 year follow-up. *Otolaryngol Head Neck Surg* 2000; **122**: 272–6.
3 Jacobsson M, Tjellstrom A, Fine L, Andersson H. A retrospective study of osseointegrated skin-penetrating titanium fixtures used for retaining facial prostheses. *Int J Oral Maxillofac Implants* 1992; **7**: 523–8.
4 Holgers KM, Thomsen P, Tjellstrom A, Bjursten LM. Immunohistochemical study of the soft tissue around long-term skin-penetrating titanium implants. *Biomaterials* 1995; **16**: 611–6.
5 Thewes M, Kretschmer R, Gfesser M *et al*. Immunohistochemical characterization of the perivascular infiltrate cells in tissues adjacent to stainless steel implants compared with titanium implants. *Arch Orthop Trauma Surg* 2001; **121**: 223–6.

Skin lesions in drug addicts

The skin is the tissue most prominently affected by intravenous drug addiction. A wide range of cutaneous complications are seen and may occur as a direct result of injection into veins or arteries, from subcutaneous deposition of the drug, and as a consequence of dissemination of the drug or contaminants in the injection fluid [1]. Skin changes have also been described when addictive drugs have been taken by routes other than an injection. One study of drug addicts attending a specialist clinic found that 86% of subjects had cutaneous complications of their IV drug abuse [2].

The drug addict will seldom disclose his or her addiction during a routine skin examination and therefore the dermatologist should be aware of the more common stigmata of drug abuse. Puncture scars in a linear distribution over a vein, or parallel to it, were seen in all of 54 addicts examined [3]. A study has demonstrated the typical progression in the use of venous access sites over time, starting at the antecubital fossae followed by the upper arms and then the hands [4]. As accessible veins become sclerosed the addict will use veins in the neck, feet, legs, groins, digits and even the penis [4]. When all veins have been destroyed, addicts may inject subcutaneously or intramuscularly (known as 'skin popping') or use arteries. The granulation tissue of chronic ulcers can also be used as a site of injection [5]. Post-inflammatory hyperpigmentation occurs at sites of injections; more specifically 'soot tattooing' may occur from flamed needles. Thrombosed subcutaneous veins can be felt as fibrous cords and oedema is a common occurrence when most of the vessels in an extremity have been damaged. Circular scars are characteristic of skin popping. Decorative and sometimes informative tattoos may be found over injection sites in intravenous drug abusers.

Cutaneous infections are a common complication of IV drug abuse. Abscesses, cellulitis and necrotizing lesions occur frequently; one study of intravenous drug users found that 11% of subjects reported having at least one abscess in the past 6 months [6]. Most bacterial infections are caused by the subject's own skin flora, with *Staphylococcus aureus* and streptococcus species being the most common pathogens [7]. A number of factors contribute to skin infection, including contamination of drugs, non-sterile equipment, lack of aseptic technique, HIV-positivity, intradermal injection and 'booting' (repeatedly flushing and pulling back during injection) [8]. Injecting 'speedballs' (a mixture of cocaine and heroin) is a recognized risk factor for skin abscesses; it has been suggested that the vasoconstrictive effect of cocaine may enhance the risk of skin sepsis [9]. Other bacterial pathogens isolated in skin infections include Gram-negative and anaerobic organisms, which may originate from the mouth since drug addicts are known to use saliva as a skin cleanser and as a drug diluent. An epidemic of wound botulism occurred in California during the 1990s in conjunction with increased use of black-tar heroin, a form of heroin produced in Mexico [10]. Patients had injected the drug subcutaneously, suggesting the combined role of skin popping and the type of heroin in heightening the risk of wound botulism. There has also been a cluster of tetanus cases in England among drug users, suggesting contamination of drugs with *Clostridium tetani* [11]. Necrotizing fasciitis due to clostridial infection is also seen in injectors of black-tar heroin [12].

Necrotizing ulcers and cutaneous necrosis may develop as a result of a range of factors including skin popping, irritant properties of drug or adulterant, thrombosis and infection. Cutaneous necrosis may also result from intra-arterial injection. Use of this route is accompanied by post-injection pain, oedema and cyanosis [13]. Mechanisms for vascular injury include vasoconstriction (especially with cocaine or amphetamine) and particles within the injected drug acting as emboli. Free-base cocaine ('crack') taken by inhalation has been associated with acrocyanosis, severe necrotizing livedo reticularis and muscle infarction [14].

Injections of the analgesic drug pentazocine may cause ulceration, panniculitis, sclerosis and hyperpigmentation [15]. Methadone, commonly prescribed to manage opiate addiction, is most frequently dispensed as a syrup taken orally, but tablets and an injectable solution are also available. Extensive skin fibrosis and ulceration has been described in a patient who injected methadone several times daily for several years [16].

A syndrome brought about by systemic candidiasis, presenting with purulent nodules in the scalp and follicular pustules in other hair-bearing areas, tenderness over various bones and cartilages and distinctive eye lesions, has been described in intravenous heroin addicts [17]. This unusual candidal infection has been attributed to the use of lemon juice as a solvent for the drug and has also occurred with buprenorphine dissolved in juice from a 'plastic lemon' [18]. The skin itself may, however, be the source of *Candida albicans*, the profuse sweating associated with heroin usage and drug-related immunosuppression contributing to the follicular localization of the skin lesions and the pattern of dissemination that occurs [19].

Itching at the site of the injection or in the centre of the face is a common initial effect of heroin, but passes off after 2–3 weeks on the drug. Parasthesiae from cocaine or methyl amphetamine may lead to excoriation and scarring. Such findings would be significant in a young patient in whom scabies has been excluded. Piloerection is a well-known feature of the opiate abstinence syndrome.

In South Africa, a distinctive brown staining of the palmar surface of the first finger web is associated with smoking cannabis by means of a broken-off bottle neck [20].

The anabolic and androgenic steroids are liable to abuse in athletes and body builders, and should be considered in cases of seborrhoea, acne, hirsutism and striae distensae when appropriate [21].

A papular and pustular facial eruption has been attributed to *N*-methyl-3,4-methylenedioxyamphetamine (MDMA)—'ecstasy pimples' [22].

References

1 Del Guidice P. Cutaneous complications of intravenous drug abuse. *Br J Dermatol* 2004; **150**: 1–10.

2 Weidman AI, Fellner MJ. Cutaneous manifestations of heroin and other addictive drugs. *N Y State J Med* 1971; **71**: 2643–6.

3 Vollum DI. Skin lesions in drug addicts. *BMJ* 1970; **2**: 647–50.

4 Darke S, Ross J, Kaye S. Physical injecting sites among injecting drug users in Sydney, Australia. *Drug Alcohol Depend* 2001; **62**: 77–82.

5 Abidin MR, Gillinov MA, Topol BM *et al*. Injection of illicit drugs into the granulation tissue of chronic ulcers. *Ann Plast Surg* 1990; **24**: 268–70.

6 Vishov D, Sullivan M, Astemborski J, Nelson KE. Bacterial infections and skin cleaning prior to infection among intravenous drug users. *Public Health Rep* 1992; **107**: 595–8.

7 Gordon RJ, Lowy FD. Bacterial infections in drug users. *New Engl J Med* 2005; **353**: 1945–54.

8 Murphy EL, DeVita D, Liu H *et al*. Risk factors for skin and soft tissue abscesses among drug users: a case control study. *Clin Infect Dis* 2001; **33**: 35–40.

9 Spijkerman IJ, van Ameijeden EJ, Mientjes GH *et al*. Human immunodeficiency virus infection and other risk factors for skin abscesses and endocarditis among injection drug users. *J Clin Epidemiol* 1996; **49**: 1149–54.

10 Werner SB, Passaro D, McGee J *et al*. Wound botulism in California, 1951–1998: recent epidemic in heroin injectors. *Clin Infect Dis* 2000; **31**: 1018–24.

11 Akbulut D, Dennis J, Gent M *et al*. Wound botulism in injectors of drugs: upsurge of cases in England during 2004. *Euro Surveill* 2005; **10**: 172–4.

12 Dunbar NM, Harruff RC. Necrotising fasciitis: manifestations, microbiology and connection with black tar heroin. *J Forensic Sci* 2007; **52**: 920–3.

13 Maxwell TM, Olcott C, Blaisdell FW. Vascular complications of drug abuse. *Arch Surg* 1972; **105**: 875–82.

14 Zamora-Quezada JC, Dinermen H, Stadecker MJ *et al*. Muscle and skin infarction after free-basing cocaine (crack). *Ann Intern Med* 1988; **82**: 1275–6.

15 Palestine RF, Millns JL, Spigel JL, Schroeter AL. Skin manifestations of pentazocine abuse. *J Am Acad Dermatol* 1980; **2**: 47–55.

16 Farrant P, Creamer D, Fuller C. Extensive cutaneous fibrosis and ulceration caused by methadone injection. *Clin Exp Dermatol* 2005; **30**: 87–8.

17 Collingnon PJ, Sorrell TC. Disseminated candidiasis: evidence of a distinctive syndrome in heroin abusers. *BMJ* 1983; **287**: 861–2.

18 Hay RJ. Systemic candidiasis in heroin addicts. *BMJ* 1986; **292**: 1096.

19 Scheidegger C, Frei R. Disseminated candidiasis in a drug addict not using heroin. *J Infect Dis* 1989; **159**: 1007–8.

20 Lamont DL, Duflou JALC, Coates D. Dagga-smoker's hand: a new physical sign? *S Afr Med J* 1988; **44**: 30–5.

21 Scott MJ Jr, Scott MJ III. Dermatologists and anabolic-androgenic drug abuse. *Cutis* 1989; **44**: 30–5.

22 Wollina U, Kammler HJ, Hesselbarth N *et al*. Ecstasy pimples: a new facial dermatosis. *Dermatol* 1998; **197**: 171–3.

Skin hazards of swimming and diving

The increasing popularity of aquatic leisure activities has brought into prominence a wide variety of water-related dermatoses [1,2] (Table 28.7). Amateurs in underwater swimming and scuba diving are not always conversant with the hazards, particularly if these activities are carried out in unaccustomed waters on holiday.

General hazards

The hazards of UV radiation associated with swimming and aquatic sports are discussed in Chapter 29. People falling from boats into very cold water can die within minutes unless specially protected from heat loss. Prolonged immersion in warmer sea water can cause electrolyte imbalance by percutaneous absorption (immersion imbalance). Dry skin after swimming ('swimmer's xerosis') may in part be brought about by an osmotic gradient; other factors include dilution of sebum and use of soap afterwards [1]. The relationship of external otitis ('swimmer's ear') to water sports is discussed in Chapter 68. Cold urticaria and aquagenic urticaria and pruritus are discussed in Chapter 22.

Bacterial contamination from sewage disposal accounts for many cases of gastrointestinal disorders in swimmers using coastal resorts, even in the UK [3], and in those bathing in recreational rivers [4]. Skin infections resulting from faecal organisms may also be more common in contaminated rivers [3], and skin irritation

Table 28.7 Some water-related dermatoses.

General
Sunburn
Cold urticaria
Aquagenic pruritus
Dry skin (swimmer's xerosis)
Swimmer's ear (external otitis)
Contact reactions
Bathing costumes
Wetsuits
Snorkel masks, goggles, etc.
Fresh water
Swimming pools
Fungal infection, verrucae
Chlorine and bromine irritation
Chapping in atopics
Aquagenic acne
Green and blond discoloration of hair
Swimming pool granuloma
Jacuzzi/hot tubs
Pseudomonas folliculitis
Sauna
Miliaria
Tinea versicolor
Rivers, lakes
Cercarial itch
Trench foot
Streams
Onchocerciasis
Showers
Aquagenic pruritus
Sea water
Immersion syndrome
Algae dermatitis
Jellyfish and other venomous stings
'Sea-bather's eruption'
Coral abrasions and sea-urchin injuries
Surfer's nodules
Deep-sea diving
Otitis externa
Intertrigo
Staphylococcal infections
Scalds, flash burns
Abrasions from wetsuit folds
Pruritus, erythema (decompression)
Tropical (e.g. sponge divers)
Venomous bites and stings
Coral, sea urchin injuries

can occur from toxins released by blue–green algae in inland waters [3]. Occasionally skin infections acquired while bathing can be due to unusual organisms such as *Prototheca* [5]. 'Bikini bottom' is a nodular folliculitis of the inferior buttocks, probably caused more by poral occlusion from not changing out of a damp swimming costume than by specific pathogens [6].

Allergic contact dermatitis can occur, for example to bathing costume elastic or dyes, goggles, snorkel masks or mouthpieces [7]. Rarely, toxic leukoderma from use of goggles has been reported [8].

Traumatic conditions include 'surfer's knees', water-slap injuries on the anterior thighs of speed swimmers, rope burns on the extremities of water skiers [9], 'purpura gogglorum' caused by the effects of pressure and suction [10] and 'swimmer's shoulder'—an erythematous rough plaque caused by friction from the unshaven chin while swimming freestyle [11].

Swimming pools and whirlpools [12,13]

Swimming pools and similar aquatic environments can be associated with a number of dermatological problems. As well as those engaging in sports and leisure pursuits, others such as hydrotherapists can be affected [14]. Chlorine causes irritation in subjects with dry skin or atopic dermatitis. Contact urticaria from exposure to chlorinated pool water has also been described [15]. 'Aquagenic acne' is attributed to rebound hyperactivity of the sebaceous glands, an irritating effect of chlorine on pilosebaceous duct orifices and poral obstruction by overhydration [1]. Chemical conjunctivitis may occur if the subject swims with the eyes open. Bromine containing pool and spa water disinfectants are increasingly used and probably produce a similar risk for skin and eye irritation [16]. The use of communal changing room facilities may increase the risk of spread of verrucae and tinea pedis. *Mycobacterium marinum* infections are discussed in Chapter 31. The bleaching effect of chlorine may lighten the colour of hair if bathing and sun exposure are excessive. In competitive swimmers even black hair can become golden; mechanisms involved include damage to the cuticle, entry of hypochlorous acid and resultant damage to melanosomes [17]. Green tinting of hair may occur in blondes from frequent swimming in pools, probably because of exposure to copper-based algicides. Regular shampooing and 3% hydrogen peroxide lotion may decrease this effect [18,19].

Pseudomonas folliculitis and periporitis

Pseudomonas aeruginosa has been associated with outbreaks of folliculitis, mainly in those using whirlpools (Jacuzzis) and hot tubs, although in some cases the source has been indoor swimming pools [20–22]. Inflatable swimming pools may represent a particular hazard, even when the water in them is adequately disinfected, probably because they remain contaminated when collapsed [23]. *Pseudomonas aeruginosa* is able to withstand relatively high temperatures and high chlorine levels. The organism colonizes the over-hydrated stratum corneum of the follicular ostia. Symptoms usually appear 8–48 h after exposure, quite often with multiple members of a family being affected [24]. The rash is usually itchy and polymorphous, with erythematous macules, papules, vesicles and pustules. The areas most affected tend to be those covered by the bathing suit. The head and neck are rarely affected. There may be associated conjunctivitis, pharyngitis and, occasionally, swollen and painful breasts, abdominal symptoms and lymphadenopathy.

The term 'pseudomonas hot foot syndrome' was used to describe a distinctive painful nodular dermatosis on the soles of children who had been exposed to *P. aeruginosa* in a heated wading pool with a grit-coated floor [25]. Subsequently an outbreak of this condition has been described in 33 children using a hot tub at a pool party; painful palmar as well as plantar lesions were

described, and some cases had low-grade pyrexia [26]. The validity of some cases has been challenged, nodular eccrine hidradenitis of the feet being proposed as a differential diagnosis.

'Hot-tub dermatitis' is discussed further in Chapter 30. Acute external otitis, also usually caused by *Pseudomonas* infection, may occur concurrently.

Treatment is symptomatic. The problem usually clears spontaneously over 7–10 days.

Outdoor swimming

Sea bathing

Many hazards ranging from the trivial to the fatal can occur in seabathers [7]. These include the distinctive stings and other lesions inflicted by members of the phylum *Cnidaria*, which includes jellyfish, sea anemones, corals and hydroids [27]; 'seabather's eruption'; irritant and toxic contact reactions to seaweed, bryozoa (e.g. Dogger Bank itch), sponges, bristle worms, sea cucumbers and some fishes; physical injury from the scales of elasmobranch fish, such as dog fish and skate; lacerations from coral; suction injury by some ray fish; puncture wounds from sea urchins (Fig. 28.18) and some molluscs; and octopus bites and fish stings [28]. These aquatic injuries are all considered in detail in Chapter 38.

Two distinct pruritic papular dermatoses are associated with microscopic cercarial larvae in contaminated water, namely swimmer's itch, discussed here, and seabather's eruption (see Chapter 38).

Swimmer's itch [2,29–31]

This is an allergic response to the larvae of animal schistosomes for which humans are not the primary host. The biology is discussed further in Chapter 38. Swimmer's itch occurs 12–24 h after exposure to the larvae of animal schistosomes, usually in fresh water, although less often in salt water. Outbreaks are more common in the summer in temperate climates. The risk for getting the condition is increased by the time spent in the water and when there is an onshore wind [32].



Fig. 28.18 Sea-urchin granulomas. The nail discoloration is caused by potassium permanganate. (Courtesy of Bristol Royal Infirmary, Bristol, UK.)

The initial symptom may be a prickling sensation soon after leaving the water, corresponding to when the larvae penetrate the skin, and can last an hour or so. Erythematous macules appear 10–15 min after penetration, mainly on areas not protected by the swimming costume. If the individual is not sensitized to the cercariae, symptoms and signs subside in less than 12 h. In the sensitized, lesions evolve over 10–20 h into intensely itchy papules, which can coalesce into plaques. Itching and the papular eruption can last 1–2 weeks. In severe cases, usually those repeatedly exposed to cercariae, lesions may evolve into vesicles and pustules, and systemic symptoms such as headache and fever can occur.

The epidermis shows spongiosis with collections of neutrophils and eosinophils. Occasionally, biopsies taken within 48 h of the exposure may show cercariae in the outer epidermis [31,33].

Seabather's eruption, caused by cnidarians (see Chapter 38), may be similar, with pruritic papular lesions, but tends to maximally affect the skin covered by the swimsuit and only occurs in salt water. Other possibilities may include arthropod bites of various types and seaweed dermatitis.

Covering the skin, for example with a wetsuit, may be protective. Unfortunately application of various chemicals intended to prevent cercariae penetrating skin have proven ineffective [34]. Vigorous towelling down after swimming is said to reduce cercarial penetration. Topical steroid creams, and topical antipruritics such as 0.5% menthol or calamine lotion, may improve the pruritus.

Professional deep-sea diving [35]

A considerable experience has accumulated over the past three to four decades as a result of marine oil drilling, where divers may spend up to 90 days at considerable depths. These individuals live in close proximity, in a pressurized environment with a high partial pressure of oxygen, a high temperature and sometimes humidity exceeding 90%, conditions that favour *Pseudomonas* external otitis [36]. Longitudinal studies of the genotypes of isolates have indicated that relatively few are pathogenic, and the environment, particularly fresh water used for washing, etc., is more important than person-to-person transfer [37]. This problem may be preventable by good prophylactic hygiene, and by the use of aluminium acetate eardrops. Staphylococcal infections of the skin can also be troublesome within diving suits and are more likely to be transferred between individuals [38]. They often seem less amenable to antibiotic therapy than usual (perhaps because of the high temperature and humidity), and MRSA has recently been documented in this situation [38]. Scalds may occur from overheating of the diving suit, and flash burns from welding procedures are an occasional hazard. Skin squeezing at the folds of the suits may cause linear abrasions. During decompression, the diver may suffer from pruritus and erythema; a more severe lymphoedematous peau d'orange occasionally occurs. Furthermore, if the diver is underwater for a long time, the equivalent of a 'napkin eruption' can develop from micturition within the clothing.

References

1 Basler RS, Basler GC, Palmer AH, Garcia MA. Special skin symptoms seen in swimmers. *J Am Acad Dermatol* 2000; **43**: 299–305.
2 Burke WA, ed. Coastal and marine dermatology. *Dermatol Ther* 2002; **15**: 1–61.
3 Walker A. Swimming: the hazards of taking a dip. *BMJ* 1992; **304**: 242–5.
4 Ferley JP, Zmirou D, Balducci F *et al.* Epidemiological significance of microbiological pollution criteria for river recreational waters. *Int J Epidemiol* 1989; **18**: 198–205.
5 Qureshi HS, Dunne WM, Nakhleh RE. Pathologic quiz case. Unremitting ulcer in a scuba diver. *Arch Pathol Lab Med* 2001; **125**: 450–2.
6 Basler RSW, Basler DL, Basler GC, Garcia MA. Cutaneous injuries in women athletes. *Dermatol Nurs* 1998; **10**: 9–18.
7 Fisher AA. *Atlas of Aquatic Dermatology*. New York: Grune & Stratton, 1978.
8 Goette DK. Raccoon-like periorbital leukoderma from contact with swim goggles. *Contact Dermatitis* 1984; **10**: 129–31.
9 Spoor HJ. Sports identification marks. *Cutis* 1977; **19**: 453–6.
10 Jowett NI, Jowett SG. Ocular purpura in a swimmer. *Postgrad Med J* 1997; **73**: 819–20.
11 Koehn GG. Skin injuries in sports medicine. *J Am Acad Dermatol* 1991; **24**: 152.
12 Sarnaik AP, Vohra MP, Sturman SW *et al.* Medical problems of the swimmer. *Clin Sports Med* 1986; **5**: 47–64.
13 El Baze P, Ortonne JP. Les infections et les dermatoses acquises dans les piscines. *Ann Dermatol Vénéréol* 1991; **118**: 973–7.
14 Lazarov A, Nevo K, Pardo A, Froom P. Self-reported skin disease in hydrotherapists working in swimming pools. *Contact Dermatitis* 2005; **53**: 327–31.
15 Neering H. Contact urticaria from chlorinated swimming pool water. *Contact Dermatitis* 1977; **3**: 279–300.
16 Kelsall HL, Sim MR. Skin irritation in users of brominated pools. *Int J Environ Health Res* 2001; **11**: 29–40.
17 Nanko H, Mutoh Y, Atsumi R *et al.* Hair-discoloration of Japanese elite swimmers. *J Dermatol* 2000; **27**: 625–34.
18 Lampe RM, Henderson AC, Hansen GH. Green hair. *JAMA* 1977; **237**: 2092.
19 Goette DV. Swimmer's green hair. *Arch Dermatol* 1978; **114**: 127–8.
20 Washburn J, Jacobson JA, Marston E *et al. Pseudomonas aeruginosa* rash associated with a whirlpool. *JAMA* 1976; **235**: 2205–7.
21 Hopkins RS, Abbott DO, Wallace LE. Follicular dermatitis outbreak caused by *Pseudomonas aeruginosa* associated with a motel's indoor swimming pool. *Public Health Rep* 1981; **96**: 246–9.
22 Anon. Skin rash associated with pool exposure: Minnesota. *Morb Mortal Wkly Rep* 1975; **24**: 166–71.
23 Tate D, Mawer S, Newton A. Outbreak of *Pseudomonas aeruginosa* folliculitis associated with a swimming pool inflatable. *Epidemiol Infect* 2003; **130**: 187–92.
24 Silverman AR, Nieland ML. Hot tub dermatitis: a familial outbreak of *Pseudomonas folliculitis*. *J Am Acad Dermatol* 1983; **8**: 153–6.
25 Fiorillo L, Zucker M, Sawyer D, Lin AN. The pseudomonas hot-foot syndrome. *N Engl J Med* 2001; **345**: 335–8.
26 Yu Y, Cheng AS, Wang L *et al*. Hot tub folliculitis or hot hand-foot syndrome caused by *Pseudomonas aeruginosa*. *J Am Acad Dermatol* 2007; **57**: 596–600.
27 Burke WA. Cnidarians and human skin. *Dermatol Ther* 2002; **15**: 18–25.
28 Scharf MJ. Cutaneous injuries and envenomations from fish, sharks and rays. *Dermatol Ther* 2002; **15**: 47–57.
29 Hoeffler DF. 'Swimmers' itch' (cercarial dermatitis). *Cutis* 1977; **19**: 461–7.
30 Kirschenbaum MB. Swimmer's itch: a review and case report. *Cutis* 1979; **23**: 212–6.
31 Baird JK, Wear DJ. Cercarial dermatitis: the swimmer's itch. *Clin Dermatol* 1987; **5**: 88–91.
32 Verbrugge LM, Rainey JJ, Reimink RL, Blankespoor HD. Prospective study of swimmer's itch incidence and severity. *J Parasitol* 2004; **90**: 697–704.
33 Gonzalez E. Schistosomiasis, cercarial dermatitis, and marine dermatitis. *Dermatol Clin* 1989; **7**: 291–300.
34 Caumes E, Felder-Moinet S, Couzigou C *et al*. Failure of an ointment based on IR3535 (ethyl butylacetylaminopropionate) to prevent an outbreak of cercarial dermatitis during swimming races across Lake Annecy, France. *Ann Trop Med Parasitol* 2003; **97**: 157–63.
35 Hunter D, ed. *The Diseases of the Occupations*, 6th edn. London: Hodder and Stoughton, 1978: 618–31.
36 Alcock SR. Acute otitis externa in divers working in the North Sea: a microbiological survey of seven saturation dives. *J Hyg* 1977; **78**: 395–409.
37 Ahlen C, Mandal LH, Iversen OJ. The impact of environmental *Pseudomonas aeruginosa* genotypes on skin infections in occupational saturation diving systems. *Scand J Infect Dis* 2001; **33**: 413–9.
38 Wang J, Barth S, Richardson M *et al*. An outbreak of Methicillin-resistant *Staphylococcus aureus* cutaneous infection in a saturation diving facility. *Undersea Hyperb Med* 2003; **30**: 277–84.

Vibration

Vibration is defined as a repetitive movement about a point of equilibrium. Transmission of vibration energy to the skin has been associated with a number of chronic biological consequences, the best defined of which is the hand–arm vibration syndrome (HAVS) (see below and Table 28.8). It is also recognized that vibration can induce localized hyperhidrosis, callus formation, vibratory angioedema and a condition characterized by pain, swelling and erythrocyanosis [1]. Vibration may be a contributory factor to the hypothenar hammer syndrome (p. 28.26). Potentially beneficial effects have been ascribed to short-term exposure to vibration, such as elevation of skin temperature and increased lymphatic clearance [2]. The monographs by Griffin [3] and Pelmear *et al*. [4] deal comprehensively with the study of vibration and its medical consequences.

Table 28.8 Vibration injury: Stockholm Workshop Scales.

	Stages	Grade	Description
Vascular component	0V		No attacks
	1V	Mild	Occasional attacks affecting only the tips of one or more fingers
	2V	Moderate	Occasional attacks affecting distal or middle (rarely also proximal) phalanges of one or more fingers
	3V	Severe	Frequent attacks affecting all phalanges of most fingers
	4V	Very severe	As in stage 3, with trophic changes in the fingertips
Sensorineural	0 SN		Vibration-exposed but no symptoms
	1 SN		Intermittent numbness with or without tingling
	2 SN		Intermittent or persistent numbness, reduced to sensory perception
	3 SN		Intermittent or persistent numbness, reduced tactile descrimination and/or manipulative dexterity

Hand–arm vibration syndrome

Synonyms
- Vibration white finger
- Vibration syndrome

The term 'vibration white finger' has long been used for Raynaud's phenomenon resulting from the use of handheld vibratory tools. Recognition that there are also neurological and musculoskeletal consequences of vibration exposure in the exposed limb led to the now-preferred term hand–arm vibration syndrome (HAVS) [5–8]. Vibration-related changes can also occur in the feet [9].

Aetiology. Almost any vibratory source within the range 4–5000 Hz can produce HAVS if sufficiently intense. The time of exposure to vibrations may be as little as 1 month to more than 30 years, but increased exposure is associated with an increased risk; a longitudinal study of Swedish car mechanics showed a prevalence of vibration white finger rising from 15% to 25% after 20 years' exposure [10]. There are numerous variables that determine whether or not the condition occurs [11]. Some relate to the equipment, some to the environment and others to the individual [12]. Thus, low ambient temperature, firm gripping of the equipment and smoking are risk factors [13,14]. Under experimental conditions a vibration frequency of 125 Hz has been shown to induce greater changes in finger circulation than lower or higher frequencies [15]. A study of vibration transmission at various frequencies has shown that, at low frequencies (<25 Hz), energy absorption into the palms is greater than into the fingers, but is similar at higher frequencies (>100 Hz) [16]. The same study demonstrated that vibration energy absorption by fingers is independent of the type of hand–handle coupling [16]. There is some evidence to suggest that exposure to intermittent vibration has a less severe effect than continuous vibration [17]. Existing vascular disease and vasoconstrictive medications may be risk factors in some cases [18]. HAVS tends not to occur in hot climates; a study of quarry workers in Vietnam found no evidence of vibration white finger amongst rock drill operators [19].

The most common tools causing HAVS are percussive metalworking machines, such as riveting and fettling tools, drills, impact wrenches, jack hammers, road-breaking tools and chainsaws. In many other occupations there is some risk, albeit less well studied [20]. In high-risk occupations, the incidence and prevalence can be 90% or more [10,21]. The condition has even been described in a teenager making prolonged use of a hand-held vibrating computer game [22].

Prevalence. In the UK approximately 500 000 workers are exposed to vibration and of these about 20 000 suffer moderate to severe HAVS [7].

Pathophysiology and pathology. There are vascular and neurological changes. There may also be changes in connective tissues and in the blood, the latter probably occurring secondary to endothelial damage.

The initial events are not well understood [23]. The following documented changes are likely to be important: mechanoreceptor nerve endings and non-medullated fibres become damaged [24], there is a more generalized loss of neuronal activity than in primary Raynaud's phenomenon [25] and there is selective damage to α_1-adrenergic receptors in vessels causing an excessive vasoconstrictor response from the predominant α_2-receptors [13,26,27]. There is also a reduction of cutaneous nerve fibres which express calcitonin gene-related peptide, a powerful vasodilator [28]. An ultrastructural study of forearm skin biopsies demonstrated a significant reduction in epidermal nerve density in workers exposed to hand-transmitted vibration compared with controls [29]. Nerve conduction velocity along the distal part of the radial nerve is reduced in patients with vibration white finger when compared with normal controls, again identifying a putative neurogenic pathophysiology [30]. Other structural neural changes noted include loss of myelin, increased numbers of Schwann cells and fibrosis [31].

Vascular lumina are reduced, probably by both internal thickening and smooth muscle hypertrophy [24,32–34]. There is an increase in fibrous tissue within and around blood vessels [35] and arterial thrombosis can occur [36]. Laser Doppler flowmetry studies demonstrated a longer time to maximal reactive hyperaemia after a standard provocation in vibration white finger compared to primary Raynaud's phenomenon, a finding that suggests the involvement of arterial occlusive disease in addition to microcirculatory vasospasm [37]. An *in vivo* study has demonstrated that there is a decreased vasodilator response in finger skin of patients with vibration white finger when challenged with histamine and endothelin-1 [38]. These findings are in contrast to asymptomatic vibration-exposed workers who showed normal responses to both mediators, while patients with primary Raynaud's disease had a normal histamine-induced flare, but a reduced vasodilatation with endothelin-1 [38]. Soluble intercellular adhesion molecule 1 (ICAM-1) levels are increased, as in scleroderma, suggesting that neutrophils may adhere and contribute to the microvascular damage [39]. Whole-blood viscosity may be elevated [40], although the importance of this is uncertain.

A generalized abnormality in the autonomic nervous system [41] may cause orthostatic hypotension [42] and vasoconstriction of limbs not directly exposed to vibration [43]. There is an association with hearing loss in vibration white finger which is not explained purely by occupational exposure to noise [44]. Auditory impairment may be caused by ischaemia in the inner ear [45], via damage to the central nervous system [46] and exacerbated by the effects of vibration on the autonomic nervous system [47,48].

As well as damage to nerves, there is evidence of damage to muscles, especially the intrinsic muscles of the hand [49]. Bone cysts have been described in HAVS but may be a coincidental finding and not purely a result of vibration injury [50].

Clinical features. There are three possible major components to the HAVS: circulatory, neural and musculoskeletal [51].

After a highly variable latent period, the initial symptom is usually tingling and/or numbness in one finger. This often occurs directly after using the vibrating tool and also at night. This sensory change is followed by episodes of blanching, initially of

the tip of the finger most exposed to the vibration source, with progression towards the base, and then increasing numbers of digits are affected. The thumb below the tip is usually spared. The pattern of digits affected reflects the subject's grip on the tool and extent of involvement increases with cumulative vibration exposure. Attacks are usually precipitated by cold and sometimes damp conditions, most common early in the morning and during rest periods rather than work. However many patients experience attacks which are unprovoked and unpredictable. The attacks may last 15–120 min followed by painful reactive hyperaemia. With progression of the disease there is reduction in touch sensation, and difficulty doing fine manual work. Muscle fatigue and weakness are common, probably because of incomplete muscle contraction.

Late in the disease, attacks of pallor wane but there is persistent dusky cyanosis, swelling and stiffness of the digits and focal areas of necrosis of the fingertips. When the latent period is short, the symptoms and signs of HAVS tend to be more severe and more rapidly progressive.

The toes can be affected, either directly (e.g. from exposure to a vibrating platform) or by reflex sympathetic spasm.

Other changes attributed to vibration injury include carpal tunnel syndrome [52,53], although this may be more a result of mechanical and ischaemic factors [54].

Patients with HAVS should be staged as part of the assessment of their disability, for each hand separately. The Stockholm Workshop Scales [5,55] are most widely used (Table 28.8).

Diagnostic tests. The diagnosis of HAVS is based on a history of vibration exposure before the onset of symptoms, and exclusion of other causes of Raynaud's phenomenon, such as primary Raynaud's disease, thoracic outlet syndrome, syringomyelia, spinal cord compression, collagen vascular disease, peripheral vascular disease and vasoconstrictive drugs [6,56,57].

A variety of tests have been used in diagnosis and assessment of vascular, neurological and musculoskeletal abnormalities [57,58]. For the purposes of assessing a claim for industrial injury compensation, certain tests may be regarded as the most reliable [59]. Thus, in the UK the following are recommended: finger systolic blood pressure following cooling, to assess vascular abnormalities; either vibrometry or aesthesiometry, for neurological dysfunction; and grip strength [60,61]. These tests are likely to be available only in centres specializing in evaluation of HAVS. In general, a reduced finger systolic blood pressure following cooling is indicative of vibration white finger, whereas zero finger systolic blood pressure suggests Raynaud's phenomenon [62]. Laser Doppler fluxmetry can be used to assess skin blood flow after cold provocation and can discriminate between vibration white finger patients who demonstrate significantly lower perfusion compared with controls [63].

Even with a battery of tests it may be difficult to determine which patients will benefit from carpal tunnel release [64].

Prognosis. Early stages of HAVS are reversible, but advanced stages in patients over 45 years are irreversible and may progress despite withdrawal from vibration [2,65]. One observational study demonstrated that 43% of patients with stage 2 vibration white finger at first examination and 70% of patients with stage 3 still suffered from finger blanching attacks 15 years after presentation [66]. However, if measures are taken early in the course of disease, improvement is possible [67].

Treatment. It is important to maintain central body temperature and to avoid allowing the hands to become cold. Mittens are preferable to gloves. Smoking should be strongly discouraged. If possible, further vibration exposure should be avoided; if this is not feasible, frequent work breaks should be allowed.

Calcium-channel antagonists such as nifedipine can help the vascular symptoms. Other drugs that may be useful include α-adrenoreceptor antagonists such as thymoxamine and some prostanoids. A case report has indicated a positive response to iloprost infusions in a patient with severe hand–arm vibration syndrome [68]. Other remedies used in Raynaud's syndrome are given in Chapter 51. Sympathectomy is not generally effective.

Prevention. Because the more advanced stages of HAVS are irreversible, preventive measures and surveillance of at-risk workers are widely regarded as essential. Various steps can be taken to reduce exposure, for example automation [69], shorter shifts, anti-vibration gloves and pads on the tools. Much effort has been made to redesign equipment so as to reduce vibration [70,71] and the need for excessive grip strength. In a large Finnish study of forestry workers, vibration white finger decreased from 13% to 4% over a 19-year period during which time anti-vibration chainsaws were introduced [72]. Workers should be informed of the hazards of their occupation, and should wear warm antivibratory gloves, avoid smoking and undergo regular medical surveillance. It is best for those at risk to avoid medications that can cause vasoconstriction (e.g. β-blockers).

Current industry standards in the USA and Europe are reviewed in [73].

Other vasomotor symptoms

A condition in which pain, swelling and erythrocyanosis is induced by high-speed electrical tools (frequency 166–833 Hz) was described many years ago [1]; this syndrome is not provoked by exposure to cold.

Vibratory angio-oedema

Unlike the other dermatological phenomena induced by vibration, vibratory angio-oedema tends to occur at low frequencies (approximately 10 Hz) [74], such as are produced by handling a power lawnmower, or by rubbing or towelling the skin. The condition may be quite common among mountain bikers [75]. Vibratory angio-oedema is considered in more detail in Chapter 22, together with other physical urticarias.

References

1 Dart EE. Effects of high-speed vibrating tools on operators engaged in the aeroplane industry. *Occup Med* 1946; **1**: 515–50.

2 Ryan TJ. Vibration: good or bad. *Clin Exp Dermatol* 1981; **6**: 179–89.

3 Griffin MJ. *Handbook of Human Vibration*. London: Academic Press, 1990.

4 Pelmear PL, Taylor W, Waiserman DE. *Hand–Arm Vibration: a Comprehensive Guide for Occupational Health Professionals*. New York: Van Nostrand Reinhold, 1992.

5 Gemne G, Pyykkö I, Taylor W *et al.* The Stockholm workshop scale for the classification of cold-induced Raynaud's phenomenon in the hand–arm vibration syndrome (revision of the Taylor–Pelmear Scale). *Scand J Work Environ Health* 1987; **13**: 275–8.
6 Taylor W. The hand–arm vibration syndrome (HAVS): secondary Raynaud's phenomenon of occupational origin. *Proc R Coll Phys Edin* 1989; **19**: 7–13.
7 Chetter C, Kent PJ, Kester RC. The hand arm vibration syndrome: a review. *Cardiovasc Surg* 1998; **6**: 1–9.
8 Hadler NM. Vibration white finger revisited. *J Occup Environ Med* 1998; **40**: 9.
9 Toibana N, Ishikawa N, Sakakibasa H *et al.* Raynaud's phenomenon of fingers and toes among vibration-exposed patients. *Nagoya J Med Sci* 1994; **57** (Suppl.): 121–8.
10 Barregard L, Ehrenstrom L, Marcus K. Hand-arm vibration syndrome in Swedish car mechanics. *Occup Environ Med* 2003; **60**: 287–94.
11 Griffin MJ. Foundations of hand-transmitted vibration standards. *Nagoya J Med Sci* 1994; **57** (Suppl.): 147–64.
12 Gemne G. Pathophysiology of white fingers in workers using hand-held vibrating tools. *Nagoya J Med Sci* 1994; **57** (Suppl.): 87–97.
13 Ekenvall L, Lindblad LE. Effect of tobacco use on vibration white finger disease. *J Occup Med* 1989; **30**: 13–6.
14 Virokannas H, Anttonen H, Pramila S. Combined effect of hand–arm vibration and smoking on white finger in different age groups. *Arch Complex Environ Stud* 1991; **3**: 7–12.
15 Bovenzi M, Lindsell CJ, Griffin MJ. Acute vascular response to the frequency of vibration transmitted to the hand. *Occup Environ Med* 2000; **54**: 422–30.
16 Dong RG, Schopper AW, McDowell TW *et al*. Vibration energy absorption (VEA) in human fingers-hand-arm system. *Med Eng Phys* 2004; **26**: 483–92.
17 Bovenzi M, Welsh AJ, Griffin MJ. Acute effects of continuous and intermittent vibration on finger circulation. *Int Arch Occup Environ Health* 2004; **77**: 255–63.
18 Guignard JC. Evaluation of exposure to vibration. In: Cralley LV, Cralley LJ, eds. *Patty's Industrial Hygiene and Toxicology*, Vol. III. *Theory and Rationale of Industrial Hygiene Practice*. New York: Wiley Interscience, 1979: 465–524.
19 Futatsuka M, Shono M, Sakakibara H, Quoc Quan P. Hand arm vibration syndrome among quarry workers in Vietnam. *J Occup Health* 2005; **47**: 165–70.
20 Palmer KT, Griffin MJ, Syddall H *et al.* Risk of hand–arm vibration syndrome according to occupation and sources of exposure to hand-transmitted vibration: a national survey. *Am J Ind Med* 2001; **39**: 389–96.
21 Behrens VJ, Pelmear PL. Epidemiology of hand–arm vibration syndrome. In: Pelmear PL, Taylor W, Wasserman DE, eds. *Hand–Arm Vibration: a Comprehensive Guide for Occupational Health Professionals*. New York: Van Nostrand Reinhold, 1992: 105–21.
22 Cleary AG, McKendrick H, Sills JA. Hand–arm vibration syndrome may be associated with prolonged use of vibrating computer games. *BMJ* 2002; **324**: 301.
23 Gemne G. Disorders in workers using hand-held vibrating tools. In: Pelmear PL, Taylor W, Wasserman DE, eds. *Hand–Arm Vibration: a Comprehensive Guide for Occupational Health Professionals*. New York: Van Nostrand Reinhold, 1992: 41–76.
24 Takeuchi T, Imanishi H. Histopathologic observations in finger biopsy from 30 patients with Raynaud's phenomenon of occupational origin. *J Kumamoto Med Soc* 1984; **58**: 56–70.
25 Goldsmith PC, Abadia Molina F, Bunker CB *et al.* Cutaneous nerve depletion and vibration white finger. *J R Soc Med* 1994; **87**: 377–81.
26 Lindblad LE, Ekenvall L. Alpha-adrenoceptors inhibition in patients with vibration white fingers. *Kurume Med J* 1990; **37** (Suppl.): 595–9.
27 Ekenvall L, Lindblad LE, Norbeck O *et al.* Alpha-adrenoreceptors and cold-induced vasoconstriction in human finger skin. *Am J Physiol* 1988; **255**: 1000–3.
28 Goldsmith PC, Molina FA, Bunker CB *et al*. Deficiency of immunoreactive calcitonin gene-related peptide. *JR Soc Med* 1994; **87**: 377–81.
29 Liang H-W, Hsieh S-T, Cheng T-J *et al*. Reduced epidermal nerve density among hand-transmitted vibration-exposed workers. *J Occup Environ Med* 2006; **48**: 549–55.
30 Hirata M, Sakakibara H, Abe M. Reduced sensory nerve conduction velocity of the distal part of the radial nerve among patients with vibration syndrome. *Electromyogr Clin Neurophysiol* 2002; **42**: 113–8.
31 Stromberg T, Dahlin LB, Lundborg G. Structural nerve changes at wrist level in workers exposed to vibration. *Occup Environ Med* 1997; **54**: 307–11.
32 Walton KW. The pathology of Raynaud's phenomenon of occupational origin. In: Taylor W, ed. *The Vibration Syndrome*. London: Academic Press, 1974: 109–28.
33 Takeuchi T, Futatsuka M, Imanishi H *et al.* Pathological changes observed in the finger biopsy of patients with vibration induced white finger. *Scand J Work Environ Health* 1986; **12**: 280–3.
34 Okada A, Inaba R, Furuno T. Occurrence of intimal thickening of the peripheral arteries in response to local vibration. *Br J Ind Med* 1987; **44**: 470–5.
35 Hashimoto K, Craig RS. Acrosclerosis associated with vibration: an electron microscopic study. *J Cutan Pathol* 1980; **7**: 373–86.
36 Noel B. Pathophysiology and classification of the vibration white finger. *Int Arch Occup Environ Health* 2000; **73**: 150–5.
37 Ziegler S, Gschwandtner M, Zoch C *et al*. Laser Doppler anemometry distinguishes primary Raynaud phenomenon from VWF syndrome. *Microvasc Res* 2004; **68**: 203–8.
38 Dowd PM, Goldsmith PC, Chopra S *et al*. Cutaneous responses to endothelin-1 and histamine in patients with vibration white finger. *J Invest Dermatol* 1998; **110**: 127–31.
39 Kennedy G, Khan F, McLaren M, Belch JJF. Endothelial activation and response in patients with hand arm vibration syndrome. *Eur J Clin Invest* 1999; **29**: 577–81.
40 Okada A, Inaba R, Furuno T *et al.* Usefulness of blood parameters, especially viscosity, for the diagnosis and elucidation of pathogenic mechanisms of the hand–arm vibration syndrome. *Scand J Work Environ Health* 1987; **13**: 358–72.
41 Sakakibara H, Yamada S. Vibration syndrome and autonomic nervous system. *Cent Eur J Public Health* 1995; **3**: 11–4.
42 Färkkilä M, Pykkö I, Heinonen E. Vibration stress and the autonomic nervous system. *Kurume Med J* 1990; **37** (Suppl.): 553–60.
43 Sakakibara H. Sympathetic responses to hand–arm vibration and symptoms of the foot. *Nagoya J Med Sci* 1994; **57** (Suppl.): 99–111.
44 Palmer KT, Griffin MJ, Syddall HE *et al*. Raynaud's phenomenon, vibration induced white finger, and difficulties in hearing. *Occup Environ Med* 2002; **59**: 640–2.
45 Pyykkö I, Färkkilä M, Inaba R *et al.* Effect of hand–arm vibration on inner ear and cardiac functions in man. *Nagoya J Med Sci* 1994; **57** (Suppl.): 113–9.
46 Hirata M, Matsumoto T, Toibana N *et al.* Involvement in the central nervous system of patients with vibration syndrome. In: Dupuis H, Christ E, Sandover DJ *et al*., eds. *Proceedings of the 6th International Conference on Hand–Arm Vibration, Bonn 1992*. Essen, Germany: Schriftreihe des Hauptverbandes der Gewerblichen Berufsgenossenschaften, 1992: 311–7.
47 Pykkö I, Starck J, Färkkilä M *et al.* Hand–arm vibration in the aetiology of hearing loss of lumberjacks. *Br J Ind Med* 1981; **38**: 281–9.
48 Iki M, Kurumantani N, Satoh M *et al.* Hearing loss of forest workers with vibration induced white finger: a 5 year follow-up. *Int Arch Occup Environ Health* 1989; **61**: 437–42.
49 Friden J. Vibration damage to the hand: clinical presentation, prognosis and length and severity of vibration required. *J Hand Surg* 2001; **5**: 471–4.
50 Gemne G, Saraste H. Bone and joint pathology in workers using hand-held vibratory tools: an overview. *Scand J Work Environ Health* 1987; **13**: 290–300.
51 Pelmear PL, Taylor W. Hand–arm vibration syndrome. *J Fam Prac* 1994; **33**: 180–5.
52 Wieslander G, Norback D, Gothe CJ *et al.* Carpal tunnel syndrome (CTS) and exposure to vibration, repetitive wrist movements and heavy manual work: a case-referent study. *Br J Ind Med* 1989; **46**: 43–7.
53 Koskimies K, Färkkilä M, Pykkö I *et al.* Carpal tunnel syndrome in vibration disease. *Br J Ind Med* 1990; **47**: 411–6.
54 Carragee EJ, Hentz VR. Repetitive trauma and nerve compression. *Orthop Clin North Am* 1988; **19**: 157–64.
55 Brammer AJ, Taylor W, Lundborg G. Sensorineural stages of the hand–arm vibration syndrome. *Scand J Work Environ Health* 1987; **13**: 279–83.
56 Pelmear PL, Taylor W. Clinical evaluation. In: Pelmear PL, Taylor W, Wasserman DE, eds. *Hand–Arm Vibration: a Comprehensive Guide for Occupational Health Professionals*. New York: Van Nostrand Reinhold, 1992: 41–76.
57 Pelmear PL, Taylor W. Hand–arm vibration syndrome: clinical evaluation and prevention. *J Occup Med* 1991; **33**: 1144–9.
58 McGeoch KL, Taylor W, Gilmour WH. The use of objective tests as an aid to the assessment of hand–arm vibration syndrome by the Stockholm classification. In: Dupuis H, Christ E, Sandover DJ *et al*., eds. *Proceedings of the 6th International*

Conference on Hand–Arm Vibration, Bonn 1992. Essen, Germany: Schriftreihe des Hauptverbandes der gewerblichen Berufsgenossenschaften, 1992: 783–92.
59 Bilgi C, Pelmear PL. Hand–arm vibration (HAVS): a guide to medical impairment assessment. *J Occup Med* 1993; **35**: 936–42.
60 Harrington JM. *Hand–Arm Vibration Syndrome (Vascular and Neurological Components Involving the Fingers and the Thumb)*. London: HMSO, Department of Social Security, 1995.
61 Lawson IJ, Nevell DA. Review of objective tests for the hand–arm vibration syndrome. *Occup Med* 1997; **47**: 15–20.
62 Griffin MJ, Bovenzi M. The diagnosis of disorders caused by hand-transmitted vibration: Southampton Workshop 2000. *Int Arch Occup Environ Health* 2002; **75**: 1–5.
63 Terada K, Miyai N, Maejima Y *et al*. Laser Doppler imaging of skin blood flow for assessing peripheral vascular impairment in hand-arm vibration syndrome. *Ind Health* 2007; **45**: 309–17.
64 Stromberg T, Dahlin LB, Rosen I, Lundborg G. Neurophysiological findings in vibration-exposed male workers. *J Hand Surg* 1999; **24**: 203–9.
65 Futatsuka M, Ueno T, Sakurai T. Follow up study of vibration-induced white finger in chain saw operators. *Br J Ind Med* 1985; **42**: 267–71.
66 Kurozawa Y, Nasu Y, Hosoda T, Nose T. Long-term follow-up study on patients with vibration-induced white finger (VWF). *J Occup Environ Med* 2002; **44**: 1203–6.
67 Lawson IJ, McGeoch KL. How likely is it that Stockholm Stage 1 of the hand arm vibration syndrome will progress to Stages 2 and 3? *Occup Med* 1999; **49**: 401–2.
68 Meloni M, Torrazza M, Ledda R. Effect of therapy with iloprost in hand-arm vibration syndrome. *Occup Med* 2004; **54**: 261–4.
69 Starck J, Pykkö I, Koskimies K *et al*. Vibration exposure and prevention in Finland. *Nagoya J Med Sci* 1994; **57** (Suppl.): 203–10.
70 Yonekawa Y. Technical preventive measures in Japan. *Nagoya J Med Sci* 1994; **57** (Suppl.): 219–28.
71 Wasserman DE. Vibration exposure and prevention in the United States. *Nagoya J Med Sci* 1994; **57** (Suppl.): 211–8.
72 Sutinen P, Toppila E, Starck J *et al*. Hand-arm vibration syndrome with use of anti-vibration chain saws: 19-year follow-up of forestry workers. *Int Arch Occup Environ Health* 2006; **79**: 665–71.
73 Pelmear PL, Leong D. Review of occupational standards and guidelines for hand–arm (segmental) vibration syndrome (HAVS). *Appl Occup Environ Hyg* 2000; **15**: 291–302.
74 Lawlor F, Black AK, Breathnach AS *et al*. Vibratory angioedema: lesion induction, clinical features, laboratory and ultrastructural findings and response to therapy. *Br J Dermatol* 1989; **120**: 93–9.
75 Mathelier-Fusade C, Vermeulen C, Leynadier F. Angio-oedeme vibratoire. *Ann Dermatol Vénéréol* 2001; **128**: 750–3.

Reactions to internal mechanical stress

Tissue expansion [1]

Skin and subcutaneous tissues clearly expand during pregnancy and morbid obesity. The recognition that skin can be expanded artificially by certain African tribal customs involving the upper lip and ear led surgeons to develop methods of tissue expansion [2–5].

The standard method is to carry out the expansion over a 2–8-week period by inflating sacs inserted beneath the skin. Other techniques include external traction systems [6,7] and intraoperative techniques to produce expansion rapidly [8–11]. Another approach to expand skin is with negative pressure generated inside specially designed cups [12].

The response of skin and soft tissue to progressive expansion has mainly been studied in relation to progressively inflated silicone implants [13]. The main changes [14] are seen in the dermis, where there is reduction in thickness. The rate of thinning is maximal in the first few weeks of expansion and then decreases because of compensatory mechanisms. Within a few days of implantation, a dense fibrous capsule forms around the expander. The number of fibroblasts and their metabolic activity increase, and there is also evidence for increased metabolic activity in the myofibroblasts [15]. Collagen fibres are morphologically normal, but elastic fibres become thickened and appear more compact [15]. The epidermis undergoes increased mitotic activity and maintains its thickness [4,16]. The appendages become separated with expansion of skin but probably are otherwise normal. There is a proliferation of blood vessels, particularly at the junction between the expansion chamber and the tissue around it. This increased vascularity is clearly of value when expanded skin is used in plastic surgical manoeuvres [17]. In an animal model the biomechanical and biorheological properties of recently expanded skin were markedly different from normal skin but normalized over the following 6 months [18]. At a molecular level, various cellular mechanisms seem to be involved, including the cytoskeleton, extracellular matrix and several interrelated signal transduction pathways, with protein kinase C having a central role [19,20].

In intraoperative tissue expansion, the skin is stretched beyond its inherent extensibility by a device, usually for 30 min, allowing direct closure under much reduced tension. In such rapidly expanded skin, the collagen fibres become aligned in the direction of the stretching force, and elongated; the epidermal thickness remains unaltered [21].

Adverse effects of tissue expanders include infection, rupture of the expander, haematoma and seroma, infection and skin necrosis. Striae do not normally develop in expanded skin, but this has been described as a complication [22].

References

1 Marcus J, Horan DB, Robinson JK. Tissue expansion: past, present, and future. *J Am Acad Dermatol* 1990; **23**: 813–25.
2 Neuman CG. The expansion of an area of skin by progressive distention of a subcutaneous balloon. *Plast Reconstr Surg* 1957; **19**: 124–30.
3 Radovan C. Breast reconstruction after mastectomy using the temporary expander. *Plast Reconstr Surg* 1981; **69**: 195–206.
4 Olenius M, Johansson O. Variations in epidermal thickness in expanded human breast skin. *Scand J Plast Reconstr Hand Surg* 1995; **29**: 15–20.
5 Swanson NA, Argenta LC. Tissue expansion. In: Callen JP, Dahl MV, Golitz LE *et al*., eds. *Advances in Dermatology*, Vol. 3. Chicago: Year Book Medical, 1988: 243–58.
6 Brongo S, Pilegaard J, Blomqvist G. Clinical experiences with the external tissue extender. *Scand J Plast Reconstr Surg* 1997; **31**: 57–63.
7 Molea G, Schonauer F, Blasi F. Progressive skin extension: clinical and histological evaluation of a modified procedure using Kirschner wires. *Br J Plast Surg* 1999; **52**: 205–8.
8 Sasaki GH. Intra-operative sustained limited expansion (ISLE) as an immediate reconstructive technique. *Clin Plast Surg* 1987; **14**: 563–73.
9 Johnson TM, Brown MD, Sullivan MJ *et al*. Immediate intra-operative tissue expansion. *J Am Acad Dermatol* 1990; **22**: 283–7.
10 Schmidt SC, Logan SE, Hayden JM *et al*. Continuous versus conventional tissue expansion: experimental verification of a new technique. *Plast Reconstr Surg* 1991; **87**: 10–5.
11 Petro JA, Niazi ZBM. Immediate skin expansion: an old concept by a novel and inexpensive technique. *Ann Plast Surg* 1996; **36**: 479–84.
12 Lasheen AE, Salim A, Hefny MR, Al-Bakly E. External tissue expansion successfully achieved using negative pressure. *Surg Today* 2004; **34**: 193–6.
13 Austad ED, Rose GL. A self-inflicting tissue expander. *Plast Reconstr Surg* 1982; **70**: 588–92.

14 Austad ED, Pasyk KA, McClatchey KD *et al.* Histomorphologic evaluation of guinea pig skin and soft tissue after controlled tissue expansion. *Plast Reconstr Surg* 1982; **70**: 704–10.
15 Pasyk KA, Austad ED, McClatchey KD *et al.* Electron microscopic evaluation of guinea pig skin and soft tissues 'expanded' with a self-inflating silicone implant. *Plast Reconstr Surg* 1982; **70**: 37–45.
16 Austad ED, Thomas SB, Pasyk K. Tissue expansion: dividend or loan? *Plast Reconstr Surg* 1986; **78**: 63–7.
17 Cherry GW, Austad F, Pasyk K *et al.* Increased survival and vascularity of random-pattern skin flaps elevated in controlled, expanded skin. *Plast Reconstr Surg* 1983; **72**: 680–5.
18 Zeng YJ, Liu YH, Xu CQ *et al*. Biomechanical properties of skin in vitro for different expansion methods. *Clin Biomech (Bristol)* 2004; **19**: 853–7.
19 Takei T, Mills I, Arai K, Sumpio BE. Molecular basis for tissue expansion: clinical implications for the surgeon. *Plast Reconstr Surg* 1998; **102**: 247.
20 De Filippo RE, Atala A. Stretch and growth: the molecular and physiologic influences of tissue expansion. *Plast Reconstr Surg* 2002; **109**: 2450–62.
21 Melis P, Noorlander ML, van der Horst CMAM *et al.* Rapid alignment of collagen fibers in the dermis of undermined and not undermined skin stretched with a skin-stretching device. *Plast Reconstr Surg* 2002; **109**: 674–80.
22 Chan WY, Akhtar S, Phipps AR. Striae distensae in tissue-expanded skin in the upper arm. *Ann Plast Surg* 2006; **57**: 240–1.

Piezogenic pedal papules

This rather cumbersome title, derived from 'piesis' (pressure), has been given to soft skin-coloured papules and nodules that appear on the side of the heel, usually the medial aspect (Fig. 28.19), when the subject is standing, and disappear when weight is taken off the foot [1]. Observation of healthy subjects has shown that such papules are common, although painless and indeed often unnoticed [2–6]. The frequency of the condition makes it difficult to assess the assertion that piezogenic pedal papules can be familial [7] and also that there is an increased frequency in some diseases such as Ehlers–Danlos syndrome [8]. In a population study there was no association with hypermobile joints [5]. It has also been described in several patient with Prader–Willi syndrome [9].

Pain on standing is usually the reason for presentation, although some patients do express curiosity about the papules even when they are symptomless.

Similar papules have also been noticed on the lateral edge of the hand [10] and wrist [11], and piezogenic palmar papules have recently been described as a physical sign of suprafascial palmar lipoma [12].

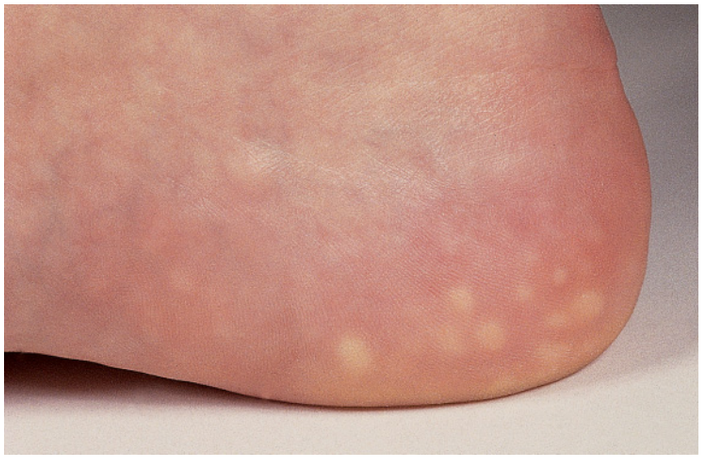


Fig. 28.19 Piezogenic pedal papules.

Pathogenesis. Painless papules consist of normal fat tissue [3], but when pain occurs it has been attributed to herniation of the fat into the dermis with a resultant reduction in dermal thickness [10,13]. Postulated reasons for this pain include a defect in septation of the adipose tissue [13] and ischaemia resulting from extrusion of fat within its vascular supply and associated nerves [14].

Treatment. When piezogenic pedal papules of the feet are painful, improvement of the symptom can sometimes be achieved by avoidance of prolonged standing and, when relevant, loss of weight. Compression hosiery [15], electroacupuncture [16] and injections of equal parts of betamethasone with bupivacaine [17] have been reported to relieve symptoms. Supportive rubber footpads and heel cups can also be helpful. If conservative measures fail, small excisions of the papules can be curative [18].

References

1 Cohen HJ, Gibbs RC, Minkin W *et al.* Painful piezogenic pedal papules. *Arch Dermatol* 1970; **101**: 112–3.
2 Kohn SR, Blasi JM. Piezogenic pedal papules. *Arch Dermatol* 1972; **106**: 597–8.
3 Schlappner OLA, Wood MG, Gerstein W *et al.* Painful and non-painful piezogenic pedal papules. *Arch Dermatol* 1972; **106**: 729–33.
4 Woerdeman MJ, van Dijk E. Piezogenic papules of the feet. *Acta Derm Venereol (Stockh)* 1972; **52**: 411–4.
5 Van Straaten EA, van Langen IM, Oorthuys JWE *et al.* Piezogenic papules of the feet in healthy children and their possible relation with connective tissue disorders. *Pediatr Dermatol* 1991; **8**: 277–9.
6 Zaidi Z, Jafri N, Noori B *et al.* Piezogenic papules: a study of 100 cases. *J Pak Med Assoc* 1995; **45**: 93–4.
7 Gibney MD, Glaser DA. Piezogenic pedal papules in two family members. *Cutis* 1996; **57**: 260–2.
8 Kahana M, Feinstein A, Tabachnic E *et al.* Painful piezogenic pedal papules in patients with Ehlers–Danlos syndrome. *J Am Acad Dermatol* 1987; **17**: 205–9.
9 Schepis C, Greco D, Siragusa M, Romano C. Piezogenic pedal papules during Prader-Willi syndrome. *J Eur Acad Dermatol Venereol* 2005; **19**: 136–7
10 Plewig G, Braun-Falco O. Piezogene knötchen druckbedingte fersenund handkantenknötchen. *Hautarzt* 1973; **24**: 114–8.
11 Laing VB, Fleischer AB. Piezogenic wrist papules: a common and asymptomatic finding. *J Am Acad Dermatol* 1991; **24**: 415–7.
12 Cox NH, Broome G. Piezogenic palmar papules: a novel physical sign of palmar lipoma. *Br J Dermatol* 2008; **159**: 757–8.
13 Harman RRM, Matthews CNA. Painful piezogenic pedal papules. *Br J Dermatol* 1974; **90**: 573–4.
14 Shelley WB, Rawnsley HM. Painful feet due to herniation of fat. *JAMA* 1968; **209**: 308–9.
15 Boni R, Dummer R. Compression therapy in painful piezogenic pedal papules. *Arch Dermatol* 1996; **132**: 127–8.
16 Woodrow SL, Brereton-Smith G, Handfield-Jones S. Painful piezogenic pedal papules: response to local electro-acupuncture. *Br J Dermatol* 1997; **136**: 628–30.
17 Doukas DJ, Holmes J, Leonard JA. A nonsurgical approach to painful piezogenic pedal papules. *Cutis* 2004; **73**: 339–40, 346.
18 Ronnen M, Suster S, Huszar M *et al.* Solitary painful piezogenic pedal papule in a patient with rheumatoid arthritis. *Int J Dermatol* 1987; **26**: 240–1.

Muscle herniation of the limbs

The first comprehensive review of muscle hernias in the limbs was in a series of military recruits in 1929 [1]. Most occur in the lower leg, especially over the anterior tibial compartment, although other sites include the forearm [2]. The hernias may be single or multiple, and on one or both sides. The swelling may be painful

but is often asymptomatic. Anterior muscle herniation becomes more apparent when the patient is in the 'fencer's lunge' position, that is with the weight-bearing hip, knee and ankle all flexed, and it disappears again when in the supine position. The differential diagnosis includes lipoma, angiolipoma, neurilemmoma, liposarcoma and varicosities.

Pathogenesis. The defect in the connective tissue which allows herniation is often at the site of penetration of vessels and nerves. Muscle herniation is classified as constitutional or post-traumatic. As well as various external injuries, sudden muscle contraction can cause weakening of the fascia. Precipitating factors include vigorous exercise and prolonged standing.

Investigation. Dynamic ultrasonography [3] is usually sufficient in confirming the diagnosis although MRI may be useful in some cases [2,4].

Treatment. Unless there are symptoms, treatment is not recommended. Mild discomfort can often be relieved with support hosiery. Various surgical repair methods have been described. Direct closure has been associated with the risk of compartment syndrome and mesh grafting seems preferable [5,6].

References

1 Ihde H. On muscle hernia of the leg. *Acta Chir Scand* 1929; **65**: 97–120.
2 Kendi TK, Altinok D, Erdal HH, Kara S. Imaging in the diagnosis of symptomatic forearm muscle herniation. *Skeletal Radiol* 2003; **32**: 364–6.
3 Bates DG. Dynamic ultrasound findings of bilateral anterior tibialis muscle herniation in a pediatric patient. *Pediatr Radiol* 2001; **31**: 753–5.
4 Mellado JM, Perez del Palomar L. Muscle hernias of the lower leg: MRI findings. *Skeletal Radiol* 1999; **28**: 465–9.
5 Siliprandi L, Martini G, Chiarelli A, Mazzoleni F. Surgical repair of an anterior tibialis muscle hernia with Mersilene mesh. *Plast Reconstr Surg* 1993; **91**: 154–7.
6 Marques A, Brenda E, Amarante MT. Bilateral multiple muscle hernias of the leg repaired with Marlex mesh. *Br J Plast Surg* 1994; **47**: 444–6.

Mechanical trauma and skin neoplasia

Patients often describe an injury preceding the appearance of a cutaneous malignancy. However, the role of trauma in such cases is complicated by fallibility of the memory and uncertainty of the nature of the skin prior to the injury. Also, in many instances the injury is multifactorial, possibly involving a foreign body, heat, a chemical carcinogen such as tar or soot, as well as mechanical trauma [1,2].

When a single episode of mechanical injury to normal skin has been followed by carcinoma, the wound has often healed slowly, broken down repeatedly or failed to heal, and the neoplasm is nearly always a basal cell carcinoma [3–6]. On circumstantial evidence, basal cell carcinoma of the sole has been attributed to trauma in some cases [7].

Occasional instances of squamous carcinoma have been reported [8,9] but these have not followed simple mechanical trauma and have been complicated by other factors, such as foreign material left in the skin. Bowen's disease has been reported arising in a scar [10]. Basal cell carcinoma and squamous cell carcinoma have been recorded at sites of vaccination to smallpox [11–15], tattoos [16,17] and bacillus Calmette–Guérin (BCG) immunization [18]. Basal cell carcinoma has been reported at a skin graft recipient site [19]. The role of trauma in the genesis of malignant melanoma has been considered, but there is no strong supportive evidence [20,21]. Occasional instances of melanoma have been recorded in relation to immunization sites [22,23] as have sarcomas [24,25]. Lymphoma has rarely been associated with preceding trauma [26].

The development of a malignant neoplasm can be divided into at least three stages: initiation, promotion and progression. Environmental factors may be relevant for any of these stages [27]. Using a mouse model in which the initiator was the chemical carcinogen dimethylbenzanthracene, it has been shown that repeated abrasion is an effective promoter of both papillomas and carcinomas of the skin [28,29]. It has not proved possible to initiate carcinogenesis with surgically induced ulceration [30].

In the clinical context, however, the role of repeated mechanical trauma in the genesis of skin malignancy remains speculative [31]. For medicolegal purposes, the association of trauma with ensuing skin cancer should fulfil criteria that were laid down long ago, but remain valid [32]: authenticity and sufficient severity of the injury, previous integrity of the wounded part, tumour originating within the boundaries of the injury, histological variety of cancer compatible with an origin from local tissue, and a latent period.

References

1 Dix CR. Occupational trauma and skin cancer. *Plast Reconstr Surg* 1960; **26**: 546–54.
2 Wein AJ, Graham WP, Royster HP. Chronic wounds can lead to cancer. *Int J Occup Health Safety* 1974; **43**: 41–3.
3 Neuman Z, Ben-Hur N, Shulman J. Trauma and skin cancer. *Plast Reconstr Surg* 1963; **32**: 649–56.
4 Ewing MR. The significance of a single injury in the causation of basal cell carcinoma of the skin. *Aust NZ J Surg* 1971; **41**: 140–7.
5 Rustin MHA, Chambers TJ, Munro DD. Post-traumatic basal cell carcinomas. *Clin Exp Dermatol* 1984; **9**: 379–83.
6 Noodleman FR, Pollack SV. Trauma as a possible etiologic factor in basal cell carcinoma. *J Dermatol Surg Oncol* 1986; **12**: 841–6.
7 Roth MJ, Stern JB, Haupt HM *et al.* Basal cell carcinoma of the sole. *J Cutan Pathol* 1995; **22**: 349–53.
8 Stilwell JH, Clare G. Malignancy following a single injury to the skin. *Br J Plast Surg* 1980; **33**: 74–6.
9 Rao GSS, James JH. Squamous cell carcinoma presenting as a painful scar following a single injury. *Br J Plast Surg* 1988; **41**: 197–9.
10 Keefe M, Smith GD. Bowen's disease arising in a scar: a case report and review of the relationship between trauma and malignancy. *Clin Exp Dermatol* 1991; **16**: 478–80.
11 Zelickson AS. Basal cell epithelioma at site of and following smallpox vaccination: report of a case. *Arch Dermatol* 1968; **98**: 35–6.
12 Reed WB, Wilson Jones E. Malignant tumours as a late complication of vaccination. *Arch Dermatol* 1968; **98**: 132–5.
13 Finnerty EF, Folan DW. Multiple focal squamous cell carcinoma in a vaccination scar. *Cutis* 1972; **10**: 727–8.
14 Upton GL, Wilson JW. Basal-cell carcinoma arising in a vaccination scar. *Cutis* 1973; **11**: 49–51.
15 Castrow FFII, Williams TE. Basal cell epithelioma occurring in a smallpox vaccination scar. *J Dermatol Surg* 1979; **2**: 151–2.
16 Earley MJ. Basal cell carcinoma arising in tattoos. *Br J Plast Surg* 1983; **36**: 258–9.
17 Wiener DA, Sher RK. Basal cell carcinoma arising in a tattoo. *Cutis* 1987; **39**: 125–6.
18 Panizzon R. Basal cell epithelioma in a BCG vaccination scar. *Arch Dermatol* 1980; **116**: 381.

19 Cox NH. Basal cell carcinoma in a skin graft recipient site. *Practitioner* 1984; **228**: 997–8.
20 Briggs JC. The role of trauma in the aetiology of malignant melanoma: a review article. *Br J Plast Surg* 1984; **37**: 514–6.
21 Kaskel P, Kind P, Sander S *et al.* Trauma and melanoma formation: a true association? *Br J Dermatol* 2000; **143**: 749–53.
22 Lokich JJ. Malignant melanoma arising *de novo* within a BCG scarification site (Letter). *Lancet* 1975; **1**: 331–2.
23 Marmelzat W, Hirsch P, Martel S. Malignant melanoma in smallpox vaccination scars. *Arch Dermatol* 1964; **89**: 823–6.
24 Slater DN, Parsons MA, Fussey IV. Malignant fibrous histiocytoma arising in a smallpox vaccination scar. *Br J Dermatol* 1981; **105**: 215–7.
25 McLelland J, Chu T. Dermatofibrosarcoma protuberans arising in a BCG vaccination scar. *Arch Dermatol* 1988; **124**: 496–7.
26 Morioka T, Tashima T, Nishio S *et al.* Malignant lymphoma of the scalp at the site of a previous blunt trauma: report of two cases. *Surg Neurol* 1994; **42**: 117–20.
27 Pitot HC. Environmental modifiers in carcinogenesis. *IARC Sci Pub* 1982; **49**: 165–76.
28 Argyris TS. Promotion of epidermal carcinogenesis by repeated damage to mouse skin. *Am J Ind Med* 1985; **8**: 329–37.
29 Argyris TS. Epidermal tumor promotion by damage in the skin of mice. In: Slaga TJ, Klein-Szanto SJP, Boutwell RK *et al.*, eds. *Skin Carcinogenesis: Mechanisms and Human Relevance*. New York: Alan R. Liss, 1989: 63–80.
30 Hasegawa R, St John M, Tibbels TS *et al.* Evaluation of epidermal cell kinetics following freezing or wounding of mouse skin and their potential as initiators of carcinogenesis. *J Invest Dermatol* 1987; **88**: 652–6.
31 Downing JG. Cancer of skin and occupational trauma. *JAMA* 1952; **148**: 245–52.
32 Ewing J. Modern attitude toward traumatic cancer. *Arch Pathol* 1935; **19**: 690–728.

Reactions to cold

D. Creamer, pp. 28.63–28.74

Physiological reactions to cold

The maintenance of a steady core body temperature is achieved by various thermoregulatory mechanisms, not least of which is control of the skin's blood flow. Exposure to cold causes constriction of the arterioles and veins by a direct mechanism mediated in part by endothelial synthesis of the vasoconstrictor peptide endothelin-1 [1]. A reflex increase in sympathetic tone is triggered by cold receptors in the skin and, if the blood temperature falls, by the hypothalamic heat-regulating centre. Heat conservation is further enhanced by a counter-current exchange system between arteries and veins in the limbs. Cold-induced vasoconstriction causes shunting of blood to the deep venous system which allows heat to be transferred from arteries to veins. Consequently, arterial blood passing into the limbs is cooler, venous blood returning to the body is warmer and less heat is lost to the outside environment.

Persistent exposure of fingers to cold leads to the 'hunting reaction' of Lewis in which there are repeated cycles of vasodilatation following periods of vasoconstriction [2]. Cold-induced vasoconstriction is a heat-preserving, protective mechanism but prolonged vasospasm may jeopardize the vitality of the skin. Therefore a transient vasodilatory response, mediated by the opening of arteriovenous anastamoses, protects against skin necrosis. With continued cold exposure, there is a phasic increase and decrease in blood flow through the cutaneous microvasculature. However, when core temperature is under threat the hunting reaction stops and vasoconstriction persists [2].

Cold-induced vasoconstriction causes a rise in intracapillary pressure and increased filtration of fluid into the interstitium, resulting in haemoconcentration and a reduction in plasma volume. Other physiological effects of cold include increased blood viscosity, slowing of the dissociation of oxyhaemoglobin to haemoglobin, diminished conduction velocity in cutaneous nerves and changes in platelet adhesiveness [3].

References

1 Fyhrquist F, Saijonmaa O, Metsarinne K *et al.* Raised plasma endothelin-1 concentration following cold pressor test. *Biochem Biophys Res Commun* 1990; **169**: 217–21.
2 Lewis T. Observations upon the reactions of the vessels of the human skin to cold. *Heart* 1930; **15**: 177–208.
3 Kattlove HE, Alexander B. The effect of cold on platelets: cold-induced platelet aggregation. *Blood* 1971; **38**: 39–48.

Diseases caused or aggravated by cold

The ambient temperature and duration of exposure will determine the type and degree of injury sustained by all people when exposed to severe cold. However, there is a variable endogenous susceptibility to cold; certain individuals suffer cold-related disorders on exposure to modest degrees of cold which would be tolerated without ill effect by other normal individuals. Hence, cold-induced diseases can be divided into two groups: (i) diseases of cold exposure, and (ii) diseases of abnormal susceptibility to cold (Table 28.9).

Diseases of cold exposure

Frostbite

Aetiology and pathology. Frostbite is the term used to describe tissue damage caused by freezing. Skin and subcutaneous tissues are at risk of frostbite when exposed to cold air, liquids or metals.

Most cases of frostbite are seen in winter sports enthusiasts and climbers who have been stranded in exposed sites in cold weather.

Table 28.9 Diseases caused or aggravated by cold.

Diseases of cold exposure
Frostbite
Trench foot
Diseases of abnormal susceptibility to cold
Raynaud's phenomenon (see also Chapter 51)
Livedo reticularis (Chapter 49)
Cryoglobulinaemia (Chapters 49 and 50)
Cold agglutinins
Cold haemolysis
Cold urticaria (Chapter 22)
Perniosis
Acrocyanosis
Erythrocyanosis
Cold erythema
Cold panniculitis (Chapter 46)
Neonatal cold injury (Chapter 17)

Frostbite also occurs in soldiers, homeless people and those who work outdoors in cold climates. The risk of frostbite increases with alcohol use and smoking [1].

Freeze-induced damage results largely from the formation of ice in both intracellular and extracellular compartments [2]. Fast freezing tends to produce intracellular ice, while slow freezing causes the formation of extracellular ice. Ice crystals not only injure cellular architecture but also disturb the flux of electrolytes and water across cell membranes [3]. The degree of cryodamage is also influenced by the rate of thawing. Slow re-warming causes the formation of larger, more destructive ice crystals and the development of greater osmotic stresses. As well as direct effects on cells, tissue damage in frostbite is compounded by cold-induced vascular and haematological responses. Reflex vasoconstriction in the extremities results in decreased capillary perfusion, which is aggravated by cold-induced hyperviscosity and a tendency to thrombus formation [4].

Clinical features. The parts of the body that can be least protected from cold are affected—toes, feet, fingers, ears, nose and cheeks. Frostnip involves the skin only and is characterized by painful erythema, which normalizes with re-warming. In superficial frostbite there is involvement of skin and subcutis with erythema accompanied initially by pain and then a sense of warmth. The affected skin becomes waxy and white. The injury in deep frostbite extends to the subcutaneous tissues and may involve nerves, major vessels, muscle and bone, resulting in joint immobility and paralysis [5]. A new method of classifying frostbite severity has been proposed: first degree, leading to complete recovery; second degree, requiring soft tissue amputation only; third degree, requiring bone amputation; fourth degree, necessitating major amputation and complicated by systemic effects [6].

The extent and severity of tissue damage become apparent on re-warming. Erythema and mild pain lasting for a few hours occur following mild frostbite. Blistering, full-thickness skin necrosis and gangrene can be seen in severe cases [7].

Damage to nerves and blood vessels can lead to parasthesiae, abnormal sensitivity to cold and hyperhidrosis, which may last for months to years [7].

Treatment. Rapid re-warming by immersion in water at 40–42°C for 20 min is recommended. Exposure to higher temperatures is contraindicated. Further tissue trauma must be avoided. A retrospective study has indicated a reduction in the need for digital amputation if intra-arterial infusion of tissue plasminogen activator is given within 48 h of injury [8]. Vasodilator drugs may also improve outcome [9]. Technetium 99 bone scintigraphy may be helpful in evaluating outcome in frostbite injury and indicating the level of amputation needed in severe cases [10]. Surgical removal of gangrenous tissue should be delayed until there is a distinct demarcation between viable and non-viable tissue, a process that usually takes several weeks.

References

1 Golant A, Nord RM, Paksima N, Posner MA. Cold exposure injuries to the extremities. *J Am Acad Orthop Surg* 2008; **16**: 704–15.

2 Meryman HT. Tissue freezing and local cold injury. *Physiol Rev* 1957; **37**: 233–51.

3 Granberg PO. Freezing cold injury. *Arctic Med Res* 1991; **50** (Suppl. 6): 76–9.

4 Zook N, Hussmann J, Brown R *et al*. Microcirculatory studies of frostbite injury. *Ann Plast Surg* 1998; **40**: 246–53.

5 Ward M. Frostbite. *BMJ* 1974; **i**: 67–70.

6 Cauchy E, Chetaille E, Marchand V, Marsigny B. Retrospective study of 70 cases of severe frostbite lesions: a proposed new classification scheme. *Wilderness Environ Med* 2001; **12**: 248–55.

7 Killian H. *Cold and Frost Injuries*. Berlin: Springer, 1981.

8 Bruen KJ, Ballard JR, Morris SE *et al*. Reduction of the incidence of amputation in frostbite injury with thrombolytic therapy. *Arch Surg* 2007; **142**: 546–51.

9 Murphy J, Banwell P, Roberts A, McGrouther D. Frostbite: pathogenesis and treatment. *J Trauma* 2000; **48**: 171–8.

10 Cauchy E, Marsigny B, Allamel G *et al*. The value of technetium 99 scintigraphy in the prognosis of amputation in severe frostbite injuries of the extremeties: a retrospective study of 92 severe frostbite injuries. *J Hand Surg Am* 2000; **25**: 969–78.

Trench foot

Synonym

- Immersion foot

Aetiology and pathology. Trench foot and immersion foot are regarded as similar processes. Trench foot was a common problem suffered by soldiers in the early years of trench warfare in the First World War [1] but is now mostly encountered among the homeless population [2]. Affected individuals develop numbness of the feet and distal legs accompanied by skin changes caused by non-freezing cold injury; this is compounded by wet conditions and aggravated by leg dependency, immobility and constrictive footwear. Smoking and peripheral vascular disease probably contribute to the severity of tissue damage.

The pathological changes are those of dependent oedema and lymphovenous stasis. Perivascular inflammation occurs and in severe cases arterial occlusion and ischaemic necrosis. There is damage to both myelinated and unmyelinated nerve fibres [3].

Clinical features. Affected legs and feet are cold and anaesthetic. There is erythema, oedema, tenderness and, in severe cases, areas of superficial gangrene. On re-warming there is worsening oedema, hyperaemia and painful parasthesiae. Initially the ability to sweat is lost but with time there is hyperhidrosis, cold sensitivity and vasomotor instability. Changes may persist for months or years.

Treatment. The best approach is prevention, but once the condition has occurred bed-rest and analgesics are helpful. Conservative excision of necrotic tissue may be necessary and antibiotics should be given if there is evidence of infection.

References

1 Atenstaedt R. Trench foot: the medical response in the first world war 1914–18. *Wilderness Environ Med* 2006; **17**: 282–9.

2 Wrenn K. Immersion foot. A problem of the homeless in the 1990s. *Arch Intern Med* 1991; **151**: 785–8.

3 Irwin MS, Sanders R, Green CJ, Terenghi G. Neuropathy in non-freezing cold injury (trench foot). *J Roy Soc Med* 1997; **90**: 433–8.

Diseases of abnormal sensitivity to cold

Perniosis

Synonym
- Chilblains

Aetiology and pathology. Perniosis and chilblains are terms used to describe localized inflammatory lesions on acral skin, which occur as an abnormal reaction to cold in susceptible individuals [1]. There may be a genetic influence in perniosis since several generations within a family can be affected [1]. Other aetiological factors include poor nutrition, anorexia nervosa and systemic diseases, most typically lupus erythematosus and haematological malignancy [2–4].

In perniosis there is a persistent cold-induced vasoconstriction of the deep cutaneous arterioles with concomitant dilatation of the smaller, superficial vessels. This is in contrast with normal subjects, in whom cold exposure induces cutaneous vasoconstriction succeeded by vasodilatation, a homeostatic mechanism necessary for the maintenance of reperfusion. Investigation of cutaneous nerves in patients with perniosis demonstrated no quantitative or qualitative difference in immunoreactivity for substance P, neuropeptide Y, calcitonin gene-related peptide or vasoactive intestinal peptide compared to controls [5]. However, in the affected skin of patients with acral perniosis, who also had a past history of very low body weight, immunohistochemistry revealed a great increase in nerve bundles in the papillary dermis, some with an abnormal morphology [5]. This indicates that in uncomplicated perniosis the neuronal supply to the microvasculature is normal and suggests that the pathology involves the microvessels themselves.

The histopathology of perniosis most usually demonstrates dermal oedema with superficial and deep dermal inflammation [6]. The mononuclear cell infiltration, mostly T-cells, is primarily perivascular but also occurs in a peri-eccrine distribution [7]. Epidermal changes in chilblains consist mainly of necrotic keratinocytes and spongiosis. Perniosis occurring on the lateral thigh is characterized by an intense mononuclear cell infiltrate extending throughout the dermis and into the subcutaneous fat, with 'fluffy oedema' of blood vessel walls [6]. In these cases of deep perniosis dermal oedema is not a prominent feature. Inflammation occurring in the deeper dermis and subcutis may be explained by the combined effects of external cooling together with insulation from internal warming [6].

Clinical features. Perniosis occurs in susceptible individuals during the autumn or winter in a climate which is both cold and humid. The lesions are red-purple and usually macular, papular or nodular. Plaque-like chilblains also occur, as do lesions with an annular morphology. Perniosis develops symmetrically on acral skin, in particular the fingers and toes but other body extremities may be involved including the heels, lower legs, nose and ears. Pruritus and burning pain are common, although some lesions may be asymptomatic. In severe cases blistering and ulceration may occur. Each lesion tends to undergo spontaneous resolution after 2–3 weeks; however, in some patients chilblains persist throughout the winter and occasionally continue to develop in the summer.

There are less common variants: in papular perniosis, crops of small chilblains develop on the sides of the fingers often on a background of acrocyanosis [8]. Perniosis occurring on the outer thighs has been reported in women who are horse-riding enthusiasts ('equestrian panniculitis') [9]. Clinically these lesions are composed of clustered papules or plaques, which may ulcerate. Tight-fitting trousers, such as riding breeches, have been implicated aetiologically [9]. In chronic perniosis, especially in the presence of arterial disease or prolonged cold exposure, irreversible changes of fibrosis, lymphoedema and hyperkeratosis may occur, altering the physical signs.

Chilblain lupus erythematosus (LE) (also known as Hutchinson's lupus) is a form of cutaneous LE which presents in a similar way to idiopathic perniosis. Erythrocyanotic papules, located on the fingers and toes, develop in cold weather and tend to persist, in some cases becoming ulcerated [10]. Chilblain LE may be accompanied by discoid LE or other forms of cutaneous LE. Up to 20% of patients with chilblain LE develop systemic LE [10].

Chilblains may also complicate haematological malignancy, typically myelodysplastic syndrome and chronic myelomonocytic leukaemia (Chapter 62). Cyanotic swelling of acral digital skin, particularly the toes, has been reported in these patients [11]. The onset of perniosis may coincide with a blast crisis, which can be demonstrated on the skin biopsy by the presence of large, atypical mononuclear cells in the perivascular infiltrate [12].

Treatment. Warm clothing and central heating generally prevents perniosis. Susceptible individuals must avoid cold, damp conditions and should not smoke. A double-blind, placebo-controlled study demonstrated the efficacy of nifedipine in clearing existing chilblains and preventing the development of new lesions [13]. A study has demonstrated the successful treatment of chilblain lupus erythematosus with mycophenolate mofetil [14].

References

1 Goette DK. Chilblains (perniosis). *J Am Acad Dermatol* 1990; **23**: 257–62.
2 White KP, Rothe MJ, Milanese A, Grant-Kels JM. Perniosis in association with anorexia nervosa. *Paediatr Dermatol* 1994; **11**: 1–5.
3 Millard LG, Rowell NR. Chilblain lupus erythematosus (Hurtchinson). *Br J Dermatol* 1978; **98**: 497–506.
4 Kelly JW, Dowling JP. Pernio: a possible association with chronic myelomonocytic leukaemia. *Arch Dermatol* 1985; **121**: 1048–52.
5 Goldsmith PC, Leslie TA, Polak JM, Dowd PM. Acrocyanosis and perniosis: an investigation of cutaneous neuronal and endothelial peptides in digital skin. *Skin Pharmacol* 1994; **7**: 156.
6 Wall LM, Smith NP. Perniosis: a histopathological review. *Clin Exp Dermatol* 1981; **6**: 263–71.
7 Cribier B, Djeridi N, Peltre B, Grosshans E. A histologic and immunohistochemical study of chilblains. *J Am Acad Dermatol* 2001; **45**: 924–9.
8 Wessagowit P, Asawanonda P, Noppakun N. Papular perniosis mimicking erythema multiforme. *Int J Dermatol* 2000; **39**: 527–9.
9 Beacham BE, Cooper PH, Buchanan CS, Weary PE. Equestrian cold panniculitis in women. *Arch Dermatol* 1980; **116**: 1025–7.
10 Hedrich CM, Fiebig B, Hauck FH *et al*. Chilblain lupus erythematosus—a review of the literature. *Clin Rheumatol* 2008; **27**: 949–54.
11 Kelly JW, Dowling JP. Pernio: a possible association with chronic myelomonocytic leukaemia. *Arch Dermatol* 1985; **121**: 1048–52.

Table 28.10 Aetiology of acrocyanosis.

Idiopathic
Secondary
Autoimmune
Connective tissue disorders
Primary and secondary antiphospholipid antibody syndrome
Neoplastic
Benign and malignant paraproteinaemias
Paraneoplastic syndrome
Cold agglutinin disease
Cryoglobulinaemia
Eating disorders
Anorexia nervosa
Bulimia nervosa
Orthostatic disorders
Chronic orthostatic intolerance
Postural orthostatic tachycardia syndrome of adolescents
Adolescent chronic fatigue syndrome
Neurological disorders
Brachial plexus neuropathy
Chronic arsenic poisoning
Drugs
Butyl nitrate
Interferon-α (2a)
Metabolic diseases
Fucidosis
Ethylmalonic encephalopathy
Psychiatric
Mental retardation
Schizophrenia
Essential thrombocythaemia

Table 28.11 Classification of livedo reticularis.

1 Physiological livedo reticularis
Cutis marmorata
2 Idiopathic or primary livedo reticularis
Congenital
Cutis marmorata telangiectatica congenita
Acquired idiopathic
Uncomplicated
With winter ulceration
With summer ulceration
With systemic vascular involvement
3 Secondary livedo reticularis
Intravascular obstruction
Stasis
Paralysis
Cardiac failure
Amantadine therapy
Occlusive disease
Emboli [2,3]
Oxalosis (primary hyperoxaluria) [4,5]
Compressed air
Bismuth, pentazocine, non-steroidal anti-inflammatory drugs, minocycline [6]
Thrombocythaemia [7,8]
Cryoglobulins
Cold agglutinins
Vessel wall disease
Arteriosclerosis
Arteritis
Polyarteritis nodosa
Systemic lupus erythematosus
Antiphospholipid syndrome
Rheumatoid arthritis
Dermatomyositis
Lymphoma
Pancreatitis
Infections
Tuberculosis
Syphilis
Hepatitis C
Brucellosis
Coxiella burnetii
Hyperparathyroidism and hypercalcaemia [9]
Calciphylaxis [10]

12 Yazawa H, Saga K, Omori F *et al*. The chilblain-like eruption as a diagnostic clue to the blast crisis of chronic myelocytic leukaemia. *J Am Acad Dermatol* 2004; **50**: S42–S44.
13 Rustin MH, Newton JA, Smith NP *et al*. The treatment of chilblains with nifedipine. *Br J Dermatol* 1989; **120**: 267–75.
14 Boehm I, Bieber T. Chilblain lupus erythematosus Hutchinson: successful treatment with mycophenolate mofetil. *Arch Dermatol* 2001; **137**: 235–6.

Acrocyanosis

Aetiology and pathology. Acrocyanosis is a persistent cyanotic or erythrocyanotic mottled discoloration of the hands and, less commonly, feet and face. It may be idiopathic or secondary to a number of systemic disorders, including an underlying malignancy [1] (Table 28.10). Sometimes there is a family history indicating a genetic basis. Rarely, it is drug-induced (Table 28.10).

There is vasospasm of peripheral arterioles, aggravated by cold, and dilatation of the subpapillary venous plexus [2]. The condition is most probably a primary vascular defect since studies have not demonstrated a deficit of neuronal supply to the cutaneous vessels [3]. Decreased acral blood flow may be further compromised by plasma hyperviscosity. In ethylmalonic encephalopathy—a rare metabolic disorder with neuromotor delay, hyperlactic acidaemia and orthostatic acrocyanosis—a mutation has been demonstrated in *ETHE1*, a gene encoding a mitochondrial matrix protein [4].

Clinical features. Idiopathic acrocyanosis usually starts in adolescence and persists into adult life. The changes may be transient after cold exposure but usually persist during the winter and even throughout the summer months. Clinically there is a painless mottled duskiness of both hands in the presence of normal peripheral pulses. Similar changes may be seen on the feet and face. Trophic changes, such as ulceration, are absent. In some individuals acrocyanosis spontaneously remits. Acrocyanosis must be distinguished from Raynaud's phenomenon, which occurs episodically with triphasic colour changes and often involves just a few digits. Arterial and venous occlusion must be excluded. In cases of acrocyanosis developing for the first time in adult life a secondary cause should be sought (Table 28.10).

Treatment. There is no effective medical treatment for acrocyanosis. Vasodilator therapies, such as the calcium channel antagonists, do not appear to be beneficial.

Drug-induced acrocyanosis will be improved by cessation of the culprit drug. Treatment of an underlying systemic disorder may improve the appearance in secondary acrocyanosis.

References

1 Poszepczynska-Guigne E, Viguier M, Chosidow O *et al*. Paraneoplastic acral vascular syndrome: epidemiologic features, clinical manifestations and disease sequelae. *J Am Acad Dermatol* 2002; **47**: 47–52.

2 Sivula A. Vascular reactions in acrocyanosis. *Angiology* 1966; **17**: 269–74.

3 Goldsmith PC, Leslie TA, Polak JM, Dowd PM. Acrocyanosis and perniosis: an investigation of cutaneous neural and endothelial peptides in digital skin. *Skin Pharmacol* 1994; **7**: 563–73.

4 Tiranti V, D'Adamo P, Briem E *et al*. Ethylmalonic encephalopathy is caused by mutations in ETHE1, a gene encoding a mitochondrial matrix protein. *Am J Hum Genet* 2004; **74**: 239–52.

Erythrocyanosis

Aetiology and pathology. Erythrocyanosis is a persistent, dusky erythema occurring at sites with a thick layer of underlying subcutaneous fat, such as the thighs and lower legs. Erythrocyanosis is seen less commonly on the buttocks and arms. It is exacerbated by cold and therefore usually more prominent during the winter. It has been hypothesized that the subcutaneous fat in these sites acts to insulate the superficial vessels from the warmth of the underlying blood supply, thus rendering them susceptible to cold exposure.

Clinical features. Erythrocyanosis is seen on the lower legs of adolescent girls, the thighs and buttocks of overweight boys and the thighs and lower legs of middle-aged women. Very occasionally it can occur on the forearms of infants. It is characterized by dusky discoloration of the skin and may be accompanied by keratosis pilaris, angiokeratomas and telangiectases. Nodular perniotic lesions occurring after cold exposure may complicate erythrocyanosis. Oedema and fibrosis may be seen as chronic manifestations of erythrocyanosis. The disorder may persist indefinitely but spontaneous improvement can occur in adolescent patients.

Treatment. Warm clothing, exercise, weight reduction and elastic support hosiery may be helpful. Vasodilators, such as calcium channel antagonists, are of limited value.

Livedo reticularis

Synonyms
- Livedo racemosa
- Livedo annularis

Definition. Livedo reticularis is a mottled, cyanotic discoloration of the skin, which has a characteristic network pattern. It is accentuated by cold.

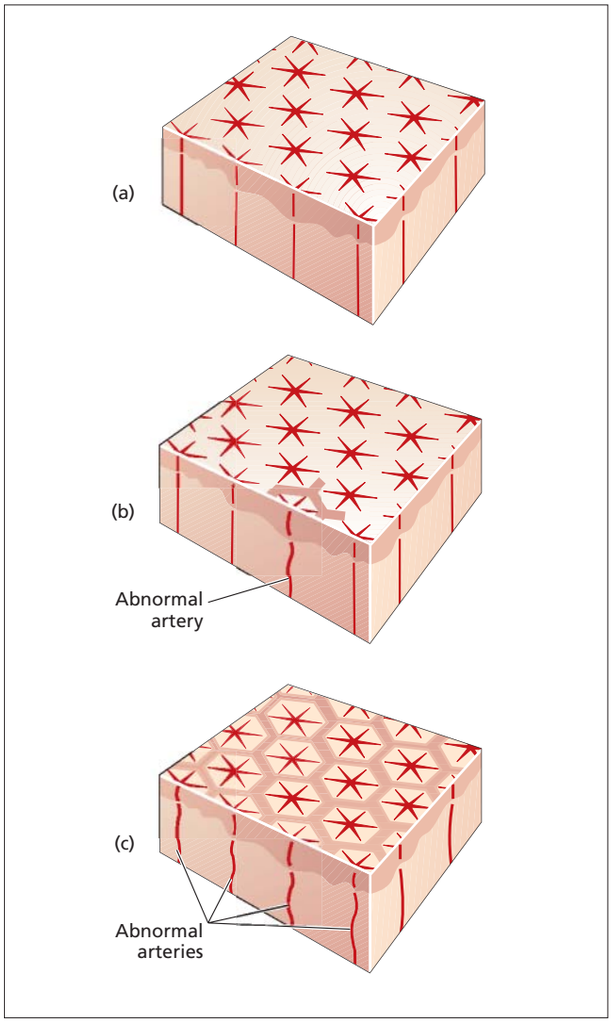


Fig. 28.20 Diagrammatic representation of (a) normal vasculature; (b) livedo racemosa due to patchy arterial pathology; (c) livedo reticularis due to diffuse arterial pathology.

Aetiology and pathology. The blood supply of the skin is arranged in cones, the bases of which measure 1–4 cm in diameter and lie on the skin's surface [1]. Each cone is supplied by an arteriole, which passes through the dermis perpendicular to the surface. When blood flow through the feeding arterioles is diminished, deoxygenated blood at the anastamotic junctions produces a cyanotic network pattern on the skin which is livedo reticularis (Fig. 28.20).

Livedo reticularis may be physiological, idiopathic or secondary to intravascular obstruction or vessel wall disease (Table 28.11).

Clinical features. Livedo reticularis most commonly occurs on the legs but the arms and trunk may also be affected. Cold usually exacerbates the cyanotic discoloration while leg elevation tends to decrease the intensity of the colour changes. Diffuse arterial

disease or hyperviscosity problems give rise to diffuse livedo reticularis; limited arterial disease leads to patchy mottling. In many cases livedo reticularis forms a complete network, in other cases there is a branching configuration, known as livedo racemosa. Ulceration of the dark areas occurs rarely but, if present, suggests significant large vessel vasculitis or intraluminal thrombosis. The appearance of livedo reticularis is initially reversible if the underlying cause is treated, but with chronic problems permanent telangiectases develop.

Physiological livedo reticularis

Synonym
- Cutis marmorata

Cutic marmorata is a transient cyanotic mottling of the skin which occurs as a physiological response to cold exposure and disappears with warming. It is usually encountered in healthy infants and resolves during the first year of life. Involvement of the trunk as well as the limbs is common. Physiological livedo reticularis rarely occurs in adults, but in this situation is often associated with a disorder that causes stasis within blood vessels, for example paralysis.

Congenital livedo reticularis

Synonym
- Cutis marmorata telangiectatica congenita

This is a rare developmental defect, present at birth, characterized by a red-purple vascular network [11–13]. Lesions are usually asymmetrical, typically on a limb, less often involving the torso or head. The reticulated area is persistent and enhanced by cold, crying and exercise. Skin atrophy may accompany the livedo. Usually congenital livedo reticularis occurs in isolation but it may be associated with a variety of other congenital abnormalities.

In most cases the condition gradually resolves, with most improvement occurring during the first 2 years of life.

Acquired idiopathic livedo reticularis

This occurs predominantly in young adult and middle-aged women. Mild degrees are harmless, more severe cases are associated with ulceration, usually in the winter. The mottling is at first transient and occurs on exposure to cold. Permanent livedo may develop with time. Tingling and numbness of the skin, and sometimes oedema, may be present.

The diagnosis is clinical and can only be made once other disorders have been ruled out, including erythema ab igne, capillary naevi and angioma serpiginosum and causes of secondary livedo reticularis.

Livedo reticularis occurs in 20–25% of migraine sufferers and in this subset stroke is more frequent, raising the possibility that livedo reticularis can be used as a clinical marker to identify those migraine sufferers with an increased risk of stroke [14].

References

1 Unna PG. *The Histopathology of the Diseases of the Skin* (Walker N. transl.). Edinburgh: Clay, 1896.
2 Falanga V, Fine MJ, Kapoor WN. The cutaneous manifestations of cholesterol crystal embolization. *Arch Dermatol* 1986; **112**: 1194–8.
3 Pennington M, Yeager J, Skelton H, Smith KJ. Cholesterol embolization syndrome: cutaneous histopathological features and the variable onset of symptoms in patients with different risk factors. *Br J Dermatol* 2002; **146**: 511–7.
4 Greer KE, Cooper PH, Campbell F *et al.* Primary oxalosis with livedo reticularis. *Arch Dermatol* 1980; **116**: 213–4.
5 Shih HA, Kao DM, Elenitsas R, Deyden JJ. Livedo reticularis, ulcers and peripheral gangrene: cutaneous manifestations of primary hyperoxaluria. *Arch Dermatol* 2000; **136**: 1272–4.
6 Mann RJ, Gostelow BE, Meacock DJ *et al.* Pentazocine ulcers. *J R Soc Med* 1982; **75**: 903–9.
7 Champion RH, Rook A. Idiopathic thrombocythemia. Cutaneous manifestations. *Arch Dermatol* 1963; **87**: 302–5.
8 Singh AK, Wetherley-Mein G. Microvascular occlusive lesions in primary thrombocythaemia. *Br J Haematol* 1977; **36**: 553–64.
9 Winkelmann RK, Keating FR. Cutaneous vascular calcification, gangrene and hyperparathyroidism. *Br J Dermatol* 1970; **83**: 263–8.
10 Howe SC, Murray JD, Reeves RT *et al.* Calciphylaxis, a poorly understood clinical syndrome: more case reports and a review of the literature. *Ann Vasc Surg* 2001; **15**: 470–3.
11 Kurczynski TW. Hereditary cutis marmorata telangiectatica congenita. *Pediatrics* 1982; **70**: 32–3.
12 Piscascia DD, Esterly NB. Cutis marmorata telangiectatica congenita: report of 22 cases. *J Am Acad Dermatol* 1989; **20**: 1098–104.
13 Rogers M, Poyzer KG. Cutis marmorata telangiectatica congenita. *Arch Dermatol* 1982; **118**: 895–9.
14 Tiretjen GE, Al Qasmi MM, Shukairy MS. Livedo reticularis and migraine: a marker for stroke risk? *Headache* 2002; **42**: 352–5.

Raynaud's phenomenon

Definition. Raynaud's phenomenon is defined as episodic digital ischaemia occurring in response to cold or emotional stimuli. It is characterized by sequential colour changes, white (pallor), blue (cyanosis) and red (rubor). Pallor is essential for the diagnosis. However, in severe recalcitrant Raynaud's phenomenon, particularly in association with a connective tissue disease, attacks of long duration may occur in which the initial pallor is short-lived and succeeded by prolonged cyanosis. Primary Raynaud's phenomenon (also called Raynaud's disease) is idiopathic and occurs as an isolated innocuous disorder (Table 28.12). Secondary Raynaud's phenomenon occurs in association with underlying diseases, or is caused by physical factors or drugs (Table 28.13).

Aetiology and pathology. The sequential colour changes were first described by Maurice Raynaud in 1862 [1]. In 1901, Jonathan

Table 28.12 Criteria for the diagnosis of primary Raynaud's phenomenon.

Intermittent attacks of discoloration of extremities
Absence of evidence of organic peripheral arterial occlusion
Symmetrical or bilateral distribution
Exclusion of any disease, occupation, trauma or drug ingestion that could give rise to vasospastic abnormalities
Absence of immunological abnormalities
Female sex, age under 25 years
History of cold intolerance since childhood
Normal nail fold capillaries

Table 28.13 Causes of Raynaud's phenomenon.

Primary Raynaud's phenomenon (Raynaud's disease)
Secondary Raynaud's phenomenon
Trauma or vibration
Reflex sympathetic dystrophy
Vibration exposure
Arteriovenous fistula
Hypothenar hammer syndrome (ulnar artery thrombosis)
Intra-arterial drug administration
Connective tissue disease and vasculitis
Systemic sclerosis
Systemic lupus erythematosus
Rheumatoid arthritis
Sjögren's syndrome
Mixed connective tissue disease
Dermatomyositis
Temporal arteritis
Hepatitis B antigen vasculitis
Obstructive arterial disease
Atherosclerosis
Thromboangiitis obliterans (Buerger's disease)
Hypothenar hammer syndrome (ulnar artery thrombosis)
Neurological disease
Thoracic outlet syndrome (cervical rib)
Carpal tunnel syndrome
Hypothenar hammer syndrome
Reflex sympathetic dystrophy
Haematological disease
Cryoglobulinaemia
Cold agglutinins
Paroxysmal haemoglobinuria
Waldenström's macroglobulinaemia
Drugs and toxins
Ergot
β-Blockers
Methysergide
Bleomycin
Amfetamines (amphetamines)
Imipramine
Bromocriptine
Clonidine
Ciclosporin (cyclosporin)
Oral contraceptives
Vinyl chloride
Nitroglycerin withdrawal
Heavy metals
Miscellaneous
Paraneoplastic syndrome
Chronic renal failure
Primary pulmonary hypertension
Hypothyroidism
Anorexia nervosa

Hutchinson reported that there were several causes for the phenomenon [2] and, subsequently, Allen and Brown established clinical criteria to distinguish innocent primary Raynaud's phenomenon from secondary Raynaud's phenomenon [3]. The advent of immunological tests for the connective tissue diseases has helped refine the diagnosis of primary Raynaud's phenomenon (Table 28.12).

Studies of prevalence in Raynaud's phenomenon have been hampered by differences in diagnostic criteria and survey technique. Population-based surveys have reported a prevalence between 6% and 20% in women and between 3% and 12.5% in men [4]. There is some evidence for an increased prevalence of Raynaud's phenomenon in family members of affected individuals, suggesting a genetic susceptibility [5]. A genome linkage study of affected individuals within a family indicated five candidate regions with possible linkage of which three were potential candidate genes: the beta subunit of the muscle acetylcholine receptor and the serotonin 1B and 1E receptors [6].

The pathogenesis of Raynaud's phenomenon is centred on a functional unit composed of vascular endothelium, smooth muscle cells and nerve endings. This integrated neurovascular system responds to a range of soluble mediators and physical stimuli, which determine the balance between vasoconstriction and vasodilatation. In primary Raynaud's phenomenon the vascular changes are considered to be functional. By contrast, in secondary Raynaud's phenomenon there are structural vascular changes, most clearly delineated in patients with systemic sclerosis. Severe intimal hyperplasia consisting of collagen deposits is often associated with intravascular thrombi, which can completely occlude the lumen [7]. In systemic sclerosis there is also distorted nailfold capillary architecture with dilated loops and areas of vessel dropout.

Aberrant expression of endogenous vasodilatory substances (nitric oxide, prostacyclin, prostaglandin and leukotrienes) and vasoconstrictors (endothelin, angiotensin II and thromboxane A2) has been implicated in the pathogenesis of Raynaud's phenomenon [8]. A disturbance in vascular homeostasis may lead to uncontrolled vasoconstriction and studies have demonstrated down-regulation of nitric oxide and up-regulation of endothelin-1 in Raynaud's phenomenon patients [9,10]. Investigation into innervation pathways of vascular smooth muscle have highlighted a prominent role for α2c-adrenoreceptors in cold-induced vasoconstriction [11]. Studies of Raynaud's phenomenon patients have demonstrated that, compared to normal controls, the increased contractile response to cold and α2-adrenergic agonists is associated with increased activity of protein tyrosine kinase and tyrosine phosphorylation in vascular smooth muscle [12].

Clinical features. Primary Raynaud's phenomenon is commoner in women, in the proportion of at least 5:1 [13]. The age of onset is usually under 40 years, but it may occur over this age. Age and sex distribution of secondary cases is that of the underlying disease, and is not therefore so restricted to the female sex. Raynaud's phenomenon affects the hands and, less often, the feet; changes elsewhere are exceptional, although the tongue can be involved [14].

A typical attack consists of sudden pallor of one or more digits, followed after a few minutes by cyanosis or sometimes by erythema. In primary Raynaud's phenomenon the condition is usually symmetrical and involves several digits. In secondary Raynaud's phenomenon only one or a few digits are affected and asymmetry is not unusual. Attacks are usually precipitated by cold, either

local or of the whole body, by pressure or by psychological stimuli. Episodes may occur infrequently or many times each day. Severe cases, which are usually of secondary type, may be complicated by telangiectases of the nail fold, thinning and ridging of the nail, and atrophy or sclerosis of the fingers (sclerodactyly). Skin necrosis is extremely rare in primary Raynaud's phenomenon but not uncommon in secondary Raynaud's phenomenon and may result in destruction of the digits. The disease tends to run a variable course: in primary Raynaud's phenomenon the outcome is good in 80% of cases, but some disability occurs in 20%; in secondary Raynaud's phenomenon the prognosis is that of the underlying disease.

Diagnosis. The diagnosis of Raynaud's phenomenon can usually be made on the basis of the history. Acrocyanosis is distinguished by the absence of paroxysmal pallor.

Application of the criteria listed in Table 28.12 is sufficient in most cases to distinguish primary from secondary Raynaud's phenomenon. The history should exclude those cases due to vibration and heavy metal and ergot intoxication. Buerger's disease and other organic arterial diseases are very rare causes of Raynaud's phenomenon. The thoracic outlet syndrome and cervical rib must be excluded in atypical cases and where asymmetry occurs. Such disorders require full neurological examination, observation of the effect on the pulse of movement at the shoulder girdle, and radiological investigation. An underlying neoplasm must be sought in any case with sudden onset in adult life, especially in men, and if digital tip necrosis occurs.

Female patients with age of onset over 25 years, no pre-existing cold intolerance, no occupational, traumatic or drug-related aetiology, and no history of a low body weight should be regarded as being at high risk of developing connective tissue disease. The presence of abnormal capillaries on nail fold microscopy is suggestive of a diagnosis of secondary Raynaud's phenomenon. In particular, Raynaud's phenomenon is a common presenting symptom of systemic sclerosis, but if there are no other signs within 2 years of onset, systemic sclerosis is less likely to develop. The presence of circulating autoantibodies (antinuclear, anticentromere and anti-Scl 70 antibodies) should be regarded as indicating a connective tissue disease until proven otherwise.

A search for cryoglobulins and cold agglutinins should be made in a patient developing Raynaud's phenomenon.

Treatment. An understanding of the pathophysiology of Raynaud's phenomenon directs treatment strategies while recent advances in key pathways have revealed potential targets for novel therapies [15].

A meta-analysis of 18 randomized, placebo-controlled, double-blinded trials assessed the efficacy of calcium channel blockers against placebo in patients with primary Raynaud's phenomenon and found a decrease in attacks and reduction in symptom severity [16]. Recommended doses of nifedipine range from 30 to 180 mg daily and for amlodipine between 5 and 20 mg daily. Slow release or long-acting preparations are recommended to improve compliance and reduce side effects, nonetheless discontinuation occurs in approximately 15% of subjects because of headaches and leg oedema [17].

In a double-blind, placebo-controlled study of 16 patients with secondary Raynaud's phenomenon, sildenafil 50 mg twice daily demonstrated significant improvement in mean attack rates and duration [18]. Sildenafil is a phosphodiesterase inhibitor and acts by increasing the vasodilatory effect of both nitric oxide and prostacyclin.

Intravenous infusion of vasodilatory prostaglandins can reverse ischaemic complications in Raynaud's phenomenon. Iloprost, a prostacyclin analogue, is commonly administered to patients with severe digital ulceration. In a randomized, placebo-controlled, double-blind study of 131 patients with systemic sclerosis, the mean weekly number of Raynaud's attacks significantly decreased on iloprost compared with placebo [19]. Repeated treatments with iloprost during one year was found to be more effective than nifedipine in reducing the severity score of Raynaud's phenomenon in patients with systemic sclerosis [20].

A study of bosentan, an endothelin receptor antagonist, demonstrated a marked reduction in new digital ulcers in systemic sclerosis patients but did not decrease the frequency or severity of Raynaud's attacks [21]. A randomized, controlled trial demonstrated that the angiotensin II receptor antagonist losartan significantly reduced the frequency and severity of vasoconstrictive episodes in patients with primary Raynaud's phenomenon and in Raynaud's phenomenon secondary to systemic sclerosis [22].

Topical glyceryl trinitrate, a nitric oxide donor, significantly reduced the number and severity of Raynaud's attacks in individuals with primary Raynaud's phenomenon and secondary Raynaud's phenomenon compared with placebo [23]; 2% glyceryl trinitrate was associated with headaches whereas 1% glyceryl trinitrate reduced the incidence of side effects but maintained a similar improvement in Raynaud's phenomenon symptoms [23].

References

1 Raynaud M. On local asphyxia and symmetrical gangrene of the extremities. In: Barlow T, trans. *Selected Monographs*, Vol. 121. London: New Sydenham Society, 1888.

2 Hutchinson J. Raynaud's phenomenon. *Med Press Circ* 1901; **72**: 403–5.

3 Allen EV, Brown GE. Raynaud's disease: a critical review of the minimum requisites for diagnosis. *Am J Med Sci* 1932; **183**: 187–200.

4 Fraenkel L. Raynaud's phenomenon: epidemiology and risk factors. *Curr Rheumatol Rep* 2002; **4**: 123–8.

5 Freedman RR, Mayes MD. Familial aggregation of primary Raynaud's disease. *Arthritis Rheum* 1996; **39**: 1189–91.

6 Susol E, MacGregor AJ, Barrett JH *et al*. A two-stage, genome-wide screen for susceptibility loci in primary Raynaud's phenomenon. *Arthritis Rheum* 2000; **43**: 1641–6.

7 Vajda K, Kadar A, Kali A, Urai L. Ultrastructural investigations of finger pulp biopsies: a study of 31 patients with Raynaud's phenomenon. *Ultrastruct Pathol* 1982; **3**: 175–86.

8 Bakst R, Merola JF, Franks AG, Sanchez M. Raynaud's phenomenon: pathogenesis and management. *J Am Acad Dermatol* 2008; **59**: 633–53.

9 Rajagopalan S, Pfenninger D, Kehrer C *et al*. Increased asymmetric dimethylarginine and endothelin 1 levels in secondary Raynaud's phenomenon: implications for vascular dysfunction and progression of disease. *Arthritis Rheum* 2003; **48**: 1992–2000.

10 Zamora MR, O'Brien RF, Rutherford RB, Weil JV. Serum endothelin-1 concentrations and cold provocation in primary Raynaud's phenomenon. *Lancet* 1990; **336**: 1144–7.

11 Chotani MA, Flavahan S, Nitra S *et al*. Silent alpha (2c)-adrenergic receptors enable cold-induced vasoconstriction in cutaneous arteries. *Am J Physiol Heart Circ Physiol* 2000; **278**: H1075–H1083.

12 Furspan PB, Chatterjee S, Maynes MD, Freedman RR. Increased tyrosine phosphorylation mediates the cooling-induced contraction and increased vascular reactivity of Raynaud's disease. *Arhtritis Rheum* 2004; **50**: 1578–85.
13 Maricq HR, Weinrich MC, Keil JE, LeRoy EC. Prevalence of Raynaud phenomenon in the general population: a preliminary study by questionnaire. *J Chronic Dis* 1986; **39**: 1189–91.
14 Giunta JL. Raynaud's phenomenon with oral manifestations. *Arch Dermatol* 1975; **111**: 78–80.
15 Boin F, Wigley FM. Understanding, assessing and treating Raynaud's phenomenon. *Curr Opin Rheum* 2005; **17**: 752–60.
16 Thompson AE, Pope JE. Calcium channel blockers for primary Raynaud's phenomenon: a meta-analysis. *Rheumatology* 2005; **44**: 145–50.
17 Fredrick MW, Wise R, Haythornthwaite J *et al*. Comparison of sustained-release nifedipine and temperature biofeedback for treatment of primary Raynaud phenomenon. *Arch Intern Med* 2000; **160**: 1101–8.
18 Fries R, Shariat K, von Wilmowsky H, Bohm M. Sildenafil in the treatment of Raynaud's phenomenon resistant to vasodilatory therapy. *Circulation* 2005; **112**: 2980–5.
19 Wigley FM, Wise RA, Seibold JR *et al*. Intravenous iloprost infusion in patients with Raynaud phenomenon secondary to systemic sclerosis. *Ann Intern Med* 1994; **120**: 199–206.
20 Scorza R, Caronni M, Mascagni B *et al*. Effects of long-term cyclic iloprost therapy in systemic sclerosis with Raynaud's phenomenon. *Clin Exp Rheumatol* 2001; **19**: 503–8.
21 Korn JH, Mayes M, Matucci Cerinic M *et al*. Digital ulcers in systemic sclerosis: prevention by treatment with bosentan, an oral endothelin receptor antagonist. *Arthritis Rheum* 2004; **50**: 3985–93.
22 Dziadzio M, Denton CP, Smith R *et al*. Losartan therapy for Raynaud's phenomenon and scleroderma: clinical and biochemical findings in a fifteen-week, randomised, parallel-group, controlled trial. *Arthritis Rheum* 1999; **42**: 2646–55.
23 Teh LS, Manning J, Moore T *et al*. Sustained-release transdermal glyceryl trinitrate patches as a treatment for primary and secondary Raynaud's phenomenon. *Br J Rheumatol* 1995; **34**: 636–41.

Cryoglobulinaemia

Cryoglobulinaemia refers to the presence of immunoglobulin complexes which precipitate *in vitro* when cooled below body temperature [1]. Cutaneous features in cryoglobulinaemia occur as a consequence of intravascular precipitation of cryoglobulins in the small vessels of the skin or as an immune complex disease (Chapter 49). In the demonstration of cryoglobulins, venous blood is drawn into a warm syringe and allowed to clot at 37°C. The serum (or plasma if cryofibrinogen is suspected) is cooled to 4–5°C and any precipitate noted. This should redissolve on warming. The amounts of cryoglobulin reported to cause symptoms are very variable: less than 25 mg/dL may rarely be associated with symptoms; much higher levels may be symptomless. Levels as high as 80 g/L have been recorded.

Type I cryoglobulins are single monoclonal immunoglobulins usually associated with haematological disorders, such as multiple myeloma, macroglobulinaemia and lymphoma. Type II mixed cryoglobulins are composed of a monoclonal component (usually IgMκ) with rheumatoid factor activity against polyclonal IgG. In type III mixed cryoglobulins, all the components are polyclonal [2]. Mixed cryoglobulinaemia is most commonly associated with hepatitis C virus (HCV) infection and is mainly of type III [3]. Other infections are also implicated in mixed cryoglobulinaemia, including hepatitis B and HIV, and cases are also seen in conjunction with autoimmune diseases, such as Sjögren's syndrome, SLE and rheumatoid arthritis [2].

Mixed cryoglobulinaemia causes a systemic vasculitis with multiorgan involvement, mainly skin, joints, kidneys and peripheral nerves. The most usual skin manifestation is purpura on the lower legs, which may develop after cooling of the extremities. In cryoglobulinaemia of all types other skin signs are livedo reticularis, Raynaud's phenomenon, atypical ulceration of the legs, digital skin necrosis and cold urticaria [4]. If cryoglobulinaemic vasculitis is suspected clinically, investigations should demonstrate circulating cryoglobulins, high rheumatoid factor titre, low C4 levels and leukocytoclastic vasculitis of the small blood vessels on skin biopsy. Histopathology of cryoglobulinaemia without vasculitis will reveal homogeneous, eosinophilic material within the vascular lumina of dermal vessels, which corresponds to cryoglobulin deposits.

Treatment of mixed cryoglobulinaemia is aimed at reducing immune complex activity by immunosuppression (prednisolone and cyclophosphamide) and plasmapheresis. In the presence of HCV infection, therapy should also be directed at viral eradication with pegylated interferon and ribavirin. Recently reports have demonstrated benefit from the use of rituximab, a chimeric monoclonal anti-CD20 antibody, which exerts a selective B-cell control [5].

References

1 Levo Y. Nature of cryoglobulinaemia. *Lancet* 1980; **i**: 285–6.
2 Tedeschi A, Barate C, Minola E, Morra E. Cryoglobulinaemia. *Blood Rev* 2007; **21**: 182–200.
3 Vigano M, Lampertico P, Rumi MG *et al*. Natural history and clinical impact of cryoglobulins in chronic hepatitis C. *Gastroenterology* 2007; **133**: 835–42.
4 Cohen SJ, Pettelkow MR, Su WP. Cutaneous manifestations of cryoglobulinaemia. Clinical and histopathologic study of seventy-two patients. *J Am Acad Dermatol* 1991; **25**: 21–7.
5 Zaja F, De Vita S, Mazzaro C *et al*. Efficacy and safety of rituximab in type II mixed cryoglobulinaemia. *Blood* 2003; **101**: 3827–34.

Cold agglutinins

Cold agglutinin disease is a disorder of autoimmune haemolysis in which cold-sensitive immunoglobulins react against erythrocyte surface antigens. In primary cold agglutinin disease, a bone marrow monoclonal $CD20^+$ κ^+ B-lymphocyte population is often demonstrated, while lymphoplasmacytic lymphoma may underlie the production of cold agglutinins in other patients [1]. Cases may also be secondary to a variety of diseases, notably mycoplasma and Epstein Barr virus infections. Cutaneous features occur mainly on acral sites and include Raynaud's phenomenon, acrocyanosis and skin necrosis. The results of therapy with corticosteroids, alkylating agents and interferon-α have been poor; however, studies of the chimeric anti-CD20 antibody rituximab have produced good response rates [2].

References

1 Berentsen S, Beiske K, Tjonnfjord GE. Primary chronic cold agglutinin disease: an update on pathogenesis, clinical features and therapy. *Haematology* 2007; **12**: 361–70.
2 Berentsen S, Tjonnfjord GE, Bradevold R *et al*. Favourable response to therapy with the anti-CD 20 monoclonal antibody rituximab in primary cold agglutinin disease. *Br J Haematol* 2001; **115**: 79–83.

Effects of heat and infrared radiation

The physical and biochemical effects of infrared (IR) radiation, comprising approximately 40% of solar irradiation, have been

relatively neglected [1], but are the subject of a comprehensive review [2].

IR is the segment of the electromagnetic spectrum that extends between red visible light and microwaves and radiowaves. The wavelengths range from 0.75 µm (750 nm) to 100 µm. As with UV radiation, there is an arbitrary subdivision into near IR (0.75–3 µm), middle IR (3–30 µm) and far IR (30–100 µm). Energy is inversely proportional to wavelength, therefore most biological effects are seen at shorter wavelengths. IR causes molecular vibration, the most obvious effect of which is to raise temperature. Radiation from 0.75 to 0.8 µm can cause photochemical reactions. Some wavelengths of IR are strongly absorbed by water—both in the atmosphere and in the hydrated stratum corneum. Transmitted IR can penetrate up to 30 mm [3]. The major sources of IR radiation are the sun and IR lamps but in clinical practice various forms of radiant heater in the home and workplace, hot water bottles, heating pads etc. are important.

Most experimental work into the effects of IR radiation on skin have used sources that emit UV and/or visible radiation as well, and the data are conflicting.

Experimental effects

Acute effects

IR alone produces erythema, which disappears by 6 h [4]. Histological studies have shown vasodilatation and mast cell degranulation [5]. The mediators have been studied in suction blisters and are essentially similar to those found in UVB erythema: free arachidonic acid, prostaglandins PGD_2, PGE_2, PGF_2 and 6 oxo-$PGF_{1\alpha}$. The free arachidonic acid level is still high after 72 h [6]. Epidermal proliferation is reduced by IR and does not become normal until after 7 days [7].

Prior heating with IR reduces the phototoxic response to methoxypsoralen and UVA [8]. The interaction between UV and IR radiation has been evaluated but with conflicting results [8–10] and further studies are needed.

Chronic effects

In a mouse model, over a 45-week period, the histological effects of radiation were studied, using a visible plus IR source—alone, in combination with UVA and UVB, and with UV followed by IR [11]. There was deposition of fibres with the staining properties of elastin in animals receiving only visible plus IR radiation, and an augmentation of the elastosis was attributable to UV. As with clinical solar elastosis, there was also an increase in ground substance.

Carcinogenesis

IR radiation can coagulate protein and nucleic acid and is synergistic with UV radiation in denaturing DNA. The production of UVB-induced cyclobutane dimers is temperature dependent [12], therefore this tumour-initiating event is likely to be augmented by IR. DNA repair after UV- and X-ray-induced damage is slower at 41–43°C than at 37°C, as occurs with heating resulting from IR [13]. It has been shown that mice heated to 35–38°C had a shorter latent period for UVR-induced tumours than controls [14,15]. Heat, wind and humidity have been shown to enhance UV carcinogenesis [16].

Erythema ab igne

Definition. A characteristic reticular telangiectatic and pigmented dermatosis, resulting from repeated or prolonged exposure to IR radiation, insufficient to produce a burn. It most commonly affects the legs of women.

Aetiology. The condition, once common in the UK, has become rare since the introduction of central heating, although it is still sometimes seen in rural areas among elderly people who stand or sit closely over fires, or who are habituated to the use of hot water bottles. It may be a valuable sign of hypothyroidism. A resurgence of the condition in the USA affects not only the elderly but also impecunious students [1], because of the high cost of central heating.

Sources other than domestic heating may be responsible for erythema ab igne at other body sites. Examples include the repeated application of hot water bottles or heated pads for chronic backache, recliner chairs with built-in heaters [17] and even bathing in hot water [18]. Among occupations, foundry men and bakers, and the various tasks that involve carrying heated coals (see below) are sometimes relevant. The car heater may be a cause [19]. Erythema ab igne has been found on the thighs of laptop computer users [20–23]. It has been reported as a useful marker of chronic pancreatitis because local heat relieves the abdominal pain [24] but also occurs when heat is applied for other real and imagined pains [25], including cancer [26]. In mentally disturbed patients with thermophilia, bizarre areas of erythema ab igne are sometimes encountered.

Histopathology [27–29]. In the early stages, epidermal atrophy, dermal pigmentation and vasodilatation are evident. Basophilic degeneration of the connective tissue, focal hyperkeratosis and epithelial cellular atypia occur later, closely resembling the changes induced by actinic damage [30]. Electron microscopy shows similar changes in the elastic fibres as found in chronic sun exposure [31]. There can be loss of type IV collagen from the basement membrane zone [32]. Keratoses and eventually squamous cell carcinomas may form (see below).

Clinical features. Any surface of the body is susceptible [33] and the condition can occur at all ages including children [34]. Following a single exposure to IR radiation of a subthreshold intensity, a mild and transient reticular erythema occurs. Further or repeated exposure causes a more marked erythema with noticeable hyperpigmentation and, sometimes, superficial epidermal atrophy. Subepidermal blistering [35] can occur in the affected skin (Fig. 28.21). The cumulative effects of small and repeated thermal exposures often clear during the summer months but involution gradually becomes less complete. The changes caused by repeated and prolonged exposure to IR radiation eventually resemble those of poikiloderma, with reticulate telangiectasia, atrophy, melanosis and diffuse hyperkeratosis.



Fig. 28.21 Erythema ab igne with subepidermal bulla formation.

The distribution of the dermatosis depends not only on the direction of the incident radiation, but also on the contour of the skin and the interposition of clothing. When erythema ab igne results from sitting in front of the fire, people may sit sideways, causing the outer aspect of one leg and the inner aspect of the other to be particularly affected. Others habitually sit directly in front, and a strictly symmetrical eruption is seen. In severely affected individuals the reticular pattern is lost, a wide area of skin becoming pigmented and atrophic, with only the periphery showing the characteristic pattern.

An unusual variant has been described in elderly immobile females with lymphoedema in which there are reticulate ridges of tissue that can be compressed [36].

Rarely, lichen planus, psoriasis or chilblain lupus may appear as a Koebner phenomenon in the affected area.

Diagnosis. Although diagnosis is usually straightforward, there may be confusion with livedo reticularis, in which changes are strictly symmetrical and telangiectatic rather than pigmented. When large vessels are involved, nodules and ulcers may coexist with livedo reticularis, a triad diagnostic of a severe vasculitis (see Chapters 49 and 50).

Management. Hypothyroidism should be excluded. In elderly women living alone, erythema ab igne may be a sign of hypothermia. The help of ancillary social services may be needed. Advice should be given on clothing and efforts made to improve the microvascular circulation. 5-fluorouracil cream has been used to eliminate the dyskeratotic keratinocytes [37].

Heat-associated carcinomas

Squamous carcinomas of the skin occurring in areas of heat damage have been known from ancient times, often regarded as exotic curios and their significance has been overlooked [38]. They include the Kang cancer of northern China [39] and Japan [40] from sleeping on beds of hot bricks, the Kangri cancer of Kashmir [41,42] from wearing pots of hot coals and the Kairo cancer of Japan caused by carrying metallic benzene-burning flasks—all devices to counteract cold. 'Turf' cancer of the legs of rural Irish women has been associated with standing for long periods of time over peat fires [43]. Simultaneous occurrence of Merkel cell carcinoma with squamous carcinoma has been recorded [44,45]. Basal cell carcinomas and actinic keratoses have been reported at a site on the cheeks of those wearing rimless glasses, where the temperature is higher than the surrounding skin because of focusing of the sun's rays [46,47].

Skin cancer following burns is discussed on p. 28.90.

References

1 Kligman LH, Kligman AM. Reflections on heat. *Br J Dermatol* 1984; **110**: 369–79.
2 Dover JS, Phillips TJ, Arndt KA. Cutaneous effects and therapeutic uses of heat with emphasis on infrared radiation. *J Am Acad Dermatol* 1989; **20**: 278–86.
3 Anderson RR, Parish JA. The optics of human skin. *J Invest Dermatol* 1989; **77**: 13–9.
4 Pullman H, Mores E, Reinbach S. Effect of infrared and UVA rays in the human skin and their efficacy in the treatment of atopic dermatitis. *Z Hautkr* 1985; **60**: 171–7.
5 Schulze HG, Schmidt R, Marle G. Infrared erythema. *Z Hautkr* 1985; **60**: 938–44.
6 Juhlin L, Civier A, Shroot S *et al.* Effect of infrared radiation on the recoverable levels of free arachidonic acid and prostaglandins in human forearm skin. *J Invest Dermatol* 1983; **81**: 297–300.
7 Schmidt R, Pullman H, Steigleder GK. Effect of infrared radiation on the kinetics of guinea pig's epidermis cells: comparison with UV radiation effect. *Z Hautkr* 1985; **60**: 947–56.
8 Kaidbey E, Witkowski TA, Kligman AM. The influence of infrared radiation on short term ultraviolet radiation-induced injuries. *Arch Dermatol* 1982; **118**: 315–8.
9 Hill L, Eidenow AA. Biological action of light: the influence of temperature. *Proc R Soc Lond* 1923; **95**: 163–80.
10 Park HJ, Youn JI, Lee YS. The influence of infrared radiation on ultraviolet-induced skin injury. *Korean J Dermatol* 1984; **22**: 176–82.
11 Kligman LH. Intensification of ultraviolet induced dermal damage by infrared radiation. *Arch Dermatol Res* 1982; **272**: 229–38.
12 Niggli HJ, Cerutti PA. Temperature dependence of induction of cyclobutane-type pyrimidine photodimers in human fibroblasts by 313 nm light. *Photochem Photobiol* 1983; **37**: 467–9.
13 Corry PM, Robinson S, Getz S. Hyperthermic effects on DNA-repair mechanisms. *Radiology* 1977; **123**: 475.
14 Bain JA, Rusch HP, Kline BE. The effects of temperature upon ultraviolet carcinogenesis with wavelengths of 2800–3400 Å. *Cancer Res* 1943; **3**: 610–2.
15 Freeman RG, Knox JM. Influence of temperature on ultraviolet injury. *Arch Dermatol* 1964; **89**: 858–64.
16 Owen DW, Knox JM. Influence of heat, wind and humidity on ultraviolet radiation injury. *Natl Cancer Inst Monogr* 1978; **50**: 161–7.
17 Meffert JJ, Davis BM. Furniture-induced erythema ab igne. *J Am Acad Dermatol* 1996; **34**: 516–7.
18 Lin SJ, Hsu CJ, Chiu HC. Erythema ab igne caused by frequent hot bathing. *Acta Derm Venereol* 2002; **82**: 478–9.
19 Helm TN, Spigel GT, Helm KF. Erythema ab igne caused by a car heater. *Cutis* 1997; **59**: 81–2.
20 Jagtman BA. Erythema ab igne due to a laptop computer. *Contact Dermatitis* 2004; **50**: 105.
21 Bilic M, Adams BB. Erythema ab igne induced by a laptop computer. *J Am Acad Dermatol* 2004; **50**: 973–4.
22 Maalouf E, Simantov A, Rosenbaum F, Chosidow O. Erythema ab igne as an unexpected computer side-effect. *Dermatology* 2006; **212**: 392–3.
23 Mohr MR, Scott KA, Pariser RM, Hood AF. Laptop computer-induced erythema ab igne: a case report. *Cutis* 2007; **79**: 59–60.
24 Mok DWH, Blumgart LH. Erythema ab igne in chronic pancreatic pain: a diagnostic sign. *J R Soc Med* 1984; **77**: 299–301.
25 Rudolph CM, Soyer HP, Wolf PM, Kerl H. Hot-water-bottle rash: not only a sign of chronic pancreatitis. *Lancet* 1998; **351**: 667.

26 MacHale J, Chambers F, O'Connell PR. Erythema ab igne: an unusual manifestation of cancer-related pain. *Pain* 2000; **87**: 107–8.
27 Finlayson GR, Sams WM Jr, Smith JG Jr. Erythema ab igne: a histopathological study. *J Invest Dermatol* 1966; **46**: 104–8.
28 Johnson WC, Butterworth T. Erythema ab igne elastosis. *Arch Dermatol* 1971; **104**: 128–31.
29 Shahrad P, Marks R. The wages of warmth: changes in erythema ab igne. *Br J Dermatol* 1977; **97**: 179–86.
30 Kligman AM. Early destructive effect of sunlight in human skin. *JAMA* 1969; **210**: 2377–80.
31 Cavallari V, Cicciarello R, Torre V *et al.* Chronic heat-induced skin lesions (erythema ab igne): ultrastructural studies. *Ultrastruct Pathol* 2001; **25**: 93–7.
32 Yasuda K, Wada E, Kitagawa N *et al.* Palmar erythema ab igne without detectable type IV collagen at the basement membrane zone. *J Dermatol* 1996; **23**: 484–8.
33 Milligan A, Graham Brown RAC. Erythema ab igne affecting the palms. *Clin Exp Dermatol* 1989; **14**: 168–9.
34 Wilson NJE, Sharpe GR. Erythema ab igne in a child with atopic eczema. *Clin Exp Dermatol* 1999; **24**: 336–9.
35 Flanagan N, Watson R, Sweeney E, Barnes L. Bullous erythema ab igne. *Br J Dermatol* 1996; **134**: 1151–65.
36 Cox NH, Paterson WD, Popple AW. A reticulate vascular abnormality in patients with lymphoedema: observations in eight patients. *Br J Dermatol* 1996; **135**: 92–7.
37 Sahl WJ Jr, Taira JW. Erythema ab igne: treatment with 5-fluorouracil cream. *J Am Acad Dermatol* 1992; **27**: 109–10.
38 Peterkin GA. Malignant change in erythema ab igne. *BMJ* 1955; **2**: 1599–602.
39 Laycock HT. The 'Kang Cancer' of north-west China. *BMJ* 1948; **1**: 982.
40 Akasaka T, Kon S. Two cases of squamous cell carcinoma arising from erythema ab igne. *Nippon Hifuka Gakkai Zasshi* 1989; **99**: 735–42.
41 Neve EF. Kangri-burn cancer. *BMJ* 1923; **2**: 1255–6.
42 Mulay DM. Skin cancer in India. In: Urbach F, ed. *The Biology of Cutaneous Cancer. Natl Cancer Inst Monogr* 1963; **10**: 215–24.
43 Cross F. On a turf (peat) fire cancer: malignant change superimposed on erythema ab igne. *Proc R Soc Med* 1967; **60**: 1307–8.
44 Jones SC, Tyring SK, Lee PC *et al.* Development of neuroendocrine (Merkel cell) carcinoma mixed with squamous cell carcinoma in erythema ab igne. *Arch Dermatol* 1988; **124**: 110–3.
45 Hewitt HB, Sherif A, Kerr KM *et al.* Merkel cell and squamous cell carcinomas arising in erythema ab igne. *Br J Dermatol* 1993; **128**: 591–2.
46 Corson EF, Knoll GM, Luscombe HA *et al.* Role of spectacle lenses in production of cutaneous changes, especially epithelioma. *Arch Dermatol* 1949; **54**: 435–48.
47 Kligman LH, Kligman AM (quoting Koscard E). Reflections on heat. *Br J Dermatol* 1984; **110**: 369–75.

Burns

A. Burd, pp. 28.74–28.92

Prevention and epidemiology. The burn injury is unique in the breadth of the spectrum of possible effects. The essential injury is caused by a pathological flux of energy within a tissue that results in a disruption of functional integrity [1]. The source of the energy may be thermal, electrical, chemical or radiation. The devastating consequences of the major burn injury and the long-term consequences of even small burns, in terms of scarring leading to disability and deformity, make prevention a key priority in burns care. Prevention and epidemiology are intimately linked but the reality is that the epidemiological studies of burn injury are frequently hospital-based and, without looking at defined populations, and in particular age stratifications, levels of risk cannot be determined. Prevention is a multifactorial process involving measures by the individual and by society and can be considered in the prevention hexagon (Fig. 28.22) [2]. Focused epidemiological studies can look at specific patient groups to identify recurring behaviour patterns that are associated with injury, and prevention strategies suggested [3,4].

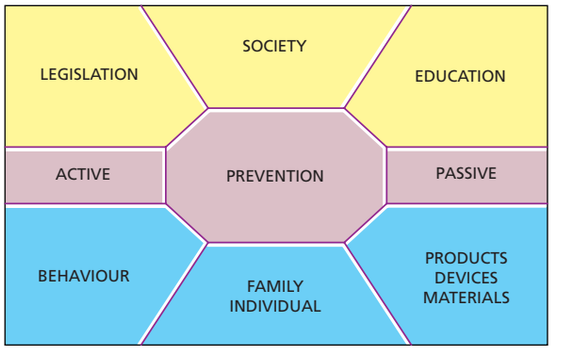


Fig. 28.22 The prevention hexagon. This figure represents the multidimensional nature of burns prevention. This can be looked at from the perspective of society or the perspective of the individual. For society, legislation is an active process, whilst for the individual, active prevention would involve a behavioural change. Conversely for society, education is a passive process whilst for the individual the safety features of products, devices and materials create a safer environment.

In developed countries where there is a strict adherence to health and safety issues, the incidence of industrial burns has shown a gratifying decrease [5]. There have also been changes in the pattern of domestic injuries. Major flame burns from house fires have decreased but there are still a large number of scalds in the second year of life when children are developing independent mobility but have not yet learnt fear. The truce incidence of burns in any population is difficult to determine because of the wide spectrum of the injury. Serious burns will be treated in specialist units. In the UK, there are 5000–6000 admissions to such units annually. An equal number of patients are seen and treated as outpatients in specialist clinics, and for each such patient approximately a further five are treated in accident and emergency departments without referral to a specialist clinic. An additional unknown number of burns are self-treated in the general population or treated in general practice.

Pathophysiology. The pathophysiological reaction to a burn injury is complex and varies with the cause. In thermal injuries, the changes in the burn wound are mainly caused by the direct effects of heat but superimposed on these are changes associated with an acute inflammatory process. It is these latter changes that account for the widespread and devastating effects of major burns on the entire range of homeostatic functions of the body [6].

The initial local response to a sudden increase in body surface temperature is the dilatation of blood vessels in an attempt to dissipate heat. A further increase in tissue temperature triggers an inflammatory response, mediated by peptides and low-molecular-weight substances that regulate the cellular function and microenvironment of the tissues. The key cells in the post-burn inflammatory response are the polymorphonuclear leukocyte, mast cell and endothelial cells. These, together with platelets, are the prime components responsible for the mediation, progression

and resolution of the inflammatory response. Activation of complement and coagulation cascades with the release of histamine from mast cells results in a short phase of vasodilatation and plasma protein leakage from post-capillary venules, resulting in local oedema formation. Intracellular proteases released as a result of cell damage activate kallikrein, which is responsible for transforming kininogen to kinin. Kinins have several effects, including vasodilatation, pain stimulation and leukocyte migration. A delayed phase of leukocyte and platelet margination then results in the release of prostaglandins, prostacyclins, thromboxanes, leukotrienes and lipoxins, which is accompanied by a substantial increase in microvascular permeability and changes in vasomotor control. The prolonged post-traumatic phase of vasodilatation and antiplatelet aggregation is regulated through endothelial cells via two different mediators: prostaglandin I_2 (PGI_2) and nitric oxide. Hypercoagulability of the lymph and the plasma has been observed 2–3 h after injury and correlates with the finding of increased levels of kinins in lymph.

Disseminated intravascular coagulation may also accompany a severe burn. As the tissues are infiltrated by leukocytes, the efficient elimination and destruction of injured tissue is effected. Neurotransmitters are also involved, especially substance P, which evokes vasodilatation and plasma protein leakage, and calcitonin gene related peptide, which is a potent vasodilator.

Burn depth. An accurate determination of the depth of injury is an important consideration when formulating a management plan for a burn patient. Theoretically, wound biopsy with histopathological examination would seem to be a very precise method for achieving this determination. Clinically, however, it is necessary to accept that burn wounds are rarely homogeneous in nature and partial thickness burns may well be of mixed depth. Biopsies will leave permanent scars in partial thickness wounds; they are also expensive and time-consuming to process. In addition, the burn wound is a dynamic entity and it may take up to a week for a stable state to be achieved.

In current burns practice, histology is rarely performed outside of research studies. Nevertheless, because of the importance of determining burn depth as a guide to wound management there are a number of alternative strategies being explored to objectively determine burn depth; these include laser Doppler perfusion imaging [7], dielectric measurement [8], photo acoustic microscopy [9], near infrared spectroscopy [10] and circulating plasma cell-free DNA [11]. The clinical estimation of burn depth is discussed below.

References

1 Lee RC, Astumian RD. The physicochemical basis for thermal and nonthermal 'burn' injuries. *Burns* 1996; **22**: 509–19.
2 Burd A, Ahmed K. Mosquito-net burns and the prevention hexagon. *Burns* 2007; **33**: 261–3.
3 Tse T, Poon CH, Tse KH, Tsui TK, Ayyappan T, Burd A. Paediatric burn prevention: an epidemiological approach. *Burns* 2006; **32**: 229–34.
4 Wong P, Choy VY, Ng JS *et al*. Elderly burn prevention: a novel epidemiological approach. *Burns* 2007; **33**: 995–1000.
5 Herndon DN. *Total Burn Care*, 3rd edn. London: Saunders, 2007.
6 Arturson G. Pathophysiology of the burn wound and pharmacological treatments. *Burn* 1996; **22**: 255–74.
7 Droog EJ, Steenbergen W, Sjoberg F. Measurement of depth of burns by laser Doppler perfusion imaging. *Burns* 2001; **27**: 561–8.
8 Papp A, Lahtinen T, Harma M *et al*. Dielectric measurement in experimental burns: a new tool for burn depth determination? *Plast Reconstr Surg* 2006; **117**: 889–901.
9 Zhang HF, Maslov K, Stoica G, Wang LV. Imaging acute thermal burns by photoacoustic microscopy. *J Biomed Opt* 2006; **11**: 054033.
10 Cross KM, Leonardi L, Payette JR *et al*. Clinical utilization of near-infrared spectroscopy devices for burn depth assessment. *Wound Repair Regen* 2007; **15**: 332–40.
11 Chiu TW, Young R, Chan LY *et al*. Plasma cell-free DNA as an indicator of severity of injury in burn patients. *Clin Chem Lab Med* 2006; **44**: 13–7.

Clinical aspects

The rationalization of the care of burns patients requires effective prehospital management, transportation and assessment, and triage in a hospital emergency department. The importance of education and communication at this level cannot be overestimated. Subsequent, safe transfer of a stable patient to a specialized burns unit initiates the next phase of treatment. There are some excellent accounts of acute [1] and total burn care [2,3]. The account that follows is an overview of the immediate assessment and management of a burn, and is aimed at the non-burns specialist who may be faced with the emergency care and short-term treatment of such patients.

First aid and prehospital management

Stop the burning process

The patient must be removed from the source of injury and the ongoing damage halted. Obviously care must be taken to ensure that rescuers and helpers do not themselves become injured but this can and does happen. This is a particular problem with electrical and chemical injuries. Patients sustaining chemical injuries should have clothing removed as quickly as possible and copious irrigation with water is the key to first aid. In chemical burns, the tissue damage is very much a function of the concentration of the agent and the duration of exposure, therefore in the otherwise fit patient, copious irrigation at the scene of the accident is preferable rather than immediate transfer to an emergency centre. It is essential to be aware of the possible dangers of handling contaminated clothing; appropriate protective clothing, including gloves and eye protection, should be available for the emergency services.

With electrical injuries, the source of electrical current should be identified and switched off, if possible, and the victim moved from the source of the current using non-conductive materials.

In flame burns, the first priority is to extinguish the source of the burn, which can be accomplished by rolling the patient on the ground, by application of a smothering blanket or coat or by the use of water or extinguishing foams. The next priority, as with scald burns, is to promote cooling. This is best performed with water or water-soaked towels. Early cooling can reduce the depth of the burn and reduce pain, but caution must be exercised as a significant drop in body temperature can result in hypothermia.

Primary survey

The primary survey is the rapid assessment of the patient to ensure immediate survival. Attention is focused on airway, breathing, circulation and cervical spine immobilization. The most immediate threat is to the airway. This is always a problem when there

has been significant smoke inhalation, but also when there have been burns of the face or neck. Upper airway oedema can develop rapidly, compromising the patency of the airway. Oxygen 100% should be available and administered. The patency of the airway should be assured using customary techniques. The neck is extended and, if the victim is unconscious and the tongue appears to be obstructing the airway, an oropharyngeal airway should be inserted. If upper airway obstruction appears to be developing, for example if there is severe and progressive hoarseness after severe smoke inhalation, the insertion of an endotracheal tube may be necessary. It should be noted, however, that it is rare for oedema to develop in under 30–40 min from the time of removal from the fire. It is far better for correct placement of an oro-endotracheal tube to be performed by an anaesthetist in controlled circumstances than for the blind nasal intubation by an inexperienced paramedic or emergency physician.

It is important to establish that there is a pulse. In a large burn, this may be more meaningful than blood pressure measurement in establishing that there is a circulation.

Sometimes, the incident that has resulted in the burn may have caused other injuries, for example in automobile accidents, explosions and house fires. In these situations, it is very important to be aware of the possibility of spinal cord injury. Cervical spine immobilization must be accomplished using an appropriate cervical collar until the patient can be appropriately evaluated.

Secondary assessment

The secondary assessment involves a thorough head to toe examination of the patient. A rapid check is made of the patient's head, neck, thorax, abdomen, upper and lower limbs to ensure that no other life-threatening injuries are present and that, if they are, the appropriate measures are taken. It is also appropriate at this time to ascertain, if possible, any relevant past medical history, medications or allergies and to establish the mechanism and time of injury.

It may be appropriate to establish an intravenous line but it must be recognized that in a major burn access is going to be a significant problem, and it is essential not to damage possible sites for cannulation. If it is possible to get a patient to hospital within 60 min of injury, an intravenous line is not essential and may be deferred.

With regard to the burn wound, the patient should be wrapped in clean dressings. Sterility is not important. No topical antimicrobial dressings should be applied. The priority is to transport the patient to hospital, and unnecessary delay should be avoided. Covering the wound may diminish the pain, and small aliquots of intravenous analgesia may be given.

During the process of transport, the receiving accident department should be notified of the incoming patient and the severity of the problem so that appropriate receiving staff and facilities can be mobilized. The determination of the severity of the injury is, however, particularly difficult for those who do not have regular experience of assessing burns patients.

Important information includes:

1 Age
2 Sex
3 Type of injury
4 Brief details of incident
5 Time of injury
6 Extent of injury
7 Associated injuries
8 General status of patient.

Assessment in the hospital accident department

The assessment of the patient in the accident department is essentially the same as for any trauma patient, with treatment priorities based on the stability of the vital signs and the mechanism of injury [3]. The logical sequence of treatment priorities can be quickly established using the same overview as briefly described in the prehospital treatment. Two unique aspects of burns are critical determinants of severity: the depth of the burn and the area of the burn.

Depth of burn [4,5]

Burns can be simply classified as being partial (Figs 28.23 & 28.24) or full thickness (Fig. 28.25); partial thickness burns are then sub-



Fig. 28.23 A superficial partial thickness burn in a young girl who fell into a bath of hot water. Clothing marks are visible. The burns were completely healed by 5 days.



Fig. 28.24 A deep partial thickness burn of the back sustained in an explosion. The scorched skin has been débrided. The burns healed within 3 weeks with conservative therapy.

divided into superficial partial thickness and deep partial thickness (Fig. 28.26). This classification is very important in subsequent decisions regarding surgical management of the burn, but in the initial assessment other factors will determine the more immediate aspects of treatment, including whether to refer the patient to a specialized burns centre. It is possible to make an estimate of the depth of the burn from the clinical appearance (Table 28.14).

Area of burn

The assessment of area of the burn is important as it directly affects the fluid resuscitation of the patient together with the disposition of the patient. Various methods are available to determine the percentage of the body surface that is burnt. The simplest method is the 'Rule of Nines', which divides the body surface into areas of 9% or multiples of 9% (Fig. 28.27).

In the infant or child, a more accurate assessment can be made using the Lund and Browder chart, which takes into account the relative changes in proportions of head and legs in the growing child (Fig. 28.28).

A further guide to estimating the area of the burn is to realize that the size of a hand can be useful for assessing the total area of scattered burns. Although generally described as the closed palm of the patient being equal to approximately 1% of the body surface area (BSA), this concept has been re-examined and redefined; the 'handprint' (the whole palmar surface of the hand, including the palm and volar aspect of the unspread digits) actually approximates to 1% of BSA [6]. It is important not to include simple erythema in the estimation of the burn injury. Erythema is a reversible hyperaemia, which is not associated with tissue damage. As such it will not give rise to the pathophysiological changes that occur with tissue destruction, which may require intravenous fluid replacement.



Fig. 28.25 A full thickness fatal burn in an elderly woman whose nightdress caught fire on a gas cooker.

Fluid resuscitation [7,8]

The hypovolaemic shock that follows burn injury is caused by a shift of fluid from the vascular to the extravascular compartment. The more extensive the burn, the more extensive the shift of fluid. This fluid shift is a progressive phenomenon, which is maximal within hours of the burn and can persist for several days after the burn. As a simple guide, all patients who have burns in excess of 10% BSA should be commenced on intravenous resuscitation. Intravenous fluid resuscitation is also indicated for all patients with inhalation injury and other associated injuries. A minimum of two large-bore intravenous cannulae should be inserted, preferably through unburned tissue. After insertion, blood should be taken for blood grouping and cross-matching, and baseline laboratory studies that include a complete blood count, serum electrolytes, glucose, blood urea nitrogen and creatinine. As soon as

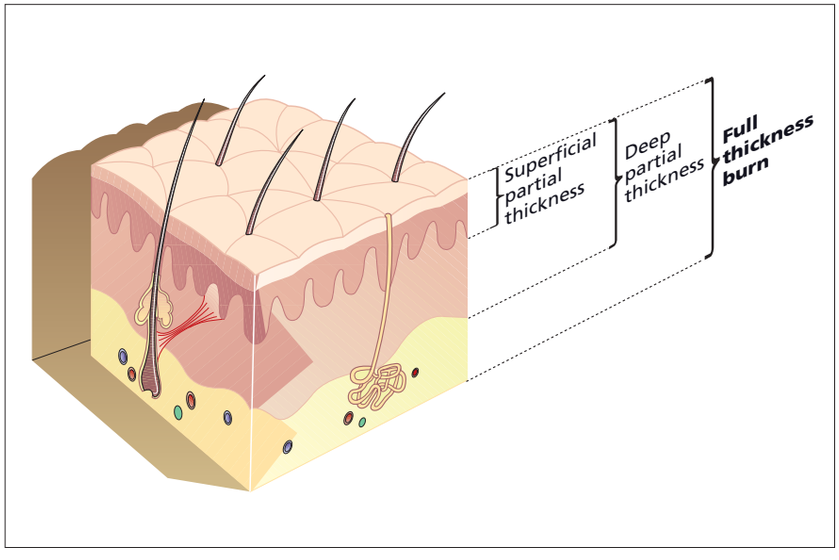


Fig. 28.26 Burns are classified according to their thickness.

Table 28.14 Clinical features of partial and full thickness burns.

Depth	Colour	Blisters	Capillary refill	Sensation
Superficial partial thickness	Pink	±	Present	Painful
Deep partial thickness	Red/pale	±	No	±
Full thickness	White	No	No	No

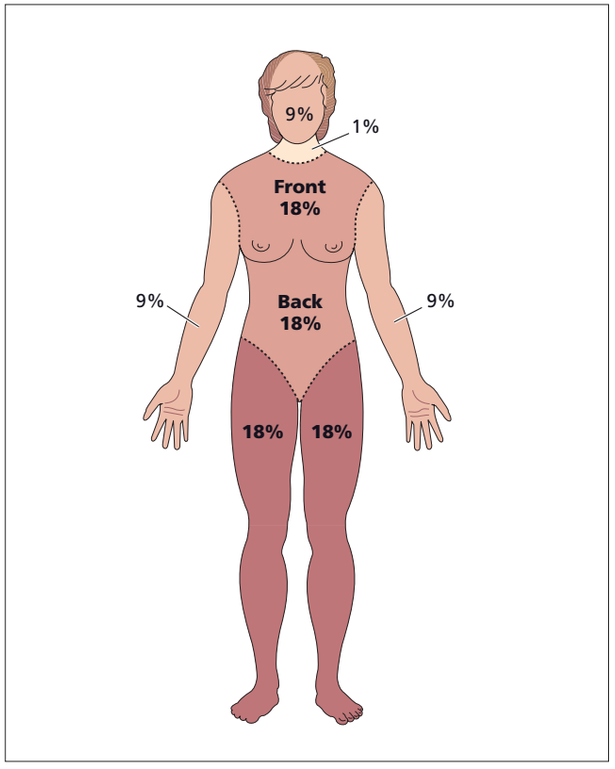


Fig. 28.27 The Rule of Nines.

feasible the patient should be weighed, as resuscitation formulae are based on a combination of body weight and area of burn.

The intravenous fluid infusion has to be regulated to give in the first 24 h:

- *Adults*: 2–4 mL Hartmann's solution/kg body weight/% BSA burn
- *Children*: 3–4 mL Hartmann's solution/kg body weight/% BSA burn.

The intravenous fluid rate is adjusted to give half of the estimated volume in the first 8 h post-burn. The remaining half of the estimated resuscitation volume should be administered over the subsequent 16 hours of the first day post-burn.

In children, there should be an additional element given for maintenance fluids because of the increased evaporative fluid losses. Maintenance requirements for the first 24 h are 1000 mL for the first year of life, plus 100 mL for each subsequent year of life up to 5 years of age. A 5-year-old child would thus require the following maintenance fluids in the first 24 h:

$$1000\,\text{mL} + (4 \times 100) = 1400\,\text{mL}$$

The formula is only a guide, and clinical and laboratory monitoring are essential to tailor the fluid requirements to the individual patient.

The goal of resuscitation is to maintain vital organ function while avoiding the complications of inadequate or excessive fluid infusion. Excessive volumes of intravenous fluid can increase tissue oedema formation and compromise tissue oxygenation. Pulmonary and/or cerebral oedema are particularly problematic. Inadequate fluid resuscitation can cause diminished perfusion of the renal and mesenteric vascular beds, which can lead to organ failure [8].

Urine output

Urine output is the single best indicator of fluid resuscitation in the uncomplicated burn. Accurate measurement of urinary output requires the insertion of an indwelling Foley catheter. Acceptable hydration is indicated by a urine output of more than 0.5 mL/kg/h in an adult and 1.0 mL/kg/h in a child. In the initial stage of resuscitation, diuretics are not usually indicated. Patients with high-voltage electrical injuries or crush injuries may have myoglobin and/or haemoglobin in the urine. This predisposes to renal tubular obstruction. In this situation, an osmotic diuresis should be promoted by giving intravenous mannitol 1 g/kg (20% solution), and urinary alkalinization should be considered. The urine can be alkalinized using isotonic sodium bicarbonate intravenously at a rate sufficient to maintain urinary pH > 6.5 without the plasma pH exceeding 7.45. The urine pH should be monitored 4-hourly, and acid–base balance and serum electrolytes 6-hourly. This is continued until the myoglobinuria and/or haemoglobinuria disappears.

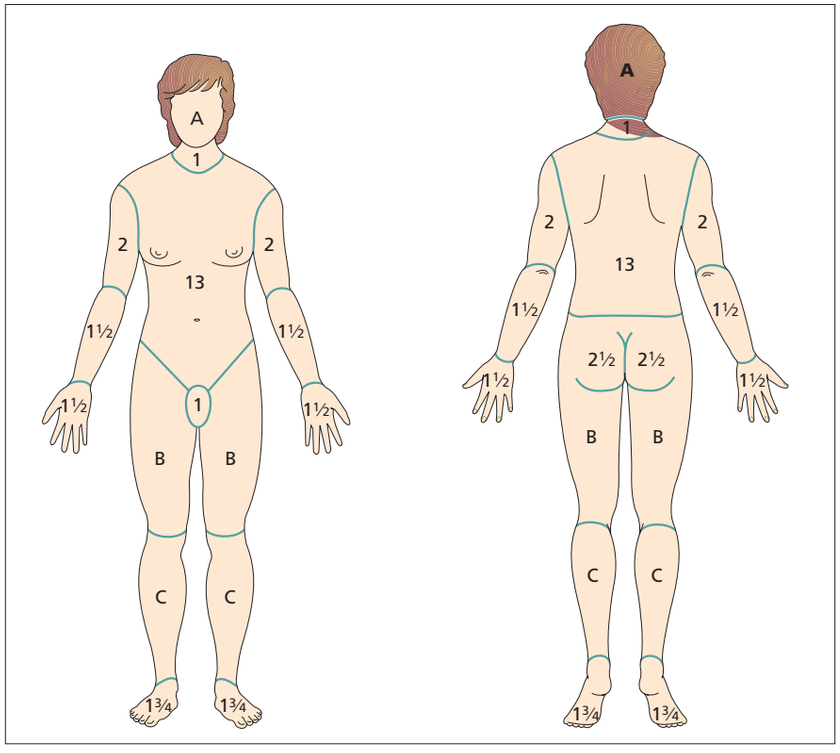
Gastrointestinal tract decompression

In the immediate and early stages of management of the major burn, it is important to be aware that the patient may require surgery and general anaesthesia. The patient should be given nil by mouth until seen and assessed by a burns physician. It is appropriate to insert a nasogastric tube. This can decompress the stomach, which may become distended from the combination of the stress response to trauma together with diminished peristalsis in the gastrointestinal tract associated with use of narcotic analgesia.

Immediate wound care

Very little needs to be done to the burn wound itself prior to assessment by the burns physician. Frequent reassessment is necessary to look for harmful effects of the wound on ventilatory and circulatory function with a view to undertaking escharotomies to relieve the splinting effect of the wound.

The patient must be kept warm and dry. It is essential to prevent the traumatized patient from becoming hypothermic, and wet dressings should be avoided on the burns. Appropriate dressings will depend upon local conditions and duration of transport. Clean surgical drapes can be used to cover the patient. Clingfilm can be used if there is no danger of hyperthermia; in cold climates 'space blankets' may be useful.



	Relative percentage of body surface area affected by growth					
Area	**Age 0**	**1**	**5**	**10**	**15**	**Adult**
A = ½ of Head	9½	8½	6½	5½	4½	3½
B = ½ of one Thigh	2¾	3¼	4	4½	4½	4¾
C = ½ of one Leg	2½	2½	2¾	3	3¼	3½

Fig. 28.28 Lund and Browder chart.

Pain relief

There are two aspects to the pain experienced by the burn victim: one is the physical pain from the injury, but another major component is the psychological trauma that the victim suffers. Morphine is indicated for both pain relief and as a powerful anxiolytic. It should be given only by the intravenous route, as changes in peripheral perfusion make the subcutaneous or intramuscular route unpredictable. In adults, a dosage of 1–4 mg i.v. every 2–4 h is indicated for severe pain. For children, the dosage of morphine should be modified according to the weight of the child, using 0.2 mg/kg i.v. in the first instance, and subsequently titrating the dose according to the response.

Additional medication

The need for tetanus prophylaxis is based on the patient's immunization status and the nature of the wound. All patients with burns in excess of 10% BSA should receive 0.5 mL tetanus toxoid. If prior immunization is unclear or unknown, 250 units of tetanus immunoglobulin are also given.

Decompression

The concept of escharotomy has long been associated with acute burns care. Nevertheless the practice of escharotomy is frequently flawed and there is considerable diversity in the teaching of the procedure. It is proposed that there should be a fundamental change in the teaching of acute burn management and the concept of decompression should be promoted [9] (Table 28.15). In circumferential burns of chest, abdomen and limbs the skin can lose its normal plasticity and create the outer limit of a 'closed compartment'. In very severe cases the rise in tissue pressure in a limb can lead to complete cessation of arterial inflow and loss of distal limb perfusion. It is, however, possible to have adequate distal perfusion in the presence of a compromised microcirculation in the limb muscles. In the chest the consequence of the raised tissue pressure can be decreased respiratory excursion and decreased ventilatory function. The rise in compartmental pressures is usually insidious and there is a need to constantly review the signs of peripheral perfusion but also feel the limb for increasing tenseness. In the lung, ventilation pressures can be measured and in the abdomen,

Table 28.15 Points to consider in the application of decompression. Decompression is a continual process and does not depend on clearly defined and quantifiable parameters. Judgment is needed particularly in the late presentation. On balance it is perhaps better to err on the side of decompression in the early presentation (<12 h post-burn) and against decompression in the late presentation (>24 h post-burn).

Factors	Responses for consideration
Constricting material	Remove rings, tight clothing, tight bandages
Positioning	Level of the heart
Fluids	Consider colloids from 12–24 hours
Circumferential full and deep partial-thickness burns	Surgery strongly indicated irrespective of signs and symptoms
Extensive burns with large volume resuscitation even in non-circumferential burns	Surgery must be considered (even in non-burned limbs)
Full thickness burns	Consider fasciotomy
Skin incision	Consider as for fasciotomy
Availability of optimum conditions	In theatre General anaesthetic Aseptic technique Coagulating diathermy
Monitoring	Consider practicality and feasibility
Clinic assessment	Again. Again. Again.
Late presentation >24 h	Consider leaving limb undecompressed if periphery viable

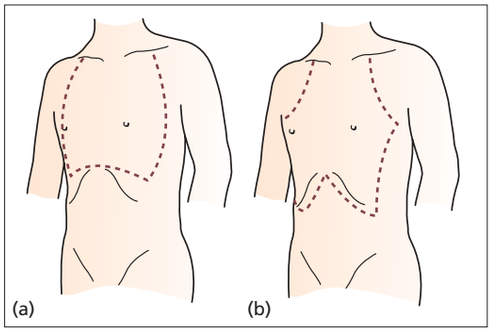


Fig. 28.29 (a) Depicts the often reproduced diagram of chest decompression that indicates a transverse release mid-way between the costal margin and the nipple and (b) shows a release which is just below and parallel to the costal margin. The latter release will effectively separate the abdomen and thorax and reduce resistance to ventilation. (Reproduced from Burd *et al.* [9], with permission.)

pressures can be measured via the urinary bladder. Where there is concern about progressive rise in tissue pressures which are threatening adequate tissue oxygenation, then surgical intervention has to be considered. Releasing the tension in the skin and superficial fascia may result in improved perfusion and loss of limb tension. If this does not happen then release of the deep fascia may be necessary. Surgical decompression should ideally be undertaken in an operating room environment, under general anaesthesia and using electrocautery to seal the wounds. Traditionally, incisions have been mid-axial but there is accumulating evidence to move away from this approach to incisions based more on anatomy and functional release. Incisions for the chest are shown in Fig. 28.29. The important points to note are making a long lateral release and connecting these with a transverse incision below the costal margin. This releases the anterior chest skin from the abdomen and allows for intercostal as well as diaphragmatic breathing. Fig. 28.30 shows the skin incisions for a medial arm release and for a ventral forearm release. In the thigh a single axial lateral or medial release will usually suffice and in the calf two incisions will be needed to give access to the four lower limb compartments (Fig. 28.31). When undertaking decompression it is reasonable to perform an escharotomy through these incisions, and then to assess the result before releasing the deep fascia.

Triage

When the burn patient has been evaluated and stabilized, a decision has to made about further treatment. There are recognized criteria for those burns that should be referred to a specialized burns unit (Table 28.16). Local conditions may dictate modifications to this list, but if there is any doubt about a patient's suitability of transfer, there should be direct consultation with the burns unit physician.

Transfer of the patient

The decision to transfer a patient becomes more difficult when there are associated injuries. The treatment of these may take precedence over the treatment of the burn, for example an intra-abdominal injury, major long-bone fracture, open-chest injury or intracranial bleed. A senior clinician should be involved in the referring hospital and a decision should be made jointly with a senior specialist in the burns unit. Once a decision has been made to transfer a patient to the burns unit, it is essential that he or she is properly stabilized before transfer. Essential prerequisites are listed in Table 28.17.

Documentation

It is essential to include all available information about the nature of the injury as well as the physical findings and extent of the burns. In addition, there should be a clear flow chart documenting resuscitation measures, drugs given and blood results. Doctor-to-doctor contact is essential to ensure the safe transfer of the patient. This is particularly the case where a patient has been intubated in the referring hospital. The communication should be a two-way process, and the burns unit should inform the referring hospital of the outcome of treatment of the burn patient, not only as a matter of professional courtesy but also from the point of view of continuing medical education.

Overview of continued fluid resuscitation

In most situations, the continued resuscitation of the burns patient will take place in a specialized centre. There will be occasions, however, as a result of associated injuries or problems with transport, where a non-burns specialist may have to supervise the management of the patient through the critical period of fluid resuscitation.

The patient who has been managed in the orderly manner as described above is in the best condition to move into the next

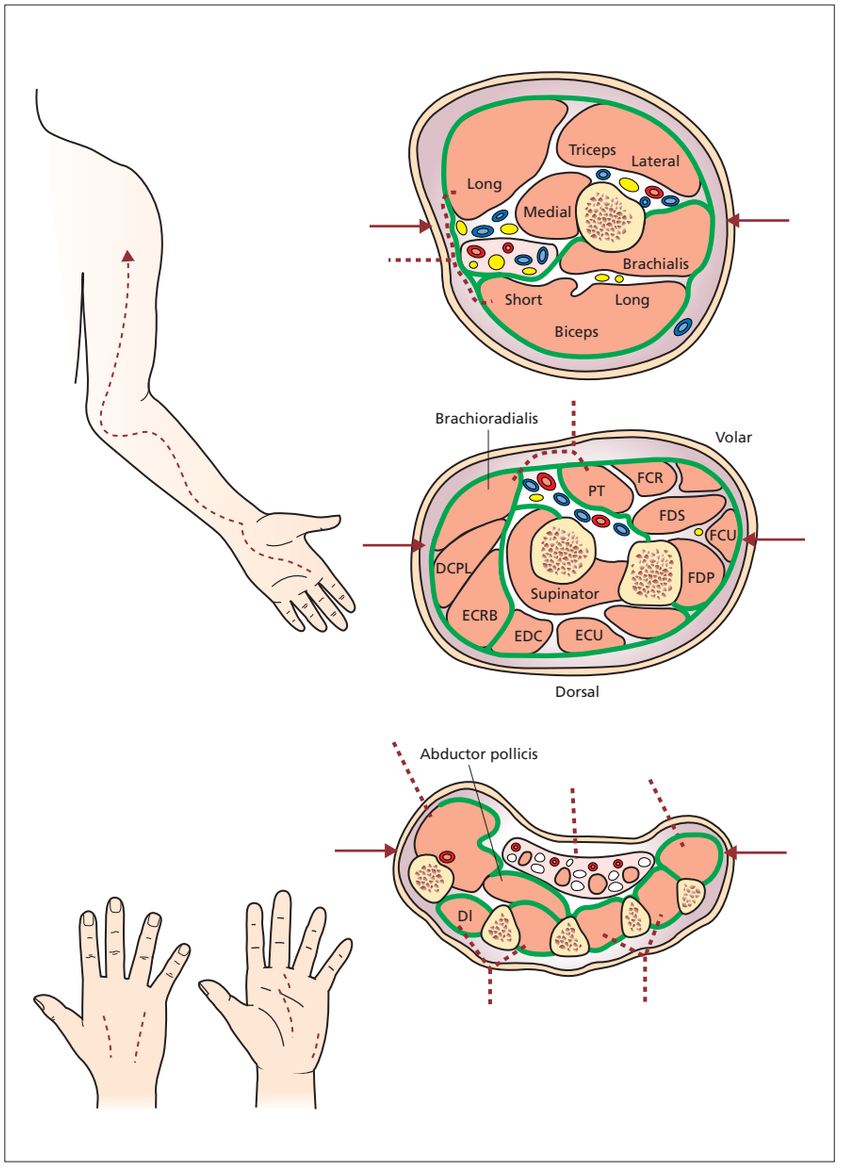


Fig. 28.30 Cross-section of upper limb anatomy depicting the escharotomy incision (red arrow) and the fasciotomy incision (dashed line). (Reproduced from Burd *et al.* [9], with permission.)

critical phase of proper fluid management. Mortality in the first 24–48 h post-burn has decreased considerably with increasing understanding of the massive fluid shifts from the intravascular to the extravascular (intracellular and interstitial) spaces that occur during the burns shock phase. The primary goal of fluid therapy is to replace the fluid sequestered as a result of the thermal injury. It is obvious from the many formulae that have been proposed over the years that there is no universally accepted burns resuscitation formula. It must be emphasized that whatever formula is used, it is only a guideline and the actual amounts of fluid given should be varied according to clinical response.

In principle, the least amount of fluid should be given to maintain adequate organ perfusion, and the infused fluid must contain sodium to replace the extracellular salt lost into the burned tissue and into the cell. In the past, there has been great debate over the relative merits of crystalloid versus colloid resuscitation regimens. In the absence of convincing clinical evidence to support either, the burns physician should take into account local practices, availability and cost of solutions, and should develop a protocol that can be safely and effectively adhered to but that will provide the flexibility to take into account individual patient requirements.

In this overview, the fluid to be infused in the first 24 h is derived from a consensus formula recommended by the Advanced Burn Life Support Course in the USA and the Emergency Management of Severe Burns Course from Australia and New Zealand. The figures are based on the Parkland formula.

However, it must be recognized that plasma proteins are extremely important in the circulation, as they generate the inward oncotic force that counteracts the outward capillary hydrostatic force. It has been demonstrated experimentally that restoration and maintenance of plasma protein concentrations are not effective until 8 h post-burn, at which time normal levels can be

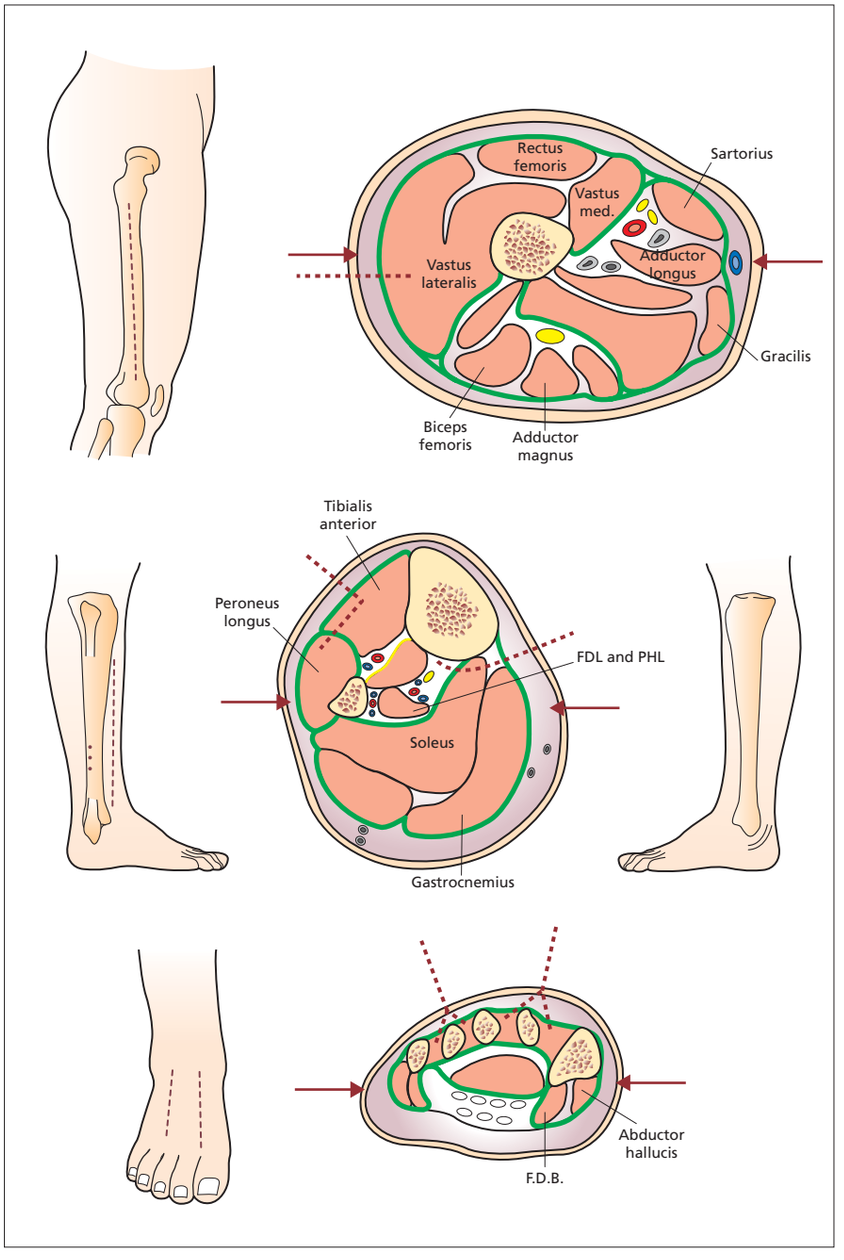


Fig. 28.31 Cross-section of lower limb anatomy depicting the escharotomy incision (red arrow) and the fasciotomy incision (dashed line). (Reproduced from Burd *et al.* [9], with permission.)

Table 28.16 Criteria for referral to a burn centre.

Burns greater than 10% BSA
Burns that involve and threaten functional or cosmetic impairment of the face, hands, feet, genitalia, perineum and major joints
Full thickness burns greater than 5% BSA
Electrical burns
Chemical burns
Burns associated with inhalational injury
Circumferential burns of limbs or chest
Burns at the extremes of age (children and elderly)
Burn injury in patients with pre-existing medical disorders which could complicate management, prolong recovery, or affect mortality
Any burn patient with concomitant trauma

BSA, body surface area.

Table 28.17 Essential measures to be performed before transfer to a specialist burns unit.

1 Respiratory support
- 100% oxygen with or without intubation

2 Circulatory support
- Intravenous access + infusion + urethral catheter

3 Gastrointestinal decompression

4 Wound care

5 Pain medication

6 Tetanus immunization

maintained with infusion. With this in mind, it is recommended that colloid should be introduced into the resuscitation regimen once the initial phase of massive fluid shift has begun to stabilize. While this may occur as early as 12 h post-burn, a consensus recommendation is to introduce the colloid in the second 24 h using 0.3–0.5 mL of colloid/kg body weight/% BSA burned. The colloid should be 5% normal serum albumin (50 g/L).

Monitoring response to resuscitation

There is no single parameter of perfusion in the burn patient that can be considered to be a completely reliable indicator of tissue oxygenation. Therefore, a combination of observations should be made. As the severity of the burn increases so does the need for more complex and invasive monitoring [10].

Continuous monitoring

Cardiac monitoring. Arrhythmias are not worrying in the young patient so long as oxygenation is adequate, but are a major concern in the patient over 45 years of age in whom they may be the first indicator of hypoxia or of electrolyte and acid–base abnormalities.

Arterial blood pressure *per se* is an insensitive measure of volume status because of the increased sympathetic tone in the early stage of resuscitation. However, a minimal level of perfusion pressure must be maintained and therefore blood-pressure monitoring must be established. An arterial line may be required if the patient is haemodynamically unstable and if frequent blood gases are required.

Pulse oximetry can provide continuous information on the oxygen-haemoglobin saturation and is non-invasive.

Body temperature. The core and peripheral temperature should be recorded. The burn patient is very prone to hypothermia with the infusion of cool fluids, and it must be recognized that thermoregulation is abnormal in burns. The damage to the skin interferes with normal mechanisms of heat conservation and dissipation; in children, there is also a disturbance of hypothalamic control. This has two important consequences:

1 Pyrexia in children in the first 36 h post-burn is most probably not related to infection.
2 Core–peripheral temperature gradients become unreliable indicators of haemodynamic status.

Fluid balance. During the first 24 h post-burn, in the absence of an abnormal solute load (e.g. glucose, mannitol or alcohol, which may falsely increase urine output in the presence of hypoperfusion), urine output should reflect the glomerular filtration rate and therefore renal perfusion. A urine output of 0.5–1.0 mL/kg/h normally reflects adequate renal blood flow. The rate of fluid administration should be increased if urine output is below 0.5 mL/kg/h but this should not be too rapid as boluses will cause marked transient increases in venous pressure and thus will significantly increase oedema. A urine output of more than 1.0 mL/kg/h usually means too much fluid is being given, with the possibility of excess oedema formation. Myoglobinuria will cause red discoloration of the urine (Figs 28.32 & 28.33).



Fig. 28.32 Total burning of the legs in a patient who fell asleep smoking and woke up with the bed on fire. Skin, fat, muscle, tendon and bone were all burnt.

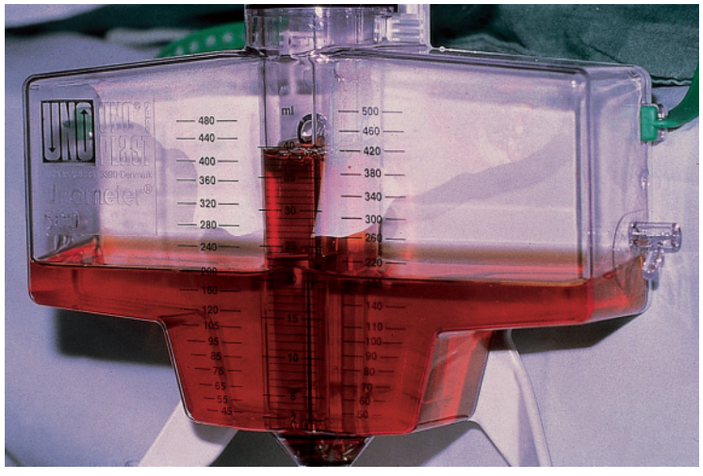


Fig. 28.33 The urine in the same patient showing the bright-red colour of myoglobinuria.

Monitoring central venous pressure (CVP) or pulmonary artery wedge pressure may be necessary. In the early stage of resuscitation of a patient with a large burn, the CVP is usually low, in the region of 0–5 cmH_2O even with adequate fluid resuscitation, but can be used to follow trends. The majority of young patients, even with massive burns, do not require pulmonary artery wedge pressure monitoring for initial resuscitation, and the morbidity associated with pulmonary artery lines may outweigh the benefits. As with the CVP, the pulmonary artery wedge pressure is usually normal to low (6–10 mmHg) after a burn even when adequate perfusion is present. Hypoperfusion is almost always caused by hypovolaemia.

The interpretation of the values obtained by this level of intensive monitoring is the domain of the intensive care specialist. In patients with severe burns, unlike other forms of trauma, the ideal values for more complex cardiorespiratory variables such as measurements of oxygen delivery and consumption are at present unknown, and aggressive attempts to optimize microcirculatory

blood flow by the use of volume loading, inotropes or vasodilators may be inappropriate. This is because generation of high intravascular pressures in the presence of a generalized capillary leak may only serve to increase the rate of fluid loss and to exacerbate the oedema-related complications of increased tissue pressure and decreased tissue oxygen tension.

Intermittent monitoring

Haemoglobin and haematocrit. Baseline values are useful but thereafter changes in values may not accurately reflect changes in blood volume because of the selective loss of plasma from the blood. Haemoconcentration invariably occurs after large burns, and normalization of blood volume will take some 24–48 h. Blood loss during this time can be underestimated, for example from escharotomies, internal bleeding or associated with fractures, because the rate of plasma loss may exceed the rate of whole-blood loss resulting in a normal haematocrit despite severe volume depletion.

Electrolytes. As the initial losses are primarily from plasma, the sodium, chloride and potassium values remain relatively constant despite hypovolaemia and vary mainly as a result of the type of resuscitation fluid used. Osmotic hyponatraemia occurs in the presence of a solute such as glucose or mannitol to which cells, including osmoreceptors, are incompletely permeable (solutes to which cells are readily permeable such as ethanol or urea do not exert the osmotic effect to expand extracellular volume and lower the plasma sodium concentration).

Water intoxication occurs when sodium losses are replaced by hypo-osmolar solution or if hyponatraemia is corrected too rapidly.

The term sick-cell syndrome is used by some to describe clinical states of hyponatraemia associated with profound systemic disease such as renal and hepatic failure. It is also described in burns where it is thought to result from hypovolaemia, infection, anaemia or undernutrition. Dysfunction of the cellular sodium–potassium adenosine triphosphatase pump is thought to be the cause. If other causes of hyponatraemia have been excluded, this diagnosis should be considered if there is reversal of the sodium : potassium ratio (normally >1) to <1. Treatment is directed at the primary cause.

Elevated potassium levels occur if there is marked haemolysis or rhabdomyolysis, or if renal disease is present. It is important to note, however, that potassium-sparing drugs have prolonged effects, and that actual hyperkalaemia may occur in the absence of significant renal dysfunction. Emergency management should be given if serum potassium exceeds 7.0 mmol/L, or if there is widening of the QRS complexes, heart block or dysrhythmia.

Creatinine and blood urea nitrogen. It is useful to establish baseline values to rule out intrinsic renal disease. Thereafter, changing figures indicate trends in resuscitation.

Coagulation screen. Initial values of prothrombin time, partial thromboplastin time and platelet count are useful in the resuscitation phase to establish baseline values. It is not common to replace clotting factors and platelets during the first 36 h, although this may become a critical issue in the later stages of burn management.

Chest X-ray. If the patient is ventilated, a daily chest X-ray should be obtained. The development of pulmonary problems following smoke inhalation is a progressive phenomenon and requires intensive and specialized care.

Burn wound management [5]

The management of the burn wound is in a continuous state of evolution and is not without controversy. The principle is to achieve healing as quickly as possible with the minimum of scarring. One of the problems concerning burn wound management relates to the phenomenon alluded to earlier, the 'burns spectrum'. There are two critical aspects that determine the severity of burn injury: the depth of the burn and its extent.

The vast majority of burns are small and superficial and may be self-treated, or treated in emergency rooms or by general practitioners. These burns are best treated by deroofing blisters, gentle cleansing with saline and the application of a non-adherent dressing overlain with an absorbent layer.

When the depth of burn is greater, the role for conservative treatment becomes more controversial. Surgery is definitely indicated for full thickness burns unless there are overriding clinical considerations to the contrary.

The major controversy surrounds the management of the deep partial thickness burn. These burns can and will heal if allowed to do so in an environment that protects the wound from infection. Healing can take several weeks, however, and there is a high incidence of hypertrophic scarring in deep partial thickness burns that have been allowed to heal spontaneously. The decision will depend on the experience of the burn surgeon because there have been no extensive randomized controlled trials to indicate the 'best' approach. The controversy is of particular relevance to the vast majority of children's burns, which are scalds, and which are often of 'indeterminate' depth. Some burn surgeons advocate waiting until the depth of burn declares itself at approximately 48 h; if it is assessed that the burn will not heal within 7–10 days, the patient will be taken to the operating room and the dead tissue tangentially excised until there is a wound bed of viable tissue on which a split-thickness autograft can be placed. The arguments for this approach include rapid wound closure with less likelihood of infection, shorter hospital stay and improved cosmetic result. This approach will mean that certain patients might have unnecessary surgery, with the risks of general anaesthesia and an additional wound at the donor site. Other surgeons advocate waiting for 10–14 days before making the assessment, and then grafting only those areas that look unlikely to heal by 3 weeks. This approach reduces the likelihood of unnecessary or extensive surgery, but does require a longer time to complete healing with an increased time of exposure to the risk of infection and a greater chance of hypertrophic scarring.

A third approach, which is particularly suitable for children in whom scalds predominate, is to perform an examination under anaesthetic at 3–5 days post-burn. At this stage the depth of burn is assessed clinically by assessing turgor in the tissues, as well as the presence or absence of blanching or 'fixed' staining of the



Fig. 28.34 (a) An 11-month-old child with a deep dermal scald exhibiting fixed staining in the wound; (b) covered with closed meshed glycerolized human allograft; (c) 2 weeks later the allograft is dry and spontaneously separating; (d) allogenic skin all removed, healed burn that did not develop hypertrophy. (Reprinted from [10], © 2002, with permission from Elsevier Science.)

burned skin. Even in the presence of fixed staining, indicating a deeper dermal burn, if there is absence of maceration of the wound, a biological dressing can be applied after thorough cleansing. Figure 28.34 shows the progression of healing after the application of glycerolized human cadaver skin [11]. While the surgical management of the burn wound is not within the remit of the dermatologist, advice may be sought regarding management of the burn wound in the acute stage. It is very important that the preferences of the local specialist centre are known as the application of different dressing materials may radically alter the appearance of the burn wound and thus affect the surgical decision-making process.

The critical determinant regarding whether to treat surgically or conservatively is the depth of burn. While there have been many attempts to develop techniques to achieve this objectively, the most common and practical clinical approach remains the assessment by an experienced burn surgeon who will use visual and tactile cues. Such clinical subjective assessment is only 70–80% accurate as compared to the use of laser Doppler imaging; although this technique remains in the research domain at present, its incorporation into routine clinical practice would give a more predictable outcome to the management of the burn wound.

Use of topical antimicrobial treatment, as with dressings, should not interfere with the wound appearance, and has to be balanced with the very real risks of infection developing within the burn wound. Early colonization of the burn wound is likely to be associated with Gram-positive cocci. Patterns of microbial activity vary between units and within time; *Streptococcus pyogenes* group A used to be regarded as the most serious pathogen but there is now far more concern about staphylococcal toxaemia, particularly in children with small burns.

Where early surgery is not the practice or is not indicated for some other reason, topical antibacterial creams were commonly used. Silver sulfadiazine 1% cream, with or without chlorhexidine,



Fig. 28.35 A full thickness skin defect that has been treated with Integra® for 3 weeks. The outer silicone layer is here being removed. New dermis has been formed, and is now ready for a thin graft.

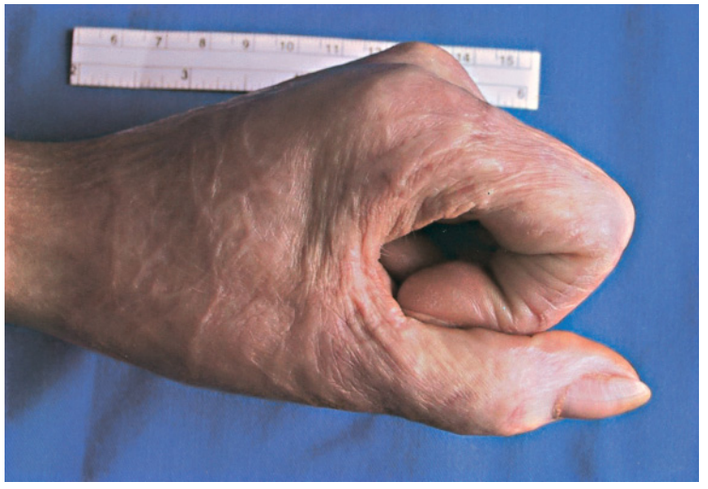


Fig. 28.36 Six years after applying Integra® to resurface a full thickness burn on the left hand the skin shows multiple fine wrinkles. The patient was aged 19 years.

is active against Gram-negative bacteria, including *Pseudomonas* spp. Typically, the cream is spread liberally on to dressings and applied to large areas. A subsequent development of the use of silver sulphadiazine cream was the incorporation of cerium nitrate. The cerium nitrate effectively tannalizes the burned tissue, thus forming a dry antibacterial eschar. This was subsequently easy to remove surgically, compared with the more macerated eschar of the silver sulphadiazine alone. The use of cream formulations is, however, now being surpassed by the application of silver-containing dressings. These allow the sustained release of silver and increase the interval between dressing changes. Dressing designs are varied, based on laminates, hydrofibres, foams and gels. Antimicrobial and also cytotoxic effects of the dressings vary [12,13]. Alternative dressing regimes continue to be explored and non-medicated dressings have been reported to be effective for burn wounds, particularly for superficial burns [14,15].

Surgical intervention

Surgery essentially involves removing the irreversibly damaged burned tissue and closing the wound. Surgery can involve tangential shaving of partial thickness burns or excision of full thickness burns. The surgeon now has an increasing number of options for closing the burn wound. When the wound is small, an autograft is the method of choice. The larger the burn area, the smaller the available donor sites for obtaining autografts. It is in these larger burns that great advances in terms of survival have been made with the trend towards early surgery and burn wound closure. Wound closure has been achieved using a wide range of materials including human allografts, fresh, frozen and glycerolized porcine xenografts, *in vitro* cultured keratinocytes used as both allo- and autografts, together with a variety of synthetic materials used as temporary dressings. Continuing interest is focused on burn wound closure using a dermal regeneration template, Integra® [16]. This synthetic bilaminate membrane is manufactured using biological raw materials (Fig. 28.35). The dermal analogue is an open lattice of fibres made of bovine collagen covalently linked to chondroitin-5-sulphate. The temporary outer layer, the epidermal analogue, is medical grade silicon, which is subsequently replaced with an ultrathin epidermal autograft. The collagen-GAG dermal analogue has a three-dimensional architecture similar to that of normal dermis and completely biodegrades after 30 days. It thus serves as a scaffold for the ingrowth of fibroblasts and endothelial cells, facilitating the formation of a neodermis. This functions like a human dermis in terms of biomechanical performance and response to growth. Six-year follow-up of Integra® used in reconstruction after burn scar revision does show the phenomenon of 'premature ageing' in some cases (Fig. 28.36) and the search for new biomaterials continues [17,18].

General care

Small and minor burns require little care other than the specific treatment of the burn wound. Larger burns, however, require more specialized and extensive care. After the period of fluid resuscitation and early stabilization, with or without surgery, there will be a prolonged period of treatment and rehabilitation, which can be physically and psychologically demanding [19]. Constant attention must be paid in the earlier phases to reducing the risks of infection; early feeding with high-protein high-calorie diets with added vitamins and minerals is important to counteract the hypercatabolic response to the burn injury. While there have been considerable improvements in survival, major burns are still associated with a significant mortality and morbidity. It is important to balance encouragement and hope for recovery with realism that survival is not always certain and recovery is a long process. It must also be appreciated, particularly in children, that the magnitude of the physical trauma is mirrored by the magnitude of the psychological trauma to the parents and relatives. Great sensitivity is required by those caring for these patients, and professional counselling should be available for the relatives.

References

1 Kao CC, Garner WL. Acute burns. *Plast Reconstr Surg* 2000; **105**: 2482–92.
2 Atiyeh BS, Gunn W, Hayek SN. State of the art in burn treatment. *World J Surg* 2005; **29**: 131–48.
3 Herndon DN, ed. *Total Burn Care*, 3rd edn. London: Saunders, 2007.

4 Singh V, Devgan L, Bhat S, Milner SM. The pathogenesis of burn wound conversion. *Ann Plast Surg* 2007; **59**: 109–15.
5 Burd A, Chiu T. Allogenic skin in the treatment of burns. *Clin Dermatol* 2005; **23**: 376–87.
6 Thomas CL, Finlay AY. The 'handprint' approximates to 1% of the total body surface area whereas the 'palm minus the fingers' does not. *Br J Dermatol* 2007; **157**: 1080–1.
7 Baker RH, Akhavani MA, Jallali N. Resuscitation of thermal injuries in the United Kingdom and Ireland. *J Plast Reconstr Aesthet Surg* 2007; **60**: 682–5.
8 Klein MB, Havden D, Elson C *et al*. The association between fluid administration and outcome following major burn: a multicenter study. *Ann Surg* 2007; **245**: 622–8.
9 Burd A, Norohna FV, Ahmed K *et al*. Decompression not escharotomy in acute burns. *Burns* 2006; **32**: 284–92.
10 Miller JG, Bunting P, Burd DAR, Edwards JD. Early cardiorespiratory patterns in patients with major burns and pulmonary insufficiency. *Burns* 1994; **20**: 542–6.
11 Burd A, Lam PK, Lau H. Allogenic skin: transplant or dressing? *Burns* 2002; **28**: 358–66.
12 Ip M, Lui SL, Poon VK *et al*. Antimicrobial activities of silver dressings: an in vitro comparison. *J Med Microbiol* 2006; **55**: 59–63.
13 Burd A, Kwok CH, Hung SC *et al*. A comparative study of the cytotoxicity of silver-based dressings in monolayer cell, tissue explant and animal models. *Wound Repair Regen* 2007; **15**: 94–104.
14 Burd A. Evaluating the use of hydrogel sheet dressings in comprehensive burn wound care. *Ostomy Wound Manage* 2007; **53**: 52–62.
15 Chiu T, Burd A. 'Xenograft' dressing in the treatment of burns. *Clin Dermatol* 2005; **23**: 419–23.
16 Jones I, Currie L, Martin R. A guide to biological skin substitutes. *Br J Plast Surg* 2002; **55**: 185–93.
17 Boyce ST. Design principles for composition and performance of cultured skin substitutes. *Burns* 2001; **27**: 523–33.
18 Balasubramani M, Kumar TR, Babu M. Skin substitutes: a review. *Burns* 2001; **27**: 534–44.
19 Hurren JS. Rehabilitation of the burned patient: James Laing Memorial essay for 1993. *Burns* 1995; **21**: 116–26.

Stem cell strategies in burns care [1]

The potential of stem cell strategies to modulate disease processes and biological pathways is being explored in many fields in medicine. In burn care there are two major areas under active research that are likely to have an impact on clinical practice in the next few years. The first area is the potential to support the role of the marrow in providing an endogenous reserve of stem cells by infusing exogenous, stem cell-rich products. The most likely product to be used is ABO-matched human umbilical cord blood. The rationale for this treatment is based on a hypothesis outlined in Fig. 28.37. Basically, the marrow is subject to suppression from toxins released by the burn wound and subsequent sepsis whilst at the same time there is an increased demand for marrow support to promote healing and light sepsis. The marrow represents a considerable reserve for stem cell support but in the prolonged and extensive injury marrow 'exhaustion' can occur.

With regard to the burn wound, the greatest challenge that remains is how to achieve definitive closure with a permanent epithelial layer. The prospect of achieving this with cultured human umbilical cord lining cells is being actively explored. The most exciting aspect about this is the possibility of finding 'universal donor' keratinocytes that could be prepared in advance and applied at a much earlier stage of burn wound management than is currently possible. The strategies are shown in Fig. 28.38 and the options are discussed in detail in a review article [1].

Reference

1 Burd A, Ahmed K, Lam S, Ayyappan T, Huang L. Stem cell strategies in burns care. *Burns* 2007; **33**: 282–91.

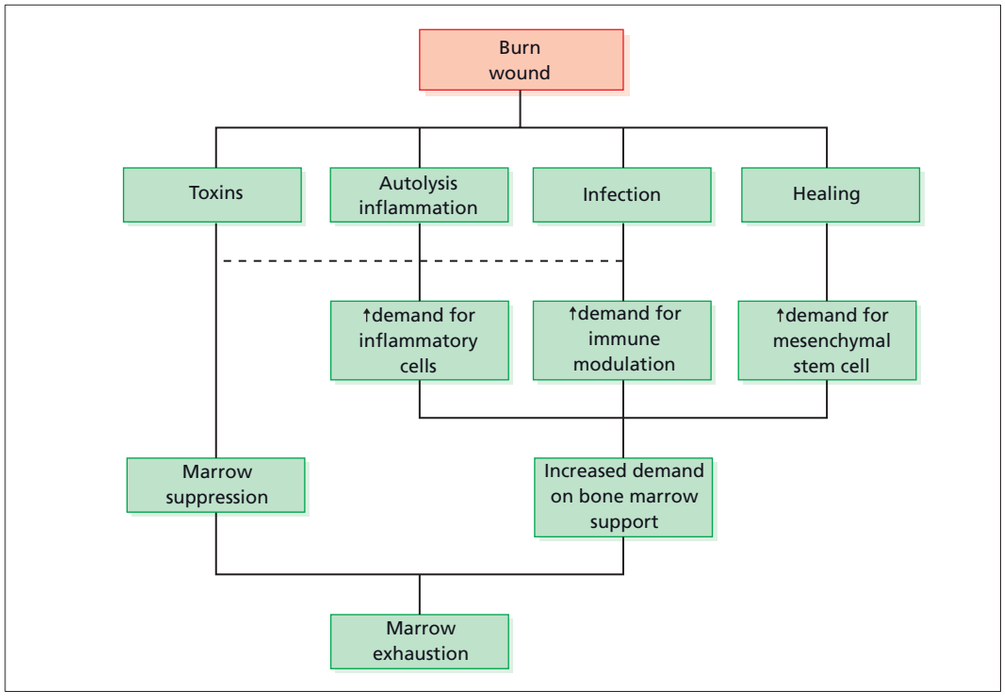


Fig. 28.37 Diagrammatic representation of hypothesis supporting use of stem cells in burns management. (Reproduced from Burd *et al.* [1], with permission.)

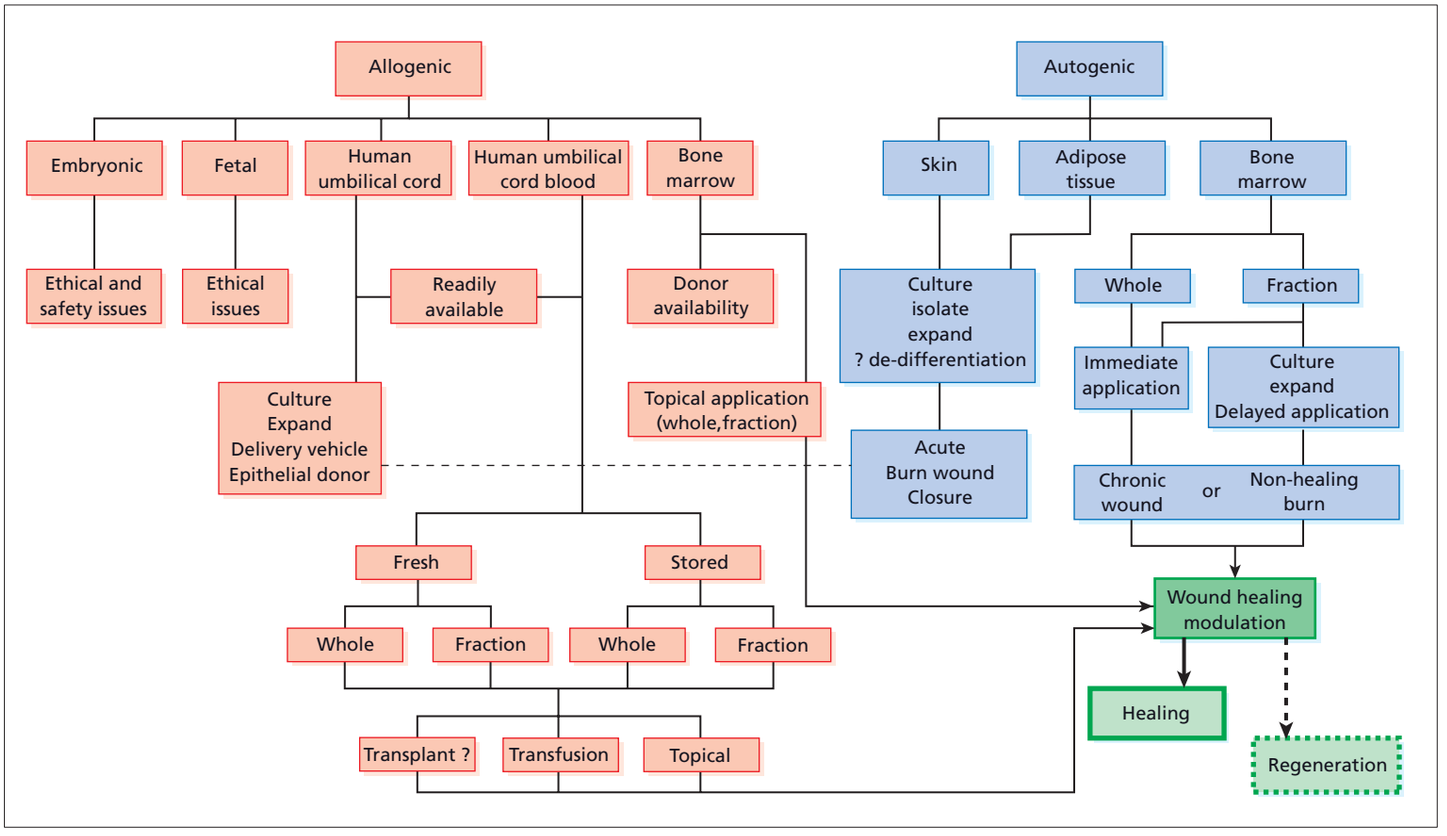


Fig. 28.38 Diagrammatic overview of stem cell strategies. (Reproduced from Burd *et al.* [1], with permission.)

Cutaneous sequelae of burns

Superficial partial thickness burns will heal without scarring, although there may be some loss of pigment, which is usually temporary. Deeper burns are associated with scarring and there is a high incidence of hypertrophic scarring, especially in the deeper partial thickness burns that have been allowed to heal conservatively (Fig. 28.39). Hypertrophic scars go through a phase of many months when they can be intensely pruritic and this can be a significant problem for children. Pressure garments (Fig. 28.40) and silicone gel and elastomers are used in the management of hypertrophic scars [1]. Occasionally, the scarring can result in functional problems that require surgical intervention (Fig. 28.41). Aesthetic problems related to scarring and contracture with deformity also require combined approaches of splinting and surgical intervention, which may need to be repeated over a considerable period of time. Late neoplastic change in burn scars is discussed below.

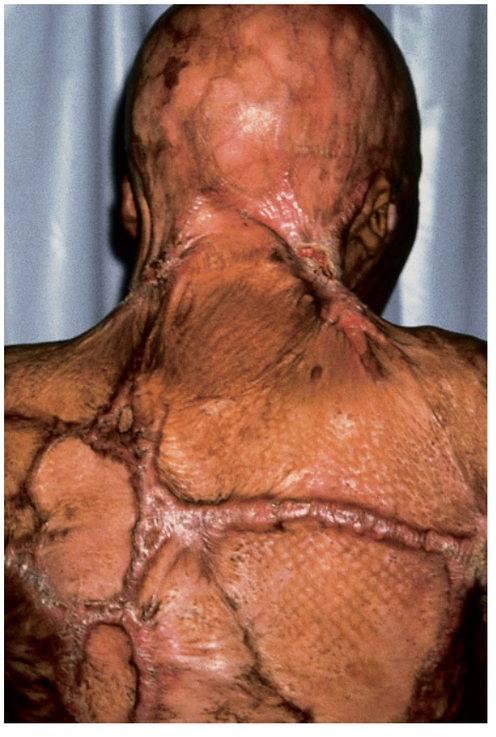


Fig. 28.39 Hypertrophic scarring in a burn in a dark-skinned person. Areas on the back were grafted and the burn scars between the grafts became hypertrophic.

Reference

1 Davey RB. Burn scar contracture release: a simplified technique utilizing contact media. *Burns* 1996; **22**: 406–8.

Electrical burns

These occur from environmental, domestic and industrial sources and present a unique form of trauma, which may affect multiple organ systems and present challenging problems for clinical man-



Fig. 28.40 Commercially available pressure garments made by Biersdorf.



Fig. 28.41 Contracture of the shoulder resulting from scarring of the axilla.

agement. Electrical burns are arbitrarily classified as high- or low-tension injuries, with low-tension burns being less than 1000 V and high-tension burns greater than 1000 V. Electrical injuries account for approximately 3% of burn patients admitted to specialized centres, and the majority come from contact with the domestic 240 V alternating current at 50 Hz single phase. Other sources of current are the high-voltage power lines that pose a threat not only to workers but also to sports enthusiasts involved in pursuits such as fishing, hang-gliding, parachuting and kite-flying [1,2]. Other injuries are associated with electrification in rail transport, both the overhead lines and the 'third' rail. Finally, car batteries cause a significant number of injuries to car mechanics (usually in amateurs).

The pathophysiology of the electrical injury is complex [3] and not completely understood. Historically, the mechanism was thought to be heat, as the passage of electric current through a solid conductor results in the conversion of electric energy to heat (the joule effect). However, it is probable that significant damage is also produced directly by the effect of the electric current inducing cell membrane breakdown, a phenomenon called electroporation. Clinically, the severity of injury relates to the voltage, the thickness and wetness of the skin and the duration of contact. The location of the entry and exit points determine the areas that will have been potentially damaged. High-voltage injuries may result in extensive muscle damage with subsequent risk of renal failure. All organs between the entry and exit points are liable to injury, and cardiac standstill can occur.

Electrical burns show distinct histological features. The nuclei of the basal cells, and sometimes of the more superficial epidermal cells, appear stretched vertically. There may be dermal–epidermal separation, with elongated degenerated cytoplasmic processes from the basal cells protruding into this space.

Management of the patient with electrical injury involves general supportive treatment as well as specific wound treatment [4]. If there are electrocardiogram (ECG) abnormalities then continuous cardiac monitoring is necessary together with pharmacological treatment of any dysrhythmia. Fluid resuscitation may be indicated. It must be appreciated that the extent of the injury is often 'hidden' with deep muscle damage. Because of this, fluid requirements may considerably exceed those predicted by the cutaneous burn alone. A particular concern is myoglobinuria with the risk of renal failure, in which case a brisk urine output should be encouraged with the use of mannitol (see above).

Historically, the teaching on wound management was that there was delayed muscle necrosis and therefore that early wound débridement and wound closure was contraindicated. Current thinking is that débridement of obviously necrotic tissue should be performed as early as possible, preferably soon after admission at the same time as escharotomies, fasciotomies and nerve decompression are undertaken [5]. Wound closure should, however, be delayed for a short period to allow progressive tissue damage to declare itself [6]. This damage is thought to result from the effects of the electroporation. The tissue damage resulting from this would be recognized several days after injury when arachidonic acid metabolites have caused microvascular ischaemic cell death.



Fig. 28.42 These lesions raised the suspicion of child abuse because they were initially thought to be caused by multiple cigarette burns but in fact they were caused by repeated accidental burns from an enuresis alarm.

Lightning burns are not infrequent and can produce a variety of injuries. Characteristically, there are arborescent lesions (Lichtenberg figures), which are erythematous, mottled or charred, and small linear burns at the site of metal objects held in the hands or in clothing pockets. However, the skin lesions are overshadowed by the general effects of respiratory arrest, gastric dilatation, ileus, cerebral oedema and fractures.

Electrical flash burns can occur with both low- and high-tension injuries. These involve the exposed areas, typically hands and face. Superficial flash burns can be treated conservatively but deeper ones will require surgery in specialist units. Extensive flash burns will require intravenous fluid resuscitation.

Miscellaneous electrical burns

There are a number of electrical burns that can give rise to medicolegal issues because they can mimic torture or child abuse. For example, burns that were actually caused by a defective enuresis alarm system were similar to cigarette burns, which, because of their shape and multiplicity, were thought unlikely to have been caused accidentally (Fig. 28.42).

References

1 Chi L, Ning YD, Jun QF *et al.* Electrical injuries from graphite fishing rods. *Burns* 1996; **22**: 638–40.

2 Campbell DC, Nano T, Pegg SP. Pattern of burn injury in hang-glider pilots. *Burns* 1996; **22**: 328–30.

3 Lee RC, Astumian RD. The physicochemical basis of thermal and non-thermal 'burn' injuries. *Burns* 1996; **71**: 509–19.

4 Hussman J, Kucan JO, Russell RC *et al.* Electrical injuries: morbidity, outcome and treatment rationale. *Burns* 1995; **21**: 530–5.

5 Nettelblad H, Thuomas KA, Sjoberg F. Magnetic resonance imaging: a new diagnostic aid in the care of high-voltage electrical burns. *Burns* 1996; **22**: 117–9.

6 Thomas SS. Electrical burns of the mouth: still searching for an answer. *Burns* 1996; **22**: 137–40.

Laser burns [1,2]

When laser energy is absorbed by skin, it is converted into heat. The principal chromophores are melanin and haemoglobin. The effects on the skin are determined by a number of variables, such as wavelength of the laser emission, power, duration of exposure, direction of the beam and skin colour. The carbon dioxide laser produces non-specific destruction, often vaporizing the skin with a narrow zone of coagulative necrosis adjacent to the healthy tissues. In contrast, the wavelength of the tuneable dye laser can be chosen for maximal absorption by one component of the skin, and with very brief duration pulses the damage can be restricted. Laser light of 577 nm, delivered in impulses of nanoseconds' duration, is used to treat port-wine stains without scarring. Histologically, damage is limited to the superficial dermal vessels. When thermal damage is more extensive, hypertrophic scarring can occur; this is a more significant risk with the argon laser.

References

1 Gaston P, Humzah MD, Quaba AA. The pulsed tuneable dye laser as an aid in the management of post-burn scarring. *Burns* 1996; **22**: 203–5.

2 Fretzin S, Beeson WH, Hanke CW. Ignition potential of the 585-nm pulsed dye laser: review of the literature and safety recommendations. *Dermatol Surg* 1996; **22**: 699–702.

Microwave radiation burns [1]

Microwave radiation is non-ionizing high-frequency short-wavelength radiation, which generates heat by its effects on water molecules. Accidental exposure to microwave radiation has caused burns sufficient to result in amputation [2]. Lesser injuries have been followed by paraesthesia. Two cases of children deliberately injured by microwave ovens have been described in which the injuries were sharply demarcated [3]. Subsequent studies of the effects of microwave radiation on piglet skin and the underlying tissues indicated that, when sufficient microwave energy was given to burn the skin and muscles or viscera, there was relatively little injury to the subcutaneous fat [4]. This sparing of the fat appears to be a unique property of the microwave burn.

References

1 Budd R. Burns associated with the use of microwave ovens. *J Microw Power Electromagn Energy* 1992; **27**: 160–3.

2 Alexander RA, Surrell JA, Cohle SD. Microwave oven burns to children. *Paediatrics* 1987; **79**: 255–60.

3 Dickason WL, Barutt JP. Investigation of an acute microwave oven hand injury. *J Hand Surg* 1984; **9A**: 132–5.

4 Surrell JA, Alexander RC, Cohle SD *et al.* Effects of microwave radiation on living tissues. *J Trauma* 1987; **27**: 935–9.

Burns and skin neoplasia

Malignant transformation in burn scars was described by Marjolin in 1828. Clinical features to suggest the development of malignancy include: induration and persistence of ulceration after a burn; the appearance of an elevated border at the edge of a post-burn ulcer; breakdown of a burn scar with an indurated base; and nodule formation within a burn scar.



Fig. 28.43 Chronic ulceration of a burn scar with malignant degeneration (Marjolin's ulcer). (Courtesy of Dr L. Sacks, Frenchay Hospital, Bristol, UK.)

Most malignancies arising in burns scars derive from epithelial keratinocytes, although melanoma, sarcoma and schwannoma have also been described [1–5]. The frequency with which burn scars develop a neoplasm is unknown, but in a previous generation it was estimated that approximately 2% of squamous carcinoma and 0.5% of basal cell carcinomas arose in burn scars. Most carcinomas that develop in burns scars are squamous in type [6,7]. Neoplastic change is more likely when there is delayed healing or repeated ulceration (Fig. 28.43), and the incidence of carcinoma is reduced if such wounds are grafted at an early stage [8]. Burn scar carcinoma is most common in the lower limb and in limb flexures. Most squamous carcinomas occur after a long latent period, sometimes several decades, although it is shorter in the elderly. Uncommonly, a carcinoma may arise within weeks or months of a burn: this short latent period neoplasm is more commonly basal than squamous cell in type. Metastasis to regional nodes is much more common in the squamous carcinomas arising in burn scars than those associated with actinic damage. It occurred in 16 of 44 cases, of whom 15 died [9]. Metastases occurred in 20% in one series [8] and 36% of another [10]. The prognosis is worse for lower limb lesions [9].

Basal cell carcinomas occurring in burns scars are more common on the head and neck, in actinically damaged skin and in older patients [8]. Carcinoma following exposure to hot metal fragments, as occurs in welders, is more likely to be basal than squamous cell type [11].

It is not known how burns result in carcinogenesis. When the latent period is short, and a neoplasm develops in sun-damaged skin, it is likely that the burn is acting as a promoter. When the latent period is long, other mechanisms are more likely. Burning itself may act as an initiator of carcinogenesis [12]. When the burn results in chronic ulceration or repeated cycles of healing and ulceration, this in itself may act as a promoter. Because squamous carcinoma can occur even when the damaged area is grafted, the carcinogenic stimulus may arise in the dermis in some situations. It is also possible that locally impaired immune function contributes to the development of malignancy.

For medicolegal purposes, the criteria established long ago [13] for associating a carcinoma with a previous burn are still valid.

References

1 Ikeda I, Kageshita T, Ono T. Multiple malignant melanoma and squamous cell carcinoma in a burn scar. *Dermatology* 1995; **191**: 328–32.
2 Nishimoto S, Matsushita T, Matsumoto K, Adachi S. A rare case of burn scar malignancy. *Burns* 1996; **22**: 497–9.
3 Scott JR, Morris R, McPhaden AR *et al.* Malignant schwannoma in a burn scar. *Burns* 1996; **22**: 494–6.
4 Gargan TJ, Mitchell L, Plaus W. Burn scar sarcoma. *Ann Plast Surg* 1988; **20**: 477–80.
5 Ko T, Tada H, Hatoko M *et al.* Trichilemmal carcinoma developing in a burn scar: a report of two cases. *J Dermatol* 1996; **23**: 463–8.
6 Tamura A, Ohnishi O, Ishikawa O, Miyachi Y. Flow cytometric DNA content analysis on squamous cell carcinomas according to the preceding lesions. *Br J Dermatol* 1996; **134**: 40–3.
7 Chowdri NA, Darzi MA. Post-burn scar carcinomas in Kashmiris. *Burns* 1996; **22**: 477–82.
8 Treves N, Pack GT. The development of cancer in burn scar. *Surg Gynecol Obstet* 1930; **51**: 749–82.
9 Novick M, Gard DA, Hardy SB *et al.* Burn scar carcinoma: a review and analysis of 46 cases. *J Trauma* 1977; **17**: 809–17.
10 Arons MS, Lynch JB, Lewis SR *et al.* Scar tissue carcinoma. I. A clinical study with special reference to burn scar carcinoma. *Ann Surg* 1965; **161**: 171–88.
11 Dix CR. Occupational trauma and skin cancer. *Plast Reconstr Surg* 1960; **26**: 546–54.
12 Saffiotti U, Shubik P. The role of burning in carcinogenesis. *Br J Cancer* 1956; **10**: 54–6.
13 Ewing J. Modern attitude toward traumatic cancer. *Arch Pathol* 1935; **19**: 690–728.

Abuse by burning

Regrettably, human beings sometimes cause serious injury to others, including members of their family circle and especially those who are helpless, such as young children or elderly parents. Abuse may be wilful and malicious but in many cases it is caused by thoughtless neglect. The problem of deliberate injury to children by burning has been identified for over 20 years [1,2]. Similar aggressive acts towards dependent elderly are not widely recognized but it is highly probable that there is a much higher frequency of this type of injury than is reported in the literature [3,4] and that, as with child abuse, the more burn-care professionals become sensitive to the possibility of abuse of the elderly, then the more the observed incidence will rise. Burning has been the mechanism of abuse in about 10% of cases of child abuse. The incidence of abuse associated with childhood burns varies considerably from 1% to 25% of burn admissions to specialized centres.

It can be very difficult to diagnose a non-accidental injury but there are a few features that should give cause for concern (see also p. 28.34):

1 A child is brought for treatment by an unrelated adult.
2 There is an unexplained delay in seeking treatment.
3 The parents seem to be responding inappropriately to the injured child (e.g. they are inattentive or unconcerned).
4 Blame for the injury is placed on another person (usually not present).
5 The injury is not consistent with the history.

Inflicted burns can have characteristic patterns of injury (Fig. 28.44) [5]. The majority of non-accidental burns in children are scalds; these may be spill injuries or immersion burns. Immersion



Fig. 28.44 This pattern of a heating grill on the buttocks of a child was a result of child abuse.



Fig. 28.45 This child with 'staphylococcal scalded skin syndrome' and no history of burns was originally admitted to a burns unit as a case of suspected child abuse.

burns are very rare as accidental injuries in children under 1 year of age. Suspicious features are burns of glove and stocking distribution or the classical 'doughnut' of spared skin on the buttock on a child who has been forced to sit in a bath of hot water [6]. Flame burns are less common. Contact burns may occur with the placing of a child against a hot object or by branding the child with cigarettes or a domestic iron.

While the diagnosis of child abuse is very important, the misdiagnosis of abuse can be a tragedy that can destroy family groups. It is very important therefore to be aware of injuries that may simulate abuse. Cutaneous infections can mimic deliberate injury, for example impetigo, severe napkin rash and staphylococcal scalded skin syndrome (Fig. 28.45). Hypersensitivity can sometimes be mistaken for intentional burns. Photodermatitis can be caused when substances in certain fruits or plants come into contact with skin exposed to sunlight. A pattern of erythema and blistering can develop that simulates a splash burn. Without a history of injury, abuse may be suspected. Cigarette burns can be accidental but multiple cigarette burns are pathognomonic for child abuse.

The patterns of abuse of the elderly are less well documented, but the author has knowledge of cases of immersion of physically dependent elderly people in hot baths resulting in burns. While this may not come into the category of malicious abuse, it is at least indicative of negligence on the part of the carer. Another distressing injury comes from contact burns against hot water pipes or radiators. These can be sustained by elderly people collapsing in the night and not being able to move away from the source of heat. There may be no conscious abuse but the exposure of at-risk individuals to preventable environmental hazards, together with the lack of supervision, may constitute negligence. While there is legislation that protects children (e.g. fireguards are a legal requirement when there are children under a specified age in a room), the same degree of legislation does not yet apply to dependent elderly people. This situation will probably change, particularly as the at-risk elderly population increases.

Abuse by burning is a very disturbing and emotive injury. It is essential that, while a high index of suspicion should be maintained with burns patients at the extremes of age, these suspicions should be thoroughly and sensitively pursued. Multidisciplinary teams should be established to undertake this investigation. Experienced and trained professionals will then have to confront the suspected abuser if appropriate.

References

1 Ludwig S, Kornbers AE, eds. *Child Abuse: a Medical Reference*. New York: Churchill Livingstone, 1992.
2 Blakeney PE, Herndon DN. Abuse by burning. In: Herndon DN, ed. *Total Burn Care*. London: Saunders, 1996: 550–5.
3 Bowden M, Grant S, Vogel B, Prasad J. The elderly, disabled and handicapped adult burned through abuse and neglect. *Burns* 1988; **14**: 447–50.
4 Krob M, Johnson A, Jordan M. Burned and battered adults. *J Burn Care Rehabil* 1986; **7**: 529–31.
5 Renz BM, Sherman R. Child abuse by scalding. *J Med Assoc Georgia* 1992; **81**: 574–8.
6 Stratman E, Melski J. Scald abuse. *Arch Dermatol* 2002; **138**: 318–20.

Miscellaneous reactions

C.T.C. Kennedy and D. Creamer, pp. 28.92–28.94

Blackening of the skin by metals

Synonym
- Black dermographism

The black discoloration produced when the skin is stroked against certain metals is called black dermographism [1]. Unlike other forms of dermographism it has a purely physical, not a physiological, basis. It is caused by the abrasive effect of powders on the skin, which rub against a relatively soft metal, generating particles that are so small that they absorb but cannot reflect light [2]. Any powder harder than a metal with which it is in contact can abrade the metal and produce skin blackening. Calamine lotion (zinc and ferric oxide), face powders (zinc oxide, titanium dioxide and ferric oxide) and some dentifrices containing pumice readily produced the phenomenon from gold, silver or platinum jewellery. In some individuals who exhibit black dermographism, the powder originates from the workplace.

Pure gold (24 carat) does not seem to have the property of skin blackening, possibly because the surface has more plasticity and deforms rather than fragments when friction is applied [3].

In addition to the presence of powders on the skin, factors that increase the likelihood of blackening include dryness and roughness of the skin, and amino acids in sweat (especially those containing sulphur, which can produce black complexes with gold). Sodium chloride (e.g. from sweat and sea water), which may promote corrosion, and tarnishing of the base metal in gold alloys, can both contribute to the phenomenon.

Black dermographism can mask a contact allergic dermatitis to gold [4].

Blackening of the skin can be treated by simply washing with soap and water, and it can be prevented if the skin that will be in contact with the metal is carefully cleansed free of powder.

References

1 Urbach E, Pillsbury DM. Black dermographism. *JAMA* 1943; **121**: 485–90.
2 Fisher AA. Black dermographism: mechanism for formation of black color. *Cutis* 1993; **52**: 17–9.
3 Rapson WS. Skin contact with gold and gold alloys. *Contact Dermatitis* 1985; **13**: 56–65.
4 Guin JD. Black dermographism and gold dermatitis. *Contact Dermatitis* 1999; **41**: 114–5.

Rusting

Certain individuals have the ability to corrode metal. This comes to light in apprentices in the precision engineering industry and makes them unable to pursue their career. Such individuals are known as 'rusters' [1].

Rusters tend to have hyperhidrosis [2] and the mechanism of the electrolytic corrosion has been investigated in detail [1]. 'Rusters' have an increased secretion of salt in their sweat [3].

The composition of the steel being handled is important; with increasing amounts of copper, the phenomenon is less likely to occur [2].

Treatment is difficult. Measures to reduce hyperhidrosis such as aluminium chloride hexahydrate under occlusion may help, as can hand washing and protective gloves [2].

References

1 Burton JL, Pye RJ, Brookes DB. Metal corrosion by chloride in sweat. *Br J Dermatol* 1976; **95**: 417–22.
2 Jensen G, Nielsen E. 'Rusters': the corrosive action of palmar sweat. II. Physical and chemical factors in palmar hyperhidrosis. *Acta Derm Venereol (Stockh)* 1979; **59**: 139–43.
3 Collins KJ. The corrosion of metal by palmar sweat. *Br J Ind Med* 1957; **14**: 191–7.

Finger wrinkling

Wrinkling of the glabrous skin of the hands and feet after immersion in water is not fully understood. Entry of water into keratinocytes is partly responsible [1,2] but it also depends on an intact sympathetic nervous system [3,4]. A proposed mechanism is that water enters the sweat glands, producing altered electrolyte concentrations, and the afferent message then sent triggers autonomic fibres to mediate vasoconstriction [5,6]. During vasoconstriction there is shrinkage of the glomus organs of Hoyer-Grosser [7] and these structures are anchored to the dermoepidermal junction.

Abnormal skin wrinkling can be used as an assessment of autonomic dysfunction, for example in diabetes mellitus [8], familial dysautonomia and Parkinson's disease [9]. It may be useful as a more general test of nerve integrity, for example in paediatric or comatose patients [10]. Normal subjects can, however, show reduced wrinkling [11]. Otherwise functionally normal replanted fingers have abnormal finger wrinkling and vasodilate rather than vasoconstrict when immersed in water [12].

It has long been known that some patients with cystic fibrosis (CF) have excessive skin wrinkling [13] and it is now known that this is associated with a specific CF mutation [14].

References

1 Danielson D. Wrinkling of the human skin. *J Biomechanics* 1977; **10**: 201–4.
2 Tsai N, Kirkham S. Fingertip skin wrinkling—the effect of varying tonicity. *J Hand Surg (Br)* 2005; **30**: 273–5.
3 Bull C, Henry JA. Finger wrinkling as a test of autonomic function. *BMJ* 1977; **i**: 551–2.
4 Braham J, Sadeh M, Sarova-Pinhas I. Skin wrinkling on immersion of hands. *Arch Neurol* 1979; **36**: 113–4.
5 Wilder-Smith EP, Chow A. Water-immersion wrinkling is due to vasoconstriction. *Muscle Nerve* 2003; **27**: 307–11.
6 Wilder-Smith EP. Water immersion wrinkling—physiology and use as an indicator of sympathetic function. *Clin Auton Res* 2004; **14**: 125–31.
7 Gorgas K, Bock P, Tischendorf F, Curri SB. The fine structure of human digital arterio-venous anastomoses (Hoyer-Grosser's organs). *Anat Embryol (Berl)* 1977; **150**: 269–89.
8 Clark CV, Pentland B, Ewing DJ, Clarke BF. Decreased skin wrinkling in diabetes mellitus. *Diabetes Care* 1984; **7**: 224–7.
9 Djaldetti R, Melamed E, Gadoth N. Abnormal skin wrinkling in the less affected side in hemiparkinsonism: a possible test for sympathetic dysfunction in Parkinson's disease. *Biomed Pharmacother* 2001; **55**: 475–8.
10 Tindall A, Dawood R, Povlsen B. Case of the month: the skin wrinkle test: a simple nerve injury test for paediatric and uncooperative patients. *Emerg Med J* 2006; **23**: 883–6.
11 Alvarez G. Finger wrinkling after immersion in water. *BMJ* 1980; **281**: 1070.
12 Hsieh CH, Huang KF, LiLiang PC *et al.* Paradoxical response to water immersion in replanted fingers. *Clin Auton Res* 2006; **16**: 223–7.
13 Elliott RB. Wrinkling of skin in cystic fibrosis. *Lancet* 1974; **ii**: 108.
14 Katz KA, Yan AC, Turner ML. Aquagenic wrinkling of the palms in patients with cystic fibrosis homozygous for the delta F508 CFTR mutation. *Arch Dermatol* 2005; **141**: 621–4.

Carbon monoxide poisoning [1]

Carbon monoxide poisoning is still an important cause of death. Exposure is most likely from vehicle exhaust fumes and heating appliances using gas, coal, wood or kerosene in poorly ventilated rooms. The risk is greater at high altitude because atmospheric oxygen is reduced [2].

Symptoms and signs become increasingly apparent with circulating levels of carboxyhaemoglobin above 30%, and coma, convulsions and cardiorespiratory arrest are likely to occur with concentrations of 60% or more.

A burning sensation may be the earliest symptom in mild cases [3]. The distinctive vivid erythematous or oedematous plaques may appear, especially at pressure sites, within hours after carbon monoxide poisoning [4] but this often-quoted 'cherry red' change only occurs in about 1% of cases of carbon monoxide poisoning [5].

Vesicles and bullae may develop, often in a geographical pattern [6,7]. The lesions simulate those seen in barbiturate

poisoning or after cerebral vascular accidents or drug-induced coma.

Histologically, the bullae show epidermal necrosis, intraepidermal vesiculation and necrosis of the secreting portions of the sweat glands [4,6]. Spontaneous resolution occurs, in those who survive, in about 15 days [4,8]. Pressure and hypoxia are probably the main factors in the pathogenesis.

In addition to CNS and cardiovascular complications, survivors may have other problems which include haemolytic anaemia, renal insufficiency from rhabdomyositis, and peripheral neuropathies.

Treatment. This is with 100% oxygen, administered by a tightly fitted face mask or, if necessary, endotracheal intubation and mechanical ventilation. General supportive measures may also be required.

References

1 Nagy R, Greer KE, Harman LE Jr. Cutaneous manifestations of acute carbon monoxide poisoning. *Cutis* 1979; **24**: 381–3.

2 Mehta SR, Niyogi M, Kasthuri AS *et al*. Carbon monoxide poisoning. *J Assoc Physicians India* 2001; **49**: 622–5.

3 Levit F. Skin discomfort as a presenting sign of carbon monoxide poisoning. *J Am Acad Dermatol* 1995; **32**: 671.

4 Achten G, Ledoux-Corbusier M, Thys J-P. Intoxication a l'oxyde de carbone et lesions cutanées. *Ann Dermatol Syphiligr* 1971; **98**: 421–8.

5 Gorman DF, Clayton D, Gilligan JE, Webb RK. A longitudinal study of 100 consecutive admissions for carbon monoxide poisoning to the Royal Adelaide Hospital. *Anaesth Intensive Care* 1992; **20**: 311–6.

6 Leavell UW, Farley CH, McIntyre JS. Cutaneous changes in a patient with carbon monoxide poisoning. *Arch Dermatol* 1969; **99**: 429–33.

7 Long PI. Dermal changes associated with carbon monoxide poisoning. *JAMA* 1968; **205**: 120.

8 Mandy S, Ackerman AB. Characteristic traumatic skin lesions in drug-induced coma. *JAMA* 1970; **213**: 253–6.

CHAPTER 29
Cutaneous Photobiology

J.L.M. Hawk[1], *A.R. Young*[2] *& J. Ferguson*[3]

[1]St John's Institute of Dermatology, St Thomas' Hospital, London, UK
[2]St John's Institute of Dermatology, Guy's Hospital, London, UK
[3]Photobiology Unit, Ninewells Hospital and Medical School, Dundee, UK

Basic principles of cutaneous photobiology, 29.1
Ultraviolet radiation (UVR), its production and measurement, 29.1
UVR interactions with matter, 29.3
Environmental exposure to UVR, 29.4
Normal cutaneous effects of UVR exposure, 29.5
Early effects, 29.5
Acute systemic effects, 29.6
Late effects, 29.7
Skin phototypes, 29.8
Prophylactic measures to minimize human cutaneous UVR exposure, 29.8
Abnormal cutaneous effects of UVR exposure: the photodermatoses, 29.9
Acquired disorders with a probable autoimmune basis, 29.9
DNA repair-defective diseases (see Chapter 15)
Drug- and chemical-induced photosensitivity:
Exogenous, 29.20
Endogenous—the cutaneous porphyrias (see Chapter 59)
Dermatoses sometimes exacerbated by UVR, 29.22
Clinical evaluation of the patient with suspected cutaneous photosensitivity, 29.23
Further investigation of the patient with cutaneous photosensitivity, 29.23

Basic principles of cutaneous photobiology

A.R. Young, pp. 29.1–29.9

Definition. Photobiology is the study of the effects of UV and visible radiation on living matter. Cutaneous (dermatological) photobiology is concerned with those effects on skin.

Ultraviolet radiation (UVR), its production and measurement

The nature of UVR [1]

UV and visible radiation, which comprises a very small part of the electromagnetic radiation spectrum (Fig. 29.1), is energy released during the transition of a molecular electron from a higher energy outer molecular orbital to a less energetic inner one. Each such emission, known as a photon, is a discrete oscillating electromagnetic pulse of energy E (Joules, J), wavelength λ (nanometres, nm, 10^{-9} m) and velocity through space c (3×10^8 m/s), such that $E = hc/\lambda$, where $h = 6.63 \times 10^{-34}$ J/s (Planck's constant) (Fig. 29.2). Thus, a 300-nm photon has energy 6.63×10^{-19} J, where 1 J is defined as the work required to accelerate 1 kg over 1 m in 1 s to a velocity of 1 m/s in a frictionless environment. Repeated molecular emissions from a point source lead to multiple spherical radiation wavefronts, each of total energy equal to the sum of the individual photon energies, but diverging with gradually diminishing intensity per unit surface area. The amount of such energy incident on a surface is known as the radiant exposure, exposure dose or fluence (J/m^2, formerly mJ/cm^2), and the rate of incidence as the irradiance, dose rate or intensity (W/m^2, formerly mW/cm^2), where 1 W = 1 Watt = 1 J/s.

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

The UVR spectrum, 100–400 nm, comprises three wavebands: UVC (100–280 nm, commonly but less precisely, 200–290 nm), UVB (280–315 nm, 290–320 nm) and UVA (315–400 nm or 320–400 nm); visible light is 400–700 nm. UVA has recently been subdivided into UVA-I (340–400 nm) and UVA-II (320–340 nm) because, biologically speaking, the effects of UVA-II are more like those of UVB, in which the UVR absorbing molecule, known as the chromophore, is also the biologically important target molecule. The effects of UVA-I are thought to be mediated via reactive oxygen species (ROS) which damage critical molecular targets.

Sources of UVR [2–4] (Fig. 29.3)

UVR is emitted spontaneously in large amounts by the sun and other stars. Terrestrial sunlight, modified by the Earth's atmosphere, contains both UVB and UVA. At noon, when the sun is high, the UVB content is approximately 5% and UVA accounts for the remaining 95%. However, when the sun is lower, early or late in the day, the UVA content is even higher. UVR is also produced by artificial sources, the most common in dermatological photobiology being gas discharge lamps, glass or quartz columns containing molecules of mercury vapour or xenon gas; these are excited to emit UVR by constant collisions with electrons passed through them between electrodes. The simplest are low-pressure mercury arc lamps emitting 254 nm UVC radiation, which are useful in a limited fashion for research and germicidal purposes. Alternatively, alkaline earth phosphor coatings may convert these into reliable broad-spectrum UVB or UVA fluorescent tubes, commonly used for phototherapy or basic cutaneous phototesting.

More compact and of higher output, however, are medium-pressure mercury lamps, which emit a discrete spectrum of wavelengths ranging from the UVC to the infrared; but these require cumbersome power supplies and are relatively inefficient. Hence, they are now rarely used except for occasional localized UVB phototherapy (Alpine and Hanovia sunlamps), contact UVB and

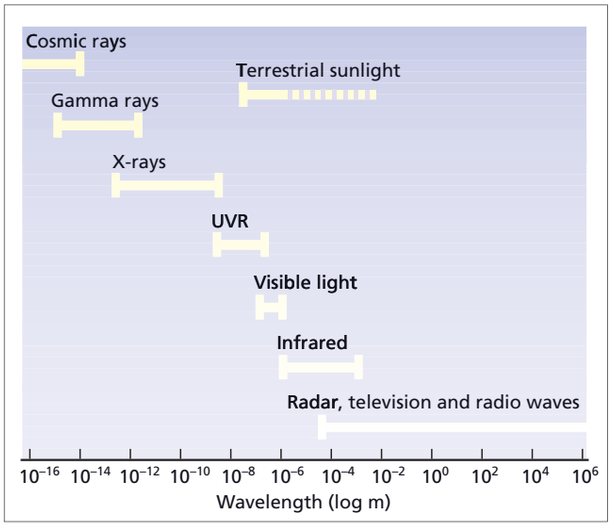


Fig. 29.1 The electromagnetic spectrum.

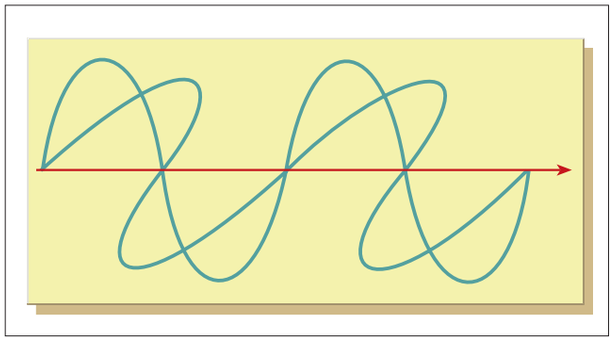


Fig. 29.2 Schematic representation of electromagnetic wave.

UVC phototherapy (Kromayer lamp) and fluorescence diagnosis (Wood's lamp).

The powerful high-pressure xenon arc lamp, although also bulky, when appropriately filtered has a smooth, broad, approximately solar-simulating emission throughout the whole UVR, visible and infrared wavebands, and is thus increasingly used in solar simulators for clinical investigation and research. More recently, metal halide lamps have been developed for high-dose UVA-I phototherapy [5]. A new development, with promise in dermatology, is the light-emitting diode (LED) [6].

Outside photobiology, fluorescent visible tubes, regularly used for room lighting, emit moderate amounts of UVA but minimal UVB, whereas incandescent tungsten light bulbs produce only trivial quantities of each, apart from the brighter quartz halogen type, which can produce considerably more.

Optical components for the modification of UVR [7]

The intensity, spectral content and direction of propagation of a UVR beam may be modified for photobiological purposes by systems of lenses, mirrors, filters and radiation-dispersing elements. The most complex of these, used particularly for precise cutaneous phototesting, is the irradiation monochromator, comprising a high-pressure xenon arc source, radiation focusing lens or mirror, entrance aperture, collimating mirror, dispersing prism or grating, telescope mirror and exit aperture, from which emerges a selected narrow adjustable radiation waveband.

Dosimetry (radiometry) of UVR [8,9]

For measurement purposes, radiation energy from a particular UVR spectrum of interest is converted into a meter readout. The British Photodermatology Group (BPG) has published guidelines for dosimetry in phototherapy [9]. The total irradiance over such a waveband is assessed by means of a radiometer, made up of a radiation filter, input optics and a detector. It is very important that a given radiometer is calibrated for a given UVR source, and

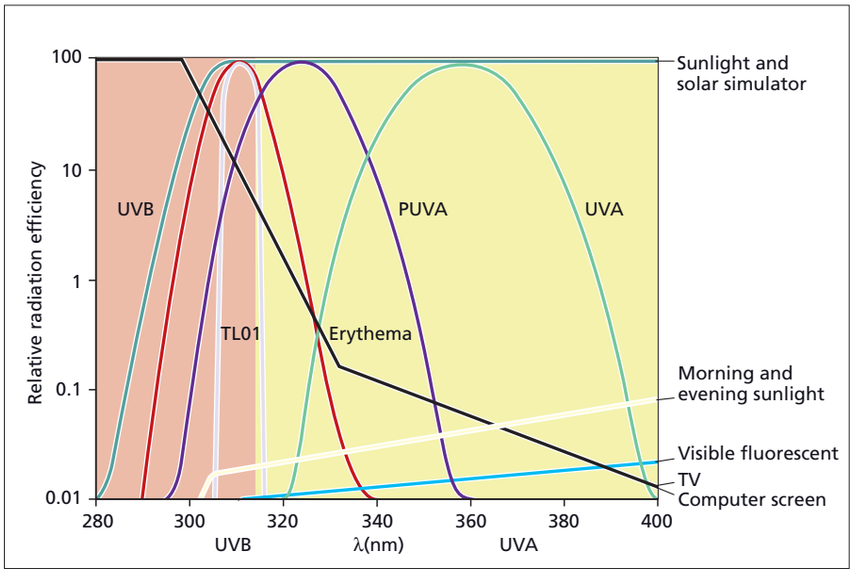


Fig. 29.3 Approximate emission spectra of typical sources encountered in dermatological photobiology and elsewhere, with action spectrum for human cutaneous erythema for comparison.

failure to do this can result in significant measurement errors. A radiometer gives an integrated irradiance. Calibration can be done against a much more detailed, nanometer by nanometer, spectral irradiance, which is measured with the much more complex spectroradiometer. Until recently, these devices included at least one monochromator instead of a filter, and could give a dynamic range over several orders of magnitude. This allowed them to identify 'contaminating' radiation (e.g. small amounts of UVB in a supposedly UVA source) that may be biologically important, especially in the characterization of emission spectra for research purposes. There has been a recent development of portable simple-to-use diode array spectroradiometers, but these tend to lack the sensitivity of monochromator-based devices.

References

1 Diffey BL, Kochevar IE. Basic principles of photobiology. In: Lim HW, Hönigsmann H, Hawk JLM, eds. *Photodermatology*. New York: Informa Healthcare USA Inc, 2007: 15–27.
2 Diffey BL, ed. The production of ultraviolet radiation. In: *Ultraviolet Radiation in Medicine*. Bristol: Adam Hilger, 1982: 12–35.
3 Magnus IA, ed. Artificial sources for irradiation. In: *Dermatological Photobiology*. Oxford: Blackwell Scientific Publications, 1976: 41–53.
4 Parrish JA, Anderson RR, Urbach F *et al*. *UVA: Biological Effects of Ultraviolet Radiation with Emphasis on Human Responses to Longwave Ultraviolet*. New York: Plenum Press, 1978: 7–35.
5 Mang R, Krutmann J. UVA-1 phototherapy. *Photodermatol Photoimmunol Photomed* 2005; **21**: 103–8.
6 Barolet D. Light emitting diodes (LEDs) in dermatology. *Semin Cutan Med Surg* 2008; **27**: 227–38.
7 Diffey BL, ed. Optical components. In: *Ultraviolet Radiation in Medicine*. Bristol: Adam Hilger, 1982: 36–59.
8 Diffey BL. Dosimetry of ultraviolet radiation. In: Lowe NJ, Shaath NA, Pathak MA, eds. *Sunscreens: Development, Evaluation and Regulatory Aspects*, 2nd edn. New York: Marcel Dekker, 1997: 175–88.
9 Taylor DK, Anstey AV, Coleman AJ *et al*. Guidelines for dosimetry and calibration in ultraviolet radiation therapy: a report of a British Photodermatology Group workshop. *Br J Dermatol* 2002; **146**: 755–63.

UVR interactions with matter

General [1–5]

Radiation incident on a surface is either reflected, or transmitted and scattered within the medium beneath, particularly at short wavelengths, by collision with the contained particles. It then eventually exits, unless it first collides with and is absorbed by an appropriately structured molecular moiety, known as a chromophore (Fig. 29.4). Any of a broad range of contiguous wavelengths, each representing equivalent photon energies, the so-called absorption spectrum, may be absorbed, with slightly differing probabilities (Fig. 29.5), leading to electronic excitation to an outer, higher energy molecular orbital (Fig. 29.6), enabling chemical reactions to occur and leading to possible clinical consequences such as skin sunburning, photoageing or cancer. More usually, however, the electron rapidly returns to its resting state, accompanied by harmless, longer wavelength radiation re-emission.

UVR interaction with atmosphere [6,7]

Solar radiation incident upon the Earth's atmospheric envelope is either reflected, or transmitted and attenuated, principally by gas molecule and water droplet scattering at wavelengths above 330 nm, by stratospheric ozone absorption between 200 and 330 nm, and by oxygen absorption below 200 nm. Extraterrestrial sunlight intensity is thereby reduced to about 1350–900 W/m^2 at the Earth's surface, comprising around 450 W/m^2 for visible light, up to about 40–50 W/m^2 for UVA and 2 W/m^2 for UVB, and the remainder for infrared.

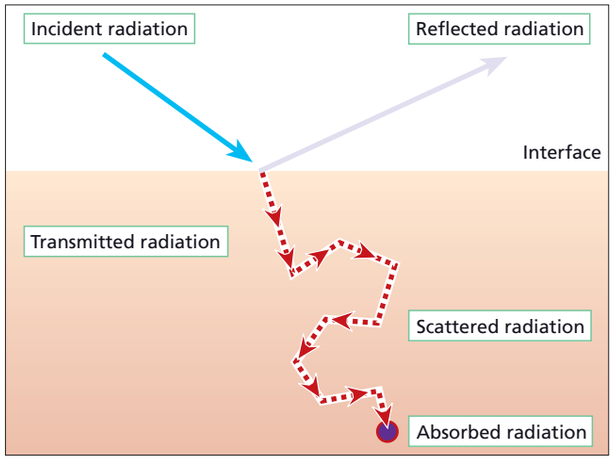


Fig. 29.4 Interaction of UVR with physical matter.

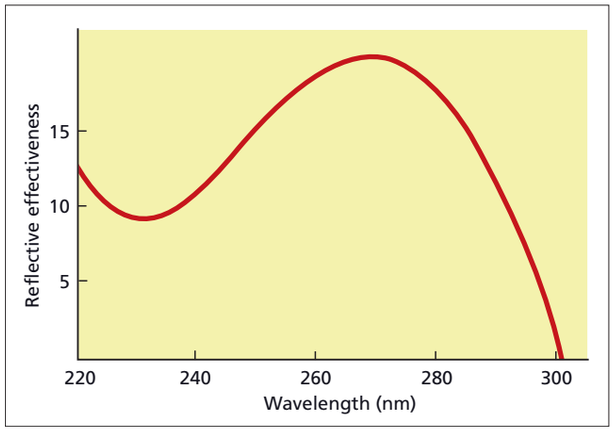


Fig. 29.5 Typical appearance of wavelength probability curve for excitation of orbiting electron to outer electronic orbital (absorption spectrum).

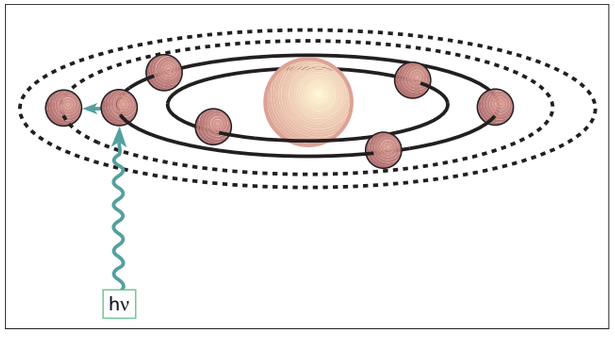


Fig. 29.6 Schematic representation of photon absorption, leading to excitation of orbiting electron to outer electronic orbital.

UVR interaction with skin [1–3,8–10]

Approximately 5% of the UVR incident on skin is diffusely reflected, the remainder being transmitted, scattered and absorbed, or passed out of the medium (Fig. 29.4) [2]. Thus, transmitted radiation below approximately 300 nm is largely attenuated within the epidermis by chromophores such as urocanic acid, DNA, RNA, tryptophan, tyrosine and melanin, whereas dermal DNA, RNA and the amino acids in elastin and collagen presumably absorb any radiation that passes through the epidermis. At approximately 300 nm and above, UVR is more readily transmitted to the dermis, after initial variable absorption by epidermal chromophores, followed by reflection back from dermal collagen bundles to the environment; in addition, minor absorption by intravascular haemoglobin, tissue bilirubin and β-carotene in fat is possible.

DNA is almost certainly the most important skin chromophore, with UVR-induced lesions potentially severely inhibiting cellular metabolism or leading to mutation or cell death by apoptosis or necrosis. DNA photoproducts include cyclobutane pyrimidine dimers (CPD), pyrimidine (6–4) pyrimidone and Dewar photoproducts, 8-hydroxy-2′-deoxyguanosine (8-0HdG), DNA hydration products, DNA–protein and DNA–DNA cross-links, and thymine glycols, all of which are largely but not necessarily completely repaired by specific enzymatic processes. DNA photolesions in the epidermis, such as CPD, can be readily detected *in vivo* after sub-erythemal and erythemal UVR exposures.

References

1 Lui H, Anderson RR. Radiation sources and interaction with skin: In: Lim HW, Hönigsmann H, Hawk JLM, eds. *Photodermatology*. New York: Informa Healthcare USA Inc, 2007: 29–40.

2 Harber LC, Bickers DR, Kochevar I *et al*. The photochemistry of cutaneous molecules. In: Harber LC, Bickers DR, eds. *Photosensitivity Diseases: Principles of Diagnosis and Treatment*, 2nd edn. Philadelphia: BC Decker, 1989: 36–45.

3 Harber LC, Bickers DR, Lamola A. Principles of light absorption and photochemistry. In: Harber LC, Bickers DR, eds. *Photosensitivity Diseases: Principles of Diagnosis and Treatment*, 2nd edn. Philadelphia: BC Decker, 1989: 25–35.

4 Magnus IA, ed. Optical reactions between radiation and matter. In: *Dermatological Photobiology*. Oxford: Blackwell Scientific Publications, 1976: 11–21.

5 Magnus IA, ed. Chemical aspects of reactions between radiation and matter. In: *Dermatological Photobiology*. Oxford: Blackwell Scientific Publications, 1976: 22–34.

6 Diffey BL, ed. The production of ultraviolet radiation. In: *Ultraviolet Radiation in Medicine*. Bristol: Adam Hilger, 1982: 12–5.

7 Magnus IA, ed. Sunlight. In: *Dermatological Photobiology*. Oxford: Blackwell Scientific Publications, 1976: 35–40.

8 Chadwick CA, Potten CS, Nikaido O *et al*. The detection of cyclobutane thymine dimers, (6–4) photolesions and the Dewar photoisomers in sections of UV-irradiated human skin using specific antibodies, and the demonstration of depth penetration effects. *J Photochem Photobiol B* 1995; **28**: 163–70.

9 Young AR. The molecular and genetic effects of ultraviolet radiation exposure on skin cells. In: Hawk JLM, ed. *Photodermatology*. London: Arnold, 1999: 25–42.

10 Sheehan JM, Craig N, Chadwick CA *et al*. Repeated ultraviolet exposure affords the same protection against DNA photodamage and erythema in human skin types II and IV but is associated with faster DNA repair in skin type IV. *J Invest Dermatol* 2002; **118**: 825–9.

Environmental exposure to UVR [1–7]

The sun is the principal source of environmental UVR. The standard erythema dose (SED) has been advocated as the best means of quantifying UVR exposure. A SED is equivalent to an erythemally effective exposure of 100 J/m^2 and is independent of individual sensitivity to UVR and the specific UVR spectrum. An exposure of 2–4 SEDs would be expected to produce a mild sunburn on previously unexposed skin. Several studies have been done in which personal UVR exposure has been measured over extended periods in different populations in spring/summer in Copenhagen, Denmark (56°N) using time-stamped personal electronic dosimeters. In people working indoors without 'risk, or sun-seeking, behaviour' the median daily dose was 0.3 SED (range 0–3.9) on working days and 0.6 SED (range 0.1–3.5 SED) on days off [3]. It has been estimated that indoor workers in northern Europe receive about 200 SEDs/year, which is approximately 5% of the total available ambient radiation. Of this annual dose, 50% is received in just 33 days of the year. Outdoor workers would be exposed to 400–600 SEDs/year. Not surprisingly, higher daily exposures have been measured, using polysulphone badges, in Queensland, Australia with, for example, Brisbane (27.4°S) home workers having weekday shoulder exposure medians of 2.0–8.0 SEDs depending on time of year [4]. Outdoor workers at the same latitude showed values of 3.0–10.0 SEDs. It has been estimated that the average American is exposed to about 250 SEDs per working year, mostly in the spring and summer [5]. This can be increased by 78 SEDs (i.e. about 30%) with a 3-week vacation (i.e. by 3.7 SEDs per day) when sunscreens are more likely to be worn. Children spend more time out of doors and it is estimated that those in the UK receive an annual dose of about 300 SEDs. Behaviour is a major determinant of UVR exposure, such that it is possible for children in the UK to have higher solar exposure levels than in Queensland, Australia [6]. The use of tanning devices is increasingly popular, and one European study on sunbeds and melanoma reported that more than 50% of the study control population had used such devices [7]. Other artificial sources may also be important; some indoor workers are significantly irradiated by, for example, arc welding devices and hospital phototherapy equipment. Office workers and home dwellers may be at risk from low-intensity UVR from fluorescent or, more importantly, quartz halogen lamps used for indoor lighting.

References

1 Diffey BL. Ultraviolet radiation and human health. *Clin Dermatol* 1998; **16**: 83–9.

2 Diffey BL. Human exposure to ultraviolet radiation. In: Hawk JLM, ed. *Photodermatology*. London: Arnold, 1999: 5–24.

3 Thieden E, Philipsen PA, Heydenreich J *et al*. UV radiation exposure related to age, sex, occupation, and sun behaviour based on time-stamped personal dosimeter readings. *Arch Dermatol* 2004; **140**: 197–203.

4 Parisi AV, Meldrum LR, Kimlin MG *et al*. Evaluation of differences in ultraviolet exposure during weekend and weekday activities. *Phys Med Biol* 2000; **45**: 2253–62.

5 Godar DE, Wengraitis SP, Shreffler J *et al*. UV doses of Americans. *Photochem Photobiol* 2001; **73**: 621–9.

6 Diffey BL, Gies HP. The confounding influence of sun exposure in melanoma. *Lancet* 1998; **351**: 1101–2.

7 Bataille V, Boniol M, De Vries E *et al*. A multicentre epidemiological study on sunbed use and cutaneous melanoma in Europe. *Eur J Cancer* 2005; **41**: 2141–9.

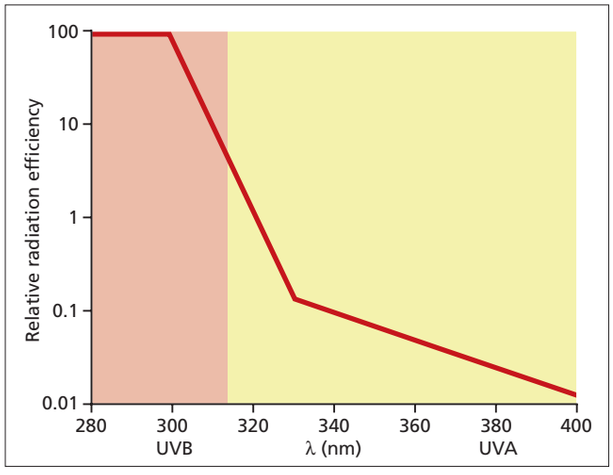


Fig. 29.7 Action spectrum for induction of erythema in human skin.

Normal cutaneous effects of UVR exposure

Early effects

Inflammation

UVR absorption by skin chromophores leads to widespread epidermal and dermal cellular damage, which is associated with inflammation [1]. DNA is probably the primary molecular target of injury [2], as a result of both direct UVB absorption and also secondary UVA-induced photosensitization reactions. Nuclear transcription factors and cytokine production are also induced at this stage [3,4], very likely by the same DNA damage [5], leading to increased production of serum and epidermal interleukins [3], with consequent cellular adhesion molecule activation [6], mild neutrophil and moderate mononuclear cell infiltration [7], and the release of various inflammatory mediators, such as prostaglandin E_2 and nitric oxide [8]. Clinically, erythema, pain, warmth and, in severe cases, swelling and loss of function, develop over hours to days. These changes are accompanied histologically by epidermal spongiosis and, except after UVA, the formation of sunburn cells (apoptotic cells) [9], along with dermal vasodilatation, oedema and neutrophil and mononuclear cell infiltration [7]. UVR wavelengths around 300 nm are the most DNA damaging and erythemogenic [2]. The lowest dose to induce erythema is known as the minimal erythema dose (MED), and is around 500 J/m^2 for the UVC–UVB boundary (280 nm), 250 J/m^2 for UVB (300 nm) and 320 kJ/m^2 for UVA (360 nm) (Fig. 29.7).

Tanning

Immediate

Immediate, often greyish, tanning of irradiated skin, lasting for a minute or so up to hours, may occur within seconds of exposure to 20–120 kJ/m^2 of UVA, and perhaps also short-wavelength visible radiation, particularly in more pigmented subjects. This probably results from photo-oxidative darkening and cellular redistribution of epidermal melanocytic melanin, although sunburning sensitivity is not apparently decreased by this response; however, supranuclear melanin caps present in strategically important basal layer cells may protect vulnerable genetic sites.

Delayed

Delayed (facultative) tanning is the process by which UVR-induced melanin synthesis is transferred from melanocyte dendrites to adjacent keratinocytes. Sunburning sensitivity in white skin is thereby moderately decreased by about two- to four-fold [10,11]. This tan typically persists for weeks to months, and gradually appears over hours to days after cutaneous exposure to around 400 J/m^2 of broad-band UVB (somewhat greater than the MED, particularly in fair-skinned subjects), 150–200 kJ/m^2 of broad-band UVA (somewhat less than the MED) or 100 J/m^2 of UVC (about equal to the MED). Overall, the action spectrum for delayed tanning is similar to that for erythema and provides circumstantial evidence for DNA as an important chromophore. Molecular studies support the role of DNA damage and the CPD in particular [12]. Recent mouse studies show that UVR-induced activation of p53, probably via DNA damage, stimulates the production of pro-opiomelanocortin (POMC) which is post-translationally cleaved into three products, including α-melanocyte stimulating hormone (α-MSH). This binds to the melanocortin 1 receptor (MC1R) which triggers a cascade of signalling events that leads to the synthesis of melanin from tyrosine via the induction of tyrosinase [13,14].

Hyperplasia

Skin hyperplasia, persisting for a month or two, develops over hours to days following UVB or UVC (but generally not UVA) exposure, and results from a marked increase in cell mitosis, DNA, RNA and protein synthesis rates, after some hours of early inactivity. The stimulus for this is unknown but, as for tanning, may conceivably be UVR-induced cellular DNA damage. The epidermis and dermis, particularly the inert stratum corneum, thicken as a result by up to two to four times, thereby apparently giving some protection against subsequent UVR-induced inflammation, an effect that combines with and may perhaps supersede the concomitant protection from tanning, particularly in fair-skinned races.

Immunological changes

The skin is a major immunological organ in which the epidermal dendritic Langerhans' cells normally present antigens to naïve T cells. It is now well established that UVR has profound effects on skin immunity that are mediated by alterations to the antigen-presenting capacity of Langerhans' cells and the stimulation of abnormal antigen presentation by CD11b macrophages [15]. These alterations are the result of UVR-induced changes to the chemical microenvironment of the skin, in particular the cytokine profile [4].

UVR has been shown to inhibit the induction and elicitation phases of the contact hypersensitivity response (CHS) in mice and in humans. Mouse studies have shown that UVR-induced immunosuppression has a major role in skin cancer, and a similar role is suspected in humans. A single sub-erythemal exposure of solar simulated radiation (SSR) suppresses the induction phase of the CHS in sun-sensitive skin types I/II (Table 29.1). An erythemal

Table 29.1 Characteristics of different skin phototypes, namely response to sun exposure, with I fairest, VI darkest.

Skin phototype	Characteristics
I	Always burns, never tans
II	Usually burns, sometimes tans
III	Sometimes burns, usually tans
IV	Never burns, always tans
V	Moderate constitutive pigmentation
VI	Marked constitutive pigmentation

exposure was necessary to give a comparable level of immunosuppression in sun-tolerant skin types III/IV and this difference may be a factor in the differing susceptibilities of skin types I/II and III/IV to skin cancer [16]. The most likely chromophores for the immunomodulatory effects of UVR are DNA [17] and stratum corneum-bound urocanic acid (UCA) which undergoes a *trans* to *cis* isomerization in the presence of UVR. *Cis*-, but not *trans*-, UCA has recently been shown to induce gene transcription and synthesis of immunomodulatory mediators in human keratinocytes *in vitro* [18]. Recent studies suggest that whereas UVR suppresses adaptive immune responses, such as CHS, it may induce the innate immune response by stimulating the production of antimicrobial peptides in human skin such as psoriasin [19]. Thus, there may be beneficial effects of UVR on immunity. Furthermore, a degree of UVR-induced suppression of adaptive immunity may be beneficial in the prevention of immune responses to photoantigens, as is suspected in the case of polymorphic light eruption [20].

Photo-onycholysis

A few subjects develop recurrent, probably UVA-induced, photo-onycholysis of nails exposed to strong sunlight, conceivably from photosensitization by endogenous photoactive cutaneous substances such as porphyrin in the presence of high-intensity UVA exposure, a process probably similar to those operating in drug- or porphyria-associated photo-onycholysis [21].

References

1 Clydesdale GJ, Dandie GH, Muller HK. Ultraviolet light induced injury: immunological and inflammatory effects. *Immunol Cell Biol* 2001; **79**: 547–68.

2 Young AR, Chadwick CA, Harrison GI *et al*. The similarity of action spectra for thymine dimers in human epidermis and erythema suggests that DNA is the chromophore for erythema. *J Invest Dermatol* 1998; **111**: 982–8.

3 Soter NA. Acute effects of ultraviolet radiation on the skin. *Semin Dermatol* 1990; **9**: 11–5.

4 Barr RM, Walker SL, Tsang W *et al*. Suppressed alloantigen presentation, increased TNF-α, IL-1, IL-Ra, IL-10, and modulation of TNF-R in UV-irradiated human skin. *J Invest Dermatol* 1999; **112**: 692–8.

5 Nishigori C, Yarosh DB, Ullrich SE *et al*. Evidence that DNA damage triggers interleukin 10 production in UV-irradiated murine keratinocytes. *Proc Natl Acad Sci USA* 1996; **93**: 10354–9.

6 Norris P, Poston RN, Thomas S *et al*. The expression of endothelial leukocyte adhesion molecule-1 (ELAM-1), intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1) in experimental cutaneous inflammation: a comparison of ultraviolet B erythema and delayed hypersensitivity. *J Invest Dermatol* 1991; **96**: 763–70.

7 Hawk JLM, Murphy GM, Holden CA. The presence of neutrophils in human cutaneous ultraviolet-B inflammation. *Br J Dermatol* 1988; **118**: 27–30.

8 Rhodes LE, Belgi G, Parslew R *et al*. Ultraviolet-B-induced erythema is mediated by nitric oxide and prostaglandin E_2 in combination. *J Invest Dermatol* 2001; **117**: 880–5.

9 Sheehan JM, Young AR. The sunburn cell revisited: an update of mechanistic aspects. *Photochem Photobiol Sci* 2002; **1**: 365–77.

10 Young AR, Sheehan JM. UV-induced pigmentation in human skin. In: Giacomoni PU, ed. *Sun Protection in Man*. St Louis, MO: Elsevier, 2001: 357–75.

11 Agar N, Young AR. Melanogenesis: a photoprotective response to DNA damage? *Mut Res* 2005; **571**: 121–32.

12 Eller MS, Yaar M, Gilchrest BA. DNA damage and melanogenesis. *Nature* 1994; **372**: 413–4.

13 Cui R, Widlund HR, Feige E *et al*. Central role of p53 in the suntan response and pathologic hyperpigmentation. *Cell* 2007; **128**: 853–64.

14 Tran T-NT, Schulman J, Fisher DE. UV and pigmentation: molecular mechanisms and social controversies. *Pigment Cell Melanoma Res* 2008; **21**: 509–16.

15 Novakovic L, Lee S, Orchard GE *et al*. Effects of solar-simulated radiation dose fractionation on CD1a Langerhans' cells and CD11b macrophages in human skin. *Br J Dermatol* 2001; **145**: 237–44.

16 Kelly DA, Young AR, McGregor JM *et al*. Sensitivity to sunburn associated with susceptibility to ultraviolet radiation-induced suppression of cutaneous cell-mediated immunity. *J Exp Med* 2000; **191**: 561–6.

17 Walker SL, Young AR. An action spectrum (290–320nm) for TNFα protein in human skin in vivo suggests that basal layer epidermal DNA is the chromophore. *PNAS* 2007; **104**: 19051–4.

18 Kaneko K, Smetana-Just U, Matsui M *et al*. *cis*-urocanic acid initiates gene transcription in primary human keratinocytes. *J Immunol* 2008; **181**: 217–24.

19 Glaser R, Navid F, Schuller W *et al*. UV-B radiation induces the expression of antimicrobial peptides in human keratinocytes in vitro and in vivo. *J Allergy Clin Immunol* 2009; **123**: 1117–23.

20 van de Pas CB, Kelly DA, Seed PT *et al*. Ultraviolet-radiation-induced erythema and suppression of contact hypersensitivity responses in patients with polymorphic light eruption. *J Invest Dermatol* 2004; **122**: 295–9.

21 Logan RA, Hawk JLM. Spontaneous photo-onycholysis. *Br J Dermatol* 1985; **113**: 605–10.

Acute systemic effects

Vitamin D synthesis

UVB radiation converts epidermal 7-dehydrocholesterol (provitamin D_3) into previtamin D_3, which is then non-enzymatically isomerized in a temperature-dependent way to vitamin D_3 (cholecalciferol) and transported by plasma vitamin D-binding protein into the circulation, reaching a maximum within 12–24 h after UVB exposure. The physiologically active vitamin D_3 is 1α,25-dihydroxyvitamin D_3 (calcitriol) that requires two enzymatically controlled hydroxylation steps. There is an ever expanding literature on the possible health benefits of UVR-induced vitamin D [1,2], which alongside reports of vitamin D deficiency and insufficiency in many populations, even in sunny countries [3,4], has led some people to advocate greater solar UVR exposure. The International Agency for Research on Cancer (IARC) recently reviewed the extensive data on the relationship between vitamin D and cancer [5] and came to the conclusion that the existing, mostly epidemiological data, should be tested by well-designed, randomized controlled trials.

Feel-good and health factors

Solar radiation is essential for life and the provision of human well-being, offering warmth and light, but the UV component of such radiation does not appear to be necessary, apart from vitamin D synthesis. There is a long history of widely claimed mood-enhancing and health-giving properties of sunlight [6,7] which

have been treated with scepticism, but recent data suggest that these may be real and require further investigation. The possible beneficial effects of UVR on innate immunity have been discussed under Immunological changes, above in this chapter. Apart from α-MSH, another cleavage product of POMC is β-endorphin, an opioid peptide with mood-altering properties [8]. Indeed, one small study has shown that the opioid antagonist naltrexone could induce withdrawal symptoms in 50% of frequent tanners (four/eight) but not in any infrequent control tanners (none/eight) [9].

References

1 Kimlin MG. Geographic location and vitamin D synthesis. *Mol Aspects Med* 2008; **29**: 453–61.
2 Tremlett H, van der Mel IAF, Pittas F *et al*. Monthly ambient sunlight, infections and relapse rates in multiple sclerosis. *Neuroepidemiology* 2008; **31**: 271–9.
3 Kimlin M, Harrison S, Nowak M *et al*. Does a high UV environment ensure adequate vitamin D status? *J Photochem Photobiol B: Biol* 2007; **89**: 139–47.
4 Holmes VA, Barnes MS, Alexander HD *et al*. Vitamin D deficiency and insufficiency in pregnant women: a longitudinal study. *Br J Nutrit* 2009; *in press.*
5 *IARC Working Group Reports*. Vol 5. *Vitamin D and Cancer*. Lyon: International Agency for Cancer Research, 2008.
6 Colbrook D. Artificial sunlight treatment in industry: a report on the results of three trials—in an office, a factory and a coalmine. *Industrial Health Research Board, Report no. 89*. London: Medical Research Council, 1946.
7 Ronge HE. Ultraviolet irradiation with artificial illumination: a technical, physiological and hygienic study. *Acta Physiol Scand* 1948; **15** (Suppl. 49): 1–35.
8 Cui R, Widlund HR, Feige E *et al*. Central role of p53 in the suntan response and pathologic hyperpigmentation. *Cell* 2007; **128**: 853–64.
9 Kaur M, Liguori A, Lang W *et al*. Induction of withdrawal like symptoms in a small randomized, controlled trial of opioid blockade in frequent tanners. *J Am Acad Dermatol* 2006; **54**: 709–11.

Late effects

Pseudoporphyria

Regular skin exposure to the predominantly UVA radiation from sunbeds, or perhaps also to strong sunlight during the use of high-protection UVB sunscreens, may lead over weeks or months to largely reversible cutaneous blistering and fragility, as well as to superficial atrophic scarring, as occurs in the hepatic porphyrias, particularly in fair-skinned subjects [1]. This may conceivably be the result of photosensitization by endogenous photoactive cutaneous substances such as porphyrin in the presence of high-intensity UVA exposure, a process probably similar to those operating in drug-associated pseudoporphyria and the hepatic porphyrias.

Photoageing

Skin photoageing is the gradual deterioration of cutaneous structure and function following long-term recurrent exposure to sunlight or artificial UVR sources. These events are superimposed on intrinsic chronological skin ageing [2]. The epidermis and dermis are both affected, probably principally by UVB, but the dermis may be affected to some extent by UVA. Cutaneous fine and coarse wrinkling, dryness, coarseness, telangiectasia, yellowness, mottled pigmentation, laxity, loss of tensile strength and comedones are characteristic. Histologically, there is a mild inflammatory infiltrate and profuse upper dermal accumulation of a form of amorphous degenerate elastic tissue, known as elastosis. *In vivo* studies provide evidence for an important role for UVR-induced signalling pathways [3] that induce matrix metalloproteinases (MMP), which degrade collagen, the major structural protein of the dermis [4]. Recent studies suggest that DNA photodamage, the CPD in particular, may be the trigger for MMP induction [5]. There is also evidence that UVR-induced damage to mitochondrial DNA is important in photoageing [6]. Restriction of UVR exposure and the use of high-SPF broad-spectrum sunscreens may slow progression of this process, and long-term use of the topical retinoid all-*trans* retinoic acid, and to a lesser extent of α-hydroxyacid preparations, may improve any changes already present [3].

Photocarcinogenesis

Human epidemiological and animal studies strongly suggest that chronic cutaneous UVB and, to a lesser extent, UVA exposure are responsible for the induction of most non-melanoma skin cancers, and probably of melanomas as well, although it has been suggested that UVA may play a relatively more important part in the latter [7]. A number of UVR-induced cutaneous events appear to be important, including characteristic mutations (C → T and CC → TT) of the *p53* tumour suppressor gene in actinic keratoses, squamous cell carcinoma, and basal cell carcinoma and the PTCH gene in basal cell carcinoma [8,9]. Until recently, there was very little direct molecular data to support the role of UVR in human malignant melanoma. However, a recent study has reported the presence of UVR-induced mutations in the *PTEN* (phosphatase and tensin homologue) tumour suppressor gene in melanomas in xeroderma pigmentosum (XP) patients [10].

Long-term topical use of the retinoid tretinoin may perhaps very slowly improve actinic keratoses, and topical 5-fluorouracil cream and liquid nitrogen cryotherapy are very effective in the rapid treatment of these lesions. However, for fully developed skin cancers treatment with surgery or radiotherapy is required (see Chapters 77 & 79).

References

1 Murphy GM, Wright J, Nicholls DSH *et al*. Sunbed-induced pseudoporphyria. *Br J Dermatol* 1989; **120**: 555–62.
2 Herschenfeld RE, Gilchrest BA. The cumulative effects of ultraviolet radiation on the skin: photoageing. In: Hawk JLM, ed. *Photodermatology*. London: Arnold, 1999: 69–89.
3 Yaar M, Gilchrest BA. Photoageing: mechanism, prevention and therapy. *Br J Dermatol* 2007; **157**: 874–87.
4 Fisher GJ, Kang S, Varani J *et al*. Mechanisms of photoaging and chronological skin aging. *Arch Dermatol* 2002; **138**: 1462–70.
5 Dong KK, Damaghi N, Picart SD *et al*. UV-induced DNA damage initiates release of MMP-1 in human skin. *Exp Dermatol* 2008; **17**: 1037–44.
6 Schroeder P, Gremmel T, Berneburg M *et al*. Partial depletion of mitochondrial DNA from human skin fibroblasts induces a gene expression profile reminiscent of photoaged skin. *J Invest Dermatol* 2008; **128**: 2297–303.
7 Wang SQ, Setlow R, Berwick M *et al*. Ultraviolet A and melanoma: a review. *J Am Acad Dermatol* 2001; **44**: 837–46.
8 Brash DE, Ziegler A, Jonason *et al*. Sunlight and sunburn in human skin cancer: p53, apoptosis, and tumor promotion. *J Invest Dermatol Symp Proc* 1996; **1**: 136–42.
9 Heitzer E, Lassacher A, Quehenberger F *et al*. UV fingerprints predominate in the PTCG mutation spectra of basal cell carcinoma independent of clinical phenotype. *J Invest Dermatol* 2007; **127**: 2872–81.
10 Wang Y, DiGiovanna JJ, Stern JB *et al*. Evidence of ultraviolet type mutations in xeroderma pigmentosum melanomas. *PNAS* 2009; **106**: 6279–84.

Skin phototypes

An individual's genetically determined cutaneous sunburning and tanning tendency following UVR exposure may be roughly graded by self-assessed skin phototype (Table 29.1) [1,2]. This assists in the determination of safe but effective regimens for phototherapy and photochemotherapy, as well as an individual's susceptibility to sunburn and skin cancer, and thus the degree of photoprotection required. In general, MED increases with skin type, but there is considerable overlap between skin types, such that a skin type I may have the same MED as a skin type IV [3]. Thus, although broadly useful, skin type assessment is only a guide.

References

1 Stern RS, Momtaz TK. Skin typing for assessment of skin cancer risk and acute response to UV-B and oral methoxsalen photochemotherapy. *Arch Dermatol* 1984; **120**: 869–73.

2 Fitzpatrick TB. The validity and practicality of sun-reactive skin types I through VI. *Arch Dermatol* 1988; **124**: 869–71.

3 Harrison GI, Young AR. Ultraviolet-radiation induced erythema in human skin. *Methods* 2002; **28**: 14–9.

Prophylactic measures to minimize human cutaneous UVR exposure

Restriction of skin exposure to direct sunlight is advisable when UVR intensity is high, such as following short atmospheric radiation transit at times around the solar zenith, particularly at high altitudes, low latitudes and in summer (Fig. 29.8); furthermore, because much of this UVR is incident from areas of blue sky as a result of normal atmospheric molecular and aerosol scattering, exposure to sky light should also be minimized at such times. Finally, as UVR intensity is increased by reflection from snow by up to 85%, sand by 25% and rippling water by perhaps 5%, but decreased by only 20–90% by cloud cover and 60% for every 50 cm travelled through water, extra care should also be taken when these factors apply, particularly in alpine areas or near the sea. Radiation intensity is not, however, significantly altered by any accompanying heat, cold, wind or visible light.

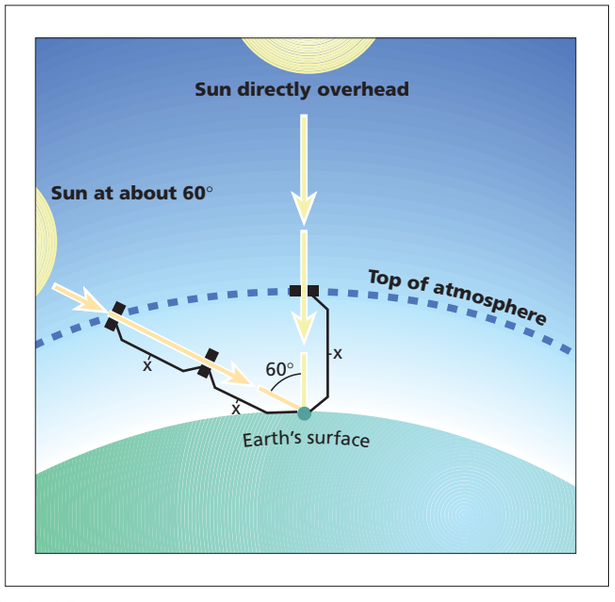


Fig. 29.8 UVR path lengths for differing solar elevations.

Clothing

Clothing consisting of close-weave, loose-fitting material covering as much of the skin as fashionably acceptable provides protection against UVR exposure, and if opaque to visible light is generally protective against UVR as well; in particular, broad-brimmed headwear is useful for the face and scalp. Several companies now produce clothes with a UV protection factor (UPF).

Sunscreens

Sunscreens are topical preparations that attenuate UVR intensity by reflecting, scattering or absorbing it. Traditional reflectant/scattering sunscreens remit both UVB and UVA from a film of inert mineral oxide micropigments, usually zinc oxide or titanium dioxide in a suitable vehicle. There has been a more recent development of an organic micropigment which absorbs, scatters and reflects UVR. Thus, the oft used classification of chemical (organic) and physical (mineral micropigments) can no longer apply.

The efficacy of a sunscreen is determined by its ability to afford protection against erythema, which is primarily caused by solar UVB but with some contribution (15–20%) from UVA. The measure of protection, assessed under controlled laboratory conditions, is known as the sun protection factor (SPF) [1,2] and is the multiple by which UVR exposure may be increased, after sunscreen application, before burning begins. One requirement of SPF assessment is the application of 2 mg/cm^2 of skin. However, several studies have shown that people typically apply much less and so will receive a much lower level of protection than the labelled SPF [3]. Assessment of UVA protection has been controversial, but the European Commission has recently recommended that the minimum level of UVA protection should be a UVA protection factor of one-third of the SPF, as determined by the persistent pigment darkening method. Sunscreen resistance to removal by water, known as 'substantivity', may also be quantified in terms of its rate of loss of efficacy on submerged skin [1]. Highly substantive preparations are clearly preferable in circumstances where they may be washed or rubbed off.

Avoidance of sunburn requires restriction of UVR exposure, covering up with appropriate clothing and the use of high-SPF broad-spectrum sunscreens. If burning occurs in spite of these precautions, treatment is largely symptomatic, and involves the administration of oral fluids, particularly in severe cases, the application of soothing topical emollient creams or evaporating lotions and, more actively, the use of topical or oral non-steroidal (or perhaps occasionally steroidal) anti-inflammatory agents from the earliest onset of symptoms. On rare occasions, sunburning may be severe or life-threatening and then requires treatment as for thermal burns.

The regular, adequate prophylactic application of high SPF, broad-spectrum sunscreens may be helpful in minimizing some non-erythema short-term effects of cutaneous UVR exposure [4,5]. The application of high-SPF sunscreens may prevent actinic keratoses [6] and squamous cell carcinoma [7]. Overall, there is no evidence to suggest that sunscreen use can prevent basal cell carcinoma or malignant melanoma [7,8]. The action spectra for erythema and the photosynthesis of previtamin D_3 are very similar in the UVB region and there has been some concern that sunscreen use might be detrimental to vitamin D status, but to date this has not been supported by studies.

Absorbent (organic) products have traditionally been the most popular; they act well against UVB and are also cosmetically satisfactory, although cutaneous irritation and contact or photocontact dermatitis are possible hazards [1,2]. For the UVA-induced photodermatoses and very photosensitive normal subjects, however, the relatively inert, mineral oxide-containing preparations, although less cosmetically appealing, have been preferred, as they are less irritating and less liable to cause contact sensitivity, as well as being very effective against both UVB and UVA. A good range of increasingly effective UVA absorbers is available, especially in Europe [9]. Combination preparations that absorb, scatter and reflect have also become more common, and appear to provide optimal cover in all circumstances except severe UVA photosensitivity.

High SPF (15–25) products providing substantial UVA protection are suitable for all purposes, particularly the photodermatoses, but many have a mild propensity to induce contact sensitization and appear white on the skin [1,2], so that lower levels of protection (10–15) may sometimes be more satisfactory for normal, particularly darker, skins and moderate exposures. In the UK, certain highly protective sunscreens may be prescribed as so-called 'borderline substances' for the treatment of abnormal photosensitivity, the exact choice depending on the circumstances in which the preparation is to be used (Table 29.2).

Table 29.2 Sunscreens currently available in the UK for prescription as borderline substances. Note, however, that formulations may be regularly altered.

Sunscreen*	Active ingredients	Spectral efficacy
Delph Lotion SPF30	Ethylhexyl *p*-methoxycinnamate 4.8%, oxybenzone 1.5%, avobenzone 4.0%, titanium dioxide 2.5%	Good UVB, good UVA
E45 Sun Block Lotion SPF30+	Zinc oxide 16.0%, titanium dioxide 6.4%	Very good UVB, good UVA
Spectraban Ultra Lotion SPF 28	Octyldimethyl *p*-aminobenzoic acid 8%, butyl methoxydibenzoylmethane 2%, oxybenzone 3%, titanium dioxide 2%	Good UVB, moderate UVA
Sunsense Ultra Lotion SPF50+	Octyl methoxycinnamate 7·5%, oxybenzone 3%, titanium dioxide 3%	Very good UVB, good UVA
Uvistat Cream SPF50	Ethylhexyl methoxycinnamate 10%, methylene bis-benzotriazolyl tetramethylbutylphenol 6%, butyl methoxydibenzoylmethane 5%, titanium dioxide 4.8%, octocrylene 4%, isoamyl *p*-methoxycinnamate 2%	Very good UVB, very good UVA
Uvistat Lipscreen SPF50	Ethylhexyl methoxycinnamate 10%, butyl methoxydibenzoylmethane 5%, titanium dioxide 3%, octocrylene 4%, bis-ethylhexyloxyphenol methoxyphenyl triazine 3%	Very good UVB, very good UVA
Uvistat Cream SPF30	Ethylhexyl methoxycinnamate 7.5%, butyl methoxydibenzoylmethane 5%, titanium dioxide 5.2%, octocrylene 4%, methylene bis-benzotriazolyl tetramethylbutylphenol 1.5%	Good UVB, good UVA

* Trade names.

References

1 Lowe NJ, Friedlander J. Sunscreens: rationale for use to reduce photodamage and phototoxicity. In: Lowe NJ, Shaath NA, Pathak MA, eds. *Sunscreens: Development, Evaluation and Regulatory Aspects*, 2nd edn. New York: Marcel Dekker, 1997: 35–58.

2 Lim HW, Hönigsmann H. Photoprotection. In: Lim HW, Hönigsmann H, Hawk JLM, eds. *Photodermatology*. New York: Informa Healthcare USA Inc, 2007: 267–78.

3 Diffey BL. People do not apply enough sunscreen for protection. *BMJ* 1996; **313**: 942.

4 Proby CM, Baker CS, Morton O *et al*. New broad-spectrum sunscreen for polymorphic light eruption. *Lancet* 1993; **341**: 1347–8.

5 Young AR. Are broad-spectrum sunscreens necessary for immunoprotection? *J Invest Dermatol* 2003; **121**: ix–x.

6 Darlington S, Williams G, Neal R *et al*. A randomized controlled trial to assess sunscreen application and beta carotene supplementation in the prevention of solar keratoses. *Arch Dermatol* 2003; **139**: 451–5.

7 *IARC Handbooks of Cancer Prevention*, Vol. 5, *Sunscreens*. Lyon: International Agency for Cancer Research, 2001.

8 Huncharek M, Kupelnick B. Use of topical sunscreens and the risk of malignant melanoma: a meta-analysis of 9067 patients from 11 case–control studies. *Am J Public Health* 2002; **92**: 1173–7.

9 Yaar M, Gilchrest BA. Photoageing: mechanism, prevention and therapy. *Br J Dermatol* 2007; **157**: 874–87.

Abnormal cutaneous effects of UVR exposure: the photodermatoses

J.L.M. Hawk, pp. 29.9–29.15

Acquired disorders with a probable autoimmune basis (Table 29.3)

Polymorphic light eruption

Definition. Polymorphic light eruption (PLE) is a common, intermittent, sunlight or artificial UVR-induced eruption, particularly at temperate latitudes, affecting subjects of any race within hours to rarely days of exposure, thereafter lasting days to a week or two once exposure ceases. The eruption is generally symmetrical, itchy, erythematous or skin-coloured, papular and non-scarring, but sometimes plaque-like, vesicular, bullous or a combination of these. It usually affects exposed skin, but rarely also on covered areas. It is commoner in young women, often worse in spring, and probably a delayed-type hypersensitivity (DTH)

Table 29.3 Distinguishing features of acquired, probably autoimmune photodermatoses.

Disease	Clinical features	Specific investigations (estimation of antinuclear factor and extractable nuclear antibody titres always essential, screening for blood, urine and stool porphyrins essential if any suggestion of porphyria)	Differential diagnosis	Treatment (in all cases restriction of UVR exposure, wearing of appropriate clothing cover and use of high-protection broad-spectrum sunscreens is a necessary basic approach)
Polymorphic light eruption	Very common, affects mostly young women at temperate latitudes. Transient, summer sun-induced, non-scarring, erythematous, itchy, symmetrical, papulovesicular eruption of usually only some exposed areas. Onset in hours, resolution in days. Examination in remission normal.	History most important in diagnosis. Histology useful, not fully diagnostic in uncertain cases, direct immunofluorescence negative. Solar, solar-simulated or broad-band UVA irradiation may induce rash. Monochromatic irradiation tests may often induce abnormal responses. Lupus must be excluded by serology.	Persistent lymphocytic infiltrations, e.g. Jessner's, solar urticaria, light-exacerbated seborrhoeic dermatitis, lupus erythematosus, and on history many other light-exacerbated dermatoses, erythropoietic protoporphyria.	Prophylactic, low-dose broad- or narrowband UVB or PUVA for frequent attacks, short-term topical, oral or injected steroids for infrequent, especially vacation attacks, very rarely ciclosporin, azathioprine for intractable disease.
Actinic prurigo	Rare, persistent PLE variant, affects mostly girls, adult females, may resolve in adolescence or persist indefinitely. UVR-induced, papular or nodular eruption, itchy, symmetrical, excoriated, fades towards covered sites, may sometimes spread to affect buttocks. Worse in summer, fades in winter, may flare with sun exposure. Superficial pock, linear, facial scarring possible. Clinical PLE may accompany.	Clinical features most important. Solar, solar-simulated or broad-band UVA irradiation may induce PLE-like rash. Monochromatic irradiation tests may often induce abnormal responses. HLA-DRB1*0401 (DR4) positivity in 80–90% of patients (30% normals), DRB1*0407 in 60% (6% normals), very supportive if present.	PLE, nodular prurigo, atopic prurigo, insect bites, atopic eczema, scabies, erythropoietic protoporphyria if facial scarring present.	Topical, occasional intermittent oral, steroids and emollients; prophylactic low-dose UVB or PUVA, particularly before rash appears in spring, low-dose oral thalidomide, intermittent if possible, with care to avoid pregnancy, and peripheral neuropathy through regular nerve conduction studies. In severe, unresponsive cases, ciclosporin if appropriate and thalidomide unsuitable.
Hydroa vacciniforme	Very rare. Affects mostly children, often remits in adolescence. Intermittent, summer sun-induced, stinging, scattered or confluent, symmetrical, vesicular, partly papular or plaque eruption of usually only some exposed areas. Onset in hours, crusting in days, disfiguring pock scars in weeks.	Clinical features most important. Histology usually pathognomonic. Solar simulated, broad-band UVB or especially UVA irradiation may induce rash, monochromatic irradiation, especially 340nm UVA, an abnormal erythema. Viral and porphyrin studies negative.	PLE, actinic prurigo, herpes simplex, xeroderma pigmentosum, erythropoietic protoporphyria, because of facial scarring.	Largely intractable but high-protection, broad-spectrum sunscreens sometimes useful, prophylactic, low-dose UVB or PUVA reported to help but care needed to avoid inducing rash, hydroxychloroquine suggested effective but very questionable, recently oral omega-3 fatty acids also suggested possibly useful.
Solar urticaria	Rare, affects all ages, both sexes. Intermittent, UVR-, especially UVA-, or visible light-induced, non-scarring, wealing eruption of some or usually all exposed areas. Onset in 5–10min, resolution in 1–2h. Often year-round. Very rarely secondary to lupus, drug or chemical use, erythropoietic protoporphyria. Examination in remission normal.	Clinical features important. Broad-band UVB, UVA or visible, or monochromatic, irradiation usually but not always elicits rash, defines action spectrum.	PLE, drug or chemical photosensitivity, erythropoietic protoporphyria, other urticarias, particularly heat, occasionally cholinergic.	High-dose, non-sedating antihistamines, prophylactic UVB or PUVA, induction of tolerance by daily exposure to action spectrum wavelengths, plasmapheresis, intravenous immunoglobulin.
Chronic actinic dermatitis	Rare. Affects mostly elderly men, often outdoor enthusiasts, may follow endogenous eczema, occasionally affects younger atopics, rarely human immunodeficiency virus sufferers. Chronic, UVR- and sometimes also visible light-induced, itchy, excoriated, lichenified or pseudolymphomatous, eczematous eruption, especially of exposed skin, sometimes generalized. Worse in summer, may flare after sun exposure. Allergic, especially airborne, contact dermatitis often coexists.	Broadband UVB, UVA or visible, or monochromatic, irradiation elicits eruption, defines action spectrum, necessary for diagnosis. Histology often characteristic. Patch and photopatch tests frequently positive to exacerbating allergens. $CD4^+/CD8^+$ T-cell ratio generally reduced in skin and circulating blood, particularly in florid cases.	Atopic or seborrhoeic eczemas, particularly light- exacerbated, allergic, especially airborne, contact dermatitis, cutaneous T-cell lymphoma, all forms of erythroderma.	Topical steroids and emollients, high-protection, broad-spectrum, non-irritating sunscreens, intermittent oral steroids, topical tacrolimus, oral immunosuppressive therapy with azathioprine, ciclosporin, mycophenolate or rarely thioguanine, intermittent if possible, long-term, very low-dose UVB or PUVA, given under initial high-dose oral steroid cover several days weekly, weaning off steroids over weeks and reducing exposure frequency over months to about once monthly.

reaction against endogenous cutaneous photoantigen, as a result of genetically-impaired UVR-induced suppression of the induction phase of the reaction.

Aetiology. The eruption of PLE is inducible by ultraviolet [1], and perhaps also rarely visible [2] radiation exposure, whether from sunlight or artificial sources, particularly sunbeds [3]. Of these, early summer sunlight at temperate latitudes is most often the trigger, with artificial emissions less likely to provoke the rash, although careful, solar-simulated [4,5] or UVA [6,7] irradiation, particularly of regularly affected sites, if necessary daily over 2–3 days, is not infrequently effective. Broadband UVB [8] has also been useful, although less reliably, while monochromatic irradiation may demonstrate lower than normal MEDs or abnormal papular responses in over half of patients [9]. Given these uncertainties, however precise action spectra for PLE induction have been difficult to determine, particularly as they clearly vary between patients but, broadly speaking, perhaps about a quarter of patients are sensitive to just UVB, a quarter to both UVB and UVA, and a half to just UVA [7,10].

PLE appears to have a genetic basis [11,12], affecting patients' families one and a half times more commonly than the general population [12], with perhaps some 70% of the population carrying a susceptibility allele. However, disease expression in genetically susceptible individuals is then heavily dependent on environmental factors [12].

PLE had long seemed likely on clinical grounds to be a DTH reaction against UVR-induced cutaneous antigen, and a study of sequential skin biopsies from rash induced by low-dose, solar-simulated irradiation eventually provided experimental support for this, showing increased numbers of dermal and epidermal antigen-presenting cells, along with a predominantly $CD4^+$, perivascular T-lymphocyte infiltrate within hours, followed by a mostly $CD8^+$ infiltrate within 2–3 days [4]. This was clearly distinct from the immunosuppressive response of similarly irradiated normal subjects [13]. Later work supported this further by demonstrating adhesion molecule activation patterns for E-selectin, vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) [14], also typical of DTH [15], as also did the associated release of interleukins (IL)-6, -8 and possibly -1 [16], along with a reduced expression of IL-4, IL-10 and tumour necrosis factor (TNF)-α, compared with that in unaffected individuals [16,17]. Finally, the stimulation of autologous peripheral blood lymphocytes *in vitro* by UVR-irradiated PLE keratinocytes, but not normal keratinocytes, provided further support now of a more direct nature, for UVR-induced antigen production in PLE [18].

The likely genetic difference leading to these changes was then shown to be a much easier induction of cutaneous antigen recognition following UVR exposure in PLE patients than in normal individuals, in whom this ability is significantly more suppressed, as shown by an increased patient susceptibility to dinitrochlorobenzene contact sensitization (a known DTH response) following solar-simulated irradiation [19,20]. Once sensitization is achieved, however, both PLE patients and normals then immunosuppress moderately but equally after UVR exposure during later elicitation of the DNCB reaction [21]. This suppression of the induction phase of DTH in normal subjects may well have evolved to prevent the occurrence of PLE as a normal reaction, even though making later skin cancer more likely. Underlying genetic characteristics permitting continuing antigen recognition in PLE after UVR exposure may possibly be an abnormal Langerhans' cell resistance to depletion by such exposure [4,22], or more likely at least partly a reduced capacity to handle free radical insult through abnormal glutathione depletion, with increased putative antigen production as a possible result [23]. However, recent gene microarray studies have further suggested that an inherited deficiency of apoptotic cell clearance genes may also strongly contribute, such clearance apparently being necessary to permit immunosuppression, and also to diminish antigen persistence and thus its easier recognition [24]. These overall findings almost explain why PLE is rare at low latitudes, where UVR intensity is high, such that the diminished immunosuppressive capabilities of PLE are often overcome, and also why prophylactic photo(chemo)therapy is frequently effective.

Definitive UVR molecular absorbers initiating the PLE rash have not been identified, but may perhaps sometimes be a heat-shock protein detected in PLE-affected but not unaffected or UVB-irradiated normal skin [25]. More likely, however, is that a variety of absorbers are responsible, either by becoming antigenic themselves or by inducing secondary photosensitized antigen production [23].

Pathology [26]. There is variable epidermal spongiosis and dermal, perivascular and periadnexal, predominantly lymphocytic infiltration with oedema, often extending deep into the dermis in older lesions. Eosinophils and neutrophils may rarely be present. Focal interface change and mild basal hydropic degeneration may occasionally raise the possibility of lupus; exceptionally, a prominent dermal infiltrate may suggest lymphoma.

Clinical features [1] (Fig. 29.9). PLE is commonest in temperate regions, affecting 10–20% of people in such areas [12,27–29], particularly young women, with far fewer suffering in tropical regions [28,30]. All ethnic groups appear susceptible, dark skins perhaps even facilitating expression of the condition [31], while familial occurrence is also common [11,12]. PLE attacks are most usual in spring and early summer following specific sun exposure, sometimes lengthy prior to an initial attack, before often diminishing gradually in severity or ceasing as summer progresses. Reflected solar UVR from winter snow and sunbed irradiation [3] may also provoke outbreaks. Several minutes to hours of exposure is generally needed, sometimes days, particularly after periods of sunlight abstinence. Pruritus almost always occurs, often within minutes, then the rash within minutes to hours, therefore lasting hours to days, rarely weeks, particularly if exposure continues. It may be localized or widespread. Variable areas of exposed or lightly clad skin may be affected, usually symmetrically but often patchily. The distribution of the eruption in any given patient is generally characteristic, although sometimes gradually varying with time or intensity of exposure. Typically affected sites are the bridge of the nose, malar areas of the cheeks, tip of the chin, sides and back of the neck, upper chest, dorsa of the hands, dorsolateral aspects of the arms, fronts and backs of the legs, and dorsa of the feet.



Fig. 29.9 Polymorphic light eruption, showing variably sized, erythematous papules.

Lesional distribution and morphology vary greatly both between and within patients, but in general there are grouped, erythematous or skin-coloured, large or small papules, sometimes coalescing into smooth or irregularly surfaced, confluent plaques. Vesicles, papulovesicles, rarely bullae, or generalized oedematous swelling, the last especially of the face, may also occur. Rarely there is pruritus alone [32]; erythema alone, with or without itch, is extremely rare. Small papular PLE sparing the face, often affecting women on vacation, is sometimes known as benign summer light eruption in continental Europe [33], and an eruption on the light-exposed helices of boys' ears, which is often vesicular and was initially reported in springtime epidemics, is sometimes called juvenile spring eruption [34–36]. This arguably also occasionally affects some adults [37]. Systemic malaise, chills, headache, fever, nausea and even linked attacks of erythema multiforme [38] very rarely accompany PLE. The condition may persist indefinitely, but often gradually improves, and sometimes remits [39].

Diagnosis. This is suggested by the history, clinical findings, negative circulating antinuclear factor and extractable nuclear antibody titres, and normal blood, urinary and stool porphyrin concentrations. In doubtful cases, lesional histology may help but is not usually diagnostic, while immunofluorescence findings are negative. If uncertainty persists, skin irradiation monochromator tests may demonstrate reduced minimal erythemal or abnormal papular responses, and broad-spectrum testing, or solar exposure if available, may elicit the eruption itself, for biopsy if necessary. Solar urticaria is distinguished by its rapid (5–10 min) onset after exposure, short (1–2 h) total time course and different lesional morphology, erythropoietic protoporphyria by its painful nature, usual lack of rash and raised red blood cell protoporphyrin concentration, light-exacerbated seborrhoeic and atopic eczema by their eczematous clinical and histological features and distributions, lupus erythematosus, which may also precede or coexist with PLE [40,41], by its characteristic circulating and cutaneous immunological findings, and erythema multiforme by its clinical features, distinctive histology and not infrequent association with a precipitating agent.

Treatment. Mild PLE may be managed by restricting UVR exposure, covering up with appropriate clothing, and applying high-protection, broad-spectrum sunscreens [42], although these last may perhaps exacerbate the condition on occasion by transmitting the often inducing UVA but not the relatively immunosuppressive UVB [13]. In more severely and frequently affected patients, prophylactic broad- or more reliably narrowband UVB phototherapy, or the probably more efficient but less convenient PUVA, is regularly helpful for many months [43,44], almost certainly through immunosuppressive activity [13,45], but with annual follow-up courses usually necessary for at least some years [46]. Suitable protocols include initial irradiation with around 70% of the predetermined broad- or narrowband UVB MED, with about 10–20% increments two to three times weekly for 4–6 weeks, or psoralen 0.6 mg/kg and UVA 0.5 J/cm^2 with about 40% UVA increments twice weekly for a month. For treatment-induced PLE flares, oral steroids may be given as below. Oral antimalarial therapy has long been advocated for prophylactic use, but probably provides at best mild protection [47,48], β-carotene probably less or none [47]. More recently, oral omega-3 fatty acids have been suggested to be as moderately helpful [49]. For occasional PLE attacks, however, or if rash develops in spite of the above measures, brief oral steroid courses—prednisolone 25–30 mg at the earliest onset of itch and then each morning until clear, but for a maximum of about 10 days every 3 months—is almost always rapidly effective and safe [50]. Injected steroid probably has a similar effect, but topical steroids much less so. Oral azathioprine [51] and ciclosporin [52] have also been effective for disabling disease.

References

1 Hönigsmann H, Hojyo-Tomoka M-T. Polymorphous light eruption, hydroa vacciniforme, and actinic prurigo. In: Lim HW, Hönigsmann H, Hawk JLM, eds. *Photodermatology*. New York: Informa Healthcare, 2007: 149–67.

2 Piletta PA, Salomon D, Beani JC, Saurat JH. A pilot with an itchy rash. *Lancet* 1996; **348**: 1142.

3 Rivers JK, Norris PG, Murphy GM *et al*. UVA sunbeds: tanning, photoprotection, acute adverse effects and immunological changes. *Br J Dermatol* 1989; **120**: 767–77.

4 Norris PG, Morris J, McGibbon DM *et al*. Polymorphic light eruption: an immunopathological study of evolving lesions. *Br J Dermatol* 1989; **120**: 173–83.

5 van de Pas CB, Hawk JL *et al*. Experimental provocation of polymorphic light eruption. *Br J Dermatol* 2003; **149** (Suppl. 64): 92–3.

6 Hölzle E, Plewig G, Hofmann C *et al*. Polymorphous light eruption. Experimental reproduction of skin lesions. *J Am Acad Dermatol* 1982; **7**: 111–25.

7 Ortel B, Tanew H, Wolff K *et al*. Polymorphous light eruption: action spectrum and photoprotection. *J Am Acad Dermatol* 1986; **14**: 748–53.

8 Miyamoto C. Polymorphous light eruption: successful reproduction of skin lesions, including papulovesicular light eruption, with ultraviolet B. *Photodermatology* 1989; **6**: 69–79.

9 Magnus IA. Studies with a monochromator in the common idiopathic photodermatoses. *Br J Dermatol* 1964; **76**: 245–64.

10 Janssens AS, Pavel S, Ling ST *et al.* Susceptibility to UV-A and UV-B provocation does not correlate with disease severity of polymorphic light eruption. *Arch Dermatol* 2007; **143**: 599–604.
11 Millard TP, Bataille V, Snieder H *et al.* The heritability of polymorphic light eruption. *J Invest Dermatol* 2000; **115**: 467–70.
12 McGregor JM, Grabczynska S, Vaughan R *et al.* Genetic modeling of abnormal photosensitivity in families with polymorphic light eruption and actinic prurigo. *J Invest Dermatol* 2000; **115**: 471–6.
13 Nishigori C, Yarosh DB, Donawho C, Kripke ML. The immune system in ultraviolet carcinogenesis. *J Invest Dermatol Symp Proc* 1996; **1**: 143–6.
14 Norris PG, Barker JNWN, Allen M *et al*. Adhesion molecule expression in polymorphic light eruption. *J Invest Dermatol* 1992; **99**: 504–8.
15 Vejlsgaard GL, Ralfkiaer E, Arnstorp C *et al*. Kinetics and characterisation of intercellular adhesion molecule-1 (ICAM-1) expression on keratinocytes in various inflammatory skin lesions and malignant cutaneous lymphomas. *J Am Acad Dermatol* 1989; **20**: 782–90.
16 Norris PG, Bacon K, Bird C *et al.* The role of interleukins 1, 6 and 8 as lymphocyte attractants in the photodermatoses polymorphic light eruption and chronic actinic dermatitis. *Clin Exp Dermatol* 1999; **24**: 321–66.
17 Kolgen W, van Meurs M, Jongsma M *et al.* Differential expression of cytokines in UV-B-exposed skin of patients with polymorphous light eruption: correlation with Langerhans cell migration and immunosuppression. *Arch Dermatol* 2004; **140**: 295–302.
18 Gonzalez-Amaro R, Baranda L, Salazar-Gonzalez JF *et al.* Immune sensitisation against epidermal antigens in polymorphous light eruption. *J Am Acad Dermatol* 1991; **24**: 70–3.
19 van de Pas CB, Kelly DA, Seed PT *et al.* Ultraviolet-radiation-induced erythema and suppression of contact hypersensitivity responses in patients with polymorphic light eruption. *J Invest Dermatol* 2004; **122**: 295–9.
20 Palmer RA, Friedmann PS. Ultraviolet radiation causes less immunosuppression in patients with polymorphic light eruption than in controls. *J Invest Dermatol* 2004; **122**: 291–4.
21 Palmer RA, Hawk JLM, Young AR, Walker SL. The effect of solar-simulated radiation on the elicitation phase of contact hypersensitivity does not differ between controls and patients with polymorphic light eruption. *J Invest Dermatol* 2005; **124**: 1308–12.
22 Kolgen W, van Weelden H, Hengst SD *et al.* $CD11b^+$ cells and ultraviolet-B-resistant $CD1a^+$ cells in skin of patients with polymorphic light eruption. *J Invest Dermatol* 1999; **113**: 4–10.
23 Millard TP, Hawk JLM, Fryer AA, McGregor JM. Protective effect of glutathione S-transferase *GSTP1* Val^{105} against polymorphic light eruption. *Br J Dermatol* 2003; **149** (Suppl. 64): 88–9.
24 Palmer RA. Keratinocytes from Polymorphic Light Eruption Patients Under-Express Genes Related to Clearance of Apoptotic Cells. PhD Thesis, King's College London 2007; 197–229.
25 McFadden JP, Norris PG, Cerio R *et al.* Heat shock protein 65 immunoreactivity in experimentally induced polymorphic light eruption. *Acta Derm Venereol (Stockh)* 1994; **74**: 283–5.
26 Hawk JLM, Calonje E. The photosensitivity disorders. In: Elder DE, Elenitsas R, Johnson BL Jr, Murphy GF eds. *Lever's Histopathology of the Skin*, 9th edn. Philadelphia: Lippincott–Raven, 2005: 345–53.
27 Morison WL, Stern RS. Polymorphous light eruption: a common reaction uncommonly recognised. *Acta Derm Venereol (Stockh)* 1982; **62**: 237–40.
28 Pao C, Norris PG, Corbett M, Hawk JLM. Polymorphic light eruption: prevalence in Australia and England. *Br J Dermatol* 1994; **130**: 62–4.
29 Ros A, Wennersten G. Current aspects of polymorphous light eruptions in Sweden. *Photodermatology* 1986; **3**: 298–302.
30 Khoo SW, Tay YK, Tham SN. Photodermatoses in a Singapore skin referral centre. *Clin Exp Dermatol* 1996; **21**: 263–8.
31 Kerr HA, Lim HW. Photodermatoses in African Americans: a retrospective analysis of 135 patients over a 7-year period. *J Am Acad Dermatol* 2007; **57**: 638–43.
32 Dover JS, Hawk JLM. Polymorphic light eruption sine eruptione. *Br J Dermatol* 1988; **118**: 73–6.
33 Thomas P, Amblard P. Lucite estivale bénigne. In*: Photodermatologie et Photothérapie*. Paris: Masson, 1988: 49–51.
34 Berth-Jones J, Norris PG, Graham-Brown RAC *et al*. Juvenile spring eruption of the ears. *Clin Exp Dermatol* 1989; **14**: 462–3.
35 Tan E, Eberhart-Phillips J, Sharples K. Juvenile spring eruption: a prevalence study. *N Z Med J* 1996; **109**: 293–5.
36 Hawk J. Juvenile spring eruption is a variant of polymorphic light eruption. *N Z Med J* 1996; **109**: 389.
37 Heathcote K, Theaker JM, Gibbins N *et al.* 'Lambing ears': a blistering disorder affecting farmers at lambing time. *Br J Dermatol* 2008; **158**: 134–7.
38 Fraser-Andrews EA, Morris-Jones R, Novakovic L, Hawk JLM. Erythema multiforme following polymorphic light eruption: a report of two cases. *Clin Exp Dermatol* 2005; **30**: 232–4.
39 Jansen CT, Karvonen J. Polymorphous light eruption. A seven-year follow-up evaluation of 114 patients. *Arch Dermatol* 1984; **120**: 862–5.
40 Murphy GM, Hawk JLM. The prevalence of antinuclear antibodies in patients with apparent polymorphic light eruption. *Br J Dermatol* 1991; **125**: 448–51.
41 Nynberg F, Hasan T, Puska P *et al*. Occurrence of polymorphous light eruption in lupus erythematosus. *Br J Dermatol* 1997; **136**: 217–21.
42 Proby CM, Baker CS, Morton O *et al*. New broad-spectrum sunscreen for polymorphic light eruption. *Lancet* 1993; **341**: 1347–8.
43 Bilsland D, George SA, Gibbs NK *et al*. A comparison of narrow band phototherapy (TL-01) and photochemotherapy (PUVA) in the management of polymorphic light eruption. *Br J Dermatol* 1993; **128**: 49–56.
44 Murphy GM, Logan RA, Lovell CR *et al*. Prophylactic PUVA and UVB therapy in polymorphic light eruption—a controlled trial. *Br J Dermatol* 1987; **116**: 531–8.
45 Friedmann PS, Ford GP, Ross J *et al*. Reappearance of epidermal Langerhans cells after PUVA therapy. *Br J Dermatol* 1983; **109**: 301–7.
46 Man I, Dawe RS, Ferguson J. Artificial hardening for polymorphic light eruption: practical points from ten years' experience. *Photodermatol Photoimmunol Photomed* 1999; **15**: 96–9.
47 Corbett MF, Hawk JLM, Herxheimer A *et al*. Controlled therapeutic trials in polymorphic light eruption. *Br J Dermatol* 1982; **107**: 571–81.
48 Murphy GM, Hawk JLM, Magnus IA. Hydroxychloroquine in polymorphic light eruption: a controlled trial with drug and visual sensitivity monitoring. *Br J Dermatol* 1987; **116**: 379–86.
49 Rhodes LE, Durham BH, Fraser WD, Friedmann PS. Dietary fish oil reduces basal and ultraviolet B-generated PGE_2 levels in skin and increases the threshold to provocation of polymorphic light eruption. *J Invest Dermatol* 1995; **105**: 532–5.
50 Patel DC, Bellaney GJ, Seed PT *et al*. Efficacy of short-course oral prednisolone in polymorphic light eruption: a randomized controlled trial. *Br J Dermatol* 2000; **143**: 828–31.
51 Norris PG, Hawk JLM. Successful treatment of severe polymorphous light eruption wih azathioprine. *Arch Dermatol* 1989; **125**: 1377–9.
52 Shipley DR, Hewitt JB. Polymorphic light eruption treated with cyclosporin. *Br J Dermatol* 2001; **144**: 446–7.

Actinic prurigo

Definition. Actinic prurigo (AP) is a rare, sunlight-induced, extremely itchy, papular or nodular, usually very excoriated eruption of light-exposed and, to a lesser extent, covered skin. It is sometimes associated with acute PLE-like attacks. It is generally worse in summer, less often in both spring and autumn, and rarely just winter. It may begin at any age, but most often in childhood, and may either resolve in adolescence or persist indefinitely. A similar condition, also called hereditary or familial polymorphous light eruption and usually relatively severe, may afflict North, Central or South Americans of native or mixed descent. AP is probably a persistent form of PLE, but is usually clinically distinct.

Aetiology. A causal role for UVR in AP is suggested by its usually greater severity in summer along with abnormal skin responses to monochromatic irradiation in about two-thirds of patients

[1–3], perhaps about half of these to UVB alone, half to both UVB and UVA and a few just to UVA. Broad-spectrum responses have not been formally reported, but solar-simulated irradiation appears on occasion to induce an acute PLE eruption that may then progress to AP. In addition, the regular association of AP with PLE in patient or family [4], and the fact that some AP patients later develop PLE or *vice versa* [3], further suggests a relationship with UVR exposure and also between the two conditions. In addition, the perivascular mononuclear cell infiltrate of early AP, not yet immunohistochemically characterized, resembles that of PLE [5]—hence AP is almost certainly a persistent PLE variant and thus also a DTH response against endogenous cutaneous photoantigen. Genetic factors, in addition to those of PLE, appear to determine the different AP phenotype. Thus over 80% of British Caucasian patients demonstrate human leukocyte antigen (HLA) type DRB1*04 (DR4), is present in only 30% of normal and PLE subjects, while 60% as against 6% have its subtype DRB1*0407 [3,6], with the latter being much more common in both normal and affected AP-susceptible Amerindians [7]. That this feature may be the determinant transforming PLE into AP is further supported by the fact that some genetic AP patients have clinical PLE but atypical lesional persistence [3]. UVR molecular absorbers initiating the AP eruption have not been investigated, but are presumably as described for PLE.

Pathology [5]. There is early, variable, epidermal acanthosis and spongiosis along with dermal perivascular mononuclear cell infiltration and oedema, indistinguishable from the features of PLE. Later, non-specific excoriation, increasing acanthosis, variable lichenification and an increasingly heavy mononuclear cell infiltrate usually supervene. Very rarely, a more bizarre picture reminiscent of cutaneous T-cell lymphoma may be present.

Clinical features [1,2,8] (Fig. 29.10). AP may begin at any age, but more commonly in children (mostly female), and either resolves in adolescence or persists indefinitely [8]. A family history of AP, or more often PLE, is common [4], whereas the incidence of personal and family atopy, previously considered a likely AP association, is probably similar to that of normal subjects. The eruption is seasonal, and although often not clearly related to sun exposure, is generally worse in summer; very rarely it may be more severe in spring and autumn, or in winter. The rash is generally very pruritic, with early erythematous papules or nodules usually becoming rapidly excoriated, crusted and scabbed, not infrequently with associated eczematization or lichenification. The face and distal limbs are most affected, the proximal limbs and forehead under the fringe less so, with the rash gradually fading towards these more frequently covered sites. Nevertheless, the sacral area and buttocks may sometimes be involved in severe cases. The limbs may also show hypo- or hyperpigmented healing lesions or flat white scars, and the face minute, linear or pitted scars. Occasionally, there may also be cheilitis and conjunctivitis, particularly, and sometimes severely, in native American patients [9,10]. Attacks of an eruption indistinguishable from PLE may also occur, generally progressing to typical AP. An association with B-cell lymphoma has also been reported on one occasion [11], but must if it exists be extremely rare.



Fig. 29.10 Actinic prurigo, showing excoriated papules, more profuse distally.

Diagnosis. This is suggested mainly by a careful history supported by appropriate examination findings, along with normal circulating antinuclear factor and extractable nuclear antibody titres, and blood, urine and stool porphyrin concentrations. In doubtful cases, early lesional histology may help. Immunofluorescence findings are negative. If uncertainty persists, irradiation monochromator tests may confirm light sensitivity in up to two-thirds of patients, and broad-spectrum irradiation may sometimes induce an acute PLE-like rash. HLA typing is helpful if HLA-DRB1*04 (DR4) is present, and particularly so if it is of the rare DRB1*0407 subtype [3,7]. Atopic eczema and prurigo, particularly light-exacerbated, may usually be distinguished by their history, appearance and distribution, insect bites by their shorter time course and often asymmetrical nature, scabies by its lack of seasonality and presence of the mite, prurigo nodularis by its lack of seasonality, usual adult onset and generally more widespread lesions, and erythropoietic protoporphyria if facial scarring is present by its elevated red blood cell protoporphyrin concentration. Nevertheless, AP diagnosis may often remain uncertain early on and depend on the disease evolution for confirmation.

Treatment. Mild AP may respond to restriction of sun exposure, use of clothing cover, regular application of high-protection, broad-spectrum sunscreens and, if rash is present, the application of topical steroids and emollients. Poorly responsive patients may sometimes do well with occasional oral steroid courses for flares, and arguably from time to time with topical tacrolimus or pimecrolimus if the rash is cleared first during winter with oral steroids or thalidomide, as below. For more persistent disease, however, prophylactic low-dose, broad- or narrowband UVB

phototherapy or PUVA given as for PLE may help [12,13], the latter preferably in bath form in children, and perhaps again most effectively after initial rash clearance. Resistant cases, however, often need oral thalidomide 50–100 mg nightly until clearance, adjusted thereafter to as low a dose as possible [8,14], although a high risk of teratogenicity and moderate risk of peripheral neuropathy necessitate extreme care in its use. However, 3 to 6-monthly nerve conduction studies generally pre-empt the latter [15]. Patients unsuitable for thalidomide appear responsive instead to oral ciclosporin, and presumably to other immunosuppressive agents as well, although such use has not yet been documented. Conjunctival manifestations respond to topical ciclosporin [16].

References

1 Magnus IA. Polymorphic light eruption and summer prurigo. In: *Dermatological Photobiology*. Oxford: Blackwell Scientific Publications, 1976: 174–88.
2 Norris PG, Hawk JLM. The idiopathic photodermatoses: polymorphic light eruption, actinic prurigo and hydroa vacciniforme. In: JLM Hawk, ed. *Photodermatology*. London: Arnold, 1999: 178–90.
3 Grabczynska SA, McGregor JM, Kondeatis E *et al*. Actinic prurigo and polymorphic light eruption: common pathogenesis and the importance of HLA-DR4/DRB1*0407. *Br J Dermatol* 1999; **140**: 232–6.
4 McGregor JM, Grabczynska S, Vaughan R *et al*. Genetic modeling of abnormal photosensitivity in families with polymorphic light eruption and actinic prurigo. *J Invest Dermatol* 2000; **115**: 471–6.
5 Hawk JLM, Calonje E. The photosensitivity disorders. In: Elder DE, Elenitsas R, Johnson BL Jr, Murphy GF, eds. *Lever's Histopathology of the Skin (Ninth Edition)*. Philadelphia: Lippincott–Raven, 2005: 345–53.
6 Menagé HduP, Vaughan RW, Baker CS *et al*. HLA-DR4 may determine expression of actinic prurigo in British patients. *J Invest Dermatol* 1996; **106**: 362–4.
7 Suarez A, Valbuena MC, Rey M, Quintana de Porras L. Association of HLA subtype DRB1 0407 in Colombian patients with actinic prurigo. *Photodermatol Photoimmunol Photomed* 2006; **22**: 55–8.
8 Kuno Y, Nagel J, Yones SS, Hawk JLM. Actinic prurigo: a 10-year follow-up study by questionnaire. *Br J Dermatol* 2003; **149** (Suppl. 64): 48–9.
9 Birt AR, Davis RA. Photodermatitis in North American Indians: familial actinic prurigo. *Int J Dermatol* 1971; **10**: 107–14.
10 Dominguez L, Hojyo MT. Actinic prurigo, a variety of polymorphous light eruption. *Int J Dermatol* 1982; **21**: 260–1.
11 Perrett CM, Harwood CA, Khorshid M *et al*. Primary cutaneous B-cell lymphoma associated with actinic prurigo. *Br J Dermatol* 2005; **153**: 186–9.
12 Collins P, Ferguson J. Narrow-band UVB (TL-01) phototherapy: an effective preventative treatment for the photodermatoses. *Br J Dermatol* 1995; **132**: 956–63.
13 Farr PM, Diffey BL. Treatment of actinic prurigo with PUVA: mechanism of action. *Br J Dermatol* 1989; **120**: 411–8.
14 Lovell CR, Hawk JLM, Calnan CD *et al*. Thalidomide in actinic prurigo. *Br J Dermatol* 1983; **108**: 467–71.
15 Sadoh DR, Hawk JL, Panayiotopoulos CP. F-chronodispersion in patients on thalidomide. *Clin Neurophysiol* 1999; **110**: 735–9.
16 McCoombes JA, Hirst LW, Green WR. Use of topical cyclosporin for conjunctival manifestations of actinic prurigo. *Am J Ophthalmol* 2000; **130**: 830–1.

Hydroa vacciniforme

J. Ferguson, pp. 29.15–29.16

Definition. Hydroa vacciniforme (HV) is a rare acquired photodermatosis, usually with onset in childhood, and characterized by vesicle, crust and scar formation that follow exposure to sunlight.

Aetiology. The origin of this condition is unknown. Spring and summer exposure, particularly to UVA wavelengths [1], appears to be responsible. Recently, an association between HV, or what may be an HV-like syndrome, and latent Epstein–Barr virus (EBV) infection has been proposed [2,3].

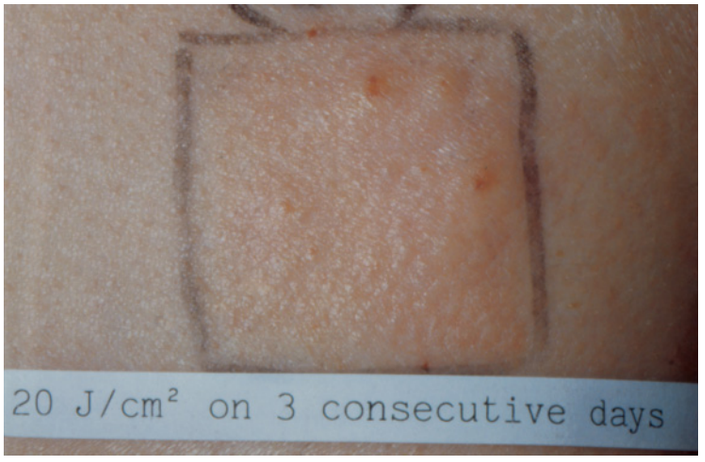


Fig. 29.11 Papulovesicles following 10 J/cm^2 three times daily to mid-upper back skin.

Pathology. Acute lesion histology is non-specific, showing a reticulate keratinocyte degeneration with spongiosis and a perivascular mononuclear cell infiltrate. Lesion biopsy days later shows ulceration, necrosis and capillary oedema followed by scarring [4]. Although monochromator testing is usually within normal limits, repetitive high-dose skin irradiation with a UVA source can induce papulovesicles [5] (Fig. 29.11).

Clinical features. Although the incidence is unknown, HV is a rare, usually sporadic, but occasionally familial [6] condition occurring equally in both sexes [7]. Presentation is usually during the first decade, but there is a late-onset variety [8]. Twelve to 24 h after exposure to direct or window glass-transmitted sunlight, pruritic, sometimes haemorrhagic vesicles and papules arise on an erythematous background, typically affecting the cheeks, ears, nose and hands (Fig. 29.12). As the lesions resolve, they enter a dry crusting phase followed by permanent scars, which can be disfiguring [9] (Fig. 29.13). In some children, acute episodes are accompanied by systemic malaise [4]. Rarely, eye involvement may take the form of anterior uveitis with corneal clouding and visual impairment [10]. HV-like lesions have been reported in association with T-cell lymphoma, and as EBV has been shown to be associated with T-cell lymphoma there is interest in the relationship between EBV, HV and lymphoma [11].

In most cases, HV resolves spontaneously by adulthood, with a typical disease duration of 9 years [7]. In a few cases, disease activity persists undiminished, even into middle age [12].

Treatment. Photoprotection with appropriate clothing and a broad-spectrum sunscreen form the standard approach. If there is no response to photoprotection, springtime prophylactic therapy using broad-band UVB, narrow-band UVB or PUVA can be beneficial [7,13,14]. Although some anecdotal evidence exists to support the use of beta-carotene/canthaxanthin [15], azathioprine



Fig. 29.12 Hydroa vacciniforme, showing vesiculation and crusting. (Courtesy of Dr M. Price, Brighton, UK.)

and antimalarial therapy, their true benefit is uncertain. Prophylactic fish oil may also be of help, although poor tolerance limits its use [16].

References

1 Sunohara A, Mizuno N, Sakai M *et al.* Action spectrum for UV erythema and reproduction of the skin lesions in hydroa vacciniforme. *Photodermatology* 1988; **5**: 139–45.

2 Wu YH, Chen HC, Hsiao PF *et al*. Hydroa vacciniforme-like Epstein-Barr virus-associated monoclonal T-lymphoproliferative disorder in a child. *Int J Dermatol* 2007; **46**: 1081–6.

3 Iwatsuki K, Xu Z, Takata M *et al.* The association of latent Epstein–Barr virus infection with hydroa vacciniforme. *Br J Dermatol* 1999; **140**: 715–21.

4 Sonnex TS, Hawk JLM. Hydroa vacciniforme: a review of 10 cases. *Br J Dermatol* 1988; **118**: 101–8.

5 Leroy D, Dompmartin A, Michel M *et al*. Factors influencing the photo-reproduction of hydroa vacciniforme lesions. *Photodermatol Photoimmunol Photomed* 1997; **13**: 98–102.

6 Gupta G, Mohamed M, Kemmett D. Familial hydroa vacciniforme. *Br J Dermatol* 1999; **140**: 124–6.

7 Gupta G, Man I, Kemmett D. Hydroa vacciniforme: a clinical and follow-up study of 17 cases. *J Am Acad Dermatol* 2000; **42**: 208–13.

8 Wong SN, Tan SH, Khoo SW. Late-onset hydroa vacciniforme: two case reports. *Br J Dermatol* 2001; **144**: 874–7.

9 Gu H, Chang B, Qian H, Li G. A clinical study on severe hydroa vacciniforme. *Chin Med J (Engl)* 1996; **109**: 645–7.

10 Bennion SD, Johnson C, Weston WL. Hydroa vacciniforme with inflammatory keratitis and secondary anterior uveitis. *Pediatr Dermatol* 1987; **4**: 320–4.

11 Chen H-H, Hsiao C-H, Chiu H-C. Hydroa vacciniforme-like primary cutaneous CD8 T-cell lymphoma. *Br J Dermatol* 2002; **147**: 587–91.

12 De Pietro U, Simoni R, Barbieri C, Girolomoni G. Hydroa vacciniforme persistent in a 60-year-old man. *Eur J Dermatol* 1999; **9**: 311–2.

13 Hann SK, Im S, Park Y-K, Lee S. Hydroa vacciniforme with unusually severe scar formation: diagnosis by repetitive UVA phototesting. *J Am Acad Dermatol* 1991; **25**: 401–3.



Fig. 29.13 Post-hydroa vacciniforme scarring.

14 Halasz CLG, Leach EE, Walther RR, Poh-Fitzpatrick MB. Hydroa vacciniforme induction of lesions with ultraviolet A. *J Am Acad Dermatol* 1983; **8**: 171.

15 Bruderer P, Shahabpour M, Christoffersen S *et al*. Hydroa vacciniforme treated by a combination of beta-carotene and canthaxanthin. *Dermatology* 1995; **190**: 343–5.

16 Rhodes LE, White SI. Dietary fish oil as a photoprotective agent in hydroa vacciniforme. *Br J Dermatol* 1998; **138**: 173–8.

Chronic actinic dermatitis

J.L.M. Hawk, pp. 29.16–29.19

Synonyms

- Photosensitivity dermatitis and actinic reticuloid (PD/AR) syndrome
- Persistent light reaction

Definition. Chronic actinic dermatitis (CAD) is a rare UVR- and rarely visible light-induced eczema of exposed and, to a lesser extent, covered skin. At times incapacitating, it is long persistent but sometimes slowly remitting. It is worse in summer and often associated with contact dermatitis, frequently airborne. It mostly affects older men, especially outdoor enthusiasts, but also rarely younger individuals with atopic eczema and perhaps occasionally human immunodeficiency virus (HIV)-infected patients. It may represent a contact dermatitis-like DTH reaction against endogenous photo-induced allergen.

Aetiology. CAD [1] is clinically and histologically an eczematous eruption reproducible at all skin sites, in the absence of exogenous photosensitizer, by UVB, UVB and UVA, or rarely UVB, UVA and short visible irradiation [2]; UVA alone may occasionally be responsible. Broad-spectrum and monochromatic exposures are both effective, frequently at considerably lower than minimal sunburning doses. Also, its clinical, histological and immunohistochemical features all resemble those of the delayed-type hypersensitivity (DTH) reaction, allergic contact dermatitis [3,4] – including the histology of its severe, pseudolymphomatous form, formerly called actinic reticuloid [1,2], which resembles that of severe, pseudolymphomatous, allergic contact dermatitis [5,6]. It is therefore extremely likely that CAD is of similar nature, but

by inference directed instead against cutaneous photo-induced endogenous antigen. This may presumably be the result of either direct UVR molecular absorption and antigenic change, or else of endogenous secondary photosensitization, suggested particularly by the fact that albumin can become antigenic *in vitro* through photo-oxidation of its component histidine [7]. CAD also often occurs in association with pre-existing widespread, often airborne, contact dermatitis to exogenous sensitizer or photosensitizer [8–10], such reactions arguably enhancing cutaneous immune function sufficiently to enable putative endogenous photo-antigen recognition during light exposure. Alternatively, or in addition, chronic photodamage may conceivably impair UVR-induced cutaneous immunosuppression such that endogenous UVR-induced skin photo-antigen is more easily recognized, as apparently occurs genetically in PLE [11,12]. Elderly outdoor workers or enthusiasts are most affected [1], and photo-ageing of their skin may well also lead to slower putative antigen removal, such that its recognition may be further facilitated. In addition, CAD may apparently develop in patients with long-standing PLE or endogenous eczema, very possibly reactions of similar predisposing nature to that suggested for allergic contact dermatitis. As the disorder becomes established and gradually progresses, the characteristic irradiation abnormalities of CAD develop [1]. Presumptive UVR molecular absorbers initiating the CAD rash have not been definitively identified, but DNA, RNA or similar or related molecules may be involved in some instances, in that the shape of the CAD action spectrum in one series of patients resembled that for sunburn inflammation [13], for which DNA is now considered the primary absorber [14]. Despite this, however, a preliminary study in which CAD skin cells were irradiated in culture with autologous lymphocytes failed to detect any antigenic response [15], although this may very possibly have been because of inappropriate experimental conditions. Nevertheless, final evidence that CAD is an allergic contact dermatitis-like reaction against endogenous cutaneous photo-antigen remains lacking.

Pathology [16]. There is epidermal spongiosis and acanthosis, sometimes with hyperplasia, and a usually deep dermal, predominantly perivascular, frequently dense, lymphohistiocytic infiltrate, sometimes with large, hyperchromatic, convoluted nuclei or mitotic figures. In addition, there may be macrophages, eosinophils and plasma cells. In very florid cases, the appearance may be indistinguishable from that of cutaneous T-cell lymphoma.

Clinical features [1,17] (Fig. 29.14). CAD is rare [18], but occurs most often at temperate latitudes [19], and affects mostly elderly men of any race [20]. There is no evidence of familial incidence. The condition may arise in apparently normal skin, or following prior endogenous eczema, photo-allergic or allergic contact dermatitis, perhaps oral drug photosensitivity [21,22], rarely PLE, and occasionally HIV infection, especially in the USA [17]. In addition, allergic contact sensitivity to ubiquitous, often airborne, substances such as plant antigens, fragrances and topical medications often coexists. The eruption generally worsens in summer or after sun exposure, an occurrence not always noted by the patient, especially as marked or continuing irradiation may rarely temporarily improve it. CAD is eczematous, whether chronic, subacute or rarely acute, severely pruritic and of patchy or confluent, often lichenified, nature. In severe, usually poorly treated, cases it characteristically demonstrates scattered or widespread, erythematous, shiny, infiltrated, pseudolymphomatous papules or plaques, arising on a background of erythema, eczema or normal skin, as may also occur in persistent allergic contact dermatitis [6]. Exposed sites are predominantly affected, particularly the face, scalp, back and sides of the neck, upper chest and dorsal aspects of the forearms and hands. There are also often sharp demarcations at lines of clothing, and sparing of the depths of skin creases, upper eyelids, fingerwebs and areas behind the ear lobes, as well as occasionally of irregular, exposed sites of the forehead or elsewhere. In addition, palmar and plantar eczema are not uncommon, eyebrow and scalp hair may be broken or lost, and erythroderma may occasionally develop.

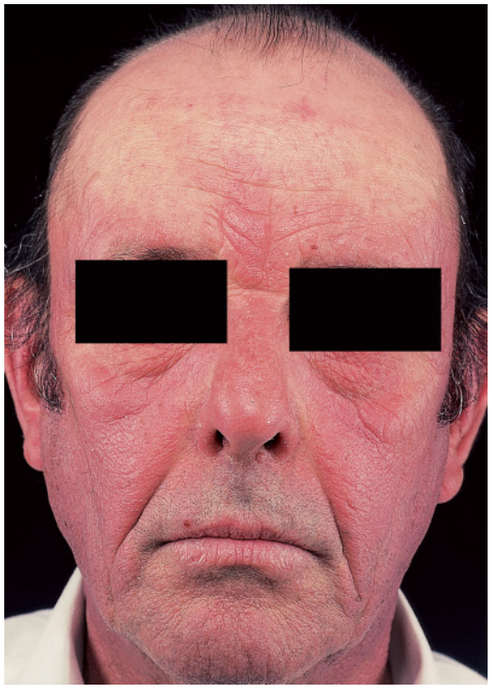


Fig. 29.14 Chronic actinic dermatitis, showing pseudolymphomatous infiltration of the face but sparing of the scalp.

Once established, CAD tends to persist over many years before moderately frequent gradual resolution [23]. Malignant lymphomatous transformation has occasionally been claimed [3], arguably following chronic antigenic stimulation in long-standing, untreated CAD, but must be extraordinarily rare, particularly as life expectancy is normal [20]. Conversely, it has been suggested that, very rarely, malignant cutaneous lymphoma may itself be markedly light-sensitive from the outset [24]. Pseudolymphomatous CAD induced by combined UVB, UVA and occasionally also visible wavelengths has previously been known as actinic reticuloid [4], eczematous CAD induced by UVB and UVA as photosensitivity dermatitis [1], and eczematous CAD evoked by UVB alone as either photosensitivity dermatitis or photosensitive eczema [25]. Finally, CAD arising in association with photo-allergic contact dermatitis was formerly known as persistent light reaction [1].

Diagnosis. This is suggested by the typical clinical findings in conjunction with normal antinuclear factor and extractable nuclear antibody titres, and normal blood, urine and stool porphyrin concentrations. In addition, there are abnormal erythematous or eczematous responses on clinically normal skin to broadband or monochromatic irradiation, often at doses much lower than the normal sunburning minimal erythema dose. The provoking wavelengths are UVB in virtually all patients, UVA also in most, and visible light in addition in some. However, a further small proportion react to UVA alone, although drug photosensitivity must be carefully excluded in such instances. In cases of uncertainty, the histological findings, usually florid in severe cases, may be helpful in confirming an eczematous response likely to be CAD. Other eczemas of light-exposed areas, even those exacerbated by UVR exposure, are generally distinguished by their normal cutaneous irradiation responses, along with other evidence in favour of the underlying disorder. In drug or chemical photosensitivity, there is often clear evidence of exposure to an inducing substance, and the eruption is generally not eczematous, unless the agent is topical and the rash therefore usually localized to the sites of application. In addition, irradiation testing is usually normal or positive only to the UVA wavelengths. In cutaneous T-cell lymphoma, which is occasionally photosensitive, the clinical picture and histology are usually definitive, and any light sensitivity and irradiation test abnormalities are usually principally in the UVA range and mild [26], except perhaps in very rare, markedly photosensitive cases [24]. However, if doubt persists, particularly in any of the latter cases, careful assessment, including T-cell receptor gene rearrangement studies, is necessary [24]. Erythrodermic CAD must be distinguished from other erythrodermas, if necessary by irradiation skin testing after clearance of the eruption in a darkened room. Significant circulating Sézary cell numbers may occur in such patients [27], but with a CD4+/CD8+ ratio generally much lower than in the malignant Sézary syndrome [28], and normal T-cell receptor gene rearrangement studies.

Treatment. Careful avoidance of exposure to UVR and, if necessary, visible light, even from fluorescent room lighting (but not tungsten lamps, computer screens or television sets) and to relevant contact allergens, is essential. Appropriate clothing cover and the use of non-irritating, broad-spectrum, high-protection sunscreens of low allergenic potential are often also helpful, although rarely fully effective alone. Topical steroid or intermittent oral steroid therapy are almost always needed. For more resistant disease, topical tacrolimus has been reported as sometimes helpful [29]. Prolonged, very low-dose PUVA or narrowband UVB phototherapy may also help [1,30,31] – initially given frequently under high-dose systemic and topical steroid cover, both tailed off over weeks, with exposure frequency also reducing gradually over months to about once monthly. If there is no response to these approaches, oral immunosuppressive therapy with ciclosporin 3.5–5mg/kg is usually effective within weeks [32], or azathioprine 1.0–2.5mg/kg [33], mycophenolate mofetil 25–40mg/kg, or very rarely thioguanine 0.5–1.5mg/kg.

References

1 Hawk JLM, Lim HW. Chronic actinic dermatitis. In: Lim HW, Hönigsmann H, Hawk JLM, eds. *Photodermatology*. New York: Informa Healthcare, 2007: 169–83.

2 Ive FA, Magnus IA, Warin RP *et al*. Actinic reticuloid: a chronic dermatosis associated with severe photosensitivity and the histological resemblance to lymphoma. *Br J Dermatol* 1969; **81**: 469–85.

3 Norris PG, Morris J, Smith NP *et al*. Chronic actinic dermatitis: an immunohistologic and photobiologic study. *J Am Acad Dermatol* 1989; **21**: 966–71.

4 Menagé HduP, Sattar NK, Haskard DO *et al*. A study of the kinetics and pattern of E-selectin, VCAM-1 and ICAM-1 expression in chronic actinic dermatitis. *Br J Dermatol* 1996; **134**: 262–8.

5 Kanerva L, Estlander T, Jolanki R. Immunohistochemistry of lymphocytes and Langerhans cells in long-lasting allergic patch tests. *Acta Derm Venereol (Stockh)* 1988; **68**: 116–22.

6 Orbaneja JG, Diez LI, Lozano JLS *et al*. Lymphomatoid contact dermatitis. A syndrome produced by epicutaneous hypersensitivity with clinical features and a histopathologic picture similar to that of mycosis fungoides. *Contact Dermatitis* 1976; **2**: 139–43.

7 Kochevar IE, Harber LC. Photoreactions of 3,3,4,5-tetrachlorosalicylanilide with proteins. *J Invest Dermatol* 1977; **68**: 151–6.

8 Addo HA, Ferguson J, Johnson BE *et al*. The relationship between exposure to fragrance materials and persistent light reaction in the photosensitivity dermatitis with actinic reticuloid syndrome. *Br J Dermatol* 1982; **107**: 261–74.

9 Addo HA, Sharma SC, Ferguson J *et al*. A study of Compositae plant extract reactions in photosensitivity dermatitis. *Photodermatology* 1985; **2**: 68–79.

10 Murphy GM, White IR, Hawk JLM. Allergic airborne contact dermatitis to Compositae with photosensitivity: chronic actinic dermatitis in evolution. *Photodermatol Photoimmunol Photomed* 1990; **7**: 38–9.

11 van de Pas CB, Kelly DA, Seed PT *et al.* Ultraviolet radiation-induced erythema and suppression of contact hypersensitivity responses in patients with polymorphic light eruption. *J Invest Dermatol* 2004; **122**: 295–9.

12 Palmer RA, Friedmann PS. Ultraviolet radiation causes less immunosuppression in patients with polymorphic light eruption than in controls. *J Invest Dermatol* 2004; **122**: 291–4.

13 Menagé HduP, Harrison GI, Potten CS *et al*. The action spectrum for induction of chronic actinic dermatitis is similar to that for sunburn inflammation. *Photochem Photobiol* 1995; **62**: 976–9.

14 Freeman SE, Hacham H, Gange RW *et al*. Wavelength dependence of pyrimidine dimer formation in DNA of human skin irradiated *in situ* with ultraviolet light. *Proc Natl Acad Sci USA* 1989; **86**: 5605–9.

15 Sepulveda-Merrill C, Menagé HduP, Hawk JLM, Breathnach SM. Functional studies of antigen presentation in induced lesions of chronic actinic dermatitis. *J Invest Dermatol* 1994; **102**: 603.

16 Hawk JLM, Calonje E. The photosensitivity disorders. In: Elder DE, Elenitsas R, Johnson BL Jr, Murphy GF, eds. *Lever's Histopathology of the Skin*, 9th edn. Philadelphia: Lippincott–Raven, 2005: 345–53.

17 Lim HW, Morison WL, Kamide R *et al*. Chronic actinic dermatitis: an analysis of 51 patients in the United States and Japan. *Arch Dermatol* 1994; **130**: 1284–9.

18 Dawe RS. Prevalences of the chronic idiopathic and metabolic photodermatoses in Scotland. *Br J Dermatol* 2006; **155**: 866.

19 Sharma VK, Sethuraman G. Parthenium dermatitis. *Dermatitis* 2007; **18**: 183–90.

20 Kerr HA, Lim HW. Photodermatoses in African Americans: a retrospective analysis of 135 patients over a 7-year period. *J Am Acad Dermatol* 2007; **57**: 638–43.

21 Wilkinson DS. Photodermatitis due to tetrachlorosalicylanilide. *Br J Dermatol* 1961; **73**: 213–9.

22 Robinson HN, Morison WL, Hood AF. Thiazide diuretic therapy and chronic photosensitivity. *Arch Dermatol* 1985; **121**: 522–4.

23 Dawe RS, Crombie IK, Ferguson J. The natural history of chronic actinic dermatitis. *Arch Dermatol* 2000; **136**: 1215–20.

24 Agar N, Morris S, Russell-Jones R, Hawk J, Whittaker S. Case report of four patients with erythrodermic cutaneous T-cell lymphoma and severe photosensitivity mimicking chronic actinic dermatitis. *Br J Dermatol* 2009; **160**: 698–703.

25 Ramsay CA, Kobza-Black A. Photosensitive eczema. *Trans St John's Hosp Dermatol Soc* 1973; **59**: 152–8.

26 Volden G, Thune PO. Light sensitivity in mycosis fungoides. *Br J Dermatol* 1977; **97**: 279–84.
27 Neild VS, Hawk JLM, Eady RAJ *et al*. Actinic reticuloid with Sézary cells. *Clin Exp Dermatol* 1982; **7**: 143–8.
28 Chu AC, Robinson D, Hawk JLM *et al*. Immunologic differentiation of the Sézary syndrome due to cutaneous T-cell lymphoma and chronic actinic dermatitis. *J Invest Dermatol* 1986; **86**: 134–7.
29 Uetsu N, Okamoto H, Fujii K *et al*. Treatment of chronic actinic dermatitis with tacrolimus ointment. *J Am Acad Dermatol* 2002; **47**: 881–4.
30 Hindson C, Spiro J, Downey A. PUVA therapy of chronic actinic dermatitis. *Br J Dermatol* 1985; **113**: 157–60.
31 Morison WL, White HAD, Gonzalez E *et al*. Oral methoxsalen photo-chemotherapy of uncommon photodermatoses. *Acta Derm Venereol (Stockh)* 1979; **59**: 366–8.
32 Norris PG, Camp RDR, Hawk JLM. Actinic reticuloid: response to cyclosporin A. *J Am Acad Dermatol* 1989; **21**: 307–9.
33 Murphy GM, Maurice PDL, Norris PG *et al*. Azathioprine in the treatment of chronic actinic dermatitis: a double-blind controlled trial with monitoring of exposure to ultraviolet radiation. *Br J Dermatol* 1989; **121**: 639–46.



Fig. 29.15 Solar urticaria provoked by window glass-transmitted sunlight. The white tracksuit stripe has failed to prevent visible wavelength penetration.

Solar urticaria

J. Ferguson, pp. 29.19–29.22

Solar urticaria (SU) may be primary (idiopathic) or secondary to porphyrias, phototoxic drugs and chemicals. Idiopathic SU is an uncommon wealing disorder induced by UVB, UVA and visible wavelengths.

Aetiology. SU is considered to be an allergic type 1 hypersensitivity response [1] mediated by histamine [2,3] and other agents. Some patients have a circulating factor (putative photoallergen), which has been reported to passively transfer the disease to normal individuals. Isolation of the transfer factor suggests it behaves like a globulin and has a molecular weight in the range of 25–1000 kDa. Provocation wavelengths, which vary between patients, may change during the disease course [4], and this suggests a range of photoallergens activated by UVB, UVA and visible light, separately or in combination. The finding of SU provoked by visible light should raise the possibility of a porphyria. In some cases, augmentation [5] by a different part of the spectrum is seen [6]; in others, visible wavelengths can inhibit provocation of urticaria [7]. The explanation of these phenomena is unknown.

Phototesting using monochromator or broad-band sources reveals immediate urticaria with a 24-h delayed erythema component. Knowledge of the wavelength dependency is important for management. If the condition is severe and unresponsive to treatment, intradermal testing with irradiated autologous serum and/or plasma may help indicate whether there might be a beneficial response to plasmapheresis. Where secondary SU is suspected, a careful drug history and tests to exclude porphyria are required.

Pathology. The histopathology of SU in provoked lesions shows at 5 min and 2 h a predominantly perivascular neutrophilic and eosinophilic infiltrate, with dermal oedema separating the collagen bundles. At 24 h, mononuclear cells predominate. In some, features of a vasculitis are seen [8–10].

Clinical features (Fig. 29.15) [11–14]. The incidence of idiopathic SU is unknown. It occurs in both sexes, with a slight female preponderance. It occurs at any age, but has a peak onset between 20 and 30 years [15]. It affects all races, although whether equally is unknown. Typically, the onset of disease is sudden, with most patients aware of tingling of sunlight-exposed skin, erythema and flare within minutes of visible radiation exposure. Occasionally, only some areas of skin may be affected, when it is termed fixed solar urticaria [16]. As with other urticarias, the symptoms and signs subside within a few hours, although rarely they may persist for 24 h [17]. A minority of patients may only describe symptomatic erythema [18], with urticaria only evident on high irradiation dose testing. Sensitivity to the provoking wavelengths varies between patients, some requiring as little as 2–3 min of light exposure whereas others require an hour or more. When the condition is severe, it can pose great problems for the patient, particularly if visible wavelengths are involved, and if unresponsive to treatment it may induce a hermit-like existence.

The weal (and often the flare) reaction is typically confined to sunlight-exposed skin with a cut-off at the edges of clothing. Occasionally, patients may experience erythema, weal and flare under thin light-coloured clothing that allows the penetration of visible wavelengths. Lesions typically fade over the following hour or two, leaving an erythema that may persist for 24 h or more, and representing a delayed component. Following each episode, the skin may be refractory to further provocation for a number of hours. If the skin reaction is severe and extensive it may be associated with nausea, bronchospasm, light-headedness and syncope [19].

Idiopathic SU resolves spontaneously in approximately 50% of cases within 5 years [15]. The disease severity may run a fluctuating course, with periods of improvement and remission.

Treatment [20]. Although some mildly affected patients only require simple light-avoidance measures, which include advice on use of dark clothing and a broad-spectrum sun barrier, others may require antihistamines taken early in the morning prior to sunlight exposure. Approximately one-third respond completely to non-sedative H_1 blockade [21], with a further one-third having partial

relief. The addition of an H_2 antagonist may provide further benefit [22]. It is curious that the response to antihistamine [21] may be drug- and dose-dependent.

Successful desensitization with photochemotherapy (PUVA) [23], UVA [24] and UVB (TL-01) [25,26] has been reported, although benefit may be short-lived. Limited treatment to normally photoexposed sites can be combined with antihistamines, and should be preceded by a minimal urticarial dose (MUD) determination.

In the severely affected patient who is unresponsive to standard therapy, plasmapheresis should be considered, particularly if the intradermal test is positive [27,28], and this can be combined with PUVA [29]. Some, but not all, have had lasting benefit from this approach. Alternatively, ciclosporin [30] or intravenous immunoglobulin [31] may be of value. Other treatments that have been reported, but which probably are not of benefit, include β-carotene [32] and antimalarials [33].

References

1 Leenutaphong V, Holzle E, Plewig G. Pathogenesis and classification of solar urticaria: a new concept. *J Am Acad Dermatol* 1989; **21**: 237–40.
2 Leenutaphong V, Holzle E, Plewig G. Solar urticaria: studies on mechanisms of tolerance. *Br J Dermatol* 1990; **122**: 601–6.
3 Neittaanmaki H, Jaaskelainen T, Harvima RJ *et al.* Solar urticaria: demonstration of histamine release and effective treatment with doxepin. *Photodermatology* 1989; **6**: 52–5.
4 Ng JC, Foley PA, Crouch RB, Baker C. Changes of photosensitivity and action spectrum with time in solar urticaria. *Photodermatol Photoimmunol Photomed* 2002; **18**: 191–5.
5 Danno K, Mori N. Solar urticaria: report of two cases with augmentation spectrum. *Photodermatol Photoimmunol Photomed* 2000; **16**: 30–3.
6 Miyauchi H, Horio T. Detection of action, inhibition and augmentation spectrum in solar urticaria. *Dermatology* 1995; **191**: 286–91.
7 Leenutaphong V. Solar urticaria induced by UVA and inhibited by visible light. *J Am Acad Dermatol* 1993; **29**: 337–40.
8 Norris PG, Murphy GM, Hawk JLM, Winkelmann RK. A histological study of the evolution of solar urticaria. *Arch Dermatol* 1988; **124**: 80–3.
9 Stinco G, Di Gaetano L, Rizzi C, Patrone P. Leukocytoclastic vasculitis in urticaria induced by sun exposure. *Photoderm Photoimmunol Photomed* 2007; **23**: 39–41.
10 Leiferman KM, Winkelmann RK. Cellular infiltrate and deposited material in solar urticaria (reply). *J Am Acad Dermatol* 1990; **23**: 951.
11 Harris A, Burge SM, George SA. Solar urticaria in an infant. *Br J Dermatol* 1997; **136**: 105–7.
12 Uetsu N, Miyauchi-Hashimoto H, Okamoto H, Horio T. The clinical and photobiological characteristics of solar urticaria in 40 patients. *Br J Dermatol* 2000; **142**: 32–8.
13 Porter AD. Urticaria solaris. *Br J Dermatol* 1954; **66**: 417–28.
14 Roelandts R, Ryckaert S. Solar urticaria: the annoying photodermatosis. *Int J Dermatol* 1999; **38**: 411–8.
15 Monfrecola G, Masturzo E, Riccardo AM *et al.* Solar urticaria: a report on 57 cases. *Am J Contact Dermat* 2000; **11**: 89–94.
16 Tuchinda C, Leenutaphong V, Sudtim S, Lim HW. Fixed solar urticaria induced by UVA and visible light: a report of a case. *Photodermatol Photoimmunol Photomed* 2005; **21**: 97–9.
17 Ghigliotti G, Brusati C, Guarrera M, Nigro A. Persistent solar urticaria: a case report. *Photodermatol Photoimmunol Photomed* 1999; **15**: 140–1.
18 Torinuki W. Two patients with solar urticaria manifesting pruritic erythema. *J Dermatol* 1992; **19**: 635–7.
19 Juhlin L, Malmros-Enander I. Solar urticaria: mechanism and treatment. *Photodermatology* 1986; **3**: 164–8.
20 Bilsland D, Ferguson J. The management of idiopathic solar urticaria. *J Dermatol Treat* 1991; **1**: 321–3.
21 Schwarze HP, Marguery MC, Journe F *et al.* Fixed solar urticaria to visible light successfully treated with fexofenadine. *Photodermatol Photoimmunol Photomed* 2001; **17**: 39–41.
22 Tokura Y, Takigawa M, Yamauchi T *et al.* Solar urticaria: a case with good therapeutic response to cimetidine. *Dermatologica* 1986; **173**: 224–8.
23 Parrish JA, Jaenicke KF, Morison WL *et al.* Solar urticaria: treatment with PUVA and mediator inhibitors. *Br J Dermatol* 1982; **106**: 575–80.
24 Dawe RS, Ferguson J. Prolonged benefit following ultraviolet A phototherapy for solar urticaria. *Br J Dermatol* 1997; **137**: 144–8.
25 Addo HA, Sharma SC. UVB phototherapy and photochemotherapy (PUVA) in the treatment of polymorphic light eruption and solar urticaria. *Br J Dermatol* 1987; **116**: 539–47.
26 Collins P, Ferguson J. Narrow-band UVB (TL-01) phototherapy: an effective preventative treatment for the photodermatoses. *Br J Dermatol* 1995; **132**: 956–63.
27 Leenutaphong V, Holzle E, Plewig G *et al.* Plasmapheresis in solar urticaria. *Photodermatology* 1987; **4**: 308–9.
28 Duschet P, Leyen P, Schwarz T *et al.* Solar urticaria: effective treatment by plasmapheresis. *Clin Exp Dermatol* 1987; **12**: 185–8.
29 Hudson-Peacock MJ, Farr PM, Diffey BL, Goodship THJ. Combined treatment of solar urticaria with plasmapheresis and PUVA. *Br J Dermatol* 1993; **128**: 440–2.
30 Edstrom DW, Ros A-M. Cyclosporin A therapy for severe solar urticaria. *Photodermatol Photoimmunol Photomed* 1997; **13**: 61–3.
31 Puech-Plottova I, Michel JL, Rouchouse B *et al.* Solar urticaria: one case treated by intravenous immunoglobulin. *Ann Dermatol Vénéréol* 2000; **127**: 831–5.
32 Kobza A, Ramsay CA, Magnus IA. Oral β-carotene therapy in actinic reticuloid and solar urticaria. *Br J Dermatol* 1973; **88**: 157–66.
33 Epstein JH, Vandenberg JJ, Wright WL. Solar urticaria. *Arch Dermatol* 1963; **88**: 135–41.

DNA repair-defective diseases

See Chapter 15.

Drug- and chemical-induced photosensitivity: exogenous [1,2]

Abnormal skin reactions to sunlight and artificial sources of UV and visible radiation induced by photosensitizing drugs and other chemicals are often labelled as exaggerated sunburn and therefore underdiagnosed. Such reactions are subdivided, according to route of administration, into systemic and topical [1–3].

Aetiology. Most photosensitivity reactions involve oxygen in a variety of ways to produce toxic photosensitizer and substrate radicals.

Most systemic photosensitizers are phototoxic (non-immunologically mediated) in mechanism. The subcellular targets vary for each drug and photoactive metabolite, and the resulting clinical spectrum of reactions may mislead the unwary. For the drug prescribing pattern in the UK and Europe, the agents most commonly responsible for photosensitivity are listed in Table 29.4 [4]. Although phototoxicity is said to occur in any individual providing there is enough phototoxin and appropriate irradiation, there is an idiosyncratic variant in which a few individuals taking the drug develop the problem whereas the great majority are unaffected. This unexplained phenomenon may account for the frequent sporadic reports of reactions attributed to a surprisingly large range of drugs. Other less common mechanisms include drug-induced lupus, pellagra and photoallergy [5]. Photoallergy is usually associated with topical exposure to agents such as non-steroidal anti-inflammatory drugs (NSAIDs), fragrances and sunscreens. Topical phototoxicity has been reported with dyestuffs

Table 29.4 A general classification of photosensitizers.

Exogenous
Drugs: antibiotics; major tranquillizers; antidepressants; anti-inflammatories; diuretics; antiarrhythmics/antihypertensives
Plant materials: psoralens
Dyestuffs: methylene blue, toluidine blue xanthenes, fluorescein, eosin, anthraquinones
Polycyclic hydrocarbons: pitch, coal tars, anthracene, acridine, fluoranthrene
Perfumes and cosmetics: musk ambrette, 6-methylcoumarin
Sunscreens: benzophenones, dibenzoylmethanes, cinnamates, PABA* esters
Miscellaneous: fabric whiteners; quinoxaline-*N*-dioxide
Endogenous
Porphyrins

* Para-aminobenzoic acid.

Table 29.5 Major patterns of cutaneous phototoxicity.

Skin reactions	Photosensitizers or diseases
Prickling or burning during exposure; immediate erythema; oedema/urticaria with higher doses; sometimes delayed erythema/hyperpigmentation	Coal tar; pitch; anthraquinone-based dyestuffs; amiodarone; chlorpromazine; erythropoietic protoporphyria; Photofrin; Foscan
Exaggerated sunburn	Chlorothiazides; quinine; demethylchlortetracycline
Telangiectasia and angiomas	Calcium-channel antagonists
Late-onset erythema; blisters with slightly higher doses; low exposures—hyperpigmentation only	Psoralens; phytophotodermatitis
Increased skin fragility giving blisters with trauma	Nalidixic acid, furosemide, tetracycline, NSAIDs, amiodarone

and psoralen-containing plants (phytophotodermatitis). Contact with the sap of members of the Umbelliferae and Rutaceae plant families followed by sunlight exposure will produce typical clinical features of linear blistering and late-onset pigmentation as seen in the phytophotodermatitis termed 'strimmer's dermatitis'. Our knowledge of photoactive drugs is obtained from anecdotal case reports, post-marketing surveillance and, more recently, controlled trials required by regulatory authorities.

Clinical features. Acute phototoxic reactions to drugs and chemicals can present with an immediate burning sensation in light-exposed sites, accompanied by erythema and, on some occasions, urticaria. Usually, these agents (Table 29.5) also produce a delayed erythema component, which may blister. Some follow the sunburn time-course, with painful erythema and blistering at 24–48 h, whereas the newest reported group, the calcium-channel antagonists, produce an exposed-site telangiectasia following years of therapy. Psoralens, whether by the topical or oral route, produce erythema delayed by 72–96 h. Pseudoporphyria, which clinically mimics porphyria cutanea tarda or variegate porphyria, is caused by a group of agents that damage the dermal–epidermal junction, probably by recurrent low-grade phototoxicity. Porphyrin levels are normal. Most photoactive drugs are UVA-dependent. With some, such as quinine and thiazides, responsible wavelengths extend into the UVB and visible regions, and the most recent intravenous anticancer photodynamic therapy agents (porfimer sodium [Photofrin] and temoporfin [Foscan]) have a UVA and visible wavelength dependency.

Post-phototoxic pigmentation, which can persist for years, is a particular feature of amiodarone, chlorpromazine and tetracyclines. With photomutagenic psoralens, multiple phototoxic episodes can result in skin malignancy [6]. Persistent photosensitivity (persistent light reactor) is a rare and little studied complication.

Topical drug usage varies between countries. Photoallergic dermatitis caused by NSAIDs, although rare in the UK, is much more common in Spain and Portugal. Drug-induced LE, although uncommon, can occur. Major topical photoallergens are listed in Table 29.6.

Table 29.6 Major reported topical photoallergens.

Sulfonamides/sulfonylureas	Sulfanilamide; tolbutamide; chlorpropamide
Phenothiazines	Promethazine; chlorpromazine
Furocoumarins	5- and 8-methoxypsoralen
Fragrances	6-methylcoumarin; musk ambrette
Sunscreens	Benzophenones; PABA esters; dibenzoylmethanes; cinnamates
NSAIDs	Piroxicam; ibuprofen; naproxen

Pellagra rarely can be precipitated by isoniazid, phenytoin and other drugs.

Prognosis. The duration of photosensitivity after stopping a photoactive drug also varies. With most psoralens it is a matter of hours, whereas photosensitivity resulting from fluoroquinolones lasts 2–3 days. It may last for up to a year with amiodarone, thiazides and quinine, and the post-phototoxic pigmentation can last even longer.

Investigation. Suspected drug-induced photosensitivity is best investigated with phototesting 'on' and after a period 'off' the drug. Clinical and phototest improvement support the diagnosis. If drug-induced lupus is suspected, lupus serology and histology will help establish that diagnosis. Photopatch testing for photoallergy should be conducted when a topical photosensitizer is suspected.

Treatment. The simplest and most effective measure is to replace the offending drug with a non-phototoxic alternative. Although this is usually straightforward, with some, such as amiodarone, it may not be possible. Reduction in drug dosage and use of an appropriate broad-spectrum sunblock and, on occasions, UVB or PUVA desensitization may be required.

References

1 Ferguson J. Photosensitivity due to drugs. *Photodermatol Photoimmunol Photomed* 2002; **18**: 262–9.
2 Gould JW, Mercurio MG, Elmets CA. Cutaneous photosensitivity diseases induced by exogenous agents. *J Am Acad Dermatol* 1995; **33**: 551–73.
3 Stein KR, Scheinfeld NS. Drug-induced photoallergic and phototoxic reactions. *Expert Opin Drug Saf* 2007; **6**: 431–43.

Table 29.7 Dermatoses not caused but sometimes aggravated by ultraviolet exposure.

Acne
Atopic eczema
Bullous pemphigoid
Carcinoid syndrome
Cutaneous T-cell lymphoma
Dermatomyositis
Disseminated superficial actinic porokeratosis
Erythema multiforme
Familial benign chronic pemphigus (Hailey–Hailey disease)
Granuloma annulare
Hartnup syndrome
Herpes simplex
Keratosis follicularis (Darier's disease)
Lichen planus
Lupus erythematosus
Lymphocytic infiltrate of Jessner
Pellagra
Pemphigus
Pemphigus foliaceus (erythematosus)
Pityriasis rubra pilaris
Psoriasis
Reticular erythematous mucinosis (REM) syndrome
Rosacea
Sarcoid
Seborrhoeic eczema
Smith–Lemli–Opitz syndrome
Transient acantholytic dermatosis (Grover's disease)
Viral infections

4 Selvaag E, Thune P. Drug photosensitivity in Norway. *Acta Derm Venereol (Stockh)* 1996; **76**: 405–6.
5 Harber LC, Bickers DR, eds. *Photosensitivity Diseases: Principles of Diagnosis and Treatment*, 2nd edn. Philadelphia: Saunders, 1988.
6 Stern RS, Laird N. The carcinogenic risk of treatments for severe psoriasis. *Cancer* 1994; **73**: 2759–64.

Drug- and chemical-induced photosensitivity: endogenous—the cutaneous porphyrias

See Chapter 59.

Dermatoses sometimes exacerbated by UVR

Synonyms
- Light-exacerbated dermatoses
- Photoexacerbated dermatoses
- Photo-aggravated dermatoses

J.L.M. Hawk, pp. 29.22–29.23

A variety of skin disorders not actually caused by UVR may sometimes be worsened by it [1] (Table 29.7), immune activity involved in their pathogenesis apparently being enhanced rather than suppressed, a feature also noted to be present without sequelae in a small proportion of normal subjects [2]. The underlying disorder may be severely exacerbated even if it is usually only minimal or even subclinical, especially in seborrhoeic [3] and to a lesser extent atopic eczema, acne [4] and psoriasis, although all these conditions much more frequently improve following UVR exposure. Such disorders represent an important proportion of all photosensitivity in some parts of the world [5]. If photoexacerbation does occur, the new eruption generally develops or worsens initially at sites typical of the underlying disorder, followed if severe by spread to other, or rarely, all exposed areas (Fig. 29.16). In light-exacerbated seborrhoeic eczema, however, an unpleasant sensation of the exposed sites may sometimes be the first or only feature. Treatment is by the restriction of UVR exposure, wearing of suitably protective clothing, application of high-protection, broad-spectrum sunscreens, and very careful therapy of the underlying disorder. In light-exacerbated seborrhoeic eczema, this especially includes the daily use of an anti-eczema shampoo, even if the scalp is at most minimally affected, which alone often reverses the general photosensitivity [3], presumably by diminishing overall disease immune reactivity. If this is insufficient, however, prophylactic low-dose phototherapy with UVB or PUVA, as for PLE, may be useful for frequent outbreaks in conditions normally responsive to such treatment, such as seborrhoeic eczema, atopic eczema or psoriasis, but not cutaneous lupus or dermatomyositis [6], which may be significantly worsened. For occasional outbreaks, as on vacation, again as for PLE, short oral courses or prior injections of steroid may be effective and safe, with topical steroids as an adjunct if necessary. Very rarely, for otherwise intractable disease, oral immunosuppressive therapy with azathioprine or ciclosporin may be needed. Light-exacerbated acne, however, generally requires oral isotretinoin [4], which is usually effective for years.



Fig. 29.16 Light-exacerbated seborrhoeic eczema of the trunk.

References

1 Werth V, Hönigsmann H. The photoaggravated dermatoses. In: Lim HW, Hönigsmann H, Hawk JLM, eds. *Photodermatology*. New York: Informa Healthcare, 2007: 251–66.
2 Palmer RA, Hawk JLM, Young AR, Walker SL. The effect of solar-simulated radiation on the elicitation phase of contact hypersensitivity does not differ between controls and patients with polymorphic light eruption. *J Invest Dermatol* 2005; **124**: 1308–12.

3 Palmer RA, Hawk JLM. Light-exacerbated seborrhoeic eczema: severe photoprovocation from subclinical disease. *Br J Dermatol* 2003; **149** (Suppl. 64): 93.
4 Norris PG, Hawk JLM. Actinic folliculitis: response to isotretinoin. *Clin Exp Dermatol* 1989; **14**: 69–71.
5 Khoo SW, Tay YK, Tham SN. Photodermatoses in a Singapore skin referral centre. *Clin Exp Dermatol* 1996; **21**: 263–8.
6 Cheong WK, Hughes GRV, Norris PG, Hawk JLM. Cutaneous photosensitivity in dermatomyositis. *Br J Dermatol* 1994; **131**: 205–8.

Clinical evaluation of the patient with suspected cutaneous photosensitivity [1]

Patients with photosensitivity usually present with either intermittent or persistent abnormalities of light-exposed areas, or rarely with erythroderma. Those with intermittent problems are themselves likely to attribute the reaction to sunlight, but if not, as is more commonly the case in individuals with persistent abnormalities or erythroderma, careful history taking is necessary, first to identify light exposure as the likely cause, and then to determine the probable specific diagnosis. Generally, relevant patient details are age at disease onset, gender, family history, any prior sunlight sensitivity, occupation, leisure activities and systemic or topical chemical or medication use. Useful details concerning the eruption are its seasonal behaviour, length of exposure for elicitation, latent interval between exposure and onset, duration, occurrence or not through glass or clothing, any associated systemic symptoms, nature of the rash as described by the patient, and its distribution. Accordingly, young women most commonly suffer polymorphic light eruption (PLE), women or girls actinic prurigo (AP), children of either sex hydroa vacciniforme (HV), xeroderma pigmentosum (XP) or erythropoietic protoporphyria (EPP), and elderly men or atopic eczema sufferers chronic actinic dermatitis (CAD), while a family history of photosensitivity is often present in PLE, AP, XP and the porphyrias. CAD is more usual in outdoor enthusiasts exposed both to sunlight and airborne contact allergens, while disease deterioration despite sunscreen use suggests possible sunscreen contact dermatitis or PLE, which itself can occasionally worsen with sunscreens. Rash onset within minutes followed by resolution within an hour or so suggests solar urticaria (SU), or photosensitivity to certain drugs such as amiodarone, and onset within 20 min to several hours with resolution over days to a week or two suggests PLE, HV (may take a month to resolve fully), EPP, XP, subacute cutaneous lupus, other light-exacerbated dermatoses, or other drug photosensitivity such as to thiazide diuretics. Systemic malaise occasionally occurs in PLE, HV, SU or cutaneous lupus. Reactions through glass or clothing suggest a disease action spectrum that includes the UVA, which is possible in most photodermatoses except normal sunburn and XP.

The nature of the rash as described by PLE patients is of small or large, raised, itchy, red or skin-coloured, often grouped, spots or blisters, sometimes running together and usually affecting only some exposed areas, whereas in HV there are blisters which heal to leave permanent scarring. In SU, raised itchy weals, also sometimes coalescent, occur. In EPP and amiodarone drug photosensitivity, a severe, burning sensation without visible signs is usual, although with prolonged exposure, firm, colourless or pink, diffuse swelling, rarely with scattered blistering, may occur in the former. In most other drug-induced photosensitivity and some XP, exaggerated sunburning responses are described, often peaking later in XP than normal at 2–3 days. In light-exacerbated dermatoses, the morphology reported generally suggests the underlying disorder, although in subacute cutaneous lupus concomitant PLE is also rarely present [2,3].

Clinically, any eruption generally affects some, rarely all, of the exposed forehead, nose, upper cheeks, point of chin, rims of ears, back and sides of neck, upper chest, dorsa of hands and feet, and limb extensor surfaces, while covered sites may sometimes also be affected to some extent. However, the light-protected hair fringe area, upper eyelids, finger webs, depths of skin creases and sites beneath the nose, lower lip, chin and earlobes are often spared, except potentially if concomitant airborne contact dermatitis is present. Excoriated papules of extensor limbs and face suggest AP, an eczematous eruption suggests CAD, or light-exacerbated atopic or seborrhoeic eczema, and skin fragility, blistering and superficial scarring a hepatic porphyria or pseudoporphyria, particularly following drug, excessive alcohol or frequent sunbed exposure. Finally, any light-aggravated tendency to erythroderma suggests CAD.

Following such assessment, a specific diagnosis is generally strongly suspected, but for complete certainty at least some further investigation, as below, is generally required.

References

1 Lim HW, Hawk JLM. Evaluation of the photosensitive patient. In: Lim HW, Hönigsmann H, Hawk JLM, eds. *Photodermatology*. New York: Informa Healthcare, 2007: 139–48.
2 Murphy GM, Hawk JLM. The prevalence of antinuclear antibodies in patients with apparent polymorphic light eruption. *Br J Dermatol* 1991; **125**: 448–51.
3 Nyberg F, Hasan T, Puska P *et al.* Occurrence of polymorphous light eruption in lupus erythematosus. *Br J Dermatol* 1997; **136**: 217–21.

Further investigation of the patient with cutaneous photosensitivity

J. Ferguson, pp. 29.23–29.24

Patients suspected of photosensitivity should have their antinuclear factor and extractable nuclear antigen (anti-SSA [Ro] and -SSB [La]) assessed. When appropriate, the cutaneous porphyrias can be excluded by spectrofluorimetry and, if necessary, by quantitative assessment of blood, urine and stool porphyrins. Histological examination of lesional or provoked skin lesions may be helpful, but is rarely diagnostic.

After taking a standard photodermatology history, investigation is to some extent disease-specific. Photobiology units often use a structured investigational referral form identifying phototest procedures such as monochromator, solar simulator and broad-spectrum larger area provocation testing [1]. As with all optical test equipment, quality control with calibrated metering and spectroradiometry is essential. Use of such devices is followed by immediate and delayed readings, and abnormality is detected by comparison with normal data. Provocation testing of larger skin areas is particularly useful in PLE and AP.

If the morphology is eczematous and an exogenous chemical is suspected, patch and photopatch testing will help identify the responsible allergen or photoallergen. Recently, photopatch testing has been standardized within Europe [2], where the most common photoallergens are the organic sunscreens. In the genophotodermatoses, assessment of DNA repair, including excision and helicase function, DNA and RNA synthesis rates, cell survival post-UVA irradiation, sister chromatid exchange frequencies and, more recently, specific mutation studies, may be required to establish the diagnosis.

References

1 British Photodermatology Group. Diagnostic phototesting in the United Kingdom. *Br J Dermatol* 1992; **127**: 297–9.

2 European Taskforce for Photopatch Testing. Photopatch testing: A consensus methodology for Europe. *J Eur Acad Dermatol Venereol* 2004; **18**: 679–82.

CHAPTER 30
Bacterial Infections

R.J. Hay[1] *& B.M. Adriaans*[2]

[1]Dermatology Department, King's College Hospital, London, UK
[2]Department of Dermatology, Gloucestershire Royal Hospital, Gloucester, UK

Normal flora of the skin, 30.2
The skin and defence, 30.5
Gram-positive bacteria, 30.6
Staphylococcus aureus, 30.6
Coagulase-negative staphylococci, 30.10
Streptococci, 30.11
Impetigo, 30.14
Ecthyma, 30.17
Cellulitis and erysipelas, 30.17
Inflammatory diseases of hair follicles, 30.21
Staphylococcal scalded skin syndrome, 30.30
Toxic shock syndrome, 30.31
Other staphylococcal and streptococcal infections, 30.32
Toxin-mediated streptococcal disease, 30.33
Coryneform bacteria, 30.35
Propionibacteria, 30.40
Anthrax, 30.40
Listeriosis, 30.42
Erysipeloid, 30.42
Gas gangrene (clostridial myonecrosis), 30.43
Gram-negative bacteria, 30.44
Meningococcal infection, 30.44
Gonococcal infection, 30.45
Acinetobacter infection, 30.46
Moraxella infection, 30.46
Chancroid, 30.47
Salmonella infection, 30.47
Pseudomonas infection, 30.48
Rhinoscleroma, 30.51
Tularaemia, 30.53
Pasteurella infection, 30.54
Plague and *Yersinia* infections, 30.54
Brucellosis, 30.55
Infections due to *Bartonella* species, 30.56
Ehrlichiosis, 30.58
Other Gram-negative bacilli, 30.59
Anaerobic bacteria, 30.59
Tropical ulcer, 30.60
Granuloma inguinale, 30.61
Spirochaetes and spiral bacteria, 30.62
Botryomycosis, 30.67
Necrotizing subcutaneous infections, 30.68
***Mycoplasma* infections, 30.69**
Chlamydiae, 30.70
Rickettsial infections, 30.72
Actinomycete infections, 30.74
Actinomycosis, 30.74
Nocardiosis, 30.76
Dermatoses possibly attributable to bacteria, 30.77

Introduction

The normal human skin is colonized by huge numbers of bacteria that live harmlessly as commensals on its surface and within its follicles. At times, overgrowth of some of these resident organisms may cause minor disease of the skin or its appendages. On other occasions, bacteria not normally found there may colonize the epidermis and lead rapidly to disease. Apart from the arrival of these frankly pathogenic organisms, a wide range of bacteria land more or less fortuitously on the skin, and linger briefly in small numbers before disappearing, unable to multiply and thrive in this relatively inhospitable environment. Bacteriological sampling will reveal the presence of these otherwise unsuspected 'transients' [1]. Organisms not normally considered as resident members of the skin flora may sometimes colonize and become established in modest numbers for relatively long periods. Bacteria of this intermediate category have been labelled temporary residents. Furthermore, certain sites such as the skin of the face may be repeatedly contaminated from the nostrils or mouth by *Staphylococcus aureus* or β-haemolytic streptococci, giving the false impression that these organisms are members of the normal facial flora. As they do not reside and replicate there, they are, as far as the face is concerned, transients.

When the skin is inflamed or otherwise abnormal, it is often difficult to determine whether an organism isolated from its surface is causing or contributing to the observed pathology [2,3]. Bacteriology reports must be interpreted with caution in the light of the known capabilities of the organism isolated. If the skin is damaged or the immune status of the subject impaired, bacteria usually regarded as non-pathogenic on the body surface may assume the role of opportunist pathogens. The number of organisms in the inoculum is of considerable importance. Within a given species there are also strain differences in virulence. Some strains have a particular tendency to cause disease, perhaps due to greater adherence to epithelial cells, perhaps because of differences in enzyme production. The underlying mechanisms are not fully understood, but the principle is well recognized.

From the point of view of host defence, there are three aspects to be considered: first, the nature and health of the epithelial surface including its ability to replicate and produce secretions; second, the interactions between commensal organisms of the normal flora and the potential parasite; and third, the cellular and

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

humoral factors acting within the body—both classical immune mechanisms and non-specific mechanisms.

Even on the skin, the most accessible of sites, the complexities of host–parasite relationships remain incompletely understood. Detailed, culture-independent studies of pathogens and commensals, and investigations of epidermal replication and of the immune capabilities of the host, are becoming feasible in a research setting. For example, recent examination of the forearms of six healthy volunteers, using sequence analysis of the bacterial 16S gene, has shown a significant diversity of microorganisms. The number of species identified was much greater that any identified by standard cultural procedures, and several unknown phyla were also reported [4]. The lessons they teach must be used to interpret the problems found in daily clinical practice, where such sophisticated methods are generally unavailable.

There is now a considerable literature on the microbiology of human skin of which these references are some of the most important texts [5–7]. For general microbiology and infectious disease, [8] and [9] are recommended.

Normal flora of the skin

Methods of sampling

Numerous methods have been used to sample the normal or commensal flora of the skin, as no one method is satisfactory for all sites or for all aspects of the work [10]. Simple qualitative studies, especially when large numbers of subjects must be sampled, are usually performed by swabbing. This should be done in a standardized manner. The number of organisms is increased by the duration of rubbing, pressure exerted and moistening the swab. Semiquantitative data and some information as to the spatial distribution of bacteria are provided by sticky tape sampling, roll tubes or replica plating. The best quantitative estimates of the total bacterial flora are determined by applying an open-ended cylinder of known cross-sectional area to the skin, introducing a small, known volume of suitable liquid vehicle (phosphate buffer plus Triton X-100) and scrubbing the surface of the skin to free the organisms. This method is useful for studying changes in the number of organisms under different environmental conditions in small numbers of subjects, but is very time consuming, and gives a poor yield of the intrafollicular anaerobes. Full-thickness skin-biopsy material should in theory provide the best sample, but in practice it is not easy to handle and this method is of course traumatic to the subject [5].

The disposal of organisms can be studied quantitatively by air sampling techniques using either settle plates or an impaction sampler while the subject performs a specified activity, for example undressing in a small room [11].

The media used for isolation clearly influence the results of sampling. Noble, although recognizing the special value of selective media, recommends in general the use of ordinary blood or serum agar for aerobic organisms and solid Brewer's thioglycolate medium without indicator but with 1% Tween 80 for *Propionibacterium acnes* [7].

For culture-independent studies using the newer molecular genetic methods, the DNA of the organisms has to be extracted, processed and amplified. Broad-range PCR primers targeted at the highly conserved regions of bacteria allow relatively easy amplification of the small subunit rRNA gene sequences. The methods have been described previously [4,12].

The normal flora

The concept of a stable, normal resident flora composed of large numbers of organisms belonging to relatively few species is well established [1]. There are some variations from subject to subject and perhaps in a given subject with time. A few geographical differences have also been noted [9]. These established flora have been confirmed by the newer genetic techniques, but many new organisms have been observed and await full bacteriological identification. The skin's ecological characteristics have been expanded by these new findings and the role of these microorganisms in skin health and disease will be most exciting [4,12].

Temporary resident bacteria may confuse the picture, being less easy to distinguish from stable commensal organisms than obvious transients. It is possible, however, to describe a basic pattern of colonization of healthy human skin from which some variations may be observed. In simple terms, dry skin supports a low level of colonization, while moist areas and those well supplied with sebaceous glands are heavily populated. Most organisms reside on the surface of the stratum corneum in the crevices between squames in the rather loose, outermost layers. These surface dwellers are not evenly distributed but are aggregated into microcolonies of varying sizes comprising perhaps 50 or several hundred cells. Some may be larger still. The hair follicles are inhabited by anaerobes (*Propionibacterium* species) in their deeper parts and nearer the surface aerobic cocci in addition to *Malassezia* species of yeasts. There are, however, no bacterial inhabitants of sweat ducts or glands, eccrine or apocrine. A variety of antimicrobial peptides are present in the eccrine glands, some more antibacterial than others, and these may be relevant [13].

The resident aerobic flora that have been cultured consist of Gram-positive cocci of *Staphylococcus* species, *Micrococcus* species and a variety of Gram-positive rods, the coryneforms or diphtheroids. These coryneform organisms are mainly *Corynebacterium* species but some have recently been recognized as *Brevibacterium* species. The only significant Gram-negative residents are *Acinetobacter* species, previously known as *Mima* and *Herellea*.

Propionibacteria are regularly found in the follicles in adult skin and are the main anaerobic residents. The species *Staphylococcus saccharolyticus* is an anaerobic *Staphylococcus* and is a member of the normal flora in about 20% of subjects. Streptococci are notable by their absence, although they may frequently be found as transients (from the mouth) on perioral skin, or other sites prior to the onset of impetigo [14].

Most cutaneous microbiologists have now accepted that the Kloos and Schleifer [15] scheme for classifying staphylococci and micrococci (Micrococcaceae) is more meaningful, at least from an ecological standpoint, than the much used Baird–Parker system [6]. Kloos and Schleifer separate *Staphylococcus* species and *Micrococcus* species on the basis of several tests. For example, *Staphylococcus* species are able to produce acid aerobically from glycerol in the presence of erythromycin (0.4 μg/ml), and they are sensitive to lysostaphin and nitrofuran at defined concentrations, whereas *Micrococcus* species are not. Separation of the two genera by these criteria is supported by molecular genetic techniques.

The genus *Staphylococcus* comprises more than 40 different species, and about 10 of these are regularly isolated from normal skin. The coagulase-positive species *Staphylococcus aureus*, however, should not be considered as a resident on healthy skin in most subjects, although it is frequently found in the anterior nares. It occurs there as a resident in about one-third of most populations and is carried on perineal skin in perhaps 20%. Healthy axillary skin, and toe clefts in shoe-wearing populations, may also harbour it in a smaller percentage of subjects. On damaged skin, for example in eczema or psoriasis, *S. aureus* may be found, sometimes widely over the skin surface.

Of the coagulase-negative resident *Staphylococcus* species, *S. hominis* and *S. epidermidis* (moist sites) are the most important numerically, but *S. capitis, S. cohnii, S. haemolyticus, S. saprophyticus* and *S. warneri* have also been isolated from many subjects. Interestingly, *S. xylosus* has also been found to be fairly common on North American skins but does not seem to be a cutaneous resident in the UK. *S. simulans* is another recognized but uncommon cutaneous *Staphylococcus* on both sides of the Atlantic [7].

Organisms of the genus *Micrococcus* are less numerous than *Staphylococcus* species on healthy skin but are relatively more important on sparsely populated, dry sites and in childhood. *M. luteus* and *M. varians* appear to be the dominant species but *M. kristinae* and *M. sedentarius* are accepted as residents and *M. lylae* may have significance in infancy [6].

Coryneforms

The coryneform (or diphtheroid) organisms are mostly aerobic, Gram-positive pleomorphic rods. The coryneform bacteria are difficult to separate by conventional taxonomic methods, and chemotaxonomic methods, such as identification of specific protein patterns on gel electrophoresis and restriction fragment length polymorphism (RFLP) analysis, are time consuming and unsuitable for routine use. A proposed scheme in which the aerobic coryneforms are divided into four *Corynebacterium* species complexes, *C. bovis, C. minutissimum, C. xerosus* and *C. hofmani*, with *Brevibacterium epidermis* and an apparently aerobic *Propionibacterium* species making up a total of six groups, has the obvious value of simplicity, which all its predecessors lacked [7]. It is notable, however, that a trichomycosis axillaris-associated group is not defined and it is not clear whether the strains included in the *C. minutissimum* complex are closely associated with clinical erythrasma. *Brevibacterium* species are clearly separable from the genus *Corynebacterium* by cell-wall composition studies, nutritional requirements and by the production of methane thiol. These relatively recently recognized organisms have now been established as normal inhabitants of the skin (at least in a sizeable minority of subjects) and are particularly associated with (but not confined to) moist sites. They are related to *Brevibacterium* species isolated from dairy products, and by the production of methane thiol are the probable cause of the cheesy odour of sweaty feet [16].

A further group of coryneforms, implicated as co-pathogens in the superficial fungal infection of hair shafts, white piedra, has been identified as *Brevibacterium mcbrellneri* [17].

Three species of *Propionibacteria*, which are anaerobic, Gram-positive, rod-shaped organisms, are now generally acknowledged as members of the resident flora in adults. *P. acnes* and *P. granulosum* are widespread, but particularly associated with follicles that have large sebaceous glands over the face and upper trunk. They have both been associated with acne lesions in which their role is a matter of considerable interest. The third species, *P. avidum*, is found in moist sites, particularly the axillae and groins. Its pathogenic potential on the skin is unclear [18].

Quantitative studies

The population of Micrococcaceae per square centimetre of the skin has been estimated as 600 for the hand, 60 for the forearm, 300 for the scapular region and 500 000–1 000 000 in the axilla [7]. Total anaerobic organisms, that is including diphtheroids as well, were reported by Williamson as averaging 1.46×10^6 for the scalp, and 2.41×10^6 for the axilla [19]. Figures for the forehead were 200 000, whilst for the forearms there were two populations of normal subjects, one tending to have high counts, with an average of 4500 organisms per square centimetre and one with low counts with just over $100/cm^2$. For the back, the average for the whole group was a little over $300/cm^2$. Anaerobic organisms are most numerous in those regions with large follicles—face, chest and back—and reports suggest numbers of 50 000 up to several million per centimetre square [20]. The follicular location of many of these organisms makes their estimation technically difficult, but Puhvel and co-workers [21] using microdissection techniques, have found the mean anaerobic count to be 3.8×10^4 per follicle. The number of organisms on a particular subject's skin varies little with time. There is, however, considerable variation within the population. Some individuals habitually carry high, and others very low, numbers of bacteria but this distribution does follow a 'log normal' curve.

Modifying factors

The influence of various factors on the microbial population has been investigated by using a quantitative sampling technique. Abstinence from washing does not increase the count. Taking a shower probably produces a brief, temporary reduction in the bacterial flora, but because it leads to the break-up of the microcolonies on the skin and a more even distribution of bacteria, it may actually cause increased dissemination of bacteria for an hour or two afterwards [7]. Season has little effect apparently, but in one investigation an increase in the number of organisms was reported with increase in external temperature and humidity, but not when either of these factors operated alone [3].

The effects of increased hydration have been studied by covering the skin with plastic film [2]. The total flora increases greatly; in the early stages, coagulase-negative staphylococci and micrococci predominate but, later, lipophilic coryneforms become numerous and micrococci diminish in importance. Gram-negative rods increase steadily with time. In jungle conditions, *Pseudomonas aeruginosa* is commonly isolated from moist areas, and in neonates nursed in high-humidity atmospheres, colonization and infection with *P. aeruginosa* occur with increased frequency [22].

Age, sex and race differences

The human skin becomes colonized from birth. Neonates are covered with vernix caseosa which has been shown to contain the

antimicrobial peptide, cathelicidin, and also lysozyme, both of which have antibacterial properties. This suggests that the infant has the capacity to secrete these substances, perhaps in preparation for bacterial colonization after birth [23]. In infants the bacterial flora is somewhat unstable and varied, being more likely to include, probably as temporary residents, streptococci and spore-forming bacilli [24]. *Micrococcus* species appear to be more prominent than on the adult skin, but *Propionibacterium* species require the increased skin lipid levels of puberty before becoming established, and are present at very low levels, if at all, before the onset of puberty. In elderly subjects, streptococci make an appearance as residents, and in this age group enteric organisms are found more often, particularly in moist sites. There is evidence that males carry higher numbers of bacteria, at least of aerobic organisms, than females [7], a fact which probably accounts for the observation that men are more likely to be disseminators of *Staphylococcus aureus*, if they are perineal carriers, than are women [25]. The subject of dispersal, of considerable importance in surgery, has been extensively reviewed by Noble [26].

Racial differences have been demonstrated in the nasal carriage of *S. aureus* in children—white individuals (at 41% positive) being more likely than black individuals (at 30%) to carry this organism [27], but comparative data on the densities of the bacterial populations of the main groups of resident organisms are lacking.

Other influences

Changes in normal flora, including an increase in the number of subjects carrying Gram-negative organisms, may occur in seriously ill patients, apparently to an extent that cannot be accounted for by the treatment they are receiving [28].

Antiseptics applied to the skin, as in the preparation of operation sites, generally remove the transient flora and reduce the resident organisms [5]. The application of agents that specifically inhibit Gram-positive cocci is generally followed by an increase in the population of Gram-negative rods [10]. Carriage of *S. aureus* may also be affected by cold weather, duration of hospital stay or needle injection [29].

The role of the normal flora

The normal flora of the skin appears to have several functions, of which the most important is probably defence against bacterial infection through bacterial interference. It is almost certainly responsible for the production of free fatty acids from skin lipids. There is now considerable evidence that *Propionibacterium acnes* and the Gram-positive cocci are capable of hydrolysing lipids of sebum to produce free fatty acids [30]. The acidic milieu which results inhibits the growth of other organisms such as *Streptococcus pyogenes* [31]. It seems likely from their localization, and from evidence comparing the effects of systemic tetracycline administration with topical neomycin application, that *P. acnes* deep in the follicles actually undertakes most of this hydrolysis [32].

Apocrine sweat is sterile and odourless when secreted. The odour develops due to bacterial action, mainly attributable to aerobic corynebacteria. Deodorants are effective largely through their antibacterial activity [33].

The flora of specialized areas [34]

Certain areas of skin have specific floras when cultured, which differ quantitatively or qualitatively from the general picture outlined above and are therefore worthy of special consideration.

The nasal vestibule

The common organisms found on swabbing are coagulase-negative staphylococci, micrococci and coryneforms. *Staphylococcus aureus* is present as a resident in about 35% of healthy subjects. *Streptococcus pyogenes* is not rare. The percentage incidence varies greatly with different populations but, as nasal carriers sometimes disseminate large numbers of organisms, their detection and treatment are most important in the control of staphylococcal and streptococcal infections.

External auditory meatus

In addition to coagulase-negative staphylococci and coryneforms, *Proteus* species, *Escherichia coli, Neisseria catarrhalis* and *N. flora* have been isolated in small but significant numbers from normal ears.

Axilla

This site supports a very high level of bacterial colonization, mostly staphylococci, micrococci and coryneforms. Some individuals have a mainly coccal flora; in others aerobic coryneforms predominate. *Propionibacterium acnes* is usually present and *P. avidum* is often found, as are *Acinetobacter* species.

Toe clefts

In shoe wearers, the fourth toe cleft is often hyperhydrated and the skin macerated. Such conditions sustain an extraordinarily large number of bacteria, mainly the common organisms of the general resident flora, but Gram-negative organisms are also found in this site. The toe web is an important site for *Brevibacterium* species, and not surprisingly *Acinetobacter* species are often isolated, as are *Alkaligenes* species. In the elderly and in tropical climates, coliforms and other organisms of the intestinal flora may be present [35].

The vulva

Organisms regularly isolated from this area include the expected coagulase-negative staphylococci, micrococci and coryneforms, with coliforms and enterococci occurring frequently as residents and as transients from faecal sources. Group B streptococci may be cultured from this site, usually in small numbers.

The perineum and groin

Coagulase-negative staphylococci, micrococci and a variety of aerobic coryneforms are usually present. Gram-negative organisms of the intestinal flora rapidly disappear after faecal contamination, but *Acinetobacter* species are resident in about 15% of subjects.

Umbilicus

The umbilicus of the newborn is frequently colonized by *Staphylococcus aureus* shortly after birth. The incidence varies greatly, but

for infants born in hospital it is probably not very different from the nasal colonization rate.

The umbilicus of the newborn may also be colonized by *Streptococcus pyogenes*, and look normal. The organisms can readily spread from infant to infant in a hospital nursery. Searches for the source of staphylococcal and streptococcal infection in a maternity unit should always include umbilical swabs from the babies.

Adherence

The ability of bacteria to stick to the skin surface, the process of adherence, has been extensively investigated. On wet surfaces, the hydrophobic nature of many bacterial walls promotes close apposition between the bacterium and human cells. In addition, there are smaller elements of the outer surface, adhesins, which also promote adhesion [36].

These are usually specific and interact with the host cell via a receptor site. Examples of bacterial adhesins include lipotechoic acid [37], found in both staphylococci and streptococci; in the latter this is located in fine cell-wall projections or fibrillae. Similar filamentous structures, fimbriae or pili, occur in many Gram-negative bacteria. Adhesins not only allow the organisms to remain on the epithelial surface, they may also regulate the relationship between different bacteria, such as the composition of microcolonies, via the interaction of complex excreted material covering the bacterial surface. The secretion of extracellular material, such as slime, allows bacteria to adhere to foreign surfaces as well as stratum corneum [38]. Where this involves suture materials or plastics such as percutaneous cannulae, heavy colonization may then be followed by invasion, resulting in abscess formation or septicaemia.

The skin and defence

The skin provides a dry, mechanical barrier from which contaminating organisms are constantly being removed by desquamation. Investigators have spread organisms on the skin surface, studied their disappearance and attempted to elucidate the factors concerned.

The early theories that the acid pH of most of the skin surface was an important defence mechanism against bacteria have now been completely rejected [7]. Desiccation appears to account for the difference in the rate at which implanted bacteria disappeared from acid and alkaline areas, the alkaline areas being more moist.

Ricketts *et al*. [39] investigated the survival of several species of bacteria on the forearm skin under plastic films of two kinds, one permeable to water vapour and one not. The plastic films were held by a frame of adhesive tape, so that the inoculated area could be sampled at intervals up to 7 days. By studying the survival of bacteria on the dry and on the moist areas thus produced, these workers concluded that a chemical mechanism was largely responsible for the destruction of *Streptococcus pyogenes*, whereas drying was responsible for the destruction of *Escherichia coli* and *Pseudomonas aeruginosa*. Both factors appeared to contribute to the elimination of *Staphylococcus aureus*. They then investigated the nature of the chemical mechanism and concluded that unsaturated fatty acids, particularly oleic acid, were the active agents. These may be produced on the skin surface as a result of the splitting of esters in the sebum by the commensal flora.

Lacey has confirmed that extraction of the fatty acids from the skin diminishes resistance to colonization by staphylococci, and that fatty acids may be neutralized to some extent by binding with neomycin [40].

The phenomenon of bacterial interference is sufficiently closely related to skin defence to be mentioned here. Colonization of some sites by one strain of staphylococci interferes with the subsequent colonization by a different strain. Shinefield *et al*. [41] deliberately colonized the noses and umbilical stumps of newborn infants against infection and disease caused by epidemic strains of *S. aureus*, and obtained most encouraging results. A similar method has been used in an attempt to prevent recurrent attacks of boils, but the technique has not found general acceptance, largely because the avirulence of the inoculated strain cannot be guaranteed. Competition for available nutrients is thought to explain this phenomenon. The organisms also produce bacteriocins (antibiotic substances) which may inhibit the growth of others [34].

When pathogens invade, the host response is via the adaptive and innate immune systems, which are interrelated. The skin participates very actively by producing antimicrobial peptides such as cathelicidin and the various defensins. These are produced by keratinocytes, but neutrophils, mast cells and platelets which are recruited to the area may also be involved in the production of antimicrobial peptides [42].

References

1 Roth RR, James CS. Microbiology of the skin—resident flora, ecology and infection. *J Am Acad Dermatol* 1989; **20**: 367–90.

2 Bibel DJ, Le Brun JR. Changes in cutaneous flora after wet occlusion. *Can J Microbiol* 1975; **21**: 496–501.

3 Duncan LM, McBride ME, Knox JM. Bacterial flora: the role of environmental factors. *J Invest Dermatol* 1969; **52**: 479–84.

4 Gao Z, Tseng C-H, Pei Z *et al*. Molecular analysis of human forearm superficial skin bacterial biota. *PNAS* 2007; **104**: 2927–32.

5 Maibach HI, Aly R, eds. *Skin Microbiology: Relevance to Clinical Infection*. New York: Springer, 1981.

6 Marples RR. Coagulase-negative staphylococci: classification and problems. In: Maibach HI, Aly R, eds. *Skin Microbiology: Relevance to Infection*. New York: Springer, 1981: 45–61.

7 Noble WC. *Microbiology of Human Skin*. London: Lloyd-Luke Medical Books, 1981.

8 Mandell GL, Douglas RG, Bennett JE. *Principles and Practice of Infectious Diseases*. New York: Churchill Livingstone, 1990.

9 Collier LH, Balors A. *Topley and Wilson's Principles of Bacteriology, Virology and Immunity*. London: Arnold, 1997.

10 Shehadeh NH, Kligman AM. The effect of topical antibacterial agents on the bacterial flora of the axilla. *J Invest Dermatol* 1963; **40**: 61–71.

11 Noble WC, Davies RR. Studies on the dispersal of staphylococci. *J Clin Pathol* 1965; **18**: 16–19.

12 Paulino LC, Tseng CH, Stober BE *et al*. Molecular analysis of fungal microbiota in samples from healthy human skin and psoriatic lesions. *J Clin Microbiol* 2006; **44**: 2933–41.

13 Rieg S, Seeber S, Steffen H *et al*. Generation of multiple stable dermicidin-derived antimicrobial peptides in sweat of different body sites. *J Invest Dermatol* 2006; **126**: 354–65.

14 Maddox JS, Ware JC, Dillon HC. The natural history of streptococcal skin infection. *J Am Acad Dermatol* 1985; **13**: 207–11.

15 Kloos WE, Schleifer KH. Simplified scheme for routine identification of human *Staphylococcus* species. *J Clin Microbiol* 1975; **1**: 82–6.

16 Sharpe ME, Law BA, Phillips BA *et al*. Methanethiol production by coryneform bacteria; strains from dairy and human skin sources and *Brevibacterium linens*. *J Gen Microbiol* 1977; **101**: 345–9.
17 McBride ME, Ellner KM, Black HS *et al*. A new *Brevibacterium* sp. isolated from infected genital hair of patients with white piedra. *J Med Microbiol* 1993; **39**: 255–61.
18 Higaki S, Kitagawa T, Morohashi M *et al*. Minocycline effectively reduces acid produced by *Proprionibacterium granulosum*. *J Dermatol* 2002; **29**: 202.
19 Williamson P. Quantitative estimation of cutaneous bacteria. In: Maibach HI, Hildick Smith G, eds. *Skin Bacteria and their Role in Infection*. New York: McGraw Hill, 1965: 3–11.
20 Somerville DA, Murphy CT. Quantitation of *Corynebacterium acnes* on healthy human skin. *J Invest Dermatol* 1973; **60**: 231–3.
21 Puhvel SM, Reisner RM, Amirian DA. Quantitation of bacteria in isolated pilosebaceous follicles in normal skin. *J Invest Dermatol* 1975; **65**: 525–31.
22 Hojyo-Tomoka MT, Marples R, Kligman AM. Pseudomonas infection in superhydrated skin. *Arch Dermatol* 1973; **107**: 723–7.
23 Marchini G, Lindow S, Brismar H *et al*. The newborn infant is protected by an innate antimicrobial barrier: peptide antibiotics are present in the skin and vernix caseosa. *Br J Dermatol* 2002; **147**: 1127–34.
24 Somerville DA. The normal flora of the skin in different age groups. *Br J Dermatol* 1969; **81**: 248–58.
25 Hill J, Howell A, Blowers R. Effect of clothing on dispersal of *Staphylococcus aureus* by males and females. *Lancet* 1974; **2**: 1131–2.
26 Noble WC. Dispersal of skin microorganisms. *Br J Dermatol* 1975; **93**: 477–83.
27 Noble WC. Carriage of *Staphylococcus aureus* and β-hemolytic streptococci in relation to race. *Acta Derm Venereol (Stockh)* 1974; **54**: 403–5.
28 Stratford B, Gallus AS, Matthiesson AM *et al*. Alteration of the superficial bacterial flora in severely ill patients. *Lancet* 1978; **1**: 68–70.
29 Tuazon CU. Skin and skin structure infections in the patients at risk: carrier state of *Staphylococcus aureus*. *Am J Med* 1984; **76**: 166–71.
30 Kellum RE, Strangfeld K, Ray LF. Acne vulgaris. Studies in the pathogenesis. Triglyceride hydrolysis by *Corynebacterium acnes in vitro*. *Arch Dermatol* 1970; **101**: 41–7.
31 Hentges DJ. The anaerobic microflora of the human body. *Clin Infect Dis* 1993; **16** (Suppl. 4): S175–80.
32 Marples RR, Downing DT, Kligman AM. Control of fatty acids in human surface lipids by *Corynebacterium acnes*. *J Invest Dermatol* 1971; **56**: 127–31.
33 Jackman PJH. Body odour—the role of skin bacteria. *Semin Dermatol* 1982; **1**: 143–8.
34 Chiller K, Selkin BA, Murakawa GJ. Skin microflora and bacterial infections of the skin. *J Invest Dermatol Symp Proc* 2001; **6**: 170–4.
35 Suter L, Rabbat RM, Nolting S. Gram-negative infection of the foot. *Mykosen* 1979; **22**: 109–14.
36 Beachey EH. Bacterial adherence: adhesin receptor interactions mediating the attachment of bacteria to mucosal surfaces. *J Infect Dis* 1981; **143**: 325–45.
37 Carruthers MM, Kabat WJ. Mediation of staphylococcal adherence to mucosal cells by lipoteichoic acid. *Infect Immun* 1983; **40**: 444–6.
38 Christensen GD, Simpson WA, Bisno AL *et al*. Adherence of slime producing strains of *Staphylococcus epidermidis* to smooth surfaces. *Infect Immun* 1982; **37**: 318–26.
39 Ricketts CR, Squire JR, Topley E. Human skin lipids with particular reference to the self-sterilizing power of the skin. *Clin Sci* 1951; **10**: 89–96.
40 Lacey RW. Loss of antibacterial action of skin after topical neomycin. *Br J Dermatol* 1969; **81**: 435–9.
41 Shinefield HR, Ribble JC, Eichenvald HF *et al*. Bacterial interference. In: Maibach HI, Hildick Smith G, eds. *Skin Bacteria and their Role in Infection*. New York: McGraw Hill, 1965: 235–52.
42 Braff MH, Bardan A, Nizet V *et al*. Cutaneous defense mechanisms by antimicrobial peptides. *J Invest Dermatol* 2005; **125**: 9–13.

Gram-positive bacteria

Staphylococcus aureus

Staphylococcus aureus, distinguished from other staphylococci by a positive test for coagulase [1], is among the most important causes of skin infections and of serious, and sometimes fatal, systemic disease. Many of the conditions of modern life have tipped the precarious balance between commensalism and parasitism in its favour. Crowded cities and hospitalization of the sick provide increased opportunities for dissemination of the organism, and the wide use of antibiotics results in selective survival of resistant strains.

Carriage

The frequency with which *S. aureus* can be isolated from the skin has been extensively studied by many different techniques. If a sufficient number of sites are sampled frequently enough, the carrier rate may approach 100%, especially if enrichment culture techniques are used. With conventional cultural techniques and random sampling, approximate rates for the resident carriage sites of *S. aureus* on the skin are: anterior nares 35%, perineum 20%, axillae 5–10% and toe webs 5–10% [2]. Resident carriage on other, dry, healthy skin surfaces is believed not to occur, but contamination from carriage sites is common, notably of the hands from the nose. In the same person, different phage types may colonize different areas.

Nasal carriage has been studied in most detail. Serial examinations suggest that some 20% of individuals are persistent nasal carriers, 60% are intermittent carriers and 20% are resistant to nasal colonization [2]. Persistent carriers have higher numbers of organisms than intermittent carriers and this may lead to more extensive dispersal of bacteria [3]. A long-term study over 8 years showed that 71% of persistent *S. aureus* nasal carriers remained carriers over the 8 years [3]. The strains isolated were genetically very similar, suggesting that nasal carriage with a specific strain may persist for several years. Intermittent carriers tend to exchange *S. aureus* strains. It is estimated that about 6% of carriers may carry more than one strain of *S. aureus* in the nose, and this may facilitate exchange of genetic material, which may be very important in deciding how to treat these individuals [4].

Genetic factors, perhaps involving bacterial adherence and immune responses, are suggested by higher nasal carriage rates in white than black skinned individuals, by studies of families and twins, by higher-than-normal rates in patients with phenylketonuria, by increased adherence in atopic eczema and by an association of nasal carriage with human leukocyte antigen (HLA)-DR3 [5–10].

In those susceptible to nasal colonization, the overall rate depends on the extent to which the many transient carriers acquire the organism by contact with persistent carriers. This at least partly underlies the increase in carriage rates following hospital admission [2], higher rates in urban than in rural areas [11] and variation in carriage rates with age.

The neonatal nose and umbilical stump [12] tend to be rapidly colonized by *S. aureus*, perhaps partly because colonization by saprophytic cocci has not yet taken place. The nasal carriage rates are rather higher (e.g. 72%) [13] in infants born in hospital and lower in those receiving antiseptics on the umbilicus. The hospital-born baby may transmit infection to other family members [14]. The nasal carriage rate falls to a minimum of 10–15% at the age of 1 year and rises again to reach adult levels by age 5 years [13].

Within the nasal passage, the anterior nares are the most readily colonized parts and are the site usually sampled. It seems that the relative lack of host defences in this area facilitates growth of the organism. However, carriage of *S. aureus* on the mucosal surfaces of the turbinates is common, and recolonization by these organisms may partly explain the difficulty of eradicating nasal *S. aureus* by topical therapy [2].

High rates of nasal carriage in atopic eczema (79%) [15] may partly derive from the heavy load of *S. aureus* on the skin, but increased adhesion of the organism to nasal mucosal cells may be relevant [9]. As a primary reservoir of *S. aureus*, nasal carriage has been identified as a major risk factor for the subsequent development of community-acquired and nosocomial infections.

Those patients on ambulatory peritoneal or haemodialysis, who carry *S. aureus* in the nose, are much more likely to get infection of the exit sites, usually with the same bacterial strain [2]. Patients with HIV infection, and AIDS related diseases, have higher carriage rates of *S. aureus* than normal, even when intravenous drug users are excluded among the HIV-positive individuals, and this is a risk factor for the subsequent severe infection with *S. aureus* [16]. The underlying mechanism for this is as yet unclear.

Various surface components of *S. aureus,* such as teichoic acid, lipoteichoic acid, fibronectin-binding proteins, and type 5 and type 8 capsular polysaccharides, have all been implicated as substances responsible for, or contributing to, binding of the organism in the nose [2]. However, not all have been successfully confirmed.

Intestinal carriage of *S. aureus* is particularly common among hospitalized patients, and this may be associated with transmission of the organism to the skin. The organism was identified not only in the nose (45%), but also in the stool (36%) of 71 hospitalized subjects [17]. The majority of these patients were persistent stool carriers. Furthermore, swabs done from environmental surfaces, such as the bedside table, showed contamination of these surfaces too. Molecular typing of the organisms showed some of the isolates from the nose and stool were clonally identical to those from the environmental sources [17].

Suppression of carriage of *S. aureus.* Nasal carriage of *S. aureus* is physiological and is not in itself an indication for treatment. Reasonable indications include prophylaxis in those whose occupations would render staphylococcal dispersal a significant hazard to others, such as operating theatre and neonatal nursery staff, and confirmed carriers among patients suffering frequent recurrences of staphylococcal infection and their household contacts [18].

Permanent eradication of carriage of *S. aureus* is not possible, but temporary elimination or a substantial reduction in numbers may be of significant clinical benefit. If the organism is cleared, eventual recolonization is to be expected, as was confirmed in a study of an isolated and well-motivated group of 28 men in an Antarctic base [19]. Whether this is a treatment failure, or subsequent infection from an exogenous source, is still unclear.

Wegener's granulomatosis seems to relapse more frequently in those with nasal carriage of *S. aureus*. Although the mechanism for this has not been identified yet [20], it would seem prudent to try and minimize the nasal carriage.

Although there are no long-term studies to identify the best method of reducing carriage, regular, long-term application of chlorhexidine cream to the appropriate sites (anterior nares, perineum or axillae) and use of an antiseptic, typically chlorhexidine or povidone-iodine, in a detergent base for daily bathing or showering including hair washing, are effective in clinical practice, although recolonization occurs soon after treatment is stopped. Povidone-iodine has some *in-vitro* activity against *S. aureus* and may be helpful with nasal carriage [21].

Oral or topical antibiotics may contribute to elimination of the organism, but in general recolonization occurs soon after the treatment is stopped [22], with two main exceptions. Intranasal mupirocin eliminated nasal *S. aureus* after a 5-day course in all patients treated, and 50% remained free of the organism after 5 months [23]. In haemodialysis patients oral rifampicin, 600 mg daily for 7–10 days cleared the organism for 3 months in 80% of cases [24]. Good results also were obtained with long-term, low-dose clindamycin, 150 mg daily for 3 months [25]. The staphylococci have become resistant to many antibiotics over the past few decades while therapeutic options have decreased.

Bacterial interference. Nasal inoculation of *S. aureus* strain 502A, of relatively low virulence, has been advocated as an artificial method of achieving bacterial interference against more virulent strains. In a study of families with recurrent furunculosis, colonization with strain 502A persisted for 6 months in 83% of treated patients and the infections became much less frequent [26]. However, strain 502A may cause occasionally severe infections, including a case of fatal septicaemia [27], and its use cannot be generally recommended.

Colonization of diseased skin by *S. aureus*

Moist lesions, and those in which the integrity of the epidermal barrier is disrupted, are readily colonized by *S. aureus*. Loss of a physical barrier against invasion is one factor, but the reported inactivation by serum of the inhibitory effect on *S. aureus* of linolenic acid [28] is of interest.

In atopic eczema high numbers of *S. aureus* are present. The organism can be isolated from 91% of chronic plaques and 100% of acute exudative lesions [15] and from uninvolved skin in 76% of patients. Numbers of *S. aureus* correlate with the severity of the eczema [29]. Adherence of *S. aureus* to nasal mucosal and skin epithelial cells [9], including specifically corneocytes [30], is increased in atopic eczema. Patients taking retinoids may develop mucocutaneous side effects, such as cheilitis and blepharoconjunctivitis. These are often associated with *S. aureus* infection.

Biologically active substances produced by *S. aureus* [31,32]

S. aureus can produce several toxins, some of which contribute to invasion and survival of the organism in the tissues. More specifically in the dermatological context are the exfoliative toxins [31] (epidermolytic toxins ET-A and ET-B) responsible for the generalized staphylococcal scalded skin syndrome and bullous impetigo. TSST-1 (toxic shock toxin) is involved in toxic shock syndrome. Staphylococcal scarlatina is thought to be mediated by

staphylococcal erythrogenic toxin or other byproducts of the organism. Superantigens from *S. aureus* may affect the evolution of atopic dermatitis. These bacterial pyrogenic toxin superantigens are encoded by a series of distinct mobile elements referred to as staphylococcal pathogenicity islands. A variety of PCR-based tests are now able to identify the genes responsible for the production of these toxins by different strains of *S. aureus* [31]. This is useful when evaluating the pathogenic potential of isolates and tracking their spread through hospitals and communities.

Panton–Valentine leukocidin is a cytotoxin causing septicaemia, skin necrosis and severe necrotizing pneumonia. The leukocidal toxin genes are detected more frequently from blood culture isolates of *S. aureus* than nasal carriage ones [31], and they may act synergistically with other virulence factors associated with the same organism.

Staphylococcal cell-wall products (teichoic acid, peptidoglycan and protein A) exert many effects on the host immune system [33,34]. Protein A may be involved in adherence of the bacterium to the host cell [30], and it can bind to the Fc portion of IgG in addition to the specific Fab fragment of IgE [35].

Resistance to staphylococcal infection

The main host defence against invading staphylococci is ingestion and killing by phagocytes. Antibodies to various *S. aureus* antigens are universally found, but appear to make a relatively small contribution to host defences and are of limited diagnostic and prognostic value [35]. Cell-mediated responses to *S. aureus* occur but their role in immunity is uncertain.

Resistance to staphylococcal infection is reduced in patients with poorly controlled diabetes [36], renal insufficiency, haematological malignancies, nutritional deficiency or alcoholism, and in those receiving corticosteroid or cytotoxic therapy. In acquired immune deficiency syndrome (AIDS), staphylococcal bacteraemia may occur [37], and angular stomatitis, facial impetigo and folliculitis are common (Chapter 35). The increased incidence of *S. aureus* infections in patients on retinoids may be partly due to increased adherence to epithelial cells [38].

Pure deficiency of cell-mediated immunity appears not to predispose to staphylococcal cutaneous infection. Immunoglobulin deficiency, including selective IgM deficiency [39], may contribute to staphylococcal skin infection, as may certain deficiencies of the complement system (Chapter 13).

In the Chediak–Higashi syndrome and chronic granulomatous disease, deficiencies of granulocyte function underlie a strong predisposition to staphylococcal and other infections. An isolated deficiency of neutrophil killing function in two siblings responded to ascorbic acid [40]. Cyclical neutropenia has also been associated with recurrent infected eczema [41].

In Job's syndrome and Buckley's syndrome [42] an increased incidence of severe staphylococcal infection is associated with eczema, markedly raised serum levels of IgE and defective neutrophil chemotaxis [43]. Staphylococcal and other infections are associated with eczema in the Wiskott–Aldrich syndrome, in which a number of immunological abnormalities occur inconstantly, including hyper-IgE. Recurrent pyoderma and folliculitis with atopic eczema were associated with deficiencies in both lymphocyte and granulocyte function in a boy and his father. The clinical and immunological abnormalities responded to conventional (H_1) antihistamine treatment [44].

Table 30.1 Involvement of *Staphylococcus aureus* in cutaneous disease.

Direct infection of skin and adjacent tissues
Impetigo
Ecthyma
Folliculitis
Furunculosis
Carbuncle
Sycosis
Occasionally in cellulitis
Others
Secondary infection
Eczema, infestations, ulcers, etc.
Cutaneous disease due to effect of bacterial toxin
Staphylococcal scalded skin syndrome
Toxic shock syndrome
Staphylococcal scarlatina
Recurrent toxin-mediated perineal erythema

Cutaneous staphylococcal infection

The main skin diseases due to *S. aureus* are listed in Table 30.1.

The staphylococci produce infections by various routes. These include direct invasion, by haematogenous spread of the organisms or by the toxins they produce.

***S. aureus* and eczema.** *S. aureus* is very frequently isolated, often in heavy growth, from lesions of eczema, especially of atopic type. The extent to which the bacteria may play a pathogenic role in the eczema has been investigated thoroughly [45].

In true infective eczema, bacteria, including *S. aureus*, are regarded as the primary stimulus for an eczematous response, although the mechanisms are uncertain.

Cytotoxic antibody and IgE reactions against bacterial (including *S. aureus*) antigens may be important in atopic and discoid eczema [46].

S. aureus was isolated from 14 of 20 children with infantile seborrhoeic dermatitis, but its pathogenicity was uncertain [47].

Secondary colonization and infection have been studied most in atopic eczema; there is a high rate of staphylococcal carriage in this condition. The staphylococci have been shown to adhere more readily to the skin of atopics, even on non-lesional skin compared with normal individuals. When overt signs of infection are present, a pathogenic role is generally accepted. There is also evidence that high bacterial density (over $10^6/cm^2$) on lesions, short of overt signs of clinical infection, significantly aggravates the eczema [29]. The staphylococci produce exotoxins with superantigenic properties, which cause T-cell activation, cytokine release and mast-cell degranulation [45,48]. Superantigens trigger Langerhans cell migration into regional lymph nodes, where they interact with T cells, which recirculate into the skin, causing augmentation of the skin immune response. These superantigens are thought to negate the effects of topical steroids. This may explain why, when bacteria are regarded as significant in a case of eczema, combined steroid and antibacterial therapy is appropriate [45].

In atopic dermatitis there also seems to be a reduction in the level of antimicrobial peptides which lyse the outer membrane of microbes. This in turn leads to a reduction in innate immunity and results in the inability of atopics to react to the load of staphylococci. Whether this is a genetic abnormality or secondary to other factors remains to be determined [45].

Atopic dermatitis is characterized by a complex of immunological abnormalities, involving interactions between IgE-bearing antigen-presenting cells, T-cell activation, mast-cell degranulation, and a combination of immediate and cellular immune responses [49]. Atopic dermatitis patients are frequently colonized with microorganisms, and skin infections are common. Recently, the importance of exposure to microbial, particularly staphylococcal superantigens, has been investigated. Following exposure, T and dendritic cells are recruited to the area, and induce inflammation. One of the chemokines expressed is CC chemokine ligand 18. This was shown to be relevant in the recruitment of the pro-inflammatory cells [50].

Antibiotic resistance

The application of antibiotics to the skin with its large potential culture area and its resident flora may increase the likelihood of the development or the transfer of antibiotic resistance [51]. Of special importance is gentamicin resistance, which can be transferred between strains of *S. aureus*, and also between coagulase-negative staphylococci and *S. aureus* [51].

Gentamicin should not be used as a first-line topical antibiotic. Topical fusidic acid and mupirocin were previously associated with a low incidence of resistance when used to treat acute infections in the community setting. This is no longer the case as fusidic acid resistance, and mupirocin resistance, have been reported widely [52,53].

Methicillin-resistant *Staphylococcus aureus* (MRSA). Resistance to the antibiotic methicillin was reported first in 1961 [54]. Over the past few decades, epidemics of methicillin-resistant *S. aureus* infection have increased in frequency throughout the world. Many hospitals have had to institute control measures to contain the spread of the infection [55]. Once established in hospitals, its survival seems to be promoted by the widespread use of antibiotics. New clones of MRSA may follow changes in the antibiotic usage [56]. Resistance to antibiotics occurs when an organism acquires a gene that allows the microbe to inactivate the antibiotic. This may occur spontaneously as a genetic mutation, or involve the acquisition of a mobile genetic element such as a plasmid, transposon, integron or gene cassette [57]. Unfortunately, MRSA carriage on the skin may persist for years, and increases the risk of spread if patients who are carriers are readmitted to hospital [58]. The risk factors identified for patients developing MRSA infection include previous antibiotic use, contact with a health-care worker or nursing home resident, residence in a long-term care facility, admission to an intensive care unit, intravenous drug use, indwelling devices, haemo- or peritoneal dialysis, nasogastric or other invasive tubes, immunosuppression and surgical procedures. Outcomes for patients infected with MRSA are worse than for those with methicillin-sensitive *S. aureus*. Identifying patients with MRSA as they are admitted to hospital would allow isolation, in an attempt to reduce exposure of other patients. However, this requires significant resources, and perhaps screening high-risk groups of patients, with some of the above mentioned risk factors, would target the investigations and be more cost-effective [59]. In the UK, most MRSA infections occur in older patients (82% over 60 years of age), the vast majority of strains are resistant to fluoroquinolones and macrolides, and are mupirocin resistant [56].

Vancomycin has traditionally been the drug of choice for treating these infections, but as treatment has to be given intravenously the duration of hospital stay is often prolonged. This increases the cost of the hospital stay, and also exposes the patient to further nosocomial infections [55]. Furthermore, the appearance of strains of staphylococci with clinical resistance to vancomycin and teicoplanin is now not uncommon. Guidelines for the treatment of MRSA infections have been published [56] and are regularly updated.

Community-acquired methicillin-resistant staphylococcal infections have become common recently, with infections reported worldwide including military personnel, prison inmates, intravenous drug users, athletes and homeless people [60]. The majority of the infections present as abscesses or folliculitis. The staphylococci are genetically distinct from those acquired in the hospital setting and often carry the Pontin Valentin leucocidin virulence gene, although there is now much cross over in the strains isolated from patients in hospital. These organisms are probably best described respectively as 'community-type' and 'health care/hospital-type' strains without specific regard for where the infection was actually acquired. Although most patients presenting with community-type staphylococcal infections will respond to drainage of the abscess, some develop bacteraemia which may require systemic antibiotic therapy [54]. The choice of antibiotic should reflect the sensitivities, and many strains are still sensitive to trimethoprimsulphamethazole and tetracycline. Resistance to fluoroquinolones and erythromycin, and thus clindamycin, limits their use. Linezolid is still currently beneficial although it is expensive. Unfortunately, multidrug resistant community-acquired MRSA has been reported [61].

References

1 Lowy FD. *Staphylococcus aureus* infections. *N Engl J Med* 1998; **339**: 520–32.
2 Kluytmans J, van Belkum A, Verbrugh H. Nasal carriage of *Staphylococcus aureus*: Epidemiology, underlying mechanisms and associated risks. *Clin Microbiol Rev* 1997; **10**: 505–20.
3 VanderBergh MF, Yzerman EP, van Belkum A *et al*. Follow up of *Staphylococcus aureus* nasal carriage after 8 years: redefining the persistent carrier state. *J Clin Microbiol* 1999; **37**: 3133–40.
4 Cespedes C, Said-Salim B, Miller M *et al*. The clonality of *Staphylococcus aureus* nasal carriage. *J Infect Dis* 2005; **191**: 444–52.
5 Aly R, Shinefield HI, Strauss WG *et al*. Bacterial adherence to nasal mucosal cells. *Infect Immun* 1977; **17**: 546–9.
6 Millian SJ, Baldwin JN, Rheins MS *et al*. Studies on the incidence of coagulase-positive staphylococci in a normal unconfined population. *Am J Publ Health* 1960; **50**: 791–8.
7 Noble WC, Valkenburg HA, Walters HL. Carriage of *Staphylococcus aureus* in random samples of a normal population. *J Hyg* 1967; **65**: 567–73.
8 Spink M, Strong S. A possible hereditary factor in the nasal carriage of staphylococci. *Lancet* 1966; **1**: 1337–9.
9 Bibel DJ, Aly R, Shinefield HR *et al*. Importance of the keratinized epithelial cell in bacterial adherence. *J Invest Dermatol* 1982; **79**: 250–3.
10 Kinsman OS, McKenna R, Noble WC. Association between histocompatibility antigens (HLA) and nasal carriage of *Staphylococcus aureus*. *J Med Microbiol* 1983; **16**: 215–20.

11 Schubert O. Studien über pathogene Staphylokokken in Südosteuropäischen und mediterranen geographischen Einheiten. *Z Hyg Infect Krankh* 1951; **132**: 465–76.
12 Rotimi VO, Duerden BI. The development of the bacterial flora in normal neonates. *J Med Microbiol* 1981; **14**: 51–62.
13 Burr ML, Howells CHL. Nasal staphylococci in children. *J Hyg* 1982; **88**: 433–7.
14 Kundsin RB, Walter CW, Ipsen J *et al*. Ecology of staphylococcal disease. *JAMA* 1963; **185**: 159–62.
15 Aly R. Bacteriology of atopic dermatitis. *Acta Derm Venereol (Stockh)* 1980; Suppl. **92**: 16–8.
16 Luzar MA, Coles GA, Faller B *et al*. *Staphylococcus aureus* nasal carriage and infection in patients on continuous ambulatory dialysis. *N Engl J Med* 1990; **322**: 505–9.
17 Bhalla A, Aron DC, Donskey C. *Staphylococcus aureus* intestinal colonization is associated with increased frequency of *S. aureus* on the skin of hospitalized patients. *BMC Infect Dis* 2007; **7**: 105–11.
18 Leigh DA. Treatment of familial staphylococcal infection. *J Antimicrob Chemother* 1979; **5**: 497–9.
19 Krikler SJ. *Staphylococcus aureus* in Antarctica: carriage and attempted eradication. *J Hyg* 1986; **97**: 427–44.
20 Stegeman C, Tervaert JW, Sluiter W *et al*. Association of chronic nasal carriage of *S. aureus* and higher relapse rates in Wegener's granulomatosis. *Ann Intern Med* 1994; **120**: 121–7.
21 Hill RL, Casewell MW. The in-vitro activity of povidone-iodine cream against *Staphylococcus aureus* and its bioavailability in nasal secetions. *J Hosp Infect* 2000; **45**: 198–205.
22 Hirschmann JV. Topical antibiotics in dermatology. *Arch Dermatol* 1988; **124**: 1691–1700.
23 Wheat LJ, Kohler RB, White A. Treatment of nasal carriers of coagulase-positive staphylococci. In: Maibach HI, Aly R, eds. *Skin Microbiology: Relevance to Clinical Infection*. New York: Springer, 1981: 50–8.
24 Chow JW, Yu VL. *S. aureus* nasal carriage in hemodialysis patients. Its role in infection and approaches to prophyloaxis. *Arch Int Med* 1989; **149**: 1258–62.
25 Klempner MS, Styrt B. Prevention of recurrent staphylococcal skin infections with low-dose oral clindamycin therapy. *JAMA* 1988; **260**: 2682–5.
26 Steele RW. Recurrent staphylococcal infections in families. *Arch Dermatol* 1980; **116**: 189–90.
27 Houck PW, Nelson JD, Kay JL. Fatal septicemia due to *Staphylococcus aureus* 502A. *Am J Dis Child* 1972; **123**: 45–8.
28 Lacey RW, Lord VL. Sensitivity of staphylococci to fatty acids: novel inactivation of linolenic acid by serum. *J Med Microbiol* 1981; **14**: 41–9.
29 Williams REA, Gibson A, Lever R *et al*. A comparison of quantitative sampling techniques of bacterial flora in atopic dermatitis and correlation with clinical state. *Br J Dermatol* 1989; **121** (Suppl. 34): 39–42.
30 Cole GW, Silverberg NL. The adherence of *Staphylococcus aureus* to human corneocytes. *Arch Dermatol* 1986; **122**: 166–9.
31 Becker K, Bierbaum G, von Eiff C *et al*. Understanding the physiology and adaptation of staphylococci: A post-genomic approach. *Int J Med Microbiol* 2007; **297**: 483–501.
32 Ginsburg CM. Staphylococcal toxin syndromes. *Pediatr Infect Dis J* 1991; **10**: 319–21.
33 Chen W-Y, Sager S, Tung E *et al*. Human peripheral blood lymphocyte activation by protein A from *Staphylococcus aureus*. *Infect Immun* 1982; **36**: 59–65.
34 Neuber K, Konig W. Effects of *Staphylococcus aureus* cell wall products (teichoic acid, peptidoglycan) and enterotoxin B on immunoglobulin (IgE, IgA, IgG) synthesis and CD23 expression in patients with atopic dermatitis. *Immunology* 1992; **75**: 23–8.
35 Friedmann SJ, Schroeter AL, Homburger HA. IgE antibodies to *Staphylococcus aureus*. *Arch Dermatol* 1985; **121**: 869–72.
36 Wang YR, Margolis D. The prevalence of diagnosed cutaneous manifestations during ambulatory diabetes visits in the United States, 1998–2002. *Dermatol* 2006; **212**: 229–34.
37 Jacobson MA, Gellermann H, Chambers H. *Staphylococcus aureus* bacteremia and recurrent staphylococcal infection in patients with acquired immunodeficiency syndrome and AIDS-related complex. *Am J Med* 1988; **85**: 172–6.
38 Lianou P, Bassaris H, Vlachodimitropoulos D *et al*. Acitretin induces an increased adherence of *S. aureus* to epithelial cells. *Acta Derm Venereol (Stockh)* 1989; **69**: 330–2.
39 Yocum MW, Strong DM, Chusid MJ *et al*. Selective immunoglobulin M (IgM) deficiency in two immunodeficient adults with recurrent staphylococcal pyoderma. *Am J Med* 1976; **60**: 486–94.
40 Rebora A, Crovata F, Dallegri F. Repeated staphylococcal pyoderma in two siblings with defective neutrophil bacterial killing. *Dermatologica* 1980; **160**: 106–12.
41 Parodi A, Parentini AM, Rebora A. Recurrent impetiginized eczema as a presenting manifestation of cyclic neutropenia. *Clin Exp Dermatol* 1993; **18**: 80–2.
42 Rebora A, Nunzi E, Pezzuolo M *et al*. Buckley's syndrome. *Br J Dermatol* 1978; **99**: 569–72.
43 Schopfer K, Baerlocher K, Price P *et al*. Staphylococcal IgE antibodies, hyperimmunoglobulinemia E and *Staphylococcus aureus* infections. *N Engl J Med* 1979; **300**: 835–8.
44 Jung LKL, Engelhard D, Kapoor N *et al*. Pyoderma, eczema and folliculitis with defective leucocyte and lymphocyte function. *Lancet* 1983; **2**: 185–7.
45 Leung D. Superantigens, steroid insensitivity and innate immunity in atopic eczema. *Acta Derm Venereol* 2005; Suppl. **215**: 11–5.
46 Hanifin JM, Lobitz WC. Newer concepts of atopic dermatitis. *Arch Dermatol* 1977; **113**: 663–70.
47 Broberg A, Faergemann J. Infantile seborrhoeic dermatitis and *Pityrosporum ovale*. *Br J Dermatol* 1989; **120**: 359–62.
48 Jappe U. Superantigens and their association with dermatological inflammatory disease: facts and hypotheses. *Acta Derm Venereol* 2000; **80**: 321–8.
49 Miraglia del Giudice M, Decimo F, Leonardi S *et al*. Immune dysregulation in atopic dermatitits. *Allergy Asthma Proc* 2006; **27**: 451–5.
50 Pivarcsi A, Gombert M, Dieu-Nosjean M-C *et al*. Chemokine Ligand 18 an atopic dermatitis-associated and dendritic cell-derived chemokine, is regulated by staphylococcal products and allergen exposure. *J Immunol* 2004; **173**: 5810–17.
51 Noble WC, Naidoo J. Evolution of antibiotic resistance in *Staphylococcus aureus*: the role of the skin. *Br J Dermatol* 1978; **98**: 481–9.
52 Simor AE, Stuart TL, Louie L *et al*. Mupirocin-resistant, methicillin-resistant *Staphylococcus aureus* strains in Canadian hospitals. *Antimicrob Agents Chemother* 2007; **51**: 3880–6.
53 Sule O, Brown NM, Willocks LJ *et al*. Fusidic acid-resistant *Staphylococcus aureus* (FRSA) carriage in patients with atopic eczema and pattern of prior topical fusidic acid use. *Int J Antimicrob Agents* 2007; **30**: 78–82.
54 Cohen PR. Community-acquired methicillin-resistant *Staphylococus aureus* skin infections: a review of epidemiology, clinical features, management and prevention. *Int J Dermatol* 2007; **46**: 1–11.
55 Lodise TP, McKinnon PS. Burden of methicillin-resistant *Staphylococcus aureus*: focus on clinical and economic outcomes. *Pharmacother* 2007; **27**: 1001–12.
56 Gemmell CG, Edwards DI, Fraise AP *et al*. Guidelines for the prophylaxis of methicillin-resistant *Staphylococcus aureus* (MRSA) infections in the UK. *J Antimicrob Chemother* 2006; **57**: 587–8.
57 Muto C, Jernigan J, Ostrowsky BE *et al*. SHEA guideline for preventing nosocomial transmission of multidrug resistant strains of *Staphylococcus aureus* and *Enterococcus*. *Infect Cont Hosp Ep* 2003; **24**: 362–86.
58 Sanford MD, Widmer AF, Bale M *et al*. Efficient detection of long-term persistence of the carriage of methicillin-resistant *Staphylococcus aureus*. *Clin Infect Dis* 1994; **19**: 1123–8.
59 Hidron AI, Kourbatova E, Halvosa JS *et al*. Risk factors for colonisation with methicillin-resistant *Staphylococcus aureus* in patients admitted to an urban hospital: Emergence of community-associated MRSA nasal carriage. *Clin Infect Dis* 2005; **41**: 159–66.
60 Elston DM. Community-acquired methicillin-resistant *Staphylococcus aureus*. *J Am Acad Dermatol* 2007; **56**: 1–16.
61 Takizawa Y, Teneike I, Nakagawa S *et al*. A Panton-Valentine leucocidin (PVL)-positive community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) strain, another such strain carrying a multiple-drug resistance plasmid, and other more typical PVL-negative MRSA strains found in Japan. *J Clin Microbiol* 2005; **43**: 3356–63.

Coagulase-negative staphylococci

These organisms are members of the normal skin flora and contribute to resistance against colonization by pathogenic bacteria [1].

Staphylococcus epidermidis [2] is the main pathogen of the group. In the otherwise healthy patient it is probably an occasional cause of minor skin infections, including superficial folliculitis, although its significance in an individual case may be difficult to judge. Secondary infection of pre-existing dermatoses, such as eczema, seems not to occur. *S. epidermidis* may cause infections in wounds and especially around implanted surgical devices. The ability to adhere to foreign bodies and produce extracellular slime during the course of colonization is thought to be important for pathogenicity [3]. The organism is able to adhere initially to the device and then also produces clusters which are multilayered. The glucosamine polymer PIA is a major contributor. The genes encoding for the biosynthesis of PIA are well recognized. The biofilm produced is important for the pathogenesis as it seems to be tolerant of antibiotics and may contribute to its persistence. The mechanisms involved in the epidemiology and pathogenesis of infection caused by coagulase-negative staphylococci have been discussed in detail by Becker *et al.* [3]. It has been increasingly recognized as a cause of major internal infections, including endocarditis [4] and septicaemia, especially in patients with immune deficiencies. A case of cellulitis in a woman with acute myelocytic leukaemia was reported [5], and the organism has been associated with vasculitis in a patient on cytotoxic therapy for ovarian carcinoma [6]. A single isolate of *S. epidermidis* from blood culture could be due to contamination, but if found repeatedly it may be regarded as probably significant. *S. saprophyticus* is a recognized cause of urinary tract infection, especially in young women [7].

Multiple antibiotic resistance is common and may be transferred to *S. aureus*.

References

1 Chiller K, Selkin BA, Murakawa G. Skin microflora and bacterial infections of the skin. *J Invest Dermatol Symp Proc* 2001; **6**: 170–4.

2 Gemmell CG. Coagulase-negative staphylococci. *J Med Microbiol* 1986; **22**: 285–95.

3 Becker K, Bierbaum G, von Eiff C *et al*. Understanding the physiology and adaptation of staphylococci: a post genomic approach. *Int J Med Microbiol* 2007; **297**: 483–501.

4 Van Eldere J, Peetermans WE, Struelens M *et al*. Polyclonal staphylococcal endocarditis caused by genetic variability. *Clin Infect Dis* 2000; **31**: 24–30.

5 Pitlik S, Fainstein V. Cellulitis caused by *Staphylococcus epidermidis* in a patient with leukemia. *Arch Dermatol* 1984; **120**: 1099–100.

6 Cantwell AR, Kelso DW. Cutaneous vasculitis associated with *Staphylococcus epidermidis*. *Am J Dermatopathol* 1982; **4**: 381–3.

7 Pead L, Maskell R, Morris J. *Staphylococcus saprophyticus* as a urinary pathogen: a six year prospective survey. *BMJ* 1985; **291**: 1157–9.

Streptococci

The streptococci are Gram-positive, catalase-negative cocci characteristically arranged in chains. They are nearly all facultative anaerobes, that is they can grow aerobically or anaerobically [1].

The Lancefield Group antigens have been the usual basis for routine classification of streptococci, and most laboratories still use these. There are at least 18 (A to R). The system covers not only the β-haemolytic streptococci to which it was originally applied, but also some α-haemolytic and non-haemolytic (γ-haemolytic) organisms. However, more detailed identification is now possible with molecular genetics, and some streptococci have been reclassified [1].

Table 30.2 Involvement of streptococci (mostly group A) in cutaneous disease.

Direct infections of skin or subcutaneous tissue
Impetigo
Ecthyma
Erysipelas
Cellulitis
Vulvovaginitis
Perianal infection
Streptococcal ulcers
Blistering distal dactylitis
Necrotizing fasciitis
Others
Secondary infection
Eczema, infestations, ulcers, etc.
Tissue damage from circulating toxin
Scarlet fever
Toxic-shock-like syndrome
Recurrent toxin-mediated perineal erythema
Skin lesions attributed to allergic hypersensitivity to streptococcal antigens
Erythema nodosum (Chapter 50)
Vasculitis (Chapter 50)
Skin disease provoked or influenced by streptococcal infection (mechanism uncertain)
Psoriasis, especially guttate forms (Chapter 20)
Kawasaki disease

The involvement of streptococci in skin disease is summarized in Table 30.2.

Streptococcus pyogenes

The major streptococcal pathogens in humans belong to group A (GAS), collectively referred to as *Streptococcus pyogenes*. These may be subdivided according to M and T surface-protein antigens. The M proteins protect the organism against phagocytosis, affect adherence to different epithelial tissues and contribute to virulence. Currently, at least 150 different M protein sequence types have been identified using molecular approaches to identify the *emm* (M protein) genes [2]. The measurement of antibody production to M proteins is difficult to prepare in the laboratory, so measurement of opacity factor, a lipoproteinase which causes serum to increase in opacity, is used instead. Antibodies to opacity factor correlate with M type. T protein antigen is also present on the surface and genes for T protein have been investigated, particularly in outbreaks where M protein has not been identified. At least four of the possible 20 T antigens are pilus-like structures on the surface of the streptococci [3]. These structures are similar to those found in Gram-negative bacteria. C5a peptidase, a proteolytic enzyme on the surface of group A streptococci, inhibits the recruitment of phagocytic cells to the site of infection, and thus plays a role in the pathogenesis of streptococcal disease [4].

Streptococcal pyrogenic exotoxins, which include the erythrogenic toxins, play an important part in endotoxic shock, and have superantigenic effects on the immune system, resulting in massive cytokine production. Currently there are at least 12 recognized streptococcal superantigens [2].

Carriage. *S. pyogenes* is carried in the throat by about 10% of the normal population and in the anterior nares less frequently.

Carriage rates are higher after clinical infection. However, in persistent throat carriers, the streptococci are thought to be internalized after invading cells and thus avoid the host responses to elimination of the bacteria [4].

The normal skin does not provide a favourable habitat for *S. pyogenes*, perhaps due partly to a bactericidal effect of skin lipids [5], and transient skin carriage is found in only 0.5 to 1.0% of individuals [6]. However, the duration of survival of streptococci on the normal skin of patients with infections, and on the hands and arms of those handling such patients, may be sufficient to allow their dispersal by this route.

Asymptomatic anal carriage is an occasional source of significant infection in contacts [7].

Streptococci colonize damaged skin, although less readily than staphylococci. They can frequently be isolated from eczematous and other moist lesions, although the borderline between colonization and infection is often difficult to define.

Strains in skin and throat. *S. pyogenes* can be divided broadly into 'throat' and 'skin' serotypes. Stronger adherence of the former to mucosal cells and of the latter to skin cells, and better survival of the latter in oleic acid and in nutritionally poorer media, may be relevant [8]. Throat strains survive poorly on skin and are infrequently found on the healthy skin even of patients with streptococcal throat infection. The strains isolated from normal skin are usually those common in streptococcal pyoderma: in a study of endemic disease [9], colonization of normal skin preceded the development of lesions in a majority of patients. Small numbers of skin strains may colonize the throat or the nose, but no streptococcal respiratory disease occurred among 1300 cases of streptococcal pyoderma in a military establishment [10]. In a study from Australia where pyoderma is endemic, throat carriage of streptococci was markedly reduced compared to levels identified in temperate areas. This suggested that skin sepsis (which affected about 90% of the population) provided some immunity to streptococcal pharyngitis [11]. However, the mechanism for this is not clear and further research is needed to confirm this finding.

Initiation and complications of infection. On experimental application under occlusion to intact normal skin, several strains of *S. pyogenes* failed to cause disease and indeed rapidly died; localized superficial infection occurred only if the skin had been scarified [12].

It is widely assumed that skin damage, albeit minor, is necessary for the development of naturally occurring streptococcal pyoderma. For infection to occur, the streptococci need to adhere to the skin and at least 11 adhesins have been recognized including M protein, lipoteichoic acid and serum opacity factor, among others. These bind to various receptors in the skin, including fibronectin, fibrinogen, vitronectin and collagen. Once the organisms have adhered, they are capable of upregulating the expression of inflammatory mediators by keratinocytes and producing streptolysin O. The streptococci have also been shown to invade epithelial cells. The intracellular environment may be less hostile for their survival and may be responsible for carriage, particularly in the throat. This may also explain treatment failures [4].

Group A streptococci may also bind plasminogen to their surface proteins via surface-expressed enolase, and secreted streptokinase, and this facilitates invasion and encourages their spread through tissues [4].

Rheumatic fever is a complication of *S. pyogenes* pharyngitis, but occurs after pyoderma rarely if at all.

Acute glomerulonephritis follows both throat and skin infections with certain 'nephritogenic' serotypes of *S. pyogenes*. There are reports of glomerulonephritis infrequently following throat, but apparently not skin, infection with group C and group G streptococci [13,14]. Tics, Tourette's syndrome, obsessive compulsive disorder and attention deficit disorder (PANDAS) have been linked to streptococcal infections [15].

Erythema nodosum and psoriasis are known to follow a streptococcal throat infection. Scleredema of Bushke has also been linked with streptococcal infection of the throat.

Management of carriage and control of epidemics. The mere presence of *S. pyogenes* in an asymptomatic subject is not in itself an indication for attempts to eradicate it. Furthermore, such attempts are often unsuccessful.

Different approaches may be considered [16]: surveillance of contacts of infected patients for clinical signs of infection; instruction in hygiene and use of antiseptics; bacteriological investigation for carriage of the organism in patients and asymptomatic contacts with a view to antibiotic treatment of positive cases; and routine penicillin administration to those at risk without prior bacteriological investigation. Factors affecting the policy in individual cases include the extent of the outbreak, the closeness of contact, a special risk of infectivity by virtue of occupation [10], and the actual or expected risk of nephritis (and, for throat infections, rheumatic fever). Residents in nursing homes may be at risk of infections with *S. pyogenes* because of the propensity of the organism to cause disease in the elderly, and the ability of the organism to spread from person to person [17].

Much work has already been done on a possible vaccine to prevent streptococcal infections [2].

Other streptococci

Group C [18] streptococci are relatively frequently found colonizing diseased skin, but they are occasional causes of impetigo, erysipelas and cellulitis. Group G streptococci [19] colonize the pharynx, intestine, vagina or skin and may be implicated in the aetiology of cellulitis or erysipelas in patients with vascular disease or those who have undergone cardiac surgery and venous ligation [20]. Where Group C or G streptococci have been involved in the aetiology of invasive disease, such as streptococcal toxic shock syndrome, underlying host factors such as malignancy or immunosuppression may have predisposed the individuals to the infections [21]. Group C streptococci have also been associated with acute rheumatic fever. Groups C and G streptococci share several virulence factors with proteins similar to the M protein of group A streptococci. Most of the Group C organisms have been identified as *S. dysgalactiae* subsp. *equisimilis* [1]. The recent increased number of severe infections caused by Group C and Group G streptococci may be related to better techniques available for isolating and identifying these organisms, increased virulence or an

enlarging population of compromised hosts [22]. However, the recent increase in the number of Group A infections was also thought to be related to increased virulence of the organism. A review of the data showed that widespread transmission of those strains prevalent in the population, their particular *emm* types, or superantigen genes, was more likely [23], and this may be so with Group C and G too.

Group B streptococci frequently colonize the anorectum (probably its natural habitat) and, secondarily, the vagina [7,24]. It is a major cause of severe infections especially in neonates [25]. Group B streptococci may be associated with invasive disease in adults, particularly in patients with chronic disease. In the skin, it appears to have a causal role in bacterial intertrigo, and may rarely cause erysipelas, cellulitis, necrotizing fasciitis and blistering distal dactylitis.

Group F streptococci may be important secondary pathogens in suppurative hidradenitis.

Group D streptococci (enterococci) are usually harmless, but have uncommonly been implicated in cellulitis and necrotizing fasciitis. These organisms only cause infection in previously damaged tissues. The enterococci have been given genus status distinct from streptococci since they differ from streptococci in many respects [1].

Lancefield group L streptococci have been reported to cause skin sepsis in two meat handlers [26] and in a patient with a facial abscess [27].

Of the α-haemolytic streptococci, *S. viridans* is commonly transferred to the skin of the face and hands from its normal habitat in the mouth; it seems to have little cutaneous significance.

Non-haemolytic streptococci are occasionally found as transients on the skin, but are feebly pathogenic under normal conditions.

Some of the microaerophilic, and the true anaerobic, streptococci may colonize wounds, and are important in progressive bacterial synergistic gangrene and some cases of necrotizing fasciitis [28].

Streptococcal serology

M protein and hyaluronic acid capsule are known to be responsible for the antiphagocytic properties of group A streptococci, and are therefore considered virulence factors. Anticapsule antibody is not opsonic and does not protect against infection by neutralizing the antiphagocytic effects of the capsule. Type-specific antibodies to the M proteins of group A streptococci persist for a few months or a year or two and protect against reinfection by the specific strain only.

The antistreptolysin O (ASO) titre is an indicator of previous infection by streptococci of groups A, C or G. The upper limit of normal is 200 units/ml and highest titres range from 2000 to 3000 units/ml. In streptococcal skin infection, however, the ASO response is weak and an unreliable guide to diagnosis.

Similarly, antibody to nicotinamide adenine dinucleotidase (NADase) may indicate group A, C or G infection but is unreliable in skin infection [20,29].

Antibodies to deoxyribonuclease (DNase) B [30] and to hyaluronidase are more regularly raised in streptococcal skin disease. DNase B antibodies are probably specific for group A streptococci. One hyaluronidase antibody is specific for group A, and another for groups C and G jointly [31]. Susceptibility of neonates to group B streptococcal infection is related to the level of capsular-type-specific antibodies in the maternal serum [21].

In some countries where streptococcal infection is common, the ASO titre may be persistently elevated so that raised titres may not be indicative of recent infection. More specific investigations may thus be required.

Genetic studies of the M (*emm)* gene superfamily have identified more than 20 genes. The IgG-binding protein gene has also been cloned and sequenced. The molecular basis of identification of bacteria has made diagnosis easier, but until this is available to more laboratories, standard serology and cultures continue to confirm diagnoses.

References

1 Facklam R. What happened to the streptococci: overview of taxonomic and nomenclature changes. *Clin Microbiol Rev* 2002; **15**: 613–30.

2 Darenberg J, Luca-Harari B, Jasir D *et al*. Molecular and clinical characteristics of invasive group A streptococcal infection in Sweden. *Clin Infect Dis* 2007; **45**: 450–8.

3 Mora M, Bensi G, Capo S *et al*. Group A *Streptococcus* produce pilus-like structures containing protective antigens and Lancefield T antigens. *PNAS* 2005; **102**: 15641–6.

4 Cunningham MW. Pathogenesis of Group A streptococcal infections. *Clin Microbiol Rev* 2000; **13**: 470–511.

5 Hentges DJ. The anaerobic microflora of the human body. *Clin Infect Dis* 1993; **16** (Suppl. 4): S175–80.

6 Wannamaker LW. Differences between streptococcal infections of the throat and of the skin. *N Engl J Med* 1970; **282**: 23–31, 78–85.

7 McKee WM, DiCaprio JM, Roberts CE *et al*. Anal carriage as the probable source of a streptococcal epidemic. *Lancet* 1966; **2**: 1007–9.

8 Noble WC. *Microbial Skin Disease: its Epidemiology*. London: Arnold, 1983.

9 Dillon HC. Post-streptococcal glomerulonephritis following pyoderma. *Rev Infect Dis* 1979; **1**: 935–43.

10 Cruikshank JG, Lightfoot NF, Sugars KH *et al*. A large outbreak of streptococcal pyoderma in a military training establishment. *J Hyg* 1982; **89**: 9–21.

11 McDonald MI, Towers RJ, Andrews RM *et al*. Low rates of streptococcal pharyngitis and high rates of pyoderma in Australian Aboriginal communities where acute rheumatic fever is hyperendemic. *Clin Infect Dis* 2006; **43**: 683–9.

12 Leyden JJ, Stewart R, Kligman AM. Experimental infections with Group A streptococci in humans. *J Invest Dermatol* 1980; **75**: 196–201.

13 Gnann JW, Gray BM, Griffin FM *et al*. Acute glomerulonephritis following Group G streptococcal infection. *J Infect Dis* 1987; **156**: 411–2.

14 Reid HFM, Bassett DCJ, Poon-King T *et al*. Group G streptococci in healthy school-children and in patients with glomerulonephritis in Trinidad. *J Hyg* 1985; **94**: 61–8.

15 Murphy ML, Pichichero ME. Prospective identification and treatment of children with paediatric autoimmune neuropsychiatric disorder associated with group A streptococcal infection (PANDAS). *Arch Pediatr Adolesc Med* 2002; **156**: 356–61.

16 Editorial. Streptococci in institutions. *Lancet* 1981; **1**: 311–2.

17 Anon. Nursing home outbreaks of invasive group A streptococcal infections—Illinois, Kansas, North Carolina and Texas. *MMWR* 1990; **39**: 577–9.

18 Salata RA, Lerner PI, Shlaes DM *et al*. Infections due to Lancefield Group C streptococci. *Medicine* 1989; **68**: 225–39.

19 Vartian C, Lerner PI, Shlaes DM *et al*. Infections due to Lancefield Group G streptococci. *Medicine* 1985; **64**: 75–87.

20 Nohlgard C, Bjorklind A, Hammar H. Group G streptococcal infections on a dermatological ward. *Acta Derm Venereol (Stockh)* 1992; **72**: 128–30.

21 Hashikawa S, Iinuma Y, Furushita M *et al*. Characterisation of Group C and G streptococcal strains that cause streptococcal toxic shock syndrome. *J Clin Microbiol* 2004; **42**: 186–92.

22 Pinho MD, Melo-Cristino J, Ramirez M. Clonal relationships between invasive and noninvasive Lancefield Group C and G Streptococci and emm-specific differences in invasiveness. *J Clin Microbiol* 2006; **44**: 841–6.

23 Rogers S, Commons R, Danchin MH *et al*. Strain prevalence rather than innate virulence potential is the major factor responsible for an increase in serious group A streptococcus infections. *J Infect Dis* 2007; **195**: 1625–33.
24 Dillon HC, Gray E, Pass MA *et al*. Anorectal and vaginal carriage of Group B streptococci during pregnancy. *J Infect Dis* 1982; **145**: 794–9.
25 Apgar BS, Grant Greenberg MS, Yen G. Prevention of Group B streptococcal disease in the newborn. *Am Fam Phys* 2005; **71**: 903–10.
26 Barnham M, Kerby J. Skin sepsis in meat handlers: observations on the causes of injury with special reference to bone. *J Hyg* 1981; **87**: 465–76.
27 Smalley DL, Doyle VR, Hollis CG *et al*. Facial abscess due to Group L streptococcal infection. *South Med J* 1982; **74**: 511–2.
28 Brook I, Frazier E. Clinical and microbiological features of necrotizing fasciitis. *J Clin Microbiol* 1995; **33**: 2382–7.
29 Leppard BJ, Seal DV, Colman G *et al*. The value of bacteriology and serology in the diagnosis of cellulitis and erysipelas. *Br J Dermatol* 1985; **112**: 559–67.
30 Schleftel J-M, Laplanche G, Freydiere M-H *et al*. Étude de la determination simultanée des antistreptolysines O et des antistreptodornase B au cours des infections streptococciques cutanées. *Ann Dermatol Vénéréol* 1982; **109**: 1031–6.
31 Wannamaker LW. Changes and changing concepts in the biology of Group A streptococci and in the epidemiology of streptococcal infections. *Rev Infect Dis* 1979; **1**: 967–73.

Impetigo

Definition. Impetigo is a contagious, superficial pyogenic infection of the skin. Two main clinical forms are recognized: non-bullous impetigo (or impetigo contagiosa of Tilbury Fox) and bullous impetigo. Bullous impetigo is accepted as a staphylococcal disease, although streptococcal bullous impetigo has been reported [1]. The non-bullous form may be caused by *Staphylococcus aureus*, by streptococci, or by both organisms together.

Bacteriology [2]. Non-bullous impetigo may be caused by both *S. aureus* and streptococci, but there has been controversy as to the relative importance of the two genera. This may partly depend on geographical variations, the streptococcal form being more prevalent in warmer climates. Some confusion may have been semantic, as some authors use the term pyoderma to apply to the streptococcal disease, reflecting the clinical differences between the two forms, and others regard pyoderma and impetigo as synonymous. *S. aureus* may be a secondary invader in streptococcal impetigo and in some such cases, depending on bacteriological techniques, it may be the predominant or the only isolate, and the evidence for streptococcal involvement may rest on serology [3].

Detailed studies of endemic pyoderma among children in the Red Lake Indian Reservation in northern Minnesota [4] detected both *S. aureus* and streptococci, each alone in a sizeable minority, but both together in 58% of cultures. Early lesions were more often purely streptococcal; in cases with both types the streptococci lasted longer, and the strain of *Staphylococcus* changed more often than that of the *Streptococcus*. The authors concluded that, in many of the mixed-culture cases, the disease was primarily streptococcal with *S. aureus* a secondary colonizer. Recent publications suggest that the staphylococci may be the predominant infectious agent in most areas [5].

The preponderance of group II phage types seen in bullous impetigo seems also to apply to the non-bullous staphylococcal disease [3]. In streptococcal impetigo, *Streptococcus pyogenes* is by far the commonest cause, but there are occasional infections with group G and group C organisms [6].

Bullous impetigo is a superficial cutaneous infection with *S. aureus*. The organism can generally be cultured from blister fluid. Injections of bacterial isolates from affected patients into newborn mice result in a generalized staphylococcal scalded skin syndrome (SSSS) [7]. Exfoliative (epidermolytic) toxin has been recovered from the blister fluid of some cases and is thought to act as a trypsin-like serine protease and cleave desmoglein 1 [8] to form the blister. The toxin is produced commonly, but not exclusively, by staphylococci of phage group II. In addition, both exfoliative toxins A and B act as superantigens, and stimulate B and T cells to proliferate [9]. The localization of the epidermal splitting in bullous impetigo compared with the widespread involvement in the generalized form is probably related to local production of the toxin, whereas in SSSS the toxin is disseminated haematogenously [10].

Epidemiology. Pure staphylococcal non-bullous impetigo [11,12] is relatively frequent throughout the world, and large outbreaks often occur. It is commoner than the streptococcal disease in temperate climates. In warmer and more humid areas, for example the southern USA, the streptococcal form predominates and is endemic. The peak seasonal incidence is in late summer [13]. The incidence in a Dutch survey was between 0.017 and 0.021 events per person-year, in Norway 0.017 and in the UK 0.01 events per person-year [11,12]. Preschool and young school-age children are most often affected. In adults, males predominate and large outbreaks may be troublesome in barracks and similar communities [14]. Although over-crowding, poor hygiene and existing skin disease, especially scabies, predispose to infection [15], many cases occur in previously healthy subjects with good living standards.

Streptococci isolated from fomites outside epidemics are frequently non-infective, but in epidemics, frequently handled materials, such as gymnasium equipment, and room dust may be important in transmitting disease. Biting insects may transfer the disease, but in addition small non-biting flies of the genus *Hippelates* can contribute to the rapid spread of the streptococcal infection in tropical and subtropical regions [3].

Bullous impetigo is usually sporadic, but clusters of cases may occur in families and other groups, and larger outbreaks are occasionally seen in institutions [16]. It is most frequent in the summer months. Bullous impetigo occurs at all ages. It is said to be commoner in childhood but adult cases are probably under-reported [17]. In the newborn, bullous impetigo may be especially widespread and was formerly called pemphigus neonatorum, as it resembles the clinical picture of pemphigus, with widespread blistering.

Minor abrasions and other skin lesions may predispose to infection if the patient or a contact carries an appropriate strain of staphylococcus [18]. An increased incidence in hospital workers has been noted [19].

Pathology. In *bullous impetigo*, the epidermis splits just below the stratum granulosum forming large blisters. Neutrophils migrate through the spongiotic epidermis into the blister cavity, which may also contain cocci. Occasional acantholytic cells may be seen, perhaps due to the action of neutrophils. The upper dermis contains an inflammatory infiltrate of neutrophils and lymphocytes.



Fig. 30.1 Staphylococcal impetigo.



Fig. 30.2 Streptococcal (group A) pyoderma.



Fig. 30.3 Bullous impetigo after disruption of bullae.

Cases with positive pemphigus-like antibodies on direct or indirect immunofluorescence have been reported [20]. When IgG from patients with pemphigus foliaceus or exfoliative toxin are injected into mice, identical blisters are formed and the histology is indistinguishable [21].

The histology is similar for *non-bullous impetigo* except that blister formation is slight and transient.

Clinical features [3,4,6]. In *non-bullous impetigo*, the initial lesion is a very thin-walled vesicle on an erythematous base. The vesicle ruptures so rapidly that it is seldom seen as such. The exuding serum dries to form yellowish brown crusts (Fig. 30.1), which are usually thicker and 'dirtier' in the streptococcal form (Fig. 30.2). Gradual, irregular, peripheral extension occurs without central healing, and multiple lesions, which are usually present, may coalesce. The crusts eventually dry and separate to leave erythema, which fades without scarring. In severe cases, there may be regional adenitis with fever and other constitutional symptoms. The face, especially around the nose and mouth, and the limbs are the sites most commonly affected, but involvement of the scalp is frequent in tinea capitis, and lesions may occur anywhere on the body, especially in children with atopic dermatitis or scabies. Involvement of the mucous membranes is rare. There is a tendency to spontaneous cure in 2–3 weeks but a prolonged course is common, particularly in the presence of underlying parasitic infestations or eczema, or in hot and humid climates. In heavily pigmented skin, the lesions may be followed by temporary hypopigmentation or hyperpigmentation.

In *bullous impetigo*, the bullae are less rapidly ruptured and become much larger; a diameter of 1–2 cm is common but they may be of very considerable size, and persist for 2 or 3 days. The contents are at first clear, later cloudy. After rupture thin, flat, brownish crusts are formed. Central healing and peripheral extension may give rise to circinate lesions (Fig. 30.3). Although the face is often affected, the lesions may occur anywhere, and may be widely and irregularly distributed, often favouring the sites of existing skin disease, especially miliaria or trivial injuries such as insect bites. The buccal mucous membrane may be involved. Commonly, rather few lesions are present, but the picture is very variable. Regional adenitis is rare.

Complications [22]. Infective complications are uncommon in the absence of systemic disease or malnutrition, although deeper infections such as cellulitis occasionally occur with the streptococcal disease.

Streptococcal impetigo accounts for the majority of cases of poststreptococcal acute glomerulonephritis (AGN) [23]. The

incidence of AGN in different series of patients with streptococcal impetigo depends on the nephritogenic potential of the infecting strain. Some never cause nephritis [13], but 25% of patients with pyoderma due to *S. pyogenes*, type M-49 are affected. The overall incidence of post-streptococcal AGN has declined in recent decades. The latent period for development of nephritis after streptococcal pyoderma is 18–21 days, compared with about 10 days for throat infection, raising the unproven possibility that early treatment of skin infection might offer a better chance of preventing the renal disease. Post-streptococcal nephritis is a significant risk factor for chronic renal disease in later life [24].

Scarlet fever, urticaria and erythema multiforme may follow streptococcal impetigo [22].

Rheumatic fever is not a complication of streptococcal impetigo [25].

Treatment. In mild and localized infection, a topical antibiotic alone may suffice. Good results have been achieved with mupirocin ointment in both staphylococcal and streptococcal impetigo, equalling oral erythromycin [26]. Fusidic acid is also effective against both organisms [27], but in order to reduce the likelihood of the development of resistance because of its value in systemic infection, it may be prudent to restrict its use as first-line topical therapy to the community if suitable alternatives are available. Topical neomycin is effective in staphylococcal infections, but less active against streptococci; bacitracin has activity against both, and the two drugs are often used in combination.

If the infection is widespread or severe, or is accompanied by lymphadenopathy, or if there is reason to suspect a nephritogenic streptococcus, an oral antibiotic such as flucloxacillin or erythromycin is indicated, although at present there is no firm evidence that this can prevent nephritis [28]. Local patterns of resistance need to be considered, as resistance of *S. aureus* to penicillin and to tetracycline is now common worldwide. The addition of a topical antibiotic or antiseptic may hasten the response and help to limit the spread of infection, although this has not been confirmed [27]. Antiseptics are less effective than appropriate antibiotics, but would provide a useful adjunct to systemic treatment, and would be rational sole therapy for impetigo where antibiotics are unavailable. Chlorhexidine and povidone–iodine would each be suitable, but controlled trials on their efficacy are not available.

Removal of infected crusts is bacteriologically and cosmetically helpful. Frequent application of an ointment, preferably containing an antibacterial agent, and washing with soap and water are as effective as messier regimens. Again, this needs to be assessed objectively.

Where impetigo is endemic among children, measures to reduce the transmission frequency of infections should be adopted. These include installing indoor water supplies, encouraging hand washing, distributing medical resources more efficiently, educating the population on health matters and instituting treatment early in the course of the disease. When handwashing was promoted, the prevalence of impetigo dropped significantly [29]. Emphasis should be placed on identification of predisposing factors such as insect bites, pediculosis, scabies and minor trauma.

References

1 Helsing P, Gaustad P. Bullous impetigo caused by group A streptococci. *Acta Derm Venereol (Stockh)* 1992; **72**: 50–1.

2 Dajani AS, Ferrieri P, Wannamaker LW. Natural history of impetigo II. Etiologic agents and bacterial interactions. *J Clin Invest* 1972; **51**: 2863–71.

3 Connor BL. Impetigo contagiosa in the United Kingdom. *Br J Dermatol* 1972; **86** (Suppl. 8): 48–54.

4 Dajani AS, Ferrieri P, Wannamaker LW. Endemic superficial pyoderma in children. *Arch Dermatol* 1973; **108**: 517–22.

5 Schachner LA. Treatment of uncomplicated skin and skin infections in the pediatric and adolescent patient populations. *J Drugs Dermatol* 2005; **4** (Suppl. 6): s30–3.

6 El Tayeb SHM, Nasr EMM, Attallah AS. Streptococcal impetigo and acute glomerulonephritis in children in Cairo. *Br J Dermatol* 1978; **98**: 53–61.

7 Melish ME, Glasgow LA. The staphylococcal scalded skin syndrome. *N Engl J Med* 1970; **282**: 1114–9.

8 Amagai M, Matsuyoushi N, Wang ZH *et al*. Toxin in bullous impetigo and staphylococcal scalded-skin syndrome targets desmoglein 1. *Nature Med* 2000; **6**: 1275–7.

9 Monday SR, Vath GM, Ferens WA *et al*. Unique superantigen activity of staphylococcal exfoliative toxins. *J Immunol* 1999; **162**: 4550–9.

10 Ginsburg CM. Staphylococcal toxin syndromes. *Pediatr Infect Dis J* 1991; **10**: 319–21.

11 Rortveit S, Rortveit G. Impetigo in epidemic and nonepidemic phases: an incidence study over $4^1/_2$ years in a general population. *Br J Dermatol* 2007; **157**: 100–5.

12 Koning S, Mohammedamin RS, van der Wouden JC *et al*. Impetigo: incidence and treatment in Dutch general practice in 1987 and 2001—results from two national surveys. *Br J Dermatol* 2006; **154**: 239–43.

13 Loffeld A, Davies P, Lewis A *et al*. Seasonal occurrence of impetigo: a retrospective 8-year review (1996–2003). *Clin Exper Dermatol* 2005; **30**: 512–4.

14 Cruikshank JG, Lightfoot NF, Sugars KH *et al*. A large outbreak of streptococcal pyoderma in a military training establishment. *J Hyg* 1982; **89**: 9–21.

15 Feldmeier H, Chhatwal GS, Guerra H. Pyoderma, group A streptococci and parasitic skin diseases—a dangerous relationship. *Trop Med Int Health* 2005; **10**: 713–6.

16 Hlady WG, Middaugh JP. An epidemic of bullous impetigo in a newborn nursery due to *Staphylococcus aureus*: epidemiology and control measures. *Alsaka Med* 1986; **28**: 99–103.

17 Lissauer TJ, Sanderson PJ, Valman HB. Re-emergence of bullous impetigo. *BMJ* 1981; **283**: 1509–10.

18 Van Toorn MJ. On the staphylococcal and streptococcal etiology of impetigo. *Dermatologica* 1961; **123**: 391–9.

19 Helgren L, Hersle K. Impetigo contagiosa. Statistical evaluation of clinical and laboratory data in 3167 patients and matched healthy controls. *Acta Derm Venereol (Stockh)* 1964; **44**: 356–61.

20 Ead RD. Pemphigus-like antibodies: a report of two cases. *Br J Dermatol* 1979; **100**: 723–5.

21 Stanley JR, Amagai M. Pemphigus, bullous impetigo and staphylococcal scalded skin syndome. *N Engl J Med* 2006; **355**: 1800–10.

22 Bisno AL, Stevens DL. Streptococcal infections of skin and soft tissues. *N Engl J Med* 1996; **334**: 240–5.

23 Berrios X, Lagomarsino E, Solar E *et al*. Post-streptococcal acute glomerulonephritis in Chile—20 years experience. *Pediatric Nephrol* 2004; **19**: 306–12.

24 White A, Hoy WE, McCredie DA. Childhood post-streptococcal glomerulonephritis is a risk factor for chronic renal disease in later life. *Med J Aust* 2001; **174**: 492–6.

25 Wannamaker LW. Differences between streptococcal infections of the throat and of the skin. *N Engl J Med* 1970; **282**: 23–31, 78–85.

26 Barton LL, Friedman AD, Sharkey AM *et al*. Impetigo contagiosa III. Comparative efficacy of oral erythromycin and topical mupirocin. *Pediatr Dermatol* 1989; **6**: 134–8.

27 Koning S, van Suijlekom-Smit LW, Nouwen J *et al*. Fusidic acid cream in the treatment of impetigo in general practice: double blind randomised placebo controlled trial. *BMJ* 2002; **324**: 203–7.

28 Stevens DL, Bisno AL, Chambers HF *et al*. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. *Clin Infect Dis* 2005; **41**: 1373–406.



Fig. 30.4 Ecthyma.

29 Luby S, Agboatwalla M, Feikin D *et al*. Effect of handwashing on child health: a randomised controlled trial. *Lancet* 2005; **366**: 225–33.

Ecthyma

Definition. Ecthyma is a pyogenic infection of the skin characterized by the formation of adherent crusts, beneath which ulceration occurs.

Aetiology. The bacteriological status of ecthyma is essentially similar to that of impetigo. It was formerly regarded as a streptococcal infection, since many cases yield a pure culture of *Streptococcus pyogenes*. From others both streptococci and staphylococci are isolated, and from some staphylococci only. Group A streptococci were grown from all of 66 cases, and coagulase-positive staphylococci from 85% of these [1]. It may prove to be a synergistic infection. In Europe, most cases occur in children, but in the tropics, where the disease is very much more common, it may occur at any age. Poor hygiene and malnutrition are predisposing factors, and minor injuries or other skin conditions, particularly scabies, may determine the site of the lesions. Several of these predisposing factors may coexist in people addicted to drugs.

Clinical features. Small bullae or pustules on an erythematous base are soon surmounted by a hard crust of dried exudate (Fig. 30.4), which increases in size by peripheral accretion. The base may become indurated and a red oedematous areola is often present. The crust is removed with difficulty, to reveal a purulent, irregular ulcer. Healing occurs after a few weeks, with scarring. The lesions are usually few but new lesions may develop by autoinoculation over a long period. The buttocks, thighs and legs are most commonly affected.

Treatment. Improved hygiene and nutrition, and treatment of scabies and any other underlying disease, are important. The antibiotic chosen should be active against both *Streptococcus pyogenes* and *Staphylococcus aureus*. Topical therapy either with sulconazole or miconazole cleared lesions satisfactorily over 1 week [2].

References

1 Kelly C, Taplin D, Allen AM. Streptococcal ecthyma. *Arch Dermatol* 1971; **103**: 306–10.

2 Nolting S, Strauss WB. Treatment of impetigo and ecthyma. A comparison of sulconazole with miconazole. *Int J Dermatol* 1988; **27**: 716–9.

Cellulitis and erysipelas

Definition. Cellulitis is strictly an acute, subacute or chronic inflammation of loose connective tissue, but the term has been applied mainly to inflammation of subcutaneous tissue in which an infective, generally bacterial, cause is proven or assumed. Erysipelas is a bacterial infection of the dermis and upper subcutaneous tissue; its hallmark is a well-defined, raised edge reflecting the more superficial (dermal) involvement. However, cellulitis may extend superficially and erysipelas deeply, so that in many cases the two processes coexist and it is impossible to make a meaningful distinction. Current usage tends to regard erysipelas as a form of cellulitis rather than a distinct entity, so that the definition of cellulitis would include inflammation of dermal as well as subcutaneous tissue. The closely similar bacteriology of the two conditions [1,2], and the demonstration of streptococcal antigens in both dermis and subcutis in both conditions [1], support this view. However, the two terms are still sometimes used in the traditional sense, especially when their typical distinctive features are being contrasted.

Bacteriology. Bacteria are present in affected tissue in small numbers, and attempts to culture them, from biopsy material, from swabs of biopsy sites, from needle aspiration of saline-injected tissue, and even from fluid from blisters or erosions when present, are often unsuccessful. Blood cultures and swabs from possible entry sites, for example wounds or inflammatory lesions, generally situated distally to the infection, occasionally yield presumably relevant organisms. Cultures of biopsy specimens, needle aspirates and probable sites of entry in 50 patients with cellulitis gave a positive result in only 26% [3]. Streptococcal serology may be helpful retrospectively [2], and immunofluorescence may identify streptococcal group antigens in biopsy specimens [1].

These studies confirm the traditional view that cellulitis and erysipelas in the immunologically normal patient are predominantly streptococcal diseases, usually involving group A organisms, but they have also demonstrated streptococci of other Lancefield groups, especially G but also C and B, in both conditions. Group B infections are seen especially under the age of 3 months [4,5]. In adults, group B streptococci may cause pelvic erysipelas especially after surgery [6]. In cellulitis (as opposed to erysipelas), *Staphylococcus aureus* is occasionally implicated alone or together with a *Streptococcus*. There is a suspicion [2] that a primary pathogenic role should not be accepted for it in all cases, as in that study all cases treated with benzylpenicillin improved rapidly even when *S. aureus* was detected; however, detailed accounts of bacterial sensitivities and individual responses to treatment were not given. *S. aureus* is occasionally isolated from lesions of erysipelas. However, in three cases out of 27 in which it was the sole isolate, there was serological evidence of streptococcal infection [1]; and another two cases responded slowly to

penicillinase-sensitive penicillins in keeping with a streptococcal cause [7]. *S. aureus* should be regarded as an occasional cause of cellulitis, but rarely if at all of classical erysipelas. *Haemophilus influenzae* type b is an important cause of facial cellulitis in young children especially up to the age of 2 years [8–10], but rarely causes cellulitis in adults [11].

In cellulitis in a setting of venous or lymphatic compromise, including limbs on which saphenous venectomy has been performed, or following surgery to the breast, non-group-A streptococci, especially groups B and G, predominate [12].

Other bacteria. A variety of other bacteria are occasionally implicated in cellulitis and erysipelas, usually in specific situations of exposure or in immunocompromised patients.

Thus, while the bacteriology of periorbital cellulitis is similar to that in other sites, orbital cellulitis, usually secondary to sinusitis, involves the major sinus pathogens, that is *Streptococcus pneumoniae*, other streptococci, *Staphylococcus aureus, Haemophilus influenzae*, and penicillin-sensitive anaerobes [2]. Cellulitis due to *Aeromonas hydrophila* can complicate injuries contaminated by water (usually fresh) or soil [13]. A case of cellulitis due to the marine organism *Vibrio alginolyticus* has been recorded [14]. Cellulitis is part of the spectrum of infection due to *Pasteurella multocida* inoculated by animal bites [15].

Erysipelas-like infections and cellulitis due to *Streptococcus pneumoniae* [16,17], *Pseudomonas aeruginosa* [18] and *Campylobacter jejuni* [19] have been reported, mostly in the immunocompromised. In such patients, *Pseudomonas aeruginosa* may cause gangrenous cellulitis and ecthyma gangrenosum [20,21]; and cellulitis may be caused by *Acinetobacter calcoaceticus* [22] and *Staphylococcus epidermidis* [23]. A case of *Bacteroides fragilis* cellulitis responding to metronidazole has been reported [24]. *Yersinia enterocolitica*, an intestinal pathogen, may also cause cellulitis [25].

Clinical features (Fig. 30.5). Erythema, heat, swelling and pain or tenderness are constant features. In erysipelas, the edge of the lesion is well-demarcated and raised, but in cellulitis it is diffuse, although cases showing both types of edge or an intermediate picture are not uncommon. In erysipelas, blistering is common, and there may be superficial haemorrhage into the blisters or in intact skin especially in elderly people. Severe cellulitis may show bullae and can progress to dermal necrosis (Fig. 30.6), and uncommonly to fasciitis or myositis. Lymphangitis and lymphadenopathy are frequent. Except in mild cases, there is constitutional upset with fever and malaise. Classical erysipelas starts abruptly and systemic symptoms may be acute and severe, but the response to treatment is more rapid.

The leg is the commonest site, and here there is usually a wound even if superficial, an ulcer, or an inflammatory lesion including interdigital fungal or bacterial infection, which can be identified as a possible portal of entry. The next most frequent site for classical streptococcal erysipelas is the face, where a traumatic entry site is less commonly seen, and where bilateral infection occasionally occurs.

Without effective treatment, complications are common—fasciitis, myositis, subcutaneous abscesses, septicaemia and, in some streptococcal cases, nephritis—and the more severe infections may be fatal, especially in infants and in the debilitated or immunosuppressed.

Childhood facial cellulitis due to *Haemophilus influenzae* type b is typically unilateral, and often associated with ipsilateral otitis media, the presumed source in those cases. The patient presents with systemic illness, and the affected cheek or periorbital tissue shows induration and discoloration, occasionally pink, but characteristically purplish blue. A similar violaceous colour may occur in childhood periorbital and buccal pneumococcal cellulitis [26].

Otherwise, periorbital cellulitis follows trauma to the eyelids or local skin sepsis and is usually streptococcal, occasionally staphylococcal. If the infection is behind the orbital septum, in the deeper orbital tissues, the term orbital cellulitis applies, and it is commonly a sequel to sinusitis, although it is to be distinguished from the periorbital oedema which may also accompany sinus infection. In addition to cutaneous signs, proptosis, ophthalmoplegia and loss of visual acuity may occur. Periorbital and orbital cellulitis may be complicated by cavernous sinus thrombosis, orbital, subperiosteal or cerebral abscess formation, or meningitis [11,27].

Severe myocardial depression has been reported in a previously healthy young woman with streptococcal cellulitis [28].

Cellulitis of the tongue in neutropenic patients may cause upper airways obstruction [29].

In the immunodeficient, the presentation may be atypical, as in two cases of erysipelas without erythema [30], and previous antibiotic treatment may modify the clinical appearances in the otherwise healthy patient.

Recurrent streptococcal cellulitis (or erysipelas) is attributed to lymphatic damage, which, although sometimes initially clinically inapparent, predisposes to further infection and further lymphatic impairment manifesting as lymphoedema (Fig. 30.7). Venous insufficiency often predisposes to recurrent erysipelas of the leg [31].

Diagnosis. Specimens for bacteriological examination should be taken from vesicle fluid or eroded or ulcerated surfaces, in addition to blood cultures. Exudative, fissured or traumatized sites distal or adjacent to limb infections may yield relevant organisms. Surface swabs from intact skin are unlikely to be helpful, but in the case of facial infections the pathogen should be sought in nose, throat, conjunctiva and sinuses. Aspiration of tissue fluid, alone or following subcutaneous infiltration of saline, occasionally results in a positive culture, but is not routinely recommended. Skin biopsy is often similarly disappointing. Identification of soluble streptococcal antigens is more effective [1]. If either of these invasive techniques is considered, care should be taken not to penetrate the fascia. However, as discussed earlier, even a combination of such techniques commonly fails to yield the pathogen, and the possibility of contamination must be remembered [1–3].

Serological studies may provide evidence of streptococcal, and less commonly staphylococcal, infection. An initial high titre may be regarded as suggestive, especially in a patient presenting several days or more after the onset, but paired sera from days 1 and 14 would be more reliable in retrospective diagnosis. Early use of antibiotics may, however, limit the antibody response. The antibodies and their significance are discussed below.



Fig. 30.5 Cellulitis/erysipelas. (a) Lower leg. (b) Extensor aspect of elbow. (c) Pinna. (d) Face.

In differentiating cellulitis of the leg from deep vein thrombosis, phlebography, plethysmography and Doppler ultrasound examination may be helpful. The protein concentration in 0.3–0.5 mL of oedema fluid aspirated from swollen subcutaneous tissue provides a rapid and inexpensive alternative; in deep vein thrombosis the average concentration was 5.5 g/L while in cellulitis it was 19.8 g/L; a level over 10 g/L was found only in cellulitis [32].

Fungi may cause cellulitis in the immunocompromised [33].

A cluster of cases closely resembling cellulitis, but bacteriologically negative and unresponsive to antibiotics, was attributed to insect bites, plant toxins or an unidentified virus [34].

Treatment. A clinical assessment as to the likely pathogen(s), as discussed earlier, should guide the initial choice of treatment. Appropriate antibiotic(s) should be given in full dosage, by the intramuscular or intravenous route in the more severe cases that are associated with septicaemia, arthritis or suspected fasciitis, although oral treatment may suffice for the milder, uncomplicated infections. In all cases, initial treatment should cover streptococci, and for facial infections in young children, *H. influenzae*. Flucloxacillin exerts a bactericidal effect on streptococci as well as staphylococci, and for this reason has been suggested as oral monotherapy in patients without systemic toxicity or co-morbidity at a dose of



Fig. 30.6 (a) Cellulitis with early dermal necrosis. (b) The same foot after 11 days; the dermis is forming a black eschar, which eventually sloughed off; the resulting ulcer healed rapidly.



Fig. 30.7 Poststreptococcal lymphoedema of pinna; this patient had frequent recurrences of cellulitis requiring long-term penicillin.

500 mg four times daily; clarithromycin 500 mg twice daily may be substituted in case of penicillin allergy. In patients admitted to hospital, it has been customary practice to combine flucloxacillin with benzylpenicillin intravenously; in the case of penicillin allergy, clarithromycin 500 mg twice daily or clindamycin 600 mg 8 hourly intravenously has been advocated. For presumed streptococcal infections, penicillin is the treatment of choice, given as benzylpenicillin 600–1200 mg 6 hourly intravenously in the more severe cases. The duration of treatment remains undefined. A randomized, double-blind, placebo-controlled trial for uncomplicated cellulitis showed that 5 days of antibiotic therapy was as good as 10 days' treatment [35]. Treatment should be continued for longer if there are any clinical indications such as extension of the cellulitis, abscess formation which may need drainage or an adverse reaction to the drug administered. Roxithromycin is an effective alternative [36]. Anticoagulant therapy should be considered if there is associated thrombophlebitis. A wider range of organisms should be considered in patients with deficient immunity, in the special situations discussed earlier and in those not responding to initial treatment. Early consultation with colleagues in microbiology is advisable.

In recurrent cases, long-term penicillin, 500 mg to 2 g daily can prevent attacks. Vigorous treatment of any local skin damage is important to prevent recurrent disease, although 50% of cases relapsed in a study on prophylaxis where tinea pedis was specifically treated early. In patients allergic to penicillin, an alternative drug, commonly erythromycin, should be taken. Some patients may require lifelong prophylaxis [37]. Recurrent episodes of cellulitis have also been associated with post-cellulitic oedema, and oedema is a risk factor for recurrent disease. Reduction of the oedema would seem beneficial [38]. Despite efforts to prevent recurrent disease with long-term prophylaxis, many patients still suffer recurrent disease [12,39,40]. Further research into the factors responsible for recurrent disease is currently being done, as this disease has a very significant morbidity.

References

1 Bernard P, Bedane C, Mounier M *et al*. Streptococcal cause of erysipelas and cellulitis in adults. *Arch Dermatol* 1989; **125**: 779–82.
2 Leppard BJ, Seal DV, Colman G *et al*. The value of bacteriology and serology in the diagnosis of cellulitis and erysipelas. *Br J Dermatol* 1985; **112**: 559–67.
3 Hook EW, Hooton TM, Horton CA *et al*. Microbiologic evaluation of cutaneous cellulitis in adults. *Arch Intern Med* 1986; **146**: 295–7.
4 Baker CJ. Group B streptococcal cellulitis—adenitis in infants. *Am J Dis Child* 1982; **136**: 631–3.
5 Hauger SB. Facial cellulitis: an early indicator of Group B streptococcal bacteremia. *Pediatrics* 1981; **67**: 376–7.
6 James WD. Cutaneous group B streptococcal infection. *Arch Dermatol* 1984; **120**: 85–6.
7 Musher DM, McKenzie SO. Infections due to *Staphylococcus aureus*. *Medicine* 1977; **56**: 383–409.
8 Ginsburg CM. *Haemophilus influenzae* type B buccal cellulitis. *J Am Acad Dermatol* 1981; **4**: 661–4.
9 Pedler SJ, Hawkey PM. Cellulitis in children caused by *Haemophilus influenzae* type b. *J Infect* 1983; **6**: 269–72.
10 Rubinstein JD, Handler SD. Orbital and periorbital cellulitis in children. *Head Neck Surg* 1982; **5**: 15–21.
11 Lai KK. *Haemophilus influenzae* type B cellulitis in an adult. *N Engl J Med* 1987; **316**: 1607–8.
12 Del Guidice P, van der Mee-Marquet N, David-Rubin F *et al*. Severe relapsing erysipelas associated with chronic *Streptococcus agalactiae* vaginal colonization. *Clin Infect Dis* 2006; **43**: 67–70.
13 Gold WI, Salit IE. *Aeromonas hydrophila* infections of skin and soft tissue: report of 11 cases and review. *Clin Infect Dis* 1993; **16**: 69–74.
14 Aelvoet G, Kets R, Pattyn SR. Cellulitis caused by *Vibrio alginolyticus*. *Acta Derm Venereol* (*Stockh*) 1983; **63**: 559–60.
15 Weber DJ, Wolfson JS, Swartz MN *et al*. *Pasteurella multocida* infections. *Medicine* 1984; **63**: 133–54.
16 Varghese R, Melo JC, Chun C-H *et al*. Erysipelas-like syndrome caused by *Streptococcus pneumoniae*. *South Med J* 1979; **72**: 757–8.
17 Lawlor MT, Crowe HM, Quintilliani R. Cellulitis due to *Streptococcus pneumoniae*. Case report and review. *Clin Infect Dis* 1992; **14**: 247–50.
18 Roberts R, Tarpay MM, Marks MI *et al*. Erysipelas-like lesions and hyperesthesia as manifestations of *Pseudomonas aeruginosa* sepsis. *JAMA* 1982; **248**: 2156–7.
19 Kerstens PJSM, Endtz HP, Meis JFGM *et al*. Erysipelas-like lesions associated with *Campylobacter jejuni* septicemia in patients with hypogamma-globulinemia. *Eur J Clin Microbiol Infect Dis* 1992; **11**: 842–7.
20 Koriech OM, Al-Dash FZ. Skin and bone necrosis following ecthyma gangrenosum in acute leukaemia—report of three cases. *Clin Exp Dermatol* 1988; **13**: 78–81.
21 Sevinsky JD, Viecens, C, Ballesteros DO *et al*. Ecthyma gangrenosum: a cutaneous manifestation of *Pseudomonas aeruginosa* sepsis. *J Am Acad Dermatol* 1993; **29**: 106–8.
22 Glew RH, Moellering RC, Kunz LJ. Infections with *Acinetobacter calcoaceticus* (*Herellea vaginicola*): clinical and laboratory studies. *Medicine* 1977; **56**: 79–97.
23 Pitlik S, Fainstein V. Cellulitis caused by *Staphylococcus epidermidis* in a patient with leukemia. *Arch Dermatol* 1984; **120**: 1099–100.
24 Cullen KW, MacBain GC. An unusual case of cellulitis associated with *Bacteroides fragilis* septicaemia. *J Hosp Infection* 1982; **3**: 303–4.
25 Krogstad P, Mendelman PM, Miller VL *et al*. Clinical and microbiologic characteristics of cutaneous infection with *Yersinia enterocolitica*. *J Infect Dis* 1992; **165**: 740–3.
26 Thirumoorthi MC, Asmar BI, Dajani AS. Violaceous discoloration in pneumococcal cellulitis. *Pediatrics* 1978; **62**: 492–3.
27 Editorial. Orbital cellulitis. *Lancet* 1986; **2**: 497.
28 Edwards JD, Schofield PM. Myocardial depression in streptococcal cellulitis. *BMJ* 1984; **288**: 816–7.
29 Smith OP, Prentice HG, Madden GM *et al*. Lingual cellulitis causing upper airways obstruction in neutropenic patients. *BMJ* 1990; **300**: 24.
30 Cupps TR, Cotton DJ, Schooley RT *et al*. Facial erysipelas in the immunocompromised host. *Arch Dermatol* 1981; **117**: 47–9.
31 Jorup-Ronstrom C, Britton S. Recurrent erysipelas: predisposing factors and costs of prophylaxis. *Infection* 1987; **15**: 105–6.
32 Berlyne GM, Kwan T, Li J *et al*. Oedema protein concentrations for differentiation of cellulitis and deep vein thrombosis. *Lancet* 1989; **2**: 728–9.
33 Jade KB, Lyons MF, Gnann JW. *Paecilomyces lilacinus* cellulitis in an immunocompromised patient. *Arch Dermatol* 1986; **122**: 1169–70.
34 Shine IB. St Helenian cellulitis. *Br J Dermatol* 1964; **76**: 357–61.
35 Hepburn MJ, Dooley D, Skidmore P *et al*. Comparison of short course (5 days) and standard (10 days) treatment of uncomplicated cellulitis. *Arch Int Med* 2004; **164**: 1669–74.
36 Bernard P, Plantin P, Roger H *et al*. Roxithromycin versus penicillin in the treatment of erysipelas in adults: a comparative study. *Br J Dermatol* 1992; **127**: 155–9.
37 Chartier C, Grosshans E. Erysipelas. *Int J Dermatol* 1990; **29**: 459–67.
38 Cox NH. Oedema as a risk factor for multiple episodes of cellulitis/erysipelas of the lower leg: a series with community follow-up. *Br J Dermatol* 2006; **155**: 947–50.
39 Vignes S, Dupuy A. Recurrence of lymphoedema-associated cellulitis (erysipelas) under prophylactic antibiotherapy: a retrospective cohort study. *J Eur Acad Dermatol Venereol* 2006; **20**: 818–22.
40 Koster JB, Kullberg BJ, van der Meer JWM. Recurrent erysipelas despite antibiotic prophylaxis: an analysis from case studies. *Neth J Med* 2007; **65**: 89–94.

Inflammatory diseases of hair follicles

Staphylococcus aureus, coagulase-negative staphylococci and physical or chemical irritation are common causes of superficial folliculitis. The deeper forms of staphylococcal folliculitis, furuncles and carbuncles are discussed separately.

Other microbial causes of folliculitis are considered elsewhere: *Pseudomonas aeruginosa* later in this chapter; Gram-negative folliculitis developing in antibiotic-treated acne in Chapter 42; *Pityrosporum* yeasts and dermatophytes in Chapter 36. Patients with human immunodeficiency virus (HIV) disease may have 'itchy folliculitis' of uncertain cause (Chapter 35).

Pseudofolliculitis due to ingrowing hairs is discussed below and in Chapter 66.

There are, however, a number of inflammatory diseases involving the hair follicle whose aetiology is complex or uncertain. Although the role of bacterial infection may be partial, secondary, unknown or absent, these disorders are included in this chapter for convenience: sycosis barbae, folliculitis keloidalis, acne necrotica, perforating folliculitis, trunk folliculitis, actinic folliculitis, disseminate and recurrent infundibulofolliculitis, eosinophilic pustular folliculitis, suppurative hidradenitis and perifolliculitis capitis. Folliculitis decalvans is considered in Chapter 66.

Superficial folliculitis

Subacute or chronic folliculitis, in which the inflammatory changes are confined to the ostium or extend only slightly below it, and which heals without scar formation, is an extremely common condition, but is usually of such little clinical importance that it has not been thoroughly investigated.

Superficial folliculitis is not always primarily or exclusively infective in origin. Physical or chemical injury to the skin may be associated with a folliculitis, the pustules of which may be sterile or may contain coagulase-negative staphylococci. Occupational contact with mineral oils or therapeutic or occupational exposure to tar products very typically produce such lesions, which in the case of oil folliculitis are associated with conspicuous oil plugging of many follicles. Other chemical irritants can cause folliculitis, which may be the only visible change, or may accompany an

eczematous reaction. Beneath adhesive plasters or adhesive dressings, a sterile folliculitis is common. Following epilation, a traumatic folliculitis may develop [1].

Occasional isolated lesions are so frequent on the neck and beard, and heal so rapidly, that they are commonly ignored. Also frequent, but more persistent, are papules or pustules on the thighs and buttocks of adolescent and young adult males and occasionally females, especially those with acne. They are usually too few and small to have attracted the patient's attention. On culture, the pustules may be sterile, but coagulase-negative staphylococci are sometimes isolated. Clinically, the lesions present as small, follicular papules or pinhead pustules. They are rarely painful. Sometimes, small crusts cover a red, pouting, follicular orifice.

Staphylococcus aureus superficial folliculitis (follicular impetigo of Bockhart) is an infection of the follicular ostium with *S. aureus*. Use of topical steroids, especially of the stronger grades, is a predisposing factor. Otherwise, it is commonest in childhood, and occurs mainly in the scalp or scalp margins or on the limbs. The individual lesion is a domed, yellow pustule, sometimes with a narrow, red areola. The pustules develop in crops and may heal within 7–10 days, but sometimes become chronic. In older children and adults, the infection may extend more deeply in some follicles as furuncles or as sycosis. In some cases, recurrent or chronic staphylococcal folliculitis may merge imperceptibly with folliculitis decalvans and related processes (Chapter 66). However, acute staphylococcal folliculitis is common and the many clinical variants of cicatrizing folliculitis are rare.

Chronic folliculitis of the legs [2,3] has been described mainly in young adult males in India. The profuse eruption of superficial and deep follicular pustules on the thighs and lower legs persisted for many years and was resistant to treatment. *S. aureus* was regularly isolated. No systemic abnormality could be detected other than hypergammaglobulinaemia. The pustular dermatitis atrophicans of the legs [4], described as accounting for 0.5% of skin disease in Lagos in West Africa, appears to be a similar condition. It occurs predominantly in males and affects symmetrically the anterior tibial surfaces of the legs, sometimes involving thighs and forearms. Miliary pustules are followed by atrophic scars.

Community-acquired methicillin resistant staphylococcal infections (CAMRSA) may present with folliculitis or an abscess. These relatively superficial infections may well progress to severe infections. Athletes participating in team sports may spread the infection to other members of the team, as may military personnel, prisoners and others who are often involved in close contact with individuals [5].

Diagnosis. Follicular pustules are readily confused by the inexperienced with the non-follicular lesions of pustular miliaria, which should be considered when a widespread papulopustular eruption develops in hot and humid conditions, on previously normal skin, or studding an existing inflammatory dermatitis. Follicular pustules are also a feature of subcorneal pustular dermatosis, in which they are grouped around the margins of plaques of erythema and scaling (Chapter 40).

Follicular pustules may occur in ringworm. The more-or-less simultaneous development of pustules on a circumscribed, red and oedematous or scaling plaque should arouse suspicion.

Where CAMRSA is suspected, swabs should be done to check the sensitivity of the organism.

Treatment. Superficial folliculitis of external chemical or physical origin will settle if the irritant is removed.

Mild staphylococcal folliculitis is often self-limiting, or may respond to cleansing or topical antiseptics. In more severe cases, antibiotics, topical or systemic, may be required. If the infection is persistent or recurrent, the usual sites of staphylococcal carriage should be sought in the patient and his or her contacts. Because CAMRSA can be spread by skin to skin contact, prevention of further infections is advisable. Hand washing is the single most important behaviour modification in the prevention of spread. Sports participants should shower regularly and all personal clothing should not be shared [5].

Daily application of 6.25% aluminium chloride hexahydrate in completely anhydrous ethyl alcohol was reported to be very effective treatment for chronic folliculitis of unspecified type, except for scalp lesions [6].

References

1 Wright RC. Traumatic folliculitis of the legs: a persistent case associated with use of a home epilating device. *J Am Acad Dermatol* 1992; **27**: 771.

2 Desai SC, Shah BH, Modi PJ, Sethi WC. Therapy of resistant pyogenic folliculitis on legs in adult males with hypergammaglobulinemia (a report of 30 cases). *Indian J Dermatol Venereol* 1964; **30**: 89–92.

3 Sugathan P, Zaconah J, Joy MI *et al*. Folliculitis cruris pustulosa et atrophicans. *Indian J Dermatol Venereol* 1973; **39**: 35–9.

4 Clarke GHV. Note on dermatitis cruris pustulosa et atrophicans. *Trans R Soc Trop Med Hyg* 1952; **46**: 558–9.

5 Cohen PR. Community-acquired methicillin-resistant *Staphylococcus aureus* skin infections: a review of epidemiology, clinical features, management and prevention. *Int J Dermatol* 2007; **46**: 1–11.

6 Shelley WB, Hurley HJ. Anhydrous formulation of aluminium chloride for chronic folliculitis. *JAMA* 1980; **244**: 1956–7.

Pseudofolliculitis

Synonym

- Pili incarnati

Aetiology [1,2]. Inflammation results from penetration into the skin of sharp tips of shaved hairs. If shaven too long, or if it escapes shaving for a few days, the hair may curve backwards after emerging from the follicle to penetrate the adjacent skin; conversely, if cut very short so that it retracts into the follicle, it may directly penetrate the follicle wall.

Curly hair is more liable to both of these aberrations so that the condition is very common and more severe in those with tightly coiled hair [2]. Skin folds or irregularities due to scarring may allow ingrowth of straight hairs. Any shaved surface in either sex [3] may be affected, but the male beard area is naturally the most common. Plucking may cause pseudofolliculitis [4], and incorrect shaving techniques may aggravate the condition. There is evidence of genetic predisposition [5]. Pseudofolliculitis of the scalp was reported in four brothers who were black and whose father had shaved their scalps [6]. Cut nasal hairs may ingrow similarly [7]. Pseudofolliculitis is particularly troublesome in the Armed Forces, where strict grooming standards demand clean shaving



Fig. 30.8 Pseudofolliculitis.

[2]. The exact prevalence is not known, although between 45 and 83% of African American men are thought to be affected [2].

Coagulase-negative staphylococci may sometimes be grown from the lesions but the condition is not primarily infective, rather a foreign body inflammatory reaction.

Clinical features (Fig. 30.8). The patient complains of minor discomfort from papules and pustules on shaven skin. In the beard area, the skin of the neck and over the jaw is most commonly affected, although lesions may occur on the cheeks too. The papules may be large and scarring, keloid formation and hyperpigmentation may ensue. It is generally possible to identify some penetrating hairs but they may not be visible in all cases. The clinical appearance may lead to significant distress [8].

The condition should be differentiated from deep folliculitis associated with furuncles and carbuncles, tinea barbae and acne.

Treatment [2,8]. The only certain cure is to stop shaving for a minimum of 4–6 weeks, to allow the inflammation to settle, but resumption of shaving will lead to relapse. Lifting out of re-entrant hairs with a needle is helpful but tedious: brushing with an abrasive sponge or toothbrush to 'release' the hair is less effective but quicker. Hair should be left about 1 mm long. This may be achieved by adjustment of individual shaving technique, or by specially designed razors [9] or electric clippers. Plucking should be avoided. Some relief is possible with topical steroid–antimicrobial combinations combined with intensive use of emollients. Hair removal with chemical depilatories or topical eflornithine hydrochloride cream may be helpful for some patients. Laser therapy has also been reported to be beneficial [8]. No formal studies have yet evaluated these products.

References

1 Strauss JS, Kligman AM. Pseudofolliculitis of the beard. *Arch Dermatol* 1956; **74**: 533–42.

2 Garcia-Zuazaga J. Pseudofolliculitis barbae. Review and update on new treatment modalities. *Military Med* 2003; **168**: 561–4.

3 Hall JC, Goetz CS, Bartholome CS *et al*. Pseudofolliculitis—revised concepts of diagnosis and treatment. *Cutis* 1979; **23**: 798–800.

4 Dilaimy M. Pseudofolliculitis of the legs. *Arch Dermatol* 1976; **112**: 507–8.

5 Alexander AM. Pseudofolliculitis diathesis. *Arch Dermatol* 1974; **109**: 729–30.

6 Smith JD, Odom RB. Pseudofolliculitis capitis. *Arch Dermatol* 1977; **113**: 328–9.

7 White SW, Rodman OG. Pseudofolliculitis vibrissa. *Arch Dermatol* 1981; **117**: 368–9.

8 Taylor S. Enhancing the care and treatment of skin of color. Part 1: the broad scope of pigmentary disorders. *Cutis* 2005; **76**: 249–55.

9 Alexander AM. Evaluation of a foil-guarded shaver in the management of pseudofolliculitis barbae. *Cutis* 1981; **27**: 534–42.

Furuncle

Synonym
- Boil

Definition. A furuncle is an acute, usually necrotic, infection of a hair follicle with *S. aureus*.

Aetiology. Furuncles are relatively uncommon in early childhood in temperate climates except in atopic subjects, but increase rapidly in frequency with the approach of puberty, and in adolescence and early adult life are a common disability [1]. In adolescence, boys are affected more than girls and the peak incidence parallels that of acne vulgaris. Furuncles in the UK are most common during the early winter months [2]. As with other superficial staphylococcal infections, the factors responsible for the outbreak and its persistence are unknown. There is seldom any evidence of impairment of the immune response. Reports on the possibility of impairment of neutrophil function are conflicting [3,4]. The infecting strain of *Staphylococcus* is usually also present in the nares or the perineum [5], which may imply that the repeated and heavy inoculation that occurs in the chronic carrier may be a necessary condition for the development of furunculosis. The surface defence mechanism, and hence the normal balance of microflora, may be disturbed in favour of the staphylococci, which may be carried for some months in the neighbourhood of recently healed lesions. From the sites of carriage, the infection is disseminated by the fingers and by clothing. Mechanical damage to the skin, even the friction of collars and belts, may determine the distribution of the lesions. Malnutrition is an important predisposing factor in some countries. Diabetes is widely believed to predispose to furunculosis, although the published evidence does not uniformly confirm this [6,7]. Furunculosis is common in patients infected with HIV. However, in a high proportion of cases in healthy young adults, no convincing predisposing factor can be incriminated.

Recent epidemics of furunculosis attributable to specific strains of staphylococci have occurred. Many of these have been associated with community-acquired staphylococcal infections. A French study of patients with furunculosis showed staphylococci in the majority of swabs, and 42% of the isolates had Panton–Valentine leukocidin (PVL) genes present. These were associated with epidemic furunculosis. Clinically the lesions showed more erythema, and were multiple. Nasal carriage of staphylococci was strongly associated with recurrent disease but not simple furunculosis (one attack) [8]. The skin and nose isolates were identical. A similar study from Japan showed 40–60% of isolates were PVL gene positive. Although the PVL locus is thought to be a strong marker for

CAMRSA, the study from Japan showed that not all of the isolates were methicillin resistant [9].

From the very common, milder, persistent and recurrent cases, a wide variety of strains common to many types of staphylococcal infection may be grown, and predisposing factors must be assumed to be of relatively greater significance, although their nature is often difficult to establish. The observation of families over a period of years showed that the same phage type may be responsible for irregular episodes of infection between long intervals of clinical quiescence [1].

Pathology. A furuncle is an abscess of a hair follicle, usually of vellus type. The perifollicular abscess is followed by necrosis with destruction of the follicle. The exact pathogenic mechanism by which staphylococci produce the abscess is not clear, but injection of PVL into rabbit skin produced necrotizing lesions. This suggests that the cytotoxin produced may have a role to play [10].

Clinical features. A furuncle first presents as a small, follicular, inflammatory nodule, soon becoming pustular and then necrotic and healing after discharge of a necrotic core to leave a violaceous macule and, ultimately, a permanent scar. The rate of development varies greatly, and necrosis may occur within 2 days or only after 2 or 3 weeks. Tenderness is invariable, and in the more acute and larger lesions there may be throbbing pain. Lesions in the nose or external ear canal can cause very severe pain. The lesions may be single or multiple, and tend to appear in crops. Occasionally, there may be fever and mild constitutional symptoms. Pyaemia and septicaemia are favoured by malnutrition. On the upper lip and cheek, cavernous sinus thrombosis is a rare and dangerous complication.

The sites commonly involved are the face and neck, the arms, wrists and fingers, the buttocks and the anogenital region.

Attacks may consist of a single crop, or of multiple crops, at irregular intervals with or without periods of freedom. The prognosis cannot be reliably determined during a first attack. In some individuals, crops continue to develop for many months or even years.

In HIV disease, furuncles may coalesce into violaceous plaques [11].

Diagnosis. Other pustular lesions must be differentiated. Furuncles are deep-seated nodules, in contrast to the lesions of superficial staphylococcal folliculitis. The vesicopustules of disseminated herpes simplex are umbilicated and appear simultaneously in large numbers on sites of active or healed eczema (Chapter 24).

The pustules of acne are but one type of lesion in a polymorphic syndrome. They are associated with papules and comedones, and are usually confined to the face and trunk. Pustules can also occur in halogen eruptions (Chapter 75), usually symmetrical and of rapid onset. Nodules and abscesses occur mainly in the axillae and perineum in hidradenitis. Single or few, large, suppurating nodules on exposed skin raise the possibility of myiasis.

Prognosis. The course of the untreated disease is infinitely variable [1] and the prognosis cannot be reliably determined during a first episode. Some patients suffer only one attack while others continue to develop recurrences over months or years, with or without periods of freedom. Where CAMRSA is prevalent, systemic infections such as bacterial endocarditis may occur [12].

Treatment. Each episode may need to be treated systemically with flucloxacillin or another penicillinase-resistant antibiotic. A topical antibacterial agent reduces contamination of the surrounding skin. Occlusive dressings should be avoided.

Recurrent cases present problems, as further lesions may develop after the end of each course of antibiotic. It may be prudent in these cases to exclude diabetes and other possible underlying conditions. Nasal and perineal carriage of *Staphylococcus aureus* in the patient and other household members should be sought; the management of carriers is discussed earlier in this chapter. Addition of rifampicin [13] or intravenous gammaglobulin to neutralize the toxin may be helpful [10].

References

1 Roodyn L. Epidemiology of staphylococcal infections. *J Hyg* 1960; **58**: 1–10.
2 Whitwell GPB, Sutherland I. Boils. An epidemiological survey. *Br J Dermatol* 1950; **62**: 109–13.
3 Cates KL, Qioe PG. Neutrophil chemotaxis in patients with *Staphylococcus aureus* furunculosis. *Infect Immunity* 1979; **26**: 1004–8.
4 Rebora A, Dallegri F, Patrone F. Neutrophil dysfunction and repeated infections: influence of levamisole and ascorbic acid. *Br J Dermatol* 1980; **102**: 49–56.
5 Valentine FCO, Hall-Smith SP. Superficial staphylococcal infection. *Lancet* 1953; **2**: 351–4.
6 Noble WC. *Microbial Skin Disease: its Epidemiology*. London: Arnold, 1983: 88.
7 Savin JA. Bacterial infections in diabetes mellitus. *Br J Dermatol* 1974; **91**: 481–7.
8 Durupt F, Major L, Bes M *et al*. Prevalence of *Staphylococcus aureus* toxins and nasal carriage in furuncles and impetigo. *Br J Dermatol* 2007; **157**: 1161–7.
9 Yamasaki O, Kaneko J, Morizane S *et al*. The association between *Staphylococcus aureus* strains carrying Panton-Valentine leukocidin genes and the development of deep-seated follicular infection. *Clin Infect Dis* 2005; **40**: 381–5.
10 Gauduchon V, Cozon G, Vandenesch F *et al*. *Stapylococcus aureus* leukocidin: a new virulence factor in cutaneous infections? An epidemiological and experimental study. *J Infect Dis* 2004; **189**: 346–53.
11 Becker BA, Frieden IJ, Odom R *et al*. Atypical plaquelike staphylococcal folliculitis in human immunodeficiency virus-infected persons. *J Am Acad Dermatol* 1989; **21**: 1024–6.
12 Bahrain M, Versiliades M, Wolff M *et al*. Five cases of bacterial endocarditis after furunculosis and the ongoing saga of community-acquired methicillin-resistant *Staphylococcus aureus* infections. *Scand J Infect Dis* 2006; **38**: 702–7.
13 Hoss DM, Feder HM. Addition of rifampicin to conventional treatment for recurrent furunculosis. *Arch Dermatol* 1995; **131**: 647–8.

Carbuncle

Aetiology. A carbuncle is a deep infection of a group of contiguous follicles with *S. aureus*, accompanied by intense inflammatory changes in the surrounding and underlying connective tissues, including the subcutaneous fat. Carbuncles occur predominantly in men, and usually in middle or old age. They may be seen in the apparently healthy but are more common in the presence of diabetes, malnutrition, cardiac failure, drug addiction or severe generalized dermatoses, such as exfoliative dermatitis or pemphigus, and during prolonged steroid therapy.

Clinical features. The term carbuncle is derived from the Latin word for a small, fiery coal, and describes the painful, hard, red

lump that is the initial stage of the infection. It is at first smooth, dome-shaped and acutely tender. It increases in size for a few days, to reach a diameter of 3–10 cm or occasionally more. Suppuration begins after some 5–7 days, and pus is discharged from the multiple follicular orifices. Necrosis of the intervening skin leaves a yellow slough surmounting a crateriform nodule. In some cases, the necrosis develops more acutely without a preliminary follicular discharge, and the entire central core of the lesion is shed, to leave a deep ulcer with a purulent floor.

Most lesions are on the back of the neck, the shoulders or the hips and thighs, and although usually solitary, may be multiple or associated with one or more furuncles.

Constitutional symptoms may accompany, or even precede by some hours, the development of the carbuncle. Fever may be high, and malaise and prostration may be extreme if the carbuncle is large or the patient's general condition poor.

In favourable cases, healing slowly takes place to leave a scar. In the frail and ill, death may occur from toxaemia or from metastatic infection.

Diagnosis. Anthrax presents the only important problem. In the typical case, the haemorrhagic crust and the vesicular margin are quite unlike a carbuncle, but sometimes certain clinical differentiation is difficult. A swab must be taken, but treatment should not be postponed until bacteriological confirmation is available.

Treatment. Flucloxacillin or another penicillinase-resistant antibiotic should be given. Diabetes and other possible underlying conditions should be sought.

Sycosis

Definition and nomenclature. Sycosis is a subacute or chronic pyogenic infection involving the whole depth of the follicle. If the follicles are destroyed with clinically evident scarring, the term lupoid sycosis, or its cumbersome synonym ulerythema sycosiforme, is applied. Folliculitis decalvans (Chapter 66) is essentially the same process involving the scalp. Many sites may be involved in the same individual.

Aetiology. Sycosis occurs mostly in males after puberty, and commonly involves the follicles of the beard. Most cases begin in the third or fourth decade, but we have seen a severe infection in a boy aged 14 years. The infecting organism is *Staphylococcus aureus*, the same phage type of which can often be isolated from the nose [1], but unknown constitutional factors must be accorded the major role in determining susceptibility, for the staphylococci do not normally penetrate more deeply than the follicular ostia. Many patients are seborrhoeic, with a greasy complexion and chronic blepharitis. Clerical and other indoor workers are affected more often than those who work in the open air.

Pathology. The affected follicle is packed with polymorphonuclear leukocytes, which infiltrate its wall. Around the follicle there is a chronic granulomatous infiltrate in which lymphocytes, plasma cells, histiocytes and foreign-body giant cells are conspicuous. The sebaceous gland, or the whole follicle, may be destroyed and replaced by scar tissue.

Clinical features [2]. The essential lesion is an oedematous, red, follicular papule or pustule centred on a hair. The individual papules remain discrete, but if neighbouring follicles are involved the perifollicular oedema may coalesce, to produce the raised plaques studded with pustules which suggested the appearance of a ripe fig to the ancient author who coined the term sycosis. In the common subacute forms, the lesions may be scattered irregularly over the beard or grouped, especially on the upper lip and below the angles of the jaw. Attacks of varying duration occur at irregular intervals over months or years. In more chronic forms, the lesions are typically clustered into plaques, especially on the upper lip and chin, and may persist for very long periods—nearly 20 years in one case [3]. There is often some crusting and scaling, but the hairs are retained and there is no evident scarring.

In lupoid sycosis, the follicles are destroyed by scarring, and active papules and pustules fringe the advancing margin around a pink atrophic scar. Granulomatous inflammatory changes may give the papules a lupoid appearance. The process usually begins in front of one ear or under the chin and extends irregularly in any direction. The scalp may be extensively involved. Rarely, a similar process affects axillary and pubic hair, or the lower legs, thighs and arms. Lupoid sycosis tends to persist indefinitely, although the rate of extension may vary from time to time.

Diagnosis. The most frequent misdiagnosis is certainly the pseudofolliculitis caused by ingrowing hairs. The papules and pustules are irregularly scattered over the sides of the neck and the angles of the jaw and are not grouped but may lie in skinfolds.

Mycotic sycosis, a kerion of the beard (Chapter 36), usually occurs on the chin or cheeks. The oedematous plaque of grouped pustules of acute onset is easily recognized. The diagnosis is suggested by the patient's contact with cattle, and confirmed by mycological examination.

Lupoid sycosis rarely simulates lupus vulgaris. The presence of pustules establishes the diagnosis. Biopsy can be undertaken if doubt remains. The scarring of lupoid sycosis may have medicolegal implications if the patient falsely attributes it to the use of radiotherapy during its early stages.

Treatment. The subacute forms are relatively easily controlled by antibiotic ointments, but tend to relapse when the application is stopped. If a nasal swab indicates a chronic carrier state, the antibiotic should also be applied to the nasal vestibules.

The chronic forms respond less readily to antibiotics, although the response may sometimes be enhanced by using a steroid–antibiotic combination. The application must often be continued indefinitely and potential sensitizers, such as neomycin, should therefore be avoided. In resistant cases a 10- to 14-day course of a systemic antibiotic deserves a trial. Any chronic nasopharyngeal sepsis should be treated. Currently, there are no established protocols for treatment of this condition.

References
1 Valentine FCO, Hall-Smith SP. Superficial staphylococcal infection. *Lancet* 1953; **2**: 351–4.
2 Meinhof W, Braun-Falco O. Uber die Folliculitis sycosiformis atrophicans Barbae Hoffmann (Sycosis lupoides Milton-Brocq, Ulerythema sycosiform Unna). *Dermatol Wochenschr* 1966; **152**: 153–67.
3 Pinkus H, Rudner E. Sycosis vulgaris agminata (Lutz). *Dermatol Wochenschr* 1965; **151**: 628–32.

Folliculitis keloidalis

Synonym
- Acne keloid

Aetiology. Folliculitis keloidalis is a chronic, inflammatory process involving the hair follicles of the nape of the neck and leading to hypertrophic scarring in papules and plaques. It occurs in males after puberty and is most frequent between the ages of 14 and 25 years, especially in black males. A study from Nigeria reported that 9.4% of all patients attending dermatology outpatients had acne keloidalis [1]. Many patients have, or have had, significant acne, and a patient with previous hidradenitis has been reported [2]. No specific organism can be isolated, although *S. aureus* is often isolated [3]. Although friction from the collar is often incriminated, the evidence is unconvincing [3]. An association between frequent haircuts (<4 weeks) in high school boys has been documented [4]. This finding, and the observation of foreign-body granulomas surrounding fragments of hair, has led to the suggestion that the process begins with penetration of cut hair into the skin, as in pseudofolliculitis, but no evidence of this was found on detailed histological examination [5].

Associated keloids in other sites seem not to have been reported, and the process is regarded as hypertrophic scarring rather than true keloid.

Pathology. The most frequent histological findings include chronic perifollicular inflammation, disappearance of sebaceous glands, destroyed follicles, lamellar fibroplasia and acute inflammation around degenerating follicular components. Serial sections may show a foreign-body reaction to hair and follicular remnants. The pathological findings seen in early lesions, perilesional skin and clinically normal skin, suggest that follicular antigens such as *Demodex*, bacteria or other skin flora, stimulate an inflammatory reaction which then destroys the sebaceous glands and follicles. The end result is scarring [5].

Clinical features. Follicular papules or pustules, often in irregularly linear groups, develop on the nape of the neck just below the hair line. Less often, they extend upwards into the scalp, and the name acne keloidalis is thus preferred to acne keloidalis nuchae. The early inflammatory stage may be inconspicuous, and the patient may first be aware of the hard, keloidal papules that follow the folliculitis. The papules may remain discrete, or may fuse into horizontal bands or irregular plaques. In other cases, the inflammatory changes are persistent and troublesome, with undermined abscesses and discharging sinuses.

The condition is extremely chronic and new lesions may continue to form at intervals for years.

Treatment. Bacterial infection should be treated if present, and antiseptics may help to reduce further or secondary infection. No evidence-based reviews of therapy options are available. Avoidance of closely shaven hair on the back of the scalp may be advised. Intralesional or topical potent steroids may reduce scarring and inflammation [5]. Oral steroids prescribed for another condition helped, but long-term treatment is unlikely to be justified [2]. In general, medical treatment is disappointing, and in troublesome cases the affected area may be excised and grafted, or excised and allowed to heal by secondary intention. Laser therapy followed by secondary intention healing has been helpful [6]. Surgery followed by radiotherapy has also been advocated previously.

References
1 Salami T, Omeife H, Samuel S. Prevalence of acne keloidalis nuchae in Nigerians. *Int J Dermatol* 2007; **46**: 482.
2 Vasily DB, Breen PC, Miller OF. Acne keloidalis nuchae: report and treatment of a severe case. *J Dermatol Surg Oncol* 1979; **5**: 228–30.
3 George AO, Akanji AO, Nduka EU *et al*. Clinical, biochemical and morphologic features of acne keloidalis in a black population. *Int J Dermatol* 1993; **32**: 714–6.
4 Khumalo NP, Jessop S, Gumedze J *et al*. Hairdressing is associated with scalp disease in African schoolchildren. *Br J Dermatol* 2007; **157**: 106–10.
5 Sperling L, Homoky C, Pratt L *et al*. Acne keloidalis is a form of primary scarring alopecia. *Arch Dermatol* 2000; **136**: 479–84.
6 Shah GK. Efficacy of diode laser for treating acne keloidalis nuchae. *Indian J Dermatol Vernereol Leprol* 2005; **71**: 31–4.

Acne necrotica (varioliformis)

Nomenclature. There are few clinical syndromes with a more confused nomenclature. The term acne necrotica has included a chronic follicular necrotizing process, which evolves into small, round scars, affecting mainly areas close to scalp margins (acne necrotica varioliformis); this is the entity discussed here. Also included has been a milder disease occurring throughout the scalp without significant scarring (acne necrotica miliaris). The relationship between the two is still uncertain, but we regard the latter as possibly synonymous with *Propionibacterium acnes* folliculitis of the scalp [1,2], which is considered below.

Aetiology. Acne necrotica varioliformis is much less common than acne necrotica miliaris. It occurs slightly more frequently in men than in women, and is usually seen between the ages of 30 and 50 years, but never before puberty.

The lesion is essentially a folliculitis, but the cause is uncertain. The most widely suggested pathogens have been *Staphylococcus aureus* and *Propionibacterium acnes*, but neither is universally accepted, and whichever (if any) microorganism(s) may be involved, it is the follicular and perifollicular necrosis, presumably mediated by host response mechanisms, which characterizes the condition.

Staphylococcus aureus is often isolated from surface swabs, but the lesions are very frequently crusted or excoriated, so that the *Staphylococcus* may be a surface contaminant or secondary pathogen, and this finding may not reflect a primary pathogenetic role [3]; in addition, treatment appropriate for staphylococcal infection is usually disappointing.

Emotional disturbance has been a frequent finding in some studies [3,4]; it has been suggested that repeated excoriation of lesions of a primary folliculitis leads to more destructive changes [3]. Histologically, however, acne necrotica varioliformis can be distinguished from excoriations as well as from pyogenic infections [5].

A response to tetracyclines is in keeping with a primary role for *Propionibacterium acnes* [3,5], as in acne necrotica miliaris, but the greater severity of the varioliformis type suggests a qualitative difference in host response.

Pathology [5]. Early lesions show a lymphocytic folliculitis with extensive individual cell necrosis of keratinocytes in the external root sheath and the surrounding epidermis, and marked subepidermal oedema. Later, the follicle and adjacent epidermis and dermis show confluent necrosis.

Clinical features. The typical lesion of acne necrotica is a red papule 2–5 mm in diameter, often umbilicated and rapidly transformed by necrosis into an adherent haemorrhagic crust, which separates after 3 or 4 weeks to leave a permanent scar, which may be varioliform. Some burning or pruritus may precede or accompany the development of new lesions, but subjective symptoms are seldom severe. The lesions are usually few in number at any one time, but exceptionally may develop in large crops. The most frequent sites are the temples and the anterior margin of the scalp. In some patients, the greater part of the hair line may be involved, but lesions more than a centimetre or two within the scalp are unusual. Much less commonly affected are the midline chest and back, and the cheeks and nose. On the nose, the lesions may be exceptionally large and destructive. In many patients they remain confined to the same region in successive attacks, for example, the temples. In some patients in whom two or three lesions develop at long intervals, acne necrotica is of little significance, but in others in whom recurrences are frequent and the lesions more numerous, they may ultimately produce disfiguring scarring.

Diagnosis. Both the distribution and the relatively short course, rarely exceeding 6 weeks, of the individual lesions should differentiate the papulonecrotic tuberculides (Chapter 31). In tertiary syphilis, the lesions are larger, grouped and asymmetrical, and not pruritic. In acne necrotica miliaris (described as *P. acnes* folliculitis below) the lesions are typically distributed throughout the scalp, and are smaller, usually more numerous, non-scarring and more itchy.

Treatment. If *Staphylococcus aureus* is isolated, a course of an appropriate antibiotic should be given, and an antiseptic shampoo may be advised. Otherwise, and if there is no response or only transient improvement, prolonged courses of an oral antibiotic as for acne, for example a tetracycline, should be given. Topical clindamycin in addition has been recommended [3]. Excoriation should be discouraged, and any significant emotional disorder managed appropriately. Doxepin has been suggested for both its psychotropic and antipruritic effects [3]. Isotretinoin has been successful in some difficult cases [6].

References

1 Hersle K, Mobacken H, Moller A. Chronic non-scarring folliculitis of the scalp. *Acta Derm Venereol (Stockh)* 1979; **59**: 249–53.
2 Maibach HI. Scalp pustules due to *Corynebacterium acnes*. *Arch Dermatol* 1967; **96**: 453–5.
3 Fisher DA. Acne necroticans (varioliformis) and *Staphylococcus aureus*. *J Am Acad Dermatol* 1988; **18**: 1136–7.
4 Calnan CD, O'Neill D. Some observations on acne necrotica. *Trans St John's Hosp Dermatol Soc* 1952; **31**: 12–6.
5 Kossard S, Collins A, McCrossin I. Necrotizing lymphocytic folliculitis: the early lesion of acne necrotica (varioliformis). *J Am Acad Dermatol* 1987; **16**: 1007–14.
6 Maibach HI. Acne necroticans (varioliformis) versus *Propionibacterium acnes* folliculitis. *J Am Acad Dermatol* 1989; **21**: 323.

Perforating folliculitis

This largely asymptomatic eruption of chronic follicular papules occurs mainly on the limbs of young adults. Histologically, the follicles are dilated and plugged with keratin. The follicular epithelium shows one or more perforations into the dermis. Hair is frequently seen close to the epithelial perforations and sometimes within the dermis, as if the inflammatory changes were a reaction to mechanical damage by the hair. Of 25 patients in the original report [1] one was diabetic, but none of the others had systemic disease.

A similar process, less regularly involving hair follicles, and with frequently superimposed nodular prurigo, is associated with renal disease and diabetes (separately or together) [2–4]. Recent studies have included such cases under the more general title of acquired perforating dermatosis [5,6].

References

1 Mehregan AH, Coskey RJ. Perforating folliculitis. *Arch Dermatol* 1968; **97**: 394–9.
2 Hudson RD, Apisarnthananax P. Renal failure and perforating folliculitis. *JAMA* 1982; **247**: 1936–7.
3 Hurwitz RM, Weiss J, Melton ME *et al*. Perforating folliculitis in association with hemodialysis. *Am J Dermatopathol* 1982; **4**: 101–8.
4 White CR, Heskel NS, Pokorny DJ. Perforating folliculitis of hemodialysis. *Am J Dermatopathol* 1982; **4**: 109–16.
5 Patterson JW. Progress in the perforating dermatoses. *Arch Dermatol* 1989; **125**: 1121–3.
6 Rapini RP, Hebert AA, Drucker CR. Acquired perforating dermatosis. *Arch Dermatol* 1989; **125**: 1074–8.

Trunk folliculitis

The authors have seen several cases of a papular and pustular folliculitic eruption on the trunk of young and middle-aged adults. Lesions number a few dozen, widely scattered over the upper trunk, unlike *Malassezia* folliculitis, and miconazole–hydrocortisone cream is ineffective. Routine bacteriology is negative, and comedones and facial acne are absent. There is no improvement on tetracyclines, erythromycin, or trimethoprim–sulphamethoxazole in short or long courses. The response to UVB therapy is good, but the condition tends to relapse within a month of stopping, and repeated courses or maintenance treatment are required.

Actinic folliculitis

Actinic folliculitis has been described in young to middle-aged adults of both sexes, and occurs repeatedly within 24 h of sun exposure. One description is of numerous, superficial follicular pustules on the upper trunk and upper outer arms, with a burning



Fig. 30.9 Disseminate and recurrent infundibulofolliculitis. (Courtesy of Dr W.A.D. Griffiths, St John's Institute of Dermatology King's College London, UK.)

sensation at the onset, resolving within 10 days [1,2]. Another report describes itchy pustules and papules on the lower face resolving within 4 days [3]. The mechanism is unknown. Sunscreens give partial protection at best. Standard acne therapy is ineffective, but the two facial cases responded to isotretinoin [3].

References

1 Nieboer C. Actinic superficial folliculitis; a new entity? *Br J Dermatol* 1985; **112**: 603–6.
2 Verbov J. Actinic folliculitis. *Br J Dermatol* 1985; **113**: 630–1.
3 Norris PG, Hawk JL. Actinic folliculitis—response to isotretinoin. *Clin Exp Dermatol* 1989; **14**: 69–71.

Disseminate and recurrent infundibulofolliculitis

This uncommon condition affects mainly black people [1], but has also been reported in white people [2,3]. Beginning in childhood or in adult life, there is a widespread eruption of follicular papules on the trunk and limbs sparing the flexures (Fig. 30.9). Itch is often, but not always, present. Occasionally, pustules develop. The course is chronic or recurrent. No infective agent has been isolated. Histologically, inflammatory changes are confined to the infundibular portion of the follicles. Oral vitamin A [3] and isotretinoin [4] have been reported to help the condition.

References

1 Hitch JM, Lunz HZ. Disseminate and recurrent infundibulofolliculitis. *Arch Dermatol* 1972; **105**: 580–3.
2 Karg E, Kiss A, Schneider I. Infundibulofolliculitis disseminata recidivans. *Hautarzt* 1986; **37**: 156–8.
3 Owen WR, Wood C. Disseminate and recurrent infundibulofolliculitis. *Arch Dermatol* 1979; **115**: 174–5.
4 Aroni K, Grapsa A, Agapitos E. Disseminate and recurrent infundibulofolliculitis: response to isotretinoin. *Drugs Dermatol* 2004; **3**: 434–5.

Eosinophilic pustular folliculitis

Synonym

- Ofuji's disease

Aetiology [1,2]. Originally most cases of eosinophilic pustular folliculitis were reported from Japan. Since then, cases have been documented worldwide. The male/female ratio is about 5:1. The peak age incidence is the third decade, but cases have occurred in all age groups. Besides the classic type, which occurs mostly in Japan, an HIV-associated, an infantile, a malignancy associated and a medication-associated variety have been described [3]. There are reports of the disease being associated with contact dermatitis, fungal infections and mites. Various chemotactic factors have been detected in the fluid of the pustules which are sterile, and it has been suggested that they may serve to localize excessive circulating eosinophils [4].

Pathology. The follicle, heavily infiltrated with eosinophils, is necrotic with degeneration of the outer root sheath. The blood eosinophil count is raised.

Clinical features. The face is the commonest site, and is the site of onset in most cases. The trunk and the upper outer arms are frequently involved, legs and scalp occasionally. Widespread involvement has occurred [4]. In about 20%, there are pustules of palms or soles, simulating palmoplantar pustulosis.

Groups of papulopustules extend peripherally with central clearing, sometimes forming by confluence annular lesions or plaques, typically 3–5 cm in diameter, before subsiding to leave slight pigmentation. Lakes of pus and erosions are sometimes seen. Itch is frequent but not invariable. Patients are systemically well. The overall course is chronic, with new crops of lesions repeatedly reappearing in affected areas, although a few cases have entered spontaneous remission.

One otherwise well patient developed pyoderma gangrenosum with a fatal outcome [5].

Cases of eosinophilic pustular folliculitis have been reported in patients with acquired immune deficiency syndrome [6] (Chapter 35), which suggests that the disease may be associated with immune dysfunction.

Treatment. A comprehensive review of the various treatments showed that no treatment is consistently effective, and treatment has to be tailored to the individual patient [2]. Systemic corticosteroids are usually but not always helpful, and topical steroids are sometimes partially effective. Dapsone works well in some cases and may be the drug of first choice [7,8]. Other reported therapies include non-steroidal anti-inflammatory drugs, for example indomethacin [9], minocycline, isotretinoin, itraconazole, cetirizine, metronidazole and colchicine [3]. UVB therapy was helpful in six AIDS-associated cases [10], although maintenance treatment was required. Interferon had also been used with some benefit. Topical pimecrolimus and tacrolimus may also be helpful [11].

References

1 Ofuji S. Eosinophilic pustular folliculitis. *Dermatologica* 1987; **174**: 53–6.
2 Ellis E, Scheinfeld N. Eosinophilic pustular folliculitis. *Am J Clin Dermatol* 2004; **5**: 189–97.
3 Takematsu H, Tagami H. Eosinophilic pustular folliculitis. Studies on possible chemotactic factors involved in the formation of pustules. *Br J Dermatol* 1986; **114**: 209–15.

4 Cutler TP. Eosinophilic pustular folliculitis. *Clin Exp Dermatol* 1981; **6**: 327–32.
5 Nunzi E, Parodi A, Rebora A. Ofuji's disease: a follow-up. *J Am Acad Dermatol* 1986; **15**: 107–8.
6 Soeprono FF, Schinella RA. Eosinophilic pustular folliculitis in patients with acquired immunodeficiency syndrome. *J Am Acad Dermatol* 1986; **14**: 1020–2.
7 Malanin G, Helander I. Eosinophilic pustular folliculitis (Ofuji's disease): response to dapsone but not to isotretinoin therapy. *J Am Acad Dermatol* 1989; **20**: 1121.
8 Steffen C. Eosinophilic pustular folliculitis (Ofuji's disease) with response to dapsone therapy. *Arch Dermatol* 1985; **121**: 921–3.
9 Kato H. Eosinophilic pustular folliculitis treated with indomethacin. *Dermatologica* 1989; **179**: 217–8.
10 Buchness MR, Lim HW, Hatcher VA *et al*. Eosinophilic pustular folliculitis in the acquired immunodeficiency syndrome: treatment with ultraviolet B phototherapy. *N Engl J Med* 1988; **318**: 1183–6.
11 Rho N-K, Kim B-J. Eosinophilic pustular folliculitis: successful treatment with topical pimecrolimus. *Clin Exp Dermatol* 2006; **32**: 108–9.

Eosinophilic pustulosis

Eosinophilic pustular folliculitis of the scalp was first reported by Lucky *et al.* [1]. The lesions that develop in infancy or childhood are characterized by recurrent crops of itchy, sterile pustules, which recur over several months or years. The sterile pustules develop on the scalp predominantly, but lesions may occur at other sites. Children may develop axillary, inguinal or cervical lymphadenopathy [2].

Histologically, the lesions demonstrate a heavy eosinophilic infiltrate in the dermis. Bacteriology is usually negative. The condition is self-limiting, but as recurrent lesions are common, dapsone may be helpful.

References

1 Lucky AQ, Esterly NB, Heskel N *et al*. Eosinophilic pustular folliculitis in infancy. *Pediatr Dermatol* 1984; **1**: 202–6.
2 Taieb A, Bassan-Andrieu L, Maleville J. Eosinophilic pustulosis of the scalp in childhood. *J Am Acad Dermatol* 1992; **27**: 55–60.

Perifolliculitis capitis (abscedens et suffodiens)

Synonym
- Dissecting cellulitis of the scalp

Definition. Perifolliculitis capitis is a rare, chronic, suppurative disease of the scalp.

Aetiology. This condition occurs predominantly between the ages of 18 and 40 and almost exclusively in men, and is more common in black males of African origin. It usually occurs alone, although often in acne subjects, but is occasionally associated with acne conglobata and suppurative hidradenitis, leading to suggestions that these three conditions may have a similar basic pathogenesis in follicular occlusion. Although the disease is thought to be infective in origin, the evidence is inconclusive, and the response to treatment with antibiotics is usually disappointing. The suggestion that it is a granulomatous response to keratin requires confirmation: keratin may be found in the dermis as a result of destruction of the follicle by other mechanisms.

Pathology [1,2]. An intense folliculitis and perifolliculitis destroys the follicles, and a chronic inflammatory infiltrate with clumps of foreign-body giant cells extends widely in the dermis. In some areas, the inflammatory changes are more acute and polymorphonuclear leukocytes predominate in the dermal and subcutaneous abscesses. The epidermis is atrophic.



Fig. 30.10 Perifolliculitis capitis. (Courtesy of St. John's Institute of Dermatology, King's College London, UK.)

Clinical features [1,3] (Fig. 30.10). The earliest lesions are firm, tender nodules, usually developing in close groups at short intervals. The hairs overlying the nodules are soon shed or are easily extracted and the follicular openings discharge pus. Nodules may coalesce to form roughly cerebriform ridges, devoid of hair on their summits, but still hairy in the clefts that separate them. Eventually, the nodules may cover the greater part of the scalp and may persist for years, before eventually healing to leave irregular scarring, which may be keloidal. Fatal squamous carcinoma has been reported [4].

Diagnosis. The diagnosis is not usually difficult. Very extensive infection with ringworm of animal origin may produce a massive kerion of the scalp, but the short history and the morphology of the lesions should suggest the diagnosis, which must be confirmed mycologically. Tufted folliculitis may be associated with follicular pustules and papules, but not the boggy abscesses of dissecting cellulitis [5].

Treatment [6]. Bacterial pathogens should be sought and treated, but cultures are often negative and even long-term treatment with antibiotics, as in acne, often disappointing. Without large clinical trials regarding best treatment, therapy recommendations are mostly based on clinical experience.

Substantial but temporary improvement has been reported with isotretinoin, particularly if the duration of therapy is prolonged by several months after clinical improvement [7]. Relapses are still possible.

Zinc sulphate 400 mg three times a day for 12 weeks, followed by half that dose for 10 weeks, resulted in complete healing with satisfactory hair regrowth in one patient with no relapse within 5 years [8]. Combined therapy with fusidic acid (both topical and

systemic), and oral zinc also proved helpful especially when zinc was continued over 6 months [9].

Oral prednisone improves the inflammatory response, but the side effects may limit its use.

Carbon dioxide and ruby laser therapy has been reported to be successful [6,10]. In recalcitrant cases, widespread excision and grafting may be considered [6,11].

References

1 Barney RE. Dissecting cellulitis of the scalp (perifolliculitis capitis abscedens et suffodiens). *Arch Dermatol* 1931; **23**: 503–18.
2 Bachynsky T, Antonyshyn OM, Ross JB. Dissecting folliculitis of the scalp. *J Dermatol Surg Oncol* 1992; **18**: 877–80.
3 Kierland RR. Unusual pyodermas (hidradenitis suppurativa, acne conglobata, dissecting cellulitis of the scalp)—a review. *Minn Med* 1951; **34**: 319–25.
4 Curry SS, Gaither DH, King LE. Squamous cell carcinoma arising in dissecting perifolliculitis of the scalp. *J Am Acad Dermatol* 1981; **4**: 673–8.
5 Annessi G. Tufted folliculitis of the scalp: a distinctive clinicohistological variant of folliculitis decalvans. *Br J Dermatol* 1998; **138**: 799–805.
6 Loo WJ, Dawber R. Dissecting cellulitis of the scalp and folliculitis decalvans. In: Lebwohl M, Heymann W, Berth-Jones J, Coulson I, eds. *Treatment of Skin Diseases*. London: Mosby, 2002: 169.
7 Scerri L, Williams HC, Allen BR. Dissecting cellulitis of the scalp: response to isotretinoin. *Br J Dermatol* 1996; **134**: 1105–8.
8 Berne B, Venge P, Ohman S. Perifolliculitis capitis abscedens et suffodiens (Hoffman). *Arch Dermatol* 1985; **121**: 1028–30.
9 Abeck D, Korting HC, Braun-Falco O. Folliculitis decalvans. Long lasting response to combined therapy with fusidic acid and zinc. *Acta Dermatol Venereol (Stockh)* 1992; **72**: 143–5.
10 Glass LF, Berman B, Lau GD. Treatment of perifolliculitis capitis abscedens et suffodiens with the carbon dioxide laser. *J Dermatol Surg Oncol* 1987; **15**: 673–6.
11 Dellon AL, Orlando JC. Perifolliculitis capitis: surgical treatment for the severe case. *Ann Plast Surg* 1982; **9**: 255–9.

Staphylococcal scalded skin syndrome

Definition. SSSS is an exfoliative dermatosis in which most of the body surface becomes erythematous and the necrotic superficial epidermis strips off. The syndrome was first described in children, but adults may be affected. Factors such as renal failure, malignancy, immunosuppression or alcohol abuse predispose adults to the disease [1], although the disease has been described in normal young adults [2]. Outbreaks of SSSS in nurseries have been reported [3].

Aetiology. The epidermal changes are produced by the exfoliative toxins secreted by the staphylococci. The majority of strains responsible are phage group II, but other phage groups have been described [4]. A mouse model of the disease confirms that the disease is caused by the exfoliative toxins [5]. In adults, blood cultures are often positive for the staphylococci, whereas this is rarely the case in children.

Clinical features [1]. The initial event is usually a localized staphylococcal infection. This may be in the skin or at a distant or 'occult' site. A few days later, patients develop fever, irritability and skin tenderness. A widespread erythematous eruption follows, which progresses rapidly to blister formation. The tender skin becomes gathered into folds and, as it shrinks, leaves raw areas which are extremely painful. The condition usually heals within 7–14 days. Swabs and cultures of blister fluids do not usually grow the staphylococci, as the blisters are mediated by the toxins which are disseminated haematogenously. The staphylococci may be isolated from the original septic site.

Pathology. Histologically, there is splitting of the epidermis between the granular and spinous layers. A few lymphocytes surround the superficial blood vessels. The disease is caused by one or more exfoliative toxins elaborated by some strains of *Staphylococcus aureus*. Two of the toxins (A and B) have been shown to cause disruption of the desmosomes by cleaving desmoglein 1 [6]. Antibodies to desmoglein may develop in some patients with SSSS [7]. The same toxins are involved in bullous impetigo, which may be regarded as a localized form of SSSS although patients with bullous impetigo do not seem to develop the same level of antibody. This may be due to the shorter duration of the disease [7]. Toxin A is chromosomally encoded whereas toxin B is plasmid derived [8]. There is some evidence that the toxins are proteases [9].

Management. The prognosis is good in children, and if antibiotics are administered early, the mortality rate is low. Children usually recover within 7 days. In adults, the overall mortality rate seems to be higher. Those patients without underlying disease recover more rapidly. Parenteral antibiotics such as methicillin, flucloxacillin, a cephalosporin or erythromycin are required.

'Scalded skin syndrome' has been used as a synonym for toxic epidermal necrolysis (TEN). However, it is now clear that cell necrosis does not occur in the staphylococcal disease, and it is widely accepted that the term 'staphylococcal TEN' is inappropriate. Where there is doubt about the diagnosis, a frozen section of peeled skin will confirm the split in the granular layer in SSSS [10]. Alternatively, a Tzanck preparation from a freshly denuded area may be helpful. In SSSS, there are a number of epithelial cells with large nuclei but no inflammatory cells, whereas in TEN there are only a few rounded epithelial cells but many inflammatory cells.

References

1 Mockenhaupt M, Idzko M, Grosber M *et al*. Epidemiology of staphylococcal scalded skin syndrome in Germany. *J Invest Dermatol* 2005; **124**: 700–3.
2 Patel GK, Varma S, Finlay AY. Staphylococcal scalded skin syndrome in healthy adults. *Br J Dermatol* 2000; **142**: 1253–5.
3 Curran JP, Al-Sahili FL. Neonatal staphylococcal scalded skin syndrome: massive outbreak due to an unusual phage type. *Pediatrics* 1980; **66**: 285–90.
4 Florman AL, Holzman RS. Nosocomial scalded skin syndrome. Ritter's disease caused by phage group 3 *Staphylococcus aureus*. *Am J Dis Child* 1980; **134**: 1043–5.
5 Melish ME, Glasgow LA. The staphylococcal scalded skin syndrome. *N Engl J Med* 1970; **282**: 1114–9.
6 Amagai M, Matsuyoshi N, Wang ZH *et al*. Toxin in bullous impetigo and staphylococcal scalded skin syndrome targets desmoglein 1. *Nat Med* 2000; **6**: 1275–7.
7 Anzai H, Stanley JR, Amagai M. Production of low titres of anti-desmoglein 1 autoantibodies in some patients with staphylococcal scalded skin syndrome. *J Invest Dermatol* 2006; **126**: 2139–41.
8 Johnson AD, Spero L, Cades JS, de Cicco BT. Purification and characterisation of different types of exfoliative toxin from *Staphylococcus aureus*. *Infect Immun* 1979; **24**: 679–84.
9 Dancer JD, Garrat R, Saldanha J *et al*. The epidermolytic toxins are serine proteases. *FEBS Lett* 1990; **268**: 129–32.
10 Amon RB, Dimond RL. Toxic epidermal necrolysis. Rapid differentiation between staphylococcal- and drug-induced disease. *Arch Dermatol* 1975; **111**: 1433–7.

Toxic shock syndrome

Definition. Fever, a rash followed in 1–3 weeks by desquamation, circulatory shock and multisystem disease characterize this syndrome, which is mediated by one or more toxins elaborated by *Staphylococcus aureus.*

Aetiology. Nearly all cases have been infected or colonized by *S. aureus.* Staphylococcal infection of any severity, at any site, at any age and in either sex may cause toxic shock syndrome [1]. However, in most of the early cases the organism was isolated from the vagina of menstruating women using tampons in the USA; in these cases, symptomatic vaginitis was common but not invariable. It seemed likely that staphylococci, perhaps introduced by hand or from perineal skin, found appropriate conditions for growth in the medium of the menstrual blood, facilitated in some way by the tampon. A strong association with absorbency, and especially with one brand, was noted. Avoidance of these materials in tampons was followed by a dramatic fall in the incidence, so that after 1985 the majority of USA cases were non-menstrual [2].

Toxic shock syndrome toxin 1 (TSST-1), previously identified as staphylococcal enterotoxin F or as pyrogenic exotoxin C [3], is produced by 80–90% of *S. aureus* isolates from affected cases, and is believed to be the main bacterial mediator of the disease, although it is likely that other toxins, probably other enterotoxins, are involved in some cases [4]. This toxin belongs to a family of bacterial pyrogenic toxin superantigens (PTSAgs) which are able to stimulate T-lymphocyte proliferation in a non-antigen specific manner. This results in fever, inflammation and shock. Most of these PTSAgs are encoded by a series of distinct mobile elements referred to as staphylococcal pathogenicity islands, which are located at specific sites in the genome and can be mobilized and transferred by other phages to other strains [5].

A similar disease has been associated with severe infections with *Streptococcus pyogenes* [6], and may be mediated by re-emergent scarlet fever toxin A [7].

Clinical features [8,9]. The onset is acute with fever and rash. Vomiting and diarrhoea are common early features, and involvement of muscle, liver, kidneys and central nervous system may follow. Circulatory shock may be severe and the mortality rate is about 7%.

The rash may be the presenting feature or may develop within the first day. A widespread macular erythema, sometimes faint, and clearing within 3 days, is commonest, but scarlatiniform and papulopustular eruptions are also described. Oedema of hands and feet may be marked. There is generalized mucous membrane erythema, especially intense in the conjunctiva, under which there may be haemorrhage. Oral, oesophageal, vaginal and bladder mucosae may ulcerate. Occasionally, vesicles and bullae may form. Towards the end of the second week, the majority of patients develop a widespread, itchy, maculopapular sometimes urticarial rash, which is thought not to be drug-induced in most cases. Thrombocytopenia may cause purpura. Desquamation is highly characteristic. It occurs 10–21 days after the onset, and may be confined to the fingertips, may affect all the palmar and plantar skin or may be generalized. Reversible patchy alopecia or telogen effluvium, and transverse ridging and partial loss of nails are later non-specific findings.

Pathology. There are no specific histological features. A perivascular mononuclear cell infiltrate and papillary oedema may occur in the dermis. In cases with blister formation the split is subepidermal [9].

Diagnosis. The diagnosis is primarily clinical, supported by the confirmation, in the great majority of cases, of staphylococcal infection. Fever, rash, and later desquamation, are required for the diagnosis; shock is a marked feature in the fully developed disease, but postural dizziness may suffice for the diagnosis in mild cases [10].

Septic shock and other infections should be excluded by appropriate investigations. Some reported adult cases of Kawasaki disease may have had toxic shock syndrome. The diseases have features in common, but Kawasaki disease can usually be differentiated by prolonged fever, cardiac involvement, generalized lymphadenopathy and absence of peripheral shock. Reports of staphylococcal scarlatina may represent milder cases of toxic shock syndrome. Ehrlichosis may present with a life-threatening illness similar to toxic shock syndrome [11]. *Clostridium sordellii* infection may be associated with toxic shock syndrome and a high mortality rate. The disease resembles the staphylococcal syndrome except that there is no associated rash; it may follow postpartum infections [12].

Treatment. Appropriate systemic antibiotic therapy should be given. Intensive general supportive measures are essential.

References

1 Reingold AL, Dan BB, Shands KN *et al*. Toxic shock syndrome not associated with menstruation. *Lancet* 1982; **1**: 1–4.

2 Broome CV. Epidemiology of toxic shock syndrome in the United States: overview. *Rev Infect Dis* 1989; **11** (Suppl. 1): S14–21.

3 Crass BA, Bergdoll MS. Toxin involvement in toxic shock syndrome. *J Infect Dis* 1986; **153**: 918–26.

4 Becker K, Bierbaum G, von Eiff C *et al*. Understanding the physiology and adaptation of staphylococci: a post-genomic approach. *Int J Med Microbiol* 2007; **297**: 483–501.

5 Novick RP. Mobile genetic elements and bacterial toxinoses: the superantigen-encoding pathogenicity islands of *Staphylococcus aureus*. *Plasmid* 2003; **49**: 93–105.

6 Cone LA, Woodard DR, Schlievert PM *et al*. Clinical and bacteriologic observations of a toxic shock-like syndrome due to *Streptococcus pyogenes*. *N Engl J Med* 1987; **317**: 146–9.

7 Parsonnet J. Mediators in the pathogenesis of toxic shock syndrome: overview. *Rev Infect Dis* 1989; **11** (Suppl. 1): S263–9.

8 Bach MC. Dermatologic signs in toxic shock syndrome—clues to diagnosis. *J Am Acad Dermatol* 1983; **8**: 343–7.

9 Chesney PJ. Clinical aspects and spectrum of illness of toxic shock syndrome: overview. *Rev Infect Dis* 1989; **11** (Suppl. 1): S1–7.

10 Wannamaker LW. Toxic shock: problems in definition and diagnosis of a new syndrome. *Ann Intern Med* 1982; **96**: 775–7.

11 Fichtenbaum CJ, Peterson LR, Weil GJ. Ehrlichiosis presenting as a life-threatening illness with features of the toxic shock syndrome. *Am J Med* 1993; **95**: 351–7.

12 McGregor JA, Soper DE, Lovell G, Todd JK. Toxic shock associated with *Clostridium sordellii* infection. *Am J Obstet Gynecol* 1989; **161**: 987–95.



Fig. 30.11 Recurrent toxin-mediated perineal erythema.

Recurrent toxin-mediated perineal erythema [1]

Clinical features. After a sore throat, patients develop an eruption in the perineal area. The rash resembles erysipelas (Fig. 30.11), but settles quicker, and is associated with very little in the way of systemic features.

Diagnosis. The diagnosis is made on clinical grounds. Patients are usually well, with a history of a sore throat. Swabs from the perineal area do not grow any specific organisms, but throat swabs may yield *Staphylococcus aureus* or *Streptococcus pyogenes*. These are usually toxin producing strains. The exact pathogenesis is still unclear.

Treatment. Patients respond well to a short course of antibiotics, which covers streptococci and staphylococci, with few sequelae.

Reference

1 Manders SM, Heymann WR, Atillasoy E *et al*. Recurrent toxin-mediated perineal erythema. *Arch Dermatol* 1996; **132**: 57–60.

Other staphylococcal and streptococcal infections

(see also Table 30.1)

Periporitis staphylogenes [1] is secondary infection with *Staphylococcus aureus* of miliaria of the newborn. It is an infection of sweat glands and should not be confused with folliculitis or furunculosis, which are rare in neonates. Pustular miliaria itself is sterile.

Staphylococcal blepharitis [2] commonly presents with hard scales on the lid margins ('squamous' type). If thicker crusts form around the lashes, their removal may leave ulceration of the follicle ('ulcerative' type). Conjunctivitis is nearly always associated.

A sporotrichoid distribution of infected nodules was reported in two cases [3], one involving *S. aureus* alone and the other a combined infection with *Streptococcus pyogenes*.

Staphylococcal fissure of the lower lip [4] may be caused by *Staphylococcus aureus*, where there is persistent fissuring at or close to the midline of the lower lip. The fissures may start in cold weather but persist for many months despite the use of emollients. Traditional signs of infection are absent, presumably because any exudate is promptly licked away. There is a rapid response to a topical antibiotic.

Acute paronychia (Chapter 65) is commonly due to *S. aureus*.

Staphylococcal scarlatina is a scarlatiniform rash, clinically indistinguishable from streptococcal scarlet fever, but without the accompanying exudative tonsillitis, which may complicate staphylococcal infection, beginning 1–9 days after the initial symptoms [5–9]. Negative Schultz–Charlton tests with streptococcal scarlet fever antitoxin suggest that the staphylococcal and streptococcal toxins are antigenically distinct [5,9].

At present there is insufficient evidence for the proposed inclusion [10] of staphylococcal scarlatina within SSSS.

References

1 Sylvest B, Eriksen KR. An outbreak of periporitis staphylogenes of complex origin. *Acta Derm Venereol (Stockh)* 1979; **59** (Suppl. 85): 181–4.
2 Smolin G, Okumoto M. Staphylococcal blepharitis. *Arch Ophthalmol* 1977; **95**: 812–6.
3 Tanaka S, Mochizuki T, Watanabe S. Sporotrichoid pyogenic bacterial infection. *Dermatologica* 1989; **178**: 228–30.
4 Evans CD, Highet AS. Staphylococcal infection in median fissure of the lower lip. *Clin Exp Dermatol* 1986; **11**: 289–91.
5 Dunnet WN, Schallibaum EM. Scarlet fever-like illness due to staphylococcal infection. *Lancet* 1960; **ii**: 1227–9.
6 Faden HS, Burke JP, Glasgow LA *et al*. Nursery outbreak of scalded skin syndrome. *Am J Dis Child* 1976; **130**: 265–8.
7 Ginsburg CM. Staphylococcal toxin syndromes. *Pediatr Infect Dis J* 1991; **19**: 319–21.
8 McCloskey RV. Scarlet fever and necrotising fasciitis caused by coagulase-positive hemolytic *Staphylococcus aureus* phage type 85. *Ann Intern Med* 1973; **78**: 85–7.
9 Rahman AN, Rammelkamp CH. Scarlet fever, toxic shock syndrome and the staphylococcus. *Am J Med Sci* 1982; **284**: 36–9.
10 Melish ME, Glasgow LA. Staphylococcal scalded skin syndrome: the expanded clinical syndrome. *J Pediatr* 1971; **78**: 958–67.

Streptococcal vulvovaginitis

Streptococcus pyogenes accounts for 10% of cases of vulvovaginitis in prepubertal girls [1]. Perianal infection occasionally coexists. The child complains of genital soreness or irritation and the skin is acutely erythematous. There may be purulent discharge or dysuria. Other bacterial causes, including *Neisseria gonorrhoeae*, cannot be distinguished clinically. The infection responds to oral penicillin or erythromycin.

Reference

1 Schwartz RH, Wientzen RL, Barsanti RG. Vulvovaginitis in prepubertal girls: the importance of Group A streptococcus. *South Med J* 1982; **75**: 446–7.

Perianal streptococcal cellulitis

The term 'cellulitis' [1,2] seems inappropriate for this superficial infection that lacks fever and other systemic symptoms, although surface swabs yield group A streptococci in all cases.

Most patients are children aged 1–10 years, but occasional adult cases are seen. Some, but not all, patients were found to harbour *Streptococcus pyogenes* in the throat, usually of the same strain, and sometimes there is a recent history of pharyngitis in a family member. In some reported cases, there had been symptoms for many weeks or months suggesting that chronic infection may occur. Perianal soreness or irritation, pain on defecation and sometimes secondary faecal retention are typical presenting symptoms. The affected skin is bright red and may be fissured. Guttate psoriasis and, in girls, vulvovaginitis are occasionally associated.

The condition responds to an oral antibiotic. Penicillin is often successful, but recurrences in some patients respond to erythromycin and topical mupirocin [3]. A 2-week course is recommended [2].

References

1 Amren DP. Unusual forms of streptococcal disease. In: Wannamaker LW, Matsen JM, eds. *Streptococci and Streptococcal Diseases*. New York: Academic Press, 1972: 73–82.
2 Marks VJ, Maksimak M. Perianal streptococcal cellulitis. *J Am Acad Dermatol* 1988; **18**: 587–8.
3 Barnett BO, Frieden IJ. Streptococcal skin diseases in children. *Semin Dermatol* 1992; **11**: 3–10.

Streptococcal ulcers

Acute ulcers, often on the legs and feet, are one of the more frequent forms of streptococcal pyoderma under humid tropical conditions [1]. Chronic ulcers of streptococcal origin may follow insect bites or abrasions, and are not uncommon [2]. Serpiginous in outline with an undermined edge and an uneven, roughly granular floor, they may persist for many months but heal rapidly with antibiotic treatment.

References

1 Allen AM, Taplin D, Twigg L. Cutaneous streptococcal infections in Vietnam. *Arch Dermatol* 1971; **104**: 271–80.
2 Goodman MH. Chronic streptococcic ulcer of the skin. *JAMA* 1938; **111**: 1427–9.

Blistering distal dactylitis

Originally this disease was described in children and caused by group A streptococci [1]. Since then, the disease has been reported in adults [2] and other organisms have been identified, including group B streptococci [3] and staphylococci [4]. A large blister containing thin, seropurulent fluid forms on the distal phalanx, usually of a finger, and typically on the palmar pad (Fig. 30.12), although it may extend to the nailfolds, and more proximal involvement of the palmar skin is sometimes seen [1]. An upper respiratory tract infection is sometimes present. One recurrent case occurred beside an ingrowing toenail [5]. The organism is cultured from blister fluid and responds to oral antibiotic treatment [6]. Topical therapy with wet dressings may be helpful [6].

References

1 McCray MK, Esterly NB. Blistering distal dactylitis. *J Am Acad Dermatol* 1981; **5**: 592–4.
2 Benson PM, Solivan G. Group B streptococcal blistering distal dactylitis in an adult diabetic. *J Am Acad Dermatol* 1987; **17**: 310–1.
3 Frieden IJ. Blistering dactylitis caused by Group B streptococci. *Pediatr Dermatol* 1989; **6**: 300–2.
4 Woroszylski A, Duran C, Tamayo L *et al*. Staphylococcal blistering dactylitis—a report of 2 cases. *Pediatr Dermatol* 1996; **13**: 292–3.



Fig. 30.12 Blistering distal dactylitis.

5 Telfer NR, Barth JH, Dawber RPR. Recurrent blistering distal dactylitis of the great toe associated with an ingrowing toenail. *Clin Exp Dermatol* 1989; **14**: 380–1.
6 Scheinfeld NS. Is blistering distal dactylitis a variant of bullous impetigo? *Clin Exp Dermatol* 2007; **32**: 314–6.

Streptococcal intertrigo and other streptococcal conditions

Intertrigo of simple mechanical origin or associated with other dermatoses is readily colonized by many organisms. Haemolytic streptococci may become established and may give rise to crusting and fissuring in the depth of the affected flexure. Such fissuring is a characteristic feature of infective eczematoid dermatitis behind the ears, and may complicate intertrigo in any site [1]. The condition can be distinguished from monilial intertrigo by the lack of satellite pustules, and from psoriasis of the flexures by the lack of scale [1].

The fissure may be healed with appropriate antibiotics, but recurrence is frequent unless the predisposing factors can be effectively eliminated.

Sporotrichoid nodular lesions yielded both *Staphylococcus aureus* and *Streptococcus pyogenes* in one case, and *Staphylococcus aureus* only in another [2].

A woman with streptococcal septicaemia developed toxic epidermal necrolysis for which no other cause was found [3].

Streptococcal throat infection was suggested as a cause of acute urticaria in children [4].

References

1 Honig PJ, Frieden IJ, Kim HJ *et al*. Streptococcal intertrigo: an underrecognized condition in children. *Pediatrics* 2003; **112**: 1427–9.
2 Tanaka S, Mochizuki T, Watanabe S. Sporotrichoid pyogenic bacterial infection. *Dermatologica* 1989; **178**: 228–30.
3 Wright KU, Ellis ME. Toxic epidermal necrolysis associated with streptococcal septicaemia. *BMJ* 1985; **291**: 312–3.
4 Schuller DE, Elvey SM. Acute urticaria associated with streptococcal infection. *Pediatrics* 1980; **65**: 592–6.

Toxin-mediated streptococcal disease

Scarlet fever

Synonym
- Scarlatina

Aetiology [1–4]. Scarlet fever is an acute infection caused by strains of *Streptococcus pyogenes* producing pyrogenic exotoxin (erythrogenic toxin, erythrotoxin), of which there are three antigenically unrelated types, A, B and C. All three are capable of producing scarlet fever. Toxin production appears to depend on the presence of a temperate bacteriophage and is exclusive to group A streptococci, a single strain of which may produce none, one, two or all three toxins [5]. In the 1970s and 1980s, type B was the most frequent toxin in the USA, Germany and England, and type C was also seen; type A is believed to have been responsible for the severe disease seen several decades ago. Whether an infected individual develops scarlet fever or a septic streptococcal illness, such as tonsillitis or cellulitis, depends on the level of antitoxic immunity, normally acquired by previous exposure.

The disease occurs throughout the world but the full syndrome is uncommon in the tropics, where surveys suggest that subclinical infections must be frequent [6]. Scarlet fever is endemic in large towns but the incidence varies greatly from year to year. The incidence in the Oxford (UK) region at a time of greater frequency of the disease was 0.3 confirmed, and 1.25 suspected, cases per 1000 per year [7]. In the last few decades, scarlet fever has been less severe than in the late 19th and early 20th centuries, perhaps because of the virtual disappearance of type A toxin [8].

The upper respiratory tract is the usual portal of entry, and although infection of surgical and other wounds may sometimes be responsible, most reports of this association have not included bacteriological examination of the throat. Droplet infection is commonest but the disease may be spread by fomites or by milk. Most cases occur between the ages of 1 and 10 years, and infections are rare in infancy and old age. In a recent (2006) outbreak of scarlet fever in the United Kingdom [9], the streptococci isolated were mostly of M-type 12. In Taiwan, the number of cases of scarlet fever has increased considerably over the past few years and the isolates mainly contained *emm*-1, *emm*-4, *emm*-12 and *emm*-22 genotypes. The genotypes isolated varied over the years although *emm*-1 was always present. This change in genotype may relate to the prevalence of strains around in the community at the time of the outbreak [10].

Pathology. The erythrogenic toxin is responsible for cutaneous vasodilatation, which may be associated with oedema and a perivascular cellular infiltrate. The toxin may also produce a degenerative myocarditis. The bacterial component of the syndrome consists of septic lesions in many organs, with abscess formation. Glomerulonephritis depends on an immunological mechanism.

An attack with a rash confers permanent, specific antitoxic immunity. The toxin produced by other strains is not neutralized, hence second attacks, although rare, can occur. Bacterial immunity is temporary and there is therefore no permanent protection against the septic manifestation of infection by the same or related strains of streptococcus.

Clinical features [9,11]. After an incubation period, which is usually 2–5 days, fever, anorexia and vomiting usher in the infection. If the throat is the portal of entry, there is an acute follicular or membranous tonsillitis, with painful lymphadenopathy. If the infection has entered a wound, there may be increased tenderness and some serous discharge.

The rash, which appears on the second day, first on the upper trunk, is a finely punctate erythema which has been likened to 'sunburn with goose pimples'. It generalizes within a few hours or over 3 or 4 days. Transverse red streaks in the skin folds due to capillary fragility are known as Pastia's lines. The face is flushed but rarely shows punctate erythema, and relative pallor around the mouth is characteristic. The lower legs are involved last and least. After 7–10 days the rash is succeeded by desquamation, branny in most areas but in large, lamellar scales on palms and soles.

The oral mucous membranes are bright red and there may be deeper red puncta on the palate. The tongue is at first heavily coated, but by the second or third day scattered, swollen, red papillae give the 'white strawberry tongue' appearance. As the epithelium is shed, the tongue becomes smooth and dark red ('red strawberry tongue') before returning to normal.

Fever usually settles in 7–10 days. The typical course of the mild or moderate case may be modified if either the toxic or septic manifestations are severe.

In the severe toxic form the eruption is very intense and may be purpuric. Fever is high and the patient is delirious or comatose. Myocarditis is often present.

In the septic forms, the local pharyngeal lesions are severe and there may be extensive oedema. Otitis media and peritonsillar abscesses are frequent. The rash may be slight.

Complications are caused either by the toxin, or by bacterial invasion of tissues by local extension or by haematogenous dissemination, or by a probably allergic reaction. Of the toxic manifestations, myocarditis is the most important. The suppurative complications include hepatitis, arthritis, meningitis and osteomyelitis. Rheumatic fever and glomerulonephritis are presumed to be allergic in origin.

At present, the prognosis is good and the mortality of treated cases is under 1%.

Second attacks are more frequent in patients in whom early antibiotic control of the initial attack has impaired the immune response [12].

Diagnosis. The classical form of the disease associated with tonsillitis is unlikely to be misdiagnosed if it is considered. The diagnosis may be supported by culture of a haemolytic streptococcus, a rising antistreptolysin-O titre and blanching of the rash around the point of injection of antitoxin—the Schultz–Charlton test. The peripheral blood usually shows polymorphonuclear leukocytosis.

Rubella, the early stage of smallpox, and some drug reactions can simulate scarlet fever. The lack of pharyngeal lesions and the distribution of the exanthem will usually enable the diagnosis to be established. Rarely, staphylococcal infections are accompanied by a scarlatiniform erythema.

In the so-called recurrent scarlatiniform erythema, repeated attacks of a somewhat similar rash, followed by exfoliation, occur without discoverable cause.

Far East scarlet-like fever occurred in epidemics in the Far East during the 1950s. The aetiological agent has been identified as *Yersinia pseudotuberculosis* IP31758, and the complete genome has now been sequenced, showing its evolution from the typical strain of *Y. pseudotuberculosis* [13].

Treatment. Penicillin should be given in full dosage for 10 days as soon as the diagnosis is suspected, to reduce the communicability of the infection. The management of the complications lies beyond the scope of this book, but the possibility of myocardial or renal damage should always be borne in mind and careful and prolonged supervision is obligatory.

References

1 Hallas G. The production of pyrogenic toxins by Group A streptococci. *J Hyg* 1985; **95**: 47–57.
2 Hamburger M, Hilles CH, Hamburger VG *et al*. Ability of different types of hemolytic streptococci to produce scarlet fever. *JAMA* 1944; **124**: 564–6.
3 Schwenkter FF, Janney JH, Gordon JE. The epidemiology of scarlet fever. *Am J Hyg* 1943; **38**: 27–98.
4 Wesselhoeft C, Weinstein L. Scarlet fever. *N Engl J Med* 1945; **232**: 500–5.
5 Schlievert PM, Bettin KM, Watson DW. Production of pyrogenic exotoxin by groups of streptococci: association with Group A. *J Infect Dis* 1979; **140**: 676–81.
6 Murray JF. Bantu immunity to scarlet fever toxin. *J Hyg* 1943; **43**: 170–2.
7 Perks EM, Mayon-White RT. The incidence of scarlet fever. *J Hyg* 1983; **91**: 203–9.
8 Cone LA, Woodard DR, Schlievert PM *et al*. Clinical and bacteriologic observations of a toxic shock-like syndrome due to *Streptococcus pyogenes*. *N Engl J Med* 1987; **317**: 146–9.
9 Hoek M, Dalling J, Thompson S *et al*. Scarlet fever outbreak in 2 nurseries in southwest England. *Euro Surveill* 2006; **11**: E060302.5.
10 Chiou C-S, Liao T-L, Wang T-H *et al*. Epidemiology and molecular characterization of *Streptococcus pyogenes* recovered from scarlet fever patients in central Taiwan from 1996–1999. *J Clin Microbiol* 2004; **2**: 3998–4006.
11 Bialecki C, Feder NM, Grant-Kels JM. The six classic childhood exanthems: a review and update. *J Am Acad Dermatol* 1989; **21**: 891–903.
12 Deutsch J, Scholz HJ. Scharlach und scharlach-zweiterkrankund heute. *Deutsche Med Wochenschr* 1967; **92**: 797–804.
13 Eppinger M, Rosovitz MJ, Fricke WF *et al*. The complete genome sequence of *Yersinia pseudotuberculosis* IP31758, the causative agent of Far East scarlet-like fever. *PLoS Genet* 2007; **3**: e142.

Streptococcal toxic shock-like syndrome

Definition. Fever, myalgia and flu-like symptoms are followed by pain in an extremity, or the abdomen. A rash followed by desquamation, circulatory shock and multisystem disease characterize the streptococcal toxic shock-like syndrome (TSLS).

Aetiology. This disorder has been associated with the recent re-emergence of invasive group A streptococcal infections. Group A streptococci are usually cultured from the blood. The streptococcal toxins are likely to be responsible for this condition, although the exact pathogenic mechanisms are currently still unknown.

Clinical features [1,2]. The disease may occur in immunocompetent children or adults.

The disease is similar to staphylococcal toxic shock syndrome, although there may be some differences. Cases of streptococcal TSLS are associated with severe invasive group A streptococcal disease, whereas staphylococcal toxic shock syndrome may be associated with either severe or trivial infection. Surgical wounds, throat infections, vaginal infections postpartum, or soft-tissue infections due to group A streptococci, may be followed by the streptococcal TSLS. The disease is associated with a high mortality rate. Complications include myositis, endophthalmitis, peritonitis and renal failure [3].

Diagnosis. Blood cultures are frequently positive, and swabs from the site of clinical infection almost always yield group A streptococcal M types 1, 3, 12 and 28. The streptococcal pyrogenic exotoxins A and B are produced in the majority of these cases.

Treatment. Penicillin, erythromycin or clindamycin would be the treatment of choice for most soft-tissue infections caused by group A streptococci. Where necrotizing fasciitis or myositis have developed, debridement, fasciotomy or amputation may be required. Intravenous gammaglobulin may be helpful to neutralize the toxin [4].

References

1 Stevens DL. Invasive group A streptococcal infections: the past, present and future. *Pediatr Infect Dis J* 1994; **13**: 561–6.
2 Torres-Martinez C, Mehta D, Levin M. Streptococcus associated toxic shock. *Arch Dis Child* 1992; **67**: 126–30.
3 Stevens DL, Tanner MH, Winship J *et al*. Severe group A streptococcal infections associated with a toxic shock-like syndrome and scarlet fever toxin A. *N Engl J Med* 1989; **321**: 1–7.
4 Barry W, Hudgins L, Donta ST, Pesanti EL. Intravenous immunoglobulin therapy for streptococcal toxic shock syndrome. *JAMA* 1992; **267**: 3315–6.

Coryneform bacteria

The term coryneform bacteria is currently used to describe Gram-positive, non-sporing, rod-shaped organisms commonly referred to as diphtheroids [1,2]. This heterogeneous group has a wide distribution in nature and is of considerable importance to the dermatologist. It embraces *Corynebacterium diphtheriae*, the cutaneous aerobic coryneforms, *Corynebacterium* and *Brevibacterium* species, as well as the anaerobic *Propionibacterium* species. Two animal species that may cause human diseases, *Listeria monocytogenes* and *Erysipelothrix insidiosa*, may be included in this group (Table 30.3).

Aerobic coryneforms of the resident normal flora

Many different strains of aerobic coryneform bacteria may be isolated from the normal human skin. Their classification remains

Table 30.3 Coryneform bacteria.

Human commensals or pathogens
Aerobic
Corynebacterium diphtheriae primarily throat
C. haemolyticum
C. pyogenes primarily skin
C. xerosis
C. hofmannii
C. minutissimum
Brevibacterium epidermis
Anaerobic
Propionibacterium acnes primarily follicular
P. granulosum
P. avidum
Pathogens of other vertebrates sometimes infecting humans
Listeria monocytogenes
Erysipelothrix rusiopathiae

unsatisfactory, but attempts to divide them into a mere six species complex on the basis of obligate lipophilicity, glucose fermentation, tyrosine clearance and nitrate reduction are encouraging to the non-specialist [1]. Apart from *Corynebacterium* species, it is now clear that *Brevibacterium* species, non-lipophilic coryneform organisms, can be isolated regularly from most human skin, especially the toe clefts [2]. It is generally accepted that trichomycosis axillaris and erythrasma are caused by an overgrowth of resident coryneforms, and there are grounds for suggesting that one of the organisms involved in pitted keratolysis is also a resident coryneform. In trichomycosis, a variety of different strains of aerobic coryneforms have been implicated, not a single species (*Corynebacterium tenuis*) as originally thought. In erythrasma, the term *Corynebacterium minutissimum* is still used, but it is probably wise to recognize that this label implies a species complex of fluorescent aerobic coryneforms capable of initiating, alone or with others, the characteristic scaling and pigmentary changes of that condition. As with so many other skin microorganisms, corynebacteria have also become resistant to many antibiotics. Groups D2 and JK of the corynebacteria are highly resistant to most antimicrobial agents, and these organisms are regularly found on the skin and mucous membranes. They may be associated with systemic infections, particularly in patients with catheters or those who are immunosuppressed [3]. Carriage of these organisms occurs on many different skin sites, especially the perineal area, suggesting that the antibiotic resistance originates in the gastrointestinal tract and then passes to the skin [3].

References

1 Noble WC. *Microbiology of Human Skin*, 2nd edn. London: Lloyd Luke, 1981.

2 Pitcher DG, Jackman PJH. The current status of aerobic cutaneous coryneform bacteria. In: Maibach HI, Aly R, eds. *Skin Microbiology: Relevance to Clinical Infection*. New York: Springer, 1981: 19–28.

3 Soriano F, Rodriguez-Tudela JL, Fernandez-Roblas R *et al*. Skin colonization by *Corynebacterium* groups D2 and JK in hospitalised patients. *J Clin Microbiol* 1988; **26**: 1878–80.

Diphtheria

Aetiology. In temperate regions, and probably also in urban areas in the tropics, *Corynebacterium diphtheriae* is isolated predominantly from the nose and throat of healthy carriers who have recovered from an attack of faucial diphtheria. In some tropical rural areas, the organism is found only rarely in the nose and throat, but is present in 30–60% of skin lesions of various types—impetigo, yaws, infected abrasions—in the indigenous population [1].

Generally, the rates of infection are considerably less in individuals receiving adequate courses of immunization, and where infections occur they are usually less severe in these groups than in the non-immunized [2]. It is likely that widespread immunization programmes have been in part responsible for the decreased incidence of diphtheria. When immunization coverage is reduced, outbreaks of diphtheria re-emerge, as in the former Soviet Union countries in the late 1990s [3]. One interesting observation is that isolates of *C. diphtheriae* from immunized subjects are less likely to be toxogenic than those from the non-immunized.

The diphtheria toxin consists of two fragments: the A polypeptide, which is the active segment, and the B fragment, which binds to cell-surface receptors. The A segment inactivates transfer RNA translocase, preventing protein synthesis.

Strains of *C. diphtheriae* differ in toxigenicity, and those isolated from chronic skin lesions often produce little toxin. All strains are lysogenic for temperate phages: strains which lose their phage lose their ability to produce toxin.

The association of *C. diphtheriae* with yaws in the Pacific area is statistically significant, and suggests that the lesions produced by the spirochaete may provide particularly suitable conditions for colonization by diphtheria.

Cutaneous diphtheria is rarely reported in temperate climates, but the diagnosis is easily overlooked [4]. An outbreak occurred in Vancouver, Canada, in all numbering 44 cases. Another report from northern Canada has stressed the persistence of diphtheria in spite of high immunization rates, and the more frequent isolation of *C. diphtheriae* from Native Americans, than from Eskimos or white people [5]. In the tropics, especially where hygienic standards are low, the infection is more readily established in pre-existing skin lesions, and in the southern USA cutaneous infections have been shown to be significant in the epidemiology of diphtheria, particularly in poor communities [6,7]. In the United Kingdom, 17 cases of cutaneous diphtheria due to toxigenic *C. diphtheriae* were reported from 1995 to 2002, all of which were travel related [8].

Pathology. Colonization of skin lesions by a strain of low virulence may not modify their morphology or produce any remote toxic effects. Such strains may provide a sufficiently strong antigenic stimulus for immunity to develop.

A toxigenic strain induces local necrotic changes and systemic effects.

Clinical features [4,5]. The typical early lesion is a superficial ulcer, rounded, oval or irregularly linear, with a clearly defined, overhanging edge. Exudate from the ulcer floor tends to form a tough grey or brownish grey, adherent membrane. Later, the ulcer may deepen and its edge become rolled, raised and avascular. There may be moderate enlargement of the regional lymph nodes. In temperate climates, the lesions occur most commonly at the umbilicus, behind the ears, in the genitocrural flexures, in a toe cleft or in a finger or toe, where a whitlow may be simulated. They may, however, develop in any pre-existing skin lesion, and in the tropics commonly complicate such conditions as desert sores. Cutaneous diphtheria may persist for 6–12 weeks, healing with scar formation.

In many cases, the lesions are less distinctive and may simulate impetigo or ecthyma. A rare clinical form has been described in children with eczema: varicelliform vesicles or pustules are succeeded by diphtheritic ulcers. For this reason the role of *C. diphtheriae* in the pathogenesis of skin lesions has been questioned, particularly as other potentially pathogenic bacteria, such as staphylococci and streptococci, may be present [4].

Systemic manifestations are characteristically absent or mild in cutaneous diphtheria, but are occasionally severe, especially in infants. In all forms, neurological complications, on which the retrospective diagnosis of diphtheria is sometimes based, occur in some 30% of cases and myocarditis in 5–10%.

Faucial diphtheria may be associated with adherent haemorrhagic crusts around the nose and mouth.

Diagnosis. The diagnosis may be suspected in persistent ulcers with an adherent membrane, but must be confirmed bacteriologically. The detection of toxin production is important for the diagnosis. A rapid detection immunochromatographic strip is useful, as the result is available after about 16 hours from taking the swab [3].

Treatment. Specific antitoxin should be administered as soon as the diagnosis is suspected: 20000–50000 units should be given intramuscularly. Penicillin or erythromycin should also be prescribed. The subsequent management will depend on whether there is neurological or cardiac involvement, and will be facilitated if the toxigenicity of the infecting strain can be established.

Erythromycin is probably the most effective compound for eradicating skin carriage.

References

1 Bray JP, Burt EG, Potter EV *et al*. Epidemic diphtheria and skin infections in Trinidad. *J Infect Dis* 1972; **126**: 34–40.
2 Kwantes W. Diphtheria in Europe. *J Hyg* 1984; **93**: 433–7.
3 Engler KH, Efstratiou A, Norn D *et al*. Immunochromatographic strip test for rapid detection of diphtheria toxin: description and multicenter evaluation in areas of low and high prevalence of diphtheria. *J Clin Microbiol* 2002; **40**: 80–3.
4 Belsey MA, LeBlanc DR. Skin infections and the epidemiology of diphtheria: acquisition and persistence of *C. diphtheria* infections. *Am J Epidemiol* 1975; **102**: 179–84.
5 Jellard CH. Diphtheria infection in Northwest Canada 1969, 1970, 1971. *J Hyg* 1972; **70**: 503–10.
6 Koopman JS, Campbell J. The role of cutaneous diphtheria infection in a diphtheria outbreak. *J Infect Dis* 1975; **131**: 239–44.
7 Pedersen AHB, Spearman J, Tronca E *et al*. Diphtheria on skid row, Seattle, Washington. *Public Health Rep* 1977; **92**: 336–42.
8 DeBenoist A, White JM, Efstratiou A *et al*. Imported cutaneous diphtheria, United Kingdom. *Emerg Infect Dis* 2004; **10**: 511–3.

C. haemolyticum infection

This organism has been reclassified as *Arcanobacterium haemolyticum* [1]. Infection with this organism usually affects the throat, and may be associated with a maculopapular rash. Patients usually present with sore throats, mild to moderate in severity with little malaise or fever, and approximately half the patients developed a maculopapular rash [1,2]. In immunocompromised patients it may cause a diphtheria-like infection and septicaemia. Lepromatous ulcers are frequently colonized with these organisms [3]. The organism produces soluble toxins including sphingomyelinase D and phospholipase D, which contribute to its virulence. The swab needs to be cultured on 5% human blood agar for isolation and identification [1]. Treatment with appropriate antibiotics is effective.

References

1 Gaston DA, Zurowski SM. *Arcanobacterium haemolyticum* pharyngitis and exanthem. Three case reports and literature review. *Arch Dermatol* 1996; **132**: 61–4.
2 Linder R. *Rhodococcus equi* and *Arcanobacterium haemolyticum*: two coryneform bacteria increasingly recognised as agents of human infection. *Emerg Infect Dis* 1997; **3**: 145–53.
3 Sturm AW, Jamil B, McAdam KP *et al*. Microbial colonisers in leprosy skin ulcers and intensity of inflammation. *Int J Lepr Other Mycobact Dis* 1996; **64**: 274–81.

C. pyogenes infection

C. pyogenes has been connected with outbreaks of skin ulceration in Thailand [1]. The organism has been reclassified as *Actinomyces pyogenes* [2]. The clinical appearances of lesions closely resemble those seen with other forms of pyoderma including tropical ulcers. Spread by flies in the area has been suggested. The pathogenetic mechanism by which these organisms produce skin necrosis has yet to be established.

References

1 Kotrajaras R, Tagami H. *Corynebacterium pyogenes*; its pathogenic mechanism in epidemic leg ulcers in Thailand. *Int J Dermatol* 1987; **21**: 407–9.
2 Reddy CA, Cornell CP, Fraga AM. Transfer of *Corynebacterium pyogenes* to the genus *Actinomyces* as *Actinomyces pyogenes* comb. nov. *Int J Syst Bacteriol* 1982; **32**: 419–29.

Erythrasma

Definition. Erythrasma is a mild, chronic, localized superficial infection of the skin caused by a group of closely related aerobic coryneform bacteria, usually known as *C. minutissimum*.

Aetiology. For over a century, erythrasma was thought to be due to an actinomycete, for which the name *Nocardia minutissima* was proposed. It is now recognized that the Gram-positive rods and filaments always found in the scales of erythrasma are coryneforms. The name *Corynebacterium minutissimum* has been given to the organisms isolated, but possibly more than one species may be involved. The epidemiology of erythrasma has not been fully elucidated. There seems to be little doubt that the organisms responsible are frequently members of the normal flora, at least in the toe clefts, and that some shift in the host–parasite relationship results in the development of classical erythrasma. A warm, humid climate is a predisposing factor. Erythrasma may be the presenting feature in diabetics [1].

Clinical infection may occur at any age but is more common among adults than children. In institutions, the incidence may increase steadily with age [2]. Among normal populations, mild toe-cleft scaling with pink fluorescence is common. Clinically important infections of the groins are much less frequent and those of the axilla are uncommoner still. Within closed communities, the condition is likely to be more prevalent: in one hospital for the mentally subnormal, the incidence in the toe clefts was 30%, in the groins 18% and in the axillae 4% [3]. The epidemiology of erythrasma has been reviewed by Holdiness [4].

A variety of erythrasma that affects the axillae, infra-mammary folds and large areas of the trunk, as well as the groins, is particularly common in obese, middle-aged black women. Diabetes was found to coexist in eight of 13 patients with lesions of this type [5].

Clinical features [4] (Fig. 30.13). Erythrasma, as detected by Wood's light examination, involves the toe clefts more frequently than any other site. As clinically manifest lesions it occurs most commonly in the groins, axillae and the intergluteal and submammary flexures. In the groins it affects the area of one or both thighs in contact with the scrotum. Lesions on the glans penis and beneath the prepuce have rarely been reported [6] but have probably



Fig. 30.13 Erythrasma. (Courtesy of St. John's Institute of Dermatology, London, UK.)

seldom been sought. The patches are of irregular shape and sharply marginated, at first red, but later becoming brown. New lesions are smooth, but older lesions tend to be finely creased or obviously scaly. In the generalized form, the sharply marginated, reddish brown plaques may cover extensive areas of the trunk and limbs.

In temperate climates most lesions are symptomless, but in the tropics particularly, irritation of lesions in the groins may lead to scratching and lichenification. Involvement of the perianal skin may present as pruritus ani, of which erythrasma is an uncommon cause.

Toe-cleft infections are often asymptomatic; the scaling, fissuring and maceration that may be present are not necessarily caused by the corynebacteria. Rarely *C. minutissimum* has been associated with systemic disease, such as recurrent abscesses or endocarditis [4].

Fluorescence under Wood's light. Coral-red fluorescence with Wood's light is attributable to coproporphyrin III and strongly suggests erythrasma, although it does not necessarily indicate active infection. The persistence of fluorescence after eradication of the coryneforms may depend on the thickness of the horny layer, for it is common at the margins of the toe webs.

Pink fluorescence is also demonstrable in some necrotic tumours and on the normal tongue, where it is not apparently caused by coryneforms. It is seen in the follicular openings of the normal skin of the face and the upper trunk, where corynebacteria or propionibacteria are the likely cause. In the groins and axillae, acanthosis nigricans may fluoresce a brilliant pink colour, presumably due to heavy colonization with fluorescent coryneforms, although other bacteria may show pink fluorescence.

Differential diagnosis. Pityriasis versicolor is most commonly confused with erythrasma, but it occurs predominantly on the upper trunk, and the individual lesions are small and are not erythematous. On the thighs, groins and pubic area, tinea cruris may be simulated, but the relative lack of inflammation, complete absence of vesiculation and absence of satellite lesions point against tinea. It is difficult to differentiate erythrasma of the toe clefts from tinea pedis or *Candida* infection, but, as in all varieties of erythrasma, the presence of coral-red fluorescence under Wood's light is diagnostic. Since many patients have both tinea pedis and erythrasma, mycological examination of scales is important. Flexural psoriasis needs to be excluded.

Prognosis. Without treatment the condition tends to persist indefinitely, although there may be spontaneous fluctuations in severity.

Laboratory identification. Scrapings from the affected skin may show bacteria and fine filaments if stained with Gram or Giemsa or even with simple potassium hydroxide clearance. Culture on Tissue Culture Medium 199 (without antibiotics) with 20% calf serum and 2% agar yields colonies that fluoresce coral red under Wood's light after 18–36 h, but cultural confirmation is not normally necessary if the clinical appearance is typical and Wood's lamp examination of the patient is positive.

Treatment. Although several treatments have been recommended for erythrasma, there are no studies comparing their effectiveness. All the current available therapies have been reviewed by Holdiness [4]. Erythrasma responds well to most topically applied azole antifungal agents, such as clotrimazole and miconazole [5]. The duration of therapy varies, but 2 weeks is usually sufficient. For more extensive lesions, erythromycin is probably the most effective approach. Alternatives include topical fucidin and oral tetracycline. Good results have also been reported with a single dose of 1 g clarithromycin [7], although clarithromycin is a more expensive drug. Relapse is a problem in some patients. In these cases the usual approach adopted is to give long-term antiseptic soaps, such as povidone–iodine, and to use drying agents, such as powders, in the affected areas. Photodynamic therapy using the porphyrin produced by the causative organisms has been tried in some patients with some benefit [8].

References

1 Montes LF, Dobson H, Dodge BG *et al*. Erythrasma and diabetes mellitus. *Arch Dermatol* 1969; **99**: 674–8.

2 Sarkany I, Taplin D, Blank H. Incidence and bacteriology of erythrasma. *Arch Dermatol* 1962; **85**: 578–82.

3 Somerville DA, Seville RH, Cunningham RC *et al*. Erythrasma in a hospital for the mentally subnormal. *Br J Dermatol* 1970; **82**: 355–60.

4 Holdiness MR. Management of cutaneous erythrasma. *Drugs* 2002; **62**: 1131–41.

5 Pitcher DG, Noble WC, Seville RH. Treatment of erythrasma with miconazole. *Clin Exp Dermatol* 1979; **4**: 453–6.

6 Rudiak AJ. Erythrasma mit ungewohnlicher Lokalisation. *Dermatol Wochenschr* 1968; **154**: 994–6.

7 Wharton J, Wilson P, Kincannon JM. Erythrasma treated with a single-dose clarithromycin. *Arch Dermatol* 1998; **134**: 671–2.
8 Darras-Vercambre S, Carpentier O, Vincent P *et al*. Photodynamic action of red light for treatment of erythrasma: preliminary results. *Photodermatol Photo* 2006; **22**: 153–6.

Trichomycosis axillaris

Synonym
- Trichomycosis nodosa

Definition and aetiology. This is a superficial infection of axillary and pubic hairs with the formation of adherent granular nodules—yellow, black or red—on the hair shaft. The misleading term 'trichomycosis' is retained in the absence of a generally agreed alternative, although it has been clear for many years that the causative agent is not a fungus [1]. Studies using transmission and scanning electron microscopy [2] have shown that the concretions consist almost exclusively of tightly packed bacteria. They grow within and between the cuticular cells and may invade the cortex [2]. Cultural studies have shown a variety of different biochemical types of aerobic *Corynebacteria* to be involved and not the single species, *C. tenuis*, as was at one time believed. These biotypes probably reflect the range of resident coryneform types in the normal axilla. It has been shown that the changes in chemical environment of these organisms may induce pigment production, perhaps explaining the different colours of the nodules, which are not attributable to different bacterial strains [3].

Clinical features. Trichomycosis occurs in both temperate and tropical climates and is not limited by race or sex. It is usually asymptomatic and the patient is often unaware of its presence. Yellow, black or red concretions are present on the hair shaft and these may be hard, or soft and nodular, or more diffuse. In the nodular varieties, the hair may be brittle and easily broken [2]. The underlying skin is normal. The axillary sweat may be yellow, black or red according to the colour of the concretions, and the clothing may be stained. The yellow type is the most common and the black the rarest. The few figures available on the prevalence of trichomycosis show it to be common.

Axillary infection was present in 27% of adult male students in one UK survey, and in 42% of male patients but only 7% of women patients in a hospital for the mentally subnormal [4]. This sex difference is largely explained by absence of axillary hair in the women. Pubic infection is less common but should not be forgotten [5].

Differential diagnosis. Pediculosis pubis, which may affect axillary as well as pubic hair, and piedra, should be considered. Examination under Wood's light is helpful. Microscopical confirmation of the diagnosis is desirable.

Laboratory identification. Potassium hydroxide mounts show the bacteria as narrow bacillary organisms in the yellow or red concretions. They are Gram positive. For culture, the hairs must be surface sterilized, and this may be satisfactorily done by immersion in 70% alcohol. Incubation at 37°C in blood agar is recommended. Light and ultrastructural studies, together with various stains, have shown that a variety of coryneforms adhere to the hair shaft and some are encapsulated in an extracellular encasing. This was thought to be an analogue of glucan synthesized by streptococci and responsible for the adhesion [6].

Treatment. Clipping the affected hairs and the application of an antimicrobial ointment, such as benzoic acid compound ointment or 1% aqueous formalin, are effective. However, the use of an effective antiperspirant such as anhydrous aluminium chloride is a rapid means of therapy.

References

1 Crissey JT, Rebell GC, Laskas JJ. Studies on the causative organisms of trichomycosis axillaris. *J Invest Dermatol* 1952; **19**: 187–97.
2 Orfanos CE, Schloesser E, Mahrle G. Hair destroying growth of *Corynebacterium tenuis* in the so-called trichomycosis axillaris. *Arch Dermatol* 1971; **103**: 632–9.
3 MacBride ME, Duncan WC, Knox JM. The effects of selenium and tellurium compounds on pigmentation of granules of trichomycosis axillaris. *Int J Dermatol* 1970; **9**: 226–31.
4 Savin JA, Somerville DA, Noble WC. The bacterial flora of trichomycosis axillaris. *J Med Microbiol* 1970; **3**: 252–6.
5 White SW, Smith J. Trichomycosis pubis. *Arch Dermatol* 1979; **115**: 444–5.
6 Shelley WB, Miller MA. Electron microscopy, histochemistry and microbiology of bacterial adhesion in trichomycosis axillaris. *J Am Acad Dermatol* 1984; **10**: 1005–14.

Pitted keratolysis

Synonym
- Keratolysis plantare sulcatum

Definition and aetiology. A superficial infection of the skin apparently caused by a species of *Corynebacterium* and producing circular erosions on the soles [1]. Filamentous and coccoid microorganisms were originally observed in skin scrapings and the organism was named *Actinomyces keratolytica*. Other reports tended to incriminate a species of *Streptomyces*, but a species of *Corynebacterium* has also been isolated, and recent work suggests that *Dermatophilus congolensis*, *Micrococcus sedentarius*, a *Corynebacterium* or a combination of these organisms, and possibly other organisms too, invade keratin softened by sweat [1–3].

There are no studies of the prevalence of the condition although it is said to be more common in tropical countries. A study of 184 German athletes found 25 affected [4].

Histology. A mixture of coccoid bacteria and filamentous microorganisms may be seen in abundance in the most superficial parts of the stratum corneum, and extending downwards between keratinocytes [4]. There is associated lysis of the keratin.

Laboratory identification. The organisms are not always easy to find in potassium hydroxide mounts but are more easily detected in Gram-stained scrapings. Culture on brain–heart infusion agar, incubated at 37°C in a mixture of pure nitrogen containing 5–10% carbon dioxide, gives minute, irregular, colourless colonies within 3–5 days [5].



Fig. 30.14 Pitted keratolysis. (Courtesy of St. John's Institute of Dermatology, King's College London, UK.)

Clinical features (Fig. 30.14). There are numerous superficial erosions of the horny layer of the soles and the undersurfaces of the toes. All parts of both soles may be affected, but pressure bearing or friction areas are most commonly affected. Conspicuous, discrete, shallow, circular lesions with a punched-out appearance coalesce in places to produce irregular erosions. There is occasionally green or brown discoloration of the horny layer. Hyperhidrosis is often associated, sometimes with maceration, stickiness and a foul odour [4,6]. Soaking the feet in water for 15 min causes swelling of the horny layer and accentuates the lesions. Irritation is minimal and in most cases patients are unaware of the condition. Under battle conditions, soreness and pain have been reported in severe cases [1,6].

Similar changes affecting the palms have been described on rare occasions in the Far East, UK and southern USA.

Differential diagnosis. The lesions are easily recognizable, but simple hyperhidrosis, erythrasma and tinea pedis have to be considered.

Treatment. Treatment of hyperhidrosis slowly brings the condition under control but a more rapid response may be obtained with fucidin ointment. Other topical antibiotics and imidazoles such as clotrimazole are reputed to be effective [1]. Botulinum toxin which reduces the hyperhidrosis has been helpful [7].

References

1 Zaias N. Pitted and ringed keratolysis. *J Am Acad Dermatol* 1982; **7**: 787–91.
2 Rubel LR. Pitted keratolysis and *Dermatophilus congolensis*. *Arch Dermatol* 1972; **105**: 584–6.
3 Nordstrum KM, McGinley KJ, Capiello L *et al*. Pitted keratolysis: the role of *Micrococcus sedentarius*. *Arch Dermatol* 1987; **123**: 1320–5.
4 Wohlrab J, Rohbrach D, Marsch WC. Keratolysis sulcata (pitted keratolysis): clinical symptoms with different histological correlates. *Br J Dermatol* 2000; **143**: 1348–9.
5 Young CN. Pitted keratolysis—a preliminary report. *Trans St John's Hosp Dermatol Soc* 1974; **60**: 77–85.
6 Takama H, Tamada Y, Yano K *et al*. Pitted keratolysis: clinical manifestations in 53 cases. *Br J Dermatol* 1997; **137**: 282–5.
7 Tamura B, Cuce LC, Souza R *et al*. Plantar hyperhidrosis and pitted keratolysis treated with Botulinum toxin injection. *Dermatol Surg* 2004; **30**: 1510–4.

Propionibacteria

Definition. Propionibacteria are anaerobic coryneforms of the resident normal flora. These Gram-positive, pleomorphic bacilli are found in large numbers and are widely distributed over the whole skin. Though formerly all termed *Corynebacterium acnes*, it is now recognized that they are more properly classified as propionibacteria and may be divided into three species. *Propionibacterium acnes* and *P. granulosum* are found predominantly in the pilosebaceous follicles of those sites where sebum is plentiful, and *P. avidum* is mainly isolated from moist intertriginous zones [1].

From its location, it is unlikely that *P. avidum* has any part in the causation of acne. *P. acnes* and *P. granulosum* may well have a key role. *P. acnes* has been studied in depth and plays an important role. The importance of *P. acnes* and *P. granulosum* in acne is considered in Chapter 42. Recently, the genomic sequence of a bacteriophage of *P. acnes* has been characterized and perhaps this may lead to phage therapy for acne in time [2].

In addition to its association with acne, *P. acnes* has been isolated from cases of endocarditis and meningitis associated with the presence of ventriculoatrial or ventriculoperitoneal shunts. It has also been proposed as a cause of indolent folliculitis [3].

References

1 Noble WC. *Microbiology of Human Skin*, 2nd edn. London: Lloyd Luke, 1981.
2 Farrar MD, Howson KM, Bojar RA *et al*. Genome sequence and analysis of a *Propionibacterium acnes* bacteriophage. *J Bacteriol* 2007; **189**: 4161–71.
3 Maibach HI. Scalp pustules due to *Corynebacterium acnes*. *Arch Dermatol* 1967; **96**: 453–5.

Anthrax

Aetiology [1,2]. Anthrax is a specific infection with *Bacillus anthracis*, a Gram-positive, encapsulated organism, which can survive as spores for over 20 years in soil. It is primarily an infection of herbivorous animals, but occasional outbreaks occur in other species. Animals are infected by ingesting the spores. Animal infections, and hence human infections, are still a serious problem in Africa (for example Zimbabwe and Chad), Pakistan, India, Iran, the Middle East and parts of Russia. Only occasional cases are seen in other areas, and these sporadic cases are easily overlooked as the diagnosis is not considered [3]. In the endemic areas, humans are infected directly from animals or animal products, and male adults are most at risk, but in some rural communities children minding cattle may be infected. There are no known cases of human-to-human spread.

Anthrax often follows occupational exposure during care of livestock or the handling of products. In western Europe, most cases of anthrax formerly occurred among workers in the wool, hair or bristle industries, or those handling animal materials imported from India, Pakistan or Africa. In many countries, stricter codes of practice for hygiene in the workplace resulted in a decline even in sporadic infections. Unsterilized imported bone meal, or sacks contaminated with it, remains a potential hazard, although

warning labels on this product appear to be effective in reducing the danger still further.

Human resistance to infection is normally high. Cutaneous inoculation is favoured by minor trauma or pre-existing skin lesions, and pulmonary and intestinal forms result from the inhalation or ingestion of spores. Systemic anthrax involves massive bacteraemia and is often fatal.

Pathology. The anthrax bacillus induces an inflammatory tissue response in which haemorrhage and necrosis are associated with a gelatinous oedema, which contains large amounts of bacterial capsular material. The bacillus is present in large numbers in the skin lesions, and in the blood in systemic infections. The major virulence factors are the binary exotoxins, oedema and lethal toxins, which are encoded on two virulence plasmids pX01 and pX02. Oedema toxin is known to inhibit neutrophil function, and is responsible for the oedema which develops locally, and lethal toxin, a zinc metalloprotease, stimulates macrophages to release tumour necrosis factor-α and interleukin-1β, which are in part responsible for sudden death in systemic disease [2].

Clinical features [1,2]. The lesion of cutaneous anthrax follows after introduction of endospores into the skin. The exposed skin, especially face, neck, hands or arms are affected most often. There may be a single or multiple lesions. Although often referred to as the 'malignant pustule', the lesion is not purulent and is often relatively painless. Between 1 and 5 days after infection, an irritable papule develops at the site of inoculation. A bulla on a red oedematous base soon follows. The bulla ruptures and forms a haemorrhagic crust around which is a zone of oedema and erythema in which may be several small vesicles. The surrounding tissues are oedematous, and although the regional lymphatic glands may be tender, their involvement is slight in relation to the severity of the lesion and lymphangitis is unusual. In some cases, particularly when the face is involved, malignant oedema, characterized by severe swelling, induration and multiple bullae, may develop, and the localized pustule is inconspicuous or absent. The clinical picture is very variable and purely or predominantly bullous lesions have been reported.

Constitutional symptoms may begin 3 or 4 days after the onset of the pustule. In severe untreated cases, malaise, high fever, toxaemia and prostration may be followed by delirium, collapse and death.

Anthrax meningitis is a rare complication of cutaneous disease.

Overall, the mortality of untreated cutaneous anthrax is between 5 and 20%, but most cases are mild and healing follows in 2–3 weeks. Severe oedema or toxaemia are of poor prognostic significance. With early and adequate antibiotic treatment, all cases are curable.

Anthrax may also cause respiratory, orophayngeal and gastrointestinal disease. In the respiratory type, a mild primary illness is followed in 2–4 days by respiratory distress. The gastrointestinal type may follow ingestion of endospore-contaminated meat from infected animals. Symptoms include haematemesis and diarrhoea with abdominal pain. Oesophageal involvement may give rise to dysphagia, local adenopathy and massive swelling of the neck [3].

Diagnosis. Staphylococcal infection, vaccinia, ecthyma gangrenosum, cat-scratch disease (formerly named para-anthrax), North American blastomycosis and sporotrichosis may need exclusion. In the authors' experience, both staphylococcal infections and cowpox can simulate anthrax very closely. Both may show the central black haemorrhagic crust and the zone of oedema and erythema. The history, rapid course, clinical appearance and lack of lymphangitis should suggest the diagnosis, which must be confirmed by bacteriological examination. Blood cultures are usually positive in systemic disease, although treatment should not be withheld while awaiting bacteriology results, as rapid deterioration may result in death. A serological test to the capsular antigens and exotoxin components is available, and a rising antibody titre to the protective and capsular antigens are indicative of recent infection or vaccination. However, these tests have little value in the acute illness. An anthraxin skin test may be suitable for rapid diagnosis of acute cases and the retrospective analysis of anthrax infections [1]. Polymerase chain reaction to amplify specific virulence markers may soon be available.

Treatment [1,2]. Treatment should not be withheld until bacteriological confirmation has been obtained. Intravenous penicillin G should be given for 7–10 days, in a dose of 4 million units 6 hourly for the first 3–4 days. Tetracycline or erythromycin can be given in the presence of allergy to penicillin or in the very rare cases in which the bacillus is resistant to penicillin. If the patient is already severely toxic when treatment is started, intravenous fluids and corticosteroids are advisable. Where bioterrorism is suspected, 6 weeks of antimicrobial treatment is recommended [2].

Vaccination gives some protection [4] and should be offered to those who are exposed in the course of their occupations, but prevention should be directed primarily at control of the disease in animals and disinfection of animal products. Prophylaxis for asymptomatic patients exposed to anthrax spores includes a 6-week course of doxycycline or ciprofloxacin.

References

1 Dixon TC, Meselson M, Guillemin J *et al*. Anthrax. *NEJM* 1999; **341**: 815–26.
2 Swartz MN. Recognition and management of anthrax—an update. *NEJM* 2001; **345**: 1621–6.
3 Kolbe A, Yuen M, Doyle BK. A case of human cutaneous anthrax. *Med J Aus* 2006; **185**: 281–2.
4 Ivins BE, Welkos SL. Recent advances in the development of an improved human anthrax vaccine. *Eur J Epidemiol* 1988; **4**: 12–9.

Other *Bacillus* species

Rarely, other species of the genus *Bacillus* may cause deep subcutaneous infections resembling necrotizing fasciitis [1,2]. *B. cereus* and *B. subtilis* may cause a variety of different infections of the eye ranging from conjunctivitis to panophthalmitis.

References

1 Sliman R, Rehm S, Shale DM. Serious infections caused by *Bacillus* species. *Medicine* 1987; **66**: 218–23.
2 Brett MM, Hood J, Brazier J *et al*. Soft tissue infections caused by spore-forming bacteria in injecting drug users in the United Kingdom. *Epidemiol Infect* 2005; **133**: 575–82.

Listeriosis

Aetiology [1–6]. Listeriosis is an infection caused by *Listeria monocytogenes*, a Gram-positive microaerophilic, motile bacillus easily confused with coryneform organisms. It can survive low temperatures and will grow at 4°C. It is a facultative, intracellular pathogen, inducing its own uptake into non-phagocytic cells and spreads from cell to cell by an actin-based motility process. In addition, most strains express internalin A, a protein required for invasion of host cells [1].

The organism is found in water and soil, and has been isolated from sewage sludge and inferior silage [2]. It infects wild, domestic and laboratory animals, and direct infection from cattle and sheep is a hazard to veterinary surgeons [3] and farmers. However, listeriosis is mainly a food-borne disease, and milk, cheese and poultry are the main sources of human disease [4]. Transplacental and birth canal infections are a well-recognized hazard to the fetus and neonate [5]. Infection of a baby from the mother's milk has been reported [6]. Otherwise, direct transfer from human to human does not seem to occur. However, *L. monocytogenes* may be carried asymptomatically in the human gut as well as the cervix and vagina, at least for short periods, so the potential for transfer of infection does exist.

Clinical features [7]. Although most cases of listeriosis are sporadic, there have been several outbreaks reported over the past 10 years. Most adult infections are now thought to be subclinical, but a mild febrile illness with gastrointestinal symptoms and loin pain may occur in otherwise healthy individuals. More serious infections with a meningitic or glandular fever-like illness are well known, and in immunocompromised patients meningitis or pneumonia may dominate the picture. Cutaneous lesions are uncommon in these cases, but when present are purpuric. During pregnancy, an indeterminate febrile illness, not necessarily severe, may occur. This may not arouse any suspicions, but the fetus may be aborted or the infant may be stillborn or premature. Neonates may develop a combination of respiratory and gastrointestinal symptoms with granulomas of the posterior pharynx, generalized erythema and dark-red or bluish papules, especially on the trunk and leg. Meningitis and septicaemia may be seen later in the neonatal period [8].

In veterinary surgeons, a mild, predominantly cutaneous form of the disease may occur 1–3 days after contact with an infected animal [3]. Fever and malaise are followed after a day or so by an eruption of discrete, dull-red papules, some of which later show central pustulation. In serious adult infections, in the immunocompromised patient and in the neonate, the prognosis is poor without treatment, at least 30% of cases being fatal [1].

Diagnosis. As there are no specific clinical features, the diagnosis will be missed unless it is borne in mind in unexplained fevers, glandular fever-like illness and meningitis. As the incubation period can be quite long (6–8 weeks) mild symptoms may be forgotten. In those at risk through occupation, or predisposing states, the diagnosis is established by blood culture, and if a high index of suspicion towards diphtheroids is maintained, through isolation from other sites. The organism grows easily on blood or nutrient agar but cold enrichment may help. Strains isolated from recent outbreaks have been characterized and designated Epidemic Clone I, or II, depending on whether they are related or divergent. The genome sequence of several strains of *Listeria monocytogenes* has been completed and may help with the understanding of its pathogenicity. Unfortunately, serology using somatic and flagellar antigens is time consuming, but can be helpful in the investigation of common source outbreaks [1].

Treatment. The drug of choice is ampicillin, but the organism is also susceptible to penicillin, erythromycin and tetracycline. Gentamicin may be used advantageously with ampicillin or penicillin, particularly in immunocompromised individuals, as synergism occurs. Prevention of contamination of foods is vital to reduce the number of outbreaks of listeriosis. Individuals at high risk of infection should be informed about cross-contamination of foods, thorough cooking of foods and storage of perishable foods [9].

References

1 Ramaswamy V, Cresence V, Rejitha J *et al*. Listeria—a review of epidemiology and pathogenesis. *J Microbial Immunol Infect* 2007; **40**: 4–13.
2 Watkins J, Sleath KP. Isolation and enumeration of *Listeria monocytogenes* from sewage, sewage sludge and river water. *J Appl Bacteriol* 1981; **50**: 1–9.
3 Kalkoff KW, Schiff W. Listeriosis of the skin caused by contact infection. *Hautarzt* 1960; **11**: 201–4.
4 Fleming DW, Cochi SL, MacDonald KL *et al*. Pasteurized milk as a vehicle of infection in an outbreak of listeriosis. *N Engl J Med* 1985; **312**: 404–7.
5 Spencer JAD. Perinatal listeriosis. *BMJ* 1987; **295**: 349.
6 Svabic-Vlahovic M, Pantic D, Pavicic M *et al*. Transmission of *Listeria monocytogenes* from mother's milk to her baby and to puppies. *Lancet* 1988; **2**: 1201.
7 Braden CR. Listeriosis. *Pediatr Infect Dis J* 2003; **22**: 745–6.
8 Chen S, Lu FL, Lee P *et al*. Neonatal listeriosis. *J Formos Med Assoc* 2007; **106**: 161–4.
9 Goulet V. What can we do to prevent listeriosis in 2006? *Clin Infect Dis* 2007; **44**: 529–30.

Erysipeloid

Aetiology [1–3]. Erysipeloid is an acute, rarely chronic, infection with *Erysipelothrix rusiopathiae* (formerly known as *E. insidiosa*). This organism is widespread in nature as a commensal or pathogen in a wide variety of animal species; it can persist in soil for many months, causing infection long after the contamination. It colonizes a wide variety of animals worldwide, including mammals, birds, fish and shellfish, and causes disease in many of these, especially in pigs. Human infection is contracted by direct contact, occasionally from living animals, but more commonly from carcasses, so that erysipeloid usually affects slaughtermen, butchers, cooks, fishermen, farmers and veterinary surgeons. The existence of L forms might explain the occasional chronic or recurrent infections [1]. The organism, *E. rusiopathiae*, produces a neuraminidase and a hyaluronidase, both of which are believed to be virulence determinants.

Pathology [3]. Cultures of deep biopsy material from the advancing edge of recent lesions occasionally yield the organism, which is Gram-positive, non-encapsulated, non-motile and non-sporulating. However, cultures are often negative, although growth is improved with 5–10% carbon dioxide. Histology shows epidermal spongiosis or vesiculation, dermal oedema, lymphangitis,

capillary engorgement and infiltration with neutrophils and eosinophils. Organisms have only rarely been detected by light microscopy. However, electron microscopy has demonstrated cell-wall-deficient bacteria (L forms), which may explain the difficulty of demonstrating the bacteria by conventional methods.

Clinical features [1,2]. Three clinical syndromes have been distinguished in humans: localized cutaneous, which is much the most common (erysipeloid of Rosenbach), generalized cutaneous and systemic, in which skin lesions may occur.

Most human infections are localized and self-limiting. About 3 days after inoculation, a hot violaceous and tender erythema develops around the inoculation site and extends centrifugally, but irregularly, with a sharp and sometimes gyrate border, which may be vesicular. Most lesions are on the hand, fingers or forearms, but any exposed area may be involved. Fever and mild constitutional symptoms such as arthralgia are present in only some 10% of cases. Extension continues for 3 or 4 days, rarely for as long as a week, but the area eventually involved is seldom more than 10 cm in diameter. Without treatment, healing normally occurs spontaneously in 2 weeks without desquamation or suppuration.

Widespread skin lesions are rare, described as violaceous, with a variable, pink advancing border and with central resolution. There may be systemic symptoms, but blood cultures are negative. This form is also usually self-limiting, but runs a more protracted course with the possibility of recurrences.

Systemic infection with *E. rhusiopathiae* infection is uncommon. Endocarditis (usually affecting the aortic valve), joint, bone, brain and pleural involvement have been described. Congestive cardiac failure, myocardial abscesses and aortic valve perforation may follow. Patients are ill, lose weight and may show localized cutaneous swellings with central necrosis, or scattered perifollicular papules. Blood cultures are usually positive with appropriate techniques.

Diagnosis. On blood agar the organisms are α-haemolytic with S (smooth) or R (rough) colonies depending on the culture conditions. Two new PCR methods have improved the detection and identification of these organisms [4]. The diagnosis of the cutaneous disease is mainly clinical. Compared with erysipelas/cellulitis, erysipeloid usually lacks constitutional symptoms and lymphangitis, the lesions are more purplish, and local joint involvement is more common.

Treatment [1–3]. Most isolated skin lesions heal spontaneously in about 4 weeks. Healing is facilitated by antibiotic therapy, as the organism remains sensitive to penicillin, ciprofloxacin or erythromycin. Tetracyclines are often satisfactory, but the sensitivity of the organism is variable. For severe or systemic infections, intravenous penicillin is required. The organism is resistant to vancomycin which is often used as empiric therapy in endocarditis due to Gram–positive organisms. As the organism may persist on environmental surfaces, thorough cleaning with antiseptics helps with decontamination (e.g. fishing boats etc.) [5].

References

1 Barnett JH, Estes SA, Wirman JA *et al*. Erysipeloid. *J Am Acad Dermatol* 1983; **9**: 116–23.

2 Gorby GL, Peacock JE. *Erysipelothrix rhusiopathiae* endocarditis: microbiologic, epidemiologic and clinical features of an occupational disease. *Rev Infect Dis* 1988; **10**: 317–25.

3 Reboli A, Farrar W. *Erysipelothrix rhusiopathiae*: an occupational pathogen. *Clin Micro Rev* 1989; **2**: 354–9.

4 Makino S, Okada Y, Maruyama T *et al*. Direct and rapid detection *of Erysipelothrix rhusiopathiae* DNA in animals by PCR. *J Clin Microbiol* 1994; **32**: 1526–31.

5 Fidalgo SG, Longbottom CJ, Riley TV. Susceptibility of *Erysipelothrix rhusiopathiae* to antimicrobial agents and home disinfectants. *Pathol* 2002; **34**: 462–5.

Gas gangrene (clostridial myonecrosis)

Aetiology. Gas gangrene designates a clinical syndrome caused by the infection of wounds with various species of *Clostridium*, alone or in combination with anaerobic streptococci, and often with aerobic organisms such as *Proteus*. The most important species of *Clostridia* involved are *C. perfringens* (formerly *C. welchii*), *C. oedematicus*, *C. septicum* and *C. histolyticum*, but other species may also play a role [1]. Heroin used by drug users may be contaminated with *C. sordellii,* which may cause life-threatening myonecrosis and fulminant shock syndrome [2].

The clostridia are anaerobic, Gram-positive, spore-forming bacilli, widely distributed in the soil and in the gastrointestinal tracts of humans and other mammals. *C. perfringens* can be isolated from the skin of the thighs, groins and buttocks of many healthy persons [1]. The α-toxin produced by *C. perfringens* is a zinc-containing phospholipase C enzyme, which is haemolytic and thought to be the main virulence factor in gas gangrene [3]. The toxin has been shown to affect neutrophil migration, platelet aggregation and may also modulate host cell metabolism [3].

A high proportion of war wounds are contaminated by clostridial spores, but clinical infection usually develops only in the presence of severely damaged, anoxic muscle. Infections may also follow vehicular accidents with crush injuries [4]. Gas gangrene used to be an infection of the greatest importance in war time; better management of casualties has reduced its incidence enormously. It is an uncommon but well-documented complication of orthopaedic surgery, particularly above-knee amputations in ischaemic limbs. In these latter patients, the organism usually originates in the patient's own bowel [1].

The incubation period varies from 12 h to 5 or 6 days, according to the species predominantly involved.

Clinical features. Deep and dirty wounds in the muscular regions of the body are most susceptible. However, abdominal and intrauterine infections also occur. The affected area becomes painful and swollen and there is increasing serous discharge from the wound. Toxaemia is severe; tachycardia and prostration develop rapidly and the patient is pale and apprehensive but often not febrile [1]. The oedema around the wound continues to spread and is associated first with brownish staining and mottling, then with bullae and later with the formation of black sloughs. Crepitation from gas in the tissues is classical but inconstant. There are usually severe systemic symptoms including tachycardia, irritability and hypotension [2].

Diagnosis. The diagnosis must be made promptly on clinical grounds supported in due course by bacterial examination of the ooze from lesions, which contains large numbers of typical, Gram-positive bacterial rods. Other non-clostridial, anaerobic bacteria may also cause gas gangrene. Blood cultures should be taken prior to antimicrobial therapy. Good anaerobic techniques should be employed to obtain the organisms. Radiology confirms gas in the tissues. Necrotizing fasciitis, Meleney's synergistic gangrene and anaerobic streptococcal infection should be considered.

Treatment. The immediate surgical debridement of all damaged tissue is essential. Penicillin in high dosage (10–20 million units) is the usual treatment [1], although there are reports of penicillin resistance among *Clostridium* species. Alternatives include clindamycin, metronidazole and imipenem [2], but antimicrobial therapy is only an adjunct to surgery.

The role of hyperbaric oxygen remains controversial because of the lack of controlled studies, and unless readily available may lead to delays in essential surgery [5]. There are, however, experimental data indicating that it reduces the mortality rates [6,7].

References

1 Darke SG, King AM, Slack WK. Gas gangrene and related infections: classification, clinical features and aetiology, management and mortality. A report of 88 cases. *Br J Surg* 1997; **64**: 104–12.

2 Brett MM, Hood J, Brazier JS *et al*. Soft tissue infections caused by spore-forming bacteria in injecting drug users in the United Kingdom. *Epidemiol Infect* 2005; **133**: 575–82.

3 Titball RW, Naylor CE, Basak AK. The *Clostridium perfringens* alpha-toxin. *Anaerobe* 1999; **5**: 51–64.

4 De A, Varaiya A, Mathur M *et al*. Bacteriological studies of gas gangrene and related infection. *Indian J Med Microbiol* 2003; **21**: 202–4.

5 Gibson A, Davis FM. Hyperbaric oxygen therapy in the management of *Clostridium perfringens* infections. *NZ Med J* 1986; **99**: 617–9.

6 Hirn M. Hyperbaric oxygen in the treatment of gas gangrene and perineal necrotising fascitis: a clinical and experimental study. *Eur J Surg Suppl* 1993; **570**: 1–36.

7 Wang C, Schwaitzberg S, Berliner E *et al*. Hyperbaric oxygen for treating wounds. A systematic review of the literature. *Arch Surg* 2003; **138**: 272–9.

Gram-negative bacteria

Meningococcal infection

Aetiology [1,2]. *Neisseria meningitidis* is a Gram-negative coccus. It can be divided into different serotypes on the basis of capsular polysaccharides, types A, B and C being the most important. All types are pathogenic. This bacterium colonizes the human upper respiratory tract, and is transmitted by droplet from patients or healthy carriers. It may cause localized infections, such as conjunctivitis and otitis media, or severe and potentially fatal disease with septicaemia and often meningitis. The factors determining whether the organism is a mere colonizer or causes mild or severe disease in the individual case are not understood. Severe disease affects mainly children under the age of 10 years, but epidemics or sporadic cases in adults may occur, for instance in institutions such as military barracks or university lodgings.

Bacteraemia is believed to be the primary event in all forms of the infection, and to be the route by which the organism reaches the meninges.

Pathology. The early petechial skin lesions result from the presence of the organisms in capillary endothelium accompanied by disseminated intravascular coagulation, with necrosis of the vessel wall or thrombosis [1]. The skin lesions occurring late in the course of acute infections or in chronic infections show a vasculitis thought to be produced by soluble antigen–antibody complexes [3].

Clinical features. The main clinical groupings of meningococcal infections are bacteraemia without sepsis, meningococcaemia without meningitis, meningitis with or without meningococcaemia and meningoencephalitis. Acute meningococcal septicaemia with or without meningitis may present as a fulminating illness, and the rash may be a very useful clue to early diagnosis. The incidence of rash is estimated at between 40 and 90%, perhaps depending on the thoroughness with which lesions in the more sparsely affected cases are sought [1]. Early skin lesions are not always haemorrhagic, and may take the form of discrete pink macules or papules a few millimetres in diameter on any part of the body, including palms and soles [4]. Purpura follows in many cases. Transient erythematous, morbilliform or urticarial eruptions are occasionally seen.

A purpuric eruption is characteristic, and occurs mainly on trunk and limbs. The petechiae are usually small and scanty, but vary in size and number. In severe cases, larger purpuric lesions may occur, including extensive ecchymoses and necrotic ulceration, particularly in dependent areas and under pressure sites, and are associated with a high mortality [5].

Vasculitis may occur during the acute illness, beginning 5–9 days after the onset, even if adequate antibiotic treatment has been given. Nodules or bullae may be sparse and confined to the limbs, or may be more numerous and widespread; the lesions may ulcerate [6]. Arteritis and episcleritis may be associated. Similar vasculitic lesions occur in chronic septicaemic infection [7], in which milder maculopapular eruptions are also seen.

There is a rare form of chronic meningococcaemia which can present with a rash, low grade fever and arthritis identical to that described for chronic gonococcaemia (see below).

Diagnosis. The diagnosis is confirmed by isolation of *N. meningitidis* from blood or cerebrospinal fluid.

Treatment and prophylaxis [1,8]. Intravenous benzylpenicillin in high doses is the treatment of choice [9]. Ceftriaxone or cefotaxime are suitable alternatives.

Rifampicin for 2 days is recommended as prophylaxis for close family contacts, but does not eliminate the need for close clinical surveillance [8]. At present vaccines are available for meningococcal infections caused by Groups A, C, Y and W-135 organisms but not Group B, although these are in development. They may be deployed in at-risk groups [10].

References

1 Bannister B. Clinical aspects of meningococcal disease. *J Med Microbiol* 1988; **26**: 161–3.
2 Raman GV. Meningococcal septicaemia and meningitis: a rising tide. *BMJ* 1988; **296**: 1141–2.
3 Greenwood BM, Whittle HC, Bryceson ADM. Allergic complications of meningococcal disease. II. Immunological investigations. *BMJ* 1973; **2**: 737–40.
4 Baxter P, Priestley B. Meningococcal rash. *Lancet* 1988; **1**: 1166–7.
5 Toews WH, Bass JW. Skin manifestations of meningococcal infection. *Am J Dis Child* 1974; **127**: 173–6.
6 Whittle HC, Abdullahi MT, Fakunle FA *et al*. Allergic complications of meningococcal disease. I. Clinical aspects. *BMJ* 1973; **2**: 733–7.
7 Nielsen LT. Chronic meningococcaemia. *Arch Dermatol* 1970; **102**: 97–101.
8 Stuart JM, Cartwright KAV, Robinson PM *et al*. Does eradication of meningococcal carriage in household contacts prevent secondary cases of meningococcal disease? *BMJ* 1989; **298**: 569–70.
9 Barquet N, Domingo P, Cayla JA *et al*. Prognostic factors of a bedside predictive model and scoring system. *JAMA* 1997; **278**: 491–6.
10 Jodar L, Feavers IM, Salisbury D, Granoff D. Development of vaccines against meningococcal disease. *Lancet* 2001; **359**: 1499–508.

Gonococcal infection

Aetiology and pathology [1,2]. *Neisseria gonorrhoeae* is a Gram-negative, aerobic diplococcus. It causes gonorrhoea, one of the commonest and most important sexually transmitted diseases. The incidence in industrialized countries fell after the high levels of World War II, and rose during the 1960s and 1970s. There were an estimated 2 million cases in the USA in 1983. The incidence is high among those at risk from HIV in countries where screening facilities are not readily available, and is rising in heterosexual couples in the West. Prostitutes are an important source of the infection, especially in developing countries [2].

The incubation period is 2–5 days (1–14 days). Genital infection affects primarily the urethra in both sexes but may spread, especially in the female to para-urethral glands and cervix, and more deeply (pelvic inflammatory disease) to endometrium, fallopian tubes and peritoneum. Local spread may involve the skin. Anorectal and oropharyngeal infections may follow relevant sexual contact. Most cases of childhood gonorrhoea are sexually transmitted [3], although accidental inoculation may account for some cases. If a mother has genital infection at the time of delivery, gonococcal ophthalmia may occur in the neonate. In the adult, the conjunctivae may be infected by autoinoculation from the genitalia [4]. Primary cutaneous infection is discussed below. Asymptomatic infection of genitalia, pharynx and rectum is common.

Disseminated gonococcal infection, which may include cutaneous lesions, occurs in about 1–3% of cases, and usually involves strains that remain sensitive to penicillin [5]. Histologically, the metastatic lesions show haemorrhage, thrombosis and vasculitis [6]. Diplococci may be detectable in the vessel wall and in the surrounding inflammatory infiltrate. Immunofluorescence may identify gonococcal antigen where Gram stain and culture are negative [7–9].

Clinical features. Gonococcal infection may be cutaneous, oral or disseminated and there may be local complications.

Primary cutaneous infection. Areas contaminated by the urethral, vaginal or rectal discharge may show multiple erosions, 0.5–2.0 cm in diameter, sharply marginated, rounded or oval but often ragged, with a light-red surface and a vivid, non-indurated areola. The erosions heal when the discharge ceases. Very rarely, there may be discrete pustules of the coronal sulcus. A gonococcal ulcer of the penis in a patient without urethritis is unusual [10], as is a chancriform primary infection of the female thigh [11].

Pustular primary lesions have been described on fingers, but in each case the skin had been injured prior to exposure [12,13]. Similarly, minor trauma from fetal monitoring electrodes is likely to have facilitated scalp infection with *N. gonorrhoeae* in offspring of infected mothers [4,14].

Primary oral infection [15]. Direct oral infection may occur *de novo* or in association with genital infection and oral sex. The clinical picture may be that of acute or chronic tonsillitis, or of gingivitis. Asymptomatic pharyngeal colonization is a well-recognized occasional finding, which responds poorly to antibiotic treatment, but seems to clear spontaneously within weeks. It does not apparently lead to mouth-to-mouth infection [16].

Local complications. Infection of Tyson's glands causes the development of firm, tender nodules on one or both sides of the fraenum. Ecthymatous lesions of the supra-pubic region have been reported in association with urethritis [17]. Infection of the median raphe of the penis presents as an indurated, red and sometimes tender ridge on the surface of the penis. Dorsal lymphangitis may lead to oedema of the penis. Infections of Littré's glands may be followed by abscess formation. An indurated nodule along the course of the urethra may discharge externally.

Infection of Bartholin's glands is the only local complication in the female which involves the skin. An acutely tender abscess up to 10 cm in diameter distends the labium (Chapter 71).

Disseminated (chronic) gonococcal infection [2,5,9,18]. The usual features are pain and swelling in or around one or several joints, fever and chills, and skin lesions, although none of these is invariable. Mucosal infection is often asymptomatic, but a positive culture is usually obtained from the site of primary infection. The joint disease may be a reactive form of synovitis, when blood cultures are commonly positive, but synovial fluid cultures negative; or suppurative arthritis, usually without skin lesions, in which synovial fluid cultures are often positive but blood cultures are negative. Fever is intermittent and may be high. The skin lesions, to which some authors apply the term septic gonococcal dermatitis [9], occur early in one or more crops, usually three or four, each of which consists of relatively few lesions, usually less than 20, scattered over the limbs. Initially there may be macules, papules or small vesicles with a red halo, but they soon develop into pustules or bullae, which may become haemorrhagic or necrotic. They heal after a few days and may leave small, superficial scars. Gonococci are only rarely cultured from the skin lesions. Erythema nodosum, erythema multiforme and urticaria have been described.

In the rare acute septicaemic forms, the patient is gravely ill, with high fever, and meningitis or endocarditis may occur. Skin lesions may be of the type described, but often take the form of non-specific, transient erythema or purpura.

Diagnosis. In bacteraemic and septicaemic forms, certain clinical diagnosis is usually impossible. There is not always a history of genital infection. Genital foci should be sought and should be cultured repeatedly. The haemorrhagic vesicles are distinctive but not pathognomonic; they may also occur in septicaemia caused by the related *N. meningitidis* and *Acinetobacter* spp. and less often by other organisms. They may simulate *Varicella*, but they spare the scalp.

Gram stain and culture of exudate or secretion remain the essential methods. In the disseminated form, repeated blood cultures and culture of aspirated fluid from affected joints are required.

Other methods, including immunological and molecular biological techniques, are not universally applicable or available.

Treatment [19,20]. Effective drugs recorded in the past include: certain penicillins, that is intramuscular aqueous procaine benzylpenicillin (procaine penicillin), or oral ampicillin or amoxicillin, all with oral probenecid; intravenous benzylpenicillin; ceftriaxone; cefoxitin; tetracycline; doxycycline; spectinomycin; and erythromycin. The choice of drug and regimen depended on the clinical condition, bacterial sensitivities, anticipated patient compliance, drug allergies and the coexistence of other suspected or confirmed diseases such as syphilis and chlamydial infection. However, the more recently recommended, single-dose regimens for gonorrhoea include ceftriaxone, cefixime, ciprofloxacin, ofloxacin, azithromycin or doxycycline [20].

References

1 Britigan BE, Cohen MS, Sparling PF. Gonococcal infection. A model of molecular pathogenesis. *N Engl J Med* 1985; **312**: 1683–94.
2 Hook EW, Holmes KK. Gonococcal infections. *Ann Intern Med* 1985; **102**: 229–43.
3 Neinstein LS, Goldenring J, Carpenter S. Nonsexual transmission of sexually transmitted diseases: an infrequent occurrence. *Pediatrics* 1984; **74**: 67–76.
4 Brook I, Rodriguez WJ, Controni G *et al*. Gonococcal scalp abscess in a newborn. *South Med J* 1980; **73**: 396–7.
5 Editorial. Disseminated gonococcal infection. *Lancet* 1984; **1**: 832–3.
6 Schapiro L, Teisch JA, Brownstein MH. Dermatohistopathology of chronic gonococcal sepsis. *Arch Dermatol* 1973; **107**: 403–6.
7 Barr J, Danielsson D. Septic gonococcal dermatitis. *BMJ* 1971; **1**: 482–5.
8 Bayer AS. Gonococcal arthritis syndromes. An update on diagnosis and management. *Postgrad Med* 1980; **67**: 200–8.
9 Kahn G, Danielsson D. Septic gonococcal dermatitis. *Arch Dermatol* 1969; **99**: 421–5.
10 Landergren G. Gonorrheal ulcer of the penis; report of a case. *Acta Derm Venereol (Stockh)* 1961; **41**: 320–3.
11 Rompalo AM, Hook EW III, Roberts PL. The acute arthritis-dermatitis syndrome. The changing importance of *Neisseria gonorrhoeae* and *Neisseria meningitidis*. *Arch Intern Med* 1987; **147**: 281–3.
12 Prager KM. Primary extragenital cutaneous gonorrhoea. *Arch Dermatol* 1973; **107**: 112–3.
13 Scott MJ. Primary cutaneous *Neisseria gonorrhoeae* infections. *Arch Dermatol* 1982; **188**: 351–2.
14 Plavidel FJ, Werch A. Gonococcal fetal scalp abscess. *Am J Obstet Gynecol* 1977; **127**: 437–8.
15 Wiesner PJ, Tronca E, Bonin P *et al*. Clinical spectrum of pharyngeal gonococcal infection. *N Engl J Med* 1973; **288**: 181–5.
16 Wallin J, Siegel MS. Pharyngeal *Neisseria gonorrhoeae*: coloniser or pathogen? *BMJ* 1979; **1**: 1462–3.
17 Glicksman JM, Short DH, Knox JM *et al*. Gonococcal skin lesions. *Arch Dermatol* 1967; **96**: 74–6.
18 O'Brien JP, Goldenberg DL, Rice PA. Disseminated gonococcal infection: a prospective analysis of 49 patients and review of pathophysiology and immune mechanisms. *Medicine (Baltimore)* 1983; **62**: 395–405.
19 Handsfield HH, McCutchan JA, Corey L *et al*. Evaluation of new anti-infective drugs for the treatment of uncomplicated gonorrhea in adults and adolescents. *Clin Infect Dis* 1992; **15** (Suppl. 1): S123–30.
20 Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines. *MMWR Morb Mortal Wkly Rep* 2002; **51** (No. RR-6): 36–42.

Acinetobacter infection

Acinetobacter species are represented by a series of strains or genomic species. Most of these belong to a large complex *A. calcoaceticus–A. baumannii*. Before this, the organisms were grouped into two Gram-negative genera, *Mima* and *Herellea.* These closely related *Acinetobacter* organisms are found as members of the resident skin flora in the axilla and groin in about 20% of normal subjects, and may occur in the toe webs and on drier sites [1–3]. They have been isolated from skin pustules and from cellulitis [4,5], but their main importance lies in their role as uncommon but undoubted opportunistic pathogens. *Acinetobacter* spp. have been found to cause septicaemia, meningitis, osteomyelitis, synovitis, burn sepsis and wound infections. In the very young and the very old particularly, the source of infection may be exogenous but endogenous infection clearly occurs, and indwelling intravenous catheters are likely routes in septicaemia. Reports of summer peaks of infection due particularly to *A. calcoaceticus–A. baumannii* complex suggest that increased sweating leading to higher carriage levels may be important [6,7].

The role of these organisms in primary skin infections is unclear, but they have been recorded as causes of cellulitis associated with indwelling intravenous lines.

References

1 Dexter HLT, Glacy J, Leonard J *et al*. Skin disease due to *Mima polymorpha*. *Arch Dermatol* 1958; **77**: 109–11.
2 Noble WC. In: Maibach HI, Aly R, eds. *Skin Microbiology: Relevance to Clinical Infection*. New York: Springer, 1981: 41.
3 Noble WC. *Microbiology of Human Skin*, 2nd edn. London: Lloyd-Luke, 1981: 223.
4 French GL, Casewell MW, Roncoroni AJ *et al*. A hospital outbreak of antibiotic-resistant *Acinetobacter anitratus*: epidemiology and control. *J Hosp Infect* 1980; **1**: 125–31.
5 Glew RH, Moellering RC, Kunz LJ. Infections with *Acinetobacter calcoaceticus* (*Herellea vaginicola*). Clinical and laboratory studies. *Medicine (Baltimore)* 1977; **56**: 79–97.
6 Retailliau HF, Hightower AW, Dixon RE *et al*. *Acinetobacter calcoaceticus*: a nosocomial pathogen with an unusual seasonal pattern. *J Infect Dis* 1979; **139**: 371–5.
7 Villegas MV, Hartstein AI. Acinetobacter outbreaks 1977–2000. *Infect Cont Hosp Ep* 2003; **51**: 1891–9.

Moraxella infection

The genus *Moraxella* includes an important respiratory pathogen *Moraxella* (*Branhamella*) *catarrhalis*. *Moraxella osloensis* has been reported as a cause of gonococcaemia-like systemic infection with skin lesions [1], bacteraemia with a petechial rash [2]; arthritis with skin lesions has been attributed to another *Moraxella* sp. [3]. These cases apart, *Moraxella* are more closely associated with respiratory infection or conjunctival inflammation than cutaneous colonization or disease [4].

References

1 Lasser AE, Goldman EJ. *Moraxella* bacteremia. *Cutis* 1978; **21**: 657–9.
2 Shah SS, Ruth A, Coffin SE. Infection due to *Moraxella osloensis*: case report and review of the literature. *Clin Infect Dis* 2000; **30**: 179–81.
3 Redfield DC, Overturf GD, Ewing N *et al*. Bacteria, arthritis and skin lesions due to *Kingella kinga*. *Arch Dis Child* 1980; **55**: 411–3.
4 Karalus R, Campagnari A. Moraxella catarrhalis: a review of an important human mucosal pathogen. *Microbes Infect* 2000; **2**: 547–59.

Chancroid

Synonyms
- Soft sore
- Chancre mou

Definition. Chancroid is a venereal disease caused by *Haemophilus ducreyi*, a Gram-negative bacillus, forming short chains. Although classified as a *Haemophilus* species it is genetically distinct.

Aetiology. The disease is prevalent in Africa, the Far East and Central and South America in communities with low hygiene standards [1]. Although previously rare in western Europe and the North American continent, it has in recent years become much more common, for example in France, Holland, Greenland and North America [2,3]. It is, however, difficult to be certain of the true incidence of this disease, as isolation of *H. ducreyi* from classical cases often failed in the past. In many studies, therefore, there is no bacteriological confirmation of the diagnosis. Clinical infection is reported very much more commonly in men than women, but the existence of an asymptomatic carrier state is not proven [4]. Chancroid may affect sex workers.

Pathology. There is a non-specific inflammatory infiltrate. Involvement of the walls of small blood vessels in the region leads to ulceration.

Clinical features [5–7]. After an incubation period of 5–8 days, ranging from 1 to several weeks, a small red papule develops and rapidly becomes pustular and then ulcerated. The ulcer, usually rounded or oval, has a ragged, undermined edge, surrounded by a red, very vascular areola. It is tender and sometimes painful, but not indurated, enlarges slowly and often gives rise to satellite ulcers; two to five in a cluster are quite often present. Multiple ulcers are commoner in women than men.

In the male, the prepuce, the balanopreputial fold or the shaft of the penis, and in the female, the labia majora, the posterior commissure and the perianal region, are the commonest sites of infection. Extragenital lesions, although rare, do occur.

The course is variable. Without treatment, the lesion may rarely disappear spontaneously in a few days. Usually it persists for some weeks and may be complicated by severe phimosis and even by gangrene, or by destructive ulceration from secondary fusospirochaetal infection. In about 50% of cases, even if the initial lesion has been transient, inguinal adenitis develops about a week after the appearance of the ulcer. The glands on one or both sides are enlarged and tender and may suppurate, leading to chronic draining lesions.

Diagnosis. The chancre of syphilis is indurated and painless, and develops after a longer incubation period, but clinical differentiation is not always easy, and mixed infections can occur. Herpes simplex may also coexist in genital lesions with *H. ducreyi* [8].

Haemophilus ducreyi may be identified in the form of chains of coccobacilli in smears from the ulcer, or preferably of pus from a bubo. Ideally it should be cultured on one of the modern selective media at 33°C in an atmosphere of high humidity [9]. Even if the organism is present, dark-ground examination for *Treponema pallidum* and serological tests for syphilis should be undertaken. There is a PCR based method which has been developed to distinguish the major causes of genital ulceration including chancroid, but it is not yet widely available.

Treatment [10–11]. The main treatment for chancroid is a single dose of azithromycin. Alternatives include ceftriaxone, ciprofloxacin or erythromycin. There is usually a rapid response to treatment. Resistance to sulphonamides, tetracyclines and trimethoprim has been reported in several countries.

References

1 Bong CT, Bauer ME, Spinola SM. *Haemophilus ducreyi*. Clinical features, epidemiology and prospects for disease control. *Microbes Infect* 2002; **4**: 1141–8.
2 Hammond GW, Slutchuk M, Scatliff J. Epidemiologic, clinical, laboratory and therapeutic features of an urban outbreak of chancroid in North America. *Rev Infect Dis* 1980; **2**: 867–79.
3 DiCarlo RP, Armentor BS, Martin DH. Chancroid epidemiology in New Orleans men. *J Infect Dis* 1995; **172**: 446–52.
4 Ronald AR. Chancroid. Recent advances in treatment and control. *Int J Dermatol* 1986; **25**: 31–3.
5 Fast MV, D'Costa LJ, Nzanze H *et al*. The clinical diagnosis of genital ulcer disease in men in the tropics. *Sex Transm Dis* 1984; **11**: 72–6.
6 Gaisin A, Heaton CL. Chancroid: alias the soft chancre. *Int J Dermatol* 1975; **14**: 188–97.
7 Story G. Clinical manifestations of chancroid. *Br J Urol* 1970; **42**: 738–43.
8 Kinghorn GR, Hafiz S, McEntegart MG. Pathogenic microbial flora of the genital ulcers in Sheffield with particular reference to herpes simplex virus and *Haemophilus ducreyi*. *Br J Vener Dis* 1981; **58**: 377–80.
9 Hannah P, Greenwood JR. Isolation and rapid identification of *Haemophilus ducreyi*. *J Clin Microbiol* 1982; **16**: 861–4.
10 Centers for Disease Control and Prevention. Sexually transmitted disease treatment guidelines. *MMWR* 2002; **51** (RR6): 1–80.
11 Dangor Y, Ballard RC, Miller SD *et al*. Treatment of chancroid. *Antimicrob Agents Chemother* 1990; **34**: 1308–11.

Salmonella infection

Aetiology. The *Salmonella* spp. are Gram-negative, motile bacilli, which are widely distributed parasites of mammals and birds. With the wider use of molecular taxonomic techniques there are now only two species recognized, *Salmonella enterica* and *S. bongori*. Within these species, there are serotypes with distinct attributes; notable amongst these are two major human pathogens *Salmonella* Typhi (the serotype is not italicized as it is not a distinct species) and *S.* Paratyphi. These are primarily human pathogens; others are primarily pathogenic for other animals, but may infect humans. Others are only pathogenic in animals other than humans. All are transmitted by contaminated food or water, with a portal of entry in the gastrointestinal tract.

The exanthematic, cutaneous manifestations accompany active infection, but metastatic abscesses may occur in carriers during periods of lowered resistance.

Veterinary surgeons handling infected cattle may develop skin lesions due to *S.* Typhimurium, and *S.* Abortusovis produced a similar clinical problem.

Clinical features [1–4]. Exanthematic eruptions are seen most frequently in untreated infections with *S. Typhi*, and occur in about 30% of cases. The classical rose spots are crops of pink papules about 5 mm in diameter, each lasting for 3–5 days, and continuing to appear at irregular intervals from the end of the first week for 10–14 days. They are most numerous on the abdomen, chest and back. Exceptionally, vesicular or haemorrhagic rashes may be seen.

In infections with *S. Paratyphi B*, the eruption occurs less frequently but may be more extensive, involving the face and limbs as well as the trunk.

In *S. Typhi*, *S. Paratyphi* C and other *Salmonella* infections, single or multiple metastatic cutaneous and subcutaneous abscesses may develop [5,6].

Infections contracted by direct inoculation present as inflammatory nodules with central pustulation. In veterinary surgeons, forearm lesions may be small, inconspicuous papules or pustules, but larger painful nodules also occur. Malaise and fever are typically absent, and spontaneous resolution within a few days is usual.

An ulcerative vulvitis or vulvovaginitis may rarely be the presenting symptom of *Salmonella* infection [1]. Wound infections, for instance in burns patients, and complications such as septic thrombophlebitis or bacteraemia can occur.

Diagnosis. The diagnosis of systemic infections must be established by culture from faeces or blood, or occasionally from the skin lesions, and confirmed by a rising antibody titre. The organism may be isolated directly from lesions contracted by inoculation. In such cases, the antibody titre does not rise.

Treatment [7]. Chloramphenicol was the original and highly effective treatment for many systemic infections. However, nowadays a fluoroquinolone such as ciprofloxacin or ofloxacin would be the treatment of choice for typhoid fever. Cephalosporins such as cefotaxime are also very useful. Unfortunately, resistance to chloramphenical, ampicillin or cotrimoxazole is common in many countries.

References

1 Cohen JL, Bartlett JA, Corey GR. Extraintestinal manifestations of *Salmonella* infections. *Medicine (Baltimore)* 1987; **66**: 349–88.

2 Hoffman TA, Ruiz CJ, Counts GW *et al*. Waterborne typhoid fever in Dade county Florida; clinical and therapeutic evaluations of 105 bacteremic patients. *Am J Med* 1975; **59**: 481–6.

3 Litwack KD, Hoke AW, Borchardt KA. Rose spots in typhoid fever. *Arch Dermatol* 1972; **105**: 252–5.

4 Black PH, Kunz LJ, Swartz MN. Salmonellosis—a review of some unusual aspects. *N Engl J Med* 1960; **262**: 811–4.

5 Gremillon DH, Geckler R, Ellenbogen C. *Salmonella* abscess; a potential nosocomial hazard. *Arch Surg* 1977; **112**: 843–6.

6 Behr MA, McDonald J. *Salmonella* neck abscess in a patient with beta-thalassemia major: case report and review. *Clin Infect Dis* 1996; **23**: 404–5.

7 Parry CM, Hien TT, Dougan G *et al*. Typhoid fever. *N Eng J Med* 2002; **347**: 1770–82.

Pseudomonas infection

Aetiology and pathology [1–3]. *Pseudomonas aeruginosa* (*P. pyocyanea*; *Bacillus pyocyaneus*) is an aerobic, Gram-negative rod, which occurs only as a transient member of the skin flora, mainly in the anogenital region, axillae and external ear, and is normally kept in check by the dominant Gram-positive cocci. It occurs in soil and water and is present in the intestine of a small percentage of adults and a high proportion of infants. It readily colonizes burns, ulcers or other moist skin lesions, and frequently contaminates bedpans, showers, sinks, urine bottles, polythene sheeting and the hands of nurses in wards in which such patients are treated. It is mainly a nosocomial pathogen. Jars of ointment may also be contaminated [4]. Systemic infections are seen frequently, largely in immunosuppressed patients or the acutely sick who have received multiple courses of antibiotics or neonatal units [3]. *Pseudomonas* infections are frequent in intensive therapy units, in neutropenic patients and as causes of nosocomial pneumonia. In older children and adults, clinical infections occur mainly in patients with debilitating diseases.

However, on the skin surface the repeated application of bactericidal agents effective against the Gram-positive flora, or prolonged maceration as in the syndrome of tropical immersion foot, favours the establishment of *Pseudomonas* even in previously healthy adults [1], and clinical infections eventually develop in a large proportion.

Experimental superhydration of the skin for 7 days with water-soaked cotton pads produced a vesiculopustular rash from which *Pseudomonas* was isolated [5]. Epidemic outbreaks of a follicular rash have affected users of overcrowded, heated swimming pools or Jacuzzis.

Under experimental conditions, *Pseudomonas* is pathogenic only in massive dosage or in damaged tissue, a pattern of behaviour that parallels that observed in humans. *Pseudomonas* appears to play a part in modifying and perpetuating some paronychial infections [6]. It is commonly isolated from chronic leg ulcers and from many other persistently moist lesions, including chronic external otitis, and, although its presence may be clinically apparent, it is uncertain to what extent it is pathogenic under these conditions. It is believed to be capable of maintaining the inflammatory changes after other organisms have been eliminated.

Typical strains produce two pigments, the blue-green pyocyanin, a phenazine derivative, and a greenish yellow pyoverdin.

Other species of *Pseudomonas* are sometimes of clinical significance. *P. cepacia* has caused lesions of the toe webs in troops training in swamp conditions [7]. The same species caused endocarditis and gangrenous ecthyma in a heroin addict [8]. This organism has now been transferred to another genus, *Burkholderia cepacia*.

Clinical features [9,10]. The commonest local infection in infancy is periumbilical, with a foul-smelling, bluish green discharge and spreading erythema. In some cases, usually under conditions of



Fig. 30.15 *Pseudomonas* infection of the foot. (Courtesy of St. John's Institute of Dermatology, King's College London, UK.)

high humidity, widely scattered pustules may break down to form necrotic ulcers. Perionychial pustules may be accompanied by green discoloration of the nails. Involvement of the lips and cheeks may be followed by progressive gangrene. Sometimes, in the severely ill or in compromised neutropenic patients, primary cutaneous invasion with extensive necrosis may develop around a local erosion [11].

Inhibition of the Gram-positive flora or dermatophytes by maceration or antibiotics allows the development of a distinctive *Pseudomonas* infection of the toe webs [1] (Fig. 30.15), also called tropical immersion foot, characterized by sharply demarcated areas of maceration and tender erosions, sometimes tinged with green, and showing green fluorescence under Wood's light. The sodden plaque tends to break down, and secondary invasion by *Candida* may follow [7].

Pseudomonas can also invade superficial wounds, particularly burns [12]. This complication still carries a high mortality as large quantities of these organisms may thrive in burn eschar, and secondary septicaemia may result. Secondarily infected burns show discoloration of the slough with extensive surrounding oedema. Fever and shock may supervene. However, careful management and use of debridement in burns units has reduced the incidence. In a recent survey, only 1% of patients with severe burns had an episode of *Pseudomonas* bacteraemia [12].

Gram-negative folliculitis seen in swimming pool or Jacuzzi users is now a well-documented entity [13,14]. It may include macular, papular or pustular lesions which are tender. Some are urticarial, suggesting insect bites. Any part of the body that has been immersed may be affected, but often the worst areas are those in contact with bathing costumes. In most cases, the rash

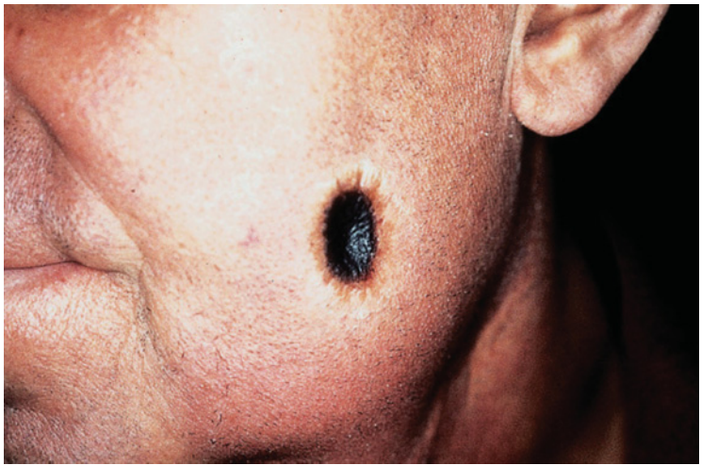


Fig. 30.16 Ecthyma gangrenosum. (Courtesy of Dr G. Scott, University College Hospital, London, UK.)

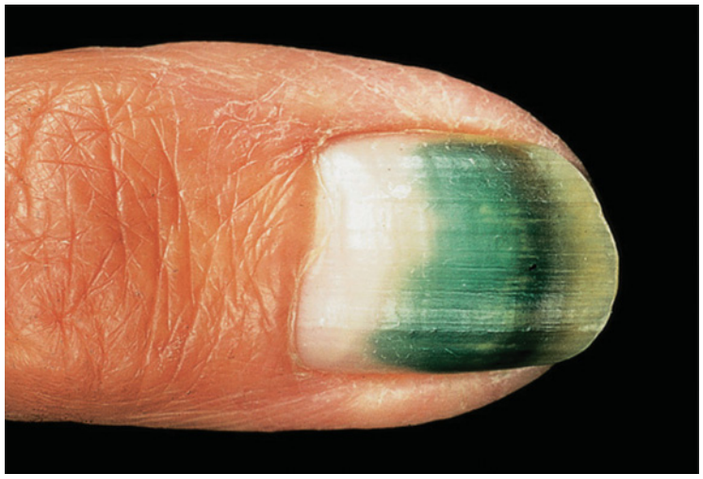


Fig. 30.17 *Pseudomonas* infection of the nail. (Courtesy of St. John's Institute of Dermatology, King's College London, UK.)

settles spontaneously within 7–10 days in the absence of re-exposure. Hot tubs and whirlpools infections are often associated with poor outflow drainage. *Pseudomonas*, usually of serotype II, may be cultured from the skin and the infected water.

Pseudomonas septicaemia most commonly occurs in the severely compromised host [15]. Usually there are no skin lesions, but in a minority of patients the skin is affected and in a variety of ways. There may be non-specific erythema, which can be tender or spontaneously painful [16], purpura or a cellulitis-like picture. Bullae may form, particularly in moist areas such as the axillae, perineum and the buttocks. These may rapidly rupture to give necrotic ulcers—ecthyma gangrenosum (Fig. 30.16).

In elderly diabetics, HIV/AIDS and neutropenic patients, the *Pseudomonas* is sometimes associated with a serious necrotic infection of the external ear known as malignant external otitis [17]. *Pseudomonas* spp. have also been implicated in severe exacerbations of acne vulgaris [18]. The presence of *Pseudomonas* spp. beneath nails with onycholysis gives rise to characteristic green discoloration (Fig. 30.17).

The prognosis of systemic infections is poor, unless there is early treatment. Local infections in infants or patients with debilitating illnesses should be regarded as potentially dangerous, for systemic extension occurs readily. The invasion of damaged skin in the otherwise normal subject may be difficult to control permanently until the lesions are healed, but has no serious significance.

Diagnosis. Bacteriological confirmation of the diagnosis is readily obtained by cultures from the skin lesions or blood. The significance of the isolation of *Pseudomonas* from non-specific lesions must be carefully evaluated on the clinical findings.

Treatment. Superficial lesions respond best if drying out is possible. One per cent acetic acid compresses, potassium permanganate soaks, povidone or silver sulfadiazine cream may be of value, but topical antibiotics (e.g. polymyxin) are generally disappointing.

In the case of burns, extensive debridement followed by topical applications of silver sulfadiazine therapy is useful, although in some cases ceftazidime can also be used. In every case where antibiotics are contemplated, it is important to base therapy on the results of *in vitro* sensitivity tests.

In septicaemia or where a severely compromised patient has superficial infection, systemic therapy using intravenous antibiotics should be started promptly under a bacteriologist's guidance. Ceftazidime, gentamicin, piperacillin, azlocillin, tobramycin and amikacin may be used in appropriate combinations [19].

References

1 Amonette RA, Rosenberg EW. Infection of the toe webs by Gram negative bacteria. *Arch Dermatol* 1973; **107**: 71–4.

2 Kreger BE, Craven DE, Carling PC *et al*. Gram-negative bacteremia. III. Reassessment of etiology, epidemiology and ecology in 612 patients. *Am J Med* 1980; **68**: 332–7.

3 Morrison AJ, Wenzel RP. Epidemiology of infections due to *Pseudomonas aeruginosa*. *Rev Infect Dis* 1984; **6** (Suppl.): 627–44.

4 Noble WC, Savin JA. Steroid cream contaminated with *Pseudomonas aeruginosa*. *Lancet* 1966; **i**: 347–8.

5 Hojyo-Tomoka MT, Marples RR, Kligman AM. *Pseudomonas* infection in superhydrated skin. *Arch Dermatol* 1973; **107**: 723–7.

6 Leyden JJ, Stewart R, Kligman AM. Experimental inoculation of *Pseudomonas aeruginosa* and *Pseudomonas cepacia* on human skin. *J Soc Cosmet Chem* 1980; **31**: 19–23.

7 Taplin D, Bassett DCJ, Mertz PM. Foot lesions associated with *Pseudomonas cepacia*. *Lancet* 1971; **i**: 568–9.

8 Mandell IN, Feiner HD, Price NM *et al*. *Pseudomonas cepacia* endocarditis and ecthyma gangrenosum. *Arch Dermatol* 1977; **113**: 199–202.

9 Greene SL, Su WP, Muller SA. Ecthyma gangrenosum. Report of clinical, histopathologic and bacteriologic aspects of eight cases. *J Am Acad Dermatol* 1984; **11**: 781–6.

10 Hall JH, Callaway JL, Tindall JP *et al*. *Pseudomonas aeruginosa* in dermatology. *Arch Dermatol* 1968; **97**: 312–8.

11 Huminer D, Siegman-Ingra Y, Morduchowicz G *et al*. Ecthyma gangrenosum without bacteremia. Report of six cases and review of the literature. *Arch Intern Med* 1987; **147**: 299–303.

12 Gang RK, Bang RL, Sanyal SC *et al*. *Pseudomonas aeruginosa* septicemia in burns. *Burns* 1999; **25**: 611–6.

13 Sausker WF, Aeling JL, Fitzpatrick JE *et al*. *Pseudomonas folliculitis* acquired from a health spa whirlpool. *JAMA* 1978; **239**: 2362–4.

14 Berger RS, Seifert MR. Whirlpool folliculitis. A review of its cause, treatment and prevention. *Cutis* 1990; **45**: 97–8.

15 Bodey GP, Jadeja L, Elting L. *Pseudomonas* bacteremia. Retrospective analysis of 410 episodes. *Arch Intern Med* 1985; **145**: 1621–6.

16 Dorff GJ, Geimer NF, Rosenthal DR *et al*. *Pseudomonas* septicemia: illustrated evolution of its skin lesions. *Arch Intern Med* 1971; **128**: 591–4.

17 Ress BD, Luntz M, Telischi FF *et al*. Necrotising external otitis in patients with AIDS. *Laryngoscope* 1997; **110**: 456–60.

18 Leyden JJ, McGinley KJ, Mills OH. *Pseudomonas aeruginosa* Gram-negative folliculitis. *Arch Dermatol* 1979; **115**: 1203–6.

19 Hughes WT, Armstrong D, Bodey GP *et al*. Guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clin Infect Dis* 2002; **34**: 730–51.

Melioidosis

Definition and aetiology [1,2]. *Burkholderia pseudomallei* (originally placed in the genus *Pseudomonas*), the causative organism, is a saprophytic bacterium, which may be isolated from soil and water in low-lying rice-growing regions of the Far East, particularly northern Thailand and in the Northern part of the Northern territory of Australia. It also occurs in Central and South America, the West Indies and Madagascar [3]. Although wild and domestic animals may become infected, it is no longer thought that animals form an important natural reservoir of infection. Transmission in humans is thought to follow environmental contamination of a minor injury. In humans, *B. pseudomallei* typically causes a severe, glanders-like illness, which may be fatal, but serological evidence and retrospective enquiries suggest that mild febrile illnesses and subclinical infections occur in human subjects and probably in animals [1]. Other rare modes of transmission include inhalation or ingestion; the incubation period is very variable.

Clinical features [2,4]. The disease may run an acute, subacute or chronic course. The acute form with fever, prostration, gastroenteritis and pneumonia may be fatal within 2–4 days, but acute pulmonary infection due to *B. pseudomallei* is the commonest clinical manifestation of the illness. Septicaemia may complicate pneumonitis or appear without localizing signs elsewhere.

Many cases are subacute and last from one to many weeks. If the initial lesion is cutaneous, local abscess formation is rapidly followed by lymphangitis, lymphadenitis and septicaemia; characteristically, multiple abscesses develop, subcutaneously or in muscles, lung, liver and spleen. These often ulcerate. After infection by inhalation, pneumonic symptoms precede the septicaemic stage. In many cases, however, the clinical picture is variable, with unexplained fever and disseminated pyogenic lesions.

Chronic forms also occur: pulmonary symptoms and metastatic abscesses are most commonly seen, and in one such patient an associated, severe urticaria cleared after treatment with tetracycline. Rarely, the infection remains limited to skin and regional lymph nodes, without systemic symptoms.

Diagnosis. The acute pneumonic and septicaemic forms can simulate tuberculosis, typhoid or staphylococcal infections. The diagnosis is established by isolating the organism or by detecting a rising antibody titre.

Treatment. The treatment of choice is ceftazidime, meropenem or imipenem. This can be combined with co-trimoxazole. Alternatives include piperacillin and cefotaxime. Abscesses require surgical

drainage once antibiotic treatment is established. Resistance to some antibiotics, including co-trimoxazole, has been reported in some endemic areas [5], and where possible antibiotic sensitivities should be determined [6].

References

1 Howe C, Sampath A, Spotnitz M. The pseudomallei group. *J Infect Dis* 1971; **24**: 598–604.
2 Prevatt AL, Hunt JS. Chronic systemic melioidosis. *Am J Med* 1953; **23**: 810–8.
3 Ashdown LR, Guard RW. The prevalence of human melioidosis in northern Queensland. *Am J Trop Med Hyg* 1984; **33**: 474–8.
4 Everett ED, Nelson R. Pulmonary melioidosis; observations in thirty nine cases. *Am Rev Respir Dis* 1976; **114**: 1175–80.
5 Chaowagul IIW, Suputtamonkol Y, Dance DAB *et al*. Relapse in melioidosis: incidence and risk factors. *J Infect Dis* 1993; **168**: 1181–5.
6 Dance DAB, Wuthiekanum V, White NJ *et al*. Antibiotic resistance in *Pseudomonas pseudomallei*. *Lancet* 1988; **1**: 994–5.

Glanders

Synonyms
- Farcy
- Equina

Definition [1,2]. Glanders is a specific infection of horses and donkeys by *Burkholderia mallei*.

Aetiology. It is now extremely rare worldwide. No accurate figures for the present world incidence are available but the disease is still endemic in horses in parts of Asia and South America. Humans are infected by direct contact with horses, the bacillus usually gaining entry through an abrasion or through the conjunctiva or nasal mucous membrane. Very rarely there may be no discernible portal of entry.

Pathology. *B. mallei* gives rise to a local adenitis, followed by necrosis and abscess formation. The infection spreads by the regional lymphatics and by metastasis.

Clinical features [2]. Glanders may be an intensely acute, rapidly fatal disease or may run a chronic relapsing course over months or years. After an incubation period varying from a few days to 2 or 3 weeks, malaise, headache and fever accompany the development at the site of inoculation of an area of cellulitis, which soon breaks down to form an irregular ulcer with an offensive, haemorrhagic, purulent discharge. If the primary site is cutaneous, the regional lymphatics become swollen and tender, and dull-red nodules along their course break down to form abscesses and sinuses. If the nasal or oral mucous membrane is the site of inoculation, there is extensive necrosis and destruction of the septum and palate. After a variable interval—a few days or many weeks—metastatic lesions begin to appear: grouped, dull-red papules, pustules or bullae, especially over the joints and face, are followed by ulcers that enlarge and coalesce. Deep subcutaneous abscesses with multiple sinuses may also occur. The symptoms that accompany septicaemia are, as expected, rigors, headache and confusion. Chest X-ray appearances range from acute abscess formation to lobar infiltration. At this stage of dissemination meningitis, pneumonia and polyarthritis may also develop. Although some cases survive for long periods with intermittent bacteraemia with severe constitutional symptoms and metastatic manifestations, others are rapidly fatal, and in general the mortality without treatment is very high.

Diagnosis. The different clinical variants may simulate sporotrichosis, acute pyogenic infections or gangrenous pyoderma. The diagnosis may be suspected on the history of contact with horses, in which, however, the infection may sometimes be clinically inapparent, but must be confirmed by isolation of the organisms and by serological tests.

Treatment [2,3]. There are few reports on the response of glanders to the newer antibiotics. Drugs that show potential promise in melioidosis are co-trimoxazole, ceftazidime and imipenem, although the latter has not been fully assessed in either condition [3]

References

1 Howe C, Miller WR. Human glanders. Report of six cases. *Ann Intern Med* 1947; **26**: 93–9.
2 Currie B. *Burkholderia pseudomallei* and *Burkholderia mallei*: meliodosis and glanders. In: Mandell G, Bennett JE, Dolin R eds. *Principles and Practice of Infectious Diseases*. New York: Elsevier Churchill Livingstone, 2005: 2622–32.
3 Srinivasan A, Kraus CN, DeShazer D *et al*. Glanders in a military research microbiologist. *N Eng J Med* 2001; **34**: 256–8.

Stenotrophomonas maltophilia infections [1]

Stenotrophomonas maltophilia, previously classified as a *Pseudomonas* sp., is a rare cause of opportunistic infection seen in cystic fibrosis or in AIDS or neutropenic patients. It can cause pneumonia or septicaemia. However, in addition it can cause cellulitis, particularly around catheter insertion sites, and also may be isolated from wound infections. Sometimes the cutaneous lesions are nodular and accompany septicaemia.

Reference

1 Sakhnini E, Weissmann A, Oren I. Fulminant *Stenotrophomonas maltophilia* soft tissue infection in immunocompromised patients: an outbreak transmitted via tap water. *Am J Med Sci* 2002; **323**: 269–72.

Rhinoscleroma

Synonym
- Scleroma

Definition. Rhinoscleroma is a chronic, slowly progressive, potentially fatal, infectious and mildly contagious disease caused by the bacterium, which is a subspecies of *Klebsiella pneumoniae rhinoscleromatis* (*Klebsiella rhinoscleromatis*), that affects the upper and lower airways. It is originally localized in the nasal fossae, and invades the upper respiratory tract and lacrimal apparatus, where it produces an infiltrating granuloma with a marked tendency to sclerosis and subsequent obstruction. It is a condition difficult to cure.

Incidence [1]. The disease occurs sporadically almost all over the world, and is endemic but rare in certain countries including

Central, East and West Africa, and Central and South America and the USA. The disease is acquired by direct or indirect contact with the nasal exudate of an infected person. The infection occurs in both sexes at any age, but it is more frequent between the ages of 20 and 40 years. It is more common in rural areas where social and hygiene standards are low.

Aetiology [1]. Rhinoscleroma is caused by *K. pneumoniae rhinoscleromatis*. This bacillus measures about 3 µm in length. It appears isolated, in pairs, or even in short chains, and is encapsulated, non-motile and Gram-negative.

Koch's postulates were not fulfilled until 1961, when Steffen and Smith [2] injected the bacillus into the nasal cavity and intracranially in mice and produced a pneumonia that in some cases became chronic and granulomatous.

Pathophysiology [3]. The disease probably begins at the junction between the stratified squamous epithelium of the vestibule and the respiratory epithelium of the nose. Most investigators agree that the mucopolysaccharide in the capsule of the bacterium may be responsible for most of the damage.

Histopathology [1]. The histopathological picture is pathognomonic. A dense infiltrate is observed consisting mainly of plasma cells and two types of highly characteristic cells, the association of which allows this process to be distinguished from other granulomas. These cells are Mikulicz cells and Russell bodies. A Mikulicz cell is a large, round, vacuolated histiocyte measuring 100–200 µm in diameter containing Giemsa or Gram-positive bacilli (A granules) or amorphous clusters of mucopolysaccharide (B granules). The Russell body or colloid body, measuring 20–40 µm, is a structure in the cytoplasm of the plasma cells, elliptical in shape, homogeneous, and extremely eosinophilic, and as such stains bright red. Inside the Mikulicz cells, the bacilli are protected from therapeutic products in the blood, and hence there is a need for long-term therapy to be active against the bacteria when they are released [4].

Clinical features [1,5]. The first manifestations are usually nasopharyngeal. Since the disease runs a very slow progressive course and the lesions are indolent, the patient tends to seek medical advice only when it has been present for several years, as general health is not impaired.

The disease progresses through three overlapping stages:

Exudative (catarrhal), rhinitic or atrophic stage. This begins with symptoms of a common cold. There is headache and difficulty in breathing, a foetid, purulent rhinorrhea of long duration (weeks or months), with scabs, dryness of the throat and occasional epistaxis (Table 30.4). Hypertrophy of the mucous membrane can be observed, especially on the septum.

Proliferative or granulomatous stage. First, there is the infiltrative period. As the symptoms of coryza begin to subside, infiltration and obstruction of the lower portion of the nasal fossae occur, with an exuberant, friable granulation tissue, crusting and induration, which later extends to the pharynx and larynx. At this time a change in the modulation and tone of the voice (hoarseness) is produced. Anaesthesia of the soft palate is frequent.

Table 30.4 Frequency of initial symptoms of rhinoscleroma, determined by review of literature. (From Miller *et al.* [6].)

Symptom	Frequency (%)
Nasal obstruction	94
Nasal deformity	32
Hoarseness	12
Epistaxis	11
Upper lip swelling	10
Sore throat	6
Epiphora	4

Table 30.5 Approximate frequency of sites involved in rhinoscleroma, determined by review of literature. (From Miller *et al.* [6].)

Site	Frequency (%)
Nose	95
Palate	31
Pharynx	18
Larynx	14
Upper lip	12
Paranasal sinuses	4
Lacrimal sac	4
Trachea	2
Orbit	1

Later on, the nodular period supervenes. From the initial localization in the septum, the disease may spread forward to invade the nasal lobule and the upper lip. Backward extension may produce laryngeal and tracheal involvement, obstruction of the respiratory tract (Table 30.5), loss of the senses of smell and taste, epistaxis and epiphora (affecting the lacrimal apparatus). Bony destruction and cervical node involvement can occur. Breathing becomes difficult and painful, and tracheotomy is sometimes necessary.

Fibrotic (sclerotic) stage. Clinical improvement occurs. The previously inflamed tissue is replaced by dense collagen. The healing process (spontaneous or after therapy) leads to anatomical distortion and stenosis of the structures affected during the proliferative stage [7].

Radiographic findings. These include non-specific paranasal sinus opacification, nasal turbinate atrophy, nasal mass with bone destruction, transglottic narrowing, vocal cord thickening, and discrete subglottic narrowing, which can be shown using plain radiography and computed tomography [8].

Laboratory findings [1]. The identification of the bacterium is not easy, and is based on its biochemical activity, which distinguishes it from other *Klebsiella* spp. However, *K. rhinoscleromatis* has a unique antigenic marker, 02K3, with 0 representing the smooth somatic antigen and K the capsular antigen. This antigenic marker

allows immunological identification using the peroxidase–antiperoxidase immune complex method. Serological reactions, such as the complement-fixation test, agglutination test and intracutaneous test, are of doubtful value.

Diagnosis. The diagnosis is based on: the clinical features—especially when the lesions are advanced or pronounced; the characteristic histopathological picture; the finding of Frisch bacilli, adequately identified bacteriologically; complement-fixation tests, but these give inconsistent results.

Differential diagnosis. Rhinoscleroma must be differentiated from other diseases involving the nasal fossae and upper respiratory tract. At the early stages, chronic bacterial rhinosinusitis and atrophic rhinitis should be considered. At the late stages, the following enter the differential diagnosis: mucocutaneous or American leishmaniasis, which is highly destructive but not as proliferative or obstructive as scleroma, and paracoccidioidomycosis, which affects especially the mucous membranes of the mouth and is accompanied by marked adenopathy and granulomatous lesions that bleed easily ('blackberry' stomatitis). Rhinosporidiosis presents with polyps in the form of soft masses with minute white spots that represent sporangia. Lethal midline (facial) granuloma, Wegener's granulomatosis and malignant epithelial tumours and sarcomas can be differentiated by their rapid evolution. Other diseases that must be considered are: tertiary syphilis with bone involvement, sarcoidosis, nasal tuberculosis, which produces atresia rather than destruction by proliferation, yaws, with its destructive form called gangosa and its proliferative osseous form called goundou, leprosy, lymphomas and nasal polyps.

Prognosis. This is essentially a chronic disease with a slowly progressive course. Relapses are frequent after apparent bacteriological cure. Involvement of trachea or bronchi inevitably worsens the prognosis. The disease is rarely associated with AIDS [9].

Treatment [10,11]. *Klebsiella rhinoscleromatis* may be sensitive to several antibiotics, including trimethoprim–sulfamethoxazole, streptomycin, tetracycline, chlortetracycline, triacetyl-oleandomycin, kanamycin, gentamicin, cephaloridine and rifampicin. It is advisable to determine the antibiotic sensitivity of each strain and to continue the treatment until bacteriological cure is obtained.

Tetracycline is one of the drugs of choice for long-term treatment, at a dose of 2 g/day, given in divided doses for 6 months, followed by 1 g/day for a similar period of time. In case of recurrence, cephalexin, at similar doses and duration, should be tried [6]. Ciprofloxacin, 250–500 mg twice a day, with meticulous nasal lavage with saline twice a day for 4 weeks, has been advocated [11,12]. Trimethoprim–sulfamethoxazole, 160–800 mg twice a day (based always on *in vitro* sensitivity studies), and betamethasone sodium phosphate, 4 mg i.m. every 3 weeks for 6 months, have been used.

During the healing process, scarring affects the upper respiratory tract, the nose, pharynx and larynx [9]. In this inactive fibrotic stage, surgical treatment may be required to correct severe structural and functional abnormalities, such as the narrowing of the nasal vestibule, nasopharyngeal stenosis and laryngeal web formation [6]. Nasal endoscopic techniques and the carbon dioxide laser have been used for the treatment of the obstructive scars [9].

References

1 Kerdel-Vegas F. *Rhinoscleroma. American Lectures in Dermatology*. Springfield: Thomas, 1963.
2 Steffen TN, Smith IM. Scleroma. *Klebsiella rhinoscleromatis* and its effect on mice. *Ann Otol Rhinol Laryngol* 1961; **70**: 935–52.
3 Andraca R, Randall SE, Kern EB. Rhinoscleroma: a growing concern in the United States? Mayo Clinic experience. *Mayo Clin Proc* 1993; **68**: 1151–7.
4 Lubin JR, Jallow SE, Wilson WR *et al*. Rhinoscleroma with exophthalmos: a case report. *Br J Ophthalmol* 1981; **65**: 14–7.
5 Furnas DW. Recognition of scleroma (rhinoscleroma). *Laryngoscope* 1968; **78**: 1948–52.
6 Miller RH, Shulman JB, Canalis RF *et al*. *Klebsiella rhinoscleromatis*: a clinical and pathogenic enigma. *Otolaryngol Head Neck Surg* 1979; **87**: 212–21.
7 Lenis A, Ruff T, Diaz JA *et al*. Rhinoscleroma. *South Med J* 1988; **81**: 1580–2.
8 Becker TS, Shum TK, Waller TS *et al*. Radiological aspects of rhinoscleroma. *Radiology* 1981; **141**: 433–8.
9 Toohill RJ. Rhinoscleroma in perspective. *Mayo Clin Proc* 1993; **68**: 1219–25.
10 Lenis A, Ruff T, Diaz J *et al*. Rhinoscleroma. *South Med J* 1988; **81**: 1580–2.
11 Borgstein J, Sada E, Cortes R. Ciprofloxacin for rhinoscleroma and ozema. *Lancet* 1993; **342**: 122.
12 Badia L, Lund VJ. A case of rhinoscleroma treated with ciprofloxacin. *J Laryngol Otol* 2001; **115**: 220–2.

Tularaemia

Aetiology and pathology [1,2]. Tularaemia results from systemic infection with the Gram-negative bacteria, *Francisella tularensis*. Wild rodent or other small animal populations are probably the main reservoir of infection, which is transmitted to humans by the bites of ticks, usually species of *Dermacentor*, or of other arthropods, or by direct contact with infected rodents [2]. The epidemiological pattern is extremely variable and infected food and water have sometimes been responsible for outbreaks in schools or camps. Most cases are sporadic. The disease is endemic in the northern hemisphere, including the USA and many parts of North and East Europe apart from the UK. Sportsmen and women and campers are most exposed to infection, but cases have occurred in laboratory workers and in housewives.

Francisella tularensis is a pleomorphic, non-motile, Gram-negative coccobacillus, which produces a powerful endotoxin. It is a facultative intracellular parasite. Histologically, the rather variable tissue reaction consists largely of reticuloendothelial cells and monocytes with focal necrosis.

Clinical features [3,4]. The incubation period varies from 1 to 10 days. The clinical manifestations depend on the portal of entry: skin, eye, or respiratory or gastrointestinal tracts. Most sporadic cases are of the ulceroglandular, glandular or oculoglandular type. A red, painful and then ulcerated nodule at the point of inoculation or tick bite is associated with enlargement and tenderness, and later with breakdown of the regional lymph nodes [3]. Systemic symptoms and toxaemia may be severe, but are often moderate, although pneumonia may occur. The typhoidal and pulmonary forms, which present with severe generalized or respiratory symptoms, respectively, run a more fulminating course.

During the toxaemic stage of all forms, cutaneous lesions may develop: a generalized eruption, maculopapular, or resembling erythema multiforme, or profuse crops of nodules, usually on the limbs, may occur [3,5]. Nodular lesions resembling erythema nodosum have also been described.

Untreated, the course may be prolonged; the mortality of the typhoidal and pulmonary forms exceeds 30%, and that of the oculoglandular form is about 5%.

Diagnosis. The organism may be cultured from the primary lesion, the lymph nodes or gastric or pharyngeal washings. Specific agglutinins appear in the serum after about 10 days and increase in titre for some 4 weeks. Cross-agglutination with the *Brucella* antigen is a possible source of error. An enzyme-linked immunosorbent assay (ELISA) is available in some laboratories.

In differential diagnosis, cat scratch disease and sporotrichosis must be excluded, as must melioidosis and glanders.

Treatment [6]. Streptomycin 12-hourly, i.m. in high doses (30–40 mg/kg body weight/day) for 3 days followed by half dosage for 3 days more, is recommended. Gentamicin is a potentially useful alternative [7]. Tetracycline controls symptoms but does not eradicate the organisms, and so relapses are frequent. Recent experience with fluoroquinones such as ciprofloxacin have been encouraging.

A live attenuated vaccine against tularaemia is available in some centres but it is usually restricted to laboratory workers at risk [8].

References

1 Boyce JM. Recent trends in the epidemiology of tularemia in the United States. *J Infect Dis* 1975; **131**: 197–9.
2 Reintjes R, Dedushaj I, Gjini A *et al*. Tularemia outbreak investigation in Kosovo. Case control and environmental studies. *Emerg Infect Dis* 2002; **8**: 69–73.
3 Syrjala H, Karvonen J, Salminen A. Skin manifestations of tularemia. A study of 88 cases in Northern Finland during 16 years (1967–83). *Acta Derm Venereol (Stockh)* 1984; **64**: 513–6.
4 Evans ME, Gregory DW, Schaffner W *et al*. Tularemia: a 30-year experience with 88 cases. *Medicine (Baltimore)* 1985; **54**: 252–69.
5 Warring WB, Ruffin JS. A tick-borne epidemic of tularemia. *N Engl J Med* 1946; **234**: 137–40.
6 Corwin WC, Stubbs SP. Further studies on the treatment of tularemia in the Ozarks. Review of 44 cases during a three year period. *JAMA* 1952; **149**: 343–5.
7 Enderlin G, Morales L, Jacobs RF *et al*. Streptomycin and alternative agents for the treatment of tularemia: review of the literature. *Clin Infect Dis* 1994; **19**: 42–7.
8 Burke DS. Immunization against tularemia. Analysis of the effectiveness of live *Francisella tularensis* vaccine in the prevention of laboratory acquired tularemia. *J Infect Dis* 1977; **135**: 55–60.

Pasteurella infection

Pasteurella multocida and related infections

Aetiology [1]. *Pasteurella multocida* is a small, Gram-negative bacillus widely distributed as a member of the normal flora of the respiratory tract or intestines of many domestic and wild animals, in which it may cause haemorrhagic septicaemia if the resistance of the host is low. The organism does not normally occur in humans, but may be demonstrable in the sputum of patients with bronchiectasis. Most human infections follow bites by cats, dogs or other animals, and scratch injuries (usually from cats) may also become infected. There are two main varieties, *P. multocida multocida* and *P. multocida septica*. Other species which can cause wound infections include *P. canis*, *P. stomatis* and *P. dagmatis*.



Fig. 30.18 *Pasteurella multocida* infection. (Courtesy of St. John's Institute of Dermatology, London, UK.)

Clinical features and diagnosis [1–3] (Fig. 30.18). Most lesions are on the hands, arms or lower legs. The clinical picture is influenced by the extent and depth of the bite. Redness and swelling around the wound may spread rapidly over a wide area and may break down to discharge greyish yellow, haemorrhagic pus through one or more sinuses. In other cases, the inflammatory changes, often associated with great tenderness, remain localized to the edges of the wound. If the bite is deep, there may be osteomyelitis or synovitis. Ten to fifteen per cent of patients are febrile and localized lymphadenopathy often develops. About 15% of patients, particularly those patients with internal disease affecting the abdominal cavity or lung, have no history of exposure to animals.

The diagnosis will be suggested by the history and is confirmed by the isolation of the slow-growing, Gram-negative bacillus.

Treatment. The infection responds to penicillin, ampicillin and cephalosporins, for example cefuroxime. However, as bite wounds are often polymicrobial it is important to follow up patients closely [4].

References

1 Weber DJ, Wolfson JS, Swartz MN *et al*. *Pasteurella multocida* infections: report of 34 cases and review of the literature. *Medicine (Baltimore)* 1984; **63**: 133–44.
2 Francis DP, Holmes MA, Brandon G. *Pasteurella multocida* infections after domestic animal bites and scratches. *JAMA* 1975; **233**: 42–8.
3 Tindall JP, Harrison CM. *Pasteurella multocida* infection due to animal bite. *Arch Dermatol* 1972; **105**: 412–6.
4 Goldstein EJC. Bite wounds and infection. *Clin Infect Dis* 1992; **14**: 633–40.

Plague and *Yersinia* infections

Aetiology and distribution. *Yersinia pestis* [1], the cause of plague, is a small, Gram-negative, non-sporing and non-motile bacillus.

With Giemsa it shows characteristic bipolar staining. It is a zoonotic infection that affects a wide variety of rodents, but particularly the urban and domestic rats, *Rattus rattus* and *R. norvegicus*, and is conveyed from them to humans by the bites of fleas (patient-to-patient transfer rarely occurs in pneumonic plague), or humans may be infected after contact with contaminated material. Plague is endemic in parts of India and the Far East, and in Madagascar and Southern and Central Africa [2,3]. Sporadic outbreaks occur in North Africa and the Middle East and there are foci of infection in the USA [4]. Occasional cases are recognized elsewhere in travellers from the endemic areas. The incubation period is 3 or 4 days, but it may occasionally be over 7 days. Following inoculation of the organism by a flea bite, the regional lymph node becomes swollen (the classic bubo of bubonic plague), and systemic spread, typically with a severe febrile illness, develops, frequently leading to death within days. Lung involvement occurs in some cases, with sputum that is highly infectious. If *Y. pestis* is inhaled, it is likely to lead to primary pulmonary infection (pneumonic plague), which is almost invariably fatal within 3 or 4 days.

In plague epidemics, mild bubonic infections with no systemic spread and truly subclinical infections both occur. Conversely, a patient may rapidly die of flea-transmitted plague without ever developing a bubo. In some instances, cerebral symptoms may be severe.

Clinical (cutaneous) features [2,5]. Although typically there is no distinct lesion at the site of the initial flea bite, an erythematous plaque may appear, become bullous and then crusted like an anthrax lesion. Such primary cutaneous lesions may occur in 10% of patients. The bubo arises in the regional lymph nodes several days later. The bubo is a swollen lymph node that becomes acutely painful. During the bacteraemic phase, a macular, erythematous or petechial rash may develop; this is sometimes frankly purpuric (the black death). Necrotic lesions that closely resemble ecthyma gangrenosum may develop [5]. These are the result of vasculitis and occlusion of vessels with fibrin thrombi.

In a few cases, umbilicated vesicles or pustules are seen, particularly over the trunk [3]. This atypical eruption has been a notable feature of certain epidemics and is generally associated with a high mortality. If bubos are excluded, cutaneous lesions probably occur in about 10% of cases in most epidemics.

Diagnosis. Despite the short incubation period, air travel may carry infected individuals to any part of the world. Even in endemic areas, sporadic cases are often misdiagnosed. The adenitis is the most characteristic feature. Aspiration of a bubo and direct examination of smears and culture confirm the diagnosis. The culture of blood and sputum should also be undertaken.

Treatment [6]. Streptomycin, gentamicin, doxycycline or chloramphenicol are all effective. The latter is mainly used where high tissue penetration is needed, for example in myocarditis.

References

1 Parkhill J, Wren BW, Thomson NR *et al*. Genome sequence of *Yersinia pestis*, the causative agent of plague. *Nature* 2001; **413**: 523–7.

2 Boisier P, Rahalison L, Rasolomaharo M *et al*. Epidemiologic features of four successive annual outbreaks of bubonic plague in Mahajanga, Madagascar. *Emerging Infect Dis* 2002; **8**: 311–6.

3 Butler T, Bell WR, Linh NN *et al*. *Yersinia pestis* in Vietnam. 1. Clinical and hematologic aspects. *J Infect Dis* 1974; **129**: S78–84.

4 Butler T. Yersinia infections. Centennial of the discovery of the plague bacillus. *Clin Infect Dis* 1994; **19**: 655–63.

5 Welty TK, Grabman J, Kompare E *et al*. Nineteen cases of plague in Arizona. A spectrum including ecthyma gangrenosum due to plague and plague in pregnancy. *West J Med* 1985; **142**: 641–6.

6 Crook LD, Tempest B. Plague. A clinical review of 27 cases. *Arch Intern Med* 1992; **152**: 1253–6.

Yersinia enterocolitica infection

Yersinia enterocolitica is an important cause of a syndrome in which diarrhoea and pain similar to appendicitis occurs. In some reported cases there is polyarthritis, and a high proportion of patients, 30% in some series, also have erythema nodosum. Lesions appear from 2 to 20 days after the onset of abdominal symptoms [1].

Reference

1 van der Heijden IM, Res PCM, Wilbrink B *et al*. Yersinia enterocolitica: a cause of chronic polyarthritis. *Clin Infect Dis* 1997; **25**: 831–7.

Brucellosis

Aetiology and pathology. Brucellosis is a widespread infection of cattle and sheep, goats and pigs with *Brucella abortus*, *B. melitensis* and *B. suis*, respectively. Humans are infected by the ingestion of contaminated milk or milk products, or by direct contact with infected animals. The incidence is therefore highest in veterinary surgeons and farmers. There are also species confined to causing disease in animals.

The organism—a Gram-negative, aerobic coccobacillus—colonizes the cells of the reticuloendothelial system and induces a granulomatous tissue response.

The histological changes in the skin lesions [1] are usually not distinctive, but there may be intense inflammatory changes around vessels showing gross intimal proliferation, and granuloma formation may occur.

Clinical features [2,3]. After an incubation period, which is usually between 5 and 30 days but may be longer, headache, backache and general malaise accompany the onset of an intermittent fever. Other symptoms, gastrointestinal or nervous, are variable. The lymph nodes and spleen are enlarged in about 50% of cases and the liver in about 25%. Skin lesions develop in about 5% but are not pathognomonic. Morbilliform, scarlatiniform and roseolar exanthems are described. Less often there may be papular, bullous or haemorrhagic lesions. Erythema multiforme-like nodules of the legs have also been reported [4,5].

The course of brucellosis is variable. The illness usually lasts for 3 or 4 months, but both acute fulminating and extremely chronic forms occur. In the latter, there may be persistent infection of bone, gall bladder or other organs.

Contact brucellosis [3]. Veterinary surgeons, and others who are in frequent contact with infected animals, may develop a high degree of allergic sensitivity to *Brucella* antigens. Contact with the

secretion of an infected animal, usually during delivery, gives rise to pruritus, erythema and wealing within a short time of contact, often followed within 48 h by a profuse eruption of fine follicular papules, many of which become vesicular or pustular, and heal in 10–14 days to leave small scars. Secondary eruptions of erythema multiforme type may develop remotely from the sites of contact.

The contamination of abrasions by *B. suis* may cause indolent ulcers [6].

Diagnosis. Systemic brucellosis can be reliably diagnosed by laboratory investigation only. There is usually no leukocytosis but there may be a relative lymphocytosis. Specific agglutinins in a titre over 1:100 must be regarded as suspicious and over 1:300 as diagnostic. Positive blood cultures can sometimes be obtained. PCR based methods are being used with increasing frequency [7].

Treatment. The recommended course of treatment for brucellosis now includes doxycycline and rifampicin, both of which should be given for at least 6 weeks. Shorter periods of therapy are frequently followed by relapse. Co-trimoxazole is an alternative drug. However, both this and single drug regimens, such as tetracycline or streptomycin, are reported to have a 10–40% relapse rate [8]. An alternative combination regimen is streptomycin and tetracycline, and the use of oxytetracycline plus gentamicin for an initial period of 5 days has been successful in children over the age of 8 years. Other drugs such as ciprofloxacin are active *in vitro* against *Brucella* spp., but their clinical role has not been fully evaluated [8].

References

1 Gee-Lew BH, Nicholas EA, Hirose FM *et al*. Unusual skin manifestations of brucellosis. *Arch Dermatol* 1983; **119**: 56–8.
2 Lulu AR, Araj GF, Khateeb MI. Human brucellosis in Kuwait. A prospective study of 400 cases. *Q J Med* 1988; **249**: 39–54.
3 Ariza J, Servitje O, Pallares R *et al*. Characteristic cutaneous lesions in patients with brucellosis. *Arch Dermatol* 1989; **125**: 380–3.
4 Milionis H, Christou L, Elisaf M. Cutaneous manifestations in brucellosis: case report and review of the literature. *Infection* 2000; **28**: 124–6.
5 Franco Vicario R, Balparda J, Santamaria JM. Cutaneous vasculitis in a patient with brucellosis. *Dermatologica* 1985; **171**: 126–8.
6 Christianson HB, Pankey GA, Applewhite ML. Ulcers of skin due to *Brucella suis*. *Arch Dermatol* 1968; **98**: 175–6.
7 Morata P, Queipo-Ortuno MI, Reguera JM *et al*. Diagnostic yield of a PCR based assay in focal complications of brucellosis. *J Clin Microbiol* 2001; **39**: 3743–6.
8 Solera J, Martinez-Alfaro E, Espinoza A. Recognition and optimal treatment of brucellosis. *Drugs* 1997; **53**: 245–56.

Infections due to *Bartonella* species

There has been a certain amount of taxonomic change about the position of species of the genus *Bartonella*, some of which were formerly classified as members of a distinct genus, *Rochalimea*. Originally classified as Rickettsiae, they are now regarded as bacteria more closely related to *Brucella* than to other genera [1]. The human diseases associated with these organisms are trench fever due to *B. quintana*, bacillary angiomatosis (*B. henselae*, *B. quintana*), cat scratch disease (*B. henselae*) and Oroya fever (*B. bacilliformis*). Other described *Bartonella* spp., such as *B. elizabethae*, have rarely been associated with human disease, for example bacteraemia.

Trench fever

Trench fever is caused by *Bartonella quintana*, which is transmitted to humans by the body louse [2]. It has been diagnosed in many different countries, usually under conditions where there have been very poor levels of hygiene. There is no known animal reservoir and it appears to be spread from person to person. After an incubation period of 5–38 days, there is a recurrent febrile illness. Most cases have a widespread maculopapular eruption, most prominent on the trunk, which fluctuates with the fever. The illness is usually mild with spontaneous recovery.

Cat scratch disease

This is a syndrome characterized by the development of peripheral lymphadenopathy after a cat scratch or bite. The causative agent is *Bartonella (Rochalimea) henselae* [3,4]. Patients with the syndrome usually have antibodies to this organism, which has also been isolated from lymph nodes. The same organism also causes a chronic form of bacteraemia in cats without any apparent ill effects.

Epidemiology [5,6]. The disease is worldwide and is most common in autumn and winter. It affects all ages, but mostly children and teenagers; 87% of 1200 cases were aged 18 years or under [6]. There is a history of cat contact, not necessarily prolonged or close, and of a local wound. In many cases it is believed that the cat is the source of the organism and the wound is the portal of entry. A scratch by a cat fulfils both requirements and is the commonest mode of infection. In a study of 1200 cases, it was found that while a bite or scratch from another animal may provide a route for infection, a feline source could nearly always be identified [6]. The cat is usually young but not ill. In only 3.5% of families was more than one member affected, and epidemics did not occur.

The diagnosis may easily be missed in mild cases, and subclinical infection may be frequent if skin-test surveys are valid, which give a 4% positive result in the general population, 18% in the families of patients and 23% in veterinary surgeons.

Pathology [6,7]. Both the primary lesions and the regional lymph nodes show characteristic, although non-specific, changes. In the early stages, there is focal reticulum-cell hyperplasia, which forms granulomas of sarcoid type. Later, there are microabscesses surrounded by a palisade of epithelioid cells and occasionally Langhans giant cells.

The earlier a lymph node is biopsied, the greater the numbers of bacilli visible with the Warthin–Starry silver stain; they are usually undetectable by the time suppuration has occurred.

Clinical features [5,6]. Three to 5 days after the inoculating event, a papule (occasionally a group of papules) may form which progresses through vesicular and crusting stages in 2 or 3 days, and may ulcerate. This lesion may be inconspicuous, or may take several weeks to regress and then often leaves a superficial scar. Its identification is of diagnostic importance, and by diligent searching, including examination of the scalp, ears and fingers, the inflammatory lesion or a residual scar can be found in over 90% of cases. About half are on the hands and arms and one-quarter on the head and neck.

Constitutional symptoms are usually mild, but fever is present in 60% of cases, persisting for a few days or 1 or 2 weeks. Illness lasting more than 2 weeks is uncommon [8].

Lymphadenopathy is present in all cases, and usually develops within 1 or 2 weeks of the initial papule, although it may not be noticed until later. The affected node is in the drainage path of the primary lesion but there is no lymphangitis. It is solitary in 85% of patients; two or three are seen occasionally. Uncommonly, bilateral lymphadenopathy is seen, but this can be explained by separate inoculations or a single one close to the midline. The glands are painful and tender and occasionally progress to suppuration and discharge before regressing in a period of weeks or months; persistent enlargement is uncommon. Recurrent lymphadenopathy is exceptional [8].

Primary inoculation of the eye, which does not require injury, causes a granulation, usually painless, and usually on the palpebral conjunctiva, followed by enlargement of the preauricular gland, constituting one of the forms of Parinaud's oculoglandular syndrome [9].

Unusual cutaneous manifestations include a maculopapular rash, urticaria, thrombocytopenic purpura, erythema nodosum, erythema multiforme and erythema marginatum; they appear to be more common among patients with severe or systemic disease [8].

Rarely, there may be systemic involvement [6,8] with arthritis, osteolytic lesions, intra-abdominal or intrathoracic lymphadenopathy, encephalopathy [10], myelitis [11], radiculitis, cerebral arteritis [12], pneumonia, pleurisy or granulomatous infection of liver or spleen.

In the uncomplicated case, there may be a polymorphonuclear leukocytosis and a slight elevation of the sedimentation rate.

Cat scratch disease, even when accompanied by the more severe complications, is benign and self-limiting.

Diagnosis. Unilateral lymphadenitis is the usual presenting feature. A history of a cat scratch days or weeks previously resulting in a granulomatous nodule distal to the gland would immediately confirm the diagnosis, and the importance of actively seeking these two features has been emphasized [6]. If they are lacking, the clinical diagnosis is made by exclusion.

Primary tuberculosis, other mycobacterial infections, lymphogranuloma, pyogenic adenitis and sporotrichosis must be considered, and in the absence of a visible inoculation lesion, lymphoma or sarcoidosis must also be excluded.

Histochemical demonstration of the bacilli in the inoculation lesion or, more commonly by the time of presentation, in the lymph node, would confirm the diagnosis. However, the organisms are increasingly difficult to detect as the disease progresses. Otherwise, histology is not specific, and biopsy is not routinely recommended. Skin testing with cat scratch disease antigen made from pus from affected lymph nodes has its advocates [6] but is not generally advised. Detection of cat scratch disease by genetic methodologies (e.g. Light Cycler) from tissue, blood or aspirated pus is very sensitive [13].

Treatment [6,14]. The value of antibiotics is debatable, despite the fact that they are used with success in bacillary angiomatosis. If treatment is contemplated, azithromycin is the antibiotic recommended. Fluctuant glands may be aspirated, but should not be incised as chronic drainage may occur. Excision of lymph nodes is not justified therapeutically, although it may occasionally be indicated for histology.

Bacillary angiomatosis

Aetiology. Bacillary angiomatosis is an uncommon disease found in AIDS patients and occasionally other patients with severe immunosuppression [15]. It is characterized by the development of friable angiomatous papules and nodules. Two *Bartonella* spp. have been associated with this infection: *B. henselae* and *B. quintana* [16]. The appearance of these lesions follows a septicaemia, which is usually mild and often passes unnoticed.

The disease has been described mostly from the USA although it is also seen in Europe. The infection is sporadic and there is not necessarily a history of exposure to cats or of skin injury. There are no known differences between skin infections caused by the two species of *Bartonella*.

Clinical manifestations. The lesions of bacillary angiomatosis are very variable [17]. They may be solitary or appear in crops, as small papules of dermal nodules. The more superficial lesions closely resemble pyogenic granulomas. They can involve any site including mucosal surfaces. Local lymphadenopathy is common. Very extensive lesions may cover parts of the face or trunk.

There is lobular proliferation of small blood vessels that contain swollen endothelial cells. These contain granular material, which consists of clumps of bacteria seen with the Warthin–Starry stain.

Complications include bacillary peliosis, where cyst-like inflammatory structures may develop in internal organs such as the liver. Again, the endothelial cells lining these spaces contain large numbers of organisms.

Diagnosis. The diagnosis is made by the appearances of the typical lesions and the presence of large clusters of bacteria on Warthin–Starry staining. Cultures are not usually taken as they are technically difficult to process. However, polymerase chain reaction (PCR) is now increasingly used [18]. Lesions have to be distinguished from those of pyogenic granulomas, molluscum contagiosum, Kaposi's sarcoma and deep fungal infections disseminated to skin. They are also very similar to those of verruca peruana.

Treatment. There are no controlled studies of treatment of this condition, but doxycycline or erythromycin are usually given. It may be necessary to use long periods of treatment for 8 weeks or longer. Relapses are common.

Oroya fever and verruga peruana

Synonym
- Carrion's disease

Definition [19]. Oroya fever is an infectious disease transmitted by *Phlebotomus* spp. and caused by the small, rod-shaped organism *Bartonella bacilliformis*.

Aetiology. It is endemic in parts of Peru, and epidemics have occurred in neighbouring Latin American countries. In the endemic areas, most individuals are infected in childhood and acquire a permanent immunity.

Clinical features [20]. The incubation period is usually about 3 weeks but ranges from 2 to 6 weeks. Two forms of infection are recognized: Oroya fever and verruga peruana; these are now known to represent two stages of infection. In the first stage (Oroya fever) there is a sudden onset of pyrexia accompanied by a rapidly progressive, haemolytic anaemia. Hepatosplenomegaly and generalized lymphadenopathy occur and a petechial or ecchymotic rash may develop. The mortality is high and many cases are accompanied by *Salmonella* septicaemia.

Verruga peruana may develop without previous Oroya fever, or may follow it weeks or months later. The eruption is composed of erythematous papules, which appear in crops and often become nodular or pedunculated. Some lesions become very large, others may be haemangiomatous or haemorrhagic. They are most numerous on the face, neck and limbs but may also involve mucous membranes. Mild constitutional symptoms and fever coexist in this form of infection, which may settle spontaneously. Lesions may persist for months or years. One characteristic is that they may be present in different stages of evolution in the same patient [21].

Diagnosis. The diagnosis should be considered only if the patient has visited the endemic areas. Verruga peruana must be distinguished from yaws, acquired haemangiomas and Kaposi's sarcoma.

The biopsy appearances of verruca peruana show lesions containing numerous small blood vessels with endothelial proliferation. There is a variable infiltrate of chronic inflammatory cells, and lesions heal with fibrosis [22].

In Oroya fever, the organism can be seen in blood films or isolated in blood cultures. Blood cultures are also positive during the active phase of the benign form, and in skin biopsies *B. bacilliformis* can be seen in the cytoplasm of endothelial cells.

Treatment. In Oroya fever, chloramphenicol 2 g/day for a week is the treatment of choice because of the frequent coexisting S*almonella* infection, but *B. bacilliformis* itself responds to ciprofloxacin, penicillin, doxycycline and streptomycin. In verruca peruana, response to antibiotics is unsatisfactory; most lesions evolve and eventually settle uninfluenced by treatment.

References

1 Relman DA, Lepp PW, Sadler KN *et al*. Phylogenetic relationships among the agent of bacillary angiomatosis, *Bartonella bacilliformis* and other alpha-proteobacteria. *Mol Microbiol* 1992; **6**: 1801–7.

2 Vinson JW. *In vitro* cultivation of the rickettsial agent of trench fever. *Bull World Health Organ* 1996; **35**: 155–64.

3 Koehler JE, Glaser CA, Tappero JW. *Rochalimea henselae* infection with the domestic cat as reservoir. *JAMA* 1994; **271**: 531–5.

4 Dolan MJ, Wong MT, Regnery RL *et al*. Syndrome of *Rochalimea henselae* suggesting cat scratch disease. *Ann Intern Med* 1993; **118**: 331–6.

5 Daniels WB, MacMurray FG. Cat scratch disease. Report of one hundred and sixty cases. *JAMA* 1954; **154**: 1247–51.

6 Carithers HA. Cat scratch disease. An overview based on a study of 1200 patients. *Am J Dis Child* 1985; **139**: 1124–33.

7 Johnson WT, Helwig EB. Cat-scratch disease: histopathologic changes in the skin. *Arch Dermatol* 1969; **100**: 148–54.

8 Margileth AM, Wear DJ, English CK. Systemic cat scratch disease. Report of 23 patients with prolonged or recurrent severe bacterial infection. *J Infect Dis* 1987; **155**: 390–402.

9 Loftus MJ, Sweeney G, Goldberg MH. Parinaud oculoglandular syndrome and cat scratch fever. *J Oral Surg* 1980; **38**: 218–20.

10 Miller P, Bell WE. Cat scratch disease with encephalopathy. *Clin Pediatr (Phila)* 1980; **19**: 233–4.

11 Pickerill RG, Milder JE. Transverse myelitis associated with cat scratch disease in an adult. *JAMA* 1981; **246**: 2840–1.

12 Selby G, Walker GL. Cerebral arteritis in cat scratch disease. *Neurology* 1979; **29**: 1413–8.

13 Zeaiter Z, Fournier PE, Greub G, Raoult D. Diagnosis of *Bartonella* endocarditis by real time nested PCR using serum. *J Clin Microbiol* 2003; **41**: 919–25.

14 Rolain JM, Brouqui P, Koehler JE *et al*. Recommendations for treatment of human infections caused by *Bartonella* species. *Antimcrob Agents Chemother* 2004; **48**: 1921–33.

15 Tappero JW, Mohle-Boetani J, Koehler JE *et al*. The epidemiology of bacillary angiomatosis and bacillary peliosis. *JAMA* 1993; **269**: 770–5.

16 Koehler JE, Quinn FD, Berger TG *et al*. Isolation of *Rochalimea henselae* from cutaneous and osseus lesions of bacillary angiomatosis. *N Engl J Med* 1992; **327**: 1625–32.

17 Cockerell CJ, LeBoit PE. Bacillary angiomatosis; a newly characterised pseudoneoplastic infectious, cutaneous vascular disorder. *J Am Acad Dermatol* 1990; **22**: 501–12.

18 Jensen WA, Fall MZ, Rooney J *et al*. Rapid identification and differentiation of *Bartonella* species using a single-step PCR assay. *J Clin Microbiol* 2000; **38**: 1717–22.

19 Maguina C, Garcia PJ, Gotuzzo E *et al*. Bartonellosis (Carrion's disease) in the modern era. *Clin Infect Dis* 2001; **33**: 772–9.

20 Kreier JP, Ristic M. The biology of hemotrophic bacteria. *Annu Rev Microbiol* 1981; **35**: 325–38.

21 Ellis BA, Rotz LD, Leake JA *et al*. An outbreak of acute bartonellosis (Oroya fever) in the Urubamba region of Peru, 1998. *Am J Trop Med Hyg* 1999; **61**: 344–9.

22 Arias-Stella J, Lieberman PH, Erlandson RA *et al*. Histology, immunohistochemistry and ultrastructure of the verruca in Carrion's disease. *Am J Surg Pathol* 1986; **10**: 595–610.

Ehrlichiosis

Ehrlichia spp. are small, Gram-negative bacteria. They form clusters of intracellular inclusion bodies known as morulae. Formerly associated predominantly with veterinary infection, a human form of the disease has been recognized more recently as a tick-borne zoonosis. A number of different species have been recognized in humans, although *E. chaffeensis* and *E. sennetsu* are most commonly involved. Most cases have been described from the USA [1], although patients with this infection have been recognized in Europe. In the USA, the distribution of the dog tick, *Dermacentor variabilis*, and the Lone Star tick, *Amblyomma americanum*, coincide with the distribution of human cases. The main target cell for these bacteria are macrophages. The infection is now often referred to as human monocyte ehrlichiosis. There is a related seasonal infection caused by spread through *Ixodes* ticks called human granulocyte anaplasmosis and caused by a closely related organism *Anaplasma phagocytophylum.*

The median incubation period is 7 days and patients generally present with fever, malaise, headache and myalgia. Over 30% of patients have a diffuse maculopapular rash and in some this becomes petechial [2]. Rashes are much less common with *Anaplasma* infections [3].

Leukopenia and thrombocytopenia may develop. *Ehrlichia sennetsu* infections that occur rarely in the Far East are similar in presentation, although rashes are uncommon [4].

The diagnosis is difficult as cultural techniques are complicated and a serological assay using immunofluorescence is employed instead. The clinical history is also important. It is important to distinguish ehrlichiosis from Rocky Mountain spotted fever, in which more patients develop a rash.

Treatment depends on the use of tetracycline or doxycycline.

References

1 Fishbein DB, Dawson JE, Robinson LE. Human ehrlichiosis in the United States 1985–90. *Ann Intern Med* 1994; **120**: 736–43.

2 Fishbein DB, Kemp A, Dawson JE *et al*. Human ehrlichiosis. Prospective active surveillance in febrile hospitalized patients. *J Infect Dis* 1989; **160**: 803–9.

3 Aguero-Rosenfeld ME, Donnarumma L, Zentamaier L *et al*. Seroprevalence of antibodies that react with *Anaplasma phagocytophila* the agent of human granulocyte ehrlichiosis in different populations in Westchester county, New York. *J Clin Microbiol* 2002; **40**: 2612–5.

4 Tachibana N. Sennetsu fever. The disease, diagnosis and treatment. In: Leive L, ed. *Microbiology*. Washington DC: American Society for Microbiology, 1986; 205–8.

Other Gram-negative bacilli

On occasions, other Gram-negative bacteria have been associated with skin disease. *Actinobacillus actinomycetem-comitans* is frequently isolated from lesions of actinomycosis along with the usual *Actinomycete* cause, giving rise to the view that it is involved in the pathogenesis of this condition [1].

The aeromonads may occasionally cause cellulitis. These bacteria are inhabitants of water and cause infections in fish and reptiles. Cellulitis or necrotizing fasciitis caused by *Aeromonas* spp. is rare, but may follow contamination of a wound in contact with fresh water [2]. It may also occur in immunocompromised patients. *Aeromonas hydrophila* is sensitive to co-trimoxazole and chloramphenicol, but usually resistant to ampicillin and other penicillins. Cellulitis can spread rapidly and may involve muscle tissue or periosteum unless treated promptly [3].

Members of the bacterial group known as dysgonic fermenters (DF), such as DF-2, may also cause severe skin lesions. These organisms are Gram-negative rods that grow poorly on most cultural media. They are thought to be zoonotic in origin, and have been isolated from the oral cavity of dogs. DF-2 causes infections in patients who have undergone splenectomy or have other predisposing conditions, where it causes an acute septicaemic illness. More indolent infections including cellulitis are seen in otherwise healthy patients [4]. However, septicaemia may also develop in this group. Eugonic fermenters (EF agents) have also been isolated from dog bites.

Eikenella corrodens, an anaerobic, Gram-negative bacillus, may cause abscesses of the skin in intravenous drug abusers. It has also been isolated from wounds caused by human bites [5].

References

1 Holm P. Studies on the aetiology of human actinomycosis. Do the other microbes of actinomycosis possess virulence? *Acta Pathol Microbiol Scand* 1951; **28**: 391–406.

2 Lin CS, Cheng SH. *Aeromonas hydrophila* sepsis presenting as meningitis and necrotising fasciitis in a man with alcoholic liver cirrhosis. *J Formos Med Assoc* 1998; **97**: 498–502.

3 Heckerling PS, Stine TM, Pottage JC *et al*. *Aeromonas hydrophila* myonecrosis and gas gangrene in a non-immunocompromised patient. *South Med J* 1983; **143**: 2005–7.

4 Hicklin H, Verghese A, Alvarez S. Dysgonic fermenter to septicemia. *Rev Infect Dis* 1987; **9**: 884–90.

5 Stoloff AL, Gillies ML. Infections with *Eikenella corrodens* in a general hospital; a report of 33 cases. *Rev Infect Dis* 1986; **8**: 50–3.

Vibrio vulnificus infections

Certain non-cholera vibrios have been found to cause severe cellulitis. *Vibrio vulnificus* is the best known of these organisms. It is found in warm sea-water areas such as around the gulf of Mexico, South America, Asia and Australia and may invade via the gastrointestinal tract, for instance, after eating raw oysters, or contaminate superficial wounds [1,2]. In predisposed patients, such as those with diabetes or chronic liver disease, and occasionally in the otherwise healthy, it may cause a septicaemic illness of rapid onset. A characteristic is the appearance, in almost two-thirds of patients, of erythema and haemorrhagic bullae or vesicles which progress to ulceration. Systemic signs include hypotension and rigors leading to multiorgan failure. The infection is often rapidly progressive and fatal. Alternatively, it may cause cellulitis, necrotizing fasciitis and ulceration after infection of a skin wound, which may then progress to septicaemia [3]. It has also been found to survive for over 24 hours on skin and then infect an abrasion [4]. Direct Gram stains of smears will show curved, Gram-negative bacilli. Although *V. vulnificus* grows readily on a variety of culture media it is important to liaise closely with the laboratory so the diagnosis is not overlooked. The main treatment is large doses of ceftazidime, ciprofloxacin or tetracycline and surgical debridement where necessary. Treatment should be initiated as early as possible.

References

1 Pollak SJ, Parris EJ, Barrett TJ *et al*. *Vibrio vulnificus* septicemia. *Arch Intern Med* 1983; **143**: 837–41.

2 Tackett CO, Brenner F, Blake PA. Clinical features and an epidemiologic study of *Vibrio vulnificus* infections. *J Infect Dis* 1984; **149**: 558–64.

3 Fujisawa H, Kohda H. Necrotising fasciitis caused by *Vibrio vulnificus* differs from that caused by streptococcal infection. *J Infect* 1998; **34**: 1–18.

4 Colondner R, Chazan B, Kopelowitz J *et al*. Unusual portal of entry of *Vibrio vulnificus*: evidence of prolonged survival on the skin. *Clin Infect Dis* 2002; **34**: 714–5.

Anaerobic bacteria

Anaerobic bacteria are organisms that cannot grow on a solid surface in the presence of oxygen. They can be divided into those that are strict anaerobes, such as *Treponema* spp., and the moderate anaerobes such as *Bacteroides fragilis*. They include both Gram-positive (e.g. *Propionibacterium* spp.) and Gram-negative (e.g. *Bacteroides* spp.) organisms and certain spiral bacteria. Most of the bacteria considered in this section are Gram-negative.

The family Bacteroidaceae consists of Gram-negative, rod-shaped bacilli with rounded or pointed ends. Some are fusiform. They are non-motile, do not form spores and are strict anaerobes [1]. Within the family are four genera: *Bacteroides*, *Prevotella*, *Porphyromonas* and *Fusobacterium.* These include the *Bacteroides fragilis* group, many of which are gastrointestinal tract commensals. The *Prevotella* spp. includes the organisms formerly known as *B. melanogenicus* and *B. oralis*, now *P. melanogenica* and *P. oralis*, respectively. The different genera can be classified according to nutritional requirements, pigmentation and morphology. Classification within the genus, *Fusobacterium* spindle-shaped bacilli, is unsatisfactory and, although a few species have been clearly defined, many isolates of commensal fusiform bacteria from animals and humans cannot be reliably identified as named species. *Fusobacterium necrophorum*, the cause of calf diphtheria and a variety of human infections, and *F. nucleatum*, a member of the normal flora of the human mouth with a pathogenic capacity, are well-characterized exceptions. *Fusobacterium ulcerans* has been isolated exclusively from tropical ulcers and contaminated mud from endemic areas.

Leptotrichia buccalis is the single species recognized in the *Leptotrichia* genus. It is a long, rod-shaped organism with pointed ends, not truly spindle-shaped, sometimes forming lengths of separate filaments. *Leptotrichia buccalis* is possibly synonymous with Vincent's fusiform organism, and therefore should not be labelled a *Fusobacterium* spp. It is an oral commensal in humans.

Bacteroides spp. are now recognized as common causes of Gram-negative bacteraemia and of abscesses. They are occasionally important in suppurative hidradenitis and in infected pilar cysts. Their role in decubitus ulcers is unclear but their frequent presence is not in doubt. Mixed infections are characteristic of this group of bacteria. In diabetic ulcers, in particular, *Bacteroides* spp. may be isolated and appear to be contributing to the clinical condition [2].

Prevotella infections dominate in intraoral infections, including pyhorrhoea and Ludwig's angina. In many cases they may act in concert with other bacteria.

Fusobacterium organisms, although a well-known cause of infections in animals, are less often isolated today from human pathological material. In the past, *F. necrophorum* was regarded as an uncommon but important human pathogen among those in contact with animals. The term necrobacillosis was applied to such infections, characterized as they were by necrosis and abscess formation. *Fusobacterium nucleatum* can be found in severe intraoral infections.

In common with many anaerobic bacteria, fusibacteria appear to synergize with other organisms, including spiral bacteria, to produce disease. They have been implicated in the pathogenesis of cancrum oris (noma) as well as tropical ulcer (*F. ulcerans*), where the production of butyric acid by these organisms contributes to tissue necrosis.

Clinical manifestations. This group of organisms are important causes of a variety of infections from sinusitis and oral abscesses to endocarditis. *Bacteroides*, *Prevotella* and *Porphyromonas* spp. in combinations may also cause abscesses below the waist area. They have also been associated with other severe cutaneous infections such as necrotizing subcutaneous infection (see below).

Treatment. Treatment of anaerobic Gram-negative infections is largely empirical, and testing the organisms for sensitivity is difficult. The choice of drugs includes metronidazole, clindamycin, imipenem and amoxicillin–clavanulate. However, advice should be sought before selecting therapy.

References

1 Summanen P. Microbiology terminology update. Clinically significant anaerobic Gram-positive and Gram-negative bacteria (excluding spirochaetes). *Clin Infect Dis* 1993; **16**: 538–53.

2 Sapico FL, Witte JL, Canawati HN *et al*. The infected foot of the diabetic patient: quantitative microbiology and analysis of clinical features. *Rev Infect Dis* 1984; **6**: S171–6.

Tropical ulcer

Synonyms

- Tropical phagedenic ulcer
- Tropical phagedena

Aetiology. Tropical ulcer is a synergistic bacterial infection that follows invasion of the skin by at least two organisms, one of which is a *Fusobacterium* spp., usually *F. ulcerans*; the others include spirochaetes or other anaerobic bacteria [1,2]. It occurs very commonly throughout the hot and humid tropical regions, in some of which, for example northern Papua New Guinea [3], it is the commonest skin disease. It has acquired in different parts of the world numerous local names, but there are few minor differences in its clinical features and course.

There is no clear evidence that host-predisposing factors play a part in the pathogenesis of this condition. Previously, malnutrition was thought to be critical to the development of tropical ulcers, but it is likely that social factors such as overcrowding are equally important. Recent studies have not shown a correlation between nutritional indices and the development of tropical ulcer [4], although the possible role of deficiencies in micronutrients is unknown. Zinc therapy, however, does not appear to hasten healing of lesions [5].

There is now considerable evidence to suggest that this disease is an infection [6]. The condition has been shown to be transmissible by inoculation of material from affected patients [7]. Recently, the appearance of early ulcers and pre-ulcerative papules has been correlated with the isolation of *F. ulcerans*, a fusobacterial species unique to tropical ulcers [1]. Other anaerobes are also sometimes isolated, and a consistent feature is the presence of spiral bacteria, which have not been isolated in culture but which have the ultrastructural features of *Treponema* spp. In late-stage ulcers, other bacteria including many aerobes such as *Staphylococcus aureus* can be found in tropical ulcers. *Fusobacterium ulcerans* causes destruction of tissue-culture cells and can synergize with other bacteria to cause destructive skin lesions in experimentally infected animals [1]. It is likely, therefore, that the infection is a synergistic anaerobic infection confined to parts of the humid tropics. While the reservoir of *F. ulcerans* is not known, it has been isolated from mud and stagnant water in endemic areas [8].



Fig. 30.19 Tropical ulcer. (Courtesy of St. John's Institute of Dermatology, London, UK.)

Clinical features (Fig. 30.19). Most tropical ulcers develop at a site of potential trauma, a scratch, cut or insect bite, and are therefore commonest on the lower legs and on the unshod foot. They are not unusual on the arms, and may occur anywhere. Ulcers developing in skin that was apparently previously healthy begin as a small papule or bulla, which may be haemorrhagic, and which soon breaks down rapidly to form a sharply defined ulcer, with a slightly indurated edge that may be undermined. An important feature is the rapid breakdown of the preulcerative papule to form a tropical ulcer [8].

The floor is covered by a foul-smelling, greyish, purulent slough. Pain is usual, and there may be fever and constitutional symptoms. There is usually no regional adenitis. If the lesion is treated promptly, even with careful dressing, the spread is limited to a lesion 2–4 cm in diameter, which heals slowly. In about 4–15% of cases, depending to some extent on the availability of primary health care, chronic ulcers may form and may involve deep structures such as tendons and periosteum [8]. Squamous epithelioma develops after 10 years or more in some such cases.

Diagnosis. While pleomorphic fusiform and spiral bacteria are important pathogenic organisms, their presence or absence is not diagnostic and their isolation in culture impracticable. The mainstays of diagnosis are the rapid onset of lesions, their clinical appearance and the clustering of cases in the locality. In endemic areas, the main differential diagnosis is between yaws, leishmaniasis, ecthyma and mycobacterial ulcers. Sores due to infected skin lesions are more indolent and smaller in size.

Treatment. Rest, elevation of the limb and adequate diet are of great importance. Any underlying chronic disease should be treated. During the early stages of the disease, penicillin or metronidazole are recommended, combined with bland local applications, and a plaster boot may be helpful in allowing early ambulation when infection has been controlled.

Early grafting has been very successful in the rapid treatment of tropical ulcers, but it is dependent on the availability of the necessary expertise and patient compliance [3].

References

1 Adriaans B, Hay RJ, Drasar B *et al*. The infectious aetiology of tropical ulcer—a study of the role of anaerobic bacteria. *Br J Dermatol* 1987; **118**: 31–7.
2 Citron DM. Update on the taxonomy and clinical aspects of the genus fusobacterium. *Clin Infect Dis* 2002; **35** (Suppl 1): S22–7.
3 Morris GE, Hay RJ, Srinavasa A *et al*. The diagnosis and management of tropical ulcer in East Sepik province of Papua New Guinea. *J Trop Med Hyg* 1989; **92**: 215–20.
4 Robinson DC, Hay RJ. Tropical ulcer in Zambia. *Trans R Soc Med Hyg* 1985; **80**: 132–7.
5 Wilkinson M, Agett P, Cole TJ. Zinc and acute tropical ulcers in Gambian children and adolescents. *Am J Clin Nutr* 1985; **41**: 43–51.
6 Kuberski T, Koteka G. An epidemic of tropical ulcer in the Cook Islands. *Am J Trop Med Hyg* 1980; **29**: 291–7.
7 McAdam I. Tropical phagadenic ulcer in Uganda. *J R Coll Surg Edinb* 1966; **11**: 196–9.
8 Robinson DC, Adriaans B, Hay RJ *et al*. The epidemiology and clinical features of tropical ulcer. *Int J Dermatol* 1988; **27**: 49–53.

Granuloma inguinale

Synonyms
- Granuloma venereum
- Donovanosis
- Ulcerating granuloma of the pudenda

Definition. Terminological confusion with the chlamydial disease lymphogranuloma inguinale must be avoided. Granuloma inguinale is a chronic granulomatous infection of the genitalia and surrounding skin caused by *Calymmatobacterium granulomatis*, formerly known as *Donovania granulomatis*. This organism has not been isolated in pure culture and therefore its taxonomic status is uncertain.

Aetiology [1]. Granuloma inguinale is widespread in the tropics and subtropics, but in most areas is relatively uncommon. It is mainly seen in Africa, South America, the Caribbean and New Guinea. Cases are rare outside these areas. In some countries, males are more frequently affected than females, but in others, such as Brazil, the disease is commoner in women. Venereal transmission, although almost certain, is not entirely proven, and infectivity is undoubtedly low. Most patients are young adults, and homosexual men are said to be more frequently infected, suggesting perhaps that the gastrointestinal tract is the natural habitat of this organism.

Calymmatobacterium granulomatis is a small, pleomorphic, nonmotile, Gram-negative bacillus showing bipolar staining. It is fastidious and was first isolated once on the yolk sac of the chick embryo, and subsequently grown on media containing egg yolk. This has not been reproduced. In tissue scrapings stained by Wright's method, *C. granulomatis* may be seen within characteristic, large mononuclear cells as Donovan bodies. *Calymmatobacterium granulomatis* cross-reacts serologically with *Klebsiella rhinoscleromatis*.

Pathology. The histological changes are not specific. In the inflammatory reaction that infiltrates the cutis and subcutis, plasma cells and polymorphonuclear leukocytes predominate. There are also some lymphocytes and large mononuclear cells containing

Donovan bodies [2]. In chronic lesions, fibrosis and epithelial hyperplasia are also present to a variable degree.

Clinical features [3,4]. The incubation period, which is not always easy to determine, is probably 9–50 days. The earliest lesion is a firm papule or nodule, which breaks down to form an ulcer with a sharply defined, overhanging edge. The ulcer is not painful and there is no adenitis.

The lesion subsequently evolves in a variety of ways, dependent on the balance between healing and destruction and the degree of epithelial hyperplasia.

Deep and rapidly extending ulceration is seen mainly in women. Serpiginous extension with or without vegetative epithelial changes occurs in the groins and other flexures.

The initial lesion is usually on the pubis, the genitalia, the perineum, the groins or the perianal region. While clinically it may appear that the lymph nodes in the groins are enlarged, this is usually caused by a subcutaneous granuloma, which may subsequently undergo necrosis. Rectal lesions have also been described.

In 3–6% of cases [5], the lesion is extragenital, occurring especially on the face, where it favours the nose and lips, but it sometimes occurs on the limbs.

Healing may occur at any stage, or slow or rapid extension may continue intermittently and irregularly for years. Secondary infection may be severe and may lead to adenitis. Temporary remissions may be followed by recrudescences, which may occur in healed scars. When the lesions are extensive, cachexia may, after a long course of many years, predispose to death from intercurrent infection.

In some patients, usually women, metastatic involvement of liver, spleen and bones may occur.

Diagnosis. In the early lesions, syphilis must be excluded by dark-ground examination and serology, and at all stages the possibility of associated syphilitic infection must be remembered.

Smears should be taken and searched for Donovan bodies. It is convenient to take the smear from part of a biopsy from the edge of the lesion, the remainder of the specimen being examined histologically. This organism can only be cultured reproducibly in human monocyte or Hep-2 cell cultures, which are not available for routine diagnostic use.

Treatment [6]. Azithromycin, tetracyclines, erythromycin, streptomycin, gentamicin and chloramphenicol are all effective. Tetracycline must be given in a dose of 500 mg, four times a day for 10–20 days. Minocycline or doxycycline may also be used. Resistance of the organism to tetracycline, although previously unknown, was reported in a single case in 1973. The most effective of the current drugs is probably azithromycin, which has the added advantage of being active against other sexually transmitted bacteria such as *Treponema pallidum* and *Haemophilus ducreyi* [7].

References

1 Goldberg J. Studies on granuloma inguinale. VII. Some epidemiological considerations of the disease. *Br J Vener Dis* 1964; **40**: 140–6.

2 Dodson RF, Fritz GS, Hubler WR *et al*. Donovanosis; a morphological study. *J Invest Dermatol* 1974; **62**: 611–4.

3 Maddocks I, Anders EM, Dennis E. Donovanosis in Papua New Guinea. *Br J Vener Dis* 1976; **52**: 190–5.

4 Rosen T, Tschen JA, Ramsdell W *et al*. Granuloma inguinale. *J Am Acad Dermatol* 1984; **11**: 433–7.

5 Brigden M, Guard R. Extragenital granuloma inguinale in Northern Queensland. *Med J Aust* 1980; **2**: 565–70.

6 Latif AS. Granuloma inguinale. In: Osoba AO, ed. *Baillière's Clinical Tropical Medicine and Communicable Diseases. Sexually Transmitted Diseases in the Tropics,* Vol. 2. London: Baillière Tindall, 1987: 163–8.

7 Bowden FJ, Mein J, Plunkett C *et al*. Pilot study of azithromycin in the treatment of genital donovanosis. *Genitourin Med* 1996; **72**: 17–20.

Spirochaetes and spiral bacteria

Spirochaetes are long, flexible, spiral organisms, motile but without external flagella. Many exist in nature in aquatic habitats [1,2]. Three genera include important human pathogens and commensals: *Treponema*, *Borrelia* and *Leptospira*. *Treponema pallidum* causes syphilis (Chapter 34); *T. pertenue* causes yaws; *T. carateum* causes pinta; *T. endemicum* causes endemic syphilis. *Borrelia recurrentis* causes louse-borne relapsing fever; *B. duttoni* and other species cause tick-borne relapsing fever; *B. burgdorferi* is the name for the *Ixodes dammini*-associated spirochaete, the cause of Lyme arthritis with associated erythema chronicum migrans. *Leptospira interrogans* complex causes leptospirosis, including Weil's disease. Commensal spirochaetes occur in the mouth (*T. microdentium* and *T. macrodentium*) and around the genitalia (*T. refringens*), as well as in the intestine. They appear to have no pathogenic potential but they are important as they may be confused with *T. pallidum*, from which they differ morphologically.

Spirillium minor, the cause of one form of rat-bite fever, is a spiral bacterium which is short, rigid and has bipolar flagella.

References

1 Tramont EC. The impact of syphilis on humankind. *Med Clin N Am* 2004; **326**: 1060–9.

2 Shell RF, Muscher DM, eds. *Pathogenesis and Immunology of Treponemal Infection*. New York: Marcel Dekker, 1983.

Non-venereal (endemic) treponematoses [1–7]

The endemic treponematoses comprise endemic syphilis, yaws and pinta, whose causative treponemes are morphologically and serologically indistinguishable.

Transmission is by skin-to-skin or mouth-to-mouth contact, and children are at greatest risk of infection. They are not sexually transmitted, and congenital infection does not appear to occur.

These diseases are similar to venereal syphilis in that they have an early stage, which includes primary and secondary lesions, and a late (tertiary) stage. The early stage is infectious. Cutaneous lesions are prominent, and mucous membranes and bones are involved in endemic syphilis and yaws.

Diagnosis is based on clinical features, identification of treponemes in mucocutaneous lesions, and serology—serological tests are identical to those for venereal syphilis. Specific treponemal tests usually remain positive for life. Treponemes are easily identified in primary and secondary lesions by dark-ground microscopy and silver stains.

Following mass treatment campaigns in the 1950s and 1960s the incidence of the endemic treponematoses was greatly reduced [3,7], but these diseases have not been totally eradicated.

Endemic syphilis

Synonyms
- Bejel
- Firjal
- Loath

Aetiology. Endemic syphilis is caused by *Treponema pallidum* subspecies *endemicum*. It occurs predominantly in the southern border of the Sahara desert and the Arabian peninsula.

Pathology. Histopathological features of lesions resemble those of venereal syphilis.

Clinical features. The *primary* lesion, which is frequently a papule or small ulcer, usually occurs in the mouth, where it often goes undetected, or on the nipples of breast-feeding women nursing infected children. *Secondary* lesions, which are similar to those of venereal syphilis, include mucous patches on the buccal mucosa or lips, a generalized papular rash, condylomata lata and generalized lymphadenopathy; painful periostitis may affect the legs and hands. Untreated, secondary lesions last for 6–9 months. The late (*tertiary*) stage is characterized by gummata of the nasopharynx that may result in destruction of the nose (gangosa), gummatous lesions in the skin, periostitis and bony gummata.

Yaws

Synonyms
- Framboesia (German and Dutch)
- Pian (French)
- Buba (Spanish)
- Bouba (Portuguese)
- Parangi (Sinhalese)

Aetiology. Yaws is caused by *T. pallidum* ssp. *pertenue*. It is a disease of tropical rural populations, occurring in the Caribbean, Central and South America, throughout tropical Africa, Southeast Asia, and the Pacific islands. Transmission is favoured by overcrowded conditions. It used to be one of the commonest tropical diseases of the skin prior to the World Health Organization's treatment campaigns in the 1950s and 60s.

Pathology. Early lesions show acanthosis, spongiosis and papillomatosis, with intraepidermal microabscesses. There is a moderate to dense dermal inflammatory infiltrate consisting of plasma cells, lymphocytes, macrophages, neutrophils and eosinophils. Numerous treponemes can be identified with silver stains. Late lesions are ulcerated, and are similar to those of tertiary cutaneous syphilis.

Clinical features. In the *primary* stage, the initial lesion ('mother yaw') is usually a solitary erythematous papule, although multiple lesions sometimes occur, at the point of entry of the treponemes. This later ulcerates and is covered by a yellowish crust. It subsequently increases in size to resemble a raspberry (hence the name framboesia), which is teeming with treponemes. The mother yaw lasts for 2–6 months, and heals spontaneously to leave an atrophic scar.

'Daughter yaws' are multiple lesions that develop in the *secondary* stage as the initial lesion heals, and they occur in successive crops. They often occur adjacent to body orifices. These early lesions are highly infectious. After several years the disease enters its late (*tertiary*) stage.

Late manifestations, which occur in approximately 10% of patients, affect the skin and bones predominantly (although ophthalmological and neurological complications have also been reported)—ulcerated cutaneous lesions, nodular and tuberous lesions ('gummatous framboesides'), palmoplantar keratoderma, juxta- articular nodes, gangosa (deforming rhinopharyngitis that produces mutilation of the centre of the face), periostitis and osteitis, mainly in long bones and giving rise to 'sabre tibia'.

Pinta

Synonyms
- Carate
- Cute
- Mal de pinto
- Morado
- Azul

Aetiology. Pinta is caused by *T. pallidum* ssp. *carateum*. Although there has been a marked decline in its prevalence over the last century it is still endemic in Mexico, and Central and South America. It affects the skin exclusively.

Pathology. Histopathology is similar in primary and secondary lesions. There is migration of lymphocytes through an oedematous and acanthotic epidermis. Some areas show lichenoid changes. There are numerous melanophages in the upper dermis. In the hypopigmented lesions of the tertiary stage, there is epidermal atrophy and loss of melanin in the basal layer. Treponemes are demonstrable in lesions of all stages.

Clinical features. In the *primary* stage of pinta a few papules or erythematosquamous plaques develop. After an interval of months or years the *secondary* stage features more extensive lesions, which are similar in appearance to the initial lesions. These are known as 'pintids'. Their initial red colour changes to brown, slate blue, black or grey, and eventually there is depigmentation intermixed with hyperpigmentation. Atrophy occurs as the late stage develops. The primary and secondary stages are infectious.

In the late (*tertiary*) stage, which takes several years to develop, there is irregular pigmentation, vitiligo-like achromia, areas of hyperkeratosis, and eventually atrophy.

Erythema dyschromicum perstans (ashy dermatosis) clinically resembles pinta, and pityriasis alba, vitiligo, atrophic lichen

planus and tuberculoid leprosy also have to be considered in the differential diagnosis.

Treatment. The treatment of all the non-venereal treponematoses is similar. The World Health Organization recommends that patients and contacts over 10 years of age are given a single intramuscular injection of 1 200 000 U of benzathine penicillin, and those under 10 years should receive 600 000 U. In individuals allergic to penicillin, tetracyclines and erythromycin are alternatives.

References

1 Antal GM, Lukehart SA, Meheus AZ. The endemic treponematoses. *Microbes Infect* 2002; **4**: 83–94.
2 Engelkens HJ, Vuzevski VD, Stolz E. Non-venereal treponematoses in tropical countries. *Clin Dermatol* 1999; **17**: 143–52.
3 Walker SL, Hay RJ. Yaws—a review of the last 50 years. *Int J Dermatol* 2000; **39**: 258–60.
4 Koff AB, Rosen T. Nonvenereal treponematoses. Yaws, endemic syphilis, and pinta. *J Am Acad Dermatol* 1993; **29**: 519–35.
5 Engelkens HJH. Endemic treponematoses. In: Faber WR, Hay RJ, Naafs B, eds. *Imported Skin Disease*. Maarssen: Elsevier, 2006: 171–80.
6 Farnsworth N, Rosen T. Endemic treponematosis: review and update. *Clin Dermatol* 2006; **24**: 181–90.
7 Asiedu K, Amouzou B, Dhariwal A *et al*. Yaws eradication: past efforts and future perspectives. *Bull World Health Organ* 2008; **86**: 499–499A.

Relapsing fever

Aetiology. There are two forms of this disease: louse-borne or epidemic relapsing fever due to *Borrelia recurrentis*, for which the human body louse is the vector, and tick-borne endemic relapsing fever caused by various species of *Borrelia*, for example, *B. duttoni* and *B. hermsi*. The louse-borne epidemic form is found in Ethiopia, the Sudan, other parts of Africa and the Far East, while the milder, sporadic tick-borne cases occur worldwide [1,2].

Clinical features [1,3]. The very variable symptom complex develops after an incubation period of about a week. High fever, headache, myalgia, vomiting and respiratory symptoms usher in the acute attack. Jaundice and hepatosplenomegaly with liver tenderness are common, and a petechial or purpuric rash, predominantly on the trunk, is found in up to 60% of patients. A remission occurs after a few days, to be followed by a relapse, and this pattern may continue for weeks. The cutaneous eruption does not, however, recur after the initial episode.

Diagnosis. Diagnosis is best confirmed by demonstration of the spirochaete in blood films using stained preparation or dark-ground illumination.

Treatment. The usual treatment is either tetracycline or erythromycin. Penicillin is an alternative. In the case of louse-borne infections, this is given as a single dose, for example, 0.5 g tetracycline [4]. Because treatment failures are more frequent in the tick-borne group, the course of therapy is usually prolonged, for instance, by giving 6-hourly treatment for up to 10 days. A severe reaction similar to the Jarisch–Herxheimer reaction is very common at the outset of treatment, particularly in louse-borne relapsing fever treated with penicillin [5].

References

1 Bryceson ADM, Parry EHO, Perine PL *et al*. Louse-borne relapsing fever. A clinical and laboratory study of 62 cases in Ethiopia and reconsideration of the literature. *Q J Med* 1970; **39**: 129–70.
2 Burgdorfer W. The epidemiology of relapsing fevers. In: Johnson RC, ed. *The Biology of Parasitic Spirochetes*. New York: Academic Press, 1976: 191–201.
3 Southern PM, Sanford JP. Relapsing fever. A clinical and microbiological review. *Medicine (Baltimore)* 1969; **48**: 129–49.
4 Perine PL, Tekiu B. Antibiotic treatment of louse borne relapsing fever in Ethiopia: a report of 377 cases. *Am J Trop Med Hyg* 1983; **32**: 1096–100.
5 Butler T, Jones PK, Wallace CK. *Borrelia recurrentis* infection; single dose antibiotic regimens and management of Jarisch–Herxheimer reaction. *J Infect Dis* 1978; **137**: 573–7.

Borrelia burgdorferi and Lyme disease

Definition. *Borrelia burgdorferi* is a spirochaete transmitted to humans by tick bites. The resulting clinical conditions are encompassed in the term Lyme disease (or Lyme borreliosis), named after the town of Lyme in Connecticut, USA, where the disease was first recognized in 1977. The characteristic eruption, erythema chronicum migrans (ECM), at the site of inoculation, is a common early manifestation, and dissemination of the infection may cause disease of the nervous system, heart and joints, in addition to other dermatoses. Differences in the disease spectrum in different geographical areas have been noted, and may be due to variation within the bacterial species [1] or to differences in diagnostic criteria and treatment practices [2].

Aetiology [1]. The principal vector of *B. burgdorferi* infection is the *Ixodes* tick, different species of which predominate in different parts of the world, their distribution corresponding to that of Lyme disease. Patients usually live close to, or have visited, woodland areas, where small mammals are necessary hosts for immature stages in the life cycle of the tick. Adult ticks may infest larger mammals, especially deer.

Lyme disease has been reported in most parts of the world but especially in the USA, where it is the commonest vector-borne infection, and in Europe, particularly in Scandinavia and central Europe. All ages and both sexes are affected. High rates of infection have occurred in areas in which the tick had recently become established in high numbers [3]. In contrast, 10 of 40 agricultural workers, with long-standing high exposure to tick bites, had positive *B. burgdorferi* serology, but Lyme disease was infrequent and mild in this group, a possible interpretation being that frequent tick bites may confer a degree of immunity [4].

Infection may occur at any time of year. Young nymphal ticks feed in early summer, when there is a marked peak in incidence of acquisition of human Lyme disease. The smaller autumn peak noted in some studies is associated with bites from adult ticks [3,5]. Deer, in particular, appear to harbour the infection in endemic areas.

After *B. burgdorferi* infection, specific antibodies are produced, but if the patient is treated early in the course of the disease, antibodies may disappear within a period of months and reinfection may occur.

Clinical features [1,6–9]. Of patients ultimately diagnosed as having Lyme disease, about 50% recall a tick bite; a bite by the



Fig. 30.20 Erythema chronicum migrans (ECM). (Courtesy of Dr A.S. Highet, York District Hospital, York, UK.)

autumn and winter feeding adult tick is more likely to be noticed than a bite by the summer feeding nymphs. About 90% develop ECM at the site of inoculation (Fig. 30.20). The eruption appears 1–36 (average 9) days after the bite, and is due to local spread of the spirochaete, usually in a ring formation enlarging at a rate of several centimetres per week. In some cases the erythema is intense, in others barely detectable; it may be entirely flat or show elevation at the centre, the periphery or both. Slight scaling is occasionally seen. Older areas of residual erythema may become dusky blue. There may be a zone of clearing behind the advancing ring producing a target-like morphology. Moderate burning or itching occurs in one-third of cases. If untreated, the lesion fades, usually within a few weeks, but the duration may vary between 1 day and 14 months. Regional lymphadenopathy and mild constitutional symptoms may occur.

Dissemination of the infection may occur within days or weeks of inoculation. Spirochaetes have been detected in affected organs, although immunological processes may also contribute. Of the over 5000 cases reported to the US Centers for Disease Control between 1983 and 1986 [5], 57% had arthritis; 18% had neural involvement, characteristically meningitis, cranial nerve palsies and peripheral radiculoneuritis; and 10% had heart disease including myocarditis, pericarditis and conduction defects. In a European series, neurological disease was prominent, but arthritis and carditis are not commonly diagnosed [6,10]. Migratory joint pains, myositis, conjunctivitis, hepatitis, generalized lymphadenopathy and splenomegaly may occur.

Two cases of fatal intrauterine infection have followed first-trimester maternal infection. In a prospective study of 19 women infected in various stages of pregnancy, there was an adverse fetal outcome in five, including one intrauterine death, but without proof of cause [11].

Other cutaneous manifestations. With dissemination of the infection, secondary lesions of ECM are seen in about 10% of patients, and are typically smaller and less migratory than the original lesion. Malar erythema in febrile cases, and a diffuse maculopapular rash, may occur. Localized urticaria, generalized urticaria, urticarial vasculitis [12] and septal panniculitis have been reported.

Lymphadenosis benigna cutis, or solitary lymphocytoma, developing near the site of the original ECM and occasionally coexisting with it, has been reported from Sweden [13]. The lesion is seen mainly on the ears or on the breast areola. *Borrelia burgdorferi* serology is usually positive, spirochaetes can be demonstrated in affected tissue, and the lesion subsides within 5 weeks of antibiotic therapy.

Acrodermatitis chronica atrophicans (ACA) (Chapter 45) is a late cutaneous manifestation of *B. burgdorferi* infection seen mainly in northern, central and eastern Europe, although a case has been reported from England [14]. The eruption develops 1 or more years after the original infection. Typical sites are hands, feet, knees and elbows. The lesion begins as an erythematous plaque, which slowly enlarges and gradually becomes violaceous and atrophic. Spirochaetes have occasionally been cultured, but *B. burgdorferi* serology is strongly positive in all cases. Lesions respond to appropriate antibiotic therapy.

Evidence for an aetiological role for *B. burgdorferi* in morphoea and lichen sclerosus has come mainly from Austria and Germany, and comprises clinical associations of these conditions with ACA and with neural disease consistent with neuroborreliosis [15]; positive *B. burgdorferi* serology in some patients with morphoea [15,16]; and histological identification of spirochaetes in biopsy material [15] and their culture from it [16,17]. However, other studies using more specific serological methods in the UK [18] and Denmark [19] have not confirmed the association.

Histology. A superficial and deep perivascular and interstitial lymphohistiocytic infiltrate containing plasma cells is characteristic of ECM [8,20]. The Warthin–Starry stain identified spirochaetes in 40% of cases [7].

In ACA, plasma cells are prominent within the lymphohistiocytic infiltrate; the epidermis is atrophic and there may be liquefaction degeneration of the basal layer and telangiectasia of the papillary dermis. Spirochaetes may be identified by the Warthin–Starry stain [14,21].

Diagnosis. In the differential diagnosis of ECM, other forms of insect- or spider-bite reactions, cellulitis and drug eruptions may be considered. Erythema multiforme may resemble multiple ECM, but in the latter, palms, soles and mucous membranes are spared [7].

Confirmation of *B. burgdorferi* infection is mainly by serology, although this is often negative in the first few weeks after inoculation. The main tests available are an ELISA, an indirect immunofluorescence test and a Western blot. The latter is particularly useful for screening negative sera or those showing indeterminate results. The incidence of false-positive results may decline with the advent of increasingly specific methods [1,22,23]. False-negative tests may be due to sequestration of antibody in immune complexes [24]. The detection of intrathecal antibody is useful in the diagnosis of Lyme neuroborreliosis [23]. PCR is increasingly being used and provides a rapid diagnostic test [25].

Treatment [1,26–28]. Patients with solitary lesions of ECM, and no more than regional lymphadenopathy and minor constitutional symptoms, that is those in whom there is no evidence of

bacterial dissemination, respond well to oral antibiotic treatment, and the incidence of serious sequelae is reduced [26]. Doxycycline 100 mg two or three times a day, or amoxicillin 500–1000 mg three times a day (perhaps with probenecid), is recommended. A 14- to 21-day course is suggested and, because of the possible severe sequelae, early treatment is advised. Cefuroxime and erythromycin are alternatives, although the latter is less active against *B. burgdorferi in vivo*.

After dissemination has occurred, the results of even intensive therapy are less impressive; whether this is due to incomplete eradication of the organism or to an immunological pathogenesis is not known. Mild systemic disease may be treated as above, but the more severe cases require intravenous treatment. Ceftriaxone 2 g daily i.v. for 2 weeks seems best, but there is still a 15% failure rate. Benzylpenicillin 24 mU daily for 2–3 weeks is also useful and chloramphenicol is a possible alternative.

Prophylactic treatment following tick bites in endemic areas may be considered, but careful inspection of the skin after walking in endemic areas and removal of ticks may be more useful.

References

1 Steere AC. Lyme disease. *N Engl J Med* 2001; **345**: 115–9.
2 Dattwyler RJ, Volkman DJ, Luft BJ *et al*. Lyme disease in Europe and North America. *Lancet* 1987; **i**: 681.
3 Lastavica CC, Wilson ML, Berardi VP *et al*. Rapid emergence of a focal epidemic of Lyme disease in coastal Massachusetts. *N Engl J Med* 1989; **320**: 133–7.
4 Guy EC, Bateman DE, Martyn CN *et al*. Lyme disease: prevalence and clinical importance of *Borrelia burgdorferi* specific IgG in forestry workers. *Lancet* 1989; **i**: 484–6.
5 Cieselski CA, Markowitz LE, Horsley R *et al*. Lyme disease surveillance in the United States, 1983–86. *Rev Infect Dis* 1989; **11** (Suppl. 6): S1435–41.
6 Asbrink E, Olsson I. Clinical manifestations of erythema chronicum migrans afzelius in 161 patients. *Acta Derm Venereol (Stockh)* 1985; **65**: 43–52.
7 Berger BW. Erythema chronicum migrans of Lyme disease. *Arch Dermatol* 1984; **120**: 1017–21.
8 Berger BW. Dermatologic manifestations of Lyme disease. *Rev Infect Dis* 1989; **11** (Suppl. 6): S1475–81.
9 Muhlemann MF. Thirteen British cases of erythema chronicum migrans, a spirochaetal disease. *Br J Dermatol* 1984; **111**: 335–9.
10 Muhlemann MF, Wright DJM. Emerging pattern of Lyme disease in the United Kingdom and Irish Republic. *Lancet* 1987; **i**: 260–2.
11 Markowitz LE, Steere AC, Benach JL *et al*. Lyme disease during pregnancy. *JAMA* 1986; **255**: 3394–6.
12 Olsson JC, Esterly NB. Urticarial vasculitis and Lyme disease. *J Am Acad Dermatol* 1990; **22**: 1114–6.
13 Hovmark A, Asbrink E, Olsson I. The spirochetal etiology of lymphadenosis benigna cutis solitaria. *Acta Derm Venereol (Stockh)* 1986; **66**: 479–84.
14 Coulson IH, Smith NP, Holden CA. Acrodermatitis chronica atrophicans with coexisting morphea. *Br J Dermatol* 1989; **121**: 263–9.
15 Aberer E, Kollegger H, Kristoferitsch W *et al*. Neuroborreliosis in morphea and lichen sclerosus et atrophicus. *J Am Acad Dermatol* 1988; **19**: 820–5.
16 Aberer E, Stanek G, Ertl M *et al*. Evidence for spirochetal origin of circumscribed scleroderma (morphea). *Acta Derm Venereol (Stockh)* 1987; **67**: 225–31.
17 Weber K, Preac-Mursic V, Reimers CD. Spirochaetes isolated from two patients with morphea. *Infection* 1988; **16**: 25–6.
18 Muhlemann MF, Wright DJM, Black D. Serology of Lyme disease. *Lancet* 1986; **i**: 553–4.
19 Halkier-Sorensen L, Kragballe K, Hansen K. Antibodies to the *Borrelia burgdorferi* flagellum in patients with scleroderma, granuloma annulare and porphyria cutanea tarda. *Acta Derm Venereol (Stockh)* 1989; **69**: 116–9.
20 Berger BW, Clemmensen OJ, Ackerman AB. Lyme disease is a spirochetosis. A review of the disease and evidence of its cause. *Am J Dermatopathol* 1983; **5**: 111–24.
21 Asbrink E, Brehmer-Andersson E, Hovmark A. Acrodermatitis chronica atrophicans—a spirochetosis. *Am J Dermatopathol* 1986; **8**: 209–19.
22 Editorial. Diagnosis of Lyme disease. *Lancet* 1989; **ii**: 198–9.
23 Steere AC, Berardi VP, Weeks KE *et al*. Evaluation of the intrathecal antibody response to *Borrelia burgdorferi* as a diagnostic test for Lyme neuroborreliosis. *J Infect Dis* 1990; **161**: 1203–9.
24 Schutzer SE, Coyle PK, Belman AL *et al*. Sequestration of antibody to *Borrelia burgdorferi* in immune complexes in seronegative Lyme disease. *Lancet* 1990; **335**: 312–5.
25 Situm M, Poje G, Grahovac B *et al*. Diagnosis of Lyme borreliosis by polymerase chain reaction. *Clin Dermatol* 2002; **20**: 147–55.
26 Lipsker D, Antoni-Bach N, Hansmann Y *et al*. Long-term prognosis of patients treated for erythema migrans in France. *Br J Dermatol* 2002; **146**: 872–6.
27 Berger BW. Treating erythema chronicum migrans of Lyme disease. *J Am Acad Dermatol* 1986; **15**: 459–63.
28 Wormser GP, Nadelman RB, Dattwyler RJ *et al*. Practice guidelines for the treatment of Lyme disease. *Clin Infect Dis* 2000; **31**(Suppl. 1): S1–14.

Leptospirosis (including Weil's disease and canicola fever)

Leptospirosis is an infection caused by organisms of the *Leptospira interrogans* complex and other genetically defined *Leptospira* species [1,2]. These leptospires are commonly carried by rodents, particularly rats, but also pigs, dogs, cattle and wild animals, such as hedgehogs and moles. Rodents especially may excrete the organism in urine persistently after recovering from infection. Human infections occur mainly in sewer workers and in those handling animals but are occasionally seen in those swimming or fishing in contaminated water. The portal of entry is usually the gastrointestinal tract but may be a cut or abrasion.

After an incubation period of 1–2 weeks, an acute febrile illness begins abruptly. The most distinctive features are muscular pains and tenderness, and intense conjunctival infection. Headache and respiratory symptoms are frequent. In some forms—Weil's disease, for example—jaundice and purpura are associated [3]. In others, such as the leptospiral form of pretibial fever and canicola fever, there is a blotchy erythema most constant on the legs. In many forms, there is a polymorphonuclear leukocytosis of the peripheral blood.

In Weil's disease, the mortality may reach 10%, but in the other forms spontaneous recovery occurs after about a week.

The diagnosis must be established by specific agglutinin reactions. PCR detection is being developed but there are still false negative results.

Treatment with large doses of penicillin [4] (or doxycycline if renal function is satisfactory) is recommended but must be given early. Haemodialysis or peritoneal dialysis may be required. In less severe cases, oral ampicillin, ceftriaxone or amoxicillin can be given.

References

1 Levett PN. Leptospirosis. *Clin Microbiol Rev* 2001; **14**: 296–326.
2 Feigin RD, Anderson DC. Human leptospirosis. *CRC Crit Rev Clin Lab Sci* 1975; **5**: 413–52.
3 Edwards CN, Nicholson GD, Hassell TA *et al*. Thrombocytopenia in leptospirosis: the absence of evidence for disseminated intravascular coagulation. *Am J Trop Med Hyg* 1986; **35**: 352–4.
4 Guidugli SJ, Castro AA, Atalah AN. Antibiotics for treating leptospirosis. *Cochrane Review*. Cochrane Library Issue 3 Oxford; 2003.

Rat-bite fevers

Spirillum minor rat-bite fever

Synonym
- Sodoku

This form of rat-bite fever is caused by a spiral flagellate organism *Spirillum minor*, and is usually transmitted by the actual bite of a rat. It is rare, with most cases being reported in Japan. It may cause disease in animal technicians bitten during the course of their work [1].

Ten or more days after the bite, the wound shows persistent inflammation and an eschar may form. A fever develops accompanied by malaise and regional lymphadenopathy [2]. A macular or maculopapular rash may become widespread, extending from the original lesion. A recurrent course with remissions and relapses accompanied by increasingly severe local inflammation and a generalized cutaneous eruption is characteristic. Arthritis, however, is rare in this type of rat-bite fever.

Sodoku may be differentiated from streptobacillary fever by finding the spiral organism in exudate or blood. Animal inoculation—intraperitoneally into mice or guinea pigs—is necessary as culture on artificial media cannot be achieved.

Untreated, most patients with *S. minor* infections recover without complication, but penicillin in low dose is rapidly effective and streptomycin or tetracycline are useful alternatives.

References
1 Anderson LC, Leary SL, Manning PJ. Rat-bite fever in animal research laboratory personnel. *Lab Anim Sci* 1983; **33**: 292–4.
2 McHugh TP, Bartlett PL, Raymond JL. Rat bite fever. Report of a fatal case. *Ann Emerg Med* 1985; **14**: 1116–8.

Streptobacillary rat-bite fever and Haverhill fever

Streptobacillus moniliformis is a natural inhabitant of the nasopharynx of rats and is the cause of the commoner and more severe form of rat-bite fever. When infection with this organism occurs in the absence of a rat bite, the term Haverhill fever is often used in recognition of an epidemic in Haverhill, Massachusetts, USA, when raw milk was thought to be the source of infection. The organism is a pleomorphic microaerophilic bacillus, sometimes showing beaded swellings.

When a rat bite is the origin of infection with this bacillus, the incubation period is short: 2–9 days. There is no sign of inflammation at the site of injury but (in most patients) a macular or petechial rash develops and involves the extremities, particularly the palms and soles [1]. There is characteristically a high fever and arthralgia of large joints [2]. Other manifestations of this infection include endocarditis and, particularly in children, diarrhoea [1]. The clinical picture is similar if not identical in Haverhill fever in which papules, vesicles, pustules and crusted lesions have been described along with late-onset pharyngitis.

The diagnosis is confirmed by blood culture. Without treatment, most cases eventually settle, but chronic arthritis and complications such as abscesses, pneumonia and endocarditis have been recorded. Penicillin is the drug of choice, continued for at least a week with high-dose therapy in patients with complications; streptomycin and the tetracyclines are alternatives.

References
1 Cunningham BB, Paller AS, Katz BZ. Rat bite fever in a pet lover. *J Am Acad Dermatol* 1998; **38**: 330–2.
2 Taber LH, Feigin RD. Spirochetal infections. *Pediatr Clin North Am* 1979; **26**: 377–411.

Legionellosis

Legionellosis is an acute respiratory infection caused by a variety of different species of the genus *Legionella*, of which *L. pneumophila* accounts for over 90% of cases [1]. One of the major features of the infection is the clustering of cases, often associated with exposure to organisms in the environment such as water-cooling systems, showers and humidifiers. The disease may present with a flu-like illness without pneumonia (Pontiac fever) or with pneumonia. In the latter a variety of different rashes from maculopapular eruptions to pretibial erythema have been described. These exanthems are not diagnostic [2].

References
1 Brenner DJ. Classification of the legionellae. *Semin Respir Infect* 1987; **2**: 90–205.
2 Fields BS, Benson RF, Besser RE. Legionella and legionaires disease: 25 years of investigation. *Clin Microbiol Rev* 2002; **15**: 506–26.

Botryomycosis

Synonyms
- Actinophytosis
- Bacterial pseudomycosis

Definition and aetiology [1,2]. Botryomycosis is a chronic granulomatous reaction to bacterial infection, containing granules resembling the sulphur granules of actinomycosis. Most cases are caused by *Staphylococcus aureus*, but from some a pure culture of *Pseudomonas* [3] has been obtained. Botryomycosis may develop in the skin or elsewhere and a variety of underlying predisposing factors have been described.

Very extensive skin forms have been described, for instance in association with diabetes [4]. In AIDS, different forms have been reported, ranging from disseminated cutaneous papules [5] to extensive perianal sinus formation [6]. In addition, botryomycosis has been recorded in a patient with follicular mucinosis [7].

A history of injury is common in skin cases, and the literature relating to experimental models as well as some early case reports stresses the importance of a foreign body as well as infection [1]. The size of bacterial inoculation may be crucial—a delicate balance between host and pathogen has been regarded as significant [8].

Pathology [2,9]. The granules contain masses of bacteria. The surrounding tissue reaction is not distinctive: histiocytes, plasma cells, lymphocytes and foreign-body giant cells predominate.

Clinical features [1,10–12]. The resemblance to actinomycosis is also evident clinically. Most lesions are on the limbs, but other sites including the perianal region and the face have been affected. In the primary cutaneous form, single or multiple abscesses of skin and subcutaneous tissues break down to discharge serous fluid through multiple sinuses, and heal after a course of many months

to leave atrophic scars. The general condition may remain good. Patients may present with a smaller, painful papule without sinus formation.

The pulmonary form may reach the skin and present as irregular masses with multiple sinuses.

Diagnosis. The key to the diagnosis is the presence of a small cluster of microorganisms on biopsy. This cluster resembles the grain of a mycetoma or sulphur granule of actinomycosis. Gram stains are often ineffective in distinguishing the morphology of the organisms, but the methenamine silver stain often works well with bacteria and their shape can be distinguished. The organisms should be identified by culture.

Treatment. Treatment depends on the nature of the organism and, where appropriate, antibacterial sensitivities should be determined. For *S. aureus* infections, flucloxacillin or erythromycin are usual. Sometimes an alternative approach such as flucloxacillin and fusidic acid can be used for very extensive lesions. The response is often determined by the presence or absence of underlying predisposing disease.

References

1 Hacker P. Botryomycosis—review. *Int J Dermatol* 1983; **22**: 455–9.
2 Winslow DJ. Botryomycosis. *Am J Pathol* 1959; **35**: 153–67.
3 Bishop GF, Greer KE, Horwitz DA. *Pseudomonas* botryomycosis. *Arch Dermatol* 1976; **112**: 1568–70.
4 Leibowitz MR, Asvat MS, Kalla AA *et al*. Extensive botryomycosis in a patient with diabetes and chronic active hepatitis. *Arch Dermatol* 1981; **117**: 739–42.
5 Patterson JW, Kitces EN, Neafie RC. Cutaneous botryomycosis in a patient with acquired immunodeficiency syndrome. *J Am Acad Dermatol* 1987; **16**: 238–42.
6 Toth IR, Kazal HL. Botryomycosis in acquired immunodeficiency syndrome. *Arch Pathol Lab Med* 1987; **111**: 246–9.
7 Harman RRM, English MP, Halford M *et al*. Botryomycosis. A complication of extensive follicular mucinosis. *Br J Dermatol* 1980; **102**: 215–22.
8 Brunken RC, Lichon-Chao N, van den Brock H. Immunologic abnormalities in botryomycosis. A case report and review of the literature. *J Am Acad Dermatol* 1983; **9**: 428–34.
9 Martin-Pasqual A, Perez AG. Botryomycosis. *Dermatologica* 1975; **151**: 302–8.
10 Templet JT, Straub R, Ko C. Botryomycosis presenting as pruritic papules in a human immunodeficiency virus-positive patient. *Cutis* 2007; **80**: 45–7.
11 Machado CR, Schubach AO, Conceição-Silva F *et al*. Botryomycosis. *Dermatology* 2005; **211**: 303–4.
12 Picou K, Batres E, Jarratt M. Botryomycosis. A bacterial cause of mycetoma. *Arch Dermatol* 1979; **115**: 609–10.

Necrotizing subcutaneous infections

There is a group of infections in which the principal focus of disease lies within soft tissues of the deep dermis, adipose tissue and subcutaneous fascia, where the hallmark of infection is extensive necrosis accompanying cellulitis [1,2]. The affected patient is usually severely ill and toxic, and there is a mortality of over 45% reported in some series [3]. The extent of infection is clearly variable with, in some cases, pathology restricted to a zone bound by fascia, while in others infection extends to involve muscle and deep vessels. The bacteria isolated from patients with these conditions have varied between different studies, and in some cases adequate bacteriological data are notably absent. This has complicated the clinical classification of these infections, as it has not been possible to validate the causative organisms. However, it has been suggested [4] that there are at least two distinct groups of infections—those caused by β-haemolytic, usually group A, streptococci and others that depend on an infection with multiple organisms, one of which is usually an anaerobe. The presence of a streptococcal aetiology is often difficult to establish with certainty, and infections without a proven cause may show striking increases in antistreptococcal antibody titres, suggesting that this may have been the original or a contributory cause [5]. The pathogenesis of the mixed bacterial infections is not well understood. Other variations include the presence or absence of muscle involvement.

While it is difficult to provide accurate data on the incidence of this infection, figures from Canada suggest that the annual incidence of necrotizing fasciitis is 1/200 000 with a 25% mortality [6].

While a complete and taxonomically valid list is difficult to compile, these infections include the following proposed types:

1 Clostridial cellulitis (gangrene)
2 Necrotizing cellulitis or fasciitis due to
  (a) streptococci, or
  (b) other bacteria
3 Progressive bacterial synergistic gangrene
4 Gangrenous cellulitis due to other pathogens such as *Pseudomonas* spp. or zygomycete fungi (mucormycosis). These are mainly seen in the immunocompromised patient or after severe trauma.

To complicate the issue, eponymous titles have been used, and Meleney's name has been associated both with streptococcal necrotizing cellulitis [7] and with progressive bacterial synergistic gangrene [8]. Likewise, Fournier's gangrene, which describes a specific cellulitic necrotizing process originally affecting the lower anterior abdominal wall and the scrotal fascia, probably includes at least two aetiologically different conditions, but in this specific site [9].

The clinical hallmark of all these infections is the appearance of necrosis in addition to cellulitis, which is often accompanied by a rapid course and considerable toxaemia. In practice, the main features of these infections are difficult to separate on clinical grounds, although there are some variations due to site of infection, and it is possible that they are part of a continuum of disease from cellulitis to myonecrosis. Death is a frequent outcome in such cases. Predisposing factors include trauma, infection, diabetes mellitus and previous surgery.

Necrotizing fasciitis, including streptococcal necrotizing cellulitis, may follow entry of group A streptococci, *Staphylococcus aureus*, *Aeromonas hydrophila*, *Vibrio vulnificus* (see above) or a mixture of other bacteria, including at least one anaerobic organism, into the skin, most commonly on the head and neck or the limbs [3]. While the portal of entry is thought to be a cut or even a surgical wound, it may be difficult to pinpoint the site of entry. Patients usually present with a hot, tender area of swelling, which is erythematous, and occasionally dusky [10]. Bullae and necrosis of underlying tissue may supervene and the overlying skin may become anaesthetic. Unfortunately, the onset may be indolent, giving rise to a

false sense of lack of urgency [11]. Swabs from the skin surface are usually negative.

The most important step in diagnosis and management is surgical exploration, in which subcutaneous tissues down to the fascia are found to be necrotic and may contain chains of Gram-positive bacilli. The skin appears to be undermined. Occasionally, group A streptococci, rarely groups B, C or D, can be isolated, or serological evidence of streptococcal infection found. In other patients, a wide range of different aerobic and anaerobic bacteria are cultured. This is an acute emergency warranting management in an intensive care unit. Diagnosing the organisms should not delay therapy, which consists of surgical debridement of the infected tissue and the immediate surrounding area. The overlying skin is usually surgically removed, although in some cases this has been laid back as a flap once the necrotic tissue has been removed. Treatment with intravenous penicillin G in high doses is recommended; metronidazole may also be used in addition. However, if antibiotics are given without surgical intervention, therapy is rarely successful. Heparinization should be used to control disseminated intravascular coagulation.

Progressive synergistic gangrene is usually seen in association with abdominal or other surgery, where there is contamination of the wound by leakage of bowel contents [12]. It may occur without apparent injury to the skin surface [13]. The organisms vary but microaerophilic streptococci, *Bacteroides* spp. or other anaerobes as well as Gram-negative bacteria are found. The wound becomes extended with surrounding necrosis and oedema, and the patient becomes toxic and unwell. The extending infection may affect muscle. Rapid deterioration of the patient's clinical state occurs with dehiscence of the surgical wound and toxaemia. Once again it is difficult to diagnose bacteriologically, and although careful culture with appropriate swabs being taken for anaerobes should be carried out, waiting for the results should not hinder start of therapy. The presence of gas in the tissue may suggest the diagnosis, but its absence does not exclude this infection. Computed tomography is a more precise method of demonstrating gas in tissues than X-ray [14].

The wound has to be explored surgically and necrotic tissue removed. The patient should receive penicillin in high dosage and a second drug should be added depending on the sensitivity of organisms isolated, but once again surgery is the most important aspect of therapy. The response rates are not high. There is no clear clinical difference between this disease and necrotizing fasciitis as long as a streptococcal aetiology is considered.

Pyoderma gangrenosum (Chapter 50) can easily resemble this disorder and indeed may sometimes be localized around a surgical wound.

Fournier's gangrene occurs where there is infection around the lower abdominal fascial plane in men, with tracking of the infection into the scrotum [8]. It may be caused by group A streptococci or multiple organisms, although it is commoner with the latter. The management is identical to that used for these infections in other sites.

It is important to consider other potential causes of acute necrosis and toxaemia, particularly in the neutropenic patient, where cellulitis associated with single, such as *Pseudomonas*, or multiple organisms can occur. The zygomycete fungal infection, mucormycosis, should also be considered and impression smears taken from the wound edges or biopsy material may be helpful in excluding this possibility.

References

1 Anaya DA, Dellinger EP. Necrotizing soft-tissue infection: diagnosis and management. *Clin Infect Dis* 2007; **44**: 705–10.

2 Singh G, Ray P, Sinha SK *et al*. Bacteriology of necrotising infections of soft tissues. *Aust NZ J Surg* 1996; **75**: 860–6.

3 Umbert IJ, Winkelmann RK, Oliver GF *et al*. Necrotizing fasciitis: a clinical, microbiologic and histopathologic study of 14 patients. *J Am Acad Dermatol* 1989; **20**: 774–81.

4 Giuliano A, Lewis F, Hadley K *et al*. Bacteriology of necrotizing fasciitis. *Am J Surg* 1977; **134**: 52–6.

5 Leppard BJ, Seal DV. The value of bacteriology and serology in the diagnosis of necrotizing fasciitis. *Br J Dermatol* 1983; **109**: 37–44.

6 Kaul R, McGeer A, Low DE. Population based surveillance for group A streptococcal necrotising fasciitis: clinical features, prognostic indicators and microbiologic analysis of 77 cases. Ontario group A streptococcal study. *Am J Med* 1997; **103**: 18–24.

7 Meleney FL. Hemolytic streptococcus gangrene. *Arch Surg* 1924; **9**: 317–64.

8 Meleney FL. Bacterial synergism in disease processes, with confirmation of the synergistic bacterial etiology of a certain type of progressive gangrene of the abdominal wall. *Ann Surg* 1931; **94**: 961–81.

9 Bahlmann JCM, Fourie IJH, Arndt TCH. Fournier's gangrene; necrotizing fasciitis of the male genitalia. *Br J Urol* 1983; **55**: 85–8.

10 Barker FG, Leppard BJ, Seal DV. Streptococcal necrotizing fasciitis. Comparison between histological and clinical features. *J Clin Pathol* 1987; **40**: 335–41.

11 Kihiczak GG, Schwartz RA, Kapila R. Necrotizing fasciitis: a deadly infection. *J Eur Acad Dermatol Venereol* 2006; **20**: 365–9.

12 Bailie FB. Infectious cutaneous gangrene—urgency in diagnosis and treatment. *Ann Plast Surg* 1987; **19**: 238–46.

13 Husseinzadeh N, Nahas WA, Manders EK *et al*. Spontaneous occurrence of synergistic bacterial gangrene following external pelvic irradiation. *Obstet Gynecol* 1984; **63**: 859–62.

14 Rogers JM, Gibson JV, Farrar WE *et al*. Usefulness of computerized tomography in evaluating necrotizing fasciitis. *South Med J* 1984; **77**: 282–3.

Mycoplasma infections

Mycoplasmas, formerly known as pleuropneumonia-like organisms, are the smallest free-living organisms. They lack a rigid cell wall but can grow, although slowly, on artificial media. There are about a dozen species known to be associated with humans [1,2]. Some, for example *Mycoplasma orale* and *M. salivarium*, are commensals in the mouth; others such as *M. hominis* and *Ureaplasma urealyticum*, are found in the healthy genital tract and may, at least in the case of *U. urealyticum*, be a cause of urethritis, as may *M. genitalium*. *Mycoplasma incognitus*, a variety of *M. fermentans*, is associated with lesions in patients with AIDS as well as other immunocompromised patients.

Mycoplasma pneumoniae is a well-recognized cause of pneumonia and minor upper respiratory tract infections, particularly in young people [3]. This organism has also been associated with meningoencephalitis, polyarthritis and other syndromes [4], such as severe erythema multiforme (Stevens–Johnson syndrome) in up to 7% of patients [5,6]. The commoner minor form of erythema multiforme in patients without clinical evidence of lower respiratory tract infection is, in a relatively small proportion of cases, also causally related to *M. pneumoniae* infection, as established by a rising titre of complement-fixing antibody and the isolation of the

organism from the skin lesions. Raynaud's phenomenon has also been reported in patients with *M. pneumoniae* infection.

In outbreaks of upper respiratory infection by *M. pneumoniae*, about one-third of patients developed rashes of various types [7,8].

Diagnosis. PCR based diagnostic methods provide the most rapid means of identifying the cause [9]. Cold agglutinins are also produced in the majority of patients. In addition, complement-fixing antibodies can be demonstrated. The agglutinins are raised early in the infection, whereas it may be several days before raised complement-fixing antibody titres can be demonstrated. Culture is time consuming.

Treatment. Tetracycline and derivatives are effective in *M. pneumoniae* infections; an alternative is erythromycin. There is no evidence that the use of antibiotics triggers the appearance of skin rashes.

References

1 Cassell GH, Cole BC. Mycoplasmas as agents of human disease. *N Engl J Med* 1981; **304**: 80–6.
2 Tully JG, Whitcomb RF, eds. *The Mycoplasmas*. New York: Academic Press, 1979.
3 Foy HM, Kenny GE, Cooney MK *et al*. Long term epidemiology of infections with *Mycoplasma pneumoniae*. *J Infect Dis* 1979; **139**: 681–8.
4 Fleming PC, Krieger E, Turner JAP *et al*. Febrile mucocutaneous syndrome with respiratory involvement, associated with isolation of *Mycoplasma pneumoniae*. *Can Med Assoc J* 1967; **97**: 1458–61.
5 Levy M, Shear NH. Mycoplasma pneumoniae infections and Stevens Johnson syndrome. *Clin Pediatr* 1991; **30**: 42–6.
6 Stutman HR. Stevens–Johnson syndrome and *Mycoplasma pneumoniae*: evidence for cutaneous infection. *J Pediatr* 1987; **111**: 845–51.
7 Lascari AD, Garfunkel JM, Mauro DG. *Varicella*-like rash associated with *Mycoplasma* infection. *Am J Dis Child* 1974; **128**: 254–6.
8 Cherry JD, Hurwitz ES, Welliver RC. *Mycoplasma pneumoniae* infections and exanthema. *J Pediatr* 1975; **87**: 369–73.
9 Schluger NW, Rom WN. The polymerase chain reaction in the diagnosis and evaluation of pulmonary infections. *Am J Resp Crit Care Med* 1995; **152**: 11–6.

Chlamydiae [1,2]

Chlamydiae are obligate intracellular parasites, but in their infectious form they have a cell wall, contain both DNA and RNA, replicate by fission, and are susceptible to broad-spectrum antibiotics, notably tetracyclines; they are therefore classed with the bacteria. There is a single genus with two subgroups or species.

Chlamydia trachomatis or subgroup A is classified into 15 serotypes with different pathogenic properties: Types A, Ba, B and C cause trachoma, an endemic ocular infection in many developing countries, frequently leading to blindness; types D to K, which are sexually transmitted, most commonly cause urethritis, but also deeper infections such as cervicitis, endometritis and salpingitis [3]. Eye infection may result from contact with infected genital secretions. There is evidence for a role in posturethritic reactive arthritis including Reiter's syndrome, namely the presence of chlamydial DNA in synovial fluid of patients with active arthritis (Chapter 20) [4].

Types L1, L2 and L3 infect predominantly lymphatic tissue and cause the sexually transmitted disease lymphogranuloma venereum.

Chlamydia psittaci or subgroup B is endemic in many species of birds and occasionally causes an interstitial pneumonitis in humans known as psittacosis or ornithosis.

References

1 Stephens RS. The cellular paradigm of chlamydial pathogenesis. *Trends Microbiol* 2003; **11**: 44–51.
2 Schachter J, Caldwell HD. Chlamydiae. *Ann Rev Microbiol* 1980; **34**: 285–309.
3 Schachter J, Grossman M. Chlamydial infections. *Ann Rev Med* 1981; **32**: 45–61.
4 Schumacher HR Jr, Gérard HC, Arayssi TK *et al*. Lower prevalence of *Chlamydia pneumoniae* DNA compared with *Chlamydia trachomatis* DNA in synovial tissue of arthritis patients. *Arthritis Rheum* 1999; **42**: 1889–93.

Lymphogranuloma venereum

Synonyms
- Lymphogranuloma inguinale
- Nicholas favre disease
- Climatic bubo

Note: This disease should not be confused with granuloma inguinale (granuloma venereum, donovanosis) caused by *Calymmatobacterium granulomatis* (see above).

Aetiology [1–3]. Lymphogranuloma venereum is caused by *Chlamydia trachomatis* types L1, L2 and L3. The organism is difficult to isolate and the diagnosis mainly depends on the serological response. Since the complement-fixation test is based on a group antigen, it is necessary to interpret with caution early records or prevalence based on this test, because the respiratory and genital *Chlamydia* cause cross-reactivity.

The human is the only natural host. Infection declined in the UK and Scandinavia without specific attempts at eradication. Most infections are sexually transmitted and the disease is common in tropical countries.

Pathology [1,4–6]. The lymphogranulomatous chancre usually shows no specific changes, but the necrotic area may be surrounded by epithelioid cells and a zone of granulation tissue rich in plasma cells.

The lymph nodes first show scattered foci of epithelioid cells, with occasional giant cells. These foci enlarge irregularly and undergo necrosis to form the stellate abscesses characteristic of the disease. The abscesses, which contain polymorphonuclear leukocytes and macrophages, are surrounded by epithelioid cells and chronic granulomatous tissue with numerous plasma cells.

In the later stages, very extensive fibrosis and large areas of coagulation necrosis are usual.

Clinical features [1,3,4,7]. After an incubation period of about 10 days (5–21 days) a small papulovesicle develops on the external genitalia, or occasionally elsewhere. The chancre is inconspicuous, heals rapidly and is often unnoticed. After an interval that is usually between 1 and 4 weeks, but may be longer, the regional lymph nodes enlarge—'climatic bubo'. The subsequent course of the disease depends on which glands are involved and on the extent and severity of the constitutional disturbance. Some cases

resolve spontaneously within a few months, but in the majority chronic symptoms persist, often with irregular acute episodes.

The inguinal syndrome is the most frequent manifestation in men. Inguinal adenitis is unilateral in 60% of cases. Lymphatic glands are at first hard and tender, but soon become matted together and within a week or two develop small areas of fluctuation, some of which break through the reddish purple overlying skin to form chronic sinuses. The groin fold frequently divides the glands characteristically into upper and lower groups—the sign of the groove. Palpable enlargement of the iliac glands often develops and may be considerable. Suppuration does not occur and spontaneous resolution ultimately takes place.

The rectal syndrome occurs mainly in women, in whom the primary lesion is often in the vagina. The pelvic glands are involved and periproctitis and proctitis are followed by a rectal stricture usually between 5 and 10 cm from the anal margin, around which fistulae frequently develop. Carcinoma is not uncommon later.

The genital syndromes occur in both sexes. Most characteristic is genital lymphoedema, which may develop a few weeks or many years after infection and gives rise to elephantiasis. The association of elephantiasis of the vulva with scarring and fistulae of the buttocks and thighs is known as esthiomene. Occasionally, small abscesses develop along the course of the superficial lymphatics draining the primary lesion and break down to form ulcers.

Urethral lesions may cause strictures and fistulae, and lymphoedema may produce a 'saxophone penis'. Extra-genital primary lesions have produced a wide variety of syndromes.

Constitutional symptoms often accompany the glandular enlargement but vary greatly in severity. Fever is usually slight, but general malaise is frequent and many patients complain of joint pain and stiffness. The spleen and liver may be enlarged. Rarely, there may be encephalitis.

Erythema nodosum occurs in about 10% of females and 2% of males, usually in the bubo stage but sometimes later.

Light sensitivity is common in white patients and develops in 30% of women and 12% of men in the subacute stage and in about 50% of chronic cases. It is first apparent about 10 weeks after infection and may persist as long as the disease remains active. Papular, urticarial or plaque-like lesions are confined to light-exposed skin and may be associated with restlessness and headache.

Occasionally, erythema multiforme and exanthemata of various types may occur during periods of activity.

Prognosis. The untreated disease usually runs an average course of 6–8 weeks and may then resolve completely. Many cases are left with the sequelae of lymphatic obstruction and some show periodic recrudescences of activity for many years. The disease is not transmitted transplacentally in humans [8].

Diagnosis. Fluctuant or discharging, painful and often unilateral adenitis, with or without a history of a primary lesion, is most likely to be confused with cat scratch disease, pyogenic infection and tuberculosis. The adenitis of infectious mononucleosis, syphilis, granuloma inguinale, Hodgkin's disease or leukaemia is less acute and usually not painful.

A suspected diagnosis should be confirmed serologically by demonstration of a rise in *Chlamydia* group-specific, complement-fixing antibody, although this is not always conclusive because the production of antibody may be reduced by antibiotic therapy. A fluorescence antibody test is more specific [9].

Culture is not practical. Biopsy of a lymph node or a smear of the bubo pus may be helpful. Molecular techniques are proving useful for surveillance [10] but are not widely available for routine diagnosis.

Treatment. Lymphogranuloma is best treated with doxycycline four times a day for 14 days. This is particularly useful where there may be infection by *Haemophilus ducreyi*; erythromycin may be used instead. This infection also responds to a single dose of azithromycin.

Early cases will usually show a response in 7–10 days, but some early, and most late, cases will require prolonged or repeated courses.

Fluctuant buboes may require aspiration to prevent spontaneous rupture, the needle being passed inferiorly from above through normal skin to reduce the risk of sinus formation [1]. Surgical incision and excision of buboes should be avoided. Other complications will often require surgical treatment.

References

1 Perine PL, Osoba AO. Lymphogranuloma venereum. In: Holmes KK, Mardh PA, Sparling PF *et al.*, eds. *Sexually Transmitted Disease*, 2nd edn. New York: McGraw-Hill, 1990; 195–204.

2 Favre M, Hellerström S. Epidemiology and prophylaxis of lymphogranuloma inguinale. *Acta Derm Venereol (Stockh)* 1954; **34** (Suppl. 30): 1–68.

3 Jebbari H, Alexander S, Ward H *et al*. Update on lymphogranuloma venereum in the United Kingdom. *Sex Transm Infect* 2007; **83**: 324–6.

4 Koteen H. Lymphogranuloma venereum. *Medicine (Baltimore)* 1945; **24**: 1–69.

5 Schachter J, Smith DE, Dawson CR *et al*. Lymphogranuloma venereum. I. Comparison of the Frei test, complement fixation test, and isolation of the agent. *J Infect Dis* 1969; **120**: 372–5.

6 Sheldon WH, Heyman A. Lymphogranuloma venereum. A histologic study of the primary lesion, bubonulus, and lymph nodes in cases proved by isolation of the virus. *Am J Pathol* 1947; **23**: 653–76.

7 Coutts WE. Lymphogranuloma venereum: a general review. *Bull World Health Organ* 1950; **2**: 545–62.

8 Sonck CK. Investigation of 120 children borne of mothers infected with lympho-granuloma inguinale. *Acta Derm Venereol (Stockh)* 1949; **29** (Suppl. 23): 1–61.

9 Klotz SA, Drutz DJ, Tam MR *et al*. Hemorrhagic proctitis due to lymphogranuloma venereum serogroup L2. Diagnosis by fluorescent monoclonal antibody. *N Engl J Med* 1983; **308**: 1563–5.

10 Siedner MJ, Pandori M, Leon SR *et al*. Facilitating lymphogranuloma venereum surveillance with the use of real time polymerase chain reaction. *Int J STD AIDS* 2007; **18**: 506–7.

Psittacosis

Synonym
- Ornithosis

Nomenclature. The name 'psittacosis' was introduced because human infections were acquired from parrots (psittacines). Subsequently, many non-psittacine birds, for example domestic and sea birds, were found to carry the infection and 'ornithosis' was introduced as a more general term. The terms are now used synonymously.

Table 30.6 Rickettsial infections.

Group	Disease	Rickettsia	Vector	Distribution
A Typhus	Epidemic typhus and Brill–Zinsser disease	*R. prowazecki*	Louse	Worldwide
	Endemic murine typhus	*R. mooseri*	Rat flea	Central and South America, Malaysia
B Spotted fever	Rocky Mountain spotted fever	*R. rickettsii*	Tick	North and South America
	Tick typhus			
	(a) African	*R. conori*	Tick	Mediterranean, Africa
	(b) Siberian	*R. siberica*	Tick	Russia, Central Asia
	(c) Queensland	*R. australis*	Tick	Australia
	Rickettsialpox	*R. akari*	Mouse mite	North America, Russia, Africa
C Scrub typhus	Tropical typhus or Japanese river typhus	*R. tsutsugamushi*	Mite	South-east Asia
D Q fever		*Coxiella burneti*		World-wide (except Scandinavia)
E Trench fever		*Rochalimaea quintana*	Body louse	Europe, Africa, North America

Aetiology. The disease is endemic not only in the parrot family, but also in over 120 species of birds, including pigeons, domestic fowl, ducks and finches, all of which have caused human infection; transmission occurs from inhalation of infected dust from excreta of sick or latently infected birds. It is caused by *Chlamydia psittaci.*

However, in many cases no bird source can be identified. Human-to-human spread by infected respiratory tract droplets is known to occur and may be commoner than previously recognized [1–3].

Clinical features [2,4,5]. The incubation period is about 2 weeks. The manifestations are very variable. There may be severe pneumonia, with cyanosis and collapse, myocardial involvement, jaundice, encephalitic symptoms and death, but many cases present only the symptoms of a mild respiratory infection without special characteristics. There may be headache and sore throat at the onset, and cough after a few days, with complete recovery during the second week. Even milder attacks are probably frequent.

Exanthemas occur occasionally, including a morbilliform eruption, and in severe cases lesions resembling the rose spots of typhoid, although sometimes of a darker hue. Erythema nodosum was noted in five of 150 cases [3] and may occur irrespective of the severity of the primary illness. Of six cases of psittacosis with erythema nodosum, two also had erythema multiforme [4]. Disseminated intravascular coagulation has been reported [5].

Diagnosis [3]. The diagnosis is based on the demonstration of antibody by microimmunofluorescence or a rise in complement fixation titres. Positive serology is often present as soon as the diagnosis is suspected, so that examination of a single serum may be helpful. Confirmation by a rise in titre may require a further 10 days, as antibody production is slow and reduced by antibiotic therapy.

The antibody is group-specific but this is not a practical limitation since the diseases caused by *Chlamydia trachomatis* are quite different.

Treatment. Tetracyclines are the drugs of choice and early administration can be life-saving. A dose of 500 mg four to six times a day should produce a response in about 48 h and should be continued for 10 days. Erythromycin is recommended for children.

References

1 Editorial. Psittacosis of non-avian origin. *Lancet* 1984; **2**: 442–3.

2 Cunha BA. The atypical pneumonias: clinical diagnosis and importance. *Clin Microbiol Infect* 2006; **12** (Suppl. 3): 12–24.

3 Nagington J. Psittacosis/ornithosis in Cambridgeshire 1975–83. *J Hyg (Lond)* 1984; **92**: 9–19.

4 Sarner M, Wilson RJ. Erythema nodosum and psittacosis: report of five cases. *BMJ* 1965; **2**: 1469–70.

5 Semel JD. Cutaneous findings in a case of psittacosis. *Arch Dermatol* 1984; **120**: 1227–9.

Rickettsial infections

Rickettsiae are regarded as small bacteria, and most are obligate intracellular parasites. They are spread by the bites of blood-sucking arthropods and cause widespread infection in endothelial cells, which may result in vascular infarcts, extravascular fluid loss and disseminated intravascular coagulation. Rickettsiae can be classed into five main groups on clinical and serological grounds (Table 30.6) [1]. Q fever has no exanthem and is not considered further.

Epidemic typhus [1]

Aetiology and pathology. Epidemic typhus is caused by *Rickettsia prowazeki* and is transmitted by the human body louse. It occurs throughout the world but epidemics are mainly associated with the displacement of populations by war or natural disasters. Humans are the only reservoir of infection.

The essential pathological lesion is produced by the multiplication of rickettsiae in the endothelial cells of small blood vessels, leading to obstruction, thrombosis, haemorrhage and perivascular inflammatory infiltration. The lesions are widely distributed but are often numerous in the skin, brain and heart.

Clinical features. After an incubation period of 7–14 days the abrupt onset of fever, headache and malaise ushers in the illness, which at first has no distinctive features. The symptoms increase in severity for several days. Between the fourth and seventh day

a rash develops in over 80% of cases. It consists of crops of pink macules about 5 mm in diameter, which appear first on the sides of the trunk and spread centrifugally, but spare the palms and soles, and spare the face, which is usually flushed with intensely injected conjunctivae. During the second week, the rash becomes deeper red and often frankly purpuric, and in severe cases may be confluent.

The other clinical manifestations and the outcome depend on the degree of involvement of the myocardium and the central nervous system. Gangrene of fingers, toes, genitalia or nose may result from vascular obstruction. Untreated, up to 40% of cases are fatal, but serious sequelae are unusual in those who recover. Death, or recovery, occurs between the second and third weeks.

Brill–Zinsser disease [1]

Synonym
- Sporadic typhus

This is the recrudescence of epidemic typhus, sometimes after many years, in individuals who have previously recovered from an attack. The clinical features are those of the primary attack, but often milder and less often with a rash.

Murine typhus [1]

Synonym
- Endemic typhus

Aetiology and pathology. Murine typhus is caused by *Rickettsia mooseri* and is spread to humans from the rodent reservoir by the rat flea, *Xenopsylla cheopsis*. The infection occurs throughout the world, but the incidence is highest in Central and South America. The pathological changes are similar to those of epidemic typhus.

Clinical features. The clinical features parallel those of epidemic typhus, but are very much milder. The rash is sparse and seldom haemorrhagic, and gangrene and other complications are rare. Recovery occurs during the second week in all but 1 or 2% of cases.

The spotted fever group

The infections in this group (Table 30.6) are spread by ticks or mites. Similar infections caused by distinct species occur in the tropical and subtropical regions of all continents. The incidence of this group of infections increased during the 1970s and 1980s [2,3].

Rocky Mountain spotted fever [1,4–6]

Aetiology and pathology. This is the most virulent of the rickettsial infections. The organism *Rickettsia rickettsii* is transmitted by the bite of various species of the tick, *Dermacentor*. It occurs in the Rocky Mountain areas of North America, in Maryland, Virginia and North Carolina, and in Mexico, Colombia and Brazil. Widespread inflammatory and destructive changes are produced in the small blood vessels, especially in the skin and central nervous system.

Clinical features. Five to 7 (range 3–12) days after the tick bite, a short period of malaise and headache is followed by fever, which sometimes rises to 39–40°C. After 3 or 4 days a maculopapular eruption appears on the wrists and ankles and soon spreads centrally to limbs, trunk and face. The palms and soles are usually involved. Except in the mildest cases, the rash becomes haemorrhagic, and in the most severe may be confluent. Acral gangrene may occur. In favourable cases, the high, irregular fever subsides during the third week, but without treatment the mortality exceeds 20%.

Tick typhus [1]

Synonyms
- Mediterranean fever
- Fievre boutonneuse
- Kenya tick typhus
- African and indian tick typhus

Aetiology. Tick typhus is caused by *Rickettsia conori*, which is transmitted by the bites of a variety of ixodid ticks. It is endemic in the countries of the Mediterranean littoral and in many parts of Africa and India. This diagnosis is often not considered in returning travellers who fail to associate the characteristic black eschar at the site of the bite with the febrile exanthem for which they seek treatment [7]. The pathological changes follow the usual rickettsial pattern (see Epidemic typhus above).

Clinical features. After an incubation period, which is usually between 5 and 7 days, the onset of fever is accompanied by headache, malaise, joint and stomach pains and, sometimes, mental confusion. Fever of 39–40°C lasts for 7–14 days. In some 80% of cases the onset of fever coincides with the development of a small ulcer—the tache noire—at the site of the tick bite. The ulcer, which is 2–5 mm in diameter, has a black necrotic centre and a red areola. The regional lymph nodes are enlarged and tender. Three or four days later, a pink, maculopapular eruption develops first on the forearms and then rapidly generalizes, involving the face, palms and soles. It increases in density for a few days and in severe cases may be haemorrhagic. The rash fades slowly after the fever subsides. Apart from weakness and lassitude, convalescence is uneventful and recovery is usual, except in the severe forms in frail or elderly people.

Leukocytoclastic vasculitis has been reported in occasional cases of *R. conori* infection [8].

Other forms of tick typhus

Other tick-borne rickettsial infections have been reported from many parts of the world, and the number of distinct infections recognized increases each year as more refined serological techniques are developed and are more widely applied.

The clinical syndromes, while showing variations in the extent of the eruption and the severity of the constitutional symptoms, all follow the same general pattern: a primary lesion, the eschar, develops at the site of the bite together with fever and influenza-like symptoms. A few days later a generalized maculopapular eruption develops and may become haemorrhagic.

Rickettsialpox [1,9]

Aetiology. *Rickettsia akari* is a parasite of the house mouse, which is transmitted to humans by the mite, *Allodermanyssus sanguineus*. It was first identified, in 1946, in New York but cases have since been reported from other areas of the USA, from Central Africa and from Russia. Because the reservoir and the vector are widely distributed, the disease may be worldwide.

Pathology. Vacuolar degeneration in the basal layer results in blurring of the dermal–epidermal junction and vesiculation best regarded as subepidermal, although regenerating epidermis may give an impression of intraepidermal separation. The superficial and middle dermal layers contain a neutrophilic and mononuclear cell infiltrate, but light and electron microscopy fail to demonstrate the organisms.

Clinical features. After an incubation period of 7–14 days, a papule appears at the site of the mite's bite, enlarges, becomes vesicular and dries to form a crust. The regional lymph nodes are enlarged. The patient often fails to notice the lesion. A few days later, influenza-like constitutional symptoms develop and persist for 4 or 5 days. Their onset is accompanied, or soon followed, by a generalized eruption of papules surmounted by small vesicles, which crust and heal in a few days. The distribution and extent of the eruption are very variable. The illness is usually mild and recovery is complete.

Many cases are probably diagnosed as atypical varicella, but the lesions of rickettsialpox are papules surmounted by vesicles, their distribution is irregular and there is usually, but not invariably, a discoverable primary lesion.

Scrub typhus [1]

Aetiology. The infective agent of scrub typhus, *Rickettsia tsutsugamushi*, is conveyed to humans from its natural rodent reservoir by the bites of the mites, *Trombicula akamushi* and *T. deliensis*, and probably by related species. The disease is widely distributed throughout the Far East and the South-West Pacific, and was a serious source of morbidity in troops in World War II.

The pathological changes are a focal vasculitis, involving the skin, lungs, heart, brain and kidneys.

Clinical features. After an incubation period of about 10 days (6–21 days) an acute fever with headache and conjunctivitis accompanies the development of the primary lesion, which is more frequently seen in white people than in Asian people. The primary lesion, or eschar, is a firm papule up to 1 mm in diameter surmounted by a vesicle, which dries to form a black crust. The regional lymph nodes are enlarged and tender. After about a week, a generalized macular or maculopapular eruption develops and may fade rapidly or persist for 7–10 days.

The clinical picture varies with the virulence of the strain. Pneumonitis and myocarditis are frequent and without treatment the mortality in some outbreaks reaches 60%. In favourable cases, the fever subsides and recovery occurs during the second or third week.

Diagnosis of rickettsial infections [1,5]

Various serological techniques and other methods are available, but are generally of retrospective value, and treatment should be started on the basis of a clinical diagnosis.

Treatment of rickettsial infections

Doxycycline is the drug of choice and treatment should be started as soon as the clinical diagnosis is made. The drug is given in full dose as a course of 7 days, except that epidemic typhus and scrub typhus respond to a single 200-mg dose of doxycycline (100 mg for children) [1]. Chloramphenicol is also effective and has been recommended for Rocky Mountain spotted fever in pregnant women and children aged 8 years and under [10]. General supportive measures are necessary in severe cases.

With louse-borne disease (epidemic typhus, trench fever), isolation and effective delousing are necessary to control the spread of infection.

References

1 Raoult D, Roux V. Rickettsioses as paradigms of new or emerging infectious disease. *Clin Microbiol Rev* 1997; **10**: 694–719.
2 Walker DDH, Fishbein DB. Epidemiology of rickettsial disease. *Eur J Epidemiol* 1991; **7**: 237–45.
3 Mansueto S, Tringali G, Walker DH. Widespread simultaneous increase in the incidence of spotted fever group rickettsioses. *J Infect Dis* 1986; **154**: 539–40.
4 Durack DT. Rus in urbe: spotted fever comes to town. *N Engl J Med* 1988; **318**: 1388–90.
5 Helmick CG, Bernard KW, D'Angelo LJ. Rocky Mountain spotted fever: clinical, laboratory, and epidemiological features of 262 cases. *J Infect Dis* 1984; **150**: 480–8.
6 Woodward TE. Rocky Mountain spotted fever. Epidemiological and early clinical signs are keys to treatment and reduced mortality. *J Infect Dis* 1984; **150**: 465–8.
7 Harris RL, Kaplan SL, Bradshaw MW *et al*. Boutonneuse fever in American travellers. *J Infect Dis* 1986; **153**: 126–31.
8 Pennell DJ, Grundy HC, Joy MD. Mediterranean spotted fever presenting as acute leucocytic vasculitis. *Lancet* 1988; **i**: 1393–4.
9 Brettman LR, Lewin S, Holzman RS *et al*. Rickettsialpox: report of an outbreak and a contemporary review. *Medicine (Baltimore)* 1981; **60**: 363–72.
10 Fishbein DB. Treatment of Rocky Mountain spotted fever. *JAMA* 1988; **260**: 3192–3.

Actinomycete infections

The actinomycetes are higher bacteria whose members cause two uncommon but important human infections: actinomycosis and nocardiosis. They show a number of unusual characteristics. *Actinomyces* spp. usually form large granules *in vivo* and *Nocardia* spp. are partially acid fast. Both form branching filaments *in vitro* and *in vivo*.

Actinomycosis

Definition. A chronic, spreading suppurative and granulomatous disease caused primarily by *Actinomyces israelii*: draining sinuses are formed through which the characteristic sulphur granules are discharged [1].

Aetiology. Actinomycetes are bacteria producing filamentous, branching hyphae. Most of the pathogenic actinomycetes occur in

nature and belong to the soil saprophytic flora. Pathogenic anaerobic actinomycetes are normal inhabitants of the human mouth, and actinomycosis is therefore acquired endogenously. In some respects, actinomycosis and mycetoma are similar. Actinomycosis differs from mycetoma in being caused by endogenous and anaerobic agents, and in having no tendency to be confined to the extremities.

Actinomycosis is caused by the invasion of the tissues by *A. israelii*, the most ubiquitous of the pathogenic actinomycetes [2]. *Actinomyces bovis*, which is isolated usually from cattle but rarely from humans, closely resembles *A. israelii*, and is considered to be identical by some authorities. Recent studies using serological and biochemical procedures have not resolved this controversy. *Actinomyces naeslundii*, *Arachnia propionica* and *Bifidobacterium eriksonii*, all inhabitants of the mouth, are rare causes of human disease [3,4]. *Actinomyces israelii* occurs in the normal mouth, and the higher incidence of the disease in rural tropical areas and in agricultural workers is difficult to explain. It has been suggested that it is more likely to affect people who live in remote areas, partly because of poor dental hygiene, and secondly because of poorer access to antibiotics to which the organisms are extremely sensitive. Trauma is thought to provide the portal of entry, and it is commonly found that actinomycosis of the jaw develops after dental extractions, pyogenic abscesses, etc. The disease is worldwide in its distribution but is seldom common. It can occur at any age, including infancy, but is rare under the age of 10 years. Although adult males are more commonly affected than females, the sex incidence is equal in childhood. Full-blown actinomycosis is also rare now in most countries where dental care is readily available. It is possible that it may cause minor dental infections, which are treated with antibiotics before major pathology can develop or a definitive diagnosis be established.

Histology [3]. The usual appearance is that of a suppurating, fibrotic inflammatory process. Small abscesses and pus-filled sinus tracts are formed. Blood spread to distant organs is unusual. In the tissues, the organism forms granular colonies from which radiate delicate mycelial filaments, some of which bear club-shaped processes (ray fungus). Surrounding the colonies a chronic neutrophil and lymphocytic infiltrate extends towards the skin, irrespective of where the primary lesion is, and this readily breaks down to form multiple fistulae from which pus containing the granules may be discharged. These so-called sulphur granules are lobulated masses of intertwining filaments. Lesions of actinomycosis almost always contain other bacteria besides *Actinomyces*, and it is thought that some of these associated organisms have a synergistic role in the development of the infection.

Clinical features. Actinomycosis can affect all organs and tissues of the body [3]. Apart from the very common minor infections of the lacrimal apparatus, five main clinical types can be recognized, depending on the primary site of infection; namely, cervicofacial (lumpy jaw), thoracic, abdominal, primary cutaneous and pelvic. In a large series, published long before pelvic infections were recognized, 56.7% of cases were in the cervicofacial area, 22.3% in the lungs and 15% in the abdomen.

Cervicofacial actinomycosis [5]. This presents as a dull-red, indurated nodule on the cheek or submaxillary region. Multiple sinuses, puckered scarring and the formation of new nodules produce an uneven, lumpy surface. The sinuses may close temporarily and later reopen or they may be replaced by other sinuses. The characteristic sulphur granules may be found in the discharging pus. The primary lesion is usually in the mandible or maxilla, and probably arises as a direct extension from a periodontal abscess formed in turn as the result of carious teeth, dental extraction or trauma to the jaw. Maxillary lesions may extend to the orbit, bones of the skull and brain. Lesions may also extend from the tonsillar crypts to the mandible. Involvement of bone occurs early, usually before sinuses are formed. Periostitis is followed by osteomyelitis with cystic spaces within the bone. The induration felt in the skin is very hard (board-like). This is the least uncommon type and is the type most often seen by dentists.

Thoracic actinomycosis. The thoracic type of actinomycosis may simulate active tuberculosis with cough, haemoptysis, night sweats and weight loss. There are no cutaneous changes unless the thoracic wall is secondarily involved. The lung may be affected as the result of aspiration of *Actinomyces* from the mouth. It is doubtful whether the normal lung can be infected, and most cases are thought to result from secondary infection of a lung abscess, tuberculosis, lung cancer, bronchiectasis, etc. Once again the organism tends to extend outwards from the lung to the skin through the thoracic wall, perhaps with osteomyelitis of the ribs and eventually with multiple draining sinuses [4].

Abdominal actinomycosis [3]. It usually begins in the appendix or caecum and is manifest either as appendicitis or a slow-growing mass with constitutional disturbance. It is thought that the organisms reach the gastrointestinal tract from the mouth and tonsils. Extension to the liver with resulting jaundice is frequent. Likewise, extension to the ovaries, kidneys, bladder or spine may occur. The organism may extend into the abdominal wall with the resultant sinus tracts appearing on the skin surface. Blood spread to distant organs occurs but is very rare.

Primary cutaneous actinomycosis. This is very uncommon and usually occurs on the exposed skin. Subcutaneous nodules extend slowly and break down to form sinuses [6] and the regional lymph nodes may be affected. This is thought to follow a similar pathogenetic mechanism to mycetoma, through implantation.

Pelvic actinomycosis. Recognized as a distinct form of the disease is pelvic actinomycosis, associated with the use of intrauterine contraceptive devices [7]. The skin is not affected in pelvic actinomycosis, but many patients with other forms of actinomycosis do have involvement of the skin causing tumour-like lesions.

Prognosis. The prognosis of any variety of actinomycosis without treatment is generally poor but the cervicofacial and cutaneous varieties may remain localized for long periods.

Differential diagnosis. Actinomycosis has a fairly typical appearance, but as the disease is rare the diagnosis may not be suspected.

The condition resembles other chronic inflammatory diseases, such as tuberculosis, syphilitic gummata, appendicitis, osteomyelitis and liver abscess, and also lung and intestinal cancer. The diagnosis is established by identifying the granules in the pus and on histological examination. Diagnosis should be confirmed by culture.

Laboratory identification. Attempts should be made to detect the characteristic sulphur granules, which provide a strong presumptive diagnosis of actinomycosis. They can generally be seen macroscopically as yellow granules up to 1–2 mm in diameter, often adherent to gauze dressings. When crushed and examined microscopically, narrow bacillary forms and elongate hyphae with occasional branching may be found. Cultures of *A. israelii* appear after anaerobic incubation at 37°C for 2–4 days on enriched media (brain–heart infusion glucose agar) as white, glistening, nodular colonies with somewhat irregular margins. Colonies of *A. bovis* are smooth, convex and shiny with clear margins.

Treatment. Actinomycosis is a chronic disease producing a marked fibrotic reaction, and it is difficult to obtain effective drug levels where required, so that a quick response to treatment should not be expected [8]. *Actinomyces israelli* is sensitive to those antibiotics that are effective in the treatment of Gram-positive bacterial infections. It is sensitive to sulphonamides, streptomycin, penicillin, chloramphenicol, chlortetracycline, oxytetracycline, tetracycline, rifampicin and erythromycin, but high doses of long-term penicillin is the therapy of choice. In severe cases, 10–12 million units of penicillin a day are administered i.v. for 12 h daily for 30–45 days. This is followed by wide surgical excision of the infected tissue and then 2–5 million units of penicillin given i.m. daily for 12–18 months, or 5 million units of penicillin V given by mouth. In an average case, daily i.m. penicillin in doses of 1–6 million units for periods of 6–8 months have been employed.

Large-scale trials are not possible with this disease, but alternatives to penicillin include tetracycline derivatives, erythromycin, chloramphenicol [8] and, more recently, imipenem [9]. Erythromycin is the most active antimicrobial *in vitro* [10].

References

1 Peabody JW, Seabury JH. Actinomycosis and nocardiosis. *Am J Med* 1960; **28**: 99–115.

2 Bennhoff DF. Actinomycosis. Diagnostic and therapeutic considerations and a review of 32 cases. *Laryngoscope* 1984; **94**: 1198–217.

3 Brown JR. Human actinomycosis. A study of 181 subjects. *Hum Pathol* 1973; **4**: 319–30.

4 Eng RHK, Corrado ML, Cleri D *et al*. Infections caused by *Actinomyces viscosus*. *Am J Clin Pathol* 1981; **75**: 113–6.

5 Sharkawy AA. Cervicofacial actinomycosis and mandibular osteomyelitis. *Infect Dis Clin North Am* 2007; **21**: 543–56.

6 Reiner SL, Harrelson JM, Miller SE *et al*. Primary actinomycosis of an extremity: a case report and review. *Rev Infect Dis* 1987; **9**: 581–9.

7 Lippes J. Pelvic actinomycosis: a review and preliminary look at prevalence. *Am J Obstet Gynecol* 1999; **180**: 265–9.

8 Schlech WF, Gelfand M, Alper B *et al*. Medical management of visceral actinomycosis. *South Med J* 1983; **76**: 921–2.

9 Edelmann M, Cullman W, Nowak KH *et al*. Treatment of abdominothoracic actinomycosis with imipenem. *Eur J Clin Microbiol* 1987; **6**: 194–5.

10 Holmberg K, Nord C, Dornbusch K. Antimicrobial *in vitro* susceptibility to *Actinomyces israelii* and *Arachnia propionica*. *Scand J Infect Dis* 1977; **9**: 40–5.

Nocardiosis

Definition. An acute-to-chronic suppurative disease caused by the aerobic actinomycete *Nocardia*. The primary infection is usually pulmonary, but there may be haematogenous spread to other organs. The central nervous system is frequently attacked. Primary cutaneous nocardiosis as well as mycetoma due to *Nocardia* spp. are both well described.

Aetiology. Nocardiosis is caused by the bacteria *N. asteroides*, *N. brasiliensis* and *N. otitidis caviarum* as well as other rarer species [1]. Like many of the fungi causing systemic mycoses, pathogenic strains of *N. asteroides* have been isolated from soil. There is general agreement that infection is therefore exogenous, for example by inhalation of contaminated dust. The frequency of mild subclinical nocardiosis is unknown, but since the organism is known to cause fatal infections in humans, the demonstration of *N. asteroides* in sputum or other materials should therefore not be disregarded. Although uncommon, the disease is no longer a rarity, as improved technique has led to the recognition of more examples of this infection. In one review, 179 cases were recorded [2].

In addition, *Nocardia* spp. can cause localized skin infections, presumably after implantation. *Nocardia asteroides*, in particular, may cause a localized abscess without dissemination—primary cutaneous nocardiosis. *Nocardia brasiliensis*, and less commonly other species, is also a common cause of actinomycetoma following entry via a wound. *Nocardia* is an opportunistic pathogen and is often found in people with progressive chronic disease or with a defect in T lymphocyte-mediated immune responses, including AIDS, and in solid organ transplant recipients. It has also been reported with Cushing's syndrome, diabetes and following the use of corticosteroids in the treatment of various diseases. Nosocomial outbreaks of nocardiosis associated with contamination of ventilation systems have been described [3].

Clinical features. In systemic nocardiosis, the clinical picture may closely simulate pulmonary or meningeal tuberculosis. Pulmonary involvement, with cough, dyspnoea, haemoptysis and fever, occurs in 75% of cases [4,5]. Involvement of the brain or meninges is present in 30% of cases, and of the skin in 30%. Spread to the skin and subcutaneous tissue produces solitary or multiple abscesses, which may involve muscles and bones [6]. The prognosis without treatment is poor.

Direct infection of the skin may result in the development of a solitary cold abscess or a local ulcer with a distal linear arrangement of multiple suppurative nodules, a lymphangitic form [7,8]. Both require treatment.

Actinomycetoma due to *Nocardia* spp. is described elsewhere (Chapter 36).

Differential diagnosis. Nocardiosis should be considered in obscure pulmonary and meningeal syndromes and in chronic suppurative disease of skin and bones.

Laboratory diagnosis. Pus or sputum smears are examined after staining by Gram, methenamine silver and acid-fast techniques for the narrow (less than 1 µm) branching hyphae, which are only partially acid fast. Cultures of *Nocardia asteroides* can be obtained on Sabouraud's glucose agar and on other isolation media from which antibacterial antibiotics are withheld. Colonies are compact, folded and glabrous, ranging from cream to red. Other *Nocardia* species are less commonly involved; *N. asteroides* or *N. otidiscaviarum* are associated with actinomycetomas.

Treatment. The treatment most widely used is co-trimoxazole, although sulphonamides are also active [9–11]. Alternatives that have been reported to be effective include ampicillin, minocycline, amikacin and imipenem. There is also difficulty in correlating the results of *in vitro* assessments of sensitivity with clinical responses [9]. In most cases it is still preferable to initiate therapy with co-trimoxazole and modify this later in the light of the clinical response.

References

1 Peabody JW, Seabury JH. Actinomycosis and nocardiosis. *Am J Med* 1960; **28**: 99–115.
2 Murray JF, Feingold SM, Froman S *et al*. The changing spectrum of nocardiosis. *Am Rev Respir Dis* 1961; **83**: 315–30.
3 Houang ET, Lovett IS, Thompson FD *et al*. *Nocardia asteroides* infection—a transmissible disease. *J Hosp Infect* 1980; **1**: 31–40.
4 Simpson GL, Stinson EB, Egger MJ *et al*. Nocardial infections in the immunocompromised host; a detailed study in a defined population. *Rev Infect Dis* 1981; **3**: 492–507.
5 Smego RA, Gallis HA. The clinical spectrum of *Nocardia brasiliensis* infections in the United States. *Rev Infect Dis* 1984; **6**: 164–80.
6 Kalb RE, Kaplan MH, Grossman ME. Cutaneous nocardiosis. *J Am Acad Dermatol* 1985; **13**: 125–33.
7 Tsuboi R, Takamori K, Ogawa H *et al*. Lymphocutaneous nocardiosis caused by *Nocardia asteroides*. *Arch Dermatol* 1986; **122**: 1183–5.
8 Thoms KM, Zimmermann O, Schupp P *et al*. *Nocardia otitidiscaviarum*: cause of long-term cutaneous abscesses on the leg of an immunocompetent man. *Arch Dermatol* 2007; **143**: 1086–7.
9 Smego RA, Moeller MB, Gallis HA. Trimethoprim-sulfamethoxazole therapy for *Nocardia* infections. *Arch Intern Med* 1983; **143**: 711–8.
10 Dewsnup DH, Wright DN. *In vitro* susceptibility of *Nocardia asteroides* to 25 antimicrobial agents. *Antimicrob Agents Chemother* 1984; **25**: 165–7.
11 Goldstein FW, Hautefort B, Acar JF. Amikacin-containing regimens for treatment of nocardiosis in immunocompromised patients. *Eur J Clin Microbiol* 1987; **6**: 198–200.

Dermatoses possibly attributable to bacteria

There are many distinctive clinical syndromes in the causation of which bacteria appear to play a principal or secondary role, but in which the lesions cannot be correlated with the known pathogenetic activities of the species isolated. An abnormal response of the tissues of the host has therefore to be postulated.

In some such syndromes, allergic hypersensitivity to the infecting organisms or their products has been demonstrated, and in others it is believed to be an important factor in determining the altered response to the bacteria.

The clinical features of many infections are modified by defects, inherited or acquired, in the host's capacity to produce a normal antibody and leukocytic response. Chronic granulomatous disease of childhood, for example, results from the failure of leukocytes to destroy certain species of ingested bacteria.

Chancriform pyoderma

This uncommon condition occurs more often in children than in adults. Cases have been reported from Europe and from North and Latin America [1]. The aetiology is uncertain, but a necrotizing reaction to a strain of *Staphylococcus aureus*, inoculated by minor trauma, has been suspected. The lesion, which is usually solitary, is often situated around the eyelids or near the mouth, or occasionally on the genitalia [1–3]. A sharply marginated ulcer, sometimes exceeding 1 cm in diameter, with an indurated base and a bright-red areola, enlarges slowly for a few days. The regional lymph nodes are enlarged and tender. Without treatment the ulcer may persist for several weeks before healing to leave a superficial scar. Treatment with antibiotics shortens the duration but the response in our experience is not dramatic.

The importance of the lesions lies in the possibilities for diagnostic confusion. Epithelioma, syphilis, primary tuberculosis, accidental vaccination, swimming-pool granuloma, leishmaniasis and dequalinium necrosis must be excluded.

References

1 Frain-Bell W. Pyodermia chancriformis faciei. *Br J Dermatol* 1957; **69**: 19–24.
2 Branom WT, Hyman AB, Rubin Z. Chancriform pyoderma. *Arch Dermatol* 1963; **87**: 736–9.
3 Torrelo A, Zambrano A. Chancriform pyoderma. *Br J Dermatol* 1996; **135**: 145–6.

Dermatitis vegetans

Synonym
- Pyoderma vegetans

Definition and nomenclature. Dermatitis or pyoderma vegetans is a condition of uncertain aetiology characterized by the development of epithelial hyperplasia and chronic granulomatous changes [1]. Crusting, sinus tract formation and ulceration may all occur in this disease. Dermatitis vegetans is thus difficult to define and almost certainly the name has been used to describe a number of differing skin rashes, such as blastomycosis-like pyoderma [2] and possibly superficial granulomatous pyoderma [3]. As the aetiology of the disease is unknown, it is not known whether these share a common pathogenesis.

Aetiology. Dermatitis vegetans may develop in any site, but the flexures are often involved. Commonly, either *Staphylococcus aureus* or group A streptococci are isolated from lesions but, as the rash does not usually respond to antibiotics alone, the role of these bacteria in the pathogenesis of the condition is unclear. The disease has been described in patients with a variety of underlying conditions, such as ulcerative colitis [1], alcoholism, lymphoma [4] and severe psoriatic arthritis [5]. It has been suggested that it is a response to heavy bacterial colonization or epidermal invasion in a patient with defective immunity [6]. The pustule-fringed variety called pyodermite vegetante of Hallopeau has been described in association with ulcerative colitis.

Pathology. The main hallmarks of the histological response are the appearance of chronic granulation responses and epithelial hyperplasia. Eosinophils are often present in the infiltrate, particularly in pyodermite vegetante. In some ways, it is the absence of other diagnostic features that supports the diagnosis of pyoderma vegetans.

Clinical features [4,5,7]. In some cases, encrusted and hyperplastic plaques appear on the skin surface. These may break down and weep and there is often central clearing. Where a prominent edge with crust formation is seen, the lesions may mimic blastomycosis. Alternatively, there may be ulceration, the condition resembling a form of pyoderma gangrenosum. In pyodermite vegetante, crusted, red plaques containing pustules have been described in multiple sites from the flexures to the scalp. Oral involvement may also occur with white plaques and pustules. Lesions may heal spontaneously but generally this is a chronic disease.

Diagnosis. This is difficult and largely depends on the exclusion of other conditions, such as specific infections, iododerma, pyoderma gangrenosum and pemphigus vegetans.

Management. It is important to exclude underlying disease such as ulcerative colitis, lymphoma or leukaemia. In doubt, repeat biopsies from the skin lesion may be necessary. There is usually a poor response to antibiotics alone, and the widespread application of antiseptics, although the latter may help to dry lesions. In some cases, topical corticosteroids appear to produce some response. There has been a report of an excellent response to etanercept in a patient who also had psoriatic arthritis [5].

References

1 Brunsting LA, Underwood LJ. Pyoderma vegetans in association with chronic ulcerative colitis. *Arch Dermatol* 1979; **60**: 161–72.
2 Su WPD, Duncan SC, Perry HO. Blastomycosis-like pyoderma. *Arch Dermatol* 1979; **115**: 170–3.
3 Wilson-Jones E, Winkelman RK. Superficial granulomatous pyoderma. A localized vegetative form of pyoderma gangrenosum. *J Am Acad Dermatol* 1988; **18**: 511–21.
4 Welch KJ, Burke WA, Park HK. Pyoderma vegetans: association with diffuse T cell lymphoma (large cell type). *J Am Acad Dermatol* 1989; **20**: 691–3.
5 Carrera C, Mascaró JM Jr, Moreno-Romero JA *et al*. Pyoderma vegetans associated with severe psoriatic arthritis: good response to etanercept. *Dermatology* 2007; **214**: 77–81.
6 Brown CS, Kligman AM. Mycosis-like pyoderma. *Arch Dermatol* 1957; **75**: 123–5.
7 Stone OJ. Hyperinflammatory proliferative (blastomycosis-like) pyodermas; review, mechanisms and therapy. *J Dermatol Surg Oncol* 1986; **12**: 271–3.

Dermatitis gangrenosa infantum

The aetiology of this rare condition is unknown. It is mainly reported to occur within the first 2 years of life. The infant presents with multiple necrotic ulcers on the skin surface. While these may arise *de novo*, they often appear on a pre-existing skin rash such as varicella or severe seborrhoeic dermatitis. The affected child is usually acutely ill with a high pyrexia and rapid deterioration follows [1], often ending in death. The histology of the few reported cases shows an acute necrotic reaction involving dermis and epidermis similar to that seen in pyoderma gangrenosum. While it is possible that, in some cases, this may be a form of infantile pyoderma gangrenosum, secondary complications, such as septicaemia, dominate the clinical picture. *Staphylococcus aureus* may be isolated from cutaneous ulcers, but it is not clear whether this is a secondary event.

Reference

1 Ratzer M. Dermatitis gangrenosa infantum. *Br J Dermatol* 1963; **75**: 206–11.

Kawasaki disease

Synonym
- Mucocutaneous lymph-node syndrome

This condition is a disease usually seen in children, often affecting those under 2 years of age [1]. It presents with fever and a generalized exanthem with lymphadenitis. Complications include myocarditis and arthritis. The aetiology is unknown, although recent evidence would support a role for bacterial superantigens as possible trigger factors.

Aetiology. The disease was first described by Kawasaki in 1967 from Japan [1], and since then other cases have been recorded from a wide variety of different countries. The condition does not appear to show a significant geographical variation in distribution. It is also more common than originally thought, with over 3000 cases occurring annually in the USA [2]. Males are more commonly affected, and the condition is also seen more often in siblings than in the general population, suggesting the possibility of transmission; however, epidemics of the disease have not been recorded [3].

Various hypotheses have been advanced to account for its symptoms. Initially, these included a rickettsial illness, as small inclusion bodies had been found in vascular endothelium. Some epidemiological evidence suggested that exposure to house-dust mite was a potential risk factor—with the possibility of transmission of an infection through contact with mites. There were also antibodies to a canine rickettsia in some patients' sera.

There has been recent evidence, however, that certain subsets of T lymphocytes ($V\beta2$ and $V\beta8$) are stimulated, suggesting activation by superantigens [4]. Superantigen (e.g. toxic shock antigens) producing strains of both *Staphylococcus aureus* and *Streptococcus pyogenes* have been isolated from the majority of patients with Kawasaki disease [5]. It has been suggested that these cause disease through wide-scale activation of immune mechanisms, with cytokine release bringing other cell types, including vascular endothelium, into an uncontrolled immunological reaction. This hypothesis has to be confirmed.

The major complication, the development of small aneurysms of the coronary arteries, is secondary to a vasculitis centring on these vessels with subsequent damage to the elastic layer [6].

Clinical features. The disease occurs in childhood, often before the age of 2 years, although cases are rarely seen in adults [1,2,7,8]. The onset is acute, with a high fever, which lasts for at least 5–7 days. The mucosae and conjunctivae are injected. In the mouth, the lips are dry and fissured, the tongue appears red with promi-

nent papillae (strawberry tongue), and the throat is injected. After 3–4 days, there is a widespread exanthem on the limbs and trunk, although it becomes localized over the distal extremities, hands and feet [9]. The area affected on the limbs becomes oedematous, and this is followed by scaling over the area previously affected, usually starting with the digits and in the periungual area. In other cases, the rash is morbilliform or erythema multiforme-like.

There is accompanying cervical lymphadenitis in many patients, although it is not always present, and may only involve a single node. Fever resolves after 1–2 weeks, but conjunctival infection and lassitude may persist. In about one-quarter of cases there is accompanying myocarditis, which may be followed by symptomatic coronary artery disease and in 1–2% by myocardial infarction. Myocarditis presents with arrhythmia or tachycardia; pericarditis and valve incompetence may also occur. Coronary disease occurs secondary to aneurysms of the coronary arteries, which may thrombose. However, these also regress over a couple of years in most patients.

Other complications include arthralgia, arthritis, severe erythema multiforme, iritis, proteinuria, hepatitis and aseptic meningitis.

Diagnosis. Abnormalities on investigation include leukocytosis and thrombocytosis with a raised erythrocyte sedimentation rate. The raised platelet count is most often seen in the post-acute phase. There is no specific diagnostic test for this syndrome.

While this condition may resemble a number of virus-associated exanthems, the presence of the typical rash and accompanying myocarditis are characteristic.

Treatment. Intravenous gammaglobulin in high dosage (2 g/kg in a single infusion over 10 h) is very helpful, and reduces the overall mortality and complications of the disease, including the risk of coronary aneurysms [10]. The treatment appears to work rapidly with resolution of fever. Aspirin is also helpful in reducing the risk of platelet aggregation, and is used short term in most patients and long term if there is evidence of coronary aneurysms.

References

1 Kawasaki T. Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children. Clinical observations in 50 cases. *Jpn J Allergol* 1967; **16**: 178–222.

2 Taubert KA, Rowley AH, Shulman ST. Nationwide survey of Kawasaki disease and acute rheumatic fever. *J Pediatr* 1991; **119**: 279–82.

3 Rauch A, Hurwitz E. Centers for Disease Control case definition of Kawasaki syndrome. *Pediatr Infect Dis* 1985; **4**: 702–3.

4 Abe J, Kotzin BL, Jujo K *et al*. Selective expansion of T cells expressing T-cell receptor variable regions *V*β2 and *V*β8 in Kawasaki disease. *Proc Natl Acad Sci USA* 1992; **89**: 4066–70.

5 Leung DYM, Meissner HC, Fulton DR *et al*. Toxic shock syndrome toxin-secreting *Staphylococcus aureus* in Kawasaki syndrome. *Lancet* 1993; **342**: 1385–8.

6 Rose V. Kawasaki syndrome—cardiovascular manifestations. *J Rheumatol* 1990; **17** (Suppl. 24): 11–4.

7 Melish ME, Hicks RV, Larson EJ. Mucocutaneous lymph node syndrome in the United States. *Am J Dis Child* 1976; **130**: 599–607.

8 *Proceedings of the Third International Kawasaki Disease Symposium*. Tokyo: Japanese Heart Foundation, 1988.

9 Butler D, Hough D, Friedman S. Adult Kawasaki syndrome. *Arch Dermatol* 1987; **123**: 1356–61.

10 Newburger JW, Takahashi M, Beisner AS *et al*. A single intravenous infusion of gammaglobulin as compared with four infusions in the treatment of acute Kawasaki syndrome. *N Engl J Med* 1991; **324**: 1633–9.

Suppurative hidradenitis

Synonyms
- Apocrinitis
- Hidradenitis suppurativa

Definition. Suppurative hidradenitis is a chronic relapsing inflammatory disease originating in apocrine gland follicles, which may become chronic and often indolent due to subcutaneous extension with induration, scarring, destruction of skin appendages and sinus formation.

Aetiology. Hidradenitis begins after puberty, when the apocrine glands are fully developed. Most sizeable studies show a preponderance of females, for example 62 of 95 [1]; 40 of 62 [2]; 19 of 32 [3]; and 22 of 24 [4]; but the reason for this is not known. Onset after the age of 40 years is uncommon, although chronic recurrent disease may occasionally persist into the seventh decade. The size and density of apocrine glands are the same in patients as in normal adults [5].

Many apocrine glands do not open directly to the skin surface, but into the upper portion of the pilosebaceous duct above the sebaceous gland. Comedones are not normally present in apocrine gland-bearing skin, but are generally seen in or around affected skin in hidradenitis patients. Comedonal occlusion of the 'apocrine gland follicle' unit therefore obstructs the outflow of the apocrine gland in addition to that of the sebaceous gland, and is believed to be the initiating event in hidradenitis. The association of suppurative hidradenitis with severe or conglobate acne and with perifolliculitis capitis (the 'follicular occlusion triad', or tetrad if pilonidal sinus is included) is impressive in a few cases [6], but is not seen in the majority of hidradenitis patients. In a series of 70 women with hidradenitis, acne was not more frequent than in controls [7]. In a genetic study involving 62 patients, eight had acne conglobata, and five of these were from one family [2]. In most cases, therefore, the aberrant and characteristic occlusive process is limited to apocrine sites. Whether the earliest inflammatory changes in the occluded gland and its associated follicle are based on pyogenic bacterial infection, or more closely resemble the acne process, is not known. After that, bacterial infection seems to be important in the extension of the disease and probably in the destructive scarring, and once the sinuses have formed, secondary bacterial infection is readily understandable. Considering the volume and purulence of the discharge in some cases, the frequent negative results on routine bacteriological examination are striking, but with attention to laboratory technique, a higher yield of potential pathogens can be obtained. In one study of 32 patients with inguinal perineal hidradenitis, the majority had pathogenic bacteria at some stage in their course; from correlation with disease activity, and the generally partial but occasionally impressive responses to antibiotic treatment, there was evidence that certain bacteria contributed to the disease process [3]. These included *Staphylococcus aureus*, anaerobic streptococci and, notably, the

microaerophilic organisms *Streptococcus milleri* (Lancefield group F), a recognized cause of purulent disease and abscesses [8,9]. Microaerophilic streptococci had been identified in six of the 13 cases studied in detail by Brunsting in 1939 [10]. Cases with *Bacteroides* spp. responding to appropriate treatment have been reported [11]. In other studies including stated or probable cases of hidradenitis, *S. aureus*, anaerobic streptococci and *Bacteroides* spp. were cultured [12,13], although not all cases yielded pathogenic bacteria.

As the apocrine gland extends well below the dermis into the less supportive subcutaneous tissue, the suppuration readily breaks through the gland and extends under the skin. The subsequent scarring process is poorly understood, but the resultant induration, tissue distortion, obliteration of appendages and the formation of partly epithelialized sinuses are hallmarks of the fully developed disease process.

There is evidence for hormonal effects in hidradenitis, apart from the necessity for pubertal development of the apocrine glands [14]. Improvement during and relapse after pregnancy, and premenstrual and menstrual exacerbation, are commonly noted by women patients, suggesting that low levels of oestrogen predispose to disease activity. Seven women developed hidradenitis while they were taking oral contraceptives, generally those with androgenic progestogens and a low oestrogen/progestogen ratio [15]. Androgen levels were on average increased compared with controls, but were normal in many individual patients [16]. In this study, hirsutism was commoner than expected, but there is no evidence of systemic virilization [7]. End-organ sensitivity may be the main mechanism for the effects of androgens in hidradenitis [14], but it is not known whether this applies to the sebaceous gland or the apocrine gland or both. Hidradenitis and acne were presenting features of acromegaly in two men [17].

Various immune defects presumably predispose to the infective element of the disease in individual cases [18–20]. Seven of 27 patients with hidradenitis had a marked reduction in T lymphocytes and a higher frequency of HLA-A1 and -B8 [21]. However, immunity in most patients appears to be intact [22].

Two of 27 cases were diabetic and a further four had impaired glucose tolerance [22]. There is no evidence to incriminate shaving, chemical depilation, deodorants or talcum powder [23]. A genetic study of 26 probands eliciting a total of 62 cases found that 48 belonged to 11 families with patterns in keeping with autosomal dominant inheritance [2]; a reluctance to admit to the disease was noted and the authors suspected under-reporting. Of 70 women with hidradenitis, 18 had a family history of the disease [7].



(a)



(b)

Fig. 30.21 (a, b) Axillary suppurative hidradenitis. (Courtesy of York District Hospital, UK.)

Pathology. In the predestructive stages, keratin plugs are seen in the apocrine gland follicles, along with inflammatory changes within and around the apocrine glands, the ducts of which may be distended with leukocytes. There is some evidence that occlusion of abnormal hair follicles may play an important part in the initiation of these lesions [24]. Groups of cocci may be seen within the glands and in the dermis. Later, the suppuration extends into the adjacent and subcutaneous tissues, where there may be a chronic inflammatory cell infiltrate involving histiocytes and giant cells related to remnants of glandular epithelium and keratinous debris. Amid dense fibrosis, there are sinus tracks lined partly by granulation tissue and partly by squamous epithelium. Skin appendages are obliterated by scarring [10,25].

Clinical features [10,26]. Suppurative hidradenitis occurs in skin containing apocrine glands. The axillae (Fig. 30.21) and the perineal region (including genital, pubic, inguinal (Fig. 30.22), and perianal areas, buttocks and upper thighs) are therefore the main sites, the more severe disease usually occurring in the latter. The



Fig. 30.22 Inguinal suppurative hidradenitis. (Courtesy of York District Hospital, York, UK.)

disease may also affect the female breast, the neck, the posterior aspect of the ears and the adjacent scalp, and the back. Onset and resolution of active inflammation often occur independently in the different areas.

Comedones, often polyporous, are usually present in or beside affected skin. Pruritus and vague discomfort may precede the development of one or more small, firm, subcutaneous nodules with pain and tenderness, and for weeks or months there may be no clinically obvious suppuration except that small pustules may surmount the nodules. If subcutaneous extension occurs it leads to indurated plaques, or, in lax, flexural skin as in the axillae and groins, to thick linear bands. Inflammatory nodules often rupture externally, giving rise to chronic sinuses with intermittent or persistent discharge of fluid consisting of serous exudate, blood and pus in varying proportions. Ulceration sometimes occurs and burrowing abscesses may perforate neighbouring structures.

The severity and the course are variable but persistence for many years with partial remissions and acute relapses is common. Episodes of acute cellulitis are sometimes a feature accompanied by fever and toxicity.

Complications. The formation of fistulae to urethra, bladder, rectum or peritoneum has occurred rarely [6,27]. Sequelae of chronic inflammation include secondary anaemia [28], hypoproteinaemia, amyloidosis, renal disease [29], interstitial keratitis [30], and peripheral and axial arthropathy [31]. Squamous carcinoma, sometimes metastatic, is an occasional complication in long-standing cases, and has occurred mainly in perineal disease [32,33]. Chronic malaise and depression are understandably present in many severe cases.

Diagnosis. Possible misdiagnoses are numerous, and vary with the stage and site. Axillary and inguinal lesions that have ulcerated may be confused with scrofuloderma. Inguinal lesions may simulate actinomycosis, granuloma inguinale or lymphogranuloma venereum. When only one or a few nodules and sinuses are present in the anogenital region, pilonidal sinus, sigmoidal diverticulitis and Crohn's disease must be excluded.

In atypical cases, the diagnosis may be difficult. The characteristic comedones should be sought and the non-specific histological changes may be negatively useful.

Treatment. Improvement in local hygiene, including weight reduction in the obese and the use of antiseptic–detergent agents for washing, is advisable.

Acute episodes and relapses should be treated as bacterial infections. Repeated specimens, and active collaboration with the microbiologist, are essential. Plausible pathogens should be treated with full doses of appropriate antibiotics, probably for 2 weeks in most cases [3]. Erythromycin, combined with metronidazole if tolerated, may be a suitable initial choice pending the results of bacteriological examination. Clindamycin [11] and minocycline are each useful in some cases. The response to this bacteriological approach is variable; a few patients achieve lasting remission, but in most the improvement is partial and relapse is common.

Long-term antibiotics, usually tetracyclines or erythromycin, in an acne-type regimen are useful in some patients. As in acne, efficacy may eventually be lost, but may be restored after a short break, for example 1 month [34]. Topical clindamycin appeared useful in a double-blind trial [35].

The anti-inflammatory effects of systemic corticosteroids may be useful in acute exacerbations, for example prednisolone 60 mg daily [36], and lower maintenance doses may give some degree of long-term control.

The choice of oral contraceptive for women with hidradenitis should probably be made from preparations with a high oestrogen/progestogen ratio, and possibly also with low androgenicity in the progestogen [16]. An oral contraceptive containing 50 mg ethinyloestradiol was shown to be useful in some cases as the sole therapy apart from topical antiseptic [37]; a regimen with the same oestrogen combined with cyproterone acetate 50 mg was no more effective, but in another study, cyproterone acetate 100 mg was superior to 50 mg [38]. A more recent study has shown clear superiority of the use of antiandrogen therapy versus antibiotics in women with hidradenitis [39].

Retinoids appear useful in some cases. Isotretinoin in a dose of about 1 mg/kg/day for 4 months was accompanied by improvement in four out of eight patients [40], but others have not seen a response [41,42]. Isotretinoin does not affect the size of apocrine glands [43]. Etretinate or acitretin may be more useful at least in some cases: a woman who had failed to respond to isotretinoin 2 mg/kg daily, improved on acitretin 0.5 mg/kg daily for 6 months; a relapse after 11 months responded to a further course [44]. The drug's effects on inflammation and on epithelial differentiation may be relevant. Lithium may trigger hidradenitis suppurativa [45].

Surgery should be considered in refractory cases. Relatively minor techniques include exteriorization, curettage and electrocoagulation of sinus tracts [46], and simple excision of troublesome areas with direct closure or grafting. However, severe disease unresponsive to medical treatment is best treated by deep and wide excision of the whole of the disease-bearing skin along with a margin of at least 1.5 cm; application of silastic foam dressings to permit eventual spontaneous healing is an alternative to grafting [47]. Following this method, recurrence rates were lower for

axillary and perianal lesions than for anterior perineal disease, although results in all these groups were generally satisfactory. Axillary surgery may be complicated by restricted arm-raising capacity. The outcome for inframammary hidradenitis was disappointing [1]. Therapy with etanercept has been beneficial in a number of reported cases [48–50].

References

1 Harrison BJ, Mudge M, Hudges LE. Recurrence after surgical treatment of hidradenitis suppurativa. *BMJ* 1987; **294**: 487–9.
2 Fitzsimmons JS, Guilbert PR, Fitzsimmons EM. Evidence of genetic factors in hidradenitis suppurativa. *Br J Dermatol* 1985; **113**: 1–8.
3 Highet AS, Warren RE, Weeks AJ. Bacteriology and antibiotic treatment of perineal suppurative hidradenitis. *Arch Dermatol* 1988; **124**: 1047–51.
4 Bell BA, Ellis H. Hydradenitis suppurativa. *J R Soc Med* 1978; **71**: 511–5.
5 Morgan WP, Hughes LE. The distribution, size and density of the apocrine glands in hidradenitis suppurativa. *Br J Surg* 1979; **66**: 853–6.
6 Moschella SL. Hidradenitis suppurativa: complications resulting in death. *JAMA* 1966; **198**: 83–5.
7 Jemec GBE. The symptomatology of hidradenitis suppurativa in women. *Br J Dermatol* 1988; **119**: 345–50.
8 Editorial. *Streptococcus milleri*, pathogen in various guises. *Lancet* 1985; **ii**: 1403–4.
9 Schlaes DM, Lerner PI, Wolinsky E *et al*. Infections due to Lancefield group F and related streptococci (*S. milleri*, *S. anginosus*). *Medicine (Baltimore)* 1981; **60**: 197–207.
10 Brunsting HA. Hidradenitis suppurativa; abscess of the apocrine sweat glands. *Arch Dermatol Syphilol* 1939; **39**: 108–20.
11 Brenner DE, Lookingbill DP. Anaerobic microorganisms in chronic suppurative hidradenitis. *Lancet* 1980; **ii**: 921–2.
12 Ghoneim ATM, McGoldrick J, Blick PWH *et al*. Aerobic and anaerobic bacteriology of subcutaneous abscesses. *Br J Surg* 1981; **68**: 498–500.
13 Hedstrom SA. Recurrent skin abscesses. *Scand J Infect Dis* 1982; **14**: 241–2.
14 Ebling FJG. Hidradenitis suppurativa: an androgen-dependent disorder. *Br J Dermatol* 1986; **115**: 259–62.
15 Stellon AJ, Wakeling M. Hidradenitis suppurativa associated with use of oral contraceptive. *BMJ* 1989; **298**: 28–9.
16 Mortimer PS, Dawber RPR, Gales MA *et al*. Mediation of hidradenitis suppurativa by androgens. *BMJ* 1986; **292**: 245–8.
17 Chalmers RJG, Ead RD, Beck MH *et al*. Acne vulgaris and hidradenitis suppurativa as presenting features of acromegaly. *BMJ* 1983; **287**: 1346–7.
18 Bentley-Phillips CB, Cooper RC, Hallett AF. Pharmacological modulation of neutrophilic phagocytic function in a patient with recurrent sepsis, pyoderma gangrenosum and impaired phagocytosis. *Br J Dermatol* 1982; **106**: 687–95.
19 Djawari D, Hornstein OP. Recurrent chronic pyoderma with cellular immunodeficiency. *Dermatologica* 1980; **161**: 116–23.
20 Ginder PA, Ousley M, Hinthorn D *et al*. Hidradenitis suppurativa: evidence for a bactericidal defect correctable by cholinergic agonist *in vitro* and *in vivo*. *J Clin Immunol* 1982; **2**: 237–41.
21 O'Loughlin S, Woods R, Kirke PN *et al*. Hidradenitis suppurativa. *Arch Dermatol* 1988; **124**: 1043–6.
22 Dvorak VC, Root RK, MacGregor RR. Host-defence mechanisms in hidradenitis suppurativa. *Arch Dermatol* 1977; **113**: 450–3.
23 Morgan WP, Leicester G. The role of depilation and deodorants in hidradenitis suppurativa. *Arch Dermatol* 1982; **118**: 101–2.
24 Yu C, Cook MG. Hidradenitis suppurativa. A disease of follicular epithelium, rather than apocrine glands. *Br J Dermatol* 1990; **122**: 763–9.
25 McKee PH. *Pathology of the Skin*. London: Gower, 1989.
26 Gordon SW. Hidradenitis suppurativa: a closer look. *J Natl Med Assoc* 1978; **70**: 339–43.
27 Buckley C, Sarkany I. Urethral fistula and sinus formation in hidradenitis suppurativa. *Clin Exp Dermatol* 1989; **14**: 158–60.
28 Tennant F, Bergeron JR, Stone OJ *et al*. Anemia associated with hidradenitis suppurativa. *Arch Dermatol* 1968; **98**: 138–40.
29 Mustafa EB, Ali SD, Kurtz LH. Hidradenitis suppurativa. Review of the literature and management of the axillary lesion. *J Natl Med Assoc* 1980; **72**: 237–43.
30 Bergeron JR, Stone OJ. Intestinal keratitis associated with hidradenitis suppurativa. *Arch Dermatol* 1967; **95**: 473–5.
31 Rosner IA, Richter DE, Huettner TL *et al*. Spondylarthropathy associated with hidradenitis suppurativa and acne conglobata. *Ann Intern Med* 1982; **97**: 520–5.
32 Alexander SJ. Squamous cell carcinoma in chronic hydradenitis suppurativa. *Cancer* 1979; **43**: 745–8.
33 Sparks MK, Kuhlman DS, Prieto A *et al*. Hypercalcaemia in association with cutaneous squamous cell carcinoma: occurrence as a late complication of hidradenitis suppurativa. *Arch Dermatol* 1985; **121**: 243–6.
34 Eady EA, Cove JH, Holland KT *et al*. Erythromycin resistant propionibacteria in antibiotic treated acne patients: association with therapeutic failure. *Br J Dermatol* 1989; **121**: 51–7.
35 Clemmensen OJ. Topical treatment of hidradenitis suppurativa with clindamycin. *Int J Dermatol* 1983; **22**: 325–8.
36 Norris JFB, Cunliffe WJ. Hidradenitis suppurativa and response to oral steroids. *Br J Dermatol* 1987; **117** (Suppl. 32): 96–8.
37 Mortimer PS, Dawber RPR, Gales MA *et al*. A double-blind controlled cross-over trial of cyproterone acetate in females with hidradenitis suppurativa. *Br J Dermatol* 1986; **115**: 263–8.
38 Sawers RS, Randall VA, Ebling FJG. Control of hidradenitis suppurativa in women using combined antiandrogen (cyproterone acetate) and oestrogen therapy. *Br J Dermatol* 1986; **115**: 269–74.
39 Kraft JN, Searles GE. Hidradenitis suppurativa in 64 female patients: retrospective study comparing oral antibiotics and antiandrogen therapy. *J Cutan Med Surg* 2007; **11**: 125–31.
40 Dicken CH, Powell ST, Spear KL. Evaluation of isotretinoin treatment of hidradenitis suppurativa. *J Am Acad Dermatol* 1984; **11**: 500–2.
41 Jones DH, Cunliffe WJ, King K. Hidradenitis suppurativa—lack of success with 13-*cis* retinoic acid. *Br J Dermatol* 1982; **107**: 252–3.
42 Norris JFB, Cunliffe WJ. Failure of treatment of familial widespread hidradenitis suppurativa with isotretinoin. *Clin Exp Dermatol* 1986; **11**: 579–83.
43 Norris JFB, Cunliffe WJ. The effect of isotretinoin on apocrine glands. *Br J Dermatol* 1988; **118**: 295–7.
44 Hogan DJ, Light MJ. Successful treatment of hidradenitis suppurativa with acitretin. *J Am Acad Dermatol* 1988; **19**: 355–6.
45 Gupta AK, Knowles SR, Gupta MA, Shear NH. Lithium therapy associated with hidradenitis suppurativa. A case report and review of the dermatologic side effects of lithium. *J Am Acad Dermatol* 1995; **32**: 382–6.
46 Newell GB, Voelter WW, Mullins JF. Treatment of hidradenitis suppurativa. *JAMA* 1973; **223**: 556–9.
47 Morgan WP, Harding KG, Richardson G *et al*. The use of Silastic foam dressing in the treatment of advanced hidradenitis suppurativa. *Br J Surg* 1980; **67**: 277–80.
48 Cusack C, Bukley C. Etanercept: effective in the management of hidradenitis suppurativa. *Br J Dermatol* 2006; **154**: 726–9.
49 Giamarellos-Bourboulis EJ, Pelekanou E, Antonopoulou A *et al*. An open-label phase II study of the safety and efficacy of etanercept for the therapy of hidradenitis suppurativa. *Br J Dermatol* 2008; **158**: 567–72.
50 Zangrilli A, Esposito M, Mio G *et al*. Long-term efficacy of etanercept in hidradenitis suppurativa. *J Eur Acad Dermatol* 2008; **22**: 1260–2.

CHAPTER 31
Mycobacterial Infections

V.M. Yates
Salford Royal NHS Foundation Trust, Manchester and Royal Bolton Hospital, Bolton, UK

Characteristics of the mycobacteria, 31.1	Introduction, 31.7	**Non-tuberculous (atypical) mycobacteria, 31.30**
Epidemiology, 31.2	Natural history, 31.8	*M. marinum*, 31.30
Immunology of tuberculosis, 31.3	Histopathology, 31.8	*M. kansasii*, 31.33
Diagnostic tests for tuberculosis, 31.6	**Tuberculosis of the skin, 31.10**	*M. ulcerans*, 31.33
Diagnosis of mycobacterial infections, 31.6	Prognosis, 31.26	Other slow growers, 31.35
Co-infection with *Mycobacterium* species and HIV, 31.7	Diagnosis, 31.26	Rapidly growing mycobacteria, 31.38
Tuberculosis, 31.7	Treatment, 31.26	Other mycobacteria, 31.41
	BCG vaccination, 31.28	

Introduction

The genus *Mycobacterium* contains more than 80 species, most of which are harmless environmental saprophytes. A few species are important pathogens of humans and other vertebrates. The most important obligate human pathogens are *Mycobacterium tuberculosis* and *M. leprae*, but others such as *M. avium* and *M. ulcerans* are also significant. Disease-causing mycobacteria other than *M. tuberculosis* have been variously known as atypical, environmental or opportunistic mycobacteria, but are perhaps now best referred to as non-tuberculous mycobacteria (NTM) [1].

Tuberculosis (TB) is likely to be as old as the human race. The DNA of *M. tuberculosis* has been detected in a Peruvian mummy, indicating that the disease crossed the Atlantic well in advance of Columbus [2], and it has recently been demonstrated in a skeleton from 300 BC. Tuberculosis is the leading cause of death from a curable infectious disease and remains an enormous and growing global health problem, particularly in sub-Saharan Africa. Approximately one-third of the world's population is infected with the *Mycobacterium tuberculosis* bacteria, with around 9 million developing active tuberculosis and almost 2 million dying from tuberculosis each year [3]. It is primarily a disease of poverty, with 95% of cases and 98% of deaths occurring in developing countries. The situation is aggravated by synergy with human immunodeficiency virus (HIV) [4], the breakdown of health care systems, the rise in multidrug-resistant (MDR) tuberculosis (defined as being resistant to isoniazid and rifampicin) [5] and recent emergence of extensively drug-resistant (XDR) tuberculosis (defined as being resistant to isoniazid, rifampicin, any fluoroquinone and at least one of the three following injectable drugs: capreomycin, kanamycin and amikacin) [6].

This chapter will deal first with the general properties and characteristics of the mycobacteria, before moving on to discuss tuberculosis and then infections with other mycobacteria. Leprosy is considered separately in Chapter 32.

Characteristics of the mycobacteria

The term 'mycobacterium' was given in 1896 to a large group of bacteria producing mould-like pellicles when grown on liquid media. All are slender, non-motile, aerobic, non-sporing rods with a waxy coating that makes them resistant to most stains. Once stained, however, they are not easily decolorized (acid-fast).

The genus can be subdivided into two subgenera, known as the fast (or rapid) growers [7] and the slow growers (which include most of the pathogens). The techniques of biochemistry and molecular biology have made the early classification of Runyon [8] obsolete for the modern mycobacteriology laboratory, since it has no true taxonomic validity [9]. Nevertheless, it is still useful for the classification of those species that may cause human disease. Runyon grouped mycobacteria by their ability to produce a yellow pigment in the dark or only in the light, and by their rate of growth (Table 31.1). This approach is being superseded because the entire sequence of the genome of *M. tuberculosis* is now known [11], and several other species of mycobacterium are also being sequenced [12].

The cell wall of the mycobacteria, which is responsible for their acid-fast staining properties, has a complex structure. The typical peptidoglycan backbone of a Gram-positive bacterial cell abuts onto a typical phospholipid plasma membrane. Outside the peptidoglycan layer, and covalently bonded to it, there is a branched polymer arabinogalactan. Onto this are attached the long chain (C60–C86) fatty acids termed mycolic acids. Numerous other lipids and glycolipids are non-covalently inserted into this lipophilic outer layer. Lipoarabinomannan (LAM, a phosphatidylinositol mannoside) is inserted into the plasma membrane and reaches out through the layers of the wall to the exterior [13].

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

Table 31.1 Mycobacteria of dermatological interest. (Adapted from Grange *et al.* [10].)

A Slow growers	
I Photochromogens	*M. marinum*, *M. kansasii*
II Scotochromogens	*M. scrofulaceum*
	M. szulgai
III Non-chromogens	*M. tuberculosis*
	M. avium
	M. ulcerans
B Rapid growers	
IV	*M. smegmatis*
	M. fortuitum
	M. chelonae/abscessus
C Non-culturable	*M. leprae*

Epidemiology

The re-emergence of *M. tuberculosis*

Tuberculosis is an ancient disease, but in Europe it was industrialization and urbanization that provoked a sharp rise in its incidence. From the mid-1700s for about a century, a pandemic of tuberculosis swept Europe. By 1800, a quarter of all deaths were caused by it [14]. Migration spread the disease to the Americas, where rates in the former Europeans peaked 50–80 years later, and to South Asia, and Central Africa, where the incidence peaked 100 years later [15]. Nevertheless, right up until the mid-20th century, the disease was being newly introduced into previously uninfected populations—for example, the Inuit of north Canada and the highland natives of Papua New Guinea [16]. In the indigenous population of Western Europe, tuberculosis rates declined from 1800 [15].

The organism responsible for tuberculosis was identified over 100 years ago; diagnostic skin tests were developed about 100 years ago; a tuberculosis vaccine has been in use for over 60 years, and chemotherapy for over 40 years. It is one of the anomalies of modern health care that, despite the availability of effective treatments and a trend of decline over the last few decades, the number of new cases of tuberculosis is again rising [17] and increases in MDR tuberculosis and XDR tuberculosis raise concerns of a global epidemic of untreatable tuberculosis [18]. The World Health Organization (WHO) estimated 8.8 million new tuberculosis cases in 2005; of which 7.4 million were in the most populous countries of Asia (Bangladesh, China, India, Indonesia and Pakistan) and sub-Saharan Africa. The WHO African region has the highest estimated incidence rate (356 per 100 000 population per year). An estimated total of 1.6 million people died of tuberculosis in 2005, including 195 000 patients infected with HIV [19]. Cases have continued to increase in Sub-Saharan Africa since the mid-1980s due to the association of tuberculosis with HIV infection, combined with poor or absent primary-care services [3,20]. Facilities to diagnose and treat multidrug resistant tuberculosis (MDR-TB), including extensively drug resistant tuberculosis (XDR-TB), are not yet widely available; the scale of the XDR-TB problem globally is not yet known [19].

Tuberculosis case numbers have been increasing in England and Wales since the late 1980s and have continued to do so in recent years [21]. Over 8000 cases were reported in 2005, a rate of 14.7 per 100 000 population. The London region accounted for 43% of cases and had the highest rate of disease (46.3 per 100 000) and meets the WHO definition of a high tuberculosis incidence area [22]. Between 2000 and 2005, the tuberculosis rate among the non-UK-born population increased from 78.2 per 100 000 to 103.3 per 100 000. In this population, those belonging to the Indian, Pakistani and Bangladeshi groups accounted for the highest number of cases (n = 2414 in 2005), while the highest rates occurred in the Black African ethnic group (399.0 per 100 000). Among non-UK-born cases, 78% had arrived in the UK 2 years or more prior to diagnosis.

Rates in the UK-born population remained relatively stable at around 4 per 100 000. The white ethnic group accounted for the largest number of cases (1352 cases in 2005), while the highest rates occurred in the Black African (41 per 100 000) and Indian, Pakistani and Bangladeshi (38.6 per 100 000) ethnic groups. Most tuberculosis cases continue to occur in young adults (in 2005, 61% were aged 15–44 years) [22].

The proportion of patients with tuberculosis in the UK co-infected with HIV has steadily risen from 3.1% in 1999 to 8.3% by the end of 2003. Co-infected patients accounted for almost a third of the increase in the number of cases of tuberculosis during this 5-year period [23].

The global impact of HIV on the incidence of tuberculosis

About one-third of the world's population have latent *M. tuberculosis* infection. About 5–10% of infected individuals are likely to develop symptomatic tuberculosis during their lives, but the risk of developing the clinical manifestations of the disease is greatly increased by HIV co-infection [3]. The global prevalence of HIV infection in patients with tuberculosis is difficult to estimate accurately as HIV testing is not done routinely in patients with tuberculosis. In the African region where WHO suggests all tuberculosis patients should be tested for HIV, about 10% of notified tuberculosis cases were tested in 2005. Among all tuberculosis patients tested for HIV, the proportion positive remained fairly constant between 2003 and 2005 at about 51% in the WHO African region and 23% worldwide [19]. HIV has probably had a smaller effect on tuberculosis prevalence than on incidence because the virus significantly reduces the life expectancy of patients with tuberculosis. Tuberculosis-attributable mortality remains high in HIV co-infection. Patients are also more likely to develop tuberculosis again after receiving treatment [24].

The epidemiology of non-tuberculous mycobacterial infections

Non-tuberculous mycobacteria (NTM) are widely distributed in the environment with high isolation rates worldwide. Organisms can be found in the soil and water, including treated water sources and, in fact, *M. kansasii*, *M. xenopi* and *M. simiae* are recovered almost exclusively from municipal water sources [25]. There is no evidence of animal to human or human to human transmission of NTM and these organisms may cause both asymptomatic infection and symptomatic disease. With the advent of the AIDS epidemic and the introduction of immunosuppressive agents, the incidence of NTM-associated disease has increased dramatically

and NTM have been acknowledged as important pathogens [26,27]. This group of pathogens has also shown to be increasing in non-immunocompromised patients [28].

Because these organisms are of relatively low pathogenicity, some host impairment or trauma providing a portal of entry is generally needed for the development of disease. The lungs, bones, joints and less frequently the skin are the chief target organs, but the clinical manifestations are as variable as those of tuberculosis itself. A mycobacterial cause should be suspected for lesions developing at the site of trauma if these follow a chronic course despite antibiotic therapy. The isolation of such organisms does not necessarily imply that they are causing disease. Of the 105 strains of mycobacteria isolated from house dust in Queensland, Australia, for example, only 56% were potentially pathogenic; *M. fortuitum* was isolated 11 times [29].

The implementation of improved clinical and laboratory diagnostic techniques will probably lead to a greater rate of diagnosis. The increase in infection rates has prompted the publication of guidelines to improve diagnosis and treatment of these unusual pathogens [30].

References

1 O'Brien RJ. The epidemiology of nontuberculous mycobacterial disease. *Clin Chest Med* 1989; **10**: 407–18.
2 Salo WL, Aufderheide AC, Buikstra J, Holcomb TA. Identification of *Mycobacterium tuberculosis* DNA in a pre-Columbian Peruvian mummy. *Proc Natl Acad Sci USA* 1994; **91**: 2091–4.
3 Dye C. Global epidemiology of tuberculosis. *Lancet* 2006; **367**: 938–40.
4 Getahun H, Harrington M, O'Brien R *et al*. Diagnosis of smear-negative pulmonary tuberculosis in people with HIV infection or AIDS in resource-constrained settings: informing urgent policy changes. *Lancet* 2007; **369**: 2042–9.
5 Aziz MA, Wright A, Laszlo A, De Muynck A *et al*. Epidemiology of antituberculous drug resistance (the Global Project on Anti-tuberculosis Drug Resistance Surveillance): an updated analysis. *Lancet* 2006; **368**: 2142–54.
6 Raviglione MC, Smith IM. XDR tuberculosis-implications for global public health. *New Eng J Med* 2007; **356**: 656–9.
7 Wallace RJ Jr. Recent changes in taxonomy and disease manifestations of the rapidly growing mycobacteria. *Eur J Clin Microbiol Infect Dis* 1994; **13**: 953–60.
8 Runyon EH. Ten mycobacterial pathogens. *Tubercle* 1974; **55**: 235–40.
9 Rogall T, Wolters J, Flohr T, Bottger EC. Towards a phylogeny and definition of species at the molecular level within the genus *Mycobacterium*. *Int J Syst Bacteriol* 1990; **40**: 323–30.
10 Grange JM, Yates MD, Collins CH. Subdivision of *Mycobacterium tuberculosis* for epidemiological purposes: a seven-year study of the 'classical' and 'Asian' types of human tubercle bacillus in South-East England. *J Hyg* 1985; **94**: 9–21.
11 Cole ST, Brosch R, Parkhill J *et al*. Deciphering the biology of *Mycobacterium tuberculosis* from the complete genome sequence. *Nature* 1998; **393**: 537–44 [published erratum appears in *Nature* 1998; **396**: 190].
12 Brosch R, Gordon SV, Buchrieser C *et al*. Comparative genomics uncovers large tandem chromosomal duplications in *Mycobacterium bovis* BCG Pasteur. *Yeast* 2000; **17**: 111–23.
13 Brennan PJ, Besra GS. Structure, function and biogenesis of the mycobacterial cell wall. *Biochem Soc Trans* 1997; **25**: 188–94.
14 Bates JH, Stead WW. The history of tuberculosis as a global epidemic. *Med Clin North Am* 1993; **77**: 1205–17.
15 Davies PD. Tuberculosis and migration. The Mitchell Lecture 1994. *J R Coll Physicians Lond* 1995; **29**: 113–8.
16 Grigg ERN. The arcana of tuberculosis. *Am Rev Tuberc* 1958; **78**: 151–72.
17 Harries AD, Dye C. Tuberculosis. *Ann Trop Med Parasitol* 2006; **100**: 415–31.
18 Padayatchi N, Friedland G. Managing multiple and extensively drug-resistant tuberculosis and HIV. *Expert Opin Pharmacother* 2007; **8**: 1035–7.
19 WHO. Global tuberculosis control: Surveillance, planning, financing. WHO report. WHO/HTM/TB/2007.376.2007.Geneva,World Health Organisation.
20 Glusker A. Global tuberculosis levels plateau while extensively drug resistant strains increase. *BMJ* 2007; **334**: 659.
21 Rose AM, Gatto AJ, Watson JM. Recent increases in tuberculosis notifications in England and Wales—real or artifact? *J Public Health Med* 2002; **24**: 136–7.
22 Health Protection Agency. Recent trends in tuberculosis: 2000–2005 annual surveillance report 2006—England, Wales and Northern Ireland. Health Protection Agency Centre for Infections, 2006.
23 Ahmed AB, Abubakar I, Delpech V *et al*. The growing impact of HIV infection on the epidemiology of tuberculosis in England and Wales 1999–2003. *Thorax* 2007; **62**: 672–6.
24 Corbett EL, Charalambous S, Moloi VM *et al*. Human immunodeficiency virus and the prevalence of undiagnosed tuberculosis in African gold miners. *Am J Respir Crit Care Med* 2004; **170**: 673–9.
25 Falkinham JO. Nontuberculous mycobacteria in the environment. *Clin Chest Med* 2002; **23**: 520–55.
26 Marras TK, Chedore P, Ying AM *et al*. Isolation of pulmonary non-tuberculous mycobacteria in Ontario, 1997–2003. *Thorax* 2007; **62**: 661–6.
27 Wagner D, Young LS. Nontuberculous mycobacterial infections; a clinical review. *Infection* 2004; **32**: 257–70.
28 Henry MT, Inamdar L, O'Riordan D *et al*. Nontuberculous mycobacteria in non-HIV patients: epidemiology, treatment and response. *Eur Respir J* 2004; **23**: 741–6.
29 Dawson DJ. Potential pathogens among strains of mycobacteria isolated from house dust. *Med J Austr* 1971; **1**: 679–81.
30 Griffiths DE, Aksamit T, Brown-Elliott BA *et al*. An official ATS/IDSA statement: diagnosis, treatment and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med* 2007; **175**: 367–416.

Immunology of tuberculosis

The three major paradoxes

Three factors in the immunology of tuberculosis remain poorly explained, as discussed below. These are the latent state, the balance between protection and immunopathology after previous exposure, and failure to eliminate persistent mycobacteria.

Following infection, only 5–10% of individuals develop progressive disease, but some bacteria remain viable in the tissues of the subclinically infected individuals. When tissues from healthy individuals living in TB-endemic countries are examined by *in situ* polymerase chain reaction (PCR), DNA from *M. tuberculosis* can be detected not only in macrophages, but also in cells such as fibroblasts and type II pneumocytes, located in lung tissue devoid of lymphocyte infiltration [1]. Neutralization of tumour necrosis factor-α (TNF-α) for the treatment of rheumatoid arthritis can lead to reactivation and progressive disease [2], and so can extreme stress, living in war zones and immunosuppression. Clearly, we need to understand more about the nature and significance of the latent state.

About 5–10% of exposed individuals manifest disease. Such overtly diseased individuals usually develop a powerful necrotizing skin-test responsiveness to the antigens of *M. tuberculosis*, and this immunopathological reaction is also likely to account for much of the lung damage. Robert Koch in the 1890s observed that killed bacteria or culture supernatant injected into the skin of tuberculous guinea pigs would evoke necrosis both at the injection site and in existing tuberculous lesions—the 'Koch phenomenon' [3]. At first, he mistakenly believed this phenomenon to represent a protective mechanism. However, attempts to treat the human disease by provoking the Koch phenomenon were often fatal, because necrosis was induced in pre-existing lesions, whether in the lung or spine [4]. Subsequent studies in the 1940s proved that

guinea pigs that had been immunized so that they developed the Koch phenomenon before challenge with living bacteria were in fact more susceptible than animals that had not been immunized at all [5]. The same is true in humans. Protection correlates with small tuberculin reactions such as those seen in recipients of bacille Calmette–Guérin (BCG) vaccine, rather than with large, necrotizing reactions [6]. A crucial question is, therefore, the difference between protection and immunopathology.

The inefficiency of this immunopathological response as a microbicidal mechanism has a second important consequence. When patients with tuberculosis are treated with the conventional antibiotics and chemotherapeutic agents, most of the organisms are killed rapidly by the drugs. However, there are 'persisters' (which may be biologically distinct from the latent bacteria discussed above) that are not eliminated by the drugs or by the immune response. The failure of the immune response to eliminate persisters, even when virtually all bacteria have been killed by drugs, is attributable to the fact that the immunopathological response does not quickly revert to the non-necrotic protective mechanism characteristic of the responses in successfully BCG-vaccinated individuals. Therefore, treatment must continue for at least 6 months, or relapse will occur [7]. A research priority is the development of immunotherapy that will 'turn off' the Koch phenomenon, and boost protective mechanisms, and so allow shorter treatment regimens.

Protective immunity to *M. tuberculosis*

The cell wall of the mycobacterium is resistant to damage mediated by antibody and complement, and immunity depends on the presence of an intact T-lymphocyte response. Experiments in mice using gene knockout and neutralizing antibodies have shown that immunity is mediated by Th1 lymphocytes that recognize antigens from *M. tuberculosis* and as a result secrete cytokines including interleukin-2 (IL-2) and interferon-γ (IFN-γ). These cells activate macrophages and enhance formation of cytotoxic T cells, which are effector systems involved in killing of the mycobacteria [8–11].

Definitive evidence that the type 1 response is also crucial for immunity to tuberculosis in man has come from the study of children with genetic defects of the type 1 cytokine system. Vaccination with BCG, an avirulent derivative of the organism responsible for bovine tuberculosis, occasionally causes disseminated infection. The IFN-γ R1 gene in such a child had a single nucleotide deletion that resulted in the creation of a premature stop codon near the N terminus [12]. A different defect in the IFN-γ receptor was identified in another study of four children with disseminated *M. fortuitum*, *M. avium* (two strains) and *M. chelonei* [13]. IL-12 receptor deficiency has also been found in otherwise healthy individuals with mycobacterial infections [14].

Despite this understanding, the precise effector mechanisms that kill *M. tuberculosis* remain controversial. There may be several pathways, some involving activation of macrophages by IFN-γ and TNF-α [15], others involving killing of the infected macrophage by cytotoxic $CD8^+$ T cells (or γ/δ T cells), with simultaneous killing of the contained bacteria [16–18], and some involving death of the bacteria during certain types of apoptosis of the infected cells [19,20]. It has proved extremely difficult to demonstrate convincing killing of *M. tuberculosis* by human peripheral blood or lung lavage cells *in vitro*.

The issue is further complicated by the multitude of T lymphocyte types, in addition to conventional $CD4^+$ and $CD8^+$ cells, which recognize components of *M. tuberculosis*. In humans and other large, long-lived animals, there are several types of T cell—including αβ T lymphocytes negative for both CD4 and CD8 molecules (so-called double-negative T cells), γ/δ T cells and certain $CD4^+$, $CD8^+$, $CD8\alpha/\alpha^+$ cells and natural killer (NK) lymphocytes—that recognize mycobacterial LAM, mycolic acids or isoprenoid glycolipids, presented by the major histocompatibility complex (MHC) class 1-like molecules of the CD1 family [21,22]. It is fascinating that the different forms of CD-1 'survey' different intracellular compartments, and so will encounter products of *M. tuberculosis* in different ways [23]. Nevertheless, the role of these cells is unclear, partly because the appropriate forms of CD1 are not present in the mouse, in which most experiments are performed.

A dominant theme in other domains of immunology is the regulatory T cell ('T_{reg}'), though these cells have received little attention in the context of tuberculosis. T_{reg} cells characteristically release IL-10 and transforming growth factor-β (TGF-β), and suppress inflammation in models of allergy, inflammatory bowel disease and autoimmunity [24]. It has been claimed that T cells cloned from the bronchoalveolar lavage of human patients with tuberculosis make both IFN-γ and IL-10, and so may be a form of T_{reg} [25]. At least one mycobacterial species has been formally proven to evoke regulatory T cells, so inappropriate or premature activation of T_{reg} is clearly a possible mechanism of failure of the immune response, and failure to eliminate persisting bacteria [26].

The role of TNF-α in tuberculosis

IFN-γ and IL-12 control mycobacteria mainly through the up-regulation of tumour necrosis factor (TNF-α), which is made predominantly by monocytes and macrophages. The critical role of TNF-α in controlling intercellular infections is made clear through the use of potent TNF-α blocking agents such as infliximab and adalimumab, and the soluble receptor etanercept, which lead to relatively high rates of active tuberculosis in those who have latent infection [27]. The risk posed by TNF-α blocking agents for predisposition to NTM infection is unknown.

Immunopathology

At present, the only viable hypothesis is that the immunopathology is related to a switch towards expression of Th2 cytokines such as IL-4. Since IgE is IL-4-dependent, the discovery some years ago that tuberculosis patients have specific IgE antibody that binds to *M. tuberculosis* should have made this clear [28]. Recent work has proved that IL-4 and IL-13 production are increased in human pulmonary tuberculosis, and correlate with cavitation and with the immunopathological features [29–33]. It was particularly $CD8^+$ cells secreting IL-4 (or more probably IL-4δ2; see below) that correlated with cavitation in van Crevel's work [31]. It was also shown by quantitative reverse transcriptase polymerase chain reaction (RT-PCR) that the IL-4 mRNA copy number correlated significantly with serum IgE, serum soluble CD30 and extent of cavitation [29,30]. Similarly, IL-4 expression can be detected in

many lesions from severe tissue-damaging tuberculosis by *in situ* hybridization [34].

Not only are expression levels markedly increased in fresh, unstimulated blood cells from tuberculosis patients [29], but T cells from tuberculosis patients cloned in response to *M. tuberculosis in vitro* release IL-4 when driven by TB antigen [32]; however, the cytokine profile secreted returns to Th1 after successful treatment [34]. This, together with the presence of *M. tuberculosis*-specific IgE [28], indicates that the increased IL-4 secretion is a true response to TB antigens. Similarly, there is accelerated disease in mice with pre-existing Th2 responses to the 'common' antigens shared with environmental saprophytic mycobacteria [35], to protein antigens of *M. tuberculosis* [36], or even to a single 16-amino acid epitope from ovalbumin expressed within the strain of recombinant *M. tuberculosis* used for challenge [37].

Interestingly, the IL-4 response in human tuberculosis differs from the Th2 response that accompanies allergic disorders, in that it involves both IL-4 and the splice variant of IL-4, IL-4δ2 [30]. In contrast, in allergic disorders there is a disproportionate rise in expression of IL-4 itself [38]. Moreover, in tuberculosis the IL-4 response occurs in the presence of a much larger Th1 response than is the case in allergic diseases.

As IL-4 expression increases, so TNF-α becomes more toxic [28,35], as is also seen in models of schistosomiasis [39] and of *Trichinella spiralis* [40]. As mentioned earlier, this increasing toxicity of TNF-α is also seen in the human disease [29].

References

1 Hernández-Pando R, Jeyanathan M, Mengistu G *et al.* Persistence of DNA from *M. tuberculosis* in superficially normal lung tissue during latent infection. *Lancet* 2000; **356**: 2133–8.

2 Keane J, Gershon S, Wise RP *et al.* Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *N Engl J Med* 2001; **345**: 1098–104.

3 Koch R. Fortsetzung über ein Heilmittel gegen Tuberculose. *Deutsch Med Wochenschr* 1891; **17**: 101–2.

4 Anderson MC. On Koch's treatment. *Lancet* 1891; **i**: 651–2.

5 Wilson GS, Schwabacher H, Maier I. The effect of the desensitisation of tuberculous guinea-pigs. *J Pathol Bacteriol* 1940; **50**: 89–109.

6 Watkins RE, Brennan R, Plant AJ. Tuberculin reactivity and the risk of tuberculosis: a review. *Int J Tuberc Lung Dis* 2000; **4**: 895–903.

7 Balasubramanian R, Sivasubramanian S, Vijayan VK *et al.* Five year results of a 3 month and two 5 month regimens for the treatment of sputumpositive pulmonary tuberculosis in South India. *Tubercle* 1990; **71**: 253–8.

8 Orme I, Flynn JL, Bloom BR. The role of $CD8^+$ T cells in immunity to tuberculosis. *Trends Microbiol* 1993; **1**: 77–8.

9 Orme IM, Andersen P, Boom WH. T cell response to *Mycobacterium tuberculosis*. *J Infect Dis* 1993; **167**: 1481–97.

10 Stenger S, Hanson DA, Teitelbaum R *et al.* An antimicrobial activity of cytolytic T cells mediated by granulysin. *Science* 1998; **282**: 121–5.

11 Silver RF, Li Q, Boom WH, Ellner JJ. Lymphocyte-dependent inhibition of growth of virulent *Mycobacterium tuberculosis* H37Rv within human monocytes: requirement for $CD4^+$ T cells in purified protein derivative-positive, but not in purified protein derivative-negative subjects. *J Immunol* 1998; **160**: 2408–17.

12 Jouanguy E, Altare F, Lamhamedi S *et al.* Interferon-γ receptor deficiency in an infant with fatal bacille Calmette-Guérin infection. *N Engl J Med* 1996; **335**: 1956–61.

13 Newport M, Huxley CM, Huston S *et al.* A mutation in the interferon-γ receptor gene and susceptibility to mycobacterial infection. *N Engl J Med* 1996; **335**: 1941–9.

14 Altare F, Durandy A, Lammas D *et al.* Impairment of mycobacterial immunity in human interleukin-12 receptor deficiency. *Science* 1998; **280**: 1432–5.

15 Hirsch CS, Ellner JJ, Russell DG, Rich EA. Complement receptor mediated uptake and tumour necrosis factor α-mediated growth inhibition of *Mycobacterium tuberculosis* by human alveolar macrophages. *J Immunol* 1994; **152**: 743–53.

16 Silva CL, Lowrie DB. Identification and characterization of murine cytotoxic T cells that kill *Mycobacterium tuberculosis*. *Infect Immun* 2000; **68**: 3269–74.

17 Cho S, Mehra V, Thoma-Uszynski S *et al.* Antimicrobial activity of MHC class I-restricted $CD8^+$ T cells in human tuberculosis. *Proc Natl Acad Sci USA* 2000; **97**: 12210–5.

18 Dieli F, Troye-Blomberg M, Ivanyi J *et al.* Granulysin-dependent killing of intracellular and extracellular *Mycobacterium tuberculosis* by Vgamma9/Vdelta2 T lymphocytes. *J Infect Dis* 2001; **184**: 1082–5.

19 Lammas DA, Stober C, Harvey CJ *et al.* ATP-induced killing of mycobacteria by human macrophages is mediated by purinergic P2Z(P2X7) receptors. *Immunity* 1997; **7**: 433–44.

20 Oddo M, Renno T, Attinger A *et al.* Fas ligand-induced apoptosis of infected human macrophages reduces the viability of intracellular *Mycobacterium tuberculosis*. *J Immunol* 1998; **160**: 5448–54.

21 Rosat JP, Grant EP, Beckman EM *et al.* CD1-restricted microbial lipid antigen-specific recognition found in the $CD8^+$ alpha beta T cell pool. *J Immunol* 1999; **162**: 366–71.

22 Moody DB, Ulrichs T, Muhlecker W *et al.* CD1c-mediated T-cell recognition of isoprenoid glycolipids in *Mycobacterium tuberculosis* infection. *Nature* 2000; **404**: 884–8.

23 Schaible UE, Hagens K, Fischer K, Collins HL, Kaufmann SH. Intersection of group I CD1 molecules and mycobacteria in different intracellular compartments of dendritic cells. *J Immunol* 2000; **164**: 4843–52.

24 Read S, Malmstrom V, Powrie F. Cytotoxic T lymphocyte-associated antigen 4 plays an essential role in the function of $CD25^{(+)}CD4^{(+)}$ regulatory cells that control intestinal inflammation. *J Exp Med* 2000; **192**: 295–302.

25 Gerosa F, Nisii C, Righetti S *et al.* $CD4^{(+)}$ T cell clones producing both interferon-gamma and interleukin-10 predominate in bronchoalveolar lavages of active pulmonary tuberculosis patients. *Clin Immunol* 1999; **92**: 224–34.

26 Zuany-Amorim C, Sawicka E, Manlius C *et al.* Suppression of airway eosinophilia by killed *Mycobacterium vaccae*-induced allergen-specific regulatory T-cells. *Nat Med* 2002; **8**: 625–9.

27 Keane J. Tumour necrosis factor blockers and reactivation of latent tuberculosis. *Clin Infect Dis* 2004; **39**: 300–2.

28 Yong AJ, Grange JM, Tee RD *et al.* Total and anti-mycobacterial IgE levels in serum from patients with tuberculosis and leprosy. *Tubercle* 1989; **70**: 273–9.

29 Seah GT, Scott GM, Rook GA. Type 2 cytokine gene activation and its relationship to extent of disease in patients with tuberculosis. *J Infect Dis* 2000; **181**: 385–9.

30 Seah GT, Rook GAW. High levels of mRNA encoding IL-4 in unstimulated peripheral blood mononuclear cells from tuberculosis patients revealed by quantitative nested RT-PCR: correlations with serum IgE levels. *Scand J Infect Dis* 2000; **33**: 106–9.

31 van Crevel R, Karyadi E, Preyers F *et al.* Increased production of interleukin 4 by $CD4^+$ and $CD8^+$ T cells from patients with tuberculosis is related to the presence of pulmonary cavities. *J Infect Dis* 2000; **181**: 1194–7.

32 Marchant A, Amedei A, Azzurri A *et al.* Polarization of PPD-specific T-cell response of patients with tuberculosis from Th0 to Th1 profile after successful antimycobacterial therapy or in vitro conditioning with interferon-alpha or interleukin-12. *Am J Respir Cell Mol Biol* 2001; **24**: 187–94.

33 Suzuki N, Kudo K, Sano Y, Ito K. Can *Mycobacterium tuberculosis* infection prevent asthma and other allergic disorders? *Int Arch Allergy Immunol* 2001; **124**: 113–6.

34 Fenhalls G, Wong A, Bezuidenhout J *et al.* In situ production of gamma interferon, interleukin-4, and tumor necrosis factor alpha mRNA in human lung tuberculous granulomas. *Infect Immun* 2000; **68**: 2827–36.

35 Hernandez-Pando R, Pavon L, Arriaga K *et al.* Pathogenesis of tuberculosis in mice exposed to low and high doses of an environmental mycobacterial saprophyte. *Infect Immun* 1997; **65**: 3317–27.

36 Lindblad EB, Elhay MJ, Silva R, Appelberg R, Andersen P. Adjuvant modulation of immune responses to tuberculosis subunit vaccines. *Infect Immun* 1997; **65**: 623–9.

37 Wangoo A, Sparer T, Brown IN *et al.* Contribution of Th1 and Th2 cells to protection and pathology in experimental models of granulomatous lung disease. *J Immunol* 2001; **166**: 3432–9.

38 Seah GT, Gao PS, Hopkin J, Rook GAW. Interleukin-4 and its alternatively spliced variant (IL-4δ2) in patients with atopic asthma. *Am J Resp Crit Care Med* 2001; **164**: 1016–8.
39 Wynn TA, Cheever AW, Jankovic D *et al*. An IL-12-based vaccination method for preventing fibrosis induced by schistosome infection. *Nature* 1995; **376**: 594–6.
40 Lawrence CE, Paterson JC, Higgins LM *et al*. IL-4-regulated enteropathy in an intestinal nematode infection. *Eur J Immunol* 1998; **28**: 2672–84.

Diagnostic tests for tuberculosis

The tuberculin skin test

The tuberculin skin test (TST) has been in use for nearly 100 years [1] and depends upon delayed-type hypersensitivity to mycobacterial antigens, following an intradermal injection of purified protein derivative (PPD). PPD is a culture filtrate of tubercle bacilli containing over 200 antigens shared with bacille Calmette–Guérin (BCG) and many NTM [2]. This lack of specificity is a major drawback in populations vaccinated with BCG, although it remains the most widely used vaccine in the world, in excess of three billion people having been vaccinated [3]. A positive test can result from clinical or latent tuberculosis infection, from BCG vaccination or from contact with environmental mycobacteria. As TST depends on a lymphocyte-induced delayed hypersensitivity reaction it is of low sensitivity in immunosuppressed patients; patients with severe illness, including those with some forms of active tuberculosis, with HIV infection and those on immunosuppressant drugs including corticosteroids, may therefore have false negative reactions [4].

Tuberculin testing should be done by the Mantoux method as this is the only technique that has been standardized and extensively validated. PPD (0.1 ml = 5 tuberculin units) is injected intradermally into the volar aspect of the forearm using a 27-gauge needle to raise a small wheal, and the diameter of the induration is read at 48 to 72 hours. Normally, a cut-off of 5 mm induration is used to determine those at high risk of tuberculosis infection, for example close contacts of an active case, patients with radiographic abnormalities consistent with tuberculosis, those with HIV infection and those immunosuppressed with corticosteroids or other agents. A cut-off of 10 mm is used in immigrants from endemic areas, health care workers, the homeless and residents of some inner cities, and those patients with diabetes, renal disease, silicosis and other conditions associated with an increased risk of latent tuberculosis. Finally a cut-off of 15 mm is used in those with no risk factors.

Tuberculin sensitivity appears within a few weeks of the onset of an infection with *M. tuberculosis*, and is usually life-long. In any community, the number of individuals who react strongly to tuberculin relates to the prevalence of active tuberculosis. It does not necessarily imply immunity to tuberculosis. Indeed, the risk of developing clinical tuberculosis in tuberculin-positive children is roughly proportional to the strength of their tuberculin reaction [5], and protection consistently correlates with small non-necrotizing responses, while large necrotic responses indicate either susceptibility or actual disease [6]. Presumably this represents the switch from a protective Th1 response to the immunopathological Koch phenomenon discussed earlier.

Weaker reactions do not correlate with the amount of active tuberculosis in a community. Some, as mentioned earlier, are due to infection with other mycobacteria, and others are due to the waning of reactivity under various influences, including ageing. Reversion after a primary infection occasionally occurs in children, and the maintenance of reactivity may depend on continuing exposure to environmental mycobacteria.

Interferon-γ assays for detection of latent tuberculosis

Recent advances in bacterial genomics and human cellular immunology have resulted in new T-cell based blood tests that detect latent tuberculosis infection by measuring *in vitro* IFN-γ release in response to antigens which are highly specific for *M. tuberculosis* but absent from BCG vaccine and most NTM. One assay, the enzyme-linked immunospot (ELISpot) (T-spot.TB; Oxford Immunotec, Oxford, UK), enumerates IFN-γ secreting T cells, while the other assay measures IFN-γ concentration in supernatant by enzyme linked immunosorbent assay (ELISA) (Quantiferon (QFT)-TB Gold; Cellestis, Carnegie, Australia) [7]. Current versions of both IFN-γ release assays (IGRAs) use more specific *M. tuberculosis* antigens: ESAT-6, CFP-10 and TB7.7. The genes encoding these antigens are found in the region of difference 1 (RDI1) of the *M. tuberculosis* genome, which is deleted from the genome of *M. bovis* BCG and certain NTM [8].

Both tests are significantly more specific than the TST in populations vaccinated by BCG and may be more reliable in children and where there is immunosuppression. The blood tests have operational advantages over the skin test because no return visit is required, results are available by the next day and repeat testing does not cause boosting [7]. However, further research and development is required to verify that the new tests can predict the risk of later development of active tuberculosis and to make it feasible to perform these tests in a reproducible fashion at low cost, particularly in developing countries [9]. The US Centers for Disease Control and Prevention has recommended that QFT replace the TST [10], whereas the UK National Institute for Health and Clinical Excellence (NICE) has suggested that IGRAs are useful adjuncts to the tuberculin test [11].

Diagnosis of mycobacterial infections

Some mycobacterial infections may be suspected from their clinical features, geographical location, or the interests or occupation of the patient. For example, *M. marinum* infections are seen in tropical aquarium owners. Others such as *M. ulcerans* may not be recognized so easily. Any obscure granulomatous or ulcerative lesion of the skin should be biopsied and cultured. This can take several weeks in the case of ‘slow growers’, and treatment may have to be initiated on the basis of clinical probabilities. During the last two decades, several rapid techniques for detection of early growth (5 to 14 days as compared to 2 to 8 weeks with conventional methods) have become available. These include the BACTEC system and Mycobacterial Growth Indicator Tube (MGIT) (BD Biosciences) and Septi-Check (Roche pharmaceuticals) [12]. The use of nucleic acid probes has dramatically simplified species identification of mycobacterial isolates over the last decade. DNA probes that react with specific mycobacterial rRNA sequences to form DNA–RNA hybrids that are detected by chemoluminescence are commercially available for *M. tuberculosis*, *M. avium* complex, *M. kansasii* and *M. gordonae* [12]. While the gene probes can help in rapid identification of isolates, gene amplifica-

tion methods (PCR) are helpful in diagnosis of paucibacillary forms of disease [13] and are discussed in the section on diagnosis of cutaneous tuberculosis.

Co-infection with *Mycobacterium* species and HIV

HIV infection is the greatest known risk factor for progression from latent tuberculosis infection to tuberculosis disease [14]. The risk of active tuberculosis in people co-infected with HIV and *M. tuberculosis* is 3–8% per year, with a lifetime risk of 50% or more [15]. It is estimated that up to 50% of HIV-infected individuals in the developing world are co-infected with mycobacteria [16]. Two-thirds of the isolates are organisms of the *M. avium* complex, and 10% are *M. tuberculosis.* The two other organisms most commonly isolated are *M. kansasii* and *M. scrofulaceum*, but more unusual species such as *M. terrae, M. xenopi, M. gordanae, M. chelonae* and *M. fortuitum* are also reported [17–20].

Roughly 5% of patients with acquired immune deficiency syndrome (AIDS) develop disseminated mycobacterial infections, which cause their death. In the case of tuberculosis, this seems usually to be by reactivation of a latent infection, and is often extra-pulmonary. In HIV-infected patients, the clinical and radiographic appearance of pulmonary tuberculosis is often atypical, and extra-pulmonary involvement, including involvement of the skin, is frequent [21]. For example, acute miliary tuberculosis of the skin and scrofuloderma may be seen [21,22]. The mechanism of acquisition of NTM in patients with HIV is not known although it is assumed to be through ingestion of the organism from an environmental source. Patients who have colonized their respiratory and gastrointestinal tracts are at greater risk of developing disseminated disease [23].

It has been suggested that anti-tuberculous chemoprophylaxis should be used in patients with HIV and coexisting latent *M. tuberculosis* infection, to prevent reactivation of tuberculosis [24]. Prophylaxis with isoniazid, in a 12-month study in Haiti, reduced the incidence of tuberculosis from 10.0 to 1.7 per 100 person-years, and delayed the progression of HIV disease [25,26]. Single-drug prophylaxis does not increase drug resistance in the community unless used in patients with active disease, and so screening for this has to be carried out if prophylaxis is being considered [25]. The cost of prophylaxis in developing countries has been assessed as favourable when compared with a course of standard antituberculous therapy and it is recommended that HIV-positive individuals who do not have active tuberculosis should be offered isoniazid preventative treatment [27,28].

The increased risk of problems with BCG vaccination [29], and recommendations covering this, are discussed in the section on BCG vaccination below.

References

1 Mantoux MC. La voie intradermique en tuberculinotherapie. *Presse Med* 1912; **20**: 146–8.
2 Huebner RE, Schein MF, Bass JB Jr. The tuberculin skin test. *Clin Infect Dis* 1993; **17**: 968–75.
3 Anderson P, Doherty TM. The success and failure of BCG: implications for a novel tuberculosis vaccine. *Nat Rev Microbiol* 2005; **3**: 656–62.
4 Menzies D, Pai M, Comstock G. Meta-analysis: new tests for the diagnosis of latent tuberculosis infection: areas of uncertainty and recommendations for research. *Ann Intern Med* 2007; **146**: 340–54.
5 Capewell S, France A, Uzel N, Leitch AG. The current value of tuberculin testing and BCG vaccination in school children. *Br J Dis Chest* 1986; **80**: 254–64.
6 Watkins RE, Brennan R, Plant AJ. Tuberculin reactivity and the risk of tuberculosis: a review. *Int J Tuberc Lung Dis* 2000; **4**: 895–903.
7 Lalvani A. Diagnosing tuberculosis infection in the 21st century: new tools to tackle an old enemy. *Chest* 2007; **131**: 1898–906.
8 Richeldi L. An update on the diagnosis of tuberculosis infection. *Am J Resp Crit Care Med* 2006; **174**: 736–42.
9 Kunst H. Diagnosis of latent tuberculosis infection: the potential role of new technologies. *Respir Med* 2006; **100**: 2098–106.
10 Mazurek GH, Jereb J, Lobue P *et al.* Guidelines for using the QuantiFERON-TB Gold test for detecting *Mycobacterium tuberculosis* infection. United States. *MMWR Recomm Rep* 2005; **54**: 49–55.
11 Royal College of Physicians. Tuberculosis: national clinical guidelines for diagnosis, management, prevention and control. London: Royal College of Physicians; 2006. Accessed at http://www.nice.org.uk.
12 Katoch VM. Newer diagnostic techniques for tuberculosis. *Indian J Med Res* 2004; **120**: 418–31.
13 Penneys NS, Craig L, Leonardi MD *et al.* Identification of *Mycobacterium tuberculosis* DNA in five different types of cutaneous lesions by the polymerase chain reaction. *Arch Dermatol* 1993; **129**: 1594–8.
14 Centers for Disease Control and Prevention. Morbidity and Mortality Weekly Report. *Morb Mortal Wkly Rep* 2007; **56**: 1103–6.
15 Selwyn PA, Hartel D, Lewis VA *et al.* A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. *N Engl J Med* 1989; **320**: 545–50.
16 Gazzard B. Tuberculosis, HIV and the developing world. *Clin Med* 2001; **1**: 62–8.
17 Chin DP, Hopewell PC. Mycobacterial complications of HIV infection. *Clin Chest Med* 1996; **17**: 697–711.
18 Carbonara S, Tortoli E, Costa D *et al.* Disseminated *Mycobacterium terrae* infection in a patient with advanced human immunodeficiency virus disease. *Clin Infect Dis* 2000; **30**: 831–5.
19 Juffermans NP, Verbon A, Danner SA *et al*. *Mycobacterium xenopi* in HIV-infected patients: an emerging pathogen. *AIDS* 1998; **12**: 1661–6.
20 Ferreira RM, Saad MH, Silva MG *et al*. Non-tuberculous mycobacteria 1: one year clinical isolates identification in Tertiary Hospital Aids Reference Center, Rio de Janerio, Brazil, in pre highly active antiretroviral therapy era. *Mem Inst Oswaldo Cruz* 2002; **97**: 725–9.
21 Rohatgi PK, Palazzolo JV, Saini NB. Acute miliary tuberculosis of the skin in acquired immunodeficiency syndrome. *J Am Acad Dermatol* 1992; **26**: 356–9.
22 Arianayagam AV, Ash S, Jones RR. Lichen scrofulosorum in a patient with AIDS. *Clin Exp Dermatol* 1994; **19**: 74–6.
23 Chin DP, Hopewell P, Stone EN *et al*. *Mycobacterium avium* complex in the respiratory or gastrointestinal tract and the risk of *Mycobacterium avium* complex bacteraemia in patients with human immunodeficiency virus infection. *J Infect Dis* 1994; **169**: 289–95.
24 Walley J, Porter J. Chemoprophylaxis in tuberculosis and HIV infection. *BMJ* 1995; **310**: 1621–2.
25 Pape JW, Jean SS, Ho JL *et al.* Effect of isoniazid prophylaxis on incidence of active tuberculosis and progression of HIV infection. *Lancet* 1993; **342**: 268–72.
26 Fitzgerald DW, Morse MM, Pape JW, Johnson WD Jr. Active tuberculosis in individuals infected with human immunodeficiency virus after isoniazid prophylaxis. *Clin Infect Dis* 2000; **31**: 1495–7.
27 Churchyard GJ, Fielding K, Charalambous S *et al.* Efficacy of secondary isoniazid preventive therapy among HIV-infected Southern Africans: time to change policy? *AIDS* 2003; **17**: 2063–70.
28 APBI Consensus Expert Committee. *J Assoc Physicians India* 2006; **54**: 219–34.
29 Quinn TC. Interactions of the human immunodeficiency virus and tuberculosis and the implications for BCG vaccination. *Rev Infect Dis* 1989; **11** (Suppl. 2): S379–84.

Tuberculosis

Introduction

In Western Europe, tuberculosis of the skin had become relatively uncommon as the incidence of all forms of tuberculosis fell up to the late 1980s [1]. Since then, numbers of notified cases of

tuberculosis have risen, especially in urban areas and in minority ethnic groups, notably those of the Indian subcontinent and black African origin and where there is HIV co-infection [2,3]. Cutaneous tuberculosis made up 4.4% of all cases of tuberculosis notified in one UK district between 1981 and 1995 [4], and 3.5% of 370 patients with tuberculosis reported from Turkey in 2003 [5]. In India in the 1950s and 1960s, cutaneous tuberculosis affected 2% of all skin outpatients. By the 1980s, this had fallen to 0.15% [6] and in two recent series published around the millennium this had fallen to 0.1% [7,8]. More recent reports from Morocco and India suggest that cutaneous tuberculosis is again becoming more prevalent with incidence rates of 2% and 0.9% respectively [9,10]. A current problem is that atypical and even standard presentations may be overlooked through lack of familiarity with the various patterns that may occur.

Natural history

M. tuberculosis and *M. bovis* are pathogenic to humans. *M. bovis* is also found in a wide range of animal species. The majority of human disease is due to *M. tuberculosis*, *M. bovis* being found in only 1–1.5% of isolates [11]. Transmission of infection within and between species is mainly by inhalation of airborne droplet nuclei particles containing *M. tuberculosis* complex, resulting in pulmonary infection. *M. bovis* may also penetrate the gastrointestinal mucosa and lymphatic tissue of the oropharynx when ingested in milk. Direct inoculation of the skin by *M. tuberculosis* complex also occurs. Survival of *Mycobacterium* species in aerosols generated from human saliva is usually less than an hour, indicating that close and prolonged contact is required for transmission of infection [12]. Studies of contact tracing have shown that 1% of close contacts are affected [13].

Spread takes place rapidly via the lymphatics to the lymph nodes draining the area of infection, and then further spread occurs via the bloodstream. In persons with intact cell-mediated immunity, activated T cells and macrophages form granulomas that limit spread of the organism. The granuloma that forms at the site of pulmonary infection constitutes the Ghon focus, and this, together with the enlarged hilar nodes, is termed the primary complex. The tuberculin test becomes positive after 3–8 weeks; this may be accompanied by fever or erythema nodosum, which is therefore a sign of a recent primary infection.

The subsequent course varies, depending on factors of virulence, resistance and the immunological responses described earlier. Often the organisms fail to thrive and the disease is arrested; less often, it progresses. Sometimes organisms may lie dormant after a primary infection, only to reactivate later, causing a recrudescence of the primary infection.

In the lung, the Ghon focus may be absorbed, become fibrotic and calcified, or may break down, liquefy and discharge bacilli into the lung. On the skin, the primary focus is a tuberculous chancre (p. 31.11). If the contiguous regional lymph nodes break down, scrofuloderma occurs (p. 31.14).

To the epidemiologist, 'primary' tuberculosis means any lesions developing within 5 years of the original infection [14], while later lesions are considered as 'secondary'. There must always be difficulty in determining whether post-primary lesions are due to the reactivation of existing disease, for example as in patients with AIDS, or due to re-infection, particularly since BCG protection diminishes with time.

Exogenous re-infection is probably rare, but does occur [15], and the reactions seen in a host already sensitized by a previous infection differ from those of the non-sensitized. A primary infection in the skin, for example, will be manifest as a cutaneous chancre whereas inoculation into a previously sensitized host may lead to tuberculosis verrucosa cutis (p. 31.12).

References

1 Ormerod LP, Charlett A, Gilham C *et al.* Geographical distribution of tuberculosis notifications in national surveys of England and Wales in 1988 and 1993. *Thorax* 1998; **53**: 176–81.

2 Rose AM, Gatto AJ, Watson JM. Recent increases in tuberculosis notifications in England and Wales—real or artifact? *J Public Health Med* 2002; **24**: 136–7.

3 Health Protection Agency. *Recent Trends in Tuberculosis: 2000–2005 Annual Surveillance Report 2006—England, Wales and Northern Ireland*. Health Protection Agency Centre for Infections, 2006.

4 Yates VM, Ormerod LP. Cutaneous tuberculosis in Blackburn district (U.K.): a 15 year prospective series. *Br J Dermatol* 1997; **136**: 483–9.

5 Kivanc-Altunay I, Baysal Z, Ekmekci TR *et al.* Incidence of cutaneous tuberculosis in patients with organ tuberculosis. *Int J Dermatol* 2003; **42**: 197–200.

6 Sehgal VN, Srivastava MD, Khurana VK *et al.* An appraisal of epidemiologic, clinical, bacteriologic, histopathologic and immunologic parameters in cutaneous tuberculosis. *Int J Dermatol* 1987; **26**: 521–6.

7 Kumar B, Rai R, Kaur I *et al.* Childhood cutaneous tuberculosis: a study over 25 years from northern India. *Int J Dermatol* 2001; **40**: 26–32.

8 Kumar B, Muralidar S. Cutaneous tuberculosis: a twenty-year prospective study. *Int J Tuberc Lung Dis* 1999; **3**: 494–500.

9 Zouhir K, Akhdari N, Nejjam F *et al.* Cutaneous tuberculosis in Morocco. *Int J Infect Dis* 2007; **11**: 209–12.

10 Pandhi D, Reddy BSN, Chowdhary S *et al.* Cutaneous tuberculosis in Indian children; the importance of screening for internal organs. *J Eur Acad Dermatol Venerol* 2004; **18**: 546–51.

11 Public Health Laboratory Service. Enhanced surveillance of *Mycobacterium bovis* in humans. *Commun Dis Wkly* 1998; **8**: 381–4.

12 Lever MS, Williams A, Bennett AM. Survival of mycobacterial species in aerosols generated from artificial saliva. *Lett Appl Microbiol* 2000; **31**: 238–41.

13 Joint Tuberculosis Committee of the British Thoracic Society. Control and prevention of tuberculosis in the United Kingdom: code of practice 2000. *Thorax* 2000; **55**: 887–901.

14 MRC Tuberculosis and Chest Disease Unit. National survey of tuberculosis notifications in England and Wales 1978–9. *BMJ* 1980; **282**: 895–8.

15 Styblo K. Epidemiology of tuberculosis. *Bull Int Union Tuberc* 1978; **53**: 141–2.

Histopathology [1]

M. tuberculosis can cause skin infection by direct inoculation into the skin, by haematogenous spread from an internal lesion and by direct contact with tuberculosis in an underlying deeper structure. Early, non-specific inflammatory changes give rise after 3–6 weeks to a characteristic tubercle. At this stage tubercle bacilli are rarely found, although inoculation cultures may be positive.

The fully formed tubercle consists of a focus of epithelioid cells containing a variable, but usually sparse, number of Langhans' giant cells and a surrounding infiltrate of mononuclear cells. The centre of the tubercle undergoes caseation necrosis and sometimes calcifies. Endovascular or perivascular changes in the vicinity of the tubercle become more marked as necrosis proceeds, and are accompanied by a cellular reaction leading to fibrosis.

Such granulomas vary greatly in appearance, depending on the virulence of the organism, the size of the inoculum and the immune status of the patient. Where cellular immunity is impaired, such

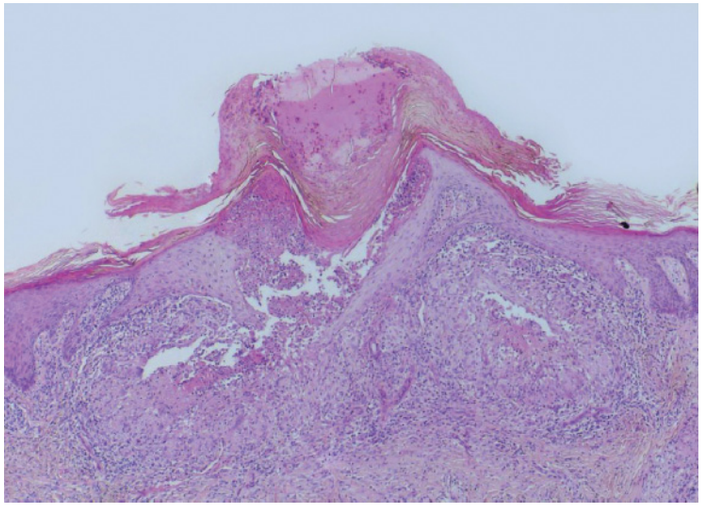


Fig. 31.1 Warty tuberculosis. The epidermis shows hyperkeratosis and acanthosis, with acute inflammation and abscess formation in the upper dermis. Ill-defined caseating granulomata with Langerhans' giant cells are present in the mid dermis. H&E stain ×120. (Courtesy of Drs M. Bamford and A. Fletcher, University of Leicester NHS Trust, UK.)

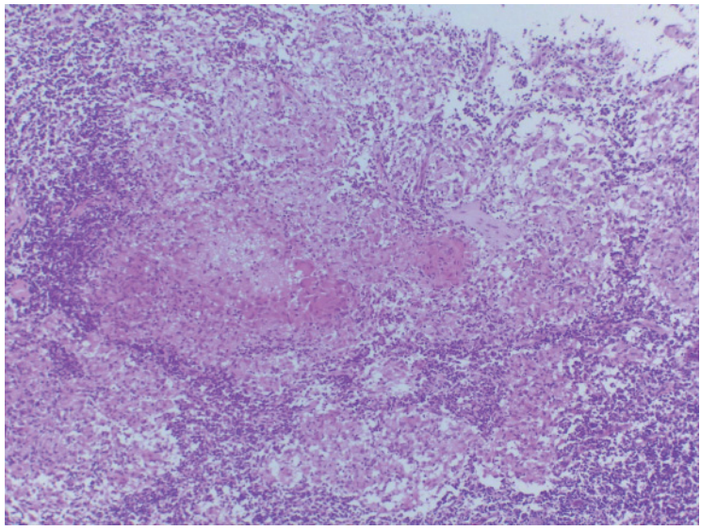


Fig. 31.2 The deep dermis in warty tuberculosis showing a granulomatous inflammatory cell infiltrate. The granulomas contain epithelioid histiocytes with prominent Langhans' giant cells and caseation. H&E stain ×140. (Courtesy of Drs M. Bamford and A. Fletcher, University of Leicester NHS Trust, UK.)

as in HIV infection and in cytotoxic or steroid therapy, the resulting pathology is less granulomatous (due to fewer activated macrophages) and there are greater numbers of bacteria found. Typical or less well-developed tuberculoid granulomas occur in many conditions other than tuberculosis (see below).

Development of the granuloma

Histochemical studies have shown that the mononuclear cells of a tubercle are blood-derived monocytes with a high content of lysosomal enzymes. They develop into macrophages which, following T-cell activation, then give rise to epithelioid cells, some fusing into multinucleated giant cells [2]. Caseation necrosis is due to the death and degeneration of these epithelioid cells and is probably mediated by cytokines such as TNF and macrophage protease.

Specific changes

Differences in the histopathological appearances depend on the balance between infection and immunological response. In the tuberculous chancre (p. 31.11), an acute necrotic neutrophilic reaction changes to a mononuclear infiltrate and, after 3–6 weeks, into typical tubercles in which the bacilli may no longer easily be seen. In *miliary* and *orificial* forms, the typical tubercle does not form or is imperfect or necrotic [3]. Bacilli are normally numerous, except in the milder neonatal form of miliary tuberculosis [4].

In *scrofuloderma*, the skin is destroyed by non-specific abscess formation and ulceration. Tubercle formation and caseation necrosis occur at the periphery, and bacilli can, with diligence, be found. In warty tuberculosis, the classical hallmarks are often missing, but there is marked hyperkeratosis, acanthosis and papillomatosis (which may be pseudoepitheliomatous) and an intense dermal infiltrate of neutrophils, lymphocytes and some giant cells (Figs 31.1 & 31.2). Bacilli are rarely demonstrable; typical tubercles are uncommon and caseation is rare.

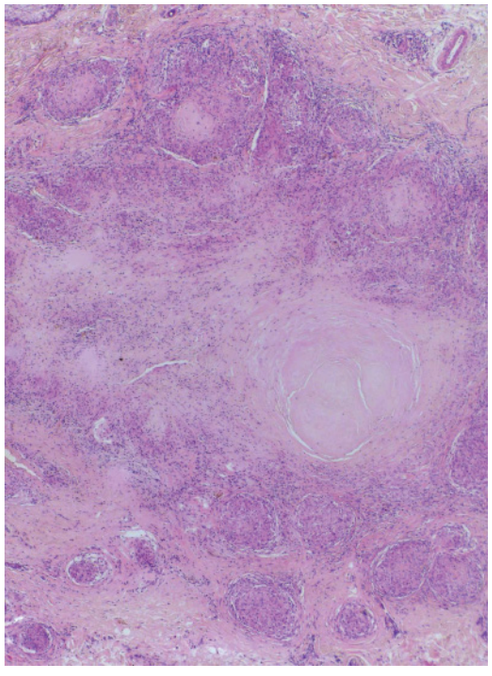


Fig. 31.3 Lupus vulgaris. Extensive caseous granulomatous inflammation in the deep dermis in lupus vulgaris. H&E stain. (Courtesy of Drs M. Bamford and A. Fletcher, University of Leicester NHS Trust, UK.)

The appearances in *lupus vulgaris* (Fig. 31.3) are variable and may give rise to diagnostic difficulty. The typical changes are those of well-marked tubercle formation with epithelioid nodules embedded in sheets of lymphocytes. Occasionally, the epidermal changes resemble those of warty tuberculosis. Caseation is usually sparse or even absent, and the amount of lymphocytic infiltrate is variable. Bacilli are seldom demonstrated, although they can

sometimes be cultured. As the lesions heal, increasing fibrosis strangles the remaining small foci of tubercle bacilli or epithelioid cells, which slowly become absorbed by the reparative process. Squamous and basal cell epithelioma may arise in long-standing lesions.

Differential diagnosis

The typical features are characteristic, but the variations may cause confusion with many other diseases, especially if caseation necrosis is absent or the subject's immune response is minimal.

It is impossible on histological grounds to differentiate the lesions of other mycobacterial infections. In sarcoidosis, all the features except caseation necrosis may be present, and differentiation from lupus vulgaris may be impossible, although the epithelioid cell foci tend to be more scattered and well defined, and are surrounded by relatively fewer lymphocytes and by reticulin. In tuberculoid leprosy, a neural and perineural involvement is the only distinguishing feature. In leishmaniasis, one must rely on finding the causative organism; similarly with blastomycosis and chromoblastomycosis. Tertiary syphilis shows more pronounced vascular changes and a plasma cell infiltrate.

A non-specific tuberculoid infiltrate, with irregular groups of epithelioid cells in an inflammatory infiltrate but without the formation of typical tubercles—as seen, for example, in rosacea or panniculitis—may also cause confusion.

References

1 Elder DE, Elenitsas R, Johnson BL Jr, Murphy GF. *Lever's Histopathology of the Skin*, 9th edn. Philadelphia, PA: Lippincott Williams and Wilkins, 2005: 561–4.
2 Adams DO. The structure of mononuclear phagocytes differentiating *in vivo*. *Am J Pathol* 1975; **80**: 1–16.
3 Regan W, Harley W. Orificial and pulmonary tuberculosis: report of a case. *Aust J Dermatol* 1979; **20**: 88–9.
4 McCray MK, Esterly NB. Cutaneous eruptions in congenital tuberculosis. *Arch Dermatol* 1981; **117**: 460–3.

Tuberculosis of the skin

The wide clinical spectrum of cutaneous tuberculosis is dependent on the route of infection (endogenous or exogenous), the immune status of the patient and whether or not there has been previous sensitization with tuberculosis. *M. tuberculosis* is the main organism responsible for cutaneous tuberculosis. Occasionally *M. bovis* and, rarely, bacille Calmette–Guérin (BCG), an attenuated form of *M. bovis,* are implicated.

Primary inoculation of the skin, usually following trauma, produces a tuberculous chancre in the non-immune host, whereas the so-called 'prosector's wart', or tuberculosis verrucosa cutis, occurs in primary infection in the immune host. Lupus vulgaris occurs mainly through haematogenous, lymphatic or contiguous spread but can occur following inoculation. Scrofuloderma results from contiguous involvement of the skin overlying tuberculosis in a deeper structure, most commonly lymphadenitis, bone or joint disease, or epididymitis. Metastatic tuberculous abscesses (tuberculous gumma) can occur due to haematogenous spread from a primary focus. This usually occurs when host resistance is suppressed, can be part of miliary tuberculosis, and results in single or multiple lesions. Orificial, perioral or perianal tuberculosis can occur following ingestion of mycobacteria from either swallowed respiratory secretions or from milk contaminated with *M. bovis*.

The tuberculids are thought to be the result of immunological reactions to haematogenously spread antigenic components of *M. tuberculosis,* usually occurring in individuals with high levels of immunity, with an extracutaneous source of *M. tuberculosis*. *M. tuberculosis*-complex DNA has been identified in some instances by PCR [1]. There are three main forms: lichen scrofulosorum, papulonecrotic tuberculid and erythema induratum of Bazin. A fourth type, nodular tuberculid, has recently been described [2,3].

The incidence of the different forms of cutaneous tuberculosis varies globally. Scrofuloderma was the commonest form in the most recent UK series [4], whereas lupus vulgaris occurred most commonly in a study from South Africa [5]. Serial reviews from Hong Kong have shown a change in the commonest form of skin tuberculosis in recent years from tuberculosis verrucosa cutis in 1968 [6] to the tuberculid erythema induratum in 1995 [7] and 2006 [8]. In India, scrofuloderma and lichen scrofulosorum [9,10] were the most frequently found forms in childhood, whereas lupus vulgaris was the commonest form in adults [10], and also in a series from Pakistan [11]. In Japan, there appears to be a trend towards increasing incidence of the tuberculids, particularly in older patients [12].

Classification

No entirely satisfactory classification exists, reflecting the difficulty in classifying a disease whose diverse manifestations are dependent on so many factors, such as the host's cell-mediated immunity and route of infection. In 1896, Darier separated proven tuberculosis lesions from the remainder. This led, inevitably, to a number of conditions being accepted as 'tuberculids' on circumstantial evidence. Confusion between true tuberculosis and a less specific 'tuberculoid' histology compounded the difficulty until the advent of effective antituberculosis drugs, when the lack of response of many of the so-called tuberculids, and their tendency to resolve spontaneously, led to a more critical evaluation of their aetiology. With the advent of new methods to detect *M. tuberculosis*-complex DNA, the position of the tuberculids has become clearer.

In 1981, Beyt *et al.* [13] classified the disease into inoculation tuberculosis, secondary tuberculosis, haematogenous tuberculosis and eruptive tuberculosis. This did not take into account immunological considerations. More recently, it has been suggested that a useful concept is the mycobacterial load [14] and that tuberculosis can be classified into multibacillary forms where there are abundant mycobacteria (e.g. scrofuloderma, tuberculous chancre and acute military tuberculosis) and paucibacillary forms where mycobacteria are difficult to isolate (e.g. lupus vulgaris, tuberculosis verrucosa cutis) (Table 31.2). In this classification the tuberculids would sit at the extreme end of the paucibacillary spectrum [15].

References

1 Degtiz K, Steidl M, Thomas P *et al.* Aetiology of tuberculids. *Lancet* 1993; **341**: 239–40.

Table 31.2 Classification of cutaneous tuberculosis.

Host immunity	Method of inoculation	Disease
Naïve host	Direct inoculation	Tuberculosis chancre (primary inoculation)
Multibacillary forms	Contiguous spread	Scrofuloderma
Low host immunity	Autoinoculation	Orificial tuberculosis
	Haematogenous spread	Acute miliary tuberculosis
		Tuberculous gumma (abscess)
Paucibacillary forms	Direct inoculation	Warty tuberculosis (verruca cutis)
High host immunity		Lupus vulgaris (some)
	Haematogenous spread	Lupus vulgaris
Tuberculids		Lichen scrofulosorum
		Papulonecrotic tuberculid
		Erythema induratum (Bazin)
		Nodular tuberculid

2 Hara K, Tsuzuki T, Takagi N *et al.* Nodular granulomatous phlebitis of the skin: a fourth type of tuberculid. *Histopathology* 1997; **30**: 129–34.
3 Motswaledi HM, Schulz EJ. *Int J Dermatol* 2006; **45**: 1337–40.
4 Yates VM, Ormerod LP. Cutaneous tuberculosis in Blackburn district (U.K.): a 15 year prospective series. *Br J Dermatol* 1997; **136**: 483–9.
5 Visser AJ, Heyl T. Skin tuberculosis as seen at Ga-Rankuwa Hospital. *Clin Exp Dermatol* 1993; **18**: 507–15.
6 Wong KO, Lee KP, Chui SF. Tuberculosis of the skin in Hong Kong (a review of 160 cases). *Br J Dermatol* 1968; **80**: 424–9.
7 Chang LY, Lo KK. Cutaneous tuberculosis in Hong Kong: a ten year retrospective study. *Int J Dermatol* 1995; **34**: 26–9.
8 Ho CK, Ho MH, Chong LY. Cutaneous tuberculosis in Hong Kong: an update. *Hong Cong Med J* 2006; **12**: 272–7.
9 Vashisht P, Sahoo B, Khurana N *et al.* Cutaneous tuberculosis in children and adolescents: a clinicohistiological study. *J Eur Acad Dermatol Venerol* 2006; **21**: 40–7.
10 Kumar B, Rai R, Kaur I *et al.* Childhood cutaneous tuberculosis: a study over 25 years from northern India. *Int J Dermatol* 2001; **40**: 26–32.
11 Bhutto AM, Solangi A, Khaskhely NM *et al.* Clinical and epidemiological observations of cutaneous tuberculosis in Larkana, Pakistan. *Int J Dermatol* 2002; **41**: 159–65.
12 Hamada M, Urabe K, Moroi Y *et al.* Epidemiology of cutaneous tuberculosis in Japan: a retrospective study from 1906 to 2002. *Int J Dermatol* 2004; **43**: 727–31.
13 Beyt BE, Ortbals DW, Santa Cruz DJ *et al.* Cutaneous mycobacteriosis: analysis of 34 cases with a new classification of the disease. *Medicine* 1981; **60**: 95–109.
14 Tigoulet F, Fournier V, Caumes E. Clinical forms of the cutaneous tuberculosis. *Bull Soc Pathol Exot* 2003; **96**: 362–7.
15 Bravo FG, Gotuzzo E. Cutaneous tuberculosis. *Clin Dermatol* 2007; **25**: 173–80.

Primary inoculation tuberculosis

Synonyms
- Tuberculous chancre
- Tuberculous primary complex

Definition. A tuberculous chancre is the result of the inoculation of *M. tuberculosis* into the skin of an individual without natural or artificially acquired immunity to this organism. The initial lesion contains many organisms (multibacillary).

Pathogenesis. The bacillus enters the skin through abrasions and minor injuries, usually on the face or limbs and commonly in children. Tuberculous chancres have followed ritual circumcision [1], infections with inadequately sterilized syringes [2], wounds [3], operations [4], ear-piercing, mouth-to-mouth artificial respiration [5] and tattooing [6]. In regions where tuberculosis is prevalent in the community, lesions may occur anywhere on the body from contact with sputum or following insect bites [7] or pyococcal infections of the skin. Sexual transmission has been reported [8,9]. *M. bovis* has recently been reported as the causative organism of a tuberculous chancre in a patient with HIV infection [10].

Incidence. This is believed to be an uncommon form of skin tuberculosis [11], but the incidence may be underestimated, particularly in areas with a high prevalence of tuberculosis.

Histopathology. The early changes are those of acute neutrophilic inflammation with necrosis occurring in both skin and affected lymph nodes. Numerous bacilli are present. After 3–6 weeks, the infiltrate becomes more granulomatous and caseation appears, coinciding with the disappearance of the bacilli.

Clinical features. The earliest lesions occur 2–4 weeks after inoculation and may be a brownish papule, nodule, or ulcer with an undermined edge and a granular haemorrhagic base. In time, the edge becomes firmer, and an adherent crust develops. When obvious trauma is absent, the initial lesion is often small, with a central silvery scale, and may show 'apple-jelly' nodules on diascopy. The lesions are commonest on the face, hands and lower extremities [12]. Apparent healing may conceal active infection below the surface and development of a cold abscess. Regional lymphadenopathy often develops after 4 to 8 weeks. Occasionally, lupoid nodules occur around the healed ulcer or deeper infection simulates scrofuloderma. Lesions closely simulating paronychia have been described on the fingers [13].

Mucosal lesions. Conjunctival lesions cause oedema and irritation [14]. Ulceration and oedema of the lids, with preauricular lymphadenitis, has been described [15]. Oral lesions are uncommon [5], but painless lesions, often misdiagnosed, may form in a tooth socket or on the gums.

Diagnosis. Any painless, non-healing ulcer or lesion with localized lymphadenopathy, especially in a child, should arouse suspicion. Acid-fast bacilli are seen in the primary skin lesion and in draining nodes in the early stages of the disease; antituberculosis therapy should be started without waiting for further proof. At this stage, the differential diagnosis includes tularaemia, sporotrichosis, or actinomycosis [16]. Bartonellosis (see Chapter 30), and especially *M. marinum* infections (p. 31.30), closely resemble primary tuberculosis, but are distinguished by their distribution or course, and cultural characteristics. The correct diagnosis is most likely to be overlooked in the anal and genital areas [1], particularly in children.

Course. If untreated the chancre will heal slowly over many months. Lupus vulgaris may develop at the site of the original lesion. Occasionally, haematogenous spread of the organism can occur with development of tuberculosis elsewhere, including

miliary tuberculosis [10]. Erythema nodosum developed in four out of 40 patients in one series [14]. The enlarged draining lymph nodes usually subside slowly, often calcifying; less often, cold abscesses and sinuses develop.

References

1 Bolgert M. La tuberculose cutanée. Historique, clinique et evolution thérapeutique. *Semin Hosp Paris* 1967; **43**: 868–88.
2 Valledor T, Exposito L, Costales F *et al.* Tuberculosis primaria de la piel en la infancia. *Rev Cubana Pediatr* 1954; **26**: 147–88.
3 Ara M, Seral C, Baselga C *et al*. Primary tuberculous chancre caused by *Mycobacterium bovis* after goring with a bull's horn. *J Am Acad Dermatol* 2000; **43**: 535–7.
4 Scuderi G, Cardia L. Nodular tuberculosis of the skin of the lids and the regional lymph glands. *Rev Bras Oftel* 1964; **23**: 183–92.
5 Heilman KM, Muschenheim C. Primary cutaneous tuberculosis resulting from mouth-to-mouth respiration. *N Engl J Med* 1965; **273**: 1035–6.
6 Horney DA, Gaither JM, Cauer R *et al.* Cutaneous inoculation tuberculosis secondary to jailhouse tattooing. *Arch Dermatol* 1985; **121**: 648–50.
7 Nenoff P, Rytter S, Schubert H. Multilocular inoculation tuberculosis of the skin after stay in Africa: detection by mycobacterial DNA using polymerase chain reaction. *Br J Dermatol* 2000; **143**: 226–8.
8 Bjornstad R. Tuberculous primary infection of the genitalia. *Acta Dermatol Venereol (Stockh)* 1947; **27**: 106–14.
9 Angus BJ, Yates M, Conlon C *et al.* Cutaneous tuberculosis of the penis and sexual transmission confirmed by molecular typing *Clin Infect Dis* 2001; **33**: E132–4.
10 Aquilar I, Grandos E, Palacios R *et al.* Fatal case of tuberculous chancre in a patient with AIDS. *J Infect* 2007; **54**: 137–9
11 Beyt BE, Ortbals DW, Santa Cruz DJ. Cutaneous mycobacteriosis: analysis of 34 cases with a new classification of the disease. *Medicine* 1981; **60**: 95–109.
12 Shanmugham-Pillai SM, Sarojini PA. Primary inoculation tuberculosis. *Indian J Dermatol Venereol Leprol* 1988; **54**: 97–8.
13 Goette DK, Jacobson KW, Doty RD. Primary inoculation tuberculosis of the skin. *Arch Dermatol* 1979; **114**: 567–9.
14 Miller FJW, Cashman JM. Peripheral tuberculosis lymphadenitis associated with a visible primary focus. *Lancet* 1955; **i**: 1286–9.
15 Kakakhel KU, Mohammad S. Tuberculosis of the conjunctiva, eyelid and periocular skin. *Pakistan J Ophthalmol* 1988; **4**: 37–40.
16 Pereira CA, Webber B, Orson JM. Primary tuberculous complex of the skin. *JAMA* 1976; **235**: 942.

Warty tuberculosis [1]

Synonym
- Tuberculosis verrucosa cutis

Definition. An indolent, warty, plaque-like form of tuberculosis occurring as a result of the inoculation of organisms into the skin of a previously infected patient who usually has a moderate or high degree of immunity. There are few organisms in the lesion (paucibacillary). It was the predominant form of tuberculosis in the Chinese in Hong Kong in the 1960s [2].

Pathogenesis. Lesions arise in three ways. The first is by accidental superinfection from extraneous sources: physicians, pathologists and post-mortem attendants are traditionally at risk (thus, 'anatomist's warts', 'prosector's warts', 'verruca necrogenica') [3]. The second is by autoinoculation with sputum in a patient with active tuberculosis. Finally, children and young adults, already infected and having some degree of immunity, may become infected from sputum by sitting on the ground or walking barefoot where the organism is present [4,5].



Fig. 31.4 Warty tuberculosis of the right ring and middle fingers with strong tuberculin reaction. (Courtesy of Dr V. Ramesh, SJ Hospital and VM Medical College, New Delhi, India.)

Histopathology. There is a striking pseudoepitheliomatous hyperplasia with superficial abscess formation. The intense, mixed infiltrate may show only sparse tuberculosis foci. Bacilli are seen only occasionally.

Clinical features. Lesions occur on those areas exposed to trauma and to infected sputum or other tuberculous material. In Europe, the lesions are most likely to occur on the hands, but in Asia the knees, ankles and buttocks are mainly involved [5,6].

The lesion starts as a small, symptomless, indurated, warty papule with a slight inflammatory areola. By gradual extension, a verrucose plaque is formed. Irregular extension at the edges leads to a serpiginous outline with finger-like projections. The centre may involute, leaving a white atrophic scar, or the whole lesion may form a massive, infiltrated papillomatous excrescence (Figs 31.4 & 31.5). The colour is purplish, red or brown. The consistency is generally firm, but there may be areas of relative softening. Pus may sometimes be expressed from these soft areas or from fissures. The lesions may resemble lupus vulgaris [7], but the sites are different. The appearance may be psoriasiform (Fig. 31.6) or keloidal. Occasionally, exudative and crusted features are predominant. Very rarely, sporotrichoid spread (Fig. 31.7) and also tuberculous lymphadenitis can occur [8].

Anomalous forms. Deeply destructive papillomatous and sclerotic forms may cause deformity of the limbs [9]. A generalized form, associated with papulonecrotic and lupoid lesions [10], occurs in patients with active disease, but is best regarded as a haematogenous form with a variable tissue response. An exuberant granulomatous form was described in the Chinese in Hong Kong [5] and is also seen in other Eastern races [6]. Tumour-like forms can occur [11].

Differential diagnosis. Subungual and digital lesions must be distinguished from warts, and those on the hands from keratoses.



Fig. 31.5 Warty tuberculosis sole of left foot with strong tuberculin reaction. (Courtesy of Dr V. Ramesh, SJ Hospital and VM Medical College, New Delhi, India.)



Fig. 31.6 Warty tuberculosis of right thigh. (Courtesy of Dr V. Ramesh, SJ Hospital and VM Medical College, New Delhi, India.)

Blastomycosis, chromoblastomycosis and actinomycosis may simulate exuberant forms, and crusted lesions may resemble leishmaniasis. Tertiary syphilis may be confused when the central scarring is surrounded by a serpiginous edge. Hypertrophic lichen planus and lichenification occasionally cause difficulty, but lesions of these disorders are multiple or itchy. Lupus vulgaris is not usually hyperkeratotic and shows apple-jelly nodules on diascopy (Chapter 5).

The lesions caused by NTM can usually only be distinguished by microbiological culture. *M. marinum* poses particular difficulties (p. 31.30). Pyoderma due to other organisms may simulate this condition; the histology differs only by the absence of tuberculoid foci.

Course. The condition responds to antituberculosis treatment; without it, extension is usually extremely slow and lesions may remain virtually inactive for months or years [9,12,13].



Fig. 31.7 Sporotrichoid spread. (Courtesy of Dr V. Ramesh, SJ Hospital and VM Medical College, New Delhi, India and the Editor of *Dermatologic Clinics*.)

Spontaneous remission may occur and usually results in atrophic scars. Active disease of other organs should be looked for, as bone, glandular or pulmonary tuberculosis may coexist [5]. Miliary tuberculosis has also been reported [14].

References

1 Grange JM, Noble WC, Yates MD *et al.* Inoculation mycobacterioses. *Clin Exp Dermatol* 1988; **13**: 211–20.

2 Lia-Yin Chong, Kuen-Kong Lo. Cutaneous tuberculosis in Hong Kong: a 10 year retrospective series. *Int J Dermatol* 1995; **34**: 26–9.

3 Lundgren R, Norman E, Asbert I. Tuberculosis infection transmitted at autopsy. *Tubercle* 1987; **68**: 147–50.

4 Mitchell PG. Tuberculosis verrucosa cutis among Chinese in Hong Kong. *Br J Dermatol* 1954; **66**: 444–8.

5 Wong KO, Lee KP, Chin SF. Tuberculosis of the skin in Hong Kong. *Br J Dermatol* 1968; **80**: 424–9.

6 Goh YS, Ong BH, Rajan VS. Tuberculosis cutis in Singapore: a two year experience. *Sing Med J* 1974; **15**: 223–6.

7 Michelson HE. Criteria for the diagnosis of certain tuberculodermas. *JAMA* 1948; **138**: 721–6.

8 Pereira MB, Gnomes MK, Pereira F. Tuberculosis verrucosa cutis associated with tuberculous lymphadenitis. *Int J Dermatol* 2000; **39**: 856–8.

9 Foo CCI, Tan HH. A case of tuberculosis verrucosa cutis—undiagnosed for 44 years and resulting in fixed-flexion deformity of the arm. *Clin Exp Dermatol* 2005; **30**: 149–51.

10 Irgang S. Ulcerative cutaneous lesions in sarcoidosis. *Br J Dermatol* 1955; **67**: 255–60.

11 Iizwa O, Aiba S, Tagami H. Tuberculosis verrucosa cutis in a tumour like form. *Br J Dermatol* 1991; **125**: 79–80.

12 Gruber PC, Whittam LR, du Vivier A. Tuberculosis verrucosa cutis on the sole of the foot. *Clin Exp Dermatol* 2002; **27**: 188–91.

13 Massellis P, Gasparini G, Caputo R *et al.* Tuberculosis verrucosa cutis which remained undiagnosed for forty-three years. *Dermatology* 1995; **191**: 145–8.

14 Padmavathy L, Lakshmana RL, Ethirajan N *et al.* Tuberculosis verrucosa cutis (TBVC)-foot with miliary tuberculosis. *Ind J Tuberculosis* 2007; **54**: 145–8.



Fig. 31.8 Scrofuloderma associated with tuberculosis of the axillary glands occurring in a 74-year-old Caucasian man prior to antituberculous therapy. (Courtesy of the Editor of the *British Journal of Dermatology*.)

Scrofuloderma

Synonym
- Tuberculosis colliquativa cutis

Definition and pathogenesis. Scrofuloderma results from the involvement and breakdown of the skin overlying a contiguous tuberculosis focus. This is usually a lymph gland, an infected bone or joint, or a lacrimal gland or duct (Figs 31.8 & 31.9) [1]. In one report, which included details of 23 patients with scrofuloderma [2], the condition occurred most commonly after cervical gland infection, less often with axillary, inguinal, epitrochlear and retroauricular gland infection, and in only two patients after infection of the tibia and fibula. The face and neck were again the most frequently affected sites for lesions in another series of 27 patients [3]. It was consistently the commonest form of cutaneous tuberculosis in childhood and adolescents in three large series from India [4–6] and in another series of adults from the UK [7].

Histopathology. There is usually an ulcerated dermal abscess with an ill-defined histiocytic component. Marked caseation necrosis, in which there are usually numerous bacteria, is seen in the deeper structures [5]. Tubercle bacilli can usually be easily isolated from the pus.

Clinical features. A bluish-red nodule overlying the infected gland or joint breaks down to form undermined ulceration with granulating tissue at the base. Numerous fistulae may intercommunicate beneath ridges of a bluish skin. Progression and scarring produce irregular adherent masses, densely fibrous in places and fluctuant or discharging in others. Excessive granulation tissue may give rise to fungating tumours. Sporotrichoid spread has been reported [8]. After healing, characteristic puckered scarring marks the site of the infection. Sweet's syndrome has been described in association with scrofuloderma [9].

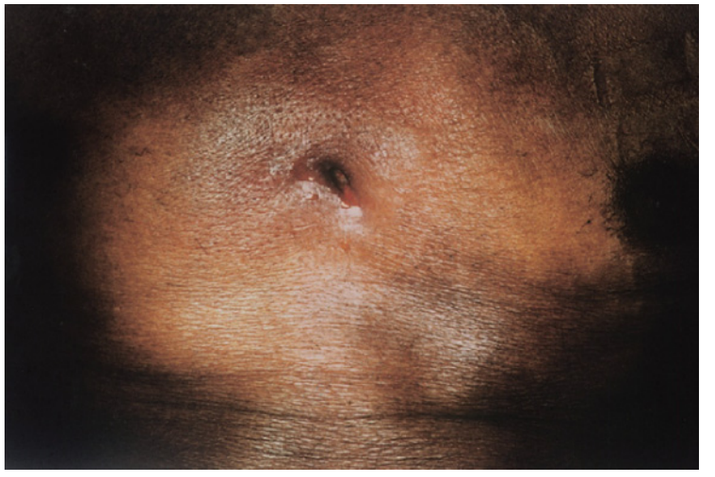


Fig. 31.9 Scrofuloderma associated with sternal tuberculosis occurring in a 62-year-old Pakistani man. (Courtesy of the Editor of the *British Journal of Dermatology*.)

Diagnosis. The nature of the underlying lesion is usually evident. The diagnosis is confirmed bacteriologically. *M. avium* complex lymphadenitis, and the more benign *M. scrofulaceum*, need to be excluded by culture [10]. Other differential diagnoses include sporotrichosis, actinomycosis, syphilitic gummas and hidradenitis suppurativa.

Course. Spontaneous healing can occur, but the course is very protracted and leaves typical, cord-like scars.

References

1 Tur E, Brenner S, Meiron Y. Scrofuloderma (tuberculosis colliquativa cutis). *Br J Dermatol* 1996; **134**: 350–2.
2 Sehgal VN, Srivastava G, Khurana VK *et al.* An appraisal of epidemiologic, clinical, bacteriologic, histopathologic and immunologic parameters in cutaneous tuberculosis. *Int J Dermatol* 1987; **26**: 521–6.
3 Ramesh V, Misra RS, Jain RK. Secondary tuberculosis of the skin: clinical features and problems in laboratory diagnosis. *Int J Dermatol* 1987; **26**: 578–81.
4 Kumar B, Rai R, Kaur I *et al.* Childhood cutaneous tuberculosis: a study over 25 years from northern India. *Int J Dermatol* 2001; **40**: 26–32.
5 Vashist P, Sahoo B, Kurana K *et al.* Cutaneous tuberculosis in children and adolescents: a clinicohistological study. *J Eur Acad Dermatol Venerol* 2007; **21**: 40–7.
6 Phandi D, Reddy BSN, Chowdhary S *et al.* Cutaneous tuberculosis in Indian children: the importance of screening for involvement of internal organs. *J Eur Acad Dermatol Venerol* 2004; **18**: 546–51.
7 Yates VM, Ormerod LP. Cutaneous tuberculosis in Blackburn district (U.K.): a 15 year prospective series. *Br J Dermatol* 1997; **136**: 483–9.
8 Ramesh V. Sporotrichoid cutaneous tuberculosis. *Clin Exp Dermatol* 2007; **32**: 680–2.
9 Mahaisaviriya P, Chaiprasert A, Manonukul J *et al.* Scrofuloderma and Sweet's syndrome. *Int J Dermatol* 2002; **41**: 28–31.



Fig. 31.10 Periorificial tuberculosis. Crusty erosions are evident on the gingival surface and mucosal surface of the lip. (Courtesy of Dr F. Nachbar, Ludwig Maximilian University, Munich, Germany, and the Editor of the *British Journal of Dermatology*.)



Fig. 31.11 Periorificial tuberculosis with granulomatous enlargement of the upper lip and lesions extending to the nose. The tongue shows erythematous erosions and ulceration. (Courtesy of Dr V. Ramesh, SJ Hospital and VM Medical College, New Delhi, India and the Editor of *Paediatric Dermatology*.)

10 Gopinathan R, Pandit D, Joshi J *et al.* Clinical and morphological variants of cutaneous tuberculosis and its relationship to mycobacterium species. *Ind J Med Microbiol* 2001; **19**: 193–6.

Orificial tuberculosis

Synonyms
- Tuberculosis cutis orificialis
- Acute tuberculous ulcer

Definition. Tuberculous infection of the mucosa or the skin adjoining orifices in a patient with advanced internal tuberculosis. It is now very rare. It occurs particularly in those with pulmonary, intestinal or anogenital disease [1]. It is a multibacillary form of cutaneous tuberculosis. Most of those affected are males.

Pathogenesis. This is normally a form of autoinoculation tuberculosis, although extraneous sources are occasionally responsible [1]. The lesions occur where there is advanced pulmonary, intestinal or genitourinary disease from which large numbers of mycobacteria are shed and inoculated into the mucous membranes of orifices. In general, local trauma determines the site of the lesions.

Histopathology. The histopathological changes are variable and are often of non-specific inflammatory type, but tubercle bacilli are usually present.

Clinical features. The affected patient is usually a severely ill adult with advanced visceral tuberculosis who may have impaired cell-mediated immunity. Lesions occur most commonly in the mouth (Fig. 31.10). Small oedematous red nodules rapidly break down to form painful, shallow ulcers with undermined bluish edges. The ulcers seldom exceed 2 cm in diameter and show no tendency to heal spontaneously; they may involve the tongue and may be associated with granulomatous swelling of the lips (Fig. 31.11)

In a series of 42 patients with orifacial disease, 69% had oral ulceration, 21% had bone involvement and 14% salivary gland and/or lymph-node involvement [2]. A tooth socket may be involved after dental extraction. Other sites include the genitalia [3], around the anus in those with intestinal tuberculosis, and other locations adjacent to an orifice draining an active tuberculous infection.

Diagnosis. Pain is the cardinal feature. There is usually evidence of disease elsewhere; 79% of one series had associated pulmonary disease [2]. The diagnosis is confirmed bacteriologically. Polymerase chain amplification of mycobacterium-specific gene segment has been demonstrated and may speed up diagnosis [4]. The tuberculin test is variable; in the later stages at least, the patient is often anergic.

Treatment. The source of the local infection must be traced and antituberculosis therapy instituted.

References

1 Ratcliff DP. Tuberculosis of the mandible. *Br Dent J* 1973; **135**: 122–4.
2 Mignogna MD, Muzio LL, Favia G *et al.* Oral tuberculosis: a clinical evaluation of 42 cases. *Oral Dis* 2000; **6**: 25–30.
3 Fejer A. Sur la question de la tuberculose des organes génitaux à propos de deux cas très rares. *Ann Dermatol Vénéréol* 1989; **29**: 488–505.
4 Nachbar F, Classen V, Nachbar T *et al.* Oral tuberculosis: detection by polymerase chain reaction. *Br J Dermatol* 1996; **135**: 106–9.

Haematogenous tuberculosis
Miliary tuberculosis

Definition and pathogenesis. Miliary tuberculosis of the skin occurs in association with generalized miliary tuberculosis and is due to haematogenous dissemination of mycobacteria into the skin. It is rare and usually affects young children or immunosuppressed patients such as those with concurrent HIV infection [1,2] or following viral infections such as measles [3].

Clinical features. The skin manifestations are often deceptive—profuse crops of minute bluish papules, vesicles, pustules or haemorrhagic lesions in a patient who is obviously ill. The vesicles may become necrotic to form small ulcers [4]. Erythematous nodules have been described [5]. The underlying disease may not be manifest, and the diagnosis is sometimes only made by the biopsy of a skin lesion showing acid-fast bacilli [6]. A search should be made for evidence of internal tuberculous infection [7].

Diagnosis. The development of an unusual exanthematic rash in an ill person with known tuberculosis or tuberculous contacts suggests the diagnosis, which should be confirmed by biopsy. Antituberculosis therapy should be started immediately if there is a strong suspicion. The tuberculin test is negative.

Course. The prognosis is poor, but response to treatment is possible.

References

1 Libraty DH, Byrd TF. Cutaneous miliary tuberculosis in the AIDS era: case report and review. *Clin Infect Dis* 1996; **23**: 706–10.

2 High WA, Evans CC, Hoang MP. Cutaneous miliary tuberculosis in two patients with hiv infection. *J Am Acad Dermatol* 2004; **50** (5 Suppl.): S100–3.

3 Schermer DR, Simpson CG, Haserick JR *et al.* Tuberculosis cutis miliaris acuta generalisata. *Arch Dermatol* 1969; **99**: 64–9.

4 del Giudice P, Bernard E, Perrin C *et al.* Unusual cutaneous manifestations of miliary tuberculosis. *Clin Infect Dis* 2000; **30**: 201.

5 Kounis NG, Constantinidis K. Unusual tuberculous skin manifestations. *Practitioner* 1979; **222**: 390–3.

6 Kennedy C, Knowles GK. Miliary tuberculosis presenting with skin lesions. *BMJ* 1975; **3**: 356.

7 Rietbroek RC, Dahlmans RP, Smedts F *et al.* Tuberculosis cutis miliaris disseminata as a manifestation of miliary tuberculosis: literature review and report of a case of recurrent skin lesions. *Rev Infect Dis* 1991; **13**: 265–9.

Lupus vulgaris

Definition. A chronic, progressive, post-primary, paucibacillary form of cutaneous tuberculosis, occurring in a person with a moderate or high degree of immunity. The characteristic lesion is a plaque, composed of soft, reddish-brown papules, the appearance on diascopy being said to resemble apple jelly. The edges of the lesion gradually extend in some areas and heal with scarring in others, sometimes causing considerable tissue destruction over many years.

Incidence. Lupus vulgaris was the most common form of tuberculosis in adults in published series from India, South Africa and Pakistan [1–3]. In Tunisia there has been an increase in the proportion of cases with lupus vulgaris, presumably reflecting greater immunity to tuberculosis in the community [4,5]. The condition appears to be more common in women than men.

Pathogenesis. Lupus vulgaris originates from an underlying focus of tuberculosis, typically in a bone, joint or lymph node, and arises by either contiguous extension of the disease from underlying affected tissue or by haematogenous or lymphatic spread. Sometimes the underlying focus is not clinically apparent, and in such cases reactivation of a latent cutaneous focus secondary to previous silent bacteraemia is postulated [6]. It can also arise after exogenous inoculation [7] or as a complication of BCG vaccination [8].

Lupus vulgaris is typically a paucibacillary form of cutaneous tuberculosis, which often makes successful culture difficult. In one series, bacilli were cultured from only 6% of nearly 4000 patients [9]. Concomitant diagnosis by both culture and detection of mycobacterial DNA using PCR has been reported and may be useful where small numbers of mycobacteria are present [10].

Histopathology. The histological features are variable. Normally, tubercles with scanty or absent central caseation, surrounded by epithelioid histiocytes and multinucleate giant cells, are present in the superficial dermis. Peripheral lymphocytes are often prominent. Occasionally, tubercle bacilli may be numerous [11]; more often, they are hard to demonstrate. The epidermis may be ulcerated with an associated mixed inflammatory infiltrate, atrophic or acanthotic. If the acanthosis is severe, giving rise to pseudoepitheliomatous hyperplasia, differentiation from squamous cell carcinoma may be a problem [12].

Clinical features. Lupus vulgaris commonly appears in normal skin as a solitary lesion, although it can arise at the site of a primary inoculation such as after a tattoo [6], in the scar of scrofuloderma or at the site of a BCG vaccination [8]. In Europe, over 80% of lesions are on the head and neck, particularly around the nose [9,13]. Next in frequency are the arms and legs, but involvement of the trunk is uncommon. In India, the face is affected less often and the buttocks and trunk more frequently [14]. In children in developing countries the lesions are often on the lower limbs and buttocks, usually occur by re-inoculation and may relate to playing without clothing or shoes [15].

The initial lesion is a small, reddish-brown, flat plaque of soft, almost gelatinous, consistency. On diascopy, the diagnostic apple-jelly nodules may be demonstrated. The lesion gradually becomes elevated, infiltrated and brown and grows by slow peripheral extension to become gyrate or discoid in shape with areas of atrophy. There is usually only a single lesion, except in disseminated forms, which usually occur in association with active pulmonary tuberculosis [16]. Sporotrichoid-like spread has also been reported [17].

The many clinical forms fall into five general patterns, depending on the local tissue response to the infection, but atypical forms are becoming more common.

1 **Plaque form** (Fig. 31.12 a,b,c,d). Flat plaques with irregular or serpiginous edge. The surface of the lesion may be smooth or covered with psoriasiform scale. Large plaques may show irregular areas of scarring with islands of active lupus tissue. The edge often becomes thickened and hyperkeratotic.

2 **Ulcerative and mutilating forms** (Fig. 31.13). Scarring and ulceration predominate. Crusts form over areas of necrosis. The deep tissues and cartilage are invaded and contractures and deformities occur. In milder forms, keratotic plugs overlying pinpoint ulcers are associated with slow scar formation.

3 **Vegetating form** (Fig. 31.14). This is characterized by marked infiltration, ulceration and necrosis with minimal scarring.



Fig. 31.12 (a) A solitary plaque of lupus vulgaris on the left cheek. (b) Lupus vulgaris of the face with lesions resembling discoid lupus erythematosis. Note strong tuberculin reaction. (c) Lupus vulgaris showing typical central atrophy and serpiginous edge. (d) Lupus vulgaris showing thickened and hypertrophic edge. (Courtesy of Dr V. Ramesh, SJ Hospital and VM Medical College, New Delhi, India.)

Mucous membranes are invaded and cartilage is slowly destroyed. When the nasal or auricular cartilage is involved, extensive destruction and disfigurement ensue.

4 **Tumour-like forms** (Fig. 31.15). The hypertrophic form presents either as soft tumour-like nodules or as epithelial hyperplasia with the production of hyperkeratotic masses. In the 'myxomatous' form, huge soft tumours occur predominantly on the ear lobes, which become grossly enlarged. Lymphoedema and vascular dilatation are sometimes marked.

5 **Papular and nodular forms.** Multiple lesions occur simultaneously in disseminated lupus—true 'miliary lupus'. This usually occurs after temporary immunosuppression as described in post-exanthematous forms, such as after measles [18].

Mucosal involvement. The nasal, buccal or conjunctival mucosa may become involved, either primarily by a papule, nodule or ulcer, or by spread from a contiguous skin lesion. Nasal lesions start as nodules, which bleed easily and then ulcerate, leading sometimes to cartilage destruction. A dry rhinitis may be an early symptom. Granulating, vegetating or ulcerating lesions of the buccal mucosa, palate, gingiva or oropharynx may occur by direct extension or by lymphatic spread from nasal lesions. These can produce stenosis of the larynx and scarring deformities of the soft palate.

Prognosis and complications. Despite long periods of indolence, the natural course of an untreated lesion is inexorably progressive.



Fig. 31.13 Nasal deformity as a late sequela of lupus vulgaris. (Courtesy of Dr V. Ramesh, SJ Hospital and VM Medical College, New Delhi, India.)



Fig. 31.14 Vegetating lupus vulgaris on the nose. (Courtesy of Dr J.E. Bothwell, Barnsley District General Hospital, Barnsley, UK.)

Scarring, contractures and tissue destruction are prominent features. The scars are usually thin, white and smooth, but are unstable and may break down or become keloidal. Active lupus vulgaris frequently reappears in scar tissue. Contraction may lead to ectropion or microstomia, which may require plastic surgery.

Squamous cell and, less commonly, basal cell carcinomas, or sarcomas, may occur insidiously in up to 8% of patients [19,20] and may be confused with renewed activity of the lupus itself (Figs 31.16 & 31.17).

Diagnosis. Because of its rarity in the UK, the index of suspicion may be low [21]. The well-established plaque with central scarring presents few difficulties, but in the early stage lupus may easily be confused with lymphocytoma, Spitz naevus or lupus erythematosus. In older patients, syphilis must be excluded. The histological features and culture results will differentiate lupus vulgaris



Fig. 31.15 Tumour like form of lupus vulgaris on the ear lobe and face. (Courtesy of Dr V. Ramesh, SJ Hospital and VM Medical College, New Delhi, India.)

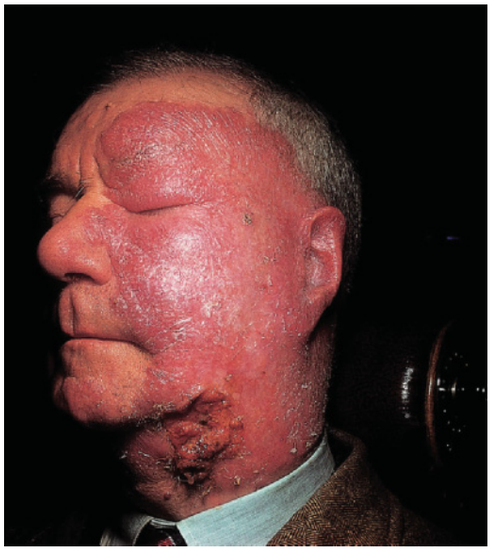


Fig. 31.16 Squamous cell carcinoma of the neck in a patient with lupus vulgaris of many years' duration.

from the deep mycoses, which may closely resemble the vegetating and crusted type. The lupoid form of leishmaniasis may be impossible to distinguish clinically. On the face, lupus may be mistaken for rosacea [21] or for a port-wine stain [22], and on an extremity for other mycobacterial infections.

Leprosy and sarcoidosis, however, are the chief causes of diagnostic difficulty. The nodules of leprosy are firmer, and other signs are present. The nodules of sarcoidosis resemble grains of sand rather than 'apple jelly': this applies to the feel on probing rather than to the colour, which is often greyish.



Fig. 31.17 A basal cell carcinoma arising in an old area of lupus vulgaris.

Lupus vulgaris may resemble psoriasis, but is more infiltrated and usually solitary; Bowen's disease can resemble both. Lupus vulgaris of the perianal area mimicking lichen simplex chronicus has also been reported [23]. Warty tuberculosis usually affects the hand and is more scaly and verrucous than lupus and the histological features are different.

A therapeutic trial of antituberculous therapy may be considered in cases where the diagnosis is difficult. A clinical response should be expected within 4–6 weeks [24].

Treatment. Standard triple antituberculosis therapy should be given. Isoniazid has in the past been used as monotherapy, but this practice is strongly discouraged, as up to 26% of patients have clinical evidence of tuberculosis at other sites [1].

References

1 Kumar B, Muralidhar S. Cutaneous tuberculosis: a twenty-year prospective series. *Int J Tuberc Lung Dis* 1999; **3**: 494–500.

2 Visser AJ, Heyl T. Skin tuberculosis as seen at Ga-Rankuwa Hospital. *Clin Exp Dermatol* 1993; **18**: 507–15.

3 Bhutto AM, Solangi A, Khaskhely NM *et al.* Clinical and epidemiological observations of cutaneous tuberculosis in Larkana, Pakistan. *Int J Dermatol* 2002; **41**: 159–65.

4 Hay RJ. Cutaneous infection with *Mycobacterium tuberculosis*: how has this altered with the changing epidemiology of tuberculosis? *Curr Op Infect Dis* 2005; **18**: 93–5.

5 Fenniche S, Ben Jennet Marrak H, Khayat O. Cutaneous tuberculosis: anatomoclinical features and clinical course. *Ann Dermatol Venereol* 2003; **130**: 1021–4.

6 Marcoval J, Servitje O, Moreno A *et al.* Lupus vulgaris: clinical, histopathologic and bacteriologic study of 10 cases. *J Am Acad Dermatol* 1992; **26**: 404–7.

7 Ghorpade A. Tattoo inoculation lupus vulgaris in two Indian ladies. *J Eur Acad Dermatol Venerol* 2006; **20**: 476–7.

8 Tan HH, Seow CS. A review of cutaneous granulomas and lupus vulgaris following BCG vaccination in a skin hospital in Singapore. *Ann Acad Med Singapore* 2002; **31**: 663–5.

9 Horwitz O. The localization of lupus vulgaris of the skin. *Acta Tuberc Scand* 1960; **39** (Suppl. 49): 1–137.

10 Steidl M, Neubert U, Volkenandt M *et al.* Lupus vulgaris confirmed by polymerase chain reaction. *Br J Dermatol* 1993; **129**: 314–8.

11 Duhra P, Grattan CE, Ryatt KS. Lupus vulgaris with numerous tubercle bacilli. *Clin Exp Dermatol* 1988; **13**: 31–3.

12 McKee PH. *Pathology of the Skin*, 2nd edn. St Louis: Mosby-Wolfe, 1996: 4.36–40.

13 Kanan MW, Ryan TJ. The localisation of granulomatous diseases and vasculitis in the nasal mucosa. In: Ryan TJ, ed. *Microvascular Injury*. London: Saunders, 1976: 195–220.

14 Sehgal VN, Waugh SA. Cutaneous tuberculosis. Current concepts. *Int J Dermatol* 1990; **29**: 237–52.

15 Vashist P, Sahoo B, Kurana K *et al.* Cutaneous tuberculosis in children and adolescents: a clinicohistological study. *J Eur Acad Dermatol Venerol* 2007; **21**: 40–7.

16 Senol M, Ozcan A, Aydin A *et al.* Disseminated lupus vulgaris and papulonecrotic tuberculid: case report. *Paediatr Dermatol* 2000; **17**: 133–5.

17 Ramesh V. Sporotrichoid cutaneous tuberculosis. *Clin Exp Dermatol* 2007; **32**: 680–2.

18 Ramesh V, Makkar R, Sood N. Lupus vulgaris postexanthematicus—a rare variant of lupus vulgaris with sarcoid-like histopathology. *Clin Exp Dermatol* 2005; **30**: 189–90.

19 Motswaledi MH, Doman C. Lupus vulgaris with squamous cell carcinoma. *J Cutan Pathol* 2007; **34**: 939–41.

20 Forstrum L. Carcinomatous change in lupus vulgaris. *Ann Clin Res* 1969; **1**: 213.

21 Warin AP, Wilson-Jones E. Cutaneous tuberculosis of the nose with unusual clinical and histological features leading to delay in the diagnosis. *Clin Exp Dermatol* 1977; **2**: 235–42.

22 Cotterill JA. Lupus vulgaris simulating a port wine stain. *Br J Dermatol* 1988; **119**: 127–8.

23 Phandi D, Reddy BS. Lupus vulgaris mimicking lichen simplex chronicus. *J Dermatol* 2001; **28**: 328–31.

24 Ramam M, Mittal R, Ramesh V. How soon does cutaneous tuberculosis respond to treatment? Implications for a therapeutic test of diagnosis. *Int J Dermatol* 2005; **44**: 121–4.

Metastatic tuberculous abscess

Synonym
- Tuberculous gumma

Definition. This form of tuberculosis is the result of haematogenous dissemination from a primary focus during periods of lowered resistance, resulting in single or multiple lesions. It is seen particularly in malnourished children or in patients who are immunosuppressed [1], and has been noted after local trauma [2] and in association with underlying lymphoma [3].

Histopathology. The features are those of tuberculous granulation tissue, with necrosis and abscess formation. Tubercle bacilli can usually be isolated from the pus.

Clinical features. A tuberculous gumma presents either as a firm subcutaneous nodule or as a fluctuant abscess (Fig. 31.18). The extremities are more often affected than the trunk. The overlying skin may break down to form an undermined ulcer, often with sinuses [3,4] (Fig. 31.19). Lesions may be multiple. Unusual and transitional forms may occur [5]. Rarely, multiple abscesses have been noted during treatment of miliary tuberculosis [6].



Fig. 31.18 Tuberculous gumma (metastatic cold abscess) in a patient with a pleural effusion. (Courtesy of Dr V. Ramesh, SJ Hospital and VM Medical College, New Delhi, India.)



Fig. 31.19 Multiple metastatic abscesses (gummas) left arm. (Courtesy of Dr V. Ramesh, SJ Hospital and VM Medical College, New Delhi, India.)

Lesions causing carpal tunnel syndrome have been well documented [7].

Diagnosis. The diagnosis is confirmed by culture.

References

1 Maejima H, Arai S, Ebata T *et al.* Tuberculous gumma associated with idiopathic thrombocytopaenic purpura: report of a Japanese female patient. *J Dermatol* 2007; **34**: 86–91.

2 Vidal D, Barnadas M, Peres M *et al.* Tuberculous gumma following venepuncture. *Br J Dermatol* 2001; **144**: 601–3.

3 Kalaria VJ, Kapila R, Schwartz RA. Tuberculous gumma (cutaneous metastatic tuberculous abscess) with underlying lymphoma. *Cutis* 2000; **66**: 277–9.

4 Difonzo EM, Lotti C, Salvini S *et al.* Tuberculous gumma in a patient with cervical lymphadenitis *Int J Dermatol* 2006; **45**: 1467–8.

5 Bolgert M. La tuberculose cutanée. Historique, clinique, et evolution thérapeutique. *Semin Hosp Paris* 1967; **43**: 868–88.

6 Mert A, Bilir M, Osturk R *et al.* Tuberculous subcutaneous abscesses developing during miliary tuberculous therapy. *Scand J Infect Dis* 2000; **32**: 37–9.

7 Lee KE. Tuberculosis presenting as carpal tunnel syndrome. *J Hand Surg (Am)* 1985; **10**: 242–5.

Unusual forms of cutaneous tuberculosis

Unusual forms of cutaneous tuberculosis are well recognized. Some of these have already been mentioned as anomalous forms of the various clinical entities. There remain a number of reported cases that are difficult to fit into any one category. They often resemble lupus vulgaris in histology and morphology, though not in site or behaviour [1,2]. Some of the bizarre manifestations seen in the past were assumed to be due to double infections, poor natural immunity or other coexistent disease as modifying factors.

Gangrenous or vegetating forms with underlying lung or glandular disease have been reported [3]. Patients with coexisting HIV infection may have atypical and widespread skin lesions [4]. Correct diagnosis requires a high index of suspicion and biopsy and culture of any unusual skin lesions. Tuberculous cellulitis-like lesions have been reported in a patient who was diabetic and taking oral corticosteroids [5]. Sehgal *et al.* reported patients with multifocal guttate tuberculosis verrucosa cutis and necklace lupus vulgaris [6].

Suspicion of a tuberculous aetiology should be aroused by painless abscess formation, indolent ulcers with bluish undermined edges, or by nodular, plaque-like or necrotic lesions that defy easy classification. It is not enough to demonstrate acid-fast bacilli—culture or PCR is necessary to confirm the species of mycobacterium. A therapeutic trial may be necessary and desirable, while awaiting laboratory results [7].

References

1 Bolgert M. La tuberculose cutanée. Historique, clinique et evolution thérapeutique. *Semin Hosp Paris* 1967; **43**: 868–88.

2 Brown FS, Anderson RH, Burnett JW. Cutaneous tuberculosis. *J Am Acad Dermatol* 1982; **6**: 101–6.

3 Dogliotti R, Leibowitz M, Smith E *et al.* Lupus vulgaris: an unusual fungating and ulcerated form in a black South African. *Int J Dermatol* 1979; **18**: 749–50.

4 Inwald D, Nelson M, Francis N *et al.* Cutaneous manifestations of mycobacterial infection in patients with AIDS. *Br J Dermatol* 1994; **130**: 111–4.

5 Lee NH, Choi EH, Lee WS *et al.* Tuberculous cellulites. *Clin Exp Dermatol* 2000; **25**: 222–3.

6 Sehgal VN, Srivastava G, Ahuja P *et al.* Unusual clinical manifestations of cutaneous tuberculosis. *J Dermatol* 1988; **15**: 334–8.

7 Ramam M, Mittal R, Ramesh V. How soon does cutaneous tuberculosis respond to treatment? Implications for a therapeutic test of diagnosis. *Int J Dermatol* 2005; **44**: 121–4.

Congenital tuberculosis [1–3]

This is now exceedingly rare. The skin manifestations may be discrete, erythematous lesions, with a central necrotic dell, occurring in infants with a febrile systemic illness.

References

1 McCray MK, Esterly NB. Cutaneous eruptions in congenital tuberculosis. *Arch Dermatol* 1981; **117**: 460–4.

2 Voyce MA, Hunt AC. Congenital tuberculosis. *Arch Dis Child* 1966; **41**: 299–300.

3 Sood M, Trehan A, Arora S *et al.* Congenital tuberculosis manifesting as cutaneous disease. *Pediatr Infect Dis J* 2000; **19**: 1109–11.

Malignant disease and cutaneous tuberculosis

Malignant disease may complicate or be associated with tuberculosis of the skin. Squamous cell and basal cell carcinomas may arise in areas of long-standing lupus vulgaris [1–3]. They may only be detected when one area of the lesion fails to respond to treatment. A plasmacytolymphoma has also been reported [4]. A pre-existing, well-controlled case of lupus vulgaris became fulminant with the onset of the lymphoma [5]. Erythema gyratum repens, usually seen in association with an internal malignancy, has been reported with pulmonary tuberculosis [6].

References

1 Haim S, Friedman-Birnbaum R. Cutaneous tuberculosis and malignancy. *Cutis* 1978; **21**: 643–7.
2 Motswaledi MH, Doman C. Lupus vulgaris with squamous cell carcinoma. *J Cutan Pathol* 2007; **34**: 939–41.
3 Forstrum L. Carcinomatous change in lupus vulgaris. *Ann Clin Res* 1969; **1**: 213.
4 Harrison PV, Marks JM. Lupus vulgaris and cutaneous lymphoma. *Clin Exp Dermatol* 1980; **5**: 73–7.
5 Schein PS, Vickers HR. Lupus vulgaris and Hodgkin's disease. *Arch Dermatol* 1972; **105**: 244–6.
6 Barber PV, Doyle L, Vickers DM. Erythema gyratum repens with pulmonary tuberculosis. *Br J Dermatol* 1978; **98**: 465–8.

The tuberculids

Definitions. The concept of tuberculids was introduced by Darier in 1896. In contrast to true skin tuberculosis, tuberculids were explained as a hypersensitivity reaction to *M. tuberculosis* or its products in a patient with significant immunity. The main features of tuberculids are a positive tuberculin test, evidence of manifest or past tuberculosis and a positive response to antituberculous therapy. There is virtually always absence of bacilli in skin biopsy specimens and culture, although PCR has detected mycobacterial DNA in some forms. Several conditions once thought to represent tuberculids are now classified as variants of rosacea.

True tuberculids can be grouped as follows:

- Micropapular: lichen scrofulosorum
- Papular: papulonecrotic tuberculid
- Nodular: erythema induratum of Bazin; nodular tuberculid.

Aetiology. The pathogenesis of the tuberculids is poorly understood. All tuberculids are thought to be due to haematogenous spread of bacilli in a person with a moderate or high degree of immunity against *M. tuberculosis*. However, it is not usually possible to detect the tubercle bacilli in tuberculids, either because they are present in a fragmented form or because they have been destroyed at the site of the tuberculids by immunological mechanisms [1]. Mycobacterial DNA has been detected in significant numbers of the papular and nodular forms of tuberculid [2–4], but not as yet in the micropapular form, lichen scrofulosorum [1]. It has therefore been suggested [3] that the papular and nodular forms of tuberculid should be regarded as forms of true post-primary tuberculosis.

Fluctuations in the immunological state of the patient may determine the development and features of the eruption. The onset of lichen scrofulosorum has been noted to occur after the initiation of antituberculous treatment and probably represents a shift in the cell-mediated immune status of the patients [1]. Papulonecrotic tuberculid developed in a patient with HIV infection after an increase in the CD4 T-lymphocyte count occurred following the addition of a second antiretroviral drug [5].

In the most recent study from Hong Kong, in which 131 patients with cutaneous tuberculid were identified, erythema induratum was by far the commonest tuberculid identified (n = 127, 96%), followed by papulonecrotic tuberculide (n = 4, 3%) [6].

References

1 Thami GP, Kaur S, Kanwar AJ *et al.* Lichen scrofulosorum: a rare manifestation of a common disease. *Pediatr Dermatol* 2002; **19**: 122–6.
2 Victor T, Jordaans HF, van Niekerk DJ *et al.* Papulonecrotic tuberculid. Identification of *Mycobacterium tuberculosis* DNA by polymerase chain reaction. *Am J Dermatopathol* 1992; **14**: 491–5.
3 Degitz K, Steidl M, Thomas P *et al.* Aetiology of tuberculids. *Lancet* 1993; **341**: 239–40.
4 Baselga E, Margall N, Barnadas MA *et al.* Detection of *Mycobacterium tuberculosis* DNA in lobular granulomatous panniculitis (erythema induratum, nodular vasculitis). *Arch Dermatol* 1997; **133**: 457–62.
5 Alsina M, Campo P, Toll A *et al.* Papulonecrotic tuberculide in a human immunodeficiency virus type 1-seropositive patient. *Br J Dermatol* 2000; **143**: 232–3.
6 Ho CK, Ho MH, Chang LY. Cutaneous tuberculosis in Hong Kong: an update. *Hong Kong Med J* 2006; **12**: 272–7.

Lichen scrofulosorum

Definition. Lichen scrofulosorum was first described by Hebra in 1868 and is a lichenoid eruption of minute papules occurring predominantly in children and adolescents with tuberculosis. It is usually associated with a strongly positive tuberculin reaction.

Pathogenesis. Previously a common tuberculid, it is now rarely seen in Europe, except among immigrants. In 1976 a series of four cases were reported in the UK [1]. More recently two larger series of eight and 39 patients have been reported from northern India [2,3]. In the largest series of 39 patients this represented 7.6% of all patients with cutaneous tuberculosis reported over a 7-year period and 84% of patients were less than 15 years of age; 72% had an associated focus of tuberculosis elsewhere in the body, either in the lymph nodes, lung, bone or intracranially [3–5]; and 15% had evidence of tubercular foci at multiple sites [3]. Up to 30% of patients may have no obvious underlying focus of tuberculosis. Lichen scrofulosorum has also been reported with *M. avium* infection [6], more recently with *M. szulgai* [7] and also after BCG vaccination [8].

Lichen scrofulosorum is thought to result from an immune response to haematological spread from an underlying tuberculous focus. Its onset in some patients may be linked to an up-regulation of their immune system [9]. Patients show a strong positive reaction to PPD often measuring 18 mm or larger. Other forms of cutaneous tuberculosis, such as lupus vulgaris, tuberculous gumma and tuberculosis verrucosa cutis, may coexist [3,10].

Histopathology. Superficial dermal granulomas surround hair follicles and sweat ducts, and may occupy several dermal papillae. Epithelioid cells, lymphocytes and occasional giant cells are seen. Usually there is no caseation. Mycobacteria are not seen in the sections and cannot be cultured from biopsy material.



Fig. 31.20 Lichen scrofulosorum of the trunk showing subtle, skin-coloured papules. (Courtesy of Dr Antonio Torrelo, Hospital del Niño Jesus, Madrid, Spain.)



Fig. 31.21 Lichen scrofulosorum showing annular and plaque like lesions with strong tuberculin reaction. (Courtesy of Dr V. Ramesh, SJ Hospital and VM Medical College, New Delhi, India and the Editor of *Dermatology Clinics*.)

Mycobacterial DNA has so far not been detected by PCR, as it has in some of the other forms of cutaneous tuberculids [1].

Clinical features. The eruption consists of symptomless, 0.5–3.0 mm, closely grouped lichenoid papules. The lesions are usually skin-coloured (Fig. 31.20), but may be yellowish or reddish-brown. They are often perifollicular and appear in groups or in an annular arrangement or plaques (Fig. 31.21). The papules may have an adherent crust or small pustule. They are mainly found on the abdomen, chest and back, and proximal limbs. There has been one reported case of lesions confined to the vulval area [11].

Diagnosis. A high index of suspicion is necessary for diagnosis as the lesions may be subtle and asymptomatic. As most patients will have a focus of tuberculosis elsewhere they should be extensively screened. Prior vaccination with BCG does not prevent this condition developing [3]. Differential diagnosis includes all asymptomatic follicular lesions, where the lesions demonstrate a tendency to group together. These include: lichen nitidus, in which the lesions are more shiny and tend to be peripheral; keratosis spinulosa, in which the lesions have spiny projections over lichenoid papules; keratosis pilaris, where the lesions are non-inflammatory and usually on the upper thighs and arms; and papular or lichenoid sarcoidosis, secondary syphilis and drug eruptions. The tuberculin reaction is normally strongly positive, but was negative in one patient with HIV infection [12].

Treatment. With specific antituberculous therapy, the lesions usually clear within 4–8 weeks without scarring.

References

1 Smith MP, Ryan TJ, Sanderson KV, Sarkany I. Lichen scrofulosorum: a report of four cases. *Br J Dermatol* 1976; **94**: 319–25.
2 Beena KR, Ramesh V, Muckherjee A. Lichen scrofulosorum—a series of eight cases. *Dermatology* 2000; **201**: 272–4.
3 Singal A, Bhattacharya SN. Lichen scrofulosorum: a prospective study of 39 patients. *Int J Dermatol* 2005; **44**: 489–93.
4 Hudson PM. Tuberculide (lichen scrofulosorum) secondary to osseous tuberculosis. *Clin Exp Dermatol* 1976; **1**: 391–4.
5 Graham-Brown RAC, Sarkany I. Lichen scrofulosorum with tuberculous dactylitis. *Br J Dermatol* 1980; **103**: 561–4.
6 Komatsu H, Terunuma A, Tabata N *et al. Mycobacterium avium* infection of the skin associated with lichen scrofulosorum: report of three cases. *Br J Dermatol* 1999; **141**: 554–7.
7 Ross GL, Chong H, Collyns T *et al.* Lichen scrofulosorum caused by Mycobacterium szulgai: a new cause of reaction. *Br J Dermatol* 2007; **156**: 586–7.
8 Evans RG, Warner J. Lichen scrofulosorum following BCG. *Arch Dis Child* 1967; **42**: 448.
9 Thami GP, Kaur S, Kanwar AJ *et al.* Lichen scrofulosorum: a rare manifestation of a common disease. *Pediatr Dermatol* 2002; **19**: 122–6.
10 Torrelo A, Valverde E, Mediero IG *et al.* Lichen scrofulosorum. *Pediatr Dermatol* 2000; **17**: 373–6.
11 Pandhi D, Mehta S, Singal A. Genital tuberculid in a female child: a new entity (childhood vulval tuberculid). *Pediatr Dermatol* 2007; **24**: 573–5.
12 Aranayagam AV, Ash S, Russell Jones R. Lichen scrofulosorum in a patient with AIDS. *Clin Exp Dermatol* 1994; **19**: 74–6.

Papulonecrotic tuberculid

Definition. An eruption of necrotizing papules, mainly affecting the extensor aspects of the extremities and occurring in symmetrical crops. Individual lesions heal with varioliform scarring [1].

The lesions are considered by some to represent the paucibacillary form of haematogenous disseminated tuberculosis [2].

Pathogenesis. An associated focus of tuberculosis can be demonstrated in many patients. This ranged from 38 to 75% of patients in three different studies [3–5]. The rapid response to antituberculous therapy usually leaves no doubt of the aetiology when a tuberculous focus cannot be found. In a series of 91 patients, papulonecrotic tuberculid evolved into lupus vulgaris in four patients [3]. Papular necrotic tuberculid has also been described after BCG vaccination [6–8], indicating possible haematogenous mycobacterial spread as a cause of this tuberculid. Mycobacteria are rarely demonstrated in skin lesions, although they were found in two of the patients who had associated lupus vulgaris in the series discussed above [3], and *M. tuberculosis* DNA has been demonstrated in skin lesions using PCR [9]. Papulonecrotic tuberculid has occurred with *M. avium* complex in a patient with HIV infection [10]. The tuberculin test is normally positive, often with a severe, and even necrotic, reaction appearing within 8–12 h.

Histopathology [5]. In fully developed lesions, a large central zone of coagulation necrosis is surrounded by inflammation extending from the superficial to the deep dermis, and sometimes into the subcutaneous tissues. A histiocytic palisade, similar to that of granuloma annulare, is seen around larger lesions. The involvement of adjacent small vessels is striking, ranging from a mild lymphocytic vasculitis to fibrinoid necrosis and thrombotic occlusion.

Clinical features (Fig. 31.22). The eruption consists of recurring crops of symmetrical, hard, dusky-red papules. These crust or ulcerate, leaving pigmented, sometimes atrophic, varioliform scars over the course of a few weeks. New crops may continue over months or years. In some cases showers of rapidly healing lesions occur, in others a chronic open ulcer may last for some months [4]. In children phlyctenular conjunctivitis may be present [5].

Young adults are predominantly affected, but papulonecrotic tuberculid has also been seen in infants and young children. Two-thirds of a large South African series were under 30 years of age [3]. The legs, knees, elbows, hands and feet are the sites of predilection, but the ears, face, buttocks and penis—sometimes alone [11–13]—may be involved. Perniotic areas may be favoured. A transition to [3], and coexistence with, lupus vulgaris [14] has been described, and also an association with erythema induratum [15,16].

Diagnosis. Differential diagnosis includes: pityriasis lichenoides, where the lesions may be more widespread and affect the palms and soles; leukocytoclastic vasculitis, whose lesions are more pleomorphic; and nodular prurigo. A verrucous variant mimicking Kyrle's disease has been described [17]. Biopsy and tuberculin testing should be carried out in all cases. PCR may be helpful and recently an IFN-γ release assay has been shown to be helpful in detecting latent tuberculous infection when PCR was negative [18]. A therapeutic trial of specific antituberculous therapy is usually decisive in doubtful cases.



Fig. 31.22 Papulonecrotic tuberculid of the legs. (Courtesy of Professor J. Aboobaker, University of Natal, Durban, South Africa.)

Treatment. Full specific antituberculous therapy should be given.

References

1 Pautrier LM. Tuberculose nodulaire dermique à petits nodules. In: Darier J, ed. *Nouvelle Pratique Dermatologique*, III. Paris: Masson, 1936; **6**: 19–30.
2 Bravo FG, Gotuzzo E. Cutaneous tuberculosis. *Clin Dermatol* 2007; **25**: 173–80.
3 Morrison JGL, Fourie ED. The papulonecrotic tuberculid: from Arthus reaction to lupus vulgaris. *Br J Dermatol* 1974; **91**: 263–70.
4 Wilson-Jones E, Winkelmann RW. Papulonecrotic tuberculide: a neglected disease in Western countries. *J Am Acad Dermatol* 1986; **14**: 815–26.
5 Jordaan HF, van Niekerk DJ, Louw M. Papulonecrotic tuberculid: a clinical, histopathological and immunohistochemical study of 15 patients. *Am J Dermatopathol* 1994; **16**: 474–85.
6 De Bruyne JI, Van Creveld S, Prakken JR. Papular tuberculids after BCG vaccination. *Acta Derm Venereol (Stockh)* 1953; **33**: 385–90.
7 Figuereido A, Poiares-Baptista A, Branco M *et al*. Papular tuberculids post-BCG vaccination. *Int J Dermatol* 1987; **26**: 291–4.
8 Muto J, Kuroda K, Tajima S. Papular tuberculides post–BCG vaccination: case report and review of the literature. *Clin Exp Dermatol* 2006; **31**: 611–2.
9 Victor T, Jordaans HF, van Niekerk DJ *et al*. Papulonecrotic tuberculid: identification of *Mycobacterium tuberculosis* DNA by polymerase chain reaction. *Am J Dermatopathol* 1992; **14**: 491–5.
10 Williams JT, Pulitzer DR, DeVillez RL. Papulonecrotic tuberculid secondary to disseminated *avium* complex. *Int J Dermatol* 1995; **34**: 217–9.
11 Kumar B, Sharma VK. Papulonecrotic tuberculides on glans penis. *Dermatologica* 1987; **174**: 151–2.
12 Nishigori C, Taniguchi S, Hayakawa M. Penis tuberculides: papulonecrotic tuberculides on the glans penis. *Dermatologica* 1986; **172**: 93–7.
13 Srivastava N, Solanki LS, Singh SP *et al*. Papulonecrotic tuberculid of the glans: worm-eaten appearance. *Int J Dermatol* 2007; **46**: 1324–5.
14 Senol M, Ozcan A, Aydin A *et al*. Disseminated lupus vulgaris and papulonecrotic tuberculid: case report. *Pediatr Dermatol* 2000; **17**: 133–5.

15 Milligan A, Chen K, Graham-Brown RAC. Two tuberculides in one patient: a case report of papulonecrotic tuberculide and erythema induratum occurring together. *Clin Exp Dermatol* 1990; **15**: 21–3.
16 Chuang YH, Kuo TT, Wang CM *et al*. Simultaneous occurrence of papulonecrotic tuberculide and erythema induratum and the identification of *Mycobacterium tuberculosis* DNA by polymerase chain reaction. *Br J Dermatol* 1997; **137**: 276–81.
17 Khandpur S, Bansal A, Ramam M *et al*. Verrucous tuberculid mimicking Kyrle disease. *Int J Dermatol* 2007; **46**: 1298–1301.
18 Tanaka R, Matsuura H, Kobashi Y. Clinical utility of an interferon-γ-based assay for mycobacterial detection in papulonecrotic tuberculid. *Br J Dermatol* 2007; **156**: 169–71.

The nodular tuberculids

Erythema induratum of Bazin [1], in which the main pathology is in the subcutaneous fat, is accepted as a true nodular tuberculid. There have been recent proposals to separate out a nodular form where there is no ulceration and in which the pathology is at the junction of the dermis and subcutaneous fat; the term 'nodular tuberculid' has been proposed for this pattern [2]. Erythema nodosum, panniculitis and, rarely, nodular vasculitis may also be evoked by tuberculosis, though other causes are more common.

Erythema induratum [1]. This was first described by Bazin in 1861 as a condition occurring 'on the legs of female laundresses and in young and plump well nourished women with the typical phenotype of those with the scrofula'. The lesions are characterized by recurrent nodular and ulcerative lesions and occur secondary to tuberculosis elsewhere in the body. Lesions are usually localized to the lower legs, but can affect other areas. In most published series, the disease has occurred at least four times more commonly in women than men [3].

Pathogenesis. Past or active foci of tuberculosis are usually present and the tuberculin test is positive. *M. tuberculosis* is seldom recovered from the lesions, but mycobacterial DNA can be found in up to 77% of skin biopsy specimens [4]. It has been suggested that purified protein derivative-specific T cells capable of producing IFN-γ may be involved in the formation of erythema induratum as a type of delayed hypersensitivity response to mycobacterial antigens at the site of skin lesions [5].

Histopathology. The features are those of either focal or diffuse, lobular or septolobular, granulomatous panniculitis in association with neutrophilic vasculitis of either large or small blood vessels. There are areas of coagulative and caseation necrosis and, usually poorly developed, granulomas, although mixed, pallisading and lipophilic granulomas can occur [6,7].

Clinical features (Fig. 31.23). An indolent eruption of ill-defined nodules, usually affecting the posterior aspect of the lower legs of young or middle-aged women. However, lesions may affect other body areas, such as the upper limbs, thighs, buttocks and trunk [6]. Follicular perniosis may be present. Lesions may ulcerate, and this may be precipitated by cold weather. The ulcers are ragged, irregular and shallow, with a bluish edge. Resolution may be slow, even with adequate therapy [8], if there are associated erythrocyanotic features.



Fig. 31.23 Erythema induratum of the legs.

Erythema induratum is rare in the UK, accounting for five out of 47 cases of cutaneous tuberculosis in a recent series of patients, all of whom were from the Indian subcontinent [9]. It is now the commonest form of cutaneous tuberculosis found in Hong Kong [3]. It may sometimes be associated with nasopharyngeal, renal and endometrial tuberculosis [10,11], and a search should be made for active tuberculosis elsewhere.

Treatment. Full specific antituberculous therapy should be given. There is no place for monotherapy as has been recommended in the past [12], as drug resistance is likely to develop, which effectively means that no treatment is being given.

Nodular tuberculid. Jordaan *et al.* [2] have documented four female patients with dull red or bluish-red non-tender, non-ulcerating, nodules 1 cm or slightly larger in size, located on the lower legs. Pathological changes of granulomatous vasculitis were situated at the junction of the deep dermis and adjacent subcutaneous fat. The Mantoux test was strongly positive in all patients, and associated pulmonary tuberculosis was present in two. All lesions cleared promptly with full antituberculous therapy. They argue that there is a case for a tuberculid where the pathological process occurs neither in the superficial dermis, as in papulonecrotic tuberculid, nor in the subcutaneous fat as in erythema induratum, but rather at the junction of the dermis and subcutaneous fat. Further cases have subsequently been reported [13,14].

Erythema nodosum. This is fully discussed in Chapter 50. Tuberculosis is now a rare cause in Western Europe and the USA, but a more frequent one in countries where the disease is still common. A tuberculous cause should always be considered in children. It occurred in nine out of 113 children with non-respiratory tuberculosis reported in the UK in 1978–79 [15].

Nodular vasculitis. This is fully discussed in Chapter 50. There is an obvious overlap with erythema induratum, though the lesions do not usually ulcerate. Women are most frequently affected, and the lesions are usually dusky, tender and persistent. Tuberculosis has caused some cases seen in the past in the UK [16]. Most

authors would now accept those of tuberculous origin to be categorized as erythema induratum and to be separate from those of non-tuberculous origin. An exhaustive search for underlying tuberculosis should be made before commencing oral steroids or other immunosuppressive agents [17].

References

1 Bazin APE. *Leçons Théoretiques et Cliniques sur la Scrofula*, 2nd edn. Paris: Delahaye, 1861: 146.
2 Jordaan HF, Schneider JW, Abdulla EAK. Nodular tuberculid: a report of four patients. *Pediatr Dermatol* 2000; **17**: 183–8.
3 Ho CK, Ho MH, Chong LY. Cutaneous tuberculosis in Hong Kong: an update. *Hong Cong Med J* 2006; **12**: 272–7.
4 Baselga E, Margall N, Barnadas MA *et al*. Detection of *Mycobacterium tuberculosis* DNA in lobular granulomatous panniculitis (erythema induratum, nodular vasculitis). *Arch Dermatol* 1997; **133**: 457–62.
5 Koga T, Kubota Y, Nakayama J *et al*. Erythema induratum in a patient with active tuberculosis of the axillary lymph node: IFN-gamma release of specific T cells. *Eur J Dermatol* 2001; **11**: 48–9.
6 Schneider JW, Jordaan HF. The histopathological spectrum of erythema induratum of Bazin. *Am J Dermatopathol* 1997; **18**: 323–33.
7 Chen YH, Yan JJ, Chao SC *et al*. Erythema induratum: a clinicopathological and polymerase chain reaction study. *J Formos Med Assoc* 2001; **100**: 244–9.
8 Forstrom L, Hannuksela M. Antituberculous treatment of erythema induratum Bazin. *Acta Derm Venereol (Stockh)* 1970; **50**: 143–7.
9 Yates VM, Ormerod LP. Cutaneous tuberculosis in Blackburn district (U.K.): a 15 year prospective series. *Br J Dermatol* 1997; **136**: 483–9.
10 Yagi M, Kawabata I, Izaki S, Hosako Y. Primary tuberculosis of the nasopharynx with erythema induratum of Bazin. *J Otorhinolaryngol Relat Spec* 1994; **56**: 291–4.
11 Del Moral RF, Ereno C, Arrinda JM, de Mon MA. Erythema induratum of Bazin and active renal tuberculosis. *J Am Acad Dermatol* 1994; **31**: 288–90.
12 Anderson S. Erythema induratum (Bazin) treated with isoniazid. *Acta Derm Venerol (Stockh)* 1970; **50**: 65–8.
13 Friedman PC, Husain S, Grossman ME. Nodular tuberculosis in a patient with HIV. *J Am Acad Dermatol* 2005; **53**: S154–6.
14 Motswaledi HM, Schulz EJ. Superficial thrombophlebitic tuberculide. *Int J Dermatol* 2006; **45**: 1337–40.
15 Medical Research Council Tuberculosis and Chest Disease Unit. Tuberculosis in children in a national survey of notifications in England and Wales 1978–9. *Arch Dis Child* 1982; **57**: 734–41.
16 Feiwel M, Munro DD. Diagnosis and treatment of erythema induratum (Bazin). *BMJ* 1965; **1**: 1109–11.
17 Lee YS, Lee SW, Lee JR *et al*. Erythema induratum with pulmonary tuberculosis: histopathological features resembling true vasculitis. *Int J Dermatol* 2001; **40**: 193–6.

Other possible tuberculids

Granulomatous mastitis (Fig. 31.24). This is a rare inflammatory disease of the breast with multiple aetiologies. Clinically and radiologically it may mimic breast cancer. The disease is most often unilateral and consists of ulcerative plaques, nodules or abscesses on the breast of a female [1]. The disease follows a chronic course and does not respond to antibiotic therapy. In endemic areas, some cases are due to tuberculosis and associated with a strongly positive tuberculin test [2,3]. On histology, granulomata are seen with fat necrosis but acid-fast bacilli are not found. PCR has been positive in some cases. TB-related granulomatous mastitis might be considered to be a form of nodular tuberculid affecting the breast tissue [4]. Such cases show an excellent response to antituberculous therapy and this is an important diagnosis to make in order to avoid unnecessary surgery or treatment with oral corticosteroids [5].



Fig. 31.24 Granulomatous mastitis due to tuberculosis. (Courtesy of Dr F.G. Bravo, Instituto de Medicina Tropical Alexander von Humboldt, Lima, Peru.)



Fig. 31.25 Acneiform-like lesions with scarring on face and ears. Tuberculoid histology with acid-fast bacilli—a true lupus miliaris disseminatus faciei. (Courtesy of Dr F.G. Bravo, Instituto de Medicina Tropical Alexander von Humboldt, Lima, Peru.)

Lupus miliaris disseminatus faciei is generally thought to be a variant of rosacea [6]. However, in areas with an extremely high TB prevalence it is possible to find patients who have papulonecrotic lesions on the face and ears leading to varicelliform scarring. Mycobacteria can sometimes be seen in the lesions, the histology of which is granulomatous. There is a positive tuberculin test and the skin lesions improve on antituberculous therapy. Such cases (Fig. 31.25) would seem to be real lupus miliaris affecting the face [4]. One may have to keep an open mind about such cases.

References

1 Tse GM, Poon CS, Ramachandram K *et al*. Granulomatous mastitis: a clinicopathological review of 26 cases. *Pathology* 2004; **36**: 254–7.
2 Mirsaeidi SM, Masjedi MR, Mansori SD *et al*. Tuberculosis of the breast: report of 4 clinical cases and literature review. *East Mediterr Health J* 2007; **13**: 670–6.
3 Elsiddig KE, Khalil EA, Elhaq IA *et al*. Granulomatous mammary disease: ten years' experience with fine needle aspiration cytology. *Int J Tuberc Lung Dis* 2003; **7**: 365–9.
4 Bravo FG, Gotuzzo E. Cutaneous tuberculosis. *Clin Dermatol* 2007; **25**: 173–80.

5 Bani-Hani KE, Yaghan RJ, Matalka II *et al.* Idiopathic granulomatous mastitis: time to avoid unnecessary mastectomies. *Breast J* 2004; **10**: 318–22.
6 Hay RJ. Cutaneous infection with *Mycobacterium tuberculosis*: how has this altered with the changing epidemiology of tuberculosis? *Curr Op Infect Dis* 2005; **18**: 93–5.

Prognosis

Now revolutionized by modern therapy, the prognosis depends largely on early and accurate diagnosis. When tuberculosis has become generalized or has affected the meninges, the prognosis must be doubtful. The mortality in patients with dual tuberculosis/HIV infection is higher than in HIV-negative patients [1,2]. In infants and young children, tuberculosis is always a serious disease.

Tuberculosis confined to the skin usually responds well to multiple therapy and a clinical response will usually occur within 4 to 6 weeks, with lupus vulgaris showing a faster response time than scrofuloderma.

Diagnosis

Several circumstances may suggest the diagnosis of cutaneous tuberculosis, but the only absolute criteria are a positive culture of *M. tuberculosis* from the lesion or successful guinea-pig inoculation, or mycobacterial DNA identification by PCR (see below). Inoculations are rarely performed now, as equally reliable results can be obtained with multiple cultures. Rapid culture diagnosis, within 2–6 days, can be achieved with the Bactec system [3].

Other indications toward the diagnosis, which are by themselves unreliable, include the following:

1 The presence of active, proven tuberculosis elsewhere in the body
2 The presence of acid-fast bacilli in the lesion itself—this will also be seen in infections with other mycobacteria
3 The histopathology
4 A positive reaction to tuberculin
5 The clinical history and physical signs
6 The effect of specific therapy.

The difficulties in separating tuberculosis from a 'tuberculoid reaction' (p. 31.10), leprosy (Chapter 32), leishmaniasis (Chapter 37), deep mycoses (Chapter 36), infections with NTM (p. 31.30), syphilis (Chapter 34) and sarcoidosis (Chapter 61), are dealt with elsewhere.

Polymerase chain reaction

The *in vitro* amplification of specific DNA sequences using the PCR has become a valuable tool in the rapid detection of slow-growing organisms such as *M. tuberculosis.* Several systems have been reported for the molecular detection of mycobacterial DNA using different parts of the mycobacterial genome to generate highly sensitive and specific probes [4–6]. Some assay systems have amplified the insertion sequence IS6110 because of the repetitive nature of this element in the *M. tuberculosis* genome [7]. Using two different primer pairs targeting the gene encoding for 16S ribosomal RNA (common to all mycobacteria), as well as the insertion sequence IS6110, may further increase the sensitivity of detection [8]. As few as two colony-forming units of *M. tuberculosis* cells, or as little as 15 fg of DNA, can be detected [9]. Using the PCR technique, mycobacterial DNA has been demonstrated in all the different histopathological variants of cutaneous tuberculosis and in two of the tuberculids (papulonecrotic tuberculid and erythema induratum) [9–13]. The technique reduces the time required for diagnosis in those cutaneous lesions where bacteria can be cultured easily, and may be particularly useful in paucibacillary lesions such as lupus vulgaris. The technique can be used in a variety of pathological specimens, including archival formalin-fixed tissue sections. A generic criticism of this technique lies in its sensitivity; tissue samples containing bacterial DNA may be positive because of bacteraemia and not necessarily because the organism is involved in the pathogenesis of the tissue lesion [12].

References

1 Grossett JH. Treatment of tuberculosis in HIV infection. *Tuberc Lung Dis* 1992; **73**: 378–83.
2 Ackah AN, Coulibaly D, Digbeu H *et al.* Response to treatment, mortality and CD4 lymphocyte counts in HIV-infected persons in Abidjan, Côte d'Ivoire. *Lancet* 1995; **345**: 607–10.
3 Neff TA. Bronchoscopy and Bactec for the diagnosis of tuberculosis. *Am Rev Respir Dis* 1986; **133**: 162.
4 Brisson-Noel A, Gicquel B, Lecossier D *et al.* Rapid diagnosis of tuberculosis by amplification of mycobacterial DNA in clinical samples. *Lancet* 1989; **ii**: 1877–80.
5 Lee BW, Tan JA, Wong SC *et al.* DNA amplification by the polymerase chain reaction for the rapid diagnosis of tuberculous meningitis: comparison of protocols involving three mycobacterial DNA sequences, IS61110, 65 kDa antigen and MPB64. *J Neurol Sci* 1994; **123**: 173–9.
6 Altimarino M, Kelly MT, Wong A *et al.* Characterisation of a DNA probe for detection of *Mycobacterium tuberculosis* complex in clinical samples by polymerase chain reaction. *J Clin Microbiol* 1992; **30**: 2173–6.
7 Eisenach KD, Cave MD, Bates JH, Crawford JT. Polymerase chain reaction amplification of a repetitive DNA sequence specific for *Mycobacterium tuberculosis. J Infect Dis* 1990; **161**: 877–81.
8 Hsiao PF, Tzen CY, Chen HC *et al.* Polymerase chain reaction based detection of *Mycobacterium tuberculosis* in tissues showing granulomatous inflammation without demonstrable acid-fast bacilli. *Int J Dermatol* 2003; **42**: 281–6.
9 Baselga E, Margall N, Barnadas MA *et al.* Detection of *Mycobacterium tuberculosis* DNA in lobular granulomatous panniculitis (erythema induratumnodular vasculitis). *Arch Dermatol* 1997; **133**: 457–62.
10 Steidl M, Neubert U, Volkenandt M *et al.* Lupus vulgaris confirmed by polymerase chain reaction. *Br J Dermatol* 1993; **129**: 314–8.
11 Nachbar F, Classen V, Nachbar T *et al.* Orificial tuberculosis: detection by polymerase chain reaction. *Br J Dermatol* 1996; **135**: 106–9.
12 Penneys NS, Craig L, Leonardi MD *et al.* Identification of *Mycobacterium tuberculosis* DNA in five different types of cutaneous lesions by the polymerase chain reaction. *Arch Dermatol* 1993; **129**: 1594–8.
13 Victor T, Jordaans HF, van Niekerk DJ *et al.* Papulonecrotic tuberculid: identification of *Mycobacterium tuberculosis* DNA by polymerase chain reaction. *Am J Dermatopathol* 1992; **14**: 491–5.

Treatment

General measures

In the UK, all patients with tuberculosis must be notified, as this is a statutory requirement [1] and initiates contact tracing if appropriate [2]. Attention to the patient as a whole is an essential part of the proper management of any cutaneous tuberculous lesion and involves a careful search for an underlying focus of disease and coexistent infections. Because of the rising incidence of drug-resistant tuberculosis, it is vital to confirm the diagnosis bacteriologically whenever possible and to obtain drug susceptibilities [3]. Tuberculosis, pulmonary or extrapulmonary, is an AIDS-defining

illness. HIV testing, with informed consent and counselling, should be considered if a risk assessment shows the patient to be from an area or background with increased risk of HIV co-infection. If pulmonary, osseous, lymph-node or renal tuberculosis is found, a combined approach with other specialists is essential, as therapy will depend upon the organs involved, the extent of the lesions and the patient's immunity.

Drug therapy

The Joint Tuberculosis Committee (JTC) 1998 guidelines [4] and NICE 2006 guidelines [5] recommend that the treatment of all patients should be supervised by physicians with full training in the management of tuberculosis and with direct working access to tuberculosis nurse specialists or health visitors. In most cases, this will be the respiratory physician of the hospital or district.

Patient non-compliance is currently the most important factor limiting successful treatment. Directly observed therapy (DOT), where the ingestion of every drug dose is witnessed, has shown improved cure rates in a number of countries [6,7] and is recommended for patients who are unlikely to comply. These include patients who are homeless, alcoholics or drug abusers, drifters, seriously mentally ill, patients with multiple drug resistances and those with a previous history of non-compliance with antituberculous medication [8]. DOT should be considered for new immigrants/refugees. DOT can be daily, but an intermittent regimen is often more convenient.

Standard drug regimens

Controlled trials have defined a number of highly effective short-course regimens, and the basic mechanisms of action of the key antituberculous drugs are now better understood [9]. Isoniazid is the most effective bactericidal drug, followed by rifampicin. Rifampicin and pyrazinamide are the most important sterilizing drugs and act by killing different populations of semi-dormant organisms or persisters. Isoniazid and rifampicin are the most effective drugs at preventing the emergence of resistance to other drugs. Streptomycin and ethambutol are weaker, but nevertheless effective, drugs.

Six-month regimens, including four drugs in the initial 2-month phase (rifampicin, isoniazid, pyrazinamide plus streptomycin or ethambutol), followed by rifampicin and isoniazid in the 4-month continuation phase, are highly effective in patients with fully sensitive organisms [10]. Combination tablets should be used whenever possible to aid compliance and to prevent monotherapy.

Drugs in present use [4]. A standard 6-month regimen for adults is now recommended by the British and American Thoracic Societies. It includes four drugs (doses for adults only are given here):

1. Isoniazid (300 mg daily) for the full 6 months
2. Rifampicin (450 mg daily for those weighing less than 50 kg and 600 mg daily above this weight) for the full 6 months
3. Pyrazinamide for the first 2 months (1.5 g daily for those weighing less than 50 kg; 2.0 g daily for those weighing over 50 kg)
4. Ethambutol for the first 2 months (dosage 15 mg/kg body weight daily).

All drugs are taken on an empty stomach once daily.

Isoniazid remains the standard drug, given in all regimens because of its efficacy, cheapness and low toxicity. Its commonest side effects are peripheral neuropathy (most common in elderly people), which can be countered by giving pyridoxine (10 mg daily) prophylactically from the start of treatment, and hepatitis in adults over 35 years of age.

During the first 2 months of *rifampicin* treatment, elevated serum transaminases are common, but therapy can usually be continued, though occasionally more severe liver damage necessitates a change of treatment. Urine, sweat and tears may be coloured orange. The induction of liver enzymes by rifampicin may reduce the effectiveness of oral contraceptives.

Pyrazinamide causes hepatitis in 1%, arthritis and the precipitation of gout and cutaneous hypersensitivity in 3.5%. The side effects of *ethambutol* include visual disturbances and rarely a retrobulbar neuritis, which is reversible if detected early so that the ethambutol can be stopped. Patients should be warned of this risk and advised to stop the drug if visual symptoms develop. Visual acuity using a Snellen chart should be carried out before treatment starts. The drug is best avoided in young children and in those with renal impairment. Vertigo and tinnitus may limit the use of *streptomycin* in patients over the age of 40 years, and in those with impaired renal function.

In summary, all antituberculous drugs may cause adverse reactions; in one study, reactions occurred in 10% of patients treated. Reactions were significantly more common in those not receiving standard antituberculosis chemotherapy [11].

HIV disease. In HIV-infected patients, there have been no controlled trials of sufficient power to detect differences in efficacy between regimens. A small clinical study suggests that standard regimens, particularly if supervised properly, are as effective in HIV-positive as in HIV-negative patients [12], hence the JTC recommends the same 6-month regimen [4]. The response rate is the same as for non-HIV-infected patients, but there are higher drug reaction rates and higher re-infection rates.

Multidrug-resistant (MDR) tuberculosis. This is defined as resistance to rifampicin and isoniazid with or without resistance to other antituberculous drugs, and is now a worldwide problem. A recent global assessment of resistance to any of the four drugs in new cases in 76 countries [13] showed a median prevalence of 10.2% (range 0.0–57.1%). The median prevalence of multidrug resistance in new cases was 1.0% (range 0.0–14.2%). Kazakhstan, Tomsk Oblast (Russia), Karakalpakstan (Uzbekistan), Estonia, Israel, the Chinese provinces Liaoning and Henan, Lithuania and Latvia reported prevalences of MDR above 6.5%. With regard to describing a country's burden of MDR, percent prevalence as well as absolute numbers must be considered. South Africa, some Chinese provinces, and some states in India have a relatively low prevalence of MDR cases but a high tuberculous burden and therefore a very high absolute number of cases.

Extremely drug-resistant (XDR) tuberculosis. Recent documentation of XDR tuberculosis, that is multidrug resistant strains with resistance to at least three of the main six classes of second-line drugs, first reported from South Africa in patients with HIV

infection, is extremely worrisome [14,15] and has global implications [16]. Treatment of such patients is complex and difficult in many developing countries that lack adequate primary care facilities and the necessary tools to detect drug resistance promptly. Ideally treatment should only be carried out by experienced physicians in hospitals with appropriate isolation facilities and in consultation with appropriate mycobacterial reference laboratories [4,5]. Currently, only rifampicin resistance can be routinely detected by molecular probes on microscopy-positive or culture-positive tissue. No other drug resistance can be routinely checked without susceptibility tests.

Modification for dermatological practice. Yates and Ormerod have shown that the standard 6-month regimen is effective in treating cutaneous tuberculosis [17]. In their series of patients, over 50% had coexisting disease elsewhere, all had a good clinical response, and there were no relapses following treatment. Historically, some forms of skin tuberculosis have been treated by isoniazid alone [18]. This is no longer appropriate, as drug resistance is likely to develop with monotherapy—and if drug resistance to isoniazid is already present, it means, in effect, that no therapy is being given.

The excision of small lesions of lupus vulgaris or warty tuberculosis, if diagnosed early, may be effective. Surgery may be helpful in scrofuloderma, sometimes shortening the time needed for chemotherapy. Plastic surgery may help the disfigurement left by treated lupus vulgaris.

References

1 Ormerod LP, Watson JM, Pozniak A *et al.* Notification of tuberculosis: an updated code of practice for England and Wales. *J R Coll Physicians* 1997; **31**: 299–303.

2 Joint Tuberculosis Committee of the British Thoracic Society. Control and prevention of tuberculosis in the United Kingdom: code of practice 2000. *Thorax* 2000; **55**: 887–901.

3 Hayward AC, Bennett DE, Herbert J *et al.* Risk factors for drug resistance in patients with tuberculosis in England and Wales 1993–94. *Thorax* 1996; **51** (Suppl. 3): S32.

4 Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax* 1998; **53**: 536–48.

5 Royal College of Physicians. Tuberculosis: national clinical guidelines for diagnosis, management, prevention and control. London: Royal College of Physicians, 2006. Accessed at http://www.nice.org.uk.

6 China Tuberculosis Control Collaboration. Results of directly observed short course chemotherapy in 112 842 Chinese patients with smear-positive tuberculosis. *Lancet* 1996; **347**: 358–62.

7 Morse DI. Directly observed therapy for tuberculosis. *BMJ* 1996; **312**: 719–20.

8 Sumartjoo E. When tuberculosis treatment fails: a social behavioral account of patient adherence. *Am J Respir Dis* 1993; **147**: 1311–20.

9 Girling DJ. The chemotherapy of tuberculosis. In: Ratle C, Stanford J, Grange JM, eds. *Biology of Mycobacteria*, Vol. 3. London: Academic Press, 1989: 285–323.

10 British Thoracic Association. A controlled trial of six months chemotherapy in pulmonary tuberculosis—first report: results during chemotherapy. *Br J Dis Chest* 1981; **75**: 141–53.

11 Ormerod LP, Bentley C. Joint Tuberculosis Committee of the British Thoracic Society. The management of pulmonary tuberculosis in England and Wales in 1993. *J R Coll Physicians Lond* 1997; **31**: 662–5.

12 Perriens JH, St Louis ME, Yiadiul B *et al.* Pulmonary tuberculosis in HIV infected patients in Zaire. *N Engl Med J* 1995; **332**: 779–84.

13 Aziz MA, Wright A, Laszio A *et al.* Epidemiology of antituberculous drug resistance (the Global project on Anti-tuberculous Drug Resistance Surveillance): an updated analysis. *Lancet* 2006; **368**: 2142–54.

14 Centers for Disease Control and Prevention. Emergence of *Mycobacterium tuberculosis* with extensive resistance to second-line drugs—worldwide 2000–2004. *MMWR Morb Mortal Wkly Rep* 2006; **55**: 301–5.

15 Gandhi NR, Moll A, Sturm AW *et al.* Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. *Lancet* 2006; **368**: 1575–80.

16 Raviglione MC, Smith IM. XDR Tuberculosis—implications for global public health. *N Eng J Med* 2007; **356**: 656–9.

17 Yates VM, Ormerod LP. Cutaneous tuberculosis in Blackburn district (U.K.): a 15 year prospective series. *Br J Dermatol* 1997; **136**: 483–9.

18 Anderson S, La C. Erythema induratum (Bazin) treated with isoniazid. *Acta Derm Venereol (Stockh)* 1970; **50**: 65–8.

BCG vaccination [1]

BCG vaccines owe their origin to the *in vitro* attenuation by Calmette and Guérin, between 1906 and 1919, of a strain of *M. bovis* [2]. Evidence of the efficacy of BCG vaccination derives from studies in infants [3] and schoolchildren. There are few data in adults to suggest that BCG vaccination offers protection if given over the age of 16 years [4,5], although absence of evidence does not necessarily mean absence of effect. In the UK, BCG vaccinations appear to reduce the incidence of childhood tuberculosis by 75% or more [6]. BCG vaccination protects the host by blocking the secondary haematogenous spread of the pathogen, limiting the primary infection to subclinical proportions [7]. In a recent report from northern India of childhood cutaneous tuberculosis, BCG vaccination appeared to protect against disseminated disease [8].

The protective effect of BCG in children is likely to last at least 15 years [9]. In the UK, it is still the policy—particularly in light of the rise in tuberculous notifications since 1987—that BCG is routinely offered in schools to all children aged 10–14 years [10,11] and to certain groups at higher risk of exposure to tuberculosis. These include infants and children of immigrants from countries with a high prevalence of tuberculosis [3], and children born to adults born in the UK but from ethnic groups originating in high-prevalence countries, children with a family history of tuberculosis, and tuberculin-negative travellers to areas of high prevalence. It should also be offered to tuberculin-negative health workers and to staff working in hostels for AIDS patients and the homeless.

Because of the risk of generalized BCG infection, BCG vaccination should not be given to individuals known to be HIV-infected in the UK [12].

Complications

After BCG vaccination, a local reaction usually occurs 2–6 weeks later as a small papule that may slowly enlarge and discharge purulent material to leave a shallow ulcer. Tuberculin conversion normally takes place within 12 weeks.

Complications are rare in relation to the number of vaccinations carried out. Excluding abnormal BCG primary complexes, all reported localized or generalized reactions among nearly 1500 million persons vaccinated between 1948 and 1974 made up less than two per million [13]. Of these, keloids, rashes and ocular manifestations accounted for 1.35 per million, and 'tuberculosis-like' lesions for 0.16 per million.

Non-specific reactions to BCG include urticaria and erythema multiforme [14]. Unusual reactions have also occurred, such as



Fig. 31.26 Atypical papular tuberculid following BCG vaccination. (Courtesy of Dr J. Muto, National Defence Medical College, Namiki, Tororozawa, Saitama, Japan.)

generalized maculopapular or purpuric eruptions associated with arthralgia and abdominal pain or myalgia, usually after repeated vaccination [15,16]. Extensive or protracted ulceration sometimes occurs.

Specific complications include tuberculous processes caused by the BCG organism. Lupus vulgaris may develop at the vaccination site, usually a few months after vaccination, but cases have been reported as long as 3 years after vaccination [17,18]. This can be a recurrent problem [19] and is more likely to occur after multiple vaccinations [20]. Scrofuloderma has also been reported [21]. Several of the tuberculids including lichen scrofulosorum [15], an atypical papular tuberculid thought to be a variant of papulonecrotic tuberculid [22] (Fig. 31.26), and erythema induratum of Bazin [23] have followed vaccination. As these are hypersensitivity reactions to *M. bovis,* antituberculous therapy is not necessary other than in immunocompromised patients. Development of basal cell carcinoma in a BCG scar has been reported [24], and disseminated cutaneous granulomas in infants with immunodeficiency syndromes [25].

Therapeutic use

BCG is used as immunotherapy in the management of superficial and *in situ* transitional cell carcinoma of the bladder. The BCG vaccine is usually instilled into the bladder on a monthly basis. Primary infection of the glans penis by *M. bovis*–BCG has been described (Fig. 31.27) after intravesical BCG treatment [26]. Distant cutaneous granulomas have been described after BCG immunotherapy for malignant melanoma [27].



Fig. 31.27 *Mycobacterium bovis*–bacillus Calmette–Guérin infection of the glans penis, showing an infiltrated red plaque containing small, deep-seated, yellow papules. (Courtesy of Dr M. Ribera, Hospital Universitari Germans, Universitat Autònoma de Barcelona, Badalona, Spain, and the Editor of the *British Journal of Dermatology*.)

References

1 Fine PEM. The BCG story: lessons from the past and implications for the future. *Rev Infect Dis* 1989; **11** (Suppl. 2): 353–9.

2 Fine PEM. BCG vaccination against tuberculosis and leprosy. *Br Med Bull* 1988; **44**: 691–703.

3 Rodrigues LC, Gill ON, Smith PG. BCG vaccination in the first year of life protects children of Indian subcontinent ethnic origin against tuberculosis in England. *J Epidemiol Community Health* 1991; **45**: 75–80.

4 Springett VH, Sutherland I. A re-examination of the variations in efficacy of BCG vaccination against tuberculosis in clinical trials. *Tuberc Lung Dis* 1994; **75**: 227–33.

5 Brewer TF, Colditz GA. Bacille Calmette–Guérin vaccination for the prevention of tuberculosis in health care workers. *Clin Infect Dis* 1995; **20**: 136–42.

6 Sutherland I, Springett VH. Effectiveness of BCG vaccination in England and Wales. *Tubercle* 1987; **68**: 81–92.

7 Fok JS, Ho RS, Orora PK *et al.* Host–parasite relationships in experimental airborne tuberculosis, 5: lack of haematogenous dissemination of *M. tuberculosis* to the lungs in animals vaccinated with BCG. *J Infect Dis* 1976; **133**: 137–44.

8 Kumar B, Rai R, Kaur I *et al.* Childhood cutaneous tuberculosis: a study over 25 years from northern India. *Int J Dermatol* 2001; **40**: 26–32.

9 Snider DE. Bacille Calmette-Guérin vaccinations and tuberculin skin tests. *JAMA* 1985; **253**: 3438–9.

10 United Kingdom Health Departments. *Immunisation Against Infectious Disease.* London: HMSO, 1996.

11 Department of Health. *Tuberculosis: Two Reports from the Interdepartmental Working Group on Tuberculosis*. Executive letter EL (96) 51, July 1996.

12 Subcommittee of the Joint Tuberculosis Committee. Guidelines on the management of tuberculosis and HIV infection in the United Kingdom. *BMJ* 1992; **284**: 1454–6.

13 Lotte A, Wasc-Hockert O, Poisson N *et al.* Complications induced by BCG vaccination: a retrospective study. *Bull Int Union Tuber* 1978; **53**: 114–6.

14 Tschen EH, Jessen T, Robertson G *et al.* Erythema multiforme as a complication of BCG scarification technique. *Arch Dermatol* 1979; **115**: 614–5.

15 Dostrovsky A, Sagher F. Dermatological complications of BCG vaccination. *Br J Dermatol* 1963; **75**: 181–92.

16 Machtey I, Bandmann M, Palant A. Unusual reaction to BCG. *Lancet* 1968; **i**: 140–1.

17 Handjani F, Delir S, Sodafi M *et al.* Lupus vulgaris following bacille Calmette–Guérin vaccination. *Br J Dermatol* 2001; **144**: 444–5.

18 Izumi AK, Matsunaga J. BCG vaccine-induced lupus vulgaris. *Arch Dermatol* 1982; **118**: 171–2.

19 Sasmaz R, Altinyazar HC, Tatlican S *et al.* Recurrent lupus vulgaris following repeated BCG (bacillus Calmette Guérin) vaccination. *J Dermatol* 2001; **28**: 762–4.
20 Horowitz O, Meyer J. The safety record of BCG vaccination and untoward reactions after vaccination. *Adv Tuberc Res* 1957; **8**: 254–71.
21 Atasoy M, Aliagaoglu C, Erdem T *et al.* Scrofuloderma following BCG vaccination. *Pediatr Dermatol* 2005; **22**: 179–80.
22 Muto J, Kuroda K, Tajima S. Papular tuberculides post-BCG vaccination: case report and review of the literature in Japan. *Clin Exp Dermatol* 2006; **31**: 611–12.
23 Inque T, Fukumoto T, Ansai S *et al.* Erythema induratum of Bazin in an infant after bacille Calmette–Guerin vaccination. *J Dermatol* 2006; **33**: 268–72.
24 Nielsen T. Basal cell epithelioma in a BCG vaccination scar [letter]. *Arch Dermatol* 1980; **115**: 678.
25 Antaya RJ, Gardener ES, Bettencourt MS *et al.* Cutaneous complications of BCG vaccination in infants with immune disorders: two cases and a review of the literature. *Pediatr Dermatol* 2001; **18**: 205–9.
26 Ribera M, Bielsa J, Manterola JM *et al. Mycobacterium bovis*–BCG infection of the glans penis: a complication of intravesical administration of bacillus Calmette–Guérin. *Br J Dermatol* 1995; **132**: 309–10.
27 Moff SL, Corey GR, Gottfredsson M. Distant cutaneous granulomas after bacilli Calmette–Guérin immunotherapy for malignant melanoma: case for direct infection. *Clin Infect Dis* 1999; **29**: 1569–70.

Tuberculosis and anti-TNF-α treatment

Reactivation of tuberculosis should be considered a risk with all antitumour necrosis factor (TNF) agents, although most reports are related to infliximab [1,2]. Miliary tuberculosis has been reported [3] and reactivation has also occurred during antibiotic prophylaxis [4]. Non-tuberculous mycobacterial disease has also been associated with anti-TNF-α treatment [5,6]. The increase in active tuberculosis in association with anti-TNF-α treatment has led to a requirement for patient screening for active and latent tuberculosis before anti-TNF treatment is given. Guidelines have recently been produced by the British Thoracic Society to assist in assessing risk and for managing *M. tuberculosis* infection and disease in patients due to start anti-TNF-α treatment [7].

References

1 Moiton MP, Richez C, Dumoulin C *et al.* Role of anti-tumour necrosis factor-alpha therapeutic agents in the emergence of infections. *Clin Microbiol Infect* 2006; **12**: 1151–3.
2 Manadan AM, Joyce K, Sequeira W *et al.* Etanercept therapy in patients with a positive tuberculin skin test. *Clin Exp Rheumatol* 2007; **25**: 743–5.
3 Stas P, D'Hoore A, Van Assche G *et al.* Miliary tuberculosis following infliximab for Crohn's disease: a case report and review of the literature. *Acta Gastroenterol Belg* 2006; **69**: 217–20.
4 Sichletidis L, Settas L, Spyrato D *et al.* Tuberculosis in patients receiving anti-TNF agents despite chemoprophylaxis. *Int J Tuberc Lung Dis* 2006; **10**: 1127–32.
5 Okubo H, Iwamoto M, Yoshio T *et al.* Rapidly aggravated *Mycobacterium avium* infection in a patient with rheumatoid arthritis treated with inflixamab. *Mod Rheumatol* 2005; **15**: 62–4.
6 Fallon JC, Patchett S, Gulman C *et al. Mycobacterium marinum* infection complicating Crohn's disease, treated with inflixamab. *Clin Exp Dermatol* 2008; **23**: 43–5.
7 British Thoracic Society Standards of Care Committee. BTS recommendations for assessing risk and for managing *Mycobacterium tuberculosis* infection and disease in patients due to start anti-TNF-α treatment. *Thorax* 2005; **60**: 800–5.

Non-tuberculous (atypical) mycobacteria

The non-tuberculous mycobacteria (NTM) are *Mycobacterium* species different from *M. tuberculosis*. In the late 1950s and 1960s, these organisms were referred to as 'atypical', as they were thought to be unusual *M. tuberculosis* strains [1]. Non-tuberculous bacteria occur much more frequently in immunocompromised hosts, and with the advent of the AIDS epidemic their clinical importance has increased. This has led to recent major advances in our understanding of their biology, epidemiology and clinical presentations; guidelines on their diagnosis and treatment have been published by the American Thoracic Society [2]. Pulmonary disease remains the commonest clinical presentation following infection with this group of organisms. The commonest NTM that cause cutaneous infection are members of the *M. fortuitum* complex (*M. fortuitum*, *M. peregrinum*, *M. chelonae*, *M. abscessus* and *M. mucogenicum*), *M. marinum* and *M. ulcerans.* In immunocompetent patients, cutaneous infection is usually a consequence of trauma, and skin lesions tend to be localized. Immunocompromised hosts show a tendency to develop widespread or disseminated lesions [3].

M. marinum

Synonyms
- Swimming pool granuloma
- Fish-tank granuloma

M. marinum (formally *M. balnei* and *M. platypoecilus*) was first isolated in 1926 by Aronson from saltwater fish carcasses in the Philadelphia aquarium [4]. In 1942, Baker and Hagan showed that the bacteria caused tuberculosis in freshwater platy fish and named the organism *M. platypoecilus.* The first report of human disease appeared in 1951 [5], when the organism was found to be the cause of granulomatous skin lesions in those using a contaminated swimming pool in Sweden and was named *M. balnei*. Subsequently, *M. balnei* and *M. platypoecilus* were shown to be the same organism, and they are now called *M. marinum*. In the late 1950s, *M. marinum* was found to be the cause of infections acquired from aquaria in humans [6].

Aetiology. The natural habitat of *M. marinum* is water, particularly enclosures of water that are not often replenished, such as swimming pools and aquaria [7]. Its distribution is worldwide, but the organism is especially prevalent in heated water in temperate climates and in the sea, natural pools, rivers and on beaches. Its vectors include fresh- or salt-water fish, snails, shellfish, dolphins and water fleas [8]. It can also be isolated from cracks in masonry, mud and from water even where chlorination appears to be sufficient [9].

On immunodiffusion analysis, the organism can be shown to possess antigens characteristic of the slow-growing mycobacteria [10], though its growth is more rapid than that of most members in that group. It will grow on ordinary laboratory media in 7–10 days if cultured at 30–33°C; significant inhibition of growth occurs at 37°C.

M. marinum is probably only pathogenic on abraded skin, although a history of trauma cannot always be elicited [11]. Strain characteristics may be important in the virulence of the organism [12].

Epidemiology. Occupational or recreational exposure to salt or fresh water occurs in the majority of cases. Most of the early

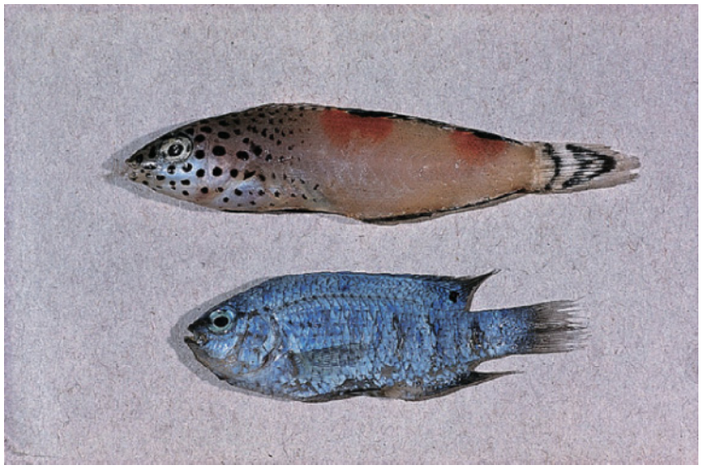


Fig. 31.28 Fish infected with *Mycobacterium marinum*. (Courtesy of Professor J.A.A. Hunter, Royal Infirmary, Edinburgh, UK.)



Fig. 31.29 *Mycobacterium marinum* infection showing sporotrichoid spread from the hand to the forearm in an aquarist. (Courtesy of Dr I.H. Coulson, Burnley General Hospital, Burnley, UK.)

proven cases of *M. marinum* infections were described in individuals frequenting swimming pools [13]. The first two cases of 'swimming-pool granuloma' in the UK were reported from Yorkshire in 1964 [14]. In one outbreak, over 300 cases were traced [15]. Similar outbreaks have occurred in Wales [16] and France [17]. The infection has also been contracted in natural bathing pools by the Dead Sea [18] and in the sea in the USA [19].

In many recent cases, the source of infection has been tropical fish tanks [20]. In a national survey of 63 culture-confirmed cases occurring in France between 1996 and 1998, inoculation related to fish tank exposure was documented in 84% of cases [21]. Ornamental fish such as the Siamese fighting fish, *Betta splendens* and the snakehead *Channa striata* are often hosts of the mycobacteria [22]. Fish tuberculosis is a chronic infection that causes wasting of the fish, but may take up to 12 months to cause death (Fig. 31.28). Most infections are acquired while cleaning out the tanks. *M. marinum* survives readily in water and can be cultured from dead fish, the sides of tanks, and sand and water samples [23]. One child developed the infection indirectly after bathing in the bath in which his father had recently cleaned a tropical fish tank [24].

Pathology. Lesions may show non-specific inflammation in the first few months, while older lesions show well-formed tuberculoid granulomas [25], with fibrinoid masses rather than caseation. Langhans' giant cells are not always present. Intracellular acid-fast bacilli—longer and broader than tubercle bacilli—are detectable in only approximately 10% of cases [11]. Epidermal changes including ulceration and pseudoepitheliomatous hyperplasia may occur in chronic lesions.

Clinical features. Skin lesions develop after an average incubation period of 2–3 weeks following inoculation of the organisms onto abraded skin. Occasionally, the incubation period can be as long as 9 months [26], leading to delays in diagnosis, as important clinical clues in the patient's history may be overlooked. The initial lesion is either a solitary nodule or pustule that may break down to form an ulcer or abscess, or that may remain as a verrucous plaque. Lesions are most common on the elbows, knees and feet of swimmers, and on the dominant hand and fingers of fish fanciers. The inhibition of *M. marinum* growth at 37°C accounts for its ability to infect the cooler body extremities whilst rarely spreading systemically.

Lesions are often multiple; in the sporotrichoid form, which occurs in approximately 20% of cases [27], nodules may extend along the line of lymphatic vessels (Fig. 31.29). The regional lymph glands may be enlarged, but never break down. Deeper infections occurred in 29% of patients in one series [21] and resulted from direct extension of the cutaneous infection. Tenosynovitis, osteomyelitis and septic arthritis can occur [28]. Immunocompromised patients may develop disseminated lesions [29,30]. The infection probably resolves spontaneously in some cases, although complete resolution may take up to 2 years [20].

Diagnosis. As with all mycobacterial disease, the diagnosis requires a high index of suspicion. A history of contact with water, fish tanks, aquaria, etc., combined with granulomatous histology, is suggestive of the diagnosis. A positive culture can be obtained in some 70–80% of cases if the organism is grown between 30 and 33°C. It is important to alert the microbiologist to the suspicion of *M. marinum* infection so that specimens are cultured in the appropriate manner. Cultures should be observed for 6 weeks, but generally colonies will be seen in 10–28 days. Species-specific monoclonal antibody against 56-kDa *M. marinum* antigens may have potential use in rapid culture identification [31]. *M. marinum* infection has also been identified using PCR-reverse cross blot hybridization assay with species-specific gene probes [32]. This may lead to more rapid diagnosis, but cultures will still be necessary to assess the antibiotic sensitivities of different strains.

Cultures are of particular value in exclusion of leishmaniasis and sporotrichosis in endemic areas, as well as to identify other atypical mycobacterial infections such as *M. kansasii*, *M. chelonei* and *M. gordonae*, all of which may spread in a sporotrichoid manner. Skin tests using antigens specific to *M. marinum* are of little value.

Treatment. There have been no comparative trials of treatment regimens for skin and soft tissue infections with *M. marinum*. One study has attempted to draw recommendations for standardized treatments by looking at treatment outcomes [21], and there are also some potentially helpful *in vitro* studies of antibiotic susceptibility patterns for *M. marinum* [33,34]. Rifampicin and rifabutin were found to be the most active drugs in these studies. The mean inhibitory concentrations of minocycline, doxycycline, clarithromycin, amikacin, sparfloxacin, moxifloxacin and sulfamethoxazole were also acceptable. Mean inhibitory concentrations were above concentration break points for ethambutol, ciprofloxacin, ofloxacin and levofloxacin and trimethoprim [33], making *in vivo* efficacy less probable. This correlates with results from one study [21] in which treatment failures were reported in half of the patients treated with these antibiotics. A recent review lists four recommended options of therapy: ethambutol and rifampicin, clarithromycin, minocycline and doxycycline [35]. A retrospective study of 16 cases of culture-positive *M. marinum* showed that clarithromycin, both on *in vitro* testing and on clinical response, was the drug of choice [36]. The authors also pointed out that clarithromycin seems to be superior to other drugs in terms of lack of significant side effects.

M. marinum is a naturally drug-resistant species [37]. A reasonable approach to treatment would seem to be to treat with two active agents (in the largest available study this was most commonly clarithromycin and rifampicin [21]), continued for 1 to 2 months after resolution of symptoms, typically 3 to 4 months in total [2]. Some experts believe that minimal disease can be treated with a single agent. Treatment failure is more usually related to involvement of deeper structures than to the antibiotic regimen [21].

Deep *M. marinum* infection involving the hand can be aggressive and may result in permanent disability. Specialists in infectious diseases and hand surgery should be consulted [38]. Surgical debridement of lesions is somewhat controversial, but may be considered when deeper structures are involved [39]. Photodynamic therapy may have some role to play [40] though more data are needed. Fish fanciers and fish salesmen are seldom aware of, or ignore, the risk of mycobacterial infection from their hobby/occupation [41]. Simple preventative measures, such as the use of gloves or covering of cuts and grazes, should be recommended to fish handlers [23]. Public health authorities should be notified when a public source of infection is identified, and other cases should be looked for. Maximum chlorination of swimming pools is effective [17].

References

1 Palenque E. Skin disease and nontuberculous atypical mycobacteria. *Int J Dermatol* 2000; **39**: 659–66.

2 Griffith DE, Aksamit T, Brown-Elliott BA *et al.* An official ATS/IDSA statement: Diagnosis, treatment and prevention of nontuberculous mycobacterial disease. *Am J Respir Crit Care Med* 2007; **175**: 367–416.

3 Bartralot R, Garcia-Patos V, Sitjas D *et al.* Clinical patterns of cutaneous nontuberculous mycobacterial infections. *Br J Dermatol* 2005; **152**: 727–34.

4 Aaronson JD. Spontaneous tuberculosis in salt water fish. *J Infect Dis* 1926; **39**: 315–20.

5 Norden A, Linell FA. A new type of pathogenic mycobacterium. *Nature* 1951; **168**: 826.

6 Pegum JS. Tuberculosis verrucosa cutis (waterborne acid-fast bacillus infection). *Proc R Soc Med* 1958; **51**: 930.

7 Falkinham JO III. Epidemiology of infection by nontuberculous mycobacteria. *Clin Microbiol Rev* 1996; **9**: 177–215.

8 Huminer D, Pitlik SD, Block C *et al.* Aquarium-borne *M. marinum* skin infection. *Arch Dermatol* 1986; **122**: 698–703.

9 Beurey J, Weber M, Vignaud JM *et al.* Mycobacterioses cutanées: enquête épidemiologique. *Ann Dermatol Vénéréol* 1981; **108**: 439–42.

10 Stanford JL, Grange JM. The meaning and structure of species as applied to mycobacteria. *Tubercle* 1974; **55**: 143–52.

11 Ang P, Rattana-Apiromyakij N, Goh CL. Retrospective study of *Mycobacterium marinum* skin infection. *Int J Dermatol* 2000; **39**: 343–7.

12 Van der Sar AM, Abdallah AM, Sparrius M *et al*. *Mycobacterium marinum* strains can be divided into two distinct types based on genetic diversity and virulence. *Infect Immun* 2004; **72**: 6306–12.

13 Linell F, Norden A. *Mycobacterium balnei*: a new acid-fast bacillus occurring in swimming pools and capable of producing skin lesions in humans. *Acta Tuber Scand* 1954; **33** (Suppl.): 1–84.

14 Morgan JK, Blowers R. Swimming-pool granuloma in Britain. *Lancet* 1964; **i**: 1034–6.

15 Mollohan CS, Romer MS. Public health significance of swimming pool granuloma. *Am J Public Health* 1961; **51**: 883–91.

16 Waddington E. An outbreak of swimming pool granuloma. *Trans St John's Hosp Dermatol Soc* 1967; **53**: 122–4.

17 Dailloux M, Morlot M, Sibbat C. Study of factors affecting the presence of atypical mycobacteria in water of a swimming pool. *Rev Epidemiol Santé Publique* 1980; **28**: 229–306.

18 Even-Paz Z, Haas H, Sachs T *et al*. *M. marinum* skin infections mimicking leishmaniasis. *Br J Dermatol* 1976; **94**: 435–42.

19 Zeligman I. *M. marinum* granuloma: a disease acquired in the tributaries of Chesapeake Bay. *Arch Dermatol* 1972; **106**: 26–31.

20 Edelstein H. *Mycobacterium marinum* skin infections: report of 31 cases and review of the literature. *Arch Intern Med* 1994; **154**: 1359–64.

21 Aubry A, Chosidow O, Caumes E *et al.* Sixty-three cases of *Mycobacterium marinum* infection: clinical features, treatment and antibiotic susceptibility of causative isolates. *Arch Intern Med* 2002; **162**: 1746–52.

22 Puttinaowarat S, Thompson KD, Kolk A *et al.* Identification of *Mycobacterium* spp. isolated from snakehead, *Channa striata* (Fowler), and Siamese fighting fish, *Betta splendens* (Regan), using polymerase chain reaction-reverse cross blot hybridization (PCR-RCBH). *J Fish Dis* 2002; **25**: 235–43.

23 Gray SF, Smith RS, Reynolds NJ *et al.* Fish tank granuloma. *BMJ* 1990; **300**: 1069–70.

24 King AJ, Fairly JA, Rasmussen JE. Disseminated cutaneous *Mycobacterium marinum* infection. *Arch Dermatol* 1983; **119**: 268–70.

25 Travis WD, Travis LB, Roberts GD *et al.* The histopathological spectrum in *Mycobacterium marinum* infection. *Arch Path Lab Med* 1985; **109**: 1109–13.

26 Jernigan JA, Farr BM. Incubation period and sources of exposure for cutaneous *Mycobacterium marinum* infection: case report and review of the literature. *Clin Infect Dis* 2000; **31**: 439–43.

27 Gluckman SJ. *Mycobacterium marinum. Clin Dermatol* 1995; **13**: 273–6.

28 Barton A, Bernstein RM, Struthers JK *et al. Mycobacterium marinum* infection causing septic arthritis and osteomyelitis. *Br J Rheumatol* 1997; **36**: 1207–9.

29 Streit M, Bohlen LM, Hunziker T *et al.* Disseminated mycobacterium marinum infection with extensive cutaneous eruption and bacteremia in an immunocompromised patient. *Eur J Dermatol* 2006; **16**: 79–83.

30 Holmes GF, Harrington SM, Romagnoli MJ *et al.* Recurrent, disseminated *Mycobacterium marinum* infection caused by the same genotypically defined strain in an immunocompromised patient. *J Clin Microbiol* 1999; **37**: 3059–61.

31 Blackwell VC, Hamilton AJ, Hay RJ. Production of a species specific monoclonal antibody against 56-kDa *Mycobacterium marinum* antigen which is potentially useful in culture identification. *FEMS Immunol Med Microbiol* 2001; **30**: 9–12.

32 Posteraro B, Sanguinetti M, Garcovich A *et al.* Polymerase chain reaction-reverse cross blot hybridization assay in the diagnosis of sporotrichoid *Mycobacterium marinum* infection. *Br J Dermatol* 1998; **139**: 872–6.

33 Aubry A, Jarlier V, Escolano S *et al.* Antibiotic susceptibility patterns of *Mycobacterium marinum. Antimicrob Agents Chemother* 2000; **44**: 3133–6.

34 Rhomberg PR, Jones RN. In vitro activity of 11 antimicrobial agents, including gatifloxacin and GAR936, tested against clinical isolates of Mycobacterium marinum. *Diag Microbial Infect Dis* 2002; **42**: 145–7.
35 Wagner D, Young LS. Nontuberculous mycobacterial infections: a clinical review. *Infection* 2004; **32**: 257–70.
36 Dodiuk-Gad R, Dyachenko P, Ziv M *et al.* Nontuberculous mycobacterial infections of the skin; A retrospective study of 25 cases. *J Am Acad Dermatol* 2007; **57**: 413–20.
37 Rallis E, Kumanantaki-Mathioudaki E. Treatment of *Mycobacterium marinum* cutaneous infections *Exp Opin Pharmacotherapy* 2007; **8**: 2965–78.
38 Rajesh G, Ip WY, Chow SP *et al.* Treating deep-seated *Mycobacterium marinum* infection in the hand: a report of three cases. *Hand Surg* 2006; **11**: 83–8.
39 Batty MA, Turner DPJ, Chamberlain ST. *Mycobacterium marinum* hand infection: case reports and review of literature. *Br J Plast Surg* 2000; **53**: 161–5.
40 Weigel SR, Kongshoj B, Wulf SC. *Mycobacterium marinum* infection cured by photodynamic therapy. *Arch Dermatol* 2006; **142**: 141–2.
41 Schmoor P, Descamps V, Bouscarat F *et al.* Tropical fish salesmen's knowledge and behavior concerning 'fish tank granuloma'. *Ann Dermatol Venerol* 2003; **130**: 425–7.

M. kansasii

M. kansasii is a slow-growing, photochromogenic bacterium of Runyon Group I that grows optimally at 37°C. Tap water is the major reservoir of infection for this organism [1]. It is found worldwide, but is particularly prevalent in temperate zones such as the USA, the UK, northern France and Belgium. Classically, *M. kansasii* infection produces a granulomatous pulmonary infection in middle-aged men with underlying lung disease [2]. It may also cause superficial cervical lymphadenopathy in young children [3], meningitis, tendonitis, synovitis, arthritis, osteomyelitis or carpal tunnel syndrome [4]. It most commonly affects persons exposed to contaminated water, particularly after local trauma. There is no evidence of person-to-person spread. First reports of the organism as a cutaneous pathogen were not until 1965 [5], and it remains rare, with only 45 cases reported in the literature in a review in 2001 [6]. In 72% of those cases, an immunological disorder resulting from chemotherapy, autoimmune disease [7], AIDS [8], renal or cardiac transplantation [9] or other predisposing factors was noted [10]. Most patients who present with very localized, primary cutaneous infection are immunocompetent, whereas the majority of persons with disseminated skin lesions or pulmonary infection are immunocompromised [2].

As a primary cutaneous disease, *M. kansasii* produces a variety of lesions, usually confined to a distal extremity. Sporotrichoid nodules [11], verrucous papules, papulopustules with necrotic centres, erythematous plaques, cellulitis [12], rhinophyma [13], single and multiple abscesses have all been reported. Papulonecrotic tuberculid skin lesions have been reported in one patient [14].

Skin lesions associated with disseminated *M. kansasii* have increased since the onset of the AIDS epidemic, and *M. kansasii* is the second most frequent cause of disseminated mycobacteriosis in AIDS patients after *M. avium* complex [15]. Disseminated visceral infection can be life-threatening.

The choice of treatment should be determined by *in vitro* sensitivity. Current recommended guidelines for treatment of *M. kansasii* extrapulmonary disease are rifampicin and ethambutol for 9 months, with continuation of therapy for a total of 15–24 months in those patients who are immunocompromised. The addition of streptomycin and/or clarithromycin or azithomycin should be considered if the condition is not responding or if there is rifampicin resistance [16]. The American Thoracic Society treatment guidelines published in 2007 [17] do not make specific recommendations for treatment of extrapulmonary disease.

References

1 Bert LP, Steadham JE. Improved techniques for isolation of *Mycobacterium kansasii* from water. *J Clin Microbiol* 1981; **13**: 969–75.
2 Stengem J, Grande JS, Hsu S. Localized primary cutaneous *Mycobacterium kansasii* infection in an immunocompromised patient. *J Am Acad Dermatol* 1999; **41**: 854–6.
3 White MP, Bangesh H, Goel KM *et al.* Non-tuberculous mycobacterial lymphadenitis. *Arch Dis Child* 1986; **61**: 368–71.
4 Mayberry JD, Mullins F, Stone OJ. Cutaneous infections due to *Mycobacterium kansasii*. *JAMA* 1965; **194**: 1135–7.
5 Chaves A, Torrelo A, Mediero IG *et al.* Primary cutaneous *Mycobacterium kansasii* infection in a child. *Pediatr Dermatol* 2001; **18**: 131–4.
6 Gerster JC, Duvoisin B, Dudler J *et al.* Tenosynovitis of the hands caused by *Mycobacterium kansasii* in a patient with scleroderma. *J Rheumatol* 2004; **31**: 2523–5.
7 Czelusta A, Moore AY. Cutaneous *Mycobacterium kansasii* infection in a patient with systemic lupus erythematosus. *J Am Acad Dermatol* 1999; **40**: 359–63.
8 Curco N, Pagerols X, Gomez L *et al. Mycobacterium kansasii* infection limited to the skin in a patient with AIDS. *Br J Dermatol* 1996; **135**: 324–6.
9 Patel R, Roberts GD, Keating MR *et al.* Infections due to nontuberculous mycobacteria in kidney, heart and liver transplants. *Clin Infect Dis* 1994; **19**: 263–73.
10 Breathnach A, Levell N, Munro C *et al.* Cutaneous *Mycobacterium kansasii* infection: a case report and review. *Clin Infect Dis* 1995; **20**: 812–7.
11 Dore N, Collins JP, Mankiewicz E. A sporotrichoid-like *M. kansasii* infection of the skin treated with minocycline hydrochloride. *Br J Dermatol* 1979; **101**: 75–9.
12 Rosen T. Cutaneous *M. kansasii* infection presenting as cellulitis. *Cutis* 1983; **31**: 87–9.
13 Klotch DW, Owens MH, Wild LM. *Mycobacterium kansasii* presenting as an unusual type of rhinophyma. *Otolaryngol Head Neck Surg* 1992; **107**: 792–5.
14 Callahan EF, Licata AL, Madison JF. Cutaneous *Mycobacterium kansasii* infection associated with a papulonecrotic tuberculid reaction. *J Am Acad Dermatol* 1997; **36**: 497–9.
15 Horsburgh CR Jr, Selick RM. The epidemiology of disseminated nontuberculous mycobacterial infection in the acquired immunodeficiency syndrome (AIDS). *Am Rev Respir Dis* 1989; **139**: 4–7.
16 Subcommittee of the Joint Committee of the British Thoracic Society. Management of opportunist mycobacterial infections: Joint Tuberculosis Committee guidelines 1999. *Thorax* 2000; **55**: 210–8.
17 Griffith DE, Aksamit T, Brown-Elliott BA *et al.* An official ATS/IDSA statement: Diagnosis, treatment and prevention of nontuberculous mycobacterial disease. *Am J Respir Crit Care Med* 2007; **175**: 367–416.

M. ulcerans

Synonym

- Numerous local names, including Buruli ulcer (Uganda)

Aetiology. *Mycobacterium ulcerans* is a slow-growing environmental mycobacterium that infects the skin and subcutaneous tissue, giving rise to a painless nodule, papule, plaque or oedema which evolves into a painless ulcer with undermined edges, often leading to disabling sequelae [1]. It grows optimally on routine mycobacteriological media at 32°C. The major virulence factor is a lipid toxin, myolactone, which causes necrosis of fat and subcutaneous tissue [2]. It is prevalent in riverine areas (swamps, lakes, slow-flowing rivers, etc.) that have a humid hot climate, but the exact mechanism of transmission of the mycobacterium is unknown [1].

In 1897, Cook in Uganda first described large ulcers, almost certainly caused by *M. ulcerans* [3]. However, the aetiological agent was not isolated until 1948 when Australian scientists were investigating a cluster of patients with unusual ulcers in eastern Victoria [4]. In the 1960s, the disease was noted to be endemic in refugee camps in Buruli, Uganda near the Nile [5]. Buruli ulcer has now been reported in over 30 countries in Africa, the Americas, Asia and the Western Pacific, mainly in tropical and subtropical regions [6], and *M. ulcerans* is the third most important pathogen of man after *M. tuberculosis* and *M. leprae.* Its emergence in several West African countries over the past decade has been dramatic, notably in Benin, Cote d'Ivoire and Ghana [7], with other important foci in French Guiana, Papua New Guinea and Australia [1]. In some African communities Buruli ulcer has replaced TB and leprosy as the most prevalent mycobacterial disease. The rising incidence of the disease, its predilection for poor rural communities, the cost of complex surgery, the lost production during illness and the reduced fitness after recovery combine to make Buruli ulcer a major socio-economic burden in areas of prevalence [8].

Epidemiology and transmission. There is evidence that *M. ulcerans* is not usually transmitted from person-to-person but that it is mainly acquired from its aquatic niches [9]. It has been recovered from aquatic insects, fish and molluscs in endemic areas [10,11], but these animals do not develop overt disease. Certain aquatic insects (*Naucoridae)* concentrate *M. ulcerans* in their salivary glands [12,13]. These insects are predators and may feed on molluscs that in turn feed off the biofilm of water plants that appear to contain *M. ulcerans* [13,14]. They have also been shown under experimental conditions to transmit the pathogen to mice after biting [13]. It is not definitely known whether insect bites represent the route of transmission to man as few patients can recall being bitten; an alternative mode of transmission may be penetrating skin injury. A recent case–control study of risk factors for Buruli ulcer supports these two theories of transmission as the use of bed nets and also the wearing of long clothing during farming activities were protective for Buruli ulcer infection [15]. Children outnumber adults in most reported series, and this fact may explain why many affected individuals have no record of previous injury or bites. Person-to-person transmission has only rarely been documented [16]. HIV infection does not seem to predispose to *M. ulcerans* [17].

Pathogenesis and pathology [18]. There is a latent period of 2 months or more before an infection becomes overt. After inoculation into the skin, *M. ulcerans* proliferates and elaborates toxins that lead to tissue necrosis. One of the toxins has been identified as mycolactone, a polyketone toxin [2], and phospholipase C has also been implicated [19]. The earliest change is an acute necrosis of dermal and subcutaneous tissue; characteristically, there is an extensive involvement of the subcutaneous fat as a septal panniculitis. The fat becomes necrotic and may calcify. Mycobacteria can be found, in spherical clumps, outside cells, in the layer of exudate on the ulcer floor, and in the fatty septae; some organisms show signs of degeneration and lose their usual rod-like shape. Necrosis of the dermis extends laterally, leading to the characteristic undermining of the ulcer edge. The organism selectively destroys those tissues within its own viable temperature range [20]; muscle is usually spared, perhaps because of its higher temperature. In the deeper dermis, a leukocytoclastic vasculitis is seen, affecting small and medium-sized vessels. After some months, healing starts and is accompanied by a lymphocytic or granulomatous reaction. Fibrosis and scarring complete the sequence.



Fig. 31.30 *Mycobacterium ulcerans* in an 8-year-old child. (Courtesy of Professor F. Portaels, Institute of Tropical Medicine, Antwerp, Belgium.)

Clinical features [21]. About 70% of patients are children below 15 years of age. The initial lesion is a small, firm, mobile, subcutaneous nodule, which may be pruritic and is usually on an arm or leg, but can be on the trunk or head. Intradermal papules have been observed in some Australian cases. Well-demarcated, painless plaques can also occur. Some cases do not progress further, but usually a nodule will break down to form a shallow necrotic ulcer, which extends rapidly and irregularly, with deeply undermined edges (Fig. 31.30). An ulcer may reach a diameter of several centimetres over the course of a few weeks. The floor of the ulcer is formed of necrotic fat, and there may be a clear mucoid discharge. Ulcers are usually single, though satellites may develop. Large lesions may be surrounded by extensive induration. There is little or no constitutional disturbance, even with severe local disease. Rarely, the onset is a diffuse, cellulitis-like infiltration, with massive oedema. Osteomyelitis can occur in bone adjacent to skin lesions, but involvement of other organs is rare. Disseminated disease has occurred in association with HIV infection [22].

The course is variable, but usually prolonged. Healing may occur after 6–9 months, but small intractable lesions may persist longer. An ulcer may grow to more than 25 cm in diameter. Necrosis may extend to muscle or bone. The fibrosis and calcification which accompany healing may lead to contractures and severe deformity.

Unfortunately, because the ulcers are painless and victims often live in remote areas, most patients do not receive medical attention until the damage is extensive. A review of 102 patients in Ghana indicated that the average length of hospital stay was more than 100 days; the infection led to 10 amputations, 12 joint contractures and two deaths from tetanus and sepsis [8].

Diagnosis. In endemic areas, suspicion should allow an early diagnosis to be made. However, sporadic or anomalous cases with ulcerating lesions, presenting when the patient has left the area [23], may be confused with tuberculosis, blastomycosis or other deep fungal infection, cellulitis or pyoderma gangrenosum. In early lesions, foreign body granuloma, epidermoid cyst, appendage tumours, and other causes of panniculitis, will come into the differential diagnosis. Bacteriological examination of smears from swabs taken from under the rim of the ulcer, or of curettage or biopsy specimens, will reveal clumps of acid-fast organisms, which can be cultured at 32°C, although this may take 6–8 weeks. IS 2404 PCR, which can be performed directly from ulcer swabs, approaches 100% sensitivity and specificity [24].

Treatment. Skin lesions can be excised, although the recurrence rate approaches 16% at 1 year [25] for small lesions and reaches 28% among late severe cases, which often require extensive radical surgery and grafting and may result in significant morbidity [1]. Most people in endemic areas do not have access to surgical care, and those that do may fail to report the disease early as they fear the possible devastating effects of surgery [26]. In view of these difficulties, the need to develop drug treatments has been one of the main priorities of the World Health Organization (WHO) since the establishment of the Buruli Ulcer Initiative in 1998 [1]. Eight weeks' treatment with a combination of rifampicin–streptomycin or rifampicin–amikacin has been shown to be effective in a murine model of Buruli ulcer [27]. Cumulative experience of treating about 300 patients in Benin, Cameroon and Ghana has shown that treatment with rifampicin and streptomycin/amikacin for 8 weeks resulted in complete healing of nearly 50% of Buruli lesions with a recurrence rate of only 2% [28]. This regimen has now been adopted by the WHO [6]. The much lower recurrence rate compared to surgery suggests that *M. ulcerans* organisms may still be present at excision margins after surgery [29]. The oedematous form of Buruli ulcer has also been shown to respond particularly well to the antibiotic regimen, presumably because mycolactone production is inhibited [29].

The complete genome sequence of *M. ulcerans* was published in 2007 and has led to the sequencing of the gene that produces mycolactone, and has revealed how mycolatone is synthesized. Future treatments might involve blocking mycolactone production [6]. BCG vaccination appears to offer some short-term protection against Buruli ulcer and may protect against osteomyelitis [30].

References

1 van der Werf TS, Stienstra Y, Johnson RC *et al. Mycobacterium ulcerans* disease. *Bull World Health Organ* 2005; **83**: 785–91.

2 George KM, Chatterjee D, Gunawardana G *et al.* Mycolactone: a polyketide toxin from *Mycobacterium ulcerans* required for virulence. *Science* 1999; **283**: 854–7.

3 Anonymous. Buruli ulcer. *BMJ* 1970; **ii**: 378–9.

4 MacCallum P, Tolhurst JC, Buckle G *et al.* A new mycobacterial infection in man. *J Pathol Bacteriol* 1948; **60**: 92–122.

5 Uganda Buruli Group. Clinical features and treatment of pre-ulcerative Buruli lesions (*Mycobacterium ulcerans* infection). Report II of the Uganda Buruli Group. *BMJ* 1970; **2**: 390–3.

6 World Health Organization. World Health Organization; 2005. Buruli ulcer disease (*Mycobacterium ulcerans* infection). Fact Sheet No.199. Updated March 2007.

7 Amofah G, Bonsu F, Tetteh C *et al.* Buruli ulcer in Ghana: results of a national case search. *Emerg Infect Dis* 2002; **8**: 167–70.

8 Asiedu K, Estuaful S. Socioeconomic implications of Buruli ulcer in Ghana: a three-year review. *Am J Trop Med Hyg* 1998; **59**: 1015–22.

9 Duker AA, Portaels F, Hale M. Pathways of *Mycobacterium ulcerans* infection: a review. *Environ Int* 2006; **32**: 567–73.

10 Portaels F, Chemial K, Elsen P *et al. Mycobacterium ulcerans* in wild animals. *Rev Sci Tech* 2001; **20**: 252–64.

11 Eddyani M, Ofori-Adjei D, Teugels G *et al.* Potential role for fish in transmission of *Mycobacterium ulcerans* disease (Buruli ulcer): an environmental study. *Environ Microbial* 2004; **70**: 5679–81.

12 Silva MT, Portaels F, Pedrosa J. Aquatic insects and *Mycobacterium ulcerans.* An association relevant to Burli ulcer control. *PloS Med* 2007; **4**: e63.

13 Marsollier L, Robert R, Aubry J *et al*. Aquatic insects as a vector for *Mycobacterium ulcerans*. *Appl Environ Microbiol* 2002; **68**: 4623–8.

14 Marsollier L, Severin T, Aubry J *et al.* Aquatic snails passive hosts of *Mycobacterium ulcerans. Appl Environ Microbiol* 2004; **70**: 6296–8.

15 Pouillot R, Matias G, Wondje CM *et al.* Risk factors for Buruli ulcer: a case control study in Cameroon. *PloS Negl Trop Dis* 2007; **1**: e 101.

16 Debacker M, Zinsou C, Aguiar J *et al. Mycobacterium ulcerans* disease (Buruli ulcer) following human bite. *Lancet* 2002; **360**: 1830.

17 Stienstra Y, van der Graaf WTA, te Meerman GJ *et al.* Susceptibility to development of *Mycobacterium ulcerans* disease: review of possible risk factors. *Trop Med Int Health* 2001; **6**: 554–62.

18 Hayman J, McQueen A. The pathology of *M. ulcerans* infection. *Pathology* 1985; **17**: 594–600.

19 Gomez A, Mve-Obiang A, Vray B *et al.* Biochemical and genetic evidence for phospholipase C activity in *Mycobacterium ulcerans*. *Infect Immunity* 2000; **68**: 2995–7.

20 Tyrrell DAS, McLauchlan SL, Goodwin CS. The growth of some mycobacteria on cultured human tissues. *Br J Exp Pathol* 1975; **56**: 99–102.

21 Hayman J. Clinical features of *M. ulcerans* infections. *Aust J Dermatol* 1985; **26**: 67–73.

22 Johnson C, Ifebe D, Hans-Moevi A *et al.* Disseminated *Mycobacterium ulcerans* disease in an HIV-positive patient: a case study. *AIDS* 2002; **16:** 1704–5.

23 Dawson JF, Allen GE. Ulcer due to *M. ulcerans* in Northern Ireland. *Clin Exp Dermatol* 1985; **10**: 572–6.

24 Russell FM, Starr M, Hayman J *et al. Mycobacterium ulcerans* infection diagnosed by polymerase chain reaction. *J Paed Child Health* 2002; **38**: 311–3.

25 Amofah G, Asamoah S, Afram-Gyening C. Effectiveness of excision of pre-ulcerative Buruli ulcer in a rural district in Ghana. *Trop Doct* 1998; **28**: 81–3.

26 Aujoulat I, Johnson C, Zinsou C *et al.* Psychological aspects of health seeking behaviours of patients with Buruli Ulcer in southern Benin. *Trop Med Int Health* 2003; **8**: 750–9.

27 World Health Organization. Provisional guidance on the role of specific antibiotics in the management of Mycobacterium ulcerans disease (Buruli ulcer). http://www.who.int/buruli/information/antibiotics/en/index.html.

28 Lefrançois S, Robert J, Chauffour A *et al.* Curing *Mycobacterium ulcerans* in mice with a combination of rifampin–streptomycin or rifampin–amicacin. *Antimicrob Agents Chemother* 2007; **51**: 645–50.

29 Wansbrough-Jones M, Phillips R. Buruli ulcer: emerging from obscurity. *Lancet* 2006; **367**: 1849–58.

30 Walsh DS, Portaels F, Meyers WM. Buruli ulcer (*Mycobacterium ulcerans* infection). *Trans R Soc Trop Med Hyg* 2008; **102**: 969–78.

Other slow growers

M. scrofulaceum, *M. szulgai* and *M. avium* are of dermatological interest.

M. scrofulaceum

Historically, *M. scrofulaceum* has been associated with cervical lymphadenitis in young children, but in recent years the frequency of this infection has declined and there are now more cases caused by *M. avium* complex [1]. Recent studies have shown that the newly described species *M. parascrofulaceum* may account for many of the clinical isolates [2]. Submandibular and submaxillary

nodes are usually involved; the disease is often unilateral with few constitutional symptoms, and can resolve spontaneously. Skin abscesses due to *M. scrofulaceum* infection have been reported [3] and also chronic ulcerative and nodular skin lesions and pulmonary infection in a patient with HIV infection [4]. Surgical treatment of infected lymph nodes is the treatment of choice. For more widespread disease, regimens similar to those used for treatment of *M. avium* complex have been recommended, as isolates of *M. scrofulaceum* have similar antibiotic susceptibility patterns [5].

M. szulgai

M. szulgai was first described in 1972 [6] and has a worldwide distribution. Infection is principally pulmonary, but infections have also involved bursae, tendon sheaths, bones, lymph nodes and skin. Skin lesions include diffuse cellulitis, nodules and sinuses [7], and multiple inflammatory skin lesions [8]. Intralesional or systemic steroids were found to be a risk factor for development of skin lesions in two-thirds of patients in one reported series [9]. Isoniazid, rifampicin, ethambutol and streptomycin have been used for treatment of *M. szulgai* infection [10].

M. avium complex

Incidence. Disseminated infections with *M. avium–intracellulare* were rare before the emergence of the AIDS epidemic, but their incidence is now rising sharply [9,11], and organisms of the *M. avium–intracellulare* complex are now one of the commonest causes of opportunistic infection in patients with AIDS [12].

Pathogenesis. The *M. avium* complex comprises *M. avium* and *M. intracellulare*; these are closely related organisms that cannot be differentiated by standard laboratory methods [13], although the separate genomes can be distinguished by PCR-aided DNA–DNA hybridization [14]. They are slow-growing organisms with optimal growth at 37°C and are ubiquitous saprophytes, found in tap water, soil, dairy products, animals and house dust [15]. Both the respiratory and gastrointestinal tracts serve as portals of entry for systemic infection, and as many as 30% of normal human faecal samples yield isolates of *M. avium* complex [16]. Skin involvement secondary to disseminated disease is uncommon and primary skin infection is rare [17].

Clinical features. Chronic pulmonary infection is the most common form of human disease, with lesions similar to tuberculosis. In immunocompetent hosts, infection usually occurs in patients with predisposing lung conditions, which include pneumoconiosis, silicosis and cystic fibrosis; the prognosis is strongly influenced by the associated disease [15]. Osteomyelitis [18] and granulomatous tenosynovitis [19] have both been reported, and *M. avium* complex is now the commonest cause of cervical lymphadenitis in children [1,20]. Involvement of the skin is uncommon, but can occur either following traumatic skin inoculation in cervical lymphadenitis, in which case sinus formation is indistinguishable from tuberculous scrofuloderma (Fig. 31.31), or in immunocompromised hosts, in whom *M. avium* may disseminate from primary visceral lesions. Skin lesions are of variable appearance and include multiple ulcers [21], nodules [22], ulcerated



Fig. 31.31 *Mycobacterium avium* complex infection of the left cheek and submandibular area, showing sinuses and resembling lupus vulgaris. (Courtesy of Dr P. Kullavanijaya, Institute of Dermatology, Bangkok, Thailand, and the Editor of the *British Journal of Dermatology*.)



Fig. 31.32 *Mycobacterium avium* complex infection presenting as an erythematous nodule with central ulceration on the extensor aspect of the forearm in an immunosuppressed patient with systemic lupus erythematosus. (Courtesy of Dr H. Kakinuma, Surugadai Nihon University Hospital, Chiyoda, Tokyo, Japan, and the Editor of the *British Journal of Dermatology*.)

nodules (Fig. 31.32), abscesses [23], painless nodules and plaques resembling lepromatous leprosy [24] or lupus vulgaris [25], and also lesions resembling prurigo nodularis [26]. Sporotrichoid spread [27] and lichen scrofulosorum have been reported with *M. avium* infection [28].

In HIV-infected patients, the most common manifestation of *M. avium* complex infection is mycobacteraemia, but skin lesions may provide a clue to the presence of disseminated *M. avium* complex infection. Infection tends to occur late in HIV disease and most frequently in patients whose $CD4^+$ cell counts have fallen below 50 cells/mm^3 [15]. The incidence of disseminated and cutaneous lesions is decreasing in most centres because of the use of highly active antiretroviral therapy (HAART), which restores some immune competence, and the use of prophylactic antimycobacterial drugs [29]. On starting HAART, some patients

may experience *M. avium* immune restoration disease due to restoration of delayed hypersensitivity responses to mycobacterial antigens. Symptoms include fever, lymphadenitis and cutaneous lesions [30].

A review of the published cases of disseminated infection in patients without AIDS emphasizes the frequent association with haematological malignancies (particularly hairy cell leukaemia), connective tissue disease and corticosteroid or cytotoxic therapy [31,32].

Diagnosis. The diagnosis may be made by blood culture, or by the culture of *M. avium–intracellulare* complex from bone marrow or liver biopsy. In patients with cutaneous lesions, culture of skin biopsy specimens or aspirated seropurulent fluid may give positive results [23]. Tissue staining for acid-fast bacilli is often negative. Histology shows non-caseating granulomas, and sometimes acid-fast bacilli within giant cells or extracellularly.

Treatment. Treatment of *M. avium* complex was unsatisfactory due to frequent MDR, but the introduction of the newer macrolides clarithromycin and azithromycin, and of rifabutin, has greatly improved treatment outcomes. These agents are, however, associated with many adverse effects and potential drug–drug interactions, particularly in those patients who are on antiretroviral therapy. Clarithromycin and azithromycin must be administered in combination with other agents such as ethambutol to prevent emergence of macrolide resistance [33]. Ciprofloxacin has also been used in some treatment regimens [34]. It is recommended that patients with lymphadenitis are treated surgically with complete excision of the nodes [33]. Surgical excision has also been used in some patients with localized skin lesions [22]. In immunocompetent patients with extrapulmonary disease, chemotherapy should probably be continued for 18–24 months. In patients with HIV disease, treatment should be life-long unless there is confidence that the immune system has been restored by HAART [35]. Azithromycin appears to be protective against disseminated *M. avium* complex in those patients unresponsive or non-adherent to HAART, but does not appear to prevent the development of immune restoration disease [36].

References

1 Wolinsky E. Mycobacterial lymphadenitis in children: a prospective study of 105 nontuberculous cases with long-term follow-up. *Clin Infect Dis* 1995; **20**: 954–63.

2 Turenne CY, Cook VJ, Burdz TV *et al*. *Mycobacterium parascrofulaceum* sp. nov., novel slowly growing scotochomogenic clinical isolate related to *Mycobacterium simiae. Int J Syst Evolu Microbiol* 2004; **54**: 1543–51.

3 Murray-Leisure KA, Egan N, Weitekamp MR. Skin lesions caused by *M. scrofulaceum*. *Arch Dermatol* 1987; **123**: 369–70.

4 Sanders JW, Walsh AD, Snider RL *et al*. Disseminated *Mycobacterium scrofulaceum* infection: a potentially treatable complication of AIDS. *Clin Infect Dis* 1995; **20**: 549–56.

5 Fry KL, Meissner PS, Falkinham JO III. Epidemiology of infection by nontuberculous mycobacteria, 6: identification and use of epidemiological markers for studies of *Mycobacterium avium*, *M. intracellulare* and *M. scrofulaceum. Am Rev Respir Dis* 1986; **134**: 39–43.

6 Marks J, Jenkins PA, Tsukamara M. *Mycobacterium szulgai*: a new pathogen. *Tubercle* 1972; **53**: 210–4.

7 Sybert A, Tsou E, Garagusi VF. Cutaneous infection due to *M. szulgai. Am Rev Respir Dis* 1977; **115**: 695–8.

8 Cross GM, Guill MA, Aton JK. Cutaneous *M. szulgai* infection. *Arch Dermatol* 1985; **121**: 247–9.

9 Maloney JM, Gregg CR, Stephens DS *et al*. Infections caused by *Mycobacterium szulgai* in humans. *Rev Infect Dis* 1987; **9**: 120–6.

10 Collins FM. Mycobacterial disease, immunosuppression and acquired immunodeficiency syndrome. *Clin Microbiol Rev* 1989; **2**: 360–77.

11 Woods GL, Washington JA 2nd. Mycobacteria other than *Mycobacterium tuberculosis:* review of microbiological and clinical aspects. *Rev Infect Dis* 1987; **9**: 275–94.

12 Lerner CW, Tapper MC. Opportunistic infection complicating acquired immune deficiency syndrome. *Medicine* 1984; **63**: 155–64.

13 Indelied CB, Kemper CA, Bermudez LM. The *Mycobacterium avium* complex. *Clin Microbiol Rev* 1993; **6**: 266–310.

14 Ito K. *Mycobacterium avium* infection of the skin and recent advances in genetic diagnostic procedures. *Jpn J Dermatol* 1996; **106**: 1277–81.

15 Falkinham JO III. Epidemiology of infection by nontuberculous mycobacteria. *Clin Microbiol* Rev 1996; **9**: 177–215.

16 Portaels F, Larsson L, Smeets P. Isolation of mycobacteria from healthy persons' stools. *Int J Lepr* 1988; **56**: 468–71.

17 Estaban J, Gorgolas M, Fernanddez-Guerrero ML *et al*. Localised cutaneous infection caused by *Mycobacterium avium* complex in an AIDS patient. *Clin Exp Dermatol* 1996; **21**: 230–1.

18 Collert S, Petrini B, Wickman K. Osteomyelitis caused by *Mycobacterium avium*. *Acta Orthop Scand* 1983; **54**: 449–51.

19 Hellinger WC, Smiluck JD, Grieder JL *et al*. Localised soft-tissue infections with *Mycobacterium avium/Mycobacterium intracellulare* complex in immunocompetent patients: granulomatous tenosynovitis of the hand and wrist. *Clin Infect Dis* 1995; **21**: 65–9.

20 Colville A. Retrospective review of culture positive mycobacterial lymphadenitis cases in children in Nottingham, 1979–1990. *Eur J Clin Microbiol Infect Dis* 1993; **12**: 192–5.

21 Cox SK, Strausbaugh LJ. Chronic cutaneous infection caused by *Mycobacterium intracellulare*. *Arch Dermatol* 1981; **117**: 794–6.

22 Ichiki Y, Hirose M, Akiyama T *et al*. Skin infection caused by *Mycobacterium avium. Br J Dermatol* 1997; **136**: 260–3.

23 Lugo-Janer G, Cruz A, Sanchez JL. Disseminated cutaneous infection caused by *Mycobacterium avium* complex. *Arch Dermatol* 1990; **126**: 1108–10.

24 Cole GW, Gerhard J. *M. avium* infection of the skin resembling lepromatous leprosy. *Br J Dermatol* 1979; **101**: 71–4.

25 Kullavanijaya P, Sirimachan S, Surarak S. Primary cutaneous infection with *Mycobacterium avium-intracellulare* complex resembling lupus vulgaris. *Br J Dermatol* 1997; **136**: 264–6.

26 Mattila JO, Vornanen M, Vaara J *et al*. Mycobacteria in prurigo nodularis. *J Am Acad Dermatol* 1996; **34**: 224–8.

27 Kayal JD, McCall CO. Sporotrichoid cutaneous *Mycobacterium avium* complex infection. *J Am Acad Dermatol* 2002; **47** (5 Suppl.): S249–50.

28 Komatsu H, Terunuma A, Tabata N, Tagami H. *Mycobacterium avium* infection of the skin associated with lichen scrofulosorum: report of three cases. *Br J Dermatol* 1999; **141**: 554–7.

29 Calista D, Morri M, Stagno A *et al*. Changing morbidity of cutaneous disease in patients with HIV after the introduction of highly active antiretroviral therapy including a protease inhibitor. *JAMA* 2000; **284**: 223–8.

30 Hassell M, French MA. *Mycobacterium avium* infection and immune restoration disease after highly active antiretroviral therapy in a patient with HIV and normal $CD4^+$ counts. *Eur J Clin Microbiol Infect Dis* 2001; **20**: 889–91.

31 Horsburgh CR, Mason UG, Farhi DC. Disseminated infection with *M. avium-intracellulare*: a report of 13 cases and review of the literature. *Medicine* 1985; **64**: 36–48.

32 Maurice PDL, Bunker C, Giles F *et al*. *M. avium-intracellulare* infection associated with hairy-cell leukaemia. *Arch Dermatol* 1988; **124**: 1545–9.

33 Griffith DE. Risk–benefit assessment of therapies for *Mycobacterium avium* complex infections. *Drug Saf* 1999; **21**: 137–52.

34 Keiser P, Nassar N, Skiest D *et al*. A retrospective study of the addition of ciprofloxacin to clarithromycin and ethambutol in the treatment of disseminated *Mycobacterium avium* complex infection. *Int J STD AIDS* 1999; **10**: 791–4.

35 Subcommittee of the Joint Committee of the British Thoracic Society. Management of opportunist mycobacterial infections: Joint Tuberculosis Committee guidelines 1999. *Thorax* 2000; **55**: 210–8.

36 Phillips P, Chan K, Hogg R *et al.* Azithromycin prophylaxis for *Mycobacterium avium* complex during the era of highly active antiretroviral therapy: evaluation of a provincial programme. *Clin Infect Dis* 2001; **32**: 1547–53.

Rapidly growing mycobacteria [1]

The species of rapidly growing mycobacteria capable of producing disease in humans are the *Mycobacterium fortuitum* group, the *M. chelonae/abscessus* group, and the *M. smegmatis* group. The *M. fortuitum* group includes *M. fortuitum* and *M. peregrinum* and the taxon known as the 'unnamed third biovariant complex'. *M. chelonae* and *M. abscessus*, along with the newly recognized *M. immunogenum*, are members of the group known collectively as the *M. chelonae/abscessus* group. PCR-based methods for identifying the hsp65 gene developed recently can reliably differentiate between members of this group, which are identical on conventional 16S rDNA sequencing [2]. The *M. smegmatis* group contains *M. smegmatis* and two newly described species, *M. goodii* and *M. wolinskyi* [2]. They cause skin, soft tissue, bone and pulmonary infection, as well as disseminated disease.

M. fortuitum complex, M. chelonae/M. abscessus and *M. smegmatis* group

These organisms are widely distributed in the environment in soil and water and may also be commensal organisms of human skin. They are extremely hardy; members of the *M. fortuitum* group and *M. smegmatis* group can grow at 45°C, and the *M. chelonae/abscessus* group and *M. mucogenicum* resist the activity of organomercurials, chlorine, 2% concentrations of formaldehyde and other commonly used disinfectants [3]. These organisms are commonly isolated from municipal tap water [4]. *M. chelonae* was found as a contaminant in a gentian violet solution [5] and *M. abscessus* has been isolated from contaminated lidocaine (Xylocaine) [6] and histamine solutions [7]. Pseudo-outbreaks have most commonly related to contaminated bronchoscopes and endoscopic cleaning machines, and to contaminated hospital water supplies [3].

Clinical cutaneous disease with these pathogens seems to follow two patterns. In the immunocompetent host, a traumatic injury is followed by the development of localized abscess formation [8]. In the immunocompromised individual, there may be no history of trauma and patients present with disseminated disease, with multiple subcutaneous nodular lesions, positive blood cultures, cervical lymphadenitis, keratitis and occasionally endocarditis [9]. A review of 63 patients with skin or soft tissue infections due to rapidly growing mycobacteria showed that patients with *M. chelonae* and *M. abscessus* infections were more likely to be older than 45 years, to be taking immunosuppressive medication and to have multiple disseminated lesions. This was in contrast to patients with *M. fortuitum* infection who were more likely to have single lesions following surgery or injury at the infected site [10]. Conditions associated with disseminated infection include organ transplantation, rheumatoid arthritis, renal failure and autoimmune disorders. Disease due to *M. chelonae* is strongly associated with concomitant corticosteroid therapy [11].

The *M. fortuitum* group accounts for 60% of community-acquired, localized cutaneous infection caused by rapidly growing mycobacteria, but is a rare cause of pulmonary disease. This group is also responsible for the majority of health-care-associated (nosocomial) cases of post-surgical wound infections and catheter infections [1]. *M. fortuitum* infection of the sternum has been reported after open-heart surgery [12], as a cause of peritonitis in patients receiving continuous ambulatory peritoneal dialysis [13], after localized microinjections (mesotherapy) for pain control [14], and after some cosmetic procedures such as liposuction [15] and prosthetic breast implants [16]. An outbreak of over 60 cases of *M. fortuitum* furunculosis was caused by infected whirlpool footbaths in a nail salon [17]. A patient with lupus vulgaris-like lesions has also recently been described [18].



Fig. 31.33 *Mycobacterium abscessus* infection causing abscesses. (Courtesy of Dr A.G. Smith, North Staffordshire Hospital, Stoke-on-Trent, UK, and the Editor of the *British Journal of Dermatology*.)

The *M. chelonae/abscessus* group is responsible for approximately 95% of disseminated cutaneous infections caused by the rapidly growing mycobacteria [1]; these organisms also cause chronic lung disease and are one of the most common isolates from cystic fibrosis patients. Post-injection abscesses are probably the commonest skin lesions caused by *M. abscessus*, which is the most pathogenic and chemotherapy-resistant of the rapidly growing mycobacteria (Fig. 31.33) [19]. An outbreak in 12 patients at an ear, nose and throat (ENT) clinic in 1969 was due to contaminated histamine injections [7]. An alternative medicine practitioner infected a total of 232 patients with contaminated lidocaine injections [6]. Infections have also been reported after liposuction and liposculpture [15]. Haemodialysis is also a risk factor [20]. A survey across the USA found that NTM were recovered from 83% of water supplies to dialysis units [4]. Two employees at a hot spring bath in Korea developed sporotrichoid lesions due to *M. abscessus* and were assumed to have been contaminated from the bath water [21].

M. chelonae causes community-acquired disease—for example, post-traumatic skin or soft-tissue infection, bone infection and disseminated cutaneous infection; sporadic nosocomial infections also occur—for example, after surgery, after injections and related to catheter use [22]. Implanted porcine heart valves themselves may be contaminated with *M. chelonae* [23]. Disseminated erythematous subcutaneous nodules are the commonest manifestation, most commonly seen on the distal parts of the limbs (Fig. 31.34), or in a sporotrichoid pattern [24]. Localized cellulitis, subcutaneous abscesses and osteomyelitis (usually following skin



Fig. 31.34 *Mycobacterium chelonae* infection of the lower limb. (Courtesy of Dr R.D. Ead, Hope Hospital, Manchester, UK.)

injury), are also seen. Sixty-two per cent of patients infected with *M. chelonae* in one series were receiving corticosteroids and 72% were immunosuppressed [10]. Infection has also been reported after acupuncture [25]. Disseminated disease is rare and HIV infection does not seem to carry a risk for *M. chelonae* infection.

Infections involving the *M. smegmatis* group have included cellulitis, localized abscesses and osteomyelitis after trauma [26]. No cases of disseminated cutaneous infection have been reported to date. Sporadic cases of catheter sepsis and infection after plastic surgery have also been noted [1].

Pathology. Abscess formation in the dermis and subcutis is the rule, but tuberculoid granulomas with or without necrosis may occur (Figs 31.35 & 31.36).

Diagnosis. These infections are easily missed; lesions may be attributed to foreign bodies, deep mycoses or osteitis. The median time from onset of symptoms to diagnosis was 86 days in the largest series available [11]. They should be considered in the differential diagnosis of chronic relapsing nodules and abscesses in immunocompromised individuals. Diagnosis is usually made by the culture of biopsy material; in the case of abscesses, a biopsy from the wall is more likely to yield the organism than is aspirated pus. They all have the distinctive ability to produce visible colonies between 5 and 7 days at temperatures ranging between 22°C and 45°C, but some strains may fail to grow at 37°C. Their identification is possible by differences in culture requirements,

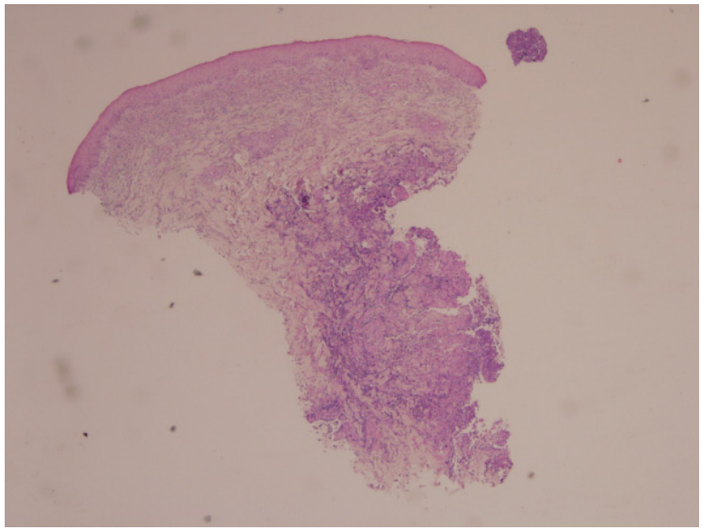


Fig. 31.35 *M. abscessus* infection, showing a cellular infiltrate in the mid and deep dermis. (Courtesy of Dr D. Rozenman, Ha'emek Medical Centre, Afula, Israel.)

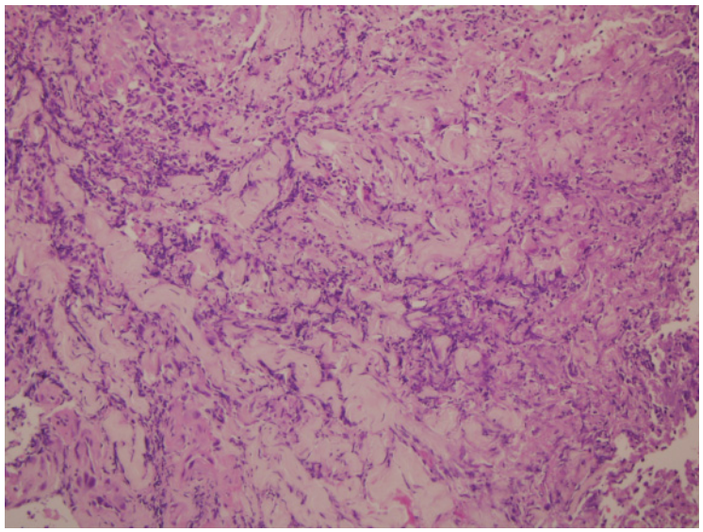


Fig. 31.36 *M. abscessus* infection, showing a heavy infiltrate of neutrophils and nuclear dust in the mid and deep dermis with abscess formation. (Courtesy of Dr D. Rozenman, Ha'emek Medical Centre, Afula, Israel.)

biochemical tests and DNA homology. Clinically, the lesions are not specific to the species involved in the infection [27].

Treatment [11,28]. There are no available studies that compare different antibacterial regimens. Current guidelines recommend susceptibility testing of all isolates, with the use of empirical therapy until susceptibilities are known. Single lesions may respond to monotherapy but disseminated cutaneous or pulmonary disease will require multidrug therapy.

The *M. fortuitum* group is much less drug-resistant than the *M. chelonae/abscessus* group, *M. fortuitum* strains usually being susceptible to amikacin, ciprofloxacin, sulfonamides, cefoxitin and imipenem. The presence of tetracycline-resistant genetic determinants in approximately 50% of members of the *M. fortuitum* group

precludes the use of tetracyclines, including doxycycline. Approximately 80% of isolates are sensitive *in vitro* to clarithromycin but recent evidence has shown that all isolates of *M. fortuitum* and related species *M. smegmatis* contain the *erm* 39 gene that confers resistance to macrolides, so clarithromycin should be used with caution. For serious skin, bone and soft tissue infection a minimum of 4 months' therapy with at least two agents is recommended.

The macrolides clarithromycin and azithromycin are the only oral agents reliably active *in vitro* against infections due to the *M. chelonae/abscessus* group. For serious skin, soft tissue and bone infection, these drugs should be combined with a parenteral medication; amikacin, cetoxitin or imipenem for a minimum of 4 months are appropriate. Amikacin is the most active of the parenteral agents. The new drug tigecycline is promising with its low MIC-values to *M. abscessus* [29]. *M. abscessus* lung disease is still generally incurable with available therapeutic agents.

The *M. smegmatis* group is uniformly sensitive to sulfonamides, doxycycline, imipenem and amikacin.

Surgical debridement may be a useful adjunct to treatment in some patients.

References

1 Brown-Elliot BA, Wallace RJ Jr. Clinical and taxonomic status of pathogenic nonpigmented or late-pigmenting rapidly growing mycobacteria. *Clin Microbial Rev* 2002; **15**: 716–46.

2 Petrini B. *Mycobacterium abscessus*: an emerging rapid-growing potential pathogen. *APMIS* 2006; **114**: 319–28.

3 Brown BA, Springer B, Steingrube VA *et al. Mycobacterium wolinskyi* sp. nov. and *Mycobacterium goodii* sp. nov., two new rapidly growing species related to *Mycobacterium smegmatis* and associated with human wound infections: a cooperative study from the International Working Group on Mycobacterial Taxonomy. *Int J Syst Bacteriol* 1999; **49**: 1493–511.

4 Wallace RJ Jr, Brown BA, Griffith DE. Nosocomial outbreaks/pseudo-outbreaks caused by nontuberculous mycobacteria. *Annu Rev Microbiol* 1998; **52**: 453–90.

5 Carson LA, Bland LA, Cusick LB *et al.* Prevalence of nontuberculous mycobacteria in water supplies of haemodialysis centers. *Appl Environ Microbiol* 1988; **54**: 3122–5.

6 Safranec TJ, Jarvis WR, Carson IA. *Mycobacterium chelonae* wound infection after plastic surgery employing contaminated gentian violet skin marking solution. *N Engl J Med* 1987; **317**: 197–201.

7 Rodriguez G, Ortegon M, Camargo D *et al.* Iatrogenic *Mycobacterium abscessus* infection: histopathology of 71 patients. *Br J Dermatol* 1997; **137**: 214–8.

8 Inman PM, Beck A, Brown AE *et al.* Outbreak of infection abscesses due to *M. abscessus. Arch Dermatol* 1969; **100**: 141–7.

9 Silvestre Salvador JF, Betlloch MI, Alfonso R *et al.* Disseminated skin infection due to *Mycobacterium fortuitum* in an immunocompetent patient. *J Eur Acad Dermatol* 1998; **11**: 158–61.

10 Wallace RJ Jr, Swenson JM, Silcox VA *et al.* Spectrum of disease due to rapidly growing mycobacteria. *Rev Infect Dis* 1983; **5**: 657–79.

11 Daniel Z, Uslan MD, Todd J *et al.* Skin and soft tissue infections due to rapidly growing mycobacteria: comparison of clinical features, treatment and susceptibility. *Arch Dermatol* 2006; **142**: 1287–92.

12 Wallace RJ, Brown BA, Onyi GO. Skin, soft tissue and bone infection due to *Myobacterium chelonae*: importance of prior corticosteroid therapy, frequency of disseminated infections, and resistance to oral antimicrobials other than clarithromycin. *J Infect Dis* 1992; **166**: 405–12.

13 Sameuls LE, Sharma S, Morris RJ *et al. Mycobacterium fortuitum* infection of the sternum: review of the literature and case illustration. *Arch Surg* 1996; **131**: 1344–6.

14 Woods GL, Hall GS, Schreiber MJ. *Mycobacterium fortuitum* peritonitis associated with continuous ambulatory peritoneal dialysis *J Clin Microbiol* 1986; **23**: 786–8.

15 Nagore E, Ramos P, Botella-Estrada R *et al*. Cutaneous infection with *Mycobacterium fortuitum* after localized microinjections (mesotherapy) treated successfully with a triple drug regimen. *Acta Derm Venereol* 2001; **81**: 291–3.

16 Murillo J, Torres M, Bofill L *et al*. Skin and wound infection by rapidly growing mycobacteria: an unexpected complication of liposuction and liposculpture. *Arch Dermatol* 2000; **136**: 1347–52.

17 Haiavy J, Tobin H. *Mycobacterium fortuitum* breast implants infection in prosthetic breast implants. *Plast Reconstr Surg* 2002; **109**: 2124–8.

18 Winthrop KL, Albridge K, South D *et al.* The clinical management and outcome of nail salon-acquired *Mycobacterium fortuitum* skin infection. *Clin Infect Dis* 2004; **38**: 38–44.

19 Lin YC, Chui HC, Hsiao CH *et al.* Cutaneous *Mycobacterium fortuitum* infection mimicking lupus vulgaris. *Br J Dermatol* 2002; **147**: 170–3.

20 Morris-Jones R, Fletcher C, Morris-Jones S *et al. Mycobacterium abscessus*: a cutaneous infection in a patient on renal replacement therapy. *Clin Exp Dermatol* 2001; **25**: 415–8.

21 Lee WJ, Kim TW, Shur KB *et al*. Sporotrichoid dermatosis caused by *Mycobacterium abscessus* from a public bath. *J Dermatol* 2000; **27**: 264–8.

22 Wallace RJ, Brown BA, Onyi GO. Skin, soft tissue and bone infection due to *Myobacterium chelonae*. *J Infect Dis* 1992; **166**: 405–12.

23 Laskowski LF, Marr JJ, Spernoga JF *et al.* Factitious mycobacteria grown from porcine heart valve cultures. *N Engl J Med* 1977; **297**: 101–2.

24 Demitsu T, Nagato H, Inoue T *et al.* Cutaneous *Mycobacterium chelonae* infection with bilateral sporotrichoid involvement. *Int J Dermatol* 2001; **40**: 597–9.

25 Woo PC, Leung KW, Wong SS *et al.* Relatively alcohol resistant mycobacteria are emerging pathogens in patients receiving acupuncture treatment. *J Clin Microbiol* 2002; **40**: 1219–24.

26 Newton JA Jr, Weiss PJ, Bowler WA *et al.* Soft tissue infection due to *Mycobacterium smegmatis*: report of two cases. *Clin Infect Dis* 1993; **16**: 531–3.

27 Palenque E. Skin disease and nontuberculous atypical mycobacteria. *Int J Dermatol* 2000; **39**: 659–66.

28 Griffith DE, Aksamit T, Brown-Elliott BA *et al.* An official ATS/IDSA statement: Diagnosis, treatment and prevention of nontuberculous mycobacterial disease. *Am J Respir Crit Care Med* 2007; **175**: 367–416.

29 Rubinstein E, Vaughn D. Tigecycline; a novel glycylcycline. *Drugs* 2005; **65**: 1317–36.

M. haemophilum

This mycobacterium was first described in 1978 in a patient with Hodgkin's disease [1]. It is an increasingly recognized pathogen in immunocompromised patients, including those with HIV infection [2], following organ transplantation, and in patients with haematological malignancies or with chronic conditions requiring prolonged immunosuppressive therapy [3]. It causes cutaneous, synovial and, less frequently, pulmonary infections [4]. It has also been isolated from otherwise healthy, immunocompetent children with lymphadenitis [5], and was recovered from 16 (18%) of a series of 89 children with cervicofacial lymphadenitis [6]. The natural habitat and means of acquisition of *M. haemophilum* are unknown.

M. haemophilum causes multiple tender cutaneous nodules, often violaceous, which may develop into abscesses or ulcers (Fig. 31.37), and occasionally may present as annular plaques [7] or panniculitis. Lesions typically occur on the extremities and are often situated over joints. This may reflect low optimal temperature growth requirements and a predilection to grow on the cooler areas of the body. Systemic features such as weight loss, tenosynovitis, joint effusions, osteomyelitis or respiratory tract symptoms may coexist. The differential diagnosis includes *M. marinum* and *M. avium* complex infections, other bacterial infections and Kaposi's sarcoma.

M. haemophilum may be cultured from the skin or other tissues or secretions, but has unique growth requirements and therefore may be relatively under-recognized and under-reported. It grows optimally at 30°C to 32°C and the growth media must contain iron.



Fig. 31.37 *Mycobacterium haemophilum* infection producing ulcerated nodules on the left knee and shin, with a non-ulcerated nodule on the medial aspect of the knee. (Courtesy of Dr J.C. Murray, Duke University Medical Center, Durham, NC, USA, and the Editor of the *British Journal of Dermatology*.)

PCR-restriction endonuclease analysis of an amplified 439-bp segment of the *hsp65* gene encoding the 65-kDa heat shock protein can be used for rapid identification of the organism [8].

Histologically, suppurative granulomas containing acid-fast bacilli are usually seen, but occasionally granulomas may be poorly formed and have varying amounts of necrosis [9].

Treatment. There are currently no standardized susceptibility methods for *M. haemophilum*. Agents that appear to be active *in vitro* include amikacin, clarithromycin, ciprofloxacin, rifampicin and rifabutin. Doxycycline and sulphonamides have shown variable susceptibility but all isolates are resistant to ethambutol [10]. Treatment is difficult. Lesions may persist despite therapy or relapse after treatment is stopped. Improvement of immunological status is the basis for successful treatment. Successful treatment has been reported with multidrug regimens including clarithromycin, rifampicin, rifabutin and ciprofloxacin [10,11]. Surgical excision alone is usually adequate treatment for lymphadenitis in immunocompetent children.

Other mycobacteria

The use of molecular testing has brought about the recognition of multiple, newly characterized mycobacterial species that were previously unrecognized by standard techniques [12]. Some are non-pathogenic, but it is likely that the majority will cause clinical disease. Some previously seldom-encountered mycobacteria are increasingly being recognized as a cause of human disease. These include *M. malmoense*, which was recently shown to be the cause of disseminated cutaneous infection in an immunocompetent patient [13], *M. xenopi*, which was reported to cause lupus vulgaris-like skin lesions [14] and disseminated cutaneous lesions in immunosuppressed patients [15], and *M. genavense* [16].

References

1 Sompolinsky D, Lagziel A, Nevah D *et al. Mycobacterium haemophilum* sp. nov. a new pathogen from humans. *Int J Syst Bacteriol* 1978; **28**: 67–75.

2 Martinelli C, Farese A, Carocci A *et al.* First case of *Mycobacterium haemophilum* infection in an AIDS patient in Italy. *J Eur Acad Dermatol Venerol* 2004; **18**: 83–5.

3 Saubolle MA, Kiehn TE, Mary H *et al. Mycobacterium haemophilum*: microbiology and expanding clinical and geographic spectra of disease in humans. *Clin Microbiol Rev* 1996; **9**: 435–47.

4 Shah MK, Sebiti A, Kiehn TE *et al. Mycobacterium haemophilum* in immunocompromised patients. *Clin Infect Dis* 2001; **33**: 330–7.

5 Samra Z, Kaufmann L, Zeharia A *et al.* Optimal detection and identification of *Mycobacterium haemophilum* in specimens from paediatric patients with cervical lymphadenopathy. *J Clin Microbiol* 1999; **37**: 832–4.

6 Bruijnesteijn van Coppenraet LE, Kuiper EJ, Lindeboom JA *et al. Mycobacterium haemophilum* and lymphadenitis in children. *Emerg Infect Dis* 2005; **11**: 62–8.

7 Friedli A, Krischer J, Hirschel B *et al.* An annular plaque due to *Mycobacterium haemophilum* infection in a patient with AIDS. *J Am Acad Dermatol* 2000; **43**: 913–5.

8 Wang SX, Sng LH, Leong LH *et al.* Direct identification of *Mycobacterium haemophilum* in skin lesions of immunocompromised patients by PCR-restriction endonuclease analysis. *J Clin Microbiol* 2004; **42**: 3336–8.

9 Busam KJ, Kiehn TE, Salob SP *et al.* Histological reactions to cutaneous infections by *Mycobacterium haemophilum*. *Am J Surg Pathol* 1999; **23**: 1379–85.

10 Griffith DE, Aksamit T, Brown-Elliott BA *et al.* An official ATS/IDSA statement: Diagnosis, treatment and prevention of nontuberculous mycobacterial disease. *Am J Respir Crit Care Med* 2007; **175**: 367–416.

11 Dever LL, Martin JW, Seaworth B *et al.* Varied presentations and responses to treatment of infections caused by *Mycobacterium haemophilum* infection in a patients with AIDS. *Clin Infect Dis* 1992; **14**: 1195–200.

12 Brown-Elliot BA, Griffith DE, Wallace RJ Jr. Newly described or emerging human species of nontuberculous mycobacteria. *Infect Dis Clin North Am* 2002; **16**: 187–220.

13 Schmoor P, Descamps V, Lebrun-Vignes B *et al. Mycobacterium malmoense* cutaneous infection in an immunocompetent patient. *Ann Dermatol Venereol* 2001; **128**: 139–40.

14 Kielh P, Eicher U, Vakilzadeh FA. Lupus-vulgaris-like atypical mycobacteriosis caused by *M. xenopi* (lupus xenopi). *Hautartzt* 1992; **43**: 569–75.

15 Jiva TM, Jacoby HM, Weymouth LA *et al. Mycobacterium xenopi*: innocent bystander or emerging pathogen? *Clin Infect Dis* 1997; **24**: 226–32.

16 Chocarra A, Gonzalez-Lopez A, Breznes MF *et al.* Disseminated infection due to *Mycobacterium malmoense* in a patient infected with human immunodeficiency virus. *Clin Infect Dis* 1994; **19**: 203–4.

CHAPTER 32

Leprosy

D.N.J. Lockwood
Hospital for Tropical Diseases, London, UK

Synonyms, 32.1
Definition, 32.1
History, 32.1
Aetiology, 32.1
Geographical distribution, 32.2
Pathogenesis of leprosy, 32.3
Histology, 32.4
Immunology, 32.6
Serology, 32.7
Clinical features of leprosy, 32.8
Reactions, 32.12
Nerve damage, 32.13
Eye involvement in leprosy, 32.13
Prognosis, 32.14
Diagnosis, 32.14
Differential diagnosis, 32.15
Treatment, 32.16
Prevention and control, 32.19
Vaccines against leprosy, 32.19

Synonyms

Hansen's disease, hanseniasis, and names in local languages in endemic areas.

Definition

A chronic granulomatous disease caused by *Mycobacterium leprae*, principally affecting peripheral nerves and skin.

History

Endemic in India and the Far East since ancient times, leprosy was imported into Europe in the 4th century BC, perhaps by the troops of Alexander the Great. The European epidemic peaked in the 13th century, then slowly died out [1]. French settlers took leprosy to Canada and African slaves took it to America. It is not known how the disease reached the Australian aborigines. Even after the discovery of the agent, *M. leprae*, by Armauer Hansen in Norway in 1873 (the first bacillus to be associated with a human disease), the infectious nature of leprosy was not readily accepted [2]. The slow spread of the disease and its familial association suggested that it was inherited. This belief, and the fear of the deformities that leprosy may cause, have contributed to the stigma and ostracization that still characterize attitudes towards leprosy. Stigma remains a major obstacle to leprosy control, despite advances in bacteriology, chemotherapy and epidemiology.

Aetiology

Mycobacterium leprae has never been grown *in vitro*. Limited growth has been achieved in the mouse footpad [3], and more widespread growth and disease in immunosuppressed and nude mice [4] and the nine-banded armadillo [5]. The latter has provided mycobacteria for genetic and biochemical analysis and the production of trial vaccines. A primate model of leprosy has been established in three species of monkey [6]. *Mycobacterium leprae* grows at 30–33°C, with a doubling time of 12 days. It is a remarkably hardy organism, remaining viable in the environment for up to 10 days [6]. The sequence of the *M. leprae* genome was published in 2001. *Mycobacterium leprae* has a 3.27-Mb genome that displays extreme reductive evolution [7]. Less than half the genome contains functional genes: many pseudogenes are present. One hundred and sixty-five genes are unique to *M. leprae*, and functions can be attributed to 29 of them. Comparison of biosynthetic pathways with *M. tuberculosis* shows that for lipolysis *M. leprae* has only two genes (*M. tuberculosis* has 22). *Mycobacterium leprae* has lost many genes for carbon catabolism, and many carbon sources (e.g. acetate and galactose) are unavailable to it. *Mycobacterium leprae* growth may be restricted to a few carbon sources on which it can maintain a balanced carbon metabolism. It has also lost anaerobic and microaerophilic electron transfer systems. *Mycobacterium leprae* has many genes for haem and iron-based proteins, but it is severely limited in its iron uptake capacity, since it has lost the ability to produce iron scavenging sideropores [8]. Restriction fragment length polymorphism (RFLP) analysis [9] suggested that *Mycobacterium leprae* was a single species, but recent work based on amino acid sequencing of *M. leprae* proteins suggests that there are subtle strain differences, and this may enable new studies on transmission [10].

Mycobacterium leprae has a complex antigenic cell wall composed of lipids, carbohydrates and proteins. The organism also synthesizes a species-specific lipid, phenolic glycolipid (PGL) [11]. Several polymerase chain reaction (PCR) probes (18 kDa, 36 kDa, 65 kDa and ribosomal RNA sequences) have been developed for the detection of *M. leprae* DNA in tissues from leprosy patients [12]. Although these are specific, they are not yet sensitive enough to be useful in diagnosing patients whose skin is bacteriologically negative on conventional staining. The molecular basis for rifampicin resistance has been elucidated and it is now possible, using a polymerase chain reaction–single strand polymorphism

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

(PCR-SSC) technique, to identify rifampicin-resistant isolates within hours [13].

References

1 Irgens LM, Bjerkedal T. Epidemiology of leprosy in Norway. The history of The National Leprosy Registry of Norway from 1856 until today. *Int J Epidemiol* 1973; **2**: 81–9.
2 Hansen GA. Undersolgelser angraaende spedalskhedens aasger. *Norsk Magazin Laegervidens Kaben* 1874; **4** (Suppl.): 1–88.
3 Levy L, Ji B. The mouse foot-pad technique for cultivation of *Mycobacterium leprae*. *Lepr Rev* 2006; **77**: 5–24.
4 Rees RJW. Animal models in leprosy. In: Rees RJW, ed. *Tuberculosis and Leprosy. British Medical Bulletin*, Vol. 44. Edinburgh: Churchill Livingstone, 1988: 650–64.
5 Storrs EE. The nine-banded armadillo: a model for leprosy and other biomedical research. *Int J Lepr Other Mycobact Dis* 1971; **39**: 703–14.
6 Rees RJ, Young DB, Hastings RC. *The Microbiology of Leprosy*. Edinburgh: Churchill Livingstone, 1994: 49–86.
7 Cole ST, Eiglmeier K, Parkhill J *et al*. Massive gene decay in the leprosy bacillus. *Nature* 2001; **409**: 1007–11.
8 Eiglmeier K, Cole ST. The integrated genome map of *Mycobacterium leprae*. *Lepr Rev* 2001; **72**: 462–9.
9 Williams DL, Gillis TP. A study of the relatedness of *Mycobacterium leprae* isolates using restriction fragment length polymorphism analysis. *Acta Leprol* 1989; **7** (Suppl. 1): 226–30.
10 Young DB. Prospects for molecular epidemiology of leprosy. *Lepr Rev* 2003; **74**: 11–17.
11 Rivoire B, Pessolani MC, Bozic CM *et al.* Chemical definition, cloning, and expression of the major protein of the leprosy bacillus. *Infect Immun* 1994; **62**: 2417–25.
12 Jamil S, Keer JT, Lucas SB *et al*. Use of polymerase chain reaction to assess efficacy of leprosy chemotherapy. *Lancet* 1993; **342**: 264–8.
13 Honore N, Cole ST. Molecular basis of rifampin resistance in *Mycobacterium leprae*. *Antimicrob Agents Chemother* 1993; **37**: 414–8.

Geographical distribution

About 4 million people have, or are disabled by, leprosy. The apparent fall in registered patients from 12 million in 1988 to 0.25 million on treatment in 2006 hides an intriguing picture. Prevalence has fallen due to a combination of effective antibiotic therapy and a change in case definition. Incidence, however, remains stable at around 250 000 new cases annually, with high rates of childhood cases [1].

India dominates the global picture with 60% of the world's leprosy cases; 86% of leprosy patients reside in six countries (India, Brazil, Indonesia, Myanmar, Madagascar and Nepal). Leprosy has not always been a tropical disease; it was endemic in Norway until the early 20th century. Nearly all the new cases now seen in Europe and North America acquired their infection abroad [2].

Leprosy is a chronic disease with a long incubation period. An average incubation time of 2–5 years has been calculated for tuberculoid cases, and 8–12 years for lepromatous cases. American servicemen who developed leprosy after serving in the tropics presented up to 20 years after their presumed exposure [3].

Although leprosy is rarely a primary cause of death, patients have a standardized death rate at least twice that of the general population due to the indirect secondary effects of the disease [4]. It is estimated that 1 million disability adjusted life years (DALY) are lost globally each year due to leprosy, with 6.3 years of healthy life being lost per patient.

Age, sex, household contact and bacille Calmette–Guérin (BCG) vaccination are important determinants of leprosy risk: leprosy incidence reaches a peak at the ages of 10–14 years [5]. An excess of male cases has regularly been found, although this may be due to women being reluctant to present to health workers with skin lesions [6]. Clustering of cases is well recognized, particularly in low endemic areas [7]. Although poor nutritional status was thought to predispose to leprosy, no good evidence substantiates this. Improved socio-economic conditions, extended schooling and good housing reduce the risk of leprosy [8]. Various genes and regions in the human genome have been linked to or associated with susceptibility to leprosy *per se* or with a particular type of leprosy. Perhaps not surprisingly these are not all reproducible in different populations.

Mira *et al*. have identified that certain alleles in the *PARK2* and *PACRG* region on chromosome 6 are associated with susceptibility to leprosy in Vietnamese and Brazilian cohorts [9]. *PARK2* is expressed by both Schwann cells and macrophages. It is an ubiquination E3 ligase and is involved in the delivery of polyubiquinated proteins to the proteosome complex involved in protein degradation [10].

In an Indian cohort homozygotes for the different alleles of the Vitamin D receptor (*VDR*) gene were associated with tuberculoid or lepromatous disease [11]. Upregulation of the *VDR* gene on macrophages is associated with increased intracellular killing of *M. tuberculosis*.

Polymorphisms of the TNF-α promoter region were shown to be associated with increased susceptibility to lepromatous leprosy [12], while in a cohort from southern Brazil the same allele was protective against leprosy *per se* [13]. A study of Malawians did not find any association of this TNF promoter with leprosy [14].

Brazilian and Indian groups have demonstrated that polymorphisms of the IL-10 promoter are associated with resistance to leprosy [15,16].

The differing and sometimes conflicting results of genetic studies may be attributed to differences in study design and sample size. It is also possible that different populations have distinct genetic susceptibilities.

Early in the HIV epidemic it was predicted that HIV infection would worsen leprosy outcomes with more patients developing lepromatous disease, an impaired response to multidrug therapy and fewer reactions. However, none of these have happened and instead HIV immune dysregulation rather than immune suppression dominates the clinical picture in patients with leprosy and HIV.

Being HIV positive does not appear to confer increased susceptibility to leprosy. The full spectrum of standard clinical and histopathological leprosy features have been seen in co-infected persons [17]. These patients also have normal granuloma formation even with low circulating CD4 counts. Co-infected patients appear to be at increased risk of developing leprosy reactions and the borderline types of leprosy dominate the clinical picture. Leprosy may also present as an IRIS phenomenon in HIV-positive patients who have recently started highly active antiretroviral therapy [18,19].

Subclinical infection with *M. leprae* is probably common, but the development of established disease is rare. There is no reliable test for determining whether a person has encountered *M. leprae* and mounted a protective immune response. In contacts of leprosy

patients, there is frequently evidence of specific sensitization to *M. leprae*, using markers of infection such as serum antibody levels, *in vitro* lymphocyte transformation tests (LTTs) and skin test responses to soluble *M. leprae* antigen [20]. Contacts of an untreated elderly man with borderline lepromatous leprosy in a British residential home showed that 23/30 and 25/30 had positive Mitsuda skin test and positive LTT responses, respectively, to *M. leprae* sonicate, but only two contacts had positive antibody (IgM PGL) responses [21]. Self-healing often occurs in early monomacular tuberculoid cases [22]. Leprosy is probably analogous to tuberculosis, in which only 10% of infections manifest as clinical disease [23]. In the 20th century there were only two reported cases of secondary transmission within Britain, cases acquired from a known case of leprosy [24].

Nasal discharges from untreated lepromatous leprosy patients, who are often undiagnosed for several years, are the main source of infection in the community [25]. In Indonesia and Ethiopia, *M. leprae* DNA has been detected in nasal swabs in up to 5% of the population [26]. Infection probably also occurs through the nose. *Mycobacterium leprae* is inhaled, multiplies on the inferior turbinates and has a brief bacteraemic phase before binding to Schwann cells and macrophages. In patients with the tuberculoid types of leprosy, *M. leprae* remains within the skin and nerve compartments and these patients are probably never infectious.

The skin is unimportant in leprosy transmission. Bacilli are rarely found in the epidermis and are only excreted by untreated lepromatous leprosy patients. The only evidence of bacilli entering via the skin comes from case reports of direct inoculation. Leprosy has been transmitted to nude mice through pricks from infected cactus thorns [27]. There is no evidence that biting arthropods transmit leprosy. It is surprising that, in contrast to tuberculosis, there are few documented cases of leprosy occurring in both the medical and non-medical attendants of leprosy patients.

References

1 Anonymous Leprosy: global situation. *Wkly Epidemiol Rec* 2007; **82**: 225–31.
2 Lockwood DN, Reid AJ. The diagnosis of leprosy is delayed in the United Kingdom. *QJM* 2001; **94**: 207–12.
3 Brubaker ML, Binford CH, Trautman JR. Occurrence of leprosy in US veterans after service in endemic areas abroad. *Public Health Rep* 1969; **84**: 1051–8.
4 Noordeen SK. Mortality in leprosy. *Indian J Med Res* 1972; **60**: 439–45.
5 Fine PE. Leprosy: the epidemiology of a slow bacterium. *Epidemiol Rev* 1982; **4**: 161–88.
6 Noordeen SK. The epidemiology of leprosy. In: Hastings RC, ed. *Leprosy.* Edinburgh: Churchill Livingstone, 1994: 15–30.
7 Feldman RA, Sturdivant M. Leprosy in Louisiana, 1855–1970. An epidemiologic study of long-term trends. *Am J Epidemiol* 1975; **102**: 303–10.
8 Ponnighaus JM, Fine PE, Sterne JA *et al.* Extended schooling and good housing conditions are associated with reduced risk of leprosy in rural Malawi. *Int J Lepr Other Mycobact Dis* 1994; **62**: 345–52.
9 Mira MT, Alcaïs A, Thuc NV *et al*. Susceptibility to leprosy is associated with PARK2 and PACRG. *Nature* 2004; **427**: 636–40.
10 Ciechanover A. The ubiquitin proteolytic system. *Neurology* 2006; **66** (Suppl. 1): 1–13.
11 Roy S, Frodsham A, Saha B *et al*. Association of vitamin D receptor genotype with leprosy type. *J Infect Dis* 1999; **179**: 187–91.
12 Roy S, McGuire W, Mascie-Taylor CG *et al*. Tumor necrosis factor promoter polymorphism and susceptibility to lepromatous leprosy. *J Infect Dis* 1997; **176**: 530–2.
13 Santos AR, Suffys PN, Vanderborght PR *et al*. Role of tumor necrosis factor-alpha and interleukin-10 promoter gene polymorphisms in leprosy. *J Infect Dis* 2002; **186**: 1687–91.
14 Fitness J, Floyd S, Warndorff DK *et al*. Large-scale candidate gene study of leprosy susceptibility in the Karonga district of northern Malawi. *Am J Trop Med Hyg* 2004; **71**: 330–40.
15 Moraes MO, Pacheco AG, Schonkeren JJ *et al*. Interleukin-10 promoter single-nucleotide polymorphisms as markers for disease susceptibility and disease severity in leprosy. *Genes Immun* 2004; **5**: 592–5.
16 Malhotra D, Darvishi K, Sood S *et al*. IL-10 promoter single nucleotide polymorphisms are significantly associated with resistance to leprosy. *Hum Genet* 2005; **118**: 295–300.
17 Sampaio EP, Caneshi JR, Nery JA *et al.* Cellular immune response to *Mycobacterium leprae* infection in human immunodeficiency virus-infected individuals. *Infect Immun* 1995; **63**: 1848–54.
18 Lawn SD, Wood C, Lockwood DNJ. Borderline tuberculoid leprosy: an immune reconstitution phenomenon in a human immuno-deficiency virus-infected person. *Clinical Infectious Diseases* 2003; **36**: e5–6.
19 Ustianowski AP, Lawn SD, Lockwood DNJ. Interactions between HIV infection and leprosy: a paradox. *Lancet Infectious Diseases* 2006; **6**: 350–60.
20 Godal T. Growing points in leprosy research. 3. Immunological detection of subclinical infection in leprosy. *Lepr Rev* 1974; **45**: 22–30.
21 Dockrell HM, Eastcott H, Young S *et al.* Possible transmission of *Mycobacterium leprae* in a group of UK leprosy contacts. *Lancet* 1991; **338**: 739–43.
22 Scott GC, Russell DA, Boughton CR, Vincin DR. Untreated leprosy: probability for shifts in Ridley–Jopling classification. Development of 'flares', or disappearance of clinically apparent disease. *Int J Lepr Other Mycobact Dis* 1976; **44**: 110–22.
23 Rees RJ, Meade TW. Comparison of the modes of spread and the incidence of tuberculosis and leprosy. *Lancet* 1974; **1**: 47–8.
24 Gill AL, Bell DR, Gill GV *et al*. Leprosy in Britain: 50 years experience in Liverpool. *QJM* 2005; **98**: 505–11.
25 Pedley JC. The nasal mucus in leprosy. *Lepr Rev* 1973; **44**: 33–5.
26 Beyene D, Aseffa A, Harboe M *et al*. Nasal carriage of Mycobacterium leprae DNA in healthy individuals in Lega Robi village, Ethiopia. *Epidemiol Infect* 2003; **131**: 841–8.
27 Chehl S, Job CK, Hastings RC. Transmission of leprosy in nude mice. *Am J Trop Med Hyg* 1985; **34**: 1161–6.

Pathogenesis of leprosy [1]

The pathogenesis, and thus the clinical features, reflect four principal causes of tissue damage (Fig. 32.1):

1 The degree to which cell-mediated immunity (CMI) is expressed [2]. Lepromatous leprosy represents a failure of CMI specifically towards *M. leprae* with resultant bacillary multiplication, spread and accumulation of antigen in infected tissues. The absence of activated lymphocytes and macrophages means that nerve damage is slow and gradual in onset. In tuberculoid leprosy, CMI is strongly expressed, so that the infection is restricted to one or a few skin sites and peripheral nerves. Lymphocytic infiltration rapidly causes nerve damage. Between those two polar forms lies the borderline forms of disease, with the extent of disease reflecting the balance between CMI and bacillary load.

2 The extent of bacillary spread and multiplication. In lepromatous leprosy, haematogenous spread of bacilli occurs [3] to cool, superficial sites, including eyes, upper respiratory mucosa, testes, small muscles and bones of hands, feet and face, as well as peripheral nerves and skin. In tuberculoid leprosy, bacillary multiplication is restricted to a few sites and bacilli are not readily found.

3 The appearance of tissue-damaging immunological complications: lepra reactions [4]. Borderline patients (borderline

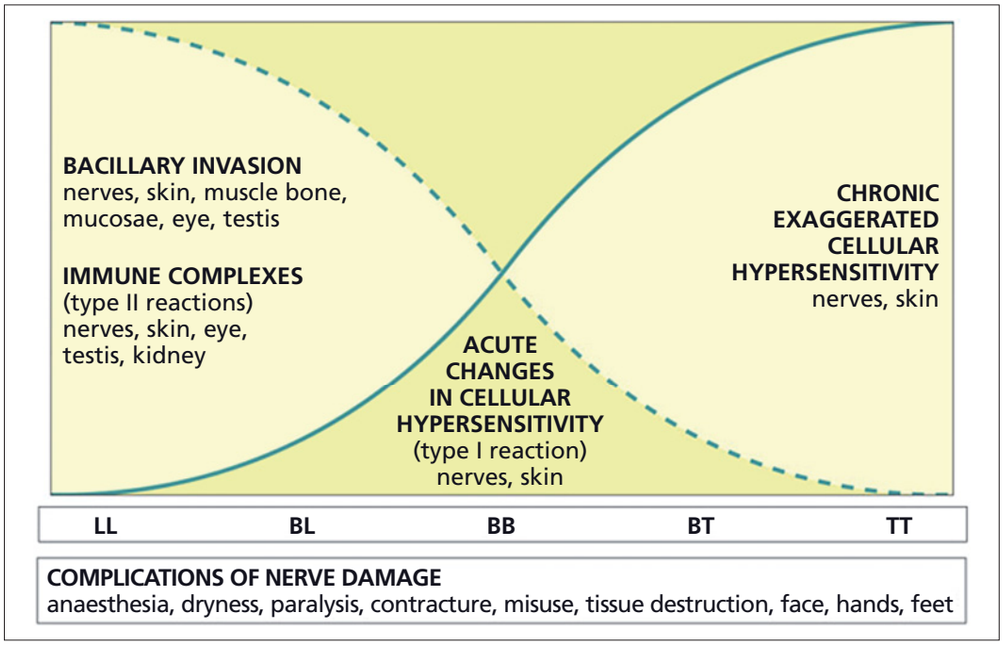


Fig. 32.1 Mechanisms of damage in leprosy, and tissues affected. Mechanisms under the broken line are characteristic of disease near the lepromatous end of the spectrum, those under the solid line of the tuberculoid end. They overlap in the centre where, in addition, instability predisposes to type 1 reactions. Abbreviations are given in text.

tuberculoid, BT; borderline, BB; borderline lepromatous, BL) are immunologically unstable and at risk of developing immune-mediated reactions. Type 1 (reversal) reactions are delayed hypersensitivity reactions caused by increased recognition of *M. leprae* antigens in skin and nerve sites. Type 2 reactions, erythema nodosum leprosum (ENL), are due in part to immune complex deposition and occur in BL and LL patients who produce antibodies and have a large antigen load.

4 The development of nerve damage and its complications. Nerve damage occurs in two settings, in skin lesions and in peripheral nerve trunks. In skin lesions, the small dermal sensory and autonomic nerve fibres supplying dermal and subcutaneous structures are damaged, causing local sensory loss and loss of sweating within the area of the skin lesion [5]. Peripheral nerve trunks are vulnerable at sites where they are superficial or are in fibro-osseous tunnels. At these points, a small increase in nerve diameter leads to raised intraneural pressure, with consequent neural compression and ischaemia. Damage to peripheral nerve trunks produces characteristic signs, with dermatomal sensory loss and dysfunction of muscles supplied by that peripheral nerve. Physiological evidence of central and peripheral autonomic nerve involvement has also been reported [6,7].

Nerve damage leads to anaesthesia, muscular weakness and contracture, and autonomic dysfunction. These permit trauma, bruising, burns, cuts and, especially, tissue necrosis from prolonged, inappropriate or repetitive trauma, which in turn lead to ulceration, secondary cellulitis and osteomyelitis and loss of tissue, so that deformity is added to disability.

References

1 Ridley DS. *Pathogenesis of Leprosy and Related Diseases*. London: Wright, 1988.

2 Myrvang B, Godal T, Feek CM *et al*. Immune response to *Mycobacterium leprae* in indeterminate leprosy patients. *Acta Pathol Microbiol Scand [B] Microbiol Immunol* 1973; **81**: 615–20.

3 Drutz DJ, Chen TS, Lu WH. The continuous bacteremia of lepromatous leprosy. *N Engl J Med* 1972; **287**: 159–64.

4 Jopling WH. Reactions in leprosy. *Lepr Rev* 1970; **41**: 62–3.

5 Dastur DK. Cutaneous nerves in leprosy: the relationship between histopathology and cutaneous sensibility. *Brain* 1955; **78**: 615–33.

6 Shah PK, Malhotra YK, Lakhotia M *et al*. Cardiovascular dysautonomia in patients with lepromatous leprosy. *Indian J Lepr* 1990; **62**: 91–7.

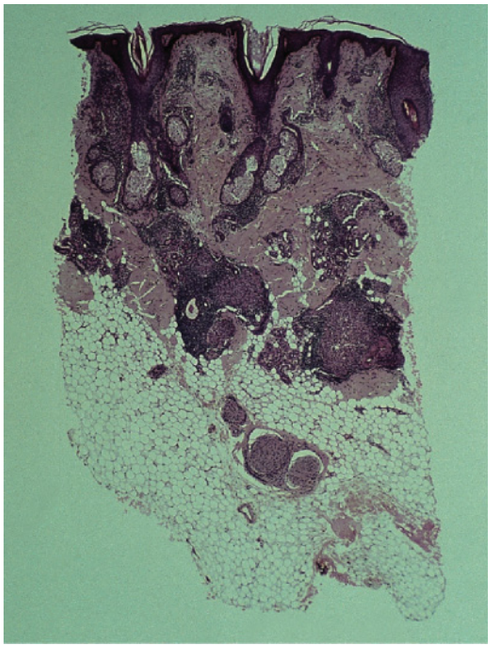
7 Beck JS, Abbot NC, Samson PD *et al*. Impairment of vasomotor reflexes in the fingertips of leprosy patients. *J Neurol Neurosurg Psychiatry* 1991; **54**: 965–71.

Histology [1]

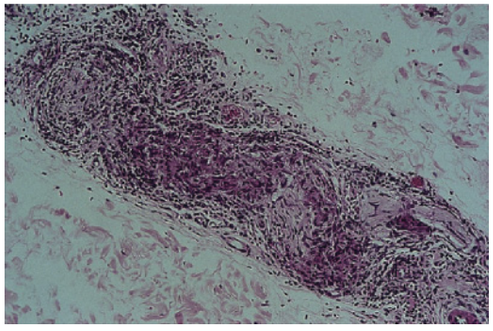
Mycobacterium leprae has a predilection for neural tissue, and the first evidence of infection is often found in the peripheral nervous system. Patients with early leprosy of both tuberculoid [2,3] and lepromatous types have abnormalities in nerve conduction studies and a histological picture of small fibre loss, with segmental demyelination and remyelination [4]. Bacilli probably enter nerves via endoneural blood vessels [5], the target cell being the Schwann cell. In the dermis, the type and degree of cellular infiltrate reflects the degree of CMI. The classification of Ridley and Jopling [6] describes five groups on the immunological spectrum, which are designated tuberculoid (TT), borderline tuberculoid (BT), borderline (BB), borderline lepromatous (BL) and lepromatous (LL). In this classification, epithelioid cells and lymphocytes at the tuberculoid end of the spectrum give place to macrophages, which appear increasingly foamy as the lepromatous pole is reached.

Tuberculoid leprosy

Tuberculoid granulomas collect in foci surrounding neurovascular elements (Fig. 32.2). The granuloma invades the papillary zone and may even erode the epidermis, but acid-fast bacilli (AFB) are not seen. Cutaneous nerves that are not completely destroyed appear greatly swollen by epithelioid cell granulomas and surrounded by a zone of lymphocytes; occasionally there may be caseation within the nerve.



(a)

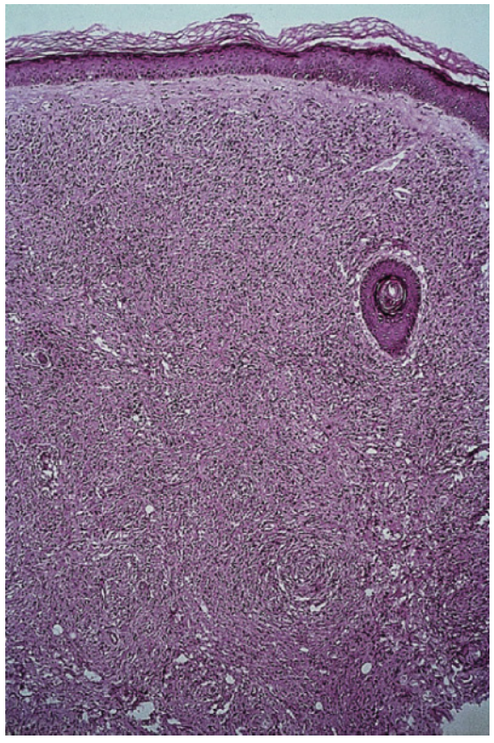


(b)

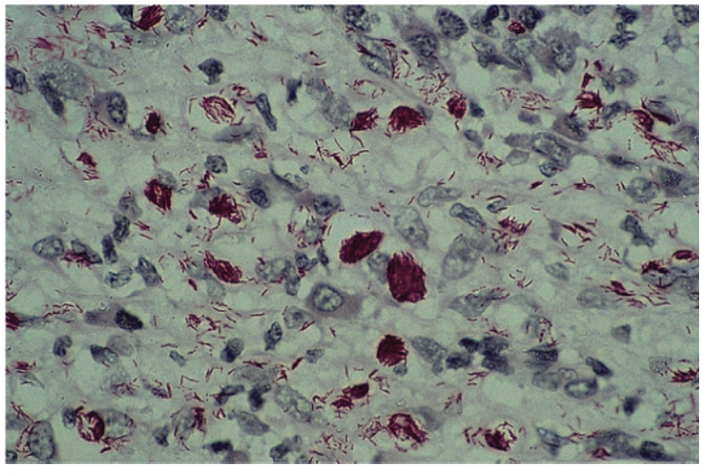
Fig. 32.2 (a) Low-power view (H&E) showing tuberculoid granulomas around nerve and skin appendages in mid-dermis and a swollen, deep dermal nerve. There is no epidermal erosion. Around the granulomas there is a dense lymphocytic infiltrate. (b) A different case. Medium-power view (H&E) of a deep nerve in tuberculoid leprosy showing granulomatous disruption of the nerve with surrounding lymphocytic infiltrate. (Courtesy of Professor S. Lucas, Kings College, London, UK.)

Lepromatous leprosy

Histological examination of skin lesions (H & E) shows thinning of epidermis and flattening of rete ridges (Fig. 32.3). The papillary layer of the dermis appears as a clear band, whilst deeper in the dermis lies the typical diffuse leproma consisting of foamy macrophages, with the addition of a few lymphocytes and plasma cells. The dermis contains enormous numbers of AFB, singly or in clumps (globi). With treatment, the leproma shows increased foamy change, vacuolates and breaks up into discrete foci with fibrocytes at the periphery. These foci shrink as treatment is continued and bacilli become fragmented and granular. In lepromatous neuropathy, there is quiet asymptomatic bacillation of Schwann cells leading to foamy degeneration of these cells. Demyelination, damage and destruction of the axis cylinder are prominent features and later Wallerian degeneration occurs [7].



(a)



(b)

Fig. 32.3 (a) Lepromatous leprosy. Medium-power view (H&E) showing thin epidermis, a clear subepidermal zone and a dense, uniform macrophage infiltrate in the dermis. Towards the bottom of the photograph there is an 'onion skin' perineurial lamination. (b) High-power view, Wade–Fite stain showing single and clustered acid-fast bacilli (AFB), part solid, part fragmented; bacillary index (BI) = 5. (Courtesy of Professor S. Lucas, Kings College, London, UK.)

Despite the large numbers of organisms in the nerve there is only a small inflammatory response; ultimately the nerve fibroses and is hyalinized [8].

Borderline leprosy

In BT leprosy, the epithelioid cell granuloma is more diffuse than in TT with a free, but narrow, papillary zone. Giant cells tend to be foreign body rather than Langhans in type, and dermal nerves

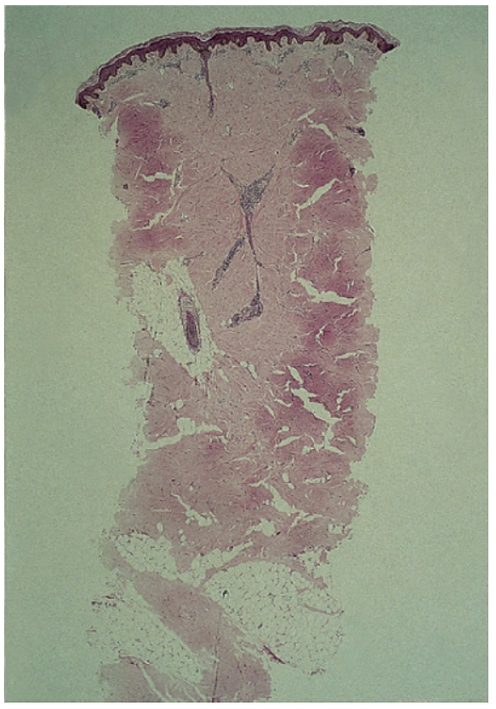
are moderately swollen by cellular infiltration, or may show only Schwann cell proliferation. AFB are usually absent or scanty. In mid-BB, there is diffuse epithelioid cell granuloma with very scanty lymphocytes and no giant cells; the papillary zone is clear, nerves are slightly swollen by cellular infiltrate, and AFB are present in moderate numbers. In BL leprosy, macrophages may show slight foamy change. Lymphocytes are present in dense clumps or are widely distributed in parts of the granuloma; a few epithelioid cells may be seen occasionally. The formation of small granulomas is characteristic of borderline leprosy and granulomatous regions may abut strands of normal looking but heavily bacillated Schwann cells [9]. Nerve damage in borderline leprosy results from a combination of lepromatous bacillation and a tuberculoid tissue damaging response producing widespread nerve damage. Acute neuritis damage occurs particularly during reversal reactions: oedema of the epithelioid cell granuloma compresses the remaining Schwann cells causing rapid functional loss in an already compromised nerve. In ENL nerve damage occurs more slowly and is probably due to inflammation associated with ENL nodule formation in nerve trunks.

Indeterminate leprosy

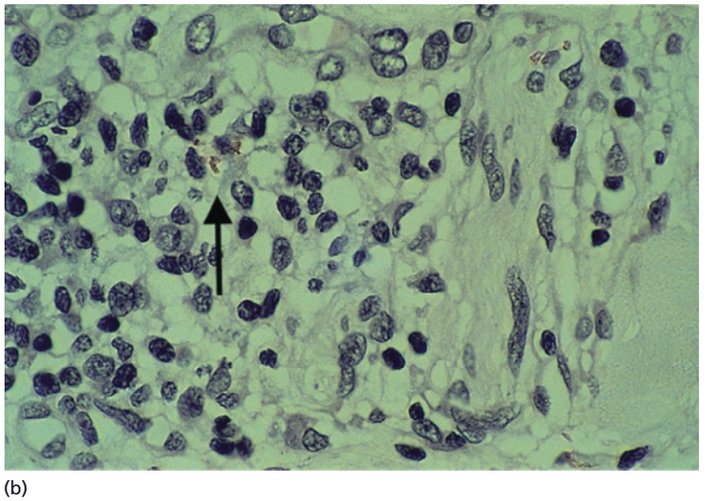
This early and transitory stage of leprosy occurs in those whose immunological state has not yet been determined, and histologically there is a scattered non-specific histiocytic and lymphocytic infiltration with some concentration around skin appendages (Fig. 32.4). Rarely, a single bacillus will be found within a dermal nerve. The indeterminate phase may last for months or years before resolving or giving way to one of the determinate types of leprosy described above.

Reactions

Type 1 reactions are characterized by an increase in lymphocytes within lesions, severe oedema with disruption of the granuloma, giant cell formation and HLA expression [10,11]. In type 2 (ENL) reactions polymorphs infiltrate the granuloma and there is vasculitis and macrophage degeneration together with breakdown of foam cells (Fig. 32.5).



(a)



(b)

Fig. 32.4 (a) Indeterminate leprosy. Low-power view (H&E) showing minimal perineurovascular inflammation in the mid-dermis. (b) High-power view, Wade–Fite stain showing one acid-fast bacillus in a Schwann cell. (Courtesy of Professor S. Lucas, Kings College, London, UK.)

References

1 Ridley DS. *Pathogenesis of Leprosy and Related Diseases*. London: Wright, 1988.

2 Antia NH, Mehta L, Shetty V, Irani PF. Clinical, electrophysiological, quantitative, histologic and ultrastructural studies of the index branch of the radial cutaneous nerve in leprosy. I. Preliminary report. *Int J Lepr Other Mycobact Dis* 1975; **43**: 106–13.

3 Mehta LN, Shetty VP, Antia NH, Irani PF. Quantitative, histologic and ultrastructural studies of the index branch of the radial cutaneous nerve in leprosy and its correlation with electrophysiologic study. *Int J Lepr Other Mycobact Dis* 1975; **43**: 256–64.

4 Shetty VP, Mehta LN, Irani PF, Antia NH. Study of the evolution of nerve damage in leprosy. Part I—Lesions of the index branch of the radial cutaneous nerve in early leprosy. *Lepr India* 1980; **52**: 5–18.

5 Weddell GM, Pearson JM. Leprosy—histopathologic aspects of nerve involvement. *Contemp Neurol Ser* 1975; **12**: 17–28.

6 Ridley DS, Jopling WH. Classification of leprosy according to immunity. A five-group system. *Int J Lepr Other Mycobact Dis* 1966; **34**: 255–73.

7 Job CK, Desikan KV. Pathologic changes and their distribution in peripheral nerves in lepromatous leprosy. *Int J Lepr Other Mycobact Dis* 1968; **36**: 257–70.

8 Job CK. Pathology of peripheral nerve lesions in lepromatous leprosy—a light and electron microscopic study. *Int J Lepr Other Mycobact Dis* 1971; **39**: 251–68.

9 Job CK. Mechanism of nerve destruction in tuberculoid-borderline leprosy. An electron-microscopic study. *J Neurol Sci* 1973; **20**: 25–38.

10 Ridley DS, Radia KB. The histological course of reactions in borderline leprosy and their outcome. *Int J Lepr Other Mycobact Dis* 1981; **49**: 383–92.

11 Lockwood DN, Lucas SB, Desikan KV *et al*. The histological diagnosis of leprosy type 1 reactions: identification of key variables and an analysis of the process of histological diagnosis. *J Clin Pathol*. 2008; **61**: 595–600.

Immunology [1]

The immune response to *M. leprae* determines not only whether disease will develop, but also which type of leprosy. The highly conserved Toll-like receptors on the surface of monocytes and

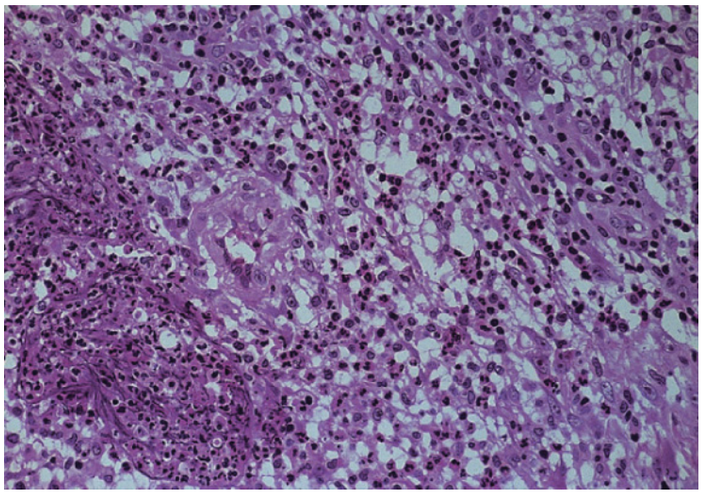


Fig. 32.5 Erythema nodosum leprosum (ENL). Medium-power view (H&E) showing foamy macrophages with infiltrating polymorphs. There is also a swollen small artery in the centre of the photograph. (Courtesy of Professor S. Lucas, Kings College, London, UK.)

macrophages recognize mycobacterial lipoproteins [2]. For *M. leprae* the TLR2/1 heterodimer is activated with monocyte differentiation into macrophages and dendritic cells [3]. The latter present antigen and activate naïve T cells by IL-12 secretion [4]. The IL-12βR2 portion of the IL-12 receptor is expressed more on Th1 lymphocytes, preferentially shifting the immune response further towards a Th1 response.

In addition, IL-2 stimulates the expansion of α/β CD8 T cells and antigen non-specific natural killer cells in the lesion. All three types of cell can produce interferon-γ (IFN-γ), the major cytokine responsible for activating bactericidal mechanisms within the parasitized macrophage [5].

In tuberculoid leprosy, there is good evidence of a strong CMI response. Tests of T-cell function such as LTTs show that tuberculoid leprosy patients respond to *M. leprae* antigens as in whole *M. leprae*, separated *M. leprae* antigens and cloned antigens (18 kDa and 65 kDa) [6]. Skin tests with lepromin, a heat-killed *M. leprae* sonicate preparation, are strongly positive in these patients. Staining of skin biopsies from tuberculoid lesions with T-cell markers shows highly organized granulomas composed predominantly of CD4 cells and macrophages, with a peripheral mantle of suppressor/cytotoxic CD8 cells [7]. This strong CMI response has been misdirected at some stage, and the end result is a late, strong cell-mediated response that clears antigen at the expense of local tissue destruction.

Lepromatous leprosy patients are unable to mount a CMI response to *M. leprae*, with a failure of the T-cell response, and lymphocytes from LL patients respond poorly in LTT to whole *M. leprae* and cloned antigens. Similarly, LL patients fail to mount a skin test response to intradermal challenge with lepromin. The anergy of the lepromatous patient is striking because it is specific for the leprosy mycobacterium. Lepromatous patients can respond to antigens of other mycobacteria such as *M. tuberculosis*, both in *in vitro* and in skin tests [8,9]. Identification of cell types in LL granulomas shows them to be a disorganized mixture of macrophages and T cells, mainly CD8 cells [10].

Both T-cell and macrophage dysfunction occur in lepromatous patients. The T-cell failure may be due to clonal anergy or active suppression. Defects in cytokine production have been demonstrated in lepromatous patients; addition of IL-2 to T-cell culture media restored the proliferative response to *M. leprae* in lepromatous patients [11], and intralesional injections of recombinant IL-2 reconstituted the local immune response with elimination of *M. leprae* from macrophages [12]. Macrophage defects described in LL disease include defective antigen presentation and recognition, defective IL-1 production, a failure of macrophages to kill *M. leprae* and a macrophage suppression of the T-cell response [2].

Studies of circulating cytokines in leprosy patients, and cytokine production in skin lesions, show that tuberculoid patients have a Th1 type response to *M. leprae* with predominant IL-2 and IFN-γ production, whilst lepromatous patients have low cytokine production and mainly of a Th2 type.

The inflammation seen in type 1 reactions is due to T-cell activity, with enhanced T-cell proliferation towards *M. leprae* antigens, increased numbers of CD4 and IL-2 producing cells in granulomas, and local production of cytokines such as IFN-γ and tumour necrosis factor-α (TNF-α) [13]. Type 1 reactions are associated with an over-production of Th1-type cytokines [14]. ENL has classically been regarded as an immune complex disorder. This is supported by the presence of immunoglobulin and complement in the lesions and circulating immune complexes [15,16]. There is also evidence of enhanced T-cell activity during ENL episodes, with increased numbers of CD4 cells [17] in lesions, and production of the cytokines TNF-α and IL-6, increased circulating IL-2 receptors and high levels of circulating TNF-α [18] in acute episodes. Despite increased immune activity during ENL episodes, lepromatous patients revert to a state of immunological unresponsiveness after an episode.

Serology

Specific anti-*M. leprae* antibodies are produced against lipoarabinomannan (LAM), PGL and the protein antigens of *M. leprae*. No single antigen has been identified for use in detecting early subclinical infection. For all three types of antigen, multibacillary patients produce antibodies prolifically, while paucibacillary patients show a variable, often undetectable, response. The evaluation of PGL serology in extensive field studies shows that more than 90% of untreated multibacillary patients have positive serology in comparison with 40–50% of paucibacillary patients and 5–10% of healthy controls [19]. PGL-1 antibodies can now be detected using a dipstick–type test (so-called lateral flow). This has been evaluated in field settings and seropositivity correlates with bacterial load measured by slit-skin smears. The use of PGL-1 antibody testing may be useful in assessing paucibacillary patients who are smear negative but have a low bacterial load and are at risk of under-treatment [20].

Lepromatous patients produce a range of autoantibodies, both organ-specific (directed against thyroid, nerve, testis and gastric mucosa), and non-specific, such as rheumatoid factors, anti-DNA, cryoglobulins and cardiolipin.

References

1 Britton WJ, Lockwood DNJ. Leprosy. *Lancet* 2004; **363**: 1209–19.
2 Brightbill HD, Libraty DH, Krutzik SR *et al*. Host defense mechanisms triggered by microbial lipoproteins through Toll-like receptors. *Science* 1999; **285**: 732–3.
3 Krutzik SR, Ochoa MT, Sieling PA *et al*. Activation and regulation of Toll-like receptors 2 and 1 in human leprosy. *Nature Medicine* 2003; **9**: 525–32.
4 Demangel C, Britton WJ. Interaction of dendritic cells with mycobacteria: where the action starts. *Immunol Cell Biol* 2000; **78**: 318–24.
5 Birdi TJ, Antia NH. The macrophage in leprosy: a review on the current status. *Int J Lepr Other Mycobact Dis* 1989; **57**: 511–25.
6 Lee SP, Stoker NG, Grant KA *et al*. Cellular immune responses of leprosy contacts to fractionated *Mycobacterium leprae* antigens. *Infect Immun* 1989; **57**: 2475–80.
7 Modlin RL, Hofman FM, Horwitz DA *et al*. *In situ* identification of cells in human leprosy granulomas with monoclonal antibodies to interleukin 2 and its receptor. *J Immunol* 1984; **132**: 3085–90.
8 Ilangumaran S, Shankernarayan N, Ramu G, Muthukkaruppan V. Antibody response to recombinant 65-kDa, 70-kDa and 18-kDa mycobacterial antigens in leprosy patients and healthy contacts in a leprosy-endemic population. *Int J Lepr Other Mycobact Dis* 1984; **62**: 245–55.
9 Paul RC, Stanford JL, Carswell JW. Multiple skin testing in leprosy. *J Hyg (Lond)* 1975; **75**: 57–68.
10 Modlin RL, Melancon-Kaplan J, Young SM *et al*. Learning from lesions: patterns of tissue inflammation in leprosy. *Proc Natl Acad Sci USA* 1988; **85**: 1213–7.
11 Haregewoin A, Godal T, Mustafa AS *et al*. T-cell conditioned media reverse T-cell unresponsiveness in lepromatous leprosy. *Nature* 1983; **303**: 342–4.
12 Kaplan G, Kiessling R, Teklemariam S *et al*. The reconstitution of cell-mediated immunity in the cutaneous lesions of lepromatous leprosy by recombinant interleukin 2. *J Exp Med* 1989; **169**: 893–907.
13 Khanolkar-Young S, Rayment N, Brickell PM *et al*. Tumour necrosis factor-α (TNF-α) synthesis is associated with the skin and peripheral nerve pathology of leprosy reversal reactions. *Clin Exp Immunol* 1995; **99**: 196–202.
14 Yamamura M, Wang X-H, Ohmen JD *et al*. Cytokine patterns of immunologically mediated tissue damage. *J Immunol* 1992; **149**: 1470–5.
15 Wemambu SN, Turk JL, Waters MF, Rees RJ. Erythema nodosum leprosum: a clinical manifestation of the arthus phenomenon. *Lancet* 1969; **2**: 933–5.
16 Kahawita IP, Lockwood DN. Towards understanding the pathology of erythema nodosum leprosum. *Trans R Soc Trop Med Hyg* 2008; **102**: 329–37.
17 Dharma Rao T, Ramchander Rao P. Enhanced cell-mediated immune response in erythema nodosum leprosum reactions of leprosy. *Int J Lepr Other Mycobact Dis* 1987; **55**: 36–42.
18 Sarno EN, Grau GE, Vieira LM, Nery JA. Serum levels of tumour necrosis factor-α and interleukin-1β during leprosy reactional states. *Clin Exp Immunol* 1991; **84**: 103–8.
19 Smith PG. The serodiagnosis of leprosy. *Lepr Rev* 1992; **63**: 97–100.
20 Bührer-Sékula S, Visschedijk J, Grossi MA *et al*. The ML flow test as a point of care test for leprosy control programmes: potential effects on classification of leprosy patients. *Lepr Rev* 2007; **78**: 70–9.

Clinical features of leprosy [1]

Early lesions and presenting symptoms

The commonest early lesion is an area of numbness on the skin, or a visible skin lesion. The classic early skin lesion, especially in surveys, is that of indeterminate leprosy, which is most commonly found on the face, extensor surface of the limbs, buttocks or trunk (Fig. 32.6) [2]. Scalp, axillae, groins and lumbar skin tend to be spared. Indeterminate lesions consist of one or more slightly hypopigmented or erythematous macules, a few centimetres in diameter, with poorly defined margins. Hair growth and nerve function are unimpaired. A biopsy may show the perineurovascular infiltrate, and only a prolonged search will reveal scanty acid-fast organisms. Alternatively, the initial skin lesion has features of one of the established forms of the disease.



Fig. 32.6 Indeterminate leprosy. Face of a Nepali child showing vague hypopigmented patch with some central healing. Note the mark of a recent slit-skin smear.

Table 32.1 Characteristics of lesions of polar leprosy.

	Tuberculoid	Lepromatous
Number of lesions	1–10	Hundreds, confluent
Distribution	Asymmetrical, anywhere	Symmetrical, avoiding 'spared' areas
Definition and clarity	Defined edge, markedly hypopigmented	Vague edge, slight hypopigmentation
Anaesthesia	Early, marked, defined, localized to skin lesions or major peripheral nerve	Late, initially slight, ill-defined, but extensive, over 'cool' areas of body
Autonomic loss	Early in skin and nerve lesions	Late, extensive as for anaesthesia
Nerve enlargement	Marked, in a few nerves	Slight but widespread
Mucosal and systemic	Absent	Common, severe during type 2 reactions
Number of *Mycobacterium leprae*	Not detectable	Numerous in all affected tissues

Patients frequently present with signs of nerve damage: weakness or anaesthesia due to a peripheral nerve lesion, or a blister, burn or ulcer in an anaesthetic hand or foot. Borderline patients may present in reaction with nerve pain, sudden palsy, multiple new skin lesions, pain in the eye, or a systemic febrile illness [3,4].

Features of established leprosy

Careful attention to the eight different clinical aspects of leprosy listed in Table 32.1 will enable accurate recognition and classification, which are prerequisites to correct treatment and accurate prognosis.

Tuberculoid leprosy

Only nerves and skin show clinical evidence of disease; lesions are few, often solitary. The condition may be purely neural, with pain and swelling of the affected nerve followed by anaesthesia and/or

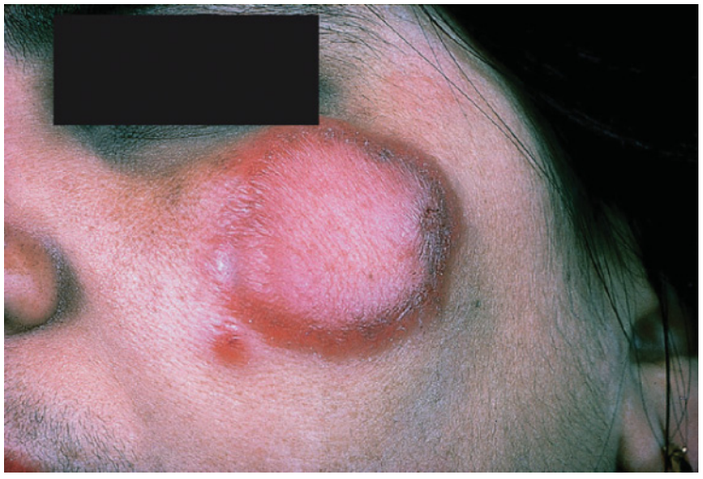


Fig. 32.7 Tuberculoid leprosy (TT). Face of Pakistani lady showing erythematous plaque with a well-defined active edge, and a small satellite lesion. On the face, such lesions may not be anaesthetic.



Fig. 32.9 Tuberculoid or borderline tuberculoid (BT/TT) leprosy. Back of a Nigerian child showing well-defined hypopigmented macule with altered skin texture. The lesion was anaesthetic.



Fig. 32.8 Tuberculoid or borderline tuberculoid (TT/BT) leprosy. Upper arm of Indian man, showing typical dry, hairless, hypopigmented plaque with scaly, erythematous edge. Such lesions are usually anaesthetic.



Fig. 32.10 Lepromatous leprosy (borderline lepromatous/lepromatous; BL/LL). Back of a Bangladeshi boy showing numerous, often confluent hypopigmented macules, with relative sparing of the midline.

muscle weakness and wasting. Alternatively, a skin lesion appears with or without evidence of nerve involvement. The typical lesion is a plaque that is conspicuous, erythematous, copper coloured or purple, with raised and clear-cut edges sloping towards a flattened and hypopigmented centre (Figs 32.7 & 32.8). Dark skins may not show the erythema. The surface is dry, hairless and insensitive, and sometimes scaly. Sensory impairment may be difficult to demonstrate on the face because of the generous supply of sensory nerve endings. If the examiner runs a finger around the lesion, just beyond the outer edge, a thickened sensory nerve may be palpated or a thickened nerve trunk may be felt in the vicinity, for example a thickened ulnar nerve if the lesion is on the arm. Less commonly the lesion is a macule, erythematous in light skins and hypopigmented (never depigmented) in dark skins (Fig. 32.9). Such macules have a dry, hairless and insensitive surface.

Lepromatous leprosy

The first clinical manifestations are usually dermal (because early nerve involvement is usually asymptomatic), but they may go unnoticed by the patient, who often complains of other early symptoms; these include nasal symptoms of stuffiness, discharge and epistaxis [5], and oedema of legs and ankles due to increased capillary stasis and permeability. Dermal signs comprise macules, diffuse papules, infiltration or nodules, or all four. Macules are small, multiple, erythematous or faintly hypopigmented, with vague edges and shiny surface (Fig. 32.10). Papules and nodules



Fig. 32.11 Lepromatous leprosy (LL). Forearm of an English man showing erythematous macules and infiltration, which characterize a relapse of dapsone-resistant lepromatous leprosy.



Fig. 32.12 Lepromatous leprosy (LL). Face of an Anglo-Indian man showing diffuse infiltration of the skin and appearance of nodules on nose and lip.

usually have normal skin colour but sometimes are erythematous (Fig. 32.11), with a bilaterally symmetrical distribution on face, arms, legs and buttocks, but may be anywhere apart from hairy scalp, axillae, groins and perineum (regions of skin with the highest temperature). Hair growth and sensation are not initially impaired over the lesions. In polar LL, diffuse infiltration and gradual thickening of the dermis may precede nodulation by months or years (Fig. 32.12). Lesions of oral mucosa occur as papules on lips and nodules on palate (which may perforate),

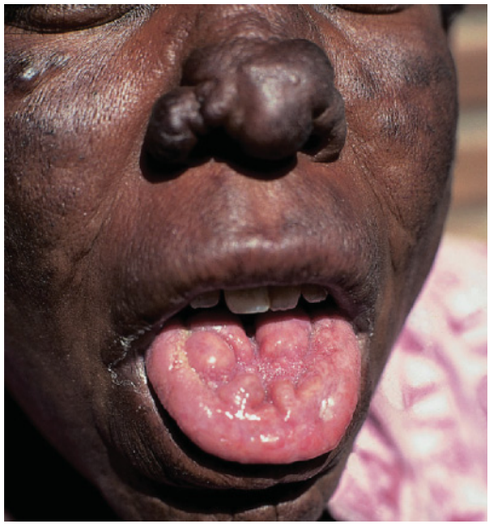


Fig. 32.13 Lepromatous leprosy (LL). Face of an Ethiopian child showing typical pattern of late lepromatous infiltration. Note the collapsed nasal bridge and the infiltration of the tongue.



Fig. 32.14 Lepromatous leprosy (LL). Examination via a nasal speculum shows a pale septal nodule and bleeding. Such lesions in untreated lepromatous patients constitute a major source of infection.

uvula, tongue and gums (Fig. 32.13). The nasal mucosa is hyperaemic or ulcerated and bleeds easily; epistaxis is common (Fig. 32.14).

The longest peripheral sensory nerve fibres are first affected, causing numbness and anaesthesia on the dorsal surfaces of hands and feet, and later on extensor surfaces of arms and legs, and finally over the trunk. Infiltration of corneal nerves causes anaesthesia, which predisposes to injury, infection and blindness if there is also lagophthalmos due to damage to the facial nerve. The hands and feet swell and may become oedematous. Radiographs may show osteoporosis in the phalanges, small osteolytic cysts and often hairline or compression fractures. The fingers may become crooked or short (Fig. 32.15). Nails are thin and brittle.



Fig. 32.15 Lepromatous leprosy (LL). Hands of an Indian man, showing swollen fingers due to leprous dactylitis and one crooked finger due to a pathological fracture. Note also the lepromatous nodules. The nail dystrophy is due to a dermatophyte infection.

If the patient remains untreated the lines of the forehead become deeper as the skin thickens (leonine facies), eyebrows and eyelashes become thinned or lost (madarosis), ear lobes are thickened, the nose becomes misshapen, and may collapse due to septal perforation and loss of the anterior nasal spine, the voice becomes hoarse and the upper incisor teeth loosen or fall out [6]. The skin of the legs becomes ichthyotic and thickened, ulcers may form on the legs when nodules break down, and a slow fibrosis of peripheral nerves results in nerve thickening and bilateral 'glove and stocking' anaesthesia. Sensation of palms and soles is retained until late in the disease. Leprous deposits in the eyes cause keratitis, iridocyclitis and iris atrophy. Testicular atrophy causes sterility, impotence and gynaecomastia.

One particular variety of lepromatous leprosy requires special mention, namely, the pure diffuse type described by Lucio and Alvarado in Mexico in 1852. The patients first notice impairment of sensation in hands and feet, and this is followed by gradual loss of eyebrows, eyelashes and body hair. At the same time, the skin of the whole body becomes diffusely thickened, rendering it stiff and smooth as in scleroderma. There may be alopecia, nasal and laryngeal involvement, and widespread small telangiectases, but cutaneous nodules and plaques do not develop. The eyes have a shining appearance [7].

Histoid lesions are distinctive round, regular, cutaneous nodules that stand out on normal skin. They are characteristic of relapse after treatment [8].

Borderline leprosy

Skin lesions are intermediate in number between those of the two polar types already described, depending on the position of the patient on the borderline spectrum, and are distributed asymmetrically. They may take the form of macules, plaques, annular lesions or bizarre-shaped bands. Plaques with a 'punched-out' appearance are characteristic of the middle of the spectrum (Fig. 32.16). Towards the tuberculoid end of the spectrum, lesions are fewer and drier (Figs 32.17 & 32.18), have more hair loss and anhidrosis, are more insensitive, and have fewer bacilli in smears and biopsies, and vice versa towards the lepromatous pole. One or more nerves are likely to be thickened and non-functioning (Fig. 32.19). Neural symptoms may precede the appearance of skin lesions by as much as 8 years [9]. When borderline leprosy downgrades to lepromatous, the resulting subpolar lepromatous leprosy (LLs) can be differentiated from polar lepromatous (LLp) because, in addition to typical lepromatous skin lesions, there are several



Fig. 32.16 Borderline (BB) leprosy. Knee of Saudi-Arabian woman, showing classical annular lesions with well-defined centres (?healing of old borderline tuberculoid, BT) contrasting with spreading erythematous infiltration. Slit-skin smears show acid-fast bacilli (AFB).



Fig. 32.17 Borderline tuberculoid leprosy. Back of Nigerian man showing large, well-defined, scaly macules with some marginal elevation. Extensive disease, such as this, may seriously impair sweating and heat control.



Fig. 32.18 Borderline tuberculoid leprosy. Arm of an Indian woman. A large, scaly macule is developing secondary ichthyotic change.



Fig. 32.19 Borderline leprosy (BL). Foot of a Bangladeshi child showing enlargement of posterior tibial and anterior tibial nerves.

asymmetrical thickened nerves and one or more typical borderline skin lesions. Damage to structures other than skin and nerves will not be manifest clinically in borderline leprosy, even though bacilli may be present in other tissue. Borderline leprosy is the commonest type of disease encountered and is unstable and 'down-grades' towards lepromatous, especially if untreated, or 'upgrades' towards tuberculoid. The clinical change lags behind the immunological and histological changes (Fig. 32.20).

Pure neuritic leprosy

Pure neuritic leprosy presents with asymmetrical involvement of peripheral nerve trunks and no visible skin lesions; on histology of a cutaneous nerve biopsy, all types of leprosy are seen [10]. It is seen most frequently, but not exclusively, in India and Nepal where it accounts for 5–10% of patients.

Reactions

Type 1 reactions occur in borderline disease and are characterized by acute neuritis and/or acutely inflamed skin lesions [11]. Nerves



Fig. 32.20 Borderline leprosy (BL). Borderline tuberculoid (BT) down-grading to BL. Back of a Nigerian woman, showing typical well-defined hypopigmented macules of BT leprosy and many small lesions, some of which are papular. Slit-skin smears showed acid-fast bacilli (AFB).



Fig. 32.21 Type 1 reaction: borderline leprosy in an Ethiopian man. Existing lesions become acutely inflamed, scale and threaten ulceration. Many small, new lesions have appeared. The histology shows a borderline tuberculoid (BT) pattern.

often become tender with loss of sensory and motor functions. Existing skin lesions become erythematous or oedematous and may desquamate or rarely ulcerate. New lesions may appear (Fig. 32.21). Occasionally, oedema of face, hands or feet is the presenting symptom, but constitutional symptoms are unusual. Patients often first present for medical advice when a previously quiescent BT lesion develops a spontaneous Type 1 reaction. A recent cohort study in India found that most Type 1 reactions occurred in the first 12 months after starting treatment [12]. Women are also at risk during the puerperium

Type 2 (ENL) reactions occur in patients with multibacillary disease (LL and BL). They may occur spontaneously (roseolar leprosy) or whilst on treatment. Up to 50% of LL and 15% of BL patients may experience ENL reactions [13]. Attacks are often acute at first, but may be prolonged or recurrent over several years



Fig. 32.22 Type 2 reaction in lepromatous leprosy in a Nigerian man: erythema nodosum leprosum (ENL). Several of the reaction nodules have broken down, releasing pus.



Fig. 32.23 Type 2 reaction in lepromatous leprosy in a Bangladeshi man, showing severe necrosis and ulceration. Erythema nodosum leprosum (ENL) tends to be more severe in Asian than in African people.

and eventually quiet but insidious, especially in the eye. ENL manifests most commonly as painful red nodules on the face and extensor surfaces of limbs. The lesions may be superficial or deep, with suppuration (Fig. 32.22), ulceration (Fig. 32.23) or brawny induration when chronic. Acute lesions crop and desquamate, fading over several days (Fig. 32.23). ENL is a systemic disorder producing fever and malaise and may be accompanied by uveitis, dactylitis, arthritis, neuritis, lymphadenitis, myositis and orchitis



Fig. 32.24 Lucio phenomenon in a Mexican man. The severe, recurrent ulceration due to deep subcutaneous vasculitis may be fatal. (Courtesy of Dr J. Keystone, The Toronto Hospital, Toronto, Canada.)

[14,15]. Peripheral nerve neuritis and uveitis with its complications of synechiae, cataract and glaucoma are the most serious complication of ENL.

The Lucio reaction only occurs in patients with Lucio leprosy [16]. It is due to infarction consequent upon deep cutaneous vasculitis, and causing the appearance of irregularly shaped erythematous patches which become dark and heal, or form bullae and necrose, leaving deep painful ulcers that are slow to heal (Fig. 32.24). The systemic upset is severe and can be fatal.

Nerve damage [17]

Of the three physiological functions of nerves, the sensory component is commonly the first and most severely affected, but occasionally there is a pure motor lesion. Autonomic dysfunction is always present in severe nerve damage [18]. In skin lesions this is associated with loss of hair growth, and of sebaceous and sweat secretion, and poor pigment formation. In a limb it causes capillary stasis, cyanosis and dryness, which predispose to fissuring. Two large cohort studies with systematic nerve examination at entry showed that the posterior tibial nerve is the most frequently affected nerve, followed by ulnar, median, lateral popliteal and facial [19,20]. Ulnar and median nerve lesions are usually low, causing small muscle but not deep flexor weakness, and anaesthesia of the two halves of the hand. Isolated median nerve lesions are unusual. Common peroneal nerve lesions cause difficulty in dorsiflexion and eversion of the foot and anaesthesia of the outer border of the foot, a combination which predisposes to traumatic damage and plantar ulceration (Fig. 32.25). Posterior tibial nerve damage is serious because it causes paralysis and contracture of the small muscles of the foot and anaesthesia of the sole.

Eye involvement in leprosy

Blindness due to leprosy is a devastating complication, especially for a patient with anaesthetic hands and feet. Eye damage results from both nerve damage and bacillary invasion, and a recent cohort study found that 2.8% of multibacillary patients were blind at diagnosis, and a further 11% patients had potentially blinding



Fig. 32.25 Necrosis blister in an anaesthetic foot. Necrotic material has tracked to soft skin from the site of trauma, beneath the metatarsal heads.

ocular pathology [21]. Lagophthalmos results from paresis of the orbicularis oculi due to involvement of the zygomatic and temporal branches of the facial (VIIth) nerve. Facial lesions cause a 10-fold increase in the risk of facial nerve damage [22]. In lepromatous disease, lagophthalmos occurs later and is usually bilateral. Damage to the ophthalmic branch of the trigeminal (Vth) nerve causes anaesthesia of the cornea and conjunctiva, which results in drying of the cornea, a reduction in blinking, and leaves the cornea at risk of minor trauma and ulceration. Bacillary invasion of the iris and ciliary body makes them extremely susceptible to reactions.

Prognosis

Antibacterial treatment for leprosy is highly effective, with low relapse rates, but needs to be taken over many months. Left untreated, borderline patients will downgrade towards the lepromatous end of the spectrum, and lepromatous patients will suffer the numerous consequences of bacillary invasion. Borderline patients are at risk of developing type 1 reactions, which may result in devastating nerve damage. BL patients may suffer either type of reaction. Many patients present with established nerve damage which cannot be reversed. Treatment of the neuritis is currently unsatisfactory, and some patients with active neuritis will develop permanent nerve damage despite treatment with corticosteroids. It is not possible to predict which patients will develop reactions or nerve damage. Nerve damage and its complications may be severely disabling, especially when all four limbs and both eyes are affected. Women are at risk of reactions during the puerperium [23].

References

1 Bryceson AD, Pfalzgraff RE. *Leprosy*, 3rd edn. Edinburgh: Churchill Livingstone, 1990.

2 Sehgal VN, Srivastava G. Indeterminate leprosy. A passing phase in the evolution of leprosy. *Lepr Rev* 1987; **58**: 291–9.

3 Iveson JM, McDougall AC, Leathem AJ, Harris HJ. Lepromatous leprosy presenting with polyarthritis, myositis, and immune-complex glomerulonephritis. *BMJ* 1975; **3**: 619–21.

4 Malin AS, Waters MF, Shehade SA, Roberts MM. Leprosy in reaction: a medical emergency. *BMJ* 1991; **302**: 1324–6.

5 Barton RP. A clinical study of the nose in lepromatous leprosy. *Lepr Rev* 1974; **45**: 135–44.

6 Moller-Christensen V. Changes in the anterior nasal spine and the alveolar process of the macillae in leprosy: a clinical examination. *Int J Lepr Other Mycobact Dis* 1974; **42**: 431–5.

7 Latapi L, Chevez Zamora A. The 'spotted' leprosy of Lucio (la lepra 'manchada' de Lucio). An introduction to its clinical and histological study. *Int J Lepr Other Mycobact Dis* 1948; **16**: 421–9.

8 Wade HW. The histoid variety of lepromatous leprosy. *Int J Lepr Other Mycobact Dis* 1963; **31**: 129–42.

9 Suneetha S, Arunthathi S, Chandi S, Kurian N, Chacko CJ. Histological studies in primary neuritic leprosy: changes in the apparently normal skin. *Lepr Rev* 1998; **69**: 351–7.

10 Mahajan PM, Jogaikar DG, Mehta JM. A study of pure neuritic leprosy: clinical experience. *Indian J Lepr* 1996; **68**: 137–41.

11 Lockwood DN, Vinayakumar S, Stanley JN *et al*. Clinical features and outcome of reversal (type 1) reactions in Hyderabad, India. *Int J Lepr Other Mycobact Dis* 1993; **61**: 8–15.

12 Van Brakel WH, Nicholls PG, Das L *et al*. The INFIR Cohort Study: assessment of sensory and motor neuropathy in leprosy at baseline. *Lepr Rev* 2005; **76**: 277–95.

13 Pocaterra L, Jain S, Reddy R *et al*. Clinical course of erythema nodosum leprosum: an 11-year cohort study in Hyderabad, India. *Am J Trop Med Hyg* 2006; **74**: 868–79.

14 Kahawita IP, Lockwood DN. Towards understanding the pathology of erythema nodosum leprosum. *Trans R Soc Trop Med Hyg* 2008; **102**: 329–37.

15 Walker SL, Waters M, Lockwood DNJ. The role of thalidomide in the management of erythema nodosum leprosum. *Lepr Rev* 2007; **78**: 197–215.

16 Rea TH, Ridley DS. Lucio's phenomenon: a comparative histological study. *Int J Lepr Other Mycobact Dis* 1979; **47**: 161–6.

17 Pearson JM, Ross WF. Nerve involvement in leprosy—pathology, differential diagnosis and principles of management. *Lepr Rev* 1975; **46**: 199–212.

18 Dabholkar VR, Gaitonde BB. A study of autonomic functions in leprosy. *Lepr India* 1982; **54**: 303–17.

19 Croft RP, Richardus JH, Nicholls PG, Smith WC. Nerve function impairment in leprosy. Design, methodology, and intake status of a prospective cohort study of 2664 new leprosy cases in Bangladesh (The Bangladesh Acute Nerve Damage Study). *Lepr Rev* 1999; **70**: 140–59.

20 Saunderson P, Gebre S, Desta K *et al*. The pattern of leprosy-related neuropathy in the AMFES patients in Ethiopia: definitions, incidence, risk factors and outcome. *Lepr Rev* 2000; **71**: 285–308.

21 Courtright P, Daniel E, Sundarrao Ravenes J *et al*. Eye disease in multibacillary leprosy patients at the time of their leprosy diagnosis: findings from the Longitudinal Study of Ocular Leprosy (LOSOL) in India, the Philippines and Ethiopia. *Lepr Rev* 2002; **73**: 225–38.

22 Hogeweg M, Faber WR. Progression of eye lesions in leprosy. Ten-year follow-up study in the Netherlands. *Int J Lepr Other Mycobact Dis* 1991; **59**: 392–7.

23 Lockwood DN, Sinha HH. Pregnancy and leprosy: a comprehensive literature review. *Int J Lepr Other Mycobact Dis* 1999; **67**: 6–12.

Diagnosis [1]

The diagnosis is usually made clinically on the basis of two out of three characteristic findings, or by the demonstration of AFB in

slit-skin smears, or by histology typical of leprosy. The cardinal signs are:

1 anaesthesia of a skin lesion, or in the distribution of a peripheral nerve, or over dorsal surfaces of hands and feet
2 thickened nerves, especially at the sites of predilection
3 typical skin lesions.

The AFB load of a patient is determined by modified Ziehl–Neelson staining of slit-skin smears. Suspect lesions, and sites commonly affected in lepromatous leprosy, should be sampled (forehead, earlobes, chin, extensor surface of the forearm, buttocks and trunk). The density of bacilli is expressed using a logarithmic scale, extending from very few AFB to many per high-power field. A mean score, the bacterial index (BI), is derived by adding the scores from each site and dividing by the number of sites sampled [2]. In untreated lepromatous leprosy, the BI is 5 or 6. The BI falls to zero in TT disease. Slit-skin smears only detect bacilli present at a concentration greater than 10^4/g tissue, and so cannot be used as a test of microbiological cure. With treatment, bacilli disappear from BB lesions in a few months and from BL lesions in a year or two. It may take 6–10 years for the last bacillary remnants to disappear from the skin in LL.

Slit-skin smears [3]

The lesion is cleaned with ether or alcohol, and a fold is gripped firmly between thumb and forefinger to render it blood free. An incision 5 mm long and 3 mm deep is made with a small-bladed scalpel (size 15 Bard Parker blade); the blade is turned at right angles to the cut, and without relaxing finger pressure, the wound is scraped several times in one direction. Fluid and pulp from the dermis, collected on one side of the blade, are gently smeared on to a glass slide. A bloody smear is useless. The smear is then fixed over a flame and stained.

Skin biopsy [4]

The incision should be made down to subcutaneous fat, so that the whole depth of the dermis is included, otherwise leprous changes in the deeper layers of the dermis will be missed.

Nerve biopsy

In pure neural leprosy a nerve biopsy is necessary to establish the diagnosis. A purely sensory thickened peripheral nerve should be sampled, for example radial cutaneous at the wrist, superficial peroneal in front of the ankle or sural nerve at the ankle.

Lepromin test

Lepromin is a crude, semi-standardized preparation of heat killed bacilli from a lepromatous nodule or infected armadillo liver. The lepromin test is a non-specific test of occasional value in classifying a case of leprosy. It is strongly positive in TT, weakly positive in BT, negative in BB, BL and LL, and unpredictable in indeterminate leprosy. Lepromin, 0.1 mL, is injected intradermally, and the reaction is read at 48 h (Fernandez reaction) or 3–4 weeks (Mitsuda reaction). The Fernandez response indicates delayed hypersensitivity to the soluble components of Lepromin. The Mitsuda reaction is a granulomatous response to particulate antigenic material. Neither test is diagnostic, since both may be positive in people with no evidence of leprosy.

Differential diagnosis

Leprosy tends to be over-diagnosed in endemic countries and under-diagnosed in non-endemic countries. Of new patients seen in the period 1995–9 at the Hospital for Tropical Diseases, London, diagnosis had been delayed in over 80% of cases [5]. Patients had been misdiagnosed by dermatologists, neurologists, orthopaedic surgeons and rheumatologists. A common problem was failure to consider leprosy as a cause of peripheral neuropathy in patients from leprosy endemic countries. These delays had serious consequences for patients, with over half of them having nerve damage and disability. In any population it is also important for the doctor to know the normal range of skin colour and texture, the common endemic skin diseases, such as onchocerciasis, that may coexist with leprosy and the common medical and artefactual practices that may cause lesions resembling those of leprosy.

Macular lesions

Birthmarks are abnormally pigmented but otherwise physiologically normal. Vitiligo lesions are depigmented; leprosy lesions are never completely depigmented. Hypopigmented lesions of eczema, especially of pityriasis alba in children, are difficult to distinguish from lepromatous macules, but their surface is often scaly and smears do not contain AFB. Pityriasis versicolor is not always scaly, but central distribution on the trunk, and the presence of minute distinct macules, are contrary to the characteristics of lepromatous macules. Lesions of tinea corporis itch and may have a vesicular edge, characteristically absent in tuberculoid patches, and scrapings usually show the fungus.

Plaques and annular lesions

In addition to ringworm (above), granuloma multiforme, sarcoidosis and cutaneous tuberculosis may resemble tuberculoid leprosy, having a similar immunological basis and often indistinguishable histological pattern. However, the lesions are not anaesthetic. Peripheral nerves may occasionally be enlarged in sarcoidosis [6].

Nodules

Cutaneous leishmaniasis causes nodules, but they usually crust and ulcerate after some weeks or months, and are seldom as numerous as those of lepromatous leprosy. Slit-skin smears, appropriately stained, reveal leishmania, and the leishmanin test is positive. Lesions of the rare, diffuse cutaneous leishmaniasis may be confusing, until slit-skin smears have been examined [7]. Post-kala-azar dermal leishmaniasis in India and East Africa has a similar distribution and appearance to the skin lesions of lepromatous leprosy [8].

Nerves

Peripheral nerve thickening is rarely seen except in leprosy. Hereditary sensory motor neuropathy type III is associated with palpable peripheral nerve hypertrophy. Amyloidosis, which can also complicate leprosy, causes thickening of peripheral nerves. Peroneal muscular atrophy (Charcot–Marie–Tooth disease) is an inherited neuropathy that causes distal atrophy and weakness. Nerve biopsy is characteristic. The causes of other polyneuropathies such as HIV infection, diabetes, alcoholism, vasculitides

Type of leprosy	Drug treatment		
	Monthly supervised	Daily self-administered	Duration of treatment
Paucibacillary	Rifampicin 600 mg	Dapsone 100 mg	6 months
Multibacillary	Rifampicin 600 mg Clofazimine 300 mg	Clofazimine 50 mg Dapsone 100 mg	12 months

Table 32.2 World Health Organization (WHO) multidrug therapy regimen.

and heavy metal poisoning should all be considered where appropriate [9].

Likewise, there are many causes of eye disease in endemic countries which may cause signs that in isolation mimic leprosy, especially trachoma, in which trichiasis and entropion follow scarring of the lids, and onchocerciasis, which causes uveitis and its complications.

References

1 Guinto RS, Abalos RM, Cellona RV. *An Atlas of Leprosy*. Tokyo: Sasakawa Memorial Health Foundation, 1983.

2 Ridley DS. Therapeutic trials in leprosy using serial biopsies. *Lepr Rev* 1958; **29**: 45–52.

3 World Health Organization. Guidelines for slit skin smears. *Int J Lepr Other Mycobact Dis* 1987; **55**: 421–2.

4 Ridley DS. *Skin Biopsy in Leprosy*. Basel: Documenta Geigy, 1977.

5 Lockwood DN, Reid AJ. The diagnosis of leprosy is delayed in the United Kingdom. *QJM* 2001; **94**: 207–12.

6 Matthews LVB. Sarcoidosis of the nervous system. *J Neurol Neurosurg Psychiatry* 1965; **28**: 23.

7 Bryceson AD. Diffuse cutaneous leishmaniasis in Ethiopia. I. The clinical and histological features of the disease. *Trans R Soc Trop Med Hyg* 1969; **63**: 708–37.

8 Munro DD, Du Vivier A, Jopling WH. Post kala-azar dermal leishmaniasis. *Br J Dermatol* 1972; **87**: 374–8.

9 Nunzi E, Fiallo P. Differential diagnosis. In: Hastings RC, ed. *Leprosy*. Edinburgh: Churchill Livingstone, 1994: 291–313.

Treatment

There are five main principles of treatment:

1 Stop the infection with chemotherapy
2 Treat reactions and reduce the risk of nerve damage
3 Educate the patient to cope with existing nerve damage, in particular anaesthesia
4 Treat the complications of nerve damage
5 Rehabilitate the patient socially and psychologically.

These objectives can only be achieved with the patient's cooperation and confidence. Wherever possible this should be done through the outpatient clinic. Patients will often need several consultations soon after diagnosis to address their fears and build up their confidence.

Chemotherapy

All leprosy patients should be given an appropriate multidrug combination. The effectiveness of dapsone against *M. leprae* was discovered in the late 1940s, and it was used widely as a single agent. This lead to the widespread development of dapsone resistance, initially presenting as disease relapse 15 years after treatment with dapsone monotherapy, but then also as primary dapsone resistance in untreated patients [1]. In response to the failure of dapsone monotherapy, the World Health Organization (WHO) proposed a multidrug regimen (MDT) for the treatment of leprosy [2]. In a multibacillary patient, there are three distinguishable types of bacilli: fully drug-sensitive bacteria, drug-resistant mutants and a small population of 'persisters', dormant non-multiplying bacilli. Treatment with a multidrug regimen should eliminate nearly all organisms. The first-line antileprosy drugs are rifampicin, dapsone and clofazimine. Table 32.2 gives the details of drug dosages and duration of treatment.

Rifampicin is a potent bactericidal for *M. leprae*. Four days after a single 600-mg dose, bacilli from a previously untreated multibacillary patient are no longer viable [3]. It acts by inhibiting DNA-dependent RNA polymerase, thereby interfering with bacterial RNA synthesis. Rifampicin is well absorbed orally. Hepatotoxicity may occur with a mild transient elevation of hepatic transaminases, but this is rare at the dosage and intervals recommended for leprosy, and is not an indication for stopping treatment. Because *M. leprae* resistance to rifampicin can develop as a one-step process, rifampicin should always be given in combination with other antileprotics [4].

Dapsone (DDS, 4,4-diaminodiphenylsulphone) acts by blocking folic acid synthesis. It is only weakly bactericidal. Oral absorption is good and it has a long half-life, averaging 28 h. Dapsone, in the doses recommended for leprosy, commonly causes mild haemolysis, and rarely anaemia or psychosis. Glucose-6-phosphate dehydrogenase deficiency seldom causes a problem and is not routinely looked for. The 'DDS syndrome', which is occasionally seen in leprosy, starts 6 weeks after commencing DDS and manifests as exfoliative dermatitis associated with lymphadenopathy, hepatosplenomegaly, fever and hepatitis, and may be fatal [5]. Agranulocytosis, hepatitis and cholestatic jaundice occur rarely with DDS therapy.

Clofazimine is a brick red, fat-soluble crystalline dye. The mechanism of its weakly bactericidal action against *M. leprae* is not known. It has an anti-inflammatory effect, which is useful in the management of ENL reactions. High drug concentrations are found in the intestinal mucosa, mesenteric lymph nodes and body fat. The most noticeable side effect is skin discoloration, ranging from red to purple-black, the degree of discoloration depending on the dose and amount of leprous infiltration. The pigmentation usually fades within 6–12 months of stopping clofazimine, although traces of discoloration may remain for up to 4 years. Urine, sputum and sweat may become pink. Clofazimine also produces a characteristic ichthyosis on the shins and forearms. Gastrointestinal side effects, ranging from mild cramps to diarrhoea and weight loss, may occur as a result of clofazimine crystal deposition in the wall of the small bowel.



Fig. 32.26 Borderline leprosy (BL). Borderline leprosy up-grading to borderline tuberculoid (BT). Buttocks of an Indian man who 'relapsed' 3 years after completing multidrug therapy for BL leprosy. The lesions here are typical hypopigmented, erythematous, scaly, plaques of BT leprosy in reaction. No acid-fast bacilli (AFB) were seen on slit-skin smears. In this situation, the distinction between (bacterial) relapse and simple reversal reaction may be impossible.

Relapse

Relapsed multibacillary patients are also retreated with triple therapy regardless of any change in classification [6].

The distinction between relapse and reaction may be difficult (Fig. 32.26). Therefore, paucibacillary patients require 2 years, and multibacillary patients at least 5 years, of monitoring after treatment. Patients can be discharged if there is no evidence of activity or reaction, but should be advised to return if new symptoms develop, especially in hands, feet or eyes. Patients with reactions or physical or psychological complications may need much longer care.

Published clinical outcomes for patients treated with the paucibacillary regimen show that 2–44% of patients had clinically active skin lesions at the end of treatment [7]. Nerve impairment occurred *de novo* in 2.5% of patients, and visible disabilities increased from 4% at enrolment to 7% at 8–10 years' follow-up. Relapse rates are low, ranging from 0% in Ethiopia [8] to 2.5% over 4 years in Malawi [9]. For patients treated with the multibacillary regime for 24 months, one study in Thailand found that 29% of lesions were still active after 3 years and that visible disabilities increased from 5% at enrolment to 13% at 8–10 years' follow-up [10]. Relapse rates have been reported from six observational studies varying from zero in China and Ethiopia to 2.04/100 person years in India. Data from West Africa [11] and India [12] shows that patients with a high initial bacterial load (BI > 4+) treated with 2 years of rifampicin, clofazimine and dapsone had a relapse rate of 8/100 person years, whereas patients treated to smear negativity had a relapse rate of 2/100 person years. These patients may form a subgroup who need treating to skin-smear negativity [13]. Susceptibility testing of *M. leprae* strains from relapsed multibacillary patients has shown them to remain drug sensitive.

Several new drugs bactericidal for *M. leprae* have been identified: fluoroquinolones, minocycline and clarithromycin. The fluoroquinolones pefloxacin and ofloxacin have a remarkable degree of bactericidal activity, with 22 daily doses killing 99.99% of viable *M. leprae* present in multibacillary cases at the start of treatment [14]. Multicentre trials of daily rifampin/ofloxacin are being conducted by the WHO and these may lead to a shortening in the duration of MDT. Daily minocycline (100 mg) treatment of multibacillary patients for 3 months resulted in killing of all viable *M. leprae* organisms [15]. Clarithromycin, given in 500 mg daily doses to multibacillary patients, has a similar bactericidal effect [16]. Antagonism between these new drugs has not been demonstrated [17]. Ofloxacin, minocycline and clarithromycin are established second-line drugs, and may replace dapsone and clofazimine. Minocycline may also cause hyperpigmentation of skin lesions, and so may not be an appropriate substitute for clofazimine if pigmentation is to be avoided [18].

A single-dose triple-drug combination (rifampicin, ofloxacin and minocycline) has been tested in India for patients with single skin lesions; 47% of patients were completely cured 18 months after treatment. Although the study had major flaws, and single-dose treatment is less effective than the conventional 6-month treatment for paucibacillary leprosy, it is an operationally attractive field regimen and has been recommended for use by the WHO [19].

The recommended length of treatment for multibacillary patients has dropped from 24 months to 12 months. There was no controlled trial data to guide this decision, but the classification of multibacillary patients had been widened, so some patients who would previously have received paucibacillary treatment for 6 months are now receiving multibacillary treatment for 12 months. New proposals include testing a common 6-month regimen of dapsone, clofazimine and rifampicin for all patients [20]. This would simplify leprosy treatment but would give 60% of patients a third drug that they do not need, and under-treat patients with a high bacterial load [21].

Reactions and neuritis [22]

Nerve damage occurs before diagnosis, during and after multidrug treatment. It may occur during a reaction or without overt signs of nerve inflammation (silent neuropathy). In field cohort studies 16–56% of newly diagnosed patients have nerve damage [23]. In a Bangladeshi study, 25% of multibacillary patients developed nerve damage during treatment [24]. This study also showed that 65% of patients with multibacillary leprosy who had nerve damage at diagnosis developed new nerve damage over a 5-year follow-up; therefore this group should be closely monitored. Analysis from a large cohort study in Ethiopia showed that standardized nerve function testing was needed monthly to detect new nerve damage early [25].

Patients frequently seek medical advice for their leprosy only when a reversal reaction develops in a previously quiescent skin lesion, or when they develop pain, weakness or numbness. Awareness of the early symptoms of reversal reactions by both patient and physician is important, because if left untreated severe nerve damage may occur. The peak time for reversal reactions is in the first 6 months of treatment [26], so it is important to warn patients

about reactions. The sudden development of reactional lesions soon after starting treatment is distressing and undermines confidence.

The treatment of reactions is aimed at controlling acute inflammation, easing pain, reversing nerve and eye damage and reassuring the patient. Multidrug therapy should be continued. Neuritis (nerve tenderness, new anaesthesia and/or motor loss) or moderately inflamed skin lesions should be treated with corticosteroids. Standardized courses of prednisolone have been used, starting at 40–60 mg daily, reducing by 5 mg every 2–4 weeks [27]. Patients with BT reactions commonly need 2–4 months of steroids, while BL patients with reactions may need 6 months' treatment. A recent Indian study compared different starting doses (60 vs. 30 mg) and durations (12 vs. 20 weeks) and showed that the longer durations gave the best outcomes. A study looking at cytokine profiles in reactional patients showed that, even after 6 months of steroid treatment, some patients still had high levels of pro-inflammmatory cytokines in their skin lesions [28]. In another approach, the prevention of reactions has been explored. In one study, multibacillary patients were randomized to either prednisolone 20 mg daily or placebo for the first 3 months of their multidrug therapy. Reactional episodes were significantly lower in the prednisolone-treated group at 4 months, but the protective effect was lost by 12 months. These studies all demonstrate that reactions are difficult to prevent and to switch off once established. Other established immunosuppressants may have a role in treating reactions; in a pilot study in Nepal, patients had equivalent outcomes whether treated with an azathioprine/prednisolone combination or prednisolone alone [29]. Ciclosporin (cyclosporin) has also been used in reactions, and again is effective in skin and nerve inflammation, but patients relapse when treatment is stopped [30].

Erythema nodosum leprosum is a difficult condition to treat, and frequently requires therapy with high-dose steroids (80 mg daily, tapered down rapidly) or thalidomide. Since ENL frequently recurs, steroid dependency can easily develop. Thalidomide (400 mg daily) is superior to steroids in controlling ENL, and is the drug of choice for young men with severe ENL [31]. Women with severe ENL may benefit from thalidomide treatment. This is a difficult decision for the woman and her physician, and needs careful discussion of the benefits and risks (phocomelia when thalidomide is taken in the first trimester). Women should use double contraception and report immediately if menstruation is delayed. Unfortunately, the problems with thalidomide mean that it is unavailable in several leprosy endemic countries despite its undoubted value. Clofazimine has a useful anti-inflammatory effect in ENL and can be used at 300 mg/day for several months. Low-grade chronic ENL, with iritis or neuritis, will require long-term suppression, preferably with thalidomide or clofazimine. Acute iridocyclitis is treated with 4-hourly instillation of 1% hydrocortisone eye drops and 1% atropine drops twice daily.

Education of the patient

Educating a leprosy patient about their disease is the key to successful management. The patient needs to be reassured that within a few days of chemotherapy they will not be infectious and can lead a normal social life. A clear explanation of the disease and refutation of myths about leprosy will help the patient come to terms with their diagnosis and may well improve compliance. It is important to emphasize that gross deformities are not the inevitable end point of disease, and that care and awareness of their limbs is as important as chemotherapy. Anxieties about transmission and reactions, as well as issues about compliance, should be addressed.

Complications of nerve damage [32,33]

The complications of nerve damage, which are the major causes of disability and deformity in leprosy, are preventable by early diagnosis, correct treatment and education of the patient. Monitoring sensation and muscle power in patient hands, feet and eyes should be part of the routine follow-up, so that new nerve damage is detected early.

Dry skin should be treated by soaking in water, followed by rubbing with emulsifying ointment or petrolatum. Callus should be rubbed down with pumice or an abrasive nylon pad, and fissures need to be covered to allow them to heal.

The morbidity and disability associated with leprosy is secondary to nerve damage. A major goal in prevention of disability is to create patient self-awareness, so that damage is minimized. The patient with an anaesthetic hand or foot needs to understand the importance of daily self-care, especially protection when doing potentially dangerous tasks, and inspection for trauma. It is helpful to identify for each patient potentially dangerous situations, such as cooking, car repairs or smoking. Soaking dry hands and feet followed by rubbing with oil keeps the skin moist and supple.

An anaesthetic foot needs the protection of an appropriate shoe. For anaesthesia alone, a well-fitting 'trainer' with firm soles and shock-absorbing inners will provide adequate protection. Once there is deformity, such as clawing, shoes must be made specially to ensure protection of pressure points and even weight distribution.

The patient should be taught to question the cause of an injury so that the risk can in the future be avoided. Plantar ulceration occurs secondary to increased pressure over bony prominences. Ulceration is treated by rest. Unlike ulcers in diabetic or ischaemic feet, ulcers in leprosy heal if they are protected from weight-bearing. No weight-bearing is permitted until the ulcer has healed. Appropriate footwear should be provided to prevent recurrence.

Weakness or paralysis

These require physiotherapy, with the objective of permitting the return of function while preventing the formation of contracture. Patients with contractures are taught exercises to prevent fixation. Contractures of hands and feet, foot drop, lagophthalmos, entropion and ectropion are amenable to surgery.

Social, psychological and vocational rehabilitation

The social and cultural background of the patient determines the nature of many of the problems that may be encountered. The patient may have difficulty in coming to terms with leprosy. The community may reject the patient. Education, gainful employment, confidence from family, friends and doctor, and plastic surgery to correct stigmatizing deformity, all have a role to play.

Prevention and control

Dermatologists now play a key role in diagnosing and treating leprosy patients. For much of the 20th century leprosy patients were detected and treated within vertical programmes dedicated to leprosy. Although these were effective they also became inefficient as the numbers of leprosy patients declined. The management of leprosy patients is now being integrated into a range of health services including combined leprosy and tuberculosis programmes, dermatology programmes and full integration with general health services. The current WHO strategy emphasizes the importance of quality services that are accessible, patient centred, provide free treatment with MDT, undertake appropriate prevention of disability, and refer patients on for the management of complications. There are now huge needs to train people to recognize leprosy. The development of referral services is also a critical need if an integrated approach is to work well.

Vaccines against leprosy

The substantial cross-reactivity between BCG and *M. leprae* has been exploited in attempts to develop a vaccine against leprosy. Trials of BCG as a vaccine against leprosy in Uganda, New Guinea, Burma and South India showed it to confer statistically significant but variable protection, ranging from 80% in Uganda to 20% in Burma, and a meta-analysis has estimated that BCG vaccination confers 50% protection against leprosy [34]. In Northern Malawi, BCG gives 50% protection against leprosy but no significant protection against tuberculosis [35]. A case–control study in Venezuela showed BCG vaccination to give 56% protection to the household contacts of leprosy patients [36]. The variability and unpredictability of BCG vaccination has led to various attempts to improve its protective efficacy. Combining BCG and killed *M. leprae* is one approach, but in both a large population-based trial in Malawi [37] and in an immunoprophylactic trial in Venezuela [38] there was no advantage with BCG plus *M. leprae* over BCG alone. Possibly the variable protection induced by BCG is due to early contact with environmental mycobacteria priming the immune system and conferring protective immunity against *M. leprae*. Vaccination with BCG after contact with environmental mycobacteria will then contribute little towards inducing improved immunity against *M. leprae* [39].

There was a WHO-led campaign to eliminate leprosy as a public health problem. Although this focused resources and energy on leprosy the effect of a target-driven approach was eventually counter-productive [40]. Leprosy patients continue to present in many countries and will need diagnosis and treatment. Leprosy is unlikely to be eradicated until there is considerable improvement in general health, wealth, living conditions and education.

References

1 Ji BH. Drug resistance in leprosy—a review. *Lepr Rev* 1985; **56**: 265–78.
2 World Health Organization. *Chemotherapy of Leprosy for Control Programmes*. Technical Report Series 675. Geneva: World Health Organization, 1982.
3 Levy L, Shepard CC, Fasal P. The bactericidal effect of rifampicin on *M. leprae* in man: (a) single doses of 600, 900 and 1200 mg; and (b) daily doses of 300 mg. *Int J Lepr Other Mycobact Dis* 1976; **44**: 183–7.
4 Jacobson RR, Hastings RC. Rifampin-resistant leprosy. *Lancet* 1976; **2**: 1304–5.
5 Frey HM, Gershon AA, Borkowsky W, Bullock WE. Fatal reaction to dapsone during treatment of leprosy. *Ann Intern Med* 1981; **94**: 777–9.
6 World Health Organization. *Chemotherapy of Leprosy*. Technical Report Series 847. Geneva: World Health Organization, 1994.
7 Lockwood DN. Leprosy. *Clin Evid* 2002; **8**: 709–20.
8 Gebre S, Saunderson P, Byass P. Relapses after fixed duration multiple drug therapy: the AMFES cohort. *Lepr Rev* 2000; **71**: 325–31.
9 Boerrigter G, Ponnighaus JM, Fine PE, Wilson RJ. Four-year follow-up results of a WHO-recommended multiple-drug regimen in paucibacillary leprosy patients in Malawi. *Int J Lepr Other Mycobact Dis* 1991; **59**: 255–61.
10 Dasananjali K, Schreuder PA, Pirayavaraporn C. A study on the effectiveness and safety of the WHO/MDT regimen in the northeast of Thailand: a prospective study, 1984–96. *Int J Lepr Other Mycobact Dis* 1997; **65**: 28–36.
11 Jamet P, Ji B. Relapse after long-term follow up of multibacillary patients treated by WHO multidrug regimen. Marchoux Chemotherapy Study Group. *Int J Lepr Other Mycobact Dis* 1995; **63**: 195–201.
12 Girdhar BK, Girdhar A, Kumar A. Relapses in multibacillary leprosy patients: effect of length of therapy. *Lepr Rev* 2000; **71**: 144–53.
13 Ji B. Rifampicin resistant leprosy: a review and a research proposal of a pilot study. *Lepr Rev* 2002; **73**: 2–8.
14 N'Deli L, Guelpa-Lauras CC, Perani EG, Grosset JH. Effectiveness of pefloxacin in the treatment of lepromatous leprosy. *Int J Lepr Other Mycobact Dis* 1990; **58**: 12–8.
15 Gelber RH, Fukuda K, Byrd S *et al*. A clinical trial of minocycline in lepromatous leprosy. *BMJ* 1992; **304**: 91–2.
16 Ji B, Jamet P, Perani EG, Bobin P, Grosset JH. Powerful bactericidal activities of clarithromycin and minocycline against *Mycobacterium leprae* in lepromatous leprosy. *J Infect Dis* 1993; **168**: 188–90.
17 Xiong JH, Ji B, Perani EG, Petinon C, Grosset JH. Further study of the effectiveness of single doses of clarithromycin and minocycline against *Mycobacterium leprae* in mice. *Int J Lepr Other Mycobact Dis* 1994; **62**: 37–42.
18 Fleming CJ, Hunt MJ, Salisbury EL *et al*. Minocycline-induced hyperpigmentation in leprosy. *Br J Dermatol* 1996; **134**: 784–7.
19 Lockwood DN. Rifampicin/minocycline and ofloxacin (ROM) for single lesions—what is the evidence? *Lepr Rev* 1997; **68**: 299–300.
20 World Health Organization. *Report of the Third Meeting of the WHO Technical Advisory Group on the Elimination of Leprosy*. Geneva: WHO/CDS/CPE/CEE, 2002.
21 Lockwood DN. Leprosy elimination—a virtual phenomenon or a reality? *BMJ* 2002; **324**: 1516–8.
22 Rose P, Waters MF. Reversal reactions in leprosy and their management. *Lepr Rev* 1991; **62**: 113–21.
23 Van Brakel WH. Peripheral neuropathy in leprosy and its consequences. *Lepr Rev* 2000; **71** (Suppl.): S146–53.
24 Croft RP, Richardus JH, Nicholls PG, Smith WC. Nerve function impairment in leprosy. Design, methodology, and intake status of a prospective cohort study of 2664 new leprosy cases in Bangladesh (The Bangladesh Acute Nerve Damage Study). *Lepr Rev* 1999; **70**: 140–59.
25 Saunderson P, Gebre S, Desta K *et al*. The pattern of leprosy-related neuropathy in the AMFES patients in Ethiopia: definitions, incidence, risk factors and outcome. *Lepr Rev* 2000; **71**: 285–308.
26 Lienhardt C, Fine PE. Type 1 reaction, neuritis and disability in leprosy. What is the current epidemiological situation? *Lepr Rev* 1994; **65**: 9–33.
27 Kiran KU, Stanley JN, Pearson JM. The outpatient treatment of nerve damage in patients with borderline leprosy using a semi-standardized steroid regimen. *Lepr Rev* 1985; **56**: 127–34.
28 Little D, Khanolkar-Young S, Coulthart A *et al*. Immunohistochemical analysis of cellular infiltrate and γ interferon, interleukin-12, and inducible nitric oxide synthase expression in leprosy type 1 (reversal) reactions before and during prednisolone treatment. *Infect Immun* 2001; **69**: 3413–7.
29 Marlowe SN, Hawksworth RA, Butlin CR *et al*. Clinical outcomes in a randomized controlled study comparing azathioprine and prednisolone versus prednisolone alone in the treatment of severe leprosy type 1 reactions in Nepal. *Trans R Soc Trop Med Hyg* 2004; **98**: 602–9.
30 Marlowe SNS, Leekassa R, Bizuneh E *et al*. Clinical response to cyclosporin A treatment in Ethiopian and Nepali patients with severe leprosy type 1 reactions (T1R). *Trans R Soc Trop Med Hyg* 2007; **101**: 1004–12.
31 Walker SL, Waters M, Lockwood DNJ. The role of thalidomide in the management of erythema nodosum leprosum. *Lep Rev* 2007; **78**: 197–215.
32 Watson JM. *Preventing Disability in Leprosy Patients*. London: The Leprosy Mission International, 1986.

33 Srinivasan H. *Prevention of Disabilities in Patients with Leprosy: a Practical Guide.* Geneva: World Health Organization, 1986.
34 Setia MS, Steinmaus C, Ho CS, Rutherford GW. The role of BCG in prevention of leprosy: a meta-analysis. *Lancet Infect Dis* 2006; **6**: 162–70.
35 Ponnighaus JM, Fine PE, Sterne JA *et al*. Efficacy of BCG vaccine against leprosy and tuberculosis in northern Malawi. *Lancet* 1992; **339**: 636–9.
36 Convit J, Smith PG, Zuniga M *et al*. BCG vaccination protects against leprosy in Venezuela: a case-control study. *Int J Lepr Other Mycobact Dis* 1993; **61**: 185–91.
37 Karonga Prevention Trial Group. Randomised controlled trial of single BCG, repeated BCG, or combined BCG and killed *Mycobacterium leprae* vaccine for prevention of leprosy and tuberculosis in Malawi. *Lancet* 1996; **348**: 17–24.
38 Convit J, Sampson C, Zuniga M *et al*. Immunoprophylactic trial with combined *Mycobacterium leprae*/BCG vaccine against leprosy: preliminary results. *Lancet* 1992; **339**: 446–50.
39 Anonymous. Bettering BCG. *Lancet* 1992; **339**: 462–3.
40 Fine PE. Leprosy: what is being 'eliminated'? *B World Health Organ* 2007; **85**: 2.

CHAPTER 33
Virus Infections

J.C. Sterling
Department of Dermatology, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK

General pathology of viral infections, 33.1
Poxviruses, 33.5
Smallpox (variola), 33.5
Vaccinia, 33.6
Monkeypox, 33.7
Cowpox, 33.7
Other orthopoxvirus infections, 33.8
Orf, 33.8
Milker's nodule, 33.10
Molluscum contagiosum, 33.11
Tanapox, 33.14
Herpesviruses, 33.14
Herpes simplex, 33.14
Varicella zoster virus, 33.22
Cytomegalovirus, 33.29
Epstein–Barr virus, 33.30
Human herpesvirus 6, 33.32
Human herpesvirus 7, 33.33
Human herpesvirus 8, 33.33
Herpes B virus, 33.34
Kaposi's varicelliform eruption including eczema herpeticum, 33.35
Polyomavirus, 33.37
Human papillomaviruses (HPV), 33.37
Warts, 33.39
Hepatitis viruses, 33.60
Hepatitis B, 33.60
Hepatitis C, 33.61
Parvoviruses, 33.62
Human parvovirus, B19, 33.62
Retroviruses, 33.64
Human T-lymphotropic viruses, 33.64
Viral insect-borne and haemorrhagic fevers, 33.66
Togaviruses, 33.66
Flaviviruses, 33.68
Other viral haemorrhagic fevers, 33.68
Rubella, 33.70
Picornaviruses, 33.71
Coxsackieviruses, 33.71
Echoviruses, 33.73
Foot and mouth disease, 33.74
Hepatitis A, 33.74
Vesicular stomatitis virus, 33.74
Myxoviruses and related RNA viruses, 33.75
Measles, 33.75
Respiratory syncytial virus, 33.76
Other cutaneous problems associated with viral infections, 33.76
Erythema multiforme, 33.76
Erythema nodosum, 33.76
Papular–purpuric gloves and socks syndrome, 33.76
TORCH syndrome, 33.76
Kikuchi–Fujimoto disease, 33.77
Polyarteritis nodosa, 33.77
Gianotti–Crosti syndrome, 33.77
Pityriasis rosea, 33.78

Introduction

A virus particle, or virion, consists of a length of nucleic acid, either RNA or DNA, within a protein shell, the capsid. The genetic information is sufficient to encode proteins involved in viral replication and production of the protective coat, but requires host cell ribosomes for translation. This absolute dependence on the host is the distinguishing feature of viruses.

A simple classification of viruses that cause illness in humans and their relationship to the skin is given in Table 33.1. This classification is followed throughout the chapter. Other viral-associated skin diseases and pityriasis rosea, a condition of uncertain but possible viral aetiology, are also discussed.

General pathology of viral infections

Pathogenesis of viral disease

For a virus to produce infection, it must gain entry into a susceptible cell within an appropriate host. Many viruses, particularly those producing systemic infection, enter the body via mucous membranes after inhalation, ingestion or contact. The skin can act as a portal of entry, although this usually depends on some breach of the barrier function of the integument, for instance a scratch or fissure or by direct inoculation. Attachment to the cell surface by means of a receptor is followed by entry of the virion into the cell, by endocytosis or phagocytosis. Viruses differ in the range and type of cells which they can infect; host specificity and tissue tropism are hallmarks of viral infections. For example, poliovirus can infect neurones and is called a neurotropic virus, while human papillomaviruses have a tropism for epithelial cells. A cell in which a particular virus can replicate is described as permissive for that virus. After entry into the cell, pre-existing cell enzymes remove or damage the capsid sufficiently for the nucleic acid to emerge.

The next stage depends on the nature of the virus. In relatively simple ones, like enteroviruses, the RNA acts as a messenger, is infectious on its own and is immediately translatable by host ribosomes into viral proteins. More complex RNA viruses, such as influenza, have non-infectious RNA, called negative-strand RNA, which has to be transcribed into messenger RNA (mRNA) by a polymerase enzyme carried in the virus itself. RNA tumour viruses contain a reverse transcriptase enzyme which synthesizes DNA from the viral RNA template. DNA viruses are generally more complex and are able to transcribe mRNA from their DNA

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

Table 33.1 A classification of human viruses.

Nucleic acid	Family	Size (nm)	Viruses	Skin changes	Main associated disease
DNA-ds	*Poxviridae*	200 × 300	*Ortho*	+	Generalized vesicular eruption
			Variola	+	
			Monkeypox	+	Localized vesicular eruption
			Vaccinia	+	
			Cowpox	+	
		150 × 200	*Para*		Localized benign cutaneous tumours
			Orf	+	
			Pseudocowpox	+	
			Molluscipox	+	Generalized benign cutaneous tumours
			Yatapox	+	Localized benign cutaneous tumours
	Herpesviridae	180–250 enveloped (100 naked)	α Herpes simplex	+	Vesicles/encephalitis
			α Varicella	+	Chickenpox/shingles
			β Cytomegalovirus	+	Congenital/in immunocompromised
			γ Epstein–Barr	+	Infectious mononucleosis
			β Human herpesvirus 6	+	Roseola infantum/exanthem subitum
			β Human herpesvirus 7	+	Macular eruption
			γ Human herpesvirus 8	+	Kaposi's sarcoma
			α B virus (monkey)	+	Encephalomyelitis
	Adenoviridae	70 naked	Subgenera A–F	–	Respiratory tract infection Conjunctivitis Haemorrhagic cystitis Gastroenteritis
	Papovaviridae	44 naked	Polyomavirus	–	Ureteric obstruction, Merkel cell carcinoma
			BK		
			JC	–	PMLE
	Papillomaviridae	55 naked	Human papillomavirus (>100 types)	+	Warts, AGIN, anogenital cancer, head and neck SCC
DNA-ds*	*Hepadnaviridae*	42 naked	Hepatitis B	+	Hepatitis
DNA-ss	*Parvoviridae*	22 naked	Human parvovirus (B19)	+	Erythema infectiosum/aplastic crisis
RNA-ss (+)	*Retroviridae*	100 enveloped	Oncoviruses	+	T-cell leukaemia
			HTLV-1, HTLV-2		Tropical spastic paraparesis
			Lentiviruses	+	AIDS
			HIV-1, HIV-2, HIV-0		
	Coronaviridae	80–150 enveloped	Coronavirus	–	URTI
	Togaviridae	42 enveloped	Rubella	+	German measles, arthralgia
			Alphaviruses	+	Rash, arthralgia
			Ross River	±	Encephalitis
			Sinbis	+	
			Chikungunya	+	
			O'Nyong-Nyong	+	
			Barmah Forest	+	
			Equine encephalitis viruses		
	Flaviviridae	42 enveloped	Hepatitis C	–	Hepatitis
			Dengue + febrile illness	(+)	
			Japanese encephalitis	–	Encephalitis
			Yellow fever	–	Hepatitis
			Tick-borne encephalitis–encephalitis		
	Caliciviridae	38 naked	Calicivirus (Norwalk)	–	Gastroenteritis
			Hepatitis E	–	Hepatitis
	Picornaviridae	27 naked	Rhinovirus	–	URTI
			Foot and mouth (cattle)	+	

(Continued)

Table 33.1 *Continued*

Nucleic acid	Family	Size (nm)	Viruses	Skin changes	Main associated disease
			Enterovirus		
			Polio	–	Polio
			coxsackie A	+	Meningitis, herpangina, hand, foot and mouth
			coxsackie B	+	Meningitis, Bornholm
			Echovirus	+	Meningitis, maculopapular eruptions
			Hepatitis A	(–)	Infectious hepatitis
RNA-ss (–)	*Rhabdoviridae*	70 × 180 enveloped	Rabies	–	Rabies
			Lyssa		
			Vesicular stomatitis virus	+	Flu-like illness
	Filoviridae	Filamentous	Marburg disease		
			Ebola disease (and see Table 33.2)		
	Paramyxoviridae	150 × 300 enveloped	Measles	+	Measles
			Mumps	–	Mumps
			Parainfluenza	–	RTI
			Respiratory syncytial virus	(+)	RTI
	Orthomyxoviridae >100	Influenza A, B, C enveloped		–	Flu
	Arenaviridae	100 × 300 enveloped	Lymphocytic choriomeningitis	–	Meningitis
			Lassa fever	(+)	
			Argentinian haemorrhagic fever	+	
			Bolivian haemorrhagic fever	+	
			Venezuelan haemorrhagic fever (and see Table 33.2)	+	
	Bunyaviridae	100 enveloped	Crimean–Congo haemorrhagic fever	(+)	
			Rift valley fever (and see Table 33.2)	(+)	
RNA-ds	*Reoviridae*	70 naked	Rotavirus	–	Gastroenteritis

ds, double stranded; ss, single stranded; ss (+), single stranded (plus strand); ss (–), single stranded (minus strand); ds*, incomplete ds; +, skin changes frequent; (+), skin changes less frequent; (–), skin changes rarely reported; –, skin changes not recognized; CIN, cervical intraepithelial neoplasia; PMLE, progressive multifocal leukoencephalopathy; RTI, respiratory tract infection; URTI, upper respiratory tract infection.

using either cell polymerase (e.g. adenoviruses) or viral polymerase (e.g. vaccinia). At the same time, replication of the viral nucleic acid also occurs.

A variety of proteins—regulatory, enzymatic and structural—are produced and these, together with the products of cell damage, probably contribute to the local and general response to the infection. The time required for new virus production in acute infections is measured in hours and the number of new virions in thousands per cell. Newly produced virions can invade adjacent cells or be carried via the bloodstream and so the infection spreads. During this process the cell itself may be destroyed by a *lytic infection* (e.g. enterovirus and herpes simplex) or damaged transiently (e.g. myxovirus). With time, an immune response develops against the virus particles and processed viral proteins, which can lead to containment and clearance of the infection.

Not all virus infections end in this fashion. Some viruses infect cells that apparently remain normal and may multiply while virus replication continues within, that is *persistent infection*. When persistently infected cells produce no infectious virus because the replication cycle is arrested, the virus is said to be *latent*. From time to time, a latent virus can become active—*reactivation*—new virions are produced and other cells are infected. This process can result in clinical signs and symptoms as in the case of cold sores (reactivated herpes simplex) and shingles (reactivated varicella-zoster). Other viruses cause cell proliferation, for example poxviruses and human papillomaviruses. Viruses can also be implicated in the process of carcinogenesis, as in the development of cervical cancer and hepatoma.

Exanthems of viral infections

Widespread exanthems may be a manifestation of viral infections that cause a viraemia. An attempt to explain the different types of viral exanthem (Table 33.2) can be made by tracing the sequence of events which follows the arrival of blood-borne virus particles in the skin, where they lodge in dermal capillary loops. Some microorganisms (e.g. some togaviruses, poxviruses and rickettsiae) can replicate in capillary endothelium, causing damage directly or by a type III hypersensitivity reaction that results in infarcts and haemorrhages. The great majority of viruses, however, act as inert foreign particles, reacting with circulating antibodies and sensitized lymphocytes to produce inflammation. Circulating immune complexes of antibody and viral antigens also localize in dermal blood vessels and are responsible for the rashes in many virus infections, for example human parvovirus. The complex cascade of inflammation in the dermis results in erythematous macules and papules.

In the case of most RNA viruses there is no replication, these are the only reactions and the intruding particle is removed (e.g.

Table 33.2 Viral exanthems.

Type of rash	Pathogen associated
Macular	Rubella
	Echovirus (esp. 2, 4, 6, 9, 11, 16, 18, 19, 23, 25, 32)
	Coxsackie A (esp. 4, 5, 6, 9, 10, 16) and B (esp. 5, 3)
	EBV (infectious mononucleosis)
	Human herpesvirus 6 (roseola)
	Human herpesvirus 7
Maculopapular	Togaviruses
	Echovirus (esp 6, 9)
	Measles
	Human parvovirus (B19) (erythema infectiosum)
Maculopapular–vesicular	Coxsackie A (occasional 5, 9, 10, 16)
	Echovirus (occasional 4, 9, 11)
	Marburg
Maculopapular–petechial	Togavirus (esp. Chikungunya) and bunyavirus haemorrhagic fevers (including Lassa)
Urticarial	Coxsackie A9 (occasional)
	Hepatitis B (occasional)
Vesicular	Herpes simplex virus
	Hand, foot and mouth disease (coxsackie 16, 4, 5)
	Vesicular stomatitis virus
Vesiculopapular	Varicella–zoster
Papulovesiculopustular	Vaccinia
	Variola
	Cowpox
Papulovesicular	Orf
	Milker's nodule
Papular	Molluscum contagiosum
	Warts
	Gianotti–Crosti

The type of rash given is the most common clinical association but it may in some patients overlap with the next category.
EBV, Epstein–Barr virus.

echoviruses, coxsackie A, most togaviruses and rubella). A few RNA viruses are, on occasion, able to enter actively metabolizing epidermal cells and replicate for a limited time, with cytolysis and production of a vesicular lesion (e.g. the vesicular exanthem of coxsackie A and some rarer vesicular exanthems).

Replicative ability in epidermal cells is mainly a feature of the DNA viruses, which may explain why this group contains those viruses capable of replication after direct inoculation of the epidermis. Vesicles and pustules result from viral replication in the epidermis, where the focal necrosis is followed by an immune response and infiltration with leukocytes. Vesicular lesions are caused by poxviruses, herpes simplex, varicella-zoster and some coxsackievirus infections. The cell proliferation caused by human papillomaviruses and molluscum results in localized tumours.

The antibody production that produces local inflammatory lesions may serve to prevent further dispersal of infection by the bloodstream. However, the cell-mediated immune response is probably the major local inflammatory factor, the means of containment and healing of the infection. When it is not competent, as in immunosuppression or immunodeficiency, there may be serious spread of the lesions, as seen in vaccinia and varicella. The factors that influence the areas of distribution of the rash and the sequence of affected regions are imperfectly understood. Where there is an area of capillary trauma, caused for example by intermittent pressure or a pre-existing area of inflammation, viruses will localize, but the caudal progression in rubella and the centripetal distribution in varicella are unexplained.

Laboratory diagnosis [1–4]

The extent to which laboratory procedures are helpful depends on the nature of the infection and locally available resources. The general condition of the patient should always be considered and it is stressed that in early pregnancy any rash should be investigated to establish the possible risk to the fetus from rubella, parvovirus or other congenital infections. A considerable expansion of technical methods is taking place and clinicians are urged to discuss current local facilities with their microbiologists. Rapid methods are often now feasible, using polymerase chain reaction (PCR) or fluorescence microscopy, so that laboratory confirmation may be possible on the day of receipt of specimens. Tissue culture can give an answer in 1 to 2 days.

Broadly, the following groups of tests are available:

1. Virus culture, usually done in cell cultures but occasionally in fertile eggs or laboratory animals
2. Examination of histological specimens for features typical of a virus infection, for example inclusion bodies or koilocytes
3. Visualization of virus by electron microscopy
4. Detection of viral antigens by immunological techniques, for example using fluorescent antibodies
5. Detection of viral nucleic acid by molecular techniques such as PCR (for DNA viruses) or reverse transcription PCR (for RNA viruses or for detection of viral transcripts)
6. Serological tests to detect seroconversion, rising antibody titres or specific antibodies, for example IgM, low-avidity IgG.

Specimens for virus isolation are most likely to be positive if taken early in the illness. After the onset, the amount of live virus declines, especially when accessible to circulating antibody.

Specimens should be sent to the laboratory with the minimum of delay. Throat swabs should mop up the maximum nasopharyngeal material and the broken-off swab head should be immersed in a virus-transport medium, kept cool if in transit for more than 1 h.

Cerebrospinal fluid should be transported rapidly, preferably chilled. Vesicle fluid is best collected in a glass capillary, which can have one end sealed but not so as to heat the fluid. An alternative is to use a sterile disposable hypodermic needle and transport it in its plastic container. A swab of vesicle fluid transported as for a throat swab is also valuable. Small biopsies from proliferative skin lesions are best transported in medium or sterile normal saline. Crusts are sent dry in a sterile bottle.

Urine is of limited value; as a special transport medium may be needed, arrangements should be made with the laboratory. Faeces should be sent as a few grams in a sterile container.

The fraction of blood—white cells, plasma or serum—most suitable for PCR varies according to the viral nucleic acid to be detected. Blood for togavirus isolation must be chilled and reach the laboratory quickly. It is best processed without delay or rapidly frozen below –40°C because of inactivation of virus by antibody.

If smallpox, Lassa fever, Marburg disease or haemorrhagic fevers are suspected, consult both the laboratory director and the local community physician before any specimens are taken.

Serological tests

Two specimens of clotted blood (5–10 mL each) should always be taken to achieve an unequivocal diagnosis in infections for which serology is available. The first must be taken as soon after the onset of symptoms as possible in order to have serum before appreciable antibody production has taken place. The second should be taken after a considered interval, depending on the type of infection. In general, 10 days is optimal, but when the antibody response immediately follows the rash, as in rubella, 5 days may suffice, provided the first blood was taken on the day of eruption of the rash.

It is a long-established convention that a fourfold or greater rise in titre between acute and convalescent sera is diagnostic. Because of technical variations it is customary to titrate both sera in parallel so that comparison of titres is accurate. Interpretation has to take into account possible anamnestic rises caused by organisms with some antigenic similarity.

Examination of a single serum may provide strong presumptive evidence of infection when it demonstrates a high relevant antibody titre, but this can be quite misleading at times as the particular antibody level may antedate the infection under consideration. The demonstration of specific IgM or IgA antibody in a single acute serum is also of diagnostic value in rubella and other infections. Unfortunately, in some infections such as human immunodeficiency virus (HIV) infections and in severely immunodeficient or immunosuppressed people, serological responses to infection are unpredictable and cannot be relied upon for diagnosis.

References

1 Knipe DM, Howley PM, Griffin DE *et al.*, eds. *Field's Virology*, 5th edn. New York: Lippincott, Williams and Wilkins, 2006.

2 Strauss JH, Strauss EG. *Viruses and Human Disease*, 2nd edn. San Diego: Academic Press, 2007.

3 Kudesia G, Wreghitt T. *Clinical and Diagnostic Virology*. Cambridge: Cambridge University Press, 2009.

4 Van Regenmortel MHV, Fauquet CM, Bishop DHL *et al.*, eds. *Virus Taxonomy*. San Diego: Academic Press, 2000. Available from: http://www.virustaxonomyonline.com/virtax/lpext.dll?f=templates&fn=main-h.htm

Poxviruses

The poxviruses are the largest animal viruses, being only slightly smaller than the smallest bacteria, and they are just visible by light microscopy. They are complex, double-stranded DNA viruses which replicate in the cytoplasm and are especially adapted to epidermal cells. Within the cytoplasm, they produce eosinophilic inclusion bodies (Guanieri bodies). They are generally resistant to physical damage; some, for example variola, have remarkable resistance to drying and can remain viable for months in crusts. Spread is mainly by direct-contact inoculation, with droplet spread in some, for example variola, which produce respiratory tract lesions. Some grow readily in eggs and tissue culture, others not at all.

The human is host for four genera:

1 *orthopoxviruses*—variola (smallpox), vaccinia, monkeypox and cowpox, which are ovoid, 300 × 250 nm
2 *parapoxviruses*—orf and milker's nodule viruses, which are cylindrical, 260 × 160 nm
3 *molluscipox*—molluscum contagiosum, intermediate in structure and 275 × 200 nm
4 *yatapox*—tanapox virus.

Smallpox (variola)

Smallpox infection is now eliminated from the world and routine vaccination against it has been abandoned. Eradication of smallpox was accepted at the 23rd World Health Assembly in May 1980 [1]. The last case of smallpox in the UK occurred in Birmingham in 1978 as a result of a laboratory accident. The last case in an endemic area was in 1977 in Somalia. Stocks of smallpox virus still exist in government agencies in the USA and Russia.

Recent global terrorism has reawakened concerns that the virus could be released as a biological weapon. This has led to a rapid increase in the number of medical and military personnel receiving vaccinia vaccination and an awareness of the clinical features of smallpox infection.

Clinical features [2–4]. After an incubation period of 10–14 days, a high fever with malaise, headache and backache are the first symptoms of smallpox. Within 1–3 days a macular eruption develops, which evolves over about 3 days into a rash of tense vesicles and then pustules. The eruption usually starts on the face and spreads caudally, usually affecting the extremities more than the trunk. The palms and soles are frequently affected. Lesions within an area are at the same stage. After about a week, the lesions dry, scab over and finally heal. Skin scarring is common following recovery, which can be marked and is still recognized in areas of the world where the infection was last evident (Fig. 33.1).

The severity of smallpox is variable. Over one-third have severe disease and mortality is between 25 and 40% of those affected.

Diagnosis. The most likely differential diagnoses are chickenpox and Kaposi's varicelliform eruption. Laboratory identification of smallpox from blister fluid is made only by designated laboratories. The virus is recognizable as an orthopoxvirus by electron microscopy and can be definitively identified by PCR amplification.

Treatment. There is no specific antiviral agent of proven efficacy for smallpox. Treatment is supportive. Strict isolation procedures must be observed and contacts of any infected individual traced as quickly as possible.

References

1 Bhattacharya S. The World Health Organization and global smallpox eradication. *J Epidemiol Community Health* 2008; **62**: 909–12.

2 Centers for Disease Control and Prevention. *Emergency Preparedness and Response. Smallpox.* 2006. Available from: www.bt.cdc.gov/agent/smallpox/.

3 Department of Health. *Guidelines for Smallpox Response and Management in the Post-Eradication Era (Smallpox Plan)*. 2003; Available from: www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4070830.

4 Moore ZS, Seward JF, Lane JM. Smallpox. *Lancet* 2006; **367**: 425–35.



Fig. 33.1 Scarring of face following smallpox infection. (Courtesy of Dr S.B. Verma, Baroda Skin Clinic, Baroda, India.)



Fig. 33.2 Vaccinia: vaccination site with generalized spread. (Courtesy of Addenbrooke's Hospital, Cambridge, UK.)

Vaccinia

Vaccinia virus is a distinct entity, named poxvirus officinalis, which is unique in that it does not occur naturally but is the first stable virus to have resulted directly from human activity in the serial propagation of viruses for human inoculation. Antigenically it closely resembles variola and is invaluable for vaccination against smallpox; culturally and molecularly, it most closely resembles cowpox and is postulated to have arisen as a mutant from cowpox [1].

Vaccination. Routine vaccination ceased in the 1970s. Vaccinia virus can potentially be used as a carrier of genes for protective antigens of other pathogenic microorganisms (recombinant vaccinia viruses), and it is used in some specialized laboratory research. It is recommended that vaccination should continue for investigators at special risk [2]. Vaccination of military personnel has also continued and more recently has increased because of the potential risk that variola could be used in biological terrorism or warfare.

Vaccination is not without risk [3,4]. Reported complications of vaccination characterized by abnormal skin lesions are as follows:

1. Generalized vaccinia (Fig. 33.2). After 6–9 days a generalized rash develops as a result of the brief viraemia following successful vaccination. Recovery is the rule.
2. Accidental infection—the result of autoinoculation from the site of vaccination to another part of the body (e.g. eye, genitalia), or inoculation of another person. Vaccinated individuals should avoid close contact with immunosuppressed or atopic people until the vaccine site is healed.
3. Eczema vaccinatum. This occurs in people with atopic eczema or a history of past eczema. Lesions occur on eczematous areas of skin about 5 days after exposure to the virus. Apparently healthy skin may also be involved. The condition is associated with high fever, lymphadenopathy and about 5% mortality rate.
4. Progressive vaccinia. The lesion at the site of vaccination fails to heal in immunodeficient people. Instead it enlarges progressively. Secondary lesions develop and they, too, enlarge. Without antiviral treatment there is usually a fatal outcome. The incidence of progressive vaccinia was about one per million vaccinations in 1968 in the USA [5].
5. Encephalomyelitis or myopericarditis can also rarely complicate vaccination.
6. The vaccination site usually scars, occasionally forms a hypertrophic scar and is rarely the site of development of a tumour such as a basal cell carcinoma [6].

References

1 Gubser C, Hue S, Kellam P *et al.* Poxvirus genomes: a phylogenetic analysis. *J Gen Virol* 2004; **85**: 105–17.

2 Wenzel RP, Nettleman MD. Smallpox vaccination for investigators using vaccinia recombinants. *Lancet* 1989; **2**: 630–1.

3 Cono J, Casey CG, Bell DM. Smallpox vaccination and adverse reactions. Guidance for clinicians. *MMWR Recomm Rep* 2003; **52**: 1–28.

4 Metzger W, Mordmueller BG. Vaccines for preventing smallpox. *Cochrane Database Syst Rev* 2007: CD004913.

5 Lane JM, Ruben FL, Neff JM *et al.* Complications of smallpox vaccination, 1968. *N Engl J Med* 1969; **281**: 1201–8.

6 Waibel KH, Walsh DS. Smallpox vaccination site complications. *Int J Dermatol* 2006; **45**: 684–8.

Monkeypox

Aetiology. The monkeypox virus can cause significant human disease similar to smallpox [1]. The orthopox virus has a natural reservoir in rodents such as squirrels, rabbits and rats but can infect monkeys, resulting in disease with vesicular skin lesions. Monkeypox in humans was first recognized in 1970 and since then cases have been described in the tropical rain forest areas of Central and West African countries, mainly in the Congo basin. The majority of cases occur in children under 10 years old, and the case fatality rate can be over 15%. In 2003, the first outbreak in an area outside Africa occurred in the central USA [2]. Thirty-seven confirmed cases of the disease followed the importation of African rodents and the spread to the American rodent, the prairie dog.

The infection can be spread from animal to human via secretions and excretions. Direct contact with an infected animal increases the chance of infection and inoculation of a scratch or wound with animal secretions is more likely to lead to more severe systemic symptoms. Human to human spread can also occur with a transmission rate of 5–10% to unvaccinated persons.

Sequencing of the virus has shown two clades; the West African and the more virulent Congo clade. Vaccination with vaccinia virus gives 85% protection.

Clinical features [3]. The incubation period is 10–15 days (range 5–25 days) with the initial onset of headache, backache, fever, sweats and chills. There may be nausea, vomiting, breathlessness and cough. After 2 days of prodromal symptoms, the rash appears, starting with papules and macules which are erythematous in white skin although the inflammation may not be visible in black skin. The lesions evolve quickly into vesicles and then pustules of about 1 cm in diameter. Over 2 to 3 weeks the lesions dry, crust and finally heal, sometimes leaving scars. The pattern of spread is usually, but not always, from trunk to extremities. The palms, soles and mucous membranes can be affected.

The acute infection is accompanied by widespread lymphadenopathy, a feature which is usually absent in smallpox.

Diagnosis. Infection will result in a rise of IgM antibodies to orthopoxviruses. Vesicle fluid contains the brick-shaped virus particles, but electron microscopy cannot distinguish the different orthopoxviruses. The virus can be cultured on the chorioallantoic membrane of eggs resulting in pocks. Molecular analysis by PCR of vesicle fluid or crusts provides the most specific diagnosis [4].

Treatment. Treatment is supportive. Theoretically, cidofovir should be active against the infection.

Prophylactic vaccinia vaccination is recommended for those working with infected individuals and up to 4 days post exposure after direct contact with an infected animal.

References

1 Di Giulio DB, Eckburg PB. Human monkeypox: an emerging zoonosis. *Lancet Infect Dis* 2004; **4**: 15–25.
2 Sale TA, Melski JW, Stratman EJ. Monkeypox: an epidemiologic and clinical comparison of African and US disease. *J Am Acad Dermatol* 2006; **55**: 478–81.
3 Jezek Z, Szczeniowski M, Paluku KM *et al.* Human monkeypox: clinical features of 282 patients. *J Infect Dis* 1987; **156**: 293–8.
4 Ropp SL, Jin Q, Knight JC *et al.* PCR strategy for identification and differentiation of small pox and other orthopoxviruses. *J Clin Microbiol* 1995; **33**: 2069–76.

Cowpox

Aetiology. Infection of cattle by this orthopoxvirus is a chance occurrence as the natural reservoir is in small wild rodents [1]. Human infection may occasionally be direct from rodents, but is more commonly acquired from domestic cats [2,3] with a seasonal increase in the late summer and autumn. Contact with animals captive in zoos can also be a source of human disease.

Cowpox appears to occur almost only in Europe [4], where human infection is uncommon and usually sporadic. Under five cases per year are reported in the UK although there is concern that declining immunity since the abandonment of smallpox vaccination could lead to increased susceptibility to the infection.

Pathology [5]. The histological appearance is very similar to vaccinia but epithelial necrosis is less rapid and there is more inflammation, erythema and haemorrhage. There are hypertrophy and proliferation of the basal layer of the epidermis and large eosinophilic cytoplasmic inclusions are seen in the lower epidermal cells.

Clinical features [5]. Humans usually acquire cowpox from cats by implantation of virus into broken skin [3]. After an incubation period of 5–7 days (range 2–14 days) a painful papule appears and rapidly becomes vesicular and haemorrhagic. It becomes pustular, may be umbilicated and is surrounded by a zone of erythema and oedema. The lesion ulcerates during the second week, then crusts over with a hard black eschar 1–3 cm in diameter. Lymphangitis and lymphadenitis are usual, and fever, myalgia and constitutional symptoms are frequent. Healing takes place in 4 or 8 weeks and usually leaves scarring.

The lesions, which are usually on the hands, arms or face, are often multiple, and may spread centrally from the periphery [6]. Conjunctivitis has also been reported [3].

Postvaccinial encephalitis is a rare complication [7]. Widespread cowpox infection mimicking eczema herpeticum has been reported in atopic or immunosuppressed patients [8–10] and an extensive but self-limiting eruption of probable cowpox occurred in the previously healthy anogenital skin of a woman with Darier's disease [11].

Diagnosis. A history of contact with cats is suggestive, especially if the animal has skin ulcers. The distribution of lesions on exposed skin is characteristic.

Differential diagnoses include orf and milker's nodules as well as primary tuberculosis, necrotizing fasciitis, foreign-body granuloma, anthrax and sporotrichosis. If lesions are widespread, chickenpox or other zoonotic orthopox virus infections should be considered.

Laboratory diagnosis may depend on available resource. Electron microscopy of a scraping or crust to visualize orthopox virus particles can give rapid results. Growth in tissue culture or on the egg chorioallantoic membrane, where characteristic haemorrhagic pocks develop, can support the diagnosis. Polymerase chain reaction using a panel of primers for poxviruses will give precision regarding the causative virus [12] and viral DNA may be detected in blood [13].

Treatment. None is required, other than control of secondary infection should this develop.

References

1 Crouch AC, Baxby D, McCracken CM *et al.* Serological evidence for the reservoir hosts of cowpox virus in British wildlife. *Epidemiol Infect* 1995; **115**: 185–91.
2 Wolfs TF, Wagenaar JA, Niesters HG *et al.* Rat-to-human transmission of Cowpox infection. *Emerg Infect Dis* 2002; **8**: 1495–6.
3 Baxby D, Bennett M, Getty B. Human cowpox 1969–93: a review based on 54 cases. *Br J Dermatol* 1994; **131**: 598–607.
4 Lewis-Jones S. Zoonotic poxvirus infections in humans. *Curr Opin Infect Dis* 2004; **17**: 81–9.
5 Laurance B. Cowpox in man. *Lancet* 1995; i: 764–6.
6 Motley RJ, Holt PJ. Cowpox presenting with sporotrichoid spread: a case report. *Br J Dermatol* 1990; **122**: 705–8.
7 Schreuder JTR, van Rijssel TG, Verlinde JD. Encephalomyelitis na besmetting met koepokken. *Ned Tijdschr Geneeskd* 1950; **94**: 2603–9.
8 Blackford S, Roberts DL, Thomas PD. Cowpox infection causing a generalized eruption in a patient with atopic dermatitis. *Br J Dermatol* 1993; **129**: 628–9.
9 Pelkonen PM, Tarvainen K, Hynninen A *et al.* Cowpox with severe generalized eruption, Finland. *Emerg Infect Dis* 2003; **9**: 1458–61.
10 Eis-Hubinger AM, Gerritzen A, Schneweis KE *et al.* Fatal cowpox-like virus infection transmitted by cat. *Lancet* 1990; **336**: 880.
11 Claudy AL, Gaudin OG, Granouillet R. Pox virus infection in Darier's disease. *Clin Exp Dermatol* 1982; **7**: 261–5.
12 Meyer H, Ropp SL, Esposito JJ. Gene for A-type inclusion body protein is useful for a polymerase chain reaction assay to differentiate orthopoxviruses. *J Virol Methods* 1997; **64**: 217–21.
13 Nitsche A, Kurth A, Pauli G. Viremia in human Cowpox virus infection. *J Clin Virol* 2007; **40**: 160–2.

Other orthopoxvirus infections

Buffalopox

This orthopoxvirus infection can occasionally spread from its usual host, the buffalo, to infect humans with reported cases mainly in India, Bangladesh, Pakistan and Egypt. The virus is most closely related to vaccinia virus and cowpoxvirus [1]. Infections occur sporadically in animals, causing ulcerated lesions on udders with transmission to humans usually resulting in localized lesions on the hands following direct contact with infected animals [2].

Individual lesions develop after an incubation period of 1–2 weeks as painful erythematous papules and nodules which progress over a few days to bullae. The lesions dry, crust and may ulcerate before healing over about a month. There may be accompanying fever and malaise and often local lymphadenopathy.

Diagnosis is supported by identification of orthopoxvirus in vesicle fluid by electron microscopy, culture of virus in fertile eggs and can be confirmed by PCR of fluid or crusts.

Cantagalo virus and Araçatuba virus [3,4]

Outbreaks of infection with these two recently identified orthopox viruses have occurred in South America. The viruses infect cattle causing ulcers on the teats and may be accidentally acquired by people working with the animals, causing lesion(s) and associated illness very similar to cowpox. The lesions occur mainly on the hands and arms. The viruses are morphologically very similar to other orthopoxviruses and molecular sequencing shows that they are both closely related to vaccinia virus.

References

1 Singh RK, Hosamani M, Balamurugan V *et al.* Buffalopox: an emerging and re-emerging zoonosis. *Anim Health Res Rev* 2007; **8**: 105–14.
2 Ramanan C, Ghorpade A, Kalra SK *et al.* Buffalopox. *Int J Dermatol* 1996; **35**: 128–30.
3 Damaso CR, Esposito JJ, Condit RC *et al.* An emergent poxvirus from humans and cattle in Rio de Janeiro State: Cantagalo virus may derive from Brazilian smallpox vaccine. *Virology* 2000; **277**: 439–49.
4 de Souza Trindade G, da Fonseca FG, Marques JT *et al.* Araçatuba virus: a vaccinialike virus associated with infection in humans and cattle. *Emerg Infect Dis* 2003; **9**: 155–60.

Orf

Synonyms

- Ecthyma contagiosum
- Contagious pustular dermatitis

Aetiology. Orf is caused by a parapoxvirus. The characteristic woven appearance of the virus is seen with negative staining on electron microscopy (Fig. 33.3). The disease is widespread in sheep



Fig. 33.3 Orf virus. Phosphotungstate preparation (× 230 000). (Courtesy of Dr J. Nagington.)



Fig. 33.4 Orf. (Courtesy of Addenbrooke's Hospital, Cambridge, UK.)



Fig. 33.5 Orf with erythema multiforme. The orf lesion on the dorsum of the forefinger has been present for 14 days; the secondary erythema multiforme for 4 days. (Courtesy of Dr A.S. Highet, York District Hospital, UK.)

and goats. Lambs are commonly infected, contracting the infection from one another or possibly from pastures where the virus may persist. Human lesions are caused by direct inoculation of infected material and are not uncommon and often self-diagnosed in farmers, shepherds, veterinary surgeons and those who bottle-feed lambs. Butchers, meat porters and cooks are sometimes infected from carcasses, especially sheeps' heads [1], and small outbreaks occasionally occur after contact with infected sacrificial animals [2]. One attack normally confers immunity, and human-to-human spread has not been recorded.

Orf occurs worldwide, but the majority of reports are from Europe and New Zealand.

Pathology [3–5]. The keratinocytes show gross inter- and intracellular oedema, vacuolization and ballooning degeneration plus eosinophilic inclusions. A dense cellular infiltrate in the dermis consists in the centre mainly of histiocytes and macrophages and peripherally of lymphocytes and plasma cells. There are very few polymorphonuclear leukocytes. Throughout the lesion there is an increased number of small blood vessels, many of which show swelling and proliferation of endothelial cells. Ultrastructural studies show viral particles only in the cytoplasm of degenerating epidermal cells [6,7].

Clinical features [1,3,8]. After an incubation period of 5 or 6 days, a small, firm, red or reddish-blue papule enlarges to form a flat-topped, haemorrhagic pustule or bulla (Fig. 33.4), often crusted in its umbilicated centre. In the fully developed lesion, which is usually 2 or 3 cm in diameter but may be as large as 5 cm, the central crust is surrounded by a rather characteristic greyish white or violaceous ring which is in turn encircled by a zone of erythema. It is sometimes irritable during the early stages and is often tender. The lesions are solitary or few in number and are common on the fingers, hands or forearms, but may be on the face. Lymphangitis and regional adenitis are not uncommon but are slight and there may be mild fever and malaise. Spontaneous recovery occurs in 3–6 weeks. Second attacks are quite common.

Persistent or fungating lesions are occasionally reported, and may resemble large pyogenic granulomas or malignant tumours. The patient is usually immunocompromised [9,10], although cases have been reported in immunocompetent individuals [11]. Satellite lesions have been reported in a child with atopic eczema [12].

Rarely a widespread, papulovesicular or bullous pemphigoid-like eruption can develop about 3 weeks after the orf infection [13,14]. These may settle spontaneously after a few weeks, or may require immunosuppressive treatment. Bullous lesions can show linear IgG and C3 deposition at the dermoepidermal junction [14,15].

Erythema multiforme occasionally develops, typically 10–14 days after the onset of orf (Fig. 33.5), and less distinctive 'toxic erythemas' are also seen.

Diagnosis. The diagnosis is easy if there is a history of contact with animals and the possibility of orf is suspected. Confirmation can be made by electron microscopy of the crust or a small biopsy [16]. Vesicle fluid should not be used as it contains very little virus. Serological tests are not available routinely, but a detectable antibody response does occur [17]. PCR of vesicle fluid, crust or biopsy can detect parapoxvirus and specific primers confirm orf virus [18].

Treatment. Treatment is usually unnecessary but secondary infection should be treated while spontaneous recovery is awaited. Large exophytic lesions can be readily dissected from the underlying dermis [11], although recurrence may occur in the immunosuppressed [19]. Cryotherapy has been used [20] and idoxuridine (40%) has been claimed to shorten the duration of the lesions [11,21]. Injection of α-interferon is of marginal benefit [19] but topical immunomodulation by imiquimod is reported to hasten clearance [5,22,23].

Cidofovir applied in a cream can also be effective in giant orf [24,25].

References

1 Hodgson-Jones IS. Orf in London. *BMJ* 1951; **1**: 795–6.
2 Uzel M, Sasmaz S, Bakaris S *et al.* A viral infection of the hand commonly seen after the feast of sacrifice: human orf (orf of the hand). *Epidemiol Infect* 2005; **133**: 653–7.
3 Leavell UW Jr, McNamara MJ, Muelling R *et al.* Orf. Report of 19 human cases with clinical and pathological observations. *JAMA* 1968; **204**: 657–64.
4 Groves RW, Wilson-Jones E, MacDonald DM. Human orf and milkers' nodules: a clinicopathological study. *J Am Acad Dermatol* 1991; **25**: 706–11.
5 Lederman ER, Green GM, DeGroot HE *et al.* Progressive orf virus infection in a patient with lymphoma: successful treatment using imiquimod. *Clin Infect Dis* 2007; **44**: e100–3.
6 Yeh HP, Soltani K. Ultrastructural studies in human orf. *Arch Dermatol* 1974; **109**: 390–2.
7 Loubet A, Leboutet MJ, Pestre M *et al.* Maladie d'orf humaine. Etude ultrastructurale de six cas. *Arch Anat Cytol Pathol* 1980; **28**: 303–6.
8 Gill MJ, Arlette J, Buchan KA *et al.* Human orf. A diagnostic consideration? *Arch Dermatol* 1990; **126**: 356–8.
9 Savage J, Black MM. 'Giant' orf of finger in a patient with a lymphoma. *Proc R Soc Med* 1972; **65**: 766–8.
10 Hunskaar S. Giant orf in a patient with chronic lymphocytic leukaemia. *Br J Dermatol* 1986; **114**: 631–4.
11 Pether JV, Guerrier CJ, Jones SM *et al.* Giant orf in a normal individual. *Br J Dermatol* 1986; **115**: 497–9.
12 Dupre A, Christol B, Bonafe JL *et al.* Orf and atopic dermatitis. *Br J Dermatol* 1981; **105**: 103–4.
13 Wilkinson JD. Orf: a family with unusual complications. *Br J Dermatol* 1977; **97**: 447–50.
14 Murphy JK, Ralfs IG. Bullous pemphigoid complicating human orf. *Br J Dermatol* 1996; **134**: 929–30.
15 White KP, Zedek DC, White WL *et al.* Orf-induced immunobullous disease: A distinct autoimmune blistering disorder. *J Am Acad Dermatol* 2008; **58**: 49–55.
16 Nagington J. Electron microscopy in differential diagnosis of poxvirus infections. *BMJ* 1964; **ii**: 1499–500.
17 Yirrell DL, Vestey JP, Norval M. Immune responses of patients to orf virus infection. *Br J Dermatol* 1994; **130**: 438–43.
18 Torfason EG, Gunadottir S. Polymerase chain reaction for laboratory diagnosis of orf virus infections. *J Clin Virol* 2002; **24**: 79–84.
19 Tan ST, Blake GB, Chambers S. Recurrent orf in an immunocompromised host. *Br J Plast Surg* 1991; **44**: 465–7.
20 Degraeve C, De Coninck A, Senneseael J *et al.* Recurrent contagious ecthyma (Orf) in an immunocompromised host successfully treated with cryotherapy. *Dermatology* 1999; **198**: 162–3.
21 Hunskaar S. A case of ecthyma contagiosum (human orf) treated with idoxuridine. *Dermatologica* 1984; **168**: 207.
22 Erbagci Z, Erbagci I, Almila Tuncel A. Rapid improvement of human orf (ecthyma contagiosum) with topical imiquimod cream: report of four complicated cases. *J Dermatolog Treat* 2005; **16**: 353–6.
23 Ara M, Zaballos P, Sanchez M *et al.* Giant and recurrent orf virus infection in a renal transplant recipient treated with imiquimod. *J Am Acad Dermatol* 2008; **58**: S39–40.
24 Geerinck K, Lukito G, Snoeck R *et al.* A case of human orf in an immunocompromised patient treated successfully with cidofovir cream. *J Med Virol* 2001; **64**: 543–9.
25 McCabe D, Weston B, Storch G. Treatment of orf poxvirus lesion with cidofovir cream. *Pediatr Infect Dis J* 2003; **22**: 1027–8.

Milker's nodule

Synonyms
- Pseudocowpox
- Paravaccinia

Aetiology. Milker's nodule virus is a parapoxvirus with the same cylindrical morphology as orf virus. In the UK it produces mild infections of the teats of cows, that is 'ring sores', and ulcers in the mouths of calves. Animal to human transmission is accidental and can occur in milkers or veterinary surgeons who examine animals. Both can produce lesions on the hands of milkers or veterinarians who examine the mouths of animals [1]. The infection may be transmitted to areas of thermal injury by contaminated fomites [2,3].



Fig. 33.6 Milker's nodule. (Courtesy of Dr J.B. Kurtz, Oxford, UK.)

Pathology [4]. Histologically there is multilocular vesicle formation in the acanthotic epidermis. Parakeratosis is often conspicuous. Cytoplasmic, or more rarely intranuclear, eosinophilic inclusions may be detectable. There is a granulomatous reaction in the upper dermis.

Clinical features [4–7] (Fig. 33.6). After an incubation period of about 5 days but up to 2 weeks, flat, red papules are formed. Within a week they appear as reddish-blue, firm, slightly tender nodules. The tense and shining epidermis becomes opaque and grey and forms a small crust over the depressed centre of the nodule. A zone of erythema usually surrounds the nodules. Many cases develop lymphangitis but there are rarely any constitutional symptoms, and resolution without scarring takes 4–6 weeks. Between two and five nodules are usually present, but they may be solitary or more numerous. They are commonly on the hands, particularly the fingers, but are occasionally seen on the face.

One or two weeks after the appearance of the nodules some patients develop a papular or papulovesicular eruption on the hands, forearms and arms, and sometimes on the legs and neck [8]. It fades in 1 or 2 weeks.

Diagnosis. Lesions appear very similar to those of orf. The nodules may be very vascular, and have been confused with pyogenic granulomas.

Isolation of the virus is slow and unreliable. Viral particles are visible by electron microscopy in biopsy or scab. Molecular detection by PCR is now possible [9].

References

1 Nagington J, Tee GH, Smith JS. Milker's nodule virus infections in Dorset and their similarity to orf. *Nature* 1965; **208**: 505–7.
2 Schuler G, Hackl JM. Multiple atypische Melkerknoten in Verbrühungsarealen. *Hautarzt* 1982; **33**: 388–90.
3 Schuler G, Honigsmann H, Wolff K. The syndrome of milker's nodules in burn injury: evidence for indirect viral transmission. *J Am Acad Dermatol* 1982; **6**: 334–9.
4 Wallace HJ. A note on milker's nodes. *Br J Dermatol* 1947; **59**: 379–83.
5 Katzenellenbogen I. Studies on milker's nodules. *Dermatologica* 1952; **105**: 69–78.
6 Leavell UW Jr, Phillips IA. Milker's nodules. Pathogenesis, tissue culture, electron microscopy, and calf inoculation. *Arch Dermatol* 1975; **111**: 1307–11.
7 Nomland R, Mc KA. Milkers' nodules; report of ten cases. *AMA Arch Derm Syphilol* 1952; **65**: 663–74.
8 Sonck CE. Milker's nodules with allergic secondary eruptions. *Acta Allergol* 1951; **4**: 241–52.
9 Inoshima Y, Morooka A, Sentsui H. Detection and diagnosis of parapoxvirus by the polymerase chain reaction. *J Virol Methods* 2000; **84**: 201–8.

Molluscum contagiosum

Aetiology. Molluscum contagiosum virus (MCV) is classified within the Poxvirus family in a specific genus, the molluscipox [1] and has features intermediate between the orthopox and parapox groups. It infects humans, causing characteristic skin papules. It cannot be grown in tissue culture or eggs, and, although not readily transmissible to laboratory animals, has been shown to produce typical changes on human skin cultured on immunoincompetent mice [2]. Restriction endonuclease and PCR analyses of MCV DNA have identified two main types, MCV-1 and MCV-2, with two much rarer types, MCV-3 and MCV-4 [3,4].

Epidemiology. The virus occurs throughout the world, most commonly causing disease in childhood. Type 1 MCV is found in the majority of infections (76–97%), and whilst there is no relationship between virus type and lesional morphology or anatomical distribution [5,6], there is some evidence to support a relatively higher incidence of MCV-2 type in adults and HIV infection compared to that in children [7].

The disease is common, but its incidence in most areas is not reliably known. Infection follows contact with infected persons or contaminated objects, but the importance of epidermal injury is unknown.

The disease is rare under the age of 1 year, perhaps due to maternally transmitted immunity and a long incubation period. In hot countries where children are lightly dressed and in close contact with one another, spread within households is not uncommon. The age of peak incidence is reported as between 2 and 5 years [8,9]. In cooler climates, however, spread within households is rare and infection may occur at a later age [8,10], perhaps correlated with use of swimming pools and shared bathing facilities [11]. A later incidence peak in young adults is attributable to sexual transmission with lesions more common in the genital area.

Infection of children through sexual abuse is presumably possible. However, to a greater extent than warts, molluscum contagiosum is seen quite commonly on the genital, perineal and surrounding skin of children, and abuse should not be regarded as likely unless there are other suspicious features.

There is a clinical impression that molluscum contagiosum is commoner in patients with atopic eczema [12], and occasional reports describe widespread infections, possibly based on impaired immunity [13]. Topical steroids and also topical calcineurin inhibitors have been suspected as a contributing factor in eczema and other patients [14–16].

Unusually widespread lesions have been reported in immunosuppressed patients with HIV disease (see Chapter 35), sarcoidosis [17], and in those receiving immunosuppressive therapy [18–20], suggesting that cell-mediated immunity is significant in control and elimination of the infection. In spite of profound immunosuppression following organ transplantation, the incidence of molluscum contagiosum infection is not greatly increased in this group and is not as common as other infections such as warts and herpes simplex [21].

Pathogenesis and pathology. The molecular pathogenesis of the lesions is uncertain but an antiapoptotic protein has been postulated to have a role [22]. The virus seems first to enter the basal epidermis where an early increase in cell division extends into the suprabasal layer [23]. The cellular proliferation produces lobulated epidermal growths which compress the papillae until they appear as fibrous septa between the lobules, which are pear-shaped with the apex upwards. The basal layer remains intact. Cells at the core of the lesion show the greatest distortion and are ultimately destroyed, and appear as large hyaline bodies (molluscum bodies) some 25 μm in diameter, containing cytoplasmic masses of virus material. These bodies are present in large numbers in the cavity, which appears near the surface at the centre of the fully developed lesion. Inflammatory changes in the dermis are absent or slight, but in lesions of long duration there may be a chronic granulomatous infiltrate. It has been suggested that the inflammatory reaction may be induced by the discharge into the dermis of the contents of a papule [24] rather than by secondary infection.

Specific antibodies have been found in about 58–73% of patients with molluscum contagiosum, and, perhaps due to unrecognized infection, in about 6–16% of controls [25,26], but these have not been demonstrated to have a role in disease clearance.

Clinical features (Fig. 33.7). The incubation period is variously estimated at 14 days to 6 months. The individual lesion is a shiny, pearly white, hemispherical, umbilicated papule which may show a central pore. It may be identified with a hand lens or dermatoscope when less than 1 mm in diameter. Enlarging slowly it may reach a diameter of 5–10 mm in 6–12 weeks. Rarely, and usually when one or very few are present, a lesion may become considerably larger. Plaques composed of many small lesions ('agminate' form or giant molluscum) occur rarely. Lesions frequently spread and the number of lesions ultimately present is sometimes very large. After trauma, or spontaneously after several months, inflammatory changes result in suppuration, crusting and eventual destruction of the lesion.

The duration both of the individual lesion and of the attack is very variable and although most cases are self-limiting within 6–9 months, it is not unusual for some to persist for 3 or 4 years [12]. Individual lesions are unlikely to persist for more than 2 months,



(a)



(b)

Fig. 33.7 Molluscum contagiosum. (a) Typical umbilicated lesions. (b) Depressed scars following infection. (Courtesy of Addenbrooke's Hospital, Cambridge, UK.)

but some lesions, particularly if solitary, may persist for up to 5 years [27].

The distribution of the lesions is influenced by the mode of infection, and by the type of clothing worn, and hence by the climate. In temperate regions they are commonly seen on the neck or on the trunk, particularly around the axillae, except in sexually transmitted infection, when the anogenital region is usually involved. In children in the tropics lesions are more common on the limbs. Widespread and refractory mollusca on the face are seen most commonly in HIV disease [28] and also with iatrogenic immunosuppression [29]. In otherwise healthy subjects occasional facial lesions are seen, particularly on the eyelids. Molluscum may affect the scalp, lips, tongue and buccal mucous membrane, and indeed any part of the body surface, including the soles where the appearance is atypical [30]. Molluscum can occur in scars and in tattoos [31]. Follicular molluscum contagiosum in four adults produced atypical, less protuberant pale papules [32].

In at least 10% of cases, particularly in atopic subjects, a patchy eczema, often very irritable, develops around one or more of the lesions a month or more after their onset [33] and erythema annulare centrifugum and erythema multiforme have also been reported in association with the infection [34,35]. Chronic conjunctivitis and superficial punctate keratitis may similarly complicate lesions on or near the eyelids [36]. The eczema and the conjunctivitis subside spontaneously when the lesion is removed.

Depressed scars or anetoderma-like lesions can remain when mollusca clear [37,38].

Diagnosis. The diagnosis of molluscum contagiosum is usually obvious when multiple lesions at different stages of evolution are present and the typical umbilicated papule is evident. The distinctive umbilication can be seen more easily with a dermatoscope or after freezing. The diagnosis can be confirmed by direct microscopy or electron microscopy of the papule contents, by histopathology or by molecular analysis [3,39,40]. The solitary molluscum may resemble a pyogenic granuloma, a keratoacanthoma or a squamous cell carcinoma and may be difficult to identify. Multiple small lesions can be confused with plane warts. In HIV disease, molluscum contagiosum may resemble cutaneous cryptococcosis (see Chapter 35).

Treatment. In many instances, therapy is not necessary and natural resolution can be awaited. The risk of dissemination of the infection can be minimized by reducing scratching, which can both damage adjacent skin and spread virus from mature papules. Associated dry skin or eczema should be treated with emollients and possibly a weak topical steroid. Transfer of infection to another individual may be reduced by avoidance of shared towels, contact sports and communal bathing.

If spontaneous clearance is slow, lesions are symptomatic, or associated eczema is troublesome, treatment may be desirable. The choice of treatment will depend on the age of the patient, and the number and position of the lesions. Treatments aim to destroy the infected epidermal cells, stimulate an immunological response or act directly against the virus.

Surgical removal of molluscum contagiosum by curettage has been used for many years [41]. Children will usually need prior application of topical anaesthetic cream with strict observance of the maximum safe dose [42]. Damage to the lesions by squeezing the contents or insertion of a pointed cocktail stick may stimulate inflammation and clearance.

Cryotherapy is effective and commonly used in older children and adults, but needs to be repeated at 3–4 weekly intervals. The carbon dioxide or pulsed dye lasers have produced useful effects [43,44] but like curettage, can cause scars. Photodynamic therapy has also been used with effect [45].

Many topical agents can be used to produce mild to moderate inflammation and hence potentially stimulate the development of an immune response against the virus. Cantharidin, trichloroacetic acid and diluted liquefied phenol are strong irritants which can both cause pain, blistering and scarring but with careful application and appropriate dilution can increase lesion clearance [37,46,47]. Topical salicylic acid preparations [12,41], tretinoin [48], adapalene [49], nitric oxide cream [50] and potassium hydroxide solution [51,52] all lead to an irritant reaction but if the strength of preparation and the frequency of application are adjusted, individuals can tolerate repeated treatments until resolution occurs.

Stimulation of the immune response may occur after destructive or inflammatory therapies. Treatment used for molluscum contagiosum with the explicit aim of enhancing the immune response and reported efficacy include induction of allergic contact dermatitis with topical dyphencyprone [53], imiquimod cream [54], intralesional interferon [55] and systemic cimetidine [56].

The antiviral agent cidofovir has recently been shown to effectively resolve molluscum lesions [57,58] (used either intravenously or topically as a 1–3% ointment or cream). It should be considered for treating extensive lesions in, for example, immunoincompetent patients where eradication has proved difficult with standard treatment regimens.

References

1 Gubser C, Hue S, Kellam P *et al.* Poxvirus genomes: a phylogenetic analysis. *J Gen Virol* 2004; **85**: 105–17.

2 Buller RM, Burnett J, Chen W *et al.* Replication of molluscum contagiosum virus. *Virology* 1995; **213**: 655–9.

3 Thompson CH. Identification and typing of molluscum contagiosum virus in clinical specimens by polymerase chain reaction. *J Med Virol* 1997; **53**: 205–11.

4 Nakamura J, Muraki Y, Yamada M *et al.* Analysis of molluscum contagiosum virus genomes isolated in Japan. *J Med Virol* 1995; **46**: 339–48.

5 Porter CD, Blake NW, Archard LC *et al.* Molluscum contagiosum virus types in genital and non-genital lesions. *Br J Dermatol* 1989; **120**: 37–41.

6 Scholz J, Rosen-Wolff A, Bugert J *et al.* Epidemiology of molluscum contagiosum using genetic analysis of the viral DNA. *J Med Virol* 1989; **27**: 87–90.

7 Thompson CH, De Zwart-Steffe RT, Biggs IM. Molecular epidemiology of Australian isolates of molluscum contagiosum. *J Med Virol* 1990; **32**: 1–9.

8 Postlethwaite R, Watt JA, Hawley TG *et al.* Features of molluscum contagiosum in the north-east of Scotland and in Fijian village settlements. *J Hyg (Lond)* 1967; **65**: 281–91.

9 Kyriakis KP, Palamaras I, Terzoudi S *et al.* Case detection rates of molluscum contagiosum in childhood. *Pediatr Dermatol* 2007; **24**: 198–9.

10 Niizeki K, Kano O, Kondo Y. An epidemic study of molluscum contagiosum. Relationship to swimming. *Dermatologica* 1984; **169**: 197–8.

11 Choong KY, Roberts LJ. Molluscum contagiosum, swimming and bathing: a clinical analysis. *Australas J Dermatol* 1999; **40**: 89–92.

12 Leslie KS, Dootson G, Sterling JC. Topical salicylic acid gel as a treatment for molluscum contagiosum in children. *J Dermatol Treat* 2005; **16**: 336–40.

13 Pauly CR, Artis WM, Jones HE. Atopic dermatitis, impaired cellular immunity, and molluscum contagiosum. *Arch Dermatol* 1979; **114**: 391–3.

14 Hellier FF. Profuse mollusca contagiosa of the face induced by corticosteroids. *Br J Dermatol* 1971; **85**: 398.

15 Goksugur N, Ozbostanci B, Goksugur SB. Molluscum contagiosum infection associated with pimecrolimus use in pityriasis alba. *Pediatr Dermatol* 2007; **24**: E63–5.

16 Fery-Blanco C, Pelletier F, Humbert P *et al.* Molluscum contagiosum profus au cours d'une dermatite atopique traitée par tacrolimus: intérêt du cidofovir. *Ann Dermatol Venereol* 2007; **134**: 457–9.

17 Ganpule M, Garretts M. Molluscum contagiosum and sarcoidosis: report of a case. *Br J Dermatol* 1971; **85**: 587–9.

18 Rosenberg EW, Yusk JW. Molluscum contagiosum. Eruption following treatment with prednisone and methotrexate. *Arch Dermatol* 1970; **101**: 439–41.

19 Cotton DW, Cooper C, Barrett DF *et al.* Severe atypical molluscum contagiosum infection in an immunocompromised host. *Br J Dermatol* 1987; **116**: 871–6.

20 Antoniou C, Kosmadaki MG, Stratigos AJ *et al.* Genital HPV lesions and molluscum contagiosum occurring in patients receiving anti-TNF-alpha therapy. *Dermatology* 2008; **216**: 364–5.

21 Euvrard S, Kanitakis J, Cochat P *et al.* Skin diseases in children with organ transplants. *J Am Acad Dermatol* 2001; **44**: 932–9.

22 Shisler JL, Moss B. Molluscum contagiosum virus inhibitors of apoptosis: The MC159 v-FLIP protein blocks Fas-induced activation of procaspases and degradation of the related MC160 protein. *Virology* 2001; **282**: 14–25.

23 Simonart T, Fayt I, Noel JC. An immunohistochemical study of abnormal keratinocyte proliferation in molluscum contagiosum. *Br J Dermatol* 2002; **146**: 609–14.

24 Henao M, Freeman RG. Inflammatory molluscum contagiosum. Clinicopathological study of seven cases. *Arch Dermatol* 1964; **90**: 479–82.

25 Shirodaria PV, Matthews RS, Samuel M. Virus-specific and anticellular antibodies in molluscum contagiosum. *Br J Dermatol* 1979; **101**: 133–40.

26 Watanabe T, Nakamura K, Wakugawa M *et al.* Antibodies to molluscum contagiosum virus in the general population and susceptible patients. *Arch Dermatol* 2000; **136**: 1518–22.

27 Funt TR. Solitary molluscum contagiosum—clinical histological study of nine cases. *Cutis* 1967; **3**: 339.

28 Katzman M, Carey JT, Elmets CA *et al.* Molluscum contagiosum and the acquired immunodeficiency syndrome: clinical and immunological details of two cases. *Br J Dermatol* 1987; **116**: 131–8.

29 Lim KS, Foo CC. Disseminated molluscum contagiosum in a patient with chronic plaque psoriasis taking methotrexate. *Clin Exp Dermatol* 2007; **32**: 591–3.

30 Bunney MH, Hunter JA, Ogilvie MM. Molluscum contagiosum of the sole. A rare diagnosis or a rare condition? *Br J Dermatol* 1969; **81**: 623–5.

31 Foulds IS. Molluscum contagiosum: an unusual complication of tattooing. *BMJ (Clin Res Ed)* 1982; **285**: 607.

32 Ive FA. Follicular molluscum contagiosum. *Br J Dermatol* 1985; **113**: 493–5.

33 De Oreo GA, Johnson HH, Binkley GW. An eczematous reaction associated with molluscum contagiosum. *Arch Dermatol* 1956; **74**: 344–8.

34 Vasily DB, Bhatia SG. Erythema annulare centrifugum and molluscum contagiosum. *Arch Dermatol* 1978; **114**: 1853.

35 Attard NR, De Silva BD. Erythema multiforme associated with resolving molluscum contagiosum. *Clin Exp Dermatol* 2007; **32**: 214–5.

36 Haellmigk C. Keratokonjunktivitis bei Molluscum Contagiosum der Lider. *Klin Monatsbl Augenheilkd* 1966; **148**: 87–91.

37 Weller R, O'Callaghan CJ, MacSween RM *et al.* Scarring in Molluscum contagiosum: comparison of physical expression and phenol ablation. *BMJ* 1999; **319**: 1540.

38 Shalders K, Ilchyshyn A, Walzman M. Secondary anetoderma following molluscum contagiosum infection. *Acta Derm Venereol* 2003; **83**: 461–2.

39 Nagington J. Electron microscopy in differential diagnosis of poxvirus infections. *BMJ* 1964; **2**: 1499–500.

40 Shelley WB, Burmeister V. Office diagnosis of molluscum contagiosum by light microscopic demonstration of virions. *Cutis* 1985; **36**: 465–6.

41 Hanna D, Hatami A, Powell J *et al.* A prospective randomized trial comparing the efficacy and adverse effects of four recognized treatments of molluscum contagiosum in children. *Pediatr Dermatol* 2006; **23**: 574–9.

42 Rönnerfält L, Fransson J, Wahlgren CF. EMLA cream provides rapid pain relief for the curettage of molluscum contagiosum in children with atopic dermatitis without causing serious application-site reactions. *Pediatr Dermatol* 1998; **15**: 309–12.

43 Friedman M, Gal D. Keloid scars as a result of CO_2 laser for molluscum contagiosum. *Obstet Gynecol* 1987; **70**: 394–6.

44 Binder B, Weger W, Komericki P *et al.* Treatment of molluscum contagiosum with a pulsed dye laser: Pilot study with 19 children. *J Dtsch Dermatol Ges* 2008; **6**: 121–5.

45 Gold MH, Moiin A. Treatment of verrucae vulgaris and molluscum contagiosum with photodynamic therapy. *Dermatol Clin* 2007; **25**: 75–80.

46 Silverberg NB, Sidbury R, Mancini AJ. Childhood molluscum contagiosum: experience with cantharidin therapy in 300 patients. *J Am Acad Dermatol* 2000; **43**: 503–7.

47 Garrett SJ, Robinson JK, Roenigk HH Jr. Trichloroacetic acid peel of molluscum contagiosum in immunocompromised patients. *J Dermatol Surg Oncol* 1992; **18**: 855–8.

48 Papa CM, Berger RS. Venereal herpes-like molluscum contagiosum: treatment with tretinoin. *Cutis* 1976; **18**: 537–40.

49 Scheinfeld N. Treatment of molluscum contagiosum: a brief review and discussion of a case successfully treated with adapelene. *Dermatol Online J* 2007; **13**: 15.

50 Ormerod AD, White MI, Shah SA *et al.* Molluscum contagiosum effectively treated with a topical acidified nitrite, nitric oxide liberating cream. *Br J Dermatol* 1999; **141**: 1051–3.

51 Short KA, Fuller LC, Higgins EM. Double-blind, randomized, placebo-controlled trial of the use of topical 10% potassium hydroxide solution in the treatment of molluscum contagiosum. *Pediatr Dermatol* 2006; **23**: 279–81.
52 Romiti R, Ribeiro AP, Romiti N. Evaluation of the effectiveness of 5% potassium hydroxide for the treatment of molluscum contagiosum. *Pediatr Dermatol* 2000; **17**: 495.
53 Kang SH, Lee D, Hoon Park J *et al.* Treatment of molluscum contagiosum with topical diphencyprone therapy. *Acta Derm Venereol* 2005; **85**: 529–30.
54 Barba AR, Kapoor S, Berman B. An open label safety study of topical imiquimod 5% cream in the treatment of Molluscum contagiosum in children. *Dermatol Online J* 2001; **7**: 20.
55 Nelson MR, Chard S, Barton SE. Intralesional interferon for the treatment of recalcitrant molluscum contagiosum in HIV antibody positive individuals—a preliminary report. *Int J STD AIDS* 1995; **6**: 351–2.
56 Dohil M, Prendiville JS. Treatment of molluscum contagiosum with oral cimetidine: clinical experience in 13 patients. *Pediatr Dermatol* 1996; **13**: 310–2.
57 Meadows KP, Tyring SK, Pavia AT *et al.* Resolution of recalcitrant molluscum contagiosum virus lesions in human immunodeficiency virus-infected patients treated with cidofovir. *Arch Dermatol* 1997; **133**: 987–90.
58 Toro JR, Wood LV, Patel NK *et al.* Topical cidofovir: a novel treatment for recalcitrant molluscum contagiosum in children infected with human immunodeficiency virus 1. *Arch Dermatol* 2000; **136**: 983–5.

Tanapox

This is an acute febrile illness associated with a localized nodular skin lesion. It is caused by tanapox virus, classified as a yatapox virus.

The infection was first seen as epidemics in 1957 and 1962 around the Tana River in Kenya but is probably more widely distributed in tropical Africa. The virus is known to affect monkeys and humans, but it is not known if other animals provide a natural reservoir. It can be acquired by inoculation through abraded skin.

Clinical features [1,2]. There is mild pre-eruptive fever accompanied by headache and backache. The lesion begins as erythema surrounding a central thickening, which slowly develops as a painful nodule to reach a maximum diameter of 15 mm by the end of the second week. Local lymph nodes are enlarged and tender. The nodule ulcerates in the third week and is followed by gradual healing, leaving a scar after about 6 weeks. Occasionally there is more than one lesion, the maximum recorded being 10, and they are usually on the limbs.

Diagnosis. The slow evolution and lack of a pustular stage are characteristic of tanapox infections. The diagnosis can be confirmed by electron microscopy which shows enveloped poxviruses. The virus does not grow on the chick chorioallantoic membrane but some strains will give a typical appearance in tissue culture.

Specific identification of tanapox can be made by PCR of DNA extracted from tissue [3].

References

1 Dhar AD, Werchniak AE, Li Y *et al.* Tanapox infection in a college student. *N Engl J Med* 2004; **350**: 361–6.
2 Jezek Z, Arita I, Szczeniowski M *et al.* Human tanapox in Zaire: clinical and epidemiological observations on cases confirmed by laboratory studies. *Bull World Health Organ* 1985; **63**: 1027–35.
3 Zimmermann P, Thordsen I, Frangoulidis D *et al.* Real-time PCR assay for the detection of tanapox virus and yaba-like disease virus. *J Virol Methods* 2005; **130**: 149–53.

Table 33.3 The herpesvirus group.

Subgroup	Virus	Abbreviation	Also called
α	Human simplex virus, type 1	HSV1	*Herpesvirus hominis* 1, HHV1
α	Human simplex virus, type 2	HSV2	*Herpesvirus hominis* 2, HHV2
α	Varicella zoster virus	VZV	*Herpesvirus varicellae*, HHV3
β	Cytomegalovirus	CMV	HHV4
β	Human herpesvirus type 6	HHV6	
β	Human herpesvirus type 7	HHV7	
γ	Epstein–Barr virus	EBV	
γ	Human herpesvirus type 8	HHV8	Kaposi's sarcoma associated herpesvirus, KSHV

Herpesviruses

The herpesvirus group consists of relatively large, enveloped DNA viruses. They replicate within the nucleus and produce typical intranuclear inclusion bodies detectable in stained preparations. They are sub-grouped according to genome similarities into the α, β and γ herpesviruses (Table 33.3) and eight members of the group can infect humans.

A feature of infection by members of the herpesvirus group is the absence of virus elimination following clinical recovery. Virus persists throughout the person's life as a latent infection in the cells for which the strain is specific. Under certain conditions, especially immune suppression, the virus may become reactivated and produce an acute infective episode with cellular damage.

Herpes simplex [1–4]

Aetiology. Herpes simplex, caused by the herpes simplex virus (HSV) or *herpesvirus hominis*, is one of the commonest infections of humans throughout the world. There are two major antigenic types: type 1, which is classically associated with facial infections; and type 2, which is typically genital, although there is considerable overlap in disease manifestations.

Both type 1 and type 2 HSV are acquired by direct contact with, or droplets from, infected secretions entering via skin or mucous membrane, where primary infection may become evident. The establishment of latent infection is common with the virus persisting in ganglia of sensory nerves innervating the primary infection site. The virus produces no viral proteins whilst latent and can therefore remain undetected by host defence mechanisms. From this condition of latency, the virus may travel peripherally along the nerve fibre, and, if it replicates in the skin or mucous membrane, may cause recurrent disease. The virus can be shed in saliva and genital secretions from asymptomatic individuals, especially in the months following the first episode of disease, although the amount shed from active lesions is 100–1000 times greater.

Primary type 1 infections occur mainly in infants and young children, when they are usually minimal and often subclinical.



Fig. 33.8 Herpes simplex. Inoculation lesion on thumb of dermatologist. (Courtesy of Dr A.S. Highet, York District Hospital, UK.)

Primary infections may rarely produce a painful, vesicular stomatitis. In crowded areas of the developing world, over 90% of children have antibody by the age of 5 years, but in more temperate areas and higher socioeconomic groups the incidence is lower in children but rises steadily with age [5]. For example, in western Europe and the USA, a quarter of children, a half to three-quarters of adolescents and young adults but up to 90% of the elderly are HSV-1 antibody positive [6–8].

Type 2 infections occur mainly after puberty, and are often transmitted sexually. Seropositivity is low in children, but about a third of young adults are seropositive for type 2 and this rises to half the population by later life [5]. The primary HSV-2 infection is more commonly symptomatic. In one sample of women, overall transmission rates between couples, from infected to uninfected partner, averaged 4–30% annually [9]. Transmission was most frequent during periods of asymptomatic shedding, which ranged from 0.5 to 4% of days sampled. The apparent increase over the last few decades in the proportion of genital infections involving HSV type 1, about 20–55% in some recent studies [10,11], may be attributable to orogenital contact. In children with genital herpes (HSV-1 or HSV-2), sexual abuse must be considered [12].

Trauma facilitates transfer of the virus to fully keratinized skin. The virus can be inoculated into any body site to cause a new infection, whether or not there has been previous infection with either type. The source may be endogenous (autoinoculation), for example to the finger especially in nail biters or thumb suckers. Examples of exogenous inoculation are lesions of the hand in health-care workers (Fig. 33.8) and others [13], facial lesions contracted during contact sports, and infection of a breastfeeding mother's nipples from the infected mouth of her baby [14].

Following primary infection, humoral and cell-mediated immune responses take place, the latter probably being more important [15]. They do not fully protect against reinfection or recurrent disease. The acquisition of HSV at a new site in a patient previously infected at a different site is referred to as a non-primary, first-episode infection. Initial (non-primary) genital herpes tends to be less severe in patients who have had previous oral infection. Where immunity is deficient (either congenitally or due to disease or drugs), both primary and recurrent herpetic infections may be increased in incidence and severity, and may run a prolonged and atypical course. Examples include patients immunosuppressed following organ or marrow transplantation, patients receiving cytotoxic therapy for malignancy [16], including cutaneous T-cell lymphoma [17], and patients with HIV infection (see Chapter 35). Topical immunomodulating treatment with corticosteroids or calcineurin inhibitors has also been implicated in herpetic eruptions [18–20].

Immunological abnormalities or variations, in addition to possible local cutaneous factors, may explain the increased incidence in atopic eczema of recurrent herpes simplex [21] and the evolution in some individuals of erythema multiforme (see p. 33.76 and Chapter 76), as well as the occasional more severe infections [22,23], including eczema herpeticum (see p. 33.35).

A maternal primary genital infection at the time of birth, before the maternal immune response has taken place, is transmitted to the infant in about 50% of cases and the neonatal infection may be severe and fatal [24]. Antiviral treatment and Caesarean section delivery should be considered. Primary infection earlier in the third trimester may cause fetal growth retardation and prematurity. However, serious morbidity is rare if non-primary, first-episode or recurrent genital infection occurs during pregnancy or at delivery, presumably because the fetus in those situations is protected by maternal antibody [25–27]. Primary oral herpes in late pregnancy does not carry such high risks for the baby [28].

Herpes simplex may occur in certain bullous disorders, complicating the presentation or disease manifestations of pemphigus [29,30], pemphigoid [31] and Hailey–Hailey disease [32], and occurring as severe infections in patients receiving immunosuppressive treatment. It has also complicated pyoderma gangrenosum in a case of chronic lymphatic leukaemia [33].

References

1 Fatahzadeh M, Schwartz RA. Human herpes simplex virus infections: epidemiology, pathogenesis, symptomatology, diagnosis, and management. *J Am Acad Dermatol* 2007; **57**: 737–63; quiz 64–6.

2 Corey L, Spear PG. Infections with herpes simplex viruses (1). *N Engl J Med* 1986; **314**: 686–91.

3 Corey L, Spear PG. Infections with herpes simplex viruses (2). *N Engl J Med* 1986; **314**: 749–57.

4 Corey L. First-episode, recurrent, and asymptomatic herpes simplex infections. *J Am Acad Dermatol* 1988; **18**: 169–72.

5 Smith JS, Robinson NJ. Age-specific prevalence of infection with herpes simplex virus types 2 and 1: a global review. *J Infect Dis* 2002; **186** (Suppl. 1): S3–28.

6 Vyse AJ, Gay NJ, Slomka MJ *et al.* The burden of infection with HSV-1 and HSV-2 in England and Wales: implications for the changing epidemiology of genital herpes. *Sex Transm Infect* 2000; **76**: 183–7.

7 Wutzler P, Doerr HW, Farber I *et al.* Seroprevalence of herpes simplex virus type 1 and type 2 in selected German populations—relevance for the incidence of genital herpes. *J Med Virol* 2000; **61**: 201–7.

8 Xu F, Schillinger JA, Sternberg MR *et al.* Seroprevalence and coinfection with herpes simplex virus type 1 and type 2 in the United States, 1988–1994. *J Infect Dis* 2002; **185**: 1019–24.

9 Koelle DM, Benedetti J, Langenberg A *et al.* Asymptomatic reactivation of herpes simplex virus in women after the first episode of genital herpes. *Ann Intern Med* 1992; **116**: 433–7.

10 Coyle PV, O'Neill HJ, Wyatt DE *et al.* Emergence of herpes simplex type 1 as the main cause of recurrent genital ulcerative disease in women in Northern Ireland. *J Clin Virol* 2003; **27**: 22–9.

11 Tran T, Druce JD, Catton MC *et al.* Changing epidemiology of genital herpes simplex virus infection in Melbourne, Australia, between 1980 and 2003. *Sex Transm Infect* 2004; **80**: 277–9.
12 Reading R, Rannan-Eliya Y. Evidence for sexual transmission of genital herpes in children. *Arch Dis Child* 2007; **92**: 608–13.
13 Gill MJ, Arlette J, Buchan K. Herpes simplex virus infection of the hand. A profile of 79 cases. *Am J Med* 1988; **84**: 89–93.
14 Dekio S, Kawasaki Y, Jidoi J. Herpes simplex on nipples inoculated from herpetic gingivostomatitis of a baby. *Clin Exp Dermatol* 1986; **11**: 664–6.
15 Vestey JP, Howie SE, Norval M *et al.* Immune responses to herpes simplex virus in patients with facial herpes simplex and those with eczema herpeticum. *Br J Dermatol* 1988; **118**: 775–82.
16 Greenberg MS, Friedman H, Cohen SG *et al.* A comparative study of herpes simplex infections in renal transplant and leukemic patients. *J Infect Dis* 1987; **156**: 280–7.
17 Vonderheid EC, Milstein HJ, Thompson KD *et al.* Chronic herpes simplex infection in cutaneous T-cell lymphomas. *Arch Dermatol* 1980; **116**: 1018–22.
18 Ambo M. Relapsing Kaposi's varicelliform eruption and herpes simplex following facial tacrolimus treatment for atopic dermatitis. *Acta Derm Venereol* 2002; **82**: 224–5.
19 Lonsdale-Eccles AA, Velangi S. Herpes simplex of the vulva evoked by topical tacrolimus treatment. *Clin Exp Dermatol* 2005; **30**: 95–6.
20 Hashizume H, Yagi H, Ohshima A *et al.* Comparable risk of herpes simplex virus infection between topical treatments with tacrolimus and corticosteroids in adults with atopic dermatitis. *Br J Dermatol* 2006; **154**: 1204–6.
21 Rystedt I, Strannegard IL, Strannegard O. Recurrent viral infections in patients with past or present atopic dermatitis. *Br J Dermatol* 1986; **114**: 575–82.
22 Leyden JJ, Baker DA. Localized herpes simplex infections in atopic dermatitis. *Arch Dermatol* 1979; **115**: 311–2.
23 David TJ, Longson M. Herpes simplex infections in atopic eczema. *Arch Dis Child* 1985; **60**: 338–43.
24 Sauerbrei A, Wutzler P. Herpes simplex and varicella-zoster virus infections during pregnancy: current concepts of prevention, diagnosis and therapy. Part 1: herpes simplex virus infections. *Med Microbiol Immunol* 2007; **196**: 89–94.
25 Brown ZA, Vontver LA, Benedetti J *et al.* Effects on infants of a first episode of genital herpes during pregnancy. *N Engl J Med* 1987; **317**: 1246–51.
26 Prober CG, Sullender WM, Yasukawa LL *et al.* Low risk of herpes simplex virus infections in neonates exposed to the virus at the time of vaginal delivery to mothers with recurrent genital herpes simplex virus infections. *N Engl J Med* 1987; **316**: 240–4.
27 Eskild A, Jeansson S, Stray-Pedersen B *et al.* Herpes simplex virus type-2 infection in pregnancy: no risk of fetal death: results from a nested case-control study within 35,940 women. *BJOG* 2002; **109**: 1030–5.
28 Pardo J, Yogev Y, Ben-Haroush A *et al.* Primary herpes simplex virus type 1 gingivostomatitis during the second and third trimester of pregnancy: foetal and pregnancy outcome. *Scand J Infect Dis* 2004; **36**: 179–81.
29 Brown P, Taylor B. Herpes simplex infection associated with pemphigus vulgaris. Case report and literature review. *J Am Acad Dermatol* 1989; **21**: 1126–8.
30 Hale EK, Bystryn JC. Atypical herpes simplex can mimic a flare of disease activity in patients with pemphigus vulgaris. *J Eur Acad Dermatol Venereol* 1999; **13**: 221–3.
31 Niederecker C, Tappeiner G, Wolff K. Generalized herpes simplex infection complicating bullous pemphigoid. *Br J Dermatol* 1995; **132**: 484–6.
32 Zaim MT, Bickers DR. Herpes simplex associated with Hailey–Hailey disease. *J Am Acad Dermatol* 1987; **17**: 701–2.
33 Wahba A, Cohen HA. Herpes simplex virus isolation from pyoderma gangrenosum lesions in a patient with chronic lymphatic leukemia. *Dermatologica* 1979; **158**: 373–8.

Pathology. In the cutaneous lesions, the cytoplasm of the infected epithelial cells becomes oedematous and the cells swell, producing the so-called 'ballooning degeneration'. Thick-walled vesicles are formed by the combination of intra- and intercellular oedema. The dermis, and later the epidermis, are infiltrated with polymorphonuclear leukocytes. Specific changes occur in the cell nuclei and different stages in the process of the development of the intranuclear inclusions can usually be seen in a single section. In addition, giant cells containing two to 15 or more nuclei are almost invariably present in cutaneous and corneal epithelium. The cytological changes are essentially the same in all organs and foci of necrosis surrounded by a zone of inflammation are characteristically found in brain and liver when these organs are involved.

Viral particles can be identified ultrastructurally, mainly in the cell nucleus, and with detailed examination, HSV types 1 and 2 can be distinguished [1].

Clinical features

Primary infection

Primary infection occurs in a previously seronegative individual and is often subclinical. When clinical lesions develop, the severity is generally greater than in recurrences. Genital primary disease is more commonly symptomatic than oral.

Herpetic gingivostomatitis [2]. This is the most common clinical manifestation of primary infection by type 1 although the sites infected by the two HSV types are not mutually exclusive. Most cases occur in children between 1 and 5 years of age but cases are well-recognized in adults. After an incubation period of approximately 5 days, the stomatitis begins with fever, which may be high, malaise, restlessness and excessive dribbling. Drinking and eating are very painful and the breath is foul-smelling. The gums are swollen, inflamed and bleed easily. Vesicles presenting as white plaques are present on the tongue, pharynx, palate and buccal mucous membranes. The plaques develop into ulcers with a yellowish pseudomembrane. The regional lymph nodes are enlarged and tender. Encephalitis is a rare complication. After 3–5 days, the fever normally subsides and recovery is usually complete in 2 weeks.

In differential diagnosis, streptococcal infections, diphtheria, candidiasis, aphthosis, coxsackie infections including herpangina, Behçet's syndrome and the Stevens–Johnson syndrome must be considered.

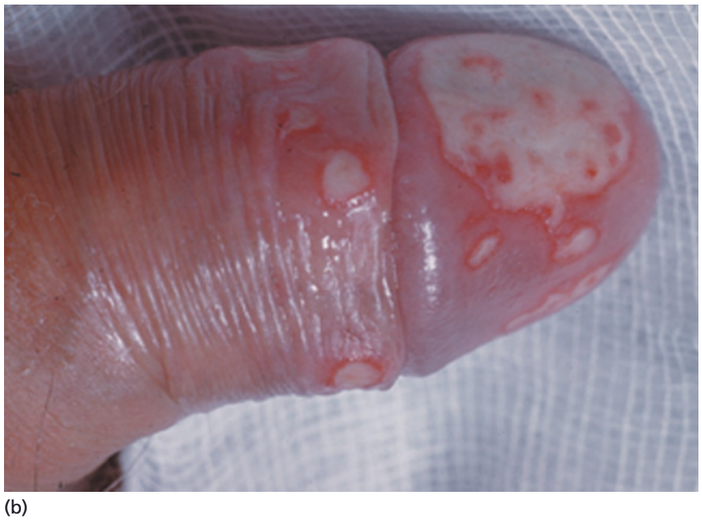
Herpes genitalis [3]. Infection in the genital area is usually sexually transmitted. HSV-2 has been the most common type in this area, although there is an increasing frequency of HSV-1 herpes genitalis, especially in young females with some studies now reporting that type 1 is found more frequently than HSV-2 [4,5]. Penile ulceration from herpetic infection (Fig. 33.9) is the most frequent type of genital ulceration seen in genitourinary medical clinics in the UK. The ulcers, which may be preceded by a general malaise, are most frequent on the glans, prepuce and shaft of the penis. They are sore or painful and last for 2–3 weeks if untreated. In male homosexuals, herpes simplex is common in the perianal area and may extend into the rectum. In HIV-infection, ulceration may become chronic.

In the female, similar lesions occur on the external genitalia and mucosae of the vulva, vagina and cervix. Pain and dysuria are common. Infection of the cervix may progress to a severe ulcerative cervicitis.

Where a person has had past HSV-1 infection, this is likely to decrease the severity of a primary HSV-2 infection, shortening the clinical course and reducing systemic symptoms.



(a)



(b)

Fig. 33.9 Herpes genitalis. (a) Scattered lesions on penile shaft. (b) Confluent lesions resulting in large erosions. (Courtesy of Addenbrooke's Hospital, Cambridge, UK.)

Keratoconjunctivitis. Primary herpes infection of the eye causes a severe and often purulent conjunctivitis with opacity and superficial ulceration of the cornea. The eyelids are grossly oedematous and there may be vesicles on the surrounding skin. The pre-auricular gland is enlarged and tender.

Inoculation herpes simplex (see Fig. 33.8). Direct inoculation of the virus into an abrasion or into normal skin gives rise to indurated papules, large bullae or irregularly scattered vesicles after an incubation period of 5–7 days. The regional nodes are enlarged but fever and constitutional symptoms are usually mild. Inoculation of the fingertips results in a 'herpetic whitlow', in which painful, deep vesicles coalesce to give a honeycombed appearance or to form a large bulla. The condition is easily confused with pyogenic infections. Recurrences of herpetic whitlow may occur, the majority are reported to be due to HSV-2 and occur in women with recurrent genital herpes [6].

Multiple crops of vesicles and pustules on plaques or erythema and oedema on the face, scalp and upper trunk, simulating impetigo and lasting some 10–12 days have occurred in wrestlers (herpes gladiatorum) [7]. On the face of the adult male the appearance of herpes may be deceptive; it may take the form of a folliculitis, but satellite umbilicated vesicles soon suggest the correct diagnosis. Facial contact during rugby is another recognized means of acquiring herpes simplex virus infection [8], commonly called 'scrumpox'.

Neonatal herpes. Primary genital herpes infection or active recurrent infection in the mother at the time of delivery makes the risk of transmission to the baby during vaginal delivery very high. Asymptomatic viral shedding between attacks or contact with acute infection in the neonatal period may also result in neonatal herpes, which has been estimated to occur in 1 : 50 000 births in the UK. The effects on the baby range in severity and may be due to disseminated disease, predominantly central nervous system, or limited to skin, eyes and mouth [9]. In the latter, there may be a vesicular eruption, or more subtle blistering or peeling of the skin. The mucosae are inflamed and may be ulcerated. If the infection is disseminated, there is likely to be lethargy, seizures, respiratory distress, hepatosplenomegaly with hepatitis and thromocytopenia. HSV can be detected by PCR in the cerebrospinal fluid. Even after treatment with aciclovir, relapse of neonatal herpes is common [10].

Complications. Eczema herpeticum is discussed below in this chapter (p. 33.35).

Pharyngitis may accompany approximately 10% of primary orofacial herpes, but also occurs in 1% of recurrent episodes of genital herpes.

Headache and meningism affected 36% of women and 11% of men in a series of 268 patients with primary genital herpes simplex [11], with full recovery. In such patients, HSV DNA can be found by PCR in the cerebrospinal fluid.

Radiculoneuropathy is seen occasionally in primary anogenital infection in women, and especially in perianal disease in homosexual men [11,12]. There may be sacral paraesthesia, urinary retention, constipation and, in men, impotence. Recovery takes a few days to a few weeks.

Disseminated or systemic infection may occur in the immunodeficient and in those neonates not protected by maternally acquired antibody, but rarely in otherwise healthy patients. Systemic infection may develop with or without widespread cutaneous lesions. At any age, encephalitis, untreated, has a high mortality and a high incidence of disability in survivors [13]; in neonates HSV-2 gave a worse prognosis than HSV-1, even with antiviral therapy [14]. HSV hepatitis is rare in adults; when severe, it is often fatal [15,16]. Lower respiratory tract infection has occurred in immunosuppressed, burned or intubated patients [17,18], and in neonates [19].

Recurrent infection

After the first infection, whether symptomatic or subclinical, there may be no further clinical manifestations throughout life. Recurrences occur in 30–50% of cases of oral herpes, but are more frequent after genital herpes infection, developing in 95% of those with type 2 HSV compared with 50% in individuals with type 1 infection [20,21].

Recurrences may be triggered by minor trauma, or by infections including febrile illnesses but also trivial, non-febrile, upper respiratory tract infections, by ultraviolet radiation [22], by trigeminal neuralgia and especially after intracranial operations for that disease [23], by other neural surgery [24], by dental surgery [25], by dermabrasion [26] or laser resurfacing [27]. Some women have more recurrences in the pre-menstrual period. Emotional stress is blamed in some cases, possibly related to the effect on immune function [28,29]. However, in many cases no reason for the eruption is evident.

Recurrent infections differ from primary infections in the smaller size of the vesicles and their close grouping, and in the usual absence of constitutional symptoms. In the immunocompetent, they do not as a rule affect the buccal mucosa, although inapparent oral shedding occurs in about 12% of the UK population.

Itching or burning precedes by an hour or two the development of small, closely grouped vesicles on an inflamed base. They usually become pustular and crusted before healing in 7–10 days without scarring. The eruption may be painful just at the onset or pain may last for a few days. They occur most frequently on the face, particularly around the mouth (Fig. 33.10), but can be situated anywhere on the body. Larger vesicles are not uncommon, especially in children. Recurrences tend to be in the same region, but not always on the identical site. Although the vesicles usually form an irregular cluster, they may be arranged in a line or in zosteriform distribution, particularly in the lower thoracic or lumbar region [30]. In such cases there may be considerable deep pain and regional lymphadenopathy. Fever, pain and lymphangitis may also be associated with herpes of the hand or forearm and further complications of oedema and persistent pain may develop [31]. Recurrent herpetic lesions are most commonly vesicular and ulcerative, but occasionally they are atypical with the appearance, for example, of folliculitis, candidal fissures or minor 'frictional ulcers'. Laboratory confirmation is needed for the accurate diagnosis of atypical lesions.



(a)



(b)

Fig. 33.10 Herpes labialis. (a) Typical recurrent lesion on upper lip. (b) More widespread recurrent lesions following streptococcal pyoderma with lymphangitis. (Courtesy of Dr A.S. Highet, York District Hospital, UK.)

Herpes genitalis. Recurrences are fairly common, occurring two to six times per year with clusters of small vesicles which produce non-indurated ulcers on the glans or shaft of the penis (see Fig. 33.9). They are of shorter duration than the initial infection. Similar lesions may occur on the labia, vagina or cervix and can cause distressingly painful symptoms. In other individuals the lesions can be unnoticed. Frequent recurrences are more likely in HSV-2 infection.

Subclinical viral shedding. Asymptomatic shedding of HSV-2 is more frequent than of HSV-1 and correlates with the frequency of symptomatic recurrences. In the first year following acquisition of HSV-2, asymptomatic shedding is more common than in subsequent years.

Complications. Constitutional symptoms rarely occur with recurrent herpes of the face or lips, some individuals report temperature disturbance, tiredness and general malaise which often precedes the onset. In one child, fever and an organic psychosis accompanied each attack [32]. Cranial nerve palsies may occur [33], sometimes with each eruption. Rarely, neuralgic pain may precede each recurrence of herpes by 1 or 2 days, a syndrome often associated with the name of Mauriac [34].

Eczema herpeticum (see p. 33.35) can be associated with recurrent as well as primary HSV.

In the immunocompromised, persistent ulcerative or verruciform lesions may occur (see Chapter 35).

If recurrent herpes simplex involves the eye, keratoconjunctivitis, dendritic ulcers, disciform or hypopyon keratitis and iridocyclitis may occur. An ophthalmological opinion should be sought.

Lymphoedema has followed recurrent attacks on a limb [35]. Secondary leukoderma may develop in pigmented skin, and herpes has been recorded as appearing in scar tissue [36].

- **Erythema multiforme** [37] (see Chapter 76) (herpes-associated erythema multiforme, HAEM). In 65% of patients with recurrent erythema multiforme there is a history of herpes labialis, usually preceding the erythema multiforme by several days to 2 weeks, but occasionally seeming to coincide with it. Although virus cannot be seen by electron microscopy or isolated, HSV antigen gB has been detected in erythema multiforme skin

lesions and HSV DNA has been demonstrated by PCR in lesions [38–40]. This evidence is not confined to cases with clinically apparent preceding herpetic lesions. Certain HLA types are associated with recurrent post-herpetic erythema multiforme or with severity of site affected [41,42]. Erythema multiforme-like eruptions which are associated with HSV are not uncommon following stem cell transplantation [43]. Treatment of recurrent HSV-associated erythema multiforme, if started by the patient in the prodrome stage (with a 5-day course of aciclovir), will often prevent development of erythema multiforme. If that is not effective and attacks are frequent, a 6-month course of prophylactic aciclovir should be tried even in patients in whom HSV is not obviously a precipitating factor [44]. Dapsone, azathioprine, ciclosporin or cimetidine have been reported to be effective in cases resistant to aciclovir or not associated with HSV [45–47].

- **Bell's palsy**. The suggestion that Bell's palsy is due to viral reactivation (HSV or VZV) has been strengthened by the detection by PCR of the HSV-1 genome in saliva, facial nerve and muscle tissue in patients with this condition [48–50]. The use of an appropriate antiviral should therefore be considered in the early management of Bell's palsy.
- **Recurrent lymphocytic meningitis**. A benign form of aseptic meningitis that lasts 3–14 days and may recur at intervals of months or years is associated with HSV [51]. HSV is detectable by PCR in the cerebrospinal fluid. Prophylactic or pre-eruptive aciclovir has been reported to prevent recurrences.
- **Encephalitis**. This severe disease can occur after the virus has established latent infection. Rapid diagnosis by PCR and treatment are essential to minimize the mortality and morbidity of the condition.

Diagnosis. Diagnosis of infection by culture of the virus from vesicle fluid usually requires only 1–5 days. Primary infections can be distinguished by seroconversion or a rise in antibody titre. Recurrences tend to produce little change in antibody titre; measurement of antibody is therefore not helpful in the diagnosis of recurrent HSV but type-specific antibodies will give some indication of the type causing reactivation episodes. For a more rapid diagnosis, viral antigen may be detectable by immunofluorescence in scrapings from lesions or the virus seen by electron microscopy in vesicle fluid. The detection of HSV DNA in the cerebrospinal fluid by PCR has become the diagnostic method of choice for herpes encephalitis and aseptic meningitis [52] and can also be used to identify the virus and the type at other sites. The use of PCR as a rapid diagnostic method is being developed to become more available and reliable [53].

References

1 Boddingius J, Dijkman H, van der Meijden W *et al.* Replication characteristics and core size of intranuclear herpes simplex virus (HSV-1) in genital skin lesions: electronmicroscopy studies of a biopsy from a female patient. *J Med Microbiol* 1987; **24**: 93–103.

2 Kolokotronis A, Doumas S. Herpes simplex virus infection, with particular reference to the progression and complications of primary herpetic gingivostomatitis. *Clin Microbiol Infect* 2006; **12**: 202–11.

3 Brugha R, Keersmaekers K, Renton A *et al.* Genital herpes infection: a review. *Int J Epidemiol* 1997; **26**: 698–709.

4 Nieuwenhuis RF, van Doornum GJ, Mulder PG *et al.* Importance of herpes simplex virus type-1 (HSV-1) in primary genital herpes. *Acta Derm Venereol* 2006; **86**: 129–34.

5 Tran T, Druce JD, Catton MC *et al.* Changing epidemiology of genital herpes simplex virus infection in Melbourne, Australia, between 1980 and 2003. *Sex Transm Infect* 2004; **80**: 277–9.

6 Gill MJ, Arlette J, Buchan KA. Herpes simplex virus infection of the hand. *J Am Acad Dermatol* 1990; **22**: 111–6.

7 Anderson BJ. The epidemiology and clinical analysis of several outbreaks of herpes gladiatorum. *Med Sci Sports Exerc* 2003; **35**: 1809–14.

8 White WB, Grant-Kels JM. Transmission of herpes simplex virus type 1 infection in rugby players. *JAMA* 1984; **252**: 533–5.

9 Caviness AC, Demmler GJ, Selwyn BJ. Clinical and laboratory features of neonatal herpes simplex virus infection: a case-control study. *Pediatr Infect Dis J* 2008; **27**: 425–30.

10 Kimura H, Futamura M, Ito Y *et al.* Relapse of neonatal herpes simplex virus infection. *Arch Dis Child (Fetal Neonatal Edn)* 2003; **88**: F483–6.

11 Corey L, Adams HG, Brown ZA *et al.* Genital herpes simplex virus infections: clinical manifestations, course, and complications. *Ann Intern Med* 1983; **98**: 958–72.

12 Goodell SE, Quinn TC, Mkrtichian E *et al.* Herpes simplex virus proctitis in homosexual men. Clinical, sigmoidoscopic, and histopathological features. *N Engl J Med* 1983; **308**: 868–71.

13 Levitz RE. Herpes simplex encephalitis: a review. *Heart Lung* 1998; **27**: 209–12.

14 Corey L, Whitley RJ, Stone EF *et al.* Difference between herpes simplex virus type 1 and type 2 neonatal encephalitis in neurological outcome. *Lancet* 1988; **1**: 1–4.

15 Norvell JP, Blei AT, Jovanovic BD *et al.* Herpes simplex virus hepatitis: an analysis of the published literature and institutional cases. *Liver Transpl* 2007; **13**: 1428–34.

16 Sharma S, Mosunjac M. Herpes simplex hepatitis in adults: a search for mucocutaneous clues. *J Clin Gastroenterol* 2004; **38**: 697–704.

17 Graham BS, Snell JD Jr. Herpes simplex virus infection of the adult lower respiratory tract. *Medicine (Baltimore)* 1983; **62**: 384–93.

18 Bruynseels P, Jorens PG, Demey HE *et al.* Herpes simplex virus in the respiratory tract of critical care patients: a prospective study. *Lancet* 2003; **362**: 1536–41.

19 Hubbell C, Dominguez R, Kohl S. Neonatal herpes simplex pneumonitis. *Rev Infect Dis* 1988; **10**: 431–8.

20 Corey L. First-episode, recurrent, and asymptomatic herpes simplex infections. *J Am Acad Dermatol* 1988; **18**: 169–72.

21 Lafferty WE, Coombs RW, Benedetti J *et al.* Recurrences after oral and genital herpes simplex virus infection. Influence of site of infection and viral type. *N Engl J Med* 1987; **316**: 1444–9.

22 Perna JJ, Mannix ML, Rooney JF *et al.* Reactivation of latent herpes simplex virus infection by ultraviolet light: a human model. *J Am Acad Dermatol* 1987; **17**: 473–8.

23 Burdick KH, Haserick JR, Gardner WJ. Herpes simplex following decompression operations for trigeminal neuralgia. Attempts to modify by local use of hydrocortisone preparations. *Arch Dermatol* 1960; **81**: 919–21.

24 Haverkos HW, Pazin GJ, Ho M *et al.* Reactivation of type 2 herpes simplex virus by thoracolumbar neurosurgery. *Ann Intern Med* 1984; **101**: 503–4.

25 Openshaw H, Bennett HE. Recurrence of herpes simplex virus after dental extraction. *J Infect Dis* 1982; **146**: 707.

26 Silverman AK, Laing KF, Swanson NA *et al.* Activation of herpes simplex following dermabrasion. Report of a patient successfully treated with intravenous acyclovir and brief review of the literature. *J Am Acad Dermatol* 1985; **13**: 103–8.

27 Johnson PJ, Hollins RR. Delayed reactivation of herpes simplex virus infection after facial laser resurfacing. *Plast Reconstr Surg* 2000; **106**: 743–4.

28 Schmidt DD, Schmidt PM, Crabtree BF *et al.* The temporal relationship of psychosocial stress to cellular immunity and herpes labialis recurrences. *Fam Med* 1991; **23**: 594–9.

29 Goldmeier D, Garvey L, Barton S. Does chronic stress lead to increased rates of recurrences of genital herpes—a review of the psychoneuroimmunological evidence? *Int J STD AIDS* 2008; **19**: 359–62.

30 Slavin HB, Ferguson JJ Jr. Zoster-like eruptions caused by the virus of herpes simplex. *Am J Med* 1950; **8**: 456–67.

31 Fletcher PG, Sterling JC. Recurrent herpes simplex virus type 2 infection of the hand complicated by persistent lymphoedema. *Australas J Dermatol* 2005; **46**: 110–3.
32 Shearer ML, Finch SM. Periodic organic psychosis associated with recurrent herpes simplex. *N Engl J Med* 1964; **271**: 494–7.
33 Sekizawa T, Nakamura S, Kogure K *et al.* Idiopathic third cranial nerve palsy associated with herpes simplex virus infection. *BMJ (Clin Res Edn)* 1987; **295**: 813.
34 Maruri CA, Diaz LA. A rare case of Mauriac neuralgic genital herpes. *Int J Dermatol* 1972; **11**: 140–3.
35 Howard WR, Taylor JS, Steck WD. Lymphatic complications of manual herpes simplex infection. *Cutis* 1979; **23**: 580–3.
36 Sharma RC, Sharma NL, Mahajan V *et al.* Wolf's isotopic response: herpes simplex appearing on scrofuloderma scar. *Int J Dermatol* 2003; **42**: 664–6.
37 Singla R, Brodell RT. Erythema multiforme due to herpes simplex virus. Recurring target lesions are the clue to diagnosis. *Postgrad Med* 1999; **106**: 151–4.
38 Darragh TM, Egbert BM, Berger TG *et al.* Identification of herpes simplex virus DNA in lesions of erythema multiforme by the polymerase chain reaction. *J Am Acad Dermatol* 1991; **24**: 23–6.
39 Ng PP, Sun YJ, Tan HH *et al.* Detection of herpes simplex virus genomic DNA in various subsets of Erythema multiforme by polymerase chain reaction. *Dermatology* 2003; **207**: 349–53.
40 Wackernagel A, Zochling N, Back B *et al.* Presence of herpes simplex virus DNA in erythema multiforme but not polymorphic light eruption. *Br J Dermatol* 2006; **155**: 1084–5.
41 Kampgen E, Burg G, Wank R. Association of herpes simplex virus-induced erythema multiforme with the human leukocyte antigen DQw3. *Arch Dermatol* 1988; **124**: 1372–5.
42 Malo A, Kampgen E, Wank R. Recurrent herpes simplex virus-induced erythema multiforme: different HLA-DQB1 alleles associate with severe mucous membrane versus skin attacks. *Scand J Immunol* 1998; **47**: 408–11.
43 Burnett JW, Laing JM, Aurelian L. Acute skin eruptions that are positive for herpes simplex virus DNA polymerase in patients with stem cell transplantation: a new manifestation within the erythema multiforme reactive dermatoses. *Arch Dermatol* 2008; **144**: 902–7.
44 Schofield JK, Tatnall FM, Leigh IM. Recurrent erythema multiforme: clinical features and treatment in a large series of patients. *Br J Dermatol* 1993; **128**: 542–5.
45 Huff JC. Acyclovir for recurrent erythema multiforme caused by herpes simplex. *J Am Acad Dermatol* 1988; **18**: 197–9.
46 Bakis S, Zagarella S. Intermittent oral cyclosporin for recurrent herpes simplex-associated erythema multiforme. *Australas J Dermatol* 2005; **46**: 18–20.
47 Kurkcuoglu N, Alli N. Cimetidine prevents recurrent erythema multiforme major resulting from herpes simplex virus infection. *J Am Acad Dermatol* 1989; **21**: 814–5.
48 Furuta Y, Fukuda S, Chida E *et al.* Reactivation of herpes simplex virus type 1 in patients with Bell's palsy. *J Med Virol* 1998; **54**: 162–6.
49 Murakami S, Mizobuchi M, Nakashiro Y *et al.* Bell palsy and herpes simplex virus: identification of viral DNA in endoneurial fluid and muscle. *Ann Intern Med* 1996; **124**: 27–30.
50 Kawaguchi K, Inamura H, Abe Y *et al.* Reactivation of herpes simplex virus type 1 and varicella-zoster virus and therapeutic effects of combination therapy with prednisolone and valacyclovir in patients with Bell's palsy. *Laryngoscope* 2007; **117**: 147–56.
51 Tedder DG, Ashley R, Tyler KL *et al.* Herpes simplex virus infection as a cause of benign recurrent lymphocytic meningitis. *Ann Intern Med* 1994; **121**: 334–8.
52 Madhavan HN, Priya K, Anand AR *et al.* Detection of herpes simplex virus (HSV) genome using polymerase chain reaction (PCR) in clinical samples: comparison of PCR with standard laboratory methods for the detection of HSV. *J Clin Virol* 1999; **14**: 145–51.
53 Rose L, Herra CM, Crowley B. Evaluation of real-time polymerase chain reaction assays for the detection of herpes simplex virus in swab specimens. *Eur J Clin Microbiol Infect Dis* 2008; **27**: 857–61.

Treatment [1–4]. Mild uncomplicated eruptions of herpes simplex require no treatment. The use of a topical antiseptic agent on affected skin may help to reduce the risk of secondary bacterial infection. In severe primary infection or troublesome recurrent disease, antiviral therapy should be instigated.

Aciclovir (acyclovir). After triple phosphorylation, this drug is incorporated into DNA where it interferes with the action of DNA polymerase and acts as a chain terminator. The first phosphorylation step is catalysed by a specific viral thymidine kinase so that the effect of the drug is confined to virus-infected cells. Aciclovir is of proven clinical value against herpes simplex and varicella zoster viruses, though the latter is somewhat less sensitive to it.

Valaciclovir and famciclovir are chemically related to aciclovir and have the same mechanism of action. They are precursor drugs; valaciclovir is converted to aciclovir and famciclovir is converted to penciclovir. They are absorbed better than aciclovir from an oral dose and have improved bioavailability.

Primary infection

Aciclovir systemically is the treatment of choice for severe or potentially severe primary herpes simplex infection, but there is no effect on establishment of virus latency and rates of recurrence after therapy. Treatment should be started as soon as possible. The usual dose is 5 mg/kg 8-hourly intravenously, though twice that dose has been used for neonatal herpes [5] and encephalitis [6]. As the drug is excreted via the kidneys the dose must be scaled down in renal failure. Transient rises in blood urea and creatinine may occur with bolus injections; slow infusion over 1 h in an adequately hydrated patient is recommended.

For less severe infections and when swallowing is not impaired, oral treatment is adequate. The usual oral dose is 200 mg five times daily for 5 or more days, but 800 mg twice daily has been used with success [5]. In children, the oral suspension given at 15 mg/kg five times per day for 7 days reduces the duration of symptoms and virus shedding [7]. Valaciclovir, 1000 mg twice daily for 10 days, is of similar efficacy to aciclovir [8].

Neonatal herpes is treated with high-dose intravenous aciclovir (60 mg/kg/day in three divided doses for 2 to 3 weeks) [5].

Recurrent infection

Recurrent herpes labialis may need no treatment if attacks are mild or infrequent [9]. Both 5% aciclovir cream and a thin hydrocolloid dressing reduce discomfort [10] but may not alter healing rate. Oral aciclovir started as soon as possible after onset of symptoms can shorten the duration and decrease the intensity of an episode [11]. If recurrences are frequent, long-term prophylactic aciclovir at a dose of 200–400 mg twice daily for 4–6 months may increase the time between episodes [3,12,13].

In the immunocompromised patient, mucocutaneous herpes simplex responds well to intravenous aciclovir [14,15] or penciclovir [16]. Post-exposure, the infection can be prevented by intravenous [17] or oral [18] aciclovir, which should be started several days before the anticipated immunosuppression and continued throughout the period of greatest risk. Longer-term prophylaxis where indicated is also effective [19].

Prophylaxis against reactivation or spread of HSV may be useful before cosmetic laser treatment of the face, as widespread herpes has been reported following such procedures [20,21].

Initial eruptions of genital herpes [22] improve significantly with oral aciclovir [23], valaciclovir [8] or famciclovir. Treatment of recurrent disease can be ineffective unless initiated rapidly and of adequate dose. Patients should have a supply of tablets in hand to be started on their own initiative [24–26]. The usual dose is: aciclovir 200 mg five times a day for 5 days or 400 mg three times a day; valaciclovir 500 mg twice daily for 3 days; famciclovir 125 mg twice a day for 5 days. Shorter courses of higher doses can be equally effective [27–29]. Frequent recurrences, and also any associated erythema multiforme [30], can be suppressed by long-term treatment, although cessation of therapy, even after several years, may allow resumption of recurrences [31]. Prophylactic doses of aciclovir vary between 200 and 1000 mg daily; a typical regimen is 400 mg twice daily, gradually reduced to find the minimum effective dose for the individual patient. Valaciclovir, 250 mg twice daily or 1 g once daily [29,32], or famciclovir 125 mg three times daily or 250 mg twice daily [29,32,33], are also effective in suppression of recurrent episodes.

Topical aciclovir is of established value for herpetic keratitis. In the treatment of recurrent eruptions of herpes labialis, and of first-episode and recurrent herpes genitalis, improvement has been demonstrated [34] but seems less impressive than that obtained by oral administration and in some studies has been ineffective [11]. Similarly, there is no strong evidence that topical aciclovir influences the disease course in recurrent cutaneous HSV. Topical penciclovir compares favourably with aciclovir [35] and reduces the duration of pain and the eruption in comparison with placebo [36].

Resistance of herpes simplex to aciclovir has not emerged as a significant problem in immunocompetent patients [37]. However, in the immunocompromised, resistant strains which cause intractable lesions have emerged following long-term or frequently repeated treatment. Resistance is usually due to a change in or loss of the viral thymidine kinase [38], or more rarely to alteration of the viral DNA polymerase [39]. The former strains may respond to antivirals that have a different mode of action (e.g. phosphonoformate, also known as foscarnet, or cidofovir, see below).

The risk to the infant from primary herpetic vulvovaginitis in the mother at the time of delivery is so great that caesarean section is indicated and prophylactic aciclovir should be considered for the neonate [40]. Primary genital herpes during the third trimester warrants consideration of treatment of the mother with oral aciclovir, although it is unclear whether this reduces the risk of neonatal herpes [41].

Other treatments. In the treatment of severe herpes simplex infection resistant to aciclovir, systemic phosphonoformate (foscarnet) may be considered [42]. An alternative antiviral is cidofovir, which acts to block DNA replication. This can be administered systemically but is also active topically. A small number of individuals with severe HSV resistant to conventional treatment have responded to cidofovir [43].

Topical idoxuridine was used historically for treatment of herpes but was superseded by the safer and more effective antiviral drugs. New formulations may enable its reconsideration as therapy [44]. Trifluorothymidine has also been used but its efficacy is uncertain [45].

Enhancement of the immune response to HSV could reduce recurrences. Vaccines against the virus are under development but not yet in clinical use. Topical imiquimod and resiquimod, which cause local release of cytokines and enhancement of antigen presentation, have shown some promise in treatment of recurrent genital herpes [46,47].

Recurrences of herpes labialis may be prevented or reduced in intensity by the use of a topical sunscreen [48].

References

1 Brady RC, Bernstein DI. Treatment of herpes simplex virus infections. *Antiviral Res* 2004; **61**: 73–81.

2 Nikkels AF, Pierard GE. Treatment of mucocutaneous presentations of herpes simplex virus infections. *Am J Clin Dermatol* 2002; **3**: 475–87.

3 Yeung-Yue KA, Brentjens MH, Lee PC *et al.* The management of herpes simplex virus infections. *Curr Opin Infect Dis* 2002; **15**: 115–22.

4 Cernik C, Gallina K, Brodell RT. The treatment of herpes simplex infections: an evidence-based review. *Arch Intern Med* 2008; **168**: 1137–44.

5 Kimberlin DW, Lin CY, Jacobs RF *et al.* Safety and efficacy of high-dose intravenous acyclovir in the management of neonatal herpes simplex virus infections. *Pediatrics* 2001; **108**: 230–8.

6 Johns DR, Gress DR. Rapid response to acyclovir in herpes zoster-associated encephalitis. *Am J Med* 1987; **82**: 560–2.

7 Amir J. Clinical aspects and antiviral therapy in primary herpetic gingivostomatitis. *Paediatr Drugs* 2001; **3**: 593–7.

8 Fife KH, Barbarash RA, Rudolph T *et al.* Valaciclovir versus acyclovir in the treatment of first-episode genital herpes infection. Results of an international, multicenter, double-blind, randomized clinical trial. The Valaciclovir International Herpes Simplex Virus Study Group. *Sex Transm Dis* 1997; **24**: 481–6.

9 Spruance SL. Prophylactic chemotherapy with acyclovir for recurrent herpes simplex labialis. *J Med Virol* 1993; Suppl **1**: 27–32.

10 Karlsmark T, Goodman JJ, Drouault Y *et al.* Randomized clinical study comparing Compeed cold sore patch to acyclovir cream 5% in the treatment of herpes simplex labialis. *J Eur Acad Dermatol Venereol* 2008; **22**: 1184–92.

11 Raborn GW, McGaw WT, Grace M *et al.* Treatment of herpes labialis with acyclovir. Review of three clinical trials. *Am J Med* 1988; **85**: 39–42.

12 Rooney JF, Straus SE, Mannix ML *et al.* Oral acyclovir to suppress frequently recurrent herpes labialis. A double-blind, placebo-controlled trial. *Ann Intern Med* 1993; **118**: 268–72.

13 Spruance SL, Kriesel JD. Treatment of herpes simplex labialis. *Herpes* 2002; **9**: 64–9.

14 Mitchell CD, Bean B, Gentry SR *et al.* Acyclovir therapy for mucocutaneous herpes simplex infections in immunocompromised patients. *Lancet* 1981; **1**: 1389–92.

15 Straus SE, Smith HA, Brickman C *et al.* Acyclovir for chronic mucocutaneous herpes simplex virus infection in immunosuppressed patients. *Ann Intern Med* 1982; **96**: 270–7.

16 Lazarus HM, Belanger R, Candoni A *et al.* Intravenous penciclovir for treatment of herpes simplex infections in immunocompromised patients: results of a multicenter, acyclovir-controlled trial. The Penciclovir Immunocompromised Study Group. *Antimicrob Agents Chemother* 1999; **43**: 1192–7.

17 Hann IM, Prentice HG, Blacklock HA *et al.* Acyclovir prophylaxis against herpes virus infections in severely immunocompromised patients: randomised double blind trial. *BMJ* 1983; **287**: 384–8.

18 Wade JC, Newton B, Flournoy N *et al.* Oral acyclovir for prevention of herpes simplex virus reactivation after marrow transplantation. *Ann Intern Med* 1984; **100**: 823–8.

19 Ljungman P, Wilczek H, Gahrton G *et al.* Long-term acyclovir prophylaxis in bone marrow transplant recipients and lymphocyte proliferation responses to herpes virus antigens in vitro. *Bone Marrow Transpl* 1986; **1**: 185–92.

20 Beeson WH, Rachel JD. Valacyclovir prophylaxis for herpes simplex virus infection or infection recurrence following laser skin resurfacing. *Dermatol Surg* 2002; **28**: 331–6.

21 Bisaccia E, Scarborough D. Herpes simplex virus prophylaxis with famciclovir in patients undergoing aesthetic facial CO_2 laser resurfacing. *Cutis* 2003; **72**: 327–8.

22 Patel R, Barton SE, Brown D *et al.* European guideline for the management of genital herpes. *Int J STD AIDS* 2001; 12 Suppl **3**: 34–9.
23 Mertz GJ, Critchlow CW, Benedetti J *et al.* Double-blind placebo-controlled trial of oral acyclovir in first-episode genital herpes simplex virus infection. *JAMA* 1984; **252**: 1147–51.
24 Nilsen AE, Aasen T, Halsos AM *et al.* Efficacy of oral acyclovir in the treatment of initial and recurrent genital herpes. *Lancet* 1982; **2**: 571–3.
25 Spruance SL, Tyring SK, DeGregorio B *et al.* A large-scale, placebo-controlled, dose-ranging trial of peroral valaciclovir for episodic treatment of recurrent herpes genitalis. Valaciclovir HSV Study Group. *Arch Intern Med* 1996; **156**: 1729–35.
26 Sacks SL, Aoki FY, Diaz-Mitoma F *et al.* Patient-initiated, twice-daily oral famciclovir for early recurrent genital herpes. A randomized, double-blind multicenter trial. Canadian Famciclovir Study Group. *JAMA* 1996; **276**: 44–9.
27 Wald A, Carrell D, Remington M *et al.* Two-day regimen of acyclovir for treatment of recurrent genital herpes simplex virus type 2 infection. *Clin Infect Dis* 2002; **34**: 944–8.
28 Bodsworth N, Bloch M, McNulty A *et al.* 2-day versus 5-day famciclovir as treatment of recurrences of genital herpes: results of the FaST study. *Sex Health* 2008; **5**: 219–25.
29 Reitano M, Tyring S, Lang W *et al.* Valaciclovir for the suppression of recurrent genital herpes simplex virus infection: a large-scale dose range-finding study. International Valaciclovir HSV Study Group. *J Infect Dis* 1998; **178**: 603–10.
30 Huff JC. Acyclovir for recurrent erythema multiforme caused by herpes simplex. *J Am Acad Dermatol* 1988; **18**: 197–9.
31 Fife KH, Crumpacker CS, Mertz GJ *et al.* Recurrence and resistance patterns of herpes simplex virus following cessation of > or = 6 years of chronic suppression with acyclovir. Acyclovir Study Group. *J Infect Dis* 1994; **169**: 1338–41.
32 Patel R, Bodsworth NJ, Woolley P *et al.* Valaciclovir for the suppression of recurrent genital HSV infection: a placebo controlled study of once daily therapy. International Valaciclovir HSV Study Group. *Genitourin Med* 1997; **73**: 105–9.
33 Mertz GJ, Loveless MO, Levin MJ *et al.* Oral famciclovir for suppression of recurrent genital herpes simplex virus infection in women. A multicenter, double-blind, placebo-controlled trial. Collaborative Famciclovir Genital Herpes Research Group. *Arch Intern Med* 1997; **157**: 343–9.
34 Spruance SL, Freeman DJ, Stewart JC *et al.* The natural history of ultraviolet radiation-induced herpes simplex labialis and response to therapy with peroral and topical formulations of acyclovir. *J Infect Dis* 1991; **163**: 728–34.
35 Lin L, Chen XS, Cui PG *et al.* Topical application of penciclovir cream for the treatment of herpes simplex facialis/labialis: a randomized, double-blind, multicentre, aciclovir-controlled trial. *J Dermatolog Treat* 2002; **13**: 67–72.
36 Raborn GW, Martel AY, Lassonde M *et al.* Effective treatment of herpes simplex labialis with penciclovir cream: combined results of two trials. *J Am Dent Assoc* 2002; **133**: 303–9.
37 Crumpacker CS. Significance of resistance of herpes simplex virus to acyclovir. *J Am Acad Dermatol* 1988; **18**: 190–5.
38 Youle MM, Hawkins DA, Collins P *et al.* Acyclovir-resistant herpes in AIDS treated with foscarnet. *Lancet* 1988; **2**: 341–2.
39 Parker AC, Craig JI, Collins P *et al.* Acyclovir-resistant herpes simplex virus infection due to altered DNA polymerase. *Lancet* 1987; **2**: 1461.
40 Gibbs RS, Mead PB. Preventing neonatal herpes—current strategies. *N Engl J Med* 1992; **326**: 946–7.
41 Hollier LM, Wendel GD. Third trimester antiviral prophylaxis for preventing maternal genital herpes simplex virus (HSV) recurrences and neonatal infection. *Cochrane Database Syst Rev* 2008: CD004946.
42 Javaly K, Wohlfeiler M, Kalayjian R *et al.* Treatment of mucocutaneous herpes simplex virus infections unresponsive to acyclovir with topical foscarnet cream in AIDS patients: a phase I/II study. *J Acquir Immune Defic Syndr* 1999; **21**: 301–6.
43 Bryant P, Sasadeusz J, Carapetis J *et al.* Successful treatment of foscarnet-resistant herpes simplex stomatitis with intravenous cidofovir in a child. *Pediatr Infect Dis J* 2001; **20**: 1083–6.
44 Seth AK, Misra A, Umrigar D. Topical liposomal gel of idoxuridine for the treatment of herpes simplex: pharmaceutical and clinical implications. *Pharm Dev Technol* 2004; **9**: 277–89.
45 Amin AR, Robinson MR, Smith DD *et al.* Trifluorothymidine 0.5% ointment in the treatment of aciclovir-resistant mucocutaneous herpes simplex in AIDS. *AIDS* 1996; **10**: 1051–3.

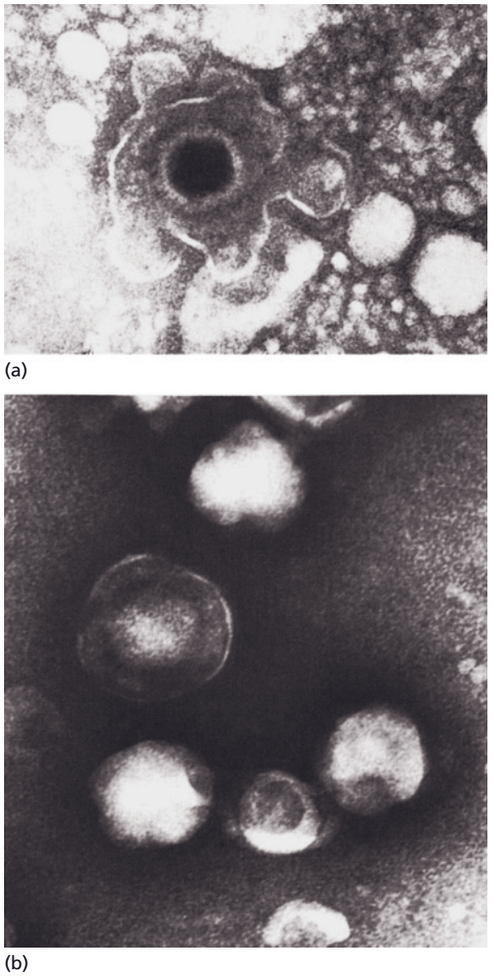


Fig. 33.11 *Herpesvirus varicellae*. Phosphotungstate preparations from vesicle fluid. (a) The dark centre is due to penetration of the capsid by phosphotungstate (× 72 000). (b) The envelope encloses the nucleocapsid and obscures detail (× 116 250). (Courtesy of Dr J. Nagington, Cambridge, UK.)

46 Bangsgaard N, Skov L. Chronic genital ulceration due to herpes simplex infection treated successfully with imiquimod. *Acta Derm Venereol* 2008; **88**: 202–3.
47 Spruance SL, Tyring SK, Smith MH *et al.* Application of a topical immune response modifier, resiquimod gel, to modify the recurrence rate of recurrent genital herpes: a pilot study. *J Infect Dis* 2001; **184**: 196–200.
48 Rooney JF, Bryson Y, Mannix ML *et al.* Prevention of ultraviolet-light-induced herpes labialis by sunscreen. *Lancet* 1991; **338**: 1419–22.

Varicella zoster virus [1]

Aetiology and epidemiology. The varicella zoster virus (VZV) (Fig. 33.11) is the cause of both varicella (chickenpox) and zoster (shingles). Three genotypes of this α-herpesvirus have been identified and shown to have geographical variation [2]. The primary infection of varicella includes viraemia and a widespread eruption, after which the virus persists in nerve ganglion cells, usually sensory. Zoster is the result of reactivation of this residual latent virus.

Varicella occurs throughout the world but infection occurs at a younger age in temperate zones compared to the tropics. In

temperate climates, cases are more common in the cooler winter and spring months. In cities, epidemics occur at irregular intervals. Subclinical infections may occur. It is estimated that in non-immune populations, approximately 15 cases per 1000 people occur per year, with over half before the age of 5 and 85% before puberty [3,4]. This leads to a seropositivity of about 95% of young adults with somewhat lower rates in tropical areas [5,6].

The virus is transmitted by droplet infection from the nasopharynx. A brief first viraemic stage, when the virus can disseminate to other organs, is followed by a second viraemia coinciding with the onset of the rash. Patients are infectious to others from about 2 days before to 5 days after the onset of the rash and 60–100% of non-immune individuals will contract the infection if exposed to someone in the infectious stage of chicken pox or zoster. Vesicle fluid contains a large amount of virus. Completely dry scabs are not infectious.

Varicella confers lasting immunity and second attacks are uncommon, especially in immunologically healthy subjects, but clinical reinfection with a mild varicella-like illness occurs occasionally [7].

Zoster (zoster = a girdle, a reference to its segmental distribution) is a sporadic affliction of individuals. The average annual incidence has been estimated at 2–4 per 1000 [8,9]. It is uncommon in childhood and the incidence increases with age. The sexes are equally affected. Zoster patients are infectious, both from virus in the lesions and, in some instances, the nasopharynx. In susceptible contacts of zoster, chickenpox can occur.

In varicella, IgG, IgM and IgA antibodies appear 2–5 days after the onset of the rash, and their levels peak during the second and third weeks. Thereafter, the titres gradually fall although IgG persists at low levels. If zoster occurs later, the levels of the IgG antibody increase rapidly and become much greater than during the primary infection. Antibodies seem to have an incomplete protective effect; maternal or administered antibody reduces the severity of infection, but does not prevent it.

Cell-mediated immunity (CMI) is more important in both protection against and control of the infection. If the primary infection occurs when CMI is impaired, as in organ-transplant patients, varicella may be severe and occasionally fatal. In patients with impaired immunity, both the incidence and severity of zoster are increased, and it is frequently complicated by disseminated cutaneous disease and systemic involvement, usually pneumonia, hepatitis or encephalitis. This is seen in malignancy, especially lymphomas, so that the incidence of zoster is at least 10% [10,11]. Also at risk are patients receiving cytotoxic or immunosuppressive therapy, especially the more profound suppression required for bone-marrow transplantation; series suggest that 30–40% of patients may have varicella zoster reactivation episodes during the first year post-transplant [12,13]. In patients infected with HIV, zoster is 10 times more common than in the normal population and may become disseminated and chronic (see Chapter 35).

Maternal varicella in the first 20 weeks of pregnancy is associated with an approximate 2% risk of fetal damage, including skin lesions, central nervous system and ocular defects, and limb hypoplasia, with a 30% mortality within the first year of life [14]. Maternal zoster in pregnancy is not associated with intrauterine infection [15]. Zoster in infancy has followed maternal varicella, the baby's primary infection having occurred *in utero* [16]. If the mother has varicella within 4 days before to 2 days after term, the neonate would have no maternal antibody and is at risk of severe varicella with a mortality rate up to 30% in the absence of treatment.

Varicella may be more severe at sites of cutaneous inflammation [17]. The factors determining the site of an eruption of zoster are often unclear, but it may be precipitated by pressure on or trauma to nerve roots, by neoplastic deposits, radiotherapy, or surgery, or other, often trivial, traumas [18].

Occasional clusters of cases of shingles are reported, and it is suggested that, uncommonly, exposure to exogenous VZV may trigger reactivation of latent virus [19].

References

1 Heininger U, Seward JF. Varicella. *Lancet* 2006; **368**: 1365–76.
2 Loparev VN, Gonzalez A, Deleon-Carnes M *et al.* Global identification of three major genotypes of varicella-zoster virus: longitudinal clustering and strategies for genotyping. *J Virol* 2004; **78**: 8349–58.
3 Choo PW, Donahue JG, Manson JE *et al.* The epidemiology of varicella and its complications. *J Infect Dis* 1995; **172**: 706–12.
4 Brisson M, Edmunds WJ. Epidemiology of varicella-zoster virus in England and Wales. *J Med Virol* 2003; 70 Suppl **1**: S9–14.
5 Heininger U, Braun-Fahrlander C, Desgrandchamps D *et al.* Seroprevalence of varicella-zoster virus immunoglobulin G antibodies in Swiss adolescents and risk factor analysis for seronegativity. *Pediatr Infect Dis J* 2001; **20**: 775–8.
6 Nardone A, de Ory F, Carton M *et al.* The comparative sero-epidemiology of varicella zoster virus in 11 countries in the European region. *Vaccine* 2007; **25**: 7866–72.
7 Gershon AA, Steinberg SP, Gelb L. Clinical reinfection with varicella-zoster virus. *J Infect Dis* 1984; **149**: 137–42.
8 Hope-Simpson RE. The nature of herpes zoster: a long-term study and a new hypothesis. *Proc R Soc Med* 1965; **58**: 9–20.
9 Yawn BP, Saddier P, Wollan PC *et al.* A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction. *Mayo Clin Proc* 2007; **82**: 1341–9.
10 Vonderheid EC, van Voorst Vader PC. Herpes zoster-varicella in cutaneous T-cell lymphomas. *Arch Dermatol* 1980; **116**: 408–12.
11 Guinee VF, Guido JJ, Pfalzgraf KA *et al.* The incidence of herpes zoster in patients with Hodgkin's disease. An analysis of prognostic factors. *Cancer* 1985; **56**: 642–8.
12 Schuchter LM, Wingard JR, Piantadosi S *et al.* Herpes zoster infection after autologous bone marrow transplantation. *Blood* 1989; **74**: 1424–7.
13 Koc Y, Miller KB, Schenkein DP *et al.* Varicella zoster virus infections following allogeneic bone marrow transplantation: frequency, risk factors, and clinical outcome. *Biol Blood Marrow Transpl* 2000; **6**: 44–9.
14 Sauerbrei A, Wutzler P. The congenital varicella syndrome. *J Perinatol* 2000; **20**: 548–54.
15 Enders G, Miller E, Cradock-Watson J *et al.* Consequences of varicella and herpes zoster in pregnancy: prospective study of 1739 cases. *Lancet* 1994; **343**: 1548–51.
16 Lewkonia IK, Jackson AA. Infantile herpes zoster after intrauterine exposure to varicella. *BMJ* 1973; **3**: 149.
17 Wilkin JK, Ribble JC, Wilkin OC. Vascular factors and the localization of varicella lesions. *J Am Acad Dermatol* 1981; **4**: 665–6.
18 Juel-Jensen BE. The natural history of shingles. Events associated with reactivation of varicella-zoster virus. *J R Coll Gen Pract* 1970; **20**: 323–7.
19 Palmer SR, Caul EO, Donald DE *et al.* An outbreak of shingles? *Lancet* 1985; **2**: 1108–11.

Pathology [1]. Following an initial period of replication in the oropharynx a viraemia causes widespread dissemination. Within a few days, a second viraemia is detectable at the time when skin lesions become evident. In the skin, in varicella, cells of the Malpighian layer show ballooning of their cytoplasm by intracellular oedema, and distinctive nuclear changes, comprising eosinophilic

inclusions and marginated chromatin. Some nuclei develop additional nuclear membranes which divide the nucleus into small compartments. The multinucleate giant cells with up to 15 nuclei, which are a characteristic feature of infections with *Herpesvirus varicellae* and *Herpesvirus hominis*, are produced mainly by cell fusion. Intracellular oedema combined with intercellular oedema forms the vesicle, the roof of which consists of the upper Malpighian and horny layers. A mild inflammatory reaction in the dermis later extends to the epidermis and the proportion of polymorphonuclear cells increases with ulceration.

In fatal cases of varicella essentially similar cytological changes with areas of focal necrosis are found in the liver, kidney and other organs [2]. The lungs show interstitial pneumonia with focal consolidation and haemorrhage.

In zoster, as well as skin lesions, there are inflammatory changes in the posterior nerve roots and ganglia and sometimes these involve the anterior horn. Virus particles have been seen in ganglion cells and Schwann cells in the affected nerve bundles [3]. More extensive changes are sometimes reported: leptomeningitis, encephalitis with local demyelination, and myelitis. Disseminated lesions in other organs may occur as in varicella.

Zoster can cause some destruction of nerve fibres in the middle and lower dermis, detectable with silver-impregnation techniques [4]. Partial denervation may persist for over a year and characteristically does so in patients with post-herpetic neuralgia [5]. Corresponding fibres in the spinal cord degenerate and there may be scarring in the region of the ganglion.

References

1 McSorley J, Shapiro L, Brownstein MH *et al*. Herpes simplex and varicella-zoster: comparative histopathology of 77 cases. *Int J Dermatol* 1974; **13**: 69–75.

2 Johnson HN. Visceral lesions associated with varicella. *Arch Pathol* 1940; **30**: 292–307.

3 Esiri MM, Tomlinson AH. Herpes zoster. Demonstration of virus in trigeminal nerve and ganglion by immunofluorescence and electron microscopy. *J Neurol Sci* 1972; **15**: 35–48.

4 Ebert MH. Histologic changes in sensory nerves of the skin in herpes zoster. *Arch Derm Syphilol* 1949; **60**: 641–8.

5 Muller SA, Winkelmann RK. Cutaneous nerve changes in zoster. *J Invest Dermatol* 1969; **52**: 71–7.

Clinical features.

Varicella (Fig. 33.12)

The incubation period is usually 14–17 days (range 9–23 days). After a day or two of fever and malaise, often slight or absent in children, an inconstant and fleeting scarlatiniform or morbilliform erythema is followed by the development of papules which very rapidly become tense, clear, unilocular vesicles. Within a few hours the contents become turbid and the pustules are surrounded by red areolae. In 2–4 days a dry crust forms and soon separates, to leave a shallow, pink depression which, in the absence of secondary infection, heals without scarring. The vesicles appear in three to five crops over 2–4 days. They are most numerous on the trunk, then on the face and scalp and on the limbs. Their distribution is centripetal, and on the limbs the eruption is more profuse on thighs and upper arms than on lower legs and forearms. A characteristic feature is the presence of lesions at different stages in each site. The total number of lesions is very variable; they may



Fig. 33.12 Varicella. (Courtesy of York District Hospital, UK.)

be few or profuse. The distribution may be modified by pre-existing inflammatory changes at the sites of which lesions may appear in increased density [1]. The vesicles in such areas tend to be at the same stage and are often small, but may occasionally be bullous. In exceptional cases of normal distribution the lesions are larger and umbilicated or varioloid. Vesicles are common in the mouth, especially on the palate, and are occasionally seen on other mucous membranes, including the conjunctiva and genitalia. On the anal mucosa they may be followed by painful ulcers.

Fever is variable in severity and duration and roughly parallels the extent of the eruption. It may be trivial or may reach 40 or 41°C for 4 or 5 days. Constitutional symptoms tend to be proportionate to the fever. In some patients pruritus is troublesome.

After about 4 days, no new crops of lesions appear and existing vesicles dry and crust. It may be 1 to 2 weeks before the crusts separate and repair of lesion sites is complete. Hyper- or hypopigmentation may persist for weeks and small, round, depressed scars can occur in about 18% [2].

Haemorrhagic varicella, in which a very extensive eruption of haemorrhagic vesicles is accompanied by high fever and severe constitutional symptoms, is rare in the previously healthy patient. It is relatively more common in some tropical regions in which malnutrition may be a factor, but most cases now seen in temperate regions occur in immunocompromised patients.

The fetal and neonatal consequences of varicella in pregnancy are discussed earlier in this chapter (p. 33.23).

Complications. These are rare in otherwise healthy children, are less infrequent in neonates and adults and are common in the immunosuppressed. Relatively short courses of oral steroid treatment in children and adults may permit the development of severe and potentially fatal chickenpox [3].

Encephalitis, often presenting with ataxia, in the otherwise healthy patient occurs in less than one per 1000 cases and complete recovery occurs in 80%. Other neurological complications are very rare. The other main systemic complications are varicella pneumonia and hepatitis [4].

Secondary infection is seldom a serious problem in temperate climates, but under tropical conditions may be severe [5] and may be complicated by septicaemia.

Cutaneous gangrene ('varicella gangrenosa') may follow secondary infection, but rarely extensive local gangrene may occur with or in the absence of proven bacterial involvement, and sometimes during a mild attack of varicella [6,7] Thrombocytopenic purpura, beginning on the fifth to 10th day and usually recovering spontaneously after 3 or 4 months, occasionally follows otherwise benign varicella.

Rhabdomyolysis has been reported in association with varicella [8].

Viral arthritis during varicella has been reported [9], although bacterial arthritis also occurs.

Reye's syndrome has been associated with preceding varicella [10].

Stevens–Johnson syndrome occurring as a consequence of varicella infection has been reported [11], and should be considered if bullae develop in addition to the typical vesicles of chickenpox. Treatment with systemic corticosteroids, in addition to aciclovir, may be necessary. Erythema multiforme has been reported immediately prior to the eruption of chickenpox or zoster [12].

Varicella in immunocompromised people may be severe and progressive with a mortality of 7–10%. Features associated with a progressive varicella include haemorrhagic varicella, pneumonitis, hepatitis, encephalitis and acute retinal necrosis syndrome. Chronic varicella with persistent hyperkeratotic lesions [13] and repeated attacks of varicella have also been observed.

Zoster

The first manifestation of zoster is usually pain, which may be severe, and may be accompanied by fever, headache, malaise and tenderness localized to areas of one or more dorsal roots. The pain may be sharply localized to the same area but may be more diffuse. The time between the start of the pain and the onset of the eruption averages 1.4 days in trigeminal zoster and 3.2 days in thoracic disease. Closely grouped red papules, rapidly becoming vesicular and then pustular, develop in a continuous or interrupted band in the area of one, occasionally two and, rarely, more contiguous dermatomes. Mucous membranes within the affected dermatomes are also involved. New vesicles continue to appear for several days. Often in children, and occasionally in adults, the eruption is the first indication of the attack. The lymph nodes draining the affected area are enlarged and tender. The pain and the constitutional symptoms subside gradually as the eruption disappears. In uncomplicated cases recovery is complete in 2–3 weeks in children and young adults, and 3–4 weeks in older patients.

Occasionally the pain is not followed by the eruption ('zoster sine eruptione') [14].

The thoracic (53%), cervical (usually C.2,3,4, 20%), trigeminal, including ophthalmic (15%) and lumbosacral (11%) (Fig. 33.13) dermatomes are most commonly involved at all ages, but the relative frequency of ophthalmic zoster increases in old age. Rarely, the eruption may be bilateral.

In some 16% of patients with zoster, vesicles develop beyond the dermatome involved within a few days of the local eruption. This is more common in the elderly but in most cases only a few lesions appear and the course of the zoster is unchanged. In patients with lymphomas or who are otherwise immunocompromised, generalized varicella ('disseminated zoster') develops and may be haemorrhagic. Rarely in such cases the zoster may successively involve further dermatomes. Systemic involvement may follow and can be fatal.



Fig. 33.13 Zoster of trunk. (Courtesy of York District Hospital, UK.)

In the elderly and undernourished the local eruption often becomes necrotic, and healing, which may require many weeks, may be followed by severe scarring. In the otherwise healthy child, zoster usually runs a benign course.

In immunosuppressed individuals, especially due to HIV infection, zoster may run a protracted course, with a small number of lesions developing into verrucous or crusted nodules (see Chapter 35).

Variations in the zoster syndrome depend on which dorsal root is involved, on the intensity of its involvement and on the extension of the inflammatory changes into the motor root and anterior horn cells. Visceral involvement may be responsible for abdominal pain, pleural pain or temporary electrocardiographic abnormalities with or without precordial pain [15].

Motor involvement [16]. This occurs overall in 5% of cases and is commoner in older patients and in those with malignancy, and in cranial compared with spinal nerve involvement. The motor weakness usually follows the pain and the eruption, by a few days to a few weeks, but occasionally precedes or accompanies them. The affected segment is usually but not always the same. Complete recovery is expected in 55% and significant improvement in a further 30%. Facial palsy in herpes zoster oticus is discussed below. In ophthalmic zoster, ocular or facial palsies may occur [17]. Zoster of the anogenital area may be associated with disturbances of defecation or urination [18].

Trigeminal nerve zoster. In ophthalmic nerve zoster (Fig. 33.14), the eye is affected in two-thirds of cases, especially when vesicles on the side of the nose indicate involvement of the nasociliary



Fig. 33.14 Ophthalmic zoster. (Courtesy of York District Hospital, UK.)

nerve (Hutchinson's sign). Ocular complications include uveitis, keratitis, conjunctivitis, conjunctival oedema (chemosis), ocular muscle palsies, proptosis, scleritis (which may be acute or delayed for 2–3 months), retinal vascular occlusion, and ulceration, scarring and even necrosis of the lid. Involvement of the ciliary ganglia may give rise to Argyll–Robertson pupil.

Zoster of the maxillary division of the trigeminal nerve produces vesicles on the uvula and tonsillar area, whilst with involvement of the mandibular division, the vesicles appear on the anterior part of the tongue, the floor of the mouth and the buccal mucous membrane. In orofacial zoster, toothache may be the presenting symptom.

Herpes zoster oticus. The facial nerve, mainly a motor nerve, has vestigial sensory fibres supplying the external ear (including pinna and meatus) and the tonsillar fossa and adjacent soft palate. Classical sensory nerve zoster in these fibres causes pain and vesicles in part or all of that distribution, though the skin involvement may be minimal and limited to the external auditory meatus. To what extent other neural elements are actually infected is debated, but swelling of the infected sensory fibres in their course through the confined spaces of the facial canal and the internal auditory meatus, leading to compression of adjacent neural structures, can explain the commonly associated features [19,20]. Thus, pressure on the facial nerve motor fibres adds facial palsy, which with the ear pain and associated vesicles completes the classical triad of the Ramsay–Hunt syndrome; compression of the vestibulocochlear nerve may cause sensorineural hearing loss, dizziness and vertigo; and involvement of the nervus intermedius or its geniculate ganglion would impair taste sensation from the anterior two-thirds of the tongue and alter lacrimation.

Herpes zoster oticus accounts for about 10% of cases of facial palsy. The paralysis is usually complete and full recovery occurs in only about 20% of untreated cases.

Post-herpetic neuralgia [21]. The commonest and most intractable sequel of zoster is post-herpetic neuralgia, generally defined as persistence or recurrence of pain more than a month after the onset of zoster, but better considered after 3 months. It is unusual in childhood and increases in incidence and severity with age. It occurs in about 30% of patients over 40 and is most frequent when the trigeminal nerve is involved. It is more likely to develop if there was prolonged dermatomal pain prior to the eruption, if the acute pain of zoster was severe and if the zoster rash was prolonged [22]. The pain has two main forms, a continuous burning pain with hyperaesthesia, and a spasmodic shooting type, but a pruritic 'crawling' paraesthesia may also occur. Allodynia, pain caused by normally innocuous stimuli, is often the most distressing symptom and occurs in 90% of people with post-herpetic neuralgia. The neuralgia varies in intensity from inconvenient to profoundly disabling.

Other complications.

1 Scar sarcoid [23] and other granulomas including granuloma annulare [24] and fungal granulomas [25] have been reported in healed zoster scars.
2 Bacterial infection of damaged skin.
3 Encephalitis or meningoencephalitis; this is more common in the elderly, the immunosuppressed and in association with disseminated zoster.
4 Acute retinal necrosis syndrome; this rare complication follows an attack of shingles affecting the ophthalmic nerve or an unrelated dermatome [26].
5 Guillain–Barré syndrome and transverse myelitis have also been noted occasionally following zoster.

References

1 de S-GL, Machado CG, Angulo JJ. Anomalous clinical pictures of varicella. *Postgrad Med J* 1963; **39**: 91–3.
2 Leung AK, Kao CP, Sauve RS. Scarring resulting from chickenpox. *Pediatr Dermatol* 2001; **18**: 378–80.
3 Rice P, Simmons K, Carr R *et al.* Near fatal chickenpox during prednisolone treatment. *BMJ* 1994; **309**: 1069–70.
4 Guess HA, Broughton DD, Melton LJ 3rd *et al.* Population-based studies of varicella complications. *Pediatrics* 1986; **78**: 723–7.
5 Maretic Z, Cooray MP. Comparisons between chickenpox in a tropical and a European country. *J Trop Med Hyg* 1963; **66**: 311–5.
6 Illingworth RS, Zachary RB. Superficial gangrene of the skin in chickenpox. *Arch Dis Child* 1955; **30**: 177–9.
7 Cortes JR, Arratia JA, Jaime R. A 12-month-old infant with Fournier gangrene associated with varicella. *Pediatr Emerg Care* 2007; **23**: 719–20.
8 al-Langawi M, al-Marri MR, al Soub H. Rhabdomyolysis associated with varicella infection. *Int J Clin Pract* 2001; **55**: 484–5.
9 Chen MK, Wang CC, Lu JJ *et al.* Varicella arthritis diagnosed by polymerase chain reaction. *J Formos Med Assoc* 1999; **98**: 519–21.
10 Lichtenstein PK, Heubi JE, Daugherty CC *et al.* Grade I Reye's syndrome. A frequent cause of vomiting and liver dysfunction after varicella and upper-respiratory-tract infection. *N Engl J Med* 1983; **309**: 133–9.
11 Bay A, Akdeniz N, Calka O *et al.* Primary varicella infection associated with Stevens-Johnson syndrome in a Turkish child. *J Dermatol* 2005; **32**: 745–50.
12 Prais D, Grisuru-Soen G, Barzilai A *et al.* Varicella zoster virus infection associated with erythema multiforme in children. *Infection* 2001; **29**: 37–9.
13 Nikkels AF, Snoeck R, Rentier B *et al.* Chronic verrucous varicella zoster virus skin lesions: clinical, histological, molecular and therapeutic aspects. *Clin Exp Dermatol* 1999; **24**: 346–53.
14 Rifkind D. The activation of varicella-zoster virus infections by immunosuppressive therapy. *J Lab Clin Med* 1966; **68**: 463–74.
15 Bilimoria S, Hutton WN, Keczkes K. Herpes zoster and electrocardiographic changes. *Br J Clin Pract* 1982; **36**: 404, 407.

16 Akiyama N. Herpes zoster infection complicated by motor paralysis. *J Dermatol* 2000; **27**: 252–7.
17 Marsh RJ, Dulley B, Kelly V. External ocular motor palsies in ophthalmic zoster: a review. *Br J Ophthalmol* 1977; **61**: 677–82.
18 Fugelso PD, Reed WB, Newman SB *et al.* Herpes zoster of the anogenital area affecting urination and defaecation. *Br J Dermatol* 1973; **89**: 285–8.
19 Aleksic SN, Budzilovich GN, Lieberman AN. Herpes zoster oticus and facial paralysis (Ramsay Hunt syndrome). Clinico-pathologic study and review of literature. *J Neurol Sci* 1973; **20**: 149–59.
20 Sweeney CJ, Gilden DH. Ramsay Hunt syndrome. *J Neurol Neurosurg Psychiatry* 2001; **71**: 149–54.
21 Kost RG, Straus SE. Postherpetic neuralgia—pathogenesis, treatment, and prevention. *N Engl J Med* 1996; **335**: 32–42.
22 Volpi A, Gatti A, Pica F *et al.* Clinical and psychosocial correlates of post-herpetic neuralgia. *J Med Virol* 2008; **80**: 1646–52.
23 Watanabe D, Kuhara T, Ishida N *et al.* Sarcoid tissue reaction on herpes zoster scars in a myelodysplastic syndrome patient: Wolf's isotopic response. *J Eur Acad Dermatol Venereol* 2009: 475–7.
24 Ruocco E, Baroni A, Cutri FT *et al.* Granuloma annulare in a site of healed herpes zoster: Wolf's isotopic response. *J Eur Acad Dermatol Venereol* 2003; **17**: 686–8.
25 Huang CW, Tu ME, Wu YH *et al.* Isotopic response of fungal granuloma following facial herpes zoster infections—report of three cases. *Int J Dermatol* 2007; **46**: 1141–5.
26 Sellitti TP, Huang AJ, Schiffman J *et al.* Association of herpes zoster ophthalmicus with acquired immunodeficiency syndrome and acute retinal necrosis. *Am J Ophthalmol* 1993; **116**: 297–301.

Diagnosis. The distinctive features of varicella are the centripetal distribution, the polymorphism in each affected site and the rapid progression of the individual lesion from vesicle to crust. Typical zoster presents few difficulties once the eruption has developed and can be confused only with zosteriform herpes simplex (see p. 33.18). This diagnosis should be excluded by culture or PCR in apparently recurrent zoster.

The virus is readily identified by electron microscopy of vesicle fluid and can be grown in tissue culture but this takes longer and is less reliable than for HSV. Detection of VZV antigen by direct fluorescent-antibody staining of a smear or of VZV DNA by PCR in a scraping from the base of a vesicle offers an alternative method. Titration of complement-fixing antibody in acute and convalescent sera may be a useful test in atypical infections. PCR analysis can permit detection of VZV and is particularly useful in patients with suspected encephalomyelitis, in whom examination of the cerebrospinal fluid can lead to rapid diagnosis [1]. In skin biopsies, the VZV proteins can be detected by immunohistochemistry [2], and the viral nucleic acid by *in situ* hybridization [3] or PCR of extracted DNA [4].

Prevention. This can be by pre-exposure vaccination, post-exposure immunoglobulin and antiviral prophylaxis.

Pre-exposure prophylaxis. A live attenuated vaccine developed from the Oka strain of VZV is effective in preventing varicella in healthy children [5]. The vaccine is given in two doses, 3 months apart, resulting in approximately 90% seroconversion with 75% of responding recipients maintaining detectable antibody for up to 10 years. The vaccine has been used in Japan and the USA for over 10 years, but is not in routine use in the UK. Given in childhood, the vaccine does not appear to affect the incidence of zoster in adulthood [6]. The vaccine can also be used in children with HIV and a $CD4^+$ count of at least 200 cells/μl [7] or children with leukaemia in remission for whom it produces a seroconversion rate of over 80% and reduces the incidence and severity of varicella [8].

Post-exposure prophylaxis. Specific zoster immune globulin (ZIG) administered within 10 days of contact reduces the severity of varicella but does not always prevent it [9]. It should be given to neonates whose mothers develop varicella within the period from 7 days before to 7 days after delivery [10]. Some advocate additional intravenous aciclovir, for the mother before delivery and the baby after delivery [11–13]. Zoster immune globulin is also indicated for healthy neonates in contact with active chicken pox or zoster, and for immunocompromised children and adults, for example organ-transplant recipients and patients who have taken oral steroids for at least 14 days within the previous 3 months who have not had previous chickenpox, if exposed to varicella or zoster [14]. It should also be given to exposed non-immune pregnant women not only to reduce the severity of chickenpox but also to reduce the risk of fetal transmission in those women who develop disease despite ZIG prophylaxis.

In later life, immunity against VZV wanes but may be boosted intermittently following contact with chickenpox. Boosting by vaccination can help to reduce the occurrence or severity of zoster or the risk of post-herpetic neuralgia [15]. The zoster vaccine is the same as the varicella vaccine but at a higher virus titre.

Antiviral prophylaxis. In the immunocompetent person, aciclovir given from about 9 days after exposure for 1 week appears to be effective in aborting or reducing the severity of chickenpox and allows immunity to develop. In the immunocompromised, such prophylaxis only delays the onset of the disease. Prophylaxis with aciclovir is effective in preventing zoster in the early months following bone-marrow transplantation [16] and is also advocated for long-term prophylaxis at low dose [17].

Treatment [15,16]. Varicella in the otherwise healthy child requires only symptomatic treatment. Some advocate the use of aciclovir in childhood chickenpox to reduce the severity and duration of the eruption [18]. Rest and analgesics are sufficient for mild attacks of zoster in the young. Soothing antiseptic applications may be helpful and secondary bacterial infection will require antibiotics.

An antiviral is indicated for varicella in adults and for severe varicella or zoster infections at any age in the immunocompromised. Treatment should be started as early as possible, preferably within the first 1 or 2 days. The virus is less sensitive to aciclovir *in vitro* than HSV and higher doses are usually recommended, typically 10 mg/kg or 500 mg/m^2 8-hourly intravenously [19] or 4 g per day orally [20]. Courses of 5, 7 and 10 days have been used and some advocate a change from intravenous to oral drug after 48 hours. In general practice, zoster is often treated with aciclovir 800 mg five times a day for 7–10 days or with valaciclovir 1 g or famciclovir 250 or 500 mg three times a day for 7 days. Such treatment prevents progression of the eruption, reduces the systemic complications of varicella and zoster, lessens zoster pain

during treatment and can reduce the risk of development of post-herpetic neuralgia [21]. In patients over 50 years old, famciclovir (500–750 mg three times a day for 7 days) started within 72 hours of the onset of shingles has also been shown to decrease the duration of post-herpetic neuralgia by approximately 2 months [22].

If the first division of the trigeminal nerve is involved, there is a risk of damage to the eye, and antiviral therapy and ophthalmological advice is indicated.

Studies of the benefits of corticosteroid therapy together with aciclovir in the treatment of shingles have given conflicting results. One study in immunologically normal patients found that, in conjunction with aciclovir, prednisolone 40 mg daily tailed off over the next 3 weeks hastened the return to normal activity, better sleep and reduced the time analgesia was required [23]. Another study [24] concluded that the addition of prednisolone conferred only a slight benefit on the rate of healing and reduction of acute pain but at the expense of an increase in adverse effects. Without antiviral cover, serious dissemination of infection due to systemic steroids is a risk.

In the treatment of herpes zoster oticus (Ramsay–Hunt syndrome), steroid therapy is better established, probably because of the central importance of inflammatory swelling in its pathogenesis. A combination of aciclovir plus prednisolone may give best results [25].

For post-herpetic *neuralgia* the use of opiates should be avoided if possible but the disorder can be prolonged and debilitating [26]. A tricyclic antidepressant such as amitriptyline [27] or nortriptylene (or clomipramine or doxepin) is useful, especially for hyperaesthesia and constant burning pain, an effect independent of any antidepressant activity. For best results, it should be given early in a dose of 25 mg daily and continued for 3–6 months. These adrenergically active antidepressants may be most effective if antiviral treatment is given during the acute attack of shingles. For stabbing pain, sodium valproate (or other anticonvulsant, e.g. clonazepam or carbamazepine) is of value. Especially in the elderly, doses should be low initially and increased every few days as required. Gabapentin or pregabalin can be useful analgesics for the pain [28]. Topical capsaicin 0.025%, a substance P depleter, may relieve pain in some patients, though its usefulness in some is limited by a burning sensation following application or increased area of allodynia [29]. Topical anaesthetic applied as a cream or a patch can also give relief [30,31].

References

1 Puchhammer-Stockl E, Popow-Kraupp T, Heinz FX *et al.* Detection of varicella-zoster virus DNA by polymerase chain reaction in the cerebrospinal fluid of patients suffering from neurological complications associated with chicken pox or herpes zoster. *J Clin Microbiol* 1991; **29**: 1513–6.

2 Coffin SE, Hodinka RL. Utility of direct immunofluorescence and virus culture for detection of varicella-zoster virus in skin lesions. *J Clin Microbiol* 1995; **33**: 2792–5.

3 Annunziato P, Lungu O, Gershon A *et al.* In situ hybridization detection of varicella zoster virus in paraffin-embedded skin biopsy samples. *Clin Diagn Virol* 1996; **7**: 69–76.

4 Schmutzhard J, Merete Riedel H, Zweygberg Wirgart B *et al.* Detection of herpes simplex virus type 1, herpes simplex virus type 2 and varicella-zoster virus in skin lesions. Comparison of real-time PCR, nested PCR and virus isolation. *J Clin Virol* 2004; **29**: 120–6.

5 Weibel RE, Neff BJ, Kuter BJ *et al.* Live attenuated varicella virus vaccine. Efficacy trial in healthy children. *N Engl J Med* 1984; **310**: 1409–15.

6 Hambleton S, Steinberg SP, Larussa PS *et al.* Risk of herpes zoster in adults immunized with varicella vaccine. *J Infect Dis* 2008; 197 Suppl **2**: S196–9.

7 Levin MJ, Gershon AA, Weinberg A *et al.* Administration of live varicella vaccine to HIV-infected children with current or past significant depression of CD4(+) T cells. *J Infect Dis* 2006; **194**: 247–55.

8 Gershon AA, Steinberg SP. Persistence of immunity to varicella in children with leukemia immunized with live attenuated varicella vaccine. *N Engl J Med* 1989; **320**: 892–7.

9 Geiser CF, Bishop Y, Myers M *et al.* Prophylaxis of varicella in children with neoplastic disease: comparative results with zoster immune plasma and gamma globulin. *Cancer* 1975; **35**: 1027–30.

10 Committee on Infectious Diseases. Expanded guidelines for use of varicella-zoster immune globulin. *Pediatrics* 1983; **72**: 886–9.

11 Carter PE, Duffy P, Lloyd DJ. Neonatal varicella infection. *Lancet* 1986; **2**: 1459–60.

12 Sills JA, Galloway A, Amegavie L *et al.* Acyclovir in prophylaxis and perinatal varicella. *Lancet* 1987; **1**: 161.

13 Huang YC, Lin TY, Lin YJ *et al.* Prophylaxis of intravenous immunoglobulin and acyclovir in perinatal varicella. *Eur J Pediatr* 2001; **160**: 91–4.

14 Centers for Disease Control. Varicella-zoster immune globulin for the prevention of chickenpox. Recommendations of the Immunization Practices Advisory Committee, Centers for Disease Control. *Ann Intern Med* 1984; **100**: 859–65.

15 Oxman MN, Levin MJ, Johnson GR *et al.* A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med* 2005; **352**: 2271–84.

16 Perren TJ, Powles RL, Easton D *et al.* Prevention of herpes zoster in patients by long-term oral acyclovir after allogeneic bone marrow transplantation. *Am J Med* 1988; **85**: 99–101.

17 Asano-Mori Y, Kanda Y, Oshima K *et al.* Long-term ultra-low-dose acyclovir against varicella-zoster virus reactivation after allogeneic hematopoietic stem cell transplantation. *Am J Hematol* 2008; **83**: 472–6.

18 Balfour HH Jr, Edelman CK, Anderson RS *et al.* Controlled trial of acyclovir for chickenpox evaluating time of initiation and duration of therapy and viral resistance. *Pediatr Infect Dis J* 2001; **20**: 919–26.

19 Al-Nakib W, Al-Kandari S, El-Khalik DM *et al.* A randomised controlled study of intravenous acyclovir (Zovirax) against placebo in adults with chickenpox. *J Infect* 1983; **6**: 49–56.

20 Feder HM Jr. Treatment of adult chickenpox with oral acyclovir. *Arch Intern Med* 1990; **150**: 2061–5.

21 Jackson JL, Gibbons R, Meyer G *et al.* The effect of treating herpes zoster with oral acyclovir in preventing postherpetic neuralgia. A meta-analysis. *Arch Intern Med* 1997; **157**: 909–12.

22 Dworkin RH, Boon RJ, Griffin DR *et al.* Postherpetic neuralgia: impact of famciclovir, age, rash severity, and acute pain in herpes zoster patients. *J Infect Dis* 1998; **178** (Suppl. 1): S76–80.

23 Whitley RJ, Gnann JW Jr, Weiss HL *et al.* Unique clinical trial design: combination acyclovir plus prednisone therapy of localized zoster in the normal host. *Antiviral Res* 1996; **29**: 67–8.

24 Wood MJ, Johnson RW, McKendrick MW *et al.* A randomized trial of acyclovir for 7 days or 21 days with and without prednisolone for treatment of acute herpes zoster. *N Engl J Med* 1994; **330**: 896–900.

25 Stafford FW, Welch AR. The use of acyclovir in Ramsay Hunt syndrome. *J Laryngol Otol* 1986; **100**: 337–40.

26 Young L. Post-herpetic neuralgia: a review of advances in treatment and prevention. *J Drugs Dermatol* 2006; **5**: 938–41.

27 Robertson DR, George CF. Treatment of post herpetic neuralgia in the elderly. *Br Med Bull* 1990; **46**: 113–23.

28 Sabatowski R, Galvez R, Cherry DA *et al.* Pregabalin reduces pain and improves sleep and mood disturbances in patients with post-herpetic neuralgia: results of a randomised, placebo-controlled clinical trial. *Pain* 2004; **109**: 26–35.

29 Petersen KL, Fields HL, Brennum J *et al.* Capsaicin evoked pain and allodynia in post-herpetic neuralgia. *Pain* 2000; **88**: 125–33.

30 Litman SJ, Vitkun SA, Poppers PJ. Use of EMLA cream in the treatment of post-herpetic neuralgia. *J Clin Anesth* 1996; **8**: 54–7.

31 Rowbotham MC, Davies PS, Verkempinck C *et al.* Lidocaine patch: double-blind controlled study of a new treatment method for post-herpetic neuralgia. *Pain* 1996; **65**: 39–44.

Cytomegalovirus

Aetiology and epidemiology. Cytomegalovirus (CMV) infections are common throughout the world and are usually inapparent. Primary infection is followed by lifelong carriage of the virus with intermittent shedding in various secretions. This may be increased by physiological stimuli such as pregnancy, and by immune suppression due to disease or therapy as in AIDS and transplant recipients, respectively.

Depending on socioeconomic conditions, between 40 and 100% of adults in a community are infected as shown by seropositivity. There are several ways of transmitting CMV which are to some extent age dependent. Intrauterine transmission occurs in 0.1–1.0% of births. Perinatal and neonatal infections arise as a result of exposure to infectious cervical secretions in the birth canal or from infected breast milk. Pre-school children may acquire CMV from oral secretions or urine of other infected infants. At an older age, sexual transmission is important. Blood transfusion is also a source of CMV, the virus being associated mainly with neutrophils. CMV may be transmitted in transplanted organs from CMV seropositive donors.

Clinical features [1,2].

Congenital CMV infection. Primary infection in the first or second trimester of pregnancy can have multiple effects on the fetus. In its most severe form there are hepatosplenomegaly, jaundice and purpura. Most cases die within 2 months and survivors usually have severe neurological damage. There may be erythropoietic tissue in the dermis derived from undifferentiated dermal mesenchyme; this presents as purple or red papules or nodules lasting 4–6 weeks ('blueberry muffin' lesions). Vesicles very rarely occur in congenital CMV disease [3]. About 15% of congenitally infected infants will have long-term neurological sequelae, especially deafness.

CMV mononucleosis. In the otherwise healthy child or adult there is usually no clinical disturbance. When symptoms do appear they resemble infectious mononucleosis with fever, lymphocytosis and mildly deranged liver function, although lymphadenopathy and splenomegaly are not usually striking. In up to a third of cases, there is a follicular, maculopapular or rubelliform eruption, often affecting the legs and lasting up to 2 days. Urticaria may occur [4]. As in Epstein–Barr virus (EBV) infectious mononucleosis, ampicillin commonly triggers a widespread eruption. Lymphocytic vasculitis manifesting as papules and plaques in a partly annular configuration, with livedo reticularis, has been described in a 7-year-old girl with CMV mononucleosis [5]. Lipschütz ulcers, more commonly associated with EBV infection, have occurred with primary CMV infection [6].

Other associations of CMV infection. CMV has been suggested as the precipitating factor in a scleroedema, scleroderma, systemic sclerosis, vitiligo and alopecia areata, but these associations are unproven. Gianotti–Crosti syndrome [7,8] (see p. 33.77) and papular purpuric 'gloves and socks' syndrome [9] (see p. 33.76) may occur together with CMV infection.

CMV in the immunosuppressed. CMV infection in the immunocompromised can be severe and even fatal, with pneumonitis, hepatitis, gastrointestinal ulceration, retinitis and superinfection with other opportunistic pathogens. Neurological complications include encephalitis, myelitis and especially myeloradiculitis when the peripheral nerve roots are infiltrated with lymphocytes in AIDS.

Skin lesions may occur in disseminated CMV infection [10], a characteristic histological feature of which is the presence of cytomegalic cells in vascular endothelium. This may progress in some cases to vasculitis. The dermatological features include a widespread eruption that may become papular and purpuric, with vesiculobullous or pustular lesions and indurated pigmented nodules or plaques [11]. Sharply demarcated ulceration may occur, mostly around the genitalia, perineum, buttocks and thighs [12]. Keratotic skin lesions and severe oral and skin ulceration have been reported [13–15], especially in AIDS.

Following a course of antiviral treatment of CMV in immunosuppressed or immunocompromised people, relapsing infection and progression of organ involvement may occur.

Diagnosis. Classically, the infection was diagnosed histologically by finding typical intranuclear inclusions surrounded by a clear halo in enlarged cells. This method is relatively insensitive, but with the addition of immunohistochemistry, cytomegalic inclusions are more readily demonstrable. Virus isolation from throat washings, urine, bronchoalveolar lavage fluid, blood or biopsy material is carried out in human embryo fibroblast cells, but it takes 5–28 days to produce a cytopathic effect seen as 'owl eye' nuclear inclusions. This can be accelerated by looking for CMV early antigen after 24–48 h culture. Rapid methods with greater sensitivity include direct detection of CMV antigenaemia and the viral DNA detection by PCR [16]. Primary infection can be diagnosed serologically by the appearance of CMV IgM and IgG antibodies. Congenital CMV can only be diagnosed confidently by virus isolation or the presence of CMV IgM antibody within 3 weeks of birth.

Treatment. Most CMV infections do not require specific therapy, but in life-threatening situations or when CMV retinitis threatens sight, two antiviral agents—ganciclovir and foscarnet—have been used with some success. Valganciclovir, a prodrug of ganciclovir, is used as prophylactic treatment in CMV antibody-negative transplant recipients receiving a solid organ from a CMV-positive donor and has also been reported to be effective as treatment for acute or recurrent CMV disease [17].

References

1 Lesher JL Jr. Cytomegalovirus infections and the skin. *J Am Acad Dermatol* 1988; **18**: 1333–8.

2 Drago F, Aragone MG, Lugani C *et al.* Cytomegalovirus infection in normal and immunocompromised humans. A review. *Dermatology* 2000; **200**: 189–95.

3 Blatt J, Kastner O, Hodes DS. Cutaneous vesicles in congenital cytomegalovirus infection. *J Pediatr* 1978; **92**: 509.

4 Humphreys DM, Myers A. Cytomegalovirus mononucleosis with urticaria. *Postgrad Med J* 1975; **51**: 404–6.

5 Weigand DA, Burgdorf WH, Tarpay MM. Vasculitis in cytomegalovirus infection. *Arch Dermatol* 1980; **116**: 1174–6.

6 Martín JM, Godoy R, Calduch L *et al.* Lipschütz acute vulval ulcers associated with primary cytomegalovirus infection. *Pediatr Dermatol* 2008; **25**: 113–5.
7 Berant M, Naveh Y, Weissman I. Papular acrodermatitis with cytomegalovirus hepatitis. *Arch Dis Child* 1983; **58**: 1024–5.
8 Taïeb A, Plantin P, Du Pasquier P *et al.* Gianotti-Crosti syndrome: a study of 26 cases. *Br J Dermatol* 1986; **115**: 49–59.
9 Carrascosa JM, Bielsa I, Ribera M *et al.* Papular-purpuric gloves-and-socks syndrome related to cytomegalovirus infection. *Dermatology* 1995; **191**: 269–70.
10 Pariser RJ. Histologically specific skin lesions in disseminated cytomegalovirus infection. *J Am Acad Dermatol* 1983; **9**: 937–46.
11 AbdullGaffar B, Raman LG, Al Muala A. Cutaneous cytomegalovirus infection in a patient with acquired immunodeficiency syndrome. *Int J Dermatol* 2008; **47**: 944–6.
12 Kaisar MO, Kirwan RM, Strutton GM *et al.* Cutaneous manifestations of cytomegalovirus disease in renal transplant recipients: a case series. *Transpl Infect Dis* 2008; **10**: 209–13.
13 Bournerias I, Boisnic S, Patey O *et al.* Unusual cutaneous cytomegalovirus involvement in patients with acquired immunodeficiency syndrome. *Arch Dermatol* 1989; **125**: 1243–6.
14 Syränen S, Leimola-Virtanen R, Schmidt-Westhausen A *et al.* Oral ulcers in AIDS patients frequently associated with cytomegalovirus (CMV) and Epstein–Barr virus (EBV) infections. *J Oral Pathol Med* 1999; **28**: 204–9.
15 Colsky AS, Jegasothy SM, Leonardi C *et al.* Diagnosis and treatment of a case of cutaneous cytomegalovirus infection with a dramatic clinical presentation. *J Am Acad Dermatol* 1998; **38**: 349–51.
16 Engelmann I, Petzold DR, Kosinska A *et al.* Rapid quantitative PCR assays for the simultaneous detection of herpes simplex virus, varicella zoster virus, cytomegalovirus, Epstein–Barr virus, and human herpesvirus 6 DNA in blood and other clinical specimens. *J Med Virol* 2008; **80**: 467–77.
17 Len O, Gavalda J, Aguado JM *et al.* Valganciclovir as treatment for cytomegalovirus disease in solid organ transplant recipients. *Clin Infect Dis* 2008; **46**: 20–7.

Epstein–Barr virus

Epstein–Barr virus (EBV) usually infects B lymphocytes and occasionally T lymphocytes or squamous epithelial cells. This tropism depends on the expression on the cell surface of the complement receptor 2 (CR2/CD21 molecule which interacts with complement C3d), to which the virus must bind before gaining entry to the cell [1].

Primary infection is followed by lifelong persistence of the virus in a latent state in resting B cells. Under certain conditions, these cells are activated when a range of viral and cellular proteins are expressed. In those EBV-infected B cells that undergo terminal differentiation or apoptosis, viral replication occurs and the cells die. No latent infection takes place in epithelial cells, although persistent infection with viral shedding may occur. In the oropharynx, liberation of virus into the saliva from localized differentiated B cells explains the spread of infection between individuals.

EBV is associated with nasopharyngeal carcinoma and with various B-lymphoproliferative lesions.

Epidemiology. In all populations, the great majority of people are infected with EBV by middle age [2]. In early childhood the virus is probably spread by contact with saliva on fingers or fomites, and in economically disadvantaged societies most infection is acquired at this stage. In more developed communities, early childhood infection is less frequent and primary infection occurs most commonly in early adult life, when kissing is the usual route of infection, though occasional droplet spread may occur. Most primary infection, especially in childhood, is asymptomatic or mild, but when it is delayed to adolescence or adulthood, clinically obvious infectious mononucleosis is more frequent [3].

Infectious mononucleosis

Synonym
- Glandular fever

Clinical features. Infectious mononucleosis is characterized by fever, sore throat with exudative pharyngotonsillitis and lymphadenopathy. Enlargement of the spleen has been recorded in about half of those acutely infected. There is a lymphocytosis with at least 10% atypical cells, and usually some abnormalities in liver-function tests indicating hepatocellular damage which results in jaundice in about 4% of those infected. Petechiae at the junction of the hard and soft palate are a distinctive feature of the disease and usually appear on the second or third day of fever.

An exanthem occurs in about 10% of cases, usually between the fourth and sixth days. Most common is a macular or maculopapular eruption of trunk or upper arms, involving face and forearms in some cases and thighs and legs occasionally. Morbilliform and scarlatiniform eruptions are sometimes seen. Acute urticaria is occasionally a presenting feature [4]. Skin lesions fade after a few days. If ampicillin is taken during the course of the illness, an extensive maculopapular or morbilliform eruption develops in over 90% of cases, 7–10 days after the start of treatment. A similar effect is occasionally seen with penicillin, tetracyclines and azithromycin [5].

Cold agglutinins are common in infectious mononucleosis, usually without clinical manifestations, but they might explain occasional cases of transient cold urticaria [6] which may occasionally be severe enough to result in ulceration [7].

Thrombocytopenic purpura is common but counts below 100 000/μl are fortunately rare. Splenic rupture and encephalitis are life-threatening complications.

Diagnosis. Diagnosis can be made by examination of a blood film for abnormal lymphocytes [8]. Tests for heterophile antibodies which agglutinate sheep or horse red blood cells become positive in 90% of patients after 1–2 weeks. This (the Paul–Bunnell) test occasionally gives false positives and is less reliable in childhood. During the infection, antibody to EBV viral capsid antigen is produced, IgM class antibody persists for a few months and IgG antibody for life. Virus isolation is a specialized technique not performed by most diagnostic laboratories but viral DNA detection by PCR in blood or tissue or *in situ* hybridization of tissue are methods which can be applied in unusual cases [9].

Lymphomas and lymphoproliferative disorders associated with EBV

EBV infection is implicated as a pathogenic factor in several proliferative and malignant disorders of the lymphoid system:

1 Burkitt's lymphoma, occurring in equatorial Africa and New Guinea, which presents classically with huge cervical lymphadenopathy.
2 Nasopharyngeal carcinoma, reported mainly in Asia, is often preceded by prolonged elevation of antibodies against EBV.
3 B-cell tumours, histologically characterized as large-cell lymphomas, which occur in immunocompromised people and

especially immunosuppressed transplant recipients. In transplant recipients, EBV-associated post-transplant lymphoproliferative disease (PTLD) occurs in 0.5–1.5% of the recipients of solid organs. Skin involvement, when present, usually presents with single or multiple papules or nodules and in rare cases the skin is the primary site of disease. There are rare reports of EBV-associated B-cell lymphoma in individuals without immunosuppression [10].

4 Natural killer (NK)/T-cell lymphoma associated with EBV can involve skin, rarely as a predominantly cutaneous disease. Prolonged immunosuppression may be a predisposing factor. A notable presenting feature in some cases is hypersensitivity to mosquito bites and suggests chronic active EBV infection [11]. Papulonecrotic lesions, especially of the face, or severe hydroa vacciniforme-like lesions have been described as presenting features of NK/T cell malignancies [12,13]. Nodular lesions and panniculitis are also reported [14]. Very rarely, the lymphoma may be intravascular, producing dusky plaques or nodules [15]. The skin lesions may be found to contain EBV RNA. These cases have been reported most commonly in Asia.

Haemophagocytic syndrome (haemophagocytic lymphohistiocytosis)

Acute EBV infection can rarely lead to this very severe disease with a high mortality. It was first described in genetic immunodeficiency syndromes such as X-linked lymphoproliferative disease [16], but also occurs in immunosuppression associated with Hodgkin's lymphoma [17], or treatment for inflammatory disease [18] or following transplantation [19]. The syndrome in immunocompetent individuals was originally described in Japanese patients, but recent reports suggest that other races can be affected [20–22].

Infection of T lymphocytes or NK cells triggers T-cell proliferation and overactivity of NK cells with overproduction of cytokines, especially interferon-α and tumour necrosis factor-α. Investigations show a high viral EBV load in blood as well as elevated acute phase reaction proteins.

The presentation is usually with fever, followed by the development of pancytopenia with coagulation defects and multiorgan failure. Lymphadenopathy, hepatosplenomegaly and haemorrhage into lungs and bowel are common and cerebral symptoms of meningitis or encephalitis may develop. The cutaneous findings may relate to coagulation defects, but reported features can include a maculopapular rash with epidermal necrosis or nodules with granulomatous inflammation [23–25].

Treatment must include full supportive care and rapid commencement of immunosuppressive as well as antiviral therapy [24,26,27].

Other cutaneous manifestations of EBV

Oral hairy leukoplakia. This is an AIDS-associated lesion presenting as white plaques on the sides of the tongue (see Chapter 35). EBV replicates in maturing epithelial cells but is not present in basal and parabasal keratinocytes. Oral hairy leukoplakia is also reported to occur in patients receiving immunosuppressive therapy [28–30] and occasionally in immunocompetent individuals [31].

Gianotti–Crosti syndrome (see p. 33.77). EBV has been reported in association with this eruption, which is believed to be a reaction to viral infection in childhood [32,33].

Lipschütz ulcers. Painful genital ulceration occurring in adolescents without venereal infection [34] can be due to primary EBV infection [35]. The sloughy ulcers are often multiple and develop in association with malaise, fever and inguinal lymphadenopathy. They heal spontaneously but somewhat slowly.

Kikuchi's histiocytic necrotizing lymphadenitis. This may occur in association with EBV infection (see p. 33.77).

Other associations. There are reports of cases of EBV infection associated with a variety of reactive dermatoses: erythema multiforme [36], erythema nodosum [37], erythema annulare centrifugum [38], acute pityriasis lichenoides [39], chronic bullous disease of childhood [40], and a predominantly facial eruption resembling inflammatory granuloma annulare [41].

References

1 Sixbey JW, Davis DS, Young LS *et al.* Human epithelial cell expression of an Epstein–Barr virus receptor. *J Gen Virol* 1987; **68**: 805–11.

2 Hesse J, Ibsen KK, Krabbe S *et al.* Prevalence of antibodies to Epstein–Barr virus (EBV) in childhood and adolescence in Denmark. *Scand J Infect Dis* 1983; **15**: 335–8.

3 Andiman WA. The Epstein–Barr virus and EB virus infections in childhood. *J Pediatr* 1979; **95**: 171–82.

4 Cowdrey SC, Reynolds JS. Acute urticaria in infectious mononucleosis. *Ann Allergy* 1969; **27**: 182–7.

5 Dakdouki GK, Obeid KH, Kanj SS. Azithromycin-induced rash in infectious mononucleosis. *Scand J Infect Dis* 2002; **34**: 939–41.

6 Wu LY, Mesko JW, Petersen BH. Cold urticaria associated with infectious mononucleosis. *Ann Allergy* 1983; **50**: 271–4.

7 Barth JH. Infectious mononucleosis (glandular fever) complicated by cold agglutinins, cold urticaria and leg ulceration. *Acta Derm Venereol* 1981; **61**: 451–2.

8 Jenson HB. Virologic diagnosis, viral monitoring, and treatment of Epstein–Barr virus infectious mononucleosis. *Curr Infect Dis Rep* 2004; **6**: 200–7.

9 Hassan R, White LR, Stefanoff CG *et al.* Epstein–Barr virus (EBV) detection and typing by PCR: a contribution to diagnostic screening of EBV-positive Burkitt's lymphoma. *Diagn Pathol* 2006; **1**: 17.

10 Tokuda Y, Fukushima M, Nakazawa K *et al.* A case of primary Epstein–Barr virus-associated cutaneous diffuse large B-cell lymphoma unassociated with iatrogenic or endogenous immune dysregulation. *J Cutan Pathol* 2008; **35**: 666–71.

11 Tokura Y, Ishihara S, Tagawa S *et al.* Hypersensitivity to mosquito bites as the primary clinical manifestation of a juvenile type of Epstein–Barr virus-associated natural killer cell leukemia/lymphoma. *J Am Acad Dermatol* 2001; **45**: 569–78.

12 Cho KH, Kim CW, Heo DS *et al.* Epstein–Barr virus-associated peripheral T-cell lymphoma in adults with hydroa vacciniforme-like lesions. *Clin Exp Dermatol* 2001; **26**: 242–7.

13 Iwatsuki K, Satoh M, Yamamoto T *et al.* Pathogenic link between hydroa vacciniforme and Epstein–Barr virus-associated hematologic disorders. *Arch Dermatol* 2006; **142**: 587–95.

14 Abe Y, Muta K, Ohshima K *et al.* Subcutaneous panniculitis by Epstein–Barr virus-infected natural killer (NK) cell proliferation terminating in aggressive subcutaneous NK cell lymphoma. *Am J Hematol* 2000; **64**: 221–5.

15 Kuo TT, Chen MJ, Kuo MC. Cutaneous intravascular NK-cell lymphoma: report of a rare variant associated with Epstein–Barr virus. *Am J Surg Pathol* 2006; **30**: 1197–201.

16 Arico M, Imashuku S, Clementi R *et al.* Hemophagocytic lymphohistiocytosis due to germline mutations in SH2D1A, the X-linked lymphoproliferative disease gene. *Blood* 2001; **97**: 1131–3.

17 Menard F, Besson C, Rince P *et al.* Hodgkin lymphoma-associated hemophagocytic syndrome: a disorder strongly correlated with Epstein–Barr virus. *Clin Infect Dis* 2008; **47**: 531–4.
18 Hayakawa I, Shirasaki F, Ikeda H *et al.* Reactive hemophagocytic syndrome in a patient with polyarteritis nodosa associated with Epstein–Barr virus reactivation. *Rheumatol Int* 2006; **26**: 573–6.
19 Gurkan A, Yakupoglu U, Yavuz A *et al.* Hemophagocytic syndrome in kidney transplant recipients: report of four cases from a single center. *Acta Haematol* 2006; **116**: 108–13.
20 Sonke GS, Ludwig I, van Oosten H *et al.* Poor outcomes of chronic active Epstein–Barr virus infection and hemophagocytic lymphohistiocytosis in non-Japanese adult patients. *Clin Infect Dis* 2008; **47**: 105–8.
21 Berry PA, Bernal W, Pagliuca A *et al.* Multiple organ failure and severe bone marrow dysfunction in two 18 year-old Caucasian patients: Epstein–Barr virus and the haemophagocytic syndrome. *Anaesthesia* 2008; **63**: 1249–54.
22 Elazary AS, Wolf DG, Amir G *et al.* Severe Epstein–Barr virus-associated hemophagocytic syndrome in six adult patients. *J Clin Virol* 2007; **40**: 156–9.
23 Kawachi Y, Itoh M, Fujisawa Y *et al.* Epidermal cell necrosis with direct epidermal infiltration of Epstein–Barr virus (EBV)-encoded small nuclear RNA-positive T lymphocytes in a patient with EBV-associated haemophagocytic syndrome. *Br J Dermatol* 2007; **157**: 1053–6.
24 Lewkowicz E, Darnige L, Auffret N *et al.* Atypical skin lesions revealing an EBV-associated hemophagocytic syndrome after a large B cell lymphoma in complete remission. *Leuk Lymphoma* 2007; **48**: 421–4.
25 Brinkmeier T, Reuter T, Metze D *et al.* Disseminated hyperkeratotic and granulomatous nodules in a child with fatal Epstein–Barr-virus-associated hemophagocytic lymphohistiocytosis. *Pediatr Dermatol* 2006; **23**: 35–8.
26 Balamuth NJ, Nichols KE, Paessler M *et al.* Use of rituximab in conjunction with immunosuppressive chemotherapy as a novel therapy for Epstein Barr virus-associated hemophagocytic lymphohistiocytosis. *J Pediatr Hematol Oncol* 2007; **29**: 569–73.
27 Vince A, Lepej SZ, Kurelac I *et al.* Virological and immunological characteristics of fatal Epstein–Barr virus mononucleosis in a 17-year-old Caucasian male presenting with meningoencephalitis and hemophagocytic syndrome. *J Neurovirol* 2007; **13**: 389–96.
28 Kanitakis J, Euvrard S, Lefrancois N *et al.* Oral hairy leukoplakia in a HIV-negative renal graft recipient. *Br J Dermatol* 1991; **124**: 483–6.
29 Fluckiger R, Laifer G, Itin P *et al.* Oral hairy leukoplakia in a patient with ulcerative colitis. *Gastroenterology* 1994; **106**: 506–8.
30 Schiodt M, Norgaard T, Greenspan JS. Oral hairy leukoplakia in an HIV-negative woman with Behcet's syndrome. *Oral Surg Oral Med Oral Pathol* 1995; **79**: 53–6.
31 Eisenberg E, Krutchkoff D, Yamase H. Incidental oral hairy leukoplakia in immunocompetent persons. A report of two cases. *Oral Surg Oral Med Oral Pathol* 1992; **74**: 332–3.
32 Revuz J, Lassale C, Weschler J. Syndrome de Gianotti-Crosti à virus Epstein–Barr. *Ann Dermatol Venereol* 1983; **110**: 767–8.
33 Terasaki K, Koura S, Tachikura T *et al.* Gianotti–Crosti syndrome associated with endogenous reactivation of Epstein–Barr virus. *Dermatology* 2003; **207**: 68–71.
34 Lipschütz B. Über eine eigenartige Geschwürsform des weiblichen Genitales (ulcus vulvae acutum). *Arch Dermatol Syph (Berlin)* 1913; **114**: 363.
35 Lampert A, Assier-Bonnet H, Chevallier B *et al.* Lipschutz's genital ulceration: a manifestation of Epstein–Barr virus primary infection. *Br J Dermatol* 1996; **135**: 663–5.
36 Chen CL, Chow KC, Wong CK *et al.* A study on Epstein–Barr virus in erythema multiforme. *Arch Dermatol Res* 1998; **290**: 446–9.
37 Bodansky HJ. Erythema nodosum and infectious mononucleosis. *BMJ* 1979; **2**: 1263.
38 Hammar H. Erythema annulare centrifugum coincident with Epstein–Barr virus infection in an infant. *Acta Paediatr Scand* 1974; **63**: 788–92.
39 Almagro M, Del Pozo J, Martinez W *et al.* Pityriasis lichenoides-like exanthem and primary infection by Epstein–Barr virus. *Int J Dermatol* 2000; **39**: 156–9.
40 Baldari U, Raccagni AA, Celli B *et al.* Chronic bullous disease of childhood following Epstein–Barr virus seroconversion: a case report. *Clin Exp Dermatol* 1996; **21**: 123–6.
41 Spencer SA, Fenske NA, Espinoza CG *et al.* Granuloma annulare-like eruption due to chronic Epstein–Barr virus infection. *Arch Dermatol* 1988; **124**: 250–5.

Human herpesvirus 6 [1]

Human herpesvirus 6 (HHV-6) was originally isolated in 1986 from peripheral blood leukocytes (B cells) of patients with HIV infection or lymphoproliferative disorders [2]. In culture, infected cells (B and especially T cells) are large and refractile and frequently contain intranuclear and/or intracytoplasmic inclusions. The virus is serologically and genomically distinct from other human herpesviruses although it is closest to CMV and its genome has some regions that cross-hybridize with CMV under stringent conditions. There are two distinct groups: group A and group B. Although there is a high degree of antigen cross-reactivity between group A and group B strains, HHV-6 B strains are almost always the cause of human disease, with HHV-6 A strains rarely implicated [3].

This virus causes roseola infantum (exanthem subitum), the most common exanthematic fever in children under the age of 2 years, with a peak incidence between 6 and 9 months, reported to account for 24% of acute febrile illness presenting at a paediatric emergency department [4]. In the acute stage of the disease there is an HHV-6 viraemia which is followed by the appearance of antibodies to the virus [5]. Seroprevalence studies have shown that by the age of 1 year, 75% of infants have antibodies to HHV-6 and 90% of adults are seropositive [6]. Subclinical infection is common and it is estimated that only about one-third develop clinical disease. After the initial infection, the virus persists and can be detected in saliva from a high percentage of healthy subjects, the likely mode of spread [7].

Clinical features

Roseola infantum (exanthem subitum) [8,9]. The incubation period is from 10 to 15 days. Fever, sometimes ranging between 39.5 and 40°C, begins abruptly, persists for 3–5 days and is usually accompanied by few or no symptoms. Irritability, inflamed tympanic membranes, ulcers at the posterior palate and uvula [10] and, occasionally, periorbital oedema and haematuria are early manifestations. As the temperature falls, an eruption of discrete rose-pink maculopapules develops on the neck and trunk; it may later spread to the arms, face and legs. The lesions may rarely become vesicular [11]. After 1 or 2 days the rash fades, leaving no scaling or pigmentation. The patient's cervical and occipital lymph nodes are usually enlarged.

Febrile convulsions are not uncommon, occurring in 13% in one series [2]. HHV-6 DNA has been demonstrated in the cerebrospinal fluid of children with both primary HHV-6 infection and also at times of recurrent seizures following exanthem subitum, which suggests that HHV-6 is a direct cause of the associated encephalitides. Fatal encephalitis is rare, but has been reported in primary infection [12]. Other complications reported are thromobcytopenia [13] and haemophagocytic syndrome [14]. During the first 2 days there may be leukocytosis but as the rash develops, leukopenia with a relative lymphopenia is usual.

The eruption of primary HHV-6 infection is almost restricted to the first 3 years of life. If primary infection occurs in adults, there may be a mononucleosis-like illness, with variable fever or rash and with mainly cervical lymphadenopathy, which may persist for up to 3 months; or an acute but self-limiting hepatitis [15,16].

Reactivation of HHV-6. In immunosuppression, latent HHV-6 may reactivate and cause a variety of symptoms [17,18]. Fever, rash, hepatitis, encephalitis, pneumonitis and bone marrow suppression are recognized.

Other manifestations. HHV-6 infection has been associated with multiple sclerosis, Guillain–Barré syndrome, chronic fatigue syndrome, lymphoproliferative disorders, pityriasis rosea (see p. 33.78) and Kikuchi–Fujimoto disease (see p. 33.77), although the importance of the associations are not clear.

Diagnosis. The lack of symptoms during the febrile phase and the appearance of the eruption as the fever subsides should suggest the diagnosis, although clinical confusion with rubella or measles is not uncommon and the picture of roseola infantum can also be caused by HHV-7 infection. Confirmation is by demonstrating a seroconversion or rise in antibody titre to HHV-6, typically by indirect immunofluorescence using cells infected with HHV-6 as antigen. IgM antibody is usually present 5–7 days after the rash, maximal 2 weeks after infection and persists for about 2 months. Virus isolation requires specialized techniques not available in most diagnostic laboratories. Molecular detection of viral RNA by RT-PCR or DNA by PCR is possible but only quantitative PCR reliably distinguishes primary from latent infection [19].

Treatment. Only symptomatic measures are usually required. Antiviral therapy with ganciclovir, cidofovir or foscarnet would be appropriate in individuals with severe disease.

References

1 Dockrell DH. Human herpesvirus 6: molecular biology and clinical features. *J Med Microbiol* 2003; **52**: 5–18.
2 Salahuddin SZ, Ablashi DV, Markham PD *et al.* Isolation of a new virus, HBLV, in patients with lymphoproliferative disorders. *Science* 1986; **234**: 596–601.
3 Tomonari A, Takahashi S, Ooi J *et al.* Human herpesvirus 6 variant A infection with fever, skin rash, and liver dysfunction in a patient after unrelated cord blood transplantation. *Bone Marrow Transplant* 2005; **36**: 1109–10.
4 Hall CB, Long CE, Schnabel KC *et al.* Human herpesvirus-6 infection in children. A prospective study of complications and reactivation. *N Engl J Med* 1994; **331**: 432–8.
5 Yamanishi K, Okuno T, Shiraki K *et al.* Identification of human herpesvirus-6 as a causal agent for exanthem subitum. *Lancet* 1988; **1**: 1065–7.
6 Okuno T, Takahashi K, Balachandra K *et al.* Seroepidemiology of human herpesvirus 6 infection in normal children and adults. *J Clin Microbiol* 1989; **27**: 651–3.
7 Levy JA, Ferro F, Greenspan D *et al.* Frequent isolation of HHV-6 from saliva and high seroprevalence of the virus in the population. *Lancet* 1990; **335**: 1047–50.
8 Okada K, Ueda K, Kusuhara K *et al.* Exanthema subitum and human herpesvirus 6 infection: clinical observations in fifty-seven cases. *Pediatr Infect Dis J* 1993; **12**: 204–8.
9 Asano Y, Yoshikawa T, Suga S *et al.* Clinical features of infants with primary human herpesvirus 6 infection (exanthem subitum, roseola infantum). *Pediatrics* 1994; **93**: 104–8.
10 Chua KB, Lam SK, AbuBakar S *et al.* The predictive value of uvulo-palatoglossal junctional ulcers as an early clinical sign of exanthem subitum due to human herpesvirus 6. *J Clin Virol* 2000; **17**: 83–90.
11 Yoshida M, Fukui K, Orita T *et al.* Exanthem subitum (roseola infantum) with vesicular lesions. *Br J Dermatol* 1995; **132**: 614–6.
12 Asano Y, Yoshikawa T, Kajita Y *et al.* Fatal encephalitis/encephalopathy in primary human herpesvirus-6 infection. *Arch Dis Child* 1992; **67**: 1484–5.
13 Hashimoto H, Maruyama H, Fujimoto K *et al.* Hematologic findings associated with thrombocytopenia during the acute phase of exanthem subitum confirmed by primary human herpesvirus-6 infection. *J Pediatr Hematol Oncol* 2002; **24**: 211–4.
14 Sugita K, Kurumada H, Eguchi M *et al.* Human herpesvirus 6 infection associated with hemophagocytic syndrome. *Acta Haematol* 1995; **93**: 108–9.
15 Niederman JC, Liu CR, Kaplan MH *et al.* Clinical and serological features of human herpesvirus-6 infection in three adults. *Lancet* 1988; **2**: 817–9.
16 Akashi K, Eizuru Y, Sumiyoshi Y *et al.* Brief report: severe infectious mononucleosis-like syndrome and primary human herpesvirus 6 infection in an adult. *N Engl J Med* 1993; **329**: 168–71.
17 Clark DA. Human herpesvirus 6 and human herpesvirus 7: emerging pathogens in transplant patients. *Int J Hematol* 2002; **76** (Suppl. 2): 246–52.
18 Ljungman P, Singh N. Human herpesvirus-6 infection in solid organ and stem cell transplant recipients. *J Clin Virol* 2006; **37** (Suppl. 1): S87–91.
19 Reddy S, Manna P. Quantitative detection and differentiation of human herpesvirus 6 subtypes in bone marrow transplant patients by using a single real-time polymerase chain reaction assay. *Biol Blood Marrow Transplant* 2005; **11**: 530–41.

Human herpesvirus 7

Frenkel *et al*. [1] isolated a new herpesvirus from human $CD4^+$ T lymphocytes in 1990. Now named human herpes-virus 7 (HHV-7), this virus is distinct from but related to HHV-6. The virus has been subsequently isolated from the peripheral blood of healthy people and has been found to be very prevalent, infecting children at a similar age to HHV-6 [2]. Quantitative PCR detection is necessary to distinguish active primary or reactivated infection from past infection [3]. At present it is not known if HHV-7 is specifically related to any disease, but, like HHV-6, it has been reported in illness with clinical features of exanthem subitum (roseola infantum) [4–6]. HHV-7 viral DNA has been detected in the blood and lesional skin of patients with pityriasis rosea, sometimes together with HHV-6, although the pathogenetic relationship is debated (see p. 33.79).

References

1 Frenkel N, Schirmer EC, Wyatt LS *et al.* Isolation of a new herpesvirus from human $CD4^+$ T cells. *Proc Natl Acad Sci USA* 1990; **87**: 748–52.
2 Clark DA, Freeland ML, Mackie LK *et al.* Prevalence of antibody to human herpesvirus 7 by age. *J Infect Dis* 1993; **168**: 251–2.
3 Fernandez C, Boutolleau D, Manichanh C *et al.* Quantitation of HHV-7 genome by real-time polymerase chain reaction assay using MGB probe technology. *J Virol Methods* 2002; **106**: 11–6.
4 Tanaka K, Kondo T, Torigoe S *et al.* Human herpesvirus 7: another causal agent for roseola (exanthem subitum). *J Pediatr* 1994; **125**: 1–5.
5 Torigoe S, Kumamoto T, Koide W *et al.* Clinical manifestations associated with human herpesvirus 7 infection. *Arch Dis Child* 1995; **72**: 518–9.
6 Bruns R, Muller CE, Wiersbitzky SK *et al.* Clinical presentations of infection by the human herpesvirus-7 (HHV-7). *Pediatr Hematol Oncol* 2000; **17**: 247–52.

Human herpesvirus 8

Synonym
- Kaposi's sarcoma-associated herpesvirus, KHSV

Since it has been recognized in association with HIV/AIDS, the epidemiology of Kaposi's sarcoma, KS, has suggested that it is caused by an infectious agent [1] (see Chapter 35). In 1994, Chang *et al*. [2] identified in AIDS-associated Kaposi's sarcoma tissue novel DNA fragments which had partial homology to other γ-herpesviruses. This virus, Kaposi's sarcoma-associated herpesvirus, KHSV, or HHV-8, has also been found in association with

classic Kaposi's sarcoma in immunocompetent people [3] and in post-transplantation KS. Prolonged immunosuppression for other reasons, including pemphigus, has rarely been associated with HHV-8 in the skin and Kaposi's sarcoma [4]. The virus is also found in primary effusion lymphomas [5] and in multicentric Castleman's disease [6].

Primary infection with HHV-8 may be subclinical or may occur with fever and maculopapular eruption. The erythematous rash can affect all areas of the body but is usually most marked on the body and limbs. Histology shows a perivascular upper dermal infiltrate which includes plasma cells [7] in which viral proteins may be detectable.

As with other herpesviruses, latent infection persists after initial infection and later reactivation episodes may occur, especially with immunosuppression. Antibody studies of healthy adults suggest that up to 80% of the population have had infection with HHV-8 in African countries, but that less than 20% of the population are seropositive in western Europe [8]. Italy has a slightly higher rate of 35% in some areas of the country. Quantitative PCR permits detection of the virus plus estimation of viral load, but is not yet in routine use.

KHSV DNA has been detected in 98% of Kaposi's sarcoma lesions and is present in the monocytes, endothelial cells and spindle cells. The mechanism by which KHSV produces tumours is different to most other malignancies. Many of the viral proteins expressed by the virus influence cell proliferation, angiogenesis and apoptosis and down-regulate local immunity. Early KS lesions are polyclonal [9] although clonal growth may develop as a late event.

A multisystem disorder reported in Castleman's disease is also attributed to HHV-8 infection [10]. In POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes) the cutaneous abnormalities include multiple haemangiomas, hyperpigmentation, hypertrichosis and thickened skin.

Treatment. Treatment of HHV-8 infection may be difficult as the primary infection is frequently subclinical or diagnosis may be made late. There is some evidence that valganciclovir may reduce viral replication in primary or reactivation episodes [11].

Treatments for HHV-8 associated KS are multiple [1]. Regression of lesions frequently occurs in AIDS with antiretroviral treatment and post-transplant with reduction of immunosuppression or with change of immunosuppressive regime to include rapamycin or sirolimus [12]. Local treatments include cryotherapy, radiotherapy, intralesional chemotherapy, intralesional interferon and topical 5% imiquimod cream [13].

References

1 Schwartz RA, Micali G, Nasca MR *et al.* Kaposi sarcoma: a continuing conundrum. *J Am Acad Dermatol* 2008; **59**: 179–206; quiz 7–8.

2 Chang Y, Cesarman E, Pessin MS *et al.* Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. *Science* 1994; **266**: 1865–9.

3 Moore PS, Chang Y. Detection of herpesvirus-like DNA sequences in Kaposi's sarcoma in patients with and without HIV infection. *N Engl J Med* 1995; **332**: 1181–5.

4 Avalos-Peralta P, Herrera A, Rios-Martin JJ *et al.* Localized Kaposi's sarcoma in a patient with pemphigus vulgaris. *J Eur Acad Dermatol Venereol* 2006; **20**: 79–83.

5 Cesarman E, Chang Y, Moore PS *et al.* Kaposi's sarcoma-associated herpesvirus-like DNA sequences in AIDS-related body-cavity-based lymphomas. *N Engl J Med* 1995; **332**: 1186–91.

6 Soulier J, Grollet L, Oksenhendler E *et al.* Kaposi's sarcoma-associated herpesvirus-like DNA sequences in multicentric Castleman's disease. *Blood* 1995; **86**: 1276–80.

7 Wyplosz B, Carlotti A, Escaut L *et al.* Initial human herpesvirus-8 rash and multicentric Castleman disease. *Clin Infect Dis* 2008; **47**: 684–8.

8 Laurent C, Meggetto F, Brousset P. Human herpesvirus 8 infections in patients with immunodeficiencies. *Hum Pathol* 2008; **39**: 983–93.

9 Gill PS, Tsai YC, Rao AP *et al.* Evidence for multiclonality in multicentric Kaposi's sarcoma. *Proc Natl Acad Sci USA* 1998; **95**: 8257–61.

10 Belec L, Mohamed AS, Authier FJ *et al.* Human herpesvirus 8 infection in patients with POEMS syndrome-associated multicentric Castleman's disease. *Blood* 1999; **93**: 3643–53.

11 Casper C, Krantz EM, Corey L *et al.* Valganciclovir for suppression of human herpesvirus-8 replication: a randomized, double-blind, placebo-controlled, crossover trial. *J Infect Dis* 2008; **198**: 23–30.

12 Stallone G, Schena A, Infante B *et al.* Sirolimus for Kaposi's sarcoma in renal-transplant recipients. *N Engl J Med* 2005; **352**: 1317–23.

13 Rosen T. Limited extent AIDS-related cutaneous Kaposi's sarcoma responsive to imiquimod 5% cream. *Int J Dermatol* 2006; **45**: 854–6.

Herpes B virus [1]

B virus, or cercopithecine herpesvirus 1 (CeHV-1), is genetically close to HSV-1 and -2 but is not naturally an infection of humans. It causes a benign enzootic infection of Asiatic monkeys (the *Macaca* genus) and readily spreads among other monkeys in captivity. The virus remains latent in infected monkeys and may reactivate spontaneously or at times of stress. The virus is highly pathogenic to humans in whom it typically causes a fulminant encephalitis which is fatal in 80% without treatment. Human infections have occurred in attendants and research workers, most frequently following monkey bites, but occasionally in those who have handled monkeys or monkey tissues and have not been bitten. Person-to-person transmission is rare. Guidelines to prevent B virus infections in monkey handlers have been published [2].

Clinical features [2]. In humans, lesions resembling herpes simplex develop after 5–21 days at the site of the bite or scratch. There may be symptoms of tingling, itching, numbness or pain before the vesicular eruption appears. The eruption may remain localized or show some extension with regional lymphangitis and lymphadenopathy. Fever, malaise, headache and abdominal pain indicate a systemic illness. Encephalitis, usually fatal, develops after 10–35 days in a high proportion of cases.

Diagnosis. There is usually a history of contact with monkeys or monkey tissue. Culture of the virus from vesicle fluid or brain biopsy material will confirm the diagnosis but must be performed in a specialized laboratory and is slow. Specific primers for PCR are available for the direct detection of B-virus DNA in blood or tissue [3]. Serological tests of paired samples can also be helpful.

Treatment. Monkey-inflicted wounds should be vigorously cleaned with soap and water and followed by iodine or alcohol. Aciclovir used early may reduce the severity of the disease but may have little impact if used late [4]. Valaciclovir orally is now the recommended treatment given as soon as possible following exposure. The dose is 1 g three times a day for 14 days.

Intravenous ganciclovir is more potent than aciclovir *in vitro* and has also been used clinically. If symptoms of B virus disease develop, treatment is with intravenous aciclovir, 12.5–15 mg/kg three times per day, or ganciclovir, 5 mg/kg twice daily [4], but if there are signs of encephalitis, ganciclovir is the treatment of choice.

References

1 Weigler BJ. Biology of B virus in macaque and human hosts: a review. *Clin Infect Dis* 1992; **14**: 555–67.

2 Cohen JI, Davenport DS, Stewart JA *et al.* Recommendations for prevention of and therapy for exposure to B virus (cercopithecine herpesvirus 1). *Clin Infect Dis* 2002; **35**: 1191–203.

3 Perelygina L, Patrusheva I, Manes N *et al.* Quantitative real-time PCR for detection of monkey B virus (Cercopithecine herpesvirus 1) in clinical samples. *J Virol Methods* 2003; **109**: 245–51.

4 Zwartouw HT, Humphreys CR, Collins P. Oral chemotherapy of fatal B virus (herpesvirus simiae) infection. *Antiviral Res* 1989; **11**: 275–83.

Kaposi's varicelliform eruption including eczema herpeticum

Aetiology. Kaposi's varicelliform eruption refers to a widespread cutaneous infection with a virus which normally causes localized or mild vesicular eruptions, occurring in a patient with pre-existing skin disease. If the skin disease is more localized, the varicelliform eruption may be limited to the affected skin. The great majority of cases are infections with HSV type 1, and are now usually called eczema herpeticum. The more general eponymous title may be used to encompass similar widespread infections with other viruses, including coxsackie A16 [1] and vaccinia [2,3] (eczema vaccinatum). The latter is rarely seen now that smallpox vaccination is limited to selected groups (see p. 33.5). Atopic eczema is by far the commonest predisposing condition, although the term eczema herpeticum has not been restricted to cases with a background of eczema. Other susceptible dermatoses include Darier's disease [4,5], pemphigus foliaceus [6,7] and benign familial pemphigus [8], with rare reports in association with Hailey–Hailey disease [9], Grover's disease [10], ichthyosis vulgaris [11], congenital ichthyosiform erythroderma [12], allergic contact dermatitis [13,14], irritant contact dermatitis [15], psoriasis [16], pityriasis rubra pilaris [17], cutaneous T-cell lymphoma [18], Sézary syndrome [19], rosacea [20], drug eruption [21] and staphylococcal scalded skin syndrome [22]. Extensive spread of herpetic infection has followed trauma or cosmetic procedures to the face such as burns [23], dermabrasion [24] and laser therapy [25].

Most herpes simplex infections in patients with atopic eczema are not unusually severe or widespread. Localized eczema herpeticum is not rare among patients with atopic eczema [26].

Eczema herpeticum can result from primary or recurrent infection [27]. When developing from a primary infection, there is more likely to be malaise, high fever and lymphopenia. Eczema herpeticum may be worse in patients with severe, especially erythrodermic, atopic eczema, but frequently occurs in mild or quiescent cases [28]. Recurrences of eczema herpeticum can occur.

Cases are seen at all ages, most commonly in the second and third decades [27,29]. No seasonal variation has been observed. In localized cases, local spread seems likely, but widespread dissemination is haematogenous.

Patients who develop eczema herpeticum are usually immunocompetent and have, or can develop, antibodies against the virus [30]. Recent studies have identified possible risk factors for the development of eczema herpeticum in individuals with atopic eczema. An early age of onset of atopic eczema, high IgE level [27], antibodies against *Malassezia sympodialis*, a poor *in vitro* response of peripheral blood mononuclear cells to HSV particles [31] and a low NK cell count [32] have all been found in eczema herpeticum patients. A further possible predisposing factor is a defect in the innate immune response as shown by a low skin level of the antimicrobial peptide cathelicidin, LL-37 [33].

An association with systemic or topical steroid treatment has not been consistently found [27,28]. Other topical and systemic immunosuppression has also been associated with eczema herpeticum, namely topical tacrolimus [34] or pimecrolimus [35]. One study from Japan has suggested that genetic variation in the IL-18 gene in individuals with atopic eczema may cause an increased propensity to develop eczema herpeticum [36]. It is possible that the predisposition to develop widespread herpes simplex is linked more with the severity of the eczema or a limited immune defect rather than with the type or quantity of treatment used.

Clinical features [2,28] (Fig. 33.15). In severe cases, after an incubation period of about 10 days (range 5–19 days), vesicles, which rapidly become pustular, erupt in massive crops. They may be confined to abnormal skin but are often widely disseminated and may generalize, simulating smallpox. They may be haemorrhagic and the face may become grossly oedematous. New crops of vesicles may appear for 5–7 days. Fever, which may be high, commonly develops 2 or 3 days after the onset of the eruption and constitutional symptoms may be severe. The regional lymph nodes are enlarged. The fever subsides after 4 or 5 days and the pustules become crusted and slowly heal, leaving little permanent scarring.

Rarely, there may be progression to potentially fatal systemic infection [37,38].

The diagnosis may be confused in localized infections by secondary bacterial infection [39], and by lesions in pre-existing blistering skin disorders, but typical vesicles or subsequent erosions, generally confined to eczematous or inflamed areas, should be sought, especially if there is a poor response to antibacterial therapy. These milder infections are usually self-limiting. Diagnosis can also be difficult when the lesions of a pre-existing bullous disorder delay recognition of the punched-out erosions of the varicelliform infection.

Recurrences of eczema herpeticum may commonly be milder than the initial episode, but are sometimes of comparable severity [28].

Treatment and prevention. Awareness of the possibility of widespread herpetic infection should be encouraged in atopic eczema patients or their parents. Patients with atopic eczema, especially those with a history of eczema herpeticum, should avoid close contact with relatives and friends with active herpes simplex.



Fig. 33.15 Eczema herpeticum. (a) Perioral. (b) Periocular. (c) Front of neck of 20-year-old man. (d) Resolving lesions ((c) Courtesy of York District Hospital, UK; (d) Courtesy of Addenbrooke's Hospital, Cambridge, UK.)

Severe cases should receive intravenous aciclovir [40,41] as early as possible. Less ill patients respond well to oral aciclovir [42] or one of the newer antiherpes agents [10]. Infection in pregnancy has been treated with aciclovir without adverse effect to the baby [43].

Bacterial infection and the underlying eczema or other dermatosis should be treated in the usual way, except that if aciclovir is being withheld, more cautious use of steroid therapy may be advisable until the viral lesions have healed.

References

1 Higgins PG, Crow KD. Recurrent Kaposi's varicelliform eruption in Darier's disease. *Br J Dermatol* 1973; **88**: 391–4.

2 Fries JH, Borne S, Barnes HL. Varicelliform eruption of Kaposi due to vaccinia virus complicating atopic eczema. *J Pediatr* 1948; **32**: 532–42.

3 Nell P, Kohl KS, Graham PL *et al.* Eczema vaccinatum as an adverse event following exposure to vaccinia virus: case definition and guidelines of data collection, analysis, and presentation of immunization safety data. *Vaccine* 2007; **25**: 5725–34.

4 Hitselberger JF, Burns RE. Darier's disease. Report of a case complicated by Kaposi's varicelliform eruption. *Arch Dermatol* 1961; **83**: 425–9.

5 Toole JW, Hofstader SL, Ramsay CA. Darier's disease and Kaposi's varicelliform eruption. *J Am Acad Dermatol* 1979; **1**: 321–4.

6 Silverstein EH, Burnett JW. Kaposi's varicelliform eruption complicating pemphigus foliaceus. *Arch Dermatol* 1967; **95**: 214–6.

7 Demitsu T, Kakurai M, Azuma R *et al.* Recalcitrant pemphigus foliaceus with Kaposi's varicelliform eruption: report of a fatal case. *Clin Exp Dermatol* 2008; **33**: 681–2.

8 Ogilvie MM, Kesseler M, Leppard BJ *et al.* Herpes simplex infections in pemphigus: an indication for urgent viral studies and specific antiviral therapy. *Br J Dermatol* 1983; **109**: 611–3.

9 Schirren H, Schirren CG, Schlupen EM *et al.* Exazerbation eines Morbus Hailey-Hailey dürch Infektion mit Herpes-simplex-Virus. Nachweis mittels Polymerasekettenreaktion. *Hautarzt* 1995; **46**: 494–7.

10 Kosann MK, Fogelman JP, Stern RL. Kaposi's varicelliform eruption in a patient with Grover's disease. *J Am Acad Dermatol* 2003; **49**: 914–5.

11 Verbov J, Munro DD, Miller A. Recurrent eczema herpeticum associated with ichthyosis vulgaris. *Br J Dermatol* 1972; **86**: 638–40.

12 Fitzgerald WC, Booker AP. Congenital ichthyosiform erythroderma; a report of two cases in siblings, one complicated by Kaposi's varicelliform eruption. *AMA Arch Derm Syphilol* 1951; **64**: 611–9.

13 Sahoo B, Handa S, Kumar B. Eczema herpeticum in parthenium dermatitis. *Contact Dermatitis* 2001; **44**: 106–7.

14 Paradisi A, Capizzi R, Guerriero G *et al.* Kaposi's varicelliform eruption complicating allergic contact dermatitis. *J Am Acad Dermatol* 2006; **54**: 732–3.

15 Morganroth GS, Glick SA, Perez MI *et al.* Kaposi's varicelliform eruption complicating irritant contact dermatitis. *J Am Acad Dermatol* 1992; **27**: 1030–1.

16 Santmyire-Rosenberger BR, Nigra TP. Psoriasis herpeticum: three cases of Kaposi's varicelliform eruption in psoriasis. *J Am Acad Dermatol* 2005; **53**: 52–6.
17 Ng SK, Ang CB, Tham A. Kaposi's varicelliform eruption in a patient with pityriasis rubra pilaris. *J Am Acad Dermatol* 1992; **27**: 263.
18 Masessa JM, Grossman ME, Knobler EH *et al.* Kaposi's varicelliform eruption in cutaneous T cell lymphoma. *J Am Acad Dermatol* 1989; **21**: 133–5.
19 Brion N, Guillaume JC, Dubertret L *et al.* Herpes cutané disseminé de l'adulte et syndrome de Sézary. *Ann Dermatol Venereol* 1981; **108**: 517–21.
20 Kucukyilmaz I, Alpsoy E, Yazar S. Kaposi's varicelliform eruption in association with rosacea. *J Am Acad Dermatol* 2004; **51**: S169–72.
21 Ajith C, Dogra S, Handa S. Kaposi's varicelliform eruption in a patient with phenytoin-induced drug rash. *Int J Dermatol* 2006; **45**: 1452–3.
22 Barrio J, Lazaro P, Barrio JL. Kaposi's varicelliform eruption and staphylococcal scalded skin syndrome in adults. *J Am Acad Dermatol* 1997; **37**: 510–1.
23 Bartralot R, Garcia-Patos V, Rodriguez-Cano L *et al.* Kaposi's varicelliform eruption in a patient with healing second degree burns. *Clin Exp Dermatol* 1996; **21**: 127–30.
24 Bestue M, Cordero A. Kaposi's varicelliform eruption in a patient with healing peribuccal dermabrasion. *Dermatol Surg* 2000; **26**: 939–40.
25 Sriprachya-Anunt S, Fitzpatrick RE, Goldman MP *et al.* Infections complicating pulsed carbon dioxide laser resurfacing for photoaged skin. *Dermatol Surg* 1997; **23**: 527–35.
26 Atherton DJ, Harper JI. Management of eczema herpeticum. *J Am Acad Dermatol* 1988; **18**: 757–8.
27 Wollenberg A, Zoch C, Wetzel S *et al.* Predisposing factors and clinical features of eczema herpeticum: a retrospective analysis of 100 cases. *J Am Acad Dermatol* 2003; **49**: 198–205.
28 David TJ, Longson M. Herpes simplex infections in atopic eczema. *Arch Dis Child* 1985; **60**: 338–43.
29 Bork K, Brauninger W. Increasing incidence of eczema herpeticum: analysis of seventy-five cases. *J Am Acad Dermatol* 1988; **19**: 1024–9.
30 Vestey JP, Howie SE, Norval M *et al.* Immune responses to herpes simplex virus in patients with facial herpes simplex and those with eczema herpeticum. *Br J Dermatol* 1988; **118**: 775–82.
31 Peng WM, Jenneck C, Bussmann C *et al.* Risk factors of atopic dermatitis patients for eczema herpeticum. *J Invest Dermatol* 2007; **127**: 1261–3.
32 Goodyear HM, McLeish P, Randall S *et al.* Immunological studies of herpes simplex virus infection in children with atopic eczema. *Br J Dermatol* 1996; **134**: 85–93.
33 Howell MD, Wollenberg A, Gallo RL *et al.* Cathelicidin deficiency predisposes to eczema herpeticum. *J Allergy Clin Immunol* 2006; **117**: 836–41.
34 Lubbe J, Pournaras CC, Saurat JH. Eczema herpeticum during treatment of atopic dermatitis with 0.1% tacrolimus ointment. *Dermatology* 2000; **201**: 249–51.
35 Segura S, Romero D, Carrera C *et al.* Eczema herpeticum during treatment of atopic dermatitis with 1% pimecrolimus cream. *Acta Derm Venereol* 2005; **85**: 524–5.
36 Osawa K, Etoh T, Ariyoshi N *et al.* Relationship between Kaposi's varicelliform eruption in Japanese patients with atopic dermatitis treated with tacrolimus ointment and genetic polymorphisms in the IL-18 gene promoter region. *J Dermatol* 2007; **34**: 531–6.
37 Sanderson IR, Brueton LA, Savage MO *et al.* Eczema herpeticum: a potentially fatal disease. *BMJ* 1987; **294**: 693–4.
38 Wollenberg A, Wetzel S, Burgdorf WH *et al.* Viral infections in atopic dermatitis: pathogenic aspects and clinical management. *J Allergy Clin Immunol* 2003; **112**: 667–74.
39 Brook I, Frazier EH, Yeager JK. Microbiology of infected eczema herpeticum. *J Am Acad Dermatol* 1998; **38**: 627–9.
40 Swart RN, Vermeer BJ, van Der Meer JW *et al.* Treatment of eczema herpeticum with acyclovir. *Arch Dermatol* 1983; **119**: 13–6.
41 Jawitz JC, Hines HC, Moshell AN. Treatment of eczema herpeticum with systemic acyclovir. *Arch Dermatol* 1985; **121**: 274–5.
42 Muelleman PJ, Doyle JA, House RF Jr. Eczema herpeticum treated with oral acyclovir. *J Am Acad Dermatol* 1986; **15**: 716–7.
43 Latta RA, Baker DA. Treatment of recurrent eczema herpeticum in pregnancy with acyclovir. *Infect Dis Obstet Gynecol* 1996; **4**: 239–42.

Polyomavirus

A polyomavirus has recently been detected in Merkel cell carcinoma of both immunosuppressed and immunocompetent individuals [1]. This virus, called Merkel cell polyomavirus, appears to be integrated into the host genome and is not able to replicate [2].

References

1 Feng H, Shuda M, Chang Y *et al.* Clonal integration of a polyomavirus in human Merkel cell carcinoma. *Science* 2008; **319**: 1096–100.
2 Shuda M, Feng H, Kwun HJ *et al.* T antigen mutations are a human tumor-specific signature for Merkel cell polyomavirus. *Proc Natl Acad Sci U S A* 2008; **105**: 16272–7.

Human papillomaviruses (HPV)

Papillomaviruses are small 50 to 55-nm-diameter DNA viruses that infect squamous epithelia, causing cell proliferation. The commonest effect of HPV infection is the development of warts (verrucae). These virus-induced tumours are pleomorphic and can affect a wide variety of sites, principally skin of extremities, genital skin and mucosa, larynx and oral mucosa. The virus infects the basal layer of the epithelium, possibly the stem cells, but viral replication takes place only in fully differentiated keratinocytes—cells of the upper stratum spinosum and stratum granulosum. The viral DNA is functionally divided into early (E) and late (L) regions; the early genes are responsible for DNA replication, transcriptional regulation and transformation while the late genes code for the structural proteins of the viral capsid. Expression of the late genes of the virus is dependent upon the differentiation of the host cell. Propagation of papillomaviruses in tissue culture *in vitro* is therefore extremely difficult, as it is hard to mimic all the necessary requirements for the completion of the virus life cycle [1,2].

HPVs form a large group of closely related viruses, distinguished one from another on the basis of their DNA. Originally, types were distinguished by DNA homology in liquid hybridization under defined conditions. Now, the ease of PCR and DNA sequencing permits a different definition of typing—a distinct genotype has greater than 10% difference in nucleotide homology within the L1 gene compared with other papillomavirus types. If the homology is greater than 90%, the strain is regarded as of that subtype [3]. The number of HPV types is continuously increasing. To date, about 100 types have been recognized and characterized. However, a large number of putative new types have been detected, which are yet to be completely evaluated. The main clinical associations of the different HPV types are shown in Table 33.4. All papillomavirus types have a tropism for stratified squamous epithelial cells, but they vary in their specificity for different anatomical sites [7]. For example, HPV-1 replicates in heavily keratinized skin of palms and soles, whereas HPV-16 has a preference for genital areas and HPV-11 replicates in genital and laryngeal epithelium.

Papillomas caused by HPVs are initially benign. In these lesions, viral genomes replicate as extrachromosomal episomes. A small

Table 33.4 The main clinical lesions caused by different human papillomavirus (HPV) types. (Data from de Villiers *et al*. [3], Cobb [4], Meyers *et al*. [5] and Calleja-Macias *et al.* [6].)

HPV type	Genus	Associated clinical conditions
1	Mu	Deep plantar and palmar warts
2	Alpha	Common warts, filiform warts, plantar warts, mosaic plantar warts
3	Alpha	Plane warts
4	Gamma	Common warts, plantar warts
5	Beta	Warts in EV and immunosuppressed, SCC in EV and immunosuppressed
6	Alpha	Anogenital warts, laryngeal papillomas
7	Alpha	Butchers' warts
8	Beta	Warts in EV and immunosuppressed, SCC in EV and immunosuppressed
9	Beta	Warts in EV and immunosuppressed, rarely SCC in EV and immunosuppressed
10	Alpha	Plane warts
11	Alpha	Anogenital warts, laryngeal papillomas, verrucous carcinoma
12	Beta	Warts in EV and immunosuppressed, SCC in EV and immunosuppressed
13	Alpha	Focal epithelial hyperplasia
14	Beta	Warts in EV and immunosuppressed, SCC in EV and immunosuppressed
15	Beta	Warts in EV and immunosuppressed, rarely SCC in EV and immunosuppressed
16	Alpha	Anogenital warts, AGIN, cervical carcinoma
17	Beta	Warts in EV and immunosuppressed, rarely SCC in EV and immunosuppressed
18	Alpha	Genital warts, AGIN, cervical carcinoma
19	Beta	Warts in EV and immunosuppressed, SCC in EV and immunosuppressed
20	Beta	Warts in EV and immunosuppressed, SCC in EV and immunosuppressed
21	Beta	Warts in EV and immunosuppressed, SCC in EV and immunosuppressed
22, 23	Beta	Warts in EV and immunosuppressed, rarely SCC in EV and immunosuppressed
24, 25	Beta	Warts in EV and immunosuppressed, SCC in EV and immunosuppressed
26	Alpha	Cutaneous lesions in immunosuppressed, genital lesions including carcinoma
27	Alpha	Common warts, anogenital warts in children
28	Alpha	Flat and common warts in normal and immunosuppressed
29	Alpha	Cutaneous warts (rare)
30	Alpha	Anogenital lesions, laryngeal carcinoma
31	Alpha	Anogenital warts, CIN, cervical carcinoma
32	Alpha	Focal epithelial hyperplasia, oral papillomas
33	Alpha	CIN, VIN, cervical cancer
34	Alpha	Orogenital warts, AGIN
35	Alpha	Anogenital warts, CIN, cervical cancer
36	Beta	Warts in EV and immunosuppressed, SCC in EV and immunosuppressed
37, 38	Beta	Warts in EV and immunosuppressed, rarely SCC in EV and immunosuppressed
39	Alpha	Anogenital warts, AGIN, cervical cancer
40	Alpha	Anogenital warts, skin and mucosal lesions in immunosuppressed, AGIN
41	Nu	Plane warts, SCC skin
42, 43	Alpha	Anogenital warts
44	Alpha	Orogenital warts
45	Alpha	Anogenital warts, AGIN, cervical cancer
46		Reclassified as HPV-20b
47	Beta	Warts in EV and immunosuppressed, SCC in EV and immunosuppressed
48	Gamma	Cutaneous warts (rare)
49	Beta	Cutaneous warts, warts in EV
50	Gamma	Cutaneous warts, warts in EV
51	Alpha	Anogenital warts, anogenital intraepithelial neoplasia
52	Alpha	Anogenital warts, AGIN, cervical cancer
53	Alpha	Anogenital warts, CIN, cervical cancer
54	Alpha	Anogenital warts, Buschke–Löwenstein tumour (rare)
55		Reclassified as subtype of HPV 44
56	Alpha	Anogenital warts, CIN, cervical cancer
57	Alpha	Common warts, orogenital warts in children, skin lesions in immunosuppressed, epidermoid cyst of sole
58	Alpha	Anogenital warts, AGIN, cervical cancer
59	Alpha	Orogenital warts, AGIN, cervical cancer
60	Gamma	Plantar epidermoid cysts, pigmented plantar warts
61, 62	Alpha	Low risk anogenital lesions
63	Mu	Cutaneous warts (rare), multiple punctate keratoses of foot
64	Alpha	Orogenital warts, low-risk anogenital lesions
65	Gamma	Common warts, plantar warts, pigmented plantar warts
66	Alpha	Anogenital warts, CIN, cervical cancer
67	Alpha	Anogenital warts, AGIN, cervical carcinoma
68	Alpha	Anogenital warts, AGIN, cervical cancer
69	Alpha	CIN
70	Alpha	Anogenital warts, AGIN, anogenital cancers
71	Alpha	Anogenital warts
72	Alpha	Anogenital warts, cervical lesions
73	Alpha	Anogenital warts, AGIN, anogenital cancers
74	Alpha	Anogenital warts
75–77	Beta	Cutaneous warts, warts in EV
78	Alpha	Cutaneous warts
80	Beta	Warts in EV and immunosuppressed, rarely SCC in EV and immunosuppressed
81	Alpha	Low risk anogenital lesions
82	Alpha	CIN
83, 84	Alpha	Low risk anogenital lesions
85 (candidate)	Alpha	AGIN, anogenital cancers
86, 87	Alpha	Low risk anogenital lesions
88	Gamma	Cutaneous warts
89	Alpha	Low risk anogenital lesions
90 (candidate)	Alpha	Anogenital warts
91 (candidate)	Alpha	Cutaneous warts, anogenital warts
92 (candidate)	Beta	Cutaneous dysplasia and SCC
93	Beta	Warts in EV and immunosuppressed, SCC in EV and immunosuppressed
94	Alpha	Cutaneous warts
95	Gamma	Common warts, plantar warts, pigmented plane warts
96 (candidate)	Beta	Cutaneous dysplasia and SCC in EV

EV, epidermodysplasia verruciformis; SCC, squamous cell carcinoma; AGIN, anogenital intraepithelial neoplasia, includes AIN, CIN, PIN, VIN, and vaginal intraepithelial neoplasia; CIN, cervical intraepithelial neoplasia; VIN, vulval intraepithelial neoplasia; PIN, penile intraepithelial neoplasia.

percentage can progress to dysplasia or neoplasia. This occurs only with certain so-called 'high-risk' or 'cancer-associated' types of HPV, and under certain circumstances, genetic and environmental, some of which are incompletely understood. The strongest association between papillomavirus infection and development of malignancy is in the case of cervical carcinoma. In the majority of malignantly transformed cells (i.e. those affected by high-risk genital HPVs), the viral DNA is integrated into the cellular chromosomes, usually with the loss of large sections of the viral genome. Viral replication does not occur, but the viral regulatory genes, E6 and E7 are always retained. The oncogenic potential of the high-risk HPV types depends upon the expression of these early genes whose products play a role in cell transformation and immortalization. This is because the E6 protein inactivates the cell's tumour-suppressor protein p53 and the E7 protein inhibits the cell's pRb protein from its normal function as a negative regulator of cell-cycle proliferation.

These clinically evident infections with HPVs will be described below, but there is also evidence that after initial infection, HPV may persist in a latent form and may be subsequently reactivated.

Subclinical and latent HPV infection. Evidence has accumulated, mainly from studies of genital skin and mucosa, for subclinical and latent HPV infection. It has been estimated that up to 70% of genital HPV infections may be subclinical (i.e. unnoticed by the patient) but detectable by full clinical examination, histology, cytology or molecular analysis. In a latent infection, there may be no morphological changes, but the viral DNA is present.

Genital HPV infection can often be subclinical but may be detected during routine cervical smear tests or on vulval or penile examination. Of 545 students attending an annual gynaecological examination in an American university, 1% were aware that they had signs of genital warts, but a further 16% had evidence of HPV infection from colposcopy, cytology or detection of HPV antigen or HPV DNA assessed by hybridization [8]. Of over 9000 women routinely screened by cervical cytology in Germany, 2.1% had simple HPV infection (koilocytosis), and 3.7% had signs of dysplasia or neoplasia; of the other (cytologically normal) cases, HPV DNA was detected by hybridization in 9% [9]. Acetowhitening of cervix or genital skin does not correlate very well with presence of HPV [10].

The highly sensitive PCR has revealed apparently very high rates of HPV cervical infection in the general population [9,11]. Longitudinal studies have suggested that many infections are transient and individuals may lose or acquire different HPV types over time but persistent, high-grade HPV infection in the cervix is a risk factor for the development of cervical intraepithelial neoplasia [12,13].

Diagnosis. Clinical diagnosis of warts is often sufficient, but atypical, subclinical or dysplastic lesions may need laboratory confirmation of HPV infection. Methods available are:

1 Histology
2 Detection of virus particles by electron microscopy—this method would not be helpful for those types of wart which have few virus particles, for example genital warts, or in high grade neoplasia or invasive cancer
3 Immunohistochemistry or immunocytochemistry using type-common or type-specific antibodies
4 DNA hybridization on tissue extracts or *in situ*
5 PCR for HPV DNA.

References

1 Bedell MA, Hudson JB, Golub TR *et al.* Amplification of human papillomavirus genomes in vitro is dependent on epithelial differentiation. *J Virol* 1991; **65**: 2254–60.
2 Meyers C, Frattini MG, Hudson JB *et al.* Biosynthesis of human papillomavirus from a continuous cell line upon epithelial differentiation. *Science* 1992; **257**: 971–3.
3 de Villiers EM, Fauquet C, Broker TR *et al.* Classification of papillomaviruses. *Virology* 2004; **324**: 17–27.
4 Cobb MW. Human papillomavirus infection. *J Am Acad Dermatol* 1990; **22**: 547–66.
5 Meyers G, Bernard HU, Delius H. *Human Papillomaviruses*. 1995. Available from: http://stdgen.northwestern.edu.
6 Calleja-Macias IE, Kalantari M, Allan B *et al.* Papillomavirus subtypes are natural and old taxa: phylogeny of human papillomavirus types 44 and 55 and 68a and -b. *J Virol* 2005; **79**: 6565–9.
7 von Knebel Doeberitz M. Papillomaviruses in human disease: Part I. Pathogenesis and epidemiology of human papillomavirus infections. *Eur J Med* 1992; **1**: 415–23.
8 Kiviat NB, Koutsky LA, Paavonen JA *et al.* Prevalence of genital papillomavirus infection among women attending a college student health clinic or a sexually transmitted disease clinic. *J Infect Dis* 1989; **159**: 293–302.
9 de Villiers EM, Wagner D, Schneider A *et al.* Human papillomavirus infections in women with and without abnormal cervical cytology. *Lancet* 1987; **2**: 703–6.
10 Wikstrom A, Hedblad MA, Johansson B *et al.* The acetic acid test in evaluation of subclinical genital papillomavirus infection: a comparative study on penoscopy, histopathology, virology and scanning electron microscopy findings. *Genitourin Med* 1992; **68**: 90–9.
11 Scandinavian Multicenter Study Group. Polymerase chain reaction and direct DNA tests in detection of human papillomavirus (HPV) DNA in cytologically normal and abnormal cervical smears. *Acta Obstet Gynecol Scand* 1992; **71**: 98–103.
12 Woodman CB, Collins S, Winter H *et al.* Natural history of cervical human papillomavirus infection in young women: a longitudinal cohort study. *Lancet* 2001; **357**: 1831–6.
13 Liaw KL, Glass AG, Manos MM *et al.* Detection of human papillomavirus DNA in cytologically normal women and subsequent cervical squamous intraepithelial lesions. *J Natl Cancer Inst* 1999; **91**: 954–60.

Warts

HPVs can infect and cause disease at any site in stratified squamous epithelium, either keratinizing (skin) or non-keratinizing (mucosa). The clinical problems encountered with such infections can be broadly divided into cutaneous warts, genital warts, oral warts and laryngeal warts.

Epidemiology. Cutaneous warts occur at any age, but are unusual in infancy and early childhood. The incidence increases during the school years to reach a peak in adolescence and early adulthood [1,2], then declines rapidly through the 20s and more gradually thereafter. In various studies, it has been estimated that 2–20% of school-age children have warts [3,4].

In countries with highly developed medical services, referral rates of warts to dermatology and genitourinary medicine clinics have greatly increased in the last 50 years. In the UK, there was a marked increase in the incidence of anogenital warts (condylomata acuminata) from the 1970s to the 1990s [5], with a continuing rise over the last decade [6]. The incidence in young adults aged

16 to 24 is estimated to be 700 per 100 000, with an overall population incidence of approximately 150 per 100 000 [7,8]. An increase in the incidence of anogenital warts in childhood has also been claimed [9], but it is unclear if this reflects increased reporting or improved methods of HPV detection and if it could result from sexual abuse or increased rates of mother to child transmission.

Incubation period

The time of acquisition of the infection can seldom be ascertained for common and plantar warts, but the incubation period has been estimated to range between a few weeks and more than a year [10], and experimental infections have taken as long as 20 months to produce clinical warts [11].

A prospective study of sexual contacts of patients with genital warts indicated an incubation period of 3 weeks to 8 months, average 2.8 months [12]. It is believed that perinatally acquired HPV infection may not manifest as genital warts for up to 2 years [13]. Only 57% of cases of laryngeal papilloma in children are diagnosed by 2 years of age [14].

Infectivity

Person-to-person transmission of genital HPV infection seems to be high as two-thirds of 97 sexual contacts of patients with genital warts themselves developed lesions within 9 months; infectivity seemed highest early in the course of the disease [12]. Close inspection by penoscopy of male sexual contacts of women with genital HPV disease has shown that 69% [15] or 88% [16] have at least small lesions.

There is no reliable information on the infectivity of common and plantar warts, but experience suggests that it is substantially less. The infectivity of maternal genital HPV as regards laryngeal papilloma in the child seems low; from 51 cases of pregnancy in women with genital warts, no cases of childhood laryngeal papilloma were seen [17]. The risk of transmission from mother to child with subsequent development of disease in the child has been estimated to be between 1 in 80 and 1 in 1500 [18].

Modes of transmission

Warts are spread by direct or indirect contact. For infection to occur, the wart virus particle may need to come into contact with a stem cell in the basal epidermal layer. Thus, impairment of the epithelial barrier function, by trauma (including mild abrasions), maceration or both, greatly predisposes to inoculation of virus, and is generally assumed to be required for infection at least in fully keratinized skin, as in the following examples.

1. Plantar warts are commonly acquired from swimming pool or shower-room floors, whose rough surfaces abrade moistened keratin from infected feet and help to inoculate virus into the softened skin of others.
2. Common hand warts may spread widely round the nails in those who bite their nails or periungual skin, over habitually sucked fingers in young children, and to the lips and surrounding skin in both cases.
3. Shaving may spread wart infection over the beard area.
4. Occupational handlers of meat, fish and poultry have high incidences of hand warts, attributed to cutaneous injury and prolonged contact with wet flesh and water.
5. Genital warts have a high infectivity. The thinner mucosal surface is presumably more susceptible to inoculation of virus than is thicker keratinized skin, but in addition lesions are commonest in sites subject to greatest coital friction in both sexes.

Iatrogenic transmission. Because of the long incubation period, iatrogenic spread would be difficult to establish and seems not to have been reported, though the possibility exists. HPV DNA has been detected on instruments used for the examination of women with clinical or subclinical HPV infection [19] and in the environment of a genitourinary medicine clinic [20]. HPV DNA is found in the smoke plume from warts treated with laser or electrocautery [21]. The common practice of dipping cotton wool swabs for a series of patients into the same flask of liquid nitrogen could transfer herpes simplex virus (used as a model, and by implication HPV) between patients [22].

Transmission of anogenital warts in adults. HPV transmission has been most closely studied in the case of anogenital warts. Acquisition most commonly follows sexual contact but it is generally agreed that anogenital warts are not always transmitted sexually. Perianal warts may accompany genital warts, either due to local spread of infection or to direct contact during anal coitus.

Occasional non-sexual acquisition of anogenital warts in adults is assumed to be possible. HPV-1 and HPV-2 may occur in genital warts [23,24]. The sensitivity of PCR analysis has shown that HPV DNA may be present on underwear and the fingers of patients with genital warts [25,26] suggesting that transmission could occur by a number of routes.

Transmission of anogenital warts in children [9,13,27]. Anogenital warts are uncommon in children, but their occurrence frequently stimulates discussion of the possibility of sexual transmission. With the lack of large-scale prospective studies, the possibility of bias in referral or in reporting should be considered, and there remains insufficient information to offer a reliable estimate of the relative frequency of sexual abuse in such cases.

Infection from the mother's genital tract at delivery [28,29] is regarded as a frequent source of childhood anogenital warts, probably including those presenting up to 2 years of age. Genital papillomaviruses transmitted from mother to baby at birth may persist in childhood [30,31] as shown by the retention of the DNA and/or a humoral response against the viral proteins. Postnatally, transmission from adults with genital warts may occur non-sexually [32] such as by sharing a bath with an infected adult. A review of reports published between 1976 and 1983 [33] found that, of the total of 21 cases, the probable route of infection was believed to be sexual in 11, prepartum or intrapartum in three, and unknown in seven. In a study of 42 children with anogenital warts in 1993, the mode of acquisition was thought to be sexual in no more than 5% [34]. Studies involving HPV typing of childhood anogenital warts have produced somewhat varying conclusions, but overall, approximately 50% have been found to harbour mucosogenital HPVs with the cutaneous types 2, 27 and 57 also commonly detected [29,35–37].

Thus, on present incomplete information, both sexual and non-sexual routes are significant in transmission of childhood

anogenital warts [38]. The long and variable incubation period, the possibility of latent or subclinical infection in the source and the problems in eliciting an accurate account of sexual contact from the child and of confirming it from the perpetrator, all make it difficult to decide which applies in an individual case. Absence of other physical evidence of molestation, location of the warts on fully keratinized skin as opposed to genital or anal mucosa, a clinical resemblance to common warts and young age of the child, perhaps up to 1–2 years at the onset of the warts, would tend to support non-sexual transmission. Where sexual abuse is suspected, the case should be referred to a paediatrician or child-abuse specialist. In addition, HPV typing is not routinely of use but might be forensically useful; the same type in child and in suspected abuser would be consistent with but not proof of sexual transmission, while different types would be strong evidence against the possibility.

References

1 Barr A, Coles RB. Plantar warts. A statistical survey. *Trans St Johns Hosp Dermatol Soc* 1966; **52**: 226–38.
2 Kilkenny M, Marks R. The descriptive epidemiology of warts in the community. *Australas J Dermatol* 1996; **37**: 80–6.
3 Williams HC, Pottier A, Strachan D. The descriptive epidemiology of warts in British schoolchildren. *Br J Dermatol* 1993; **128**: 504–11.
4 Kyriakis K, Pagana G, Michailides C *et al.* Lifetime prevalence fluctuations of common and plane viral warts. *J Eur Acad Dermatol Venereol* 2007; **21**: 260–2.
5 Simms I, Fairley CK. Epidemiology of genital warts in England and Wales: 1971 to 1994. *Genitourin Med* 1997; **73**: 365–7.
6 Simms I, Fleming DM, Lowndes CM *et al.* Surveillance of sexually transmitted diseases in general practice: a description of trends in the Royal College of General Practitioners Weekly Returns Service between 1994 and 2001. *Int J STD AIDS* 2006; **17**: 693–8.
7 Health Protection Agency. A complex picture. HIV and other sexually transmitted infections in the United Kingdom: 2006. Available from: http://www.hpa.org.uk.
8 Castellsague X, Cohet C, Puig-Tintore LM *et al.* Epidemiology and cost of treatment of genital warts in Spain. *Eur J Public Health* 2009; **19**: 106–10.
9 Armstrong DK, Handley JM. Anogenital warts in prepubertal children: pathogenesis, HPV typing and management. *Int J STD AIDS* 1997; **8**: 78–81.
10 Bunney MH. *Viral Warts: Their Biology and Treatment*. Oxford: Oxford University Press; 1982.
11 Goldschmidt H, Kligman AM. Experimental inoculation of humans with ectodermotropic viruses. *J Invest Dermatol* 1958; **31**: 175–82.
12 Oriel JD. Natural history of genital warts. *Br J Vener Dis* 1971; **47**: 1–13.
13 Oriel JD. Anogenital papillomavirus infection in children. *BMJ (Clin Res Ed)* 1988; **296**: 1484–5.
14 Bennett RS, Powell KR. Human papillomaviruses: associations between laryngeal papillomas and genital warts. *Pediatr Infect Dis J* 1987; **6**: 229–32.
15 Sand PK, Bowen LW, Blischke SO *et al.* Evaluation of male consorts of women with genital human papilloma virus infection. *Obstet Gynecol* 1986; **68**: 679–81.
16 Sedlacek TV, Cunnane M, Carpiniello V. Colposcopy in the diagnosis of penile condyloma. *Am J Obstet Gynecol* 1986; **154**: 494–6.
17 Chuang TY, Perry HO, Kurland LT *et al.* Condyloma acuminatum in Rochester, Minn., 1950–1978. I. Epidemiology and clinical features. *Arch Dermatol* 1984; **120**: 469–75.
18 Shah K, Kashima H, Polk BF *et al.* Rarity of cesarean delivery in cases of juvenile-onset respiratory papillomatosis. *Obstet Gynecol* 1986; **68**: 795–9.
19 Ferenczy A, Bergeron C, Richart RM. Human papillomavirus DNA in fomites on objects used for the management of patients with genital human papillomavirus infections. *Obstet Gynecol* 1989; **74**: 950–4.
20 Strauss S, Sastry P, Sonnex C *et al.* Contamination of environmental surfaces by genital human papillomaviruses. *Sex Transm Infect* 2002; **78**: 135–8.
21 Ferenczy A, Bergeron C, Richart RM. Human papillomavirus DNA in CO_2 laser-generated plume of smoke and its consequences to the surgeon. *Obstet Gynecol* 1990; **75**: 114–8.
22 Jones SK, Darville JM. Transmission of virus particles by cryotherapy and multi-use caustic pencils: a problem to dermatologists? *Br J Dermatol* 1989; **121**: 481–6.
23 Krzyzek RA, Watts SL, Anderson DL *et al.* Anogenital warts contain several distinct species of human papillomavirus. *J Virol* 1980; **36**: 236–44.
24 Staquet MJ, Viac J, Bustamante R *et al.* Human papilloma virus type I purified from human genital warts. *Dermatologica* 1981; **162**: 213–9.
25 Bergeron C, Ferenczy A, Richart C. Underwear: contamination by human papillomavirus infection. *Epidemiol Rev* 1990; **10**: 213–9.
26 Sonnex C, Strauss S, Gray JJ. Detection of human papillomavirus DNA on the fingers of patients with genital warts. *Sex Transm Infect* 1999; **75**: 317–9.
27 Cobb MW. Human papillomavirus infection. *J Am Acad Dermatol* 1990; **22**: 547–66.
28 Patel R, Groff DB. Condyloma acuminata in childhood. *Pediatrics* 1972; **50**: 153–4.
29 Rock B, Naghashfar Z, Barnett N *et al.* Genital tract papillomavirus infection in children. *Arch Dermatol* 1986; **122**: 1129–32.
30 Cason J, Kaye JN, Jewers RJ *et al.* Perinatal infection and persistence of human papillomavirus types 16 and 18 in infants. *J Med Virol* 1995; **47**: 209–18.
31 Puranen M, Yliskoski M, Saarikoski S *et al.* Vertical transmission of human papillomavirus from infected mothers to their newborn babies and persistence of the virus in childhood. *Am J Obstet Gynecol* 1996; **174**: 694–9.
32 Stumpf PG. Increasing occurrence of condylomata acuminata in premenarchal children. *Obstet Gynecol* 1980; **56**: 262–4.
33 Neinstein LS, Goldenring J, Carpenter S. Nonsexual transmission of sexually transmitted diseases: an infrequent occurrence. *Pediatrics* 1984; **74**: 67–76.
34 Handley J, Dinsmore W, Maw R *et al.* Anogenital warts in prepubertal children; sexual abuse or not? *Int J STD AIDS* 1993; **4**: 271–9.
35 Padel AF, Venning VA, Evans MF *et al.* Human papillomaviruses in anogenital warts in children: typing by in situ hybridisation. *BMJ* 1990; **300**: 1491–4.
36 Lacey CJ, Gibson PE, Benton EC. Human papillomaviruses in anogenital warts in children. *BMJ* 1990; **301**: 241.
37 Yun K, Joblin L. Presence of human papillomavirus DNA in condylomata acuminata in children and adolescents. *Pathology* 1993; **25**: 1–3.
38 Hornor G. Ano-genital warts in children: Sexual abuse or not? *J Pediatr Health Care* 2004; **18**: 165–70.

Pathology. Viral warts show acanthosis and hyperkeratosis, usually with the characteristic feature of koilocytosis of upper keratinocytes. In most warts there is also papillomatosis. In koilocytes and other granular layer cells, there may be basophilic nuclear inclusion bodies, which are seen ultrastucturally to be composed of arrays of viral particles. These upper epidermal cells have eosinophilic inclusions representing irregular, clumped keratohyaline granules. This cytopathic effect may show detailed features typical of the HPV type involved [1,2].

Common and plantar warts. These are characterized by hyperplasia of all layers of the epidermis. There is gross hyperkeratosis with areas of parakeratosis, and both spinous and granular layers are conspicuously thickened. Elongated and flattened rete ridges are bent inwards towards the centre of the wart. The granular layer may be disordered with foci of koilocytes. These vacuolated cells have a dark nucleus which often appears flattened or twisted. Residual features of vacuolated cells or abnormal keratohyaline granules may be seen within the parakeratotic stratum corneum. In deep palmoplantar warts caused by HPV type 1, the cytopathic changes are more marked and may be visible in the lower stratum spinosum. Common warts on the face, limbs or near mucous membranes often have a morphology similar to genital warts with exophytic growth and a variable amount of hyperkeratosis.

Plane warts. The hyperkeratosis is of a loose lamellar type and there is acanthosis without papillomatosis. Vacuolated epidermal cells are more conspicuous and contain numerous viral particles [3].

Anogenital warts. Genital warts show extreme acanthosis and papillomatosis, but the horny layer is parakeratotic and not very thick. Koilocytes may be limited in distribution and not found in all sections. The epidermal processes are wide and rounded, with a well-defined lower border. The connective tissue is frequently very oedematous and the capillaries tortuous and increased.

Differentiation from malignant condylomas may be difficult after treatment with podophyllin or podophyllotoxin or in the case of giant condylomas or Buschke–Löwenstein tumours (see p. 33.55).

References

1 Gross G, Pfister H, Hagedorn M *et al.* Correlation between human papillomavirus (HPV) type and histology of warts. *J Invest Dermatol* 1982; **78**: 160–4.
2 Croissant O, Breitburd F, Orth G. Specificity of cytopathic effect of cutaneous human papillomaviruses. *Clin Dermatol* 1985; **3**: 43–55.
3 Laurent R, Coume-Marquet S, Kienzler JL *et al.* Comparative electron microscopic study of clear cells in epidermodysplasia verruciformis and flat warts. *Arch Dermatol Res* 1978; **263**: 1–12.

Immunity to HPV [1–3]

The relative sequestration of the virus in the upper reaches of the epidermis, the lack of an animal model for HPV, the difficulty of finding never-infected control subjects, and the large number of HPV types, have delayed research and our understanding of the immune mechanisms in relation to this virus. Over recent decades, however, the ability to clone the viral genes and to produce recombinant capsid proteins and early (E) gene peptides has led to many advances. Dogs exposed to canine oral papillomavirus developed neutralizing antibodies and were protected from infection by immunization with virus-like particles of major capsid protein [4]. Cell mediated immune (CMI) responses produced in mice by injection of an HPV-16 E7 peptide protected them against subsequent challenge with HPV-16 transformed tumour cells which would otherwise have caused a lethal tumour [5]. These and many other studies in both animals and humans have led to the development of both prophylactic and therapeutic vaccines. Prophylactic vaccination against HPV types 6, 11, 16 and 18 is now in clinical use [6,7].

The principal mechanism for the rejection of warts is via the cell-mediated immune system. Warts can disappear when the immune response is stimulated, whilst in persistent disorders of CMI, the prevalence and severity of warts and the incidence of HPV-related malignancy are increased [8]. In addition, the histological changes in regressing warts are consistent with cell-mediated attack; a study of resolving plane warts showed lymphocytic and phagocytic infiltrates including helper and suppressor T cells, Langerhans' cells and satellite-cell necrosis [9]. A more detailed dissection of the immunological events occurring in resolving genital warts has shown that the lymphocytic infiltrate is predominantly of $CD8^+$ cells [10].

The apparent failure of the immune system in otherwise healthy individuals to clear warts for months or years remains incompletely understood. A subdued local immune response is suggested by the observations that Langerhans' cell numbers are reduced within warts [11] and T lymphocytes are rare within the epidermal compartment. In these patients and also those who harbour high-risk genital HPVs with the development of cancer, it is possible that there may be inability by the immune system to target certain HPV proteins, possibly due to poor antigen presentation, poor effector response or virally-induced local immunosuppression resulting in the development of tolerance [12]. The initial success of the virus in establishing infection may similarly depend in part on avoidance of detection by the innate immune response and certain immunomodulatory effects of the viral proteins.

References

1 Tyring SK. Human papillomavirus infections: epidemiology, pathogenesis, and host immune response. *J Am Acad Dermatol* 2000; **43**: S18–26.
2 Stanley M. Immune responses to human papillomavirus. *Vaccine* 2006; **24** (Suppl. 1): S16–22.
3 Frazer IH. Prevention of cervical cancer through papillomavirus vaccination. *Nat Rev Immunol* 2004; **4**: 46–54.
4 Suzich JA, Ghim SJ, Palmer-Hill FJ *et al.* Systemic immunization with papillomavirus L1 protein completely prevents the development of viral mucosal papillomas. *Proc Natl Acad Sci USA* 1995; **92**: 11553–7.
5 Feltkamp MC, Smits HL, Vierboom MP *et al.* Vaccination with cytotoxic T lymphocyte epitope-containing peptide protects against a tumor induced by human papillomavirus type 16-transformed cells. *Eur J Immunol* 1993; **23**: 2242–9.
6 Villa LL, Costa RL, Petta CA *et al.* Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. *Lancet Oncol* 2005; **6**: 271–8.
7 Markowitz LE, Dunne EF, Saraiya M *et al.* Quadrivalent human papillomavirus vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2007; **56**: 1–24.
8 Ladoyanni E, North J, Tan CY. Idiopathic CD4+ T-cell lymphocytopaenia associated with recalcitrant viral warts and squamous malignancy. *Acta Derm Venereol* 2007; **87**: 76–7.
9 Iwatsuki K, Tagami H, Takigawa M *et al.* Plane warts under spontaneous regression. Immunopathologic study on cellular constituents leading to the inflammatory reaction. *Arch Dermatol* 1986; **122**: 655–9.
10 Coleman N, Birley HD, Renton AM *et al.* Immunological events in regressing genital warts. *Am J Clin Pathol* 1994; **102**: 768–74.
11 Chardonnet Y, Viac J, Thivolet J. Langerhans cells in human warts. *Br J Dermatol* 1986; **115**: 669–75.
12 Frazer IH. Interaction of human papillomaviruses with the host immune system: a well evolved relationship. *Virology* 2009; **384**: 410–4.

Clinical features. Warts on the skin may present in a number of different morphological forms, dependent on HPV type, body site, immunological status of the patient and environmental influences. Of 1000 children under 16 with warts referred to hospital clinics in Cambridge, UK in the 1950s, 70% had common warts, 24% plantar warts, 3.5% plane warts, 2.0% filiform warts and 0.5% anogenital warts [1].

Common warts (Fig. 33.16). Common warts (excluding plantar warts) are due mainly to HPV-2, but also to the closely related types 27, 57 and types 1 and 4. Firm papules with a rough, horny surface, they range in size from less than 1 mm to over 1 cm in diameter, and by confluence can form large masses. They are most commonly situated on the backs of the hands and fingers, and, in children under 12 years of age, on the knees, but may occur anywhere on the skin. A single wart may persist unchanged for



Fig. 33.16 Common warts. (a) Hand. (b) Dorsum of finger. (c) Warts on thumb spread by thumb-sucking. (d) Periungual warts in a nail-biter. ((a) Courtesy of Addenbrooke's Hospital, Cambridge, UK; (b & c) Courtesy of Dr A.S. Highet, York District Hospital, UK; (d) Courtesy of York District Hospital.)

months or years, or large numbers may develop rapidly or after an interval. New warts may form at sites of trauma, though this Köbner-like isomorphic phenomenon is usually less marked than in plane warts.

Common warts are usually symptomless, but may be tender on the palmar aspects of the fingers, when fissured or when growing beneath the nail plate and warts on the eyelids may be associated with conjunctivitis or keratitis. Common warts account for only 1 or 2% of warts on or around the genitalia in adults; in the male they are almost always confined to the shaft of the penis. They often retain their usual morphological characteristics with dry hyperkeratosis and frequently do not resemble soft acuminate (genital) warts.

It is impossible to offer a reliable prognosis in the individual patient. About 65% of warts disappear spontaneously within 2 years [2] and 95% within 4 years [3]. There is a clinical impression that warts in adults, especially older adults, are slower to clear either with or without treatment.

Regression of common warts is asymptomatic and occurs gradually over several weeks, usually without blackening [4].

Malignant change in warts is extremely rare but has been reported in immunosuppression [5].

Periungual warts. Common warts around the nails, especially at the nail folds or beneath the nail, can disturb nail growth. Nail biting may increase the risk of infection at this site.

Malignant change in lesions with features of periungual warts is extremely rare but has been reported in immunosuppression and in association with genital HPV disease [6,7].

Plantar warts. Plantar warts are caused by HPV-1, 2, 4, 27 or 57. The deep 'myrmecia' form is due to HPV-1. Smaller lesions may contain HPV-2, 4, 27 or 57, while mosaic warts are commonly caused by HPV-2.

A plantar wart at first appears as a small shining 'sago-grain' papule, but soon assumes the typical appearance of a sharply defined, rounded lesion, with a rough, keratotic surface surrounded by a smooth collar of thickened horn. If the surface is gently pared with a scalpel the abrupt separation between the wart tissue and the protective horny ring becomes more obvious,



Fig. 33.17 Mosaic plantar wart. (Courtesy of Addenbrooke's Hospital, Cambridge, UK.)

as the epithelial ridges of the plantar skin are not continued over the surface of the wart. If the paring is continued, small bleeding points, the tips of the elongated dermal papillae, are evident. Dermoscopy can also help to distinguish a plantar wart from a corn or a callosity [8].

Most plantar warts are beneath pressure points, the heel or the metatarsal heads. Individuals may be affected by single or numerous lesions. Sometimes, a cluster of small satellite warts, the smallest of pinhead size, having at first an almost vesicular appearance, may develop around a large wart. Mosaic warts are so described from the appearance presented by a plaque of closely grouped small warts (Fig. 33.17). The angular outlines of the tightly compressed individual warts are seen when the surface is pared.

Pain is a common but variable symptom. It may be severe and disabling but may be absent, and many warts are discovered only on routine inspection. Mosaic warts are often painless.

The duration of plantar warts is very variable. Spontaneous regression occurs sooner in children than in adults and is delayed if hyperhidrosis or orthopaedic defects are present. In children before puberty the average duration is probably less than a year but in older children and adults a longer duration is not uncommon and persistence for several years is not exceptional. The number of warts present does not influence the prognosis, but mosaic warts tend to be especially persistent. Regression is occasionally clinically inflammatory, and often culminates in blackening from thrombosed blood before the lesion separates [9], but in many cases simply takes the form of apparent drying and gradual separation.

As well as the distinction from corns and calluses, plantar warts may rarely be confused with the discrete horny papules of punctate keratoderma of genetic origin (see Chapter 19) which develop during childhood or early adult life, are irregularly scattered over the palms and soles, and are often largest in pressure areas.

Plane warts (flat warts) (Fig. 33.18). Plane warts, due mainly to HPV-3 and 10, are smooth, flat or slightly elevated and are usually skin-coloured or greyish-yellow, but may be pigmented. They are round or polygonal in shape and vary in size from 1 to 5 mm or more in diameter. The face and the backs of the hands and the shins are the sites of predilection and the number present ranges from two or three to many hundreds. Contiguous warts may coalesce and a linear arrangement in scratch marks is a characteristic feature (Fig. 33.18b). Although all warts present are usually of the same type, a few common warts may be associated, especially on the backs of the hands.

Regression of plane warts is usually heralded by inflammation in the lesions [10,11], causing itch, erythema and swelling, such that previously unnoticed warts may become evident. Depigmented haloes may appear around the lesions. Resolution is usually complete within a month, and appears to be HPV-type specific as it generally occurs in all plane warts at all body sites, though not in any coexisting warts of other types.

In differential diagnosis, lichen planus causes most difficulty. It is relatively less common in children, favours the flexor aspects of the forearms, is unusual on the face and is often itchy. The mucous membranes may be involved. In contrast to the smooth, purplish, polygonal papules of lichen planus, the surface of plane warts has a stippled appearance under magnification.

In acrokeratosis verruciformis numerous warty papules are symmetrically distributed on the backs of the hands.

Filiform and digitate warts (Fig. 33.19). Filiform and digitate warts occur commonly in the male, on the face and neck, irregularly distributed, and often clustered. Digitate warts, often in small groups, also occur on the scalp in both sexes, where they are occasionally confused with epidermal naevi. Isolated warts on the limbs often assume a filiform shape.

Anogenital warts (Figs 33.20 & 33.21). Note on nomenclature: the term condyloma acuminatum (condyloma = knuckle, acuminatum = pointed; plural condylomata acuminata) was originally used to emphasize the difference between anogenital warts, which are usually protuberant, and the flatter syphilitic lesions, condylomata lata. It became an accepted term for viral anogenital warts and now may be used variously to describe protuberant anogenital warts, flat HPV lesions of external genitalia or cervix or vagina, or oral lesions.

Anogenital warts are common and are caused in 75% by HPV-6. The remainder are caused by HPV-11 or more unusual, low-risk HPVs. They are often asymptomatic, but may cause discomfort, discharge or bleeding. The typical anogenital wart is soft, pink, elongated and sometimes filiform or pedunculated. The lesions are usually multiple especially on moist surfaces, and their growth can be enhanced during pregnancy [12], or in the presence of other local infections [13]. Large malodorous masses may form on vulvar and perianal skin. This classical 'acuminate' (sometimes called papillomatous, or hyperplastic) form constitutes about two-thirds of anogenital warts. The commonest sites, the area of frenulum, corona and glans in men, and the posterior fourchette in women, correspond to the likely sites of greatest coital friction [12]. Most other lesions are flat, though more conspicuous than plane warts elsewhere, and some of these, generally on non-mucosal surfaces such as the penile shaft, pubic skin, perianal skin and groins, may be sufficiently pigmented to resemble seborrhoeic



(a)



(b)

Fig. 33.18 Plane warts. (a) Warts on knee. (b) Warts on arm with spread into a scratch. (Courtesy of Addenbrooke's Hospital, Cambridge, UK.)



Fig. 33.19 Filiform wart on forearm. (Courtesy of Addenbrooke's Hospital, Cambridge, UK.)



(a)

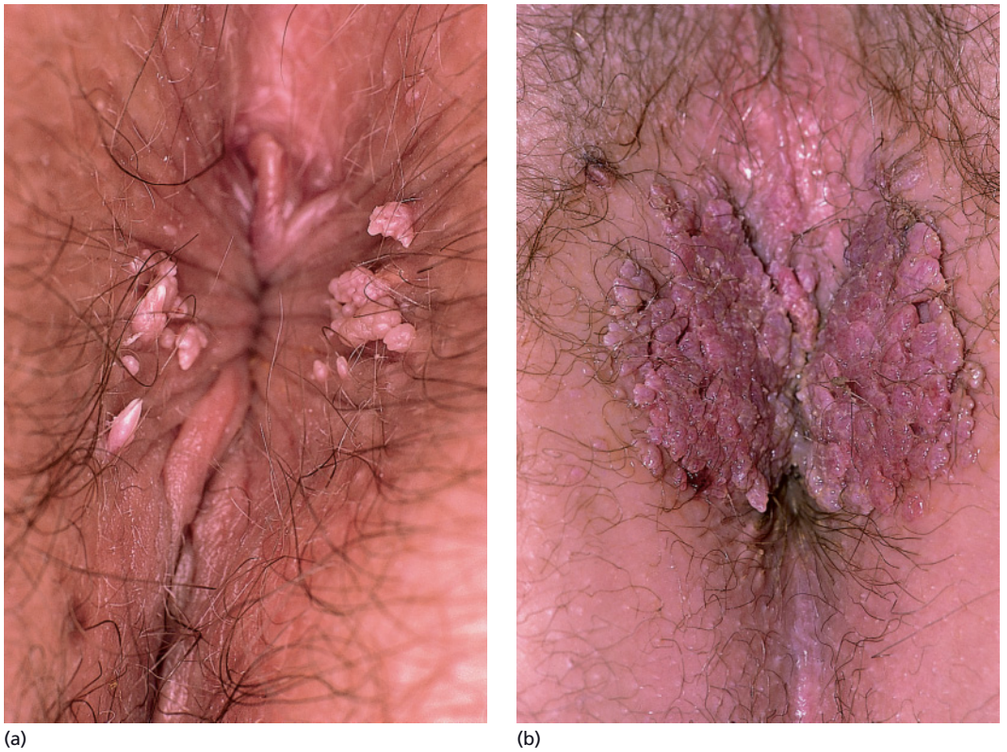


(b)



(c)

Fig. 33.20 Penile warts. (a, b) Classical condylomata acuminata. (c) This pigmented lesion was confirmed histologically to be a viral wart. (Courtesy of York District Hospital, UK.)



(a) (b)

Fig. 33.21 (a, b) Perianal warts. (Courtesy of York District Hospital, UK.)

keratoses. Both acuminate and flat types may coexist. Occasionally, only lesions resembling common warts are seen, in men usually on the penile shaft, and these may be the result of contact with common warts elsewhere on the patient or on the sexual partner [14].

In children, warts in the anogenital area are often more hyperkeratotic than in adults and may be caused by HPV types associated with cutaneous disease as well as HPV types 6 and 11.

The duration of anogenital warts varies from a few weeks to many years. Recurrences can be expected in about 25% of cases, the interval varying from 2 months to 23 years [15]. HPV DNA can be demonstrated in clinically and histologically normal skin adjacent to warts and intraepithelial neoplasia, and this latent infection correlates well with recurrence after clinical cure [16].

Patients with genital warts frequently have other genital infections. These are mainly minor conditions such as candidiasis, trichomoniasis and non-specific genital infection with occasional major venereal infections (syphilis or gonorrhoea) [15,17].

Flat anogenital warts can appear very similar to lesions of anogenital intraepithelial neoplasia containing high-risk HPVs. The presence of any type of anogenital wart should raise the possibility that the patient may also be infected with high-risk HPVs and prompt screening for anogenital intraepithelial neoplasia.

Vulval papillomatosis, with a diffuse velvety or granular appearance in the vaginal introitus, and pearly penile papules may cause confusion with the possibility of warts.

Very florid warts should warrant consideration of an underlying immune deficiency.

The development of large protuberant masses, induration, pain or serosanguinous discharge should arouse suspicion of malignant change (including Buschke–Löwenstein tumour), requiring prompt excision or biopsy and also assessment of immune status.

References

1 East Anglian Branch of the Society of Medical Officers of Health. The incidence of warts and plantar warts amongst children in East Anglia. *Med Officer* 1955; **94**: 55–9.

2 Massing AM, Epstein WL. Natural history of warts. A two-year study. *Arch Dermatol* 1963; **87**: 306–10.

3 Williams HC, Pottier A, Strachan D. The descriptive epidemiology of warts in British schoolchildren. *Br J Dermatol* 1993; **128**: 504–11.

4 Berman A, Winkelmann RK. Involuting common warts. Clinical and histopathologic findings. *J Am Acad Dermatol* 1980; **3**: 356–62.

5 Noel JC, Detremmerie O, Peny MO *et al.* Transformation of common warts into squamous cell carcinoma on sun-exposed areas in an immunosuppressed patient. *Dermatology* 1994; **189**: 308–11.

6 Baran R, Tosti A, De Berker D. Periungual keratoacanthoma preceded by a wart and followed by a verrucous carcinoma at the same site. *Acta Derm Venereol* 2003; **83**: 232–3.

7 Sau P, McMarlin SL, Sperling LC *et al.* Bowen's disease of the nail bed and periungual area. A clinicopathologic analysis of seven cases. *Arch Dermatol* 1994; **130**: 204–9.

8 Bae JM, Kang H, Kim HO *et al.* Differential diagnosis of plantar wart from corn, callus and healed wart with the aid of dermoscopy. *Br J Dermatol* 2009; **160**: 220–2.

9 Berman A, Domnitz JM, Winkelmann RK. Plantar warts recently turned black. Clinical and histopathologic findings. *Arch Dermatol* 1982; **118**: 47–51.

10 Iwatsuki K, Tagami H, Takigawa M *et al.* Plane warts under spontaneous regression. Immunopathologic study on cellular constituents leading to the inflammatory reaction. *Arch Dermatol* 1986; **122**: 655–9.

11 Rogozinski TT, Jablonska S, Jarzabek-Chorzelska M. Role of cell-mediated immunity in spontaneous regression of plane warts. *Int J Dermatol* 1988; **27**: 322–6.

12 Oriel JD. Natural history of genital warts. *Br J Vener Dis* 1971; **47**: 1–13.

13 Kinghorn GR. Genital warts: incidence of associated genital infections. *Br J Dermatol* 1978; **99**: 405–9.
14 Gross G, Ikenberg H, Gissmann L *et al.* Papillomavirus infection of the anogenital region: correlation between histology, clinical picture, and virus type. Proposal of a new nomenclature. *J Invest Dermatol* 1985; **85**: 147–52.
15 Chuang TY, Perry HO, Kurland LT *et al.* Condyloma acuminatum in Rochester, Minn., 1950–1978. I. Epidemiology and clinical features. *Arch Dermatol* 1984; **120**: 469–75.
16 Ferenczy A, Mitao M, Nagai N *et al.* Latent papillomavirus and recurring genital warts. *N Engl J Med* 1985; **313**: 784–8.
17 Fairris GM, Statham BN, Waugh MA. The investigation of patients with genital warts. *Br J Dermatol* 1984; **111**: 736–8.

Human papillomavirus and warts in special situations

Butchers' warts. Occupational handlers of meat, poultry or fish have a high incidence of hand warts where the skin is in prolonged contact with moist animal flesh. Among 1480 New York meat-trade workers, 23% of those directly handling meat had warts, compared with 10% of those employed in other tasks [1]. In a Polish study, warts affected 49% of slaughterhouse workers who had direct contact with flesh, but only 9% of those working in a slaughterhouse automated so that little handling of meat took place [2].

These lesions affect the hands, are often larger than common warts, and have a high risk of recurrence even after successful treatment. HPV-2 is frequently found in butchers' warts, but HPV-7 is present in a third to a half of lesions [2–5]. HPV-7 initially seemed specific to meat handlers, however, it has been reported occasionally in warts of non-meat handlers [4,6], and in facial and oral warts of patients with HIV disease [7].

Epidermoid plantar cysts. Epidermoid cysts of weight-bearing areas of the sole have been found to contain papillomavirus (HPV-60 and more rarely HPV-57) in several Japanese patients [8,9]. The cysts, which are thought to arise either by implantation or by infection of the eccrine duct [10], show histological features of HPV infection in the stratifying squamous wall. The upper epidermal cells produce large cytoplasmic granules and abundant viral particles.

Pigmented warts. Warts with pigmentation have been reported mainly on palms and soles in Japanese patients [11]. Melanosomes are increased within the lesions, which are associated with HPV-65 (64%), 4 (23%) and 60 (13%).

Oral warts. Oral warts, including some which appear to have been sexually transmitted [12], usually contain HPV-6 or 11 [13] and more rarely HPV-2, 57 or 16 [14]. They are common in association with HIV disease when a greater variety of HPV types may be found, including HPV-7, more usually associated with butchers' warts [7]. Antiretroviral treatment may lead to worsening of the warts rather than improvement [15]. HPV-13 and 32 seem to be almost specific for lesions of the rare, benign, familial disorder focal epithelial hyperplasia (Heck's disease) [16]. High-risk genital HPVs have been detected in over 80% of cases of oral leukoplakia, and in about 50% of cases of orophranygeal carcinoma [17].

Respiratory papillomatosis [18,19]. This condition is due most commonly to HPV-11, but also associated with other common genital types such as HPV-6 and very rarely with high-risk type 16 [20]. Childhood cases are believed to result from maternal infection, probably at birth during vaginal delivery. Latent or subclinical infection in the laryngeal mucosa presumably explains recurrences after successful treatment, and might explain adult-onset cases, although some of these may be due to sexual transmission [21]. Treatment usually involves recurrent debulking of lesions. Malignant transformation occurs very rarely and is most commonly associated with HPV type 11 [22].

Conjunctival papillomas. HPV of the low-risk mucosal type is frequently detected in conjunctival papillomas [23] with rare detection of high-risk types [24].

Nasal inverting papillomas. HPV-11 and -57 have been detected in nasal inverting papilloma and in an inverting papilloma of the maxillary sinus [25,26].

Psoriasis. The use of sensitive PCR amplification has revealed HPV sequences in patients with psoriasis and it is speculated that the virus may have a role in the disease process [27,28]. Alternatively, the abnormal barrier function of psoriatic skin may permit subsequent higher carriage and detection rate of HPV DNA [29].

References

1 Finkel ML, Finkel DJ. Warts among meat handlers. *Arch Dermatol* 1984; **120**: 1314–7.
2 Jablonska S, Obalek S, Golebiowska A *et al.* Epidemiology of butchers' warts. *Arch Dermatol Res* 1988; **280** (Suppl.): S24–8.
3 Melchers W, de Mare S, Kuitert E *et al.* Human papillomavirus and cutaneous warts in meat handlers. *J Clin Microbiol* 1993; **31**: 2547–9.
4 Keefe M, al-Ghamdi A, Coggon D *et al.* Cutaneous warts in butchers. *Br J Dermatol* 1994; **130**: 9–14.
5 Rudlinger R, Bunney MH, Grob R *et al.* Warts in fish handlers. *Br J Dermatol* 1989; **120**: 375–81.
6 de Villiers EM, Neumann C, Oltersdorf T *et al.* Butcher's wart virus (HPV 7) infections in non-butchers. *J Invest Dermatol* 1986; **87**: 236–8.
7 Greenspan D, de Villiers EM, Greenspan JS *et al.* Unusual HPV types in oral warts in association with HIV infection. *J Oral Pathol* 1988; **17**: 482–8.
8 Egawa K, Kitasato H, Honda Y *et al.* Human papillomavirus 57 identified in a plantar epidermoid cyst. *Br J Dermatol* 1998; **138**: 510–4.
9 Matsukura T, Iwasaki T, Kawashima M. Molecular cloning of a novel human papillomavirus (type 60) from a plantar cyst with characteristic pathological changes. *Virology* 1992; **190**: 561–4.
10 Egawa K. Eccrine-centred distribution of human papillomavirus 63 infection in the epidermis of the plantar skin. *Br J Dermatol* 2005; **152**: 993–6.
11 Egawa K, Honda Y, Inaba Y *et al.* Pigmented viral warts: a clinical and histopathological study including human papillomavirus typing. *Br J Dermatol* 1998; **138**: 381–9.
12 Butler S, Molinari JA, Plezia RA *et al.* Condyloma acuminatum in the oral cavity: four cases and a review. *Rev Infect Dis* 1988; **10**: 544–50.
13 Praetorius F. HPV-associated diseases of oral mucosa. *Clin Dermatol* 1997; **15**: 399–413.
14 Padayachee A, Sanders CM, Maitland NJ. A polymerase chain reaction (PCR) investigation of oral verrucae which contain HPV types 2 and 57 by in situ hybridization. *J Oral Pathol Med* 1995; **24**: 329–34.
15 King MD, Reznik DA, O'Daniels CM *et al.* Human papillomavirus-associated oral warts among human immunodeficiency virus-seropositive patients in the era of highly active antiretroviral therapy: an emerging infection. *Clin Infect Dis* 2002; **34**: 641–8.
16 Henke RP, Guerin-Reverchon I, Milde–Langosch K *et al.* In situ detection of human papillomavirus types 13 and 32 in focal epithelial hyperplasia of the oral mucosa. *J Oral Pathol Med* 1989; **18**: 419–21.

17 Tachezy R, Klozar J, Salakova M *et al.* HPV and other risk factors of oral cavity/oropharyngeal cancer in the Czech Republic. *Oral Dis* 2005; **11**: 181–5.
18 Derkay CS, Wiatrak B. Recurrent respiratory papillomatosis: a review. *Laryngoscope* 2008; **118**: 1236–47.
19 Goon P, Sonnex C, Jani P *et al.* Recurrent respiratory papillomatosis: an overview of current thinking and treatment. *Eur Arch Otorhinolaryngol* 2008; **265**: 147–51.
20 Dickens P, Srivastava G, Loke SL *et al.* Human papillomavirus 6, 11, and 16 in laryngeal papillomas. *J Pathol* 1991; **165**: 243–6.
21 Mounts P, Shah KV. Respiratory papillomatosis: etiological relation to genital tract papillomaviruses. *Prog Med Virol* 1984; **29**: 90–114.
22 Jeong WJ, Park SW, Shin M *et al.* Presence of HPV type 6 in dysplasia and carcinoma arising from recurrent respiratory papillomatosis. *Head Neck* 2009; **31**: 1095–101.
23 Minchiotti S, Masucci L, Serapiao Dos Santos M *et al.* Conjunctival papilloma and human papillomavirus: identification of HPV types by PCR. *Eur J Ophthalmol* 2006; **16**: 473–7.
24 Saegusa M, Takano Y, Hashimura M *et al.* HPV type 16 in conjunctival and junctional papilloma, dysplasia, and squamous cell carcinoma. *J Clin Pathol* 1995; **48**: 1106–10.
25 Respler DS, Jahn A, Pater A *et al.* Isolation and characterization of papillomavirus DNA from nasal inverting (schneiderian) papillomas. *Ann Otol Rhinol Laryngol* 1987; **96**: 170–3.
26 Wu TC, Trujillo JM, Kashima HK *et al.* Association of human papillomavirus with nasal neoplasia. *Lancet* 1993; **341**: 522–4.
27 Weissenborn SJ, Höpfl R, Weber F *et al.* High prevalence of a variety of epidermodysplasia verruciformis-associated human papillomaviruses in psoriatic skin of patients treated or not treated with PUVA. *J Invest Dermatol* 1999; **113**: 122–6.
28 Majewski S, Jablonska S. Possible involvement of epidermodysplasia verruciformis human papillomaviruses in the immunopathogenesis of psoriasis: a proposed hypothesis. *Exp Dermatol* 2003; **12**: 721–8.
29 Cronin JG, Mesher D, Purdie K *et al.* Beta-papillomaviruses and psoriasis: an intra-patient comparison of human papillomavirus carriage in skin and hair. *Br J Dermatol* 2008; **159**: 113–9.

Treatment [1,2]. Not all warts need treatment as many give little inconvenience and will resolve spontaneously. In addition, patients may need encouragement to persevere with long-term daily use of simpler preparations and more aggressive therapies, such as cryotherapy or surgery, have potential disadvantages. Whatever method is used there will be failures and recurrences. The best clinical guide to cure is the restoration of normal epidermal texture, including the epidermal ridge pattern where appropriate.

Advice on simple measures to limit the spread of the infection will be appreciated. Plantar warts should be covered with adequate plaster strapping, or the foot with close-fitting rubber 'verruca socks', or pool-side sandals worn at swimming pools or communal baths or showers. The spread of periungual and perioral warts is often due to biting of nails or periungual skin, and this practice must be strongly discouraged if attempted treatment is to be worthwhile; the use of adhesive strapping after the application of a 'wart paint' helps to break the habit. In addition, simple domestic hygiene, such as cleaning of baths after use and avoidance of shared towels, may be advised.

The most commonly used treatments for warts involve destruction of the area of epidermis infected with the virus. Such treatments may involve application of topical preparations or surgical approaches. Other therapies aimed at modifying the growth of the epidermis or to stimulate an immune response require either a topical or a systemic approach. Where treatment trials have been placebo-controlled, a 30% response rate generally is observed for placebo treatment.

Occlusion. Continuous duct tape occlusion of common warts for up to 2 months compared favourably with cryotherapy every 2–3 weeks in children [3], but placebo-controlled trials have not confirmed any significant effect in either adults or children [4,5].

Salicylic acid. The keratolytic effect of salicylic acid helps to reduce the thickness of warts and may stimulate an inflammatory response. A preparation containing 12–26% salicylic acid, possibly with additional lactic acid, in a quick-drying collodion or acrylate base, is the treatment of first choice for common and plantar warts. Daily use in a comparative study for 3 months achieved cure rates of 67% for hand warts, 84% for simple plantar warts and 45% for mosaic plantar warts, comparing favourably with other methods, including liquid nitrogen [6]. A review of six placebo-controlled trials confirmed this impression with 75% cured compared to 48% of placebo-treated patients [7]. Removal of surface keratin and the remnants of the previous application by gentle use of a pumice stone, emery board or foot file is a helpful preliminary in all warts and essential in very hyperkeratotic plantar warts. However, overenthusiastic abrasion is a common, if understandable, mistake, which may enhance spread of the virus by inoculation into adjacent skin. It is conceivable that abrasion of warts may help to stimulate an immune response [8]. Accurate application of a salicyclic acid preparation, avoiding normal skin, may require a fine applicator such as a sharpened matchstick or a cocktail stick, and will minimize subsequent local discomfort. After drying, a whitish deposit remains. Penetration into thick keratin, as on the sole, is enhanced by adhesive plaster occlusion, which promotes maceration of the keratin layer and a reduction in barrier function. Occlusion can improve the response rate for treatment with salicylic acid [9].

These preparations are not suitable for anogenital warts. They can be particularly irritant on facial skin, though especially careful application or the use of weaker formulations, such as 4% salicylic acid in flexible collodion, may be successful.

Collodion contains colophony which may cause allergic contact dermatitis. Long-standing warts have been observed to disappear if the patient perseveres with this inadvertent immunotherapy, but the discomfort is usually too great for this approach to be regularly useful.

Adhesive plaster containing 40% salicylic acid is useful for plantar warts. It is applied daily, cut to the shape of the wart or group of warts and held in place by plain adhesive plaster. The regular use of salicylic acid preparations on warts may need to be continued for at least 3 months and often longer.

Glutaraldehyde. The virucidal properties of glutaraldehyde can be used in wart treatment. Proprietary preparations contain 10% glutaraldehyde in aqueous ethanol [6] or in a gel formulation but there have been no controlled trials. Treated skin hardens and is coloured brown which limits acceptability on the hands, but the fact that the glutaraldehyde dries into the skin without a surface deposit which could be rubbed off makes it a useful application for warts on the feet. A preparation of 20% glutaraldehyde in

aqueous solution produced a 72% cure rate for a variety of different cutaneous warts in 25 individuals [10]. Allergic contact dermatitis to the glutaraldehyde occurs occasionally and cutaneous necrosis is a rare complication of the strong solution.

Podophyllin and podophyllotoxin. Podophyllin is a plant-derived resin containing several cytotoxic compounds in unpredictable ratios. The most active of these is podophyllotoxin. Both the crude resin and purified podophyllotoxin are used in the treatment of anogenital warts, as they are more effective on mucosal than keratinized surfaces. They act as antimitotics, disrupting the formation of the spindle on which chromosomes align at mitosis.

Results with purified podophyllotoxin, 0.5% in ethanol applied twice daily for 3 days, extending treatment to 4 or 5 days if necessary and if tolerated, gives better results than podophyllin with cure rates between 60 and 70% [11,12]. The same routine may be repeated after a week's break if lesions persist. Once-daily treatment is less effective. For both penile and vulval warts, self-application of podophyllotoxin in either solution or cream formulation can be performed by the patient and can give a higher remission rate than the use of podophyllin [13].

Podophyllin resin is not used so commonly now, but treatment should be under professional supervision. A solution of 10–25% in compound tincture of benzoin is applied accurately to the area and then allowed to dry for a few minutes. The resin should be thoroughly washed off after 4 hours, though the time can be cautiously increased if the treatment is well tolerated. Applications are repeated weekly or more often. Of over 100 men treated weekly for 6 weeks, 22% were clear 6 weeks later and a 10% solution was as effective as 25% [14].

Some local irritation, usually greatest 1 or 2 days after application, is expected with podophyllin and to a lesser extent with podophyllotoxin. Histologically, epidermal intra- and intercellular oedema, mitoses and necrosis are seen, but no signs suggesting carcinogenicity [15].

Podophyllin is contraindicated in pregnancy [16]. It should not be used on exceptionally large or bleeding areas, where its application has been followed by intrauterine death [17], vomiting, diarrhoea, liver damage, renal damage, coma, peripheral neuropathy [18], bone-marrow suppression [19] and death [20], due to presumed systemic absorption. Oral ingestion has similar effects and can be fatal [21]. The side-effect profile of podophyllotoxin appears to be safer, although the usual precautions for its use should be observed.

Podophyllin and podophyllotoxin are generally ineffective if simply applied to warts of other types, due to the lack of penetration of the keratin layer. However, they can be used with caution under occlusion [22] or in combination with salicylic acid [23]. Although clearance rates may be as high as 80–95%, acute pain can occur with intense local inflammation.

Formalin. Soaks or compresses of 2–3% formalin in water (formalin is about 37% formaldehyde in water) may be effective for plantar warts [24], but is time consuming and difficult to limit to affected skin. The affected area must be soaked in the solution for 15–20 min daily, using soft paraffin as a barrier application to protect more sensitive skin. The formalin is virucidal, but also dries and hardens the skin, facilitating paring. A comparative study of formalin soaks with either water soaks or oral saccharose showed no difference in clearance [25].

Topical 5-fluorouracil. A 5% solution of 5-fluorouracil (5-FU) carefully applied daily under occlusion for a month is more effective than placebo [26], but, if used periungually, may cause onycholysis. A combination of 5% 5-FU and 10% salicylic acid tested in several studies cleared 63% of warts, compared with 23% when using salicylic acid alone [27]. Five per cent 5-FU ointment alone [28] or cream under occlusion [29] can be effective, but hyperpigmentation as well as erythema and erosion can be limiting side effects. Intralesional injection of 40 mg/ml 5-FU weekly for up to 4 weeks produced clearance in over 60% of warts [30].

Caustics. Monochloroacetic acid, trichloroacetic acid, silver nitrate [31,32], cantharidin [33], phenol [34] and other highly irritant chemicals can be used with effect but may cause painful reactions. In treatment of genital warts, cryotherapy is slightly more effective than trichloroacetic acid alone [35].

Retinoic acid. This treatment topically may be tried in plane warts, but the best results are claimed for higher than usual concentrations and irritation is common [36]; 85% of 25 children with plane warts treated with 0.05% tretinoin cream cleared their warts compared to 32% of controls [37].

Photodynamic therapy. Systemic or topical aminolaevulinic acid can be taken up by dividing cells, metabolized to protoporphyrin and then photoactivated to produce a damaging effect on the cell. A number of open or placebo-controlled studies have shown clearance rates of 75–90% for hand and foot warts [38], plane warts [39] and even periungual warts [40]. The treatment may need to be repeated two or three times but can be limited by pain [41].

Surgery. Excision is usually to be avoided since scarring is inevitable and recurrences of the wart in the scar are frequent. However, good results have been obtained by snipping out perianal warts after subcutaneous injection of adrenaline 1 : 300000 in physiological saline under general or local anaesthesia [42]. Curettage can also be effective as treatment for filiform warts.

Curettage and cautery/electrocoagulation, usually in combination, may be used for painful or resistant warts, but carry a risk of scarring. Topical application of local anaesthetic cream to the vulva for 10 min numbed the area in over 90% of cases [43], but otherwise, and for keratinized skin, local anaesthetic injection or even general anaesthesia would be required.

A technique of blunt dissection [44] has been advocated for plantar warts.

Cryotherapy. Carbon dioxide snow and liquid nitrogen can both produce cold thermal damage to the skin. Liquid nitrogen is commonly used in hospital practice, applied either by a cotton wool bud or from a cryospray. The rate of application of freeze is affected by the size of the hole in the spray nozzle or by the size, shape and density of the cotton wool at the tip of the bud.

Any thick keratin should be pared off, especially in plantar warts [45], and the surface be dry before freezing begins. In standard treatment, the application is continued until a rim of iced tissue (easily seen as a white discoloration) about 1 mm in width develops in the normal skin surrounding the wart. This may stimulate the development of an immune response [46]. After thawing, a second freeze cycle will improve the cure rate in plantar warts, although the benefit is less marked in hand warts [47].

The response to treatment with cryotherapy is comparable to that achieved with salicylic acid [7]. Treatment repeated every 3 weeks gives a 30–70% cure rate for hand warts after 3 months [6,7,48]. More frequent treatments may improve responses although will induce more pain, and longer intervals are less effective. If this fails, or when a wart is particularly painful or deep, or both, as may occur over a bony prominence on the foot, more prolonged application, typically up to 30 s, perhaps repeated after thawing, may be used to achieve a greater destructive effect at the cost of significantly greater blistering and pain. For such treatment, local or even general [49] anaesthesia may be considered. The common practice of dipping cotton buds for different patients into a common flask containing the liquid nitrogen may carry a risk of cross-infection.

The main disadvantage of freezing is pain. This is unpredictable and surprisingly variable between patients, but in some cases, especially with longer freezing times, it may be severe and persist for many hours or even a few days. Oral aspirin and strong topical steroids may help. Swelling of the treated area and the surrounding skin begins within minutes, and where tissues are lax as in the periorbital area it may be dramatic. A blister, sometimes haemorrhagic, may ensue within a day or two. After the usual short freezing times, the reaction will be likely to have resolved within 2–3 weeks. Scarring is unlikely with freezing times under 30 s. Occasionally, damage to underlying tissues may result, for example to a tendon [50] or the nail matrix, and excessive freezing times should be avoided over nerves, for example on the sides of the fingers. Depigmentation may occur, and can be a significant cosmetic disadvantage in patients with darkly pigmented skin.

Laser. The carbon dioxide laser has been used to treat a variety of different forms of wart, both cutaneous and mucosal [51]. It can be effective in eradicating some difficult warts, such as periungual and subungual warts which have been unresponsive to other treatments. Clearance of cutaneous warts at 12 months is reported to be 55–70% [52,53]. Carbon dioxide laser therapy is well tolerated, but, as with cryotherapy, surgery or other destructive methods, can cause significant postoperative pain, scarring and temporary loss of function [51]. Hypertrophic scarring may be exacerbated by concomitant ciclosporin treatment [54]. Infectious virus can be detected in the plume during carbon dioxide laser use [55], so an operator mask and air extraction system are advised.

The pulsed dye laser produces less scarring and has been used to treat warts with cure rates of approximately 50–70%, using a minimum of two treatments [56–58]. It appears comparable to other treatments such as cryotherapy [59]. Other lasers such as the Er:YAG and the Nd:YAG can also be used [60,61].

Laser treatment for other indications has been associated with spread of facial warts [62,63].

Infrared coagulator. As another destructive method, the infrared coagulator can be used to treat warts. The reported cure rate in a series of 44 warts was 70% [64] which compares favourably with cryotherapy.

Contact sensitization. Dinitrochlorobenzene has been used to elicit a repeated contact sensitivity reaction at the site of warts and to induce clearance [53,54] but this chemical is no longer used due to the potential risk of carcinogenesis. There have been several open studies of contact sensitization with diphenylcyclopropenone (diphencyprone, DPC), using different protocols [65]. Cure rates of between 44% and 88% of patients were obtained at the end of treatment [66–68] with apparent greater efficacy than cryotherapy [69]. The side effect of itching at treatment sites is generally tolerated, but some patients develop dermatitis in other areas or widespread urticaria [70]. The use of squaric acid dibutylester as a contact allergen in such regimens may be equally efficacious and better tolerated [60].

Interferon. Different interferons (IFNs) have been administered by different routes to patients with refractory warts in various sites. These studies are seldom directly comparable, and the use of interferons in warts is still experimental.

For the most part, interferon use has been disappointing. The majority of studies have involved patients with refractory genital warts. A placebo-controlled trial of systemic IFN-α showed no benefit [71] but an open trial suggested that the patients treated with IFN-α subsequently had an improved response to cryotherapy [72]. Intralesional IFN-α or -β as monotherapy gives an overall response rate of 36–63% [73] for genital warts, but oral warts may respond slightly better [74].

IFN has been used as adjuvant therapy, together with surgery, cryotherapy or topical measures. No augmentation of clearance of HPV infection was observed by the addition of IFN-α therapy to caustic application or surgery [75], podophyllin [76] or laser ablation [77]. Used with cryotherapy, IFN-β and -γ reduced the rate of acquisition of new lesions [78] but none of the interferons when combined with cryotherapy produced any improvement in clearance rate compared with cryotherapy alone.

The most encouraging report is of complete clearance of injected warts in 11 of 12 patients with recalcitrant common and plantar warts treated with human IFN-α [79]. Cutaneous warts on the palms and soles may also be treated with intralesional IFN, using a needleless injector [80].

Imiquimod. Topical immunomodulation with imiquimod 5% cream is licensed for treatment of genital warts, superficial basal cell carcinoma and actinic keratoses. Cutaneous warts have also responded to imiquimod treatment [81], although poor penetration through the keratinized surface may necessitate twice daily application for up to 24 weeks, combination with occlusion or salicylic acid to achieve useful results [82]. Butchers' warts, facial filiform warts and plane warts [83–85] may all respond and

immunosuppression does not appear to block the therapeutic effect [85,86].

The treatment can cause irritation, discomfort and occasionally erosion at the point of application with a small risk of causing vitiligo-like depigmentation [87].

Cimetidine. Results from the use of oral cimetidine in wart treatment in adults have been conflicting. In open studies of high-dose cimetidine (30–40 mg/kg/day for 3–4 months), two-thirds demonstrated improvement or complete resolution without recurrence [88,89], but in placebo-controlled trials, no significant benefit of cimeditine therapy has been observed [90,91]. In children, cimetidine may produce slightly greater benefit [92,93] and combination treatment with levamisole may enhance the effect [94].

Zinc. Oral zinc has a mild effect on the immune system. One study of oral zinc sulphate (10 mg/kg/day) reported an 87% cure rate of warts, but there was a high incidence of side effects leading to discontinuation of therapy [95]. In a double-blind trial, zinc sulphate as a 10% aqueous solution produced a cure rate of 86% for plane warts [96].

Retinoids. Oral retinoids, by reducing epidermal proliferation, can help to debulk warts, although the infection may persist making relapse likely. Etretinate, acitretin and isotretinoin have been reported to be helpful in cases of extensive and hyperkeratotic warts in immunosuppressed patients [97–100]. Hyperkeratotic warts in otherwise healthy patients can respond to oral retinoid therapy [101,102]. This effect may be temporarily useful, perhaps in relieving pain or disability due to exceptionally hyperkeratotic warts, or in facilitating the use of other treatments.

Intralesional bleomycin [103]. Doses of this cytotoxic agent are given in units or in milligrams; 1 mg contains 1500 to 2000 U. Protocols vary, but typically bleomycin sulphate 0.25–1 mg/mL is injected up to three times to a maximum total dose of 4 mg [104]; or 1000 U/mL to two injections and a maximum total dose of 2000 U [105]. A lower concentration of 500 U/mL seemed as effective [106]. Injections are into the wart itself, confirmed by observing blanching in the lesion, the volume per injected lesion ranging between 0.2 and 1.0 mL. Injections are very painful and preceding or concurrent local anaesthesia should be considered, especially for sensitive sites such as fingers and soles [107]. A haemorrhagic eschar develops; 2–3 weeks later, it is pared down if it has not detached spontaneously. Cure rates for previously refractory warts are reported to be between 30 and 100% [106,108], with some superiority over cryotherapy [109]. Used in this way, there has been no evidence of systemic toxicity. Local complications include nail loss [110] or dystrophy [111] following periungual injections, Raynaud's phenomenon in treated fingers and local urticaria [110]. The risk of systemic absorption is a contraindication for intralesional bleomycin in pregnancy [106].

Hayes and O'Keefe [106] give useful guidance on method and contraindications. Implantation of the bleomycin from a surface application using a bifurcated needle [112], a sterile lancet [113] or the Dermojet [114] may be better tolerated.

Local heat. Repeated raising of the temperature of wart-affected skin to a maximally tolerated level of about 50°C is reported to induce wart clearance [115]. The Nd:YAG laser can be used to produce a similar effect [116].

Psychological methods. Many myths and some studies claiming that warts can be effectively treated by suggestion or 'magic' have been inadequately controlled for spontaneous regression [117]. Formal hypnosis, however, was reported to clear warts on the suggested (the more severely affected) side only, in nine of 10 patients who achieved a satisfactory depth of hypnosis, the other side of the body acting as an internal control [118]. Children appear to have a higher rate of success than adults [119]. Persistent refractory warts disappeared following hypnosis in an uncontrolled study of three immunodeficient children [118].

Radiotherapy. The use of radiotherapy for warts should never be employed routinely as a first line treatment and only used at all in exceptional circumstances due to the risk of future adverse effects. A follow-up of 100 patients showed serious post-irradiation damage in 7% and slight radiodermatitis in 31% [120] and long-term follow-up may not reveal the potentially more serious side effects [121].

Antiviral therapy. The large number of treatments listed above indicate the lack of an ideal method for eliminating warts. The antiviral cidofovir, a purine nucleotide analogue of cytosine, is incorporated into replicating DNA thus damaging cells in mitosis. It can be used systemically by infusion (5 mg/kg once weekly) [122] or locally as a 1% gel or cream [123] or by intralesional injection (2.5 mg/ml)[124] and reports suggest that it can be extremely effective. Plantar, anogenital, oral and laryngeal warts may resolve completely, even in immunodeficiency [125–128]. Grade III cervical, vulval and penile intraepithelial neoplasia also respond to this drug [129]. Side effects of systemic cidofovir include nephrotoxicity and bone marrow suppression, and local treatment of mucosal lesions can produce erosion and pain, but topical treatment of skin lesions is generally well-tolerated [130].

Therapeutic vaccination. Prophylactic vaccination to prevent primary infection with HPV types 6, 11, 16 and 18 has recently become available and is hoped, over a period of years, to lead to a gradual reduction in the number of cases of anogenital malignancies and also genital warts. The effects are type specific. Clinical trials of therapeutic vaccination for cervical carcinoma, anogenital intraepithelial neoplasia, genital warts, laryngeal papillomatosis and cutaneous warts have so far shown no dramatic response. Open trials using intralesional *Candida* antigen to produce a local hypersensitivity reaction suggest that this approach could speed wart resolution in recalcitrant cases [131].

Other treatments. Green tea extract in a topical preparation has been reported to have a useful effect in the treatment of genital warts [132].

References

1 Sterling JC, Handfield-Jones S, Hudson PM. Guidelines for the management of cutaneous warts. *Br J Dermatol* 2001; **144**: 4–11.
2 Gibbs S, Harvey I, Sterling JC *et al.* Local treatments for cutaneous warts. *Cochrane Database Syst Rev* 2003: CD001781.
3 Focht DR 3rd, Spicer C, Fairchok MP. The efficacy of duct tape vs cryotherapy in the treatment of verruca vulgaris (the common wart). *Arch Pediatr Adolesc Med* 2002; **156**: 971–4.
4 de Haen M, Spigt MG, van Uden CJ *et al.* Efficacy of duct tape vs placebo in the treatment of verruca vulgaris (warts) in primary school children. *Arch Pediatr Adolesc Med* 2006; **160**: 1121–5.
5 Wenner R, Askari SK, Cham PM *et al.* Duct tape for the treatment of common warts in adults: a double-blind randomized controlled trial. *Arch Dermatol* 2007; **143**: 309–13.
6 Bunney MH, Nolan MW, Williams DA. An assessment of methods of treating viral warts by comparative treatment trials based on a standard design. *Br J Dermatol* 1976; **94**: 667–79.
7 Gibbs S, Harvey I, Sterling J *et al.* Local treatments for cutaneous warts: systematic review. *BMJ* 2002; **325**: 461.
8 Parton AM, Sommerville RG. The treatment of plantar verrucae by triggering cell-mediated immunity. *J Br Pod Med* 1994; **49**: 205.
9 Veien NK, Madsen SM, Avrach W *et al.* The treatment of plantar warts with a keratolytic agent and occlusion. *J Dermatol Treat* 1991; **2**: 59–61.
10 Hirose R, Hori M, Shukuwa T *et al.* Topical treatment of resistant warts with glutaraldehyde. *J Dermatol* 1994; **21**: 248–53.
11 Bonnez W, Elswick RK Jr, Bailey-Farchione A *et al.* Efficacy and safety of 0.5% podofilox solution in the treatment and suppression of anogenital warts. *Am J Med* 1994; **96**: 420–5.
12 Lacey CJ, Goodall RL, Tennvall GR *et al.* Randomised controlled trial and economic evaluation of podophyllotoxin solution, podophyllotoxin cream, and podophyllin in the treatment of genital warts. *Sex Transm Infect* 2003; **79**: 270–5.
13 Hellberg D, Svarrer T, Nilsson S *et al.* Self-treatment of female external genital warts with 0.5% podophyllotoxin cream (Condyline) vs weekly applications of 20% podophyllin solution. *Int J STD AIDS* 1995; **6**: 257–61.
14 Simmons PD. Podophyllin 10% and 25% in the treatment of ano-genital warts. A comparative double-blind study. *Br J Vener Dis* 1981; **57**: 208–9.
15 Wade TR, Ackerman AB. The effects of resin of podophyllin on condyloma acuminatum. *Am J Dermatopathol* 1984; **6**: 109–22.
16 Beutner KR, von Krogh G. Current status of podophyllotoxin for the treatment of genital warts. *Semin Dermatol* 1990; **9**: 148–51.
17 Chamberlain MJ, Reynolds AL, Yeoman WB. Toxic effect of podophyllum application in pregnancy. *BMJ* 1972; **3**: 391–2.
18 Slater GE, Rumack BH, Peterson RG. Podophyllin poisoning. Systemic toxicity following cutaneous application. *Obstet Gynecol* 1978; **52**: 94–6.
19 Leslie KO, Shitamoto B. The bone marrow in systemic podophyllin toxicity. *Am J Clin Pathol* 1982; **77**: 478–80.
20 Ward JW, Clifford WS, Monaco AR *et al.* Fatal systemic poisoning following podophyllin treatment of condyloma acuminatum. *South Med J* 1954; **47**: 1204–6.
21 West WM, Ridgeway NA, Morris AJ *et al.* Fatal podophyllin ingestion. *South Med J* 1982; **75**: 1269–70.
22 Duthie DA, McCallum CD. Treatment of plantar warts with elastoplast and podophyllin. *BMJ* 1951; **2**: 216–8.
23 de Bengoa Vallejo RB, Iglesias ME, Gomez-Martin B *et al.* Application of cantharidin and podophyllotoxin for the treatment of plantar warts. *J Am Podiatr Med Assoc* 2008; **98**: 445–50.
24 Vickers CF. Treatment of plantar warts in children. *BMJ* 1961; **2**: 743–5.
25 Anderson I, Shirreffs E. The treatment of plantar warts. *Br J Dermatol* 1963; **75**: 29–32.
26 Hursthouse MW. A controlled trial on the use of topical 5–fluorouracil on viral warts. *Br J Dermatol* 1975; **92**: 93–6.
27 Zschocke I, Hartmann A, Schlobe A *et al.* Wirksamkeit und Nutzen eines 5-FU-/Salicylsäurehaltigen Präparates in der Therapie vulgärer und plantarer Warzen—systematische Literaturübersicht und Metaanalyse. *J Dtsch Dermatol Ges* 2004; **2**: 187–93.
28 Lee S, Kim JG, Chun SI. Treatment of verruca plana with 5% 5-fluorouracil ointment. *Dermatologica* 1980; **160**: 383–9.
29 Salk RS, Grogan KA, Chang TJ. Topical 5% 5-fluorouracil cream in the treatment of plantar warts: a prospective, randomized, and controlled clinical study. *J Drugs Dermatol* 2006; **5**: 418–24.
30 Yazdanfar A, Farshchian M, Fereydoonnejad M. Treatment of common warts with an intralesional mixture of 5-fluorouracil, lidocaine, and epinephrine: a prospective placebo-controlled, double-blind randomized trial. *Dermatol Surg* 2008; **34**: 656–9.
31 Yazar S, Basaran E. Efficacy of silver nitrate pencils in the treatment of common warts. *J Dermatol* 1994; **21**: 329–33.
32 Ebrahimi S, Dabiri N, Jamshidnejad E *et al.* Efficacy of 10% silver nitrate solution in the treatment of common warts: a placebo-controlled, randomized, clinical trial. *Int J Dermatol* 2007; **46**: 215–7.
33 Durmazlar SP, Atacan D, Eskioglu F. Cantharidin treatment for recalcitrant facial flat warts: A preliminary study. *J Dermatolog Treat* 2009: **20**: 114–9.
34 Banihashemi M, Pezeshkpoor F, Yazdanpanah MJ *et al.* Efficacy of 80% phenol solution in comparison with cryotherapy in the treatment of common warts of hands. *Singapore Med J* 2008; **49**: 1035–7.
35 Abdullah AN, Walzman M, Wade A. Treatment of external genital warts comparing cryotherapy (liquid nitrogen) and trichloroacetic acid. *Sex Transm Dis* 1993; **20**: 344–5.
36 De Bersaques J. Vitamin A acid in the topic treatment of warts. *Acta Derm Venereol Suppl (Stockh)* 1975; **74**: 169–70.
37 Kubeyinje EP. Evaluation of the efficacy and safety of 0.05% tretinoin cream in the treatment of plane warts in Arab children. *J Dermatol Treat* 1996; **7**: 21–2.
38 Stender IM, Na R, Fogh H *et al.* Photodynamic therapy with 5–aminolaevulinic acid or placebo for recalcitrant foot and hand warts: randomised double-blind trial. *Lancet* 2000; **355**: 963–6.
39 Mizuki D, Kaneko T, Hanada K. Successful treatment of topical photodynamic therapy using 5-aminolevulinic acid for plane warts. *Br J Dermatol* 2003; **149**: 1087–8.
40 Schroeter CA, Kaas L, Waterval JJ *et al.* Successful treatment of periungual warts using photodynamic therapy: a pilot study. *J Eur Acad Dermatol Venereol* 2007; **21**: 1170–4.
41 Stender IM, Borgbjerg FM, Villumsen J *et al.* Pain induced by photodynamic therapy of warts. *Photodermatol Photoimmunol Photomed* 2006; **22**: 304–9.
42 Thomson JP, Grace RH. The treatment of perianal and anal condylomata acuminata: a new operative technique. *J R Soc Med* 1978; **71**: 180–5.
43 Ljunghall K, Lillieborg S. Local anaesthesia with a lidocaine/prilocaine cream (EMLA) for cautery of condylomata acuminata on the vulval mucosa. The effect of timing of application of the cream. *Acta Derm Venereol* 1989; **69**: 362–5.
44 Pringle WM, Helms DC. Treatment of plantar warts by blunt dissection. *Arch Dermatol* 1973; **108**: 79–82.
45 Berth-Jones J, Hutchinson PE. Modern treatment of warts: cure rates at 3 and 6 months. *Br J Dermatol* 1992; **127**: 262–5.
46 Morison WL. In vitro assay of immunity to human wart antigen. *Br J Dermatol* 1975; **93**: 545–52.
47 Berth-Jones J, Bourke J, Eglitis H *et al.* Value of a second freeze–thaw cycle in cryotherapy of common warts. *Br J Dermatol* 1994; **131**: 883–6.
48 Bourke JF, Berth-Jones J, Hutchinson PE. Cryotherapy of common viral warts at intervals of 1, 2 and 3 weeks. *Br J Dermatol* 1995; **132**: 433–6.
49 Rademaker M, Thomas RH, Munro DD. The treatment of resistant mosaic plantar warts with aggressive cryotherapy under general anaesthetic. *Br J Dermatol* 1987; **116**: 557–60.
50 Yates VM, Scott MM, Carter ED. Rupture of tendon after cryotherapy for hand wart. *BMJ* 1988; **297**: 1106.
51 Logan RA, Zachary CB. Outcome of carbon dioxide laser therapy for persistent cutaneous viral warts. *Br J Dermatol* 1989; **121**: 99–105.
52 Lim JT, Goh CL. Carbon dioxide laser treatment of periungual and subungual viral warts. *Australas J Dermatol* 1992; **33**: 87–91.
53 Serour F, Somekh E. Successful treatment of recalcitrant warts in pediatric patients with carbon dioxide laser. *Eur J Pediatr Surg* 2003; **13**: 219–23.
54 Ozluer SM, Chuen BY, Barlow RJ *et al.* Hypertrophic scar formation following carbon dioxide laser ablation of plantar warts in cyclosporin-treated patients. *Br J Dermatol* 2001; **145**: 1005–7.
55 Sawchuk WS, Weber PJ, Lowy DR *et al.* Infectious papillomavirus in the vapor of warts treated with carbon dioxide laser or electrocoagulation: detection and protection. *J Am Acad Dermatol* 1989; **21**: 41–9.

56 Ross BS, Levine VJ, Nehal K *et al.* Pulsed dye laser treatment of warts: an update. *Dermatol Surg* 1999; **25**: 377–80.
57 Schellhaas U, Gerber W, Hammes S *et al.* Pulsed dye laser treatment is effective in the treatment of recalcitrant viral warts. *Dermatol Surg* 2008; **34**: 67–72.
58 Park HS, Choi WS. Pulsed dye laser treatment for viral warts: a study of 120 patients. *J Dermatol* 2008; **35**: 491–8.
59 Robson KJ, Cunningham NM, Kruzan KL *et al.* Pulsed-dye laser versus conventional therapy in the treatment of warts: a prospective randomized trial. *J Am Acad Dermatol* 2000; **43**: 275–80.
60 Wollina U, Konrad H, Karamfilov T. Treatment of common warts and actinic keratoses by Er:YAG laser. *J Cutan Laser Ther* 2001; **3**: 63–6.
61 Li Y, Yang K. Treatment of recalcitrant-pigmented flat warts using frequency-doubled Q-switched Nd–YAG laser. *Lasers Surg Med* 2001; **29**: 244–7.
62 Torezan LA, Osorio N, Neto CF. Development of multiple warts after skin resurfacing with CO_2 laser. *Dermatol Surg* 2000; **26**: 70–2.
63 Chen T, Frieden IJ. Development of extensive flat warts after pulsed dye laser treatment of a port-wine stain. *Dermatol Surg* 2007; **33**: 734–5.
64 Halasz CL. Treatment of common warts using the infrared coagulator. *J Dermatol Surg Oncol* 1994; **20**: 252–6.
65 Pollock B, Highet AS. An interesting response to diphencyprone (DPC) sensitization on facial warts: review of DPC treatment for viral warts. *J Dermatolog Treat* 2002; **13**: 47–50.
66 van der Steen P, van de Kerkhof P, der Kinderen D *et al.* Clinical and immunohistochemical responses of plantar warts to topical immunotherapy with diphenylcyclopropenone. *J Dermatol* 1991; **18**: 330–3.
67 Rampen FH, Steijlen PM. Diphencyprone in the management of refractory palmoplantar and periungual warts: an open study. *Dermatology* 1996; **193**: 236–8.
68 Buckley DA, Keane FM, Munn SE *et al.* Recalcitrant viral warts treated by diphencyprone immunotherapy. *Br J Dermatol* 1999; **141**: 292–6.
69 Choi MH, Seo SH, Kim IH *et al.* Comparative study on the sustained efficacy of diphencyprone immunotherapy versus cryotherapy in viral warts. *Pediatr Dermatol* 2008; **25**: 398–9.
70 Choi JE, Seo SH, Kim IH *et al.* Prospective study of urticaria after diphencyprone therapy in patients with viral warts. *Int J Dermatol* 2007; **46**: 1313–4.
71 Condyloma International Collaborative Study Group. Recurrent condylomata acuminata treated with recombinant interferon alfa-2a. A multicenter double-blind placebo-controlled clinical trial. *JAMA* 1991; **265**: 2684–7.
72 Kirby PK, Kiviat N, Beckman A *et al.* Tolerance and efficacy of recombinant human interferon gamma in the treatment of refractory genital warts. *Am J Med* 1988; **85**: 183–8.
73 Czelusta AJ, Evans T, Arany I *et al.* A guide to immunotherapy of genital warts: focus on interferon and imiquimod. *BioDrugs* 1999; **11**: 319–32.
74 Lozada-Nur F, Glick M, Schubert M *et al.* Use of intralesional interferon-alpha for the treatment of recalcitrant oral warts in patients with AIDS: a report of 4 cases. *Oral Surg Oral Med Oral Pathol* 2001; **92**: 617–22.
75 Höpel RM, Sandbichler M, Zelger BW *et al.* Adjuvant treatment of recalcitrant genitoanal warts with systemic recombinant interferon-alpha-2c. *Acta Derm Venereol* 1992; **72**: 383–6.
76 Armstrong DK, Maw RD, Dinsmore WW *et al.* A randomised, double-blind, parallel group study to compare subcutaneous interferon alpha-2a plus podophyllin with placebo plus podophyllin in the treatment of primary condylomata acuminata. *Genitourin Med* 1994; **70**: 389–93.
77 Condyloma International Collaborative Study Group. Randomized placebo-controlled double-blind combined therapy with laser surgery and systemic interferon-alpha 2a in the treatment of anogenital condylomata acuminatum. *J Infect Dis* 1993; **167**: 824–9.
78 Bonnez W, Oakes D, Bailey–Farchione A *et al.* A randomized, double-blind, placebo-controlled trial of systemically administered interferon-alpha, -beta, or -gamma in combination with cryotherapy for the treatment of condyloma acuminatum. *J Infect Dis* 1995; **171**: 1081–9.
79 Gibson JR, Harvey SG, Kemmett D *et al.* Treatment of common and plantar viral warts with human lymphoblastoid interferon-alpha—pilot studies with intralesional, intramuscular and dermojet injections. *Br J Dermatol* 1986; **115** (Suppl. 31): 76–9.
80 Brodell RT, Bredle DL. The treatment of palmar and plantar warts using natural alpha interferon and a needleless injector. *Dermatol Surg* 1995; **21**: 213–8.
81 Hengge UR, Esser S, Schultewolter T *et al.* Self-administered topical 5% imiquimod for the treatment of common warts and molluscum contagiosum. *Br J Dermatol* 2000; **143**: 1026–31.
82 Grussendorf-Conen EI, Jacobs S, Rubben A *et al.* Topical 5% imiquimod long-term treatment of cutaneous warts resistant to standard therapy modalities. *Dermatology* 2002; **205**: 139–45.
83 Poochareon V, Berman B, Villa A. Successful treatment of butcher's warts with imiquimod 5% cream. *Clin Exp Dermatol* 2003; **28** (Suppl. 1): 42–4.
84 Kim MB, Ko HC, Jang HS *et al.* Treatment of flat warts with 5% imiquimod cream. *J Eur Acad Dermatol* 2006; **20**: 1349–50.
85 Hagman JH, Bianchi L, Marulli GC *et al.* Successful treatment of multiple filiform facial warts with imiquimod 5% cream in a patient infected by human immunodeficiency virus. *Clin Exp Dermatol* 2003; **28**: 260–1.
86 Harwood CA, Perrett CM, Brown VL *et al.* Imiquimod cream 5% for recalcitrant cutaneous warts in immunosuppressed individuals. *Br J Dermatol* 2005; **152**: 122–9.
87 Brown T, Zirvi M, Cotsarelis G *et al.* Vitiligo-like hypopigmentation associated with imiquimod treatment of genital warts. *J Am Acad Dermatol* 2005; **52**: 715–6.
88 Choi YS, Hann SK, Park YK. The effect of cimetidine on verruca plana juvenilis: clinical trials in six patients. *J Dermatol* 1993; **20**: 497–500.
89 Gooptu C, Higgins CR, James MP. Treatment of viral warts with cimetidine: an open-label study. *Clin Exp Dermatol* 2000; **25**: 183–5.
90 Yilmaz E, Alpsoy E, Basaran E. Cimetidine therapy for warts: a placebo-controlled, double-blind study. *J Am Acad Dermatol* 1996; **34**: 1005–7.
91 Rogers CJ, Gibney MD, Siegfried EC *et al.* Cimetidine therapy for recalcitrant warts in adults: is it any better than placebo? *J Am Acad Dermatol* 1999; **41**: 123–7.
92 Franco I. Oral cimetidine for the management of genital and perigenital warts in children. *J Urol* 2000; **164**: 1074–5.
93 Orlow SJ, Paller A. Cimetidine therapy for multiple viral warts in children. *J Am Acad Dermatol* 1993; **28**: 794–6.
94 Parsad D, Pandhi R, Juneja A *et al.* Cimetidine and levamisole versus cimetidine alone for recalcitrant warts in children. *Pediatr Dermatol* 2001; **18**: 349–52.
95 Al-Gurairi FT, Al-Waiz M, Sharquie KE. Oral zinc sulphate in the treatment of recalcitrant viral warts: randomized placebo-controlled clinical trial. *Br J Dermatol* 2002; **146**: 423–31.
96 Sharquie KE, Khorsheed AA, Al-Nuaimy AA. Topical zinc sulphate solution for treatment of viral warts. *Saudi Med J* 2007; **28**: 1418–21.
97 Boyle J, Dick DC, MacKie RM. Treatment of extensive virus warts with etretinate (Tigason) in a patient with sarcoidosis. *Clin Exp Dermatol* 1983; **8**: 33–6.
98 Gross G, Pfister H, Hagedorn M *et al.* Effect of oral aromatic retinoid (Ro 10–9359) on human papilloma virus-2-induced common warts. *Dermatologica* 1983; **166**: 48–53.
99 Simone CD, Capizzi R, Carbone A *et al.* Use of acitretin in a case of giant common warts in an HIV-infected patient. *Eur J Dermatol* 2008; **18**: 346–7.
100 Katz RA. Isotretinoin treatment of recalcitrant warts in an immunosuppressed man. *Arch Dermatol* 1986; **122**: 19–20.
101 Gelmetti C, Cerri D, Schiuma AA *et al.* Treatment of extensive warts with etretinate: a clinical trial in 20 children. *Pediatr Dermatol* 1987; **4**: 254–8.
102 Choi YL, Lee KJ, Kim WS *et al.* Treatment of extensive and recalcitrant viral warts with acitretin. *Int J Dermatol* 2006; **45**: 480–2.
103 Lewis TG, Nydorf ED. Intralesional bleomycin for warts: a review. *J Drugs Dermatol* 2006; **5**: 499–504.
104 Bunney MH, Nolan MW, Buxton PK *et al.* The treatment of resistant warts with intralesional bleomycin: a controlled clinical trial. *Br J Dermatol* 1984; **111**: 197–207.
105 Amer M, Diab N, Ramadan A *et al.* Therapeutic evaluation for intralesional injection of bleomycin sulfate in 143 resistant warts. *J Am Acad Dermatol* 1988; **18**: 1313–6.
106 Hayes ME, O'Keefe EJ. Reduced dose of bleomycin in the treatment of recalcitrant warts. *J Am Acad Dermatol* 1986; **15**: 1002–6.
107 Manz LA, Pelachyk JM. Bleomycin-lidocaine mixture reduces pain of intralesional injection in the treatment of recalcitrant verrucae. *J Am Acad Dermatol* 1991; **25**: 524–6.
108 James MP, Collier PM, Aherne W *et al.* Histologic, pharmacologic, and immunocytochemical effects of injection of bleomycin into viral warts. *J Am Acad Dermatol* 1993; **28**: 933–7.

109 Adalatkhah H, Khalilollahi H, Amini N *et al.* Compared therapeutic efficacy between intralesional bleomycin and cryotherapy for common warts: a randomized clinical trial. *Dermatol Online J* 2007; **13**: 4.

110 Gonzalez FU, Gil MCC, Martinez AA *et al.* Cutaneous toxicity of intralesional bleomycin administration in the treatment of periungual warts. *Arch Dermatol* 1986; **122**: 974–5.

111 Miller RA. Nail dystrophy following intralesional injections of bleomycin for a periungual wart. *Arch Dermatol* 1984; **120**: 963–4.

112 Shelley WB, Shelley ED. Intralesional bleomycin sulfate therapy for warts. A novel bifurcated needle puncture technique. *Arch Dermatol* 1991; **127**: 234–6.

113 Munn SE, Higgins E, Marshall M *et al.* A new method of intralesional bleomycin therapy in the treatment of recalcitrant warts. *Br J Dermatol* 1996; **135**: 969–71.

114 Agius E, Mooney JM, Bezzina AC *et al.* Dermojet delivery of bleomycin for the treatment of recalcitrant plantar warts. *J Dermatolog Treat* 2006; **17**: 112–6.

115 Stern P, Levine N. Controlled localized heat therapy in cutaneous warts. *Arch Dermatol* 1992; **128**: 945–8.

116 Pfau A, Abd-el-Raheem TA, Baumler W *et al.* Nd:YAG laser hyperthermia in the treatment of recalcitrant verrucae vulgares (Regensburg's technique). *Acta Derm Venereol* 1994; **74**: 212–4.

117 Clarke GHV. The charming of warts. *J Invest Dermatol* 1965; **45**: 15–21.

118 Tasini MF, Hackett TP. Hypnosis in the treatment of warts in immunodeficient children. *Am J Clin Hypn* 1977; **19**: 152–4.

119 Ewin DM. Hypnotherapy for warts (verruca vulgaris): 41 consecutive cases with 33 cures. *Am J Clin Hypn* 1992; **35**: 1–10.

120 Faessler R, Kiebs A. Spätresultate von bestrahlten Plantarwarzen. *Dermatologica* 1974; **148**: 345–52.

121 Shair HM, Hanshaw WJ, Grayson LD. Radiation therapy for plantar warts. *J Dermatol Surg Oncol* 1978; **4**: 635–7.

122 Cusack C, Fitzgerald D, Clayton TM *et al.* Successful treatment of florid cutaneous warts with intravenous cidofovir in an 11-year-old girl. *Pediatr Dermatol* 2008; **25**: 387–9.

123 Matteelli A, Beltrame A, Graifemberghi S *et al.* Efficacy and tolerability of topical 1% cidofovir cream for the treatment of external anogenital warts in HIV-infected persons. *Sex Transm Dis* 2001; **28**: 343–6.

124 Orlando G, Fasolo MM, Beretta R *et al.* Intralesional or topical cidofovir (HPMPC, VISTIDE) for the treatment of recurrent genital warts in HIV-1-infected patients. *AIDS* 1999; **13**: 1978–80.

125 Davis MD, Gostout BS, McGovern RM *et al.* Large plantar wart caused by human papillomavirus-66 and resolution by topical cidofovir therapy. *J Am Acad Dermatol* 2000; **43**: 340–3.

126 Gröne D, Treudler R, de Villiers EM *et al.* Intravenous cidofovir treatment for recalcitrant warts in the setting of a patient with myelodysplastic syndrome. *J Eur Acad Dermatol Venereol* 2006; **20**: 202–5.

127 De Socio GV, Simonetti S, Rosignoli D *et al.* Topical cidofovir for severe warts in a patient affected by AIDS and Hodgkin's lymphoma. *Int J STD AIDS* 2008; **19**: 715–6.

128 Husak R, Zouboulis CC, Sander-Bahr C *et al.* Refractory human papillomavirus-associated oral warts treated topically with 1–3% cidofovir solutions in human immunodeficiency virus type 1-infected patients. *Br J Dermatol* 2005; **152**: 590–1.

129 Toro JR, Sanchez S, Turiansky G *et al.* Topical cidofovir for the treatment of dermatologic conditions: verruca, condyloma, intraepithelial neoplasia, herpes simplex and its potential use in smallpox. *Dermatol Clin* 2003; **21**: 301–9.

130 Field S, Irvine AD, Kirby B. The treatment of viral warts with topical cidofovir 1%: our experience of seven paediatric patients. *Br J Dermatol* 2009; **160**: 223–4.

131 Maronn M, Salm C, Lyon V *et al.* One-year experience with candida antigen immunotherapy for warts and molluscum. *Pediatr Dermatol* 2008; **25**: 189–92.

132 Tatti S, Swinehart JM, Thielert C *et al.* Sinecatechins, a defined green tea extract, in the treatment of external anogenital warts: a randomized controlled trial. *Obstet Gynecol* 2008; **111**: 1371–9.

HPV-associated epidermal dysplasia and neoplasia

HPVs have been associated with several different dysplastic or malignant conditions [1]. An aetiological association between infection with high-risk HPVs and the development of cervical carcinoma is clearly recognized, and evidence for a causative effect in other anogenital and head and neck cancers is emerging. High-risk HPVs are found in association with premalignancy and cancer in the oropharynx [2], the nasal cavities [3], the larynx [4], the oesophagus [5], the lung [6] and the conjunctiva [7,8]. The precise role of HPV infection and interaction with cofactors in these tumours and in cutaneous squamous cell carcinoma is yet to be clarified.

Cervical intraepithelial neoplasia (CIN) and invasive carcinoma [9]

These conditions are epidemiologically associated with sexual activity, including age of first sexual intercourse, multiplicity of partners and a history of sexually transmitted diseases, in both the female patient and her male partner(s). CIN is associated with a personal history of overt genital warts [10], and with previous penile warts [11] or penile intraepithelial neoplasia [12] in the partner.

HPV is commonly detected in dysplastic cervical lesions and is found in 90–100% of cervical cancers [13,14]. Type 16 is found most commonly and, together with HPV-18, account for 70–80% of HPV-positive lesions, although approximately 30 different HPV types can infect the cervix. In carcinoma cells, the HPV DNA is almost always integrated into the host-cell genome, in contrast to its extrachromosomal location in benign and early premalignant lesions [15].

High-risk HPVs can also be detected by sensitive PCR in a proportion, variously reported to be between 5 and 80%, of cytologically normal cervices [16,17]. This association is highest in young, sexually active women [18], in whom infection may be transient. The finding of a high-risk HPV type in the cervix increases the likelihood of progression of the disease [19].

Antibody to HPV-16 capsid antigens is present in about 75% of women with HPV-16-positive CIN and in about 55% of women with invasive carcinoma [20], sometimes predating the development of the clinical cervical disease [21].

Vulvar intraepithelial neoplasia, penile intraepithelial neoplasia, perianal intraepithelial neoplasia and Bowenoid papulosis [22] (Fig. 33.22)

Full-thickness epidermal dysplasia of the vulva, penis or perianal skin is classified as grade III vulval, penile or anal intraepithelial neoplasia (VIN, PIN, AIN) [23], although the term Bowenoid papulosis is still used by many dermatologists. High-grade VIN 3, PIN 3 and AIN 3 are all strongly associated with HPV-16 [24,25]. Small papules, usually multiple and sometimes pigmented, present on cutaneous and mucosal surfaces of the anogenital region in both sexes, often resembling simple warts, seborrhoeic keratoses or cellular melanocytic naevi. There may be areas of erythematous thickening or small erosions or ulcers. There is often a history of preceding genital warts and the disease is more common in smokers. It usually affects young to middle-aged adults, but no age is exempt. Low-grade and very occasionally some high-grade lesions may resolve spontaneously. Progression to carcinoma is considered uncommon, occurring in less than 5% [26], but a study of affected individuals in New Zealand has suggested that, untreated, VIN 3 may carry a high risk of progression to invasion [27]. Analyses of carcinomas of the vulva, penis and anus have confirmed that many harbour high-risk HPVs, especially type 16 [12,28–30].

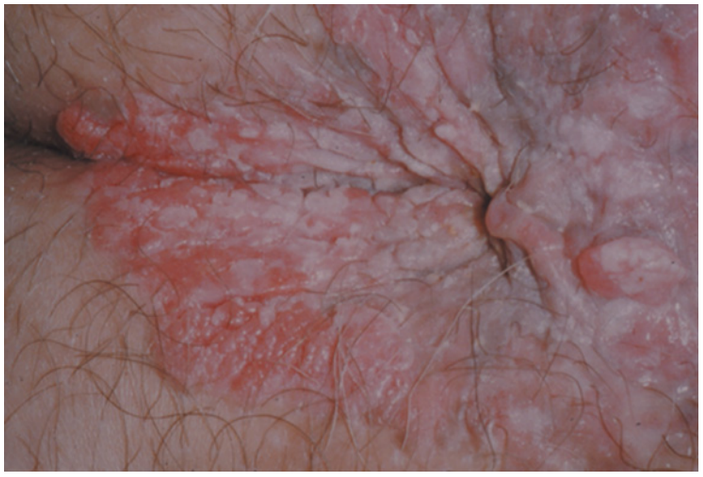


Fig. 33.22 Perianal intraepithelial neoplasia, grade III. (Courtesy of Addenbrooke's Hospital, Cambridge, UK.)



Fig. 33.23 Buschke–Löwenstein tumour. (Courtesy of Dr A.S. Highet, York District Hospital, UK.)

Persistent and refractory cases of anogenital intraepithelial neoplasia may have underlying immune deficiency and are at risk of progression to malignancy or the development of malignancy at other sites [31,32].

Conditions clinically similar to genital intraepithelial neoplasia include Bowen's disease and erythroplasia of Queyrat, which, in contrast, affect the middle-aged and elderly, present as one or a few larger flat plaques, show more advanced dysplasia and carry a significant risk of invasive malignancy.

Treatment. Extensive surgery is generally not indicated and to remove all infected tissue could be mutilating. Simple excision of small areas, cryotherapy, carbon dioxide laser and diathermy can help to contain the disease and may be curative if the dysplasia is unifocal. Good results without scarring have been reported for the Nd:YAG laser [33]. Oral retinoid therapy may be effective [34]. More recent studies with the antiviral cidofovir [35], the topical immunomodulator imiquimod [36] and therapeutic vaccination [37] offer hope of disease control.

Buschke–Löwenstein tumour (giant condyloma, verrucous carcinoma) (Fig. 33.23)

This develops from a pre-existing, benign warty lesion as an enlarging tumour in the external anogenital tract, the mouth, oesophagus or upper respiratory system. It is rare in childhood [38]. It harbours HPV-6 or -11, which are often mutated [39]. It is locally invasive on a broad front, but is well-differentiated and rarely becomes aggressively invasive or metastatic [40]. Treatment is usually surgical, often extensive, but aggressive cryotherapy [41], photodynamic therapy [42], bleomycin [43], 5-fluorouracil [38], recombinant IFN-α [44], imiquimod [45] and systemic retinoid [46] have also been used, either alone or in combination. Radiotherapy alone should be avoided as it may precipitate transformation to an anaplastic carcinoma but can be successful in combination with chemotherapy [47].

Cutaneous verrucous carcinoma or carcinoma cuniculatum develops as a locally infiltrating lesion with warty [48] and low-grade dysplastic features. The tumour is rare and can occur at any site, but is most common on the lower leg and foot [49].

Cutaneous squamous cell carcinoma without immunosuppression

The high- and low-risk HPV types that cause genital disease are also reported in certain extragenital warts and carcinomas. Although such cases are more common among the immunosuppressed, immunocompetent individuals may also be affected. Squamous cell carcinoma (SCC) or Bowen's disease of the fingertip and nailbed has been associated with high-risk genital HPVs [50–53], especially when in association with genital HPV disease. Cutaneous intraepithelial carcinoma of the skin (Bowen's disease) has been found occasionally to harbour HPV-2 [54] and a number of anogenital HPV types [55–57].

Malignant change may rarely develop in apparently normal warts, usually when very long standing [58,59], but the accuracy of the original diagnosis must always be in question [60].

Ionizing radiation may act as a cofactor for malignant change in warts [61]. Widespread actinic keratoses and cutaneous SCCs arising after arsenic treatment or PUVA photochemotherapy may also be associated with HPV infection [62,63]. With the advent of more sensitive PCR methods for detection of HPV DNA, the viral genome has been found in approximately 25–50% of keratoses and non-melanoma skin cancers of immunocompetent individuals [64]. It is DNA of the EV-associated types which is present in these lesions. The viral DNA is not exclusive to dysplasia—it can also be found in normal skin and hair follicles in 45% of people tested [65]. The exact molecular role of the virus in the development of skin cancers remains a subject of intense debate [66,67].

References

1 zur Hausen H. Papillomaviruses in the causation of human cancers—a brief historical account. *Virology* 2009; **384**: 260–5.

2 Psyrri A, DiMaio D. Human papillomavirus in cervical and head-and-neck cancer. *Nat Clin Pract Oncol* 2008; **5**: 24–31.

3 Furuta Y, Shinohara T, Sano K *et al*. Molecular pathologic study of human papillomavirus infection in inverted papilloma and squamous cell carcinoma of the nasal cavities and paranasal sinuses. *Laryngoscope* 1991; **101**: 79–85.

4 Torrente MC, Ampuero S, Abud M *et al.* Molecular detection and typing of human papillomavirus in laryngeal carcinoma specimens. *Acta Otolaryngol* 2005; **125**: 888–93.

5 de Villiers EM, Gunst K, Stein H *et al.* Esophageal squamous cell cancer in patients with head and neck cancer: Prevalence of human papillomavirus DNA sequences. *Int J Cancer* 2004; **109**: 253–8.

6 Syrjanen KJ, Syrjanen SM. Human papillomavirus DNA in bronchial squamous cell carcinomas. *Lancet* 1987; **1**: 168–9.

7 Ateenyi-Agaba C, Weiderpass E, Smet A *et al.* Epidermodysplasia verruciformis human papillomavirus types and carcinoma of the conjunctiva: a pilot study. *Br J Cancer* 2004; **90**: 1777–9.

8 Moubayed P, Mwakyoma H, Schneider DT. High frequency of human papillomavirus 6/11, 16, and 18 infections in precancerous lesions and squamous cell carcinoma of the conjunctiva in subtropical Tanzania. *Am J Clin Pathol* 2004; **122**: 938–43.

9 zur Hausen H. Papillomavirus infections—a major cause of human cancers. *Biochim Biophys Acta* 1996; **1288**: F55–78.

10 Walker PG, Singer A, Dyson JL *et al.* Natural history of cervical epithelial abnormalities in patients with vulval warts. A colposcopic study. *Br J Vener Dis* 1983; **59**: 327–9.

11 Höckenström T, Jonassen F, Knutsson F *et al.* High prevalence of cervical dysplasia in female consorts of men with genital warts. *Acta Derm Venereol* 1987; **67**: 511–6.

12 Barrasso R, De Brux J, Croissant O *et al.* High prevalence of papillomavirus-associated penile intraepithelial neoplasia in sexual partners of women with cervical intraepithelial neoplasia. *N Engl J Med* 1987; **317**: 916–23.

13 Bosch FX, Manos MM, Munoz N *et al.* Prevalence of human papillomavirus in cervical cancer: a worldwide perspective. International biological study on cervical cancer (IBSCC) Study Group. *J Natl Cancer Inst* 1995; **87**: 796–802.

14 Walboomers JM, Jacobs MV, Manos MM *et al.* Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol* 1999; **189**: 12–9.

15 Pett M, Coleman N. Integration of high-risk human papillomavirus: a key event in cervical carcinogenesis? *J Pathol* 2007; **212**: 356–67.

16 Reeves WC, Brinton LA, Garcia M *et al.* Human papillomavirus infection and cervical cancer in Latin America. *N Engl J Med* 1989; **320**: 1437–41.

17 Liaw KL, Glass AG, Manos MM *et al.* Detection of human papillomavirus DNA in cytologically normal women and subsequent cervical squamous intraepithelial lesions. *J Natl Cancer Inst* 1999; **91**: 954–60.

18 Dunne EF, Unger ER, Sternberg M *et al.* Prevalence of HPV infection among females in the United States. *JAMA* 2007; **297**: 813–9.

19 Remmink AJ, Walboomers JM, Helmerhorst TJ *et al.* The presence of persistent high-risk HPV genotypes in dysplastic cervical lesions is associated with progressive disease: natural history up to 36 months. *Int J Cancer* 1995; **61**: 306–11.

20 Nonnenmacher B, Hubbert NL, Kirnbauer R *et al.* Serologic response to human papillomavirus type 16 (HPV-16) virus-like particles in HPV-16 DNA-positive invasive cervical cancer and cervical intraepithelial neoplasia grade III patients and controls from Colombia and Spain. *J Infect Dis* 1995; **172**: 19–24.

21 Lehtinen M, Dillner J, Knekt P *et al.* Serologically diagnosed infection with human papillomavirus type 16 and risk for subsequent development of cervical carcinoma: nested case–control study. *BMJ* 1996; **312**: 537–9.

22 Gastrell FH, McConnell DT. Human papillomavirus and vulval intra-epithelial neoplasia. *Best Pract Res Clin Obstet Gynaecol* 2001; **15**: 769–82.

23 Ridley CM, Frankman O, Jones IS *et al.* New nomenclature for vulvar disease: International Society for the Study of Vulvar Disease. *Hum Pathol* 1989; **20**: 495–6.

24 Gross G, Ikenberg H, Gissmann L *et al.* Papillomavirus infection of the anogenital region: correlation between histology, clinical picture, and virus type. Proposal of a new nomenclature. *J Invest Dermatol* 1985; **85**: 147–52.

25 van Beurden M, ten Kate FJ, Smits HL *et al.* Multifocal vulvar intraepithelial neoplasia grade III and multicentric lower genital tract neoplasia is associated with transcriptionally active human papillomavirus. *Cancer* 1995; **75**: 2879–84.

26 Buscema J, Woodruff JD, Parmley TH *et al.* Carcinoma in situ of the vulva. *Obstet Gynecol* 1980; **55**: 225–30.

27 Jones RW, Rowan DM. Vulvar intraepithelial neoplasia III: a clinical study of the outcome in 113 cases with relation to the later development of invasive vulvar carcinoma. *Obstet Gynecol* 1994; **84**: 741–5.

28 McCance DJ, Kalache A, Ashdown K *et al.* Human papillomavirus types 16 and 18 in carcinomas of the penis from Brazil. *Int J Cancer* 1986; **37**: 55–9.

29 Hording U, Daugaard S, Iversen AK *et al.* Human papillomavirus type 16 in vulvar carcinoma, vulvar intraepithelial neoplasia, and associated cervical neoplasia. *Gynecol Oncol* 1991; **42**: 22–6.

30 De Vuyst H, Clifford GM, Nascimento MC *et al.* Prevalence and type distribution of human papillomavirus in carcinoma and intraepithelial neoplasia of the vulva, vagina and anus: a meta-analysis. *Int J Cancer* 2009; **124**: 1626–36.

31 Feldman SB, Sexton FM, Glenn JD *et al.* Immunosuppression in men with bowenoid papulosis. *Arch Dermatol* 1989; **125**: 651–4.

32 Rijnders RJ, van den Ende IE, Huikeshoven FJ. Suspected idiopathic CD4+ T-lymphocytopenia in a young patient with vulvar carcinoma stage IV. *Gynecol Oncol* 1996; **61**: 423–6.

33 Knoll LD, Segura JW, Benson RC Jr *et al.* Bowenoid papulosis of the penis: successful management with neodymium:YAG laser. *J Urol* 1988; **139**: 1307–9.

34 Gimeno E, Vilata JJ, Sanchez JL *et al.* Bowenoid papulosis: clinical and histological study of eight cases. *Genitourin Med* 1987; **63**: 109–13.

35 Tristram A, Fiander A. Clinical responses to Cidofovir applied topically to women with high grade vulval intraepithelial neoplasia. *Gynecol Oncol* 2005; **99**: 652–5.

36 van Seters M, van Beurden M, ten Kate FJ *et al.* Treatment of vulvar intraepithelial neoplasia with topical imiquimod. *N Engl J Med* 2008; **358**: 1465–73.

37 Baldwin PJ, van der Burg SH, Boswell CM *et al.* Vaccinia-expressed human papillomavirus 16 and 18 E6 and E7 as a therapeutic vaccination for vulval and vaginal intraepithelial neoplasia. *Clin Cancer Res* 2003; **9**: 5205–13.

38 Ambriz-Gonzalez G, Escobedo-Zavala LC, Carrillo de la Mora F *et al.* Buschke–Lowenstein tumor in childhood: a case report. *J Pediatr Surg* 2005; **40**: e25–7.

39 Rubben A, Beaudenon S, Favre M *et al.* Rearrangements of the upstream regulatory region of human papillomavirus type 6 can be found in both Buschke–Lowenstein tumours and in condylomata acuminata. *J Gen Virol* 1992; **73**: 3147–53.

40 Marsh RW, Agaliotis D, Killeen R Jr. Treatment of invasive squamous cell carcinoma complicating anal Buschke–Lowenstein tumor: a case history. *Cutis* 1995; **55**: 358–60.

41 Michelman FA, Filho AC, Moraes AM. Verrucous carcinoma of the penis treated with cryosurgery. *J Urol* 2002; **168**: 1096–7.

42 Nikkels AF, Thirion L, Quatresooz P *et al.* Photodynamic therapy for cutaneous verrucous carcinoma. *J Am Acad Dermatol* 2007; **57**: 516–9.

43 Sakurai T, Fuchigami T, Omae T *et al.* Bleomycin in verrucous squamous cell carcinoma of the oesophagus. *Postgrad Med J* 1983; **59**: 578–80.

44 Geusau A, Heinz-Peer G, Volc-Platzer B *et al.* Regression of deeply infiltrating giant condyloma (Buschke–Lowenstein tumor) following long-term intralesional interferon alfa therapy. *Arch Dermatol* 2000; **136**: 707–10.

45 Erkek E, Basar H, Bozdogan O *et al.* Giant condyloma acuminata of Buschke–Lowenstein: successful treatment with a combination of surgical excision, oral acitretin and topical imiquimod. *Clin Exp Dermatol* 2009; **34**: 266–8.

46 Mehta RK, Rytina E, Sterling JC. Treatment of verrucous carcinoma of vulva with acitretin. *Br J Dermatol* 2000; **142**: 1195–8.

47 Strojan P, Soba E, Budihna M *et al.* Radiochemotherapy with Vinblastine, Methotrexate, and Bleomycin in the treatment of verrucous carcinoma of the head and neck. *J Surg Oncol* 2005; **92**: 278–83.

48 Knobler RM, Schneider S, Neumann RA *et al.* DNA dot-blot hybridization implicates human papillomavirus type 11-DNA in epithelioma cuniculatum. *J Med Virol* 1989; **29**: 33–7.

49 Kathuria S, Rieker J, Jablokow VR *et al.* Plantar verrucous carcinoma (epithelioma cuniculatum): case report with review of the literature. *J Surg Oncol* 1986; **31**: 71–5.

50 Sato T, Morimoto A, Ishida Y *et al.* Human papillomavirus associated with Bowen's disease of the finger. *J Dermatol* 2004; **31**: 927–30.

51 Shimizu A, Tamura A, Abe M *et al.* Detection of human papillomavirus type 56 in Bowen's disease involving the nail matrix. *Br J Dermatol* 2008; **158**: 1273–9.

52 Hara H, Honda A, Suzuki H *et al.* Detection of human papillomavirus type 58 in polydactylous Bowen's disease on the fingers and toes of a woman—concurrent occurrence of invasive vulval and cervical carcinomas. *Dermatology* 2004; **209**: 218–22.

53 Mitsuishi T, Sata T, Matsukura T *et al.* The presence of mucosal human papillomavirus in Bowen's disease of the hands. *Cancer* 1997; **79**: 1911–7.

54 Pfister H, Haneke E. Demonstration of human papilloma virus type 2 DNA in Bowen's disease. *Arch Dermatol Res* 1984; **276**: 123–5.

55 Kawashima M, Jablonska S, Favre M *et al.* Characterization of a new type of human papillomavirus found in a lesion of Bowen's disease of the skin. *J Virol* 1986; **57**: 688–92.
56 Deguchi M, Tomioka Y, Mizugaki M *et al.* Detection of human papillomavirus type 33 DNA in extragenital Bowen's disease with the polymerase chain reaction. *Dermatology* 1998; **196**: 292–4.
57 Mitsuishi T, Kawashima M, Matsukura T *et al.* Human papillomavirus type 58 in Bowen's disease of the elbow. *Br J Dermatol* 2001; **144**: 384–6.
58 Grussendorf EI, Gahlen W. Metaplasia of a verruca vulgaris into spinocellular carcinoma. *Dermatologica* 1975; **150**: 295–9.
59 Guadara J, Sergi A, Labruna V *et al.* Transformation of plantar verruca into squamous cell carcinoma. *J Foot Surg* 1992; **31**: 611–4.
60 Robinette JW, Day F 3rd, Hahn P Jr. Subungual squamous cell carcinoma mistaken for a verruca. *J Am Podiatr Med Assoc* 1999; **89**: 435–7.
61 Kopelson PL, Nguyen QH, Moy RL. Verruca vulgaris and radiation exposure are associated with squamous cell carcinoma of the finger. *J Dermatol Surg Oncol* 1994; **20**: 38–41.
62 Grimmel M, de Villiers EM, Neumann C *et al.* Characterization of a new human papillomavirus (HPV 41) from disseminated warts and detection of its DNA in some skin carcinomas. *Int J Cancer* 1988; **41**: 5–9.
63 Weinstock MA, Coulter S, Bates J *et al.* Human papillomavirus and widespread cutaneous carcinoma after PUVA photochemotherapy. *Arch Dermatol* 1995; **131**: 701–4.
64 Harwood CA, Surentheran T, McGregor JM *et al.* Human papillomavirus infection and non-melanoma skin cancer in immunosuppressed and immunocompetent individuals. *J Med Virol* 2000; **61**: 289–97.
65 Boxman IL, Berkhout RJ, Mulder LH *et al.* Detection of human papillomavirus DNA in plucked hairs from renal transplant recipients and healthy volunteers. *J Invest Dermatol* 1997; **108**: 712–5.
66 Sterling JC. Human papillomaviruses and skin cancer. *J Clin Virol* 2005; **32**: S67–S71.
67 Nindl I, Gottschling M, Stockfleth E. Human papillomaviruses and non-melanoma skin cancer: basic virology and clinical manifestations. *Dis Markers* 2007; **23**: 247–59.

Epidermodysplasia verruciformis

Epidermodysplasia verruciformis (EV) is an inherited disorder [1] in which there is widespread and persistent infection with HPV, giving rise to a characteristic combination of plane warts, pityriasis versicolor-like lesions and reddish plaques. Malignant change is very common in adult life but metastasis is rare.

Aetiology. The susceptibility to the virus is inherited, usually autosomal recessive, though autosomal dominant [2] and probable X-linked dominant patterns [3] have been reported. Two loci on chromosomes 17q25 and 2p21-p24 are associated with the disease within some studied families [4]. Mutations in two genes *EVER1* and *EVER2* are linked with the disease in many but not all cases [5–7]. Impairment of cell-mediated immunity, notably T-helper-cell number and function, is commonly but not invariably found, although EV patients are not unusually susceptible to other infections. These changes are similar to, but more pronounced than, those seen in ordinary wart patients, and may be secondary to the infection rather than a primary abnormality predisposing to it. The increased natural killer (NK) cell activity in EV patients is interpreted as an appropriate response [8].

There is no impairment of DNA repair [9], and no association with HLA-A or -B antigens [10]. There are at least 20 HPV types characteristic of EV, including types most commonly found in the skin of these patients: HPVs 5, 8, 9, 12, 14, 15, 17, 19–25 and types found more rarely: HPVs 28, 36, 37, 38, 47, 49, 50, 75, 76, 77, 93 and 96. In addition, HPV-3 and 10, and rarely 29, which cause ordinary plane warts, are found in EV. Patients frequently harbour multiple HPV types [11]. HPV-5 and 8 are the main types associated with malignancy, with types 14, 17, 20 and 47 occasionally involved [12–15].

Pathology [2,16]. The histological picture is similar in the different clinical types of lesion. As in ordinary plane warts, there are hyperkeratosis and acanthosis. However, vacuolation or ballooning in the keratinocytes is more extensive, and may affect the upper half to three-quarters of the spinous layer. Viral particles can be identified ultrastructurally not only in the Malpighian cells, but also in basal cells. These viral cytopathic changes may still be seen in bowenoid lesions and early squamous cell carcinomas.

Clinical features [2,12,17–19]. Lesions on the face and neck are generally indistinguishable from plane warts, but on the trunk and limbs they tend to be larger, and of two main types. Scaly macular lesions resemble pityriasis versicolor, showing depigmentation or varying degrees of brown pigmentation. Thicker plaques are dull pink, violet or brown in colour and may resemble seborrhoeic keratoses or pigmented warts (Fig. 33.24).

The warts usually develop rapidly in childhood but may first appear at any age. They are most numerous on the face and neck and backs of the hands and feet, and may be restricted to these sites, but there are often scattered lesions elsewhere and the warts may be generalized over the entire body surface. Irregular confluence of neighbouring lesions to form lines or large plaques is often seen. Typical common warts are often present, especially on the sides of the fingers and on the palms and soles, and small warts on the vermilion border of the lips or in the urethra have occasionally been noted.

EV is remarkably persistent and may remain unchanged for decades. However, slow spontaneous regression following two pregnancies has been reported in a single case [20].

Dysplastic and malignant changes occur most often on exposed skin, commonly as actinic keratoses and Bowen's disease, suggesting that ultraviolet radiation is an important factor. Squamous cell

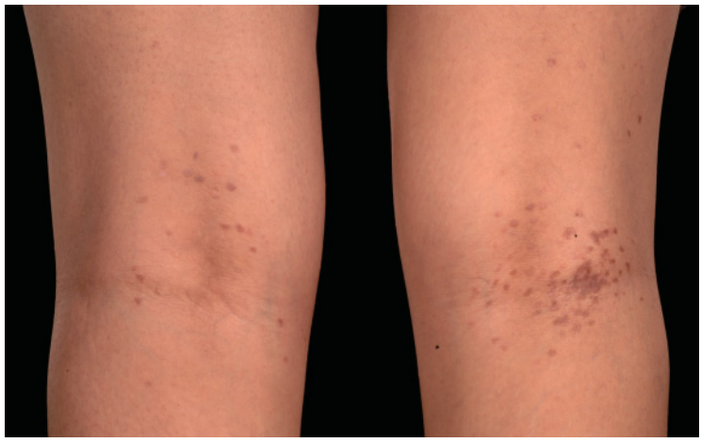


Fig. 33.24 Epidermodysplasia verruciformis. Pigmented flat warty lesions in popliteal fossae. (Courtesy of Addenbrooke's Hospital, Cambridge, UK.)

carcinoma has ultimately developed in one or more lesions in about 20–30% of reported cases, even before the age of 20 and when the lesions have been present for under 10 years. However, metastasis is rare.

Diagnosis. Acrokeratosis verruciformis (see Chapter 19) is superficially very similar. Flat, warty papules on the backs of hands and feet and on knees and elbows are present from infancy. The palms are diffusely thickened and show small keratoses and punctiform breaks in the papillary ridges. Histologically there is no vacuolation.

In lichen planus (see Chapter 41) the papules, which are usually pruritic, are pink or lilac in colour and distinctive mucosal lesions are often present. The histology is diagnostic.

EV-like syndromes in association with immunodeficiency due to many different causes have been reported (see p. 33.59 and see Chapter 35).

Treatment. Patients should be observed for the development of carcinomas and premalignant lesions, which should be excised or locally ablated. Avoidance of excessive sun exposure, with diligent use of effective sunscreen, should be advised.

The role of an oral retinoid in EV is not clear. Substantial clinical improvement is often achieved with etretinate at a typical starting dose of 1 mg/kg/day [21], but the effect is dose dependent and relapse occurs if the drug is stopped. Some cases respond poorly [22]. Whether dysplastic or malignant change is prevented by etretinate is not yet known. The combination of etretinate plus IFN-α may also produce a useful clinical effect [23]. Oral isotretinoin can also reduce the benign lesions [24,25].

Other treatments that have been tried in individual cases or small numbers of patients and shown occasional but inconsistent benefit include topical imiquimod [26,27], topical vitamin D analogue [25], topical immunotherapy with squaric acid dibutylester [28] and oral cimetidine [29,30].

References

1 Lewandowsky F, Lutz W. Ein Fall einer bisher nicht beschreibenen Hauterkrankung (Epidermodysplasia verruciformis). *Arch Dermatol Syph (Berlin)* 1922; **141**: 193–203.

2 Kanerva LO, Johansson E, Niemi KM *et al.* Epidermodysplasia verruciformis. Clinical and light- and electron-microscopic observations during etretinate therapy. *Arch Dermatol Res* 1985; **278**: 153–60.

3 Salamon T, Halepovic E, Berberovic L *et al.* Epidermodysplasia verruciformis-ähnliche Genodermatose mit Veränderungen der Nägel. *Hautarzt* 1987; **38**: 525–31.

4 Ramoz N, Taieb A, Rueda LA *et al.* Evidence for a nonallelic heterogeneity of epidermodysplasia verruciformis with two susceptibility loci mapped to chromosome regions 2p21–p24 and 17q25. *J Invest Dermatol* 2000; **114**: 1148–53.

5 Ramoz N, Rueda LA, Bouadjar B *et al.* Mutations in two adjacent novel genes are associated with epidermodysplasia verruciformis. *Nat Genet* 2002; **32**: 579–81.

6 Akgul B, Kose O, Safali M *et al.* A distinct variant of Epidermodysplasia verruciformis in a Turkish family lacking EVER1 and EVER2 mutations. *J Dermatol Sci* 2007; **46**: 214–6.

7 Zavattaro E, Azzimonti B, Mondini M *et al.* Identification of defective Fas function and variation of the perforin gene in an epidermodysplasia verruciformis patient lacking EVER1 and EVER2 mutations. *J Invest Dermatol* 2008; **128**: 732–5.

8 Majewski S, Skopinska-Rozewska E, Jablonska S *et al.* Partial defects of cell-mediated immunity in patients with epidermodysplasia verruciformis. *J Am Acad Dermatol* 1986; **15**: 966–73.

9 Proniewska M, Jablonska S. UV-induced DNA repair synthesis in patients with epidermodysplasia verruciformis. *Dermatologica* 1980; **160**: 289–96.

10 Wojtulewicz-Kurkus J, Glinski W, Jablonska S *et al.* Identification of HLA antigens in familial and non-familial epidermodysplasia verruciformis. *Dermatologica* 1985; **170**: 53–8.

11 Dell'Oste V, Azzimonti B, De Andrea M *et al.* High β-HPV DNA loads and strong seroreactivity are present in epidermodysplasia verruciformis. *J Invest Dermatol* 2008; **129**: 1026–34.

12 Lutzner MA, Blanchet-Bardon C, Orth G. Clinical observations, virologic studies, and treatment trials in patients with epidermodysplasia verruciformis, a disease induced by specific human papillomaviruses. *J Invest Dermatol* 1984; **83**: 18s–25s.

13 Gewirtzman A, Bartlett B, Tyring S. Epidermodysplasia verruciformis and human papilloma virus. *Curr Opin Infect Dis* 2008; **21**: 141–6.

14 Oliveira WR, Rady PL, Festa C *et al.* Skin cancer in epidermodysplasia verruciformis patients from Brazil. *J Eur Acad Dermatol Venereol* 2006; **20**: 1154–6.

15 Yutsudo M, Tanigaki T, Kanda R *et al.* Involvement of human papillomavirus type 20 in epidermodysplasia verruciformis skin carcinogenesis. *J Clin Microbiol* 1994; **32**: 1076–8.

16 Ruiter M, van Mullem PJ. Demonstration by electronmicroscopy of an intranuclear virus in epidermodysplasia verruciformis. *J Invest Dermatol* 1966; **47**: 247–52.

17 Jablonska S, Majewski S. Epidermodysplasia verruciformis: immunological and clinical aspects. *Curr Top Microbiol Immunol* 1994; **186**: 157–75.

18 de Oliveira WR, Festa Neto C, Rady PL *et al.* Clinical aspects of epidermodysplasia verruciformis. *J Eur Acad Dermatol Venereol* 2003; **17**: 394–8.

19 Gul U, Kilic A, Gonul M *et al.* Clinical aspects of epidermodysplasia verruciformis and review of the literature. *Int J Dermatol* 2007; **46**: 1069–72.

20 Jablonska S, Obalek S, Orth G *et al.* Regression of the lesions of epidermodysplasia verruciformis. *Br J Dermatol* 1982; **107**: 109–15.

21 Jablonska S, Obalek S, Wolska H. Follow-up of patients with epidermodysplasia verruciformis treated with etretinate. *Dermatologica* 1986; **173**: 196–9.

22 Kowalzick L, Mensing H. Failure of etretinate in epidermodysplasia verruciformis. *Dermatologica* 1986; **173**: 75–8.

23 Anadolu R, Oskay T, Erdem C *et al.* Treatment of epidermodysplasia verruciformis with a combination of acitretin and interferon alfa-2a. *J Am Acad Dermatol* 2001; **45**: 296–9.

24 Rallis E, Paparizos V, Kyriakis K *et al.* Treatment of epidermodysplasia verruciformis in human immunodeficiency virus-positive patients. *J Eur Acad Dermatol Venereol* 2009; **23**: 195–6.

25 Hayashi J, Matsui C, Mitsuishi T *et al.* Treatment of localized epidermodysplasia verruciformis with tacalcitol ointment. *Int J Dermatol* 2002; **41**: 817–20.

26 Berthelot C, Dickerson MC, Rady P *et al.* Treatment of a patient with epidermodysplasia verruciformis carrying a novel EVER2 mutation with imiquimod. *J Am Acad Dermatol* 2007; **56**: 882–6.

27 Janssen K, Lucker GP, Houwing RH *et al.* Epidermodysplasia verruciformis: unsuccessful therapeutic approach with imiquimod. *Int J Dermatol* 2007; **46** (Suppl. 3): 45–7.

28 Ishiji T, Ibe M, Kawase M *et al.* Patients with epidermodysplasia verruciformis show no response to contact immunotherapy. *Dermatology* 2001; **202**: 76–7.

29 Micali G, Nasca MR, Dall'Oglio F *et al.* Cimetidine therapy for epidermodysplasia verruciformis. *J Am Acad Dermatol* 2003; **48**: S9–10.

30 de Oliveira WR, Neto CF, Rivitti EA. The lack of a clinical effect of cimetidine in the treatment of epidermodysplasia verruciformis. *J Am Acad Dermatol* 2004; **50**: e14.

HPV in immunosuppression

Warts and HPV in immune deficiency

Chronic immune deficiency, especially of cell-mediated function, predisposes to clinically evident warts, perhaps by allowing the development of lesions from previously latent virus. The warts may be so widespread as to constitute generalized verrucosis, or to resemble epidermodysplasia verruciformis.

Solid organ transplant recipients

Long-term immunosuppression following organ transplantation is a major and common factor predisposing to severe papillomavirus infection (Fig. 33.25). One year post-transplant, 15% of 120 renal transplant recipients had warts [1], but this can rise to 90% at the end of the fifth year [2]. HPV-2 and HPV-4 warts are the most frequent. Children and adults are similarly affected and in most cases, the warts are refractory to standard methods of treatment [3].

Long-term immunosuppressed individuals may develop lesions very like those in epidermodysplasia verruciformis, with small erythematous non-warty plaques and SCCs especially on sun-exposed areas. Viral analysis from flaking, keratotic or invasive lesions has shown heterogeneity of HPV types [1,4,5], including many epidermodysplasia verruciformis-associated types. The use of degenerate primers in PCR has shown that many more, some as yet incompletely characterized, HPV types may be present in dysplastic or malignant squamous lesions [6,7] and also in clinically normal skin and hair follicles [8,9]. The incidence of anogenital intraepithelial neoplasia is also increased [10,11].



(a)



(b)

Fig 33.25 Extensive plantar warts in a renal transplant recipient. (a) Toes. (b) Sole. (Courtesy of Addenbrooke's Hospital, Cambridge, UK.)

HIV infection and AIDS (see Chapter 35)

The incidence of warts is reported to be between 5 and 27% in HIV infection. Common and plantar warts are probably somewhat increased in frequency and severity but are not a major problem in most patients. There is an increased incidence of facial and intraoral warts, many of which contain HPV-7, the 'butchers' wart' virus [12]. Perianal warts, especially in homosexual men, may be florid and refractory to treatment [13]. Anogenital intraepithelial neoplasia and progression to malignancy are increased in incidence [14]. Patients with HIV infection may also develop an EV-like syndrome with widespread plane warts, keratoses and development of cutaneous malignancy [15].

Other causes of immunodeficiency

The incidence of warts is increased in patients with Hodgkin's disease and, to a lesser extent, in those with other malignant lymphomas and chronic lymphatic leukaemia [16]. Patients with systemic lupus erythematosus (SLE) have an increased risk of warts and also anogenital disease [17,18]. Chronic, extensive plane warts were reported in a woman with immune deficiency secondary to intestinal lymphangiectasia [19]. Epidermodysplasia verruciformis-like conditions have been associated with treated Hodgkin's disease [20], lepromatous leprosy [21] and graft-versus-host disease [22].

Primary immune deficiencies, mostly involving cell-mediated immunity, may be accompanied by widespread warts, an EV-like syndrome or anogenital malignancies, for example ataxia–telangiectasia [23], Fanconi's anaemia [24], Wiskott–Aldrich syndrome [25], idiopathic CD4 lymphocytopenia [26], common variable immunodeficiency [27] and following bone marrow transplant for severe combined immunodeficiency [28]. Benign HPV disease, as well as anogenital malignancies, contribute to the spectrum of abnormalities in the WHIM syndrome: warts, hypogammaglobulinaemia, infections and myelokathesis in which white cells do not leave the bone marrow [29].

The association of warts of palms and soles, seborrhoeic keratoses of the trunk, and Bowen's disease of the face, in two brothers, who also had congenital dislocation of the hips and kyphoscoliosis, has been labelled Bittner's syndrome [30]. The patients had low IgA levels and a poor cell-mediated response.

References

1 Rudlinger R, Smith IW, Bunney MH *et al.* Human papillomavirus infections in a group of renal transplant recipients. *Br J Dermatol* 1986; **115**: 681–92.
2 Leigh IM, Glover MT. Skin cancer and warts in immunosuppressed renal transplant recipients. *Recent Results Cancer Res* 1995; **139**: 69–86.
3 Ingelfinger JR, Grupe WE, Topor M *et al.* Warts in a pediatric renal transplant population. *Dermatologica* 1977; **155**: 7–12.
4 Van der Leest RJ, Zachow KR, Ostrow RS *et al.* Human papillomavirus heterogeneity in 36 renal transplant recipients. *Arch Dermatol* 1987; **123**: 354–7.
5 Barr BB, Benton EC, McLaren K *et al.* Papillomavirus infection and skin cancer in renal allograft recipients. *Lancet* 1989; **2**: 224–5.

6 Shamanin V, zur Hausen H, Lavergne D *et al.* Human papillomavirus infections in nonmelanoma skin cancers from renal transplant recipients and nonimmunosuppressed patients. *J Natl Cancer Inst* 1996; **88**: 802–11.
7 de Jong-Tieben LM, Berkhout RJ, Smits HL *et al.* High frequency of detection of epidermodysplasia verruciformis-associated human papillomavirus DNA in biopsies from malignant and premalignant skin lesions from renal transplant recipients. *J Invest Dermatol* 1995; **105**: 367–71.
8 Boxman IL, Berkhout RJ, Mulder LH *et al.* Detection of human papillomavirus DNA in plucked hairs from renal transplant recipients and healthy volunteers. *J Invest Dermatol* 1997; **108**: 712–5.
9 Harwood CA, Surentheran T, McGregor JM *et al.* Human papillomavirus infection and non-melanoma skin cancer in immunosuppressed and immunocompetent individuals. *J Med Virol* 2000; **61**: 289–97.
10 Gentile G, Formelli G, Orsoni G *et al.* Immunosuppression and human genital papillomavirus infection. *Eur J Gynaecol Oncol* 1991; **12**: 79–81.
11 Ogunbiyi OA, Scholefield JH, Raftery AT *et al.* Prevalence of anal human papillomavirus infection and intraepithelial neoplasia in renal allograft recipients. *Br J Surg* 1994; **81**: 365–7.
12 de Villiers EM. Prevalence of HPV 7 papillomas in the oral mucosa and facial skin of patients with human immunodeficiency virus. *Arch Dermatol* 1989; **125**: 1590.
13 Rudlinger R, Grob R, Buchmann P *et al.* Anogenital warts of the condyloma acuminatum type in HIV-positive patients. *Dermatologica* 1988; **176**: 277–81.
14 Heard I, Tassie JM, Schmitz V *et al.* Increased risk of cervical disease among human immunodeficiency virus-infected women with severe immunosuppression and high human papillomavirus load. *Obstet Gynecol* 2000; **96**: 403–9.
15 Barzegar C, Paul C, Saiag P *et al.* Epidermodysplasia verruciformis-like eruption complicating human immunodeficiency virus infection. *Br J Dermatol* 1998; **139**: 122–7.
16 Morison WL. Viral warts, herpes simplex and herpes zoster in patients with secondary immune deficiencies and neoplasms. *Br J Dermatol* 1975; **92**: 625–30.
17 Korkmaz C, Urer SM. Cutaneous warts in patients with lupus erythematosus. *Rheumatol Int* 2004; **24**: 137–40.
18 Nath R, Mant C, Luxton J *et al.* High risk of human papillomavirus type 16 infections and of development of cervical squamous intraepithelial lesions in systemic lupus erythematosus patients. *Arthritis Rheum* 2007; **57**: 619–25.
19 Ross IN, Chesner I, Thompson RA *et al.* Cutaneous viral infection as a presentation of intestinal lymphangiectasia. *Br J Dermatol* 1982; **107**: 357–63.
20 Gross G, Ellinger K, Roussaki A *et al.* Epidermodysplasia verruciformis in a patient with Hodgkin's disease: characterization of a new papillomavirus type and interferon treatment. *J Invest Dermatol* 1988; **91**: 43–8.
21 Jacyk WK, Lechner W. Epidermodysplasia verruciformis in lepromatous leprosy. Report of 2 cases. *Dermatologica* 1984; **168**: 202–5.
22 Kunishige JH, Hymes SR, Madkan V *et al.* Epidermodysplasia verruciformis in the setting of graft-versus-host disease. *J Am Acad Dermatol* 2007; **57**: S78–80.
23 Barnett N, Mak H, Winkelstein JA. Extensive verrucosis in primary immunodeficiency diseases. *Arch Dermatol* 1983; **119**: 5–7.
24 Kutler DI, Wreesmann VB, Goberdhan A *et al.* Human papillomavirus DNA and p53 polymorphisms in squamous cell carcinomas from Fanconi anemia patients. *J Natl Cancer Inst* 2003; **95**: 1718–21.
25 Zinn KH, Belohradsky BH. Wiskott–Aldrich–Syndrom mit Verrucae vulgares. *Hautarzt* 1977; **28**: 664–7.
26 Stetson CL, Rapini RP, Tyring SK *et al.* $CD4^+$ T lymphocytopenia with disseminated HPV. *J Cutan Pathol* 2002; **29**: 502–5.
27 Vu J, Wallace GR, Singh R *et al.* Common variable immunodeficiency syndrome associated with epidermodysplasia verruciformis. *Am J Clin Dermatol* 2007; **8**: 307–10.
28 Descamps V, Blanchet-Bardon C, Petit A *et al.* Epidermodysplasie verruciforme (EV) après greffe de moelle pour traitement d'un déficit immunitaire combine sévère: un modèle pour comprendre le déficit immunitaire spécifique de l'EV? *Ann Dermatol Venereol* 1991; **118**: 847–50.
29 Hernandez PA, Gorlin RJ, Lukens JN *et al.* Mutations in the chemokine receptor gene CXCR4 are associated with WHIM syndrome, a combined immunodeficiency disease. *Nat Genet* 2003; **34**: 70–4.
30 Stritzler C, Sawitsky A, Stritzler R. Bittner's syndrome. *Arch Dermatol* 1971; **103**: 548–9.

Hepatitis viruses

Hepatitis B

Aetiology and pathogenesis [1,2]. The hepatitis B virus (HBV) is the smallest DNA virus to infect humans, consisting of partly double-stranded, circular DNA within a protein nucleocapsid contained within an envelope. Worldwide, 400 million people have chronic HBV infection, with the highest prevalence in Asia, Africa, Southern Europe and South America. In these areas, transmission usually occurs perinatally from mother to child or horizontally within families, whilst in areas of lower prevalence, transmission is usually intravenously or via sexual contact.

During the asymptomatic incubation period, which can be 2–4 weeks in adults but months to years after neonatal infection, antigenaemia and then antibody responses develop. As the virus replicates, the virus can be detected in serum by PCR, the HBV e antigen (a soluble protein derived from the core protein) is found in blood and antibodies develop against the nucleocapsid protein (core antigen, HBcAg). Electron microscopy of serum during this replicative phase will reveal complete virus particles (the Dane particle) and also excess surface (envelope) protein formed into small spheroids and cylinders.

If a cytotoxic immune response develops against HBcAg, symptoms and signs of an acute hepatitis develop. HBV DNA disappears from the blood but HBeAg and HBsAg are still detectable and antibodies against both HBcAg and HBeAg are detectable.

Persistence of this phase of immune response with continuing viral replication for 6 months indicates chronic infection. The likelihood of becoming a chronic carrier of HBV infection is highest (95%) if infection occurs perinatally but lowest if infection occurs as an adult (5%). If the virus is cleared effectively, neither HBV DNA nor HBV antigens are detectable, but antibodies to the surface or envelope protein (HBsAg, Australia antigen) develop and persist, providing protection against re-infection.

Cutaneous manifestations [3,4]. Most dermatological manifestations of HBV infection are related to immune complex formation [5] occurring during the incubation and early immune response phases of infection.

Serum sickness syndrome. This occurs in 20–30% of cases, usually during the prodromal phase before the onset of clinical hepatitis, clearing as liver disease becomes apparent. Urticaria and angioedema are common, as well as vasculitis [6]. Petechiae, palpable purpura and erythema multiforme-like lesions can develop and occasionally macular, maculopapular and lichenoid eruptions and erythema nodosum [7]. Arthralgia or arthritis, and headache [8] are commonly associated.

Chronic HBV infection may be associated with development of polyarteritis nodosa, leukocytoclastic vasculitis (which may clear during treatment with lamivudine [9]), Gianotti–Crosti syndrome and possibly lichen planus and pitted keratolysis [10].

Polyarteritis nodosa (PAN) (see Chapter 50). The association of HBV infection with PAN is more common in North America and

Western Europe than in areas of the world where the infection has a high prevalence. HBsAg has been detected in 8 to over 50% of patients with polyarteritis nodosa [11]. PAN associated with hepatitis B infection has cleared following treatment with lamivudine [12] and the optimal treatment for HBV-associated PAN is a combination of antiviral and immunosuppression [13].

Gianotti–Crosti syndrome (see p. 33.77). Gianotti–Crosti syndrome or papular acrodermatitis of childhood has been reported in chronic HBV infection although the strength of a possible association is uncertain [3,4].

Prophylaxis. Pre-exposure immunization is achieved by a course of three doses of recombinant surface-antigen vaccine. In many countries, universal immunization is given to infants and adolescents with the long-term goal of eradicating the disease. In other countries, a policy of selective immunization of high-risk groups has been followed. Responders to vaccination (90% of young adults) retain long-lived immunological memory that effectively sustains immunity even when the level of antibody declines.

Post-exposure treatment for infants born to highly infectious (HBeAg positive) HB-carrier mothers and for unimmunized people or in those who have failed to respond to the vaccine after accidental exposure (e.g. needlestick injuries) consists of a combination of hyperimmune globulin and vaccination.

A number of cutaneous conditions have followed hepatitis B vaccination [14,15]. These include: erythema nodosum [14], generalized granuloma annulare [16], thrombocytopenic purpura [17], Reiter's syndrome [18], Gianotti–Crosti syndrome [19], polyarteritis nodosa [20], pityriasis rosea-like eruption [20] and lichen planus [21,22]. Local reactions of pseudolymphomatous hyperplasia have also been reported [23].

References

1 Lee WM. Hepatitis B virus infection. *N Engl J Med* 1997; **337**: 1733–45.
2 Lok AS. Hepatitis B infection: pathogenesis and management. *J Hepatol* 2000; **32**: 89–97.
3 Han SH. Extrahepatic manifestations of chronic hepatitis B. *Clin Liver Dis* 2004; **8**: 403–18.
4 Pyrsopoulos NT, Reddy KR. Extrahepatic manifestations of chronic viral hepatitis. *Curr Gastroenterol Rep* 2001; **3**: 71–8.
5 Gupta RC, Kohler PF. Identification of HBsAg determinants in immune complexes from hepatitis B virus-associated vasculitis. *J Immunol* 1984; **132**: 1223–8.
6 Popp JW Jr, Harrist TJ, Dienstag JL *et al*. Cutaneous vasculitis associated with acute and chronic hepatitis. *Arch Intern Med* 1981; **141**: 623–9.
7 Maggiore G, Grifeo S, Marzani MD. Erythema nodosum and hepatitis B virus (HBV) infection. *J Am Acad Dermatol* 1983; **9**: 602–3.
8 Caroli J. Serum-sickness-like prodromata in viral hepatitis: Caroli's triad. *Lancet* 1972; **1**: 964–5.
9 Surmali Onay O, Baskin E, Ozcay F *et al*. Successful treatment of hepatitis B-associated leukocytoclastic vasculitis with lamivudine treatment in a child patient. *Rheumatol Int* 2007; **27**: 869–72.
10 Dogan B. Dermatological manifestations in hepatitis B surface antigen carriers in east region of Turkey. *J Eur Acad Dermatol Venereol* 2005; **19**: 323–5.
11 Trepo C, Guillevin L. Polyarteritis nodosa and extrahepatic manifestations of HBV infection: the case against autoimmune intervention in pathogenesis. *J Autoimmun* 2001; **16**: 269–74.
12 Bedani PL, Bergami M, Cavazzini PL *et al*. HBV-related cutaneous periarteritis nodosa in a patient 16 years after renal transplantation: efficacy of lamivudine. *J Nephrol* 2001; **14**: 428–30.
13 Guillevin L, Mahr A, Callard P *et al*. Hepatitis B virus-associated polyarteritis nodosa: clinical characteristics, outcome, and impact of treatment in 115 patients. *Medicine (Baltimore)* 2005; **84**: 313–22.
14 Goolsby PL. Erythema nodosum after Recombivax HB hepatitis B vaccine. *N Engl J Med* 1989; **321**: 1198–9.
15 Criado PR, de Oliveira Ramos R, Vasconcellos C *et al*. Two case reports of cutaneous adverse reactions following hepatitis B vaccine: lichen planus and granuloma annulare. *J Eur Acad Dermatol Venereol* 2004; **18**: 603–6.
16 Wolf F, Grezard P, Berard F *et al*. Generalized granuloma annulare and hepatitis B vaccination. *Eur J Dermatol* 1998; **8**: 435–6.
17 Poullin P, Gabriel B. Thrombocytopenic purpura after recombinant hepatitis B vaccine. *Lancet* 1994; **344**: 1293.
18 Hassan W, Oldham R. Reiter's syndrome and reactive arthritis in health care workers after vaccination. *BMJ* 1994; **309**: 94.
19 Karakas M, Durdu M, Tuncer I *et al*. Gianotti–Crosti syndrome in a child following hepatitis B virus vaccination. *J Dermatol* 2007; **34**: 117–20.
20 De Keyser F, Naeyaert JM, Hindryckx P *et al*. Immune-mediated pathology following hepatitis B vaccination. Two cases of polyarteritis nodosa and one case of pityriasis rosea-like drug eruption. *Clin Exp Rheumatol* 2000; **18**: 81–5.
21 Agrawal A, Shenoi SD. Lichen planus secondary to hepatitis B vaccination. *Indian J Dermatol Venereol Leprol* 2004; **70**: 234–5.
22 Calista D, Morri M. Lichen planus induced by hepatitis B vaccination: a new case and review of the literature. *Int J Dermatol* 2004; **43**: 562–4.
23 Stavrianeas NG, Katoulis AC, Kanelleas A *et al*. Papulonodular lichenoid and pseudolymphomatous reaction at the injection site of hepatitis B virus vaccination. *Dermatology* 2002; **205**: 166–8.

Hepatitis C

Aetiology. Hepatitis C virus (HCV) is a small, single-stranded, positive-sense RNA virus and a member of the *Flaviviridae*. It is found throughout the world, although the prevalence of seropositivity varies between 1 and 10% depending on the region. It is spread parenterally by blood and blood products, by needle sharing and perinatally from infected mothers to their babies in 1–10% of cases. Sexual transmission is at a low rate.

The virus replicates in hepatocytes and blood mononuclear cells. Most acute infections are subclinical, but in 75% of individuals, infection leads to a chronic hepatitis, which in some cases can progress to cirrhosis and occasionally development of hepatoma. Improved awareness of HCV has led to a decrease in acute infection, but, as yet, no change in chronic infection.

Cutaneous manifestations [1]. The immune response to the virus affects the degree and form of liver damage and may also contribute to extrahepatic effects. Nearly 20% of patients with HCV infection have skin disease [2].

Vasculitis. Cryoglobulins are commonly found in patients with HCV infection [3], but only some develop clinical mixed cryoglobulinaemia which presents as a systemic vasculitis, with symptoms of fatigue and arthralgia with hepatosplenomegaly and palpable purpura, particularly of the lower legs. The effects are due to the precipitation of immune complexes of HCV virions or proteins with Ig and IgM. The skin lesions show classical histological features of a leukocytoclastic vasculitis. Of patients with mixed cryoglobulinaemia, up to 80% are HCV positive.

Porphyria cutanea tarda. Liver disease is a well-recognized association of PCT, but the detection of antibodies to HCV in a high proportion of non-familial cases suggests an aetiological link.

There is geographical variation, with reports of between 30 and 85% of cases of PCT being HCV seropositive [4–8].

HCV infection has also been reported in association with lichen planus [9], Sjögren's syndrome [10], urticaria [11], erythema multiforme [12], erythema nodosum [13], pruritus [14], prurigo nodularis [15], cutaneous polyarteritis nodosa [16], pyoderma gangrenosum [17], pigmented purpuric dermatosis [18], disseminated superficial actinic porokeratosis [19], pityriasis lichenoides [20], generalized granuloma annulare [21] and necrolytic acral erythema [22], although the causality of these links is not yet certain.

Treatment. IFN-α produces a good initial response in mixed cryoglobulinaemia [23], but relapse is common and only 10–30% will achieve a satisfactory long-term response. Combination of interferon with ribavirin produces a better response [24]. Sarcoidosis has been reported to develop during treatment of HCV infection [25].

References

1 Cordel N, Chosidow O, Frances C. Cutaneous disorders associated with hepatitis C virus infection. *Ann Med Interne (Paris)* 2000; **151**: 46–52.

2 Cacoub P, Renou C, Rosenthal E *et al.* Extrahepatic manifestations associated with hepatitis C virus infection. A prospective multicenter study of 321 patients. The GERMIVIC. Groupe d'Etude et de Recherche en Médecine Interne et Maladies Infectieuses sur le Virus de l'Hépatite C. *Medicine (Baltimore)* 2000; **79**: 47–56.

3 Sansonno D, Dammacco F. Hepatitis C virus, cryoglobulinaemia, and vasculitis: immune complex relations. *Lancet Infect Dis* 2005; **5**: 227–36.

4 Cribier B, Petiau P, Keller F *et al.* Porphyria cutanea tarda and hepatitis C viral infection. A clinical and virologic study. *Arch Dermatol* 1995; **131**: 801–4.

5 Hussain I, Hepburn NC, Jones A *et al.* The association of hepatitis C viral infection with porphyria cutanea tarda in the Lothian region of Scotland. *Clin Exp Dermatol* 1996; **21**: 283–5.

6 Gisbert JP, Garcia-Buey L, Pajares JM *et al.* Prevalence of hepatitis C virus infection in porphyria cutanea tarda: systematic review and meta-analysis. *J Hepatol* 2003; **39**: 620–7.

7 Linde Y, Harper P, Floderus Y *et al.* The prevalence of hepatitis C in patients with porphyria cutanea tarda in Stockholm, Sweden. *Acta Derm Venereol* 2005; **85**: 164–6.

8 Tsukazaki N, Watanabe M, Irifune H. Porphyria cutanea tarda and hepatitis C virus infection. *Br J Dermatol* 1998; **138**: 1015–7.

9 Cribier B, Garnier C, Laustriat D *et al.* Lichen planus and hepatitis C virus infection: an epidemiologic study. *J Am Acad Dermatol* 1994; **31**: 1070–2.

10 Ramos-Casals M, Loustaud-Ratti V, De Vita S *et al.* Sjogren syndrome associated with hepatitis C virus: a multicenter analysis of 137 cases. *Medicine (Baltimore)* 2005; **84**: 81–9.

11 Reichel M, Mauro TM. Urticaria and hepatitis C. *Lancet* 1990; **336**: 822–3.

12 Antinori S, Esposito R, Aliprandi CA *et al.* Erythema multiforme and hepatitis C. *Lancet* 1991; **337**: 428.

13 Domingo P, Ris J, Martinez E *et al.* Erythema nodosum and hepatitis C. *Lancet* 1990; **336**: 1377.

14 Cribier B, Samain F, Vetter D *et al.* Systematic cutaneous examination in hepatitis C virus infected patients. *Acta Derm Venereol* 1998; **78**: 355–7.

15 Neri S, Raciti C, D'Angelo G *et al.* Hyde's prurigo nodularis and chronic HCV hepatitis. *J Hepatol* 1998; **28**: 161–4.

16 Soufir N, Descamps V, Crickx B *et al.* Hepatitis C virus infection in cutaneous polyarteritis nodosa: a retrospective study of 16 cases. *Arch Dermatol* 1999; **135**: 1001–2.

17 Keane FM, MacFarlane CS, Munn SE *et al.* Pyoderma gangrenosum and hepatitis C virus infection. *Br J Dermatol* 1998; **139**: 924–5.

18 Dessoukey MW, Abdel-Dayem H, Omar MF *et al.* Pigmented purpuric dermatosis and hepatitis profile: a report on 10 patients. *Int J Dermatol* 2005; **44**: 486–8.

19 Kono T, Kobayashi H, Ishii M *et al.* Synchronous development of disseminated superficial porokeratosis and hepatitis C virus-related hepatocellular carcinoma. *J Am Acad Dermatol* 2000; **43**: 966–8.

20 Zechini B, Teggi A, Antonelli M *et al.* A case report of pityriasis lichenoides in a patient with chronic hepatitis C. *J Infect* 2005; **51**: E23–5.

21 Granel B, Serratrice J, Rey J *et al.* Chronic hepatitis C virus infection associated with a generalized granuloma annulare. *J Am Acad Dermatol* 2000; **43**: 918–9.

22 Abdallah MA, Hull C, Horn TD. Necrolytic acral erythema: a patient from the United States successfully treated with oral zinc. *Arch Dermatol* 2005; **141**: 85–7.

23 Misiani R, Bellavita P, Fenili D *et al.* Interferon alfa-2a therapy in cryoglobulinemia associated with hepatitis C virus. *N Engl J Med* 1994; **330**: 751–6.

24 Cacoub P, Lidove O, Maisonobe T *et al.* Interferon-alpha and ribavirin treatment in patients with hepatitis C virus-related systemic vasculitis. *Arthritis Rheum* 2002; **46**: 3317–26.

25 Ramos-Casals M, Mana J, Nardi N *et al.* Sarcoidosis in patients with chronic hepatitis C virus infection: analysis of 68 cases. *Medicine (Baltimore)* 2005; **84**: 69–80.

Parvoviruses

Until recently, parvovirus B19 was the only member of the Parvovirus family known to infect humans. Molecular analysis of viruses isolated from humans has revealed that three other parvoviruses, PARV4, PARV5 and human bocavirus, can infect man.

Antibodies to PARV4 and PARV5 are not commonly found in the sera of healthy individuals, and transmission in adults is thought to be via the parenteral route [1]. Persistent infection may develop in some individuals, especially if immunosuppressed [2].

Human bocavirus infection presents most commonly in childhood with acute upper respiratory disease [3] or gastroenteritis, but most adults are seropositive [4] suggesting previous undiagnosed acute or subclinical infection. An associated erythematous maculopapular eruption on the chest or face has occasionally been observed during acute infection [5].

Human parvovirus, B19 [6,7]

Aetiology. Parvovirus B19 (Fig. 33.26) is the cause of erythema infectiosum (fifth disease) [8].

The virus was detected first in serum in 1975 [9]. The name B19 comes from the serum panel (B), sample number (19) in which the virus was discovered. Three genotypes have been distinguished, but they are serologically identical [10].

Small outbreaks of fifth disease usually occur in the spring. The distribution is worldwide with most cases being seen in children aged between 2 and 10 years. The incubation period from infection to viraemia is 6 days. The viraemia peaks at 8–9 days and at day 10 there is an almost complete loss of bone-marrow erythroid precursors. The rash of erythema infectiosum appears about day 15, as the marrow recovers and IgM antibody becomes detectable. Spread occurs by droplets from the nasopharynx with secondary attack rates of about 50% in susceptible household contacts. One infection gives lifelong immunity. In a group of 5 to 9-year-olds in the USA, 21% had evidence of past infection. Between 20 and 50% of infections are asymptomatic and, in the UK, 60% of adults are seropositive.

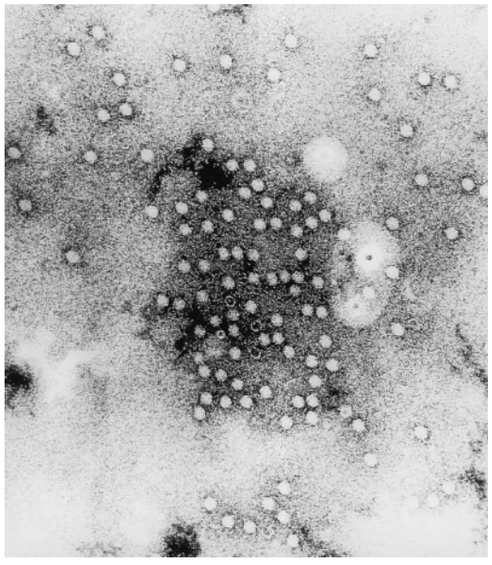


Fig 33.26 Human parvovirus (B19) in serum of patient with aplastic crisis. Negatively stained electron micrograph, ×200 000. (Courtesy of Mr T.W. Lee, John Radcliffe Hospital, Oxford.)

Pathogenesis. The major target for parvovirus B19 is the bone-marrow erythroid progenitor cell. This viral tropism is mediated through the erythrocyte P antigen (globoside) and the rare person who lacks this antigen is not susceptible to B19 infection [11]. The virus is cytotoxic for these cells which causes a halt in red-cell production. The bone marrow shows erythroid hypoplasia and occasional giant pronormoblasts. The exanthem and polyarthralgia are the result of antibody–antigen immune complexes and occur as bone-marrow recovery is underway. Persistent infection causing a severe chronic anaemia has been reported in people with congenital or acquired immune deficiency [12].

Infection in the pregnant woman has a transplacental transmission rate of about 33%. In the first trimester, this may cause spontaneous abortion and in the second trimester, fetal hydrops [13]. Intrauterine death occurs in about 10% of B19 infections in pregnancy, but infants who survive have no evidence of congenital infection. The interval between maternal infection and fetal death is often 4–5 weeks, but may be up to 11 weeks.

Clinical features

Erythema infectiosum (fifth disease) [8,14,15]. The exanthem commonly develops suddenly without prodromal symptoms although there may be mild malaise, myalgia or fever. Rose-red papules on the cheeks rapidly coalesce to form a hot, turgid erythema, almost erysipeloid, giving a 'slapped cheek' appearance. There is often perioral pallor. During the next 2–4 days maculopapules appear on the proximal extremities and extend distally to the hands and feet and proximally to the trunk, often forming a lace-like pattern. The palms and soles may be involved and acral lesions may be petechial. Rarely, lesions may be vesicular or pustular. There may be dark-red macules on the buccal and genital mucous membranes. The eruption usually fades in 6–10 days, but evanescent recurrences on previously affected sites may continue for up to 2 weeks [14,16].

In adults, polyarthralgia is often the predominant symptom of infection [17] and when the exanthem does occur, the features of facial erythema are usually less marked than in children.

While the arthropathy usually resolves in a few weeks, joint symptoms persist for more than 2 months in 10% of infected women. In some cases, the combination of parvovirus infection with rash and arthritis is accompanied by other features diagnostic of connective tissue disease such as systemic lupus erythematosus or rheumatoid arthritis [18] but a causative association has not been proved [19,20].

During the early stages there is leukocytosis with relative lymphopenia; later an eosinophilia of up to 36% may be accompanied by a lymphocytosis.

Other manifestations. Systemic vasculitis in the form of polyarteritis nodosa, Wegener's granulomatosis and arterial occlusion have been reported in association with parvovirus B19 infection [21,22]. Urticaria and angio-oedema have also been reported but a direct association with chronic urticaria is unproven [23]. Similarly, a case of acute generalized exanthematous pustulosis occurred in association with primary parvovirus B19 infection [24]. The papular-pruritic gloves and socks syndrome (see p. 33.76) is associated most commonly with parvovirus B19 infection and may also involve perioral and perianal skin.

Diagnosis. In the acute aplastic phase, virus can be detected in the serum by electron microscopy or PCR amplification of viral DNA [25]. By the time the rash appears, the virus is rapidly disappearing from the blood and the diagnosis is made by finding specific IgM antibody to human parvovirus. This antibody is present for up to 2–3 months following the acute infection. Because clinically the picture can mimic rubella, it is of utmost importance to obtain laboratory diagnosis, especially of infections during pregnancy.

The exanthem shows a perivascular mononuclear cell infiltrate with a focal interface dermatitis [26].

Treatment. Erythema infectiosum is itself harmless and no treatment is required. Chronic B19 infection causing a red-cell aplasia should be treated with intravenous immunoglobulin infusions. Treatment may result in a cure or if a relapse occurs, a further course may be required some months later.

References

1 Simmonds P, Manning A, Kenneil R *et al.* Parenteral transmission of the novel human parvovirus PARV4. *Emerg Infect Dis* 2007; **13**: 1386–8.

2 Manning A, Willey SJ, Bell JE *et al.* Comparison of tissue distribution, persistence, and molecular epidemiology of parvovirus B19 and novel human parvoviruses PARV4 and human bocavirus. *J Infect Dis* 2007; **195**: 1345–52.

3 Manning A, Russell V, Eastick K *et al.* Epidemiological profile and clinical associations of human bocavirus and other human parvoviruses. *J Infect Dis* 2006; **194**: 1283–90.

4 Allander T. Human bocavirus. *J Clin Virol* 2008; **41**: 29–33.

5 Arnold JC, Singh KK, Spector SA *et al.* Human bocavirus: prevalence and clinical spectrum at a children's hospital. *Clin Infect Dis* 2006; **43**: 283–8.

6 Cohen B. Parvovirus B19: an expanding spectrum of disease. *BMJ* 1995; **311**: 1549–52.

7 Heegaard ED, Brown KE. Human parvovirus B19. *Clin Microbiol Rev* 2002; **15**: 485–505.

8 Anderson MJ, Jones SE, Fisher-Hoch SP *et al.* Human parvovirus, the cause of erythema infectiosum (fifth disease)? *Lancet* 1983; **1**: 1378.
9 Cossart YE, Field AM, Cant B *et al.* Parvovirus-like particles in human sera. *Lancet* 1975; **1**: 72–3.
10 Ekman A, Hokynar K, Kakkola L *et al.* Biological and immunological relations among human parvovirus B19 genotypes 1 to 3. *J Virol* 2007; **81**: 6927–35.
11 Brown KE, Hibbs JR, Gallinella G *et al.* Resistance to parvovirus B19 infection due to lack of virus receptor (erythrocyte P antigen). *N Engl J Med* 1994; **330**: 1192–6.
12 Frickhofen N, Abkowitz JL, Safford M *et al.* Persistent B19 parvovirus infection in patients infected with human immunodeficiency virus type 1 (HIV-1): a treatable cause of anemia in AIDS. *Ann Intern Med* 1990; **113**: 926–33.
13 Nunoue T, Kusuhara K, Hara T. Human fetal infection with parvovirus B19: maternal infection time in gestation, viral persistence and fetal prognosis. *Pediatr Infect Dis J* 2002; **21**: 1133–6.
14 Ager EA, Chin TD, Poland JD. Epidemic erythema infectiosum. *N Engl J Med* 1966; **275**: 1326–31.
15 Bard JW, Perry HO. Erythema infectiosum. *Arch Dermatol* 1966; **93**: 49–53.
16 Condon FJ. Erythema infectiosum; report of an area-wide outbreak. *Am J Public Health Nations Health* 1959; **49**: 528–35.
17 Hayakawa H, Tara M, Niina K *et al.* A clinical study of adult human parvovirus B19 infection. *Intern Med* 2002; **41**: 295–9.
18 Fawaz-Estrup F. Human parvovirus infection: rheumatic manifestations, angioedema, C1 esterase inhibitor deficiency, ANA positivity, and possible onset of systemic lupus erythematosus. *J Rheumatol* 1996; **23**: 1180–5.
19 Hsu TC, Tsay GJ. Human parvovirus B19 infection in patients with systemic lupus erythematosus. *Rheumatology (Oxford)* 2001; **40**: 152–7.
20 Seishima M, Oyama Z, Yamamura M. Two-year follow-up study after human parvovirus B19 infection. *Dermatology* 2003; **206**: 192–6.
21 Viguier M, Guillevin L, Laroche L. Treatment of parvovirus B19-associated polyarteritis nodosa with intravenous immune globulin. *N Engl J Med* 2001; **344**: 1481–2.
22 Finkel TH, Torok TJ, Ferguson PJ *et al.* Chronic parvovirus B19 infection and systemic necrotising vasculitis: opportunistic infection or aetiological agent? *Lancet* 1994; **343**: 1255–8.
23 Vuorinen T, Lammintausta K, Kotilainen P *et al.* Presence of parvovirus B19 DNA in chronic urticaric and healthy human skin. *J Clin Virol* 2002; **25**: 217–21.
24 Ofuji S, Yamamoto O. Acute generalized exanthematous pustulosis associated with a human parvovirus B19 infection. *J Dermatol* 2007; **34**: 121–3.
25 Hokynar K, Norja P, Laitinen H *et al.* Detection and differentiation of human parvovirus variants by commercial quantitative real-time PCR tests. *J Clin Microbiol* 2004; **42**: 2013–9.
26 Magro CM, Dawood MR, Crowson AN. The cutaneous manifestations of human parvovirus B19 infection. *Hum Pathol* 2000; **31**: 488–97.

Retroviruses

Human T-lymphotropic viruses

The human T-lymphotropic viruses belong to the *Deltaretrovirus* genus of the *Retroviridae* [1]. HTLV-1 was first isolated in 1980 [2] and was associated with an aggressive form of adult T-cell leukaemia (ATL) that had been described in Japan [3]. This disease is also referred to as adult T-cell leukaemia–lymphoma (ATLL) because it usually begins as a lymphoma which progresses to a late leukaemia phase. Subsequently HTLV-1 has been associated with a chronic neurological disease—HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) [4]. It is not known what determines the form of disease the infection can take.

HTLV-2 is endemic in intravenous drug abusers throughout the Western hemisphere. The virus has been isolated from patients with a T-cell variant of hairy cell leukaemia [5] but has not yet been conclusively linked to any human disease. HTLV-3 and HTLV-4 have been isolated recently following serological testing of humans in the Cameroons [6].

HTLV-1 infection is endemic in south-west Japan, the Caribbean, sub-Saharan Africa and South America (especially Brazil and adjacent countries) with smaller foci in south-east Asia, South Africa and northern Iran [7]. The seroprevalence is between 0.1 and 15% in these areas with rates of up to 30% in affected families. In non-endemic areas of the world, seroprevalence is below 0.03% with most positive individuals being immigrants from endemic areas or intravenous drug users [8].

HTLV-1 infects $CD4^+$ T lymphocytes. After entering the cell the virus makes a DNA copy of its genome, using virally encoded reverse transcriptase. This integrates randomly into the cell genome. The proviral DNA produces proteins, most notably Tax, which regulate not only viral but also cellular promoters in adjacent genes and at a distance (a *trans*-activation mechanism). However, the role of these HTLV-1 gene products in transformation of the cell is still uncertain.

The major route of transmission of HTLV-1 is from infected mother to child via breast milk, with a 25% chance of the baby becoming infected. Horizontal spread is by sexual transmission (mainly from male to female) and by blood (leukocyte transfer is necessary).

Only about one in 80 of those infected will develop ATLL. The leukaemic cells in ATLL represent a monoclonal expansion of cells, each of which carries one or occasionally more copies of the integrated proviral DNA. These cells (called 'flower cells' because of characteristically lobulated nuclei) (Fig. 33.27) can infiltrate the dermis or subcutaneous tissue to cause nodular cutaneous lesions which may appear many years before ATLL, as long as 21 years in one case report [9]. The incubation period for ATLL has been calculated to be 15–20 years or more with the mean age of onset ranging between 40 and 60 years. Paediatric cases are rare, but not unknown, and are assumed to follow perinatal infection [10]. The interval between infection and disease is considerably shorter for TSP; 6 months to 3 years has been recorded following blood transfusion. The lifetime risk of developing ATLL, if infected with HTLV-1, is 2–5% and of developing TSP is about 0.25%.

Clinical features. Four clinical subtypes of ATLL have been defined; smouldering, chronic, acute and lymphomatous [11]. Typically these subtypes appear in sequence in a patient. The principal features of infection are lymphadenopathy, hepatosplenomegaly, hypercalcaemia and skin lesions. ATLL has a rapid, progressive course with a mean survival time of less than 1 year. Skin manifestations, which occur in two-thirds of cases [12–15] (Fig. 33.28), are:

1 Erythematous macules, papules, plaques and nodules, most commonly on the trunk, due to dermal aggregates of malignant lymphoid cells; papular lesions are often purpuric and may resemble Henoch–Schönlein purpura [16] or erythema multiforme [17]
2 Hyperpigmented rash on the face that may spread to trunk, arms and legs
3 An exfoliative dermatitis on the palms (in Afro-Caribbeans)
4 A chronic infective eczema on the face, scalp and flexures without preceding atopic eczema.

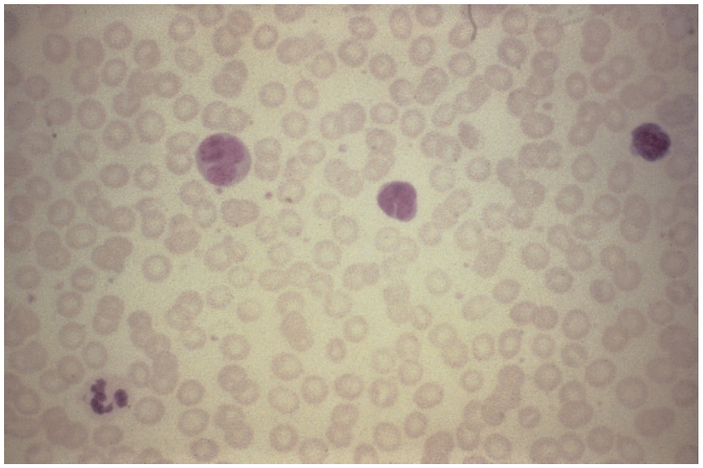


Fig. 33.27 HTLV-1 infection. 'Flower cells' in peripheral blood. (Courtesy of Dr S. Whittaker, St John's Institute, London, UK.)

HTLV-1 infection has also been associated with an inflammatory myopathy, which may show features suggestive of dermatomyositis [18]. However, it responds poorly, if at all, to systemic corticosteroids or other immunosuppressive drugs.

Diagnosis. HTLV-1 infection is confirmed by detecting antibodies to the virus in a serum sample. Cultivation and detection of the virus is only available in specialist laboratories but confirmation of infection is possible using PCR methods [19]. ATLL is diagnosed by the presence in circulating blood of pleomorphic leukaemic cells which express the surface markers of activated mature $CD4^+$ T cells ($CD2^+$, $CD4^+$, $CD7^-$, $CD8^-$ and often $CD25^+$).

Biopsy of abnormal skin shows a heavy dermal infiltrate, often with a mixed population of cells of which lymphocytes predominate. There may be prominent atypical morphology of cells and epidermotropism. The lymphoma is most commonly classified as a pleomorphic lymphoma but cases of angiocentric lymphoma [20] and CD30-positive large-cell lymphoma [21] have been reported.

Hypercalcaemia is a common and characteristic finding and bone erosions are frequently seen by X-ray. The differential diagnosis includes Sézary syndrome and mycosis fungoides, although the latter has itself been postulated to be associated with HTLV-1 [22].

Treatment. Combination therapy with zidovudine and IFN-α has successfully induced complete or partial remission [23] but maintenance therapy may be needed to prolong remission. Chemotherapy has been disappointing but stem cell bone marrow transplantation is more promising [24]. Opportunistic infections are common in ATLL and include recurrent superficial fungal infection of the skin, *Staph. aureus* infection of dermatitis, scabies, *Strongyloides stercoralis* superinfection [25] and tuberculosis. They should be actively diagnosed and managed with appropriate therapy.



(a)



(b)

Fig. 33.28 Adult T-cell leukaemia/lymphoma. (a) Widespread plaques. (b) papular lesions. (Courtesy of Dr S. Whittaker, St John's Institute, London, UK.)

References

1 Verdonck K, Gonzalez E, Van Dooren S *et al.* Human T-lymphotropic virus 1: recent knowledge about an ancient infection. *Lancet Infect Dis* 2007; **7**: 266–81.

2 Poiesz BJ, Ruscetti FW, Gazdar AF *et al.* Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T-cell lymphoma. *Proc Natl Acad Sci USA* 1980; **77**: 7415–9.

3 Uchiyama T, Yodoi J, Sagawa K *et al.* Adult T-cell leukemia: clinical and hematologic features of 16 cases. *Blood* 1977; **50**: 481–92.

4 Gessain A, Barin F, Vernant JC *et al.* Antibodies to human T-lymphotropic virus type-I in patients with tropical spastic paraparesis. *Lancet* 1985; **2**: 407–10.

5 Kalyanaraman VS, Sarngadharan MG, Robert-Guroff M *et al.* A new subtype of human T-cell leukemia virus (HTLV–II) associated with a T-cell variant of hairy cell leukemia. *Science* 1982; **218**: 571–3.

6 Mahieux R, Gessain A. The human HTLV-3 and HTLV-4 retroviruses: New members of the HTLV family. *Pathol Biol (Paris)* 2009; **57**: 161–6.

7 Proietti FA, Carneiro-Proietti AB, Catalan-Soares BC *et al.* Global epidemiology of HTLV-I infection and associated diseases. *Oncogene* 2005; **24**: 6058–68.

8 Fang CT, Williams AE, Sandler SG *et al.* Detection of antibodies to human T–lymphotropic virus type 1 (HTLV-1). *Transfusion* 1988; **28**: 179–83.
9 Bunker CB, Whittaker S, Luzzatto L *et al.* Indolent cutaneous prodrome of fatal HTLV-I infection. *Lancet* 1990; **335**: 426.
10 Pombo-de-Oliveira MS, Dobbin JA, Loureiro P *et al.* Genetic mutation and early onset of T-cell leukemia in pediatric patients infected at birth with HTLV-I. *Leuk Res* 2002; **26**: 155–61.
11 Shimoyama M. Diagnostic criteria and classification of clinical subtypes of adult T-cell leukaemia–lymphoma. A report from the Lymphoma Study Group (1984–87). *Br J Haematol* 1991; **79**: 428–37.
12 Kim JH, Durack DT. Manifestations of human T-lymphotropic virus type I infection. *Am J Med* 1988; **84**: 919–28.
13 Whittaker SJ, Ng YL, Rustin M *et al.* HTLV-1-associated cutaneous disease: a clinicopathological and molecular study of patients from the U.K. *Br J Dermatol* 1993; **128**: 483–92.
14 LaGrenade L, Hanchard B, Fletcher V *et al.* Infective dermatitis of Jamaican children: a marker for HTLV-I infection. *Lancet* 1990; **336**: 1345–7.
15 Pezeshkpoor F, Yazdanpanah MJ, Shirdel A. Specific cutaneous manifestations in adult T-cell leukemia/lymphoma. *Int J Dermatol* 2008; **47**: 359–62.
16 Tabata R, Tabata C, Namiuchi S *et al.* Adult T-cell lymphoma mimicking Henoch–Schonlein purpura. *Mod Rheumatol* 2007; **17**: 57–62.
17 Ohtani T, Deguchi M, Aiba S. Erythema multiforme-like lesions associated with lesional infiltration of tumor cells occurring with adult T-cell lymphoma/leukemia. *Int J Dermatol* 2008; **47**: 390–2.
18 Smadja D, Bellance R, Cabre P *et al.* Clinical characteristics of HTLV-1 associated dermato-polymyositis. Seven cases from Martinique. *Acta Neurol Scand* 1995; **92**: 206–12.
19 Vandamme AM, Van Laethem K, Liu HF *et al.* Use of a generic polymerase chain reaction assay detecting human T-lymphotropic virus (HTLV) types I, II and divergent simian strains in the evaluation of individuals with indeterminate HTLV serology. *J Med Virol* 1997; **52**: 1–7.
20 Shimokawa I, Ushijima N, Moriuchi R *et al.* A case of angiocentric immunoproliferative lesions (angiocentric lymphoma) associated with human T-cell lymphotropic virus type 1. *Hum Pathol* 1993; **24**: 921–3.
21 Tsuji M, Kobashi A, Hashimoto K *et al.* A case of adult T-cell leukemia/lymphoma, histologically presenting CD30–positive large cell lymphoma. *Acta Pathol Jpn* 1992; **42**: 512–7.
22 Zucker-Franklin D. The role of human T cell lymphotropic virus type I tax in the development of cutaneous T cell lymphoma. *Ann N Y Acad Sci* 2001; **941**: 86–96.
23 Hermine O, Allard I, Levy V *et al.* A prospective phase II clinical trial with the use of zidovudine and interferon-alpha in the acute and lymphoma forms of adult T-cell leukemia/lymphoma. *Hematol J* 2002; **3**: 276–82.
24 Ishitsuka K, Tamura K. Treatment of adult T-cell leukemia/lymphoma: past, present, and future. *Eur J Haematol* 2008; **80**: 185–96.
25 Hirata T, Uchima N, Kishimoto K *et al.* Impairment of host immune response against strongyloides stercoralis by human T cell lymphotropic virus type 1 infection. *Am J Trop Med Hyg* 2006; **74**: 246–9.

Viral insect-borne and haemorrhagic fevers

These conditions are conveniently grouped together (Table 33.5).

Viral haemorrhagic fevers (VHFs) are caused by viruses from four different families: *Arenaviridae*, *Bunyaviridae*, *Filoviridae* and *Flaviviridae*. The epidemiology has been reviewed [1]. Thrombocytopenia is present in all and reduced levels of coagulation factors in many [2]. Additional mechanisms which may apply in some cases are platelet dysfunction, disseminated intravascular coagulation, circulating anticoagulants and vascular injury. All can result in circulatory shock with high mortality.

The insect-borne togaviruses cause a variety of infections which are less severe than VHFs. They are seen mainly in tropical areas, but with increasing global travel, cases are now not uncommonly seen outside these areas.

References

1 Le Duc JW. Epidemiology of hemorrhagic fever viruses. *Rev Infect Dis* 1989; **11**: S672–88.
2 Geisbert TW, Jahrling PB. Exotic emerging viral diseases: progress and challenges. *Nat Med* 2004; **10**: S110–21.

Togaviruses

The viruses of this genus are mostly mosquito-borne and include the equine encephalitis viruses and many others of limited geographical distribution causing febrile illness in humans and ungulates (Table 33.5). In the majority there is no exanthem (e.g. Venezuelan equine encephalomyelitis), but Sindbis [1,2], Chikungunya [3] and O'Nyong-Nyong [4] in East, Central and South Africa are all acute febrile illnesses with severe joint pains and a maculopapular rash. In Australia and the Pacific islands, epidemic polyarthritis is associated commonly with Ross River and Barmah Forest viruses [5]. A disease with exanthem and arthralgia, seen first in Sweden in the 1960s (Ockelbo disease) [6] and in Finland in the 1970s (Pogosta disease), was found to be due to Sindbis [7].

These togavirus infections can be differentiated by the virus-specific IgM response in an enzyme-linked immunosorbent assay (ELISA) or by molecular detection of viral RNA in blood by reverse transcription polymerase chain reaction.

Chikungunya virus

Chikungunya virus infection is an emerging disease with recent epidemics in Réunion island and India, and increasing recognition in travellers. The illness presents with severe arthralgia, flu-like symptoms and, in over 50%, a skin eruption. The rash is usually maculopapular, affecting trunk and limbs, and can occasionally be itchy [8]. Ulceration of lesions has been reported [8,9].

O'Nyong-Nyong virus

The virus and the illness are very similar to Chikungunya with polyarthralgia, especially affecting the knees, ankles and feet, fever and cervical lymphadenopathy. The majority also have a maculopapular rash on body and limbs. Reports of this infection suggest that it has risen in incidence in recent years.

Ross River virus

Ross River virus infection is spread to humans by a variety of mosquito species, and is endemic in Australia and Papua New Guinea, with outbreaks reported in the Pacific islands. The most common group affected are 30 to 40-year-olds and illness is rare under the age of 10. The infection is characterized by polyarthritis, rash and general malaise [10]. After an incubation period of 3–21 days (mean 9 days) a mild fever with headache and tender, aching muscles occurs. A polyarthritis of ankles, knees, fingers and wrists is very common and rash occurs in over half. This is usually a non-itching maculopapular eruption on limbs and trunk but can occasionally be vesicular or purpuric; it may begin several days before to 11 days after the arthritis and lasts 2–10 days.

Chronic arthritis and tiredness can persist for up to 6 months with acute exacerbation and relapses. Recovery is universal and followed by lasting immunity.

This infection must be distinguished from acute rubella and in its chronic form from rheumatoid arthritis. In the acute phase,

Table 33.5 Viral insect-borne and haemorrhagic fevers.

Family	Virus	Distribution	Vector	Rash	Incubation (days)
Togaviridae	Sindbis	Africa Europe USSR	Mosquito	+	3–12
	Chikungunya	Africa India SE Asia	Mosquito	+	3–12
	O'Nyong-Nyong	Africa	Mosquito	+	3–12
	Ross River	Australia	Mosquito	+	3–21
	Barmah Forest	Australia	Mosquito	+	3–21
	Eastern, western and Venezuelan equine encephalitis	C., N. and S. America	Mosquito	–	5–15
Flaviviridae	Yellow Fever	Central Africa C. and S. America	Mosquito	–	3–6
	Dengue (*)	India SE Asia West Indies Central Africa	Mosquito	+	3–15
	West Nile	Africa India Israel	Mosquito	+	1–6
	Murray Valley	Australia	Mosquito	–	5–15
	Kunjin	Australia	Mosquito	+	8–10
	Japanese encephalitis	E. Asia	Mosquito	–	5–15
	Tick-borne encephalitis	C. Europe	Tick	–	7–14
	Omsk*	Central USSR	Tick/Rodent	–	3–8
	Kyasanur Forest*	India	Tick	–	3–8
Arenaviridae	Lassa fever*	West Africa	Rodent	+	7–18
	Junin*	Argentina	Rodent	+	7–10
	Machupo*	Bolivia	Rodent	+	7–10
	Guanarito	Venezuela	Rodent	+	7–10
Filoviridae	Marburg*	Africa	?	+	3–10
	Ebola*	Congo, Sudan	? Bat	+	3–10
Bunyaviridae	Bwamba	Africa	Mosquito	+	3–12
	Rift Valley*	Africa	Mosquito Infected animals	+	2–6
	Crimea/Congo*	S. USSR Africa Middle East	Tick	+	2–9
	Hantavirus (HFRS)*	Korea USSR, Europe N. America	Rodent	+	14–21
	Oropouche virus	C. and S. America	Mosquito	–	4–8

* Virus infections associated with haemorrhage.

infection can be detected by molecular identification of the viral RNA [11] or a rising antibody titre to Ross River virus.

Barmah Forest virus

This virus causes an illness similar to Ross River virus [12] and has been reported in Australia with a recent increase in incidence [13]. A rash occurs in 90% of those infected. These togavirus infections can be differentiated by the virus-specific IgM response in an enzyme-linked immunosorbent assay (ELISA).

References

1 Findlay GH, Whiting DA. Arbovirus exanthem from Sindbis and West Nile viruses. *Br J Dermatol* 1968; **80**: 67–74.

2 Autio P, Niemi KM, Kariniemi AL. An eruption associated with alphavirus infection. *Br J Dermatol* 1996; **135**: 320–3.

3 Pialoux G, Gauzere BA, Jaureguiberry S *et al.* Chikungunya, an epidemic arbovirosis. *Lancet Infect Dis* 2007; **7**: 319–27.

4 Kiwanuka N, Sanders EJ, Rwaguma EB *et al.* O'nyong-nyong fever in south-central Uganda, 1996–1997: clinical features and validation of a clinical case definition for surveillance purposes. *Clin Infect Dis* 1999; **29**: 1243–50.

5 Mackenzie JS, Smith DW. Mosquito-borne viruses and epidemic polyarthritis. *Med J Aust* 1996; **164**: 90–3.

6 Niklasson B, Espmark A. Ockelbo disease: arthralgia 3–4 years after infection with a Sindbis virus related agent. *Lancet* 1986; **1**: 1039–40.
7 Kurkela S, Manni T, Myllynen J *et al.* Clinical and laboratory manifestations of Sindbis virus infection: prospective study, Finland, 2002–2003. *J Infect Dis* 2005; **191**: 1820–9.
8 Inamadar AC, Palit A, Sampagavi VV *et al.* Cutaneous manifestations of chikungunya fever: observations made during a recent outbreak in south India. *Int J Dermatol* 2008; **47**: 154–9.
9 El Sayed F, Dhaybi R. Chikungunya associated with cutaneous ulcerations. *Clin Exp Dermatol* 2008; **33**: 463–4.
10 Rulli NE, Melton J, Wilmes A *et al.* The molecular and cellular aspects of arthritis due to alphavirus infections: lesson learned from Ross River virus. *Ann N Y Acad Sci* 2007; **1102**: 96–108.
11 Sellner L. A single-tube nested RT-PCR for the detection of Ross River virus. *Methods Mol Biol* 1998; **92**: 145–52.
12 Phillips DA, Murray JR, Aaskov JG *et al.* Clinical and subclinical Barmah Forest virus infection in Queensland. *Med J Aust* 1990; **152**: 463–6.
13 Jacups SP, Whelan PI, Currie BJ. Ross river virus and barmah forest virus infections: a review of history, ecology, and predictive models, with implications for tropical northern Australia. *Vector Borne Zoonotic Dis* 2008; **8**: 283–98.

Flaviviruses

This family contains the largest group of antigenically related types of both mosquito- and tick-borne viruses [1]. The majority of the diseases concerned, including the tick-borne encephalitides complex, have no cutaneous manifestations. Hepatitis C virus (see p. 33.61) does not cause haemorrhagic fever.

Yellow fever

Yellow fever is a disease which primarily affects the liver and causes abnormal liver function. Jaundice, severe leukopenia and thrombocytopenia develop. The live attenuated vaccine contains the 17D strain grown in chick embryos. It should be given to all visitors to endemic areas and in epidemics is used, together with control measures to eradicate the mosquito vectors, to halt spread.

Dengue [2,3]

Dengue is perhaps the most important mosquito-borne (mainly *Aedes aegypti*) virus disease in humans, affecting 50–100 million people annually worldwide. Since the 1980s, the disease has spread widely in Africa, Central and South America, the Indian subcontinent, Queensland, Australia and Oceania, as well as South-East Asia where annual epidemics are common. The virus causes a range of infections: asymptomatic; a febrile illness; and a haemorrhagic fever which is associated with a 1–10% mortality. The usual form after primary infection in childhood is asymptomatic.

There are four antigenically distinct dengue viruses: serotypes 1–4, and infection is followed by lifelong immunity to the infection serotype. Symptoms, especially if severe, are more common in secondary infections. No specific antiviral therapy is available, but vaccines are under development.

Dengue fever (DF) starts after an incubation period of 3–14 days as a fluctuating fever with nausea, vomiting, headache, joint and bone pain, severe backache and often a rash. The rash, which can be maculopapular or scarlatiniform and is only rarely itchy, appears on the third to fourth day of the fever. It may start on the legs and spread caudally or on the chest and trunk and spread to the face, arms and legs [4]. The rash fades as the fever subsides (day 7) but can be followed by petechiae on the arms and legs. In dark-skinned people the rash is frequently not visible.

Confirmation of dengue infection is obtained by culture or detection of the virus in blood by PCR in the acute phase or by serological studies on acute and convalescent sera.

Dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS) occur, most commonly in children, in areas where dengue is hyperepidemic and there is cocirculation of multiple serotypes of the virus. People who have been infected with one serotype and are subsequently infected with a different serotype are at greater risk of developing DHF. The acute high fever is accompanied by a haemorrhagic diathesis, which is manifest as petechiae and can be demonstrated by a positive tourniquet test.

After 2–7 days the body temperature drops and either recovery or shock ensues. Vascular permeability increases which leads to plasma loss, some of which collects as effusions in the pleural and abdominal cavities. DSS is usually fatal without meticulous fluid replacement and plasma expansion [2].

Certain clinical diagnosis from other arbovirus infections may not be possible but the combination of thromobcytopenia and haemoconcentration are highly suspicious. Measles and other exanthemata may obviously require exclusion from DF.

Treatment. Only symptomatic and supportive measures are available.

References

1 Gould EA, Solomon T. Pathogenic flaviviruses. *Lancet* 2008; **371**: 500–9.
2 World Health Organisation Website. *Regional guidelines on dengue/DHF prevention and control*, 1999, Available from: www.searo.who.int/en/Section10/Section332/Section554_2564.htm.
3 Halstead SB. Dengue. *Lancet* 2007; **370**: 1644–52.
4 Pincus LB, Grossman ME, Fox LP. The exanthem of dengue fever: Clinical features of two US tourists travelling abroad. *J Am Acad Dermatol* 2008; **58**: 308–16.

Other viral haemorrhagic fevers

These belong to the families *Arenaviridae*, *Bunyaviridae* and *Filoviridae*.

These infections are accompanied by disordered haemostasis. This may be marked, with profuse bleeding, but non-haemorrhagic disease also occurs. Viral haemorrhagic fevers (VHFs) are endemic in many countries, particularly in the tropics. They may be caused by a variety of viruses (Table 33.5). Most are zoonotic infections, the human being an accidental host, but person-to-person transmission also occurs. Nosocomial infections have been reported as have outbreaks of Ebola in rural African hospitals.

Diagnosis. Diagnosis cannot be made by clinical features alone. As these infections may closely resemble typhoid fever and malaria, it is important to exclude these treatable conditions. Laboratory diagnosis by virus isolation or demonstration of virus-specific antibodies must only be carried out at the highest level of biological containment (class 4). Suspected cases of VHF must therefore be discussed with the microbiologist before any material is taken for laboratory testing.

Arenaviridae

There are two groups of arenaviruses that cause severe VHF in humans—Lassa and the Tacaribe complex viruses [1]. Another arenavirus, lymphocytic choriomeningitis virus, causes a meningoencephalitis, not VHF. These arenaviruses are endemic in rodents.

Lassa fever

The natural host is the multimammate rat, *Mastomys natalensis*, a common rodent in West African villages [2]. Transmission to humans produces short-lived outbreaks with secondary infections by person-to-person spread in households and hospital staff. Transmission by sexual intercourse with an infected person has also been recorded. This disease was first recognized in humans in 1969 in West Africa where there are now estimated to be 100 000–300 000 infections per year. Serological surveys in endemic areas have shown that up to 50% of the population of some villages have had past infection.

Clinical features [3–5]. The incubation period of Lassa fever is 7–18 days. Fever, malaise, headache and non-productive cough herald the onset of disease. A maculopapular or petechial rash over the face, arms and thorax may be seen in white skinned individuals but is not reported in black Africans. There is usually joint and lumbar pain with a developing painful sore throat. Conjunctivitis is common. High fever and severe prostration follow. Diarrhoea, renal damage with proteinuria, central nervous system involvement with confusion, coma, convulsions and respiratory complications may all occur in the first week of illness.

Bleeding is rare but indicates a poor prognosis. The overall mortality rate is 2–4% but rises in hospitalized patients to 10–20%. Lassa fever in the third trimester of pregnancy is associated with a greater than 30% mortality rate. In survivors about a quarter develop deafness in one or both ears, which may be permanent or slowly resolve.

Diagnosis. Early diagnosis of the infection by reverse transcriptase PCR amplification of the viral RNA in serum samples or detection of antibodies by ELISA can identify those infected and help to prevent spread.

Prevention. Post-exposure prophylaxis with oral ribavirin is recommended to reduce risk of severe infection.

Treatment [5–7]. Intravenous ribavirin, a guanosine analogue, is an effective antiviral drug in Lassa fever, especially if given within 6 days of the onset of illness.

Argentinian, Bolivian and Venezuelan haemorrhagic fevers [8,9]

Argentinian, Bolivian and Venezuelan haemorrhagic fevers are caused respectively by Junin virus (natural host *Calomys musculinus*), Machupo virus (natural host *Calomys callosus*) and Guanarito virus (natural host *Sigmodon alstoni*). These viruses are grouped together as the Tacaribe complex viruses and the diseases they cause are clinically alike. The 7 to 10-day incubation is followed by a high fever, malaise and myalgia, erythema or a petechial eruption of the face, neck and upper chest, a pharyngeal enanthem and petechiae. Epistaxis and haematemesis may also occur in the first week of the illness. Shock ensues in over half the patients. These infections are associated with about a 15% mortality rate. The incidence of Argentinian haemorrhagic fever has reduced following the use of live attenuated vaccine and current treatment is with transfusion of immune plasma and possibly ribavirin [10].

References

1 Cummins D. Arenaviral haemorrhagic fevers. *Blood Rev* 1991; **5**: 129–37.
2 McCormick JB, Webb PA, Krebs JW *et al.* A prospective study of the epidemiology and ecology of Lassa fever. *J Infect Dis* 1987; **155**: 437–44.
3 McCormick JB, King IJ, Webb PA *et al.* A case–control study of the clinical diagnosis and course of Lassa fever. *J Infect Dis* 1987; **155**: 445–55.
4 Cummins D. Lassa fever. *Br J Hosp Med* 1990; **43**: 186–8, 90, 92.
5 Khan SH, Goba A, Chu M *et al.* New opportunities for field research on the pathogenesis and treatment of Lassa fever. *Antiviral Res* 2008; **78**: 103–15.
6 Bannister B, Hall A. Management of Lassa fever. *Lancet* 1986; **327**: 35–6.
7 McCormick JB, King IJ, Webb PA *et al.* Lassa fever. Effective therapy with ribavirin. *N Engl J Med* 1986; **314**: 20–6.
8 Centers for Disease Control and Prevention. Bolivian hemorrhagic fever—El Beni Department, Bolivia, 1994. *MMWR Morb Mortal Wkly Rep* 1994; **43**: 943–6.
9 Salas R, de Manzione N, Tesh RB *et al.* Venezuelan haemorrhagic fever. *Lancet* 1991; **338**: 1033–6.
10 Enria DA, Briggiler AM, Sanchez Z. Treatment of Argentine hemorrhagic fever. *Antiviral Res* 2008; **78**: 132–9.

Filoviridae

Marburg and Ebola disease

Aetiology. The disease was first observed in Marburg [1] and Frankfurt [2] in Germany and in Yugoslavia in 1967 when 30 infections, seven of which were fatal, followed the importation of a consignment of African green monkeys (*Ceropithecus aethiops*) from Uganda [3]. Further outbreaks of Marburg disease have occurred in Africa at intervals since [4,5].

In 1976, a similar outbreak of several hundred cases occurred in northern Zaire and the Sudan, caused by the closely related but antigenically distinct Ebola virus [6]. Outbreaks have occurred sporadically in Africa with one in 1995 in the Democratic Republic of Congo (formerly Zaire) affecting at least 296 individuals [7]. One-third of the cases were in health care workers, and the overall mortality rate was 79%.

The natural reservoirs of these viruses remain uncertain, but fruit bats have been identified as Ebola virus carriers [8]. Person-to-person spread occurs, probably through direct contact with blood-stained body fluids, re-use of unsterile medical equipment and needlestick injuries. Aerosol spread has not been described. Body fluids may remain infectious for as long as 80 days.

Clinical features [9–11]. These are similar for both Marburg and Ebola diseases. The incubation period is usually 1–2 weeks followed by the sudden onset of headache, and high fever and myalgia, especially lumbosacral. Diarrhoea and dehydration, hepatitis, haemorrhages and renal damage occur with many other changes due to the pantropic nature of the infection. Bleeding,

commonly gastrointestinal and mucosal, begins about the fifth day of illness.

The acute febrile stage lasts about 2 weeks and death may occur as early as the eighth or as late as the 17th day. A measles-like rash develops, more obvious on white skins, between the third and fifth day. It is mainly on the buttocks, trunk and outer aspects of upper arms. Initially erythematous macules occur around the hair follicles; these progress to maculopapular lesions next day and become confluent. An enanthem may be present as a dark-red palatal discoloration and vesicles may occur on the soft palate at the time of or just before the exanthem. Severe cases have a diffuse livid erythema over the face, trunk and limbs. After about the 16th day, desquamation occurs in survivors. Death is usually preceded by severe blood loss and shock. The mortality rate is 30–50%. Virus excretion continues for days to weeks in survivors.

References

1 Martini GA, Knauff HG, Schmidt HA *et al.* Über eine bisher unbekannte, von Affen eingeschleppte Infektionskrankheit: Marburg-Virus-Krankheit. *Dtsch Med Wochenschr* 1968; **93**: 559–71.
2 Monath TP. Lassa fever and Marburg virus disease. *WHO Chron* 1974; **28**: 212–9.
3 Stille W, Bohle E, Helm E *et al.* Über eine durch *Cercopithecus aethiops* übertragene Infektionskrankheit. ('Grüne-Meerkatzen-Krankheit', 'Green Monkey Disease'). *Dtsch Med Wochenschr* 1968; **93**: 572–82.
4 Gear JS, Cassel GA, Gear AJ *et al.* Outbreak of Marburg virus disease in Johannesburg. *BMJ* 1975; **4**: 489–93.
5 Smith DH, Johnson BK, Isaacson M *et al.* Marburg-virus disease in Kenya. *Lancet* 1982; **1**: 816–20.
6 Johnson KM, Lange JV, Webb PA *et al.* Isolation and partial characterisation of a new virus causing acute haemorrhagic fever in Zaire. *Lancet* 1977; **1**: 569–71.
7 Centers for Disease Control and Prevention. Update: outbreak of Ebola viral hemorrhagic fever—Zaire, 1995. *MMWR Morb Mortal Wkly Rep* 1995; **44**: 399.
8 Leroy EM, Kumulungui B, Pourrut X *et al.* Fruit bats as reservoirs of Ebola virus. *Nature* 2005; **438**: 575–6.
9 Andrijich VB. Marburg virus disease. The diagnosis and management of suspected cases. *S Afr Med J* 1981; **60**: 751–3.
10 Formenty P, Hatz C, Le Guenno B *et al.* Human infection due to Ebola virus, subtype Cote d'Ivoire: clinical and biologic presentation. *J Infect Dis* 1999; **179** (Suppl. 1): S48–53.
11 Zampieri CA, Sullivan NJ, Nabel GJ. Immunopathology of highly virulent pathogens: insights from Ebola virus. *Nat Immunol* 2007; **8**: 1159–64.

Bunyaviridae

A number of arthropod-borne members of the *Bunyaviridae* family (Table 33.5), such as Crimean Congo haemorrhagic fever [1], Rift Valley fever [2] and the febrile illness associated with Oropouche viruses [3], cause a serious influenza-like illness with hepatitis and haemorrhagic signs which often progress to a fatal shock syndrome. In their more severe forms, these infections may be associated with petechial rashes, bruising, mucosal bleeding and uncontrollable haemorrhage.

The hantaviruses have a rodent reservoir and are transmitted directly from animal to human [4]. Most infections are subclinical, but two types of illness are recognized:

1 Haemorrhagic fever with renal syndrome (HFRS) presents abruptly after a 2 to 4-week incubation period as a flu-like illness followed by a hypotensive phase on day 5, which can be followed by acute renal failure. Petechial bleeding and substantial haemorrhage is recorded in <10% of the cases. Mortality varies with the infecting strain from <1 to 10% and occurs typically in the oliguric phase.
2 Hantavirus pulmonary syndrome develops after inhalation of the virus and has a sudden onset with fever, cough, myalgia and headache. Pulmonary oedema and respiratory failure (adult respiratory distress syndrome) rapidly ensue and are associated with a high mortality rate.

References

1 Ergonul O. Crimean–Congo haemorrhagic fever. *Lancet Infect Dis* 2006; **6**: 203–14.
2 Al-Hazmi M, Ayoola EA, Abdurahman M *et al.* Epidemic Rift Valley fever in Saudi Arabia: a clinical study of severe illness in humans. *Clin Infect Dis* 2003; **36**: 245–52.
3 Pinheiro FP, Travassos da Rosa AP, Travassos da Rosa JF *et al.* Oropouche virus. I. A review of clinical, epidemiological, and ecological findings. *Am J Trop Med Hyg* 1981; **30**: 149–60.
4 Vapalahti O, Mustonen J, Lundkvist A *et al.* Hantavirus infections in Europe. *Lancet Infect Dis* 2003; **3**: 653–61.

Rubella [1]

Aetiology. Rubella virus is the only member of the rubivirus genus of the *Togaviridae*. Unlike other togaviruses it does not require an insect vector to spread. The disease occurs throughout the world and is endemic in large cities. Epidemics occur at irregular intervals, usually during the spring, and affect mainly older children and young adults. Transmission is by droplets from the nasopharynx and infectivity is greatest at the end of the incubation period and falls rapidly during the 4 days after the appearance of the rash. No distinctive pathological changes have been described.

Clinical features. The rash appears after an incubation period of about 14 days (range 12–21 days). Children rarely experience prodromal symptoms, but adolescents and adults have a brief prodromal illness lasting 1–5 days, consisting of fever up to 39°C, headache and malaise, sore throat without coryza and suffusion of the conjunctivae with a gritty sensation. The symptoms subside as the rash develops.

An enanthem of dull-red macules or petechiae confined to the soft palate (Forschheimer's sign) is present in up to 20% of patients during the prodromal period or on the first day of the rash. Enlargement of lymph glands begins 5–7 days before the rash appears whether or not there are prodromal symptoms, and reaches a maximum on the first or second day of the rash. The enlargement is generalized but characteristically involves the suboccipital, postauricular and cervical glands. However, these glands are not invariably affected and their involvement is not pathognomonic of rubella. The tenderness of the glands subsides after a day or two but palpable enlargement may continue for several weeks.

The rash appears first on the face and spreads rapidly downwards to the trunk and limbs. It consists of pink macules, at first discrete, but soon becoming confluent on the face as a diffuse erythema. During the second day the face begins to clear and the macules on the trunk show some coalescence, those on the limbs

remaining discrete. By the third day the trunk has cleared and by the fourth the eruption on the limbs has also faded. The rash may be absent in some 40% of cases.

The blood count may be normal, or there may be a leukopenia with an inconstant increase in plasma cells.

Complications. These are few in childhood. In older children and adults arthritis is not uncommon and affects up to 70% of females and 5% of males. The clinical picture is variable and the arthritis usually resolves within a month.

Rarely, purpura—thrombocytopenic or non-thrombocytopenic—occurs as a complication of rubella. Very rarely, encephalitis is reported.

Rubella in pregnancy. The prenatal damage produced by rubella in early pregnancy was first noted by Gregg in Australia in 1941. The overall risk of fetal damage now appears to be about 85% for primary maternal infection during the first 11 weeks [1]. Infection at this stage usually results in multiple defects. Between weeks 12 and 16 the risk of a rubella defect is about 35% and is principally that of deafness. Thereafter, although fetal infection occurs it does not result in damage. Although of considerably less risk, maternal reinfection, both symptomatic and asymptomatic, can be followed by an intrauterine infection and malformation of the fetus [2].

Heart and eye damage is most frequent in embryos infected under 6 weeks; deafness and mental deficiency occur in embryos of all ages up to about 16 weeks. Mental retardation and microcephaly may not be apparent until a year or more after prenatal infection [3]. During the neonatal period congenital rubella may give rise to a number of manifestations which are self-limiting in those infants which survive [4,5]. The most frequent is thrombocytopenic purpura, which may be manifest as a transient purpuric rash. Other features are jaundice and bone lesions which may simulate congenital syphilis.

Prophylaxis. Active immunization by inoculation with live attenuated rubella virus is employed in many countries. It was introduced in the UK in 1970 and is now routinely offered to infants aged 1–2 years old, together with measles and mumps vaccine (MMR vaccine) [6]. A preschool booster of MMR is also recommended. If they are found to be susceptible, rubella vaccine is also given to selected groups of women who require protection such as medical and nursing staff and school teachers. A quadruple vaccine including varicella has recently become available.

Pregnancy is a contraindication to vaccine and should be avoided for 4 weeks after its administration. There have, however, been no reports of damage to the fetus following inadvertent vaccination of pregnant women [7]. Arthralgia is common in adult women 2–4 weeks after vaccination and in children a rubelliform rash may occur. Vaccinated females do not seem to be infectious.

Diagnosis. In view of the fetal hazard it is unwise to rely on the clinical features for the diagnosis of rubelliform rashes. The typical features of coalescing pink macules on the face and trunk together with lymphadenopathy are suggestive, but can also be produced by enterovirus and human parvovirus infections.

Laboratory investigations must be carried out to confirm a diagnosis in pregnancy or immunosuppression. Serology remains the appropriate technique and the first clotted blood should be taken as soon as possible after the rash is noted. A second blood sample is required 7–10 days later and the haemagglutination-inhibition test [8] provides a clear answer in most instances. When the patient does not present sufficiently early, the presence of specific IgM antibody is also diagnostic of a recent infection. In pregnant contacts the presence of antibody within 14 days of contact is indicative of immunity from previous infection. In neonates the presence of IgM and continued antibody production are indicative of congenital infection. Molecular diagnosis using RT-PCR on swab samples is possible but not routine.

Treatment. There is no specific treatment.

References

1 Best JM. Rubella. *Semin Fetal Neonatal Med* 2007; **12**: 182–92.

2 Best JM, Banatvala JE, Morgan-Capner P *et al.* Fetal infection after maternal reinfection with rubella: criteria for defining reinfection. *BMJ* 1989; **299**: 773–5.

3 Hardy JB, McCracken GH Jr, Gilkeson MR *et al.* Adverse fetal outcome following maternal rubella after the first trimester of pregnancy. *JAMA* 1969; **207**: 2414–20.

4 Castrow FF 2nd, De Beukelaer M. Congenital rubella syndrome. Unusual cutaneous manifestations. *Arch Dermatol* 1968; **98**: 260–2.

5 Cooper LZ, Ziring PR, Ockerse AB *et al.* Rubella. Clinical manifestations and management. *Am J Dis Child* 1969; **118**: 18–29.

6 Asaria P, MacMahon E. Measles in the United Kingdom: can we eradicate it by 2010? *BMJ* 2006; **333**: 890–5.

7 Best JM, Banatvala JE. Rubella. In: Zuckerman AJ, Banatvala JE, Pattison JR, eds. *Principles and Practice of Clinical Virology*. Chichester: John Wiley and Sons; 1987: pp. 349–50.

8 Stewart GL, Parkman PD, Hopps HE *et al.* Rubella-virus hemagglutination-inhibition test. *N Engl J Med* 1967; **276**: 554–7.

Picornaviruses

This group includes: (i) the enteroviruses—poliomyelitis, coxsackieviruses and echoviruses; (ii) the aphthoviruses, which include foot and mouth virus; and (iii) the hepatovirus, hepatitis A. Other genera in the family do not cause skin disease.

The enteroviruses are widely distributed and comprise well over 70 antigenic types. They replicate in the alimentary tract so that spread is by droplets from the nasopharynx and by faecal contamination. Epidemics are common, especially in the warmer months of the year and affect mainly children. Infection is transient without long-term persistence (but see echoviruses). The illnesses are generally mild or subclinical, but can vary through exanthemic fevers to myocarditis and paralytic poliomyelitis. Poliomyelitis has no exanthem.

Coxsackieviruses

Coxsackieviruses are divided into two groups, A and B. There are 24 group-A serotypes and six group-B serotypes. Both are commonly found in the faeces of children in the absence of disease. Both may produce a febrile exanthematic illness, respiratory infections, aseptic meningitis and encephalitis.

Diagnosis. Infection can be confirmed by isolation of the virus from the stool, vesicle fluid or nasopharynx, in tissue culture or better in newborn mice, since only a few coxsackie A strains grow in tissue culture. Isolation from faeces alone may be misleading in the diagnosis of the disease, owing to the frequency of asymptomatic infection. Serology is of limited value. The enteroviral genome can be detected and typed in appropriate specimens by reverse transcriptase PCR [1].

Coxsackie A strains cause herpangina and hand, foot and mouth disease. Coxsackie B viruses are especially associated with epidemic pleurodynia (Bornholm disease), epidemic myalgia, myocarditis and pericarditis. A causal association between coxsackie B and juvenile dermatomyositis has been suggested [2]. As with other enteroviruses, the clinical syndrome produced by any one strain is very variable.

Herpangina

Aetiology. Herpangina is a specific infection caused by group A coxsackieviruses of types 2, 3, 4, 5, 6, 8 and 10 and group B type 3. It occurs throughout the world, affecting mainly children aged 1–7 years, but it is not uncommon in adults. Epidemics and sporadic cases are most frequent in the summer and autumn. Herpangina is often noted in cases with predominant features of hand, foot and mouth disease.

Clinical features. Fever of sudden onset, ranging from 38.5 to 40°C, is commonly the first manifestation of the disease and continues for 4 or 5 days. It is accompanied, or soon followed, by sore throat and dysphagia and occasionally by vomiting and abdominal pain. Up to 15 or 20 tiny vesicles, 1–2 mm in diameter, with a vivid red areola, develop on the pharynx, tonsils, the pillars of the fauces, the uvula and soft palate. They erode to leave ulcers, which enlarge for 2 or 3 days and heal in 4 or 5 days. Complete recovery in 5–7 days is invariable.

Diagnosis. See above. The clinical differential diagnosis is discussed in Chapter 69.

Treatment. Symptomatic measures alone are usually adequate. Allopurinol mouthwashes have been reported to be of help [3].

Hand, foot and mouth disease

Aetiology and pathology. The characteristic but somewhat variable syndrome described as hand, foot and mouth disease by Alsop [4] was first noted in Toronto in 1957 [5]. It has occurred in epidemic form in many parts of the world, and has usually been associated with coxsackie A16, but outbreaks have been caused by A5, A10 and not uncommonly by human enterovirus 71 [6]. Most cases are in young children during the autumn months, but outbreaks have occurred in communities of adults [7].

Histology is not usually performed, but shows spongiosis, intraepidermal splits progressing to vesicle formation, mononuclear cells entering the epidermis, and necrosis of individual keratinocytes. Viral particles are detectable with electron microscopy [8].



Fig. 33.29 Hand, foot and mouth disease. (Courtesy of Addenbrooke's Hospital, Cambridge, UK.)

Clinical features [4,5,7,9]. The disease is usually mild, has an incubation period of 5–7 days and lasts about 7 days. The presenting feature in adults is usually a painful stomatitis, but in children this may be mild. The oral vesicles which rapidly ulcerate resemble those of herpangina, but are rather larger and fewer in number and are irregularly distributed over the palate, buccal mucous membrane, gums and tongue. Fever is usually slight and of short duration. Skin lesions are inconstant, but when present may be characteristic, and in children may dominate the clinical picture. They are small vesicles up to 5 mm in diameter, thin-walled, pearly grey, with a narrow red areola, oval or linear rather than rounded (Fig. 33.29). They are most common on the hands, usually occurring on the sides or backs of fingers and toes, especially around the nails, and around the margins of the heels, but may be seen in the finger flexures and on the palms and soles. They are often few in number, although there may be 50 or more, and they fade over 2 or 3 days. In some cases, especially in infants, there is a more extensive exanthem, papular or vesicular, favouring the buttocks, but sometimes generalized. Relapses are rare and a chronic intermittent course is exceptional. With atopy, generalized vesicles may resembled Kaposi's varicelliform eruption [10].

Other features. Complications of hand, foot and mouth disease include hyperglycaemia, encephalitis, meningitis, left ventricular failure, myocarditis, paralysis and Guillain–Barré syndrome. Complication rates and mortality appear to be higher in outbreaks caused by enterovirus 71.

Other exanthematic coxsackie syndromes

Rashes have been reported in a proportion of cases in outbreaks of other coxsackie syndromes.

Coxsackie A4 has caused a widespread vesicular eruption lasting for up to 2 weeks [9], coxsackie A9 has been associated with a short-lived, central maculopapular eruption [11] and coxsackie A14 with a papular eruption [12].

A vesicular stomatitis involving the anterior portions of the oral cavity and the lips, associated with erythema multiforme, was caused by coxsackie B5 [13], which can also give a morbilliform exanthem [14] and coxsackie B3 may cause a prolonged papular eruption [15].

The exanthem in these and other coxsackie infections presents few features that are sufficiently constant to suggest the diagnosis, but the association with oral lesions should arouse suspicion.

A Gianotti–Crosti-like syndrome (see p. 33.77) has been associated with coxsackie A16 infection [16]. Congenital coxsackie B3 infection has been shown in a child with florid papulovesicles with nodules and ulceration, plus associated pneumonia, carditis and hepatitis [17].

References

1 Tan EL, Chow VT, Quak SH *et al.* Development of multiplex real-time hybridization probe reverse transcriptase polymerase chain reaction for specific detection and differentiation of enterovirus 71 and coxsackievirus A16. *Diagn Microbiol Infect Dis* 2008; **61**: 294–301.

2 Bowles NE, Dubowitz V, Sewry CA *et al.* Dermatomyositis, polymyositis, and coxsackie-B-virus infection. *Lancet* 1987; **1**: 1004–7.

3 Waldfahrer F, Iro H. Successful treatment of herpangina with allopurinol mouthwashes. *Laryngoscope* 1995; **105**: 1405.

4 Alsop J, Flewett TH, Foster JR. 'Hand-foot-and-mouth disease' in Birmingham in 1959. *BMJ* 1960; **2**: 1708–11.

5 Robinson CR, Doane FW, Rhodes AJ. Report of an outbreak of febrile illness with pharyngeal lesions and exanthem: Toronto, summer 1957; isolation of group A coxsackie virus. *Can Med Assoc J* 1958; **79**: 615–21.

6 Chen KT, Chang HL, Wang ST *et al.* Epidemiologic features of hand-foot-mouth disease and herpangina caused by enterovirus 71 in Taiwan, 1998–2005. *Pediatrics* 2007; **120**: e244–52.

7 Cawson RA, McSwiggan DA. An outbreak of hand-foot-and-mouth disease in a dental hospital. *Oral Surg Oral Med Oral Pathol* 1969; **27**: 451–9.

8 Haneke E. Electron microscopic demonstration of virus particles in hand, foot and mouth disease. *Dermatologica* 1985; **171**: 321–6.

9 Forman ML, Cherry JD. Enanthems associated with uncommon viral syndromes. *Pediatrics* 1968; **41**: 873–82.

10 Nahmias AJ, Froeschle JE, Feorino PM *et al.* Generalized eruption in a child with eczema due to coxsackievirus A16. *Arch Dermatol* 1968; **97**: 147–8.

11 Joncas JH, Podoski MO, Pavilanis V. Rash associated with coxsackie A9 infection. *Can Med Assoc J* 1966; **95**: 372–3.

12 White MI, Brown T. A papular eruption and acute abdominal pain associated with coxsackie A-14 virus. *Clin Exp Dermatol* 1991; **16**: 127–8.

13 Yaffee HS. Erythema multiforme caused by coxsackie B5. A possible association with epidemic pustular stomatitis of children. *Arch Dermatol* 1960; **82**: 737–9.

14 MacLean DM. Coxsackie virues and echoviruses. *Am J Med Sci* 1966; **251**: 141–58.

15 Moreira RC, Castrignano SB, Carmona R de C *et al.* An exanthematic disease epidemic associated with coxsackievirus B3 infection in a day care center. *Rev Inst Med Trop Sao Paulo* 1995; **37**: 235–8.

16 Spear KL, Winkelmann RK. Gianotti–Crosti syndrome. A review of ten cases not associated with hepatitis B. *Arch Dermatol* 1984; **120**: 891–6.

17 Sauerbrei A, Gluck B, Jung K *et al.* Congenital skin lesions caused by intrauterine infection with coxsackievirus B3. *Infection* 2000; **28**: 326–8.

Echoviruses

The echoviruses (*e*nteric-*c*ytopathic-*h*uman-*o*rphan) were so called because they occur in the human intestinal tract, are cytopathic in tissue culture and were originally believed not to cause disease in humans. It is now known that many of the 34 distinct serological types cause a wide variety of syndromes, including encephalitis, aseptic meningitis, exanthematic fever and diarrhoea and vomiting. Typically annual summer/autumn epidemics occur in which one or more serotypes predominate.

Rashes have been noted in association with at least half of the echovirus types, and are more likely to occur in children than adults. Macular, maculopapular, vesicular and petechial eruptions, and tonsillar and buccal enanthems may occur. The erythematous eruptions commonly affect the face and trunk. Close correlation between the morphology of the rash and the virus type is not seen, but the following associations have been reported:

1 Echovirus 9: rubelliform or morbilliform eruptions [1]
2 Echovirus 16: the 'Boston eruption', large pink macules on face and trunk, occasionally widespread including palms and soles, following a brief febrile illness in children or adults [2]
3 Echovirus 2: rubelliform rash [3]
4 Echoviruses 11 and 19: petechial rash [4]
5 Echoviruses 6, 11, 18 and 25: maculopapular rashes [5,6]
6 Echoviruses 23 and 32: telangiectatic macular lesions [7]
7 Echovirus 19: punctate macular rash in infants [8]
8 Echovirus 11: vesicular eruptions [9,10]

Diagnosis. Echovirus and rubella infections are often present simultaneously in a community, and the eruptions they produce may be indistinguishable. It is therefore essential for any woman developing a rash in the early stages of pregnancy to be investigated both for enterovirus and rubella infection by isolation of virus in tissue culture from throat swab and secretions, faeces or cerebrospinal fluid for the former and by serological tests for the latter.

Chronic echovirus infection

In hypogammaglobulinaemia, a condition of chronic enteroviral infection has been reported [11]. This causes progressive encephalitis which is fatal within about 4 years. A dermatomyositis-like syndrome may occur in the early stages in some of these patients. It is associated with mild, non-pitting oedema of the lower legs and a transient erythematous rash.

References

1 Lepow ML, Carver DH, Robbins FC. Clinical and epidemiologic observation on enterovirus infection in a circumscribed community during an epidemic of ECHO 9 infection. *Pediatrics* 1960; **26**: 12–26.

2 Hall CB, Cherry JD, Hatch MH *et al.* The return of Boston exanthem. Echovirus 16 infections in 1974. *Am J Dis Child* 1977; **131**: 323–6.

3 Rendtorff RC, Walker LC, Hale BD *et al.* An epidemic of echo virus 2 infection in an orphanage nursery. *Am J Hyg* 1964; **79**: 64–73.

4 Berry PJ, Nagington J. Fatal infection with echovirus 11. *Arch Dis Child* 1982; **57**: 22–9.

5 Guidotti MB. An outbreak of skin rash by echovirus 25 in an infant home. *J Infect* 1983; **6**: 67–70.

6 Miyamura K, Yamashita K, Yamadera S *et al.* An epidemic of echovirus 18 in 1988 in Japan—high association with clinical manifestation of exanthem. A report of the National Epidemiological Surveillance of Infectious Agents in Japan. *Jpn J Med Sci Biol* 1990; **43**: 51–8.

7 Cherry JD, Bobinski JE, Horvath FL *et al.* Acute hemangioma-like lesions associated with ECHO viral infections. *Pediatrics* 1969; **44**: 498–502.

8 Bacon CJ, Sims DG. Echovirus 19 infection in infants under six months. *Arch Dis Child* 1976; **51**: 631–3.

9 Cherry JD, Lerner AM, Klein JO *et al.* Echo 11 virus infections associated with exanthems. *Pediatrics* 1963; **32**: 509–16.

10 Deseda-Tous J, Byatt PH, Cherry JD. Vesicular lesions in adults due to echovirus 11 infections. *Arch Dermatol* 1977; **113**: 1705–6.

11 McKinney RE Jr, Katz SL, Wilfert CM. Chronic enteroviral meningoencephalitis in agammaglobulinemic patients. *Rev Infect Dis* 1987; **9**: 334–56.

Foot and mouth disease

Aetiology and pathology. This common and serious epidemic virus disease of farm animals in Europe, Asia and Africa very rarely infects humans [1,2]. Some cases reported under this diagnosis, but not confirmed by complement fixation or animal inoculation, may have been vesicular stomatitis or 'hand, foot and mouth' disease. True foot and mouth disease has occurred in both adults and children in direct contact with infected stock.

Clinical features. The incubation period ranges from 2 to 18 days. Malaise, headache and fever, with burning of the oral mucous membranes, are followed after 2 or 3 days by vesicles of the buccal mucous membrane, tongue and lips, and occasionally on the palms, soles and interdigital skin. The vesicles are followed by ragged ulcers and may be accompanied by pain and oedema. Sometimes only the mouth or the hands are involved. The disease tends to be more severe in infants and children than in adults, but it is usually mild, the temperature falling after a few days and the lesions healing within a week.

Diagnosis. The other mucocutaneous syndromes must be excluded (see Chapter 69). The diagnosis is confirmed by isolation of the virus from the vesicles, or by the detection of antigen from the vesicles or antibody in the serum by ELISA tests. The viral nucleic acid may be detected by reverse transcriptase PCR in problematic cases. Histology of a lesion shows loculated vesicles are in the deeper layers of the epithelium of mucous membranes and intranuclear inclusions in neighbouring cells.

Treatment. Only symptomatic measures are available.

References

1 Armstrong R, Davie J, Hedger RS. Foot-and-mouth disease in man. *BMJ* 1967; **4**: 529–30.

2 Eissner G, Bohm HO, Julich E. A human case of foot-and-mouth disease. *Ger Med Mon* 1967; **12**: 271–3.

Hepatitis A

The hepatitis A virus constitutes a unique genus in the *Picornaviridae* family. The virus is very stable in the environment and is spread by the faeco-oral route, by ingestion of contaminated food and water or through close person-to-person contact. In developing countries where hepatitis A is highly endemic, almost all the population has been infected and is immune by age 10 years. Developed countries with good water and sewage systems have very low rates of hepatitis A infection; consequently travellers from these countries to areas of high endemicity are at risk of infection.

Clinical features. The average incubation period is 30 (15–40) days. Most people suffer a prodrome of a flu-like illness, anorexia and arthralgia in the week preceding the jaundice. Occasionally, in about 10% of cases, there is a transient eruption [1], usually maculopapular, petechial or urticarial. A morbilliform eruption with predominance in sun-exposed sites [2] and a Gianotti–Crosti-like eruption in a child [3] have been reported. Occasional reports of a vasculitic eruption with relapsing or persistent hepatitis A infection have been attributed to cryoglobulinaemia [4].

During the prodrome and the early icteric phase, the patient excretes virus in the faeces and is infectious, although only a transient viraemia occurs. Sixty-five per cent of toddlers and about 90% of adults will develop jaundice. Fulminant hepatitis rarely occurs. Mortality, usually due to chronic hepatitis, in the over-50 age group is 2%.

Diagnosis. Hepatitis A must be distinguished from other causes of jaundice. The diagnosis is confirmed by detecting hepatitis A IgM antibody. The presence of IgG antibody indicates past infection (or immunization) and gives protection.

Prevention. Active immunization with inactivated vaccine or short-lived passive protection using human immunoglobulin are both available for susceptible contacts and travellers.

Treatment. Symptomatic measures are usually sufficient. The infection is of a few weeks' duration and no chronic carrier state exists. Alcohol should be avoided during the convalescent period.

References

1 Doutre MS, Beylot C. Les signes cutanés liés aux virus de l'hépatite. *Ann Dermatol Venereol* 1983; **110**: 647–54.

2 Kano Y, Kokaji T, Shiohara T. Photo-accentuated eruption and vascular deposits of immunoglobulin A associated with hepatitis A virus infection. *Dermatology* 2000; **200**: 266–9.

3 Sagi EF, Linder N, Shouval D. Papular acrodermatitis of childhood associated with hepatitis A virus infection. *Pediatr Dermatol* 1985; **3**: 31–3.

4 Inman RD, Hodge M, Johnston ME *et al.* Arthritis, vasculitis, and cryoglobulinemia associated with relapsing hepatitis A virus infection. *Ann Intern Med* 1986; **105**: 700–3.

Vesicular stomatitis virus

Aetiology and pathology. Vesicular stomatitis is a specific virus infection of horses and cattle in the Americas, Asia and Africa. It is generally mild but can mimic foot and mouth disease. It is occasionally transmitted to humans by direct or indirect contact. As the name implies vesicular stomatitis virus can cause vesicles; these are intraepithelial. Intranuclear inclusions are present in infected cells.

Clinical features [1]. The incubation period is 2 days after which there is fever with myalgia and malaise. This is occasionally followed by mild stomatitis with vesicles on the gums and buccal and pharyngeal mucosa, and lymphadenitis. Some patients develop vesicles of the fingers. Recovery is usually complete within a week.

Reference

1 Fields BN, Hawkins K. Human infection with the virus of vesicular stomatitis during an epizootic. *N Engl J Med* 1967; **277**: 989–94.

Myxoviruses and related RNA viruses

Two families are distinguishable, the *Orthomyxoviridae*, consisting of the influenza viruses A, B and C, and the *Paramyxoviridae*. The latter group comprises three genera:

1 *Paramyxovirus*, containing the parainfluenza virus and mumps
2 *Morbillivirus*, in which the human representative is measles
3 *Pneumovirus*, which contains respiratory syncytial virus (RSV).

Cutaneous manifestations are not usually produced except in measles and occasionally in RSV infections.

Measles [1]

Synonym
- Morbilli

Aetiology and pathology. Measles infection occurs from human to human via the upper respiratory tract where initial replication occurs before wide dissemination throughout the body.

The cellular receptors for the virus are the CD46 and CD150 (SLAM) molecules. During the prodromal period establishment of infection in the reticuloendothelial system, there is lymphoid hyperplasia with formation of fused multinucleate giant cells. The prodromal rash [2] appears to be the result of viraemia with lodgement of antigen and virus in the capillaries. Cells in the Koplik's spots also contain viral nucleocapsids. The conspicuous macular eruption on the fourth day is the result of the CMI response against this material. If the response is defective as in leukaemia, especially when cytotoxic drugs are used, there may be no rash but progressive viral replication to produce a giant-cell pneumonia or a fatal encephalopathy [3].

Shortly after the rash appears, measles virus causes a transient depression of the T-cell-mediated immune responses which are an important feature of the infection [4] and can persist for 1–2 months. The anergic mechanism may permit the invasion of the brain by measles virus which later produces subacute sclerosing panencephalitis. Lifelong immunity follows natural measles infection.

Clinical features. After an incubation period of about 10 days, the prodromal symptoms of fever, malaise and upper respiratory catarrh begin acutely. The conjunctivae are injected and there may be photophobia. From the second day, Koplik's spots are usually present on the buccal mucous membrane opposite the premolar teeth—bluish white spots with bright-red areolae (Fig. 33.30). Fever, catarrh and cough increase for 3–5 days. The exanthem characteristically develops on the fourth day on the forehead and behind the ears, and spreads within 24 h to the rest of the face, the trunk and the limbs. The rash is at first macular but soon forms dull red papules which tend to coalesce in irregularly concentric patterns but may be more diffusely confluent. From the sixth to the tenth day the rash fades, to leave some brownish staining and fine desquamation. In very severe forms it may be haemorrhagic.

An extensive bullous eruption may rarely develop during the acute stage of measles. In some cases this eruption has the features of Stevens–Johnson syndrome, but in others it resembles epidermal necrolysis.



Fig. 33.30 Koplik's spots on buccal mucosa in measles. (Courtesy of Dr John Kurtz, Oxford, UK.)

Complications are more common in young children, the malnourished and the chronically ill [5]. Bronchopneumonia, enteritis and otitis media are less frequent now as effective antibiotics are available. The most serious complication is encephalitis which occurs in one in 2000 cases.

Diagnosis. The features of other infective exanthems are considered in this chapter. Drug eruptions should not cause confusion as the upper respiratory catarrh and conjunctival suffusion are absent. Specific measles antibodies are usually detectable 3 or 4 days after the appearance of the rash, and maximum titres are reached 2–4 weeks later. Virus isolation is not easy but viral antigen can be detected by immunofluorescence in cell smears prepared from nasopharyngeal aspirates taken early during the illness and in skin biopsy of the exanthem [6]. Molecular diagnosis of measles is possible [7] but not yet routine.

Prevention. Passive protection is possible using normal human immunoglobulin given within 5 days of exposure, which prevents or attenuates the infection in contacts and is reserved for those children at special risk. Active immunization with live attenuated viral vaccine has reduced the incidence of measles infections. A mild illness with a rash is common during the 3 weeks following the vaccine and there are occasional reports of other eruptions post-vaccination such as Stevens–Johnson syndrome [8]. The vaccine is available as a single vaccine, but is used more commonly as the triple vaccine (measles, mumps and rubella) or as the newer quadruple vaccine which includes varicella.

The introduction of vaccination against measles is extending worldwide, with impressive reduction in mortality [9], but the prospect of global eradication of the disease is some time away. Concerns relating to the safety of vaccination in 1990s led to a reduced proportion of vaccinated children in some countries with subsequent small increases in incidence and reports of isolated outbreaks of the disease [10].

Treatment. The patient should be confined to bed and given symptomatic treatment. Children with measles, especially in areas of high mortality, should be given vitamin A (two doses of 200 000 IU) [11]. Measles pneumonia may be helped by ribavirin [12]. Antibiotics may be required to control secondary bacterial complications.

References

1 Duke T, Mgone CS. Measles: not just another viral exanthem. *Lancet* 2003; **361**: 763–73.
2 Ackerman AB, Suringa DW. Multinucleate epidermal cells in measles. *Arch Dermatol* 1971; **103**: 180–1 passim.
3 Pullan CR, Noble TC, Scott DJ *et al.* Atypical measles infections in leukaemic children on immunosuppressive treatment. *BMJ* 1976; **1**: 1562–5.
4 Anonymous. Immunology of measles. *Lancet* 1989; **2**: 780–1.
5 Perry RT, Halsey NA. The clinical significance of measles: a review. *J Infect Dis* 2004; **189** (Suppl. 1): S4–16.
6 Olding-Stenkvist E, Bjorvatn B. Rapid detection of measles virus in skin rashes by immunofluorescence. *J Infect Dis* 1976; **134**: 463–9.
7 Hummel KB, Lowe L, Bellini WJ *et al.* Development of quantitative gene-specific real-time RT-PCR assays for the detection of measles virus in clinical specimens. *J Virol Methods* 2006; **132**: 166–73.
8 Hazir T, Saleem M, Abbas KA. Stevens–Johnson syndrome following measles vaccination. *J Pak Med Assoc* 1997; **47**: 264–5.
9 Anonymous. Progress in global measles control and mortality reduction, 2000–2006. *MMWR Morb Mortal Wkly Rep* 2007; **56**: 1237–41.
10 Anonymous. Measles once again endemic in the United Kingdom. *Euro Surveill* 2008; **13**. www.eurosurveillance.org/ViewArticle.aspx?ArticleId=18919.
11 D'Souza RM, D'Souza R. Vitamin A for preventing secondary infections in children with measles—a systematic review. *J Trop Pediatr* 2002; **48**: 72–7.
12 Forni AL, Schluger NW, Roberts RB. Severe measles pneumonitis in adults: evaluation of clinical characteristics and therapy with intravenous ribavirin. *Clin Infect Dis* 1994; **19**: 454–62.

Respiratory syncytial virus

Aetiology and pathology. The virus is pleomorphic, a little smaller than measles, and derives its name from the multinucleate syncytia produced when grown in tissue-culture cells. There are two distinct subgroups, A and B, which differ most in their surface glycoprotein G. Group A viruses are more frequently detected and a higher proportion of severe infections are associated with Group A [1]. RSV causes annual epidemics during the winter months or in the rainy season in the tropics [2]. Most people have been infected by age 1 or 2 years and suffer repeated infections throughout life.

Clinical features. Infection occurs after an incubation period of 4–5 days. The virus is especially associated with bronchiolitis in babies with bronchitis and pneumonia occurring in a proportion of infections. In older children and adults upper respiratory symptoms occur, indistinguishable from a common cold. Again in old age, RSV pneumonia is not uncommon and in bone-marrow transplant recipients is associated with a high rate of mortality [3]. A transient, fine, pink, macular rash on the face and trunk has been observed in a few instances in children, but is of no diagnostic significance. Occasionally it is more extensive and involves the arms, shoulders, chest, back and buttocks [4]. The diagnosis can be achieved by rapid antibody detection or by reverse transcription PCR to detect viral nucleic acid.

References

1 Hall CB, Walsh EE, Schnabel KC *et al.* Occurrence of groups A and B of respiratory syncytial virus over 15 years: associated epidemiologic and clinical characteristics in hospitalized and ambulatory children. *J Infect Dis* 1990; **162**: 1283–90.
2 Black CP. Systematic review of the biology and medical management of respiratory syncytial virus infection. *Respir Care* 2003; **48**: 209–31, discussion 31–3.
3 Khanna N, Widmer AF, Decker M *et al.* Respiratory syncytial virus infection in patients with hematological diseases: single-center study and review of the literature. *Clin Infect Dis* 2008; **46**: 402–12.
4 Berkovich S, Kibrick S. Exanthem associated with respiratory syncytial virus infection. *J Pediatr* 1064; **65**: 368–70.

Other cutaneous problems associated with viral infections

Several cutaneous syndromes are associated with viral infections or other triggering factors.

Erythema multiforme

Erythema multiforme (see Chapter 76) may be precipitated by several different viral infections. Herpes simplex is the most commonly associated virus, but VZV, EBV, mumps, polio, orf, milker's nodule, HIV, hepatitis B and hepatitis C may all need to be considered as trigger factors.

Erythema nodosum

Septal panniculitis presenting as erythema nodosum, most commonly on the shins, is associated with a variety of conditions (see Chapter 50). Viral infections implicated as possible precipitants are milker's nodule, EBV and hepatitis B and C.

Papular–purpuric gloves and socks syndrome

An acute acral dermatosis, occurring predominantly in adults, was first described in 1990 [1]. The hands, wrists, feet and ankles are intensely pruritic and are affected with erythema and papular oedema. There may also be associated purpura and rarely petechiae. The eruption can occasionally involve the perioral and perianal skin [2]. The cutaneous features are frequently accompanied by oral inflammation and ulceration. Malaise and fever can follow a few days after the onset of the eruption but the condition settles within 2 weeks. The eruption is much less common in children, but may last a month.

In many cases, no specific cause can be identified [3], but parvovirus B19 infection has been suggested to act as the most common trigger for the syndrome [4] with measles, rubella, hepatitis B, CMV and HHV-6 infections also reported in association [5–9]. In children, EBV infection may be a trigger [10].

TORCH syndrome

The term TORCH syndrome was originally used to encompass congenital infection caused by either *Toxoplasma gondii*, rubella, cytomegalovirus or herpes simplex types 1 and 2 in which the clinical presentation was somewhat similar. In practice, there are some distinctions between the manifestations of the various infections, although all may cause cutaneous and disseminated abnormalities. Skin abnormalities of jaundice, purpura and petechiae are most common. Vesicles and mucosal ulceration may occur with herpes infection. Since the acronym has been used, several other

congenital infections are recognized to be of importance and the concept of TORCH is now of limited value [11].

Kikuchi–Fujimoto disease [12,13]

Synonyms
- Kikuchi's disease
- Histiocytic necrotizing lymphadenitis

The clinicopathological entity consists of painful lymphadenitis affecting mainly the cervical nodes associated with fever, malaise and upper respiratory tract symptoms. Occasionally, symptoms may be severe enough to mimic a malignant lymphoma. Thirty percent may have cutaneous involvement especially overlying affected lymph nodes. Erythematous, indurated plaques but also macules and papules may be seen. The disorder is most common in young women, but can affect any age. Viral infections reported in association are most commonly EBV, but also parvovirus B19, herpes simplex virus and HHV-6 and HHV-7 [14,15].

Polyarteritis nodosa (see Chapter 50)

Inflammation of medium sized vessels presenting with only cutaneous lesions or with systemic effects has been associated with infection with EBV [16] and hepatitis B and C (see pp. 33.60–61).

References

1 Harms M, Feldmann R, Saurat JH. Papular-purpuric 'gloves and socks' syndrome. *J Am Acad Dermatol* 1990; **23**: 850–4.
2 Foti C, Bonamonte D, Conserva A *et al*. Erythema infectiosum following generalized petechial eruption induced by human parvovirus B19. *New Microbiol* 2006; **29**: 45–8.
3 Feldmann R, Harms M, Saurat JH. Papular-purpuric 'gloves and socks' syndrome: not only parvovirus B19. *Dermatology* 1994; **188**: 85–7.
4 Bagot M, Revuz J. Papular-purpuric 'gloves and socks' syndrome: primary infection with parvovirus B19? *J Am Acad Dermatol* 1991; **25**: 341–2.
5 Segui N, Zayas A, Fuertes A *et al*. Papular-purpuric 'Gloves-and-Socks' syndrome related to rubella virus infection. *Dermatology* 2000; **200**: 89.
6 Ruzicka T, Kalka K, Diercks K *et al*. Papular-purpuric 'gloves and socks' syndrome associated with human herpesvirus 6 infection. *Arch Dermatol* 1998; **134**: 242–4.
7 Perez-Ferriols A, Martinez-Aparicio A, Aliaga-Boniche A. Papular-purpuric 'gloves and socks' syndrome caused by measles virus. *J Am Acad Dermatol* 1994; **30**: 291–2.
8 Velez A, Fernandez-de-la-Puebla R, Moreno JC. Second case of papular-purpuric gloves-and-socks syndrome related to hepatitis B infection. *Br J Dermatol* 2001; **145**: 515–6.
9 Carrascosa JM, Bielsa I, Ribera M *et al*. Papular-purpuric gloves-and-socks syndrome related to cytomegalovirus infection. *Dermatology* 1995; **191**: 269–70.
10 Hsieh MY, Huang PH. The juvenile variant of papular-purpuric gloves and socks syndrome and its association with viral infections. *Br J Dermatol* 2004; **151**: 201–6.
11 Anonymous. Congenital toxoplasmosis and TORCH. *Lancet* 1990; **336**: 622–4.
12 Kucukardali Y, Solmazgul E, Kunter E *et al*. Kikuchi–Fujimoto disease: analysis of 244 cases. *Clin Rheumatol* 2007; **26**: 50–4.
13 Bosch X, Guilabert A. Kikuchi–Fujimoto disease. *Orphanet J Rare Dis* 2006; **1**: 18.
14 Hudnall SD, Chen T, Amr S *et al*. Detection of human herpesvirus DNA in Kikuchi–Fujimoto disease and reactive lymphoid hyperplasia. *Int J Clin Exp Pathol* 2008; **1**: 362–8.
15 Zhang WP, Wang JH, Wang WQ *et al*. An association between parvovirus B19 and Kikuchi–Fujimoto disease. *Viral Immunol* 2007; **20**: 421–8.
16 Caldeira T, Meireles C, Cunha F *et al*. Systemic polyarteritis nodosa associated with acute Epstein–Barr virus infection. *Clin Rheumatol* 2007; **26**: 1733–5.

Gianotti–Crosti syndrome [1]

Synonym
- Papular acrodermatitis of childhood

Aetiology. Gianotti–Crosti syndrome is a characteristic cutaneous response to viral infection [2,3]. The majority of the earliest reported cases had hepatitis B infection, but several other viruses and even non-viral infections have been associated. The most common of these is EBV [4,5]. Infrequently reported, and therefore of less certain significance, are coxsackie A16 [6], coxsackie B4 and B5 [5], echovirus 7 [7], echovirus 9 [8], poliovirus [9], CMV [5], HHV6 [10], respiratory syncytial virus [9], parainfluenza virus [3], hepatitis A [11], parvovirus B19 [12], milker's nodules [13] and HIV [14]. Non-viral associations are *Mycoplasma pneumoniae* and β-haemolytic streptococci [9,15]. Occasional cases following immunization, for example combined measles, mumps, rubella vaccine [16], diphtheria, pertussis and influenza [5,17] and hepatitis A [18] or B [19] are of uncertain significance. In a minority of cases, no evidence of viral infection can be found.

The syndrome mainly affects children between the ages of 6 months and 12 years, though occasional adult female cases have occurred [20,21]. Small epidemics or clustering of cases is often observed.

Pathology [3]. The skin lesions show slight or moderate acanthosis and hyperkeratosis. In the oedematous upper dermis an infiltrate of lymphocytes and histiocytes surrounds dilated capillaries. The lymph nodes show a diffuse reticulum-cell hyperplasia, often of severe degree. When histology of bone marrow or liver is indicated, they show what appears to be a generalized, low-grade inflammatory reaction of the entire reticuloendothelial system.

Clinical features [1,22]. Over the course of 3 or 4 days a profuse eruption of dull red flat-topped papules develops first on the thighs and buttocks (Fig. 33.31), then on the extensor aspects of the arms, and finally on the face. The distinction is often asymmetrical. The fleeting appearance of a few lesions on the trunk is occasionally noted. The individual papules are 5–10 mm in diameter, and their characteristic deep red colour may later be modified by purpuric staining, especially on the legs. Itch is said not to be a feature of the hepatitis B cases, but may occur in those due to other viruses. The eruption fades in 2–8 weeks with mild desquamation. Recurrence has been reported rarely [23].

Generalized lymphadenopathy, mostly axillary and inguinal, is common but not invariable, and persists for months after the rash. Constitutional symptoms are not usually marked although there may be mild fever and lassitude. The changes in the peripheral blood are inconstant: there may be a leukopenia or a slight leukocytosis with 2–15% of monocytes; the erythrocyte sedimentation rate is not raised.

In the hepatitis B cases, liver involvement appears to be invariable, usually mild and anicteric, but occasionally there is jaundice, and histological recovery may take between 6 months and 4 years. Rarely, there is persistent hepatitis. Hepatomegaly and liver

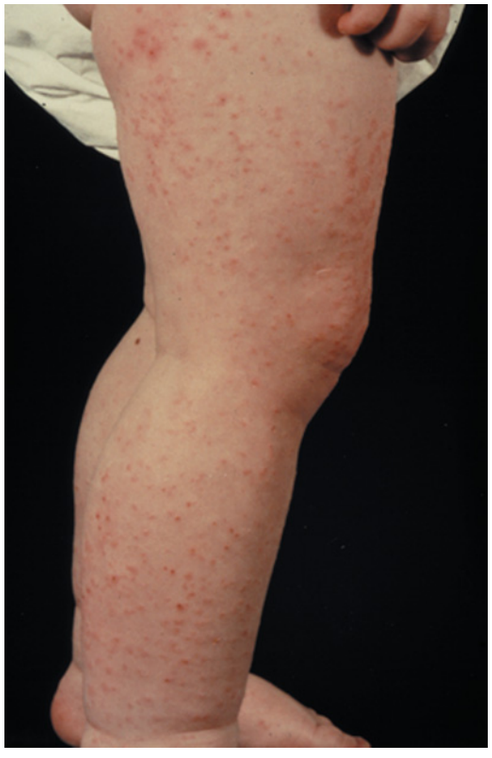


Fig. 33.31 Gianotti–Crosti syndrome. Papular eruption on leg. (Courtesy of Dr N.P. Burrows, Addenbrooke's Hospital, Cambridge, UK.)

function abnormalities each occasionally occur in HBsAg-negative cases.

Diagnosis. The skin lesions are sufficiently distinctive in morphology, distribution and duration. Differential diagnoses to consider include lichen planus, lichenoid drug eruption, scabies and erythema multiforme. It is prudent to search for a triggering infection and assess liver function.

Treatment. There is no specific treatment. Emollients and topical steroids may help to relieve pruritus.

References

1 Brandt O, Abeck D, Gianotti R *et al.* Gianotti–Crosti syndrome. *J Am Acad Dermatol* 2006; **54**: 136–45.
2 Crosti A, Gianotti F. Dermatose eruptive acro-situeé d'origine probablement virosique. *Dermatologica* 1957; **115**: 671–7.
3 Spear KL, Winkelmann RK. Gianotti–Crosti syndrome. A review of ten cases not associated with hepatitis B. *Arch Dermatol* 1984; **120**: 891–6.
4 Drago F, Crovato F, Rebora A. Gianotti–Crosti syndrome as a presenting sign of EBV-induced acute infectious mononucleosis. *Clin Exp Dermatol* 1997; **22**: 301–2.
5 Taieb A, Plantin P, Du Pasquier P *et al.* Gianotti–Crosti syndrome: a study of 26 cases. *Br J Dermatol* 1986; **115**: 49–59.
6 James WD, Odom RB, Hatch MH. Gianotti–Crosti-like eruption associated with coxsackievirus A-16 infection. *J Am Acad Dermatol* 1982; **6**: 862–6.
7 Labbe A, Peyrot J, Goumy P *et al.* Syndrome acropapulovesiculeux de l'enfant et maladie de Gianotti–Crosti. Discussion à propos de quatre observations d'étiologie virale probable. *Pediatrie* 1982; **37**: 467–71.
8 Rogers S, Connolly JH. Letter: Gianotti–Crosti syndrome and viral infection. *BMJ* 1974; **4**: 529.
9 Draelos ZK, Hansen RC, James WD. Gianotti–Crosti syndrome associated with infections other than hepatitis B. *JAMA* 1986; **256**: 2386–8.
10 Chuh AA, Chan HH, Chiu SS *et al.* A prospective case control study of the association of Gianotti–Crosti syndrome with human herpesvirus 6 and human herpesvirus 7 infections. *Pediatr Dermatol* 2002; **19**: 492–7.
11 Sagi EF, Linder N, Shouval D. Papular acrodermatitis of childhood associated with hepatitis A virus infection. *Pediatr Dermatol* 1985; **3**: 31–3.
12 Borreda D, Palomera S, Gilbert B *et al.* A propos de vingt-quatre observations d'infections à parvovirus humain B19 chez l'enfant. *Ann Pediatr (Paris)* 1992; **39**: 543–9.
13 de la Torre C. Gianotti–Crosti syndrome following milkers' nodules. *Cutis* 2004; **74**: 316–8.
14 Blauvelt A, Turner ML. Gianotti–Crosti syndrome and human immunodeficiency virus infection. *Arch Dermatol* 1994; **130**: 481–3.
15 Manoharan S, Muir J, Williamson R. Gianotti–Crosti syndrome in an adult following recent Mycoplasma pneumoniae infection. *Australas J Dermatol* 2005; **46**: 106–9.
16 Velangi SS, Tidman MJ. Gianotti–Crosti syndrome after measles, mumps and rubella vaccination. *Br J Dermatol* 1998; **139**: 1122–3.
17 Cambiaghi S, Scarabelli G, Pistritto G *et al.* Gianotti–Crosti syndrome in an adult after influenza virus vaccination. *Dermatology* 1995; **191**: 340–1.
18 Monastirli A, Varvarigou A, Pasmatzi E *et al.* Gianotti–Crosti syndrome after hepatitis A vaccination. *Acta Derm Venereol* 2007; **87**: 174–5.
19 Karakas M, Durdu M, Tuncer I *et al.* Gianotti–Crosti syndrome in a child following hepatitis B virus vaccination. *J Dermatol* 2007; **34**: 117–20.
20 Ting PT, Barankin B, Dytoc MT. Gianotti–Crosti syndrome in two adult patients. *J Cutan Med Surg* 2008; **12**: 121–5.
21 Gibbs S, Burrows N. Gianotti–Crosti syndrome in two unrelated adults. *Clin Exp Dermatol* 2000; **25**: 594–6.
22 Boeck K, Mempel M, Schmidt T *et al.* Gianotti–Crosti syndrome: clinical, serologic, and therapeutic data from nine children. *Cutis* 1998; **62**: 271–4.
23 Patrizi A, Di Lernia V, Neri I *et al.* An unusual case of recurrent Gianotti–Crosti syndrome. *Pediatr Dermatol* 1994; **11**: 283–4.

Pityriasis rosea

Definition. Pityriasis rosea is an acute, self-limiting disease, probably infective in origin, affecting mainly children and young adults, and characterized by a distinctive skin eruption and minimal constitutional symptoms.

Aetiology. Pityriasis rosea is relatively common throughout the world. In temperate regions, it is more frequent during the winter months. In tropical areas, there may also be some seasonal variation. Changes in incidence from year to year, though not great, may be statistically significant [1].

Most cases of pityriasis rosea occur between the ages of 10 and 35 years and it is uncommon in infancy, early childhood or old age. It is slightly more common in females [2,3]. Susceptibility to the disease appears not to be influenced by race or atopy, but one report suggests an association with HLA-DQB1*04 in Black people in Brazil [4].

The cause of pityriasis rosea is uncertain, but many epidemiological and clinical features suggest that an infective agent may be implicated. True epidemics have not been reported, but the reported epidemiological evidence for infectivity includes occasional family or household outbreaks, seasonal and year-to-year fluctuations [1,3,5] and statistical evidence for clustering in space and time [6]. The natural history of the disease, with a primary lesion which could correspond to the site of inoculation, a disseminated secondary eruption after an interval, mild constitutional symptoms, a self-limiting course, and the infrequency of second attacks, are all features paralleled by many diseases of

proven infective origin. Exacerbations accompanying oral steroid therapy were noted in a small series [7] and pityriasis rosea-like eruptions have been reported after bone-marrow transplantation [8], although several aetiological effects could be implicated in such a situation.

The search for a microorganism has continued for decades. Early suspicions about fungi, streptococci, spirochaetes and *Legionella* have not been confirmed, and most speculation now centres on a viral aetiology. Attempts to culture virus from affected skin have been fruitless [9]. Virus-like particles were detected ultrastructurally over 30 years ago and more recently herpesvirus-like particles have been found in 71% of pityriasis rosea lesions [10]. Involvement of two herpesviruses, HHV-6 and HHV-7, has been suggested as a cause for the eruption. The viral DNA is reported to be present in the PBMCs and lesional and unaffected skin of the majority of individuals with acute pityriasis rosea. HHV-7 is detected slightly more frequently than HHV-6, but often both viruses are found [11,12]. However, evidence of HHV-6 or HHV-7 presence and activity is also found in a proportion (10–44%) of unaffected individuals, suggesting that if there is a causal relationship, infection with the viruses does not always lead to disease. HHV-8 has also been reported as a possible causative agent [13]. Not all groups working in this field have confirmed the presence of these viruses in patients with pityriasis rosea [14,15] or have found a weaker association [16].

There are several reports associating pityriasis rosea-like eruptions with drugs. The rashes caused by arsenic, bismuth, gold, lithium and methopromazine may have been atypical lichenoid reactions. Other drugs implicated include metronidazole [17], barbiturates, clonidine, captopril [18], ketotifen [19] and adalimumab [20]. In some reports the resemblance of the eruption to pityriasis rosea has not been close, and in others coincidence might explain the association. Thus, while some drug eruptions may somewhat resemble the condition, there is no convincing evidence that typical pityriasis rosea can be caused by drugs.

Pathology [21–23]. The herald patch and the secondary lesions are similar histologically. The changes are not diagnostic. In the epidermis, spongiosis, vesicles and patchy para-keratosis are common. The upper dermis shows oedema and a mononuclear cell infiltrate from which there is exocytosis into the epidermis, where they may form pustules, mainly subcorneal. The infiltrate comprises mainly helper T lymphocytes but also Langerhans' cells, and HLA-DR antigens are expressed on the keratinocyte surface. Occasional dyskeratotic keratinocytes are seen, sometimes adjacent to a Langerhans' cell.

Clinical features [5,24] (Fig. 33.32). The eruption of pityriasis rosea follows a distinctive and remarkably constant pattern and course in most cases. Prodromal symptoms are usually absent and the vague complaints of headache and slight malaise elicited by direct questioning may not be more frequent than in healthy control subjects. The first manifestation of the disease is usually the appearance of the herald patch, which is larger and more conspicuous than the lesions of the later eruption and is usually situated on the thigh or upper arm, the trunk or the neck; rarely it may be on the face, scalp or the penis. It is a sharply defined, erythematous, round or oval plaque, soon covered by fine scale. It rapidly reaches its maximum size, usually 2–5 cm in diameter but occasionally much larger. Rarely, there may be more than one herald patch. After an interval, which is usually between 5 and 15 days, but may be as short as a few hours or as long as 2 months, the general eruption begins to appear in crops at 2 to 3-day intervals over a week or 10 days. Less often, new lesions continue to develop for several weeks. In its classical form the eruption consists of discrete oval lesions, dull pink in colour and covered by fine, dry, silvery-grey scales. The centre tends to clear and assumes a wrinkled, atrophic appearance and a tawny colour, with a marginal collarette of scale attached peripherally, with the free edge of the scale internally. The long axes of the lesions characteristically follow the lines of cleavage parallel to the ribs in a Christmas-tree pattern on the upper chest and back. The scaly lesions are commonly associated with pink macules of varying size and the eruption may be exclusively macular.

The lesions are usually said to be confined to the trunk, the base of the neck and the upper third of the arms and legs. These sites are certainly most consistently and severely affected but involvement of the face and scalp is quite common, especially in children, and in one large series of cases lesions were found on the forearms and lower legs in about 12% and 6%, respectively. Lesions on the palms are exceptional, but can occur. There may be discrete, scaly, red patches, diffuse redness and scaling or scattered small vesicles. Oral lesions are not infrequently present [25] and can consist of ill-defined red patches with some desquamation or with punctate haemorrhages, or bullae. Exceptionally, there may be lesions on the vulva.

Subjective symptoms are usually absent but there may be slight or moderate pruritus. Occasionally, slight fever, malaise and enlargement of lymphatic glands, generalized or confined to the cervical glands, may be present, and, exceptionally, more severe constitutional symptoms have been recorded, although their extreme rarity suggests that they may have been fortuitously associated and not a manifestation of the disease.

The skin lesions commonly fade after 3–6 weeks, but some clear in 1 or 2 weeks and a few persist for as long as 3 months. A longer duration, except in localized forms, is very unusual. There may be temporary hyper- or hypopigmentation, but usually the lesions vanish without trace.

Second attacks of pityriasis rosea occur in about 2% of cases after an interval of a few months or many years, and rarely, a partial or complete relapse of a fading eruption may be seen.

Pityriasis rosea may be atypical in the appearance or distribution of the lesions or in its course [26]. The herald patch is absent or undetected in about 20% of cases. The 'secondary' eruption varies greatly in extent. It may be almost generalized or may be limited to a few lesions, often around the herald patch. At times the eruption is confined to a single region, or may be maximal on the extremities almost sparing the trunk [27]. Unilateral pityriasis has been reported [28]. Especially in children, the lesions may be predominantly papular or urticarial in the early stages, but they are soon surmounted by an inconspicuous ring of fine scales. Papulovesicular, vesicular, purpuric, erythema multiforme-like lesions and even pustular forms may rarely occur [29]. In a variant of the papular form more common in Africans than Europeans, small lichenoid papules are thickly set in the edges of the lesions [30].



(a)



(b)



(c)

Fig. 33.32 Pityriasis rosea: (a) with herald patch on right of abdomen, shown in close-up in (b) (courtesy of York District Hospital, UK); (c) with herald patch on right of chest (courtesy of Dr A.S. Highet, York District Hospital, UK).

In pityriasis circinata et marginata of Vidal [31], sometimes regarded as a special form of pityriasis rosea and seen mainly in adults, the lesions are few and large, and are often localized to one region of the body, especially the axillae or groins. They tend to become confluent and may persist for several months. Rarely, this form may follow a typical generalized pityriasis rosea, but it usually occurs alone.

Pityriasis rosea occurring in the first trimester of pregnancy may be associated with a higher than normal risk of spontaneous abortion or premature delivery of an infant with hypotonia and hyporeactivity [32].

Diagnosis. In the typical, fully developed case the diagnosis usually presents little difficulty as the distribution, morphology and the absence of constitutional symptoms are sufficiently distinctive. Some patterns of drug eruption (see Chapter 75) may have to be excluded. An acute onset without a herald patch, pruritus and a tendency for the lesions to become lichenoid in appearance are suggestive features. A progressive, irritable, atypical pityriasiform eruption in a patient taking a drug which is known to provoke reactions of this nature, can be tentatively accepted, in the absence of any method of laboratory confirmation.

Seborrhoeic dermatitis may be pityriasiform. There is no herald patch, the lesions often develop slowly and are most numerous on the upper trunk near the midline, on the neck and in the scalp, and they are duller in colour with thicker and more greasy scales. Small, scaly, follicular papules may also be present. The eruption is persistent if untreated.

Secondary syphilis is the classical trap but the resemblance is not very close. The genital and oral mucosae should be examined. There is no herald patch and the lesions are roseolar or maculopapular.

The acute urticarial forms in childhood can sometimes not be identified with complete certainty on first examination unless a herald patch can be discovered. Re-examination after 2 days enables a confident diagnosis to be confirmed.

Guttate psoriasis and pityriasis lichenoides may sometimes need exclusion. In both, the lesions are papular and persistent. In psoriasis they are surmounted by silvery scales. In pityriasis lichenoides they are polymorphic, some showing haemorrhagic crusting and some adherent scales.

The hypopigmented patches with dry, branny scales of pityriasis alba are most frequent on the face, and are seen mainly in young children. The pigmented form of pityriasis versicolor does not show marginal scaling and the chronicity would be very atypical.

The herald patch and the localized forms such as pityriasis circinata are easily, and in practice frequently, confused with ringworm. The lesions of ringworm are red and oedematous and may show marginal vesiculation. In case of doubt scrapings from the edge of the lesions should be examined microscopically for mycelium.

Treatment. The common asymptomatic and self-limiting cases require no treatment [24]. If itch is troublesome, or the appearance distressing, a topical steroid, usually of moderate strength, or broadband ultraviolet irradiation (UVB) [33,34] can be helpful.

Based on the concept of HHV-6 or HHV-7 as a cause of the eruption, trials of antiviral drugs are reported. The standard dose regimen of aciclovir does not have an effect, but high-dose aciclovir (800 mg five times daily for 1 week), used early after the onset of the eruption, may lead to a more rapid clearance of skin lesions. In one report, the mean time to clearance with treatment was 18.5 days compared to 37.9 days in placebo-treated individuals [35] even though anti-HHV-6 or HHV-7 IgM antibodies could be detected in only a minority of those treated.

The use of oral erythromycin antibiotic (1 g four times a day for 2 weeks for adults) was reported to clear the disease within 2 weeks of treatment [36] but subsequent studies with erythromycin and azithromycin have not confirmed any effect [37,38].

References

1 Hellgren L. Pityriasis rosea. Die Prävalenz in Geschlechts-, Alters- und Berufsgruppen in den ganzen Bevolkerungsgruppen. *Hautarzt* 1972; **23**: 492–4.

2 Chuang TY, Ilstrup DM, Perry HO *et al.* Pityriasis rosea in Rochester, Minnesota, 1969 to 1978. *J Am Acad Dermatol* 1982; **7**: 80–9.

3 Burch PR, Rowell NR. Pityriasis rosea—an autoaggressive disease? Statistical studies in relation to aetiology and pathogenesis. *Br J Dermatol* 1970; **82**: 549–60.

4 Miranda SM, Porto LC, Pontes LF *et al.* Correlation between HLA and pityriasis rosea susceptibility in Brazilian blacks. *J Eur Acad Dermatol Venereol* 2006; **20**: 21–6.

5 Bjornberg A, Hellgren L. Pityriasis rosea. A statistical, clinical, and laboratory investigation of 826 patients and matched healthy controls. *Acta Derm Venereol Suppl (Stockh)* 1962; **42** (Suppl. 50): 1–68.

6 Messenger AG, Knox EG, Summerly R *et al.* Case clustering in pityriasis rosea: support for role of an infective agent. *BMJ (Clin Res Edn)* 1982; **284**: 371–3.

7 Leonforte JF. Pityriasis rosea: exacerbation with corticosteroid treatment. *Dermatologica* 1981; **163**: 480–1.

8 Spelman LJ, Robertson IM, Strutton GM *et al.* Pityriasis rosea-like eruption after bone marrow transplantation. *J Am Acad Dermatol* 1994; **31**: 348–51.

9 Garcia E, Silva L, Gardner PS. Pityriasis rosea—a virological study. *Br J Dermatol* 1968; **80**: 514–5.

10 Drago F, Malaguti F, Ranieri E *et al.* Human herpes virus-like particles in pityriasis rosea lesions: an electron microscopy study. *J Cutan Pathol* 2002; **29**: 359–61.

11 Watanabe T, Kawamura T, Jacob SE *et al.* Pityriasis rosea is associated with systemic active infection with both human herpesvirus-7 and human herpesvirus-6. *J Invest Dermatol* 2002; **119**: 793–7.

12 Broccolo F, Drago F, Careddu AM *et al.* Additional evidence that pityriasis rosea is associated with reactivation of human herpesvirus-6 and -7. *J Invest Dermatol* 2005; **124**: 1234–40.

13 Chuh AA, Chan PK, Lee A. The detection of human herpesvirus-8 DNA in plasma and peripheral blood mononuclear cells in adult patients with pityriasis rosea by polymerase chain reaction. *J Eur Acad Dermatol Venereol* 2006; **20**: 667–71.

14 Kempf W, Adams V, Kleinhans M *et al.* Pityriasis rosea is not associated with human herpesvirus 7. *Arch Dermatol* 1999; **135**: 1070–2.

15 Chuh AA, Chiu SS, Peiris JS. Human herpesvirus 6 and 7 DNA in peripheral blood leucocytes and plasma in patients with pityriasis rosea by polymerase chain reaction: a prospective case control study. *Acta Derm Venereol* 2001; **81**: 289–90.

16 Kosuge H, Tanaka-Taya K, Miyoshi H *et al.* Epidemiological study of human herpesvirus-6 and human herpesvirus-7 in pityriasis rosea. *Br J Dermatol* 2000; **143**: 795–8.

17 Maize JC, Tomecki KJ. Pityriasis rosea-like drug eruption secondary to metronidazole. *Arch Dermatol* 1977; **113**: 1457–8.

18 Wilkin JK, Kirkendall WM. Pityriasis rosea-like rash from captopril. *Arch Dermatol* 1982; **118**: 186–7.

19 Wolf R, Wolf D, Livni E. Pityriasis rosea and ketotifen. *Dermatologica* 1985; **171**: 355–6.

20 Rajpara SN, Ormerod AD, Gallaway L. Adalimumab-induced pityriasis rosea. *J Eur Acad Dermatol Venereol* 2007; **21**: 1294–6.

21 Bunch LW, Tilley JC. Pityriasis rosea. A histologic and serologic study. *Arch Dermatol* 1961; **84**: 79–86.

22 Okamoto H, Imamura S, Aoshima T *et al.* Dyskeratotic degeneration of epidermal cells in pityriasis rosea: light and electron microscopic studies. *Br J Dermatol* 1982; **107**: 189–94.

23 Aiba S, Tagami H. Immunohistologic studies in pityriasis rosea. Evidence for cellular immune reaction in the lesional epidermis. *Arch Dermatol* 1985; **121**: 761–5.

24 Chuh AA, Dofitas BL, Comisel GG *et al.* Interventions for pityriasis rosea. *Cochrane Database Syst Rev* 2007: CD005068.

25 Vidimos AT, Camisa C. Tongue and cheek: oral lesions in pityriasis rosea. *Cutis* 1992; **50**: 276–80.

26 Imamura S, Ozaki M, Oguchi M *et al.* Atypical pityriasis rosea. *Dermatologica* 1985; **171**: 474–7.

27 Deng Y, Li H, Chen X. Palmoplantar pityriasis rosea: two case reports. *J Eur Acad Dermatol Venereol* 2007; **21**: 406–7.

28 Del Campo DV, Barsky S, Tisocco L *et al.* Pityriasis rosea unilateralis. *Int J Dermatol* 1983; **22**: 312–3.

29 Friedman SJ. Pityriasis rosea with erythema multiforme-like lesions. *J Am Acad Dermatol* 1987; **17**: 135–6.

30 Marshall J. Pityriasis rosea; a review of its clinical aspects and a discussion of its relationship to pityriasis lichenoides et varioliformis acuta and parapsoriasis guttata. *S Afr Med J* 1956; **30**: 210–8.

31 Aquilera Maruri C, Aquilera Diaz L. Le pityriasis circiné et marginé de Vidal. Maladie autonome. *Ann Dermatol Syphilogr* 1968; **95**: 49–57.

32 Drago F, Broccolo F, Zaccaria E *et al.* Pregnancy outcome in patients with pityriasis rosea. *J Am Acad Dermatol* 2008; **58**: S78–83.

33 Leenutaphong V, Jiamton S. UVB phototherapy for pityriasis rosea: a bilateral comparison study. *J Am Acad Dermatol* 1995; **33**: 996–9.

34 Valkova S, Trashlieva M, Christova P. UVB phototherapy for pityriasis rosea. *J Eur Acad Dermatol Venereol* 2004; **18**: 111–2.

35 Drago F, Vecchio F, Rebora A. Use of high-dose acyclovir in pityriasis rosea. *J Am Acad Dermatol* 2006; **54**: 82–5.

36 Sharma PK, Yadav TP, Gautam RK *et al.* Erythromycin in pityriasis rosea: A double-blind, placebo-controlled clinical trial. *J Am Acad Dermatol* 2000; **42**: 241–4.

37 Rasi A, Tajziehchi L, Savabi-Nasab S. Oral erythromycin is ineffective in the treatment of pityriasis rosea. *J Drugs Dermatol* 2008; **7**: 35–8.

38 Amer A, Fischer H. Azithromycin does not cure pityriasis rosea. *Pediatrics* 2006; **117**: 1702–5.

CHAPTER 34

Syphilis and Bacterial Sexually Transmitted Infections

G.R. Kinghorn

Department of GU Medicine, Royal Hallamshire Hospital, Sheffield, UK

Syphilis, 34.1
General features, 34.1
Acquired syphilis, 34.6
Congenital syphilis, 34.15
Tests for syphilis, 34.18
Management of syphilis, 34.22
Syphilis control, 34.24
Gonorrhoea, 34.24
Genital *Chlamydia* infections, 34.29
Lymphogranuloma venereum, 34.32
Chancroid, 34.34
Granuloma inguinale, 34.36

Introduction

The global health burden of sexually transmitted infections and HIV is large and increasing. The World Health Organization (WHO) estimates that for syphilis, gonorrhoea, chlamydial infections and trichomoniasis there are around 340 million new cases each year. If the major viral sexually transmitted infections (STIs) are added then the prevalence may be increased threefold. However, the true prevalence is unknown, because surveillance is inadequate in many countries, especially in resource-poor countries in sub-Saharan Africa, SE Asia and the Americas, where the sexual ill-health burden is greatest.

The incidence of STIs depends as much upon social and economic factors as upon biology and behaviour. STIs thrive in situations where communities are disrupted by conflict and war, where there is a high dependence upon migrant labour that disrupts families and where commercial sex work is prevalent. They are also promoted by stigmatization, which delays presentation for treatment and reduces the resources employed for their control.

STIs are caused by a diverse group of microorganisms. Many individuals have asymptomatic early infections, and this favours onward transmission. The later complications are a serious cause of morbidity and mortality, and seriously affect reproductive health in women. STIs are a major cause of infertility as a result of damage to the Fallopian tubes from ascending infections. Adverse pregnancy outcomes in terms of ectopics, miscarriage and stillbirth are common. Postabortal and postpartum infections related to STI are thought to cause around one-third of maternal deaths worldwide. Morbidity and mortality for the fetus also occur as a result of preterm birth associated with many STIs, and from vertical transmission causing congenital infections. Premature death in adults of both sexes may also result from genital cancers associated with HPV infections and liver disease associated with sexually transmitted hepatitis B and hepatitis C. However, the greatest loss of life is now associated with HIV infection, and the synergy with STIs which favours acquisition and transmission of HIV places even greater importance upon public health control measures. In the UK, the number of newly diagnosed cases of HIV continues to rise year by year, although the cases of AIDS and related deaths are in decline because of the effectiveness of antiretroviral therapy (Fig. 34.1).

Treatment and prevention of STIs are very cost-effective and the WHO has developed a global strategy for their control. This requires a coordinated, multiagency approach involving both health education and other government services. Behaviour change and promotion of condom use can reduce individual risk. There should be appropriate health care services for both diagnosis and treatment, and the development of targeted interventions with high-risk groups such as young people (Fig. 34.2), men who have sex with men and other hard-to-reach groups such as sex workers and marginalized populations. Improved surveillance should underpin the development of local strategic planning.

A coordinated approach that has been given strong political support has been found, in some countries, to reverse rising trends in HIV and STI incidence. This will be reinforced if there are also continuing efforts to improve clinical recognition and management of these conditions.

This chapter focuses upon the cutaneous manifestations of the principal global STIs caused by bacteria.

Syphilis

General features

Definition. An infectious disease caused by *Treponema pallidum*. The systemic nature of the disease, in which there are florid clinical manifestations interspersed with periods of asymptomatic latency, is also characterized by transmission to offspring and chronic late disease in 25% of those who are untreated.

The name of the disease was drawn from a poem *Syphilis sive morbus gallicus*, written by Fracastoro of Verona in 1530, in which the mythical swineherd Syphilis refused to make sacrifices to Apollo and was smitten as a result.

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

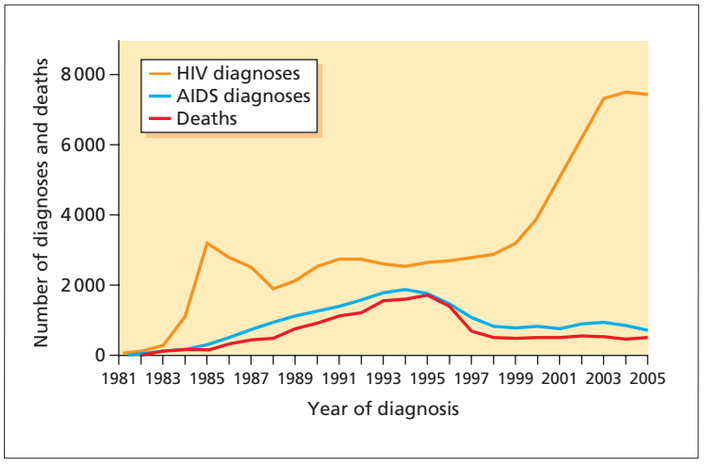


Fig. 34.1 HIV and AIDS diagnoses and deaths in the UK. Numbers will rise, for recent years, as further reports are received. Clinician reports of new HIV/AIDS diagnosis.

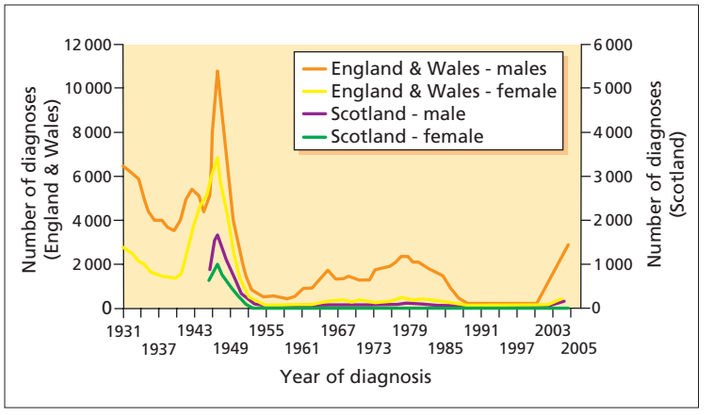


Fig. 34.3 Numbers of diagnoses of syphilis (primary, secondary and early latent) by sex, GUM clinics, England, Wales and Scotland: 1931–2005. Equivalent Scottish data are not available prior to 1945. N. Ireland data from 1931 to 2000 are incomplete and have been excluded. Data source: KC60 statutory returns and ISD(D)5\STISS data.

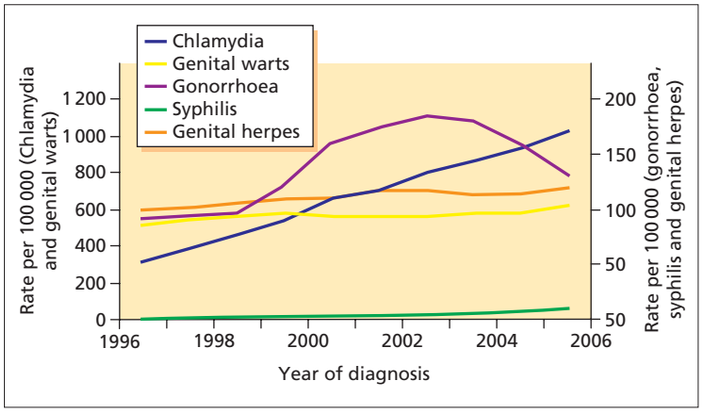


Fig. 34.2 Rates of *Chlamydia*, gonorrhoea, syphilis, genital warts and genital herpes in young people in the UK. Routine GUM returns.

Medico-social background. Syphilis, 'the great imitator', is among the most fascinating of skin diseases. It may present to the dermatologist as a sexually acquired, contagious disease or as a congenitally acquired infection. When sexually acquired, it commonly coexists with at least one other STI.

The prevalence of syphilis in a community is determined by the socio-economic structure of the country concerned, and how that structure functions [1]. Although syphilis is endemic worldwide, its steady decline over the last 400 years has been punctuated by epidemic peaks associated with unstable social conditions or upheavals. These changes include mass migrations and wars, as well as growing prosperity and economic reversals precipitating real or relative poverty.

The high incidence of syphilis in World War II peaked as thousands of demobilized men and women returned home to resettle. The period of relative socio-economic stability of the early 1950s saw a decline in all STIs, including syphilis. Its recrudescence, albeit modest compared with other sexual infections, began in the late 1950s [2–6]. It has been a variable manifestation. Population growth, with a growing proportion of young people in many societies, like increasing population movement, has increased incidence rates more directly (Fig. 34.3)

The extent to which available statistics reflect the incidence of syphilis depends on case-finding efforts, variation in notification practices and social factors that may limit, increase or reduce the interaction between infected individuals and health services [7]. Comparison of one country with another is therefore essentially meaningless.

Incidence. The WHO estimates that the annual global incidence of syphilis is approximately 12.2 million cases, most of which occur in developing countries, where the disease has remained a prominent cause of genital ulcer disease in heterosexual men and women, of stillbirth, and of neonatal morbidity and mortality. The prevalence of pregnant seropositive women is 0.1–0.6% in developed countries, but it may exceed 10% in many developing countries. The WHO estimates that only around 30% of pregnant women are screened for syphilis in sub-Saharan Africa, and seroconversion during pregnancy has been reported to occur in more than 2% of women [8]. In untreated women, about 30% will give birth to a dead baby, and another 30% will deliver a live baby with congenital syphilis, a condition with a mortality of up to 50%. Thus, congenital syphilis remains a very significant, global problem [9].

Syphilis is not as infectious as some other STIs, and the infected are readily rendered non-infectious by even short courses of antibiotics given for a wide variety of infections—not least for two common STIs, gonorrhoea and non-specific genital infection. However, the growth of penicillin and other antimicrobial resistance amongst gonococci, for example in South-East Asia but increasingly also in Western Europe, and the use of drugs that are less treponemicidal may open the way for a greater prevalence of syphilis [10,11].

Eastern Europe experienced a 50-fold increase in reported syphilis cases between 1990 and 1997, with similar increases in the Ukraine, some central Asian countries, and the Baltic States. Neighbouring Scandinavian countries have witnessed an increase in imported cases [12,13].

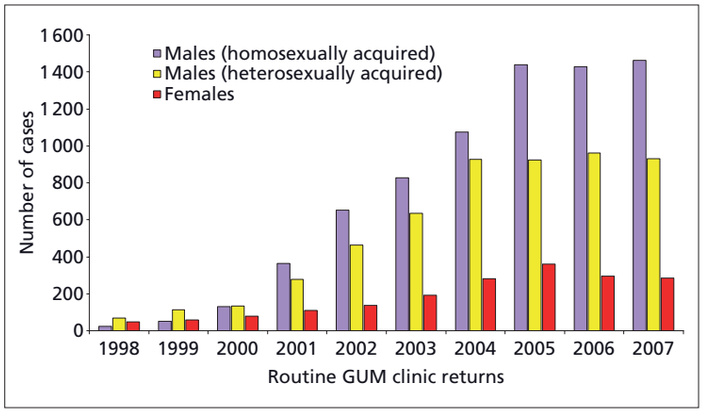


Fig. 34.4 Number of diagnoses of infectious syphilis (primary and secondary) by gender and male sexual orientation, GUM clinics, UK, 1998–2007. Data source: KC60 statutory returns and ISD(D)5 data.

In North America and the developed countries of northern Europe, syphilis had become predominantly a disease of men who have sex with men (MSM) by the 1970s. There were renewed outbreaks of heterosexual and congenital syphilis in North America during the late 1980s in the wake of the HIV epidemic [14–17]. This resurgence was mainly observed in commercial sex workers, in whom it was often associated with selling sex for drugs (especially crack cocaine), and in other persons of lower socioeconomic status. Primary and secondary syphilis cases amongst MSM are now increasing again in many states. A marked resurgence occurred in New Orleans in the wake of hurricane Katrina, which caused the closure of public STI clinic services.

Although the overall incidence of infectious syphilis in the UK was only 0.3 cases per 100 000 people in 1998, there have since been outbreaks in several cities where there was previously a low prevalence and a more than 10-fold increase in national incidence rates by 2005 [18] (Fig. 34.4).The outbreaks have been characterized by rapid increases in sexual networks, with high rates of partner change, travel or migration links with high incidence areas and an increasing predominance of homosexual transmission with a high proportion of HIV co-infection among incident cases. The male : female case ratio is 8 : 1. The highest rates occur in men aged 35–44 years and women aged 20–24 years. There was a similar trend in the increasing numbers of men who have sex with men engaging in unsafe sexual practices and who acquire syphilis and other bacterial sexually transmitted infections in Western Europe [19].

References

1 Morton RS. *Sexual Freedom and Venereal Disease*. London: Peter Owen, 1971.
2 Guthe T. The treponematoses as a world problem. *Br J Vener Dis* 1960; **36**: 67–77.
3 Idsøe O, Guthe T. The rise and fall of the treponematoses. *Br J Vener Dis* 1967; **43**: 227–43.
4 Knudson EA. A clinical study on 29 cases of debatable STS and TPI seroreactions in Greenland. *Acta Derm Venereol (Stockh)* 1974; **54**: 311–6.
5 Ministry of Health Report for England and Wales. Venereal diseases in England and Wales. *Br J Vener Dis* 1966; **42**: 50–7.
6 Schamberg IL. Syphilis and sisyphus. *Br J Vener Dis* 1963; **39**: 87–97.
7 Jacobs DS. Syphilis in Australian Aborigines in the Northern Territory. *Med J Aust* 1978; **1**: 10–2.
8 Aiken CJ. The causes of perinatal mortality in Bulawayo, Zimbabwe. *Cent Afr J Med* 1992; **38**: 263–81.
9 Schmid GP, Stoner BP, Hawkes S, Broutet N. The need and plan for global elimination of congenital syphilis. *Sex Transm Dis* 2007; **34** (Suppl. 7): S5–10.
10 WHO. *Treponemal Infections*. Technical Report Series No. 674. Geneva: World Health Organization, 1982.
11 Thirumoorthy T, Lee CT, Lim KB. Epidemiology of infectious syphilis in Singapore. *Genitourin Med* 1986; **62**: 75–7.
12 Lingolf T. Rapid increase of syphilis and gonorrhea in parts of the former USSR. *Sex Transm Dis* 1995; **22**: 160–1.
13 Rubins A, Rubins S, Jakabsone I. Syphilis and gonorrhea in the Baltic countries. *Sex Transm Infect* 2000; **76**: 214.
14 Bernstein KT, Tulloch R, Montes J *et al*. Outbreak of syphilis among men who have sex with men—Southern California, 2000. *MMWR Morb Mortal Wkly Rep* 2001; **50**: 117–20.
15 Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance 2004 Supplement, Syphilis Surveillance Report*. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, December 2005.
16 Doherty L, Fenton K, O'Flanagan D, Courtier E. Evidence for Increased Transmission of Syphilis Among Homosexual Men and Heterosexual Men and Women in Europe. *Eurosurveillance Weekly*, 2000. www.eurosurv.org/2000/001214.htm
17 Heffelfinger JD, Swint EB, Berman SM, Weinstock HS. Trends in primary and secondary syphilis among men who have sex with men in the United States. *Am J Public Health* 2007; **97**: 1076–83.
18 Simms I, Fenton K, Ashton M *et al*. The re-emergence of syphilis in the United Kingdom: the new epidemic phases. *Sex Transm Dis* 2005; **32**: 220–6.
19 Dougan S, Evans BG, Elford J. Sexually transmitted infections in Western Europe among HIV-positive men who have sex with men. *Sex Transm Dis* 2007; **34**: 783–90.

Causative organism

The causative spirochaete of syphilis, *Treponema pallidum* subsp. *pallidum*, was discovered by Schaudinn and Hoffmann in 1905 and originally was called *Spirochaeta pallidum*.

T. pallidum cannot be grown in the laboratory on any biochemical medium. Not all animals are susceptible to it. The rabbit is commonly used in laboratory studies and as a source of *T. pallidum* used in diagnostic tests. *T. pallidum* cannot be differentiated from those treponemes involved in other forms of treponematosis, nor from Nichol's strain, which was isolated in 1912 from the brain of a patient and kept alive by passage through many generations of rabbits. Another experimental treponeme, the Reiter strain, is said to have been isolated in 1922. In contrast with the Nichol's strain, it is avirulent and can be cultivated on a relatively simple medium. Freeze-dried extracts were used for many years in the Reiter protein complement fixation test.

Morphology. In daily practice, it is demonstrated by dark-field microscopy. It appears as a pale, white, fine, corkscrew organism with close and very regular coils (Fig. 34.5). Its length varies from 6 to 15 µm and its coils from 0.09 to 0.18 µm. There are between eight and 20 coils. As a practical guide, to help differentiate the organism from others like it, there are about seven to eight coils per diameter of a red blood corpuscle. It contains a periplasmic flagellum and is actively motile. The movements of the *T. pallidum* are pathognomonic. It rotates around its long axis and thus appears to quiver and screw slowly backwards and forwards; it shows a highly typical angling movement, forming both acute and obtuse angles. It shows both grace and elegance and these help to distinguish it from other genital or oral spirochaetal organisms.

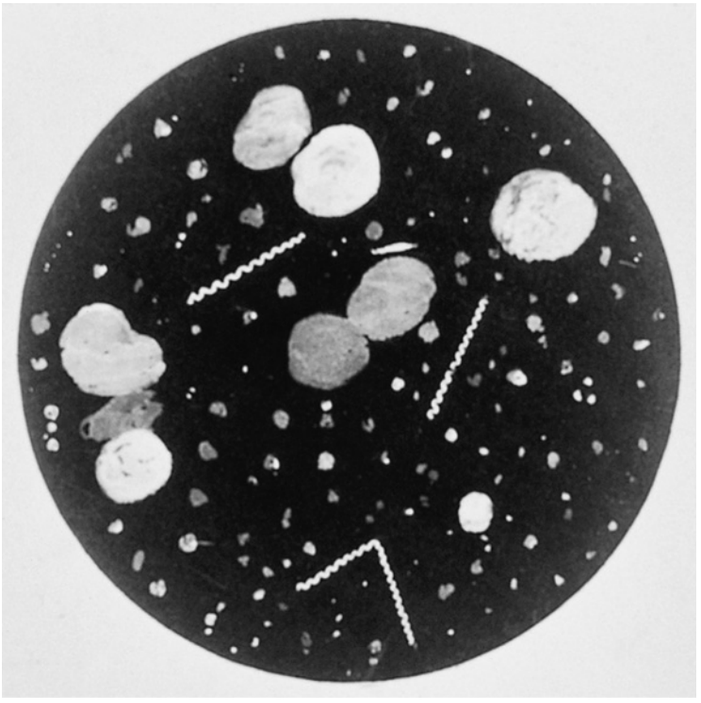


Fig. 34.5 *Treponema pallidum* showing regular spirals and marked angling.

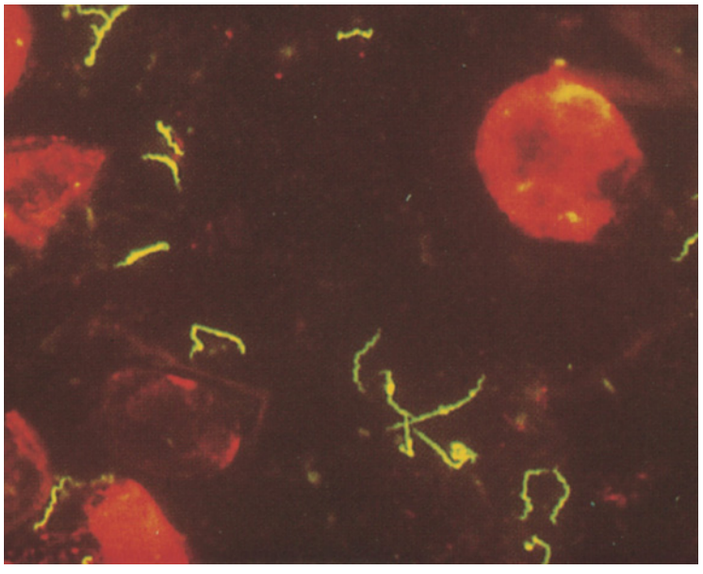


Fig. 34.6 Fluorescein-stained treponemes.

Treponemes can also be demonstrated by the direct fluorescent-antibody method [1,2], and by rapid immunofluorescent staining (RIS) of smears from lesions [3] (Fig. 34.6).

Of the several spirochaetes found in the genital area and requiring differentiation from *T. pallidum*, the most important are *Borrelia refringens* and *B. balanitidis*. Both are thicker than *T. pallidum* and have fewer and irregular coils. In addition, they move with more fidgety, snake and eel-like movements. *B. gracilis* is finer than *T. pallidum*, with closer coils and a lack of typical movements. It can be found at the gum margins between teeth.

Microbiology. The organism is microaerophilic and has evolved to become a highly invasive and persistent pathogen with little toxigenic activity and an inability to survive outside the mammalian host. It has extreme nutritional requirements due to deficiencies in biosynthetic pathways, and has a narrow equilibrium between oxygen dependence and toxicity. It cannot be cultured on artificial media but it can be propagated in organ culture, such as rabbit testis. It has a slow growth rate, optimal at 33–35°C, with a doubling time of 30–36 h. The organism is similar to, and shares extensive DNA homology with, three other pathogenic treponemes, which cause yaws, bejel and pinta.

Analysis of the genome, which is contained on a single circular chromosome with 1 138 006 base pairs, shows that the organism lacks lipopolysaccharide and lipid biosynthesis mechanisms, as well as many metabolic pathways, including for the tricarboxylic acid cycle, components of oxidative phosphorylation, and for most amino acids and vitamins. It requires D-glucose, maltose and mannose but cannot utilize other sugars [4]. It is able to use exogenously supplied amino acids and is dependent upon serum components such as fatty acids.

Treponema pallidum initiates an inflammatory response at the site of inoculation and is disseminated during the primary infection. The organism has a surface-associated hyaluronidase enzyme, which may play a role in this process. Phagocytosis by cytokine-activated macrophages, as part of a predominant T-helper (Th1)-type early response, aids bacterial clearance and resolution of the primary lesion [5]. Virulent organisms promote adhesion of lymphocytes and monocytes to human vascular cells, and this is important in immunopathogenesis [6]. As with other organisms that cause chronic disease, *T. pallidum* has evolved mechanisms for evading immune responses. A Th1–Th2 switch occurs with macrophage suppression caused by prostaglandin E2 down-regulation; however, the molecular mechanisms remain poorly understood [7]. Depressed cell-mediated responses occur during the later stages of syphilis, and a lowered $CD4^+$ lymphocyte count has been reported [8].

Pathogenesis. Relatively few genes are involved in pathogenesis. It has been postulated that the immunoevasiveness of *T. pallidum* is the result of the organism's unusual molecular architecture. The outer membrane lacks lipopolysaccharide and contains few, poorly immunogenic transmembrane proteins; the highly immunogenic proteins are lipoproteins anchored predominantly to the periplasmic leaflet of the cytoplasmic membrane [9]. The *T. pallidum* repeat protein genes (TPR) occupy 2% of the genome and encode for a group of potential virulence factors, which are targets for strong cellular and humoral responses. The TPR-K proteins demonstrate marked antigenic variation [10].

The dominant immunogen is a 47-kDa membrane lipoprotein, which can induce synthesis of tumour necrosis factor-α. Immunoblotting has also shown IgG responses to an antigen of 65 kDa that is shared with non-pathogenic treponemes, and antigens of 44.5, 17 and 15.5 kDa that are specific for *T. pallidum*.

Natural history

Stages. The clinical presentation of syphilis is extremely diverse and may occur decades after initial infection. Syphilis, if untreated, may pass through four stages: primary, secondary, latent and late. The first two stages are contagious. They seldom last more than 2 years and do not exceed 4 years. Latency may last from 5 to 50 years. Only 25–30% of patients present with late, chronic, crippling or killing manifestations. The frequency of these late manifestations continues to decline, and in many countries they are now rare.

Incubation period. The incubation period of syphilis is generally given as 9–90 days, and varies inversely with the size of the spirochaete inoculum. Typically, most genital primary sores appear 3 weeks after exposure. Enlarged glands appear in one groin after a further week and can usually be detected in both groins 5 weeks after infection. Reactive reaginic serological tests are detectable at 5.5–6 weeks, the macular rash at 8 weeks, papular lesions at 3 months and condylomas at 6 months.

Course of untreated syphilis. Several investigations have helped to elucidate the natural history of untreated syphilis, for example the Oslo study of untreated syphilis [11] and the Tuskegee study [12]. Regarding the first of these, Caesar Boeck believed that *no* treatment was better than using mercury. He therefore kept some 2000 infectious syphilitics in hospital for 1–12 months (average 3–6 months), that is until all traces of their infection had gone. Gjestland [11] made a follow-up study of 1147 and summarized the findings as follows:

- 24% developed mucocutaneous relapses
- 11% died of syphilis
- 16% developed benign late manifestations, usually cutaneous nodules or gummata
- 10% developed cardiovascular syphilitic lesions
- 6% developed neurosyphilis.

It would appear therefore that long before the arsenicals and penicillin were introduced, at least 60% of people with syphilis lived and died without developing serious symptoms of their infections.

Histopathology

The fundamental pathological changes in syphilis are the same in early and late disease. They occur in and around blood vessels in the form of a perivascular infiltration of lymphocytes and plasma cells, accompanied by intimal proliferation in both arteries and veins (endarteritis obliterans).

In early lesions, perivascular infiltration by lymphocytes and plasma cells is accompanied by intimal proliferation in arteries and veins. This leads to ischaemia and ulceration. Organisms are most numerous in the walls of capillaries and lymphatic vessels. They can be demonstrated by Levaditi's silver stain or by the fluorescent antibody technique [13]. The papular skin lesions of secondary syphilis also show endothelial swelling in dermal vessels.

In late lesions, the characteristic lesion of mucocutanous surfaces is the syphilitic gumma. Granulation tissue forms with histiocytes, fibroblasts and epithelioid cells. Endarteritis obliterans and necrotic areas are pronounced. Gummata most often originate in subcutaneous tissues and spread in all directions. Spirochaetes are not readily demonstrable in these lesions.

Heubner's arteritis occurs in cardiovascular and meningovascular syphilis. It is characterized by lymphocytic and plasma cell infiltration of the vasa vasorum and adventitia of large and medium-sized vessels. Occlusion of the vasa vasorum results in medial necrosis and fibroblast proliferation. There is associated subintimal proliferation, which leads to luminal occlusion and thrombosis.

Some manifestations of syphilis (e.g. neuropathy) are immune-complex mediated.

Transmission. Transmission occurs almost exclusively during sexual intercourse, including by oro-genital contact [14]. *T. pallidum* is very sensitive to drying and heat, and also to soap and weak disinfectants. It can probably penetrate intact skin and mucous membrane but more readily enters the body through microscopic or visible breaks in the epidermis. Treponemataemia is established even before the appearance of the primary lesion. Syphilis therefore can be transmitted by blood transfusion. In deep inoculation, as by accidental puncture with a needle or in transfusion, no primary lesion appears. This is called syphilis d'emblee.

Congenital syphilis is acquired by placental transmission of infection from the mother. The longer the mother has had syphilis, the less likely she is to transmit it.

References

1 Edwards EA. Detecting *Treponema pallidum* in primary lesions by the fluorescent antibody technique. *Public Health Rep* 1962; **77**: 427–43.

2 Jue R, Puffer J, Wood RM *et al*. Comparison of the fluorescent and conventional darkfield methods for the detection of *Treponema pallidum* in syphilitic lesions. *Am J Clin Pathol* 1967; **47**: 809–11.

3 Kellogg OS, Deacon WE. A new rapid immunofluorescent staining technique for identification of *Treponema pallidum* and *Neisseria gonorrhoeae*. *Proc Soc Exp Biol Med* 1964; **115**: 963–5.

4 Norris SJ, Cox DL, Weinstock GM. Biology of *Treponema pallidum*: correlation of functional activities with genome sequence data. *J Mol Microbiol Biotechnol* 2001; **3**: 37–62.

5 Van Voorhis WC, Barrett LK, Koelle DM *et al*. Primary and secondary syphilis lesions contain mRNA for Th1 cytokines. *J Infect Dis* 1996; **173**: 491–5.

6 Riley BS, Oppenheimer-Marks N, Radolf JD, Norgard MV. Virulent *Treponema pallidum* promotes adhesion of leukocytes to human vascular endothelial cells. *Infect Immun* 1994; **62**: 4622–5.

7 Fitzgerald TJ. The Th1/Th2-like switch in syphilitic infection: is it detrimental? *Infect Immun* 1992; **60**: 3475–9.

8 Pope V, Larsen SA, Rice RJ *et al*. Flow cytometric analysis of peripheral blood lymphocyte immunophenotypes in persons infected with *Treponema pallidum*. *Clin Diagn Lab Immunol* 1994; **1**: 121–4.

9 LaFond RE, Molini BJ, Van Voorhis WC, Lukehart SA. Antigenic variation of TprK V regions abrogates specific antibody binding in syphilis. *Infect Immun* 2006; **74**: 6244–51.

10 Radolf JD. *Treponema pallidum* and the quest for outer membrane proteins. *Mol Microbiol* 1995; **16**: 1067–73.

11 Gjestland T. The Oslo study of untreated syphilis. *Acta Derm Venereol (Stockh)* 1955; **35** (Suppl. 34): 3–368.

12 Talbot MD, Morton RS. The Tuskegee study of untreated syphilis. *Eur J STD* 1984; **1**: 125–32.

13 Yobs AR, Brown L, Hunter EF. Fluorescent antibody technique in early syphilis. *Arch Pathol* 1964; **77**: 220–9.

14 Edwards S, Carne C. Oral sex and the transmission of non-viral STIs. *Sex Transm Infect* 1998; **74**: 95–100.



Fig. 34.7 Small but well-circumscribed primary syphilis. (All sores in the coronal sulcus are indurated.) Serology was negative.



Fig. 34.8 Primary syphilis: meatal chancre.

Acquired syphilis

Primary syphilis (Figs 34.7–34.11)

The primary chancre appears at the site of initial treponemal invasion of the dermis. Initial lesions are papular but rapidly ulcerate. It may occur on any skin or mucous membrane surface and is usually situated on the external genitalia.

The typical primary sore appears as a regularly edged, regularly based, hard and button-like ulceration measuring up to 1 cm in diameter. Unless secondarily infected, primary sores are not painful. The ulcer is often surrounded by a narrow, red border,



Fig. 34.9 Healing primary chancre of 3 weeks' duration. It was accompanied by bilateral adenitis. Dark-field and serological tests were positive.



Fig. 34.10 Slightly indurated primary chancre of 2 days' duration. It was neither painful nor tender. It points to the need for a high index of suspicion concerning all genital lesions. Dark-field microscopy prevents diagnostic error and embarrassment.



Fig. 34.11 Extragenital chancre of the lip. (Courtesy of Dr P. Taylor, Bristol Royal Infirmary, Bristol, UK.)

1–2 mm wide. This marks the limits of the inflammatory reaction and is most productive of *T. pallidum*. The lesion may be crusted due to drying of serous exudate. The induration of the ulcer is probably the best-known characteristic, but it should be remembered that all lesions in the coronal sulcus of the penis are indurated. 'Kissing' ulcers, sometimes hourglass in shape, are not uncommon. About 50% of lesions are atypical and lack one or more of the classical features. If the infection is inoculated into pre-existing lesions such as anal fissure, genital herpes or balanitis, the chancre may assume the shape of these conditions. In most cases, there is only a single chancre. Multiple chancres may appear simultaneously or within a few days of each other. Without treatment, the chancre persists for a period that can vary considerably, but seldom, if ever, exceeds 3 months. As a rule, it heals spontaneously in 3–8 weeks. In about one-third of cases, it leaves a regularly edged, slightly depressed, thin, depigmented, atrophic scar.

The appearance of the genital and perianal chancre is followed by swelling of the inguinal lymph nodes, initially unilateral. Maxillary and submental lymph nodes enlarge when infection is in or around the oral cavity. Wherever they appear, the enlarged glands are discrete, rubbery and free from fixation to skin or underlying tissues.

Sites. In men, the chancre most usually occurs on the glans penis, near the frenum or on the underside of the prepuce. Less commonly, the primary lesion appears on the shaft of the penis. If near the hilt, it may be called a 'condom chancre'. Less common sites are the pubic region or the external urinary meatus where it may masquerade as non-specific urethritis with scanty serous discharge. Lesions are often surrounded by oedema. Subprepucial lesions may be accompanied by some degree of acquired phimosis and in such cases lymphangitis dorsalis penis may occur; it is felt as an indolent 'string', some 2 mm in diameter.

In homosexually acquired syphilis, the anus and rectum may be sites of primary infection. Anal lesions may present as an indurated fissure. Pain may be a feature, as may itch and bleeding, especially after defecation. Like genital primary lesions, extragenital sores are accompanied by regional adenitis.

In women, most cases of early syphilis have reached the secondary stage when diagnosed [1]. A chancre is less frequently demonstrated, partly because the primary lesion may be on or in the cervix. The most common sites for a vulvar chancre are the labia minora or majora, around the urethral orifice, on the clitoris or, quite commonly, on the posterior commissure where it may masquerade as an indurated irregular fissure. Surrounding vulval oedema is common. A chancre very rarely occurs on the vaginal wall.

Extragenital chancres may be found on the lips as a result of kissing, cunnilingus or fellatio (Fig. 34.11). The indurated ulcer may be surrounded by oedema. Chancres of tongue and tonsil and primary lesions of the fingers, acquired occupationally or in sexual foreplay, also occur. Other extragenital chancres may follow from nibbling or biting the nipple, the ear, neck or arm.

Differential diagnosis. A wide variety of diseases can affect the genitals and must be considered. Genital herpes and balanoposthitis have typical clinical features, although they may occur with a chancre. Secondarily infected traumatic sores may look like chancres. Chancroid should be considered, and not only in subtropical areas of the world. Sporadic epidemic outbreaks of clinically modified chancroid have been reported in the UK, Canada and Kenya. Improved techniques for culture of *Haemophilus ducreyi* have been widely sought in several countries. The organism appears to be more common as a secondary invader than previously believed. Carrier states in both men and women are described. In general, the lesions described are rarely of the destructive and painful type previously believed to be classical [2].

In lymphogranuloma venereum, 'inflammatory bubo' may resemble the unilateral and bilateral adenitis of early syphilis. Unlike syphilis, the glands are usually matted, adherent to the inflamed skin and show a tendency to central fluctuation.

Excoriated secondary syphilitic papules in women can be confused with multiple small chancres. *Chancre redux* is a recurrence of the primary sore at its original site [3]. Tertiary syphilis, tuberculous ulceration, cancer or pre-cancerous dermatoses such as erythroplasia of Queyrat and Bowen's disease, can occasionally cause difficulty. The papules of scabies on the glans or on the shaft of the penis may arouse strong suspicions. Any lesion at the site of a healed primary has been labelled pseudochancre redux [3,4].

On the cervix, a chancre may easily be taken for an 'erosion' or a cancer [5], especially when suspected syphilis is not the reason for examination.

With a chancre on the lip, the most important differential diagnosis is facial herpes simplex. Apart from the appearance, the recurrent nature of herpes is helpful. Secondarily infected traumatic lesions with oedema may closely resemble a chancre, as may cancer of the lip. Traumatic ulcers of the tongue can sometimes be infiltrated. Behçet's syndrome with both oral and vulvar lesions may present a problem. Tonsillar chancres may be mistaken for tonsillitis, glandular fever or Vincent's angina. When the accompanying angular or submental adenopathy is painless, syphilis should be seriously considered.

A long-standing whitlow or paronychia ought to lead to examination for both herpesvirus and *T. pallidum*. Where epitrochlear or axillary adenitis is painless, serological tests for syphilis are indicated.



Fig. 34.12 Secondary syphilis. Like the macular rashes of other infections, it is not associated with the presence locally of the causative organism. It also appears at a recognized time after exposure; in this infection, 8 weeks after exposure. It is most readily seen, following the lines of cleavage of the skin of the trunk, in daylight.



Fig. 34.13 Papulosquamous secondary syphilis involving the palm. (Courtesy of Dr P. Taylor, Bristol Royal Infirmary, Bristol, UK.)

In 'modern' societies, all oral and rectal lesions should give rise to suspicion of possible syphilis. Anal fissures and anal warts, 'haemorrhoids', anal discharge and irritation or a finding of some form of sexually transmitted proctitis, for example due to gonorrhoea, herpesvirus or *Chlamydia trachomatis*, should alert the physician to the possibility of concomitant syphilis. In the rectum, a chancre may be mistaken for a cancer.

Secondary syphilis (Figs 34.12–34.23)

Secondary syphilis is the stage when generalized manifestations occur on the skin and mucous membranes. Serological tests are always positive in immunocompetent persons. Rashes in secondary syphilis have three common features:

1 they do not itch
2 they are coppery red
3 the lesions are symmetrically distributed.

The manifestations of generalized treponemal dissemination first appear at around 8 weeks. Constitutional symptoms consist of fever, headache, and bone and joint pains that are more pronounced at night. There is wide diversity in physical features.

Rashes are the commonest feature. They are initially macular and become papular by 3 months.



Fig. 34.14 Typical coppery red papules in secondary syphilis.

Macular syphilide (roseolar rash). This is the earliest generalized syphilide. It appears as symmetrical, coppery red, round and oval spots of no substance. On the back, the lesions clearly follow the lines of cleavage of the skin. The patients should be examined in daylight, as it is easy to overlook an early or fading rash. The roseolar spots do not scale or itch and, being in some patients sparse and evanescent, may pass unnoticed. Roseola is easily overlooked and seldom diagnosed in patients with deeply pigmented skin. When a roseola is fading, it sometimes leaves a



(a)



(b)

Fig. 34.15 (a) Symmetrically distributed, coppery red and non-itchy rash typical of secondary syphilis. The only suggestion of syphilis in the partner was a history of laryngitis 5 months earlier. Her serological tests were strongly positive. (b) Plantar rash of secondary syphilis.



Fig. 34.16 Secondary syphilis imitating seborrhoeic dermatitis. Note the coppery red corona veneris.



Fig. 34.17 Secondary syphilis presenting as 'split' papules at the angles of the mouth.

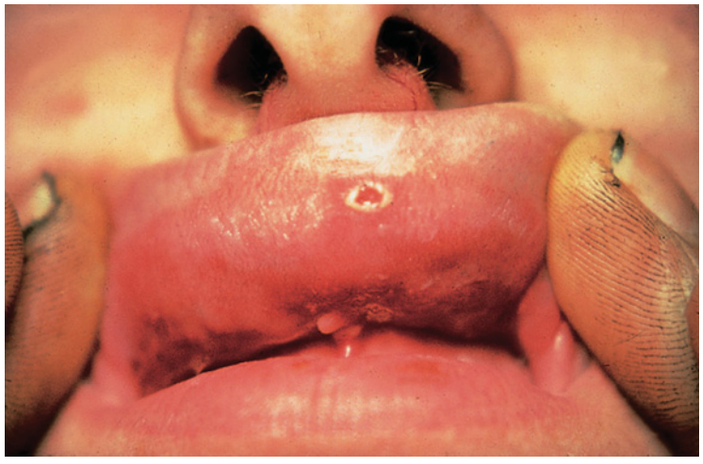


Fig. 34.18 Secondary syphilis. This eroded papule was the only lesion. Similar solitary lesions, demonstrating *Treponema pallidum*, are occasionally found just inside the anus in asymptomatic contacts.



Fig. 34.19 Papules. These were the only evidence of reinfection in the regular consort of a pregnant woman referred from an antenatal clinic with strongly positive serological tests for syphilis. She was an undeclared, regular consort when the man was originally treated for primary syphilis, 18 months earlier.



Fig. 34.20 Psoriasiform papules in secondary syphilis. Such lesions, sometimes shiny when squames are shed, of palms and soles are most commonly found in people of African origin.



Fig. 34.21 Mucous patches around vaginal introitus.

pattern of depigmented spots on a hyperpigmented background. Such a *leukoderma syphiliticum* is most commonly located on the back or sides of the neck and was formerly known as 'the necklace of Venus'.

Papular syphilide. The papule is the basic lesion of secondary syphilis. Individual papules seldom exceed 0.5 cm in diameter. Its



Fig. 34.22 Here the lesions are more exuberant. The sodden surface epithelium has been shed to reveal lesions describable as 'moist papules'.



Fig. 34.23 When large opposing papules coalesce, as in the perianal region, the surface epithelium becomes sodden. Such lesions are called condylomata lata. *Treponema pallidum* organisms abound in them. They rarely appear in infections of less than 6 months' duration.

particular form of presentation can vary widely depending on the nature and colour of the patient's skin, the site affected and the climate, hygiene and clothing. Papular rashes may recur and be punctuated by spells of apparent latency. More usually, early papular rashes are in fact maculopapular and they have an even and generalized distribution all over the body. However, a purely coppery red papular rash, widely and symmetrically distributed, may also be seen.

The typical papule is firm and round, although the largest may be oval. Early papules tend to be shiny, but gradually a thin layer of scale forms and is quickly shed. This is the typical papulosquamous syphilide. Older lesions tend to be more pigmented. In the late phases of a papular syphilide, nummular lesions, 1–3 cm in diameter and covered by massive layers of scales, may closely resemble psoriasis. Because the underlying lesions are exuding serum, the scales are easily removed. Psoriasiform papules of the palms and soles are especially common in black people as are annular and circinate papular rashes. Such rashes may resemble granuloma annulare, annular sarcoid or scaly varieties of tinea.

On macerated skin surfaces and mucous membranes, eroded weeping papules with a tendency to hypertrophy often appear. On the genitals, for example, at the penoscrotal junction, there may be small eroded papules flush with the skin or hypertrophic, coalesced papules (condylomata lata). Such lesions more commonly occur around the anus and the vulva. In men, the papules frequently occupy the entire surface of the glans penis, the coronal sulcus and the inner aspect of the prepuce. Partial or complete acquired phimosis is not infrequent in such cases. The free margin of the prepuce may be a circle of tender, fissured ('split') papules. In women, in the axillae and beneath the breasts, small, superficial, eroded, lentil-sized (about 0.3 cm) papules are sometimes seen, but more typical are hypertrophic papules, which may affect the adjacent mucous membrane. In the last stages of pregnancy, hypertrophic, coalesced, sodden-surfaced papules may be very pronounced. Later, the papules are more irregularly distributed but show a predilection for certain sites, such as the corners of the mouth, angles of the nose, the palms and soles and body folds such as beneath the breasts or in the axillae. The face is often affected, particularly if the patient has greasy skin. The seborrhoeic areas involved are the same as those involved in acne vulgaris and seborrhoeic dermatitis. Sometimes, the papules form a line along the hair margin, the *corona veneris*.

Hyperkeratotic lesions of the palms and soles may flake, peel and fissure. Hypertrophic papules between the toes may resemble severe tinea pedis.

Micropapular and miliary eruptions are especially seen late in the second stage, that is about a year or more after infection. Characteristics of such a lichenoid syphilide include small conical or spinular elements, which tend to be arranged in groups of varying size over the body. A *corymbose syphilide* is one with a large central papule surrounded by small satellite papules.

Pustular ulcerative syphilide, which characterized the 16th-century epidemic, is now all but unknown. Lesions that most nearly resemble this nowadays are the crusted papule of the scalp where brushing and combing tears papules, which ooze serum and which may become secondarily infected. Such lesions, unlike other syphilides, may leave scars. Atypical facial plaques or ulcerated nodules (lues maligna) are more common with co-existing HIV infection [6].

Syphilitic alopecia. Patchy hair loss is characteristic of syphilis. The hair falls leaving small, scattered, irregularly thinned, 'moth-eaten' patches of semi-baldness. The eyebrows and beard may be affected [7,8]. Syphilitic alopecia may be accompanied by a more generalized, diffuse alopecia associated with generalized infection and anaemia.

Nails. Syphilitic paronychia with secondary onychia is sometimes seen in the secondary stage. It has no special characteristics.

Lesions of the mucous membranes. On the mucous membranes, the basic papular eruptions are less distinctive, but they tend to be symmetrically distributed (Fig. 34.21). As the surface epithelium dies, it turns grey and forms round or oval mucous patches on the palate or inner aspects of the lips and cheeks. These mucous patches may coalesce to form 'snail-track' ulcers. Ulceration is not common. Sharply defined, round or oval lesions devoid of dead epithelium may appear on the tongue and may be associated with flattened papillae. Bilateral syphilitic tonsillitis may coexist, as may syphilitic laryngitis associated with eroded papules and hoarseness.

Generalized lymphadenopathy. Occurs in 50% of secondary syphilis cases. As in the localized lymphadenopathy of primary infection, the nodes are painless, discrete, mobile, rubbery and vary in size from about 0.5 to 2 cm.

Neurological involvement. During the secondary stage, the central nervous system may be invaded. Abnormalities in the CSF, such as raised cell count and increased protein, can be found in at least 15% of cases [5]. Less often, serological tests are positive in the CSF. The patient may complain of headache only. Occasionally, meningitis may present as paralysis of one or more cranial nerves. Meningomyelitis with paraplegia and double incontinence is rare.

Other systemic features of secondary syphilis include panuveitis [9], periostitis and joint effusions, glomerulonephritis, hepatitis, gastritis and myocarditis.

The lesions of secondary syphilis resolve spontaneously in a variable time period and most patients enter the latency stage within the first year of infection. In some, especially the immunocompromised, primary or secondary lesions may recur.

Differential diagnosis. The skin manifestations of secondary syphilis are so variable that it must be considered in the diagnosis of all dermatoses that are in any way atypical. Some of these dermatoses have already been mentioned.

With the macular rash, drug eruptions must first be considered. The history, itching and lack of adenopathy aid differentiation. Measles and rubella may cause difficulty, but it is pityriasis rosea that is most often called into question. The presence of a herald patch and the collarette of scales distinguish this condition from macular syphilis.

With papular eruptions, many diseases can cause difficulty in diagnosis, and it has to be remembered that people with seborrhoeic dermatitis or psoriasis can also have syphilis. Lichen planus with its shiny, angled, violaceous lesions, should seldom cause difficulty. Acne vulgaris and seborrhoeic dermatitis may confuse the unwary, as may impetigo and occasionally leprosy or tuberculosis if the face is affected. In the anogenital region, condylomata lata have been diagnosed as haemorrhoids and as condylomata acuminata. Balanitis circinata, hyperkeratotic lesions of Reiter's disease and genital herpes may also lead to misdiagnosis.

The micropapular varieties of syphilis can be confused with keratosis pilaris, lichen scrofulosorum, trichophytide and lichen planopilaris. Eruptions of palms and soles may bear a striking resemblance to psoriasis and scaling mycoses.

With oral lesions, the question of aphthae has first to be considered. The painful nature of the lesions contrasts with syphilis and the aphthous lesions are markedly areolated [10]. Tonsillitis or tonsillar papules with lymphadenopathy may make differential diagnosis from infectious mononucleosis a difficult clinical problem. An accompanying morbilliform rash, perhaps precipitated by administration of ampicillin, may add to the confusion, especially as the condition is sometimes accompanied by false-positive serological tests for syphilis.

Latent syphilis

In latent syphilis there are no clinical stigmata of active disease, although disease remains detectable by positive serological tests. In early latency, within 2 years of infection, vertical transmission of infection may still occur, but sexual transmission is less likely in the absence of mucocutaneous lesions. The late manifestations of syphilis subsequently arise, often decades later, in about 25% of those who have latent syphilis.

To establish a diagnosis of latent syphilis, strict criteria are called for. Clinical evidence of active, early, late or congenital syphilis must be absent; the CSF must be normal and a chest X-ray (preferably postero-anterior and left oblique, to view the aorta at a right angle) must also be normal. Positive (reactive) serological tests for syphilis must be confirmed by examination of a second specimen.

The differential diagnosis may be from biological false-positive reactions or from other treponematoses, particularly yaws in immigrants to Westernized countries. The presence of a scar of a primary chancre or leukoderma syphiliticum at the back of the neck may be helpful. Yaws is usually acquired by children living in poor rural conditions in the tropics. Presenting in adulthood with positive serological tests for syphilis, they may give a history of yaws or chronic sores or bone pains, or they may know of the disease in their family, school or parish. Some have clinical or radiological evidence of old periostitis in their long bones [11]. Much the same may apply to bejel [12].

Great care is called for in assessing immigrant patients. For example, in the UK, one would hesitate to diagnose old yaws in a West Indian immigrant under the age of 40 years. The World Health Organization declared Jamaica free of yaws in 1950, and it has remained free of the disease. On the other hand, yaws has been recrudescing in West African countries for more than 20 years, and the differentiation of latent syphilis from old yaws in immigrants from that part of the world may now present problems.



Fig. 34.24 Late syphilis. Coalescing, circinate papular lesions. Note the typical coppery red colour. *Treponema pallidum* organisms are not found in such lesions. The clinical diagnosis is confirmed serologically.

Tertiary syphilis

After a period of latency of up to 20 years, manifestations of late syphilis can occur. However, screening for syphilis in blood donors and pregnant women has contributed greatly to the prevention of late syphilis. In addition, since the commencement of the antibiotic era, many latent and asymptomatic late syphilitics have happened to receive penicillin or other treponemicidal antibiotics in circumstances unconnected with syphilis ('happenstance antibiotic therapy'). Such inadvertent therapy has also contributed to the decline of late syphilis, so that it is becoming rare in many parts of the Western world including the UK and the USA.

Late skin syphilis appears in two types: the superficial or nodular syphilide and a deeper gummatous syphilide. Transitional forms also occur.

Nodular or tubercular syphilide (Figs 34.24 & 34.25). The lesions are protruding, firm, coppery red nodules (larger than 0.5 cm diameter). On dependent limbs, they may be cyanotic. The nodules appear in groups with a tendency to a circinate arrangement, that is forming interwoven circles and part of circles. As the disease heals centrally, it extends peripherally. The spread does not take place equally in all directions, so that the outline may be horseshoe shaped, tongued, kidney shaped or serpiginous. Some nodular eruptions resemble granuloma annulare or annular forms of sarcoid. Their histology resembles secondary syphilis. In other cases, the abundance of waxy scales gives the eruption a psoriasiform appearance. Most frequently, serpiginous nodulo-ulcerative eruptions are covered by massive crusts. Even the smallest ulcers have a punched-out appearance.

Lesions of nodular syphilis can appear anywhere on the body, but favour the extensor surfaces of the arms, the back and the face. They are symptomless. Where they have spread extensively, smooth, soft, finely wrinkled ('cigarette paper') central scarring is a feature. In their early stages, these scars may be pink, but after



Fig. 34.25 Late syphilis. Nodulocutaneous syphilide in a 62-year-old woman with positive serology. The lesions healed completely within 3 weeks of starting treatment with penicillin.



Fig. 34.26 A gumma is a syphilitic swelling with a tendency to ulcerate. The ulcers tend to be 'punched out' in the case of skin gummata.



Fig. 34.27 Healing gumma. Delay in diagnosis is suggested by widespread pigmentation and scarring. Response to treatment was slow and the final scarring led to permanent oedema of the foot, sometimes called 'paradoxical healing'.

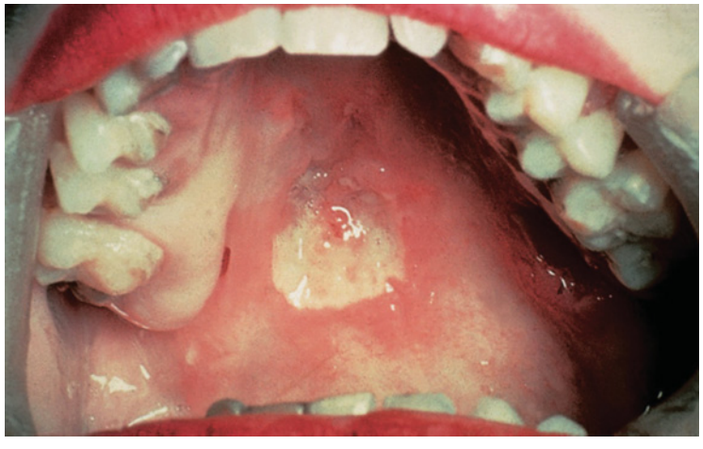


Fig. 34.28 Gumma of the palate. This is a favoured site for such lesions in both acquired and congenital syphilis.

a year or two they are white. Nodular syphilis spreads slowly but more rapidly than lupus, producing a lesion of similar size in months rather than years.

Gumma (Figs 34.26–34.28). The characteristic lesions of tertiary syphilis appear 3–10 years after infection and consist of granulomas or gummata. The granulomas appear as cutaneous plaques or nodules of irregular shape and outline and are often single lesions on the arms, back and face. They have a tendency for central necrosis and ulceration and for peripheral healing with tissue-paper scarring. They most often originate in the subcutis, growing in all directions, that is into the dermis and epidermis as well as the deeper tissues. Gummata which start in bone or muscle also tend to ulcerate the skin, and their true origin may be difficult to determine. Gummatous changes sometimes take place more superficially with scattered, small ulcerations along the margins. This form is difficult to differentiate from a nodular syphilide.

Gummata are usually painless even when they ulcerate. Their central necrotic tissue may turn into a slimy, stringy mass, and it is this that gives rise to the name 'gumma'. Multiple gummata tend to coalesce, the bridges of skin between them gradually undergoing necrosis. Such ulcerations offer a wide variety of scalloped and geometrical patterns. A 'punched out' appearance is characteristic.

Gummata vary in size from 2 to 10 cm. They favour the scalp, face, sternoclavicular areas of the chest and lateral calf.

Late mucous membrane lesions. Gummata not infrequently attack the palate, both the hard and the soft, with tissue destruction that may lead to loss of the uvula and scarring or perforation of the hard palate. In cases of congenital syphilis, destruction of the nasal septum may also occur, producing saddle-nose deformity. They may also cause painless testicular swelling, mimicking a tumour; portal hypertension and portosystemic anastomoses; and diffuse interstitial glossitis. Late syphilis of the tongue may present with localized or diffuse changes, that is the solitary gumma or diffuse gummatous infiltration. The latter often passes through a stage of chronic interstitial glossitis with fissuring and, later, obvious leukoplakia with patchy necrosis, sometimes associated with trauma from the teeth. In other cases, changes are more superficial, with red, smooth, glazed areas and loss of papillae. Although sometimes painless, these changes may be accompanied by discomfort on eating hot or acid foods. All the forms of tongue involvement described are recognized as precancerous, so that even after adequate antisyphilitic treatment, regular observation of the patient is an essential element of sound management.

Differential diagnosis. Skin reactions to bromides and iodides commonly deceived the physician in the past. On the face, lupus vulgaris, epithelioma and Bowen's disease can cause diagnostic difficulties. Midline granuloma, sycosis barbae, infiltrated forms of rosacea and lupus erythematosus have all been confused with late syphilis. On the trunk and limbs, it can resemble circinate psoriasis, leukaemic infiltrations and mycosis fungoides. On the legs, gummatous ulceration can look very like a venous ulcer. Bazin's disease may also be simulated.

The changes in the tongue should not be confused with the congenital deformity of scrotal tongue, when the tongue remains quite soft. Where leukoplakia is associated with interstitial glossitis, or fibrotic nodules, biopsy is necessary to exclude carcinoma.

The serious forms of neurosyphilis such as tabes dorsalis and general paralysis, and cardiovascular syphilis, although detectable earlier, may take 20 or more years to become clinically evident.

Cardiovascular syphilis

The typical lesion of cardiovascular syphilis is aortitis affecting the ascending aorta and appearing 10–30 years after infection. The aortitis may be asymptomatic and detected as dilatation of the ascending aorta on chest X-ray, often accompanied by linear calcification of the aortic wall, or it may lead to stretching and incompetence of the aortic valve, left ventricular failure, or aneurysm formation. Aneurysms may be associated with a variety of syndromes caused by pressure on adjacent structures in the mediastinum, and they may cause sudden death from rupture. Other symptoms include angina pectoris from associated coronary ostial stenosis. Cardiovascular syphilis is more commonly associated with neurosyphilis than with gummatous disease.

Neurosyphilis

Neurosyphilis is characterized by a number of heterogeneous syndromes [13,14]. The differential diagnosis of neurosyphilis covers the whole spectrum of neurological and psychiatric conditions. The onset can occur weeks or decades after treponemal dissemination.

Asymptomatic neurosyphilis precedes the development of clinically apparent disease and accounts for one-third of all neurosyphilis. It occurs in 10% of those with latent disease and has a peak incidence at 12–18 months after infection. It reverts spontaneously in 70% of patients.

Meningeal neurosyphilis usually has its onset during secondary disease and is characterized by symptoms of headache, confusion, nausea and vomiting, neck stiffness and photophobia. There may be focal seizures, aphasia, delirium and papilloedema. Cranial nerve palsies cause unilateral or bilateral facial weakness and sensorineural deafness [15].

Meningovascular syphilis occurs most frequently between 4 and 7 years after infection. The clinical features of hemiparesis, seizures and aphasia reflect multiple areas of infarction from diffuse arteritis.

Gummatous neurosyphilis results in features typical of a space-occupying lesion.

Parenchymatous syphilis appears later and has become rare in its classic forms in the antibiotic era. The peak incidence of general paralysis from parenchymatous disease of the brain used to be 10–20 years after infection. The onset is insidious with subtle deterioration in cognitive function and psychiatric symptoms that mimic those of other mental disorders. As the disease progresses neurological signs develop, including pupillary abnormalities, hypotonia of the face and limbs, intention tremors and hyper-reflexia.

Tabetic neurosyphilis was the most common form of neurosyphilis in the pre-antibiotic era, with an onset 15–25 years after primary infection. The most characteristic symptom is of lightning pains—sudden paroxysms of lancinating pain affecting the lower limbs. Other early symptoms include paraesthesia, progressive ataxia, and bowel and bladder dysfunction.

Syphilis and HIV infection

There is epidemiological synergy between HIV and other sexually transmitted infections [16]. Syphilis increases the risk of HIV acquisition and onward transmission. HIV infection may alter the natural history of syphilis [17].

In most patients with early HIV infection, the clinical features, serological test results and response to treatment are similar to those in non-HIV-infected persons. With advancing immunosuppression, all of these may be significantly altered. Lues maligna, neurological and ocular involvement [18–21] have been reported more commonly.

References

1 Dunlop EMC. Some aspects of infectious syphilis today. *Public Health* 1964; **78**: 259–67.
2 Kinghorn GR, Hafiz S, McEntergart MG. Pathogenic microbiological flora of genital ulcers in Sheffield with particular reference to herpes simplex virus and *Haemophilus ducreyi*. *Br J Vener Dis* 1982; **58**: 377–80.
3 Evans AJ, Summerly R. Pseudo-chancre redux with negative serology. *Br J Vener Dis* 1964; **40**: 222–4.
4 Lannigan-O'Keefe FM. Pseudo-chancre redux. *BMJ* 1964; **ii**: 212.
5 Gallup DG, Cowherd DW. Syphilitic cervicitis. A report on a case. *Obstet Gynecol* 1978; **52** (Suppl. 1): 125–45.
6 Don PC, Rubinstein R, Christie S. Malignant syphilis (lues maligna) and concurrent infection with HIV. *Int J Dermatol* 1995; **34**: 403–7.
7 Van der Ploeg DE, Stagnone JJ. Eyebrow alopecia in secondary syphilis. *Arch Dermatol* 1982; **90**: 172–3.
8 Van der Willigen AH, Peereboom-Wynia JDR. Hair studies in patients with primary and secondary syphilis. *Acta Derm Venereol (Stockh)* 1987; **67**: 250–4.
9 Margo CE, Hamed LM. Ocular syphilis. *Surv Ophthalmol* 1992; **37**: 203–5.
10 Masterton G. Oro-genital aphthosis. *Br J Vener Dis* 1965; **41**: 282–96.
11 Laird SM. Yaws in Manchester. *Br J Vener Dis* 1955; **31**: 30–2.
12 Wray PM. Bejel in Sheffield. *Br J Vener Dis* 1966; **42**: 25–7.
13 Johnson RA, White M. Syphilis in the 1990s: cutaneous and neurologic manifestations. *Semin Neurol* 1992; **12**: 287–98.
14 Scheck DN, Hook EW III. Neurosyphilis. *Infect Dis Clin North Am* 1994; **8**: 769–85.
15 Morrison AW. On syphilis and the ear—an otologist's view. *Genitourin Med* 1992; **68**: 420–2.
16 Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. *Sex Transm Infect* 1999; **75**: 3–17.
17 Zetola NM, Klausner JD. Syphilis and HIV infection: an update. *Clin Infect Dis* 2007; **44**: 1222–8.
18 Yinnon AM, Coury-Doniger P, Polito R, Richman RC. Serologic response to treatment of syphilis in patients with HIV infection. *Arch Intern Med* 1996; **156**: 321–5.
19 Hutchinson CM, Hook EW III, Shepherd M *et al*. Altered clinical presentation of early syphilis in patients with human immunodeficiency virus infection. *Ann Intern Med* 1994; **121**: 94–100.
20 Brightbill TC, Ihmeidan IH, Post MJ *et al*. Neurosyphilis in HIV-positive and HIV-negative patients: neuroimaging findings. *Am J Neuroradiol* 1995; **16**: 703–11.
21 Malone JL, Wallace MR, Hendrick BB *et al*. Syphilis and neurosyphilis in a human immunodeficiency virus type-1 seropositive population: evidence for frequent serologic relapse after therapy. *Am J Med* 1995; **99**: 55–63.

Congenital syphilis

Despite the fact that congenital syphilis can be prevented by detection and treatment of infected expectant mothers, it still occurs with distressing frequency in many parts of the world. This is in spite of the long-established cost-effectiveness of public health measures [1] and repeated reminders [2,3], showing that it is not enough to establish control and prevention of syphilis, but to ensure, year in year out, that both are maintained. Only a few countries, the UK included, have achieved and maintained single figures for incidence of early congenital syphilis over more than a decade [1–4]. The need for antenatal testing and treatment is greater in the multiparous than the primiparous. A woman in the early contagious stage will almost certainly infect her unborn child by haematogenous spread of treponemes to, and through, the placenta. The chances of the fetus being infected in the latent or late stages depend largely on the duration of the expectant mother's infection, and it may be overall as high as 60%. Whether syphilis in the fetus occurs as a first-trimester infection with *T. pallidum* is still debated [5].

The fetus may be overwhelmed by an infection, which is usually more massive than occurs in acquired syphilis. Abortion, stillbirth or early neonatal death are common outcomes. When infections occur late in pregnancy, or are milder, the child is born alive but prematurely. Some children are born apparently healthy and signs may be delayed for days, weeks or months. Children without early signs of congenital syphilis or with unrecognized signs may develop overt symptoms and signs in their teens. The division between early and late congenital syphilis is usually placed at the end of the second year of life.

Incidence. The incidence of congenital syphilis varies from one country to another, and probably depends more on the prevalence of early acquired infection in a country than the quality of the antenatal care [6,7]. In most of the Westernized world it is now rarely seen.

In the UK, the number of cases of congenital syphilis in children under 2 years of age declined from 17 in 1995 to 2 in 1999. The corresponding numbers of cases of congenital syphilis in those aged 2 years or more were, respectively, 27 and 21 [8,9]. However, the recent resurgence in heterosexual cases of infectious syphilis gives rise to concern and is reflected in the rise in annual cases to 35 in 2005.

The annual incidence of congenital syphilis in infants aged less than 1 year in the USA increased from 3.0 per 100 000 live births in 1980 to a peak of 107.3 per 100 000 live births in 1990. The very large increase in reported cases has been artificially elevated by the introduction of a new reporting system [10–12], which takes account of epidemiological factors, especially maternal treatment status, in addition to cases showing characteristic clinical stigmata. The annual incidence has since declined to 8 cases per 100 000 live births in 2005 [13].

The clinical description of congenital syphilis includes:

1 early congenital syphilis
2 late congenital syphilis
3 the stigmata, including scars and deformities that are the consequences of early and later congenital syphilis.

Early congenital syphilis

Many infants with congenital syphilis are asymptomatic at birth. The placenta may show proliferative vascular changes and there may be acute inflammation of the umbilical cord (funisitis) [14]. Early congenital syphilis is manifest as rhinitis with serosanguinous nasal discharge, vesiculobullous eruptions of the skin and oral mucous patches. Skin lesions on the lips, nostrils and anus heal with radiating scars (rhagades). In addition, there are often bone abnormalities, characterized by diaphyseal periostitis, osteochondritis and a positive Wimberger's sign, which may present with limb pseudoparesis. Other features include chorioretinitis, visceral lesions causing pneumonia alba, hepatosplenomegaly associated with jaundice, and the nephrotic syndrome.

Mucous membranes. Syphilitic rhinitis, generally described as 'snuffles', is the most important and frequent sign. It is manifest as a profuse, serous nasal discharge in which *T. pallidum* can readily be demonstrated. The inflammatory process can lead to severe nasal cartilage and bone destruction.

The skin. The rash resembles the acquired papular rash in being coppery red. Individual lesions may be relatively large. They are chiefly found on the extremities, especially the palms and soles, which may show a homogeneous, shiny, coppery red infiltration. Lesions on the face may present as deeply fissured ('split') papules at the angles of the mouth or lateral to the external nares. The eruptions often become papulosquamous and anal condylomas may be present. Paronychia is said to be typical. *T. pallidum* can be demonstrated in serum from any of these lesions.

'*Pemphigus syphiliticus*' occurs in some babies. The bullae most commonly occur on the red infiltrated palms and soles described in the previous section. Their serous contents contain abundant active treponemes. The bullae of staphylococcal impetigo (pemphigus neonatorum) erupt on normal skin. Other bullous diseases in neonates are described elsewhere (Chapter 39).

A napkin dermatitis is sometimes mistaken for syphilis. The syphilitic papules are generally less 'hypertrophic' and the appearance less eczematous than in napkin dermatitis.

Other features. Osteochondritis is an early and common sign. In a 1985 study in Zambia, X-ray changes were found in 95% of 202 cases less than 6 months of age [15]. Osteochondritis occurs at the end of long bones, particularly the lower end of the tibia and fibula. The zone between the bone and the cartilage becomes broad and irregular. It shows as a very tender, painful swelling and may lead to Parrot's pseudoparalysis. Even without treatment, it tends, like other signs, to disappear within the first year of life. It may be confused with rickets or trauma from physical abuse.

Later, there may be periosteal changes or, more rarely, a characteristic osteomyelitis syphilitica in one or more phalanges (*syphilitic dactylitis*).

Hepato- and splenomegaly, sometimes with jaundice, are common, as is anaemia. Thrombocytopenia has been demonstrated [16]. Meningitis and meningoencephalitis with convulsions have been described, with bulging of the fontanelle, neck stiffness and, later, hydrocephalus and severe intellectual impairment. Choroiditis may occur, but anterior uveitis is rare.

Late congenital syphilis

In late congenital syphilis (presenting after 2 years of age) there may be a variety of skeletal developmental defects and a characteristic facies. Dental abnormalities occur. Other features include hydrocephalus and mental retardation, as well as other typical lesions of gummatous and neurosyphilis.

The common problem is to differentiate latent or late acquired syphilis from late congenital syphilis. In some patients, the situation is further complicated by the possibility of non-venereal treponematoses. The results of serological tests for syphilis (STS), both reaginic and specific, are of marginal help at best. One must rely on a thorough history, including antibiotic history, and clinical examination to establish a diagnosis of late congenital syphilis. The examination of the mother and siblings, often essential, may have to be augmented by the examination of a spouse and children.

Late congenital syphilitic eruptions of skin and mucous membranes are essentially like those of late acquired syphilis, for example nodular syphilides, gummata and periostitis. Signs characteristic of congenital syphilis alone must therefore be sought. They are of great diagnostic importance as they generally appear in children from 5 to 16 years of age.

Interstitial keratitis is the commonest and most serious late lesion [17]. It is rare before 6 years of age and over 40 years [18]. Both eyes are usually affected and recurrences are recognized. Attacks may have a 3-month course. There is spotty or diffuse clouding of the cornea, with pronounced ciliary and pericorneal injection. 'Brush-like' vessels are seen penetrating from the sclera into the deeper layers of the cornea. This vascularization is best seen with a slit lamp [19]. Vision is soon affected, and photophobia and pain are marked features. Iridocyclitis and choroidoretinitis may coexist. The condition is not directly influenced by anti-syphilitic treatment. Patients must be referred to an ophthalmologist. Corticosteroid eye drops or subconjunctival injections are indicated, and may well have to continue for 3 months or longer to prevent relapse of this 'allergic' phenomenon [20]. Corticosteroid therapy, if well supervised, almost certainly eliminates the danger of blindness.

Clutton's joints. This is a painless synovitis affecting the knees. Apart from increased joint space there are no radiological findings. The condition resolves spontaneously over several months. It is uninfluenced by antisyphilitic treatment [21].

Bone involvement. Periostitis of the long bones is common, particularly of the tibiae, which may become thickened and bent antero-posteriorly ('sabre tibiae'). Exostosis and eburnation may occur. Rarely, there may be changes in the inner ends of the clavicles or localized destruction of the outer table of the skull. Gumma of the palate is common, with residual perforation of the hard palate. A similar condition of the vomer is well recognized.

Eighth-nerve deafness (neurolabyrinthitis). This is a characteristic and moderately common complication. It is eventually bilateral in most cases. It may follow interstitial keratitis after some years. Tinnitus and vertigo are common prodromal symptoms and may continue and accompany the increasing perceptive deafness. The condition is uninfluenced by antisyphilitic treatment. Corticosteroid treatment has a variable beneficial effect in a modest majority of cases [22].

Cardiovascular syphilis. If it occurs at all, it is extremely rare [23,24].

Neurosyphilis. Cerebrospinal changes are not rare. Juvenile general paralysis may start between 6 and 21 years. Tabes is less frequent.

The possibility of third-generation congenital syphilis is very small.

Stigmata

Lasting changes in the shape of scars and defects caused by congenital infection have diagnostic importance in distinguishing it from acquired syphilis.

The teeth. One of the most common and characteristic stigmata is deformity of the upper, central incisor teeth [25]. These so-called



Fig. 34.29 Late congenital syphilis. The upper central incisors may be peg- or barrel-shaped. They are called 'Hutchinson's teeth'.



Fig. 34.30 Hutchinson's teeth are commonly notched at the free margin.

'Hutchinson's teeth' are due to defective development of permanent teeth buds, and are often associated with abnormalities in the development of the upper jaw (Figs 34.29–34.31). The incisors are conical or barrel shaped, with a degree of notching at the free edge. They may be well separated and converge or diverge. Some are described as 'screwdriver teeth'. Rarely, other incisors may show damage, or the teeth are irregularly spaced. Another deformity, not so characteristic, is the 'mulberry molar'—usually the first molar—which has a flat, occlusive surface with only poorly enamelled rudiments of the usual cusps.

Interstitial keratitis, Hutchinson's teeth and eighth-nerve deafness form 'Hutchinson's triad'. Other stigmata are rhagades at the corner of the mouth, broad-based, saddleback nose, 'dish face', Parrot's nodes on the skull, the 'pepper-and-salt' fundus, due to scarred choroiditis, and optic atrophy.

The features of congenital syphilis are summarized in Table 34.1 [26].



Fig. 34.31 This 32-year-old woman, referred with positive serology from an antenatal clinic, had insisted on an impression of her teeth being taken before extraction. She had been wearing artificial Hutchinson's incisors for 2 years.

References

1 Stray-Pederson B. Economic evaluation of maternal screening to prevent congenital syphilis. *Sex Transm Dis* 1983; **10**: 167–72.

2 Clay J. Ante-natal screening for syphilis (Editorial). *BMJ* 1989: **299**: 409–10.

3 Nicoll A, Moisley C. Ante-natal screening for syphilis (Editorial). *BMJ* 1994; **308**: 1253–4.

4 Simms I, Ward H. Congenital syphilis in the United Kingdom. *Sex Transm Infect* 2006; **82**: 1.

5 Harter CA, Benirschke K. Fetal syphilis in the first trimester. *Am J Obstet Gynecol* 1976; **124**: 705–11.

6 Moore JE. Recent advances in the study of venereal diseases. *Br J Vener Dis* 1949; **45**: 169–78.

7 Laird SM. Elimination of congenital syphilis. *Br J Vener Dis* 1959; **35**: 15–9.

8 PHLS, DHSS & PS and the Scottish ISD(D5) Collaborative Group. *Sexually Transmitted Infections in the UK: New Episodes Seen at Genitourinary Medicine Clinics. 1995 to 2000.* London: Public Health Laboratory Service, 2001.

9 Welch J. Antenatal screening for syphilis (Editorial). *BMJ* 1998; **317**: 1605–6.

10 Desenclos JC, Scaggs M, Wroen JE. Characteristics of mothers of live infants with congenital syphilis in Florida, 1987–89. *Am J Epidemiol* 1992; **136**: 657–61.

11 McFarlin BL, Bottoms SF, Dock BS, Isada NB. Epidemic syphilis: maternal factors associated with congenital infection. *Am J Obstet Gynecol* 1994; **170**: 535–40.

12 Thompson BL, Matuszak D, Dwyer DM *et al*. Congenital syphilis in Maryland 1989–91: the effect of changing the definition and opportunities for prevention. *Sex Transm Dis* 1995; **22**: 364–9.

13 Centers for Disease Control and Prevention. *STD Surveillance 2005 National Profile*. http://www.cdc.gov/STD/stats/syphilis.htm

14 Schwartz DA, Larsen SA, Beck-Sangue C *et al*. Pathology of the umbilical cord in congenital syphilis: analysis of 25 specimens using histochemistry and immunofluorescent antibody to *Treponema pallidum*. *Hum Pathol* 1995; **26**: 784–91.

15 Hirø SK, Bhat GJ, Patel JB *et al*. Early congenital syphilis: clinico-radiological features in 202 patients. *Sex Transm Dis* 1985; **12**: 177–83.

16 Freiman I, Super M. Thrombocytopenia and congenital syphilis in South African Bantu infants. *Arch Dis Child* 1966; **41**: 87–90.

17 Dunlop EMC, Zwink RB. Incidence of corneal changes in congenital syphilis. *Br J Vener Dis* 1954; **30**: 201–9.

18 Robinson RCV. Congenital syphilis. *Arch Dermatol* 1969; **99**: 599–610.

19 Britten MJA, Palmer CAL. Glaucoma and inactive syphilitic interstitial keratitis. *Br J Ophthalmol* 1964; **48**: 181–90.

20 Horne GO. Topical cortisone in syphilitic interstitial keratitis. *Br J Vener Dis* 1955; **31**: 9–24.

21 Borella L, Goobar JE, Clark GM. Synovitis of the knee joints in late congenital syphilis. *JAMA* 1962; **180**: 190–2.

22 Morrison AW. Management of severe deafness in adults. *Proc R Soc Med* 1969; **62**: 959–67.

23 Bonugli FS. Involvement of aortic valve and ascending aorta in congenital syphilis. *Br J Vener Dis* 1961; **37**: 257–67.

Table 34.1 Features of congenital syphilis. (Modified from Parish [26].)

	Early	Late
Birthweight	Low birthweight: may be <2500 g	
Mucocutaneous	Snuffles	Rhagades
	Maculopapular rash	Gummata
	Pustules	Palatal perforation
	Mucous patches	
	Condylomata lata	
	Vesiculobullous lesions	
	Rhagades	
	Desquamation	
	Alopecia	
Dental		Hutchinson's teeth
		Mulberry molars
Laryngeal	Hoarse cry	
Ocular	Chorioretinitis	Interstitial keratitis
	Uveitis	Uveitis
	Glaucoma	Glaucoma
Gastrointestinal	Hepatosplenomegaly	
	Pancreatitis	
	Enteritis	
Renal	Nephritis	
	Oedema and ascites	
Lymphatics	Lymphadenopathy	
Haematological	Thrombocytopenia	
	Anaemia	
	Disseminated intravascular coagulation	
Central nervous system	Aseptic meningitis	Mental delay
	Chronic meningovascular syphilis	8th-nerve deafness
	Cranial nerve palsies	Convulsive disorders
	Hydrocephalus	Paresis and paralysis
		Tabes dorsalis
Skeletal	Periostitis	Periostitis causing frontal and parietal bossing
	Osteochondritis causing pseudoparalysis	Sabre tibiae, scaphoid scapula
	Osteitis	Thickening of medial part of clavicle
		Short maxilla and protuberant mandible
		Saddle nose
		Clutton's joints

24 White RJ. Aortic incompetence associated with congenital syphilis. *Br J Vener Dis* 1965; **41**: 149.
25 Bradlaw RV. The dental stigmata of prenatal syphilis. *Oral Med Oral Pathol* 1953; **6**: 147–58.
26 Parish JL. Treponemal infections in the pediatric population. *Clin Dermatol* 2000; **18**: 687–700.

Tests for syphilis

Dark-field microscopy

Treponema pallidum can be identified from lesions of primary, secondary or early congenital syphilis by dark-field microscopy. In primary syphilis, it makes the diagnosis possible before measurable antibodies appear. In secondary syphilis, it provides immediate confirmation of a clinical diagnosis. The organism has a characteristic morphology and motility, with a sinusoidal profile and a wavelength and amplitude of 1.1 and 0.4 μm, respectively [1].

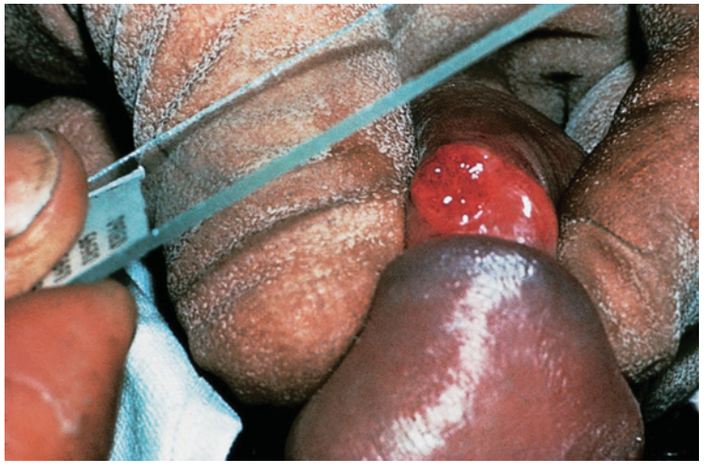


Fig. 34.32 Typical solitary, regularly edged, regularly based and indurated primary sore or chancre. Cleaned with saline and firmly rubbed with dry gauze it oozes serum. In view of endarteritis, bleeding is nearly absent. A specimen is being taken for dark-field microscopy.

The sore should be thoroughly cleaned with saline washes and/or saline compresses. A course of oral sulphonamides may be initiated. Where lesions are dry and crusted, it is necessary to scrape with a Volkmann's spoon or open scarifier. Suspected secondary lesions almost always require scarifying, and patience is needed if *T. pallidum* is to be demonstrated. Time must be allowed for red cells to settle so that clear serum can be obtained for microscopy (Fig. 34.32).

If the lesion is syphilitic, bleeding will not be marked. After scraping, some 5 min should be allowed for red cells to settle. The serum can then be collected and examined. Special care is indicated when assessing treponemes found in serum from oral lesions. If a suspected primary lesion has been treated with antiseptic or antibiotic remedies or if there is a marked secondary infection of the sore, the examination may not be successful. Repeat testing on two or more consecutive days is advised.

In all highly suspect genital and/or oral lesions where it proves impossible to demonstrate *T. pallidum*, lymph-node puncture material, mixed with injected sterile saline (0.5 mL), should be examined. Any treponeme found will always be *T. pallidum*.

In women, some 25% of the primary sores occur on or in the uterine cervix. A primary sore may be obvious on examination. In other cases, the cervix is oedematous, enlarged and pale. The suspicion that there is a primary lesion in the cervical canal can be confirmed by dark-field microscopy of material obtained 'blindly' from the cervical canal by a platinum loop. *T. pallidum* has also been demonstrated in material from the apparently healthy cervical canal of named contacts of early syphilis.

The organism can also be identified by direct immunofluorescent antibody testing where no facilities for dark-field microscopy exist.

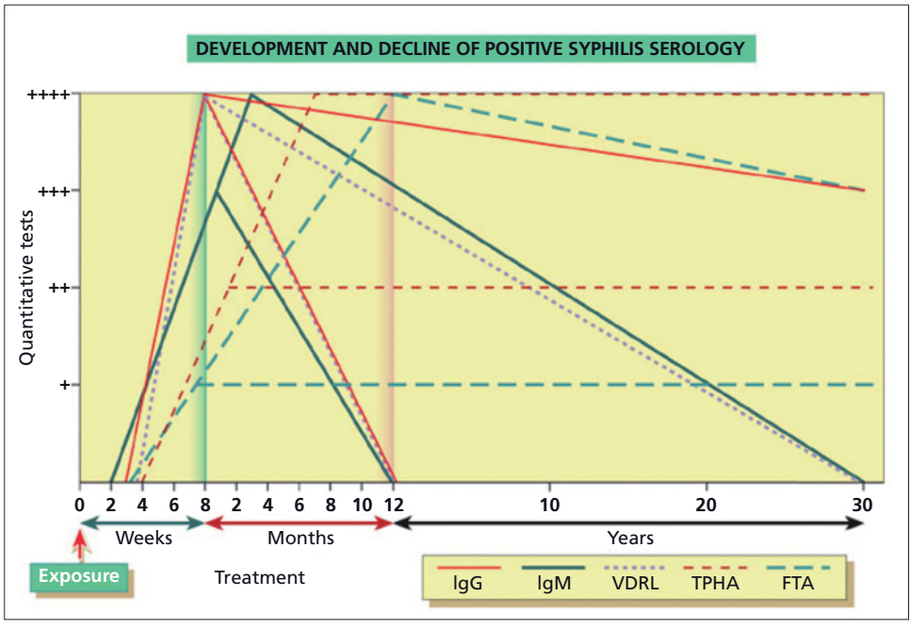


Fig. 34.33 Serological responses in syphilis as prompted by early infection, time and treatment. VDRL, Venereal Disease Research Laboratory; TPHA, *Treponema pallidum* haemagglutination test; FTA, fluorescent treponemal antibody.

In biopsy specimens from late syphilis, or in atypical early lesions, it may be possible to identify the organism by silver stains such as Warthin–Starry preparations or by direct immunofluorescent antibody testing.

Molecular amplification tests

Polymerase chain reaction (PCR) diagnosis has been based upon primers and probes prepared from the 47-kDa gene. After a 40-cycle series of denaturing, annealing and extension, the PCR products can be visualized by electrophoresis or Southern blot hybridization with a ^{32}P-labelled probe and then autoradiography. This technique should be of greatest value in detecting the low numbers of treponemal products in neurosyphilis; it should also be useful in congenital syphilis, in which the interpretation of serological test results may be difficult. Molecular amplification tests have also been successfully used in multiplex systems to investigate the aetiology of genital ulcers.

RNA amplification is more sensitive than PCR, and positive results are indicative of living organisms. The reverse-transcriptase PCR uses the 16 S ribosomal RNA of *T. pallidum* as the template.

Molecular diagnosis on lymph node biopsy specimens has been described [2].

Multiplex testing for *T. pallidum* and other genital ulcer pathogens is available in a few specialized laboratories using their own primers, but no commercial system is currently available.

Serological tests (Fig. 34.33)

The STS and serological tests for other treponematoses can be divided into reaginic or non-treponemal tests, and specific or treponemal tests. The antibodies detected by the treponemal tests may be further divided into those generated by specific antigens, present only in pathogenic treponemes, and those shared with non-pathogenic treponemes (group antibodies). This distinction has significance in so far as different types of antibody may influence results of several serological tests. The immune responses in all the treponematoses appear to be the same, and there is no test which will differentiate one treponematosis from another.

Standard non-treponemal tests. The non-treponemal tests detect IgM and IgG antibodies to lipoidal material released from damaged host cells and to lipoidal-like antigens of *T. pallidum*. There are four tests available that use the Venereal Disease Research Laboratory (VDRL) antigen (consisting of cardiolipin, cholesterol and lecithin) as the principal component. These tests are quantitative and are useful in assessing response to treatment. Reactivity to these tests does not develop until 1–4 weeks after the chancre appears in primary syphilis. Titres are highest in secondary syphilis. The prozone phenomenon occurs in 2% of sera; undiluted sera give negative results because of antibody excess, the presence of blocking antibodies, or both. The titre slowly declines after the secondary stage, and it may spontaneously become negative in some cases of late latent syphilis and neurosyphilis.

The VDRL slide test is widely used and requires the microscopic demonstration of antigen–antibody flocculations in heat-inactivated serum.

The unheated serum reagin (USR) test is similar to the VDRL test but does not require preheated serum, because the antigen has been stabilized.

The rapid plasma reagin (RPR) test and toluidine red unheated serum test (TRUST) use either charcoal or red paint pigment added to the USR reagent to enhance visualization of the antigen–antibody flocculations. The flocculations are visible macroscopically. This test can be performed in consulting rooms, clinics and laboratories where facilities, experience and personnel are limited.

Treponemal antigen tests. Specific treponemal antibody tests are used for confirmatory testing. They detect antibodies to antigenic determinants of treponemes. They are qualitative procedures and are not helpful in assessing treatment responses; once positive, they tend to remain positive for life, irrespective of treatment. They are used to differentiate true-positives from false-positives in the standard non-treponemal antibody tests.

The hunt for a test giving 100% sensitivity and specificity has gone through several stages. In 1949, Nelson and Mayer [3] proved that serum from syphilitic patients contains an antibody which in the presence of complement inhibits the normal movements of virulent *T. pallidum* (specific treponemal immobilizing antibody). For this test—the TPI (*T. pallidum* immobilization) test—virulent *T. pallidum* are used (the Nichol's strain) obtained from rabbits. The reaction of the treponemes in the presence of the patient's serum is observed by dark-field microscopy. If 50% or more of the treponemes are immobilized, the test is reported as positive; if less than 20%, it is negative. In 99% of cases, the result is very clear-cut and certainly very specific, probably nearly 100% [4,5]. The test is time consuming and therefore expensive.

The TPI becomes positive a few days to a week later than the reagin tests, that is later in the primary stage. In the late stage it is almost always positive, although a negative result may occur. The great importance of the TPI has been its specificity, making it possible to distinguish biological false-positive reaginic reactions from genuine positives.

With early treatment of syphilis, the TPI may become negative. However, if the disease has been untreated for more than 5–6 months, the reaction is likely to remain positive for the rest of the patient's life, despite any later treatment. The TPI became a 'gold standard'.

The fluorescent treponemal antibody absorption (FTA-ABS) test [6–8] and the FTA-ABS double-staining (FTA-ABS DS) test are both indirect immunofluorescent tests. The double stain test employs a fluorochrome-labelled counterstain for *T. pallidum* and an antihuman IgG conjugate labelled with tetra-methyl rhodamine isothiocyanate to detect antibody in patient serum. False-positive results may occur in about 1% of sera; possible causes include technical error, Lyme borreliosis, pregnancy, genital herpes, alcoholic cirrhosis and connective tissue diseases such as systemic lupus erythematosus and scleroderma.

The *Treponema pallidum* haemagglutination test (TPHA) was first described by Rathlev in 1967 [9]. A microtechnique has since gained popularity. In all forms, the TPHA is simple to perform and results are readily reproducible [10]. The test is very sensitive and specific [11,12]. The microhaemagglutination assay for antibodies to *T. pallidum* (MHA-TP) detects passive haemagglutination of erythrocytes sensitized with ultrasonicated Nichol's strain *T. pallidum*. In many laboratories, the TPHA has been replaced by the similar *T. pallidum* particle agglutination (TPPA) test that uses gelatine particles rather than erythrocytes as the carrier. It is more sensitive than the FTA-ABS.

Treponemal enzyme immunoassay (EIA) commercial tests were initially designed as confirmatory tests for syphilis [13]. Serum is added to microwells coated with a treponemal antigen. After incubation, an enzyme-labelled antihuman immunoglobulin conjugate and enzyme substrate are added to detect antigen–antibody reaction. The test can be modified to detect specific IgM antibody.

Western blot. *Treponema pallidum* western blot is available in some research laboratories and has similar sensitivity and specificity to the FTA-ABS test [14]. The presence of antibodies to the immunodeterminants with molecular weights 15.5, 17, 44.5 and 47 kDa appears to be diagnostic for acquired syphilis. When an IgM-specific conjugate is used, the test has value in the diagnosis of congenital syphilis.

Rapid point-of-care tests for syphilis. The resurgence of syphilis worldwide and limited laboratory diagnostic facilities in high-prevalence countries has stimulated the development of rapid point-of-care tests [15]. These can be performed outside a laboratory setting with minimal training and no equipment using a finger-prick blood sample. The tests are simple, are not affected by prozone effects, and can be transported and stored at temperatures <30°C. Their sensitivity is 85–98% and their specificity 93–98%. They are used for targeted screening in resource-poor countries, especially for screening of pregnant women and other high-risk groups. In developed countries, their use is also being studied in outreach settings with MSM, sex-workers and their clients.

Guidelines for serological screening

There are many commercial tests in any given format whose performance characteristics vary. Recent studies suggest that a treponemal EIA used as a single test is an appropriate alternative to the combined VDRL/RPR and TPHA screen. It has a higher specificity than the FTA-ABS. The test also has advantages of automated or semi-automated processing and objective reading of results, and can be interfaced with laboratory computer systems to allow electronic laboratory report generation.

Screening can be performed by either EIA or the combined VDRL/TPHA. Positive results are confirmed with a treponemal test of a different type. It is essential to confirm the presumptive serological diagnosis of syphilis on a second patient specimen.

Biological false-positive reactions

All the tests in use can produce biologically false-positive results. Reagins can be found in the blood of most normal people, and it is possible to make tests for reagins so sensitive that a high percentage of positives can be demonstrated. Some apparently healthy persons produce reagins in excess. They are classified as biologically false-positive (BFP) reactors. BFP reactions may be acute or chronic, that is they last less than or more than 6 months. The same occurs in association with acute and chronic diseases. Persistently low-titre-positive reagin tests with repeatedly negative treponemal tests are the rule in acute BFP reactions. They rarely last more than 3 months. Strongly positive reactions are more common in chronic BFP reactors.

Among the commonest associations with acute BFP reactions are the following: malaria, leprosy (especially the lepromatous form) [16,17], typhus, respiratory tract infection (especially viral pneumonia), infectious mononucleosis, active pulmonary tuberculosis, hepatitis, subacute bacterial endocarditis, measles,

chickenpox, filariasis, trypanosomiasis, leptospirosis and relapsing fever. BFP reactions are also reported in connection with pregnancy [18] and narcotic addiction.

Chronic BFP reactions are associated with autoimmune diseases and dysgammaglobulinaemia. Chronic BFP reactions may exist for some time and herald the onset of connective tissue disease by some years, for example systemic lupus erythematosus (especially in rhesus-negative women), polyarteritis nodosa and rheumatoid arthritis [19,20].

Not all authors agree that the VDRL is the most likely test to be associated with BFP reactions. One study, which concentrated on the phenomenon associated with dermatological diseases, found that the FTA and FTA/ABS tests most often produced BFP reactions [21]. In some elderly persons, BFP reactions with FTA/ABS are associated with connective tissue diseases, and in addition with the presence in healthy people of 'rheumatoid factor'; but ageing itself may be responsible [22–24].

A completely new cause of false-positive FTA/ABS was described in 1986 by Hunter *et al*. [25] at CDC, Atlanta, USA. They investigated patients with Lyme disease, and compared their serological findings with specimens from patients with syphilis. Cross-reactivity with the causative spirochaete of Lyme disease could be absorbed out with *T. phagedenis* (Reiter's strain).

Examination of CSF

Indications for examination of cerebrospinal fluid (CSF) in syphilis include:

- neurological, ophthalmic, or auditory symptoms and signs
- other clinical evidence of active infection—aortitis, gumma, iritis
- treatment failure
- HIV infection
- serum non-treponemal titre of more than 32 if duration of syphilis is over 1 year and
- non-penicillin-based treatment regimen planned.

Many clinicians consider an examination of CSF unnecessary in early syphilis, but prefer to examine it before discharging the patient as cured, after 1–2 years post-treatment follow-up. In untreated asymptomatic late syphilis, a CSF examination should always be done. A normal CSF is by definition an essential prerequisite for a diagnosis of latent syphilis.

The typical CSF findings of neurosyphilis consist of:

- moderate mononuclear pleiocytosis (10–400 cells/mL)
- elevated total protein (0.46–2.0 g/L) and
- positive CSF VDRL.

The CSF VDRL is highly specific and false-positive results are rare in the absence of blood contamination. A negative CSF VDRL does not exclude neurosyphilis, although non-treponemal serological tests usually remain positive in both serum and CSF in such cases.

Reactivity to tests using treponemal antigens, particularly to the FTA/ABS test and/or TPHA test, may be caused by transudation of *T. pallidum*-specific IgG from the serum of patients with adequately treated disease, and therefore is not necessarily a sign of active CNS involvement. On the other hand, non-reactivity of the CSF to these assays in all probability excludes the diagnosis of neurosyphilis.

Evaluation of neonates for congenital syphilis

It is recommended that the following investigations be carried out in the children born to seropositive mothers if there has been no documented treatment completion at least 4 weeks before delivery, or if a non-penicillin regimen was administered, or if relapse or re-infection is suspected:

- examination for stigmata of congenital syphilis
- X-ray long bones for evidence of periostitis and
- CSF examination.

Infection of the neonate is also suggested if the serum non-treponemal antibody titre is four or more times more than the mother's, or if specific IgM treponemal antibody tests are positive. Passively transferred maternal IgG antibody can persist in the infant's serum for up to 12 months [26].

References

1 Larsen SA, Steiner BM, Rudolph AH. Laboratory diagnosis and interpretation of tests for syphilis. *Clin Microbiol Rev* 1995; **8**: 1–21.

2 Kouznetsov AV, Prinz JC. Molecular diagnosis of syphilis: the Schaudinn-Hofmann lymph-node biopsy. *Lancet* 2002; **360**: 388–9.

3 Nelson RA, Mayer MM. Immobilization of *Treponema pallidum in vitro* by antibody produced in syphilitic infection. *J Exp Med* 1949; **89**: 369–93.

4 Laurell AB, Hederstedt B. Fractionation of TPI antibodies and Wassermann reagins. *Acta Pathol Microbiol Scand* 1958; **44**: 88–91.

5 Wilkinson AE. Studies on the treponemal immobilization test. *Br J Vener Dis* 1954; **30**: 144–55.

6 Deacon WE, Falcone VH, Harris AD. A fluorescent test for treponemal antibodies. *Proc Soc Exp Biol Med* 1957; **96**: 477–80.

7 Nielsen HA, Idsøe O. Evaluation of the fluorescent treponemal antibody test (FTA). *Acta Pathol Microbiol Scand* 1963; **57**: 331–47.

8 Deacon WE, Lucas JB, Price EV. Fluorescent treponemal antibody absorption (FTA/ABS) test for syphilis. *JAMA* 1966; **198**: 624–8.

9 Rathlev T. Haemagglutination test utilizing pathogenic *Treponema pallidum* for the sero-diagnosis of syphilis. *Br J Vener Dis* 1967; **43**: 181–5.

10 Sequiera PJL, Eldridge AE. Treponema haemagglutination test. *Br J Vener Dis* 1973; **49**: 242–8.

11 O'Neil P, Warner RW, Nicol CS. *Treponema pallidum* haemagglutination assay in the routine serodiagnosis of treponemal disease. *Br J Vener Dis* 1973; **49**: 427–31.

12 Robertson DHH, McMillan A, Young H *et al*. Clinical value of the *Treponema pallidum* haemagglutination test. *Br J Vener Dis* 1975; **51**: 79–82.

13 Eggelston SI, Turner AJL, for the PHLS Syphilis Serology Working Group. Serological testing for syphilis. *Commun Dis Public Health* 2000; **3**: 158–62.

14 Byrne RE, Laska S, Bell M *et al*. Evaluation of a *Treponema pallidum* Western immunoblot assay as a confirmatory test for syphilis. *J Clin Microbiol* 1992; **30**: 115–22.

15 Herring AJ, Ballard RC, Pope V *et al*. A multi-centre evaluation of nine rapid, point-of-care syphilis tests using archived sera. *Sex Transm Infect* 2006; **82**: v7–12.

16 Forster WD, Kerchan LLO. Biologically false positive Wassermann reactions in Uganda. *Br J Vener Dis* 1966; **42**: 272–5.

17 Garner MR, Backhouse JL, Collins CA *et al*. Serological tests for treponemal infection in leprosy patients. *Br J Vener Dis* 1969; **45**: 19–22.

18 British Co-operative Clinical Group. An examination of the treponemal immobilization test in the investigation of positive serological tests for syphilis in pregnancy. *Br J Vener Dis* 1959; **35**: 162–8.

19 Catterall RD. Collagen disease and the chronic biological false positive phenomenon. *QJM* 1961; **30**: 41–55.

20 Moore JE, Mohr CF. Biologically false positive serologic tests for syphilis. *JAMA* 1951; **150**: 467–73.

21 Gibowski M, Neumann E. Non-specific test results to syphilis in dermatological diseases. *Br J Vener Dis* 1980; **56**: 17–9.

22 Kraus SJ, Haserick JR, Lantz MA. Atypical FTA-ABS test fluorescence in lupus erythematous patients. *JAMA* 1970; **211**: 2140–1.

23 McKenna CH, Schroeter AL, Kierland RR *et al*. The fluorescent treponemal antibody absorbed (FTA-ABS) test beading phenomenon in connective tissue diseases. *Mayo Clin Proc* 1973; **48**: 545–8.
24 Shore RN, Faricelli JA. Borderline and reactive FTA-ABS results in lupus erythematous. *Arch Dermatol* 1977; **113**: 37–41.
25 Hunter EF, Russel S, Farshy CE *et al*. Evaluation of sera from patients with Lyme disease by FTA/ABS test for syphilis. *Sex Transm Dis* 1986; **13**: 232–6.
26 Chang SN, Chung KY, Lee MG, Lee JB. Seroreversion of the serological tests for syphilis in the newborns born to treated syphilitic mothers. *Genitourin Med* 1995; **71**: 68–70.

Management of syphilis

Overview

Current treatment regimens are largely based on over 50 years' clinical experience with penicillin, expert opinion and open clinical studies [1–4], although there have been some recent randomized clinical trials [5–7]. Many antibiotics, with the notable exceptions of the aminoglycosides and sulphonamides, have some treponemicidal activity, and their administration for other conditions may abort or modify the natural history of syphilis [8].

Parenteral penicillin G is the preferred drug at all stages of syphilis; the preparations used, the dosage and the duration of treatment depend on the clinical stage and disease manifestations. Penicillin remains not only the most effective treponemicide, but it is easy to administer, has few side effects and is relatively inexpensive. Results continue to be excellent in all forms and stages of treponemal disease, and there are no signs that *T. pallidum* has developed resistance to this antibiotic. Injectable penicillins are generally preferred to oral preparations, because of problems of patient compliance and uncertain absorption from the gastrointestinal tract.

Adequate treatment requires the maintenance of serum concentrations in excess of 0.03 U/mL for at least 10 days. A single intramuscular dose of 600 000 U of aqueous procaine penicillin gives an effective serum concentration for at least 24 h; in comparison, a single intramuscular dose of 2 400 000 U of benzathine penicillin G maintains effective levels for about 2 weeks. As this preparation may cause pain on injection, 1.2 mU are usually given in the upper and outer quadrant of each buttock (Table 34.2).

It should be noted that although benzathine penicillin G is recommended first line therapy for most syphilis cases, it is an unlicensed medication in the UK. The unlicensed status of the medicine should be explained to the patient and a record that it is being given with the patient's consent entered in the case notes.

Treatment of late syphilis theoretically may require a longer duration of therapy because organisms are dividing more slowly, but the validity of this concept has not been addressed. The penetration of aqueous procaine penicillin into the CSF (as into the aqueous humour) is poor; that of erythromycin is poorer and that of benzathine penicillin, poorest of the three [9] (Table 34.3). For treatment of neurosyphilis, high dosages of crystalline benzylpenicillin G, plus probenicid, should be considered. Desensitization of penicillin-allergic patients is recommended (Table 34.4).

In patients who are hypersensitive to penicillin, regimens based on tetracycline, doxycycline, erythromycin and chloramphenicol have all been successfully used to treat syphilis; however, success is less assured than with penicillin. Azithromycin, given in dosages of 500 mg daily for 10 days, or in a single 2-g dosage, has recently been successful, but there are concerns about the emergence of antimicrobial resistance [5,7].

All patients with syphilis should be offered screening for other sexually transmitted infections and HIV. Serological testing for HIV should be repeated after 3 months in those persons presenting with primary syphilis who initially test negative.

Pregnant women. Only penicillin-based regimens have documented efficacy, and desensitization should be considered in those who are allergic. Those women who have had documented treatment for syphilis in the past do not need retreatment in the current or subsequent pregnancies so long as there is no clinical evidence of syphilis, and the VDRL or RPR titre is negative.

First-line treatment is with procaine penicillin G. Alternative drug therapies include erythromycin or azithromycin.

Table 34.2 Recommended treatment regimens for early syphilis.

First line
• Benzathine penicillin G 2.4 MU i.m. single dose or ×2 (day 1 and 8)
• Procaine penicillin G 600 000 U i.m. daily ×10
Penicillin allergy
• Doxycycline 100 mg twice daily orally for 14 days
• Erythromycin 500 mg four times daily orally for 14 days
• Azithromycin 500 mg daily orally for 10 days
• Ceftriaxone 500 mg daily i.m. for 10 days (if no anaphylaxis to penicillin)

Table 34.3 Recommended treatment regimens for late and cardiovascular syphilis. (BASHH Clinical Effectiveness Guidelines, 2002.)

First-line therapies
• Benzathine penicillin G 2.4 MU i.m. weekly ×3 (day 1, 8 and 15)
• Procaine penicillin G 600 000 units i.m. daily ×17
Second-line therapies
• Doxycycline 200 mg twice daily orally for 28 days (if penicillin allergic)
• Amoxicillin 2 g three times daily orally plus probenecid 500 mg four times daily orally for 28 days

Table 34.4 Recommended treatment regimens for neurosyphilis. (BASHH Clinical Effectiveness Guidelines, 2002.)

First-line therapies
• Procaine penicillin 2 g i.m. daily plus probenecid 500 mg orally four times daily for 17 days
• Benzylpenicillin 18–24 MU daily, given as 3–4 MU i.v. every four hours for 17 days
Second-line therapies
• Doxycycline 200 mg orally twice daily for 28 days
• Amoxicillin 2 g orally three times daily plus probenecid 500 mg orally four times daily for 28 days
All patients with neurological syphilis should be considered for corticosteroid cover at the start of the therapy (see Jarisch–Herxheimer reaction)

Table 34.5 Recommended treatment regimens for congenital syphilis. (BASHH Clinical Effectiveness Guidelines, 2002.)

- Benzylpenicillin sodium 100 000–150 000 U/kg i.v. daily (in divided doses given as 50 000 U/kg 12-hourly in the first 7 days of life and 8-hourly thereafter) for 10 days
- Procaine penicillin G 50 000 U/kg i.m. daily for 10 days

Treatment of syphilis in HIV-seropositive individuals. It is recommended that CSF examination be performed in all patients with syphilis who are HIV seropositive. Generally, recommended regimens are the same as those in HIV-negative individuals if CSF examination is normal [10]. Ceftriaxone has been successfully used in a pilot study [6].

Treatment of congenital syphilis (Table 34.5). The optimal treatment of congenital syphilis is unknown. Regimens that have been recommended for early congenital syphilis are intravenous aqueous crystalline penicillin G, 100 000–150 000 U/kg/day given as 50 000 U/kg every 12 h for the first 7 days of life and every 8 h thereafter for a total of 10 days [11]. An alternative is procaine penicillin G 50 000 U/kg/dose i.m. daily for 10 days for infants with normal CSF findings. In children who are identified as having reactive serological tests for syphilis after the neonatal period, maternal serology and records should be reviewed to assess whether the child has congenital or acquired syphilis. Any child at risk for congenital syphilis should be fully evaluated and tested for HIV infection. The recommended regimen is aqueous crystalline penicillin G 200 000–300 000 U/kg/day i.v., administered as 50 000 U/kg every 4–6 h for 10 days.

In children with late congenital syphilis presenting after 2 years of age, regimens should be the same as those recommended for late acquired disease.

Penicillin reactions

Accidental deaths following treatment are very rare and mainly due to anaphylactic shock reactions to penicillin. In addition to early and late allergic reactions and the Jarisch–Herxheimer reaction, *Hoigne reactions* (acute psychotic symptoms due to inadvertent intravenous injection of procaine in procaine penicillin) are recognized.

If penicillin is used in patients with a history of allergy, it is advisable to keep the patient under observation for 15–20 min after the injection. An emergency kit should always be available.

Jarisch–Herxheimer reaction. The Jarisch–Herxheimer reaction is an acute febrile reaction that occurs in many patients within 24 h of commencing treatment. It is mediated by cytokines. Headache, myalgia, bone pains and an exacerbation of skin lesions may accompany the fever. It must be differentiated from penicillin allergy. Patients should be advised that it might occur. Symptoms may be controlled by antipyretics. The fever (38–40°C) rarely persists more than 8 h.

In pregnant women the reaction may induce early labour or cause fetal distress. In late neurosyphilis and cardiovascular syphilis, the Jarisch–Herxheimer reaction can be more serious and may be associated with life-threatening sequelae. Many clinicians advocate a short course of corticosteroids to lessen its effects in these patients; one such regimen is to prescribe oral prednisolone 30–60 mg daily for 3 days, beginning syphilis treatment 24 h after the first dose.

Follow-up

Follow-up for clinical and serological assessment should be done at 3, 6 and 12 months after the completion of treatment in early syphilis. Recurrence is due more often to reinfection than to relapse.

Reinfections are more likely during the first year after penicillin therapy. Non-treponemal antibody test titres correlate with disease activity and will usually become negative with time after successful treatment. In some patients, who are described as being 'reagin-fast', low titre positivity in these tests may persist for life. Apart from up to 25% of patients treated for primary syphilis, the treponemal antibody tests will continue to remain positive after successful treatment.

In late latent or tertiary benign syphilis, a 2-year follow-up is adequate. Quantitative non-treponemal serological testing is repeated at 3 and 6 months, and each 6 months thereafter. Follow-up of cardiovascular and clinical neurosyphilis should be for life.

Treatment failure is suggested by a fourfold increase in titres, less than a fourfold decrease in pretreatment titres within 12–24 months, and development of symptoms or signs attributable to syphilis. All treatment failures require CSF examination. In cases of serological or clinical relapse, retreatment with double doses is recommended.

In latent syphilis, a 2-year follow-up is adequate. The same applies to late benign syphilis. In neurosyphilis, it is usual to repeat the CSF examination every 6 months until the cell count has become normal. There is a slower response of the CSF VDRL and total protein. Retreatment should be considered if the cell count shows an inadequate response or if all of these parameters have not returned to normal by 2 years. In cases of serological or clinical relapse, retreatment with double penicillin doses is recommended. Patients treated for neurological or cardiovascular syphilis should be followed up for many years.

Management of sexual contacts

It is recommended that attempts be made to identify, trace and offer further investigation to at-risk sexual contacts. In early syphilis, these are those contacts occurring within 3 months plus the duration of symptoms for primary syphilis, within 6 months plus the duration of symptoms for secondary syphilis and within 1 year for early latent disease. All long-term partners of patients with late syphilis should be offered investigation.

Many clinicians recommend presumptive treatment of all sexual contacts within the 90-day period preceding patient presentation of early syphilis if serological test results are not immediately available and if follow-up cannot be assured.

Prognosis

Cure rates with initial treatment of early syphilis are better than 95%. The long-term outcome of adequately treated cases is

excellent. In late syphilis, infection can usually be arrested although some treponemes may persist in less accessible sites (e.g. the eye and nervous system). As long as immune function is normal, this rarely has clinical sequelae. The outlook for HIV-positive and other immunocompromised patients appears to be less assured; however, long-term studies in these patients are needed.

References

1 Clinical Effectiveness Group. *National Guideline for the Management of Early Syphilis*. Association of Genitourinary Medicine (AGUM) and Medical Society for the Study of Venereal Diseases (MSSVD). www.mssvd.org.uk/PDF/CEG2001/early$Final0502.pdf
2 Clinical Effectiveness Group. *National Guideline for the Management of Late Syphilis*. Association of Genitourinary Medicine (AGUM) and Medical Society for the Study of Venereal Diseases (MSSVD). www.mssvd.org.uk/PDF/CEG2001/late$Final0502.pdf
3 Goh BT, van der Voorst Vader PC. European guideline for the management of syphilis. *Intern J STD AIDS* 2001; **12** (Suppl. 3): 14–26.
4 Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2006. *MMWR* 2006; **55** (RR11): 1–94.
5 Hook EW 3rd, Martin DH, Stephens J *et al*. A randomized, comparative pilot study of azithromycin versus benzathine penicillin G for treatment of early syphilis. *Sex Transm Dis* 2002; **29**: 486–90.
6 Smith NH, Musher DM, Huang DB *et al*. Response of HIV-infected patients with asymptomatic syphilis to intensive intramuscular therapy with ceftriaxone or procaine penicillin. *Int J STD AIDS* 2004; **15**: 328–32.
7 Riedner G, Rusizoka M, Todd J *et al*. Single-dose azithromycin versus penicillin G benzathine for the treatment of early syphilis. *N Engl J Med* 2005; **353**: 1236–44.
8 Ronald AR, Silverman M, McCutchan JA *et al*. Evaluation of new anti-infective drugs for the treatment of syphilis. *Clin Infect Dis* 1992; **15** (Suppl. 1): 140–7.
9 Gordon SM, Eaton ME, George R *et al*. The response of symptomatic neurosyphilis to high-dose intravenous penicillin G in patients with human immunodeficiency virus infection. *N Engl J Med* 1994; **331**: 1469–73.
10 Malone JL, Wallace MR, Hendrick BB *et al.* Syphilis and neurosyphilis in a human immunodeficiency virus type-1 seropositive population: evidence for frequent serologic relapse after therapy. *Am J Med* 1995; **99**: 55–63.
11 Paryani SG, Vaughn AJ, Crosby M, Lawrence S. Treatment of asymptomatic congenital syphilis: benzathine versus procaine penicillin G therapy. *J Pediatr* 1994; **125**: 471–5.

Syphilis control

The control of syphilis is favoured by a combination of factors:

- a long incubation period with a relatively low transmission rate
- self-limiting symptomatic periods with long asymptomatic periods of presumably low infectivity
- low cost and ready availability of screening test
- effective, simple and inexpensive therapy.

The risk factors for acquisition of syphilis mirror those of other STIs, and primary prevention depends on similar methods, such as reducing the number of sexual partners and consistent use of condoms. Community outreach activities should target education at persons at high risk. Single-dose treatment with intramuscular benzathine penicillin G and oral azithromycin have been employed as treatment for incubating syphilis [1]. Administration of treponemicidal antibiotics to treat other STIs, such as gonorrhoea and chancroid, may also abort incubating concurrent syphilis. The development of a vaccine against syphilis has long been inhibited by the inability to grow the organism on artificial media, although the recent sequencing of the *T. pallidum* genome should advance new research efforts.

Secondary prevention by early diagnosis, treatment, partner notification [2], education and counselling remain the mainstay of prevention efforts [2,3]. Access to prompt and appropriate services for infected persons is essential. In many developed countries, clinic-based specialist services have long been established. In developing countries, the WHO has recommended that STI management be integrated into basic health care and reproductive health services [4–6]. The syndromic approach to management of genital ulceration should always include administration of treatment effective against syphilis.

Serological screening for syphilis remains a cost-effective measure for control. Congenital syphilis may be prevented by maternal screening and treatment during early pregnancy [7,8]. In a location where the prevalence of untreated syphilis in pregnant women is 8%, antenatal screening and treatment costs $4–18 per disability life year saved. In Europe, screening remains a routine part of antenatal care, usually at about 12 weeks' gestation. In developing countries, where congenital syphilis is more common, the disease occurs when there has been no maternal screening, when no treatment has been administered in response to positive tests, or when primary infection occurs later in pregnancy. Repeat screening during the final trimester or at delivery is advocated in high prevalence regions [9].

References

1 Hook EW III, Stephens J, Ennis DM. Azithromycin compared with penicillin G benzathine for treatment of incubating syphilis. *Ann Intern Med* 1999; **313**: 434–7.
2 Engelgau MM, Woernie CH, Rolfs RT *et al*. Control of epidemic syphilis: the results of an intervention campaign using social networks. *Sex Transm Dis* 1995; **22**: 203–9.
3 Kohl KS, Farley TA, Ewell J, Scioneaux J. Usefulness of partner notification for syphilis control. *Sex Transm Dis* 1999; **26**: 201–7.
4 WHO. *Treponemal Infections*. Technical Reports Series 674. Geneva: World Health Organization, 1982.
5 WHO. *Control of Sexually Transmitted Diseases*. Geneva: World Health Organization, 1985.
6 WHO. *Expert Committee on Venereal Diseases and Treponematoses*. Sixth Report. Technical Report Series, No. 736. Geneva: World Health Organization, 1986.
7 Terris-Prestholt F, Watson-Jones D, Mugeye K *et al*. Is antenatal syphilis screening still cost effective in sub-Saharan Africa? *Sex Transm Infect* 2003; **79**: 375–81.
8 Blandford JM, Gift TL, Vasaikar S *et al*. Cost-effectiveness of on-site antenatal screening to prevent congenital syphilis in rural eastern Cape Province, Republic of South Africa. *Sex Transm Dis* 2007; **34** (Suppl. 7): S61–6.
9 Qulohle DC, Hoosen AA, Moodley J *et al*. Serological screening for sexually transmitted diseases in pregnancy: is there any value in re-screening for HIV and syphilis at the time of delivery? *Genitourin Med* 1995; **71**: 65–7.

Gonorrhoea

This disease is caused by *Neisseria gonorrhoeae*. It is, after *Chlamydia*, the second most commonly reported bacterial STI in the UK and other developed countries.

Causative organism. *N. gonorrhoeae* is a Gram-negative, aerobic diplococcus that principally infects host columnar epithelium. Outside the human host the organism is delicate, but within the body it has a large capability to effect antigenic variation that helps it evade the host immune response and to develop antimicrobial resistance [1].

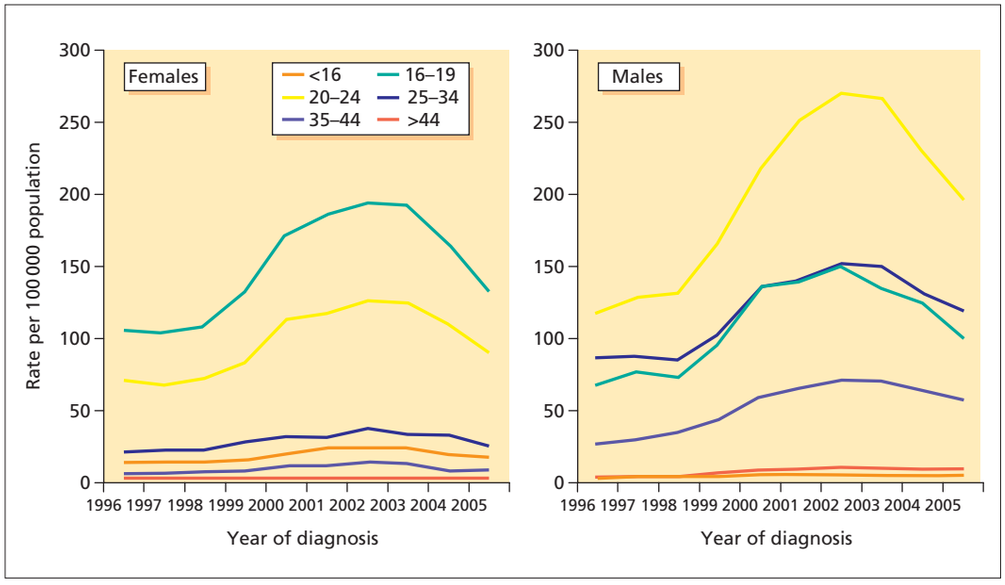


Fig. 34.34 Rates of uncomplicated gonorrhoea infection by age group. Data sources: KC60 and STIS/ISD(D)5 returns from GUM clinics.

Gonococci attach to host mucosal cells with the aid of pili and outer membrane proteins, and then penetrate between cells to the subepithelial space. The host mounts an acute inflammatory response which leads to epithelial sloughing, submucosal microabscesses and purulent discharge.

Epidemiology. It is estimated that there are around 60 million new cases each year worldwide [2]. Disease rates are unknown for most countries because of inadequate surveillance and reporting systems, but it is widely thought that rates of the disease and its complications are very much higher in the developing countries of Africa, Asia and Latin America. In these countries, gonorrhoea rates in pregnant women of up to 10% have been reported. There has been a recent, small decline in annual reported cases in the UK [3] and North America [4] after a sharp rise during the previous decade (Fig. 34.34).

As with other STIs, the highest rates of infection occur in young people, especially in teenage women and men in their early twenties. Infection rates have also been increasing in older age groups. Gonorrhoea is most prevalent in large conurbations, in black populations, and in men who have sex with men (MSM) (Fig. 34.35). Socio-economic and behavioural factors, and patterns of sexual mixing, affect its spread.

Gonorrhoea has a high infectivity and is easily transmitted before symptoms appear.

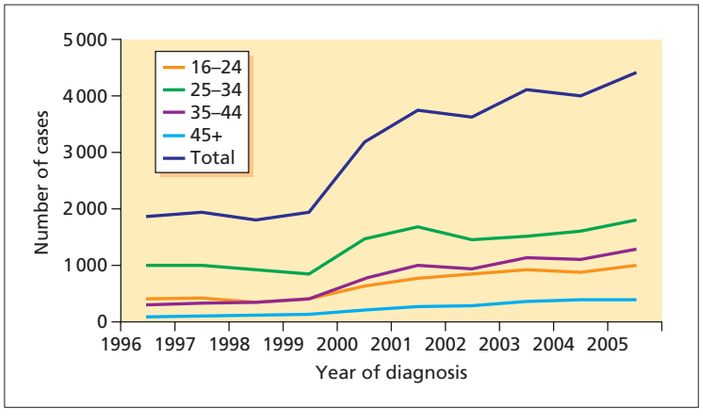


Fig. 34.35 Diagnosis of uncomplicated gonorrhoea among MSM, UK.

Clinical features. The incubation period is short and symptoms typically have their onset 1–5 days after sexual contact with an infective person.

In males, the usual presentation is with acute urethritis. There is rapid onset of severe burning dysuria accompanied by a purulent discharge, which is often profuse (Fig. 34.36). In MSM, there may also be rectal and pharyngeal infections. Gonococcal proctitis may be asymptomatic but may also present with rectal pain, tenesmus and discharge (Fig. 34.37a). Infection of the oropharynx may present with exudative pharyngitis and cervical lymphadenopathy, but is also commonly asymptomatic.

In females, the primary site of infection is the cervix (Fig. 34.37b), but the urethra, rectum and pharynx are other sites of infection that should be tested. Symptomatic infections manifest as excessive vaginal discharge, dysuria, deep dyspareunia and intermenstrual bleeding. However, a majority of women with early infections report no symptoms.

Another less common site of infection in adults is the eye, where autoinoculation of the organism from infected anogenital sites leads to acute conjunctivitis. This presents as an acutely painful red eye with purulent discharge that may progress to panophthalmitis and loss of vision.

Gonococcal conjunctivitis is more often associated with newborn babies as ophthalmia neonatorum, which usually occurs in the first week after birth (Fig. 34.38). Prompt recognition and treatment is essential to prevent permanent visual damage.

Complications. Complications may occur as a result of local abscess formation, from ascending infections and from haematogenous spread.

Periurethral abscess may occur in either sex and lead to fistula formation and subsequent urethral stricture. In females, gonorrhoea should also be considered as a possible cause for a Bartholin's abscess.

Ascending infection in men causes acute prostatitis, with symptoms of urinary frequency, stranguria and back or perineal pain.



Fig. 34.36 Gonococcal urethritis.

It may also present as unilateral or bilateral painful testicular swelling resulting from acute epididymo-orchitis.

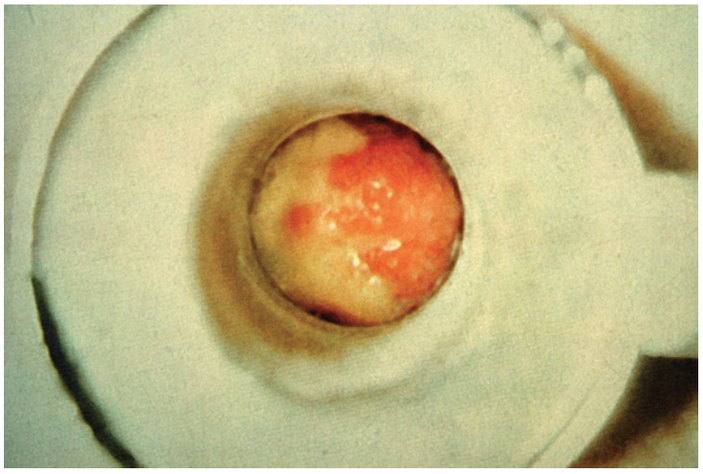
In women, ascending infections cause pelvic inflammatory disease. This is usually acute in onset, with lower abdominal and pelvic pain, fever, and marked adnexal and cervical motion tenderness on bimanual pelvic examination. Tubo-ovarian abscess and scarring of the Fallopian tubes resulting in tubal-factor infertility may ensue.

Acute perihepatitis (Fitz–Hugh Curtis syndrome) [5] may also occur with either gonorrhoea, *Chlamydia* or mixed infections. It presents as fever, and a complaint of right upper quadrant pain and tenderness that mimics acute cholecystitis. Perihepatitis, resulting from inflammation of the liver capsule, generally occurs in much younger women than those who typicallly suffer from cholecystitis. Periappendicitis caused by either gonococcal or chlamydial infections has a similar pathogenesis.

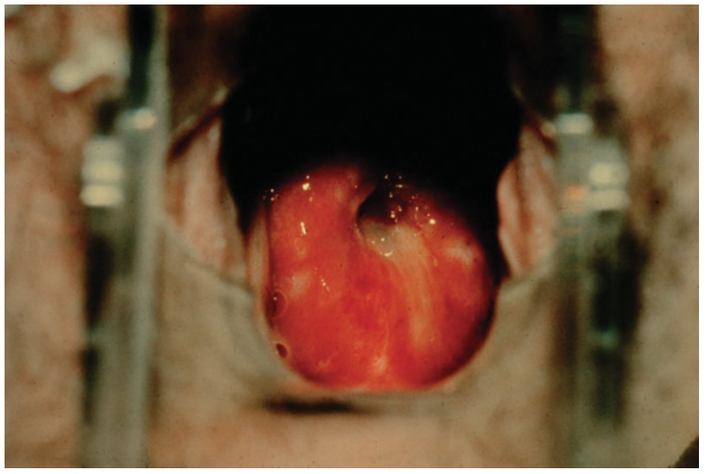
Disseminated gonococcal infection (DGI). This occurs in 0.5–3% of patients from haematogenous spread. It is facilitated by host and microbial factors, and may follow gonococcal infection at any anogenital or extragenital site. It is three times more common in women than men; in the latter it is more often seen in MSM [6].

Typically, genital symptoms are absent. In women, recent menstruation, pregnancy and recent childbirth predispose to its occurrence. It is also more frequent where there are congenital or acquired complement deficiencies, especially of terminal components (C5–), and in systemic lupus erythematosus.

Certain gonococcal strains are more often associated with DGI. These include those with specific nutritional requirements (auxotype ahu that requires arginine, hypoxanthine and uracil for growth), or contain low-molecular-weight protein 1a (porin serotype 1A) or fail to express outer membrane protein II, which affect attachment to cells and phagocytes and are more resistant to the bactericidal effects of human serum. In the past, gonococcal isolates from DGI were typically highly sensitive to penicillin, but antimicrobial-resistant strains with β-lactamase may also be responsible.



(a)



(b)

Fig. 34.37 Gonorrhoea. (a) Proctitis. (b) Cervicitis.

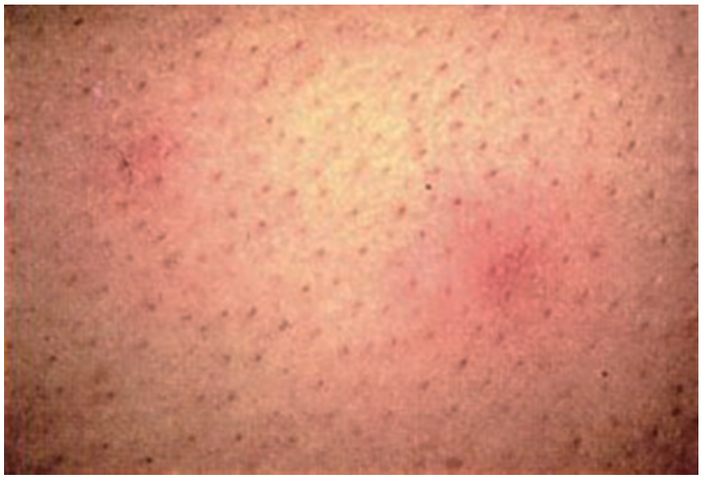


Fig. 34.38 Gonococcal ophthalmia neonatorum.

The classic presentation is with a dermatitis–arthritis syndrome in a patient with mild fever. The skin lesions are small, tender and initially maculopapular. A central vesicle or pustule appears and haemorrhage and necrosis commonly ensues. Lesions occur in crops, usually number five to 40, and are most commonly seen peripherally near affected joints. They may also occur on the torso, and the palms and soles (Fig. 34.39).

Joint or tendon pain is the most common accompanying feature. Tenosynovitis often affects the hands and fingers. It may be accompanied by a migratory polyarthralgia, affecting the knees, elbows, wrists, metacarpophalangeal joints and ankle joints. There is a high yield of positive blood cultures in such cases.

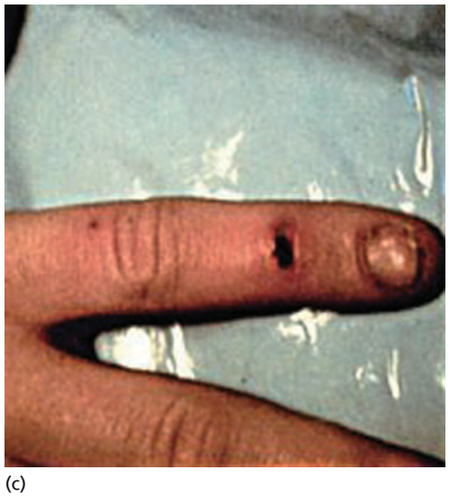
Later, one-third will develop a suppurative arthritis, that most commonly affects the knee. By this stage, skin lesions have usually disappeared and blood cultures are often negative. Rarely, pericarditis and endocarditis may also occur at this later stage. The



(a)



(b)



(c)



(d)

Fig. 34.39 Disseminated gonococcal infection. (a) Early macular lesion. (b) Haemorrhagic pustule. (c) Papule with central necrosis. (d) Arthritis of the foot.

latter is more common in men, usually affects the aortic valve, and presents with the subacute onset of chest pain, fever, chills and malaise. Meningitis, similar to that caused by meningococci, but with a less rapid course, is rare but well recognized.

Diagnosis.

Microscopy. A rapid presumptive diagnosis can be made by the identification of Gram-negative intracellular diplococci within phagocytes in stained smears from anogenital sites. Confirmation is by culture of the organism and differentiation from other *Neisseria* species by antigenic or biochemical testing.

Culture. The gonococcus is a fastidious organism and requires appropriate methods of specimen collection and transportation to the laboratory. Specimens are plated onto nutritive, selective media and incubated in a humid atmosphere containing 5% CO_2. Culture remains the gold standard for diagnosing gonorrhoea, and also allows the testing of isolates for antimicrobial sensitivities.

NAATs. However, problems associated with specimen transportation and cultures have prompted the development of nucleic acid amplification tests (NAATs), which are commonly combined in assays for *Chlamydia* [7,8]. These use a variety of platforms and test methodologies, including PCR, strand displacement assay, transcription-mediated amplification assay (TMA) and 16s RNA detection. These tests are not licensed for non-genital samples, do not produce isolates that allow antimicrobial sensitivity, have low sensitivity when used on urine specimens in women and can produce false-positive results from cross-reactions with other pathogenic and commensal *Neisseria* species [9]. Thus, it is advisable that if such tests are used for screening, especially in low prevalence populations, results are viewed as being presumptive, and confirmation is sought by repeat sampling for culture.

NAATs can also be modified to allow molecular analysis of isolates that are useful in epidemiological studies and network analysis [10,11].

Management.

The gonococcus has a marked propensity to develop antimicrobial resistance. The WHO recommends that only antimicrobial regimens that can assure >95% cure rates are employed. In most parts of the world, this means that penicillin, tetracycline, some macrolides and quinolones are no longer first-line therapy [12–15].

In the UK, first-line treatment involves single dosage regimens with a third generation cephalosporin, such as i.m. ceftriaxone or oral cefixime. Treatment failures or infections in penicillin-allergic patients are usually treated with i.m. spectinomycin [16] (Table 34.6).

In complicated infections, more prolonged courses of treatment are employed. These will usually contain an agent effective against *C. trachomatis*, which often coexists with gonorrhoea.

Patients with gonorrhoea should always be fully assessed and screened for other STIs and HIV, asked to assist with partner notification efforts, and be offered non-judgemental education, counselling and support.

Table 34.6 Recommended regimens for treatment of gonorrhoea.

Uncomplicated anogenital infection in adults
• Ceftriaxone 250 mg i.m. as a single dose
• Cefixime 400 mg orally as a single dose
• Spectinomycin 2 g i.m. as a single dose
Pregnancy and breastfeeding
The above regimens are suitable for pregnant women
In addition, where regional prevalence of penicillin-resistant *N. gonorrhoeae* is ≤5%
• Amoxycillin 3 g plus probenecid 1 g orally as a single dose
• Ampicillin 2 g plus probenecid 1 g orally as a single dose

The prevalence of gonorrhoea is a good measure of the effectiveness of control measures against STIs and HIV. Some countries have now set national targets to try to reduce the incidence of gonorrhoea.

References

1 Lutwick LI. Gonococcal infections. *E-medicine*, 2007. http://www.emedicine.com/med/topic922.htm.

2 WHO. *Global Strategy for the Prevention and Control of Sexually Transmitted Infections: 2006–2015. Key messages*. Geneva: WHO, 2006.

3 Fenton KA, Lowndes CM. Recent trends in the epidemiology of sexually transmitted infections in the European Union. *Sex Transm Infect* 2004; **80**: 255–63.

4 Aral SO, Fenton KA, Holmes KK. Sexually transmitted diseases in the USA: temporal trends. *Sex Transm Infect* 2007; **83**: 257–66.

5 Peter NG, Clark LR, Jaeger JR. Fitz-Hugh-Curtis syndrome: a diagnosis to consider in women with right upper quadrant pain. *Cleve Clin J Med* 2004; **71**: 233–9.

6 Rice PA. Gonococcal arthritis (disseminated gonococcal infection). *Infect Dis Clin North Am* 2005; **19**: 853–61.

7 Cook RL, Hutchison SL, Østergaard L *et al*. Systematic review: noninvasive testing for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. *Ann Intern Med* 2005; **142**: 914–25.

8 Chernesky MA, Jang DE. APTIMA transcription-mediated amplification assays for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. *Expert Rev Mol Diagn* 2006; **6**: 519–25.

9 Whiley DM, Tapsall JW, Sloots TP. Nucleic acid amplification testing for *Neisseria gonorrhoeae*: an ongoing challenge. *J Mol Diagn* 2006; **8**: 3–15.

10 Choudhury B, Risley CL, Ghani AC *et al*. Identification of individuals with gonorrhoea within sexual networks: a population-based study. *Lancet* 2006; **368**: 139–46.

11 Bilek N, Martin IM, Bell G *et al*. Concordance between *Neisseria gonorrhoeae* genotypes recovered from known sexual contacts. *J Clin Microbiol* 2007; **45**: 3564–7.

12 Martin IMC, Hoffmann S, Ison CA. European Surveillance of Sexually Transmitted Infections (ESSTI): the first combined antimicrobial susceptibility data for *Neisseria gonorrhoeae* in Western Europe. *J Antimicrob Chemother* 2006; **58**: 587–93.

13 CDC, Worokowski KA, Berman SM. Sexually transmitted diseases treatment guidelines. *MMWR Recomm Rep* 2006; **55** (RR–11): 1–94.

14 CDC. Update to CDC's sexually transmitted diseases treatment guidelines, 2006: fluoroquinolones no longer recommended for treatment of gonococcal infections. *MMWR Morb Mortal Wkly Rep* 2007; **56**: 332–6.

15 Newman LM, Moran JS, Workowski KA. Update on the management of gonorrhoea in adults in the United States. *Clin Infect Dis* 2007; **44** (Suppl. 3): S84–101.

16 Clinical Effectiveness Group, BASHH. *National Guideline on the Diagnosis and Treatment of Gonorrhoea in Adults* 2005. www.bashh.org/guidelines/2005/gc_final_0805.pdf.

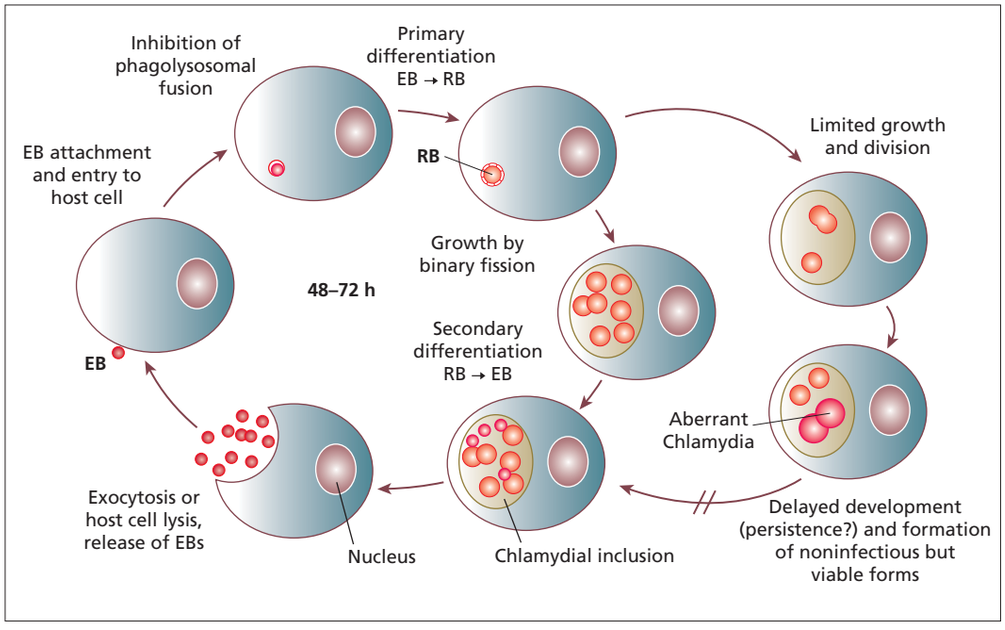


Fig. 34.40 Developmental cycle of *Chlamydia*. EB, elementary body; RB, reticulate body.

Genital *Chlamydia* infections

Chlamydia trachomatis is a common cause of acute and chronic infections worldwide. *C. trachomatis* A–C strains are responsible for ocular trachoma, which is a major cause of blindness. Genital *Chlamydia* D–K strain infections are considered the world's most common sexually transmitted bacterial pathogens, causing both acute and chronic infections affecting the genital tract and other organs. The frequent absence of symptoms associated with early infections facilitates their spread.

Causative organism. Chlamydiae are obligate intracellular parasites. They exhibit a peculiar two-stage developmental cycle that includes an extracellular, infectious elementary body and an intracellular, vegetative reticulate body (Fig. 34.40).

This cycle begins when infectious, metabolically inert elementary bodies (EBs) attach to and stimulate uptake by the host cell. The internalized EB remains within a host-derived vacuole, termed an inclusion, and differentiates into a larger, metabolically active reticulate body (RB). The RB multiplies by binary fission, and after 8 to 12 rounds of multiplication, the RBs differentiate to EBs asynchronously. At 48–72 h post-infection, EB progeny are released from the host cell to initiate another cycle. *In vivo*, the persistence of *Chlamydia* may be induced by certain antibiotics, by nutritional deficiencies and by interferon-γ [1]. The precise role of persistent infections in the maintenance of genital *Chlamydia* reservoirs is currently not well understood.

Epidemiology. The number of diagnoses of genital *Chlamydia* infections has risen steadily since the mid-1990s in the UK. Risk factors for infection include age <25 years, new sexual partner or more than one sexual partner in the past year (a new sexual partner being more important than number of partners) and lack of consistent use of condoms [2]. Prevalence studies indicate that approximately 10% of sexually active people aged less than 25 years are currently infected (Fig. 34.41). In response to the evidence of high and increasing rates of infection, the UK Government has introduced a national chlamydial screening programme (NCSP) [3–5].

Clinical features. In males, asymptomatic infection may occur in up to 50%. In GUM clinics, men commonly present with signs and symptoms of anterior urethritis, consisting of mucopurulent urethral discharge and dysuria, with an onset 1–3 weeks after intercourse with an infected partner (Fig. 34.42a). In men practising receptive anal intercourse, rectal infections may occur. These are often without symptoms, but some will have proctitis manifest as anal discharge and discomfort [6].

In females, 70% of infections are asymptomatic. Others present with a variety of symptoms including post-coital or intermenstrual bleeding, lower abdominal pain, vaginal discharge and dysuria. Typically, in such patients there are signs of mucopurulent cervicitis and/or contact bleeding (Fig. 34.42b).

Extragenital infections also occur. Pharyngeal infections are usually asymptomatic. Infection of the eye causes acute follicular conjunctivitis which is usually, but not always, associated with genital infection.

Complications. In men, local complications include periurethral abscess and urethral stricture. Ascending infection causes epididymo-orchitis.

In the absence of treatment, 10–40% of infected women will develop pelvic inflammatory disease (PID), with a significant proportion of these cases being asymptomatic or having mild, atypical symptoms. PID can result in tubal factor infertility, ectopic pregnancy and chronic pelvic pain. The risk of developing PID

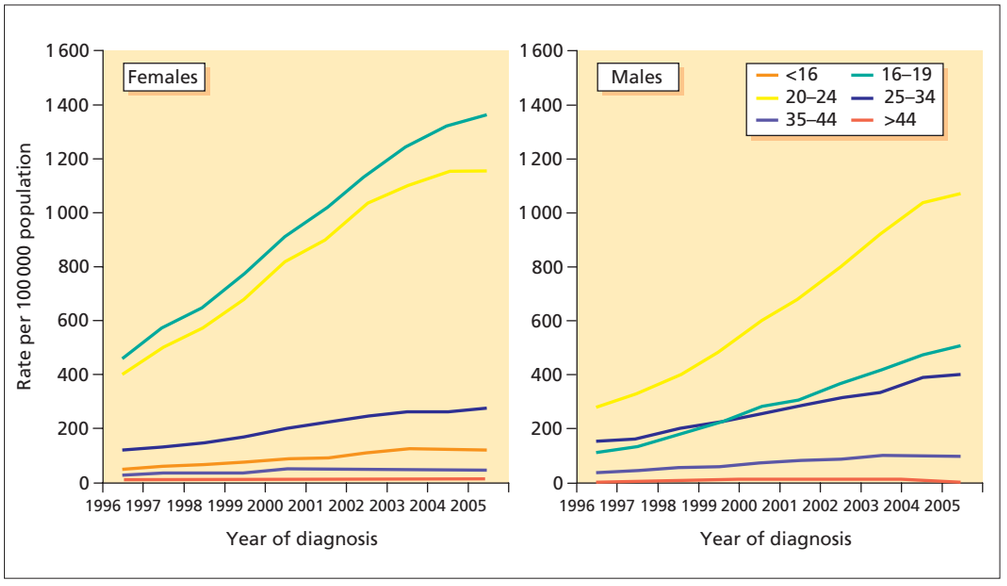
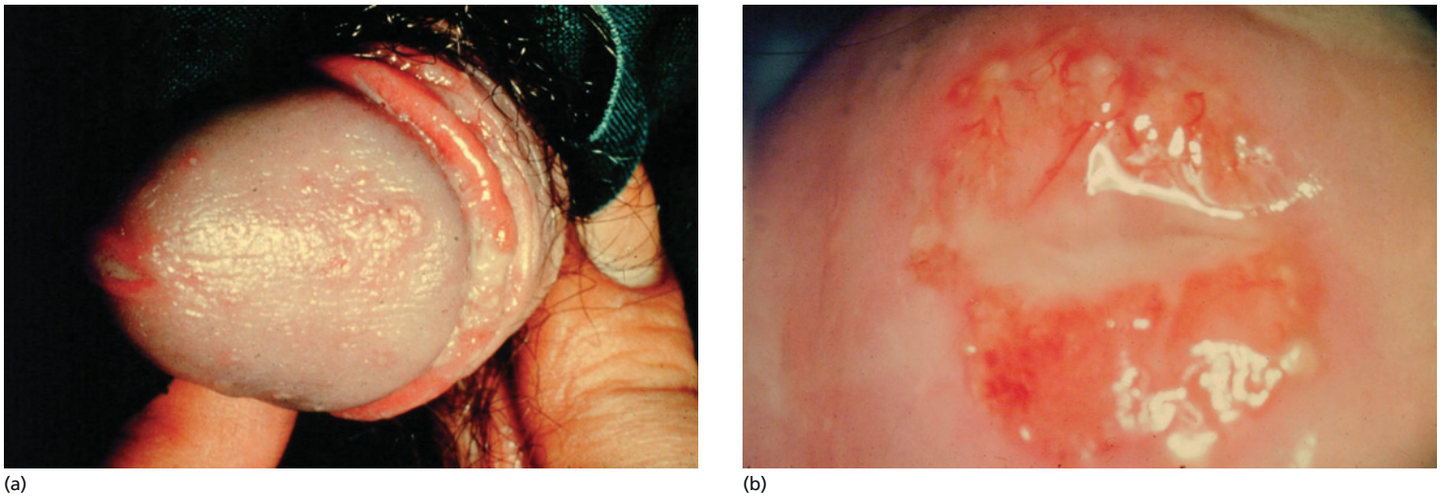


Fig. 34.41 Rates of genital chlamydial infection by age group. UK data 1996–2005. Data sources: KC60 and STIS/ISD(D)5 returns from GUM clinics.



(a) (b)

Fig. 34.42 Genital *Chlamydia* infection. (a) Urethritis. (b) Cervicitis.

increases with each recurrence of *C. trachomatis* infection, as does the risk of reproductive sequelae. Fitz–Hugh–Curtis syndrome presents as upper right-sided abdominal pain caused by perihepatitis. Fibrinous 'violin-string' adhesions can be seen at laparoscopy [7].

Vertical transmission causes neonatal conjunctivitis, pneumonia and failure to thrive in the first 3 months of life.

Around 1–3% of adults will develop sexually acquired reactive arthritis. The classical triad of Reiter's syndrome consists of urethritis, arthritis and conjunctivitis. Not all of these features are necessarily present. In addition, there may be other distinct mucocutaneous manifestations including circinate balanitis, erosions affecting the buccal and rectal mucosa and keratoderma blenorrhagica (Fig. 34.43).

Diagnosis.

Nucleic acid amplification tests (NAATs). These tests have now become the standard for all cases, including medicolegal cases. There are a variety of test types and platforms which all have a sensitivity of 90–95% [8,9]. In autumn 2006, a new genetic variant of CT was reported that contained a 377-bp deletion in the cryptic plasmid contained by all genital *Chlamydia* strains, which is situated in the area targeted by some commercial CT assays [10]. This was initially detected in Sweden but has since been reported in other countries, and may cause false-negative results.

In men, first-void urine samples give equally as good results as urethral swabs, and being painless have higher patient acceptability. In females, an endocervical swab is preferred, although first-void urine samples and self-taken vaginal swabs give results that are almost as good [11–13].

Currently, none of the NAATs has FDA approval for rectal, pharyngeal or conjunctival testing. Only culture or direct fluorescent antibody (DFA) are recommended.

Cell culture. This has a high specificity but a sensitivity of between 60 and 80%. It is more demanding of specimen type, collection



Fig. 34.43 Reiter's syndrome. (a) Circinate balanitis. (b) Chlamydial follicular conjunctivitis. (c) Acute arthritis with effusion. (d) Keratoderma blenorrhagica.

and transportation. Moreover, it requires special laboratory expertise and is now available in few laboratories.

Direct fluorescent antibody (DFA). These tests use monoclonal antibodies targeted at *C. trachomatis* elementary bodies. They are labour intensive and require skilled personnel, but are useful for specimens taken from extragenital sites.

Management. Uncomplicated infections are usually treated with tetracycline or macrolide antibiotics [14]. Single-dose azithromycin is simple, convenient and has high patient compliance. Patients treated with doxycycline should be advised about the risk of photosensitivity. Management should also include screening for other STIs and HIV, contact tracing of sexual partners, and advice about avoidance of re-exposure to untreated partners, and risk reduction methods for the future.

Although high cure rates are reported with standard treatment, and generally test of cure for *Chlamydia* infections is not mandatory, it is recognized that persistence of *Chlamydia* may occur and that there is often a high rate of reinfection [15]. In view of this, some clinicians recommend that patients are reviewed to assess their compliance, and to retest at 4–6 weeks after treatment completion, especially pregnant women and those with disease complications.

References

1 Hogan RJ, Mathews SA, Mukhopadhyay S *et al*. Chlamydial persistence: beyond the biphasic paradigm. *Infect Immun* 2004; **72**: 1843–55.

2 Low N, McCarthy A, Macleod J *et al*. Chlamydia Screening Studies Project Group. Epidemiological, social, diagnostic and economic evaluation of population screening for genital chlamydial infection. *Health Technol Assess* 2007; **11**: iii–iv, ix–xii, 1–165.

3 Simms I, Battison T, Macintosh M *et al*. The National Chlamydia Screening Programme and the NICE guidance on one-to-one interventions: remember the under-25s. *Sex Transm Infect* 2007; **83**: 171.

4 Adams EJ, Turner KM, Edmunds WJ. The cost effectiveness of opportunistic chlamydia screening in England. *Sex Transm Infect* 2007; **83**: 267–74.

5 Scott Lamontagne D, Baster K, Emmett L *et al*. Chlamydia Recall Study Advisory Group. Incidence and reinfection rates of genital chlamydial infection among women aged 16–24 years attending general practice, family planning and genitourinary medicine clinics in England: a prospective cohort study by the Chlamydia Recall Study Advisory Group. *Sex Transm Infect* 2007; **83**: 292–303.

6 Hamlyn E, Taylor C. Sexually transmitted proctitis. *Postgrad Med J* 2006; **82**: 733–6.
7 Nozu T, Komiyama H. Fitz-Hugh-Curtis syndrome. *Ann Intern Med* 2006; **45**: 221–2.
8 Chernesky MA, Jang DE. APTIMA transcription-mediated amplification assays for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. *Expert Rev Mol Diagn* 2006; **6**: 519–25.
9 Hadgu A. Issues in *Chlamydia trachomatis* testing by nucleic acid amplification test. *J Infect Dis* 2006; **193**: 1335–6.
10 Björkman J, Jonsson L, Nilsson P. Prevalence of the new genetic variant of *Chlamydia trachomatis* in Södra Älvsborg County, Västra Götaland Region, Sweden. *Eurosurveillance* 2007; 6. http://www.eurosurveillance.org/ew/2007/070614.asp#4
11 Skidmore S, Horner P, Herring A *et al*. Chlamydia Screening Studies (ClaSS) Project Group. Vulvovaginal-swab or first-catch urine specimen to detect *Chlamydia trachomatis* in women in a community setting? *J Clin Microbiol* 2006; **44**: 4389–94.
12 Hoebe CJ, Rademaker CW, Brouwers EE *et al*. Acceptability of self-taken vaginal swabs and first-catch urine samples for the diagnosis of urogenital *Chlamydia trachomatis* and *Neisseria gonorrhoeae* with an amplified DNA assay in young women attending a public health sexually transmitted disease clinic. *Sex Transm Dis* 2006; **33**: 491–5.
13 Keane FE, Bendall R, Saulsbury N, Haddon L. A comparison of self-taken vulvovaginal and cervical samples for the diagnosis of *Chlamydia trachomatis* infection by polymerase chain reaction. *Int J STD AIDS* 2007; **18**: 98–100.
14 Clinical Effectiveness Group 2006. *UK National Guideline for the Management of Genital Tract Infection with Chlamydia trachomatis*. www.bashh.org/guidelines/2006/chlamydia_0706.pdf
15 Peterman TA, Tian LH, Metcalf CA *et al*. RESPECT-2 Study Group. High incidence of new sexually transmitted infections in the year following a sexually transmitted infection: a case for rescreening. *Ann Intern Med* 2006; **145**: 564–72.

Lymphogranuloma venereum

Lymphogranuloma venereum (LGV) is a sexually transmitted disease that is caused by certain *Chlamydia trachomatis* serovars that primarily infect the lymphatics. It was initially described in 1833 by Wallace, defined as a distinct clinical entity by Durand, Nicolas and Favre in 1913, and is also known as tropical or climactic bubo, lymphopathia venerea, lymphogranuloma inguinale and poradenitis inguinalis [1].

Causative organism. LGV is caused by *Chlamydia trachomatis* serovars L1, L2 and L3, which, unlike the oculogenital D–K strains that cause mucosal disease, invade and damage lymphatics. The organism enters through skin breaks and abrasions or crosses the epithelial cells of mucous membranes, and travels via the lymphatics to multiply within mononuclear phagocytes in regional lymph nodes. Thrombolymphangitis and perilymphangitis occur and are associated with necrosis and the formation of stellate abscesses. Fistulae and sinus tract formation may ensue. Healing with fibrosis disrupts lymphatic drainage, leading to chronic oedema.

In the bowel wall, ulceration occurs with granulomatous change and crypt abscesses. Stricture formation often follows fibrotic healing.

Epidemiology. LGV has long been prevalent in tropical countries of Africa, Asia, the Caribbean, and Central and South America. Classical disease is usually acquired heterosexually and is manifest as genital ulceration with suppurative regional lymphadenopathy [2].

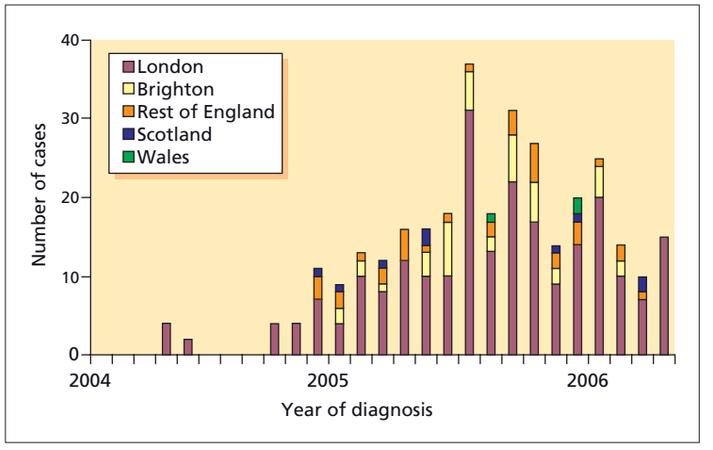


Fig. 34.44 Laboratory confirmed cases of LGV, UK, Jan. 2004 to March 2006. Enhanced LGV surveillance.

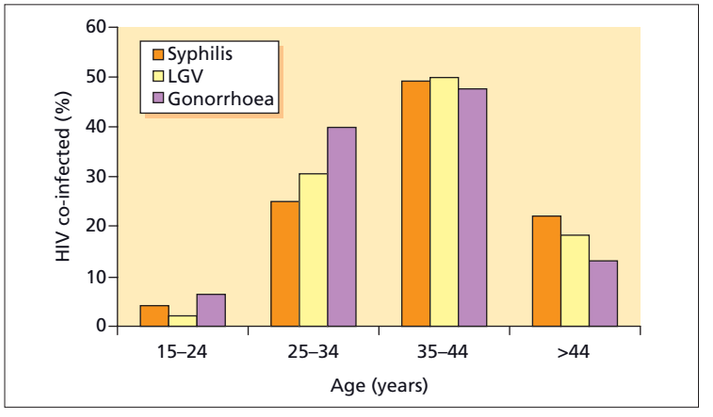


Fig. 34.45 Co-infection of HIV with syphilis, gonorrhoea and LGV among MSM, UK: 2005. Gonococcal resistance to antimicrobials surveillance and enhanced surveillance for LGV and syphilis.

It has been rare in developed countries, being mainly seen as an imported infection in travellers returning from endemic countries. However, in 2003 a cluster of cases were reported from the Netherlands in men who have sex with men (MSM) presenting with proctocolitis [3,4]. Since then, similar outbreaks have been reported from many European countries and North America. Between 2003 and 2006, over 400 cases had been confirmed by the Sexually Transmitted Diseases Reference Laboratory in the UK, mainly in young to middle-aged MSM of white ethnicity [5] (Fig. 34.44). Many of the affected men had participated in high risk sexual behaviour with multiple sexual partners and in practices with a high risk of anal trauma. There has been a high incidence of concurrent infection with both HIV and hepatitis C [6] (Fig. 34.45).

Clinical features. LGV occurs in three stages. The majority of LGV infections in the primary and secondary stages may go undetected.

The primary stage, occurring 3–30 days after transmission, is characterized by the appearance of a transient herpetiform ulcer



Fig. 34.46 Lymphogranuloma venereum. Inguinal syndrome showing 'sign of the groove'.

at the site of inoculation. This is most often unnoticed, heals rapidly and usually leaves no scar.

The secondary stage occurs after 2–6 weeks, is classically described as the inguinal syndrome, and is characterized by painful inguinal lymphadenitis and associated constitutional symptoms. The lesion is tender, initially unilateral, and frequently progresses to suppurative bubos with multiple fistulae formation. Enlargement of the femoral and inguinal lymph nodes separated by the inguinal ligament produces the 'sign of the groove' in about one-third of cases (Fig. 34.46). The differential diagnosis is wide and includes syphilis, chancroid, granuloma inguinale, cat-scratch disease, tularaemia, plague, mycobacterial disease and lymphoproliferative disorders.

In women, external lymphadenopathy is less common because the primary involvement is usually on the cervix or other internal surfaces which drain to the perirectal and deep iliac lymph nodes. The presenting symptoms of their involvement may mimic those of pelvic inflammatory disease, tubo-ovarian abscess or appendicitis.

In MSM engaging in receptive anal intercourse, the secondary stage presents as an anorectal syndrome. Patients complain of mucopurulent anal discharge, rectal pain and bleeding, tenesmus and constipation. Ulcerative proctocolitis similar to that in inflammatory bowel disease is seen. Other differential diagnoses include enteric infections; other STIs caused by gonorrhoea, oculogenital strains of *C. trachomatis*, herpes simplex virus and cytomegalovirus; and actinomycosis and schistosomiasis.

The tertiary stage of LGV may occur many years after the initial stages. The manifestations result from fibrosis and lymphatic obstruction. Elephantiasis of the external genitalia causes polypoid growths, fistulae, chronic ulceration, scarring and deformity. Late complications also include rectal strictures, and chronic rectovaginal and urethral fistulae, and are reported to predispose to malignant change.

Diagnosis. LGV should be considered in the differential diagnosis in patients presenting with genital ulceration, inguinal lymphadenopathy, proctocolitis or rectal stricture. The diagnosis is confirmed by detection of the L serovar of *C. trachomatis* from the site of infection. Specimens may be obtained from ulcers and the rectum; bubo aspirate less commonly reveals organisms. Culture tests are now rarely performed [7]. The diagnostic method of choice is by nucleic acid amplification tests and confirmation by real-time PCR assays for LGV-specific DNA [8,9]. Serological testing may be undertaken using microimmunofluorescent (MIF) antibody testing to the L-serovar in specialized laboratories. An MIF titre >1:128 is strongly suggestive of LGV, but serological testing lacks sensitivity in early infections. Previously, complement fixation tests were used, but these lack sensitivity and specificity and are now rarely employed. The Frei intradermal test, which was based on a positive hypersensitivity reaction to a purified chlamydial antigen, is now only of historical interest [10].

Imaging studies using CT or MRI scan may be useful if retroperitoneal adenitis or intra-abdominal abscess is suspected, and a barium enema may reveal the characteristic elongated stricture in rectal LGV.

Screening for other sexually transmitted infections, including HIV, and viral hepatitis B and C, should be undertaken.

Table 34.7 Recommended regimens for the treatment of LGV. (BASHH Clinical Effectiveness Guidelines, 2007.)

- Doxycycline 100 mg twice daily orally for 21 days
- Tetracycline 500 mg four times daily for 21 days
- Minocycline 300 mg loading dose followed by 200 mg twice daily for 21 days
- Erythromycin 500 mg four times daily orally for 21 days

Management. The recommended treatment is with doxycycline 100 mg twice daily or erythromycin 500 mg four times daily for 3 weeks [11,12]. Patients require regular review until clinical manifestations resolve. Azithromycin may also be effective, although there is a lack of recent prospective treatment studies (Table 34.7).

Bubos may require repeated aspiration. Longer-term complications such as fistulae and strictures may require surgery to alleviate symptoms.

Prevention. Early treatment improves the prognosis and reduces transmission. Because of the diverse manifestations, patients may present to a variety of clinical specialties so increased awareness of the resurgence of LGV in developed countries is important.

Many countries have established enhanced surveillance schemes and facilitated access to diagnostic laboratories with the capability to undertake molecular diagnosis of LGV. Targeted interventions aimed at improved control of STIs and HIV in MSM may also help improve control in developed countries.

References

1 Richardson D, Goldmeier D. Lymphogranuloma venereum: an emerging cause of proctitis in men who have sex with men. *Int J STD AIDS* 2007; **18**: 11–4.

2 Mabey D, Peeling RW. Lymphogranuloma venereum. *Sex Transm Infect* 2002; **78**: 90–2.

3 Nieuwenhuis RF, Ossewaarde JM, Gotz HM *et al*. Resurgence of lymphogranuloma venereum in Western Europe: an outbreak of *Chlamydia trachomatis* serovar L2 proctitis in The Netherlands among men who have sex with men. *Clin Infect Dis* 2004; **39**: 996–1003.

4 Gotz HM, van Doornum G, Niesters HG *et al*. A cluster of acute hepatitis C virus infection among men who have sex with men—results from contact tracing and public health implications. *AIDS* 2005; **19**: 969–74.
5 Ward H, Martin I, MacDonald N *et al*. *Lymphogranuloma venereum* in the United Kingdom. *Clin Infect Dis* 2007; **44**: 26–32.
6 Hamill M, Benn P, Carder C *et al*. The clinical manifestations of lymphogranuloma venereum (LGV) versus non-LGV strains of *Chlamydia trachomatis*: a case-control study in homosexual men. *Int J STD AIDS* 2007; **18**: 472–5.
7 Morre SA, Spaargaren J, Fennema JS *et al*. Real-time polymerase chain reaction to diagnose lymphogranuloma venereum. *Emerg Infect Dis* 2005; **11**: 1311–2.
8 Pathella P, Blank S, Shillinger JA. Lymphogranuloma venereum: old pathogen, new story. *Curr Infect Dis Rep* 2007; **44**: 143–50.
9 Sturm PD, Moodley P, Govender K *et al*. Molecular diagnosis of lymphogranuloma venereum in patients with genital ulcer disease. *J Clin Microbiol* 2005; **43**: 2973–5.
10 Perine PL, Stamm WE. Lymphogranuloma venereum. In: Holmes KK, Sparling PF, Mardh PA *et al*., eds. *Sexually Transmitted Diseases*, 3rd edn. New York: McGraw Hill, 1999: 423–32.
11 British Association of Sexual Health and HIV. *2006 National Guideline for the Management of Lymphogranuloma Venereum (LGV)*. www.bashh.org/guidelines/2007/lgv_gdl_revised_final2_1106.pdf
12 Centres for Disease Control and Prevention. *2006 STD Treatment Guidelines*. www.cdc.gov/std/treatment/

Chancroid

Chancroid (ulcus molle; soft chancre; Ducrey's disease), one of the three venereal diseases originally defined in the 1917 UK legislation, is a genital ulcer disease (GUD) caused by the bacterium, *Haemophilus ducreyi*. Although previously endemic, it has become rare in most developed countries. In the UK, it is usually imported by travellers returning from resource-poor parts of the world where it remains common [1].

Causative organism. *Haemophilus ducreyi* is a Gram-negative bacillus which has similar growth requirements and biochemical properties to other *Haemophilus* species, but shows differences by rRNA analyses that suggest it is more closely linked to the *Actinobacillus* cluster of the Pasteurellaceae. It has a single 1.7-MB chromosome and details of the DNA genome have been published. The organism has considerable potential to develop antimicrobial resistance via both plasmid and chromosomally-mediated mechanisms. It remains extracellular in clinical lesions, is able to avoid phagocytosis by granulocytes and macrophages, and mediates damage by the production of various toxins and by cytokine induction [2].

The organism is fastidious, requires complex, expensive nutritive media, and grows best at 32–33°C in a humid atmosphere containing 5% CO_2. Different strains grow preferentially on different media. Culture is not routine in most laboratories.

There are no commercial tests available for the detection of *H. ducreyi* by nucleic acid amplification, but a number of in-house tests have been described in higher prevalence areas. This is often combined with detection of herpes simplex virus and *T. pallidum* in multiplex tests [3,4].

Epidemiology. Chancroid remains endemic in Africa, Asia, Latin America and the Caribbean. Even there it has become less common following the introduction of syndromic management protocols for GUD and, as in developed countries, it has become replaced by herpes simplex virus as the most common infective cause of GUD [5–7]. Typically, it is found in locations where migrant labour is common, families are disrupted and commercial sex work thrives. The usual reservoir is unrecognized infection in commercial sex workers. It remains a matter of dispute whether true asymptomatic carriage occurs.

Sporadic outbreaks of chancroid, spreading from infections acquired abroad, are occasionally reported in Europe and North America.



Fig. 34.47 Chancroidal penile ulceration.

Clinical features. The incubation period of chancroid is usually short, between 3 and 10 days. An inflammatory papule develops at the sites of inoculation, in which micropustules develop and then progress to form ulcers. The lesions are usually multiple, up to 1 cm in diameter, tender, have ragged undermined edges and a purulent base, and bleed easily.

Lesions are more common in uncircumcised men and are usually located in the coronal sulcus or on the inner aspect of the prepuce (Fig. 34.47). Perianal lesions occur in MSM. In women, lesions may be recognized at the vaginal introitus or on the labia; vaginal and cervical lesions may also occur but often go unnoticed. In one-third of cases, there is accompanying inguinal lymphadenitis, which may progress to suppurating bubo formation. Fluctuant inguinal abscesses will rupture and discharge (Figs 34.48 & 34.49).

Other complications are uncommon. Phagadenic ulceration and resulting genital deformity may occur with secondary infection. Extragenital lesions may occur via autoinoculation to the fingers or thighs. Lesions of the lips and oral cavity have been described. Systemic disease does not occur.

Vertical transmission and neonatal disease is extremely rare. Recently, chronic skin ulceration of the legs caused by *H. ducreyi* in children visiting Samoa has been described [8].

HIV infection and chancroid. Chancroid is important for its role in facilitating acquisition and transmission of HIV infection. In HIV-infected patients, chancroidal lesions are usually unchanged,



Fig. 34.48 Giant penile chancroid with inguinal bubo.



Fig. 34.49 Chancroidal ulceration of the penis with discharging inguinal bubo.

although in those with more advanced immunosuppresion lesions may be more numerous, slower to heal, and more often fail to respond to single-dose treatment regimens. Prompt treatment of chancroid may reduce local and systemic HIV replication [9].

Diagnosis. Testing for *H. ducreyi* is not routinely available in most UK diagnostic laboratories.

Direct detection by microscopy of smears from chancroidal lesions typically shows sheets of the organism in a 'shoal of fish' pattern, but this has low sensitivity and specificity and is no longer recommended. Specimens for culture or for PCR diagnosis may be considered, where appropriate facilities are available, in patients with suspicious lesions returning from endemic countries, or in their partners.

GUD often has a mixed aetiology so tests for other genital pathogens are essential and follow-up serological testing for syphilis and HIV infection should be performed.

Serological tests have been described that may be useful in epidemiological studies, but these have no role in routine patient management.

Table 34.8 Recommended regimens for treatment of chancroid. (BASHH Clinical Effectiveness Guidelines, September 2007.)

- Azithromycin 1 g orally in a single dose
- Ceftriaxone 250 mg i.m. in a single dose
- Ciprofloxacin 500 mg orally in a single dose
- Ciprofloxacin 500 mg orally twice a day for 3 days
- Erythromycin base 500 mg orally four times a day for 7 days

Management. Single-dose treatment with either ciprofloxacin 500 mg or azithromycin 1 g, both given orally, or ceftriaxone 250 mg i.m. are associated with cure rates in excess of 90% [10,11]. Erythromycin, given as 500 mg four times daily for 7 days, is also effective, but is associated with poorer compliance (Table 34.8).

Fluctuant bubos should be aspirated, with care being taken to introduce the needle through adjacent areas of healthy skin.

Prevention. Improved sexual health care and prompt use of syndromic management for GUD has led to a reduction in the incidence of chancroid in endemic areas [12]. Epidemiological treatment for partners exposed to the index patient from 2 weeks prior to symptom onset is recommended.

Male circumcision has recently been clearly demonstrated to reduce the risk of chancroid [13]. In countries with a high HIV prevalence, the introduction of circumcision and other new HIV prevention measures may help to significantly reduce the incidence of chancroid.

References

1 Lewis DA, Ison CA. Chancroid. *Sex Transm Infect* 2006; **82** (Suppl. 4): 19–20.

2 Bauer ME, Townsend CA, Ronald AR, Spinola SM. Localization of *Haemophilus ducreyi* in naturally acquired chancroidal ulcers. *Microbes Infect* 2006; **8**: 2465–8.

3 Mackay IM, Harnett G, Jeoffreys N *et al*. Detection and discrimination of herpes simplex viruses, *Haemophilus ducreyi*, *Treponema pallidum*, and *Calymmatobacterium* (*Klebsiella*) *granulomatis* from genital ulcers. *Clin Infect Dis* 2006; **42**: 1431–8.

4 Liu AY, Jiang MJ, Yin YP, Sun JF. Detection of pathogens causing genital ulcer disease by multiplex polymerase chain reaction. *Chin Med Sci J* 2005; **20**: 273–5.

5 Ahmed HJ, Mbwana J, Gunnarsson E *et al*. Etiology of genital ulcer disease and association with human immunodeficiency virus infection in two Tanzanian cities. *Sex Transm Dis* 2003; **30**: 114–9.

6 Riedner G, Todd J, Rusizoka M *et al*. Possible reasons for an increase in the proportion of genital ulcers due to herpes simplex virus from a cohort of female bar workers in Tanzania. *Sex Transm Infect* 2007; **83**: 91–6.

7 Nilsen A, Kasubi MJ, Mohn SC *et al*. Herpes simplex virus infection and genital ulcer disease among patients with sexually transmitted infections in Dar es Salaam, Tanzania. *Acta Derm Venereol* 2007; **87**: 355–9.

8 Ussher JE, Wilson E, Campanella S *et al*. *Haemophilus ducreyi* causing chronic skin ulceration in children visiting Samoa. *Clin Infect Dis* 2007; **44**: e85–7.

9 Janowicz DM, Tenner-Racz K, Racz P *et al*. Experimental infection with *Haemophilus ducreyi* in persons who are infected with HIV does not cause local or augment systemic viral replication. *J Infect Dis* 2007; **195**: 1443–51.

10 Annan NT, Lewis DA. Treatment of chancroid in resource-poor countries. *Expert Rev Anti Infect Ther* 2005; **3**: 295–306.

11 Roy-Leon JE, Lauzon WD, Toye B *et al*. In vitro and in vivo activity of combination antimicrobial agents on *Haemophilus ducreyi*. *J Antimicrob Chemother* 2005; **56**: 552–8.

12 Hoyo C, Hoffman I, Moser BK *et al*. Improving the accuracy of syndromic diagnosis of genital ulcer disease in Malawi. *Sex Transm Dis* 2005; **32**: 231–7.

13 Weiss HA, Thomas SL, Munabi SK, Hayes RJ. Male circumcision and risk of syphilis, chancroid, and genital herpes: a systematic review and meta-analysis. *Sex Transm Infect* 2006; **82**: 101–10.

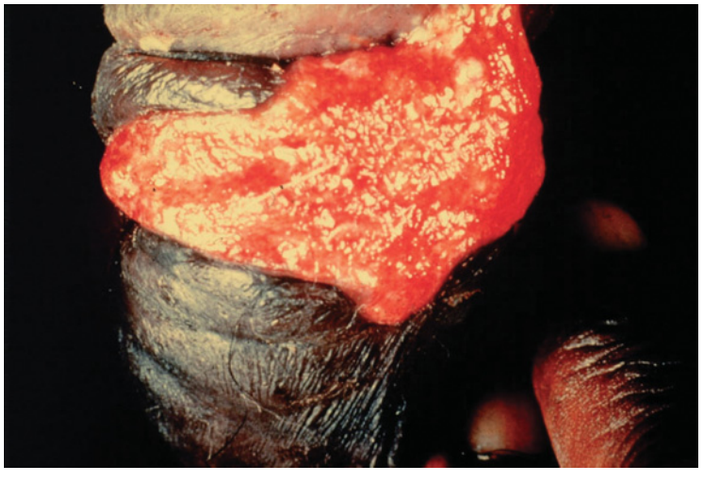


Fig. 34.50 Granuloma inguinale. Beefy-red penile granuloma.



Fig. 34.51 Granuloma inguinale. Inguinal granulomas.



Fig. 34.52 Granuloma inguinale. Vulval granulomas.

Granuloma inguinale

Granuloma inguinale, also known as Donovanosis, is uncommon in the UK [1]. It is a rare cause of genital ulcer disease, may be followed by genital disfigurement, and has the potential for malignant change [2,3]. Much about the condition is imperfectly understood.

Causative organism. The causative organism is *Calymmatobacterium granulomatis*, a Gram-negative organism which shares phylogenetic similarity with *Klebsiella* species. Some authorities have suggested that the organism be reclassified as *Klebsiella granulomatis* [4,5].

Epidemiology. The condition is found mainly in hot and tropical geographical locations, most often in marginalized populations with poor access to health care. In recent years, it has been most commonly reported in South Africa, Southern India, Indonesia, Vietnam and the Aboriginal populations of Australia. Sporadic cases have also been reported from the Caribbean countries and Brazil.

Granuloma inguinale is generally regarded as being a sexually transmitted disease because of the usual genital location of lesions, increased incidence in those individuals and age groups with the highest sexual activity, and its association with other STIs. Non-venereal spread has been reported in non-sexually active children, as has transmission to the neonate during vaginal delivery. The incubation period of the condition is not precisely known, but is generally considered to be long, and was around 50 days when human experimental inoculation was performed.

Clinical features. The initial lesion is a papule or subcutaneous nodule that ulcerates [6]. The typical lesions, which may be multiple, consist of large beefy-red, non-tender granulomatous ulcers that bleed easily and gradually extend (Fig. 34.50). Raised lesions with a hypertrophic, irregular edge may also occur. Secondary infection can result in necrotic, foul-smelling, deep ulcers. Some lesions may show spontaneous healing to give dry, fibrotic lesions and scarring.

Lesions commonly occur on the coronal sulcus or inner aspect of the penile prepuce in uncircumcised men, on the anus in MSM, and the labia or vaginal introitus in females. Cervical lesions occur and have to be differentiated from those of carcinoma and genital tuberculosis. Lymphadenopathy is not usual unless there are other ulcer pathogens present, but subcutaneous extension of granulomas may mimic enlarged inguinal lymph nodes (Figs 34.51 & 34.52). Extragenital lesions occur in a few cases, most often on the lips and oral cavity, or on the trunk. The former are presumed to occur from orogenital sexual contact, and the latter from autoinoculation. Rarely, dissemination to bone and liver have been reported, more commonly in pregnant women and those with cervical infection.

Granuloma inguinale may be followed by pseudo-elephantiasis, resulting from persistent granulomas which may constrict

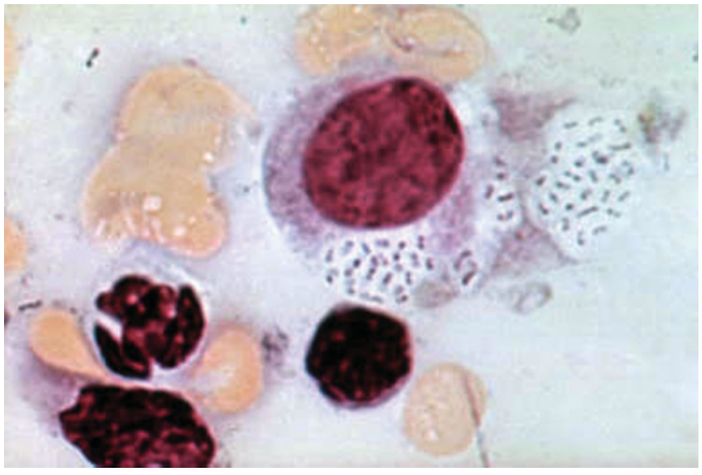


Fig. 34.53 Biopsy smear. Mononuclear cells containing causative organism showing bipolar staining.

lymphatics, by genital scarring and disfigurement. Malignant change may occur in longstanding lesions.

The differential diagnosis includes other causes of genital ulcer disease, which may coexist, other infective conditions such as genital amoebiasis and tuberculosis, other granulomatous lesions such as Crohn's disease, and genital cancers.

Diagnosis.

Microscopy. The diagnosis is generally made by microscopic identification of Donovan bodies from lesions. These are found in large mononuclear cells of the monocyte/macrophage lineage whose cytoplasm contains numerous organisms, 0.5–0.7 by 1–1.5 µm in size, that show bipolar staining ('safety-pin appearance') (Fig. 34.53).

Specimens may be prepared from smears taken directly from lesions, but sensitivity of the test is increased by preparing smears from the underside of biopsy specimens [7]. Giemsa, Wright's or Leishman's stains are usually used [8,9]. Donovan bodies have been reported in Papanicolaou-stained smears from the cervix.

Histology. Histological examination shows epithelial proliferation with a heavy infiltrate of plasma cells and neutrophils, with few lymphocytes.

Culture. This is rarely undertaken or successful because the organism is extremely fastidious, but success in both a monocyte co-culture system [10] or modified *Chlamydia* culture [11] have been reported.

PCR. More recently, a PCR-based diagnostic test has been reported from Australia as a research technique [12], but there is no commercial test generally available.

There is no serological test of proven reliability.

It is important that a full range of investigations for other STIs, especially those causing GUD, and for HIV should be undertaken. Sexual partners should be sought for examination.

Management. The treatment of choice is azithromycin [13]. There are various regimens. The WHO recommend 1 g orally immediately, followed by 500 mg daily for 3 weeks or until complete lesion healing. Alternatively, azithromycin may be administered as 1 g orally at weekly intervals, for a minimum of 3 weeks.

Alternative antibiotics include co-trimoxazole 960 mg twice daily, ciprofloxacin 750 mg twice daily, or doxycycline 100 mg twice daily for 3 weeks. Some specialists recommend the addition of an aminoglycoside (e.g. gentamicin 1 mg/kg i.v. every 8 h) to these regimens if improvement is not evident within the first few days of therapy.

Co-infection with HIV infection. There have been some reports of longer time to healing in HIV-infected persons with granuloma inguinale, but there is no clear consensus on whether HIV infection alters clinical presentation or disease management.

Prevention. The comparative rarity of the condition in most developed countries has made granuloma inguinale one of the least studied and understood of the causes of GUD. Primary prevention efforts are the same as those being advocated for other STIs, and secondary prevention depends upon active case management and contact tracing.

Further research effort is needed and should focus upon improved diagnostic methods and their inclusion in multiplex-PCR investigation of genital ulcer pathogens.

References

1 Donovan C. Ulcerating granuloma of the pudenda. *Indian Medical Gazette* 1905; **40**: 414.
2 O'Farrell N. Donovanosis. *Sex Transm Infect* 2002; **78**: 452–7.
3 Richens J. Donovanosis (granuloma inguinale). *Sex Transm Infect* 2006; **82** (Suppl. IV): iv21–iv22.
4 Carter JS, Bowden FJ, Bastian I *et al.* Phylogenetic evidence for reclassification of *Calymmatobacterium granulomatis* as *Klebsiella granulomatis* comb nov. *Int J Systematic Bacteriol* 1999; **49**: 1695–700.
5 Kharsany AB, Hoosen AA, Kiepiela P *et al*. Phylogenetic analysis of *Calymmatobacterium granulomatis* based on 16S rRNA gene sequences. *J Med Microbiol* 1999; **48**: 841–7.
6 Hart G. Donovanosis (granuloma inguinale). *Clin Infect Dis* 1997; **25**: 24–32.
7 Cannefax GR. The technique of the tissue spread method for demonstrating Donovan bodies. *J Vener Dis Inform* 1948; **29**: 210–4.
8 Sehgal VN, Jain MK. Tissue section Donovan bodies—identification through slow Giemsa (overnight) technique. *Dermatologica* 1987; **174**: 228–31.
9 O'Farrell N, Hoosen AA, Coetzee K *et al*. A rapid stain for the diagnosis of granuloma inguinale. *Genitourin Med* 1990; **66**: 200–1.
10 Kharsany AB, Hoosen AA, Kiepiela P *et al*. Growth and cultural characteristics of *Calymmatobacterium granulomatis*—the aetiological agent of granuloma inguinale (donovanosis). *J Med Microbiol* 1997; **46**: 579–85.
11 Carter J, Hutton S, Sriprakash KS *et al.* Culture of the causative organism of donovanosis (*Calymmatobacterium granulomatis*) in HEp-2 cells. *J Clin Microbiol* 1997; **35**: 2915–7.
12 Carter J, Bowden FJ, Sriprakash KS *et al*. Diagnostic polymerase chain reaction for donovanosis. *Clin Infect Dis* 1999; **28**: 1168–9.
13 Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2006. *MMWR* 2006; **55** (RR11): 1–94.

CHAPTER 35
HIV and the Skin

C.B. Bunker[1] *& F. Gotch*[2]

[1]Chelsea and Westminster and Royal Marsden Hospitals, and Faculty of Medicine, Imperial College, London, UK
[2] Faculty of Medicine, Imperial College, Chelsea and Westminster Hospital, London, UK

HIV infection, 35.1
Epidemiological trends, 35.1
Molecular epidemiology, 35.2
Virology, 35.3
Immunology, 35.3
AIDS case definition, 35.4
Natural history, 35.5
HIV treatment, 35.5
Dermatological manifestations of HIV infection, 35.8
Acute primary HIV infection/seroconversion, 35.10
Pruritus, xerosis and ichthyosis, 35.11
Pigmentary disorders, 35.12
Coagulopathies, 35.12
Inflammatory dermatoses, 35.13
Drug reactions, 35.20
Infections, 35.24
Neoplasms, 35.36
Special situations, 35.41

Introduction

It is now 25 years since acquired immune deficiency syndrome (AIDS) was first recognized as a novel disease. Within 2 years of defining AIDS as a distinctive syndrome in 1981, the human immunodeficiency virus (HIV) was identified as the causative agent. HIV infection is acquired sexually, from blood or blood products, or vertically from an infected mother during pregnancy, birth or breastfeeding. The virus infects immunocompetent cells including CD4 T cells and macrophages. It creates variable patterns of disease in individuals, groups and races but all are characterized by evolving, sometimes fulminant immunodysfunction (AIDS) affecting many systems of the body.

Dermatological involvement in AIDS has been appreciated since the disease was first recognized as a cryptic acquired immune deficiency illness in homosexual men and before the causative virus was identified. Mucocutaneous involvement establishes criteria for diagnosis and staging; the prognostic significance of some complications, for example pruritic papular eruption/eosinophilic folliculitis, hairy leukoplakia and Kaposi's sarcoma (KS), was well recognized before specific treatments were introduced. The proportion of patients with skin complications and the number of these manifestations in any one patient increase as HIV progresses and AIDS develops. The incidence and severity of several common cutaneous diseases (such as mollusca, herpes simplex, seborrhoeic dermatitis) are increased in patients with HIV and this correlates in many instances with the absolute numbers of CD4 T cells. The effect HIV infection may have on some dermatological conditions such as psoriasis and leprosy is less clear-cut. Since the recognition of AIDS there have been many case reports of uncommon dermatoses in HIV-positive patients where an association is speculative. The skin and mucosae may be routes for infection by and targets for prevention (e.g. by male circumcision) or treatment of HIV (e.g. by Langerhans' cell fusion inhibitors). Human immunodeficiency virus has been demonstrated in the dermis of infected individuals and may be present in Langerhans' cells. Different cytokine expression patterns distinguish different cutaneous manifestations. The advent of highly active antiretroviral therapy (HAART) has been largely beneficial to patients with HIV-associated skin disease, but novel side effects of these drugs (such as lipodystrophy) have emerged and the skin can be affected by manifestations of the immune reconstitution inflammatory syndrome/immune reconstitution disease (IRIS/IRD).

The dermatological complications of HIV and AIDS may be distressing to patients and difficult for dermatologists to diagnose and manage. Also, some dermatoses presenting in the populace at large need to be regarded as possible 'indicator conditions' to prompt advice about, and initiation of, HIV testing. A move to 'normalization' of HIV testing through 'opt out protocols' is advocated in clinical practice so as to decrease the number of patients presenting with more advanced disease and diminish the scale of unsuspecting forward transmission. This is especially important as patients successfully treated with HAART can achieve the same mortality rates as the general population.

However, the dermatological manifestations of HIV are of further interest in that the 'experiment of nature' sheds light on both the immunopathological natural history of HIV infection and the aetiology of common and rarer dermatoses that happen to be found with a higher incidence in HIV-infected than non-HIV-infected patients. Their occurrence emphasizes the importance of the skin as a dynamic immunological organ.

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

HIV infection

Epidemiological trends

AIDS was first described as a distinct clinical entity in 1981 [1]. HIV.1 infection now represents a global pandemic. In 2006, there

Table 35.1 Global trends in the HIV pandemic. (From [2].)

Region	Epidemic started	Adults and children living with HIV/AIDS	Adult prevalence rate (%)*	Main mode of transmission in adults
Sub-Saharan Africa	Late 1970s, early 1980s	24.5 M	6.1	Heterosexual
North Africa and Middle East	Late 1980s	440 000	0.2	Heterosexual, IDU
Asia	Late 1980s	8.3 M	0.4	Heterosexual, IDU, MSM
Latin America	Late 1970s, early 1980s	1.6 M	0.5	MSM, IDU, heterosexual
Caribbean	Late 1970s, early 1980s	330 000	1.6	Heterosexual, MSM
Eastern Europe	Early 1990s	1.5 M	0.8	IDU
Western Europe, Central Europe, North America	Late 1970s, early 1980s	2 M	0.5	MSM, IDU, heterosexual
Oceania	Late 1970s, early 1980s	78 000	0.3	MSM
Total/mean		39.45 M	1.0	

IDU, transmission through injecting drug use; MSM, sexual transmission among men who have sex with men.
* The proportion of adults (15–49 years of age) living with HIV/AIDS in December 2006.

were an estimated 2.9 million deaths from AIDS worldwide. Of AIDS cases, 95% occur in non-industrialized countries, 75% in sub-Saharan Africa. An estimated 39.5 (34.1–47.1) million people were believed to be living with HIV infection in December 2006 [2].

Global trends in the HIV pandemic are shown in Table 35.1. These data are sourced from UNAIDS [2] who take estimates available from published studies and combine them with unpublished data, collected as part of AIDS control programmes in many countries, to provide national estimates of prevalence and deaths. Of adult infections, 47.5% are thought to be in women, and 6% of the total numbers of infections are in children under 15 years of age.

In the UK, an average of more than 2500 HIV infections was reported each year between 1991 and 1997 [3]; 66% of these were from London. At the end of 2005, the number of adults living with HIV in the UK was estimated to have risen to 63 500 (of whom 32% had not been diagnosed) according to the Health Protection Agency's (HPA) annual report on HIV/AIDS and STIs. More than half of all infections in the UK are thought to be in homosexual men, 29% are as a result of heterosexual sex, and intravenous drug use accounted for 7%, except in Scotland, where it accounted for 20% of infections. Less than 1% of HIV infections diagnosed are attributed to blood, tissue or bloodfactor treatment, and almost all of these infections were acquired before the widespread introduction of screening of donors.

Molecular epidemiology

One of the major characteristics of HIVs is their extremely high genetic variability. This extensive heterogeneity is a result of the high error rate of reverse transcriptase [4] and the extremely fast turnover of virions in HIV-infected individuals [5,6]. In addition, the reverse transcriptase enzyme is highly recombinogenic [7], so that radically different genomic combinations may be generated in individuals infected by genetically diverse viruses. Recombination requires the simultaneous infection of a cell with two different pro-viruses, allowing the encapsidation of one RNA transcript from each pro-virus into the heterozygous virion. After the subsequent infection of a new cell, the reverse transcriptase, moving back and forth between the two RNA templates, generates a newly synthesized retroviral DNA sequence that is a recombinant between the two parental genomes [7–9]. It is now well established that recombination events between different subtypes or clades of HIV are relatively common, and may result in circulating recombinant forms (CRFs) of HIV. Members of one distinct CRF should resemble each other over the entire genome, with similar break-points reflecting similar ancestry from the same recombination event(s).

Two main types of HIV infect humans: HIV.1 and HIV.2. Worldwide, HIV.1 is by far the commonest cause of AIDS. HIV.2, which differs in a number of its regulatory genes and is found predominantly in West Africa, apparently causes immune deficiency and AIDS more slowly than HIV.1, and is less infectious with lower rates of either sexual or mother-to-child transmission.

Phylogenetic analyses of many samples of HIV.1, isolated from diverse geographical origins, have revealed that they can be divided into *groups*, *subtypes* (or *clades*), *sub-subtypes* and *CRFs* [10–13]. Groups are the distinctive HIV.1 lineages: M (major), N (new) and O (outlier). The vast majority of HIV.1 strains found worldwide and responsible for the pandemic belong to the M lineage. Group O is endemic in Cameroon and neighbouring countries, and group N has only very recently been identified in West Central Africa.

Within group M there are further genetic subtypes or clades which are approximately equidistantly related to each other and represent a homogeneous group not resembling any other subtype across their entire genome. There are at present nine subtypes of HIV.1 identified: A–D, F–H, J and K. All known representatives of what was initially described as subtype E appear, in fact, to be recombinants of subtypes A and E and are now designated CRF01-AE. Within some subtypes further phylogenetic structure can be identified, for example subtype or clade F is divided into two sub-subtypes or subclades F1 and F2. It is also clear that clades B and D might be better considered as subclades of a single subtype, but for historical reasons it is difficult to change these descriptions [14].

Table 35.2 Clades of HIV.

Clade	Estimated incidence 2000 (%)	Primary geographical distribution
A	27	East, West and Central Africa, Eastern Europe
B	12.3	USA, UK, Australia
C	47.2	South Africa, India, China
D	5.3	East Africa
A/E	3.2	South-East Asia
F, G, H, J, K	5.0	Central Africa, Caribbean, Latin America

Different subtypes of HIV.1 are predominantly found at different geographical locations, although in no country of the world is a single subtype circulating alone. The contribution of the different clades to the worldwide pandemic has been calculated [15–17] (Table 35.2).

Virology

HIV is a single-stranded RNA virus. The structure of the virus is complex, with three major structural genes: *gag* (coding for nuclear proteins), *pol* (coding for reverse transcriptase) and *env* (coding for the envelope). The rate of transcription of the genome is controlled by a number of regulatory genes including *rev, tat* and *nef*, and there are a number of other small accessory genes important for infection (*vif*, *vpu*, *vpr*).

The virus gains access to the cells by docking the envelope protein on the CD4 receptor and on co-receptors (primarily CCR5 on monocytes/macrophages, and CXCR4 on T cells). The process of fusion and inward passage of the genetic material of the virus is accomplished by the transmembrane envelope protein gp41 coming into contact with the cell surface. Components of the *gag* protein have an important chaperone function within the cell and allow reverse transcription to occur and the circular DNA product to be transported to the nucleus of the cell. There, a virally encoded enzyme, integrase, cleaves the circular DNA and inserts it into the host DNA, repairing the insertion sites. Pro-viral DNA may remain integrated for a substantial period of time before viral transcriptional events are triggered when the cell becomes activated. Initial transcriptional products are the regulatory proteins *rev*, *tat* and *nef*. The *tat* protein increases viral transcription, and *rev* acts in *cis* to enhance replication by interacting with *rev* regulatory elements within the viral genome; *nef* has a number of putative functions, one of which may be to reduce the amount of major histocompatibility complex (MHC) class I antigen on the cell surface and thus impede recognition of the infected cell by cytotoxic T cells (see below). The *vpr* gene is involved in nuclear transport and may down-regulate cellular apoptosis. The *vpu* gene may down-regulate the amount of CD4 receptor protein being produced in the endoplasmic reticulum. Viral products of transcription are then transported to the cytoplasm, where the nuclear capsid proteins may again have an important chaperone function. Viral proteins are produced as a long polyprotein that is split into active proteins by the virally encoded protease enzyme. Viral RNA and viral proteins are then assembled around the nuclear capsid antigen, and when the virus is fully assembled it buds from the cell surface.

It is now realized that enormous amounts of viral RNA are continually released into the plasma (>10^8 viral particles per day) in untreated HIV-infected patients [5,6].

Immunology

The immune system is capable of mounting very strong attacks on invading pathogens and in many cases is able to eliminate them completely. Unfortunately this does not seem to be the case with HIV infection, except perhaps in a very few individuals in whom exposure to the virus has resulted in specific cellular immune responses to the virus, but who have neither seroconverted nor become productively infected [18]. Although often strong and apparently useful anti-HIV responses are induced in HIV-infected individuals, these do not seem to have the capability of clearing viral infection; however, in some individuals immune responses apparently play a role in allowing the host to coexist with the virus without progression to disease (long-term non-progressor patients; see 'Natural history' below and [19]).

Primary infection with HIV results in natural or innate immune responses that are mobilized within hours of infection and include inflammation, non-specific activation of macrophages, natural killer cells and complement, and release of cytokines.

After antigenic stimulation, acquired immune responses are primed. These responses emerge at the same time as clearance of viraemia and rebound of CD4 T cells is seen. These HIV-specific responses are outlined below.

Specific humoral or antibody responses [20]. These consist of neutralizing antibodies to the envelope proteins of the virus and other non-neutralizing antibodies to internal viral proteins such as *gag*. Specific secretory IgA mucosal antibodies are also produced. Neutralizing antibodies are usually measurable by 12 weeks after infection.

Specific cellular (T-lymphocyte) responses [21]. CD8 T lymphocytes or cytotoxic T cells (CTLs) form a primary component of the critical cellular immune response induced by HIV infection. CTLs are differentiated from existing CTL precursors, and express T-cell receptor molecules capable of recognizing specific viral epitopes presented in the context of human leukocyte antigen (HLA) or MHC molecules at the surface of infected target cells. Mature CTLs are functional 5–10 days after antigenic stimulation, recognizing, binding and then lysing the infected target cell. Virus-specific CTLs evolve faster than antibody responses and are often induced before seroconversion and before viral RNA has reached peak titres. Thus CD8 CTLs are temporally associated with the fall in viraemia during acute infection, and there is good evidence that CTLs play a major role in the control of HIV infection at this time and later in HIV disease. Evidence for strong CD8 antiviral pressure can be appreciated by the number and variety of strategies which viruses have evolved to avoid apoptosis and CTL recognition, thus prolonging the life of the virally infected cell and enabling viral replication and dissemination [22]. In addition to the lysis

of infected cells, CD8 T cells can reduce viral replication by the production of soluble factors. These factors are not antigen specific but their production requires specific T-cell activation. Anti-HIV effects have been found for interferon (IFN)-γ, interleukin (IL)-10, IL-13, IL-16 and the C-C chemokines MIP (macrophage inhibitory protein)-1α, MIP-1β and RANTES (regulated upon activation, normal T-cell expressed and secreted). Such soluble factors may also have profound effects on other opportunistic infections including those affecting the skin.

CD4 T-cell responses induced by HIV infection provide help to both HIV-specific CTLs and B cells. CD4 T-helper cells recognize antigen in the context of HLA class II molecules on the surface of antigen-presenting cells such as dendritic cells. CD4 responses to a variety of HIV proteins (including *env*, *gag* and *nef*) have been demonstrated in early disease, but immunological abnormalities in T-helper function occur very early in HIV infection, even before CD4 T-cell numbers diminish in the peripheral blood. Furthermore, advances in our understanding of HIV.1 pathogenesis reveal that mucosal tissues, primarily in the gastrointestinal tract, are major sites for early viral replication and CD4 T-cell destruction, and may represent the major viral reservoir [23]. Reduced proliferative capacity and diminished IL-2 production in response to stimulation by exogenous antigens (including those from HIV and other pathogens) is one of the hallmarks of HIV disease.

On recognition of their specific antigen, naïve CD4 T cells differentiate from a common (Th0) precursor into T-helper (Th)1 cells, which differentially secrete IL-2, IFN-γ, transforming growth factor-β and IL-12 and can activate macrophages and 'help' CTLs, or into Th2 cells, which secrete IL-4, IL-5, IL-6 and IL-10 that can activate B cells to proliferate and differentiate into antibody-producing plasma cells.

Central to the cellular immune response is the dendritic cell, which is the most potent antigen-presenting cell. However, such cells on mucosal surfaces (Langerhans' cells) may be some of the first targets in transmission; as well as transporting viral antigens across mucosal barriers and presenting them to CD4 cells, dendritic cells may themselves become infected with HIV, and their function compromised.

It should be noted that the immunosuppressive nature of HIV infection, where CD4 T cells are infected and destroyed, may have a profound effect on immune responses to other pathogens, many of which result in dermatological disease and are described later in this chapter. It is interesting to observe that HAART, which has a profound effect on HIV replication and enables some CD4 T-cell reconstitution, may also result in the re-emergence of useful opportunistic infection-specific cellular immune responses. Unfortunately, for reasons which are not well understood, HIV-specific responses are often not reconstituted. However, many AIDS-defining opportunistic infections, including diseases of the skin, may be resolved or avoided, and consequently HAART has had a profound effect on morbidity and mortality in HIV disease.

AIDS case definition

As tests for HIV infection have become more accurate and our understanding of the infection's pathogenesis has become clearer, the need for an epidemiological definition of AIDS has diminished. However, it is of interest to consider the indicator conditions that have been used in the case definition of AIDS in adults, as shown in Table 35.3. The rank order of AIDS diagnoses reported to the Centers for Disease Control (USA) in 1996 is shown in Table 35.4 [24,25].

Changes in the natural history of HIV which have followed the introduction of HAART in the mid-1990s include a sharp reduction in the frequency of KS and a decrease in *Pneumocystis carinii* (now *P. jiroveci*) pneumonia, reflecting the impact of prophylaxis

Table 35.3 Indicator conditions in the case definition of AIDS in adults.

Candidosis of oesophagus, trachea, bronchi or lungs
Cervical cancer, invasive*
Coccidioidomycosis, extrapulmonary*
Cryptococcosis, extrapulmonary
Cryptosporidiosis with diarrhoea for >1 month
Cytomegalovirus of any organ other than liver, spleen or lymph nodes
Herpes simplex with mucocutaneous ulcer for >1 month or bronchitis, pneumonitis oesophagitis
Histoplasmosis, extrapulmonary*
HIV-associated dementia: disabling cognitive and/or motor dysfunction interfering with occupation or activities of daily living
HIV-associated wasting:* involuntary weight loss of >10% of baseline plus chronic diarrhoea (more than two loose stools per day for >30 days) or chronic weakness and documented enigmatic fever for >30 days
Isosporosis with diarrhoea for >1 month*
Kaposi's sarcoma in patient younger than 60 years (or older than 60*)
Lymphoma of brain in patient younger than 60 years (or older than 60*)
Lymphoma, non-Hodgkin's of B-cell or unknown immunological phenotype and histology showing small non-cleaved lymphoma or immunoblastic sarcoma
Mycobacterium avium or *M. kansasii*, disseminated
Mycobacterium tuberculosis, disseminated*
Mycobacterium tuberculosis, pulmonary*
Nocardiosis*
Penicilliosis
Pneumocystis carinii pneumonia
Pneumonia, recurrent (bacterial)*
Progressive multifocal leukoencephalopathy
Salmonella septicaemia (non-typhoid), recurrent*
Strongyloidosis, extraintestinal
Toxoplasmosis of internal organ

* Requires positive HIV serology.

Table 35.4 Rank order of AIDS diagnoses reported to the Centers for Disease Control (USA) in 1996.

Pneumocystis carinii pneumonia	20%
Wasting	14%
Cytomegalovirus disease	6%
Kaposi's sarcoma	6%
Tuberculosis	5%
Disseminated *Mycobacterium avium–intracellulare* infection	4%
Chronic herpes simplex	4%
Recurrent bacterial pneumonia	4%
HIV-associated dementia	4%
Toxoplasmosis	3%

and possible reconstitution of immune responses specific for opportunistic pathogens. The median CD4 T-cell count at the time of an AIDS-defining complication in those parts of the world where HAART is available is now 67×10^6/L. However, it should be remembered that, at present, such efficacious therapy is not available to the vast majority of persons infected with HIV.

It should also be noted that the AIDS case definition in children may be different from that in adults [26]. Furthermore, it is currently considered that in clinical care HIV disease should be viewed as a continuum, rather than just the presence or absence of AIDS. This continuum includes primary infection, symptomatic infection, early symptomatic state (previously known as AIDS-related complex), late symptomatic disease and advanced disease.

Natural history

Prospective epidemiological studies in HIV-infected but untreated individuals with known dates of seroconversion have allowed us to quantify many aspects of the natural history of HIV disease, and have shown that the course of HIV infection may vary considerably in different individuals. Thus, although some individuals develop AIDS within 2–3 years, and are termed 'rapid progressors', others remain free from AIDS for more than 10–15 years, and are termed 'long-term non-progressors' or 'long-term survivors'. In the absence of treatment, the average time from seroconversion to the development of AIDS is 8–11.6 years, with a median time of approximately 10 years. Interestingly, this median survival time is the same in the USA as it is in Uganda [27]. It should be noted that most existing data were obtained before the availability (in the West) of antiretroviral (ARV) drugs and prophylaxis for *Pneumocystiis jiroveci* pneumonia. Clearly such drug treatment, when available, has a profound and beneficial effect on the natural history of HIV disease.

Certain clinical and laboratory factors are known to influence and help predict the rate of disease progression to AIDS in the HIV-infected individual. Rates of progression appear similar by gender, race and risk category after adjustment for access to health care. The predictors for progression to AIDS may be summarized as follows.

- *Transmission risk group*. Time from HIV seroconversion to AIDS is approximately 7 years in transfusion recipients, 10 years for haemophiliacs, 10 years for intravenous drug users and 10–12 years for homosexual men.
- *Age at onset of infection*. It has been reported that for patients aged 16–24 years at time of HIV acquisition the median time from seroconversion to AIDS is 15 years, whereas for those aged over 35 at seroconversion it is 6 years.
- *Clinical indicators*. Patients with symptomatic primary HIV infection (about 75% of all) progress more rapidly than those with asymptomatic seroconversion. Other clinical markers of progression include the development of oral thrush, oral hairy leukoplakia, herpes zoster, constitutional symptoms and weight loss.
- *CD4 T-cell count*. CD4 T-cell counts and their decline over time are very important predictors of disease progression. On average the CD4 T-cell count decreases by $40–80 \times 10^6$/L annually; an acceleration in CD4 T-cell decline heralds progression of disease. A CD4 T-cell count of $<200 \times 10^6$/L is diagnostic of AIDS, and the median survival time in an untreated patient with a CD4 T-cell count of $<200 \times 10^6$/L is 38–40 months. The average CD4 T-cell count for the most common AIDS-defining conditions is in the range of $20–100 \times 10^6$/L.
- *Viral load*. Plasma HIV RNA viral load correlates well with the extent of viral replication in an infected individual. Progressively increasing HIV RNA concentrations can signal the development of advancing immunodeficiency. A single measurement of plasma RNA viral load early in infection is a powerful predictor of the subsequent risk of progression to AIDS and death. The combined measurement of CD4 T-cell count and viral load is an extremely accurate method for assessing the prognosis of infected patients.

Other factors that may be predictive of HIV disease progression have not been well defined. Thus co-infection with other pathogens such as cytomegalovirus (CMV), Epstein–Barr virus, hepatitis B or malaria has not been shown conclusively to accelerate disease progression. Intriguingly, it has been suggested that co-infection with hepatitis G may reduce the rates of HIV progression. The genetic background of the patient has relevance. Genetic markers of progression that have been defined include polymorphisms in genes such as *CCR5*, which influences the ability of cells to become infected with HIV, and differences in HLA class I alleles, which may influence immune responses. The size and route of the initial inoculum of virus may have an important role to play, as may the pathogenicity, virulence, attenuation state or genotype of the infecting virus.

HIV treatment

Antiretroviral treatment of HIV began in the mid-1980s with the nucleoside analogue (nucleoside reverse transcriptase inhibitor-NRTI) zidovudine (azidothymidine: AZT, ZDV) and the demonstration that this was better than placebo in the treatment of symptomatic disease. However, the treatment of HIV infection was revolutionized in developed countries as a result of the introduction of HAART. This has reduced short-term mortality and markedly increased quality of life by preventing opportunistic diseases [28]. HAART has developed as a result of controlled trials showing that dual nucleoside analogue therapy improves survival compared with zidovudine (AZT, ZDV) monotherapy [29], and that three-drug therapy, consisting of two nucleoside analogues and a protease inhibitor (PI), is superior to two drugs [30].

One of the causes of drug failure is the development of viral mutations displaying reduced sensitivity to drugs. Such mutations may arise either because of selection of mutants already existing in the viral swarm or the *de novo* generation of new mutations as a result of selective pressure by the drugs. Avoidance of the development of drug resistance requires drugs to be used in combination, making selection or generation of new resistant mutations more difficult, and by the use of potent therapy, which suppresses viral replication as completely as possible.

The dramatic improvements in survival with the use of HAART coincided with the development of two new potent classes of drugs. Following incorporation of viral DNA into the host genome, viral progeny are produced as a result of the transcription of this DNA, which accompanies cell activation. This produces polyproteins, which to be effective have to be digested by a virally coded protease. A variety of inhibitors of this protease (PIs) are now available to clinicians and all are extremely potent.

The other potent class of compounds are the non-nucleoside reverse transcriptase inhibitors (NNRTIs). As described previously, the virus encodes for a unique enzyme, reverse transcriptase, that is responsible for converting viral RNA into a DNA copy, which is then incorporated in the host genome. The originally introduced therapies for HIV were all nucleoside analogues, which act as chain terminators of the growing DNA chain. Reverse transcriptase can also be inhibited very potently by a variety of chemicals that act in a pocket of the reverse transcriptase closely adjacent to the catalytic site. The potency of these drugs was only appreciated when they were given to individuals who had not previously received treatment, accompanied by nucleoside analogues [31]. This combination inhibits viral replication sufficiently completely to prevent selection of viral mutants with resistance to the NNRTI class [32]. Novel ARV drugs include integrase inhibitors, fusion inhibitors and potential compounds that might target HIV proteins essential for efficient viral replication such as Vif, Vpr, Tat, Rev and Nef [33].

Current guidelines for when to start treatment can be obtained from the British HIV Association (BHIVA) at http://www.bhiva.org [34]. The original hypothesis for optimum treatment of HIV infection was 'hit hard and hit early' [35], that is to use potent regimens and to use them early in the disease course with the hope of completely eradicating evidence of infection within a finite period. Unfortunately, as our understanding of the pathogenesis of HIV infection has improved, this hypothesis has turned out to be unrealistic, perhaps most importantly because HIV is also incorporated into long-lived cells which generally divide very occasionally [36], and which may be relatively inaccessible to immune effector cells. It is only during the process of cellular replication that anti-HIV drugs are active, and therefore the early hopes of eradication within a 3 to 4-year period have not been realized, and it is likely that present treatment will be required lifelong to continually suppress viral replication. Early treatment was also advocated because it was assumed that HIV caused irreversible deletions in the immune repertoire and so if treatment was started late patients would remain susceptible to opportunistic infections. Fortunately, this has been shown not to be the case. Even individuals treated in late disease show considerable reconstitution of the immune repertoire [37,38].

Perhaps the most important practical reason for renewed caution about the timing of initiating antiretroviral therapy was the emergence of a variety of drug toxicities that were unsuspected at the time the drugs were originally licensed. For the nucleoside analogue class this includes mitochondrial toxicity and lactic acidosis [39], and for the PIs a variety of abnormalities of lipid metabolism. However, the greatest obstacle to a more complete understanding of these syndromes is that, of necessity, most of the present studies are observational and cross-sectional and represent the end result of processes that have been present in the patient for some years.

New drugs are being developed in the classes available at present, that is NRTIs, NNRTIs and PIs. The main objective of such new drugs is to improve adherence to treatment by enhancing the convenience of the regimen or to diminish side effects. Thus the PI, atazanavir, appears to be free of blood lipid abnormalities in controlled trials [40], but whether this will translate into freedom from the lipid redistribution syndrome remains to be determined. Classes of drugs that attack new targets within the replication cycle of HIV are also being developed; the most advanced of these are those which inhibit the process of fusion. This is an important example of where an understanding of the detailed mechanisms involved in viral fusion have led to the development of new drugs. The most advanced of these is enfuvirtide (T20). This drug inhibits the contraction of the helical coils associated with gp41, which normally contract and bring the surface of the envelope protein of the virus (gp120) into close contact with the cell surface. The disadvantage of this drug is that it has to be given by subcutaneous injection once or twice a day, and it therefore seems unlikely that this drug will be tolerated in the long term for naïve patients. Its chief benefit is likely to be in patients who are failing other therapies.

Also in the process of development are a variety of small molecules that are orally bioavailable and which may inhibit the interaction between HIV and the second receptor on the host cell surface, that is CCR5 or CXCR4. Such drugs have been shown to produce viral load reductions in phase I studies by inhibiting the CCR5 receptor, although the drug JM3100, which inhibits CXCR4, has not shown equivalent benefit [41]. At an even earlier stage of development are products that inhibit the interaction between the CD4 receptor and the conserved portion of gp120. These molecules are highly potent *in vitro*; however, some HIV strains are relatively resistant to its action. In the future it is hoped that a variety of fusion inhibitors may act synergistically, thereby allowing some of the older drugs with an important side effect profile to be used less often.

New drugs, more tolerable regimens, limited development of resistance in fully adherent patients and increasing recognition of non-AIDS related morbidity (e.g. myocardial infarction, stroke, cirrhosis, renal failure) and non-AIDS-related cancers are some of the factors behind a move to earlier introduction of treatment, at CD4 counts around 350×10^6/L; randomized trials are needed to evaluate the benefits of initiating treatment at higher CD4 counts, for example 500×10^6/L [42].

The overall success of HAART is such that now HIV-infected adults with a CD4 cell count greater than 500×10^6/L on long-term combination treatment reach the same mortality rates as the general population [43]. However, there will always be challenging patients and clinical situations. Treatment may fail for many reasons—from poor compliance and adherence to drug resistance. The principles of second line, third line and salvage treatment are available from the BHIVA (http://www.bhiva.org) [34].

Drugs are listed by class in Tables 35.5–35.7; the principal non-dermatological side effects are included. Mucocutaneous side effects are detailed on pp. 35.20–24 and 35.41–45, and in Tables 35.16–35.17 and 35.23–35.24. Lipid abnormalities and

Table 35.5 Nucleoside reverse transcriptase inhibitors (NRTIs). (From [47–49].)

Drug	Side effects
All NRTIs	Nausea, vomiting, abdominal pain, diarrhoea, pancreatitis, lactic acidosis, hepatotoxicity, cough, dyspnoea, bone marrow suppression, fatigue, arthralgia, myalgia, headache, insomnia, fever
Abacavir	HLA B*5701 hypersensitivity syndrome
Didanosine (ddI, DDI)	Bloating, peripheral neuropathy, gynaecomastia, gout, lipoatrophy
Emtricitabine (FTC)	Nausea, headache, fatigue, bad dreams
Lamivudine (3TC)	Peripheral neuropathy
Stavudine (d4T)	Peripheral neuropathy, gynaecomastia, lipoatrophy†
Tenofovir (nucleotide)	Fanconi's syndrome, renal dysfunction, osteoporosis, osteomalacia
Zalcitabine (ddC, DDC)*	Peripheral neuropathy
Zidovudine (AZT/ZDV)	Myopathy, lipoatrophy

* No longer available.
† Lipoatrophy is commoner with stavudine (d4T) than zidovudine (AZT/ZDV) and didanosine (ddI, DDI).

Table 35.6 Non-nucleoside reverse transcriptase inhibitors (NNRTIs). (From [48–50].)

Drug	Side effects
Delavirdine	Biochemical hepatitis
Efavirenz	Insomnia, nightmares, depression
Nevirapine	Clinical and biochemical hepatitis

Table 35.7 Protease inhibitors (PIs). (From [48,49,51].)

Drug	Side effects
All PIs	Lipohypertrophy especially with NRTIs, dyslipidaemia, insulin resistance, hyperglycaemia, anorexia, nausea, diarrhoea, vomiting, abdominal pain, flatulence, hepatotoxicity, pancreatitis, blood dyscrasias, insomnia, fatigue, headache, dizziness, neurotoxicity, myositis, rhabdomyolysis, osteonecrosis, dysgeusia, anaphylaxis
Amprenavir	Gynaecomastia
Atazanavir	Hypertension, gynaecomastia
Darunavir	Gynaecomastia (with ritonavir*)
Fosamprenavir (pro drug of amprenavir)	Depression
Indinavir	Nephrolithiasis, haematuria, hyperbilirubinaemia, porphyria
Lopinavir	Hypertension, myocardial infarction, gynaecomastia, Cushing's, hypothyroidism, lactic acidosis (with ritonavir*)
Nelfinavir	Gynaecomastia
Ritonavir*	Hypertension, gynaecomastia, epilepsy, thrombophlebitis
Saquinavir	Gynaecomastia, candidosis
Tipranavir	Dyspnoea

* Ritonavir in doses so low as to lack antiviral activity 'boosts' the activity of the other PIs. Such a combination with lopinavir (Kaletra) is available in the UK.

lipodystrophy are discussed on p. 35.22. The cutaneous manifestations of immune restoration disease are covered on p. 35.46 and in Table 35.26.

The most serious dermatological side-effects of ARVs are: (i) Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) with nevirapine (less commonly, efavirenz); and (ii) pharmacogenetic abacavir hypersensitivity [44]. The judicious use of nevirapine involves 'safe' starting CD4 counts ($<250 \times 10^6$/L in women and $<400 \times 10^6$/L in men) and an initial dose of 200 mg/day escalating after 2 weeks if no rash or hepatic complications ensue; not every patient developing a rash needs to stop treatment [45]. HLAB*5701 testing has abolished the abacavir hypersensitivity syndrome (previous incidence about 8%) [44].

Dermatologists should be aware of the risks of drug interactions in treating patients with HIV on HAART, particularly because of the metabolism of PIs by the cytochrome P450 system in the liver [46].

References

1 Centers for Disease Control. Kaposi's sarcoma and *Pneumocystis* pneumonia among homosexual men: New York and California. *MMWR* 1981; **30**: 305–8.
2 UNAIDS. *AIDS Epidemic Update* 2006. http://www.unaids.org.
3 AIDS and HIV in the United Kingdom. *Communicable Dis Report* 1988; **8** (13).
4 Preston BD, Poiesz BJ, Loeb LA. Fidelity of HIV.1 reverse transcriptase. *Science* 1988; **242**: 1168–71.
5 Ho DD, Neumann AU, Perelson AS *et al*. Rapid turnover of plasma virions and CD4 lymphocytes in HIV.1 infection. *Nature* 1995; **373**: 123–6.
6 Wei X, Ghosh SK, Taylor ME *et al*. Viral dynamics in human immunodeficiency virus type 1 infection. *Nature* 1995; **373**: 117–22.
7 Hu WS, Temin HM. Retroviral recombination and reverse transcription. *Science* 1990; **250**: 1227–33.
8 Goodrich DW, Duesberg PH. Retroviral recombination during reverse transcription. *Proc Natl Acad Sci USA* 1990; **87**: 2050–6.
9 Stuhlmann H, Berg P. Homologous recombination of copackaged retrovirus RNAs during reverse transcription. *J Virol* 1992; **66**: 2378–88.
10 Robertson DL, Hahn BH, Sharp PM. Recombination in AIDS viruses. *J Mol Evol* 1995; **40**: 249–59.
11 Robertson DL, Anderson JP, Bradac JA *et al*. HIV.1 Nomenclature proposal. *Science* 2000; **288**: 55–6.
12 Robertson DL, Anderson JP, Bradac JA *et al*. HIV.1 Nomenclature proposal. In: *Human Retroviruses and AIDS*. Los Alamos National Laboratory, 1999.
13 Vanden Haesevelde M, Decourt JL, De Leys RJ *et al*. Genomic cloning and complete sequence analysis of a highly divergent African human immunodeficiency virus isolate. *J Virol* 1994; **68**: 1586–96.
14 Peters M. Recombinant HIV sequences: their role in the global epidemic. In: *HIV Molecular Immunology*, 2000: 1.39–1.54.
15 UNAIDS. *Report on the Global HIV/AIDS Epidemic*. Geneva: UNAIDS, 2000.
16 Morison L. The global epidemiology of HIV/AIDS. *Br Med Bull* 2001; **58**: 7–18.
17 Osmanov S, Pattou C, Walker N *et al*. Estimated global distribution and regional spread of HIV-1 genetic subtypes in the year 2000. *J Acquir Immune Defic Syndr* 2002; **29**: 184–90.
18 Bernard N, Yannakis C, Lee J, Tsoukas C. HIV specific cytotoxic T lymphocyte activity in HIV-exposed seronegative persons. *J Infect Dis* 1999; **179**: 538–47.
19 Gea-Banacloche J, Migueles S, Martineo L *et al*. Maintenance of large numbers of virus specific CD8 T cells in HIV infected progressors and long-term non-progressors. *J Immunol* 2000; **165**: 1082–92.
20 Parren PW, Moore J, Burton D, Sattentau Q. The neutralising antibody response to HIV-1: viral evasion and escape from humoral immunity. *AIDS* 1999; **13**: S137–S162.
21 Wilkinson J, Gotch FM. Immune interventions. *Br Med Bull* 2001; **58**: 187–203.
22 Meinl E, Fickenscher H, Thome M *et al*. Anti-apoptotic strategies of lymphotropic viruses. *Immunol Today* 1998; **19**: 474–9.

23 Veazey R, Lackner A. The mucosal immune system and HIV.1 infection. *AIDS Rev* 2003; **5**: 245–52.
24 Easterbrook PJ. Epidemiology of HIV and AIDS. In: Gazzard BG, ed. *Chelsea and Westminster Hospital AIDS Care Handbook*. London: Mediscript, 1999: 1–15.
25 Gazzard B. Natural history of HIV infection. In: Gazzard BG, ed. *AIDS Care Handbook.* London: Mediscript, 2002: 1–11.
26 Barnhart H, Caldwell M, Thomas P *et al.* Natural history of HIV disease in perinatally infected children: an analysis from the Paediatric Spectrum of Disease project. *Pediatrics* 1996; **97**: 710–6.
27 Morgan D, Whitworth J. The natural history of HIV.1 infection in Africa. *Nat Med* 2001; **7**: 143–5.
28 Palella FJ Jr, Delaney KM, Moorman AC *et al.* Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med* 1998; **338**: 853–60.
29 Delta Coordinating Committee. Delta: a randomised double-blind controlled trial comparing combinations of zidovudine plus didanosine or zalcitabine with zidovudine alone in HIV-infected individuals. *Lancet* 1996; **348**: 283–91.
30 Gulick RM, Mellors JW, Havlir D *et al*. Treatment with indinavir, zidovudine, and lamivudine in adults with human immunodeficiency virus infection and prior antiretroviral therapy. *N Engl J Med* 1997; **337**: 734–9.
31 Montaner JS, Reiss P, Cooper D *et al.* A randomized, double-blind trial comparing combinations of nevirapine, didanosine, and zidovudine for HIV-infected patients: the INCAS Trial. Italy, The Netherlands, Canada and Australia Study. *JAMA* 1998; **279**: 930–7.
32 Staszewski S, Morales-Ramirez J, Tashima K. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. *N Engl J Med* 1999; **341**: 1865–73.
33 Hatano H, Deeks SG. Drug resistant HIV. *BMJ* 2007; **334**: 1124–5.
34 Gazzard B (on behalf of the BHIVA Writing Committee). British HIV Association (BHIVA) guidelines for the treatment of HIV-infected adults with antiretroviral therapy (2006). *HIV Med* 2006; **7**: 487–503.
35 Ho DD. Time to hit HIV, early and hard. *N Engl J Med* 1995; **333**: 450–1.
36 Chun TW, Carruth L, Finzi D *et al.* Quantification of latent tissue reservoirs and total body viral load in HIV-1 infection. *Nature* 1997; **387**: 183–8.
37 Phillips A, Staszewski S, Weber R. Viral load changes in response to antiretroviral therapy according to the baseline CD4 lymphocyte count and viral load. *AIDS* 2000; **14**: S3 (abstract PL3.5).
38 Cozzi-Lepri A, Phillips A, d'Aminio Monforte A. When to start HAART in chronically HIV-infected patients? A collection of pieces of evidence from the I.C.O.N.A. study. *AIDS* 2000; **41**: S3 (abstract PL3.4).
39 Chattha G, Arieff AI, Cummings C, Tierney LM Jr. Lactic acidosis complicating the acquired immunodeficiency syndrome. *Ann Intern Med* 1993; **118**: 37–9.
40 Haas D, Zala C, Schrader S. Therapy with atazanavir in patients failing highly active anti-retroviral therapy: a randomised comparative pilot trial. *AIDS* 2004; **18**(4): 704–5.
41 Dameta R, Rabin L, Hincenbergs M. Antiviral efficacy in vivo of the anti-human immunodeficiency virus bicyclam SDZ SID 791 (JM 3100), an inhibitor of infectious cell entry. *Antimicrob Agents Chemother* 1996; **40**: 750–4.
42 Phillips AN, Gazzard BG, Clumeck N *et al*. When should antiretroviral therapy for HIV be started? *BMJ* 2007; **334**: 76–8.
43 Lewden C, Chene G, Morlat P *et al*. HIV-infected adults with a CD4 cell count greater than 500 cells/mm^3 on long-term combination antiretroviral therapy reach same mortality rates as the general population. *J Acquir Immune Defic Syndr* 2007; **46**: 72–7.
44 Owen A, Pirmohamed M, Khoo SH, Back DJ. Pharmacogenetics of HIV therapy. *Pharmacogenet Genomics* 2006; **16**: 693–703.
45 Taiwo BO. Nevirapine toxicity. *Int J STD AIDS* 2006; **17**: 364–9.
46 Robertson SM, Penzak SR, Pau A. Drug interactions in the management of HIV infection; an update. *Expert Opin Pharmacother* 2007; **8**: 2947–63.
47 Moyle G, Gazzard BG. Nucleoside analogue reverse trancriptase inhibitors. In: Gazzard BG, ed. *AIDS Care Handbook.* London: Mediscript, 2002: 317–27.
48 Ward HA, Russo GG, Shrum J. Cutaneous manifestations of anti-retroviral therapy. *J Am Acad Dermatol* 2002; **46**: 284–93.
49 Litt JZ. *Drug Eruption Reference Manual*, 14th edn. New York: Informa Healthcare, 2008.
50 Moyle G, Gazzard BG. Non-nucleoside reverse transcriptase inhibitors. In: Gazzard BG, ed. *AIDS Care Handbook*. London: Mediscript, 2002: 329–32.
51 Moyle G, Gazzard BG. Protease inhibitors. In: Gazzard BG, ed. *AIDS Care Handbook.* London: Mediscript, 2002: 333–40.

Dermatological manifestations of HIV infection

Skin disease may provide the first suspicion of the diagnosis of HIV infection, cause significant morbidity as the disease progresses and point to a diagnosis with important systemic implications. The number of mucocutaneous diseases, like the CD4 T-cell count, is a prognostic indicator of the development of AIDS and overall survival [1]. Cutaneous manifestations of HIV can be considered as good clinical indicators to predict and assess the underlying immune status in resource-poor countries [2]. Some skin problems are less consequential than other manifestations of HIV infection but many are very distressing to patients [3] and some potentially very serious or fatal [4–7]. Although some situations are clinically straightforward and readily amenable to satisfactory intervention, all of the dermatological complications of HIV infection can be a challenge to diagnose and manage. They may present with unusual symptoms and signs, coexist with other pathologies and be altered by treatment; drug reactions are common [3,4–7]; wound healing is impaired [8].

In general, HIV dermatology presents five broad challenges to the dermatologist. Firstly, there is the opportunity to make the initial diagnosis of HIV in patients with a seroconversion illness or with subtle or florid manifestations of one or other dermatoses associated with underlying HIV infection. Next, there is differentiating whether a skin problem is caused by HIV infection or by HIV therapy [9,10]. Thirdly, the dermatologist's therapeutic imagination and experience is occasionally tested. Then there is the imperative for clinicians to be aware of the risks and prevention measures of occupational exposure to HIV [11]. Lastly, there are the implications for what can be learnt from the study of HIV-associated skin disorders for the better understanding of the skin in HIV specifically, and in human health and disease generally: the virus has been demonstrated in the cutis of infected individuals; cutaneous dendritic cells and Langerhans' cells may be the main targets in acute HIV infection and contribute to the pathogenesis of skin disease in chronic infection [12–15]; different cytokine expression patterns distinguish different cutaneous manifestations [16–18]; involvement of cutaneous nerves [19–21] may contribute to the pathogenesis of HIV-related dermatoses [22]; and the skin and mucosae may be targets for prevention (e.g. by male circumcision) or treatment of HIV (e.g. by Langerhans' cell fusion inhibitors) [23,24].

Until recently, suspecting, or failing to suspect, that a patient presenting with a common dermatosis known to be associated with HIV infection might be HIV positive has not been so important. Indeed, in the past the patient's best psychological and fiscal interests might have been better served by relative ignorance. However, the benefits of earlier diagnosis that have ensued from HAART place a greater onus on the clinician than hitherto to

discuss HIV risk with patients presenting with skin diseases known to be associated with HIV and to recommend assessment, counselling and testing. A high index of suspicion is essential, especially in assessing high-risk patients, but there is a move to 'normalization' of HIV testing through 'opt out protocols' where 'indicator conditions' (e.g. in the case of dermatology, seborrhoeic dermatitis, psoriasis, shingles, mollusca, warts and fungal infections) are diagnosed in the general populace. The aim of this approach is to decrease the number of patients presenting with more advanced disease and diminish the scale of unsuspecting forward transmission [25]. An alternative scenario is the evaluation of the patient already known to have HIV infection who presents with dermatological symptoms and whose physician is concerned that the skin condition is a complication of HIV or its treatment. HAART has significantly reduced the cutaneous morbidity of HIV infection but adverse cutaneous reactions to treatment are common [9,26–28].

Conventional clinical dermatological history taking and examination are the beginning of the diagnostic endeavour. Some dermatoses can be diagnosed confidently on clinical grounds, but experience has shown that it is easy to be misled. Immunopathophysiological and neurovascular mechanisms in the skin determine the symptomatic and morphological presentation of all skin diseases, so it is not surprising that 'things look different' in HIV-infected patients. Several cutaneous conditions may coincide, sometimes within a single lesion. The commonest dermatological conditions associated with HIV infection are listed in Table 35.8.

Investigations are frequently necessary. Skin scrapings may be examined microscopically in the clinic (after clearing with potassium hydroxide) for the presence of fungal hyphae or spores. Swabs for bacteria and viruses and scrapings for fungi may be taken for laboratory microscopic examination and culture. Skin biopsy is often undertaken. The operator and assistants should wear gloves, gowns and eyeglasses or safety goggles. Representative samples of lesional skin should be carefully selected for histopathology and culture for fungi and acid-fast bacilli. Many laboratories decline to perform direct immunofluorescence. It is the responsibility of clinicians to take due care in the collection and submission of all pathological material for investigations so that no hazard is created for themselves, staff or other patients.

Table 35.8 Common dermatological conditions in HIV infection. (From [7].)

Pruritus/xerosis/ichthyosis
Nodular prurigo
Folliculitis
Eosinophilic folliculitis
Pruritic papular eruption
Seborrhoeic dermatitis
Psoriasis
Drug eruptions
Herpes simplex
Herpes zoster
Viral warts
Mollusca
Oral and vaginal candidosis
Tinea (including onychomycosis)
Scabies
Basal cell carcinoma
Squamous cell carcinoma
Kaposi's sarcoma

References

1 Jensen BL, Weisman K, Sindrup JH *et al*. Incidence and prognostic significance of skin disease in patients with HIV/AIDS: a 5-year observational study. *Acta Derm Venereol (Stockh)* 2000; **80**: 140–3.

2 Raju PV, Rao GR, Ramani TV, Vandana S. Skin disease: clinical indicator of immune status in human immunodeficiency virus (HIV) infection. *Int J Dermatol* 2005; **44**: 646–9.

3 Hawkins T. Appearance-related side effects of HIV-1 treatment. *AIDS Patient Care STDS* 2006; **20**: 6–18.

4 Bunker CB. Dermatological problems in HIV and AIDS. In: Miller A, ed. *Medical Management of HIV and AIDS*. London: Springer, 1996.

5 Rico MJ, Myers SA, Sanchez MR. Guidelines of care for dermatologic conditions in patients infected with HIV. Guidelines/Outcomes Committee, American Academy of Dermatology. *J Am Acad Dermatol* 1997; **37**: 450–72.

6 Aftergut K, Cockerell CJ. Update on the cutaneous manifestations of HIV infection. Clinical and pathologic features. *Dermatol Clin* 1999; **17**: 445–71.

7 Bunker CB, Staughton RCD. HIV-associated disease: dermatology. In: Gazzard BG, ed. *AIDS Care Handbook*. London: Mediscript, 2002: 115–39.

8 Mzezewa S, Jönsson K, Sibanda E *et al*. HIV infection reduces skin graft survival in burn injuries: a prospective study. *Br J Plas Surg* 2003; **56**: 740–5.

9 Kong HH, Myers SA. Cutaneous effects of highly active antiretroviral therapy in HIV-infected patients. *Dermatol Ther* 2005; **18**: 58–66.

10 Martins CR. Cutaneous drug reactions associated with newer antiretroviral agents. *J Drugs Dermatol* 2006; **5**: 976–82.

11 Nori S, Greene MA, Schrager HM, Falanga V. Infectious occupational exposures in dermatology—A review of risks and prevention measures *J Am Acad Dermatol* 2005; **53**: 1010–9.

12 Blauvelt A, Katz SI. The skin as target, vector, and effector organ in human immunodeficiency virus disease. *J Invest Dermatol* 1995; **105**: 122S–126S.

13 Simonitsch I, Geusau A, Chott A, Jurecka W. Cutaneous dendritic cells are main targets in acute HIV-1-infection. *Mod Pathol* 2000; **13**: 1232–7.

14 Galhardo MCG, Alvarebga FF, Schueler G *et al*. Normal skin of HIV-infected individuals contains increased numbers of dermal CD8 T cells and normal numbers of Langerhans cells. *Braz J Med Biol Res* 2004; **37**: 745–53.

15 Donoval BA, Landay AL, Moses S *et al*. HIV-1 target cells in foreskins of African men with varying histories of sexually transmitted infections. *Am J Clin Pathol* 2006; **125**: 386–91.

16 Breuer-McHam JN, Marshall GD, Lewis DE, Duvic M. Distinct serum cytokines in AIDS-related skin diseases. *Viral Immunol* 1998; **11**: 215–20.

17 Breuer-McHam JN, Ledbetter LS, Sarris AH, Duvic M. Cytokine expression patterns distinguish HIV associated skin diseases. *Exp Dermatol* 2000; **9**: 341–50.

18 Price P, Morahan G, Huang D *et al*. Polymorphisms in cytokine genes define subpopulations of HIV-1 patients who experienced immune restoration diseases. *AIDS* 2002; **16**: 2043–7.

19 Polydefkis M, Yiannoutsos CT, Cohen BA *et al*. Reduced intraepidermal nerve fiber density in HIV-associated sensory neuropathy. *Neurology* 2002; **58**: 115–9.

20 Herrmann DN, McDermott MP, Sowden JE *et al*. Is skin biopsy a predictor of transition to symptomatic HIV neuropathy? A longitudinal study. *Neurology* 2006; **66**: 857–61.

21 Zhou L, Kitch DW, Evans SR *et al*. NARC and ACTG A5117 Study Group. Correlates of epidermal nerve fiber densities in HIV-associated distal sensory polyneuropathy. *Neurology* 2007; **68**: 2113–9.

22 Rowe A, Mallon E, Rosenberger P *et al*. Depletion of cutaneous peptidergic innervation in HIV-associated xerosis. *J Invest Dermatol* 1999; **112**: 284–9.

23 Abdool-Karim Q. Prevention of HIV by male circumcision. *BMJ* 2007; **335**: 4–5.

24 Sugaya M, Hartley O, Root MJ, Blauvelt A. C34, a membrane fusion inhibitor, blocks HIV infection of Langerhans cells and viral transmission to T cells. *J Invest Dermatol* 2007; **127**: 1436–43.
25 Anonymous. Standards for HIV clinical care. British HIV Association March 2007: p. 19. http://www.bhiva.org
26 Calista D, Morri M, Stagno A, Boschini A. Changing morbidity of cutaneous diseases in patients with HIV after the introduction of highly active antiretroviral therapy including a protease inhibitor. *Am J Clin Dermatol* 2002; **3**: 59–62.
27 Maurer T, Rodriques LK, Ameil N *et al*. The effect of highly active antiretroviral therapy on dermatologic disease in a longitudinal study of HIV type 1-infected women. *Clin Infect Dis* 2004; **38**: 579–84.
28 Seone Reula E, Bellon JM, Gurbindo D, Munoz-Fernandez MA. Role of antiretroviral therapies in mucocutaneous manifestations in HIV-infected children over a period of two decades. *Br J Dermatol* 2005; **153**: 382–9.

Acute primary HIV infection/seroconversion

Acute primary HIV infection may be clinically silent but up to 90% of patients develop a non-specific, symptomatic illness 1–6 weeks after exposure, that lasts a few days to several months but usually less than a fortnight [1]. Symptoms and signs (Table 35.9) are often those of a non-specific viral infection, similar to infectious mononucleosis with lassitude, fever, arthralgia, myalgia and lymphadenopathy. Weight loss, nausea, vomiting and diarrhoea are common. Headache and photophobia may signify aseptic meningitis and cognitive dysfunction encephalitis, although other recognized neurological presentations include Bell's palsy, brachial neuritis, radiculopathy, peripheral neuropathy and Guillain–Barré syndrome. Table 35.9 lists the frequency and duration of the principal clinical manifestations of primary HIV infection [2].

Table 35.9 Clinical manifestations of primary HIV infection. (From [2].)

Clinical manifestation	Frequency (%)	Mean duration (days)
Fever (>38°C)	77	17
Fatigue	66	24
Erythematous maculopapular rash	56	15
Myalgia	55	18
Headache	51	26
Pharyngitis	44	12
Cervical lymphadenopathy	39	15
Arthralgia	31	23
Oral ulcer	29	13
Odynophagia	28	16
Axillary lymphadenopathy	24	164
Weight loss	24	29
Nausea	24	18
Diarrhoea	23	13
Night sweats	22	15
Cough	22	18
Anorexia	21	15
Inguinal lymphadenopathy	20	9
Abdominal pain	19	15
Oral candidosis	17	10
Vomiting	12	10
Photophobia	12	11
Sore eyes	12	13
Genital ulcer	7	14
Tonsillitis	7	13
Depression	6	23
Dizziness	6	11

Table 35.10 Dermatological manifestations of HIV seroconversion. (From [3].)

Exanthema
Enanthema
Urticaria
Toxic erythema
Erythema multiforme
Oropharyngeal candidosis
Acute genitocrural intertrigo
Oral ulceration
Genital ulceration

The principal dermatological manifestations of seroconversion are given in Table 35.10 [3]. A rash is found in up to 75% of people with symptomatic seroconversion. A symmetrical maculopapular erythematous exanthem, notably of face, palms and soles, occurs. Pale pink macules and perifollicular erythematous papules have been described. Occasionally there may be urticarial or vesicular lesions, and alopecia. The histology is characterized by an upper dermal, perimicrovascular and periappendageal $CD8^+$ lymphocytic infiltrate with a mixed perivascular $CD1a^+$ dendritic cell/$CD8/CD4^+$ lymphocytic infiltrate. Epidermal changes may be absent or range from vacuolation and spongiosis to epidermal necrosis [4,5]. Painful oral ulceration, genital ulceration, erythema multiforme and Stevens–Johnson syndrome may occur [6–9]. Acute erosive genitocrural intertrigo has been described [10]. If the CD4 count falls precipitously, oral candidosis can develop. The exanthem may represent infection of cutaneous Langerhans' cells and the orogenital lesions sites of viral inoculation [11].

Thus, primary infection, including non-specific dermatological reaction patterns, may go unnoticed, unreported or undiagnosed. Because the dermatological and other manifestations of seroconversion are non-specific, there is a differential diagnosis (Table 35.11). In the past, syphilis was the great imitator, perhaps now it is HIV [12]. It must also be appreciated that two (or more) illnesses may coexist.

The greater the number, severity and duration of the manifestations, the more likely a more rapid progression of HIV disease will occur in that individual (Table 35.12) [2,13,14].

Precise diagnosis and exclusion of other causes can be complicated in the acute stage by interpretation of bacteriological and virological results (e.g. serological diagnosis of syphilis). There may be lymphopenia (usually a modest fall in CD4 count, mild rise in CD8 and inverted CD4/CD8 ratio) and thrombocytopenia and a biochemical hepatitis or cholestatic biochemical profile. A skin biopsy may not be helpful, showing non-specific histology: spongiosis, apoptosis, interface dermatitis and mild perivascular chronic inflammatory infiltrate. Seroconversion illness is diagnosed by positive plasma HIV polymerase chain reaction (PCR) alongside negative or equivocal HIV antibody tests (Table 35.13) [2].

References

1 Kahn JO, Walker BD. Acute human immunodeficiency virus type 1 infection (review). *N Engl J Med* 1998; **339**: 33–9.

Table 35.11 Differential diagnosis of primary HIV infection. (From [3].)

Toxic erythema (and its differential diagnosis, drugs, infections, connective tissue disease)
Urticaria (and its differential diagnosis, drugs, infections, connective tissue disease, neoplasia)
Erythema multiforme (and its differential diagnosis)
Orogenital ulceration (and its differential diagnosis, drugs, infections, connective tissue disease, immunobullous disease, Behçet's syndrome, Stevens–Johnson syndrome)
Pityriasis rosea
Guttate psoriasis
Reiter's syndrome
Still's disease
Infections
Epstein–Barr virus
Cytomegalovirus
Parvovirus B19
Herpes simplex virus
Human T-lymphotropic virus type 1 and 2
Hepatitis A, B and C
Gonococcaemia
Syphilis
Rheumatic fever
Toxoplasmosis
Causes of meningoencephalitis and pneumonitis
Drug reactions

Table 35.12 Useful prognostic indicators around primary infection. (From [2].)

Clinical (soon after initial infection)	Laboratory (3–4 months after infection)
Presence of symptoms	CD4 T-cell count
Duration of symptoms (>14 days)	Quantitative viral load (HIV RNA measurement)
Number of symptoms (more than three symptoms)	Polymerase chain reaction b-DNA
Candidosis	β_2-Microglobulin
Acquisition of HIV from an individual with advanced HIV disease	
Neurological involvement	

b-DNA, branched chain DNA.

Table 35.13 Diagnosis of primary HIV infection. (From [2].)

Essential assays
Enzyme-linked immunosorbent assay (ELISA)
Western blot (should also be able to detect HIV. 2 infection)
HIV. 1 p24 antigen testing
HIV DNA or RNA polymerase chain reaction (PCR)
Supplementary tests after inconclusive ELISA results
HIV DNA or RNA PCR if not previously performed
HIV RNA quantification (especially if ARV therapy is being contemplated)
T-cell subset enumeration
Exclusion of other viral illnesses (e.g. cytomegalovirus, Epstein–Barr virus)

2 Hawkins D. Seroconversion and early disease. In: Gazzard BG, ed. *AIDS Care Handbook*. London: Mediscript, 2002: 33–43.
3 Bunker CB, Staughton RCD. HIV-associated disease: dermatology. In: Gazzard BG, ed. *AIDS Care Handbook*. London: Mediscript, 2002: 115–39.
4 Goldman GD, Milstone LM, Shapiro PE. Histologic findings in acute HIV exanthema. *J Cutan Pathol* 1995; **22**: 371–3.
5 Kobayashi S, Segawa S, Kawashima M *et al*. A case of symptomatic primary HIV infection. *J Dermatol* 2005; **32**: 137–42.
6 Lewis DA, Brook MG. Erythema multiforme as a presentation of human immunodeficiency virus seroconversion illness. *Int J STD AIDS* 1992; **3**: 56–7.
7 Kinloch-de Loës S, de Saussure P, Saurat J *et al*. Symptomatic primary infection due to human immunodeficiency virus type 1. Review of 31 cases. *Clin Infect Dis* 1993; **17**: 59–65.
8 Mortier E, Zahar JR, Gros I *et al*. Primary infection with human immunodeficiency virus that presented as Stevens–Johnson syndrome. *Clin Infect Dis* 1994; **19**: 798.
9 Alessi E, Cusini M. The exanthem of HIV-1 seroconversion syndrome. *Int J Dermatol* 1995; **34**: 238–9.
10 Calikoglu E, Soravia-Dunand VA, Perriard J *et al*. Acute genitocrural intertrigo: a sign of primary immunodeficiency virus type 1 infection. *Dermatology* 2001; **203**: 171–3.
11 Porras-Luque JI, Valks R, Casal EC, Fernandez-Herrera JM. Generalized exanthem with palmoplantar involvement and genital ulcerations. Acute primary HIV infection. *Arch Dermatol* 1998; **134**: 1279, 1282.
12 Calza AM, Kinloch S, Mainetti C *et al*. Primary human immunodeficiency virus infection mimicking syphilis. *J Infect Dis* 1991; **164**: 615–6.
13 Vanhems P, Allard R, Cooper DA *et al*. Acute human immunodeficiency virus type 1 disease as a mononucleosis-like illness: is the diagnosis too restrictive? *Clin Infect Dis* 1997; **24**: 965–70.
14 Vanhems P, Lambert J, Cooper DA *et al*. Severity and prognosis of acute human immunodeficiency virus type 1 illness: a dose–response relationship. *Clin Infect Dis* 1998; **26**: 323–9.

Pruritus, xerosis and ichthyosis

Idiopathic pruritus, xerosis and ichthyosis are common in HIV and can be variably symptomatic [1–3]. HIV belongs in the differential diagnosis of generalized pruritus (see Chapter 21) [4]. Itching patients must be evaluated carefully to exclude a specific pruritic dermatosis (e.g. scabies, atopic dermatitis, pruritic papular eruption of HIV and eosinophilic folliculitis) and the medical causes of generalized pruritus (e.g. hepatic and renal disease and lymphoma). Excoriations, eczematization and impetiginization can complicate scratching. Prurigo excoriee and prurigo nodularis may eventuate [5,6]. Measurement of the serum level of IgE and skin swabs, scrapings and biopsy may be helpful.

The mechanism of HIV-related xerosis is uncertain but cutaneous peptidergic neuronal loss has been demonstrated [7]. Severe intractable pruritus with eosinophilia may indicate a subset of HIV-infected patients with hyperactivation of humoral immunity and augmented viral load [8]. Pruritus and xerosis are also side effects of ARVs, especially the PIs (see Chapter 21) [9].

Treatment follows conventional lines and includes phototherapy [1,2,10,11]. Thalidomide has been used for prurigo nodularis [12].

References

1 Gelfand JM, Rudikoff D. Evaluation and treatment of itching in HIV-infected patients. *Mt Sinai J Med* 2001; **68**: 298–308.
2 Singh F, Rudikoff D. HIV-associated pruritus: etiology and management. *Am J Clin Dermatol* 2003; **4**: 177–88.
3 Wiwanikit V. Prevalence of dermatoloogical disorders in Thai HIV-infected patients correlated with different CD4 lymphocyte count statuses: a note on 120 cases. *Int J Dermatol* 2004; **43**: 265–8.

4 Hoover WD Jr, Lang PG. Pruritus in HIV infection. *J Am Acad Dermatol* 1991; **24**: 1020–1.
5 Gelfand JM, Rudikoff D. Evaluation and treatment of itching in HIV-infected patients. *Mt Sinai J Med* 200; **68**: 298–308.
6 Maurer TA. Dermatologic manifestations of HIV infection. *Top HIV Med* 2005; **13**: 149–54.
7 Rowe A, Mallon E, Rosenberger P *et al*. Depletion of cutaneous peptidergic innervation in HIV-associated xerosis. *J Invest Dermatol* 1999; **112**: 284–9.
8 Milazzo F, Piconi S, Trabattoni D *et al*. Intractable pruritus in HIV infection: immunologic characterization. *Oral Dis* 1998; **4**: 16–21.
9 Colebunders R, Vandenbruaene M. The changing spectrum of the cutaneous manifestations of HIV disease. *Arch Dermatol* 1999; **135**: 471.
10 Lim HW, Vallurupalli S, Meola T, Soter NA. UVB phototherapy is an effective treatment for pruritus in patients infected with HIV. *J Am Acad Dermatol* 1997; **37**: 414–7.
11 Finkelstein M, Berman B. HIV and AIDS in inpatient dermatology. Approach to the consultation. *Dermatol Clin* 2000; **18**: 509–20.
12 Maurer T, Poncelet A, Berger T. Thalidomide treatment for prurigo nodularis in human immunodeficiency virus-infected subjects: efficacy and risk of neuropathy. *Arch Dermatol* 2004; **140**: 845–9.

Pigmentary disorders

Hyperpigmentation of skin (and nails and mucosae) is frequently recognized in HIV-positive people. Explanations include drugs such as zidovudine (AZT, ZDV), hydroxyurea and indinovir [1], opportunistic infections such as toxoplasmosis and hypoadrenalism. Generalized hyperpigmentation may be a sign of late infection in its own right [2]. *Acanthosis nigricans* has been reported in untreated HIV and as a part of the metabolic syndrome and insulin resistance due to HAART and PIs [3–5].

Vitiligo (including spontaneous and HAART-related repigmentation) has been reported [1,6–11].

References

1 Terheggen F, Frissen J, Weigel H *et al*. Nail, hair and skin hyperpigmentation associated with indinavir therapy. *AIDS* 2004; **18**: 1612.
2 Grover C, Kubba S, Bansal S *et al*. Pigmentation: a potential cutaneous marker for AIDS? *J Dermatol* 2004; **31**: 756–60.
3 Marfatia YS, Sharma A. Acanthosis nigricans in an HIV seropositive: is there a correlation? *Indian J Dermatol Venereol Leprol* 2006; **72**: 383–4.
4 Mellor-Pita S, Yebra-Bango M, Alfaro-Martinez J, Suarez E. Acanthosis nigricans: a new manifestation of insulin resistance in patients receiving treatment with protease inhibitors. *Clin Inf Dis* 2002; **34**: 716–7.
5 Mur A, Seidel V, Lopez-Vilchez MA *et al*. Acanthosis nigricans as an adverse effect of highly active antiretroviral therapy in an adolescent girl with human immunodeficiency virus infection. *Ped Inf Dis J* 2005; **24**: 742–3.
6 Duvic M, Rapini R, Hoots WK, Mansell PW. Human immunodeficiency virus-associated vitiligo: expression of autoimmunity with immunodeficiency? *J Am Acad Dermatol* 1987; **17**: 656–62.
7 Cho M, Cohen PR, Duvic M. Vitiligo and alopecia areata in patients with human immunodeficiency virus infection. *South Med J* 1995; **88**: 489–91.
8 Grandhe NP, Dogra S, Kumar B. Spontaneous repigmentation of vitiligo in an untreated HIV-positive patient. *J Eur Acad Dermatol Venereol* 2006; **20**: 234–5.
9 Antony FC, Marsden RA. Vitiligo in association with human immunodeficiency virus infection. *J Eur Acad Dermatol Venereol* 2003; **17**: 456–8.
10 McGowan JW 4th, Long JB, Johnson CA, Lynn A. Disseminated vitiligo associated with AIDS. *Cutis* 2006; **77**: 169–73.
11 Niamba P, Traoré A, Taïeb A. Vitiligo in a black patient associated with HIV infection and repigmentation under antiretroviral therapy. [In French.] *Ann Dermatol Venereol* 2007; **134**: 272–3.

Coagulopathies

HIV-related thrombocytopenic purpura (Fig. 35.1) may present to a dermatologist; it can be mistaken for KS [1,2]. Thrombotic thrombocytopenic purpura is also associated with HIV [3]. HIV-infected patients are at increased risk of venous and arterial thrombosis (smoking and hypertriglyceridaemia are associated risk factors [4]) and cutaneous ulceration or infarcts. Possible explanations include acquired protein S deficiency [5], antiphospholipid syndrome [6], calciphylaxis and HIV renal disease [7], Degos' disease [8] and CMV viraemia [9].



Fig. 35.1 Thrombocytopenic purpura: purpuric macule on the finger. (Courtesy of Professor C.B. Bunker and Medical Illustration UK Ltd, Chelsea and Westminster Hospital, London, UK.)

References

1 Sood R, Rakkar AS, Carmosino L *et al*. Thrombotic thrombocytopenic purpura in HIV infection: a report of two cases. *AIDS Patient Care STDS* 1996; **10**: 3249–52.
2 Gruszecki AC, Wehrli G, Ragland BD *et al*. Management of a patient with HIV infection-induced anemia and thrombocytopenia who presented with thrombotic thrombocytopenic purpura. *Am J Hematol* 2002; **69**: 228–31.
3 Robertson C, Wiselka MJ. Thrombotic thrombocytopaenic purpura occurring in consecutive pregnancies in an HIV-infected patient. *Int J STD AIDS* 2007; **18**: 142–3.
4 Micieli E, Dentali F, Giola M *et al*. Venous and arterial thrombosis in patients with HIV infection. *Blood Coagul Fibrinolysis* 2007; **18**: 259–63.
5 Dillmon MS, Saag MS, Hamza SH *et al*. Unusual thromboses associated with protein S deficiency in patients with acquired immunodeficiency syndrome: case reports and review of the literature. *AIDS Res Hum Retroviruses* 2005; **21**: 753–6.
6 Hassoun A, Al-Kadhimi Z, Cervia J. HIV infection and antiphospholipid antibody: literature review and link to the antiphospholipid syndrome. *AIDS Patient Care STDS* 2004; **18**: 333–40.
7 Cockerell CJ, Dolan ET. Widespread cutaneous and systemic calcification (calciphylaxis) in patients with the acquired immunodeficiency syndrome and renal disease. *J Am Acad Dermatol* 1992; **26**: 559–62.
8 Requena L, Farina C, Barat A. Degos disease in a patient with acquired immunodeficiency syndrome. *J Am Acad Dermatol* 1998; **38**: 852–6.
9 Smith K, Skelton H, Yeager J, Wagner K. Cutaneous thrombosis in human immunodeficiency virus type 1-positive patients and cytomegalovirus viremia. *Arch Dermatol* 1995; **131**: 357–8.

Table 35.14 Inflammatory dermatoses less commonly associated with HIV. (From [1–10].)

- Erythroderma [11]
- Photosensitivity [12–17]
- Kwashiorkor [18]
- Allergic contact dermatitis [19–21]
- Chronic actinic dermatitis [22,23]
- Prurigo nodularis [24–26]
- Urticarias [27]
- Erythema annulare centrifugum [28]
- Persistent insect bite reaction
- Hyperimmunoglobulin E syndrome [29]
- Hypereosinophilic syndrome [30–32]
- Granuloma annulare
- Papuloerythroderma [33]
- Pityriasis rubra pilaris [34,35]
- Lichen spinulosus [36]
- Pityriasis lichenoides [37]
- Pityriasis rosea (persistent) [38]
- Erythema dyschromicum perstans/ashy dermatosis of Ramirez [39]
- Acne vulgaris and variants/HIV follicular syndrome [34,40,41]
- Perforating folliculitis [42]
- Neutrophilic eccrine hidradenitis [43]
- Lichenoid granulomatous papular dermatosis
- Lichen amyloid [44,45]
- Varicose ulceration [46]
- Acrocyanosis ± cryoglobulinaemia, *Pneumocystis carinii* septicaemia (butyl nitrite) [47]
- Perniosis [48]
- Erythema nodosum [49–51]
- Vasculitis [52,53]
  - Henoch–Schönlein purpura and nephritis [54]
  - Erythema elevatum diutinum [55–57]
  - Polyarteritis nodosa [58,59]
  - Parvovirus B19/papular purpuric, gloves and socks syndrome [60,61]
  - Kawasaki-like syndrome [62]
  - Red finger syndrome [63–66]
  - Livedo reticularis/Raynaud's phenomenon/cryoglobulinaemia/hepatitis C [67]
  - Degos' disease [68]
  - Behçet's disease [69]
  - Pyoderma gangrenosum [70,71]
  - Sweet's neutrophilic dermatosis [72,73]
  - Antiphospholipid syndrome [74]
  - Atypical neutrophilic dermatoses [75]
- Systemic lupus erythematosus [76]
- Relapsing polychondritis [66,69,77]
- Anetoderma [78–81]
- Transient acantholytic dermatosis/Grover's disease [82]
- Subcorneal pustular dermatosis [83]
- Autoimmune bullous diseases
  - Bullous pemphigoid [84,85]
  - Cicatricial pemphigoid [86]
  - Pemphigus [84,87–89]
  - Dermatitis herpetiformis [90,91]
- Acrodermatitis enteropathica [92,93]
- Eccrine squamous syringometaplasia (±cytomegalovirus) [94,95]
- Cutaneous mucinoses [96]
  - Reticular erythematous mucinosis [97]
  - Lichen myxoedematosus/papular mucinosis [98–100]
  - Eccrine ductal mucinosis and follicular mucinosis (with scabies) [95]
  - Scleroedema [96]
- Atypical cutaneous lymphoproliferative disorders/$CD8^+$ pseudolymphoma [101–103]
  - Rosai–Dorfman disease (rosacea-like eruption) [104]
  - Palpable arciform migratory erythema [105]
- Dermatitis artefacta [106]

Inflammatory dermatoses

The commonest of the inflammatory dermatoses associated with HIV infection (see Table 35.8) are discussed below. Table 35.14 lists inflammatory dermatoses that have been less frequently observed in the context of HIV infection [1–10].

Erythroderma may have several causes and the same differential diagnostic approach employed in general dermatology is recommended; in a young black patient, erythroderma may be a marker for HIV infection [11]. Balanoposthitis, proctitis, piles, perianal ulceration, abscess, fissure and fistula are prevalent in homosexual men and in HIV infection [107–110]; anogenital problems are discussed in Chapter 71.

References

1 Bunker CB. Dermatological problems in HIV and AIDS. In: Miller A, ed. *Medical Management of HIV and AIDS*. London: Springer, 1996.
2 Bunker CB, Staughton RCD. HIV-associated disease: dermatology. In: Gazzard BG, ed. *AIDS Care Handbook*. London: Mediscript, 2002: 115–39.
3 Penneys MS. *Skin Manifestations of AIDS*. London: Martin Dunitz, 1990.
4 Duvic M. Papulosquamous disorders associated with human immunodeficiency virus infection. *Dermatol Clin* 1991; **9**: 523–30.
5 Cockerell CJ. Non-infectious inflammatory skin diseases in HIV-infected individuals. *Dermatol Clin* 1991; **9**: 531–42.
6 Cowley NC, Staughton RCD. Human immunodeficiency virus-related skin disease. *Curr Opin Infect Dis* 1991; **4**: 659–66.
7 Cockerell CJ. Organ-specific manifestations of HIV infection. II. Update on cutaneous manifestations of HIV infection. *AIDS* 1993; **7** (Suppl. 1): S213–S218.
8 Rico MJ, Myers SA, Sanchez MR. Guidelines of care for dermatologic conditions in patients infected with HIV. Guidelines/Outcomes Committee, American Academy of Dermatology. *J Am Acad Dermatol* 1997; **37**: 450–72.
9 Aftergut K, Cockerell CJ. Update on the cutaneous manifestations of HIV infection. Clinical and pathologic features. *Dermatol Clin* 1999; **17**: 445–71.
10 Maurer TA. Dermatologic manifestations of HIV infection. *Top HIV Med* 2005; **13**: 149–54.
11 Morar N, Dlova N, Gupta AK *et al*. Erythroderma: a comparison between HIV positive and negative patients. *Int J Dermatol* 1999; **38**: 895–900.
12 Kaporis A, Lim HW, Moy J *et al*. Skin response to ultraviolet B light in patients infected with human immunodeficiency virus. *Photodermatol Photoimmunol Photomed* 1996; **11**: 188–91.
13 Aubin F, Parriaux N, Robert C *et al*. Cutaneous reaction to ultraviolet irradiation in human-immunodeficiency-virus-infected patients. A case–control study. *Dermatology* 1999; **198**: 256–60.
14 Vin-Christian K, Epstein JH, Maurer TA *et al*. Photosensitivity in HIV-infected individuals. *J Dermatol* 2000; **27**: 361–9.
15 Smith KJ, Skelton HG, Yeager J *et al*. Histopathologic features seen in cutaneous photoeruptions in HIV-positive patients. Military Medical Consortium for the Advancement of Retroviral Research (MMCARR). *Int J Dermatol* 1997; **36**: 745–53.

16 Bilu D, Mamelak AJ, Nguyen RH-N *et al*. Clinical and epidemiologic characterization of photosensitivity in HIV-positive individuals. *Photodermatol Photoimmunol Photomed* 2004; **20**: 175–83.
17 Queiroz Zancanaro PC, McGirt LY, Mamelak AJ *et al*. Cutaneous manifestations of HIV in the era of highly active antiretroviral therapy: an institutional urban clinic experience. *J Am Acad Dermatol* 2006; **54**: 581–8.
18 Alam M, Grossman ME, Longley BJ, Schneiderman PI. Kwashiorkor in patients with AIDS. *Cutis* 2001; **67**: 321–7.
19 Smith KJ, Skelton HG, Nelson A *et al*. Preservation of allergic contact dermatitis to poison ivy (urushiol) in late HIV disease. The implication and relevance to immunotherapy with contact allergens. *Dermatology* 1997; **195**: 145–9.
20 Bellegrandi S, Rosso R, Mattiacci G *et al*. Contact dermatitis in subjects infected with HIV type 1. *J Am Acad Dermatol* 1999; **40**: 777–9.
21 Smith KJ, Buckley R, Skelton H. Lamivudine (3TC)-induced contact dermatitis. *Cutis* 2000; **65**: 227–9.
22 Meola T, Sanchez M, Lim HW *et al*. Chronic actinic dermatitis associated with human immunodeficiency virus infection. *Br J Dermatol* 1997; **137**: 431–6.
23 Wong SN, Khoo LS. Chronic actinic dermatitis as the presenting feature of HIV infection in three Chinese males. *Clin Exp Dermatol* 2003; **28**: 265–8.
24 Matthews SN, Cockerell CJ. Prurigo nodularis in HIV-infected individuals. *Int J Dermatol* 1998; **37**: 401–9.
25 Herranz P, Pizarro A, De Lucas R *et al*. Treatment of AIDS-associated prurigo nodularis with thalidomide. *Clin Exp Dermatol* 1998; **23**: 233–5.
26 Maurer T, Poncelet A, Berger T. Thalidomide treatment for prurigo nodularis in human immunodeficiency virus-infected subjects: efficacy and risk of neuropathy. *Arch Dermatol* 2004; **140**: 845–9.
27 Fearfield LA, Gazzard B, Bunker CB. Aquagenic urticaria and human immunodeficiency virus infection: treatment with stanozolol. *Br J Dermatol* 1997; **137**: 620–2.
28 González-Vela MC, González-López MA, Val-Bernal JF *et al*. Erythema annulare centrifugum in a HIV-positive patient. *Int J Dermatol* 2006; **45**: 1423–5.
29 Blanche P, Bachmeyer C, Buvry C, Sicard D. Hyperimmunoglobulinaemia E syndrome in HIV infection. *J Am Acad Dermatol* 1997; **36**: 106–7.
30 Drabick JJ, Magill AJ, Smith KJ *et al*. Hypereosinophilic syndrome associated with HIV infection. Military Medical Consortium for Applied Retroviral Research. *South Med J* 1994; **87**: 525–9.
31 Morgan MB, Viloria J, Morgan JD, Suarez-Hoyos J. Human immunodeficiency virus infection and hypereosinophilic syndrome. *J Florida Med Assoc* 1994; **81**: 401–2.
32 Smith KJ, Skelton HG, Drabick JJ *et al*. Hypereosinophilia secondary to immunodysregulation in patients with HIV-1 disease. *Arch Dermatol* 1994; **130**: 119–21.
33 Lonnee ER, Toonstra J, van der Putte SC *et al*. Papulo-erythroderma of Ofuji in a HIV-infected patient. *Br J Dermatol* 1996; **135**: 500–1.
34 Martin AG, Weaver CC, Cockerell CJ, Berger TG. Pityriasis rubra pilaris in the setting of HIV infection: clinical behaviour and association with explosive cystic acne. *Br J Dermatol* 1992; **126**: 671–20.
35 Gonzalez-Lopez A, Velasco E, Pozo T, Del Villar A. HIV-associated pityriasis rubra pilaris responsive to triple antiretroviral therapy. *Br J Dermatol* 1999; **140**: 931–4.
36 Cohen SJ, Dicken CH. Generalized lichen spinulosus in an HIV-positive man. *J Am Acad Dermatol* 1991; **25**: 116–8.
37 Ostlere LS, Langtry JAA, Branfoot AC, Staughton RCD. HIV seropositivity in association with pityriasis lichenoides et varioliformis acuta. *Clin Exp Dermatol* 1992; **17**: 36–7.
38 Kaplan MH, Sadick N, McNutt NS *et al*. Dermatologic findings and manifestations of acquired immunodeficiency syndrome (AIDS). *J Am Acad Dermatol* 1987; **16**: 485–506.
39 Molinero J, Vilata JJ, Nagore E *et al*. Ashy dermatosis in an HIV antibody-positive patient. *Acta Derm Venereol (Stockh)* 2000; **80**: 78–9.
40 Harms M, Pechere M, Krischer J *et al*. Oral isotretinoin in HIV-positive women with acne: report of three cases. *Dermatology* 1998; **196**: 163–4.
41 Blasdale C, Turner RJ, Leonard N *et al*. Spontaneous clinical improvement in HIV-associated follicular syndrome. *Clin Exp Dermatol* 2004; **29**: 480–2.
42 Rubio FA, Herranz P, Robayna G *et al*. Perforating folliculitis: report of a cases in an HIV-infected man. *J Am Acad Dermatol* 1999; **40**: 300–2.
43 Sevila A, Morell A, Banuls J *et al*. Neutrophilic eccrine hidradenitis in an HIV-infected patient. *Int J Dermatol* 1996; **35**: 651–2.
44 Buezo GF, Peñas PF, Daudén Tello E *et al*. Lichen amyloidosus and human immunodeficiency virus infection. *Dermatology* 1995; **191**: 56–8.
45 Goller M, Cohen PR, Duvic M. Lichen amylodosis presenting as a papular pruritus syndrome in a human-immunodeficiency-virus-infected man. *Dermatology* 1997; **194**: 62–4.
46 Mastroianni A, Cancerllieri C. Local treatment of a chronic leg ulcer with GM-CSF in a patient with HIV infection. *Sex Transm Infect* 1999; **75**: 203–4.
47 Hoegl L, Thoma-Greber E, Poppinger J, Rocken M. Butyl nitrite-induced acrocyanosis in an HIV-infected patient. *Arch Dermatol* 1999; **135**: 90–1.
48 Crowson AN, Magro CM. Idiopathic perniosis and its mimics: a clinical and histological study of 38 cases. *Hum Pathol* 1997; **28**: 478–84.
49 Fegueux S, Maslo C, de Truchis P *et al*. Erythema nodosum in HIV-infected patients. *J Am Acad Dermatol* 1991; **25**: 113.
50 Hohl D, Gueissaz F, Gerain J, Frenk E. Erythema nodosum and AIDS. *Hautarzt* 1992; **43**: 86–8.
51 Louthrenoo W, Lertprasertsuke N, Kasitanon N, Sukitawut W. Erythema nodosum as a manifestation of HIV infection. *Asian Pac J Allergy Immunol* 2002; **20**: 175–8.
52 Gherardi R, Belec L, Mhiri C *et al*. The spectrum of vasculitis in human immunodeficiency virus-infected patients: a clinicopathological evaluation. *Arthritis Rheum* 1993; **36**: 1164–74.
53 Chetty R. Vasculitides associated with HIV infection. *J Clin Pathol* 2001; **54**: 275–8.
54 Hidaka H, Okada T, Matsumoto H *et al*. Henoch–Schönlein purpura nephritis in a patient infected with the human immunodeficiency virus. *Nippon Jinzo Gakkai Shi* 2003; **45**: 387–92.
55 Soni BP, Williford PM, White WL. Erythematous nodules in a patent infected with the human immunodeficiency virus. Erythema elevatum diulinum (EED). *Arch Dermatol* 1998; **134**: 232–3.
56 Muratori S, Carrera C, Gorani A, Alessi E. Erythema elevatum diutinum and HIV infection: a report of five cases. *Br J Dermatol* 1999; **141**: 335–8.
57 Martin JI, Dronda F, Chaves F. Erythema elevatum diutinum, a clinical entity to be considered in patients infected with HIV-1. *Clin Exp Dermatol* 2001; **26**: 725–6.
58 Font C, Miro O, Pedrol E *et al*. Polyarteritis nodosa in human immunodeficiency virus infection: report of four cases and review of the literature. *Br J Rheumatol* 1996; **35**: 796–9.
59 Massari M, Salvarani C, Portioli I *et al*. Polyarteritis nodosa and HIV infection: no evidence of a direct pathogenic role of HIV. *Infection* 1996; **24**: 159–61.
60 Martinelli C, Azzi A, Buffini G *et al*. Cutaneous vasculitis due to human parvovirus B19 in an HIV-infected patient: report of a case. *AIDS* 1997; **11**: 1891–3.
61 Ghigliotti G, Mazzarello G, Nigro A *et al*. Papular-purpuric gloves and socks syndrome in HIV-positive patients. *J Am Acad Dermatol* 2000; **43**: 916–7.
62 Johnson RM, Little JR, Storch GA. Kawasaki-like syndromes associated with human immunodeficiency virus infection. *Clin Infect Dis* 2001; **32**: 1628–34.
63 Abajo P, Porras-Luque JI, Buezo GF *et al*. Red finger syndrome associated with necrotizing vasculitis in an HIV-infected patient with hepatitis B. *Br J Dermatol* 1998; **139**: 154–5.
64 Courvoisier S, Grob H, Weisser M *et al*. Relationship between erythema of the proximal nailfold in HIV-infected patients and hepatitis C virus infection. *Eur J Clin Microbiol Infect Dis* 1998; **17**: 596–7.
65 Fraga J, Abajo P, Buezo GF *et al*. Red finger syndrome associated with necrotizing vasculitis in an HIV-infected patient with hepatitis B. *Br J Dermatol* 1998; **139**: 154–6.
66 Doutre MS, Bernard N, Beylot-Barry M *et al*. Red fingers syndrome: acrosyndrome related to vascular growth endothelial factor? *Clin Exp Dermatol* 2001; **26**: 219–20.
67 Munoz-Perez MA, Rodriguez-Pichardo A, Camacho G, Colmenero MA. Livedo retiularis and Raynaud's phenomenon associated with cryoglobulinaemia but not related to hepatitis C virus in an HIV-1-positive patient. *Eur J Dermatol* 1998; **8**: 357–8.
68 Requena L, Farina C, Barat A. Degos disease in a patient with acquired immunodeficiency syndrome. *J Am Acad Dermatol* 1998; **38**: 852–6.
69 Belzunegui J, Cancio J, Pego JM *et al*. Relapsing polychondritis and Behcet's syndrome in a patient with HIV infection. *Ann Rheum Dis* 1995; **54**: 780.
70 Clark HH, Cohen PR. Pyoderma gangrenosum in an HIV-infected patient. *J Am Acad Dermatol* 1995; **32**: 912–4.

71 Kreuter A, Gambichler T, Hoffmann K *et al*. Association of HIV infection, pyoderma gangrenosum and psoriasis. *Acta Derm Venereol (Stockh)* 2002; **82**: 150–2.
72 Bevilacqua S, Hermans P, Van Laethem Y *et al*. Sweet's syndrome in an HIV-infected patient. *AIDS* 1999; **13**: 728–9.
73 Tan AW, Tan HH, Lim PL. Bullous Sweet's syndrome following influenza vaccination in a HIV-infected patient. *Int J Dermatol* 2006; **45**: 1254–5.
74 Hassoun A, Al-Kadhimi Z, Cervia J. HIV infection and antiphospholipid antibody: literature review and link to the antiphospholipid syndrome. *AIDS Patient Care STDS* 2004; **18**: 333–40.
75 Berger TG, Dhar A, McCalmont TH. Neutrophilic dermatoses in HIV infection. *J Am Acad Dermatol* 1994; **31**: 1045–7.
76 Sommer S, Piyadigamage A, Goodfield MJ. Systemic lupus erythematosus or infection with HIV, or both? *Clin Exp Dermatol* 2004; **29**: 393–5.
77 Dolev JC, Maurer TA, Reddy SG *et al*. Relapsing polychondritis in HIV-infected patients: a report of two cases. *J Am Acad Dermatol* 2004; **51**: 1023–5.
78 Ruiz-Rodriguez R, Longaker M, Berger TG. Anetoderma and human immunodeficiency virus infection. *Arch Dermatol* 1992; **128**: 661–2.
79 Lindstrom J, Smith KJ, Skelton HG *et al*. Increased anticardiolipin antibodies associated with the development of anetoderma in HIV-1 disease. Military Medical Consortium for the Advancement of Retroviral Research (MMCARR). *Int J Dermatol* 1995; **34**: 408–15.
80 Inamadar AC, Palit A, Athanikar SB *et al*. Generalized anetoderma in a patient with HIV and dual mycobacterial infection. *Lepr Rev* 2003; **74**: 275–8.
81 Mastrolorenzo A, Tiradritti L, Vichi F *et al*. Primary anetoderma and HIV infection: a case report. *AIDS Read* 2006; **16**: 92–6; discussion 94–5.
82 Breustedt W, Audring H, Sonnichsen N. Transitory acantholytic dermatosis (Grover) in an HIV infected patient. *Z Hautkr* 1990; **65**: 754–6.
83 Calista D. Subcorneal pustular dermatosis in a patient with AIDS. *J Eur Acad Dermatol Venereol* 2003; **17**: 469–90.
84 Bull RH, Fallowfield ME, Marsden RA. Autoimmune blistering diseases associated with HIV infection. *Clin Exp Dermatol* 1994; **19**: 47–50.
85 Kinloch-de Loes S, Didierjean L, Rieckhoff-Cantoni L *et al*. Bullous pemphigoid autoantibodies, HIV-infection and pruritic papular eruption. *AIDS* 1991; **5**: 451–4.
86 Lish KM, Washenik K, Yancey KB *et al*. Anti-epiligrin cicatricial pemphigoid in a patient with HIV. *J Am Acad Dermatol* 1997; **36**: 486–8.
87 Mahe A, Flageul B, Prost C, Intrato L. Pemphigus vegetans in an HIV-infected man. *Clin Exp Dermatol* 1994; **19**: 447.
88 Cunha P, Focaccia R, Diaz L. Evolution of endemic pemphigus foliaceus after HIV-1 infection. *J Am Acad Dermatol* 1995; **32**: 809–11.
89 Splaver A, Silos S, Lowell B *et al*. Case report: pemphigus vulgaris in a patient infected with HIV. *AIDS Patient Care STDS* 2000; **14**: 295–6.
90 Mitsuhashi Y, Hohl D. Dermatitis herpetiformis in a patient with acquired immunodeficiency syndrome-related complex. *J Am Acad Dermatol* 1988; **18**: 583.
91 Hasson A, Gutierrez MC, Martin L *et al*. Dermatitis herpetiformis and AIDS-related complex. *J Am Acad Dermatol* 1990; **22**: 1117–9.
92 Tong TK, Andrew LR, Albert A, Mickell JJ. Childhood acquired immunodeficiency syndrome manifesting as acrodermatitis enteropathica. *J Pediatr* 1986; **108**: 426–8.
93 Reichel M, Mauro TM, Ziboh VA *et al*. Acrodermatitis enteropathica in a patient with the acquired immunodeficiency syndrome. *Arch Dermatol* 1992; **128**: 415–7.
94 Chetty R, Bramdev A, Govender D. Cytomegalovirus induced syringosquamous metaplasia. *Am J Dermatopathol* 1999; **21**: 487–900.
95 Daudén E, Martin R, Feal C *et al*. Eccrine ductal mucinosis in a human immunodeficiency virus-positive patient with probable scabies. *Br J Dermatol* 2000; **143**: 1335–6.
96 Rongioletti F, Ghigliotti G, De Marchi R, Rebora A. Cutaneous mucinoses and HIV infection. *Br J Dermatol* 1998; **139**: 1077–80.
97 Morris-Jones R, Mallon E, Francis N *et al*. Reticular erythematous mucinosis associated with human immunodeficiency virus infection. *Retinoids* 2001; **17**: 5–57.
98 Tarantini G, Zerboni R, Muratori S *et al*. Lichen myxoedematosus in a patient with AIDS. *Br J Dermatol* 1996; **134**: 1122–4.
99 Azana JM, De Misa RF, Casado J *et al*. Papular mucinosis associated with human-immunodeficiency-virus infection. *Int J Dermatol* 1996; **35**: 652–4.
100 Dominguez Auñon JD, Postigo Llorente C, Llamas Martin R *et al*. Lichen myxoedematosus associated with human immunodeficiency virus infection—report of two cases and review of the literature. *Clin Exp Dermatol* 1997; **22**: 265–8.
101 Bachelez H, Hadida F, Parizot C *et al*. Oligoclonal expansion of HIV-specific cytotoxic CD8 T lymphocytes in the skin of HIV-1 infected patients with cutaneous pseudolymphoma. *J Clin Invest* 1998; **101**: 2506–16.
102 Friedler S, Parisi MT, Waldo E *et al*. Atypical cutaneous lymphoproliferative disorder in patients with HIV infection. *Int J Dermatol* 1999; **38**: 111–8.
103 Schartz NEC, de la Blanchardiére A, Alaoui S *et al*. Regression of $CD8^+$ pseudolymphoma after HIV antiviral triple therapy. *J Am Adac Dermatol* 2003; **49**: 139–41.
104 Pitamber HV, Grayson W. Five cases of cutaneous Rosai–Dorfman disease. *Clin Exp Dermatol* 2003; **28**: 17–21.
105 Muche JM, Toppe E, Sterry W, Haas N. Palpable arciform migratory erythema in an HIV patient, a $CD8^+$ pseudolymphoma. *J Cutan Pathol* 2004; **31**: 379–82.
106 Saez-de-Ocariz M, Duran-McKinster C, Orozo-Covarrubias L, Ruiz-Maldonado R. Dermatitis artefacta in a teenager after awareness of his HIV-positive diagnosis. *Clin Exp Dermatol* 2005; **30**: 92–3.
107 Bunker CB. *Male Genital Skin Disease*. Saunders, 2004.
108 Carr ND, Mercey D, Slack WW. Non-condylomatous perianal skin disease in homosexual men. *Br J Surg* 1989; **76**: 1064–6.
109 Denis BJ, May T, Bigard MA, Canton P. Anal and perianal lesions in symptomatic HIV infections. Prospective study of a series of 190 patients. *Gastroenterol Clin Biol* 1992; **16**: 148–54.
110 Yuhan R, De Orsay CI, Pino A *et al*. Anorectal disease in HIV-infected patients. *Dis Colon Rectum* 1998; **41**: 1367–70.

Seborrhoeic dermatitis

Only 1–3% of the general population have seborrhoeic dermatitis compared with 20–85% of patients with HIV. Seborrhoeic dermatitis is commoner in seropositive than in seronegative homosexual men, and among infected patients it is more prevalent and has an earlier onset in homosexuals and bisexuals compared with intravenous drug users [1]. Although found in seropositive individuals who are otherwise well, its severity is increased at CD4 T-cell counts below 100×10^6/L. This phenomenon is not adequately explained. The consensus is that classical seborrhoeic dermatitis represents an aberrant cutaneous reaction to commensal *Malassezia* yeast species. Probably the cutaneous immune dysfunction caused by HIV alters the host–organism relationship. The severity of seborrhoeic dermatitis may be related to yeast density or yeast strain [2,3]. There is a correlation between the numbers of yeast cells intimately associated with keratinocytes and the clinical severity of seborrhoeic dermatitis in patients with AIDS [4]. Patients taking ketoconazole have a lower prevalence of seborrhoeic dermatitis [5]. Also, imidazole treatment elicits clinical improvement, with a concomitant decrease in the numbers of *Malassezia* organisms per keratinocyte [6]. Abnormalities of skin surface lipids are not associated with the development of seborrhoeic dermatitis but are associated with HIV infection itself [7]. Seborrhoeic dermatitis has been related to low plasma zinc levels but this may not be significant [8]. Neuroendocrine and sebotropic factors are influenced by HIV infection and seborrhoeic dermatitis and neurological disease may coexist in some patients. Seborrhoeic dermatitis is essentially a hyperproliferative dermatosis and keratinocyte stimulation may result from HIV infection because of either monocyte-derived lymphokines or a direct effect of the virus itself [9].



Fig. 35.2 Seborrhoeic dermatitis on the face. (Courtesy of Professor C.B. Bunker and Medical Illustration UK Ltd, Chelsea and Westminster Hospital, London, UK.)

Itchy, scaly patches are found at the classical sites for seborrhoeic dermatitis (Fig. 35.2) and elsewhere. There may be folliculitis. Erythroderma has been reported [10]. An association of erythroderma, xerosis and seborrhoeic dermatitis with the development of dementia and spinal cord disease has been noted [9]. Extensive refractory seborrhoeic dermatitis appears to occur particularly in conjunction with pulmonary tuberculosis and AIDS in Zambia [11].

The differential diagnosis includes other causes of erythroderma and of folliculitis, eczema, psoriasis and dermatophytosis. Scrapings can be examined for fungi to exclude tinea, and *Malassezia* sp. may be seen in large numbers. Skin biopsy may show hyperkeratosis, acanthosis, spongiosis, spotty keratinocyte necrosis, leukocytosis and subcorneal neutrophil infiltration. A deeper lymphocytic infiltration of sebaceous glands and a more perivascular neutrophilic (with occasional leukocytoclasis) and plasma cell infiltrate is seen in HIV compared with classical seborrhoeic dermatitis [9,12]. The histology may be very similar to psoriasis.

Management follows conventional lines: emollients, topical steroids and antifungals and oral imidazoles. Topical pimecrolimus is effective [13]. Although clinical improvement of seborrhoeic dermatitis is often reported after immune reconstitution with HAART, Schaub *et al*. [1] have opined that antiretroviral treatment does not influence the prevalence, onset or disease-free survival times.

References

1 Schaub NA, Drewe J, Sponagel L *et al*. Is there a relation between risk groups or initial CD4 T cell counts and prevalence of seborrheic dermatitis in HIV-infected patients? *Dermatology* 1999; **198**: 126–9.

2 Schechtman RC, Midgley G, Hay RJ. HIV disease and *Malassezia* yeasts: a quantitative study of patients presenting with seborrhoeic dermatitis. *Br J Dermatol* 1995; **133**: 694–8.

3 Pechère M, Saurat J-H. *Malassezia* yeast density in HIV-positive individuals. *Br J Dermatol* 1997; **136**: 138–9.

4 Wikler JR, Nieboer C, Willemze R. Quantitiative skin cultures of *Pityrosporum* yeasts in patients seropositive for the human immunodeficiency virus with and without seborrheic dermatitis. *J Am Acad Dermatol* 1992; **27**: 37–9.

5 Coldiron BM, Bergstresser PR. Prevalence and spectrum of skin disease in patients infected with human immunodeficiency virus. *Arch Dermatol* 1989; **125**: 357–61.

6 Groisser D, Bottone EJ, Lebwohl M. Association of *Pityrosporum orbiculare* (*Malassezia furfur*) with seborrhoeic dermatitis in patients with acquired immunodeficiency syndrome (AIDS). *J Am Acad Dermatol* 1989; **20**: 770–3.

7 Vidal C, Girard P-M, Dompmartin D *et al*. Seborrhoeic dermatitis and HIV infection: qualitative analysis of skin surface lipids in men seropositive and seronegative for HIV. *J Am Acad Dermatol* 1990; **23**: 1106–10.

8 Basset-Seguin N, Sotto A, Guillot B *et al*. Zinc status in HIV-infected patients: relation to the presence or absence of seborrhoeic dermatitis. *J Am Acad Dermatol* 1998; **38**: 276–8.

9 Kaplan MH, Sadick N, McNutt NS *et al*. Dermatologic findings and manifestations of acquired immunodeficiency syndrome (AIDS). *J Am Acad Dermatol* 1987; **16**: 485–506.

10 Duvic M. Papulosquamous disorders associated with human immunodeficiency virus infection. *Dermatol Clin* 1991; **9**: 523–30.

11 Hira SK, Wadhawan D, Kamanga J *et al*. Cutaneous manifestations of human immuno-deficiency virus in Lusaka, Zambia. *J Am Acad Dermatol* 1988; **19**: 451–7.

12 Soeprono FF, Schinella RA, Cockerell CJ, Comite SL. Seborrhoeic-like dermatitis of acquired immunodeficiency syndrome. *J Am Acad Dermatol* 1986; **14**: 242–8.

13 de Moraes AP, de Arruda EA, Vitoriano MA *et al*. An open-label efficacy pilot study with pimecrolimus cream 1% in adults with facial seborrhoeic dermatitis infected with HIV. *J Eur Acad Dermatol Venereol* 2007; **21**: 596–601.

Atopic dermatitis

Atopic dermatitis or an atopic dermatitis-like condition has been thought to be common in children with HIV [1,2], but atopy is common anyway. A recent study has shown no increase in the prevalence of atopy in perinatally HIV-infected children compared with the general population [3]. In adults there have been reports of patients whose atopic dermatitis recurred or worsened during the course of HIV infection [4] and hyper-IgE syndrome has also been described [5]. Others believe atopic dermatitis is not affected by HIV [6,7]. A decreased frequency of atopic diseases, fewer positive radioallergosorbent tests and lower average levels of IgE in HIV-positive compared with HIV-negative homosexual individuals has been found [8], as has dysregulation of IgE synthesis [9]. Fungal allergen-specific IgE responses may contribute to the pathogenesis of eczematous skin disease in HIV-infected individuals [10].

References

1 Prose NS. Cutaneous manifestations of HIV infection in children. *Dermatol Clin* 1991; **9**: 543–50.

2 Ball LM, Harper JI. Atopic eczema in HIV seropositive haemophiliacs. *Lancet* 1987; **ii**: 627–8.

3 Bowser CS, Kaye J, Joks RO *et al*. IgE and atopy in perinatally HIV-infected children. *Pediatr Allergy Immunol* 2007; **18**: 298–303.

4 Parkin JM, Eales LJ, Galazka AR, Pinching AJ. Atopic manifestations of the acquired immunodeficiency syndrome: response to recombinant interferon gamma. *BMJ* 1987; **294**: 1185–6.

5 Lin RY, Smith JK. IgE and human immunodeficiency virus infection. *Ann Allergy* 1988; **61**: 269–72.

6 Duvic M. Papulosquamous disorders associated with human immunodeficiency virus infection. *Dermatol Clin* 1991; **9**: 523–30.

7 Cockerell CJ. Non-infectious inflammatory skin diseases in HIV-infected individuals. *Dermatol Clin* 1991; **9**: 531–42.

8 Ring J, Froschl M, Brunner R, Braun-Falco O. LAV/HTLV III infection and atopy: serum IgE and specific IgE antibodies to environmental allergens. *Acta Derm Venereol (Stockh)* 1986; **66**: 530–2.

9 Magnan A, Vervloet D. Le SIDA: un modèle pour l'étude de l'atopie? *Rev Mal Respir* 1995; **12**: 177–83.

10 Nissen D, Nolte HP, Ermin H *et al*. Evaluation of IgE-sensitization to fungi in HIV postitive patients with eczematous skin reactions. *Ann Allergy Asthma Immunol* 1999; **83**: 153–9.

Psoriasis

Psoriasis is prevalent (2%) in the general population and can worsen or appear for the first time (often very severely) in HIV infection [1,2] but may regress preterminally [3]. It may (5%) [4] or may not (1%) [5] be more prevalent in the HIV-infected population. HIV-associated psoriasis provides some insights into the pathogenesis of the disease, but the apparent paradox is still not well explained [6]. Most patients with HIV-associated psoriasis are positive for HLA-Cw0602, as are HIV-negative patients with streptococcal-associated guttate psoriasis [7,8]. There are decreased numbers of epidermal Langerhans' cells in the skin of HIV-infected individuals, as there may be, contentiously, in psoriasis [9–12]. Langerhans' cells are infected by HIV and either the viral burden or HIV gene products may alter the antigen-presenting function of these cells. HIV gene products may have a role in the pathogenesis of proliferative epidermal disorders; transgenic mice that express some HIV genes in skin develop a diffuse psoriasiform epidermal hyperplasia [13]. There may be a selective defect in soluble antigen recognition by CD4 T lymphocytes, and numbers of CD8 T lymphocytes increase until just before death creating an increased CD8/CD4 T-cell ratio in skin. Polyclonal B-cell activation, increased numbers of γδ T lymphocytes, decreased natural killer cell function, increased macrophage nitric oxide production, hypercolonization of the skin with *Staphylococcus aureus*, increased substance P production by infected immune cells and defective reticuloendothelial cell function have all been postulated [6] .

The classical clinical presentations of psoriasis are detailed in Chapter 20. Psoriasis in HIV-infected patients may be florid, severe and atypical (Fig. 35.3). Reiter's syndrome (arthritis, urethritis and conjunctivitis), within the same clinical continuum as psoriasis in genetically predisposed individuals, occurs in HIV, sometimes very severely [14,15].

The differential diagnosis of psoriasis includes seborrhoeic dermatitis, atopic dermatitis, dermatophytosis, drug eruption and mycosis fungoides. A psoriasiform eruption with the histological features of verruciform xanthoma has been described [16]. Investigations include mycology and skin biopsy.

Conventional treatment options for psoriasis serve most patients well. Moderate to severe psoriasis (with or without arthritis) should be regarded as an indication for HAART. There is no evidence that the theoretical risks and complications of phototherapy are clinically deleterious to individual patients [17–20]. T-cell numbers are unaffected and the *gag* p24 antigen and HIV RNA levels may or may not increase [18,21]. Overriding the theoretical concerns about immunosuppression and photocarcinogenesis is the clinical need to relieve the morbidity of the severe, atypical, refractory psoriasis often seen in HIV [5]. PUVA may be superior to UVB therapy [22].

Ciclosporin and methotrexate have caused serious complications in HIV-infected patients, such as leukopenia and fulminant KS [23,24]. The synthetic retinoid etretinate and its successor acitretin have been most useful therapies for severe Reiter's syndrome and psoriasis in HIV infection, often alongside phototherapy [1,14,15,25]. Treatment with zidovudine (AZT, ZDV) improves psoriasis [1]; specific constituents of HAART regimens, such as ritonavir and zalcitabine (dideoxycytidine, ddC, DDC; this drug is no longer available) appear to do likewise, with concomitant improvement of the clinical condition and virological status of the patient [26,27]. Classically, HIV infection contraindicates the use of anti-TNF-α directed therapy in psoriasis. However, etanercept improved HIV-related psoriasis and arthritis in one patient but frequent infectious complications meant that it had to be discontinued [28]. Also, two patients with psoriatic arthritis experienced dramatic improvements in skin and joint disease with infliximab [29]. Daclizumab (anti-CD25 IL2 receptor) has been used successfully in one patient with erythrodermic psoriasis [30]. Claims have been made for the efficacy of cimetidine [31]. Serendipitous success due to carbamazepine has been witnessed [32].



Fig. 35.3 Severe plantar psoriasis in HIV infection. (Courtesy of Professor C.B. Bunker and Medical Illustration UK Ltd, Chelsea and Westminster Hospital, London, UK.)

References

1 Duvic M. Papulosquamous disorders associated with human immunodeficiency virus infection. *Dermatol Clin* 1991; **9**: 523–30.

2 Mallon E, Bunker CB. HIV-associated psoriasis. *AIDS Patient Care STDS* 2000; **14**: 239–46.

3 Colebunders R, Blot K, Meriens V, Dock P. Psoriasis regression in terminal AIDS. *Lancet* 1992; **339**: 1110.

4 Porras B, Costner M, Friedman-Kien AE, Cockerell CJ. Update on cutaneous manifestations of HIV infection. *Med Clin North Am* 1998; **82**: 1033–80.

5 Finkelstein M, Berman B. HIV and AIDS in inpatient dermatology. Approach to the consultation. *Dermatol Clin* 2000; **18**: 509–20.

6 Namazi MR. Paradoxical exacerbation of psoriasis in AIDS: proposed explanations including the potential roles of substance P and Gram-negative bacteria. *Autoimmunity* 2004; **37**: 67–71.

7 Mallon E, Young D, Bunce M *et al*. HLA-Cw*0602 and HIV associated psoriasis. *Br J Dermatol* 1998; **139**: 527–33.

8 Mallon E, Bunce M, Savoie H *et al*. HLA-C and guttate psoriasis. *Br J Dermatol* 2000; **143**: 1177–82.
9 Ranki A, Lauharanta J, Kanerva L. Effect of etretinate on the distribution of Langerhans cells and T lymphocytes in psoriatic skin. *Arch Dermatol Res* 1984; **276**: 102–4.
10 Kalter DC, Gendelman HE, Meltzer MS. Monocytes, dendritic cells, and Langerhans cells in immunodeficiency virus infection. *Dermatol Clin* 1991; **9**: 415–28.
11 Van Neer F, Zemelman V, Cerio R *et al*. The role of factor XIIIa-positive dermal dendrocytes in HIV-1-positive psoriatics. *Br J Dermatol* 1993; **128**: 29–33.
12 Zemelman V, Van Neer F, Roberts N *et al*. Epidermal Langerhans cells, HIV-1 infection and psoriasis. *Br J Dermatol* 1994; **130**: 307–11.
13 Kopp JB, Rooney JF, Wohlenberg C *et al*. Cutaneous disorders and viral gene expression in HIV-1 transgenic mice. *AIDS Res Hum Retrovirus* 1993; **9**: 267–75.
14 Williams HC, Du Vivier AW. Etretinate and AIDS-related Reiter's disease. *Br J Dermatol* 1991; **124**: 389–92.
15 Blanche P. Acitretin and AIDS-related Reiter's disease. *Clin Exp Rheumatol* 1999; **17**: 105–6.
16 Smith KJ, Skelton HG, Angritt P. Changes of verruciform xanthoma in an HIV-1 patient wih diffuse psoriasiform skin disease. *Am J Dermatol* 1995; **17**: 185–8.
17 Ranki A, Puska P, Mattinen S *et al*. Effect of PUVA on immunologic and virologic findings in HIV-infected patients. *J Am Acad Dermatol* 1991; **24**: 404–10.
18 Breuer-McHam J, Marshall G, Adu-Oppong A *et al*. Alterations in HIV expression in AIDS patients with psoriasis and pruritus treated with phototherapy. *J Am Acad Dermatol* 1999; **40**: 48–60.
19 Akaraphanth R, Lim HW. HIV, UV and immunosuppression. *Photodermatol Photoimmunol Photomed* 1999; **15**: 28–31.
20 Houpt KR, Beer JZ, Horn TD *et al*. Ultraviolet therapy of HIV-infected individuals: a panel discussion. *Semin Cutan Med Surg* 1997; **16**: 241–5.
21 Horn TD, Morison WL, Farzadegan H *et al*. Effects of psoralens plus UVA radiation (PUVA) on HIV-1 in human beings: a pilot study. *J Am Acad Dermatol* 1994; **31**: 735–40.
22 Morison WL. PUVA therapy is preferable to UVB phototherapy in the management of HIV-associated dermatoses. *Photochem Photobiol* 1996; **64**: 267–8.
23 Tourne L, Dures P, Van Vooren JP *et al*. Alleviation of HIV-associated psoriasis and psoriatic arthritis with cyclosporine. *J Am Acad Dermatol* 1997; **37**: 501–2.
24 Allen BR. Use of cyclosporin for psoriasis in HIV-positive patient. *Lancet* 1992; **339**: 686.
25 Buccheri L, Katchen BR, Karter AJ, Cohen SR. Acitretin therapy is effective for psoriasis associated with human immunodeficiency virus infection. *Arch Dermatol* 1997; **133**: 711–5.
26 Berthelot P, Guglielminotti C, Fresard A *et al*. Dramatic cutaneous psoriasis improvement in a patient with the human immunodeficiency virus treated with 2,3-dideoxycytidine and ritonavir. *Arch Dermatol* 1997; **133**: 531.
27 Fischer T, Schworer H, Vente C *et al*. Clinical improvement of HIV-associated psoriasis parallels a reduction of HIV viral load induced by effective antiretroviral therapy. *AIDS* 1999; **13**: 628–9.
28 Aboulafia DM, Bundow D, Wilske K, Ochs UL. Etanercept for the treatment of human immunodeficiency virus associated psoriatic arthritis. *May Clin Proc* 2000; **75**: 1093–8.
29 Sellam J, Bouvard B, Masson C *et al*. Use of infliximab to treat psoriatic arthritis in HIV-positive patients. *Joint Bone Spine* 2007; **74**: 197–200.
30 Dichmann S, Mrowietz U, Schopf E, Norgauer J. Humanized monoclonal anti-CD2 antibody as a novel therapeutic option in HIV-associated psoriatic erythroderma. *J Am Acad Dermatol* 2002; **47**: 635–6.
31 Stashower ME, Yeager JK, Smith KJ *et al*. Cimetidine as therapy for treatment-resistant psoriasis in a patient with acquired immunodeficiency syndrome. *Arch Dermatol* 1993; **129**: 848–50.
32 Smith KJ, Decker C, Yeager J, Skelton HG, Baskin S. Therapeutic efficacy of carbamazepine in a HIV-1-positive patient with psoriatic erythroderma. *J Am Acad Dermatol* 1997; **37**: 851–4.

Eosinophilic folliculitis

Eosinophilic folliculitis is an HIV-specific disorder [1,2] related to Ofuji's disease (see Chapter 23). Originally thought to be an early sign of HIV infection, it is actually an uncommon presenting manifestation and especially rare in women [3]. It occurs at CD4 T-cell counts of 250–300 $\times$ 10^6/L identifying patients at immediate risk of developing opportunistic infections. Clinical overlap with the pruritic papular eruption of HIV and bacterial, pityrosporum or acneiform folliculitis occurs [4], and this complicates interpretation of the earlier literature. The cause is unknown but Th2 cytokines (IL-4, IL-5), RANTES and eotaxin are increased in lesional skin [5], a different cytokine profile compared with pruritic papular eruption [6]; foscarnet has been implicated in the development of eosinophilic folliculitis [7].



Fig. 35.4 Eosinophilic folliculitis: excoriated papules on the trunk. (Courtesy of Professor C.B. Bunker and Medical Illustration UK Ltd, Chelsea and Westminster Hospital, London, UK.)

Eosinophilic folliculitis presents as a centripetal (face and trunk) eruption of pruritic, erythematous, perifollicular papules and pustules (Fig. 35.4). Patients with eosinophilic folliculitis may be subclinically photosensitive [8]. It mimics staphylococcal or *Pityrosporum* folliculitis and acne vulgaris, with which it can coexist. Histology is characteristic, with degranulating eosinophils and mast cells in a perifollicular distribution [9]. The clinicopathological differential diagnosis is discussed on p. 35.24. There may be a peripheral eosinophilia and elevated levels of IgE. Swabs are negative; the lesions are sterile. Treatment can be problematic but the disease has virtually disappeared in the developed world in recent years with the introduction of HAART, although immune reconstitution exacerbations have been reported [10,11]. Phototherapy is the most successful treatment modality but other treatments that have been tried include topical disodium cromoglycate, potent topical steroids, topical tacrolimus, oral antihistamines such as astemizole and cetirizine, oral antibiotics (erythromycin, tetracyclines, co-trimoxazole), oral itraconazole (for its antieosinophilic effect), oral dapsone, oral indomethacin and oral isotretinoin [12–19]. Eosinophilic folliculitis may be an indication for HAART but may require treatment as above when exacerbated by HAART as part of IRD.

References

1 Ferrandiz C, Ribera M, Barranco JC *et al*. Eosinophilic pustular folliculitis in patients with acquired immunodeficiency syndrome. *Int J Dermatol* 1992; **31**: 193–5.
2 Fearfield LA, Rowe A, Francis N *et al*. Itchy folliculitis and human immunodeficiency virus infection: clinicopathological and immunological features, pathogenesis and treatment. *Br J Dermatol* 1999; **141**: 3–11.

3 Teofoli P, Barbieri C, Pallotta S *et al*. Pruritic eosinophilic papular eruption revealing HIV infection. *Eur J Dermatol* 2002; **12**: 600–2.
4 Budavari JM, Grayson W. Papular follicular eruptions in human immunodeficiency virus-positive patients in South Africa. *Int J Dermatol* 2007; **46**: 706–10.
5 Amerio P, Verdolini R, Proietto G *et al*. Role of Th2 cytokines, RANTES and eotaxin in AIDS-associated eosinophilic folliculitis. *Acta Derm Venereol (Stockh)* 2001; **81**: 92–5.
6 Aires JM, Rosatelli JB, de Castro Figueiredo JF, Roselino AM. Cytokines in the pruritic papular eruption of HIV. *Int J Dermatol* 2000; **39**: 903–6.
7 Roos TC, Albrecht H. Foscarnet-associated eosinophilic folliculitis in a patient with AIDS. *J Am Acad Dermatol* 2001; **44**: 546–7.
8 Vin-Christian K, Epstein JH, Maurer TA *et al*. Photosensitivity in HIV-infected individuals. *J Dermatol* 2000; **27**: 361–9.
9 Holmes RB, Martins C, Horn T. The histopathology of folliculitis in HIV-infected patients. *J Cutan Pathol* 2002; **29**: 93–5.
10 Costner M, Cockerell CJ. The changing spectrum of the cutaneous manifestations of HIV disease. *Arch Dermatol* 1998; **134**: 1290.
11 Rajendran PM, Dolev JC, Heaphy MR Jr, Maurer T. Eosinophilic folliculitis before and after the introduction of antiretroviral therapy. *Arch Dermatol* 2005; **141**: 1227–31.
12 Kuwano Y, Watanabe R, Fujimoto M *et al*. Treatment of HIV-associated eosinophilic pustular folliculitis with narrow-band UVB. *Int J Dermatol* 2006; **45**: 1265–7.
13 Harris DW, Ostlere L, Buckley C *et al*. Eosinophilic pustular folliculitis in an HIV-positive man: response to cetirizine. *Br J Dermatol* 1992; **126**: 392–4.
14 Bunker CB. Dermatological problems in HIV and AIDS. In: Miller A, ed. *Medical Management of HIV and AIDS*. London: Springer, 1996.
15 Downs AM, Lear JT, Oxley JD, Kennedy CT. AIDS associated eosinophilic folliculitis which responded to both high dose co-trimoxazole and low dose isotretinoin. *Sex Transm Infect* 1998; **74**: 229–30.
16 Finkelstein M, Berman B. HIV and AIDS in inpatient dermatology. Approach to the consultation. *Dermatol Clin* 2000; **18**: 509–20.
17 Toutous-Trellu L, Abraham S, Pechère M *et al*. Topical tacrolimus for effective treatment of eosinophilic folliculitis associated with human immunodeficiency virus infection. *Arch Dermatol* 2005; **141**: 1203–8.
18 Maurer TA. Dermatologic manifestations of HIV infection. *Top HIV Med* 2005; **13**: 149–54.
19 Nerv SJ, Scwartz RA, Dmochowski M. Eosinophilic pustular folliculitis: a 40 year retrospect. *JAAD* 2006; **55**: 285–9.

Pruritic papular eruption

Pruritic papular eruption (PPE) is a common cutaneous manifestation of HIV, the prevalence varying between 10 and 60% depending on geographical area [1–5]. It is common in Africa and Asia. It has some interesting similarities with the papular eruption of pregnancy (see Chapter 8). Insect bite hypersensitivity, as in papular urticaria (see Chapter 38), is the likely pathomechanism [4,6,7]. The majority (84% of Ugandan patients) have histology characteristic of arthropod bites and patients blame mosquitoes [4]. Interestingly, in another study, 75% had circulating bullous pemphigoid autoantibodies and up to 30% met the diagnostic criteria for bullous pemphigoid on histology, western blotting, immunofluorescence and immunoelectron microscopy [8]. Although increased CD8 lymphocytes, increased IL5 and abundant eosinophils point to a Th2 response, the immunophenotypic profile of PPE differs from that of eosinophilic folliculitis [5,7,9,10]. PPE is a sign of an advanced degree of immunosuppression and may often be the first sign of HIV, occurring at CD4 T-cell counts below $100–200 \times 10^6$/L (median 46/μL in one study) [3,4,5,11] with the severity of the rash inversely proportional to the CD4 count [4]. PPE presents as excoriated, erythematous, urticarial papules associated with eosinophilia and elevated IgE. Scars from scratching and infection can be disfiguring and stigmatizing [4]. The clinical differential diagnosis includes nodular prurigo, prebullous pemphigoid, scabies, papulonecrotic tuberculid, drug eruption, photodermatitis, secondary syphilis, onchodermatitis and eosinophilic, pityrosporum, bacterial and acneiform folliculitis; there is significant clinical overlap and this can cause difficulty in interpreting the earlier literature. Histology shows wedge-shaped, moderately dense, superficial and deep perivascular and interstitial lymphocytic and eosinophilic infiltrates; the epidermis is hyperplastic and there may be a spongiotic punctum [4]. The treatment of PPE is similar to that of eosinophilic folliculitis, with phototherapy the linchpin; thalidomide and pentoxifylline (oxpentifylline) have been claimed to be efficacious [12–14]. It is a strong clinical indication for initiating HAART.

References

1 Hira SK, Wadhawan D, Kamanga J *et al*. Cutaneous manifestations of human immuno-deficiency virus in Lusaka, Zambia. *J Am Acad Dermatol* 1988; **19**: 451–7.
2 Rosen T. Pruritic papular eruption of AIDS. *J Am Acad Dermatol* 1991; **25**: 866–7.
3 Boonchai W, Laohasrisakul R, Manonukul J, Kulthanan K. Pruritic papular eruption in HIV seropositive patients: a cutaneous marker for immunosuppression. *Int J Dermatol* 1999; **38**: 348–50.
4 Resneck JS Jr, Van Beek M, Furmanski L *et al*. Etiology of pruritic papular eruption with HIV infection in Uganda. *JAMA* 2004; **292**: 2614–21.
5 Ramos H, Pagliari C, Takakura CF *et al*. Pruritic papular eruption associated with HIV-etiopathogenesis evaluated by clinical, immunohistochemical, and ultrastructural analysis. *J Dermatol* 2005; **32**: 549–56.
6 Palungwachira P, Chirachanakul P, Palungwachira P *et al*. Cutaneous findings in HIV-1 positive patients in Thailand. *J Dermatol* 2000; **28**: 584–5.
7 Rosatelli JB, Roselino AM. Hyper-IgE, eosinophilia, and immediate cutaneous hypersensitivity to insect antigens in the pruritic papular eruption of human immunodeficiency virus. *Arch Dermatol* 2001; **137**: 672–3.
8 Kinloch-de Loes S, Didierjean L, Rieckhoff-Cantoni L *et al*. Bullous pemphigoid autoantibodies, HIV-infection and pruritic papular eruption. *AIDS* 1991; **5**: 451–4.
9 Aires JM, Rosatelli JB, de Castro Figueiredo JF, Roselino AM. Cytokines in the pruritic papular eruption of HIV. *Int J Dermatol* 2000; **39**: 903–6.
10 Amerio P, Verdolini R, Proietto G *et al*. Role of Th2 cytokines, RANTES and eotaxin in AIDS-associated eosinophilic folliculitis. *Acta Derm Venereol (Stockh)* 2001; **81**: 92–5.
11 Gelfand JM, Rudikoff D. Evaluation and treatment of itching in HIV-infected patients. *Mt Sinai J Med* 2001; **68**: 298–308.
12 Finkelstein M, Berman B. HIV and AIDS in inpatient dermatology. Approach to the consultation. *Dermatol Clin* 2000; **18**: 509–20.
13 Berman B, Flores F, Burke G. Efficacy of pentoxifylline in the treatment of the pruritic papular eruption of HIV-infected persons. *J Am Acad Dermatol* 1998; **38**: 955–9.
14 Pardo RJ, Bogaert MA, Penneys NS *et al*. UVB phototherapy of the pruritic papular eruption of the acquired immunodeficiency syndrome. *J Am Acad Dermatol* 1992; **26**: 423–8.

Granuloma annulare

Localized, generalized, diffuse and atypical (including oral and perforating) forms of granuloma annulare (see Chapter 60) occur in HIV infection [1–4] (Fig. 35.5). Violaceous lesions may mimic KS. Lesions have simulated mollusca in one case [5]. An association with zalcitabine (ddC, DDC; no longer available) treatment has been mooted [6]. Cultures are negative [2]. There is a variable response to HAART.

References

1 Cohen PR, Grossman ME, Silvers DN, DeLeo VA. Human immunodeficiency virus-associated granuloma annulare. *Int J STD AIDS* 1991; **2**: 168–71.

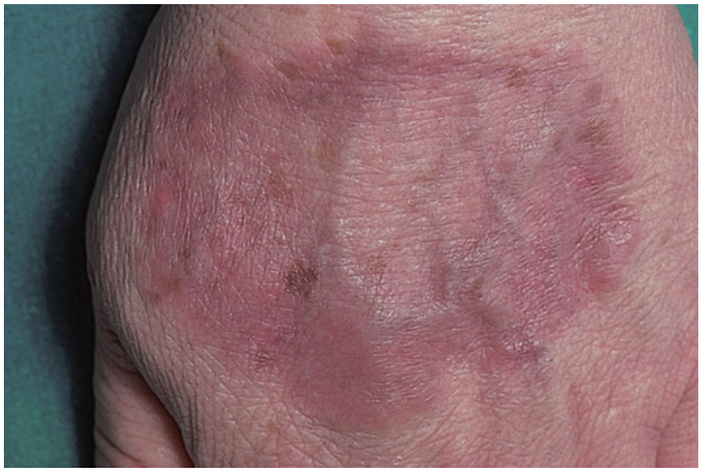


Fig. 35.5 Granuloma annulare on the hand. (Courtesy of Professor C.B. Bunker and Media Resources UCL, London, UK.)

2 O'Moore EJ, Nandawani R, Uthayakumar S *et al*. HIV-associated granuloma annulare (HAGA): a report of 6 cases. *Br J Dermatol* 2000; **142**: 1054–6.
3 Huerter CJ, Bass J, Bergfeld WF, Tubbs RR. Perforating granuloma annulare in a patient with acquired immunodeficiency syndrome. Immunohistologic evaluation of the cellular infiltrate. *Arch Dermatol* 1987; **123**: 1217–20.
4 Morris SD, Cerio R, Paige DG. An unusual presentation of diffuse granuloma annulare in an HIV-positive patient—immunohistochemical evidence of predominant CD8 lymphocytes. *Clin Exp Dermatol* 2002; **27**: 205–8.
5 Kapembwa MS, Goolamali SK, Price A, Boyle S. Granuloma annulare masquerading as molluscum contagiosum-like eruption in an HIV-positive African woman. *J Am Acad Dermatol* 2003; **49**: S184–6.
6 Penas PF, Jones-Caballero M, Garcia-Diez A. Association between zalcitabine therapy for human immunodeficiency virus and granuloma annulare? *Arch Dermatol* 2001; **137**: 964.

Porphyria cutanea tarda

Porphyria cutanea tarda (see Chapter 59) is polyfactorial in HIV [1]. Familial influences, viral hepatitis B and C (e.g. in haemophiliacs), alcohol and sunlight may be involved. *N*-acetylcysteine has been used for treatment [2].

References

1 Blauvelt A, Harris HR, Hogan DJ *et al*. Porphyria cutanea tarda and human immunodeficiency virus infection. *Int J Dermatol* 1992; **31**: 474–9.
2 Binet H, Simonart T, Van Vooren JP *et al*. Porphyria cutanea tarda in a human immunodeficiency virus-infected patient: treatment with N-acetyl-cysteine. *Int J Dermatol* 1998; **37**: 718–9.

Drug reactions

Drug reactions (see Chapter 75) are a common challenge in HIV dermatology [1–4].

The types of drug eruption that have been encountered are summarized in Table 35.15. A morbilliform toxic erythema is the usual reaction seen (with fever, arthralgia, abnormal liver function tests and eosinophilia). Erythema multiforme, Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN)/Lyell's syndrome hypersensitivity syndromes, DRESS (drug rash with eosinophilia and systemic symptoms) syndrome (Table 35.16), erythroderma, vasculitis, fixed drug eruptions, cutaneous photosensitivity, photocutaneous drug eruptions and skin sensitivity to radiotherapy have all been encountered [1,2,5–14]. Co-trimoxazole (sulfamethoxazole–trimethoprim), dapsone, pentamidine and antituberculous chemotherapy, especially with rifampicin, thioacetazone (thiacetazone) and ethambutol, pose particular risks [6,7]. Phenytoin hypersensitivity syndrome can masquerade as a PUO [15]. Probenecid (given to reduce the nephrotoxicity of cidofovir) can cause a hypersensitivity reaction [16].

Table 35.15 Cutaneous side effects of non-ARV drugs in patients with HIV/AIDS. (From [4,6,80].)

Morbilliform toxic erythema
Erythema multiforme, SJS, TEN, hypersensitivity syndrome, DRESS syndrome (see Table 35.16)
Erythroderma
Anaphylaxis, urticaria, angio-oedema
Xerosis, cheilitis
Lichenoid reactions
Psoriasis
Photodermatitis
Purpura
Orogenital ulceration
Vasculitis
Fixed drug eruptions
Pentamidine: also causes ulcers at the site of injection
Foscarnet: penile ulceration
Saquinavir
Palmar/plantar keratoderma: glucan
Flagellate erythema: bleomycin
Eosinophilic folliculitis: foscarnet
Acrocyanosis: butyl nitrite

SJS, Stevens Johnson syndrome; TEN, toxic epidermal necrolysis; DRESS, drug rash with eosinophilia and systemic symptoms.

Table 35.16 Drugs implicated in erythema multiforme, Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), hypersensitivity syndrome, and DRESS syndrome in patients with HIV/AIDS. (From [4,6,8–10,29,33,39,81,82].)

Abacavir
Allopurinol
Amprenavir
Carbamazepine
Co-trimoxazole (sulfamethoxazole–trimethoprim)
Efavirenz
Fluconazole
Griseofulvin
Indinavir
Nevirapine
Nitrofurantoin (in pregnancy)
Phenytoin
Probenecid
Pyrimethamine
Saquinavir
Streptomycin
Sulfadiazine
Sulfadoxine
Thioacetazone (thiacetazone)
Vancomycin
Zidovudine (AZT, ZDV)
Traditional Chinese medicines

DRESS, drug rash with eosinophilia and systemic symptoms.

Table 35.17 Principal cutaneous side effects of ARV drugs. (From [4,6,9,28,83–88].)

Drug	Side effect
Nucleoside reverse transcriptase inhibitors (NRTIs)	
All NRTIs	Pruritus, xanthem, urticaria
Abacavir	HLA B5701 hypersensitivity syndrome, SJS, TEN, Kawasaki syndrome, anaphylaxis, lipodystrophy
Didanosine (ddI, DDI)	Vasculitis, purpura, SJS, anaphylaxis, Ofuji's papuloerythroderma, gynaecomastia, lipodystrophy, acral erythema, diaphoresis
Emtricitabine (FTC)	Hyperpigmentation
Lamivudine (3TC)	Vasculitis, anaphylaxis, angio-oedema, allergic contact dermatitis, gynaecomastia, lipodystrophy, diaphoresis
Stavudine (d4T)	Lipodystrophy, gynaecomastia, neutrophilic eccrine hidradenitis, tendon xanthomas, diaphoresis
Tenofovir	Maculopapular toxic erythema, diaphoresis
Zalcitabine* (ddC, DDC)	Anaphylaxis, angio-oedema, acne, photosensitivity, erythroderma, granuloma annulare, bullous eruption, diaphoresis
Zidovudine (AZT, ZDV)	Exanthem, erythema multiforme and SJS, polymyositis, erythroderma, porphyria cutanea tarda, purpura, vasculitis, insect bite reaction, discoloration of the skin (also mucosa and nails) especially in dark-skinned individuals), neutrophilic eccrine hidradenitis, acne, bullous eruption, lipodystrophy, bromhidrosis, diaphoresis
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	
All NNRTIs	Pruritus, exanthem, SJS/TEN
Delavirdine*	Xerosis, urticaria, angio-oedema, dermatitis, vesicobullous eruption, purpura, vasculitis, seborrhoea, gynaecomastia, diaphoresis
Efavirenz	Eczema, photosensitivity, gynaecomastia, leukocytoclastic vasculitis, urticaria, flushing, folliculitis
Nevirapine	DRESS, angioedema, anaphylaxis, lipodystrophy
Protease inhibitors (PIs)	
All PIs	Exanthem, SJS/TEN, pruritus, xerosis, hypersensitivity syndrome, anaphylaxis, panniculitis, toxic pustoloderma, tendon xanthomas, lipodystrophy, acanthosis nigricans
Amprenavir	Significant incidence of rash (20–30%)
Atazanavir	Eczema, photosensitivity, seborrhoea, urticaria, vesicobullous eruption, purpura, gynaecomastia, diaphoresis
Darunavir	Hyperhidrosis (with ritonavir), sulphonamide therefore incidence of rash high (7%)
Fosamprenavir (pro-drug of amprenavir)	Significant incidence of rash (20%)
Indinavir	Erythroderma dermatitis, folliculitis, pigmentation (skin, nail and hair), seborrhoea, urticaria, vasculitis, paronychia/pyogenic granuloma, striae, lipomatosis, porphyria, gynaecomastia, paraesthesia, diaphoresis, bromhidrosis
Nelfinavir	Urticaria, dermatitis, lichenoid reaction, palmar erythema, vasculitis, gynaecomastia
Ritonavir	Urticaria, IgA-mediated hypersensitivity, acne, seborrhoea, bullous eruption, dermatitis, folliculitis, granulomas, ecchymosis, haematoma, paraesthesia, diaphoresis
Saquinavir	Photosensitivity, urticaria, acne, bullous eruption, dermatitis, seborrhoeic dermatitis, folliculitis, papulovesicular eruptions, furunculosis, herpes simplex, herpes zoster, candidosis, hyperpigmentation, psoriasis, warts, fixed drug eruption, gynaecomastia, paraesthesia, diaphoresis
Tipranavir	Photosensitivity
Fusion inhibitors	
Enfuvirtide	Injection site reactions, xerosis, pruritus, exanthem, acne, herpes simplex, papillomas, ecchymosis, paraesthesia

DRESS, drug rash with eosinophilia and systemic symptoms.
* No longer available.

Of patients with *Pneumocystis jiroveci* pneumonia treated with co-trimoxazole, 60% experience fever, nausea, vomiting and a rash [17]. Amoxicillin (amoxycillin)–clavulanate causes a skin eruption in about half of HIV-infected patients who receive the drug compared with more than 90% of patients with acute lymphoblastic leukaemia or infectious mononucleosis and 3–10% of the general population [18].

Glucan has been implicated in causing palmoplantar keratoderma [19]. The striking flagellate erythema due to bleomycin has been observed in HIV [20,21], but this is relatively common in general oncological practice. Pustular psoriasiform reactions to pegylated doxorubicin (used for KS) have been seen [22]. Fixed drug eruptions are associated with pentamidine, which can also cause ulcers at the site of injection [8,23], and foscarnet, which causes penile ulceration [24]. Interferons may precipitate ulceration at injection sites [25]. Hydroxyurea can result in mucocutaneous hyperpigmentation (and melanonychia; see later) [26]. Butylnitrite may produce acrocyanosis [27].

The principal cutaneous side effects of the ARV drugs are listed in Table 35.17. The side effects of ARVs on the oropharynx, hair and nails are discussed on p. 35.41–44 (see also Tables 35.23 & 35.24).

Exanthems, erythema multiforme, Stevens–Johnson syndrome and toxic epidermal necrolysis can be complications of the components of HAART [6,9,28–37]. As in other causes of toxic epidermal necrolysis, intravenous gammaglobulin may be an effective treatment [6,38,39]. The syndrome of drug rash with eosinophilia and systemic symptoms (DRESS) has been reported with nevirapine [39]. Abacavir is associated with a hypersensitivity syndrome of fever, gastrointestinal symptomatology, malaise and in about 70% of patients a rash, but this has virtually disappeared following screening for HLA-B*5701 [29,40,41].

An exanthematous pustulosis has been reported including with lopinavir–ritonavir (Kaletra) [42,43]. Nelfinavir can cause urticaria [44]. Erythroderma, abdominal pain and renal failure has been described with indinavir [45]. An anaphylactoid reaction and allergic contact dermatitis to lamivudine have been reported [46]. Ritonavir can cause an IgA-mediated hypersensitivity syndrome, haematoma formation and subcutaneous granulomas [28,47]. Didanosine (ddI, DDI) has been associated with papuloerythroderma of Ofuji [28].

Xerosis and cheilitis are common with PIs [48]. Some cases of granuloma annulare have been blamed on zalcitabine (ddC, DDC) but it is no longer available. Fixed drug eruption has been reported with saquinavir [49]. Photosensitivity and photoallergic dermatitis have been documented with saquinavir and efavirenz [50–52]. Gynaecomastia has complicated stavudine (d4T) and didanosine (ddI, DDI) treatment [53]. Indinavir has precipitated acute porphyria [54]. Panniculitis has been blamed on ritonavir and nelfinavir [55]. Painful perioral and peripheral paraesthesiae and bullae have been associated with ritonavir and peripheral paraesthesia with indinavir [56]. Enfuvirtide causes injection-site reactions including pruritus, pain, erythema, induration, nodules and scleroderma [57,58].

The mechanisms of common drug reactions are not clearly known but correspond to classical immunopathological models. In HIV, acute or reactivated Epstein–Barr virus, CMV or other viruses, polyclonal B-cell activation, hypereosinophilia, hypergammaglobulinaemia, immune complex formation, and the generation of autoantibodies and autoreactive T-cell clones that interact with drug or tissue complexes are hypothetical pathomechanisms. However, glutathione deficiency, slow acetylation and active viral infections have been shown not to be correlated with sulfonamide sensitivity in patients with AIDS [59]. It has been proposed that the pattern of immune dysregulation (decreased Th1 cytokines; increased Th2 cytokines; increased IgE, IgA and eosinophils) predisposes to drug hypersensitivity. For example, co-trimoxazole exacerbates this hypersensitivity by decreasing Th1 responses; macrolides increase Th1 responses [4,6].

It is common experience that adverse reactions to co-trimoxazole may disappear with continued therapy and that some patients will tolerate rechallenge with amoxicillin–clavulanate. *N*-acetylcysteine pre-treatment may prevent co-trimoxazole hypersensitivity [60]. Prednisolone does not prevent sulfonamide or nevirapine-induced cutaneous hypersensitivity [59,61]. Tolerance has been induced for nevirapine and nelfinavir [62]. Drug hypersensitivity can also disappear at very low CD4 T-cell counts ($<20 \times 10^6$/L) and before death occurs. Therefore, a prior drug reaction does not constitute an *absolute* contraindication to continued or further treatment with a particular drug.

The ability of all PIs and some NRTIs, especially stavudine (d4T), to cause lipodystrophy is a matter of both intense clinical frustration (because the appearances are distressing and stigmatizing to patients [63]) and mechanistic fascination. Fat loss (lipoatrophy) from the nasolabial folds, cheeks and extremities occurs, with fat accumulation (lipohypertrophy) in the abdominal and dorsocervical (buffalo hump) and mammary regions. Up to 80% of patients on HAART may develop facial lipoatrophy within 10 months of starting treatment [64], depending on regimen. With newer regimens not containing stavudine (d4T) or zidovudine (AZT), this is much rarer. The syndrome is completed by hyperlipidaemia, insulin resistance (including acanthosis nigricans) and lactic acidaemia. Mitochondrial toxicity is one proposed mechanism [40]. There is concern about accelerated atherosclerosis and cardiovascular disease [65–68]. Benign symmetrical lipomatosis [69], striae [70] and tendon xanthomas [71,72] have been reported.

Also of interest to dermatologists are the retinoid-like effects of the PIs, particularly indinavir–paronychia, periungual pyogenic granuloma-like lesions, xerosis and cheilitis, and curly hair. The mechanism is uncertain [73–76] but experience shows that isotretinoin (for acne) can be used safely and effectively alongside PIs. Concomitant administration has paradoxically resulted in *lower* plasma retinoid levels [77].

Treatment of lipodystrophy is challenging, but some successful approaches include direct excision, ultrasonic-assisted lipuction, suction assisted lipectomy, fat injections, soft tissue fillers, human growth hormone and releasing factor, leptin, metformin and thiazolidinediones [41,64,78,79].

References

1 Coopman SA, Stern RS. Cutaneous drug reactions in human immunodeficiency virus infection. *Arch Dermatol* 1991; **127**: 714–7.

2 Coopman SA, Johnson RA, Platt R, Stern RS. Cutaneous disease and drug reaction in HIV infection. *N Engl J Med* 1993; **328**: 1670–4.

3 Heller HM. Adverse cutaneous drug eruptions in patients with human immunodeficiency virus-1 infection. *Clin Dermatol* 2000; **18**: 485–9.

4 Todd G. Adverse cutaneous drug eruptions and HIV: a clinician's global perspective. *Dermat Clin* 2006; **24**: 459–72.

5 Morar N, Dlova N, Gupta AK *et al*. Erythroderma: a comparison between HIV positive and negative patients. *Int J Dermatol* 1999; **38**: 895–900.

6 Okwera A, Johnson JL, Vjecha MJ *et al*. Risk factors for adverse drug reactions during thiacetazone treatment of pulmonary tuberculosis in human immunodeficiency virus infected adults. *Int J Tuberc Lung Dis* 1997; **1**: 441–5.

7 Bunker CB, Staughton RCD. HIV-associated disease: dermatology. In: Gazzard BG, ed. *AIDS Care Handbook*. London: Mediscript, 2002: 115–39.

8 Rustin MHA, Bunker CB, Dowd PM, Robinson TWE. Erythema multiforme due to griseofulvin. *Br J Dermatol* 1989; **120**: 455–8.

9 Penneys MS. *Skin Manifestations of AIDS*. London: Martin Dunitz, 1990.

10 Rotunda A, Hirsch RJ, Scheinfeld N, Weinberg JM. Severe cutaneous reactions associated with the use of human immunodeficiency virus medications. *Acta Derm Venereol* 2003; **83**: 1–9.

11 Rzany B, Mockenhaupt M, Stocker U *et al*. Incidence of Stevens–Johnson syndrome and toxic epidermal necrolysis in patients with the acquired immunodeficiency syndrome in Germany. *Arch Dermatol* 1993; **129**: 1059.

12 Bilu D, Mamelak AJ, Nguyen RH-N *et al*. Clinical and epidemiologic characterization of photosensitivity in HIV-positive individuals. *Photodermatol Photoimmunol Photomed* 2004; **20**: 175–83.

13 Gherardi R, Belec L, Mhiri C *et al*. The spectrum of vasculitis in human immunodeficiency virus-infected patients: a clinicopathological evaluation. *Arthritis Rheum* 1993; **36**: 1164–74.

14 Smith KJ, Skelton HG, Tuur S *et al*. Increased cutaneous toxicity to ionizing radiation in HIV-positive patients. Military Medical Consortium for the Advancement of Retroviral Research (MMCARR). *Int J Dermatol* 1997; **36**: 779–82.

15 Bedimo RJ, Geisler WM. Phenytoin hypersensitivity syndrome masquerading as fever and systemic illness of unknown origin in an HIV-infected patient. *Int J STD AIDS* 2005; **16**: 178–9.

16 Myers KW, Katial RK, Engler RJ. Probenecid hypersensitivity in AIDS: a case report. *Ann Allergy Asthma Immunol* 1998; **80**: 416–8.

17 Kovacs JA, Masur H. *Pneumocystis carinii* pneumonia: therapy and prophylaxis. *J Infect Dis* 1988; **158**: 254–9.

18 Battegay M, Opravil M, Wuthrich B, Luthy R. Rash with amoxicillin–clavulanate therapy in HIV-infected patients. *Lancet* 1989; **ii**: 1100.

19 Duvic M, Reisman M, Finley V *et al*. Glucan-induced keratoderma in acquired immunodeficiency syndrome. *Arch Dermatol* 1987; **123**: 751–6.
20 Caumes E, Katlama C, Guermonprez G *et al*. Cutaneous side-effects of bleomycin in AIDS patients with Kaposi's sarcoma. *Lancet* 1990; **336**: 1593.
21 Nandwani R, Money-Kyrle J, Hawkins DA *et al*. Bleomycin-induced flagellate dermatitis in AIDS patients with Kaposi's sarcoma. *J Eur Acad Dermatol Venereol* 1995; **4**: 89–93.
22 Kreuter A, Gambichler T, Schlottman R *et al*. Psoriasiform pustular eruptions from pegylated-liposomal doxorubicin in AIDS-related Kaposi's sarcoma. *Acta Derm Venereol (Stockh)* 2001; **81**: 224.
23 Jones RS Jr, Collier-Brown C, Suh B. Localized cutaneous reaction to intravenous pentamidine. *Clin Infect Dis* 1992; **15**: 561–2.
24 Fegeux S, Salmon D, Picard C *et al*. Penile ulcerations with foscarnet. *Lancet* 1990; **335**: 547.
25 Virgili A, Corazza M, Lombardi AR, Sighinolfi L. Cutaneous ulcers due to interferon seem not to be related to the dosage. *J Eur Acad Dermatol Venereol* 1999; **13**: 141–3.
26 Laughon SK, Shinn LL, Nunley JR. Melanonychia and mucucutaneous hyperpigmentation due to hydroxyurea use in an HIV-infected patient. *Int J Dermatol* 2000; **39**: 928–31.
27 Hoegl L, Thoma-Greber E, Poppinger J, Rocken M. Butyl nitrite-induced acrocyanosis in an HIV-infected patient. *Arch Dermatol* 1999; **135**: 90–1.
28 Ward HA, Russo GG, Shrum J. Cutaneous manifestations of anti-retroviral therapy. *J Am Acad Dermatol* 2002; **46**: 284–93.
29 Kong HH, Myers SA. Cutaneous effects of highly active antiretroviral therapy in HIV-infected patients. *Dermatol Ther* 2005; **18**: 58–66.
30 Martins CR. Cutaneous drug reactions associated with newer antiretroviral agents. *J Drugs Dermatol* 2006; **5**: 976–82.
31 Lockhart SM, Rathbun RC, Stephens JR *et al*. Cutaneous reactions with tenofovir disoproxil fumarate: a report of nine cases. *AIDS* 2007; **21**: 1370–3.
32 Shilad A, Predanic M, Perni SC *et al*. Human immunodeficiency virus, pregnancy and Stevens-Johnson syndrome. *Obstet Gynecol* 2005; **105**: 1254–6.
33 Calista D. Maculo-papular rash induced by lopinavir/ritonavir. *Eur J Dermatol* 2005; **15**: 97–8.
34 Ouagari Z, Tubiana R, Mohand HA *et al*. Skin rash associated with atazanavir: report of three cases. *AIDS* 2006; **20**: 1207–8.
35 Warren KJ, Boxwell DE, Kim NY, Drolet BA. Nevirapine-associated Stevens–Johnson syndrome. *Lancet* 1997; **351**: 567.
36 Fortuny C, Vicente MA, Medina MM, Gonzalez-Ensenat A. Rash as side-effect of nelfinavir in children. *AIDS* 2000; **14**: 335–6.
37 Phan TG, Wong RC, Crotty K, Adelstein S. Toxic epidermal necrolysis in acquired immunodeficiency syndrome treated with intravenous gammaglobulin. *Australas J Dermatol* 1999; **40**: 153–7.
38 Tan A, Tan HH, Lee CC, Ng SK. Treatment of toxic epidermal necrolysis in AIDS with intravenous immunoglobulins. *Clin Exp Dermatol* 2003; **28**: 269–71.
39 Bourezane Y, Salard D, Hoen B *et al*. DRESS (drug rash with eosinophilia and systemic symptoms) syndrome associated with nevirapine therapy. *Clin Infect Dis* 1998; **27**: 1321–2.
40 Phillips EJ, Knowles SR, Shear N. Cutaneous manifestations of antiviral therapy. *J Am Acad Dermatol* 2002; **48**: 985–6.
41 Waters LJ, Mandalia S, Gazzard B, Nelson M. Prospective HLA-B*5701 screening and abacavir hypersensitivity: a single centre experience. *AIDS* 2007; **21**: 2533–4.
42 Aquilina C, Viraben R, Roueire A. Acute generalized exanthematous pustulosis: a cutaneous adverse effect due to prophylactic antiviral therapy with protease inhibitor. *Arch Intern Med* 1998; **158**: 2160–1.
43 Ghosn J, Duvivier C, Tubiana R *et al*. Acute generalized exanthematous pustulosis induced by HIV postexposure prophylaxis with lopinavir-ritonavir. *Clin Infect Dis* 2005; **41**: 1360–1.
44 Demoley P, Messaad D, Trylesinski A *et al*. Nelfinavir-induced urticaria and successful desensitization. *J Allergy Clin Immunol* 1998; **102**: 875–6.
45 Rietsema WJ. Fever, erythroderma, abdominal pain, and renal failure following initiation of indinavir therapy. *Clin Infect Dis* 1997; **25**: 1268–9.
46 Kainer MA, Mijch A. Anaphylactoid reaction, angioedema, and urticaria associated with lamivudine. *Lancet* 1996; **348**: 1519.
47 Kawsar M, El-Gadi S. Subcutaneous granulomatous lesions related to ritonavir therapy in a HIV infected patient. *Int J STD AIDS* 2002; **13**: 273–4.
48 Garcia-Silva J, Almargo M, Juega J *et al*. Protease inhibitor-related paronychia, ingrown toenails, desquamative cheilitis and cutaneous xerosis. *AIDS* 2000; **14**: 1289–91.
49 Smith KJ, Yeager J, Skelton H. Fixed drug eruption to human immunodeficiency virus-1 protease inhibitor. *Cutis* 2000; **66**: 29–32.
50 Winter AJ, Pywell JM, Ilchyshyn JM *et al*. Photosensitivity due to saquinavir. *Genitourin Med* 1997; **73**: 323.
51 Newell A, Avila C, Rodgers ME. Photosensitivity reaction of efavirenz. *Sex Transm Infect* 2000; **76**: 221.
52 Treudler R, Husak R, Raisova M *et al*. Efavirenz-induced photoallergic dermatitis in HIV. *AIDS* 2001; **15**: 1085–6.
53 Aquilina C, Viraben R. Gynaecomastia in a male patient during stavudine and didanosine treatment for HIV infection. *Int J STD AIDS* 2001; **12**: 481–2.
54 Fox PA, Boag FC, Hawkins DA, Francis N. Acute porphyria following commencement of indinavir. *AIDS* 1999; **13**: 622–3.
55 Popp AL, Armstrong D, Sepkowitz KA. Recurrent panniculitis in a patient receiving protease inhibitor therapy for human immunodeficiency virus infection. *Clin Infect Dis* 1999; **29**: 936–7.
56 Colebunders R, De Droogh E, Pelgrom Y *et al*. Painful hyperaesthesia caused by protease inhibitors? *Infection* 1998; **26**: 250–1.
57 Maggi P, Ladisa N, Cinori E *et al*. Cutaneous injection site reactions to long-term therapy with enfuvirtide. *J Antimicrob Chemother* 2004; **53**: 678–81.
58 Shahar E, Moar C, Pollack S. Successful desensitisation of enfuvirtide-induced skin hypersensitivity reaction. *AIDS* 2005; **19**: 451–2.
59 Eliaszewicz M, Flahault A, Roujeau J-C *et al*. Prospective evaluation of risk factors of cutaneous drug reactions to sulfonamides in patients with AIDS. *J Am Acad Dermatol* 2002; **47**: 40–6.
60 Akerlund B, Tynell E, Bratt G *et al*. *N*-Acetylcysteine treatment and the risk of toxic reactions to trimethoprim–sulphamethoxazole in primary *Pneumocystis carinii* prophylaxis in HIV-infected patients. *J Infect* 1997; **35**: 143–7.
61 Rey D, Partisani M, Krantz V *et al*. Prednisolone does not prevent the occurrence of nevirapine-induced rashes. *AIDS* 1999; **13**: 2307.
62 Demoley P, Messaad D, Fabre J *et al*. Nevirapine-induced cutaneous hypersensitivity reactions and successful tolerance induction. *J Allergy Clin Immunol* 1999; **104**: 504–5.
63 Hawkins T. Appearance-related side effects of HIV-1 treatment. *AIDS Patient Care STDS* 2006; **20**: 6–18.
64 Burgess CM, Quiroga RM. Assessment of the safety and efficacy of poly-L-lactic acid for the treatment of HIV-associated facial lipoatrophy. *J Am Acad Dermatol* 2005; **52**: 233–9.
65 Graber AL. Syndrome of lipodystrophy, hyperlipidaemia, insulin resistance and diabetes in treated patients with human immunodeficiency virus infection. *Endocr Pract* 2001; **7**: 430–7.
66 Mallon PW, Cooper DA, Carr A. HIV-associated lipodystrophy. *HIV Med* 2001; **2**: 166–73.
67 Holstein A, Plaschke A, Egberts EH. Lipodystrophy and metabolic disorders as complication of antiretroviral therapy of HIV infection. *Exp Clin Endocrinol Diabetes* 2001; **109**: 389–92.
68 Kester KE, Visvesara GS, McEvoy C. Reduction of buffalo hump by switching to amprenavir in an HIV-infected patient. *Arch Intern Med* 2001; **30**: 200–3.
69 Hengel I, Watts NB, Lennox JL. Benign symmetric lipomatosis associated with protease inhibitors. *Lancet* 1997; **350**: 1596.
70 Darvay A, Acland K, Lynn W, Russell-Jones R. Striae formation in two HIV-positive persons receiving protease inhibitors. *J Am Acad Dermatol* 1999; **41**: 467–9.
71 Leung N, Hegele RA, Lewis GF. Rapid development of massive tendon xanthomas following highly active antiretroviral therapy. *Ann Intern Med* 2002; **137**: 624.
72 Brown CA, Lesher JL, Peterson CM. Tuberous and tendinous xanthomata secondary to ritonavir-associated hyperlipidemia. *J Am Acad Dermatol* 2005; **52** (5 Suppl. 1): S86–9.
73 Padberg J, Schurmann D, Grobusch M, Bergmann F. Drug interaction of isotretinoin and protease inhibitors: support for the cellular retinoic acid-binding protein-1 theory of lipodystrophy? *AIDS* 1999; **13**: 284–5.
74 Colebunders R, Bottieau E, de Mey I. Curly hair and lipodystrophy as a result of highly active antiretroviral treatment? *Arch Dermatol* 2000; **136**: 1064–5.

75 Sass JO, Jakob-Solder B, Heitger A *et al*. Paronychia with pyogenic granuloma in a child treated with indinavir: the retinoid-mediated side effect theory revisited. *Dermatology* 2000; **200**: 40–2.
76 Garcia-Silva J, Almagro M, Pena-Penabad C, Fonseca E. Indinavir-induced retinoid-like effects: incidence, clinical features and management. *Drug Saf* 2002; **25**: 993–1003.
77 Sass JO, Padberg J. Human isotretinoin metabolism during indinavir therapy. *AIDS Res Hum Retroviruses* 2000; **16**: 1451–2.
78 Hultman CS, McPhail LE, Donaldson JH, Wohl DA. Surgical management of HIV-associated lipodystrophy: role of ultrasonic-assisted liposuction and suction-assisted lipectomy in the treatment of lipohypertrophy. *Ann Plas Surg* 2007; **58**: 255–63.
79 Jones DH, Carruthers A, Orentreich D *et al*. Highly purified 1000-cSt silicone oil for treatment of human immunodeficiency virus-associated facial lipoatrophy: an open pilot trial. *Dermatol Surg* 2004; **30**: 1279–86.
80 Cockerell CJ. Non-infectious inflammatory skin diseases in HIV-infected individuals. *Dermatol Clin* 1991; **9**: 531–42.
81 Vidal C, Gonzalez Quintela A, Fuente R. Toxic epidermal necrolysis due to vancomycin. *Ann Allergy* 1992; **68**: 345–7.
82 Girao L, Franca I, Robalo Nunes J *et al*. Toxic epidermal necrolysis in a patient infected with human immunodeficiency virus-2. *J Eur Acad Dermatovenereol* 2002; **16**: 91–3.
83 Litt JZ. *Drug Eruption Manual*, 14th edn. New York: Informa Healthcare, 2008.
84 Anon. *British National Formulary* 2007; **54**: 324–32.
85 Terheggen F, Frissen J, Weigel H *et al*. Nail, hair and skin hyperpigmentation associated with indinavir therapy. *AIDS* 2004; **18**: 1612.
86 Sevila A, Morell A, Banuls J *et al*. Neutrophilic eccrine hidradenitis in an HIV-infected patient. *Int J Dermatol* 1996; **35**: 651–2.
87 Bessen LJ, Greene JB, Louise E *et al*. Severe polymyositis-like syndrome associated with zidovudine therapy or AIDS and ARC. *N Engl J Med* 1988; **311**: 708.
88 Torres RA, Lin RV, Lee M, Barr MR. Zidovudine-induced leukocytoclastic vasculitis. *Arch Intern Med* 1992; **152**: 850.

Infections

Bacterial infections

Cellulitis and soft tissue infection are under-appreciated complications of HIV infection. They are continuing causes of morbidity in the HAART era and the majority (over 80%) will be community-acquired [1]. Cutaneous bacterial infection poses the risks of bacteraemia and septicaemia (up to 25% of episodes) or may *signify* systemic infection. Central lines, concomitant chemotherapy, injectable drug abuse and the presence of other skin diseases present additional risks [1–4]. Skin flora (e.g. *P. acnes*) can be systemically pathogenic in the immunoincompetent, necessitating great circumspection in skin antisepsis prior to surgery and instrumentation [5]. The clinician must be alert to the dermatological signs of systemic bacterial infection, such as splinter haemorrhages and acral papulonecrotic lesions. A high index of suspicion and a low threshold for performing microbiological investigations and skin biopsies (including Gram stain and special stains and cultures) should be inculcated to allow precise diagnosis and specific treatment. *Staphylococcus aureus*, *Pseudomonas* spp., *Escherichia coli* and *Streptococcus pyogenes* are the commonest isolates in that order; polymicrobial infection may be present in up to 40% of cases [1]. Systemic antibiotics should be chosen on the basis of the clinical situation and sensitivities, when they become known; possible methicillin resistance should be anticipated. Abscesses should be treated by surgical drainage but also biopsied and cultured, including for mycobacteria and fungi [6].

Staphylococcal infection must be considered when a patient presents with the common scenario of folliculitis. Clinical differentiation between staphylococcal folliculitis, malassezia folliculitis, dermatophyte folliculitis, eosinophilic folliculitis, demodex folliculitis and acne vulgaris or rosacea may be very challenging and these entities may coexist; very rarely, micrococcus, *Acinetobacter baumanii* and *Clostridium perfringens* folliculitis and herpes simplex and zoster viral folliculitis have been encountered [7–12]. Cryptococcosis has presented as a corporeal pseudofolliculitis [13]. Intertriginous staphylococcal folliculitis may mimic candidosis. Histologically, other patterns of folliculitis may be recognized, for example commonly a lymphocytic folliculitis or perifolliculitis with mixed inflammation are seen, and more rarely follicular rupture with granulomatous inflammation [14].

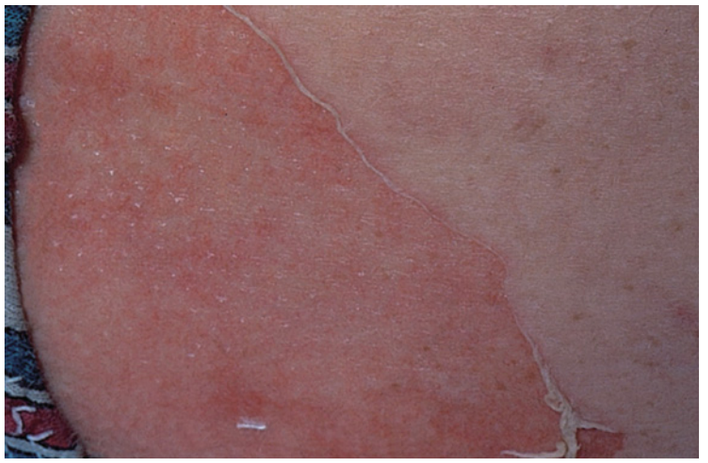


Fig. 35.6 Staphylococcal scalded skin syndrome: staphylococcal pneumonia in HIV-positive intravenous drug addict. (Courtesy of Professor C.B. Bunker and Medical Illustration UK Ltd, Chelsea and Westminster Hospital, London, UK.)

Secondary staphylococcal infection of the skin may be a complication of many of the inflammatory dermatoses discussed earlier. It is becoming an increasing problem, perhaps because of decreased usage of trimethoprim–sulphamethoxazole prophylaxis in the HAART era [15].

Methicillin-resistant *Staphylococcus aureus* (MRSA) is presenting an emerging challenge to the HIV-positive individual. Initially, MRSA carriage did not seem to be an appreciable problem in HIV-positive outpatients but this has changed and community-acquired MRSA skin infections are increasing in the USA [16–24]. Risk factors include high-risk sex, drug use, CD4 $<50 \times 10^6$/L, $\log_{10}$ HIV viral load copies/mL, absence of co-trimoxazole prophylaxis, partners with skin infections, recent hospitalization, prior MRSA infection and recent receipt of a β-lactam antibiotic [20,22,25–27]. Isolates are susceptible to co-trimoxazole, tetracycline and clindamycin [22], but inducible resistance to clindamycin is increasing [27].

Besides folliculitis, manifestations of staphylococcal infections in HIV include bullous impetigo, ecthyma, abscesses, botromycosis and staphylococcal scalded skin (Fig. 35.6) and toxic shock syndromes [28–32]. Subcutaneous abscesses due to staphylococci may complicate injection or intravenous-line sites. Surgical drainage is an important part of abscess management.

Group A *Streptococcus* erysipelas and lymphadenitis has been reported [33]. *Pseudomonas aeruginosa* is an important potential



Fig. 35.7 Bacillary angiomatosis: purple nodules on the face. (Courtesy of Professor C.B. Bunker and Medical Illustration UK Ltd, Chelsea and Westminster Hospital, London, UK.)

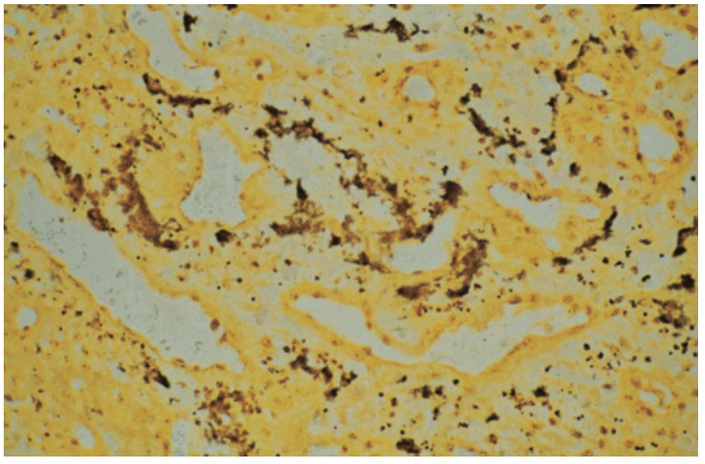


Fig. 35.8 Bacillary angiomatosis: Warthin–Starry silver staining of *Bartonella bacilliformis* and proliferative vascular channels. (Courtesy of Dr N. Francis, Imperial College School of Medicine, London, UK.)

cutaneous pathogen in HIV infection and AIDS. *Ecthyma gangrenosum* and *panniculitis* may be pointers to *Pseudomonas* septicaemia [34–37].

Fournier's gangrene is a hazard with a high mortality in AIDS and may complicate chemotherapy [37,38].

Bacillary angiomatosis, originally entitled 'epithelioid (haem) angiomatosisis', is caused by the Gram-negative cat-scratch disease organism *Bartonella* (previously *Rochalimaea*) *henselae* affecting the skin [1,39]. When it was first encountered, clinicians were intrigued by the similarity of bacillary angiomatosis to the cutaneous stigmata of chronic infection with *Bartonella bacilliformis*, the 'forma mular of verruga peruana'. These lesions may occur in the chronic phase of Oroya fever and are clinically and histologically very similar to those of bacillary angiomatosis. Bacillary angiomatosis presents with purple, papular and nodular vascular lesions resembling KS (Fig. 35.7). Patients with bacillary angiomatosis do not appear to have an overt, acute, febrile haemolytic illness. Diagnosis is achieved by skin biopsy. Histologically, bacillary angiomatosis is distinguished from KS by being a lobular vascular proliferation where the abnormal, enlarged endothelial cells are epithelioid rather than spindled and by having a prominent neutrophilic infiltrate and neutrophil debris; there may be pseudoepitheliomatous hyperplasia [40]. The abnormal vascular spaces, lined with proliferating endothelium, contain *B. bacilliformis*. The clumps of organisms can be demonstrated by Warthin–Starry silver staining (Fig. 35.8), immunoperoxidase staining of lesional tissue (where the bacilli are found within the abnormally proliferative cutaneous vasculature) or electron microscopy. Bacillary angiomatosis responds to oral erythromycin in most patients; isoniazid, rifampicin, ethambutol or clofazimine, either in addition to or instead of erythromycin, have also been used.

Syphilis (see Chapter 34) may present atypically in HIV infection [2], confounding the clinical recognition of the classical dermatological manifestations of primary chancre, the papulosquamous eruption of secondary syphilis and gumma [23]. The interpretation of serological tests can be complicated; they are not as sensitive in the immunoincompetent and so false negatives are a hazard [41–43]. Dermatologists should regard all genital, perianal and oral ulceration and any papulosquamous eruption with great suspicion and handle them with circumspection [44]. Rarer manifestations of syphilis not previously encountered by this generation of physicians, such as keratoderma, lues maligna (necrotic red nodules) and nodular syphilis (simulating lymphoma) have been reported [45–47].

Similar problems with yaws [48] have not been significant in clinical practice. *Lyme borreliosis* pseudolymphoma [49] and a persistent erythema chronicum migrans (with meningoradiculitis) have occurred [50].

Reinfection with, or reactivation of, *Mycobacterium tuberculosis* seems to occur early in HIV infection and extrapulmonary, including cutaneous, tuberculosis (see Chapter 31) is common [51]. The clinical presentation is diverse, including scrofula [52], scattered violaceous papules [53], acute miliary tuberculosis of the skin [54–56], keratotic papules, nodules and palmar/plantar keratoderma [57] and tuberculides [58,59]. Tuberculous lymphadenitis has been said to be a characteristic manifestation in HIV and in intravenous drug users co-infected with tuberculosis [60]. Management of tuberculous co-infection in about one-third of the estimated 30–40 million people infected with HIV poses particular challenges and is a specialist field [61].

Atypical mycobacterial skin disease in patients infected with HIV is usually due to *Mycobacterium avium–intracellulare*. This occurs as part of a disseminated infection in up to one-third of patients [62] at CD4 T-cell counts below 50×10^6/L (rare below 200×10^6/L). Lesions described include violaceous papules, nodules and ulcers and simulating histoid leprosy [63,64]. Concomitant *M. tuberculosis*, *M. avium–intracellulare* and CMV has been seen [65]. *M. avium* complex has been isolated from an HIV-positive woman with erythema multiforme [66]. Skin involvement has also been reported with *M. kansasii* [53], *M. haemophilum* [67–69], *M. fortuitum* [70], *M. lentiflavum* [71] and *M. marinum* [72]. In these instances the eruption has probably occurred after primary infection of the skin by the organism but a fatal case of

disseminated *M. marinum* has occurred [73]. Sporotrichoid spread (see Chapter 31) can involve an affected limb emanating from a distal primary site [74,75]. Aggressive multifocal Buruli ulcer due to *M. ulcerans* has been described [76].

The diagnosis of mycobacterial infection can be problematic because characteristic histopathological features such as caseating granuloma may be absent due to diminished cell-mediated immunity [77]. Spindle cell pseudotumours may be seen [78]. All biopsies where tuberculosis and/or atypical mycobacterial infection are suspected should be stained for acid-fast bacilli (which may be very numerous because of diminished cell-mediated immunity) and a separate portion sent for mycobacterial culture under appropriate laboratory conditions.

Prophylaxis and treatment of tuberculosis and atypical mycobacterial disease depends on the clinical scenario (including CD4 count) and the results of microbiological investigations (including sensitivity testing) and is an expert area. HAART and specific conventional antituberculous drugs are used. Atypical mycobacterial infection is treated with a macrolide and ethambutol.

Unlike other mycobacterial disease, the epidemiological and clinical features of leprosy have not been signally modified by the HIV pandemic [79–81] with the exception of reported manifestations of IRIS/IRD (p. 35.46) [82–84]. It is likely that this phenomenon will be increasingly seen. Two co-infected HAART-naïve patients who developed type 1 leprosy reactions (analogous to IRD/IRIS) have been reported [85].

Other bacterial infections. Cutaneous granulomas due to *Corynebacterium minutissimun* [86], extragenital donovanosis [87], an unusual presentation of chancroid [88], a paranasal ulcer due to *Chryseomonas luteola* [89], rickettsial pox [90], an abscess due to *Peptostreptococcus ivorii* [91], a disseminated papular eruption caused by *Serratia marcescens* [92] and erythematous plaques on the legs due to *Campylobacter* [93] have been described.

References

1 Manfredi R, Calza L, Chiodo F. Epidemiology and microbiology of cellulitis and bacterial soft tissue infection during HIV disease: a 10-year survey. *J Cutan Pathol* 2002; **29**: 168–72.

2 Skoutelis AT, Murphy RL, MacDonell KB *et al.* Indwelling central venous catheter infections in patients with the acquired immunodeficiency syndrome. *J Acquir Immune Defic Syndr* 1990; **3**: 335–42.

3 Redondo P, Molano E, Lloret P, Bauza A. 'Skin popping' ulceration in an HIV patient. Successful treatment with antiretroviral drugs and stanozolol. *Int J STD AIDS* 2002; **13**: 508–9.

4 Colfax G, Shoptaw S. The methamphetamine epidemic: implications for HIV prevention and treatment. *Curr HIV/AIDS Rep* 2005; **2**: 194–9.

5 Cambanis A, Tata E, Wirkom V. Proprionibacter acnes complicating HIV-associated tuberculous pericardial effusion in Cameroon. *Cardiovasc J S Afr* 2006; **17**: 255–6.

6 Bunker CB, Staughton RCD. HIV-associated disease: dermatology. In: Gazzard BG, ed. *AIDS Care Handbook*. London: Mediscript, 2002: 115–39.

7 Berger TG, Greene I. Bacterial, viral, fungal and parasitic infections in HIV disease and AIDS. *Dermatol Clin* 1991; **9**: 465–92.

8 Caumes E, Mommeja-Marin H, Chosidow O *et al*. Facial folliculitis due to *Clostridium perfringens* in a patient infected with human immunodeficiency virus. *Clin Infect Dis* 1998; **26**: 501–2.

9 Smith KJ, Neafie R, Yeager J, Skelton HG. Micrococcus folliculitis in HIV-1 disease. *Br J Dermatol* 1999; **141**: 558–61.

10 Weinberg JM, Turiansky GW, James WD. Viral folliculitis. *AIDS Patient Care STDS* 1999; **13**: 513–6.

11 Johnson RA. Dermatophyte infections in human immune deficiency virus (HIV) disease. *J Am Acad Dermatol* 2000; **43** (5 Suppl.): S135–S142.

12 Bachmeyer C, Landgraf N, Cordier F *et al*. Acinetobacter baumanii folliculitis in a patient with AIDS. *Clin Exp Dermatol* 2005; **30**: 256–8.

13 Coker LR, Swain R, Morris R, McCall CO. Disseminated cryptococcosis presenting as pseudofolliculitis in an AIDS patient. *Cutis* 2000; **66**: 207–10.

14 Holmes RB, Martins C, Horn T. The histopathology of folliculitis in HIV-infected patients. *J Cutan Pathol* 2002; **29**: 93–5.

15 Maurer TA. Dermatologic manifestations of HIV infection. *Top HIV Med* 2005; **13**: 149–54.

16 Klein PA, Greene WH, Fuhrer J, Clark RA. Prevalence of methicillin-resistant *Staphylococcus aureus* in outpatients with psoriasis, atopic dermatitis, or HIV infection. *Arch Dermatol* 1997; **133**: 1463–5.

17 Smith NP, Nelson MR, Azadian B, Gazzard BG. An outbreak of methicillin-resistant *Staphoylococcus aureus* (MRSA) infection in HIV-seropositive persons. *Int J STD AIDS* 1998; **9**: 726–30.

18 Onorato M, Borucki MH, Baillargeon G *et al*. Risk factors for colonization or infection due to methicillin-resistant *Staphylococcus aureus* in HIV-positive patients: a retrospective case–control study. *Infect Control Hosp Epidemiol* 1999; **20**: 26–30.

19 Tumbarello M, De Gaetano Donati K, Tacconelli E *et al*. Risk factors and predictors of mortality of methicillin-reisistant *Staphylococcus aureus* (MRSA) bacteraemia in HIV-infected patients. *J Antimicrob Chemother* 2002; **50**: 375–82.

20 Hidron AI, Kourbatova EV, Halvosa JS *et al*. Risk factors for colonization with methicillin-resistant Staphylococcus aureus (MRSA) in patients admitted to an urban hospital: emergence of community-associated MRSA nasal carriage. *Clin Infect Dis* 2005; **41**: 159–66.

21 Anderson EJ, Hawkins C, Bolon MK, Palella FJ. A series of skin and soft tissue infections due to methicillin-resistant Staphylococcus aureus in HIV-infected patients. *J Acquir Immune Defic Syndr* 2006; **41**: 125–7.

22 Skiest D, Brown K, Hester J *et al*. Community-onset methicillin-resistant Staphylococcus aureus in an urban HIV clinic. *HIV Med* 2006; **7**: 361–8.

23 Elston DM. Community-acquired methicillin-resistant Staphylococcus aureus. *J Am Acad Dermatol* 2007; **56**: 1–16.

24 Shastry L, Rahimian J, Lascher S. Community-associated methicillin-resistant Staphylococcus aureus skin and soft tissue infections in men who have sex with men in New York City. *Arch Intern Med* 2007; **167**: 854–7.

25 Lee NE, Taylor MM, Bancroft E *et al*. Risk factors for community-associated methicillin-resistant Staphylococcus aureus skin infections among HIV-positive men who have sex with men. *Clin Infect Dis* 2005; **40**: 1529–34.

26 Mathews WC, Caperna JC, Barber RE *et al*. Incidence of and risk factors for clinically significant methicillin-resistant Staphylococcus aureus infection in a cohort of HIV-infected adults. *J Acquir Immune Defic Syndr* 2005; **40**: 155–60.

27 Crum-Cianflone NF. Recurrent neck infection in a person with HIV/AIDS. *AIDS Read* 2006; **16**: 129–32.

28 Donovan B, Rohrsteim R, Bassett I, Mulhall BP. Bullous impetigo in homosexual men: a risk factor for HIV infection. *Genitourin Med* 1992; **68**: 159–61.

29 Donohue D, Robinson B, Goldberg NS. Staphylococcal scalded skin syndrome in a woman with chronic renal failure exposed to human immunodeficiency virus. *Cutis* 1991; **47**: 317–8.

30 Cone LA, Woodard DR, Byrd RG *et al*. A recalcitrant, erythematous, desquamating disorder associated with toxin-producing staphylococci in patients with AIDS. *J Infect Dis* 1992; **165**: 638–43.

31 Farrell AM, Ross JS, Umasankar S, Bunker CB. Staphylococcal scalded skin syndrome in an HIV-1 seropositive man. *Br J Dermatol* 1996; **134**: 962–5.

32 de Vries HJ, van Noesel CJ, Hoekzema R, Hulsebosch HJ. Botryomycosis in an HIV-positive patient. *J Eur Acad Dermatol Venereol* 2003; **17**: 87–90.

33 Janssen F, Zelinsky-Guning A, Caumer E, Decares HM. Group A streptococcal cellulitis–adenitis in a patient with acquired immunodeficiency syndrome. *J Am Acad Dermatol* 1991; **24**: 363–5.

34 Khan MO, Montecalvo MA, Davis I, Wormser GP. Ecthyma gangrenosum in patients with acquired immunodeficiency syndrome. *Cutis* 2000; **66**: 121–3.

35 El Baze P, Thyss A, Vinti H *et al*. A study of nineteen immunocompromised patients with extensive skin lesions caused by *Pseudomonas aeruginosa* with and without bacteremia. *Acta Derm Venereol (Stockh)* 1991; **71**: 411–5.

36 Smith RA, Ross JS, Branfoot AC *et al*. Panniculitis with *Pseudomonas* septicaemia in AIDS. *J Eur Acad Dermatol Venereol* 1995; **4**: 166–9.

37 Kim EJ, Foad M, Travers R. Ecthyma gangrenosum in an AIDS patient with normal neutrophil count. *J Am Acad Dermatol* 1999; **41**: 840–1.
38 Bunker CB. *Male Genital Skin Disease*. London: Saunders, 2004: 158–60.
39 Plettenberg A, Lorenzen T, Burtsche BT *et al*. Bacillary angiomatosis in HIV-infected patients: an epidemiological and clinical study. *Dermatology* 2000; **201**: 326–31.
40 Amsbaugh S, Huiras E, Wang NS *et al*. Bacillary angiomatosis associated with pseudoepitheliomatous hyperplasia. *Am J Dermatopathol* 2006; **28**: 32–5.
41 Musher DM, Hamill RJ, Baughn RE. Effect of human immunodeficiency virus (HIV) infection on the course of syphilis and on the response to treatment. *Ann Intern Med* 1990; **113**: 872–81.
42 Fonseca E, Garcia-Silva J, del Pozo J *et al*. Syphilis in an HIV infected patient misdiagnosed as leprosy. *J Cutan Pathol* 1999; **26**: 51–4.
43 Kingston AA, Vujevich J, Shapiro M *et al*. Seronegative secondary syphilis in 2 patients coinfected with human immunodeficiency virus. *Arch Dermatol* 2005; **141**: 431–3.
44 Ajithkumar K. Unusual skin ulceration in an HIV-positive patient who had cutaneous syphilis and neurosyphilis. *Br J Dermatol* 1998; **138**: 366–7.
45 Glover RA, Piaquadio DJ, Kern S, Cockerell CJ. An unusual presentation of secondary syphilis in a patient with human immunodeficiency virus infection. A case report and review of the literature. *Arch Dermatol* 1992; **128**: 530–4.
46 Baniandrés Rodriguez O, Nieto Perea O, Moya Alonso L, Carillo Gijón R, Harto Castaño A. Nodular secondary syphilis in a HIV patient mimicking cutaneous lymphoma. *An Med Interna* 2004; **21**: 241–3.
47 D'Amico R, Zalusky R. A case of lues maligna in a patient with acquired immunodeficiency syndrome (AIDS). *Scand J Infect Dis* 2005; **37**: 697–700.
48 Noordhoek GT, van Embden JD. Yaws, an endemic treponematosis reconsidered in the HIV era. *Eur J Clin Microbiol Infect Dis* 1991; **10**: 4–5.
49 Bratzke B, Stadler R, Gollnick H *et al*. *Borrelia burgdorferi*-induced pseudolymphoma with pathogen cultivation in an HIV-1 positive patient. *Hautarzt* 1989; **40**: 504–9.
50 Cordoliani F, Vignon-Pennamen MD, Assous MV *et al*. Atypical Lyme borreliosis in an HIV-infected man. *Br J Dermatol* 1997; **137**: 437–9.
51 Anonymous. Skin tuberculosis surges. *AIDS Patient Care STDS* 1998; **12**: 739.
52 Pedersen C, Nielsen JO. Tuberculosis in homosexual men with HIV disease. *Scand J Infect Dis* 1987; **19**: 289–90.
53 Penneys MS. *Skin Manifestations of AIDS*. London: Martin Dunitz, 1990.
54 Rohatgi PK, Palazzolo JV, Saini NB. Acute miliary tuberculosis of the skin in acquired immunodeficiency syndrome. *J Am Acad Dermatol* 1992; **26**: 356–9.
55 Daikos GL, Uttamchandani RB, Tuda C *et al*. Disseminated miliary tuberculosis of the skin in patients with AIDS: report of four cases. *Clin Infect Dis* 1998; **27**: 205–8.
56 High WA, Evans CC, Hoang MP. Cutaneous military tuberculosis in two patients with HIV infection. *J Am Acad Dermatol* 2004; **50**: S110–3.
57 Mehlmauer MA. Keratotic papules and nodules and hyperkeratosis of palms and soles in a patient with tuberculosis and AIDS-related complex. *J Am Acad Dermatol* 1990; **23**: 381–5.
58 Farrell AM, Roberts NM, Walsh JC, Staughton RC. A painful rash with AIDS. *Lancet* 1996; **347**: 372.
59 Friedman PC, Husain S, Grossman ME. Nodular tuberculid in a patient with HIV. *J Am Acad Dermatol* 2005; **53**: S154–6.
60 Aguado JM, Castrillo JM. Lymphadenitis as a characteristic manifestation of disseminated tuberculosis in intravenous drug abusers infected with human immunodeficiency virus. *J Infect* 1987; **14**: 191–3.
61 Colebunders R, Lambert ML. Management of co-infection with HIV and TB. *BMJ* 2002; **324**: 802–3.
62 Hawkins CC, Gold JWM, Whimby E *et al*. *Mycobacterium avium* complex infections in patients with the acquired immunodeficiency syndrome. *Ann Intern Med* 1986; **105**: 184–8.
63 Freed JA, Pervez NK, Chen V *et al*. Cutaneous mycobacteriosis: occurrence and significance in two patients with the acquired immunodeficiency syndrome. *Arch Dermatol* 1987; **123**: 1601–3.
64 Boyd AS, Robbins J. Cutaneous *Mycobacterium avium intracellulare* infection in an HIV^+ patient mimicking histoid leprosy. *Am J Dermatopathol* 2005; **27**: 39–41.
65 Nunez M, Miralles ES, Hilara Y *et al*. Concurrent cytomegalovirus, *M. tuberculosis* and *M. avium-intracellulare* cutaneous infection in an HIV patient. *J Dermatol* 1997; **24**: 401–4.
66 Brown T, Yen A. Isolation of *Mycobacterium avium* complex from erythema multiforme. *J Am Acad Dermatol* 1998; **39**: 493–5.
67 Holton J, Nye P, Miller R. *Mycobacterium haemophilum* infection in a patient with AIDS. *J Infect* 1991; **23**: 303–6.
68 Kristjansson M, Bieluch VM, Byeff PD. *Mycobacterium haemophilum* infection in immunocompromised patients: case report and review of the literature. *Rev Infect Dis* 1991; **13**: 906–10.
69 Geisler WM, Harrington RD, Wallis CK *et al*. Broad spectrum of dermatologic manifestations caused by *Mycobacterium haemophilum* infection. *Arch Dermatol* 2002; **138**: 229–30.
70 Sack JB. Disseminated infection due to *Mycobacterium fortuitum* in a patient with AIDS. *Rev Infect Dis* 1990; **12**: 961–3.
71 Montejo M, Goicoetxea J, Agnesta N *et al*. Cutaneous infection by *Mycobacterium lentiflavum* in a patient with HIV. *Dermatol* 2006; **213**: 173–4.
72 Kaplan MH, Sadick N, McNutt NS *et al.* Dermatologic findings and manifestations of acquired immunodeficiency syndrome (AIDS). *J Am Acad Dermatol* 1987; **16**: 485–506.
73 Tchornobay AM, Claudy AL, Perrot JL *et al*. Fatal disseminated *Mycobacterium marinum* infection. *Int J Dermatol* 1992; **31**: 286–7.
74 Zukervar P, Canillot S, Gayrard L, Perrot H. Sporotrichoid *Mycobacterium marinum* infection in a patient infected with human immunodeficiency virus. *Ann Dermatol Vénéréol* 1991; **118**: 111–3.
75 Kayal JD, McCall CO. Sporotrichoid cutaneous *Mycobacterium avium* complex infection. *J Am Acad Dermatol* 2002; **47**: S249–50.
76 Toll A, Gallardo F, Ferran M *et al* Aggressive multifocal Buruli ulcer with associated osteomyelitis in an HIV-positive patient. *Clin Exp Dermatol* 2005; **30**: 649–51.
77 Smith KJ, Skelton HG III, Angritt P. Histopathologic features of HIV-associated skin disease. *Dermatol Clin* 1991; **9**: 551–8.
78 Liou JH, Huang PY, Hung CC, Hsiao CH. Mycobacterial spindle cell pseudotumor of skin. *J Formos Med Assoc* 2003; **102**: 342–5.
79 Meyers WM. Leprosy. *Dermatol Clin* 1992; **10**: 73–96.
80 Awofeso N. AIDS and tuberculosis/leprosy in Nigeria: the urbanisation factor. *Acta Leprol* 1995; **9**: 149–51.
81 Kar HK, Sharma P. Does concomitant HIV infection have any epidemiological, clinical, immunopathological and therapeutic relevance in leprosy? *Indian J Lepr* 2007; **79**: 45–60.
82 Pignataro P, Rocha Ada S, Nery JA *et al*. Leprosy and AIDS: two cases of increasing inflammatory reactions at the start of highly active antiretroviral therapy. *Eur J Clin Microbiol Infect Dis* 2004; **23**: 408–11.
83 Couppié P, Abel S, Voinchet H *et al*. Immune reconstitution inflammatory syndrome associated with HIV and leprosy. *Arch Dermatol* 2004; **140**: 997–1000.
84 Narang T, Dogra S, Kaur I. Borderline tuberculoid leprosy with type 1 reaction in an HIV patient—a phenomenon of immune reconstitution. *Int J Lepr Other Mycobact Dis* 2005; **73**: 203–5.
85 Trindade MA, Valente NY, Manini MI *et al*. Two patients coinfected with *Mycobacterium leprae* and human immunodeficiency virus type 1 and naive for antiretroviral therapy who exhibited type 1 leprosy reactions mimicking the immune reconstitution inflammatory syndrome. *J Clin Microbiol* 2006; **44**: 4616–8.
86 Santos-Juanes J, Galache C, Martínez-Cordero A *et al*. Cutaneous granulomas caused by corynebacterium minutissimum in an HIV-infected man. *J Eur Acad Dermatol Venereol* 2002; **16**: 638–49.
87 Sanders CJ. Extragenital donovanosis in a patient with AIDS. *Sex Transm Infect* 1998; **74**: 142–3.
88 Quale J, Teplitz E, Augenbraun M. Atypical presentation of chancroid in a patient infected with the human immunodeficiency virus. *Am J Med* 1990; **88**: 43–4.
89 Ghosh SK. A rare infection caused by *Chryseomonas luteola*. *J Infect* 2000; **41**: 109–10.
90 Sanders S, Di Costanzo D, Leach J *et al*. Rickettsialpox in a patient with HIV infection. *J Am Acad Dermatol* 2003; **48**: 286–9.
91 Eiring P, Wagner D. Peptostreptococcus ivorii-associated skin abscess in a HIV-infected patient. *Anaerobe* 1999; **5**: 1–3.
92 Munoz-Perez MA, Rodriguez-Pichardo A, Camach F. Disseminated papular eruption caused by Serratia marcescens: a new cutaneous manifestation in HIV-positive patients. *AIDS* 1996; **10**: 1179–80.

93 Rajendran PM, Hurst E, Ruben B, Maurer T. *Campylobacter* presenting as erythematous plaques on the lowere extremity of a man with human immunodeficiency virus. *Arch Dermatol* 2006; **142**: 1240–1.

Viral infections

Herpes simplex. Severe, chronic, ulcerative, perianal disease (Fig. 35.9) caused by herpes simplex virus (HSV)-2 (human herpesvirus 2, HHV-2) was one of the first features of AIDS to be reported [1]. HSV-1 and HSV-2 infections (see Chapter 33) are extremely common during the course of HIV illness [2,3]. Although anogenital involvement is frequent, any site can be affected with acute lesions that are vesicobullous but which become chronic, eroded and crusted, vegetative, or ulcerating; HSV infection may not be self-limiting as it is in normal individuals. Persistent necrotic digits [4] and perioral ulceration may occur. A facial folliculitis (sycosis) has been reported [5], as has Kaposi's varicelliform eruption after laser resurfacing [6]. Secondary bacterial infection is probably universal. Coinfection with *Candida* can contribute to atypical presentations [7]. Concomitant infection with CMV has also been seen [8]. Resolution can occur with specific treatment for HSV and general HIV treatment. However, herpetic lesions recur; the impact of HAART has been to improve this situation, although HSV IRIS/IRD is now a recognized phenomenon and can be difficult to treat see Fig. 35.28) [9].

Diagnosis depends on clinical suspicion supported by electron microscopy of fresh lesional fluid, DNA hybridization, immunofluorescence and viral culture; additionally, acute and convalescent sera may be examined for HSV antibodies (IgM and IgG). A skin biopsy may show typical cytopathic signs and positive immunostaining for HSV. In the USA, the Tzanck test is popular for rapid identification of multinucleate giant cells, which are not pathognomonic because they are seen also in varicella, herpes zoster and pemphigus [10,11].



Fig. 35.9 Chronic perianal ulceration in herpes simplex infection before the era of highly active antiretroviral therapy.

The treatment of HSV infection in HIV requires the systemic deployment of specific antiviral drugs (of which aciclovir is the prototype), including prophylactically [2]. The approach should be aggressive because HSV activates HIV replication [12]. Topical and systemic treatments for secondary bacterial infection are often necessary. HSV mutants (i.e. those with mutant or absent viral thymidine kinase) are responsible for HSV resistance, although progressive HSV-2 infection has been reported despite aciclovir therapy and demonstrable sensitivity of isolates to aciclovir. Intravenous vidarabine has been effective in aciclovir-resistant herpes simplex, but foscarnet (trisodium phosphoformate), which is a direct inhibitor of HSV DNA polymerase, is better for severe HSV-2. Famciclovir [13] and valaciclovir are alternatives to aciclovir. Cidofovir is a DNA polymerase inhibitor used in CMV infection, but is also effective against HSV.

Varicella-zoster virus. Reactivation of varicella-zoster virus (VZV, HHV-3; see Chapter 33) frequently accompanies HIV infection and can be severe [2,14]. Recurrences of VZV do occur in HIV-negative people and in up to 20% of HIV-negative immunocompromised patients. The frequency of recurrence in HIV-positive individuals is unknown. It is controversial whether all patients presenting with dermatomal VZV should be counselled about HIV testing but it is regarded as a predictor of HIV infection in African patients [15]. Reactivation of VZV is the commonest cutaneous manifestation of immune restoration disease [16].

The distribution of the eruption is characteristically dermatomal but differentiation from herpes simplex may not always be clinically certain. Ophthalmic zoster may be complicated by conjunctivitis or optic neuritis, so ophthalmological input is advised. The involvement of sacral nerves may cause acute retention of urine, haemorrhagic cystitis and constipation. Other manifestations include motor zoster, zoster encephalomyelitis and purpura fulminans.

A non-bullous folliculitis has been described [5]. A chronic verrucous dermatomal form can occur (Fig. 35.10). An atypical, sometimes protracted, disseminated VZV eruption of sparse but ecthymatous necrotic lesions is occasionally seen, but there is usually a concomitant dermatomal recurrence. Linear Darier disease with chronic zoster superinfection has been reported [17]. The differential diagnosis includes *Pseudomonas* ecthyma gangrenosum and disseminated infection with atypical mycobacteria, fungi, vaccinia or HSV. Central nervous system and pulmonary or central neurological involvement should be suspected. The clinical diagnosis is supported by virological methods and occasionally by biopsy.

An important component of management is the treatment of pain. Potent analgesia may be supplemented by carbamazepine and dosulepin. Intractable post-herpetic neuralgia may require specialized pain control. A topical or systemic antibiotic is often needed for secondary infection. Oral prednisolone is given by some. Systemic parenteral therapy with aciclovir is indicated in HIV-associated herpes zoster especially when sight, sphincteric



Fig. 35.10 Chronic verrucous herpes zoster. (Courtesy of Professor C.B. Bunker and Medical Illustration UK Ltd, Chelsea and Westminster Hospital, London, UK.)

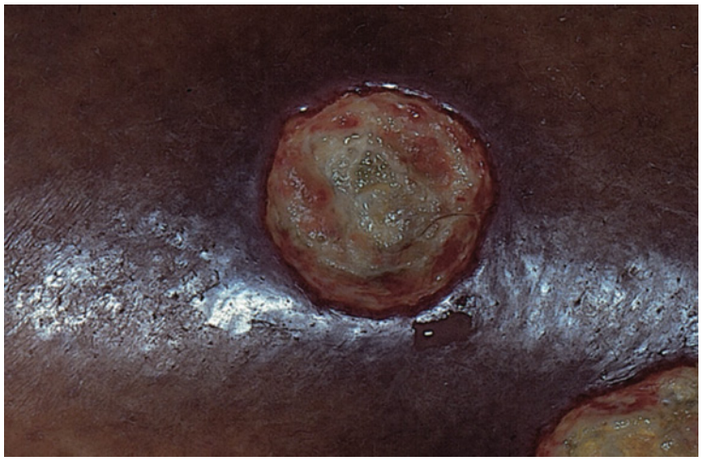


Fig. 35.11 Cytomegalovirus vasculitis: leg ulcers. (Courtesy of Professor C.B. Bunker and Medical Illustration UK Ltd, Chelsea and Westminster Hospital, London, UK.)

function and facial expression are threatened and where pulmonary or neurological involvement is suspected. Disseminated VZV infection can be severe with a poor prognosis. Intravenous high-dose aciclovir is the treatment of choice. Intercurrent intramuscular VZV immunoglobulin has been used to prevent recurrences and may be used intravenously if aciclovir fails. Emerging aciclovir resistance may become a problem but vidarabine and recombinant IFN-α are possible alternatives [18]. Vaccination may boost immunity and varicella immune globulin can prevent or modify the clinical illness [14].

Cytomegalovirus. Reactivation of CMV in HIV infection occurs with a CD4 count below 50×10^6/L. Despite the frequency of ocular (blindness), gastrointestinal (dysphagia, diarrhoea), neurological (encephalopathy) and adrenal (postural hypotension) disease, skin involvement with CMV is relatively uncommon in HIV, but when CMV affects the skin the mortality was about 85% in 6 months [19]. It is possible that cutaneous involvement goes unnoticed and hence is underdiagnosed. Purpura, papules, nodules, verrucous plaques and painful ulcers (Fig. 35.11), including of the perineum, and nodular prurigo (Fig. 35.12) have been described [20,21]. The differential diagnosis of these clinical



Fig. 35.12 Cytomegalovirus infection: nodular prurigo-like eruption on the back. (Courtesy of Professor C.B. Bunker and Medical Illustration UK Ltd, Chelsea and Westminster Hospital, London, UK.)

possibilities is broad. HSV and CMV skin involvement may be seen concurrently [11] and concomitant CMV, *M. tuberculosis*, *M. avium–intracellulare* and mucormycosis have been documented [22,23]. It has been argued that CMV does not play a significant role in most of the cutaneous lesions where it is found [24].

CMV infection should be suspected histologically if dermal capillary neoangiogenesis, fibrinoid thrombi, necrotic endothelial cells, epidermal hyperplasia, acantholysis and keratinocyte degeneration are seen. Keratinocytes and endothelial cells contain characteristic CMV inclusions. Syringosquamous metaplasia has been observed [25,26]. Immunohistochemistry, *in situ* hybridization and electron microscopy may be employed. Skin biopsy material can be cultured with human fibroblasts to demonstrate the cytopathic effect; the demonstration of CMV viraemia can be similarly achieved by the co-culturing of a patient's leukocytes [27]. Serological testing may be difficult to interpret.

Treatment and prophylaxis centres on immunoreconstitution with HAART, although a severe cutaneous ulcerative eruption has been reported after the initiation of HAART and possibly represents IRD [28]. Intravenous foscarnet, ganciclovir and cidofovir are specific treatments [29]. Mutations in the viral kinase allow the development of drug resistance.

Human papillomavirus. Human papillomavirus (HPV) infection of the skin is discussed in Chapter 33. Warts are found in about 5–30% of patients with HIV [2,30,31]. Anogenital warts (condylomata acuminata) may be a non-specific and insensitive marker for HIV infection. Around 40% of men who have sex with men (MSM)



Fig. 35.13 Human papillomavirus infection: myrmecia on the great toe. (Courtesy of Professor C.B. Bunker and Media Resources UCL, London, UK.)



Fig. 35.14 Epidermodysplasia verruciformis in human papillomavirus infection: discrete and confluent warty papules on the right cheek and neck. (Courtesy of Professor C.B. Bunker and Imperial College School of Medicine, London, UK.)

diagnosed with HIV may have genital warts at presentation [32]. HPV-6 and HPV-11 (not associated with malignant potential) have been identified as the types most frequently found [33]. Anogenital HPV infection is a risk factor for anogenital cancer particularly of the anus (and cervix) yet it is rare for condylomas to contain HPV-16, which has a well-documented association with anal carcinoma. MSM have a higher incidence of both perianal warts and *in situ* and invasive anal carcinoma. Yet genital warts are more frequent in seropositive intravenous drug users. HIV infection may alter and worsen the expression and consequences of anogenital HPV infection [34–36]; HPV-16 and other oncogenic types have been found in carcinoma *in situ*, and high-grade dysplasia has been found in genital warts from HIV-positive individuals [37,38]. The risk of progression of anal intraepithelial neoplasia associated with anal HPV infection to invasive squamous carcinoma was thought to be low [39]. However anal cancer is 50 times and penis cancer 5 times commoner in HIV (see Chapter 71). Invasive cervical cancer is possibly more common but does behave more aggressively and is an AIDS-defining diagnosis.

The clinical diagnosis of warts is straightforward when classical sites are involved with lesions of typical morphology. In patients with HIV, warts may be extensive (Fig. 35.13), numerous, exuberant and admixed with other pathologies (e.g. mollusca). HPV may be found in, and presumably contributes to the causation of, Bowen's disease, erythroplasia of Queyrat and Bowenoid papulosis (clinically like viral warts, often pigmented, with the histology of Bowen's disease/squamous carcinoma *in situ*), and invasive penile, anal and cervical cancer. A pattern resembling the rare, inherited condition, epidermodysplasia verruciformis, can occur (Fig. 35.14), presenting in some patients as a pityriasis versicolor-like eruption [40–43].

CD4 T-cell estimation and HIV testing should be considered in any patient with atypical clinical presentations of viral warts. Occasionally, a skin biopsy may be necessary, particularly if *in situ* or invasive squamous cell malignancy is suspected. Conventional treatments may fail. Topical imiquimod [44] and topical and intravenous cidofovir have been used [45–47]. HAART can lead to regression of warts, but some patients have been seen whose warts persist or return after many years remission; this seems to be related to low nadir or mean CD4 [48–52] and/or is a manifestation of IRD [9].

Mollusca. Mollusca are caused by infection with molluscipoxvirus (see Chapter 33) and frequently affect the skin of patients with HIV [53], homosexual seropositive patients more than intravenous drug users [34]. There may be several or many papular or larger nodular lesions, particularly on the face and neck. Often, in the context of HIV infection, the lesions do not manifest pathognomonic classical morphology (Fig. 35.15) and are not typically domed in shape and lack the characteristic central umbilication or delling [54]. A cheek abscess has been described [55]. The differential diagnosis includes sebaceous hyperplasia, syringoma, warts, cryptococcosis and histoplasmosis, and even basal cell carcinoma. These entities can all concur and be found in the same clinical lesion. Mollusca are diagnosed with the greatest confidence by skin biopsy because the clinical morphology in the HIV-positive patient may not be pathognomonic. The classical histological features (see Chapter 33) are usually present.

Mollusca vary widely in response to conventional treatment [2]. The introduction of HAART can elicit resolution, but an increased incidence has also been reported [48,52]. Topical imiquimod may also be effective. Topical and systemic cidofovir may be beneficial

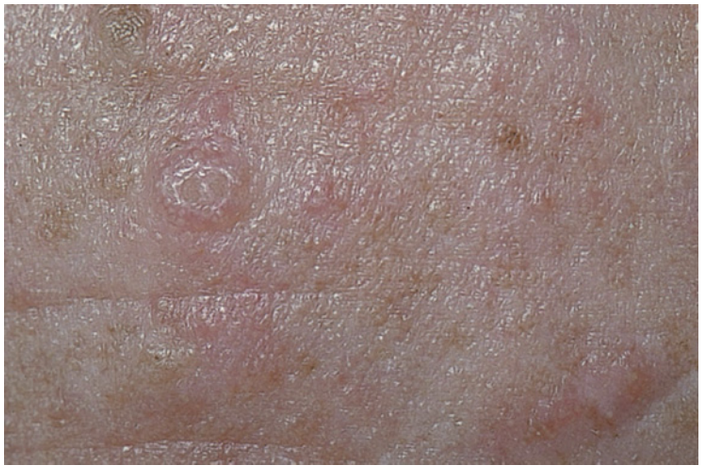


Fig. 35.15 Atypical mollusca: flesh-coloured papules and nodules on the forehead. (Courtesy of Professor C.B. Bunker and Media Resources UCL, London, UK.)

for severe recalcitrant molluscum [46,56]. Electron-beam treatment has been employed [57].

Other viral infections. Parvovirus B19 can cause cutaneous vasculitis [58] and a persistent papular–purpuric gloves and socks syndrome with anaemia [59].

References

1 Siegal FP, Lopez C, Hammer GS *et al*. Severe acquired immunodeficiency in male homosexuals manifested by chronic perianal ulcerative herpes simplex lesions. *N Engl J Med* 1981; **25**: 500–6.
2 Berger TG, Greene I. Bacterial, viral, fungal and parasitic infections in HIV disease and AIDS. *Dermatol Clin* 1991; **9**: 465–92.
3 Langtry JAA, Ostlere LS, Hawkins DA, Staughton RCD. The difficulty in diagnosis of cutaneous herpes simplex virus infection in patients with AIDS. *Clin Exp Dermatol* 1994; **19**: 224–6.
4 Baden LA, Bigby M, Kwan T. Persistent necrotic digits in a patient with the acquired immunodeficiency syndrome. Herpes simplex virus infection. *Arch Dermatol* 1991; **127**: 113–6.
5 Weinberg JM, Turiansky GW, James WD. Viral folliculitis. *AIDS Patient Care STDS* 1999; **13**: 513–6.
6 Rodriguez-Serna M, Mercader P, Pardo J *et al*. Kaposi's varicelliform eruption in an HIV-positive patient after laser resurfacing. *J Eur Acad Dermatol Venereol* 2004; **18**: 711–2.
7 Panasiti V, Devirgiliis V, Borroni RG *et al*. Atypical cutaneous manifestation of HSV-2 with *Candida albicans* co-infection in a patient with HIV-1. *J Infect* 2007; **54**: e55–7.
8 Smith KJ, Skelton HG III, Angritt P. Histopathologic features of HIV-associated skin disease. *Dermatol Clin* 1991; **9**: 551–8.
9 Lehloenya R, Meintjes G. Dermatologic manifestations of the immune reconstitution inflammatory syndrome. *Dermatol Clin* 2006; **24**: 549–70, vii.
10 Penneys MS. *Skin Manifestations of AIDS*. London: Martin Dunitz, 1990.
11 Smith KJ, Skelton HG III, James WD, Angritt P. Concurrent epidermal involvement of cytomegalovirus and herpes simplex virus in two HIV-infected patients. Military Medical Consortium for Applied Retroviral Research (MMCARR). *J Am Acad Dermatol* 1991; **25**: 500–6.
12 Schacker T. The role of HSV in the transmission and progression of HIV. *Herpes* 2001; **8**: 46–9.
13 Schacker T, Hu HL, Koelle DM *et al*. Famciclovir for the suppression of symptomatic and asymptomatic herpes simplex virus reactivation in HIV-infected persons. A double-blind, placebo-controlled trial. *Ann Intern Med* 1998; **128**: 21–8.
14 Vafai A, Berger M. Zoster in patients infected with HIV: a review. *Am J Med Sci* 2001; **321**: 372–80.
15 Colebunders R, Mann JM, Francis H *et al*. Herpes zoster in African patients: a clinical predictor of human immunodeficiency virus infection. *J Infect Dis* 1988; **157**: 314–8.
16 Jacobson MA. Editorial comment: another new immune reconstitution syndrome. *AIDS Read* 2002; **12**: 456–7.
17 Abraham S, Jones A, Toutous-Trellu L *et al*. Linear Darier disease with herpes zoster superinfection treated successfully by brivudine. *Br J Dermatol* 2006; **154**: 365–7.
18 Cohen PR, Grossman ME. Clinical features of human immunodeficiency virus-associated disseminated herpes zoster infection: a review of the literature. *Clin Exp Dermatol* 1989; **14**: 273–6.
19 Lee JY. Cytomegalovirus infection involving the skin in immunocompromised hosts. A clinicopathologic study. *Am J Clin Pathol* 1989; **92**: 96–100.
20 Chiewchanvit S, Thamprasert K, Siriunkgul S. Disseminated cutaneous cytomegalic inclusion disease resembling prurigo nodularis in a HIV-infected patient: a case report and literature review. *J Med Assoc Thai* 1993; **76**: 581–4.
21 Ramdial PK, Dlova NC, Sydney C. Cytomegalovirus neuritis in perineal ulcers. *J Cutan Pathol* 2002; **29**: 439–44.
22 Nunez M, Miralles ES, Hilara Y *et al*. Concurrent cytomegalovirus, *M. tuberculosis* and *M. avium-intracellulare* cutaneous infection in an HIV patient. *J Dermatol* 1997; **24**: 401–4.
23 Samant JS, Namgoong SH, Parveen T, Katner HP. Cytomegalovirus vasculitis and mucormycosis coinfection in late-stage HIV/AIDS. *Am J Med Sci* 2007; **333**: 122–4.
24 Daudén E, Fernández-Buezo G, Fraga J *et al*. Mucocutaneous presence of cytomegalovirus associated with human immunodeficiency virus infection. *Arch Dermatol* 2001; **137**: 443–8.
25 Chetty R, Bramdev A, Govender D. Cytomegalovirus induced syringosquamous metaplasia. *Am J Dermatopathol* 1999; **21**: 487–900.
26 Daudén E, Martin R, Feal C *et al*. Eccrine ductal mucinosis in a human immunodeficiency virus-positive patient with probable scabies. *Br J Dermatol* 2000; **143**: 1335–6.
27 Toome BK, Bowers KE, Scott GA. Diagnosis of cutaneous cytomegalovirus infection: a review and report of a case. *J Am Acad Dermatol* 1991; **24**: 857–63.
28 Qazi NA, Morlese JF, Walsh JC *et al*. Severe cutaneous ulceration secondary to cytomegalovirus inclusion disease during successful immune reconstitution with HAART. *AIDS Read* 2002; **12**: 452–7.
29 Moyle G, Gazzard BG. Opportunistic infections and tumours. Cytomegalovirus infection. In: Gazzard BG, ed. *AIDS Care Handbook*. London: Mediscript, 2002: 71–80.
30 Barbosa P. Plantar verrucae and HIV infection. *Clin Podiatr Med Surg* 1998; **15**: 317–27.
31 Anonymous. Clinicians should check women with HPV for HIV. *Aids Alert* 1999; **14**: 39–41.
32 Kreuter A, Weiland U, Brockmeyer NH. For the German Network of Competence HIV/AIDS. Genital human papillomavirus-associated (pre-) malignant skin diseases drastically increase in the era of highly active antiretroviral therapy for HIV infection. *J Am Acad Dermatol* 2006; **55**: 1116–7.
33 Silverberg MJ, Ahdieh L, Munoz A *et al*. The impact of HIV infection and immunodeficiency on human papillomavirus type 6 or 11 infection and on genital warts. *Sex Transm Dis* 2002; **29**: 427–35.
34 Reynaud-Mendel B, Janier M, Gerbaka J *et al*. Dermatologic findings in HIV-1-infected patients: a prospective study with emphasis on CD4 cell count. *Dermatology* 1996; **192**: 325–8.
35 Arany I, Evans T, Tyring SK. Tissue specific HPV expression and down-regulation of local immune responses in condylomas from HIV seropositive individuals. *Sex Transm Infect* 1998; **74**: 349–53.
36 Arany I, Tyring SK. Systemic immunosuppression by HIV infection influences HPV transcription and thus local immune responses in condyloma acuminatum. *Int J STD AIDS* 1998; **9**: 268–71.
37 Bradshaw BR, Nuovo GJ, DiCostanzo D, Cohen SR. Human papillomavirus type 16 in a homosexual man. Association with perianal carcinoma in situ and condyloma acuminatum. *Arch Dermatol* 1992; **128**: 949–52.
38 Bryan JT, Stoler MH, Tyring SK *et al*. High-grade dysplasia in genital warts from two patients infected with the human immunodeficiency virus. *J Med Virol* 1998; **54**: 69–73.
39 Morgan AR, Miles AJ, Wastell C. Anal warts and squamous carcinoma-in-situ of the anal canal. *J R Soc Med* 1994; **87**: 15.

40 Berger TG, Sawchuk WS, Leonardi C *et al*. Epidermodysplasia verruciformis-associated papillomavirus infection complicating human immunodeficiency virus disease. *Br J Dermatol* 1991; **124**: 79–83.
41 Barzegar C, Paul C, Saiag P *et al*. Epidermodysplasia verruciformis-like eruption complicating human immunodeficiency virus infection. *Br J Dermatol* 1998; **139**: 122–7.
42 Davison SC, Francis N, Maclean K, Bunker CB. Acquired epidermodysplasia verruciformis in HIV infection. *Clin Exp Dermatol* 2004; **29**: 311–2.
43 Haas N, Fuchs PG, Hermes B, Henz BM. Remission of epidermodysplasia verruciformis-like skin eruption after highly active antiretroviral therapy in a human immunodeficiency virus-positive patient. *Br J Dermatol* 2001; **145**: 669–70.
44 Juschka U, Hartmann M. Topical treatment of common warts in an HIV-positive patient with imiquimod 5% cream. *Clin Exp Dermatol* 2003; **28** (Suppl. 1): 48–50.
45 Schurmann D, Bergmann F, Temmesfeld-Wollbruck B *et al*. Topical cidofovir is effective in treating extensive penile condylomata acuminata. *AIDS* 2000; **14**: 1075–6.
46 Calista D. Topical cidofovir for severe cutaneous human papillomavirus and molluscum contagiosum infections in patients with HIV/AIDS. A pilot study. *J Eur Acad Dermatol Venereol* 2000; **14**: 484–8.
47 Kottke MD, Parker SRS. Intravenous cidofovir-induced resolution of disfiguring cutaneous human papillomavirus infection. *J Am Acad Dermatol* 2006; **55**: 533–6.
48 Costner M, Cockerell CJ. The changing spectrum of the cutaneous manifestations of HIV disease. *Arch Dermatol* 1998; **134**: 1290.
49 Spach DH, Colven R. Resolution of recalcitrant hand warts in an HIV-infected patient treated with potent antiretroviral therapy. *J Am Acad Dermatol* 1999; **40**: 818–21.
50 Rodrigues LK, Baker T, Maurer T. Cutaneous warts in HIV-positive patients undergoing highly active antiretroviral therapy. *Arch Dermatol* 2001; **137**: 1103–4.
51 Turnbull JR, Husak R, Treudler R *et al*. Regression of multiple viral warts in a human immunodeficiency virus-infected patient treated by triple antiretroviral therapy. *Br J Dermatol* 2002; **146**: 330.
52 Queiroz Zancanaro PC, McGirt LY, Mamelak AJ *et al*. Cutaneous manifestations of HIV in the era of highly active antiretroviral therapy: an institutional urban clinic experience. *J Am Acad Dermatol* 2006; **54**: 581–8.
53 Petersen CS, Gerstoft J. Molluscum contagiosum in HIV-infected patients. *Dermatology* 1992; **184**: 19–21.
54 Mastrolorenzo A, Urbano FG, Salimbeni L *et al*. Atypical molluscum contagiosum infection in an HIV-infected patient. *Int J Dermatol* 1998; **37**: 378–80.
55 Bates CM, Carey PB, Dhar J, Hart CA. Molluscum contagiosum: a novel presentation. *Int J STD AIDS* 2001; **12**: 614–5.
56 Meadows KP, Tyring SK, Pavia AT, Rallis TM. Resolution of recalcitrant molluscum contagiosum virus lesions in human immunodeficiency virus-infected-patients treated with cidofovir. *Arch Dermatol* 1997; **133**: 987–90.
57 Scolaro MJ, Gordon P. Electron-beam therapy for AIDS-related molluscum contagiosum lesions: preliminary experience. *Radiology* 1999; **210**: 479–82.
58 Martinelli C, Azzi A, Buffini G *et al*. Cutaneous vasculitis due to human parvovirus B19 in an HIV-infected patient: report of a case. *AIDS* 1997; **11**: 1891–3.
59 Ghigliotti G, Mazzarello G, Nigro A *et al*. Papular–purpuric gloves and socks syndrome in HIV-positive patients. *J Am Acad Dermatol* 2000; **43**: 916–7.

Fungal infections

Candidosis. Oral candidosis has classically been associated with immunosuppressive states and was one of the first features to be recognized in the early days of the HIV epidemic before the syndrome was clearly defined and the causative agent identified [1]. Oesophageal candidosis is an AIDS-defining diagnosis. It is commoner in homosexual seropositive patients than intravenous drug users [2]. Treatment is with ketoconazole or fluconazole. Resistance can occur. Long-term prophylaxis with azoles is avoided. Oral candidosis predicts AIDS in a median of 2 years and so is an indication for institution of prophylaxis for *Pneumocystis jiroveci* and HAART. Practically all people with HIV infection will have *Candida* as a pathogen at some stage in their disease [3]. Vaginal candidosis can occur early in HIV infection [4]. *Candida* is also responsible for paronychia, onychodystrophy, angular cheilitis and intertriginous candidosis [5,6]. A generalized cutaneous eruption of papules and nodules has been described [7]. *Candida krusei* fungaemia occurs in HIV/AIDS patients previously exposed to azole antifungals and skin lesions may be common [8].

Dermatophytosis. Generally, dermatophytes are only occasionally responsible for cutaneous infection in immunocompromised patients [9], but the situation is subtly different in HIV infection [10]. Homosexual men are very likely to have a superficial fungal infection regardless of their HIV status. For example, in Sweden, Torssander *et al*. [11] showed that 37% of seropositive homosexual men had mycologically proven toe cleft dermatophytosis, usually *Trichophyton rubrum*, compared with about 30% of seronegative homosexual men and about 9% of heterosexual men. Clinical findings, for example interdigital scaling, similar to those of tinea pedis are very common in men. Dermatophytes can be isolated from normal toe clefts in about 7% of homosexual men (regardless of HIV status) but not from clinically normal toe clefts in heterosexual men. Tinea incognito secondary to chronic potent topical steroid misuse for another dermatosis may develop. Widespread dermatophytosis is not common in HIV/AIDS; Torssander *et al*. found dermatophytes only in the groins, toe clefts and toenails. However, atypical tinea corporis (Fig. 35.16), folliculitis and extensive and deep, invasive dermatophytosis, including Majocci's granuloma, can occur [10,12–15].



Fig. 35.16 Tinea corporis and faciei. (Courtesy of Professor C.B. Bunker and Medical Illustration UK Ltd, Chelsea and Westminster Hospital, London, UK.)



Fig. 35.17 Cryptococcosis: necrotizing papules and nodules on the right ear and neck. (Courtesy of Professor C.B. Bunker and Medical Illustration UK Ltd, Chelsea and Westminster Hospital, London, UK.)

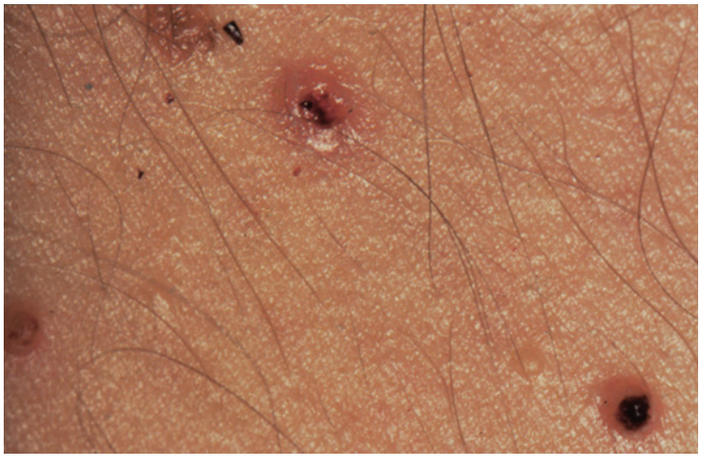


Fig. 35.18 Cryptococcosis: necrotizing papules. (Courtesy of Professor C.B. Bunker and Medical Illustration UK Ltd, Chelsea and Westminster Hospital, London, UK.)

Onychomycosis is frequently seen in HIV and AIDS. *Trichophyton rubrum* is the commonest pathogen [16]. Psoriasis and the yellow nail syndrome should be considered in the differential diagnosis of nail discoloration and dystrophy. Mycological confirmation should be obtained. Improvement of onychomycosis with HAART in the absence of specific antifungal treatment has been observed [17].

Esoteric superficial fungal infections have also been reported. A patient presented with 'dirty' brown spots on the scrotum from which were co-cultured the dematiaceous fungi *Bipolaris* and *Curvularia* [18]. A new species, *Trichophyton eboreum*, has been isolated from an HIV patient with tinea pedis [19].

Dermatophyte infection is treated with conventional topical and systemic therapy (see Chapter 36) depending on clinical assessment and the results of mycology. Oral terbinafine is safe and efficacious [20].

Cryptococcosis. *Cryptococcus neoformans* infection affects 5–10% of patients with AIDS in the UK and USA and 30–40% in Africa. Brain, lung and skin are sites of predilection. Up to 20% of patients with disseminated disease may have skin involvement. In HIV/AIDS cryptococcal skin involvement should be suspected when papulonodular necrotizing skin lesions with central umbilication, like molluscum contagiosum (Figs 35.17 & 35.18), are encountered in the context of neurological or pulmonary disease. Herpetiform lesions, violaceous lichenoid lesions, an acneiform papulopustular and nodular eruption on the chin, rhinophyma, a warty tumour on the foot, a pseudofolliculitis and *Cryptococcus* admixed with, and mimicking, KS have also been described [21–23].

Systemic diagnosis is by serology, blood culture, urine culture and lumbar puncture (including serology, culture and India-ink staining). Cutaneous diagnosis is by skin biopsy with special stains for the cryptococcal capsule (e.g. mucicarmine) and culture, or Tzanck preparation [24].

Treatment aims to eradicate the disease in the immunocompetent patient and to control symptoms in the patient with advanced HIV disease. Intravenous liposomal amphotericin and oral fluconazole are the mainstays of treatment. Primary and secondary prophylaxis is with oral fluconazole. Cryptococcal meningitis has a poor prognosis even with treatment.

Histoplasmosis. Extrapulmonary infection with histoplasmosis is an indicator condition in the case definition of AIDS (Table 35.3). Histoplasmosis is very rare in the UK and Europe so a travel history is important, but some autochthonous HIV-associated cases have occurred in Europe. In endemic areas, such as North, Central and Latin America, Africa, India or the Far East, 20–50% of patients with AIDS will develop histoplasmosis at CD4 counts below 200×10^6/L. The systemic presentation can mimic tuberculosis. There is fever, lymphadenopathy, hepatosplenomegaly, lung disease and pancytopenia. Patients may also be alcoholics and heavy smokers. It may be fatal (compared with the self-limiting bronchopneumonia seen in immunocompetent individuals). Disseminated histoplasmosis may produce skin involvement in up to 10% of patients in the USA but in between 38 and 85% of Latin American cases. The skin may be the most frequent site of localized infection (8.3%). A wide morphological spectrum of lesions is seen. Papules, crusted papules and oral involvement with erosions and ulcers are commonest, with more variation in lesions associated with higher CD4 counts. An exanthem, lesions resembling molluscum contagiosum, acneiform folliculitis, psoriasiform eruptions including keratotic plaques, vasculitic lesions, erythema multiforme-like lesions, an exfoliative dermatitis, depressed pits on the palms and soles and lesions admixed with KS, have been described [10,25–32].

Systemic diagnosis is by chest X-ray, Wright's staining of a blood film (demonstrating intracellular fungi), blood cultures, and lymph node, liver or skin biopsy or Tzank cytology [24,33] and culture. *Histoplasma capsulatum* can be demonstrated by Gomori methenamine silver stain of a skin biopsy section.

Treatment is by HAART and itraconazole and/or amphotericin with long-term itraconazole secondary prophylaxis because relapse is so common [10,30,34].

Other fungal infections. Coccidioidomycosis is endemic in southwest USA; extrapulmonary disease is an AIDS-defining diagnosis but skin lesions seem rare [10]. Penicilliosis is an AIDS-defining diagnosis and causes fever, lymphadenopathy, hepatosplenomegaly skin lesions and anaemia [35–39]. Numerous ulcers have been attributed to cutaneous sporotrichosis [3,40]. Paracoccidioidomycosis (50%) [41,42], blastomycosis [43], nocardiasis [44–47], primary cutaneous aspergillosis [48,49], mucormycosis [50,51], *Paecilomyces lilacinus* infection [52] and cutaneous protothecosis [53,54] have all been reported in HIV/AIDS.

References

1 Gottlieb MS, Schroff R, Schanker HM *et al. Pneumocystis carinii* pneumonia and mucosal candidosis in previously healthy homosexual men. *N Eng J Med* 1981; **305**: 1425–30.

2 Reynaud-Mendel B, Janier M, Gerbaka J *et al*. Dermatologic findings in HIV-1-infected patients: a prospective study with emphasis on CD4 cell count. *Dermatology* 1996; **192**: 325–8.

3 Berger TG, Greene I. Bacterial, viral, fungal and parasitic infections in HIV disease and AIDS. *Dermatol Clin* 1991; **9**: 465–92.

4 Josephine M, Issac E, George A *et al*. Patterns of skin manifestations and their relationship with CD4 counts among HIV/AIDS patients in Cameroon. *Int J Dermatol* 2006; **45**: 280–4.

5 Kaplan MH, Sadick N, McNutt NS *et al.* Dermatologic findings and manifestations of acquired immunodeficiency syndrome (AIDS). *J Am Acad Dermatol* 1987; **16**: 485–506.

6 Tosti A, Piraccini BM, Lorenzi S, D'Antuono A. *Candida* onchomycosis in an HIV infection. *Eur J Dermatol* 1998; **8**: 173–4.

7 Kreuter A, Teichmann M, Stuecker M *et al*. Generalised fungal infection in a patient with AIDS appearing as skin papules. *Eur J Med Res* 2003; **8**: 435–7.

8 Muñoz P, Sánchez-Somolinos M, Alcalá L *et al*. Candida krusei fungaemia: antifungals susceptibility and clinical presentation of an uncommon entity during 15 years in a single general hospital. *J Antimicrob Chemother* 2005; **55**: 188–93.

9 Koranda FC, Dehmel EM, Kahn G, Penn I. Cutaneous complications in immunosuppressed renal homograft recipients. *JAMA* 1974; **229**: 419–24.

10 Johnson RA. HIV disease: mucocutaneous fungal infections in HIV disease. *Clin Dermatol* 2000; **18**: 411–22.

11 Torssander J, Karlsson A, Morfeldt-Manson L *et al.* Dermatophytosis and HIV infection: a study in homosexual men. *Acta Derm Venereol (Stockh)* 1988; **68**: 53–6.

12 Munoz-Perez MA, Rodriguez-Pichardo A, Camacho F, Rios JJ. Extensive and deep dermatophytosis caused by *Trichophyton mentagrophytes* var. *interdigitalis* in an HIV-1 positive patient. *J Eur Acad Dermatol Venereol* 2000; **14**: 61–3.

13 Kwon KS, Jang HS, Son HS *et al*. Widespread and invasive Trichophyton rubrum infection mimicking Kaposi's sarcoma in a patient with AIDS. *J Dermatol* 2004; **31**: 839–43.

14 Luque AG, Biasoli MS, Sortino MA *et al*. Atypical tinea corporis caused by microsporum gypseum in a subject with acquired immune deficiency syndrome. *J Eur Acad Dermatol Venereol* 2001; **15**: 374–5.

15 Galhardo MC, Wanke B, Reis RS *et al*. Disseminated dermatophytosis caused by Microsporum gypseum in an AIDS patient: response to terbinafine and amorolfine. *Mycoses* 2004; **47**: 238–41.

16 Dompmartin D, Dompmartin A, Deluol AM *et al*. Onychomycosis and AIDS: clinical and laboratory findings in 62 patients. *Int J Dermatol* 1990; **29**: 337–9.

17 Tachikawa N, Yasuoka A, Oka S. Improvement of onychomycosis without antifungal therapy after initiation of highly active anti-retroviral therapy (HAART) in an HIV-infected patient. *Jpn J Infect Dis* 1999; **52**: 245–6.

18 Duvic M, Lowe L. Superficial phaeohypomycosis of the scrotum in a patient with the acquired immunodeficiency syndrome. *Arch Dermatol* 1987; **123**: 1597–9.

19 Brasch J, Gräser Y. Trichophyton eboreum sp. nov. isolated from human skin. *J Clin Microbiol* 2005; **43**: 5230–7.

20 Rich P, Houpt KR, LaMarca A *et al*. Safety and efficacy of short-duration oral terbinafine for the treatment of tinea corporis or tinea cruris in subjects with HIV infection or diabetes. *Cutis* 2001; **68**: 15–22.

21 Ricchi E, Manfredi R, Scarani P *et al*. Cutaneous cryptococcosis and AIDS. *J Am Acad Dermatol* 1991; **25**: 335–6.

22 Blauvelt A, Kerdel FA. Cutaneous cryptococcosis mimicking Kaposi's sarcoma as the initial manifestation of disseminated disease. *Int J Dermatol* 1992; **31**: 279–80.

23 Coker LR, Swain R, Morris R, McCall CO. Disseminated cryptococcosis presenting as pseudofolliculitis in an AIDS patient. *Cutis* 2000; **66**: 207–10.

24 Jimenez-Acosta FJ, Vicandim B, Viguer JM *et al*. Diagnostic value of cutaneous cytology in opportunistic fungal infections of patients with acquired immunodeficiency syndrome. *J Am Acad Dermatol* 1988; **18**: 383–4.

25 Penneys NS. *Skin Manifestations of AIDS*. London: Martin Dunitz, 1990.

26 Lindgren AM, Fallon JD, Horan RF. Psoriasiform papules in the acquired immunodeficiency syndrome. Disseminated histoplasmosis in AIDS. *Arch Dermatol* 1991; **127**: 722–3.

27 Cole MC, Cohen PR, Satra KH, Grossman ME. The concurrent presence of systemic disease pathogens and cutaneous Kaposi's sarcoma in the same lesion. *Histoplasma capsulatum* and Kaposi's sarcoma coexisting in a single skin lesion in a patient with AIDS. *J Am Acad Dermatol* 1992; **26**: 285–7.

28 Casariego Z, Kelly GR, Perez H *et al*. Disseminated histoplasmosis with orofacial involvement in HIV-1-infected patients with AIDS: manifestation and treatment. *Oral Dis* 1997; **3**: 184–7.

29 Ramdial P, Mosam A, Dlova NC *et al*. Disseminated cutaneous histoplasmosis in patients infected with human immunodeficiency virus. *J Cutan Pathol* 2002; **29**: 215–25.

30 Antinori S, Magni C, Nebuloni M *et al*. Histoplasmosis among human immunodeficiency virus-infected people in Europe: report of 4 cases and review of the literature. *Medicine (Baltimore)* 2006; **85**: 22–36.

31 Casotti JA, Motta TQ, Ferreira CU Jr, Cerutti C Jr. Disseminated histoplasmosis in HIV positive patients in Espirito Santo state, Brazil: a clinical-laboratory study of 12 cases (1999–2001). *Braz J Infect Dis* 2006; **10**: 327–30.

32 Cunha VS, Zampese MS, Aquino VR *et al*. Mucocutaneous manifestations of disseminated histoplasmosis in patients with acquired immunodeficiency syndrome: particular aspects in a Latin-American population. *Clin Exp Dermatol* 2007; **32**: 25.

33 Lesher JL, Knight FJ. Tzanck preparation as a diagnostic aid in disseminated histoplasmosis. *J Am Acad Dermatol* 1986; **15**: 534–5.

34 Tobón AM, Agudela CA, Rosero DS *et al*. Disseminated histoplasmosis: a comparative study between patients with acquired immunodeficiency syndrome and non-human immunodeficiency virus-infected individuals. *Am J Trop Med Hyg* 2005; **73**: 576–82.

35 Chiewchanvit S, Mahanupab P, Hirunsri P, Vanittanakow N. Cutaneous manifestations of disseminated *Penicillium marneffei* mycosis in five HIV-infected patients. *Mycoses* 1991; **34**: 245–9.

36 Kullavanijaya P. Penicilliosis in AIDS. *J Dermatol* 2001; **28**: 667–70.

37 Huynh TX, Nguyen HC, Dinh Nguyen HM *et al*. Penicillium marneffei infection and AIDS. A review of 12 cases reported in the Tropical Diseases Centre, Ho Chi Minh City (Vietnam). *Sante* 2003; **13**: 149–53.

38 Maniar JK, Chitale AR, Miskeen A *et al*. Penicillium marneffei infection: an AIDS-defining illness. *Indian J Dermatol Venereol Leprol* 2005; **71**: 202–4.

39 Lupi O, Tyring SK, McGinnis MR. Tropical dermatology: fungal tropical diseases. *J Am Acad Dermatol* 2005; **53**: 931–51.

40 Carvalho MT, de Castro AP, Baby C *et al*. Disseminated cutaneous sporotrichosis in a patient with AIDS: report of a case. *Rev Soc Bras Med Trop* 2002; **35**: 655–9.

41 Bakos L, Kronfeld M, Hampe S *et al*. Disseminated paracoccidioidomycosis with skin lesions in a patient with acquired immunodeficiency syndrome. *J Am Acad Dermatol* 1989; **20**: 854–5.

42 Paniago AM, de Freitas AC, Aguiar ES *et al*. Paracoccidioidomycosis in patients with human immunodeficiency virus: review of 12 cases observed in an endemic region in Brazil. *J Infect* 2005; **51**: 248–52.
43 Battle SE, Skillman DR, Maguire JH, Bennett KS. Acquired immunodeficiency syndrome-related blastomycosis in an unusual geographic location. *Milit Med* 2001; **166**: 1026–8.
44 Boixeda P, Espana A, Suarez J *et al*. Cutaneous nocardiosis and human immunodeficiency virus infection. *Int J Dermatol* 1991; **11**: 804–5.
45 Lee CC, Loo LW, Lam MS. Case reports of nocardiosis in patients with human immunodeficiency virus (HIV) infection. *Ann Acad Med Singapore* 2000; **29**: 119–26.
46 Pintado V, Gómez-Mampaso E, Cobo J *et al*. Nocardial infections in patients infected with the human immunodeficiency virus. *Clin Microbiol Infect* 2003; **9**: 716–20.
47 Diego C, Ambrosioni JC, Abel G *et al*. Disseminated nocardiosis caused by *Nocardia abscessus* in an HIV-infected patient: first reported case. *AIDS* 2005; **19**: 1330–1.
48 Hunt SJ, Nagi C, Gross KG *et al*. Primary cutaneous aspergillosis near central venous catheters in patients with the acquired immunodeficiency syndrome. *Arch Dermatol* 1992; **128**: 1229–32.
49 Arikan S, Uzun O, Cetinkaya Y *et al*. Primary cutaneous aspergillosis in human immunodeficiency virus-infected patients: two cases and review. *Clin Infect Dis* 1998; **27**: 641–3.
50 Pérez-Uribe A, Molina de Soschin D, Arenas R, Reyes M. Primary cutaneous mucormycosis. Report of a case in a HIV patient. *Rev Iberoam Micol* 2005; **22**: 118–21.
51 Samant JS, Namgoong SH, Parveen T, Katner HP. Cytomegalovirus vasculitis and mucormycosis coinfection in late-stage HIV/AIDS. *Am J Med Sci* 2007; **333**: 122–4.
52 Martin CA, Roberts S, Greenberg RN. Voriconazole treatment of disseminated paecilomyces infection in a patient with acquired immunodeficiency syndrome. *Clin Infect Dis* 2002; **35**: e78–81.
53 Piyophirapong S, Linpiyawan R, Mahaisavariya P *et al*. Cutaneous protothecosis in an AIDS patient. *Br J Dermatol* 2002; **146**: 713–5.
54 Pascual JS, Balos LL, Baer AN. Disseminated *Prototheca wickerhamii* infection with arthritis and tenosynovitis. *J Rheumatol* 2004; **31**: 1861–5.

Protozoal infections

Pneumocystis carinii (now *jiroveci*) pneumonia is common in HIV infection but disseminated disease and cutaneous involvement are rare [1,2]. Two patients have been described with mass lesions in the external auditory canal. Spread from middle ear infection (itself due to retrograde spread from the pharynx via the Eustachian tube) was the probable mechanism. Lesions masquerading as KS have been described [3].

Cryptosporidiosis and microsporidiosis can cause skin lesions [4,5]. Disseminated amoebiasis may rarely cause skin manifestations but the dermatological involvement may lead to diagnosis of the systemic illness. A solitary papule of the thigh, a soleus muscle abscess, disseminated skin lesions, and cutaneous ulceration have been described [6–9]. Anogenital ulceration due to amoebiasis should lead to the suspicion of underlying HIV infection [10,11].

Endemic protozoal diseases such as leishmaniasis may behave differently in the HIV-infected patient and also mimic or complicate KS and dermatofibroma; cutaneous nodules and ulcers, digital necrosis, linear brown macules of the digits and palms, ulceration of the tongue, a tattoo reaction and cutaneous hyperpigmentation and atypical disseminated leishmaniasis resembling post kala-azar dermal leishmaniasis have been described [12–25]. Patients have a higher rate of recurrence or reinfection and their disease is more difficult to treat compared with HIV-negative individuals [21]. However, cutaneous detection of *Leishmania* is frequent in individuals with visceral leishmaniasis and sometimes *Leishmania* is associated with skin changes attributable to other pathogenic processes so its presence does not imply a causative role [23]. IRIS/IRD-associated leishmaniasis is recognized (see Table 35.26).

Reactivation of American trypanosomiasis (Chagas' disease) in AIDs may manifest with skin lesions [26].

References

1 Hennessey NP, Parro EL, Cockerell CJ. Cutaneous *Pneumocystis carinii* infection in patients with acquired immunodeficiency syndrome. *Arch Dermatol* 1991; **127**: 1699–701.
2 Berger TG, Greene I. Bacterial, viral, fungal and parasitic infections in HIV disease and AIDS. *Dermatol Clin* 1991; **9**: 465–92.
3 Litwin MA, Williams CM. Cutaneous *Pneumocystis carinii* infection mimicking Kaposi sarcoma. *Ann Intern Med* 1992; **117**: 45–9.
4 Eeftinck Schattenkerk JK, van Gool T, van Ketel RJ, Bartelsman JF. Microsporidiosis in HIV-1 infected individuals. *Lancet* 1991; **338**: 323.
5 Kester KE, Turiansky GW, McEvoy PL. Nodular cutaneous microsporidiosis in a patient with AIDS and successful treatment with long-term oral clindamycin. *Ann Intern Med* 1998; **128**: 911–4.
6 Smith KJ, Skelton HG III, Angritt P. Histopathologic features of HIV-associated skin disease. *Dermatol Clin* 1991; **9**: 551–8.
7 May LP, Sidhu GS, Buchness MR. Diagnosis of *Acanthamoeba* infection by cutaneous manifestations in a man seropositive to HIV. *J Am Acad Dermatol* 1992; **26**: 352–5.
8 Mauro S, Torno Jr, Babapour R *et al*. Cutaneous acanthamoebiasis in AIDS. *J Am Acad Dermatol* 2000; **42**: 351–4.
9 Paltiel M, Powewll E, Lynch J *et al*. Disseminated cutaneous acanthemebiasis: a case report and review of the literature. *Cutis* 2004; **73**: 241–8.
10 Gbery IP, Dheja D, Kacou DE *et al*. Chronic genital ulcerations and HIV infection: 29 cases. *Med Trop* 1999; **59**: 279–82.
11 Bumb RA, Mehta RD. Amoebiasis cutis in HIV positive patient. *Indian J Dermatol Venereol Leprol* 2006; **72**: 224–6.
12 Pialoux G, Hannequin C, Dupon B, Ravisse P. Cutaneous leishmaniasis in an AIDS patient: cure with itraconazole. *J Infect Dis* 1990; **162**: 1221–2.
13 Alvar J, Canacate C, Gutierrez-Solar B *et al*. Leishmania and human immunodeficiency virus coinfection: the first 10 years. *Clin Microbiol Rev* 1997; **10**: 298–319.
14 Sabbatani S, Isuierdo Calzado A, Ferro A *et al*. Atypical leishmaniasis in an HIV-2-seropositive patient from Guinea-Bissau. *AIDS* 1991; **5**: 899–901.
15 Romeu J, Milla F, Batlle M *et al*. Visceral leishmaniasis involving lung and a cutaneous Kaposi's sarcoma lesion. *AIDS* 1991; **5**: 1272.
16 Rios-Buceta L, Buezo GF, Peñas PF *et al*. Post-kala-azar dermal leishmaniasis in an HIV-patient. *Int J Dermatol* 1996; **35**: 303–4.
17 Gonzalez-Beato MJ, Moyano B, Sanchez C *et al*. Kaposi's sarcoma-like lesions and other nodules as cutaneous involvement in AIDS-related visceral leishmaniasis. *Br J Dermatol* 2000; **143**: 1316–8.
18 Castellano VM, Rodriguez-Peralto JL, Alonso S *et al*. Dermatofibroma parasitized by *Leishmania* in HIV infection: a new morphologic expression of dermal Kala Azar in an immunodepressed patient. *J Cutan Pathol* 1999; **26**: 516–9.
19 Colebunders R, Depraetere K, Verstraeten T *et al*. Unusual cutaneous lesions in two patients with visceral leishmaniasis and HIV infection. *J Am Acad Dermatol* 1999; **41**: 847–50.
20 Puig L, Pradinaud R. Leishmania and HIV co-infection: dermatological manifestations. *Ann Trop Med Parasitol* 2003; **97** (Suppl. 1): 107–14.
21 Couppié P, Clyti E, Sobesky M *et al*. Comparative study of cutaneous leishmaniasis in human immunodeficiency virus (HIV)-infected patients and non-HIV-infected patients in French Guiana. *Br J Dermatol* 2004; **151**: 1165–71.
22 Boumis E, Chinello P, Della Rocca C *et al*. Atypical disseminated leishmaniasis in an HIV-infected patient. *Int J STD AIDS* 2006; **17**: 351–3.
23 Bosch RJ, Rodrigo AB, Sánchez P *et al*. Presence of Leishmania organisms in specific and non-specific skin lesions in HIV-infected individuals with visceral leishmaniasis. *Int J Dermatol* 2002; **41**: 670–5.
24 Pérez C, Solías Y, Rodríguez G. Diffuse cutaneous leishmaniasis in a patient with AIDS. [Article in Spanish.] *Biomedica* 2006; **26**: 485–97.



Fig. 35.19 Norwegian scabies: interdigital scale.

25 Catorze G, Alberto J, Afonso A *et al*. Leishmania infantum/HIV co-infection: cutaneous lesions following treatment of visceral leishmaniasis. [Article in French.] *Ann Dermatol Venereol* 2006; **133**: 39–42.
26 Sartori AM, Sotto MN, Braz LM *et al*. Reactivation of Chagas disease manifested by skin lesions in a patient with AIDS. *Trans R Soc Trop Med Hyg* 1999; **93**: 631–2.

Scabies

Scabies (see Chapter 38) occurs frequently in HIV-infected patients [1,2] and may have unusual clinical features (Fig. 35.19) for example the skin of the head and neck is often involved, which is highly unusual in non-HIV-infected adults. It is important to have a high index of suspicion. Scabies has been endemic in the HIV population in London and there are occasional epidemic outbreaks on HIV wards, in hospices and in the community. Transmission is by sexual intercourse, nursing, comforting and massage. Norwegian/crusted scabies [3] is highly contagious and its diagnosis should arouse suspicion of underlying HIV infection [4]. Crusted scabies in HIV infection may be localized to the soles [5] or the genitals [6]. Eccrine ductal and follicular mucinosis have been found on histology [7]. Treatment follows conventional lines but eradication may be difficult. Topical sulphur and oral ivermectin can be useful [8,9].

References

1 Orkin M. Scabies in AIDS. *Semin Dermatol* 1993; **12**: 9–14.
2 Funkhouser ME, Omohundro C, Ross A, Berger TG. Management of scabies in patients with human immunodeficiency syndrome. *Arch Dermatol* 1993; **129**: 911–3.
3 Farrell A, Ross JS, Barton SE, Bunker CB. Multiple pilomatricomas and myotonic dystrophy in a patient with AIDS. *Clin Exp Dermatol* 1995; **20**: 423–4.
4 Brites C, Wey M, Pedroso C, Badaró R. Severe and Norwegian scabies are strongly associated with retroviral (HIV-1/HTLV-1) infection in Bahia, Brazil. *AIDS* 2002; **16**: 1292–3.
5 Bitman LM, Rabinowitz AD. Hyperkeratotic plantar plaques in an HIV-positive patient. Crusted scabies, localized to the soles. *Arch Dermatol* 1998; **134**: 1019, 1022–3.
6 Perna AG, Bell K, Rosen T. Localised genital Norwegian scabies in an AIDS patient. *Sex Transm Infect* 2004; **80**: 72–3.
7 Daudén E, Porras JI, Buezo GF, García-Díez A. Eccrine squamous syringometaplasia and cytomegalovirus. *Am J Dermatopathol* 2000; **22**: 559–61.
8 Taplin D, Meinking TL. Treatment of HIV-related scabies with emphasis on the efficacy of ivermectin. *Semin Cutan Med Surg* 1997; **16**: 235–40.
9 Alberici F, Pagani L, Ratti G, Viale P. Ivermectin alone or in combination with benzyl benzoate in the treatment of human immunodeficiency virus-associated scabies. *Br J Dermatol* 2000; **142**: 969–72.

Miscellaneous

Demodex (see Chapter 38) can cause dermatological morbidity in HIV-infected patients. A pruritic, papulonodular folliculitic eruption of the face and neck and torso is recognized responsive to acaricides, including ivermectin [1,2]. Also described have been a rosaceal eruption [3] and an ivory white, poorly defined, indurated plaque on the temple [4].

Cutaneous larva migrans has presented with fever in an HIV-infected individual after commencement of treatment with zidovudine (AZT, ZDV) and didanosine (ddI, DDI) [5].

HIV-positive patients with oncocerciasis have higher onchocercal skin scores than those who are not HIV infected [6].

Malakoplakia is an uncommon granulomatous reaction to infection (bacteria, mycobacteria and fungi) usually of the genital tract and cases in HIV have been reported [7,8].

References

1 Dominey A, Rosen T, Fschen J. Papulonodular demodicidosis associated with the acquired immunodeficiency syndrome. *J Am Acad Dermatol* 1989; **20**: 197–201.
2 Clyti E, Macher M, Sainte-Marie D *et al*. Ivermectin treatment of three cases of demodecidosis during human immunodeficiency virus infection. *Int J Dermatol* 2006; **45**: 1066–8.
3 Jansen T, Kastner U, Kreuter A, Altmeyer P. Rosacea-like demodicidosis associated with acquired immunodeficiency syndrome. *Br J Dermatol* 2001; **144**: 139–42.
4 Sarro R, Hong J, Elgart M. An unusual demodicidosis manifestation in a patient with AIDS. *J Am Acad Dermatol* 1998; **38**: 120–1.
5 Edwards SK, Carne CA. Larva migrans as a cause of fever in an HIV-positive man. *Int J STD AIDS* 1998; **9**: 54–5.
6 Kipp W, Bamuhiiga J, Rubaale T. Simulium neavei-transmitted onchocerciasis: HIV infection increases severity of onchocercal skin disease in a small sample of patients. *Trans R Soc Trop Med Hyg* 2003; **97**: 310–1.
7 Barnard M, Chalvardjian A. Cutaneous malakoplakia in a patient with acquired immunodeficiency syndrome (AIDS). *Am J Dermatopathol* 1998; **20**: 185–8.
8 Savant SR, Amladi ST, Kangle SD *et al*. Cutaneous malakoplakia in an HIV-positive patient. *Int J STD AIDS* 2007; **18**: 435–6.

Neoplasms

Kaposi's sarcoma (see Chapter 56)

Classical sporadic KS, African endemic KS, Greek (Peloponnesian) endemic KS, iatrogenic immunosuppression-associated KS and AIDS-related KS are recognized [1,2]. KS has been encountered in HIV-negative homosexual men [3]. The prevalence of KS in patients infected with HIV has declined throughout the epidemic. KS is caused by infection with human herpes virus (HHV)-8 (KSHV). It is probably transmitted sexually, more by the faecooral route or the ejaculate than by blood, in HIV-positive homosexual men [4–8]. However, KS is also seen in non-homosexuals and in children arising from other routes of transmission, for example saliva [9,10]. The pathogenesis of KS is thought to involve angiogenic and proinflammatory effects on endothelial cells that proliferate to form characteristic spindle-cell tumours [11]. KS appearing at the sites of application of topical tacrolimus pre-



Fig. 35.20 Purple nodules on the palate in a patient with Kaposi's sarcoma. (Courtesy of Professor C.B. Bunker and Media Resources UCL, London, UK.)



Fig. 35.21 Kaposi's sarcoma: multiple purple nodules and plaques on the back. (Courtesy of Professor C.B. Bunker and Medical Illustration UK Ltd, Chelsea and Westminster Hospital, London, UK.)

scribed for seborrhoeic dermatitis in a patient undergoing treatment with HAART has been reported [12].

HIV/AIDS-related KS may be a disseminated disease with gastrointestinal and pulmonary involvement. Cutaneous KS is multicentric and often involves the face, oral mucosa, palate (Fig. 35.20) and genitalia. Lesions may be multiple, follow skin creases and may be grouped or linear and koebnerize (Fig. 35.21). Lymphoedema may eventuate [13,14]. The classical lesion in HIV is a purple patch, plaque or nodule, which may ulcerate; phimosis may occur [15]. There may be diagnostic difficulty with morphologically banal lesions in at-risk or worried individuals and the importance of having a high index of suspicion and skin biopsy must be stressed. The common differential diagnosis (Table 35.18) [16] includes naevi, histiocytoma and lymphangioma [17], although cryptococcosis [18,19], histoplasmosis [20], leishmaniasis [21,22], lesions due to *Pneumocystis* [23], and dermatophytosis [24] may also mimic and/or complicate KS. Candida has been found within KS lesions [25]. Pyogenic granuloma and bacillary angiomatosis masquerading as KS are important to consider and confirm or exclude.

Table 35.18 Differential diagnosis of Kaposi's sarcoma. (From [16].)

Naevus
Histiocytoma
Cryptococcosis
Histoplasmosis
Leishmaniasis
Pneumocystis
Dermatophytosis
Angioma
Bacillary angiomatosis
Pyogenic granuloma
Melanoma

Table 35.19 Modified AIDS Clinical Trials Group (1997) staging of Kaposi's sarcoma. (From [27].)

TIS staging of KS	Good risk (all of the following)	Poor risk (any of the following)
(T) Tumour	Confined to skin, lymph nodes or minimal oral disease	Tumour-associated oedema or ulceration Extensive oral KS Gastrointestinal KS KS in other non-nodal viscera
(I) Immune status	CD4 count >150/mm^3	CD4 <150/mm^3
(S) Systemic illness	Karnovsky performance status >70	Karnovsky performance status <70 or other HIV-related illness

The differential diagnosis of oral lesions is discussed on p. 35.42 and includes the other causes of mouth ulcers and tumours, candidosis, lichen planus, drug eruption and angina bullosa haemorrhagica. The differential diagnosis of genital lesions includes psoriasis, lichen planus, lichen sclerosus, fixed drug eruption, Zoon's balanitis and erythroplasia of Queyrat.

Diagnosis is either clinical or clinicopathological. The histological features of KS are well described [26] and consist of dilated, irregularly shaped, vascular structures that are typically slit-like in a fully developed nodular lesion. The differential diagnosis may be clarified by immunohistochemical techniques that identify endothelial cells (immunostaining for factor VIII-related antigen and *Ulex europaeus* lectin), which have been thought to be the cell of origin of KS. Staging of KS takes into account tumour bulk, systemic illness and immunosuppression. Clinicopathologically, disease is referred to as patch, plaque, nodular or visceral/disseminated stage (Table 35.19) [27].

Systemic and local treatments that have been employed in KS are summarized in Table 35.20. HAART itself can be very effective [28,29]. Indeed, institution of HAART may prevent KS [30]. However, recently, men with unremitting cutaneous KS have been reported despite HAART, raising the question of immunosenescence [31,32]. Radiotherapy can cause significant sequelae, for example radiodermatitis, in survivors.

References

1 Fine RM. AIDS-related Kaposi's sarcoma. *Int J Dermatol* 1992; **31**: 471.
2 Dal Maso L, Serraino D, Franceschi S. Epidemiology of HIV-associated malignancies. *Cancer Treatment Res* 2001; **104**: 1–18.

Table 35.20 Treatments for Kaposi's sarcoma. (From [16,27,30].)

Local treatment
Cryotherapy
Radiotherapy
Topical retinoids: alitretinoin [33]
Topical antivirals: cidofovir, docosanol [34]
Intralesional, e.g. IFN-α, TNF-α, vinca alkaloids
Surgery, e.g. curettage, cautery, infrared coagulation [35]
Laser
Photodynamic therapy [36]
Cosmetic camouflage

Systemic treatment
Highly active antiretroviral therapy (HAART)
Isotretinoin
Cidofovir
Intravenous chemotherapy, e.g. anthracyclines such as liposomal daunorubicin, liposomal doxorubicin, bleomycin, paclitaxel [37], vincristine, etoposide
Human chorionic gonadotrophin [38]
Interleukin-4 [39]
Imatinib mesylate (platelet derived growth factor/c-kit receptor inhibitor) [40]

Summary of current recommendations
Early-stage KS (T0 stage)
HAART (Level of evidence III B)
Consider local radiotherapy or liposomal anthracycline for rapidly progressing or cosmetically disfiguring disease (Level of evidence III B)

Advanced-stage KS (T1 stage)
HAART and liposomal anthracycline (either daunorubicin 40 mg/m^2 every 14 days or doxorubicin 20 mg/m^2 every 21 days) (Level of evidence Ib A)

Anthracycline-refractory KS
HAART and paclitaxel (100 mg/m^2 every 14 days) (Level of evidence III B)

IFN, interferon; TNF, tumour necrosis factor.

3 Archer CB, Spittle MF, Smith NP. Kaposi's sarcoma in a homosexual: 10 years on. *Clin Exp Dermatol* 1989; **14**: 233–6.
4 Antman K, Chang Y. Medical progress: Kaposi's sarcoma. *N Engl J Med* 2000; **342**: 1027–38.
5 Kreuter A, Schugt I, Hartmann M *et al*. Dermatological diseases and signs of HIV infection. *Eur J Med Res* 2002; **7**: 57–62.
6 Martró E, Esteve A, Schultz TF *et al*. Risk factors for human Herpesvirus 8 infection and AIDS-associated Kaposi's sarcoma among men who have sex with men in a European multicentre study. *Int J Cancer* 2007; **120**: 1129–35.
7 Pica F, Volpi A. Transmission of human herpesvirus 8: an update. *Curr Opin Infect Dis* 2007; **20**: 152–6.
8 Greene W, Kuhne K, Ye F *et al*. Molecular biology of KSHV in relation to AIDS-associated oncogenesis. *Cancer Treat Res* 2007; **133**: 69–127.
9 Cattani P, Capuano M, Cerimele F *et al*. Human herpesvirus 8 seroprevalence and evaluation of nonsexual transmission routes by detection of DNA in clinical specimens from human immunodeficiency virus-seronegative patients from central and southern Italy, with and without Kaposi's sarcoma. *J Clin Microbiol* 1999; **37**: 1150–3.
10 Vitale F, Viviano E, Perna AM *et al*. Serological and virological evidence of non-sexual transmission of human herpesvirus type 8 (HHV8). *Epidemiol Infect* 2000; **125**: 671–5.
11 Pyakurel P, Pak F, Mwakigonja AR *et al*. KSHV/HHV-8 and HIV infection in Kaposi's sarcoma development. *Infect Agent Cancer* 2007; **2**: 4.
12 Schmutz J-L, Barbaud A, Trechot P. Maladie de Kaposi chez un sujet sidéen après application de tacrolimus (Protopic). *Ann Dermatol Venereol* 2006; **133**: 303.
13 Hengge UR, Stocks K, Goos M. Acquired immune deficiency syndrome-related hyperkeratotic Kaposi's sarcoma with severe lymphoedema: report of five cases. *Br J Dermatol* 2000; **142**: 501–5.
14 Ramdial PK, Chetty R, Singh B *et al*. Lymphedematous HIV-associated Kaposi's sarcoma. *J Cutan Pathol* 2006; **33**: 474–81.
15 Morris-Jones R, Fearfield L, Nelson M *et al*. Acute stridor and phimosis secondary to Kaposi's sarcoma. *Retinoids* 2000; **16**: 41–2.
16 Bunker CB, Staughton RCD. HIV-associated disease: dermatology. In: Gazzard BG, ed. *AIDS Care Handbook*. London: Mediscript, 2002: 115–39.
17 Davis DA, Scott DM. Lymphangioma-like Kaposi's sarcoma: etiology and literature review. *J Am Acad Dermatol* 2000; **43**: 123–7.
18 Ricchi E, Manfredi R, Scarani P *et al*. Cutaneous cryptococcosis and AIDS. *J Am Acad Dermatol* 1991; **25**: 335–6.
19 Blauvelt A, Kerdel FA. Cutaneous cryptococcosis mimicking Kaposi's sarcoma as the initial manifestation of disseminated disease. *Int J Dermatol* 1992; **31**: 279–80.
20 Cole MC, Cohen PR, Satra KH, Grossman ME. The concurrent presence of systemic disease pathogens and cutaneous Kaposi's sarcoma in the same lesion. *Histoplasma capsulatum* and Kaposi's sarcoma coexisting in a single skin lesion in a patient with AIDS. *J Am Acad Dermatol* 1992; **26**: 285–7.
21 Romeu J, Milla F, Batlle M *et al*. Visceral leishmaniasis involving lung and a cutaneous Kaposi's sarcoma lesion. *AIDS* 1991; **5**: 1272.
22 Gonzalez-Beato MJ, Moyano B, Sanchez C *et al*. Kaposi's sarcoma-like lesions and other nodules as cutaneous involvement in AIDS-related visceral leishmaniasis. *Br J Dermatol* 2000; **143**: 1316–8.
23 Litwin MA, Williams CM. Cutaneous *Pneumocystis carinii* infection mimicking Kaposi sarcoma. *Ann Intern Med* 1992; **117**: 45–9.
24 Crosby DL, Berger TG, Woosley JT, Resnick SD. Dermatophytosis mimicking Kaposi's sarcoma in human immunodeficiency virus disease. *Dermatologica* 1991; **182**: 135–7.
25 Marquart KH. Electron microscopy reveals fungal cells within tumor tissue from two African patients with AIDS-associated Kaposi sarcoma. *Ultrastruct Pathol* 2006; **30**: 187–92.
26 Smith KJ, Skelton HG III, Angritt P. Histopathologic features of HIV-associated skin disease. *Dermatol Clin* 1991; **9**: 551–8.
27 Bower M, Portsmouth S. HIV-associated malignancy. In: Gazzard BG, ed. *AIDS Care Handbook*. London: Mediscript, 2002: 99–114.
28 Costner M, Cockerell CJ. The changing spectrum of the cutaneous manifestations of HIV disease. *Arch Dermatol* 1998; **134**: 1290.
29 Pellet C, Chevret S, Blum L *et al*. Virologic and immunologic parameters that predict clinical response of AIDS-associated Kaposi's sarcoma to highly active antiretroviral therapy. *J Invest Dermatol* 2001; **117**: 858–63.
30 Bower M. *BHIVA Guidelines: HIV associated malignancies*. http://www.bhiva.org
31 Maurer T, Ponte M, Leslie K. HIV-associated Kaposi's sarcoma with a high CD4 count and a low viral load. *N Engl J Med* 2007; **357**: 1352–3.
32 Krown SE, Lee JY, Dittmer DP. More on HIV-associated Kaposi's sarcoma. *N Engl J Med* 2007; **358**: 535–6.
33 Duvic M, Friedmany-Kien AE, Looney DJ *et al*. Topical treatment of cutaneous lesions of acquired immunodeficiency syndrome-related Kaposi sarcoma using alitretinoin gel: results of phase 1 and 2 trials. *Arch Dermatol* 2000; **136**: 1461–9.
34 Scolaro MJ, Gunnill LB, Pope LE *et al*. The antiviral drug docosanol as a treatment for Kaposi's sarcoma lesions in HIV type 1-infected patients: a pilot clinical study. *AIDS Res Hum Retroviruses* 2001; **17**: 35–43.
35 Langtry JAA, Bottomley DM, Phillips RH, Staughton RCD. The infra-red coagulator in the treatment of AIDS-related Kaposi's sarcoma and a comparison with radiotherapy. *Clin Exp Dermatol* 1994; **19**: 23–5.
36 Tardivo JP, Del Giglio A, Paschoel LH, Baptista MS. New photodynamic therapy protocol to treat AIDS-related Kaposi's sarcoma. *Photomed Laser Surg* 2006; **24**: 528–31.
37 Tulpule A, Groopman J, Saville MW *et al*. Multicenter trial of low-dose paclitaxel in patients with advanced AIDS-related Kaposi sarcoma. *Cancer* 2002; **95**: 147–54.
38 Gill PS, McLaughlin T, Espina BM *et al*. Phase I study of human chorionic gonadotropin given subcutaneously to patents with acquired immunodeficiency syndrome-related mucocutaneous Kaposi's sarcoma. *J Natl Cancer Inst* 1997; **89**: 1797–802.
39 Tulpule A, Joshi B, DeGuzman N *et al*. Interleukin-4 in the treatment of AIDS-related Kaposi's sarcoma. *Ann Oncol* 1997; **8**: 79–83.
40 Koon HB, Bubley GJ, Pantanowitz L *et al*. Imatinib-induced regression of AIDS-related Kaposi's sarcoma. *J Clin Oncol* 2005; **23**: 982–9.

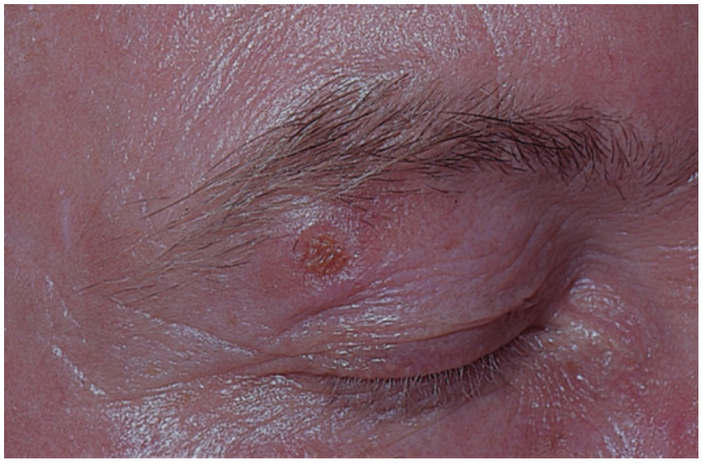


Fig. 35.22 Squamous carcinoma: ulcerated nodule on the right upper eyelid. (Courtesy of Professor C.B. Bunker and Medical Illustration UK Ltd, Chelsea and Westminster Hospital, London, UK.)

Melanoma and non-melanoma skin cancer

The incidence of non-AIDS defining cancers (NADCs) is increasing (melanoma, Hodgkin's lymphoma, leukaemia, liver, respiratory, anal, oropharyngeal and prostate cancers), but it is unclear whether this reflects a true increase in incidence or is a consequence of increased surveillance, detection and reporting [1,2]. Primary skin malignancies constitute the most frequent NADCs amongst HIV-positive people [3]. AIDS patients have a three- to fivefold risk of developing a non-melanoma skin cancer and the ratio of squamous cell carcinoma (SCC) to basal cell carcinoma (BCC) in HIV infected individuals is 1:7, compared to 1.8:1 in renal transplant patients [4]. Melanoma is probably more common [1–3] although one UK study has found a decreased incidence [5]. Anal cancer is increasing since HAART [2] and is the fourth most common cancer in MSM [6]. Sun exposure is possibly more important in causation than immunosuppression [1,7]. The role of HPV in anogenital and oral cancer, epidermoplasia verruciformis and nail unit SCC is established, but it is unlikely (although controversial) to be critical in most cutaneous HIV-associated SCC [4,8,9].

Clinically, actinic keratoses are very common; atypicality should prompt more vigorous assessment and more aggressive treatment. SCC may present atypically, at a younger age, at unusual sites (e.g. the nail fold) and be multifocal and aggressive with a high risk of recurrence and metastasis with a high mortality (Figs 35.22 & 35.23) [4,9–12]. BCC may be multiple and is commonly of the superficial type. Infundibulocystic, micronodular neurotropic and morpheiform variants, and even metastatic BCC have been reported, but generally BCC is *not* thought to behave more aggressively in the HIV-infected population [4,13–15]. Porokeratosis is associated with immunosuppression, sun damage and HIV [16]. Anogenital squamous cancer and precancer and their relationship to HPV and HIV are discussed in Chapter 71 [3,17,18].

Melanoma (Fig. 35.24) may present atypically, appearing as 'normal' naevi or 'benign macules' or multiple 'nevoid lesions', and behave more aggressively with decreased disease-free and overall survival rates; low CD4 counts indicate a poorer prognosis although the Breslow thickness is unrelated to the CD4 count at presentation [4,19–21].



Fig. 35.23 Metastatic squamous carcinoma: zosteriform ulceration of the left axilla and chest. (Courtesy of Professor C.B. Bunker and Medical Illustration UK Ltd., London, UK.)

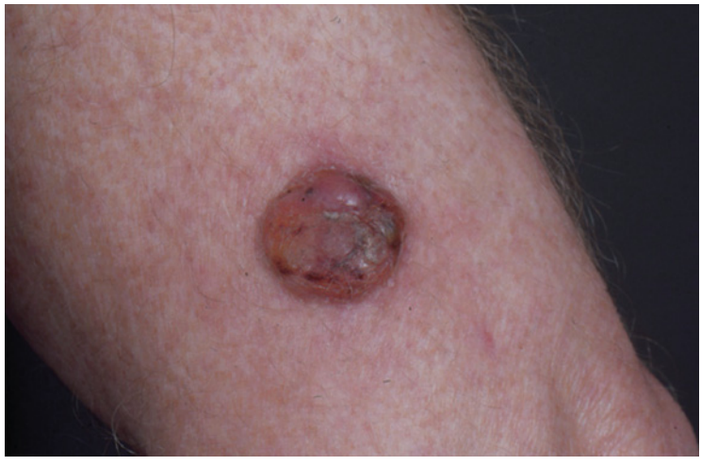


Fig. 35.24 Melanoma: rapidly growing (2/12) amelanotic nodule on the left arm. Breslow thickness >10 mm. (Courtesy of Professor C.B. Bunker and Medical Illustration UK Ltd, Chelsea and Westminster Hospital, London, UK.)

Although conventional treatment protocols should be followed for the management of BCC, SCC and melanoma in HIV practice, mindful of the potential aggressivity of SCC and melanoma, assiduous attention to local excisional margin control, more extensive investigation for regional or disseminated disease and closer follow-up in patients with SCC and melanoma are advocated [21,22]. BCC and SCC have been reported to remit with HAART [23,24]. Topical imiquimod has been used for treatment of BCC in

HIV [25] and is useful for the common scenario of multifocal superficial BCCs.

Patients receiving HAART and therefore surviving HIV longer, even indefinitely, need to have careful dermatological evaluation and follow-up, including of the anogenital skin and mucosa. They should be warned about the possible synergistic risk of the sun and HIV. All new or changing skin lesions should be evaluated assiduously, with a low threshold for biopsy.

References

1 Pantanowitz L, Schlecht HPO, Dezube BJ. The growing problem of non-AIDS-defining malignancies in HIV. *Curr Opin Oncol* 2006; **18**: 469–72.
2 Hessol NA, Pipkin S, Schwarcz S *et al*. The impact of highly active antiretroviral therapy on non-AIDS-defining cancers among adults with AIDS. *Am J Epidemiol* 2007; **165**: 1143–53.
3 Burgi A, Brodine S, Wegner S *et al*. Incidence and risk factors for the occurrence of non-AIDS-defining cancers among human immunodeficiency virus-infected individuals. *Cancer* 2005; **104**: 1505–11.
4 Wilkins K, Turner R, Dolev JC *et al*. Cutaneous malignancy and human immunodeficiency virus disease. *J Am Acad Dermatol* 2006; **54**: 189–206.
5 Newnham A, Harris J, Evans HS *et al*. The risk of cancer in HIV-infected people in southeast England: a cohort study. *Br J Cancer* 2005; **92**: 194–200.
6 Kreuter A, Weiland U, Brockmeyer NH, German Network of Competence HIV/AIDS. Genital human papillomavirus-associated (pre-) malignant skin diseases drastically increase in the era of highly active antiretroviral therapy for HIV infection. *J Am Acad Dermatol* 2006; **55**: 1116–7.
7 de Boer WA, Danner SA. HIV infection and squamous cell carcinoma of sun exposed skin. AIDS 1990; **4**: 91.
8 Maurer TA, Christian KV, Kerschmann RL *et al*. Cutaneous squamous cell carcinoma in human immunodeficiency virus-infected patients. A study of epidemiologic risk factors, human papillomavirus, and p53 expression. *Arch Dermatol* 1997; **133**: 577–83.
9 Kreuter A, Brockmeyer NH, Pfister H *et al*. Competence Network HIV/AIDS. Human papillomavirus type 26-associated periungual squamous cell carcinoma in situ in a HIV-infected patient with concomitant penile and anal intraepithelial neoplasia. *J Am Acad Dermatol* 2005; **53**: 737–9.
10 Fearfield LA, Nelson M, Francis N, Bunker CB. Cutaneous squamous cell carcinoma with zosteriform metastases in a human immunodeficiency virus-infected patient. *Br J Dermatol* 2000; **142**: 573–4.
11 Neves-Motta R, Ferry FR, Basilio-de-Oliveira CA *et al*. Highly aggressive squamous cell carcinoma in an HIV-infected patient. *Rev Soc Bras Med Trop* 2004; **37**: 496–8.
12 Nguyen P, Vin-Christian K, Ming ME, Berger T. Aggressive squamous cell carcinomas in persons infected with the human immunodeficiency virus. *Arch Dermatol* 2002; **138**: 758–63.
13 Kagen MH, Hirsch RJ, Chu P *et al*. Multiple infundibulocystic basal cell carcinomas in association with human immunodeficiency virus. *J Cutan Pathol* 2000; **27**: 316–8.
14 Wu ML, Guitart J. Unusual neurotropism. *Am J Dermatopathol* 2000; **22**: 468–9.
15 Johnson DF, Keppen M, Sitz KV. Metastatic basal cell carcinoma in acquired immunodeficiency syndrome-related complex. *JAMA* 1987; **257**: 340–3.
16 Rodriguez EA, Jakubowicz, Chinchilla DA *et al*. Porokeratosis of Mibelli and HIV-infection. *Int J Dermatol* 1996; **35**: 402–4.
17 Kotlarewsky M, Freeman JB, Cameron W, Grikmard LJ. Anal intraepithelial dysplasia and squamous carcinoma in immunosuppressed patients. *Can J Surg* 2001; **44**: 450–4.
18 Welton ML, Sharkey FE, Kahlenberg MS. The etiology and epidemiology of anal cancer. *Surg Oncol Clin N Am* 2004; **13**: 263–75.
19 Pereira F, Carey W, Shibata H *et al*. Multiple nevoid malignant melanomas in a patient with AIDS: the role of proliferating cell nuclear antigen in the diagnosis. *J Am Acad Dermatol* 2002; **47** (2 Suppl.): S172–4.
20 Sass U, Kolivras A, André J. Malignant 'animal-type' melanoma in a seropositive African man. *J Am Acad Dermatol* 2006; **54**: 547–8.
21 Webster RM, Sarwar, N, Bunker CB, Brock CS. A case series of HIV-positive patients with malignant melanoma. *J HIV Therapy* 2007; **12**: 75–8.

Table 35.21 Benign and malignant cutaneous neoplasms reported in association with HIV.

Common or classical associations
Kaposi's sarcoma
Actinic keratosis
Basal cell carcinoma
Squamous carcinoma
Melanoma
Lymphoma
Rare and speculative associations
Eruptive seborrhoeic keratoses (Leser–Trélat) [1]
Eruptive nevi (dysplastic histology) [2]
Histiocytoma—solitary, multiple and eruptive: exclude leishmaniasis [3–6]
Xanthomas [7–10].
Pilomatrixoma (in association with myotonic dystrophy) [11]
Leiomyoma and angioleiomyoma (including EBV-associated) [12,13]
Metastatic tufted angioma [14]
Dermatofibrosarcoma protuberans [15]
Sebaceous carcinoma [16]
Merkel cell carcinoma [17–19]

22 Wilkins K, Dolev JC, Turner R *et al*. Approach to the treatment of cutaneous malignancy in HIV-infected patients. *Dermatol Ther* 2005; **18**: 77–86.
23 Chan SY, Madan V, Lear JT, Helbert M. Highly active antiretroviral therapy-induced regression of basal cell carcinomas in a patient with acquired immunodeficiency and Gorlin syndrome. *Br J Dermatol* 2006; **154**: 1079–80.
24 Honda KS. HIV and skin cancer. *Dermatol Clin* 2006; **24**: 521–30.
25 Scott DR. Eradication of basal cell cancer in an HIV positive patient with topical imiquimod. *J Drugs Dermatol* 2004; **3**: 602.

Other tumours

The benign and malignant skin neoplasms that have been reported in association with HIV are listed in Table 35.21.

References

1 Inamadar AC, Palit A. Eruptive seborrhoeic keratosis in human immunodeficiency virus infection: a coincidence or 'the sign of Leser–Trélat' *Br J Dermatol* 2003; **149**: 419–46.
2 Betlloch I, Amador C, Chiner E *et al*. Eruptive melanocytic nevi in human immunodeficiency virus infection. *Int J Dermatol* 1991; **30**: 303.
3 Kanitakis J, Carbonnel E, Delmonte S *et al*. Multiple eruptive dermatofibromas in a patient with HIV infection: case report and literature review. *J Cutan Pathol* 2000; **27**: 54–6.
4 Bachmeyer C, Cordier F, Blum L *et al*. Multiple eruptive dermatofibromas after highly active antiretroviral therapy. *Br J Dermatol* 2000; **143**: 1336–7.
5 Castellano VM, Rodriguez-Peralto JL, Alonso S *et al*. Dermatofibroma parasitized by *Leishmania* in HIV infection: a new morphologic expression of dermal Kala Azar in an immunodepressed patient. *J Cutan Pathol* 1999; **26**: 516–9.
6 Forsyth SF, Lawn SD, Miller RF *et al*. Multiple dermatofibroma-like lesions in a human immunodeficiency virus-positive patient coinfected with visceral leishmaniasis. *Br J Dermatol* 2003; **148**: 171–92.
7 Smith KJ, Yeager J, Skelton HG. Histologically distinctive papular neutrophilic xanthomas in HIV-1 patients. *Am J Surg Pathol* 1997; **21**: 545–9.
8 Ramsay HM, Garraido MC, Smith AG. Normolipaemic xanthomas in association with human immunodeficiency virus infection. *Br J Dermatol* 2000; **142**: 571–3.
9 Leung N, Hegele RA, Lewis GF. Rapid development of massive tendon xanthomas following highly active antiretroviral therapy. *Ann Intern Med* 2002; **137**: 624.
10 Brown CA, Lesher JL, Peterson CM. Tuberous and tendinous xanthomata secondary to ritonavir-associated hyperlipidemia. *J Am Acad Dermatol* 2005; **52** (Suppl. 1): S86–9.

11 Farrell AM, Ross J, Bunker CB, Staughton RCD. Crusted scabies with scalp involvement in HIV-1 infection. *Br J Dermatol* 1998; **138**: 192–3.
12 Kanitakis J, Carbonnel E, Chouvet B *et al*. Cutaneous leiomyomas (piloleiomyomas) in adult patients with human immunodeficiency virus infection. *Br J Dermatol* 2000; **143**: 1338–40.
13 Chang JY-F, Wang C-S, Hung C-C *et al*. Multiple Epstein-Barr virus-associated subcutaneous angioleiomyomas in a patient with acquired immunodeficiency syndrome. *Br J Dermatol* 2002; **147**: 563–7.
14 Bang RH, Padilla RS. Metastatic tufted angioma. *Int J STD AIDS* 2000; **11**: 414.
15 Sapadin AN, Gelfand JM, Howe KL *et al*. Dermatofibrosarcoma protuberans in two patients with acquired immunodeficiency syndrome. *Cutis* 2000; **65**: 85–8.
16 Kuwahara RT, Rudolph TM, Skinner RB Jr, Rasberry RD. A large ulcerated tumor on the back. Diagnosis: solitary giant sebaceous carcinoma in a human immunodeficiency virus-positive patient. *Arch Dermatol* 2001; **137**: 1367–72.
17 Engels EA, Frisch M, Goedert JJ *et al*. Merkel cell carcinoma and HIV infection. *Lancet* 2002; **359**: 497–8.
18 Colebunders R, Bottieau E, van den Brande J *et al*. Merkel cell carcinoma and multiple basal cell carcinomas in an African albino woman with HIV infection. *HIV Med* 2004; **5**: 452–4.
19 Cone LA, Gade-Andavolu R, Lesnick RH *et al*. Merkel cell carcinoma in an HIV-1 infected man. *AIDS* 2006; **20**: 474–5.

Lymphoma

A spectrum of involvement of the skin with lymphoma is seen in HIV/AIDS [1].

Non-Hodgkin's B-cell lymphomas are common in HIV [2] and can cause skin lesions [3,4]. The majority are monomorphic but some polymorphic types may be seen as in post-transplant patients [5]. Plasmablastic lymphoma is a rare, EBV associated, variant of diffuse large-cell lymphoma that often involves the oral cavity in HIV-positive patients but can affect the skin and be self-healing [6,7]. HHV-8 can be associated with solid lymphomas [8].

The relationship of Hodgkin's disease to HIV has been controversial [3,9,10]; several hundred cases have been reported. HIV-associated Hodgkin's disease differs from non-HIV-associated disease by manifesting 'B' symptoms more commonly, a more advanced stage at presentation, extranodal disease, a higher incidence of Epstein–Barr virus in affected tissue, predominant mixed cellularity and lymphocyte-depleted histologies, a less complete response rate, a higher relapse relate and a significantly shortened median survival [9]. It can manifest as a panniculitis [11]. Multiple myeloma has presented in the skin with primary cutaneous plasmacytomas [12]. Chloroma (granulocytic sarcoma) has been reported [13].

Cutaneous T-cell lymphoma (mycosis fungoides and Sézary syndrome) may be associated with HIV/AIDS [14,15]. Subcutaneous panniculitis-like T cell lymphoma has been reported [16].

Castleman's disease is discussed in Chapter 41 [17]. A primary cutaneous KSHV/HHV8-associated plasmablastic lymphoma in a patient with Castleman's disease has been described [18]. Cutaneous mucinoses, and $CD8^+$ pseudolymphomas are referenced in Table 35.14.

References

1 Beylot-Barry M, Vergier B, Masquelier B *et al*. The spectrum of cutaneous lymphomas in HIV infection: a study of 21 cases. *Am J Surg Pathol* 1999; **23**: 1208–16.
2 Dal Maso L, Serraino D, Franceschi S. Epidemiology of HIV-associated malignancies. *Cancer Treatment Res* 2001; **104**: 1–18.
3 Schwartz JJ, Dias BM, Safai B. HIV-related malignancy. *Dermatol Clin* 1991; **9**: 503–16.
4 Cockerell CJ. Organ-specific manifestations of HIV infection. II. Update on cutaneous manifestations of HIV infection. *AIDS* 1993; **7** (Suppl. 1): S213–S218.
5 Nador RG, Chadburn A, Gundappa G *et al*. Human immunodeficiency virus (HIV)-associated polymorphic lymphoproliferative disorders. *Am J Surg Pathol* 2003; **27**: 293–302.
6 Häusermann P, Khanna N, Buess M *et al*. Cutaneous plasmablastic lymphoma in an HIV-positive male: an unrecognised cutaneous manifestation. *Dermatology* 2004; **208**: 287–90.
7 Gilberte M, Gallardo F, Bellosillo B *et al*. Recurrent and self-healing cutaneous monoclonal plasmablastic infiltrates in a patient with AIDS and Kaposi sarcoma. *Br J Dermatol* 2005; **153**: 828–32.
8 Aboulafia DM. HHV-8- and EBV-associated nonepidermotrophic large B-cell lymphoma presenting as a foot rash in a man with AIDS. *AIDS Patient Care STDS* 2002; **16**: 139–45.
9 Bower M, Portsmouth S. HIV-associated malignancy. In: Gazzard BG, ed. *AIDS Care Handbook*. London: Mediscript, 2002: 99–114.
10 Hessol NA, Pipkin S, Schwarcz S *et al*. The impact of highly active antiretroviral therapy on non-AIDS-defining cancers among adults with AIDS. *Am J Epidemiol* 2007; **165**: 1143–53.
11 Porras B, Costner M, Friedman-Kien AE, Cockerell CJ. Update on cutaneous manifestations of HIV infection. *Med Clin North Am* 1998; **82**: 1033–80.
12 Lallemand F, Fritsch L, Cywiner-Golenzer C, Rozenbaum W. Multiple myeloma in an HIV-positive man presenting with primary cutaneous plasmacytomas and spinal cord compression. *J Am Acad Dermatol* 1998; **39**: 506–8.
13 Rizzo M, Magro G, Castaldo P, Tucci L. Granulocytic sarcoma (chloroma) in HIV patient: a report. *Forensic Sci Int* 2004; **146** (Suppl): S57–8.
14 Myskowski PL. Cutaneous T-cell lymphoma and human immunodeficiency virus. The spectrum broadens. *Arch Dermatol* 1991; **127**: 1045–7.
15 Hivnor CM, Nguyen V, Rook AH *et al*. $CD8^+$ lymphoma in a patient with human immunodeficiency virus. *Arch Dermatol* 2005; **141**: 1321–2.
16 Joseph LD, Panicker VK, Prathiba D, Damodharan J. Subcutaneous panniculitis-like T cell lymphoma in a HIV positive patient. *J Assoc Physicians India* 2005; **53**: 314–6.
17 Bottieau E, Colebunders R, Schroyens W *et al*. Multicentric Castleman's disease in 2 patients with HIV infection, unresponsive to antiviral therapy. *Acta Clin Belg* 2000; **55**: 97–101.
18 Liu W, Lacouture ME, Jiang J *et al*. KSHV/HHV8-associated primary cutaneous plasmablastic lymphoma in a patient with Castleman's disease and Kaposi's sarcoma. *J Cutan Pathol* 2006; **33** (Supp. 2): 46–51.

Special situations

Hair and nails

The abnormalities of hair and nails associated with HIV infection and its treatment are listed in Tables 35.22 and 35.23 (Fig. 35.25) [1–6].

A striking case of kwashiorkor with hair and nail changes has been documented [7]. Acquired trichomegaly of the eyelashes may be a marker of advanced HIV infection [5,8].

Up to 70% of HIV-infected individuals can have nail changes [2]. Onychomycosis is usually due to *T. rubrum* or uncommon *Candida* species [2]. Some African patients with the yellow nail syndrome [9] have AIDS *and* tuberculous pleural effusion or pneumonia; the yellow nail syndrome is a recognized association of chronic pulmonary disease (see Chapter 65). Paronychia and ingrown toenail are particular complications of indinavir and probably not lamivudine, as has been suggested [10,11].

References

1 Prose NS, Abson KG, Scher RK. Disorders of the nails and hair associated with human immunodeficiency virus infection. *Int J Dermatol* 1992; **31**: 453–7.
2 Cribier B, Mena ML, Rey D *et al*. Nail changes in patients infected with human immunodeficiency virus. A prospective controlled study. *Arch Dermatol* 1998; **134**: 1216–20.

Table 35.22 Abnormalities of the hair and nails in HIV infection. (From [1–5].)

Hair
Patchy and diffuse alopecia/telogen effluvium [12]
Fine hair
Eyelash trichomegaly [5,8]
Alopecia (non-specific)
Alopecia areata (Fig. 35.25) and universalis [13]
Nails
Clubbing
Half and half nails
Transverse (Beau's lines) and longitudinal ridging
Loss of the lunula
Leukonychia
Blue nails [14]
Longitudinal melanonychia
Yellow nail syndrome [9]
Periungual erythema [15]
Onycholysis and onychoschizia
Onychomycosis [2]

Table 35.23 Abnormalities of the hair and nails due to treatments in HIV infection. (From [1–4,6].)

Hair
Eyelash hypertrichosis: zidovudine (AZT, ZDV)
Alopecia (non-specific): atazanavir, delaviridine, didanosine (ddI, DDI), efavirenz, indinavir, lamivudine (3TC), lopinavir, ritonavir, saquinavir, stavudine (d4T), zidovudine (AZT, ZDV), zalcitabine (ddC, DDC) [16–20]
Alopecia universalis: IRIS/IRD [21]
Curly hair: HAART
Pigmentation: indinavir [20]
Nails
Pigmentation: zidovudine (AZT, ZDV), indinavir [20]
Longitudinal melanonychia: zidovudine (AZT, ZDV) [22–24]
Melanonychia: hydroxyurea [17,18]
Paronychia/pyogenic granuloma: indinavir, ritonavir, zidovudine (AZT, ZDV), and lamivudine (3TC)—disputed and rare [10,11]

3 Bunker CB, Staughton RCD. HIV-associated disease: dermatology. In: Gazzard BG, ed. *AIDS Care Handbook*. London: Mediscript, 2002: 115–39.
4 Ward HA, Russo GG, Shrum J. Cutaneous manifestations of anti-retroviral therapy. *J Am Acad Dermatol* 2002; **46**: 284–93.
5 Mirmirani P, Hessol NA, Maurer TA *et al*. Hair changes in women. From the Women's interagency HIV study. *Arch Dermatol* 2003; **139**: 105–6.
6 Litt JZ. *Drug Eruption Manual*, 14th edn. New York: Informa Healthcare, 2008.
7 Alam M, Grossman ME, Longley BJ, Schneiderman PI. Kwashiorkor in patients with AIDS. *Cutis* 2001; **67**: 321–4, 327.
8 Kaplan MH, Dadick NS, Talmor M. Acquired trichomegaly of the eyelashes: a cutaneous marker of acquired immunodeficiency syndrome. *J Am Acad Dermatol* 1991; **25**: 801–4.
9 Hira SK, Wadhawan D, Kamanga J *et al*. Cutaneous manifestations of human immuno-deficiency virus in Lusaka, Zambia. *J Am Acad Dermatol* 1988; **19**: 451–7.
10 Bourezane Y, Thalamy B, Viel JF *et al*. Ingrown toenail and indinavir: case–control study demonstrates strong relationship. *AIDS* 1999; **13**: 2181–2.
11 Williams LH, Fleckman P. Painless periungal pyogenic granulomata associated with reverse transcriptase inhibitor therapy in a patient with human immuno-deficiency virus infection. *Br J Dermatol* 2007; **156**: 163–4.
12 Barcaui CB, Gonçalves da Silva AM, Sotto MN, Genser B. Stem cell apoptosis in HIV-1 alopecia. *J Cutan Pathol* 2006; **33**: 667–71.



Fig. 35.25 Alopecia areata. (Courtesy of Professor C.B. Bunker and Medical Illustration UK Ltd, Chelsea and Westminster Hospital, London, UK.)

13 Ostlere LS, Langtry JAA, Staughton RCD, Samrasinghe PL. Alopecia universalis in a patient seropositive for the human immunodeficiency virus. *J Am Acad Dermatol* 1992; **27**: 630–1.
14 Leppard B. Blue nails are a sign of HIV infection. *Int J STD AIDS* 1999; **10**: 479–82.
15 Ruiz-Avila P, Tercedor J, Rodenas JM. Periungual erythema in HIV-infected patients. *J Am Acad Dermatol* 1997; **37**: 1018–9.
16 d'Arminio Monforte A, Testa L, Gianotto M *et al*. Indinavir-related alopecia. *AIDS* 1998; **12**: 328.
17 Colebunders R, Vandenbruaene M. The changing spectrum of the cutaneous manifestations of HIV disease. *Arch Dermatol* 1999; **135**: 471.
18 Harry TC, Matthews M, Salvary I. Indinavir use: associated reversible hair loss and mood disturbance. *Int J STD AIDS* 2000; **11**: 474–6.
19 Moyle G, Gazzard BG. Nucleoside analogue reverse trancriptase inhibitors. In: Gazzard BG, ed. *AIDS Care Handbook*. London: Mediscript, 2002: 317–27.
20 Terheggen F, Frissen J, Weigel H *et al*. Nail, hair and skin hyperpigmentation associated with indinavir therapy. *AIDS* 2004; **18**: 1612.
21 Sereti I, Sarlis NJ, Arioglu E *et al*. Alopecia universalis and Graves' disease in the setting of immune restoration after highly active antiretroviral therapy. *AIDS* 2001; **15**: 138–40.
22 Cockerell CJ. Non-infectious inflammatory skin diseases in HIV-infected individuals. *Dermatol Clin* 1991; **9**: 531–42.
23 Joyner S, Lee D, Hay P, Lau R. Hydroxyurea-induced nail pigmentation in HIV patients. *HIV Med* 1999; **1**: 40–2.
24 Laughon SK, Shinn LL, Nunley JR. Melanonychia and mucucutaneous hyperpigmentation due to hydroxyurea use in an HIV-infected patient. *Int J Dermatol* 2000; **39**: 928–31.

Oropharynx

Many oral manifestations have been reported in acute HIV infection and seroconversion [1]. Transient intraoral redness, erosions and ulcers and candidosis are all described. Xerostomia is common. HIV infection must be excluded in the differential diagnosis of Sjögren's syndrome [2]. Salivary gland swelling is frequently seen in children but less so in adults infected with HIV [3].

Oral symptoms and signs are common in established HIV infection. Smoking and alcohol ingestion contribute to the morbidity [1,4]. Distressing mouth ulceration occurs frequently. The differential diagnosis includes malignancy (KS and lymphoma), HSV, CMV, fungal infections, Behçet's disease, drug-induced ulceration (e.g. didanosisne—ddI, DDI), and idiopathic aphthous ulceration. Thalidomide has proved useful for the last of these [5] at a dose of 100 mg nightly for 2 weeks followed by maintenance therapy



Fig. 35.26 Hairy leukoplakia. (Courtesy of Professor C.B. Bunker and Media Resources UCL Trust, London, UK.)



Fig. 35.27 Cheilitis caused by indinavir. (Courtesy of Professor C.B. Bunker and Imperial College School of Medicine, London, UK.)

of 100 mg every 5 days, with monitoring to avoid peripheral neuropathy [6]; however, HAART is also effective [7].

Oral candidosis is very common in HIV-positive individuals and almost universal in AIDS. The extent and persistence of the disease are responsible for much morbidity in patients with HIV and AIDS. Sometimes the entire oropharynx, larynx and oesophagus may be involved but mild forms with just angular cheilitis and/or focal red or white patches on the oral mucosa, palate or tongue are seen [1,4,8,9].

Severe periodontal disease is also not unusual [1,4]. Gangrenous stomatitis, due to opportunistic anaerobic organisms and *Candida*, *Pseudomonas* and staphylococci, causes severely symptomatic perioral ulceration complicated by pain, bleeding and inability to feed [10]. A necrotizing ulcerative stomatitis with histology resembling extranodal Kikuchi's disease has also been described [11] as has cancrum oris (noma) [12].

Hairy leukoplakia is a new clinical entity that has emerged during the HIV epidemic and is probably associated with Epstein–Barr virus infection [1,3,4]. It is particularly important because it is an early specific sign of HIV infection, with the sinister implication that 75% of patients develop AIDS within 2–3 years. It is usually asymptomatic, although patients have often noticed the appearance of a roughened patch along the lateral margin of the tongue (Fig. 35.26). To the patient it may feel rough and to the physician it may look craggy but it is not truly 'hairy'. Other intraoral sites have been reported. The differential diagnosis includes trauma, *Candida*, leukoplakia, lichen planus and white-sponge naevus. Hairy leukoplakia has not yet been shown to involve other mucosal or extramucosal sites. White-sponge naevus may be familial and may occur on the tongue. Intriguingly, oral hairy leukoplakia and oral warts rarely coexist [13]. Biopsy may be necessary. Hairy leukoplakia is now known to occur in other immunocompromised people and has even been reported in healthy individuals. Treatment options include topical podophyllin, topical retinoids, topical gentian violet, cryotherapy, surgical excision, oral aciclovir, vacicolvir and famciclovir [14,15], but it responds to HAART.

HSV infection is common in and around the mouth. Painful, red, eroded lesions are characteristic and the extent and chronicity or frequent recurrences cause much debility. Just over 1% of HIV-infected individuals have oral HPV infection [3]. CMV may present similarly.

KS occurs frequently in the mouth, often the palate. It appears as red patches, plaques or nodules (Fig. 35.20). The early red lesions may be mistaken for HSV or *Candida*. The differential diagnosis also includes the other causes of mouth ulcers and tumours, lichen planus, drug eruptions and angina bullosa haemorrhagica (see Chapter 69).

Other problems that can affect the oral cavity include petechiae from thrombocytopenia [3], tuberculosis [16], disseminated histoplasmosis [17,18], sporotrichosis [19], and paracoccidioidomycosis (40%) [20,21], hyperpigmentation and oral labial melanotic macules [3,22], warts and warty carcinoma due to HPV [23], oropharyngeal cancer [24], lymphoma, and the side effects of radiotherapy and drugs (Fig. 35.27, Table 35.24) [3,25,26]. IFN, foscarnet and zalcitabine (ddc, DDC) can cause mouth ulceration but foscarnet is used rarely now and zalcitabine is no longer available.

References

1 Greenspan D, Greenspan JS. Oral manifestations of HIV infection. *Dermatol Clin* 1991; **9**: 517–22.

2 Fox RI, Liu AY. Sjögren's syndrome in dermatology. *Clin Dermatol* 2006; **24**: 393–413.

3 Schiodt M. Less common oral lesions associated with HIV infection: prevalence and classification. *Oral Dis* 1997; **3** (Suppl.): S208–S213.

4 Bendick C, Scheifele C, Reichart PA. Oral manifestations in 101 Cambodians with HIV and AIDS. *J Oral Pathol Med* 2002; **31**: 1–4.

5 Stirling DI. Thalidomide and its impact in dermatology. *Semin Cutan Med Surg* 1998; **17**: 231–42.

6 Bunker CB, Staughton RCD. HIV-associated disease: dermatology. In: Gazzard BG, ed. *AIDS Care Handbook*. London: Mediscript, 2002: 115–39.

7 Dalmau J, Alegre M Domingo P, Alomar A. Major oral aphthous ulceration on HIV-1 infection: successful response after highly active antiretroviral therapy. *J Eur Acad Dermatol Venereol* 2007; **21**: 126–7.

8 Gottlieb MS, Schroff R, Schanker HM *et al. Pneumocystis carinii* pneumonia and mucosal candidosis in previously healthy homosexual men. *N Engl J Med* 1981; **305**: 1425–30.

Table 35.24 Oral side effects of drugs and radiotherapy given for HIV infection. (From [3,25–27].)

Drug	Oral side effect
Abacavir	Oral ulceration, perioral paraesthesia
Amprenavir	Dysgeusia, perioral paraesthesia
Atazanavir	Oral ulceration, dysgeusia
Delaviridine	Oral ulceration, xerostomia, gingivitis, stomatitis, sialorrhoea, lingual oedema, dysgeusia
Didanosine (ddI, DDI)	Oral ulceration, dysgeusia, xerostomia
Efavirenz	Xerostomia
Enfuvirtide (T20)	Dysgeusia
Fosamprenavir (pro-drug of amprenavir)	Dysgeusia, perioral paraesthesia
Foscarnet	Oral ulceration
Hydroxyurea	Oral pigmentation
Indinavir	Cheilitis, xerostomia, oral ulceration, dysgeusia, gingivitis
Interferon	Oral ulceration
Lopinavir	Oral ulceration, xerostomia, gingivitis, sialadenitis
Nelfinavir	Oral ulceration, perioral paraesthesia
Nevirapine	Oral ulceration, gingivitis
Ritonavir	Cheilitis, oral ulceration, xerostomia, gingivitis, ageusia and dysgeusia, perioral paraesthesia, oral candidosis
Saquinavir	Oral ulceration, gingivitis, glossitis, stomatitis, perioral paraesthesia
Zalcitabine (ddC, DDC)*	Oral ulceration, xerostomia, ageusia and dysgeusia, gingivitis, stomatitis, glossitis, glossodynia
Zidovudine (AZT, ZDV)	Oral ulceration, oral pigmentation, dysgeusia, lichenoid eruption, gingivitis
PIs	Cheilitis (Fig. 35.27)

* No longer available.

9 Lilly EA, Hart DJ, Leigh JE *et al*. Tissue-associated cytokine expression in HIV-positive persons with oropharyngeal candidiasis. *J Infect Dis* 2004; **190**: 605–12.

10 Giovanni M, Zucotti GV, Fiocchi A. Gangrenous stomatitis in a child with AIDS. *Lancet* 1989; **ii**: 1400.

11 Jones AC, Gulley ML, Freedman PD Necrotizing ulcerative stomatitis in human immunodeficiency virus-seropositive individuals: a review of the histopathologic, immunohistochemical, and virologic characteristics of 18 cases. *Oral Surg Oral Med Oral Pathol* 2000; **89**: 323–32.

12 Naidoo S, Chikte UM. Noma (cancrum oris): case report in a 4-year-old HIV-positive South African child. *S Afr Dental J* 2000; **55**: 683–6.

13 Lilly EA, Cameron JE, Shetty KV *et al*. Lack of evidence for local immune activity in oral hairy leukoplakia and oral wart lesions. *Oral Microbiol Immunol* 2005; **20**: 154–62.

14 Pastore L, De Benedittis M, Petruzzi M *et al*. Efficacy of famciclovir in the treatment of oral hairy leukoplakia. *Br J Dermatol* 2006; **154**: 378–9.

15 Bhandarkar SS, MacKelfresh J, Fried L, Arbiser JL. Targeted therapy of oral hairy leukoplakia with gentian violet. *J Am Acad Dermatol* 2008; **58**: 711–2.

16 Miziara ID. Tuberculosis affecting the oral cavity in Brazilian HIV-infected patients. *Oral Surg Oral Med Oral Pathol* 2005; **100**: 179–82.

17 Penneys MS. *Skin Manifestations of AIDS*. London: Martin Dunitz, 1990.

18 Casariego Z, Kelly GR, Perez H *et al*. Disseminated histoplasmosis with orofacial involvement in HIV-1-infected patients with AIDS: manifestation and treatment. *Oral Dis* 1997; **3**: 184–7.

19 Aarestrup FM, Guerra RO, Vieira BJC, Unha RM. Oral manifestation of sporotrichosis in AIDS patients. *Oral Dis* 2001; **7**: 134–6.

20 Giovani EM, Mantesso A, Loducca SV, Magalhaes MH. Paracoccidioidomycosis in an HIV-positive patient: a case report with gingival aspects. *Oral Dis* 2000; **6**: 327–9.

21 Paniago AM, de Freitas AC, Aguiar ES *et al*. Paracoccidioidomycosis in patients with human immunodeficiency virus: review of 12 cases observed in an endemic region in Brazil. *J Infect* 2005; **51**: 248–52.

22 Cohen LM, Callen JP. Oral and labial melanotic macules in a patient infected with human immunodeficiency virus. *J Am Acad Dermatol* 1992; **26**: 653–4.

23 Piatelli A, Rubini C, Fiorini M, Iezzi T. Warty carcinoma of the oral mucosa in an HIV patient. *Oral Oncol* 2001; **37**: 665–7.

24 Hessol NA, Pipkin S, Schwarcz S, Cress RD, Bacchetti P, Scheer S. The impact of highly active antiretroviral therapy on non-AIDS-defining cancers among adults with AIDS. *Am J Epidemiol* 2007; **165**: 1143–53.

25 Moyle G, Gazzard BG. Nucleoside analogue reverse trancriptase inhibitors. In: Gazzard BG, ed. *AIDS Care Handbook*. London: Mediscript, 2002: 317–27.

26 Moyle G, Gazzard BG. Protease inhibitors. In: Gazzard BG, ed. *AIDS Care Handbook*. London: Mediscript, 2002: 333–40.

27 Litt JZ. *Drug Eruption Manual*, 14th edn. New York: Informa Healthcare, 2008.

Women

Women and children represent the fastest growing subpopulations of HIV-infected patients in the developed world. Women are more susceptible than men to acquisition of HIV and often sustain more damage to their health from the disease [1]. There are few significant differences in dermatological morbidity between HIV-infected men and women save that women have less KS and hairy leukoplakia and possibly onychomycosis and that mollusca may appear earlier in women [2]; eosinophilic folliculitis is held to be very rare in women [3]; antibiotics such as nitrofurantoin given during pregnancy may be more risky for Stevens–Johnson syndrome [4]. Thrombotic thrombocytopenic purpura may complicate pregnancy [5] but pregnancy does not generally seem to affect the occurrence of HIV-associated dermatoses [6]. Cutaneous manifestations in HIV-infected women are improved by HAART [7].

References

1 Madkan VK, Giancola AA, Sra KK *et al*. Sex differences in the transmission, prevention, and disease manifestations of sexually transmitted diseases. *Arch Dermatol* 2006; **142**: 365–70.

2 Barton J, Buchness M. Nongenital dermatologic disease in HIV-infected women. *J Am Acad Dermatol* 1999; **40**: 938–48.

3 Teofoli P, Barbieri C, Pallotta S *et al*. Pruritic eosinophilic papular eruption revealing HIV infection. *Eur J Dermatol*. 2002; **12**: 600–2.

4 Shilad A, Predanic M, Perni SC *et al*. Human immunodeficiency virus, pregnancy and Stevens-Johnson syndrome. *Obstet Gynecol* 2005; **105**: 1254–6.

5 Robertson C, Wiselka MJ. Thrombotic thrombocytopaenic purpura occurring in consecutive pregnancies in an HIV-infected patient. *Int J STD AIDS* 2007; **18**: 142–3.

6 Alonso N, Lugo-Somolinos A, Torres-Paoli D, Sánchez JL. Prevalence of skin disease in HIV-positive pregnant women. *Int J Dermatol* 2003; **42**: 521–3.

7 Maurer T, Rodriques LK, Ameil N *et al*. The effect of highly active antiretroviral therapy on dermatologic disease in a longitudinal study of HIV type 1-infected women. *Clin Infect Dis* 2004; **38**: 579–84.

Children

Children and women represent the fastest growing subpopulations of HIV-infected patients in the developed world. Paediatric HIV infection shows differences compared with adults. Vertical transmission from an infected mother is the usual mode of infection. There is a challenging and broad differential diagnosis of immunosuppression in children (Table 35.25) [1]; all of these conditions may have cutaneous manifestations.

Dermatological disease is common in children with HIV/AIDS [2–6]. Concomitant infection and malnutrition are important

Table 35.25 Differential diagnosis of childhood immunosuppression.

Di George's syndrome
Ataxia–telangiectasia
Wiskott–Aldrich syndrome
Agammaglobulinaemias
T-cell and B-cell immunodeficiencies
Malnutrition
Malignancy
Congenital infections
Iatrogenic immunosuppression
Graft-versus-host disease

confounders [6]. Oral candidosis may affect up to one-third [5]. Atopic dermatitis is controversial; previously thought to be commoner, a recent study has shown no increase in the prevalence of atopy in perinatally HIV-infected children compared with the general population [7]. Unclassified eczematous eruptions are certainly seen. An eruption resembling seborrhoeic dermatitis has been described. Widespread nappy dermatitis can occur. The pruritic papular eruption is common and, as in adults, so are drug eruptions.

About half of children with advanced HIV disease can be expected to suffer a serious bacterial infection and 20% of these involve the skin. The commonest organism is *Staphylococcus aureus* and the usual clinical patterns are of cellulitis, impetigo, folliculitis and abscess formation; a persistent staphylococcal folliculitis may also be seen. The most common fungal infection is candidosis, 75% of 36 children in one study. Dermatophyte infection is frequently encountered (tinea capitis, tinea corporis and onychomycosis). HSV infection of the skin and mucosae is common and may be very serious and chronic; likewise disseminated zoster infection [5]. Paediatric exanthematous diseases such as measles may behave atypically and with more complications [8]. Persistent verrucous varicella in a 3-year-old girl has been described as the first manifestation of HIV infection [9]. In HIV infection, molluscum lesions have a predilection for the face rather than the trunk. Perianal warts have been reported and it is likely that persistent HPV infection at other sites will become more widely seen, although digital warts and verrucae are a common, if not universal, experience in childhood.

KS is rare (about 5%) and often affects other organs, with sparing of the skin. Non-Hodgkin's and other lymphomas with cutaneous involvement are even rarer [6].

There have been reports of skin changes compatible with pellagra, scurvy and acquired zinc deficiency (acrodermatitis enteropathica), attributed to malnutrition and malabsorption associated with chronic infectious diarrhoea caused by opportunistic organisms [6,10].

Drug eruptions are common as in adults [6]. HAART-associated lipohypertrophy is rare; lipoatrophy is associated with a raised serum CRP [11]. Non-specific findings in paediatric HIV practice include exanthematous rashes and cutis marmorata or livedo appearance [12], cold urticaria and idiopathic urticaria, long eyelashes requiring frequent trimming, patchy alopecia (common), erythema dyschromicum perstans (ashy dermatosis) and pyoderma gangrenosum [13]. Children infected with HIV are at risk of child abuse [4]. Cutaneous manifestations in HIV-infected children improve with HAART [14].

References

1 Bunker CB, Staughton RCD. HIV-associated disease: dermatology. In: Gazzard BG, ed. *AIDS Care Handbook*. London: Mediscript, 2002: 115–39.
2 Prose NS. Cutaneous manifestations of HIV infection in children. *Dermatol Clin* 1991; **9**: 543–50.
3 El Hachem M, Bernardi S, Pianosi G *et al*. Mucocutaneous manifestations in children with HIV infection and AIDS. *Pediatr Dermatol* 1998; **15**: 429–34.
4 Laude TA. Manifestations of HIV disease in children. *Clin Dermatol* 2000; **18**: 457–67.
5 Wananukul S, Deekajorndech T, Panchareon C, Thisyakorn U. Mucocutaneous findings in pediatric AIDS related to degree of immunosuppression. *Pediatr Dermatol* 2003; **20**: 289–94.
6 Rennert WP. Non-infectious cutaneous manifestations of HIV infection in children. *AIDS Reader* 2006; **16**: 103–5.
7 Bowser CS, Kaye J, Joks RO *et al*. IgE and atopy in perinatally HIV-infected children. *Pediatr Allergy Immunol* 2007; **18**: 298–303.
8 De Carvalho V, Marinoni LP, Martins LF *et al*. Measles in children with HIV infection: report of five cases. *Braz J Infect Dis* 2003; **7**: 346–52.
9 Zampogna JC, Flowers FP. Persistent verrucous varicella as the initial manifestation of HIV infection. *J Am Acad Dermatol* 2001; **44**: 391–4.
10 Tong TK, Andrew LR, Albert A, Mickell JJ. Childhood acquired immunodeficiency syndrome manifesting as acrodermatitis enteropathica. *J Pediatr* 1986; **108**: 426–8.
11 Hartman K, Verweel G, de Groot R, Hartwig NG. Detection of lipoatrophy in human immunodeficiency virus-1-infected children treated with highly active antiretroviral therapy. *Pediatr Infect Dis J* 2006; **25**: 427–31.
12 Penneys MS. *Skin Manifestations of AIDS*. London: Martin Dunitz, 1990.
13 Paller AS, Sahn EE, Garen PD *et al*. Pyoderma gangrenosum in pediatric acquired immunodeficiency syndrome. *J Pediatr* 1990; **117**: 63–6.
14 Seone Reula E, Bellon JM, Gurbindo D *et al*. Role of antiretroviral therapies in mucocutaneous manifestations in HIV-infected children over a period of two decades. *Br J Dermatol* 2005; **153**: 382–9.

Haemophiliacs

Atopic dermatitis (in children), seborrhoeic dermatitis, candidosis, dermatophyte infection and folliculitis occur with increased prevalence in HIV-positive compared with HIV-negative haemophiliacs. These conditions may develop earlier in infected haemophiliacs than in MSM [1,2].

References

1 Ball LM, Harper JI. Atopic eczema in HIV seropositive haemophiliacs. *Lancet* 1987; **ii**: 627–8.
2 Telfer NR, Mathews JM, Wojnarowska F. Skin diseases in haemophiliacs with and without antibodies to the human immunodeficiency virus (HIV): further evidence of altered disease behaviour in different risk groups? *Br J Dermatol* 1989; **120**: 795–9.

Intravenous drug users

Drug abusers may have severe ecthyma and abscesses complicating injection sites but there is often concomitant malnutrition and liver disease [1]. Oral candidosis and seborrhoeic dermatitis are the most common skin problems; KS and oral hairy leukoplakia are rare [2]. MRSA is an increasing problem. Reynaud-Mendel *et al*. [3] found that genital warts were commoner in HIV-infected intravenous drug users than in male homosexuals. Tuberculous lymphadenitis has been said to be a characteristic manifestation in intravenous drug users co-infected with tuberculosis [4].

References

1 Ebright JR, Pieper B. Skin and soft tissue infections in injection drug abusers. *Infectious Disease Clinics of North America* 2002; **16**: 697–712.

2 Munoz-Perez MA, Rodrifuez-Pichardo A, Camacho F, Calmenero MA. Dermatological findings correlated with CD4 lymphocyte counts in a prospective 3 year study of 1161 patients with human immunodeficiency virus disease predominantly acquired through intravenous drug abuse. *Br J Dermatol* 1998; **139**: 33–9.

3 Reynaud-Mendel B, Janier M, Gerbaka J *et al*. Dermatologic findings in HIV-1-infected patients: a prospective study with emphasis on CD4 cell count. *Dermatology* 1996; **192**: 325–8.

4 Aguado JM, Castrillo JM. Lymphadenitis as a characteristic manifestation of disseminated tuberculosis in intravenous drug abusers infected with human immunodeficiency virus. *J Infect* 1987; **14**: 191–3.

Immune reconstitution (inflammatory) syndrome/ immune restoration disease (IRIS/IRD)

Antiretroviral therapy and subsequent immune restoration with HAART can precipitate exacerbations of immune or inflammatory disease—the immune reconstitution (inflammatory) syndrome (IRIS) or immune restoration disease (IRD). Immunorestoration may reactivate the host response to latent infections or unmask autoimmune diseases in genetically susceptible individuals. Examples are progressive multifocal leukoencephalopathy, uveitis or vitreitis in CMV retinitis, sarcoidosis, hepatitis C reactivation and lymphadenitis in tuberculosis and *M. avium–intracellulare* infection [1–6]. Distinct cytokine-mediated mechanisms contribute to IRIS/IRD associated with herpes virus and mycobacterial infections [7]. Approximately half of all IRIS/IRD events are dermatological [8]. Those that have been reported are listed in Table 35.26.

Table 35.26 Dermatological manifestations of IRIS/IRD. (From [3,8].)

- Human herpes viruses
  - HSV-1, -2 chronic oronasal and anogenital disease (Fig. 35.28) [9]
  - VZV (HHV-3)
  - CMV (HHV-6) acute multifocal cutaneous ulceration (Fig. 35.29) [11]
  - KSHV (HHV-8) [10]
- Other viruses
  - HPV warts [12]; oral warts; inflammation of existing warts
  - mollusca [13]
- Mycobacteria [14]
  - tuberculosis [15]
  - atypical mycobacterial infections [16]
  - leprosy [17–19]
- Fungi
  - candidosis
  - tinea corporis
  - cryptococcosis
  - histoplasmosis
- Post-kala-azar dermal leishmaniasis [20,21]
- Inflammatory reactions related to infective agents
  - 'immune recovery folliculitis' ?re-emergent hypersensitivity to *Demodex* and *Malassezia* [22,23]
  - severe seborrhoeic dermatitis ?hypersensitivity to *Malassesia* [24]
  - alopecia
- Idiopathic inflammatory reactions
  - photosensitivity [13]
  - papular pruritic eruption [25]
  - eosinophilic folliculitis [25,26,27]
  - lupus erythematosus [28]
  - sarcoid [5,29]
  - granulomatous reactions to tattoos, foreign bodies and tribal medicines [30–32]
  - alopecia universalis associated with Graves' disease [33].
  - repigmentation of vitiligo [34]
  - acne vulgaris/rosacea [35,36]
  - relapsing polychondritis [37]
- Miscellaneous
  - eruptive dermatofibroma
  - dyshidrosis

References

1 Connick E. Immune reconstitution in HIV-1-infected individuals treated with potent antiretroviral therapy. *J Invest Dermatol Symposium Proceedings* 2001; **6**: 212–8.

2 Colebunders R, Lambert ML. Management of co-infection with HIV and TB. *BMJ* 2002; **324**: 802–3.

3 Finkelstein M, Berman B. HIV and AIDS in inpatient dermatology. Approach to the consultation. *Dermatol Clin* 2000; **18**: 509–20.

4 Jacobson MA. Editorial comment: another new immune reconstitution syndrome. *Aids Read* 2002; **12**: 456–7.

5 Roustan G, Yebra M, Rodriguez-Braojos O *et al*. Cutaneous and pulmonary sarcoidosis in a patient with HIV after highly active antiretroviral therapy. *Int J Dermatol* 2007; **46**: 68–71.

6 Farrand RA, Cartledge JD, Connolly J *et al*. Immune reconstitution sarcoidosis presenting with hypercalcaemia and renal failure in HIV infection. *Int J STD AIDS* 2007; **18**: 138–9.

7 Price P, Morahan G, Huang D *et al*. Polymorphisms in cytokine genes define subpopulations of HIV-1 patients who experienced immune restoration diseases. *AIDS* 2002; **16**: 2043–7.

8 Lehloenya R, Meintjes G. Dermatologic manifestations of the immune reconstitution inflammatory syndrome. *Dermatol Clin* 2006; **24**: 549–70, vii.

9 Fox PA, Barton SE, Francis N *et al*. Chronic erosive herpes simplex virus infection of the penis, a possible immune reconstitution disease. *HIV Medicine* 1999; **1**: 10–8.

10 Bower M, Nelson M, Young AM *et al*. Immune reconstitution inflammatory syndrome associated with Kaposi's sarcoma. *J Clin Oncol* 2005; **23**: 5224–8.

11 Qazi NA, Morlese JF, Walsh JC *et al*. Severe cutaneous ulceration secondary to cytomegalovirus inclusion disease during successful immune reconstitution with HAART. *AIDS Read* 2002; **12**: 452–7.

12 Rodrigues LK, Baker T, Maurer T. Cutaneous warts in HIV-positive patients undergoing highly active antiretroviral therapy. *Arch Dermatol* 2001; **137**: 1103–4.

13 Queiroz Zancanaro PC, McGirt LY, Mamelak AJ *et al*. Cutaneous manifestations of HIV in the era of highly active antiretroviral therapy: An institutional urban clinic experience. *J Am Acad Dermatol* 2006; **54**: 581–8.

14 Sotto A, Guillot B, Dandurand M, Jourand J. Exacerbation of skin mycobacterial lesions under highly active antiretroviral therapy of an HIV-infected patient. *AIDS* 1999; **13**: 1790–1.

15 Maccari F, Descamps V, Duval X *et al*. Skin manifestation of immune restoration syndrome in treated tuberculosis. *Ann Dermatol Venereol* 2001; **128**: 1028–30.

16 Bachmeyer C, Thibaut M, Khuoy L *et al*. Subcutaneous and muscular abscesses due to mycobacterium avium intracellulare in a patient with AIDS as a manifestation of immune restoration. *Br J Dermatol* 2004; **150**: 397–8.

17 Pignataro P, Rocha Ada S *et al*. Leprosy and AIDS: two cases of increasing inflammatory reactions at the start of highly active antiretroviral therapy. *Eur J Clin Microbiol Infect Dis* 2004; **23**: 408–11.

18 Couppié P, Abel S, Voinchet H *et al*. Immune reconstitution inflammatory syndrome associated with HIV and leprosy. *Arch Dermatol* 2004; **140**: 997–1000.

19 Narang T, Dogra S, Kaur I. Borderline tuberculoid leprosy with type 1 reaction in an HIV patient—a phenomenon of immune reconstitution. *Int J Lepr Other Mycobact Dis* 2005; **73**: 203–5.

20 Gilad J, Borer A, Hallel-Halevy D *et al*. Post-kala-azar dermal leishmaniasis manifesting after initiation of highly active anti-retroviral therapy in a patient with human immunodeficiency virus infection. *Isr Med Assoc J* 2001; **3**: 451–2.



Fig. 35.28 Herpes simplex immune restoration disease: chronic erosions on the penis. (Courtesy of Professor C.B. Bunker and Medical Illustration UK Ltd, Chelsea and Westminster Hospital, London, UK.)



Fig. 35.29 Cytomegalovirus immune restoration disease: necrotizing impetiginized ulcer on the left ear. (Courtesy of Professor C.B. Bunker and Imperial College School of Medicine, London, UK.)

21 Antinori S, Longhi E, Bestetti G *et al*. Post-kala-azar dermal leishmaniasis as an immune reconstitution inflammatory syndrome in a patient with acquired immune deficiency syndrome. *Br J Dermatol* 2007; **157**: 1032–6.

22 Bouscarat F, Maube E, Matheron S, Descamps V. Immune recovery inflammatory folliculitis. *AIDS* 2000; **14**: 617–8.

23 Delfos NM, Collen AF, Kroon FP. Demodex folliculitis: a skin manifestation of immune reconstitution disease. *AIDS* 2004; **18**: 701–2.

24 Hardcastle NJ, Tunbridge AJ, Shum KW *et al*. Alopecia in association with severe seborrhoeic dermatitis following combination antiretroviral therapy for acute retroviral syndrome. *J Eur Acad Dermatol Venereol* 2005; **19**: 631–3.

25 Colebunders R, Castlenuovo B, Byakwaga H. HIV eosinophilic folliculitis in Uganda. *Arch Dermatol* 2006; **142**: 934.

26 Moyle M, Woolley IJ, Theveajan I, Korman TM. Eosinophilic folliculitis: an example of 'immune reconstitution folliculitis'. *AIDS* 2004; **18**: 2350–2.

27 Rajendran PM, Dolev JC, Heaphy MR Jr, Maurer T. Eosinophilic folliculitis before and after the introduction of antiretroviral therapy. *Arch Dermatol* 2005; **141**: 1227–31.

28 Chamberlain AJ, Hollowood K, Turner RJ, Byren I. Tumid lupus erythematosus occurring following highly active antiretroviral therapy for HIV infection: a manifestation of immune restoration. *J Am Acad Dermatol* 2004; **51**: S161–5.

29 Mirmirani P, Maurer TA, Herndier B *et al*. Sarcoidosis in a patient with AIDS: a manifestation of immune restoration syndrome. *J Am Acad Dermatol* 1999; **41**: 285–6.

30 Farrant P, Higgins E. A Granulomatous response to tribal medicine as a feature of the immune reconstitution syndrome. *Clin Exp Dermatol* 2004; **29**: 366–8.

31 Murray CA, Dekoven J, Spaner D. Foreign body granuloma: a new manifestation of immune restoration syndrome. *J Cutan Med Surg* 2003; **7**: 38–42.

32 Silvestre JF, Albares MP, Ramon R *et al*. Cutaneous intolerance to tattoos in a patient with human immunodeficiency virus: a manifestation of the immune restoration syndrome. *Arch Dermatol* 2001; **137**: 669–70.

33 Sereti I, Sarlis NJ, Arioglu E *et al*. Alopecia universalis and Graves' diseaes in the setting of immune restoration after highly active antiretroviral therapy. *AIDS* 2001; **15**: 138–40.

34 Antony FC, Marsden RA. Vitiligo in association with human immunodeficiency virus infection. *J Eur Acad Dermatol Venereol* 2003; **17**: 456–8.

35 Kreuter A, Schlottmann R, Altmeyer P, Brockmeyer NH. Acne vulgaris as an immune reconstitution syndrome in a patient with AIDS after initiation of antiretroviral therapy. *J Eur Acad Dermatol Venereol* 2002; **16**: 638–49.

36 Scott CJ, Staughton RCD, Bunker CB, Asboe D. Acne vulgaris and acne rosacea as part of immune reconstitution disease in HIV-1 infected patients starting anti-retroviral therapy. *Int J STD AIDS* 2008; **19**: 493–5.

37 Dolev JC, Maurer TA, Reddy SG *et al*. Relapsing polychondritis in HIV-infected patients: a report of two cases. *J Am Acad Dermatol* 2004; **51**: 1023–5.

CHAPTER 36
Mycology

R.J. Hay[1] *& H.R. Ashbee*[2]

[1]Dermatology Department, King's College Hospital, London, UK
[2]Mycology Reference Centre, Leeds General Infirmary, Leeds, UK

Superficial mycoses, 36.5
Laboratory methods, 36.5
Pityriasis versicolor, 36.10
Other cutaneous disorders associated with *Malassezia* yeasts, 36.13
Tinea nigra, 36.14
Black piedra, 36.15
White piedra, 36.16
Otomycosis, 36.17
Miscellaneous superficial fungal infections caused by saprophytic moulds, 36.17
Dermatophytosis, 36.18
Infections caused by *Scytalidium* species, 36.51
Onychomycosis caused by other non-dermatophyte moulds, 36.53
Candidosis, 36.56
Subcutaneous mycoses, 36.69
Laboratory methods, 36.69
Sporotrichosis, 36.70
Mycetoma, 36.72
Chromoblastomycosis, 36.75
Phaeohyphomycosis, 36.77
Lobomycosis, 36.77
Rhinosporidiosis, 36.78
Subcutaneous zygomycosis, 36.78
Systemic mycoses, 36.79
Laboratory methods, 36.80
Histoplasmosis, 36.80
Blastomycosis, 36.83
Coccidioidomycosis, 36.85
Paracoccidioidomycosis, 36.87
Infections caused by *Penicillium marneffei*, 36.88
Cryptococcosis, 36.89
Systemic candidosis, 36.91
Zygomycosis, 36.91
Unusual causes of skin lesions among opportunistic systemic mycoses, 36.92
Cutaneous infection caused by *Pneumocystis jiroveci*, 36.92
Infections caused by *Pythium insidiosum*, 36.92
Protothecosis, 36.92
Glossary, 36.93

Introduction

Every dermatologist should be familiar, not only with the common superficial mycoses, but also with the cutaneous manifestations of subcutaneous and systemic infections. With increasing numbers of people taking advantage of the ease of worldwide travel, mycoses that were previously regarded as geographically limited can now be seen in any part of the world. Furthermore, in recent years the number of fungi recognized as human pathogens has risen, caused partly by an increasing population of debilitated and immunocompromised patients. Fungi that were considered non-pathogenic are now being recovered as opportunistic pathogens. The routine identification of the majority of pathogenic fungi still relies largely on the direct observation of their morphology rather than comparison of DNA patterns, and this requires a knowledge of some of the fundamental features of fungal classification and structure. Over the last 20 years, a precise and complex terminology has been developed to describe the characteristic features that may be observed [1–4] and an outline knowledge of this is essential in order to appreciate the often subtle differences that distinguish fungal pathogens.

Fungi are ubiquitous, capable of colonizing almost any environment, and generally play an invaluable part in the decomposition and recycling of organic matter. Although they were once believed to be descended from plants, it was recognized over 20 years ago that they represent a distinct kingdom, and that certain features of their biochemistry, such as the pathway of lysine synthesis, are quite different from those found in bacteria and plants. With the use of molecular techniques, it is now recognized that the organisms originally included in this kingdom of Fungi contained at least three phylogenetically distinct groups, and some phyla have now been reclassified in the kingdoms Protozoa and Chromista. Almost all the fungi previously regarded as human pathogens, however, remain in the reclassified Fungi [5]. They have probably evolved from protozoan ancestors, and the kingdom Fungi is now believed to have originated before the separation of Animalia and Plantae. All fungi are heterotrophic and must exist as saprophytes or parasites. However, relatively few of the estimated quarter of a million species are pathogens of humans or other warm-blooded animals. The vast majority exist purely as saprophytes or plant parasites and, even among the few that do cause human disease, many have a well-established saprophytic or plant parasitic life cycle in which human infection has no role.

Members of the kingdom Fungi show all the typical eukaryotic features, such as the organization of genetic material into chromosomes enclosed within a membrane-bound nucleus, mitochondria and ribosomes. Unlike animal cells, however, their cells are enclosed by a rigid cell wall containing varying amounts of chitin, a polymer of *N*-acetyl glucosamine, and β-glucans. The wall also contains mannans, glycoproteins and enzymes, some of which are secreted into the surrounding environment and break down complex organic compounds prior to their absorption. Fungi have

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

an absorptive mode of nutrition. Within the cell wall, the cytoplasm is bounded by a plasma membrane in which the predominant sterol is not cholesterol, as in humans, but ergosterol.

The fungi may be broadly divided into two basic forms: moulds and yeasts. Moulds are made up of long nucleate filaments called hyphae (singular hypha), which are either largely coenocytic (see Fig. 36.56) or divided into a series of cells by regular cross walls or septa (singular septum) (see Fig. 36.17a). Hyphae grow continuously at the apical tip, where the cell wall is constantly plasticized and new material added. This is the most metabolically active area of the cytoplasm. Further back, the cells may become vacuolated, and often the cytoplasm is reduced to a thin layer lining the cell membrane. Hyphae branch regularly, the branches diverging away from the parent hypha to utilize the environment to the maximum extent. Typically, the longest cell is at the apex of the hypha. The cytoplasm streams continuously, and the majority of septa contain pores that allow the movement of cytoplasm and even of organelles from one cell to another. An aggregation of hyphae is termed a mycelium, and the whole mass of the fungus is the thallus. Growth of a mould on solid media results in a circular colony, and in liquid media the mould forms a ball. Moulds produce cottony or velvety colonies in culture, and even large structures such as mushrooms are simply made up of a mass of hyphae.

In the yeasts, the main phase of the life cycle is unicellular, made up of ovoid to globose cells which usually reproduce by budding (see Fig. 36.43) or, more rarely, by fission. After budding, when the daughter cell separates from the parent, a distinct bud scar is left behind. In addition, however, some pathogens can also form filaments that may be true hyphae, similar to those of moulds, or pseudohyphae which develop when two cells fail to separate after budding, and simply elongate and lie end to end forming a chain. Pseudohyphae may be distinguished from true hyphae by the characteristic constrictions that may be seen at the points where two cells meet (see Fig. 36.43), and the shortness of the apical cell. Yeasts produce soft, pasty or mucoid colonies.

Some fungi can completely switch their form of growth depending on the environmental conditions. These are termed thermally and nutritionally dimorphic fungi, and include several of the major respiratory pathogens, such as *Histoplasma capsulatum* and *Coccidioides immitis*. When cultured at room temperature, these fungi are typical moulds, yet in human tissues or on special media at 37°C they convert into yeasts or other non-filamentous forms.

Fungi reproduce both sexually and asexually, sometimes simultaneously. The sexual phase is termed the teleomorph and the asexual phase the anamorph; when both are present the growth is termed the holomorph. Much confusion has arisen because at the moment it is quite legitimate to give the sexual and asexual stages of growth completely different names. Thus, the dermatophyte *Trichophyton mentagrophytes* was originally described and named in the asexual phase in 1896. When a sexual phase was discovered in 1967, it was called *Arthroderma benhamiae*. Currently, both names are correct and their usage is simply determined by the phase isolated. If both sexual and asexual forms are present simultaneously, the sexual name has precedence. In the laboratory, sexual phases of pathogens are rarely seen, as the majority of fungi are heterothallic, which means that sexual reproduction requires the presence of two or sometimes four different mating types. Relatively few fungi can reproduce sexually by the mating of hyphae from a single mycelium, a condition termed homothallic.

In an attempt to reflect true phylogenetic relationships, the formal classification of fungi is based upon the features of the sexual phase of growth. This involves the fusion of two nuclei followed by meiotic division. Unlike higher plants and animals, many of the fungi are haploid for the major part of the life cycle, the diploid phase being relatively short lived. Three groups of sexually reproducing fungi, *Zygomycota*, *Ascomycota* and *Basidiomycota*, contain human pathogens (Table 36.1). A fourth, completely artificial group, the *Deuteromycota* or Fungi Imperfecti, was originally created to include those fungi with no known sexual phase, and the asexual phases of the *Ascomycota* and *Basidiomycota*. With the more sophisticated techniques available today, such as ultrastructural data on septa and genetic sequencing, these asexual 'mitosporic' species can now be placed within the recognized sexual groups, and it is possible that at some time in the future the artificial form-phylum *Deuteromycota* will disappear from the literature.

The *Zygomycota* are all moulds, and reproduce sexually by the formation of thick-walled zygospores following the fusion of two outgrowths arising from the hyphae. The hyphae of the

Table 36.1 Classification of fungi.

Phylum	Growth form	Hyphae (if present)	Sexual propagules	Asexual propagules
Zygomycota	Moulds	Broad Few septa	Zygospores	Sporangiospores
Ascomycota	Moulds Yeasts	Narrow Regular septa	Ascospores	Conidia*
Basidiomycota	Moulds Yeasts	Narrow Regular septa Clamp connections	Basidiospores	Conidia*
Deuteromycota	Moulds Yeasts	Narrow Regular septa	None	Conidia

* The asexual conidia of the *Ascomycota* and *Basidiomycota* are classified in the *Deuteromycota*.

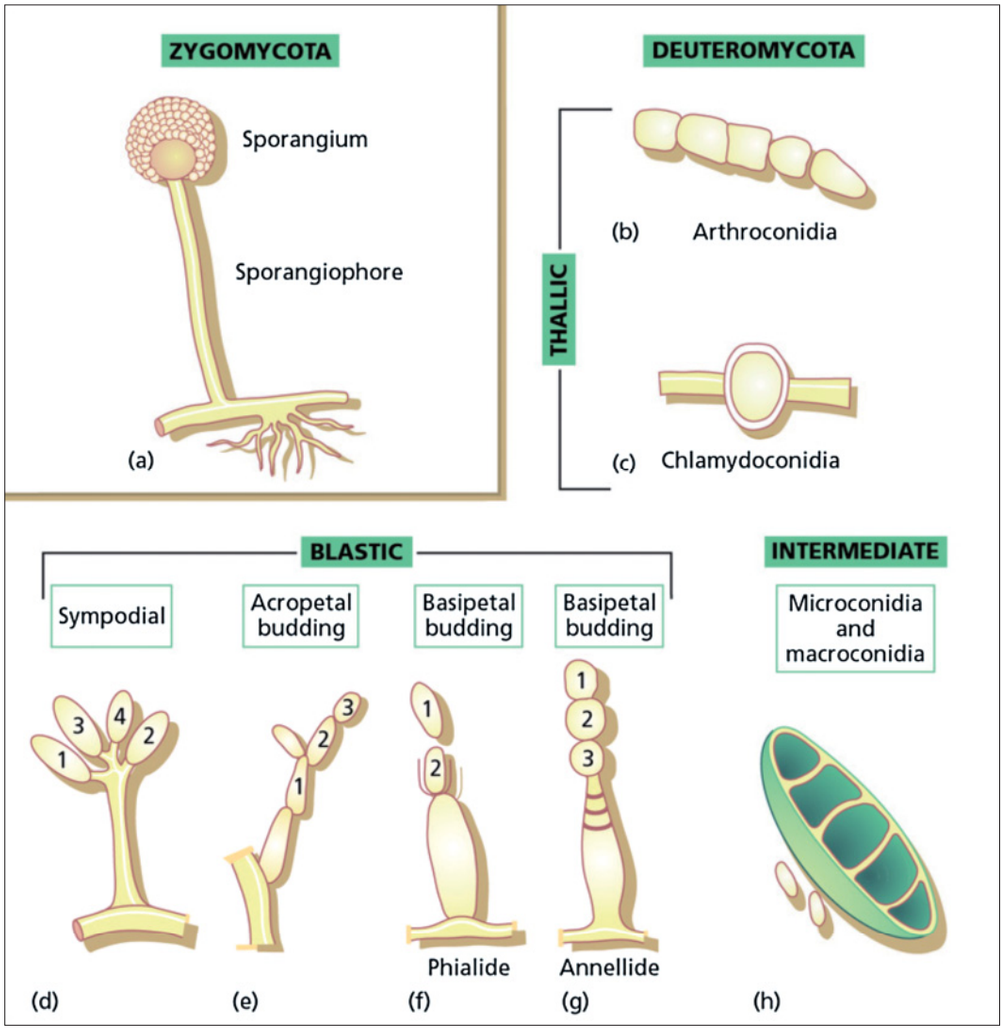


Fig. 36.1 Asexual reproduction in fungi. *Zygomycota*. The most characteristic form of asexual reproduction is the production of sporangia and sporangiospores (a). *Deuteromycota*. Asexual conidia may be formed by two main processes: thallic conidiation results in the production of arthroconidia (b) and chlamydoconidia (c). Blastic conidiation may take several forms, including sympodial conidiogenous cells (d), acropetal budding (e) and basipetal budding from phialides (f) or annellides (g). The conidia of the dermatophytes do not fit in with this thallic–blastic division, but show features of both. They are also examples of fungi that produce two kinds of conidia simultaneously, which differ in size. These are termed microconidia and macroconidia (h).

Zygomycota are very characteristic, being both extremely wide and often sparsely septate. The septa that are formed usually cut off sporing structures and old parts of the mycelium, and are complete, so that damage to any part of the hypha will result in the death of the whole aseptate length. Branching in this group is typically at right angles. Asexual reproduction is usually by means of sporangiospores formed by the cleavage of cytoplasm within a sporangium. This is a sac-like structure, which is supported by a specialized hypha, the sporangiophore (Fig. 36.1a).

The *Ascomycota* contains both moulds and yeasts. Sexual reproduction is by the production of ascospores, formed within a sac-like ascus. These asci may themselves be contained within a specialized fruiting body or ascoma, which may be large enough to be visible to the naked eye. The hyphae of the *Ascomycota* have a lamellate cell wall, with a thin electron-dense outer layer and a thicker electron-transparent inner layer. The hyphae are narrow and regularly septate, but passage of cytoplasm and even nuclei from one cell to the next is made possible by the presence of a pore in the centre of each septum. When hyphae are damaged, however, this septal pore quickly becomes plugged by structures termed Woronin bodies, limiting the damage to those particular cells that were injured. A few of the *Ascomycota* have multiple pores in their septa.

In the *Basidiomycota*, sexual reproduction is by the production of basidiospores formed externally on sterigmata protruding from a club-shaped basidium. Many of this group produce the complex structures we know as mushrooms and toadstools, with gills, covered by basidia, raised above the ground to aid in airborne dispersal of the spores. Others, such as the rusts, smuts and basidiomycetous yeasts, are microscopic. The cell walls of the *Basidiomycota* are lamellate and electron dense. When present, the hyphae are narrow and septate. The septal pore structure in this group is more complex and characteristic, and usually comprises a lip-like extension termed a dolipore, which may be surrounded by perforated membranes called parenthosomes. These allow passage of cytoplasm, but not nuclei, from one cell to the next. In the *Ascomycota* and the *Basidiomycota*, after fusion of hyphal initials of opposite mating type, subsequent fusion of the two nuclei may be delayed, so that for part of the life cycle these cells contain two nuclei of opposite mating type, a state termed dikaryotic. For this

reason, some workers combine these two groups into the *Dikaryomycota*. It is characteristic of the *Basidiomycota* that when a dikaryotic hyphal cell divides, a hook-like structure known as a clamp connection is formed between the two resulting cells as a way of allowing one daughter nucleus of each type to migrate into each cell.

The form-phylum *Deuteromycota* was artificially constructed, as the phylogenetic relationships of many of the asexual fungi contained within it could not at that time be fully determined. The asexual propagules of all the fungi classified in this group were called conidia. Three main divisions were recognized in the *Deuteromycota* and are current in the literature: *Blastomycetes*, which are yeasts reproducing by budding; *Hyphomycetes*, which are moulds bearing the conidia exposed unprotected on the hyphae; and *Coelomycetes*, where the conidiogenous cells that produce the conidia are enclosed in a specialized protective fruiting structure, either a flask-shaped pycnidium or a saucer-shaped acervulus. The majority of fungi isolated in the laboratory are *Hyphomycetes*, and this group may be further subdivided according to colour into fungi that have dark hyphae—dematiaceous fungi—and those that are pale or brightly coloured—moniliaceous fungi. An amazing variety of conidia are formed by these fungi, and their laboratory identification still relies almost entirely on the study of the method of conidial formation or ontogeny and conidial morphology.

Two main methods of conidial production are seen in the *Hyphomycetes*: thallic and blastic (Fig. 36.1). In thallic conidiation, a whole cell or section of a hypha is transformed into the conidium. The most common examples of this are arthroconidia (Fig. 36.1b), when a hypha produces a series of septa, forming a chain of cells that separate at maturity, and chlamydoconidia, which are formed when a single cell becomes thick walled and acts as a storage and survival cell but does not disarticulate at maturity (Fig. 36.1c).

In blastic conidiation, the conidium is formed by 'blowing out' or budding from only a small weakened area of the cell wall of the conidiogenous cell. If both the outer and the inner cell wall are blown out to form the conidial wall the budding is termed holoblastic. If the first conidium ruptures the outer cell wall, and only the inner cell wall is blown out as the conidial wall, the budding is termed enteroblastic. An enormous range of blastic conidia are produced, but certain basic patterns of conidial development may be recognized. Holoblastic conidia include solitary conidia, which may simply be produced by the blowing out of a small part of the hyphal wall, to form a lateral or terminal conidium. In other fungi, more specialized conidiogenous cells are found, and these may produce a succession of holoblastic conidia. Examples of this include those fungi with sympodial conidiogenous cells (Fig. 36.1d), where after the first conidium has been formed, the conidiogenous cell continues to grow and produces a second conidium slightly ahead of and to one side of the base of the first conidium. It then repeats the process, forming a third conidium slightly ahead of and to the opposite side of the second conidium. This eventually results in a zig-zag appearance, with conidia coming off alternately on each side of the fertile cell. Such conidiogenous cells are very characteristic and are termed geniculate.

Many of the fungi with sympodial conidiation have multicellular conidia, either with transverse septa—phragmoconidia—or with both transverse and vertical septa—dictyoconidia.

Chains of holoblastic conidia may be formed by acropetal budding (Fig. 36.1e), where, after the cell has budded, the cells remain attached and a further conidium is produced by the budding of the daughter cell. This continues building up a chain of cells with the youngest at the tip of the chain. The chains may branch.

Enteroblastic chains of conidia with the youngest cell at the bottom of the chain are termed basipetal, and are formed by the repeated blowing out of the inner layer of the cell wall of specialized structures termed phialides and annellides. Phialides are often flask shaped, and may have a pronounced collarette—a flaring ring of wall material surrounding the apex of the cell. The phialoconidia are formed by repeated budding at exactly the same point at the tip of phialide, which does not increase in length during this process (Fig. 36.1f). In contrast, as a series of annelloconidia is formed, the cell apex proliferates slightly as each conidium is produced, leaving a series of ring-like scars at the tip of the cell, and the annellide becomes progressively narrower and longer (Fig. 36.1g). Conidia produced by phialides and annellides may aggregate to form balls rather than chains.

A number of pathogens produce conidia that are not strictly thallic or blastic, and which show a particular method of separation from the hypha. A specialized cell at the base of the conidium breaks, leaving a frill of wall material at the base of the conidium. These conidia are termed aleurioconidia.

Another feature that is seen in several fungal pathogens is polymorphism—the simultaneous production of more than one form of conidium. For instance, in the case of the dermatophytes two types of conidia are formed, which differ greatly in size; in such instances, the larger conidium is termed a macroconidium and the smaller a microconidium (Fig. 36.1h).

References

1 Cole GT, Samson RA. *Patterns of Development in Conidial Fungi*. London: Pitman, 1979.

2 De Hoog GS, Guarro J, Gene J, Figueras MJ. *Atlas of Clinical Fungi*. Centraalbureau voor Schimmelcultures, Universitat Rovira I Virgili, 2000.

3 Campbell CK, Johnson EM, Philpot CM, Warnock DW. *Identification of Pathogenic Fungi*. London: Public Health Laboratory Service, 1996.

4 Kwon-Chung KJ, Bennett JE. *Medical Mycology*. Philadelphia: Lea & Febiger, 1992.

5 Hawkesworth DL, Kirk PM. *Ainsworth and Bisby's Dictionary of the Fungi*, 8th edn. Wallingford: CAB International, 1995.

Nomenclature

Nomenclature is the system whereby the correct names are applied to specific organisms, and is a necessary adjunct to any system of classification. In mycology, as in other sciences, the lack of a uniform approach towards the recognition and description of new species of fungi led to the accumulation of a bewildering number and variety of names in the literature. As an example, *Candida albicans* has been described and redescribed many times since its original description in 1850. A classic taxonomical work [1] lists no fewer than 110 species in 22 genera for this fungus. The need to provide a single name for a single species becomes obvious, particularly when so many synonyms have been proposed for one and the same organism. In order to provide some conformity and stability to the naming of fungi (separate consideration is given to bacterial and zoological nomenclature), a series of principles, rules

and recommendations have been incorporated into an internationally recognized code, whose authoritative guidance has done much to bring order to a state of confusion.

As well as confusion in specific names, disease names have also given rise to controversy. As an increasing number of fungi have been shown to be capable of causing infection, particularly as opportunists in only a limited number of recorded cases, the habit of using the generic name of the fungus to produce a new disease name has become increasingly unwieldy, particularly when fungi are so frequently re-examined and often renamed. Well-established disease names have been retained, but where a new pathogen or pathology is involved the International Society for Human and Animal Mycology [2] recommends that individual mycoses should be named as often as possible in the form 'pathology A caused by pathogen B'. Thus, the use of such terms as fusariosis and trichosporonosis is best discouraged, and replaced by use of 'eumycetoma caused by *Fusarium* species' or 'disseminated mycosis caused by *Trichosporon* species'.

Disease names used throughout this text are based on lists published independently by the Council for the International Organization of the Medical Sciences (CIOMS) [3] and the International Society for Human and Animal Mycology [2].

References

1 Kurtzman CP, Fell JW, Van Rij Kreger NJW, eds. *The Yeasts*, 4th edn. Amsterdam: North Holland, 1998.

2 International Society for Human and Animal Mycology. *J Med Vet Mycol* 1992; **30**: 1–10.

3 *International Nomenclature of Diseases*, Vol. II. 2. *Mycoses*. Council for the International Organization of the Medical Sciences (CIOMS), 1982.

Superficial mycoses

In this section we describe infections of the skin and mucosal surface, superficial mycoses. These are sometimes split into superficial and cutaneous mycoses.

The superficial fungal infections include dermatophytosis, candidosis and a range of non-dermatophyte infections of the skin and nails, such as dermatomycoses caused by *Scytalidium* species and onychomycosis caused by other non-dermatophyte moulds. Some of the fungi causing these infections are present in the environment, but others, such as *Candida albicans* and *Malassezia* spp., have an intimate association with humans and are part of the normal flora of the gut and skin, respectively. Only a few, such as the anthropophilic dermatophytes, have evolved to the point where they have become almost completely reliant on the human host for survival.

Laboratory methods

The laboratory diagnosis of superficial fungal infections relies first on the direct microscopical observation of the pathogen in samples from the affected area. This is usually followed by culture and the specific identification of the fungus. For the laboratory to provide the optimum performance, the quantity and the quality of the material examined is critical. Because for most samples, both culture and microscopic examination will be performed, it is essential that as much clinical material as possible is submitted to the laboratory to allow both diagnostic methods to be carried out.

Collection of material

Skin

Disposable scalpel blades of the solid type held vertically to the skin are used to obtain scrapings. Alternatively, heat-sterilized, blunt, banana-shaped scalpels, which are available from chiropody firms, may be used. Cleaning of the skin with alcohol may be useful if the patient has applied ointment or powder, but is not usually necessary. If the lesion has a definite edge, the material should be taken from the active margin, otherwise a general scraping is adequate. In cases of partially treated pityriasis versicolor, when very little scaling is present, it is possible to take a sample by pressing a strip of sticky tape (Sellotape®) on to the lesion and then on to a drop of mounting fluid on a slide and use this for the direct examination. The method is less suitable for direct examination of samples from the cutaneous mycoses [1]. If it is difficult to obtain sufficient material for culture in cases of dermatophytosis, transport swabs are a good back-up, as is usual with candidosis. When blisters are present, a pair of fine scissors may be used to cut off a blister roof for microscopical examination and culture; such samples are often packed with hyphae.

The scrapings should be collected and transported in folded paper, which keeps the specimen dry, thus preventing overgrowth of bacterial contaminants. Plastic containers are unsuitable, as the skin adheres to the sides and is difficult to remove. The use of glass slides, which then have to be transported to the laboratory, is hazardous as they are frequently broken. Squares of brightly coloured paper card are ideal; these may then be carefully folded and secured by a paper clip. The details of the patient, exact site of the lesion, and time of sampling, animal contact or recent travel should then be clearly recorded. Specially designed commercial transport packs for hair, skin and nail samples are available from several sources. Dermatophytes in skin scrapings may remain viable for months, and yeasts for several weeks.

Hairs

Hairs to be examined for the presence of black or white piedra may be simply cut off at skin level. If dermatophytosis is suspected, the hairs should be removed with the roots intact; cut hairs are unsuitable. In many instances, the affected hairs may be recognized because they are dull and broken but, if not, the fact that they slip out easily with fine forceps may also help in selecting the right material. This is particularly useful in examining scalp or beard kerions caused by *Trichophyton verrucosum*, where relatively little fungus may provoke a severe reaction, and it may be necessary to test many hairs before an infected hair is found. In those instances where the hairs break off very short, as in black-dot infections, a scalp scraping will yield the best material, with the infected roots appearing as tiny stumps among the skin scales. It should be noted that in cases of steroid-treated tinea corporis or tinea incognito the examination of vellus hairs may be the easiest method of diagnosis as, although fungi such as *T. rubrum* rarely invade the hair shaft, they may colonize the hair follicle.

In addition to collecting scales and hairs, brush samples are an excellent method for the culture of scalp infections, and may also

be useful in testing suspected animal sources of infection [2–4]; however, microscopy cannot be performed on them. A sterile plastic scalp massager or disposable toothbrush is brushed firmly through the hair at least 10 times, and is then pressed against the culture medium in a 90-mm Petri dish. This simple technique is an extremely sensitive culture method, and is invaluable when screening large numbers of children. Several hundred children may be examined in a day by performing a Wood's light examination and taking a brush sample from each child, which can then be taken back to the laboratory for culture. Cultures from infected children produce a fungal colony from many of the inoculation points; contacts of infected children usually yield only a few colonies. In cases of kerion, when brush sampling may be unsuitable and painful, a transport swab wiped over the lesion will usually pick up enough conidia to give a positive culture.

Wood's light examination. The recognition that hair infected by certain dermatophytes produces a characteristic fluorescence in ultraviolet (UV) light filtered by Wood's glass was an important advance in medical mycology. Wood's glass, which consists of barium silicate containing about 9% nickel oxide, transmits rays of wavelength above 365 nm. Most sources of UV light are suitable. The nature and source of the fluorescent substances in infected hairs are not fully understood, but tryptophan metabolites produced by dermatophytes may be involved [5]. The hair remains fluorescent after the fungus has ceased to be viable, and the fluorescent material can be extracted from the hair in hot water [6,7] or in a cold solution of sodium bromide [5]. The colour of the fluorescence is influenced by the pH of the solution [6]. Because fungi growing in culture or on hair *in vitro* do not fluoresce in this way, the phenomenon must be attributed to some substance produced by the interaction of the fungus and the growing hair. Its chemical nature has not been defined, and the suggestion that it may be a pteridine has been challenged [7–10].

Only some of the dermatophytes capable of invading hair will induce fluorescence, but these include members of the genus *Microsporum* (e.g. *M. audouinii* and *M. canis*), which are common in a number of densely populated parts of the world. Hairs infected by these species produce a brilliant green fluorescence, easily recognized in a darkened room. Only the fully invaded portions of the shaft develop this property. In recent infections or at the spreading margin of early lesions, the fluorescent part of the hair may not yet have emerged from the follicle, and can be detected only after the hair is plucked. Among other *Microsporum* species and variants, only *M. canis* var. *distortum* and *M. ferrugineum* regularly induce fluorescence, and *M. gypseum* and *M. nanum* occasionally do so. *Trichophyton schoenleinii* causes a paler green fluorescence of infected hair. In favus, the fluorescent hairs tend to be long, in contrast to the short, broken stumps characteristic of *Microsporum* infections.

In areas where *Microsporum* infections are prevalent, the Wood's light is an essential tool in the diagnosis and treatment of the individual patient, and in the control of epidemics. The lamp is easily transportable and can be taken to schools or institutions for the rapid examination of contacts. The most common sources of error are the bluish or purplish fluorescence produced by ointments containing petrolatum, scales, serum, exudates, an insufficiently darkened room, light reflected from the examiner's white coat and the failure to remember that not all fungi cause fluorescence. Correctly performed and interpreted, the test is virtually specific, but absence of fluorescence in some infections with *M. audouinii* and *M. canis* has been reported [11]. The lamp can be used in the detection of subclinical infection, and to assess response to treatment or spontaneous cure. The Wood's lamp is also of value in the diagnosis of pityriasis versicolor, where the scales fluoresce yellow in some cases. A similar yellow fluorescence, presumably because of the presence of yeasts of *Malassezia* species, may be seen in some cases of severe dandruff, in cradle cap in infants and in the follicular orifices of the face and upper trunk in normal subjects.

Nail

The diagnosis of onychomycosis is complicated by the fact that the isolation of the pathogen in culture from nail material is more difficult to achieve than for skin and hair samples. In the majority of nail infections, the material for examination is taken from the distal end of the nail, despite the fact that the infection is advancing proximally. The hyphae at the distal end of the nail are less likely to be viable [12]. Unfortunately, it is usually not practicable to take deep samples from the proximal advancing edge with minimum discomfort to the patient. The full thickness of the nail should be sampled, as most infections start in the hyponychium. Debris from under the nail is a fruitful source of material, which may be scraped out using the flat end of a dental probe. Superficial scrapings are inadequate, except in cases of superficial white onychomycosis or proximal subungual onychomycosis.

In cases of paronychia, the nail fold may be moistened with saline using a wet swab, and the flat end of a dental probe may be gently pushed into the fold to withdraw material for direct examination and culture. After this, a swab should also be taken for culture.

As the isolation of fungi from nail material is difficult, samples should also be taken from any skin lesions that may be present, as these are very likely to be invaded by the same pathogen as the nail, and cultures are more likely to be positive. It is essential when submitting nail material to the laboratory to specify whether the sample is a fingernail or toenail, as some pathogens are more prevalent in one than the other.

Mucous membranes

The mouth or vagina may be sampled using a blunt scalpel or by using swabs. If the specimen is not to be examined immediately, swabs with transport medium are preferable, as yeasts rapidly die in dry conditions. However, delays in processing of transport medium swabs will allow multiplication of yeasts in the samples.

Ear

Scrapings from the external ear canal may be supplemented with swab samples.

References

1 Milne LJR, Barnetson RStC. Diagnosis of dermatophytoses using vinyl adhesive tape. *Sabouraudia* 1974; **12**: 162–5.

2 Ive FA. The carrier stage of tinea capitis in Nigeria. *Br J Dermatol* 1966; **78**: 219–21.

3 MacKenzie DWR. Hairbrush diagnosis in detection and eradication of non-fluorescent scalp ringworm. *BMJ* 1963; **ii**: 363–5.
4 Friedlander SF, Pickering B, Cunninham BB *et al*. Use of the cotton swab method in diagnosing tinea capitis. *Pediatrics* 1999; **104**: 276–9.
5 Rebell G, Taplin D. Dermatophytes—their recognition and identification. University of Miami Press, 2nd edn, 1974.
6 Davidson AM, Gregory PH. Note on an investigation into the fluorescence of hairs infected by certain fungi. *Can J Res* 1932; **7**: 378–85.
7 Wolf FT. Chemical nature of the fluorescent pigment produced in *Microsporum*-infected hair. *Nature* 1957; **4591**: 860–1.
8 Felsher Z. Observations on the fluorescent material in hairs infected by *Microsporon* in tinea capitis. *J Invest Dermatol* 1949; **12**: 139–44.
9 Chattaway FW, Barlow AJE. The fluorescent material produced *in vivo* by certain dermatophytes. *J Gen Microbiol* 1954; **11**: 506–11.
10 Chattaway FW, Barlow AJE. Fluorescent substances produced by dermatophytes. *Nature* 1958; **181**: 281.
11 Beare JM, Walker J. Non-fluorescent *Microsporum audouinii* and *canis* infections of the scalp. *Br J Dermatol* 1955; **67**: 101–4.
12 Gentles JC. Laboratory investigations of dermatophyte infections of nails. *Sabouraudia* 1971; **9**: 149–52.

Direct examination

For routine examination, specimens are usually mounted in 10–30% potassium hydroxide; the higher the percentage, the faster the specimen will clear. For skin scrapings and nails, warming gently over the pilot light of a Bunsen burner will speed up the process, but boiling should be avoided, if possible, as this tends to encourage the formation of artefacts, which may confuse the inexperienced observer. It is impossible to soften skin and nail samples too much, for the thinner the specimen, the easier it will be to observe the fungal elements. The cover slip should be pressed down firmly to obtain a monolayer of cells before microscopic observation. Excess potassium hydroxide will etch microscope lenses, so it must be removed by blotting with small squares of filter paper or tissue. A few minutes spent carefully preparing the specimen in this way are well spent. Nail specimens take longer to clear than skin, but if small pieces and debris are taken, they will usually soften within 10 min. In those instances where the nails do not soften satisfactorily, the slide may be put in a 37°C incubator for 1 h, and the material can then be flattened. In contrast to skin and nail samples, infected hairs are very delicate, and if heated or left in mounting fluid for more than a few minutes tend to disintegrate, obscuring the characteristic arrangement of the arthroconidia. They should therefore be examined as soon as possible after mounting. If examining specimens using bright-field illumination, the lighting is critical; overillumination, particularly when scanning the slide under low power (×10), will render the fungal elements invisible. The light should therefore be low initially and then raised when the presence of fungus is confirmed by examination with a higher power lens (×20 or ×40). An alternative clearing agent, which does not require warming of the specimen, is 10% sodium sulphide solution [1,2].

With experience, bright-field examination of specimens cleared in this way is quick and relatively straightforward. However, several authors have recommended a variety of techniques to make observation of the fungal elements easier. Phase-contrast and dark-field microscopy can produce good results [3], but do require that the specimen be really thin, and thus may need a longer period of softening of the material than bright-field microscopy. The addition of 35% dimethylsulphoxide to the potassium hydroxide may speed up softening, but overdigestion is then a problem, and the specimens should be examined within 1–2 h. Dimethylacetamide or dimethylformamide have been suggested as alternatives [4]. Several stains such as Congo red, methylene blue and cotton blue have been recommended to enhance the contrast between fungus and skin, but again these require a fully softened specimen. One stain that has been extremely useful is Parker's stain, made by the mixing of equal volumes of potassium hydroxide and Parker's blue–black Quink permanent fountain pen ink [5]. Unfortunately, the manufacturers have now changed the formulation of the ink and the new product no longer stains hyphae; when current stocks are finished this stain will become unavailable.

Fluorescence microscopy using either acridine orange [6] or a fluorescent brightener such as Calcofluor white or Blankophor [1,2], which specifically stain polysaccharides in the fungal cell wall, is becoming increasingly popular. Comparative studies of different methods used in direct examination [2,7–9] concluded that most of the recommended staining procedures for direct microscopic examination were no better than the classic potassium hydroxide method, but that if a fluorescence microscope is available, the use of fluorescent brighteners does give superior results. A more recent study [10] concluded that fluorescence microscopy using Blancophor P flussig in sodium sulphide solution was quicker, and produced significantly fewer direct microscopy negative samples, which subsequently yielded fungus on culture, than bright-field microscopy using sodium sulphide solution alone. In the authors' experience the fluorescent technique is superior to bright-field microscopy and strongly recommended, particularly for nail samples.

Whatever method is used, the ability to find fungi on direct examination of samples is largely a matter of practice. The beginner may well be confused initially by the common artefacts that may be present, such as mosaic fungus—cholesterol-forming polygonal deposits around cells—air bubbles, fibres and crystals, but with practice it becomes progressively easier to find the fungi and distinguish the various infections.

Several workers advocate the histopathological processing of nail material and staining with a fungus-specific stain such as periodic acid–Schiff (PAS) as a routine measure [7]. It has been suggested that this not only confirms that the nail plate is actually invaded, but also reduces the number of false-negative direct reports, where fungus is cultured from a microscopically negative nail. Although histological processing of samples has been shown to yield a higher rate of positivity than culture, the rates were similar to those obtained with potassium hydroxide microscopy [9,10] and, as the facilities for histopathological processing may not be available in a small laboratory, routine microscopy using a fluorescent technique is still the method of choice.

Culture (Table 36.2)

For some of the superficial mycoses, the appearance of the fungal elements observed on direct examination is so characteristic that culture is not strictly necessary for diagnosis of the infection. This is certainly true of pityriasis versicolor and, to a lesser degree, black piedra, white piedra and tinea nigra. For otomycosis, in contrast, culture is essential, as the range of organisms that can

Table 36.2 Cultural conditions for isolation of superficial and cutaneous pathogens.

Disease	Causative organisms	Media		Antibiotics		Temperature		Maximum length incubation (days)
		GP	MEA	Cyc	Chlor	26–28°	37°	
Black piedra	*Piedrai hortae*	+	+	+	+	+		28
White piedra	*Trichosporon* spp.	+	+	–	+	+		14
Tinea nigra	*Phaeoannellomyces werneckii*	+	+	–	+	+		21
Dermatophytosis	*Trichophyton* spp. *Microsporum* spp. *Epidermophyton* spp.	+	+	+	+	+		21–28
Dermatomycoses caused by *Scytalidium* spp.	*Scytalidium dimidiatum* *Scytalidium hyalinum*	+		–	+	+		21
Onychomycosis caused by non-dermatophyte moulds	*Scopulariopsis* spp. *Acremonium* spp. *Fusarium* spp., etc.	+	+	–	+	+		21
Candidosis	*Candida* spp.	+	+	–	+	+	+	7
Otomycosis	*Aspergillus* spp. *Candida* spp., etc.	+	+	–	+	+	+	21

Chlor, chloramphenicol 0.05 g/L; Cyc, cycloheximide 0.4 g/L; GP, glucose–peptone agar; MEA, malt extract agar; + recommended; – not recommended.

cause infection is enormous, and the specific identification of the pathogen will have a profound effect on the therapy selected. Similarly, differences in the response of the different pathogenic yeasts to some of antifungals, such as fluconazole, necessitates identification down to species level, at least in patients on long-term treatment. The situation with dermatophyte infections is rather different because, although on direct examination of skin and nail samples the different species are indistinguishable, generally all the dermatophyte species have been believed to respond similarly to the major systemic and topical antifungals available, and treatment has been initiated on the basis of the direct examination. However, this may not be true with some of the more recent antifungals developed. In addition, culture will provide valuable information on the possible source of infection and the likelihood of spread of the disease. Culture of specimens with negative direct microscopical results is also desirable, as it will allow the detection of the small percentage of cases where prolonged therapy, or a very inflammatory host reaction, may make the microscopical detection of the fungus in the skin difficult. The non-dermatophytic moulds capable of infecting skin or nail, such as *Scytalidium* species and *Scopulariopsis brevicaulis*, can be diagnosed on the basis of direct microscopy, but this requires considerable expertise, and in addition mixed infections with dermatophytes do occur, so that it is advisable to always perform cultures in these cases.

Fungi grow readily on simple media containing glucose and preferably an organic nitrogen source; they are not particularly fastidious. The primary culture medium used therefore is largely a matter of personal choice. Many laboratories will select a simple glucose/peptone agar, either with 4% sugar, 1% peptone and an acid pH (Sabouraud's dextrose agar) or with 2% sugar, 1% peptone and a neutral pH (Emmon's modification). Antibacterial antibiotics such as gentamycin (0.0025%) and/or chloramphenicol (0.005%) may be added to reduce contamination and, if a dermatophyte infection has been diagnosed, the addition of cycloheximide at 0.04% will inhibit the growth of non-dermatophyte moulds. This antibiotic must be excluded, however, if infection by a non-dermatophyte mould such as *Scytalidium* or candidosis is suspected as, although *C. albicans* is not affected, many of the less common species of *Candida* found, particularly in nail and mucous membrane sites, will be inhibited. For sites where non-dermatophyte moulds such as *Scytalidium dimidiatum* may be significant—palms, soles, toe webs and nails—it is simplest to perform duplicate cultures on media with and without cycloheximide. Sabouraud's dextrose agar is available from a number of different commercial sources. It should be noted, however, that variations in the different makes, particularly the type of peptone included, will affect the overall morphology of the isolates, and cause differences in pigmentation and texture of the fungal colonies, particularly of dermatophytes. It is easiest therefore to become familiar with the morphology of these pathogens on one brand only. One should also note carefully which formulations have cycloheximide and/or chloramphenicol already incorporated (e.g. Mycosel® and Mycobiotic® agars) and which require their addition. Another medium that is frequently used for primary culture is 3–4% malt extract agar, which is also commercially available.

As incubation is much longer than for bacterial cultures, the medium should be poured relatively thickly to prevent drying out; 30 mL/90-mm Petri dish is adequate. The majority of laboratories now perform their cultures in disposable plastic Petri dishes, but if screw-capped glass bottles or tubes are used, the tops must be left slightly loose to provide adequate aeration. For moulds, the temperature of incubation should be 26–28°C and cultures should be held for a maximum of 3–4 weeks, although routinely 2 weeks is used. For *Candida* species, the temperature of incubation should be 37°C, and plates may be discarded after 48 hours. As some *Trichosporon* species will not grow at 37°C, incubation should be at 26–28°C for up to 2 weeks.

References

1 Baudraz-Rosselet F, Monod M, Porchet S, Frenk E *et al.* Retrospective study on the efficacy of two methods of microscopical examination in dermatological mycology. *J Mycol Med* 1992; **2**: 148–50.
2 Monod M, Baudraz-Rosselet F, Ramelet AA *et al*. Direct mycological examination in dermatology: a comparison of different methods. *Dermatologica* 1989; **179**: 183–6.
3 Milne LJR. Direct microscopy. In: Evans EGV, Richardson MD, eds. *Medical Mycology: a Practical Approach*. Oxford: IRL Press, 1989: 17–45.
4 Kejda J. Die Anwendung von Dimethylacetamid (DMAC) und Dimethylformamid (DMFA) zur schnelleren mikroskopischen Diagnostik der Dermatophytosen. *Hautarzt* 1967; **18**: 545–6.
5 Cohen MM. A simple procedure for staining tinea versicolor (*M. furfur*) with fountain pen ink. *J Invest Dermatol* 1954; **22**: 9–10.
6 Chick EW, Behar VS. A simple fluorescent method for the detection of superficial fungi in skin and hair: a combined stain with acridine orange and potassium hydroxide. *J Invest Dermatol* 1961; **37**: 103–6.
7 Suarez MD, Silvers DN, Scher RK *et al*. Histologic evaluation of nail clippings in diagnosing onychomycosis. *Arch Dermatol* 1991; **127**: 1517–9.
8 Haldane DJM, Robart E. A comparison of calcofluor white, potassium hydroxide, and culture for the laboratory diagnosis of superficial fungal infection. *Diagn Microbiol Infect Dis* 1990; **13**: 337–9.
9 Hsiao YP, Lin HS, Wu TW *et al.* A comparative study of KOH test, PAS staining and fungal culture in diagnosis of onychomycosis in Taiwan. *J Dermatol Sci* 2007; **45**: 138–40.
10 Karimzadegan-Nia M, Mir-Amin-Mohammadi A, Bouzari N *et al*. Comparison of direct smear, culture and histology for the diagnosis of onychomycosis. *Aust J Dermatol* 2007; **48**: 18–21.

Molecular diagnostics

Increasingly, there has been an interest in diagnosing mycoses without the use of either classical microscopic examination or culture of samples, but by using molecular techniques. In the mid 1990s several groups reported the use of molecular techniques, including polymerase chain reaction analysis (PCR), for the identification and classification of dermatophytes after culture [1–4], but more recently methods have been developed for the primary diagnosis of dermatophytosis [5–7]. Molecular methods for primary diagnosis initially had limited success rates with only 30–40% of culture-positive samples being positive [5], but more recent studies have demonstrated sensitivity rates of 84% [6], with the added bonus that identification of the dermatophyte is performed concurrently. The time to diagnosis is substantially reduced in the absence of culture and is now achievable in 48 h [6]. For *Malassezia*-associated conditions, identification can also be performed direct from skin scales, without culture [8], however as speciation of *Malassezia* is not usually performed in routine laboratories, the relevance of this technique is likely to be limited. As the cost of performing molecular analysis comes down, routine diagnosis of dermatophytosis with molecular methods may become a reality, but only in laboratories with sufficient throughput of samples and staff with the necessary training.

References

1 Bock M, Maiwald M, Kappe R *et al*. Polymerase chain reaction based detection of dermatophyte DNA with fungus-specific primer system. *Mycoses* 1994; **37**: 79–84.
2 Mochizuki T, Uehara M, Menon T, Ranganathan S. Minipreparation of total cellular DNA is useful as an alternative molecular marker of mitochondrial DNA for the identification of *Trichophyton mentagrophytes* and *T. rubrum*. *Mycoses* 1996; **39**: 31–5.
3 Liu D, Coloe S, Baird R, Pedersen J. Molecular determination of dermatophyte fungi using the arbitrarily primed polymerase chain reaction. *Brit J Dermatol* 1997; **137**: 351–5.
4 Sommer S, Barton RC, Wilkinson SM *et al*. Microbiological and molecular diagnosis of deep localized cutaneous infection with *Trichophyton mentagrophytes*. *Brit J Dermatol* 1999; **141**: 323–5.
5 El Fari M, Tietz HJ, Presber W *et al*. Development of an oligonucleotide probe specific for *Trichophyton rubrum*. *Br J Dermatol* 1999; **141**: 240–5.
6 Kardjeva V, Summerbell R, Kantardjiev T *et al.* Fourty eight hour diagnosis of onychomycosis with subtyping of strains of *Trichophyton rubrum* strains. *J Clin Microbiol* 2006; **44**: 1419–27.
7 Sugita T, Shiraki Y, Hiruma M. Real-time PCR TaqMan assay for detecting *Trichophyton tonsurans*, a causative agent of tinea capitis, from hairbrushes. *Med Mycol* 2006; **44**: 579–81.
8 Gaitanis G, Velegraki A, Frangoulis E *et al.* Identification of *Malassezia* species from patient skin scales by PCR-RFLP. *Clin Microbiol Infect* 2002; **8**: 162–73.

Identification of isolates

Yeasts

The identification of yeasts requires morphological data together with physiological and biochemical investigations. Examination of the yeast colony should include recording of colour and texture. Microscopic features of note may include the size and shape of the budding cells (blastoconidia), and the presence of pseudohyphae, true hyphae, capsules, arthroconidia and ascospores. In the case of *C. albicans*, the formation of terminal vesicles (chlamydospores) on cornmeal or rice agar supplemented with Tween 80, or the production of germ tubes after incubation in serum at 37°C for 2–3 h, allows specific identification. For speciation of other pathogenic yeasts, physiological tests must be performed. An increasing number of commercially produced yeast identification kits are available and widely used, including the API 32C® (bioMerieux) and the Auxacolor 2® (Sanofi Diagnostic Pasteur). Primary isolation media that allow the specific identification of certain species to be made by the production of a characteristic colour are also now available. On Albicans ID® medium (bioMerieux), *C. albicans* colonies develop a blue colour; on Chromagar® (Becton and Dickinson) *C. tropicalis*, *C. krusei* and *C. albicans* produce blue, pink and green coloured colonies, respectively. These media facilitate the detection of mixed infections, which has become increasingly important because of the relative insensitivity of certain *Candida* species to some of the currently available antifungal drugs, but should not be used as the sole method of identification of yeast species.

Moulds

The identification of moulds relies almost entirely on examination of the colonial and microscopical morphology. Examination of the fungal colonies should include noting the colour of the surface and reverse of the culture, and the presence of any pigment diffusing into the medium. The texture of the surface of the colony is also important, and terms such as downy, powdery, granular and glabrous are widely used (see Glossary, p. 36.93). Hyphae that project above the surface of the agar—aerial hyphae—and growth completely submerged in the medium may also be characteristic. Folding may take very characteristic forms, either radial, circular or cerebriform (see Glossary, p. 36.93).

Microscopic features to note include the shape and size of the conidia, their colour, septation and the presence of wall thickenings or other ornamentation. The arrangement of the conidia on the conidiogenous cell and the type of conidiation is of critical importance. Such microscopic features may be observed using a

needle mount, a sticky tape strip or a slide culture. The simplest method is a needle mount, when a portion of the growth is removed with a stiff wire needle, and teased out in a drop of a suitable stain, such as lactophenol cotton blue. A cover slip is applied and the sample examined microscopically. The disadvantage of this method is that, as it entails relatively rough handling of the material, it is inevitable that many of the conidia will become detached from the hyphae. A method that will retain more of the conidia in position is to apply a piece of sticky tape, sticky surface down, onto the surface of the colony, and then mount this in a drop of stain and examine the preparation directly through the back of the tape. The sticky tape strip is extremely useful for the examination of colonies with many conidia. The most successful but time-consuming method for examining the details of conidial structure and formation, however, is the slide culture [1]. In this method, the fungus is inoculated onto the four sides of a square of agar, sandwiched between a glass slide and cover slip, and maintained in a sterile Petri dish with a moist atmosphere. The fungus grows out from the agar block directly onto the glass of the cover slip and slide, which may be used to prepare two undisturbed mounts of the growing fungus. When sealed with nail polish, these form permanent preparations.

Reference

1 Riddell R. Permanent stained mycological preparations obtained by slide culture. *Mycologia* 1950; **42**: 265–70.

Pityriasis versicolor

Synonyms
- Tinea versicolor
- Dermatomycosis furfuracea
- Tinea flavea
- Liver spots
- Chromophytosis

Definition. A mild, chronic infection of the skin caused by *Malassezia* yeasts, and characterized by discrete or confluent, scaly, discoloured or depigmented areas, mainly on the upper trunk.

Aetiology. The normal flora of the skin includes a number of morphologically distinct lipophilic yeasts. It was thought that a single polymorphic yeast, *Pityrosporum ovale*, or two species, *P. ovale* and *P. orbiculare*, were present, but it is now recognized that this genus name was invalid, and these yeasts were reclassified in the genus *Malassezia* as a single species, *M. furfur*. However, genetic analysis has now demonstrated that the situation is far more complex, and at least 12 separate species of lipophilic yeasts have been described, of which eight occur relatively commonly on the human skin. The lipid-dependent species currently included within the genus are *M. sympodialis*, *M. globosa*, *M. restricta*, *M. slooffiae*, *M. furfur*, *M. obtusa* [1] and the recently described *M. dermatis* [2], *M. japonica* [3], *M. yamotoensis* [4], *M. nana* [5], *M. caprae* and *M. equina* [6]. One lipophilic but not totally lipid-dependent species, *M. pachydermatis*, is more often found on animal skin. The isolates previously known as *M. furfur* therefore probably include a complex of species. Colonization by these species is especially dense in the scalp, the upper trunk and flexures, areas rich in sebaceous glands and their secretions. Various studies have examined the distribution of the different species in normal skin from various sites and in lesional skin in various *Malassezia*-associated dermatoses. Some have included direct microscopical observation or counting of yeasts, some rely on cultures alone. However, as different workers have used different sampling techniques, few of them quantitative, and different culture media, the studies are not directly comparable. Some authors have found that *M. globosa* is most frequently associated with pityriasis versicolor [7], but others have found *M. sympodialis* [8,9] and *M. furfur* [10] as the predominant species, and *M. sympodialis* is found most commonly on normal skin [11]. Microscopy of the scales of pityriasis versicolor nearly always reveals thick-walled, spherical yeast forms budding from a narrow base—compatible with *M. globosa*—and coarse septate mycelium often broken up into short filaments. In some instances, however, more commonly in tropical zones [12–14], mycelium is observed together with oval yeasts budding from a broad base, a morphology more suggestive of *M. furfur* or *M. obtusa* [11]. Initially it was found impossible to demonstrate the mycelial phase of *Malassezia* species *in vitro*, but in 1977 three groups succeeded in showing interconversion of the yeast and mycelial forms, using a variety of substances [15–17].

Pityriasis versicolor in most cases represents a shift in the relationship between a human and his or her resident yeast flora. Factors contributing to the change are probably multiple. It is known that some *Malassezia* species more readily become mycelial, and have perhaps a slightly greater pathogenic potential. A positive family history among blood relations is found more often than chance would suggest in pityriasis versicolor, but whether this is caused by a genetically determined host susceptibility factor, or the greater opportunity for heavy colonization by *Malassezia* species, is at present unknown. Conjugal cases also occur, and it is possible that in some instances infection does not arise from the individual's own autochthonous flora but by transmission from another individual [18].

The factors predisposing to the development of pityriasis versicolor are varied, but most attention has been devoted to environmental factors and individual host susceptibility. In a warm climate there are more hyphae associated with *Malassezia* yeasts in normal skin. The sexes are probably equally prone to this condition, but there are certainly differences in susceptibility at different ages [19,20]. In temperate zones, the condition is rare in childhood but becomes more common in the late teens, with a peak in the early twenties. Infections in old age are rare. In tropical climates, the condition is more common than in temperate zones, and as many as 40% of some populations may be affected [21]. Although no reliable figures are available for colder climates, the prevalence is almost certainly less than 1%. In temperate zones, among patients who can give a reliable history, the onset is more often in the warmer months of the year [20]. Pityriasis versicolor has been claimed to be more common in various disease states, but only in Cushing's syndrome, spontaneous and iatrogenic [22], and possibly in malnutrition are these suggestions reliably supported by evidence. Pregnancy and oral contraceptives may have some influence in increasing susceptibility, but firm data are lacking. Pityriasis versicolor does not appear to be more common in

acquired immune deficiency syndrome (AIDS) patients [23]. There have been many attempts to explain susceptibility in terms of physical and biochemical abnormalities, but a variety of differing and conflicting results leaves the problem unresolved. Application of oils to the skin may increase susceptibility but is not proven.

There is ample evidence of an antibody response to *Malassezia* species in subjects without pityriasis versicolor. There have been many studies on humoral response to *Malassezia* species in patients with pityriasis versicolor and controls but, prior to the recognition of the new species, antigens used were probably made from a number of different species, making the often conflicting results difficult to interpret. Similarly, studies of cell-mediated responses have also produced conflicting results with a wide range of antigens [24,25]. One interesting new approach has been to use mycelial-phase antigens and this has shown significantly greater lymphocyte transformation responses in pityriasis versicolor patients compared to controls [26]. The initial view that patients with pityriasis versicolor have a cell-mediated deficiency specific to *Malassezia* species or depletion of specifically reactive T cells from the blood has been questioned [25]. Reviews of the immunology of diseases associated with *Malassezia* species are recommended to those interested in these aspects [27,28]. T-cell inhibition by a lipid component of the *Malassezia* cell wall has recently been reported [29].

Malassezia species do not attack the hair shaft, nails or mucous membranes, but there are many reports of pulmonary and systemic infections in infants on long-term intravenous lipid therapy caused by *Malassezia* [28].

Histology and pathogenesis. In those patients who do produce a cellular response, hyperkeratosis, parakeratosis and slight acanthosis, with a mild inflammatory infiltrate in the upper dermis, are the characteristic histological changes. Immunophenotyping of the infiltrates has revealed a dominance of memory T cells, an accumulation of macrophages and a lack of B cells [30]. A marked accumulation of Langerhans' cells in the epidermis, reduced expression of cellular activation markers and the presence of suppressor T cells were also demonstrated. The infecting organism is usually present in the upper layers of the stratum corneum, and on electron microscopy may be seen to invade not only between but within the keratinized cells. Corneocyte counts have demonstrated an increased cell turnover in affected skin. There have been several mechanisms postulated for the alterations in pigmentation, including the production of dicarboxylic acids produced by *Malassezia* species (e.g. azaleic acid) which cause competitive inhibition of tyrosinase and perhaps a direct cytotoxic effect on hyperactive melanocytes [31]. However, such acids had no effect on normal melanocytes in tissue culture. The explanation for the hyperpigmentation seen in fair-skinned subjects remains obscure, although electron microscopy reveals abnormally large melanosomes in hyperpigmented lesions, and smaller-than-normal melanosomes in hypopigmented ones [32,33]. It has been noted that total epidermal pigmentation is reduced in hypopigmented lesions; a thicker keratin layer in hyperpigmented lesions may be significant [34].

Clinical features [11,14,18]. The patient usually complains only of a patchy and varying change of skin colour, but mild irritation is sometimes noticed. The primary lesion is a sharply demarcated macule, sometimes slightly erythematous, but characterized essentially by fine, branny scaling (Fig. 36.2). Typically, the eruption shows large confluent areas, scattered oval patches and outlying macules. Where scaling is minimal, it may be emphasized by firm scraping or stretching of the skin, but a sticky tape strip is a better alternative. The site most commonly affected is the upper trunk, but there is often spread to the upper arms, the neck and the abdomen. Lesions in the axillae and groins, and on the thighs and genitalia occur, and extension down the forearms on to the backs of the hands, and into the popliteal fossae is by no means rare; this is often associated with oval yeast forms in direct microscopy. Facial and scalp involvement are well recognized in the tropics, and occasional cases in which only these areas are affected are seen. Palmar lesions have been reported from the tropics, and rarely occur in temperate zones. A few unusual cases have been described where the disorder appears to have been localized by occlusion or pressure, as under the straps of a rucksack.

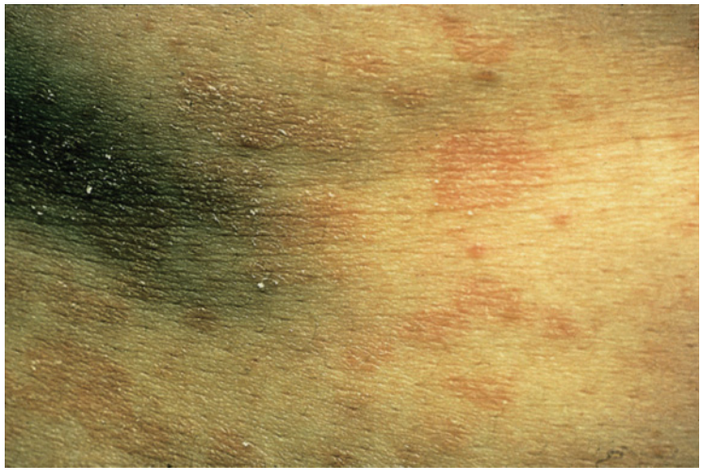


Fig. 36.2 Pityriasis versicolor.

The term versicolor is particularly apt. The colour of the scales may vary from pale ochre to medium brown. In the untanned white skin, the affected areas are darker than normal, but they fail to respond to light exposure; in the suntanned subject, the abnormal skin is commonly paler, as it usually is in black people. In ordinary cases that settle spontaneously or as a result of treatment, the residual depigmentation may remain for many months without any scaling. Under the Wood's lamp, the scaly lesions may show pale yellow fluorescence, and unsuspected macular lesions more widely scattered are often revealed by this technique.

Differential diagnosis. Vitiligo and chloasma are normally distinguishable by their complete absence of scaling. Seborrhoeic dermatitis, pityriasis rosea, secondary syphilis, pinta and tinea corporis show more inflammatory change than pityriasis versicolor, and none of these ever has the even, fine scale of the latter condition. Erythrasma may closely mimic pityriasis versicolor with pigmentary change and scaling, but satellite lesions are less common, and pink fluorescence under the Wood's lamp is often present. Erythrasma and pityriasis versicolor may occasionally coexist.

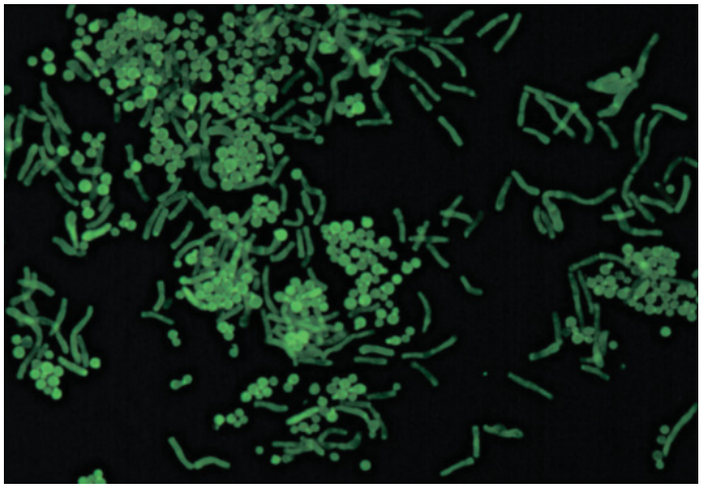


Fig. 36.3 Pityriasis versicolor. Skin scales mounted in KOH and calcofluor white, ultraviolet (UV) illumination. The hyphae diagnostic of the condition have taken up the stain immediately. *Malassezia* yeasts are also present. (Courtesy of the Department of Medical Mycology, St John's Institute of Dermatology, King's College London, London, UK.)

Laboratory diagnosis. The finding on direct examination of coarse mycelium, fragmented to short filaments 2–5 µm wide and up to 25 µm long, together with spherical, thick-walled yeasts 2–8 µm in diameter confirms the presence of the condition (Fig. 36.3). Occasionally, oval yeasts may be seen. However, it is the mycelium that is the diagnostic feature, and sometimes this predominates to the extent that there are few yeast forms. The characteristic appearance on microscopy has been likened to 'spaghetti and meatballs' or 'bananas and grapes'. As they are members of the normal flora, isolation of *Malassezia* species from scrapings is of no diagnostic value, and is not normally undertaken by diagnostic laboratories.

Treatment. There are a number of different methods of treatment [11]. The topical azole antifungals work well in pityriasis versicolor, and there is no significant difference in results achieved by different compounds [35]. The usual time to recovery is 2–3 weeks. However, there is increasing evidence that shorter application periods using appropriate formulations such as lotions may work after only one or two applications. As has been shown with oral itraconazole, the organisms die rapidly after exposure to azoles, but in view of the thickened *Malassezia* cell wall are not rapidly cleared from the epidermis, giving the false impression of a persistent infection [36,37]. Terbinafine 1% cream is also effective in pityriasis versicolor. The main problem with the use of topical antifungals is the difficulty of applying creams to such a wide body surface area. A possible solution to this is provided by the shampoo version of ketoconazole, and although it has not been fully evaluated in pityriasis versicolor, two or three applications of the shampoo appear to clear most infections.

A second, cheaper approach is the application of 2.5% selenium sulphide in a detergent base (Selsun® shampoo). It is applied to all the affected areas and left overnight. The liquid is pinkish yellow and is best applied at bedtime and should be washed off the next morning. Estimates vary as to the most appropriate length of treatment, and in many cases it is necessary to apply the material regularly (e.g. every other night over 2 weeks). In some patients, however, one or two applications may be sufficient. The principal advantages of selenium sulphide are its low cost and the convenience of application. On the other hand, it is irritant if inadvertently applied to the face or genitalia, necessitating care in its application. It also stains clothes and bedding. Alternatives include 20% sodium hyposulphite solution, and 50:50 propylene glycol in water. The latter has also been used intermittently as long-term suppressive therapy to prevent relapse [38].

Both oral ketoconazole and itraconazole are also very effective in cases of pityriasis versicolor. The dose of ketoconazole recommended varies, but some patients respond to a single 400-mg dose; others may require longer periods of treatment [39,40]. While opinions differ as to the appropriate place for oral therapy, the authors usually reserve oral itraconazole for recalcitrant cases. Itraconazole is active against pityriasis versicolor in a total dosage of 800–1000 mg [37], usually given over 5 days.

Relapse is unfortunately very common, whatever the primary treatment; in all but the most resistant cases it is probably simplest to re-treat each episode rather than resort to long-term suppressive therapy. Patients should be warned that repigmentation may take several months, as otherwise they will often report treatment failure, even when the organisms have been destroyed, simply because the hypopigmentation persists.

References

1 Gueho E, Midgley G, Guillot J. The genus *Malassezia* with description of four new species. *Antonie Van Leeuwenhoek* 1996; **69**: 337–55.

2 Sugita T, Takashima M, Shinoda T *et al*. New yeast species *Malassezia dermatis*, isolated from patients with atopic dermatitis. *J Clin Microbiol* 2002; **40**: 1363–7.

3 Sugita T, Takashima M, Kodama M *et al*. Description of a new yeast species, *Malassezia japonica*, and its detection in patients with atopic dermatitis and healthy subjects. *J Clin Microbiol* 2003; **41**: 4695–9.

4 Sugita T, Tajima M, Takashima M *et al*. A new yeast, *Malassezia yamotoensis*, isolated from a patient with seborrhoeic dermatitis, and its distribution in patients and healthy subjects. *Microbiol Immunol* 2004; **48**: 579–83.

5 Hirai A, Kano R, Makimura K *et al*. *Malassezia nana* sp. nov., a novel lipid-dependent yeast species isolated from animals. *Int J System Evol Microbiol* 2004; **54**: 623–7.

6 Cabanes FJ, Theelen B, Castella G *et al*. Two new lipid-dependent *Malassezia* species from domestic animals. *FEMS Yeast Research* 2007; **7**: 1064–76.

7 Crespo-Erchiga V, Ojeda Martos A, Vera Casano A *et al*. *Malassezia globosa* as the causative agent of pityriasis versicolor. *Brit J Dermatol* 1999; **143**: 799–803.

8 Gupta AK, Kohli Y, Faergemann J *et al*. Epidemiology of *Malassezia* yeasts associated with pityriasis versicolor in Ontario, Canada. *Med Mycol* 2001; **39**: 199–206.

9 Gupta AK, Kohli Y, Summerbell RC *et al*. Quantitative culture of Malassezia species from different body sites of individuals with or without dermatoses. *Med Mycol* 2001; **39**: 243–51.

10 De Quinzada M. *Estudio de las Especies de Malassezia relacionadas con la Patologia Cutanea Pitiriasis versicolor en Panama*. Doctoral thesis 2005, University of Panama.

11 Crespo Erchiga V, Delgado Florencio V. *Malassezia* species in skin diseases. *Curr Opin Infect Dis* 2002; **15**: 133–42.

12 Piamphongsant T. Pityriasis pigmentosa: clinical features of pathogenic *Pityrosporum ovale*. *J Dermatol* 1983; **10**: 355–60.

13 Borelli D. Pitiriasis versicolor por *Malassezia ovalis*. *Mycopathologia* 1985; **89**: 147–53.

14 Roberts SOB. Pityriasis versicolor. In: Verbov JL, ed. *Superficial Fungal Infections*. Lancaster: MTP Press, 1986: 47–72.

15 Dorn M, Roehnert K. Dimorphism of *Pityrosporum orbiculare* in a defined culture medium. *J Invest Dermatol* 1977; **69**: 244–8.

16 Nazzaro-Porro M, Passi S, Caprilli F. Induction of hyphae in cultures in *Pityrosporum* by cholesterol and cholesterol esters. *J Invest Dermatol* 1977; **69**: 531–4.
17 Salkin IF, Gordon MA. Polymorphism of *Malassezia furfur*. *Can J Microbiol* 1977; **23**: 471–5.
18 Roberts SOB. Pityriasis versicolor: a clinical and mycological investigation. *Br J Dermatol* 1969; **81**: 315–26.
19 Del Palacio Hernanz A, Delgado Vicente S, Menendez Ramos F *et al*. Randomized comparative clinical trial of itraconazole and selenium sulfide shampoo for the treatment of pityriasis versicolor. *Rev Infect Dis* 1987; **9** (Suppl. 1): S121–7.
20 Roberts SOB. *Pityrosporum orbiculare*: incidence and distribution on clinically normal skin. *Br J Dermatol* 1969; **81**: 264–9.
21 Marples MJ. The incidence of certain skin diseases in Western Samoa: a preliminary survey. *Trans R Soc Trop Med Hyg* 1950; **44**: 319–32.
22 Burke RC. Tinea versicolor: susceptibility factors and experimental infections in human beings. *J Invest Dermatol* 1961; **36**: 398–402.
23 Mathes BM, Douglas MC. Seborrheic dermatitis in patients with acquired immunodeficiency syndrome. *J Am Acad Dermatol* 1985; **13**: 947–51.
24 Midgley G, Hay RJ. Serological responses to *Pityrosporum (Malassezia)* in seborrhoeic dermatitis demonstrated by ELISA and western blotting. *Bull Soc Fr Med Mycol* 1983; **17**: 267–78.
25 Ashbee HR, Ingham E, Holland KT *et al*. Cell-mediated immune responses to *Malassezia furfur* serovars A, B and C in patients with pityriasis versicolor, seborrheic dermatitis and controls. *Exp Dermatol* 1994; **3**: 106–12.
26 Saadatzadeh MR, Ashbee HR, Cunliffe WJ, Ingham E. Cell mediated immunity to the mycelial phase of *Malassezia* spp. in patients with pityriasis versicolor and controls. *Br J Dermatol* 2001; **144**: 77–84.
27 Ashbee HR. Recent developments in the immunology and biology of *Malassezia* species. *FEMS Immunol Med Microbiol* 2006; **47**: 14–23.
28 Ashbee HR. Update on the genus *Malassezia*. *Med Mycol* 2007; **45**: 287–303.
29 Kesavan S, Walters CE, Holland KT *et al*. The effects of *Malassezia* on pro-inflammatory cytokine production by human peripheral blood mononuclear cells *in vitro*. *Med Mycol* 1998; **36**: 97–106.
30 Brasch J, Martens H, Sterry W. Langerhans' cell accumulation in chronic tinea pedis and pityriasis versicolor. *Clin Exp Dermatol* 1993; **18**: 329–32.
31 Nazzaro-Porro M, Passi S. Identification of tyrosinase inhibitors in cultures of *Pityrosporum*. *J Invest Dermatol* 1978; **71**: 389–402.
32 Breathnach AS, Nazzaro-Porro M, Martin B. Ultrastructure of skin in pityriasis versicolor. *Minerva Dermatol* 1975; **10**: 457–69.
33 El-Gothamy Z, Abdel-Fattah A, Choly AF. Tinea versicolor hypopigmentation: histochemical and therapeutic studies. *Int J Dermatol* 1975; **14**: 510–5.
34 Galadari I, El Komy M, Mousa A *et al*. Tinea versicolor: histologic and ultrastructural investigation of pigmentary changes. *Int J Dermatol* 1992; **31**: 253–6.
35 Svejgaard E. Double blind trial of miconazole in dermatomycosis. *Acta Derm Venereol (Stockh)* 1973; **53**: 497–9.
36 Galimberti RL, Villalba I, Galarza S *et al*. Itraconazole in pityriasis versicolor: ultrastructural changes in *Malassezia furfur* produced during treatment. *Rev Infect Dis* 1987; **9** (Suppl. 1): 134–8.
37 Delescluse J. Itraconazole in tinea versicolor: a review. *J Am Acad Dermatol* 1990; **23**: 551–4.
38 Faergemann J, Fredriksson T. Propylene glycol in the treatment of pityriasis versicolor. *Acta Derm Venereol (Stockh)* 1980; **60**: 92–3.
39 Hay RJ, Midgley G. Short course ketoconazole therapy in pityriasis versicolor. *Clin Exp Dermatol* 1984; **9**: 571–3.
40 Jacobs PH. Evolution in the treatment of pityriasis versicolor. In: Meinhof W, ed. *Oral Therapy in Dermatomycoses: a Step Forward*. Oxford: Medicine Publishing Foundation, 1985: 107–10.

Other cutaneous disorders associated with *Malassezia* yeasts

Lipophilic yeasts of the genus *Malassezia* are part of the normal skin flora, and therefore any evidence that they are either directly or indirectly implicated in the pathogenesis of skin disease is often difficult to assess.

For many years, it has been known that *Malassezia* yeasts are found in large quantities in the scales of seborrhoeic dermatitis, both on the scalp and elsewhere. This was attributed to hyperproliferation of the epidermis, the assumption being that the organisms were merely colonizing this particular site. The same was thought to be the case with skin-surface bacteria [1]. However, it has become apparent that most patients with seborrhoeic dermatitis or scaling of the scalp (dandruff) clear on treatment with azole antifungal agents coincidentally with the disappearance of the yeasts, and that if they relapse after therapy this occurs when the organisms reappear [2,3]. The circumstantial evidence, therefore, that the two events are causally related is very strong. In animals, it is possible to induce skin scaling that bears some resemblance to seborrhoeic dermatitis after the application of *Malassezia* yeasts [4]. Some but not all authors have reported that patients with seborrhoeic dermatitis have significantly raised levels of antibody to these organisms [5], but do not appear to develop contact sensitization to antigenic extracts. One further intriguing piece of evidence is that seborrhoeic dermatitis is one of the earliest and most consistent abnormalities seen in patients with AIDS not on antiretrovirals [6,7]. Yet, as with seborrhoeic dermatitis in non-AIDS patients, there is no consistent correlation between colonization and primary disease, although numbers of yeasts are higher in those with low CD4 counts. All these observations reinforce the view that adult-type seborrhoeic dermatitis is directly related to *Malassezia* yeasts but not to a single species [8]. The relationship between infant seborrhoeic dermatitis and these organisms is less well established. The mechanisms by which they induce skin changes are not known, and the possibilities of direct lipase activity [9] or antibody-mediated epidermal damage [5] have both been considered. It is also apparent that a small percentage of patients with typical seborrhoeic dermatitis do not respond to azole antifungals, and the exact mode of pathogenesis is not clear. However, it is possible that a number of different stimuli can trigger this common condition, of which the most common is *Malassezia*.

A further observation is that certain patients with eczema affecting the head and neck may also respond to topically applied azole antifungals, and also show immediate-type hypersensitivity to extracts of *Malassezia* [10]. Patients have usually had childhood atopic disease or are atopic on family history, and the condition is most often seen in young adults.

The second condition associated with *Malassezia* yeasts is a form of folliculitis on the back and upper trunk. *Malassezia* folliculitis is a clinically distinct condition, most often seen in teenagers or young adult males [11,12]. Lesions are itchy papules and pustules, which are often diffusely scattered on the shoulders and back. The itching and distribution distinguish them from acne vulgaris. Patients often report the development of lesions following a holiday in the sun or it may be found in patients who are acutely ill, for example in an intensive care unit. The condition responds well to oral itraconazole or ketoconazole shampoo. Biopsies taken from typical cases show clusters of yeasts within follicles surrounded by inflammatory cells; this is distinguishable from the colonization of follicular openings that can be seen in normal individuals. The exact pathogenesis of the condition is unknown, but treatment with oral antifungals is highly effective. *Malassezia* yeasts have also been associated with other skin conditions such as confluent and reticulate papillomatosis [13–15]. However, their presence in this condition is not invariable, and their removal with

antifungals not necessarily followed by significant changes in the skin lesions. In addition, some patients respond to minocycline. Finally, there is a variant of psoriasis that has been termed 'sebopsoriasis' where, it is speculated, lipophilic yeasts may have a pathogenic role [16]. While clinically this condition shows some features of both psoriasis and seborrhoeic dermatitis, it still needs to be defined more clearly before it is possible to ascribe a role to the yeast flora.

References

1 Leyden JJ, McGinley KJ, Kligman AM. The role of microorganisms in dandruff. *Arch Dermatol* 1976; **112**: 333–8.
2 Gosse RM, Vanderwyk RW. The relationship of a nystatin resistant strain of *Pityrosporum ovale* to dandruff. *J Soc Cosmet Chem* 1969; **20**: 603–9.
3 Shuster S. Aetiology of dandruff and the mode of action of therapeutic agents. *Br J Dermatol* 1984; **111**: 235–42.
4 Faergemann J, Fredriksson T. Experimental infections in rabbits and humans with *Pityrosporum orbiculare* and *P. ovale. J Invest Dermatol* 1981; **77**: 314–8.
5 Midgley G, Hay RJ. Serological responses to *Pityrosporum (Malassezia)* in seborrhoeic dermatitis demonstrated by ELISA and western blotting. *Bull Soc Fr Med Mycol* 1988; **17**: 267–78.
6 Mathes BM, Douglas MC. Seborrhoeic dermatitis in patients with acquired immunodeficiency syndrome. *J Am Acad Dermatol* 1985; **113**: 947–51.
7 Soeprono FF, Schinella RA, Cockerell CJ *et al*. Seborrhoeic-like dermatitis of acquired immunodeficiency syndrome. *J Am Acad Dermatol* 1986; **14**: 242–8.
8 Crespo Erchiga V, Delgado Florencio V. *Malassezia* species in skin diseases. *Curr Opin Infect Dis* 2002; **15**: 133–42.
9 Wilde PF, Stewart PS. A study of the fatty acid metabolism of the yeast *Pityrosporum ovale. Biochem J* 1968; **108**: 225–31.
10 Hjorth N, Clemmensen OJ. Treatment of dermatitis of the head and neck with ketoconazole in patients with type 1 hypersensitivity for *Pityrosporum orbiculare. Semin Dermatol* 1983; **2**: 26–9.
11 Back O, Faergemann J, Hornquist R. *Pityrosporum* folliculitis: a common disease of the young and middle aged. *J Am Acad Dermatol* 1985; **12**: 56–61.
12 Archer-Dubon C, Icaza-Chivez ME, Orozco-Topete R *et al*. An epidemic outbreak of *Malassezia* folliculitis in three adult patients in an intensive care unit: a previously unrecognized nosocomial infection. *Int J Dermatol* 1999; **38**: 453–6.
13 Faergemann J, Fredriksson T, Nathorst-Windahl G. One case of confluent and reticulate papillomatosis (Gougerot–Carteaud). *Acta Derm Venereol (Stockh)* 1980; **60**: 269–71.
14 Roberts SOB, Lachapelle JM. Confluent and reticulate papillomatosis (Gougerot–Carteaud) and *Pityrosporum orbiculare. Br J Dermatol* 1969; **81**: 841–3.
15 Yesudian P, Kamalam S, Raszack A. Confluent and reticulate papillomatosis (Gougerot–Carteaud). *Acta Derm Venereol (Stockh)* 1973; **53**: 381–4.
16 Rosenberg EW, Belew PW. Improvement of psoriasis of the scalp with ketoconazole. *Arch Dermatol* 1982; **118**: 370–1.

Tinea nigra

Synonyms
- Tinea nigra palmaris
- Keratomycosis nigricans palmaris
- Pityriasis nigra

Definition. Tinea nigra is an asymptomatic, superficial fungal infection generally affecting the skin of the palms and characterized by deeply pigmented, macular, non-scaly patches.

Aetiology. Tinea nigra is generally caused by *Hortaea werneckii* (synonym *Exophiala werneckii*, *Phaeoannellomyces werneckii*) [1]. A different organism, *Stenella araguata,* has been isolated from some cases diagnosed in Venezuela [2,3]. The disease occurs sporadically in many parts of the world, including the Americas and the Caribbean, South Africa, Australia, Europe and the Far East. It is thought to be acquired by direct inoculation into the skin and can easily be reproduced experimentally by scarifying the skin and applying a pure culture of *H. werneckii* under a bandage. The incubation period in separate studies was reported to be 10–15 days and 7 weeks, respectively.

Histology. There is thickening of the stratum corneum in which hyphae are present. Inflammatory reaction in the dermis is minimal.

Clinical features [4]. The lesions are asymptomatic, macular, sharply defined and not scaly. The most distinctive feature is the brown or black colour, resembling a silver nitrate stain. The palms are most commonly affected [5,6] in cases reported in the western hemisphere, but other areas of the body such as the soles and, more rarely, neck and trunk have been recorded, particularly in Asia. By uneven rate of spread or coalescence of lesions, irregular outlines are produced. Spontaneous clearance is very unusual.

Differential diagnosis. The black colour and the absence of scaling differentiate the condition from pityriasis versicolor. The pigmented lesions of Addison's disease, syphilis, pinta and junctional naevi of the palm may have to be differentiated, and mycological examination of scales is usually required.

Laboratory diagnosis. Microscopy of infected epidermal scales in potassium hydroxide mounts reveals abundant brown branched closely septate hyphae up to 5 µm in diameter, and elongated budding cells (Fig. 36.4). Inoculation of specimens onto Sabouraud's agar and incubation at 30°C yields slow-growing colonies.

Hortaea werneckii. Colony: cultures on glucose peptone agar may be relatively slow growing, and initially yield a dirty white to grey moist yeast-like colony, which darkens to olive-green to



Fig. 36.4 Tinea nigra. Skin scales mounted in 30% potassium hydroxide, bright field. The natural brown colour of the septate hyphae is apparent. (Courtesy of the Department of Medical Mycology, St John's Institute of Dermatology, King's College London, London, UK.)

black, and over the course of several days becomes more filamentous and velvety. Microscopy: examination of young cultures reveals annellidic yeast-like budding cells, which are often uniseptate, the septum being dark in mature cells. The conidia are initially hyaline but become brown on maturity. Hyphae in older cultures produce intercalary and lateral conidiogenous cells, which are annellidic or sympodial.

Treatment. Topical azole creams such as econazole and ketoconazole [7] are effective. The condition also responds to the topical application of fungicidal preparations such as Benzoic Acid Ointment Compound BPC. Thiabendazole 2% in 90% dimethylsulphoxide once a day for 14 days gives good results, as does the ordinary commercially available 10% thabendazole suspension.

References

1 McGinnis MR, Schell WA, Carson J. *Phaeoannellomyces* and the Phaeococcomycetaceae: a new dematiaceous blastomycete taxa. *Sabouraudia* 1985; **23**: 179–88.
2 McGinnis MR, Padhye AA. *Cladosporium castellani* is a synonym of *Stenella araguata*. *Mycotaxon* 1978; **7**: 415–8.
3 Perez C, Colella MT, Olaizola C *et al*. Tinea nigra: report of twelve cases in Venezuela. *Mycopathologia* 2005; **160**: 235–8.
4 Carr JF, Lewes CW. Tinea nigra palmaris. *Arch Dermatol* 1975; **111**: 904–5.
5 Hall J, Perry VE. Tinea nigra palmaris: differentiation from malignant melanoma or junctional nevi. *Cutis* 1998; **62**: 45–6.
6 Severo LC, Bassanesi MC, Londero AT. Tinea nigra: report of four cases observed in Rio Grande do Sul (Brazil) and a review of Brazilian literature. *Mycopathologia* 1994; **126**: 157–62.
7 Burke WA. Tinea nigra: treatment with topical ketoconazole. *Cutis* 1993; **52**: 209–11.

Black piedra

Synonyms
- Tinea nodosa
- Trichomycosis nodularis

Definition. A fungal infection confined to hair shafts and resulting in the formation of hard, dark, superficial nodules thereon.

Aetiology. Black piedra is caused by the fungus *Piedraia hortae*. It occurs in humid wet tropical regions [1] in the Americas and in South-East Asia, and affects monkeys as well as humans [2]. The infection was thought to be more common in males than females, but a study among the Zoro indians of Brazil [3] showed no significant difference between the sexes. The same study showed a prevalence of infection of 57% in subjects over the age of 11 years.

Clinical features. Black piedra is characterized by the presence of firmly adherent, black, gritty, hard nodules on the hairs of the scalp, or less frequently of the beard, moustache or pubic area. The nodules vary in size from microscopic to 1 mm or more in diameter, and their thickness often tapers, either from one end to the other or from the middle to the edge. They are usually multiple, and oval or elongate in shape. Subcuticular fungal growth may rupture the cuticle, and the fungus may then grow on the outside of the cuticle, completely surrounding the hair shaft. Because the fungus grows into the hair shaft, the hair may fracture easily. Untreated, the infection may last for months or years.



Fig. 36.5 Black piedra. Hairs mounted in 30% KOH, bright field. The dark nodules are formed of dematiaceous hyphae cemented together to form a hard mass. (Courtesy of the Department of Medical Mycology, St John's Institute of Dermatology, King's College London, London, UK.)

Histology. In histological section or in potassium hydroxide mounts, the nodules are observed to be made up of closely packed brown hyphae held in a mass by a viscous or cement-like substance (Fig. 36.5). At the edges of the nodule, regularly aligned hyphal strands and arthroconidia, 4–8 µm in diameter, can be seen, while in the thicker parts club-shaped asci containing eight elongated ascospores may be formed. The ascospores have a polar filament at each end, and can be observed by crushing or sectioning the nodule. *Piedraia hortae* is almost unique among the human pathogenic fungi in producing sexual spores in its parasitic phase.

Laboratory diagnosis. The direct examination is so characteristic that culture is not absolutely necessary. If culture is performed, it should be noted that the fungus is not inhibited by cycloheximide.

***Piedraia hortae*.** Colony: the culture is slow growing, compact, domed and black. Microscopy: brown, thick-walled, septate hyphae and chlamydoconidia are present. Asci and ascospores may be present in the thicker portion of the colony [4], but are not formed by every isolate.

Treatment. Shaving or cutting the hair effects a cure. To prevent recurrence, antifungal preparations such as Benzoic Acid Ointment Compound BPC or a 1 : 2000 solution of mercury perchloride may be applied to the hair after shampooing. A first case treated with terbinafine has been reported [5].

References

1 Adam BA, Soo Hoo TS, Chong KC. Black piedra in West Malaysia. *Aust J Dermatol* 1977; **18**: 45–7.
2 Takashio M, de Vroey C. Piedra noire chez des chimpanzées du Zaire. *Sabouraudia* 1975; **13**: 58–62.

3 Coimbra CEA, Santos RV. Black piedra among the Zoro indians from Amazonia (Brazil). *Mycopathologia* 1989; **107**: 57–60.
4 Chong KC, Adam BA, Soo Hoo TS. Morphology of *Piedraia hortae*. *Sabouraudia* 1975; **13**: 157–60.
5 Gip L. Black piedra: the first case treated with terbinafine (Lamisil). *Br J Dermatol* 1994; **130** (Suppl. 43): 26–8.

White piedra

Synonym
- Trichosporosis nodosa

Definition. A fungal infection confined to hair shafts and resulting in the formation of soft, white, grey or brown superficial nodules.

Aetiology. Until 1994, the aetiological agent of white piedra was considered to be the basidiomycetous yeast *Trichosporon beigelii*, but genetic analysis has now determined that this name covered a complex of different species [1].The agent of capital white piedra is now considered to be *T. ovoides*, while organisms reported from crural white piedra include *T. inkin*, *T. asahii* and *T. mucoides*. The infection occurs in South America, Africa, central and eastern Europe, and Japan [2,3]. The horse and certain species of monkey may be affected. The cases occasionally observed in temperate countries have usually been in visitors from the tropics, but cases have occurred in both Europe and the USA in individuals who have never left these regions [4]. A study in equatorial Africa demonstrated a prevalence of 18% in inguinal specimens from 449 female subjects [2].

Clinical features. White piedra is characterized by the presence of soft, white or light brown nodules. The infection is more common on the hairs of the beard, moustache and genital areas than the scalp [5,6]. The fungus grows both within and outside the hair shaft, and the hair shaft may be weakened and break off. The nodules are transparent, easily detached from the hair and vary in size from microscopic to 1 mm in diameter. The underlying skin is not affected and there is no fluorescence under Wood's light.

There is evidence that some cases may be sexually transmitted [7]. In addition, it has been postulated that the bacteria known to accompany the concretions of the fungi on hair, now identified as a new species of *Brevibacterium*, *B. mcbrellneri* [8], may have a synergistic role in the infection [9]. The strong proteolytic activity of the bacterium may facilitate hair shaft invasion by both yeast and bacterium, while fungal byproducts may stimulate bacterial growth. There is an increased carriage rate of perianal '*T. beigelii*' reported in human immunodeficiency virus (HIV)-positive individuals, suggesting that this region may provide a reservoir for carriage. Interestingly, there does not appear to be an increased incidence of hair shaft infection in these patients.

Histology. The nodules of white piedra are in the form of a sheath, which may extend around the hair shaft. There may be extensive growth within the hair, giving rise to the characteristic nodular swellings on the hair shaft. The hyphae segment into arthroconidia 2–4 μm in diameter, and budding blastoconidia may also be seen (Fig. 36.6).

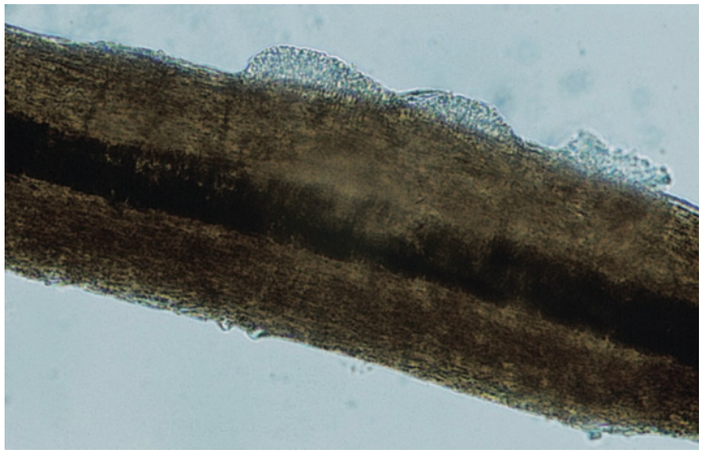


Fig. 36.6 White piedra. Hair mounted in KOH, bright field. The gelatinous nodules formed by various *Trichosporon* species surround the hair. (Courtesy of the Department of Medical Mycology, St John's Institute of Dermatology, King's College London, London, UK.)

Differential diagnosis. The presence of pruritus and the distinctive shape of egg cases of pediculi should serve to distinguish pediculosis from piedra, but microscopical examination is desirable.

Laboratory diagnosis. Most *Trichosporon* species are inhibited by cycloheximide, so this antibiotic should be excluded from the culture medium. As a few isolates fail to grow at 37°C, it is also advisable to incubate at 28–30°C.

***Trichosporon* species.** Colony: the colonies of *Trichosporon* species develop rapidly and are soft, creamy and wrinkled, and sometimes mucoid [10]. Microscopy: the genus *Trichosporon* is characterized by the presence of hyphae, arthroconidia and budding cells. These are best observed with a deep cut streak on a cornmeal or rice agar supplemented with Tween 80. Physiological tests: the species recently recognized using genetic analyses can be identified in the routine laboratory using their morphological characteristics, together with carbohydrate assimilation patterns determined by the commercial API 32C® system (bioMerieux), failure or ability to grow at 37°C and relative sensitivity to cycloheximide [1].

Treatment. As with black piedra, shaving or cutting the hair may effect a cure. Responses to concentrated topical antifungals, azoles and allyamines have been reported but are unpredictable.

References

1 Gueho E, Improvisi L, de Hoog GS, Dupont B. *Trichosporon* on humans: a practical account. *Mycoses* 1994; **37**: 3–10.
2 Therizol-Ferly M, Kombila M, Gomez de Diaz M *et al*. White piedra and *Trichosporon* species in equatorial Africa: 1. History and clinical aspects: an analysis of 449 superficial inguinal specimens. *Mycoses* 1994; **37**: 249–53.
3 Benson PM, Lapins NA, Odom RB. White piedra. *Arch Dermatol* 1983; **119**: 602–4.
4 Coquilla BH, Kraus EW. Trichosporosis (white piedra): four cases in the United States. *J Assoc Milit Dermatol* 1983; **9**: 27–9.
5 Kalter DCA, Tschen JA, Cernoch PL *et al*. Genital white piedra: epidemiology, microbiology and therapy. *J Am Acad Dermatol* 1986; **14**: 982–93.

6 Lassus A, Kanerva L, Stubbs S *et al*. White piedra. *Arch Dermatol* 1982; **118**: 208–11.
7 Grainger CR. White piedra: a case with evidence of spread by contact. *Trans R Soc Trop Med Hyg* 1986; **80**: 87.
8 McBride ME, Ellner KM, Black HS *et al*. A new *Brevibacterium* sp. isolated from infected genital hair of patients with white piedra. *J Med Microbiol* 1993; **39**: 255–61.
9 Ellner KM, McBride M, Kalter DC *et al*. White piedra: evidence for a synergistic infection. *Br J Dermatol* 1990; **123**: 355–63.
10 Mok WY, Barreto da Silva MS. Mycoflora of the human dermal surface. *Can J Microbiol* 1984; **30**: 1205–9.

Otomycosis

Synonym
- Mycotic otitis externa

Definition and clinical features. A chronic inflammatory condition of the external auditory canal caused by fungal infection (external otitis in general, including the differential diagnosis and the management, is considered in Chapter 68). In some patients with external otitis, fungi may be isolated from swabs or scrapings, and indeed material taken from the normal external ear may on occasions yield a variety of moulds [1]. Such isolates are more common in tropical regions. Very occasionally in external otitis, the fungus isolated appears to be playing a pathogenic part, perhaps even a primary one. The species most commonly accepted as pathogens in this situation include *Aspergillus niger*. Other species implicated as pathogens include *A. fumigatus* and other *Aspergillus* species [2,3], *Scedosporium apiospermum*, numerous other moulds and *Candida* species.

The inflamed, itchy and sometimes painful external canal usually discharges a little serous fluid. In advanced cases of true mycotic otitis, an overgrowth of fungal hyphae may produce a mass of white material suggesting damp cotton wool, lodged in the external canal. Where *A. niger* is the causative organism, the mat of fungus is often covered by black fruiting heads [4]. In severely immunocompromised patients, the external auditory meatus can be extensively eroded by fungal invasion to produce a necrotic form of otitis externa [5]. This form may spread to involve other sites including the middle ear and the mastoids. The pinna may be the site of several mycotic diseases including chromomycosis [6], sporotrichosis [7] and tinea [4], but such infections usually spare the external auditory meatus.

Laboratory diagnosis. Interpretation of the relevance of organisms recovered from swabs taken from the ear may be difficult and a light growth of a mould may be of little significance. *Rhizopus*, *Absidia*, *Mucor* or *Penicillium*, or indeed *Aspergillus* species, in small amounts mean little, except in immunocompromised patients, where they may be more important. Similarly, a light growth of *Candida* may reflect colonization or contamination, although this organism can cause external otitis. The criteria for accepting the fungus as having an aetiological role are the absence of any significant bacterial pathogens and the presence of large masses of fungi, that may sometimes be seen on examination of the patient. If there is a considerable amount of fungal material in specimens taken for direct examination, this may be adequate evidence. Signs and symptoms present in otomycosis are largely similar to those of otitis due to other aetiological agents, although pruritus and discharge have been shown to be more common in fungal-associated disease in one study [2].

***Aspergillus niger*.** Colony: growing rapidly, the colony initially has a white or cream surface, which becomes black as the conidia are produced. The reverse remains pale cream to celadon green. Microscopy: the conidiophores arise at right angles to the supporting hyphae, and have a swollen globose vesicle at their tip, which is completely covered by a layer of supporting cells or metulae. These metulae support a layer of phialides, which produce chains of dark brown, rough-walled phialoconidia. The bottom end of the conidiophore ends in a foot cell inserted in the supporting hypha.

Treatment [4,8,9]. Careful toilet, with removal of debris and fungal material from the ears, is of paramount importance. Various local applications have been suggested. One routine consists of applying 2% thymol in 70% alcohol during cleansing, followed by 50% metacresyl acetate or olive oil on a pledget of cotton wool left for 24 h. Clotrimazole lotion has been employed with success in both *Aspergillus* and *Candida* infections. Bifonazole lotion and cream were effective in the majority of 35 patients included in a long-term study attempting to correlate the bacterial and fungal flora in patients with symptomatic otomycosis [9]. Oral itraconazole has been used in the aggressive invasive form of otitis externa.

References

1 Kingery FA. The myth of otomycosis. *JAMA* 1965; **191**: 129–36.
2 Kurnatowski P, Filipiak A. Otomycosis: prevalence, clinical symptoms, therapeutic procedures. *Mycoses* 2001; **44**: 472–9.
3 Ho T, Vrabec JT, Yoo D *et al.* Otomycosis: clinical features and treatment implications. *Otolaryngology—Head and Neck Surgery* 2006; **135**: 787–91.
4 Grigoriou D, Font N. Les otomycoses. *Dermatologica* 1970; **141**: 138–42.
5 Bickley LS, Betts RF, Parkins CW. Atypical invasive external otitis from *Aspergillus*. *Arch Otolaryngol Head Neck Surg* 1988; **114**: 1024–8.
6 Iwatsu T, Takano M, Okamoto S. Auricular chromomycosis. *Arch Dermatol* 1983; **119**: 87–9.
7 Cox RL, Reller LB. Auricular sporotrichosis in a brick mason. *Arch Dermatol* 1979; **115**: 1229–30.
8 El-Gothamy MAB, El-Gothamy Z. Otomycosis: a new line of treatment. *Castellania* 1977; **5**: 215–6.
9 Del Palacio A, Lopez-Suso MJ, Moore MK *et al*. Long-term follow-up of otomycosis and its treatment with bifonazole. *J Med Vet Mycol* 1993; **31**: 435–47.

Miscellaneous superficial fungal infections caused by saprophytic moulds

The normal skin, especially the scalp and toe clefts, is commonly contaminated with spores or even short lengths of mycelium of saprophytic species. Where the fungal mycelium is pigmented or where distinctive spores are concerned, they may be recognized in direct examination of skin scrapings. If cycloheximide-free media are used, they may be readily cultured. Usually, such species are present in small amounts, and may without difficulty be dismissed as contaminants that have impacted on the skin, in the same way as the pollen grains occasionally observed. From time to time, however, reports appear in the dermatological literature of cases in which species such as those of *Aspergillus* [1] appear to

colonize damaged tissues, become firmly established and perhaps cause secondary tissue destruction. Most authors counsel caution before accepting any sort of pathogenic role for the moulds in these cases.

Laboratory diagnosis and management. In situations like these, it is important to take repeated scrapings, to use cycloheximide-free media in culture and then to weigh the facts carefully before assuming that the organism is anything more than a contaminant. In many cases, simple correction of local precipitating factors, such as maceration or occlusive dressings, may be all that is needed.

Reference

1 English MP. Invasion of the skin by filamentous non-dermatophyte fungi. *Br J Dermatol* 1968; **80**: 282–6.

Dermatophytosis

Introduction

Dermatophytes are related fungi [1,2] capable of causing skin changes of the type known as ringworm or dermatophytosis. Thus defined, the ringworm species are all moulds belonging to three asexual genera: *Microsporum*, *Trichophyton* and *Epidermophyton*. Forty years ago, the sexual state of dermatophytes was unknown, and this phase of the life cycle has still not been found for many of the common species. However, in those species where the sexual state has been identified, all the organisms are classified in the single genus *Arthroderma* in the phylum Ascomycota [3]. A list of synonyms of sexual and asexual names is included for reference (Table 36.3). However, as sexual states are not routinely seen in the diagnostic laboratory, the asexual anamorph names will be used throughout this section.

In addition to the recognized pathogens, a number of fungi have been discovered that are keratinophilic and that are clearly close relatives of the ringworm fungi—indeed, some are even classified in the same three anamorph genera—but that are soil dwellers and non-pathogenic. Although some authors include these fungi within the dermatophytes, in the authors' opinion they are better classified in the broader group of keratinophilic fungi, retaining the term dermatophyte for those species that can act as true superficial pathogens.

The taxonomy of dermatophytes is an ever changing area and the use of molecular techniques to examine the relatedness of species has led to many controversies and conflicts in the literature. Gräser *et al*. suggested, on the basis of ribosomal internal transcribed spacers (ITS), that *Trichophyton equinum* var. *autotrophicum* should be considered synonymous with *T. tonsurans* [4]. However, this is a matter of conflict and debate among taxonomists in this area [5,6], and this synonymy was later formally rejected [7]. Detailed discussions on the molecular taxonomy of dermatophytes are beyond the scope of this volume and interested readers are referred to a review on this subject [8].

The three asexual dermatophyte genera are distinguished by the morphology of the large, multicellular macroconidia that are produced [9]. In the genus *Microsporum*, the macroconidia are rough, usually thick walled and range from fusiform to obovate in shape with 1–12 or more septa. Those of *Trichophyton* species are thin walled, smooth and may be cylindrical, fusiform or clavate in shape, with up to 12 transverse septa. In *Epidermophyton*, the macroconidium is clavate, broadened and rounded at its distal pole, thin walled and has up to five septa; the conidia are smooth when first formed, but as the colony ages discrete wall thickenings may be observed.

Apart from the mycological classification of dermatophytes, it has been traditional for clinical and epidemiological reasons to group dermatophytes that infect humans according to their ecological niche: geophilic species originating in the soil (Table 36.4), zoophilic species having animal origins (Table 36.4) and anthropophilic species, which are largely restricted to human skin (Table 36.5). However, these three groups are not always sharply demarcated. Species that are clearly geophilic may contaminate or infect the coats of animals, especially small rodents, and may thus infect humans through an intermediate animal host. Similarly, animal species may shed infective material on to the soil and, although incapable of multiplying there, fungal elements may survive long enough to be isolated in a soil survey [10]. In the case of species affecting farm animals, their environment, cow sheds and fences

Table 36.3 Asexual–sexual connections of dermatophytes.

Asexual state	Sexual state
Microsporum canis	*Arthroderma otae*
Microsporum fulvum	*Arthroderma fulvum*
Microsporum gypseum	*Arthroderma incurvatum*
Microsporum gypseum	*Arthroderma gypseum*
Microsporum nanum	*Arthroderma obtusum*
Microsporum persicolor	*Arthroderma persicolor*
Trichophyton mentagrophytes	*Arthroderma benhamiae*
Trichophyton mentagrophytes	*Arthroderma vanbreuseghemii*
Trichophyton simii	*Arthroderma simii*

Table 36.4 Geophilic and zoophilic dermatophytes.

	Geographical distribution	Major host
Geophilic species		
*Microsporum gypseum**	Worldwide	
Microsporum praecox	USA, western Europe	
Zoophilic species		
Microsporum canis var. *canis*	Worldwide	Cat, dog
var. *distortum*	New Zealand, USA	Cat, dog
Microsporum equinum	Worldwide	Horse
Microsporum gallinae	Worldwide	Fowl
Microsporum nanum	Worldwide	Pigs
Microsporum persicolor	Americas, Europe	Voles
Trichophyton equinum	Worldwide	Horse
Trichophyton mentagrophytes		
var. *mentagrophytes*	Worldwide	Rodents
var. *erinacei*	Europe, New Zealand	Hedgehogs
var. *quinckeanum*	Worldwide	Mice
Trichophyton simii	India	Monkey
Trichophyton verrucosum	Worldwide	Cattle

* This asexual species is a complex of three sexual species.

Table 36.5 Anthropophilic dermatophytes.

Species	Geographical distribution
Epidermophyton floccosum	Worldwide
Microsporum audouinii	Worldwide
var. *rivalieri*	Africa
var. *langeronii*	Africa
Microsporum ferrugineum	Far East, eastern Europe, Africa
Trichophyton concentricum	Pacific, South-East Asia, Latin America
Trichophyton gourvilii	Central Africa
Trichophyton mentagrophytes var. *interdigitale*	Worldwide
Trichophyton megninii	Mediterranean
Trichophyton rubrum	Worldwide
Trichophyton schoenleinii	Worldwide
Trichophyton soudanense	Sub-Saharan Africa
Trichophyton tonsurans	Worldwide
Trichophyton violaceum	North Africa, India, Middle East
Trichophyton yaoundei	Central Africa

may be contaminated by desquamated keratinocytes or hair containing fungal spores, just as the floors around swimming baths, school classrooms and the air of hospital clinics may be contaminated by anthropophilic species [10].

The distribution of the zoophilic species reflects that of the major animal hosts. Those geographically limited include *Microsporum canis* var. *distortum*, *M. persicolor*, *Trichophyton mentagrophytes* var. *erinacei* and *T. simii* (Table 36.4). Many of the anthropophilic species are also geographically limited and the classic endemic distributions are indicated in Table 36.5. However, to some degree these must reflect the distribution of diagnostic facilities, and data for some areas are slight or outdated. Also, the anthropophilic dermatophytes are spread by movements of individuals and groups. For example, species classically thought of as African, such as *T. soudanense*, have been isolated in the USA and Europe with some regularity. The European infections have not been among immigrants from the endemic areas alone, but also in children born in Europe of African immigrants and, more rarely, among the endemic European population. Some of the species that have been regarded as cosmopolitan, such as *T. schoenleinii*, are currently rarely isolated in the USA and many parts of western Europe, although in some areas, particularly parts of Africa, they remain endemic.

It must also be appreciated that these distributions are not static, and the range of species in some areas may change dramatically and quickly. For instance, in one central London laboratory during the period between 1980 and 1990, the most common isolate from tinea capitis was the zoophilic organism *M. canis*. In contrast, during 2003 and 2004 *T. tonsurans*, a species that was rarely seen in the 1980s, was responsible for 87% of scalp infections (S. Howell, St John's Institute of Dermatology, King's College London, unpublished data). A resurgence of infection by other anthropophilic species, such as *T. soudanense* and *M. audouinii*, has also been noted in London during the period between 1993 and 2004 (S. Howell, St John's Institute of Dermatology, King's College London, unpublished data). A recent review has highlighted the shifting epidemiology of dermatophytosis both in the UK and worldwide [11].

From the evolutionary point of view, it is likely that the anthropophilic species represent the end of a line, starting with non-pathogenic keratinophilic soil species, existing as saprophytes on keratinous debris, passing through the geophilic dermatophytes and the zoophilic species. The increased specialization that this evolutionary trend implies seems to be accompanied by a progressive loss of the sexual state and a reduction in the production of conidia, particularly macroconidia, and a loss of certain mating types [12–14]. Virtually all the non-pathogenic, keratinophilic species and geophilic dermatophytes have demonstrable sexual states, as do a few of the zoophilic group, particularly those infecting animals living in burrows or dens and thus soil-associated. However, dermatophytes that infect larger animals, such as *T. verrucosum* from cattle, *T. equinum* from horses and the anthropophilic dermatophytes, have as yet no known sexual state. It has been suggested that this transition from sexual to asexual life cycles had led to an unprecedented level of adaptive radiation among the anthropophilic dermatophytes, resulting in a large number of species and variants. Other factors that may have contributed to the adaptive radiation on humans include the separation of the human skin into distinct areas differing in the distribution of sebaceous glands and hairs, resulting in a marked affinity for particular body sites among the anthropophiles, which is not seen in zoophiles.

Characteristically, zoophilic species tend to produce highly inflammatory reactions in humans and this may lead to a spontaneous cure. Anthropophilic species produce mild but chronic lesions. There are many exceptions to this useful generalization, and the degree of inflammatory response depends in part on the site of infection—large follicles of scalp and beard are associated with an intense reaction—and the immune status of the host [15].

An important characteristic of the dermatophytes as parasites is their restriction to dead keratinized tissue. Although the inflammatory responses of ringworm infection involve the dermis and the Malpighian stratum of the epidermis, the fungus itself is found growing only within the stratum corneum of the epidermis, within and around the fully keratinized hair shaft, and in the nail plate and keratinized nail bed. Within these keratinized tissues, the fungus exists only as mycelium and arthroconidia. In this parasitic phase of fungal growth, there are no micro- or macroconidia and no specialized vegetative structures, such as spiral or pectinate hyphae. For these reasons, precise identification of the species of an infecting dermatophyte is generally impossible on direct microscopy of skin or nail.

In dermatophyte infections involving hair, the fungus invades the follicle from the adjacent stratum corneum and follows one of several precise patterns of growth. In the case of *M. canis* and *M. audouinii*, for example, the fungus penetrates the keratinized hair at about mid-follicular level, having grown down on the hair surface [16]. It then grows downwards within the hair towards the bulb, until the zone of incomplete keratinization is reached. Growth is then arrested, or rather slowed and resisted. An equilibrium is established, the fungal mycelium invading new, fully keratinized hair shaft at the same rate as it is formed, but never growing down

into the incompletely keratinized tissue. Further up the shaft, hyphae from the existing mycelium grow outwards from inside the hair and proliferate on its surface. These secondary, extrapilary hyphae are tortuous; they fragment into small arthroconidia, which rapidly round up to become spherical structures, and are seen as a packed mosaic of spores coating the surface of the hair. This is the small-spored ectothrix type of hair invasion.

Other species of dermatophytes show different patterns of hair invasion. *T. verrucosum* and *T. mentagrophytes* var. *mentagrophytes*, like the *Microsporum* species, show arthroconidia on the surface of the hair and hyphae within it, but these conidia are larger and are arranged in straight chains. This is known as large-spored ectothrix hair invasion. *T. tonsurans* and *T. violaceum*, among others, produce an endothrix type of hair invasion, with the hyphae inside the hair fragmenting completely into a mass of relatively large arthroconidia, which are retained entirely within the hair shaft. *T. schoenleinii*, the cause of favus, is different again. The hyphae within the hair are fewer in number than in other endothrix infections and do not break up into a mass of arthroconidia but run intact through the hair, forming tunnels within its structure. When mounted in potassium hydroxide, these tunnels formed originally around the hyphae, which subsequently degenerate, form the characteristic air spaces seen. While in favus the infected hair commonly grows to normal lengths, in endothrix infections where arthroconidia are formed the hair shaft, being severely weakened, breaks at the skin surface. In small-spored ectothrix infections the shaft tends to fracture a few millimetres above the surface.

All these parasitic patterns are very different from the mode of growth of dermatophytes on hair *in vitro* [17]. If plucked hair is inoculated with any of the *T. mentagrophytes* varieties, for example, frond-like fungal hyphae develop on the surface and lift the cuticle cells. Conical pits are then formed perpendicular to the surface of the hair as penetration of the keratinized hair cortex occurs. Intrapilary growth follows along the hair shaft in both directions, and micro- and macroconidia may be produced. There are no linear chains of arthroconidia on the surface. Moreover, if a hair, parasitized *in vivo*, is plucked, and then cultured *in vitro*, the specialized growth pattern initially established will cease and the saprophytic phase, with the development of micro- and macroconidia, will rapidly follow.

References

1 Makimura K, Tamura Y, Mochizuki T *et al*. Phylogenetic classification and species identification of dermatophyte strains based on DNA sequences of Nuclear Ribosomal Internal Transcribed Spacer 1 regions. *J Clin Microbiol* 1999; **37**: 920–4.

2 Lui D, Coloe S, Baird R *et al*. Application of PCR to the identification of dermatophyte fungi. *J Med Microbiol* 2000; **49**: 493–7.

3 Weitzman I, McGinnis MR, Padhye AA, Ajello L. The genus *Arthroderma* and its later synonym *Nannizzia*. *Mycotaxon* 1986; **25**: 505–18.

4 Gräser Y, Kuijpers AFA, Presber W, de Hoog GS. Molecular taxonomy of *Trichophyton mentagrophytes* and *T. tonsurans*. *Med Mycol* 1999; **37**: 315–30.

5 Woodgyer A. The curious adventure of *Trichophyton equinum* in the realm of molecular biology: a modern fairy tale. *Med Mycol* 2004; **42**: 397–403.

6 Summerbell RC, Haugland R, Li A, Gupta AK. Ribosomal RNA gene internal transcribed spacer 1 and 2 equences of asexual, anthropophilic dermatophytes related to *Trichophyton rubrum*. *J Clin Microbiol* 1999; **37**: 4005–11.

7 Summerbell RC. *Trichophyton, Microsporum, Epidermophyton*, and agents of superficial mycosis. In: Murray PR, Baron EJ, Jorgensen JH *et al*., eds. *Manual of Clinical Microbiology*, 8th ed. Washington DC, USA: ASM Press, 2003: 1798–819.

8 Gräser Y, de Hoog GS, Summerbell, RC. Dermatophytes: recognizing species of clonal fungi. *Med Mycol* 2006; **44**: 199–209.

9 Emmons CW. Dermatophytes: natural groupings based on the form of the spores and accessory organs. *Arch Dermatol Syphilol* 1934; **30**: 337–62.

10 Barlow AJE, English MP. Mycology. In: Rook A, ed. *Recent Advances in Dermatology*, Vol. 3. Edinburgh: Churchill Livingstone, 1973: 33–47.

11 Borman AM, Campbell CK, Fraser M, Johnson EM. Analysis of the dermatophyte species isolated in the British Isles between 1980 and 2005 and review of worldwide dermatophyte trends over the last three decades. *Med Mycol* 2007; **45**: 131–41.

12 Rippon JW. *Medical Mycology: the Pathogenic Fungi and the Pathogenic Actinomycetes*, 3rd edn. Philadelphia: Saunders, 1988: 169–275.

13 Tanaka S, Summerbell RC, Tsuboi R *et al*. Advances in dermatophytes and dermatophytosis. *J Med Vet Mycol* 1992; **30** (Suppl. 1): 29–39.

14 Weitzman I, Summerbell R. The dermatophytes. *Clin Microbiol Rev* 1995; **8**: 240–59.

15 Jones HE, Reinhardt JH, Rinaldi MG. A clinical, mycological and immunological survey of dermatophytosis. *Arch Dermatol* 1973; **108**: 61–8.

16 Kligman AM. The pathogenesis of tinea capitis due to *Microsporum audouinii* and *Microsporum canis*. *J Invest Dermatol* 1952; **18**: 231–46.

17 Rebell G, Taplin D. *Dermatophytes: Their Recognition and Identification*, 2nd edn. Miami: University of Miami Press, 1970.

Pathogenesis of infection

Invasion of the epidermis by dermatophytes follows a common pattern, starting with adherence between arthroconidia and keratinocytes, followed by penetration through and between cells and the development of a host response.

Adherence

On the stratum corneum, the first phase of dermatophyte invasion involves the adherence of infectious arthroconidia to keratinocytes. *In vitro*, this process is completed after about 2 h of contact, at which stage germination and penetration of the keratinocyte occurs [1]. Different dermatophytes show similar kinetics, which are also unaffected by the source of the keratinocytes. The germination of arthroconidia and hyphal prolongation which follows adherence proceeds radially, and *in vitro* there is evidence of indentation of keratinocyte layers beneath the growing hyphae, possibly resulting from enzymic action [2].

Penetration

Dermatophytes are keratinophilic. Evidence for this ranges from the ability of many dermatophytes to invade hair and nail *in vitro*, and the demonstration of genetically regulated production of proteases with keratin specificity. *In vitro*, non-keratin substances extracted from keratinized tissues will support growth of dermatophytes [3]. Dermatophytes produce a variety of proteolytic enzymes, which range in size from 40 to over 200 kDa [4]. There is evidence in *T. mentagrophytes* that both a cell-free and a membrane-bound keratinase are present [5]. One group of workers has demonstrated that keratinase activity from certain dermatophytes is inducible by low-molecular-weight peptides released from the epidermis by the action of other fungal proteinases [6]. From this it can be seen that the precise part that keratin-specific enzymes play in fungal invasion of the stratum corneum is not entirely clear, and that other proteinases and even mechanical forces caused by hyphal growth may have a role. Clinically, there appears to be a certain amount of heterogeneity in substrate preference as, while all dermatophyte species invade the stratum corneum of the skin, different species vary widely in their capacity to invade hair and nail. *T.*

rubrum rarely invades hair but frequently invades nail; *Epidermophyton floccosum* never invades hair and only occasionally nail. In addition, other factors, such as those concerned with host resistance (e.g. serum), have a role in limiting the ability of dermatophytes to penetrate further than the stratum corneum [7].

Recently, in *Microsporum canis* three genes, *SUB1*, *SUB2* and *SUB3*, have been identified as responsible for synthesis of metalloproteases associated with infection [8].

Host resistance and immunology

Defence against the fungi causing ringworm depends on both innate and acquired immune mechanisms [9], the latter requiring the activation of immunological memory [10]. Serum factors appear to be able to inhibit the growth of dermatophytes *in vitro* and on cultured explants of skin. It is not entirely clear what is responsible for this, but unsaturated transferrin is one candidate, which inhibits the growth of dermatophytes by binding to the hyphae [11]. Its mode of action appears to be independent of iron-binding capacity. In experimental infections of skin grafted on to *nu/nu* mice, there is evidence of increased turnover of epidermis, which occurs in the absence of effective T-lymphocyte-mediated defence [12]. A further potentially important mode of defence is provided by the presence of fatty acids from sebaceous glands, which inhibit dermatophyte growth *in vitro*. This activity appears to reside in saturated fatty acids with chain lengths of 7, 9, 11 and 13 carbon residues. It has been postulated that their presence on the skin in postpubertal children may account for the spontaneous resolution of tinea capitis after this age, and the rarity of new infections in adults. Undecenoic acid derivatives are a practical example where fatty acids have been used for the treatment of dermatophytosis. Whatever the influence of these factors, it is clear that in experimentally infected mice the initial inflammatory changes occur as early in the process as 4 h after infection. This suggests that endogenous mechanisms may attract leukocytes [13], and the role of inflammatory mediators, such as the eicosanoids, in this respect needs to be investigated.

Skin also contains a range of antimicrobial peptides, including human β-defensins (hBDs), cathelicidin LL-37 and dermicin [14]. These peptides are known to have activity against bacteria, viruses and fungi and play a key role in protection against skin infections. Their activity against dermatophytes has not been tested to date, although they are known to have killing activity against *Candida albicans* [15], so their role in defence against dermatophytes is yet to be fully elucidated.

It has also been found that dermatophytes are chemotactic and that they can activate the alternative pathway of complement activation. This has been demonstrated for *T. rubrum*, *T. mentagrophytes* [13] and fungi causing endothrix scalp infections, such as *T. violaceum*. The production of cytokines, such as interleukin-1 (IL-1), by keratinocytes has not been investigated in the mobilization of neutrophil defences. It has been shown that neutrophils, and to a lesser extent monocytes, can kill dermatophyte conidia. This activity depends both on intra- and extracellular mechanisms, and the generation of the respiratory burst is an important stage in this process [16]. Dermatophytes produce catalase and superoxide dismutase, which may act as defence against the phagocyte-generated free radicals.

By contrast, there is little evidence that antibodies to dermatophytes are protective. Patients with widespread infections, such as tinea imbricata, may have high antibody titres [17]. The presence of elevated IgE, in particular, is associated with chronicity (see below) [18]. Transfer of specific serum containing a high titre of antibody to irradiated mice does not confer immunity on recipients. It is still premature to rule out a role for antibody, as dermatophytes show some cytological changes when grown in the presence of specific antibody *in vitro*. However, there is strong evidence that the development of cellular immunity via sensitized T lymphocytes is a key factor in immunological defence. Lymphocytes bearing T-helper phenotypic markers are responsible for transferring immunity to infection to naïve recipient mice [19]. In humans, the appearance of inflammation in ringworm correlates with the development of delayed-type skin reactivity to trichophytin [20–22] and cytokines such as interferon-γ. Chronic infections are associated with poor T-lymphocyte-mediated response to specific fungal antigens, suggesting that depression of responses is responsible for the poor clinical response [20,23]. Langerhans' cells can act as antigen-presenting cells for dermatophyte antigens.

The reason for failure of immunity in persistent infections, and its relationship with chronicity, are still not well understood. There is an association between the presence of atopy and chronic dermatophytosis, with a high proportion of those with persistent disease having atopy (usually asthma or hay fever) as well as immediate-type hypersensitivity and raised IgE levels [20,23]. It has been suggested that modulation of T-lymphocyte activity either locally or systemically may be responsible. Possible mechanisms include activation of a type 2 helper T (Th2) lymphocyte pathway, which might explain the spectrum of antibody responses; and although interferon-γ is detected in infection, there is also evidence of the production of IL4 associated with a Th2 pathway [24]. It has been found that dermatophyte antigens, including those that contain mannose residues, can reversibly suppress lymphocyte proliferation, but not the expression of human leukocyte antigen (HLA) DR [25]. Patients with persistent infection have detectable levels of circulating antigen [26]. Both are possible factors in the regulation of immunity in dermatophytosis.

Patients with dermatophytosis are usually otherwise healthy. However, altered or chronic infections have been noted in a number of patient groups, such as those with chronic mucocutaneous candidosis, AIDS [27], and patients on corticosteroid therapy or with endogenous Cushing's syndrome. There is also the raised incidence of atopy in patients with chronic infection, suggesting that host factors may well determine the clinical course. However, this is not the only factor, and it has been found that where there is ample facility for the spread of infection (e.g. among coalminers), the incidence of atopy is no different to that seen in uninfected co-workers [28].

Other factors affecting infection

Age, sex, genetic and racial factors

The known differences in the incidence of ringworm infection between the age groups and sexes seem, in general, to reflect differing rates of exposure and of sebum production, differing clothing and fluctuations of immunity with old age. There may be

ethnic differences in susceptibility, for example in tinea capitis, but the pathogenetic mechanisms are not clearly established [29]. In tinea imbricata, a genetic susceptibility factor inherited as an autosomal recessive has been suggested [30]. It has also been postulated that a genetically determined factor(s) may be wholly or partly responsible for family clusters of cases of infection [31]. The definitive proof awaits the demonstration of appropriate genetic abnormalities at a molecular level.

Endocrine and metabolic factors

There is no reliable evidence that diabetic patients are especially susceptible to dermatophyte infection [32], even though diabetes may affect the course of established infections; for example, diabetic patients with tinea pedis are more likely to develop onychomycosis. In malnutrition and in Cushing's syndrome, the apparently diminished resistance to infection may well have followed depressed cellular immunity.

Temperature and microenvironment

Dermatophytes grow poorly at 37°C. Although this factor may contribute to the lack of deeper penetration of the epidermis and dermis, intravenous injection will result in progressive infection in experimental animals models of dermatophytosis. Raised carbon dioxide tension is known to facilitate arthroconidial formation, and may also aid either adhesion or penetration [33]. Moisture is also important for germination of arthroconidia on keratinocytes.

Competing organisms and co-pathogens

The ability of certain dermatophyte species to produce penicillin-like antibiotics may allow these fungi to regulate the bacterial flora [34]. Although there is some competitive interaction [35], *Staphylococcus aureus* may occasionally act as a co-pathogen, increasing the degree of inflammation in dermatophyte infections [35].

Histopathology

The clinical appearances of the various forms of ringworm infection are the result of the combination of direct damage to the keratinized tissues by the fungus (this applies mainly in hair and nail infections), and of the inflammatory host response. The latter varies widely. At one extreme there is the simple hyperkeratosis seen, for instance, in dry-type *T. rubrum* infections; at the other is the pustular, highly inflammatory kerion seen most frequently in zoophilic infections, such as those caused by *T. verrucosum*. This subject has been extensively reviewed [36]. *T. rubrum*, for instance, may provoke the epidermal changes seen in chronic dermatitis with hyperkeratosis, patchy parakeratosis, hyper- or hypogranulosis, spongiosis, mononuclear invasion, and mild or moderate acanthosis. The accompanying dermal infiltrate of lymphocytes and histiocytes is largely perivascular. The picture may be more inflammatory with superficial crusting, and the more acute inflammatory changes in the epidermis may at times become vesicular, to the extent of mimicking acute contact dermatitis. Other changes described include an erythema multiforme-like process with subepidermal bullae [36], and dermal blood-vessel changes of vasculitis, accompanied by an infiltrate of lymphocytes, histiocytes, neutrophils and eosinophils. Another further histological pattern is a granuloma faciale type of reaction, in which the epidermis and the upper dermis are substantially normal, but the mid-dermis has an infiltrate of neutrophils, eosinophils, lymphocytes, histiocytes and plasma cells in close proximity to dilated blood vessels.

Pustular reactions may be subcorneal or follicular. The folliculitis and perifolliculitis are normally associated with fungal remnants in the follicles. Inflammatory changes range from spongiosis of the outer root sheath, to deep perifollicular granulomatous inflammation showing areas of necrosis and foreign-body giant cells, perhaps induced by fragments of hair exuded from disrupted follicles. In cases of kerion, the histology is that of a combined subacute dermatitis and a marked folliculitis, with disrupted follicles and a diffuse granulomatous inflammatory response with many foreign-body giant cells, blood-vessel changes and fibrosis [36].

In classical annular ringworm, the rim of the lesion is marked by clear inflammatory changes including a perivascular infiltrate of lymphocytes. By contrast, in the central zone inflammation is usually less, possibly following elimination of the fungus in the stratum corneum. For reasons that are not entirely clear but that may depend on the persistence of immunological surveillance [10], previously infected skin remains free of fungal hyphae compared with uninfected, and fungal growth proceeds centrifugally. The epidermal turnover rate is normal within the ring, but more than four times as rapid in the zone where inflammation is maximal. Central clearance is often partial and, in tinea imbricata caused by *T. concentricum*, successive waves of fungal growth occur in skin previously cleared of infection, but overall mycelial expansion is centrifugal.

References

1 Zurita J, Hay RJ. The adherence of dermatophyte microconidia and arthroconidia to human keratinocytes *in vitro*. *J Invest Dermatol* 1987; **89**: 529–34.

2 Al Jabre SHM, Richardson MD, Scott EM *et al*. Adherence of arthroconidia and germlings of anthropophilic and zoophilic varieties of *Trichophyton mentagrophytes* to human corneocytes as an early event in the pathogenesis of dermatophytosis. *Clin Exp Dermatol* 1993; **18**: 231–5.

3 Raubitschek F, Maoz R. Invasion of nails *in vitro* by certain dermatophytes. *J Invest Dermatol* 1957; **28**: 261–8.

4 Lambkin E, Hamilton A, Hay RJ. Partial purification and characterization of a 235000 M_r extracellular proteinase from *Trichophyton rubrum*. *Mycoses* 1994; **37**: 85–92.

5 Yu RJ, Harmon SR, Grappel SF. Two cell bound keratinases of *Trichophyton mentagrophytes*. *J Invest Dermatol* 1971; **56**: 27–32.

6 Siesenop U, Bohm KH. Comparative studies on keratinase production of *Trichophyton mentagrophytes* of animal origin. *Mycoses* 1995; **38**: 205–9.

7 Wagner DK, Sohnle PG. Cutaneous defences against dermatophytes and yeasts. *Clin Microbiol Rev* 1995; **8**: 317–55.

8 Descamps F, Brouta F, Monod M *et al*. Mignon B. Isolation of a *Microsporum canis* gene family encoding three subtilisin-like proteases expressed *in vivo*. *J Invest Dermatol* 2002; **119**: 830–5.

9 Sohnle PG. Dermatophytosis. In: Cox RA, ed. *Immunology of Fungal Diseases*. Florida: CRC Press, 1989; 1–27.

10 Poulain D, Tronchin G, Vernes A *et al*. Experimental study of resistance to infection by *Trichophyton mentagrophytes*: demonstration of memory T cells. *J Invest Dermatol* 1980; **74**: 205–11.

11 King RD, Khan HA, Foye JC *et al*. Transferrin, iron and dermatophytes. 1. Serum dermatophyte inhibitory component definitely identified as unsaturated transferrin. *J Lab Clin Med* 1975; **86**: 204–12.

12 Green F, Lee KW, Balish E. Chronic *T. mentagrophytes* dermatophytosis of guinea pig skin grafts on nude mice. *J Invest Dermatol* 1982; **79**: 125–31.

13 Davies RR, Zaini F. Drugs affecting *Trichophyton rubrum* induced neutrophil chemotaxis *in vitro*. *Clin Exp Dermatol* 1988; **13**: 228–31.

14 Niyonsaba F, Ogawa H. Protective roles of the skin against infection: Implication of naturally occurring human antimicrobial agents β-defensins, cathelicidin LL-37 and lysozyme. *J Dermatol Sci* 2005; **40**: 157–68.
15 Schittek B, Hipfel R, Sauer B *et al*. Dermcidin: a novel human antibiotic peptide secreted by sweat glands. *Nature Immunol* 2001; **2**: 1133–7.
16 Calderon RA, Hay RJ. Fungicidal activity of human neutrophils and monocytes on dermatophyte fungi, *Trichophyton quinckeanum* and *Trichophyton rubrum*. *Immunology* 1986; **61**: 289–95.
17 Hay RJ, Reid S, Talwat E *et al*. Immune responses of patients with tinea imbricata. *Br J Dermatol* 1983; **108**: 581–9.
18 Kaaman T, von Stedingk LV, von Stedingk M *et al*. ELISA determined serological reactivity against purified trichophytin in dermatophytosis. *Acta Derm Venereol (Stockh)* 1981; **61**: 313–7.
19 Calderon RA, Hay RJ. Cell-mediated immunity in experimental murine dermatophytosis. II. Adoptive transfer of immunity to dermatophyte infection by lymphoid cells from donors with acute or chronic infections. *Immunology* 1984; **53**: 405–10.
20 Jones HE, Reinhardt JH, Rinaldi MG. Acquired immunity to dermatophytosis. *Arch Dermatol* 1974; **109**: 840–8.
21 Jones HE, Reinhardt JH, Rinaldi MG. Model dermatophytosis in naturally infected subjects. *Arch Dermatol* 1974; **110**: 369–74.
22 Rasmussen JE, Ahmed AR. Trichophytin reactions in children with tinea capitis. *Arch Dermatol* 1978; **114**: 371–2.
23 Hay RJ, Shennan G. Chronic dermatophyte infections. II. Antibody and cell-mediated immune responses. *Br J Dermatol* 1982; **106**: 191–5.
24 Koga T, Shimizu A, Nakayama J. Interferon-gamma production in peripheral lymphocytes of patients with tinea pedis: comparison of patients with and without tinea unguium. *Med Mycol* 2001; **39**: 87–90.
25 MacGregor JM, Hamilton A, Hay RJ. Possible mechanisms of immune modulation in chronic dermatophytoses: an *in vitro* study. *Br J Dermatol* 1992; **127**: 233–8.
26 Mayou SC, Calderon RA, Goodfellow A *et al*. Deep (subcutaneous) dermatophyte infection presenting with unilateral lymphoedema. *Clin Exp Dermatol* 1987; **12**: 385–8.
27 Torssander J, Karlsson A, Morfeldt-Mason L *et al*. Dermatophytosis and HIV infection: a study in homosexual men. *Acta Derm Venereol (Stockh)* 1988; **68**: 53–9.
28 Hay RJ, Campbell CK, Wingfield R *et al*. A comparative study of dermatophytosis in coal miners and dermatological outpatients. *Br J Indust Med* 1983; **40**: 353–5.
29 Blank F, Mann SJ, Peak PA. Distribution of dermatophytes according to age, ethnic group and sex. *Sabouraudia* 1974; **12**: 352–61.
30 Serjeantson S, Lawrence G. Autosomal recessive inheritance of susceptibility to tinea imbricata. *Lancet* 1977; **i**: 13–5.
31 Hay RJ. Genetic susceptibility to dermatophytosis. *Eur J Epidemiol* 1992; **8**: 346–9.
32 Hay RJ. Chronic dermatophyte infections. I. Clinical and mycological features. *Br J Dermatol* 1982; **106**: 1–6.
33 Allen AM, King RD. Occlusion, carbon dioxide and fungal skin infections. *Lancet* 1978; **1**: 360–2.
34 Bibel DJ, Smiljanic RJ. Interactions of *Trichophyton mentagrophytes* and micrococci on skin culture. *J Invest Dermatol* 1979; **72**: 133–7.
35 Leyden JJ, Kligman AM. Interdigital athletes foot: the interaction of dermatophytes and residual bacteria. *Arch Dermatol* 1978; **114**: 1466–72.
36 Graham JH, Barosso-Tobila C. Dermatophytosis. In: Baker RD, ed. *The Pathologic Anatomy of the Mycoses*. Berlin: Springer-Verlag, 1971: 211–35.

Clinical forms of ringworm infection

The clinical features of dermatophyte infections result from a combination of keratin destruction and an inflammatory host response. The wide variation in clinical presentation depends upon the species and probably the strain of the fungus concerned, upon the size of the inoculum, upon the site of the body infected and upon the immune status of the host. In the following sections, the traditional division of ringworm into different syndromes according to the site of the body infected is followed because it is of considerable merit in terms of diagnosis and management.

Tinea corporis

Synonyms
- Ringworm of the body
- Tinea circinata

Definition. Ringworm of the glabrous skin. The clinical manifestations result from invasion and proliferation of the causal fungi in the stratum corneum. Terminal hair in the affected parts may be invaded. By definition, it includes lesions of the trunk and limbs, excluding ringworm of specialized sites such as the scalp, feet and groins, which are considered below.

Species concerned. All known dermatophytes can produce lesions of the glabrous skin. A comprehensive list of causal species thus corresponds to a complete list of dermatophytes. For any part of the world, the causes of tinea corporis can be assessed by reference to the prevailing dermatophyte flora in the region [1–3]. Some species have predilections for particular parts of the body; for example, *M. audouinii*, classically a cause of tinea capitis, and *T. rubrum*, which most commonly causes tinea pedis but these can, and on many occasions do, cause tinea corporis [4,5].

Pathogenesis. Natural infection is acquired by the deposition of viable arthrospores or hyphae on the surface of the susceptible individual. The source of infection is usually an active lesion on an animal or on another human, although fomite transmission is known to occur, and infection from soil is a well-established if unusual occurrence. In young children infected with *T. rubrum* and *E. floccosum*, half of the infections may come from their parents. In geriatric wards, epidemics may occur [1]. Spread from existing localized infection (e.g. feet, groins, scalp and nails) is not uncommon. Invasion of the skin at the site of infection is followed by centrifugal spread through the horny layer of the epidermis. After this period of establishment (incubation), which lasts 1–3 weeks, the tissue responses to infection become evident. The characteristic annular appearance of many ringworm infections results from the elimination of the fungus from the centre of the lesion, and the subsequent resolution of the inflammatory host response at that site. This area usually becomes resistant to reinfection, although a second wave of centrifugal spread from the original site may occur with the formation of concentric erythematous inflammatory rings. However, many lesions lack any tendency to central clearing. The natural history is very variable. Some inflammatory cases of animal infection resolve spontaneously in a few months, while a typical case of *T. rubrum* tinea corporis may persist for years.

Clinical features. The site of infection is typically on exposed skin, unless the infection represents an extension from a pre-existing infection. In such cases, infection may spread from the scalp, down the neck on to the upper trunk, or from the groins on to the buttocks and lower trunk. Characteristic lesions are circular, usually sharply marginated with a raised edge (Fig. 36.7). Single lesions occur, or there may be multiple plaques. The latter may remain discrete or become confluent. This clinical pattern is often modified in patients with defects in cellular immune responses [6].



Fig. 36.7 Tinea circinata: ringworm.



Fig. 36.8 Nodular folliculitis caused by *Trichophyton rubrum*.

The degree of inflammation is very variable. This feature depends not only on the species of the fungus and the immune status of the host, but it is also very roughly proportional to the extent of follicular invasion; thus, tinea corporis is generally less inflammatory than tinea capitis or tinea barbae. In inflammatory lesions, pustules or vesicles may dominate and even in mild infections close observation may reveal one or two small pustules. Rarely, frank bullae have been reported as an extreme expression of inflammatory change. In less inflammatory infections, scaling is a common but not constant finding. Central resolution, which, as has already been stated, is a common but not invariable feature of tinea corporis, is perhaps more frequent in inflammatory lesions, but it is by no means confined to them. The process is often incomplete, and the central skin may show postinflammatory pigmentation, a change of texture or residual erythematous dermal nodules.

Special forms and species variations. Lesions of the glabrous skin caused by *M. canis* are not rare. They are as common in adults as in children, and are characteristically annular. *M. audouinii* produces short-lived lesions of tinea corporis in perhaps one-third of cases of scalp infection [7]. *T. verrucosum* from cattle, *T. mentagrophytes* var. *erinacei* from hedgehogs, *T. mentagrophytes* var. *mentagrophytes* from small rodents in general, and *M. persicolor* from voles, are all likely to cause inflammatory lesions of exposed skin. Although classically a cause of kerion, *T. verrucosum* can lead to extensive annular lesions of the upper trunk, especially in children [8]. These often start around the neck.

The ubiquitous anthropophilic species *T. rubrum* may invade the buttocks and lower back, as well as more distant sites of the trunk as an extension from tinea cruris. Similar patterns are seen occasionally with *E. floccosum* and *T. megninii*. In infants, ringworm is rare, but the moist conditions of the napkin area may predispose to *E. floccosum* or *T. rubrum* infections [1].

Tinea corporis resulting from *T. rubrum* is often particularly extensive, and the inflammatory margin difficult to distinguish [9]. On the legs and usually extending from the feet, *T. rubrum* may cause typical lesions with raised margins, but rather psoriasiform lichenified plaques without central clearing may also occur, and a variety of vasculitis-like lesions are recognized. The perifollicular granulomatous papules are classical (Fig. 36.8) [10,11], but erythema induratum-like plaques sometimes occur with an almost haemorrhagic appearance.

Tinea imbricata (Tokelau) [12] resulting from *T. concentricum*, an anthropophilic dermatophyte found in southern Asia, the islands of the South Pacific and in Guatemala, southern Mexico and Brazil, causes a distinctive infection. It seems to affect mainly the native peoples of these areas, and although susceptibility may be inherited as an autosomal recessive character [13], it occurs in both sexes and at all ages. Occasional cases may be seen elsewhere in travellers from these regions [14]. The infection begins as a scaling ring; centrifugal spread follows, but within the area of central clearing a second wave of scaling soon arises. The process is repeated to give numerous concentric rings (Fig. 36.9) and, as the natural history is normally extremely prolonged, the whole body may become affected. Pruritus is intense and may lead to lichenification. Hypopigmentation may accompany the lesions [15].

Atypical deep forms of tinea corporis occur. There are some reports of extensive and persistent cases of tinea corporis, in which dermal or subcutaneous involvement has been a feature [16,17]. Occasionally, a specific defect of immune function has been detected, such as a missing plasma factor. In other patients, depression of cellular immune responses is associated with the presence of a serum factor, possibly circulating antigen or immune complexes [6,18]. Such cases may present with dermal nodules, abscesses or draining sinuses [19]. A few particularly bizarre



Fig. 36.9 Tinea imbricata affecting the upper arm.

dermatophyte infections with invasion of bone, central nervous system and lymph nodes have been reported [16,20], but no satisfactory explanation for the highly unusual behaviour of otherwise superficial pathogens is as yet forthcoming.

Differential diagnosis. Although tinea corporis can masquerade as any of a vast number of skin diseases, in practice the diagnosis is usually straightforward.

The characteristic lesions seen with infection resulting from *M. canis* are easily diagnosed, but atypical infections caused by the more exotic fungi and by *T. rubrum* can, on occasion, cause great difficulty. Indeed, the possibility that any red scaly rash on the body is a fungus infection should be considered, because the lesions produced by fungi are so curiously variable. Seborrhoeic dermatitis often causes difficulty, but the condition is symmetrical and there is often associated seborrhoeic dermatitis of the scalp and perhaps intertrigo in the body folds. Psoriasis can lead to confusion in those cases in which the distribution is not quite typical. Its presence on the knees, elbows and scalp, and associated psoriasis of the nails, particularly if pitting is present, is helpful. Patches of impetigo are often confused, particularly when of the circinate type. The finding of staphylococci on a skin swab does not, of course, exclude tinea. Lichenification of a patch of tinea (e.g. of the leg) can mimic lichen simplex very closely. Nummular eczema is a common source of error. The plaques of papulovesicles tend to occur symmetrically on the limbs. Pityriasis rosea is also symmetrical and characteristically confined to the trunk and proximal parts of the limbs, but the herald patch, if seen, is almost impossible to differentiate from ringworm without microscopic examination of scales. Candidosis, tertiary syphilis and pityriasis versicolor should be excluded.

References

1 De Vroey C. Epidemiology of ringworm (dermatophytosis). *Semin Dermatol* 1985; **4**: 185–200.
2 Philpott CM. Geographic distribution of dermatophytes: a review. *J Hyg* 1978; **80**: 301–13.
3 Rippon JW. Epidemiology and emerging patterns of dermatophyte species. In: McGinnis MR, ed. *Current Topics in Medical Mycology*. New York: Springer, 1985; **1**: 208–34.
4 Bhardway G, Hajini GH, Khan IA *et al*. Dermatophytosis in Kashmir, India. *Mykosen* 1987; **30**: 135–8.
5 Blank H, Taplin D, Zaias N. Cutaneous *Trichophyton mentagrophytes* infections in Vietnam. *Arch Dermatol* 1969; **99**: 135–44.
6 Allen DE, Synderman R, Meadows L *et al*. Generalized *Microsporum audouinii* infection and depressed cellular immunity associated with a missing plasma factor for lymphocyte blastogenesis. *Am J Med* 1977; **63**: 991–1000.
7 Friedman L, Derbes VJ. The question of immunity in ringworm infection. *Ann NY Acad Sci* 1960; **89**: 178–83.
8 Hall FR. Ringworm contracted from cattle in Western New York State. *Arch Dermatol* 1966; **94**: 35–7.
9 Rosman N. Infection with *Trichophyton rubrum. Br J Dermatol* 1966; **78**: 208–12.
10 Blank H, Smith JG. Widespread *Trichophyton rubrum* granulomas treated with griseofulvin. *Arch Dermatol* 1960; **81**: 779–85.
11 Wilson JW, Plunkett DA. Nodular granulomatous perifolliculitis due to *Trichophyton rubrum. Arch Dermatol* 1954; **64**: 258–77.
12 Hay RJ. Tinea imbricata. In: Van den Bossche H, Hay RJ, Rinaldi M, eds. *Current Topics in Medical Mycology*, Vol. 2. New York: Springer, 1987: 55–72.
13 Serjeantson S, Lawrence G. Autosomal recessive inheritance of susceptibility to tinea imbricata. *Lancet* 1977; **1**: 13–5.
14 Logan R, Kobza-Black A. Tinea imbricata in a British nurse. *Clin Exp Dermatol* 1988; **13**: 232–3.
15 Hay RJ, Reid S, Talwat E *et al*. Endemic tinea imbricata: a study on Goodenough Island, Papua New Guinea. *Trans R Soc Trop Med* 1984; **78**: 246–51.
16 Liautaud B, Marill FG. La maladie dermatophytique: observations Algeriene récentes. *Bull Soc Fr Pathol Exotique* 1984; **77**: 637–48.
17 Sommer S, Barton RC, Wilkinson SM *et al*. Microbiological and molecular diagnosis of deep localized cutaneous infection with *Trichophyton mentagrophytes. Br J Dermatol* 1999; **141**: 323–5.
18 Mayou SC, Calderon RA, Goodfellow A *et al*. Deep (subcutaneous) dermatophyte infection presenting with unilateral lymphoedema. *Clin Exp Dermatol* 1987; **12**: 385–8.
19 Swart E, Smith FJA. *Trichophyton violaceum* abscesses. *Br J Dermatol* 1979; **101**: 177–83.
20 Chastain MA, Reed RJ, Pankey GA. Deep dermatophytosis: report of two cases and review of the literature. *Cutis* 2001; **67**: 457–62.

Tinea capitis

Synonyms
- Ringworm of the scalp
- Tinea tonsurans

Definition. Ringworm of the scalp in which the essential feature is invasion of hair shafts by a dermatophyte fungus. Ringworm of the beard area, although essentially similar, is discussed separately. Tinea capitis is predominantly an infection of children, although adult cases are seen, particularly with *T. tonsurans* infections. Tinea capitis may also be seen in adults with AIDS.

Species concerned. Most species of dermatophyte are capable of invading hair but some species (e.g. *M. audouinii*, *T. schoenleinii*

and *T. violaceum*) have a distinct predilection for the hair shaft. *E. floccosum*, *T. concentricum* and *T. mentagrophytes* var. *interdigitale* are exceptional in apparently never causing tinea capitis. All dermatophytes causing scalp ringworm can invade glabrous skin and many attack nails as well. Those species of dermatophyte fungi most likely to be causing tinea capitis vary from country to country and from region to region [1–5]. Moreover, in any given location, the species may change with time, particularly as new organisms are introduced by immigration [6,7]. In tinea capitis, anthropophilic species predominate.

The principal feature of tinea capitis in recent years has been the rise of *M. canis* as the dominant organism in infections in some parts of Europe [4], and the spread of *T. tonsurans* in urban communities in the USA [3]. A similar rise in the prevalence of *T. tonsurans* has recently been recorded in urban areas of the UK [8] and in some other European countries [9].

Pathogenesis. The principles of hair invasion and the distinctions between *in vitro* and *in vivo* activity have been already outlined. The spores of ringworm fungi causing tinea capitis can be demonstrated in the air in close proximity to patients with the condition. It is highly likely that scalp hair acts as a trapping device, and it is known that contamination of hair without demonstrable clinical findings may occur among classmates of children with tinea capitis [10,11]. From the classical experimental work of Kligman [12,13] on *M. audouinii*, it is clear that if actual hair infection is to occur, invasion of the stratum corneum of the scalp skin must first develop. Trauma assists inoculation, which is followed, after approximately 3 weeks, by clinical evidence of hair shaft infection. Spread to other follicles proceeds, then for a period of variable duration the infection persists but does not spread further. Finally, there is a period of regression with or without an inflammatory phase.

There are several distinct types of hair invasion that are worthy of note.

***Microsporum* type.** This may be a small-spored ectothrix caused by *M. audouinii*, *M. audouinii* var. *rivalieri*, *M. canis*, *M. canis* var. *distortum*, *M. equinum* or *M. ferrugineum*. In this type, the hair shaft is invaded in mid-follicle. The intrapilary hyphae continue to grow inwards towards the bulb of the hair. Secondary, extrapilary hyphae burst out and grow in a tortuous manner over the surface of the hair shaft, which is growing outwards continuously. These secondary, extrapilary hyphae segment to produce a mass of small arthroconidia (2–3 µm diameter), each one of which becomes rounded off and eventually spherical. The size of these conidia is such that they cannot easily be distinguished as separate structures under the low power of the microscope. Fluorescence under the Wood's lamp is characteristically present in this type of hair invasion.

A similar type of hair invasion occurs with other *Microsporum* species (e.g. *M. gypseum*, *M. fulvum*, *M. nanum* and *M. vanbreuseghemii*). The spores, although similarly arranged, are larger, in this case about 5–8 µm. Fluorescence has been reported in some cases.

***Trichophyton* types.** These may be large-spored ectothrix (in chains) caused by *T. verrucosum*, *T. mentagrophytes* var. *mentagrophytes*, *T. mentagrophytes* var. *erinacei*, *T. megninii* or *T. rubrum* (rarely). The arthroconidia are spherical, arranged in straight chains and again confined to the external surface of the hair shaft. They apparently arise from straight primary extrapilary hyphae, rather than from the hyphae inside the hair. Although size varies with species, up to 10 µm in the case of *T. verrucosum*, they are all larger than those seen in small-spored ectothrix *Microsporum* infection, and individually distinctly visible under the low power of the microscope. There is no fluorescence.

The endothrix type may be caused by *T. tonsurans*, *T. soudanense*, *T. violaceum*, *T. yaoundei*, *T. gourvilii* or *T. rubrum* (rare). Intrapilary hyphae fragment into arthroconidia up to 8 µm in diameter, which are entirely contained within and completely fill the hair shaft. Hair thus affected is especially fragile, and breaks off close to the scalp surface. This type is non-fluorescent.

The favic type is caused by *T. schoenleinii*. Broad, regularly septate hyphae and air spaces are seen in the hair shaft, but disarticulated arthroconidia are absent. The affected hair is less damaged than in other types, and may continue to grow to considerable lengths. Greenish grey fluorescence is present [14]. Air spaces are characteristic and fungal hyphae form clusters in the vicinity of hair follicles.

Clinical features. The clinical appearance of ringworm of the scalp is most variable, depending on the type of hair invasion, the level of host resistance and the degree of inflammatory host response [15,16]. The appearance therefore may vary from a few dull grey, broken-off hairs with a little scaling, detectable only on careful inspection, to a severe, painful, inflammatory mass covering most of the scalp. Itching is variable. In all types, the cardinal features are partial hair loss with inflammation of some degree (Fig. 36.10). It is useful to recognize several basic clinical pictures, as described below.

Small-spored ectothrix type. In *M. audouinii* [1] and *M. ferrugineum* infections, the basic lesions are patches of partial alopecia, often circular in shape, but showing numerous broken-off hairs, dull grey from their coating of arthrospores. Inflammation is

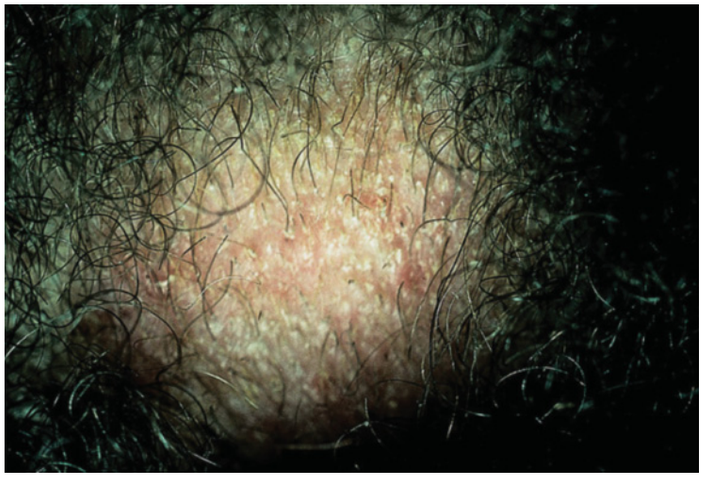


Fig. 36.10 Tinea capitis caused by *Microsporum canis*.

minimal, but fine scaling is characteristic, usually with a fairly sharp margin. There may be several or many such patches arranged more or less randomly. In *M. canis* and in the much rarer *M. canis* var. *distortum* infections, the picture is similar but there is typically more inflammatory change. In infections caused by all these species, green fluorescence under the Wood's lamp is usual, but occasional non-fluorescent cases have been reported, and may not be rare with *M. ferrugineum* (perhaps as many as 10%) [17]. Children are affected much more frequently than adults, although the occasional case of tinea capitis in older patients must not be forgotten [18,19]. The attack rate for epidemic infections caused by anthropophilic species may be as high as 30%, within a school class for example, but it is commonly lower than that [20]. In the past, infection rates of both *M. audouinii* and *M. canis* have been higher in boys than girls [1], often at least twice as high.

Kerion. The most severe pattern of reaction is known as a kerion. It is a painful, inflammatory mass in which such hairs as remain are loose. Follicles may be seen discharging pus, there may be sinus formation, and on rare occasions mycetoma-like grains may be found [21]. Thick crusting with matting of adjacent hairs is common. The area affected may be limited, but multiple plaques are not rare, and occasionally a large confluent lesion may involve much of the scalp. Lymphadenopathy is frequent. Although this violent reaction is usually caused by one of the zoophilic species, typically *T. verrucosum* or *T. mentagrophytes* var. *mentagrophytes*, occasionally a geophilic organism will be isolated, and anthropophilic infections that have been smouldering quietly for weeks may suddenly become inflammatory and develop into kerions if a high degree of hypersensitivity develops [22]. The possibility that a bacterial co-pathogen may be playing some part should not be ignored, and in this type of case a swab sent to the bacterial laboratory is a useful procedure in addition to the plucking of hairs for mycology. Generally, however, pustule formation represents an inflammatory response to the fungus itself [23].

Agminate folliculitis, a somewhat less severe inflammatory ringworm of the scalp consisting of sharply defined, dull red plaques studded with follicular pustules, is also seen in zoophilic infections.

Endothrix infections. In *T. tonsurans* [20,24,25] and *T. violaceum* [25,26] infections, a relatively non-inflammatory type of patchy baldness occurs. Formation of black dots (swollen hair shafts) as the affected hair breaks at the surface of the scalp is classical in this condition, but such findings may be inconspicuous [27]. The patches, which are usually multiple, may show minimal scaling, sometimes mimicking discoid lupus erythematosus, sometimes seborrhoeic dermatitis [28,29]. They are commonly angular in outline rather than round. Other forms include diffuse and patchy alopecia, even with involvement of single isolated hair shafts and without scales. The common clinical types are gray patch (scaling with patchy hair loss), black dot and diffuse alopecia. A low-grade folliculitis is also often seen, while sometimes a frank kerion may develop. The three African species, *T. soudanense*, *T. yaoundei* and *T. gourvilii*, induce very similar lesions, in which the inflammatory reaction is usually mild but occasionally severe. Approximately 2 or 3% of patients have some nail involvement [30,31] or lesions on the face.

Favus. Infection with *T. schoenleinii* is now seen rarely and sporadically in a variety of countries, such as South Africa [32], Ethiopia, where it is still endemic, as well as the Middle East, Pakistan, USA, Canada, the UK and Australia. The classical picture of tinea capitis caused by this organism is characterized by the presence of yellowish cup-shaped crusts known as scutula [33]. Each scutulum develops round a hair, which pierces it centrally. Adjacent crusts enlarge to become confluent and form a mass of yellow crusting. Many patients may show less distinctive changes, in early cases perhaps amounting to no more than perifollicular redness and some matting of the hair. Extensive, patchy hair loss with cicatricial alopecia and atrophy among patches of normal hair may be found in long-standing cases, where much of the hair loss is irreversible. In such patients, the glabrous skin is commonly affected by the development of similar yellowish crusts. Although the initial infection is probably a childhood event in nearly all cases, it shows little if any tendency to clear spontaneously at puberty, particularly in women. Families with several generations affected are well recognized [14].

Differential diagnosis. The differential diagnosis of tinea capitis includes all conditions capable of causing patchy baldness with inflammatory changes of the scalp. Alopecia areata may show erythema and, although of itself it is not a scaly condition, it may coexist with seborrhoeic dermatitis. Such cases can be confusing, although careful examination usually shows that the scaling and the hair loss are not co-extensive. Exclamation-mark hairs must be distinguished from broken hairs of tinea capitis. Traumatic alopecia from hairdressing procedures and trichotillomania may also be confused [34]. Seborrhoeic dermatitis is usually more diffuse than tinea capitis, but in tinea amiantacea the changes are often localized. In this condition, the scaling is adherent to the hair, but breakage of the hair shaft does not normally occur. In psoriasis, hair loss is found only occasionally, and again broken-off hairs are not usually present.

In impetigo, which may be secondary to pediculosis of the scalp, loosening of the hair is not normally present, but matting and crusting due to secondary staphylococcal infection may be present in inflammatory ringworm. A carbuncle of the scalp is much more acutely painful, and shedding of loosened hairs much less evident than in kerion. Discoid lupus erythematosus, lichen planus and other causes of cicatricial alopecia may sometimes have to be considered.

Control [35,36]. It is of considerable importance with scalp ringworm to discover the species involved. Clearly, some information may be obtained from the clinical picture, the presence or absence of fluorescence, etc., but culture is required for this to be firmly established. Where animal species are concerned, the source should be proved mycologically; it is not always the expected one. Domestic pets can often be treated successfully and economically with griseofulvin. Cattle ringworm in calves will normally settle spontaneously. A group of highly infected laboratory mice should probably be destroyed.

With anthropophilic infections, careful investigation of the outbreak or epidemic is recommended, and exclusion of children from school is not recommended [37]. It may also be resented by the parents and lead to non-compliance with treatment. With zoophilic infections such as *M. canis* ringworm, children can normally be allowed to remain at school as infectivity from human to human is small. The main treatments in all these conditions are terbinafine or griseofulvin. Topical therapy has little place, although it is sensible to remove matted crusts and to follow a routine of frequent shampooing.

References

1 Hay RJ. *Tinea Capitis*. London: Mosby Wolfe, 1999.
2 Clayton YM, Midgley G. Tinea capitis in schoolchildren in London. *Hautarzt* 1977; **28**: 32–4.
3 Elewski BE. Tinea capitis: a current perspective. *J Am Acad Dermatol* 2000; **42**: 1–20.
4 Ginter-Hanselmayer G, Stary A, Messeritsch-Fanta C. Current situation of tinea capitis in southeastern Austria. *Clin Dermatol* 2002; **20**: 183–6.
5 Verhagen AR. Distribution of dermatophytes causing tinea capitis in Africa. *Trop Geograph Med* 1978; **26**: 101–20.
6 Karaoui R, Selim M, Mousa A. Incidence of dermatophytosis in Kuwait. *Sabouraudia* 1979; **17**: 131–7.
7 Elewski B. Tinea capitis. *Dermatol Clin* 1996; **14**: 23–31.
8 Hay RJ, Clayton YM, De Silva N *et al*. Tinea capitis in south-east London: a new pattern of infection with public health implications. *Br J Dermatol* 1996; **135**: 955–8.
9 Hay RJ, Robles W, Midgley G, Moore MK; European Confederation of Medical Mycology Working Party on Tinea Capitis. Tinea capitis in Europe: new perspective on an old problem. *J Eur Acad Dermatol Venereol* 2001; **15**: 229–33.
10 MacKenzie DWR. Hairbrush technique in detection and eradication of non-fluorescent scalp ringworm. *BMJ* 1963; **ii**: 363–5.
11 Wright S, Robertson VJ. An institutional survey of tinea capitis in Harare, Zimbabwe and a trial of miconazole cream versus Whitfield's ointment in its treatment. *Clin Exp Dermatol* 1986; **11**: 371–7.
12 Kligman AM. The pathogenesis of tinea capitis due to *Microsporum audouinii* and *Microsporum canis*. *J Invest Dermatol* 1952; **18**: 231–46.
13 Kligman AM. Tinea capitis due to *Microsporum audouinii* and *M. canis*. *Arch Dermatol* 1955; **71**: 313–48.
14 Joly J, Delage G. Favus: 20 indigenous cases in Province of Quebec. *Arch Dermatol* 1973; **114**: 1647–8.
15 Gugnani HC, Njoku-Obi ANU. Tinea capitis in school children in East Nigeria. *Mykosen* 1986; **29**: 132–44.
16 Ive FA. The carrier state of tinea capitis in Nigeria. *Br J Dermatol* 1966; **78**: 219–21.
17 De Vroey C. Epidemiology of ringworm (dermatophytosis). *Semin Dermatol* 1985; **4**: 185–200.
18 Purlsey TV, Raimer SS. Tinea capitis in the elderly. *Int J Dermatol* 1980; **19**: 220–1.
19 Ridley CM. Tinea capitis in an elderly woman. *Clin Exp Dermatol* 1979; **4**: 247–9.
20 Beare JM. Tinea capitis due to *Trichophyton sulphureum*. *Br J Dermatol* 1956; **68**: 193–9.
21 West BC, Kwon-Chung KJ. Mycetoma caused by *Microsporum audouinii*. *Am J Clin Pathol* 1980; **73**: 447–54.
22 Rasmussen JE, Ahmed AR. Trichophytin reactions in children with tinea capitis. *Arch Dermatol* 1978; **114**: 371–2.
23 Birt AR, Wilt JC. Mycology, bacteriology and histopathology of suppurative ringworm. *Arch Dermatol* 1957; **69**: 441–8.
24 Branson DN, Desai DR, Barsky S *et al*. An epidemic of infection with *Trichophyton tonsurans* revealed in a 20-year-old survey of fungal infections in Chicago. *J Am Acad Dermatol* 1983; **8**: 322–30.
25 Rudolph AH. The diagnosis and treatment of tinea capitis due to *Trichophyton tonsurans*. *Int J Dermatol* 1985; **24**: 426–31.
26 Willigen AH, Oranje AP, Ameijden SW-A *et al*. Tinea capitis in the Netherlands. *Mycoses* 1990; **33**: 46–50.
27 Babel D, Baughman SA. Evaluation of the carrier state in juvenile tinea capitis caused by *Trichophyton tonsurans*. *J Am Acad Dermatol* 1989; **21**: 1209–12.
28 Pipkin JL. Tinea capitis in the adult and adolescent. *Arch Dermatol* 1952; **66**: 9–40.
29 Prevost E. Non-fluorescent tinea capitis in Charleston, SC: a diagnostic problem. *JAMA* 1979; **242**: 1765–7.
30 Kalter DC, Hay RJ. Onychomycosis due to *Trichophyton soudanense*. *Clin Exp Dermatol* 1988; **13**: 221–7.
31 Vanbreuseghem R. *Trichophyton soudanense* infection in and outside Africa. *Br J Dermatol* 1968; **80**: 140–8.
32 Scott DB, Scott FP. Dermatophytoses in South Africa. *Sabouraudia* 1973; **11**: 279–82.
33 Blank F. Human favus in Quebec. *Dermatologica* 1962; **125**: 369–81.
34 Shockman J, Urbach F. Tinea capitis in Philadelphia. *Int J Dermatol* 1983; **22**: 521–4.
35 Krowchuk DP, Lucky AW, Primmer SI. Current status of the identification and management of tinea capitis. *Paediatrics* 1983; **72**: 625–31.
36 Roberts SOB. Treatment of superficial and subcutaneous mycoses. In: Speller DCE, ed. *Antifungal Chemotherapy*. Chichester: Wiley, 1980: 255–83.
37 Seale ER, Richardson JB. *Trichophyton tonsurans*: follow-up of treated and untreated cases. *Arch Dermatol* 1960; **81**: 125–32.

Tinea barbae

Synonym
- Ringworm of the beard

Definition. Ringworm of the beard and moustache areas of the face with invasion of coarse hairs. It is thus a disease of the adult male. Tinea of the chin and upper lip in females and children are considered as tinea faciei (ringworm of the glabrous skin of the face).

Species concerned. The animal species *T. verrucosum* and *T. mentagrophytes* var. *mentagrophytes* are responsible for the great majority of cases [1]. *M. canis* is an uncommon cause (eyelashes may be affected in some cases) as is *T. mentagrophytes* var. *erinacei*. The anthropophilic species, *T. violaceum*, *T. schoenleinii*, *T. megninii* and *T. rubrum* [2] are recognized as occasional causes.

Pathogenesis. Although tinea barbae has attracted fewer investigations than tinea capitis, all the available clinical evidence points to a similar pathogenesis. Spread of *T. tonsurans* infections amongst athletes, such as wrestlers, who have close facial contact is well recognized. Infections with *T. verrucosum* and *T. mentagrophytes* var. *mentagrophytes* lead to large-spored ectothrix invasion with the spores in chains. The other less commonly involved species produce their own characteristic type of hair invasion.

Clinical features. The affected men are commonly farm workers in cases caused by the two main species, *T. mentagrophytes* var. *mentagrophytes* and *T. verrucosum*. The clinical picture in these is that of a highly inflammatory pustular folliculitis, often showing all the features of a kerion. Hairs of the beard or moustache regions are surrounded by red inflammatory papules or pustules, usually with exudation or crusting. Many hairs within the affected areas are loose and easily removed with the forceps without causing pain. These inflammatory lesions, although tending eventually to settle spontaneously, often persist for some months. Some infections are less severe and consist of dry, circular, reddish, scaly

lesions enclosing lustreless hair stumps, which are either broken off close to the surface of the skin or plug the follicles.

Differential diagnosis. The classical, highly inflammatory lesions are distinguished from boils by their relative lack of pain. Loosened hairs, although present in some bacterial infections, are rarely as obvious as they are in tinea barbae. The quieter cases of tinea must be distinguished from bacterial folliculitis, acne, rosacea and pseudofolliculitis. The presence of *Staphylococcus aureus* on a swab taken from lesions in this area does not exclude ringworm, as bacterial colonization or frank co-infection may occur in tinea barbae. Unfortunately, mycological cultures are often negative.

Control. Cases of tinea barbae are likely to continue to occur sporadically until more satisfactory means of controlling ringworm in cattle are found. Early diagnosis and prompt treatment of the individual patient and the encouragement of high standards of hygiene in the livestock industry are as much as can be expected in the present state of knowledge. A vaccine against *T. verrucosum* in cattle has resulted in a reduced incidence of infection, not only in cows but also among their human contacts in some countries in eastern Europe [3].

References

1 De Vroey C. Epidemiology of ringworm (dermatophytosis). *Semin Dermatol* 1985; **4**: 185–200.

2 Ive FA, Marks R. Tinea incognito. *BMJ* 1968; **iii**: 216–21.

3 Sarkisov AK, Koromyslov G. *Proposals for the Prevention and Control of Dermatophytoses Common to Man and Animals*. WHO Doc, Zoon/83.62. Geneva: WHO, 1993.

Tinea faciei

Synonyms

- Ringworm of the face
- Tinea faciale

Definition. Infection of the glabrous skin of the face with a dermatophyte fungus (the moustache and beard areas of the adult male are excluded).

Species concerned. *T. mentagrophytes* var. *mentagrophytes* and *T. rubrum* predominate but *T. tonsurans*, *M. audouinii* and *M. canis* are also common causes worldwide. *T. concentricum* frequently spreads to the face in cases of tinea imbricata and, as with tinea corporis, all dermatophytes must be considered potentially capable of producing this condition.

Pathogenesis. Facial skin may be infected either by direct inoculation of a dermatophyte fungus from an external source (e.g. *T. mentagrophytes* var. *mentagrophytes* from an infected pet mouse) or there may be secondary spread from pre-existing tinea of another body site. The latter pattern is likely to occur with *T. rubrum* as well as with *T. concentricum* infections. *T. tonsurans* infection of the face can be seen in wrestlers.

Clinical features. The prime reason for separating tinea faciei from tinea corporis in this account is to draw attention to the frequency of misdiagnosis in facial ringworm [1]. The clinical features vary considerably, but complaints of itching, burning and exacerbation after sun exposure are common. The last mentioned symptom is a frequent source of diagnostic error [2]. There will often be a history of exposure to animals. Erythema is usual, but scaling is present in fewer than two-thirds of cases. A substantial proportion of patients do show annular or circinate lesions, and induration with a raised margin is present in about half (Fig. 36.11). Simple papular lesions, and in some cases completely flat patches of erythema, also occur. A few vesicles or pustules may be found, but these are rarely conspicuous. The application of topical steroids may be expected to modify the appearance still further, and in the authors' experience this complication is as frequent among patients with tinea faciei as it is in those with tinea cruris.



Fig. 36.11 Tinea faciei caused by *Trichophyton rubrum*.

Differential diagnosis. Because of light sensitivity, the frequent absence of scaling and the somewhat nondescript appearance, this condition may be confused with discoid lupus erythematosus (DLE) [1] and polymorphic light eruption. Moreover, tinea faciei coexisting with DLE has been described [3]. Bowenoid solar keratoses, psoriasis, impetigo, rosacea, seborrhoeic dermatitis [4] and benign lymphocytic infiltrates must also be considered. Reluctance to biopsy the face adds to the problem, but if the possibility of tinea faciei is remembered, careful examination and scrapings taken from the skin surface, even if this is not obviously scaly, should enable a diagnosis to be made. General examination of the skin, particularly the scalp, should not be forgotten. If topical steroids have been applied, a cessation of the therapy may be followed a few days later by a great increase in scaling and by appearances much more readily diagnosable.

Control. Pets and laboratory animals may require treatment or elimination according to their value. It is customary to give short-term oral antifungal treatment, but the authors have seen minimal lesions respond well to topical imidazoles. Long-standing steroid-modified cases, especially those resulting from *T. rubrum*, may require prolonged oral antifungal therapy.

References

1 Gilgar RS, Tindall JP, Elson M. Lupus erythematosus-like tinea of the face (tinea faciale). *JAMA* 1971; **215**: 2091–4.
2 Pravda DJ, Pugliese MM. Tinea faciei. *Arch Dermatol* 1978; **114**: 250–2.
3 Safer LF, Lang PG, Demetree JW *et al*. Tinea faciei coexistent with discoid lupus erythematosus. *Arch Dermatol* 1981; **117**: 121–2.
4 Pernicario C, Peters MS. Tinea faciale mimicking seborrheic dermatitis in a patient with AIDS. *N Engl J Med* 1986; **314**: 315–6.

Tinea pedis

Synonyms
- Foot ringworm
- Athlete's foot

Definition. Infection of the feet or toes with a dermatophyte fungus. The term athlete's foot is used by some to imply any form of toe cleft intertrigo. In this account, we therefore prefer the terms tinea pedis or foot ringworm, which clearly exclude infections caused by bacteria, *Candida* and non-dermatophyte moulds.

Species concerned. Three anthropophilic species, *T. rubrum*, *T. mentagrophytes* var. *interdigitale* and *E. floccosum*, are together responsible for the vast majority of cases of foot ringworm throughout the world. Double infections with any two of these species occur and, for precision, especially in clinical surveys, it is useful to adopt a standard terminology to describe them. Combined infections are those in which different species are present in the same lesion. Concurrent infections are those in which different species are found in different lesions at the same time, and consecutive infections are those in which the same patient has a different organism at the single site on different occasions. Other species, including zoophilic ones, occur occasionally as a cause of tinea pedis. In countries where *T. violaceum* is common, foot involvement with this anthropophilic species is sometimes seen and may be very intractable [1]. The relative numerical importance of the three main species of dermatophyte can be discovered from the extensive published data on foot ringworm seen in dermatological clinics throughout the world. Although minor variations are frequent, an average clinic sample would be: *T. rubrum* infections, 70%; *T. mentagrophytes* var. *interdigitale* infections, 15%; *E. floccosum* infections, less than 10%; mixed infections, 5%. The prevalence of *T. rubrum* infections has been growing over several decades [2]. Prior to 1970, in surveys of populations consisting of subjects in institutions, coal mines [3] or swimming baths [4], the relative frequency of infections with *T. mentagrophytes* var. *interdigitale* was higher than those caused by *T. rubrum*. *T. mentagrophytes* var. *interdigitale* would outnumber *T. rubrum* by as much as eight to one [5,6]. Since 1980, surveys in industry have indicated that this pattern is changing, with over 80% of isolates being *T. rubrum*. A high proportion of patients also have Gram-negative bacterial infection of the web spaces [7,8].

Pathogenesis. Tinea pedis is the most common form of dermatophyte infection in the UK and North America [9], and probably throughout the developed world. Occlusion of toe clefts through wearing shoes predisposes to this condition, which is in most cases initially a lateral web space infection. The condition is more common in adults than children, but may begin to occur in young children aged 6 or more. The mean age of onset was 15 years in one survey [10]. Overall prevalence within the community and including all age groups is not reliably known, but extrapolation from the most useful surveys [4,10] suggests that in the developed world at any one time as many as 10% of the total population may be expected to have dermatophyte infections of the toe clefts. Adult males probably have about a 20% chance of developing tinea pedis, while among women only 5% are likely to become chronically infected. Living in an institution, especially where washing facilities are shared, is likely to increase the chances of infection [10,11]. Prevalence figures as high as 80% have been reported among German miners, and in some wards of a long-stay hospital more than two-thirds of the patients were infected [11]. Nevertheless, tinea pedis may be equally well transmitted within the family bathroom [12]. Among dermatological outpatients with *T. rubrum* infections there is a significant excess of atopics [13], but in a study of coalminers with recurrent *T. rubrum* tinea pedis this was not so [14], suggesting perhaps that reinfection from the environment is important in their case.

Experimental evidence [15] suggests the importance of maceration in dermatophyte infections of the toe clefts. These moist conditions probably favour growth of the fungus directly, and damage the stratum corneum at the same time. A simultaneous increase in the bacterial flora is likely and may also play a part. There is growing evidence that during some symptomatic episodes in chronic tinea pedis, resident bacteria, such as large-colony coryneforms, may be acting as important co-pathogens, but whether or not they assist in initiating new infections remains, so far, unknown [16].

Although dermatophytes are occasionally isolated from clinically normal toe clefts, and a contrary situation exists in which mildly abnormal toe clefts yield no dermatophytes, it is now generally held that where dermatophytes are present (in perhaps 10% of the population) they do cause abnormalities, and are not in the true sense members of the normal skin flora. The sex differences in the level of tinea pedis may be partly explained by different exposure to the causal fungi. In this context, in one survey the level of infection among men who attended swimming baths was higher than those that did not. In contrast, surveys at a swimming bath showed that the level of infection among girl swimmers was only one-quarter of that among boy swimmers [4]. However, further enquiry showed that the girls swam much less than the boys, so that there was, even in this instance, a true difference in exposure, although both groups went swimming. The sex difference in choice of footwear—men generally wearing more occlusive and heavier footwear throughout the year than women—is probably important and this correlates well with the known rarity of interdigital tinea pedis among those who habitually go barefoot [17].

Clinical features. The most common form of tinea pedis is an intertriginous dermatitis characterized by peeling, maceration and fissuring affecting the lateral toe clefts, and sometimes spreading to involve the undersurface of the toes. This picture may be produced by any of the three species. Itching is a common complaint in warm weather. The condition is highly persistent. In *T. rubrum*



Fig. 36.12 Dry-type *Trichophyton rubrum* infection.



Fig. 36.14 *Trichophyton mentagrophytes* var. *interdigitale* infection: bullous lesion on the sole.



Fig. 36.13 Tinea pedis spreading to the dorsum of the foot.

infections, a scaling hyperkeratotic variety, which is particularly chronic and resistant to treatment and which affects the soles, heels and sides of the feet, is often found. The affected areas are pink and covered with fine silvery white scales. If the foot is extensively involved, the term 'moccasin foot' or dry-type infection are sometimes applied (Fig. 36.12). The dorsal surfaces of the toes and feet are not often affected (Fig. 36.13), but associated nail infection is very common. As well as itching of the feet, the patient may also complain of their smell, and secondary bacterial infection, with fissuring in the toe clefts, may aggravate symptoms [16].

The changes produced by *T. mentagrophytes* var. *interdigitale* vary from mild insignificant scaling in the toe clefts to severe acute inflammatory reactions affecting all parts of the feet [18]. A vesiculobullous reaction is more likely to be caused by this species than by any other fungus (Fig. 36.14). The reaction may occasionally extend over the whole sole. It may be preceded for months or years by maceration or fissuring in the toe clefts. Vesicles may become pustules, and when they rupture they tend to leave collarettes of scaling with the intervening skin normal, or showing various degrees of scaling and inflammation. This variety of ringworm frequently goes on to apparent spontaneous cure, but tends to recur in warm weather; indeed, under hot humid conditions the inflammatory reaction may be extremely incapacitating. There may be associated hyperhidrosis.

Apart from mild toe cleft intertrigo, *E. floccosum* may produce on occasions a vesicular infection of the sole similar to that typically produced by *T. mentagrophytes* var. *interdigitale*, or a dry hyperkeratotic condition resembling infections caused by *T. rubrum*. With *Epidermophyton* infections, there is significantly less toenail involvement than with *T. rubrum* or *T. mentagrophytes* var. *interdigitale*, but chronicity of the skin infection may be just as troublesome.

When the lesions on the feet are acutely vesicular, irrespective of the fungus responsible, a vesicular allergic reaction (ide) may develop on the uninfected hands. This clinical picture, which closely simulates pompholyx, was vastly overdiagnosed in the past but is now known to be quite uncommon, and an ide reaction of this type should not be considered unless the primary foot condition is acutely inflammatory.

The presence of interdigital tinea pedis is a risk factor for cellulitis in patients with lymphoedema.

Differential diagnosis. *Scytalidium* and *Fusarium* infection may mimic interdigital tinea pedis, the former also produces dry type infections. Where changes are largely restricted to the toe cleft, erythrasma, which is usually asymptomatic and rarely causes fissures, and candidosis, which is characterized by a build-up of rather more white macerated skin, must both be considered. Other bacterial infections with staphylococci or streptococci or Gram-negative organisms, including *Acinetobacter* species, can produce inflammation and often odour. Any of these organisms may coexist with tinea pedis, contributing to a greater or lesser extent to the abnormalities seen. Apart from swabs and scrapings for bacteria and ringworm organisms, the Wood's lamp, which may show pink fluorescence for erythrasma and a greenish blue for *Pseudomonas* infections, may be useful.

Soft corns or callosities, sometimes with sinus formation, are common in the lateral toe clefts, especially in women. Younger children do not commonly suffer from foot ringworm but frequently have eczema of the foot such as juvenile plantar dermatosis. Where the sole of the foot is affected without obvious involvement of the toe cleft, a diagnosis of pustular psoriasis must be considered. The latter condition more commonly affects the heels than does tinea, but this is not a reliable criterion. Psoriasis, pityriasis rubra pilaris, Reiter's syndrome, contact dermatitis from nylon dyes or shoe materials, and tylosis may all need to be excluded. Scrapings by which a positive diagnosis of tinea pedis may be established should always be taken, and they may need to be repeated if an initial negative result is incompatible with the clinical features.

Control. Clearly, if infected individuals avoided exposing others to their infection by not walking on the floors of communal changing rooms and by avoiding swimming baths, the level of infection in the community would fall. Because such large numbers of people are involved, many of whom are completely asymptomatic, this is usually not feasible. Moreover, eradication of these fungi from the toe clefts is often a long and tedious process, and elimination of the organism may never be achieved. Among industrial workers using communal showers, it is virtually impossible to avoid continual exposure to infection. There are two simple measures that do seem fruitful. Frequent hosing of the floors of shower rooms and the sides of swimming baths does reduce the prevalence of dermatophytes on these surfaces, and probably would lead to a reduction of infection in time. This should certainly be encouraged. Satisfactory antifungal powder is readily available, and encouragement of its use has been demonstrated to be effective in the long-term reduction of tinea pedis at one swimming bath.

References

1 Pock-Steen B. Persistent mycosis of the nails caused by *Trichophyton violaceum*. *Acta Derm Venereol (Stockh)* 1967; **47**: 34–6.
2 de Vroey C. Epidemiology of ringworm (dermatophytosis). *Semin Dermatol* 1985; **4**: 185–200.
3 Gentles GC, Holmes JG. Foot ringworm in coal miners. *Br J Indust Med* 1957; **14**: 22–9.
4 Gentles GC, Evans EGV. Foot infection in swimming baths. *BMJ* 1973; **3**: 260–2.
5 English MP, Gibson MD. Studies in the epidemiology of tinea pedis. I and II. Tinea pedis in school children. *BMJ* 1959; **i**: 1442–5; 1446–8.
6 English MP, Gibson MD, Warin RP. Studies in the epidemiology of tinea pedis. vi. Tinea pedis in a boy's boarding school. *BMJ* 1961; **i**: 1083–6.
7 Hope YM, Clayton YM, Hay RJ *et al*. Foot infection in coal miners: a reassessment. *Br J Dermatol* 1985; **112**: 405–13.
8 Howell SA, Clayton YM, Phan QC *et al*. Tinea pedis: the relationship between symptoms and host characteristics. *Microbiol Ecol Health Dis* 1988; **1**: 131–8.
9 Rothman S, Knox G, Windhorst D. Tinea pedis: a source of infection in the family. *Arch Dermatol* 1957; **75**: 270–1.
10 Jones HE, Reinhardt JH, Rinaldi MG. A clinical, mycological and immunological survey of dermatophytes. *Arch Dermatol* 1973; **108**: 61–8.
11 English MP. Tinea pedis as a public health problem. *Br J Dermatol* 1969; **81**: 705–7.
12 English MP. *Trichophyton rubrum* infection in families. *BMJ* 1959; **i**: 744–6.
13 Hay RJ. Chronic dermatophyte infections. I. Clinical and mycological features. *Br J Dermatol* 1982; **106**: 1–6.
14 Hay RJ, Campbell CK, Wingfield R *et al*. A comparative study of dermatophytosis in coal miners and dermatological outpatients. *Br J Indust Med* 1983; **40**: 353–5.
15 Strauss JS, Kligman AM. An experimental study of the tinea pedis and onychomycosis of the foot. *Arch Dermatol* 1957; **76**: 70–9.
16 Leyden JJ, Kligman AM. Interdigital athlete's foot: the interaction of dermatophytes and residual bacteria. *Arch Dermatol* 1978; **114**: 1466–72.
17 Rippon JW. Epidemiology and emerging patterns of dermatophyte species. In: *Current Topics in Medical Mycology*, Vol 1. New York: Springer, 1985: 208–34.
18 Blank H, Taplin D, Zaias N. Cutaneous *Trichophyton mentagrophytes* infection in Vietnam. *Arch Dermatol* 1969; **99**: 135–44.

Tinea manuum

Synonym
- Ringworm of the hand

Definition. Any species of dermatophyte may affect the skin of the hand. Infections of the dorsal surface present no specific features and are considered as ringworm of the glabrous skin under tinea corporis. This section is therefore concerned with ringworm of palmar skin and with infections beginning under rings.

Species concerned. For the most part, the organisms concerned are the three anthropophilic species involved in tinea pedis. *T. rubrum* is, among cases coming to the skin clinics, the most common cause by far. *E. floccosum* and *T. mentagrophytes* var. *interdigitale* are involved in a small minority of cases and mainly in the presence of pre-existing palmar plantar keratoderma such as tylosis.

The anthropophilic species *T. violaceum* may also produce this clinical picture and animal species may occasionally infect the palmar skin. *T. mentagrophytes* var. *erinacei* from contact with hedgehogs has been notable in this regard.

Pathogenesis. In most cases, apart from animal infections, there is pre-existing foot infection with or without toenail involvement. A special mention should be made of ringworm beginning under rings, wrist watches, and where anatomical deformities or occupational usage predispose to maceration between the fingers. Here, there may be a particular susceptibility to *T. mentagrophytes* var. *interdigitale* infections, and in such cases infection may occur without obvious foot involvement [1]. Poor peripheral circulation and palmar keratoderma are other possible predisposing factors [2].

Clinical features. *T. rubrum* infection may take several different clinical forms. Hyperkeratosis of the palms and fingers affecting the skin diffusely is the most common variety, and is unilateral in about half of cases. The accentuation of the flexural creases is a characteristic feature. Other clinical variants include crescentic exfoliating scales, circumscribed vesicular patches, discrete red papular and follicular scaly patches, and erythematous scaly sheets on the dorsal surface of the hand. The latter forms are more likely to be zoophilic infections.

Differential diagnosis. Dermatophyte infections of the palm are often quiet and chronic, commonly passing unnoticed or misdiagnosed. Contact dermatitis, especially the primary irritant variety, psoriasis, pityriasis rubra pilaris, constitutional eczemas, keratoderma, syphilis and post-streptococcal peeling must all be considered. In ring infections and web space cases with anato-

mical deformity, candidosis and bacterial intertrigo should be excluded.

Unilateral scaling should always alert the clinician to the necessity of taking scrapings. Nail changes may help: pitting suggests psoriasis, but subungual hyperkeratosis if present should always be scraped. If the palmar infection spreads to the dorsal surface, more classical annular lesions may be seen, although this happens relatively infrequently. Tinea manuum, like tinea cruris and tinea faciei, is sometimes modified by inappropriate treatment with topical steroids leading to further diagnostic difficulties.

Control. The prevalence of tinea manuum is directly related to the level of tinea pedis in the population. Prompt treatment of tinea pedis and the use of separate towels are sensible measures that can be recommended, but it is likely that tinea manuum will continue to occur sporadically and a greater awareness of this condition, so that it may be recognized promptly, is of prime importance.

References

1 Marcussen PV. Mycotic infections of the hands. *Acta Derm Venereol (Stockh)* 1956; **36**: 272–8.

2 Elmros T, Liden S. Hereditary palmoplantar keratoderma: incidence of dermatophyte infections and the results of treatment with retinoic acid. *Acta Dermatol Venereol (Stockh)* 1983; **63**: 254–7.

Tinea cruris

Synonyms

- Ringworm of the groin
- Dhobie itch
- Eczema marginatum

Definition. Infection of the groins by a species of dermatophyte.

Species concerned. The causal species are those implicated in foot ringworm but in different proportions. *T. rubrum* is the main cause [1]; *T. mentagrophytes* var. *interdigitale* and *E. floccosum* also account for some cases.

Pathogenesis. Ringworm of the groins is a common condition throughout the world, and is probably more prevalent in tropical zones and particularly among migrants from temperate countries. The warm humid conditions in this site seem important [2]. This condition has always been much more common in men than in women [3].

Apart from the numerous cases of autoinfection from the foot to the groin [4], the sharing of towels and sports clothing is important [5]. In cases thus contracted, the toe clefts may be normal.

Clinical features. Whatever the causal species, itching is a predominant feature. The lesions in the early stages are erythematous plaques, curved with sharp margins extending from the groin down the thighs. Scaling is variable, and occasionally may mask the inflammatory changes. Vesiculation is rare, but dermal nodules forming beading along the edge are commonly found in older lesions. One or two minute pustules are often detected if sought with care. Some central clearance is usually present, but is often incomplete with nodules scattered throughout the affected area.

Satellite lesions, if present, are few in number and relatively large. Spread to the scrotum is common, but scaling is minimal and inflammation inconspicuous against a background erythema [6]. *E. floccosum* infections are clinically indistinguishable from *T. rubrum* infections, but are often not associated with tinea pedis. *T. rubrum* cases are classically chronic and sometimes more nodular. The rarer *T. mentagrophytes* var. *interdigitale* infections may be vesicular and inflammatory. Extension of infection from the groins to other sites is common, in *T. rubrum* classically to the buttocks, the lower back and the abdomen. The penis is occasionally affected.

Differential diagnosis. Candidosis, which is more common in women, does not have a distinct raised margin. White pustules are often found, satellite lesions are numerous and small, and the frayed peeling edge that occurs as the tiny pustules rupture is characteristic. Pityriasis versicolor may be localized to the groin but is usually non-inflammatory and asymptomatic, as is erythrasma. Central clearing is rarely found in either of these infections.

Intertrigo with heavy bacterial colonization is common in the obese subject of either sex. It may show a sharp margin, but this edge is usually a simple curve where the opposed skin surfaces meet. In many cases, extension upwards from the groin is as prominent as that down the thigh, a feature usually absent in tinea cruris. The central skin is often macerated and the submammary, periumbilical and axillary skin may also be affected, resembling flexural seborrhoeic dermatitis. However, this feature is not a completely reliable distinguishing criterion, as *E. floccosum* in particular may involve the axillae and the submammary areas. Psoriasis and mycosis fungoides may occasionally mimic tinea cruris, but characteristic lesions in other sites can usually be found. In atopic eczema there may be lichenification, but these changes usually extend up towards the hip. Contact dermatitis from clothing or deodorants may confuse, and Hailey–Hailey disease and flexural Darier's disease require consideration.

Topical steroids lead to suppression of the physical signs of tinea cruris.

Control. Greater control of foot ringworm might lead to fewer cases of tinea cruris. A person suffering from tinea pedis or cruris should not lend towels to others, even if they have been laundered. In the tropics, sensible clothing and prompt treatment of tinea pedis are probably of considerable importance. Topical therapy is often sufficient to control early cases, but long-established *T. rubrum* infection will require terbinafine or itraconazole.

References

1 Foster KW, Ghannoum MA, Elewski BE. Epidemiologic surveillance of cutaneous fungal infection in the United States from 1999 to 2002. *J Am Acad Dermatol* 2004; **50**: 748–52.

2 Amer M, Taha M, Tossan Z *et al*. The frequency of causative dermatophytes in Egypt. *Int J Dermatol* 1981; **20**: 431–4.

3 Blank F, Mann SJ, Peak PA. Distribution of dermatophytes according to age, ethnic group and sex. *Sabouraudia* 1974; **12**: 352–61.

4 Rosman N. Infection with *Trichophyton rubrum*. *Br J Dermatol* 1966; **78**: 208–12.

5 Blank F, Mann SJ. *Trichophyton rubrum* infection according to age, anatomical distribution and sex. *Br J Dermatol* 1975; **92**: 171–4.
6 La Touche CJ. Scrotal dermatophytosis. *Br J Dermatol* 1967; **79**: 339–44.

Onychomycosis caused by dermatophytes

Synonyms
- Ringworm of the nails
- Tinea unguium

Definition. Invasion of the nail plates by species of dermatophytes. A different category of onychomycosis is associated with certain other species of filamentous fungi that are frequently found in dystrophic nails; these are considered separately [1,2].

Species concerned. The principal dermatophytes concerned are: (i) with associated foot and hand infections—*T. rubrum*, *T. mentagrophytes* var. *interdigitale* and *E. floccosum*; (ii) with associated scalp infections—*T. tonsurans*, *T. violaceum* and *T. soudanensei*.

Pathogenesis. Ringworm of the nails occurs in all parts of the world, and almost all dermatophytes have been reported to infect nails at one time or another [3]. Although nail infections may be the only manifestation of fungus disease in a patient, in the great majority of cases they are associated with tinea pedis or tinea manuum, and the three dermatophytes most commonly implicated are therefore *T. rubrum*, *T. mentagrophytes* var. *interdigitale* and, rarely, *E. floccosum* [4–6].

T. soudanense has been reported as a cause of onychomycosis, and other dermatophytes usually encountered as a cause of tinea capitis, such as *T. tonsurans* and *T. violaceum*, not infrequently infect fingernails. In regions or populations where tinea pedis is uncommon and tinea capitis caused by these fungi is frequent, they are likely to predominate as a cause of onychomycosis.

It is likely that *T. rubrum* invades the nail plate with relative ease [3]. *T. rubrum* predominates in fingernail infections, owing no doubt to the prevalence of that species in tinea manuum. It is also the main cause of infection of the toenails. *T. mentagrophytes* var. *interdigitale* is a less common cause, and often only affects the great toenail. Invasion of the nail plate usually occurs either from the lateral nail fold or from the free edge and an elaborate network of channels and lacunae is formed [7], leading to opacity and eventually destruction and crumbling of the nail plate. Subungual hyperkeratosis, sometimes difficult to distinguish from softening of the nail plate proper, frequently occurs, but the mechanism of its production is obscure. As might be expected from the age distribution of tinea pedis, onychomycosis is largely a disease of adults [8], but children, especially those in institutions and in households where the adults are infected with *T. rubrum*, may be infected from time to time. A poor peripheral circulation is frequently blamed for resistance to treatment [9]. It may also be a factor in susceptibility. Nails that have been traumatized and nails of elderly people, where the linear growth is slow, are both unduly susceptible to infection.

Clinical features [2]. Five distinct patterns of tinea unguium have been described.



Fig. 36.15 Onychomycosis caused by *Trichophyton rubrum*.

Distal and lateral subungual onychomycosis. Distal and lateral subungual onychomycosis (DLSO) is the most common pattern of infection, and usually presents as a streak or a patch of discoloration, white or yellow at the free edge of the nail plate, often near the lateral nail fold. The initial invasion of the hyponychium shows through a relatively normal dorsal nail plate. It commonly spreads towards the base of the nail and may occasionally become darker brown or black (Fig. 36.15). The nail plate becomes obviously thickened, and may crack as it is lifted up by the accumulation of soft subungual hyperkeratosis. A later phase of invasion may lead to massive destruction of the nail plate (total dystrophic onychomycosis; TDO). Although commonly starting with a single affected nail, other digits later become invaded. The variation in the severity of damage is sometimes marked, so that minor changes, a little discoloration or just fraying of the nails, may be all that is seen. Indeed, nail clippings may reveal fungus mycelium in nails that appear completely normal [10].

Superficial white onychomycosis. Superficial white onychomycosis (SWO) is a less common presentation and can produce a distinct form of nail invasion in which the dorsal surface of the nail plate is eroded in well-circumscribed powdery white patches, often away from the free edge [11]. Striate banding may also occur. It is distinguishable from other causes of leukonychia by the powdery nature of the white material, which can easily be scraped away. The whole surface of the nail plate may be thus affected, and occasionally this picture may also coexist with deep invasion of the nail plate of the ordinary type starting at the free edge. In some patients, superficial infection appears to originate from beneath the proximal nail fold and such cases respond poorly to topical therapy. Although more common with *T. mentagrophytes* var. *interdigitale*, it can occasionally be seen in *T. rubrum* infections and also occurs with certain non-dermatophytes, for example *Fusarium* spp. Toenails are usually affected, but in AIDS patients SWO of both toe- and fingernails has been reported [12]. In AIDS patients, superficial infection may coexist with proximal nail plate invasion (see below).

Proximal subungual onychomycosis. This is a pattern that was very uncommon, but in the last 10 years has become particularly associated with AIDS patients. Rapid invasion of the nail plate from the posterior nail fold may develop to produce a white nail with only marginal increase in thickness [12]. The most common cause is currently *T. rubrum*, although in the past more unusual species such as *T. megninii* were associated with this picture. The origin of these infections is not clear.

Endonyx onychomycosis. This is seen with infection caused by dermatophytes that cause endothrix scalp infections, notably *T. soudanense*. The nail plate is scarred with pits and lamellar splits. The invasion occurs from the top surface, but penetrates deeply into the nail plate.

Totally dystrophic onychomycosis. This is the final common pathway for severe infection where the nail plate is completely destroyed.

On occasion, patients with onycholysis alone may have positive cultures of dermatophytes, suggesting that carriage of dermatophytes without invasion is possible [13].

Differential diagnosis. The destructive changes of the nail plate and nail bed produced by dermatophytes can be mimicked closely by psoriasis. Fine pitting of the dorsal nail plate is never produced by fungal infections and strongly suggests psoriasis, as does the oil-drop sign away from the free edge. The irregularly buckled nail of eczema and the ridged or dysplastic nail of lichen planus must be distinguished. Paronychia, caused either by bacteria or by *Candida*, usually affects the nail plate proximally and laterally, while the free edge is often spared, at least initially. Conversely, swelling of the nail fold is rare in dermatophyte infections, and purulent discharge is never a feature of uncomplicated tinea unguium. Onycholysis and other nail dystrophies must be considered. Ringworm of the nails is rarely symmetrical, and it is common to find the nails of only one hand affected. The skin of the feet and of the palms should always be examined carefully. Nail clippings or scrapings are essential, and direct microscopy should be carried out with great care, as culture often fails with nail plate material [10,14]. For this reason, it is wise to sample any obvious skin lesions present, as these are usually infected with the same organism and will be more likely to yield a positive culture [15]. It must be remembered that double pathologies do occur and a nail, dystrophic from some other cause, may become invaded by a dermatophyte fungus. This is not uncommon with onychogryphosis. New molecular diagnostic methods may help to resolve some of these uncertainties [16].

Control. Proper early treatment of tinea pedis and manuum would almost certainly reduce the prevalence of tinea unguium.

References

1 Baran R, Hay RJ, Haneke E, Tosti A. *Onychomycosis: the Current Approach to Diagnosis and Treatment*. Oxford: Taylor and Francis, 2006.
2 Zaias N. Onychomycosis. *Arch Dermatol* 1970; **105**: 262–74.
3 English MP. Nails and fungi. *Br J Dermatol* 1976; **74**: 697–701.
4 English M, Atkinson R. An improved method for the isolation of fungi from onychomycosis. *Br J Dermatol* 1973; **88**: 273–6.
5 Walshe MM, English MP. Fungi in nails. *Br J Dermatol* 1966; **78**: 198–207.
6 Zaias N, Oertel I, Elliott DF. Fungi in toe nails. *J Invest Dermatol* 1969; **53**: 140–2.
7 Alkiewicz J. Transverse net in the diagnosis of onychomycosis. *Arch Dermatol* 1947; **58**: 385–8.
8 Philpot CM, Shuttleworth D. Dermatophyte onychomycosis in children. *Clin Exp Dermatol* 1989; **14**: 203–5.
9 Sowinski W. *Trichophyton* entrance sites in the nails of man. In: Drouhet E, ed. *Proceedings of the Vth Congress of the International Society for Human and Animal Mycology*. Paris: Institut Pasteur, 1971: 111–2.
10 Davies RR. Mycological tests and onychomycosis. *J Clin Pathol* 1968; **21**: 729–30.
11 Zaias N. Superficial white onychomycosis. *Sabouraudia* 1966; **5**: 99–103.
12 Dompmartin D, Dompmartin A, Deluol AM *et al*. Onychomycosis and AIDS. *Int J Dermatol* 1990; **29**: 337–9.
13 Baran R, Badillet G. Primary onycholysis of the big toe nails: review of 133 cases. *Br J Dermatol* 1982; **106**: 529–31.
14 Achten G, Wanet-Rouard J. Onychomycosis in the laboratory. *Mykosen* 1978; **21** (Suppl. 1): 125–8.
15 Midgley G, Moore MK. Nail infections. *Dermatol Clin* 1996; **14**: 41–9.
16 Binstock JM. Molecular biology techniques for identifying dermatophytes and their possible use in diagnosing onychomycosis in human toenail: a review. *J Am Podiatric Med Assoc* 2007; **97**: 134–44.

Steroid-modified tinea

Synonym
- Tinea incognito

Definition. Ringworm infections modified by corticosteroids, systemic or topical, prescribed for some pre-existing pathology or given mistakenly for the treatment of misdiagnosed tinea.

Pathogenesis and clinical features [1–3]. Normally, the clinical diagnosis of tinea depends heavily on the inflammatory changes involved. This inflammatory response may be almost totally suppressed by corticosteroids, systemic or topical. At the same time, it is probable that the resistance to infection mediated by the immune response, especially the cell-mediated response, is diminished by corticosteroids. In this situation, the patient suffers doubly: the infection is less likely to be diagnosed, and the patient has been rendered more susceptible to that infection.

With patients on systemic steroids (perhaps treated with additional immunosuppressive agents or irradiation [4]), the degree of modification is often minor, but even in these cases it may be sufficient to mislead (Fig. 36.16), especially on the face. With topical steroids, the degree of modification can be profound. The usual sites where this problem occurs are the groins, lower legs, face and hands, but tinea circinata elsewhere may be steroid treated.

The history is characteristic. The patient is often satisfied initially with the treatment. Itching is controlled and the inflammatory signs settle. He or she stops applying the cream, the eruption relapses, with varying rapidity. Further applications bring renewed relief and the cycles are repeated. In the groins, the patient may develop few persistent nodules, which become unsuppressible by the steroid preparation.

Typically, the raised margin is diminished. Scaling is lost and the inflammation is reduced to a few nondescript nodules. Often, a bruise-like brownish discoloration is seen, especially in the groins. On the face, the picture may be modified by a superimposed



Fig. 36.16 Tinea corporis in a patient on systemic corticosteroids.

perioral dermatitis with papules and tiny pustules. Steroid-modified eyelid infection may closely resemble a sty. With chronic use, atrophy, telangiectasia and, in the groins and axillae, striae are likely to be observed. In some cases, concentric rings of erythema are seen among the atrophy and telangiectasia. Presumably, these represent waves of fungal growth. The eruption remains localized but, especially in *E. floccosum* infections, it spreads more widely than one would expect in the unmodified case. Accumulation of fungal hyphae may lead to cross-infection, as has been reported with steroid-modified *T. violaceum* infection in a dermatology ward [1]. Strong fluorinated steroids seem most likely to produce this syndrome, but even 1% hydrocortisone cream can, on occasions, modify tinea to a confusing extent.

Diagnosis. The differential diagnosis of other steroid-modified infections in the groin, particularly candidosis, must be considered, and these may be indistinguishable without cessation of therapy and mycological investigations. A ready awareness that the face, groins and the hands are sites of diagnostic error is important in alerting the physician, and the history is usually extremely suggestive. Scrapings may be difficult to obtain in a patient who is currently applying a steroid cream, but if he or she stops it for a few days an upsurge of inflammation with marked scaling often occurs, making clinical diagnosis easier and facilitating the taking of scrapings. In such samples, fungal mycelium is usually abundant but scrapings taken while steroids are still being applied may show very few fungal elements, unless a fluorescent whitener is used [5].

References

1 Faergemann J, Frederiksson T, Herczka O *et al*. Tinea incognito as a source for an epidemic of *Trichophyton violaceum* infection in a dermatologic ward. *Int J Dermatol* 1983; **22**: 39–42.

2 Ive FA, Marks R. Tinea incognito. *BMJ* 1968; **iii**: 216–21.

3 Marks R, Dawber RPR. *In situ* microbiology of the stratum corneum. *Arch Dermatol* 1972; **105**: 216–21.

4 Maor MH. Dermatophytosis confined to irradiated skin: a case report. *Int J Radiol Oncol Biol Phys* 1988; **14**: 825–6.

5 Gip L, Abelia J. Differential staining of fungi in clinical specimens using a fluorescent whitening agent (Blankophor). *Mykosen* 1987; **30**: 21–4.

Dermatophytide reactions

Synonyms
- Microsporide
- Trichophytide or epidermophytide (according to genus)

Definition. A non-infective cutaneous eruption representing an allergic response to a distant focus of dermatophyte infection.

Pathogenesis and criteria. Jadassohn in 1918 first described a dermatophytide reaction in a patient with a kerion. Since then a great many cutaneous eruptions have been labelled unconvincingly as dermatophytides. It is now clear [1] that the essential criteria required for the diagnosis of an ide reaction to a dermatophyte infection are:

1 Proven dermatophyte infection, which usually becomes highly inflamed before the appearance of the secondary rash.
2 A distant eruption, which is demonstrably free of ringworm fungus.
3 Spontaneous disappearance of the rash when the ringworm infection settles, with or without treatment.

Even with these criteria, ide reactions may be overdiagnosed. An additional criterion has been recommended; the morphology of the ide eruption should match one of the well-recognized types.

Clinical features. The focus of infection is often a kerion, for instance caused by *T. verrucosum*, but the species is not important as long as it provokes inflammation. Highly inflammatory tinea pedis may be insufficient. The main ide reactions are well established.

1 A widespread eruption of small follicular papules grouped or diffusely scattered. The eruption is symmetrical, usually pronounced on the trunk, but in severe cases extending down limbs, even at times covering the face. Sometimes the follicular papules are topped by horny spines. The common cause of this type of ide reaction is a scalp ringworm kerion, typically caused by *T. verrucosum*. On occasions, *T. tonsurans* and *M. audouinii* may be responsible, when they produce inflamed ringworm. Treatment of the original ringworm lesion may play a part in initiating the process.
2 A pompholyx-like ide affecting the web spaces and palmar surfaces of the fingers, the palms and sometimes the dorsal surfaces of the hands. This eruption is characteristically associated with an acutely inflammatory tinea pedis, which may have arisen spontaneously or as a result of inappropriate treatment. The palmar and web space skin may be covered with papules or vesicles. On occasions, bullae or pustules may occur. Clinically, this is indistinguishable from a constitutional eczema of the pompholyx variety, and the diagnosis of a dermatophytide in this clinical situation demands rigorous application of the criteria outlined above. In the past, failure to adhere to these criteria has led to inordinate overdiagnosis of this uncommon syndrome.

Of the many other suggested morphologies for ide reactions, erythema nodosum seems most acceptable [2]. There are a few published accounts of this, and the authors are aware of other cases that fit the above criteria.

It is possible that erythema multiforme, erythema annulare and urticaria may, on occasions, be manifestations of an allergic reaction to the ringworm infection, but such instances must be extremely rare and the clinician is cautioned to apply critical judgement vigorously before accepting new examples of such associations in his or her own practice, or indeed in new published accounts.

References

1 Kaaman T, Torssander J. Dermatophytid: a misdiagnosed entity. *Acta Derm Venereol (Stockh)* 1983; **63**: 404–8.

2 Peck SM. Fungus antigens and their importance as sensitizers in the general population. *Ann NY Acad Sci* 1950; **50**: 1362–5.

Laboratory diagnosis

The isolation and identification of dermatophytes is a relatively simple process and needs only basic laboratory facilities. The features of the most common species will therefore be outlined and illustrated grown on 2% glucose, 1% mycological peptone (Oxoid) agar supplemented with 0.04% cycloheximide and 0.005% chloramphenicol at 26°C. Illustrations of the more unusual species are beyond the scope of this chapter and the reader is referred to more specialized texts [1–3].

All the dermatophyte species appear identical in skin and nail samples. Septate hyphae are observed, which may branch without constriction at the branching point and which display an even diameter along their length (Fig. 36.17a). In some specimens, the hyphae fragment into arthroconidia, which disarticulate when mature, and may then round up and increase notably in size (Fig. 36.17b). These germinate to produce true hyphae. Hair invasion results in four distinct patterns: small-spored ectothrix, large-spored ectothrix, arthrosporic endothrix and favus endothrix (Fig. 36.17c–f) and these are readily distinguishable by the arrangement and the size of the fungal elements. When trying to determine whether infection is endothrix or ectothrix, it is useful to note that the pigment in the hair clearly delineates the edge of the hair shaft, and can be used as a marker to judge whether the fungus is entirely confined within the hair, or has formed an ectothrix sheath of arthroconidia on the surface.

Most isolates can be identified directly from the primary culture, but if sporulation is poor, a number of media may be used to encourage the production of conidia, including potato dextrose agar and lactritmel agar [4]. A few simple physiological tests, such as growth on polished rice grains, the production of urease, the ability to penetrate human hair *in vitro* and specific vitamin requirements, may be used to confirm the identification of certain species (Table 36.6).

In recent years there have been numerous molecular studies of dermatophyte taxonomy. As a result, various changes have been recommended to the nomenclature and separation of the classically recognized species. These include the merging of some anthropophilic and zoophilic species (e.g. *T. equinum* and *T. tonsurans*) and of some morphologically very distinct species, such as *T. soudanense* and *T. violaceum* [1]. The changes have not been universally accepted, and in this text the classic species are retained. In cases where cultures are completely atypical morphologically, however, molecular methods such as polymerase chain reaction patterns and ribosomal DNA analysis will allow species identification. Whether the cost can be justified in all but the most exceptional cases is questionable.

Genus Microsporum

When present, macroconidia are species specific; their production is enhanced by subculture on to lactritmel agar. Microconidia are similar in most species, clavate to elongate and borne along the sides of the hyphae, and thus not useful in species identification. The presence of specialized hyphae, such as racquet hyphae, where the cells are swollen at one end, and pectinate hyphae, which bear unilateral flattened comb-like protrusions, may be helpful.

M. audouinii (Fig. 36.18a–c). Colony: in many isolates the surface is white to tan with thin, sometimes silky growth, which has been compared to mouse fur. Other strains may have a thicker, downy white surface. The colour on the reverse of the colony is salmon pink to tan. Microscopy: in most isolates macroconidia are absent and the most characteristic features may be the presence of terminal and intercalary chlamydoconidia and racquet hyphae. However, in isolates where macroconidia are present, they are large, unevenly septate, variably rough and thick-walled, and often have a constricted centre and irregular shape. Physiological tests: *M. audouinii* grows poorly or not at all on polished rice grains.

M. audouinii var. *rivalieri* is a variant found mainly in Africa, but also reported from North America and Europe. The colony surface is white, with a distinctive ground-glass texture and radial or more complex cerebriform folding. Microscopically, macroconidia may be present, but the most characteristic feature is the presence of numerous pectinate hyphae. On primary culture, some isolates produce well-developed antler hyphae, which may cause confusion with *T. schoenleinii*. Subculture on to lactritmel agar may stimulate macroconidial production in these isolates and the characteristic small-spored ectothrix mode of *in vivo* hair infection will also aid in their correct identification.

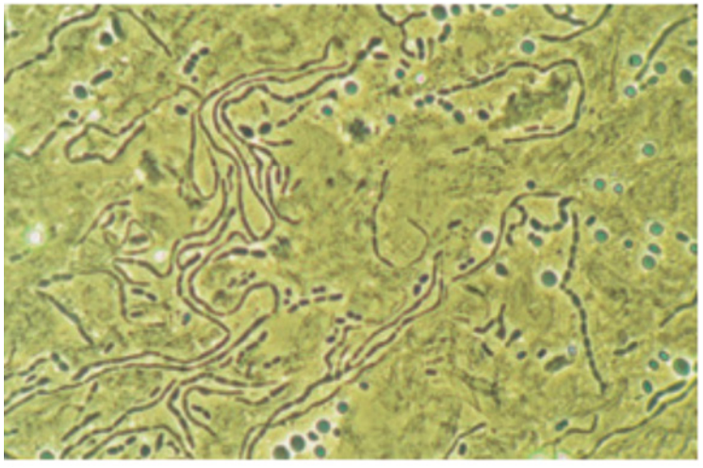
M. canis (Fig. 36.19a,b). Colony: the surface is white, thinning towards the edge to reveal the yellow or orange reverse pigment. The texture may be cottony, with a buff centre caused by the abundant production of macroconidia; alternatively, the surface may be thinner, silky or patchily cottony and entirely white. Radial folds may be present. Microscopy: macroconidia are rough, particularly at the tip, with thick outer walls and up to 16 cells. They are spindle-shaped and may show a slightly bent apical beak. Physiological tests: *M. canis* grows well on polished rice grains. This medium also encourages macroconidial production.

A glabrous variant (Fig. 36.20) has been described with heaped, leathery yellow or orange–brown colonies with feathery edges [5]; this mutant quickly reverts to the normal colonial form and produces typical macroconidia if cultured on rice grains.

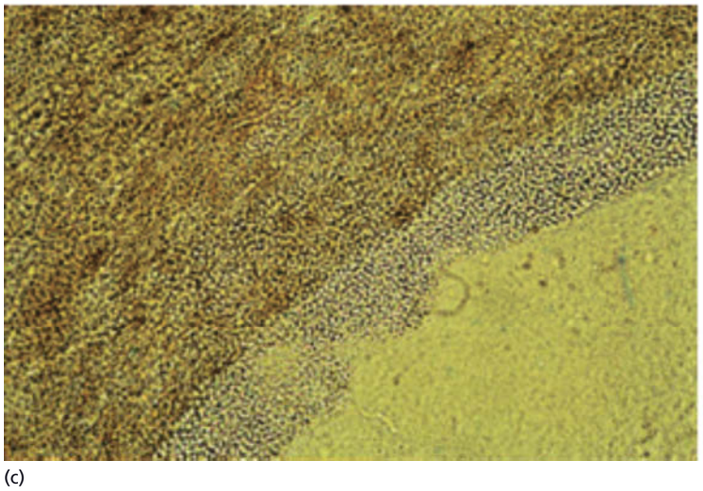
M. canis var. *distortum* is a variety found in Australia, New Zealand and the Americas. The rough, thick-walled macroconidia are grossly distorted and bent and abundant microconidia may be present.



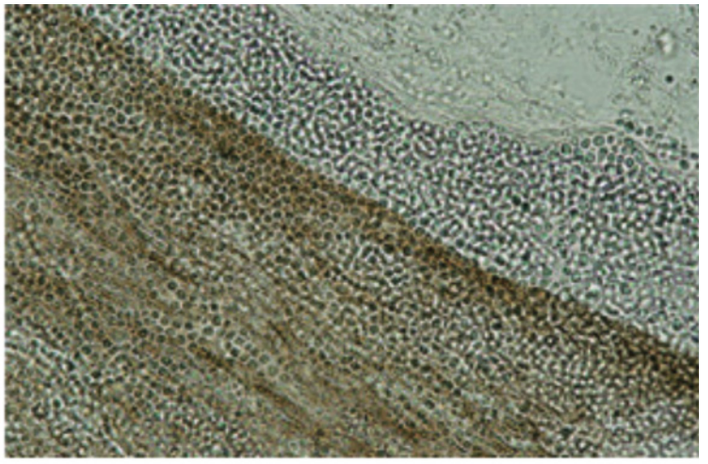
(a)



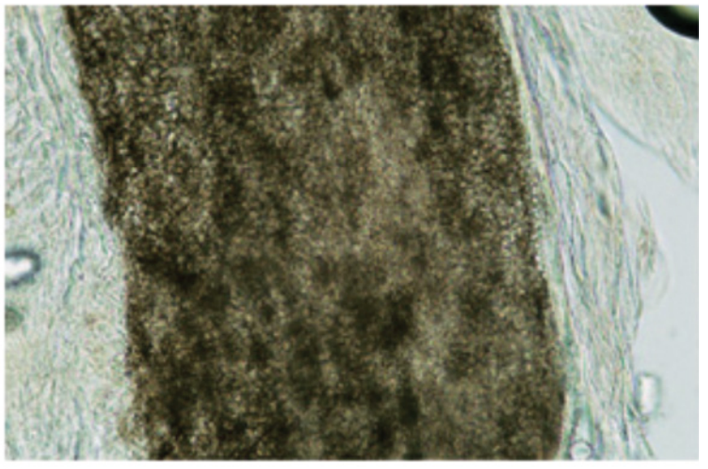
(b)



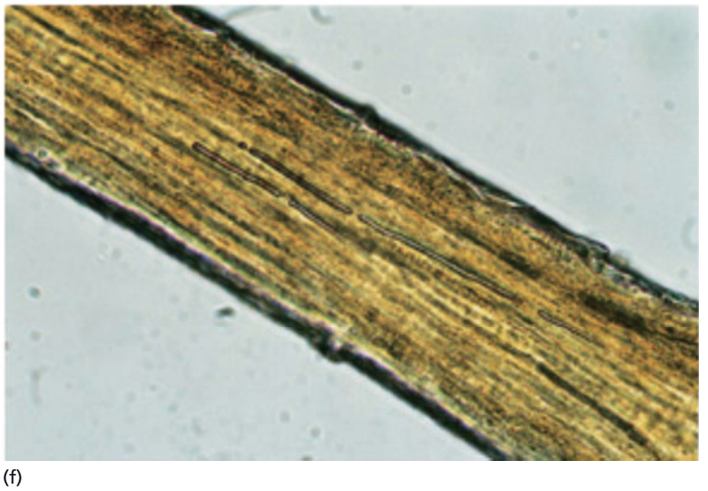
(c)



(d)



(e)



(f)

Fig. 36.17 Dermatophytosis. (a) Skin scales mounted in 30% KOH, Nomarski illumination. The hyphae are very even in diameter and regularly septate. (b) Skin scales mounted in 30% KOH, phase contrast. The hyphae are fragmenting to form arthroconidia, which may increase notably in size and round up as they mature. (c) Small-spored ectothrix hair invasion, 30% KOH bright field. The brown pigment delimits the edge of the hair, and the sheath of small arthroconidia that has formed on the surface of the hair is clearly visible. (d) Large-spored ectothrix hair invasion, 30% KOH, bright field. The sheath surrounding the hair is formed of arthroconidia, which are significantly larger than those seen in small-spored ectothrix infections. (e) Endothrix hair invasion, 30% KOH, bright field. The fungus inside the hair has broken up into a mass of large arthroconidia. These are retained entirely within the hair shaft. (f) Favus hair. The fungus is entirely confined within the hair shaft but does not fragment into arthroconidia. When first immersed in KOH, air is trapped around the hyphae forming the characteristic, long air spaces. These rapidly fill in with KOH, when the hyphae themselves become visible. (Courtesy of the Department of Medical Mycology, St John's Institute of Dermatology, King's College London, London, UK.)

Table 36.6 Physiological tests used in the identification of dermatophytes.

Production of urease
Filter-sterilized urea agar base (Difco) is mixed with sterile molten agar and allowed to set. The medium is then inoculated with the test organism. After incubation at 26°C for 7 days, if urea is degraded the colour turns from yellow to magenta red.

Penetration of human hair in vitro
Sterile human hair is suspended in sterile distilled water supplemented with yeast extract. The test organism is inoculated onto the hairs. After 2 weeks' incubation at 26°C, hairs are mounted to look for wedge-shaped penetrations perpendicular to the hair axis.

Vitamin tests
Trichophyton agars 1–7 (Difco) are used to determine vitamin requirements. Agar 1 is a casein-based, vitamin-free control; agar 2 is supplemented with inositol; agar 3 with thiamine and inositol; and agar 4 with thiamine alone. Agar 5 contains nicotinic acid. Agar 6 is an ammonium nitrate vitamin-free control for Agar 7, which is supplemented with histidine. Small, agar-free inocula are transferred from Sabouraud's agar plates and incubated for 2–3 weeks at 26°C.

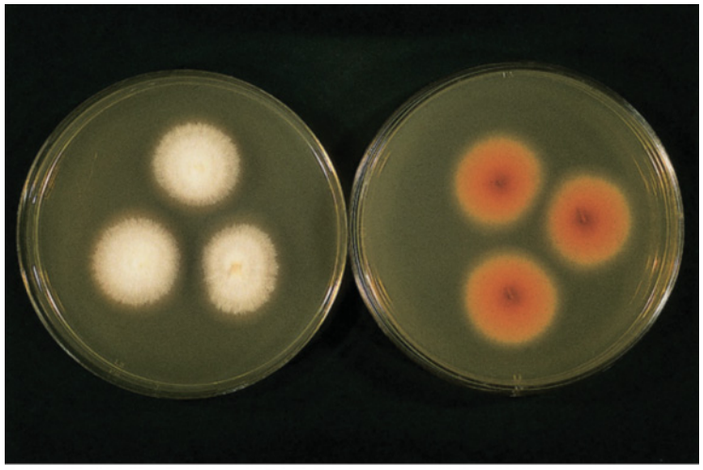
Growth on rice grains
Ordinary white rice is covered with distilled water and autoclaved. The test organisms are then inoculated straight onto the surface, and growth is assessed after 2–3 weeks' incubation at 26°C.

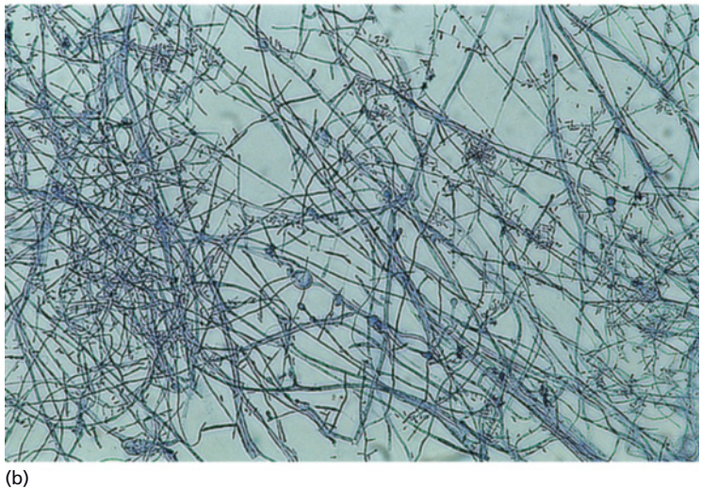
Growth on 1% peptone agar
On this sugar-free medium *Microsporum persicolor* will produce a pink surface colour, in contrast to *Trichophyton mentagrophytes* var. *mentagrophytes*, which remains white.

M. equinum. Colony: the short surface mycelium is white to pale buff with regular, deep radial grooves. The reverse is pink or salmon. Microscopy: the macroconidia are characteristic. They are rough and thick-walled but shorter and wider than those of *M. canis*, usually with one to four cells.

M. ferrugineum. Colony: restricted glabrous heaped colonies, yellow to rust in colour or more spreading, downy colonies similar to *M. audouinii*. The pigment is often lost on subculture. Microscopy: thick 'bamboo' hyphae with prominent septa may be the only notable feature, although rare macroconidia resembling those of *M. canis* may be produced.

M. gypseum (Fig. 36.21a,b). Mating studies have demonstrated that the fungus traditionally known as *M. gypseum* is actually a complex containing three separate species: *A. fulvum* (Anamorph *M. fulvum*), *A. incurvatum* (Anamorph *M. gypseum*) and *A. gypseum* (Anamorph *M. gypseum*). Colony: all the species produce rapidly growing colonies with a cinnamon or brown powdery surface. *M. fulvum* typically has a much thicker, more floccose surface texture; in *M. gypseum* the surface is almost completely flat. The reverse is yellow-buff to brown or may have red overtones. Microscopy: the numerous macroconidia are thin-walled, finely roughened over their entire surface and have up to six septa. The shape is very symmetrical, broadly fusiform with rounded ends, and has variously been described as cigar- or boat-shaped.


(a)


(b)

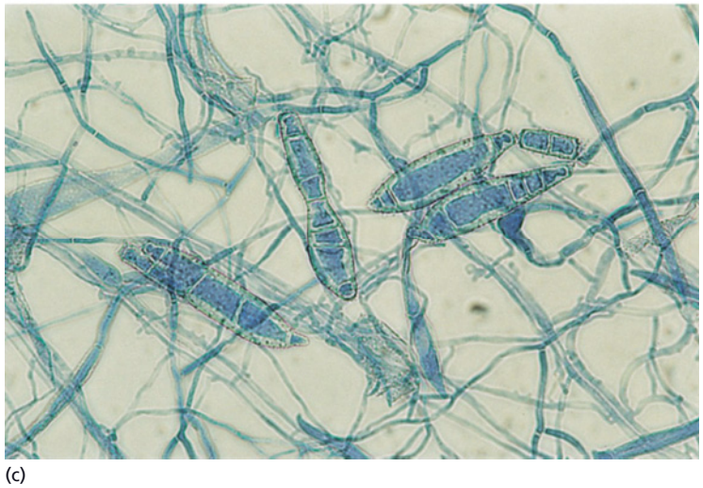

(c)

Fig. 36.18 (a) *Microsporum audouinii* colony: reverse of colony shown on right. (b) *Microsporum audouinii* microscopy, bright field. In many isolates chlamydoconidia, raquet hyphae and microconidia may be the only features of note. (c) *Microsporum audouinii* microscopy, bright field. In some isolates, macroconidia are observed. These are large, unevenly septate and may have a waisted appearance. (Courtesy of the Department of Medical Mycology, St John's Institute of Dermatology, King's College London, London, UK.)



(a)



(b)

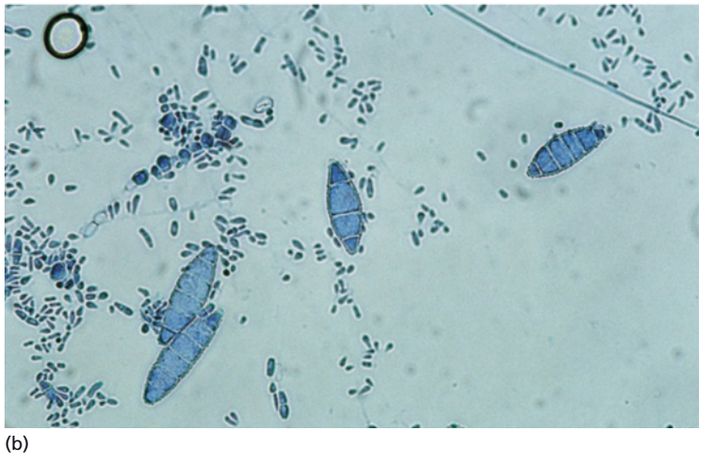
Fig. 36.19 (a) *Microsporum canis* colony; reverse of colony shown on right. (b) *Microsporum canis* microscopy, bright field. The macroconidia are characteristic, thick-walled and fusiform, often with a tilted, apical beak. They are rough with the most pronounced thickenings at the apical tip. (Courtesy of the Department of Medical Mycology, St John's Institute of Dermatology, King's College London, London, UK.)



Fig. 36.20 *Microsporum canis* glabrous form colony. (Courtesy of the Department of Medical Mycology, St John's Institute of Dermatology, King's College London, London, UK.)



(a)



(b)

Fig. 36.21 (a) *Microsporum gypseum* colony. (b) *Microsporum gypseum* microscopy, bright field, the macroconidia are abundant and characteristic, with a symmetrical cigar shape and thin, finely roughened cell walls. (Courtesy of the Department of Medical Mycology, St John's Institute of Dermatology, King's College London, London, UK.)

M. nanum. Colony: moderate to rapidly growing, flat powdery colonies with a buff surface and red-brown reverse. Microscopy: characteristic thin-walled, rough, obovate macroconidia with usually a single septum are abundantly produced.

M. persicolor. Colony: the surface of the colony is creamy buff, sometimes with pale pink tones. The texture is noticeably thicker than that seen in *T. mentagrophytes* var. *mentagrophytes*. The reverse is buff to brown and may also develop pink or reddish tones. Microscopy: very similar to *T. mentagrophytes* var. *mentagrophytes*. Many clavate to spherical microconidia are present, and arranged in grape-like clusters and along the hyphae. Young microconidia are pyriform and match-stick hyphae with an elongated basal cell carrying a microconidium at its tip may be observed. Tightly coiled, spiral hyphae are usually present. Thin-walled elongated macroconidia appear smooth on primary isolation media and usually contain six cells. Physiological tests: on medium free of sugar (1% peptone agar), *M. persicolor* colonies produce a rose-

pink surface colour; *T. mentagrophytes* var. *mentagrophytes* retains a white surface on this medium. On 3% salt agar, macroconidia are more obviously rough.

Genus Trichophyton

Macroconidia are rarely formed by most of the anthropophilic species, and may not be particularly distinctive when they are. They are smooth and thin-walled. The size, shape and arrangement of the microconidia is useful in species identification, together with the presence of features such as coiled spiral hyphae, abundant chlamydospore production and special physiological requirements.

T. concentricum. Colony: the compact, heaped, folded colonies have a grey, tan or brown surface; initially glabrous, a thin short surface mycelium may develop. The reverse may be tan, brown or have reddish tones. Microscopy: conidia are absent. The hyphae may be swollen and distorted with numerous chlamydospores and occasional antler hyphae, or unremarkable. Physiological tests: 50% of isolates are stimulated by thiamine.

As the morphological features of this fungus are not very distinctive, it may be confused with other glabrous anthropophilic *Trichophyton* species, such as *T. yaoundei* or unpigmented isolates of *T. violaceum*. However, the clinical features of infection are so characteristic that they will aid in the identification.

T. equinum. Colony: in young cultures, the surface is very thin, revealing the reverse brown pigment. The reverse is initially brown in the centre with an outer yellow edge. As the culture matures, the surface texture thickens and becomes uniformly white and the reverse uniformly deep reddish brown. Microscopy: elongate to pyriform microconidia are arranged along the sides of the hyphae. Cylindrical, smooth, thin-walled macroconidia are rarely observed. Physiological tests: with the exception of some isolates from New Zealand and Australia, this fungus has a specific vitamin requirement for nicotinic acid.

T. gourvilii. Colony: the centre of the colony is garnet red to lavender, waxy, heaped, folded and surrounded by a flat, white, silky edge with an eyelash fringe. The reverse is cream to buff. Microscopy: clavate or pyriform microconidia are arranged along the sides of the hyphae.

T. megninii. Colony: the colony is very similar to downy *T. rubrum* isolates. The surface is white, developing pink or rose tones. The texture is velvety or downy, often with radial folds. The reverse is reddish brown to wine red. Microscopy: as in *T. rubrum*, pyriform microconidia are arranged along the sides of the hyphae. Physiological tests: when grown on a medium with an inorganic nitrogen source, this fungus has a specific requirement for L-histidine. Unlike *T. rubrum* it is urease positive.

T. mentagrophytes* var. *mentagrophytes (Fig. 36.22a,b). Colony: the colonies are fast growing with an intensely granular surface, which may be entirely white or develop a cream centre. The edge of the colony is thinner and may be spiky or stellate. The reverse is yellow, tan or red to brown. Microscopy: the spherical microconidia are arranged in grape-like bunches and to a lesser extent along the hyphae. Coiled spiral hyphae are usually present, and in many isolates thin-walled, cylindrical macroconidia with up to eight cells may be present. Physiological tests: the fungus is urease positive and penetrates human hair *in vitro*.

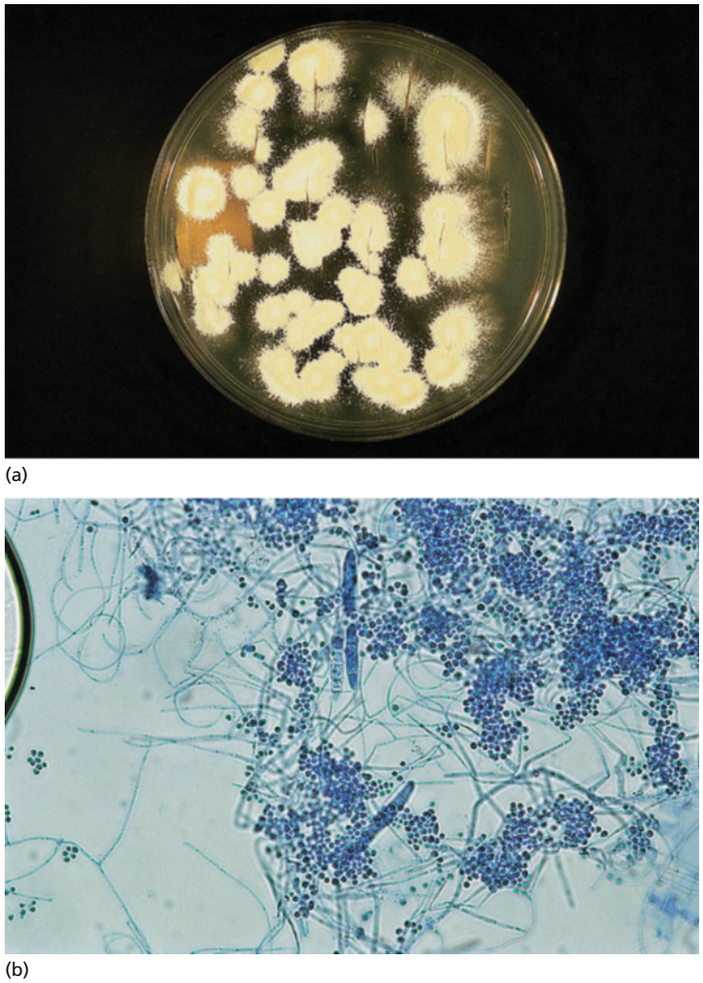


Fig. 36.22 *Trichophyton mentagrophytes* var. *mentagrophytes*. (a) Colony. (b) Microscopy, bright field. Round microconidia are arranged in clusters. Spiral hyphae and thin-walled, smooth, cylindrical macroconidia may also be present. (Courtesy of the Department of Medical Mycology, St John's Institute of Dermatology, King's College London, London, UK.)

T. mentagrophytes* var. *erinacei. Colony: the rapidly growing colonies have a flat, white intensely granular surface. The reverse is a bright canary yellow. Microscopy: elongate microconidia, even longer than those of *T. rubrum*, are arranged along the sides of the hyphae. Spiral hyphae and smooth thin-walled macroconidia may be present in some isolates. Physiological tests: unlike other variants of *T. mentagrophytes*, the fungus is urease negative, but will penetrate human hair *in vitro*. Some workers believe that this fungus should be regarded as a separate species, *T. erinacei*.

T. mentagrophytes* var. *quinckeanum. Colony: the surface is white, velvety or downy and often folded in the centre. The reverse

is buff to cream. The colony has been reported to have a distinctive sour smell. Microscopy: pyriform microconidia are arranged along the sides of the hyphae. Physiological tests: produces a Wood's light-positive hair infection in mice with characteristic scutula.

T. mentagrophytes* var. *interdigitale (Fig. 36.23). Colony: the most typical isolates are rapidly growing with a white powdery surface, which develops a cream centre (Fig. 36.23a). A few isolates may develop a pinkish surface. The reverse is tan or reddish brown, often with a paler edge. Less typical downy forms have a fluffier white surface, sometimes slightly cream in the centre and folded (Fig. 36.23b). The reverse is pale cream to buff. Microscopy: powdery isolates may be very similar to *T. mentagrophytes* var. *mentagrophytes* with spherical microconidia arranged in bunches; spiral hyphae and macroconidia are present in some isolates. The fluffier downy isolates have pyriform microconidia arranged along the sides of the hyphae. Physiological tests: the fungus is urease positive and penetrates human hair *in vitro*.



(a)



(b)

Fig. 36.23 *Trichophyton mentagrophytes* var. *interdigitale*. (a) Typical colony form; reverse of colony is shown on right. (b) More unusual colony forms. The upper colony is of the downy white form and the lower colonies show an intricately folded, beige form. (Courtesy of the Department of Medical Mycology, St John's Institute of Dermatology, King's College London, London, UK.)

The 'nodulare' form of *T. mentagrophytes* var. *interdigitale* has a predominantly glabrous, waxy surface devoid of aerial hyphae and feathery subsurface growth. Both the surface and reverse of the colony are orange–red in colour. Small areas of more typical white growth may be present. Nodular bodies are present on microscopical examination. This variety is relatively unstable, and may quickly sector out into a powdery or downy colonial form.

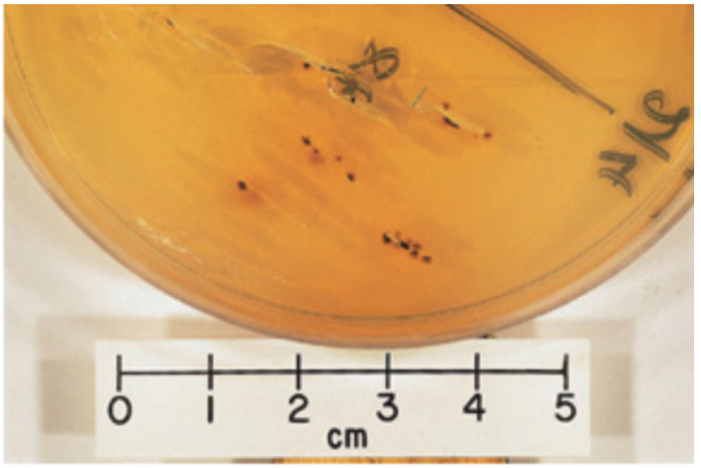
***T. rubrum*.** This is probably the most morphologically variable dermatophyte species and several distinct colonial forms are regularly isolated. Only the most common will be described here.

1. *Downy form.* The most commonly isolated form in temperate zones (Fig. 36.24a,b). Colony: the surface of the colony is white, downy or cottony, and domed. The reverse of the colony is initially dark brown, usually with a paler cream border, but after incubation for 3–4 weeks produces the typical deep red pigment characteristic of this species. Microscopy: small tear-shaped, clavate or elongate microconidia are arranged along the sides of the hyphae. In some isolates microconidia may be scanty. Physiological tests: the fungus is urease negative and does not perforate human hair *in vitro*.
2. *Melanoid form* (Fig. 36.24c). Colony: similar to the downy form, but characterized by producing a brown melanoid pigment that diffuses into the medium and masks any red pigment on the reverse of the colony. Microscopy: small tear-shaped microconidia are arranged along the sides of the hyphae.
3. *Dysgonic form* (Fig. 36.24d). Colony: slow-growing, tiny, deep-red colonies with a brittle texture. This form is relatively unstable and will quickly revert to the more typical downy form.
4. *Granular form* (Fig. 36.24e,f). Colony: the surface is powdery or granular, cream to pink and often raised and folded in the centre. The reverse is red-brown. Microscopy: numerous smooth, thin-walled, cylindrical or pencil-shaped macroconidia are produced; some macroconidia may have constricted septa. Typical tear-shaped microconidia are also present. Physiological tests: this form is urease positive and may penetrate human hair *in vitro*.
5. *Yellow form.* The surface may be similar to the more usual downy form or it may be smooth, leathery and yellow. The reverse is yellow; the red pigment characteristic of *T. rubrum* is completely absent. In instances where microconidia are not observed it may be difficult to show that this is indeed a dermatophyte. However, pigmentation and sporulation may be enhanced on lactritmel agar.

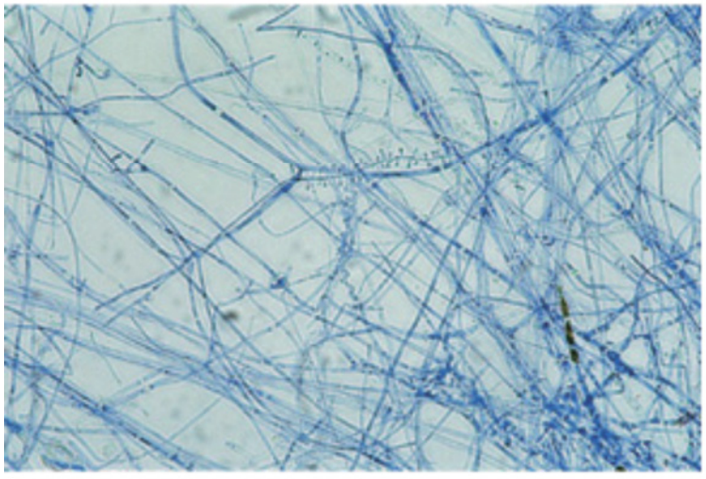
T. schoenleinii (Fig. 36.25a,b). Colony: on primary isolation, the colonies may be glabrous or velvety, usually heaped and folded, and often with a fringe of hyphae at the edge submerged in the culture medium. The surface is white to cream and reverse pale. On repeated subculture, most isolates become downy. Microscopy: conidia are usually absent. Characteristic dichotomously branching hyphae with flattened tips, termed chandelier or antler hyphae, are present in fresh cultures. These may be readily observed by focusing on the back of the primary culture plate with a ×10 objective. Swollen, distorted hyphae with many chlamydoconidia are also usually present.



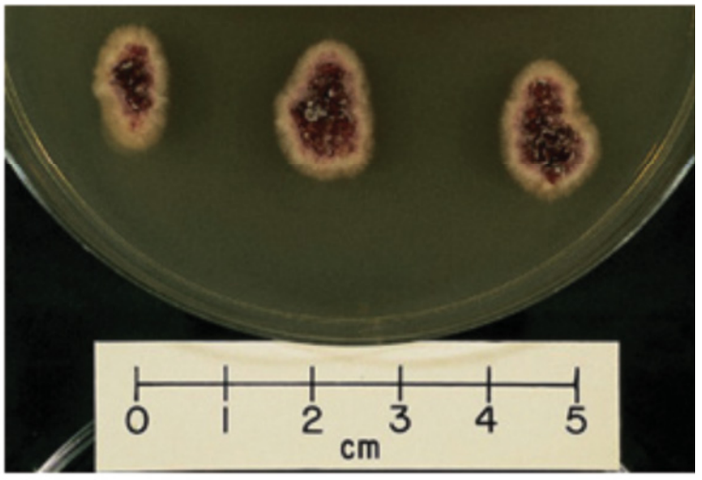
(a)



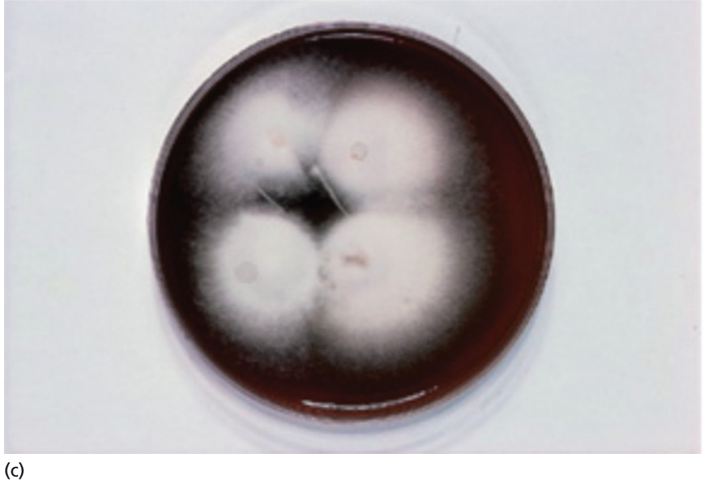
(d)



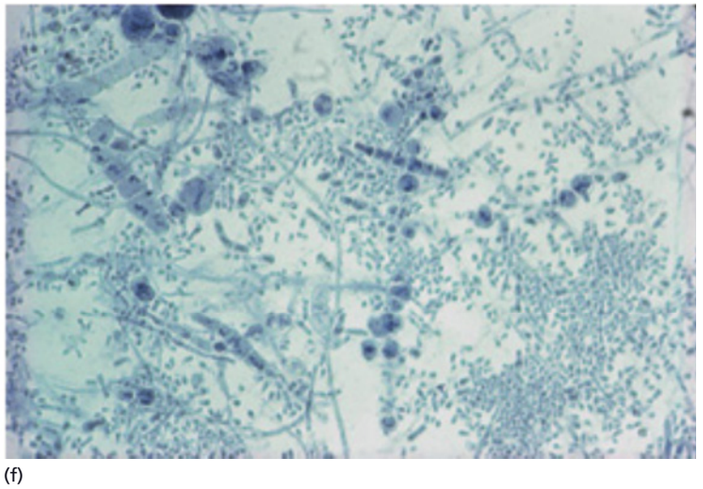
(b)



(e)

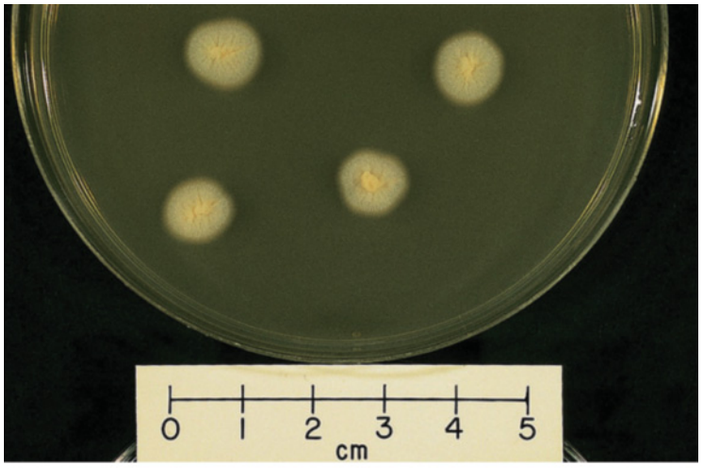


(c)

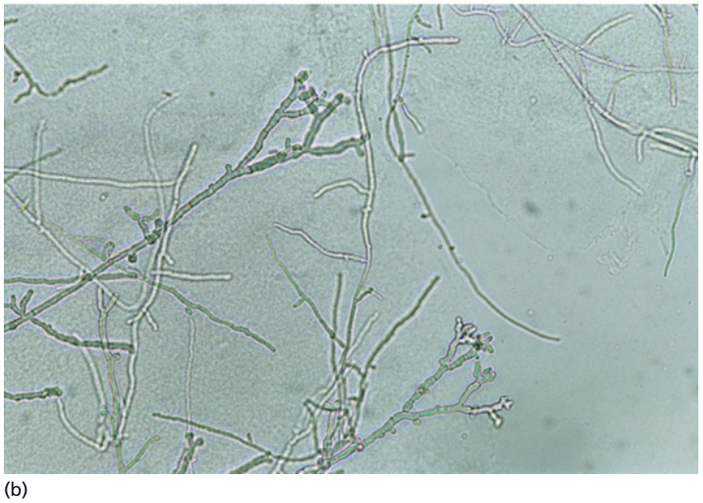


(f)

Fig. 36.24 *Trichophyton rubrum*. (a) Downy colony; reverse of colony shown on right. (b) Downy form microscopy, bright field. Clavate to elongate microconidia are arranged along the sides of the hyphae. They may be scanty in some isolates. (c) Melanoid colony form. A brown pigment diffuses into the agar medium. (d) Dysgonic colony form. Growth is initially very restricted and the tiny colonies a deep red. They usually revert to a more typical downy form within 2–3 weeks. (e) Granular form colony, with a powdery pink surface often raised and folded in the centre. (f) Granular form microscopy, bright field. Cylindrical, smooth-walled macroconidia are abundant and may become swollen as they mature with constricted septa. Microconidia and chlamydoconidia may also be abundant. (Courtesy of the Department of Medical Mycology, St John's Institute of Dermatology, King's College London, London, UK.)



(a)

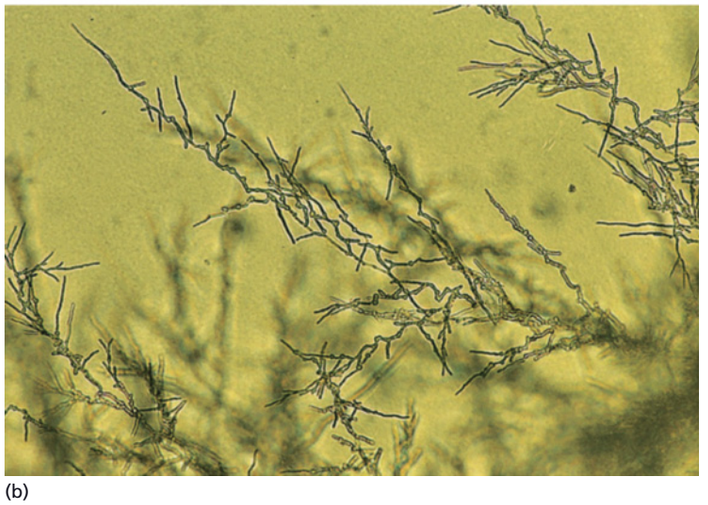


(b)

Fig. 36.25 *Trichophyton schoenleinii*. (a) Colony. (b) Microscopy, bright field. Typical antler hyphae may be observed by examining through the back of the culture plate with a ×10 or ×20 objective. The antlers branch dichotomously and have flattened tips. (Courtesy of the Department of Medical Mycology, St John's Institute of Dermatology, King's College London, London, UK.)



(a)



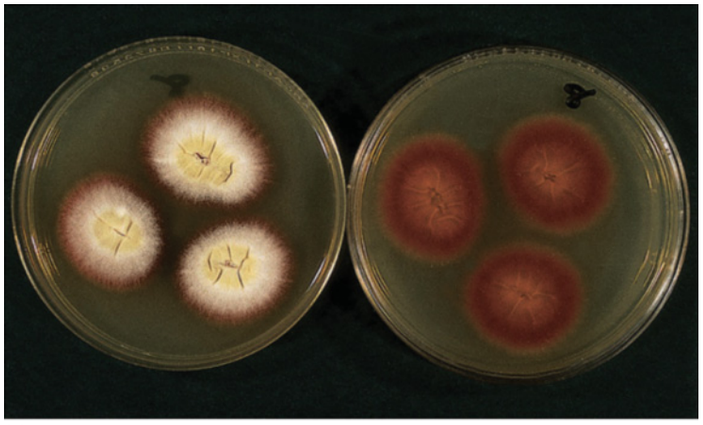
(b)

Fig. 36.26 *Trichophyton soudanense*. (a) Colony forms. A typical apricot yellow and a red isolate are illustrated. (b) Microscopy, bright field. The stiff hyphae with many arthroconidia and reflexive branching may be observed directly through the back of the culture plate. (Courtesy of the Department of Medical Mycology, St John's Institute of Dermatology, King's College London, London, UK.)

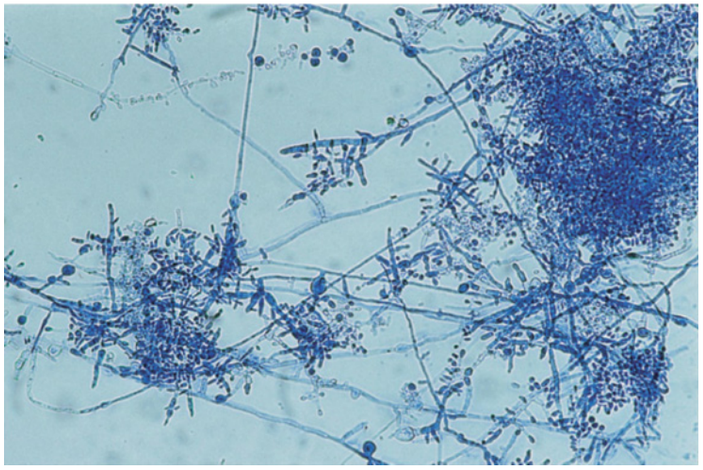
T. simii. Colony: the surface is flat and granular, pale at the edges and buff or sometimes pink in the centre. The reverse is usually yellow to red-brown. Microscopy: many smooth-walled macroconidia are produced, often outnumbering the number of clavate to pyriform microconidia. The macroconidia are thin-walled, cylindrical or torpedo-shaped and are characterized by the development of constricted septa, and the fact that certain of the cells swell to produce endochlamydoconidia as they age.

T. soudanense (Fig. 36.26a,b). Colony: the colony is relatively slow growing, glabrous and leathery or brittle in texture, with a characteristic stellate or eyelash fringe around the edge. The colour is typically apricot to yellow, but isolates producing purple or red colonies are also common. Microscopy: when examined through the back of the primary culture plate using a ×10 objective, the hyphae appear stiff and 'brush-like'. They are very regularly septate, and the formation of arthroconidia produces a zig-zag appearance. Reflexive branching back towards the centre of the colony is a characteristic feature. Pyriform microconidia may be present.

T. tonsurans (Fig. 36.27a,b). Colony: the colony surface is velvety or powdery and may be grey, cream or yellow in colour, more rarely brown in the centre. Some isolates produce very sparse surface mycelium, so that the reverse brown pigmentation shows through. Circular or radial folds are often present. The reverse is typically chocolate brown, mahogany or yellow. Microscopy: the most characteristic feature is that the microconidia are noticeably larger than those of *T. mentagrophytes* or *T. rubrum* and very variable in shape. They range from clavate to elongate, and swollen 'balloon' microconidia and stalked, match-stick microconidia are also observed. In the majority of isolates, chlamydoconidia are numerous and in some isolates spiral hyphae and macroconidia are present. Physiological tests: this fungus has a specific vitamin requirement for thiamine.



(a)

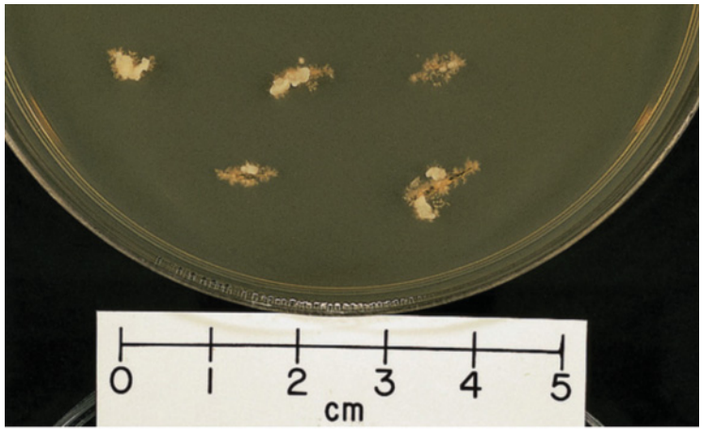


(b)

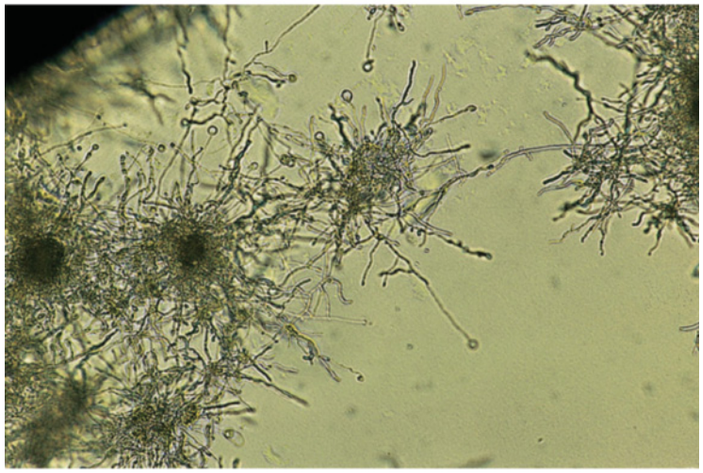
Fig. 36.27 *Trichophyton tonsurans*. (a) Colony; reverse of colony shown on right. (b) Microscopy, bright field. The microconidia are large and vary considerably in their shape. Chlamydoconidia are often abundant. Macroconidia and spiral hyphae are occasionally seen. (Courtesy of the Department of Medical Mycology, St John's Institute of Dermatology, King's College London, London, UK.)

T. verrucosum (Fig. 36.28a–c). Colony: this is a very slow-growing fungus, and after 2 weeks of incubation at 26°C the white or grey waxy colonies may still be barely visible. Growth is better at 37°C so, if cattle ringworm is suspected, incubation at both temperatures is recommended. Microscopy: examining the reverse of the primary plate under a ×10 objective, colonies incubated at 26°C show short hyphae with terminal chlamydoconidia. In contrast, colonies incubated at 37°C produce very characteristic long chains of chlamydoconidia. Clavate or elongate microconidia may be present along the sides of the hyphae. Rat-tailed macroconidia may be produced on depleted media. Physiological tests: most isolates have a requirement for thiamine and inositol. In a few, growth is enhanced by thiamine alone.

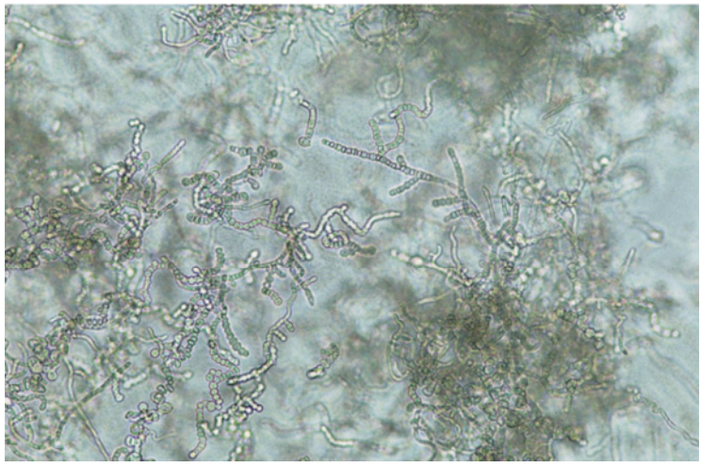
T. violaceum (Fig. 36.29). Colony: the slow-growing, glabrous colonies have a waxy or leathery texture. Characteristically they are deep purple–red in colour, but some isolates take several weeks to pigment, or retain unpigmented sectors. Occasionally, isolates fail to pigment at all. Microscopy: microconidia and



(a)



(b)



(c)

Fig. 36.28 *Trichophyton verrucosum*. (a) Colony. (b) Microscopy 26°C, bright field. Through the back of the culture dish, the small colonies are characterized by the development of hyphae with terminal swellings or chlamydoconidia. (c) Microscopy 37°C, bright field. Grown at a higher temperature, characteristic long chains of chlamydoconidia are observed. (Courtesy of the Department of Medical Mycology, St John's Institute of Dermatology, King's College London, London, UK.)

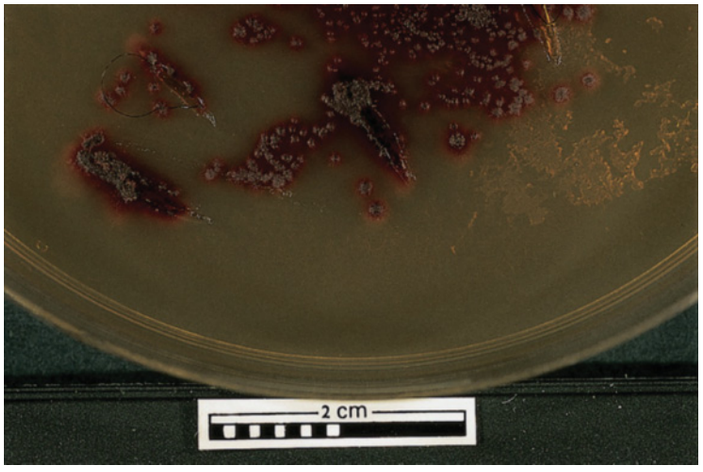


Fig. 36.29 *Trichophyton violaceum* colony. (Courtesy of the Department of Medical Mycology, St John's Institute of Dermatology, King's College London, London, UK.)

macroconidia are usually absent. Chlamydoconidia and distorted hyphae may be present. Physiological tests: growth is stimulated by thiamine.

T. yaoundei. Colony: the colonies are initially glabrous, white to cream. As they age, the surface may develop a velvety texture and tan to brown colour; a diffusable brown pigment may be produced. Microscopy: irregular hyphae and chlamydoconidia may be present; clavate microconidia are rare. Physiological tests: the lack of vitamin requirements will distinguish this species from *T. verrucosum* and unpigmented isolates of *T. violaceum*.

Genus Epidermophyton

Identified by the characteristic macroconidia and lack of microconidia.

E. floccosum (Fig. 36.30a,b). Colony: this species grows rapidly to form velvety or suede-like colonies, which may remain flat or develop central or radial folds. The colour is typically khaki or olive green and some isolates produce tufts of floccose sterile white mycelium on the surface of the colony. Microscopy: large clavate macroconidia with a rounded apical end and up to six cells are rapidly formed. They are thin-walled and initially smooth, but may develop a few discrete thickenings as they age. Microconidia are absent. Chlamydoconidia are abundant and predominate in older cultures.

References

1 De Hoog GS, Guarro J, Gene J, Figueras MJ, eds. *Atlas of Clinical Fungi*. Baarn: Centraalbureau voor Schimmelcultures/Universitat Rovira i Virgili, 2000.

2 Kane J, Summerbell R, Sigler L *et al*. *Laboratory Handbook of Dermatophytes*. Belmont, CA: Star, 1997.

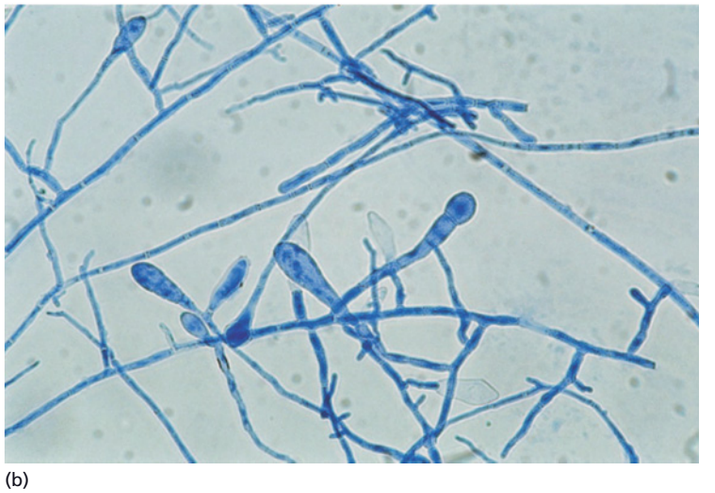
3 Weitzman I, Padhye AA. Dermatophytes: gross and microscopic. *Dermatol Clin* 1996; **4**: 9–22.

4 Segretain GE, Drouhet F, Mariat F. *Diagnostic de Laboratoire en Mycologie Medicale*. Paris: Maloine, 1987.

5 Midgley G. A glabrous *Microsporum canis* in Greater London. *Sabouraudia* 1981; **19**: 71–7.



(a)



(b)

Fig. 36.30 *Epidermophyton floccosum*. (a) Colony. (b) Microscopy, bright field. The clavate macroconidia are characteristic. Microconidia are absent but chlamydoconidia are very common. (Courtesy of the Department of Medical Mycology, St John's Institute of Dermatology, King's College London, London, UK.)

Therapy and management of ringworm infections

The treatment of fungal infection is now comparatively straightforward, and cure rates for many forms of dermatophytosis over 90%. In addition to treatment, some other management measures are generally helpful.

The identification of the causative agent is useful, particularly in tinea corporis and tinea capitis where treatment of an infected animal source is important in order to prevent other infections. In the case of tinea capitis, it will also provide information on the risk of spread to other children at home or in the school.

Prevention of dermatophytosis is not practicable except in situations where there is a high risk of spread to other individuals. These include shower rooms in industry or in the armed forces or schools. In the case of tinea pedis, improvement of hygiene in swimming baths may result in lower levels of infection. Frequent washing of changing room floors and walkways will remove infective material in skin scales. The provision of tolnaftate powder

at a swimming bath and encouragement to use it prophylactically has been shown to reduce levels of toe cleft tinea pedis caused by *T. mentagrophytes* var. *interdigitale*, although it had little effect on *T. rubrum*. Clearly, infected individuals using these facilities should be encouraged to seek treatment. In industry or in schools, prompt treatment of infection combined with simple hygienic measures such as washing shower room floors with an antiseptic will be useful. It is less easy to prevent spread of tinea pedis in households; treatment of infection and care in keeping to personal towels are both sensible measures. Even with less care, family members often remain free of infection in spite of persistent cases of tinea pedis in their midst.

In the case of tinea capitis, it may be necessary to take preventative action [1]. This is particularly important if there is any evidence of an increasing number of cases of tinea capitis in schools. It is important to establish the nature of the infections, and whether the organisms are anthropophilic. There are no proven methods of ensuring eradication of infection in schools, but early identification of infected children and prompt treatment are probably the best approaches to adopt. An additional precaution is the use of a topical antifungal, which is likely to reduce spread while having little effect on the infection itself [1]. There is evidence that selenium sulphide or ketoconazole shampoo may reduce the incidence of positive cultures in children receiving griseofulvin. The issue of keeping children off school remains controversial. The value of this measure in limiting spread has to be weighed carefully against its possible effect on compliance with surveillance and treatment. Therefore, this issue has to be considered in conjunction with the local situation. In one such outbreak in London, the policy adopted was to advise treatment for all infected children with griseofulvin plus selenium sulphide or ketoconazole shampoo, to allow them to attend school once on treatment, and to screen classes with scalp brushes if there were more than two children infected.

Therapeutic agents

The treatment of dermatophyte infections usually involves the use of oral terbinafine, fluconazole itraconazole, griseofulvin or one of several well-tried topical preparations (Table 36.7). All those noted have been shown to be effective in a substantial majority of patients, provided they are used regularly.

Terbinafine [2,3]**.** Terbinafine is a member of the allylamine antifungals, a relatively newly developed group of drugs, which act by the inhibition of squalene epoxidase in the formation of the fungal cell membrane. This enzyme acts at an early stage in membrane biosynthesis, and the accumulation of squalene is thought to destabilize the cell membrane. The two main antifungal compounds are naftifine and terbinafine. Both are active *in vitro* against dermatophytes in addition to other fungi; terbinafine is also active against *Sporothrix schenckii*, some *Aspergillus* species and *Histoplasma capsulatum*, in addition to other fungi. *In vitro* there is little difference between the dosage at which the drug inhibits cell growth and that at which the fungal cell is killed (the drug is fungicidal rather than fungistatic). Terbinafine can be given topically or orally. When given orally, it is rapidly taken up into the stratum corneum and it persists in nails at high concentrations for several months. These may exceed the minimum inhibitory concentration 80 days after the end of therapy [4]. Terbinafine is given orally in a dosage of 250 mg/day. It has produced rapid and long-lasting remissions in both nail disease [5,6] and persistent tinea pedis, as well as tinea corporis. A smaller tablet form of 125 mg is available in some countries for treatment of children. The frequency of relapse is much lower than with griseofulvin. It also has activity against most of the agents of tinea capitis, particularly *Trichophyton* species, although it is not licensed for this indication in many countries [7]. There are few drug interactions reported for terbinafine, and side effects are uncommon. Some patients describe abdominal fullness and nausea. Taste loss may occur

Table 36.7 Topical antifungal agents used in dermatophyte infections.

Compound	Available as	Comments
Benzoic acid compound (Whitfield's ointment)	Ointment	Cheap
Undecenoates—various brands available	Ointment, powder	Cheap
Tolnaftate	Cream, powder, lotion	Cheap
Imidazoles		
Miconazole, clotrimazole, econazole, sulconazole,* ketoconazole, bifonazole*	Cream, powder, lotion, spray, shampoo (ketoconazole)	Broad spectrum including antibacterial (not ketoconazole)
Tioconazole nail solution*	Nail treatment	Expensive
Bifonazole urea*	Nail treatment	Expensive
Allylamines		
Terbinafine, naftifine*	Cream	Very rapid Expensive
Amorolfine*	Cream, nail lacquer	Can be used on nails Expensive
Cyclopyroxolamine*	Cream	Broad spectrum

* Availability varies in different countries.

occasionally but is reversible. Hepatic reactions, although reported, are exceptionally rare. Skin rashes including erythema multiforme or toxic epidermal necrolysis are also seen on occasion.

Itraconazole [8,9]. This is an orally active azole of the triazole series. It has similar activity to ketoconazole, but without the risk of hepatotoxicity. Its mode of action is through the inhibition of the cytochrome P-450-dependent demethylation stage in the formation of ergosterol on the fungal cell membrane. It is active *in vitro* against all the main superficial fungal pathogens including *Candida albicans*, as well as a wide range of fungi that cause deep infections from *Histoplasma capsulatum* to *Penicillium marneffei*. Itraconazole rapidly penetrates to the outer stratum corneum and is also found in sebum. It is avidly bound to keratin-containing tissues, and in nail, for instance, may persist long after cessation of therapy. It has been shown that after 3 months of 200 mg/day itraconazole, levels in the toenail persist for up to 6 months [10]. This feature allows a range of different dose regimens. These have evolved so that the initial treatments first described involving 100 mg/day itraconazole have been superseded by higher or intermittent (pulsed) therapy. It is active against a wide range of dermatophytes and is effective in regimens of 100 mg for 15 days in tinea cruris and corporis, or 30 days in tinea pedis. The currently preferred regimen uses 400 mg/day, given as two daily doses of 200 mg. In tinea corporis, 1 week of therapy is sufficient, and in tinea pedis 2 weeks. For onychomycosis, a regimen of 400 mg/day for 1 week every month for 3 months is usually given. Occasionally, longer periods of treatment are needed [11]. Although it is not licensed yet in many countries for the treatment of tinea capitis [12], it is effective in this indication. There is some evidence that its absorption is impaired in the presence of phenobarbital. It also interacts with coumarin anticoagulants, ciclosporin, rifampicin, digoxin, statins and astemizole and terfenadine. It should not be given together with the latter antihistamines, as they may cause cardiac arrythmias. Side effects are not common and mainly consist of nausea and abdominal discomfort. Hepatic reactions are exceptional.

Griseofulvin [13]. This is a metabolic product derived from several species of *Penicillium*, which was first isolated from *P. griseofulvum*. Its activity, which is fungistatic, is largely restricted to dermatophyte infections. The mode of action appears to be in part through inhibition of the formation of intracellular microtubules. Resistance to griseofulvin among dermatophytes is rare. The smaller particle size microcrystalline preparations of griseofulvin are better absorbed than those with larger particles, and the micronized form is now the standard preparation. Unlike itraconazole, griseofulvin is not firmly bound to keratin.

The usual human regimen is 10 mg/kg/day given in tablet form, or solution form for children. The solution form is not available in many countries. Treatment duration varies between 2 and 4 weeks for tinea corporis to over 1 year for onychomycosis of toenails. In tinea capitis, a single dose of 1–2 g griseofulvin has been reported to be effective in some patients with tinea capitis [14]. Drug interaction with phenobarbital and coumarin anticoagulants occur [13]. Headaches and nausea are common complaints on griseofulvin; however, serious side effects have been extremely rare. There are a few reports of apparent precipitation or exacerbation of systemic lupus erythematosus (SLE) and porphyrias by griseofulvin. Occasionally, urticarial rashes are seen and light sensitivity eruptions (distinct from lupus erythematosus and porphyria) have occasionally been reported.

The use of griseofulvin has largely been superseded in many countries by terbinafine or itraconazole, except in tinea capitis.

Ketoconazole [15]. This orally active imidazole is a broad-spectrum antifungal agent. In ringworm infections requiring systemic treatment, it offers an alternative agent and is given in a 200–400 mg/day regimen with food (for adults). Hepatitis is a proven complication, occurring in 1 in 10 000 patients. Because of this, ketoconazole is reserved for second-line therapy. At high doses, ketoconazole may also inhibit androgen biosynthesis [15].

Fluconazole [16]. Fluconazole is an orally active triazole antifungal used for the treatment of *Candida* infections and systemic mycoses. However, it also has activity against dermatophyte fungi. It is given in a regimen of 150 mg/week for 2–3 weeks for tinea corporis and tinea cruris, and somewhat longer for dry-type tinea pedis. It is also reported to be effective given in weekly doses in onychomycosis, although the exact length of treatment necessary is not clear as yet. There are fewer interactions than with itraconazole but, like the latter, side effects are rare and mainly confined to gastrointestinal discomfort. However, drug resistance in *Candida* species, particularly *C. krusei* and *C. glabrata*, has been described. There is *C. albicans* resistance in AIDS patients [17].

There is little data at present on the use of posaconazole and voriconazole in dermatophytosis.

Topical applications. A great variety of topical applications have been used for the treatment of ringworm infections. The short list includes a few preferred preparations (Table 36.7), which have been soundly tested, and which in the authors' clinical experience and the published controlled trials are of very comparable effectiveness [18–22]. In all cases, allergic contact dermatitis is rare. Irritant effects may occur with any of them, especially on raw skin and in fissures between the toes. Benzoic acid compound ointment (Whitfield's ointment), full strength, is not advised for tender skin, such as the scrotum or the groins, and in such sites should only be used diluted to half-strength with its vehicle (emulsifying ointment). Magenta paint (Castellani's paint) is still used in some cases of inflammatory tinea pedis, particularly when bacterial infection coexists, although potassium permanganate followed by a topical antifungal is preferred. Imidazoles for topical use, such as clotrimazole, econazole and ketoconazole, are now well established as effective remedies in ringworm infections with an extremely low incidence of adverse reactions; other drugs in this group, miconazole, isoconazole, tioconazole and sulconazole, are equally effective [23,24]. Alternatives include topical terbinafine and amorolfine. Terbinafine applied topically has been shown to produce responses in some dermatophyte infections in very short periods. For instance, 1 week of topical terbinafine was found to be more effective than 4 weeks of clotrimazole in tinea pedis. Amorolfine, a morpholine, is mainly used as a treatment for onychomycosis in the form of a 5% nail lacquer [25] applied after abrading the nail

once or twice weekly. It is more effective when used as combination therapy for onychomycosis with terbinafine or itraconazole.

Treatment regimen

The different syndromes of ringworm infections require different treatment regimens. The evidence base has only recently been reviewed in the case of some infections and among published clinical trials there are very few with long-term follow-up. Generally, topical therapies are used for localized or mild infections, oral antifungals for the more extensive infections. The newer oral azoles, such as fluconazole or itraconazole and terbinafine, are now the preferred oral treatments for extensive or severe dermatophytosis rather than griseofulvin. Although cheaper than the alternatives, griseofulvin is usually slower and, in many studies, less effective.

Tinea corporis. Localized tinea corporis, especially of recent origin, commonly responds to topical therapy applied twice daily, usually for about a month. Topical terbinafine often works in a shorter time (e.g. 2 weeks). In more widespread infections of recent onset, oral terbinafine or itraconazole will generally be preferred, and may be expected to clear the condition in about 2–3 weeks, depending on the dosage used. With griseofulvin, much longer term treatment is needed, for up to several months with extensive infections. With *T. concentricum*, treatment failures may occur with griseofulvin. Both terbinafine and itraconazole are effective in tinea imbricata, but the most appropriate regimen is not clear.

Tinea capitis. Topical therapy has little place in the management of this condition except as an adjunct to oral therapy. Griseofulvin should therefore be given. Although massive single-dose therapy and intermittent dose regimens (25 mg/kg twice a week) have had some success, in general, conventional continuous daily therapy is advisable (10 mg/kg). In small-spored ectothrix infections, griseofulvin for at least 6 weeks is usually adequate. In some *T. tonsurans* and *T. schoenleinii* infections, much longer courses and sometimes higher dosage (20 mg/kg/day) of griseofulvin therapy may be needed. With scalp kerions, careful removal of crusts using wet compresses should not be neglected, and the possibility of coexisting bacterial infection should be considered. If confirmed by swabs, systemic antibacterial chemotherapy should be instituted. In general, the kerions are less painful than their inflammatory appearance suggests, but analgesics may be needed. Occasionally, in children with extensive kerions, frequent attendance at the outpatient clinic where skilled nursing is available may be of great value, and is much appreciated by the worried parents. Permanent hair loss from scarring is usually less than would be expected.

Both itraconazole and terbinafine are now licensed in a few countries for use in children, and are alternatives for certain infections such as those caused by *Trichophyton* species, although there are fewer data and, in some cases—particularly with terbinafine—they have appeared to be less effective in disease caused by *Microsporum* species. The best length of treatment for *T. tonsurans* and *T. violaceum* infections with terbinafine appears to be 1 month. There is some evidence that higher doses of terbinafine may be more effective for *Microsporum*. The appropriate length of treatment with either itraconazole or fluconazole is not established, although both appear to be effective against *T. tonsurans*. Ketoconazole shampoo or selenium sulphide can be used to prevent spread in the early phases of therapy, when used in combination with an oral treatment. In severely inflammatory forms, there has been some argument in favour of using oral steroids to inhibit the inflammatory response. While this view has its supporters, we tend to review all cases early after the institution of antifungal therapy, and only use oral steroids in severe cases with widespread ide reactions.

Tinea barbae. Beard infections usually respond satisfactorily to itraconazole or terbinafine, sometimes in combination with topical therapy over a period of 4–6 weeks. Fairly long-term follow-up is recommended, and late recurrences undoubtedly occur.

Tinea faciei. In localized cases, promptly diagnosed topical therapy seems to work well, especially with tolnaftate or one of the imidazoles. Where delay has occurred before the diagnosis is established, and especially when steroid therapy has modified the condition, terbinafine or itraconazole is generally preferred. Most cases will clear in 3 or 4 weeks, certainly in 6 weeks, but long-standing infections may occasionally need longer periods of treatment.

Tinea pedis. For very mild toe cleft changes and for prophylaxis at swimming baths, one of the topical preparations is recommended. Tolnaftate powder, for instance, has proven value, and the imidazoles are likely to be equally effective. For toe cleft changes that are more than trivial, a cream is generally preferred and any of the listed preparations can be confidently recommended for minor forms of tinea pedis. Azole preparations are cheap and are usually effective in up to 30 days, but topical terbinafine can be used for 1–7 days; it is more expensive. If the toe clefts are very inflamed and secondary bacterial infection is likely, a brief period with rest and bland applications may be necessary. Magenta paint initially used at half strength, potassium permanganate solution or aluminium chloride solution 20–30% twice daily have considerable advantages. Clearly, if there is any evidence of serious bacterial infection, swabs should be taken; if there is clinical evidence of cellulitis, patients should receive a systemic antibacterial antibiotic.

In dry-type tinea pedis, usually caused by *T. rubrum*, terbinafine or itraconazole are of great value. Speed of recovery is faster and relapse rates less than with griseofulvin. Treatments using terbinafine 250 mg/day for 2 weeks or itraconazole 400 mg/day for 1–2 weeks are usually given.

Tinea cruris. In cases of recent onset, topical therapy can be expected to be curative within 2–4 weeks. Any of the local applications listed is satisfactory, but benzoic acid compound ointment (Whitfield's ointment) should be prescribed at half strength. Tolnaftate, terbinafine and the imidazoles are better tolerated in the flexural areas, and if the diagnosis is in doubt terbinafine and the imidazoles have the advantage of being effective against *Candida* as well. Where the condition has been present for many months, or has spread to the pubic area, the natal cleft or the buttocks, and

where topical steroids have been used, systemic treatment is strongly recommended. Terbinafine and itraconazole usually produce a remission in 1–2 weeks [26]. Some patients relapse even after this therapy, although it appears less likely to occur than with griseofulvin. A longer course of therapy may work in these recalcitrant cases.

Tinea manuum. Chronic ringworm infections of the palm are not easily cleared, and oral therapy is always needed. Itraconazole and terbinafine are both effective in this condition. Most cases clear with 2–4 weeks of treatment although it may be advisable to review the results a few months after the end of treatment. With griseofulvin, longer periods of treatment are necessary. Many patients will require 3 months of therapy and may even relapse after that.

Onychomycosis caused by dermatophytes. In general, fingernail infections with ringworm fungi respond satisfactorily to oral terbinafine 250 mg/day for 6 weeks or itraconazole 400 mg/day for 1 week, given monthly for 2–3 months. With griseofulvin [27], clearance may be expected in about 4 months, but longer treatment regimens, up to 8 months or even 1 year, are often needed. In the case of toenails, longer periods of treatment may be necessary; for example, terbinafine 250 mg/day for 3 months or itraconazole 400 mg/day for 1 week given monthly for 3–4 months. One large clinical trial has shown better efficacy with terbinafine than itraconazole [28]. Some, possibly 15% of patients, fail to respond to these drugs, and there is a strong clinical impression that results are much better in younger patients in whom faster linear nail growth and relative absence of coexisting ischaemic or traumatic dystrophy are probably important factors. Poor peripheral circulation seems to have an adverse effect on treatment.

Avulsion of the nail or removal of the infected areas with a drill or burr as adjuncts to antifungals are occasionally valuable. The use of 40% urea cream under occlusive dressing is an alternative approach to treatment [29], particularly in oral treatment failures. The addition of the imidazole, 1% bifonazole, to the urea paste has produced good responses in some patients with involvement of the entire nail plate [30]. When a single great toenail is infected, these procedures are worthy of serious consideration. Unfortunately, there has been no reliable controlled evaluation of their worth, and avulsion is certainly not without its drawbacks. Topical therapy for nail infections has been used in the past with poor results, except in superficial white onychomycosis caused by ringworm infection, where it may well be effective. Other topical agents reported to be effective—28% tioconazole, ciclopyroxolamine and amorolfine nail paint—have all produced remissions in some studies, although these are seldom frequent enough to encourage sole use of these preparations, except in early or superficial infections or as adjuncts to oral therapy. The use of combined treatment with either terbinafine or itraconazole with amorolfine may be more effective than oral therapy alone [31].

Steroid-modified ringworm. Whatever site is affected, it is often best to treat steroid-modified ringworm with oral therapy, allowing a few applications of topical steroid to continue until the terbinafine or itraconazole has begun to take effect. It is wise to use 1% hydrocortisone cream or at least a weaker steroid than that originally prescribed, and also to warn the patient about a possible rebound in spite of these measures. Follow-up to ensure steroid cream has been stopped and cure obtained is mandatory.

Treatment failures

Failure of topical therapy. Most failures of topical therapy are caused by inaccurate diagnosis or by inappropriate use of topical therapy (e.g. in hairy areas), or because the treatment is not used. Once or twice daily application for several weeks is usually required for success, and many patients, particularly if their symptoms are minor, will not achieve this unless they are carefully supervised and enthusiastically encouraged. Paradoxically, some non-fungal conditions may be improved considerably by one of the antidermatophyte preparations, and these remedies should not be used empirically to establish the diagnosis of ringworm infection. Many dermatoses respond, at least temporarily, to any bland application, and imidazole compounds in particular have considerable antibacterial properties.

Failure of oral therapy. When a patient fails to respond to terbinafine, fluconazole or itraconazole, the following points should be checked:

1. Is the diagnosis correct? If necessary repeat scrapings.
2. Has the patient been taking the tablets regularly?
3. Is the patient taking any potentially competitive drugs?
4. In spite of taking them correctly, is the patient failing to absorb the antibiotic? Estimation of itraconazole levels, which is sometimes poorly absorbed, may be helpful.
5. In some patients with onychomycosis, poor penetration of drugs into defined linear streaks or nail edge areas of nail plate infection may account for treatment failure. Surgical removal of these abnormal nail areas, often after softening with urea ointment, may be useful.
6. Is there coexisting pathology such as HIV/AIDS or arterial disease?
7. Is a co-pathogen or secondary infection present? This should be considered in feet and in the case of kerions, and perhaps in groin infections too. In nails, the coexistence of non-dermatophyte fungus should be considered. *Scopulariopsis brevicaulis*, apart from causing infections of the toenails in its own right, may coexist with *T. rubrum* or *T. mentagrophytes* var. *interdigitale* and seems, at least on occasions, to cause failure of treatment. Nail removal may be indicated in this instance.
8. Antifungal resistance. This phenomenon is sufficiently uncommon among dermatophytes to make routine testing unnecessary [30], but where treatment failure occurs without other explanation, it is possible to estimate the sensitivity of the causal organism. This should be performed by a specialist laboratory. Apart from true resistance, tolerance, in which the organism apparently becomes clinically resistant to drug in the tissues but is sensitive *in vitro*, may also be important.
9. Reinfection. As ringworm fungi can frequently be isolated from the environment, when there are cases of ringworm of the scalp, and from clothing after laundering, it is highly likely that patients whose infection has been eradicated may be reinfected from these sources. Unfortunately, there is no proven way to avoid this.

Despite running through this checklist, dermatologists may not come up with an adequate explanation for treatment failure. In these situations, the use of one of the alternatives is a logical further step.

References

1 Krowchuk DP, Lucky AW, Primmer SI. Current status of the identification and management of tinea capitis. *Pediatrics* 1983; **72**: 625–31.
2 Hay RJ, Del Palacio Hernanz A, eds. First symposium on terbinafine. *Clin Exp Dermatol* 1989; **14**: 97–127.
3 Ryder NS, Meith H. Allylamine antifungal drugs. In: Borgers M, Hay R, Rinaldi MG, eds. *Current Topics in Medical Mycology*, Vol. 4. New York: Springer, 1992: 158–88.
4 Faergemann J, Zehender H, Millerioux L. Levels of terbinafine in plasma, stratum corneum, dermis–epidermis (without stratum corneum), sebum, hair and nails during and after 250 mg terbinafine orally once daily for 7 and 14 days. *Clin Exp Dermatol* 1994; **19**: 121–6.
5 Van der Schroeff JG, Cirkel PKS, Crijns MB *et al*. A randomised treatment duration-finding study of terbinafine in onychomycosis. *Br J Dermatol* 1992; **126** (Suppl. 39): 36–9.
6 Goodfield MJD, Rowell NR, Forster RA *et al*. Treatment of dermatophyte infection of the finger- and toenails with terbinafine (SF 86–327, Lamisil), an orally active fungicidal agent. *Br J Dermatol* 1989; **121**: 753–8.
7 Elewski B. Cutaneous mycoses in children. *Br J Dermatol* 1996; **134** (Suppl. 46): 7–11.
8 Grant SM, Clissold SP. Itraconazole: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in superficial and systemic mycoses. *Drugs* 1989; **37**: 310–44.
9 Hay RJ, ed. *Itraconazole*. Manchester: Adis, 1994.
10 Willemsen M, De Doncker P, Willems J *et al*. Post-treatment itraconazole levels in the nail. *J Am Acad Dermatol* 1992; **131**: 919–22.
11 Degreef H, Marien K, De Veylder H *et al*. Itraconazole in the treatment of dermatophytoses: a comparison of two daily dosages. *Rev Infect Dis* 1987; **9** (Suppl. 1): 104–8.
12 Legendre R, Esola-Moire J. Itraconazole in the treatment of tinea capitis. *J Am Acad Dermatol* 1990; **23**: 559–60.
13 Davies RR. Griseofulvin. In: Speller DCE, ed. *Antifungal Chemotherapy*. Chichester: Wiley, 1980: 149–82.
14 Beghin D, Vanbreuseghem R. Traitment des dermatophyties du cuir chevelu par une dose unique de griséofulvine; essai d'une dose reduite. *Ann Soc Belg Med Trop* 1974; **54**: 477–81.
15 Jones HE, ed. *Ketoconazole Today: a Review of Clinical Experience*. Manchester: Adis, 1987.
16 Powderly WB, Van't Wout JW, eds. *Fluconazole*. Marius, UK, 1992.
17 Baily GG, Perry FM, Denning DW, Mandal BH. Fluconazole resistant candidiasis in an HIV cohort. *AIDS* 1994; **8**: 787–92.
18 Botter AA. Topical treatment of nail and skin infections with miconazole, a new broad-spectrum antimycotic. *Mykosen* 1971; **14**: 187–91.
19 Burgess MA, Bodey GP. Clotrimazole (Bay b 5097): *in vitro* and clinical pharmacological studies. *Antimicrob Agents Chemother* 1972; **2**: 423–9.
20 Clayton YM, Connor BL. Comparison of clotrimazole cream, Whitfield's ointment and nystatin ointment for the topical treatment of ringworm infections, pityriasis versicolor, erythrasma and candidiasis. *Br J Dermatol* 1973; **89**: 297–303.
21 Clayton YM, Knight AG. A clinical double blind trial of topical miconazole and clotrimazole against superficial fungal infection and erythrasma. *Clin Exp Dermatol* 1976; **1**: 225–9.
22 Keller K. Klinische Erfahrungen mit den neuen Antimykotikum Econazol. *Schweiz Rundschau Med* 1974; **63**: 722–4.
23 Fromtling RA. Imidazoles as medically important antifungal agents: an overview. *Drugs Today* 1984; **20**: 325–49.
24 Speller DCE, ed. The imidazoles. In: *Antifungal Chemotherapy*. Chichester: Wiley, 1980: 107–48.
25 Reinel D. Topical treatment of onychomycosis with amorolfine 5% nail lacquer: comparative efficacy and tolerability of once and twice weekly use. *Dermatology* 1992; **182** (Suppl.): 21–4.
26 Panconesi E, DiFonzo E. Treatment of dermatophytoses and pityriasis versicolor with itraconazole. *Rev Infect Dis* 1987; **9** (Suppl. 1): S109–11.
27 Roberts DT. Onychomycosis: current treatment and future challenges. *Br J Dermatol* 1999; **141** (Suppl. 56): 1–4.
28 Evans EG, Sigurgeirsson B. Double blind, randomised study of continuous terbinafine compared with intermittent itraconazole in treatment of toenail onychomycosis. The LION Study Group. *BMJ* 1999; **318**: 1031–5.
29 White MI, Clayton YM. The treatment of fungus and yeast infections of nails by the method of chemical removal. *Clin Exp Dermatol* 1982; **7**: 272–6.
30 Hay RJ, Roberts D, Richardson M *et al*. The evaluation of bifonazole 12% and 40% urea paste in the management of onychomycosis. *Clin Exp Dermatol* 1988; **13**: 164–7.
31 Baran R, Feuilhade M, Datry A *et al*. A randomized trial of amorolfine 5% solution nail lacquer combined with oral terbinafine compared with terbinafine alone in the treatment of dermatophytic toenail onychomycoses affecting the matrix region. *Br J Dermatol* 2000; **142**: 1177–83.

Infections caused by *Scytalidium* species

Aetiology. *Scytalidium dimidiatum*, previously known as *Hendersonula toruloidea*, is a secondary pathogen of higher plants, found mainly in tropical areas, but also in the USA and the Mediterranean region. This grey to black mould is now recognized as the cause of ringworm-like infections of the palms, soles, toe webs and nails [1–4]. *S. hyalinum*, a variant non-pigmented form of *S. dimidiatum*, can also mimic tinea pedis and manuum and invade the nail plate [5]. These two moulds evoke the same clinical picture.

Although these infections were first diagnosed in the UK in patients who were immigrants from the West Indies, East Africa and the Indian subcontinent, reports from areas where they may be truly endemic, such as the Caribbean [6], West Africa [7–9] and Thailand [10], have shown that infection by *Scytalidium* species is extremely common. Infection has also been seen in Europeans who have merely visited an endemic area for a vacation.

Clinical features. These fungi are capable of producing toe cleft changes and involvement of the palms and soles. In this, they closely resemble the dry-type infection caused by *Trichophyton rubrum* affecting the palms or soles [5]. Lesions are often asymptomatic and only discovered on routine inspection. In fingernails, the nail changes start at the lateral and distal edges, and there may be extensive undermining of the nail without corresponding thickening of the nail plate (Fig. 36.31). The nails may fracture



Fig. 36.31 Onychomycosis caused by *Scytalidium dimidiatum*: early onycholysis.

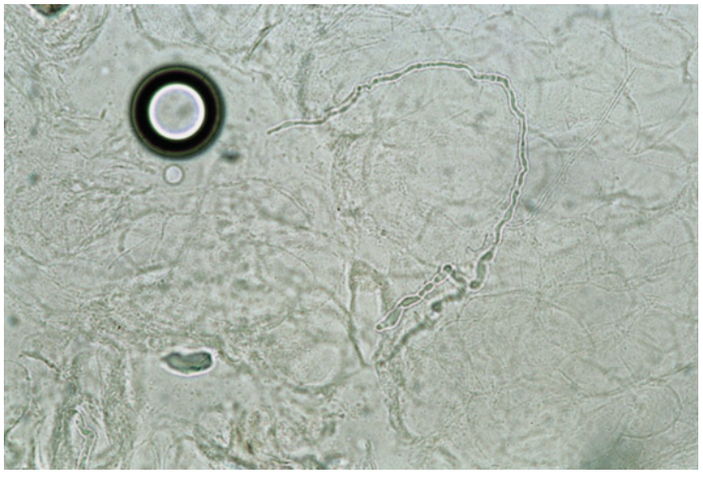


Fig. 36.32 Infection by *Scytalidium* species. Skin scales mounted in 30% KOH, bright field. The hyaline hyphae superficially resemble those of dermatophytes, but are very uneven in diameter. One- to two-celled arthroconidia may be observed. (Courtesy of the Department of Medical Mycology, St John's Institute of Dermatology, King's College London, London, UK.)



Fig. 36.33 *Scytalidium dimidiatum* colony forms. The fast-growing form (right) fills a 90-mm Petri dish in a few days and develops profuse aerial mycelium. The velvety, slow-growing form grows at the same rate as a dermatophyte. (Courtesy of the Department of Medical Mycology, St John's Institute of Dermatology, King's College London, London, UK.)

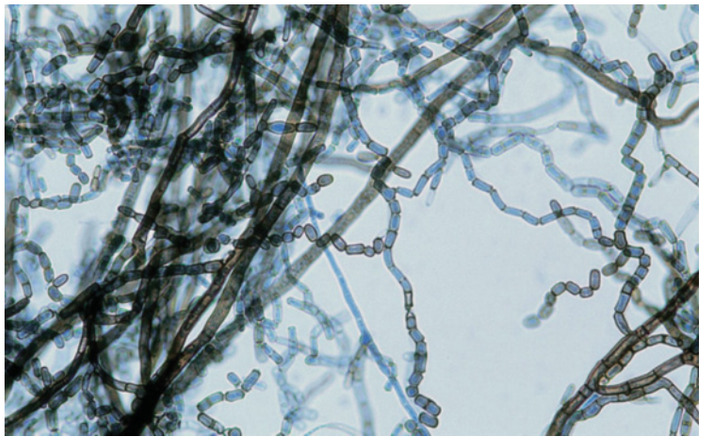


Fig. 36.34 *Scytalidium dimidiatum* microscopy, bright field. Chains of brown, one- to two-celled arthroconidia are characteristic. They may be scanty in the slow-growing form. (Courtesy of the Department of Medical Mycology, St John's Institute of Dermatology, King's College London, London, UK.)

transversely in due course. Paronychia often accompanies these changes. Usually, yeasts are not present under the nail fold, suggesting that the changes are caused by *Scytalidium* alone. In the toenails, the changes are usually identical to those seen in dermatophyte infections. Occasionally, there may be increased pigmentation in the nail plate, but this should not be confused with idiopathic longitudinal pigmented streaking of the nail. This change is most prominent in white people with nail infections [11]. The infection is confined to areas of thickly keratinized skin, and involvement of less heavily keratinized areas, such as the groins, or dorsum of the hand or foot, is not found.

Laboratory diagnosis. Although pigmented brown hyphae have occasionally been observed in skin and nail samples infected by *S. dimidiatum*, in the vast majority of cases the hyphae are hyaline and appear very similar to those of dermatophytes. Typically, however, they are more irregular, varying noticeably in width along the length of a single hypha [12] (Fig. 36.32). With experience, a preliminary diagnosis of *Scytalidium* infection may be made on the basis of direct microscopy alone.

Both *S. dimidiatum* and *S. hyalinum* are sensitive to cycloheximide, and this antibiotic must be excluded from the culture medium. As mixed infections by *Scytalidium* species and dermatophytes have been recorded, duplicate cultures with and without cycloheximide are ideal, and will allow the isolation of both dermatophyte and non-dermatophyte. Mixed infections of dermatophytes and *S. dimidiatum* and *S. hyalinum* have also been reported.

S. dimidiatum. Colony: variable colonial morphology [13] (Fig. 36.33). One form grows very rapidly and produces a high aerial mycelium, which completely fills a 90-mm Petri dish in a few days. The other common form grows more slowly, at about the same rate as a dermatophyte and does not produce aerial hyphae, but has a velvety surface texture. Both are pale initially, but darken to black and mouse grey, respectively, as they mature. Microscopy: branching chains of one- to two-celled brown arthroconidia are observed (Fig. 36.34). These are abundant in the fast-growing cultures, but may be scanty in the slow-growing form. Coiled hyphae and rough-walled hyphae are usually present in the slow-growing cultures. *S. dimidiatum* produces melanin both in culture and *in vivo* [14].

S. hyalinum. Colony: the fungus grows rapidly, and in a few days produces a white to cream colony with a moderately high aerial mycelium and buff reverse (Fig. 36.35). Microscopy: chains of hyaline one- to two-celled arthroconidia are produced.

Treatment. There is no reproducibly effective therapy, although individual patients may respond to treatment with topical azoles. Both organisms may be sensitive *in vitro* to itraconazole or terbinafine, but infections seldom respond to these drugs clinically.



Fig. 36.35 *Scytalidium hyalinum* colony. (Courtesy of the Department of Medical Mycology, St John's Institute of Dermatology, King's College London, London, UK.)

References

1 Campbell CK, Kurwa A, Abdel Aziz AHM *et al*. Fungal infection of skin and nails by *Hendersonula toruloidea*. *Br J Dermatol* 1973; **89**: 98–9.
2 Gentles JC, Evans EGV. Infection of the feet and nails with *Hendersonula toruloidea*. *Sabouraudia* 1970; **8**: 72–5.
3 Greer DL, Gutierrez MM. Tinea pedis caused by *Hendersonula torubloidea*. *J Am Acad Dermatol* 1987; **16**: 1111–5.
4 Gugnani HC, Nzelibe FK, Osunkwo IC. Onychomycosis due to *Hendersonula toruloidea* in Nigeria. *J Med Vet Mycol* 1986; **24**: 239–41.
5 Hay RJ, Moore MK. Clinical features of superficial fungal infections caused by *Hendersonula toruloidea* and *Scytalidium hyalinum*. *Br J Dermatol* 1984; **110**: 677–83.
6 Allison VY, Hay RJ, Campbell CK. *Hendersonula toruloidea* and *Scytalidium hyalinum* infections in Tobago. *Br J Dermatol* 1984; **111**: 371–2.
7 Gugnani HC, Oyeka C. Foot infections caused by *Hendersonula toruloidea* in coal miners. *J Med Vet Mycol* 1989; **27**: 169–79.
8 Kombila M, Martz M, Gomez de Diaz M *et al*. *Hendersonula toruloidea* as an agent of mycotic foot infection in Gabon. *J Med Vet Mycol* 1990; **28**: 215–23.
9 Oyeka CA, Gugnani HC. Skin infections due to *Hendersonula toruloidea*, *Scytalidium hyalinum*, *Fusarium solani* and dermatophytes in cement factory workers. *J Mycol Med* 1992; **2**: 197–201.
10 Ungpakorn R, Lohaprathan S, Reangchainam S. Prevalence of foot diseases in outpatients attending the Institute of Dermatology, Bangkok, Thailand. *Clin Exp Dermatol* 2004; **29**: 87–90.
11 Jones SK, White JE, Jacobs PH *et al*. *Hendersonula toruloidea* infection of the nails in Caucasians. *Clin Exp Dermatol* 1985; **10**: 444–7.
12 Moore MK. The infection of human skin and nail by *Scytalidium* species. In: Borgers M, ed. *Current Topics in Medical Mycology*, Vol. 4. New York: Springer, 1991: 1–42.
13 Moore MK. Morphological and physiological studies of isolates of *Hendersonula toruloidea* Nattrass cultured from human skin and nail samples. *J Med Vet Mycol* 1988; **26**: 25–39.
14 Morris-Jones R, Youngchim S, Hextall JM, Gomez BL *et al*. Scytalidium dimidiatum causing recalcitrant subcutaneous lesions produces melanin. *J Clin Micro* 2004; **42**: 3789–94.

Onychomycosis caused by other non-dermatophyte moulds

Definition. Broadly, the term onychomycosis describes any fungal infection of the nail plate. Ringworm infections, *Candida* infections and *Scytalidium* infections are considered separately, and these organisms are considered to be primary pathogens. However, a wide variety of other non-dermatophyte moulds have been reported from abnormal nails, most often toenails, and in such cases their significance needs very careful assessment [1]. Many of these putative pathogens are common in the environment, and may be isolated as contaminants, particularly on media free of cycloheximide. It is therefore essential in cases where such moulds are implicated in onychomycosis to correlate the morphological findings on direct microscopy with those of the isolate. A considerable proportion of dermatophyte infected nails with typical hyphae present on direct microscopy will fail to yield a dermatophyte on culture. In these instances, the isolation of a few colonies of a contaminating mould may be misinterpreted. In other instances, a non-dermatophyte mould may be isolated in addition to a dermatophyte, and once more, unless evidence suggestive of a mixed infection has been obtained on direct microscopy [2], in most instances this will represent simple contamination. Before the isolation of a non-dermatophyte can be considered significant, re-examination of the patient is essential in order to confirm the infection. A second direct examination will allow any unusual features of the fungus in the nail to be assessed. Atypical morphology, such as the presence of large numbers of fronding hyphae, or even the production of characteristic conidia within the nail, may be present. In such instances, a second culture on medium free of cycloheximide may allow reisolation of the same mould and confirm the infection. Concurrent culture with cycloheximide is also recommended to confirm the absence of a dermatophyte, or it may in some instances prove the presence of a mixed infection, for nails rendered abnormal by a primary dermatophyte infection may occasionally be secondarily invaded by moulds. It is noteworthy that in unmixed infections, these non-dermatophytes, unlike *Scytalidium* species, are incapable of producing concurrent skin infection.

Using reliable criteria, one survey in Canada [3] of over 2500 isolates from infected nail samples found that *Scopulariopsis brevicaulis* made up 1.6% of the total, and that species of *Aspergillus* and *Fusarium* comprised a further 0.3% of the total. Similarly, a working group of the British Society for Medical Mycology [4] has estimated that approximately 5% of cases of onychomycosis are caused by non-dermatophyte moulds. Such data confirm the view that a few moulds are fairly regularly reported from a small percentage of the total cases of onychomycosis, and their isolation may suggest that they are playing some part in the pathology, although whether their removal with antifungal therapy will result in clinical recovery remains to be established. By far the most common of these isolates is *Scopulariopsis brevicaulis*, which does appear capable of attacking undamaged nails or ones showing only trivial abnormalities. In cases of superficial white onychomycosis, species of *Acremonium*, *Fusarium* and *Aspergillus* may be isolated rather than *Trichophyton mentagrophytes* var. *interdigitale*. Since 1990, *Onychocola canadensis* has been recognized as a cause of onychomycosis, after its original description in nine subjects from Canada and New Zealand [5,6].

Scopulariopsis infections [2]

Scopulariopsis brevicaulis is a common saprophytic mould that does not attack the skin. When it causes nail dystrophy, the clinical features may be indistinguishable from those of a ringworm infection,



Fig. 36.36 Onychomycosis caused by *Scopulariopsis brevicaulis*.

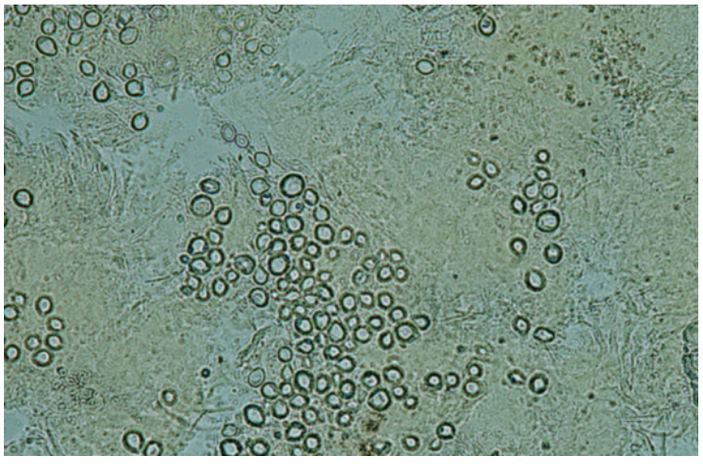
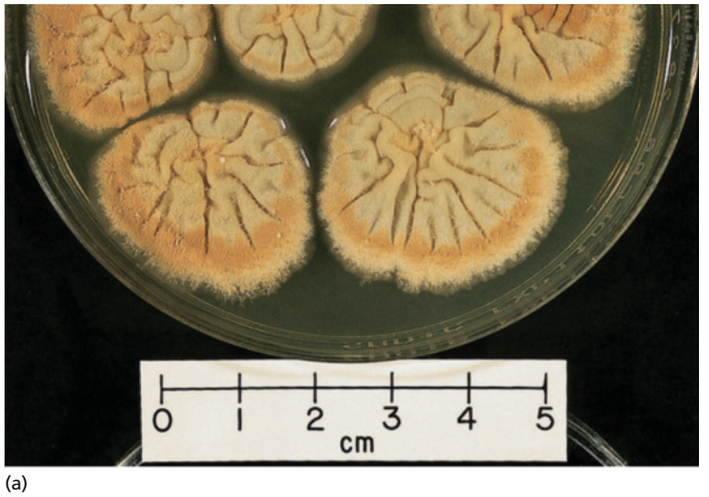
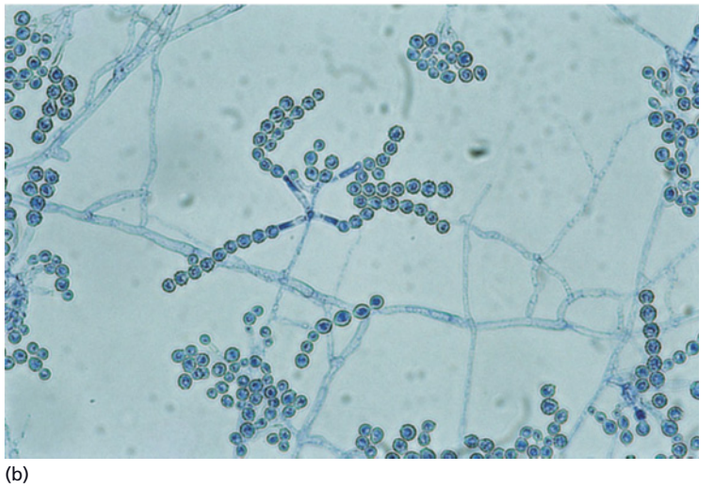


Fig. 36.37 Onychomycosis caused by *Scopulariopsis brevicaulis*. Nail mounted in KOH, bright field. The characteristic conidia are relatively thick-walled, oval or lemon-shaped with a truncate base. (Courtesy of the Department of Medical Mycology, St John's Institute of Dermatology, King's College London, London, UK.)



(a)



(b)

Fig. 36.38 *Scopulariopsis brevicaulis*. (a) Colony. On media free of cycloheximide, the colonies are initially waxy and deeply folded, but production of conidia rapidly produces a brown colour on the colony surface. (b) Microscopy, bright field. Chains of rough-walled conidia are formed from annellides. (Courtesy of the Department of Medical Mycology, St John's Institute of Dermatology, King's College London, London, UK.)

but where there is heavy invasion its brown spores may discolour the nail, producing a cinnamon colour (Fig. 36.36), best seen end-on in the area of subungual hyperkeratosis. The great toenails are most often affected, but other toenails and, very occasionally, fingernails are involved. Dermatophyte infections of the skin and of the *Scopulariopsis*-infected nail plate itself may coexist.

Laboratory diagnosis. The distribution of the fungus in the infected nail material is often patchy, but where conidia are found they are quite distinctive, being approximately spherical or lemon-shaped with one flat, basal facet. The thick cell walls and truncate bases of the conidia distinguish them from the arthroconidia of dermatophytes. The surfaces of the conidia appear smooth (Fig. 36.37). The mould is partially sensitive to cycloheximide and, in most instances, if cycloheximide-containing medium is used for isolation, the fungus will grow but remain compact, pale and intricately folded, producing few conidia.

Scopulariopsis brevicaulis (Fig. 36.38a,b). Colony: on cycloheximide-free medium, the fungus grows rapidly to produce a powdery cinnamon brown surface, often with radial or cerebriform folds. The reverse is cream to brown. Microscopy: chains of basipetal conidia are formed from annellides. The conidia are rough, lemon-shaped or obovoidal with a truncate base.

Management. It is essential to search carefully for a coexisting dermatophyte infection, particularly if there are cutaneous changes. Treatment of pure *Scopulariopsis* infections is difficult. Occasionally, patients may respond to a topically applied lotion such as econazole. However, the most common approach is to use 40% urea paste as a method of chemical nail avulsion and, following removal of the infected plate, an azole antifungal cream or lotion is applied daily to the nail bed until the new nail has completely formed. Itraconazole 400 mg/day for 1 week monthly for 3–4 months may be of help [7].

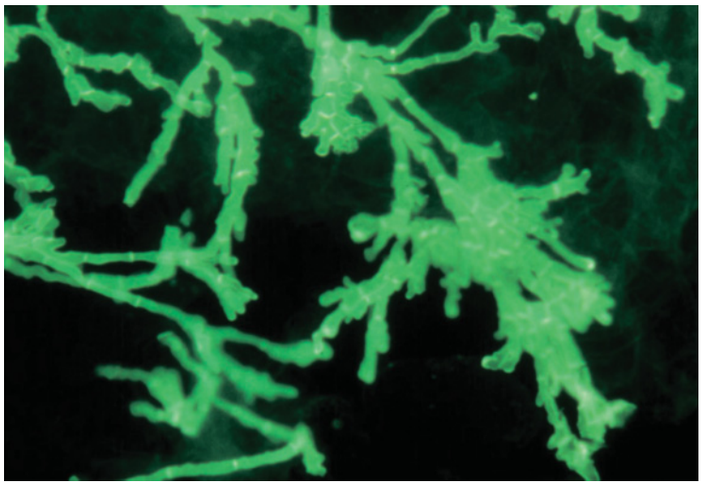


Fig. 36.39 Superficial white onychomycosis caused by non-dermatophyte moulds. Nail mounted in KOH and Calcofluor white, UV illumination. Bizarre, fronding hyphae may be observed (Courtesy of the Department of Medical Mycology, St John's Institute of Dermatology, King's College London, London, UK.)

Superficial white onychomycosis

Non-dermatophyte moulds that cause SWO produce a clinical picture identical to that seen in SWO caused by *Trichophyton mentagrophytes* var. *interdigitale*. However, one distinguishing feature is the lack of accompanying skin lesions.

Laboratory diagnosis. Direct examination of the nail material often reveals bizarre, atypical hyphal forms (Fig. 36.39) and extensive fronding hyphae. However, some degree of fronding may be seen in dermatophyte infections. The most commonly isolated species, which include *Acremonium strictum*, *Aspergillus terreus* and *Fusarium* species [8], grow rapidly if cycloheximide is omitted from the culture medium.

Acremonium strictum. Colony: the rapidly growing colonies are slimy to waxy with a few central tufts of aerial mycelium and are pink, beige or orange in colour. Microscopy: elongate narrow phialides arise at right angles from the slender hyphae. The ellipsoidal conidia collect as a slimy ball at the apex of the phialide.

Aspergillus terreus. Colony: colonies are rapidly growing, powdery with a cinnamon brown surface and pale yellow reverse. Microscopy: the vesicle at the apex of the stout conidiophore bears metulae and phialides only on the upper two-thirds of its surface. Long chains of small, smooth, brown phialoconidia are produced, which form a columnar head.

***Fusarium* species.** Colony: rapidly growing, woolly colonies may have a pink, purple or pale brown surface and reverse. Microscopy: the genus *Fusarium* is characterized by the production from phialides of curved multicellular macroconidia, with a distinct foot cell at the base. Microconidia are also formed and are unicellular or bicellular, ovoid to ellipsoidal. They collect as slimy balls or chains at the apices of the phialides. Chlamydoconidia may also be present.

Management. Results of treatment are unpredictable, but a trial of therapy with amorolfine 5%, tioconazole 28% or removal of the nail with 40% urea is worth attempting.

Onychomycosis caused by *Onychocola canadensis*

This fungus was only recognized as a pathogen in 1990. Nails display yellow or grey discoloration and hyperkeratosis with a build-up of subungual debris. Direct microscopy reveals irregular hyaline, sometimes golden or brown hyphae, together with barrel-shaped or round arthroconidia. The fungus grows in the presence of cycloheximide as a very slowly developing, restricted, glabrous, pale-grey mould, which after 5–6 weeks eventually produces delicate chains of hyaline, waisted arthroconidia.

Management. A single patient treated with griseofulvin showed some clinical improvement after 6 months, but the direct microscopy remained positive.

Miscellaneous mould infections

In contrast to the fungi described above, an enormous variety of other moulds have been implicated in one or only very few cases of onychomycosis. These include *Pseudeurotium ovalis*, *Pyrenochaeta unguius hominis*, *Lasiodiploidea theobromae*, *Curvularia lunata* and many others [9]. Investigations of abnormal toenails, especially in elderly people, have shown that an appreciable minority are colonized by non-dermatophyte fungi, usually moulds, often *Aspergillus* species. Fingernails are much less often invaded. These moulds are generally accepted as existing purely saprophytically. Although they may conceivably add to the primary damage caused by ischaemia, trauma or a dermatosis, they are, in general, of little practical importance to the patient. For the dermatologist, their significance lies in the fact that they must be distinguished from dermatophytes. Moreover, a dystrophic nail caused by ischaemia, secondarily colonized by *Aspergillus* species, is likely to regrow abnormally even if the fungus is eliminated by avulsion. Unlike *Scopulariopsis* infections, secondary mould invasion often affects several nails and indeed all may be invaded.

Of all the other non-dermatophyte moulds that may cause nail disease *Fusarium* is the most frequently associated. In addition to causing SWO, *Fusarium* species may also cause proximal subungual onychomycosis and other patterns of nail invasion; it can also cause interdigital infection.

References

1 Midgley G, Moore MK, Cook C, Phan QG. Mycology of nail disorders. *J Am Acad Dermatol* 1994; **31**: S68–74.

2 Onsberg P. *Scopulariopsis brevicaulis* in nails. *Dermatologica* 1980; **161**: 259–64.

3 Summerbell RC, Kane J, Krajden S. Onychomycosis, tinea pedis and tinea manuum caused by non-dermatophytic filamentous fungi. *Mycoses* 1989; **32**: 609–19.

4 Denning DW, Evans EVG, Kibbler CC *et al*. Fungal nail disease: a guide to good practice. Report of a Working Group of the British Society for Medical Mycology. *BMJ* 1995; **311**: 1277–81.

5 Sigler L, Congly H. Toenail infection by *Onychocola canadensis* gen. et sp. nov. *J Med Vet Mycol* 1990; **28**: 405–17.

6 Sigler L, Abbott SP, Woodgyer AJ. New records of nail and skin infection due to *Onychocola canadensis* and description of its teleomorph *Arachnomyces nodosetosus* sp. nov. *J Med Vet Mycol* 1994; **32**: 275–85.

7 Gupta AK, Gregurek-Novak T, Konnikov N. Itraconazole and terbinafine treatment of some non-dermatophyte molds causing onychomycosis of the toes and a review of the literature. *J Cut Med* 2001; **5**: 206–10.
8 Zaias N. Superficial white onychomycosis. *Sabouraudia* 1966; **5**: 99–103.
9 Hanecke E. Fungal infections of the nail. *Semin Dermatol* 1991; **10**: 41–53.

Candidosis

Synonyms
- Candidiasis
- Moniliasis
- Thrush

Definition. Candidosis is an infection caused by the yeasts of the genus *Candida*. Superficial infections of the mucous membranes and skin are numerically most important, but deep invasive disease such as septicaemia, endocarditis and meningitis can also occur and these are considered in the section on systemic mycoses.

Aetiology [1]. *C. albicans* is an oval yeast 2–6 × 3–9 μm in size, which can produce budding cells, pseudohyphae and true hyphae. This ability to simultaneously display several morphological forms is known as polymorphism. Although hyphae are likely to be produced during the process of tissue invasion, yeasts without hyphae may also occur in invasive disease, particularly in infections caused by non-*albicans Candida* species. Apart from *C. albicans*, the genus *Candida* includes over 100 species, most of which are neither commensals nor parasites on humans. Other species of *Candida*, for example *C. tropicalis*, *C. dubliniensis*, *C. parapsilosis*, *C. guilliermondii*, *C. krusei*, *C. pseudotropicalis*, *C. lusitaniae*, *C. zeylanoides* and *C. glabrata* (formerly *Torulopsis glabrata*), are occasional causes of human candidosis, particularly in disseminated infections. The epidemiology of candidosis is changing and, where once *C. albicans* was the predominant species isolated from clinical samples, in some countries other species are now very common.

Candida ecology and the commensal or parasite role [2]

Gastrointestinal tract carriage

C. albicans is a frequent, but not invariable, normal commensal of the gastrointestinal tract. Colonization with *C. albicans*, or another species, may occur during birth directly from the birth canal, at some time during infancy or perhaps later in life. Colonization of the mouth early in life is often followed by frank pathological changes, but if the organism is acquired later it is usually established asymptomatically.

The literature on oral carriage rates is extensive and in his review Odds [1] concludes that fewer than 26% of normal subjects carry yeasts in the mouth, and that *C. albicans* carriage rates are about 18%. Surveys of the oral flora of hospital patients show higher figures. Isolation rates of yeasts from faecal specimens and rectal swabs are also higher than those from oral samples. Odds suggests figures of nearly 47% for yeast carriage, and just under 41% for *C. albicans* on the basis of published studies.

If specialized techniques or repeated sampling are used, the proportion of healthy adults carrying *Candida* in the gastrointestinal tract may be demonstrably higher, even rising to two-thirds. Moreover, if antibacterial antibiotics effective against the resident gastrointestinal bacterial flora are given by mouth, *Candida* carrier rates rise—as demonstrated by a single oral or rectal swab [3]. Clearly, the density and composition of the gastrointestinal yeast flora varies from individual to individual, and influences the chances of isolation.

Studies of *Candida* serology and skin tests suggest that a substantial proportion of those not colonized by yeasts may have been exposed to *Candida* in the past. The practical implication of this is that normal individuals show a wide range in the density of carriage of *Candida* species as assessed, for instance, by mouth swabs. Extraneous factors such as oral antibiotic therapy are likely to increase not only the incidence of carriage, but also the number of organisms present and the chances of invasion of tissue.

Vaginal carriage [4]

The healthy vagina may be colonized by yeasts—most commonly *C. albicans*, sometimes *C. glabrata*—in a small proportion of women [5]. The percentage of vaginal carriers differs widely in different surveys, but a figure of 12.7% for *C. albicans* is probably accurate. Higher rates are found in hospital patients, even without vaginal disease [1]. Pregnancy, oral contraceptives and the use of intrauterine devices have all been associated with elevated carrier rates [6].

Cutaneous carriage

Generally, neither *C. albicans* nor any other species of *Candida* is a permanent member of the normal flora of the skin. At the same time, skin adjacent to the body orifices and the skin of the fingers, which are in frequent contact with the mouth, often yield *C. albicans* and sometimes other species, particularly *C. parapsilosis* and *C. guilliermondii* [7]. *Candida* may be a persistent colonizer of moist intertriginous sites in individuals [8] as well as the subungual space in patients with pre-existing nail disease. Age and climate are important in this connection. Samples from the very young and the very old are more likely to yield *Candida*.

Carriage in other sites

The bronchial tree is not normally colonized by *Candida*, and where the organism is isolated from sputum specimens, at least in low amounts, it can be assumed that it has come from the mouth or oropharynx. It is apparent that swallowing a massive quantity of *Candida* cells will result in the transfer of these yeasts rapidly through the gut wall into the circulation, presumably via the portal vein and the liver [9]. Whether such 'persorption' of *Candida* cells occurs in normal situations is not known, but it may be a portal of entry in the neutropenic patient.

C. albicans can occasionally be cultured from the environment, usually in situations where there are heavily infected subjects [1], human or animal; for example, it has been isolated from a nursery where there was an epidemic of oral thrush, from hospital bed linen, and from the air of dermatology clinics. Normally, however, *Candida* is not part of the air-borne microflora. Except for neonatal and conjugal infections, most cases of candidosis probably result from infection of the host by his or her own commensal yeasts. Studies using typing [10] confirm the view that most infections are endogenous, and generally infection follows a shift in the existing host–yeast relationship. This shift from commensal to parasite results from a variety of influences. To date, an increase in yeast

virulence has not been shown to be important. Isolates of *C. albicans* might be expected to differ in their capacity to cause damage in the human host [11]. In practice, such variations are hard to demonstrate, with the exception of a few specific mutations such as defective protease production.

Genetic methods of typing *Candida* strains have provided a means of investigating the spread of organisms within individual patients, groups or hospital wards [12]. They have indicated that spread of predominant strains can occur either between individuals or in hospitals. In one well-documented outbreak, an isolate that resisted normal hand-washing procedures was the cause of a number of infections in an intensive care unit [13]. This indicates that strains carried by patients may be replaced by others with different biological characteristics. These techniques can now be used to determine important issues, such as the acquisition of drug resistance [14]. *C. albicans* may also demonstrate an unusual phenomenon known as phenotypic switching, whereby a strain may change morphology or another phenotypic character such as drug sensitivity in response to a change in growth conditions; such changes are reversible and not associated with genetic variation [15].

References

1 Odds FC. *Candida and Candidosis*. London: Baillière Tindall, 1988.
2 Noble WC. *Microbiology of Human Skin*, 2nd edn. London: Lloyd-Luke, 1980: 263–90.
3 Samaranayake LP, MacFarlane TW, eds. *Oral Candidosis*. London: Wright, 1990.
4 Kaufman RH, ed. Vulvovaginal candidiasis: a symposium. *J Reprod Med* 1986; **31**: 639–72.
5 Gough DM, Warnock DW, Turner A *et al*. Candidosis of the genital tract in non-pregnant women. *Eur J Obstet Gynecol Reprod Biol* 1985; **19**: 237–46.
6 Spellacy WN, Zaias N, Buhi WC *et al*. Vaginal yeast growth and contraceptive practices. *Obstet Gynecol* 1971; **38**: 343–9.
7 Clayton YM, Noble WC. Observations on the epidemiology of *Candida albicans*. *J Clin Pathol* 1966; **19**: 76–8.
8 Lynch PJ, Minkin W, Smith EB. Ecology of *Candida albicans* in candidiasis of the groin. *Arch Dermatol* 1969; **99**: 154–60.
9 Krause W, Matheis H, Wulf K. Fungaemia and funguria after oral administration of *Candida albicans*. *Lancet* 1969; **i**: 598–9.
10 Warnock DW, Speller DCE, Milne JD *et al*. Epidemiological investigation of patients with vulvovaginal candidosis: application of a resistogram method for strain differentiation of *Candida albicans*. *Br J Vener Dis* 1979; **55**: 357–61.
11 Poulain D, Tronchin G, Lefebvre B *et al*. Antigenic variability between *Candida albicans* blastospores isolated from healthy subjects and patients with *Candida* infection. *Sabouraudia* 1982; **20**: 173–7.
12 Vargas KG, Joly S. Carriage frequency, intensity of carriage, and strains of oral yeast species vary in the progression to oral candidiasis in human immunodeficiency virus-positive individuals. *J Clin Microbiol* 2002; **40**: 341–50.
13 Burnie JP, Odds FC, Lee W *et al*. Outbreak of systemic *Candida albicans* in an intensive care unit caused by cross infection. *BMJ* 1985; **290**: 746–8.
14 Powderly WG, Robinson K, Keath EJ. Molecular epidemiology of recurrent oral candidiasis in human immunodeficiency virus-positive patients: evidence for two patterns of recurrence. *J Infect Dis* 1993; **168**: 463–6.
15 Soll DER, Slutsky B, MacKenzie S *et al*. Switching systems in *Candida albicans* and their possible roles in oral candidiasis. In: MacKenzie IC, Squier CA, Dabelsteen D, eds. *Oral Mucosal Diseases: Biology, Etiology and Therapy*. Denmark: Laegeforeningens-Forlag, 1987: 52–9.

Pathogenesis

Fungal virulence

In animal experiments, some *Candida* species have been shown to be less virulent than *C. albicans*, a finding that conforms well with clinical experience. Generally, the most common pathogen in skin disease is *C. albicans*, although increasingly other species are isolated in vaginal infections and from immunocompromised patients.

Enzymes and toxins

Factors such as the production of an acid proteinase by certain strains of *C. albicans* are also known to affect pathogenicity. Proteinase-negative strains are known to be less virulent [1]; laboratory-generated gene-defective strains have not been shown to be less virulent.

Yeast–mycelial shift [2]

In oral and cutaneous candidosis, scrapings examined microscopically usually show *Candida* in both budding and mycelial forms. In histopathology of invasive candidosis, hyphae are usually present. This suggests that the production of hyphae may contribute to fungal virulence.

Adherence

The ability of yeast forms to adhere to the underlying epithelium is also an important prerequisite for tissue invasion [3–5]. Adherence of *Candida* to epithelial surfaces is mediated through a number of receptor interactions. *Candida* adhesins are either based on cell-wall mannan or protein components. Among the latter is a *Candida* surface C3d-binding protein [6]. It has also been shown that proteinase production is necessary for adherence.

Other factors

In vivo, a wide variety of factors have at various times been claimed to be important in stimulating mycelium formation [7]. Temperatures above 35°C, low oxygen tension, liquid media, non-sulphur-containing amino acids, a polysaccharide carbon source, serum and a pH of 7.5 are the most convincing factors in experimental studies [8]. However, it is difficult to relate these experimental results to the *in vivo* situation. *Candida albicans* also produces melanin, a factor known to affect resistance to immunological responses.

The effects of ecological pressures from other organisms are of considerable importance [9]. Both in the gastrointestinal tract and on the skin, removal of competing bacteria leads to an increase in yeast numbers, an important prerequisite to invasion. Work on the competition between *Candida* and bacteria in saliva suggests that a crucial factor is the amount of available glucose [9,10], and that if this is elevated and plentiful, as in diabetes, the bacterial flora will not inhibit the yeast [11]. Mechanisms other than nutrient depletion may possibly apply. In other situations (e.g. the finger web), bacteria, especially Gram-negatives, may act as co-pathogens rather than competitors, their presence enhancing the pathogenicity of the yeast. In addition, the presence of bacteria may impair the ability of *Candida* to adhere to the underlying substrate [12].

References

1 Kwon-Chung KJ, Lehman D, Good C, Magee PT. Genetic evidence for role of extracellular proteinase in virulence of *Candida albicans*. *Infect Immun* 1985; **49**: 571–5.
2 Soll DR. The regulation of cellular differentiation in the dimorphic yeast, *Candida albicans*. *Bioessays* 1986; **5**: 5–10.

3 Blackwell CC, Thom SM, Weir DM *et al*. Host–parasite interactions underlying non-secretion of blood group antigens and susceptibility to infection by *Candida albicans*. In: Lark DL, ed. *Protein Carbohydrate Interactions in Biological Systems*. London: Academic, 1986: 231–3.
4 Douglas LJ. Adhesion to surfaces. In: Rose AH, Harrison JS, eds. *The Yeasts*, Vol. 2. London: Academic, 1987: 239–80.
5 MacCourtis J, Douglas LJ. Relationship between cell surface composition, adherence and virulence of *Candida albicans*. *Infect Immun* 1984; **45**: 6–12.
6 Saxena A, Calderone RA. Purification and characterisation of the extracellular C3d-binding protein of *Candida albicans*. *Infect Immun* 1990; **58**: 309–14.
7 Odds FC. *Candida and Candidosis*. London: Baillière Tindall, 1988.
8 Gloor M, Geilhof A, Ronneberger G *et al*. Biochemical and physiological parameters on the healthy skin surface of persons with candidal intertrigo and of persons with tinea cruris. *Arch Dermatol Res* 1976; **257**: 203–11.
9 Auger P, Joly J. Étude de quelques facteurs de la pathogenese des infections *Candida albicans*. *Sabouraudia* 1975; **13**: 263–73.
10 Knight L, Fletcher J. Growth of *Candida albicans* in saliva: stimulation by glucose associated with antibiotics, corticosteroids and diabetes mellitus. *J Infect Dis* 1971; **123**: 371–7.
11 Kennedy MJ. Inhibition of *Candida albicans* by anaerobic oral flora of mice *in vitro*. *Sabouraudia* 1981; **19**: 205–8.
12 Sobel JD, Myers P, Levison ME *et al*. Comparison of bacterial and fungal adherence to vaginal exfoliated epithelial cells and human vaginal epithelial culture cells. *Infect Immun* 1982; **35**: 697–701.

Host factors

Host factors involved in mucocutaneous candidosis are numerous. It has long been recognized that the very old, the very young and the very ill are susceptible to oral thrush. However, a variety of other factors are also involved, and many patients have more than one predisposing factor. In the mouth, carbohydrate levels are important; food debris, likely to be present in the mouth of the severely ill patient with inadequate oral hygiene, should not be ignored and may be as significant as diabetic saliva. In Sjögren's syndrome, *Candida* carriage and probable susceptibility to candidosis are high, a fact attributed to low saliva flow rates. Whether this correlates with changes in pH as has been suggested, or with IgA levels, or whether it simply leads to poor oral hygiene as the mouth is inadequately washed by saliva, is not known. High glucose levels in urine, general tissue fluids and sweat may make diabetics more susceptible to candidosis [1]. Phagocytosis is also impaired in diabetics. In practice, infection in diabetics is largely confined to *Candida* vulvovaginitis and balanitis.

Any form of local tissue damage may be important in the pathogenesis of candidosis [2]. Experimental removal of the stratum corneum facilitates the establishment of cutaneous candidosis, and with a given inoculum increases the severity of the response [3], possibly by increasing the availability of adhesion receptors. In the mouth, the wearing of dentures undoubtedly increases susceptibility, but whether this is primarily because of trauma, food debris or the restriction in saliva flow is not clear. On the skin, maceration is of fundamental importance, and in experimental candidosis high moisture levels, usually provided by occlusion, are a prerequisite. Although several surveys have shown higher levels of *Candida* carriage on psoriatic and eczematous skin, and one other study [4] has claimed that *Candida* paronychia is more common in psoriatics, in general candidosis is not a common complication of either psoriasis or eczema. Indeed, *Candida* does not readily colonize such diseased skin without prior removal of the bacteria [3].

Furthermore, in experimentally infected guinea pigs there is increased epidermal cell turnover, which develops after *Candida* infection, possibly through a cellular immune mechanism. In this case, increased shedding of stratum corneum correlates well with recovery from infection [5].

Higgs and Wells [6] showed that some patients with chronic mucocutaneous candidosis had iron deficiency. With iron replacement therapy, their resistance to *Candida* infection increased. On the other hand, *in vitro* experiments indicate that unsaturated transferrin acts as an inhibitor to *C. albicans*. Iron reverses this effect.

Serum factors

Apart from transferrin, other serum factors affecting *C. albicans*, such as clumping factor, have been described [7]. Short of actual clumping, even the well-known effect of serum in encouraging *C. albicans* to produce germ tubes and mycelium may be disadvantageous. Hyphae longer than 200 µm are poorly phagocytosed, and not readily killed by leukocytes [8]. The presence of heavy, persistent *Candida* infection has, on some occasions, led to the appearance of factors present in serum that, far from being advantageous, resulted in the inhibition of T-cell function; an effect demonstrable with other leukocytes *in vitro*, and that was reversed by anti-*Candida* therapy [9]. It is likely that this is a circulating antigenic product of *Candida* such as mannan, which is known to affect immune responsiveness, blocking antibody or an immune complex.

Endocrine factors [10]

Apart from diabetes, a variety of endocrinopathies have been mentioned as susceptibility factors in candidosis. There is little doubt that Cushing's syndrome, whether spontaneous or iatrogenic, increases susceptibility to a wide range of infections including candidosis. The mechanism seems to be a direct suppression of immune mechanisms, especially T-cell function. In addition to these two conditions, familial endocrinopathy presenting with Addison's disease, hypoparathyroidism and hypothyroidism have all been found to occur in association with some cases of chronic mucocutaneous candidosis. Mutations in the *AIRE* (autoimmune regulator) gene have been identified in some patients [11]. Treatment of the endocrine abnormality does not improve the *Candida* infection and other factors are probably involved.

Immunological factors

Intensive investigation of patients with the syndrome of chronic mucocutaneous candidosis, and studies of a wide range of patients with primary immune defects, indicate clearly that in the defence against *Candida* infection, both superficial and deep-seated, cell-mediated immunity is of paramount importance, coupled with normal phagocytosis and killing by polymorphs and macrophages [12,13]. Circulating humoral antibodies or secretory IgA may have some role [14]. Absence of specific anti-*Candida* IgA salivary antibody in cases of chronic mucocutaneous candidosis was subsequently shown to be associated with depressed T-cell function, a factor now thought to be more important. However, in children wearing orthodontic appliances, the risk of candidosis is higher in those with low salivary IgA levels.

While systemic corticosteroids act to increase the susceptibility to candidosis by diminishing immune functions, the practical importance of topical steroids in this connection is not so well understood. However, there is evidence that an inflammatory response to *Candida*, which can be produced experimentally in humans [15] but not in the rat [2], by dead disintegrated *Candida* cells, as well as by living organisms, can be suppressed by topical steroids. The description of large granulomatous lesions in the napkin area of infants with candidosis treated with steroids suggests that it may also enhance the real susceptibility to the organisms, as might be expected if fewer lymphocytes and phagocytic cells are present.

The susceptibility of elderly and severely ill people, especially those with leukaemia, lymphomas and carcinomatosis, probably lies, in large measure, in the depression of cell-mediated immunity. In AIDS this is clearly the case.

Patients with defective T-lymphocyte function, such as those with AIDS, appear to be particularly susceptible to mucosal or cutaneous candidosis, but not systemic infections [16]. Congenitally T-cell-deficient mice (*nu/nu*) do not show reproducible increased susceptibility to systemic infection by *Candida*. In fact, some investigators have found heightened resistance, suggesting that T-lymphocyte activity alone does not account for resistance to systemic invasion [17]. By contrast, in patients with chronic mucocutaneous candidosis, the most consistent abnormalities have been those of T-lymphocyte function, particularly cytokine expression [9], even though some of these are now thought to be secondary to immunoregulation induced by the infection.

Patients with defective neutrophil or macrophage function are susceptible to both superficial and systemic candidosis. The activity of neutrophils and macrophages in phagocytosis and killing of *Candida in vitro* has been demonstrated [18,19]. In addition, some cytokines such as interferon-γ appear to interact with these cells to enhance killing of the organism. It appears that there is therefore substantial interplay between different immune mechanisms in defence against candidosis.

References

1 Tapper-Jones LM, Aldred MJ, Walker DM *et al*. Candidal infections and populations of *Candida albicans* in mouths of diabetics. *J Clin Pathol* 1981; **34**: 706–11.
2 Ray TL, Wuepper KD. Experimental cutaneous candidiasis in rodents. *J Invest Dermatol* 1976; **66**: 29–33.
3 Rebora A, Marples RM, Kligman AM. Experimental infection with *Candida albicans*. *Arch Dermatol* 1973; **108**: 69–73.
4 Ganor S. Diseases sometimes associated with psoriasis. I. Candidosis. *Dermatologica* 1977; **154**: 268–72.
5 Sohnle PG, Frank MM, Kirkpatrick CH. Mechanisms involved in elimination of organisms in experimental cutaneous *Candida albicans* infections in guinea pigs. *J Immunol* 1976; **117**: 523–30.
6 Higgs JM, Wells RS. Chronic mucocutaneous candidiasis: associated abnormalities of iron metabolism. *Br J Dermatol* 1972; **86** (Suppl.): 88–102.
7 Louria DB, Smith JK, Brayton RG *et al*. Anticandida factors in serum and their inhibitors. I. Clinical and laboratory observations. *J Infect Dis* 1972; **125**: 102–14.
8 Davies RR, Denning TJV. *Candida albicans* and the fungicidal activity of the blood. *Sabouraudia* 1972; **10**: 301–12.
9 Kirkpatrick CH. Chronic mucocutaneous candidiasis. *Pediatr Infect Dis J* 2001; **20**: 197–206.
10 Odds FC. *Candida and Candidosis*. London: Baillière Tindall, 1988.
11 Halonen M, Eskelin P, Myhre AG *et al*. *AIRE* mutations and human leukocyte antigen genotypes as determinants of the autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy phenotype. *J Clin Endocrinol Metab* 2002; **87**: 2568–74.
12 Lehrer RI. The fungicidal mechanisms of human monocytes. I. Evidence for myeloperoxidase linked and myeloperoxidase independent candidacidal mechanisms. *J Clin Invest* 1975; **55**: 338–46.
13 Levitz SM, Diamond RD. Killing of *Aspergillus fumigatus* spores and *Candida albicans* yeast phase by iron–hydrogen peroxide cytotoxic system: comparison with the myeloperoxide halide system. *Infect Immunol* 1984; **43**: 1100–2.
14 Grappel SF, Calderone RA. Effect of antibodies on the respiration and morphology of *Candida albicans*. *Sabouraudia* 1976; **14**: 51–60.
15 Maibach HI, Kligman AM. The biology of experimental human cutaneous moniliasis (*Candida albicans*). *Arch Dermatol* 1962; **85**: 233–55.
16 Torssander J, Morfeldt-Mauson L, Biberfeld G *et al*. Oral *Candida albicans* in HIV infection. *Scand J Infect* 1987; **189**: 291–5.
17 Lee KW, Balish E. Systemic candidiasis in germ free, flora defined and conventional nude and thymus-bearing mice. *J Retic Endothel Soc* 1981; **29**: 71–7.
18 Cech P, Lehrer RI. Heterogeneity of human neutrophil phagolysosomes: functional consequences for candidacidal activity. *Blood* 1984; **64**: 908–17.
19 Selsted ME, Harwig SSL. Purification, primary structure and antimicrobial activities of a guinea pig neutrophil defensin. *Infect Immunol* 1987; **55**: 2281–6.

Candidosis and AIDS

In the untreated HIV-positive population, oral *Candida* carriage rates are generally high, and this has been confirmed by the finding that carriage rates are, for instance, higher in HIV-positive homosexual males than in a control group of HIV-negative homosexual men [1]. Another study of HIV-positive patients without clinical evidence of oral candidosis showed that 24% of 261 individuals were carrying *C. albicans* on the tongue or buccal mucosa. Colonization rates were higher in intravenous drug abusers, Center for Disease Control (CDC) group category C and in those with lymphopenia. In addition, patients with CD4 cell depletion and those with elevated β_2-microglobulin levels were more likely to be carriers [2]. Combination antiretroviral therapy usually reverses these findings.

The relationship between CD4 counts, as a guide to disease progression, and oral candidosis in AIDS patients has been studied by a number of authors. Oral thrush does appear to reflect viral load [3]. Both hairy leukoplakia and oral candidosis are markers for increased rate of progression to AIDS [4]. The presence of oral candidosis may have implications for survival in some patients. For instance, HIV-positive patients with oral candidosis but who have no other features of AIDS have a poorer survival rate than those without [5]. However, it is important to remember that immunologically related factors such as CD4 counts are not the only determinants of oral candidosis. Another factor implicated as a possible predisposing cause of oral *Candida* infection in AIDS patients is the salivary flow rate.

The evidence that persistent vaginal candidosis is associated with AIDS is less convincing.

References

1 Torssander J, Morfeldt-Manson L, Biberfeld G *et al*. Oral *Candida albicans* in HIV infection. *Scand J Infect Dis* 1987; **19**: 291–5.
2 Fetter A, Partisani M, Koenig H *et al*. Asymptomatic oral *Candida albicans* carriage in HIV-infection: frequency and predisposing factors. *J Oral Pathol Med* 1993; **22**: 57–9.
3 Campo J, Del Romero J, Castilla J. Oral candidiasis as a clinical marker related to viral load, CD4 lymphocyte count and CD4 lymphocyte percentage in HIV-infected patients. *J Oral Pathol Med* 2001; **31**: 5–10.
4 Badri M, Maartens G, Wood R. Predictors and prognostic value of oral hairy leukoplakia and oral candidiasis in South African HIV-infected patients. *S Afr Dent J* 2001; **56**: 592–6.

5 Lin RY, Goodhart P. The role of oral candidiasis in survival and hospitalization patterns: analysis of an inner city hospital immunodeficiency virus/acquired immune deficiency syndrome registry. *Am J Med Sci* 1993; **306**: 345–53.

Histology [1,2]

The range of clinical manifestations caused by *C. albicans* and other *Candida* species is paralleled by the variety of pathological changes seen in inflamed tissues. However, there are certain generalizations that can usefully be made about histology of candidosis of epithelial surfaces. Fungal elements are almost always restricted to the outer layers of epithelium, including the stratum corneum. On the skin, particularly in acute infections, mycelium may be very sparse, and indeed yeast forms may be present in only small numbers. There seems also to be less likelihood of finding mycelium in infectious species other than *C. albicans*.

Apart from the presence of the fungus, acute oral candidosis is characterized by inflammatory changes with the formation of a pseudomembrane of epithelial and inflammatory cells [1]. In the oral epithelium and in the cutaneous epidermis, the inflammatory infiltrate consists predominantly of polymorphs, which may form microabscesses or subcorneal pustules. Splitting of the epidermis often follows. In the dermis, the inflammatory infiltrate is a mixture of lymphocytes, plasma cells (especially in the mouth) and histiocytes. In chronic cases, hyperplasia with parakeratosis and acanthosis of the epithelium is associated with a mixed chronic inflammatory infiltrate. In chronic cutaneous lesions, hyperkeratosis with acanthosis may be seen, and in *Candida* granuloma of the skin, a dense mixed cell infiltrate may include giant cells [3]. Although the matter is still somewhat controversial, it seems probable that in chronic oral cases, neoplastic change secondary to candidosis may develop as a late feature [4].

References

1 Chandler FW, Watts JC. *Pathologic Diagnosis of Fungal Infections*. Chicago: ASCP, 1987: 97–112.
2 Odds FC. *Candida and Candidosis*. London: Baillière Tindall, 1988.
3 Aronson IK, Soltani K. Chronic mucocutaneous candidiasis: a review. *Mycopathologia* 1976; **60**: 17–25.
4 Cawson RA. Leukoplakia and oral cancer. *J R Soc Med* 1969; **62**: 610–4.

Clinical syndromes of candidosis

Oral candidosis [1]

Acute pseudomembranous candidosis (oral thrush; acute pseudomembranous candidiasis) [2,3]. The characteristic sign of this condition is a sharply defined patch of creamy, crumbly, curd-like white pseudomembrane, which, when removed, leaves an underlying erythematous base. This membrane consists of desquamated epithelial cells, fibrin, leukocytes and fungal mycelium that attaches it to the inflamed epithelium. There may be one or many patches. The buccal epithelium on the cheeks, the gums or the palate may be affected. In immunocompromised patients, the tongue may be affected as well. In severe cases, extension to the pharynx or the oesophagus may occur, and erosion and ulceration are occasional complications.

The condition occurs most commonly in the first weeks of life, and the preterm infant may be especially susceptible. Apart from in neonatal oral candidosis (as distinct from *Candida* carriage), acute pseudomembranous candidosis is usually secondary to local or general predisposing factors. For instance, it may present in the neutropenic patient or those with AIDS [4–6]. In both cases, the clinical changes are often erosive with severe symptoms resulting in inadequate food intake because of pain. Extension of lesions to the buccal mucosa, tongue and oesophagus is common in these groups. Coincident oral infection with herpes simplex virus may occur in both groups [7]. Oral candidosis is the most common secondary infection in those with AIDS, and recurrent or more prolonged episodes are to be expected in these patients [8].

Acute erythematous candidosis (acute atrophic oral candidiasis; 'antibiotic sore tongue') [9]. In this condition, there is marked soreness and denuded atrophic erythematous mucous membranes, particularly on the dorsum of the tongue. It may follow pseudomembranous candidosis, when traces of the residual membrane will often be found. It is especially associated with antibacterial antibiotic therapy, but may also develop in HIV-positive subjects and patients taking inhaled steroids. In these cases, the tongue is often markedly affected.

Chronic pseudomembranous candidosis. This does not differ clinically from the acute pseudomembranous variety but, as the name suggests, lesions are very persistent. It occurs principally in immunocompromised patients.

Chronic erythematous candidosis (chronic atrophic candidiasis; denture sore mouth; denture stomatitis) [10]. Some soreness in the epithelium in the denture-bearing area is said to affect nearly one-quarter of all denture wearers and most, if not all cases appear to be caused by candidosis. A similar problem may also occur in children wearing orthodontic appliances.

Elimination of *Candida* alone does not usually result in complete recovery, and it is likely that other factors such as chronic mechanical irritation and bacterial colonization have a role in the pathogenesis of this condition.

The condition is normally confined to the upper denture-bearing area, the palate and gums. The affected mucous membranes show a variable bright red or dusky erythema, fairly sharply defined at the margin of the denture. The epithelium is often shiny and atrophic, and there may be marked oedema, in some areas at least. In late cases, secondary papillomatosis may occur. There is often an associated angular cheilitis, and that is the feature that frequently brings the patient to seek dental or medical advice, for the symptoms from the palatal area are often minimal. The excess of female patients over males remains unexplained. The vast majority of patients of either sex are otherwise fit. Underlying defects of immunity are not to be expected in this syndrome. However, AIDS patients with erythematous candidosis may enter a chronic phase.

Chronic plaque-like candidosis (chronic hyperplastic candidiasis; Candida leukoplakia) [11]. Very persistent, firm, irregular white plaques occur in the mouth, commonly on the cheek or the tongue. Most patients are male and generally over the age of 30 years but the onset of the disorder is difficult to date, as symptoms are mild, only slight soreness and roughness being noticed. Around the hyperplastic area, there may be a margin of erythema. Unlike the

pseudomembrane of oral thrush, this plaque cannot be easily removed. In most cases, serious predisposing factors are not present, although this appearance, particularly an extensive form, may occur in patients with chronic mucocutaneous candidosis. Smokers appear to be particularly prone to develop this form of oral candidosis [12].

The significance of this condition lies in the fact that it must be differentiated from other types of leukoplakia as, although the affected areas may undergo malignant change [13,14], it may eventually clear with prolonged anti-*Candida* therapy.

Chronic nodular candidosis. This is a rare form, where the clinical appearance that usually affects the tongue is cobbled. It is most often seen in certain patients with chronic mucocutaneous candidosis.

Angular cheilitis (angular stomatitis; perleche) [15]. Soreness at the angles of the mouth extending outwards in the folds of the facial skin is a well-known syndrome, not always associated with *Candida* infection. It is perhaps best considered as an intertrigo in which different organisms may play a part, *Candida* being the most common. Nutritional status and mechanical factors (e.g. the depth of the fold), the presence of moisture from persistent salivation or licking the lips may also be important. The yeasts involved clearly come from the mouth, and the association with denture stomatitis is important.

Although the condition may present acutely, it is common to find a long history of soreness and cracking at the angles of the mouth and a fluctuating course is typical. Obviously, the oral cavity should be examined carefully in such cases and swabs taken from that site to establish the presence of *Candida* carriage, as well as from the affected skin at the angles.

Median rhomboid glossitis [16]. This condition, characterized by a more-or-less diamond-shaped area on the dorsum of the tongue with loss of papillae, occurs as an acquired condition. It has been regarded in the past as a developmental abnormality, but current opinion suggests that it is simply a variant of chronic plaque-like candidosis.

Candidosis, steroids and the mouth. Apart from systemic steroid therapy, local applications of steroids in the form of steroid creams, mouthwashes and lozenges for the treatment of aphthosis or lichen planus of the mouth or steroid aerosols for asthma may predispose to candidosis, sometimes occurring as a secondary invasion of the primary pathology.

Other conditions associated with *Candida* in the mouth. *Candida* can secondarily invade other oral conditions such as ulcerative lichen planus [17], leukokeratosis and white-sponge naevus. On the lips, invasion of traumatic cheilitis may complicate management. In all cases, the removal of *Candida* often speeds the recovery even though the yeast is only a contributory cause.

Candidosis of the skin and genital mucous membranes

Most cases of cutaneous candidosis occur in the skin folds or where occlusion from clothing or medical dressings produces abnormally moist conditions. Areas close to the body orifices [18] and the fingers, which are frequently contaminated with saliva, are also at risk.



Fig. 36.40 *Candida* infection of the groins.

***Candida* intertrigo (flexural candidosis).** Any skin fold may be affected, especially in the obese subject. Signs are typically erythema and a little moist exudation starting deep in the fold (Fig. 36.40). As the condition develops, it spreads beyond the area of contact, usually developing the typical features of candidosis with a fringed, irregular edge and subcorneal pustules rupturing to give tiny erosions, and then further peeling of the stratum corneum. Satellite lesions, pustular or papular, are classical. Soreness, and itching, which may on occasions be intense, is usual. Topical steroids, prescribed for relief of the latter symptoms, may modify the inflammatory signs and cause diagnostic confusion. Where the web spaces of the toes or the fingers are affected, marked maceration with a thick, white, horny layer is usually prominent. In the case of the hands, some abnormality, including wide, fat fingers, appears to predispose to infection. In this particular syndrome, often known as erosio-interdigitalis blastomycetica or interdigital candidosis, *Candida* and Gram-negative bacteria are often co-pathogens [19]. Similar interdigital infections of the feet may occur in very hot climates, particularly in those with heavy footwear, for example army personnel. Apart from skin folds, macerated skin under rings and dressings may become infected with *Candida*.

The differential diagnosis of intertriginous candidosis includes tinea, seborrhoeic dermatitis, bacterial intertrigo, flexural psoriasis, Hailey–Hailey disease and flexural Darier's disease. It is important to establish that the *Candida* species are present by taking a scraping or swab. Although it is useful to find mycelia, their absence does not exclude the diagnosis, and the culture of *Candida* from an inflamed lesion of a skin fold usually justifies instigation of anti-*Candida* treatment. Bacterial co-pathogens should be considered.

Vulvovaginitis (vulvovaginal thrush) [18,20]. This condition affects around 75% of women of child-bearing age and presents with itching and soreness, and with a thick, creamy white

discharge. Most women with vaginal candidosis have no evidence of underlying disease.

It is more common in pregnancy. In the non-pregnant, it is said to be more prevalent in the premenstruum, but a fluctuating course not clearly related to the menstrual cycle is frequent. Although commoner in sexually active subjects, it has been described in childhood, sexually inexperienced and elderly people. Typically, there is dusky red erythema of the vaginal mucosa and the vulval skin, with curdy white flecks of discharge, but on occasions the only sign is erythema. The rash may extend onto the perineum and into the groins. The perianal area is often affected. In extensive cases, subcorneal pustules may be seen peripherally. In pregnancy, the picture is modified by marked physiological leukorrhoea.

Candida vulvovaginitis may become recurrent and in around 5% of women it appears to be a chronic condition [21]. In chronic cases, the vaginal mucosa may become glazed and atrophic. There may be considerable vaginal soreness or irritation as well as dyspareunia. Management of the recurrent or chronic case is difficult; the condition causes considerable distress. It is important in such patients to evaluate the presence of *Candida* during repeated episodes where there are symptoms, to establish that recurrence of signs of disease is associated with recurrence of *Candida* as other causes of vaginosis or *Chlamydia* infection are often confused. Molecular typing of isolates from women suffering from recurrent episodes demonstrated that in most cases the same strain is responsible for the recurrences, suggesting that clearance of the organism was not achieved by standard courses of antifungal therapy [21]. Although vaginal candidosis has been reported to occur with an increased frequency in women with AIDS, and in some cases the infection is resistant to therapy, this is not always the case; many patients present with an acute and treatable episode. In this it differs from the situation seen with oral candidosis.

Trichomonas infection, although it usually produces watery brown discharge, and bacterial vulvovaginitis, should both be considered in the differential diagnosis, and in pregnancy physiological leukorrhoea. Dermatoses affecting the vulva may mimic this condition (e.g. psoriasis, contact dermatitis, lichen sclerosus).

Candida balanitis [22]. The skin of the glans penis, especially in the uncircumcised, may sometimes be colonized by *Candida* asymptomatically [23]. When *Candida* balanitis develops, it is usual to find either abundant vaginal *Candida* carriage or frank vulvovaginitis in the sexual partner, although this is variable. In the mildest cases, transient tiny papules or pustules develop on the glans penis a few hours after intercourse, and rupture, leaving a peeling edge. Some may settle spontaneously without going through the full evolution. This mild form is usually associated with a little soreness and irritation. In some men, the condition continues in this intermittent form. In more severe and chronic cases, the inflammatory changes become persistent over the glans and the prepuce. Involvement of the groins sometimes coexists, especially in hot weather.

In the case of balanitis, bacteria and herpes simplex require consideration in the differential diagnosis, but few of the common venereal diseases are episodic like candidosis. Psoriasis and lichen planus, although sometimes fluctuating, should not be a cause of confusion, except with the chronic established lesion, in which case plasma-cell balanitis and erythroplasia must be excluded, as must lichen sclerosus. The diagnosis in both sexes is confirmed by finding the organism, preferably in large numbers. However, even scanty amounts of *Candida* isolated from cases with typical clinical features demand active and sometimes prolonged therapy. In the male, it must be stated that failure to find the organism does not exclude the diagnosis if swabs or scrapings were not taken during the acute phase. It is wise to consider diabetes in cases of genital yeast infections, as florid persistent lesions spreading beyond the genitalia seem most likely to be associated with that condition. Although the large majority of patients with genital candidosis will not have diabetes, it is appropriate to test for glycosuria in persistent or recurrent cases.

Perianal and scrotal candidosis. Perianal and scrotal candidosis may occur with, or independently of, genital involvement. Although usually starting around the anal margin with non-specific erythema, soreness and irritation, subsequent spread along the natal cleft is common, with classical features developing as it extends. Involvement of the scrotum is usually in the form of a nondescript erythema and subcorneal pustules are rarely seen. Candidosis must be included in the differential diagnosis of unexplained erythema of scrotal skin. Secondary infection of flexural psoriasis with *Candida* may have to be considered.

It has been suggested that a more objective assessment can be provided by taking quantitative cultures to determine the density of *Candida* more accurately [24]. For practical purposes this is not necessary, and dense growth of organisms on swab culture or the presence of diagnostic clinical features such as satellite pustules are usually taken as indications for treatment.

Napkin candidosis (diaper candidiasis). *C. albicans* is commonly isolated from the moist skin of the buttocks and genitalia of the infant but is more prevalent where the skin is affected by napkin rash [24]. In some instances, the classical subcorneal pustules, a fringed irregular border and satellite lesions are found. In these cases, there is little doubt that the organism is playing a pathogenic part, and it is likely to be found in the faeces [10,24]. In other nondescript cases of napkin eruption from which the organism is isolated, the role of the yeast is in doubt. Steroid creams applied to this site not only modify the clinical features but they are probably advantageous to *Candida*. Moreover, if the bacterial flora has been suppressed by a topical antibiotic, this will also favour yeast growth. All these factors should be considered in any napkin rash.

In acrodermatitis enteropathica in which zinc deficiency plays a central role, there may be a secondary *Candida* infection, particularly of the napkin area.

In all but the most trivial cases of napkin eruption, a moistened swab or a scraping should be taken to discover whether or not *Candida* is present on the affected skin. If *Candida* is present, particularly in large numbers, even if the features are non-specific, a trial of anti-*Candida* therapy is generally indicated.

Nodular or granulomatous candidosis of the napkin area (granuloma gluteale infantum) [25,26]. This rare condition presents with an eruption over the buttocks, genitalia, upper thighs and pubis, within which develop nodules, sometimes as large as 2 cm across, bluish or brownish in colour, reminiscent of Kaposi's sarcoma [25]. The primary napkin dermatitis may clear leaving only the nodules. Some examples have marked scaling and hyperkeratosis over the lesions, in others the epidermis appears to be normal. Histological changes are those of an intense dermal infiltrate with lymphocytes, eosinophils and histiocytes.

The natural history of this condition has not been elucidated. Successful management involves removal of microorganisms, avoidance of topical steroids and general measures to ensure adequate dryness in the region.

Candida paronychia

Candida species, not always *C. albicans*, can be isolated from the majority of cases of chronic paronychia [27,28]. The yeast is thought to have an aetiological role in this condition, but bacteria and irritant or allergic contact dermatitis also play a part, although the contribution of each varies from patient to patient and with the chronicity of the disease.

This condition is chiefly found among those whose hands are frequently immersed in water, but in chefs and pastry cooks the presence of organic debris such as flour and other carbohydrates may be equally important. The condition is less common in the UK than formerly. Toenail folds are not usually affected. Some experimental confirmation of the role of *Candida* has been achieved by occluding the nail fold in the presence of the yeast, but fully developed, chronic paronychia has not been produced experimentally.

Clinical features. Typically, several fingers are chronically infected, but one or all may be involved. The nail fold is red and swollen, and there is loss of the cuticle, and detachment of the nail fold from the dorsal surface of the nail plate, leading to pocketing. Occasionally, thick white pus may discharge; often force is needed to express it. The patient usually has marked tenderness, and spontaneous pain is an occasional feature. Nail dystrophy with buckling of the nail plate and some discoloration and onycholysis around the lateral nail fold frequently occur, but massive destruction of the nail plate is rare. Many patients, particularly those who are resistant to treatment, appear to have a poor peripheral circulation. A link with psoriasis has been reported [29].

Onychomycosis resulting from Candida

There are three main manifestations of *Candida* infection of the nail apparatus [30]. The most common is onycholysis distal and lateral subungual onychomycosis (DLSO) associated with paronychia. Complete destruction of the nail plate is also seen in some patients with chronic mucocutaneous candidosis. In addition to these conditions, erosion of the distal and lateral nail plate of the fingernails, not usually progressing to total nail dystrophy, has been associated with *C. albicans* invasion of the nail [31]. This is not common, but when it occurs it is most often seen in women. Two important predisposing conditions are Raynaud's phenomenon or disease and Cushing's syndrome. The main clues that the yeast is a significant pathogen are erosion of the distal nail plate, presence of yeasts and hyphae in nail on direct microscopy and the isolation of *C. albicans*. Such cases respond well and completely to oral antifungals such as itraconazole. Very rarely, *Candida* may invade the nail plate in the neonatal period, sometimes causing an isolated nail dystrophy with evidence of penetration of the superior aspect of the nail plate. In addition to these conditions, *Candida* is not infrequently isolated from the undersurface of the nail plate in patients with onycholysis resulting from other causes. Antifungal therapy in these circumstances does not produce any improvement.

Differential diagnosis. It is usual in chronic paronychia to establish which organisms are present, and a platinum loop introduced into the nail fold may be more valuable than a swab for this. It must be plated out promptly. When nail plate involvement is suspected, clippings should be taken.

Congenital candidosis [32]

This, as the name implies, represents established candidosis, usually of the skin and birth membranes present at the time of birth, and following intrauterine infection. It is quite distinct from oral thrush of the neonate in which the organism is acquired, at the very earliest, from the birth canal during delivery.

Factors associated with this condition have included prematurity, although this has not been noted in some cases, and the presence of an intrauterine foreign body, usually a contraceptive device. The amniotic fluid may be turbid at delivery [32,33]. The skin is the most common site for lesions, which are usually present at birth. The lesions are typically discrete vesicles or pustules on an erythematous base. The face and chest are first affected by the rash, which generally spreads over the next few days after delivery. In over 10% there is evidence of spread to deep sites such as the lungs. Although there has been a high level of mortality reported with such cases, the cause of death is usually related to other complications of prematurity rather than candidosis *per se*.

Such widespread skin infections are believed to follow contamination of the skin surface during birth, and the high incidence of intrauterine infection or vaginal candidosis associated with this disease would support this contention. Such cases are distinct from the more common neonatal systemic candidosis, a septicaemic illness associated with extreme prematurity, where skin involvement is not common.

Candida allergy [23]

In normal subjects skin testing with *Candida* antigens and serological studies may reveal evidence of antibodies to *C. albicans* and to other *Candida* species. A variety of clinical features attributed to *Candida* allergy have been described and include urticaria, ordinary annular erythema, bullous annular erythema and generalized pruritus. Even palmoplantar pustulosis has been linked to delayed hypersensitivity to *Candida* antigen. The concept of a candidide remains largely unsubstantiated in that the cutaneous reactions have often been ascribed to normal gut carriage. The so-called ide eruptions are not specific morphologically, and even the enthusiast for *Candida* allergy claims only a small percentage of cases of annular erythema, for example, is causally associated

with *Candida*. Observant open-mindedness with a hint of scepticism would seem to be the right approach in this difficult area.

The term *Candida* allergy or *Candida* syndrome is also used to describe a constellation of symptoms ranging from headache to malaise and depression, allegedly secondary to colonization of the gastrointestinal tract with yeasts. However, there is no objective evidence to connect these symptoms with the presence or absence of *Candida*.

References

1 Samaranayake LP, Yaacob HB. Classification of oral candidosis. In: Samaranayake LP, MacFarlane TW, eds. *Oral Candidosis*. London: Wright, 1990: 15–21.
2 Cawson RA. Thrush in adult outpatients. *Dent Pract Dent Rec* 1965; **15**: 361–4.
3 Samaranayake LP, MacFarlane TW, eds. *Oral Candidosis*, London: Wright, 1990.
4 Khongkunthian P, Grote M, Isaratanan W. Oral manifestations in 45 HIV-positive children from Northern Thailand. *J Oral Pathol Med* 2001; **30**: 549–52.
5 Michaud M, Baehner RL, Bixler D *et al*. Oral manifestations of acute leukaemia in children. *J Am Dent Assoc* 1977; **95**: 1145–50.
6 Pindborg JJ. Classification of oral lesions associated with HIV infection. *Oral Surg Oral Med Oral Pathol* 1989; **67**: 292–5.
7 Klein RS, Harris CA, Small CB *et al*. Oral candidiasis in high-risk patients as the initial manifestation of the acquired immunodeficiency syndrome. *N Engl J Med* 1984; **311**: 354–7.
8 Tavitian A, Raufman JP, Rosenthal LE. Oral candidiasis as a marker for esophageal candidiasis in the acquired immunodeficiency syndrome. *Ann Intern Med* 1986; **104**: 54–5.
9 Dreizen S. Oral candidiasis. *Am J Med* 1984; **30**: 28–33.
10 Budtz-Jorgensen E. The significance of *Candida albicans* in denture stomatitis. *Scand J Dent Res* 1974; **82**: 151–90.
11 Holmstrup P, Bessermann M. Clinical, therapeutic and pathogenic aspects of chronic oral multifocal candidiasis. *Oral Surg Oral Med Oral Pathol* 1983; **56**: 388–95.
12 Arendorf TM, Walker DM, Kingdom RJ *et al*. Tobacco smoking and denture wearing in oral candidal leukoplakia. *Br Dent J* 1983; **155**: 340–3.
13 Cawson RA. Leukoplakia and oral cancer. *J R Soc Med* 1969; **62**: 610–4.
14 Field EA, Field JK, Martin MV. Does *Candida* have a role in oral epithelial neoplasia? *J Med Vet Mycol* 1989; **27**: 277–94.
15 Ohman SC, Dahlen G, Moller A *et al*. Angular cheilitis: a clinical and microbial study. *J Oral Pathol* 1985; **15**: 213–7.
16 Cooke BED. Median rhomboid glossitis: candidiasis and not a developmental anomaly. *Br J Dermatol* 1975; **93**: 399–405.
17 Simon M, Hornstein OP. Prevalence rate of *Candida* in the oral cavity of patients with lichen planus. *Arch Dermatol Res* 1980; **267**: 317–8.
18 Odds FC. Genital candidosis. *Clin Exp Dermatol* 1982; **7**: 343–54.
19 Rosen T. Cutaneous candidiasis. In: Bodey GP, Fainstein V, eds. *Candidiasis*. New York: Raven, 1985: 227–40.
20 Sobel JD. Recurrent vulvovaginal candidiasis. *N Engl J Med* 1986; **315**: 1455–8.
21 El Din SS, Reynolds MT, Ashbee HR *et al.* An investigation into the pathogenesis of vulvo-vaginal candidosis. *Sex Transm Inf* 2001; **77**: 179–83.
22 Oriel JD, Partridge BM, Denny ML *et al*. Genital yeast infections. *BMJ* 1972; **4**: 761–6.
23 Odds FC. *Candida and Candidosis*. London: Baillière Tindall, 1988.
24 Rebore A, Leyden JJ. Napkin (diaper) dermatitis and gastro-intestinal carriage of *Candida albicans*. *Br J Dermatol* 1981; **105**: 551–5.
25 Keiichi U, Nakayasu K, Takaishi Y. Kaposi sarcoma-like granuloma on diaper dermatitis. *Arch Dermatol* 1973; **107**: 605–7.
26 Tappeiner J, Pfleger L. Granuloma gluteale infantum. *Hautarzt* 1971; **22**: 383–8.
27 Frain-Bell W. Chronic paronychia: short review of 590 cases. *Trans St John's Hosp Dermatol Soc* 1957; **38**: 29–30.
28 Stone OJ, Mullins JF. Chronic paronychia: microbiology and histopathology. *Arch Dermatol* 1962; **86**: 324–7.
29 Ganor S. Diseases sometimes associated with psoriasis. I. Candidosis. *Dermatologica* 1977; **154**: 268–72.
30 Zaias N. Onychomycosis. *Arch Dermatol* 1972; **105**: 263–7.
31 Hay RJ, Baran R, Moore MK *et al*. *Candida* onychomycosis: an evaluation of the role of *Candida* species in nail disease. *Br J Dermatol* 1988; **118**: 47–58.
32 Whyte RK, De Hussain Z, Sa DJ. Antenatal infections with *Candida* species. *Arch Dis Child* 1982; **57**: 528–35.
33 Hood IC, De Browning D, Sa DJ *et al*. Fetal inflammatory responses in second trimester candidal chorioamnionitis. *Early Hum Dev* 1985; **11**: 1–10.

Chronic mucocutaneous candidosis

Persistent *Candida* infection of the mouth, the skin and the nails, refractory to conventional topical therapy, is a distinct syndrome occurring as a more-or-less isolated feature. Sometimes it is associated with a variety of other infections, both cutaneous and systemic [1,2]. Many cases form part of the autoimmune polyendocrinopathy candida ectodermal dystrophy syndrome (APECED).

Clinical features [1]. With minor variations, the syndrome consists of the following features, usually starting in infancy or early childhood:

1 Persistent oral thrush, responding only partially to conventional therapy, or relapsing promptly after apparently successful treatment. Chronic hypertrophic changes may follow (Fig. 36.41).
2 Cutaneous candidosis. Often intertriginous skin is involved, but also the face and the hands, and sometimes the condition is widespread over the trunk and limbs. In long-standing lesions, the cutaneous changes are often atypical, suggesting ringworm. In some patients, markedly thickened areas with gross hyperkeratosis may form. However, lesions may also develop as deep dermal nodules or small macules. Scalp involvement is not rare in this syndrome. Dermatophytosis in such patients may present in a similar manner.
3 Paronychia is commonly a feature, often with extensive nail plate invasion and total dystrophic onychomycosis [3]. The important findings are nail invasion at an early age, often proceeding to complete nail involvement (Fig. 36.42). Here, the nail plate is thickened and the whole terminal phalanx may become encased in hyperkeratotic infected skin.
4 Seborrhoeic dermatitis can be very persistent in these patients. Alopecia areata, vitiligo and other organ-specific inflammation such as keratitis are seen in patients with endocrinopathy.

Patients with this syndrome comprise a heterogeneous group, which was originally classified by Higgs and Wells [2,4] into



Fig. 36.41 Chronic oral candidosis.



Fig. 36.42 *Candida* onychomycosis in a patient with chronic mucocutaneous candidosis.

several distinct categories using genetic and clinical criteria. It is probably best to exclude from the syndrome of chronic mucocutaneous candidosis those patients who present with a well-documented, underlying immune defect, such as severe combined immunodeficiency or agammaglobulinaemia, where severe candidosis may form a minor part of the secondary infectious complications. In these patients, mucosal candidosis is usually overshadowed by other serious infections, such as recurrent pneumonia or aspergillosis. In contrast, in patients with chronic mucocutaneous candidosis (CMC), the skin and mucous membrane infections dominate the clinical pattern [1]. However, it is important to recognize that all patients with this syndrome may develop other infections, most commonly human papillomavirus infections (warts) and dermatophytosis, in addition to other features, such as recurrent aphthous ulcers, seborrhoeic dermatitis and alopecia areata.

The main body of CMC patients develop signs in early childhood, and usually *Candida* infection is the presenting feature [5]. While a number of different forms of immune defect have been described in these patients [6], the abnormalities are neither constant nor diagnostic and may reverse with antifungal therapy. Within the childhood-onset group, there are a number of different variants that show features in common. Such features should not be taken as inflexible markers of a particular type, as there is probably considerable overlap in clinical expression between the different groups. The different types are as follows:

1 *Autosomal recessive CMC* [7]. This usually starts in the first decade with persistent oral and nail plate infections. Generally, the health of these patients is good and they do not develop endocrine defects. They also tend to improve with increasing age.
2 *Autosomal dominant CMC* [8]. There are now a number of well-documented pedigrees of families with the dominant form of CMC. Generally, they are more severely affected than those with the recessive variety, and other infections, such as dermatophytosis, may be particularly troublesome.
3 *Idopathic CMC* [4]. Some of the original group of patients labelled as 'idiopathic' have now produced affected offspring, and it is likely that some of these patients belong to the autosomal dominant group. Indeed, it is not possible to exclude the possibility that all may eventually be classified with these. However, it remains a useful subgroup to describe the most severely affected patients, who may have other infections and often develop bronchiectasis and pulmonary bullae. Their candidosis is also very severe with oesophageal involvement and the appearance of 'granulomas'. The term *Candida* granuloma was originally used to describe these severely affected patients, who may produce sheets of hyperkeratosis caused by *Candida* infection on the skin and scalp. It has been suggested that this appearance follows attraction of neutrophils into an area of infection, but because of defective function these are unable to destroy the invading yeasts. In practice, the main histological features are hyperkeratosis with only the occasional granuloma in the dermis. Rarely, patients have been reported from this group who develop other systemic diseases, such as cryptococcosis or miliary tuberculosis. Survival into adult life is still not universal in these children.
4 *CMC associated with endocrinopathy.* The majority of these patients appear to have the familial polyendocrinopathy syndrome [9,10]. Mutations of the autoimmune regulator gene appear to be correlated with this syndrome in many cases [10]. The condition is usually seen in early childhood, and occasionally the onset of *Candida* infection may predate the appearance of endocrine disease by as much as 10 years. The main cluster of endocrine abnormalities is hypoparathyroidism with hypoadrenocorticalism. In addition, other autoimmune abnormalities can occur, such as pernicious anaemia, vitiligo [11] and ovarian failure. This condition is also inherited as an autosomal recessive condition [12]. The severity of the patient's candidosis is very variable, and it is not uncommon to find that one affected sibling has extensive infection while another has only mild but chronic oral candidiasis.

   A further group of CMC patients has CMC with associated hypothyroidism [13]. The inheritance of this abnormality is vertical, suggesting autosomal dominant transmission. The clinical features are similar to those of other patients with endocrinopathy. It is important to recognize this group in view of the different genetic risk. A mutation has recently been mapped to chromosome 2p [14] and there is no known association with the AIRE gene.
5 *Late-onset CMC* [15,16]. Occasionally, adult patients are found to have the syndrome of CMC. The best-documented cases have been associated with a thymoma [3], but the occasional sporadic infection in a patient with no detectable abnormality may be recognized. Patients with SLE occasionally develop the severe nail changes and oral manifestations of this condition. The sudden onset of chronic oral candidosis in an adult should be investigated as it may be the initial presentation of another condition such as HIV infection. Vaginal candidosis can occur but does not become chronic in these patients.

Immunological abnormalities [1]. It is still not possible to correlate precisely defects of immune function with different clinical variants of the CMC syndrome, and indeed, with current investigative techniques, a substantial minority of cases have no

demonstrable defect of immune function at all [5]. To date, a variety of defects of delayed hypersensitivity has been shown to be important. Defects of phagocytosis or killing, both in macrophages and polymorphs, must be considered, but myeloperoxidase deficiency, found in a few cases of systemic candidosis, has not been present in any patient with the chronic mucocutaneous syndrome. Recently, raised levels of neutralizing autoantibodies to interferon-α subtypes have been detected in a high proportion of patients with Candida endocrinopathy [6]

In addition, it is known that certain antigenic components of *C. albicans*, such as mannan and some glycoproteins, are immunomodulatory [17]. Reversal of immune defects, such as absent delayed-type hypersensitivity to *Candida* antigens, has been seen with successful clearance of candidosis in CMC patients.

Diagnosis. The diagnosis of this condition normally requires the elapse of time and repeated failure to respond to conservative treatment. Confusion may occur with persistent ringworm infections, and indeed in some reported cases candidosis and dermatophytosis have coexisted. A family history is of obvious importance, and special note should be taken of other infections, cutaneous or systemic. Full endocrine investigation is also indicated.

References

1 Collins SM, Dominguez M, Ilmarinen T, Costigan C, Irvine AD. Dermatological manifestations of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome. *Br J Dermatol* 2006; **154**: 1088–93.

2 Wells RS. Chronic mucocutaneous candidiasis: a clinical classification. *Proc R Soc Med* 1973; **66**: 801–2.

3 San Filippo J. Chronic mucocutaneous candidiasis associated with malignant thymoma and systemic lupus erythematosus with hypergammaglobulinemia: a case report and literature review. *Cutis* 2006; **78**: 57–60.

4 Higgs JM, Wells RS. Chronic mucocutaneous candidiasis associated with abnormalities of iron metabolism. *Br J Dermatol* 1972; **86** (Suppl. 8): 88–102.

5 Kirkpatrick CH, Rich RB, Bennet JE. Chronic mucocutaneous candidiasis: model building in cellular immunology. *Ann Intern Med* 1971; **74**: 955–78.

6 Meager A, Visvalingam K, Peterson P *et al*. Anti-interferon autoantibodies in autoimmune polyendocrinopathy syndrome type 1. *PLoS Medicine/Public Library of Science* 2006; **3**: e289.

7 Wells RS, Higgs JM, MacDonald D *et al*. Familial chronic mucocutaneous candidiasis. *J Med Genet* 1972; **9**: 642–3.

8 Sams WM, Jorizzo JL, Snyderman R *et al*. Chronic mucocutaneous candidiasis: immunological studies of three generations of a single family. *Am J Med* 1979; **67**: 948–59.

9 Perheentupa J. Autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy *J Clin Endocrinol Metabol* 2006; **91**: 2843–50.

10 Meriluoto T, Halonen M, Pelto-Huikko M *et al*. The autoimmune regulator: a key toward understanding the molecular pathogenesis of autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy. *Keio J Med* 2001; **50**: 225–39.

11 Howanitz N, Nordlund JL, Lerner AB *et al*. Autoantibodies to melanocytes: occurrence in patients with vitiligo and chronic mucocutaneous candidiasis. *Arch Dermatol* 1981; **117**: 705–8.

12 Ahonen P, Koskimies S, Lokki ML *et al*. The expression of autoimmune polyglandular disease type 1 appears associated with several HLA-A antigens but not with HLA-DR. *J Clin Endocrinol Metab* 1988; **66**: 1152–7.

13 Coleman R, Hay RJ. Chronic mucocutaneous candidosis associated with hypothyroidism: a distinct syndrome. *Br J Dermatol* 1997; **136**: 24–9.

14 Atkinson TP, Schaffer AA, Grimbacher B. An immune defect causing dominant chronic mucocutaneous candidiasis and thyroid disease maps to chromosome 2p in a single family. *Am J Hum Genet* 2001; **69**: 791–803.

15 Montes LF, Carter RE, Moreland N *et al*. Generalized cutaneous candidiasis associated with diffuse myopathy and thymoma. *JAMA* 1968; **204**: 351–4.

16 Rycroft RJG, Vadimarrson H, Bannister LH *et al*. Chronic mucocutaneous candidiasis of late onset, thymoma and myopathy: report of 4 cases. *Clin Exp Dermatol* 1976; **1**: 59–74.

17 Durandy A, Fischer A, Le Deist F *et al*. Mannan specific and mannan induced T-cell suppressive activity in patients with chronic mucocutaneous candidosis. *J Clin Immunol* 1987; **7**: 400–10.

Laboratory diagnosis

As *C. albicans* is a common commensal, the interpretation of cultural findings has to be related to the clinical appearances. A scanty growth of *C. albicans* from the skin or from a mucocutaneous site may be meaningless without evidence of infection from a positive direct microscopy.

On direct examination of skin or nail material, the oval thin-walled yeasts bud on a narrow base, and are usually accompanied by filaments, either true hyphae or pseudohyphae (Fig. 36.43). Occasionally, particularly when a non-*albicans* yeast is present, filaments may be absent. The size and shape of the yeasts observed may also suggest the presence of a non-*albicans* yeast; for example, the budding cells of *C. krusei* are noticeably larger and more elongate than those of *C. albicans*. Isolation and identification of *C. albicans* is simple. At 37°C, on media free of cycloheximide, colonies from swabs and skin samples usually appear within 1–3 days. However, growth from thicker skin and nail material can be slower, so plates should be held for a week before reporting as negative. Chromogenic agars have now been developed that allow the identification of *C. albicans* on primary culture. On Albicans ID® agar (bioMerieux), the colonies of *C. albicans* are blue and all other yeasts cream or white. On Chromagar® (Becton and Dickinson), colonies of *C. albicans*, *C. tropicalis* and *C. krusei* are green, blue and pink, respectively, although use of these media alone may not be reliable for differentiating species.

***Candida albicans*.** Colony: the colonies on glucose–peptone agar are white to cream and soft in texture (Fig. 36.44). Some isolates may produce wrinkled 'rough' colonies and some may produce

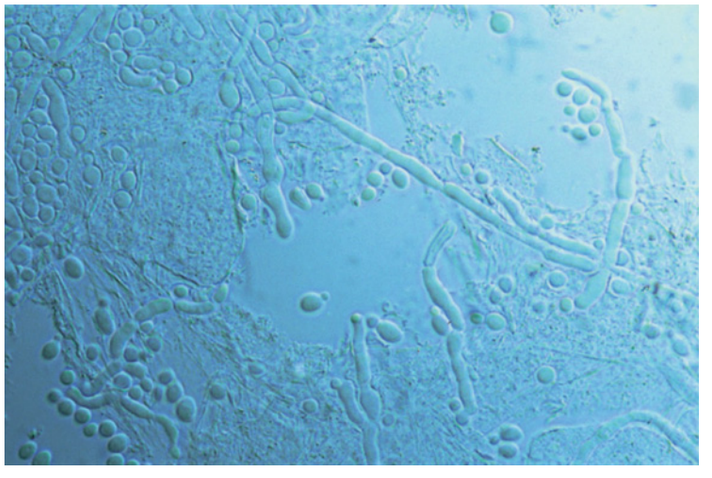


Fig. 36.43 Candidosis. Skin scales mounted in 30% KOH, Nomarski illumination, oil. Budding yeasts and slender filaments are observed. (Courtesy of the Department of Medical Mycology, St John's Institute of Dermatology, King's College London, London, UK.)

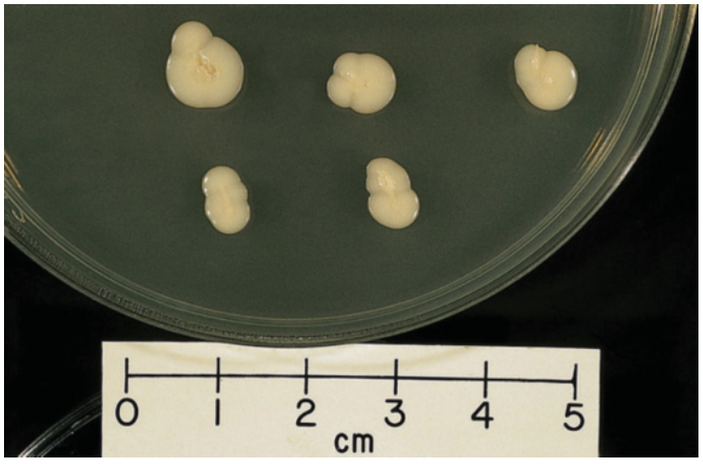


Fig. 36.44 *Candida albicans* colonies. (Courtesy of the Department of Medical Mycology, St John's Institute of Dermatology, King's College London, London, UK.)

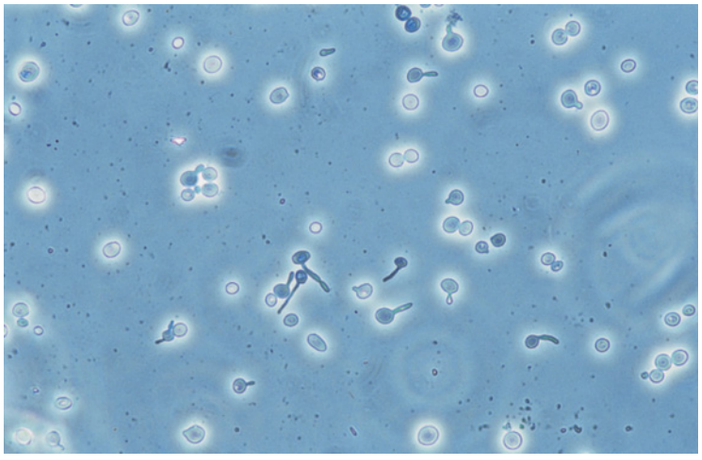


Fig. 36.46 A second method for specific identification of *Candida albicans* is the observation of germ tubes in serum after incubation at 37°C for 2–4 h. (Courtesy of the Department of Medical Mycology, St John's Institute of Dermatology, King's College London, London, UK.)

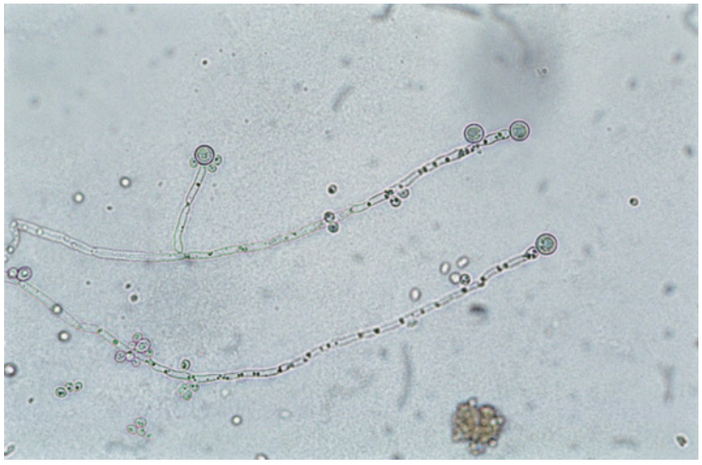


Fig. 36.45 Specific identification of *Candida albicans* can be made by the observation of filaments with thick-walled terminal vesicles when cultured on a depleted medium such as rice–agar supplemented with Tween. (Courtesy of the Department of Medical Mycology, St John's Institute of Dermatology, King's College London, London, UK.)

an obvious fringe of pseudohyphae around the edge of the colony. Microscopy: mounts from primary culture plates will reveal predominantly budding yeast cells. The production of filaments is best examined on depleted media, such as cornmeal agar, or rice extract agar supplemented with Tween 80. The morphology of *C. albicans* on these media allows identification, for in addition to filaments and budding yeasts, *C. albicans* produces rounded refractile vesicles, usually erroneously termed chlamydospores (8–12 µm diameter), at the sides and ends of the filaments (Fig. 36.45). These are produced within 24–96 h of incubation at 26°C. *C. albicans* also differs from most other species of *Candida* by the production of rudimentary true hyphae—germ tubes—when lightly inoculated into serum and incubated at 37°C for 2–4 h (Fig. 36.46). The only other species that is germ-tube positive and produces vesicles on depleted media is *C. dubliniensis*, a yeast associated predominantly with oral infections in HIV-positive patients.

Other *Candida* species. Colony: the different species produce colonies that vary slightly in texture, colour and production of obvious pseudohyphae. With experience, these differences may be recognized on the primary culture plates, but specific identification always requires study both of the morphology and physiology of each isolate. Microscopy: the majority of pathogenic *Candida* species—*C. glabrata* is a notable exception—will produce filaments and budding yeasts, but not chlamydospores, on depleted media, and the appearance of these filaments and yeasts is subtly different and characteristic for each species. The presence or absence of filaments is a key characteristic that is necessary for the identification of all *Candida* yeasts. Physiological tests: a battery of physiological tests, such as sugar and nitrogen source assimilations, and determination of the presence or absence of urease, are used. The development of commercial yeast identification systems, such as the API 32C® (bioMerieux) and the Auxacolour® (Sanofi), have greatly facilitated this task, and such kits are widely used. It has become particularly necessary to speciate non-*albicans* yeasts, because of the realization that some of these species may show innate resistance to some antifungals; for example, *C. glabrata* and *C. krusei* are often resistant to fluconazole.

Treatment of candidosis

General principles [1]

In the treatment of candidosis, it is important to be aware of the necessity of altering both localized and general susceptibility factors. In the mouth, for instance, this involves frequent toilet in the seriously ill, and denture hygiene in other patients, whereas in *Candida* infections affecting the skin, careful drying of affected sites is important. In many cases, topical antifungal therapy alone is sufficient to produce a response, but in immunocompromised patients with oropharyngeal candidosis, oral systemic therapy may be necessary to treat concomitant oesophageal infection, as well as being the most effective treatment for oral candidosis in AIDS patients. In addition, oral antifungals are used to prevent systemic candidosis in neutropenic patients. Although the success

of this approach is often contested, it is nonetheless a common practice. Apart from these indications, and CMC and onychomycosis, the main indications for systemic anti-*Candida* therapy are *Candida* septicaemia and deep-seated candidosis. Combination antiretroviral therapy in AIDS patients improves the therapeutic outcome significantly.

Therapeutic agents

The polyene antibiotics amphotericin and nystatin are effective against *Candida* species and most other yeast pathogens. Even though the polyenes have been used over many years, resistance by *C. albicans* and other *Candida* species, with the possible exception of *C. lusitaniae*, to these antibiotics is very rare. They are all safe to use topically, and contact dermatitis is rare. Of these drugs, only amphotericin is used systemically, and this must be given by intravenous infusion. Intravenous lipid-associated amphotericin B compounds, including a liposomal formulation (AmBisome), a colloidal dispersion (ABCD) and a lipid complex (ABLC), are also widely used. These compounds have the advantage of producing reduced renal toxicity. Gastrointestinal absorption of all the polyenes is limited; after oral administration, only 5–10% is taken up. The other important group of agents effective against *Candida* are the imidazoles. Clotrimazole, miconazole and econazole are the best known in topical use, and significant resistance to them has not developed in *Candida* species [2]. Contact allergy, although reported, seems to be almost as rare as reactions to the polyenes. The most useful treatments are with the two triazoles, fluconazole [3] and itraconazole [4], that are also effective in these conditions, and have the additional advantage that hepatotoxicity, seen with ketoconazole, is exceptionally rare with both drugs. The usual daily doses are itraconazole 100–200 mg and fluconazole 100–400 mg, or ketoconazole 200 mg. In addition, fluconazole can be given for systemic candidosis as an intravenous compound. A formulation of itraconazole in cyclodextrin solution provides better absorption in severely immunocompromised patients. Resistance to ketoconazole has been reported in CMC patients receiving long-term therapy with the drug. Similarly, primary resistance to fluconazole has been recorded with some *C. albicans* isolates, and particularly with *C. krusei*, *C. dubliniensis* and *C. glabrata*. Secondary drug resistance in *C. albicans* can occur in AIDS patients receiving fluconazole for long-term management of oropharyngeal candidosis [5]. However, *Candida* infection and resistance is less common in patients receiving highly active antiretroviral (HAART) therapy [6]. New azoles active against *Candida* species include voriconazole and posaconazole. Both have been used for severe oropharyngeal and oesophageal infection. In addition caspofungin, an intravenous fungal cell wall inhibitor, is another new anti-*Candida* agent.

Flucytosine is an agent that is absorbed from the gut, is relatively safe and very potent against those strains of *Candida* that retain their sensitivity. Unfortunately, resistance developing during treatment is not uncommon, and this drug is now only occasionally used for systemic candidosis, usually in combination with intravenous amphotericin B.

Treatment of the different clinical forms

Oral candidosis. In infants, suspensions of nystatin, amphotericin or miconazole gel applied several times a day are usually adequate for treating oral thrush. In the adult patient, removal of the dentures with careful hygiene at night is important. Regular amphotericin lozenges, nystatin or amphotericin tablets or oral nystatin suspension are effective in non-immunocompromised patients. The duration of the treatment varies with the condition: 10–14 days may be enough in acute cases. For treatment of unresponsive and chronic cases, such as those with hyperplastic candidosis, the responses to topical therapy are often poor, and either fluconazole (100–200 mg/day) or itraconazole (100–200 mg/day) are more effective. Voriconazole or posaconazole are alternatives. In patients with chronic oral candidosis, a biopsy may be justified to exclude leukoplakia. Angular stomatitis usually responds to treatment of the primary oral condition, although a topical antifungal applied to the area may speed recovery.

Oral candidosis in patients with AIDS or CMC, by contrast, frequently fails to respond to topical polyene therapy. In these conditions, the best approach is to use oral ketoconazole [7,8], itraconazole [9] or fluconazole [10,11]. If possible, therapy should be given intermittently if there is a recurrence, because of the risk of resistance developing with continuous therapy. Treatment is usually given until there is symptomatic recovery, which is usually quicker with fluconazole than the capsule formulation of itraconazole. A cyclodextrin solution of itraconazole is also quicker than the capsule form.

Genital candidosis. Acute vulvovaginitis can be treated with a single-dose topical preparation (pessary, ovule), such as clotrimazole, econazole or isoconazole. Longer courses of these compounds (e.g. 14 days), as well as the polyenes, such as nystatin, are also available. If there is coexistent involvement of the skin, a topically applied cream should also be used. However single-day oral therapy with fluconazole 150 mg is widely available and both effective and convenient; itraconazole 600 mg is an alternative. Efficacy is similar to that seen with topical drugs. There is no reliable method of curing recurrent vaginal candidosis.

Balanitis usually responds satisfactorily to topical antifungals applied several times a day, but if there is a source of infection in the sexual partner this should be treated appropriately, and diabetes, if discovered, obviously requires management. Conjugal cases need simultaneous and often prolonged therapy.

Flexural candidosis. *Candida* intertrigo requires specific topical therapy (azole or polyene creams) usually continued for about 2 weeks, but treatment may be required for longer periods, and is likely to fail if attention is not given to drying the affected area. In some patients with moist *Candida* intertrigo, potassium permanganate soaks are more effective. Attention should be given to treating concomitant bacteria; once again, potassium permanganate is useful for this purpose. In finger or toe web infections, topical antifungal therapy, combined with use of open footwear in the case of infections of the feet, is appropriate.

Napkin candidosis. In infants, rashes in the napkin area should be investigated for *Candida* and, if present, this can be treated topically. The antifungal should be combined with a general regimen for napkin dermatitis, with frequent napkin changes. In seborrhoeic dermatitis, a weak topical steroid is appropriate for the

disseminated dry lesions, but steroids should be avoided on the napkin area itself.

Paronychia and onychomycosis. *Candida* paronychia requires prolonged topical therapy with frequent applications of polyenes, imidazoles or non-specific remedies, such as 4% thymol in chloroform. Lotions are probably preferable to creams. There have been too few studies of either itraconazole or fluconazole to comment on their effectiveness in paronychia. Whatever anti-*Candida* regimen is chosen, it must be followed by general measures, such as ensuring adequate drying of the hands. The hands should be kept warm and a poor peripheral circulation improved if at all possible. In many patients, particularly in the chronic phases of paronychia, the role of *Candida* is more contentious and other factors such as irritant or allergic contact dermatitis may have a role. For this reason, in chronic cases, concomitant use of a topical corticosteroid is a logical approach. In proven *Candida* onychomycosis, fluconazole or itraconazole [9] offer a real hope of success.

Congenital candidosis. In congenital candidosis of the skin, topical therapy alone is required, but where there is systemic involvement, clearly amphotericin B or fluconazole should be considered.

Chronic mucocutaneous candidosis. Treatment of this condition depends critically on antifungal chemotherapy [12]. Attempts have been made to restore T-cell function, by the use of transfer factor [13], or thymosin, or grafting compatible lymphocytes from blood or marrow, or fetal thymic tissue [14], and non-specific measures such as restoration of normal iron stores when these are defective. Systemic anti-*Candida* therapy with fluconazole, itraconazole or voriconazole is likely to be necessary, and may need to be prolonged and repeated.

Once a remission has been induced, maintenance therapy should not be used in view of the risk of antifungal resistance. In a few patients, reduction of the load of *Candida* antigen seems to result in restoration of normal immunological responses, such as delayed hypersensitivity. Attention must be given to any endocrine factors as, although such treatment is not likely to lead to improvement in the candidosis, it may have considerable importance on the child's health and development. Endocrine screening tests should be repeated, even if initially negative, as patients with endocrinopathy may develop endocrine disease years after the first appearance of candidosis. Where appropriate, parents should be given genetic counselling. The possibility of coexisting dermatophytosis should not be forgotten, but it should respond satisfactorily to itraconazole or terbinafine.

References

1 Edwards JE. *Candida* species. In: Mandell GL, Bennett JE, Dolin R, eds. *Principles and Practice of Infectious Diseases*, 5th edn. Philadelphia: Churchill Livingstone, 2000: 2656–74.

2 Clayton YM, Connor BL. Comparison of clotrimazole cream, Whitfield's ointment and nystatin ointment for the topical treatment of ringworm infections, pityriasis versicolor, erythrasma and candidiasis. *Br J Dermatol* 1973; **89**: 297–303.

3 Grant SM, Clissold SP. Fluconazole: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in superficial and systemic mycoses. *Drugs* 1990; **39**: 877–916.

4 Grant SM, Clissold SP. Itraconazole: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in superficial and systemic mycoses. *Drugs* 1989; **37**: 310–44.

5 Ellepola AN, Samaranayake LP. Oral candidal infections and antimycotics. *Crit Rev Oral Biol Med* 2000; **11**: 172–98.

6 Detels R, Tarwater P, Phair JP *et al*. Effectiveness of potent antiretroviral therapies on the incidence of opportunistic infections before and after AIDS diagnosis. *AIDS* 2001; **15**: 347–55.

7 Drouhet E, Dupont B. Laboratory and clinical assessment of ketoconazole in deep-seated mycoses. *Am J Med* 1983; **74** (Suppl.): 30–47.

8 Hay RJ, Clayton YM. The treatment of patients with chronic mucocutaneous candidiasis and *Candida* onychomycosis with oral ketoconazole. *Clin Exp Dermatol* 1982; **7**: 155–62.

9 Hay RJ, Clayton YM. Treatment of chronic dermatophytosis and chronic oral candidosis with itraconazole. *Rev Infect Dis* 1987; **9** (Suppl. 1): 114–8.

10 Dupont B, Drouhet E. Fluconazole in the management of oropharyngeal candidosis in a predominantly HIV positive group of patients. *J Med Vet Mycol* 1988; **26**: 67–72.

11 Hay RJ, Clayton YM. Fluconazole in the management of patients with chronic mucocutaneous candidosis. *Br J Dermatol* 1988; **119**: 683–4.

12 Hay RJ. Management of chronic mucocutaneous candidosis. *Clin Exp Dermatol* 1981; **6**: 515–9.

13 Pabst HF, Swanson R. Successful treatment of candidiasis with transfer factor. *BMJ* 1972; **2**: 2442–3.

14 Levy RL, Huang SW, Bach ML *et al*. Thymic transplantation in a case of chronic mucocutaneous candidiasis. *Lancet* 1971; **ii**: 898–900.

Subcutaneous mycoses

Subcutaneous mycoses, or mycoses of implantation, are sporadically occurring infections caused by fungi present in the natural environment, which are directly inoculated into the dermis or subcutaneous tissue through a penetrating injury. They are seldom common even in endemic areas, and are mainly seen in the tropics, although, as many have long incubation periods, they may be seen in countries outside these endemic areas in patients who were originally infected elsewhere. The most common of these infections are sporotrichosis, mycetoma and chromoblastomycosis; rarer infections are phaeohyphomycosis, lobomycosis, rhinosporidiosis and subcutaneous zygomycosis.

The diagnosis of the subcutaneous mycoses is made initially by direct examination and examination of histopathological sections. Culture is not necessarily difficult, but identification of the more unusual pathogens may require the help of a reference mycological laboratory. Additionally, some isolates, particularly from cases of eumycotic mycetoma and phaeohyphomycosis, may fail to sporulate on primary isolation, and special media or conditions of incubation may be required to encourage conidial production. The description of all the potential pathogens is outside the scope of this chapter, although brief descriptions of the most common isolates are included. Molecular identification methods are also available, but only in specialist centres.

Laboratory methods

Collection of samples

Materials from patients thought to have subcutaneous mycoses are obtained from a variety of sources. Occasionally, superficial scrapings from a lesion may be useful, but generally pus or exudates discharging or obtained by aspiration, and biopsies, ideally both from the edge and from the centre of the lesion, are required

for satisfactory diagnosis. All samples are placed in sterile containers for immediate despatch to the laboratory. To prevent drying out of the material tissue, biopsy specimens intended for culture must be placed in sterile saline or wrapped in moistened sterile gauze if they cannot be processed immediately. Delays in processing samples will increase the likelihood of bacteria or saprophytic fungi contaminating the samples.

Direct examination and histopathology

A simple potassium hydroxide mount may be enough to give a preliminary diagnosis in some cases. For example, typical organisms may be observed in superficial crusts from chromoblastomycosis lesions, and pus containing grains from mycetoma patients can be used to immediately differentiate fungi from actinomycetes. Generally, histopathology will be more informative. Of the specific fungal stains, the silver impregnation procedure (Grocott, Gomori) and PAS are most commonly used and give excellent results, but in some instances examination with haemotoxylin and eosin is valuable to determine whether the infecting fungus is naturally pigmented (dematiaceous). Details of the appearances of individual mycoses are dealt with more fully in the relevant sections of this chapter and are well reviewed in standard textbooks [1–4].

Culture and identification of isolates

Generally, tissue samples should be finely divided, either by grinding or cutting into small pieces using sterile scalpel blades. The exception to this is material suspected of being infected with a zygomycete, where the largely aseptate hyphae are particularly fragile and will not survive such fine division. Although glucose–peptone agar alone can be used for primary isolation of the subcutaneous pathogens, a number of other media are also commonly used, including inhibitory mould agar (BBL) and brain–heart infusion agar (Difco), with or without the addition of 5–10% sheep's blood. Antibacterial antibiotics, such as chloramphenicol (0.005%) and gentamicin (0.0025%) are usually incorporated into the agar, and cycloheximide may be added for the culture of *Sporothrix schenckii* and the agents of chromoblastomycosis. If sufficient material is available, incubation at 26–30°C and 37°C on a variety of media is recommended. Although many organisms will grow quite quickly, cultures should be held for 6 weeks before being reported negative. If isolates fail to sporulate on the primary culture plate, subculture on to potato dextrose agar (Oxoid) or half-strength cornmeal agar (Oxoid) and incubation in the light may be necessary to encourage conidial production.

References

1 Chandler FW, Watts JC. *Pathologic Diagnosis of Fungal Infection*. Chicago: ASPC, 1987.
2 Salzfelder K. *Atlas of Fungal Pathology*. Dordrecht: Kluwer Academic, 1990.
3 Rippon JW. *Medical Mycology: the Pathogenic Fungi and the Pathogenic Actinomycetes*. Philadelphia: Saunders, 1988.
4 Kwon-Chung KJ, Bennett JE. *Medical Mycology*. Pennsylvania: Lea & Febiger, 1992.

Sporotrichosis

Definition. An acute or chronic fungal infection caused by *Sporothrix schenckii* [1]. There are both cutaneous and systemic forms of sporotrichosis.

Aetiology. Sporotrichosis is caused by the dimorphic fungus *S. schenckii* [2]. It occurs in both temperate and tropical zones. Less than 20 cases of sporotrichosis diagnosed in the UK have been published. The disease was common in France between 1905 and 1920, and occasional cases are reported from other European countries. It occurs sporadically in North, South and Central America, Egypt, Japan and Australia [3] and has been particularly prominent in the mining areas of South Africa and, more recently, Rio de Janeiro state, Brazil. The incidence, and possibly the geographical distribution, are dependent on climate.

In Uruguay, it has been shown that the incidence is highest in the autumn and first half of the winter (high humidity and temperatures between 16 and 22°C) [4]. These conditions favour saprophytic growth of *S. schenckii*. Sporotrichosis is rare in semiarid areas. The fungus grows on decaying vegetable matter, for example the timber in mines. It has been shown that the timber harbours the fungus before being taken underground [5], and that the source is probably the soil in the vicinity of the mines. *S. schenckii* could be recovered from the feet of mine workers who did not have sporotrichosis.

The disease may also occur in other groups occupationally exposed to the organism, such as workers using straw as packing material, forestry workers [6], florists or gardeners.

In most cases of cutaneous sporotrichosis, the fungus is introduced into the skin or mucous membrane by trauma, as in a minor puncture wound caused by a thorn or to a splinter, or perhaps an insect bite. Sporotrichosis is not contagious, although transmission has been recorded from cats. Adult males are, by their occupation, most exposed to the risk of infection. Systemic sporotrichosis is rare, and the portal of entry is thought to be the lung in these cases.

Unexplained areas of hyperendemicity have been described in certain countries, where unexpectedly high numbers of the local population develop cutaneous lesions of sporotrichosis and appear to be sensitized on skin testing with sporotrichin [7]. In one endemic zone, spread of infection by infected domestic cats has been proposed [8].

A family epidemic of cutaneous sporotrichosis was described among four children who became infected after playing in hay. On rare occasions it has been seen in young children. The incubation period is variable, but is usually 8–30 days.

Histology. *S. schenckii* may remain localized in the subcutaneous tissue, may spread locally in the subcutaneous lymphatics or, rarely, may be widely disseminated in the bloodstream after pulmonary infection. Underlying host immunity probably determines the form that the infection assumes. The fungus provokes a mixed granulomatous reaction with neutrophil foci. The fungus is present in the tissue, usually in the form of small (3–5 μm) cigar-shaped or oval yeasts, and these may, on occasion, be surrounded by a thick, radiate, eosinophilic substance, which forms the distinctive asteroid bodies (Fig. 36.47) [9]. A mycelial form of the fungus in tissue has occasionally been reported [10].

Clinical features. The main clinical varieties of sporotrichosis are the cutaneous and the systemic forms. In turn, cutaneous

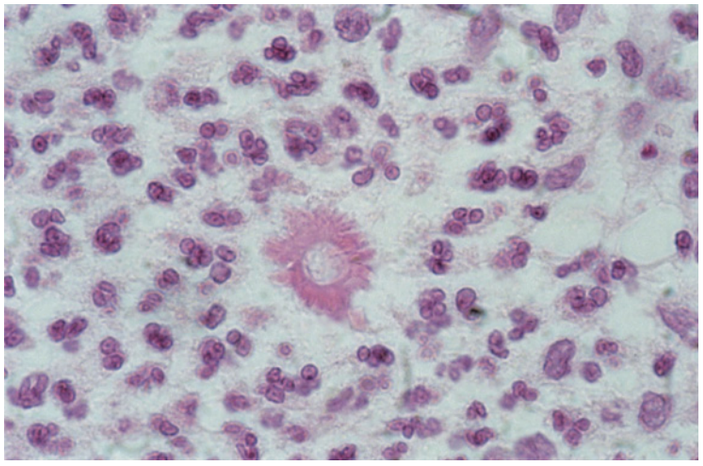


Fig. 36.47 Sporotrichosis: tissue section stained with haematoxylin and eosin. Organisms are usually very scanty but asteroid bodies, representing a foreign body tissue reaction, may be observed. (Courtesy of the Department of Medical Mycology, St John's Institute of Dermatology, King's College London, London, UK.)



Fig. 36.48 Lymphangitic sporotrichosis.

sporotrichosis is normally divided into two main types, the lymphangitic and fixed forms, but occasionally atypical varieties such as mycetoma-like or cellulitic forms may occur [2].

The most common type of sporotrichosis is the localized lymphatic variety, which follows the implantation of spores in a wound. This therefore usually occurs on exposed skin, often on the upper extremity [2,11], and is known as lymphangitic sporotrichosis. A nodule or pustule forms, which may break down into a small ulcer. Untreated, the disease usually follows a chronic course, which is characterized by involvement of lymphatics from the draining area; a chain of lymphatic nodules develops (Fig. 36.48). New nodules appear at intervals of a few days. These soften and ulcerate, and are connected by tender lymphatic cords [12]. A thin purulent discharge may come from the primary lesion and the earliest lymphatic nodules. As the disease becomes chronic, the regional lymph nodes become swollen and may break down. The primary lesion may heal spontaneously leaving the lymphatic nodes enlarged. The general health of the patient may not be affected.

The fixed variety, where the pathogen remains more or less localized at the point of inoculation, is less common [2,13]. The lesions may be acneiform, nodular, ulcerated or verrucous; the latter form is occasionally very extensive. Less commonly, there may be infiltrated plaques or red scaly patches. An ulcer may be gummatous or may simulate an epithelioma. The plaques may suggest leishmaniasis or tuberculosis. It is thought that this variety may reflect a high degree of immunity on the part of the patient. The variable morphology of this type is notable.

The reason for the difference in clinical behaviour of the two principal forms of cutaneous sporotrichosis is unknown, although changes in temperature sensitivity of the organisms [14] or in the host's immune response [2] have both been suggested. It is possible that some sporotrichosis infections are self-healing. Others are chronic and may mimic mycetoma or stasis ulcers. In AIDS patients, multiple cutaneous lesions may develop, suggesting cutaneous spread.

The less common systemic form probably follows inhalation, and presents either with local pulmonary disease or focal or widely disseminated lesions in the joints, meninges and skin [15]. There is some evidence that systemic sporotrichosis occurs in patients with some defect in host defence, such as alcoholics. This is in contrast to the cutaneous variety, which occurs in perfectly healthy individuals. Where sporotrichosis has been reported in AIDS patients, the lesions have usually been widespread and have affected internal organs as well as the skin [16].

In the systemic type, which is rare, ulcerated nodules may develop anywhere on the body or mucous membranes, and visceral lesions may occur. No organ is immune and bones or joints may be involved. Occasionally, vascular lesions resembling polyarteritis nodosa may be found. If untreated, this type is fatal but systemic sporotrichosis is exceedingly rare.

Differential diagnosis. Sporotrichosis can simulate granulomatous lesions of almost any other origin, and the diagnosis must be considered in all cases when the initial lesions have followed an injury.

The main conditions that may resemble sporotrichosis are mycobacterial infections and leishmaniasis. The mycobacterial infection caused by *Mycobacterium marinum* (fish-tank granuloma) may closely resemble lymphangitic sporotrichosis.

Laboratory diagnosis. *S. schenckii* is very rarely present in quantity in infected tissues, and direct microscopy of clinical material is of little or no value in confirming a diagnosis because its presence may easily be overlooked. Fluorescent antibody techniques have been successfully employed in locating the pathogenic phase *in vivo* [17]. The fungus grows readily on common agar media.

S. schenckii. Colony: the colonies are leathery, moist and initially white or cream with a wrinkled surface. As the colonies age, they may become progressively darker until they are brown or black. Microscopy: the slender (2-µm) hyphae bear small, oval to pyriform, hyaline conidia produced along the sides of the hyphae and sympodially at the ends of delicate conidiophores arising at right

angles from the hyphae. The arrangement of the conidia at the apex of the conidiogenous cell is often described as palmate or flower-like, with each conidium attached by a denticle to the small vesicle. In many strains (particularly when freshly isolated), oval, round or triangular dark brown thick-walled conidia are also produced, and it is partly the production of these conidia that results in the development of darkly pigmented colonies. However, pigmentation has also been reported to vary according to the culture medium and to increase with the addition of thiamine. Physiological tests: to confirm the identification, it is essential to convert this thermally dimorphic fungus to the yeast phase, as fungi that are non-pathogenic and morphologically very similar may be isolated as contaminants. This is best achieved on brain–heart infusion agar supplemented with sheep's blood and incubated at 37°C. The yeasts are typically oval or cigar-shaped. A variety, *S. schenckii* var. *luriei*, has been isolated from rare cases.

Treatment. While cases have been described where spontaneous remission has been seen to occur [18], it is the usual practice to treat patients with sporotrichosis. Itraconazole 100–200 mg/day or terbinafine 250 mg/day are both effective and well tolerated. However, at these dosages the length of treatment is not significantly different to that used with potassium iodide [19]. However, they may be useful in patients who do not respond to the latter or in systemic cases. In the latter, treatment with intravenous amphotericin B may also be helpful. Potassium iodide in large oral doses is effective in the localized types, and should be continued for 3–4 weeks after clinical cure. It is cheap and effective, although side effects are common. A recommended schedule is five drops initially, increasing to 4–6 mL of saturated potassium iodide three times daily. Patient tolerance may require a lower maximum dose [20].

As with chromoblastomycosis, the local application of heat may produce recovery in some patients.

References

1 Travassos LR, Lloyd KO. *Sporothrix schenckii* and related species of *Ceratocystis*. *Microbiol Rev* 1980; **44**: 683–721.
2 Ramos-e-Silva M, Vasconcelos C, Carneiro S, Cestari T. Sporotrichosis. *Clin Dermatol* 2007; **25**: 181–7.
3 Auld JC, Beardmore GL. Sporotrichosis in Queensland: a review of 137 cases at the Royal Brisbane Hospital. *Aust J Dermatol* 1979; **20**: 14–22.
4 Mackinnon JE, Conti Diaz IA, Gezuek E *et al*. Isolation of *Sporothrix schenckii* from nature. *Sabouraudia* 1967; **93**: 38–45.
5 Findlay GH. The epidemiology of sporotrichosis in the Transvaal. *Sabouraudia* 1970; **6**: 231–6.
6 Powell KE, Taylor A, Phillips BJ *et al*. Cutaneous sporotrichosis in forestry workers: epidemic due to contaminated sphagnum moss. *JAMA* 1978; **240**: 232–8.
7 Bustamante B, Campos PE. Endemic sporotrichosis. *Curr Opin Infect Dis* 2001; **14**: 145–9.
8 da Rosa AC, Scroferneker ML, Vettorato R *et al*. Epidemiology of sporotrichosis: a study of 304 cases in Brazil. *J Am Acad Dermatol* 2005; **52**: 451–9.
9 Rodriguez Toro G. El cuerpo asteroide de la esporotricosis: especifidad y diferenciacion de otras formas asteroides. *Biomedica* 1985; **5**: 11–23.
10 Brand FA, Van Niekerk V. An atypical strain of *Sporothrix* from South Africa. *J Pathol Bacteriol* 1968; **96**: 39–44.
11 Itoh M, Okamoto S, Kanya H. Survey of 260 cases of sporotrichosis. *Dermatologica* 1986; **172**: 203–13.
12 Fetter BF, Tindall JP. Cutaneous sporotrichosis: clinical study of nine cases utilizing an improved technique for demonstration. *Arch Pathol* 1964; **78**: 613–7.
13 Velasco O, Gonzalez Ochoa A. Esporotricosis en individuos con esporotricina positiva previa. *Rev Invest Salud Publica* 1971; **31**: 53–5.
14 Kwong-Chung KI. Comparison of isolates of *Sporothrix schenckii* obtained from fixed cutaneous lesions with isolates from other types of lesions. *J Infect Dis* 1979; **139**: 422–31.
15 Brian M, Strom R. Multiarticular sporotrichosis. *JAMA* 1978; **240**: 556–7.
16 Bibler MR, Luber HJ, Glueck HI *et al*. Disseminated sporotrichosis in a patient with HIV infection after treatment for acquired factor VIII inhibitor. *JAMA* 1986; **256**: 3125–6.
17 Kaplan W, Kraft DE. Demonstration of pathogenic fungi in formalin fixed tissue by immunofluorescence. *Am J Clin Pathol* 1969; **52**: 420–32.
18 Bargman H. Sporotrichosis of the skin with spontaneous cure. *J Am Acad Dermatol* 1983; **8**: 261–2.
19 Restrepo A, Robledo A, Gomez I *et al*. Itraconazole therapy in lymphangitic and cutaneous sporotrichosis. *Arch Dermatol* 1986; **122**: 413–7.
20 Kauffman CA. Sporotrichosis. *Clin Infect Dis* 1999; **29**: 231–6.

Mycetoma

Synonyms
- Maduromycosis
- Madura foot

Definition. A localized chronic infection caused by various species of fungi or actinomycetes, and characterized by the formation of aggregates of the causative organisms (grains) within abscesses. This results in severe damage to skin, subcutaneous tissues and bones of the feet, hands and other parts of the body, and grains are discharged to the surface through draining sinuses.

Aetiology [1]. Mycetoma may be caused by various species of fungi (eumycetoma) and aerobic actinomycetes (actinomycetoma), which occur as saprophytes in soil or on plants [2]. From these sources, they are implanted subcutaneously, usually after a penetrating injury [3,4]. The disease is largely confined to tropical and subtropical climates, usually among agricultural workers. Adult males are therefore most often infected. A few cases have occurred in Europe and North America, but in many such cases the patients have originated from the tropics and the infection was imported. These cases also illustrate clearly that the disease may not become troublesome until many years (20–30 years) after the initial injury. The condition, which is not contagious, is characterized by the presence of different coloured grains, which represent microcolonies of the organisms. The aetiological agents listed in Table 36.8 include only the most commonly isolated fungi.

The relative frequency with which the different species are encountered varies from country to country [5,6]. Actinomycetomas caused by *Nocardia* species are most common in Central America and Mexico. In other parts of the world, the most common organism is a eumycetoma agent, *Madurella mycetomatis*. The actinomycete, *Streptomyces somaliensis*, is most often isolated from patients originating from Sudan and the Middle East [7]. The causative organisms have been isolated from either soil or plant material, including thorns from *Acacia* bushes in endemic areas or identified in soil using molecular probes. It is unusual to find a clinically distinct predisposing abnormality in patients with mycetoma. It is thought that the implanted organisms survive in subcutaneous tissue because they are able to develop a number of adaptive changes—from cell-wall thickening to extracellular

Table 36.8 Main aetiological agents of mycetoma.

Fungi	Actinomycetes
Dark grain	
Madurella mycetomatis	*Actinomadura madurae*
Madurella grisea	*Actinomadura pelletieri*
Leptosphaeria senegalensis	*Streptomyces somaliensis*
Curvularia lunata	*Nocardia brasiliensis*
	Nocardia otitidis-caviarum
	Nocardia asteroides
Pale grain	
Scedosporium apiospermum	
Neotestudina rosatii	
Acremonium spp.	
Fusarium spp.	



Fig. 36.49 Mycetoma caused by *Madurella grisea*.

melanin deposition—which allow them to resist neutrophil attack.

Histology [4,8]. The causal organisms produce a chronic inflammatory reaction leading to focal neutrophil abscess formation, with scattered giant cells and fibrosis. Grains in the form of white, yellow, red or black granules are found in the centre of the inflammatory response [9], and may be discharged in pus through multiple sinuses on to the skin surface. Secondary bacterial infection may occur but this is not common [10]. The destructive process slowly extends deeply into the underlying tissues, and invades muscle and bones. A haematoxylin and eosin preparation is sufficient to distinguish between eumycetoma and actinomycetoma.

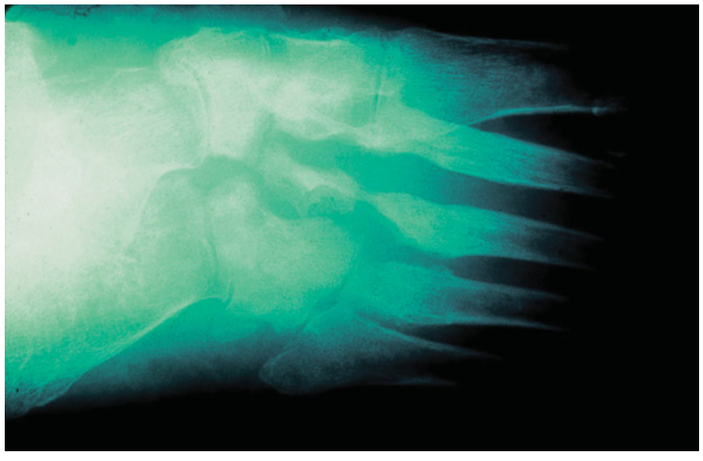


Fig. 36.50 Erosive X-ray changes in a mycetoma.

Clinical features. The clinical features are essentially the same no matter which fungus or actinomycete is concerned [11,12]. Because trauma favours infection, most lesions are on the foot and lower leg, but they may occur anywhere on the body [13]. The earliest stage is a firm, painless nodule but, with time, papules, pustules which break down to form draining sinuses, appear on the skin surface (Fig. 36.49). The whole area becomes hard and swollen, often without significant pain [14]. Extension to underlying bones and joints gives rise to periostitis, osteomyelitis and arthritis (Fig. 36.50). In advanced cases, destruction of bone within an infected area may be almost complete, and gross deformity may result [15,16]. There are usually multiple sinus tracts draining pus. These may remain open for months or may close and reopen, or may be replaced by new sinuses. The discharge may be purulent or seropurulent. The condition is comparatively painless and usually develops slowly (Fig. 36.51), but eventually results in gross swelling of the affected foot or other parts with serious deformity. Lymph node involvement is rare [17].

Imaging techniques contribute greatly to assessment of the destruction. Magnetic resonance imaging (MRI) provides the most comprehensive method [16,18].



Fig. 36.51 Eumycetoma affecting the foot.

Differential diagnosis. Chronic osteomyelitis of bacterial or tuberculous aetiology may resemble mycetoma, particularly in the early stages. In early mycetoma, it may be necessary to incise

pustules that represent foci of inflammation, necrosis and sinuses that have not yet ruptured through the skin; they often contain grains. Pus should be examined under the microscope for the presence of grains, which may then be processed for histology or examined directly in potassium hydroxide. If the infection is eumycotic, when crushed under the cover slip the grains will be seen to consist of masses of fungal mycelium with hyphae 2–6 µm in diameter. Chlamydoconidia are frequently formed at the periphery or in the centre of the grains. Actinomycotic grains will be seen to consist of masses of much narrower bacterial filaments 0.5–1.0 µm in diameter. If there are no discharging sinuses, biopsy may be required. In elephantiasis there are no sinus tracts.

Laboratory diagnosis. A tentative diagnosis sufficient to initiate treatment may be made on the basis of grain colour, texture and direct microscopic appearance [4]. For instance, black grains are always caused by fungi and red grains by an actinomycete. Eumycetomas with black grains are termed dark-grain eumycetomas, and many of the fungal species responsible produce hard or brittle grains with a brown, cement-like substance surrounding the hyphae. Eumycetomas with white or yellow grains are termed pale-grain eumycetomas and most contain no cement and have a soft texture (Fig. 36.52).

In eumycotic disease, the final identification of the infecting fungus requires the isolation of the causal agent in culture or application of molecular diagnostic techniques [19]. As the surfaces of the grains are frequently contaminated by bacteria, washing with saline containing antibacterials is recommended prior to inoculating the culture medium. Some grains may be nonviable. Primary isolates may require subculture on to nutritionally depleted media, such as half-strength cornmeal agar, to induce sporulation, and may fail to sporulate completely. Referral to a reference mycology laboratory for identification is recommended. Serology is helpful in some cases.

Only the two most frequently isolated species are described.

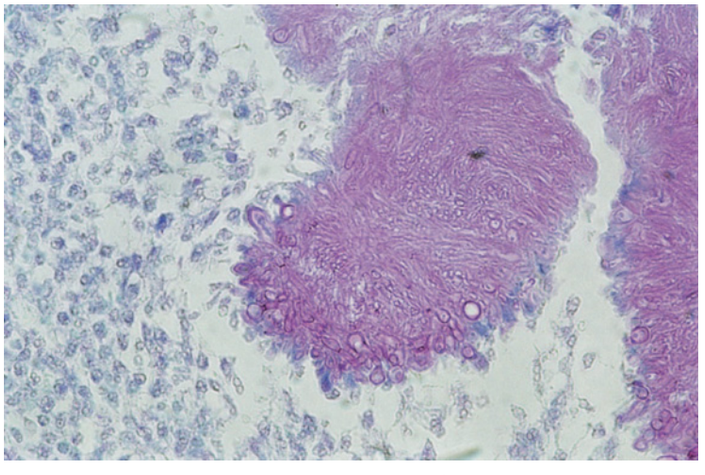


Fig. 36.52 Mycetoma: tissue section. Distinct hyphal filaments, stained pink with periodic acid–Schiff (PAS), are clearly visible in a pale-grained eumycetoma. (Courtesy of the Department of Medical Mycology, St John's Institute of Dermatology, King's College London, London, UK.)

Madurella mycetomatis. Colony: the colonial form shows great variation. Colonies are initially pale and leathery, but after a few days become olive, ochre brown or grey in colour and may produce a diffusible brown pigment. Growth is faster at 37°C than 28°C. Microscopy: on nutritionally poor media, spherical conidia may be formed from flask-shaped phialides. Primary cultures may produce large chlamydoconidia but are otherwise usually sterile.

Scedosporium apiospermum. Colony: the colony grows rapidly with a floccose grey or brown–grey surface and white to dark grey reverse. Microscopy: oval, light brown, relatively thick-walled conidia with a truncate base are formed singly along the hyphae or in small groups from annellides. A second form of conidiation is seen in some isolates with the production of coremia—tufts of hyphae held together—which produce smaller hyaline annelloconidia at their tips. This is a homothallic species and the sexual phase with ascospores may be formed on primary culture. In these instances, the teleomorph is reported as *Pseudallescheria boydii*.

Treatment. Localized lesions that can be excised without residual disability are best so treated. In other cases, medical treatment should first be attempted, although chemotherapy of mycetomas caused by fungi has, so far, been found to be quite unsatisfactory in most cases, despite the fact that certain fungi have been found to be relatively sensitive *in vitro* to therapeutic agents such as amphotericin B [1].

Infection by species of actinomycetes may be susceptible to chemotherapeutic agents. The combination of dapsone with streptomycin or co-trimoxazole plus streptomycin has been reported to give good results [20]. An alternative second drug is rifampicin. Amikacin may also be used in recalcitrant *Nocardia* infections.

Among the fungal causes of mycetoma, *M. mycetomatis* is the most sensitive to therapy, as it responds to ketoconazole in some cases [1]. For the others, a trial of therapy with griseofulvin, terbinafine, voriconazole or itraconazole is worth attempting as, even though it may not be curative, the progress of the infection may be slowed [21]. Radical surgery, usually amputation, should be considered carefully. Removal of a limb may deprive the patient of livelihood in many countries and this will need to be taken into consideration. However, it remains the only effective means of removing the infection in some patients.

References

1 Fahal AH. Mycetoma: a thorn in the flesh. *Trans Roy Soc Trop Med Hyg* 2004; **98**: 3–11.

2 Ahmed A, Adelmann D, Fahal A *et al*. Environmental occurrence of *Madurella* mycetomatis, the major agent of human eumycetoma in Sudan. *J Clin Microbiol* 2002; **40**: 1031–6.

3 Macotela-Ruiz E, Mariat F. Sur la production de mycetomes experimentaux par *Nocardia brasiliensis* et *Nocardia asteroides*. *Bull Soc Pathol Exot* 1963; **56**: 46–54.

4 Mariat F, Destombes P, Segretain G. The mycetomas: clinical features, pathology, etiology and epidemiology. *Contrib Microbiol Immunol* 1977; **4**: 1–39.

5 Lavalle P. Micetomas: la experiencia mexicana. Problemas actuales. In: *Proceedings of the Second International Sympsoium on Mycetomas*. Taxco, 1987: 66–73.

6 Tight RR, Bartlett MS. Actinomycetoma in the United States. *Rev Infect Dis* 1981; **3**: 1139–50.

7 Hay RJ, Mackenzie DW. Mycetoma (Madura foot) in the United Kingdom: a survey of forty-four cases. *Clin Exp Dermatol* 1983; **8**: 553–63.

8 Destombes P. Histological diagnosis of mycetoma granules. In: *Proceedings of the First International Symposium on Mycetoma*. Venezuela: Barroeta, 1978: 80–94.

9 Findlay GH, Vismer HF. Black grain mycetoma: a study of the chemistry, formation and significance of the tissue grain in *Madurella mycetomi* infection. *Br J Dermatol* 1974; **91**: 297–303.
10 Wethered DB, Markey MA, Hay RJ *et al*. Ultrastructural and immunogenic changes in the formation of mycetoma grains. *J Med Vet Mycol* 1986; **25**: 39–46.
11 Mahgoub ES, Murray IG. *Mycetoma*. London: Heinemann Medical, 1973.
12 Zaias N. Mycetoma. *Arch Dermatol* 1969; **99**: 215–25.
13 Gumaa SA, Mahgoub ES, El Sid MA. Mycetoma of the head and neck. *Am J Trop Med Hyg* 1986; **35**: 594–600.
14 Palestine RF, Rogers RS. Diagnosis and treatment of mycetoma. *J Am Acad Dermatol* 1982; **6**: 107–11.
15 Abd El, Bagi ME. New radiographic classification of bone involvement in pedal mycetoma. *Am J Roentgenol* 2003; **180**: 665–8.
16 Sarris I, Berendt AR, Athanasous N, Ostlere SJ. MRI of mycetoma of the foot: two cases demonstrating the dot-in-circle sign. *Skeletal Radiol* 2003; **32**: 179–83.
17 El Hassan AM, Mahgoub ES. Lymph-node involvement in mycetoma. *Trans R Soc Trop Med Hyg* 1972; **66**: 165–9.
18 Czechowski J, Nork M, Haas D *et al*. MR and other imaging methods in the investigation of mycetomas. *Acta Radiol* 2001; **42**: 24–6.
19 Yera H, Bougnoux ME, Jeanrot C *et al*. Mycetoma of the foot caused by Fusarium solani: identification of the etiologic agent by DNA sequencing. *J Clin Microbiol* 2004; **41**: 1805–8.
20 Mahgoub ES. Medical management of mycetoma. *WHO Bull* 1976; **54**: 303–10.
21 Lacroix C, de Kerviler E, Morel P *et al*. Madurella mycetomatis mycetoma treated successfully with oral voriconazole. *Br J Dermatol* 2005; **152**: 1067–8.

Chromoblastomycosis

Synonyms
- Chromomycosis
- Verrucous dermatitis

Definition. A chronic fungal infection of the skin and subcutaneous tissues caused by pigmented fungi, which produce thick-walled single- or multicelled clusters (sclerotic or muriform bodies) in tissue, and which are characterized by the production of slow-growing exophytic lesions, usually on the feet and legs [1].

Aetiology. Chromoblastomycosis is caused by several fungi, the most common of which are *Phialophora verrucosa*, *Fonsecaea pedrosoi*, *F. compacta* and *Cladophialophora carrionii* (recent synonym *Cladosporium carrionii*) [2]. Other rare causes include *Rhinocladiella aquaspersa*. The nomenclature of these fungi has been reviewed by McGinnis [3].

The causal fungi have been isolated from wood and soil, and the infection usually results from trauma, such as a puncture from a splinter of wood [4]. The condition is usually found in rural communities [5]. It has been reported from Central, South and North America [6], Cuba, Jamaica, Martinique, and also from many other countries including India, South Africa, Madagascar, Australia and northern Europe. It is occasionally seen as an imported infection in the UK.

Adult male agricultural workers are most often affected, but the condition has been reported in children.

Histology. The histology is that of a foreign-body granuloma, with isolated areas of microabscess formation. In the organized granuloma, mainly within giant cells, groups of fungal cells may be seen. Because the cells are chestnut or golden brown in colour, they are easily distinguished in the infiltrate. The cells are characteristically divided in several planes of division by thick septa and are termed muriform or sclerotic cells (Fig. 36.53). There is marked pseudoepitheliomatous hyperplasia in the epidermis, and in some areas apparent transepidermal elimination of fungal cells, which can be found in the stratum corneum. The tissue between the granulomatous nodules shows chronic fibrosis. When ulceration has occurred there is usually secondary bacterial infection.



Fig. 36.53 Chromoblastomycosis: tissue section. The natural brown pigment of the fungal muriform cells is clearly visible. The cells divide by fission and may form septa in more than one plane of division. (Courtesy of the Department of Medical Mycology, St John's Institute of Dermatology, King's College London, London, UK.)

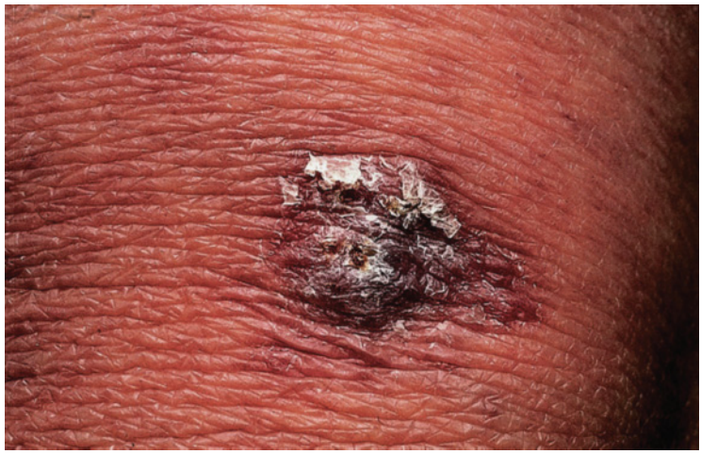


Fig. 36.54 Early lesion of chromoblastomycosis.

Clinical features [7,8]. The lesions are usually found on exposed sites (Fig. 36.54), particularly the feet, legs, arms, face and neck. A warty papule slowly enlarges to form a hypertrophic plaque [9,10]. In some lesions, the plaque is flat and expands slowly with central scarring. The early lesion may occasionally be an ulcer. Eventually, after months or many years, large hyperkeratotic masses are formed, and these may be as large as 3 cm thick (Fig. 36.55). Secondary ulceration may occur. The lesion is usually painless unless



Fig. 36.55 Plaque-type chromoblastomycosis.

the presence of secondary infection causes itching and pain. Satellite lesions are produced by scratching, and there may be lymphatic spread to adjacent areas. Haematogenous spread has occurred but is rare, and brain abscesses have been described. Secondary infection may eventually lead after several years to lymphatic stasis with the production of elephantiasis. Some forms of the infection produce psoriasiform lesions. Squamous carcinomas may develop in chronic lesions.

Differential diagnosis. The disease must be differentiated from blastomycosis (by the absence of a sharp border containing minute abscesses) and also the absence of pulmonary lesions, cutaneous tuberculosis, leishmaniasis, syphilis and yaws. Biopsy and culture of material for the associated fungi will establish the diagnosis.

Laboratory diagnosis. Irrespective of species, the pathogen can be seen in biopsy sections as deeply pigmented, thick-walled muriform or sclerotic cells. Occasionally, in superficial skin scrapings from the surface of the lesions, pigmented hyphae rather than sclerotic cells are seen. Multiplication *in vivo* is by fission rather than budding, and this results in the production of single, two- or multiple-celled clusters.

In culture, the colonies of all species are dark grey–green to black and velvety or downy, with a black reverse. Three forms of conidial production are observed in the most common agents of infection: acropetal budding, production of phialides and sympodial conidiation. Some agents are polymorphic, demonstrating more than one type of conidiation simultaneously, and this has caused some confusion in the nomenclature of these agents. They are named according to the dominant form of conidiation.

Phialophora verrucosa. Microscopy: the dominant form of conidiation is the production of flask-shaped phialides with a pronounced dark collarette at the apex. These are produced laterally or terminally. The hyaline thin-walled elliptical conidia are produced at the tip of the phialide in basipetal succession and collect as balls. On nutritionally weak media, a few sympodial or acropetal conidiogenous cells may also be observed.

Fonsecaea pedrosoi. Microscopy: the dominant form of conidiation is sympodial with the conidia confined to the upper part of the cell. The brown single-celled conidia are produced on short denticles and may in turn produce secondary conidia in a similar manner. Conidia produced by acropetal budding are also present in the majority of isolates, and some isolates will produce scanty phialides.

Cladophialophora carrionii. Microscopy: acropetal budding is dominant, producing long chains of pale, oval or lemon-shaped conidia. The chains branch at frequent intervals. On starvation media, such as half-strength cornmeal agar, bulbous phialides may be produced by the conversion of some of the cells within the branched chains.

Treatment. The main treatment of chromoblastomycosis involves the use of antifungal chemotherapy. Itraconazole (100–200 mg daily) or terbinafine (250 mg daily) is often successful, although responses to both are thought to be better if the causative organism is *C. carrionii* [11,12]. Flucytosine used on its own or combined with amphotericin B [13] may also be effective, but resistance to flucytosine may develop if it is used on its own. Other approaches to treatment have included the use of cryotherapy or the local application of heat [14]. The use of surgery is contentious; in larger plaques there is a risk in pursuing this approach as satellite lesions may develop around the excision site. Surgery is really only indicated in very small lesions, and even in these should be combined with chemotherapy.

References

1 López Martínez R, Méndez Tovar LJ. Chromoblastomycosis. *Clin Dermatol* 2007; **25**: 188–94.
2 Carrion AL. Chromoblastomycosis and related infections. *Int J Dermatol* 1975; **14**: 27–32.
3 McGinnis MR. Chromoblastomycosis and phaeohyphomycosis: new concepts, diagnosis and mycology. *J Am Acad Dermatol* 1983; **8**: 1–16.
4 Gezuele E, Mackinnon JE, Conti-Diaz IA. The frequent isolation of *Phialophora verrucosa* and *Phialophora pedrosoi* from natural sources. *Sabouraudia* 1972; **10**: 266–73.
5 Banks IS, Palmieri JR, Lanoie L *et al*. Chromomycosis in Zaire. *Int J Dermatol* 1985; **24**: 302–7.
6 Silva JP, de Souza W, Rozental S. Chromoblastomycosis: a retrospective study of 325 cases on Amazonic Region (Brazil). *Mycopathologia* 1999; **143**: 171–5.
7 Minotto R, Bernardi CD, Mallmann LF *et al*. Chromoblastomycosis: a review of 100 cases in the state of Rio Grande do Sul, Brazil. *J Am Acad Dermatol* 2001; **44**: 585–92.
8 Vollum D. Chromomycosis: a review. *Br J Dermatol* 1977; **96**: 454–8.
9 Batres E, Wolf JE, Rudolph AH *et al*. Transepithelial elimination of cutaneous chromomycosis. *Arch Dermatol* 1978; **114**: 1231–2.
10 Goette DK, Robertson D. Transepithelial elimination in chromomycosis. *Arch Dermatol* 1984; **120**: 400–1.
11 Kumarasinghe SP, Kumarasinghe MP. Itraconazole pulse therapy in chromoblastomycosis. *Eur J Dermatol* 2000; **10**: 220–2.
12 Perez A. Terbinafine: broad new spectrum of indications in several subcutaneous and systemic and parasitic diseases. *Mycoses* 1999; **42** (Suppl. 2): 111–4.
13 Lopez CF, Alvarenga RJ, Cisalpina EO *et al*. Six years' experience in treatment of chromomycosis with 5-fluorocytosine. *Int J Dermatol* 1978; **17**: 414–8.
14 Tagami H, Ginoza M, Imaizumi S *et al*. Successful treatment of chromomycosis with topical heat therapy. *J Am Acad Dermatol* 1984; **10**: 615–9.

Phaeohyphomycosis

Synonym
- Phaeomycotic subcutaneous cyst

Definition. Phaeohyphomycosis is a rare, and generally localized, subcutaneous or intramuscular infection, usually a cyst or abscess caused by a range of brown-pigmented (dematiaceous) fungi including *Exophiala jeanselmei*, *Exophiala dermatitidis*, *Bipolaris* species, *Alternaria alternata* and others that form pigmented hyphae in tissue [1]. Systemic forms of phaeohyphomycosis also exist.

Aetiology. The pathogen probably originates by implantation from an exogenous source, and occasionally fragments of plant tissue can be found in lesions. Infection begins with a firm, sometimes tender nodule, which may develop into a large cyst up to several centimetres in diameter. The overlying epidermis is not conspicuously thickened. There is no tendency towards lymphatic spread, and dissemination is exceedingly uncommon. Some patients are immunocompromised, usually through steroid therapy. An ever-increasing number of fungi have been reported as agents of phaeohyphomycosis: a review lists 104 species [2]. The most common causative organisms are shown in Table 36.9.

Histopathology. The diagnosis should be confirmed by biopsy, and it is important to exclude other cystic structures such as Baker's cysts. The fungi can be seen in the inflammatory lining of the cyst wall. Specific fungal stains such as Grocott or PAS will mask the natural colour of the hyphae, but in haematoxylin and eosin sections the brown colour may be obvious. In some cases, however, the hyphae appear unpigmented and the Masson Fontana stain for melanin must be used to reveal the presence of the fungal pigment. Beaded or distorted hyphae are frequently reported, and sections through these structures may give the appearance of yeast-like structures.

Laboratory diagnosis. The organisms are not usually difficult to grow from the lesions, but the fact that so many different species may be involved, together with the failure of some primary isolates to sporulate, means that their identification may require the help of a specialist laboratory. The major dematiaceous pathogens are well illustrated and described in the review by Dixon and Polak-Wyss [3].

Exophiala jeanselmei. Colony: this fungus belongs to the group sometimes termed 'black yeasts'. The colony is initially glabrous or moist, and black in colour. As the culture matures, it becomes more filamentous and eventually is covered with a grey velvety mycelium. Microscopy: initially, the culture is made up of single cells, which are annellides reproducing by budding. When the filamentous stage has developed, the septate brown hyphae bear slender annellides producing elliptical conidia, which collect in a mass at the tip of the conidiogenous cell or slide down to form a row along the side of the annellide. Physiological tests: will not grow at 40°C.

Bipolaris species. Colony: the colonies grow rapidly. Initially downy and pale grey, the colour darkens to olive grey or black on both surface and reverse. Microscopy: the conidiogenous cells are geniculate, producing the brown multicellular phragmoconidia in a sympodial sequence. The hilum at the base of the conidium is only slightly protuberant.

Table 36.9 Major aetiological agents of phaeohyphomycosis.

Exophiala jeanselmei	*Bipolaris* spp.
Exophiala dermatitidis	*Exserohilum* spp.
Cladophialophora bantiana	*Alternria* spp.
Phialophora spp.	*Alternaria* spp.

Treatment. The usual treatment is excision, and although there are no published studies to establish efficacy, an appropriate antifungal such as itraconazole is often given after surgery.

References

1 Chandler FW, Ajello L, Kaplan W. *A Colour Atlas and Text Book of the Histopathology of Mycotic Diseases*. London: Wolfe, 1980: 92–8.
2 Rinaldi MR. Phaeohyphomycosis. *Dermatol Clin* 1996; **14**: 147–53.
3 Dixon DM, Polak-Wyss A. The medically important dematiaceous fungi and their identification. *Mycoses* 1991; **34**: 1–18.

Lobomycosis

Synonyms
- Keloidal blastomycosis
- Lobo's disease

Definition. This rare disease is characterized by keloidal skin lesions that remain fairly well localized and apparently do not affect the general health of the patient.

Aetiology. The disease was first observed in 1931 in a patient from the Amazon valley and other cases have been seen there [1] and throughout central and northern South America.

The causal fungus, which has never been isolated in culture, is *Lacazia loboi* [2]. It is thought that the agent might be associated with water and gain entry through a wound [3]. In most cases studied, the disease has been present for periods of many years. Infections have been reported in fresh-water dolphins [4].

Histology. Fungi and giant cells are abundant in the lesions, which are granulomatous and apparently devoid of collagenous fibrosis. The fungus cells are usually round or lemon-shaped, sometimes joined one to the other with a narrow tubular neck. They measure about 8 µm in diameter and have a thick wall [5].

Clinical features [1,6]. Lesions may be found anywhere on the body, but are usually on exposed parts: legs, arms and face. They can, in most instances, be associated with injuries to the skin, and spread from one site to another is thought to be by autoinoculation following injury. There is no marked lymphangitis and no visceral dissemination. Old chronic lesions present as elevated crusted

fungoid plaques. Squamous cell carcinoma may occasionally develop in chronic lesions [1].

Differential diagnosis. Clinically, the disease most closely resembles chromoblastomycosis. Microscopic examination of biopsy material will establish the diagnosis.

Laboratory diagnosis. The fungus has not been isolated in culture, and mycological confirmation depends on recognition of the characteristic cells of *Lacazia loboi* in tissue. This is easily performed with potassium hydroxide mounts of epidermal crusts or sections, which need not be specially stained.

Treatment. There is no effective medical therapy for lobomycosis and where possible lesions are excised surgically.

References

1 Paniz-Mondolfi AE, Reyes Jaimes O, Dávila Jones L. Lobomycosis in Venezuela. *Int J Dermatol* 2007; **46**: 180–5.
2 Taborda PR, Taborda VA, McGinnis MR. Lacazia loboi gen. nov., comb. nov., the etiologic agent of lobomycosis. *J Clin Microbiol* 1999; **37**: 2031–3.
3 Baruzzi RG, Marcopito LF. Lobomycosis. In: Hay RJ, ed. *Baillière's Clinical Tropical Medicine and Communicable Diseases*, Vol. 4. *Tropical Fungal Infections*. London: Baillière Tindall, 1989: 97–112.
4 Caldwell DK, Caldwell MC, Woodward JC *et al*. Lobomycosis as a disease of the Atlantic bottlenosed dolphin (*Tursiops truncatus*, Montagu 1821). *Am J Trop Med Hyg* 1975; **24**: 105–14.
5 Woodward JC. Electron microscopic study of lobomycosis (*Loboa loboi*). *Lab Invest* 1972; **27**: 606–12.
6 Machado PA. Polimorfismo das lesoes dermatologicas na blastomicose de Jorge Lobo entre os indios Caiabi. *Acta Amazonica* 1972; **2**: 93–7.

Rhinosporidiosis

Definition and aetiology. A chronic granulomatous mycosis caused by *Rhinosporidium seeberi*, inducing polyps of the mucous membrane. The organism has never been isolated *in vitro*, but through genetic studies, its taxonomic position is now clearer, and it is regarded as an aquatic member of the Protista rather than a fungus.

Rhinosporidiosis has occurred in many parts of the world rarely and sporadically, but it is endemic in India and Sri Lanka [1]. In one review, 51 cases were described from Uganda [2]. Adult male workers are the persons most likely to be infected.

Histology. The histology is superficially like that of a nasal polyp but with conspicuous, sharply defined, globular cysts up to 0.5 mm in diameter. Occasionally, microabscesses may be found.

Clinical features. Vascular polyps, which may be pedunculated, occur on any mucosal surface [3]. The mucous membrane of the nose, the nasopharynx or the soft palate is involved in three-quarters of cases, and the conjunctiva or the lacrimal sac in a proportion of the others. Lesions are also found on other mucous membrane surfaces, such as the larynx, penis, vagina, rectum and sometimes also on the skin, to which it is presumed to have spread from a primary site on the nearby mucous membrane [4]. They become hyperplastic and may reach an enormous size, extending from the nostrils to the pharynx or outwards over the lip [5]. The pink or red surface is lobulated and cauliflower-like. Close examination of the surface reveals small white spots, which represent mature sporangia of the fungus. The disease may last for many years. Spontaneous resolution has been observed rarely. It is not contagious. Obstruction to breathing is usually the chief complaint. On the genitalia, the lesions look like condylomas. If the eye is involved there is conjunctivitis and photophobia, and the weight of the polyps may cause eversion of the lid.

Differential diagnosis. Typical lesions are easily recognized by their pink–purple colour, friable consistency and the presence of the white sporangia within the polyp itself. Atypical lesions should be differentiated from warts, condylomas and haemorrhoids.

Laboratory diagnosis. The causative organisms cannot be cultured, and the diagnosis depends on histopathology—recognition of the sporangia seen on the surface of the polyp or in tissue sections. Depending on maturity, these may attain diameters of 0.5 mm, and can be readily seen by the naked eye as firm white cysts on or just below the surface. Microscopically, these are single, thick-walled and spherical, and when fully differentiated are packed with numerous rounded endospores, 6–7 μm in diameter. Immature and collapsed discharged sporangia are also present [6].

Treatment. Surgical removal resulting in complete eradication of the disease is the treatment of choice.

References

1 Arseculeratne SN. Rhinosporidiosis: what is the cause? *Curr Opin Infect Dis* 2005; **18**: 113–8.
2 Owor R, Wamukota WM. Rhinosporidiosis in Uganda: a review of 51 cases. *East Afr Med J* 1978; **55**: 582–6.
3 Lasser A, Smith HW. Rhinosporidiosis. *Arch Otolaryngol* 1976; **102**: 308–12.
4 Christian EC, Kovi J. Three cases of rhinosporidiosis in Ghana. *Ghana Med J* 1966; **5**: 63–4.
5 Chitravel V, Sundarum BM, Subramanian S *et al*. Recurrent rhinosporidiosis in man: case reports. *Mycopathologia* 1981; **73**: 79–82.
6 Vanbreuseghem R. Ultrastructure of *Rhinosporidium seeberi*. *Int J Dermatol* 1973; **12**: 20–8.

Subcutaneous zygomycosis

Synonyms
- Basidiobolomycosis
- Subcutaneous phycomycosis
- Conidiobolomycosis
- Rhinoentomophthoromycosis

Definition. A localized subcutaneous and predominantly tropical mycosis characterized by chronic, woody swelling of subcutaneous tissue.

Aetiology. Subcutaneous zygomycosis caused by *Basidiobolus ranarum* was initially described in Indonesia [1,2], but cases have since been reported in Africa and South-East Asian countries. Subcutaneous zygomycosis caused by *Conidiobolus coronatus* (rhinoentomophthoromycosis) is another localized zygomycotic infection



Fig. 36.56 Subcutaneous zygomycosis: tissue section. Wide, aseptate hyphae stained black with Grocott methenamine silver (GMS) are characteristic of infection by a zygomycete. (Courtesy of the Department of Medical Mycology, St John's Institute of Dermatology, King's College London, London, UK.)

affecting animals and humans [3]. Reported from the West Indies, Africa, India and South America, infection may result in gross but non-painful facial swelling originating from the nasal mucosae or sinuses. In their natural environment, both fungi are associated with decaying vegetation and the gastrointestinal tracts of frogs.

Histology. The lesion is an eosinophilic granuloma lying deep in the subcutaneous tissue and largely replacing fat. Wide, sparsely septate hyphae, branching at right angles, are scattered throughout the granuloma [4,5] (Fig. 36.56) and there is often dense fibrosis.

Clinical features. There is a slowly spreading, painless, subcutaneous swelling without other obvious clinical signs [6–8]. It may be single, or there may be multiple satellite lesions. The disc-shaped masses have a uniform hard consistency [9], and they do not pit.

The smooth rounded edge, which may be lobulated, can be raised up by inserting the fingers underneath it. Pain and tenderness may be absent or, less often, pronounced. The overlying skin may be tense, oedematous, desquamating, hyperpigmented or normal. Ulceration does not occur, and the regional lymph glands are not often enlarged [10].

In *Basidiobolus* infections, the lesion usually involves the limbs or limb-girdle areas and the infection is most often seen in children. The clinical features of *Conidiobolus* infections (rhinoentomophthoromycosis) are similar but affect the face, apparently spreading from the region of the inferior turbinates to involve the central facial tissues. It is mainly seen in young adults. Both subcutaneous infections are very disfiguring.

Rarely, deep invasion with *Conidiobolus* has been described, and is usually not associated with skin lesions [11].

Differential diagnosis. Histological and mycological examinations are required for accurate diagnosis, but lymphatic oedema, which lacks the distinctive edge, subcutaneous malignant lymphoma, which grows more rapidly, and induration round an infection site, where there is pain and tenderness, have to be considered [12].

Laboratory diagnosis. The diagnosis is usually established histologically by biopsy, but culture is not difficult.

Basidiobolus ranarum. Colony: on cycloheximide-free media at 30°C, *B. ranarum* grows very rapidly as waxy cream or yellow colonies with many radial folds. Microscopy: the hyphae are broad, 8–20 µm in diameter and have few septa. After 10–14 days, sexual zygospores with a prominent beak may be produced. In addition, unicellular sporangia—sporangiola—are formed, which are forcibly ejected into the air from the tip of the sporangiophore.

Conidiobolus coronatus. Colony: the colonies are waxy white to grey, becoming more powdery and beige as a short aerial mycelium develops. Microscopy: wide, sparsely septate hyphae are present. Sporangiola are forcibly discharged, and impact on the sides and lid of the Petri dish. Some sporangiola may form small protuberances or villi all over their surfaces.

Treatment. Itraconazole is useful in this condition. Lesions also usually respond to oral treatment with potassium iodide given in similar doses to those used in sporotrichosis. There is some evidence that co-trimoxazole can be used in addition in conidiobolomycosis.

References

1 Prabhu RM, Patel R. Mucormycosis and entomophthoramycosis: a review of the clinical manifestations, diagnosis and treatment. *Clin Microbiol Infect* 2004; **10** (Suppl. 1): 31–47.

2 Martinson FD. Clinical, epidemiological and therapeutic aspects of entomophthromycosis. *Ann Soc Belge Med Trop* 1972; **52**: 329–42.

3 Andrade ZA, Paula LA, Sherlock A. Nasal granuloma caused by *Entomophthora coronata*. *Am J Trop Med Hyg* 1967; **16**: 31–3.

4 Gilbert EF, Khoury GH, Pore RS. Histopathological identification of *Entomophthora phycomycosis*. *Arch Pathol* 1970; **90**: 583–7.

5 Stratsmaa BR, Zimmerman LE, Gass JDM. Phycomycosis: a clinicopathologic study of fifty-one cases. *Lab Invest* 1962; **11**: 963–85.

6 Antonelli M, Vignetti P, Dahir M *et al*. Entomophthoromycosis due to *Basidiobolus* in Somalia. *Trans R Soc Trop Med Hyg* 1987; **81**: 186–7.

7 Gugnani HC. A review of zygomycosis due to *Basidiobolus ranarum*. *Eur J Epidemiol* 1999; **15**: 923–9.

8 Kamalam A, Thambiah AS. Muscle invasion by *Basidiobolus haptosporus*. *Sabouraudia* 1984; **22**: 273–7.

9 Herstoff JK, Bogarrs H, MacDonald CJ. Rhinophycomycosis entomophthorae. *Arch Dermatol* 1978; **114**: 1674–8.

10 Busapakum R, Youngchaiyud U, Sriumpai S *et al*. Disseminated infection with *Conidiobolus incongruens*. *Sabouraudia* 1983; **21**: 323–30.

11 Tan DC, Hsu LY, Koh LP *et al*. Severe conidiobolomycosis complicating induction chemotherapy in a patient with acute lymphoblastic leukaemia. *Br J Haematol* 2005; **129**: 447–9.

12 Segura JJ, Gionzale K, Berrocal J *et al*. Rhinoentomophthoromycosis: report of the first two cases observed in Costa Rica (Central America) and review of the literature. *Am J Trop Med Hyg* 1981; **30**: 1078–84.

Systemic mycoses

The systemic mycoses are fungal infections that involve deep structures, and that have the propensity to disseminate, usually via the bloodstream, from the original focus of infection. They

include two main groups of disease: the endemic mycoses and the opportunistic systemic mycoses.

Endemic mycoses are usually acquired via inhalation of the causative organisms. They therefore have a common mode of pathogenesis. In many cases, infections are asymptomatic and the primary infection can only be detected in retrospect by a positive skin test, as in tuberculosis. These mycoses have defined areas of endemicity, which may have a characteristic climate or flora and fauna. The main endemic mycoses are histoplasmosis (classical and African types), blastomycosis, coccidioidomycosis, paracoccidioidomycosis and infection caused by *Penicillium marneffei*. The clinical manifestations of these infections are affected by the underlying state of the patient, and many of them develop in the presence of particular immunodeficiency states, notably AIDS. Cryptococcosis shares features of both endemic mycoses and the second group, the opportunistic infections. However, as it can affect the healthy and is a primary respiratory infection caused by a fungus that occupies a specific ecological niche, it will be considered here with the endemic infections.

The opportunistic systemic mycoses are those systemic infections that only occur in patients with some underlying predisposition. In contrast to the endemic mycoses, they may occur in any geographical area and their clinical manifestations are very variable, depending on the predisposition and mode of entry of the fungus.

Laboratory methods

The dimorphic fungi causing the endemic mycoses are extremely hazardous to the laboratory worker, and must be handled in containment level 3 conditions. Laboratory infections and fatalities have been recorded. These organisms should never be cultured in Petri dishes, which pose too great a threat of aerosol dissemination. Cultures should be performed in capped bottles or tubes. The laboratory must be alerted to the possibility of a dimorphic pathogen when the specimen is submitted for examination.

Serological tests

Serological tests are of considerable value in the diagnosis of the endemic mycoses. In the endemic infections, immunodiffusion tests may demonstrate the presence of specific precipitin bands, for example, the H and M bands in histoplasmosis, and complement fixation tests are also routinely performed in suspected cases of histoplasmosis, coccidioidomycosis and paracoccidioidomycosis. The cross-reactivity of fungal antigens can be a problem, however, and this is true of antigens of *Blastomyces dermatitidis*, which cross-react with those of other dimorphic pathogens. In the opportunistic systemic mycoses, serology is also useful but may be more difficult to interpret. Many normal individuals will have detectable antibodies to *Candida* species, resulting from exposure in the environment, so that changes in titre have more significance than a single positive test. Many patients with opportunistic infections caused by *Candida* species or *Aspergillus* species will be unable to raise any antibody responses. For this reason, methods of detection of antigen or fungal metabolites are currently of most interest. However, antigenaemia is transient and detection may require serial samples. The situation is reversed in cryptococcosis, however, where the detection of antigen rather than antibody has proved to be virtually diagnostic, and commercial latex particle agglutination or enzyme-linked immunosorbent assay (ELISA) tests for cryptococcal antigen are routinely used.

Direct examination and histopathology

As with the subcutaneous infections, in some instances a simple wet mount of samples such as sputum or bronchoalveolar lavage fluid can show characteristic fungal structures. For example, observation of encapsulated yeasts in cerebrospinal fluid is diagnostic of cryptococcosis, and spherules of *C. immitis* may be detected in sputum. Histopathological investigations may allow the recognition of all the dimorphic fungi, zygomycetes and *Cryptococcus*, but cannot distinguish some of the rarer pathogens such as *Fusarium* species and *Scedosporium apiospermum* reliably from *Aspergillus*.

Culture and identification of isolates

Suitable media are similar to those described for the subcutaneous fungi. Incubation should be performed at around 30°C and also at 37°C if sufficient material is available. Many of the opportunistic pathogens will grow in a few days, but some of the dimorphic fungi grow relatively slowly, and cultures should be held for a minimum of 4–6 weeks.

Isolation of any of the dimorphic pathogens is always considered significant. The identification of the five major dimorphic agents may, however, be complicated by the fact that in some cases they can be morphologically atypical or sterile. Exoantigen tests and nucleic acid probes for specific identification of these pathogens have now been developed. These techniques involve less handling of these pathogens and are far quicker than the traditionally used methods for converting the organisms to their parasitic phase *in vitro*.

The situation is rather different with the opportunistic infections, where the pathogens are widespread in the environment. The isolation of a few colonies of *Aspergillus* from a non-sterile site such as sputum may be difficult to interpret. However, the isolation of an opportunistic pathogen from a normally sterile site should always be taken seriously.

The use of molecular diagnostic methods such as PCR-based identification methods for the diagnosis of systemic mycoses will increase, although such tests have seldom been standardized. They are mainly used in the commoner mycoses such as systemic *Candida* infections and candidaemia. They have excellent sensitivity and specificity and are likely to be used with increasing frequency in the future, as they are more rapid than culture-based methods.

Histoplasmosis

Synonyms
- Darling's disease
- Histoplasmosis capsulati

Definition. A highly infectious mycosis caused by *Histoplasma capsulatum* and affecting primarily the lungs, where it is generally asymptomatic [1]. The fungus is intracellular, parasitizing the

reticuloendothelial system and involving the spleen, liver, kidney, central nervous system and other organs. Rarely, the disease may become chronic, progressive and fatal.

Aetiology. Histoplasmosis results from infection with the dimorphic fungus, *H. capsulatum.* Previously two varieties of the fungus were differentiated—var. *capsulatum*, or the closely related *H.* var. *duboisii*. The two varieties are differentiated on the basis of the yeast phase cell sizes, with var. *capsulatum* having smaller cells than those of var. *duboisii*. However, recent molecular studies demonstrated that there were multiple clades within *H. capsulatum* and that the assignment of three varieties (including *H. capsulatum* var. *farciminosum* in horses and var. *duboisii*) were not phylogenetically relevant [2]. The African clade contained isolates previously classed as *H. capsulatum* var. *duboisii*, as well as *H. capsulatum* var. *capsulatum* and var. *farciminosum.* However, despite this there are important differences between the two morphological forms in their epidemiology and clinical manifestations (see below). They show some subtle antigenic differences but their mycelial phases are identical. Therefore the old terminology, var. *capsulatum* and var. *duboisii*, will be used here until there is a clearer genetic explanation for these differences.

The disease caused by *H. capsulatum* var. *capsulatum*, referred to here as histoplasmosis (small-form histoplasmosis), is widely distributed throughout the world, occurring in some 60 temperate and tropical countries in the Americas, Africa and Australasia [1]. It has been widely studied in the USA, where the number of human infections has been estimated at 30 million. It is highly endemic in the Mississippi and the Ohio valleys of the USA. In certain areas, more than 80% of the population are known to have acquired the infection, as revealed by cutaneous reactivity to histoplasmin [3]. Infections with the *duboisii* form, known as African histoplasmosis or large-form histoplasmosis, have been reported only from Africa. Infants and children are frequently infected, and among adults the rate is highest in male agricultural workers.

H. capsulatum exists as a saprophyte in nature, and has often been isolated from soil, particularly when contaminated with chicken feathers or droppings. Other birds, such as starlings, and bats have also been implicated in the establishment of saprophytic reservoirs of infection. The fungus has been demonstrated in the soil of caves inhabited by bats, and in endemic areas histoplasmosis is recognized as a hazard to cave explorers. *H. capsulatum* var. *capsulatum* has been isolated from the organs and faeces of house-dwellings bats in Panama. Its spores are infectious not only to humans, but also to small animals such as dogs, cats and rats. The disease is not transmitted from human to human or from animal to human, but by the inhalation of air-borne conidia. Epidemics have occurred from time to time among people exposed to spore-charged atmospheres when exploring caves or cleaning out sites rich in the excrement of birds. Infection may follow introduction of spores through skin and mucous membranes, as in laboratory workers. Lymphoma appears to favour the development of the infection [4]. In addition, histoplasmosis is an important complicating infection in patients with AIDS [5,6].

Histology. *Histoplasma* is predominantly an intracellular parasite, growing within the cells of the reticuloendothelial system as an oval yeast (Fig. 36.57). All phagocytic cells of the reticuloendothelial system are involved, including those in the liver, spleen, lymph nodes and bone marrow, so that the cytoplasm is swollen with masses of fungal cells. There is at first little tissue reaction; later, necrosis takes place to be followed by granulomatous changes and fibrosis. *H. duboisii* is usually distinctive in having a much larger tissue form; it often elicits an inflammatory response in which giant cells predominate.

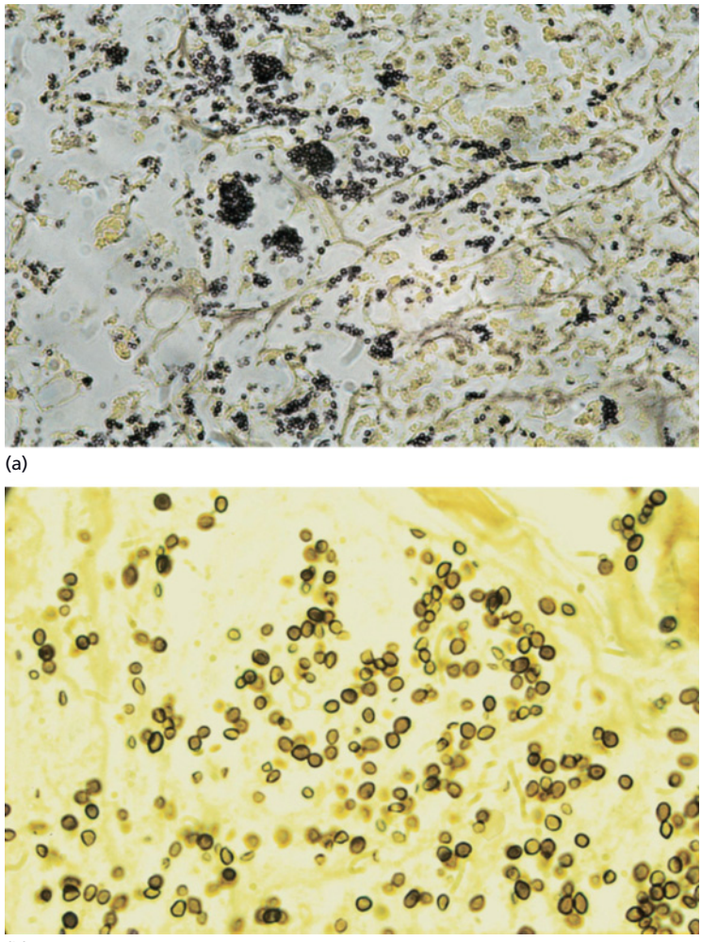


Fig. 36.57 Histoplasmosis var. *capsulatum*. (a) Tissue section. The tiny yeasts, stained black with GMS, are largely intracellular. (b) Oil immersion. The typical budding yeasts are clearly visible. Compare with *Penicillium marneffei* infection, Fig. 36.62. (Courtesy of the Department of Medical Mycology, St John's Institute of Dermatology, King's College London, London, UK.)

Clinical features [1]. Benign forms of the disease, which heal by calcification, are indistinguishable on X-ray from tuberculosis. The spectrum of disease includes asymptomatic as well as symptomatic and benign infections, and the progressive disseminated variety with blood spread to all organs. Primary coin lesions have been demonstrated as well as areas of cavitation. All varieties are reminiscent of tuberculosis.

Skin lesions are more common with *H. duboisii* than with *H. capsulatum*. Indeed, whereas the skin is rarely affected in

histoplasmosis except in AIDS patients, it is often involved in African histoplasmosis.

Although primary inoculation can rarely produce a local granuloma or ulcer, most skin lesions in histoplasmosis arise following dissemination from the primary pulmonary focus. Papules, ulcers, nodules, granulomas, abscesses, fistulae, scars and pigmentary changes may be seen, and there may be secondary involvement of the skin with osteomyelitis [7]. Involvement of the skin in some immunosuppressed patients may produce a condition resembling cellulitis [7].

Asymptomatic forms of histoplasmosis, indicated by the presence of positive skin-test reactivity without evidence of infection, are common in endemic areas [3]. It is likely that this form of exposure is the dominant pattern, unless other factors such as a massive inoculum (exposure in a bat-infested cave) or defective host defence are present.

The four main clinical varieties of histoplasmosis are acute pulmonary, acute disseminated, and chronic pulmonary and disseminated forms.

Acute pulmonary histoplasmosis. The patient has the usual symptoms of acute infection of the lungs, and X-ray examination of the chest reveals diffuse mottling or localized infiltration. However, this acute pulmonary form must be considered uncommon, as a great majority of people in endemic areas who have shown reactions to histoplasmin testing and are assumed to have acquired their infection by the pulmonary route have done so without developing recognizable signs and symptoms. Even in such cases, the organism is not limited to the lungs but is disseminated throughout all parts of the reticuloendothelial system. Associated erythema multiforme or erythema nodosum have been observed. This skin reaction occurs very early in the disease, but the association with histoplasmosis may not be apparent for several weeks.

Acute disseminated form. In this uncommon type, the lungs may be consolidated as a result of inhalation of many spores of *Histoplasma* and, although the pulmonary signs are prominent, there are also enlargement of the liver and spleen, fever, anaemia, loss of appetite and generalized enlargement of lymph glands. In such circumstances, any of the manifestations listed may be prominent, and the clinical features can be infinitely variable. Pulmonary manifestations may simulate miliary tuberculosis. Indurated granulomatous ulcers of the mouth, nose and larynx are often present and are distinctive [8]. Progressive emaciation, induced by gastrointestinal involvement, contributes to a fatal outcome after a course of weeks or months. Cutaneous or mucocutaneous granulomas are often seen in association with disseminated disease [9,10]. This is the form seen in patients with AIDS [11]. In AIDS patients, multiple small skin nodules may develop, the skin being more often involved than in other patient groups [4,5]. Often, papules have central softening.

Chronic pulmonary histoplasmosis. This usually occurs in adults, and also closely resembles tuberculosis with pulmonary involvement.

Chronic disseminated forms. These may appear months or years after a patient has left an endemic area. The most common clinical presenting features are oral ulceration and Addison's disease caused by adrenal infiltration. Mouth ulcers are large and may be chronic [8]; laryngeal involvement, ulceration or granuloma formation may also occur. Patients should be investigated for adrenal insufficiency, as this may appear for the first time during treatment. Ultrasound scans are useful for screening for adrenal enlargement [12].

Primary cutaneous histoplasmosis. This is very rare and appears after inoculation of the organism into the skin. The primary lesion is a nodule or indurated ulcer and there is often local lymphadenopathy [1].

Other forms of histoplasmosis. Other forms can be recognized. Dissemination may occur shortly after infection, or there may be a latent period of many years. Moreover, the severity of the condition may be influenced by various predisposing causes, including leukaemia, corticosteroid treatment, lymphoma, diabetes, carcinoma, AIDS and systemic collagen disease [11,13].

Diagnosis. The diagnosis of histoplasmosis is established by identifying the small intracellular yeast cells (2–5 µm) of *Histoplasma* in sputum, peripheral blood, bone marrow or in biopsy specimens. Lymph node aspiration may also be employed. Care should be taken in areas endemic for *Penicillium marneffei*, as the two organisms are of a similar size, although the latter shows characteristic septal formation rather than budding. The identity of the organism should be confirmed by culture. Some workers consider that cultures should be continued for up to 12 weeks before reporting negative results.

***H. capsulatum*.** Colony: at 30°C the growth may initially be waxy, but surface mycelium usually develops to produce white or tan cottony colonies. Microscopy: two types of conidia are formed: large (8–15 µm), rounded or occasionally pear-shaped, unicellular, tuberculate macroconidia; and small, oval, smooth or roughened microconidia. Physiological tests: ideally, cultural identification should be confirmed by demonstrating eluted *Histoplasma*-specific antigens, by using an exoantigen test or a nucleic acid hybridization test. However, if these techniques are not available, a suitable medium for conversion to the yeast phase is brain–heart infusion agar supplemented with 10% sheep's blood, 1% glucose and 0.1% cysteine. Serological tests: the intradermal histoplasmin skin test is an epidemiological tool that is of no help in diagnosis because it is negative in many patients with disseminated histoplasmosis. A rising complement fixation titre indicates dissemination. Precipitins are also valuable because some antigens, designated H and M, correlate well with active or recent infection [14]. The histoplasmin skin test should not be performed before the serological test, as it may produce a rise in the serological titre. Several serological kits are now sold commercially for both complement fixation and double diffusion tests.

A significant development has been the use of a serological test for the detection of circulating *Histoplasma* antigens [15], which is particularly helpful in AIDS patients.

African histoplasmosis. The clinical appearance of African forms of histoplasmosis are variable, and the disease is sporadic and uncommon [16]. It is confined to the areas south of the Sahara and north of the Zambezi river. The most common sites clinically involved in African histoplasmosis are the skin and bone, although lymph nodes and other areas including the lungs may be affected [17]. Skin lesions range from small papules resembling molluscum contagiosum, to abscesses or ulcers [18]. It is useful to screen patients with a bone scan or X-rays to exclude bone foci of infection [19]. The course of the disease is usually chronic, although some patients appear to develop a more rapidly progressive, disseminated type of infection. However, this form of histoplasmosis has only rarely been seen in AIDS patients. The diagnosis is confirmed by microscopy (direct or histopathology) and culture. Serology, using conventional tests, is often negative in African histoplasmosis.

Treatment. The choice of therapy for histoplasmosis has become considerably wider in recent years. For many disseminated or localized forms of the disease, oral itraconazole is highly effective [20], including the treatment of the disease in AIDS patients, where long-term suppressive therapy is usually needed. It appears that the use of HAART may reduce the requirement for maintenance therapy in some cases. Posaconazole and fluconazole are alternatives [20]. Amphotericin B is useful and is used in those with widespread and severe infections, particularly where an intravenous drug is needed [3]. The acute pulmonary forms of histoplasmosis require no specific antifungal therapy.

In African histoplasmosis, there is evidence that itraconazole or ketoconazole are effective [21]. An alternative in severe cases is amphotericin B [18]. Some patients with solitary skin lesions may simply respond to excision without chemotherapy, although antifungals should be given where possible.

References

1 Kauffman CA. Histoplasmosis: a clinical and laboratory update. *Clin Microbiol Rev* 2007; **20**: 115–32.
2 Kasuga T, White TJ, Koenig G *et al*. Phylogeography of the fungal pathogen. *Histoplasma capsulatum*. *Mol Ecol* 2003; **12**: 3383–401.
3 Edwards LB, Acquaviva FA, Livesay VT *et al*. An atlas of sensitivity to tuberculin, PPD-B and histoplasmin in the United States. *Am Rev Respir Dis* 1969; **99** (Suppl.): 1–132.
4 Goodwin RA, Loyd JE, DesPrez RM. Histoplasmosis in normal hosts. *Medicine* 1981; **60**: 231–66.
5 Barton EN, Roberts L, Ince WE *et al*. Cutaneous histoplasmosis in the acquired immunodeficiency syndrome: a report of three cases from Trinidad. *Trop Geogr Med* 1988; **40**: 153–7.
6 Kalter CD, Tschen JA, Klima M. Maculopapular rash in a patient with acquired immunodeficiency syndrome. *Arch Dermatol* 1985; **121**: 1454–7.
7 Goodwin RA, Shapiro JL, Thurman GH *et al*. Disseminated histoplasmosis. *Medicine* 1980; **59**: 1–33.
8 Toth BB, Frame RR. Oral histoplasmosis: diagnostic complications and treatment. *Oral Surg* 1983; **55**: 597–600.
9 Basset A, Basset M, Hocquet P *et al*. Formes cutanées de l'histoplasmose africaine. *Bull Soc Derm Syph* 1963; **70**: 61–4.
10 Negroni R. Manifestations cutaneas de la histoplasmose. *Rev Argent Microbiol* 1978; **1**: 5–16.
11 Wheat LJ, Slama TG, Norton JA *et al*. Histoplasmosis in the acquired immune deficiency syndrome. *Am J Med* 1985; **78**: 203–10.
12 Wilson DA, Nguyen CL, Tytle TL *et al*. Sonography of the adrenal glands in chronic disseminated histoplasmosis. *J Ultrasound Med* 1986; **5**: 69–73.
13 Johnson PC, Khardori N, Najjar AF *et al*. Progressive disseminated histoplasmosis in patients with the acquired immunodeficiency syndrome. *Am J Med* 1988; **85**: 152–8.
14 Davies SF. Serodiagnosis of histoplasmosis. *Semin Respir Infect* 1986; **1**: 9–15.
15 Wheat LJ, Kohler RB, Tewari RP. Diagnosis of disseminated histoplasmosis by detection of *Histoplasma capsulatum* antigen in serum and urine specimens. *N Engl J Med* 1986; **314**: 83–8.
16 Drouhet E. African histoplasmosis. In: Hay RJ, ed. *Baillières Clinical Tropical Medicine and Communicable Diseases*, Vol. 4. *Tropical Fungal Infections*. London: Baillière Tindall, 1989: 221–4.
17 Williams AO, Lawson EA, Lucas AO. African histoplasmosis due to *Histoplasma duboisii*. *Arch Pathol* 1971; **92**: 306–18.
18 Lucas AO. Cutaneous manifestations of African histoplasmosis. *Br J Dermatol* 1970; **82**: 435–4.
19 Cockshott WP, Lucas AG. Radiological findings in *Histoplasma duboisii* infections. *Br J Radiol* 1964; **37**: 653–60.
20 Negroni R, Palmieri O, Koren F *et al*. Oral treatment of paracoccidioidomycosis and histoplasmosis with itraconazole in humans. *Rev Infect Dis* 1987; **9** (Suppl. 1): 47–50.
21 Velho GC, Cabral JM, Massa A. African histoplasmosis: therapeutic efficacy of itraconazole. *J Eur Acad Dermatol Venereol* 1998; **10**: 77–80.

Blastomycosis

Synonyms
- North American blastomycosis
- Gilchrist's disease

Definition. A chronic granulomatous and suppurative mycosis caused by *Blastomyces dermatitidis*, affecting primarily the lungs but with disseminating forms affecting skin, bones, central nervous system and other sites.

Aetiology. The condition was originally thought to be restricted to the North American continent where it extends from Canada, particularly Quebec, through the USA with occasional cases in Mexico and Central America. The largest number of cases is seen in the Mississippi valley [1]. Blastomycosis, however, is now known to be widely distributed in Africa, with the largest numbers of cases coming from Zimbabwe [2,3], and cases have been reported from the Middle East [4], India [5] and Poland.

B. dermatitidis has only rarely been isolated from the environment. Studies suggest that its natural substrate may be wood debris or soil close to rivers or subject to flooding [6,7]. The fungus can grow in sterile soil in the laboratory, and it is believed that humans are infected by the inhalation of spores from a saprophytic source. However, primary skin infection also occurs, particularly in laboratory workers or pathologists. The incidence of infections tends to be highest in rural areas [1] and in agricultural workers. Human–human transmission does not normally take place. As with most of the systemic mycoses, adult males are most commonly affected, the majority being between the ages of 30 and 50 years. Indeed, some 86% of recorded cases are males. The fungus has also been recovered from domestic animals (e.g. the dog).

Histology. *B. dermatitidis* produces budding yeasts with a characteristic broad base to the bud in the tissues. The tissue reaction, and ultimately the course and prognosis, are determined by the immunological response of the patient. Primary lesions, usually

pulmonary, sometimes cutaneous, develop 1–3 weeks after infection and are associated with regional lymphadenopathy. The skin lesions that follow bloodstream dissemination show marked epidermal hyperplasia, which may be pseudoepitheliomatous in degree. Intra- and subepidermal polymorphonuclear abscesses and a granulomatous infiltrate are found in the dermis. These include giant cells of Langhans' type, which contain the round or oval organisms with thick, refractile walls. Disseminated skin lesions may also take the form of abscesses with organisms in their walls or within giant cells, and a non-specific granulomatous infiltrate.

Clinical features [8]. There are three forms of blastomycosis: primary cutaneous, pulmonary and disseminated.

Primary cutaneous blastomycosis. This is very rare and follows trauma to the skin and the introduction of fungus. The condition has been seen mainly in laboratory workers (e.g. pathologists carrying out autopsy examinations) [9]. After inoculation, an erythematous, indurated area with a chancre appears in 1–2 weeks with associated lymphangitis and lymphadenopathy. There may be some constitutional reaction. There is a strong tendency towards spontaneous recovery.

Pulmonary blastomycosis. This is very similar to pulmonary tuberculosis. There may be no symptoms, or there may be low-grade fever, chest pain, cough and haemoptysis. Occasionally, erythema nodosum develops [8]. The pulmonary lesion may resolve, or there may be cavity formation with lung abscess. In most cases, other organs are also affected [10]. The disease, if untreated, may frequently disseminate and often progresses to death. Mild, asymptomatic, self-limiting infections, common in histoplasmosis and coccidioidomycosis, may occur [11], but are probably uncommon.

Disseminated blastomycosis. When the infection spreads from the chest, lesions develop in many organs, commonly the skin, bones and central nervous system [12]. Mucous membranes are rarely involved. One or many skin lesions may be present [13]. These are often symmetrical and usually on the trunk rather than on the exposed parts. Each consists of a papule or nodule that may ulcerate and discharge pus. The lesions enlarge at the periphery, and tend to show central scarring, which may be dense. Eventually, after a relentless progress for months, the lesion is serpiginous in outline, the borders are raised and warty (Fig. 36.58) and have a violaceous margin studded with miliary abscesses containing the organisms [8].

Other patients may present with nodules and abscesses. African patients with blastomycosis have a higher frequency of skin and bone involvement [2].

Differential diagnosis. The microabscesses are the distinctive clinical feature, but the chronic granulomas of the skin must be differentiated from tuberculosis, syphilis, leprosy, pyoderma gangrenosum and drug reactions resulting from bromides and iodides. Pulmonary lesions, which are invariably present, necessitate X-ray examinations of the chest and differentiation from tuberculosis and other infections, and from neoplasia. The diagnosis of the skin lesions is established by direct microscopy of pus in 10% potassium hydroxide and confirmed by culture or biopsy.



Fig. 36.58 Cutaneous blastomycosis. (Courtesy of Dr M. James, Royal Berkshire Hospital, Reading, UK.)

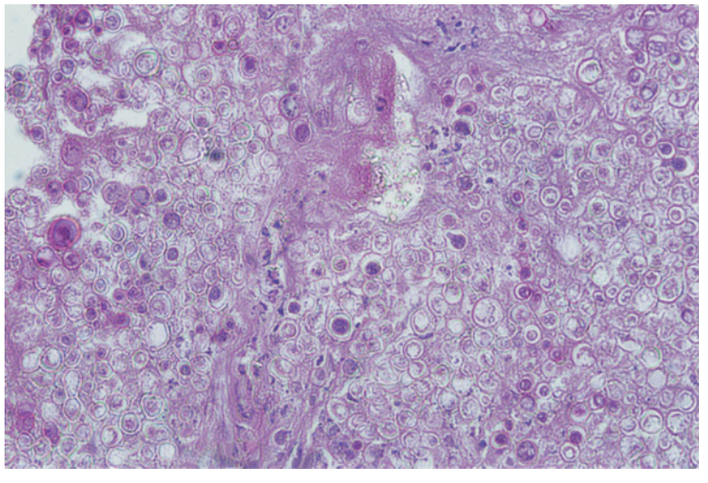


Fig. 36.59 North American blastomycosis tissue section. The large yeasts, stained pink with PAS, are characterized by the broad base of the buds. (Courtesy of the Department of Medical Mycology, St John's Institute of Dermatology, King's College London, London, UK.)

Laboratory diagnosis. The fungus can be observed in potassium hydroxide mounts of pus or scrapings as rather thick-walled, rounded, refractile, spherical yeasts with broad-based buds. In tissue, sections must be scanned carefully to identify organisms with the characteristic broad bud (Fig. 36.59).

B. dermatitidis. Colony: in culture at 30°C, mycelium is developed, the colonies being initially waxy, then cottony and white to tan. Microscopy: small, rounded or pear-shaped conidia (2–5 µm) are produced on short stalks arising at right angles from the hyphae. Physiological tests: exoantigen tests or nucleic acid probes are available for safe and rapid identification of the organism.

Alternatively, conversion to the yeast phase can be achieved on blood–glucose–cysteine agar. Serological tests: precipitating antibodies to *B. dermatitidis* are often present in the serum of infected subjects and a characteristic precipitin line, the E band, has been described in a high proportion of established cases [8].

Treatment. In most cases, itraconazole appears to be effective and has the advantage that it can be given orally [14]. The best regimen is not clear, but at least 400 mg should be given initially. Amphotericin B is still used for the treatment of widespread disseminated forms of blastomycosis [8]. Ketoconazole is an alternative therapy [15].

References

1 Bradsher RW, Chapman SW, Pappas PG. Blastomycosis. *Infect Dis Clin North Am* 2003; **17**: 21–40.
2 Emerson PA, Higgins E, Branfoot A. North American blastomycosis in Africans. *Br J Dis Chest* 1984; **78**: 286–91.
3 Sudman MS, Kaplan W. Antigenic relationship between American and African isolates of *Blastomyces dermatitidis* as determined by immuno-fluorescence. *Appl Microbiol* 1974; **27**: 496–9.
4 Kingston M, El-Mishad MM, Ashraf AM. Blastomycosis in Saudia Arabia. *Am J Trop Med Hyg* 1980; **29**: 464–6.
5 Randhawa HS, Khan ZV, Gaur SN. *Blastomyces dermatitidis* in India: first report of its isolation from clinical material. *Sabouraudia* 1983; **21**: 215–21.
6 Klein BS, Vergeront JM, Disalvo AF *et al*. Two outbreaks of blastomycosis along rivers in Wisconsin. *Am Rev Respir Dis* 1987; **136**: 1333–8.
7 Klein BS, Vergeront JM, Weeks RJ *et al*. Isolation of *Blastomyces dermatitidis* in soil associated with a large outbreak of blastomycosis in Wisconsin. *N Engl J Med* 1986; **314**: 529–34.
8 Sarosi GA, Davies F. Blastomycosis. *Am Rev Respir Dis* 1979; **120**: 911–38.
9 Larsh HW, Schwartz J. Accidental inoculation blastomycosis. *Cutis* 1977; **19**: 334–5.
10 Domer JE. *Blastomyces dermatitidis*. In: Szaniszlo PJ, ed. *Fungal Dimorphism*. New York: Plenum, 1985: 46–51.
11 Sarosi GA, Davies SF, Philips JR. Self-limited blastomycosis: a report of 39 cases. *Semin Respir Infect* 1986; **1**: 40–4.
12 Recht LD, Davies SF, Eckman MR *et al*. Blastomycosis in immunosuppressed patients. *Am Rev Respir Dis* 1982; **125**: 359–62.
13 Witorsch P, Utz JP. North American blastomycosis: a study of 40 patients. *Medicine* 1968; **47**: 169–200.
14 Dismukes WE, Badsher RW, Cloud GC *et al*. Itraconazole therapy for blastomycosis and histoplasmosis: NIAID Mycoses Study Group. *Am J Med* 1993; **93**: 489–97.
15 MacManus EJ, Jones JM. The use of ketoconazole in the treatment of blastomycosis. *Am Rev Respir Dis* 1986; **133**: 141–3.

Coccidioidomycosis

Synonyms
- Coccidioidal granuloma
- Valley fever
- San Joaquin valley fever
- Desert rheumatism

Definition. A (primary) respiratory fungal infection caused by *Coccidioides immitis* and *C. posadasii*, which may become progressive and disseminated, with severe or fatal forms.

Aetiology. Coccidioidomycosis is endemic in desert areas of the south-western states of the USA, and in parts of Central and South America [1]. Molecular studies have shown that there are two species of *Coccidioides*, *C. immitis* which occurs only in California and *C. posadasii* which occurs elsewhere [2]. However, on the basis of clinical and microbiological characteristics these two species cannot be differentiated routinely. Cases described outside this area are imported infections. The climate in endemic areas is characterized by high mean January and July temperatures and an annual rainfall of 12–50 cm. There is clear evidence that human infection may develop from very short residence in, or even a journey through, an endemic area, so that with increasing travel, cases of coccidioidomycosis are found in many parts of the world. Skin tests have shown that the incidence in endemic areas may be as high as 95%. It is a widespread and important disease only within these regions, affecting individuals of all ages. The fungus is a soil inhabitant; infection of humans and a wide variety of domestic and wild animals is acquired by inhalation of fungus-laden dust particles. The control of dust therefore becomes important in prevention of the disease [3]. Primary infection of the skin is rare but is known to occur [4].

Histology. The inhaled spores (arthroconidia of the saprophytic mycelial phase) develop in the lung tissue to form spherules—large, round, endospore-containing structures, which when mature are usually 30–80 µm in diameter (Fig. 36.60). Between 2 and 6 weeks after exposure, the patient becomes sensitive to an intradermal skin test using the fungal antigen, coccidioidin. The primary lesion is associated with regional lymphadenopathy, but usually there is no further spread. If secondary dissemination occurs, granulomatous lesions with giant cells and epithelioid cells are produced. Usually in active lesions, spherules with endospores can be demonstrated with routine staining, but in lesions with immature, empty or degenerate fungal spherules this may be difficult or impossible. Spherules may be seen within the cytoplasm of histiocytes and in giant cells of the foreign-body type. The fungus can be easily demonstrated by the use of special fungus stains such as PAS or silver impregnation stains.

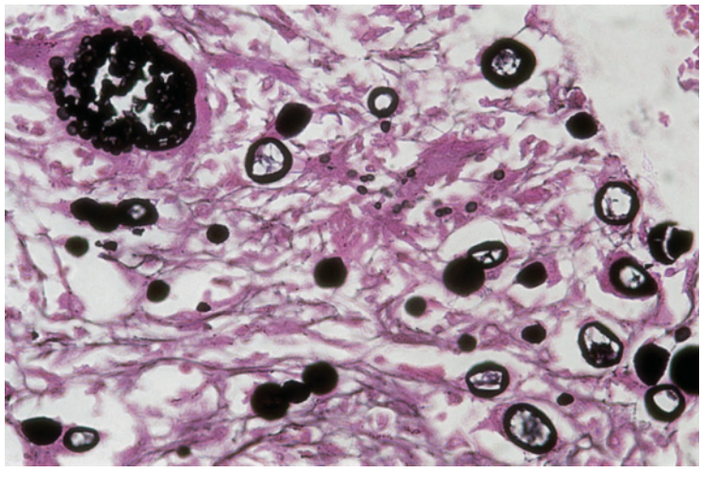


Fig. 36.60 Coccidioidomycosis tissue section. Spherules of various sizes are stained black with GMS. In the top left-hand part of the slide, freshly released endospores are visible. (Courtesy of the Department of Medical Mycology, St John's Institute of Dermatology, King's College London, London, UK.)

Clinical features [1]. The severity of coccidioidomycosis varies from a very mild, inapparent, upper respiratory tract infection to an acute, disseminated fatal disease. The primary pulmonary form, which is the most common form, is sometimes asymptomatic, but may simulate influenza or, occasionally, pulmonary tuberculosis. Erythema multiforme or erythema nodosum occurs from the third to the seventh week in some 3–25% of patients, particularly in females. In endemic areas, coccidioidomycosis is often the most common cause of erythema nodosum. There may be accompanying uveitis and arthralgia.

Pulmonary symptoms, when present, include pain resembling pleurisy, and often very sudden and acute shortness of breath, cough and associated pyrexia. Generalized aches, malaise and lassitude may occur, and there may be severe headache. An early generalized macular erythematous rash is seen in 10% of patients. The exceedingly rare primary skin lesions are painless, firm, indurated nodules often occurring 1–3 weeks after some form of local trauma. Regional lymphadenopathy develops but spontaneous healing follows after a few weeks [5].

Disseminated coccidioidomycosis is very uncommon and develops in fewer than 0.5% of infected individuals, usually in black, Filipino or immunosuppressed patients [6]. It may develop rapidly by blood spread of endospores to all organs, or insidiously from a pulmonary lesion after a period of quiescence. The death rate in acute disseminated disease, or with meningitis, is very high [7]. Disseminated lesions may occur in the skin, subcutaneous tissues, bones, joints and all organs. The skin lesions may appear as abscesses, granulomas, ulcers or discharging sinuses, particularly if there is underlying bone or joint disease [4].

Persistent and progressive pulmonary involvement and dissemination of infection are seen, including the appearance of multiple skin lesions in patients with AIDS [8]. Prolonged and progressive pulmonary infection may also occur in AIDS patients.

Differential diagnosis. The clinical manifestations of the disease are so varied that the condition must be differentiated from most chronic infectious conditions. Residence in, or travel through, an endemic area might suggest the diagnosis.

Prognosis. The prognosis for the primary form is excellent; for the acute disseminated forms it is very poor indeed, with all stages in between.

Laboratory diagnosis. The large (usually 30–80 µm, exceptionally larger) globular spherules may be seen in potassium hydroxide mounts of sputum, cerebrospinal fluid or pus. Confirmation depends on the isolation of the fungus in culture.

***C. immitis* and *C. posadasii*.** Colony: cultures of *C. immitis* and *C. posadasii* are mycelial, fast-growing, initially waxy then cottony and white to tan [9]. Microscopy: characteristic thick-walled arthroconidia, separated from each other by alternate empty cells, are observed. Physiological tests: exoantigen testing and nucleic acid probes are available for identification. If necessary, conversion can be achieved using modified Converse medium [10]. Serological tests: these are of value in diagnosis and prognosis of the disease. Thus, precipitins develop in up to 90% of infected individuals within 2–4 weeks, but are short lived; complement fixing (CF) antibodies are characteristic of more severe infections and increase to a maximum after 6 months. A rise of CF antibodies indicates dissemination while a decrease parallels clinical improvement.

Skin tests with coccidioidin are of little value in diagnosing infections. Positive reactions are of no diagnostic value in individuals from endemic areas, but may be helpful in subjects whose visits have been recent and brief [2]. Patients with coccidioidomycosis may cross-react to histoplasmin, but responses are usually much milder, and seldom cause confusion with the specific reaction to coccidioidin. Spherulin, derived from the tissue form of *C. immitis*, is reported to be superior to coccidioidin in detecting cutaneous hypersensitivity in both epidemiological and clinical settings [11]. In severe infections, cutaneous anergy is common [12].

Treatment [1]. In the primary pulmonary infection, no specific therapy apart from rest is necessary. There is little evidence that the use of an oral azole, such as itraconazole, in patients with erythema nodosum is helpful in reducing symptoms, and it may aggravate the situation. For disseminated disease, the approach depends on the form of disease. Oral fluconazole, itraconazole, voriconazole and posaconazole [5] are effective in some forms of localized infection such as solitary disseminated skin lesions. Itraconazole may be effective in other disseminated forms of disease [13]. Intravenous amphotericin B is used for many of the clinical forms of coccidioidomycosis [14]. The most difficult complications to treat at present are meningitis and joint infections. Neither of these responds well even to newer therapies, although temporary improvements may be achieved.

References

1 Crum NF, Lederman ER, Stafford CM *et al*. Coccidioidomycosis: a descriptive survey of a reemerging disease. Clinical characteristics and current controversies. *Medicine* 2004; **83**: 149–75.

2 Fisher MC, Koenig GL, White TJ, Taylor JV. Molecular and phenotypic description of *Coccidioides posadasii* sp nov., previously recognized as the non-Californian population of *Coccidioides immitis*. *Mycologia* 2002; **94**: 73–84.

3 Egeberg RO, Ely AF. *Coccidioides immitis* in the soil of the southern San Joaquin valley. *Am J Med Sci* 1956; **23**: 151–6.

4 Chang A, Tung RC, McGillis TS *et al*. Primary cutaneous coccidioidomycosis. *J Am Acad Dermatol* 2003; **49**: 944–9.

5 Ganer A, Arathoon E, Stevens DA. Initial experience in therapy for progressive mycoses with itraconazole, the first clinically studied triazole. *Rev Infect Dis* 1987; **9** (Suppl. 1): S77–86.

6 Deresinski SC, Stevens DA. Coccidioidomycosis in compromised hosts. *Medicine* 1974; **54**: 489–500.

7 Bouza E, Dreyer JS, Hewitt WL *et al*. Coccidioidal meningitis: an analysis of thirty one cases and review of the literature. *Medicine* 1981; **60**: 139–44.

8 Bronniman DA, Adam RD, Galgiani JN *et al*. Coccidioidomycosis in the acquired immunodeficiency syndrome. *Ann Intern Med* 1987; **106**: 373–9.

9 Standard PG, Kaufman L. Immunological procedure for the rapid and specific identification of *Coccidioides immitis* cultures. *J Clin Microbiol* 1977; **5**: 149–53.

10 Sun SH, Huppert M, Vukovich KR. Rapid *in vitro* conversion and identification of *Coccidioides immitis*. *J Clin Microbiol* 1976; **3**: 186–200.

11 Gifford J, Catanzaro A. A comparison of coccidioidin and spherulin skin testing in the diagnosis of coccidioidomycosis. *Am Rev Respir Dis* 1981; **124**: 440–4.

12 Cox RA, Vivas JR, Gross R *et al*. *In vivo* and *in vitro* cell mediated responses in coccidioidomycosis. *Am Rev Respir Dis* 1976; **114**: 937–42.

13 DeFelice R, Galgiani JN, Campbell SC *et al*. Ketoconazole treatment of coccidioidomycosis: evaluation of 60 patients during 3 years of study. *Am J Med* 1982; **72**: 681–7.
14 Winn WA. Coccidioidomycosis and amphotericin B. *Med Clin North Am* 1963; **47**: 1131–48.

Paracoccidioidomycosis

Synonyms
- South American blastomycosis
- Paracoccidioidal granuloma

Definition. A chronic granulomatous fungal infection caused by *Paracoccidioides brasiliensis*, affecting the skin, mucous membranes, lymph nodes and internal organs [1].

Aetiology. Paracoccidioidomycosis has been reported from most Latin American countries, but the infection is most commonly found in Brazil, particularly in the state of Sao Paulo [2], Colombia and Argentina. The infection is not known in other continents. Adult males between the ages of 20 and 50 years are most frequently infected, although exposure rates are equal across the two sexes [3]. It is thought that the fungus occurs as a saprophyte on vegetation or in soil [4]. The disease is not transmitted directly from person to person. The condition is much more frequent in rural areas.

P. brasiliensis is likely to gain entry to the body after inhalation via the respiratory tract, as with the other dimorphic fungal infections. Susceptibility to *P. brasiliensis* may be related to HLA-A9. This antigen has been found more frequently in progressive pulmonary forms of the disease than in patients with extrapulmonary involvement. The inhibition of the yeast phase, the form seen in human infections, is at least partially dependent on the binding of oestrogen by the fungus, which may account for the marked sex difference in susceptibility.

Histology [5]. The reaction resembles that seen in blastomycosis, namely granulomas with pyogenic inflammation; giant cells are conspicuous and these frequently contain the rounded budding cells. Exceptionally, these may attain diameters of 60 µm. The tendency to produce many multilateral buds in tissue sections is diagnostic (Fig. 36.61). In the skin and mucous membranes, there is pseudoepitheliomatous hyperplasia with severe granulomatous inflammation; intraepithelial abscesses occur and these frequently communicate with the surface.

Clinical features. The most common site of infection is the lung (pulmonary form), although skin and mucous membranes (mucocutaneous form) or lymph nodes (lymphatic form) are also often involved. Many patients have a mixed type of infection with involvement of different organ systems. In most patients, the disease is only slowly progressive.

Patients with pulmonary lesions present with weight loss and chronic cough. The lesions may be bilateral and nodular on X-ray, and there is often extensive fibrosis [6]. Mucocutaneous lesions may be present in patients with lung disease, or occur on their own. Oral or circumoral lesions are common in the mucocutaneous forms of paracoccidioidomycosis, although they may also occur in the nose, conjunctivae or anus. Lesions may be localized or diffuse. If in the mouth, a severe painful ulcerating stomatitis occurs. The ulcers become granulomatous and spread over the mucous membranes (the so-called 'mulberry-like erosion'). Lesions of the gums are common: they loosen the teeth, which are usually lost. The tongue may be involved. The skin lesions may begin at the mucocutaneous junction by direct extension from the mouth, or there may be satellite lesions from autoinoculation. Haematogenous or lymphatic spread results in subcutaneous abscesses. The cervical lymph nodes are sometimes enlarged early. They are palpable, painful, adherent to the overlying skin and may eventually suppurate with chronic sinus formation. If systemic spread occurs, the spleen, intestines, lungs and liver are involved; it is said that the intestines are often affected, with lesions eroding into the lumen [7]. Bone lesions have been seen and the adrenals may be destroyed. The central nervous system may also be affected [1]. Untreated, the disease was fatal in a few months to a few years in 43% of proved cases [6,7]. The extensive, painful mouth lesions with loss of teeth interfere with feeding, and the patient becomes cachectic. Paracoccidioidomycosis is uncommon but does occur in AIDS patients, and widespread infections may develop in young adults or older children without recognizable predisposition.

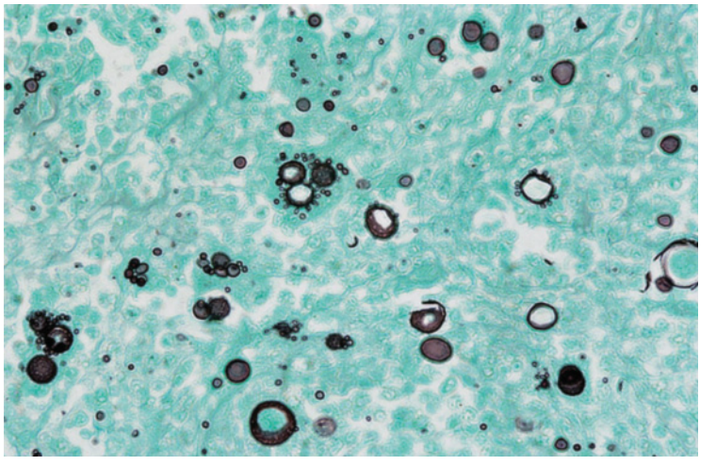


Fig. 36.61 Paracoccidioidomycosis. The yeasts, stained black with GMS, are characterized by the numerous peripheral buds produced. (Courtesy of the Department of Medical Mycology, St John's Institute of Dermatology, King's College London, London, UK.)

Differential diagnosis. The frequency with which the mouth and gums are involved with loss of teeth, the fact that there is no central scar formation, and the presence of marked lymphadenitis and lymphadenopathy differentiates paracoccidioidomycosis from blastomycosis. Other conditions to be considered are tuberculosis, syphilis, histoplasmosis, actinomycosis, sporotrichosis, rhinoscleroma and leishmaniasis. The organisms are readily found in biopsy specimens or in scrapings from the mucous membrane lesions. Aspiration of pus from lymph nodes will also provide material for microscopic examination and culture.

Laboratory diagnosis. Pus, exudates and scrapings examined in potassium hydroxide mounts may show rounded refractile cells,

which can be distinguished from *Blastomyces dermatitidis* when the characteristic multiple budding is seen. Yeasts range from 2 to 30 μm in diameter.

P. brasiliensis. Colony: growth is much slower and more restricted than that of *B. dermatitidis*. Initially flat or wrinkled and leathery, the colonies develop tufts of white to tan aerial mycelium. Microscopy: the hyaline, unicellular, pear-shaped conidia (3–4 μm) are borne directly on the hyphae or on short stalks. Very few conidia are produced. Physiological tests: an exoantigen test is available to identify the isolates; alternatively, conversion can be achieved on brain–heart infusion agar supplemented with 10% sheep's blood. Serological tests: both complement fixation and immunodiffusion assays are useful in the diagnosis of this condition. An antigen detection test is useful in monitoring therapy [8], although this is not widely available.

Treatment. The treatment of choice in most cases is itraconazole, which can produce remissions in 3–6 months [9,10]. Ketoconazole is an alternative. Relapse is common, and long-term surveillance should be carried out. Some patients, particularly those with more rapidly progressive and extensive infections, may require amphotericin B [1].

Paracoccidioidomycosis is often associated with severe fibrosis, and in oropharyngeal lesions contractures or laryngeal strictures can occur during or after therapy.

References

1 Visbal G, San-Blas G, Murgich J, Franco H. Paracoccidioides brasiliensis, paracoccidioidomycosis, and antifungal antibiotics. *Curr Drug Targets Infect Disord* 2005; **5**: 211–26.

2 Greer DL, Restrepo A. The epidemiology of paracoccidioidomycosis. In: Al Doory E, ed. *The Epidemiology of Human Mycotic Diseases*. Springfield: Thomas, 1975: 117–41.

3 Restrepo A, Salazar ME, Cano LE *et al*. Estrogens inhibit mycelium to yeast transformation in the fungus *P. brasiliensis*: implications for resistance of females to paracoccidioidomycosis. *Infect Immunol* 1984; **46**: 346–53.

4 Simoes LB, Marques SA, Bagagli E. Distribution of paracoccidioidomycosis: determination of ecologic correlates through spatial analyses. *Med Mycol* 2004; **42**: 517–23.

5 Franco MF. Host–parasite relationship in paracoccidioidomycosis. *J Med Vet Mycol* 1978; **25**: 5–18.

6 Restrepo A, Robledo M, Giraldo R *et al*. The gamut of paracoccidioidomycosis. *Am J Med* 1976; **61**: 33–42.

7 Sugar AM, Restrepo A, Stevens DA. Paracoccidioidomycosis in the immunosuppressed host: report of a case and review of the literature. *Am Rev Respir Dis* 1984; **129**: 349–52.

8 Gomez B, Figueroa JI, Hamilton AJ *et al*. Antigenaemia in paracoccidioidomycosis: detection of the 87 kDa determinant in patients during and after antifungal therapy. *J Clin Microbiol* 1998; **36**: 3309–16.

9 Negroni R, Palmieri O, Karen K *et al*. Oral treatment of paracoccidioidomycosis and histoplasmosis with itraconazole in humans. *Rev Infect Dis* 1987; **9** (Suppl. 1): 47–50.

10 Menezes VM, Soares BG, Fontes CJ. Drugs for treating paracoccidioidomycosis. *Cochrane Database Syst Rev* 2006: CD004967.

Infections caused by *Penicillium marneffei*

Synonym

- Penicilliosis

Definition. *Penicillium marneffei* is a recently recognized fungal pathogen that causes a disseminated mycosis in both healthy and immunocompromised patients [1]. There is a strong association with AIDS.

Aetiology. Although the causative organism is thought to originate from soil, it has not been isolated from this source. *P. marneffei* infections in humans are confined to South-East Asia, particularly Thailand, South China and Vietnam [2,3]. However, there are reports in other Asian countries, and imported cases have been seen in Europe and the USA [4]. Natural infections occur in bamboo rats, which are large, underground-dwelling rodents. Infections can occur in apparently healthy individuals, but it is a particular problem in severely immunocompromised patients in the endemic area.

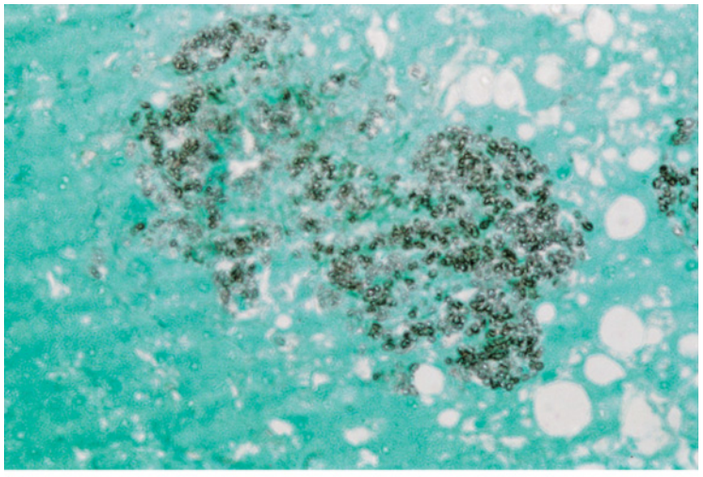
Clinical features. It is not known if there is a subclinical form of *Penicillium* infection (cf. histoplasmosis). However, patients may present with respiratory symptoms, such as cough, chest pain and fever, or with signs of dissemination such as anaemia, multiple skin papules and hepatosplenomegaly. Skin lesions occur in over 50% of cases. They are small papules, ulcers or molluscum-like lesions. They are usually widely scattered on the face and trunk. *P. marneffei* infections are also seen in travellers to the endemic area. Left untreated, this infection is fatal.

Differential diagnosis. The main differential is with other disseminated mycoses, such as histoplasmosis and cryptococcosis, which can also be found in the endemic area in AIDS patients. Biopsy and, where necessary, culture will distinguish between the different causes.

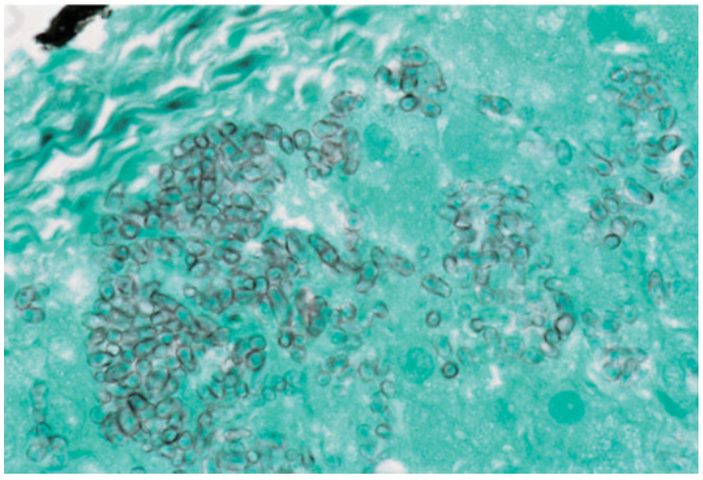
Diagnosis. *Penicillium marneffei* forms characteristic cells which are divided by a septum in tissue (Fig. 36.62). It does not produce buds. However, most cells in biopsy material are small oval structures similar in size to *Histoplasma capsulatum*. Occasionally, larger banana-shaped cells are seen. The diagnosis can be made from appropriately stained biopsies, smears and blood films, although with experience the typical cells can be distinguished on simple stains such as leishmanin.

P. marneffei. Colony: in culture, *P. marneffei* grows rapidly on glucose–peptone agar as a green or greyish mould. It produces a diffusible red pigment. Microscopy: typical *Penicillium* conidiophores and phialoconidia are produced. Physiological tests: on glucose–peptone agar after incubation for 14 days at 37°C, the organism produces dry, yeast-like colonies. The cells are oval to elliptical and reproduce by fission. Serological tests such as western blot are available in specialized centres.

Treatment. In severe cases, amphotericin B is necessary. However, there is usually a good response to itraconazole 200–400 mg/day, but this may have to be given for a long period to prevent relapse.



(a)



(b)

Fig. 36.62 Infection by *Penicillium marneffei*. (a) Tissue section. The tiny organisms are largely intracellular and look very similar to histoplasmosis at this magnification. (b) Oil immersion. The organisms divide by a central septum, rather than by budding. Sausage-shaped cells are also clearly visible. (Courtesy of the Department of Medical Mycology, St John's Institute of Dermatology, King's College London, London, UK.)

References

1 Drouhet E. Penicilliosis due to *Penicillium marneffei*: a new emerging systemic mycosis in AIDS patients travelling or living in South-East Asia: review of 44 cases reported in HIV infected patients during the last 5 years compared to cases of non-AIDS patients reported over 20 years. *J Mycol Med* 1993; **4**: 195–224.

2 Liyan X, Changming L, Xianyi Z *et al*. Fifteen cases of penicilliosis in Guangdong, China. *Mycopathologia* 2004; **158**: 151–5.

3 Suppuratpinyo K, Khamwan C, Baosoung V *et al*. Disseminated *Penicillium marneffei* infection in South-East Asia. *Lancet* 1994; **344**: 110–3.

4 Hilmarsdottir J, Meynard JL, Rogeaux O *et al*. Disseminated *Penicillium marneffei* infection associated with human immunodeficiency virus: a report of two cases and a review of 35 published cases. *J Acquir Immune Defic Syndr* 1993; **6**: 466–71.

Cryptococcosis

Definition. An acute, subacute or chronic infection caused by the encapsulated yeast *Cryptococcus neoformans*. There is a marked predilection for the brain and meninges, although the lungs and occasionally the skin and other parts of the body may be involved.

Aetiology. Cryptococcosis, unlike many other systemic mycoses, occurs throughout the world [1]. The condition is not excessively rare, and the diagnosis is frequently unsuspected. It is particularly associated with AIDS and is now seen regularly in these patients if they are not receiving antiviral therapy. Cryptococcosis is caused by a single species of fungus *C. neoformans*, which comprises two variants: *C. neoformans* var. *neoformans* and *C. neoformans* var. *gattii*. These correspond to cryptococcal serotypes known as A, D, AD and B and C, respectively [1]. Controversially, it has been suggested that var. *neoformans* should be split further into var. *neoformans* (serotype D) and a new variety, var. *grubii* (serotype A), although there is still discussion as to the validity of this split [2]. Interest has been stimulated by the observation that in Europe and much of the USA the *neoformans* variety was dominant, whereas in much of the tropics including Africa the *gattii* form was more common [3]. With the spread of HIV infection, the *neoformans* variety is overwhelmingly found in AIDS patients. The *neoformans* variety exists as a saprophyte in nature, being particularly abundant in soils enriched with pigeon droppings. By contrast, the *gattii* variant has been isolated from leaf and bark debris from red gum trees. Under certain conditions sexual stages are formed. These have been named *Filobasidiella neoformans* and *Filobasidiella bacillispora*, corresponding to the *neoformans* and *gattii* varieties, respectively. Unusual among pathogenic fungi, the sexual stage is a basidiomycete. It is not known if spores produced by the sexual phase (basidiospores) constitute infectious propagules. Studies *in vitro* have shown that yeast cells of *C. neoformans* are susceptible to soil microorganisms, including bacteria and amoebae.

Animal–human, or human–human transmission of the disease has not been reported. Bird droppings act as an excellent culture medium, and probably play an important part in promoting multiplication of the fungus in contaminated soil and the provision of a significant reservoir of infection in the case of var. *neoformans*. The inhalation of small yeast forms that have been aerosolized is likely to be the main route of infection. It is assumed that var. *gattii* infections follow a similar route of infection, although the exact mode of pathogenesis is still not known.

The disease usually occurs between the ages of 30 and 60 years, and is uncommon in childhood. Susceptibility is greatly increased by immunodeficiency states and neoplastic diseases, especially Hodgkin's disease. Recognizable predispositions include AIDS, malignant lymphomas, sarcoidosis, collagen disease, carcinoma and systemic corticosteroid therapy [4]. Cryptococcosis has also been associated with immunosuppression in patients following renal transplantation. However, the main underlying disease is AIDS [5]. The incidence of cryptococcosis in patients with established AIDS varies in different countries from 3–5% in the USA to 4% in the UK and over 12% in parts of Africa (e.g. Zaire) and of Thailand. This resulted in an increase in the numbers of patients although this has decreased with wider availability of antiretrovirals.

The respiratory tract is the usual portal of entry, but primary cutaneous lesions may occur. *C. neoformans* is unusual among pathogenic fungi in its predilection for invasion of the central

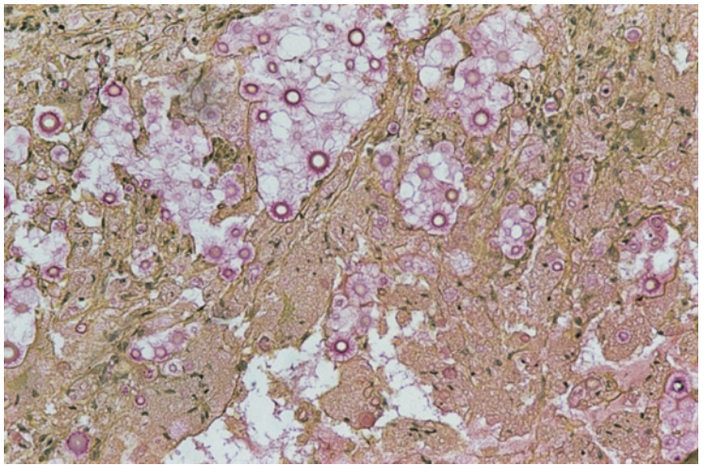


Fig. 36.63 Cryptococcosis tissue section. The mucicarmine stains the capsule specifically. The radiate spiny appearance is caused by shrinkage during processing. (Courtesy of the Department of Medical Mycology, St John's Institute of Dermatology, King's College London, London, UK.)

nervous system. Strains of serotype D are more likely to be found in skin lesions which occur in 10–15% of cases of disseminated cryptococcosis.

Histology. There may be minimal inflammatory reaction. The characteristic lesion consists of encapsulated budding cells mixed with a network of connective tissue, which enlarges and compresses the surrounding tissues [6]. A specific stain for the capsule—mucicarmine—is available (Fig. 36.63). Alternatively, a granulomatous reaction without caseation may be seen [7]. These clusters of cells are seen in most tissues of the body, but particularly in the central nervous system. In rare instances, cryptococci may proliferate in infected tissues in a non-encapsulated form. An acute inflammatory or granulomatous reaction is then seen, with overall resemblances to blastomycosis or histoplasmosis.

Clinical features [7]. Systemic involvement is usual, and the central nervous system manifestations often predominate, presenting as a chronic meningitis or as focal brain lesions simulating a tumour. There is low-grade fever and general decline in health, ending in coma and death, usually within a year but sometimes after a fluctuating course with periods of remission over many years. Pulmonary or urinary tract cryptococcosis may occur without involvement of the central nervous system when the prognosis is believed to be favourable, as it is in the rare cutaneous forms. In the disseminated disease, cutaneous lesions may precede or follow the signs of involvement of the central nervous system and lungs. These cutaneous and mucous membrane lesions, which occur in about 10 and 3% of cases, respectively, are seldom pathognomonic [8–10]. Most frequent are firm or cystic, slow-growing, subcutaneous, erythema nodosum-like swellings. Acneiform papules or pustules are characteristic of widespread systemic infection. They often occur around the nose and mouth. Any of these lesions may ulcerate or ulcers may develop in primarily unaffected skin, when they are often punched out with a rather distinctive rolled edge, or are multiple and resemble molluscum contagiosum. Direct extension of infection to the skin from bony lesions may occur, and mucosal lesions have been reported.

Often, the term primary cutaneous cryptococcosis is used erroneously to describe a solitary lesion of *Cryptococcus* on the skin, as in many such cases there is evidence of systemic spread, implying that the skin lesion has developed after bloodstream spread from a primary lung focus [4]. Documented cases of primary cutaneous infection by inoculation are exceptional.

In AIDS patients, the manifestations of cryptococcosis are not greatly different to those seen in other groups. However, often the symptoms of meningitis are minimal and there is evidence of wide dissemination, such as positive blood cultures or multiple skin lesions [1,11]. The skin lesions are often papules with central softening.

Differential diagnosis. Cryptococci may be recognized in smears of pus and of cerebrospinal fluid. When there is cutaneous involvement, cryptococci may be seen readily in and cultured from biopsy material. Their identity should be confirmed by culture. The diagnosis should particularly be considered when inflammatory nodules or ulcers develop in AIDS patients. However, similar lesions occur with other systemic mycoses, notably histoplasmosis and infections caused by *Penicillium marneffei*.

Laboratory diagnosis. The large (5–15 µm) budding cells with their characteristic capsules are best observed by direct microscopy of cerebrospinal fluid or pus in India ink or nigrosin mounts. Material suspected of containing *C. neoformans* should not be inoculated on to media containing cycloheximide, which inhibits growth. Incubation at 30°C for up to 4 weeks is sufficient.

C. neoformans. Colony: the growth is soft, cream to pale brown and usually mucoid. Isolation of *C. neoformans* is facilitated by its tendency to form brown colonies on media made selective by the addition of various melanin precursors (e.g. *Guizotia* seed or caffeic acid media). Microscopy: yeasts alone are formed; no filaments are produced. Physiological tests: identification is based on such cultural characteristics as the ability to grow at 37°C, urease production, phenoloxidase production, and ability to assimilate creatinine and various carbohydrates. As with the identification of *Candida* species, commercial kits are widely used to identify *Cryptococcus neoformans*. Serological tests: these are rapid, specific and useful, particularly in disseminated or central nervous system infections. Serodiagnosis is dependent on the detection of cryptococcal capsular antigen, using either a latex agglutination test or an ELISA assay. High titres are found in AIDS patients in serum and cerebrospinal fluid. However, non-AIDS patients with single, localized skin lesions are often antigen negative.

Treatment. The mainstay of treatment in the non-AIDS patient is intravenous amphotericin B combined with flucytosine [12]. This should be used in most cases, except in the occasional patient without serious underlying disease, who has focal infections, such as a skin lesion, and in whom there is no evidence of systemic spread, where fluconazole 400–600 mg/day may be used. In AIDS patients, the situation is more complicated as although rapid control can be obtained, maintenance therapy is usually used long

term after initial treatment, although most patients on HAART appear to achieve remission [13]. The current strategy adopted by most units is to use amphotericin B with or without flucytosine for 7–14 days to induce remission, followed by long-term oral maintenance with fluconazole 200–400 mg/day given as outpatient therapy. Itraconazole is an alternative for long-term therapy. The use of higher doses of fluconazole is also effective.

References

1 Chayakulkeeree M, Perfect JR. Cryptococcosis. *Infect Dis Clin North Am* 2006; **20**: 507–44.
2 Franzot SP, Salkin IF, Casadevall A. *Cryptococcus neoformans* var. *grubii*: separate varietal status for *Cryptococcus neoformans* serotype A isolates. *J Clin Microbiol* 1999; **37**: 838–40.
3 Swinne D, de Vroey C. Epidemiologie de la cryptococcose. *Rev Iberica Micol* 1987; **4**: 77–83.
4 Hay RJ. *Cryptococcus neoformans* and cutaneous cryptococcosis. *Semin Dermatol* 1985; **4**: 252–9.
5 Dismukes WE. Cryptococcal meningitis in patients with AIDS. *J Infect Dis* 1988; **157**: 5624–7.
6 Drouhet E, Destombes P, Carrizales D. Cryptococcose cutanée: confrontations histologiques et mycologiques. *Bull Soc Fr Dermatol Syph* 1970; **77**: 735–41.
7 Rook A, Woods B. Cutaneous cryptococcosis. *Br J Dermatol* 1962; **74**: 43–9.
8 Gauder JP. Cryptococcal cellulitis. *JAMA* 1978; **237**: 672–3.
9 Sarosi GA, Silberfarb PM, Tosh FE. Cutaneous cryptococcosis. *Arch Dermatol* 1971; **104**: 1–3.
10 Schupbach CW, Wheeler CE, Briggaman RA *et al*. Cutaneous manifestations of disseminated cryptococcosis. *Arch Dermatol* 1976; **112**: 1734–40.
11 Kovacs JA, Kovacs AA, Polis M *et al*. Cryptococcosis in the acquired immunodeficiency syndrome. *Ann Intern Med* 1985; **103**: 533–8.
12 Segal BH, Steinbach WJ. Combination antifungals: an update. *Expert Rev Anti Infect Ther* 2007; **5**: 883–92.
13 Aberg JA, Price RW, Heeren DM *et al*. A pilot study of the discontinuation of antifungal therapy for disseminated cryptococcal disease in patients with acquired immunodeficiency syndrome, following immunologic response to antiretroviral therapy. *J Infect Dis* 2002; **185**: 1179–82.

Systemic candidosis

A general account of systemic candidosis is outside the scope of this text, but certain aspects do impinge upon the dermatologist, and are therefore considered [1,2].

In most cases of systemic candidosis, the causal organism originates in the patient's own gastrointestinal tract, and in patients with leukaemia or other serious illness a history of mucocutaneous candidiasis in the past is the indication for vigilance, and perhaps for prophylaxis with oral anti-*Candida* agents. Invasion by *Candida* along intravenous infusion lines is also important, and maceration or signs suggestive of cutaneous candidosis on adjacent skin should not be ignored. Drug addicts are particularly at risk.

Typical lesions start as macules, become papular or nodular, and may show a pale centre. Some are likely to be haemorrhagic and may break down to form ecthyma gangrenosum-like lesions. Subcorneal pustules are not a feature, but follicular invasion by *Candida* leading to pustules and nodules in the coarse hair-bearing areas of the scalp, beard, axilla and pubis may be characteristic of *Candida* septicaemia in heroin abusers [3]. Fever, diffuse muscle tenderness and an erythematous macular rash are regarded as an indication for prompt skin biopsy in any compromised patient. Histology of a skin lesion showing *Candida* cells in the dermis provides a rapid diagnosis, often before blood culture is positive. Unfortunately, only a minority of patients with *Candida* septicaemia manifest skin lesions, but when present they should not be ignored.

The treatment of systemic candidosis with intravenous amphotericin B, caspofungin or fluconazole drugs is beyond the scope of this volume. Satisfactory management may demand facilities for the measurement of blood levels of some of these agents (e.g. flucytosine) and a careful watch should be kept on renal function. With flucytosine or fluconazole, isolates of the *Candida* strain should be tested for sensitivity if the patient fails to respond. Wherever possible, the predisposing pathology should be treated, and where immunosuppression has been used this should be reduced to minimum levels if possible.

References

1 Bodey G, Luna M. Skin lesions associated with disseminated candidiasis. *JAMA* 1974; **229**: 1466–8.
2 Darcis JM, Etienne M, Demonty J *et al*. *Candida albicans* septicaemia in heroin addicts. *Am J Dermatopathol* 1986; **8**: 501–4.
3 Dupont B, Drouhet E. Cutaneous, ocular and osteoarticular candidiasis in heroin addicts: new clinical and therapeutic aspects in 38 patients. *J Infect Dis* 1985; **152**: 577–9.

Zygomycosis

Synonyms
- Mucormycosis
- Phycomycosis

Zygomycosis is caused predominantly by species of *Rhizomucor*, *Absidia* and *Rhizopus*. *Cunninghamella bertholletiae* and *Saksenaea vasiformis* are less common causes. Although they are frequent in the natural environment, they are rare causes of invasive disease in patients made susceptible by poorly controlled diabetes, neutropenia or renal disease [1,2]. Fatal infections have been reported in patients with burns. Apart from invasion of necrotic burned areas or after severe trauma involving contact with soil, for example after a landslide, zygomycosis of the skin is uncommon. Lesions are progressive and necrotic ulcers similar to those described under necrotizing fasciitis.

Necrotizing infections of the skin associated with the application of dressings contaminated with *Rhizopus rhizopodiformis* [3], and with *R. microsporus* from wooden spatulae have been described [4]. Cutaneous lesions have been described in patients with lymphoma and kidney transplants [2]. Zygomycosis is usually diagnosed in autopsy or biopsy sections, based on the recognition of the broad and generally non-septate hyphae. As early treatment is essential, the use of frozen sections from skin lesions for rapid histopathological examination has been advocated. However, provided adequate samples are taken, they can be grown from tissue. Infections may respond to intravenous amphotericin, and recent results with lipid-associated amphotericin B formulations have been encouraging.

References

1 Bigby TD, Serota ML, Tierney LM *et al*. Clinical spectrum of pulmonary mucormycosis. *Chest* 1986; **89**: 435–9.
2 Carbone KM, Pennington LR, Gimenez LF *et al*. Mucormycosis in renal transplant patients: report of two cases and review of the literature. *QJM* 1985; **57**: 825–31.

3 Gartenberg G, Bottone EJ, Keutsch GT *et al*. Hospital acquired mucormycosis (*Rhizopus rhizopodiformis*) of skin and subcutaneous tissue: epidemiology, mycology and treatment. *N Engl J Med* 1978; **299**: 1115–8.
4 Mitchell SJ, Gray J, Morgan MEI *et al*. Nosocomial infection with *Rhizopus microsporus* in preterm infants associated with wooden tongue depressors. *Lancet* 1996; **348**: 441–3.

Unusual causes of skin lesions among opportunistic systemic mycoses

Most of the organisms that can invade the immunocompromised patient may cause skin lesions. Some of these infections, such as candidosis, zygomycosis and cryptococcosis, have been described previously. However, other organisms that can cause skin disease include *Aspergillus* [1,2], *Trichosporon* [3] and *Fusarium* [4]; all of these may affect the neutropenic patient.

Aspergillus and *Trichosporon* usually produce large, scattered necrotic lesions, although with the latter, smaller papules and pustules have been seen. *Fusarium* and, more rarely, *Acremonium* infection may produce target-like lesions, which may undergo central necrosis. In some cases of *Fusarium* infection, scattered skin lesions have been accompanied by digital cellulitis and superficial white onychomycosis caused by the same organism.

Skin involvement has also been described in a variety of invasive infections affecting the paranasal sinuses such as those caused by *Exophiala dermatidis*. Skin lesions in these infections develop in severely sick patients. However, skin biopsy will sometimes reveal the true diagnosis. Treatment for these infections is usually amphotericin B. The response rates in both *Fusarium* and *Trichosporon* infections are low, and a lipid-associated amphotericin B formulation is often used instead.

References

1 Carlisle JR. Primary cutaneous aspergillosis in a leukaemic child. *Arch Dermatol* 1978; **114**: 78–80.
2 Allo MA, Miller J, Townsend T *et al*. Primary cutaneous aspergillosis associated with Hickman intravenous catheters. *N Engl J Med* 1987; **317**: 1105–8.
3 Nahass GT, Rosenberg SP, Leonardi CL *et al*. Disseminated infection with *Trichosporon beigelii*. *Arch Dermatol* 1993; **129**: 1020–3.
4 Rabodonirana M, Piens MA, Monier MF *et al*. *Fusarium* infections in immunocompromised patients: case report and literature review. *Eur J Clin Microbiol Infect Dis* 1994; **13**: 152–61.

Cutaneous infection caused by *Pneumocystis jiroveci*

Pneumocystis jiroveci is an opportunistic fungal pathogen that is found in immunocompromised patients, including neonates, solid-organ transplant recipients and AIDS patients. *Pneumocystis* was previously regarded as a protozoan, but more recent DNA analysis has shown that it is best regarded as a fungus, although in certain structural features, such as its cell membrane, it differs from the fungal norm. Usually a pulmonary infection, it has rarely been found to cause skin lesions in AIDS patients [1]. The organisms stain with methenamine silver and appear as round, non-budding structures 5–10 µm in diameter. Treatment is with co-trimoxazole or pentamidine.

Reference

1 Raviglione MC. Extrapulmonary pneumocystosis: the first 50 cases. *Rev Infect Dis* 1990; **12**: 1127–38.

Infections caused by *Pythium insidiosum*

Infections caused by *Pythium* species (swamp cancer, Florida horse leech) were first recognized in animals in 1884, affecting mainly horses and mules. Since 1987, a number of cases of human infection have been reported, nearly all of them from Thailand and in farmers exposed to swampy areas. Affected patients have usually had severe infections with ascending gangrene of the lower limbs. Most have had an underlying haemoglobinopathy such as thalassaemia [1]. The organisms appear to invade blood vessels with large, sparsely septate hyphae, 3–20 µm in diameter, similar to those seen in zygomycosis. It is now recognized, however, that the organism is not a true fungus and is probably more closely related to the algae. It is possible to isolate *P. insidiosum* on glucose–peptone agar, but production of the characteristic motile biflagellate zoospores, necessary to speciate the isolate, requires special media and expertise [2].

There is no known effective treatment, apart from high doses of amphotericin B and amputation.

References

1 Sathapatayavongs B, Leelachaikul P, Prachaktam R *et al*. Human pythiosis associated with thalassaemia haemoglobinopathy syndrome. *J Infect Dis* 1989; **159**: 274–80.
2 De Cock AWAM, Mendoza L, Padhye AA *et al*. *Pythium insidiosum* sp. nov., the aetiologic agent of pythiosis. *J Clin Microbiol* 1987; **25**: 344–9.

Protothecosis

Prototheca is generally accepted as a genus of achloric algae embracing three species of worldwide distribution: *P. wickerhamii*, *P. zopfii* and *P. stagnora*. The first two species are established as rare and opportunistic pathogens in humans [1]. Infections with green and blue-green algae, although recorded, are rarer still. Lesions confined to skin and subcutaneous tissues are generally located on exposed sites, and may be associated with trauma [2,3]. Papules, nodules, ulcers and multiple granulomatous lesions have all been described. In such cases, the organisms may be found in the dermis and epidermis. Protothecal bursitis, particularly of the olecranon bursa after injury, is also well documented, as are a few examples of widespread cutaneous, subcutaneous or deep infection in immunocompromised hosts including AIDS patients [4]. Colonization of nails has been reported, and *Prototheca* may occur as transients on the skin. Spontaneous recovery has occurred in one cutaneous infection. However, surgical excision is recommended for localized lesions, and systemic amphotericin B, ketoconazole [5] or itraconazole have proved effective on occasions.

References

1 Davies RR, Wilkinson JL. Human protothecosis: supplementary studies. *Ann Trop Med Parasitol* 1967; **61**: 112–5.
2 Mayhall CG, Miller CW, Eisen AZ *et al*. Cutaneous protothecosis. *Arch Dermatol* 1976; **112**: 1749–52.
3 Sudman MS. Protothecosis: a critical review. *Am J Clin Pathol* 1974; **61**: 10–9.
4 Venezio FR, Lavoo E, Williams JE *et al*. Progressive cutaneous protothecosis. *Am J Clin Pathol* 1982; **77**: 485–8.
5 Pegram PS, Kerns FT, Wasilauskas BL *et al*. Successful ketoconazole treatment of protothecosis with ketoconazole associated hepatotoxicity. *Arch Intern Med* 1983; **143**: 1802–6.

Glossary

anamorph an asexual state.
anthropophilic adapted to humans.
arthroconidium a spore resulting from the breaking up of a hypha into separate cells; characteristic of parasitic form of ringworm fungi.
asexual reproduction not involving prior union of two nuclei.
blastospore a spore formed by budding.
cerebriform complex folding similar to the brain surface.
chlamydospore a thick-walled cell, intercalary or terminal, containing stored food and able to function as a spore.
clavate club-shaped.
cleistothecium a reproductive structure associated with the sexual state of ringworm fungi.
conidiophore a specialized structure of varying complexity that bears conidiogenous cells.
conidium an asexual spore.
dermatophyte a ringworm fungus.
dimorphic having two distinct forms, which often correspond to saprophytic and parasitic phases, respectively.
downy fluffy.
ectothrix dermatophyte hair infection with hyphae inside the hair and a sheath of spores outside the hair.
endospore spore formed internally (e.g. a sporangiospore).
endothrix dermatophyte hair infection with fungus confined to the inside of a hair.
faviform waxy, restricted honeycomb-like growth of certain dermatophytes.
floccose cottony.
fusiform spindle-shaped.
geophilic soil-inhabiting.
glabrous smooth, leathery.
grain compact agglomeration of fungal or actinomycete elements formed *in vivo*.
granular texture similar to icing sugar.
hypha one of the branching filaments, septate or non-septate, that make up the vegetative mycelium (q.v.) of moulds.
intercalary not terminal.
kerion an intensely inflammatory ringworm lesion.
macroconidium the larger of the two types of conidia in those fungi that bear large and small (microconidia) spores.
microconidium the smaller of the two types of conidia in those fungi that bear large and small conidia.
mycelium the collective name for a mass of hyphae.
mycosis a fungal disease.
obovate inverted egg-shape.
pleomorphic strictly having two or more forms; used frequently to describe non-sporing (sterile) cultures of dermatophytes.
powdery with a texture like face powder.
pseudohyphae hypha-like structure produced by elongation of budding yeasts lying end to end.
pyriform pear-shaped.
sessile without a stalk.
spiral vegetative hypha assuming spiral forms.
sporangium asexual reproductive body in *Zygomycetes*.
spore a reproductive unit; formed sexually or asexually, sometimes multicellular.
sporophore a spore-bearing structure.
tuberculate covered with peg-like outgrowths.
zoophilic adapted to an animal host.

CHAPTER 37
Parasitic Worms and Protozoa

F. Vega-López[1] *& R.J. Hay*[2]

[1]University College Hospital, London, UK
[2]Dermatology Department, King's College Hospital NHS Trust, London, UK

Infection with human nematodes, 37.3
Onchocerciasis, 37.4
Streptocerciasis, 37.8
Lymphatic filariasis, 37.8
Loiasis, 37.11
Dracunculiasis, 37.12
Enterobiasis, 37.13
Ancylostomiasis, 37.14
Strongyloidiasis, 37.15
Infection with nematodes of other animals, 37.16
Cutaneous larva migrans, 37.16
Visceral larva migrans: toxocariasis, 37.17
Gnathostomiasis, 37.18
Dirofilariasis, 37.19
Trichinosis, 37.19
Infection with trematodes, 37.20
Schistosomiasis, 37.20
Cercarial dermatitis, 37.22
Paragonimiasis, 37.23
Infection with cestodes, 37.24
Echinococcosis, 37.24
Cysticercosis, 37.25
Sparganosis, 37.26
Infection with protozoa, 37.27
Malaria, 37.27
Amoebiasis, 37.27
Trichomonads, 37.29
Trypanosomiasis, 37.29
Leishmaniasis, 37.33
Toxoplasmosis, 37.44

Introduction

A parasite is defined as an organism that depends upon a living host for one or more of its essential metabolic requirements. This definition does not imply that the relationship necessarily damages the host, and occasionally two organisms benefit mutually from a close association, one extreme within a wide range of relationships.

Many terms have been used to describe the relationships between parasites and their hosts; but few can be given an exact or exclusive definition. It is not, for example, possible to draw a sharp line between so-called endoparasites living within the body, which, in the case of some intestinal worms, may not invade the tissues, and ectoparasites living on the body surface, which, like the scabies mite, may in fact penetrate the epidermis. Similarly, when more than one species of host is successively infected during the life history of a parasite, they are not described in consistent terms. The definitive or final host is usually designated as the one in which the parasite reaches sexual maturity, and the intermediate host is one in which it undergoes larval development or an asexual phase. Thus, the human is definitive host for the so-called pork tapeworm *Taenia solium*, but may also act as an intermediate host in harbouring the bladder worm or cysticercus stage, which normally occurs in the pig. On the other hand, the human—as well as the sheep, the cow and the pig—is the intermediate host for *Echinococcus granulosus*, the hydatid cyst, and the dog, which harbours the tapeworm stage in its gut, is the definitive host. This logic is not exactly applied. The human is usually regarded as the definitive host of the malarial parasite of the genus *Plasmodium*, though sexual maturity is reached only within the mosquito. In practice, the anthropocentric view usually prevails: when the life history of a parasite involves alternations of human and arthropod hosts, the human is designated the definitive host and the arthropod the intermediate host or vector. A consequence of such illogicality is that the parasite now appears to be host specific only in respect of the vector, and not in respect of the so-designated definitive host. Humans share hospitality for *Plasmodium* spp. with other mammalian species, which are termed reservoirs.

Parasites that affect humans exemplify a variety of life histories [1–10]. At one extreme are species that need not leave the host even from one generation to the next; *Sarcoptes scabiei* is an example. At the other extreme are species that are only dependent on the host for the briefest contact, such as the female mosquito, which needs only a single meal of human blood before she can reproduce. In between these limits, there is a range of types of contact between parasite and hosts. Some forms spend part of their life history free-living, and only part as ectoparasites or endoparasites. Ticks, for example, while remaining for most of the time on their hosts, may drop off to lay eggs in the soil, and the larvae of hookworms hatch from the egg in the soil before burrowing their way through the skin to become gut parasites. Another category would include those parasites that spend all of their lives in the host, except for an egg or cyst stage that is transferred to another host without the intervention of a free-living phase; the roundworm, *Ascaris lumbricoides*, is an example. Lastly, there are those parasites with one or more intermediate hosts or vectors. Examples of dermatological interest are the guinea-worm *Dracunculus medinensis*, for which

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

Table 37.1 Worms commonly causing cutaneous disease.

Nematodes (roundworms)
Necator americanus
Ancylostoma duodenale
Ancylostoma spp.
Strongyloides stercoralis
Enterobius vermicularis
Gnathostoma spinigerum
Trichinella spiralis
Dracunculus medinensis
Onchocerca volvulus
Mansonella streptocerca
Loa loa
Dirofilaria spp.
Wuchereria bancrofti
Brugia malayi and *B. timori*
Cestodes (flatworms)
Taenia solium
Echinococcus granulosus and *E. multilocularis*
Spirometra spp.
Trematodes (flukes)
Schistosoma mansoni
S. haematobium
S. japonicum
Schistosoma spp.
Paragonimus spp.

the fresh-water crustacea of the genus *Cyclops* act as intermediate hosts, and *Loa loa*, a roundworm causing Calabar swellings, which is transmitted by flies of the genus *Chrysops*.

A number of biological considerations are of relevance to dermatological diagnosis and treatment. Cutaneous lesions may result from direct damage by or presence of the parasite, or develop indirectly at non-infected sites. In scabies, for example, inflammatory lesions are found in regions other than those that actually contain *Sarcoptes* spp. Skin disease due to parasites may be localized to a single site, or it may be only one manifestation of systemic infection. A parasite may enter the body via the skin, and may sometimes get no further, or the parasite may be ingested, when the skin lesions are either fortuitous, such as those caused by bladder worms, or serve as escape channels for propagation of the parasite, as are the ulcers caused by *Dracunculus* spp.

The principal groups of parasitic animals that cause skin disease are the protozoa, the helminth worms, which include the class Nematoda (roundworms) belonging to the phylum Nemathelminthes, the classes Trematoda (flukes) and Cestoda (tapeworms), both belonging to the phylum Platyhelminthes (Table 37.1), and the classes Insecta and Arachnida, both of the phylum Arthropoda.

The parasitic protozoa of dermatological interest include members of three classes. Belonging to the class Sarcodina is *Entamoeba histolytica*, an amoeba that infects the intestine causing amoebic dysentery, but which may occasionally invade the skin where it causes ulcers. Among the Flagellata (or Mastigophora) are classed the species of *Trypanosoma* that cause Chagas' disease, transmitted by species of 'kissing bugs', and African sleeping sickness, transmitted by tsetse flies: all these diseases have cutaneous manifestations. Other important flagellate parasites are the species of *Leishmania*, some responsible for systemic and others for superficial infections, which are also transmitted by insect vectors.

The nematodes include both parasitic roundworms and forms that live free in water or soil. Both free-living and parasitic forms go through a similar series of intermediate phases during their life cycle, but in soil-living forms all these stages take place in a single environment. In comparing the life histories of parasitic species, it is convenient first to consider species such as *Ancylostoma*, *Necator* and *Strongyloides* in which the eggs hatch in the soil to produce free-living larvae. *Strongyloides stercoralis* is an example of particular interest, because it is capable either of undergoing a complete life cycle free in the soil, or of infecting humans or other animals. Female worms living in the soil produce partially developed eggs, which soon hatch into rhabditiform larvae. These larvae undergo a series of four phase changes while growing into adults, and this free-living cycle is essentially similar to that of any non-parasitic soil nematode. When environmental conditions become unfavourable, however, the rhabditiform larvae develop into more slender filariform larvae, which are non-feeding but infective to mammalian hosts. These larvae can infect cats and dogs by being eaten, but in humans they usually penetrate by way of the skin, where they cause a transitory 'ground' itch. They enter the bloodstream and are carried to the lungs, whence after penetrating the alveoli they pass up the bronchi and the trachea to the buccal cavity. Thus, they are swallowed, eventually reaching the intestine where they develop to adults. A third type of life cycle, which is completely parasitic, can occur by the hatching and development of the larvae in the gut lumen. At the filariform stage, the larvae burrow through the mucosa into the blood vessels, and hence make their way via the lungs back to the intestine, where they mature.

The life histories of *Strongyloides* spp. provide some of the models for other species. In the hookworm, *Ancylostoma duodenale*, for example, eggs that pass out with the faeces hatch, within 24 h in moist warm soil, to rhabditiform larvae. These larvae grow rapidly, moult twice and in about a week become filariform, the stage that is infective to humans. The young worms crawl to a high point of moist vegetation and wait for a new host. They penetrate the skin, enter blood or lymph vessels where they are carried to the lungs, and undergo a migratory journey by way of alveoli, bronchi, trachea and buccal cavity to the small intestine. Here, a final phase occurs, and the young worm attaches itself to the intestinal wall, where it feeds and matures to an adult: by about 5 weeks after the original penetration of the skin it can produce new eggs. The American hookworm, *Necator americanus*, has a similar life history, and filariform larvae of other species, which do not infect the gut of humans, can nevertheless penetrate the skin and cause local 'creeping eruption'.

The problem of host infection has been solved in other ways by different species of nematodes. In the species *Ascaris*, the human roundworm, pairing of male and female worms occurs in the intestine of the host, and the eggs, each in a highly resistant capsule, pass out with the faeces. Growth and development of the embryo takes place within the egg, but the larvae do not hatch into the soil: the process is delayed until the eggs are ingested by

a new host. After hatching in the intestine, the larvae burrow through the intestinal wall to reach the lymphatic or blood vessels and make the same tour through the body as species of *Strongyloides* or hookworm larvae. The threadworm or pinworm, *Enterobius vermicularis*, another intestinal parasite of humans, differs from *Ascaris* spp. in that the eggs are not deposited in the intestine, but discharged by the female after it has crawled out through the anus of the host, and in that the larvae undergo no migratory journey after ingestion by a new host.

In species of *Dracunculus*, the guinea-worm, the problem of reinfection is solved by the role of an intermediate host, *Cyclops* spp., which is ingested by the definitive host. The adult worms live in the connective tissue of humans and other vertebrates, especially the tissue just under the skin, and they can migrate from one site to another. The cutaneous lesion is a hole in the host skin through which a part of the female worm projects and, when the infected host skin gets in contact with water, sets free large numbers of larval worms. *Trichinella spiralis* is an intestinal parasite of the human and a number of other mammals. The young larvae are shed from the female and burrow through the host tissues to the blood vessels, where they are carried to all parts of the body. The vast majority of the larvae encyst in striated muscles, where they gradually become encapsulated. The life cycle can continue only if the infected muscle is eaten by another host: humans usually become infected by eating undercooked pork. The human parasites, *Wuchereria bancrofti*, which lives in the lymphatic vessels, and *Onchocerca volvulus* and *Loa loa*, which live in connective tissue, all produce microfilarial larvae in the host. Infection of new hosts is by bloodsucking or tissue-feeding insects, respectively, mosquitoes (*Anopheles* spp.), coffee flies (*Simulium* spp.) and deer flies (*Chrysops* spp.).

Trematodes that infect humans all belong to the order Digenea. Flukes are parasites of various cavities of the body, such as the intestine, the ducts associated with the alimentary canal, the bladder or the lungs. Eggs are discharged to pass out of the body, where their further development requires water and a mollusc. The egg is either eaten by a snail or it hatches into a free-swimming, ciliated larva, known as a miracidium, which finds its way into a snail. In the snail, the miracidium gives rise to a sporocyst, and an asexual reproductive cycle takes place, producing a number of larvae known as rediae. Within each redia, there may develop either a further generation of rediae or a number of motile larvae known as cercariae. Cercariae can enter a new host in a number of ways. In the sheep liver fluke, *Fasciola hepatica*, they form cysts on blades of grass and are ingested by the host. In the human liver fluke, *Clonorchis sinensis*, the cercariae penetrate the skin of fish, where they encyst as metacercariae. Humans are infected by eating uncooked, infected fish. In the various species of *Schistosoma*, however, the cercariae enter the human host by way of the skin. Of particular interest is the fact that cercariae of flukes parasitic in various birds and mammals, which cannot fully infect humans, can actually enter the skin and cause cutaneous symptoms known as cercarial dermatitis or swimmer's itch.

The Cestodes, or tapeworms, are entirely parasitic throughout their life histories, and have at least two hosts, one of which harbours the adult stage in the gut, and a second that harbours the bladder worm stage in the body cavity or tissues. Humans may, for example, become infected with the tapeworm stage of *Taenia solium*, of which the bladder-worm stage normally occurs in the pig, or by the bladder worm of *Echinococcus* spp., of which the tapeworm stage occurs in the dog and other mammals. Cysticercosis, which may affect human skin, can occur also from *Taenia solium*. Cestodes belonging to the family Diphyllobothriidae, parasites of humans, other mammals and birds, have a so-called plerocercoid larva stage in copepod crustacea, fish or other aquatic animals. Larvae of this kind from intermediate hosts, such as frogs or snakes, may sometimes infect the skin of humans, causing a condition known as sparganosis.

Parasitic worms and protozoa cause a high proportion of the world's transmissible diseases, particularly in the tropics and subtropics, and they are responsible for some of the most dramatic and serious of the affections of the skin. Worms commonly causing cutaneous disease are shown in Table 37.1. In many instances, simple and effective preventive measures are available, which, when fully applied, should greatly reduce the world incidence. The global campaign for the eradication of guinea-worm is an example of a programme where simple steps have virtually eliminated what was once a common problem.

References

1 John DT, Petri WA. *Markell and Voge's Medical Parasitology*. St Louis, USA: Saunders, 2006.
2 Garcia LS. *Diagnostic Medical Parasitology*, 5th edn. Washington, DC: American Society For Microbiology, 2007.
3 Cooper RA, Stewart B. *A Colour Atlas of Medical Parasitology*. Queensland, Australia: Knowledge Books and Software, 2006.
4 Marr J, Nilsen T, Komunieki R. *Molecular Parasitology*. Amsterdam: Academic Press, 2002.
5 Colley DG, LoVerde PT, Saviolo I. Medical helminthology in the 21st century. *Science* 2001; **293**: 1437–8.
6 Muller R. *Worms and Human Disease*. Wallingford: CABI Publishing, 2002.
7 Noble ER, Noble GA, eds. *Parasitology: the Biology of Animal Parasites*, 3rd edn. Philadelphia: Lea and Febiger, 1973.
8 Rogers WP, ed. *The Nature of Parasitism*. New York: Academic Press, 1962.
9 Schmidt GD, Roberts LS, eds. *Foundations of Parasitology*, 2nd edn. St Louis: Mosby, 1981.
10 Smyth JD, ed. *Introduction to Animal Parasitology*, 2nd edn. London: Hodder and Stoughton, 1976.

Bibliography

Beaver PC, Jung RC, Cupp EW, eds. *Clinical Parasitology*, 9th edn. Philadelphia: Lea and Febiger, 1984.
Binford CH, Connor DH, eds. *Pathology of Tropical and Extraordinary Diseases*. Washington, DC: US Government Printing Office, 1976.
Cook GC, ed. *Parasitic Disease in Clinical Practice*. London: Springer-Verlag, 1990.
Cook GC, ed. *Manson's Tropical Diseases*, 20th edn. London: Saunders, 1996.
Kettle DS, ed. *Medical and Veterinary Entomology*. London: Croom-Helm, 1984.
Soulsby EJL, ed. *Helminths, Arthropods and Protozoa of Domesticated Animals*, 7th edn. London: Baillière Tindall, 1982.
Waltzer PD, Genta R, eds. *Parasitic Infections in the Compromised Host*. New York: Marcel Dekker, 1989.

Infection with human nematodes

In these infections, the human is an obligatory host at some stage of the life cycle of the parasite. Helminths, including nematodes, may be long lived—up to 30 years for *Schistosoma* spp. and 17 years for *Onchocerca* spp. for example—and constant reinfection

in endemic countries gives rise to heavy worm burdens. All nematodes must spend part of their life cycle outside the human body, either on soil or in water, or in an insect, crustacean or vertebrate intermediate host. *Strongyloides stercoralis* is the exception to this rule: autoinfection with this worm permits lifelong infections in humans. With some species of nematode, the worm is masked from immune recognition, and large worm burdens may be tolerated with remarkably little clinical effect. With others, inflammation, often in response to naturally dying worms or their progeny, causes severe disease. By contrast, some helminths make excessive demands on the body's nutritional reserves.

Onchocerciasis

Synonyms
- Blinding filariasis
- River blindness
- Coastal erysipelas
- Mal morado

Aetiology and epidemiology. Onchocerciasis is a filarial disease caused by *Onchocerca volvulus*. The worm affects inhabitants of certain areas in tropical Africa, from Senegal right across to Tanzania, and in Yemen, Central America, southern Mexico, Guatemala, Colombia, Ecuador and Venezuela [1]. The clinical manifestations of onchocerciasis in the New World show subtle differences in appearance and distribution, but the infection is otherwise the same [2–4]. The disease has been estimated to affect over 19 million people, of whom the vast majority live in Africa. A comprehensive control programme is now reducing the disease burden throughout the endemic areas [1]. The male adult worms measure 20–45 mm, and the female 230–700 mm in length; much longer than any other insect-borne filariae. Their progeny are sheathless microfilariae occurring in two sizes, approximately 200 µm and 300 µm long.

The vectors of the disease are tiny, humpbacked black flies of the family Simuliidae (buffalo gnats). In Africa, the species *Simulium damnosum* is mainly, but not exclusively, responsible, causing very itchy bites as it transmits the disease. The larvae develop in the thoracic muscles of the flies, and 7 days after infection are fully developed in the labium of the proboscis.

Human infections with zoonotic onchocerca have been reported in the Crimean region, Illinois and Switzerland [5].

Pathology [6,7]. Mature worms and microfilariae are found in granulomatous dermal nodules (onchocercal nodules), often situated on the scalp of their hosts in Central America, but in Africa near bony prominences on the trunk and limbs or in the natal cleft. The nodules measure some 3–35 mm in diameter, and consist of an outer layer of fibroblasts, which contains the parasites in an organized, fibrinous exudate. Inflammatory cells and, sometimes, giant cells tend to accumulate around the worms. Calcification may also occur.

Microfilariae migrate mainly in the dermis. Their death causes an inflammatory response. The longer the disease lasts, the more these changes are replaced by fibrosis and atrophy of dermis and epidermis [7,8].



Fig. 37.1 Microfilaria of *Onchocerca volvulus* in the upper dermis. Note the absence of inflammation around the live organism. (Courtesy of Dr C. McDougall, Slade Hospital, Oxford, UK.)

The numbers of microfilariae vary greatly. In some instances, there is a dense, predominantly perivascular, reaction with mononuclear cells and eosinophils, but few microfilariae [9]. At its severest, this is accompanied by marked acanthosis and hyperkeratosis. The reason for this extreme reaction is unknown, but serum from patients with this form of onchocerciasis recognize a collagen antigen expressed by a specific nematode gene, suggesting that cross-reaction between antibodies to *Onchocerca* and human collagen might play a role in the pathogenesis of this condition [10]. Often in individuals with minimal clinical lesions and dermal inflammation, there is the highest density of dermal microfilariae (Fig. 37.1). In these patients, there is evidence of defective T-lymphocyte stimulation by certain filarial antigens, which can be reversed by treatment [11]. Conversely, activation of T-cell-mediated pathways is associated with the highly inflammatory forms such as lichenified onchodermatitis (LOD) (see below).

Microfilariae also invade the eye, where they cause keratitis, posterior choroiditis, uveitis and optic neuritis, which can lead to blindness. Reports of microfilariae in blood have been rare and sporadic, and this finding is usually associated with diethylcarbamazine (DEC) therapy [12]. In others, it is difficult to exclude the possibility of concomitant infection with other filarial worms.

Free microfilariae also penetrate superficial lymphatic vessels, and may be found in the urine, tears, sputum, cerebrospinal fluid (CSF) and, occasionally, in vaginal smears or irrigation sediment.



Fig. 37.2 Acute papular onchodermatitis in a Nigerian. Early in the disease the papules are usually urticarial.

Clinical features [1,4,7,13]. The commonest symptoms and signs are pruritus, onchocercal dermatitis, nodules and, in areas of high endemicity, blindness. The disease may be detectable as early as 6 months of age, and presents with pruritus, often confined to a limb or other circumscribed body site, and a non-specific papular rash worsened by scratching.

In many patients, however, the skin may appear clinically normal, even when microfilarial counts in skin snips are found to be high. The skin changes seen in onchocerciasis vary with the age of the patient, the location of the infection on the skin surface and the geographical and climatic region where the infection occurs. Nonetheless, it is possible to define certain changes that are common features in onchodermatitis, although their prevalence varies from area to area. These changes have been classified as acute papular onchodermatitis (APOD) (Fig. 37.2), chronic papular onchodermatitis (CPOD) (Fig. 37.3), lichenified onchodermatitis (LOD), atrophy and hypopigmentation [13]. In children and in the earliest cases in endemic areas, the skin has an infiltrated appearance, with obliteration of surface markings. This is confined to one skin area and is often accompanied by the appearance of small, itching papules or pustules (APOD). The oedematous features are often more pronounced in Europeans with the disease, when it may present with localized oedema [14]. In Europeans, blotchy erythema and urticated papules are common early signs. The early rash is usually seen on exposed sites, such as the shoulders and around the pelvis. In Central America, acute swelling on the face and cheeks with erythema and itching, known as erisipela de la costa, is also a manifestation of this acute phase. Patients may continue to present with this pattern over months and years in the early phases of the disease.

As the infection evolves, localized areas of scarring and CPOD (Fig. 37.3) are seen. These may coexist with the acute papular eruption, but chronic lesions are excoriated papules and flat-topped scars with hyperpigmentation and some lichenification. The buttocks and shoulders are common sites for this rash.

Lichenified onchodermatitis may well represent an extreme form of the last clinical pattern. When fully developed, it is a



Fig. 37.3 Chronic papular onchodermatitis. Lesions are starting to lichenify.

lichenified itchy rash confined to one limb or contiguous area (Fig. 37.4), commonly the leg, although sometimes two or more areas are affected [9,11]. The rash is composed of itchy papules and nodules, which become confluent. The lesion is characteristically hyperpigmented, and it is known in Arabic-speaking areas as Sowda. Gross enlargement of the regional lymph nodes is an important feature. Interestingly, it is found mainly in East Africa (Sudan [15], Ethiopia) and Yemen. It is less common in West Africa or South America. There is some evidence that this pattern of skin change is associated with very low microfilarial loads; it may also improve symptomatically over time with loss of itching and lichenification, but increasing microfilarial loads. LOD is mainly seen in teenagers and young adults.

Atrophy (Fig. 37.5) is probably a consequence of long-standing onchocerciasis. It may develop after any of the patterns described previously, or arise from apparently normal but infected skin sites. The commonest sites to detect early atrophic changes are over the buttocks, shoulders or lower limbs. The skin becomes dry and shiny, with fine wrinkles resembling tissue paper. An extreme form of this secondary ichthyosis is known as lizard skin. It is believed that degenerative changes leading to loss of dermal elastic fibres, combined with other factors, such as massive inguinal lymphadenopathy, may give rise to the hanging groin, which is an apron-like fold of skin in the inguinal region [16] containing lymph nodes. Depigmentation is a common feature of late-stage onchodermatitis [17]. It is most commonly seen bilaterally over the pretibial region, but may affect the inguinal regions, bony prominences and the shoulders (Fig. 37.6). The patches of hypopigmentation are spotty, with islands of normal-appearing skin, but large coalescent sheets of depigmentation are present in late-stage



Fig. 37.4 Late lichenified onchodermatitis (pachyderma).



Fig. 37.6 Depigmentation over the shin in late onchocerciasis (leopard skin). This is common in African endemic areas. Note the stick for the blind.



Fig. 37.5 Late onchocerciasis. Atrophy of skin and damage to supporting tissue cause the skin to sag in folds (lizard skin).

disease. The name leopard skin is used to describe this change. While it is important to recognize that other causes of hypopigmentation, such as amyloid deposition, may also produce such changes in certain endemic areas, the presence of leopard skin in the community is used as an indicator of the prevalence of onchocerciasis in the population.

In many, if not most, patients with chronic onchocerciasis, it is possible to feel nodules containing the adult worms (Fig. 37.7).



Fig. 37.7 Cutaneous oedema and cutaneous and subcutaneous nodules in a Nigerian with onchocerciasis.

They are usually found over the pelvic or pectoral regions, although the top of the natal cleft is often a good site to find them. In South and Central American cases, the nodules are often found on the head.

Other clinical variants of onchocerciasis may occur. These include an acute urticarial eruption seen in Zaire and, in Central America, an inflammatory rash accompanied by hyperpigmentation known as 'mal morado'.

In endemic areas where onchocerciasis is found, the majority of the population may be affected; they will also have other skin diseases. There is little evidence that the presence of onchocerciasis affects the clinical appearances of these. However, it has been suggested that lepromatous leprosy [18] and widespread tinea corporis [4] are commoner in certain patients with onchocerciasis.

The major complication of onchocerciasis is severe visual impairment and blindness. It is the commonest cause of blindness in endemic areas. Ocular manifestations range from punctate and sclerosing keratitis, associated with the presence of microfilariae in the cornea and anterior chamber, to retinal pigmentation, optic atrophy, scarring and blindness. Onchocerciasis may result in blindness rates in endemic communities of 5–10% [19].

Prognosis. In endemic areas, the rate of infection increases up to the age of 50 years and no relative immunity is acquired. Symptoms increase in severity without treatment until atrophic changes are complete.

Diagnosis. Clinically, the diagnosis is usually evident, but other causes of prolonged pruritus and lichenification must be excluded, particularly scabies. Typical burrows may be hard to find in patients with scabies, and great tenacity is needed to demonstrate an acarus. Skin snips for active microfilariae are taken with the corneoscleral punch or by raising a little 'tent' of skin with a needle. This is then shaved off with a very sharp blade without bleeding, placed in normal saline in a microtitre well covered with transparent adhesive tape, or placed under a cover slip and examined microscopically 1–4 h later. The buttocks and legs are often most heavily infected, and are most likely to yield microfilariae. Nodules may be excised and examined histologically for adult worms and microfilariae. The white-cell count shows a leukocytosis with relative eosinophilia. The filarial immunofluorescence test or enzyme-linked immunosorbent assay (ELISA) is positive in 60–90% of cases.

Treatment. The treatment of onchocerciasis has been improved significantly by the development of the microfilaricide, ivermectin. This drug is given orally in a single dose of 100–200 µg/kg [20]. This results in a prolonged suppression of microfilarial counts in skin snips, and improvement in skin symptoms and reversible eye changes [21]. Microfilarial counts remain very low for 6 months, then rise slowly but do not reach pretreatment levels within 1 year. Patients may be retreated after 6–12 months. In patients with low parasite loads, such as travellers returning from an endemic country, about 30% will *not* relapse after each treatment [22]. The drug is well tolerated and side effects are seldom severe. Side effects that are seen include pruritus, skin oedema, arthralgia, malaise and fever. In particular, no acute eye changes accompany therapy [23]. Ivermectin has become the mainstay of population-based programmes for the control and elimination of onchocerciasis with striking effect [24].



Fig. 37.8 Acute papular onchodermatitis in a European. Exacerbation and oedema are characteristic of the Mazzotti reaction following a dose of diethylcarbamazine.

The alternative drug regimen, now rarely used, involves the use of diethylcarbamazine (DEC), which may cause severe exacerbation of skin (Fig. 37.8) and eye disease, even blindness [25]. DEC kills the microfilariae and is given as follows:

1 First 3 days 1 mg/kg body weight once
2 Second 4 days 2 mg/kg body weight once
3 Second week 4 mg/kg body weight three times a day
4 Third week 4 mg/kg body weight three times a day.

In heavily infected patients, or in those with severe dermatitis or with eye involvement, prednisone may be given at a daily dose in adults of 40 mg, starting the day before DEC and continuing for a few days until the reaction has settled. Collapse and death have occurred in heavily infected patients during treatment. The sharp accentuation of symptoms after a single 50 mg dose of DEC may be used as a diagnostic test where skin snips are negative (Mazzotti's test). Repeated courses are usually necessary until the patient is symptom-free.

Ocular reactions need treatment with corticosteroid eye drops and mydriatics.

Suramin is a drug that kills adult worms (macrofilaricide). However, it can cause severe adverse reactions and is now seldom used. Another approach now seldom used is nodulectomy, usually combined with a microfilaricide. In South America, some studies have shown that nodulectomy alone without drugs may reduce microfilarial levels by over 60% by 5 months after surgery [26]. It may reduce the burden of eye disease but it does not cure the disease, nor reduce transmission. A further novel approach has been to destroy the endobacterium, *Wolbachia*, which results in sterilization of female adult worms. A clinical trial using doxycycline has demonstrated that this approach in selected areas can result in an effective reduction in macrofilaria [27].

References

1 Boatin BA, Richards FO Jr. Control of onchocerciasis. *Adv Parasitol* 2006; **61**: 349–94.
2 Ewert A, Corredor A, Lightener L *et al*. Onchocerciasis focus in Colombia: follow up study after 12 years. *Am J Trop Med Hyg* 1979; **28**: 486–91.
3 Brown SG. Onchocercal depigmentation. *Trans R Soc Trop Med Hyg* 1960; **534**: 325–9.
4 Hay RJ, Mackenzie CD, Guderian R *et al*. Onchodermatitis—correlation between skin disease and parasitic load in an endemic focus in Ecuador. *Br J Dermatol* 1989; **121**: 187–98.
5 Beaver PC, Horner GS, Bilos JZ. Zoonotic onchocerciasis in a resident of Illinois and observations on the identification of *Onchocerca* species. *Am J Trop Med Hyg* 1974; **23**: 595–9.
6 Connor DH, Morrison NE, Kerdel-Vegas F *et al*. Onchocerciasis. Onchocercal dermatitis, lymphadenitis and elephantiasis in the Ubangi territory. *Hum Pathol* 1970; **1**: 553–79.
7 Gibson DW, Heggie C, Connor DH. Clinical and pathologic aspects of onchocerciasis. *Pathol Annu* 1980; **15**: 195–240.
8 Mackenzie CD. Eosinophil leukocytes in filarial infections. *Trans R Soc Trop Med Hyg* 1980; **74**: 51–8.
9 Connor DH, Gibson DW, Neafie RC *et al*. Sowda—onchocerciasis in North Yemen. A clinicopathologic study of 18 patients. *Am J Trop Med Hyg* 1983; **32**: 123–37.
10 Garate T, Conraths FJ, Harnett W *et al*. Identification of *Onchocerca volvulus* collagen as an antigen mainly recognised by antibodies in chronic hyper-reactive onchodermatitis (sowda). *Am J Trop Med Hyg* 1996; **54**: 490–7.
11 Akuffo H, Maasho K, Lavebratt C *et al*. Ivermectin-induced immunopotentiation in onchocerciasis; recognition of selected antigens following a single dose of ivermectin. *Clin Exp Immunol* 1996; **103**: 244–52.
12 Guderian RH, Mackenzie CD, Proano JR. Onchocerciasis in Ecuador. Absence of microfilaremia. *J Trop Med Hyg* 1987; **90**: 213–4.
13 Murdoch M, Hay RJ, Mackenzie CD *et al*. A new clinical classification for the skin lesions of onchocerciasis. *Br J Dermatol* 1993; **129**: 260–9.
14 Ezzedine K, Malvy D, Dhaussy I *et al*. Onchocerciasis-associated limb swelling in a traveler returning from Cameroon. *J Travel Med* 2006; **13**: 50–3.
15 Mackenzie CD, Williams JF, O'Day J *et al*. Onchocerciasis in South-Western Sudan; parasitological and clinical characteristics. *Am J Trop Med Hyg* 1987; **36**: 371–82.
16 Nelson GS. Hanging groin and hernia, complications of onchocerciasis. *Trans R Soc Trop Med Hyg* 1958; **52**: 272–5.
17 Guderian RH, Swanson D, Casillo R *et al*. Onchocerciasis in Ecuador. 1. Prevalence and distribution in the province of Esmeraldas. *Trop Med Parasitol* 1983; **34**: 143–8.
18 Prost A, Nebout M, Rougement A. Lepromatous leprosy and onchocerciasis. *BMJ* 1979; **i**: 589–90.
19 Brown R, Shannon R. Prevalence, intensity and ocular manifestations of *Onchocerca volvulus* infection in Dimbelenge, Zaire. *Ann Soc Belg Med Trop* 1989; **69**: 137–42.
20 Aziz MA, Diallo S, Diop IM *et al*. Efficacy and tolerance of ivermectin in human onchocerciasis. *Lancet* 1982; **ii**: 171–3.
21 Whitworth JA, Downham MD, Lahai G, Maude GH. A community trial of ivermectin for onchocerciasis in Sierra Leone: compliance and parasitological profiles after three and a half years of intervention. *Trop Med Int Health* 1996; **1**: 52–8.
22 Godfrey-Faussett P, Dow C, Black EM, Bryceson ADM. Ivermectin in the treatment of onchocerciasis in Britain. *Trop Med Parasitol* 1991; **42**: 82–4.
23 Rothova A, van der Lelij A, Stilma JS *et al*. Side effects of ivermectin in treatment of onchocerciasis. *Lancet* 1989; **i**: 1439–41.
24 Mas J, Ascaso C, Escaramis G *et al*. Reduction in the prevalence and intensity of infection in Onchocerca volvulus microfilariae according to ethnicity and community after 8 years of ivermectin treatment on the island of Bioko, Equatorial Guinea. *Trop Med Internat Health* 2006; **11**: 1082–91.
25 Bryceson ADM, Warrell DA, Pope HM. Dangerous reactions to treatment of onchocerciasis with diethylcarbamazine. *BMJ* 1977; **i**: 742–4.
26 Guderian RH, Proano R, Beck B *et al*. The reduction in microfilarial loads in the skin and eye after nodulectomy in Ecuadorian onchocerciasis. *Trop Med Parasitol* 1987; **38**: 272–8.
27 Hoerauf A, Specht S, Büttner M *et al*. Wolbachia endobacteria depletion by doxycycline as antifilarial therapy has macrofilaricidal activity in onchocerciasis: a randomized placebo-controlled study. *Med Microbiol Immunol* 2008; **197**: 295–311.



Fig. 37.9 Streptocerciasis. Pigmentary changes and nodules in a patient from Zaire. (Courtesy of the Armed Forces Institute of Pathology, Washington, DC, USA.)

Streptocerciasis

Streptocerciasis is an infection caused by the filarial nematode, *Mansonella streptocerca*. The disease is seen mainly in parts of West and Central Africa in rainforest areas, where it may be found in the majority of the population [1]. Chimpanzees in the endemic area may also be infected.

Adult worms of *M. streptocerca* can be found in the dermis, particularly around the upper trunk; microfilariae are also seen in the dermis.

The skin rash is rather similar to that seen with onchocerciasis, with acute or lichenified itching papules (Fig. 37.9). More widespread lichenification may also occur, and hypopigmented macules are common. Secondary enlargement of the local lymph nodes is seen in many patients. The diagnosis can be made by finding microfilariae in skin snips. These are less active than those of onchocerciasis, and the microfilarial tip may curl in a typical 'shepherd's crook' appearance. The main therapy is ivermectin.

Infections caused by two other *Mansonella* spp., *M. ozzardi* and *M. perstans*, are seen in Latin America and Africa, respectively, where the parasites are a cause of microfilaraemia; patients, however, are symptomless.

Reference

1 Fischer P, Bamuhiiga J, Büttner DW. Treatment of human *Mansonella streptocerca* infection with ivermectin. *Trop Med Int Health* 1997; **2**: 191–9.

Lymphatic filariasis

Synonym
- Tropical elephantiasis

Aetiology and epidemiology [1]. This is a disease due to infection with the filarial worms *Wuchereria bancrofti*, *Brugia malayi* or *B. timori*, of which the first is the commonest. Most authorities agree that clinically the diseases caused by the two genera of filariae are indistinguishable. Infections due to *W. bancrofti* are more widespread than the others [2]. They occur between the latitudes of 40° north and 30° south. The areas with the highest incidence of infection are South-East Asia and sub-Saharan Africa. In the New World, there are fewer endemic foci: Guyana, Haiti and parts of Brazil. Control has been achieved in some other countries such as Taiwan and Japan. It is estimated that about 250 million people are infected. *Brugia malayi* is mainly confined to South-East Asia and as far north as Korea, particularly in rural rainforest areas [3]. The most restricted of this group is *B. timori*, which is found in certain of the Indonesian islands [4].

Transmission and pathology [4]. The disease is transmitted by many species of anthropophilic mosquitoes of the genera *Culex*, *Aedes*, *Mansonia* and *Anopheles*. In ingested human blood in which microfilariae are present, the organisms lose their sheaths in the mosquito's stomach, and in less than 24 h have entered the thoracic muscles. Metamorphosis proceeds, and mature larvae migrate to the labella 10 days after infection of the insect. Here they are ready to be transmitted to the next human by biting.

In humans, larvae pass through peripheral lymphatics, develop and migrate centrally and eventually grow into adults, which mate in lymphatics proximal to lymph nodes. Fertilized females discharge their microfilariae, which may be found in peripheral blood 12 months after the initial infection. The discharge is cyclical and occurs principally at night. These microfilariae can pass the placental barrier. The adults are found coiled up in dilated lymphatics.

Immunity to filarial infections is complex. Otherwise healthy individuals from within the endemic area have both antibody and T-lymphocyte-mediated immune responses. By contrast, those with active infections and episodic microfilaraemia may show reduced cellular immunity, suggesting that antigens from the organisms may modulate immunity. The worms may also carry symbiotic bacteria of the genus *Wolbachia*. These are antigenic, although their contribution to inflammatory reactions is unknown.

Pathology. The presence of adult worms in the lymphatics with the resulting inflammatory response is the cause of the main pathological feature—lymphatic obstruction (Fig. 37.10). Leakage of lymph may contribute to tissue damage. Circulation of microfilariae in the bloodstream has remarkably little effect, although their entrapment in the lungs may cause tropical pulmonary eosinophilia.

Clinical features. Many of those infected do not appear to develop signs of infection, and such signs that occur vary considerably from patient to patient [5–7]. The first signs are often swelling, tenderness and erythema on the arms, legs or scrotum. Swellings may be firm, and fixed nodules and urticaria have also been described at this stage. Cellulitis, which is common, may be mild or severe and is recurrent. In the severest form it presents with fever and sweats and the painful enlargement of lymph nodes, particularly the inguinal group. Lymphangitis can accompany some attacks. Milder forms of cellulitis with more localized erythema and tender swellings also occur repeatedly. Other complications include orchitis, which is commonly followed by hydrocoele and scrotal oedema, and recurrent epididymitis. Abscesses deep in the limb muscles, or more superficially located in lymphatics, occur.

Repeated attacks of oedema and cellulitis, often associated with interdigital cracking, may be followed over a number of years by evidence of lymphatic obstruction (Fig. 37.11). In males, these commonly present as hydrocoeles, but lower leg oedema and elephantiasis may also develop. Hydrocoele or thickening of the

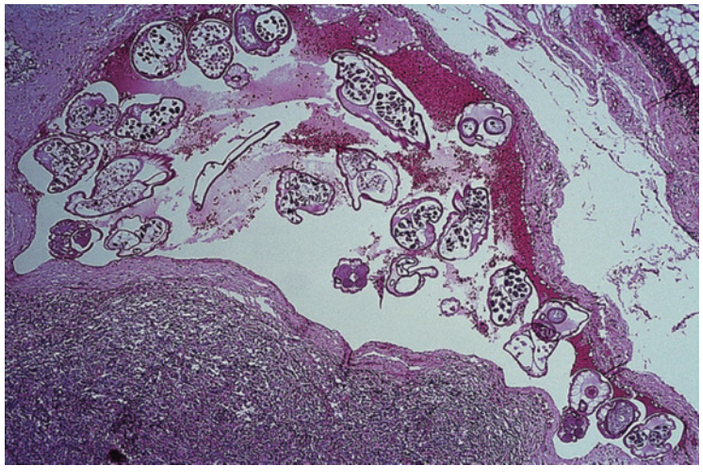


Fig. 37.10 Lymphatic filariasis (low power, H&E). Female adult *Wuchereria bancrofti* within lymph node sinus. Multiple cross-sections of worm are seen. (Courtesy of Professor S.B. Lucas, King's College London, UK.)



Fig. 37.11 Lymphangiogram showing tortuous, dilated lymphatic vessels in the leg of a patient with lymphatic filariasis from Mauritius.

scrotal skin is common in many endemic areas, and may affect up to 25% of the adult male population [8]. Limb oedema of a varying extent and nature is also common and passes through several grades of severity before becoming gross elephantiasis. This may be followed by recurrent episodes of secondary infection, and the appearance of warty thickening of the skin. The legs are usually affected, but arms, breast and genitalia may also be involved. A further complication is rupture of dilated abdominal lymphatics into the urinary tract, to produce episodic chyluria.

Diagnosis. In an endemic area, it may be possible to make the diagnosis on clinical grounds, before the stage at which microfilariae appear in the blood, as well as in the chronic condition. Biopsy of an enlarged lymph node may be diagnostic.

Microfilariae are demonstrated in the blood especially in acute cases, either in a thick blood film or by passing heparinized blood through a millipore filter, which retains the microfilariae, which can then be seen easily under the microscope. In the periodic form of filariasis, blood should be sampled between midnight and 02.00 hours.

An alternative procedure is to repeat blood films 1 h after a single dose of diethylcarbamazine (DEC) 100 mg. This releases more microfilariae into the circulation. However, some cases of filariasis do not appear to develop detectable filaraemia.

Another approach to diagnosis is the use of serology, where an indirect immunofluorescence or ELISA is positive in a high percentage of those affected, although it is not specific for each organism. An antigen detection system is also used [9]. A polymerase chain reaction (PCR)-based test has been applied to the detection of *W. bancrofti* genomic DNA in blood [10]. It is important to recognize the current deficiencies in the laboratory confirmation of this disease, as no single test is even 90% accurate.

Filarial lymphangitis must be distinguished from bacterial lymphadenitis, with its signs of a portal of entry. Genital lesions may resemble lymphogranuloma venereum with adenopathy and oedema. The Frei test will be negative.

Treatment. The management and elimination of lymphatic filariasis has become the focus of a group of research units, governmental organizations, non-governmental organizations (NGOs) and charities collectively known as the Global Alliance for the Elimination of Lymphatic Filariasis [11]. Two phases of their programme have been developed: parasite elimination and morbidity control. Parasite elimination depends on the use of chemotherapy through mass drug administration (MDA), which is also used for the treatment of individual patients. Diethylcarbamazine (DEC) has long been the main treatment [12,13], but is usually given with albendazole or as fortified salt in MDA programmes.

The dosage for individual patients is the same as for the treatment of onchocerciasis (see above), although higher doses at monthly intervals have also been given. The predominant effect of the drug is on the viability of microfilariae, but it has relatively little impact on adult worms. It may be necessary to repeat the course after a few months if microfilariae reappear in the blood.

No fatal complication has ever been reported from this use of DEC, but side effects occur, notably anorexia, nausea, vomiting, giddiness, headache, drowsiness and acute allergic reactions due to destruction of microfilariae and adult filariae.

Special care should be taken in areas where both lymphatic filariasis and onchocerciasis coexist, in view of the potentially serious nature of DEC reactions in the latter [8].

There is also experience with ivermectin, and it is effective in lymphatic filariasis. The drug works more rapidly than DEC, and microfilaraemia is reduced to 14–30% of pretreatment levels 6 months after therapy. There are also similar adverse reactions to ivermectin in patients with this condition. The dose is usually 400 μg/kg. Ivermectin does not kill adult worms, so recurrence of microfilaraemia is common and further treatments are often necessary [14]. Administration with DEC is an effective approach to MDA.

Morbidity control is approached through a combination of lower limb exercise and regular cleansing, combined with treatment of potential portals of entry of bacteria, such as infected web spaces which may be caused by fungal or bacterial infection [15]. There is evidence that this can reduce limb swelling considerably, even in late stages. These approaches are being developed across a range of endemic areas. Surgical approaches may improve the appearance of affected limbs either in the early stages by creating a lymph node–venous shunt, or by removing subcutaneous tissue and grafting of split-skin onto a muscle bed (Charle's operation) [16] in established elephantiasis. Repeated drainage and surgery may be required for severe hydrocoeles.

References

1 Sasa M, ed. *Human Filariasis. A Global Survey of Epidemiology and Control*. Baltimore: University Park Press, 1976.

2 Wilson T. Filariasis in Malaya—a general review. *Trans R Soc Trop Med Hyg* 1961; **55**: 154–9.

3 Denham DA, McGreevey PB. Brugian filariasis. Epidemiology and experimental studies. *Adv Parasitol* 1977; **16**: 243–52.

4 Dennis DT, Partono F, Atmosoedjono PS, Saroso JS. Timor filariasis: epidemiologic and clinical features in a defined community. *Am J Trop Med Hyg* 1976; **25**: 797–802.

5 Davis BR. Filariasis. *Dermatol Clin* 1989; **7**: 313–21.

6 Feinsod FM, Faris R, Gad A *et al*. Clinical manifestations of *Wucheria bancrofti* filariasis in an endemic village in the Nile delta. *Ann Soc Belge Med Trop* 1987; **67**: 259–65.

7 Partono F. Filariasis in Indonesia. Clinical manifestations and basic concepts of treatment and control. *Trans R Soc Trop Med Hyg* 1984; **78**: 9–12.

8 Ciba Foundation. Filariasis. *Ciba Found Symp* 1987; **127**: 1–305.

9 Weil, GJ, Ramzy RMR. Diagnostic tools for filariasis elimination programs. *Trends Parasitol* 2007; **23**: 78–82.

10 Zhong M, McCarthy J, Bierwert L *et al*. A polymerase chain reaction assay for detection of the parasite *Wuchereria bancrofti* in human blood. *Am J Trop Med Hyg* 1996; **54**: 357–63.

11 Anonymous. Global programme to eliminate lymphatic filariasis. *Weekly Epidemiological Record* 2007; **82**: 361–80.

12 Forsyth K. New approaches to the control of lymphatic filariasis using diethylcarbamazine. *PNG Med J* 1987; **30**: 189–91.

13 Reddy M, Gill SS, Kalkar SR *et al*. Oral drug therapy for multiple neglected tropical diseases: a systematic review. *JAMA* 2007; **298**: 1911–24.

14 Moulia-Pelat JP, Nguyen LN, Hascoet H *et al*. Advantages of an annual single dose of ivermectin 400 micrograms/kg plus diethylcarbamazine for community treatment of bancroftian filariasis. *Trans R Soc Trop Med Hyg* 1995; **86**: 682–5.

15 Addiss DG, Brady MA. Morbidity management in the Global Programme to Eliminate Lymphatic Filariasis: a review of the scientific literature. *Filaria J* 2007; **15**; 2.

16 Dandapat MC, Mohapatro SK, Mohanty SS. Filarial lymphoedema and elephantiasis of the lower limb; a review of 44 cases. *Br J Surg* 1986; **73**: 451–3.

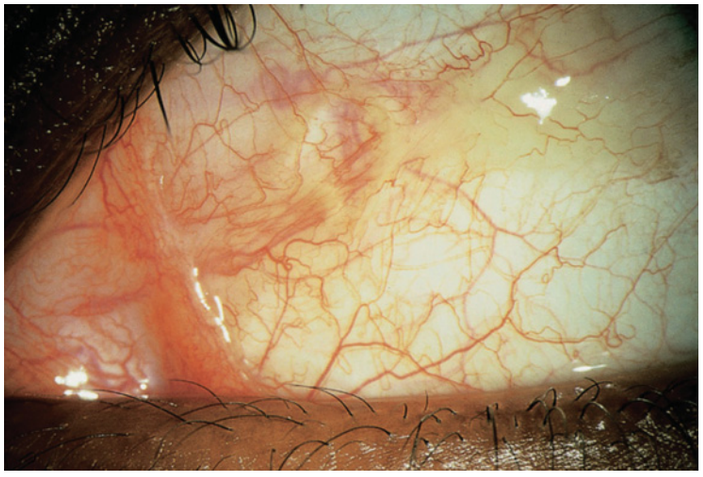


Fig. 37.12 *Loa loa*. Creamy white adult worm crossing the conjunctiva of a Nigerian patient.

Loiasis

Synonyms
- Calabar swellings
- Fugitive swellings
- Loa loa filariasis
- African eye worm

Aetiology [1,2]. Human loiasis is restricted to the damp forest areas of West and Central Africa from 8° north to 5° south of the Equator, from the Gulf of Guinea across to the Great Lakes. It is particularly prevalent in the Cameroons and on the Ogowe River. Its distribution includes the coastal plain, and follows the Zaire River 500 miles inland. It is also found in southern Sudan. *Loa loa*, the eye worm, is transmitted to humans by blood-sucking tabanid flies of the genus *Chrysops* (deer fly, horse fly and mangrove fly), which bite by day, principally *C. silacea* and *C. dimidiata*. Infection is transmitted by the fly from person to person, and hill houses built at the level of the forest canopy or in cleared plantations are especially susceptible sites for the acquisition of the disease.

Pathology and clinical features [1,3]. Larvae are liberated from *Chrysops* spp. when it presses the labella against the skin to take a blood meal. They then enter the tissues through the puncture made by the proboscis. About 1 year after infection of the host, adult worms may appear under the skin or in the conjunctiva, but microfilariae in the blood are not discoverable until 5 months later [4]. The parasite migrates in fascial planes, from which microfilariae are released and travel up lymphatics to the bloodstream to be lodged in the lungs. The adult makes frequent journeys through the skin connective tissues, and has often been seen on the fingers, trunk, scalp, lingual frenulum, loose penile skin, eyelids, beneath the conjunctiva and in the anterior chamber of the eye [5]. These migrations may cause a pricking, itching, creeping sensation or may be symptomless, although when the parasite appears in the conjunctiva, considerable irritation is usual. When the eye is involved, unilateral palpebral oedema may develop and the worm may be seen actually crossing the eye (Fig. 37.12).



Fig. 37.13 Calabar swelling of dorsum of left hand in a European patient with loaiasis. In this case no microfilariae were seen in the blood.

In certain patients, including expatriates who come to live in an endemic area, these wanderings cause temporary, shifting, oedematous swellings—Calabar swellings. These affect mainly the arm and hand (Fig. 37.13), although they may appear on any part of the body. They develop rapidly and may be painful or itchy, lasting for several days.

Allergic manifestations, such as eosinophilia and angio-oedema, are often more severe in visitors who originate from a non-endemic area. They have been correlated with high IgG and IgE levels, and increased lymphocyte blastogenesis to filarial antigens [6].

Adult worms may die and calcify. Additional complications reported in loiasis include encephalitis, meningitis and glomerulonephritis [7].

The life expectancy of adult worms is at least 4 years, and may be as much as 15 years. Cases in immigrants have been reported in Australia, Zimbabwe and in North America [5,8].

Diagnosis [3,4]. Clinical diagnosis, based on the presence of Calabar swellings, the sighting of adult worms and eosinophilia in a patient from an endemic area, is usually reliable. Microfilariae may be demonstrated in a sample of daytime blood as for *Bancroftian filariasis* (Fig. 37.14).

Filarial serology by immunofluorescence or ELISA is usually positive, but not genus specific. It is particularly helpful in patients without microfilaraemia.

Treatment. One course of treatment with diethylcarbamazine (DEC) is usually curative. Side effects are few and mild, although there may be an allergic reaction with one or more large Calabar swellings, fever, malaise, swelling of joints, joint pains



Fig. 37.14 Microfilaria of *Loa loa* stained with Giemsa on a micropore filter, after filtration of 10 mL blood taken at 12.00 hours. (Courtesy of Mr A.H. Moody, Hospital for Tropical Diseases, London, UK.)

and pruritus. There is a risk of encephalitis in heavy infections with headache, giddiness, vomiting, purpura and eosinophilia. Steroid therapy starting 1 day before DEC will prevent severe reactions as in onchocerciasis (see above) and is recommended for all microfilaraemic patients. After DEC therapy, elongated subcutaneous nodules, indicating the presence of adult worms, may appear [8].

Ivermectin also produces good responses in loiasis, and reduces microfilaraemia [9]. It is given in doses of 200 µg/kg. While it is generally well tolerated, adverse events, such as impaired conscious state and arthralgia, can be seen in those with high levels of microfilaraemia [10]. Ivermectin does not kill adult worms, however.

Adult worms can sometimes be removed from the conjunctiva surgically.

References

1 Takougang I, Meli J, Lamlenn S *et al*. Loiasis—a neglected and under-estimated affliction: endemicity, morbidity and perceptions in eastern Cameroon. *Ann Trop Med Parasitol* 2007; **101**: 151–60.

2 Davis BR. Filariasis. *Dermatol Clin* 1989; **7**: 313–21.

3 Churchill DR, Morris C, Fakoya A *et al*. Clinical and laboratory features of patients with loiasis (*Loa-loa* filariasis) in the UK. *J Infect* 1996; **33**: 103–9.

4 Fain A. Update; les problemes actuel de la loase. *Bull World Health Organ* 1978; **56**: 155–67.

5 Hubler WR, Gregory JF, Knox JM. Loiasis. *Arch Dermatol* 1973; **108**: 835–6.

6 Nutman TB, Reese W, Poindexter RW *et al*. Immunologic correlates of the hyperresponsive syndrome of loiasis. *J Infect Dis* 1988; **157**: 544–50.

7 Pillay VKG, Kirch E, Kurtzman NA. Glomerulopathy associated with filarial loiasis. *JAMA* 1973; **225**: 179–81.

8 De Silva DJ, Strouthidis NG, Tariq S, Davies N. An unusual cause of acute lid swelling. *Eye* 2006; **20**: 271–2.

9 Richard-Lenoble D, Komhla M, Rupp EA *et al*. Ivermectin in loiasis and concomitant *O. volvulus* and *M. perstans* infection. *Am J Trop Med Hyg* 1988; **39**: 480–3.

10 Pion SD, Filipe JA, Kamgno J *et al*. Microfilarial distribution of Loa loa in the human host: population dynamics and epidemiological implications. *Parasitology* 2006; **133**: 101–9.

Dracunculiasis

Synonyms
- Dracontiasis
- Guinea-worm
- Medina worm
- Dragon worm

Aetiology and epidemiology. Dracunculiasis is a chronic infection of humans due to the nematode, *Dracunculus medinensis* [1]. The disease occurs in India and West Africa as well as areas in East and Central Africa [2], Saudi Arabia, Yemen, Iran, Pakistan and the West Pacific. The disease was estimated to infect over 50 million people [3]. In some areas, it was particularly common: in Oyo state in Nigeria, for instance, it was found to infect 32% of a large survey population [4]. However, over the past 10 years there has been a highly successful campaign to eliminate this infestation, and the incidence of this disease has been reduced enormously to a few pockets of infection. This campaign organized through various different agencies and led by the Carter Foundation, Atlanta has been one of the success stories of tropical public health [3].

Pathology [5]. The adult female worm matures over a 1-year period in humans and discharges larvae through an ulcerated skin lesion. Millions of these larvae are produced, particularly on contact with water; these survive for 3–4 days and can develop further in copepods or water fleas (*Cyclops* spp. such as *C. leukarti*). After ingestion by the *Cyclops*, they pass through two developmental stages before reaching the infective third stage (L3) after 2 weeks. Humans are infected via drinking water containing infected *Cyclops* spp.; the larvae are released and penetrate the intestine. Further maturation occurs in the retroperitoneal space or other sites; mating occurs after about 3 months, and the males subsequently die. The females grow and migrate downwards, usually to the lower limbs. Aberrant migration can, however, occur [6]. The female penetrates the skin of the leg and can then discharge larvae after exposure to water. Each female contains 2–3 million larvae. Migration of the worm and larval forms is largely subclinical. Disease is associated with the presence of the adult female in subcutaneous tissue in the lower limbs.

Dracunculiasis is a disease found in poor rural populations. It can be spread in and around communal drinking or washing areas or wells.

Clinical features [1]. Immediately before the appearance of part of the adult female through the skin, there may be generalized symptoms such as fever, pruritus, urticaria and oedema [7]. Dyspnoea and diarrhoea may also occur. Usually, however, the first sign of the infection is the appearance of a small papule or vesicle, which expands and bursts over 4–5 days. When this occurs, commonly on the lower limb, there is intense localized itching. This is often followed by the emergence of part of the female worm through the skin (Fig. 37.15). The surrounding ulcer is covered with slough, which usually becomes secondarily infected. The worm itself is often palpable. Infections with two or more worms



Fig. 37.15 Guinea-worm. Adult female *Dracunculus medinensis* emerging from the skin of a Nigerian patient. (Courtesy of Dr R. Muller, CAB International Institute of Parasitology, St Albans, UK.)

may also occur. Eventually, the worms may be resorbed or calcify.

Secondary infection is very common, and may incapacitate the patient. It is a major cause of morbidity [7]. The common infecting organism is *Staphylococcus aureus*, but the open wound may also serve as a portal of entry for tetanus. Sometimes, *Dracunculus* may find its way into other sites [8], such as the knee joint, and cause intra-articular infection.

Diagnosis. The appearance of the worm under the skin is typical. However, the adult can be induced to shed larvae onto a glass slide, which can be examined microscopically, by applying water to the extruded segment. Worms may also calcify in tissue and can be visualized on X-ray [2]. There is usually an eosinophilia.

Treatment. The object of treatment is the removal of the worm. This is now facilitated by oral treatment with an oral benzimidazole, such as metronidazole or thiabendazole. After a few days, the inflammation lessens and it may be possible to extract the worm gently. It may be difficult to extract the worm if mebendazole is used [9]. The more traditional approach is to induce the worm to discharge larvae by applying water or ethyl chloride and to wind the free end around a matchstick. By gradually winding more and more of the worm onto the spool, the whole nematode can be recovered. It is important not to exert tension or the worm will break and cause severe allergic cellulitis. The procedure is therefore carried out slowly over a few days.

In addition, all cases should be treated with local antiseptics, tetanus toxoid and, if necessary, broad-spectrum antibiotics [7]. The drug treatment described above does not affect the larvae or prevent transmission. The latter is best accomplished by public health programmes designed to provide clean drinking water, by sieving or filtration to remove *Cyclops*. Chemical control of *Cyclops* using larvicides such as Temefos is also possible. Considerable progress has been made in the past decade in instituting effective public health measures for the control of dracunculiasis. Since 1986, the estimated prevalence has been reduced by 98% from an initial figure of 3.5 million [10].

References

1 Elgart ML. Onchocerciasis and dracunculosis. *Dermatol Clin* 1989; **7**: 323–30.
2 Watts SJ. Dracunculiasis in Africa in 1986. Its geographic extent, incidence and at-risk population. *Am J Trop Med Hyg* 1987; **37**: 119–25
3 Ruiz-Tiben E, Hopkins DR. Dracunculiasis (Guinea worm disease) eradication. *Adv Parasitol* 2006; **61**: 275–309.
4 Ilegdodu VA, Christensen BL, Wise RA *et al*. Age and sex differences in new and recurrent cases of guinea-worm disease in Nigeria. *Trans R Soc Trop Med Hyg* 1987; **81**: 674–6.
5 Muller R. Dracunculus and dracunculiasis. *Adv Parasitol* 1971; **9**: 73–91.
6 Pendse AK, Soni BM, Omprakash R *et al*. Testicular dracunculosis—a distinct clinical entity. *Br J Urol* 1982; **54**: 56–8.
7 Adeyeba OA. Secondary infections in dracunculiasis. Bacteria and morbidity. *Int J Zoonoses* 1985; **12**: 147–9.
8 Ramdas A. Chronic encysted guinea-worm lesion. *Ind Med Gaz* 1953; **88**: 391–2.
9 Chippaux JP. Mebendazole treatment of dracunculiasis. *Trans R Soc Trop Med Hyg* 1991; **85**: 280–2.
10 Barry M. The tail end of guinea worm—global eradication without a drug or a vaccine. *New Eng J Med* 2007; **356**: 2561–4.

Enterobiasis

Synonyms
- Threadworm
- Pinworm
- Seatworm
- Oxyuriasis

Aetiology. *Enterobius vermicularis* is the commonest human intestinal worm, with a worldwide distribution. It is more prevalent in cold climates, and is associated with crowding and poverty. Children are most commonly affected, and females more than males. Whole families and communities, notably schools, may be infected [1]. Male and female worms develop in the caecum, becoming mature 2–8 weeks after ingestion of fertile eggs. Gravid female worms migrate to the anus, and at night crawl on the perianal skin where they lay up to 16 000 eggs and expire. The eggs mature within a few hours. Transmission is by ingestion of eggs, most commonly carried by fingernails, because of the itching during sleep. Hands may also become contaminated through sharing a bed or bedroom. Occasionally, transmission is airborne from infected dust, in which eggs may survive for up to 13 days. Adult worms live for 6–12 weeks.

Pathogenesis. Gravid female worms migrating on the skin cause intense itching, although not in all infected people. It is not known whether an allergic reaction is involved. Adult worms may burrow

into the submucosa of the appendix or bowel and be associated with inflammation, although causation has not been clearly established. Female worms may migrate from the anus to the vagina, causing irritation and inflammation, and from there to the fallopian tubes or even peritoneal cavity, causing salpingitis and occasionally peritoneal nodules.

Clinical features. Anal and perineal pruritus at night, with sleeplessness and irritability, are the leading symptoms. Perineal intertrigo, nocturia, secondarily infected excoriations, localized urticaria [2], vulval irritation and mucoid discharge may occur [3]. Peritonitis and salpingitis [4,5] are described. It is important to realize, however, that a large number of infected children are asymptomatic.

Diagnosis. This may sometimes be made by seeing the 10-mm long female worms on the perineum at night, on toilet paper or in the stools. If possible, worms should be positively identified in a laboratory, to avoid confusion with proglotids of *Dipylidium caninum*. However, the best procedure is to wind a 6-cm strip of adhesive cellulose tape over the butt end of a test tube or a wooden spatula, sticky side outward. This is then rubbed over the perianal skin (preferably on waking) and the diagnostic eggs and adults stick to it. A drop of toluene is placed on a microscope slide and the tape is spread on it and examined microscopically.

Treatment. Of the several anthelminthic drugs available, mebendazole is probably the most effective, acting against all stages of the worm. In mass treatment campaigns, a single dose of 100-mg mebendazole cures over 90% of infections [6], but reinfection is common. More efficient is 100 mg twice daily for 3 days, repeated after 2 weeks. The whole family should be treated. In the interval, scrupulous attention should be paid to cleanliness of hands and nails on rising, after defecation and before eating. After each dosing, the bed linen is changed, and the bedroom vacuum cleaned. Even so, relapses may occur and periodic retreatment may be needed. Pyrvinium 5 mg/kg, piperazine 100 mg/kg and pyrantel pamoate 10 mg/kg are also effective.

References

1 Schaffner W. Die Bedeutung der Stabibfektion für die Oxyuriasis. *Munch Med Wochenschr* 1944; **32**: 411–4.

2 Clark RF. Localized urticaria due to *Enterobius vermicularis*. *Arch Dermatol* 1961; **84**: 1026–9.

3 O'Brien TJ. Paediatric vulvovaginitis. *Australas J Dermatol* 1995; **36**: 216–8.

4 Broadbent V. Children's worms. *BMJ* 1975; **i**: 89.

5 Pearson RD, Irons RP, Irons RP Jr. Chronic pelvic peritonitis due to the pinworm *Enterobius vermicularis*. *JAMA* 1981; **245**: 1340–1.

6 Brugmans JP, Thienpont DC, Van Wijngaarden I *et al*. Mebendazole in enterobiasis. Radiochemical and pilot clinical study in 1278 subjects. *JAMA* 1971; **217**: 313–5.

Ancylostomiasis

Synonym

- Hookworm disease

'Ground itch', 'dew itch' and 'uncinarial dermatitis' all describe a variable and transient eruption due to skin penetration by larvae of the hookworms *Ancylostoma duodenale* and *Necator americanus*, and the roundworm *Strongyloides stercoralis*.

Aetiology. *Necator americanus* and *A. duodenale* are human hookworms very widely distributed in the tropics and subtropics. *Necator americanus* predominates in Central and South Africa, southern Asia and Melanesia, and is almost the sole hookworm in the New World and Polynesia. It rivals malaria in the store of misery and ill health that it creates [1]. *Ancylostoma duodenale* is the only human hookworm in Europe, the Mediterranean coast, central and northern Asia, and is more prevalent than *Necator* spp. in China, Japan and some parts of Indonesia.

Pathogenesis. The adult worms live in the jejunum with the head firmly attached to the mucosa and cause bleeding: *Necator americanus* 0.03 mL of blood per worm per day and *A. duodenale* 0.2 mL of blood per worm per day. They live for up to 5 years [2]. Bleeding leads to anaemia, hypoproteinaemia, digestive disturbances and retarded development [3]. Thousands of eggs are passed in the faeces. Eggs can survive varying periods of cold or drought, but under favourable conditions of warmth and humidity, hatch into motile rhabditiform larvae. After 5 days and further moults, the infective filariform larvae form. They migrate upwards through soil and grass and, after a period of contact of 5–10 min, can penetrate intact human skin. Walking barefoot is the commonest way of getting infected. Favourable places for transmission include soil around houses, places of work such as plantations and cultivated fields, and mines. Exceptionally, transmission occurs in England during a long hot summer, in playgrounds or picnic sites and formerly in mines where temperatures remain above 20°C [4].

After penetrating the skin, larvae migrate within a day or two via the bloodstream to the lungs, pass up the bronchial tree, are swallowed and pass down the oesophagus, reaching the duodenum and jejunum, where they mature in 4–6 weeks. In passing through the lungs they cause acute alveolitis or pneumonitis.

Clinical features. Larvae penetrating the skin cause ground itch: severe pruritus accompanied by erythema and often a papular or papulovesicular rash [5]. The rash is most commonly on the feet, and may be accompanied by a generalized urticaria. The rash is more common with *Necator* infections, and may become secondarily infected as a result of scratching. Larvae passing through the lungs cause a syndrome of cough, wheeze and dyspnoea, which lasts for several days. Adult worms in the gut cause abdominal pain, diarrhoea and, occasionally, melaena. Later, features of iron-deficiency anaemia, with haemoglobin levels as low as 5 g/dL, and hypoproteinaemia develop with pallor, oedema, puffy face and listlessness. Changes in the texture of skin and hair resemble those seen in kwashiorkor [6].

Diagnosis. Clinical and circumstantial evidence point to a diagnosis of ground itch. Löeffler's syndrome is characterized by eosinophilia and patchy pneumonitis seen radiologically. Established infections are diagnosed by demonstrating characteristic eggs in the faeces.

Treatment. Ground itch is treated symptomatically with an antipruritic cream, such as crotamiton with 1% hydrocortisone, or oral antihistamines. Pulmonary symptoms, if severe, respond to a few days' corticosteroids. Established infections respond to a 3-day course of albendazole or mebendazole or pyrantel pamoate [7]. Where ivermectin is used in community programmes with albendazole, it has also reduced the frequency of infections significantly. Oral iron is given for iron deficiency.

References

1 Keumer A, Bundy D. Seventy five years of solicitude. *Nature* 1989; **337**: 114–5.
2 Rochet M, Leyrisse M. The nature and causes of 'hookworm anaemia'. *Am J Trop Med Hyg* 1966; **15**: 1030–2.
3 Borrero J, Restrepo A, Betro D *et al*. Clinical and laboratory studies on hookworm disease in Colombia. *Am J Trop Med Hyg* 1961; **10**: 735–8.
4 Buckley JJC, Pester FRN. Hookworm infections acquired in Britain. *BMJ* 1965; **ii**: 106–7.
5 Chaudhry AZ, Longworth DL. Cutaneous manifestations of intestinal helminthic infections. *Dermatol Clin* 1989; **7**: 275–90.
6 Gilles HM, Williams EJW, Ball PAJ. Hookworm infection and anaemia. *Q Rev Med* 1964; **33**: 1–24.
7 Reddy M, Gill SS, Kalkar SR *et al*. Oral drug therapy for multiple neglected tropical diseases: a systematic review. *JAMA* 2007; **298**: 1911–24.

Strongyloidiasis

Synonyms
- Strongyloidal ground itch
- Larva currens

Strongyloides stercoralis is a widespread, parasitic roundworm with a life cycle and distribution similar to that of the hookworm, but with important differences [1]. It occurs in warm, especially damp, climates and is especially prevalent in South-East Asia.

Aetiology. Adult male and female worms, 3 mm long, live in the mucosal crypts of the duodenum and jejunum; eggs hatch quickly and rhabditiform larvae are passed in the faeces. In soil, they may either moult into infective filariform larvae, or set up a free-living cycle, with the production of more infective larvae. Infective larvae penetrate human skin, to establish new infections or augment existing ones. Alternatively, larvae mature in the gut and reinfect the patient by penetrating the mucosa or the perianal skin. This autoinfection is capable of maintaining the infection indefinitely, and predisposes to the syndrome of hyperinfection, in which extremely heavy worm loads build up and leave the confines of the gut, in patients who are immunosuppressed by corticosteroid drugs or Hodgkin's disease, or debilitated by advanced age, tuberculosis or other severe infection, ketoacidosis or burns [2].

Pathology [3]. Penetration of the skin by filariform larvae may cause dermatitis. Adult worms give rise to duodenitis and jejunitis, which may cause diarrhoea and malabsorption. Migrating larvae in the skin give rise to a weal-and-flare response, which follows the path of the larva. Hyperinfection causes severe enteritis with fluid loss, and paralytic ileus, pneumonia, meningoencephalitis and secondary Gram-negative bacterial septicaemia with shock and disseminated intravascular coagulation.



Fig. 37.16 Larva currens rash of *Strongyloides stercoralis*. The weal and flare will have disappeared in a few hours.

Clinical features. Ground itch of initial infection is similar to that seen in hookworm disease. Intestinal infection causes abdominal pain, diarrhoea and, if severe, weight loss or stunting of growth in children [4]. Associated allergic phenomena are common. Urticaria occurs in 66% of cases of strongyloidiasis among patients who have had the infection for over 45 years [5]: IgE levels are raised. Thirty per cent of these individuals also suffer from larva currens, the urticarial weal and flare of migrating subcutaneous larvae. Tracks are seen anywhere on the skin between knees and nipples (Fig. 37.16), but especially around the anus and buttocks. They move at a rate of several centimetres an hour and can traverse the abdomen in a single day, to be gone the next day: features that distinguish the rash from that of larva migrans (see below). Tracks may be several centimetres long or consist simply of one or more urticarial papules. Tracks may be linear or serpiginous but the rash may be less distinctive, mimicking a drug eruption [6].

Heavy infection causes severe diarrhoea, with fluid and electrolyte loss; signs of ileus may develop. Fever, abdominal distension, cough, dyspnoea, mental changes and unconsciousness may develop, and the patient may become shocked. Shock commonly indicates a complicating Gram-negative septicaemia. Cough, dyspnoea and chest signs suggest pneumonia. A widespread petechial or purpuric rash may be seen [7]. Strongyloides infections have also been associated with immune reconstitution syndrome in HIV-positive patients where increased generalized symptoms and pruritus were triggered by antiretroviral therapy [8].

Diagnosis [9]. Larvae of *Strongyloides* spp. are demonstrated in the faeces, by one of several concentration or culture techniques. Diagnostic yield is increased by examining samples of jejunal juice, most conveniently obtained by a 'string test' (Enterotest capsule) or jejunal biopsy. In a few centres, a strongyloides antibody test is available. Except in the hyperinfection syndrome, eosinophilia is common and tests for malabsorption may be positive.

Treatment. Ivermectin in a single oral dose of 200 µg/kg body weight, to be repeated on day 7, is also effective. For cases of

hyperinfection, ivermectin is given daily until symptoms resolve. Until recently, thiabendazole had been the drug of choice, given in a dose of 25 mg/kg body weight orally twice daily for 3 days, and repeated after 2 and 4 weeks. Side effects are common, and include headache, malaise, nausea and vomiting. Albendazole is also effective in a dose of 400 mg/day for 3 days, and is free of toxicity. Faecal and jejunal samples should be examined for larvae after 3 and 6 months.

References

1 Segarra-Newnham M. Manifestations, diagnosis, and treatment of *Strongyloides stercoralis* infection. *Ann Pharmacother* 2007; **41**: 1992–2001.
2 Igra-Siegman Y, Kapila R, Sen P *et al*. Syndrome of hyperinfection with *Strongyloides stercoralis*. *Rev Infect Dis* 1981; **3**: 397–407.
3 Neva FA. Biology and immunology of human strongyloidiasis. *J Infect Dis* 1986; **153**: 397–406.
4 Burke JA. Strongyloidiasis in childhood. *Am J Dis Child* 1978; **132**: 1130–6.
5 Gill GV, Bell DR. *Strongyloides stercoralis* infection in former Far East prisoners of war. *BMJ* 1979; **ii**: 572–4.
6 Ly MN, Bethel SL, Usmani AS *et al*. Cutaneous *Strongyloides stercoralis* infection: an unusual presentation. *J Am Acad Dermatol* 2003; **49**: S157–60.
7 von Kuster LC, Genta RM. Cutaneous manifestations of strongyloidiasis. *Arch Dermatol* 1988; **124**: 1826–30.
8 Lanzafame M, Faggian F, Lattuada E *et al*. Strongyloidiasis in an HIV-1-infected patient after highly active antiretroviral therapy-induced immune restoration. *J Infect Dis* 2005; **191**: 1027.
9 Pelletier LL, Baker CB, Gamm AA *et al*. Diagnosis and evaluation of chronic strongyloidiasis in ex-prisoners of war. *J Infect Dis* 1988; **157**: 573–6.

Infection with nematodes of other animals

Nematodes that do not normally parasitize humans are often unable to mature or develop fully, or to home to their normal site in the body. Biologically, the human is a dead-end host. The infective larvae tend to wander, causing one of several forms of larva migrans, or the adult worm migrates, causing migratory allergic phenomena. Worms reach unusual sites and give rise to eosinophilic granulomas, occasionally in important sites, such as the eye, causing blindness, or the lungs, causing radiological confusion. In other infections, full development may take place and humans act as accidental intermediate hosts.

Cutaneous larva migrans

Synonyms
- Creeping eruption
- Sand-worm eruption
- Plumber's itch
- Duckhunter's itch

Cutaneous larva migrans in a clinical term for a distinctive cutaneous eruption that has numerous causes. The prime features, as the name suggests, are that the lesions creep or migrate, and that they are due to the presence of moving parasites in the skin. Visceral larva migrans also occurs (see below).

Aetiology [1]. Causes of creeping eruption include *Ancylostoma brasiliense*, *A. caninum*, *A. ceylonicum*, *Uncinaria stenocephala* and *Bubostomum phlebotomum*. These are all hookworms of various animals, of which the first, the dog hookworm, is the commonest cause of creeping eruption in humans. *Anatrichosoma cutaneum*, a parasite of monkeys in the Far East, is a rare cause. *Strongyloides stercoralis* causes a distinctive form of cutaneous larva migrans. *Dirofilaria repens* and *Spirometra* spp. cause a subcutaneous granuloma that may migrate very slowly. *Gnathostoma* spp. and *Loa loa* cause migratory evanescent subcutaneous swellings. Cutaneous myiasis due to larvae of flies of the genera *Gasterophilus* and *Hypoderma* may cause a creeping eruption similar to that caused by the animal hookworms. Only the helminths that cause creeping eruption are considered further here.

Adult hookworms live in the intestines of dogs and cats, and their ova are deposited in the animals' faeces. Under favourable conditions of humidity and temperature, the ova hatch into infective larvae, which will penetrate human skin. Sandy, warm, moist, shaded areas are particularly favourable, and numerous infections are acquired by children in sandpits, plumbers under houses, farm-workers under outbuildings, hunters in hides, gardeners from the soil and seabathers from the sandy shore above the ebb and flow of the tides. The condition is common in all warm climates, and may occur in northern Europe during a hot summer. Outbreaks in groups of holiday makers who mostly acquired the condition by direct skin contact with infested sand while on tropical beach holidays have been described [2].

Clinical [3]. The larvae may cause a non-specific dermatitis at the site of penetration where the skin has been in contact with infected soil. This is commonly the feet, hands and buttocks. They can then lie quiet for weeks or months, or immediately begin creeping activity with the production of a wandering thread-like line about 3 mm wide. This is exceedingly itchy, slightly raised, flesh-coloured or pink, and forms bizarre, serpentine patterns. Large numbers of larvae may be active at the same time, with the formation of a disorganized series of loops and tortuous tracks (Fig. 37.17).

The larvae advance at a rate of a few millimetres to a few centimetres daily, and are somewhat in front of the head of the track. The wanderings of an individual larva are usually confined to a relatively small area, but exceptionally it travels much further. Itching leads to scratching and secondary changes of dermatitis and bacterial infection. In later stages, these tracks are difficult to see, the path being marked by small itchy and discontinuous nodules.

The disease is self-limiting. Estimates for the natural duration of the disease vary considerably. This variation almost certainly depends on the species of larva observed, and this is usually unknown. In one study, 25–33% of larvae died every 4 weeks, whereas in another (presumed due to *Ancylostoma brasiliense*) 81% of lesions disappeared in 4 weeks [4]. Some persist for many months.

Larva migrans can be accompanied by Löeffler's syndrome of pulmonary eosinophilia, particularly in severe infestations [5].

Diagnosis. The classic clinical picture of wandering, advancing, serpentine and itchy lesions is easily recognized, but may be atypical, hidden by vesicles and scaling, or spoiled by scratching and secondary infection.



Fig. 37.17 Cutaneous larva migrans (creeping eruption). There are several tortuous, indurated, inflamed worm tracks, in some of which may be seen a blister that marks the head of the track.

Larva currens and migratory myiasis must be distinguished and, in the Orient, gnathostomiasis.

Biopsy in larva migrans is of little value, as the larvae have advanced beyond the clinical lesions.

Treatment. Ivermectin in a single dose of 200 µg/kg body weight is the main treatment [6]. Albendazole 400 mg/day by mouth for 3 days is also effective, although in some cases the responses are poor. An alternative choice of treatment is the topical application of 10% thiabendazole. Either the commercially available oral preparation may be used directly [7], or two 0.5-g tablets of thiabendazole are ground and mixed in 10-g petrolatum and applied twice daily. Well over 95% of the tracks clear within a week. Oral thiabendazole is less effective and more toxic.

References

1 Beaver PC, Jung RC, Cupp EW, eds. *Clinical Parasitology*. Philadelphia: Lea and Febiger, 1984: 281–3.

2 Blackwell V, Vega-Lopez F. Cutaneous larva migrans. Clinical features and management of 44 cases presenting in the returned traveller. *Br J Dermatol* 2001; **145**: 434–7.

3 Jelinek T, Maiwald H, Nothdurft HD, Loscher T. Cutaneous larva migrans in travelers. Synopsis of histories, symptoms, and treatment of 98 patients. *Clin Infect Dis* 1994; **19**: 1062–6.

4 Katz R, Ziegler J, Blank H. The natural course of creeping eruption and treatment with thiabendazole. *Arch Dermatol* 1975; **91**: 420–4.

5 Wright DO, Gold EM. Löeffler's syndrome associated with creeping eruption (cutaneous helminthiasis). *Arch Intern Med* 1946; **75**: 303–12.

6 Dourmishev AL, Dourmishev LA, Schwartz RA. Ivermectin: pharmacology and application in dermatology. *Int J Dermatol* 2005; **44**: 981–8.

7 Davis CM, Israel RM. Treatment of creeping eruption with topical thiabendazole. *Arch Dermatol* 1968; **97**: 325–6.

Visceral larva migrans: toxocariasis

Many non-human and human helminths may be found migrating in human organs at some stage of their life cycle, but the syndrome of visceral larva migrans is synonymous with the severe form of toxocariasis.

Aetiology. This infection is caused by *Toxocara canis*, *T. cati* and *T. malayensis*, the common roundworms of dogs, cats and wild carnivores. The domestic dog is thought to be the most important source of human infection, and the prevalence of infection in dogs may be high, reaching 73% in New York State and 100% in puppies in Brisbane [1]. Infection is intense in puppies because of transplacental infection, which is augmented by infection from breast milk and contaminated bed litter [2]. Eggs are passed in dog faeces. Humans are most commonly infected by ingesting eggs in soil, or in contaminated food or water. Children are especially at risk when playing in parks or other areas frequented by dogs, or from domestic puppies that have not been regularly wormed. Ova remain infective on soil for many months.

The incidence of human infections is not finally established, but skin tests on apparently healthy subjects suggest that at least 2% of the general population of the UK acquire the infection [2]. The incidence is higher in those in close contact with animals, especially under primitive living conditions. Of a rural population in Pennsylvania, 54% were infected [3].

Pathogenesis. In humans, the second-stage larvae migrate from the intestine to most parts of the body, but notably to liver, lungs, muscles and brain where they eventually die in eosinophilic granulomas.

Clinical features. Most human infections are asymptomatic, or at least unrecognized. Persistent eosinophilia is, however, probably invariably present [4]; counts of over 25×10^9/L are common. In a proportion of infected children, the full syndrome of visceral larva migrans develops. The essential features, apart from eosinophilia, are cough and dyspnoea, failure to gain weight, muscle pains and sometimes fever. The liver is enlarged. Hyperglobulinaemia is frequent. The syndrome is self-limiting after a few months if reinfection is prevented.

Since so many cases are undiagnosed, the incidence of cutaneous manifestations is unknown. Generalized pruritus and urticarial or papular eruptions of the trunk and legs are most frequently reported. Migrating panniculitis, although rarely reported, is distinctive and perhaps pathognomonic: substantial, tender, subcutaneous nodules vanish after 1 or 2 weeks [3,5].

In a minority of infected individuals, who have never experienced visceral larva migrans, a wandering larva causes an ocular granuloma simulating a neoplasm [6].

Diagnosis. This is reliably confirmed by biopsy of the liver or of a cutaneous nodule. Fluorescent antibody and ELISA techniques are helpful [7]. Molecular methods also show promise in distinguishing between the main pathogens [8].

Treatment. Treatment responses are often unsatisfactory. Albendazole may prove to be the best treatment [9]; in the case of ocular infection, vitrectomy is often combined with medical treatment. Cure rates are low with diethylcarbamazine or thiabendazole.

References

1 Despommier D. Toxocariasis: clinical aspects, epidemiology, medical ecology, and molecular aspects. *Clin Microbiol Rev* 2003; **16**: 265–72.
2 Woodruff AW. Toxocariasis. *BMJ* 1970; **ii**: 663–4.
3 Rook A, Staughton R. The cutaneous manifestations of toxocariasis. *Dermatologica* 1972; **144**: 129–43.
4 Beaver PC. Toxocariasis (visceral larva migrans) in relation to tropical eosinophilia. *Bull Soc Pathol Exot* 1962; **55**: 555–76.
5 Heiner DC, Kevy SV. Visceral larva migrans. Report of the syndrome in three siblings. *N Engl J Med* 1956; **254**: 629–36.
6 Shields JA. Ocular toxocariasis: a review. *Surv Ophthalmol* 1984; **28**: 361–81.
7 Glickman LT, Schantz P, Dombroske R *et al*. Evaluation of serological tests for visceral larva migrans. *Am J Trop Med Hyg* 1978; **27**: 492–8.
8 Li MW, Lin RQ, Chen HH *et al*. PCR tools for the verification of the specific identity of ascaridoid nematodes from dogs and cats. *Mol Cell Probes* 2007; **21**: 349–54.
9 Bhatia V, Sarin SK. Hepatic visceral larva migrans. Evolution of the lesion, diagnosis, and role of high-dose albendazole therapy. *Am J Gastroenterol* 1994; **89**: 624–7.

Gnathostomiasis

Gnathostomiasis is an infection caused by *Gnathostoma spinigerum*, *G. hispidium* and *G. nipponicum*, the definitive host of which are cats, wild felines, dogs and certain other animals that eat fish, snakes and frogs [1]. Human gnathostomiasis occurs throughout South-East Asia, east of and including Bangladesh, China, Japan, Indonesia and the Philippines. The greatest number of cases is in Thailand. There are also reports from Mexico [1].

Aetiology. Adult worms live in the stomach of the carnivore. Eggs are passed in the faeces, hatch in water and are ingested by a species of *Cyclops*, in which they transform further. When *Cyclops* is ingested by frogs, snakes or fish the larvae develop to the third stage in the flesh of the animals, which in turn are eaten by the definitive host, thus completing the cycle. Humans are infected either by ingesting *Cyclops* in water or by eating inadequately cooked flesh of an intermediate host. Worms removed from a person are most commonly third-stage larvae or immature adults, which measure 2–4 mm long and are rust brown in colour due to ingested blood. The head of the worm is crowned by 4–8 rows of hooklets (Fig. 37.18) and the anterior half of the body is covered in leaf-like spines. Rarely, a mature male worm, up to 12 mm long, has been found [2].

Pathogenesis. Larvae ingested by humans wander, mainly in subcutaneous tissues and muscles, causing deep tunnels, which form the sites of episodes of inflammation or abscess formation. Histology shows intense infiltration with neutrophils, plasma cells, chronic inflammatory cells and especially eosinophils. Less common sites of infection include the brain and eye.

Clinical features. The commonest presentation is of intermittent, migratory, subcutaneous swellings, several centimetres in diameter. They are firm, warm, red, painful and last up to 4 weeks, before disappearing and returning nearby. They occur most commonly on the upper parts of the body, including the orbit. Abscesses may develop subcutaneously or in muscle [3].

Fatal encephalomyelitis has also been described [4]. Isolated swellings may simulate inflammatory or neoplastic disease of other internal organs.

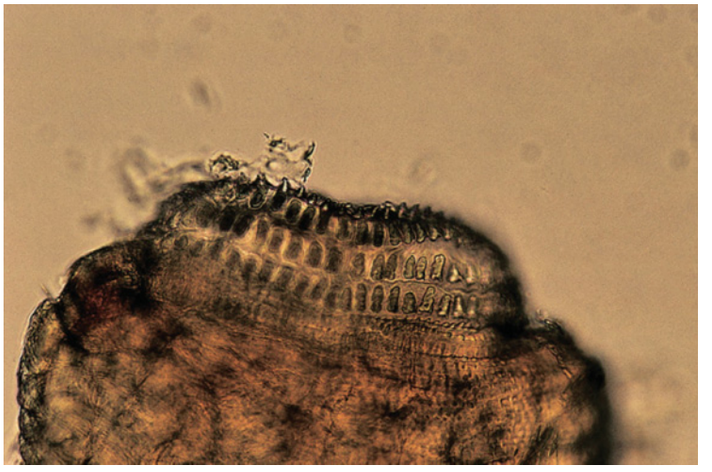


Fig. 37.18 *Gnathostoma spinigerum*. Head of adult worm that was extruded from a subcutaneous swelling in a patient from Bangladesh. The crown of hooklets is characteristic. (Courtesy of Dr P.L. Chiodini, Hospital for Tropical Diseases, London, UK.)

Diagnosis. Geographical history, clinical features and a peripheral eosinophilia suggest the diagnosis, which is confirmed by surgical extraction of the worm. Occasionally, a worm is expelled through the skin. A reliable serological test is available through some specialist centres.

Differential diagnosis. Other nematodes that may cause similar clinical pictures include *Lagochilascaris minor*, a cause of subcutaneous abscesses in Surinam and Central America, *Thelazia callipaeda*, which parasitizes the conjunctival sac in the Far East, and *Gongylonema pulchrum*, a cosmopolitan parasite of pigs, bears, hedgehogs and monkeys that causes migratory lesions in the oropharyngeal submucosa of humans [5].

Treatment. Albendazole in a dose of 400 mg/day for 21 days or ivermectin 200 µg/kg single dose are effective [6]. Other anthelmintics have not proven useful. Worms may be removed surgically. Treatment of worms of the face is important, to prevent ocular involvement [7].

References

1 Ligon BL. Gnathostomiasis: a review of a previously localized zoonosis now crossing numerous geographical boundaries. *Semin Pediatr Infect Dis* 2005; **16**: 137–43.
2 Radomyos P, Daengsvang S. A brief report on *Gnathostoma spinigerum* specimens obtained from human cases. *Southeast Asian J Trop Med Public Health* 1987; **18**: 215–7.
3 Rusnak JM, Lucey DR. Clinical gnathostomiasis. Case report and review of the English-language literature. *Clin Infect Dis* 1993; **16**: 33–50.
4 Bunang T, Comer DS, Punyagupta S. Eosinophilic myeloencephalitis caused by *Gnathostoma spinigerum*. Neuropathology of nine cases. *J Neurol Sci* 1970; **10**: 419–34.

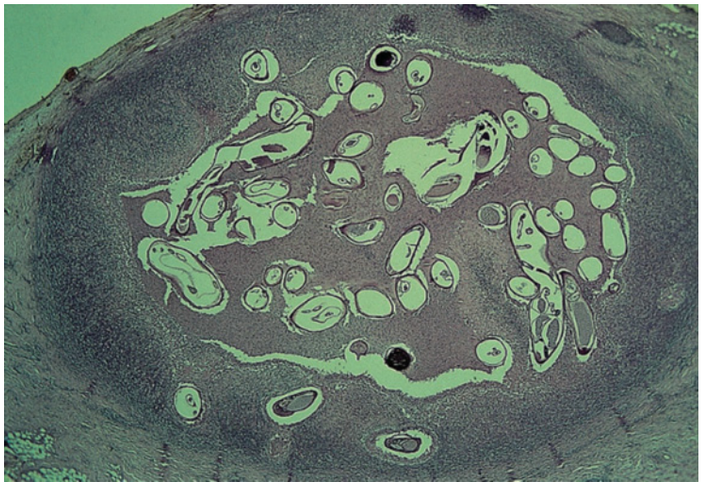


Fig. 37.19 Dirofilariasis. Low-power view of cold abscess from the cheek. It shows degenerate coiled *Dirofilaria* worm within an abscess, and surrounding lymphocytic infiltrate and fibrosis. (Courtesy of Professor S.B. Lucas, King's College, London, UK.)

5 Nash TE. Visceral larva migrans and other unusual helminth infections. In: Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas and Bennett's Principles and Practice of Infectious Disease*, 5th edn. Edinburgh: Churchill Livingstone, 2000: 2965–70.

6 Nontasut P, Bussaratid V, Chullawichit S *et al*. Comparison of ivermectin and albendazole treatment of gnathostomiasis. *Southeast Asian J Trop Med Pub Health* 2000; **31**: 374–9.

7 Bathrick ME, Mango CA, Mueller JF. Intraocular gnathostomiasis. *Ophthalmology* 1981; **88**: 1293–5.

Dirofilariasis

Aetiology. Dirofilariasis is an infection by filarial nematodes of the genus *Dirofilaria*. There are two forms of the disease:

1 Subcutaneous dirofilariasis caused by *D. tenuis* (*D. conjunctivae*), *D. ursi*, *D. subdermata* and *D. repens*
2 Pulmonary dirofilariasis caused by *D. immitis*, the dog heart worm.

Dirofilaria ursi and the related *D. subdermata* are natural parasites of bears and porcupines, respectively.

Subcutaneous dirofilariasis

Geographical distribution and life cycle. Most cases are reported from the southern USA, but there are occasional reports from Africa, Asia and South America. *Dirofilaria repens* is a subcutaneous parasite of dogs and cats and *D. tenuis* of raccoons in the USA. Transmission to humans is thought to be by mosquitoes.

Clinical features [1–3]. The lesion is usually a tender, occasionally migratory, subcutaneous nodule which develops over a few weeks. Common sites are eyelid, scrotum, breast, arm and leg. The worm may also be seen in the conjunctiva and is present within a foreign-body granulomatous reaction in the nodule (Fig. 37.19). Microfilariae are not found in the blood.

Diagnosis and treatment [4]. This is made by extracting the worm from the lesion, or by identifying it in an excised specimen. Treatment is by surgical removal.

References

1 Beaver PC, Orihel TC. Human infection with filariae of animals in the United States. *Am J Trop Med Hyg* 1965; **14**: 1010–29.

2 Beaver PC, Wolfson JS, Waldron MA *et al*. *Dirofilaria ursi* like parasites acquired by humans in the northern United States and Canada: report of two cases and brief review. *Am J Trop Med Hyg* 1987; **37**: 357–62.

3 Payan HM. Human infection with *Dirofilaria*. *Arch Dermatol* 1978; **114**: 593–4.

4 Guitierrez Y. Diagnostic features of zoonotic filariae in tissue sections. *Hum Pathol* 1984; **15**: 514–25.

Trichinosis

Synonyms
- Trichiniasis
- Trichinelliasis

Trichinosis is an infection of intestine and muscle, with *Trichinella spiralis*, a natural parasite of a wide range of carnivores. The human is normally an end host. A variety of allergic phenomena characterize human infection. Trichinosis is distributed worldwide. It is an important disease both in Europe and in the USA and has been found in Africa, south of the Sahara.

Aetiology. Encysted larvae of *Trichinella spiralis* are ingested in meat, hatch in the duodenum, penetrate the submucosa, and within 5 days have matured and mated and started producing 200–2000 invasive larvae, which reach muscles where they become encysted and infective to a fresh host within 21 days. The adult worms live less than 2 months. Cysts may calcify, but the larvae remain viable for many years and can outlive their dead host by 10 days [1].

Humans acquire the disease by eating raw or undercooked meat infected by *Trichinella spiralis*— such as bush pig in Africa, polar and black bear meat in Alaska and the Arctic. Entire polar expeditions have died of the infection after eating polar bear.

Pathogenesis. Intestinal infection causes partial villous atrophy and mucosal and submucosal inflammation. The deposition of larvae in muscles is associated with oedema, loss of cross-striations and basophilic degeneration (Fig. 37.20). The coiled larvae are surrounded by an inflammatory infiltrate of lymphocytes and macrophages until they become encapsulated.

Clinical features [2,3]. The disease may be symptomless or mild, but generally, after a moderate infection with the 'muscle worms', severe symptoms resembling acute food poisoning ensue rapidly. These are followed within a week by an acute illness with fever, generalized muscle pain and tenderness, sweating, periorbital oedema, conjunctivitis, some paralysis of the muscles of the tongue, jaw and respiration, with a transient maculopapular rash of the extremities, and splinter haemorrhages beneath the nails.

In severe infections, there is involvement of the heart and central nervous system (CNS). A necrotizing vasculopathy equivalent to classic polyarteritis nodosa is described [4].

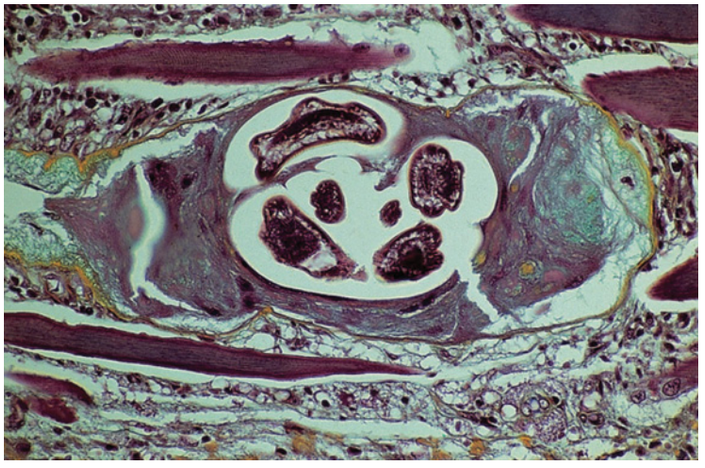


Fig. 37.20 Trichinosis. Medium-power view, Movat stain, showing *Trichinella* worm within a 'nurse cell' in skeletal muscle. There is surrounding oedema, muscle disruption and lymphocytic infiltrate. (Courtesy of Professor S.B. Lucas, King's College, London, UK.)

Diagnosis. Within a week of eating inadequately cooked meat, especially pork, clinical features suggest the diagnosis. Worms may be found in faeces in the second to fourth week of the infection, and after 4 weeks in biopsied muscle. The eosinophil count, erythrocyte sedimentation rate and serum creatine phosphokinase are all raised. After 3 weeks, antibodies become detectable. Bentonite flocculation and ELISA [5] are the tests most commonly used.

Treatment. Corticosteroids are life saving in suppressing allergic reaction at the height of larval spread. Mebendazole and thiabendazole reduce the severity of infection if given early enough in the acute disease, but albendazole is possibly more effective [6,7]. However, once the parasites are encysted in muscle antiparasitics are ineffective.

References

1 Acha PN, Szyfres B. *Zoonoses and Communicable Diseases Common to Man and Animals, Vol. 3, Parasitoses*. Washington DC: Pan American Health Organization, 2003.

2 Oppenheim JM, Whims CB, Frisch AW. Trichinosis. Clinical and laboratory observations in a group of 256 cases. *Mil Surg* 1947; **101**: 294–6.

3 Schmitt N, Browner EJ, Simon PC *et al*. Trichinosis from bear meat and adulterated pork: a major outbreak in British Colombia. *Can Med Assoc J* 1972; **107**: 1087–9.

4 Frayha RA. Trichinosis-related polyarteritis nodosa. *Am J Med* 1981; **71**: 307–12.

5 Van Knappen F, Franchimont JH, Verdonk AR *et al*. Detection of specific immunoglobulins (IgG, IgM, IgA, IgE) and total IgE levels in human trichinosis by means of the enzyme-linked immunosorbent assay (ELISA). *Am J Trop Med Hyg* 1982; **31**: 937–46.

6 Clausen MR, Meyer CN, Krantz C *et al*. *Trichinella* infection and clinical diseases. *Q J Med* 1996; **89**: 631–6.

7 Watt G, Silachamroon U. Areas of uncertainty in the management of human trichinellosis: a clinical perspective. *Expert Rev Anti Infect Ther* 2004; **2**: 649–52.

Infection with trematodes

Synonyms
- Flukes
- Flatworms

Trematodes are non-segmented, single-sex worms, flattened like a leaf and without a formal organ of attachment. Pairs of adult worms live in a hollow viscus (vein, gut, bile duct, lung), from whence eggs make their way into faeces, urine or sputum. The eggs must enter water, hatch and infect a species of snail, in which a cycle of development and multiplication occurs, resulting in the release of motile cercariae. These either penetrate human skin or enter a resting stage in aquatic plants, fish or crustacea, and are later eaten. Trematodes are important and common parasites of humans, especially in Africa and the Far East. They cause skin disease either as a result of cercarial penetration, by the ectopic deposition of adult worms or their eggs, or by causing allergic phenomena.

Schistosomiasis

Synonym
- Bilharziasis

Schistosomiasis or bilharziasis is a serious systemic disease due to different species of human schistosomes or blood flukes [1]. Rashes may occur during the invasive stage of this disease, when the skin is being penetrated by cercariae, and later there may be skin involvement at or near mucocutaneous surfaces, and less commonly at more distant sites on the trunk, following dissemination of ova.

A second group of non-human schistosomes cause cutaneous symptoms only. This situation follows penetration of cercariae into the skin, but further development of the flukes in humans is arrested and there are no sequelae. The condition 'swimmer's itch' or cercarial dermatitis is an example of this process.

Skin manifestations of this common disease of tropical and subtropical distribution are incidental features of the underlying disease. They may be grouped as follows [2]:

1 Schistosomal dermatitis
2 Urticarial reactions in the early weeks of the disease
3 Paragenital granulomas and fistulous tracts
4 Ectopic cutaneous schistosomiasis.

Ectopic sites of egg deposition probably arise through migration of adults via the paravertebral venous plexus.

Aetiology [3]. Schistosomiasis is caused by the human blood flukes *Schistosoma mansoni*, *S. japonicum* and *S. haematobium*. Two other species, *S. mekongi* and *S. intercalatum*, are more rarely associated with infection in humans.

Humans infected with *S. mansoni* and *S. japonicum* excrete eggs in the faeces, and with *S. haematobium* excrete eggs in the urine. On contact with water, these eggs develop into miracidia, which undergo further development in certain aquatic snails. From these, free-swimming cercariae are released, which are capable of

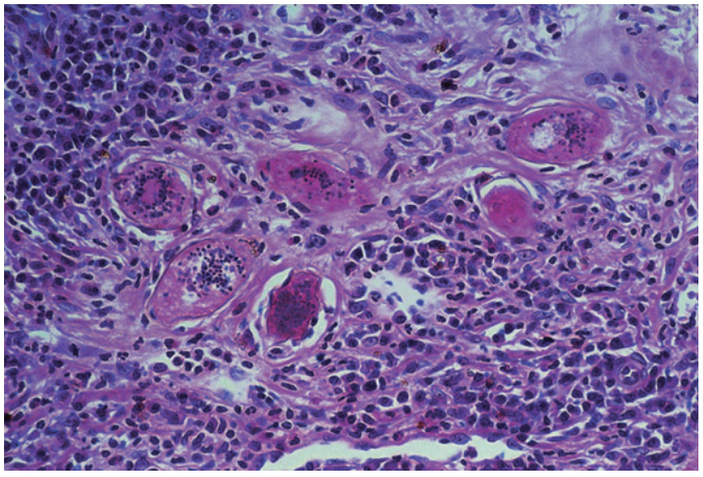


Fig. 37.21 Schistosomiasis of the vulva (medium power, H&E) showing six schistosome eggs with surrounding lymphoplasmocytic infiltration. (Courtesy of Professor S.B. Lucas, King's College, London, UK.)



Fig. 37.22 Schistosomiasis of the vulva and anus. Condylomatous lesions containing granulomas around schistosome ova. (Courtesy of Professor G. Nelson, Liverpool School of Tropical Medicine, Liverpool, UK.)

penetrating human skin to produce the infection [4]. The organisms can pass rapidly through the epidermis, and enter the venous blood within 24 h of contact with human skin. The larvae are then carried through the heart and lungs, and mature into flukes in the intrahepatic portion of the portal system.

Finally, the mature flukes pass from the portal system into pelvic veins, where eggs are laid. *Schistosoma mansoni* and *S. japonicum* localize primarily in the veins around the rectum and colon, while *S. haematobium* invades vesical and, sometimes, rectal veins with the production of haematuria and other urinary symptoms. Ova work their way out of the veins into the tissues, where they cause the formation of granulomas in which there is a pseudotubercle arrangement of inflammatory cells rich in eosinophils and histiocytes, and occasional giant cells, surrounding the diagnostic ova [5]. Lesions occurring away from the characteristic sites of egg deposition are termed 'ectopic' (Fig. 37.21). Disease due to the commonest agent, *S. mansoni*, is endemic in Africa and South America (especially the Nile delta and North-East Brazil). *Schistosoma japonicum* occurs in the Far East, and *S. haematobium* extensively in Africa (especially in the Nile and Rift Valleys), Arabia, Malagasy and South-West India [6].

High prevalence rates in workers immigrant to temperate climates [1,7], outbreaks among foreign personnel employed in endemic areas and occasional case reports of the disease in individuals who have left those areas, reflect the frequency with which infections such as schistosomiasis are encountered outside their endemic area. Infections may also be seen in short-term visitors to an endemic zone, particularly if they have swum in an infected lake or river.

Clinical features. Skin involvement may occur either as a result of the initial penetration of the skin by water-borne, free-living cercariae (an intermediate stage in the life cycle), during an immune-complex-mediated phase of the infection, Katayama fever [8], or in the later stages of infection following ectopic localization of worms or ova [9].

1 *Schistosomal dermatitis.* Penetration by cercariae of parts of the epidermis in contact with water may pass unnoticed, or cause an itchy papular eruption indistinguishable from swimmer's itch (cercarial dermatitis due to non-human flukes). The symptoms of itching usually last only for a few hours after leaving the water, although mild erythema may persist for longer. In sensitized individuals, however, papules and itching persist for about a week [2].
2 *Urticarial reactions.* Four to eight weeks after penetration of the skin by cercariae, urticaria may occur. This is particularly severe in *S. japonicum* infection, together with fever, purpura, malaise, arthralgia, abdominal cramps, diarrhoea and enlargement of liver and spleen. In some areas, for example China and Japan, this feature is so prominent that the disease is called 'urticarial fever' or Katayama disease. Eosinophilia is also typical. The symptoms resolve in about 4–6 weeks.
3 *Paragenital granulomas and fistulous tracts.* In areas of high endemicity, cutaneous bilharziasis of the perineum and external genital regions is not uncommon [10,11]. This follows direct spread of adult flukes to adjacent vasculature. Granulomatous genital condylomas occur, and fistulous tracts with extensive firm masses, honeycombed by sinuses, are characteristically found on the perineum, groins or buttocks (Fig. 37.22).

Ectopic cutaneous schistosomiasis [12–14]. Ova may become deposited in the skin as well as in other ectopic sites, such as conjunctiva, lungs and CNS. They arise following embolism of ova from adults, which are localized in abnormal sites, such as the paravertebral plexus [2]. The trunk is almost invariably the site of ectopic cutaneous involvement. The primary lesion is a flesh-coloured, firm papule reaching a size of 2–3 mm, and ovoid in shape. These papules agglomerate to form slightly raised plaques with irregular contours. Later still, some plaques develop a surface protuberance, and deepen in colour but retain their irregular, ovoid contours. The skin over old nodules may be deeply pigmented and scaly, and may later ulcerate. The para-umbilical area



Fig. 37.23 *Schistosoma haematobium* ovum in urine. (Courtesy of Mr A.H. Moody, Hospital for Tropical Diseases, London, UK.)

is a common site [12] but other areas may be involved (Fig. 37.22) and, in some cases, the lesions have a segmental or zosteriform distribution [7,14]. With treatment, these lesions slowly disappear in about 5 months. A facial hypopigmented plaque is described.

The major complications of schistosomiasis are due to infections affecting the liver (fibrosis), intestinal involvement and bladder infection, which may lead to carcinoma of the bladder. Other sites of involvement include the kidneys, heart, CNS and retina [4].

Diagnosis. The characteristic ova may be found in stools or urine (Fig. 37.23). On occasions, rectal biopsy is an alternative method of finding ova. The latter have a characteristic morphology. Serological methods are useful for screening. Immunofluorescence and ELISA are commonly used. Ectopic cutaneous schistosomiasis is diagnosed by biopsy. Histology shows epithelioid cell granulomas containing degenerate ova (Fig. 37.21).

Treatment. Praziquantel is given as a single dose of 20 mg/kg twice in 1 day, except in infections due to *S. japonicum*, where 20 mg/kg three times in 1 day is administered [15]. Cure rates are high with this regimen, and there are few side effects such as abdominal discomfort and headache. However, there are increasing reports of treatment failures and resistance has been recorded in laboratory testing [16]. Other drugs that are available include metrifonate for *S. haematobium* and oxamniquinine for *S. mansoni*. In early infections, the results of therapy are excellent, although reinfection is a continuing risk. Cercarial dermatitis resolves spontaneously. However, many of the complications of the infection such as hepatic fibrosis, portal hypertension and ureteric stenosis are irreversible, due to scar formation.

References

1 Mahmoud AAF, ed. Schistosomiasis. In: Mahmoud AAF, ed. *Clinical Tropical Medicine and Communicable Diseases*. London: Baillière Tindall, 1987: 1–32.

2 Gonzalez E. Schistosomiasis, cercarial dermatitis and marine dermatitis. *Dermatol Clin* 1989; **7**: 291–300.

3 Sturrock RF. Biology and ecology of human schistosomes. In: Mahmoud AAF, ed. *Clinical Tropical Medicine and Communicable Diseases*. London: Baillière Tindall, 1987: 249–66.

4 Davis A. Recent advances in schistosomiasis. *Q J Med* 1986; **58**: 95–110.

5 Warren KS, Domingo EO, Cowan RBT. Granuloma formation around schistosome eggs as a manifestation of delayed hypersensitivity. *Am J Pathol* 1967; **51**: 735–81.

6 WHO. *Atlas of the Global Distribution of Schistosomiasis*. Geneva: World Health Organization Parasitic Diseases Programme, 1987.

7 Milligan A, Burns DA. Ectopic cutaneous schistosomiasis and schistosomal ocular inflammatory disease. *Br J Dermatol* 1988; **119**: 793–8.

8 Colley DG, Savage AM, Lewis FA. Host responses induced and elicited by cercariae, schistosomata and cercarial antigen preparations. *Am J Trop Med Hyg* 1977; **26** (Suppl.): 88–91.

9 Torres VM. Dermatological manifestations of *Schistosomiasis mansoni*. *Arch Dermatol* 1976; **112**: 1539–42.

10 Adeyemi-Doro FAB, Osoba AO, Junaid TA. Perigenital cutaneous schistosomiasis. *Br J Vener Dis* 1979; **55**: 446–9.

11 Davis-Reed L, Theis JH. Cutaneous schistosomiasis: report of a case and review of the literature. *J Am Acad Dermatol* 2000; **42**: 678–80.

12 MacDonald DM, Morrison DA. Cutaneous ectopic schistosomiasis. *BMJ* 1976; **2**: 619–20.

13 Farrell AM, Woodrow D, Bryceson AD *et al*. Ectopic cutaneous schistosomiasis: extragenital involvement with progressive upward spread. *Br J Dermatol* 1996; **135**: 110–2.

14 Obasi OE. Cutaneous schistosomiasis in Nigeria. An update. *Br J Dermatol* 1986; **114**: 597–602.

15 Mahmoud AAF. Praziquantel for the treatment of helminthic infections. In: Stollerman GH, ed. *Advances in Internal Medicine*, Vol. 32. Chicago: Year Book, 1987: 419–34.

16 Caffrey CR. Chemotherapy of schistosomiasis: present and future. *Curr Opin Chem Biol* 2007; **11**: 433–9.

Cercarial dermatitis

Cercarial dermatitis is the name given to a group of skin disorders having a common aetiology—penetration of the skin by free-living cercarial stages of non-human schistosomes [1]. There are a number of local names for these conditions, such as swimmer's itch, clam digger's itch, sedge pool itch, koganbyo and sawah itch. While the clinical features of the condition are similar whatever the aetiology, there are three main types of cercarial dermatitis.

1 *Fresh-water avian cercarial dermatitis* [2,3]. This follows penetration of the skin by cercariae of avian blood flukes. The intermediate hosts are fresh-water molluscs. The flukes belong to the genera *Trichobilharzia*, *Gigantobilharzia* and *Ornithobilharzia*. The condition has been described from many different parts of the world including North America, particularly the lakes region of the USA, Canada, Europe, Africa and the Far East [2,4]. In some countries, it affects patients with particular occupations such as rice farmers working in the paddyfields.

2 *Sea-water avian cercarial dermatitis* [5]. This follows invasion of the skin by blood flukes whose definitive hosts are sea birds. While it is recorded less frequently than infections caused by fresh-water species, it accounts for the condition, seen in the Atlantic seaboard of the USA, known as clam-digger's itch. The intermediate hosts are marine molluscs. The term 'sea bather's eruption' is used to describe a variety of different rashes that may develop after sea bathing. It is likely that it includes a number of different conditions from jellyfish dermatitis to eruptions due to toxic algae. A sea water form of cercarial dermatitis is therefore one cause of sea bather's eruption [1].

3 *Fresh-water mammalian cercarial dermatitis* [4]. This has been reported mainly from the Far East, and the definitive hosts for the schistosomes in this condition are mammals such as water buffaloes.

Attempts to find common features connecting the likely locations for cercarial infections have not been entirely successful. It is apparent, however, that areas endemic for cercarial dermatitis usually have abundant, submerged vegetation harbouring the intermediate hosts. Hot spells of weather have also been associated with a higher risk of the development of symptoms [6].

Pathogenesis. The pathogenesis of cercarial dermatitis is not completely understood, although the kinetics of the clinical response suggest that sensitization is involved. The first phase of epidermal penetration is accompanied by dermal oedema, which is followed by a brisk neutrophil reaction.

Clinical features. Most forms of cercarial dermatitis have common features, although their intensity varies between different individuals [2]. The first sign of an infection is the development of a tingling sensation after contact with water. This lasts for about 1 h and there may be a fine macular erythema. After 10–15 h, there is usually a second phase with the appearance of multiple itchy papules with surrounding erythema. These may evolve into vesicles or oedematous lesions. The whole reaction takes about a week to resolve. The papules closely resemble small insect bites. There are no long-term sequelae.

Treatment. Treatment is entirely symptomatic. Although brisk rubbing with a dry towel seems sensible advice, there is no evidence that it prevents the second phase of responses [1]. Patients can be treated with antihistamines or topical applications such as crotamiton. Preventative measures are seldom called for as infections tend to be sporadic. Control of vegetation in endemic areas or of the snail population are possibilities, but seldom practised unless the more serious problem of schistosomiasis is also present.

References

1 Baird JK, Wear DJ. Cercarial dermatitis. The swimmer's itch. *Clin Dermatol* 1987; **5**: 88–91.
2 Hoeffler DF. Swimmer's itch. *Cutis* 1977; **19**: 461–7.
3 Rao VG, Dash AP, Agrawal MC *et al*. Cercarial dermatitis in central India: an emerging health problem among tribal communities. *Ann Trop Med Parasitol* 2007; **101**: 409–11.
4 Knight R, Worms NJ. An outbreak of cercarial dermatitis in Britain. *Trans R Soc Trop Med Hyg* 1972; **66**: 21–4.
5 Hutton RF. *Schistosome cercariae* as a probable cause of sea bather's eruption. *Bull Mar Sci Gulf Coast* 1952; **2**: 346–8.
6 Bernhardt MJ, Mandojana RM. Sea bathers eruption. *Clin Dermatol* 1987; **5**: 101–2.

Paragonimiasis

Infections caused by the lung fluke, *Paragonimus westermani*, are found in the Far East, West Pacific and in parts of India and Central Africa [1]. Similar species, *P. africanus* and *P. peruviana*, cause disease in the Cameroons and Central and South America, respectively [2]. In China, two rare species, *P. szechuanensis* and *P. hueitungensis*, have been recorded as causes of migratory subcutaneous nodules in humans. The adult worms are found in the respiratory tract, from which eggs are coughed up and swallowed, thus entering the faeces. Miracidia are released on contact with water and seek and penetrate snails. These in turn are the first intermediate hosts, and liberate cercaria, which then enter the muscles of fresh-water crustaceans such as crayfish. Human infection results from ingestion of inadequately cooked crabs and crayfish. Ingested metacercaria penetrate the intestinal wall and make their way through the diaphragm to the lungs. Adult worms encyst in the lungs (Fig. 37.24) and cause a chronic cough with fever and sweats. Brown-stained sputum is characteristic. Flukes may also reach ectopic sites such as the peritoneum, brain or skin.

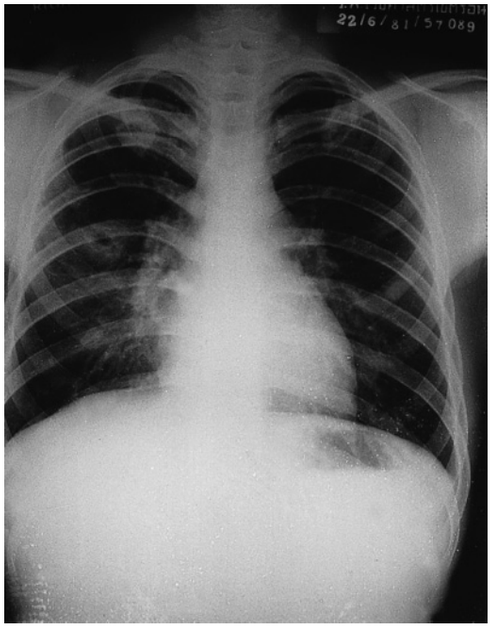


Fig. 37.24 Paragonimiasis. Chest X-ray showing three discrete opacities, in two of which cavitation is present, characteristic of the disease in Thailand. (Courtesy of Professor D.A. Warrell, Oxford Radcliffe Hospital, Oxford, UK.)

Skin lesions of paragonimiasis are large, mobile subcutaneous lesions, which develop into cold abscesses [3]. They can occur at any site including the conjunctiva, and may enlarge rapidly to reach a diameter of 10 cm or more. The larger lesions are often painful but they may rupture spontaneously.

The diagnosis can be confirmed by demonstrating the characteristic ova in sputum or in aspirates from cutaneous lesions.

This infection responds well to praziquantel in a dose of 25 mg/kg three times in a single day [4].

References

1 Blair D, Xu ZB, Agatsuma T. Paragonimiasis and the genus Paragonimus. *Adv Parasitol* 1999; **42**: 113–222.
2 Sogandares-Bernal F, Seed JR. American paragonimiasis. *Curr Top Comp Pathobiol* 1973; **2**: 1–56.
3 Dainichi T, Nakahara T, Moroi Y *et al*. A case of cutaneous paragonimiasis with pleural effusion. *Int J Dermatol* 2003; **42**: 699–702.
4 Sabrio P, Lanzas R, Arrieta G, Arguedas A. *Paragonimus mexicanus* pericarditis. Report of two cases and review of the literature. *J Trop Med Hyg* 1995; **98**: 316–8.

Infection with cestodes

Synonym
- Tapeworms

Tapeworms are flat, ribbon-like worms composed of a variable number of segments called proglottids. The anterior segment or scolex comprises the head, which carries hooks or suckers for attachment to the intestinal mucosa, and a narrow neck from which the proglottids develop. As the hermaphroditic proglottids mature, they become motile sacs full of eggs, which separate from the worm and pass in the faeces or wriggle through the anus. Adult tapeworms inhabit the intestinal lumen of a wide range of natural hosts. Eggs are taken up by an intermediate host and undergo often complex larval development; in some species, there may be two or more intermediate hosts, each supporting a different phase of larval development. The human is a natural host to certain tapeworms, and may be an accidental host to others. Generally speaking, infection with adult worms causes little or no disease, but infection with the larval stages may be serious [1].

Tapeworms that infect humans may be divided into two orders, Cyclophyllidea and Pseudophyllidea, within each of which certain species may cause skin disease.

Cyclophyllidea

Echinococcus granulosus and E. multilocularis. Tapeworms, respectively, of dogs and foxes. Larval stages cause echinococcosis, or hydatid disease in humans.

Taenia saginata. The beef tapeworm of humans. Causes taeniasis. No skin parasitization.

Taenia solium. The pork tapeworm of humans. Causes (i) taeniasis; and (ii) cysticercosis.

Multiceps multiceps. A tapeworm of dogs and wolves. Its larval stage (coenurus) may parasitize human brain and other organs [2].

Multiceps serialis. A tapeworm of dogs, wolves and foxes, whose larval stages may parasitize human muscle or subcutaneous tissue [3].

Multiceps brauni. A tapeworm of dogs whose coenurus may parasitize subcutaneous tissue and the eye in humans [2,4,5].

Pseudophyllidea

Spirometra spp. Tapeworms of carnivores. The larval forms (spargana) cause sparganosis in humans.

Diphyllobothrium latum. The fish tapeworm of humans. Causes diphyllobothriasis.

Echinococcosis

Synonym
- Hydatid disease

Two species in the genus *Echinococcus* parasitize humans with the formation of hydatids, namely *E. granulosus* and *E. multilocularis* [6]. Adult *E. granulosus* lives in the intestine of the dog and, if ova are accidentally swallowed by humans or other animals, hydatid cysts develop. Sheep are the commonest intermediate hosts. Similarly, adult *E. multilocularis* lives in the bowel of red fox and arctic fox. Mice, voles and lemmings are the intermediate hosts.

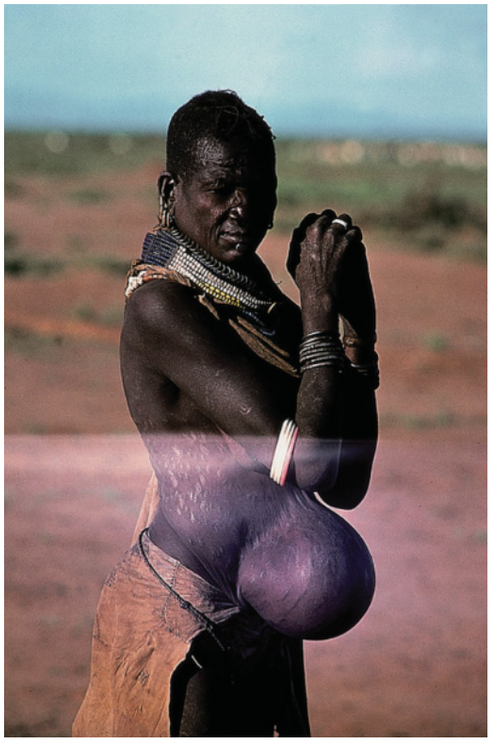


Fig. 37.25 Hydatid disease. Subcutaneous hydatid cyst presenting as a hernia, in a woman from Turkana, Kenya. (Courtesy of Dr C.N.L. MacPherson, Liverpool School of Tropical Medicine, Liverpool, UK.)

Pathogenesis. Humans become infected by ingesting eggs in food or water that has been contaminated by, usually, dog faeces. In endemic countries, especially those where sheep rearing is not accompanied by strict regulations, children's hands readily pick up the eggs from the coats of dogs. Eggs hatch in gastric acid and penetrate the wall of the duodenum, and are distributed via the bloodstream, mainly to liver and lungs, but bones and any other organ may also be infected. The larvae develop into fluid-filled cysts whose germinal layer produces numerous protoscolices, capable of becoming the scolices of adult worms after ingestion by the definitive host.

Cysts of *E. granulosus* tend to grow slowly and bud inwards, producing daughter cysts. Those of *E. multilocularis* may bud outwards, and thus spread through the tissues like a cancer.

Clinical features. The commonest manifestation is an enlarged liver. Leakage of antigenic fluid from the cyst may cause wheeze, urticaria and eosinophilia. Rupture of the cyst may cause local signs and anaphylaxis. Hydatid cysts (Fig. 37.25) may be palpable in muscle or subcutaneous tissues as firm, painless swellings, often up to the size of an orange. They may be fluctuant. The overlying skin is normal.

Diagnosis. Clinical diagnosis is aided by X-ray or computed tomography (CT) examination of the lungs and sonographic ultrasound of the liver.

Excision of a subcutaneous cyst is conclusive. Great care must be taken not to spill any cyst fluid, which may give rise to further cysts. Complement fixation and ELISA are useful serological tests.

Treatment. This is essentially surgical. Formalin 2% or silver nitrate 0.5% should be used as a scolicidal adjunct [7]. Albendazole [8] is used in conservative management.

References

1 Smyth JD, Heath DD. Pathogenesis of larval cestodes in mammals. *Helm Abstract* 1970; **39**: 1–23.
2 Templeton AC. Anatomical and geographical location of human coenurus infection. *Trop Geogr Med* 1971; **23**: 105–8.
3 Oriel TC, Gonzalez F, Beaver PC. Coenurus from neck of Texas woman. *Am J Trop Med Hyg* 1970; **19**: 255–7.
4 Williams PH, Templeton AC. Infection of the eye by tapeworm coenurus. *Br J Ophthalmol* 1971; **55**: 766–9.
5 Wilson VCLC, Wayte DM, Addae RO. Human coenurosis—the first reported case from Ghana. *Trans R Soc Trop Med Hyg* 1972; **66**: 611–7.
6 WHO. *Bull World Health Organ* 1968; **39**: 1–136.
7 Saidi F, Nazarian I. Surgical treatment of hydatid cysts by freezing of cyst wall and instillation of 0.5% silver nitrate solution. *N Engl J Med* 1971; **284**: 1346–50.
8 Horton RF. Chemotherapy of *Echinococcus* infection in man with albendazole. *Trans R Soc Trop Med Hyg* 1989; **33**: 97–102.

Cysticercosis

Synonym
- Larval taeniasis

Aetiology. *Taenia solium*, the pork tapeworm, is responsible for producing human intestinal infection with the tapeworm (taeniasis), and the lodging of the larval stage (*Cysticercus cellulosae*) in numerous organs, especially subcutaneous tissue, muscle and brain, with the production of the disease cysticercosis.

In taeniasis, the adult *T. solium* lives attached to the wall of the small intestine and may reach a length of 7 m. Inadequately heated or frozen pork is the sole source of human infection with the adult worm, but humans and other primates may harbour the cysticercus stage.

Human infections with *Cysticercus cellulosae* are due to: ingestion of eggs in contaminated food or drink; eggs from an individual's own intestinal infection being introduced into the mouth on dirty hands; or internal autoinfection as a result of vomiting—eggs must be digested in gastric acid.

Taenia solium is an important human parasite with a wide, although shrinking, distribution. It is most frequent in Eastern Europe, China, Manchuria, Pakistan, India, Mexico and Central and South America. Its prevalence depends upon insanitary human faeces disposal and the eating of undercooked pork.

Pathology. The cysticerci are found most frequently in subcutaneous tissue and muscle, but may occur in any organ of the body, especially the brain. The growing cyst provokes a non-specific inflammatory reaction, which may be followed by fibrosis and eventual calcification.

Clinical features. Adult worms in the intestine cause little or no reaction, although the passing of writhing fragments is distressing. The cysticerci form nodules in subcutaneous tissue muscles (rarely with widespread muscular enlargement), eye [1], eyelid [2], lungs and brain and other organs, which may seriously interfere with function depending on their position. Major exacerbation of symptoms, such as epilepsy or intracranial obstruction, coincides with death of the larvae. The disease in the skin is known as cysticercosis cellulosae cutis, and the subcutaneous nodules formed are 1–2 cm in diameter (Fig. 37.26). They are rubbery and firm, rounded and painless and may remain unchanged for many years. Their numbers vary from one to hundreds, and when the diagnosis is entertained, search must be made for other lesions.



Fig. 37.26 Cysticercosis in a man from North India. A subcutaneous cyst is seen over the sternum. (Courtesy of Dr A.P. Hall, Hospital for Tropical Diseases, London, UK.)

Diagnosis. *Taeniasis*: eggs in the stool cannot be differentiated morphologically from those of *T. saginata*, but examination of gravid proglottids allows exact identification. *Cysticercosis*: the histology of an excised cyst is diagnostic. Serology is helpful, but cross-reactions occur with hydatid disease.

X-ray examination frequently shows calcification in muscle (Fig. 37.27), although rarely in brain. CT shows typical appearances in brain and muscle.

Treatment. Subcutaneous cysticerci are important only in as much as they point to the possibility of more serious cerebral infection, which should be looked for. Individual subcutaneous cysts may be removed surgically if desired. Cerebral disease is treated with praziquantel 25 mg/kg daily for 10 days, under steroid cover. Adult tapeworms are treated with praziquantel in a dose of 10 mg/kg once. Obstructive lesions of the brain require surgical relief.

Prognosis is good in taeniasis, but in cysticercosis it is serious when vital organs are involved.

References

1 Keane JR. Neuro-ophthalmic signs and symptoms of cysticercosis. *Arch Ophthalmol* 1982; **100**: 1445–8.
2 Jampol LM, Caldwell BH, Albert DM. Cysticercus cellulosae in the eyelid. *Arch Dermatol* 1973; **89**: 319–20.



Fig. 37.27 Calcified cysticercal cysts in muscles of thighs and pelvis.

Sparganosis

Sparganosis is a tissue infection with plerocercoid larvae or spargana of a number of species of pseudophyllidean tapeworms of the genus *Spirometra*. Patric Manson described the first case, in Amoy China in 1882. The Greek word sparganon means swaddling clothes, and describes the slender, ribbon-like character of the larval worm. The infection is common throughout Asia, especially the Far East, but also occurs in Australia, the Americas and southern Europe.

Aetiology. Adult spirometra parasitize the gut of canines and felines. Eggs passed into water develop into procercoid larvae in copepod hosts of the genera *Diaptomus* and *Cyclops*. These are eaten by frogs, lizards, snakes, birds and some mammals, including mice and monkeys, in which the plerocercoid larvae develop, in muscle sheaths. Humans are infected either by the application of raw flesh to the skin or eye, usually as a medicinal poultice, or through eating uncooked flesh or drinking water containing infected copepods.

Pathogenesis and clinical features [1]. Ingestion sparganosis occurs a variable time after eating infected flesh, or drinking infected copepods. The larvae penetrate the intestine and develop into spargana, particularly in subcutaneous tissues and muscle. The invaded areas become oedematous and form painful lumps, in the centres of which the white, ribbon-like spargana move. Their death results in very intense inflammation with destruction of tissue and massive eosinophilia [2]. Clinically, the lesions can assume a more nodular consistency with an insidious onset; they may last for several years and can also migrate. Localized elephantiasis also results due to lymphatic invasion.

Application sparganosis. The spargana migrate into the inflamed part causing an immediate, severe local pruritus. Subsequently, signs of sparganosis may be very hard to differentiate from those of the primary inflammation for which the flesh poultice was applied. Redness, pain and swelling increase in severity over a few days or very few weeks, and the worms become localized in small nodules surrounded by pus (Fig. 37.28). Ocular sparganosis frequently results in panophthalmitis and loss of the globe.



(a)



(b)

Fig. 37.28 (a) Fibrous, encapsulated, cold abscess from the groin, which contained (b) a 22-cm long sparganum. (Courtesy of Professor S.B. Lucas, King's College London, UK.)

Sparganum proliferum. This is a rare form in which the sparganum branches and divides, producing thousands of mainly subcutaneous spargana, which form subcutaneous nodules and itchy papules [3]. There may be a severe systemic illness with fever and eosinophilia.

Diagnosis. This is made from the history and by recovery of spargana after incision.

Treatment. This is by surgical removal and drainage.

References

1 Norman SH, Kreutner A Jr. Sparganosis. Clinical and pathologic observations in ten cases. *South Med J* 1980; **73**: 297–300.
2 Taylor RL. Sparganosis in the United States. Report of a case. *Am J Clin Pathol* 1976; **66**: 560–4.
3 Beaver PC, Rolon FA. Proliferating larval cestode in a man in Paraguay. A case report and review. *Am J Trop Med Hyg* 1981; **30**: 625–37.

Infection with protozoa

Of the protozoa that give rise to skin disease or may cause changes in the skin indirectly, only *Leishmania* are natural parasites of the skin, in the sense that part of their life cycle must be spent in it. Even so, humans are often simply an accidental host in a zoonotic infection. *Entamoeba histolytica* may occasionally invade the skin, usually as an extension of an existing visceral lesion. Free-living amoebae, of the genus *Acanthamoeba*, may cause a primary lesion in skin, eye or ear, before invading the brain [1]. *Trypanosoma*, of the species that infect humans in Africa and America, may cause florid chancres soon after inoculation, but thereafter cause rashes indirectly. *Toxoplasma* causes an exanthem as part of the secondary stage of the infection, and *Trichomonas*, a mucosal parasite, causes inflammation of skin adjacent to the infected mucosa. Cutaneous manifestations of malaria, due to several species of *Plasmodium*, are simply a reflection of the severity of the systemic infection, or of drug toxicity.

Malaria

Malaria is caused by parasites of the genus *Plasmodium*, and is transmitted to humans by the bites of numerous species of mosquito belonging to the genus *Anopheles*. It causes a febrile systemic illness, which may be fatal in expatriates and in children in endemic areas in the tropics, and is a major cause of chronic ill health [2].

The mosquito bite can give rise to considerable skin reaction, and the disease itself to numerous cutaneous manifestations. In the early cold stage of benign tertian malaria (*P. vivax*) there is vasoconstriction and gooseflesh; in the hot stage, flushing of the face and to a less extent other parts of the skin, and in the sweating stage, very profuse sweating. These manifestations are common to all diseases characterized by rigors caused by release of endotoxin or 'endotoxin-like' substances. Malaria commonly causes jaundice, and the skin in Europeans and Asians may have a curious grey or greenish hue. In severe malaria, there may be bleeding from the gums or gastrointestinal tract, and conjunctival petechiae may be seen, but cutaneous petechiae are rare. Herpes simplex and, occasionally, herpes zoster may develop.

Several of the drugs used in treatment of chemoprophylaxis cause skin problems. Chloroquine causes pruritus, especially in black people's skins, often severe enough to arrest treatment [3]. It responds to antihistamines, although the cause is unknown and there is never a rash. Various skin eruptions may occur, and psoriasis may be aggravated. Fansidar contains pyrimethamine and sulfadoxine. Epidermal necrolysis and Stevens–Johnson syndrome occur, sometimes fatally [4]. Quinine may cause rashes, notably toxic erythema and urticaria.

References

1 Martinez AJ. Acanthamoebiasis and immunosuppression. A case report. *J Neuropathol Exp Neurol* 1982; **41**: 548–57.
2 Bruce-Chwatt LJ. In: Gilles H, Warrell DA, eds. *Bruce-Chwatt's Essential Malariology*, 3rd edn. London: Heinemann, 1993.
3 Sowunmi A, Walker O, Salako LA. Pruritus and antimalarial drugs in Africans. *Lancet* 1989; **ii**: 213.
4 Miller KD, Lobel HO, Satriale RF *et al*. Severe cutaneous reactions among American travellers using pyrimethamine–sulfadoxine (Fansidar) for malaria prophylaxis. *Am J Trop Med Hyg* 1986; **35**: 451–8.

Amoebiasis

Amoebiasis due to *Entamoeba histolytica* is arguably the third most important human parasitic infection, after malaria and schistosomiasis, being especially prevalent in South-East Asia and Central America, but the organism is found in all warm and temperate parts of the world where hygiene is inadequate [1,2].

Aetiology. *Entamoeba histolytica* inhabits the lumen of the human caecum, colon and rectum. Free-living trophozoites 10–60 μm in diameter, encyst and divide. Cysts passed in the faeces may survive up to 30 days, depending upon conditions of humidity and temperature, and survive chlorination. They are transmitted in contaminated water or food, especially salads, or by hands or flies, or by male homosexual intercourse. Ingested cysts that survive gastric acid complete the cycle. Isoenzyme electrophoretic analysis of cultured isolates suggest that pathogenic and non-pathogenic strains (zymodemes) of *E. histolytica* exist, but these cannot be distinguished morphologically [3].

Pathogenesis. Trophozoites of a pathogenic zymodeme may, under conditions that have not been determined, invade the mucosa of the large bowel, causing amoebic dysentery [4]. Amoebae that escape the bowel into the bloodstream may set up metastatic lesions, which develop into abscesses, most commonly in the liver. Cutaneous amoebiasis (Fig. 37.29) [5] develops when invasive amoebiasis escapes from the bowel to contiguous skin, usually around the anus or a colostomy, or after appendicectomy, or when amoebae are implanted in another mucosa, most commonly the vagina, cervix uteri or glans penis, and rarely in the mouth. Rupture or surgical intervention of an amoebic abscess is a less common source of cutaneous infection. Amoebae lyse the skin and subcutaneous tissues and mucosae involved, producing necrosis and gangrenous sloughing. *Entamoeba histolytica* is one of the most powerful organisms in terms of its lytic capacity, and this is mediated through amoebapores following the binding to the host's tissue in a lectin-like manner [6].

Clinical features [5,7]. Commonly, one or more lesions appear at the anus or on the buttocks and spread as sloughing, coalescing ulcers [8] (Fig. 37.30). The course of the disease varies from less than 2 weeks to as long as 2 years, the more rapid and destructive lesions tending to occur in the young. The skin lesion itself is not diagnostic and is either a deeply invading ulcer or an ulcerated granuloma (amoeboma). It is usually seen as a serpiginous ulcer with distinct, raised, thickened, often undermined, edges and with an erythematous rim about 2 cm wide, haemopurulent exudate and necrotic slough. It is intensely painful. Regional adenitis is usual.

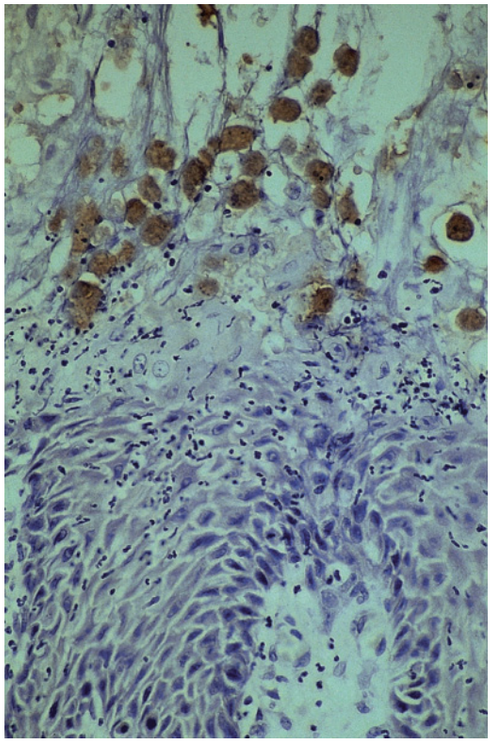


Fig. 37.29 Cutaneous amoebiasis. High-power view of skin biopsy, showing *Entamoeba histolytica* trophozoites on the epidermis, causing necrosis. The amoebae are stained with immunoperoxidase and are brown. (Courtesy of Professor S.B. Lucas, King's College London, UK.)



Fig. 37.30 Cutaneous amoebiasis. Rapidly spreading ulcer around a colostomy in a patient with intestinal amoebiasis. (Courtesy of Meddia (Medical and Diagnostic Services), Basel.)

All ages are affected. The vulva is particularly likely to be invaded in the infant with amoebic dysentery. Penile amoebiasis may occur in homosexual men [9], but invasive amoebiasis is not especially common in homosexual men or in patients with human immunodeficiency virus (HIV) infection [10].

Diagnosis. Cutaneous amoebiasis can spread very rapidly and terminate fatally, so early diagnosis is important. A solitary lesion may be mistaken for an epithelioma or for tuberculosis verrucosa cutis. On the penis when regional lymphadenopathy is present, syphilis or lymphogranuloma venereum may be confused. Examination of fresh material from the cutaneous lesion regularly discloses amoebae. Material should be taken from the edge of the ulcer avoiding necrotic tissue and examined at once under the microscope. The demonstration of motile trophozoites containing red blood cells is diagnostic. Histology of the ulcer edge will reveal amoebae, but the identification of the parasite in sections stained by haematoxylin and eosin may be difficult (Fig. 37.29). Amoebic trophozoites in faeces, biopsy, necropsy or abscess aspirate are revealed with much greater accuracy by immunofluorescence or immunoperoxidase staining. Serological tests are helpful, and the indirect immunofluorescent antibody test is positive in the serum of near 100% of patients with amoebic liver abscess, and in about 70% of patients with intestinal amoebiasis. Serial stool examinations should be performed.

The prognosis is serious in the neglected case, particularly in infants, but with early diagnosis and treatment it is good. It is important to appreciate that a history of dysentery is not essential to the diagnosis of amoebiasis of the skin.

Treatment. Treatment of invasive amoebiasis is with metronidazole [11]. The recommended adult dose is 800 mg orally three times a day for 10 days. This may be combined with diloxanide furoate 500 mg three times a day, or be followed by oral diiodohydroxyquin 650 mg three times a day for 21 days, to eliminate intestinal cysts.

Local cleaning of cutaneous ulcers with antiseptic solutions may be necessary.

Where a hepatic abscess needs to be drained, this is most safely done by needle aspiration.

Effective treatment is usually followed by complete healing of the skin without the need for plastic surgery.

References

1 Stamm WP. Amoebiasis in England and Wales. *BMJ* 1975; **ii**: 452–3.

2 Walsh JA. Problems in recognition and diagnosis of amoebiasis: estimations of global magnitude of morbidity and mortality. *Rev Infect Dis* 1986; **8**: 228–38.

3 Sergeaunt PG. The reliability of *Entamoeba histolytica* zymodemes in clinical diagnosis. *Parasitol Today* 1987; **3**: 40–3.

4 Martinez-Palomo A. The pathogenesis of amoebiasis. *Parasitol Today* 1987; **3**: 111–8.

5 Paul M, Abeyaratne M. Cutaneous amoebiasis. *Br J Surg* 1961; **49**: 288–91.

6 Leippe M, Andra J, Nickel R *et al*. Amoebapores, a family of membrano-lytic peptides from cytoplasmic granules of *Entamoeba histolytica*: isolation, primary structure, and pore formation in bacterial cytoplasmic membranes. *Mol Microbiol* 1994; **14**: 895–904.

7 Patterson M, Schoppe LE. The presentation of amoebiasis. *Med Clin North Am* 1982; **66**: 689–705.

8 Fujita WH, Barr RJ, Gottschalk HR. Cutaneous amoebiasis. *Arch Dermatol* 1981; **117**: 309–10.

9 Phillips SC, Mildvan D, William DC *et al*. Sexual transmission of enteric protozoa and helminths in a venereal disease clinic population. *N Engl J Med* 1981; **305**: 603–6.

10 Allason-Jones E, Mindel A, Sargeaunt P *et al*. Outcome of untreated infection with *Entamoeba histolytica* in homosexual men with and without HIV antibody. *BMJ* 1988: **297**: 654–6.

11 Knight R. The chemotherapy of amoebiasis. *J Antimicrob Chemother* 1980; **6**: 577–93.

Trichomonads

Three trichomonads occur in humans. *Trichomonas vaginalis* invades the vagina, urethra and prostate and is pathogenic, causing trichomoniasis. *Trichomonas hominis* is found in the intestine and *T. tenax* in the mouth and occasionally the lung: neither is considered pathogenic [1].

Trichomoniasis

Trichomonas vaginalis is found worldwide affecting all races, but is eight times commoner in black people than in white people [2]. It invades the vagina and urethra in women, causing vaginitis and vulvitis with a characteristic pale-yellow, frothy discharge [3,4]. Vulval soreness and pruritus with inflammation of the surrounding skin are common, whereas infection of Skene's or Bartholin's glands with abscess formation rarely occurs.

Trichomoniasis characteristically causes a copious discharge with vaginal soreness or irritation and urinary frequency. The odour of the discharge is often unpleasant, although this feature is not specific. In many cases, bubbles can be seen in the discharge and the vaginal mucosal and cervical surfaces are infected and sometimes covered with punctate haemorrhages. The pH of the discharge is usually higher than the normal 4.5.

Although commonest in the second and third decades, the infection may occur at any age and has been reported in nearly 17% of babies aged from 1 day to 11 months. Many adults are asymptomatic carriers, particularly males. It can be isolated from up to 15% of men with non-specific urethritis. Discharge in males is scant.

The condition is frequently associated with gonorrhoea [5]. Transmission is usually by sexual intercourse, with an incubation period of 4–21 days. Occasional non-sexual transmission has been reported. In males, the condition occurs with non-specific urethritis in up to 5% of cases, and balanitis may also occur [6]. The organism may be harboured in the prostate without symptoms.

Diagnosis. In women, diagnosis is usually easily confirmed by examination of a wet film by phase contrast or dark-field microscopy [7], but culture, usually in Feinberg–Whittington medium, gives the most reliable results. On the other hand, in males, examination of centrifuged urine or prostatic fluid following massage is only occasionally positive, and in many men it is not possible to confirm a clinical diagnosis. Examination of a stained dry film is neither easy nor reliable.

Sexual partners should always be examined, and in both sexes specimens taken to exclude other causes of sexually transmitted disease.

Treatment. Standard treatment is with metronidazole 400 mg twice a day for 5 days [8,9]. Alcohol should be avoided during treatment. Single-dose treatments have been advocated with this drug. Gastrointestinal disturbances are common. Benzimidazole drugs should be avoided in the first 3 months of pregnancy.

Clotrimazole has been shown to have some activity [6] and one 100-mg pessary daily for 6 days may be tried. Older remedies such as acetarsol pessaries or hydrargarphen pessaries, two a night for 3 weeks, are still valuable. Simple douching may relieve vaginal symptoms (20 mL of vinegar to 1 L of warm water).

References

1 Honigberg B. Trichomonads of importance in human medicine. In: Kreier JP, ed. *Parasitic Protozoa*, Vol. 2. New York: Academic Press, 1978: 275–86.
2 Ogunbanjo BO, Osoba AO. *Trichomonal* vaginitis in Nigerian women. *Trop Geogr Med* 1984; **26**: 67–74.
3 Brown MT. Trichomoniasis. *Practitioner* 1972; **209**: 639–45.
4 Caterall RD. *Trichomonal* infection of the genital tract. *Med Clin North Am* 1972; **56**: 1203–21.
5 Langley JG, Goldsmith JM, Davies N. Venereal trichomoniasis; role of man. *Genitourin Med* 1987; **63**: 264–7.
6 Lossick JG. Treatment of *Trichomonas vaginalis* infection. *Rev Infect Dis* 1982; **4** (Suppl.): S801–8.
7 Fouts AC, Kraus SJ. *Trichomonas vaginalis*. Reevaluation of its clinical presentation and laboratory diagnosis. *J Infect Dis* 1980; **141**: 137–52.
8 Robbie MO, Sweet RL. Metronidazole. Use in obstetrics and gynecology. A review. *Am J Obstet Gynecol* 1983; **145**: 865–81.
9 Sears SD, O'Hare J. *In vitro* susceptibility testing of *Trichomonas vaginalis* to 50 antimicrobial agents. *Antimicrob Agents Chemother* 1988; **69**: 524–5.

Trypanosomiasis

Protozoa of the genus *Trypanosoma* cause the widespread tropical disease trypanosomiasis. There are African and American forms.

African trypanosomiasis

Synonym
- Sleeping sickness

Aetiology and epidemiology. The disease is endemic in a belt running across Africa, limited approximately by lat. 15°N and lat. 15°S. *Trypanosoma gambiense* is the cause in West Africa, and the more virulent *T. rhodesiense* in East Africa to the east and south of Lake Victoria [1]. Occasional cases are imported into countries where the parasite is not endemic [2].

The human is the main natural host of *T. gambiense*, and the disease is transmitted by blood-sucking tsetse flies of the genus *Glossina*, the intermediate hosts *G. palpalis* and other related species are the most important. On the other hand, *T. rhodesiense* (which morphologically resembles *T. gambiense* but is biologically very different) is transmitted by *G. morsitans* and related species. The natural hosts are wild animals, notably antelope, and the human is a 'dead-end' host.

Age, sex, race and occupation have no influence on susceptibility to trypanosomiasis, except in so far as they affect exposure to tsetse flies. *Trypanosoma gambiense* sleeping sickness tends to be an endemic disease, affecting rural communities, with localized outbreaks, while *T. rhodesiense* sleeping sickness causes sporadic infections in herdsmen, hunters and tourists. In some parts of the 'tsetse fly belt' the incidence is high, and, as the same flies transmit bovine trypanosomiasis to livestock, farmers cannot keep cattle and poverty and malnutrition are rife.

Intrauterine transmission has been recorded infrequently. Preventive measures involved removal of entire villages to tsetse-free land. Mass survey and treatment were very successful in reducing the infection rate in Nigeria from 10.9% (1931–40) to 0.14% (1958) [1].

Pathogenesis. Trypanosomes develop, at the site of inoculation by the tsetse fly, from metacyclic forms to mature forms in about



Fig. 37.31 Trypanosomal chancre due to *Trypanosoma rhodesiense* infection, appearing 6 days after the bite of the tsetse fly. The lesion is swollen, inflamed and haemorrhagic.



Fig. 37.32 Trypanosomal rash (same patient as Fig. 37.31). The maculopapular rash is becoming haemorrhagic.

10 days, and then enter the bloodstream. Within this time, the patient starts to develop an antibody response to the infection. The immunological reaction to the trypanosomes in the skin causes the chancre. The systemic clinical illness coincides with invasion of the bloodstream. The early pathology is, thereafter, mainly in the lymph nodes, at first those draining the sore and then generally, with an increase in lymphocytes and plasma cells, but the appearances are not specific, and trypanosomes are not easily seen histologically. In *T. rhodesiense* infections, the lymphoplasmocytic infiltrate is also found in the myocardium, and this myocarditis may be fatal. In late trypanosomiasis, the meninges become invaded with the same infiltrate, and then the brain, especially around the basal ganglia. Gliosis and cerebral atrophy follow. The cause of these pathological changes is poorly understood, although it is known that there is a polyclonal B-lymphocyte activation with the production of very high levels of IgM, and circulating immune complexes [3].

Clinical features [4,5]. Within a few days of the infected bite, a trypanosomal chancre starts to develop (Fig. 37.31). It is a round, raised, red, hot, tender lesion, 2–5 cm or more in diameter, spreading to cover, for example, the entire surface of the forearm over the ensuing few days. There may be a tiny central punctum, and a blister with fluid rich in trypanosomes may appear on its surface. The chancre is present in 70–90% of people infected with *T. rhodesiense*, less regularly with *T. gambiense*, but fades within a few weeks. It is usually accompanied by local lymphadenopathy. The chancre heralds the onset of fever and systemic illness and generalized lymphadenopathy, which characterize the second phase of the illness. This is rapid and severe in *T. rhodesiense* infections, but gradual, mild, intermittent or even absent clinically in *T. gambiense* infections [6].

During this phase of the illness, there may be oedema of hands, feet and face, and transient erythematous or urticarial rashes, which are often circinate or annular, poorly defined, pale centrally, and commonest on the trunk. The rash may be haemorrhagic (Fig. 37.32). They are difficult to see in African skins. When the CNS is invaded, the patient experiences behavioural changes, alterations in sleep patterns, extrapyramidal signs and finally coma. These occur months after the onset of *T. rhodesiense* infections, if the patient has not died in the secondary phase, and 1–3 years after the onset of *T. gambiense* infections. At this stage, pruritus and excoriations from scratching are common, and the patient is emaciated. Death is often due to intercurrent infection due to the immune suppression.

Diagnosis. Within a few days of the onset of fever, trypanosomes may be demonstrated in simple thin blood films in *T. rhodesiense* infections. However, in *T. gambiense* infections, thick films (Fig. 37.33) or concentration techniques [7] may be necessary. A more profitable approach is puncture and aspiration of the enlarged posterior cervical lymph nodes. Trypanosomes are seen undulating between the lymphocytes in the wet preparation, or well defined in a Giemsa-stained preparation. Cerebral involvement is

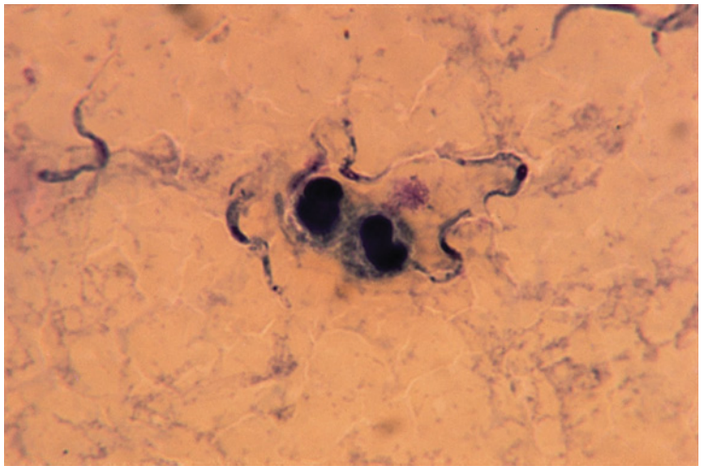


Fig. 37.33 Trypanosomes in a thick blood film, stained with Giemsa. (Courtesy of Dr P.L. Chiodini, Hospital for Tropical Diseases, London, UK.)

characterized by raised protein in the CSF, containing IgM, and a raised cell count comprising lymphocytes and morula cells (plasma cells distorted by vesicles of IgM). Serological tests, including ELISA and immunofluorescence, may be helpful. Serum IgM levels are often grossly elevated, and there may be an anaemia. On diagnosis, a lumbar puncture is mandatory to establish whether the CNS has been invaded.

Treatment. A single course of suramin, preferably, or pentamidine isethionate is usually sufficient, if given before CNS invasion. Dosages are: suramin sodium 200 mg (test dose) i.v., followed by 1 g/week for five doses; pentamidine isethionate 4 mg/kg i.m. on alternate days for five doses. Both drugs are seriously toxic [8].

After CNS invasion melarsoprol is used [7,8], often with corticosteroids [9].

References

1 Foulkes JR. Human trypanosomiasis in Africa. *BMJ* 1981; **283**: 1172–4.
2 Spencer HC, Gibson JJ, Brodsky RE *et al*. Imported African trypanosomiasis in the United States. *Ann Intern Med* 1975; **82**: 633–8.
3 Greenwood BM, Whittle HC. The pathogenesis of sleeping sickness. *Trans R Soc Trop Med Hyg* 1980; **74**: 716–25.
4 Gelfand M. The early clinical features of rhodesiense trypanosomiasis with special reference to the 'chancre' (local reaction). *Trans R Soc Trop Med Hyg* 1966; **60**: 376–9.
5 Merklen FP, Riou MV, Solente G *et al*. Trypanosomiase cutaneé, type d'érythme annulaire centrifuge avec manifestations ganglionnaires discretes. *Bull Soc Fr Dermatol* 1956; **63**: 424–5.
6 Scott JA, Davidson RN, Moody AH *et al*. Diagnosing multiple parasitic infections: trypanosomiasis, loiasis and schistosomiasis in a single case. *Scand J Infect Dis* 1991; **23**: 777–80.
7 Greenwood BM. African trypanosomiasis. In: Weatherall DJ, Ledingham JGG, Warrell DA, eds. *Oxford Textbook of Medicine*, 2nd edn. Oxford: Oxford University Press, 1987.
8 Robertson DHH. The treatment of sleeping sickness (mainly due to *Trypanosoma rhodesiense*) with melarsoprol. II. An assessment of its curative value. *Trans R Soc Trop Med Hyg* 1963; **57**: 176–83.
9 Foulkes JR. An evaluation of prednisolone as a routine adjunct to the treatment of *T. rhodesiense. J Trop Med Hyg* 1975; **78**: 72–4.

American trypanosomiasis

Synonyms
- Chagas' disease
- South-American trypanosomiasis
- Trypanosomiasis cruzi
- Chagas–Mazza disease
- Schizotrypanosomiasis
- Opilacao

Definition. Chagas' disease is a parasitic disease of the tissues and blood caused by the flagellate *Trypanosoma* (*Schyzotrypanum*) *cruzi* and transmitted to humans and other mammals by blood-sucking bugs of the family *Triatomidae*. It occurs predominantly in rural areas in the tropical zones of the American continent.

Incidence. The insect vectors are widely distributed in the American continent from lat. 42°N in the USA to lat. 43°S in Argentina [1]. *Trypanosoma cruzi* attacks humans and other mammals, and the disease it produces can be regarded as a zoonosis. The area of distribution of the disease is more limited than the range of the reduviid bugs that transmit it, since those found at the two extremes of the continent are wild species, while the domestic types, concerned in the transmission of the infection to humans, occur between lat. 25°N in Mexico and lat. 28°S in Argentina [1].

Age does not influence the incidence of infection, although the acute forms are more frequently observed in children. The sexes are equally affected and there is no evidence of a racial factor. Occupation plays an important role because it is a rural disease and the vectors are found in rural dwellings, especially in huts or shacks with palm leaf roofs [2].

Aetiology. The disease is caused by *T. cruzi*, which bears some resemblance morphologically to the trypanosomes causing sleeping sickness in Africa. In the blood, the organism is 15–20 μm in length and of variable width, and has the typical undulant membrane and flagellum in an anterior position. The nucleus is central, the kinetoplast rod-shaped or oval and situated posteriorly. After transformation into the amastigote stage, *T. cruzi* multiplies only in tissue cells, being an obligatory tissue-cell parasite.

Vector. The disease is transmitted by blood-sucking insects of large size: Hemipteran, reduviid bugs (assassin or kissing bugs), belonging to the family *Triatomidae*, particularly *Panstrongylus megistus* (Brazil), *Triatoma infestans* (Southern Brazil, Uruguay, Paraguay, Bolivia, Southern Peru, Chile and Argentina) [1] and *Rhodnius proxlixus* (Venezuela, Colombia, Guianas and Central America). The larva, nymph and the adult insect can transmit the infection. They are active during the night. After ingestion, the trypanosomes multiply in the vector's intestine by longitudinal division, and within 3 or 4 weeks transform into the metacyclic form, which is infective to humans. Once the insect has been infected, it remains so for the rest of its life. The disease has many non-human reservoirs, including cats, dogs, monkeys, pigs, squirrels, rats, skunks, racoons, opossums, porcupines and armadillos.

Transmission occurs by contamination through small cuts and abrasions on the skin, or through the normal mucous membranes of the eyes and lips when the vector, at the moment of biting, deposits its stools containing the infective metacyclic trypanosome [2]. The bite wound itself may provide the portal of entry [3].

Pathology. The tissues react almost immediately to the penetration of the metacyclic trypanosomes, producing oedema and cellular infiltration, which cause subcutaneous swelling. The infection spreads rapidly to the lymphatics, and the regional glands become oedematous and infiltrated with plasma cells and lymphocytes. The spleen and liver enlarge. The trypanosomes penetrate immediately into the cells of the reticuloendothelial system at the site of the inoculation and transform into the leishmania form, later returning to the interstitial spaces and blood in the form of trypanosomes, penetrating again into the cells to repeat the cycle in different organs and systems. The most striking invasion is that of the spleen macrophages, the Kupffer cells of the liver and the cells of the striated muscles [4]. The inflammation and scarring that follows invasion of the myocardium may have serious consequences.

Clinical features. The great majority of infections do not present any clinical manifestations in the early phase. Signs of early disease appear on the fifth day after inoculation: these are both local and general. Eighty per cent of the acute cases show the portal of entry in the conjunctiva, as evidenced by the 'eye sign' or 'Romaña's sign', also known as the 'ophthalmoganglionar complex' (oculoglandular complex), characterized by unilateral oedema of the eyelids and inflammation of the lacrimal gland (Fig. 37.34). Cutaneous inoculation results in the 'cutaneous adenopathy complex' or 'inoculation chagoma' and is less common. The general manifestations consist of moderate to high fever accompanied by headache, myalgia, weakness, particularly pronounced in children, in whom the disease may end fatally from acute meningoencephalitis or myocarditis. Hepatosplenomegaly, oedema and various forms of exanthem ('schizotripanides') are frequent [1]. Forms called oedematous, neuropsychiatric, meningoencephalitic, respiratory, gastrointestinal and pseudotyphoid have been described [2]. The subacute and chronic forms almost always present with heart manifestations—chagasic myocarditis—and digestive manifestations, such as mega-colon and mega-oesophagus. Megasyndromes are common in Brazil but absent in Venezuela. Congenital forms transmitted transplacentally or by the mother's milk are rare.

Prognosis. This is serious in acute cases in children, especially in the meningoencephalitic form, and when the myocardium is extensively involved. In the subacute and chronic forms it depends entirely on the degree of involvement of the heart. Sudden death by thromboembolic accidents and by blockage of the conduction system of the heart may occur. Chronic heart failure is frequently observed in the advanced cases.

Diagnosis. In the acute phase, the diagnosis is made by finding the parasite in the blood by direct examination, or by means of stained thick and thin smears, lymph-gland biopsy, blood culture, animal inoculation and by the so-called xenodiagnosis of Brumpt: the reduviid bugs grown in the laboratory and free from infection are allowed to bite the forearm of the subject under suspicion and feed on the blood, after which the faeces of these insects are examined for metacyclic forms between 30 and 60 days later [2]. In the subacute and chronic forms, laboratory tests are of great help, particularly those based on the complement-fixation test using antigen from culture forms of *T. cruzi* (Machado–Guerreiro's test).



Fig. 37.34 Chagas' disease. Unilateral oedema of the eyelids and orbit (Chagas–Mazza–Romaña's sign). (Courtesy of Professor M. Miles, London School of Hygiene and Tropical Medicine, London, UK.)

Treatment. The acute stage (including congenital Chagas' disease and transfusion acute disease) should be treated with a trypanocidal drug, either nifurtimox (Lampit) given by mouth (8 mg/kg) for 60 or 90 days, or benznidazole (Rochagan), oral dose (6 mg/kg) for 30 or 60 days. A rare side effect is an exfoliative dermatitis. Both drugs produce anorexia, weight loss, headache and dizziness, gastric irritation and, occasionally, peripheral neuritis (12–30%). Allopurinol has recently been used [5].

Control. Improvement of environmental conditions should be attempted, especially those of the dwellings, eliminating palm leaf roofs. The insects can be destroyed with dieldrin and gamma benzene hexachloride. Chemotherapy of the infective cases may help to break the natural cycle of the disease.

References

1 Romaña C. *Enfermedad de Chagas*. Buenos Aires, Argentina: Lopez Libreros Editores, 1963.

2 Pifano F. *Aspectos de Medicina Tropical de Venezuela*. Caracas: OBE, 1964.

3 Levin MJ, Mesri E, Benarous R *et al*. Identification of major *Trypanosoma cruzi* antigenic determinants in chronic Chagas' heart disease. *Am J Trop Med Hyg* 1989; **41**: 530–8.

4 Losavio A, Jones MC, Sanz OP *et al*. A sequential study of the peripheral nervous system involvement in experimental Chagas' disease. *Am J Trop Med Hyg* 1989; **41**: 539–47.

5 Gallerano RH, Marr JJ, Sosa RR. Therapeutic efficacy of allopurinol in patients with chronic Chagas' disease. *Am J Trop Med Hyg* 1990; **43**: 159–66.

Leishmaniasis

The leishmaniases are a group of diseases caused by several species of the genus *Leishmania*. Each species tends to occupy a particular zoogeographical zone and the disease is endemic in 88 countries. It has been estimated that 1.5 million new cases of cutaneous leishmaniasis occur annually and more than 80% of the total of cases affect individuals in developing countries. Brazil, Iran, Afghanistan and Sudan suffer the highest prevalence and the disease is a priority for public health in all hyperendemic regions of the world. The species are morphologically identical, and are distinguished by isoenzyme pattern and DNA analysis. Monoclonal antibodies have also proved useful for rapid identification of isolates, especially in the field [1]. Clinical patterns are poor indicators of species, although certain disease characteristics may be commonly associated with a particular species [2]. *Leishmania* spp. undergo a cycle of development in the gut of female sandflies, of the genera *Phlebotomus* in the Old World, and *Lutzomyia* and *Psychodopygus* in the New World.

In its vertebrate host, the amastigote form of the parasite is found in cells of the reticuloendothelial system or in the dermis following severe parasite load and mononuclear cell necrosis. It is round or oval, 2–3 µm in diameter, with no protruding flagellum. The nucleus and kinetoplast stain deeply with the Romanovsky stains, giving the organism its characteristic appearance. In the sandfly and in artificial culture media, *Leishmania* spp. are the elongated promastigote stage, motile with an anterior flagellum.

Sandflies find their precise requirements for temperature and humidity in a wide variety of niches, commonly in rodent burrows, and crevices and holes in banks, trees and houses in the Old World, and in tree canopies and forest litter in the New World [3]. Infection is transmitted by the bite of the fly, usually at night and outdoors; however, infected vectors can take a blood meal during the day if disturbed and also are responsible for inoculating parasites indoors within the household environment. Commonly, the infection is zoonotic; one species of *Leishmania* may be associated with one, or many, natural vertebrate hosts, which provide the reservoir of infection. Humans are commonly accidental hosts, although there are situations in which they may be the reservoir in an anthroponotic cycle. For these reasons, human leishmaniasis has a very wide geographical distribution and range of climate and altitude (Fig. 37.35), and different epidemiological patterns (Table 37.2) [4].

Human leishmaniasis is usually classified as cutaneous or visceral, but the species that cause visceral disease may also cause skin lesions. In South and Central America, skin disease due to parasites of the *L. brasiliensis* complex may be complicated by the

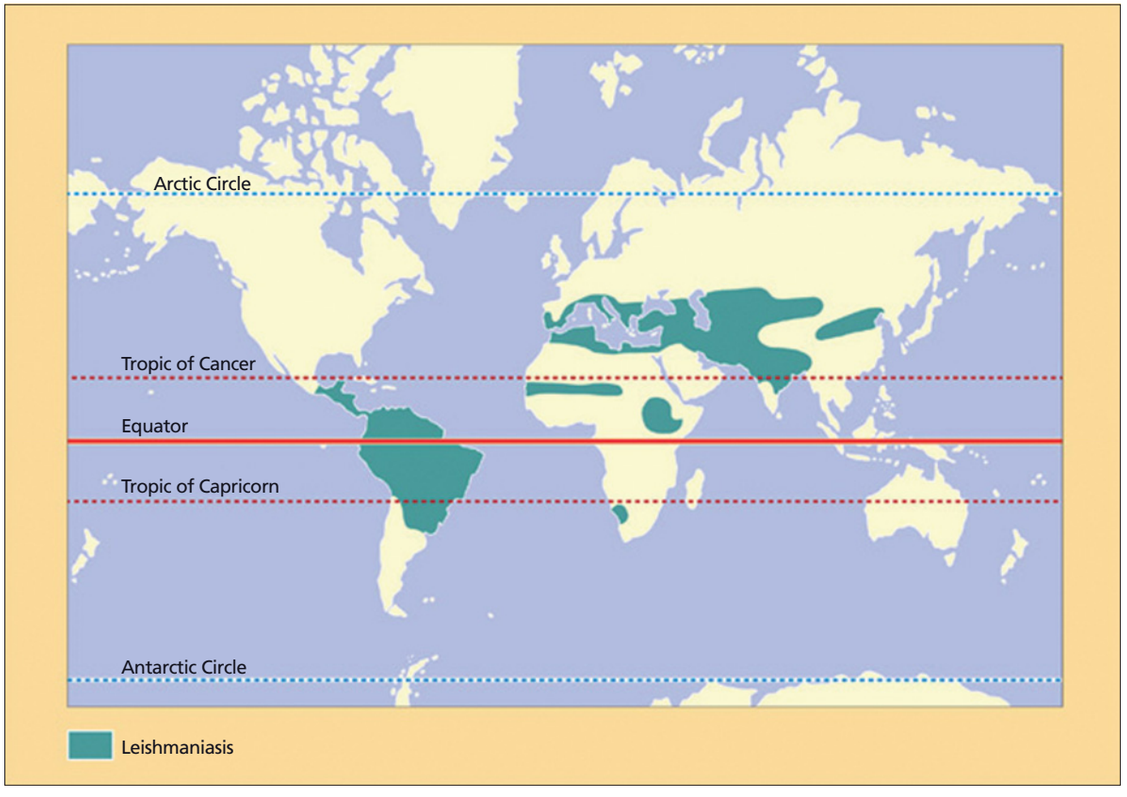


Fig. 37.35 World distribution of human leishmaniasis.

Table 37.2 Epidemiology of leishmaniasis. (Courtesy of Weatherall *et al.* [4].)

Organism	Geography	Reservoir	Vector
Old World			
Leishmania donovani	North-East India, Bangladesh, Burma	Humans	*Phlebotomus argentipes*
L. infantum	Mediterranean basin, Middle-East, China, Central Asia	Dogs, foxes, jackals	*P. ariasi*, *P. perniciosus*
L. donovani (Africa)	Sudan, Kenya, Horn of Africa, ?Senegambia	?Rodents in Sudan, ?canines, ?humans	*P. orientalis*, *P. martini*
L. major	Semi-deserts in Middle East, North India, Pakistan, North Africa, Sudan, Central Asia	Gerbils (especially *Rhombomys*, *Meriones*)	*P. papatasii*
L. major	Sub-Saharan savanna, Sudan	Rodents (especially *Arvicanthus*, *Tatera*)	*P. duboscqi*
L. tropica	Towns in Middle East, Mediterranean basin, Central Asia	Humans, ?dogs	*P. sergenti*
L. aethiopica	Highlands of Kenya, Ethiopia	Hyraxes (*Procavia*, *Heterohyrax*)	*P. longipes*, *P. pedifer*
New World			
L. chagasi	Central America, northern South America, esp. Brazil, Venezuela	Foxes	*Lutzomyia longipalpis*
L. mexicana mexicana	Yucatan, Belize, Guatemala	Forest rodents (especially *Ototylomys* and *Peromyscus yucatanicus*)	*Lu. olmeca*, *Lu. cruciata*
L. m. amazonensis	Tropical forests of South America	Forest rodents (especially *Proechimys*, *Oryzomys*)	*Lu. flaviscutellata*
L. brasiliensis brasiliensis	Tropical forests of South and Central America	?Forest rodents	*Psychodopygus wellcomei*, *Lutzomyia* spp.
L. b. guyanensis	Guyanas, Surinam, into Brazil, Venezuela	Sloths (*Choleopus*), arboreal anteaters (*Tamandna*)	*Lu. umbratilis*
L. b. panamensis	Panama, Costa Rica, Colombia	Sloths (*Choleopus*)	*Lu. trapidoi*
L. b. peruviana	West Andes of Peru, Argentine highlands	Dogs	*Lu. verrucarum*, *Lu. peruensis*

development of metastatic mucosal or mucocutaneous lesions. Mucosal disease is relatively rare with the other species [5].

Old World cutaneous leishmaniasis

Synonyms
- Oriental sore
- Bouton D'Orient
- Delhi boil
- Aleppo boil

Aetiology and epidemiology. Cutaneous leishmaniasis of the Old World is due to *L. major*, *L. tropica*, *L. aethiopica* and to *L. donovani infantum*, which is responsible for all the cutaneous disease on the northern Mediterranean littoral west of Greece and for some of the disease in North Africa [6,7] (Table 37.2). In endemic areas where transmission is stable, children are especially affected, and the cumulative rate of infection as determined by the presence of scars and positive leishmanin tests may approach 100%. In less stable situations, for example around oases, epidemics occur affecting all ages and sexes [8]. The disease is commonly imported into non-endemic countries by immigrants and returning travellers.

Pathogenesis. Sandflies inoculate the infective metacyclic promastigotes when taking a blood meal from the superficial vascular network in the human dermis. Inoculated promastigotes are taken up by histiocytes and newly immigrated monocytes, in which they multiply. Most inoculations do not seem to result in clinical disease as phagocytosis, and complement-mediated killing of leishmania parasites results in clearing of the infection. A minority of successful parasite inoculations result in localized or disseminated clinical cutaneous leishmaniasis. After a period of time, which depends on parasite species, size of inoculum, and the host's cellular immune response, a clinical lesion appears. This lesion comprises parasitized macrophages, lymphocytes and plasma cells, with little structure (Fig. 37.36) [9]. With time, piecemeal and focal necrosis of parasitized cells is found, probably the result of

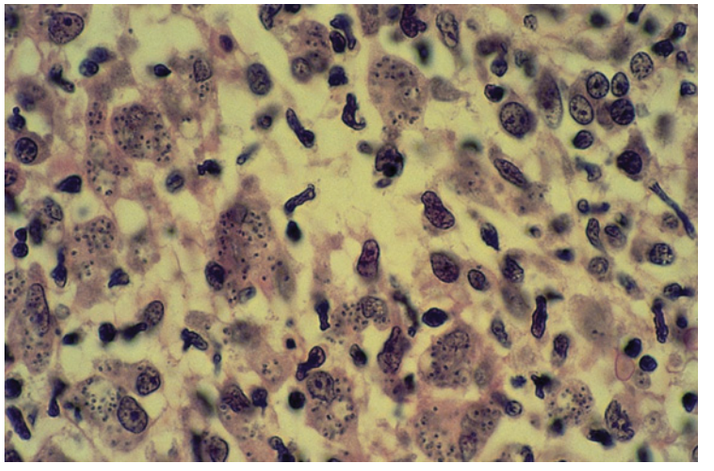


Fig. 37.36 Cutaneous leishmaniasis (high power, H&E); biopsy of early lesion, showing abundant amastigotes in macrophages, and a few plasma cells. (Courtesy of Professor S.B. Lucas, King's College London, UK.)

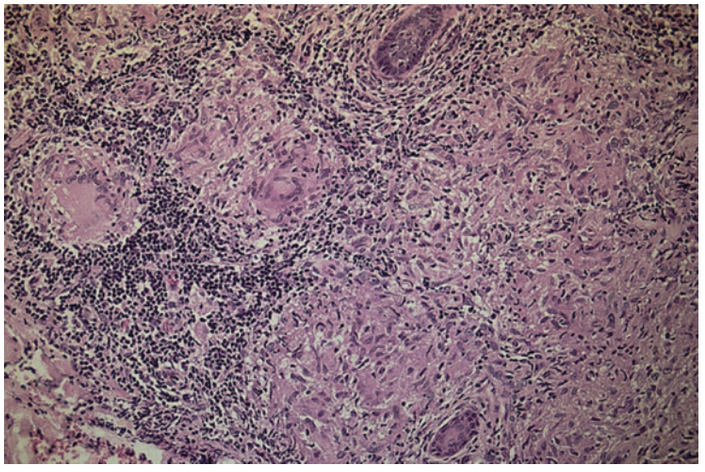


Fig. 37.37 Chronic cutaneous leishmaniasis. Granulomatous dermatitis without necrosis. There are no amastigotes to be found in this case, and the differential diagnosis may be difficult between the other granulomatous dermatitides. (Courtesy of Professor S.B. Lucas, King's College London, UK.)

antibody-dependent cell-mediated immunity. The overlying epidermis becomes hyperkeratotic and breaks down, causing an ulcer whose surface is covered in a crust composed of hyperkeratotic debris, dried exudate, dead cells, and live and dead parasites. This activity continues for several months, while the lesion appears clinically static. In other, especially chronic, cases the more classical epithelioid cell, and sometimes giant cell granuloma, develops with relatively little necrosis, but similar epidermal changes (Fig. 37.37). In these cases, parasites are difficult to find [10]. Rarely, when cell-mediated immunity fails to develop, as in diffuse cutaneous leishmaniasis, histology shows masses of parasitized, often vacuolated, macrophages, with little or no lymphocytic infiltrate, and a normal or attenuated epidermis [11].

Clinical features [12]. Most previously uninfected individuals are susceptible. The incubation period is usually measured in months, but ranges from a few days to over a year. One or more lesions occur on unclothed parts of the body, particularly on acral skin over bony prominences easily bitten by *Phlebotomus*, usually in a child. The face, neck and arms are the commonest targets. Lesions do not necessarily occur all at exactly the same time, but in endemic areas a family of children may all present with lesions and a history strongly suggesting infected sandfly bites all acquired in the same room on the same night.

The natural history of the lesions due to the four species tends to differ but there is much overlap, reflecting the variety in host response [2], so that lesions and their outcome are not always characteristic of the species (Table 37.3) [4]. The sequence of nodule, crusting, ulceration and healing with scar formation is common to all the self-healing sores.

Cutaneous leishmaniasis due to *L. major*: wet, rural or zoonotic cutaneous leishmaniasis [13,14]. After a short incubation period of less than 2 months, a red furuncle-like nodule appears at the site of inoculation (Fig. 37.38). After 2 weeks a central crust forms. The crust may persist (Fig. 37.39), or fall away revealing the underlying ulcer (Fig. 37.40). The ulcer and the raised, red margin enlarge over the next 2–3 months, and the lesion reaches a diameter of 3–6 cm. Multiple, small, secondary nodules (2–4 mm) sometimes occur around the lesion in lymphatics. Healing takes place in 2–6 months and leaves a scar. This type of cutaneous leishmaniasis is acquired in a rural area, where the infecting organisms are also rodent parasites and are poorly adapted to humans. It is an example of a zoonosis.

Table 37.3 Clinical features of cutaneous leishmaniasis. (Courtesy of Weatherall *et al.* [4].)

Parasite and lesion	Natural outcome	Treatment
Leishmania major		
Self-healing rural sores	3–5 months Disabling scars	Physical/topical/IL/nil Sb 20 mg/kg/day × 2–3 weeks (?Some unresponsive)
L. tropica		
Self-healing urban sores	10–14 months	Physical/topical/IL/nil Sb 20 mg/kg/day × 2–3 weeks
Leishmaniasis recidivans	>10 years destructive	Sb 20 mg/kg/day × 3–6 weeks
L. aethiopica		
Self-healing, nodular	2–5 years	Physical/topical/nil
Mucocutaneous	>10 years destructive	Pentamidine 4 mg/kg/week × 8
DCL	Persists, disfiguring	Pentamidine 4 mg/kg/week × months
L. m. mexicana		
Self-healing	6–8 months	Physical/topical/IL/nil Sb 20 mg/kg/day × 2–3 weeks
Chiclero ear	>10 years, destructive	Sb 20 mg/kg/day × ?
L. m. amazonensis		
Self-healing	?Duration	?Sb 20 mg/kg/day × 3 weeks
DCL	Persists, relapses, disfiguring	Sb 20 mg/kg/day × months
L. b. brasiliensis		
Self-healing	?Duration, later mucocutaneous	Sb 20 mg/kg/day × 3–4 weeks
Mucocutaneous	Persists, destructive	Sb 20 mg/kg/day × 4 weeks, or amphotericin B
L. b. guyanensis		
Self-healing	?6–8 months	Sb 20 mg/kg/day × 3 weeks
Lymphatic nodules 'pian bois'	?Late espundia	If poorly responsive to Sb, use pentamidine
L. b. panamensis		
Self-healing	?Duration ?Late espundia	Sb 20 mg/kg/day × 3 weeks
L. b. peruviana		
Self-healing	?Duration	Physical/topical/nil Sb 20 mg/kg/day × 2–3 weeks

DCL, diffuse cutaneous leishmaniasis; Sb, antimony as pentavalent antimonial; IL, intralesional injection.

Cutaneous leishmaniasis due to *L. tropica*: dry, urban or anthroponotic leishmaniasis [15]. After an incubation period of more than 2 months, a small, brownish nodule appears, which becomes a slowly extending plaque 1–2 cm in diameter in about 6 months.



Fig. 37.38 Cutaneous leishmaniasis due to *Leishmania major*: early papules, one of which is starting to show central crusting.



Fig. 37.39 Cutaneous leishmaniasis due to *Leishmania major* from Saudi Arabia, showing marked and persistent crusting.

At this stage, shallow ulceration appears in the centre, which develops a closely adherent crust. Multiple secondary nodules occur much less frequently than in the 'wet' form. After 8–12 months, the lesion starts to regress and the ulcer heals, leaving a scar. The average time from nodule to scar is about 1 year, approximately twice as long as in the 'wet' form. Rare forms of viscerotropic infections by *L. tropica* have been described in war veterans who acquired the parasite in the Middle East and in cases of Indian kala-azar [16].

Cutaneous leishmaniasis due to *L. aethiopica* [11]. Lesions are most commonly central on the face, and single. Satellite papules accuminate into a large, spreading nodule that may not crust or ulcerate (Fig. 37.41). Lesions are seldom much inflamed, and heal over 2–5 years. If the sandfly bite has been on the mucosal border of the nose or mouth, primary mucocutaneous leishmaniasis (MCL) may develop, producing swelling of lips or nose, and persist for many years (Fig. 37.42), although without the gross destruction seen in Latin America caused by *L. brasiliensis*.



Fig. 37.40 Cutaneous leishmaniasis due to *Leishmania major* from Sudan. An ulcer with a raised edge.



Fig. 37.41 Cutaneous leishmaniasis due to *Leishmania aethiopica* from Kenya. A large nodule with many satellite papules and abundant parasites.

Cutaneous leishmaniasis due to *L. donovani* infantum [7]. Whereas infants infected with this parasite tend to get visceral leishmaniasis, adults are more likely to develop simple self-healing cutaneous disease, without concurrent or subsequent visceral involvement. The appearance and evolution of the lesions is typically slow and mild, when compared with that of *L. major*, with which it coexists in North Africa [6] (Fig. 37.43). Solitary mucosal lesions have occasionally been reported [5].

In addition to the classical self-healing sores, there are two types of cutaneous leishmaniasis that are chronic, and may not heal spontaneously.



Fig. 37.42 Nasal involvement, and marked inflammatory oedema in leishmaniasis due to *Leishmania aethiopica* in Ethiopia.



Fig. 37.43 Cutaneous leishmaniasis due to *Leishmania infantum*, from Spain. The fleshy nodule, with relatively little inflammation, is characteristic.

Leishmaniasis recidivans: chronic leishmaniasis, lupoid leishmaniasis [10]. It has been estimated that approximately 4% of *L. tropica* infections from Iran and Afghanistan will develop this chronic form of the disease. Brown-red or brown-yellow papules appear, usually close to a scar of an old lesion of cutaneous leishmaniasis or actually in the scar. They coalesce and form a plaque closely resembling lupus vulgaris, even to the formation of apple-jelly nodules (Fig. 37.44). The lesions frequently worsen in the summer and may ulcerate or form concentric rings. Rare keloidal and verrucous forms on the lower limbs are described. A psoriasiform type also occurs and may cover large areas of the body.



Fig. 37.44 Leishmaniasis recidivans (lupoid leishmaniasis) from Baghdad, showing active papules cropping in the edge of the scar of the healed sore. (Courtesy of Professor G. Rahim.)

The recidivans lesion is the result of a peculiar host reaction in which cellular immunity fails to sterilize the lesion, despite the presence of exaggerated hypersensitivity. Although not as destructive as lupus vulgaris, lupoid leishmaniasis may persist and spread slowly for many years [17]. Investigations to demonstrate the parasite or leishmanial DNA in the affected skin are commonly negative.

Diffuse cutaneous leishmaniasis: disseminated cutaneous leishmaniasis, leishmaniasis cutis diffusa. In the Old World this form of the disease is due to *L. aethiopica* and has certain characteristic features [11].

1. There is an initial lesion, which spreads locally, and from which the disease disseminates to other parts of the skin, often involving large areas (Fig. 37.45).
2. The lesions are nodules that do not ulcerate.
3. There is a superabundance of parasites in the lesions.
4. The histology is characteristic in that macrophages full of amastigotes predominate.
5. Internal organs are not invaded and there is no history of kala-azar.
6. The leishmanin test and other tests of specific cellular immunity are negative.
7. The disease progresses slowly and becomes chronic.
8. Treatment produces only gradual improvement and relapse is the rule.

Under the influence of treatment, the histology changes towards the tuberculoid in a proportion of patients, and they may recover completely. Cases of coincident leishmaniasis and leprosy have been described, and show that the immune deficiency of each condition is specific [18].

Diagnosis. In endemic areas, or in travellers returned from endemic areas, the clinical diagnosis is not difficult in the case of



Fig. 37.45 Diffuse cutaneous leishmaniasis due to *Leishmania aethiopica* in Ethiopia. The face is covered with infiltration and nodulation but there is no ulceration.

typical sores. A positive diagnosis of cutaneous leishmaniasis (Old World and New World types) can be suggested, and in most cases confirmed, by the presence of one or more of the following criteria:

1 History of exposure to an endemic area in the previous weeks or months
2 History of sandfly bites in the previous weeks or months
3 History of high-risk activities such as sleeping outdoors, jungle or desert trekking
4 Non-healing chronic nodular, violaceous ulcer for 4–6 weeks or longer
5 Demonstration of amastigotes in Giemsa-stained smears from infected skin by direct microscopy
6 Demonstration of intracellular amastigotes in the dermis of H & E sections of skin
7 Presence of leishmanial granulomas in the dermis in H & E specimens
8 Growth of promastigotes in Nicolle–Novy–MacNeal (NNN) culture medium from lesional specimens
9 Demonstration of leishmanial DNA by the PCR.

Deeper, subcutaneous sores (the so-called volcano lesion), sores arising from lymphatic spread, or chronic sores in which scarring predominates may present difficulties. Confirmation is through demonstration of the parasite. Usually, this is best achieved by making a smear of material from the sore and staining it with Wright's, Giemsa or Leishman's stain on a microscope slide. The smear may be made from the exudate from the sore, and is often positive even if purulent because secondary bacterial infection is unusual. Alternatively, a slit-skin smear is made, as for leprosy (Chapter 32), being careful to avoid taking blood from the nodular part of the lesion. Parasites are usually readily seen in sores that have not yet started to heal, but are difficult to see thereafter. Alternatively, material may be obtained through a needle or with a dental broach [19].

Ideally, material should also be cultured on NNN or similar medium. At the time of taking the lesional skin biopsy for histological examination, a portion of it should be cultured, and dab smears made from the cut surface of the other portion before it is fixed. Leishmania are harder to see and identify in sections than in smears. In chronic leishmaniasis especially, histology may not be able to distinguish leishmaniasis from sarcoidosis, tuberculosis or other tuberculoid pathologies. However, in acute forms with or without the presence of amastigotes, the presence of a granuloma has a high diagnostic sensitivity.

In all forms of cutaneous leishmaniasis, the leishmanin test will be positive once the stage of crusting has been reached [19]. The test is negative in the diffuse anergic forms. The leishmanin test, also called the Montenegro test, particularly in Central and South America, is a suspension of 5×10^6 cultured promastigotes of *Leishmania* spp. (*L. major* is commonly used for cutaneous diagnosis in Old World leishmaniasis) per mL of 0.5% phenol saline: 0.1 mL is injected into the volar surface of the forearm and the result read at 48–72 h. The antigen is normally standardized so that an induration of 5 mm or more, measured by the ballpoint technique, is positive [1]. While interpreting the result in an individual patient, it is important to take into consideration the prevalence rate in the control population. This intradermal skin test is not useful for the diagnosis of current cutaneous leishmaniasis as a positive result may indicate previous sensitization. Moreover, there are also problems of cross-reactivity amongst different *Leishmania* spp., and therefore the Montenegro test is not useful for particular epidemiological settings where infections by different *Leishmania* spp. overlap.

Molecular diagnostic tests to detect leishmanial DNA by PCR have been available for several years. Assays can be carried out by using nuclear DNA, and more recently the diagnostic sensitivity was significantly enhanced by using kinetoplast minicircle DNA [20]. The sensitivity of this test has been reported to be between 92% and 98% with 100% specificity by several authors [20]. A variety of clinical specimens, including cotton swabs and archival smears or paraffin-embedded skin sections, can be used as the DNA source for the PCR diagnosis. Ideally, the diagnosis of cutaneous leishmaniasis should achieve a species- and subspecies-specific level, as this has therapeutic and prognostic implications.

Treatment [21]. Most sores will heal spontaneously, but their duration cannot be predicted in an individual case. It is reasonable to try topical methods of treatment for simple sores, and to reserve the systemic use of pentavalent antimonials for problematic sores: these include sores where scarring would be disabling or severely disfiguring; sores that will not heal easily, for example on the lower leg or over a joint; sores involving mucosa or cartilage; or sores that might be due to parasites of the *L. brasiliensis* group.

Heating a sore to 40–42°C for several hours each day promotes healing but is technically difficult [22]. Small single sores may be frozen with carbon dioxide snow [23], curetted under local anaesthetic [24] or infiltrated with 1–2 mL sodium stibogluconate or meglumine antimoniate, on one or two occasions a few days apart. Careful attention to technique is essential [25]. Preliminary studies using the aminoglycoside aminosidine or paromomycin in an

ointment looked promising, but problems of formulation have yet to be solved [26]. Weekly intralesional sodium stibogluconate and daily oral itraconazole 100 mg or allopurinol 10–20 mg/kg for 6 to 8 weeks, have been successfully used to treat most *L. major*, *L. donovani* and *L. tropica* simple infections by the author (FVL).

Systemic treatment is with sodium stibogluconate or meglumine antimoniate by intravenous or intramuscular injection in a single daily dose of 20 mg antimony/kg, for as long as it takes to produce clinical and parasitological healing and a few days longer: usually 15–21 days [27]. Sores due to *L. brasiliensis* should be treated for the full 21 days [28]. *Leishmania aethiopica* is not sensitive to antimony at this dosage [29] and, when systemic treatment is justified, patients should be treated with pentamidine isethionate in a dose of 4 mg salt/kg once a week for as long as necessary [30]. Patients with diffuse cutaneous leishmaniasis require treatment for many months beyond clinical and demonstrable parasitic cure [30]. Leishmaniasis recidivans (lupoid) may respond to local infiltration after nodulectomy, or systemic antimonials. The additional use of steroids has helped some cases [14]. Severe scarring may require plastic repair. After healing, patients are normally immune to reinfection with the same species, although second sores in old age, or due to a parasite of a different zymodeme, have been reported. Cutaneous leishmaniasis in the immunocompromised host may manifest many years after exposure to the infective bite.

It is clear that the available treatments for cutaneous leishmaniasis are far from being satisfactory. Even more, reported therapeutic failures with pentavalent antimonials have been described as an increasing problem in endemic regions for visceral leishmaniasis in India and also as an emerging problem in New World cutaneous leishmaniasis amongst returned travellers to the UK [31]. Novel approaches include combination therapeutic regimens using antimonials and immunostimulating agents. Intravenous treatment with pentavalent antimonials results in a number of common adverse reactions and side effects including hepatic, pancreatic, musculoskeletal and cardiac toxicity. Elderly patients seem to be more frequently and severely affected by these symptoms.

American cutaneous leishmaniasis and mucosal leishmaniasis (MCL)

Synonyms
- American leishmaniasis
- South American leishmaniasis
- Espundia
- Pian bois
- Uta
- Chiclero's ulcer
- Bush yaws
- Picatura de pito

Aetiology and epidemiology. The site of development of leishmania in the gut of New World sandflies differs from that in Old World sandflies, and the parasites have been redesignated by the addition of the subgenus *vianna*, for example *Leishmania viannia brasiliensis* [32], but in this chapter the older, simpler terminology is retained, by which the parasites that cause disease in humans fall into the *L. brasiliensis* and *L. mexicana* complexes. American leishmaniasis is an endemic and mainly rural disease of damp, forested country in South and Central America [32]. It becomes epidemic among young people who go to work in the forests, 25% of young soldiers fighting in the jungle in certain areas and in villagers settled on land recently torn from the tropical forest. The optimum time for transmission is immediately after the rainy season.

Additionally, *L. b. brasiliensis* is becoming increasingly periurban [27], with a number of opportunistic hosts, including dogs and donkeys (whose true reservoir status is questionable). *Leishmania brasiliensis peruviana* is, by contrast, part of a mountainous zoonosis among peridomestic dogs, causing an endemic human infection that affects children especially. Vectors and reservoirs are given in Table 37.2. As increasing numbers of new species of parasite are identified, it is becoming clear that each is associated with its own complex of reservoir hosts and vector sandflies.

Pathogenesis. The pathology of the skin lesions does not differ significantly from that of Old World sores. The necrotic pattern, with ulceration of the overlying epidermis, is common [9]. Although recovery from an infection confers lifelong immunity against reinfection with the same species of parasite, that immunity does not develop early enough or adequately to prevent the blood-borne metastatic spread of parasites of the *L. brasiliensis* complex, especially *L. b. brasiliensis* itself, to the mucosa of the nose, mouth, palate or larynx. Here, they may later start to multiply and be recognized immunologically, and cause severe destructive lesions, known as espundia (Portuguese: a sponge) [33]. Histology of the mucosal lesion [34] shows a collection of lymphocytes and plasma cells around small arterioles in the nasal submucosa. Occasional leishmania are present in the vascular endothelial cells. Oedema, congestion and proliferation of vascular endothelium progress, leading to desquamation and necrosis of the overlying mucosa and underlying cartilage. Endarteritis and thrombosis add to the tissue destruction. Vascular supply is so reduced that only fibrous tissue remains.

Clinical features [35]. The main types of American leishmaniasis are as follows.

Cutaneous leishmaniasis due to *L. mexicana* complex. The vector of *L. m. mexicana* bites humans reluctantly, so only those who spend long periods of time in the forest, such as chicle collectors, are at risk. The lesions behave like those of *L. major* or *L. tropica*. Most are on the side of the face or behind the ears (Table 37.3). Lesions on the pinna of the ear may invade cartilage, take many years to heal and destroy the pinna [36]. *Leishmania mexicana amazonensis* is extremely common in forest rodents, but the vector is not anthropophilic, so human infections are rare. A large proportion of them give rise to diffuse cutaneous leishmaniasis, which does not differ significantly from its counterpart in the Old World, due to *L. aethiopica* [29].

Cutaneous leishmaniasis due to *L. brasiliensis* complex [37]. Sores are often large deep ulcers, usually with a raised edge. Sores due to *L. b. guyanensis* are often fleshy and protuberant, usually on the



Fig. 37.46 Mucosal leishmaniasis due to *Leishmania brasiliensis* in Brazil. The nasal septum anteriorly is most severely affected. (Courtesy of Dr L. Bakos, Porto Alegre, Brazil.)



Fig. 37.47 Severe mucocutaneous leishmaniasis from Brazil. (Courtesy of Professor P. Marsden, University of Brasilia, Brazil.)

limbs, often multiple, and resemble those of yaws, 'pian bois' [38]. This parasite and *L. b. panamensis* are especially associated with lesions along the draining lymphatics, but these may occur with any species. The lymphatic lesions may remain discrete small nodules, or may become inflamed and break through the skin to resemble the primary lesion. Lymphadenopathy is seldom marked.

American MCL [39,40]. Up to 40% of patients with sores due to *L. b. brasiliensis*, and a very much smaller proportion with sores due to *L. b. panamensis* and *L. b. guyanensis*, may develop mucosal lesions: 50% of mucosal lesions develop within 2 years of the appearance of the skin lesion, and 90% within 10 years. Delays of 35 years are recorded [33]. About 15% of patients with MCL give no previous history of a skin sore. The nasal mucosa is almost always affected, and in one-third of patients a second site is also involved, in the pharynx, palate, larynx or upper lip, in that order (Fig. 37.46). The usual initial lesion is a nodule on the inferior turbinate or septum, which causes stuffiness and obstruction. The destructive pathology perforates the septum and over years may destroy the nose, palate and lips (Fig. 37.47), which may become gross and protuberant, or scarred and constricted, causing difficulties in speech and eating. Death may supervene from secondary infection, starvation or laryngeal obstruction (Fig. 37.48). Spontaneous healing is virtually unknown.

Cutaneous leishmaniasis due to *L. b. peruviana*: 'uta' [35]. Lesions are less severe than those of *L. b. brasiliensis*. They heal spontaneously and are not known to cause MCL.



Fig. 37.48 Mucosal leishmaniasis from Brazil. A fatal case, showing the extensive laryngeal involvement. (Courtesy of Professor P. Marsden, University of Brasilia, Brazil.)

Diagnosis. The principles are the same as for cutaneous leishmaniasis of the Old World, but the differentials of syphilis, yaws, rhinoscleroma, sporotrichosis, histoplasmosis, leprosy and, especially, blastomycosis must also be considered. Lesions of sarcoidosis, lupus vulgaris and cutaneous T-cell lymphomas (CTCLs) can also resemble cutaneous leishmaniasis. For the diagnosis of MCL, the nasal lesion must be sampled, after careful cleaning, for culture, as well as examined by impression Giemsa smear and histology. Problems of contaminating infection can be avoided by inoculating some of the material into a hamster.

Treatment [12]. This is summarized in Table 37.3. Lesions due to *L. b. guyanensis* are particularly liable to relapse. Lesions due to *L. b. brasiliensis* should be treated systemically for a week beyond parasitological cure, in order to prevent MCL from developing

[28]. Previously untreated patients with MCL respond to pentavalent antimonials in a dose of 20 mg/kg/day, if given daily for 3–4 weeks [41]. Only 20% of relapsed patients will respond to the drug. Amphotericin is the drug of second choice, given in a dose of 1 mg/kg on alternate days for 2 months. Treatment that is inadequate in dose or duration leads to relapse and drug resistance. Secondary infection should be treated. Corticosteroids are useful to prevent laryngeal oedema that can otherwise complicate the start of treatment of laryngeal disease.

Cutaneous leishmaniasis in the returned traveller. Common and rare forms of cutaneous leishmaniasis are increasingly being described in non-endemic regions of the world. A recent retrospective survey at the Hospital for Tropical Diseases in London disclosed more than 50 new cases, including Old and New World cutaneous infections by *L. tropica, L. viannia braziliensis, L. major* and *L. donovani* complex. Patients with infections acquired in the New World manifested a more severe clinical picture and therefore sought medical referral at an earlier stage. The diagnosis was established by all four standard investigations including Giemsa smears for direct microscopy, H&E histology, parasitological culture and molecular diagnosis by PCR. Intravenous or intralesional treatment with sodium stibogluconate and other less frequently used agents resulted in cure for most of these patients [42]. Daily oral itraconazol or allopurinol in combination with weekly intralesional sodium stibogluconate has been successful in our hospital for most cases of simple cutaneous leishmaniasis. Educational strategies to increase the awareness of cutaneous leishmaniasis as an emerging problem in the UK are being directed at general practitioners, dermatologists and the public.

Visceral leishmaniasis

Synonyms
- Kala-azar
- 'Death fever'
- Dum-dum fever

Leishmania donovani donovani and its close relative *L. donovani infantum* are, by contrast with the other species of *Leishmania* that infect humans, normally viscerotropic, and cause a severe systemic infection, which may be accompanied by cutaneous manifestations.

Aetiology. There are four main zoogeographical zones in which visceral leishmaniasis is found (see Table 37.2). Transmission is peridomestic and tends to be stable in the Mediterranean focus. Dogs are the reservoir. Young children are most commonly affected. Infected adults tend to develop self-healing skin sores. In Brazil, peridomestic transmission from raiding foxes affects older children. A similar age group is affected in East Africa, where transmission takes place outside the houses in the evenings. In India, where the human is the reservoir, epidemics occur every 15 years or so and all age groups, previously uninfected, are susceptible. Travellers and tourists of any age group are susceptible in any of the four zones.

Pathogenesis. In over 90% of cases, the infection is subclinical and cutaneous hypersensitivity and immunity develop [43]. In the others, especially in the malnourished, the parasite invades and multiplies in reticuloendothelial cells of the spleen, liver, lymphoid tissue, bone marrow and gut submucosa. This reticuloendothelial bombardment is associated with the overproduction of polyclonal IgG, specific antibody production, and the formation of high titres of immune complexes and various autoantibodies. The spleen and, to a lesser extent, the liver become enlarged, and hypersplenism ensues, causing anaemia, leukopenia and thrombocytopenia. Organ function is usually well preserved until late in the disease, but specific and non-specific indices of cell-mediated immunity are depressed, and secondary infections are common and often fatal [44].

Clinical features [45]. After an incubation period of weeks to months, sometimes exceeding a year, fever develops, either insidiously or abruptly. The commonest additional symptoms are fatigue, discomfort from the presence of the enlarged spleen and cough, diarrhoea and epistaxis. Gross splenomegaly is the dominant physical sign; hepatomegaly, lymphadenopathy in some endemic zones, and signs of malnutrition, including pedal oedema, red, straight hair in Africans, and wasting also occur.

In a few cases in Africa, a primary skin sore has been described, like those of cutaneous leishmaniasis. Rarely, there may be an accompanying mucosal lesion. In Indian people especially, the skin of the face, hands, feet and abdomen becomes hyperpigmented, even black: kala-azar means black sickness. Despite epistaxis and sometimes jaundice, there is no evidence of cutaneous bleeding. In Iran, patients have been seen with numerous skin lesions [46].

Post-kala-azar dermal leishmaniasis (PKDL) (dermal leishmanoid). In 5% of East African patients, and 20% of Indian patients, a rash develops after the visceral disease has healed, either spontaneously or following treatment. A small proportion of patients with PKDL give no previous history of visceral disease. In Africa [47] the rash begins during convalescence, appearing on the cheeks, chin, ears and extensor aspects of forearms, buttocks and lower legs (Fig. 37.49). Usually, the rash comprises discrete papules, which on histological examination show a tuberculoid histology with scanty parasites. The leishmanin test is positive. The rash heals spontaneously over a few months. Presumably it represents the acquisition of specific cellular immunity that is clearing up scattered parasites that remained in the skin. Both cellular immunity and pentavalent antimonials are less efficient in the skin than in the viscera.

In India, by contrast, the rash appears 1–2 years after recovery, as hypopigmented macules, similar in appearance and distribution to those of lepromatous leprosy (Fig. 37.50). After a variable period of years or months, diffuse nodulation begins to develop in these macules (Fig. 37.51). The rash is progressive over many years and seldom heals spontaneously. The tongue, palate and genitalia may be involved. There may be lymphadenopathy, but the viscera are spared and there are no features of relapse of the previous systemic infection. Presumably, this condition represents



Fig. 37.49 Post-kala-azar dermal leishmaniasis. Typical facial papules in a Kenyan arising 6 weeks after treatment and healing spontaneously. (Courtesy of Dr J.D. Chulay.)

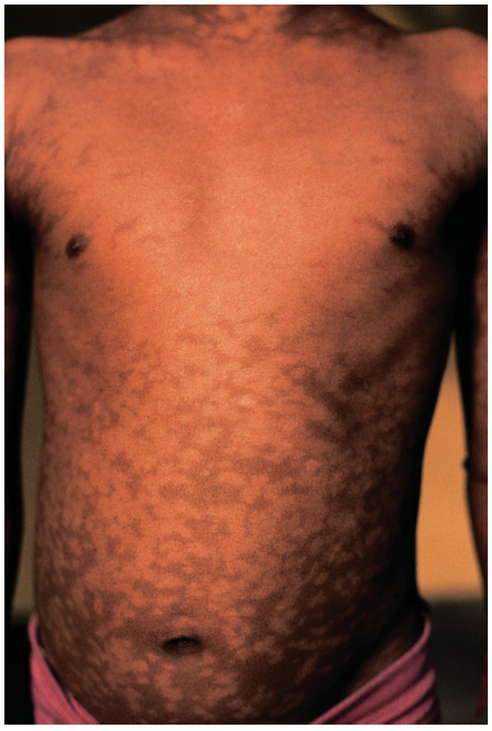


Fig. 37.50 Post-kala-azar dermal leishmaniasis in an Indian person showing the extensive hypopigmented macular rash.

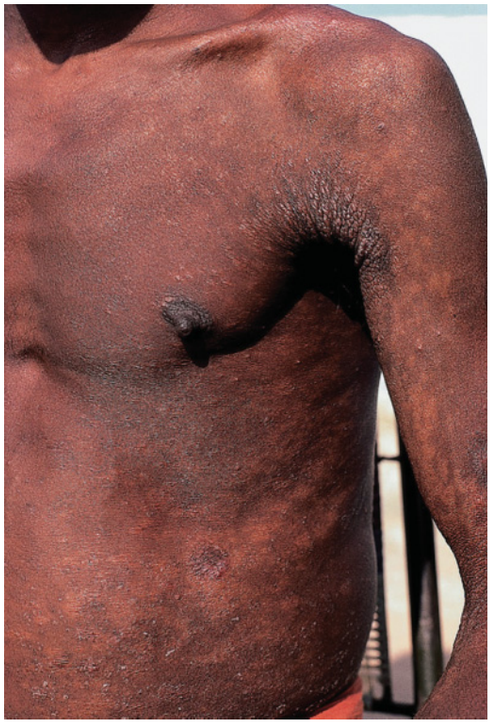


Fig. 37.51 Post-kala-azar dermal leishmaniasis in an Indian person. A later stage than that shown in Fig. 37.50. Papules are beginning to develop.

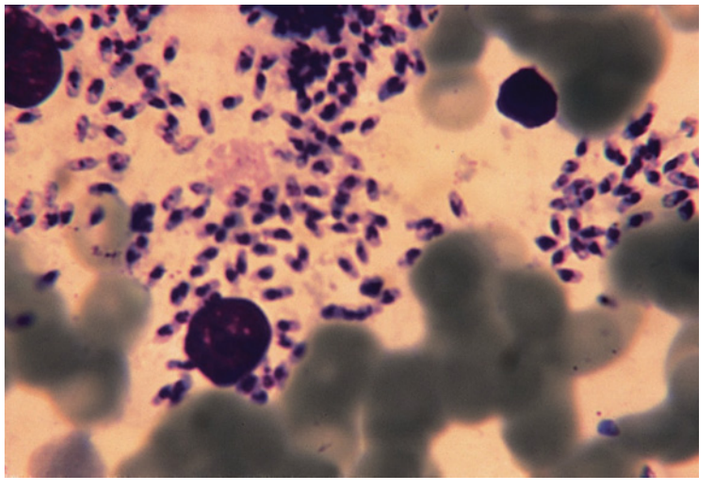


Fig. 37.52 Amastigotes of *Leishmania infantum* in a bone marrow smear from a patient with visceral leishmaniasis and the acquired immune deficiency syndrome. (Courtesy of Mr A.H. Moody, Hospital for Tropical Diseases, London, UK.)

cellular immunity against a dermotropic mutant of *L. donovani.* PKDL is thought to represent the intraepidemic reservoir of infection of visceral leishmaniasis in India. Histology shows a poorly differentiated infiltrate of chronic inflammatory cells, with a variable number of leishmania in dermal macrophages [48]. The leishmanin test is usually negative, but becomes positive after successful treatment [49].

Diagnosis. In visceral leishmaniasis, parasites may be demonstrated in aspirates of spleen, bone marrow, liver or lymph node, in that order of likelihood (Fig. 37.52). In PKDL, slit-skin smears are usually positive. Antibodies to *Leishmania* spp. may be demonstrated by a variety of techniques: indirect immunofluorescence, ELISA and direct agglutination tests are commonly performed [50]. The leishmanin test is negative, except in African PKDL.

Treatment. For visceral leishmaniasis, sodium stibogluconate is used, as for cutaneous leishmaniasis for 21–30 days, according to the endemic zone [27]. African PKDL does not require further treatment. Indian PKDL is treated with a further course of sodium stibogluconate.

Visceral leishmaniasis in patients with HIV infection [51]

The main area of overlap of these two infections is in southern Europe, especially Spain. Leishmaniasis may be acquired prior to or after the HIV infection, and may thus be primary or secondary to the HIV infection. In some patients, typical characteristics of fever and splenomegaly have not been present, and serological tests have been negative. On occasion, the parasite has been discovered by chance, for example in the biopsy of Kaposi's sarcoma, and disseminated dermatofibroma-like lesions containing amastigotes have been described in a patient with acquired immune deficiency syndrome (AIDS) coinfected with visceral *L. donovani* [52]. Aspirates of bone marrow and spleen show extremely heavy parasitization. Relapse and mortality rates are high. Treatment should be prolonged and monitored by splenic aspirates.

References

1 Leewenberg J, Bryceson ADM, Mbugua GG *et al*. The use of the leishmanin test to define transmission in Baringo District, Kenya. *E Afr Med J* 1983; **60**: 81–4.
2 Bryceson ADM. Clinical variations associated with various taxa of Leishmania. In: *Coll Int CNRS/INSERM 1984.* Montpelier: IMEEE, 1986: 221–8.
3 Lainson R. The American leishmaniases. Some observations on their ecology and epidemiology. *Trans R Soc Trop Med Hyg* 1983; **77**: 569–96.
4 Weatherall DJ, Ledingham JGG, Warrell DA, eds. *Oxford Textbook of Medicine*, 2nd edn. Oxford: Oxford University Press, 1987.
5 Rioux JA, Groubert JR, Lanotte G *et al*. Un cas de leishmaniose autochtone de la muqueuse nasale. *Les Cahiers D'orl* 1980; **15**: 423–5.
6 Bellazoug S, Ammar-Khodja A, Belkoid M *et al*. La leishmaniose cutanée du nord d'Algerie. *Bull Soc Pathol Exot Filiales* 1985; **75**: 615–22.
7 Briffa CV. Cutaneous leishmaniasis in the Maltese Islands. *Br J Dermatol* 1985; **113**: 370–1.
8 Bellazoug S. Une épidemie de leishmaniose cutanée dans la région de M'Sila (Algérie). *Bull Soc Pathol Exot* 1983; **75**: 497–504.
9 Ridley DS. A histological classification of cutaneous leishmaniasis and its geographical expression. *Trans R Soc Trop Med Hyg* 1980; **74**: 515–21.
10 Bowling J, Vega-López F. Lupoid leishmaniasis. *Clin Exp Dermatol* 2003; **28**: 683–5.
11 Bryceson ADM. Diffuse cutaneous leishmaniasis in Ethiopia. I. The clinical and histological features of the disease. *Trans R Soc Trop Med Hyg* 1969; **63**: 708–37.
12 Dowlati Y. Cutaneous leishmaniasis. *Int J Dermatol* 1979; **18**: 362–8.
13 Nadim A, Fagih M. The epidemiology of cutaneous leishmaniasis in Isfahan province of Iran. *Trans R Soc Trop Med Hyg* 1968; **61**: 534–49.
14 Rahim GF, Tatar IH. Oriental sore in Iraq. *Bull Endem Dis (Baghdad)* 1966; **8**: 29–54.
15 Kozevnikov PK. Two nosological forms of cutaneous leishmaniasis. *Am J Trop Med Hyg* 1963; **12**: 719–24.
16 Sacks DL, Kenney RT, Kreutzer RD *et al*. Indian kala-azar caused by *Leishmania tropica*. *Lancet* 1995; **345**: 959–61.
17 Evan-Paz Z, Sagher F. Some basic medical problems illustrated by experiments with cutaneous leishmaniasis. *S Afr Med J* 1961; **35**: 567–81.
18 Barnetson RS, Bryceson ADM. Cutaneous leishmaniasis and leprosy. *Trans R Soc Trop Med Hyg* 1978; **72**: 160–3.
19 Griffiths WA, Dutz W. Repeated tissue sampling with a dental broach. A trial in cutaneous leishmaniasis. *Br J Dermatol* 1975; **93**: 43–5.
20 Vega-López F. Diagnosis of cutaneous leishmaniasis. *Curr Opin Infect Dis* 2003; **16**: 97–101.
21 Bryceson A. Therapy in man. In: Peters W, Killick-Kendrick R, eds. *The Leishmaniases in Biology and Medicine*, Vol. 2. London: Academic Press, 1987: 56–61.
22 Neva FA, Petersen EA, Corsey R *et al*. Observations on local heat treatment for cutaneous leishmaniasis. *Am J Trop Med Hyg* 1984; **33**: 800–4.
23 Bassiouny A, El Meshad M, Talaat M *et al*. Cryosurgery in cutaneous leishmaniasis. *Br J Dermatol* 1982; **107**: 467–74.
24 Currie MA. Treatment of cutaneous leishmaniasis by curettage. *BMJ* 1983; **287**: 1053–6.
25 Duperrat B, Puissaant A, Fischer R *et al*. Leishmaniose cutanée plurifocale traitée par glucantime intralésionelle. *Bull Soc Fr Dermatol Syphiligr* 1966; **73**: 219–20.
26 El-On J, Weinrauch L, Livshin R *et al*. Topical treatment of recurrent cutaneous leishmaniasis with ointment containing paromomycin and methylbenzathonium chloride. *BMJ* 1985; **291**: 704–5.
27 WHO. *The Leishmaniases. Report of WHO Expert Committee.* Technical Report Series, 701. Geneva: World Health Organization, 1984.
28 Ballou WR, McClain JB, Gordon DM *et al*. Safety and efficacy of high dose sodium stibogluconate therapy of American cutaneous leishmaniasis. *Lancet* 1987; **ii**: 12–6.
29 Chulay JD, Anzeze EM, Koech DK *et al*. High dose sodium stibogluconate treatment of cutaneous leishmaniasis in Kenya. *Trans R Soc Trop Med Hyg* 1983; **77**: 717–21.
30 Bryceson ADM. Diffuse cutaneous leishmaniasis. II. Treatment. *Trans R Soc Trop Med Hyg* 1970; **64**: 369–79.
31 Lawn SD, Yardley V, Watson J, Vega-López F *et al*. New World cutaneous leishmaniasis in returned travellers: treatment failures using intravenous sodium stibogluconate. *Trans Roy Soc Trop Med Hyg* 2004; **97**: 443–4.
32 Lainson R, Shaw JJ. Evolution, classification and geographical distribution. In: Peters W, Killick-Kendrick R, eds. *The Leishmaniases in Biology and Medicine*, Vol. 1. London: Academic Press, 1987: 1–120.
33 Walton BC, Chinel LV, Eguiya V *et al*. Onset of espundia after many years of occult infection with *Leishmania braziliensis*. *Am J Trop Med Hyg* 1973; **22**: 696–8.
34 Klotz O, Lindenberg H. The pathology of leishmaniasis of the nose. *Am J Trop Med Hyg* 1923; **3**: 117–41.
35 Walton BC. American cutaneous and mucocutaneous leishmaniasis. In: Peters W, Killick-Kendrick R, eds. *The Leishmaniases in Biology and Medicine*, Vol. 2. London: Academic Press, 1987: 637–44.
36 Biagi FF. The treatment of Mexican cutaneous leishmaniasis (chicle ulcer). *Med Mex* 1953; **33**: 435–8.
37 Llanos-Cuentas EA, Marsden PD, Lago EL *et al*. Human mucocutaneous leishmaniasis in Tres Bracos, Bahia-Brazil: an area of *Leishmania braziliensis braziliensis* infection. III. Cutaneous disease, presentation and evolution. *Rev Soc Bras Med Trop* 1984; **17**: 169–77.
38 Floch PH. Sur deux observations intéressantes de leishmaniose forestière américaine. *Bull Soc Path Exot* 1954; **47**: 509–13.
39 Marsden PD. Mucosal leishmaniasis ('espundia' Escomel, 1911). *Trans R Soc Trop Med Hyg* 1986; **80**: 859–76.
40 Marsden PD, Llanos-Cuentos EA, Lago EL *et al*. Human mucocutaneous leishmaniasis in Tres Bracos, Bahia-Brazil: an area of *Leishmania braziliensis braziliensis* transmission. III. Mucosal disease, presentation and initial evolution. *Rev Soc Bras Med Trop* 1984; **17**: 179–86.
41 Marsden PD, Sampaio RN, Carvalho EM *et al*. High continuous antimony therapy in two patients with unresponsive mucosal lesions. *Am J Trop Med Hyg* 1985; **34**: 710–3.
42 Scarisbrick JJ, Chiodini PL, Vega-López F *et al.* Clinical features and diagnosis of 42 travellers with cutaneous leishmaniasis. *Travel Med Infect Dis* 2006; **4**: 14–21.
43 Pampiglione S, Manson-Bahr PEC, La Placa M *et al*. Studies on Mediterranean leishmaniasis. 3. The leishmanin test in kala-azar. *Trans R Soc Trop Med Hyg* 1975; **69**: 60–8.
44 Ho M, Koech DK, Iha DW *et al*. Immunosuppression in Kenyan visceral leishmaniasis. *Clin Exp Immunol* 1983; **51**: 207–14.
45 Rees PH, Kager PA. Visceral leishmaniasis and postkala-azar dermal leishmaniasis. In: Peters W, Killick-Kendrick R, eds. *The Leishmaniases in Biology and Medicine*, Vol. 2. London: Academic Press, 1987: 114–22.
46 Kumar PV, Sadeghi E, Torabi S. Kala azar with disseminated dermal leishmaniasis. *Am J Trop Med Hyg* 1989; **40**: 150–3.
47 Rashid JR, Chunge CN, Oster CN *et al*. Post kala-azar dermal leishmaniasis occurring after long cure of visceral leishmaniasis in Kenya. *E Afr Med J* 1986; **63**: 365–71.
48 Sen Gupta PC, Bhattacharjee B. Histopathology of post kala-azar dermal leishmaniasis. *J Trop Med Hyg* 1953; **56**: 110–6.

49 Haldar JP, Ghose S, Saha KC *et al*. Cell mediated immune response in Indian kala azar and post-kala-azar dermal leishmaniasis. *Infect Immun* 1983; **42**: 702–7.
50 Ho M, Leewenberg J, Mbugua G *et al*. An enzyme-linked immunosorbent assay (ELISA) for field diagnosis of visceral leishmaniasis. *Am J Trop Med Hyg* 1983; **32**: 943–6.
51 Montalban CK, Martinez-Fernandez R, Calleja JL *et al*. Visceral leishmaniasis (kala-azar) as an opportunistic infection in patients infected with the human immunodeficiency virus in Spain. *Rev Infect Dis* 1989; **11**: 655–60.
52 Forsyth SF, Lawn SD, Miller RF *et al*. Multiple dermatofibroma-like lesions in a HIV-positive patient coinfected with visceral leishmaniasis. *Br J Dermatol* 2003; **148**: 185–6.

Toxoplasmosis

Aetiology. The disease is caused by *Toxoplasma gondii*, a tiny sporozoon often assuming a crescentic shape, first identified in 1908 in a North African rodent, *Ctenodactylus gondii*. Cats are definitive hosts and a form of *Toxoplasma* cyst can be found in their faeces. Rodents and birds are the intermediate hosts. Larger mammals including humans are infected incidentally, by eating raw, infected meat or by ingesting oocysts in contaminated food or water.

Pathogenesis. The organism tends to invade the reticuloendothelial system and the endothelium of the blood vessels, forming granulomas with necrosis of affected tissues. Toxoplasmosis causes four types of disease in humans [1]:

1 An acute febrile lymphadenopathy
2 Fetal infection, causing brain damage
3 Ocular disease, usually due to reactivation of fetal infection
4 Disseminated disease in immunocompromised patients, including those with HIV infection, causing fulminating encephalitis.

Skin changes are uncommon and non-specific. In the congenital disease [1], macular and haemorrhagic eruptions predominate. Occasionally, abnormal hair growth and exfoliative dermatitis have been seen. In the acquired disease, macular, maculopapular, papular and haemorrhagic eruptions also occur and may be followed by scarlatiniform desquamation. A wide variety of other lesions have been described including bullae, nodules, livedo annularis, urticaria and an eruption like pityriasis lichenoides; conclusive evidence of a causal relationship is frequently wanting. A dermatomyositis-like syndrome is described [2,3].

Diagnosis is made on clinical evidence, and may be confirmed by demonstration of the organism in biopsy of lymph node, liver or spleen, bone marrow, or in cerebrospinal and ventricular fluid. Usually, the diagnosis is made serologically. Several methods are available, among them:

1 The Sabin–Feldman dye test, positive early and declining over 1–2 years, which measures mainly IgG antibodies
2 Direct agglutination of formalinized parasites—useful for screening, detects IgM and IgG antibodies
3 Indirect fluorescence—simple and safe, can be used to distinguish IgM from IgG antibodies, as can an IgM ELISA.

Treatment. The sulphonamides and pyrimethamine (Daraprim) act synergistically and are effective [4]. Severe side effects may occur due to interference with folic acid metabolism. For this reason, infections in immunologically normal individuals are not usually treated.

References

1 Beverley JKA. Congenital toxoplasma infections. *Proc R Soc Med* 1960; **53**: 111–3.
2 Pollock JL. Toxoplasmosis appearing to be dermatomyositis. *Arch Dermatol* 1979; **115**: 736–7.
3 Topi GC, D'Alessandro L, Catricata C *et al*. Dermatomyositis-like syndrome due to toxoplasma. *Br J Dermatol* 1979; **101**: 589–91.
4 McCabe RE, Remington JS. *Toxoplasma gondii*. In: Mandell GL, Douglas RG, Bennett JE, eds. *Principles and Practice of Infectious Disease*, 2nd edn. New York: Wiley, 1983: 1540–9.

CHAPTER 38

Diseases Caused by Arthropods and Other Noxious Animals

D.A. Burns
Leicester Royal Infirmary, Leicester, UK

Mechanisms of skin injury by arthropods, 38.1
Susceptibility to infestation or attack, 38.2
Histopathology of arthropod bites and stings, 38.2
Clinical features of arthropod bites, 38.3
Diagnosis, 38.3
Insect repellents, 38.5
Class Insecta, 38.5
Mosquitoes, gnats, midges and flies (Diptera), 38.5
Fleas (Siphonaptera), 38.11
Bees, wasps and ants (Hymenoptera), 38.13
Lice (Phthiraptera), 38.15
Bugs (Hemiptera), 38.23
Thrips (Thysanoptera), 38.26
Beetles (Coleoptera), 38.26
Cockroaches (Dictyoptera), 38.28
Locusts (Orthoptera), 38.28
Butterflies and moths (Lepidoptera), 38.28
Class Arachnida, 38.30
Spiders (Araneae), 38.30
Scorpions (Scorpiones), 38.33
Ticks (Acari), 38.33
Mites (Acari), 38.36
Class Chilopoda (centipedes) and Diplopoda (millipedes), 38.54
Other noxious or venomous invertebrates, 38.55
Leeches (Hirudinea), 38.55
Jellyfish, sea anemones, corals (Cnidaria), 38.55
Sea mats (Bryozoa), 38.58
Sea urchins (Echinoidea), 38.58
Sponges (Porifera), 38.59
Mollusca, 38.59
Noxious or venomous vertebrates, 38.59
Venomous fish, 38.59
Snake bites, 38.60
Other animal bites, 38.60
Dog and cat bites, 38.60
Seal finger, 38.61
Rodent bites, 38.61
Human bites, 38.61

Mechanisms of skin injury by arthropods

Arthropods produce their effects on the skin by a variety of mechanisms [1–4], more than one of which may be implicated simultaneously.

Mechanical trauma

The puncture wound or laceration produced by the penetration of the skin seldom causes serious disturbance to the host. The nature of the trauma inflicted depends upon the structure of the mouthparts, which show wide variation between different species. There are two methods of feeding on blood: 'vessel feeders' insert the tip of their mouthparts into a capillary, and 'pool feeders' lacerate the skin, damage blood vessels, and feed on the extravasated blood. Vessel feeders include sucking lice (Anoplura) and most mosquitoes, and pool feeders include stable flies and tsetse flies.

Injection of irritant, cytotoxic or pharmacologically active substances

An injected substance may contain pharmacologically active agents that produce local or, if in sufficient quantity, systemic effects. Salivary secretions and sting venoms may contain various enzymes such as: hyaluronidase, proteases, peptidases and phospholipases; kinins; histamine-liberating agents; histamine; 5-hydroxytryptamine or acetylcholine.

Injection of potential allergens

The vast majority of reactions to arthropod bites or stings depend upon the presence in the host, of specific antibodies to antigenic substances in the arthropod saliva or venom. Investigation of extracts of venom sacs and salivary glands from many species, using modern immunological techniques, has demonstrated the presence of numerous antigens, some specific for a single species, and others common to several related species or even to related genera.

The type of reaction provoked by an arthropod bite or sting in an individual patient largely depends on previous exposure to the same or related species. When an individual is bitten for the first time by a species whose salivary secretions contain no directly injurious substance there is commonly no reaction. After repeated bites, sensitivity starts to develop, manifest by an itchy papule developing about 24 h after each bite, and persisting for several days. With prolonged exposure, an immediate weal reaction occurs, to be followed by the delayed papular reaction. After a further period of exposure, the delayed reaction no longer occurs, and eventually there is no reaction at all. The patient is then said to be immune. Mellanby [5] demonstrated this sequence of events with mosquito bites, and a similar response is seen with the bites of many other arthropods.

Some patients show a severe, systemic hypersensitivity to arthropod allergens, manifested by anaphylaxis. The antigenic substances in the venoms of Hymenoptera (bees, wasps, hornets) are more likely to induce severe systemic hypersensitivity reactions than are the antigens of most other insects.

The capacity of a patient to respond to an antigenic stimulus is also an important factor in determining the reaction to an

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

arthropod. The reactions of patients who are immunosuppressed, as a result of either disease or therapy, are modified. Examples of this include the occurrence of crusted scabies in immunosuppressed individuals, and the response to bites in patients with chronic lymphatic leukaemia, human immunodeficiency virus (HIV) infection, and Epstein–Barr virus-associated natural killer cell leukaemia/lymphoma (see p. 38.6).

Secondary infection
Bacterial infection may be introduced at the time of the bite, but commonly gains entry as a result of scratching, and may confuse the clinical picture. Compartment syndrome caused by streptococcal cellulitis complicating an insect bite has been described [6].

Invasion of the host's tissues
Certain flies cause myiasis, in which the host's tissues are invaded by larvae (see p. 38.8).

Contact reactions
Simple contact with the secretions of certain arthropods, or with their living or dead bodies, may provoke irritant or allergic contact reactions. For example, the secretions of blister beetles produce a severe irritant reaction, and repeated handling of cockroaches may induce contact urticaria and dermatitis.

Reactions to retained mouthparts
Persistent granulomatous papules or nodules may be provoked by retained mouthparts, for example those of ticks.

Transmission of disease
Many diseases have arthropod vectors, for example malaria (mosquitoes), leishmaniasis (sandflies) and typhus (lice).

Susceptibility to infestation or attack
There are a number of environmental and social factors that determine the range of arthropod species to which an individual is exposed.

Persons living and working in tropical climates tend to wear fewer clothes, and therefore expose larger areas of the body to bites and stings. Clothing itself is essential to the existence of the body louse, and areas of constriction of clothing affect the distribution of the skin lesions caused by certain mites (e.g. harvest mites).

Certain occupations carry an increased risk of reactions to arthropods [7]. Forestry workers, for example, may be exposed to the urticating hairs of the caterpillars of certain species of Lepidoptera, and dock workers handling foodstuffs may be attacked by mites infesting the cargo.

In some societies, humans are exposed to attack by the parasites of the domestic animals with which they cohabit.

Housing can influence exposure to arthropod attack in a number of ways. Overcrowded homes favour transmission of ectoparasites, such as lice and the scabies mite, and dilapidated housing provides an ideal habitat for bed bugs. Spiders and scorpions will take up residence in garages, outhouses and woodpiles.

The methods by which an arthropod is attracted to its host species include body heat, carbon dioxide in exhaled air (e.g. mosquitoes, ticks, fleas, bedbugs), and displacement of air or vibrations caused by the host (e.g. fleas) [8]. Human sweat contains mosquito attractants, and anhidrotic subjects are unattractive to mosquitoes [9,10]. The human skin microflora may be responsible for producing compounds that attract mosquitoes and, as there is variation in the microflora between individuals, body odour probably contributes to susceptibility to biting [11,12]. Human odour also appears to play a part in attracting sandflies [13]. Pregnant women appear to be more attractive to mosquitoes than the non-pregnant [14,15].

There is also a suggestion of increased susceptibility to mosquito bites in patients with HIV infection receiving antiretroviral therapy and suffering from lipoatrophy [16].

Alcohol ingestion also seems to promote mosquito attraction [17].

Certain species of flies are attracted to skin ulcers and purulent material, in which they lay their eggs.

Insect pheromones play a part in attacks by large numbers of Hymenoptera. Honeybees, when stinging, emit an alarm pheromone from glands in their sting chambers, and this guides other bees to attack an intruder.

References

1 Alexander JO'D. General considerations. In: *Arthropods and Human Skin*. Berlin: Springer-Verlag, 1984: 3–9.
2 Bagnall B, Rook A. Arthropods and the skin. In: Rook A, ed. *Recent Advances in Dermatology*, Vol. 4. Edinburgh: Churchill Livingstone, 1977: 59–90.
3 Stawiski MA. Insect bites and stings. *Emerg Clin North Am* 1985; **3**: 785–808.
4 Walton GS. Cutaneous responses to arthropods. In: Verbov J, ed. *New Clinical Applications in Dermatology. Talking Points in Dermatology III*. Dordrecht, the Netherlands: Kluwer Academic Publishers, 1988: 103–24.
5 Mellanby K. Man's reaction to mosquito bites. *Nature* 1946; **158**: 554.
6 Evans AV, Darvay A, Jenkins IH, Russell-Jones R. Compartment syndrome following an insect bite. *Br J Dermatol* 2001; **144**: 636–8.
7 Krinsky W. Dermatoses associated with the bites of mites and ticks (Arthropodi: Acari). *Int J Dermatol* 1983; **22**: 75–91.
8 Marshall AG. *The Ecology of Ectoparasitic Insects*. London: Academic Press, 1981.
9 Khan AA, Maibach HI, Strauss WG, Fisher JL. Increased attractiveness of man to mosquitoes with induced eccrine sweating. *Nature* 1969; **223**: 859–60.
10 Maibach HI, Khan AA, Strauss WG *et al*. Attraction of anhidrotic subjects to mosquitoes. *Arch Dermatol* 1966; **94**: 215–7.
11 Keystone JS. Of bites and body odour. *Lancet* 1996; **347**: 1423.
12 Lu T, Qiu YT, Wang G *et al*. Odor coding in the maxillary palp of the malaria vector mosquito *Anopheles gambiae*. *Current Biology* 2007; **17**: 1533–44.
13 Hamilton JG, Ramsoondar TM. Attraction of *Lutzomyia longipalpis* to human skin odours. *Med Vet Entomol* 1994; **8**: 375–80.
14 Lindsay S, Ansell J, Selman C *et al*. Effect of pregnancy on exposure to malaria mosquitoes. *Lancet* 2000; **355**: 1972.
15 Espinosa FM, Alecrim WD, Daniel-Ribeiro CT. Attraction of mosquitoes to pregnant women. *Lancet* 2000; **356**: 685.
16 Greub G, Fellay J, Telenti A. HIV lipoatrophy and mosquito bites. *Clin Infect Dis* 2002; **34**: 288–9.
17 Shirai O, Tsuda T, Kitagawa S *et al*. Alcohol ingestion stimulates mosquito attraction. *J Am Mosq Control Assoc* 2002; **18**: 91–6.

Histopathology of arthropod bites and stings [1–3]
The histopathological changes associated with arthropod bites depend upon a number of factors, including the arthropod involved, the type of immunological reaction provoked, and the duration of the lesion.

In papular urticaria there is prominent papillary dermal oedema and a perivascular chronic inflammatory infiltrate with a significant admixture of eosinophils.



Fig. 38.1 Typical papular urticaria. In this case, in response to flea bites.

Bullous reactions develop beneath a more or less intact epidermis, and may be multilocular.

Chronic reactions often have a pseudolymphomatous appearance. The dermis contains a dense inflammatory infiltrate of lymphoid cells and histiocytes, with an admixture of eosinophils and plasma cells, and the presence of atypical mononuclear cells with hyperchromatic nuclei. Secondary lymphoid follicles with germinal centres are sometimes formed. Multinucleated cells may also occur. If retained mouthparts are present, there may also be giant cells of foreign-body type.

Additional histopathological features associated with particular arthropods are noted in the relevant sections of this chapter.

References

1 Weedon D. *Skin Pathology*, 2nd edn. Edinburgh: Churchill Livingstone, 2005: 738–49.

2 Calnan CD. Persistent insect bites. *Trans St John's Hosp Dermatol Soc* 1969; **55**: 198–201.

3 Ploysangam T, Breneman DL, Mutasim DF. Cutaneous pseudolymphomas. *J Am Acad Dermatol* 1998; **38**: 877–95.

Clinical features of arthropod bites

The very large number of species of biting and stinging arthropods, their different feeding habits, and the variation in individual patients' responses to the various irritants and allergens injected determine the diversity of clinical features. The type and distribution of lesions produced by individual arthropods are discussed in the relevant sections throughout this chapter.

The most frequently encountered response is papular urticaria (Fig. 38.1). Initially, an extremely itchy urticarial weal develops at the site of the bite, and this is succeeded by a firm pruritic papule, which usually persists for several days. The weal and papule may show a central haemorrhagic punctum, and the papule may be surmounted by a tiny vesicle. Lesions are often grouped in clusters, and develop in crops at irregular intervals.

The number and distribution of skin lesions produced by the bites depend upon the type of exposure and the feeding habits of the arthropod involved. New bites by the same species will often cause a recrudescence of activity in existing lesions.



Fig. 38.2 Bullous lesions in response to arthropod bites. (Courtesy of Dr F.A. Ive, Durham, UK.)

Bullous reactions are common on the lower legs (Fig. 38.2), but may occur in other sites, especially in children. In the presence of lower limb venous hypertension, haemorrhagic or ulcerated lesions may develop. More severe local changes are sometimes found, with cellulitis and lymphangitis in the apparent absence of secondary infection. Eruptive pseudoangiomatosis-like lesions have also been reported as a response to arthropod bites [1,2].

Irritation is an almost constant symptom, and rubbing and scratching may increase the inflammatory changes, and induce eczematization. When the bites are very numerous, or if the local reaction is severe, there may be fever and malaise.

Secondary infection is a common complication, and may be manifest as impetigo, folliculitis, cellulitis and lymphangitis.

Anaphylactic shock is unusual except after Hymenoptera stings, but is occasionally seen with some other arthropods.

Bite reactions may persist for months. Tick attachment sites, in which the mouthparts may be retained, are the most likely to persist, but so may bites of mosquitoes and other arthropods.

References

1 Restano L, Cavalli R, Colonna C *et al*. Eruptive pseudoangiomatosis caused by an insect bite. *J Am Acad Dermatol* 2005; **52**: 174–5.

2 Ban M, Ichiki Y, Kitajima Y. An outbreak of eruptive pseudoangiomatosis-like lesions due to mosquito bites: erythema punctatum Higuchi. *Dermatology* 2004; **208**: 356–9.

Diagnosis

The diagnosis of arthropod bites is often self-evident, for example when the patient has spent the afternoon in the garden on a hot day in summer and subsequently develops typical lesions on



Fig. 38.3 Typical heavy scale in the coat of a dog suffering from *Cheyletiella* infestation.



Fig. 38.4 Typical 'pepper and salt' appearance of flea eggs and faeces in the debris from a cat's bedding.

exposed areas of skin. However, difficulty arises when the source of the bites is not immediately obvious.

The distribution of the bites may provide a clue to their origin, for example localization to the abdomen and thighs in cheyletiellosis or contact with sarcoptic mange in dogs, and involvement of the legs below the knees when the lesions are produced by cat or dog fleas. Patients should be asked about domestic pets; not only their own, but also those in the homes of close relatives who are visited regularly, as ectoparasites associated with pet animals are often the source of persistent arthropod bites. If the bites are not localized, but scattered all over the body, consider reactions to arthropods biting in the patient's bedroom, such as bird fleas, bird mites or bedbugs. Enquire if the patient has recently moved house. It may be that the previous owners of the new home kept pet animals, and have left a legacy of domestic flea infestation. Even if the house remained empty for a considerable time before the new owners took up residence, the flea population will be waiting in cocoons to emerge when the new occupants arrive. Adult fleas can survive starvation for variable lengths of time depending upon species and environmental conditions [1,2]—a newly emerged and unfed dog flea, *Ctenocephalides canis*, will survive for approximately 60 days. In the absence of their natural hosts, such animal flea populations will not usually survive for more than a few months.

If the history and examination do not suggest a possible source for the problem, or if the dermatologist wishes to confirm a suspected source, the following procedures may be useful [3,4].

1 The patient's pet animals should be examined, if possible, for signs of skin disease. Cheyletiellosis and canine scabies produce characteristic changes on an affected animal [5]. Skin scrapings will confirm sarcoptic mange, and vigorous combing of scale from the coat of a dog suffering from cheyletiellosis (Fig. 38.3) will provide material in which *Cheyletiella* mites may be identified. If the animal cannot be examined, the patient should be provided with a sheet of black paper, and asked to collect brushings or combings from the animal's coat for subsequent examination.
2 If domestic infestation with cat or dog fleas is suspected, this can often be confirmed by examination of debris from the pet's bedding. The patient is supplied with a large polythene bag and instructed to place the pet's bedding in the bag and shake it vigorously for a few minutes. The bedding is then removed, the bag sealed, and delivered to the dermatologist for microscopy of the debris. Macroscopically, flea eggs and faeces have a 'pepper and salt' appearance (Fig. 38.4), and the larvae are grub-like. For identification, adult fleas should be 'cleared' in 10% potassium hydroxide for 24 h so that the majority of the pigment is removed and the anatomical details revealed. Cat and dog fleas are readily identified, but if unfamiliar species are encountered, the help of an entomologist with an interest in Siphonaptera should be sought. Correct identification of fleas is important so that proper control measures may be carried out [6].
3 If problems from bird fleas or bird mites are suspected, it is often of value to examine dust obtained with a vacuum cleaner from bedrooms. This is, however, time consuming and requires some expertise.
4 It may be necessary to visit the patient's home to establish whether there are birds' nests under the eaves, which might be a source of fleas or mites, or to take specimens from household pets.
5 Mites that might have relevance to human dermatoses may be isolated from clothing, furnishings or bedding by the techniques described by Hewitt *et al*. [7].

An entomologist is often invaluable in these situations, not only for identification of arthropods, but also to advise about their relevance to the situation. An arthropod discovered at the scene of the crime may only be an innocent bystander.

In some cases, in spite of extensive efforts, the source of the bites remains unknown, and the dermatologist can then only treat the problem symptomatically with oral antihistamines, topical antipruritics and insect repellents.

References

1 Busvine JR. *Insects and Hygiene*. London: Chapman and Hall, 1980.
2 Marshall AG. *The Ecology of Ectoparasitic Insects*. London: Academic Press, 1981.

3 Burns DA. The investigation and management of arthropod bites acquired in the home. *Clin Exp Dermatol* 1987; **12**: 114–20.
4 Hewitt M, Walton GS, Waterhouse M. Pet animal infestation and human skin lesions. *Br J Dermatol* 1971; **85**: 215–25.
5 Scott DW, Miller WH, Griffin CE. *Muller and Kirk's Small Animal Dermatology*, 6th edn. Philadelphia: WB Saunders, 2000.
6 Hosie G. Observations on the occurrence of *Ceratophyllus gallinae* around new housing estates in the west of Scotland. In: Traub R, Starcke H, eds. *Fleas*. Rotterdam: AA Balkema, 1980: 415–20.
7 Hewitt M, Barrow GI, Miller DC *et al*. Mites in the personal environment and their role in skin disease. *Br J Dermatol* 1973; **89**: 401–9.

Insect repellents [1–4]

There are several strategies that can be employed in attempts to avoid arthropod bites/stings and arthropod-related disease transmission, including protective clothing, insecticide-impregnated netting and repellents. With regard to the last mentioned, there are two principal categories of commercially available insect repellents—plant-derived essential oils and synthetic chemicals. The former group includes citronella, oil of eucalyptus, peppermint, tea-tree oil, lavender, soybean oil and neem oil. DEET (*N*,*N*-diethyl-*m*-toluamide [or *N*,*N*-diethyl-3-methylbenzamide]), the most widely used repellent, is an example of the latter.

Recently introduced repellents include DEPA (*N*,*N*-diethyl phenylacetamide), PMD (para-menthane-3,8-diol) and picaridin, a synthetic derivative of pepper.

Unfortunately, with many of these agents, their volatility means that the repellent effect is transient, and benefit can only be sustained by repeated application. In addition, effectiveness is often limited to a narrow spectrum of susceptible arthropods.

References

1 Brown M, Hebert AA. Insect repellents: an overview. *J Am Acad Dermatol* 1997; **36**: 243–9.
2 Fradin MS, Day JF. Comparative efficacy of insect repellents against mosquito bites. *N Engl J Med* 2002; **347**: 13–8.
3 Elston DM. Prevention of arthropod-related disease. *J Am Acad Dermatol* 2004; **51**: 947–54.
4 Debboun M, Frances SP, Strickman DA. *Insect Repellents: Principles, Methods and Uses*. Boca Raton: CRC Press, 2006.

Class Insecta

Mosquitoes, gnats, midges and flies (Diptera)

The order Diptera is one of the largest of the insect orders. Diptera are two-winged flies with a single pair of membranous forewings, and with hindwings modified as balancing organs (halteres). Most feed on nectar, plant exudates or decaying animal and vegetable matter, but some are blood-sucking, and some have larvae parasitic on humans. To the dermatologist, the Diptera are important as biting insects and as the cause of myiasis, in addition to their capacity to transmit disease.

The Diptera are currently usually classified in two suborders based on characteristics shown by larvae, pupae and adults—the Nematocera and the Brachycera. Detailed information on the morphology, biology and medical importance of Diptera is provided in comprehensive texts by Kettle [1], and Lane and Crosskey [2].

Suborder Nematocera (long-horned flies)

The Nematocera are small flies with long, many-segmented, filamentous antennae. With a few exceptions the medically important species are blood-suckers.

Family Culicidae (mosquitoes)

Mosquitoes have worldwide distribution, and are responsible for the transmission of a number of diseases, including malaria, filariasis, yellow fever, West Nile virus and dengue fever. Human malaria is transmitted exclusively by *Anopheles* species. Both male and female mosquitoes will imbibe sweet juices from flowers or ripe fruit, but only the females pierce the skin and suck the blood of vertebrate animals. Most mosquitoes are nocturnal feeders, but a few species are diurnal. The eggs of mosquitoes are deposited on or near water, and adults develop via aquatic larval and pupal stages.

Family Psychodidae (sandflies)

These are tiny (2–3 mm long), hairy flies with lanceolate wings and long legs. They are widely distributed, especially in the tropics and subtropics.

Genus *Phlebotomus*. Species of *Phlebotomus* are vectors of cutaneous and visceral leishmaniasis in the Old World. *Phlebotomus* species are also vectors of sandfly or papatasi fever. *Phlebotomus* bites cause a condition known as harara (urticaria multiformis endemica) in Israel and the surrounding countries.

Genus *Lutzomyia*. *Lutzomyia* species are vectors of cutaneous and visceral leishmaniasis and bartonellosis in the New World.

Family Simuliidae [3]

Popularly known as blackflies, and with a worldwide distribution, these are small (2–6 mm) flies with a characteristic humped thorax, and short, broad wings. They breed only in areas of fast-flowing water, and bite during the day.

Over large parts of the tropics several species of blackfly are responsible for transmission of onchocerciasis—principally the *Simulium damnosum* complex (several closely related species) in West Africa, *S. neavei* in East Africa, *S. metallicum* in Venezuela and *S. ochraceum* in Guatemala. In temperate regions, the greatest problem caused by simuliids is their painful bites, and some species are such a persistent nuisance at certain times of the year that they may make large areas unpleasant to live or work in. In Yugoslavia, the notorious Golubatz fly, *S. columbaschense* (*S. columbaczense*), which bred in the Danube at Golubatz, caused both mortality among livestock and human misery until environmental changes eliminated it. In North America, the most troublesome biting species are *S. venustum*, which is holarctic and occurs from Alaska to Greenland and south to Texas and South Carolina, and *Prosimulium mixtum*, which occurs in the north-eastern USA and eastern Canada.

S. posticatum (the Blandford fly), formerly named *S. austeni* Edwards, is widely distributed throughout Europe and European Russia. In England, it is found in an arc running from East Anglia through Oxfordshire into Dorset. In the Stour valley area of Dorset, particularly in the region of Blandford Forum, the fly is notorious

for the severity of the reaction to its bites [4–6]. It had not been known as a pest in the UK prior to the 1960s. The eggs are laid in cracks in vertical river banks, a short distance above the water [7]. The larvae are concentrated in stretches of fast-flowing water immediately downstream of barrages and weirs, where they attach themselves to weeds or stones and feed on phytoplankton. Adults hatch in May, and are on the wing in May, June and early July. Females require a blood meal before oviposition, and although they will bite various wild and domestic animals, they appear to prefer humans and dogs. In the 1990s, biological control, using a bacterium (*Bacillus thuringiensis* var *Israelensis*) that selectively targeted the fly larvae, significantly reduced the severity of the problem.

Family Ceratopogonidae (biting midges; 'punkies'; 'no-see-ums')

These small flies (1–3 mm in length) have a worldwide distribution, and are notorious as biting pests. The biting midges of the West Highlands of Scotland (the commonest species of which is *Culicoides impunctatus*), for example, are an intolerable nuisance, and pose a problem to the Scottish tourist industry [8]. Males and females feed on nectar, but most females require a blood meal for maturation of the ovaries and egg production. There are four genera that suck blood: *Culicoides, Leptoconops, Austroconops* and *Forcipomyia* (subgenus *Lasiohelea*). They breed in rivers, swamps and marshes; they often occur in swarms and will readily attack any mammal in their vicinity. A few species enter homes and bite at night.

The genus *Culicoides* is widely distributed. *Leptoconops* species are largely restricted to the warmer parts of the Old and New World. *Austroconops* contains only one species, which is restricted to western Australia. *Lasiohelea* species are principally associated with tropical and subtropical rain forests.

Suborder Brachycera (circular-seamed flies, muscoid flies and short-horned flies)

The Brachycera are stout-bodied flies with short antennae, often composed of three segments, and never more than six.

Family Tabanidae

Many species of three genera of this family will attack humans—*Tabanus* (horse flies), *Chrysops* (deer flies) and *Haematopota* (clegs). They are large flies, and have a worldwide distribution. Only females suck blood. Tabanid flies act as vectors for loiasis and tularaemia, and some species may transmit anthrax mechanically [9].

Family Rhagionidae (snipe flies)

Species of *Symphoromyia* occurring in the Palaearctic and Nearctic regions are vicious biters. *Atherix* is another blood-sucking genus in the Nearctic and Neotropical regions, and *Spaniopsis* is troublesome in Australia.

Family Chloropidae (eye flies; frit flies)

These flies are about 2 mm in length. The adults of some species are attracted to open sores, body secretions, and the eyes, particularly eyes with a copious discharge. *Hippelates* and *Siphunculina* species are associated with humans and can act as mechanical vectors of yaws, conjunctivitis and streptococcal skin infection.

Family Muscidae (house flies; stable flies; tsetse flies)

This family includes the familiar house fly *Musca domestica* and the lesser house fly *Fannia canicularis*. These do not bite, but may act as mechanical vectors of disease. The muscids *Stomoxys calcitrans* (stable fly) and *Haematobia* species (horn flies) have mouthparts modified for sucking blood. They usually feed on large quadrupeds, but can inflict painful bites on humans. Tsetse flies are vectors of trypanosomiasis. They are confined to Africa south of the Sahara.

Family Hippoboscidae (flat flies; louse flies; keds)

Members of this family are blood-sucking ectoparasites of birds and animals. Several species of ked have been recorded as biting humans [10,11].

Members of several other families of Diptera are important in that their larvae may cause myiasis (p. 38.8).

Clinical features [12,13]. The clinical features of the bites of insects of this large and diverse order are variable. The nature of the pharmacologically active substances injected, and the degree of acquired allergic sensitivity to the antigenic substances in the saliva, are the main factors that determine the reaction. For most of the Diptera, the allergic component is by far the more important. The nature of any injected toxins is usually unknown and the effects attributable to them are usually slight. The clinical picture will also be influenced by the biting habits of the species concerned.

The reaction to mosquito bites is determined by previous exposure, and the sequence of events following multiple bites was elucidated by Mellanby [13]. In an individual not previously exposed, the bites produce no response. With subsequent bites, a delayed reaction occurs, consisting of pruritic papules, which develop approximately 24 h after the bites and persist for several days. After repeated bites for several weeks, the response changes, with the appearance of an immediate weal at the bite site. This resolves after about 2 h, to be replaced by the delayed reaction. Further exposure provokes the immediate reaction, but not the delayed response. Eventually, tolerance is acquired, and no reaction occurs. Studies of the bite reaction in relation to age have shown an increase in immediate reactions from early childhood to adolescence, and a decrease thereafter. The appearance and intensity of delayed reactions decreases with age [14]. It has been proved conclusively that the mosquito salivary glands are the source of the antigens responsible for the bite reactions [15].

Anaphylactic reactions to mosquito bites are rare [16]. Gaig *et al*. reported a patient with a serum sickness-like illness associated with mosquito bites [17]. Severe local reactions are not uncommon, and in highly sensitive subjects bullae, cellulitis and eczematization are often seen, especially on the legs. Gravitational factors probably play a role in the development of bullae on the legs [18]. Exaggerated hypersensitivity responses to mosquito bites have been reported in patients suffering from chronic lymphatic leukaemia [19–22]. However, although the clinical picture and histological features are typical of arthropod bites, in many cases patients

do not recall being bitten [21,23]. Exaggerated responses to mosquito bites have also been described in patients with HIV infection [24,25], and a chronic pruritic eruption in patients with AIDS in South Florida has been attributed to mosquito bites [26].

In recent years, there have been a number of reports from Japan of severe hypersensitivity to mosquito bites preceding the development of malignant histiocytosis [27–29]. This has now been characterized as a disease in which there is a triad of hypersensitivity to mosquito bites, chronic Epstein–Barr virus infection, and natural killer cell leukaemia/lymphoma [30–32]. It affects predominantly Japanese in the first two decades of life. The skin lesions are bullae, which develop at mosquito bite sites, undergo necrosis, and heal with residual scarring. Accompanying the skin lesions are systemic features, principally high fever and general malaise. Affected individuals die of haemophagocytic syndrome (malignant histiocytosis).

Multiple sandfly bites are responsible for the syndrome known as harara (urticaria multiformis endemica), which occurs in Israel and surrounding countries [33]. Skin lesions occur on exposed parts of the body, and are composed of urticated papules and papulovesicles, and bullous lesions, frequently with secondary infection.

The bites of Simuliidae, which may be very numerous, are on exposed skin. The sites of the bites are often marked by a small blood crust with surrounding ecchymosis. Within a few hours, small, pruritic papules develop, and these resolve after several days. However, severe reactions with marked oedema of the limbs and constitutional upset occasionally occur, and in some cases nodules and discoid eczematous areas persist at the sites of the bites for several months [34]. The bites of the Blandford fly occur most frequently on the legs, and women are principally affected [5,6]. The bites often produce a severe local reaction, with oedema and blistering, and may be accompanied by systemic manifestations, including pyrexia, arthralgia and meningism.

The biting midges of the family Ceratopogonidae generally cause small, papular lesions on exposed parts of the skin, but wealing and bulla formation may occur in sensitized individuals. Weal-like lesions, papules and persistent nodules have been described following bites from *Leptoconops torrens* in California [35].

Midges of the family Chironomidae are closely related to ceratopogonids. These midges do not bite, but hypersensitivity to their larvae, used as aquarium fish food and as bait, is well recognized [36,37], and includes contact urticaria [38] and protein contact dermatitis [39].

The bites of keds may be followed by the development of persistent pruritic papules [11].

The bites of horse flies and stable flies are often very painful and frequently become secondarily infected.

References

1 Kettle DS. *Medical and Veterinary Entomology*, 2nd edn. Wallingford: CAB International, 1995.

2 Lane RP, Crosskey RW, eds. *Medical Insects and Arachnids*. London: Chapman and Hall, 1993.

3 Laird M, ed. *Blackflies*. London: Academic Press, 1981.

4 Hansford RG, Ladle M. The medical importance and behaviour of *Simulium austeni* Edwards (Diptera: Simuliidae) in England. *Bull Entomol Res* 1979; **69**: 33–41.

5 Healing TD, Dlugolecka MD, Morgan DTJ *et al*. The Blandford fly. *Communicable Diseases Report*, 1 July 1988.

6 Inskip H, Campbell L, Godfrey K, Coggon D. A survey of the prevalence of biting by the Blandford fly during 1993. *Br J Dermatol* 1996; **134**: 696–9.

7 Welton JS, Bass JAB, Ladle M *et al*. Distribution of oviposition sites and characteristics of egg development in the 'Blandford fly' *Simulium posticatum* (Diptera: Simuliidae). *J Appl Ecol* 1987; **24**: 865–79.

8 Stuart AE, Evans A, Brooks C *et al*. The biting midge of the West Highlands: fifty years of research. *Scott Med J* 1996; **41**: 143–6.

9 McKendrick DRA. Anthrax and its transmission to humans. *Cent Afr J Med* 1980; **26**: 126–9.

10 Alexander JO'D. Reactions to Dipterous biting flies. In: *Arthropods and Human Skin*. Berlin: Springer-Verlag, 1984: 115–33.

11 Rantanen T, Reunala T, Vuojolahti P, Hackman W. Persistent pruritic papules from deer ked bites. *Acta Derm Venereol (Stockh)* 1982; **62**: 307–11.

12 Allen JR. Mosquitoes and other biting flies. In: Parish CL, Nutting WB, Schwartzman RM, eds. *Cutaneous Infestations of Man and Animal*. New York: Praeger, 1983: 344–55.

13 Mellanby K. Man's reaction to mosquito bites. *Nature* 1946; **158**: 554.

14 Oka K, Ohtaki N. Clinical observations of mosquito bite reactions in man: a survey of the relationship between age and bite reaction. *J Dermatol* 1989; **16**: 212–9.

15 Hudson A, Bowman L, Orr CWM. Effects of absence of saliva on blood feeding by mosquitoes. *Science* 1960; **131**: 1730–1.

16 Galindo PA, Gomez E, Borja J *et al*. Mosquito bite hypersensitivity. *Allergol Immunopathol (Madr)* 1998; **26**: 251–4.

17 Gaig P, Garcia-Ortega P, Enrique E *et al*. Serum sickness-like syndrome due to mosquito bite. *J Invest Allergol Clin Immunol* 1999; **9**: 190–2.

18 Walker GB, Harrison PV. Seasonal bullous eruption due to mosquitoes. *Clin Exp Dermatol* 1985; **10**: 127–32.

19 Lidén S, Bäck O, Tärnvik A. Chronic lymphatic leukaemia, malignant melanomas and mosquito hypersensitivity. *Acta Derm Venereol (Stockh)* 1977; **57**: 81–92.

20 Weed RI. Exaggerated delayed hypersensitivity to mosquito bites in chronic lymphatic leukaemia. *Blood* 1965; **26**: 257–68.

21 Davis MDP, Perniciaro C, Dahl PR *et al*. Exaggerated arthropod-bite lesions in patients with chronic lymphocytic leukemia: a clinical, histopathologic, and immunopathologic study of eight patients. *J Am Acad Dermatol* 1998; **39**: 27–35.

22 Rongioletti F, Rebora A. Follicular mucinosis in exaggerated arthropod-bite reactions of patients with chronic lymphocytic leukemia. *J Am Acad Dermatol* 1999; **41**: 500.

23 Barzilai A, Shpiro D, Goldberg I *et al*. Insect bite-like reaction in patients with hematologic malignant neoplasms. *Arch Dermatol* 1999; **135**: 1503–7.

24 Diven DG, Newton RC, Ramsy KM. Heightened cutaneous reactions to mosquito bites in patients with acquired immunodeficiency syndrome receiving zidovudine. *Arch Intern Med* 1988; **148**: 2296.

25 Smith KJ, Skelton HG 3rd, Vogel P *et al*. Exaggerated insect bite reactions in patients positive for HIV. *J Am Acad Dermatol* 1993; **29**: 269–72.

26 Penneys NS, Nayar JK, Bernstein H, Knight JW. Chronic pruritic eruption in patients with acquired immunodeficiency syndrome associated with increased antibody titers to mosquito salivary gland antigens. *J Am Acad Dermatol* 1989; **21**: 421–5.

27 Hidano A, Kawakami M, Yago A. Hypersensitivity to mosquito bite and malignant histiocytosis. *Jpn J Exp Med* 1982; **52**: 303–6.

28 Mohri S, Kawashima Y, Uchigata Y *et al*. A case of mosquito hypersensitivity terminating as malignant histiocytosis. *J Dermatol* 1982; **9**: 437–43.

29 Suenaga Y. Mosquito bites: especially on mosquito hypersensitivity and malignant histiocytosis. *Nishinihon Hifuka* 1987; **49**: 252–9.

30 Ohsawa T, Morimura T, Hagari Y *et al*. A case of exaggerated mosquito-bite hypersensitivity with Epstein-Barr virus-positive inflammatory cells in the bite lesion. *Acta Derm Venereol (Stockh)* 2001; **81**: 360–3.

31 Ishihara S, Yabuta R, Tokura Y *et al*. Hypersensitivity to mosquito bites is not an allergic disease, but an Epstein-Barr virus-associated lymphoproliferative disease. *Int J Haematol* 2000; **72**: 223–8.

32 Tokura Y, Ishihara S, Tagawa S *et al*. Hypersensitivity to mosquito bites as the primary clinical manifestation of a juvenile type of Epstein-Barr virus-associated natural killer cell leukemia/lymphoma. *J Am Acad Dermatol* 2001; **45**: 569–78.

33 Dostrovsky A. Urticaria multiformis endemica (Harara). In: Simons RDCP, ed. *Handbook of Tropical Dermatology*. Amsterdam: Elsevier, 1953: 889–94.

34 Gudgel EF, Grauer FH. Acute and chronic reactions to black fly bites (*Simulium* fly). *Arch Dermatol Syphilol* 1954; **70**: 609–15.
35 Steffen C. Clinical and histopathologic correlation of midge bites. *Arch Dermatol* 1981; **117**: 785–7.
36 Galindo PA, Feo F, Gomez E *et al*. Hypersensitivity to chironomid larvae. *J Investig Allergol Clin Immunol* 1998; **8**: 219–25.
37 Cabrerizo-Ballesteros S, de Barrio M, Baeza ML *et al*. Allergy to chironomid larvae (red midge larvae) in non-professional handlers of fishfood. *J Investig Allergol Clin Immunol* 2006; **16**: 63–8.
38 Galindo PA, Melero R, Garcia R *et al*. Contact urticaria from chironomids. *Contact Dermatitis* 1996; **34**: 297.
39 De Jaegher C, Goossens A. Protein contact dermatitis from midge larva (*Chironomus thummi thummi*). *Contact Dermatitis* 1999; **41**: 173.

Myiasis

Myiasis is the infestation of body tissues of humans and animals by the larvae (maggots) of Diptera [1–6]. Parasitologically, flies may be classified into two main myiasis-producing groups: obligatory and facultative. Obligatory myiasis-producers always pass their larval stage parasitically in the body of an animal. Larvae of facultative myiasis-producers usually develop on decaying flesh or vegetable matter, but may infest wounds.

Clinically, myiasis can be classified according to the part of the body affected. Cutaneous myiasis includes wound myiasis, and furuncular myiasis, in which larvae penetrate and develop within the skin. In nasopharyngeal myiasis, the nose, sinuses and pharynx are affected, and ophthalmomyiasis involves the eye, orbit and periorbital tissues. Intestinal and urogenital myiasis involve invasion of the alimentary tract or urogenital system.

The flies responsible for myiasis in humans include the following groups.

Family Muscidae

Eggs of *Fannia canicularis* (lesser house fly) and *Musca domestica* (house fly) may be deposited on ulcers and give rise to wound myiasis [7].

Family Calliphoridae (blowflies)

Genus *Cochliomyia* (*Callitroga*). These New World screwworms are distributed in the Americas, but are no longer established in North America, following intensive eradication efforts involving the release of a huge number of sterile male flies. Cases of myiasis involve the larvae of only two species of *Cochliomyia*: *C. macellaria* and *C. hominivorax* (*americana*). The larva of *C. macellaria* is a facultative parasite, which may be responsible for secondary infestation of wounds. Larvae of *C. hominivorax* are obligatory parasites, which feed on living tissue and can penetrate unbroken skin [8–10], but they may also infest wounds.

Genus *Chrysomya*. The Old World equivalent of *Cochliomyia*, *Chrysomya bezziana*, the Old World screwworm, is important medically as the larvae are obligate parasites in wounds.

Genus *Cordylobia*. *Cordylobia anthropophaga*, the 'tumbu' fly, is widespread in tropical Africa south of the Sahara [11], and most reported cases of tumbu fly myiasis are acquired in Africa [12,13]. There are, however, reports of myiasis acquired elsewhere, including Spain [14], Portugal [15] and Saudi Arabia [16]. Tumbu fly myiasis occurring in two boys who had never been to Africa might have been acquired as a result of their father, who made frequent visits to Africa, bringing tumbu fly eggs back amongst his possessions [17]. *C.* (*Stasisia*) *rodhaini*, the only other species of *Cordylobia* known to infest humans, has a more limited distribution in tropical Africa, principally the rainforest areas. Extensive furuncular myiasis due to *C. rodhaini* has been reported in an Italian man who acquired the problem while working in Ethiopia [18]. Eggs are not laid on the host, but on sand or soil, especially if contaminated by urine or faeces. They may also be deposited on clothing and linen hanging out to dry. After hatching, the larva raises its cephalic end searching for a suitable host. In the wild, rats are the usual host, but around human habitation, dogs and humans are common hosts. The larva attaches itself by means of its oral hooks, and rapidly penetrates the skin. When development is complete, usually in 14–16 days, it drops to the ground to pupate.

Genus *Auchmeromyia*. Although strictly not a cause of myiasis, the larva of the fly *Auchmeromyia senegalensis*, the Congo floor maggot, is a blood-sucking parasite of humans. This fly occurs throughout tropical Africa, where it lives in native huts and lays its eggs in the soil of the floor. The larvae lie buried in the soil during the day, but emerge at night to feed on the sleeping occupants of the huts. Once engorged, they drop off the host and burrow back into the soil.

Other genera. Larvae of members of the genera *Phormia* (black blowflies) [19–21], *Lucilia* (greenbottle) and *Calliphora* (bluebottle) may also be secondary invaders of wounds in man. In a study of wound myiasis in urban and suburban USA (in which homelessness, alcoholism and peripheral vascular disease were frequent co-factors) the majority of species identified were blowflies, the most common being *Lucilia sericata* [22].

There has been a recent resurgence of interest in the use of maggots (usually those of the greenbottle, *Lucilia sericata*) for wound debridement, an added bonus of which is their ingestion of methicillin-resistant *Staph. aureus* (MRSA) [23].

Family Sarcophagidae (flesh flies)

Genus *Sarcophaga*. There are occasional reports of members of this genus infesting wounds [24].

Genus *Wohlfahrtia*. These flies are similar to *Sarcophaga* and are important myiasis-causing flies in camels and sheep. The larvae of *Wohlfahrtia magnifica* may be deposited in the ear, eye or nose, and cause extensive destruction of healthy tissue. Delir *et al*. reported an Iranian woman with a cavity in the left labium majus occupied by a number of *W. magnifica* larvae [25]. *W. magnifica* occurs in south-eastern Europe, southern and Asiatic Russia, the Middle East and North Africa. *W. vigil* and *W. opaca* are North American species whose females deposit larvae on the skin of young animals, resulting in furuncular myiasis. Lesions are identical to those of *Dermatobia*. Human furuncular myiasis occurs only in young babies, as the larvae are unable to penetrate adult skin [26].



Fig. 38.5 Third instar larva of *Dermatobia hominis* (the human botfly). Note the rows of backward-pointing spines.

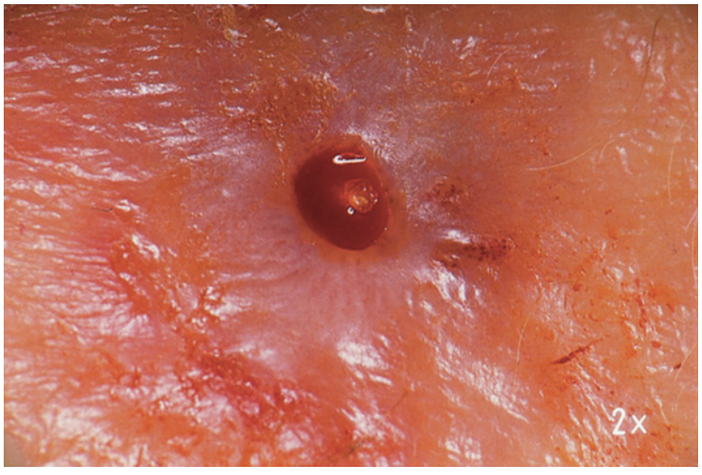


Fig. 38.6 Furuncle-like lesion produced by *Dermatobia hominis*. The tail of the larva is visible in the centre of the lesion.

Family Oestridae

Genus *Cuterebra* (rodent or rabbit botfly). Rabbits and rodents are the natural hosts for the larvae of these flies, which are sometimes responsible for human furuncular myiasis [27–29]. Baird *et al*. [30] reviewed 54 cases of North American cuterebrid myiasis.

Genus *Dermatobia* (human botfly). *Dermatobia hominis* is the only species in the genus. It is a bluebottle-like fly found in the neotropical areas of the New World, extending from southern Mexico to northern Argentina. It occurs in areas where temperature and humidity are relatively high, principally lowland forests. *D. hominis* causes cutaneous myiasis in a wide range of mammalian hosts, including humans, and is particularly important as a parasite of cattle.

The female fly does not deposit her eggs directly, but uses other insects, such as day-flying mosquitoes and blood-sucking flies, as vectors to carry her eggs to the host. She grasps the insect vector in midair and deposits a number of eggs on its abdomen. When the vector subsequently feeds on a potential host the eggs hatch and the larvae rapidly burrow into the skin (Fig. 38.5). Larval development lasts approximately 50–60 days, following which the larva emerges, drops to the ground and pupates. Human botfly myiasis should always be considered as a cause of boil-like lesions in patients who have recently returned from endemic areas [31–37].

Genus *Gasterophilus* (horse botfly). A form of migratory cutaneous myiasis known as 'creeping eruption' is caused by *Gasterophilus* larvae. The Gasterophilinae are mainly parasites of the alimentary tract of horses, but occasionally larvae of certain species of *Gasterophilus*, including *G. haemorrhoidalis* and *G. pecorum*, penetrate human skin.

Genus *Oestrus* (sheep nostril fly). *Oestrus ovis*, which develops in the nasopharyngeal passages of sheep and goats, and *Rhinoestrus purpureus*, which parasitizes horses, are occasionally responsible for human myiasis, especially ophthalmomyiasis [38,39].

Genus *Hypoderma* (warble flies). The larvae of *Hypoderma* species are obligate parasites of cattle. Man is an abnormal host for *Hypoderma*, and the larvae do not mature fully. After penetrating the skin, the larvae produce migratory subcutaneous swellings [40]. They may also invade the eye, producing severe damage. Marked eosinophilia may accompany infestation, and Starr *et al*. [41] reported a cattle rancher in whom an illness marked by pleuritis, pericarditis and myositis, and due to infestation with *H. lineatum*, mimicked the hypereosinophilic syndrome.

Clinical features [3–6,32]. The habits of the flies and their larvae determine the variations in the clinical manifestations for which they are responsible.

Traumatic or wound myiasis has been a serious complication of war wounds in tropical areas, and is sometimes seen in neglected ulcers or wounds in most parts of the world [42]. The eggs or larvae (maggots) can be seen, often in large numbers, in the suppurating tissues.

Obligatory cutaneous myiasis occurs in two main clinical forms; in both there may be mild constitutional symptoms and eosinophilia. Both occur mainly on exposed skin—often the face, scalp, arms or legs. In the furuncular form, boil-like lesions develop gradually over a few days. Each lesion has a central punctum, which discharges serosanguinous fluid. The posterior end of the larva, equipped with a group of spiracles, is usually visible in the punctum, and its movements may be noticed by the patient (Fig. 38.6). The lesions are often extremely painful. The inflammatory reaction around the lesions may be accompanied by lymphangitis and regional lymphadenopathy. Once the larva has emerged, or has been removed, the lesions rapidly resolve. The flies causing furuncular myiasis in humans are *Dermatobia hominis, Cuterebra, Cordylobia anthropophaga, Cordylobia (Stasisia) rodhaini, Wohlfahrtia* species and *Hypoderma* species. The inflammatory nodular lesions produced by *Hypoderma* species are migratory.

The second principal clinical form is a creeping eruption, resembling cutaneous larva migrans, in which a tortuous, thread-like red line with a terminal vesicle marks the passage of the larva

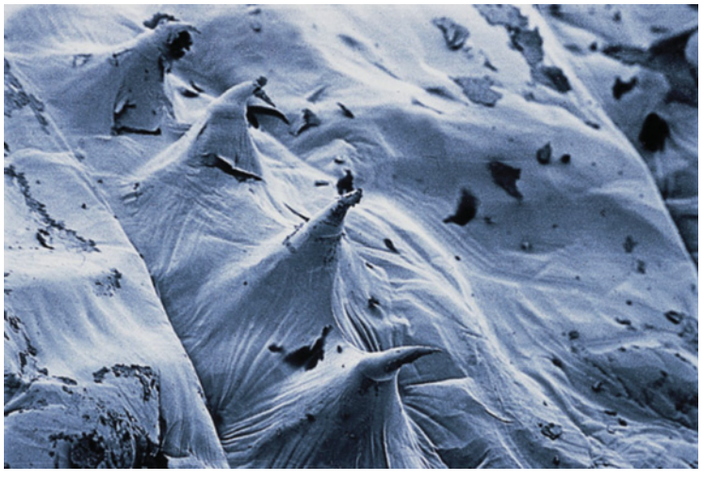


Fig. 38.7 Scanning electron micrograph of the spines on a *Dermatobia hominis* larva.

through the skin. The larva lies ahead of the vesicle in apparently normal skin. This form of myiasis is produced by *Gasterophilus* larvae.

Ultrasonography has been used to facilitate diagnosis and assist in location of *Dermatobia* larvae [43].

Treatment. The larva of *Cordylobia* can often be expressed by firm pressure around the edges of the lesion, but the punctum may require enlarging surgically.

The larva of *Dermatobia hominis* has a bulbous anterior end equipped with rows of spines (Fig. 38.7) that help to anchor it in the skin and make its removal by manual pressure difficult [44]. Traditional methods of treatment include occluding the punctum with pork fat [45,46], blocking the spiracles of the larva and stimulating premature extrusion. A similar result may be obtained with mineral oil, petrolatum or butter. Surgical management is most frequently recommended: the punctum is enlarged by cruciate incisions, and this enables removal of an intact larva [47]. The injection of lignocaine (lidocaine) underneath the nodule may be sufficient to push the larva out [48], and Li Loong *et al*. [49] also found that injection of 2 ml of 2% lidocaine into the blind end of the cavity facilitated non-surgical removal of the larva.

Ivermectin has been used both topically and orally in the management of myiasis [50–55].

Wound myiasis requires debridement and irrigation to remove larvae, and treatment of secondary infection.

References

1 Zumpt F. *Myiasis in Man and Animals in the Old World*. London: Butterworths, 1965.
2 Hall MJR, Smith KGV. Diptera causing myiasis in man. In: Lane RP, Crosskey RW, eds. *Medical Insects and Arachnids*. London: Chapman and Hall, 1993: 429.
3 Alexander JO'D. Cutaneous myiasis. In: *Arthropods and Human Skin*. Berlin: Springer-Verlag, 1984: 87–113.
4 Hall M, Wall R. Myiasis of humans and domestic animals. *Adv Parasitol* 1995; **35**: 257–334.
5 Kettle DS. *Medical and Veterinary Entomology*, 2nd edn. Wallingford: CAB International, 1995: 268–91.
6 Burns DA. Myiasis. In: Faber WR, Hay RJ, Naafs B, eds. *Imported Skin Diseases*. Maarssen: Elsevier, 2006: 251–8.
7 Logan JCP, Walkey M. A case of endemic cutaneous myiasis. *Br J Dermatol* 1964; **76**: 218–22.
8 Macias EC, Graham AJ, Green M *et al*. Cutaneous myiasis in South Texas. *N Engl J Med* 1973; **291**: 1239–41.
9 Poindexter HA. Cutaneous myiasis. *Arch Dermatol* 1979; **115**: 235.
10 Schreiber MM, Schuckmell N, Sampsel J. Human myiasis. *JAMA* 1964; **188**: 828–9.
11 Gunther S. Clinical and epidemiological aspects of the dermal tumbufly-myiasis in Equatorial-Africa. *Br J Dermatol* 1971; **85**: 226–31.
12 Lodi A, Bruscagin C, Gianni C *et al*. Myiasis due to *Cordylobia anthropophaga* (Tumbu-fly). *Int J Dermatol* 1994; **33**: 127–8.
13 Hasegawa M, Harada T, Kojima Y *et al*. An imported case of furuncular myiasis due to *Cordylobia anthropophaga* which emerged in Japan. *Br J Dermatol* 2000; **143**: 912–4.
14 Laurence BR, Herman FG. Tumbu fly (*Cordylobia*) infection outside Africa. *Trans R Soc Trop Med Hyg* 1973; **67**: 888.
15 Curtis SJ, Edwards C, Athulathmuda C *et al*. Case of the month: cutaneous myiasis in a returning traveller from the Algarve: first report of tumbu maggots, *Cordylobia anthropophaga*, acquired in Portugal. *Emerg Med J* 2006; **23**: 236–7.
16 Omar MS, Abdalla RE. Cutaneous myiasis caused by tumbu fly larvae, *Cordylobia anthropophaga* in southwestern Saudi Arabia. *Trop Med Parasitol* 1992; **43**: 128–9.
17 Bailey GG, Moody AH. Cutaneous myiasis caused by larvae of *Cordylobia anthropophaga* acquired in Europe. *BMJ* 1985; **290**: 1473–4.
18 Pampiglione S, Schiavon S, Fioravanti ML. Extensive furuncular myiasis due to *Cordylobia rodhaini* larvae. *Br J Dermatol* 1992; **126**: 418–9.
19 Alexis JB, Mittleman RE. An unusual case of *Phormia regina* myiasis of the scalp. *Am J Clin Pathol* 1988; **90**: 734–7.
20 Hall RD, Anderson PC, Clark DP. A case of human myiasis caused by *Phormia regina* (Diptera: Calliphoridae) in Missouri, USA. *J Med Entomol* 1986; **23**: 578–9.
21 Reames MK, Christensen C, Luce EA. The use of maggots in wound debridement. *Ann Plast Surg* 1988; **21**: 388–91.
22 Sherman RA. Wound myiasis in urban and suburban United States. *Arch Intern Med* 2000; **160**: 2004–14.
23 Sherman RA, Hall MJR, Thomas S. Medicinal maggots: an ancient remedy for some contemporary afflictions. *Annu Rev Entomol* 2000; **45**: 55–81.
24 Arbit E, Varon RE, Brem SS. Myiatic scalp and skull infection with Diptera *Sarcophaga*: case report. *Neurosurgery* 1986; **18**: 361–2.
25 Delir S, Handjani F, Emad M, Ardehali S. Vulvar myiasis due to *Wohlfahrtia magnifica*. *Clin Exp Dermatol* 1999; **24**: 279–80.
26 Smith FD, Shaffer KL, Gasseling PA, McFadden HW Jr. Furuncular myiasis caused by *Wohlfahrtia vigil* (Walker). *Arch Dermatol* 1981; **117**: 119–20.
27 Schiff TA. Furuncular cutaneous myiasis caused by *Cuterebra* larva. *J Am Acad Dermatol* 1993; **28**: 261–3.
28 Goddard J. Human infestation with rodent botfly larvae: a new route of entry? *South Med J* 1997; **90**: 254–5.
29 Keth AC. Three incidents of human myiasis by rodent *Cuterebra* (Diptera: Cuterebridae) larvae in a localized region of western Pennsylvania. *J Med Entomol* 1999; **36**: 831–2.
30 Baird JK, Baird CR, Sabrosky CW. North American cuterebrid myiasis. *J Am Acad Dermatol* 1989; **21**: 763–72.
31 Keech JP. *Dermatobia hominis*—in Belize. *J R Army Med Corps* 1981; **127**: 131–3.
32 Lane RP, Lovell CR, Griffiths WAD *et al*. Human cutaneous myiasis—a review and report of three cases due to *Dermatobia hominis*. *Clin Exp Dermatol* 1987; **12**: 40–5.
33 Jelinek T, Nothdurft HD, Rieder N, Löscher T. Cutaneous myiasis: review of 13 cases in travelers returning from tropical countries. *Int J Dermatol* 1995; **34**: 624–6.
34 Gordon PM, Hepburn NC, Williams AE, Bunney MH. Cutaneous myiasis due to *Dermatobia hominis*: a report of six cases. *Br J Dermatol* 1995; **132**: 811–4.
35 Gewirtzman A, Rabinowitz H. Botfly infestation (myiasis) masquerading as furunculosis. *Cutis* 1999; **63**: 71–2.
36 Veraldi S, Gorani A, Suss L, Tadini G. Cutaneous myiasis caused by *Dermatobia hominis*. *Pediatr Dermatol* 1998; **15**: 116–8.
37 Maier H, Hönigsmann H. Furuncular myiasis caused by *Dermatobia hominis*, the human botfly. *J Am Acad Dermatol* 2004; **50**: S26–30.

38 Omar MS, Das AB, Osman NI. External ophthalmomyiasis due to the sheep nostril botfly larva *Oestrus ovis* in Saudi Arabia. *Ann Trop Med Parasitol* 1988; **82**: 221–3.
39 Fekry AA, el Serougi OA, Ayoub SA. Oestrus ovis (sheep nasal fly) infesting the eyes and nose of a camel keeper family. *J Egypt Soc Parasitol* 1997; **27**: 493–6.
40 Morgan RJ, Moss HB, Honska WL. Myiasis. *Arch Dermatol* 1964; **90**: 180–4.
41 Starr J, Pruett J, Yunginger JW, Gleich GJ. Myiasis due to *Hypoderma lineatum* infection mimicking the hypereosinophilic syndrome. *Mayo Clin Proc* 2000; **75**: 755–9.
42 Spigel GT. Opportunistic cutaneous myiasis. *Arch Dermatol* 1988; **124**: 1014–5.
43 Bowry R, Cottingham RL. Use of ultrasound to aid management of late presentation of *Dermatobia hominis* larva infestation. *J Accid Emerg Med* 1997; **14**: 177–86.
44 Möhrenschlager M, Mempel M, Weichenmeier I *et al*. Scanning electron microscopy of *Dermatobia hominis* reveals cutaneous anchoring features. *J Am Acad Dermatol* 2007; **57**: 716–8.
45 Ruch DM. Bot fly myiasis. *Arch Dermatol* 1967; **96**: 677–80.
46 Sauder DN, Hall RP 3rd, Wurster CF. Dermal myiasis: the porcine lipid cure. *Arch Dermatol* 1981; **117**: 681–2.
47 Richards KA, Brieva J. Myiasis in a pregnant woman and an effective, sterile method of surgical extraction. *Dermatol Surg* 2000; **26**: 955–7.
48 Nunzi E, Rongioletti F, Rebora A. Removal of *Dermatobia hominis* larvae. *Arch Dermatol* 1986; **122**: 140.
49 Li Loong PT, Lui H, Buck HW. Cutaneous myiasis: a simple and effective technique for extraction of *Dermatobia hominis* larvae. *Int J Dermatol* 1992; **31**: 657–9.
50 Jelinek T, Nothdurft HD, Rieder N *et al*. Cutaneous myiasis: review of 13 cases in travellers returning from tropical countries. *Int J Dermatol* 1995; **34**: 624–6.
51 Denion E, Dalens PH, Couppié P *et al*. External ophthalmomyiasis caused by *Dermatobia hominis*. A retrospective study of nine cases and a review of the literature. *Acta Ophthalmol Scand* 2004; **82**: 576–84.
52 Dourmishev AL, Dourmishev LA, Schwartz RA. Ivermectin: pharmacology and application in dermatology. *Int J Dermatol* 2005; **44**: 981–8.
53 Osorio J, Moncada L, Molano A *et al*. Role of ivermectin in the treatment of severe orbital myiasis due to *Cochliomyia hominivorax*. *Clin Infect Dis* 2006; **43**: e57–9.
54 Clyti E, Nacher M, Merrien L *et al*. Myiasis owing to *Dermatobia hominis* in a HIV-infected subject: treatment by topical ivermectin. *Int J Dermatol* 2007; **46**: 52–4.
55 Wakamatsu TH, Pierre-Filho PTP. Ophthalmomyiasis externa caused by *Dermatobia hominis*: a successful treatment with oral ivermectin. *Eye* 2006; **20**: 1088–90.

Fleas (Siphonaptera)

Fleas are small (1–8 mm long), wingless, laterally compressed insects whose adults are blood-sucking ectoparasites of mammals and birds. Approximately 2000 species and subspecies are known. The larvae of fleas are not parasitic, but feed on organic material that they find in the nest or dwelling-place of the host [1,2].

The order Siphonaptera contains three families of medical importance.

Family Tungidae

This family contains tropical species that burrow in human skin (see Tungiasis, p. 38.12).

Family Pulicidae

Members of this family occur throughout the world, and some species transmit plague and murine typhus [3]. Cat fleas have been shown to be vectors of *Bartonella henselae*, the pathogen responsible for cat-scratch disease and bacillary angiomatosis [4,5]. Many species are important only for the irritability of their bites. The species most frequently parasitizing humans are the human flea, *Pulex irritans*, and the cat and dog fleas, *Ctenocephalides felis* and *Ctenocephalides canis*, but other species will bite humans in the absence of their normal host. The tropical rat flea, *Xenopsylla cheopis*, is the vector of bubonic plague.

The adult female flea lays her eggs during feeding on the host, and the eggs fall to the ground, where an important food source for the larvae is the faeces of the adult flea. The larvae subsequently form cocoons, and under suitable conditions of temperature and humidity the life cycle may be completed in a few weeks. However, the cocoon stage can sometimes last as long as a year, and the flea may emerge only in response to vibrations produced by the movement of possible hosts.

In a household occupied by infested pet dogs or cats, fleas in various stages of development are found in the animals' bedding, and on carpets and soft furnishings. In a survey carried out in the UK in 2005, the prevalence of flea infestation in domestic cats was 21.09% (98.93% of fleas were *C. felis*) and in dogs 6.82% (93.15% of fleas were *C. felis*) [6].

Family Ceratophyllidae

Species in this family are mainly parasitic on rodents and birds. Bird fleas overwinter in cocoons in birds' nests, and emerge in spring. At this time they can become household pests, as they may gain access to bedrooms from nests under the eaves.

Flea infestation in humans

Infestation with the human flea, *Pulex irritans*, occurs mainly in congested communities with low standards of hygiene. It is now rare in developed countries. Cat and dog flea infestation in the home is, however, common.

Animal fleas are common throughout the world, and persons in contact with domestic animals are frequently bitten. Severe attacks are sometimes experienced by individuals moving into premises long empty, but previously occupied by pet cats or dogs. The vibration caused by footsteps triggers the emergence of fleas from their cocoons. Attacks are more likely to occur when the fleas do not have access to their usual host. Household infestations with bird fleas may occur from nests or nest boxes on or near the house [7], and similar problems may occur in the workplace [8]. An outbreak of papular urticaria in a nursery school was traced to an infestation with dog fleas from a fox's burrow beneath the building [9]. Similar problems were caused by *Ctenocephalides felis* entering houses from raccoons which had bred in the cavity between two houses [10], and by *Pulex simulans* originating from a skunk in a basement [11].

Clinical features [12,13]. Flea bites usually provoke typical papular urticaria in a sensitized individual. Occasionally, the reaction is more severe, and bullae may occur. The lesions may be grouped in lines or irregular clusters. Cat and dog flea bites occur predominantly on the legs below the knees, and are most profuse around the ankles (Fig. 38.8), but they can also occur on the forearms. They are much more common in women than men, as trousers and socks protect the legs. Bites from bird fleas tend to be more extensive, as the sleeping occupants of bedrooms usually provide larger areas of exposed flesh.

Confirmation of flea infestation [14]. If flea infestation from pet animals is suspected, this can be confirmed by microscopical examination of debris from the animals' bedding material (p. 38.4).



Fig. 38.8 Typical distribution of cat or dog flea bites on the legs.

The principal sign of flea infestation in an affected animal is the presence of dried concretions of flea faeces on the animal's coat. Some animals will also have signs of flea allergy dermatitis, with areas of crusting and alopecia, most frequently on the lower back and the base of the tail.

If fleas from another source are suspected of causing bites, it may be necessary to examine samples taken with a vacuum cleaner from rooms, or to visit the suspect premises. It is important to identify the flea species responsible for an infestation so that efforts at eradication may be accurately directed at the source [15]. Cat fleas (Fig. 38.9), dog fleas and common bird fleas may be readily identified after 'clearing' in 10% potassium hydroxide for 48 h [3], but the help of an entomologist should be sought.

Treatment. In recent years, the development of topical and oral agents such as fipronil, imidacloprid, lufenuron and selamectin has revolutionized domestic cat and dog flea control [16].

Pest-control companies will deal with flea infestation from other sources.

References

1 Busvine JR. *Insects and Hygiene*. London: Chapman and Hall, 1980: 245–56.
2 Kettle DS. *Medical and Veterinary Entomology*, 2nd edn. Wallingford: CAB International, 1995: 323–43.
3 Bibikova VA. Contemporary views on the interrelationships between fleas and the pathogens of human and animal diseases. *Annu Rev Entomol* 1977; **22**: 23–32.
4 Chomal BB, Kasten RW, Floyd-Hawkins K *et al*. Experimental transmission of *Bartonella henselae* by the cat flea. *J Clin Microbiol* 1996; **34**: 1952–6.



Fig. 38.9 *Ctenocephalides felis*, the cat flea.

5 Flexman JP, Lavis NJ, Kay ID *et al*. *Bartonella henselae* is a causative agent of cat scratch disease in Australia. *J Infect* 1995; **31**: 241–5.
6 Bond R, Riddle A, Mottram L *et al*. Survey of flea infestation in dogs and cats in the United Kingdom during 2005. *Vet Rec* 2007; **160**: 503–6.
7 Wolff K. Vogelflöhe als fakultative Ektoparasiten des Menschen. *Schweiz Rundschau Med* 1975; **64**: 1173–5.
8 Chua EC, Goh KJ. A flea-borne outbreak of dermatitis. *Ann Acad Med Singapore* 1987; **16**: 648–50.
9 Rothenborg HW. Of fleas and foxes. *Arch Dermatol* 1975; **111**: 1215–6.
10 Hunter KW, Campbell AR, Sayles PC. Human infestation by cat fleas; *Ctenocephalides* (Siphonaptera: Pulicidae), from suburban raccoons. *J Med Entomol* 1979; **16**: 547.
11 Keh B. Indoor infestation of *Pulex simulans* (Siphonaptera: Pulicidae) causing dermatosis in a family in Berkeley, California. *California Vector Views* 1978; **25**: 7–11.
12 Alexander JO'D. Flea bites and other diseases caused by fleas. In: *Arthropods and Human Skin*. Berlin: Springer-Verlag, 1984: 159–71.
13 Dickey RF. Papular urticaria—hordes of fleas in the living room. *Cutis* 1967; **3**: 345–8.
14 Burns DA. The investigation and management of arthropod bite reactions acquired in the home. *Clin Exp Dermatol* 1987; **12**: 114–20.
15 Hosie G. Observations on the occurrence of *Ceratophyllus gallinae* around new housing estates in the West of Scotland. In: Traub R, Starcke H, eds. *Fleas*. Rotterdam: AA Balkema, 1980: 415–20.
16 Rust MK. Advances in the control of *Ctenocephalides felis* (cat flea) on cats and dogs. *Trends Parasitol* 2005; **21**: 232–6.

Tungiasis

Aetiology. Tungiasis is caused by the sand flea *Tunga penetrans*, also known as the jigger, or chigoe. Originally a native of South America, it subsequently spread to Africa [1,2]. In recent years tungiasis has reappeared in Mexico [3], where it was previously last recorded in 1948. The ease of world travel has contributed to tungiasis being encountered in non-endemic areas [1,2,4–9].

T. penetrans is the smallest known flea (1 mm long). Its larvae develop in dry, sandy soil, and development from egg to adult takes about 3 weeks in favourable conditions. The impregnated female flea burrows into the feet of mammals, preferring humans and pigs. In humans, the fleas establish themselves between the



Fig. 38.10 Tungiasis, showing a characteristic lesion on the sole of the foot. (Courtesy of Dr N.H. Cox, Cumberland Infirmary, Carlisle, UK.)

toes, under the nails, and on the soles, but other parts of the body may be affected. Once embedded in the skin, the flea's abdomen enlarges to the size of a pea, and large numbers of eggs are produced. The eggs are subsequently gradually extruded over a period of 2 weeks, and the female flea dies and is sloughed from the skin [10].

Pathology. Anatomical components of the flea are sufficiently distinctive to enable a diagnosis of tungiasis to be made histologically [11].

Clinical features [2,12]. The presence of the fleas causes intense irritation. The typical appearance of an individual lesion is initially a black dot surrounded by a halo of erythema, followed by enlargement to form a mother of pearl-coloured papule with a central, dark punctum, produced by the enlarging flea abdomen (Fig. 38.10). Secondary infection is common, and tetanus has often complicated tungiasis in the past [13]. In severe cases, the feet may be honeycombed by multiple lesions, causing serious discomfort and disability. Use of the dermatoscope aids diagnosis by demonstrating the surface features [14,15].

Treatment [16]. The flea should be completely removed from the skin. This can be accomplished by enlarging the surface punctum and extracting the flea with tweezers, curettage and cautery, or excision.

A plant-based repellent, assessed in Brazil, proved to be extremely effective in preventing infestation with *T. penetrans* [17].

The unwary traveller may well acquire tungiasis, and those visiting endemic areas should be warned to wear stout shoes, and not to sit on the ground.

References

1 Douglas-Jones AG, Llewelyn MB, Mills CM. Cutaneous infection with *Tunga penetrans*. *Br J Dermatol* 1995; **133**: 125–7.

2 Feldmeier H, Heukelbach J. Tungiasis. In: Faber WR, Hay RJ, Naafs B, eds. *Imported Skin Disease*. Maarssen: Elsevier, 2006: 233–41.

3 Ibáñez-Bernal S, Velasco-Castrejón O. New records of human tungiasis in Mexico (Siphonaptera: Tungidae). *J Med Entomol* 1996; **33**: 988–9.

4 Sanusi ID, Brown EB, Shepard TG *et al*. Tungiasis: report of one case and review of the 14 reported cases in the United States. *J Am Acad Dermatol* 1989; **20**: 941–4.

5 Spradbery JP, Bromley J, Dixon R, Tetlow L. Tungiasis in Australia: an exotic disease threat. *Med J Aust* 1994; **161**: 173.

6 Wardhaugh AD, Norris JFB. A case of imported tungiasis in Scotland initially mimicking verrucae vulgaris. *Scott Med J* 1994; **39**: 146–7.

7 Gelmetti C, Carrera C, Veraldi S. Tungiasis in a 3-year-old child. *Pediatr Dermatol* 2000; **17**: 293–5.

8 Fein H, Naseem S, Witte DP *et al*. Tungiasis in North America: a report of 2 cases in internationally adopted children. *J Pediatr* 2001; **139**: 744–6.

9 Grunwald MH, Shai A, Mosovich B, Avinoach I. Tungiasis. *Australas J Dermatol* 2000; **41**: 46–7.

10 Smit FGAM. Siphonaptera. In: Smith KGV, ed. *Insects and other Arthropods of Medical Importance*. London: The Trustees of the British Museum (Natural History), 1973: 327–8.

11 Smith MD, Procop GW. Typical histologic features of *Tunga penetrans* in skin biopsies. *Arch Path Lab Med* 2002; **126**: 714–6.

12 Alexander JO'D. Tungiasis. In: *Arthropods and Human Skin*. Berlin: Springer-Verlag, 1984: 171–6.

13 Feldmeier H, Heukelbach J, Eisele M *et al*. Bacterial superinfection in human tungiasis. *Trop Med Int Health* 2002; **7**: 559–64.

14 Bauer J, Forschner A, Garbe C *et al*. Dermoscopy of tungiasis. *Arch Dermatol* 2004; **140**: 761–3.

15 Di Stefani A, Rudolph CM, Hofmann-Wellenhof R, Müllegger RR. An additional dermoscopic feature of tungiasis. *Arch Dermatol* 2005; **141**: 1045–6.

16 Heukelbach J. Revision on tungiasis: treatment options and prevention. *Expert Rev Anti Infect Ther* 2006; **4**: 151–7.

17 Feldmeier H, Kehr JD, Heukelbach J. A plant-based repellent protects against *Tunga penetrans* infestation and sand flea disease. *Acta Trop* 2006; **99**: 126–36.

Bees, wasps and ants (Hymenoptera)

The adults of many species in this large order of insects have evolved a sting apparatus. The sting may or may not be barbed. Some use the sting in defence, and others use it offensively in hunting for food. Males have no sting apparatus. Humans are frequently stung by these insects, with reactions varying from local discomfort to fatal anaphylaxis.

The Hymenoptera are readily recognized by the narrow waist (isthmus) connecting the abdomen to the thorax. Some of the more important families include the following.

Superfamily Apoidea (bees)

Honeybees (Apis mellifera)

Honeybees possess a barbed sting. When humans are stung, the bee is unable to remove the sting. The sting and venom apparatus are avulsed from the bee's abdomen in its struggles, but the venom apparatus continues to function and pump in more venom.

'Africanized' honeybees, the product of interbreeding between bees from southern Africa and European species, have caused significant problems in recent years [1]. These aggressive ('killer') bees, which have characteristics of their African antecedents, including strong colony defensive behaviour, have migrated northward from Brazil to the southern USA.

Humblebees; bumblebees (Bombus spp.)

The sting is not barbed, and the bumblebee is therefore able to sting repeatedly. Most species are inoffensive, and only sting defensively when severely provoked.

Superfamily Vespoidea

Family Vespidae (social wasps)

This family includes wasps, yellow-jackets and hornets. Species of *Vespa, Vespula* and *Polistes* inflict painful stings. Wasps can also sting repeatedly, as they either have small barbs or none at all on their stings.

Superfamily Bethyloidea

These are small, solitary wasps. They sometimes become abundant in houses. They are parasitic on the larvae of *Lepidoptera* and *Coleoptera*. *Scleroderma domesticum, Epyris californicus* and *Cephalonomia gallicola* may inflict troublesome stings [2,3].

Superfamily Scolioidea

Family Formicidae (ants)

Many ant species are equipped with powerful stings, including the Australian jumper and bull ants [4,5], and *Solenopsis*, the fire ant. Fire ants, so called because of the burning pain of their stings, have been particularly problematic in recent years in the USA. There are several native species of fire ant in the USA, but it is the red and black imported fire ants *S. invicta* and *S. richteri*, inadvertently brought to the United States from South America, that have become troublesome pests [2,6–9]. *S. invicta* is also well established in two locations of the Brisbane area of Australia [10]. Wood imported from South America was the source of fire ants responsible for anaphylaxis in a woman in Málaga, Spain [11].

The fire ant first uses its powerful mandibles to grip its victim, and drives its non-barbed sting into the skin. It then rotates about the point of attachment of the mandibles and inflicts further stings in a circular pattern [7–9,12]. Although largely outdoor insects, fire ants may move into dwellings, causing problems for the inhabitants [13].

Species of *Pogonomyrmex* (harvester ants) may inflict multiple painful stings [2,14].

Venoms [15–29]

The composition of venoms is complex. Pharmacologically active and antigenic substances are both present, and an individual's reaction to the sting is determined partly by the quantity of the former, and partly by the degree of acquired hypersensitivity to the latter. Hymenoptera venom contains vasoactive amines, small polypeptides, and larger protein molecules. The components of vespid (wasps, yellow-jackets and hornets) venoms include histamine, serotonin, mast-cell degranulating peptide, wasp kinin, phospholipases, hyaluronidase and antigen 5. The three major allergens in vespid venoms are phospholipases, hyaluronidase and antigen 5. The venom of the honeybee contains histamine, mast-cell degranulating peptide, melittin, phospholipase A_2, hyaluronidase and acid phosphatase. The three proteins in honeybee venom which are important allergens are phospholipase A_2, hyaluronidase and acid phosphatase. In addition, the polypeptide melittin is also antigenic. Bumblebee venom appears to be chemically and antigenically related to honeybee venom [22].

Study of fire ant venom was impeded for many years by the extreme difficulty in obtaining sufficient amounts. The venom is composed of 90–95% water-insoluble piperidine alkaloids [23], which are not allergenic but are responsible for the local reaction at the sting site. When commercial-grade venom became available, several potent allergenic proteins were identified [8,24]. Antigenic similarity between fire ant venom, bee and wasp venoms and scorpion venom has been demonstrated [25,26].

Allergy to Hymenoptera venom is mediated by IgE antibodies. The antigenic substances in the venom of many Hymenoptera are more liable to induce high degrees of hypersensitivity of the immediate type than are the antigens of most other insects.

Clinical features [15,16,27,28]. Reactions to bee and wasp stings may be classified as local and systemic. Both may have a toxic or a hypersensitive mechanism. The typical local toxic reaction produced by pharmacologically active components of the venom is burning pain, which may be very severe, followed by erythema and oedema. This local reaction subsides in a few hours. The systemic toxic effects of multiple stings include hypotension, generalized vasodilatation, severe headache, vomiting, diarrhoea and shock, and the cumulative effect of a large number of stings may be fatal, particularly in children.

In some cases, hypersensitivity produces only a more intense local reaction manifest as increased oedema, usually developing within the first half hour, but occasionally delayed for several hours. If a generalized anaphylactic reaction occurs, this is usually within a few minutes of the sting. The manifestations of a generalized reaction may be classified as cutaneous (pruritus, erythema, urticaria and angio-oedema), respiratory (laryngeal oedema, bronchospasm), or vascular (tachycardia, hypotension, shock). These features may occur separately or in combination, and in varying degrees of severity.

Occasionally, late-onset reactions to stings occur [17]. In some patients, an urticarial reaction develops several hours after the sting, and in others a serum sickness-like reaction occurs, with urticaria, joint swelling and arthralgia.

A patient with a foreign-body granuloma and IgE pseudolymphoma following multiple bee stings has been reported [30], and another with an eosinophilic foreign body granuloma after multiple self-administered bee stings as treatment in traditional Korean medicine [31].

Skin lesions produced by fire ants typically occur in clusters [7–9]. The site of attachment of the mandibles may be marked by two minute haemorrhagic puncta. The initial reaction to the sting is the development of a weal, followed within a few hours by a vesicle. The fluid in the vesicle gradually becomes cloudy, and after 8–10 h the typical lesion is an umbilicated pustule on a red, oedematous base. The pustule subsequently ruptures, forming a crust, and after several days the lesions heal, frequently leaving small scars. Hand–foot syndrome associated with multiple fire ant stings has been described [32].

Systemic hypersensitivity reactions may also occur, and feature generalized urticaria and angio-oedema, wheezing, nausea and vomiting, and hypotension [7,33,34]. These manifestations may increase in severity with successive attacks, and fatal anaphylaxis can occur [9].

Treatment [28,35,36]. Local reactions to Hymenoptera stings may be treated with oral antihistamines. The treatment of choice for

anaphylaxis is intramuscular epinephrine (adrenaline) (in adults, a dose of 0.5 ml 1:1000 solution should be administered, and repeated after about 5 minutes in the absence of clinical improvement or if deterioration occurs after the initial treatment), followed by chlorpheniramine (10–20 mg, intramuscular or slow intravenous) and hydrocortisone (100–500 mg, intramuscular or slow intravenous) [36]. Patients at risk of an anaphylactic response to Hymenoptera stings should wear a device such as a MedicAlert warning bracelet, in case they are discovered unconscious following a sting. They should also carry a sting emergency kit, and receive instruction in self-administration of epinephrine.

The introduction of venom immunotherapy has reduced the risk of anaphylaxis in Hymenoptera-sensitive patients. It is thought to exert its beneficial effect by stimulating the development of IgG (blocking) antibodies against the venom allergens. This prophylactic measure is indicated in patients with a history of life-threatening reactions to stings, positive skin tests, and presence of venom-specific serum IgE. However, such therapy should only be carried out in specialized units.

Conventional advice with regard to honeybee stings is that the sting should be immediately scraped off, never pinched. A study by Visscher *et al*. [37] suggests that the method of removal does not affect the quantity of venom received and is therefore unimportant; the sting should simply be removed as rapidly as possible.

References

1 Schumacher MJ, Egen NB. Significance of africanized bees for public health: a review. *Arch Intern Med* 1995; **155**: 2038–43.
2 James MT, Harwood RF, eds. *Herms's Medical Entomology*, 6th edn. London: Macmillan, 1976.
3 Lahourcade M. Quelques précisions sur la morphologie et la biologie de *Sclerodema domestica* Latr. petit Hyménoptère Béthylide vulnérant. *Ann Parasitol* 1962; **37**: 848–60.
4 Sutherland SK. *Venomous Creatures of Australia*. Melbourne: Oxford University Press, 1982.
5 Trinca JC. Insect allergy in Australia: results of a five-year survey. *Med J Aust* 1964; **2**: 659–63.
6 Kemp SF, de Shazo RD, Moffitt JE *et al*. Expanding habitat of the imported fire ant (*Solenopsis invicta*): a public health concern. *J Allergy Clin Immunol* 2000; **105**: 683–91.
7 Hoffman DR. Fire ant venom allergy. *Allergy* 1995; **50**: 535–44.
8 Stafford CT. Hypersensitivity to fire ant venom. *Ann Allergy Asthma Immunol* 1996; **77**: 87–95.
9 Prahlow JA, Barnard JJ. Fatal anaphylaxis due to fire ant stings. *Am J Forensic Med Pathol* 1998; **19**: 137–42.
10 Solley GO, Vanderwoude C, Knight GK. Anaphylaxis due to red imported fire ant sting. *Med J Aust* 2002; **176**: 521–3.
11 Fernández-Meléndez S, Miranda A, García-González JJ *et al*. Anaphylaxis caused by imported fire ant stings in Málaga, Spain. *J Investig Allergol Clin Immunol* 2007; **17**: 48–9.
12 Smith JD, Smith EB. Multiple fire ant stings. A complication of alcoholism. *Arch Dermatol* 1971; **103**: 438–41.
13 De Shazo RD, Williams DF. Multiple fire ant stings indoors. *South Med J* 1995; **88**: 712–5.
14 Weber NA. The stings of the harvesting ant *Pogonomyrmex occidentalis* (Cresson), with a note on populations (Hymenoptera). *Entomol News* 1959; **70**: 85–90.
15 Alexander JO'D. Hymenoptera stings. In: *Arthropods and Human Skin*. Berlin: Springer-Verlag, 1984: 135–58.
16 Schmidt JO. Allergy to venomous insects. In: Graham JM, ed. *The Hive and the Honey Bee*. Hamilton, Illinois: Dadant, 1992: 1209–69.
17 Reisman RE, Livingstone A. Late onset reactions, including serum sickness, after insect stings. *J Allergy Clin Immunol* 1989; **84**: 331–7.
18 Valentine MD. Insect venom allergy: diagnosis and treatment. *J Allergy Clin Immunol* 1984; **73**: 299–305.
19 King TP, Kochoumian L, Joslyn A. Wasp venom proteins: phospholipase A and B. *Arch Biochem Biophys* 1984; **230**: 1–12.
20 Hoffman DR. Allergens in Hymenoptera venom. XIII. Isolation and purification of protein components from three species of vespid venoms. *J Allergy Clin Immunol* 1985; **75**: 599–605.
21 Hoffman DR. Allergens in bee venom. III. Identification of allergen B of bee venom as an acid phosphatase. *J Allergy Clin Immunol* 1977; **59**: 364–6.
22 Hoffman DR, Jacobson RS. Allergens in Hymenoptera venom XXVII: bumblebee venom allergy and allergens. *J Allergy Clin Immunol* 1996; **97**: 812–21.
23 Brand JM, Blum MS, Fales HM *et al*. Fire ant venoms: comparative analyses of alkaloidal components. *Toxicon* 1972; **10**: 259–71.
24 Hoffman DR. Allergens in Hymenoptera venom XXIV: the amino acid sequences of imported fire ant venom allergens *Sol i* II, *Sol i* III, and *Sol i* IV. *J Allergy Clin Immunol* 1993; **91**: 71–9.
25 Hoffman DR, Dove DE, Moffitt JE *et al*. Allergens in Hymenoptera venom. XXI. Cross-reactivity and multiple reactivity between fire ant venom and bee and wasp venoms. *J Allergy Clin Immunol* 1988; **82**: 828–34.
26 Nugent JS, More DR, Hagan LL *et al*. Cross-reactivity between allergens in the common striped scorpion and the imported fire ant. *J Allergy Clin Immunol* 2004; **114**: 383–6.
27 Reisman RE. Insect stings. *N Engl J Med* 1994; **133**: 523–7.
28 Ewan PW. Venom allergy. *BMJ* 1998; **316**: 1365–8.
29 Antonicelli L, Bilò MB, Bonifazi F. Epidemiology of Hymenoptera allergy. *Curr Opin Allergy Clin Immunol* 2002; **2**: 341–6.
30 Hermes B, Haas N, Grabbe J, Czarnetzki BM. Foreign-body granuloma and IgE-pseudolymphoma after multiple bee stings. *Br J Dermatol* 1994; **130**: 780–4.
31 Park J-H, Kim JG, Cha S-H, Park SD. Eosinophilic foreign body granuloma after multiple self-administered bee stings. *Br J Dermatol* 1998; **139**: 1102–5.
32 Carr ME. Hand-foot syndrome in a patient with multiple fire ant stings. *South Med J* 2004; **97**: 707–9.
33 Lockey RF. Systemic reactions to stinging ants. *J Allergy Clin Immunol* 1974; **54**: 132–46.
34 Schmid WH. Medical implications; imported fire ants *Solenopsis invicta*. *Cutis* 1977; **19**: 794–7.
35 Reisman RE. Venom hypersensitivity. *J Allergy Clin Immunol* 1994; **94**: 651–8.
36 Project Team of the Resuscitation Council (UK). Emergency medical treatment of anaphylactic reactions. *J Accid Emerg Med* 1999; **16**: 243–7.
37 Visscher PK, Vetter RS, Camazine S. Removing bee stings. *Lancet* 1996; **348**: 301–2.

Lice (Phthiraptera)

Lice are members of the order Phthiraptera. They are wingless, dorsoventrally flattened insects, which are obligate ectoparasites of birds and mammals. The Phthiraptera are highly host-specific and spend their entire lives on the host. Members of the suborder Anoplura are blood-sucking ectoparasites of mammals.

Humans are parasitized by three species of Anoplura: *Pediculus capitis*, the head louse, *Pediculus humanus*, the clothing or body louse, and *Pthirus pubis*, the pubic or crab louse. Head lice and clothing lice are morphologically almost identical, and are capable of interbreeding, but on the host they maintain their territorial preferences. *Pthirus pubis* is morphologically quite distinct from *Pediculus*. It is a louse that has only one close relative in the insect world, a species living on gorillas (*Pthirus gorillae*) and the ancestor of human pubic lice. It is thought that our human ancestors acquired pubic lice from gorillas, perhaps by sharing their bedding material or by humans feeding on gorillas. Interestingly, chimpanzees, our closest primate relative, are parasitized by *Pediculus* species (*P. schaeffi*) but not by *Pthirus*, and orangutans do not have lice.

Pthirus is the correct zoological name for the crab louse—the name should have been *Phthirus*, but a misprint was inadvertently



Fig. 38.11 *Pediculus capitis*, the head louse.

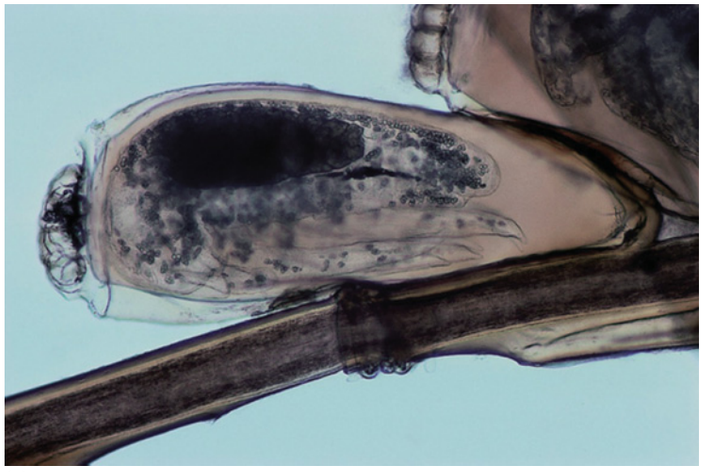
accepted by the International Committee on Zoological Nomenclature [1].

Morphology and biology [1–12]

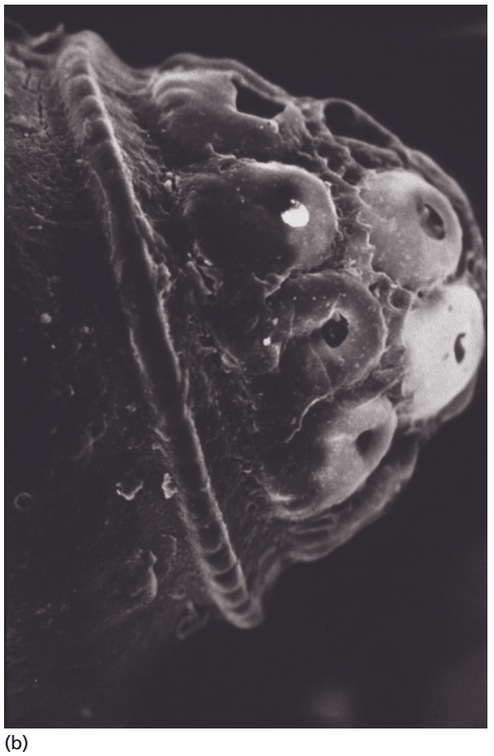
***Pediculus capitis* (head louse).** The adult female is a greyish white insect 3–4 mm long (Fig. 38.11). The male is slightly smaller. The claws on the legs are adapted for clinging to hair.

During her lifespan of approximately 40 days, the female lays an average of about seven eggs daily. The eggs are cemented to hair shafts with a chitinous cement material secreted by the female's accessory glands [13] (Fig. 38.12a). In temperate climates, in order to provide a suitable temperature for incubation, the eggs are attached to hair close to the surface of the scalp. They are oval, flesh coloured and have a lid (operculum) capping the free end of the egg (Fig. 38.12b). The operculum is pushed off by the emerging louse nymph. Once the louse has emerged, the empty egg case or 'nit' appears white, and is easier to see than the intact eggs close to the scalp surface. Eggs hatch in about 8 days and, following three moults, the louse nymph reaches maturity in approximately 10 days.

***Pediculus humanus* (clothing or body louse).** This louse is almost identical in appearance to the head louse, and its development is similar. Its natural habitat is the clothing of its host, and it only visits the skin to feed. Its eggs are cemented to clothing fibres, with a preference for clothing close to the skin. Seams are a favoured site for oviposition. It thrives in situations where normal hygiene is lacking. The clothing louse and its eggs will not survive high-temperature washing and ironing, and it is intolerant of temperature changes in its environment. It is therefore a parasite of individuals whose clothing is rarely changed or washed.



(a)



(b)

Fig. 38.12 (a) Head louse eggs cemented to a hair shaft. (b) Scanning electron micrograph of the operculum on a head louse egg.

***Pthirus pubis* (pubic or crab louse).** The crab louse is quite distinctive in appearance (Fig. 38.13) and habits from *Pediculus*. Its body is squat, and the second and third pairs of legs carry heavy, pincer-like claws. When static, the crab louse uses these huge claws to grip adjacent hairs close to the skin surface (Fig. 38.14). Its eggs are light brown in colour and, like those of the head louse, are cemented to the hair of the host (Fig. 38.15). It is adapted to living in hair of a particular density. Scalp hair, except at the scalp margins, is too dense, but the crab louse will colonize axillary hair, eyebrows, eyelashes, beard hair, and hair on the trunk and limbs, in addition to pubic hair. It is mainly sedentary, but becomes active



Fig. 38.13 *Pthirus pubis*, the crab louse.

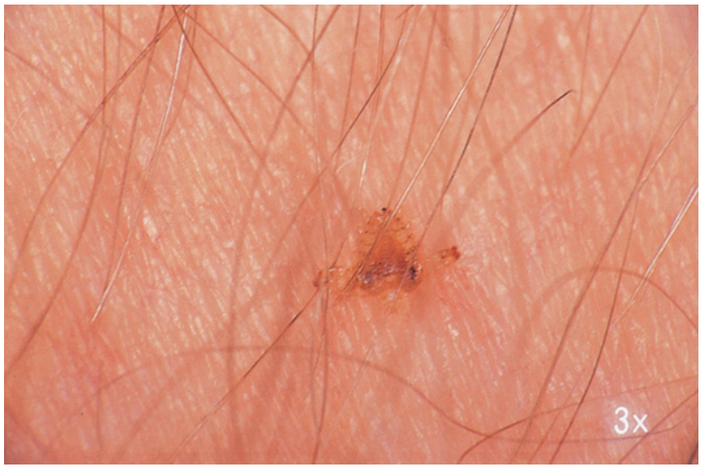


Fig. 38.14 Crab louse clinging to hairs on the abdomen.

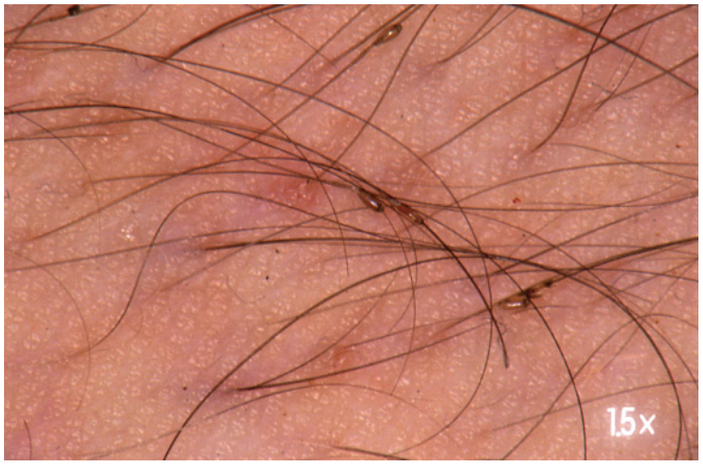


Fig. 38.15 Crab louse eggs attached to abdominal hair.

at night when the host is sleeping [14]. It moves by transferring its grip from one hair to another. The crab louse has difficulty moving when taken from its host, whereas head and clothing lice are quite mobile off the host.

Pthirus pubis is a specific parasite of humans, but its transfer to a dog has been recorded [15].

The Anoplura are vessel feeders (solenophages), introducing their mouthparts directly into a blood vessel to withdraw blood [16,17]. The components responsible for probing the skin and piercing a blood vessel are a group of stylets, which are kept withdrawn within the head unless the insect is feeding. In the front of the head is a small, snout-like tube, the haustellum, which is soft, eversible and armed with teeth. When the louse is about to feed, the haustellum is everted and the buccal teeth rotated outwards (Fig. 38.16a). The teeth cut into the epidermis and the haustellum is driven into the skin. It eventually comes to rest with the buccal teeth fully everted, anchoring the mouthparts (Fig. 38.16b). Once fixed in the skin, a bundle of stylets is pushed forward through the opening in the haustellum by protractor muscles within the head of the louse (Fig. 38.16c). The stylets are advanced into the dermis as a single bundle or fascicle, and probe for a small blood vessel.

References

1 Nuttall GHF. The biology of *Pediculus humanus*. *Parasitology* 1917; **10**: 80–185.
2 Buxton PA. *The Louse: an Account of the Lice which Infest Man and their Medical Importance and Control*, 2nd edn. London: Edward Arnold, 1947.
3 Maunder JW. The appreciation of lice. *Proc R Inst Great Britain* 1983; **55**: 1–31.
4 Alexander JO'D. Infestation with Anoplura—lice. In: *Arthropods and Human Skin*. Berlin: Springer-Verlag, 1984: 29–55.
5 Busvine JR. Pediculosis: biology of the parasites. In: Orkin M, Maibach HI, eds. *Cutaneous Infestations and Insect Bites*. New York: Marcel Dekker, 1985: 163–74.
6 Burgess I. Human lice and their management. *Adv Parasitol* 1995; **36**: 271–342.
7 Burns DA, Sims TA. A closer look at *Pthirus pubis*. *Br J Dermatol* 1988; **118**: 497–503.
8 Nuttall GHF. The biology of *Phthirus pubis*. *Parasitology* 1917; **10**: 383–405.
9 Burkhart CN, Gunning W, Burkhart CG. Scanning electron microscopic examination of the egg of the pubic louse (Anoplura: *Pthirus pubis*). *Int J Dermatol* 2000; **39**: 201–2.
10 Kraus SJ, Glassman LH. The crab louse—review of physiology and study of anatomy as seen by the scanning electron microscope. *J Am Vener Dis Assoc* 1976; **2**: 12–18.
11 Ko CJ, Elston DM. Pediculosis. *J Am Acad Dermatol* 2004; **50**: 1–12.
12 Burgess IF. Human lice and their control. *Annu Rev Entomol* 2004; **49**: 457–81.
13 Burkhart CN, Burkhart CG. Head lice: scientific assessment of the nit sheath with clinical ramifications and therapeutic options. *J Am Acad Dermatol* 2005; **53**: 129–33.
14 Burgess I, Maunder JW, Myint TT. Maintenance of the crab louse, *Pthirus pubis*, in the laboratory and behavioural studies using volunteers. *Community Med* 1983; **5**: 238–41.
15 Frye FL, Furman DP. Phthiriasis in a dog. *J Am Vet Med Assoc* 1968; **152**: 1113.
16 Lavoipierre MMJ. Feeding mechanism of blood-sucking arthropods. *Nature* 1965; **208**: 302–3.
17 Lavoipierre MMJ. Feeding mechanism of *Haematopinus suis*, on the transilluminated mouse ear. *Exp Parasitol* 1967; **20**: 303–11.

Head lice (*Pediculosis capitis*)

Prevalence and epidemiology [1–3]. The head louse has a worldwide distribution, and head louse infection is common both in developed and developing countries. However, precise data on current prevalence are relatively sparse.

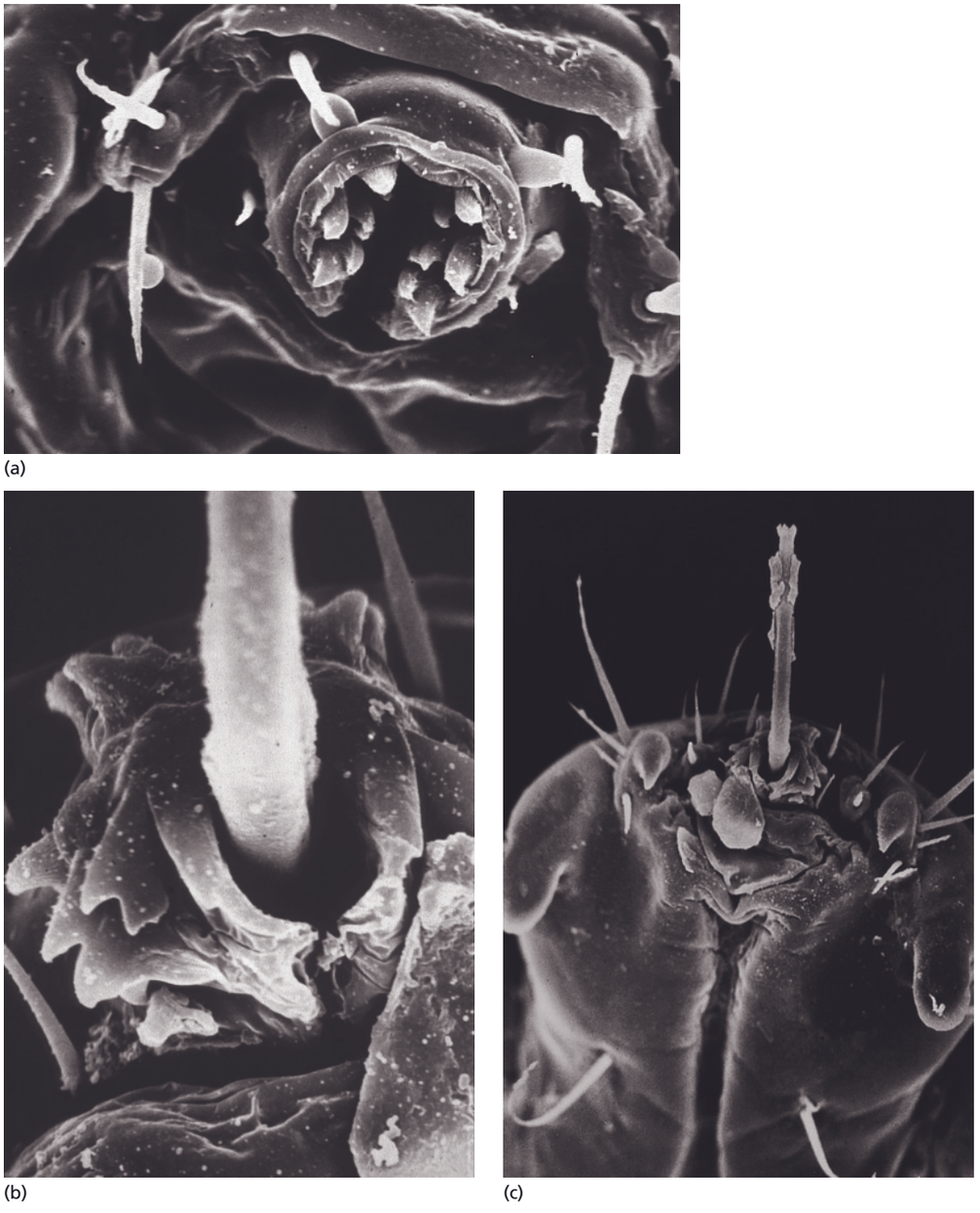


Fig. 38.16 Scanning electron micrograph of a crab louse showing: (a) haustellum with buccal teeth; (b) everted buccal teeth; (c) the protruded stylet bundle.

In England, in the past, head lice were common in industrial conurbations. In 10 industrial cities, in 1941, about 40% of preschool-age boys and 50% of girls had head lice [4]. In contrast, infection rates in rural communities were low. A survey of schoolchildren in 1975 [5] showed an overall prevalence of 2.44%, with the highest rates in the more deprived, central areas of large conurbations. Once again the infection rate was higher in urban than in rural areas. However, in the early 1980s, there was a resurgence of infection, and the increase occurred mainly in middle-class, often professional families, especially in suburban and rural areas [6]. Hence, in more recent years, the head louse has become classless and cosmopolitan. It is of interest to note that in a recent survey in Jordan, there was a significant association between social class and infection rates, there being much higher infection rates in lower socio-economic classes [7].

High rates of head louse infection have been reported from the USA, Canada and several other countries; a review by Gratz [1] provides a comprehensive survey of published information relating to prevalence.

Head lice are more common on children, particularly in the age range 3–11 years, than on adults, and most surveys have shown that girls are more frequently infected than boys. Behaviour patterns in girls and boys at different ages probably influence rates of infection [8]. For example, in primary schools children are organized into small groups around desks, and head to head contact is frequent. In addition, hair contact is probably more likely between

girls than boys. Older children tend to be more independent, and more separated from their peers. The contribution of hair length to infection is contentious. Some studies have not shown any correlation between hair length and louse infection rates, but in others children with longer hair have had higher infection rates. A survey from Israel, in which detection of infection was by means of a louse comb, rather than direct visual inspection, found a significantly higher infection rate in children with long and medium length hair than in those with short hair [9]. In the author's experience, in the UK, most adults with head lice are mothers who have acquired them from their children.

Several authors have noted a low incidence of head louse infection in black Americans [10–12], although infection rates in black Africans are high [1]. It has been suggested that the use of pomades by black Americans provides an environment unsuited to establishment of infection [10], but head lice are quite common in the Indian subcontinent, where hair oils and creams are frequently used [13]. A survey in Brazil found the same prevalence in blacks as in whites [14]. A factor which could influence transmission between ethnic groups is the specialization in the louse with regard to modification of the legs to grasp hairs of different cross-sectional shape [15].

It is thought that the majority of head louse infections are acquired by direct head-to-head contact, optimal conditions for transfer being when hairs are parallel and slow-moving [16]. Spread of lice is encouraged by poverty, poor hygiene and overcrowding. Overcrowding is perhaps the most important factor. Lack of hygiene alone does not encourage head louse infection.

There are conflicting opinions about the importance of fomites in transmission of head lice [6,17], and in practice the putative role of caps, scarves, combs and brushes is difficult to confirm or refute [18].

In Australia, an examination, employing a vacuum cleaner fitted with a filter, of classroom floors in schools in which there was an overall prevalence of head lice of 20.9%, did not reveal any lice on the floors [19], indicating that there is no requirement for anti-louse measures on carpets and floors.

Clinical features. Although many individuals are asymptomatic [20], scalp pruritus is the characteristic manifestation of head louse infection. Secondary bacterial infection may occur as a result of scratching, and concomitant head louse infection must always be considered in cases of scalp impetigo. Pruritic papular lesions may occur on the nape of the neck, and occasionally a generalized non-specific pruritic eruption develops [21]. In severe, neglected cases, pus and exudate may produce matting of the hair—a state that has been termed 'plica polonica', from its prevalence in Poland in the early part of the 20th century. However, matting of the hair can occur in the absence of louse infection, and it has been suggested that this term should be discarded [22].

The empty egg cases ('nits') are easily identified, and occur in greatest density on the parietal and occipital regions (Fig. 38.17). However, on naked-eye inspection, they may be confused with peripilar keratin casts ('pseudonits'; hair muffs) [23,24] or dried globules of cheap hair lacquer.

Detection of adult lice and nymphs provides evidence of an 'active' infection, whereas the presence of eggs and egg-cases alone merely indicates that infection has occurred at some time. The most reliable method of diagnosing current, active infection is by detection combing, which has been shown to be superior to direct visual examination of the hair and scalp [9,25–27]. This is an important criterion for several reasons:

1 It is recommended that individuals who do not have evidence of active infection should not receive chemical treatment [27].
2 Participants in clinical trials of pediculicides should have live lice or 'lice and eggs' present on the head before enrolment, not just eggs alone.
3 Children who do not have evidence of active infection may be inappropriately excluded from school [27–29].



Fig. 38.17 Numerous head louse eggs and empty egg cases.

Treatment [2,3,27,30–33]. Chemical pediculicides have been important in the control of head lice for many years. In the UK, malathion and carbaryl (carbaril) replaced lindane, following evidence of the development of resistance to organochlorines [34], although use of carbaryl was restricted when data was released which suggested a potential carcinogenic effect of long-term oral administration to rodents [35]. Both were originally shown to be efficient pediculicides and to have good, but not complete, ovicidal activity [34,36–39].

A few years later, pyrethrins synergized with piperonyl butoxide, and the synthetic pyrethroids permethrin and phenothrin [40–42] became available, and have been used in many parts of the world.

General guidelines for the use of these chemical pediculicides have included advice to repeat treatment after 10 days [43] because of limited ovicidal activity, and that lotion and liquid formulations are preferable to shampoos as the latter expose the insects to

relatively low concentrations of insecticide which, in the long term, will favour the development of resistance. Preparations with an aqueous basis are less likely to irritate an excoriated scalp than alcoholic solutions, do not irritate the bronchi of asthmatics, and are not flammable. Family members should be examined, and treated if they show evidence of active infection by the presence of live lice.

The formulation of the marketed products influences their efficacy, because components (excipients) other than the active ingredient may also have pediculicidal activity [44,45].

However, there is now evidence of widespread malathion and pyrethroid resistance [46–53], and the emergence of carbaryl resistance in the UK [48]. The last mentioned is of interest in that the restricted use of carbaryl in the UK was probably a factor contributing to the delayed emergence of resistance in comparison with malathion and synthetic pyrethroids, which have been widely available over-the-counter. Similarly, a factor in the continued efficacy of malathion demonstrated in a study in South Florida, USA, was probably the commercial failure, and therefore limited use, of previously marketed malathion preparations [54].

Hence, choice of chemical treatment for head louse infection should be guided not only by evidence of pediculicidal activity from well-conducted clinical trials, but also by local patterns of resistance [56]. From a practical point of view, if a correctly applied pediculicide has failed to eradicate an infection, a different pharmacological class of agent should be used—for example, change from a synthetic pyrethroid to malathion, or *vice versa*.

A new approach to treatment is the introduction of agents designed to asphyxiate lice [56,57]. As Elston [33] points out, there is little potential for the development of resistance, and parents who are concerned about the use of currently available chemical pediculicides on their children may be more willing to use these new products. A preparation containing dimeticone 4% has been marketed [56].

Physical treatment is an alternative to the use of chemical agents and, in the UK, the 'Bug Busting' (Community Hygiene Concern, London, UK) wet-combing method has been promoted as a treatment for head lice. The technique involves ordinary shampooing of the hair, followed by the application of generous amounts of conditioner, and combing using a fine-tooth comb to remove lice. This procedure is repeated every 4 days for 2 weeks [58–62]. A battery-powered device, the 'Robi comb', which kills lice as it is used to comb through the hair, is also available, and devices that deliver hot air to the hair and scalp are also said to be effective at louse eradication [63,64].

Simply shaving the head may be acceptable in some communities, but is not in others [65,66].

Other treatments that have been employed to eradicate head lice include crotamiton [67], and topical and oral ivermectin [68–70]. Although the results of oral ivermectin treatment were not impressive, it is likely that this is because ivermectin has no ovicidal activity, and two doses separated by an interval of 10 days would be more effective.

Oral therapy with cotrimoxazole has been reported to be effective in eradicating head lice [71,72]. This is probably because the antibiotic is ingested by the louse and affects its symbiotic bacteria [73]. These bacteria are essential for louse survival, and treatments directed at them might provide alternative means of louse control [74]. There is also a report of the efficacy of oral thiabendazole [75].

There is anecdotal, and some *in vitro*, evidence of pediculicidal activity of plant-derived essential oils such as lavender oil, tea tree oil [76] and neem [77,78].

Empty egg cases persist for some time until they are gradually worn away by repeated washing, but are otherwise difficult to dislodge, and their presence should not be a reason for excluding children from school [79].

A head louse repellent containing piperonal was produced several years ago [80] and, more recently, others containing plant-derived essential oils have been marketed. There is some evidence that citronella is an effective louse repellent [81], but repellency of other plant-derived oils is limited [82].

Useful sources for guidance on treatment of head lice include the UK CKS (Prodigy) Database (http://cks.library.nhs.uk/home) and the US Centers for Disease Control and Prevention site (http://www.cdc.gov/lice/).

References

1 Gratz NG. *Human Lice. Their Prevalence, Control and Resistance to Insecticides. A Review 1985–1997*. World Health Organization, 1997. WHO/CTD/WHOPES/97.8.
2 Chosidow O. Scabies and pediculosis. *Lancet* 2000; **355**: 819–26.
3 Burgess IF. Human lice and their control. *Annu Rev Entomol* 2004; **49**: 457–81.
4 Mellanby K. The incidence of head lice in England. *Med Off* 1941; **65**: 39–43.
5 Donaldson RJ. *The Head Louse in England: Prevalence Amongst Schoolchildren*. London: The Health Education Council, 1975.
6 Maunder JW. The head louse resurgence. *Maternal Child Health* 1983; **8**: 51–6.
7 Amr ZS, Nusier MN. Pediculosis capitis in northern Jordan. *Int J Dermatol* 2000; **39**: 919–21.
8 Downs AMR, Stafford KA, Stewart GH, Coles GC. Factors that may be influencing the prevalence of head lice in British school children. *Pediatr Dermatol* 2000; **17**: 72–4.
9 Mumcuoglu KY, Friger M, Ioffe-Uspensky I *et al*. Louse comb versus direct visual examination for the diagnosis of head louse infestations. *Pediatr Dermatol* 2001; **18**: 9–12.
10 Litt JZ. The quiddity of the head louse. *Arch Dermatol* 1978; **114**: 1099.
11 Slonka GF, McKinley TW, McCroan JE *et al*. Epidemiology of an outbreak of head lice in Georgia. *Am J Trop Med Hyg* 1976; **25**: 739–43.
12 Juranek DD. Pediculus capitis in school children. Epidemiological trends, risk factors and recommendations for control. In: Orkin M, Maibach HI, eds. *Cutaneous Infestations and Insect Bites*. New York: Marcel Dekker; 1985: 199–211.
13 Bhutani LK. Pediculosis capitis. *Arch Dermatol* 1979; **115**: 675.
14 de Madureira PR. Pediculosis and ethnic groups. *Int J Dermatol* 1991; **30**: 524.
15 Donaldson RJ. Head lice. In: Donaldson RJ, ed. *Parasites and Western Man*. Lancaster: MTP Press; 1979: 57–77.
16 Canyon DV, Speare R, Muller R. Spatial and kinetic factors for the transfer of head lice (*Pediculus capitis*) between hairs. *J Invest Dermatol* 2002; **119**: 629–31.
17 Fine BC. Controversy about pediculosis capitis. *N Engl J Med* 1984; **311**: 801.
18 Juranek DD, Jessup CA, Coll B. Pediculosis: the Philadelphia school problem. In: Parish LC, Nutting WB, Schwartzman RM, eds. *Cutaneous Infestations of Man and Animal*. New York: Praeger, 1983: 151–63.
19 Speare R, Thomas G, Cahill C. Head lice are not found on floors in primary school classrooms. *Aust N Z J Public Health* 2002; **26**: 208–11.
20 Mumcuoglu KY, Klaus S, Kafka D *et al*. Clinical observations related to head lice infestation. *J Am Acad Dermatol* 1991; **25**: 248–51.
21 Ronchese F. Generalized dermatitis from pediculosis capitis. *N Engl J Med* 1946; **234**: 665–6.
22 Parish LC. Plica polonica. In: Parish LC, Nutting WB, Schwartzman RM, eds. *Cutaneous Infestations of Man and Animal*. New York: Praeger, 1983: 43–9.
23 Held JL, Bernstein RM. Hair casts or pseudonits acquired following psychological trauma. *Cutis* 1989; **43**: 380–1.

24 Scott MJ Jr, Scott MJ Sr. Nits or not? Pseudonits—simple office diagnosis. *JAMA* 1980; **243**: 2325–6.
25 De Maeseneer J, Blokland I, Willems S *et al*. Wet combing versus traditional scalp inspection to detect head lice in schoolchildren: observational study. *BMJ* 2000; **321**: 1187–8.
26 Bingham P, Kirk S, Hill N, Figueroa J. The methodology and operation of a pilot randomized control trial of the effectiveness of the Bug Busting method against a single application insecticide product for head louse treatment. *Public Health* 2000; **114**: 265–8.
27 Mumcuoglu KY, Barker SC, Burgess IF *et al*. International guidelines for effective control of head louse infestations. *J Drugs Dermatol* 2007; **6**: 409–14.
28 Pollack RJ, Kiszewski AE, Spielman A. Overdiagnosis and consequent mismanagement of head louse infestation in North America. *Pediatr Infect Dis J* 2000; **19**: 689–94.
29 Williams LK, Reichert A, MacKenzie WR. Lice, nits and school policy. *Pediatrics* 2001; **107**: 1011–5.
30 Burgess I. Human lice and their management. *Adv Parasitol* 1995; **36**: 271–342.
31 Roberts RJ. Head lice. *N Engl J Med* 2002; **346**: 1645–50.
32 Elston DM. Drugs used in the treatment of pediculosis. *J Drugs Dermatol* 2005; **4**: 207–11.
33 Elston DM. Nit picking. *J Am Acad Dermatol* 2005; **53**: 164–7.
34 Maunder JW. Resistance to organochlorine insecticides in head lice and trials using alternative compounds. *Med Off* 1971; **125**: 27–9.
35 Boulton A. Britain restricts lice treatment. *BMJ* 1995; **311**: 1322.
36 Maunder JW. Use of malathion in the treatment of lousy children. *Community Med* 1971; **126**: 145–7.
37 Maunder JW. Clinical and laboratory trials employing carbaryl against the human head louse, *Pediculus humanus capitis* (de Geer). *Clin Exp Dermatol* 1981; **6**: 605–12.
38 Taplin D, Castillero PM, Spiegel J *et al*. Malathion for treatment of *Pediculus humanus* var *capitis* infestation. *JAMA* 1982; **247**: 3103–5.
39 Urcuyo FG, Zaias N. Malathion lotion as an insecticide and ovicide in head louse infestation. *Int J Dermatol* 1986; **25**: 60–2.
40 Carson DS, Tribble PW, Weart CW. Pyrethrins combined with piperonyl butoxide (RID) vs 1% permethrin (NIX) in the treatment of head lice. *Am J Dis Child* 1988; **142**: 768–9.
41 Burgess IF, Brown CM, Burgess NA. Synergized pyrethrin mousse, a new approach to head lice eradication: efficacy in field and laboratory studies. *Clin Ther* 1994; **16**: 57–64.
42 Taplin D, Meinking TL. Pyrethrins and pyrethroids in dermatology. *Arch Dermatol* 1990; **126**: 213–21.
43 Mumcuoglu KY. Effective treatment of head louse with pediculicides. *J Drugs Dermatol* 2006; **5**: 451–2.
44 Burgess I. Carbaryl lotions for head lice—new laboratory tests show variations in efficacy. *Pharm J* 1990; **245**: 159–61.
45 Burgess I. Malathion lotions for head lice—a less reliable treatment than commonly believed. *Pharm J* 1991; **247**: 630–2.
46 Burgess IF, Peock S, Brown CM, Kaufman J. Head lice resistant to pyrethroid insecticides in Britain. *BMJ* 1995; **311**: 752.
47 Downs AMR, Stafford KA, Harvey I, Coles GC. Evidence of double resistance to permethrin and malathion in head lice. *Br J Dermatol* 1999; **141**: 508–11.
48 Downs AMR, Stafford KA, Hunt LP *et al*. Widespread insecticide resistance in head lice to the over-the-counter pediculocides in England, and the emergence of carbaryl resistance. *Br J Dermatol* 2002; **146**: 88–93.
49 Izri MA, Briere C. Premiers cas de résistance de *Pediculus capitis* Linné 1758 au malathion en France. *Presse Med* 1995; **24**: 1444.
50 Chosidow O, Chastang C, Brue C *et al*. Controlled study of malathion and *d*-phenothrin for *Pediculus humanus* var *capitis*-infested schoolchildren. *Lancet* 1994; **344**: 1724–7.
51 Mumcuoglu KY, Hemingway J, Miller J *et al*. Permethrin resistance in the head louse *Pediculus capitis* from Israel. *Med Vet Entomol* 1995; **9**: 427–32.
52 Picollo MI, Vassena CV, Mougabure Cueto GA *et al*. Resistance to insecticides and effect of synergists on permethrin toxicity in *Pediculus capitis* (Anoplura: Pediculidae) from Buenos Aires. *J Med Entomol* 2000; **37**: 721–5.
53 Burkhart CG, Burkhart CN. Clinical evidence of lice resistance to over-the-counter products. *J Cutan Med Surg* 2000; **4**: 199–201.
54 Meinking TL, Serrano L, Hard B *et al*. Comparative in vitro pediculicidal efficacy of treatments in a resistant head louse population in the United States. *Arch Dermatol* 2002; **138**: 220–4.
55 Dodd C. Treatment of head lice: choice of treatment will depend on local patterns of resistance. *BMJ* 2001; **323**: 1084.
56 Burgess IF, Brown CM, Lee PN. Treatment of head louse infestation with 4% dimeticone lotion: randomised controlled equivalence trial. *BMJ* 2005; **330**: 1423.
57 Burkhart CG, Burkhart CN. Asphyxiation of lice with topical agents, not a reality . . . yet. *J Am Acad Dermatol* 2006; **54**: 721–2.
58 Ibarra J, Hall DMB. Head lice in schoolchildren. *Arch Dis Child* 1996; **75**: 471–3.
59 Roberts RJ, Casey D, Morgan DA, Petrovic M. Comparison of wet combing with malathion for treatment of head lice in the UK: a pragmatic randomized controlled trial. *Lancet* 2000; **356**: 540–4.
60 Hill N, Moor G, Cameron MM *et al*. Single blind, randomised, comparative study of the Bug Buster kit and over the counter pediculicide treatments against head lice in the United Kingdom. *BMJ* 2005; **331**: 384–7.
61 Dawes M. Combing and combating head lice. *BMJ* 2005; **331**: 362–3.
62 Chosidow O. Bug Buster for head lice. Is it effective? *Arch Dermatol* 2006; **142**: 1635–7.
63 Kersten H. Hot air is an effective treatment for head lice. *J Pediatr* 2007; **150**: 562–3.
64 Goates BM, Atkin JS, Wilding KG *et al*. An effective nonchemical treatment for head lice: a lot of hot air. *Pediatrics* 2006; **118**: 1962–70.
65 Lwegaba A. Shaving can be safer head lice treatment than insecticides. *BMJ* 2005; **330**: 1510.
66 Brenton CM. Shaving for head lice is unnecessary and distressing. *BMJ* 2005; **331**: 405.
67 Karacic I, Yawalkar SJ. A single application of crotamiton lotion in the treatment of patients with pediculosis capitis. *Int J Dermatol* 1982; **21**: 611–3.
68 Youssef MYM, Sadaka HAH, Eissa MM, El-Ariny AE. Topical application of ivermectin for human ectoparasites. *Am J Trop Med Hyg* 1995; **53**: 652–3.
69 Dunne LC, Malone CJ, Whitworth JAG. A field study on the effects of ivermectin on ectoparasites of man. *Trans R Soc Trop Med Hyg* 1991; **85**: 550–1.
70 Glaziou P, Nyguyen LN, Moulia-Pelat JP *et al*. Efficacy of ivermectin for the treatment of head lice (pediculosis capitis). *Trop Med Parasitol* 1994; **45**: 253–4.
71 Campos R, Moreira AAB, Castilho VLP *et al*. Cura da pediculosa da cabeca por meio do cotrimoxazol administrado pela via oral. *Rev Inst Med Trop Sao Paulo* 1981; **23**: 28–30.
72 Shashindran CH, Gandhi IS, Krishnasamy S *et al*. Oral therapy of pediculosis capitis with cotrimoxazole. *Br J Dermatol* 1978; **98**: 699.
73 Burns DA. Action of cotrimoxazole on head lice. *Br J Dermatol* 1987; **117**: 399–400.
74 Burkhart CN, Burkhart CG. Bacterial symbiotes, their presence in head lice, and potential treatment avenues. *J Cutan Med Surg* 2006; **10**: 2–6.
75 Namazi MR. Treatment of pediculosis capitis with thiabendazole: a pilot study. *Int J Dermatol* 2003; **42**: 973–6.
76 Mills C, Cleary BJ, Gilmer JF, Walsh JJ. Inhibition of acetylcholinesterase by tea tree oil. *J Pharm Pharmacol* 2004; **56**: 375–9.
77 Heukelbach J, Oliveira FAS, Speare R. A new shampoo based on neem (*Azadirachta indica*) is highly effective against head lice in vitro. *Parasitol Res* 2006; **99**: 353–6.
78 Abdel Ghaffar F, Semmler M. Efficacy of neem seed extract shampoo on head lice of naturally infected humans in Egypt. *Parasitol Res* 2007; **100**: 329–32.
79 Mumcuoglu KY, Meinking TA, Burkhart CN, Burkhart CG. Head louse infestations: the no nit policy and its consequences. *Int J Dermatol* 2006; **45**: 891–6.
80 Burgess I. New head louse repellent. *Br J Dermatol* 1993; **128**: 357–8.
81 Mumcuoglu KY, Magdassi S, Miller J *et al*. Repellency of citronella for head lice: double-blind randomized trial of efficacy and safety. *Isr Med Assoc J* 2004; **6**: 756–9.
82 Canyon DV, Speare R. A comparison of botanical and synthetic substances commonly used to prevent head lice (*Pediculus humanus* var *capitis*) infestation. *Int J Dermatol* 2007; **46**: 422–6.

Clothing/body lice (*Pediculosis corporis*)

Prevalence and epidemiology [1–3]. *Pediculosis corporis* occurs throughout the world, although it is now uncommon in developed



Fig. 38.18 Clothing lice and eggs.



Fig. 38.19 Crab louse eggs on the eyelashes.

countries. The clothing louse is the louse of poverty and neglect, and flourishes in overcrowded, unhygienic situations on individuals who rarely remove their clothing. In the Western world today, those harbouring lice are mainly vagrants.

The number of lice and eggs on the clothing varies greatly. In most infected individuals the population is small, but in some there may be thousands of lice.

The clothing louse is the vector of epidemic typhus, trench fever and louse-borne relapsing fever. Epidemic typhus has been responsible for huge mortality in the past [4,5].

Clinical features [3,6]. In most infected persons, itching is the principal complaint. Pruritus is the result of sensitization to louse salivary antigens. Others, who have not become sensitized or have acquired tolerance to the bites, are asymptomatic. The body is often covered in excoriations, and there may be secondary bacterial infection. In those who have harboured clothing lice for long periods of time the skin is often hyperpigmented (so-called 'vagabonds' disease'; morbus errorum), and this is probably a post-inflammatory phenomenon.

Lice and eggs should be sought in the clothing (Fig. 38.18).

Treatment. It is the clothing, not the patient, which requires treatment. Tumble-drying is a most effective means of killing both lice and eggs [2]. High-temperature laundering of undergarments and dry cleaning of outer clothing are also effective.

In dealing with large numbers of infected individuals, insecticides have been used to treat clothing. The emergence of lice resistant to dichlorodiphenyltrichloroethane (DDT) and lindane led to the introduction of malathion dusting powder [7,8] and, more recently, permethrin-treated clothing has been shown to be toxic to clothing lice [9].

References

1 Buxton PA. *The Louse*, 2nd edn. London: Edward Arnold, 1947.

2 Maunder JW. Pediculosis corporis; an updating of attitudes. *Environ Health* 1983; May: 130–2.

3 Burgess I. Human lice and their management. *Adv Parasitol* 1995; **36**: 271–342.

4 Hobson W. Of lice and men. In: *World Health and History*. Bristol: J Wright and Sons, 1963: 29–41.

5 Zinsser H. *Rats, Lice and History*. London: Macmillan, 1985.

6 Alexander JO'D. Infestation with Anoplura—lice. In: *Arthropods and Human Skin*. Berlin: Springer-Verlag, 1984: 29–55.

7 Barnes WW, Eldridge BF, Greenberg JH *et al*. A field evaluation of malathion dust for the control of body lice. *J Econ Entomol* 1962; **55**: 591–4.

8 Hayes WJ Jr, Mattson AM, Short JG *et al*. Safety of malathion dusting powder for louse control. *Bull WHO* 1960; **22**: 503–14.

9 Scholdt LL, Rogers EJ Jr, Gerberg EJ *et al*. Effectiveness of permethrin-treated military uniform fabric against human body lice. *Milit Med* 1989; **154**: 90–3.

Crab lice (*Phthiriasis pubis*)

Prevalence and epidemiology [1–3]. Crab lice are transmitted by close physical contact, usually sexual, and infection with these lice occurs most frequently among sexually active young adults. It is standard practice in genitourinary medicine (GUM) clinics to monitor prevalence rates of sexually transmitted infections, including crab lice. A marked decline in the number of female cases in one department in the UK led to the suggestion that waxing of pubic hair, particularly the fashion known as the 'Brazilian', was an important factor responsible for the decline [4]!

Because many patients with crab louse infection who attend GUM clinics are found to be suffering from other sexually transmitted infections [5–8], screening for these is indicated.

Clinical features. Itching, mainly in the evening and at night, is the principal symptom. Close inspection of affected areas will reveal lice grasping hairs close to the skin surface, and louse eggs attached to the hair shafts. Louse faeces are often visible as rust-coloured speckles on the skin and hair, and the underclothes may be spotted with altered blood.

When crab lice are discovered on the pubic area, other hairy areas of the body should be examined, as these lice may colonize eyebrows, eyelashes (Fig. 38.19), beard, axillae, areolar hair and the scalp margins [9–13]. In heavy infections in men, the hair on the trunk and limbs may be extensively colonized. A case has been reported in which the presence of an enormous population of lice was attributed to inappropriate use of topical steroids [14].

Blue–grey macules (maculae caeruleae) are occasionally seen on the skin [15–17], but their precise pathogenesis is unknown.

Bullous lesions attributed to crab lice have been reported [18,19].

In children, crab lice may colonize the eyelashes and scalp [20–23]. Infection in children is usually acquired by close physical contact with infected parents. As an isolated finding, it is not indicative of sexual abuse, although this may occasionally occur [24].

Treatment [3,25–31]. Malathion, pyrethrins with piperonyl butoxide, pyrethroids and carbaryl may be used to treat crab lice. In view of the possibility of involvement of axillary and body hair it is preferable to treat the whole of the trunk and limbs, and the scalp may also require treatment. Alcohol-based preparations may be irritating when applied to the scrotum, and an aqueous base is preferable. Treatment should be repeated after an interval of 7–10 days. All sexual contacts should also be treated.

Eyelash infection (phthiriasis palpebrarum). [32,33] Although mechanical removal of lice and eggs with fine forceps [34] or epilation of the lashes with their attached eggs are obvious remedies, these procedures are uncomfortable, and are not recommended. Cryotherapy has been used to destroy crab lice on the lashes [35], and the use of fluorescein in concentrations of 10–20% is also said to be effective [36].

Any ointment might be expected to interfere with the respiratory function of the louse by blocking its spiracles, and the use of a thick application of white soft paraffin (white petrolatum; Vaseline) twice daily for 2–3 weeks has been recommended [37,38]. Yellow mercuric oxide ointment was frequently used in the past, and physostigmine ointment was also a popular remedy, particularly among ophthalmologists [31,39–41]. A drawback is the ocular effect of physostigmine, which causes pupillary constriction and paralysis of accommodation. Oral ivermectin, given as two doses a week apart, cured four patients with eyelash crab lice [42].

Argon laser phototherapy has also been employed [43].

White soft paraffin is the treatment of choice.

References

1 Buxton PA. *The Louse*, 2nd edn. London: Edward Arnold, 1947.
2 Nayyar KC, Stolz E. Scabies and pediculosis pubis. In: Hims JR, ed. *Recent Advances in Sexually Transmitted Diseases*, Vol. 2. Edinburgh: Churchill Livingstone, 1981: 240–4.
3 Burgess I. Human lice and their management. *Adv Parasitol* 1995; **36**: 271–342.
4 Armstrong NR, Wilson JD. Did the 'Brazilian' kill the pubic louse? *Sex Transm Infect* 2006; **82**: 265–6.
5 Fisher L, Morton RS. *Phthirus pubis* infestation. *Br J Vener Dis* 1970; **46**: 326–9.
6 Chapel TA, Katta T, Kuszmar T, De Giusti D. Pediculosis pubis in a clinic for treatment of sexually transmitted diseases. *Sex Transm Dis* 1979; **6**: 257–60.
7 Opaneye AA, Jayaweera DT, Walzman M, Wade AA. Pediculosis pubis: a surrogate marker for sexually transmitted diseases. *J R Soc Health* 1993; **113**: 6–7.
8 Pierzchalski JL, Bretl DA, Matson SC. *Phthirus pubis* as a predictor for *Chlamydia* infections in adolescents. *Sex Transm Dis* 2002; **29**: 331–4.
9 Chitchang S, Yodmani B. Phthiriasis capitis. *J Med Assoc Thailand* 1983; **66**: 728–9.
10 Elgart ML, Higdon RS. Pediculosis pubis of the scalp. *Arch Dermatol* 1973; **107**: 916–7.
11 Mueller JF. Pubic lice from the scalp hair; a report of two cases. *J Parasitol* 1973; **59**: 943–4.
12 Signore RJ, Love J, Boucree MC. Scalp infestation with *Phthirus pubis*. *Arch Dermatol* 1989: **125**: 133.
13 Witkowski JA, Parish LC. Phthiriasis capitis. *Int J Dermatol* 1979; **18**: 559–60.
14 Nielsen AO, Secher L. Pediculosis pubis in a patient treated with topical steroids. *Cutis* 1980; **25**: 655–8.
15 Pavlovsky EN, Stein AK. Maculae caeruleae and *Phthirus pubis*. *Parasitology* 1924; **16**: 145–9.
16 Payne JF. Maculae caeruleae and other symptoms produced by pediculi pubis. *Br J Dermatol* 1890; **2**: 209–12.
17 Safdi SA, Farrington J. Constitutional reactions and maculae ceruleae attending phthiriasis pubis. *Am J Med Sci* 1947: **214**: 308–11.
18 Kern AB. Bullous eruption due to pediculosis pubis. *Arch Dermatol Syphilol* 1952; **65**: 334–9.
19 Brenner S, Yust I. Bullous eruption in a case of bullous pediculid. *Cutis* 1988; **41**: 281.
20 Alexander JO'D. *Phthirus pubis* infestation of the eyelashes. *JAMA* 1983; **250**: 32.
21 Goldman L. *Phthirus pubis* infestation of the scalp and cilia in young children. *Arch Dermatol Syphilol* 1948; **57**: 274.
22 Goldman L, Friedman LS. Infection of scalp and cilia with *Phthirus pubis* in a nineteen month old baby. *Am J Dis Child* 1941; **61**: 344–6.
23 Korting CW. Phthiriasis palpebrarum—und ihre ersten historischen Erwahnungen. *Hautarzt* 1967; **18**: 73–4.
24 Scott MJ, Esterly NB. Eyelash infestation by *Phthirus pubis* as a manifestation of child abuse. *Pediatr Dermatol* 1983; **1**: 179.
25 Kalter DC, Sperber J, Rosen T *et al*. Treatment of pediculosis pubis. *Arch Dermatol* 1987; **123**: 1315–9.
26 Clinical Effectiveness Group (Association of Genitourinary Medicine and the Medical Society for the Study of Venereal Diseases). National guideline for the management of *Phthirus pubis* infestation. *Sex Transm Inf* 1999; **75** (Suppl. 1): S78–9.
27 Scott GR. European guideline for the management of pediculosis pubis. *Int J STD & AIDS* 2001; **12** (Suppl. 3): 62.
28 Department of Health. http://cks.library.nhs.uk/pubic_lice
29 Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines 2002. *MMWR* 2002; **51/RR–6**: 67–8.
30 Wendel K, Rompalo A. Scabies and pediculosis pubis: an update of treatment regimens and general review. *Clin Infect Dis* 2002; **35** (Suppl. 2): S146–51.
31 Ko CJ, Elston DM. Pediculosis. *J Am Acad Dermatol* 2004; **50**: 1–12.
32 Burns DA. The treatment of *Phthirus pubis* infestation of the eyelashes. *Br J Dermatol* 1987; **117**: 741–3.
33 Couch JM, Green WR, Hirst LW *et al*. Diagnosing and treating *Phthirus pubis* palpebrarum. *Surv Ophthalmol* 1982; **26**: 219–25.
34 Ronchese F. Treatment of pediculosis ciliorum in an infant. *N Engl J Med* 1953; **249**: 897–8.
35 Awan KJ. Cryotherapy in phthiriasis palpebrarum. *Am J Ophthalmol* 1977; **83**: 906–7.
36 Mathew M, D'Souza P, Mehta DK. A new treatment of phthiriasis palpebrarum. *Ann Ophthalmol* 1982; **14**: 439–41.
37 Orkin M, Epstein E, Maibach HI. Treatment of today's scabies and pediculosis. *JAMA* 1976; **236**: 1136–9.
38 Rasmussen JE. Pediculosis and the pediatrician. *Pediatr Dermatol* 1984; **2**: 74–9.
39 Chin GN, Denslow GT. Pediculosis ciliaris. *J Pediatr Ophthalmol Strabismus* 1978; **15**: 173–5.
40 Duke-Elder S, MacFaul PA. *System of Ophthalmology*, Vol. XIII. *The Ocular Adnexa. Part 1: Diseases of the Eyelids*. London: Henry Kimpton, 1974: 196–9.
41 Orkin M. Pediculosis today. *Minn Med* 1974; **53**: 848–52.
42 Burkhart CN, Burkhart CG. Oral ivermectin therapy for phthiriasis palpebrarum. *Arch Ophthalmol* 2000; **118**: 134–5.
43 Awan KJ. Argon laser phototherapy of phthiriasis palpebrarum. *Ophthalmic Surg* 1986; **17**: 813–4.

Bugs (Hemiptera)

Family Cimicidae (including bedbugs) [1–4]

All the Cimicidae are blood-sucking, temporary ectoparasites of birds and mammals. Two-thirds of the species in this family are parasites of bats. It has been suggested that Cimicidae became

adapted to feeding on humans when cave dwellers took up residence alongside the bats.

Genus *Cimex*. *C. lectularius* (the common bedbug) is cosmopolitan, and common throughout Europe, North America, North Africa, North India, Siberia, North China, South Africa, Australia and South America. Until recently, bedbugs have been rare in the UK, but an increase in the number of cases referred to Brighton Public Health Laboratory Service in 1999 suggested that they might be becoming more common [5], and subsequently there has been evidence of a resurgence of these parasites in the developed world. This could be related to insecticide resistance and/or dissemination as a consequence of the increase in international tourism [4,6,7].

C. pipistrelli (the batbug), originating in a bat roost in a house, was responsible for itchy skin lesions in one of the house occupants [8].

C. hemipterus (the tropical bedbug) is less tolerant of low temperatures than *C. lectularius*. This bug is confined to tropical and subtropical regions, including India, Burma, Malaya, South China and Central Africa.

Genus *Leptocimex*. *L. boueti* has a limited distribution in West Africa, where it parasitizes humans and bats.

Genus *Oeciacus*. Several species are usually found on birds and in their nests, for example *Oeciacus hirundinis*, the martin bug [9] and *O. vicarius*, the swallow bug. They may invade houses from nests under the eaves, and will bite humans readily, but it is unlikely that they can complete their lifecycles on human blood, or take up residence in houses as bedbugs do.

Genus *Haematosiphon*. *H. inodorus*, the only species in this genus, is also known as the Mexican chicken bug. As the name suggests, its major host is the chicken, but it can be a serious pest in human domiciles if these are close to chicken roosts.

Ecology [4,10]. Bedbugs are 4–5 mm in length, with dorsoventrally flattened, oval bodies, the forewings reduced to scale-like pads, and the hindwings absent (Fig. 38.20). The mouthparts are modified into a proboscis adapted for piercing and sucking.

Female bedbugs deposit their pearly white, flask-shaped eggs in the crevices of floors and walls, in furniture, bedframes and mattresses. Each female lays about 300 eggs in her lifetime. The eggs hatch after about 10 days: the nymphal stage lasts approximately 6 weeks, during which time the bug moults five times.

Bedbugs normally feed at night, usually about an hour before dawn, but they may feed during the day if circumstances are favourable [11]. Searching for a food source is erratic, and is probably at random at distances greater than a few centimetres, but in the final approach to the host, both temperature and odour play a part in guiding the bug. Feeding time is relatively short (3–12 min). During feeding, the bedbug injects saliva containing an anticoagulant and anaesthetic. In the absence of a suitable food supply, however, adult bed bugs can survive starvation, in ideal circumstances, for a year or more.



Fig. 38.20 *Cimex lectularius*, the bedbug. (Courtesy of Oxford Scientific Films.)

In the absence of its usual host, *C. lectularius* will attack other animals, and Cimicidae normally parasitic on other hosts are similarly prepared to attack humans, invading houses from birds' nests or chicken runs.

Clinical features. The bites of the bedbug are painless, and the attention of the victim is only drawn to the bites by the reaction they produce. They commonly occur on the face and neck, hands and arms, but may occasionally be generalized. In the individual not sensitized by previous exposure, there may be no symptoms at any stage, and only a purpuric macule indicates the site of the bite. Late-onset reactions may occur in some cases [12]. In sensitized subjects intensely irritating weals or papules surmounted by haemorrhagic puncta are the characteristic reaction. In some cases where the reaction is severe, bullae predominate [13–16], and in one patient with bullous lesions it was demonstrated that their serum contained specific IgE antibodies against the *C. lectularius* salivary gland protein nitrophorin [17].

The bites of other Cimicidae are essentially similar, but their distribution depends on the method of exposure.

Bedbugs as vectors of disease [4]. It is not known with certainty whether bedbugs act as vectors for any disease in humans, but their possible role in the transmission of hepatitis B and C, and HIV infection, has been investigated [18–26]. Hepatitis B virus persists for up to 6 weeks in the bedbug's body [18,22,23]. It has been suggested that mechanical transmission to humans could occur via infected bug faeces, or when bugs are crushed during feeding. Hepatitis C virus RNA was not detected in bedbugs after feeding on blood with a high viral titre [22].

Initially, it was suggested that bedbugs might act as vectors for HIV [24], but it was later concluded that this is unlikely [25,26].

Haematosiphoniasis [27]. Haematosiphoniasis is the name given to the cutaneous lesions caused by the bites of *Haematosiphon inodorus* (the Mexican chicken bug). Polymorphic lesions, consisting of weals, papules, vesicles, pustules and scabs, occur predominantly on exposed parts of the body.

References

1 British Museum (Natural History). *The Bed Bug*. London: Trustees of the British Museum (Natural History), 1973. (Economic series, no. 5.)
2 Usinger RL. *Monograph of Cimicidae (Hemiptera-Heteroptera)*. Entomological Society of America, Thomas Say Foundation, Vol. 7, 1966.
3 Kettle DS. *Medical and Veterinary Entomology*, 2nd edn. Wallingford: CAB International, 1995: 344–60.
4 Klaus R, Siva-Jothy MT. Biology of the bed bugs (Cimicidae). *Annu Rev Entomol* 2007; **52**: 351–74.
5 Paul J, Bates J. Is infestation with the common bedbug increasing? *BMJ* 2000; **320**: 1141.
6 Romero A, Potter MF, Potter DA, Haynes KF. Insecticide resistance in the bed bug: a factor in the pest's sudden resurgence. *J Med Entomol* 2007; **44**: 175–8.
7 Ter Poorten MC, Prose NS. The return of the common bed bug. *Pediatr Dermatol* 2005; **22**: 183–7.
8 Whyte AS, Garnett PA, Whittington AE. Bats in the belfry, bugs in the bed? *Lancet* 2001; **357**: 604.
9 Beatson SH. Control of the martin bug *Oeciacus hirundinis*. *Environ Health* 1971; **74**: 283–5.
10 Marshall AG. *The Ecology of Ectoparasitic Insects*. London: Academic Press, 1981: 146–7.
11 Kinnear J. Epidemic of bullous erythema on legs due to bed-bugs. *Lancet* 1948; **ii**: 55.
12 Sansom JE, Reynolds NJ, Peachey RDG. Delayed reaction to bed bug bites. *Arch Dermatol* 1992; **128**: 272–3.
13 Tharakaram S. Bullous eruption due to *Cimex lectularius*. *Clin Exp Dermatol* 1999; **24**: 241–2.
14 Fletcher CL, Ardern-Jones MR, Hay RJ. Widespread bullous eruption due to multiple bed bug bites. *Clin Exp Dermatol* 2002; **27**: 74–5.
15 Liebold K, Schliemann WS, Wollina U. Disseminated bullous eruption with systemic reaction caused by *Cimex lectularius*. *J Eur Acad Dermatol Venereol* 2003; **17**: 461–3.
16 Masetti M, Bruschi F. Bedbug infestations recorded in central Italy. *Parasitol Int* 2007; **56**: 81–3.
17 Leverkus M, Jochim RC, Schäd S *et al*. Bullous allergic hypersensitivity to bed bug bites mediated by IgE against salivary nitrophorin. *J Invest Dermatol* 2006; **126**: 91–6.
18 Ogston CW, Wittenstein FS, London WT *et al*. Persistence of hepatitis B surface antigen in the bedbug *Cimex hemipterus* (Fabr.). *J Infect Dis* 1979; **140**: 411–4.
19 Jupp PG, McElligott SE, Lecatsas G. The mechanical transmission of hepatitis B virus by the common bedbug (*Cimex lectularius* L.) in South Africa. *S Afr Med J* 1983; **63**: 77–81.
20 Myaans MV, Hall AJ, Inskip HM *et al*. Do bedbugs transmit hepatitis B? *Lancet* 1994; **343**: 761–3.
21 Rothberg AD, Pick W. Do bedbugs transmit hepatitis B? *Lancet* 1994; **344**: 125.
22 Silverman AL, Qu LH, Blow J *et al*. Assessment of hepatitis B virus DNA and hepatitis C virus RNA in the common bedbug (*Cimex lectularius* L.) and kissing bug (*Rodnius prolixus*). *Am J Gastroenterol* 2001; **96**: 2194–8.
23 Blow JA, Turell MJ, Silverman AL, Walker ED. Stercorarial shedding and transtadial transmission of hepatitis B virus by common bed bugs (Hemiptera: Cimicidae). *J Med Entomol* 2001; **38**: 694–700.
24 Lyons SF, Jupp PG, Schoub BD. Survival of HIV in the common bedbug. *Lancet* 1986; **ii**: 45.
25 Jupp PG, Lyons SF. Experimental assessment of bedbugs (*Cimex lectularius* and *Cimex hemipterus*) and mosquitoes (*Aedes aegypti formosus*) as vectors of human immunodeficiency virus. *AIDS* 1987; **1**: 171–4.
26 Webb PA, Happ CM, Maupin GO *et al*. Potential for insect transmission of HIV: experimental exposure of *Cimex hemipterus* and *Toxorhynchites amboinensis* to human immunodeficiency virus. *J Infect Dis* 1989; **160**: 970–7.
27 Andrade RN. Haematosiphoniasis. In: Simons RDC, ed. *Handbook of Tropical Dermatology*, Vol. 2. Amsterdam: Elsevier, 1953: 905–7.

Family Anthocoridae

The Anthocoridae are related to the Cimicidae. Bugs of this family are mostly predacious on other insects, but are known to bite humans occasionally. *Lyctocoris campestris* is a cosmopolitan species closely associated with humans, for example in haystacks and granaries [1]. *Anthocoris kingi* and *Anthocoris nemorum* will also bite humans [2]. Another anthocorid bug, *Dufouriellus ater*, attacked many workers in a clothing factory in north-east England [3].

References

1 Woodward TE. A case of persistent attacks on a human by *Lyctocoris campestris* (F.) (Hem., Anthocoridae). *Entomol Month Mag* 1951; **87**: 44.
2 Ghauri MSK. Anthocoridae. In: Smith KGV, ed. *Insects and other Arthropods of Medical Importance*. London: The Trustees of the British Museum (Natural History), 1973: 389.
3 Dolling WR. *Dufouriellus ater* (Dufour) (Hemiptera: Anthocoridae) biting industrial workers in Britain. *Trans R Soc Trop Med Hyg* 1977; **71**: 355.

Family Pentatomidae

Palomena prasina (the green shield bug), a member of this family, has been reported as the cause of perioral blistering in a small child [1].

Reference

1 Jones SK, Strong L, Burton JL. Perioral blisters in a bug-biting baby. *Br J Dermatol* 1988; **119**: 121–5.

Kissing bugs, assassin bugs and cone-nosed bugs (Reduviidae)

The majority of species of Reduviidae are predators on other insects, and are commonly called assassin bugs for this reason, but some attack humans and other animals. Most species are encountered in North, Central and South America, but some occur in Africa, the Middle and Far East, and in Australia. The subfamily Triatominae is the most important medically, and includes those species which feed exclusively by sucking the blood of vertebrate animals. Adult triatomines are large insects, commonly measuring 20–28 mm in length. They have an elongated head with a prominent proboscis and long, four-jointed antennae (Fig. 38.21).

The Triatominae are largely confined to the western hemisphere, with the majority of species being distributed in North, Central and South America. In the USA, *Triatoma sanguisuga* has the widest distribution, extending from the south-eastern and Mid-Atlantic States westwards, including Texas. Triatomines feed on a wide range of hosts, and domestic species feed on humans and domestic animals. They are of medical importance as vectors of *Trypanosoma cruzi* in Chagas' disease [1,2].



Fig. 38.21 Cone-nose bug. (Courtesy of Oxford Scientific Films.)

Ecology. In nature, triatomine bugs form colonies in the habitat of their host, for example a small mammal's nest or animal lair. In the south-western USA, infestations are often found in the nests of wood rats. Some species, however, have become totally domesticated, and live and breed in human dwellings, laying their eggs in cracks and crevices in the floors and walls. The young hatch as nymphs, which are miniature versions of the adults. Nymphs and adults hide in crevices during the day and emerge at night to feed.

Clinical features [3,4]. The bites of the predatory species of reduviid bugs (assassin bugs) are purely defensive, and are usually extremely painful [5,6]. The bites of the blood-sucking Triatominae, however, are painless—this is essential to the parasite if it is to feed undisturbed. In an individual not previously exposed to the bites, there will be little reaction, but with repeated exposure hypersensitivity develops, and reactions ranging from pruritic papules to haemorrhagic nodules and bullae may occur.

References

1 Ghauri MSK. Reduviidae (including Triatominae) (cone nose-bugs, kissing-bugs and assassin-bugs). In: Smith KCV, ed. *Insects and other Arthropods of Medical Importance*. London: The Trustees of the British Museum (Natural History), 1973: 378–85.
2 Cook ML, Lee DJ. Effects on humans of bites of Australian non-bloodsucking Reduviid bugs. *Med J Aust* 1977; **ii**: 833–5.
3 Alexander JO'D. Infestation by Hemiptera. In: *Arthropods and Human Skin*. Berlin: Springer-Verlag, 1984: 57–74.
4 Shields TS, Walsh EN. 'Kissing bug' bite. *Arch Dermatol* 1956; **74**: 14–21.
5 Kettle DS. *Medical and Veterinary Entomology*, 2nd edn. Wallingford: CAB International, 1995: 344–60.
6 Smith FD, Miller NC, Camazzo SJ *et al*. Insect bite by *Argilus cristatus*, a North American Reduviid. *Arch Dermatol* 1958; **77**: 324–30.

Thrips (Thysanoptera)

Thrips ('thunder flies') are tiny, winged insects, 1–2 mm in length, and usually yellowish brown or black in colour. The name thrips is derived from the Greek, meaning 'wood louse'. The order Thysanoptera ('fringe wing') comprises about 5000 species with a worldwide distribution. The majority feed on plant juices and some are important agricultural pests [1]. Some species are predatory on other arthropods. A few species appear able to suck blood, and there are a number of reports that thrips can be responsible for skin lesions [2–7]. Most thrips, however, are unable to penetrate the human epidermis, and probably cause itching and prickling sensations only by their movement on the skin surface and their efforts to obtain water from perspiration.

Clinical features. Thrip bites, which occur on exposed skin, produce tiny puncta and small, pink macules or papules [2,4]. Large numbers of American soldiers in Hawaii developed hypoanaesthetic papular lesions surrounded by blanched halos, which, it was suggested, were caused by Cuban laurel thrips [8]. However, attempts to reproduce lesions by placing live thrips in contact with the skin were unsuccessful, and the cause of this distinctive dermatosis remains unknown [9].

References

1 Lewis T. *Thrips: their Biology, Ecology and Economic Importance*. London: Academic Press, 1973.
2 Bailey SF. Thrips attacking man. *Can Entomol* 1936; **68**: 95–8.
3 Herms WB, James MT. *Medical Entomology*, 5th edn. New York: Macmillan, 1961: 538–9.
4 Fishman HC. Thrips. *Arch Dermatol* 1987; **123**: 993–4.
5 Mumcuoglu KY, Volman Y. Thrips' stings in Israel: a case report. *Isr J Med Sci* 1988; **24**: 715.
6 Leigheb G, Tiberio R, Filosa G *et al*. Thysanoptera dermatitis. *J Eur Acad Dermatol Venereol* 2005; **19**: 722–4.
7 Cooper RG. Dermatitis and conjunctivitis in workers on an ostrich farm following thrips infestation. *Indian J Med Res* 2007; **125**: 588–9.
8 Goldstein N, Skipworth GB. Papular eruption secondary to thrips bites. Halos in Hawaii. *JAMA* 1968; **203**: 53–5.
9 Aeling JL. Hypoanesthetic halos in Hawaii. *Cutis* 1974; **14**: 541–4.

Beetles (Coleoptera)

Beetles are insects whose forewings are modified to form hard wing cases for the membranous or reduced hind wings. There are over 370 000 known species, but it is likely that many more await discovery. They are mainly terrestrial and the majority feed on decaying animal or vegetable matter, but some are predaceous on other insects. Several species may provoke skin lesions and are of interest to the dermatologist.

Vesicating species [1–4]

Family Meloidae (oil beetles, blister beetles)

Most of the beetles in this group only cause problems when crushed on the skin, but some may emit their vesicating fluid without being crushed. The family is large and widely distributed. Many species contain the irritant cantharidin, which commonly is called 'Spanish fly'. Contact with the skin produces an irritant dermatitis and bullae. Cantharidin has an undeserved reputation as an aphrodisiac, which is unfortunate for a chemical capable of producing severe toxicity. It has been used in blistering plasters and hair restorers, and in the treatment of warts and molluscum contagiosum.

Lytta vesicatoria is perhaps the best known of the blister beetles. It is a large, bright metallic green beetle, which lives mainly in the Mediterranean region, but is sporadically found further north, occasionally as far as England.

Other vesicating species include *Epicauta* spp. (USA, Mexico, India, Sudan, Senegal) [5], *Mylabris* spp. (Nigeria, India) [6,7], *Psalydolytta* spp. (Gambia) [8] and *Cylindrothorax melanocephala* (Gambia) [8].

Family Staphylinidae (rove beetles) [9–11]

The genus *Paederus*, found worldwide, includes many species containing a vesicant, pederin, which is chemically distinct from cantharidin. Pederin is released when the beetles are crushed, provoking an acute irritant contact dermatitis. Lesions may be plaque-like, linear (when a beetle has been brushed off the skin, leaving a streak of pederin on the skin surface), or 'kissing' (when a beetle has been crushed between two flexural surfaces). A major outbreak of vesicular dermatitis on Okinawa in 1966 was traced to contact with the beetle *Paederus fuscipes* [12], and a number of other reports have documented *Paederus* dermatitis from several

parts of the world [13–18], including an outbreak which occurred in a military unit training in the Arizona desert during heavy rain and flooding [19]. A plague of whiplash rove beetles (*Paederus australis*) forced evacuation of an aboriginal community in the Northern Territory of Australia [20]. *P. sabaeus* has been responsible for several outbreaks of dermatitis in Africa at the end of the rainy season [21–23].

You *et al*. [24] reported a case of bullous contact dermatitis following the use of crushed *Paederus* beetles for the treatment of vitiligo.

Histopathological changes of *Paederus* dermatitis include intraepidermal and subepidermal blistering, epidermal necrosis and acantholysis [25].

It has been proposed that the biblical third, fourth and sixth plagues of Egypt might have been related to rove beetles and the bullous lesions they cause [26].

Family Oedemeridae [3]

Oxycopis vittata has been reported as causing a blistering dermatitis in Puerto Rico [27]. *Sessinia* species (coconut beetles) have caused blistering in the Gilbert Islands [7].

Thelyphassa lineata produced a bullous dermatosis in a large number of New Zealand Army personnel [28], and there is a report of blister beetle dermatosis in Hawaii caused by *Thelyphassa apicata* [29].

Family Paussidae

Cerapterus concolor, an inhabitant of ants' nests, can eject a blistering liquid when disturbed [30].

Family Tenebrionidae (darkling beetles)

Many species inhabit wood, flour and grain stores. *Tribolium castaneum* (the 'rust-red flour beetle') has caused a pruritic eruption in workers handling infested jute packing bags [31]. The secretion of *Tribolium* species is mainly composed of quinones.

Species of *Blaps* can eject defensive secretions which are irritant and cause blistering.

Clinical features [2–4]. Usually, lesions are produced only when the beetle is crushed on the skin. A weal forms rapidly and is followed by a blister after 12–24 h. The blisters are sometimes linear 'whiplash dermatitis'. A characteristic feature is the development of kissing lesions, where a blister comes into contact with another area. Blisters induced in a small child by *Mylabris bifasciata* were associated with severe systemic manifestations of cantharidin poisoning [6].

Allergenic species

Family Dermestidae [32]

The beetles in this cosmopolitan family feed on hides, woollen materials and stored food. The adult beetles are not known to be directly injurious to humans, but their larvae are covered with hairs, which may cause skin lesions.

Papular urticaria in a child, caused by the larvae of *Dermestes maculatus* Degeer, has been reported, but it was uncertain whether the reaction to the hairs was irritant or allergic [33]. *Dermestes peruvianus* was responsible for dermatitis, vasculitis, cervical lymphadenopathy and pulmonary nodular interstitial infiltrates in a man whose bed was colonized by the beetles [34].

The irritating hairs from the larvae of carpet beetles (*Anthrenus* spp.) may also cause skin lesions [35–37]. There is also a report of the damaging effect of *Anthrenus* larvae on paraffin-embedded tissue specimens, especially the sectioned surface of hyperkeratotic lesions [38].

Clinical features. The skin lesions are not distinctive. Dermatitis, urticaria and papular urticaria may occur.

References

1 Theodorides J. The parasitological, medical and veterinary importance of Coleoptera. *Acta Trop* 1950; **7**: 48–60.
2 Alexander JO'D. *Arthropods and Human Skin*. Berlin: Springer-Verlag, 1984; 75–85.
3 Nicholls DSH, Christmas TI, Greig DE. Oedemerid blister beetle dermatosis: a review. *J Am Acad Dermatol* 1990; **22**: 815–9.
4 Southcott RV. Injuries from Coleoptera. *Med J Aust* 1989; **151**: 654–9.
5 Lehmann CF, Pipkin JL, Ressmann AC. Blister beetle dermatosis. *Arch Dermatol* 1955; **71**: 36–8.
6 Browne SG. Cantharidin poisoning due to a 'blister beetle'. *BMJ* 1960; **2**: 1290–1.
7 Smith KGV. Coleoptera and other insects. In: Smith KGV, ed. *Insects and other Arthropods of Medical Importance*. London: The Trustees of the British Museum (Natural History), 1973: 413–5.
8 Giglioli MEC. Some observations on blister beetles, family Meloidae, in Gambia, West Africa. *Trans R Soc Trop Med Hyg* 1965; **59**: 657–63.
9 Kerdel-Vegas F, Goihman-Yahr M. *Paederus* dermatitis. *Arch Dermatol* 1966; **94**: 175–85.
10 George AO. *Paederus* dermatitis—a mimic. *Contact Dermatitis* 1993; **29**: 212–3.
11 Brazzelli V, Martinoli S, Prestinari F *et al*. Staphylinid blister beetle dermatitis. *Contact Dermatitis* 2002; **46**: 183–4.
12 Armstrong RN, Winfield JL. Staphylinidae dermatitis on Okinawa. *J Med Entomol* 1968; **5**: 362.
13 Kamaladasa SD, Perera WD, Weeratunge L. An outbreak of *Paederus* dermatitis in a suburban hospital in Sri Lanka. *Int J Dermatol* 1997; **36**: 34–6.
14 Sendur N, Savk E, Karaman G. *Paederus* dermatitis: a report of 46 cases in Aydin, Turkey. *Dermatology* 1999; **199**: 353–5.
15 Uslular C, Kavukçu H, Alptekïn D *et al*. An epidemicity of *Paederus* species in Cukurova region. *Cutis* 2002; **69**: 277–9.
16 Zargari O, Kimyai AA, Fathalikhani F, Panahi M. *Paederus* dermatitis in northern Iran: a report of 156 cases. *Int J Dermatol* 2003; **42**: 608–12.
17 Qadir SNR, Raza N, Rahman SB. *Paederus* dermatitis in Sierra Leone. *Dermatol Online J* 2006; **12**: 9.
18 Gnanaraj P, Venugopal V, Mozhi MK, Pandurangan CN. An outbreak of *Paederus* dermatitis in a suburban hospital in South India: a report of 123 cases and review of literature. *J Am Acad Dermatol* 2007; **57**: 297–300.
19 Claborn DM, Polo JM, Olson PE *et al*. Staphylinid (rove) beetle dermatitis outbreak in the American southwest? *Mil Med* 1999; **164**: 209–13.
20 Todd RE, Guthridge SL, Montgomery BL. Evacuation of an Aboriginal community in response to an outbreak of blistering dermatitis induced by a beetle (*Paederus australis*). *Med J Aust* 1996; **164**: 238–40.
21 Penchenier L, Mouchet J, Cross B *et al*. Invasions de *Paederus sabaeus* (Coleoptera Staphylinidae) en Afrique centrale. 1. Aspects entomologiques et epidemiologiques. *Bull Soc Pathol Exot* 1994; **97**: 45–8.
22 Chandenier J, Quezede P, Chandenier B *et al*. Invasions de *Paederus sabaeus* (Coleoptera Staphylinidae) en Afrique centrale. 2. Aspects clinique et therapeutiques a Brazzaville. *Bull Soc Pathol Exot* 1994; **87**: 49–51.
23 Okiwelu SN, Umeozor OC, Akpan AJ. An outbreak of the vesicating beetle *Paederus sabaeus* Er. (Coleoptera: Staphylinidae) in Rivers State, Nigeria. *Ann Trop Med Parasitol* 1996; **90**: 345–6.
24 You DO, Kang JD, Youn NH, Park SD. Bullous contact dermatitis caused by self-applied crushed *Paederus fuscipes* for the treatment of vitiligo. *Cutis* 2003; **72**: 385–8.

25 Borroni G, Brazzelli V, Rosso R, Pavan M. *Paederus fuscipes* dermatitis. A histopathological study. *Am J Dermatopathol* 1991; **13**: 467–74.
26 Norton SA, Lyons C. Blister beetles and the ten plagues. *Lancet* 2002; **359**: 1950.
27 Fleisher TL, Fox I. Oedemerid beetle dermatitis. *Arch Dermatol* 1970; **101**: 601–5.
28 Christmas TI, Nicholls D, Holloway BA *et al*. Blister beetle dermatosis in New Zealand. *NZ Med J* 1987; **100**: 515–7.
29 Samlaska CP, Samuelson GA, Faran ME, Shparago NI. Blister beetle dermatosis in Hawaii caused by *Thelyphassa apicata* (Fairmaire). *Pediatr Dermatol* 1992; **9**: 246–50.
30 De Meillon B. A note on two beetles of medical interest in Natal. *S Afr Med J* 1937; **11**: 479.
31 Williamson DM. Itching eruption in miners caused by a rare beetle (*Triboleum castaneum*). *Br J Dermatol* 1964; **76**: 388–9.
32 Freeman P. Dermestidae. In: Freeman P, ed. *Common Insect Pests of Stored Food Products. A Guide to their Identification*. London: Trustees of the British Museum (Natural History), 1980: 27–32.
33 Rustin MHA, Munro DD. Papular urticaria caused by *Dermestes maculatus* Degeer. *Clin Exp Dermatol* 1984; **9**: 317–21.
34 Ramachandran S, Hern J, Almeyda J *et al*. Contact dermatitis with cervical lymphadenopathy following exposure to the hide beetle, *Dermestes peruvianus*. *Br J Dermatol* 1997; **136**: 943–5.
35 Cormia FE, Lewis GM. Contact dermatitis from beetles, with a report of a case due to the carpet beetle (*Anthrenus scrophulariae*). *NY State J Med* 1948; **48**: 2037–9.
36 Ahmed AR, Moy R, Barr AR *et al*. Carpet beetle dermatitis. *J Am Acad Dermatol* 1981; **5**: 428–31.
37 Horster S, Prinz JC, Holm N, Wollenberg A. *Anthrenus*—Dermatitis. *Hautarzt* 2002; **53**: 328–31.
38 Jurecka W, Gebhart W, Mainitz M. *Anthrenus* sp. The paraffin block eater bug. *Am J Dermatopathol* 1987; **9**: 204–7.

Cockroaches (Dictyoptera)

Cockroaches are members of the order Dictyoptera, suborder Blattaria. They belong to one of the primitive orders of insects, being allied to crickets, grasshoppers, preying mantids and stick insects. Cockroaches were originally adapted to hot climates, but a number of species have established themselves in cool climates by living inside warm human habitations. They are active nocturnally, and are attracted to any organic material that may serve as food. This theoretically makes them potential mechanical vectors of pathogenic organisms. The main pest species are *Periplaneta americana*, *P. australasiae*, *Blatta orientalis* and *Blatella germanica*.

Clinical features [1,2]. Contact urticaria and dermatitis have been described in laboratory workers and others handling cockroaches constantly [3–5], and urticated papules developed in a medical records clerk exposed to copious insect debris containing fragments of *B. germanica* when clearing old case notes from a derelict hut [6]. Chronic urticaria in a child has been attributed to cockroach hypersensitivity [7].

References

1 Alexander JO'D. Thysanoptera and Dictyoptera, suborder Blattaria. In: *Arthropods and Human Skin*. Berlin: Springer-Verlag, 1984: 22–7.
2 Roth LM, Willis ER. *The Medical and Veterinary Importance of Cockroaches*. Smithsonian Miscellaneous Collections 134 (No. 10), 1957: 1–147.
3 Bernton HS, Brown H. Insect allergy: the allergenic potentials of the cockroach. *South Med J* 1969; **62**: 1207–10.
4 Zschunke E. Contact urticaria, dermatitis and asthma from cockroaches. *Contact Dermatitis* 1978; **4**: 313–4.
5 Zschunke E. Contact urticaria, contact dermatitis, and asthma from cockroaches. *Arch Dermatol* 1978; **114**: 1715–6.
6 Monk BE, Pembroke AC. Cockroach dermatitis: an occupational hazard. *BMJ* 1987; **294**: 935.
7 Tahan F. Chronic urticaria with cockroach hypersensitivity. *Pediatr Dermatol* 2006; **23**: 300–1.

Locusts (Orthoptera)

Sensitivity reactions, manifest as asthma and allergic rhinitis, are a recognized occupational hazard in those working with laboratory colonies of locusts [1,2]. The principal allergen appears to derive from the peritrophic membrane, which is present in the gut and surrounds faeces [2].

Contact urticaria to locusts has been reported by Monk [3] in a laboratory research worker who handled a large number of locusts. The patient produced a positive reaction to locust antigen on prick testing and a wealing reaction at the site of contact with a live locust. Similarly, worsening of asthma, and urticaria in an atopic research laboratory worker, on exposure to grasshoppers, has been described [4].

References

1 Frankland AW. Locust sensitivity. *Ann Allergy* 1953; **11**: 445–53.
2 Tee RD, Gordon DJ, Newman Taylor AJ. Allergy to locusts (*Schistocerca gregaria* and *Locusta migratoria*). *J Allergy Clin Immunol* 1985; **75**: 122.
3 Monk BE. Contact urticaria to locusts. *Br J Dermatol* 1988; **118**: 707–8.
4 Soparkar GR, Patel PC, Cockroft DW. Inhalant atopic sensitivity to grasshoppers in research laboratories. *J Allergy Clin Immunol* 1993; **92**: 61–5.

Butterflies and moths (Lepidoptera)

Many members of this large order are of importance to the dermatologist because of the irritant properties of the hairs or spines of the caterpillars and sometimes of the adults. Skin lesions in the majority of cases are produced by a combination of mechanical and pharmacological effects [1,2]. The offending caterpillars are distributed through many different families [1,3]. Some of the species that have been recorded as causing damage to human skin are shown in Table 38.1.

Aetiology of skin lesions [1,2,16,17,26–29]. The term 'lepidopterism' is applied to the ill effects on humans of a structure or product of some part of a moth or butterfly at any stage of its life history. Some authors apply the term 'erucism' to injurious effects from caterpillars, and 'lepidopterism' to ill effects from adults. In the majority of cases, damage to human skin and mucosae occurs as a result of epithelial penetration by the 'hairs' (setae) of caterpillars. In addition to a foreign-body reaction there is often an effect from venom. Setae develop from trichogen cells of the epidermis. They are hollow, and may function as sensory receptors or communicate with a poison gland cell and contain venom. They commonly have barbs, which hold them in place when they have penetrated the skin. In some families of moths, the caterpillars have clumps of much smaller setae known as 'dart hairs' or 'spicules', which are pointed at both ends and carry fine barbs. The point of attachment to the caterpillar is very narrow and easily fractured; hence, contact with the caterpillar may release huge numbers of these tiny darts. Such dart hairs are present in a number of species, including the brown-tail moth (*Euproctis crysorrhoea*) (Fig. 38.22) and the pine processionary caterpillar

Table 38.1 Some Lepidoptera species responsible for skin damage.

Family Lymantriidae (Tussock moths)
Euproctis crysorrhoea (the brown-tail moth): the most important urticating species in the UK [4]
E. edwardsi (the mistletoe brown-tail moth) [5,6]
E. similis (the yellow-tail moth) [7,8]
E. flava (the oriental tussock moth)
Lymantria dispar (the gypsy moth) [9]
Orygia pseudotsugata (the Douglas fir tussock moth) [10]
Family Arctiidae (Tiger moths)
Hyphantria cunea [11]
Family Thaumetopoiedae (Processionary caterpillars)
Thaumetopoea (Cnethocampa) processionea [12]
T. pinivora [13]
T. wilkinsoni [14]
T. pityocampa [15–17]
Family Megalopygidae (Flannel moths)
Megalopyge opercularis [18,19]
Family Cochlididae (Eucleidae; Limacodidae)
Sibine stimulea [20]
Family Saturniidae
Hylesia species [21,22]
Automeris io (the bull's eye moth) [23]
Hemileuca maia (the buck moth) [24]
Family Lasiocampidae
Lasiocampa quercus
Eriogaster lanestris (the small eggar moth) [7]
Dendrolimus punctatus [25]



Fig. 38.22 Caterpillar of *Euproctis crysorrhoea*, the brown-tail moth. (Courtesy of D. Fox/Oxford Scientific Films.)

(*Thaumetopoea pityocampa*). Setae are also woven into cocoons, and into the webs of the silk-spinning caterpillars.

Spines are an extension of the cuticle of the caterpillar and contain venom. The spines either have a terminal plug of inspissated material at their open ends, which is released by pressure, or a weak point at which the spine fractures to allow the venom to escape. Poisonous spines occur particularly on the caterpillars of the moth families Cochlididae (Eucleidae; Limacodidae), Saturniidae and Megalopygidae.

The venoms present in the setae and spines of caterpillars of a number of families of Lepidoptera have been studied, but not fully elucidated. Some contain histamine, histamine liberators, serotonin and proteases [14,30–33]. Lamy *et al*. [34] isolated a protein, thaumetopoein, from pine processionary caterpillar hairs. This has a direct effect on mast cells, leading to degranulation, and explains the urticating properties of these caterpillars. However, IgE-mediated hypersensitivity also appears to be responsible for some reactions to *Thaumetopoea* [35–37], and Moneo *et al*. [38] have demonstrated a 15-kDa IgE-binding protein in a larval extract. Immediate and delayed-type reactions to *Euproctis pseudoconspersa* caterpillar venom extracts have also been demonstrated [39].

In some species—for example moths of the genus *Hylesia* (family Saturniidae)—irritating setae are carried by the adults. This genus is notorious for causing outbreaks of 'butterfly itch', 'moth dermatitis' or 'Caripito itch' [21] in tropical South America.

Clinical features [1,2,40]. Irritation may be experienced immediately after contact with the offending caterpillars, or may be delayed for hours or even days, depending on the species. Itching is followed by the development of small urticarial papules, sometimes surmounted by vesicles. Alexander [41] noted marked bruising in children who had been in contact with *Euproctis crysorrhoea* caterpillars. Urticaria and eyelid oedema may also occur, and Inal *et al*. [42] described severe orofacial oedema in a 15-month-old boy who had a pine processionary caterpillar in his mouth. In severe eruptions there may be constitutional symptoms of malaise and mild pyrexia. The severity and distribution of the eruption depend mainly on the route and intensity of exposure, but the most common sites are the exposed parts of the body. Lesions usually resolve in a few days. When contact with caterpillars is suspected as the cause of a dermatosis, Sellotape stripping of affected areas and subsequent microscopy may be used to demonstrate setae [43].

Contact with *Megalopyge* caterpillars [18,19] produces immediate, intense, burning local pain accompanied by a spreading erythema around the puncture sites. The affected area becomes oedematous, and there is often lymphangitis and regional lymphadenopathy. The local changes may be accompanied by pyrexia, headache, nausea and vomiting, particularly in children [44].

In the eye, caterpillar setae may cause a variety of changes ranging from conjunctivitis to ophthalmia nodosa [45,46] and even panophthalmitis.

References

1 Alexander JO'D. Reactions to Lepidoptera. In: *Arthropods and Human Skin*. Berlin: Springer-Verlag, 1984: 177–97.

2 Southcott RV. Lepidoptera and skin infestation. In: Parish CL, Nutting WB, Schwartzman RM, eds. *Cutaneous Infestations of Man and Animal*. New York: Praeger, 1983: 304–43.

3 Henwood BP, MacDonald DM. Caterpillar dermatitis. *Clin Exp Dermatol* 1983; **8**: 77–93.

4 Blair CP. The browntail moth, its caterpillar and their rash. *Clin Exp Dermatol* 1979; **4**: 215–22.

5 Dunlop K, Freeman S. Caterpillar dermatitis. *Australas J Dermatol* 1997; **38**: 193–5.

6 Balit CR, Ptolemy HC, Geary MJ *et al*. Outbreak of caterpillar dermatitis caused by airborne hairs of the mistletoe browntail moth (*Euproctis edwardsi*). *Med J Aust* 2001; **175**: 641–3.

7 Hellier FF, Warin RP. Caterpillar dermatitis. *BMJ* 1967; **2**: 346–8.
8 Su De-Long. Mulberry tussock moth dermatitis. A study of an epidemic of unknown origin. *J Epidemiol Community Health* 1981; **35**: 1–4.
9 Tuthill RW, Canada AT, Wilcock K *et al*. An epidemiologic study of gypsy moth rash. *Am J Public Health* 1984; **74**: 799–803.
10 Hoover AW, Nelson E. Skin symptoms attributed to tussock moth infestation. *Cutis* 1974; **13**: 597–600.
11 Knuckles MLF, Hodge SJ, White AF. Fall webworm dermatitis. *Int J Dermatol* 1987; **26**: 320–1.
12 Hesler LS, Logan TM, Benenson MW, Moser C. Acute dermatitis from oak processionary caterpillars in a U.S. military community in Germany. *Mil Med* 1999; **164**: 767–70.
13 Moschen M, Policaro RD, Savastano C. Insolita dermatite bollosa da processionaria del pino. *Arch Ital Dermatol Venereol Sessiol* 1969; **33**: 474–80.
14 Ziprkowski L, Rolant F. Study of the toxin from the poison hairs of *Thaumetopoea wilkinsoni* caterpillars. *J Invest Dermatol* 1966; **46**: 439–45.
15 Vega JM, Moneo I, Armentia A *et al*. Anaphylaxis to a pine caterpillar. *Allergy* 1997; **52**: 1244–5.
16 Vega JM, Moneo I, Armentia A *et al*. Allergy to the pine processionary caterpillar (*Thaumetopoea pityocampa*). *Clin Exp Allergy* 1999; **29**: 1418–23.
17 Vega JM, Moneo I, Armentia A *et al*. Pine processionary caterpillar as a new cause of immunologic contact urticaria. *Contact Dermatitis* 2000; **43**: 129–32.
18 McGovern JP, Barkin GD, McElhenney TR *et al*. *Megalopyge opercularis*. Observations of its life history, natural history of its sting in man, and report of an epidemic. *JAMA* 1961; **175**: 1155–8.
19 Gardner TL, Elston DM. Painful papulovesicles produced by the puss caterpillar. *Cutis* 1997; **60**: 125–6.
20 Edwards EK Jr, Edwards EK, Kowalczyk AP. Contact urticaria and allergic contact dermatitis to the saddleback caterpillar with histologic correlation. *Int J Dermatol* 1986; **25**: 467.
21 Dinehart SM, Archer ME, Wolf JE Jr *et al*. Caripito itch. Dermatitis from contact with *Hylesia* moths. *J Am Acad Dermatol* 1985; **13**: 743–7.
22 Hill WR, Rubenstein AD, Kovacs J Jr. Dermatitis resulting from contact with moths (genus *Hylesia*). *JAMA* 1948; **138**: 737–40.
23 Jones DL, Miller JH. Pathology of the dermatitis produced by the urticating caterpillar *Automeris io*. *Arch Dermatol* 1959; **79**: 81–5.
24 Walker RB, Thomas T, Cupit D, Giaquinto-Shreves J. An epidemic of caterpillar sting dermatitis in a rural West Virginia community. *W Va Med J* 1993; **89**: 58–60.
25 Lawson JP, Liu Y. Pinemoth caterpillar disease. *Skeletal Radiol* 1986; **15**: 422–7.
26 De Jong MCJM, Bleumink E, Nater JP. Investigative studies of the dermatitis caused by the larvae of the brown-tail moth (*Euproctis crysorrhoea* Linn.): I. Clinical and experimental findings. *Arch Dermatol Res* 1975; **253**: 287–300.
27 De Jong MCJM, Hoedemaker PhJ, Jongebloed WL *et al*. Investigative studies of the dermatitis caused by the larva of the brown-tail moth (*Euproctis crysorrhoea* Linn.): II. Histopathology of skin lesions and scanning electron microscopy of their causative setae. *Arch Dermatol Res* 1976; **255**: 177–91.
28 Pesce H, Delgado A. Poisoning from adult moths and caterpillars. In: Bucherl W, Buckley EE, eds. *Venomous Animals and their Venoms*, Vol. III. *Venomous Invertebrates*. New York: Academic Press, 1971: 119–56.
29 Picarelli ZP, Valle JR. Pharmacological studies on caterpillar venoms. In: Bucherl W, Buckley EE, eds. *Venomous Animals and their Venoms*, Vol. II. *Venomous Invertebrates*. New York: Academic Press, 1971: 103–18.
30 De Jong MCJM, Bleumink E. Investigative studies of the dermatitis caused by the larva of the brown-tail moth (*Euproctis crysorrhoea* Linn.): III. Chemical analysis of skin reactive substances. *Arch Dermatol Res* 1977; **259**: 247–62.
31 De Jong MCJM, Bleumink E. Investigative studies of the dermatitis caused by the larva of the brown-tail moth (*Euproctis crysorrhoea* Linn.): IV. Further characterization of skin reactive substances. *Arch Dermatol Res* 1977; **259**: 263–81.
32 Dinehart SM, Jorizzo JL, Soter NA *et al*. Evidence for histamine in the urticating hairs of *Hylesia* moths. *J Invest Dermatol* 1987; **88**: 691–3.
33 Hall-Smith PJ, Graham P. Beware the furry caterpillar. *Clin Exp Dermatol* 1980; **5**: 261–2.
34 Lamy M, Pastureaud M-H, Novak F *et al*. Thaumetopoein: an urticating protein from the hairs and integument of the pine processionary caterpillar (*Thaumetopoea pityocampa* Schiff., Lepidoptera, Thaumetopoeidae). *Toxicon* 1986; **24**: 347–56.
35 Werno J, Lamy M, Vincendeau P. Caterpillar hairs as allergens. *Lancet* 1993; **342**: 936–7.
36 Fuentes-Aparicio V, de Barrio-Fernández M, Rubio-Sotés M *et al*. Non-occupational allergy caused by the pine processionary caterpillar (*Thaumetopoea pityocampa*). *Allergol Immunopathol Madr* 2004; **32**: 69–75.
37 Fuentes-Aparicio V, Zapatero-Remón L, Martínez-Molero MI *et al*. Allergy to pine processionary caterpillar (*Thaumetopoea pityocampa*) in children. *Allergol Immunopathol Madr* 2006; **34**: 59–63.
38 Moneo I, Vega JM, Caballero ML *et al*. Isolation and characterization of Tha p 1, a major allergen from the pine processionary caterpillar *Thaumetopoea pityocampa*. *Allergy* 2003; **58**: 34–7.
39 Natsuaki M. Immediate and delayed-type reactions in caterpillar dermatitis. *J Dermatol* 2002; **29**: 471–6.
40 Southcott RV. Lepidopterism in the Australian region. *Rec Adelaide Children's Hosp* 1978; **2**: 87–173.
41 Alexander S. The browntail moth, its caterpillar and their rash. *Clin Exp Dermatol* 1980; **5**: 261.
42 Inal A, Altintas DU, Güvenmez HK *et al*. Life-threatening facial edema due to pine caterpillar mimicking an allergic event. *Allergol Immunopathol Madr* 2006; **34**: 171–3.
43 Carruthers R. Caterpillar dermatitis. *BMJ* 1967; **2**: 765.
44 Finkelstein Y, Raikhlin-Eisencraft B, Taitelman U. Systemic manifestations of erucism: a case report. *Vet Hum Toxicol* 1988; **30**: 573–4.
45 Haluska FC, Puliafito CA, Henriquez A *et al*. Experimental gypsy moth (*Lymantria dispar*) ophthalmia nodosa. *Arch Ophthalmol* 1983; **101**: 799–801.
46 Watson PG, Sevel D. Ophthalmia nodosa. *Br J Ophthalmol* 1966; **50**: 209–17.

Class Arachnida

Arachnida are readily distinguished from insects, as the adults have no wings or antennae and possess four pairs of legs. Unlike insects, where the body is divided into three segments (head, thorax and abdomen), arachnids have only two, the cephalothorax, from which the legs arise, and the abdomen.

The Arachnida are classified in seven orders, only three of which are of medical importance:

1 Araneae (spiders)
2 Scorpiones (scorpions)
3 Acari (ticks and mites).

Spiders (Araneae)

The appearance of many of the larger spiders inspires terror or disgust, but very few of the many thousands of species are dangerous to humans. Spiders are, for the most part, shy and avoid contact with humans. Almost all are venomous and bite, but only a few have chelicerae strong enough to penetrate human skin, and in most cases the bites are trivial. The European tarantula, *Lycosa tarantula*, which inspired the tarantella in Italy in the Middle Ages, inflicts a temporarily painful, but harmless bite. Some lycosid spiders in South America, for example *Lycosa antibucana*, cause severe swelling and lymphangitis. In the USA, the term 'tarantula' is erroneously applied to the large 'bird' or 'crab' spiders of the family Theraphosidae, which attack only when vigorously provoked, and whose bite may be painful but not dangerous. Some colourful species kept as pets, for example *Brachypelma smithi*, are among several that have urticating hairs capable of causing prolonged pruritus. Many spiders whose bites are dangerous, and sometimes fatal, are small, inconspicuous and unimpressive.

The clinical syndrome following the bite of a spider is known as arachnidism. The form of arachnidism caused by species of the



Fig. 38.23 *Latrodectus mactans*, the black-widow spider. (Courtesy of S. Camazine/Oxford Scientific Films.)



Fig. 38.24 *Atrax robustus*, the Sydney funnel-web spider (defensive posture). (Courtesy of Mantis Wildlife Films/Oxford Scientific Films.)

family Loxoscelidae is known as loxoscelism, and that by widow spiders (*Latrodectus* species) latrodectism.

Air transport of crates of fruit and other materials may introduce exotic species to countries in which they are unable to multiply but can survive long enough to attack humans.

Arachnidism [1–4]

Family Theridiidae

Genus *Latrodectus* (widow spiders). Spiders of this genus are widely distributed throughout the world. *Latrodectus mactans* (Fig. 38.23), the black-widow spider, occurs throughout subtropical and tropical regions. Other species have a similar, but more limited, range, although some extend to the temperate regions of Russia and Canada.

The female of *L. mactans* is glossy black, with a body length of 1.5 cm and a leg span of up to 5 cm. She normally spins her web in empty burrows or under stones, but may be found in dark corners of barns, garages, store rooms or outdoor lavatories. She bites humans only in self-defence. *Latrodectus* venom is considered to be one of the most potent toxins, exceeding that of snake venoms, but the dose injected is minute in relation to the body weight of a human victim. The toxins of all species of *Latrodectus* that have been studied appear to be closely related, and the symptoms from envenomation are similar.

Latrodectus hasselti, the red-back spider, is common in Australia [5]. A report from Fremantle documented 150 admissions for red-back spider bites over a 6-year period from 1982 to 1987 inclusive, and estimated the annual cases at between 830 and 1950 [6].

Latrodectus geometricus, the brown-widow spider, bites reluctantly, but is occasionally troublesome to vineyard workers in South Africa.

Clinical features (latrodectism) [1–3,7–10]. In the days of the outdoor lavatory, *Latrodectus* webs were often spun across the toilet seat, and this led to the frequent occurrence of bites on the buttocks and genitalia. The bite of *Latrodectus* species is fairly painless, but within a few minutes increasingly severe pain develops and becomes generalized. Cramp-like or colicky abdominal pain is particularly common. Puncta may be visible at the site of the bite, and there is local erythema and oedema. There is frequently profuse sweating, and neuromuscular involvement causes paraesthesiae, incoordination and paralysis. The pain begins to subside within 24 h, and other symptoms resolve within 2–3 days, although weakness and lethargy may persist for longer. However, without treatment the bite may be fatal in young children or in the elderly and frail.

Treatment. Species-specific antivenoms are available for *Latrodectus* bites, and there is evidence that red-back spider antivenom prevents toxicity of other widow spider venoms [11,12].

Family Hexathelidae

Genera *Atrax/Hadronyche* (Australia and south Pacific) and *Macrothele* (Taiwan and parts of eastern Asia)—funnel-web spiders. Perhaps the best known of these is the Sydney funnel-web spider, *Atrax robustus* [5] (Fig. 38.24), a large, aggressive spider that is nocturnal and predominantly insectivorous. It normally lives under rocks and logs, but the spread of the Sydney suburbs into its habitat provided similar hiding places under houses.

Clinical features [4,13,14]. The bite of funnel-web spiders is invariably painful. From the majority of bites, especially those of female spiders, no general symptoms follow, and recovery is uneventful. However, the large amount of venom from male spiders may cause severe systemic symptoms. Nausea and vomiting are early features, accompanied by abdominal pain, profuse sweating, piloerection, muscle fasciculation, lacrimation, excess salivation, dyspnoea and pulmonary oedema. Several fatalities were recorded prior to the development of an antivenom.

Treatment. The compression bandage-splinting method of first aid is effective in delaying onset of envenomation and may enhance local inactivation of venom. Severe reactions will require hospital admission and full supportive measures. Funnel-web spider antivenom is very effective.

Family Sicariidae (formerly Loxoscelidae)

Genus *Loxosceles* ('fiddleback', 'violin', 'brown recluse' spiders). There are a number of species of *Loxosceles* in North and South America, with about 13 in the USA, several of which are known to induce human skin necrosis: *reclusa, laeta, deserta, arizonica* and *rufescens* [4,15]. The most notorious is *L. reclusa*, the brown recluse spider, which is tan to brown in colour, with a dark-brown, violin-shaped marking on the dorsum of the cephalothorax—hence the names 'fiddleback' and 'violin' spider. *L. reclusa* is active mainly at night. Its natural habitat is in dark areas beneath rocks and in holes and caves. It is also found in homes, in areas that are dark, dirty and undisturbed, such as attics, cupboards and garages.

Loxosceles laeta also occurs widely in South America. *Loxosceles rufescens* is widespread in southern Australia.

Clinical features (loxoscelism) [1–4,8,16]. There are two distinct clinical forms of loxoscelism: necrotic cutaneous loxoscelism, and the much less frequent viscerocutaneous loxoscelism. The clinical manifestations depend upon the age and health of the victim, the amount of venom injected and the site of the bite—fatty areas such as the proximal thigh and the buttocks show more cutaneous reaction and extensive involvement of the entire subcutaneous layer.

In necrotic cutaneous loxoscelism, there is local damage to the skin and subcutaneous tissues, but systemic symptoms are mild. The bite of the spider is usually relatively painless. However, after an interval of minutes or hours, severe pain develops at the site, accompanied by erythema, oedema and a central bulla. In severe envenomation, a 'target' lesion is seen—central blue/purple discoloration surrounded by an ischaemic halo and an outer ring of erythema (the 'red, white and blue' sign). After 3 or 4 days, the central area becomes necrotic, and an eschar develops. The eschar is eventually shed, leaving an ulcer which may take a considerable time to heal. The size of maximum necrosis appears to be predictive of time to complete healing [16]. Robb *et al*. [17] described a patient with a generalized vasculitic exanthem following a brown recluse spider bite.

In viscerocutaneous loxoscelism, systemic involvement is indicated by pyrexia, severe malaise, restlessness and headache. Within 24 h of the onset of general symptoms, ecchymoses, jaundice, haematuria and haemoglobinuria indicate massive intravascular haemolysis, which may result in death [18].

Treatment [4,8,15]. *R*est, application of *I*ce *C*ompresses and *E*levation (RICE therapy) help to reduce inflammation and pain. Although dapsone has been said to be beneficial, its use is controversial and there is no prospective study demonstrating its efficacy [19].

Family Lycosidae (wolf spiders)

There are a few reports of bites by members of the genus *Lycosa* [4,20,21]. They usually cause only local pain, swelling and erythema, without cutaneous necrosis or significant systemic symptoms.

Other venomous species [3–5,22–25]

Spiders of several other families may cause unpleasant bites. Long-legged sac spiders of the genus *Chiracanthium* (family Miturgidae), which are found in many parts of the world, may cause local pain, oedema, and small areas of necrosis [4,24]. *Tegenaria agrestis* (family Agelenidae), the hobo spider (previously known as the aggressive house spider), is a cause of necrotic arachnidism in the north-west USA [4,23,24]. Members of the families Gnaphosidae, Salticidae (jumping spiders), Sparassidae (huntsmen spiders), and Oxyopidae (lynx spiders) all occasionally bite humans, but the effects are usually mild, unless there is secondary bacterial infection.

Public concern with regard to the toxic effects of white-tailed spiders (*Lampona cylindrata* and *L. murina*) is not supported by studies which have shown that these spiders are unlikely to cause necrotic arachnidism [26,27].

References

1 Alexander JO'D. Spider bites. In: *Arthropods and Human Skin*. Berlin: Springer-Verlag, 1984: 209–26.
2 King LE Jr. Spider bites. *Arch Dermatol* 1987; **123**: 41–3.
3 Wong RC, Hughes SE, Voorhees JJ. Spider bites. *Arch Dermatol* 1987; **123**: 98–104.
4 Sams HH, Dunnick CA, Smith ML, King LE Jr. Necrotic arachnidism. *J Am Acad Dermatol* 2001; **44**: 561–73.
5 Southcott RV. *Australian Harmful Arachnids and their Allies*. Mitcham: RV Southcott, 1978.
6 Jelinek GA, Banham NDG, Dunjey SJ. Red-back spider-bites at Fremantle Hospital 1982–1987. *Med J Aust* 1989; **150**: 693–5.
7 Maretic Z. Latrodectism: variations in clinical manifestations produced by *Latrodectus* species of spiders. *Toxicon* 1983; **21**: 457–66.
8 Stawiski MA. Insect bites and stings. *Emerg Med Clin North Am* 1985; **3**: 785–808.
9 Sutherland SK, Trinka JC. Survey of 2144 cases of red-back spider bites. Australia and New Zealand 1963–1976. *Med J Aust* 1978; **2**: 620–3.
10 Jelinek GA. Widow spider envenomation (latrodectism): a worldwide problem. *Wild Environ Med* 1997; **8**: 226–31.
11 Daly FF, Hill RE, Bogdan GM, Dart RC. Neutralization of *Latrodectus mactans* and *L. hesperus* venom by redback (*L. hasselti*) antivenom. *J Toxicol Clin Toxicol* 2001; **39**: 125–7.
12 Graudins A, Padula M, Broady K, Nicholson G. Red-back spider (*Latrodectus hasselti*) antivenom prevents the toxicity of widow spider venoms. *Ann Emerg Med* 2001; **37**: 154–60.
13 Sutherland SK. The Sydney funnel-web spider (*Atrax robustus*): 3. A review of some clinical records of human envenomation. *Med J Aust* 1972; **2**: 643–7.
14 Miller MK, Whyte IM, White J, Keir PM. Clinical features and management of *Hadronyche* envenomation in man. *Toxicon* 2000; **38**: 409–27.
15 Swanson DL, Vetter RS. Bites of brown recluse spiders and suspected necrotic arachnidism. *N Engl J Med* 2005; **352**: 700–7.
16 Sams HH, Hearth SB, Long LL *et al*. Nineteen documented cases of *Loxosceles reclusa* envenomation. *J Am Acad Dermatol* 2001; **44**: 603–8.
17 Robb CW, Hayes BB, Boyd AS. Generalized vasculitic exanthem following *Loxosceles reclusa* envenomation. *J Cutan Pathol* 2007; **34**: 513–4.
18 Williams ST, Khare VK, Johnston GA, Blackall DP. Severe intravascular haemolysis associated with brown recluse spider envenomation. A report of two cases and a review of the literature. *Am J Clin Pathol* 1995; **104**: 463–7.
19 Elston DM, Miller SD, Young RJ 3rd *et al*. Comparison of colchicine, dapsone, triamcinolone and diphenhydramine therapy for the treatment of brown recluse spider envenomation. *Arch Dermatol* 2005; **141**: 595–7.
20 Campbell DS, Rees RS, King LE. Wolf spider bites. *Cutis* 1987; **39**: 113–4.
21 Redman JF. Human envenomation by a lycosid. *Arch Dermatol* 1974; **110**: 111–2.
22 Krensky WL. Envenomation by the sac spider *Chiracanthium mildei*. *Cutis* 1987; **40**: 127–9.
23 Vest DK. Necrotic arachnidism in the northwest United States and its probable relationship to *Tegenaria agrestis* (Walckenaer) spiders. *Toxicon* 1987; **25**: 175–84.
24 Anonymous. Necrotic arachnidism—Pacific Northwest, 1988–1996. *MMWR Morb Mortal Wkly Rep* 1996; **45**: 433–6.



Fig. 38.25 Australian scorpion (*Urodacus* species). (Courtesy of Mantis Wildlife Films/Oxford Scientific Films.)

25 White J, Hirst D, Hender E. 36 cases of bites by spiders, including the white-tailed spider, *Lampona cylindrata*. *Med J Aust* 1989; **150**: 401–3.
26 Isbister GK, Gray MR. White-tail spider bite: a prospective study of 130 definite bites by *Lampona* species. *Med J Aust* 2003; **179**: 199–202.
27 Banks J, Sirvid P, Vink C. White-tailed spider bites—arachnophobia fallout. *N Z Med J* 2004; **117**: 1188.

Scorpions (Scorpiones)

Scorpions are arachnids of the order Scorpiones, and are widely distributed in the tropics and subtropics. Their poisonous stings are responsible for considerable morbidity and mortality [1–3]. The venom is carried in the curved sting at the tip of the tail, which is swung over the scorpion's head to strike its prey. The principal components are neurotoxins [3,4], but some venoms also contain 5-hydroxytryptamine, histamine and kinins.

Many scorpions are quite harmless, and their stings of little consequence. Most of the dangerous species belong to the family Buthidae [5]. Species of *Androctonus* and *Buthus* are important in the Middle East and North Africa, and *Centruroides* species cause problems in the southern USA and Mexico. *Tityus* species are responsible for numerous episodes of envenomation in Brazil [6]. Throughout the world many of the deaths from scorpion stings are in infants and young children.

Australia has a number of species of scorpions (Fig. 38.25), but their stings are relatively innocuous [7].

Clinical features [8–12]. The effects of scorpion stings may be local or systemic, and they vary according to the species responsible. The local effects are usually immediate severe burning pain and hyperaesthesia, and there may be marked swelling. Systemic effects include restlessness, profuse sweating, muscle spasms, difficulty with speech, marked increase in salivary and lacrimal secretion, nausea, vomiting, convulsions, hypertension, cardiac arrhythmias, myocarditis and pulmonary oedema. Death is usually due to respiratory or cardiac failure.

Treatment [7,9,12]. Ice packs should be applied, and the injection of local anaesthetic around the sting site will help to reduce the pain. Specific antivenoms are available.

References

1 Mazzotti L, Bravo-Becherelle MA. Scorpionism in the Mexican Republic. In: Keegan HL, MacFarlane WV, eds. *Venomous and Poisonous Animals and Noxious Plants of the Pacific Region*. Oxford: Pergamon, 1963: 119–31.
2 Stahnke HL. Arizona's lethal scorpion. *Ariz Med* 1972; **29**: 490–3.
3 Balozet L. Scorpionism in the Old World. In: Bucherl W, Buckley EE, eds. *Venomous Animals and their Venom*, Vol. III. *Venomous Invertebrates*. New York: Academic, 1971: 349–71.
4 Allen C. Arachnid envenomations. *Emerg Clin North Am* 1992; **10**: 269–98.
5 Sheals JG. Arachnids (scorpions, spiders, ticks, etc.). In: Smith KGV, ed. *Insects and other Arthropods of Medical Importance*. London: The Trustees of the British Museum (Natural History), 1973: 417–72.
6 Freire-Maia L, Campos JA, Amaral CFS. Approaches to the treatment of scorpion envenoming. *Toxicon* 1994; **32**: 1009–14.
7 Southcott RV. *Australian Harmful Arachnids and their Allies*. Mitcham: RV Southcott, 1978.
8 Alexander JO'D. Scorpion stings. In: *Arthropods and Human Skin*. Berlin: Springer-Verlag, 1984: 199–207.
9 Gueron M, Yaron R. Cardiovascular manifestations of severe scorpion sting. Clinicopathologic correlations. *Chest* 1970; **57**: 156–62.
10 Warrell DA. Animal poisons—scorpion stings. In: Manson-Bahr PEC, Bell DR, eds. *Manson's Tropical Diseases*, 19th edn. London: Baillière Tindall, 1987: 889–90.
11 Carbonaro PA, Janniger CK, Schwartz RA. Scorpion sting reactions. *Cutis* 1996; **57**: 139–41.
12 Amitai Y. Clinical manifestations and management of scorpion envenomation. *Public Health Rev* 1998; **26**: 257–63.

Ticks (Acari)

Ticks are large acarines, which are blood-sucking ectoparasites of vertebrates. They are important vectors of diseases such as tick-borne relapsing fever, a number of viral and rickettsial infections, and Lyme disease.

Morphology and biology [1]. Ticks are typical arachnids, possessing mouthparts referred to as the capitulum, an unsegmented body, and four pairs of legs in the adult. Larval ticks have three pairs of legs.

There are two major families: the Ixodidae (hard ticks) and the Argasidae (soft ticks). The term 'hard' refers to the dorsal chitinous shield or scutum, which is present in the Ixodidae but not in the Argasidae. In Ixodidae, the scutum covers the whole dorsum in the male but only a small anterior part in the female. In Argasids there is little difference between the sexes. The mouthparts of Ixodid ticks project forwards and are easily visible from above, whereas those of the Argasid ticks can only be seen from below. A conspicuous component of the mouthparts is the toothed hypostome (Figs 38.26 and 38.27).

Ixodid ticks have four stages in their life cycle: egg, larva, nymph and adult. The larva and nymph require blood meals before further development can occur, and the adult female (Fig. 38.28) also requires a blood meal before egg laying. The female lays one large batch of eggs and then dies. Some Ixodids use one host for larval, nymphal and adult stages (one-host ticks), whereas others require two or, more usually, three separate hosts.

To find suitable hosts the larvae, nymphs and adults climb low vegetation and raise the first pair of legs ('questing'), which carry sense organs (Haller's organ). These organs are sensitive to a number of stimuli, including the carbon dioxide in the exhalations of a potential host. If the host brushes past the vegetation the tick will immediately grasp the animal's coat. Argasidae undergo

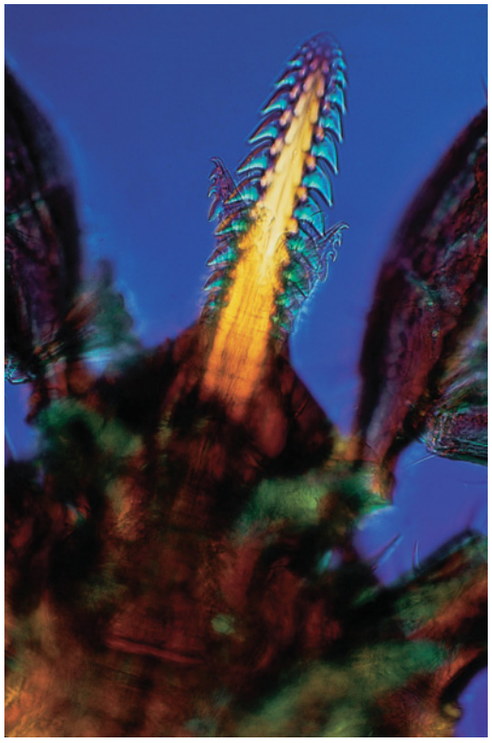


Fig. 38.26 Mouthparts of *Ixodes ricinus* nymph to show the toothed hypostome (interference contrast microscopy).

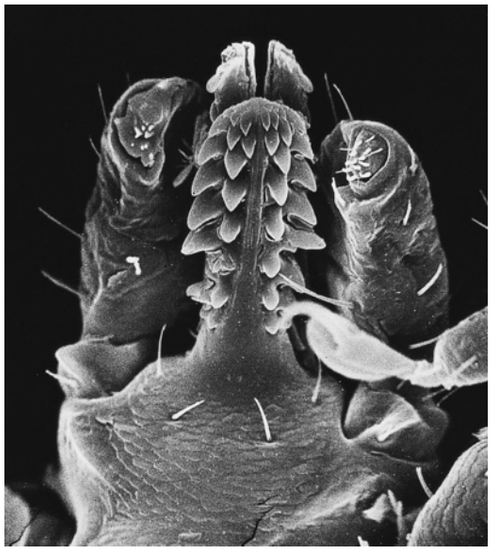


Fig. 38.27 Scanning electron micrograph of tick mouthparts.

several nymphal stages, and the adult female feeds a number of times during her lifetime, laying several batches of eggs. Ixodid ticks feed on the host for several days, whereas Argasids visit their hosts nocturnally to feed for only a few minutes. Argasids are mainly parasites of birds, bats and humans. Most ticks are essentially parasites of wild animals, and humans are incidental hosts.



(a)



(b)

Fig. 38.28 *Ixodes ricinus*, the sheep tick (engorged female). (a) Dorsal view. (b) Ventral view.

When attaching itself to the host, the tick uses its toothed chelicerae to cut into the epidermis, before thrusting the hypostome into the opening and gradually penetrating the dermis. The hypostome becomes anchored by a protein cement, produced by the salivary glands, which forms a cone around the hypostome and interlocks with its teeth [1,2]. Argasids, being rapid feeders, do not attach themselves as securely as Ixodid ticks.

Ticks as vectors of disease [1,3,4]. Within the large family of Ixodid ticks, there are several genera of medical importance, including *Dermacentor, Haemaphysalis, Rhipicephalus, Amblyomma, Hyalomma* and *Ixodes*.

Dermacentor species act as vectors for a number of diseases, including Rocky Mountain spotted fever, Siberian tick typhus, Colorado tick fever and several types of viral encephalitis.

Haemaphysalis species may also carry Rocky Mountain spotted fever, Siberian tick typhus and Colorado tick fever.

Rhipicephalus sanguineus (the brown dog tick) transmits *Rickettsia conorii*, the causative organism of boutonneuse fever (Mediterranean spotted fever). *Rh. sanguineus* is normally confined to the tropics, but it may be encountered in temperate climates in centrally heated houses [5]. Ticks of the genus *Amblyomma* transmit *Rickettsia africae*, the organism responsible for African tick bite fever, tularaemia and human granulocytic anaplasmosis (ehrlichiosis) [6–8]. In recent years, *A. americanum* (the lone star tick) has been recognized as a vector for *Borrelia lonestari*, the organism thought to be responsible for southern tick-associated rash illness (STARI), a Lyme disease-like infection [9].

Ixodes species are important vectors of certain haemorrhagic fevers and viral encephalitis, and also of Lyme disease (Chapter 30). They may also transmit babesiosis to humans [10]. The principal vectors of Lyme disease are the sheep tick *Ixodes ricinus* in Europe, and *Ixodes dammini* (East coast) and *Ixodes pacificus* (West coast) in the USA.

Various species of Argasidae may also act as vectors of disease, the most important being *Ornithodoros* species, which transmit tick-borne relapsing fever. In Israel, *O. tholozani* (the cave tick), which is endemic in the Middle East, is the vector of *Borrelia persica*, a causative agent of relapsing fever [11].

Pathology [3]. At the point of penetration of the tick mouthparts there is coagulation necrosis of the epidermis and papillary dermis [12]. Surrounding the hypostome is the homogeneous cement [13]. The punctured epidermis shows parakeratosis, spongiosis and frequently pseudoepitheliomatous hyperplasia. There is marked dilatation of upper dermal blood vessels, and a dense perivascular infiltrate of neutrophils and lymphocytes. Histology of the bite site several weeks after removal of the tick shows a perivascular and periadnexal infiltrate of lymphocytes, plasma cells and histiocytes [14,15]. Foreign-body giant cells may also be present in the infiltrate. If the hypostome has been damaged during removal of the tick, fragments of the mouthparts may be seen.

Clinical features [3]. In the case of Ixodid ticks, it is usually the parasite itself that attracts the patient's attention. Larvae, nymphs or adults may be discovered attached to the skin, and humans usually become accidental hosts when walking through, or sitting in, an area that contains ticks [16]. Larval ticks, sometimes referred to as 'seed ticks', are very small, and may go unnoticed unless present in large numbers [17–19]. Pruritic papules were a prominent feature of larval *Amblyomma* tick bites in a case reported by Fisher *et al*. [20]. A papular urticarial response to ticks has been reported in berry pickers [21], and the author has seen papular urticaria developing within a few days of contact with numerous larval ticks of *I. ricinus*.

Auto-eczematization has been reported in association with a tick bite granuloma [22]. Temporary alopecia may develop around the sites of tick attachment to the scalp [15,23]. Bullae [24] and extensive bruising [25] at the feeding sites of Argasid ticks have been reported, and anaphylaxis may be provoked by Ixodid bites [26]. In boutonneuse fever, there is an eschar (tâche noire; black spot) at the site of the bite of the infected tick (Fig. 38.29),



Fig. 38.29 Tâche noire on the leg in boutonneuse fever.

accompanied by a maculopapular rash, and African tick bite fever is associated with multiple inoculation eschars, often located on the legs [6]. The bites of the cave tick, Ornithodoros *tholozani*, produce characteristic deep red, crusted papules or nodules, with a central punctum [11]. The colour of engorged ticks has led patients to suspect they were melanomas [27].

Tick paralysis [28,29]

Tick paralysis is an ascending flaccid paralysis probably caused by a neurotoxin injected by the feeding tick. Occasionally, bulbar paralysis, respiratory failure and death occur. The site of action of the toxin appears to be in the region of the neuromuscular synapse. If the tick is removed, all the signs usually resolve rapidly, but sometimes recovery is slow. Children are more frequently affected than adults.

Tick paralysis occurs in particular localities in association with specific ticks [3]. Offending species include Dermacentor *andersoni* and *D. variabilis* (USA); *Ixodes holocyclus* (Australia); *I. pilosus* (South Africa); *I. ricinus, I. hexagonus* and *Rhipicephalus sanguineus* (Europe).

Lyme disease

See Chapter 30.

Tick removal

Various methods for removal of ticks have been suggested, including the application of iodine, ether, chloroform, petrol and

kerosene. Sherman [30] suggested a few drops of clear nail varnish, and Dolan and McKinsey [31] 2% lignocaine (lidocaine) jelly. Karras [32] also found viscous lidocaine to be effective.

Ticks should not be removed by a sudden forcible movement, as this will often leave the mouthparts embedded in the skin. Gripping the tick with forceps or tweezers, as close to the skin as possible, and gentle traction usually succeeds when other methods have failed [33]. There are also several commercially available tick-removal tools.

References

1 Arthur DR. *Ticks and Disease*. Oxford: Pergamon, 1961.
2 Chinery WA. The nature and origin of the 'cement' substance at the site of attachment and feeding of adult *Haemaphysalis spingera* (Ixodidae). *J Med Entomol* 1973; **10**: 355–62.
3 Alexander JO'D. The effects of tick bites. In: *Arthropods and Human Skin*. Berlin: Springer-Verlag, 1984: 363–82.
4 Sheals JG. Arachnids (scorpions, spiders, ticks, etc.). In: Smith KGV, ed. *Insects and other Arthropods of Medical Importance*. London: The Trustees of the British Museum (Natural History), 1973: 417–72.
5 Fox MT, Sykes TJ. Establishment of the tropical dog tick, *Rhipicephalus sanguineus*, in a house in London. *Vet Rec* 1985; **116**: 661–2.
6 Roux O, Desruelles F, Delaunay P *et al*. Ticks and photo safari in South Africa. *Br J Dermatol* 2000; **143**: 1109–10.
7 Childs JE, Paddock CD. The ascendancy of *Amblyomma americanum* as a vector of pathogens affecting humans in the United States. *Annu Rev Entomol* 2003; **48**: 307–37.
8 Elston DM. Human infestation by larval *Amblyomma* ticks. *Arch Dermatol* 2006; **142**: 497–500.
9 Varela AS, Luttrell MP, Howerth EW *et al*. First culture isolation of *Borrelia lonestari*, putative agent of southern tick-associated rash illness. *J Clin Microbiol* 2004; **42**: 1163–9.
10 Ruebush TK II, Cassaday PB, Marsh HJ *et al*. Human babesiosis on Nantucket Island. *Ann Intern Med* 1977; **86**: 6–9.
11 Leker R, Felsenstein I, Raveh D *et al*. *Ornithodoros tholozani* bites: a unique clinical picture. *J Am Acad Dermatol* 1992; **27**: 1025–6.
12 Patterson JW, Fitzwater JE, Connell J. Localized tick bite reaction. *Cutis* 1979; **24**: 160–72.
13 Aoki K, Kamata H, Iida T *et al*. Tick bite: two cases studied by scanning electron microscopy. *Br J Dermatol* 1984; **110**: 233–40.
14 Goldman L. Tick bite granuloma: failure of prevention of lesion by excision of tick bite area. *Am J Trop Med Hyg* 1963; **12**: 246–8.
15 Heyl T. Tick bite alopecia. *Clin Exp Dermatol* 1982; **7**: 537–42.
16 Pearce RL, Grove DI. Tick infestation in soldiers who were bivouacked in the Perth region. *Med J Aust* 1987; **146**: 238–40.
17 Fujiwara K, Ono T, Kawashima K. Multiple larval tick infestation of man. *J Dermatol* 1981; **8**: 157–9.
18 Jones BE. Human 'seed tick' infestation. *Arch Dermatol* 1981; **117**: 812–4.
19 Duckworth PF Jr, Hayden GF, Reed CN. Human infestation by *Amblyomma americanum* larvae ('seed ticks'). *South Med J* 1985; **78**: 751–3.
20 Fisher EJ, Mo J, Lucky AW. Multiple pruritic papules from lone star tick larvae bites. *Arch Dermatol* 2006; **142**: 491–4.
21 Wakkerman CThB, van Rijn JFA. Strophulus arthropodicus, verursacht durch Ixodidan. *Hautarzt* 1965; **16**: 37–8.
22 Shasky DR. Tick bite granuloma with autoeczematization. *Arch Dermatol* 1972; **106**: 916.
23 Ross MS, Friede H. Alopecia due to tick bite. *Arch Dermatol* 1955; **71**: 524–5.
24 Hoogstraal H, Gallagher MD. Blisters, pruritus and fever after bites by the Arabian tick *Ornithodorus* (*Alectorobius*) *muesebecki*. *Lancet* 1982; **ii**: 288–9.
25 Condy JR, Norval RAI, Blackbum NK *et al*. The effects of the bites of *Argas brumpti* (Acarina: Argasidae) on humans. *Cent Afr J Med* 1980; **26**: 212–3.
26 Fernandez-Soto P, Davila I, Laffond E *et al*. Tick-bite-induced anaphylaxis in Spain. *Ann Trop Med Parasitol* 2000; **95**: 97–103.
27 Halpern SM, Munro DD. Tickborne melanoma? *BMJ* 1994; **309**: 1693.
28 Dworkin MS, Shoemaker PC, Anderson DE Jr. Tick paralysis: 33 human cases in Washington State, 1946–1996. *Clin Infect Dis* 1999; **29**: 1435–9.
29 Greenstein P. Tick paralysis. *Med Clin North Am* 2002; **86**: 441–6.
30 Sherman WT. Polishing off ticks. *N Engl J Med* 1983; **309**: 992.
31 Dolan DL, Mckinsey JJ. Removing a tick. *North Carolina Med J* 1985; **46**: 471.
32 Karras D. Tick removal. *Ann Emerg Med* 1998; **32**: 519.
33 Needham GR. Evaluation of five popular methods for tick removal. *Pediatrics* 1985; **75**: 997–1002.

Mites (Acari)

Family Sarcoptidae

Scabies. Scabies in humans and other animals is caused by mites of the family Sarcoptidae, which includes *Sarcoptes scabiei*, the scabies mite, and *Notoedres cati*, a mange mite of cats.

The *Sarcoptes* causing scabies in humans and sarcoptic mange in many other animals are physiological variants of a single species, *S. scabiei*. Their host specificity is not complete, but they usually survive for only a short period on another host.

Human scabies. Human scabies has played a modest, but not insignificant role in history; the story of scabies has been related in detail by Hebra [1], Beeson [2], Heilesen [3], Friedman [4] and Parish [5].

Morphology and biology of the scabies mite [3,6–12]. *Sarcoptes scabiei* var. *hominis* has an ovoid body, flattened dorsoventrally. The adult female measures approximately 0.4 mm long by 0.3 mm broad, and the smaller male 0.2 mm long by 0.15 mm broad. The body is creamy white and is marked by transverse corrugations, and on its dorsal surface by bristles and spines (denticles). There are four pairs of short legs; the anterior two pairs end in elongated peduncles tipped with small suckers. In the female, the rear two pairs of legs end in long bristles (setae) (Fig. 38.30), whereas in the male bristles are present on the third pair and peduncles with suckers on the fourth.

Copulation occurs in a small burrow excavated by the female. After copulation, the fertilized female enlarges the burrow and begins egg laying. The burrow is not confined to the stratum corneum, but is inclined downwards into the epidermis. Eggs and mite faeces are deposited behind the female in the burrow. Approximately 40–50 eggs are laid by each female during a lifespan of 4–6

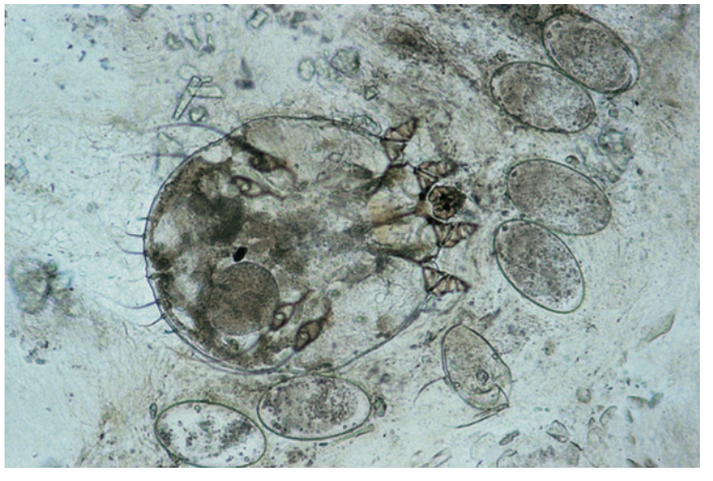


Fig. 38.30 *Sarcoptes scabiei*, the scabies mite. Female with eggs.

weeks, during which time she does not leave the burrow. Six-legged larvae emerge from the eggs after 3–4 days and escape from the burrow by cutting through its roof. The larvae then dig short burrows (moulting pockets) in which they transform into nymphs. After further moults, adult males and females develop.

The mites show a preference for certain sites in which to burrow, and appear to avoid areas with a high density of pilosebaceous follicles. The average number of adult female mites on an individual suffering from the common form of scabies is about 12 [13–15]. Only in crusted (Norwegian) scabies are large numbers of mites present.

References

1 Hebra F von. *On Diseases of the Skin including the Exanthemata*, Vol. II. London: The New Sydenham Society, 1868: 164–252.
2 Beeson BB. Acarus scabiei. Study of its history. *Arch Dermatol Syphilol* 1927; **16**: 294–307.
3 Heilesen B. Studies on Acarus scabiei and scabies. *Acta Derm Venereol Suppl (Stockh)* 1946; **14**: 1–370.
4 Friedman R. *The Story of Scabies*. New York: Froben, 1948.
5 Parish LC. History of scabies. In: Orkin M, Maibach HI, eds. *Cutaneous Infestations and Insect Bites*. New York: Marcel Dekker 1985: 3–8.
6 Alexander JO'D. Scabies. In: *Arthropods and Human Skin*. Berlin: Springer-Verlag, 1984: 227–92.
7 Fain A. Etude de la variabilité de *Sarcoptes scabiei* avec une révision des Sarcoptidae. *Acta Zool Pathol Antverp* 1960; **47**: 1–196.
8 Pascual AM, Asensio A, Vasquez R. Morphologie du *Sarcoptes scabiei* (variété *hominis*) au microscope éléctronique à balayage. *Ann Dermatol Vénéréol* 1977; **104**: 719–23.
9 Van Neste D, Mrena E, Marchal G. Le cycle évolutif du *Sarcoptes scabiei* (var. *hominis*): une étude en microscopie éléctronique à balayage. *Ann Dermatol Vénéréol* 1981; **108**: 355–61.
10 Burgess I. *Sarcoptes scabiei* and scabies. *Adv Parasitol* 1994; **33**: 235–92.
11 Arlian LC, Runyan RA, Achar S *et al*. Survival and infestivity of *Sarcoptes scabiei* var. *canis* and var. *hominis*. *J Am Acad Dermatol* 1984; **11**: 210–5.
12 Van Neste DJJ. Human scabies in perspective. *Int J Dermatol* 1988; **27**: 10–5.
13 Bartley WC, Mellanby K. The parasitology of human scabies (women and children). *Parasitology* 1944; **35**: 207–8.
14 Johnson CG, Mellanby K. The parasitology of human scabies. *Parasitology* 1942; **34**: 282–90.
15 Mellanby K. *Scabies*. Hampton: EW Classey, 1972.

Prevalence and epidemiology [1–6]. Scabies affects all races and social classes worldwide, but accurate figures of its prevalence are difficult to obtain. A study by Downs *et al*. [7] on data collected in the UK between 1967 and 1996 showed a high incidence of scabies in the late 1960s and early 1970s, a drop during the 1980s, and a rise throughout the 1990s. A Danish study, which assessed data collected between 1900 and 1975 [8], showed incidence rates in the 1960s and 70s similar to those in the UK study, and high incidence rates during the two World Wars. However, a rise in incidence started 2 years prior to hostilities on both occasions. Data from records kept in Edinburgh, UK also showed rises in incidence associated with the World Wars, but coinciding precisely with their onset [9].

Also noted by Downs *et al*. [7] were a higher prevalence in urban areas, the north of the UK, and in women and children, and greater frequency in the winter than the summer. Several other studies have noted this seasonal variation [10,11].

A decline in the number of cases of scabies in developed countries in the 1950s was followed by an upsurge in the mid-1960s, mentioned by several authors [12–14]. One suggested cause of the increased frequency of scabies in the 1960s was sexual promiscuity, but some authors believe this is unlikely in view of a lack of correlation with trends in sexually transmitted diseases [13,15]. A proposed explanation for the cyclical fluctuations in prevalence in developed countries is the 'herd immunity' theory [2,13]. This suggests that an epidemic of scabies confers a degree of immunity, so that a further epidemic will not occur until a new, susceptible population has arisen. However, the persistent high levels of scabies in many underdeveloped countries, without any marked cyclical variation, are evidence against this view.

Scabies is most common in children and young adults, but may occur at any age, and in the UK in recent years it has become frequent in the elderly in residential and nursing home environments. In a questionnaire survey of dermatologists in UK hospitals, reported in 2000 [16], respondents estimated that approximately 30% of all cases of scabies they encountered occurred in institutions such as care homes and hospitals. Although some outbreaks are related to cases of crusted scabies, others appear to originate from residents who have ordinary scabies with many burrows, and therefore a large mite population, or from infected carers. Close contact between residents and carers in these homes is common—for example, carers often hold the hands of residents to provide support when walking.

The overall sex incidence is probably equal.

Whereas all racial groups are susceptible, there are some differences between races, which are probably related to customs and social factors rather than inherent susceptibility. Some reports suggested that black Americans appeared less susceptible [17,18], but this was disputed [19]. In a study of a multiracial population in Hawaii [20], scabies was far more frequent in white people and Hawaiians than in Japanese and Filipinos, and this was thought to be related to family size and social customs.

Overcrowding, which is common in underdeveloped countries and is almost invariably associated with poverty and poor hygiene, encourages the spread of scabies.

Scabies is usually transmitted by close physical contact, such as prolonged hand-holding or the sharing of a bed. Indirect spread by clothing or bedding is unimportant in ordinary scabies, as demonstrated by the meticulous studies of Mellanby [21,22]. It is often suggested that fertilized female mites are responsible for transmission, although there is no firm evidence to support this contention, but it seems unlikely in view of their relatively small numbers and inclination to remain within their burrows. There are far greater numbers of immature mites on the skin surface, and their involvement in scabies transmission would appear more plausible.

A study from Sheffield, UK [23], showed that scabies was introduced into households mainly by schoolchildren and teenagers, especially by girls. The authors suggested that the frequent occurrence of scabies in teenage girls could be due to contact with younger children in large families, and the habit of holding hands. The commonest sources of infection were friends and relatives outside the home, and schools did not appear to play any appreciable part.

Away from the host, scabies mites survive for 24–36 h at room conditions (21°C and 40–80% relative humidity) [24], and live

mites have been demonstrated in dust samples collected in the homes of infected patients [25].

References

1 Alexander JO'D. Scabies. In: *Arthropods and Human Skin*. Berlin: Springer-Verlag, 1984; 227–92.
2 Mellanby K. The incidence of scabies. In: *Scabies*. Hampton: EW Classey, 1972; 43–8.
3 Burgess I. *Sarcoptes scabiei* and scabies. *Adv Parasitol* 1994; **33**: 235–92.
4 Chosidow O. Scabies and pediculosis. *Lancet* 2000; **355**: 819–26.
5 Burkhart CG. Scabies: an epidemiologic reassessment. *Ann Intern Med* 1983; **98**: 498–503.
6 Hengge UR, Currie BJ, Jäger G *et al*. Scabies: a ubiquitous neglected skin disease. *Lancet Infect Dis* 2006; **6**: 769–79.
7 Downs AMR, Harvey I, Kennedy CTC. The epidemiology of head lice and scabies in the UK. *Epidemiol Infect* 1999; **122**: 471–7.
8 Christophersen J. The epidemiology of scabies in Denmark, 1900–1975. *Arch Dermatol* 1978; **114**: 747–50.
9 Savin JA. Scabies in Edinburgh from 1815 to 2000. *J R Soc Med* 2005; **98**: 124–9.
10 Mimouni D, Ankol OE, Davidovitch N *et al*. Seasonality trends of scabies in a young adult population: a 20-year follow-up. *Br J Dermatol* 2003; **149**: 157–9.
11 Downs AMR. Seasonal variation in scabies. *Br J Dermatol* 2004; **150**: 602–3.
12 Orkin M, Maibach HI. This scabies pandemic. *N Engl J Med* 1978; **298**: 496–8.
13 Shrank AB, Alexander SL. Scabies: another epidemic? *BMJ* 1967; **1**: 669–71.
14 Wilson TS. Scabies and pediculosis. A study of the incidence in Glasgow from the early nineteen twenties. *Med Off* 1969; **122**: 125–7.
15 Melton LJ, Brazin SA, Damm SR. Scabies in the United States Navy. *Am J Public Health* 1978; **60**: 776–8.
16 Bennett CE, Keefe M, Reynolds JC. Perception of the incidence of scabies and efficacy of treatment in UK hospitals. *Br J Dermatol* 2000; **143**: 1337–8.
17 Alexander AM. Role of race in scabies infestation. *Arch Dermatol* 1978; **114**: 627.
18 Kelly AP. Scabies in blacks. *Arch Dermatol* 1978; **114**: 1245.
19 Rietschel RL, Lewis CW, Jones HE *et al*. Scabies and role of race. *Arch Dermatol* 1979; **115**: 109–10.
20 Funaki B, Elpern DJ. Scabies epidemiology, Kauai, Hawaii, 1981–1985. *Int J Dermatol* 1987; **26**: 590–2.
21 Mellanby K. The transmission of scabies. *BMJ* 1941; **2**: 405–6.
22 Mellanby K. *Human Guinea Pigs*. London: Victor Gollancz, 1945.
23 Church RE, Knowelden J. Scabies in Sheffield: a family infestation. *BMJ* 1978; **1**: 761–3.
24 Arlian LG, Runyan RA, Achar S *et al*. Survival and infestivity of *Sarcoptes scabiei* var. *canis* and var. *hominis*. *J Am Acad Dermatol* 1984; **11**: 210–5.
25 Arlian LG, Estes SA, Vyszenski-Moher DL. Prevalence of *Sarcoptes scabiei* in the homes and nursing homes of scabietic patients. *J Am Acad Dermatol* 1988; **19**: 806–11.

Immunology [1–6]. Allergic sensitivity to the mite or its products appears to play an important role in determining the development of lesions other than burrows, and in producing pruritus. However, the sequence of immunological events is unclear and requires further elucidation.

Evidence suggests that both immediate and delayed-type hypersensitivity are involved. Skin tests with mite extracts have given equivocal results, although positive immediate-type reactions to intradermal tests have frequently been obtained in patients within a few months of scabies infection. Normal IgE levels were reported in one series of scabies patients [7], but later studies have shown significantly elevated levels in many individuals [8–11].

Marked eosinophilia was a feature of two patients who had scabies coexistent with disorders of keratinization [12].

Involvement of delayed-type hypersensitivity in the production of inflammatory papules and nodules is suggested by the histological changes and predominance of T lymphocytes in the cutaneous infiltrate [13,14]. Experiments to determine if an extract of *S. scabiei* influenced cytokine expression by T lymphocytes showed increased production of IL-10, a finding which led to the suggestion that this may play a role in depressing the inflammatory and immune responses, and thereby in delaying onset of symptoms [15].

Other immunological findings include high serum IgG and IgM, and low IgA [7,10], with levels returning to normal after treatment. IgM and C3 deposits have been demonstrated at the dermo-epidermal junction in the region of burrows [16,17], and circulating immune complexes have been found in the serum after treatment of scabies [18].

The frequency of human leukocyte antigen (HLA)-A11 was found to be higher among patients with scabies than in a normal population in Norway [19].

References

1 Alexander JO'D. Scabies. In: *Arthropods and Human Skin*. Berlin: Springer-Verlag, 1984: 227–92.
2 Dahl MV. The immune system in scabies. In: Orkin M, Maibach HI, eds. *Cutaneous Infestations and Insect Bites*. New York: Marcel Dekker, 1985: 75–83.
3 Falk ES, Bolle R. *In vitro* demonstration of specific immunological hypersensitivity to scabies mite. *Br J Dermatol* 1980; **103**: 367–73.
4 Van Neste DJJ. Human scabies in perspective. *Int J Dermatol* 1988; **27**: 10–5.
5 Burgess I. *Sarcoptes scabiei* and scabies. *Adv Parasitol* 1994; **33**: 235–92.
6 Hengge UR, Currie BJ, Jäger G *et al*. Scabies: a ubiquitous neglected skin disease. *Lancet Infect Dis* 2006; **6**: 769–79.
7 Hancock BW, Ward AM. Serum immunoglobulin in scabies. *J Invest Dermatol* 1974; **63**: 482–4.
8 Araujo-Fontaine A, Thierry R, Heid E. Les IgE sériques dans la gale. *Ann Dermatol Vénéréol* 1977; **104**: 203–5.
9 Chevrant-Breton J, Desrues E, Auvray E *et al*. IgE sériques et gale humaine. *Ann Dermatol Vénéréol* 1981; **108**: 979–83.
10 Falk ES. Serum immunoglobulin values in patients with scabies. *Br J Dermatol* 1980; **102**: 57–61.
11 Christensen JD, Schwartz B, Graudal C *et al*. Serum IgE antibodies to the scabies mite. *Int J Dermatol* 1985; **24**: 313–5.
12 Sluzevich JC, Sheth AP, Lucky AW. Persistent eosinophilia as a presenting sign of scabies in patients with disorders of keratinization. *Arch Dermatol* 2007; **143**: 670–3.
13 Arlian LG. Host–parasite interactions of *Sarcoptes scabiei* (Acari). In: Channabasavanna GP, Viraktamath GA, eds. *Progress in Acarology*, Vol. 1. New Delhi: Oxford and IBH, 1988: 123–31.
14 Reunala T, Ranki A, Rantanen T *et al*. Inflammatory cells in skin lesions of scabies. *Clin Exp Dermatol* 1984; **9**: 70–7.
15 Arlian LG, Morgan MS, Paul CC. Evidence that scabies mites (Acari: Sarcoptidae) influence production of interleukin-10 and the function of T-regulatory cells (Tr 1) in humans. *J Med Entomol* 2006; **43**: 283–7.
16 Frentz G, Veien NK, Eriksen K. Immunofluorescence studies in scabies. *J Cutan Pathol* 1977; **4**: 191–3.
17 Hoefling KK, Schroeter AL. Dermatoimmunopathology of scabies. *J Am Acad Dermatol* 1980; **3**: 237–40.
18 Van Neste D, Sakion J. Circulating antigen antibody complexes in scabies. *Dermatologica* 1978; **157**: 221–4.
19 Falk ES, Thorsby E. HLA antigens in patients with scabies. *Br J Dermatol* 1981; **104**: 317–20.

Clinical features [1,2]. Itching is usually the most obvious manifestation of scabies. It is generally worst at night and when the patient is warm. The onset occurs 3–4 weeks after the infection is acquired, and coincides with a widespread eruption of inflammatory papules. Reinfection of a previously cured individual, however, provokes immediate symptoms [3].



Fig. 38.31 Numerous scabies burrows on the palm.

The pathognomonic lesions of scabies are burrows, which appear as slightly raised, brownish, tortuous lesions (Fig. 38.31). The point of entry of the mite, the most superficial part of the burrow, has a slightly scaly appearance, and at the distal end there may be a tiny vesicle, adjacent to which is the female mite. There may be few or many burrows, and in patients with a good standard of hygiene they may be difficult to find. Burrows occur on the wrists, the borders of the hands, the sides of the fingers and the finger web spaces, the feet, particularly the instep and, in males, on the genitalia. They are often present on the palms and soles of young children and the elderly. In adults other than the elderly, burrows may occur on the palms in women, but they are less frequently found on the palms in men, particularly heavy manual workers. Burrows on the trunk are uncommon in adults, but may be found in the elderly and in infants. They may be seen on the head and neck in babies, but rarely in adults. The scalp was, however, involved in an adult who was applying a topical steroid for seborrhoeic dermatitis [4], and scalp involvement in ordinary scabies may be a reason for relapse [5]. The reason for this pattern of distribution of burrows is not understood, but the mites appear to prefer non-hairy skin and areas of low sebum production.

The pruritic papules that accompany the development of hypersensitivity occur predominantly around the axillae, in the periareolar regions, on the abdomen, particularly the periumbilical region, and on the buttocks and thighs. Histology shows epidermal spongiosis, with intraepidermal microabscesses containing neutrophils and eosinophils, and a dermal perivascular infiltrate of eosinophils, histiocytes and lymphocytes [6,7]. Indurated, inflammatory nodules sometimes occur, particularly on the axillae, groins, scrotum and penis. They are intensely itchy, and may persist for weeks or months after the scabies has been effectively treated [8–10]. The histological changes seen in these persistent scabies nodules may simulate lymphoma, with a dense, pleomorphic dermal infiltrate composed of plasma cells, eosinophils, lymphocytes, histiocytes and reticulum cells [6,11]. T lymphocytes are the predominant cells in the dermal infiltrate of both papular and nodular lesions [12,13].

Inflammatory papules or nodules, sometimes surmounted by burrows, on the male genitalia are characteristic of scabies (Fig. 38.32). The genitalia of males suspected of suffering from scabies should always be examined, as these lesions may provide an important diagnostic clue if burrows are difficult to find.



Fig. 38.32 Inflammatory papules on the penis in scabies.

Nail involvement in crusted (Norwegian) scabies is frequent, but it is uncommon in ordinary scabies [14]. Its presence may be a reason for relapse [15].

In addition to these primary manifestations, secondary features may occur, and can confuse the clinical picture. Eczematous changes are common, and may be widespread and severe. The inappropriate use of topical steroids may further modify the clinical picture to mimic other dermatoses (see crusted scabies)—so-called 'scabies incognito' [16]. Secondary infection, manifest as folliculitis or impetigo, may also be severe and extensive. In the tropics and subtropics, where nephritogenic strains of β-haemolytic streptococci may be responsible for secondary sepsis, glomerulonephritis occurs as a complication of scabies, but this must be exceedingly rare in temperate climates.

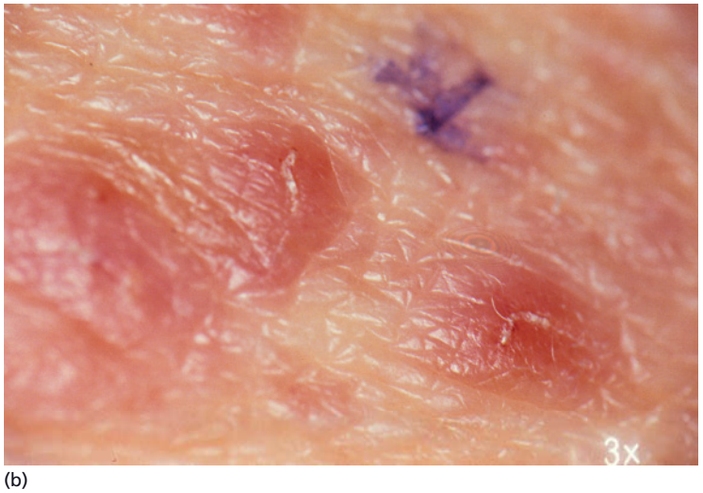
A bullous pemphigoid-like eruption may occur in association with scabies [17–25], and in many of the reported cases immunofluorescence studies showed immunoglobulin deposition in the basement membrane zone of the bullous lesions. The demonstration of circulating antibodies against BP180 and/or BP230 in two patients with scabies and bullous lesions [23] indicates that scabies may induce true bullous pemphigoid.

Cutaneous vasculitis is an unusual presentation of scabies [26–28].

Scabies in babies. The clinical features of scabies in infants and young children differ in certain respects from those in older children and adults [29,30]. In addition to the more extensive



(a)



(b)

Fig. 38.33 (a) Multiple truncal papules, surmounted by burrows (b), in an elderly woman.

distribution of burrows mentioned above, vesicular and vesiculopustular lesions on the hands and feet are frequent, extensive eczematization is often present, and there may be multiple crusted nodules on the trunk and limbs.

Bullous lesions have been described in a child [31].

Scabies in the elderly. Burrows commonly occur on the palms and soles, and may be very numerous. Truncal papulosquamous lesions, often surmounted by burrows, are common (Fig. 38.33). Secondary eczematization is often troublesome.

References

1 Alexander JO'D. Scabies. In: *Arthropods and Human Skin*. Berlin: Springer-Verlag, 1984: 227–92.
2 Chosidow O. Scabies and pediculosis. *Lancet* 2000; **355**: 819–26.
3 Mellanby K. The development of symptoms, parasitic infection and immunity in human scabies. *Parasitology* 1944; **35**: 197–206.
4 Elmros T, Hornqvist R. Infestation of scabies in the scalp area. *Acta Derm Venereol (Stockh)* 1981; **61**: 360–2.
5 Alinovi A, Pretto ME. Scabietic infestation of the scalp: a clue for puzzling relapses. *J Am Acad Dermatol* 1994; **31**: 492–3.
6 Fernandez N, Torres A, Ackermann AB. Pathologic findings in human scabies. *Arch Dermatol* 1977; **113**: 320–4.
7 Hejazi N, Mehregan AH. Scabies. Histological study of inflammatory lesions. *Arch Dermatol* 1975; **111**: 37–9.
8 Grant PW, Keczkes K. Persistent nodules in scabies. *Arch Dermatol* 1964; **89**: 239–42.
9 Konstantinov D, Stanoeva L. Persistent scabious nodules. *Dermatologica* 1973; **147**: 321–7.
10 Samman PD. Persistent scabious nodules. *Br J Dermatol* 1963; **75**: 35.
11 Thomson J, Cochrane T, Cochran R *et al*. Histology simulating reticulosis in persistent nodular scabies. *Br J Dermatol* 1974; **90**: 421–9.
12 Arlian LG. Host–parasite interactions of *Sarcoptes scabiei* (Acari). In: Channabasavanna GP, Viraktamath CA, eds. *Progress in Acarology*, Vol. 1. New Delhi: Oxford and IBH, 1988: 123–31.
13 Reunala T, Ranki A, Rantanen T *et al*. Inflammatory cells in skin lesions of scabies. *Clin Exp Dermatol* 1984; **9**: 70–7.
14 Saruta T, Nakamizo Y. Usual scabies with nail infestation. *Arch Dermatol* 1978; **114**: 956–7.
15 Witkowski JA, Parish LC. Scabies. Subungual areas harbor mites. *JAMA* 1984; **252**: 1318–9.
16 Orkin M. Special forms of scabies. In: Orkin M, Maibach HI, eds. *Cutaneous Infestations and Insect Bites*. New York: Marcel Dekker, 1985: 25–30.
17 Viraben R, Dupre A. Scabies mimicking bullous pemphigoid. *J Am Acad Dermatol* 1989; **20**: 134–6.
18 Ostlere LS, Harris D, Rustin MHA. Scabies associated with a bullous pemphigoid-like eruption. *Br J Dermatol* 1993; **128**: 217–9.
19 Bhawan J, Milstone E, Malhotra R *et al*. Scabies presenting as bullous pemphigoid-like eruption. *J Am Acad Dermatol* 1991; **24**: 179–81.
20 Parodi A, Saino M, Rebora A. Bullous pemphigoid-like scabies. *Clin Exp Dermatol* 1993; **18**: 293.
21 Slawsky LD, Maroon M, Tyler WB, Miller FO 3rd. Association of scabies with a bullous pemphigoid-like eruption. *J Am Acad Dermatol* 1996; **34**: 878–9.
22 Haustein UF. Bullous scabies. *Dermatology* 1995; **190**: 83–4.
23 Konishi N, Suzuki K, Tokura Y *et al*. Bullous eruption associated with scabies: evidence for scabetic induction of true bullous pemphigoid. *Acta Derm Venereol (Stockh)* 2000; **80**: 281–3.
24 Pereiro M Jr, Roson E, Sanchez-Aguilar D, Toribio J. Scabies presenting as a blistering eruption. *Cutis* 2001; **68**: 279–80.
25 Nakamura E, Taniguchi H, Ohtaki N. A case of crusted scabies with a bullous pemphigoid-like eruption and nail involvement. *J Dermatol* 2006; **33**: 196–201.
26 Menné T, Christophersen J, Gram N, Bjerrehus T. Scabetic leukocytoclastic vasculitis with focal glomerulonephritis. *Acta Derm Venereol (Stockh)* 1984; **64**: 445–7.
27 Valks R, Buezo GF, Dauden E. Scabies and leucocytoclastic vasculitis in an HIV-seropositive man. *Int J Dermatol* 1996; **35**: 605–6.
28 Jarrett P, Snow J. Scabies presenting as a necrotizing vasculitis in the presence of lupus anticoagulant. *Br J Dermatol* 1998; **139**: 701–3.
29 Burns BR, Lampe RM, Hansen CH. Neonatal scabies. *Am J Dis Child* 1979; **133**: 1031–4.
30 Hurwitz S. Scabies in babies. *Am J Dis Child* 1973; **126**: 226–8.
31 Bean SF. Bullous scabies. *JAMA* 1974; **230**: 878.

Diagnosis [1–3]. The typical history of pruritus with nocturnal exacerbations, and the distribution of the eruption of inflammatory papules, should suggest the diagnosis. The presence of genital lesions in males is pathognomonic. Absolute confirmation can only be made by the discovery of burrows and microscopical

examination. A burrow is gently scraped off the skin with a blunt scalpel, and the material placed in a drop of 10% potassium hydroxide or mineral oil on a microscope slide. The presence of mites, eggs or fragments of egg shells confirms the diagnosis.

Dermatoscopy is useful for detecting burrows and visualizing their contents [4,5], the mite in its burrow resembling a 'jet-with-contrail'.

Occasionally, burrows are difficult or impossible to find, and the diagnosis can then only be presumptive, based on the history, distribution of the papular eruption and the presence of contact cases within the family. However, in difficult diagnostic situations and atypical cases, polymerase chain reaction has been employed as a diagnostic tool [6].

References

1 Walton SF, Holt DC, Currie BJ, Kemp DJ. Scabies: new future for a neglected disease. *Adv Parasitol* 2004; **57**: 309–76.

2 Heukelbach J, Feldmeier H. Scabies. *Lancet* 2006; **367**: 1767–74.

3 Hengge UR, Currie BJ, Jäger G *et al*. Scabies: a ubiquitous neglected skin disease. *Lancet Infect Dis* 2006; **6**: 769–79.

4 Argenziano G, Fabbrocini G, Delfino M. Epiluminescence microscopy. A new approach to in vivo detection of Sarcoptes scabiei. *Arch Dermatol* 1997; **133**: 751–3.

5 Brunetti B, Vitiello A, Delfino S, Sammarco E. Findings *in vivo* of *Sarcoptes scabiei* with incident light microscopy. *Eur J Dermatol* 1998; **8**: 266–7.

6 Bezold G, Lange M, Schiener R *et al*. Hidden scabies: diagnosis by polymerase chain reaction. *Br J Dermatol* 2001; **144**: 614–8.

Treatment [1–6]. There have been many suggested remedies for scabies. Sulphur has been used for centuries, and sulphur ointment is still employed in some parts of the world. Used excessively, or in high concentration, it may cause irritation, but 10% sulphur in yellow soft paraffin is, in general, safe and effective. A concentration of 2.5% may be used for scabies in infants and young children [1].

Rotenone, an extract of Derris root, was employed in the 1940s [7,8], but frequently produced scrotal dermatitis. Monosulfiram (chemically similar to disufiram (Antabuse)) was used as definitive treatment [9,10] and also, in the form of soap, as a prophylactic measure in communities where scabies was endemic [11–13]. An Antabuse effect could occur if alcohol was ingested during or soon after treatment [14].

There are several currently available scabicides. The choice of therapy is determined not only by efficacy and potential toxicity, but also by considerations such as cost, ease of application, the presence of secondary eczematization and the age of the patient.

Although for many years a hot bath and vigorous scrubbing of the sites of burrows was considered essential, Mellanby *et al*. [15] demonstrated that this was not necessary.

Benzyl benzoate. Although benzyl benzoate is now synthesized, it occurs naturally in balsams of Peru and Tolu: balsam of Peru has been used as a scabicide in the past. In 1937, the Danish dermatologist Kissmeyer [16] reported the effectiveness of benzyl benzoate in the treatment of 8000 cases of scabies, and it rapidly became popular [15,17–19]. Employed as a 25% emulsion, it should remain on the skin for 24 h. There are a number of suggested treatment regimens, but little has been published on their comparative efficacy. Most involve two or three applications, either within 24 h, on successive days, or separated by intervals of a week. Benzyl benzoate is irritant, and patients should be warned about overuse. Because it is effective and inexpensive, it is still used in many parts of the world.

Gamma benzene hexachloride (lindane). A single application, washed off after 12–24 h, is usually recommended, but it has been demonstrated that a 6-h application is equally effective [20]. Topical lindane is absorbed through the skin, especially if the barrier function of the epidermis is compromised [21–24]. There are a number of reports of adverse neurological effects, principally seizures, attributed to lindane [21,23,25–28], but toxicity was usually the result of excessive topical application or accidental ingestion. A comparison of percutaneous absorption of lindane and permethrin concluded than 5% permethrin cream is at least 40 times less likely to cause toxic effects than 1% lindane lotion [29]. However, critical assessment of lindane as a scabicide led to the conclusion that it is safe if used correctly [30,31].

There are anecdotal reports from several parts of the world, including the UK and USA, of lindane treatment failures, suggesting the emergence of lindane-resistant scabies mites.

Although still employed as a scabicide in some parts of the world, its use has been discontinued in several countries.

Malathion. Malathion 0.5% in an aqueous base is employed as a scabicide [32,33]. It should be left on the skin for 24 h, with a second application after an interval of a week.

Permethrin. Permethrin 5% dermal cream is an effective scabicide [34–36]. It should be washed off after 8–12 h, with a second application after an interval of a week. At present, it is the topical treatment of choice.

A survey of dermatologists in the UK revealed that the majority used permethrin cream for treating scabies, and about half reported treatment failures with malathion [37].

Other topical treatments include thiabendazole [38,39] and crotamiton [40]. Both have limited scabicidal activity, and several applications on consecutive days are required. Activity of essential oils against mites has been reported—including tea tree oil [41], neem, turmeric, bush tea essential oil, coconut oil and jojoba [42].

Ivermectin [5,43–45]. Ivermectin is structurally similar to the macrolide antibiotics, but does not have antibacterial activity. It is, however, active against a number of ecto- and endoparasites. It has been extensively employed in veterinary medicine, and in humans is used to treat filarial disease, principally onchocerciasis. It is not licensed for use in scabies in humans, with the exception of France. Glaziou *et al*. [46] compared oral ivermectin with topical benzyl benzoate for the treatment of scabies, and found that the former produced a higher cure rate. A comparison of the effectiveness of topical permethrin with oral ivermectin showed that a single application of permethrin is superior to a single dose of ivermectin, but two doses of ivermectin (with a 2-week interval between) are as effective as a single application of permethrin [47]. Comparison of ivermectin with lindane showed that they are equally effective [48]. It has also been reported that a specially

formulated topical ivermectin preparation was effective in treating scabies [49]. Oral ivermectin has proved particularly useful in the treatment of crusted scabies (see below). Ivermectin is apparently a safe drug with a low incidence of adverse effects. Many of the reported adverse effects have occurred in individuals given ivermectin for the treatment of filariasis, in whom serious reactions were thought to be related to death of the parasites [50]. A report suggesting a pattern of excess deaths in elderly people in a residential unit, who were given ivermectin to control a scabies outbreak, raised concerns about its safety [51]. However, the conclusions of this report were challenged [52,53], and other authors' findings regarding its safety are reassuring [54,55]. It also appears to be safe in children [56].

A single dose of 200 µg/kg body weight will be effective in many cases of ordinary scabies but, presumably because of a lack of ovicidal activity, higher cure rates are obtained with two doses separated by an interval of a week.

Because it is effective, inexpensive, and easy to administer, ivermectin might prove particularly useful in the management of institutional outbreaks of scabies (see below). Leppard and Naburi controlled an outbreak of scabies in a prison in Tanzania by giving ivermectin to 1153 prisoners [57].

Resistance to ivermectin in crusted scabies has been documented (see below) [58].

Liquid scabicides are most conveniently applied with a 2″ (5 cm) paintbrush. Scabicides should be applied to the whole body, except the head and neck, although the latter should be included if there is clinical evidence of involvement, and a non-irritant agent employed. Patients should be provided with written instructions explaining their treatment regimen and a warning against excessive use. They should be advised that itching will persist for a few days, but will usually resolve within 2 weeks. A topical antipruritic, such as crotamiton combined with hydrocortisone, may be used on residual itchy areas. All members of the family and close physical contacts should be treated, whether symptomatic or not. Disinfestation of clothing and bedding, other than by ordinary laundering, is not necessary.

Secondary infection should be treated with a systemic antibiotic. If eczematization is severe, a non-irritant scabicide should be used.

Treatment of infants and young children. Benzyl benzoate should be diluted with two or three parts water if used on infants and young children. Prolonged or repeated applications of benzyl benzoate or lindane should be avoided. Permethrin cream is the treatment of choice.

Scabicides in pregnancy and breast feeding. The literature is replete with cautionary advice relating to the use of scabicides in pregnancy, but having indicated which scabicides are best avoided authors rarely commit themselves to stating what they recommend. This is understandable in view of concern about potential toxic effects on the fetus but, to this author's knowledge, there is no documented evidence that any of the currently available scabicides has been responsible for harmful effects in pregnancy. Current UK Clinical Knowledge Summaries (CKS) guidelines suggest using permethrin, with malathion as an alternative. It is suggested that topical agents should be removed from the nipples before breast feeding, and reapplied thereafter.

Persistent scabies nodules. Potent topical steroids are usually used in treatment of these itchy nodules, but they are often slow to respond. Topical pimecrolimus was of benefit in a recalcitrant case [59].

References

1 Alexander JO'D. Scabies. In: *Arthropods and Human Skin*. Berlin: Springer-Verlag, 1984: 227–92.
2 Burgess I. *Sarcoptes scabiei* and scabies. *Adv Parasitol* 1994; **33**: 235–92.
3 Chosidow O. Scabies and pediculosis. *Lancet* 2000; **355**: 819–26.
4 Walton SF, Holt DC, Currie BJ, Kemp DJ. Scabies: new future for a neglected disease. *Adv Parasitol* 2004; **57**: 309–76.
5 Hengge UR, Currie BJ, Jäger G *et al*. Scabies: a ubiquitous neglected skin disease. *Lancet Infect Dis* 2006; **6**: 769–79.
6 Strong M, Johnstone PW. Interventions for treating scabies. *The Cochrane Database of Systematic Reviews*. 2007, Issue 3.
7 Saunders L. The Derris root treatment of scabies. *BMJ* 1941; **1**: 624–6.
8 Thomas CC, Miller E. Rotenone in the treatment of scabies. *Am J Med Sci* 1940; **199**: 670–7.
9 Bradshaw DB. Tetraethylthiuram monosulphide in the treatment of scabies. *Lancet* 1944; **ii**: 273–4.
10 Clayton TM. Treatment of scabies by T.E.T.M.S. *BMJ* 1943; **1**: 443–5.
11 Bartley W, Unsworth K, Gordon RM. The rise in incidence of scabies in a closed community using ordinary soap, and its subsequent fall on the substitution of 5% Tetmosol soap. *BMJ* 1945; **1**: 332–3.
12 Gordon RM, Davey TH, Unsworth K *et al*. Control of scabies by use of soap impregnated with tetra-ethylthiuram monosulphide ('Tetmosol'). *BMJ* 1944; **1**: 603–6.
13 Mellanby K. Scabies prophylaxis using 'Tetmosol' soap. *BMJ* 1945; **1**: 38–9.
14 Gold S. A skinful of alcohol. *Lancet* 1966; **ii**: 1417.
15 Mellanby K, Johnson CG, Bartley WC. The treatment of scabies. *BMJ* 1942; **2**: 1–4.
16 Kissmeyer A. Rapid ambulatory treatment of scabies with benzyl benzoate lotion. *Lancet* 1937; **i**: 21.
17 Graham JR. Scabies treated with one application of benzyl benzoate. *BMJ* 1943; **1**: 413–4.
18 King RE. The benzyl benzoate treatment of scabies. *BMJ* 1944; **2**: 626–7.
19 Mackenzie IF. Scabies treated by a benzyl benzoate emulsion. *BMJ* 1941; **2**: 403–5.
20 Taplin D, Rivera A, Walker JG *et al*. A comparative trial of three treatment schedules for the eradication of scabies. *J Am Acad Dermatol* 1983; **9**: 550–4.
21 Friedman SJ. Lindane neurotoxic reaction in non-bullous congenital ichthyosiform erythroderma. *Arch Dermatol* 1987; **123**: 1056–8.
22 Ginsburg CM, Lowry W, Reisch JS. Absorption of lindane (gamma benzene hexachloride) in infants and children. *J Pediatr* 1977; **91**: 998–1000.
23 Pramanik AK, Hansen RC. Transcutaneous gamma benzene hexachloride absorption and toxicity in infants and children. *Arch Dermatol* 1979; **115**: 1224–5.
24 Solomon LM, Fahmer L, West DP. Gamma benzene hexachloride toxicity. *Arch Dermatol* 1977; **113**: 353–7.
25 Davies JE, Dedhia HV, Morgade C *et al*. Lindane poisonings. *Arch Dermatol* 1983: **119**: 142–4.
26 Lee B, Groth P. Suspected reaction to gamma benzene hexachloride. *JAMA* 1976; **236**: 2846.
27 Lee B, Groth P. Scabies: transcutaneous poisoning during treatment. *Pediatrics* 1977; **59**: 643.
28 Telch J, Jarvis DA. Acute intoxication with lindane (gamma benzene hexachloride). *Can Med Assoc J* 1982; **126**: 662–3.
29 Franz TJ, Lehman PA, Franz SF, Guin JD. Comparative percutaneous absorption of lindane and permethrin. *Arch Dermatol* 1996; **132**: 901–5.
30 Rasmussen JE. The problem of lindane. *J Am Acad Dermatol* 1981; **5**: 507–16.
31 Rasmussen JE. Lindane. A prudent approach. *Arch Dermatol* 1987; **123**: 1008–10.

32 Hanna NF, Clay JC, Harris JRW. *Sarcoptes scabiei* infestation treated with malathion liquid. *Br J Vener Dis* 1978; **54**: 354.
33 Burgess I, Robinson RJF, Robinson J *et al*. Aqueous malathion 0.5% as a scabicide: a clinical trial. *BMJ* 1986; **292**: 1172.
34 Schultz MW, Gomez M, Hansen RC *et al*. Comparative study of 5% permethrin cream and 1% lindane lotion for the treatment of scabies. *Arch Dermatol* 1990; **126**: 167–70.
35 Taplin D, Meinking TL, Porcelain SL *et al*. Permethrin 5% dermal cream: a new treatment for scabies. *J Am Acad Dermatol* 1986; **15**: 995–1001.
36 Van Der Rhee HJ, Farquhar JA, Vermeulen NPE. Efficacy and transdermal absorption of permethrin in scabies patients. *Acta Derm Venereol (Stockh)* 1989; **69**: 170–82.
37 Bennett CE, Keefe M, Reynolds JC. Perceptions of the incidence of scabies and efficacy of treatment in UK hospitals. *Br J Dermatol* 2000; **143**: 1337–8.
38 Biagi F, Delgado-Y-Garnica R. First therapeutic trials in the treatment of scabies with thiabendazole cream. *Int J Dermatol* 1974; **13**: 102–3.
39 Hernandez-Perez E. Topically applied thiabendazole in the treatment of scabies. *Arch Dermatol* 1976; **112**: 1400–1.
40 Cubela V, Yawalkar SJ. Clinical experience with crotamiton cream and lotion in the treatment of infants with scabies. *Br J Clin Pract* 1978; **32**: 229–31.
41 Walton SF, McKinnon M, Pizzutto S *et al*. Acaricidal activity of *Melaleuca alternifolia* (tea tree) oil: *in vitro* sensitivity of *Sarcoptes scabiei* var *hominis* to terpinen-4-ol. *Arch Dermatol* 2004; **140**: 563–6.
42 Heukelbach J, Feldmeier H. Scabies. *Lancet* 2006; **367**: 1767–74.
43 Del Giudice P, Marty P. Ivermectin. New therapeutic weapon in dermatology? *Arch Dermatol* 1999; **135**: 705–6.
44 Del Giudice P. Ivermectin in scabies. *Curr Opin Infect Dis* 2002; **15**: 123–6.
45 Dourmishev AL, Dourmishev LA, Schwartz RA. Ivermectin: pharmacology and application in dermatology. *Int J Dermatol* 2005; **44**: 981–8.
46 Glaziou P, Cartel JL, Alzieu P *et al*. Comparison of ivermectin and benzyl benzoate for treatment of scabies. *Trop Med Parasitol* 1993; **44**: 331–2.
47 Usha V, Gopalakrishnan Nair TV. A comparative study of oral ivermectin and topical permethrin cream in the treatment of scabies. *J Am Acad Dermatol* 2000; **42**: 236–40.
48 Chouela EN, Abeldaño AM, Pellerano G *et al*. Equivalent therapeutic efficacy and safety of ivermectin and lindane in the treatment of human scabies. *Arch Dermatol* 1999; **135**: 651–5.
49 Youssef MYM, Sadaka HAH, Eissa MM, El-Ariny AF. Topical application of ivermectin for human ectoparasites. *Am J Trop Med Hyg* 1995; **53**: 652–3.
50 Gardon J, Gardon-Wendel N, Demanga-Ngangue *et al*. Serious reactions after mass treatment of onchocerciasis with ivermectin in an area endemic for *Loa loa* infection. *Lancet* 1997; **350**: 18–22.
51 Barkwell R, Shields S. Deaths associated with ivermectin treatment of scabies. *Lancet* 1997; **349**: 1144–5.
52 Reintjes R, Hoek C. Deaths associated with ivermectin for scabies. *Lancet* 1997; **350**: 215.
53 Coyne PE, Addiss DG. Deaths associated with ivermectin for scabies. *Lancet* 1997; **350**: 215–6.
54 Alexander NDE, Bockarie MJ, Kastens WA *et al*. Absence of ivermectin-associated excess deaths. *Trans R Soc Trop Med Hyg* 1998; **92**: 342.
55 Del Giudice P, Marty P, Gari-Toussaint M, Le Fichoux Y. Ivermectin in elderly patients. *Arch Dermatol* 1999; **135**: 351–2.
56 Del Mar Sáez-de-Ocariz M, McKinster CD, Orozco-Covarrubias L *et al*. Treatment of 18 children with scabies or cutaneous larva migrans using ivermectin. *Clin Exp Dermatol* 2002; **27**: 264–7.
57 Leppard B, Naburi AE. The use of ivermectin in controlling an outbreak of scabies in a prison. *Br J Dermatol* 2000; **143**: 520–3.
58 Currie BJ, Harumal P, McKinnon M, Walton SF. First documentation of *in vivo* and *in vitro* ivermectin resistance in *Sarcoptes scabiei*. *Clin Infect Dis* 2004; **39**: e8–12.
59 Larangeira de Almeida H Jr. Treatment of steroid-resistant nodular scabies with topical pimecrolimus. *J Am Acad Dermatol* 2005; **53**: 357–8.

Crusted scabies

Synonym
- Norwegian scabies

Table 38.2 Contributory factors associated with crusted (Norwegian) scabies.

Skin anaesthesia
Sensory neuropathy
Spinal injury
Hansen's disease
Mental impairment
Down's syndrome
Dementia
Physical incapacity
Paresis
Severe arthropathy
Epidermolysis bullosa
Immunosuppression
Drugs
Leukaemia/lymphoma
HIV/AIDS
HTLV-1 infection

The appellation 'Norwegian' derives from the description in Norway by Danielssen and Boeck [1] of a type of scabies in which huge numbers of mites were present in lepers. Hebra referred to this as 'scabies Norvegica Boecki' [2]. It has been suggested that 'Norwegian' should be discarded and replaced by 'crusted' [3,4].

Crusted scabies is an infection with *Sarcoptes scabiei* var. *hominis* in which the mite population is enormous, and may number millions. The grossly thickened horny layer is honeycombed with cavities which contain large numbers of mites, and these are shed into the environment of the patient [5]. An undiagnosed case of crusted scabies may be the source of an outbreak of common scabies.

Aetiology and pathogenesis [6,7] (Table 38.2). In common scabies, there are few mites, probably because scratching destroys the burrows. A good standard of hygiene may also help to control the mite population. In crusted scabies, the host's response to the mites is modified, allowing them to multiply.

Patients with skin anaesthesia secondary to sensory neuropathy or spinal injury obviously do not perceive itch and therefore do not scratch [8]. Patients who are mentally retarded or suffer from dementia may develop crusted scabies [9], and Down's syndrome is a frequent association [3,10–13]. The reason for this association with mental abnormality is not completely understood, but lack of appreciation of pruritus may be important.

In some patients who are physically severely incapacitated, as a result of paresis [14,15] or severe arthropathy, the main reason for the development of crusted scabies is probably a physical inability to scratch in response to itching. It has also been described as a complication of dystrophic epidermolysis bullosa [16], in which an inability to scratch because of an absence of fingernails may have been a contributory factor, and in a patient with epidermolysis bullosa simplex [17].

Crusted scabies may develop in patients who are immunosuppressed, either as a result of disease [18–20] or therapy [20–23]—including with infliximab [24]. In recent years there have been



Fig. 38.34 Crusted (Norwegian) scabies.

numerous reports of its occurrence in patients with HIV infection, and it is also an indicator of HTLV-1 infection [25–29]. Crusted scabies has also resulted from inappropriate use of potent fluorinated topical steroids [30–32] and pimecrolimus [33]. Suppression of sensitivity to the mites reduces itching, so there is less scratching and destruction of burrows.

Crusted scabies sometimes occurs in otherwise healthy individuals [34,35], and in northern Australia, where crusted scabies is a problem in the Aboriginal population, 42% of a series of 78 patients had no identifiable risk factors [36].

Clinical features [6,36,37]. Large, warty crusts form on the hands and feet (Fig. 38.34), and the palms and soles may be irregularly thickened and fissured. The nail apparatus is frequently affected, with masses of horny debris accumulating beneath thickened and discoloured nails (Fig. 38.35). Longitudinal nail splitting has been described [38]. Erythema and scaling occur on the face, neck, scalp (Fig. 38.36) and trunk, and may generalize. Localized genital crusting may also occur [39,40]. The extent of the erythroderma and the warty plaques varies greatly, and either may predominate. It has been suggested that *Staphylococcus aureus* colonizing burrows might play a part in initiating the erythroderma [41]. Itching is often absent or slight, but may occasionally be severe. Generalized lymphadenopathy is present in some cases, and blood eosinophilia and elevated IgE levels are common [36,42].

Crusted scabies may masquerade as hyperkeratotic eczema, psoriasis, Darier's disease [43], contact dermatitis [44] and Langerhans' cell histiocytosis [45].

The diagnosis is readily confirmed by examination of scrapings, which will be teeming with mites and eggs.



Fig. 38.35 Grossly dystrophic nails in crusted scabies.

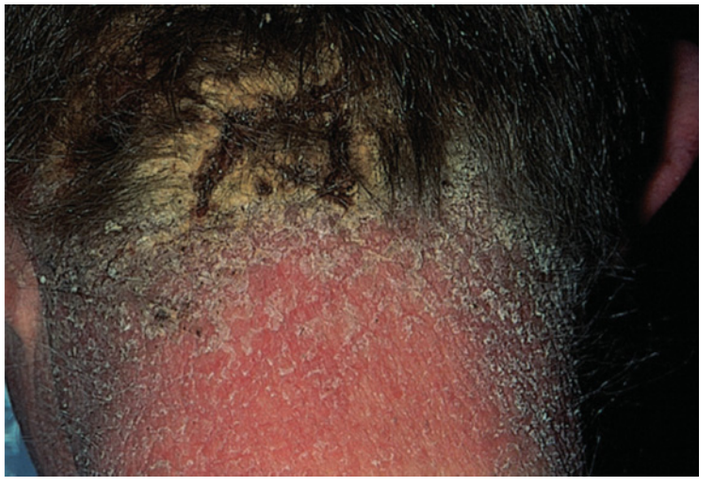


Fig. 38.36 Severe scalp involvement in crusted scabies.

Treatment [37,46–51]. A patient with crusted scabies should be admitted to hospital for treatment. They may be treated with topical scabicides, but prolonged therapy involving several applications is often required, and incomplete response is not uncommon. In recent years, ivermectin has become the treatment of choice for crusted scabies, either alone or in combination with a topical agent. The most effective regimen appears to be two doses of ivermectin (200 μg/kg body weight), separated by an interval of a week, combined with a topical scabicide. The nails should be cut short, and a topical scabicide applied beneath their free edges.

However, Currie *et al*. [52] reported evidence of resistance to ivermectin in two patients who had received multiple doses for recurrences of crusted scabies.

Institutional outbreaks of scabies. There are numerous reports of outbreaks affecting both patients and medical personnel in hospitals and residential care/nursing homes, and many of these are associated with undiagnosed cases of crusted scabies. Nursing and medical staff in contact with such a patient may develop the

common type of scabies, but frequently the first lesions seen are pruritic papules on the limbs, without any clinical evidence of burrows. The presence of papules and nodules surmounted by burrows, on the abdomen, buttocks and limbs of several contacts of a case of crusted scabies has been described [53].

The management of an institutional outbreak of scabies requires control measures to deal with all residents/patients and health-care workers [54–58]. In this situation, all the patients or residents should be examined to detect any cases of severe or crusted scabies, and such individuals should be isolated until cured. Any personnel coming into contact with such a patient should wear long-sleeved gowns and gloves. All individuals on an affected ward or in a residential home, and all medical and nursing staff and their families, should receive prophylaxis with a topical scabicide. Bedding should be laundered. It has been suggested that during treatment of institutional outbreaks, particular attention should be paid to the nails, in view of the subungual persistence of mites [59]. Cases of crusted scabies should be treated as outlined above.

References

1 Danielssen DC, Boeck W. *Traite de la Spedalsked ou Elephantiasis des Grecs*. Paris: JB Baillière, 1848.
2 Hebra F von. S. Norvegica. In: *On Diseases of the Skin including the Exanthemata*, Vol. II. London: The New Sydenham Society, 1868: 213–6.
3 Calnan CD. Crusted scabies. *Br J Dermatol* 1950; **62**: 71–8.
4 Parish LC, Lomholt G. Crusted scabies: alias Norwegian scabies. *Int J Dermatol* 1976; **15**: 747–8.
5 Carslaw RW, Dobson RM, Hood AJK *et al*. Mites in the environment of cases of Norwegian scabies. *Br J Dermatol* 1975; **92**: 333–7.
6 Alexander JO'D. *Arthropods and Human Skin*. Berlin: Springer-Verlag, 1984.
7 Burgess I. *Sarcoptes scabiei* and scabies. *Adv Parasitol* 1994; **33**: 235–92.
8 Carslaw RW. Scabies in a spinal injuries ward. *BMJ* 1975; **2**: 617.
9 Herridge CF. Norwegian scabies (crusted scabies). *BMJ* 1963; **1**: 239–40.
10 Burks JW Jr, Jung R, George WM. Norwegian scabies. *Arch Dermatol* 1956; **74**: 131–40.
11 Hubler WR Jr, Clabaugh W. Epidemic Norwegian scabies. *Arch Dermatol* 1976; **112**: 179–81.
12 Maguire HC Jr, Kligman AM. Norwegian scabies. *Arch Dermatol* 1960; **82**: 62–4.
13 Ingram JT. Ward epidemic from Norwegian scabies. *Br J Dermatol* 1951; **63**: 311–7.
14 Wolf R, Krakowski A. Atypical crusted scabies. *J Am Acad Dermatol* 1987; **17**: 434–6.
15 Dick GF, Burgdorf WHC, Gentry WC. Norwegian scabies in Bloom's syndrome. *Arch Dermatol* 1979; **115**: 212–3.
16 Van Der Wal VB, Van Voorst Vader PC, Mandema JM, Jonkman MF. Crusted (Norwegian) scabies in a patient with dystrophic epidermolysis bullosa. *Br J Dermatol* 1999; **141**: 918–21.
17 Torrelo A, Zambrano A. Crusted scabies in a girl with epidermolysis bullosa simplex. *Br J Dermatol* 2000; **142**: 197–8.
18 Logan JCP, Grant PW, Keczkes K. Norwegian scabies and lymphatic leukaemia. *Br J Dermatol* 1967; **79**: 303–5.
19 Suzumiya J, Sumiyoshi A, Kuroki Y *et al*. Crusted (Norwegian) scabies with adult T-cell leukemia. *Arch Dermatol* 1985; **121**: 903–4.
20 Yonekura K, Kanekura T, Kanzaki T *et al*. Crusted scabies in an adult T-cell leukaemia/lymphoma patient successfully treated with oral ivermectin. *J Dermatol* 2006; **33**: 139–41.
21 Barnes L, McCallister RE, Lucky AW. Crusted (Norwegian) scabies. Occurrence in a child undergoing bone marrow transplant. *Arch Dermatol* 1987; **123**: 95–7.
22 Espy PD, Jolly HW Jr. Norwegian scabies. Occurrence in a patient undergoing immunosuppression. *Arch Dermatol* 1976; **112**: 193–6.
23 Paterson WD, Allen BR, Beveridge CW. Norwegian scabies during immunosuppressive therapy. *BMJ* 1973; **4**: 211–2.
24 Pipitone MA, Adams B, Sheth A *et al*. Crusted scabies in a patient being treated with infliximab for juvenile rheumatoid arthritis. *J Am Acad Dermatol* 2005; **52**: 719–20.
25 Daisley H, Charles W, Suite M. Crusted (Norwegian) scabies as a pre-diagnostic indicator for HTLV-1 infection. *Trans R Soc Trop Med Hyg* 1993; **87**: 295.
26 Del Giudice P, Sainte Marie D, Gerard Y *et al*. Is crusted (Norwegian) scabies a marker of adult T cell leukemia/lymphoma in human T lymphotropic type 1-seropositive patients? *J Infect Dis* 1997; **176**: 1090–2.
27 Brites C, Weyll M, Pedroso C, Badaró R. Severe and Norwegian scabies are strongly associated with retroviral (HIV-1/HTLV-1) infection in Bahia, Brazil. *AIDS* 2002; **16**: 1292–3.
28 Bergman JN, Dodd WA, Trotter MJ *et al*. Crusted scabies in association with human T-cell lymphotropic virus 1. *J Cutan Med Surg* 1999; **3**: 148–52.
29 Blas M, Bravo F, Castillo W *et al*. Norwegian scabies in Peru: the impact of human T cell lymphotropic virus type 1 infection. *Am J Trop Med Hyg* 2005; **72**: 855–7.
30 Clayton R, Farrow S. Norwegian scabies following topical steroid therapy. *Postgrad Med J* 1975; **51**: 657–9.
31 Macmillan AL. Unusual features of scabies associated with topical fluorinated steroids. *Br J Dermatol* 1972; **87**: 496–7.
32 Millard LG. Norwegian scabies developing during treatment with fluorinated steroid therapy. *Acta Derm Venereol (Stockh)* 1977; **57**: 86–8.
33 Ruiz-Maldonado R. Pimecrolimus related crusted scabies in an infant. *Pediatr Dermatol* 2006; **23**: 299–300.
34 Judge MR, Kobza-Black A. Crusted scabies in pregnancy. *Br J Dermatol* 1995; **132**: 116–9.
35 Baysal V, Yildirim M, Türkman C *et al*. Crusted scabies in a healthy infant. *J Eur Acad Dermatol Venereol* 2004; **18**: 188–90.
36 Roberts LJ, Huffam SE, Walton SF, Currie BJ. Crusted scabies: clinical and immunological findings in seventy-eight patients and a review of the literature. *J Infect* 2005; **50**: 375–81.
37 Guldbakke KK, Khachemoune A. Crusted scabies: a clinical review. *J Drugs Dermatol* 2006; **5**: 221–7.
38 Weatherhead SC, Speight EL. Crusted scabies as a cause of longitudinal nail splitting. *Clin Exp Dermatol* 2004; **29**: 315.
39 Perna AG, Bell K, Rosen T. Localized genital Norwegian scabies in an AIDS patient. *Sex Transm Infect* 2004; **80**: 72–3.
40 Bakos L, Reusch MC, D'Elia P *et al*. Crusted scabies of the vulva. *J Eur Acad Dermatol Venereol* 2007; **21**: 682–4.
41 Shelley WB, Shelley ED, Burmeister V. *Staphylococcus aureus* colonization of burrows in erythrodermic Norwegian scabies. *J Am Acad Dermatol* 1988; **19**: 673–8.
42 Arlian LG, Morgan MS, Estes SA *et al*. Circulating IgE in patients with ordinary and crusted scabies. *J Med Entomol* 2004; **41**: 74–7.
43 Anolik MA, Rudolph RI. Scabies simulating Darier disease in an immunosuppressed host. *Arch Dermatol* 1976; **112**: 73–4.
44 Wolf R, Wolf D, Viskoper RJ *et al*. Norwegian-type scabies mimicking contact dermatitis. *Postgrad Med* 1985; **78**: 228–30.
45 Kartono F, Lee EW, Lanum D *et al*. Crusted Norwegian scabies in an adult with Langerhans cell histiocytosis. *Arch Dermatol* 2007; **143**: 626–8.
46 Meinking TL, Taplin D, Hermida JL *et al*. The treatment of scabies with ivermectin. *N Engl J Med* 1995; **333**: 26–30.
47 Huffam SE, Currie BJ. Ivermectin for *Sarcoptes scabiei* hyperinfestation. *Int J Infect Dis* 1998; **2**: 152–4.
48 Chosidow O. Scabies and pediculosis. *Lancet* 2000; **355**: 819–26.
49 Alberici F, Pagani L, Ratti G, Viale P. Ivermectin alone or in combination with benzyl benzoate in the treatment of human immunodeficiency virus-associated scabies. *Br J Dermatol* 2000; **142**: 969–72.
50 Del Giudice P. Ivermectin in scabies. *Curr Opin Infect Dis* 2002; **15**: 123–6.
51 Santoro AF, Rezac MA, Lee JB. Current trends in ivermectin usage for scabies. *J Drugs Dermatol* 2003; **2**: 397–401.
52 Currie BJ, Harumal P, McKinnon M *et al*. First documentation of *in vivo* and *in vitro* ivermectin resistance in *Sarcoptes scabiei*. *Clin Infect Dis* 2004; **39**: e8–12.
53 Moberg SAW, Lowhagen G-BE, Hersle KS. An epidemic of scabies with unusual features and treatment resistance in a nursing home. *J Am Acad Dermatol* 1984; **11**: 242–4.
54 Andersen BM, Haugen H, Rasch M *et al*. Outbreak of scabies in Norwegian nursing homes and home care patients: control and prevention. *J Hosp Infect* 2000; **45**: 160–4.

55 Paasch U, Haustein UF. Management of endemic outbreaks of scabies with allethrin, permethrin and ivermectin. *Int J Dermatol* 2000; **39**: 463–70.
56 Obasanjo OO, Wu P, Conlon M *et al*. An outbreak of scabies in a teaching hospital: lessons learned. *Infect Cont Hosp Ep* 2001; **22**: 13–18.
57 Sheinfeld N. Controlling scabies in institutional settings: a review of medications, treatment models, and implementation. *Am J Clin Dermatol* 2004; **5**: 31–7.
58 Vorou R, Remoudaki HD, Maltezou HC. Nosocomial scabies. *J Hosp Infect* 2007; **65**: 9–14.
59 Scher RK. Subungual scabies. *Am J Dermatopathol* 1983; **5**: 187–9.

Animal scabies

Transmission of animal scabies to humans is probably rare, because of the relative host specificity of the mites [1]. However, recurrent exposure to animal scabies mites can produce troublesome and diagnostically puzzling lesions.

Many varieties of *Sarcoptes scabiei* have been incriminated, including the following.

1 The mites causing sarcoptic mange in horses, cattle, buffalo, pigs, camels, monkeys, sheep and goats [2–7].
2 *Sarcoptes scabiei* var. *canis* commonly causes transient skin lesions in those in contact with infested dogs [8–14]. Exceptionally, scrapings from human skin have shown mites and eggs, and symptoms have persisted after contact with the animal has ceased [15]. Canine scabies has been experimentally transferred to humans [16]. Affected animals have areas of scaling and hair loss on the ears, face and limbs [17] (Chapter 2).
3 *Notoedres cati*, the cause of sarcoptic mange in cats, is almost unknown in the UK, but where it is endemic in the cat population, as in India [18] and Japan [19], human skin lesions may occur.

Clinical features. Skin lesions resulting from contact with animal scabies vary in extent and distribution, according to the mode of exposure. The eruption is usually composed of small, pruritic weals or papules, which are frequently excoriated, and resemble human scabies, but without burrows. Lesions from exposure to sarcoptic mange in dogs and notoedric mange in cats usually occur at sites of contact with the animal, principally the chest, abdomen, thighs and forearms.

Treatment. If contact with animal scabies is suspected, the diagnosis can only be confirmed by examining the suspect animal and obtaining skin scrapings from it. Affected animals should be treated by a veterinary practitioner.

Human skin lesions are self-limiting, and will resolve once exposure to the affected animal has ceased, or it has been treated.

References

1 Arlian LG, Runyan RA, Estes SA. Cross infestivity of *Sarcoptes scabiei*. *J Am Acad Dermatol* 1984; **10**: 979–86.
2 Chakrabarti A, Chatterjee A, Chakrabarti K *et al*. Human scabies from contact with water buffaloes infested with *Sarcoptes scabiei* var. *bubalis*. *Ann Trop Med Parasitol* 1981; **75**: 353–7.
3 Chakravorty AN, Ghosh S, Banerjee AK. Case notes of scabies in a family transmitted from goats. *Indian Med Gaz* 1953; **88**: 153–4.
4 Fain A. Epidemiological problems of scabies. *Int J Dermatol* 1978; **17**: 20–30.
5 Goldman L, Feldman MD. Human infestation with scabies of monkeys. *Arch Dermatol Syphilol* 1949; **59**: 175–8.
6 Macdonald RAS. Observations on an extensive human infection by sarcoptic mange of the horse. *Lancet* 1922; **i**: 738–9.
7 Toomey N. Scabies of animal origin. *Urol Cutan Rev* 1922; **26**: 473–89.
8 Beck AL Jr. Animal scabies affecting man. *Arch Dermatol* 1965; **91**: 54–5.
9 Charlesworth EN, Johnson JL. An epidemic of canine scabies in man. *Arch Dermatol* 1974; **110**: 572–4.
10 Emde RN. Sarcoptic mange in the human. *Arch Dermatol* 1961; **84**: 633–6.
11 Ruiz-Maldonado R, Tamayo L, Dominguez J. Norwegian scabies due to *Sarcoptes scabiei* var. *canis*. *Arch Dermatol* 1977; **113**: 1733.
12 Smith EB, Claypoole TF. Canine scabies in dogs and humans. *JAMA* 1967; **199**: 59–64.
13 Tannenbaum MH. Canine scabies in man: a report of human mange. *JAMA* 1965; **193**: 141–2.
14 Thomsett LR. Mite infestations of man contracted from dogs and cats. *BMJ* 1968; **3**: 93–5.
15 Norins AL. Canine scabies in children. 'Puppy dog' dermatitis. *Am J Dis Child* 1969; **117**: 239–42.
16 Estes SA, Kummel B, Arlian L. Experimental canine scabies in humans. *J Am Acad Dermatol* 1983; **9**: 397–401.
17 Scott DW, Miller WH, Griffin CE. *Muller and Kirk's Small Animal Dermatology*. Philadelphia: WB Saunders, 2000.
18 Chakrabarti A. Human notoedric scabies from contact with cats infested with *Notoedres cati*. *Int J Dermatol* 1986; **25**: 646–8.
19 Ito K, Ito Y, Kondo S *et al*. Animal scabies in humans. *Bull Pharmacol Res Inst* 1968; **77**: 1–8.

Family Knemidokoptidae

Knemidokoptes mutans causes scaly leg in domestic poultry, and *Mesoknemidokoptes laevis* is a closely related mite which causes depluming itch in poultry—both have caused skin lesions in humans [1].

Family Psoroptidae

Mites of the family Psoroptidae cause mange in domestic animals. Species of *Chorioptes* and *Psoroptes* from cattle, horses and sheep have occasionally affected humans [1]. *Otodectes cynotis* is a common parasite in the ears of cats and dogs, and has been discovered in the ears of a patient suffering from otitis externa [2]. It was also considered to be responsible for a pruritic dermatosis in a patient whose dog was infested [3].

Family Listrophoridae

Listrophorus gibbus, a common parasite of the domestic rabbit [4], has been reported as causing papular urticaria in a child [5].

References

1 Toomey N. Scabies of animal origin. *Urol Cutan Rev* 1922; **26**: 473–89.
2 Van de Heyning J, Thienpont D. Otitis externa caused by the mite *Otodectes cynotis*. *Laryngoscope* 1977; **87**: 1938–41.
3 Herwick RP. Lesions caused by canine ear mites. *Arch Dermatol* 1978; **114**: 130.
4 Owen D. Common parasites of laboratory rodents and lagomorphs. *Medical Research Council Laboratory Animals Centre Handbook*, No. 1. London: HMSO, 1972.
5 Burns DA. Papular urticaria produced by the mite *Listrophorus gibbus*. *Clin Exp Dermatol* 1987; **12**: 200–1.

Mites of stored products [1,2]

Storage mite allergy is a well-recognized problem in certain occupations, including farmers, grain elevator workers and bakers. In addition to respiratory allergy, skin lesions can occur.

Family Acaridae

These mites attack flour, grain, dried meat, cheese and dried fruit.

Acarus siro is the most important pest of storage premises, and is found on flour, grain and, occasionally, cheese. It may cause skin lesions on those who handle these products.

Tyrophagus putrescentiae [3–6] is mostly found in stored food with a high fat and protein content such as dried eggs, ham, herring meal, cheese, nuts and copra. *Tyrophagus longior* is found on cheese, grain, hay and copra [7].

Suidasia nesbitti is particularly associated with wheat pollards and bran, and has been recorded as causing dermatitis in humans [8].

Rhizoglyphus species occur on flower bulbs and have caused dermatitis in persons handling stored bulbs.

Family Carpoglyphidae

Carpoglyphus passularum (*lactis*) is found on all kinds of dried fruit, and may cause dermatitis [9,10].

Family Glycyphagidae

Glycyphagus domesticus is a widely distributed species, often found in large numbers on plant and animal remains in houses and stables. It has also been found in flour, wheat, hay, tobacco, cheese and ham. *Glycyphagus destructor* is often abundant in hay, straw and grain.

Pathogenesis of food-mite dermatitis. It has been suggested that the dermatitis caused by these mites, which are not haematophagous, results from irritation by mite products, either faecal or secretory [5]. However, the pathomechanics of the response do not appear to have been studied in detail.

Dockers and warehouse workers handling stored products are most at risk, but shopkeepers and domestic workers are occasionally affected.

Clinical features [11]. The eruption provoked by these mites is sometimes called 'copra itch' or 'grocer's itch', and is often composed of minute, intensely pruritic papules or papulovesicles on exposed parts of the body, principally on the head and neck, and forearms, but occasionally more widespread. The appearance of the eruption on the face may suggest an acute contact dermatitis.

References

1 Hughes AM. *The Mites of Stored Food and Houses*, 2nd edn. Ministry of Agriculture, Fisheries and Food Technical Bulletin, No. 9. London: HMSO, 1976.
2 Tee RD. Allergy to storage mites. *Clin Exp Allergy* 1994; **24**: 636–40.
3 Estévez DQ. Occupational contact urticaria-dermatitis by *Tyrophagus putrescentiae*. *Contact Dermatitis* 2006; **55**: 308–9.
4 Fields JP, Hoke AW, Cronce PC. Cheese mite dermatitis. *Arch Dermatol* 1968; **98**: 669–70.
5 Vidal C, Rial A. Airborne contact dermatitis from *Tyrophagus putrescentiae*. *Contact Dermatitis* 1998; **33**: 181.
6 Armentia A, Fernández A, Pérez-Santos C *et al*. Occupational allergy to mites in salty ham, chorizo and cheese. *Allergol Immunopathol Madr* 1994; **22**: 152–4.
7 Thomas EWP. Dermatitis due to *Tyroglyphus longior* Gerv. var Castellani, Hirst in cheese dust. *Br J Dermatol* 1942; **54**: 313–9.
8 Kilpiö O, Pirilä V. A new tyroglyphid mite causing dermatitis. *Acta Derm Venereol Suppl. (Stockh)* 1952; **29**: 197–200.
9 Pirilä V. On cheese and fig mite dermatitis. *Acta Derm Venereol (Stockh)* 1951; **31**: 630–7.
10 Pirilä V, Kilpiö O. Occupational mite dermatitis. *Acta Derm Venereol (Stockh)* 1954; **34**: 368–71.
11 Alexander JO'D. Skin eruptions caused by mites from stored food. In: *Arthropods and Human Skin*. Berlin: Springer-Verlag, 1984: 345–52.

House-dust mites (HDM)

Dermatophagoides pteronyssinus, the HDM, was first discovered by Trouessart in dust shaken from tanned mammal skins [1]. It was subsequently established that it is widely distributed in the human environment in house dust and beds [2,3]. It occurs worldwide, and has been reported from all inhabited continents [4]. It is commonly associated with *Euroglyphus maynei* and *Dermatophagoides farinae*, which are related species in the same family, the Pyroglyphidae. In the USA, *D. farinae* appears to be more plentiful in house dust than *D. pteronyssinus* [5].

The largest numbers of mites are found in houses that are damp and inadequately heated [4]. Numbers vary seasonally, increasing in early summer to reach a maximum by early autumn. In the UK, numbers are low in winter and increase in spring, when temperature and relative humidity rise [6].

The main food of *D. pteronyssinus* is human skin scales [7]. Xerophylic moulds, especially *Aspergillus penicilloides*, are essential for the growth and survival of *D. pteronyssinus*. The moulds digest lipid in the scales which is toxic to the mites.

The major HDM allergens (Der p1 and Der f1) are present in the faecal pellets.

Role in atopic eczema [8–13]. The role of the HDM in the pathogenesis of atopic eczema remains controversial, although there is increasing evidence of involvement of HDM allergen in the disease.

Several studies have indicated that, in many individuals, the condition can be improved by techniques designed to reduce exposure to HDM allergen [14–20], although the benefits on clinical status appear to be greater in children than in adults [21], and it is not possible to predict which patients will benefit. One study demonstrated that the houses of patients with moderate to severe atopic eczema had more HDMs than controls [22]. Measures employed to reduce the HDM allergen load include regular vacuum cleaning of carpets, or their removal, bedding covers made of material such as microporous Goretex®, and the use of acaricides, including benzyl benzoate and permethrin [23].

Hepple and Macmillan [24] have attributed a case of purpuric dermatosis to house-dust mite allergy.

References

1 Hughes AM. *The Mites of Stored Food and Houses*. Ministry of Agriculture, Fisheries and Food Technical Bulletin 9. London, HMSO, 1976.
2 Maunsell K, Wraith DG, Cunnington AM. Mites and house-dust allergy in bronchial asthma. *Lancet* 1968; **i**: 1267–70.
3 Sesay HR, Dobson RM. Studies on the mite fauna of house dust in Scotland with special reference to that of bedding. *Acarologia* 1972; **14**: 384–92.
4 Spieksma FThM, Spieksma-Boezeman MIA. The mite fauna of house dust with particular reference to the house dust mite *Dermatophagoides pteronyssinus* (Trouessart 1897) (Psoroptidae: Sarcoptiformes). *Acarologia* 1967; **9**: 226–41.
5 Wharton GW. Mites and commercial extracts of house dust. *Science* 1970; **167**: 1382–3.
6 Hughes AM, Maunsell K. A study of a population of house dust mite in its natural environment. *Clin Allergy* 1973; **3**: 127–31.

7 Voorhorst R, Spieksma FThM, Varekamp H. *House-dust Atopy and the House-dust Mite Dermatophagoides pteronyssinus (Trouessart 1897)*. Leiden: Stafleu's Scientific Publishing, 1969.
8 Platts-Mills TAE, Mitchell EB, Rowntree S *et al*. The role of house dust mite allergens in atopic dermatitis. *Clin Exp Dermatol* 1983; **8**: 233–47.
9 Tupker RA, De Monchy JGR, Coenraads PJ *et al*. Induction of atopic dermatitis by inhalation of house dust mite. *J Allergy Clin Immunol* 1996; **97**: 1064–70.
10 Reitamo S, Visa K, Kahonen *et al*. Eczematous reactions in atopic patients caused by epicutaneous testing with inhalent allergens. *Br J Dermatol* 1986; **114**: 303–9.
11 Norris PG, Schofield O, Camp RDR. A study of the role of house dust mite in atopic dermatitis. *Br J Dermatol* 1988; **118**: 435–40.
12 Shah D, Hales J, Cooper D, Camp R. Recognition of pathogenically relevant house dust mite hypersensitivity in adults with atopic dermatitis: a new approach? *J Allergy Clin Immunol* 2002; **109**: 1012–8.
13 Beltrani VS. The role of house dust mites and other aeroallergens in atopic dermatitis. *Clin Dermatol* 2003; **21**: 177–82.
14 Casimir GJA, Duchateau J, Gossart B *et al*. Atopic dermatitis: role of food and house dust mite allergens. *Pediatrics* 1993; **92**: 252–6.
15 August PJ. House dust mite causes atopic eczema. A preliminary study. *Br J Dermatol* 1984; **111** (Suppl. 26): 10–11.
16 Roberts DLL. House dust mite avoidance and atopic dermatitis. *Br J Dermatol* 1984; **110**: 735–6.
17 Tan BB, Weald D, Strickland I, Friedmann PS. Double-blind controlled trial of effect of housedust-mite allergen avoidance on atopic dermatitis. *Lancet* 1996; **347**: 15–18.
18 Ricci G, Patrizi A, Specchia F *et al*. Effect of house dust mite avoidance measures in children with atopic dermatitis. *Br J Dermatol* 2000; **143**: 379–84.
19 Friedmann PS. Dust mite avoidance in atopic dermatitis. *Clin Exp Dermatol* 1999; **24**: 433–7.
20 Arshad SH, Bateman B, Sadeghnejad A *et al*. Prevention of allergic disease during childhood by allergen avoidance: the Isle of Wight prevention study. *J Allergy Clin Immunol* 2007; **119**: 307–13.
21 Gutgesell C, Heise S, Seubert S *et al*. Double-blind placebo-controlled house dust mite control measures in adult patients with atopic dermatitis. *Br J Dermatol* 2001; **145**: 70–4.
22 Beck H-I, Korsgaard J. Atopic dermatitis and house dust mites. *Br J Dermatol* 1989; **120**: 245–51.
23 Cameron MM. Can house dust mite-triggered atopic dermatitis be alleviated using acaricides? *Br J Dermatol* 1997; **137**: 1–8.
24 Hepple S, Macmillan AL. Purpuric dermatosis due to house-dust mite (*Dermatophagoides* spp.) allergy: a case report. *Clin Allergy* 1973; **3**: 23–31.

Pyemotes mites

Pyemotes mites are all primarily parasites of insects or their larvae. They only affect humans when the latter come into contact with the food of their natural hosts.

The mite *Pyemotes tritici* preys on the larvae of many species of insect infesting grain, straw or hay, and stored foodstuffs. Another species, *P. ventricosus*, preys on the larvae of wood-boring beetles, including the common furniture beetle *Anobium punctatum*. There has been some confusion about nomenclature of *Pyemotes* species [1].

Pyemotes mites have been responsible for attacks of dermatitis in those shovelling grain or coming into contact with infested straw [2] and husk rice [3]. The dermatitis has been referred to by a number of terms, including 'barley itch', 'grain-shovellers' itch', 'grain itch', 'straw itch', 'cotton-seed dermatitis' and 'acarodermatitis urticarioides'. *Pyemotes* dermatitis has been reported in shop workers coming into contact with wheat used for decorative purposes [4–6]. Dermatitis in workers in a food mixing shed at a piggery was attributed to *P. herfsi* [7], and *P. zwoelferi* was incriminated in dermatitis acquired by contact with a package of everlasting flowers [8]. Dermatitis in a fisherman handling crab pots made of cherry wood was probably caused by *P. beckeri* [9].

An outbreak of dermatitis in a small hospital in Queensland, Australia, was attributed to *Pyemotes* mites originating in an adjacent grain storage facility [10].

Clinical features [11,12]. The lesions are urticated papules surmounted by vesicles; occasionally they may be bullous. They are often very numerous, and their distribution depends upon the mode of exposure. In grain handlers, they are usually on the forearms and neck, but they may be profuse around the waist and in the groins.

References

1 Moser JC. Biosystematics of the straw itch mite with special reference to nomenclature and dermatology. *Trans R Entomol Soc Lond* 1975; **127**: 185–91.
2 Booth BH, Jones RW. Epidemiological and clinical study of grain itch. *JAMA* 1952; **150**: 1575–9.
3 Uenotsuchi T, Satoh E, Kiryu H, Yano Y. *Pyemotes* dermatitis caused by indirect contact with husk rice. *Br J Dermatol* 2000; **143**: 680–2.
4 Rycroft RJG, Kennedy C. *Pyemotes* dermatitis in display artists. *Clin Exp Dermatol* 1981; **6**: 629–34.
5 Betz TG, Davis BL, Fournier PV *et al*. Occupational dermatitis associated with straw itch mites (*Pyemotes ventricosus*). *JAMA* 1982; **247**: 2821–3.
6 Grob M, Dorn K, Lautenschlager S. Eine kleine Epidemie durch *Pyemotes* spezies. *Hautarzt* 1998; **49**: 838–43.
7 Samsinak K, Chmela J, Vobrazkova E. *Pyemotes herfsi* (Oudemans, 1936) as causative agent of another mass dermatitis in Europe (Acari, Pyemotidae). *Folia Parasitol* 1979; **26**: 51–4.
8 Le Fichoux Y, Rack G, Motte P *et al*. Dermatite prurigineuse due à *Pyemotes zwoelferi* Krczal, 1963. A propos de plusieurs cas dans les Alpes-Maritimes. *Acta Trop* 1980; **37**: 83–9.
9 Hewitt M, Barrow GI, Miller DC *et al*. A case of *Pyemotes* dermatitis. With a note on the role of these mites in skin disease. *Br J Dermatol* 1976; **94**: 423–30.
10 Letchford J, Strungs I, Farrell D. *Pyemotes* species strongly implicated in an outbreak of dermatitis in a Queensland country hospital. *Pathology* 1994; **26**: 330–2.
11 Alexander JO'D. Pyemotes infestation. In: *Arthropods and Human Skin*. Berlin: Springer-Verlag, 1984: 317–25.
12 Fine RM, Scott HG. Straw itch mite dermatitis caused by *Pyemotes ventricosus*: comparative aspects. *South Med J* 1965; **58**: 416–20.

Family Tydeidae

Dermatitis in eight woodworkers in Perugia, Italy, was attributed to contact with *Pronematus davisi* mites on wood imported from North America [1]. This mite has a worldwide distribution, and is widespread in North America, where it usually lives under bark.

Reference

1 Stingeni L, Principato M. Epidemic occupational dermatitis caused by Pronematus davisi (Acari: Tydeidae). *Br J Dermatol* 2002; **146**: 929–30.

Plant mites

Some mites of the family Tetranychidae ('spider mites') cause cutaneous irritation or urtication in humans [1–4]. These mites are phytophagous and occur on every type of crop and ornamental plant. The name 'spider mites' is derived from the silk webbing they produce from palpal glands.

References

1 Derrick EH. A tetranychid mite which may attack man. *Aust J Sci* 1954; **17**: 67–8.

2 Desch CE Jr. Mites causing or transmitting human disease. In: Parish LC, Nutting WB, Schwartzman RM, eds. *Cutaneous Infestations of Man and Animal*. New York: Praeger, 1983: 261–83.
3 Manson DCM. The spider mite family Tetranychidae in New Zealand V—*Tetranychus* (*Tetranychus*) *moutensis*. A new species of spider mite from flax (*Phormium tenax* Forst). *N Z J Sci* 1970; **13**: 323–7.
4 Southcott RV. *Australian Harmful Arachnids and their Allies*. Mitcham: Southcott RV, 1978.
5 Jeebhay MF, Baatjies R, Chang YS *et al*. Risk factors for allergy due to the two-spotted spider mite (*Tetranychus urticae*) among table grape farm workers. *Int Arch Allergy Immunol* 2007; **144**: 143–9.

Cheyletiella mites

Biology and epidemiology. Species of *Cheyletiella* mites are non-burrowing, obligatory parasites of certain mammals, predominantly dogs, cats and rabbits. The entire life cycle is completed on the host. Each egg is attached to a hair shaft by means of a fine thread, which is woven around it into a cocoon-like structure by the female mite. The adult mite develops via a larval and two nymphal stages. Adult mites move rapidly over the skin surface in pseudotunnels in keratinous debris. They use their hook-like palpi to attach themselves to the host while feeding on tissue fluids [1,2].

Cheyletiella mites were first reported as attacking humans by Lomholt [3] of Copenhagen, and in 1938 a case was reported from England [4]. It gradually became apparent that *Cheyletiella* infestation of dogs, cats and rabbits was common in most European countries, in the USA [5], in Canada [6] and in Australasia [7,8]. The distribution of these mites is likely to be worldwide. Many earlier reports incorrectly identified the species as *C. parasitivorax* when it was probably *C. yasguri*. It is now clear that *C. parasitivorax* is predominantly a parasite of rabbits, *C. yasguri* of dogs, and *C. blakei* of cats [9,10]. The three species are morphologically very similar, but distinguishable by the shape of a special sensory organ on the dorsal surface of genu I [10–12].

It is not clear from the limited information available whether the incidence of these mites is increasing, or whether infestation is becoming more frequently recognized. An investigation in the Netherlands [13] of 41 households, in which two or more cats were kept, showed *Cheyletiella* infestation of the animals in 27; 20% of the human contacts had skin lesions. Any age, breed or sex of animal may be affected. In dogs, cheyletiellosis is particularly common in boxers.

Most affected animals are asymptomatic, but some may suffer from pruritus. The most obvious sign of infestation is excessive dandruff, especially on the back, which is often known as 'walking dandruff' [14] or 'mobile dandruff' by veterinary dermatologists.

Clinical features in humans [15–17]. The typical clinical picture is of large numbers of intensely itchy papules (Fig. 38.37). Surmounting the papules there may be tiny vesicles, and older lesions may show small areas of necrosis. Bullous lesions may occur [18,19]. The distribution of lesions corresponds to areas of contact with an infested animal, the abdomen and thighs being frequently involved as a result of an animal sitting on its owner's lap. The chest and arms may also be affected from carrying the animal. Dobrosavljevic *et al*. [20] reported a woman whose skin lesions were accompanied by eosinophilia, 'increased immune complexes' and rheumatological symptoms.



(a)

(b)

Fig. 38.37 (a) and (b) Abdominal lesions in cheyletiellosis.

In a case with an extensive eruption, intradermal skin testing with an extract of *Cheyletiella* mites produced both immediate and delayed hypersensitivity responses [21].

Confirmation of the diagnosis [22]. The diagnosis may be confirmed by examination of combings from the animal's coat for the presence of mites. The suspect animal should be placed on a sheet of black paper, and the coat, particularly along the back, vigorously combed, preferably with a fine-toothed comb. The debris collected can then be examined microscopically (Fig. 38.38).



Fig. 38.38 *Cheyletiella yasguri.*

Treatment. The affected animal should be treated by a veterinary practitioner. Human skin lesions may be treated with a topical antipruritic. Once an animal has been treated effectively, there will be no further lesions on its owner.

References

1 Fox TS, Ewing SA. Morphologic features, behavior, and life history of *Cheyletiella yasguri*. *Am J Vet Res* 1969; **30**: 269–85.
2 Miller WH Jr. *Cheyletiella* infestation. In: Parish LC, Nutting WB, Schwartzman RM eds. *Cutaneous Infestations of Man and Animal*. New York: Praeger, 1983: 255–60.
3 Lomholt S. To Tilfaelde af Dyrefnat hos Mennesket (*Cheiletiella parasitivorax*). *Hospitalstidende* 1918; **61**: 1098–9.
4 Davies JHT. Another acarine disease. *Br J Dermatol* 1938; **50**: 243–4.
5 Keh B. Intense pruritus in man and concurrent infestation of *Cheyletiella blakei* Smiley (Acari: Cheyletiellidae) on cats in a home in California. *Calif Vector Views* 1975; **22**: 1–4.
6 Ayalew L, Vaillancourt M. Observations on an outbreak of infestation of dogs with *Cheyletiella yasguri* and its public health implications. *Can Vet J* 1976; **17**: 184–91.
7 Moxham JW, Goldfinch TT, Heath ACG. *Cheyletiella parasitivorax* infestation of cats associated with skin lesions of man. *NZ Vet J* 1968; **16**: 50–2.
8 Taylor RM. *Cheyletiella parasitivorax* infestation of a cat and associated skin lesions of man. *Aust Vet J* 1969; **45**: 435.
9 Gething MA, Walton GS. Possible host specificity of *Cheyletiella* mites. *Vet Rec* 1972; **88**: 512.
10 Smiley RL. A review of the family Cheyletiellidae (Acarina). *Ann Entomol Soc Am* 1970; **63**: 1056–78.
11 Hewitt M, Turk SM. *Cheyletiella* sp. in the personal environment. *Br J Dermatol* 1974; **90**: 679–83.
12 Van Bronswijk JEMH, de Kreek EJ. *Cheyletiella* (Acari: Cheyletiellidae) of dog, cat and domesticated rabbit: a review. *J Med Entomol* 1976; **13**: 315–27.
13 Ottenschot TRF, Gil D. Cheyletiellosis in long-haired cats. *Tijdschrg Diergeneesk* 1978; **103**: 1104–8.
14 Scott DW, Miller WH, Griffin CE. *Muller and Kirk's Small Animal Dermatology*. Philadelphia: WB Saunders, 2000.
15 Alexander JO'D. Infestation with cheyletiellid mites. In: *Arthropods and Human Skin*. Berlin: Springer-Verlag, 1984: 327–35.
16 Hewitt M, Walton GS, Waterhouse M. Pet animal infestations and human skin lesions. *Br J Dermatol* 1971; **85**: 215–25.
17 Wagner R, Stallmeister N. *Cheyletiella* dermatitis in humans, dogs and cats. *Br J Dermatol* 2000; **143**: 1110–2.
18 Cvancara JL, Elston DM. Bullous eruption in a patient with systemic lupus erythematosus: mite dermatitis caused by *Cheyletiella blakei*. *J Am Acad Dermatol* 1997; **37**: 265–7.
19 Tsianakas P, Polack B, Pinquier L *et al*. La cheyletellose: une étiologie inhabituelle d'éruption vesiculobulleuse. *Ann Dermatol Venereol* 2000; **127**: 826–9.
20 Dobrosavljevic DD, Popovic ND, Radovanovic SS. Systemic manifestations of *Cheyletiella* infestation in man. *Int J Dermatol* 2007; **46**: 397–9.
21 Maurice PDL, Schofield O, Griffiths WAD. *Cheyletiella* dermatitis: a case report and the role of specific immunological hypersensitivity in its pathogenesis. *Clin Exp Dermatol* 1987; **12**: 381–4.
22 Burns DA. The investigation and management of arthropod bite reactions acquired in the home. *Clin Exp Dermatol* 1987; **12**: 114–20.

Harvest mites (Trombiculidae)

Harvest mites belong to the family Trombiculidae. More than 1200 species of trombiculids have been described, and many may attack human beings or livestock [1]. They are parasitic as larvae, but free-living as nymphs and adults. The larvae may cause troublesome dermatitis (trombidiosis; scrub itch), and some are important vectors of rickettsial disease. They have many common names throughout the world, for example orange tawny (Ireland), chigger, red bug (USA).

The eggs are laid in soil. The six-legged larvae which emerge climb onto low vegetation to wait for suitable vertebrate hosts. On the host the larvae move to areas where the skin is thin, such as the ears, axillae, groins and genitalia. There they pierce the skin with their cheliceral claws and inject saliva, which has cytolytic properties, into the epidermis [2]. This action forms a tube-like canal (stylosome) through which the mites feed on tissue fluids and cell debris. Once engorged, they fall to the ground and develop into eight-legged adults via a nymphal stage. Nymphs and adults feed on vegetable debris and the eggs of insects and other arthropods.

Neotrombicula autumnalis, the European harvest mite, is widely distributed throughout Europe. In the UK [3], the larval mites are most numerous from May to October, with a peak in September. The most favoured natural host is the rabbit. *Neotrombicula autumnalis* is not known to transmit disease.

Eutrombicula alfreddugesi and *E. splendens* are the most common chiggers attacking man in the USA, and *E. batatas* is an important dermatitis-producing species in South America.

In South-East Asia, Australia and the Pacific Islands, trombidiosis is commonly caused by *E. wichmanni*, and species of *Odontacarus* and *Schoengastia* [4,5].

Species of *Leptotrombidium* including *L. akamushi*, *L. pallidum* and *L. deliense* are important vectors of scrub typhus (tsutsugamushi disease), caused by *Orientia tsutsugamushi* [6]. *L. akamushi* has a wide distribution, ranging from Japan and China southwards through South-East Asia to Indonesia and eastwards throughout the Philippines to New Guinea. *L. deliense* occurs in China, the Indian subcontinent, Malaya, Indonesia, the Philippines, New Guinea and Australia. The natural hosts of *L. akamushi* and *L. deliense* are rodents and insectivores. *L. subquadratum* has been reported as a cause of pruritus and dermatitis in dogs and humans in South Africa [7].

Clinical features [4,8,9]. Humans are infested while working in or walking through grass or low vegetation. The response to the bites of harvest mites appears to be determined by the irritant effect of

the mites' saliva and an acquired hypersensitivity to salivary antigens. Within a few hours, erythematous macules appear at the sites of the bites, and these gradually develop into extremely itchy papules or papulovesicles.

The distribution of lesions is determined by the preference of mites for thin skin, and the clothing of the host. Lesions commonly occur around the feet and ankles, the groins and genitalia, the axillae, the wrists and antecubital fossae, and areas constricted by clothing, such as the waistline. In heavy infestations, the whole body may be covered in lesions.

Chigger bites on the penis in children are responsible for a seasonal acute hypersensitivity reaction in the USA known as the 'summer penile syndrome' [10].

Trombiculid mite bites have provided evidence to implicate a suspect in a murder investigation [11].

References

1 Kettle DS. Acari—Prostigmata and Gamasida (chiggers, blood-sucking mites). In: *Medical and Veterinary Entomology*. London: Croom Helm, 1984: 380–405.
2 Jones BM. The penetration of the host tissue by the harvest mite, *Trombicula autumnalis* Shaw. *Parasitology* 1950; **40**: 247–60.
3 Richards WS. The distribution and biology of the harvest mite in Great Britain (Trombiculidae, Acarina). *Parasitology* 1950; **40**: 118–26.
4 Alexander JO'D. Infestation with trombiculid mite larvae. In: *Arthropods and Human Skin*. Berlin: Springer-Verlag 1984: 353–62.
5 Sheals JG. Arachnida (scorpions, spiders, ticks etc.). In: Smith KGV, ed. *Insects and other Arthropods of Medical Importance*. London: The Trustees of the British Museum (Natural History), 1973: 417–72.
6 Uchikawa K, Kumada N. Endemic outbreaks of tsutsugamushi disease in Japan and vector chiggers (Trombidiformes: Trombiculidae). In: Channabasavanna GP, Viraktamath CA, eds. *Progress in Acarology*, Vol. 1. New Delhi: Oxford and IBH, 1988: 103–6.
7 Heyne H, Ueckermann EA, Coetzee L. First report of a parasitic mite, *Leptotrombidium* (*Hypotrombidium*) *subquadratum* (Lawrence) (Acari: Trombiculidae: Trombiculinae), from dogs and children in the Bloemfontein area, South Africa. *J S Afr Vet Assoc* 2001; **72**: 105–6.
8 Krinsky WL. Dermatoses associated with the bites of mites and ticks (Arthropoda: Acari). *Int J Dermatol* 1983; **22**: 75–91.
9 Poulson PA. Cutaneous reactions to some parasitic arthropods with special reference to the harvest mite (*Trombicula autumnalis* Shaw). *Acta Derm Venereol Suppl. (Stockh)* 1952; **29**: 290–3.
10 Smith GA, Sharma V, Knapp JF, Shields BJ. The summer penile syndrome: seasonal acute hypersensitivity reaction caused by chigger bites on the penis. *Pediatr Emerg Care* 1998; **14**: 116–8.
11 Pritchard JG, Kossoris PD, Leibovitch RA *et al*. Implications of trombiculid mite bites: report of a case and submission of evidence in a murder trial. *J Forensic Sci* 1986; **32**: 301–6.

Bird, rodent and reptile mites (Gamasida)

Family Dermanyssidae [1,2]

Dermanyssid mites are haematophagous parasites of birds and mammals. *Dermanyssus gallinae* (Fig. 38.39), the red poultry mite, is a common parasite of domestic and wild birds. Poultry keepers, veterinary practitioners and others in direct contact with birds are sometimes attacked. Other dermanyssid mites responsible for dermatitis include *D. hirundinis* and *D. americanus*. Avian mites may enter buildings from birds' nests via windows, ventilation grilles or air conditioners, causing skin lesions on the occupants [3–7]. Mites on cage birds may cause similar problems [8]. Lucky *et al*. [9] reported itchy papular lesions related to contact with pet gerbils infested with *D. gallinae* and *Ornythonyssus sylviarum* (see below), and reviewed other reported cases of avian mite bites.



Fig. 38.39 *Dermanyssus gallinae*: Comparison in size with the head of a match.

Liponyssoides sanguineus, the house mouse mite, is an ectoparasite of small rodents. It is of medical importance because it is the vector of *Rickettsia akari*, the agent causing rickettsial pox.

Family Macronyssidae [1]

Members of the Macronyssidae are haematophagous ectoparasites of birds, mammals and reptiles.

Ornithonyssus sylviarum (the northern fowl mite) and *O. bursa* (the tropical fowl mite) are pests of domestic and wild birds, and occasionally attack humans [10–13]. *Ornithonyssus bacoti*, although known as the tropical rat mite, is cosmopolitan, occurring in both tropical and temperate areas of the world. There are a number of reports of its effects on humans in close proximity to infested rats, mice, hamsters and gerbils [14–20].

Ophionyssus natricis, a snake mite, caused skin lesions in a family owning a pet python [21].

Clinical features [2,16]. The clinical effects vary according to the route and severity of infestation and the degree of the host's response. Most commonly, there is a profuse eruption of small, intensely itchy weals or papules, sometimes grouped, and often asymmetrical. The lesions may have a central punctum, and vesicles occasionally occur in the centre of the papules, especially in children. Because of the intense pruritus, excoriations are common, and secondary infection may occur.

There is no characteristic distribution, as this is determined by the situation in which the bites are acquired. Those handling infested poultry tend to have lesions on the hands and forearms, whereas persons attacked by mites in bedding have more extensive bites. Occasionally, lesions are grouped adjacent to areas of tight clothing around the waistline. Rossiter [22] reported otitis externa associated with *D. gallinae* in two poultry catchers.

In heavy infestations, the causative mites are often noticed by those affected, and any specimens obtained should be sent for identification to an entomologist familiar with Acari. When mite infestation is suspected, but no specimens are available, it may be necessary to visit the patient's home or workplace to determine the source of the problem.

References

1 Kettle DS. *Medical and Veterinary Entomology*. London: Croom Helm, 1984: 391–9.
2 Alexander JO'D. Infestation with gamasid mites. In: *Arthropods and Human Skin*. Berlin: Springer-Verlag, 1984: 303–15.
3 Auger P, Nantel J, Meunier N *et al*. Skin acariasis caused by *Dermanyssus gallinae* (de Geer): an in-hospital outbreak. *Can Med Assoc J* 1979; **120**: 700–3.
4 Naltsas S, Hodge SJ, Gataky GJ Jr *et al*. Eczematous dermatitis caused by *Dermanyssus americanus*. *Cutis* 1980; **25**: 429–31.
5 Regan AM, Metersky ML, Craven DE. Nosocomial dermatitis and pruritus caused by pigeon mite infestation. *Arch Intern Med* 1987; **147**: 2185–7.
6 Sexton DJ, Haynes B. Bird-mite infestation in a university hospital. *Lancet* 1975; **i**: 445.
7 Uesugi Y, Aiba S, Suetake T, Tagami H. Multiple infestations with avian mites within a family. *Int J Dermatol* 1994; **33**: 566–7.
8 Sulzberger MB, Kaminstein I. Avian itch mites as a cause of human dermatoses. *Arch Dermatol Syphilol* 1936; **33**: 60–72.
9 Lucky AW, Sayers P, Argus D, Lucky A. Avian mite bites acquired from a new source—pet gerbils. *Arch Dermatol* 2001; **137**: 167–70.
10 Hidano A, Asanuma K. Acariasis caused by bird mites. *Arch Dermatol* 1976; **112**: 882–3.
11 Lodha KR. The occurrence of tropical fowl mite *Ornithonyssus* (*Bdellonyssus, Liponyssus*) *bursa* on man in Rajasthan (India). *Vet Rec* 1969; **84**: 363–5.
12 Tarshis IB. A sorptive dust for control of the northern fowl mite, *Ornithonyssus sylviarum*, infesting dwellings. *J Econ Entomol* 1964; **57**: 110–1.
13 Orton DI, Warren LJ, Wilkinson JD. Avian mite dermatitis. *Clin Exp Dermatol* 2000; **25**: 129–31.
14 Charlesworth EN, Clegern RW. Tropical rat mite dermatitis. *Arch Dermatol* 1977; **113**: 937–8.
15 Fox JG. Outbreak of tropical rat mite dermatitis in laboratory personnel. *Arch Dermatol* 1982; **118**: 676–8.
16 Engel PM, Welzel J, Maass M *et al*. Tropical rat mite dermatitis: case report and review. *Clin Infect Dis* 1998; **27**: 1465–9.
17 Chung SL, Hwang SJ, Kwon SB *et al*. Outbreak of rat mite dermatitis in medical students. *Int J Dermatol* 1998; **37**: 591–4.
18 Creel NB, Crowe MA, Mullen GR. Pet hamsters as a source of rat mite dermatitis. *Cutis* 2003; **71**: 457–61.
19 Beck W, Pfister K. Auftreten der Tropischen Rattenmilbe (*Ornithonyssus bacoti*) bei Nagern und Menschen in München: 3 Fallberichte. *Wien Klin Wochenschr* 2004; **116** (Suppl. 4): 65–8.
20 Baumstark J, Beck W, Hofmann H. Outbreak of tropical rat mite (*Ornithonyssus bacoti*) dermatitis in a home for disabled persons. *Dermatology-Basel* 2007; **215**: 66–8.
21 Schultz H. Human infestation by *Ophionyssus natricis* snake mite. *Br J Dermatol* 1975; **93**: 695–7.
22 Rossiter A. Occupational otitis externa in chicken catchers. *J Laryngol Otol* 1997; **111**: 366–7.

Follicle mites (Demodicidae)

Demodex folliculorum (Simon), the follicle mite, is an obligate parasite of the human pilosebaceous follicle. It was first discovered in cerumen by the anatomist Jakob Henle in 1841, but it was the dermatologist Gustav Simon who provided the first complete description of the parasite, under the name *Acarus folliculorum*, in 1842 [1,2]. The generic name *Demodex* was created for it in 1843 by the zoologist Richard Owen.

Morphology and biology [1,3–5]. *D. folliculorum* measures 0.3–0.4 mm in length, and has an elongated, striated abdomen, giving it a worm-like appearance (Fig. 38.40). A morphologically distinct species, *D. brevis* Akbulatova, has been recognized [6]. *D. folliculorum* occupies the hair follicle, and the smaller *D. brevis* the sebaceous and meibomian glands.

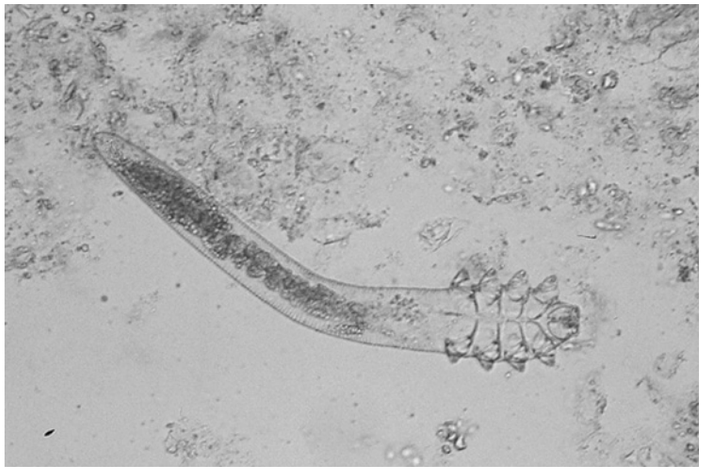


Fig. 38.40 *Demodex folliculorum*, the follicle mite.

The lifespan of *D. folliculorum* is thought to be approximately 2 weeks [5]. The heart-shaped eggs hatch to produce hexapod larvae, and the eight-legged adults develop via two nymphal stages.

Follicle mites show a predilection for areas of high sebum production [7] and they have been shown to contain lipase [8]. They are most numerous on the forehead, cheeks, nose and nasolabial folds, but they are also found on the scalp, in the external ear, in eyelash follicles and meibomian glands, and on the upper chest and nipples. They have also been discovered on the penis, mons veneris, buttocks and in ectopic sebaceous glands in the buccal mucosa [9]. *D. folliculorum* assumes a head-down position in the follicle, often with the tip of the abdomen protruding from the follicular orifice. Follicle mites are quite motile, and migrate from follicle to follicle. Most infested follicles contain two to six mites, but occasionally they are much more numerous. Mites have been isolated from individuals of all ages, except neonates [10]. Transmission to infants probably occurs as a result of close maternal contact. The prevalence of both *D. folliculorum* and *D. brevis* increases with age [11,12] and it is likely that with adequate sampling techniques mites could be discovered in some follicles in the entire adult population. The skin-surface biopsy technique is a useful method of assessing the population density and distribution of *Demodex* mites [13–15].

References

1 Hirst S. *Studies on Acari*, No. 1. *The Genus Demodex, Owen*. London: British Museum (Natural History), 1919.
2 King DF, King LAC, Rabson SM. *Demodex folliculorum* of Simon. *J Am Acad Dermatol* 1983; **8**: 907–8.
3 Nutting WB. Hair follicle mites (Acari: Demodicidae) of man. *Int J Dermatol* 1976; **15**: 79–98.
4 Nutting WB. Biology and pathology of hair follicle mites (Demodicidae). In: Parish LC, Nutting WB, Schwartzman RM, eds. *Cutaneous Infestations of Man and Animal*. New York: Praeger, 1983: 181–99.
5 Spickett SG. Studies on *Demodex folliculorum* Simon (1842). I. Life history. *Parasitology* 1961; **51**: 181–92.
6 Desch C, Nutting WB. *Demodex folliculorum* (Simon) and *D. brevis* Akbulatova of man: redescription and reevaluation. *J Parasitol* 1972; **58**: 169–77.
7 Riechers R, Kopf AW. Cutaneous infestation with *Demodex folliculorum* in man. A quantitative approach based on dermal–epidermal separation. *J Invest Dermatol* 1969; **52**: 103–6.

8 Jimenez-Acosta F, Planas L, Penneys N. *Demodex* mites contain immunoreactive lipase. *Arch Dermatol* 1989; **125**: 1436–7.
9 Franklin CD, Underwood JCE. *Demodex* infestation of oral mucosal sebaceous glands. *Oral Surg* 1986; **61**: 80–2.
10 Ku Quizun. An epidemiological investigation of human demodicidosis. *Chin J Dermatol* 1982; **15**: 89–93.
11 Aylesworth R, Vance JC. *Demodex folliculorum* and *Demodex brevis* in cutaneous biopsies. *J Am Acad Dermatol* 1982; **7**: 583–9.
12 Sengbusch HG, Hauswirth JW. Prevalence of hair follicle mites, *Demodex folliculorum* and *D. brevis* (Acari: Demodicidae), in a selected human population in western New York, USA. *J Med Entomol* 1986; **23**: 384–8.
13 Forton F, Seys B. Density of *Demodex folliculorum* in rosacea: a case-control study using standardized skin-surface biopsy. *Br J Dermatol* 1993; **128**: 650–9.
14 Bonnar E, Eustace P, Powell FC. The *Demodex* mite population in rosacea. *J Am Acad Dermatol* 1993; **28**: 443–8.
15 Clark SM, Dykes P, Bowden P, Marks R. The role of *Demodex* mites in rosacea. *Br J Dermatol* 1997; **137** (Suppl. 50): 48 (Abstract).

Pathogenicity. *D. folliculorum* has been implicated in the pathogenesis of a condition named *pityriasis folliculorum* [1–4]. This was originally described as occurring predominantly in middle-aged or older women who rarely washed their faces, but used large quantities of make-up and cleansing creams. The lack of washing and use of facial cosmetics were considered to be aetiological factors, but a similar appearance has subsequently been described in women who washed their faces regularly [4,5]. This dermatosis is characterized by diffuse facial erythema and follicular plugs, which impart a 'nutmeg grater' appearance to the skin. In reported cases, skin scrapings have contained unusually large numbers of *Demodex*, and the condition has responded to treatment with topical acaricides.

The question of the pathogenic role of *Demodex* in rosacea has prompted much debate in the past [6,7]. Although studies employing skin surface biopsy have shown statistically significant increases in the density of *Demodex* mites in the facial skin of patients with rosacea compared with controls [8–12], it is still not clear whether rosacea merely provides a suitable environment for multiplication of the mites, or whether the mites play a role in initiating the disease. Skin biopsies taken from patients with rosacea, following topical therapy with suphur, failed to show any correlation between clinical improvement and reduction in mite population [13]. In large studies of the histopathology of rosacea [14,15], *Demodex* was conspicuously absent from areas of inflammation in sections in which it was present elsewhere.

It has been suggested that a local, delayed hypersensitivity response to *Demodex* antigens might be partly responsible for the inflammatory component of rosacea [14], and the observation that most T-cells in the granulomatous infiltrate surrounding extrafollicular *Demodex* are helper-inducer T-cells [16] lends support to the hypothesis that the pathogenesis of rosacea involves a cell-mediated immune response. A recent report has also noted that bacterial antigens associated with *Bacillus oleronius*, isolated from *D. folliculorum*, have the potential to stimulate an inflammatory response in patients with papulopustular rosacea [17].

Although extrafollicular *Demodex* or fragments of *Demodex* may be found in the granulomatous lesions of rosacea [18,19], its role in their induction has not been established. The mite may simply be displaced because the hair follicles have been destroyed by the inflammatory process.

A view that the beneficial effects of metronidazole in rosacea might be mediated through an action against *Demodex* [20] was not supported by the finding that mites can survive high concentrations of this drug *in vitro* [21].

Rosacea-like eruptions in which large numbers of mites could be demonstrated and which responded to therapy with acaricides [2,22–25] or metronidazole [26] have been described. The effectiveness of acaricidal treatment can be evaluated by skin surface biopsy [27].

Demodex has been implicated in the causation of papular and papulopustular lesions in immunosuppressed individuals, including children with leukaemia [28–31], a patient with tumour stage mycosis fungoides [32], and patients with HIV infection [33–36].

Facial lesions attributed to *Demodex* have been described in immunocompetent children, in the form of a localized scaly patch [37], rosacea-like and pityriasis folliculorum-like lesions [38], and scalp lesions mimicking favus in another child [39].

A study of *D. folliculorum* density in perioral dermatitis suggested that increased mite density was a secondary phenomenon related to topical steroids, and also showed that mite density increased significantly in relation to the length of treatment [40].

Demodex is present in eyelash follicles, and has been implicated in the pathogenesis of blepharitis in some patients [41–43], although its importance as a cause is disputed [44]. The observation of fungal spores [45] and *Mycobacterium leprae* [46,47] within *Demodex* mites has led to the suggestion that the mites may act as vectors for these organisms.

References

1 Ayres S Jr. Pityriasis folliculorum (*Demodex*). *Arch Dermatol Syphilol* 1930; **21**: 19–24.
2 Ayres S Jr, Ayres S 3rd. Demodectic eruptions (Demodicosis) in the human. *Arch Dermatol* 1961; **93**: 816–27.
3 Lawrence H, Brodie R. Pityriasis folliculorum (*Demodex*). *Med J Aust* 1931; **1**: 529–30.
4 Dominey A, Tschen J, Rosen T *et al*. Pityriasis folliculorum revisited. *J Am Acad Dermatol* 1989; **21**: 81–4.
5 Fariña MC, Requena L, Sarasa JL *et al*. Spinulosis of the face as a manifestation of demodicidosis. *Br J Dermatol* 1998; **138**: 901–3.
6 Rufli T, Mumcuoglu Y. The hair follicle mites *Demodex folliculorum* and *Demodex brevis*. Biology and medical importance. *Dermatologica* 1981; **162**: 1–11.
7 Burns DA. Follicle mites and their role in disease. *Clin Exp Dermatol* 1992; **133**: 294–9.
8 Bonnar E, Eustace P, Powell FC. The *Demodex* mite population in rosacea. *J Am Acad Dermatol* 1993; **28**: 443–8.
9 Diaz-Perez JL. *Demodex* mites in rosacea. *J Am Acad Dermatol* 1994; **30**: 812–3.
10 Forton F, Seys B. Density of *Demodex folliculorum* in rosacea: a case-control study using standardized skin-surface biopsy. *Br J Dermatol* 1993; **128**: 650–9.
11 Clark SM, Dykes P, Bowden P, Marks R. The role of *Demodex* mites in rosacea. *Br J Dermatol* 1997; **137** (Suppl. 50): 48 (Abstract).
12 Erbagci Z, Ozgöztasi O. The significance of *Demodex folliculorum* density in rosacea. *Int J Dermatol* 1998; **37**: 421–5.
13 Robinson TWE. *Demodex folliculorum* and rosacea. *Arch Dermatol* 1965; **92**: 542–4.
14 Marks R, Harcourt-Webster JN. Histopathology of rosacea. *Arch Dermatol* 1969; **100**: 683–91.
15 Ramelet A-A, Perroulaz G. Rosacée: étude histopathologique de 75 cas. *Ann Dermatol Vénéréol* 1988; **115**: 801–6.
16 Rufli T, Buchner SA. T-cell subsets in acne rosacea lesions and the possible role of *Demodex folliculorum*. *Dermatologica* 1984; **169**: 1–5.
17 Lacey N, Delaney S, Kavanagh K, Powell FC. Mite-related bacterial antigens stimulate inflammatory cells in rosacea. *Br J Dermatol* 2007; **157**: 474–81.

18 Grosshans EM, Kremer M, Maleville J. *Demodex folliculorum* und die Histogenese der granulomatösen Rosacea. *Hautarzt* 1974; **25**: 166–77.
19 Grosshans EM, Kremer M, Maleville J *et al*. Du rôle des *Demodex folliculorum* dans l'histogénèse de la rosacée granulomateuse. *Bull Soc Fr Dermatol Syphilgr* 1972; **79**: 639–41.
20 Kürkçüoglu N, Atakan N. Metronidazole in the treatment of rosacea. *Arch Dermatol* 1984; **120**: 837.
21 Persi A, Rebora A. Metronidazole in the treatment of rosacea. *Arch Dermatol* 1985; **121**: 307–8.
22 Ayres S Jr. Rosacea-like demodicosis. *Calif Med* 1963; **98**: 328–30.
23 Lindmaier A, Jurecka W, Lindemayr H. Demodicosis mimicking granulomatous rosacea and transient acantholytic dermatosis (Grover's disease). *Dermatologica* 1987; **175**: 200–4.
24 Shelley WB, Shelley ED, Burmeister V. Unilateral demodectic rosacea. *J Am Acad Dermatol* 1989; **20**: 915–7.
25 Forstinger C, Kittler H, Binder M. Treatment of rosacea-like demodicidosis with oral ivermectin and topical permethrin cream. *J Am Acad Dermatol* 1999; **41**: 775–7.
26 Hoekzema R, Hulsebosch HJ, Bos JD. Demodicidosis or rosacea: what did we treat? *Br J Dermatol* 1995; **133**: 294–9.
27 Forton F, Seys B, Marchal J-L, Song M. *Demodex folliculorum* and topical treatment: acaricidal action evaluated by standardized skin surface biopsy. *Br J Dermatol* 1998; **138**: 461–6.
28 Sahn EE, Sheridan DM. Demodicidosis in a child with leukemia. *J Am Acad Dermatol* 1992; **27**: 799–801.
29 Ivy SP, Mackall CL, Gore L *et al*. Demodicidosis in childhood acute lymphoblastic leukemia: an opportunistic infection occurring with immunosuppression. *J Pediatr* 1995; **127**: 751–4.
30 Castanet J, Monpoux F, Mariani R *et al*. Demodicidosis in an immunodeficient child. *Pediatr Dermatol* 1997; **14**: 219–20.
31 Damian D, Rogers M. Demodex infestation in a child with leukaemia: treatment with ivermectin and permethrin. *Int J Dermatol* 2003; **42**: 724–6.
32 Nakagawa T, Sasaki M, Fujita K *et al*. *Demodex* folliculitis on the trunk of a patient with mycosis fungoides. *Clin Exp Dermatol* 1996; **21**: 148–50.
33 Ashack RJ, Frost ML, Norins AL. Papular pruritic eruption of *Demodex* folliculitis in patients with acquired immunodeficiency syndrome. *J Am Acad Dermatol* 1989; **21**: 306–7.
34 Dominey A, Rosen T, Tschen J. Papulonodular demodicidosis associated with acquired immunodeficiency syndrome. *J Am Acad Dermatol* 1989; **20**: 197–201.
35 Sanchez-Viera M, Hernanz JM, Sampelayo T *et al*. Granulomatous rosacea in a child infected with the human immunodeficiency virus. *J Am Acad Dermatol* 1992; **27**: 1010–11.
36 Jansen T, Kastner U, Kreuter A, Altmeyer P. Rosacea-like demodicidosis associated with acquired immunodeficiency syndrome. *Br J Dermatol* 2001; **144**: 139–42.
37 Won JH, Ahn SK, Lee SH. Unusual manifestation of demodicidosis in a child. *Int J Dermatol* 1993; **32**: 822.
38 Patrizi A, Neri I, Chieregato C, Misciali M. Demodicidosis in immunocompetent young children: report of eight cases. *Dermatology* 1997; **195**: 239–42.
39 García-Vargas A, Mayorga-Rodríguez JA, Sandoval-Tress C. Scalp demodicidosis mimicking favus in a 6-year-old boy. *J Am Acad Dermatol* 2007; **57** (Suppl.): S19–21.
40 Dolenc VM, Pohar M, Lunder T. Density of *Demodex folliculorum* in perioral dermatitis. *Acta Derm Venereol (Stockh)* 2005; **85**: 211–5.
41 Duke-Elder S, MacFaul PA. Demodectic blepharitis. In: *System of Ophthalmology: The Ocular Adnexa*, Part 1. *Diseases of the Eyelids*. London: Henry Kimpton, 1974: 226–30.
42 Nevyas HJ, Nevyas AS. *Demodex folliculorum* and blepharitis. In: Parish LC, Nutting WB, Schwartzman RM, eds. *Cutaneous Infestations of Man and Animal*. New York: Praeger, 1983: 209–17.
43 Post CF, Juhlin E. *Demodex folliculorum* and blepharitis. *Arch Dermatol* 1963; **88**: 298–302.
44 Norn MS. *Demodex folliculorum*. Incidence and possible pathogenic role in the human eyelid. *Acta Ophthalmol* 1970; **106** (Suppl.): 1–85.
45 Wolf R, Ophir J, Avigad J *et al*. The hair follicle mites (*Demodex* spp.). Could they be vectors of pathogenic microorganisms? *Acta Derm Venereol (Stockh)* 1988; **68**: 535–7.
46 Nutting WB, Kirchheimer WF, Pfalzgraff RE. Demodicidiasis and leprosy. (Review and proposal.) *Lepr Rev* 1966; **37**: 209–16.
47 Spickett SG. A preliminary note on *Demodex folliculorum* Simon (1842) as a possible vector of leprosy. *Lepr Rev* 1961; **32**: 263–8.

Class Chilopoda (centipedes) and Diplopoda (millipedes)

Centipedes

Centipedes are elongated arthropods, with bodies composed of many segments, each bearing one pair of legs. They are nocturnally active carnivores, and feed on insects. Some of the giant species also feed on small mice and birds. The first pair of legs is modified, and provided with powerful hollow claws, which are used to grip prey and inject venom from poison glands in the basal segments of the legs.

The claws of smaller species of centipedes are unable to penetrate human skin, but some tropical and subtropical species, principally members of the orders Scutigeromorpha and the giant Scolopendromorpha, can inflict painful 'bites' [1–5]. The bites cause local pain, erythema and oedema, which may persist for several hours. Systemic symptoms include nausea, dizziness and pyrexia.

Millipedes

Millipedes also have multisegmented bodies, and most segments bear two pairs of legs (Fig. 38.41). They feed mainly on decaying vegetable matter, and are generally regarded as harmless, but some large tropical species can cause injury to humans when acting defensively. The injurious effects of the defensive secretions of the giant Spirobolid millipedes of tropical and subtropical zones are well known to the indigenous populations of these areas.

Millipedes have numerous 'repugnatorial' glands distributed along the body segments, which provide a chemical defence system, and it is the corrosive secretions of these glands which may cause burns on the skin. In the majority of species, these secretions ooze out and form droplets around the foramina of the



Fig. 38.41 Giant millipede. (Courtesy of M. Fogden/Oxford Scientific Films.)

glands, but a few species are capable of squirting the fluid for some distance [6,7]. Millipede secretions contain benzoquinones and hydroquinones.

Clinical features of millipede burns [1,6,8–10]. Children often try to pick up millipedes, and are therefore at most risk of burns from the corrosive defensive secretions. If millipede secretions enter the eye, they produce a severe irritant conjunctivitis. Contact with the skin produces a local burning sensation and a yellowish-brown stain, which gradually darkens to deep mahogany or purple–brown. This colour is produced by oxidation of the quinones in the secretions. The lesions blister within a day or two, but in the absence of secondary infection, will heal and desquamate in 10–14 days. The discoloration may persist for months. In dark-skinned individuals, persistent hypopigmentation is a common sequel.

Treatment [6]. Skin lesions should be washed with copious amounts of water to remove any remaining secretions, and the area cleaned with alcohol (a solvent of benzoquinones) if available. Blisters should be treated with a topical antiseptic. Ocular injuries should be dealt with by an ophthalmologist.

References

1 Alexander JO'D. Centipede bites and millipede burns. In: *Arthropods and Human Skin*. Berlin: Springer-Verlag, 1984: 383–9.
2 Burnett JW, Calton GJ, Morgan RJ. Centipedes. *Cutis* 1986; **37**: 241.
3 Lin T-J, Yang C-C, Yang G-Y *et al*. Features of centipede bites in Taiwan. *Trop Geogr Med* 1995; **47**: 300–2.
4 Elston DM. What's eating you? Centipedes (Chilopoda). *Cutis* 1999; **64**: 83.
5 Bush SP, King BO, Norris RL, Stockwell SA. Centipede envenomation. *Wild Environ Med* 2001; **12**: 93–9.
6 Radford AJ. Millipede burns in man. *Trop Geogr Med* 1975; **27**: 279–87.
7 Roth LM, Eisner T. Chemical defences of arthropods. *Ann Rev Entomol* 1962; **7**: 107–36.
8 Shpall S, Frieden I. Mahogany discolouration of the skin due to the defensive secretion of a millipede. *Pediatr Dermatol* 1991; **8**: 25–7.
9 Mason GH, Thomson HDP, Fergin P, Anderson R. The burning millipede. *Med J Aust* 1994; **160**: 718, 726.
10 Elston DM. What's eating you? Millipedes (Diplopoda). *Cutis* 2001; **67**: 452.

Other noxious or venomous invertebrates

Leeches (Hirudinea)

Leeches are classified in the phylum Annelida (segmented worms). Fresh-water leeches were used in bloodletting in Europe in the 18th and 19th centuries [1]. Although several species of leeches were used, the medicinal leech, *Hirudo medicinalis*, was the most popular. A large specimen of *H. medicinalis* may measure about 12 cm when fully extended. The body tapers towards each extremity, where it is provided with a muscular disc or sucker. Within the anterior sucker is the mouth, bordered by three jaws. Leeches attach themselves to the skin using these powerful jaws, and feed until engorged, when they release their grip and drop to the ground. Their saliva possesses anticoagulant, fibrinolytic, vasodilator and probably also anaesthetic properties. Some of the substances introduced by leeches during feeding are antigenic, and if sensitization to these substances develops the reaction to the bite may be urticarial or bullous [2]. Multiple pseudolymphomas have occurred following application of leeches to the legs [3].

In recent years, there has been a revival of interest in the use of leeches for therapeutic purposes. They are being employed in microvascular surgery to salvage replants or skin flaps whose viability is threatened by venous congestion [4,5], and also for drainage of large haematomas. Unfortunately, the use of leeches carries the risk of introducing wound infection, most frequently with *Aeromonas hydrophila*, a Gram-negative rod, but occasionally other organisms are involved [6–9]. *Aeromonas* is part of the normal gut flora of the leech, where it is thought to be essential to aid digestion of a blood meal, as proteolytic enzymes are virtually absent from the leech gut. Many plastic surgeons who use leeches employ antibiotic prophylaxis to protect against wound infection.

References

1 Adams SL. The medicinal leech. A page from the Annelids of Internal Medicine. *Ann Intern Med* 1988; **109**: 399–405.
2 Heldt TJ. Allergy to leeches. *Henry Ford Hosp Med Bull* 1961; **9**: 498–519.
3 Smolle J, Cerroni L, Kerl H. Multiple pseudolymphomas caused by *Hirudo medicinalis* therapy. *J Am Acad Dermatol* 2000; **43**: 867–9.
4 Haycox CL, Odland PB, Coltrera MD, Raugi GJ. Indications and complications of medicinal leech therapy. *J Am Acad Dermatol* 1995; **33**: 1053–5.
5 Conforti ML, Connor NP, Heisey DM, Hartig GK. Evaluation of performance characteristics of the medicinal leech (*Hirudo medicinalis*) for the treatment of venous congestion. *Plast Reconstr Surg* 2002; **109**: 228–35.
6 Mercer NSG, Beere DM, Bornemisza AJ *et al*. Medicinal leeches as sources of wound infection. *BMJ* 1987; **294**: 937.
7 Varghese MR, Farr RW, Wax MK *et al*. *Vibrio fluvialis* wound infection associated with medicinal leech therapy. *Clin Infect Dis* 1996; **22**: 709–10.
8 Pereira JA, Greig JR, Liddy H *et al*. Leech-borne *Serratia marcescens* infection. *Br J Plast Surg* 1998; **51**: 640–1.
9 Bauters TGM, Buyle FMA, Verschraegen G *et al*. Infection risk related to the use of medicinal leeches. *Pharm World Sci* 2007; **29**: 122–5.

Jellyfish, sea anemones, corals (Cnidaria)

The phylum Cnidaria [1–3] includes the jellyfish, sea anemones and corals. All are aquatic and the majority are marine. Three of the four classes of the phylum have a medusa or 'jellyfish' stage in their life cycles. Cnidarians have tentacles bearing batteries of stinging cells (nematocysts) which are used for defence and capturing prey. Within each nematocyst is a spirally coiled thread that can be everted, uncoiled and forcibly ejected. In contact with prey, or with human skin, the nematocysts are discharged and the threads inject venom. The nature and toxic effects of the venom vary with species. Many species inflict at least some discomfort on humans, and some are potentially dangerous [3–7].

Class Hydrozoa. This class includes the fire corals and free-floating members of the subclass Siphonophora. The Siphonophora are colonial organisms in which a number of individuals, specialized for different functions, are structurally associated. Perhaps the best known siphonophoran is *Physalia*, the Portuguese man-of-war. This has the local name of 'bluebottle' in Australia. It has an air-filled float, which acts as a sail, and trailing tentacles. The nematocysts occur in 'batteries' or 'sting buttons' along the tentacles, and contact with them results in extrusion of numerous nematocysts and the inoculation of venom.

Class Cubozoa. Often referred to as 'box jellyfish', several species are dangerous to humans [3]. The most notorious is *Chironex fleckeri*, which has been responsible for a number of deaths in Australian waters. Other dangerous species include *Carybdea rastoni* (the 'jimble'), *Carukia barnesi* (the 'Irukandji') [8], the 'Morbakka' ('fire jelly'; Moreton Bay stinger) [9], and the Hawaiian box jellyfish, *Alatina moseri.*

Class Scyphozoa. The medusa is the dominant form of the life cycle. Jellyfish of this class are distributed worldwide, and some have medical significance. *Pelagia noctiluca* (the 'mauve stinger') is one of these, which is well known in the Mediterranean and Adriatic but has a wide distribution in the oceans of the world.

Class Anthozoa. This class contains several thousand species, including the sea anemones, the soft corals and the stony or true corals. Several species of sea anemone are known to inflict painful stings [2,3,10,11]. The reef-forming corals may cause injury to the skin with their nematocysts, or with their calcareous outer skeletons [12].

Clinical features [3,13–15]. Contact with *Physalia* tentacles usually results in a linear erythematous eruption accompanied by severe local pain. Because of the arrangement of 'sting buttons' of nematocysts there is a beaded pattern of local, small weals. In humans, pain and skin lesions are usually the limits of toxicity, but occasionally more severe reactions occur [16]. Haemolysis and acute renal failure in a 4-year-old girl [17], and fatalities, have been reported [18,19].

The local effects of box jellyfish tentacle contact are immediate, severe pain, and linear weals with a white, ischaemic centre. Larger weals may have a typical 'cross-hatched' or 'frosted-ladder' pattern corresponding to the architecture of the tentacles. Partial or full thickness skin necrosis may result. Box jellyfish may be responsible not only for local lesions but also for severe systemic effects, which may result in death [3,4,8,20–23].

In addition to acute skin lesions, which are regarded as toxic in nature, there may be delayed, persistent or recurrent eruptions at the original sites of cnidarian envenomation [24–31]. Recurrent episodes may be single or multiple, and may take the form of erythema, urticarial lesions, papules or plaques. A delayed hypersensitivity response to jellyfish antigens has been demonstrated by a positive patch-test reaction to a nematocyst preparation from *Olindias sambaquiensis* [32].

Other reported sequelae of jellyfish stings include erythema nodosum [33], cold urticaria [34] and Mondor's disease [35].

Envenomation by fire corals usually produces immediate burning or stinging pain, followed by urticarial lesions at the site of contact. These may in turn be followed by a localized vesiculobullous eruption, and subsequently chronic granulomatous and lichenoid lesions [36–38]. Stinging of an aquarium shop worker by a stony coral, *Euphyllia picteti*, has been reported [39].

Seabather's eruption [40–45]. Itchy, erythematous papules and weals occur predominantly under swimwear, and lesions are usually concentrated in tight-fitting areas (Fig. 38.42). The organisms become trapped under the bathing costume, and discharge of nematocysts is triggered. It is probable that a similar clinical picture can be produced by different coelenterates in different waters. In Florida, the Gulf of Mexico and the Caribbean, *Linuche unguiculata* (thimble jellyfish) appears to be responsible, and evidence has recently been presented that all three free-swimming stages of this jellyfish can cause seabather's eruption [46]. Specific IgG antibodies against *L. unguiculata* antigen have been demonstrated by enzyme-linked immunosorbent assay (ELISA) in patients with seabather's eruption [47]. Cases in the Long Island region, New York, have been attributed to larvae of the sea anemone *Edwardsiella lineata* [40].



Fig. 38.42 Seabather's eruption. (Courtesy of Dr R. MacSween, Kingston, Ontario, Canada.)

It should be noted that seabather's eruption as described above is completely distinct from 'swimmer's itch' or 'clam digger's itch', an eruption due to cercarial organisms and affecting mainly uncovered skin (Chapter 37), although both can occur in salt water and the terms are sometimes loosely applied.

Pathology. The acute changes in the skin resulting from cnidarian stings consist of intracellular oedema of keratinocytes, many of which have pyknotic nuclei, and a lymphocytic infiltrate in an oedematous superficial dermis [48]. Nematocysts were visible penetrating the epidermis in a 5-year-old child who suffered fatal envenomation from *Chironex fleckeri* [49].

Histology of recurrent reactions shows a spongiotic vesicular dermatitis with a dense perivascular lympho-histiocytic infiltrate, often containing large numbers of eosinophils [26,50]. There is oedema of the papillary dermis. Immunohistochemical studies suggest that Langerhans' cells and helper T lymphocytes play a central role, and that type IV delayed hypersensitivity is involved

in the pathogenesis of the lesions [50]. Epithelioid granulomas and large $CD30^+$ lymphocytes were present in a delayed reaction to a fire coral [51].

Treatment [3,15,52,53]. Inhibition of further discharge of nematocysts is an important aspect of first aid for some cnidarian stings. Vinegar inhibits discharge of the nematocysts of all the box jellyfish, and should be poured over the affected area of skin as soon as possible. It is available in containers on beaches in Australia. However, in other jellyfish, nematocyst discharge is not inhibited, and may be provoked by vinegar.

The application of cold packs provides relief of mild to moderate pain resulting from stings by *Physalia* and a number of species of jellyfish, but it has been demonstrated that heat appears to be even more effective in pain relief, probably by toxin inactivation. This observation may have wider therapeutic implications in the management of jellyfish envenomation [54,55].

An antivenom is available for use in *Chironex fleckeri* envenomation.

In Australia, protective clothing, in the form of Lycra 'stinger suits', is extremely useful in the prevention of jellyfish envenomation.

References

1 Southcott RV. Coelenterates of medical importance. In: Keegan HL, Macfarlane WV, eds. *Venomous and Poisonous Animals and Noxious Plants of the Pacific Region*. Oxford: Pergamon, 1963: 41–65.
2 Halstead BW. *Poisonous and Venomous Marine Animals of the World*, 2nd edn. Princeton: Darwin Press, 1988.
3 Williamson JA, Fenner PJ, Burnett JW, Rifkin JF (eds). *Venomous and Poisonous Marine Animals*. Sydney: University of New South Wales Press, 1996.
4 Currie BJ, Jacups SP. Prospective study of *Chironex fleckeri* and other box jellyfish stings in the 'Top End' of Australia's Northern Territory. *Med J Aust* 2005; **183**: 631–6.
5 Burnett JW, Calton GJ, Burnett HW. Local and systemic reactions from jellyfish stings. *Clin Dermatol* 1987; **5**: 14–28.
6 Burnett JW, Calton GJ, Burnett HW. Jellyfish envenomation syndromes. *J Am Acad Dermatol* 1986; **14**: 100–6.
7 Halstead BW. Coelenterate (cnidarian) stings and wounds. *Clin Dermatol* 1987; **5**: 8–13.
8 Little M, Mulcahy RF. A year's experiencee of Irukandji envenomation in far north Queensland. *Med J Aust* 1998; **169**: 638–41.
9 Fenner PJ, Fitzpatrick PF, Hartwick RJ *et al*. 'Morbakka', another cubomedusan. *Med J Aust* 1985; **143**: 550–5.
10 Maretic Z, Russell FE. Stings by the sea anemone *Anemonia sulcata* in the Adriatic sea. *Am J Trop Med Hyg* 1983; **32**: 891–6.
11 Sanchez-Rodriquez J, Zugasti-Cruz A, Burnett JW. Cutaneous stings from *Bartholomea annulata*. *Contact Dermatitis* 2001; **44**: 314–5.
12 Preston FS. Coral ulcer. *BMJ* 1950; **1**: 642–4.
13 McGoldrick J, Marx JA. Marine envenomations part 2: invertebrates. *J Emerg Med* 1992; **10**: 71–7.
14 Rietschel RL, Fowler JF Jr. *Fisher's Contact Dermatitis*, 5th edn. Philadelphia: Lippincott Williams and Wilkins, 2001: 687–713.
15 Tibballs J. Australian venomous jellyfish, envenomation syndromes, toxins and therapy. *Toxicon* 2006; **48**: 830–59.
16 Edwards EK Jr, Edwards EK Sr. Immediate, anaphylactic and delayed reactions to jellyfish. *Contact Dermatitis* 2000; **43**: 244–5.
17 Guess HA, Saviteer PL, Morris CR. Hemolysis and acute renal failure following a Portuguese man-of-war sting. *Pediatrics* 1982; **70**: 979–81.
18 Stein MR, Marraccini JV, Rothschild NE *et al*. Fatal Portuguese man-o'-war (*Physalia physalis*) envenomation. *Ann Emerg Med* 1989; **18**: 312–5.
19 Burnett JW, Gable WD. A fatal jellyfish envenomation by the Portuguese man-o'-war. *Toxicon* 1989; **27**: 823–4.
20 Little M, Pereira P, Carrette T, Seymour J. Jellyfish responsible for the Irukandji syndrome. *Q J Med* 2006; **99**: 425–7.
21 Gershwin L. Jellyfish responsible for Irukandji syndrome. *Q J Med* 2006; **99**: 801–2.
22 Fenner PJ. Jellyfish responsible for Irukandji syndrome. *Q J Med* 2006; **99**: 802–3.
23 Little M. Jellyfish responsible for Irukandji syndrome. *Q J Med* 2006; **99**: 803–4.
24 Burnett JW, Calton GJ. Recurrent eruption following a solitary envenomation by the cnidarian *Stomalophous meleagris*. *Toxicon* 1985; **23**: 1010–4.
25 Burnett JW, Hepper KP, Aurelian L *et al*. Recurrent eruptions following unusual solitary coelenterate envenomations. *J Am Acad Dermatol* 1987; **17**: 86–92.
26 Reed KM, Bronstein BR, Baden HP. Delayed and persistent cutaneous reactions to coelenterates. *J Am Acad Dermatol* 1984; **10**: 462–6.
27 O'Donnell BF, Tan CY. Persistent contact dermatitis from jellyfish sting. *Contact Dermatitis* 1993; **28**: 112–3.
28 O'Reilly GM, Isbister GK, Lawrie PM *et al*. Prospective study of jellyfish stings from tropical Australia, including the major box jellyfish *Chironex fleckeri*. *Med J Aust* 2001; **175**: 652–5.
29 Tamanaha RH, Izumi AK. Persistent cutaneous hypersensitivity reaction after a Hawaiian box jellyfish sting (*Carybdea alata*). *J Am Acad Dermatol* 1996; **35**: 991–3.
30 Uri S, Marina G, Liubov G. Severe delayed cutaneous reaction due to Mediterranean jellyfish (*Rhopilema nomadica*) envenomation. *Contact Dermatitis* 2005; **52**: 282–3.
31 Ulrich H, Landthaler M, Vogt T. Granulomatous jellyfish dermatitis. *J Dtsch Dermatol Ges* 2007; **5**: 493–5.
32 Kokelj F, Stinco G, Avian M *et al*. Cell-mediated sensitization to jellyfish antigens confirmed by positive patch test to *Olindias sambaquiensis* preparations. *J Am Acad Dermatol* 1995; **33**: 307–9.
33 Auerbach PS, Hays JT. Erythema nodosum following a jellyfish sting. *J Emerg Med* 1987; **5**: 487–91.
34 Mathelier-Fusade P, Leynadier F. Acquired cold urticaria after jellyfish sting. *Contact Dermatitis* 1993; **29**: 273.
35 Ingram DM, Sheiner HJ, Ginsberg AM. Mondor's disease of the breast resulting from jellyfish sting. *Med J Aust* 1992; **157**: 836–7.
36 Addy JH. Red Sea coral contact dermatitis. *Int J Dermatol* 1991; **30**: 271–3.
37 Camarasa JG, Nogues Antich E, Serra-Baldrich E. Red Sea coral contact dermatitis. *Contact Dermatitis* 1993; **29**: 285–6.
38 Fisher AA. Aquatic dermatitis, part I. Dermatitis caused by coelenterates. *Cutis* 1999; **64**: 84–8.
39 Tong D. Coral dermatitis in the aquarium industry. *Contact Dermatitis* 1995; **33**: 207–8.
40 Freudenthal AR. Seabather's eruption: range extended northward and a causative organism identified. *Rev Int Oceanogr Med* 1991; **101**: 137–47.
41 Tomchik RS, Russell MT, Szmant AM, Black NA. Clinical perspectives on seabather's eruption, also known as 'sea lice'. *JAMA* 1993; **269**: 1669–72.
42 Freudenthal AR, Joseph PR. Seabather's eruption. *N Engl J Med* 1993; **329**: 542–4.
43 Wong DE, Meinking TL, Rosen LB *et al*. Seabather's eruption. Clinical, histologic, and immunologic features. *J Am Acad Dermatol* 1994; **30**: 399–406.
44 MacSween RM, Williams HC. Seabather's eruption—a case of Caribbean itch. *BMJ* 1996; **312**: 957–8.
45 Ubillos SS, Vuong D, Sinnott JT, Sakalosky PE. Seabather's eruption. *South Med J* 1995; **88**: 1163–5.
46 Segura-Puertas L, Ramos ME, Aramburo C *et al*. One *Linuche* mystery solved: all 3 stages of the coronate syphomedusa *Linuche unguiculata* cause seabather's eruption. *J Am Acad Dermatol* 2001; **44**: 624–8.
47 Burnett JW, Kumar S, Malecki JM, Szmant AM. The antibody response in seabather's eruption. *Toxicon* 1995; **33**: 99–104.
48 Letot B, Piérard-Franchimont C, Piérard GE. Acute reactions to coelenterates. *Dermatologica* 1990; **180**: 224–7.
49 Strutton G, Lumley J. Cutaneous light microscopic and ultrastructural changes in a fatal case of jellyfish envenomation. *J Cutan Pathol* 1988; **15**: 249–55.
50 Piérard GE, Letot B, Piérard-Franchimont C. Histologic study of delayed reactions to coelenterates. *J Am Acad Dermatol* 1990; **22**: 599–601.
51 Miracco C, Lalinga AV, Sbano P *et al*. Delayed skin reaction to Red Sea coral injury showing superficial granulomas and atypical CD30+ lymphocytes: report of a case. *Br J Dermatol* 2001; **145**: 849–51.

52 Exton DR, Fenner PJ, Williamson JA. Cold packs: effective topical analgesia in the treatment of painful stings by *Physalia* and other jellyfish. *Med J Aust* 1989; **151**: 625–6.
53 Fenner PJ, Williamson JA, Burnett JW, Rifkin J. First aid treatment of jellyfish stings in Australia. *Med J Aust* 1993; **158**: 498–501.
54 Taylor JG. Treatment of jellyfish stings. *Med J Austral* 2007; **186**: 43.
55 Loten C, Stokes B, Worsley D *et al*. A randomised controlled trial of hot water (45°C) immersion versus ice packs for pain relief in bluebottle stings. *Med J Austral* 2006; **184**: 329–33.

Sea mats (Bryozoa)

The Bryozoa are small, sedentary, colonial animals, which usually form mat-like encrustations on rocks, seaweeds or other surfaces. Severe occupational dermatitis resulting from contact with *Alcyonidium diaphanum* ('sea chervil') was originally described in North Sea fishermen, and named 'Dogger Bank itch' because of its association with the Dogger Bank fishing grounds. However, *A. diaphanum* is widely distributed in waters around the British Isles and mainland Europe [1,2]. The dermatitis occurs during the summer months, principally because the organism, which becomes detached in winter storms, proliferates in spring and summer, and is therefore encountered in greater amounts by fishermen. It is an acute papular, occasionally bullous, contact dermatitis on the hands, arms and face [3–6], which may have a photoallergic component [5]. The allergen is the (2-hydroxyethyl) dimethylsulphoxonium ion, a metabolite produced by the bryozoan [7,8]. Hypersensitivity to another bryozoan, *Electra pilosa*, has also been described [5,6].

References

1 Porter JS, Ellis JR, Hayward PJ *et al*. Geographic variation in abundance and morphology of the bryozoan *Alcyonidium diaphanum* (Ctenostomata: Alcyonidiidae) in UK coastal waters. *J Mar Biol Ass UK* 2002; **82**: 529–35.
2 Pathmanaban ON, Porter JS, White IR. Dogger Bank itch in the eastern English Channel: a newly described geographical distribution of an old problem. *Clin Exp Dermatol* 2005; **30**: 622–6.
3 Newhouse ML. Dogger Bank itch: survey of trawlermen. *BMJ* 1966; **1**: 1142–5.
4 Newhouse ML. Dogger Bank itch. *Proc R Soc Med* 1966; **59**: 1119–20.
5 Jeanmougin M, Lemarchand-Venecie F, Hoang XD *et al*. Eczéma professionel avec photosensibilité par contact de bryozoaires. *Ann Dermatol Venereol* 1987; **114**: 353–7.
6 Ashworth J, Curry FM, White IR, Rycroft RJG. Occupational allergic contact dermatitis in east coast of England fishermen: newly described hypersensitivities to marine organisms. *Contact Dermatitis* 1990; **22**: 185–6.
7 Carlé JS, Christophersen C. Dogger Bank itch. 4. An eczema-causing sulfoxonium ion from the marine animal, *Alcyonidium gelatinosum* [Bryozoa]. *Toxicon* 1982; **20**: 307–10.
8 Carlé JS, Thybo H, Christophersen C. Dogger bank itch (3). Isolation, structure determination and synthesis of a hapten. *Contact Dermatitis* 1982; **8**: 43–7.

Sea urchins (Echinoidea)

The Echinoidea, or sea urchins, form part of the phylum Echinodermata, which also includes the starfishes and sea cucumbers [1–3]. Sea urchins are usually spherical or ovoid, and are enclosed in a shell of closely fitting plates supplied with numerous moveable spines. The spines are formed by calcification of a cylindrical projection of subepidermal connective tissue. Situated between the spines are three-jawed pedicellariae, some of which are venomous. They are used to seize prey, and also in defence. In some species of sea urchins, the spines are also venomous.

Pathogenesis of skin lesions. Many species can cause unpleasant lesions of different types [4,5]—intense local pain and swelling following envenomation by spines or pedicellariae; secondary infection of the spine puncture wounds; development of implantation epidermoid cysts from fragments of epithelium driven into the wounds by the spines; late development of granulomatous skin lesions; synovitis, and joint damage if the spines penetrate joint cavities [6]; occasionally, systemic upset accompanies the local changes.

Pathology [7]. In chronic lesions a granulomatous inflammatory reaction predominates, with foreign-body or sarcoidal types the most frequent. Non-granulomatous chronic inflammation may also occur.

Clinical features [1,3–5]. Envenomation by sea urchins produces immediate burning pain, which may be very intense and persists for several hours. The degree of local swelling is variable, but is sometimes severe. In the absence of secondary infection, the puncture wounds heal within a week or two.

Delayed granulomatous reactions usually develop several months after the original injury, and take the form of bluish papules or nodules at the sites of penetration of the spines. On the digits, there may be diffuse fusiform swelling and limitation of movement. These lesions are very persistent if not treated.

A patient with a pruritic erythematous eruption on the knees and ankles following injury by a sea urchin produced a positive patch-test reaction to an extract of sea-urchin spines [8].

It has been suggested that *Mycobacterium marinum* may play a pathogenic role in some cases of sea urchin granuloma [9].

Treatment [4,5]. Immediate treatment consists of careful removal of spines and pedicellariae. Immersion of the affected area in hot water will provide pain relief. Local inhabitants in certain areas where sea-urchin injuries are common apply hot candle wax to the area [10]. The spines are difficult to remove surgically, but erbium-yttrium-aluminium-garnet (Er:YAG) laser ablation has proved effective [11]. If the spines have penetrated a joint, surgical exploration is advisable. The granulomatous lesions may be treated with intralesional steroid.

References

1 Halstead BW. *Poisonous and Venomous Marine Animals of the World*, 2nd edn. Princeton: Darwin Press, 1988.
2 Edmonds C. *Dangerous Marine Animals of the Indo-Pacific Region*. Newport, Australia: Wedneil Publications, 1978.
3 Williamson JA, Fenner PJ, Burnett JW, Rifkin JF (eds). *Venomous and Poisonous Marine Animals*. Sydney: University of New South Wales Press, 1996.
4 McGoldrick J, Marx JA. Marine envenomation part 2: invertebrates. *J Emerg Med* 1992; **10**: 71–7.
5 Rietschel RL, Fowler JF Jr. *Fisher's Contact Dermatitis*, 5th edn. Philadelphia: Lippincott Williams and Wilkins, 2001.
6 Cracchiolo A 3rd, Goldberg L. Local and systemic reactions to puncture injuries by the sea urchin spine and the date palm thorn. *Arthritis Rheum* 1977; **20**: 1206–12.
7 De la Torre C, Toribio J. Sea-urchin granuloma: histologic profile. A pathologic study of 50 biopsies. *J Cut Pathol* 2001; **28**: 223–8.
8 Asada M, Komura J, Hosokawa H *et al*. A case of delayed hypersensitivity reaction following a sea-urchin sting. *Dermatologica* 1990; **180**: 99–101.

9 De la Torre C, Vega A, Carracedo A, Toribio J. Identification of *Mycobacterium marinum* in sea-urchin granulomas. *Br J Dermatol* 2001; **145**: 114–6.
10 Laird P. Sea-urchin injuries. *Lancet* 1995; **346**: 1240.
11 Böer A, Ochsendorf FR, Beier C, Kaufmann R. Effective removal of sea-urchin spines by erbium:YAG laser ablation. *Br J Dermatol* 2001; **145**: 169–70.

Sponges (Porifera) [1,2]

Tedania ignis (the fire sponge) is capable of producing a severe dermatitis, and has also been reported as inducing erythema multiforme-like lesions of the face, palms and soles 10 days after contact [3]. Dermatitis may also be caused by several other sponges, including *Neofibularia nolitangere* (the poison bun sponge) and *Microciona prolifera* (the red sponge).

References

1 Williamson JA, Fenner PJ, Burnett JW, Rifkin JF (eds). *Venomous and Poisonous Marine Animals*. Sydney: University of New South Wales Press, 1996.
2 Rietschel RL, Fowler JF Jr. *Fisher's Contact Dermatitis*, 5th edn. Philadelphia: Lippincott Williams and Wilkins, 2001.
3 Yaffee HS, Stargardter F. Erythema multiforme from *Tedania ignis*. *Arch Dermatol* 1963; **87**: 601–4.

Mollusca

The only important venomous univalve molluscs are cone shells of the genus *Conus* [1–3]. All the species of this genus possess a venom apparatus, and several species have caused human injury.

The stings are painful puncture wounds, with local ischaemia, cyanosis and numbness, the numbness quickly spreading to involve the whole body. The sting of some species, particularly *C. geographus* [2,4], may be fatal.

The very small floating mollusc *Creseis acicula* Rang has been incriminated as a cause of stings in bathers in Florida [5].

The tiny blue-ringed octopus (*Hapalochlaena maculosa*), a member of the Cephalopoda class of molluscs, and found mainly in Australian coastal waters, has been called the world's most deadly octopus. When agitated, the blue rings become very prominent. The bite of this octopus contains salivary toxins that may cause severe systemic symptoms culminating in death, usually from respiratory failure [6,7]. Cutaneous problems following *H. maculosa* bites include intense pruritus and urticaria [3,6,8].

Erythema, oedema and a burning sensation followed the bite of *Octopus apollyon*, succeeded by a persistent erythematous plaque and lymphoedema [9].

References

1 Halstead BW. *Poisonous and Venomous Marine Animals of the World*, 2nd edn. Princeton: Darwin Press, 1988.
2 Kohn AJ. Venomous marine snails of the genus *Conus*. In: Keegan HL, Macfarlane WV, eds. *Venomous and Poisonous Animals and Noxious Plants of the Pacific Region*. Oxford: Pergamon, 1963: 83–96.
3 McGoldrick J, Marx JA. Marine envenomations part 2: invertebrates. *J Emerg Med* 1992; **10**: 71–7.
4 Fegan D, Andresen D. *Conus geographus* envenomation. *Lancet* 1997; **349**: 1672.
5 Hutton RF. Marine dermatosis. *Arch Dermatol* 1960; **82**: 951–6.
6 Sutherland SK, Lane WR. Toxins and mode of envenomation of the common ringed or blue-banded octopus. *Med J Aust* 1969; **1**: 893–8.
7 Williamson JA, Fenner PJ, Burnett JW, Rifkin JF. *Venomous and Poisonous Marine Animals*. Sydney: University of New South Wales Press, 1996.
8 Edmonds C. A non-fatal case of blue-ringed octopus bite. *Med J Aust* 1969; **2**: 601.
9 Brazzelli V, Baldini F, Nolli G *et al*. *Octopus apollyon* bite. *Contact Dermatitis* 1999; **40**: 169–70.

Noxious or venomous vertebrates

Venomous fish [1–3]

Numerous species of fish are capable of inflicting painful or even dangerous stings by means of dorsal or caudal spines provided with complex venom glands.

Venomous species are not confined to tropical waters. The lesser weeverfish, *Echiichthys vipera* [4,5], the spiny dogfish (*Squalus acanthias*) and several species of stingray occur on the Atlantic coasts, and can inflict serious stings.

In warmer waters, species of stingray, scorpionfish, catfish [6], rabbitfish, stonefish [7], the aptly named 'bearded ghoul', stargazers and toadfish are potentially dangerous. In many cases, injuries are the result of the victim inadvertently stepping on the fish in shallow water. The tail of the stingray carries serrated spines containing venom glands surrounded by an integumentary sheath. Treading on the fish results in a reflex 'whip' of the tail, which drives the spines into the skin, usually on the leg [8]. Several of these venomous species bury themselves in the sand in shallow waters, with their spines protruding, and are therefore a hazard to bathers.

Clinical features. Injuries commonly occur on the feet or legs, as a result of the victim stepping on the fish. Fish stings are usually immediately painful. They present as painful lacerations or puncture wounds. Intense pain may continue for several hours, and swelling and erythema around the wounds may simulate an infective cellulitis. With some species, systemic symptoms may occur. Raynaud's phenomenon affecting individual digits penetrated by weever fish spines has been reported [9,10]. Stingray spines may cause lacerations, or may be driven into the skin and break off. If the integumentary sheath ruptures, envenomation occurs. In severe stingray wounds, the affected area appears dusky or cyanotic, and later becomes erythematous or mottled, with necrosis of underlying fat and muscle [11].

The inflammatory infiltrate in one case of stingray envenomation contained numerous mononuclear cells, many of which were TIA+, suggesting that an immunological reaction might contribute to the delayed healing commonly seen after stingray injury [12].

Treatment. The venom of the weeverfish, like that of the stingray, stonefish and other venomous fish, is an unstable protein which is heat labile, and hot water is very effective in treating the stings [3,13–15]. The injured part should be immersed in hot water (someone other than the victim should gauge the temperature), and this will diminish the pain. An antivenom is available for stonefish stings.

References

1 Halstead BW. *Poisonous and Venomous Marine Animals of the World*, 2nd edn. Princeton: The Darwin Press, 1988.
2 Halstead BW, Mitchell LR. A review of the venomous fishes of the Pacific area. In: Keegan HL, Macfarlane VN, eds. *Venomous and Poisonous Animals and Noxious Plants of the Pacific Region*. Oxford: Pergamon, 1963: 173–202.

3 Williamson JA, Fenner PJ, Burnett JW, Rifkin JF. *Venomous and Poisonous Marine Animals*. Sydney: University of New South Wales Press, 1996.
4 Cain D. Weever fish sting: an unusual problem. *BMJ* 1983; **287**: 406–7.
5 Davies RS, Evans RJ. Weever fish stings: a report of two cases presenting to an accident and emergency department. *J Accid Emerg Med* 1996; **13**: 139–41.
6 Scoggin CH. Catfish stings. *JAMA* 1975; **231**: 176–7.
7 Burnett JW. Aquatic adversaries: stonefish. *Cutis* 1998; **62**: 269–70.
8 Fenner J, Williamson JA, Skinner RA. Fatal and non-fatal stingray envenomation. *Med J Aust* 1989; **151**: 621–5.
9 Carducci M, Mussi A, Leone G, Catricalà C. Raynaud's phenomenon secondary to weever fish stings. *Arch Dermatol* 1996; **132**: 838–9.
10 Mayser P, Dreyer F, Repp H. Persistierende Hautreaktion und Raynaud-Syndrom nach einem Stich durch den Fisch Echiichthys draco. *Hautarzt* 2003; **54**: 633–7.
11 Auerbach PS. Marine envenomations. *N Engl J Med* 1991; **325**: 486–93.
12 Germain M, Smith KJ, Skelton H. the cutaneous infiltrate to stingray envenomation contains increased TIA+ cells. *Br J Dermatol* 2000; **143**: 1074–7.
13 Russell FE. Weever fish sting: the last word. *BMJ* 1983; **287**: 981–2.
14 Warrell DA, Fenner PJ. Venomous bites and stings. *Br Med Bull* 1993; **49**: 423–39.
15 Isbister GK. Venomous fish stings in tropical northern Australia. *Am J Emerg Med* 2001; **19**: 561–5.

Snake bites

The highest incidence of snake bites is in South America, West Africa, the Indian subcontinent and South-East Asia [1,2]. In India, there are an estimated 10 000 to 50 000 deaths a year, and in Burma, snake bites cause about 1000 deaths a year [3].

The effects of snake envenomation vary according to the composition of the venom, for example, bites of the spitting cobra (*Naja nigricollis*) produce local swelling and necrosis, haematological abnormalities and complement depletion [4]; the venom of the Malayan krait (*Bungarus candidus*) contains a toxin (bungarotoxin) that interferes with transmission at the neuromuscular junction [5]; marked coagulation disturbances occur after envenomation by Australian brown snakes (genus *Pseudonaja*) [6]. Surveys of deaths from snake bite in Australia [7,8] have shown that the majority were due to brown snakes.

Treatment [8]. The first-aid and field management of victims of snake bites in Australia changed when the compression bandage–splinting method of first-aid treatment was introduced by Sutherland [9], and shown to be effective [10]. This method consists of the application of a firm compression bandage to the limb that has sustained the bite, and its immobilization by splinting. The centripetal flow of venom is markedly impeded by this procedure. The offending snake should be killed if possible, and kept for identification by a qualified herpetologist. If the snake cannot be identified, venom detection kits are used on swabs taken from the bite site to determine the appropriate antivenom. Unfortunately, there is limited availability of antivenoms in other parts of the world [3].

References

1 Warrell DA. Venomous bites and stings in the tropical world. *Med J Aust* 1993; **159**: 773–9.
2 Warrell DA, Fenner PJ. Venomous bites and stings. *Br Med Bull* 1993; **49**: 423–39.
3 McNamee D. Tackling venomous snake bites worldwide. *Lancet* 2001; **357**: 1680.
4 Warrell DA, Greenwood BM, Davidson NMcD *et al*. Necrosis, haemorrhage and complement depletion following bites by the spitting cobra (*Naja nigricollis*). *Q J Med* 1976; **45**: 1–22.
5 Warrell DA, Looareesuwan S, White NJ *et al*. Severe neurotoxic envenoming by the Malayan krait *Bungarus candidus* (Linnaeus): response to antivenom and anticholinesterase. *BMJ* 1983; **286**: 678–80.
6 Morling AC, Marshall LR, Herrmann RP. Thrombocytopenia after brown snake envenomation. *Med J Aust* 1989; **151**: 627–8.
7 Sutherland SK. Deaths from snake bite in Australia, 1981–1991. *Med J Aust* 1992; **157**: 740–5.
8 Sutherland SK, Leonard RL. Snakebite deaths in Australia 1992–1994 and a management update. *Med J Aust* 1995; **163**: 616–8.
9 Sutherland SK. *Venomous Creatures of Australia—a Field Guide with Notes on First Aid*. Melbourne: Oxford University Press, 1982.
10 Pearn J, Morrison J, Charles N *et al*. First-aid of snake bite. Efficacy of a constrictive bandage with limb immobilization in the management of human envenomation. *Med J Aust* 1981; **2**: 293–5.

Other animal bites

An enormous variety of other animals may occasionally bite humans. Most bites cause a variable degree of crushing and tearing of the skin, and the devitalized tissue readily becomes infected by the wide range of microorganisms found in the mouths of animals.

Dog and cat bites [1–5]

The highest incidence of dog bites occurs in school-aged children, and boys are bitten twice as often as girls. In contrast, wounds caused by cats occur more commonly in girls.

Most infections which develop from dog and cat bites are polymicrobial, and include aerobic (*Staphylococcus* species, *Streptococcus* species and *Corynebacterium* species) and anaerobic (*Bacteroides fragilis, Prevotella, Porphyromonas, Peptostreptococcus, Fusobacterium* species and *Veillonella parvula*) organisms. Cat scratch disease, caused by *Bartonella henselae*, can follow a bite from a cat. There are a number of other potentially pathogenic organisms, including the following:

Capnocytophaga (formerly dysgonic fermenter type 2 [DF2]) [1,4,6–8]

Capnocytophaga canimorsus is part of the normal oral flora of healthy dogs, cats and a number of other animals.

The majority of reported *Capnocytophaga* infections have been associated with exposure to animals, about 80% following exposure to or bites from dogs. Previous splenectomy and alcoholism are important predisposing factors, but infection may occur in perfectly healthy persons.

The spectrum of illness ranges from local wound infection to fulminant septicaemia. Skin lesions include a localized eschar at the site of the bite, cellulitis, non-specific macular or maculopapular lesions, erythema multiforme [5], petechiae, purpura fulminans and symmetrical peripheral gangrene. The more severe changes occur as a consequence of septicaemia and disseminated intravascular coagulation [6–8].

Confirmation of infection depends upon identifying Gram-negative rods within polymorphs on peripheral blood films, and isolation from blood and tissue cultures. The organism is sensitive to penicillin and ciprofloxacin.

Pasteurella multocida [1,4]

This is an aerobic Gram-negative coccobacillus, which is a normal component of the oral flora of dogs and cats, and is frequently

isolated from infected bites. It is a virulent pathogen, which provokes an intense inflammatory response and is likely to cause metastatic infection. Tenosynovitis is a consequence of infection, particularly in hand bites.

Seal finger

Seal finger may be encountered wherever sealing takes place, and amongst wildlife workers and others who handle seals in zoos and aquaria [9,10]. It is associated with *Mycoplasma* spp. carried by seals [11].

The usual clinical picture is of a painful, swollen, slightly erythematous finger. There are usually no constitutional symptoms. Many cases resolve spontaneously with no sequelae, but in others joint involvement may lead to synovitis, osteitis, fibrosis of periarticular tissues and disfiguring arthropathy.

Tetracyclines are the treatment of choice [12].

Rodent bites

There are a number of reports of anaphylaxis following rodent bites [13–15].

Human bites

Human bites are quite common, clenched fist injuries ('fight bites') being the most prevalent, and may introduce dangerous bacterial infection [4]. Necrotizing fasciitis caused by group A streptococci has resulted from a human bite on the calf (at a Bavarian Oktoberfest!) [16]. Transmission of herpesvirus types 1 and 2, and hepatitis B and C, has also been documented. An epidemic of hepatitis B was traced to a carrier in a residential institution for the mentally retarded who regularly bit his fellow residents [17]. Biting is also a possible transmission mode for HIV infection [18].

A traumatic neuroma following a human bite on the forearm has been reported [19].

The possibility of physical abuse should be considered in children with human bites. However, most bites in children are inflicted by other children [20].

Treatment [1,5,21]. All animal and human bites are potentially dangerous, and thorough irrigation with normal saline, exploration and debridement are recommended. UK guidelines [21] recommend antibiotic prophylaxis with co-amoxiclav (amoxicillin and potassium clavulanate) for all human bites, and that this agent should also be used for the prophylaxis of 'high risk' animal bite wounds (this includes hand, foot and facial injuries, puncture wounds, and people at risk of wound infection complications, such as those who are immunosuppressed, diabetic, have cirrhosis, are asplenic, or have prosthetic heart valves).

Rabies should be considered as a possible sequel to any animal bite if this occurs in countries in which the disease is endemic.

References

1 Morgan M, Palmer J. Dog bites. *BMJ* 2007; **334**: 413–7.
2 Rosenkrans JA. Animal and human bites. In: Barkin RM, ed. *Pediatric Emergency Medicine*, 2nd edn. St Louis: Mosby, 1997: 459–64.
3 Wright JC. Repeated cat bites in Dallas: characteristics of the cats, the victims and the attack events. *Public Health Rep* 1990; **105**: 420–4.
4 Griego RD, Rosen T, Orengo IF, Wolf JE. Dog, cat, and human bites: a review. *J Am Acad Dermatol* 1995; **33**: 1019–29.
5 Talan DA, Citron DM, Abrahamian FM *et al*. Bacteriologic analysis of infected cat and dog bites. *N Engl J Med* 1999; **340**: 85–92.
6 Pers C, Gahrn-Hansen B, Frederiksen W. *Capnocytophaga canimorsus* septicaemia in Denmark, 1982–1995: review of 39 cases. *Clin Infect Dis* 1996; **23**: 71–5.
7 Herbst JS, Raffanti S, Pathy A *et al*. Dysgonic fermenter type 2 septicemia with purpura fulminans. Dermatologic features of a zoonosis acquired from household pets. *Arch Dermatol* 1989; **125**: 1380–2.
8 Aslam A. Life-threatening *Capnocytophaga canimorsus* infection after dog bite. *J R Soc Med* 1999; **92**: 140–1.
9 Landau BM, Hegarty MA. Seal finger. *BMJ* 1989; **299**: 928.
10 Lewin MR, Knott P, Lo M. Seal finger. *Lancet* 2004; **364**: 448.
11 Baker AS, Ruoff KL, Madoff S. Isolation of *Mycoplasma* species from a patient with seal finger. *Clin Infect Dis* 1998; **27**: 1168–70.
12 Hartley JW, Pitcher D. Seal finger—tetracycline is first line. *J Infect* 2002; **45**: 71–5.
13 Teasdale EL, Davies GE, Slovak A. Anaphylaxis after bites by rodents. *BMJ* 1983; **286**: 1480.
14 Thewes M, Rakoski J, Ring J. Anaphylactic reaction after a mouse bite in a 9-year-old girl. *Br J Dermatol* 1999; **141**: 179.
15 Tomitaka A, Suzuki K, Akamatsu H, Matsunaga K. Anaphylaxis after hamster bites: a rare case? *Contact Dermatitis* 2002; **46**: 113.
16 Wienert P, Heiss J, Rinecker H, Sing A. A human bite. *Lancet* 1999; **354**: 572.
17 Cancio-Bello TP, de Medina M, Shorey J *et al*. An institutional outbreak of hepatitis B related to a human biting carrier. *J Infect Dis* 1982; **146**: 652–6.
18 Pretty IA, Anderson GS, Sweet DJ. Human bites and the risk of human immunodeficiency virus transmission. *Am J Forensic Med Pathol* 1999; **20**: 232–9.
19 Thami GP, Kaur S, Kanwar AJ. Traumatic neuroma following a human bite. *Clin Exp Dermatol* 2002; **27**: 76–7.
20 Baker MD, Moore SE. Human bites in children. *Am J Dis Child* 1987; **141**: 1285–90.
21 http://cks.library.nhs.uk/bites_human_and_animal

CHAPTER 39
Genetic Blistering Diseases

J.-D. Fine[1] *& S.M. Burge*[2]

[1]School of Medicine, Vanderbilt University, Nashville, TN, USA
[2]Churchill Hospital, Oxford, UK

Epidermolysis bullosa, 39.1
Definition and classification, 39.1
Prevalence and incidence, 39.3
Epidermolysis bullosa simplex, 39.3
Junctional epidermolysis bullosa, 39.9
Dystrophic epidermolysis bullosa, 39.15
Diagnosis, 39.24
Differential diagnosis, 39.27
Treatment, 39.27
Hailey–Hailey disease, 39.32
Segmental Hailey–Hailey disease, 39.37

Introduction

The hereditary blistering disorders described in this chapter, although uncommon, may have a dramatic impact on the patient and their family, and severe economic consequences for their relatives and health services. These diseases have been the subject of intensive study in recent years, and the discovery of the causative genes underlying Hailey–Hailey disease, Kindler syndrome, and all the major types of epidermolysis bullosa (EB), has increased our knowledge not only of the pathogenesis of these disorders, but also of the normal biology of the skin. This is exemplified by the way the graded severity of the clinical features, and associated structural changes in the dermal–epidermal junction, of the dystrophic forms of EB, can be explained by the nature of the mutations in the *COL7A1* gene encoding the structural protein, collagen VII [1], as can differences in the severity of EB simplex be explained by the sites and types of mutations which occur in the genes encoding for keratins 5 and 14. The strategies used to track down the genetic causes of Hailey–Hailey disease, Kindler syndrome and EB provide interesting contrasts. In most forms of inherited EB, the candidate genes and proteins were suggested by earlier ultrastructural and immunohistochemical studies of the skin of affected patients before linkage and mutation analysis pinpointed conclusively the locus and identity of the causative gene. There were no similar clues to discovering the causative gene, *ATP2C1*, in Hailey–Hailey disease, or the gene associated with Kindler syndrome. Indeed, before it was found that mutations in *ATP2C1* could result in Hailey–Hailey disease [2] and in the gene encoding for the protein, kindlin, in Kindler syndrome, most dermatologists or skin biologists were unaware of their existence.

Knowledge of the ultrastructure and molecular composition of the epidermis and dermal–epidermal junction is necessary for understanding the tissue and molecular pathology that underlies this group of disorders.

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

References

1 Hovnanian A, Rochat A, Bodemer C *et al*. Characterization of 18 new mutations in *COL7A1* in recessive dystrophic epidermolysis bullosa provides evidence for distinct molecular mechanisms underlying defective anchoring fibril formation. *Am J Hum Genet* 1997; **61**: 599–610.

2 Hu Z, Bonifas JM, Beech J *et al.* Mutations in *ATP2C1*, encoding a calcium pump, cause Hailey–Hailey disease. *Nat Genet* 2000; **24**: 61–5.

Epidermolysis bullosa

J.-D. Fine, pp. 39.1–39.32

Definition and classification

EB comprises a group of genetically determined skin fragility disorders characterized by blistering of the skin and mucosae following mild mechanical trauma. The alternative term therefore is *mechanobullous diseases* [1]. The descriptive term *epidermolysis* is illogical because epidermal disruption is not the primary change in two of three main categories of EB. However, the name *epidermolysis bullosa*, as originally used by Koebner [2] in 1886, is now so well established in the literature that it is still the preferred term.

Classification of this complex and heterogeneous group of disorders is difficult, and not helped by the large variety of names and eponyms that have traditionally been used. Initial classification schemes were based largely on the mode of inheritance and clinical studies involving relatively few patients and families [3, reviewed in 4]. While these early observations were clearly important in establishing EB as an entity, a major step forward was made by Pearson [5] who used electron microscopy to show that the ultrastructural level of tissue cleavage (blister formation) in the skin is distinctive in the three major groups of EB: EB simplex, junctional EB and dystrophic EB. Subsequent studies have revealed a number of associated ultrastructural abnormalities, which have also proved to be important in the diagnosis and classification of EB [6–9]. In addition, the application of immunohistochemical studies, particularly a specialized form of immunofluorescence microscopy known as immunofluorescence mapping, has had a major role in differentiating certain forms of EB, and in helping to

Table 39.1 Revised classification system for epidermolysis bullosa (EB) [13].

Site of cleavage	Major EB type	EB subtypes	Targeted gene product(s)
Epidermolytic	EB simplex		
	Suprabasal	Plakophilin deficiency	plakophilin-1
		Lethal acantholytic EBS	desmoplakin
		EBS superficialis	unknown
	Basal	Localized EBS	keratins 5 & 14
		EBS, Dowling–Meara	keratins 5 & 14
		EBS, generalized other	keratins 5 & 14
		EBS, autosomal recessive	keratin 14
		EBS with mottled hyperpigmentation	keratin 5
		EBS with muscular dystrophy	plectin
		EBS, Ogna	plectin
		EBS, migratory circinate	keratin 5
		EBS with pyloric atresia	α6β4 integrin, plectin
Lamina lucidolytic	Junctional EB	JEB, Herlitz	laminin 5 (laminin 332)
		JEB, non-Herlitz	laminin 5 (laminin 332); type XVII collagen
		JEB with pyloric atresia	α6β4 integrin
		JEB, inversa	laminin 5 (laminin 332)
		JEB, late onset	unknown
		LOC syndrome	laminin 5 (laminin 332)
Dermolytic	Dystrophic EB		
	Dominant DEB	DDEB, generalized	type VII collagen
		DDEB, acral	type VII collagen
		DDEB, pretibial	type VII collagen
		DDEB, pruriginosa	type VII collagen
		DDEB, nails only	type VII collagen
		DDEB-bullous dermolysis of the newborn	type VII collagen
	Recessive DEB	RDEB, severe generalized	type VII collagen
		RDEB, generalized, other	type VII collagen
		RDEB, inversa	type VII collagen
		RDEB, pruriginosa	type VII collagen
		RDEB, centripetalis	type VII collagen
		RDEB, bullous dermolysis of the newborn	type VII collagen
Mixed	Kindler syndrome		kindlin-1

uncover the underlying molecular abnormalities by demonstrating specific antigenic changes in the dermal–epidermal junction of patients with different forms of the disease [10–12]. In 2008, a new classification system was proposed for EB which takes into account phenotypes and genotypes of EB discovered more recently, as well as selected entities (such as Kindler syndrome and plakophilin deficiency) which, although previously not included within the breadth of EB, share with more traditional forms of EB the presence of inherited mechanical fragility and blistering [13]. As a correlate, some entities were renamed so as to better facilitate their recognition by clinicians, and many of the eponyms were eliminated. This is summarized in Table 39.1.

This newly revised classification scheme, based on the recommendations of an international consensus group of clinicians with expertise in EB, supersedes two previously published schemes [14,15] and is targeted for use by clinicians. Whenever possible, molecular differences have been taken in account, although it is still believed that genotype–phenotype correlation is too weak within most EB types to argue instead for adoption of a classification system which first requires elucidation of mutations in every patient. The latter is further hampered by the inability of patients in some countries to readily afford DNA testing. Nevertheless, the ever increasing knowledge of the molecular basis of EB will doubtless continue to be crucial for enabling accurate diagnosis, mainly for genetic counselling and prognosis, and will eventually be the basis for gene therapy.

References

1 Pearson RW. The mechanobullous diseases (epidermolysis bullosa). In: Fitzpatrick TB, Arndt KA, Clark WH *et al*. eds. *Dermatology in General Medicine*. New York: McGraw-Hill, 1971: 621–47.

2 Koebner H. Hereditare anlage zur blasenbildung (epidermolysis bullosa hereditare). *Dtsch Med Wochenschr* 1886; **12**: 21–2.

3 Cockayne EA. *Inherited Abnormalities in the Skin and its Appendages*. London: Oxford University Press, 1993: 118–33.

4 Gedde-Dahl T Jr. *Epidermolysis Bullosa: a Clinical, Genetic and Epidemiological Study*. Baltimore: Johns Hopkins University Press, 1971.

5 Pearson RW. Studies on the pathogenesis of epidermolysis bullosa. *J Invest Dermatol* 1962; **39**: 551–75.

6 Briggaman RA, Wheeler CE Jr. Epidermolysis bullosa dystrophica recessive: a possible role of anchoring fibrils in the pathogenesis. *J Invest Dermatol* 1975; **65**: 203–11.

7 Eady RAJ, McGrath JA, McMillan JR. Ultrastructural clues to genetic disorders of skin: the dermal–epidermal junction. *J Invest Dermatol* 1994; **103**: 13S–8S.
8 Anton-Lamprecht I. Ultrastructural identification of basic abnormalities as clues to genetic disorders of the epidermis. *J Invest Dermatol* 1994; **103**: 6S–12S.
9 Smith L. Ultrastructural findings in epidermolysis bullosa. *Arch Dermatol* 1993; **129**: 1578–84.
10 Eady RAJ, Tidman MJ, Heagerty AHM, Kennedy AR. Approaches to the study of epidermolysis bullosa. *Curr Probl Dermatol* 1987; **17**: 127–41.
11 Fine J-D. Structure and antigenicity of the skin basement membrane zone. *J Cutan Pathol* 1991; **18**: 401–9.
12 Christiano AM, Uitto J. Molecular complexity of the cutaneous basement membrane zone. *Exp Dermatol* 1996; **5**: 1–11.
13 Fine J-D, Eady RAJ, Bauer EA *et al*. The classification of inherited epidermolysis bullosa (EB): Report of the Third International Consensus Meeting on Diagnosis and Classification. *J Am Acad Derm* 2008; **58**: 931–50.
14 Fine J-D, Bauer EA, Briggaman RA *et al*. Revised clinical and laboratory criteria for subtypes of inherited epidermolysis bullosa. *J Am Acad Dermatol* 1991; **24**: 119–35.
15 Fine J-D, Eady RA, Bauer EA *et al*. Revised classification system for inherited epidermolysis bullosa. Report of the Second International Consensus Meeting on Diagnosis and Classification of Epidermolysis Bullosa. *J Am Acad Dermatol* 2000; **42**: 1051–66.

Prevalence and incidence

The most accurate data available on the incidence and prevalence of EB are derived from the National EB Registry (USA) project, a longitudinal study of approximately 3300 patients within the continental USA [1]. The incidence and prevalence of EB are estimated to be 19.60 per million live births and 8.22 per million population, respectively. Similarly, the incidence and prevalence rates for EB simplex are 10.75 and 4.60; junctional EB 2.04 and 0.44; dominant dystrophic EB 2.86 and 0.99; and recessive dystrophic EB 2.04 and 0.92, respectively. Comparison of these data with those derived from smaller populations (e.g. in Norway [2], Finland [3], Croatia [4], Northern Ireland [5], Scotland [6] and Italy [7]) suggests little if any differences reported across the major types and subtypes of EB (reviewed in [1]). These data suggest that there is no gender, racial, ethnic or geographical predilection for EB. It should be remembered, however, that these reported rates probably underestimate the true prevalence and incidence of EB, especially the clinically milder forms, because of recruitment or selection bias.

References

1 Fine J-D, Johnson LB, Suchindran C *et al*. The epidemiology of inherited epidermolysis bullosa: findings in the US, Canadian and European study populations. In: Fine J-D, Bauer EA, McGuire J, Moshell A, eds. *Clinical, Epidemiologic and Laboratory Advances and the Findings of the National Epidermolysis Bullosa Registry*. Baltimore: Johns Hopkins University Press, 1999: 101–13.
2 Gedde-Dahl T Jr. *Epidermolysis Bullosa: a Clinical, Genetic and Epidemiological Study*. Baltimore: Johns Hopkins University Press, 1971.
3 Kero M. Occurrence of epidermolysis bullosa in Finland. *Acta Derm Venereol (Stockh)* 1984; **64**: 57–62.
4 Pavicic Z, Kmet-Vizintin P, Kansky A, Dobric I. Occurrence of hereditary bullous epidermolysis in Croatia. *Pediatr Dermatol* 1990; **7**: 108–10.
5 McKenna KE, Walsh MY, Bingham EA. Epidermolysis in Northern Ireland. *Br J Dermatol* 1992; **127**: 318–21.
6 Horn HIM, Priestley GC, Eady RAJ, Tidman MJ. The prevalence of epidermolysis bullosa in Scotland. *Br J Dermatol* 1997; **136**: 560–4.
7 Tadini G, Gaulandri L, Colombi M *et al*. The Italian registry of hereditary epidermolysis bullosa. *G Ital Dermatol Venereol* 2005; **140**: 359–72.

Epidermolysis bullosa simplex

EB simplex is the most frequent form of EB, accounting for at least 50% of patients enrolled by the National EB Registry (USA) [1].

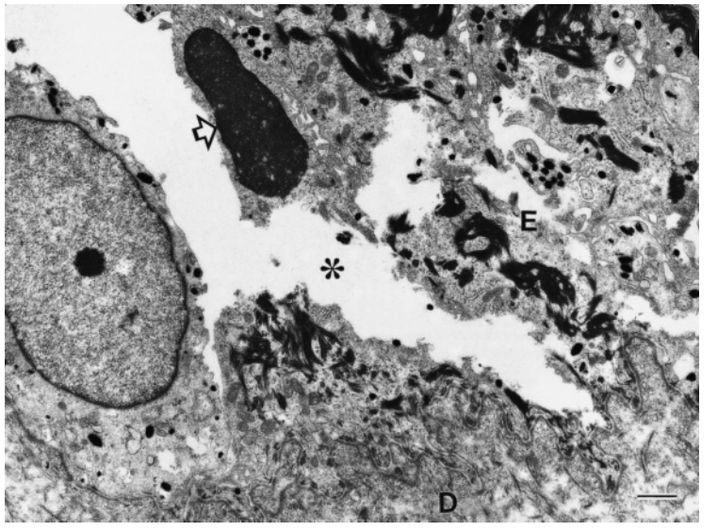


Fig. 39.1 Electron micrograph showing blister formation in epidermolysis bullosa simplex (Dowling–Meara). A split (*) is present in the epidermal basal layer (E), which contains electron-dense tonofilament (keratin) clumps (arrow). D, dermis; Bar = 1 μm. (Courtesy of Professor R.A.J. Eady, St John's Institute of Dermatology, London, U.K.)

Given the recognized underreporting of EB simplex, it is likely that at least two-thirds of all EB patients have this form of EB. The inheritance is chiefly autosomal dominant, and it is not uncommon to see affected individuals in three generations. Rarely, EB simplex may be transmitted as an autosomal recessive trait.

Reference

1 Fine J-D, Johnson LB, Suchindran C *et al*. The epidemiology of inherited epidermolysis bullosa: findings in the US, Canadian and European study populations. In: Fine J-D, Bauer EA, McGuire J, Moshell A, eds. *Clinical, Epidemiologic and Laboratory Advances and the Findings of the National Epidermolysis Bullosa Registry*. Baltimore: Johns Hopkins University Press, 1999: 101–13.

Molecular pathology [1,2]

In all forms of EB simplex, blister formation is intraepidermal. Most EB subtypes begin with the disruption of basal keratinocytes, although rare subtypes ('suprabasal') result from mechanical instability and cleavage within the uppermost epidermis. Genetic linkage analysis [3] and transgenic mouse experiments [4] led to the discovery that mutations in the basal keratin pair, K5 and K14, could result in EB simplex. It was shown that expression of mutant keratins in cultured cells gave rise to dense keratin aggregates [5]. Similar aggregates or keratin filament clumps were seen in the basal epidermis (Fig. 39.1) [6,7] or cultured keratinocytes [8] of patients with the Dowling–Meara form of EB simplex. Immunoelectron microscopic studies labelled the abnormal filament clumps with K5 and K14 antibodies [9]. In general, a correlation exists between the position of the mutation on the *KRT5* or *KRT14* genes and the resulting phenotype (Fig. 39.2). For example, the most severe form of EB simplex, the Dowling–Meara subtype, is usually caused by missense mutations in the initiation or termination peptides of the rod domains [10,11], which are evolutionarily highly conserved and thought to have a critical role in keratin filament assembly and structural integrity. Mutations in *KRT5* and

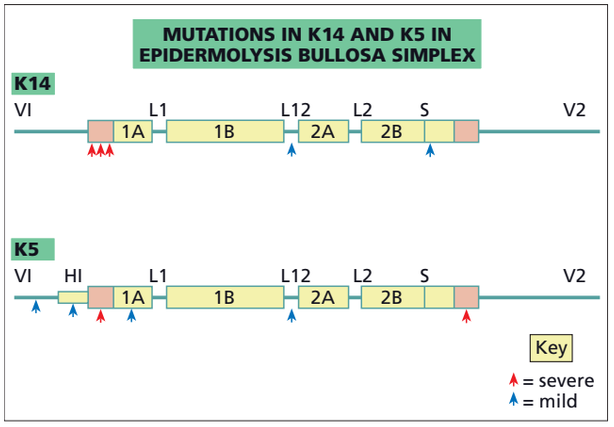


Fig. 39.2 Schematic representation of the type II (keratin 5) and type I (keratin 14) proteins, with position of mutations (arrowed). Each keratin has an α-helical rod domain (boxed areas) with head and tail domains at each end. The pink boxes represent the highly conserved helix boundary sequence motifs. The mutations causing Dowling–Meara epidermolysis bullosa simplex occur in these boundary peptides and are known to be highly disruptive to keratin filament assembly. (Modified from a figure provided by Professor E.B. Lane.) (Courtesy of Professor R.A.J. Eady, St John's Institute of Dermatology, London, U.K.)

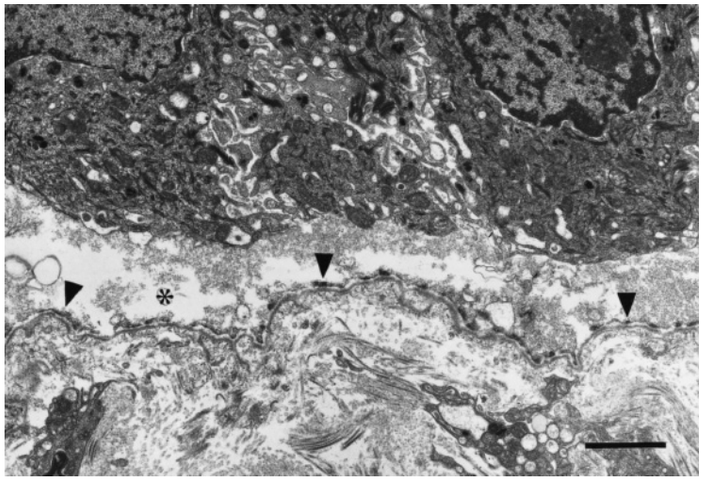


Fig. 39.3 Electron micrograph showing a low level of intraepidermal blister formation in epidermolysis bullosa simplex associated with muscular dystrophy. The split (*) is above hemidesmosomes (arrowheads) and associated plasma membrane. Bar = 2 μm. (Courtesy of Professor R.A.J. Eady, St John's Institute of Dermatology, London, U.K.)

KRT14 have also been described in localized EBS (formerly named Weber–Cockayne EBS) [12–14]. In this subtype of EB simplex, which is milder than the Dowling–Meara form, mutations occur outside the highly conserved boundary motifs, and chiefly in other parts of rod domain or the L12 linker region [13]. In the localized or non-Dowling–Meara generalized variants of EB simplex (formerly named Koebner EB simplex) and in the form of EB simplex associated with mottled pigmentation, the basal cell keratin filaments are not consistently abnormal and do not show the major changes that characterize Dowling–Meara EB simplex. A heterozygous C to T transition at base position 71 in the non-helical VI domain of *KRT5*, causing a proline to leucine substitution, has been reported in three unrelated families with EB simplex and mottled pigmentation [15,16]. The cause of the pigmentary changes is unknown. Recessive forms of EB simplex would appear to be very rare; however, at least two families with autosomal recessive EB simplex with a Weber–Cockayne phenotype have been recognized [17,18]. In three cases with widespread blistering, more in keeping with a Koebner phenotype, normal keratin filaments were absent in the basal epidermal layer, as was K14 protein expression [19–21]. However, K5 expression appeared normal. These cases were thought to represent the first functional knockouts of K14. Subsequently, a large kindred with EB simplex was described, also with ablation of K14, caused by a homozygous splice-site mutation [22]. A further autosomal recessive form of EB is associated with muscular dystrophy, and on occasion other abnormalities affecting the central nervous system. The ultrastructural level of tissue separation begins at a very low level in the basal cells, just above the hemidesmosomes and adjacent basal plasma membrane (Fig. 39.3) [23–28]. The level of cleavage in this form of EB may appear, in part, to be within the lamina lucida; therefore these ultrastructural findings, together with the clinical similarities of this form of EB with non-Herlitz junctional EB (see below), have led to the description of 'pseudojunctional EB' [28].

Immunofluorescence microscopy of skin from affected individuals shows diminished or absent staining for plectin [25–27], a 500-kDa protein, which is distributed among a variety of tissues, including stratified squamous epithelia, nerve and muscle [29,30]. Homozygous mutations in the plectin gene, *PLEC1* on chromosome 8q24, have been described in several families with the disease [26,27, reviewed in 31] and in two unrelated children with EB simplex associated with mucosal lesions in the respiratory tract, but without evidence of concurrent myopathy [32]. The rare autosomal dominant, Ogna form of EB simplex has also been found to be caused by a *PLEC1* mutation [33]. Recently two extremely rare entities, plakophilin deficiency and lethal acantholytic EBSEB simplex, both associated with suprabasal blistering, have been shown to result from mutations in the genes encoding for plakophilin-1 and desmoplakin, respectively [34,35].

Certain patients, who might otherwise have been diagnosed as having a form of junctional EB, by virtue of their clinical presentation or molecular findings, have been found to have an intraepidermal level of tissue cleavage in their skin, and have therefore been classified (or reclassified) as having EB simplex. This applies mainly to patients with EB associated with pyloric atresia [36,37], but has also been described in patients whose mutations result in deletions of the cytoplasmic domains of collagen XVII [38] or β4 integrin [39].

References

1 Leigh IM, Lane EB. Mutations in the genes for epidermal keratins in epidermolysis bullosa and epidermolytic hyperkeratosis. *Arch Dermatol* 1993; **129**: 1571–7.

2 Irvine AD, McLean WHI. Human keratin diseases: the increasing spectrum of disease and subtlety of the phenotype–genotype correlation. *Br J Dermatol* 1999; **140**: 815–28.

3 Bonifas JM, Rothman AL, Epstein EH. Epidermolysis bullosa simplex: evidence in two families for keratin gene abnormalities. *Science* 1991; **254**: 1202–5.

4 Vassar R, Coulombe PA, Degenstein L *et al*. Mutant keratin expression in transgenic mice causes marked abnormalities resembling a human genetic skin disease. *Cell* 1991; **64**: 365–80.

5 Albers K, Fuchs E. Expression of mutant keratin cDNAs in epithelial cells reveals possible mechanisms for initiation and assembly of intermediate filaments. *J Cell Biol* 1989; **108**: 1477–93.
6 Anton-Lamprecht I, Schnyder UW. Epidermolysis bullosa herpetiformis Dowling–Meara: report of a case and pathomorphogenesis. *Dermatologica* 1982; **164**: 221–98.
7 Niemi KM, Kero M, Kanerva L, Mattila R. Epidermolysis bullosa simplex: a new histological subgroup. *Arch Dermatol* 1983; **119**: 138–41.
8 Kitajima Y, Inoue S, Yaoita H. Abnormal organization of keratin intermediate filaments in cultured keratinocytes of epidermolysis bullosa simplex. *Arch Dermatol Res* 1989; **281**: 5–10.
9 Ishida-Yamamoto A, McGrath JA, Chapman SJ *et al.* Epidermolysis bullosa simplex (Dowling–Meara type) is a genetic disease characterized by an abnormal keratin filament network involving keratins K5 and K14. *J Invest Dermatol* 1991; **97**: 959–68.
10 Coulombe PA, Hutton ME, Letai A *et al.* Point mutations in human keratin 14 genes of epidermolysis bullosa simplex patients: genetic and functional analysis. *Cell* 1991; **66**: 1301–11.
11 Lane EB, Rugg EL, Navsaria H *et al.* A mutation in the conserved helix termination peptide of keratin 5 in hereditary skin blistering. *Nature* 1992; **356**: 244–6.
12 Humphries MM, Sheils DM, Farrar GH *et al.* A mutation (Met-to-Arg) in the type I keratin (K14) gene responsible for autosomal dominant epidermolysis bullosa simplex. *Hum Mutat* 1993; **2**: 37–42.
13 Rugg EL, Morley SM, Smith FJD *et al.* Missing links: keratin mutations in Weber–Cockayne EBS families implicate the central L12 linker domain in effective cytoskeleton function. *Nat Genet* 1993; **5**: 294–300.
14 Chan Y-M, Yu Q-C, Fine J-D, Fuchs E. The genetic basis of Weber–Cockayne epidermolysis bullosa simplex. *Proc Natl Acad Sci USA* 1993; **90**: 7414–8.
15 Yu Q-C, Gedde-Dahl T, Fine J-D, Fuchs E. The genetic basis of epidermolysis bullosa simplex with mottled pigmentation. *Proc Natl Acad Sci USA* 1996; **93**: 9079–84.
16 Irvine AD, McKenna KE, Jenkinson H, Hughes HE. A mutation in the VI domain of keratin 5 causes epidermolysis bullosa simplex with mottled pigmentation. *J Invest Dermatol* 1997; **108**: 809–10.
17 Fine J-D, Johnson L, Wright T, Horiguchi Y. Epidermolysis bullosa simplex: identification of a kindred with autosomal recessive transmission of the Weber–Cockayne variety. *Pediatr Dermatol* 1989; **6**: 1–5.
18 Hovnanian A, Pollack E, Hilal L *et al.* A missense mutation in the rod domain of keratin 14 associated with recessive epidermolysis bullosa simplex. *Nat Genet* 1993; **2**: 327–32.
19 Rugg EL, McLean WHI, Lane EB *et al.* A functional 'knockout' for human keratin 14. *Genes Dev* 1994; **8**: 2563–73.
20 Chan Y, Anton-Lamprecht I, Yu Q-C *et al.* A human keratin 14 'knockout': the absence of K14 leads to severe epidermolysis bullosa simplex and a function for an intermediate filament protein. *Genes Dev* 1994; **8**: 2574–87.
21 Jonkman MF, Heeres K, Pas HH *et al.* Effects of keratin 14 ablation on the clinical and cellular phenotype in a kindred with recessive epidermolysis bullosa simplex. *J Invest Dermatol* 1996; **107**: 764–9.
22 Corden LD, Mellerio J, Gratian M *et al.* Homozygous nonsense mutation in helix 2 of K14 causes severe recessive epidermolysis bullosa simplex. *Hum Mutat* 1998; **11**: 279–85.
23 Niemi KM, Sommer H, Kero M *et al.* Epidermolysis bullosa simplex associated with muscular dystrophy with recessive inheritance. *Arch Dermatol* 1988; **124**: 551–4.
24 Fine J-D, Stenn J, Johnson L *et al.* Autosomal recessive epidermolysis bullosa simplex: generalized phenotypic features suggestive of junctional or dystrophic epidermolysis bullosa, and association with neuromuscular diseases. *Arch Dermatol* 1989; **125**: 931–8.
25 Gache Y, Chavanas S, Lacour JP *et al.* Defective expression of plectin/HD1 in epidermolysis bullosa simplex with muscular dystrophy. *J Clin Invest* 1996; **97**: 2289–98.
26 Smith FJD, Eady RAJ, Leigh IM *et al.* Plectin deficiency results in muscular dystrophy with epidermolysis bullosa. *Nat Genet* 1996; **13**: 450–6.
27 McLean WHI, Pulkkinen L, Smith FJD *et al.* Loss of plectin causes epidermolysis bullosa with muscular dystrophy: cDNA cloning and genomic organization. *Genes Dev* 1996; **10**: 1724–35.
28 Gedde-Dahl T Jr. Epidermolysis bullosa simplex (intraepidermal epidermolysis bullosa) and allied conditions. In: Wojnarowska F, Briggaman RA, eds. *Management of Blistering Diseases*. London: Chapman & Hall, 1990: 189–211.
29 Wiche G, Krepler R, Artlieb U *et al.* Occurrence and immunolocalization of plectin in tissues. *J Cell Biol* 1983; **97**: 887–901.
30 Hieda Y, Nishizawa Y, Uematsu J, Owaribe K. Identification of a new hemidesmosomal protein, HD1: a major high molecular mass component of isolated hemidesmosomes. *J Cell Biol* 1992; **116**: 1497–506.
31 Pulkkinen L, Smith FJD, Shimizu H *et al.* Homozygous deletion mutations in the plectin gene (*PLEC1*) in patients with epidermolysis bullosa simplex associated with late-onset muscular dystrophy. *Hum Mol Genet* 1996; **5**: 1539–46.
32 Mellerio JE, McMillan JR, McGrath JA *et al.* Recessive epidermolysis bullosa simplex associated with plectin mutations: infantile respiratory complications in two unrelated cases. *Br J Dermatol* 1997; **137**: 898–906.
33 Koss-Harnes D, Hoyheim B, Anton-Lamprecht I *et al.* A site-specific plectin mutation causes dominant epidermolysis bullosa simplex Ogna: two identical *de novo* mutations. *J Invest Dermatol* 2002; **118**: 87–93.
34 McGrath JA, McMillan JR, Shemano CS *et al*. Mutations in the plakophilin 1 gene result in ectordemal dysplasia/skin fragility syndrome. *Nat Genet* 1997; **17**: 240–4.
35 Jonkman MF, Pasmooij AM, Pasmans SG *et al*. Loss of desmoplakin tail causes lethal acantholytic epidermolysis bullosa. *Am J Hum Genet* 2005; **77**: 653–60.
36 Smith LT. Ultrastructural findings in epidermolysis bullosa. *Arch Dermatol* 1993; **129**: 1578–84.
37 McMillan JR, McGrath JA, Tidman MJ, Eady RAJ. Hemidesmosomes show abnormal association with the keratin filament network in junctional forms of epidermolysis bullosa. *J Invest Dematol* 1998; **110**: 132–7.
38 Jonkman MF, Pas HH, Nijenhuis M *et al*. Deletion of a cytoplasmic domain of integrin β4 causes epidermolysis bullosa simplex. *J Invest Dermatol* 2002; **119**: 1275–81.
39 Huber M, Floeth M, Borradori L *et al.* Deletion of the cytoplasmic domain of BP180/collagen XVII causes a phenotype with predominant features of epidermolysis bullosa simplex. *J Invest Dermatol* 2002; **118**: 185–92.

Clinical subtypes

The various clinical subtypes of EB simplex are as follows.

Suprabasal subtypes of EB simplex

Epidermolysis bullosa simplex superficialis

Epidermal cleavage is typically just beneath the stratum corneum. This autosomal dominant condition, originally reported in seven patients [1], is characterized by the presence of superficial erosions rather than intact blisters, similar to those seen in pemphigus foliaceous. Healing results in localized atrophic scarring or post-inflammatory hyperpigmentation. The finding of mutations within the type VII collagen gene, *COL7A1*, in one kindred with EB superficialis [2], suggested that the diagnosis was an atypical form of dystrophic EB rather than EB simplex in these cases. Further molecular studies are needed to clarify whether other patients with EB superficialis also have mutations in *COL7A1*.

References

1 Fine J-D, Johnson L, Wright T. Epidermolysis bullosa simplex superficialis: a new variant of epidermolysis bullosa characterized by subcorneal skin cleavage mimicking peeling skin syndrome. *Arch Dermatol* 1989; **125**: 633–8.
2 Martinez-Mir A, Liu J, Gordon D *et al.* EB simplex superficialis resulting from a mutation in the type VII collagen gene. *J Invest Dermatol* 2002; **118**: 547–9.

Plakophilin-1 deficiency and lethal acantholytic EB simplex

Two recently recognized disorders, plakophilin deficiency and lethal acantholytic EB simplex, have been included among the

suprabasal subtypes of EB simplex. The former is an autosomal recessive form of ectodermal dysplasia associated with congenital skin fragility, caused by mutations in the plakophilin 1 gene [1,2]. It appears at birth and is generalized in distribution. Superficial erosions, oftentimes circinate in configuration, and, to a lesser extent, also blistering, are characteristic features of this entity. Other clinical findings may include abnormal nails, hypotrichosis, focal keratoderma, perioral and tongue fissures, constipation, oesophageal stricture, blepharitis, and absent or sparse eyelashes. Lethal acantholytic EB, as described by Jonkman *et al.* [3] in a single patient, is associated with mutations in the gene encoding for desmoplakin. Also autosomal recessive, it is present at birth and generalized in skin distribution. A characteristic feature is the presence of oozing erosions rather than frank blisters. Other findings include markedly abnormal nails, neonatal teeth, intraoral erosions and alopecia of the scalp. The gastrointestinal, genitourinary, and respiratory tracts are also involved.

References

1 McGrath JA, McMillan JR, Shemanko CS *et al.* Mutations in the plakophilin 1 gene result in ectodermal dysplasia–skin fragility syndrome. *Nat Genet* 1997; **17**: 240–4.

2 Hamada T, South AP, Mitsuhashi Y *et al.* Genotype–phenotype correlation in skin fragility–ectodermal dysplasia syndrome resulting from mutations in plakophilin 1. *Exp Dermatol* 2002; **11**: 107–14.

3 Jonkman MF, Pasmooji AM, Pasmans SG *et al*. Loss of desmoplaskin tail causes lethal acantholytic epidermolysis bullosa. *Am J Hum Genet* 2005; **77**: 653–60.

Basal subtypes of EB simplex

Localized EB simplex (formerly Weber–Cockayne EBS)

This is the most common type of EB. The palms and soles (Fig. 39.4) are mainly affected, with the exception of the sides of the toes, where blistering may be particularly painful. Many patients have blisters only on the feet, and a minority (approximately 10%) will have blisters at other sites, such as the waist or neck, especially in hot weather and after friction from clothing or other sources. In the large majority of patients, blistering starts in childhood, but there are reports of the onset being delayed until early adult life, and brought out by strenuous physical activity [1]. The condition is always worse in warm weather. Hyperhidrosis of the feet is common; this increases friction, which also exacerbates blistering. The blisters usually heal without clinically significant scarring or milia formation, although both may infrequently be seen. Discrete and sometimes punctate calluses are very common, especially in adults. Although troublesome blistering or ulceration of the oral mucosa is rare, at least 25% of infants may develop occasional small intraoral lesions, especially palatal and worsened by trauma from feeding bottle nipples. The hair and teeth are normal; nail dystrophy is infrequent, and is usually localized and mild when it does occur.



Fig. 39.4 Blisters on a foot in a patient with localized epidermolysis bullosa simplex. (Courtesy of Professor R.A.J. Eady, St John's Institute of Dermatology, London, U.K.)

Reference

1 Lin AN, Carter DM, eds. Epidermolysis bullosa simplex: a clinical overview. In: *Epidermolysis Bullosa: Basic and Clinical Aspects*. New York: Springer, 1992: 89–117.

Generalized epidermolysis bullosa simplex, non-Dowling–Meara variant (formerly Koebner EBS) [1,2]

This is one of the two major subtypes of generalized EB simplex. Although usually mild, approximately 60% of patients have localized scarring and approximately 16% have milia. Development of hair, teeth and nails is normal. The nails rarely may be involved by blisters, but are only temporarily shed. Blisters appear within the first year and may be present at birth. In infancy, they commonly appear on the occiput, back and legs, while in childhood the hands and feet are often affected, although the palms and soles are not preferentially involved, as in localized EB simplex. In common with other forms of EB simplex, blistering is worse in warm weather. Although blistering occurs throughout life, some patients are alleged to improve after puberty.

In some authors' experience, this subtype of EB simplex is rare in comparison with the localized or Dowling–Meara forms of EB simplex. At times it may be difficult to readily distinguish this EB simplex subtype from patients with documented localized EB simplex who are experiencing a severe flare. In particular, approximately 10% of patients with the localized form of EB will at some time have experienced blistering at sites other than the palms and soles (see above) [2]. Such individuals were recognized by Cockayne [3]. In the autosomal recessive cases, oral blistering with dental caries may be a feature, and nail dystrophy is common.

References

1 Lin AN, Carter DM, eds. Epidermolysis bullosa simplex: a clinical overview. In: *Epidermolysis Bullosa: Basic and Clinical Aspects*. New York: Springer, 1992: 89–117.

2 DeVries DT, Johnson LB, Weiner M *et al*. Relative extent of skin involvement in inherited epidermolysis bullosa (EB); composite regional anatomic diagrams based on the findings of the National EB Registry, 1986–2002. *J Am Acad Dermatol* 2004; **50**: 572–81.

3 Cockayne EA. *Inherited Abnormalities of the Skin and its Appendages*. London: Oxford University Press, 1933: 118–33.

Dowling–Meara epidermolysis bullosa simplex

Synonym

- Epidermolysis bullosa herpetiformis

In 1954, Dowling and Meara [1] described four unrelated children (aged 3–7.5 years) with unusual trauma-induced or spontaneous

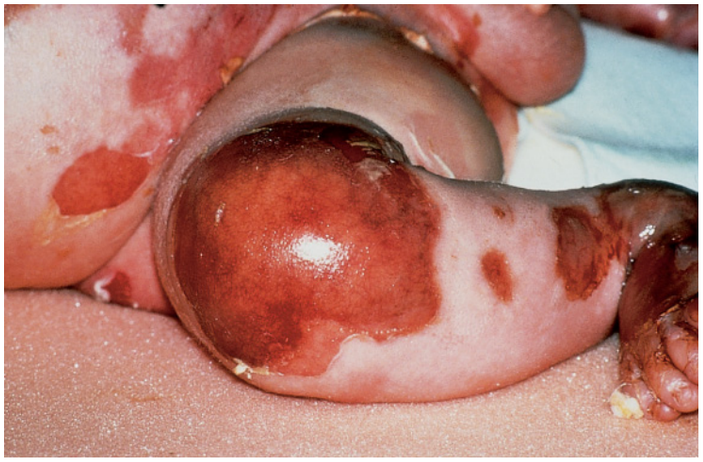


Fig. 39.5 Extensive erosions in a neonate with epidermolysis bullosa simplex (Dowling–Meara). (Courtesy of Professor R.A.J. Eady, St John's Institute of Dermatology, London, U.K.)

blistering. The blisters healed without leaving scars, and tended to occur in groups that were reminiscent of those seen in dermatitis herpetiformis. Similar cases have since been described [2–10]. In infancy, blistering may be severe and extensive (Fig. 39.5) with involvement of the mucous membranes, shedding of nails and formation of milia. The differential diagnosis at this age may include both the junctional and generalized recessive dystrophic forms of EB. Therefore, a diagnostic skin biopsy is mandatory. After several months, blistering of the palms and soles becomes more frequent, as it does elsewhere. The distinctive feature of this condition is spontaneous herpetiform, annular or arcuate blistering on the trunk, limbs and neck (Fig. 39.6). However, when the blistering is severe and widespread, this pathognomonic grouping of lesions may not be obvious, so the correct diagnosis may be missed, and patients misclassified as having generalized non-Dowling–Meara EB simplex. Healing of the blisters may leave mild hyperpigmentation; localized atrophic scarring affects approximately 40% of patients, and milia are seen in approximately 20%. Irregular hyperkeratosis of the palms and soles, eventually developing into a confluent keratoderma (Fig. 39.7), first appears in childhood, and may rarely lead to a flexion deformity of the hands, associated with a severe keratoderma [5]. The general condition tends to improve with age [2]. Clearing of skin lesions has been noted in some patients with a fever, and after warm saline soaks [2].



Fig. 39.6 Grouped blisters on an erythematous base in epidermolysis bullosa simplex (Dowling–Meara). (Courtesy of Professor R.A.J. Eady, St John's Institute of Dermatology, London, U.K.)



Fig. 39.7 Hyperkeratosis of the soles in epidermolysis bullosa simplex (Dowling–Meara). (Courtesy of Professor R.A.J. Eady, St John's Institute of Dermatology, London, U.K.)

References

1 Dowling GB, Meara RH. Epidermolysis bullosa resembling juvenile dermatitis herpetiformis. *Br J Dermatol* 1954; **66**: 139–43.

2 Gedde-Dahl J-T, Anton-Lamprecht I. Epidermolysis bullosa. In: Emery AEH, Rimoin DL, eds. *Principles and Practice of Medical Genetics*. Edinburgh: Churchill Livingstone, 1983: 672–87.

3 Anton-Lamprecht I, Schnyder UW. Epidermolysis bullosa herpetiformis Dowling–Meara. *Dermatologica* 1982; **164**: 221–35.

4 Niemi K-M, Kero M, Kanerva L, Mattila R. Epidermolysis bullosa simplex: a new histological subgroup. *Arch Dermatol* 1983; **119**: 138–41.

5 Shemanko CS, Mellerio JE, Tidman MJ *et al*. Severe palmoplantar hyperkeratosis in Dowling–Meara epidermolysis bullosa simplex caused by a mutation in the keratin 14 gene. *J Invest Dermatol* 1998; **111**: 893–5.

6 Buchbinder LHY, Lucky AW, Ballard E *et al.* Severe infantile epidermolysis bullosa simplex. *Arch Dermatol* 1986; **122**: 190–8.
7 Medinica-Mojsilovic L, Fenske NA, Espinoza CG. Epidermolysis bullosa herpetiformis with mottled pigmentation and an unusual punctate keratoderma. *Arch Dermatol* 1986; **122**: 900–8
8 Blanchet-Bardon C, Nazarro V, Raynaud F *et al.* Epidermolyse bulleuse dominante de Dowling–Meara: une epidermolyse bulleuse intraepidermique qui cache bien son prognostic. *Ann Dermatol Vénéréol* 1987; **114**: 341–8.
9 Hacham-Zadeh S, Rappersberg K, Livshin R, Konrad K. Epidermolysis bullosa herpetiformis Dowling–Meara in a large family. *J Am Acad Dermatol* 1988; **18**: 702–6.
10 McGrath JA, Ishida-Yamamoto A, Tidman MJ *et al.* Epidermolysis bullosa simplex (Dowling–Meara): a clinicopathological review. *Br J Dermatol* 1992; **126**: 421–30.

Epidermolysis bullosa simplex Ogna

This autosomal dominant condition was named after the village in Norway where the first affected family originated [1]. There is seasonal blistering of hands and feet, and occasionally elsewhere. This rare subtype of EB is distinguishable by a generalized bruising tendency, haemorrhagic bullae and onychogryphotic great toenails [1].

Reference

1 Gedde-Dahl T. *Epidermolysis Bullosa: a Clinical, Genetic and Epidemiological Study*. Baltimore: Johns Hopkins University Press, 1971.

Epidermolysis bullosa simplex with mottled pigmentation

This rare condition can be distinguished from other forms of EB simplex by the associated pigmentary changes [1–5], which are present at birth or appear during infancy. There is a reticulate pattern of small, tan-coloured macular lesions, which fade with age. They may cover the entire skin surface but preferentially involve the neck, upper trunk or extremities. Blistering may be localized, mimicking Weber–Cockayne disease, or become more generalized. Punctate keratoses on the palms and soles have been noted in some cases [2,3]. Mild localized skin atrophy and nail dystrophy are also features of the condition [5].

References

1 Fischer T, Gedde-Dahl T. Epidermolysis bullosa simplex with mottled pigmentation. *Clin Genet* 1979; **15**: 228–38.
2 Boss JM, Matthews CNA, Peachey RDG *et al.* Speckled hyperpigmentation, palmo-plantar punctate keratoses and childhood blistering. *Br J Dermatol* 1981; **105**: 579–85.
3 Matthews CNA, Peachey RDG. Epidermolysis bullosa with pigmentation and palmar and plantar keratoses. *Br J Dermatol* 1977; **97** (Suppl. 15): 44–6.
4 Bruckner-Tuderman L, Vogel A, Ruegger S *et al.* Epidermolysis bullosa simplex with mottled pigmentation. *J Am Acad Dermatol* 1989; **21**: 425–32.
5 Coleman R, Harper JI, Lake BD. Epidermolysis bullosa simplex with mottled pigmentation. *Br J Dermatol* 1993; **128**: 679–85.

Autosomal recessive epidermolysis bullosa simplex with neuromuscular disease

Several families have been described in which skin fragility and blistering are associated with a neuromuscular disorder, chiefly muscular dystrophy [1–5], although myasthenia gravis [3] and spinal muscular atrophy [6] have also been described. The blisters, which affect the skin and oral mucosa, are present at birth or soon afterwards. Muscle weakness and wasting may be severe and evident in early childhood, or milder and detectable later in life. Mental retardation has been reported [2], as has early death [1]. The widespread blistering is associated with atrophic scarring, milia, nail dystrophy and alopecia, oftentimes mimicking junctional or dystrophic EB. Two children with homozygous null mutations developed supraglottic scarring and hoarseness; one required a tracheostomy [7].

References

1 Kletter G, Evans OB, Lee JA *et al.* Congenital muscular dystrophy and epidermolysis bullosa simplex. *J Pediatr* 1989; **114**: 104–7.
2 Niemi KM, Sommer H, Kero M *et al.* Epidermolysis bullosa simplex associated with muscular dystrophy with recessive inheritance. *Arch Dermatol* 1988; **124**: 551–4.
3 Fine J-D, Stenn J, Johnson L *et al.* Autosomal recessive epidermolysis bullosa simplex: generalized phenotypic features suggestive of junctional or dystrophic epidermolysis bullosa, and association with neuromuscular diseases. *Arch Dermatol* 1989; **125**: 931–8.
4 Doriguzzi C, Palmucci I, Mongini T *et al.* Congenital muscular dystrophy associated with familial junctional epidermolysis bullosa letalis. *Eur Neurol* 1993; **33**: 454–60.
5 Patrizi A, Di Lernia V, Neri I *et al.* Epidermolysis bullosa simplex associated with muscular dystrophy: a new case. *Pediatr Dermatol* 1994; **11**: 342–5.
6 Weiss DJ, Fried GW. Epidermolysis bullosa simplex associated with spinal muscle atrophy. *Int J Dermatol* 1993; **32**: 592–3.
7 Mellerio JE, McMillan JR, McGrath JA *et al.* Recessive epidermolysis bullosa simplex associated with plectin mutations: infantile respiratory complications in two unrelated cases. *Br J Dermatol* 1997; **137**: 898–906.

Epidermolysis bullosa simplex with pyloric atresia

Pyloric atresia may rarely occur in the setting of EB simplex. Affected infants tend to have generalized skin disease. Although only a few cases have yet been reported, this entity appears to be as severe as junctional EB with pyloric atresia.

Reference

1 Morrell D, Rubenstein D, Briggaman R *et al.* Congenital pyloric atresia in a newborn with extensive aplasia cutis congenita and epidermolysis bullosa simplex. *Br J Dermatol* 2000; **143**: 1342–3.

Lethal autosomal recessive epidermolysis bullosa simplex

A kindred of 13 Sudanese patients has been reported with the autosomal recessive form of EB simplex [1]. Blistering was present at or very shortly after birth and was generalized, with no associated scarring or milia, and with a predilection for the more distal portion of the limbs. The oral mucosa was only mildly affected, and the nails, teeth and hair were not affected. Most of the affected children died during the first 2 years of life; only one patient reached adolescence.

Electron microscopy of the skin of these patients was reported to reveal a paucity of tonofilaments in the basal epidermal cells. A published electron micrograph is reminiscent of the ultrastructural features seen in an unrelated case of North African origin whose autosomal recessive EB simplex was found to be caused by a homozygous null mutation in the keratin 14 gene [2].

References

1 Salih MA, Lake BD, Hag MA, Atherton DJ. Lethal epidermolytic epidermolysis bullosa: a new autosomal recessive type of epidermolysis bullosa. *Br J Dermatol* 1985; **113**: 135–43.
2 Rugg EL, McLean WHI, Lane EB *et al.* A functional 'knockout' for human keratin 14. *Genes Dev* 1994; **8**: 2563–73.

Epidermolysis bullosa simplex, migratory circinate

Gu *et al*. [1] described two families with an autosomal dominant form of EB simplex characterized by migratory circinate erythema and postinflammatory hyperpigmentation. Present at birth, blistering was generalized in distribution. The underlying cause of this entity was a frameshift and delay stop codon in the keratin 5 gene.

Reference

1 Gu L-H, Kim S-C, Ichiki Y *et al*. A usual frameshift and delayed termination codon mutation in keratin 5 causes a novel type of epidermolysis bullosa simplex with migratory circinate erythema. *J Invest Dermatol* 2003; **121**: 482–5.

Kallin's syndrome

The single report on this disorder [1] included two sisters whose surname was Kallin. Both had blistering chiefly of the hands and feet, nail dystrophy, absent teeth and alopecia. One sister was partially deaf. Light microscopy showed a mid-epidermal cleavage in the skin of one sister, and a substratum corneal split in the other. From the limited information available, it is uncertain whether Kallin's syndrome is a distinct form of EB. For this reason, it is currently not included within the latest classification system.

Reference

1 Nielsen PG, Sjuland E. Epidermolysis bullosa simplex localisata associated with anodontia, hair and nail disorders. *Acta Derm Venereol (Stockh)* 1985; **65**: 526–30.

Junctional epidermolysis bullosa

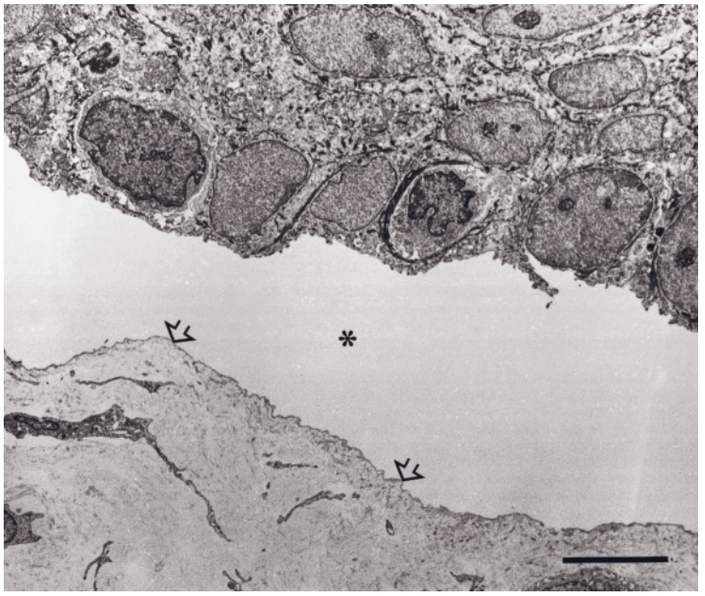
All the variants of this disorder are characterized by autosomal recessive inheritance and by blister formation at the level of the lamina lucida. Conventionally, junctional EB is divided into two main categories: the Herlitz and non-Herlitz forms. Although the term EB letalis was originally ascribed to Herlitz JEB, this term is no longer recommended because it is well recognized that *any* EB subtype may also rarely have a lethal outcome, especially in infancy. The term *indeterminate* junctional EB has been used to classify infants who have diagnostic biopsy evidence of junctional EB, but who have not lived long enough to allow clinical segregation into the Herlitz or non-Herlitz subtypes. The term *EB atrophicans* has also been used to describe patients with junctional blistering and atrophic scarring [1]. We do not recommend the use of this latter term because other forms of EB may be associated with atrophic scarring, and the abbreviation 'EBA' could potentially cause confusion with its more usual association with EB acquisita.

Reference

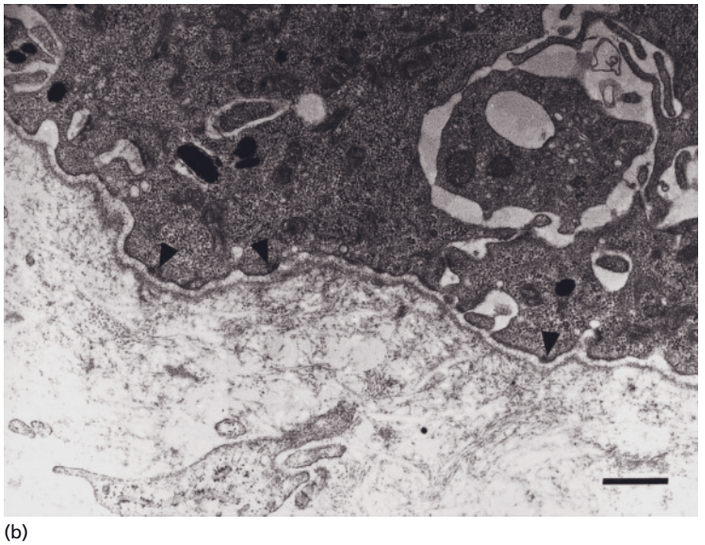
1 Gedde-Dahl T Jr, Anton-Lamprecht I. Epidermolysis bullosa. In: Emery AEH, Rimoin DL, eds. *Principles and Practice of Medical Genetics*. London: Churchill Livingstone, 1983: 672–87.

Molecular pathology [1,2]

Electron microscopy shows that the level of tissue separation in all forms of junctional EB is through the lamina lucida of the basement-membrane zone immediately beneath the plasma membrane of basal epidermal cells (Fig. 39.8a). The hemidesmosomes tend to be sparse and very small, especially in the more severe forms of the disease (Fig. 39.8b) [3–5]. In addition, the hemidesmosome subbasal dense plates may be indistinct or attenuated [4,5], and the association between hemidesmosomes and the basal keratinocyte keratin filament network is reduced [5]. Keratinocytes from junctional EB patients have shown similar ultrastructural changes *in vitro* [6,7] or after grafting on to nude mice [8]. These hemidesmosome abnormalities are most prominent in the Herlitz form of junctional EB and the subtype associated with pyloric atresia. Although the latter is normally classified as a form of



(a)



(b)

Fig. 39.8 Electron micrographs of the dermal–epidermal junction in Herlitz junctional epidermolysis bullosa. (a) A clean split (*) is present at the level of the lamina lucida. A row of closely apposed basal keratinocytes is at the top of the split, and a continuous lamina densa (open arrowheads) is below. Bar = 5 μm. (b) In intact skin, hemidesmosomes (arrowheads) are sparse and much smaller than normal. Bar = 1 μm. (Courtesy of Professor R.A.J. Eady, St John's Institute of Dermatology, London, U.K.)

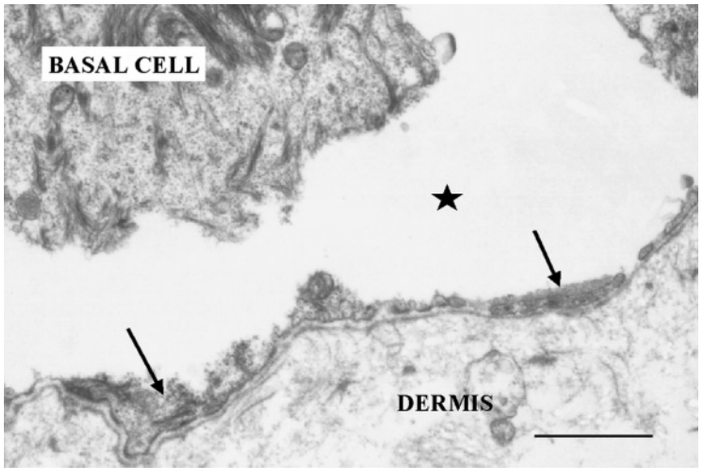


Fig. 39.9 Epidermolysis bullosa with pyloric atresia. A split (star) is present at a very low level in the basal epidermal layer, leaving fragments of basal cells at the base. Bar = 2 μm. (Courtesy of Professor R.A.J. Eady, St John's Institute of Dermatology, London, U.K.)

junctional EB, the ultrastructural level of cleavage is not consistently restricted to the lamina lucida, and may occur intraepidermally at a level just above the basal plasma membrane of the basal keratinocytes (Fig. 39.9) [9]. This is similar therefore to the level of tissue disruption occurring in the skin of knockout mice with ablation of the β4 integrin subunit [10]. It may also resemble the ultrastructural abnormality seen in patients with autosomal recessive EB simplex resulting from defects in plectin (see p. 39.4) [11–13]. In the non-Herlitz forms of junctional EB, the hemidesmosome ultrastructure is variable, and individual hemidesmosomes may show little if any discernible abnormality [4].

Immunofluorescence microscopy indicated an abnormality in the expression of the anchoring filament protein laminin 5 (also known as laminin 332) in the skin of patients with Herlitz junctional EB and in certain patients with non-Herlitz phenotypes [14–16]. Molecular analysis subsequently showed that the Herlitz form of the disease may be caused by mutations in any of the three laminin 5 genes, *LAMA3*, *LAMB3* and *LAMC2* (Fig. 39.10), encoding the α3, β3 and γ2 polypeptide chains, respectively, which copolymerize to form the heterotrimeric laminin 5 protein. The mutations reported so far in Herlitz junctional EB have been homozygous or compound heterozygous premature termination codon mutations [17–20]. These would be expected to result in the production of unstable RNA transcripts and a severely truncated non-functional protein, leading to reduced adhesion at the dermal–epidermal junction and marked skin fragility. The majority of mutations have been found in the *LAMB3* gene, with evidence for mutational hotspots leading to recurrent mutations R42X and R635X [21]. The mutation R635X was found in seven of 24 (29%) mutant alleles in a study of 12 British families with Herlitz junctional EB [22]. The mutation represents a C-to-T transition at a CpG dinucleotide and probably results from deamination of 5-methylcytosine to thymine, a recognized cause of human genetic disease [22].

Non-Herlitz junctional EB (previously known as generalized atrophic benign EB; GABEB) may also result from laminin 5 (laminin 332) gene pathology [23,24]. In a family with non-Herlitz

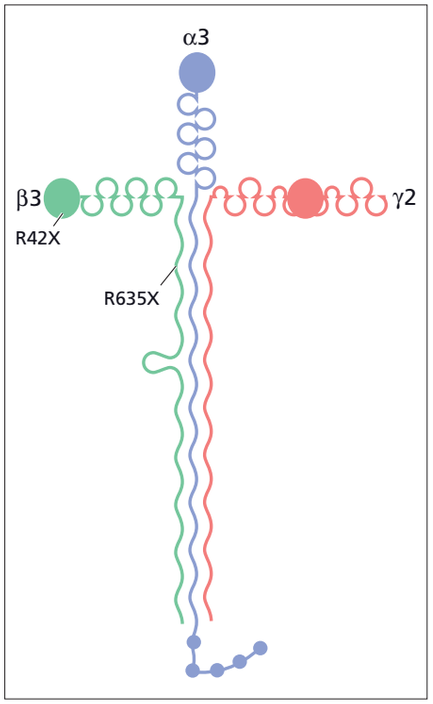


Fig. 39.10 Schematic representation of laminin 5, a heterotrimer comprising α3, β3 and γ2 chains encoded by the *LAMA3*, *LAMB3* and *LAMC2* genes, respectively. The relative positions of two premature stop codon mutations giving rise to R42X and R635X on the β3 chain are shown. These mutations together account for about 50% of all laminin 5 mutations underlying junctional epidermolysis bullosa. (Courtesy of Professor R.A.J. Eady, St John's Institute of Dermatology, London, U.K.)

EB, there was a premature termination codon mutation in exon 3 of one *LAMB3* allele and a missense mutation in exon 7 in the other allele. Exons 3 and 7 encode part of the domain VI on the short arm of the β3 chain. Because this globular domain is thought to be involved with the interaction between laminin 5 and other basement-membrane proteins, such as laminin 6, these mutations might therefore cause destabilization of the macromolecular network involved in adhesion at the dermal–epidermal junction [23].

Other patients with non-Herlitz junctional EB may instead have mutations in the *COL17A1* gene encoding another anchoring filament component, collagen XVII (also known as the 180-kDa bullous pemphigoid antigen [BP180] or BPAG2) [25,26]. The strong similarity in the clinical phenotype of non-Herlitz junctional EB patients with either collagen XVII or laminin 5 gene pathology suggests that the attribution of GABEB is not specific to a particular genotype. Evidence for the role of collagen XVII in odontogenesis is provided by the finding of a combination of a glycine substitution mutation in the helical domain of one *COL17A1* allele, and an internal duplication in the other allele, in a patient with fairly mild skin changes but severe dental abnormalities [27]. The patient's offspring inherited the glycine substitution mutation but had normal second *COL17A1* alleles. Interestingly, although their skins were clinically normal, they had inherited the dental anomaly.

Patients with the subtype of junctional EB associated with pyloric atresia may have a reduced expression of the α6β4 integrin in their skin, as shown by indirect immunofluorescence [28–30]. Staining for other antigens, including laminin 5, is usually normal. The α6β4 integrin is a hemidesmosome-associated heteropolymer and receptor for laminin 5. Knockout mouse experiments with targeted removal of the β4 and α6 subunits showed that homozygous (−/−) mice manifested widespread epithelial separation from the underlying stroma and major ultrastructural changes in the hemidesmosomes [10,31,32]. Mutations in genes for the β4 and α6 integrin chains, *ITGB4* and *ITGA6*, have been shown to underlie this form of EB [33–36] and, in some cases, the phenotype may be predicted by the nature of the mutations.

References

1 Eady RAJ, Dunnill MGS. Epidermolysis bullosa: hereditary skin fragility diseases as paradigms in cell biology. *Arch Dermatol Res* 1994; **287**: 2–9.

2 Christiano AM, Uitto J. Molecular complexity of the cutaneous basement membrane zone. *Exp Dermatol* 1996; **5**: 1–11.

3 Eady RAJ, McGrath JA, McMillan JR. Ultrastructural clues to genetic disorders of skin: the dermal–epidermal junction. *J Invest Dermatol* 1994; **103**: 13s–8s.

4 Tidman MJ, Eady RAJ. Hemidesmosome heterogeneity in junctional epidermolysis bullosa revealed by morphometric analysis. *J Invest Dermatol* 1986; **86**: 51–6.

5 McMillan JR, McGrath JA, Tidman MJ, Eady RAJ. Hemidesmosomes show abnormal association with the keratin filament network in junctional forms of epidermolysis bullosa. *J Invest Dermatol* 1998; **110**: 132–7.

6 Leigh IM, Tidman MJ, Eady RAJ. Epidermolysis bullosa: preliminary observations of blister formation in keratinocyte cultures. *Br J Dermatol* 1984; **111**: 527–32.

7 Chapman SJ, Leigh IM, Tidman MJ, Eady RAJ. Abnormal expression of hemidesmosome-like structures by junctional epidermolysis bullosa keratinocytes *in vitro*. *Br J Dermatol* 1990; **123**: 137–44.

8 Thomas L, Faure M, Cambazard F *et al.* Cultured epithelia from junctional epidermolysis bullosa letalis keratinocytes express the main phenotypic characteristics of the disease. *Br J Dermatol* 1990; **122**: 137–45.

9 Smith LT. Ultrastructural findings in epidermolysis bullosa. *Arch Dermatol* 1993; **129**: 1578–84.

10 van der Neut R, Krimpenfort P, Calafat J *et al.* Epithelial detachment due to absence of hemidesmosomes in integrin beta 4 null mice. *Nat Genet* 1996; **13**: 366–9.

11 Gache Y, Chavanas S, Lacour JP *et al.* Defective expression of plectin/HD1 in epidermolysis bullosa simplex with muscular dystrophy. *J Clin Invest* 1996; **97**: 2289–98.

12 Smith FJD, Eady RAJ, Leigh IM *et al.* Plectin deficiency results in muscular dystrophy with epidermolysis bullosa. *Nat Genet* 1996; **13**: 450.

13 Gedde-Dahl T Jr. Epidermolysis bullosa simplex (intraepidermal epidermolysis bullosa) and allied conditions. In: Wojnarowska F, Briggaman RA, eds. *Management of Blistering Diseases.* London: Chapman & Hall, 1990: 189–211.

14 Heagerty AHM, Kennedy AR, Eady RAJ *et al.* GB3 monoclonal antibody for diagnosis of junctional epidermolysis bullosa. *Lancet* 1986; **1**: 660.

15 Verrando P, Blanchet-Bardon P, Pisani A *et al.* Monoclonal antibody GB3 defines a widespread defect of several basement membranes and a keratinocyte dysfunction in patients with lethal junctional epidermolysis bullosa. *Lab Invest* 1991; **64**: 85–92.

16 Schofield OMV, Fine JD, Pasini A *et al.* GB3 monoclonal antibody for diagnosis of junctional epidermolysis bullosa: result of a multicentre study. *J Am Acad Dermatol* 1990; **23**: 1078–83.

17 Pulkkinen L, Christiano AM, Airenne T *et al.* Mutations in the γ2 chain gene (*LAMC2*) of kalinin/laminin 5 in the junctional forms of epidermolysis bullosa. *Nat Genet* 1994; **6**: 293–7.

18 Aberdam D, Galliano MF, Vailly J *et al.* Herlitz's junctional epidermolysis bullosa is linked to mutations in the gene (*LAMC2*) for the γ2 subunit of nicein/kalinin (laminin-5). *Nat Genet* 1994; **6**: 299–304.

19 Pulkkinen L, Christiano AM, Gerecke D *et al.* A homozygous nonsense mutation in the β3 chain gene of laminin 5 (*LAMB3*) in Herlitz junctional epidermolysis bullosa. *Genomics* 1994; **24**: 357–60.

20 Kivirikko S, McGrath JA, Baudoin C *et al.* A homozygous nonsense mutation in the α3 chain gene of laminin 5 (*LAMA3*) in lethal (Herlitz) junctional epidermolysis bullosa. *Hum Mol Genet* 1995; **10**: 229–34.

21 Kivirikko S, McGrath JA, Pulkinnen L *et al.* Mutational hotspots in the *LAMB3* gene in the lethal (Herlitz) type of junctional epidermolysis bullosa. *Hum Mol Genet* 1996; **5**: 231–7.

22 Ashton GHS, Mellerio JE, Dunnill MGS *et al.* A recurrent laminin 5 mutation in British patients with lethal (Herlitz) junctional epidermolysis bullosa: evidence for a mutational hotspot rather than propagation of an ancestral allele. *Br J Dermatol* 1997; **136**: 674–7.

23 McGrath JA, Pulkkinen L, Christiano AM *et al.* Altered laminin 5 expression due to mutations in the gene encoding the β3 chain (*LAMB3*) in generalized atrophic benign epidermolysis bullosa. *J Invest Dermatol* 1995; **104**: 467–74.

24 McGrath JA, Christiano AM, Pulkinnen L *et al.* Compound heterozygosity for nonsense and missense mutations in the *LAMB3* gene in non-lethal junctional epidermolysis bullosa. *J Invest Dermatol* 1996; **106**: 1157–9.

25 Jonkman MF, De Jong MCJM, Heeres K *et al.* 180-kD bullous pemphigoid antigen (BP180) is deficient in generalized atrophic benign epidermolysis bullosa. *J Clin Invest* 1995; **95**: 1345–52.

26 McGrath JA, Gatalica B, Christiano AM *et al.* Mutations in the 180-kD bullous pemphigoid antigen (BPAG2), a hemidesmosomal transmembrane collagen (*COL17A1*), in generalized atrophic benign epidermolysis bullosa. *Nat Genet* 1995; **11**: 83–6.

27 McGrath JA, Gatalica B, Li K *et al.* Compound heterozygosity for a dominant glycine substitution and a recessive internal duplication mutation results in junctional epidermolysis bullosa and abnormal dentition. *Am J Pathol* 1996; **148**: 1787–96.

28 Philips RJ, Aplin JD, Lake BD. Antigenic expression of integrin α6β4 in junctional epidermolysis bullosa. *Histopathology* 1994; **24**: 571–6.

29 Brown TA, Gil SG, Sybert VA *et al.* Defective integrin α6β4 expression in the skin of patients with junctional epidermolysis bullosa and pyloric atresia. *J Invest Dermatol* 1996; **107**: 384–91.

30 Shimizu H, Suzumori K, Hatta N, Nishikawa T. Absence of detectable α6 integrin in pyloric atresia–junctional epidermolysis bullosa syndrome. *Arch Dermatol* 1996; **132**: 919–25.

31 Georges-Labouesse E, Messaddeq N, Yehia G *et al.* Absence of integrin α6 leads to epidermolysis bullosa and neonatal death in mice. *Nat Genet* 1996; **13**: 370–3.

32 Dowling J, YuQC, Fuchs E. β4 integrin is required for hemidesmosome formation, cell adhesion and cell survival. *J Cell Biol* 1996; **134**: 559–72.

33 Vidal F, Aberdam D, Miquel C *et al.* Integrin β4 mutations associated with junctional epidermolysis bullosa with pyloric atresia. *Nat Genet* 1995; **10**: 229–34.

34 Pulkkinen L, Kimonis VE, Xu Y *et al.* Homozygous α6 integrin mutations in junctional epidermolysis bullosa with congenital duodenal atresia. *Hum Mol Genet* 1997; **6**: 669–74.

35 Nakano A, Pulkkinen L, Murrell D *et al.* Epidermolysis bullosa with congenital pyloric atresia: novel mutations in the β4 integrin gene (*ITGB4*) and genotype–phenotype correlations. *Pediatr Res* 2001; **49**: 618–26.

36 Mellerio JE, Pulkkinen L, McMillan JR *et al.* Pyloric atresia–junctional epidermolysis bullosa syndrome: mutations in the integrin β4 gene (*ITGB4*) in two unrelated patients with mild disease. *Br J Dermatol* 1998; **139**: 862–71.

Clinical subtypes

Junctional EB has the following subtypes.

Herlitz junctional epidermolysis bullosa [1,2]

Synonyms

- Epidermolysis bullosa letalis
- Epidermolysis bullosa atrophicans generalisata gravis



Fig. 39.11 Facial erosions in junctional epidermolysis bullosa (Herlitz). (Courtesy of Professor R.A.J. Eady, St John's Institute of Dermatology, London, U.K.)



Fig. 39.12 Junctional epidermolysis bullosa (Herlitz). (Courtesy of Professor R.A.J. Eady, St John's Institute of Dermatology, London, U.K.)

Blistering and erosions are present at or soon after birth and rapidly become generalized. The whole skin is extremely fragile and lifting or turning the baby may cause extensive blistering or peeling away of the epidermis. Eroded areas are often very slow to heal. Healing may result in atrophic scarring. Milia are not generally seen, although they may occur after secondary infection. Involvement of the oral and pharyngeal mucosa is frequent and may be severe; hoarseness and stridor may indicate laryngeal or supraglottic involvement, most notably potentially life-threatening stenosis or stricture [3,4]. Vesicles have been reported in the trachea and bronchioles post-mortem [5,6]. There is no further risk of tracheolaryngeal compromise on or after about age 6. Many infants die early in infancy with overwhelming infection or from failure to thrive [7], but those surviving the first few months will often develop distinctive lesions characterized by non-healing, crusted erosions containing exuberant granulation tissue [1,8]. These typical lesions occur symmetrically around the nose and mouth (Fig. 39.11) but also in other sites including the neck, trunk, buttocks, and rarely within the uppermost respiratory tree (Fig. 39.12). The combination of chronic infection and loss of protein and iron from the skin, in addition to poor feeding, contributes to impaired healing and refractory anaemia [9]. The teeth show abnormal enamel formation, but normal dentine [10], and as a result are malformed, pitted and lost prematurely. Following blistering and erosions, the formation of exuberant granulation tissue on the nail folds and nail bed leads to shedding of the nails and bulbous changes of the fingertips (Fig. 39.13). Blisters may occur on the cornea, resulting in pain, erosions, scarring, and, very rarely, blindness [11]. A variety of genitourinary tract complications may occur including urethral meatal stenosis, urinary retention, hydronephrosis and bladder hypertrophy [12]. Squamous cell carcinoma, similar to that occurring in dystrophic EB (see below), may also occur in non-Herlitz junctional EB [13–15], at times with a fatal outcome. Keratoacanthoma has also been reported [16].



Fig. 39.13 Nail changes in junctional epidermolysis bullosa (Herlitz). (Courtesy of Professor R.A.J. Eady, St John's Institute of Dermatology, London, U.K.)

References

1 Lin AN, Carter DM, eds. Junctional epidermolysis bullosa: a clinical overview. In: *Epidermolysis Bullosa: Basic and Clinical Aspects*. New York: Springer, 1992: 118–34.

2 Eady RAJ, Tidman MJ. Junctional epidermolysis bullosa. In: Wojnarowska F, Briggaman RA. *Management of Blistering Diseases*. London: Chapman & Hall, 1990: 213–23.

3 Davies H, Atherton DJ. Acute laryngeal obstruction in junctional epidermolysis bullosa. *Pediatr Dermatol* 1987; **4**: 98–101.

4 Fine JD, Johnson LB, Weiner M *et al*. Tracheolaryngeal complications of inherited epidermolysis bullosa. *Laryngoscope* 2007; **117**: 1652–60.

5 Madison TG, Barter RA. Epidermolysis bullosa hereditaria letalis. *Arch Dis Child* 1961; **36**: 337–9.

6 Pearson RW, Potter B, Strauss F. Epidermolysis bullosa hereditaria letalis. *Arch Dermatol* 1974; **109**: 349–55.

7 Fine JD, Johnson LB, Weiner M *et al*. Cause-specific risks of childhood death in inherited epidermolysis bullosa. *J Pediatrics* 2008; **152**: 276–80.

8 Cross HE, Wells RS, Esterly JR. Inheritance in epidermolysis bullosa letalis. *Med Genet* 1968; **5**: 189–96.

9 Hruby MA, Esterly NB. Anemia in epidermolysis bullosa letalis. *Am J Dis Child* 1973; **125**: 696–9.

10 Wright JT, Johnson LB, Fine JD. Developmental defects of enamel in humans with hereditary epidermolysis bullosa. *Arch Oral Biol* 1993; **38**: 945–55.

11 Fine JD, Johnson LB, Weiner M *et al*. Eye involvement in inherited epidermolysis bullosa (EB): experience of the National EB Registry. *Am J Ophthalmol* 2004; **138**: 254–62.



Fig. 39.14 Pitting and discoloration of teeth in non-Herlitz junctional epidermolysis bullosa. (Courtesy of Professor R.A.J. Eady, St John's Institute of Dermatology, London, U.K.)

12 Fine J-D, Johnson LB, Weiner M *et al*. Genitourinary complications of inherited epidermolysis bullosa (EB): experience of the National EB Registry and review of the literature. *J Urol* 2004; **172**: 2040–4.

13 Parker SC, Schofield OMV, Black MM, Eady RAJ. Non-lethal junctional epidermolysis bullosa complicated by squamous cell carcinoma. In: Priestley GC, Tidman MJ, Weiss JB, Eady RAJ, eds. *Epidermolysis Bullosa: a Comprehensive Review of Classification, Management and Laboratory Studies*. Crowthorne: Dystrophic Epidermolysis Bullosa Research Association, 1990: 103–6.

14 Swensson O, Swensson O, Christophers E. Generalized atrophic benign epidermolysis bullosa in two siblings complicated by multiple squamous cell carcinomas. *Arch Dermatol* 1998; **134**: 199–203.

15 Weber F, Bauer JW, Sepp N *et al.* Squamous cell carcinoma in junctional and dystrophic epidermolysis bullosa. *Acta Derm Venereol* 2001; **81**: 189–92.

16 Pellicano R, Fabrizi G, Cerimele D. Multiple keratoacanthomas and junctional epidermolysis bullosa: a therapeutic conundrum. *Arch Dermatol* 1990; **126**: 305–6.

Generalized non-Herlitz junctional epidermolysis bullosa

Synonyms
- Epidermolysis bullosa atrophicans generalisata mitis
- Generalized atrophic benign epidermolysis bullosa (GABEB)

Hashimoto *et al*. [1] first described this condition in 1976. Hintner and Wolff [2] coined the acronym GABEB. The early clinical course may be similar to the Herlitz form of junctional EB with generalized skin fragility and blistering, but the patients usually survive to adulthood [2–8]. Although blistering persists, there is gradual lessening in severity of the disease with age. Mucous membranes are involved, but less severely than in the Herlitz form of junctional EB. The teeth show severe enamel defects (Fig. 39.14) and may fail to erupt normally. The nails are dystrophic and frequently missing, especially on the toes. Approximately 3–5% of patients may develop a degree of pseudosyndactyly, clinically suggestive of dystrophic EB. These patients were originally said to have 'cicatricial' junctional EB (see below). Typically, the lesions in non-Herlitz junctional EB heal with atrophic scarring, which can easily be mistaken for the scarring seen in dystrophic EB, especially on the lower legs (Fig. 39.15) or backs of the hands. Post-inflammatory hypopigmentation or depigmentation may be present in areas of scarring. An important sign of this form of EB is the poor hair development; the alopecia affects the scalp (Fig. 39.16), eyebrows and eyelashes, and body hair is also sparse or absent. Pigmented naevi, or acquired macular hyperpigmented lesions with irregular borders, are common [2–4]. Oesophageal stricture [2], laryngeal involvement [3], oral erosions [2,3,6], corneal ulcers [6,9], hypoacusis [1,2] and urethral stricture [10,11] have all been reported.



Fig. 39.15 Atrophic scarring on lower legs and toenail dystrophy in non-Herlitz junctional epidermolysis bullosa. (Courtesy of Professor R.A.J. Eady, St John's Institute of Dermatology, London, U.K.)



Fig. 39.16 Alopecia in non-Herlitz junctional epidermolysis bullosa. (Courtesy of Professor R.A.J. Eady, St John's Institute of Dermatology, London, U.K.)



Fig. 39.17 Hyperkeratosis with erosions on soles in non-Herlitz junctional epidermolysis bullosa. (Courtesy of Professor R.A.J. Eady, St John's Institute of Dermatology, London, U.K.)

Localized junctional epidermolysis bullosa

Localized forms of non-Herlitz junctional EB have been recognized [12,13]. Typical clinical manifestations include nail dystrophy, dental enamel changes and blistering involving the lower legs and feet only [10,12]. In a second report of two affected sisters, the skin was generally fragile, but the atrophic changes were most noticeable on the lower legs and dorsa of the feet. The nails were dystrophic, but hair and teeth appeared normal [13]. Chronic, painful erosions associated with hyperkeratosis were present on the soles. In the rare form of 'inverse' non-Herlitz junctional EB [14,15], the whole skin is fragile and blistering starts during the neonatal period in rather generalized distribution. Later, the lesions affect chiefly the groin, perineum and axillae ('inverse' sites). Healing may result in small, atrophic, white streaks. Dysplastic teeth, erosions of the cornea and feet (Fig. 39.17) and nail dystrophy, are all features.

References

1 Hashimoto I, Schnyder UW, Anton-Lamprecht I. Epidermolysis bullosa hereditaria with junctional blistering in an adult. *Dermatologica* 1976; **152**: 72–86.

2 Hintner H, Wolff K. Generalized atrophic benign epidermolysis bullosa. *Arch Dermatol* 1982; **118**: 375–84.

3 Paller AS, Fine J-D, Kaplan S *et al.* The generalized atrophic benign form of junctional epidermolysis bullosa: experience with four patients. *Arch Dermatol* 1986; **122**: 704–10.

4 Bauer JW, Schaeppi H, Kaserer C *et al.* Large melanocytic naevi in hereditary epidermolysis bullosa. *J Am Acad Dermatol* 2001; **44**: 577–84.

5 Foldes C, Wallach D, Aubiniere E *et al.* Generalized atrophic benign form of junctional epidermolysis bullosa. *Dermatologica* 1988; **176**: 83–90.

6 Schofield OMV, Eady RAJ. Generalized atrophic benign epidermolysis bullosa. In: Priestley GC, Tidman MJ, Weiss JB, Eady RAJ, eds. *Epidermolysis Bullosa: a Comprehensive Review of Classification, Management and Laboratory Studies*. Crowthorne: Dystrophic Epidermolysis Bullosa Research Association, 1990: 97–102.

7 McGrath JA, Pulkkinen L, Christiano AM *et al.* Altered laminin 5 expression due to mutations in the gene encoding the β3 chain (*LAMB3*) in generalized atrophic benign epidermolysis bullosa. *J Invest Dermatol* 1994; **74**: 197–200.

8 Jonkman MF, De Jong MCJM, Heeres K *et al.* Generalized atrophic benign epidermolysis bullosa. *Arch Dermatol* 1996; **132**: 145–50.

9 Fine JD, Johnson LB, Weiner M *et al.* Eye involvement in inherited epidermolysis bullosa (EB): experience of the National EB Registry. *Am J Ophthalmol* 2004; **138**: 254–62.

10 Mikio I, Mamoru K, Hiroshi H, Yoichiro S. Junctional epidermolysis bullosa with urethral stricture. *Dermatologica* 1987; **175**: 244–8.

11 Fine J-D, Johnson LB, Weiner M *et al.* Genitourinary complications of inherited epidermolysis bullosa (EB): experience of the National EB Registry and review of the literature. *J Urol* 2004; **172**: 2040–4.

12 Schnyder UW, Anton-Lamprecht I. Zur Klinik der Epidermolysen mit junktionaler Blasenbildung. *Dermatologica* 1979; **159**: 402–6.

13 Heagerty AHM, Tidman MJ, Bor S, Eady RAJ. Non-lethal junctional epidermolysis bullosa in two adult sisters. *J R Soc Med* 1985; **78** (Suppl. 11): 32–3.

14 Gedde-Dahl T, Anton-Lamprecht I. Epidermolysis bullosa. In: Emery AEH, Rimoin DL, eds. *Principles and Practice of Medical Genetics*. London: Churchill Livingstone, 1983: 672–87.

15 Ridley CM. Epidermolysis bullosa with unusual features: inversa type. *Proc R Soc Med* 1977; **70**: 576–7.

Junctional epidermolysis bullosa with pyloric atresia

This rare disorder is normally included as a subtype of junctional EB, although, not uncommonly, the true level of blistering has been found to be in the cytoplasm of basal keratinocytes, just above the plasma membrane, rather than within lamina lucida. These latter cases therefore might more appropriately be classified as EB simplex (see p. 39.3) and have therefore now been also included under this major EB heading. Many with this disorder have now been reported [1], yet only a few have survived beyond the first few months of life. Blistering is usually present at birth, following a pregnancy complicated by polyhydramnios. The lesions are usually widespread and can result in atrophic scarring. The teeth are hypoplastic, lacking normal enamel, and the nails are dystrophic. Early attempts at feeding result in vomiting, which is not bile-stained. In a series of five patients [2], four died at the age of 1–2 months; the fifth survived for over 4 years, but had constant haematuria and dysuria and recurrent urinary tract infections. Hayashi *et al.* [1] have made a strong case for surgical correction of the congenital pyloric atresia. Of the five patients in their report, four (aged 17 months to 16 years) were moderately well, despite complications such as retarded growth and hydronephrosis. The fifth patient died of respiratory distress, probably caused by aspiration, and had renal complications. The variable clinical outcome in this disorder will probably be explained, to some degree, by the nature of the mutations affecting either the α6 or β4 integrin subunits [3].

References

1 Hayashi AH, Galliani CA, Gillis DA. Congenital pyloric atresia and junctional epidermolysis bullosa: a report of long-term survival and a review of the literature. *J Pediatr Surg* 1991; **26**: 1341–5.

2 Valari MD, Phillips RJ, Lake BD, Harper JI. Junctional epidermolysis bullosa and pyloric atresia: a distinct entity—clinical and pathological studies in five patients. *Br J Dermatol* 1995; **133**: 732–6.

3 Mellerio JE, Pulkkinen L, McMillan JR *et al.* Pyloric atresia–junctional epidermolysis bullosa syndrome: mutations in the integrin β4 gene (*ITGB4*) in two unrelated patients with mild disease. *Br J Dermatol* 1998; **139**: 862–71.

Late-onset junctional epidermolysis bullosa

Synonym
- Epidermolysis bullosa progressiva

This condition was originally named EB dystrophica–neurotrophica by Gedde-Dahl because of the association of partial deafness [1]. The onset is delayed until childhood or adolescence, and nail dystrophy is a common presentation. Blistering occurs on the hands and feet. Later, knees and elbows are involved. Progressive atrophic changes lead to early loss of fingerprint patterns and mild finger contractures. The tooth enamel may be defective and the tongue papillae may disappear [2]. The oral mucosa is sometimes involved. The ultrastructural changes are said to be distinctive and show widening of the lamina lucida with deposition of amorphous material. The hemidesmosomes are ultrastructurally normal [2–4]. The molecular basis is unknown.

References
1 Gedde-Dahl T, ed. *Epidermolysis Bullosa: a Clinical Genetic and Epidemiological Study*. Baltimore: Johns Hopkins University Press, 1971.
2 Haber RM, Hanna W. Epidermolysis bullosa progressiva. *J Am Acad Dermatol* 1987; **16**: 195–200.
3 Gedde-Dahl T, Anton-Lamprecht I. Epidermolysis bullosa. In: Emery AEH, Rimoin DL, eds. *Principles and Practice of Medical Genetics*. London: Churchill Livingstone, 1983: 672–87.
4 Bircher AJ, Lang-Muritano M, Pfaltz M, Bruckner-Tuderman L. Epidermolysis bullosa junctionalis progressiva in three siblings. *Br J Dermatol* 1993; **128**: 429–35.

Cicatricial junctional epidermolysis bullosa

Three patients have been reported in whom blistering had healed with scarring and resulted in loss of nails, alopecia, syndactyly and contractures. The oral mucosa was involved and there was stenosis of the anterior nares [1]. Based on findings through 1999 [2], in which about 3% of all of the National EB Registry patients were found to have some degree of pseudosyndactyly, this rare phenotype has been included under the heading of non-Herlitz junctional EB. There is no evidence that this form of junctional EB has a distinct genotype.

References
1 Haber RM, Hanna W, Ramsey CA *et al.* Cicatricial junctional epidermolysis bullosa. *J Am Acad Dermatol* 1985; **12**: 836–44.
2 Fine J-D, Eady RAJ, Bauer EA *et al.* Revised classification system for inherited epidermolysis bullosa: report of the second international consensus meeting on diagnosis and classification of epidermolysis bullosa. *J Am Acad Dermatol* 2000; **42**: 1051–66.

Laryngo-onycho-cutaneous syndrome (LOC syndrome)

Synonym
- Shabbir's syndrome

This disorder, described by Shabbir *et al.* [1], included 22 patients from 13 mostly consanguineous Pakistani families. It starts in infancy and affects both sexes. Chronic erosive lesions affect the face, mainly around the nose and mouth, and, to a lesser extent, the limbs, trunk and genitalia. The nails are also involved and the third constant feature is hoarseness. The teeth may be notched. In a detailed study of three children, Phillips *et al.* [2] emphasized the additional feature of conjunctival lesions, which were also constant in their patients. Although originally considered as an entity distinct from junctional EB, LOC syndrome has recently been included as a subtype, since it is associated with mechanical fragility of the skin, ultrastructural features of the hemidesmosomes consistent with junctional EB, and mutations in the laminin 5 gene.

References
1 Shabbir G, Hassan M, Kamzi A. Laryngo-onycho-cutaneous syndrome. *Biomedica* 1986; **2**: 15–25.
2 Phillips RJ, Atherton DJ, Gibbs ML *et al.* Laryngo-onycho-cutaneous syndrome: an inherited epithelial defect. *Arch Dis Child* 1994; **70**: 319–26.

Dystrophic epidermolysis bullosa

The dystrophic forms of EB are characterized by skin fragility, blistering, scarring, nail changes and milia formation. Unlike junctional EB, there are both autosomal recessive and autosomal dominant subtypes. Recent studies have shown a number of genotypic and phenotypic differences between these two major subtypes of dystrophic EB, and a number of newer clinical variants have emerged. However, the definition of the subtypes of dystrophic EB is somewhat arbitrary, representing more quantitative than qualitative phenotypic differences [1]. Genotype–phenotype correlation is relatively weak among recessive dystrophic EB patients, and there are no significant hotspots within the *COL7A* gene.

Reference
1 Fine J-D. Classification of inherited epidermolysis bullosa: current approach, pitfalls, unanswered questions, and future directions. In: Fine J-D, Bauer EA, McGuire J, Moshell A, eds. *Epidermolysis Bullosa: Clinical, Epidemiologic, and Laboratory Advances, and the Findings of the National Epidermolysis Bullosa Registry*. Baltimore: Johns Hopkins University Press, 1999: 20–47.

Molecular pathology [1–3]

In contrast to EB simplex or junctional EB, in which several genes are now recognized in the pathogenesis of these disorders, both autosomal dominant and recessive forms of dystrophic EB are caused by mutations in a single gene, *COL7A1*, which encodes the anchoring fibril protein, type VII collagen.

Ultrastructurally, the level of blistering or tissue cleavage in all dystrophic forms of EB is immediately below the lamina densa of the epidermal basement membrane, at a site normally occupied by anchoring fibrils (Fig. 39.18) (see Chapter 3 for a fuller description of these and other structures in the basement-membrane zone) [3].

Quantitative electron microscopy and immunoelectron microscopy have shown that anchoring fibrils in dystrophic EB are reduced in number, morphologically altered or completely absent [4,5]. Immunofluorescence staining of the skin of patients using antitype VII collagen antibodies showed that the normal bright linear staining is absent in severe generalized recessive dystrophic EB, but present in dominant dystrophic EB [6–8]. In the milder or more localized form of recessive dystrophic EB, the

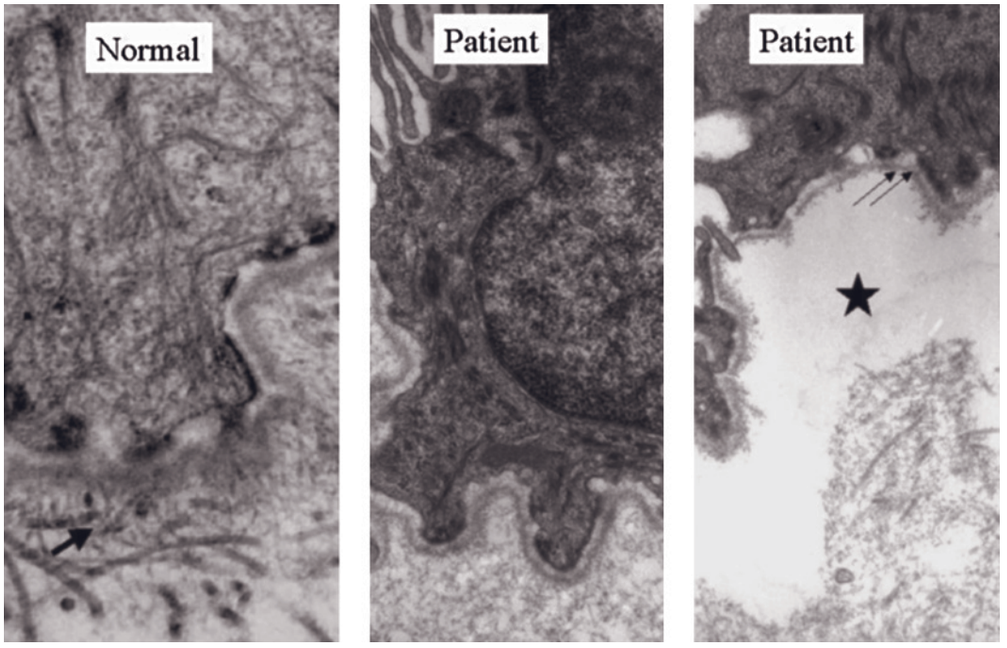


Fig. 39.18 Electron micrographs demonstrating blister formation in dystrophic epidermolysis bullosa. (a) Anchoring fibrils (arrow) are present in the dermal–epidermal junction in normal skin, (b) but are absent in patients' skin. (c) Early blister formation (star) beneath the lamina densa (double arrows). (Courtesy of Professor R.A.J. Eady, St John's Institute of Dermatology, London, U.K.)

immunoreactivity may be attenuated or normal in intensity. In the 'inverse' form of recessive dystrophic EB, type VII collagen is normally expressed but the anchoring fibrils are structurally abnormal [9]. These ultrastructural and immunohistochemical findings indicated that type VII collagen was the candidate gene for at least the recessive forms of dystrophic EB and probably for the dominant form too. These clues were supported by genetic linkage of both dominant and recessive forms of dystrophic EB with the type VII collagen gene locus [10–13], which had been mapped to chromosome 3p21 [14]. Other studies showing abnormalities of collagenase in skin and dermal fibroblasts from patients with recessive dystrophic EB indicated that the collagenase gene was also a candidate [15]. However, this was not borne out by subsequent linkage analysis [16,17] although many experts still believe that altered collagenase activity may play a secondary role in the aberrant wound healing seen in recessive dystrophic EB.

Cloning and sequencing of the human type VII collagen gene (*COL7A1*) and cDNA revealed that the gene is highly complex, containing a total of 118 exons within approximately 32 kb of genomic DNA [14,18–21]. Type VII collagen is a homotrimer (α_1[VII]$_3$) in which each pro-α chain has a large amino-terminal non-collagenous domain (NC-1), a central collagenous domain of Gly-X-Y repeats with several interruptions, and a small carboxy-terminal non-collagenous domain (NC-2). The formation of antiparallel dimers involves cleavage of the NC-2 domain [22]. Anchoring fibrils consist of laterally associated aggregates of the dimers.

Numerous *COL7A1* mutations have been documented. The most severe (Hallopeau–Siemens) subtype of recessive dystrophic EB is caused by premature termination codon mutations on both *COL7A1* alleles [23–26]. Heterozygote carriers of these mutations are phenotypically normal, and it is presumed that a truncated polypeptide, encoded by the mutant allele, is unable to take part in triple helix formation without its collagenous domain, leaving the wild-type polypeptide free to form normal trimers [1]. Ultrastructural morphometric analysis has shown that the number of anchoring fibrils is reduced to about half the normal value in the heterozygotes [27]. In the milder forms of recessive dystrophic EB, typically a premature termination codon mutation on one allele combines with a missense mutation or in-frame deletion on the second allele [28]. The net result is thought to be synthesis of type VII collagen molecules that assemble into unstable and relatively weak anchoring fibrils.

Detailed studies correlating clinical, ultrastructural and immunofluorescence changes with different combinations of mutations in *COL7A1* have helped in the understanding of the phenotype diversity in recessive dystrophic EB [29,30]. Dominant dystrophic forms of EB have been shown exclusively to be associated with glycine substitutions within the triple helical collagenous domain of the type VII molecule, characterized by a Gly-X-Y repeating amino-acid sequence [1,31]. These mutations are thought to have a dominant negative effect on the processing or function of the normal gene product. The amino acid substitutions are likely to destabilize the triple helix, impair the normal secretion of the molecules and make them susceptible to intracellular degradation. Assuming equal expression of both normal and mutant alleles, only approximately 13% of the triple-helical molecules will be normal [1]. This would help to explain the ultrastructural observations of reduced numbers of anchoring fibrils, some of which appear normal [4,5].

In the absence of a positive family history, it is often difficult to determine whether a single patient with mild to moderately severe dystrophic EB will have autosomal recessive or *de novo* dominant

disease. Recent molecular studies of *COL7A1* have established that the vast majority of such cases are recessive in nature. Nevertheless, a small number of *de novo* dominant patients have been documented. Three patients with *de novo* dominant disease were found to have the same glycine substitution mutation, G2043R in *COL7A1*. This mutation is the most common *COL7A1* mutation in dominant dystrophic EB throughout the world. These cases emphasize the importance of molecular analysis in providing accurate genetic counselling in patients with apparent sporadic dystrophic EB [32,33].

In addition to their occurrence in classical forms of dominant dystrophic EB, glycine substitution mutations have been demonstrated in rarer variants including Bart's syndrome [34], pretibial dystrophic EB [35] and EB pruriginosa [36,37]. Other types of *COL7A1* mutations may also occur in EB pruriginosa [37].

Considerable research is now being focused on the mechanisms of carcinogenesis in recessive dystrophic EB. In one intriguing study utilizing a mouse model, data were presented which suggested that the tendency for recessive dystrophic EB keratinocytes to develop into squamous cell carcinomas was dependent on expression of the NC1 domain of type VII collagen [38]. Very recently, however, other data were published which suggest that this proposed mechanism, as elegant as it appears, is an oversimplified one, since tumours have also now been proven to occur in patients lacking any detectable expression of type VII collagen [39].

References

1 Uitto J, Pulkkinen L. Molecular genetics of heritable blistering disorders. *Arch Dermatol* 2001; **137**: 1458–61.

2 Eady RAJ, Dunnill MGS. Epidermolysis bullosa: hereditary skin fragility diseases as paradigms in cell biology. *Arch Dermatol Res* 1994; **287**: 2–9.

3 Eady RAJ, McGrath JA, McMillan JR. Ultrastructural clues to genetic disorders of skin: the dermal–epidermal junction. *J Invest Dermatol* 1994; **103**: 13S–8S.

4 Tidman MJ, Eady RAJ. Evaluation of anchoring fibrils and other components of the dermal–epidermal junction in dystrophic epidermolysis bullosa by a quantitative ultrastructural technique. *J Invest Dermatol* 1985; **84**: 374–7.

5 McGrath JA, Ishida-Yamamoto A, O'Grady A *et al.* Structural variations in anchoring fibrils in dystrophic epidermolysis bullosa: correlation with type VII collagen expression. *J Invest Dermatol* 1993; **100**: 366–72.

6 Heagerty AHM, Kennedy AR, Leigh IM *et al.* Identification of an epidermal basement membrane defect in recessive dystrophic epidermolysis bullosa by LH7.2 monoclonal antibody: use in diagnosis. *Br J Dermatol* 1986; **115**: 125–31.

7 Leigh IM, Eady RAJ, Heagerty AHM *et al.* Type VII collagen is a normal component of epidermal basement membrane, which shows altered expression in recessive dystrophic epidermolysis bullosa. *J Invest Dermatol* 1988; **90**: 639–42.

8 Bruckner-Tuderman L, Ruegger S *et al.* Lack of type VII collagen in unaffected skin of patients with severe recessive dystrophic epidermolysis bullosa. *Dermatologica* 1988; **176**: 57–64.

9 Bruckner-Tuderman L, Niemi KM, Kero M *et al.* Type VII collagen is expressed but anchoring fibrils are defective in dystrophic epidermolysis bullosa inversa. *Br J Dermatol* 1990; **122**: 383–90.

10 Ryynanen M, Knowlton RG, Parente MG *et al.* Human type VII collagen: genetic linkage of the gene (*COL7A1*) on chromosome 3 to dominant dystrophic epidermolysis bullosa. *Am J Hum Genet* 1991; **49**: 797–803.

11 Al-Imara L, Richards AJ, Eady RAJ *et al.* Linkage of autosomal dominant dystrophic epidermolysis bullosa in three British families to the marker DS32 close to the *COL7A1* locus. *J Med Genet* 1992; **29**: 381–2.

12 Hovnanian AP, Duquesnoy P, Blanchet-Bardon C *et al.* Genetic linkage of recessive dystrophic epidermolysis bullosa to the type VII gene. *J Clin Invest* 1992; **90**: 1033–7.

13 Dunnill MGS, Richards AJ, Milana G *et al.* Genetic linkage to type VII collagen gene in 26 families with generalized recessive dystrophic epidermolysis bullosa and anchoring fibril abnormalities. *J Med Genet* 1994; **31**: 745–8.

14 Parente MG, Chung LC, Ryynanen J *et al.* Human type VII collagen: cDNA cloning and chromosomal mapping of the gene. *Proc Natl Acad Sci USA* 1991; **88**: 6931–5.

15 Bauer EA. Collagenase in recessive dystrophic epidermolysis bullosa. *Ann NY Acad Sci* 1985; **460**: 311–20.

16 Hovnanian A, Duquesnoy P, Amselem S *et al.* Exclusion of linkage between the collagenase gene and generalized recessive dystrophic epidermolysis bullosa phenotype. *J Clin Invest* 1991; **88**: 1716–21.

17 Colombe M, Gardella R, Zoppi N *et al.* Exclusion of stromelysin-1, stromelysin-2, interstitial collagenase and fibronectin genes as the mutant loci in a family with recessive epidermolysis bullosa dystrophica and a form of cerebellar ataxia. *Hum Genet* 1992; **89**: 503–7.

18 Christiano AM, Hoffman GG, Chung-Honet LC *et al.* Structural organization of the human type VII collagen gene (*COL7A1*), composed of more exons than any previously characterized gene. *Genomics* 1994; **21**: 169–79.

19 Christiano AM, Greenspan DS, Lee S, Uitto J. Cloning of human type VII collagen: complete primary sequence of the α1 (VII) chain and identification of intragenic polymorphisms. *J Biol Chem* 1994; **269**: 20256–62.

20 Gammon WR, Abernethy ML, Padilla KM *et al.* Non-collagenous (NC-1) domain of collagen VII resembles multidomain adhesion proteins involved in tissue-specific organization of extracellular matrix. *J Invest Dermatol* 1992; **99**: 691–6.

21 Greenspan DS. The carboxy-terminal half of type VII collagen, including the non-collagenous NC-2 domain and intron–exon organization of the corresponding region of the *COL7A1* gene. *Hum Mol Genet* 1993; **2**: 273–8.

22 Bruckner-Tuderman L, Nilssen O, Zimmermann DR *et al.* Immunohistochemical and mutation analyses demonstrate that procollagen VII is processed to collagen VII through removal of the NC-2 domain. *J Cell Biol* 1995; **131**: 551–9.

23 Christiano A, Anhalt G, Gibbons S *et al.* Premature termination codons in the type VII collagen gene (*COL7A1*) underlie severe, mutilating recessive dystrophic epidermolysis bullosa. *Genomics* 1994; **21**: 160–8.

24 Hilal L, Rochat A, Duquesnoy P *et al.* A homozygous insertion-deletion in the type VII collagen gene (*COL7A1*) in Hallopeau–Siemens dystrophic epidermolysis bullosa. *Nat Genet* 1993; **4**: 287–93.

25 Dunnill MGS, Richards AJ, Milina G *et al.* A novel homozygous point mutation in the collagen VII gene (*COL7A1*) in two cousins with recessive dystrophic epidermolysis bullosa. *Hum Mol Genet* 1994; **3**: 1693–4.

26 Varki R, Sadowski S, Uitto J, Pfendner E. Epidermolysis bullosa. II. Type VII collagen mutations and phenotype/genotype correlations in dystrophic subtypes. *J Med Genet* 2007; **44**: 181–92.

27 Tidman MJ, Eady RAJ. Structural and functional properties of the dermo-epidermal junction in obligate heterozygotes for recessive forms of epidermolysis bullosa. *Arch Dermatol* 1996; **112**: 278–81.

28 Christiano AM, Greenspan DS, Hoffman GG *et al.* A missense mutation in type VII collagen in two affected siblings with recessive dystrophic epidermolysis bullosa. *Nat Genet* 1993; **4**: 62–6.

29 Dunnill MGS, McGrath JA, Richards AJ *et al.* Clinicopathological correlations of compound heterozygous *COL7A1* mutations in recessive dystrophic epidermolysis bullosa. *J Invest Dermatol* 1996; **107**: 171–7.

30 Shimizu H, McGrath JA, Christiano AM *et al.* Molecular basis of recessive dystrophic epidermolysis bullosa: genotype–phenotype correlations in a case of moderate clinical severity. *J Invest Dermatol* 1996; **106**: 119–24.

31 Christiano AM, Ryynanen M, Uitto J. Dominant dystrophic epidermolysis bullosa: identification of a Gly–Ser substitution in the triple-helical domain of type VII collagen. *Proc Natl Acad Sci USA* 1994; **91**: 3459–553.

32 Kon A, McGrath JA, Pulkkinen L *et al.* Glycine substitution mutations in the type VII collagen gene (*COL7A1*) in dystrophic epidermolysis bullosa: implications for genetic counselling. *J Invest Dermatol* 1997; **108**: 224–8.

33 Wessagowit V, Ashton GH, Mohammedi R *et al.* Three cases of *de novo* dominant dystrophic epidermolysis bullosa associated with the mutation G2043R in *COL7A1*. *Clin Exp Dermatol* 2001; **26**: 97–9.

34 Christiano AM, Bart BJ, Epstein EH, Uitto J. Genetic basis of Bart's syndrome: a glycine substitution in the type VII collagen gene. *J Invest Dermatol* 1996; **106**: 1340–2.

35 Christiano AM, Lee J-Y, Chan WJ *et al*. Pretibial epidermolysis bullosa: genetic linkage to *COL7A1* and identification of a glycine-to-cysteine substitution in the triple helical domain of type VII collagen. *Hum Mol Genet* 1995; **4**: 1579–83.
36 Lee JY-Y, Pulkkinen L, Liu H-S *et al*. A glycine-to-arginine substitution in the triple helical domain of type VII collagen in a family with dominant dystrophic epidermolysis bullosa pruriginosa. *J Invest Dermatol* 1997; **108**: 947–9.
37 Mellerio JE, Ashton GH, Mohammedi R *et al*. Allelic heterogeneity of dominant and recessive *COL7A1* mutations underlying epidermolysis bullosa pruriginosa. *J Invest Dermatol* 1999; **112**: 984–7.
38 Ortiz-Urda S, Garcia J, Chen L *et al*. Type VII collagen is required for Ras-driven human epidermal tumorigenesis. *Science* 2005; **307**: 1773–6.
39 Pourreyron C, Cox G, Mao X *et al*. Patients with recessive dystrophic epidermolysis bullosa develop squamous-cell carcinoma regardless of type VII collagen expression. *J Invest Dermatol* 2007; **127**: 2438–44.

Clinical subtypes

Dystrophic EB has the following subtypes.

Autosomal recessive forms

Severe generalized recessive dystrophic epidermolysis bullosa (formerly named Hallopeau–Siemens variant) [1]

Synonyms

- Polydysplastic epidermolysis bullosa
- Epidermolysis bullosa dystrophica generalisata gravis

Bullae are present at birth or appear in early infancy. The clinical presentation may include localized absence of skin ('Bart's syndrome') especially affecting the hands, feet and lower legs in a flame-shaped, glove or sock-like distribution [2]. The skin can be extremely fragile in this form of EB. Blisters develop spontaneously or after the mildest trauma on any part of the skin and may be haemorrhagic. Healing lesions leave atrophic scars like cigarette paper; thicker scars may occur particularly over the large joints, such as the knees. Milia formation is a nearly constant feature. Although the whole of the skin is fragile and at high risk of developing blisters, the main sites of predilection are those subjected to repeated friction and other forms of physical trauma. These include the knees, elbows, hands, feet, back of the neck, shoulders and over the spine (Fig. 39.19). Ulcers over the spine or shoulders may heal extremely slowly. Chronic erosions and ulcers tend to become covered with a slough, often associated with heaped-up crusting and scaling, increasing the risk of secondary infection. Occasionally these lesions heal with excessive granulation tissue, reminiscent of that seen in Herlitz junctional EB. Pruritus is frequent, and constant rubbing and scratching may induce blisters. Considerable pain may be associated with dressing changes.

The scalp is often involved. Hair growth on the scalp and body is impaired and scarring alopecia may occur (Fig. 39.20). During childhood, repeated blistering with progressive scarring causes fusion ('pseudosyndactyly') of adjacent fingers and toes [3]. If left untreated, the digits then undergo progressive contractures and gradually become encased in a cocoon-like covering of thin scar tissue (Fig. 39.21). Disuse of the hands results in bony resorption and muscle atrophy.

Non-cutaneous epithelia are also at risk of developing blisters, erosions and scars. Oral lesions may be severe, leading to marked



Fig. 39.19 Extensive lesions on the back in generalized recessive dystrophic epidermolysis bullosa. (Courtesy of Professor R.A.J. Eady, St John's Institute of Dermatology, London, U.K.)



Fig. 39.20 Scarring alopecia in generalized recessive dystrophic epidermolysis bullosa. (Courtesy of Professor R.A.J. Eady, St John's Institute of Dermatology, London, U.K.)



Fig. 39.21 Mitten hand deformity in generalized recessive dystrophic epidermolysis bullosa. (Courtesy of Professor R.A.J. Eady, St John's Institute of Dermatology, London, U.K.)



Fig. 39.22 Dental changes and blistering on lips in generalized recessive dystrophic epidermolysis bullosa. (Courtesy of Professor R.A.J. Eady, St John's Institute of Dermatology, London, U.K.)

ankyloglossia and microstomia. Patients are often unable to protrude the tongue outside the mouth, or to open the mouth normally. The gums are fragile, and gentle tooth brushing may induce epithelial disruption with bleeding. The lingual papillae are lost and the surface of the tongue becomes smooth, shiny and atrophic. Although there is no evidence for a primary abnormality of dental enamel in dystrophic EB, the teeth are at a high risk of developing caries (Fig. 39.22) because of prolonged exposure to food. This stems from a reduced ability to chew the food normally and diminished circulation of saliva. Oral secretory immunity may be compromised [4]. In one series, the frequency of caries in the recessive dystrophic form of EB was about five times greater than in dominant dystrophic EB [5]. The loss of dentition has several ramifications. First, the intake of solid food is impaired, with potential consequences affecting the patient's nutrition and tendency to suffer with constipation. Secondly, there is a secondary loss of bone within the alveolar ridges of the jaw, preventing later corrective dental treatment such as the use of tooth implants.

Oesophageal involvement is a serious and invariable complication of this form of EB [6–9]. It may occur very early in life, even in infancy, and by the age of 20–30 years will have affected most patients. Blistering in the oesophagus may cause acute pain and dysphagia, manifesting with difficulty in swallowing solids. With time, partial or complete obstruction may result from oesophageal stricture, caused by scarring and fibrosis; or from web formation [7,9]. Stricture occurs more frequently in the upper third of the oesophagus, and may be multiple. In time, the oesophagus is thought to shorten as a result of fibrosis and is then possibly at additional risk from gastro-oesophageal reflux. Rare complications of oesophageal involvement include spontaneous perforation [8] and bringing up an oesophageal cast. Oesophageal involvement is another cause of poor nutrition.

Perianal blistering, erosions and painful fissures are common in childhood [7]. Later, anal stenosis from scarring may develop. These changes will contribute to a child's reluctance to defecate, leading to faecal retention, abdominal pain and bloating. Chronic constipation and eventual faecal impaction are also common. A low-fibre diet adds to this complication [6]. A minority of patients may experience urethral meatal stenosis [10].

The main ocular complications include symblepharon, which in its more severe form may involve joining of the lid margin to the peripheral cornea; limbal broadening, which is often asymptomatic; corneal erosions; and corneal opacity or scarring, presumably resulting from recurrent corneal blisters and erosions [11–13].

General physical development is retarded. Most patients are very thin and have a short stature. Some blood vitamin and trace metal levels are low [14] and immune function may be impaired because of reduced natural killer cell activity [15]. Severe refractory multifactorial anaemia adds to management problems. Osteopenia and osteoporosis are not uncommon in patients with severe generalized recessive dystrophic EB.

An important sequela of this form of EB is the development of squamous cell carcinomas, which occurs in the majority of patients with both major subtypes of generalized recessive dystrophic EB, as well as a subset of those with inverse disease. These are often multiple primary tumours which, histologically, are usually well differentiated. They may be difficult to identify clinically at an early stage, appearing as a non-healing erosion or crusted or hyperkeratotic lesion. In keeping with other scar carcinomas, these tumours behave aggressively and often metastasize, eventually with a fatal outcome. Life-table analysis from the National EB Registry [16,17] indicates the high probability of death within 5 years of diagnosis of the first squamous cell carcinoma. Patients as young as 13 years may be at risk of developing cancer [18]. These tumours usually arise in any chronically scarred area of skin (Fig. 39.23). Less frequently, they may occur in mouth (including the tongue) and very rarely within the oesophagus [19]. The large majority of carcinomas are on the limbs, often in areas of chronic, non-healing ulceration [20]. The tumours tend to recur locally, despite primary treatment using an apparently wide-surgical excision or Mohs' surgical resection. Recurrences and metastases are generally unresponsive to chemotherapy or radiotherapy. There is also a low but increased risk of developing malignant melanoma in childhood [16], but the incidence of other internal malignancies does not appear to be increased. Systemic amyloidosis is a further complication [21,22] that may involve internal organs



Fig. 39.23 Squamous cell carcinoma arising in an area of chronic scarring in a patient with generalized recessive dystrophic epidermolysis bullosa. (Courtesy of Professor R.A.J. Eady, St John's Institute of Dermatology, London, U.K.)

such as the heart or kidneys. The lifetime risk of death from renal disease, either due to glomerulonephritis (presumably post-streptococcal) or amyloidosis, is about 12% for patients with severe generalized recessive dystrophic EB [23].

Most patients experience a delay in development of secondary sexual changes. Despite the severity of the skin disorder, sexual function may be sufficiently normal in some female patients to undergo an uncomplicated pregnancy with the vaginal delivery of a normal healthy child (R.A.J. Eady & S. Bewley, unpublished observations 1996) [24].

References

1 Briggaman RA. Recessive dystrophic epidermolysis bullosa. In: Lin AN, Carter DM, eds. *Epidermolysis Bullosa: Basic and Clinical Aspects*. New York: Springer, 1992: 135–51.

2 Wojnarowska FT, Eady RAJ, Wells RS. Dystrophic epidermolysis bullosa presenting with congenital localized absence of skin: report of four cases. *Br J Dermatol* 1983; **108**: 471–83.

3 Fine J-D, Johnson LB, Weiner M *et al*. Pseudosyndactyly and musculoskeletal deformities in inherited epidermolysis bullosa (EB): experience of the National EB Registry, 1986–2002. *J Hand Surg (Br and European Vol.)* 2005; **30B**: 14–22.

4 Sweet SP, Ballsdon AE, Harris JC *et al*. Impaired secretory immunity in dystrophic epidermolysis bullosa. *Oral Microbiol Immunol* 1999; **14**: 316–20.

5 Putnam JJ, Sterra GW. Dental aspects of epidermolysis bullosa. In: Lin AN, Carter DM, eds. *Epidermolysis Bullosa: Basic and Clinical Aspects*. New York: Springer, 1992: 135–51.

6 Travis SPL, McGrath JA, Turnbull AJ *et al*. Oral and gastrointestinal manifestations of epidermolysis bullosa. *Lancet* 1992; **340**: 1505–6.

7 Fine J-D, Johnson LB, Weiner M *et al*. Gastrointestinal complications of inherited epidermolysis bullosa: cumulative experience of the National EB Registry. *J Ped Gastroenterol Nutr* 2008; **46**: 147–58.

8 Nix TE, Christianson HB. Epidermolysis bullosa of the oesophagus: report of two cases and review of the literature. *South Med J* 1965; **58**: 612–20.

9 Marsden RA, Gowar FJS, MacDonald AF, Main RA. Epidermolysis bullosa of the oesophagus with oesophageal web formation. *Thorax* 1974; **29**: 287–95.

10 Fine J-D, Johnson LB, Weiner M *et al*. Genitourinary complications of inherited epidermolysis bullosa (EB): experience of the National EB Registry and review of the literature. *J Urol* 2004; **172**: 2040–4.

11 Gans LA. Eye lesions in epidermolysis bullosa. *Arch Dermatol* 1988; **124**: 762–4.

12 McDonnell PJ, Spalton DJ. The ocular signs and complications of epidermolysis bullosa. *J R Soc Med* 1988; **81**: 576–8.

13 Fine J-D, Johnson LB, Weiner M *et al*. Eye involvement in inherited epidermolysis bullosa (EB): experience of the National EB Registry. *Am J Ophthalmol* 2004; **138**: 254–62.

14 Fine J-D, Tamara T, Johnson L. Blood vitamin and trace metal levels in epidermolysis bullosa. *Arch Dermatol* 1989; **125**: 374–9.

15 Trying SK, Chopra V, Johnson L, Fine J-D. Natural killer cell activity is reduced in patients with severe forms of epidermolysis bullosa. *Arch Dermatol* 1989; **125**: 797–800.

16 Fine J-D, Johnson LB, Suchindran C *et al.* Cancer and inherited EB: the NEBR experience. In: Fine J-D, Bauer EA, McGuire J, Moshell A. *Epidermolysis Bullosa: Clinical, Epidemiologic, and Laboratory Advances, and the Findings of the National Epidermolysis Bullosa Registry.* Baltimore: Johns Hopkins University Press, 1999: 175–92.

17 Fine J-D, Johnson LB, Suchindran C *et al.* Premature death and inherited EB: contigency table and lifetable analyses of the NEBR study population. In: Fine J-D, Bauer EA, McGuire J, Moshell A. *Epidermolysis Bullosa: Clinical, Epidemiologic, and Laboratory Advances, and the Findings of the National Epidermolysis Bullosa Registry.* Baltimore: Johns Hopkins University Press, 1999: 206–24.

18 Ayman T, Yerebakan O, Ciftcioglu MA, Alpsoy E. A 13-year-old girl with recessive dystrophic epidermolysis bullosa presenting with squamous cell carcinoma. *Pediatr Dermatol* 2002; **19**: 436–8.

19 Sonneck HJ, Hantzschll K. Über einen Fall von Epidermolysis bullosa dystrophica mit Oesophagusstenose, und Kardiacarcinom. *Hautarzt* 1961; **12**: 124–5.

20 McGrath JA, Schofield OMV, Mayou BJ *et al.* Epidermolysis bullosa complicated by squamous cell carcinoma: report of 10 cases. *J Cutan Pathol* 1992; **19**: 116–23.

21 Bourke JF, Browne G, Gaffney EF, Young M. Fatal systemic amyloidosis (AA type) in two sisters with dystrophic epidermolysis bullosa. *J Am Acad Dermatol* 1995; **33**: 370–2.

22 Kaneko K, Kakuta M, Ohtomo Y *et al.* Renal amyloidosis in recessive dystrophic epidermolysis bullosa. *Dermatology* 2000; **200**: 209–12.

23 Fine J-D, Johnson LB, Weiner M *et al*. Inherited epidermolysis bullosa (EB) and the risk of death from renal disease: experience of the National EB Registry. *Am J Kidney Dis* 2004; **44**: 651–60.

24 Buscher U, Wessel J, Anton-Lamprecht I, Dudenhausen JW. Pregnancy and delivery in a patient with mutilating dystrophic epidermolysis bullosa (Hallopeau–Siemens type). *Obstet Gynecol* 1997; **89**: 817–20.

Generalized recessive dystrophic epidermolysis bullosa, other (previously named non-Hallopeau–Siemens subtype)

The condition shares several cutaneous and extracutaneous features with severe generalized recessive dystrophic EB, but is generally much milder. The skin and mucosae are very fragile, but lesions, including nail changes, milia and atrophic scarring, tend to be more localized, and similar to those seen in classical dominant dystrophic EB (Fig. 39.24). Growth retardation and anaemia are usually mild. Pseudosyndactyly, oesophageal involvement and squamous cell carcinoma may also occur, but these complications are usually milder or less frequent than in Hallopeau–Siemens dystrophic EB.

Inverse recessive dystrophic epidermolysis bullosa [1,2]

The primary areas of blistering and scarring include the groins, axillae, neck (Fig. 39.25) and lumbar area. Traumatic corneal erosions and oesophageal lesions are common. Nail dystrophy, mucous membrane involvement and dental changes are similar to those in the generalized form of the condition. Patients are also at risk of developing squamous cell carcinoma.

References

1 Gedde-Dahl TL, ed. *Epidermolysis Bullosa: a Clinical, Genetic and Epidemiological Study.* Baltimore: Johns Hopkins University Press, 1971.

2 Pearson RM, Paller AS. Dermolytic (dystrophic) epidermolysis bullosa inversa. *Arch Dermatol* 1988; **124**: 544–7.



Fig. 39.24 Nails in localized recessive dystrophic epidermolysis bullosa. (Courtesy of Professor R.A.J. Eady, St John's Institute of Dermatology, London, U.K.)



Fig. 39.25 Scarring and erosions affecting the axilla and neck in the inverse form of recessive dystrophic epidermolysis bullosa. (Courtesy of Professor R.A.J. Eady, St John's Institute of Dermatology, London, U.K.)

Autosomal dominant forms

Generalized dominant dystrophic epidermolysis bullosa

Synonym

- Hyperplastic (Cockayne–Touraine) and albopapuloid (Pasini) variants

A problem with most classifications of EB [1] has been the convention of subdividing the majority of cases of dominant dystrophic EB into the mutually exclusive Cockayne–Touraine or Pasini variants. In 1928, Pasini described a single family whose EB was distinguished by the presence of numerous white papules that he called 'albopapuloid' lesions. In other respects, it is unclear how such individuals can confidently be distinguished from those with the so-called 'Cockayne–Touraine' phenotype. It has been said that one form tends to be more severe than the other, but the issue is clouded by the fact that albopapuloid lesions, which are most often seen on the trunk (Fig. 39.26), are probably not specific, and variations in the onset and severity of the disease have been described, even within the same kindreds [1,2]. Differences in ultrastructural and biochemical findings have also been reported (see [1] for review). The histogenesis of albopapuloid lesions is unclear, and reports have alluded to both epidermal and dermal abnormalities, including alterations of collagen and elastic tissue (reviewed in [2]). For those reasons these particular eponymous descriptions have been abandoned and, in the absence of genotypic proof to the contrary, are both included under the heading of generalized dominant dystrophic EB. The main feature of dominant dystrophic EB is that the skin is generally less fragile than in severe generalized recessive dystrophic EB. Blisters usually follow sharp knocks or glancing blows rather than mild friction, and therefore can be difficult to induce for a diagnostic skin biopsy. Indeed, of all forms of EB, including EB simplex, skin from patients with dominant dystrophic EB is the least likely to be induced to blister following conventional diagnostic techniques. Blisters mainly occur in skin overlying bony prominences, such as the knees and ankles, and dorsa of the hands or feet. The most consistent findings are localized scarring with milia formation and dystrophic nails. Nail dystrophy is probably the most important diagnostic feature of the disease, especially in adults, because many patients have only limited scarring, which becomes less noticeable with age. The nail plates, particularly of the large toes, are often diminutive (Fig. 39.27) or entirely absent, where the normal nail is replaced by atrophic scar tissue. Blistering in the mouth is usually mild and the teeth are generally normal. However, perianal lesions may cause considerable pain, especially in children. In rare kindreds, an occasional family member may present solely with nail dystrophy.

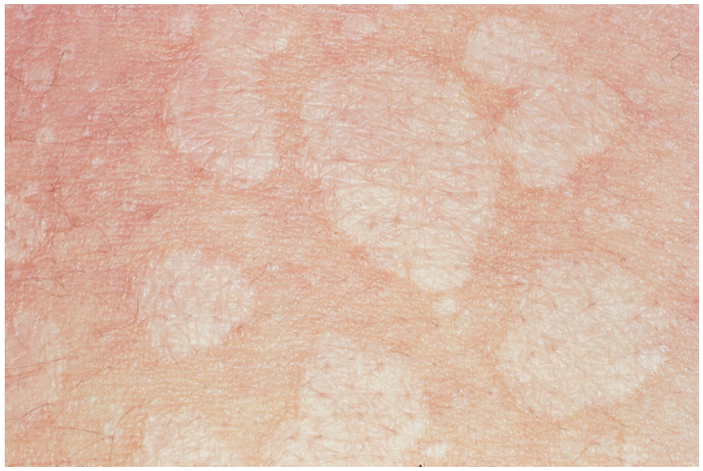


Fig. 39.26 Albopapuloid lesions on the lower back of a patient with dominant dystrophic epidermolysis bullosa. (Courtesy of Professor R.A.J. Eady, St John's Institute of Dermatology, London, U.K.)



Fig. 39.27 Nail changes and scarring of skin on the backs of toes in dominant dystrophic epidermolysis bullosa. (Courtesy of Professor R.A.J. Eady, St John's Institute of Dermatology, London, U.K.)

Clinically, it is often impossible to distinguish this form of dominant dystrophic EB from the localized recessive dystrophic forms, making genetic counselling impossible in the absence of a positive family history or accurate molecular diagnosis.

References

1 Eady RAJ. Current perspectives and differential diagnosis in epidermolysis bullosa. In: Lin AN, Carter DM. *Epidermolysis Bullosa: Basic and Clinical Aspects*. New York: Springer, 1992: 3–15.

2 Kemmet D, Spencer M-J, Tidman MJ. An unusual pedigree of dystrophic epidermolysis bullosa. In: Priestley GC, Tidman MJ, Weiss JB, Eady RAJ, eds. *Epidermolysis Bullosa: a Comprehensive Review of Classification, Management and Laboratory Studies*. Crowthorne: Dystrophic Epidermolysis Bullosa Research Association, 1990: 89–92.

Congenital localized absence of skin

Synonym
- Bart's syndrome

In 1966, Bart described a kindred with localized absence of the skin over the lower legs associated with cutaneous blistering and mucous membrane and nail involvement [1]. The condition, which appeared to follow an autosomal dominant mode of inheritance, was thought to be a form of EB simplex [2]. However, localized absence of the skin has been reported by others in association with simplex [3], junctional [4,5] and dystrophic EB [6]. In view of these findings, congenital localized absence of the skin should be regarded now as a manifestation of EB, instead of a separate entity or syndrome. The original family described by Bart has since been shown to have dominant dystrophic EB, caused by a glycine substitution mutation in *COL7A1* [7].

References

1 Bart BJ, Gorlin RJ, Anderson E *et al.* Congenital localized absence of skin and associated abnormalities resembling epidermolysis bullosa. *Arch Dermatol* 1966; **93**: 296–304.

2 Bart BJ. Epidermolysis bullosa and congenital localized absence of skin. *Arch Dermatol* 1970; **101**: 78–81.

3 Smith AN, Cram DE. A mechanobullous disease of the newborn (Bart's syndrome). *Arch Dermatol* 1978; **114**: 81–4.

4 Herlitz G. Kongenitaler, nicht syphilitischer Pemphigus: Eine Ubersicht nebst Beschreibung einer neuen Krankheitsform (epidermolysis bullosa hereditaria letalis). *Acta Paediatr* 1934–35; **17**: 315–7.

5 Skoven I, Drzewiecki KT. Congenital localized skin defect and epidermolysis bullosa, hereditaria letalis. *Acta Derm Venereol (Stockh)* 1979; **59**: 533–7.

6 Wojnarowska FT, Eady RAJ, Wells RS. Dystrophic epidermolysis bullosa presenting with congenital localized absence of skin: report of four cases. *Br J Dermatol* 1983; **108**: 477–83.

7 Christiano AM, Bart BJ, Epstein EH, Uitto J. Genetic basis of Bart's syndrome: a glycine substitution in the type VII collagen gene. *J Invest Dermatol* 1996; **106**: 1340–2.

Pretibial dystrophic epidermolysis bullosa

In 1946, Kuske [1] reported a patient with itching, blisters, atrophy and scarring on the shins. There were further reports of similar patients [2,3]. In one family with a dominant transmission of the disease, the clinical features were variable [3]. Several authors have referred to this condition as pretibial EB [4–6], given the tendency for the lesions to develop in the pretibial areas. Lesions are usually violaceous, mimicking lichen planus. Nails on both hands and feet tend to be dystrophic. This condition is an autosomal dominant one.

Epidermolysis bullosa pruriginosa

In 1994, McGrath *et al.* [7] delineated a group of eight patients with a highly distinctive phenotype in which the overriding symptom is severe pruritus. The authors named the condition 'EB pruriginosa' to highlight this combination of clinical features. EB pruriginosa presents either at birth with mild acral blistering and erosions, or during infancy or childhood. Violaceous papular and nodular lesions, often in a linear arrangement, are mainly confined to the shins (Fig. 39.28) and forearms, although rare lesions may occur on the trunk. In adults, the lesions are chiefly lichenified plaques. Histologically, a split may be evident at the dermal–epidermal junction, although frank blisters are rarely seen. Apart from scarring with milia, toenail dystrophy is a consistent finding in adult patients.

Most cases are sporadic. However, both autosomal recessive and dominant inheritance is recognized [8]. The cause of the severe pruritus is unknown; however, a number of patients have raised blood levels of immunoglobulin E (IgE) (R.A.J. Eady, unpublished observations 1997), suggesting a possible atopic background. Clinically, EB pruriginosa has to be distinguished from lichen simplex, hypertrophic lichen planus, Nékam's disease, cutaneous amyloidosis and dermatitis artefacta [9]. It shares several features with the pretibial form of dystrophic EB, but is clinically much more striking.

References

1 Kuske H. Epidermolysis traumatica: regionar uber beiden Tibiae zur Atrophie fuhrend mit dominanter Vererbung. *Dermatologica* 1946; **91**: 304–5.

2 Kennedy C. Epidermolysis bullosa dystrophica. *Proc R Soc Med* 1974; **67**: 1240–1.

3 Russell Jones R. Epidermolysis bullosa: report of a family and discussion of the dominant dystrophic types. *Clin Exp Dermatol* 1979; **4**: 303–8.

4 Furue M, Ando I, Inoue Y *et al.* Pretibial epidermolysis bullosa. *Arch Dermatol* 1986; **122**: 310–3.

5 Portugal H. Symmetrische bullosis der unteren Extremitäten. *Hautarzt* 1959; **10**: 170–3.



Fig. 39.28 Violaceous lesions in a partly linear distribution in a patient with epidermolysis bullosa pruriginosa. (Courtesy of Professor R.A.J. Eady, St John's Institute of Dermatology, London, U.K.)

6 Garcia-Perez A, Carapeto FJ. Pretibial epidermolysis bullosa: report of two families and review of the literature. *Dermatologica* 1975; **150**: 122–8.

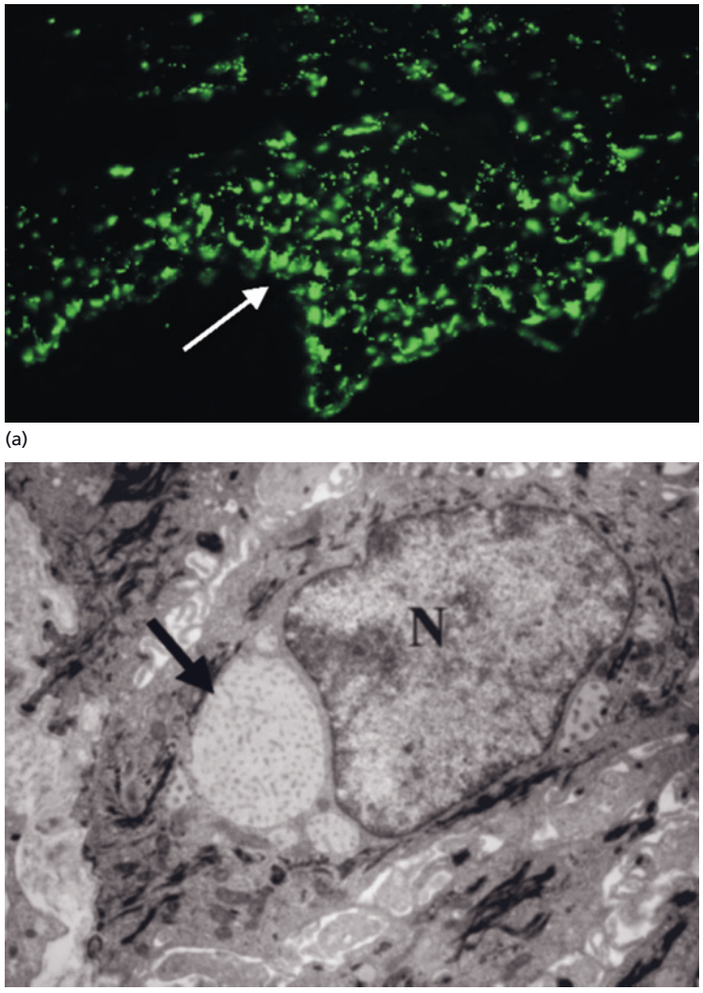
7 McGrath JA, Schofield OMV, Eady RAJ. Epidermolysis bullosa pruriginosa: dystrophic epidermolysis bullosa with distinctive clinicopathological features. *Br J Dermatol* 1994; **130**: 617–25.

8 Mellerio JE, Ashton GH, Mohammedi R *et al.* Allelic heterogeneity of dominant and recessive *COL7A1* mutations underlying epidermolysis bullosa pruriginosa. *J Invest Dermatol* 1999; **112**: 984–7.

9 Goulden V, Handfield-Jones S, Neild V, Black MM. Linear prurigo simulating dermatitis artefacta in dominant dystrophic epidermolysis bullosa. *Br J Dermatol* 1993; **129**: 443–6.

Bullous dermolysis of the newborn

In 1985, Hashimoto *et al.* [1] reported a newborn with blistering developing on the extremities soon after birth. The bullae quickly resolved and there was apparently no scarring or milia formation. However, others have subsequently reported focal atrophic scarring, milia, and/or nail dystrophy, as well as more generalized blistering, in some affected family members. The name 'transient bullous dermolysis of the newborn' was coined to describe this uniquely self-limited clinical course associated with a sublamina densa level of cleavage. Ultrastructurally, the basal epidermal keratinocytes were shown to contain electron-dense stellate bodies. The skin condition resolved completely and a year later there were only mild residual pigmentary changes. Later, Fine *et al.* [2] used immunofluorescence and immunoelectron microscopy to show that these intracellular inclusions contained type VII collagen, and that the underlying dermal–epidermal junction usually lacked normal anchoring fibrils and type VII collagen staining (Fig. 39.29). The phenotype of these patients resembled a mild dominant or localized recessive form of dystrophic EB, and included small



(a)

(b)

Fig. 39.29 Bullous dermolysis of the newborn. (a) Indirect immunofluorescence micrograph showing granular staining in the basal and suprabasal layers with LH7.2 (anticollagen VII) antibody, yet absence of the normal linear staining at the dermal–epidemal junction (arrow). (b) Electron micrograph showing a large intracellular inclusion (arrow) beneath a basal cell nucleus (N). (Courtesy of Professor R.A.J. Eady, St John's Institute of Dermatology, London, U.K.)

numbers of tense blisters, milia and mild focal atrophic scarring. Fine *et al.* [2] further demonstrated that these immunohistochemical features tended to revert to that of normal non-EB skin, showing intense uniform linear immunostaining of the dermal–epidermal junction with antibodies to type VII collagen, at about the time most blister formation had ceased. It was thought that this phenomenon represents a transient secondary abnormality in packaging, transport or incorporation of a presumably mutated type VII collagen into the dermal–epidermal junction during early infancy in these patients. Since rare patients continue to develop blistering beyond infancy, the condition has recently been renamed bullous dermolysis of the newborn.

The clinical and microscopic features were later confirmed by Schofield *et al.* [3] in other patients. Smith and Sybert [4], however, described similar ultrastructural and immunocytochemical findings in a patient with recessive dystrophic EB whose prognosis was poor. Phillips *et al.* [5] also showed that the presence of

intraepidermal type VII collagen in infancy was not always predictive of a good clinical outcome.

One of the kindreds reported by Fine *et al.* [2] has since been shown to have a *COL7A1* mutation typical of dominant dystrophic EB [6]. *COL7A1* mutations have also been reported in other cases [7].

References

1 Hashimoto K, Matsumoto M, Iacobelli D. Transient bullous dermolysis of the newborn. *Arch Dermatol* 1985; **121**: 1429–38.

2 Fine J-D, Horiguchi Y, Stein DI *et al.* Intraepidermal type VII collagen: evidence for abnormal intracytoplasmic processing of a major basement membrane protein in rare patients with dominant and possibly localized recessive forms of dystrophic epidermolysis bullosa. *J Am Acad Dermatol* 1990; **22**: 188–95.

3 Schofield OMV, Ishida-Yamamoto A, McGrath J *et al.* Transient bullous dermolysis of the newborn: a disorder of type VII collagen secretion. *Br J Dermatol* 1991; **125** (Suppl. 38): 89.

4 Smith LT, Sybert VP. Intra-epidermal retention of type VII collagen in a patient with recessive dystrophic epidermolysis bullosa. *J Invest Dermatol* 1990; **94**: 261–4.

5 Phillips RJ, Harper JI, Lake BD. Intraepidermal collagen type VII in dystrophic epidermolysis bullosa: report of five new cases. *Br J Dermatol* 1992; **126**: 222–30.

6 Christiano AM, Fine JD, Uitto J. Genetic basis of dominantly inherited transient bullous dermolysis of the newborn: a splice site mutation in the type VII collagen gene. *J Invest Dermatol* 1997; **109**: 811–4.

7 Hammami-Hauasli N, Raghunath M, Kuster W, Bruckner-Tuderman L. Transient bullous dermolysis of the newborn associated with compound heterozygosity for recessive and dominant *COL7A1* mutations. *J Invest Dermatol* 1998; **111**: 1214–9.

Recessive dystrophic EB, centripetalis

A patient was reported who had generalized blistering at birth but within the first year of life had her skin disease activity confined to the hands and feet [1]. Over several decades her blistering slowly progressed proximally, in centripetal manner, with active blistering and milia only along the active edges and atrophic scarring and nail dystrophy distally. At the time of death in late adulthood from unrelated causes, no blistering was yet present on the trunk, face, or neck. A *COL7A1* mutation was demonstrated.

Reference

1 Fine J-D, Osment LS, Gay S. Dystrophic epidermolysis bullosa: a new variant characterized by progressive symmetrical centripetal involvement with scarring. *Arch Dermatol* 1985; **121**: 1014–7.

Diagnosis

Despite the impressive advances in the molecular genetics of different forms of EB, the initial diagnosis still relies largely on a careful clinical examination, enquiry into the family history and establishing the level of blister formation [1]. Because the clinical features may be unhelpful or even misleading, especially in a neonate, the diagnosis will often rely on microscopic analysis of a skin biopsy. Electron microscopy and immunofluorescence mapping are still the best methods for evaluating EB skin samples. The cryopreserved tissues obtained for immunofluorescence mapping may also be stained with specific monoclonal and polyclonal antibodies so as to provide additionally useful diagnostic information. Ideally, tissue should be acquired at the same time for evaluation by both techniques.

Skin biopsy

The main objectives of skin biopsy are first to establish the level of blistering or tissue separation and, secondly, to search for other clues that may be indicative of the underlying disorder and therefore helpful in the diagnosis. The importance of the correct biopsy technique cannot be overstressed. Most blisters that are clinically evident, and especially those with bloodstained contents, are often more than 12 h old and therefore too old for diagnostic purposes. Older blisters may cause severe diagnostic difficulty because false-negative immunostaining caused by proteolytic antigen degradation, re-epithelialization under the blister roof and multiple cleavage planes may all occur. A sample of non-blistered skin that has been gently rubbed to produce a mild erythema is preferable, because this will usually contain a cleavage plane with few if any secondary changes.

Because the diagnostic signs are mostly seen in and around the dermal–epidermal junction, shave biopsy samples are preferable to thicker specimens when electron microscopy is being contemplated. Small punch or shave biopsies may be obtained for immunofluorescence mapping. Care must be taken to ensure that a sufficient amount of dermis is present, to allow examination of the entire dermal–epidermal junction. It is often better to take two or three small pieces for different types of examination, such as electron microscopy and immunofluorescence. Attempts to subdivide a larger biopsy specimen can result in detachment of the epidermis from the dermis and spoil the sample for critical microscopic analysis. The samples should be immediately immersed in suitable fixative for electron microscopy, or in a freezing liquid, such as isopentane precooled with liquid nitrogen, after embedding in OCT Tissue-Tek Compound (Miles Inc, Diagnostics Division, IN 46515, USA), for immunofluorescence. The samples can then be stored in a –70°C freezer or in liquid nitrogen until required for analysis. Michel's transport medium can be used for both immunofluorescence and electron microscopy [2], although the ultrastructural preservation will be variable and often inadequate for detailed electron microscopic analysis.

References

1 Eady RAJ, Tidman MJ. Diagnosing epidermolysis bullosa. *Br J Dermatol* 1983; **108**: 621–8.

2 Vaughan Jones SA, Palmer I, Bhogal BS *et al.* The use of Michel's transport medium for immunofluorescence and immunoelectron microscopy in autoimmune bullous diseases. *J Cutan Pathol* 1995; **22**: 365–70.

Electron microscopy

The chief purpose is to demonstrate the level of tissue separation or blistering [1,2]. As indicated in the sections on molecular pathology of EB subtypes, the split is intraepidermal in EB simplex, in junctional EB it is through the lamina lucida, just below the lowermost plasma membrane of basal cells, and in dystrophic EB it is beneath the lamina densa. In Kindler syndrome the cleavage plane may be within and above the lamina lucida. Other ultrastructural features important for diagnosis are that hemidesmosomes are

generally sparse and small in the more severe forms of junctional EB [3,4] and anchoring fibrils are reduced in number, absent or structurally abnormal in dystrophic forms of EB [5–7]. A clear distinction cannot be made between the dominant and localized recessive dystrophic forms, even with morphometric analysis of anchoring fibrils [3]. Intraepidermal electron-dense stellate bodies are a marker of bullous dermolysis of the newborn (Fig. 39.29). In the Herlitz form of junctional EB and in the form of EB associated with pyloric atresia, hemidesmosome plaques are often minute, and subbasal dense plates are severely attenuated or absent.

In EB simplex, the most striking changes are seen in the Dowling–Meara form, where tonofilament clumping in basal keratinocytes (Fig. 39.1) is pathognomonic [8]. In the rare generalized or autosomal recessive forms of EB simplex, the tonofilaments may be severely depleted or absent from the basal cells. In EB superficialis, the cleavage level is usually subcorneal. Despite their value in diagnosis in most instances, the ultrastructural features in a given diagnostic biopsy sample can be difficult to interpret. Briggaman [9] has illustrated how the level of cleavage may appear to vary, not only between skin samples from the same patient but also within the same sample.

References

1 Eady RAJ, Tidman MJ. Diagnosing epidermolysis bullosa. *Br J Dermatol* 1983; **108**: 621–6.

2 Hanna W, Silverman F, Boxall L, Krafchik BR. Ultrastructural features of epidermolysis bullosa. *Ultrastruct Pathol* 1983; **5**: 29–36.

3 Hashimoto I, Gedde-Dahl T Jr, Schnyder UW, Anton Lamprecht L. Ultrastructural studies in epidermolysis bullosa hereditaria. IV. Recessive dystrophic types with junctional blistering (infantile or Herlitz–Pearson type and adult type). *Arch Dermatol Res* 1976; **257**: 17–32.

4 Tidman MJ, Eady RAJ. Hemidesmosome heterogeneity in junctional epidermolysis bullosa revealed by morphometric analysis. *J Invest Dermatol* 1986; **96**: 51–6.

5 Briggaman RA, Wheeler CE Jr. Epidermolysis bullosa dystrophica-recessive: a possible role of anchoring fibrils in the pathogenesis. *J Invest Dermatol* 1975; **65**: 203–11.

6 Tidman MJ, Eady RAJ. Evaluation of anchoring fibrils and other components of the dermal–epidermal junction in dystrophic epidermolysis bullosa by a quantitative ultrastructural technique. *J Invest Dermatol* 1985; **84**: 374–7.

7 McGrath JA, Ishida-Yamamoto A, O'Grady A *et al*. Structural variations in anchoring fibrils in dystrophic epidermolysis bullosa: correlation with type VII collagen expression. *J Invest Dermatol* 1993; **100**: 366–72.

8 Anton-Lamprecht I, Schnyder UW. Epidermolysis bullosa herpetiformis Dowling–Meara: report of a case and pathomorphogenesis. *Dermatologica* 1982; **164**: 221–35.

9 Briggaman RA. Structural changes of the dermo-epidermal junction in epidermolysis bullosa. In: Priestley GC, Tidman MJ, Weiss JB, Eady RAJ, eds. *Epidermolysis Bullosa: a Comprehensive Review of Classification, Management and Laboratory Studies.* Crowthorne: Dystrophic Epidermolysis Bullosa Research Association, 1990: 50–61.

Antigen mapping

As an alternative to electron microscopy, the level of blister formation can be determined using indirect immunohistochemical staining [1–3]. The aim is not to look for reduced expression of skin antigens, but to stain the dermal–epidermal zone using antibodies to proteins that are strongly expressed in both normal skin and skin from patients with different forms of EB. For example, sera from bullous pemphigoid patients or, preferably, an anti-BP230 antibody can be used to stain the lower surface of basal cells (containing hemidesmosomes), and antikeratin 14 antibody to stain the cytoplasm of basal epidermal cells. Anti-type IV collagen antibody will stain the lamina densa of the epidermal basement membrane, whereas anti-laminin-1 antibody will stain the upper lamina lucida. In EB simplex, all antibodies (except antikeratin) stain only the base of the split. Antikeratin stains the roof and the floor (but this is difficult to see in low-level separations). In junctional EB, antikeratin, anti-laminin-1 and bullous pemphigoid antibodies stain the roof; whereas anti-type IV collagen staining is on the floor. In dystrophic EB, all antibodies stain only the roof of the split.

References

1 Hintner H, Stingl G, Schuler G *et al*. Immunofluorescence mapping of antigenic determinants within the dermal–epidermal junction in the mechanobullous diseases. *J Invest Dermatol* 1981; **76**: 113–8.

2 McGrath JA, Burrows NP, Russell Jones R, Eady RAJ. Epidermolysis bullosa simplex Dowling–Meara: troublesome blistering and pruritus in an adult patient. *Dermatology* 1993; **186**: 68.

3 Prieto VG, McNutt NS. Immunohistochemical detection of keratin with the monoclonal antibody MNF 116 is useful in the diagnosis of epidermolysis bullosa simplex. *J Cutan Pathol* 1994; **21**: 118–22.

Use of specific antibody probes

This method can be very valuable in diagnosis when used together with electron microscopy or antigen mapping. The purpose is to demonstrate a reduction in, or absence of, expression of certain antigens in the dermal–epidermal junction, which may be indicative of specific abnormalities in junctional and dystrophic forms of EB, as well as Kindler syndrome [1]. Several relevant studies have already been referred to under the sections on molecular pathology of EB subtypes.

In Herlitz and some non-Herlitz cases of junctional EB, caused by laminin 5 mutations, abnormal staining for laminin 5 can be shown using monoclonal antibodies GB3 [2] and K140 [3] (Fig. 39.30). In non-Herlitz junctional EB (generalized atrophic benign EB) with BP180 defects, staining is reduced with anti-BP180, but not with antilaminin 5 antibodies [4]. Antibodies to the α6 or β4 integrin chains will show reduced staining in the skin of patients with EB associated with pyloric atresia [5].

The monoclonal antibody 19-DEJ-1, recognizing 'uncein', an anchoring filament antigen possibly representing a protein with homology with a non-muscle myosin (J.-D. Fine, unpublished data), shows reduced or absent staining in all forms of junctional EB and in approximately 25% of individuals with recessive dystrophic EB [6,7]. LH 7.2 monoclonal antibody, reacting with the amino terminal of the type VII collagen molecule, is probably the most widely used antibody for the diagnosis of recessive dystrophic EB [8]. In cases of EB simplex associated with muscular dystrophy, reduced or absent staining will be found using antibodies to plectin, or HD1 (an antigen that is homologous with plectin) [9–11]. Kindlin-1 staining will be reduced in skin specimens from patients with Kindler syndrome.

References

1 Fine J-D. Structure and antigenicity of the skin basement membrane zone. *J Cutan Pathol* 1991; **18**: 401–9.

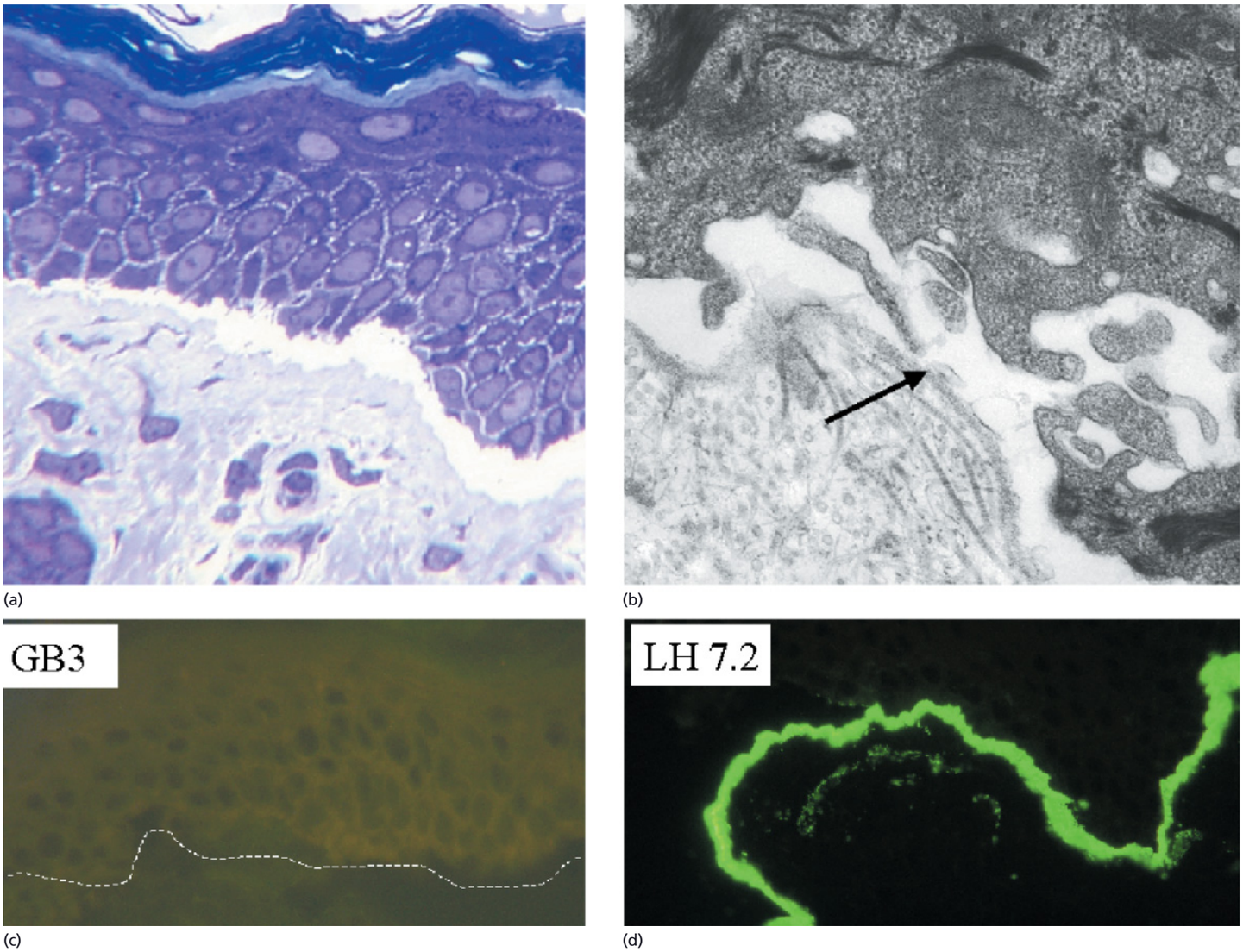


Fig. 39.30 Combined use of (a) light microscopy, (b) electron microscopy, and (c,d) indirect immunofluorescence microscopy for the diagnosis of Herlitz junctional EB. (a) A split in a semi-thin (1 μm thick) resin section has occurred in (b) the lamina lucida, just above the lamina densa (arrow). (c,d) In frozen sections, (c) GB3 (antilaminin 5) staining is negative, whereas (d) LH7.2 (anticollagen VII) staining is normal. (Courtesy of Professor R.A.J. Eady, St John's Institute of Dermatology, London, U.K.)

2 Schofield OMV, Fine J-D, Pasini A *et al.* GB3 monoclonal antibody for diagnosis of junctional epidermolysis bullosa: result of a multicentre study. *J Am Acad Dermatol* 1990; **23**: 1078–83.
3 Meneguzzi G, Marinkovich MP, Aberdam D *et al.* Kalinin is abnormally expressed in epithelial basement membranes of Herlitz's junctional epidermolysis bullosa patients. *Exp Dermatol* 1992; **1**: 221–9.
4 McGrath JA, Eady RAJ. The role of immunohistochemistry in the diagnosis of non-lethal forms of junctional epidermolysis bullosa. *J Dermatol Sci* 1997; **14**: 68–75.
5 Phillips RJ, Aplin JD, Lake BD. Antigenic expression of integrin α6β4 in junctional epidermolysis bullosa. *Histopathology* 1994; **24**: 571–6.
6 Fine J-D, Horiguchi Y, Couchman JR. 19-DEJ-1, a hemidesmosome-anchoring filament complex-associated monoclonal antibody: definition of a new skin basement membrane antigenic defect in junctional and dystrophic epidermolysis bullosa. *Arch Dermatol* 1989; **125**: 520–3.
7 Fine J-D. 19-DEJ-1, a monoclonal antibody to the hemidesmosome-anchoring filament complex, is the only reliable immunohistochemical probe for all major forms of junctional epidermolysis bullosa. *Arch Dermatol* 1990; **126**: 1187–90.
8 Heagerty AHM, Kennedy AR, Leigh IM *et al.* Identification of an epidermal basement membrane defect in recessive forms of dystrophic epidermolysis bullosa by LH 7.2 monoclonal antibody: use in diagnosis. *Br J Dermatol* 1986; **115**: 125–31.
9 Gache Y, Chavanas S, Lacour JP *et al.* Defective expression of plectin/HD1 in epidermolysis bullosa simplex with muscular dystrophy. *J Clin Invest* 1996; **97**: 2289–98.
10 Smith FJD, Eady RAJ, Leigh IM *et al.* Plectin deficiency results in muscular dystrophy with epidermolysis bullosa. *Nat Genet* 1996; **13**: 450–6.
11 Okumura M, Uematsu J, Hirako Y *et al.* Identification of the hemidesmosomal 500 kDa protein (HD1) as plectin. *J Biochem (Tokyo)* 1999; **126**: 1144–50.

Molecular diagnosis

With the discovery of over 10 distinct genes underlying different variants of EB, DNA-based techniques have had an increasingly important application in the diagnosis and prenatal diagnosis of

EB. The information gained from molecular diagnosis is especially useful for genetic counselling and prognosis. When a patient is first seen in the clinic or neonatal unit, it is important to make provision for molecular diagnosis in the management plan, and obtain venous blood or cheek mucosa brushings (collected in ethylenediamine tetra-acetic acid tubes, and *not* in heparin or citrate) for subsequent DNA extraction and analysis in the laboratory.

An example of the power of molecular diagnosis is the ability to discover whether a patient has a dominant or recessive form of dystrophic EB, where neither the family history, a skin biopsy nor the clinical phenotype has been able to provide the information. In a cohort of some 180 families in which distinct *COL7A1* mutations had been identified, there was evidence of only one case derived from a *de novo* germ-line-dominant mutation in a parent [1]. This implies that the large majority of apparently sporadic 'new' cases, with no known family history of EB, are likely to have a recessive rather than a dominant form of dystrophic EB [1]. However, the presumptive *de novo* occurrence of a glycine substitution mutation has also been reported [2,3]. The possibility of germ-line mutations inherited in patients with 'sporadic' dominant dystrophic EB should also be considered [4]. Molecular diagnosis can be valuable in the differentiation of Herlitz from non-Herlitz EB (e.g. in a child) where the skin biopsy findings, including the immunofluorescence results, are equivocal.

The developments in the molecular genetics of the dystrophic and junctional forms of EB have already had a major impact on prenatal diagnosis. First trimester DNA testing is now an option for couples at risk of having affected children (see Chapter 16). Knowledge of mutation 'hotspots' within a population can reduce the time and expense of extensive screening for mutations that might otherwise be necessary [5]. The issue of mutation screening of family members of affected individuals, or unrelated partners, often arises during genetic counselling. In relatives not known to be at high risk of either being a carrier of a recessive gene and therefore of having an affected child, genetic screening may not be offered, or even encouraged. However, there are rare instances where prior screening may have averted an affected pregnancy [6].

References

1 Christiano AM, Uitto J. Molecular complexity of the cutaneous basement membrane zone. *Exp Dermatol* 1996; **5**: 1–11.

2 Kon A, McGrath JA, Pulkkinen L *et al.* Glycine substitution mutations in the type VII collagen gene (*COL7A1*) in dystrophic epidermolysis bullosa: implications for genetic counselling. *J Invest Dermatol* 1997; **108**: 224–8.

3 Wessagowit V, Ashton GH, Mohammedi R *et al.* Three cases of *de novo* dominant dystrophic epidermolysis bullosa associated with the mutation G2043R in *COL7A1*. *Clin Exp Dermatol* 2001; **26**: 97–9.

4 Cserhalmi-Friedman PB, Garzon MC, Guzman E *et al.* Maternal germ-line mosaicism in dominant dystrophic epidermolysis bullosa. *J Invest Dermatol* 2001; **117**: 1327–8.

5 Ashton GH, Mellerio JE, Dunnill MGS *et al.* A recurrent laminin 5 mutation in British patients with lethal (Herlitz) junctional epidermolysis bullosa: evidence for a mutational hotspot rather than propagation of an ancestral allele. *Br J Dermatol* 1997; **136**: 674–7.

6 Klausegger A, Pulkkinen L, Pohla-Gubo G *et al.* Is screening of the candidate gene necessary in unrelated partners of members of families with Herlitz junctional epidermolysis bullosa? *J Invest Dermatol* 2001; **116**: 474–5.

Differential diagnosis

Differentiating EB from non-EB, or one form of EB from another, can be very difficult, especially in the neonatal period. At this stage, the following disorders may need to be included in the differential diagnosis of EB: bullous congenital ichthyosiform erythroderma; staphyloccocal scalded skin syndrome; bullous impetigo; incontinentia pigmenti; neonatal herpes simplex; autoimmune bullous disease, such as pemphigus or herpes gestationis, acquired transplacentally; aplasia cutis; focal dermal hypoplasia; and Gunther's disease.

In infants, older children or adults, some autoimmune bullous diseases, such as bullous pemphigoid, cicatricial pemphigoid or linear IgA disease, may show overlapping features with junctional EB or Dowling–Meara EB simplex. EB acquisita may resemble dystrophic EB. Usually the timing of the onset of blistering will allow inherited EB to be distinguished from the autoimmune immunobullous disorders. Pachyonychia congenita, skin peeling syndrome and ichthyosis bullosa of Siemens may rarely be confused with EB in older children or adults.

In the past, Mendes da Costa disease [1] was considered to be a form of EB simplex. The pathogenesis of this rare X-linked disorder, reported in a Dutch family, is still poorly understood. Although blisters are seen, they are not trauma induced [2]. As such, this entity is no longer included within the current classification system for EB.

References

1 Mendes da Costa S, van der Valk JW. Typus maculatis der bullosen hereditaren dystrophie. *Arch Dermatol Syphilol* 1908; **91**: 1.

2 Woerdeman MJ. Dystrophia bullosa hereditaria typus maculatus. *Acta Derm Venereol (Stockh)* 1957; **111**: 678–86.

Treatment

At this point in time there is no specific treatment for any form of EB, and the mainstay of clinical management is based on protection and avoidance of provoking factors. In the more severe forms of EB, it should be remembered that the whole skin and other stratified squamous epithelia, including the oral mucosa, are extremely fragile and vulnerable to blistering from the slightest friction or scrapes. In the milder forms, blistering may not always result from mild friction and may only follow sharp knocks to the skin. Major challenges include the treatment of the neonate with severe generalized disease and the older child, adolescent or adult with the chronic disability that accompanies the severe form of recessive dystrophic EB.

Management of neonates and infants

Because severe blistering and erosions may be associated with junctional, dystrophic or simplex forms of EB in the neonate, an early objective is to establish the diagnosis from an appropriate skin biopsy (see above). This may be particularly relevant for a newborn with Dowling–Meara EB simplex, where the clinical appearance may be confused with Herlitz junctional EB or even dystrophic EB, suggesting a much graver prognosis. The early management of neonates with EB should, where possible, be undertaken in a specialist neonatal or paediatric unit, which has the expertise, staff and resources to manage these vulnerable

babies. A key to successful treatment is expert nursing care. Paediatric nurse specialists with experience of caring for babies and children with EB are often best placed to help with coordinating hospital treatment, training parents and non-specialist nurses at other centres to handle and treat the patients, and prepare for the child's return home. In these specialist centres [1], babies with EB are nursed on thick foam pads, which are covered by a silk sheet. This allows the babies to be held, fed and nursed without subjecting them to undue trauma. The erosions are cleaned with sterile normal saline and covered in comfortable non-adherent dressings. Some EB specialists may prefer to use a topical antiseptic such as stabilized hydrogen peroxide cream (Hioxyl, Quinoderm, UK) or 1% chlorhexidine cream, rather than topical antibiotics, chiefly because of the risk of emergence of antibiotic-resistant bacteria. Another preference is to treat open wounds with 1% silver sulfadiazine cream (Flamazine, Smith and Nephew, UK) or an ointment containing polymyxin B or bacitracin. The topical antibiotic mupirocin is not recommended for regular use, especially in hospital practice, because of the emergence of mupirocin-resistant *Staphylococcus aureus* [2,3]. However, its use for short periods (up to 7 days) in the home, for localized infected areas, is normally safe and effective [4]. Among the newer dressings now favoured for use in children and older patients are Mepitel and Mepilex (Molynycke, Luton, UK). Mepitel is a porous, mildly adherent silicone-based material, which can be left in place for up to 7 days. Any exudate is usually able to pass through the holes in this dressing to be absorbed by a secondary gauze dressing, which can be changed more frequently. Mepilex has a foam backing which provides more protection where needed.

Management of severe generalized recessive dystrophic epidermolysis bullosa

Patients with the more severe forms of recessive dystrophic EB will often survive into middle age and will therefore require continuing care throughout life [5]. Ideally, they should be seen at 6-monthly intervals in a multidisciplinary clinic with expertise to help with the particular needs of these patients. Special precautions should be taken in the use of adhesive tapes, sphygmomanometer cuffs, tourniquets and any other instruments or appliances that might lead to blister formation or shearing of the skin or mucous membranes. The following systems require particular attention.

Oral and dental care [6,7]

Microstomia, intraoral fibrosis and tethering of the tongue (ankyloglossia) make access and examination of the teeth and mucosa difficult. Treatment should start in early childhood, so the involvement of a paediatric dentist with specialist knowledge of the dental complications affecting children with EB is important. Wherever necessary, reconstructive measures should be applied to permanent and primary teeth, to maintain function. These include treatment of caries, and meticulous cleaning of tooth surfaces. Crown placement and even tooth implants (in adults) have been used successfully in some patients. More frequent preventive measures include daily fluoride supplements and the use of a mouthwash containing sodium fluoride and aqueous chlorhexidine.



Fig. 39.31 Barium swallow radiograph showing constriction in the upper oesophagus in recessive dystrophic epidermolysis bullosa. (Courtesy of Professor R.A.J. Eady, St John's Institute of Dermatology, London, U.K.)

Gastrointestinal tract and nutrition [8–12]

Dysphagia and pain on swallowing are common. Oesophageal strictures may be demonstrated by X-ray examination (including barium swallow and cine radiography) (Fig. 39.31) or by endoscopy. Oesophageal spasm, often accompanying an acute obstruction, can sometimes be relieved by administration of calcium-channel blocking agents. More permanent blockage requires an endoscopically guided balloon dilatation [8], which will usually have to be repeated, perhaps several times each year. More radical treatment has included surgical excision of the stricture followed by anastomosis, and colonic interposition [9]. Most patients have gastro-oesophageal reflux, which should be treated with a proton pump inhibitor to prevent further damage to the lining of the oesophagus with the risk of secondary scarring and oesophageal shortening. Constipation is inevitable and often chronic in these patients. The cause is complex and associated in some degree with inadequate fibre in the diet. A high-fibre diet is therefore important, and patients who have difficulty in eating sufficient fibre may benefit from nutritional supplements such as Enrich (Abbot Laboratories Ltd, Maidstone, Berks, UK). Osmotic and stimulant laxatives, as well as faecal softeners, may all have a role and be prescribed according to an individual patient's needs. Lactulose is often the first choice of laxative to be used in treating constipation in children and adults.

Anal blistering and erosions contribute to the constipation and faecal retention, especially in children. Glycerol suppositories used in conjunction with a topical anaesthetic preparation may help. If faecal impaction occurs, more drastic measures, including

manual removal of faeces under general anaesthesia, may be required.

Trying to ensure adequate nutrition with a balanced diet is especially important to maintain growth in children [10,11]. A deficiency of vitamins and trace elements (including zinc and iron) is frequent [12]. Comprehensive nutritional supplementation is only partly effective in maintaining adequate growth, and controlling anaemia and wound healing. The advice of an EB dietician is essential. Feeding through a gastrostomy allows appropriate nutrition in addition to the administration of supplements such as iron, zinc and multivitamins, which children may find difficult to take by mouth [13]. Gastrostomy feeding can be delivered overnight in the home [13]. Parenteral nutrition has also been used [10].

Eyes

External abrasions should be dealt with urgently; they usually require topical treatment with an antibiotic and anaesthetic. Scarring of the lids following blistering may result in inadequate lid closure and loss of normal protection to the eyes. Plastic surgical reconstruction may be indicated. Artificial tears are a useful lubricant.

Musculoskeletal system

Although early exercises and physiotherapy may be helpful, the progress of finger and hand contractures with eventual mitten-type deformity is virtually inevitable. Contractures and tight tethering by scar tissue may also affect elbows and knees. Surgical release of the contracted fingers is a highly specialized procedure and requires skin grafting and postoperative splinting [14–16]. The benefit from surgery is only temporary because most patients need further surgical treatment within a few years. The feet may be involved in a similar process, but a 'degloving' procedure is not recommended, because the foot deformities do not usually prevent the patients from standing or walking.

Anaemia

All patients with the more severe forms of recessive dystrophic EB are anaemic, and the picture is that of an anaemia of chronic disease. Despite the administration of oral iron supplements, the iron stores are usually low as assessed by serum ferritin levels. In patients with widespread lesions and secondary infection, the serum ferritin may not accurately reflect the need for supplementary iron. Instead, the serum iron level may be a better indicator of the requirement for iron replacement in these patients. Parenteral iron is painful if given intramuscularly, especially where the muscles are thin and wasted. Anaphylaxis is a potential risk of intravenous administration. Venofer (Synar-Med, UK), an iron hydroxide preparation, can be given intravenously, and has been used repeatedly in several dystrophic EB patients, with a good response and no serious side effects [17,18]. The haemoglobin levels generally increased, and the patients' sense of well-being improved. Transfusion of packed red cells may be required, especially when the blood haemoglobin level falls below approximately 7.00 g/dL, or when the patient becomes short of breath and more easily fatigued than usual.

Bony abnormalities

Virtually all patients have bony changes, mainly osteoporosis [19]. The cause is multifactorial, and is related to poor nutrition, relative immobility in some patients and previous treatment with systemic glucocorticoids. This last point is especially relevant in older patients. Regular checking of bone density, especially of the hips and spine, usually by dual-energy X-ray absorptiometry (DEXA), is now part of routine management. Treatment with calcium supplements and biphosphonates may be indicated.

Genitourinary tract abnormalities

Patients may infrequently develop a variety of genitourinary and renal complications. Urological intervention is recommended whenever function is compromised although occasionally this has resulted in worsened scar formation. Dialysis has been successfully performed in rare patients having endstage renal disease.

Systemic treatment

Long-term systemic corticosteroid treatment is not used now because of the high risk of complications, and phenytoin, which had appeared to control blistering in certain patients in an open study [20], did not prove to be more effective than placebo in a controlled trial [21]. Other systemic drugs that have been tried with mixed results in small numbers of patients include vitamin E [22,23], minocycline [24], ciclosporin [25,26] and retinoic acid [27]. Although, theoretically, the systemic use of a retinoid such as isotretinoin or acetretin might reduce the risk of squamous cell carcinomas in these patients, there is no evidence yet in support of this presumably lifelong treatment. In addition, in a recent phase 1 trial of low-dose isotretinoin in recessive dystrophic EB, some of the patients treated complained of increased mechanical fragility, blistering and/or itching as the dosage approached 0.5 mg/kg/day [28].

Skin grafting

Autologous split-thickness skin grafts have had short- to longer-term beneficial effects in the treatment of chronic ulcers or erosions in patients with generalized recessive dystrophic EB [29] or pretibial EB [30,31]. The treatment was found to be more effective when allogeneic keratinocytes were added to the split-skin grafts [31]. Cultured keratinocytes have also been used successfully in the treatment of junctional EB [32,33]. Repeated applications of autologous [32] or maternally derived [33] cells were used in the treatment of facial erosions in three children, and allogeneic keratinocytes were effective in promoting re-epithelialization of extensive erosions on the trunk and upper limbs of an infant [34]. Similar benefit was seen in a patient with recessive dystrophic EB [35]. The effects of applying allogeneic keratinoyctes to split-skin graft donor sites on the thigh were studied in 10 patients with severe recessive dystrophic EB [36]. There was no overall difference in the rate of wound healing, in comparison to similar non-treated sites. However, the treatment was effective in relieving pain in several patients.

Skin bioequivalents have also been used in the treatment of EB simplex, junctional EB [37,38] and dystrophic EB, with mixed results [37–39]. Concerns have been raised about the relative efficacy, especially in the long term, of treatment with bioequivalents,

including the commercially available Apligraf (Novartis), until more comprehensive data based on controlled trials become available [40]. Anecdotal evidence from the National EB Registry suggests that such treatments are often either ineffective or any benefits may be relatively short lived (J.-D. Fine, unpublished data).

Pain management

Patients with EB frequently experience severe pain, which is unresponsive to conventional treatment with non-opiate-based or non-steroidal anti-inflammatory agents. Unfortunately, systemic opiates are addictive and tend to exacerbate chronic constipation, making their chronic use highly undesirable. However, recent experience has found that the use of topical opiates, including diamorphine, may be effective in the treatment of pain in EB patients, reducing the need for powerful systemic analgesia (E. Pillay, F. Keane and R.A.J. Eady, unpublished data). Its use is particularly beneficial when chronic pain is associated with chronic ulcers and erosions, accompanied in some patients by squamous cell carcinoma. Amitriptyline is useful in pain management in both adults and children [41]. Amitriptyline and cognitive–behavioural techniques were effective in relieving chronic pain and discomfort in an 11-year-old child with junctional EB [41]. Oral midazolam 0.33 mg/kg administered 20 min prior to baths and dressing changes substantially improved the patient's tolerance of wound care [42].

Cancer and recessive dystrophic epidermolysis bullosa [43]

Squamous cell carcinomas are expected to occur in nearly every patient with Hallopeau–Siemens disease, as well as in a minority of patients with non-Hallopeau–Siemens and inverse forms of recessive dystrophic EB (Figs 39.32 & 39.33). Meticulous surveillance, preferably with the aid of serial photography, should be performed regularly (at least every 6 months), from the age of 10 years, and any suspicious lesion should be immediately biopsied. Those lesions that fail to reveal cancer histologically, and yet remain atypical in appearance or healing pattern, such as a non-healing erosion, should be re-biopsied, because it is possible to miss an early squamous cell carcinoma, given the tendency of these tumours to be well differentiated histologically and to show only focal areas of neoplastic change. Wide surgical excision is recommended, and careful serial follow-up examinations should be implemented, seeking possible local or regional recurrences. Amputation of an affected limb may eventually be required in some cases. Although still unproven, there may be a role for sentinel node biopsy in the management of these patients. There is also no evidence yet in support of using the Mohs' surgical technique instead of conventional wide surgical excision. Regional metastases, for example those arising within the axillary vault, may benefit from at least partial surgical debulking, even if extensive, to reduce the size of non-healing, painful, malodorous or chronically infected lesions. Neither chemotherapy nor radiotherapy has been shown to provide lasting benefit in the treatment of primary or secondary tumours. However, radiotherapy, like surgery, may be used for reducing the tumour mass. In most patients it does not appear to make blistering worse (J.-D. Fine, unpublished data, 2007).

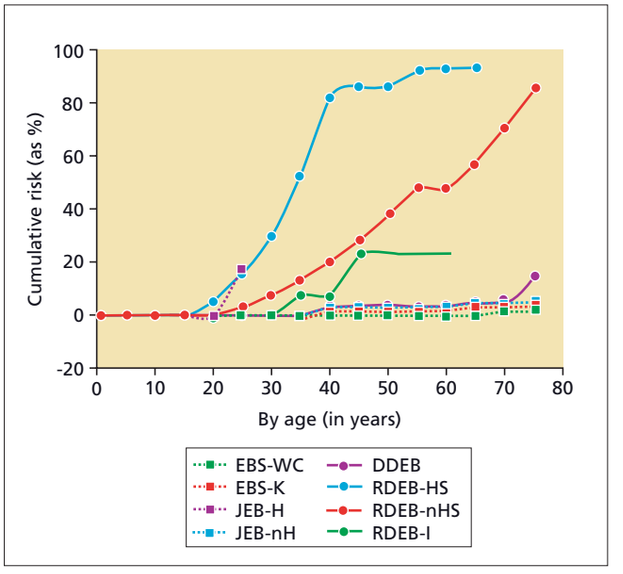


Fig. 39.32 Cumulative risk of death from squamous cell carcinoma in different forms of epidermolysis bullosa, per data from the National EB Registry, 1986–2002. EBS-WC, epidermolysis bullosa simplex (Weber–Cockayne); EBS-K, EB simplex (Koebner); JEB-H, junctional EB (Herlitz); n-H, non-Herlitz; DDEB, dominant dystrophic EB; RDEB-HS, recessive dystrophic EB (Hallopeau–Siemens); n-HS, non-Hallopeau–Siemens; RDEB-I, inversa. (J.-D. Fine, [43].)

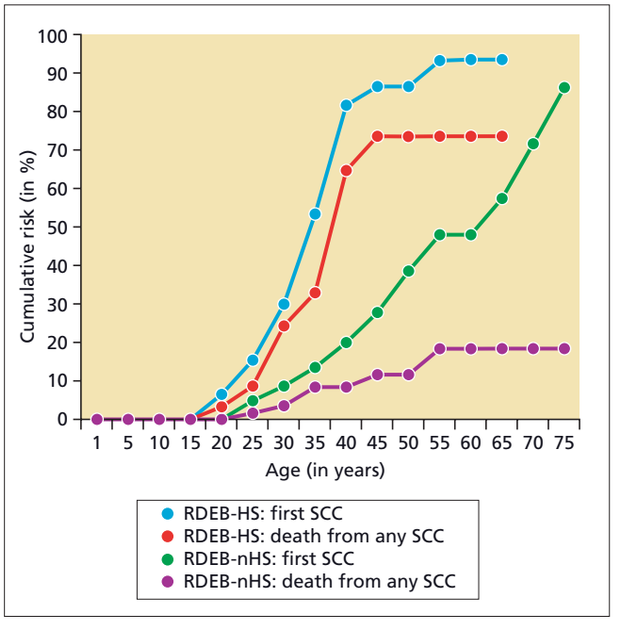


Fig. 39.33 Cumulative risk of developing first squamous cell carcinoma (SCC), and death from SCC in recessive dystrophic epidermolysis bullosa, per data from the National EB Registry, 1986–2002. (J.-D. Fine, [43].)

Treatment of epidermolysis bullosa simplex

Heat and humidity lower the threshold for blistering in patients with EB simplex, and measures to reduce both these factors are therefore important. Patients with Weber–Cockayne or Dowling–Meara EB simplex should wear well-fitting well-ventilated shoes,

preferably with a soft inner lining. Cotton socks are preferable to wool or synthetic fibres, and double-layer sports socks provide extra protection from friction and absorb sweat well. The application of aqueous solutions containing alcohol or glutaraldehyde [44] has been found useful, but is not necessarily recommended as glutaraldehyde is potentially irritant and toxic. Iontophoresis and the application of aluminium chloride hexahydrate [45] have also been used in attempts to suppress sweating. However, in a controlled trial of 20% aluminium chloride hexahydrate for the treatment of Weber–Cockayne EB simplex, there was no difference between the active drug and placebo in suppressing blistering [46]. In two small case series or clinical trials, oral tetracycline was noted to be effective in reducing the rate of blistering in some patients with EB simplex [47,48].

Newer forms of treatment, including gene therapy

Newer specific methods of treating EB have been slow to emerge. However, it is likely that genetically engineered growth factors and other cytokines that are able to influence wound healing will soon be available for clinical trials, or even clinical practice [49]. Such advances could clearly have an important impact on the management of chronic erosions in junctional and dystrophic EB, although their potential role in the treatment of lesions in internal organs, such as the oesophagus, may be less clear. There is a pressing need for an effective means to halt and possibly reverse the relentless progression of digital fusion and hand contractures seen in recessive dystrophic EB. Another critical need is the development of the means whereby squamous cell carcinomas can be prevented from occurring in these patients, as well as more effective means of treatment if they should arise.

Although as yet unavailable for use in routine clinical practice, gene therapy [50–55] is nevertheless a realistic goal for the future treatment of more severe autosomal recessive forms of EB. There are numerous obstacles, but each is potentially surmountable, given time and sufficient resources. Different methods of introducing DNA into skin or skin cells *ex vivo* are currently being explored. The objective is to introduce one normal allele into somatic cells that, in recessive forms of EB, would have two mutant genes. The strategy includes finding effective and safe methods for targeting 'normal' genes into the right place (e.g. the nucleus of an epidermal stem cell) and keeping the gene activated under controlled conditions. The introduced gene must be able to undergo transcription and translation in the synthesis of an appropriate product, such as a basement-membrane protein, which then has to be secreted by the cells and incorporated into the extracellular matrix in a way that will allow it to be functionally effective. The gene product may be at risk of being rapidly degraded, neutralized (by autoantibodies), shed (inside a differentiating keratinocyte) or being otherwise inactivated. As part of a proof-of-principle trial, a few patients with non-Herlitz junctional EB have now undergone grafting with small skin bioequivalents containing the corrected laminin-5 gene, following removal of the genetically abnormal epidermis. These grafts have remained blister-free for over a year, suggesting that this technique might indeed have eventual clinical applicability in autosomal recessive forms of EB. Further clinical trials are currently underway.

For autosomal dominant disorders, including dominant dystrophic EB or EB simplex, the strategy will be different. Under these conditions, rather than introducing a further normal gene, the objective will be to try to inactivate or nullify the action of the mutant gene, which usually exerts a 'dominant-negative' effect on its normal paired allele. One approach involves antisense DNA and RNA strategies [55], which currently are being explored particularly for use in the treatment of cancer. Another possible approach being investigated is to up-regulate another structural protein within keratinocytes (for example, another minor keratin in patients with EB simplex) so as to override the structural instability caused by the presence of keratin 5 or 14 mutations.

A direct result of the recent advances in the molecular genetics of different forms of EB has been the development of DNA-based first-trimester prenatal diagnosis. This has already been used for the benefit of many couples at high risk of having affected children (see Chapter 16). The introduction of preimplantation genetic diagnosis will broaden the available options in the overall management of those affected by EB.

References

1 Atherton DJ. *Epidermolysis Bullosa*. In: Harper J, ed. *Inherited Skin Disorders: the Genodermatoses*. Oxford: Butterworth–Heinemann, 1996: 53–68.

2 Rahman M, Noble WC, Cookson B. Mupirocin-resistant *Staphylococcus aureus* (Letter). *Lancet* 1987; **2**: 387.

3 Moy JA, Caldwell-Brown D, Lin AN, Carter DM. Emergence of mupirocin-resistant *Staphylococcus aureus* in chronic wounds of patients with epidermolysis bullosa. *J Am Acad Dermatol* 1990; **22**: 893–5.

4 Lin AN, Caldwell D, Varghese M *et al.* Efficacy of long-term mupirocin therapy in epidermolysis bullosa and its effect on growth and lifespan of cultured fibroblasts. *J Invest Dermatol* 1986; **87**: 152.

5 Dunnill MGS, Eady RAJ. The management of dystrophic epidermolysis bullosa. *Clin Exp Dermatol* 1995; **20**: 179–88.

6 Wright JT. Comprehensive dental care and general anesthetic management of hereditary epidermolysis bullosa: a review of 14 cases. *Oral Surg Oral Med Oral Pathol* 1990; **70**: 573–8.

7 Wright JT, Fine J-D, Johnson L. Hereditary epidermolysis bullosa: oral manifestations and dental management. *Pediatr Dent* 1993; **15**: 242–7.

8 Kern IB, Eisenberg M, Willis S. Management of oesophageal stenosis in epidermolysis bullosa dystrophica. *Arch Dis Child* 1989; **64**: 551–6.

9 Absolon KB, Finney LA, Waddill GM, Hatchett C. Esophageal reconstruction—colon transplant—in two brothers with epidermolysis bullosa. *Surgery* 1969; **65**: 832–6.

10 Tesi D, Lin AN. Nutritional management of the epidermolysis bullosa patient. In: Lin AN, Carter DM, eds. *Epidermolysis Bullosa: Basic and Clinical Aspects*. New York: Springer, 1992: 261–6.

11 Haynes L. Epidermolysis bullosa. In: Shaw V, Lawsib M, eds. *Clinical Paediatric Dietetics*. Oxford: Blackwell Scientific Publications, 1994: 295–302.

12 Fine J-D, Tamura T, Johnson L. Blood vitamin and trace metal levels in epidermolysis bullosa. *Arch Dermatol* 1989; **125**: 374–9.

13 Haynes L, Atherton DJ, Ade-Ajayi N *et al.* Gastrostomy and growth in dystrophic epidermolysis bullosa. *Br J Dermatol* 1996; **134**: 872–9.

14 Greidler JL, Flatt AE. Surgical restoration of the hand in epidermolysis bullosa. *Arch Dermatol* 1988; **124**: 765–7.

15 Terrill PJ, Mayou BJ, Pemberton J. Experience in the surgical management of the hand in dystrophic epidermolysis bullosa. *Br J Plast Surg* 1992; **45**: 435–42.

16 Ladd AL, Kibele A, Gibbons LVN. Surgical treatment and postoperative splinting of recessive dystrophic epidermolysis bullosa. *J Hand Surg* 1996; **21A**: 888–97.

17 Atherton DJ, Cox I, Hann L. Intravenous iron (III) hydroxide–sucrose complex for anaemia in epidermolysis bullosa. *Br J Dermatol* 1999; **140**: 773.

18 Keane FM, Mellerio JE, Ellison J *et al.* Treatment of anaemia in dystrophic epidermolysis bullosa with intravenous iron (III) hydroxide–sucrose complex. *Br J Dermatol* 2000; **143** (Suppl. 57): 51–2.
19 Keane FM, Fine J-D, Pillay E *et al.* Osteopenia and osteoporosis in recessive dystrophic epidermolysis bullosa. *Br J Dermatol* 2001; **145** (Suppl. 145): 14.
20 Cooper TW, Bauer EA. Therapeutic efficacy of phenytoin in recessive dystrophic epidermolysis. *Arch Dermatol* 1984; **120**: 490–5.
21 Caldwell-Brown D, Stern RS, Lin AN, Carter DM. Lack of efficacy of phenytoin in recessive dystrophic epidermolysis bullosa. *N Engl J Med* 1992; **327**: 163–7.
22 Michaelson JD, Schmidt JD, Dresden MH, Duncan C. Vitamin E treatment of epidermolysis bullosa. *Arch Dermatol* 1974; **109**: 67–9.
23 Adams RH, Main RA, Marsden RA. A controlled study of vitamin E treatment in epidermolysis bullosa. *Br J Dermatol* 1975; **93** (Suppl. 11): 10.
24 White JE. Minocycline for dystrophic epidermolysis bullosa. *Lancet* 1989; **i**: 166.
25 Husz S, Olah J, Korom I *et al.* Cyclosporin for dystrophic epidermolysis bullosa. *Lancet* 1989; **ii**: 1393–4.
26 del-Rio E. Prevention of blisters in dystrophic epidermolysis bullosa with cyclosporine. *J Am Acad Dermatol* 1993; **29**: 1038–9.
27 Cooper TW, Tabas M, Bauer EA. Retinoic acid in recessive dystrophic epidermolysis bullosa. In: Saurat JH, ed. *Retinoids: New Trends in Research and Therapy*. New York: Karger, 1985: 219–24.
28 Fine J-D, Weiner M, Stein A, Suchindran C, Johnson LB. Chemoprevention of squamous cell carcinoma in recessive dystrophic epidermolysis bullosa: results of a Phase 1 trial of systemic isotretinoin. *J Am Acad Dermatol* 2004; **50**: 563–71.
29 Terrill PJ, Mayou BJ, McKee P, Eady RAJ. The surgical treatment of epidermolysis bullosa. *Br J Plast Surg* 1992; **45**: 426–34.
30 Furue M, Ando I, Inoue Y *et al.* Pretibial epidermolysis bullosa: successful therapy with a skin graft. *Arch Dermatol* 1986; **122**: 310–3.
31 Beele H, Naeyaert J-M, Monstrey S, Kint A. Ulcers in pretibial epidermolysis bullosa. *Arch Dermatol* 1995; **131**: 990–2.
32 Carter DM, Lin AN, Varghese MC *et al.* Treatment of junctional epidermolysis bullosa with epidermal autografts. *J Am Acad Dermatol* 1987; **17**: 246–50.
33 Hill JC, Grimwood RE, Parsons DS. Treatment of chronic erosions of junctional epidermolysis bullosa with human epidermal allografts. *J Dermatol Surg Oncol* 1992; **18**: 396–400.
34 Roseeuw D, DeRaeve L, Dangoisse C, Ramet J. Treatment of epidermolysis bullosa with human cultured epidermal allografts. *Dermatology* 1994; **189** (Suppl. 2): 68–70.
35 McGuire J, Birchnall N, Cuono C *et al.* Successful engraftment of allogeneic keratinocyte cultures in recessive dystrophic epidermolysis bullosa. *J Invest Dermatol* 1987; **88**: 506.
36 McGrath JA, Schofield OMV, Ishida-Yamamoto A *et al.* Cultured keratinocyte allografts and wound healing in severe recessive dystrophic epidermolysis bullosa. *J Am Acad Dermatol* 1993; **29**: 407–19.
37 Falabella AF, Schachner LA, Valencia IC, Eaglstein WH. The use of tissue-engineered skin (Apligraf) to treat a newborn with epidermolysis bullosa. *Arch Dermatol* 1999; **135**: 1219–22.
38 Falabella AF, Valencia IC, Eaglstein WH, Schachner LA. Tissue-engineered skin (Apligraf) in the healing of patients with epidermolysis bullosa wounds. *Arch Dermatol* 2000; **136**: 1225–30.
39 Jiang QJ, Izakovic J, Zenker M *et al.* Treatment of two patients with Herlitz junctional epidermolysis bullosa with artificial skin bioequivalents. *J Pediatr* 2002; **141**: 553–9.
40 Fine J-D. Skin bioequivalents and their role in the treatment of inherited epidermolysis bullosa. *Arch Dermatol* 2000; **136**: 1259–60.
41 Herod J, Denyer J, Goldman A, Howard R. Epidermolysis bullosa in children: pathophysiology, anaesthesia and pain management. *Paediatr Anaesth* 2002; **12**: 388–97.
42 Chiu YK, Prendiville JS, Bennett SM, Montgomery CJ, Oberlander TF. Pain management of junctional epidermolysis bullosa in an 11-year-old boy. *Pediatr Dermatol* 1999; **16**: 465–8.
43 Fine J-D, Johnson LB, Weiner M, Li K-P, Suchindran C. Inherited epidermolysis bullosa (EB) and the risk of life-threatening skin-derived cancers: experience of the National EB Registry, 1986–2006. *J Am Acad Dermatol* 2009; **60**: 203–11.
44 DeGrosseilliers J-P, Brisson P. Localized epidermolysis bullosa: report of two cases and evaluation of therapy with glutaraldehyde. *Arch Dermatol* 1974; **109**: 70–2.
45 Tkach JR. Treatment of recurrent bullous eruption of the hands and feet (Weber–Cockayne disease) with topical aluminium chloride. *J Am Acad Dermatol* 1982; **6**: 1095–6.
46 Younger IR, Priestley GC, Tidman MJ. Aluminium chloride hexahydrate and blistering in epidermolysis bullosa simplex. *J Am Acad Dermatol* 1990; **23**: 930–1.
47 Retief CR, Malkinson FD, Pearson RW. Two familial cases of epidermolysis bullosa simplex successfully treated with tetracycline. *Arch Dermatol* 1999; **135**: 997–8.
48 Weiner M, Stein A, Cash S, DeLeoz J, Fine J-D. Tetracycline and epidermolysis bullosa simplex: a double-blind, placebo-controlled, crossover randomized clinical trial. *Br J Dermatol* 2004; **150**: 613–4.
49 Fine J-D. Epidermolysis bullosa: a genetic disease of altered cell adhesion and wound healing, and the possible clinical utility of topically applied thymosin b4. *Ann NY Acad Sci* 2007; **1112**: 396–406.
50 Vogel JC. Keratinocyte gene therapy. *Arch Dermatol* 1993; **129**: 1478–83.
51 Spirito F, Meneguzzi G, Danos O, Mezzina M. Cutaneous gene transfer and therapy: the present and the future. *J Gene Med* 2001; **3**: 21–31.
52 Chen M, Kasahara N, Keene DR *et al.* Restoration of type VII collagen expression and function in dystrophic epidermolysis bullosa. *Nat Genet* 2002; **32**: 670–5.
53 Ortiz-Urda S, Lin Q, Green CL *et al.* Injection of genetically engineered fibroblasts corrects regenerated human epidermolysis bullosa skin tissue. *J Clin Invest* 2003; **111**: 251–5.
54 Ortiz-Urda S, Thyagarajan B, Keene DR *et al.* Stable non-viral genetic correction of inherited human skin disease. *Nat Med* 2002; **8**: 1166–70.
55 Dellambra E, Pellegrini G, Guerra L *et al.* Toward epidermal stem cell-mediated *ex vivo* gene therapy of junctional epidermolysis bullosa. *Hum Gene Ther* 2000; **11**: 2283–7.
56 Gibson I. Antisense DNA and RNA strategies: new approaches to therapy. *J R Coll Phys (Lond)* 1994; **28**: 507–11.

Hailey–Hailey disease

S.M. Burge, pp. 39.32–39.37

Synonym
- Familial benign chronic pemphigus

Hailey–Hailey disease (Mendelian Inheritance in Man (MIM) accession number 169600) is a rare intraepidermal, blistering disease that is inherited as an autosomal dominant with a prevalence of around 1 in 50 000. The condition, which was described by the Hailey brothers in 1939, is characterized by recurrent vesicles and erosions, usually affecting the neck, axillae and groins [1–3].

Aetiology. Hailey–Hailey disease is caused by mutations in one copy of *ATP2C1*, a gene on chromosome 3q21 that encodes the human secretory-pathway Ca^{2+}/Mn^{2+}-ATPase isoform 1 (hSPCA1) on the Golgi membrane. The wide variety of mutations do not cluster to 'hotspots' in the gene or correlate with phenotype [4–7]. Protein expression is reduced and SPCA1 haploinsufficiency is the mechanism for the dominant pattern of inheritance [8–10]. Darier's disease (MIM 124200), a condition that shares many clinical and pathological features with Hailey–Hailey disease, is caused by mutations in the *ATP2A2* gene encoding a calcium ATPase located in the sarco/endoplasmic reticulum (SERCA2) (see Chapter 19).

Pathogenesis. Intracellular Ca^{2+} stores play a pivotal role in maintaining epidermal integrity, but it is not yet entirely clear how loss of one functional allele of *ATP2C1* leads to the changes in adhesion that typify Hailey–Hailey disease [11–14].

ATP2C1 is expressed by keratinocytes, but immunohistochemical data are conflicting. Some authors suggest the gene is most highly expressed in the undifferentiated basal cell layer of normal epidermis [15] while others have found labelling of both basal and suprabasal cells [14]. The gene product, SPCA1, regulates the concentration of both Ca^{2+} and Mn^{2+} in the Golgi complex. Mutations in *ATP2C1* may preferentially affect the skin because keratinocytes are unable to compensate for partial loss of SPCA1 [16].

Reduced Ca^{2+} or Mn^{2+} stores in the Golgi, increased cytosolic Ca^{2+} concentrations, abnormal Ca^{2+} oscillations (cycles of release and uptake) and/or decreased cellular ATP stores in Hailey–Hailey disease may affect a wide range of cellular processes including gene transcription, keratinocyte signalling, post-translational modifications or trafficking of adhesion proteins, the assembly of adhesion junctions and keratinocyte differentiation [14,15,17–21]. Normally, extracellular Ca^{2+} concentrations increase fourfold between the basal and superficial epidermal layers, but this calcium gradient is attenuated in Hailey–Hailey disease with a marked reduction in the total [Ca^{2+}] in the granular layer [18]. The attenuated gradient may alter keratinocyte differentiation, proliferation, adhesion and/or motility [20,21].

Cultured Hailey–Hailey disease keratinocytes demonstrate abnormal adhesion [22–24], impaired calcium metabolism [5,25], reduced expression of involucrin (a marker of differentiation) [19] and impairment of Ca^{2+}-induced actin reorganization [17]. *In vitro* acantholysis is reduced by corticosteroids, serine protease inhibitors and vitamin D_3 analogues, but not by retinoids [24,26].

Ultraviolet irradiation (UVB) aggravates Hailey–Hailey disease and has been used to detect carriers of the disease gene [27]. UVB reduces the expression of *ATP2C1* mRNA in cultured normal keratinocytes [28], but the reduction is inhibited by corticosteroids, retinoids, ciclosporin and vitamin D_3 [29]. Although UVB impairs the adhesion of cultured keratinocytes from patients with Hailey–Hailey disease, this impairment is no greater than in normal keratinocytes suggesting that other factors may be necessary for UVB to provoke acantholysis *in vivo* [30].

A number of pro-inflammatory cytokines down-regulate the expression of *ATP2C1* [28,29] and this may explain why insults such as friction, freezing or suction induce acantholysis in the normal looking skin of affected patients and how cutaneous infections exacerbate disease [3,31]. In rats, oral lithium suppresses the expression of both SERCA2 (the cause of Darier's disease) and PMR1 (the homologue of SPCA1) [32], but exacerbations of Hailey–Hailey disease have not been reported in patients taking lithium, although lithium does exacerbate Darier's disease (see Chapter 19).

Histopathology. Acantholytic clefts and bullae form above the basal cells. The suprabasal cells separate partially from one another, so clusters of loosely coherent cells float in the bullae. Widespread partial acantholysis gives the epidermis the appearance of a 'dilapidated brick wall' (Fig. 39.34). In contrast to autoimmune pemphigus, intracellular IgG and complement are not detected in the epidermis.

The primary event appears to be dissolution of the desmosomal attachment plaque [33]. Keratin filaments separate from desmosomal plaques and aggregate in perinuclear whorls [34–36].

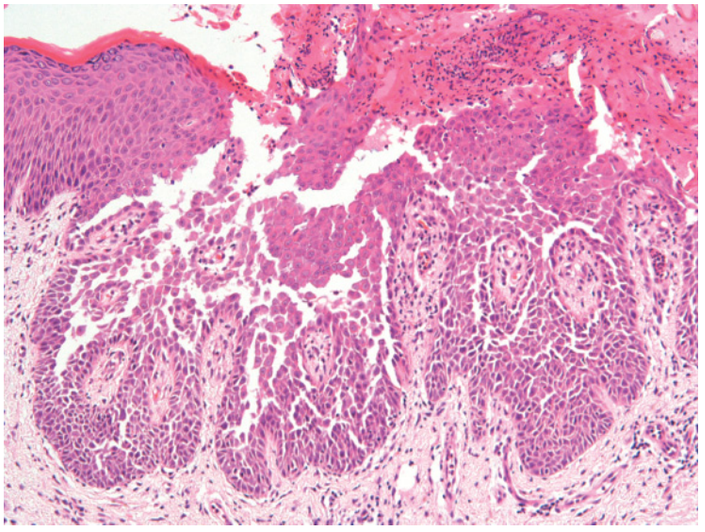


Fig. 39.34 Skin showing prominent spinous layer acantholysis giving the so-called 'dilapidated brick wall' appearance. There is overlying scale crust, but little dyskeratosis. (Courtesy of Professor R.A.J. Eady, St John's Institute of Dermatology, London, U.K.)

The components of desmosomes, adherens junctions, gap junctions and the cytoskeleton are distributed normally in uninvolved skin. Desmosomal components, E-cadherin and connexins are internalized in acantholytic cells [37–40] and extracellular epitopes of cadherins are lost [41]. The expression of P-cadherin is up-regulated in a number of acantholytic conditions including Hailey–Hailey disease [42].

References

1 Hailey H, Hailey H. Familial benign chronic pemphigus. *Arch Dermatol Syphilol* 1939; **39**: 679–85.

2 Richard G, Linse R, Hadlich J *et al*. Zur genetik des pemphigus benignus chronicus familiaris Hailey–Hailey. *Dermatol Monatsschr* 1990; **176**: 673–81.

3 Burge SM. Hailey–Hailey disease: the clinical features, response to treatment and prognosis. *Br J Dermatol* 1992; **126**: 275–82.

4 Sudbrak R, Brown J, Dobson-Stone C *et al*. Hailey–Hailey disease is caused by mutations in ATP2C1 encoding a novel Ca^{2+} pump. *Hum Mol Genet* 2000; **9**: 1131–40.

5 Hu Z, Bonifas JM, Beech J *et al*. Mutations in ATP2C1, encoding a calcium pump, cause Hailey–Hailey disease. *Nat Genet* 2000; **24**: 61–5.

6 Ikeda S, Shigihara T, Mayuzumi N *et al*. Mutations of ATP2C1 in Japanese patients with Hailey–Hailey disease: intrafamilial and interfamilial phenotypic variations and lack of correlation with mutation patterns. *J Invest Dermatol* 2001; **117**: 1654–6.

7 Dobson-Stone C, Fairclough R, Dunne E *et al*. Hailey–Hailey disease: molecular and clinical characterization of novel mutations in the ATP2C1 gene. *J Invest Dermatol* 2002; **118**: 338–43.

8 Fairclough RJ, Dode L, Vanoevelen J *et al*. Effect of Hailey–Hailey Disease mutations on the function of a new variant of human secretory pathway Ca^{2+}/Mn^{2+}-ATPase (hSPCA1). *J Biol Chem* 2003; **278**: 24721–30.

9 Fairclough RJ, Lonie L, Van Baelen K *et al*. Hailey–Hailey disease: identification of novel mutations in ATP2C1 and effect of missense mutation A528P on protein expression levels. *J Invest Dermatol* 2004; **123**: 67–71.

10 Kawada H, Nishiyama C, Takagi A *et al*. Transcriptional regulation of ATP2C1 gene by Sp1 and YY1 and reduced function of its promoter in Hailey–Hailey disease keratinocytes. *J Invest Dermatol* 2005; **124**: 1206–14.

11 Dhitavat J, Fairclough RJ, Hovnanian A *et al*. Calcium pumps and keratinocytes: lessons from Darier's disease and Hailey–Hailey disease. *Br J Dermatol* 2004; **150**: 821–8.

12 Foggia L, Hovnanian A. Calcium pump disorders of the skin. *Am J Med Genet C Semin Med Genet* 2004; **131C**: 20–31.
13 Szigeti R, Kellermayer R. Autosomal-dominant calcium ATPase disorders. *J Invest Dermatol* 2006; **126**: 2370–6.
14 Missiaen L, Dode L, Vanoevelen J *et al.* Calcium in the Golgi apparatus. *Cell Calcium* 2007; **41**: 405–16.
15 Yoshida M, Yamasaki K, Daiho T *et al.* ATP2C1 is specifically localized in the basal layer of normal epidermis and its depletion triggers keratinocyte differentiation. *J Dermatol Sci* 2006; **43**: 21–33.
16 Callewaert G, Parys JB, De Smedt H *et al.* Similar $Ca^{(2+)}$-signaling properties in keratinocytes and in COS-1 cells overexpressing the secretory-pathway $Ca^{(2+)}$-ATPase SPCA1. *Cell Calcium* 2003; **34**: 157–62.
17 Aronchik I, Behne MJ, Leypoldt L *et al.* Actin reorganization is abnormal and cellular ATP is decreased in Hailey–Hailey keratinocytes. *J Invest Dermatol* 2003; **121**: 681–7.
18 Behne MJ, Tu CL, Aronchik I *et al.* Human keratinocyte ATP2C1 localizes to the Golgi and controls Golgi Ca^{2+} stores. *J Invest Dermatol* 2003; **121**: 688–94.
19 Aberg KM, Racz E, Behne MJ *et al.* Involucrin expression is decreased in Hailey–Hailey keratinocytes owing to increased involucrin mRNA degradation. *J Invest Dermatol* 2007; **127**: 1973–9.
20 Tu CL, Chang W, Bikle DD. The role of the calcium sensing receptor in regulating intracellular calcium handling in human epidermal keratinocytes. *J Invest Dermatol* 2007; **127**: 1074–83.
21 Mauro TM. CaR talk: the calcium receptor finds new places to park. *J Invest Dermatol* 2007; **127**: 991–2.
22 De Dobbeleer G, De Graef C, Mpoudi E *et al.* Reproduction of the characteristic morphologic changes of familial benign chronic pemphigus in cultures of lesional keratinocytes onto dead deepidermized dermis. *J Am Acad Dermatol* 1989; **21**: 961–5.
23 Regnier M, Ortonne J-P, Darmon M. Histological defects of chronic benign familial pemphigus expressed in tissue culture. *Arch Dermatol Res* 1990; **281**: 538–40.
24 Ikeda S, Ogawa H. Effects of steroid, retinoid and protease inhibitors on the formation of acantholysis induced in organ culture of skins from patients with benign familial chronic pemphigus. *J Invest Dermatol* 1991; **97**: 644–8.
25 Leinonen PT, Myllyla RM, Hagg PM *et al.* Keratinocytes cultured from patients with Hailey–Hailey disease and Darier disease display distinct patterns of calcium regulation. *Br J Dermatol* 2005; **153**: 113–7.
26 Aoki T, Hashimoto H, Koseki S *et al.* 1alpha,24-dihydroxyvitamin D3 (tacalcitol) is effective against Hailey–Hailey disease both in vivo and in vitro. *Br J Dermatol* 1998; **139**: 897–901.
27 Richard G, Linse R, Harth W. Morbus Hailey–Hailey. Fruherfassung von merkmal stragern durch einen UV-provokationstest-klinische relevanz der methode UV. *Hautarzt* 1993; **44**: 376–9.
28 Mayuzumi N, Ikeda S, Kawada H *et al.* Effects of ultraviolet B irradiation, pro-inflammatory cytokines and raised extracellular calcium concentration on the expression of ATP2A2 and ATP2C1. *Br J Dermatol* 2005; **152**: 697–701.
29 Mayuzumi N, Ikeda S, Kawada H *et al.* Effects of drugs and anticytokine antibodies on expression of ATP2A2 and ATP2C1 in cultured normal human keratinocytes. *Br J Dermatol* 2005; **152**: 920–4.
30 Bernards M, Korge BP. Desmosome assembly and keratin network formation after Ca2+/serum induction and UVB radiation in Hailey–Hailey keratinocytes. *J Invest Dermatol* 2000; **114**: 1058–61.
31 Galimberti RL, Kowalczuk AM, Bianchi O *et al.* Chronic benign familial pemphigus. *Int J Dermatol* 1988; **27**: 495–500.
32 Sule N, Teszas A, Kalman E *et al.* Lithium suppresses epidermal SERCA2 and PMR1 levels in the rat. *Pathol Oncol Res* 2006; **12**: 234–6.
33 Hashimoto K, Fujiwara K, Harada M *et al.* Junctional proteins of keratinocytes in Grover's disease, Hailey–Hailey's disease and Darier's disease. *J Dermatol* 1995; **22**: 159–70.
34 Wilgram G, Caulfield J, Lever W. An electronmicroscopic study of acantholysis and dyskeratosis in Hailey and Hailey's disease. *J Invest Dermatol* 1962; **39**: 373–81.
35 Nurnberger F, Muller G. Elektronmikroskopische untersuchungen uber die akantholyse bei pemphigus familiaris benignus. *Arch Klin Exp Dermatol* 1967; **228**: 208–19.
36 Gottlieb S, Lutzner M. Hailey–Hailey disease: an electron microscopic study. *J Invest Dermatol* 1970; **54**: 368–76.
37 Burge SM, Garrod DR. An immunohistological study of desmosomes in Darier's disease and Hailey–Hailey disease. *Br J Dermatol* 1991; **124**: 242–51.
38 Burge SM, Cederholm-Williams SA, Garrod DR *et al.* Cell adhesion in Hailey–Hailey disease and Darier's disease: immunocytological and explant-tissue-culture studies. *Br J Dermatol* 1991; **125**: 426–35.
39 Bergman R, Levy R, Pam Z *et al.* A study of keratin expression in benign familial chronic pemphigus. *Am J Dermatopathol* 1992; **14**: 32–6.
40 Haftek M, Kowalewski C, Mesnil M *et al.* Internalization of gap junctions in benign familial pemphigus (Hailey–Hailey disease) and keratosis follicularis (Darier's disease). *Br J Dermatol* 1999; **141**: 224–30.
41 Hakuno M, Shimizu H, Akiyama M *et al.* Dissociation of intra- and extracellular domains of desmosomal cadherins and E-cadherin in Hailey–Hailey disease and Darier's disease. *Br J Dermatol* 2000; **142**: 702–11.
42 Hakuno M, Akiyama M, Shimizu H *et al.* Upregulation of P-cadherin expression in the lesional skin of pemphigus, Hailey–Hailey disease and Darier's disease. *J Cutan Pathol* 2001; **28**: 277–81.

Clinical features. The condition usually presents in the third or fourth decade [1]. Flaccid vesicopustules, crusted erosions or expanding circinate plaques appear in areas exposed to friction such as the sides of the neck, axillae, groins and perineum. Involvement may be restricted to one site but can be generalized [2]. Lesions extend peripherally, healing in the centre (Fig. 39.35). Flexural disease may be hypertrophic and malodorous with soft, flat, moist vegetations and fissures (rhagades) (Fig. 39.36).

Itch and pain are common and flexural disease may be disabling, particularly if the groins are affected. Even mild disease may reduce quality of life [3,4]. Asymptomatic, longitudinal, white bands are present in the nails of some patients [1] (Fig. 39.37). Mucosal involvement is uncommon, but conjunctival, oral, oesophageal and vaginal involvement have been described [1,5].

Hailey–Hailey disease may koebnerize into inflammatory conditions such as psoriasis or seborrhoeic dermatitis [6,7] and is exacerbated by cutaneous insults causing inflammation such as contact dermatitis, UVB irradiation, sweating, friction, cutaneous infections or scabies [1,8–10].

Complications. The possibility of allergic contact dermatitis should be considered in patients with Hailey–Hailey disease but, although allergies have been described, the frequency of positive



Fig. 39.35 Hailey–Hailey disease. Spreading annular plaque with a crusted rim. (Courtesy of Professor R.A.J. Eady, St John's Institute of Dermatology, London, U.K.)

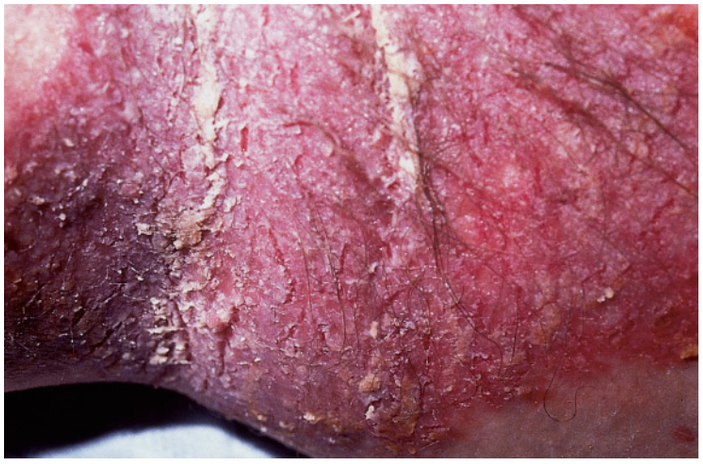


Fig. 39.36 Hailey–Hailey disease. Typical hypertrophic, malodorous axillary plaque with painful fissures (rhagades). (Courtesy of Professor R.A.J. Eady, St John's Institute of Dermatology, London, U.K.)

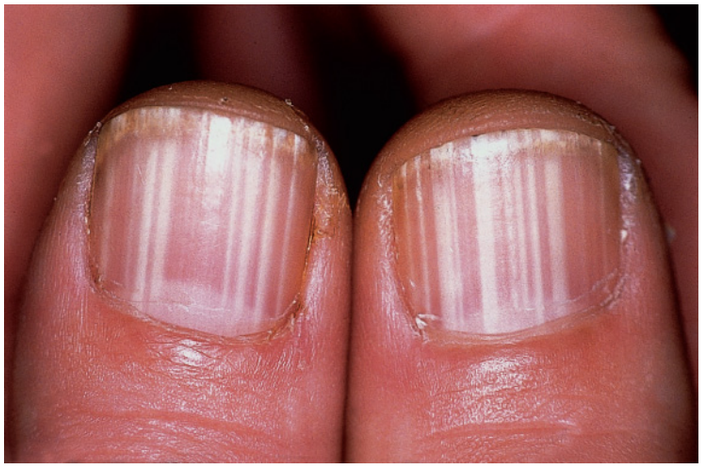


Fig. 39.37 Hailey–Hailey disease. Longitudinal white bands in the nails may be a helpful diagnostic sign. (Courtesy of Professor R.A.J. Eady, St John's Institute of Dermatology, London, U.K.)

patch tests is probably not increased [11,12]. Hailey–Hailey disease may be diagnosed serendipitously in the patch test clinic, when removal of adhesive tapes used for holding the patches in place causes extensive, painful erosions [8,13].

Human papillomas virus has been found in perineal verrucoid lesions [14,15]. Rarely, carcinomas have been reported in skin affected by Hailey–Hailey disease, sometimes linked to infection with human papillomas virus [16–19]. The incidence of squamous cell cancer (SCC) of skin and oesophagus is increased in aged mice that are heterozygous for the mutation in SPCA1 [20]. Large studies are needed to determine if mutations in SPCA1 predispose to the development of SCC in humans, but published clinical experience does not support such an association.

Affective disorder has been reported to cosegregate with Hailey–Hailey disease in three families [21–23].

Prognosis. Remissions are common and the condition may improve in old age [1,24].

Differential diagnosis

Clinical. Misdiagnosis is frequent [1,25,26]. Lesions may simulate impetigo, eczema, candida intertrigo or tinea corporis. Hailey–Hailey disease should be considered in patients complaining of 'reactions' to adhesive dressings [13]. Herpes simplex virus causes painful exacerbations, which may be difficult to differentiate from vesicular Hailey–Hailey disease [27,28]. Severe disease may simulate erythema multiforme or toxic epidermal necrolysis [2]. Hypertrophic vulval lesions may suggest malignancy [1].

Diagnostic difficulties are compounded because Hailey–Hailey disease may respond to the treatments such as antibacterials or topical corticosteroids that are used for some of these conditions, but longitudinal white bands in the nails may help to confirm the diagnosis [1,29].

Vegetating flexural disease occurs in both pemphigus vegetans and Darier's disease. Oral lesions distinguish pemphigus vegetans. Darier's disease is characterized by hyperkeratotic papules as well as a distinctive nail dystrophy (see Chapter 19).

Localized perineal papules and plaques with an acantholytic histology have been reported in patients without other features of Hailey–Hailey disease [30–32]. The relationships between this condition, Hailey–Hailey disease and Darier's disease might be clarified by genetic studies.

Histological. Hailey–Hailey disease must be differentiated from Darier's disease and pemphigus. Epidermal hyperplasia and suprabasal separation occur in both Darier's disease and Hailey–Hailey disease, but acantholysis tends to be more widespread in fully developed lesions of Hailey–Hailey disease while dyskeratosis with corps ronds and grains is more prominent in Darier's disease [33]. In pemphigus, the acantholytic cells are less well preserved and immunoglobulin and complement are deposited between the keratinocytes.

Investigations. The diagnosis should be confirmed by skin biopsy. Fungal, viral and bacterial infections exacerbate and perpetuate disease and should be excluded by culture. Patch testing should be considered in patients with long-standing disease.

Treatment. Simple measures should be tried to reduce skin friction and keep flexures dry, including weight loss if appropriate, loose cool clothing and absorbent pads in skin folds.

Combinations of moderate to potent topical corticosteroids with antibacterial and/or antifungal agents may be effective, particularly if topical steroids are applied promptly to early lesions, but no controlled trials have been performed [1]. The potency of topical corticosteroids should be reduced as soon as possible to prevent atrophy [34]. Systemic corticosteroids have been recommended for widespread disease [25,35,36]. Treatment may up-regulate SPCA1 expression either indirectly through an effect on cytokine production or by a direct effect on keratinocytes [37,38].

The role of antiseptics, antibiotics and/or topical antifungal agents as steroid-sparing agents is unproven, but long-term antimicrobial treatment appears to be helpful [1,25,39]. Topical tetra-

cyclines, aminoglycosides, fusidic acid or imidazoles may be added to a topical corticosteroid. Topical aminoglycosides may have the added benefit of reversing the effects of pathogenic nonsense mutations by inducing readthrough of stop mutations [40]. Low-dose oral tetracyclines, erythromycin or flucloxacillin should also be entertained. Oral treatment of herpes simplex should be considered in patients with unresponsive, painful disease.

Without controlled trials the evidence base for the efficacy of any of the following is poor: ciclosporin topically and orally (3–4 mg/kg/day) [41–43], topical tacrolimus [44,45], topical vitamin D_3 analogues [46,47], oral retinoids [48–50] and etanercept [51].

Botulinum toxin (axillary or inframammary) may help by reducing sweating [52–54], as may breast reduction [55].

Although ultraviolet light may exacerbate Hailey–Hailey disease, PUVA was apparently effective in some patients [56,57]. Suberythemal UVB controlled both psoriasis and co-existing Hailey–Hailey disease in another patient [58]. Superficial radiotherapy may produce temporary benefit [59].

The long-term benefit of any surgical approach is equally uncertain, but many have been recommended for recalcitrant disease including: cryosurgery [25], excision with or without grafting [60,61], dermabrasion [62,63], electrodesiccation [64], various forms of laser surgery [53,65–67] and photodynamic therapy [68]. Outcomes are not always satisfactory [69,70].

References

1 Burge SM. Hailey–Hailey disease: The clinical features, response to treatment and prognosis. *Br J Dermatol* 1992; **126**: 275–82.

2 Chave TA, Milligan A. Acute generalized Hailey–Hailey disease. *Clin Exp Dermatol* 2002; **27**: 290–2.

3 Harris A, Burge SM, Dykes PJ *et al.* Handicap in Darier's disease and Hailey–Hailey disease. *Br J Dermatol* 1996; **135**: 959–63.

4 Gisondi P, Sampogna F, Annessi G *et al.* Severe impairment of quality of life in Hailey–Hailey disease. *Acta Derm Venereol* 2005; **85**: 132–5.

5 Oguz O, Gokler G, Ocakoglu O *et al.* Conjunctival involvement in familial chronic benign pemphigus (Hailey–Hailey disease). *Int J Dermatol* 1997; **36**: 282–5.

6 Morales A, Livingood C, Hu F. Familial benign chronic pemphigus. *Arch Dermatol* 1966; **93**: 324–8.

7 Marren P, Burge S. Seborrhoeic dermatitis of the scalp—a manifestation of Hailey–Hailey disease in a predisposed individual? *Br J Dermatol* 1992; **126**: 294–6.

8 Peppiatt T, Keefe M, White JE. Hailey–Hailey disease—exacerbation by herpes simplex virus and patch tests. *Clin Exp Dermatol* 1992; **17**: 201–2.

9 Rudolph CM, Kranke B, Turek TD *et al.* Contact irritation provoking Hailey–Hailey disease. *Contact Dermatitis* 2001; **44**: 371.

10 Gerdsen R, Hartl C, Christ S *et al.* Hailey–Hailey disease: exacerbation by scabies. *Br J Dermatol* 2001; **144**: 211–2.

11 Reitamo S, Remitz A, Lauerma AI *et al.* Contact allergies in patients with familial benign chronic pemphigus (Hailey–Hailey disease). *J Am Acad Dermatol* 1989; **21**: 506–10.

12 Maniscalco M, Viviano E, Segreto A *et al.* Malattia di Hailey–Hailey. *Specializzati Oggi—Dermatologia* 1993; **2**: 26–8.

13 Walker SL, Beck MH. Undiagnosed Hailey–Hailey disease causing painful erosive skin changes during patch testing. *Br J Dermatol* 2005; **153**: 233–4.

14 Chen MY, Chiu HC, Su LH *et al.* Presence of human papillomavirus type 6 DNA in the perineal verrucoid lesions of Hailey–Hailey disease. *J Eur Acad Dermatol Venereol* 2006; **20**: 1356–7.

15 Chan CC, Thong HY, Chan YC *et al.* Human papillomavirus type 5 infection in a patient with Hailey–Hailey disease successfully treated with imiquimod. *Br J Dermatol* 2007; **156**: 579–81.

16 Chun SI, Whang KC, Su WPD. Squamous cell carcinoma arising in Hailey–Hailey disease. *J Cutan Pathol* 1988; **15**: 234–7.

17 Holst VA, Fair KP, Wilson BB *et al.* Squamous cell carcinoma arising in Hailey–Hailey disease. *J Am Acad Dermatol* 2000; **43**: 368–71.

18 Cockayne SE, Rassl DM, Thomas SE. Squamous cell carcinoma arising in Hailey–Hailey disease of the vulva. *Br J Dermatol* 2000; **142**: 540–2.

19 Ochiai T, Honda A, Morishima T *et al.* Human papillomavirus types 16 and 39 in a vulval carcinoma occurring in a woman with Hailey–Hailey disease. *Br J Dermatol* 1999; **140**: 509–13.

20 Okunade GW, Miller ML, Azhar M *et al.* Loss of the Atp2c1 secretory pathway Ca^{2+}-ATPase (SPCA1) in mice causes Golgi stress, apoptosis, and mid-gestational death in homozygous embryos and squamous cell tumors in adult heterozygotes. *J Biol Chem* 2007; **282**: 26517–27.

21 Korner J, Rietschel M, Nothen MM *et al.* Familial cosegregation of affective disorder and Hailey–Hailey disease. *Br J Psychiatry* 1993; **163**: 109–10.

22 Wilk M, Rietschel M, Korner J *et al.* Pemphigus chronicus benignus familiaris (morbus Hailey–Hailey) und biplare affektive erkrankung bei drei mitgliedern einer familie. *Hautarzt* 1994; **45**: 313–7.

23 Yokota K, Sawamura D. Hailey–Hailey disease with affective disorder: report of a case with novel ATP2C1 gene mutation. *J Dermatol Sci* 2006; **43**: 150–1.

24 Palmer D, Perry H. Benign familial chronic pemphigus. *Arch Dermatol* 1962; **86**: 493–502.

25 Galimberti RL, Kowalczuk AM, Bianchi O *et al.* Chronic benign familial pemphigus. *Int J Dermatol* 1988; **27**: 495–500.

26 Mak RK, Reynaert SM, Agar N *et al.* Hailey–Hailey disease failing to respond to treatment. *Clin Exp Dermatol* 2005; **30**: 598–9.

27 Otsuka F, Niimura M, Harada S *et al.* Generalized herpes simplex. Complicating Hailey–Hailey's disease. *J Dermatol* 1981; **8**: 63–8.

28 Stallmann D, Schmoeckel C. Morbus Hailey–Hailey mit dissemination und eczema herpeticatum unter etretinattherapie. *Hautarzt* 1988; **39**: 454–6.

29 Meawad OB, Assaf HM. Longitudinal white streaks of fingernails: a useful clinical marker in genital verrucoid Hailey–Hailey disease. *J Eur Acad Dermatol Venereol* 1995; **5**: 177–80.

30 Cooper PH. Acantholytic dermatosis localized to the vulvocrural area. *J Cutan Pathol* 1989; **16**: 81–4.

31 Wong TY, Mihm Mc Jr. Acantholytic dermatosis localized to genitalia and crural areas of male patients: a report of three cases. *J Cutan Pathol* 1994; **21**: 27–32.

32 Langenberg A, Berger TG, Cardelli M *et al.* Genital benign chronic pemphigus (Hailey–Hailey disease) presenting as condylomas. *J Am Acad Dermatol* 1992; **26**: 951–5.

33 Steffen CG. Familial benign chronic pemphigus. *Am J Dermatopathol* 1987; **9**: 58–73.

34 Ikeda S, Suga Y, Ogawa H. Successful management of Hailey–Hailey disease with potent topical steroid ointment. *J Dermatol Sci* 1993; **5**: 205–11.

35 Marsch W, Stüttgen G. Generalized Hailey–Hailey disease. *Br J Dermatol* 1978; **99**: 553–60.

36 Defresne C, Adam C, De Marneffe K. Pemphigus chronique benin familial de Hailey–Hailey. *Dermatologica* 1982; **165**: 624–6.

37 Mayuzumi N, Ikeda S, Kawada H *et al.* Effects of ultraviolet B irradiation, proinflammatory cytokines and raised extracellular calcium concentration on the expression of ATP2A2 and ATP2C1. *Br J Dermatol* 2005; **152**: 697–701.

38 Mayuzumi N, Ikeda S, Kawada H *et al.* Effects of drugs and anticytokine antibodies on expression of ATP2A2 and ATP2C1 in cultured normal human keratinocytes. *Br J Dermatol* 2005; **152**: 920–4.

39 Leyden J, Marples R. Superinfection induced by antibiotics in familial benign chronic pemphigus. *Acta Derm Venereol (Stockh)* 1973; **53**: 61–4.

40 Kellermayer R, Szigeti R, Keeling KM *et al.* Aminoglycosides as potential pharmacogenetic agents in the treatment of Hailey–Hailey disease. *J Invest Dermatol* 2006; **126**: 229–31.

41 Jitsukawa K, Ring J, Weyer U *et al.* Topical cyclosporine in chronic benign familial pemphigus (Hailey–Hailey disease). *J Am Acad Dermatol* 1992; **27**: 625–6.

42 Cecchi R, Bartoli L, Brunetti L *et al.* Pemfigo familiare benigno (malattia di Hailey–Hailey) trattato con ciclosporina A orale. *G Ital Dermatol Venereol* 1993; **128**: 615–7.

43 BerthJones J, Smith SG, GrahamBrown RAC. Benign familial chronic pemphigus (Hailey–Hailey disease) responds to cyclosporin. *Clin Expt Dermatol* 1995; **20**: 70–2.

44 Umar SA, Bhattacharjee P, Brodell RT. Treatment of Hailey–Hailey disease with tacrolimus ointment and clobetasol propionate foam. *J Drugs Dermatol* 2004; **3**: 200–3.
45 Rocha Paris F, Fidalgo A, Baptista J *et al.* Topical tacrolimus in Hailey–Hailey disease. *Int J Tissue React* 2005; **27**: 151–4.
46 Bianchi L, Chimenti MS, Giunta A. Treatment of Hailey–Hailey disease with topical calcitriol. *J Am Acad Dermatol* 2004; **51**: 475–6.
47 Rajpara SM, King CM. Hailey–Hailey disease responsive to topical calcitriol. *Br J Dermatol* 2005; **152**: 816–7.
48 Hunt MJ, Salisbury EL, Painter DM *et al.* Vesiculobullous Hailey–Hailey disease: successful treatment with oral retinoids. *Australas J Dermatol* 1996; **37**: 196–8.
49 Mashiko M, Akiyama M, Tsuji-Abe Y *et al.* Bacterial infection-induced generalized Hailey–Hailey disease successfully treated by etretinate. *Clin Exp Dermatol* 2006; **31**: 57–9.
50 Berger EM, Galadari HI, Gottlieb AB. Successful treatment of Hailey–Hailey disease with acitretin. *J Drugs Dermatol* 2007; **6**: 734–6.
51 Norman R, Greenberg RG, Jackson JM. Case reports of etanercept in inflammatory dermatoses. *J Am Acad Dermatol* 2006; **54**: S139–42.
52 Lapiere JC, Hirsh A, Gordon KB *et al.* Botulinum toxin type A for the treatment of axillary Hailey–Hailey disease. *Dermatol Surg* 2000; **26**: 371–4.
53 Konrad H, Karamfilov T, Wollina U. Intracutaneous botulinum toxin A versus ablative therapy of Hailey–Hailey disease—a case report. *J Cosmet Laser Ther* 2001; **3**: 181–4.
54 Kang NG, Yoon TJ, Kim TH. Botulinum toxin type A as an effective adjuvant therapy for Hailey–Hailey disease. *Dermatol Surg* 2002; **28**: 543.
55 Aubert JP, Folchetti G, Berbis P *et al.* Traitement chirugical de la maladie de Hailey–Hailey ou pemphigus chronique benin familial. A propos d'une localisation sous-mammaire. *Ann Chir Plast Esthet* 1993; **38**: 568–71.
56 Hums R. PUVA-therapie bei pemphigus chronicus benignus familaris Hailey–Hailey. *Dermatol Monatsschr* 1984; **170**: 715–8.
57 Il'in II, Molochkov KA. The photochemotherapy of Hailey–Hailey disease. *Vestn Dermatol Venerol* 1990; **7**: 64–6.
58 Hayakawa K, Shiohara T. Coexistence of psoriasis and familial benign chronic pemphigus: efficacy of ultraviolet B treatment. *Br J Dermatol* 1999; **140**: 374–5.
59 Roos DE, Reid CM. Benign familial pemphigus: little benefit from superficial radiotherapy. *Australas J Dermatol* 2002; **43**: 305–8.
60 Guerin-Surville H, Guerin-Surville L, Le-Louarn C *et al.* Traitement chirurgical de la maladie de Hailey–Hailey par greffes chirurgicales. (2e presentation): resultats avec 5 ans de recul. *Ann Dermatol Venereol* 1989; **116**: 904–5.
61 Shons AR. Wide excision of perineal Hailey–Hailey disease with healing by secondary intention. *Br J Plast Surg* 1989; **42**: 230–2.
62 Kirtschig G, Gieler U, Happle R. Treatment of Hailey–Hailey disease by dermabrasion. *J Am Acad Dermatol* 1993; **28**: 784–6.
63 Hamm H, Metze D, Brocker EB. Hailey–Hailey disease: eradication by dermabrasion. *Arch Dermatol* 1993; **130**: 1143–9.
64 Quitadamo MJ, Spencer SK, Roenigk RK. Surgical management of Hailey–Hailey disease. *J Am Acad Dermatol* 1991; **25**: 342–3.
65 Kartamaa M, Reitamo S. Familial benign chronic pemphigus (Hailey–Hailey disease): treatment with carbon dioxide laser vaporization. *Arch Dermatol* 1992; **128**: 646–8.
66 Beier C, Kaufmann R. Efficacy of erbium : YAG laser ablation in Darier disease and Hailey–Hailey disease. *Arch Dermatol* 1999; **135**: 423–7.
67 Christian MM, Moy RL. Treatment of Hailey–Hailey disease (or benign familial pemphigus) using short pulsed and short dwell time carbon dioxide lasers. *Dermatol Surg* 1999; **25**: 661–3.
68 Ruiz-Rodriguez R, Alvarez JG, Jaen P *et al.* Photodynamic therapy with 5-aminolevulinic acid for recalcitrant familial benign pemphigus (Hailey–Hailey disease). *J Am Acad Dermatol* 2002; **47**: 740–2.
69 Konig A, Horster S, Vakilzadeh F *et al.* Type 2 segmental manifestation of Hailey–Hailey disease: poor therapeutic response to dermabrasion is due to severe involvement of adnexal structures. *Eur J Dermatol* 2000; **10**: 265–8.
70 Downs A. Smoothbeam laser treatment may help improve hidradenitis suppurativa but not Hailey–Hailey disease. *J Cosmet Laser Ther* 2004; **6**: 163–4.

Segmental Hailey–Hailey disease

A linear acantholytic dermatosis with the clinicopathological features of Hailey–Hailey disease has been described affecting one side of the body. These features may be explained by a localized postzygotic mutation in *ATP2C1* resulting in type 1 mosaicism [1].

A patient with a family history of Hailey–Hailey disease presented in infancy with a linear acantholytic dermatosis following Blaschko's lines, but typical Hailey–Hailey disease involving body folds appeared in the third decade. This patient has a type-2 mosaicism with segmental lesions superimposed on the ordinary phenotype. A germline mutation affected one allele, but a postzygotic mutation early in development affected the other allele resulting in loss of heterozygosity and severely affected segmental lesions [2].

References

1 Hwang LY, Lee JB, Richard G *et al.* Type 1 segmental manifestation of Hailey–Hailey disease. *J Am Acad Dermatol* 2003; **49**: 712–4.
2 Poblete-Gutierrez P, Wiederholt T, Konig A *et al.* Allelic loss underlies type 2 segmental Hailey–Hailey disease, providing molecular confirmation of a novel genetic concept. *J Clin Invest* 2004; **114**: 1467–74.

CHAPTER 40
Immunobullous Diseases

F. Wojnarowska & V.A. Venning
Churchill Hospital, Oxford, UK

Intercellular adhesion in the epidermis, 40.1
Intraepidermal immunobullous diseases, 40.3
Pemphigus, 40.3
Pemphigus vulgaris and pemphigus vegetans, 40.3
Pemphigus foliaceus and its variants, 40.13
Induced pemphigus, 40.18
Intercellular IgA dermatosis and subcorneal pustular dermatosis, 40.19
Paraneoplastic pemphigus, 40.22
Structure of the dermoepidermal junction, 40.24
Subepidermal immunobullous diseases, 40.25
Bullous pemphigoid, 40.26
Mucous membrane pemphigoid, 40.35
Pemphigoid gestationis, 40.41
Linear IgA disease, 40.45
Epidermolysis bullosa acquisita, 40.51
Bullous systemic lupus erythematosus, 40.56
Dermatitis herpetiformis, 40.58

Introduction

The bullous diseases discussed in this chapter, although uncommon, have a dramatic impact on the patient and their relatives and have severe economic consequences for the family and health services. These diseases have been the subject of intensive investigation in recent years, and the study of both the genetic and autoimmune diseases has made major contributions to our knowledge of the biology of the skin. The identification of the specific target antigens for the autoantibodies in the autoimmune bullous diseases has led to the discovery of many components of the desmosome and the adhesion complex linking the epidermis to the dermis (Fig. 40.1; also see Fig. 40.11). In parallel with this work has been the realization that mutations of these same proteins are the basis of some of the genetic bullous diseases. The molecular biology of the genetic abnormalities is beginning to reveal how the fine structure of these proteins enables them to perform their function (see Chapter 39).

The immunological diseases are classified largely by their clinical presentation, histopathology and immunopathology. The increased use of immunoblotting and immunoelectron microscopy to define these diseases has revealed that the target antigens and specific epitopes may be common to more than one clinical entity. Thus, the clinician is still the final arbiter for diagnosis.

A comprehension of the ultrastructural anatomy and composition of the areas under discussion greatly facilitates an understanding of the diseases that produce chronic blistering of the skin and mucous membranes (see Chapter 3).

The immunobullous diseases are characterized by pathogenic autoantibodies directed at target antigens whose function is either cell-to-cell adhesion within the epidermis or adhesion of stratified squamous epithelium to dermis or mesenchyme. These target antigens are components of desmosomes or the functional unit of the basement membrane zone known as the adhesion complex and are shown in Figs 40.1 and 40.11. The clinical, immunopathological and immunogenetic features of these diseases are shown in Tables 40.2, 40.3, 40.5 and 40.6. Dermatitis herpetiformis is the one possible exception, as the relevant target antigen has not yet been identified.

The most important techniques for the investigation of patients with immunobullous disease are histopathology, and direct and indirect immunofluorescence. Research techniques such as immunoblotting and immunoelectron microscopy may refine the diagnosis in the individual patient but do not replace the clinical findings [1].

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

Reference

1 Kirtschig G, Wojnarowska F. Autoimmune blistering diseases: an update of diagnostic methods and investigations. *Clin Exp Dermatol* 1994; **19**: 97–112.

Intercellular adhesion in the epidermis

Adhesion between keratinocytes is mediated predominantly by cell adhesion molecules of the cadherin family, localized in two specialized intercellular adhesion junctions: desmosomes and intermediate or adherens junctions. Desmosomes are small, electron-dense structures that link the intermediate filament within cells to the plasma membrane and to adjacent cells. The possible arrangement of desmosomal components is illustrated in Fig. 40.1. The major adhesion components of desmosomes are the desmosomal cadherins, desmogleins and desmocollins. The cadherins are transmembrane glycoproteins each having an extracellular domain, a transmembrane domain and a cytoplasmic domain, which links to the cytoskeleton. Adhesion is probably regulated by complex interactions between the cytoplasmic domains of cadherins and cytoplasmic proteins such as catenins or plakoglobin [1–3] (for a detailed discussion see Chapter 3).

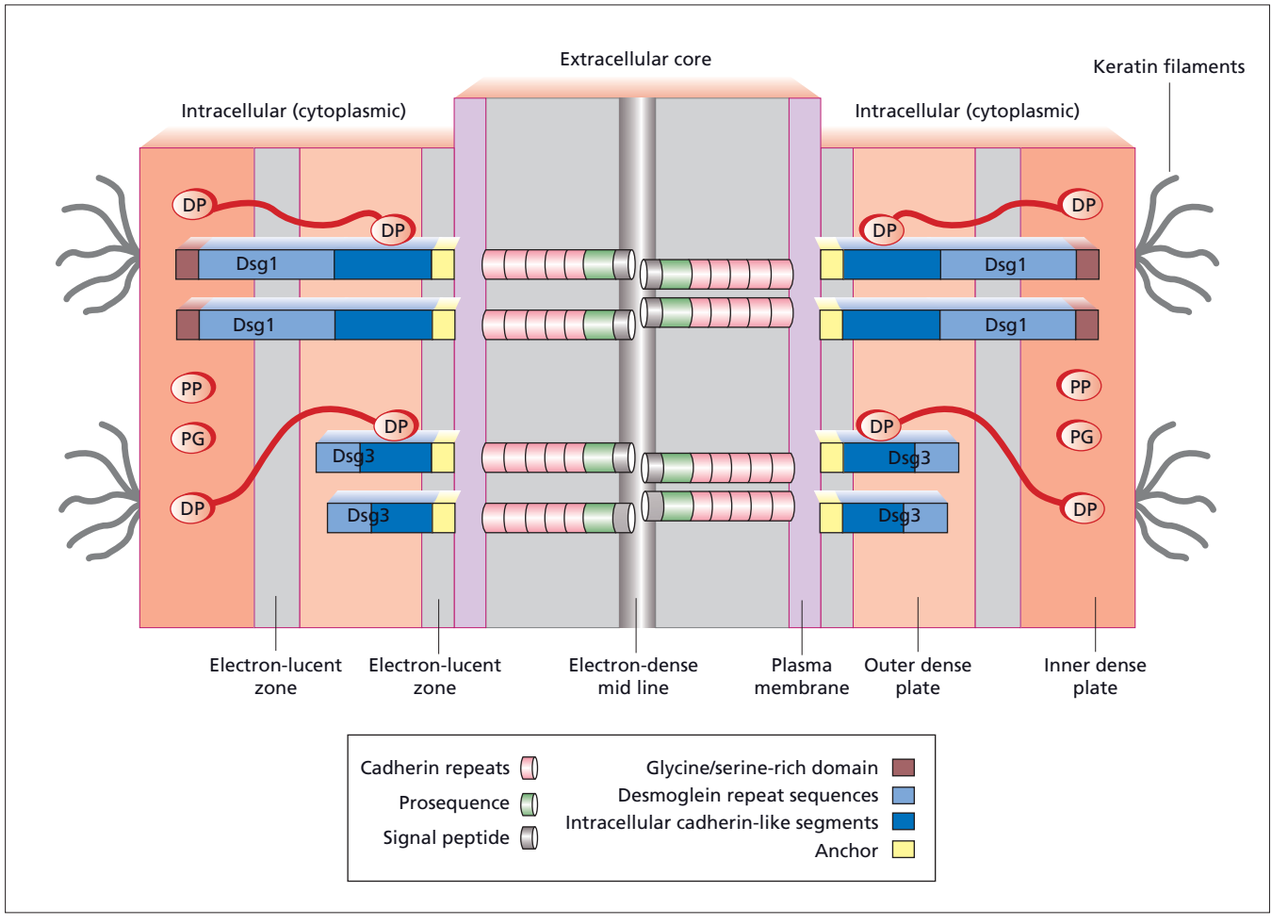


Fig. 40.1 Diagrammatic representation of the molecular components of the desmosome. DP, desmoplakin; Dsg1, desmoglein 1; Dsg3, desmoglein 3; N, amino terminal; PG, plakoglobin; PP, plakophilin. (Courtesy of Dr J. Allen, Oxford Radcliffe Hospital, Oxford, UK.)

The desmoglein subfamily comprises at least three related proteins: desmoglein-1, desmoglein-2 and desmoglein-3. Desmoglein-1 is recognized by sera from patients with the autoimmune blistering disease pemphigus foliaceus and some with pemphigus vulgaris. Desmoglein-1 is also the target of protease-mediated damage by staphylococcal exotoxins [4]. Desmoglein-3 is the target antigen in pemphigus vulgaris. The desmocollins also exist in more than one isoform, and are recognized by sera from some patients with IgA pemphigus.

The expression of desmosomal cadherins varies during differentiation, and expression in human skin differs from that in mucosal epithelium. Desmoglein-3 is expressed only in the basal and suprabasal layers of the epidermis whereas desmoglein-1 is found throughout the epidermis, particularly in the upper layers [5–7]. In mucosae, desmoglein-3 is strongly expressed throughout whereas desmoglein-1 is expressed only weakly [8,9]. In neonatal epidermis, the distribution of desmogleins resembles that of the adult mucosa [10,11].

Desmosomes have well-defined, submembranous plaques, containing non-glycosylated proteins plakoglobin, desmoplakins-1 and 2 and plakophilin. Plakoglobin, present in both desmosomes and adherens junctions, may interact with cadherins to regulate adhesion [12,13]. Desmoplakin-1 and 2 belong to a multigene family of intermediate filament organizing proteins (plakins), which includes the bullous pemphigoid antigen (BP230), present in the hemidesmosomes of the basement membrane zone, and plectin, a widely distributed intermediate filament-associated protein [12]. Less well characterized plakins, localizing to the desmosome, are envoplakin and periplakin [14]. Plakin autoantibodies are present in the blistering disease paraneoplastic pemphigus, a condition which is associated with lymphoid malignancies, thymomas or poorly differentiated sarcomas [15]. Keratin intermediate filaments insert into the desmosomal plaque, where their amino termini interact with the carboxy termini of desmoplakin. Desmoplakins, plakoglobin, and possibly also plakophilin-1, are attached to desmosomal cadherins and to each other in a complex arrangement [3,16,17].

Adherens junctions

Epithelial cadherin (E-cadherin) is present in adherens junctions. Interactions between cytoplasmic domains on E-cadherin and cytoplasmic proteins called catenins are essential for normal adhesion. Plakoglobin, which is similar in structure to β-catenin, may also form complexes with E-cadherin [12]. Vinculin and α-actinin, cytoplasmic proteins present in adherens junctions, may link to bundles of actin microfilaments to influence the organization of

the filaments. These are not currently identified as target antigens in immunobullous diseases.

References

1 Kemler R. From cadherins to catenins: cytoplasmic protein interactions and regulation of cell adhesion. *Trends Genet* 1993; **9**: 317–21.
2 Buxton RS, Magee AI. Structure and interactions of desmosomal and other cadherins. *Semin Cell Biol* 1992; **3**: 157–67.
3 Garrod D, Chidgey M. Desmosome structure, composition and function. *Biochim Biophys Acta* 2008; **1778**: 572–87.
4 Hanakawa Y, Schechter NM, Lin C *et al.* Molecular mechanisms of blister formation in bullous impetigo and staphylococcal scalded skin syndrome. *J Clin Invest* 2002; **110**: 53–60.
5 Amagai M, Koch PJ, Nishikawa T *et al.* Pemphigus vulgaris antigen (desmoglein 3) is localized in the lower epidermis, the site of blister formation in patients. *J Invest Dermatol* 1996; **106**: 351–5.
6 Hashimoto T, Amagai M, Garrod DR *et al.* Immunofluorescence and immunoblot studies on the reactivity of pemphigus vulgaris and pemphigus foliaceus sera with desmoglein 3 and desmoglein 1. *Epithelial Cell Biol* 1995; **4**: 63–9.
7 Mahoney MG, Wang Z, Rothenberger K *et al.* Explanations for the clinical and microscopic localization of lesions in pemphigus foliaceus and vulgaris. *J Clin Invest* 1999; **103**: 461–8.
8 Shirakata Y, Amagai M, Hanakawa Y *et al.* Lack of mucosal involvement in pemphigus foliaceus may be due to low expression of desmoglein 1. *J Invest Dermatol* 1998; **110**: 76–8.
9 Harman KE, Gratian MJ, Bhogal BS *et al.* The use of two substrates to improve the sensitivity of indirect immunofluorescence in the diagnosis of pemphigus. *Br J Dermatol* 2000; **142**: 1135–9.
10 Wu H, Wang ZH, Yan A *et al.* Protection against pemphigus foliaceus by desmoglein 3 in neonates. *N Engl J Med* 2000; **343**: 31–5.
11 Campo-Voegeli A, Muniz F, Mascaro JM *et al.* Neonatal pemphigus vulgaris with extensive mucocutaneous lesions from a mother with oral pemphigus vulgaris. *Br J Dermatol* 2002; **147**: 801–5.
12 Peifer M, McCrea PD, Green KJ *et al.* The vertebrate adhesive junction proteins beta-catenin and plakoglobin and the Drosophila segment polarity gene armadillo form a multigene family with similar properties. *J Cell Biol* 1992; **118**: 681–91.
13 Roh JY, Stanley JR. Plakoglobin binding by human Dsg3 (pemphigus vulgaris antigen) in keratinocytes requires the cadherin-like intracytoplasmic segment. *J Invest Dermatol* 1995; **104**: 720–4.
14 DiColandrea T, Karashima T, Maatta A *et al.* Subcellular distribution of envoplakin and periplakin: insights into their role as precursors of the epidermal cornified envelope. *J Cell Biol* 2000; **151**: 573–86.
15 Mahoney MG, Aho S, Uitto J *et al.* The members of the plakin family of proteins recognized by paraneoplastic pemphigus antibodies include periplakin. *J Invest Dermatol* 1998; **111**: 308–13.
16 McMillan JR, Shimizu H. Desmosomes: structure and function in normal and diseased epidermis. *J Dermatol* 2001; **28**: 291–8.
17 North AJ, Bardsley WG, Hyam J *et al.* Molecular map of the desmosomal plaque. *J Cell Sci* 1999; **112**: 4325–36.

Intraepidermal immunobullous diseases

Blisters form within the epidermis in the pemphigus group of immunobullous diseases. The antibodies in these diseases react with intercellular adhesion molecules. Immunoreactants are deposited between keratinocytes, intercellular bridges disappear and keratinocytes separate from one another, a change known as acantholysis.

Pemphigus

Definition. Pemphigus derived from the Greek *pemphix* meaning blister or bubble. The term 'pemphigus' once covered most of the bullous eruptions of the skin, but diagnostic tests have improved and the bullous diseases have been reclassified. A number of distinct subgroups of pemphigus have emerged and many of the autoantigens have been identified. The antibodies are directed against epidermal cadherins, a family of calcium-dependent cell–cell adhesion molecules. The two major subtypes, pemphigus vulgaris and pemphigus foliaceus, are distinguished by the level of cleavage within the epidermis. Splitting is suprabasal in pemphigus vulgaris and its rare vegetating form, pemphigus vegetans. Blistering is more superficial in pemphigus foliaceus and related subtypes.

The classification of pemphigus, its clinical features, immunopathology and immunogenetics are summarized in Tables 40.1, 40.2 and 40.3.

Table 40.1 Types of pemphigus.

Pemphigus vulgaris
variant: pemphigus vegetans
Pemphigus foliaceus
variant: pemphigus herpetiformis
variant: pemphigus erythematosus
Induced pemphigus
Intercellular IgA dermatosis
Paraneoplastic pemphigus

Pemphigus vulgaris and pemphigus vegetans

Aetiology. Pemphigus vulgaris affects all races and both sexes [1]. It is a disease of middle age, which affects children rarely, but patients are younger at presentation in India than in Western countries [2].

Pemphigus vulgaris accounts for around 70% of all cases of pemphigus and may be the commonest autoimmune blistering disease in Eastern countries, such as India, Malaysia, China and the Middle East [2–4]. The Jewish race, especially Ashkenazi Jews, have an increased susceptibility to pemphigus vulgaris [1]. In South Africa, pemphigus vulgaris is commoner in Indians than in Black or Caucasian races [5]. Pemphigus is less common in the West.

Predisposition to pemphigus is linked to genetic factors. First-degree relatives of patients with pemphigus vulgaris are more susceptible to the development of autoimmune diseases than are controls [6,7] and have a higher incidence of circulating antidesmoglein antibodies [8]. Certain MHC class II genotypes are common in patients with pemphigus vulgaris and cross racial barriers. Alleles of HLA-DRB1*0402 and -DRB1*1401, -DQB1*0503 subtypes confer disease risk [9–13] and may do so by structural change in peptide binding sites, influencing antigen presentation and recognition by T cells [12,14]. In British and Indian patients certain haplotypes of the desmoglein-3 gene also confer risk for pemphigus vulgaris and this appears to be additive to the effect of HLA-DR [15]. Susceptibility may also be determined by genes encoding immunoglobulins [16] or by genes within the HLA class I antigen processing machinery [17].

Table 40.2 The intraepidermal immunobullous diseases: clinical features.

Disease	Patients	Cutaneous distribution	Mucosal involvement	Lesions	Disease associations	Treatment	Prognosis
Pemphigus vulgaris	Middle age	Scalp, face, flexures, may be generalized	Always oropharynx, conjunctiva, genital	Flaccid blisters, erosions, flexural vegetations	Autoimmune disease, thymoma	Steroids, immunosuppressives, dapsone	Variable, may remit
Pemphigus vegetans	Middle age	Flexural	Oral	Vesicles, pustules, erosions, vegetating plaques		Steroids, immunosuppressives, dapsone	Variable, may remit
Pemphigus foliaceus	Middle age	Scalp, face, chest, upper back, rarely generalized 'seborrhoeic'	None	Scaly papules, crusted erosions, erythroderma		Steroids (topical, intralesional, systemic), immunosuppressives	Benign but chronic
Endemic pemphigus foliaceus	Children, young adults	Head, neck, generalized	Uncommon	Flaccid blisters, erosions, verrucous lesions, erythroderma		Steroids, immunosuppressives, antimalarials	Chronic mortality <10%
Intercelluar IgA dermatosis	Adults, children	Axillae, groins, face, scalp, proximal limbs	Uncommon	Flaccid pustules annular or circinate configuration	IgA monoclonal gammopathy	Dapsone	Chronic indolent
Paraneoplastic pemphigus	Adults, children	Upper body, palmoplantar	Severe mucositis	Polymorphous, bullae, erosions, 'target lesions'	Lymphoproliferative disease, Castleman's, other malignancies	Tumour resection, steroids, immunosuppression	Very poor

Table 40.3 The intraepidermal immunobullous diseases: immunopathology and immunogenetics.

Disease	Direct IMF	Isotype	Target antigens	Antigens (kDa)	Epitopes	Location	Immunogenetics
							MHC class I and II
Pemphigus vulgaris/ pemphigus vegetans	Intercellular	IgG (few IgM, IgA)	Desmoglein 3, sometimes desmoglein 1 desmocollins	130	Amino-terminal of extracellular domain	Desmosome	DRB1*0402 DRB1*1401
Pemphigus foliaceus	Intercellular	IgG	Desmoglein 1, sometimes desmocollins	160	Amino-terminal of extracellular domain	Desmosome	HLA-DRB1*14
Endemic pemphigus foliaceus	Intercellular	IgG	Desmoglein 1, sometimes desmocollins	160	Amino-terminal of extracellular domain	Desmosome	Several susceptibility alleles, all with same amino acid sequence in *DRB-1* gene DRB1*0102 DRB1*0404, *1402 or *1406
Paraneoplastic pemphigus	Intercellular and subepidermal	IgG	Plakins (desmoplakin, envoplakin BP230, periplakin)		Various	Desmosomes, BMZ; stratified, simple and transitional epithelia	Unknown

BMZ, basement-membrane zone; HLA, human leukocyte antigen; IMF, immunofluorescence; MHC, major histocompatibility complex.

Pemphigus occurs in patients with other disorders characterized by immunological disturbances. Thymoma or myasthenia gravis have been reported in a number of patients. Some have all three diseases [1]. Pemphigus may develop in patients with lupus erythematosus (see Pemphigus erythematosus, below). Bullous pemphigoid and pemphigus have coexisted [18]. Pemphigus has been reported in patients with lymphoproliferative diseases such as Castleman's tumours (see Paraneoplastic pemphigus, below). Viral DNA (herpes simplex, EB virus, human herpes viruses 6 and 8) has been detected in some skin biopsies or peripheral blood mononuclear cells from pemphigus patients [19,20] and pemphigus has coexisted with HIV infection [21]. An epidemiological review of Iranian pemphigus vulgaris patients suggested a positive correlation with oral contraceptive use and pesticide exposure but a possibly protective effect from cigarette smoking [22].

References

1 Korman NJ. Pemphigus. *Dermatol Clin* 1990; **8**: 689–700.
2 Wilson C, Wojnarowska F, Mehra NK *et al.* Pemphigus in Oxford, UK, and New Delhi, India: a comparative study of disease characteristics and HLA antigens. *Dermatology* 1994; **189** (Suppl. 1): 108–10.
3 Adam BA. Bullous diseases in Malaysia: epidemiology and natural history. *Int J Dermatol* 1992; **31**: 42–5.
4 Chams-Davatchi C, Valikhani M, Daneshpazhooh M *et al.* Pemphigus: analysis of 1209 cases. *Int J Dermatol* 2005; **44**: 470–6.
5 Aboobaker J, Morar N, Ramdial PK *et al.* Pemphigus in South Africa. *Int J Dermatol* 2001; **40**: 115–9.
6 Firooz A, Mazhar A, Ahmed AR. Prevalence of autoimmune diseases in the family members of patients with pemphigus vulgaris. *J Am Acad Dermatol* 1994; **31**: 434–7.
7 Starzycki Z, Chorzelski TP, Jablonska S. Familial pemphigus vulgaris in mother and daughter. *Int J Dermatol* 1998; **37**: 211–4.
8 Brandsen R, Frusic-Zlotkin M, Lyubimov H *et al.* Circulating pemphigus IgG in families of patients with pemphigus: comparison of indirect immunofluorescence, direct immunofluorescence, and immunoblotting. *J Am Acad Dermatol* 1997; **36**: 44–52.
9 Ahmed AR, Yunis EJ, Khatri K *et al.* Major histocompatibility complex haplotype studies in Ashkenazi Jewish patients with pemphigus vulgaris. *Proc Natl Acad Sci USA* 1990; **87**: 7658–62.
10 Ahmed AR, Wagner R, Khatri K *et al.* Major histocompatibility complex haplotypes and class II genes in non-Jewish patients with pemphigus vulgaris. *Proc Natl Acad Sci USA* 1991; **88**: 5056–60.
11 Ahmed AR, Mohimen A, Yunis EJ *et al.* Linkage of pemphigus vulgaris antibody to the major histocompatibility complex in healthy relatives of patients. *J Exp Med* 1993; **177**: 419–24.
12 Miyagawa S, Amagai M, Niizeki H *et al.* HLA-DRB1 polymorphisms and autoimmune responses to desmogleins in Japanese patients with pemphigus. *Tissue Antigens* 1999; **54**: 333–40.
13 Lee E, Lendas KA, Chow S *et al.* Disease relevant HLA class II alleles isolated by genotypic, haplotypic, and sequence analysis in North American Caucasians with pemphigus vulgaris. *Hum Immunol* 2006; **67**: 125–39.
14 Wucherpfennig KW, Yu B, Bhol K *et al.* Structural basis for major histocompatibility complex (MHC)-linked susceptibility to autoimmunity: charged residues of a single MHC binding pocket confer selective presentation of self-peptides in pemphigus vulgaris. *Proc Natl Acad Sci USA* 1995; **92**: 11935–9.
15 Capon F, Bharkhada J, Cochrane NE *et al.* Evidence of an association between desmoglein 3 haplotypes and pemphigus vulgaris. *Br J Dermatol* 2006; **154**: 67–71.
16 Gibson WT, Walter MA, Ahmed AR *et al.* The immunoglobulin heavy chain and disease association: application to pemphigus vulgaris. *Hum Genet* 1994; **94**: 675–83.
17 Slomov E, Loewenthal R, Korostishevsky M *et al.* Pemphigus vulgaris is associated with the transporter associated with antigen processing (TAP) system. *Hum Immunol* 2005; **66**: 1213–22.
18 Sami N, Ahmed AR. Dual diagnosis of pemphigus and pemphigoid. Retrospective review of thirty cases in the literature. *Dermatology* 2001; **202**: 293–301.
19 Memar OM, Rady PL, Goldblum RM *et al.* Human herpesvirus 8 DNA sequences in blistering skin from patients with pemphigus. *Arch Dermatol* 1997; **133**: 1247–51.
20 Tufano M, Baroni A, Buommino E *et al.* Detection of virus DNA in peripheral blood mononuclear cells and skin lesions of patients with pemphigus by polymerase chain reaction. *Br J Dermatol* 1999; **141**: 1033–9.
21 Lateef A, Packles MR, White SM *et al.* Pemphigus vegetans in association with human immunodeficiency virus. *Int J Dermatol* 1999; **38**: 778–81.
22 Valikhani M, Kavusi S, Chams-Davatchi C *et al.* Pemphigus and associated environmental factors: a case-control study. *Clin Exp Dermatol* 2007; **32**: 256–60.

Pathogenesis. Autoantibodies against the surface of keratinocytes occur in pemphigus and both clinical and experimental observations indicate that circulating autoantibodies are pathogenic [1].

Pemphigus vulgaris antigen

The pemphigus vulgaris antigen, also known as desmoglein-3, is the desmosomal cadherin involved in mediating intercellular adhesion in the epidermis [2]. Pemphigus antibody binds to an extracellular domain on the amino-terminal region of desmoglein-3 where it may have a direct effect on the function of the desmosomal cadherins [3,4].

Desmoglein-3 is found in desmosomes [4] and possibly elsewhere on the cell membrane of keratinocytes [5]. It is detected early in keratinocyte differentiation, primarily in the lower epidermis [6–9] and is expressed more strongly in buccal mucosa and scalp skin than in skin from the trunk [10]. This contrasts with the pattern of expression of the pemphigus foliaceus antigen, desmoglein-1, which is present throughout the epidermis, more intensely in the upper layers, but only weakly expressed in mucosae [11].

Antibodies in pemphigus

Desmoglein antibodies. Where both desmogleins are expressed, it has been suggested that one molecule is able to compensate for the loss of function of the other [12] and the distribution of lesions in different forms of pemphigus is consistent with the epidermal distribution of the different desmoglein isoforms. Pemphigus vulgaris patients who only have desmoglein-3 antibodies tend to have lesions limited to the mucous membranes [13–15], where the relative lack of desmoglein-1 is unable to compensate, thus leading to acantholysis. Pemphigus vulgaris patients with antibodies to both desmogleins usually develop widespread mucocutaneous blistering [13,15,16] with bullae confined to the suprabasal epidermis, the location where both cadherins appear to be essential to maintain cell–cell adhesion. In general, cases evolving from mucosal-dominant to mucocutaneous pemphigus vulgaris or from pemphigus vulgaris to pemphigus foliaceus, or more rarely *vice versa*, the shift in clinical features usually correlates with changes in the reactivity of serum against the different desmoglein isoforms [17–21]. However, cases where there is no correlation between antibody profile and clinical phenotype are well recognized, indicating that antidesmoglein antibodies alone are not the sole effectors of pemphigus [22–25].

Although there is homology between desmogleins-1 and 3, the antibodies are not thought to be cross-reactive. One interpretation for this phenomenon is 'epitope spreading', that is tissue damage from a primary autoimmune or inflammatory response results in exposure of new epitopes on the same or another molecule to produce a secondary autoimmune response [26]. Desmoglein-1 antibodies are commoner in Indian patients, suggesting that antibody profile does not simply reflect disease duration, but is determined by other, possibly racial, factors [27].

The pathogenicity of desmoglein antibodies is supported by several lines of evidence. Most studies have shown a correlation between disease activity and titre of antibody [28–30]. Transplacental transfer of maternal pemphigus vulgaris antibodies may cause transient blisters in the newborn [31]. In the neonatal mouse model, passive transfer of pemphigus vulgaris IgG causes suprabasal acantholysis [32]. Blistering is prevented by prior absorption of antibodies with the extracellular domain of the pemphigus vulgaris desmoglein-3 antigen [33]. Acantholysis can be induced

in mice by desmoglein-3 antibodies alone but is greatly enhanced by addition of desmoglein-1 antibodies [34].

Autoantibody production is T-cell dependent and autoreactive Th1 and Th2 cells specific for desmoglein-3 occur in pemphigus vulgaris [35]. The pathogenecity of desmoglein antibodies depends on their titre and subclass. Patients with active disease have antibodies of both IgG1 and IgG4 subclasses, but the IgG4 antibodies are pathogenic [36,37]. Pathogenicity is also related to epitope specificity, disease activity correlating with reactivity against non-conformational NH_2-terminal epitopes of the desmoglein 3 ectodomain [38,39].

Non-desmoglein antibodies. Pemphigus vulgaris sera may also contain autoantibodies to desmocollins [40,41]. Antibodies to e-cadherin have also been detected, some but not all of which cross-react with desmoglein-1 [42].

Antibodies to non-cadherin antigens have also been reported. Antidesmoplakin in addition to antidesmoglein antibodies have been reported in severe pemphigus vulgaris [43]. Antibodies to cholinergic receptors have been observed in pemphigus sera [44] and cholinergic agonists can inhibit acantholysis induced by pemphigus sera *in vitro* and have an apparent steroid-sparing effect *in vivo* in pemphigus [45]. The relative contribution and significance of all the various antibodies described in pemphigus remain to be elucidated [46,47].

The mechanism of acantholysis

The mechanisms involved in cell separation (acantholysis) are not fully understood. One hypothesis is that antibody binding may cause direct inhibition of the adhesive function of desmogleins by 'steric hindrance' [38]. However, separation between desmosomes is not the earliest event and keratinocyte shrinkage and collapse of the cytoskeleton precede visible acantholysis [48].

Binding of pemphigus vulgaris antibody results in activation of a variety of intracellular signalling pathways with phosphorylation of keratinocyte proteins, including activation of EGF-receptor and phosphorylation of its downstream substrates (p38 mitogen-activated protein kinase (p38MAPK), Fas apoptotic cascade) [49,50]. Specific inhibition of p38MAPK can prevent pemphigus vulgaris blistering *in vivo* in mice [49,50].

Pemphigus antibody fixes components of complement to the surface of epidermal cells [51]. Pemphigus antibodies can induce acantholysis in complement-deficient mice [52]. In skin organ cultures and epidermal cell cultures acantholysis can occur in the absence of complement [53], although addition of complement enhances pathogenicity. Antibody binding may activate complement with the release of inflammatory mediators [54] and recruitment of activated T cells [55].

Complement activation in pemphigus is increased by interleukin (IL)-1-α and tumour necrosis factor (TNF)-α [56]. IL-1, thromboxane B_2 and leukotriene B_4 are present in blister fluid [54]. TNF-α and IL-6 are found in serum and lesional skin of pemphigus patients and can induce plasminogen activators and plasmin activity [57–60]. Treatment of pemphigus with infliximab, monoclonal antibody to TNF-α, produces rapid, albeit short-lived, reduction of blistering [61].

Proteinase inhibitors, antibodies to plasminogen activators and inhibitors of plasminogen activators can block the acantholysis induced by pemphigus antibodies in experimental models [57,62]. However, acantholysis induced by pemphigus antibodies occurs in plasminogen activator knockout mice [63] and plasminogen activator activity does not correlate well with disease activity in models of pemphigus [64], nor does proteolysis account for all the ultrastructural changes seen in epidermal cells damaged by pemphigus vulgaris antibodies [65].

References

1 Stanley JR. Defective cell–cell adhesion in the epidermis. *Ciba Found Symp* 1995; **189**: 107–20; discussion 20–3, 74–6.

2 Amagai M, Klaus-Kovtun V, Stanley JR. Autoantibodies against a novel epithelial cadherin in pemphigus vulgaris, a disease of cell adhesion. *Cell* 1991; **67**: 869–77.

3 Amagai M, Karpati S, Prussick R *et al.* Autoantibodies against the amino-terminal cadherin-like binding domain of pemphigus vulgaris antigen are pathogenic. *J Clin Invest* 1992; **90**: 919–26.

4 Karpati S, Amagai M, Prussick R *et al.* Pemphigus vulgaris antigen, a desmoglein type of cadherin, is localized within keratinocyte desmosomes. *J Cell Biol* 1993; **122**: 409–15.

5 Boulinguez S, Bedane C, Cadilhac H *et al.* Ultrastructural localisation of pemphigus vulgaris and pemphigus foliaceus antigens by indirect immunoelectron microscopy. Apropos of 7 cases. *Ann Dermatol Venereol* 1995; **122**: 417–21.

6 Iwatsuki K, Harada H, Zhang JZ *et al.* Regulation of pemphigus and desmosomal antigen expression by keratinocyte differentiation. *Dermatology* 1994; **189** (Suppl. 1): 67–71.

7 Hashimoto T, Amagai M, Garrod DR *et al.* Immunofluorescence and immunoblot studies on the reactivity of pemphigus vulgaris and pemphigus foliaceus sera with desmoglein 3 and desmoglein 1. *Epithelial Cell Biol* 1995; **4**: 63–9.

8 Shimizu H, Masunaga T, Ishiko A *et al.* Pemphigus vulgaris and pemphigus foliaceus sera show an inversely graded binding pattern to extracellular regions of desmosomes in different layers of human epidermis. *J Invest Dermatol* 1995; **105**: 153–9.

9 Amagai M, Koch PJ, Nishikawa T *et al.* Pemphigus vulgaris antigen (desmoglein 3) is localized in the lower epidermis, the site of blister formation in patients. *J Invest Dermatol* 1996; **106**: 351–5.

10 Ioannides D, Hytiroglou P, Phelps RG *et al.* Regional variation in the expression of pemphigus foliaceus, pemphigus erythematosus, and pemphigus vulgaris antigens in human skin. *J Invest Dermatol* 1991; **96**: 159–61.

11 Shirakata Y, Amagai M, Hanakawa Y *et al.* Lack of mucosal involvement in pemphigus foliaceus may be due to low expression of desmoglein 1. *J Invest Dermatol* 1998; **110**: 76–8.

12 Burge SM, Wilson CL, Dean D *et al.* An immunohistological study of desmosomal components in pemphigus. *Br J Dermatol* 1993; **128**: 363–70.

13 Ishii K, Amagai M, Hall RP *et al.* Characterization of autoantibodies in pemphigus using antigen-specific enzyme-linked immunosorbent assays with baculovirus-expressed recombinant desmogleins. *J Immunol* 1997; **159**: 2010–7.

14 Ding X, Aoki V, Mascaro JM Jr *et al.* Mucosal and mucocutaneous (generalized) pemphigus vulgaris show distinct autoantibody profiles. *J Invest Dermatol* 1997; **109**: 592–6.

15 Amagai M, Tsunoda K, Zillikens D *et al.* The clinical phenotype of pemphigus is defined by the anti-desmoglein autoantibody profile. *J Am Acad Dermatol* 1999; **40**: 167–70.

16 Miyagawa S, Amagai M, Iida T *et al.* Late development of antidesmoglein 1 antibodies in pemphigus vulgaris: correlation with disease progression. *Br J Dermatol* 1999; **141**: 1084–7.

17 Ishii K, Amagai M, Ohata Y *et al.* Development of pemphigus vulgaris in a patient with pemphigus foliaceus: antidesmoglein antibody profile shift confirmed by enzyme-linked immunosorbent assay. *J Am Acad Dermatol* 2000; **42**: 859–61.

18 Sami N, Bhol KC, Ahmed AR. Diagnostic features of pemphigus vulgaris in patients with pemphigus foliaceus: detection of both autoantibodies, long-term follow-up and treatment responses. *Clin Exp Immunol* 2001; **125**: 492–8.

19 Komai A, Amagai M, Ishii K *et al.* The clinical transition between pemphigus foliaceus and pemphigus vulgaris correlates well with the changes in autoantibody profile assessed by an enzyme-linked immunosorbent assay. *Br J Dermatol* 2001; **144**: 1177–82.

20 Tsuji Y, Kawashima T, Yokota K *et al.* Clinical and serological transition from pemphigus vulgaris to pemphigus foliaceus demonstrated by desmoglein ELISA system. *Arch Dermatol* 2002; **138**: 95–6.

21 Harman KE, Gratian MJ, Shirlaw PJ *et al.* The transition of pemphigus vulgaris into pemphigus foliaceus: a reflection of changing desmoglein 1 and 3 autoantibody levels in pemphigus vulgaris. *Br J Dermatol* 2002; **146**: 684–7.

22 Yoshida K, Takae Y, Saito H *et al.* Cutaneous type pemphigus vulgaris: a rare clinical phenotype of pemphigus. *J Am Acad Dermatol* 2005; **52**: 839–45.

23 Herrero-Gonzalez JE, Mascaro JM Jr, Iranzo P *et al.* Atypical pemphigus: discordance between clinicopathological findings and the antigenic profile in four cases. *J Cutan Pathol* 2006; **33**: 502–7.

24 Olszewska M, Gerlicz Z, Blaszczyk M. Cutaneous pemphigus vulgaris. *J Eur Acad Dermatol Venereol* 2007; **21**: 698–9.

25 Weitz D, Bystryn JC. Frequency of shifts over time in the profile of antidesmoglein antibodies in pemphigus vulgaris. *Arch Dermatol* 2007; **143**: 1073–4.

26 Ding X, Diaz LA, Fairley JA *et al.* The anti-desmoglein 1 autoantibodies in pemphigus vulgaris sera are pathogenic. *J Invest Dermatol* 1999; **112**: 739–43.

27 Harman KE, Gratian MJ, Bhogal BS *et al.* A study of desmoglein 1 autoantibodies in pemphigus vulgaris: racial differences in frequency and the association with a more severe phenotype. *Br J Dermatol* 2000; **143**: 343–8.

28 Fitzpatrick R, Newcomer R. Correlation of disease activity and antibody titres in pemphigus. *Arch Dermatol* 1980; **116**: 285–90.

29 Harman KE, Seed PT, Gratian MJ *et al.* The severity of cutaneous and oral pemphigus is related to desmoglein 1 and 3 antibody levels. *Br J Dermatol* 2001; **144**: 775–80.

30 Cheng SW, Amagai M, Nishikawa T. Monitoring disease activity in pemphigus with enzyme-linked immunosorbent assay using recombinant desmogleins 1 and 3. *Br J Dermatol* 2002; **147**: 261–5.

31 Ruach M, Ohel G, Rahav D *et al.* Pemphigus vulgaris and pregnancy. *Obstet Gynecol Surv* 1995; **50**: 755–60.

32 Anhalt GJ, Labib RS, Voorhees JJ *et al.* Induction of pemphigus in neonatal mice by passive transfer of IgG from patients with the disease. *N Engl J Med* 1982; **306**: 1189–96.

33 Amagai M, Hashimoto T, Shimizu N *et al.* Absorption of pathogenic autoantibodies by the extracellular domain of pemphigus vulgaris antigen (Dsg3) produced by baculovirus. *J Clin Invest* 1994; **94**: 59–67.

34 Mahoney MG, Wang Z, Rothenberger K *et al.* Explanations for the clinical and microscopic localization of lesions in pemphigus foliaceus and vulgaris. *J Clin Invest* 1999; **103**: 461–8.

35 Hertl M. Humoral and cellular autoimmunity in autoimmune bullous skin disorders. *Int Arch Allergy Immunol* 2000; **122**: 91–100.

36 Bhol K, Mohimen A, Ahmed AR. Correlation of subclasses of IgG with disease activity in pemphigus vulgaris. *Dermatology* 1994; **189** (Suppl. 1): 85–9.

37 Bhol K, Natarajan K, Nagarwalla N *et al.* Correlation of peptide specificity and IgG subclass with pathogenic and nonpathogenic autoantibodies in pemphigus vulgaris: a model for autoimmunity. *Proc Natl Acad Sci USA* 1995; **92**: 5239–43.

38 Tsunoda K, Ota T, Aoki M *et al.* Induction of pemphigus phenotype by a mouse monoclonal antibody against the amino-terminal adhesive interface of desmoglein 3. *J Immunol* 2003; **170**: 2170–8.

39 Muller R, Svoboda V, Wenzel E *et al.* IgG reactivity against non-conformational NH-terminal epitopes of the desmoglein 3 ectodomain relates to clinical activity and phenotype of pemphigus vulgaris. *Exp Dermatol* 2006; **15**: 606–14.

40 Dmochowski M, Hashimoto T, Garrod DR *et al.* Desmocollins I and II are recognized by certain sera from patients with various types of pemphigus, particularly Brazilian pemphigus foliaceus. *J Invest Dermatol* 1993; **100**: 380–4.

41 Hashimoto T, Amagai M, Watanabe K *et al.* A case of pemphigus vulgaris showing reactivity with pemphigus antigens (Dsg1 and Dsg3) and desmocollins. *J Invest Dermatol* 1995; **104**: 541–4.

42 Evangelista F, Dasher DA, Diaz LA *et al.* E-cadherin is an additional immunological target for pemphigus autoantibodies. *J Invest Dermatol* 2008; **128**: 1710–8.

43 Cozzani E, Dal Bello MG, Mastrogiacomo A *et al.* Antidesmoplakin antibodies in pemphigus vulgaris. *Br J Dermatol* 2006; **154**: 624–8.

44 Nguyen VT, Ndoye A, Shultz LD *et al.* Antibodies against keratinocyte antigens other than desmogleins 1 and 3 can induce pemphigus vulgaris-like lesions. *J Clin Invest* 2000; **106**: 1467–79.

45 Nguyen VT, Arredondo J, Chernyavsky AI *et al.* Pemphigus vulgaris acantholysis ameliorated by cholinergic agonists. *Arch Dermatol* 2004; **140**: 327–34.

46 Stanley JR, Nishikawa T, Diaz LA *et al.* Pemphigus: is there another half of the story? *J Invest Dermatol* 2001; **116**: 489–90.

47 Amagai M, Ahmed AR, Kitajima Y *et al.* Are desmoglein autoantibodies essential for the immunopathogenesis of pemphigus vulgaris, or just 'witnesses of disease'? *Exp Dermatol* 2006; **15**: 815–31.

48 Lever W. *Pemphigus and Pemphigoid*. Springfield: Thomas, 1965.

49 Berkowitz P, Hu P, Warren S *et al.* p38MAPK inhibition prevents disease in pemphigus vulgaris mice. *Proc Natl Acad Sci USA* 2006; **103**: 12855–60.

50 Frusic-Zlotkin M, Pergamentz R, Michel B *et al.* The interaction of pemphigus autoimmunoglobulins with epidermal cells: activation of the fas apoptotic pathway and the use of caspase activity for pathogenicity tests of pemphigus patients. *Ann N Y Acad Sci* 2005; **1050**: 371–9.

51 Kawana S, Geoghegan WD, Jordon RE *et al.* Deposition of the membrane attack complex of complement in pemphigus vulgaris and pemphigus foliaceus skin. *J Invest Dermatol* 1989; **92**: 588–92.

52 Anhalt GJ, Till GO, Diaz LA *et al.* Defining the role of complement in experimental pemphigus vulgaris in mice. *J Immunol* 1986; **137**: 2835–40.

53 Schiltz JR, Michel B. Production of epidermal acantholysis in normal human skin in vitro by the IgG fraction from pemphigus serum. *J Invest Dermatol* 1976; **67**: 254–60.

54 Grando SA, Glukhenky BT, Drannik GN *et al.* Mediators of inflammation in blister fluids from patients with pemphigus vulgaris and bullous pemphigoid. *Arch Dermatol* 1989; **125**: 925–30.

55 Zillikens D, Ambach A, Zentner A *et al.* Evidence for cell-mediated immune mechanisms in the pathology of pemphigus. *Br J Dermatol* 1993; **128**: 636–43.

56 Feliciani C, Toto P, Amerio P. In vitro C3 mRNA expression in Pemphigus vulgaris: complement activation is increased by IL-1alpha and TNF-alpha. *J Cutan Med Surg* 1999; **3**: 140–4.

57 Morioka S, Lazarus G, Jensen P. Involvement of urokinase type plasminogen activator in acantholysis induced by pemphigus IgG. *J Invest Dermatol* 1987; **89**: 474–7.

58 Reinhartz J, Naher H, Mai H *et al.* Plasminogen activation in lesional skin of pemphigus vulgaris type Neumann. *Arch Dermatol Res* 1993; **284**: 432–9.

59 Feliciani C, Toto P, Wang B *et al.* Urokinase plasminogen activator mRNA is induced by IL-1alpha and TNF-alpha in in vitro acantholysis. *Exp Dermatol* 2003; **12**: 466–71.

60 Lopez-Robles E, Avalos-Diaz E, Vega-Memije E *et al.* TNFalpha and IL-6 are mediators in the blistering process of pemphigus. *Int J Dermatol* 2001; **40**: 185–8.

61 Jacobi A, Shuler G, Hertl M. Rapid control of therapy-refractory pemphigus vulgaris by treatment with the tumour necrosis factor-alpha inhibitor infliximab. *Br J Dermatol* 2005; **153**: 448–9.

62 Hashimoto K, Wun T-C, Baird J. Characterization of keratinocyte plasminogen activator inhibitors and demonstration of the prevention of pemphigus IgG induced acantholysis by a purified plasminogen activator inhibitor. *J Invest Dermatol* 1989; **92**: 310–5.

63 Mahoney MG, Wang ZH, Stanley JR. Pemphigus vulgaris and pemphigus foliaceus antibodies are pathogenic in plasminogen activator knockout mice. *J Invest Dermatol* 1999; **113**: 22–5.

64 Anhalt GJ, Patel HP, Labib RS *et al.* Dexamethasone inhibits plasminogen activator activity in experimental pemphigus in vivo but does not block acantholysis. *J Immunol* 1986; **136**: 113–7.

65 Takahashi Y, Patel HP, Labib RS *et al.* Experimentally induced pemphigus vulgaris in neonatal BALB/c mice: a time-course study of clinical, immunologic, ultrastructural, and cytochemical changes. *J Invest Dermatol* 1985; **84**: 41–6.

Pathology. The earliest histological changes consist of intercellular oedema with loss of intercellular attachments in the basal layer. Suprabasal epidermal cells separate from the basal cells to form clefts and blisters. Basal cells remain attached to the basement membrane but separate from one another and stand like a 'row of

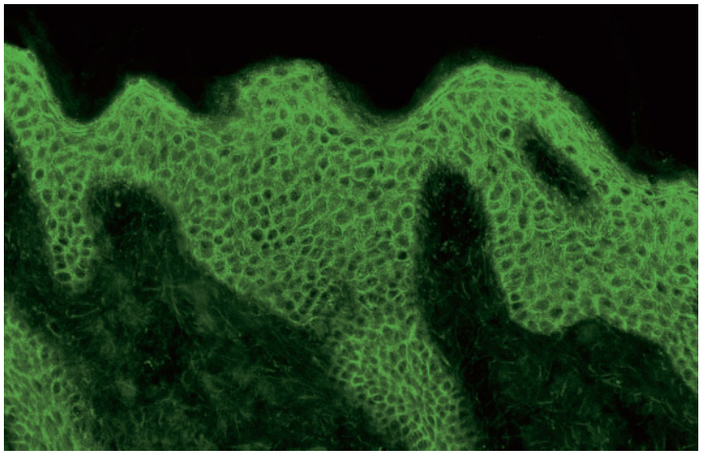


Fig. 40.2 Immunofluorescence showing intercellular IgG throughout the epidermis of a patient with pemphigus vulgaris.

tombstones' on the floor of the blister. Blister cavities contain some acantholytic cells. A smear taken from the base of a blister or an oral erosion (Tzank preparation) contains acantholytic cells. Clefting may extend into the walls of adnexae. Blistering is preceded by eosinophilic spongiosis in some cases. The superficial dermis has a mild, superficial, mixed inflammatory infiltrate which includes some eosinophils [1].

Electron microscopy has shown that widening of the intercellular space is followed by splitting of the desmosome junctions. When the cells separate from each other, the intracellular cytokeratin tonofilaments retract around the nucleus and the desmosomal plaques disappear. The attachment of basal cells to the basement membrane is not affected [2,3].

The diagnosis of pemphigus is confirmed by direct immunofluorescence which shows IgG deposited on the surface of keratinocytes throughout the epidermis, in and around lesions (Fig. 40.2). IgG1 and IgG4 are the most common subclasses; C3, IgM and IgA are present less frequently than IgG. Direct immunofluorescence may be the most sensitive method for diagnosing oral pemphigus [4].

Circulating pemphigus autoantibodies are detected by indirect immunofluorescence in over 80% of patients. The use of more than one substrate improves sensitivity, oesophageal substrate being preferable for the detection of antibodies to desmoglein-3 [5]. A disadvantage of immunofluorescence methods is the difficulty in distinguishing pemphigus vulgaris from pemphigus foliaceus on staining pattern alone. Recombinant desmogleins (DG1 and DG3) have been used recently to develop a sensitive and specific ELISA assay for serodiagnosis of pemphigus [6,7]. Using ELISA over 95% of pemphigus vulgaris patients have detectable desmoglein-3 antibodies and around 50% have desmoglein-1 antibodies. In appropriate dilutions, antidesmoglein-1 ELISA assays can be used to monitor disease activity [8].

Antibodies may be detected in patients without pemphigus [9]. Pemphigus-like circulating intercellular antibodies have been reported in conditions such as thermal burns [10], toxic epidermal necrolysis [9], penicillin reactions [11], staphylococcal scalded skin syndrome [12] and in first-degree relatives of relatives of pemphigus patients [13,14].

References

1 Lever W. *Pemphigus and Pemphigoid*. Springfield: Thomas, 1965.
2 Hashimoto K, Lever WF. An ultrastructural study of cell junctions in pemphigus vulgaris. *Arch Dermatol* 1970; **101**: 287–98.
3 Takahashi Y, Patel HP, Labib RS *et al.* Experimentally induced pemphigus vulgaris in neonatal BALB/c mice: a time-course study of clinical, immunologic, ultrastructural, and cytochemical changes. *J Invest Dermatol* 1985; **84**: 41–6.
4 Helander SD, Rogers RS III. The sensitivity and specificity of direct immunofluorescence testing in disorders of mucous membranes. *J Am Acad Dermatol* 1994; **30**: 65–75.
5 Harman KE, Gratian MJ, Bhogal BS *et al.* The use of two substrates to improve the sensitivity of indirect immunofluorescence in the diagnosis of pemphigus. *Br J Dermatol* 2000; **142**: 1135–9.
6 Ishii K, Amagai M, Hall RP *et al.* Characterization of autoantibodies in pemphigus using antigen-specific enzyme-linked immunosorbent assays with baculovirus-expressed recombinant desmogleins. *J Immunol* 1997; **159**: 2010–7.
7 Amagai M, Komai A, Hashimoto T *et al.* Usefulness of enzyme-linked immunosorbent assay using recombinant desmogleins 1 and 3 for serodiagnosis of pemphigus. *Br J Dermatol* 1999; **140**: 351–7.
8 Cheng SW, Amagai M, Nishikawa T. Monitoring disease activity in pemphigus with enzyme-linked immunosorbent assay using recombinant desmogleins 1 and 3. *Br J Dermatol* 2002; **147**: 261–5.
9 Ahmed A, Workman A. Anti-intercellular substance antibody: presence in serum of 14 patients without pemphigus. *Arch Dermatol* 1983; **119**: 17–21.
10 Thivolet J, Beyvin A. Recherche par immunofluorescence d'anticorps seriques vis-vis des constituants de l'epiderme chez les brutes. *Experientia* 1968; **24**: 945–6.
11 Fellner MJ, Mark AS. Penicillin- and ampicillin-induced pemphigus vulgaris. *Int J Dermatol* 1980; **19**: 392–3.
12 Anzai H, Stanley JR, Amagai M. Production of low titers of anti-desmoglein 1 IgG autoantibodies in some patients with staphylococcal scalded skin syndrome. *J Invest Dermatol* 2006; **126**: 2139–41.
13 Ahmed AR, Mohimen A, Yunis EJ *et al.* Linkage of pemphigus vulgaris antibody to the major histocompatibility complex in healthy relatives of patients. *J Exp Med* 1993; **177**: 419–24.
14 Kricheli D, David M, Frusic-Zlotkin M *et al.* The distribution of pemphigus vulgaris-IgG subclasses and their reactivity with desmoglein 3 and 1 in pemphigus patients and their first-degree relatives. *Br J Dermatol* 2000; **143**: 337–42.

Clinical features of pemphigus vulgaris. Nearly all patients have mucosal lesions, and pemphigus vulgaris presents with oral lesions in 50 to 70% of patients. These may precede cutaneous lesions by months or be the only manifestation of the disease [1–3]. Intact bullae are rare in the mouth. More commonly patients have ill-defined, irregularly shaped buccal or palatal erosions, which are slow to heal (Fig. 40.3). The erosions extend peripherally with shedding of the epithelium [4]. Other mucosal surfaces may be involved, including the conjunctiva [5], nasal, pharynx [6], larynx, oesophagus [7,8], urethra, vulva [9] and cervix [10].

Most patients develop cutaneous lesions. Involvement may rarely remain localized to one site [11] but more commonly becomes widespread. The disease has a predilection for the scalp, face, axillae, groins and pressure points (Figs 40.4 & 40.5). Flaccid blisters filled with clear fluid either arise on normal skin or an erythematous base. The contents soon become turbid or the blisters rupture, producing painful erosions which extend at the edges as more epidermis is lost. At this stage, firm sliding pressure with a finger will separate normal-looking epidermis from dermis, producing an erosion—the Nikolsky sign. The Nikolsky sign is positive in pemphigus and more rarely in toxic epidermal necrolysis. Blisters can also be extended by vertical pressure, a phenomenon which occurs in many blistering diseases. Healing occurs without

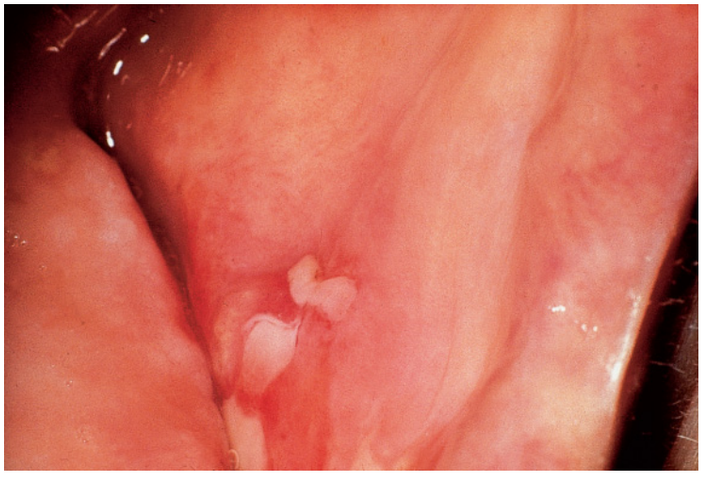


Fig. 40.3 Pemphigus vulgaris. Erosions in mouth. (Courtesy of Dr R.J. Pye, Addenbrooke's Hospital, Cambridge, UK.)



Fig. 40.5 Pemphigus vulgaris. Flaccid bullae and erosions on the forearm. (Courtesy of Dr R.J. Pye, Addenbrooke's Hospital, Cambridge, UK.)



Fig. 40.4 Pemphigus vulgaris. Erosions and healing areas on the back. (Courtesy of Dr R.J. Pye, Addenbrooke's Hospital, Cambridge, UK.)

scarring but pigmentary change and acanthomas may occur in resolving lesions [12].

Lesions in skin folds readily form vegetating granulations, and flexural pemphigus vulgaris merges with its variant pemphigus vegetans. Nail dystrophies, acute paronychia and subungual haematomas have been observed in pemphigus [13,14]. Rare patients are described with typical suprabasal pemphigus vulgaris type lesions but confined to the skin and sparing the mucosae despite antibodies to desmoglein-1 and 3 [15,16]. It is unknown whether these are transient presentations capable of clinical or serological evolution.

Severe pemphigus in pregnancy may be associated with fetal prematurity and death, but it is difficult to separate the effects of treatment from those of the disease. Generally, the baby is healthy [17] although neonatal pemphigus may occur with mucosal or mucocutaneous lesions which, generally, are short-lived [18–20].

Prognosis. The severity and natural history are variable, but before treatment with Contico steroids most patients with pemphigus vulgaris died [21]. Treatment with systemic steroids has reduced the mortality to between 5% and 15% [2,22], but some of these patients succumb to the complications of therapy. Morbidity and mortality are related to the extent of disease, the maximum dose of prednisolone required to induce remission and the presence of co-morbidities [2,21,23–25]. Disease activity generally decreases with time and most relapses occur in the first 2 years after diagnosis [26]. The outlook is worse in Jews [22] and in older patients [25].

References

1 Krain LS. Pemphigus. Epidemiologic and survival characteristics of 59 patients, 1955–1973. *Arch Dermatol* 1974; **110**: 862–5.

2 Rosenberg FR, Sanders S, Nelson CT. Pemphigus: a 20-year review of 107 patients treated with corticosteroids. *Arch Dermatol* 1976; **112**: 962–70.

3 Ryan JG. Pemphigus. A 20-year survey of experience with 70 cases. *Arch Dermatol* 1971; **104**: 14–20.

4 Zegarelli DJ, Zegarelli EV. Intraoral pemphigus vulgaris. *Oral Surg Oral Med Oral Pathol* 1977; **44**: 384–93.

5 Hodak E, Kremer I, David M *et al.* Conjunctival involvement in pemphigus vulgaris: a clinical, histopathological and immunofluorescence study. *Br J Dermatol* 1990; **123**: 615–20.

6 Hale EK, Bystryn JC. Laryngeal and nasal involvement in pemphigus vulgaris. *J Am Acad Dermatol* 2001; **44**: 609–11.

7 Lurie R, Trattner A, David M *et al.* Esophageal involvement in pemphigus vulgaris: report of two cases and review of the literature. *Dermatologica* 1990; **181**: 233–6.

8 Trattner A, Lurie R, Leiser A *et al.* Esophageal involvement in pemphigus vulgaris: a clinical, histologic, and immunopathologic study. *J Am Acad Dermatol* 1991; **24**: 223–6.

9 Marren P, Wojnarowska F, Venning V *et al.* Vulvar involvement in autoimmune bullous diseases. *J Reprod Med* 1993; **38**: 101–7.

10 Sagher F, Bercovici B, Romem R. Nikolsky sign on cervix uteri in pemphigus. *Br J Dermatol* 1974; **90**: 407–11.
11 Lapiere K, Caers S, Lambert J. A case of long-lasting localized pemphigus vulgaris of the scalp. *Dermatology* 2004; **209**: 162–3.
12 Yesudian PD, Krishnan SG, Jayaraman M *et al.* Postpemphigus acanthomata: a sign of clinical activity? *Int J Dermatol* 1997; **36**: 194–6.
13 Berker DD, Dalziel K, Dawber RP *et al.* Pemphigus associated with nail dystrophy. *Br J Dermatol* 1993; **129**: 461–4.
14 Kolivras A, Gheeraert P, Andre J. Nail destruction in pemphigus vulgaris. *Dermatology* 2003; **206**: 351–2.
15 Nagasaka A, Matsue H, Miyahara A *et al.* Pemphigus vulgaris with no mucosal lesions showing pemphigus-foliaceus-like skin manifestations: Is there a 'cutaneous type' of pemphigus vulgaris? *Dermatology* 2005; **211**: 372–4.
16 Yoshida K, Takae Y, Saito H *et al.* Cutaneous type pemphigus vulgaris: a rare clinical phenotype of pemphigus. *J Am Acad Dermatol* 2005; **52**: 839–45.
17 Goldberg NS, DeFeo C, Kirshenbaum N. Pemphigus vulgaris and pregnancy: risk factors and recommendations. *J Am Acad Dermatol* 1993; **28**: 877–9.
18 Hern S, Vaughan Jones SA, Setterfield J *et al.* Pemphigus vulgaris in pregnancy with favourable foetal prognosis. *Clin Exp Dermatol* 1998; **23**: 260–3.
19 Chowdhury MM, Natarajan S. Neonatal pemphigus vulgaris associated with mild oral pemphigus vulgaris in the mother during pregnancy. *Br J Dermatol* 1998; **139**: 500–3.
20 Bjarnason B, Flosadottir E. Childhood, neonatal, and stillborn pemphigus vulgaris. *Int J Dermatol* 1999; **38**: 680–8.
21 Ahmed AR, Moy R. Death in pemphigus. *J Am Acad Dermatol* 1982; **7**: 221–8.
22 Carson PJ, Hameed A, Ahmed AR. Influence of treatment on the clinical course of pemphigus vulgaris. *J Am Acad Dermatol* 1996; **34**: 645–52.
23 Savin JA. Some factors affecting prognosis in pemphigus vulgaris and pemphigoid. *Br J Dermatol* 1981; **104**: 415–20.
24 Mourellou O, Chaidemenos GC, Koussidou T *et al.* The treatment of pemphigus vulgaris. Experience with 48 patients seen over an 11-year period. *Br J Dermatol* 1995; **133**: 83–7.
25 Stamm C, Thivolet J. Weaning of systemic steroid treatment in pemphigus: a twelve year retrospective study on 270 French patients. *Eur J Dermatol* 1995; **5**: 664–70.
26 Kyriakis KP, Tosca AD. Epidemiologic observations on the natural course of pemphigus vulgaris. *Int J Dermatol* 1998; **37**: 215–9.

Pemphigus vegetans

Definition. Pemphigus vegetans is a rare variant of pemphigus vulgaris which is characterized by vegetating erosions, primarily in flexures. Two subtypes are recognized: Neumann pemphigus vegetans and Hallopeau pemphigus vegetans. These may be considered to form a clinical spectrum from the severe Neumann type to the mild Hallopeau type [1].

Aetiology/pathogenesis. Antibodies react with the 130 kDa pemphigus vulgaris antigen and possibly other antigens in both types of pemphigus vegetans [2–6]. Antibodies in the Hallopeau type also react with desmocollins 1 and 2 [7]. Complement fixation might be responsible for the marked cutaneous infiltration of neutrophils and eosinophils, which is so typical in pemphigus vegetans [3].

Pathology. The vegetating lesions are hyperkeratotic, papillomatous and acanthotic. Some suprabasal clefts may contain eosinophils but few acantholytic cells are present. Intraepidermal eosinophilic abscesses may be present in older lesions. Early lesions in the Neumann type show suprabasal acantholysis and intraepidermal vesicles without eosinophils. Eosinophilic spongiosis or eosinophilic microabscesses are common in the early pustular lesions of the Hallopeau type [8]. The dermis contains a heavy infiltrate of lymphocytes and eosinophils with few neutrophils.



Fig. 40.6 Pemphigus vegetans. Vegetations with no evidence of blistering. (Courtesy of Dr R.J. Pye, Addenbrooke's Hospital, Cambridge, UK.)

Direct immunofluorescence demonstrates intercellular IgG sometimes with C3. Circulating intercellular antibodies can be detected in most patients by indirect immunofluorescence.

Clinical features. The disease affects chiefly middle-aged adults. Involvement of the oral mucosa is almost invariable. Lesions are primarily flexural, although vegetations may occur at any site [8]. The subdivision into Neumann and Hallopeau types is mainly of historical interest.

Neumann type (Fig. 40.6). Vesicles and bullae rupture to form hypertrophic granulating erosions, which bleed easily. The lesions evolve into vegetating masses exuding serum and pus. The edges are studded with small pustules. Erosions at the edge of the lesions induce new vegetations, which eventually become dry, hyperkeratotic and fissured.

Hallopeau type (synonyms pyodermite végétante, pyoderma vegetans). Pustules rather than vesicles characterize early lesions but these soon progress to vegetating plaques. As in the Neumann type, the vegetations are studded with pustules. In one patient, pemphigus foliaceus preceded the onset of pemphigus vegetans of Hallopeau [9].

Prognosis. The course of the Neumann type of pemphigus vegetans is similar to pemphigus vulgaris but is generally prolonged. The Hallopeau type is more benign and spontaneous remission is possible.

References

1 Ahmed AR, Blose DA. Pemphigus vegetans. Neumann type and Hallopeau type. *Int J Dermatol* 1984; **23**: 135–41.
2 Parodi A, Stanley JR, Ciaccio M *et al.* Epidermal antigens in pemphigus vegetans. Report of a case. *Br J Dermatol* 1988; **119**: 799–802.
3 Hashizume H, Iwatsuki K, Takigawa M. Epidermal antigens and complement-binding anti-intercellular antibodies in pemphigus vegetans, Hallopeau type. *Br J Dermatol* 1993; **129**: 739–43.

4 Ohata Y, Komiya H, Kawahara Y *et al.* A case of Neumann type pemphigus vegetans showing reactivity with the 130 kD pemphigus vulgaris antigen. *Acta Derm Venereol* 1996; **76**: 169–70.
5 Ohata Y, Hashimoto T, Nishikawa T. Comparative study of autoantigens for various bullous skin diseases by immunoblotting using different dermo-epidermal separation techniques. *Clin Exp Dermatol* 1995; **20**: 454–8.
6 Arnold J, Rose C, Amagai M *et al.* Pemphigus vegetans with autoantibodies directed against recombinant desmoglein 3. *Aktuelle Dermatologie* 2000; **26**: 241–4.
7 Hashimoto K, Hashimoto T, Higashiyama M *et al.* Detection of anti-desmocollins I and II autoantibodies in two cases of Hallopeau type pemphigus vegetans by immunoblot analysis. *J Dermatol Sci* 1994; **7**: 100–6.
8 Lever W. *Pemphigus and Pemphigoid*. Springfield: Thomas, 1965.
9 Cecchi R, Tuci F, Brunetti L *et al.* Pemphigus vegetans of Hallopeau following pemphigus foliaceus. *J Eur Acad Dermatol Venereol* 1994; **3**: 67–70.

Differential diagnosis of pemphigus vulgaris and pemphigus vegetans. Patients with mucosal lesions present to dental surgeons, oral surgeons and gynaecologists. Erosions may simulate acute herpetic stomatitis, erythema multiforme, aphthous ulcers or bullous lichen planus. Bullae are transient in the mouth and biopsies of erosions may not be diagnostic. Smears taken from the base of an erosion may show acantholytic cells (Tzank preparation). Direct immunofluorescence is the most accurate way to diagnose mucosal pemphigus [1]. Specimens may be posted to a suitable laboratory in Michels medium if facilities for snap-freezing and storage of the tissues are not available [2]. Indirect immunofluorescence may be a useful confirmatory test.

The diagnosis is less difficult when the patients have cutaneous blisters or erosions. Blisters in pemphigoid are tense and may be haemorrhagic. A Tzank preparation taken from the base of a blister in pemphigoid has no acantholytic cells. The diagnosis of pemphigoid is confirmed histologically by showing subepidermal bullae with immunoreactants in the basement membrane zone.

Acute erythema multiforme is a short-lived disorder that may blister, but is easily differentiated from pemphigus histologically.

Blistering in dermatitis herpetiformis is subepidermal and direct immunofluorescence of involved and uninvolved skin shows a granular deposition of IgA in the basement membrane zone.

Vegetating, pustular lesions in flexures must be differentiated from chronic infections or Hailey–Hailey disease (benign familial chronic pemphigus). Vegetating plaques mimicking pemphigus vegetans have been seen in IgA pemphigus [3] and paraneoplastic pemphigus [4]. The hyperkeratotic lesions of chronic pemphigus vegetans may simulate cutaneous tumours. The histology may be misinterpreted if immunofluorescence studies are not performed [5].

The histological differential includes Darier's disease, Hailey–Hailey disease (benign familial chronic pemphigus) and transient acantholytic dermatosis (Grover's disease). These conditions have distinctive clinical features in addition to negative immunofluorescence studies. Eosinophilic spongiosis may be an early histological manifestation of either pemphigus or bullous pemphigoid [6]. Immunofluorescence studies are needed to confirm the diagnosis.

References

1 Helander SD, Rogers RS III. The sensitivity and specificity of direct immunofluorescence testing in disorders of mucous membranes. *J Am Acad Dermatol* 1994; **30**: 65–75.
2 Jones SAV, Sales J, McGrath J *et al.* A retrospective analysis of tissue fixed immunoreactants from skin biopsies maintained in Michel's medium. *Dermatology* 1994; **189**: 131–2.
3 Weston WL, Friednash M, Hashimoto T *et al.* A novel childhood pemphigus vegetans variant of intraepidermal neutrophilic IgA dermatosis. *J Am Acad Dermatol* 1998; **38**: 635–8.
4 Sapadin AN, Anhalt GJ. Paraneoplastic pemphigus with a pemphigus vegetans-like plaque as the only cutaneous manifestation. *J Am Acad Dermatol* 1998; **39**: 867–71.
5 Venning V, Burge S, Dalziel K *et al.* Pemphigus vegetans masquerading as multiple squamous cell carcinoma. *Br J Dermatol* 1990; **123** (Suppl. 37): 112–3.
6 Crotty C, Pittelkow M, Muller SA. Eosinophilic spongiosis: a clinicopathologic review of seventy-one cases. *J Am Acad Dermatol* 1983; **8**: 337–43.

Treatment of pemphigus vulgaris and pemphigus vegetans. The introduction of corticosteroids has greatly reduced mortality, but a significant morbidity remains [1]. Numerous steroid regimens, with and without immunosuppressive agents, have been recommended but randomized, controlled trials for regimens are few. Treatment has been the subject of a number of reviews [2–4].

Monitoring activity of disease

In the acute phase the progress of the disease should be evaluated clinically. Once blistering stops and erosions heal, changes in the titre of circulating pemphigus antibody may help in guiding the dose of steroids [5,6]. Direct immunofluorescence studies of normal skin have also been recommended to predict remission or relapse [6].

Topical therapy

Patients who present with oral disease and mild cutaneous involvement may remain in this localized phase for months. Potent topical or intralesional steroids may reduce the requirement for oral steroids. Topical anticholinergic gel (pilocarpine gel) is reported to help healing of oral erosions [7].Good oral hygiene, including treatment of periodontal disease, is important.

Opportunist infection is the major cause of death in patients with widespread blistering who are also immunosuppressed. Potassium permanganate and topical antiseptics may help reduce the risk of cutaneous infection, whilst topical nystatin, amphotericin or one of the imidazoles will reduce the risk of oral candida.

Systemic therapy

Corticosteroids. Prednisolone with an adjuvant is the preferred treatment for pemphigus vulgaris [3]. Prednisolone 1.0 to 1.5 mg/kg/day in combination with topical or intralesional steroids is sufficient to control disease in many patients. The dose should be titrated to the clinical response [8] but it is important to stop oral steroids when the disease is inactive rather than maintain patients on a homeopathic dose [9].

Patients with generalized disease may require more aggressive immunosuppression to suppress blistering, but the major difficulty in managing these patients is achieving a balance between the risks associated with high-dose steroid therapy and those of poorly controlled disease. High doses of prednisolone, 120–240 mg/day, have been recommended for severe pemphigus, but the risks are considerable [1,10,11]. Prednisolone 60–100 mg/day or IV pulses of either 1 g methylprednisolone or 100 mg dexamethasone are safer alternatives [9,12,13].

Adjunctive treatments. A number of immunosuppressive agents have been recommended as adjuncts to oral steroids [2,3,14]. Azathioprine is widely used in a dose of 2.5 mg/kg/day. The combination of prednisolone and azathioprine is more effective than prednisolone alone both in terms of mortality and remission [3,15,16]. One randomized, controlled trial of pemphigus treatment found azathioprine to be the most effective steroid-sparing agent, followed by cyclophosphamide (pulse therapy) and mycophenolate mofetil [17]. Another trial found azathioprine and mycophenolate mofetil to be equally effective [18]. Azathioprine may be an effective monotherapy in mild cases, although the therapeutic effect is delayed for 3 to 5 weeks.

Cyclophosphamide alone is not effective in pemphigus, but cyclophosphamide 1–3 mg/kg/day is an effective alternative to azathioprine in combination with steroids. The combination is more effective than steroids alone [3,14,19]. Monthly IV pulses of cyclophosphamide with dexamethasone combined with low-dose oral cyclophosphamide have been used with great success [12,16,20]. Remission was maintained with low doses of oral cyclophosphamide [12].

Mycophenolate mofetil (2 g/d) has been found helpful as a steroid sparing agent in some [21–23]. One randomized, controlled trial found mycophenolate mofetil to be a less effective adjunct than azathioprine [17], while another smaller trial found no difference in efficacy between the two [1].

Tetracycline in combination with prednisolone has been reported as useful in an uncontrolled study [24]. A small controlled study showed superiority over prednisolone and azathioprine [25]. Oral or intramuscular gold in addition to steroids reduces mortality and increases the number of patents in remission [3,14].

Ciclosporin alone is not helpful in the acute phase of the disease. Ciclosporin, 5 mg/kg/day, has been used in combination with steroids, particularly in patients with haematological abnormalities [14,26–28]. However, a comparative study found no advantage over prednisolone alone [29]. Topical ciclosporin mouthwash has been found to be helpful in severe oral pemphigus [30].

Dapsone has been advocated as an adjunct in some patients with mild disease [19,31]. A prospective, placebo-controlled study of dapsone as an adjunct with prednisolone showed a modest steroid-sparing effect [32].

Methotrexate is seldom used as there were concerns about toxicity with the high doses that were used [14]. One retrospective review of the literature suggested that methotrexate neither reduced mortality nor changed the number of patients in remission [3]. Others have found that moderate doses of methotrexate (10–17.5 mg/week) permitted withdrawal of prednisolone in steroid-dependent patients [33].

Depletion of B-lymphocytes using the anti-CD-20 monoclonal antibody rituximab has produced remission in some [34] but not all [35] patients with treatment-resistant disease. Life-threatening sepsis is a serious concern.

Removal of circulating antibodies by plasmapheresis [14] or by immunoadsorption [36,37] has induced remission, but concomitant immunosuppression with steroids or cyclophosphamide is needed to prevent a rebound increase in the synthesis of antibody. Sepsis is a serious complication.

Other therapies tried for resistant cases of pemphigus include PUVA and extracorporeal photophoresis [14]. High dose intravenous immunoglobulin (IVIg) is capable of inducing rapid remission but the benefit is short-lived [38,39]. IVIg has been reported as beneficial as a steroid-sparing agent [40]. Acetretin has been used in conjunction with prednisolone in pemphigus vegetans [41] and the TNF blockers infliximab [42] and etanercept [43] have also been reported as beneficial.

References

1 Rosenberg FR, Sanders S, Nelson CT. Pemphigus: a 20-year review of 107 patients treated with corticosteroids. *Arch Dermatol* 1976; **112**: 962–70.

2 Bystryn JC, Steinman NM. The adjuvant therapy of pemphigus. An update. *Arch Dermatol* 1996; **132**: 203–12.

3 Carson PJ, Hameed A, Ahmed AR. Influence of treatment on the clinical course of pemphigus vulgaris. *J Am Acad Dermatol* 1996; **34**: 645–52.

4 Dick SE, Werth VP. Pemphigus: a treatment update. *Autoimmunity* 2006; **39**: 591–9.

5 Cheng SW, Amagai M, Nishikawa T. Monitoring disease activity in pemphigus with enzyme-linked immunosorbent assay using recombinant desmogleins 1 and 3. *Br J Dermatol* 2002; **147**: 261–5.

6 O'Loughlin S, Goldman GC, Provost TT. Fate of pemphigus antibody following successful therapy. Preliminary evaluation of pemphigus antibody determinations to regulate therapy. *Arch Dermatol* 1978; **114**: 1769–72.

7 Iraji F, Yoosefi A. Healing effect of Pilocarpine gel 4% on skin lesions of pemphigus vulgaris. *Int J Dermatol* 2006; **45**: 743–6.

8 Chrysomallis F, Ioannides D, Teknetzis A *et al.* Treatment of oral pemphigus vulgaris. *Int J Dermatol* 1994; **33**: 803–7.

9 Stamm C, Thivolet J. Weaning of systemic steroid treatment in pemphigus: a twelve year retrospective study on 270 French patients. *Eurpean J Dermatol* 1995; **5**: 664–70.

10 Bystryn JC. Adjuvant therapy of pemphigus. *Arch Dermatol* 1984; **120**: 941–51.

11 Mourellou O, Chaidemenos GC, Koussidou T *et al.* The treatment of pemphigus vulgaris. Experience with 48 patients seen over an 11-year period. *Br J Dermatol* 1995; **133**: 83–7.

12 Pasricha JS, Khaitan BK, Raman RS *et al.* Dexamethasone-cyclophosphamide pulse therapy for pemphigus. *Int J Dermatol* 1995; **34**: 875–82.

13 Chryssomallis F, Dimitriades A, Chaidemenos GC *et al.* Steroid-pulse therapy in pemphigus vulgaris long term follow-up. *Int J Dermatol* 1995; **34**: 438–42.

14 Huilgol SC, Black MM. Management of the immunobullous disorders. II. Pemphigus. *Clin Exp Dermatol* 1995; **20**: 283–93.

15 Aberer W, Wolff-Schreiner EC, Stingl G *et al.* Azathioprine in the treatment of pemphigus vulgaris. A long-term follow-up. *J Am Acad Dermatol* 1987; **16**: 527–33.

16 Pandya AG, Sontheimer RD. Treatment of pemphigus vulgaris with pulse intravenous cyclophosphamide. *Arch Dermatol* 1992; **128**: 1626–30.

17 Chams-Davatchi C, Esmaili N, Daneshpazhooh M *et al.* Randomized controlled open-label trial of four treatment regimens for pemphigus vulgaris. *J Am Acad Dermatol* 2007; **57**: 622–8.

18 Beissert S, Werfel T, Frieling U *et al.* A comparison of oral methylprednisolone plus azathioprine or mycophenolate mofetil for the treatment of pemphigus. *Arch Dermatol* 2006; **142**: 1447–54.

19 Piamphongsant T, Ophaswongse S. Treatment of pemphigus. *Int J Dermatol* 1991; **30**: 139–46.

20 Kanwar AJ, Kaur S, Thami GP. Long-term efficacy of dexamethasone-cyclophosphamide pulse therapy in pemphigus. *Dermatology* 2002; **204**: 228–31.

21 Enk AH, Knop J. Mycophenolate is effective in the treatment of pemphigus vulgaris. *Arch Dermatol* 1999; **135**: 54–6.

22 Mimouni D, Anhalt GJ, Cummins DL *et al.* Treatment of pemphigus vulgaris and pemphigus foliaceus with mycophenolate mofetil. *Arch Dermatol* 2003; **139**: 739–42.

23 Powell AM, Albert S, Al Fares S *et al.* An evaluation of the usefulness of mycophenolate mofetil in pemphigus. *Br J Dermatol* 2003; **149**: 138–45.

24 Chaffins ML, Collison D, Fivenson DP. Treatment of pemphigus and linear IgA dermatosis with nicotinamide and tetracycline: a review of 13 cases. *J Am Acad Dermatol* 1993; **28**: 998–1000.

25 Calebotta A, Saenz AM, Gonzalez F *et al.* Pemphigus vulgaris: benefits of tetracycline as adjuvant therapy in a series of thirteen patients. *Int J Dermatol* 1999; **38**: 217–21.
26 Barthelemy H, Frappaz A, Cambazard F *et al.* Treatment of nine cases of pemphigus vulgaris with cyclosporine. *J Am Acad Dermatol* 1988; **18**: 1262–6.
27 Campolmi P, Bonan P, Lotti T *et al.* The role of cyclosporine A in the treatment of pemphigus erythematosus. *Int J Dermatol* 1991; **30**: 890–2.
28 Lapidoth M, David M, Ben-Amitai D *et al.* The efficacy of combined treatment with prednisone and cyclosporine in patients with pemphigus: preliminary study. *J Am Acad Dermatol* 1994; **30**: 752–7.
29 Ioannides D, Chrysomallis F, Bystryn JC. Ineffectiveness of cyclosporine as an adjuvant to corticosteroids in the treatment of pemphigus. *Arch Dermatol* 2000; **136**: 868–72.
30 Gooptu C, Staughton RC. Use of topical cyclosporin in oral pemphigus. *J Am Acad Dermatol* 1998; **38**: 860–1.
31 Basset N, Guillot B, Michel B *et al.* Dapsone as initial treatment in superficial pemphigus. Report of nine cases. *Arch Dermatol* 1987; **123**: 783–5.
32 Werth VP, Fivenson D, Pandya AG *et al.* Multicenter randomized, double-blind, placebo-controlled, clinical trial of dapsone as a glucocorticoid-sparing agent in maintenance-phase pemphigus vulgaris. *Arch Dermatol* 2008; **144**: 25–32.
33 Smith TJ, Bystryn JC. Methotrexate as an adjuvant treatment for pemphigus vulgaris. *Arch Dermatol* 1999; **135**: 1275–6.
34 Schmidt E, Seitz CS, Benoit S *et al.* Rituximab in autoimmune bullous diseases: mixed responses and adverse effects. *Br J Dermatol* 2007; **156**: 352–6.
35 Goh MS, McCormack C, Dinh HV *et al.* Rituximab in the adjuvant treatment of pemphigus vulgaris: a prospective open-label pilot study in five patients. *Br J Dermatol* 2007; **156**: 990–6.
36 Luftl M, Stauber A, Mainka A *et al.* Successful removal of pathogenic autoantibodies in pemphigus by immunoadsorption with a tryptophan-linked polyvinylalcohol adsorber. *Br J Dermatol* 2003; **149**: 598–605.
37 Shimanovich I, Herzog S, Schmidt E *et al.* Improved protocol for treatment of pemphigus vulgaris with protein A immunoadsorption. *Clin Exp Dermatol* 2006; **31**: 768–74.
38 Harman KE, Black MM. High-dose intravenous immune globulin for the treatment of autoimmune blistering diseases: an evaluation of its use in 14 cases. *Br J Dermatol* 1999; **140**: 865–74.
39 Engineer L, Bhol KC, Ahmed AR. Analysis of current data on the use of intravenous immunoglobulins in management of pemphigus vulgaris. *J Am Acad Dermatol* 2000; **43**: 1049–57.
40 Baum S, Scope A, Barzilai A *et al.* The role of IVIg treatment in severe pemphigus vulgaris. *J Eur Acad Dermatol Venereol* 2006; **20**: 548–52.
41 Ichimiya M, Yamamoto K, Muto M. Successful treatment of pemphigus vegetans by addition of etretinate to systemic steroids. *Clin Exp Dermatol* 1998; **23**: 178–80.
42 Jacobi A, Shuler G, Hertl M. Rapid control of therapy-refractory pemphigus vulgaris by treatment with the tumour necrosis factor-alpha inhibitor infliximab. *Br J Dermatol* 2005; **153**: 448–9.
43 Berookhim B, Fischer HD, Weinberg JM. Treatment of recalcitrant pemphigus vulgaris with the tumor necrosis factor alpha antagonist etanercept. *Cutis* 2004; **74**: 245–7.

Pemphigus foliaceus and its variants

Definition. Blistering in this group of autoimmune diseases is high in the epidermis, either in the granular layer or just beneath the stratum corneum.

Aetiology. Pemphigus foliaceus is less common worldwide than pemphigus vulgaris and in most parts of the world probably accounts for only 10–20% of cases of pemphigus [1–5]. Endemic pemphigus foliaceus is common in rural parts of South America, particularly certain states of Brazil, where it also known as fogo selvagem (wild fire) [6] and in rural Tunisia [7]. It is probably triggered by an environmental factor (see below). Pemphigus foliaceus is also more common than pemphigus vulgaris in Mali, Libya and in South Africa, where it predominantly affects black races [8,9]. Susceptibility to pemphigus foliaceus has been correlated with the presence of HLA-DR4, DR-14 and DR-1 alleles, but unlike pemphigus vulgaris no single allele has been associated with the disease. Sporadic and endemic forms of PF show similar HLA susceptibility alleles. Susceptibility to both sporadic and endemic PF is also associated with a single nucleotide polymorphism in the gene for desmoglein-1 and a cytokine (IL-6) gene polymorphism predisposes to endemic pemphigus foliaceus [10].

Pathogenesis. Experimental evidence suggests that autoantibodies in all forms of pemphigus foliaceus are pathogenic.

Pemphigus foliaceus antigen. Sera from all forms of pemphigus foliaceus recognize epitopes located in the extracellular aminoterminal domain of desmoglein-1, a 160-kDa desmosomal cadherin [11–14]. The epitopes recognized by autoantibodies in endemic pemphigus foliaceus may differ from those in the non-endemic form [15]. Rare cases of pemphigus foliaceus evolving into pemphigus vulgaris develop antibodies to desmoglein-3 [16–21]. A small subset of pemphigus foliaceus sera have both desmoglein-3 and desmoglein-1 antibodies in the absence of clinical evolution [22]. Some sera, particularly from endemic pemphigus foliaceus, also contain autoantibodies directed against desmocollins 1 and 2 [23,24]. Cases of pemphigus foliaceus with antibodies to desmoplakin [25] and to keratinocyte cholinergic receptors [26] have also been reported. Their significance is unknown.

Localization of antigen. Immunoelectron microscopy has demonstrated that the antibodies bind exclusively to desmosomes [27,28]. Pemphigus foliaceus antigen (desmoglein-1) is expressed more strongly in skin from their upper torso than from the lower torso or scalp [29]. In culture the antigens are only expressed by stratified keratinocytes [30]. Although direct immunofluorescence may be positive around keratinocytes throughout the epidermis, pemphigus foliaceus sera bind to significantly more desmosomes in the upper epidermis than the lower epidermis, the reciprocal of the pattern with pemphigus vulgaris sera [31], thus the pattern of binding correlates with the histological level of split in the epidermis. Antibody binding may have a direct effect on the function of the desmosomal cadherins in the upper epidermis, causing detachment of keratinocytes. Desmoglein-1 is present but only weakly expressed in mucosae [32] accounting for the lack of mucosal involvement in pemphigus foliaceus.

Antibodies. Patients with both sporadic and endemic forms of pemphigus foliaceus have anti-DG1 antibodies, the titre correlating both with the extent and activity of the disease [33,34]. Recently, using more sensitive ELISA techniques, anti-DG antibodies (both DG1 and DG3) have also been detected in unaffected individuals living in areas where endemic pemphigus foliaceus is prevalent [35,36]. Subsequent development of pemphigus foliaceus in some of these individuals was preceded by a marked increase in antibody titres [35]. The pathogenic autoantibodies in all forms of pemphigus foliaceus are predominantly in the IgG4 subclass [12,37,38]. Immunohistological staining for desmosomal

components appears abnormal in skin from patients with pemphigus foliaceus, possibly altered by binding of autoantibodies [39,40].

Pathogenicity. Purified IgG fractions induce loss of cell adhesion in skin organ cultures and neonatal mice with the typical histological findings of pemphigus foliaceus. Complement is not required. Antigen-specific immunoadsorption of the autoantibodies prevents blisters [41,42].

Proteases. Proteolysis may augment the acantholytic process as in pemphigus vulgaris (see above). High concentrations of plasminogen induce foliaceus-like acantholysis in cultured skin. Pemphigus foliaceus antibodies stimulate epidermal cells to secrete plasminogen activator, but secretion is reduced by corticosteroids. Antibodies against the plasminogen activator, urokinase, block acantholysis induced by pemphigus foliaceus IgG [43].

References

1 Ryan JG. Pemphigus. A 20-year survey of experience with 70 cases. *Arch Dermatol* 1971; **104**: 14–20.

2 Beutner EH, Chorzelski TP. Studies on etiologic factors in pemphigus. *J Cutan Pathol* 1976; **3**: 67–74.

3 Rosenberg FR, Sanders S, Nelson CT. Pemphigus: a 20-year review of 107 patients treated with corticosteroids. *Arch Dermatol* 1976; **112**: 962–70.

4 Krain LS. Pemphigus. Epidemiologic and survival characteristics of 59 patients, 1955–1973. *Arch Dermatol* 1974; **110**: 862–5.

5 Wilson C, Wojnarowska F, Mehra NK *et al.* Pemphigus in Oxford, UK, and New Delhi, India: a comparative study of disease characteristics and HLA antigens. *Dermatology* 1994; **189** Suppl 1: 108–10.

6 Diaz LA, Sampaio SA, Rivitti EA *et al.* Endemic pemphigus foliaceus (fogo selvagem). I. Clinical features and immunopathology. *J Am Acad Dermatol* 1989; **20**: 657–69.

7 Bastuji-Garin S, Souissi R, Blum L *et al.* Comparative epidemiology of pemphigus in Tunisia and France: unusual incidence of pemphigus foliaceus in young Tunisian women. *J Invest Dermatol* 1995; **104**: 302–5.

8 Mahe A, Flageul B, Cisse I *et al.* Pemphigus in Mali: a study of 30 cases. *Br J Dermatol* 1996; **134**: 114–9.

9 Aboobaker J, Morar N, Ramdial PK *et al.* Pemphigus in South Africa. *Int J Dermatol* 2001; **40**: 115–9.

10 Tron F, Gilbert D, Mouquet H *et al.* Genetic factors in pemphigus. *J Autoimmun* 2005; **24**: 319–28.

11 Stanley JR, Klaus-Kovtun V, Sampaio SA. Antigenic specificity of fogo selvagem autoantibodies is similar to North American pemphigus foliaceus and distinct from pemphigus vulgaris autoantibodies. *J Invest Dermatol* 1986; **87**: 197–201.

12 Allen EM, Giudice GJ, Diaz LA. Subclass reactivity of pemphigus foliaceus autoantibodies with recombinant human desmoglein. *J Invest Dermatol* 1993; **100**: 685–91.

13 Dmochowski M, Hashimoto T, Amagai M *et al.* The extracellular aminoterminal domain of bovine desmoglein 1 (Dsg1) is recognized only by certain pemphigus foliaceus sera, whereas its intracellular domain is recognized by both pemphigus vulgaris and pemphigus foliaceus sera. *J Invest Dermatol* 1994; **103**: 173–7.

14 Olague-Alcala M, Giudice GJ, Diaz LA. Pemphigus foliaceus sera recognize an N-terminal fragment of bovine desmoglein 1. *J Invest Dermatol* 1994; **102**: 882–5.

15 Akiyama M, Hashimoto T, Sugiura M *et al.* Ultrastructural localization of Brazilian pemphigus foliaceus (fogo selvagem) antigens in cultured human squamous cell carcinoma cells. *Br J Dermatol* 1993; **128**: 378–83.

16 Ishii K, Amagai M, Ohata Y *et al.* Development of pemphigus vulgaris in a patient with pemphigus foliaceus: antidesmoglein antibody profile shift confirmed by enzyme-linked immunosorbent assay. *J Am Acad Dermatol* 2000; **42**: 859–61.

17 Tsuji Y, Kawashima T, Yokota K *et al.* Clinical and serological transition from pemphigus vulgaris to pemphigus foliaceus demonstrated by desmoglein ELISA system. *Arch Dermatol* 2002; **138**: 95–6.

18 Harman KE, Gratian MJ, Shirlaw PJ *et al.* The transition of pemphigus vulgaris into pemphigus foliaceus: a reflection of changing desmoglein 1 and 3 autoantibody levels in pemphigus vulgaris. *Br J Dermatol* 2002; **146**: 684–7.

19 Sami N, Bhol KC, Ahmed AR. Diagnostic features of pemphigus vulgaris in patients with pemphigus foliaceus: detection of both autoantibodies, long-term follow-up and treatment responses. *Clin Exp Immunol* 2001; **125**: 492–8.

20 Komai A, Amagai M, Ishii K *et al.* The clinical transition between pemphigus foliaceus and pemphigus vulgaris correlates well with the changes in autoantibody profile assessed by an enzyme-linked immunosorbent assay. *Br J Dermatol* 2001; **144**: 1177–82.

21 Muller E, Kernland K, Caldelari R *et al.* Unusual pemphigus phenotype in the presence of a Dsg1 and Dsg3 autoantibody profile. *J Invest Dermatol* 2002; **118**: 551–5.

22 Arteaga LA, Prisayanh PS, Warren SJ *et al.* A subset of pemphigus foliaceus patients exhibits pathogenic autoantibodies against both desmoglein-1 and desmoglein-3. *J Invest Dermatol* 2002; **118**: 806–11.

23 Dmochowski M, Hashimoto T, Garrod DR *et al.* Desmocollins I and II are recognized by certain sera from patients with various types of pemphigus, particularly Brazilian pemphigus foliaceus. *J Invest Dermatol* 1993; **100**: 380–4.

24 Dmochowski M, Hashimoto T, Chidgey MA *et al.* Demonstration of antibodies to bovine desmocollin isoforms in certain pemphigus sera. *Br J Dermatol* 1995; **133**: 519–25.

25 Jiao D, Bystryn JC. Sensitivity of indirect immunofluorescence, substrate specificity, and immunoblotting in the diagnosis of pemphigus. *J Am Acad Dermatol* 1997; **37**: 211–6.

26 Nguyen VT, Ndoye A, Shultz LD *et al.* Antibodies against keratinocyte antigens other than desmogleins 1 and 3 can induce pemphigus vulgaris-like lesions. *J Clin Invest* 2000; **106**: 1467–79.

27 Rappersberger K, Roos N, Stanley JR. Immunomorphologic and biochemical identification of the pemphigus foliaceous autoantigen within desmosomes. *J Invest Dermatol* 1992; **99**: 323–30.

28 Boulinguez S, Bedane C, Cadilhac H *et al.* [Ultrastructural localisation of pemphigus vulgaris and pemphigus foliaceus antigens by indirect immunoelectron microscopy. Apropos of 7 cases]. *Ann Dermatol Venereol* 1995; **122**: 417–21.

29 Ioannides D, Hytiroglou P, Phelps RG *et al.* Regional variation in the expression of pemphigus foliaceus, pemphigus erythematosus, and pemphigus vulgaris antigens in human skin. *J Invest Dermatol* 1991; **96**: 159–61.

30 Iwatsuki K, Harada H, Zhang JZ *et al.* Regulation of pemphigus and desmosomal antigen expression by keratinocyte differentiation. *Dermatology* 1994; **189** (Suppl. 1): 67–71.

31 Shimizu H, Masunaga T, Ishiko A *et al.* Pemphigus vulgaris and pemphigus foliaceus sera show an inversely graded binding pattern to extracellular regions of desmosomes in different layers of human epidermis. *J Invest Dermatol* 1995; **105**: 153–9.

32 Shirakata Y, Amagai M, Hanakawa Y *et al.* Lack of mucosal involvement in pemphigus foliaceus may be due to low expression of desmoglein 1. *J Invest Dermatol* 1998; **110**: 76–8.

33 Stanley JR. Defective cell-cell adhesion in the epidermis. *Ciba Found Symp* 1995; **189**: 107–20; discussion 20–3, 74–6.

34 Squiquera HL, Diaz LA, Sampaio SA *et al.* Serologic abnormalities in patients with endemic pemphigus foliaceus (Fogo selvagem), their relatives, and normal donors from endemic and non-endemic areas of Brazil. *J Invest Dermatol* 1988; **91**: 189–91.

35 Warren SJ, Lin MS, Giudice GJ *et al.* The prevalence of antibodies against desmoglein 1 in endemic pemphigus foliaceus in Brazil. Cooperative Group on Fogo Selvagem Research. *N Engl J Med* 2000; **343**: 23–30.

36 Amagai M. Non-pathogenic anti-desmoglein 3 IgG autoantibodues in Fogo Selvagem. *J Invest Dermatol* 2006; **126**: 1931–2.

37 Rock B, Labib RS, Diaz LA. Monovalent Fab' immunoglobulin fragments from endemic pemphigus foliaceus autoantibodies reproduce the human disease in neonatal Balb/c mice. *J Clin Invest* 1990; **85**: 296–9.

38 Calvanico NJ, Swartz SJ, Diaz LA. Affinity immunoblotting studies on the restriction of autoantibodies from endemic pemphigus foliaceus patients. *J Autoimmun* 1993; **6**: 145–57.

39 Burge SM, Wilson CL, Dean D *et al.* An immunohistological study of desmosomal components in pemphigus. *Br J Dermatol* 1993; **128**: 363–70.
40 Carlotti A, Balaton AJ, de Muret A *et al.* Autoimmune pemphigus. A distinct staining pattern with an anti-desmoglein antibody. *Arch Dermatol* 1993; **129**: 596–9.
41 Rock B, Martins CR, Theofilopoulos AN *et al.* The pathogenic effect of IgG4 autoantibodies in endemic pemphigus foliaceus (fogo selvagem). *N Engl J Med* 1989; **320**: 1463–9.
42 Amagai M, Hashimoto T, Green KJ *et al.* Antigen-specific immunoadsorption of pathogenic autoantibodies in pemphigus foliaceus. *J Invest Dermatol* 1995; **104**: 895–901.
43 Morioka S, Lazarus G, Jensen P. Involvement of urokinase type plasminogen activator in acantholysis induced by pemphigus IgG. *J Invest Dermatol* 1987; **89**: 474–7.

Pathology. In early lesions, vacuoles form in the intercellular spaces in the upper levels of the epidermis. These coalesce to form clefts and superficial bullae high in the granular layer or immediately below the stratum corneum. Bullae contain fibrin, some neutrophils and scattered acantholytic keratinocytes. Eosinophilic spongiosis [1] or neutrophilic spongiosis [2] may precede blisters. Frank neutrophilic pustules have been described [3]. Older lesions are acanthotic, papillomatous and hyperkeratotic with focal parakeratosis. Dyskeratotic cells in the granular layer of older lesions distinguish pemphigus foliaceus from pemphigus vulgaris [4]. A mixed inflammatory infiltrate of eosinophils and neutrophils occupies the superficial dermis.

Direct and indirect immunofluorescent findings are usually indistinguishable from pemphigus vulgaris with intercellular IgG and C3 throughout the epidermis. Occasionally intercellular staining is restricted to the upper layers of epidermis, both on direct and indirect immunofluorescence [5]. Rarely, intercellular IgA is detected by direct immunofluorescence [6]. Indirect immunofluorescence is positive in over 85% of pemphigus foliaceus sera, ELISA detects anti-desmoglein-1 antibodies in up to 71% of patients but immunoblotting is less sensitive (43%) [7].

Electron microscopy demonstrates loss of desmosomes, detachment of keratin tonofilaments and dyskeratosis [4].

References

1 Crotty C, Pittelkow M, Muller SA. Eosinophilic spongiosis: a clinicopathologic review of seventy-one cases. *J Am Acad Dermatol* 1983; **8**: 337–43.
2 Hoss DM, Shea CR, Grant-Kels JM. Neutrophilic spongiosis in pemphigus. *Arch Dermatol* 1996; **132**: 315–8.
3 Matsuo K, Komai A, Ishii K *et al.* Pemphigus foliaceus with prominent neutrophilic pustules. *Br J Dermatol* 2001; **145**: 132–6.
4 Wilgram G, Caulfield J, Madgic M. An electron microscopic study of acantholysis and dyskeratosis in pemphigus foliaceous. *J Invest Dermatol* 1964; **43**: 287–99.
5 Rodriguez J, Bystryn JC. Pemphigus foliaceus associated with absence of intercellular antigens in lower layers of epidermis. *Arch Dermatol* 1977; **113**: 1696–9.
6 Beutner EH, Chorzelski TP, Wilson RM *et al.* IgA pemphigus foliaceus. Report of two cases and a review of the literature. *J Am Acad Dermatol* 1989; **20**: 89–97.
7 Jiao D, Bystryn JC. Sensitivity of indirect immunofluorescence, substrate specificity, and immunoblotting in the diagnosis of pemphigus. *J Am Acad Dermatol* 1997; **37**: 211–6.

Clinical features. Pemphigus foliaceus is less severe than pemphigus vulgaris. Most cases are idiopathic but penicillamine and other drugs containing thiol groups, for example captopril, have been implicated (see section on induced pemphigus, below). The onset is usually insidious with scattered, scaly lesions involving the 'seborrhoeic' areas: scalp, face, chest and upper back (Figs 40.7 & 40.8). Localized disease slowly extends. Blistering may not be obvious because the cleavage is superficial and the small flaccid blisters rupture easily. Scales separate leaving well-demarcated, crusted erosions surrounded by erythema, sometimes with small vesicles along the borders. Erosions are both painful and offensive. Eventually the patient may become erythrodermic with crusted, oozing red skin (Fig. 40.9). Oral lesions are uncommon [1].



Fig. 40.7 Pemphigus foliaceus. Well-demarcated crusted lesions scattered over the chest.



Fig. 40.8 Pemphigus foliaceus. Sharply demarcated areas of erythema, crusting and scaling with no obvious bullae.

Although the antibodies in pemphigus foliaceus can cross the placenta, the neonate is not usually affected [2]. In two cases in which the neonate did develop pemphigus foliaceus, both mother and neonate had very high antibody titres [3,4].

Clinical variants of pemphigus foliaceus

Pemphigus resembling dermatitis herpetiformis. A rare and atypical variant of pemphigus resembles dermatitis herpetiformis in its early phase (pemphigus herpetiformis) [5,6]. Widespread



Fig. 40.9 Pemphigus foliaceus. This man became erythrodermic and then developed widespread, painful erosions.

clusters of pruritic papules and vesicles develop on an erythematous background. Biopsies show subcorneal pustules, eosinophilic spongiosis or features of dermatitis herpetiformis without acantholysis but immunofluorescence studies reveal intercellular staining. Patients possess circulating IgG intercellular autoantibodies which recognize either desmoglein-1 [7,8] or desmoglein-3 [8,9] or neither antigen [8]. The condition usually evolves into classical pemphigus foliaceus but has also been described preceding pemphigus vulgaris [7]. In general the clinical course is benign.

Pemphigus erythematosus (Senear–Usher syndrome). Pemphigus erythematosus is a variant of pemphigus foliaceus, originally described by Senear and Usher [10–12]. Patients have immunological features of both lupus erythematosus and pemphigus, that is granular IgG and C3 at the basement membrane zone, intercellular IgG and C3 in the epidermis and circulating antinuclear antibodies [13]. The antibodies recognize the pemphigus foliaceus antigen, desmoglein-1 [14]. Progression to systemic lupus erythematosus is rare. Pemphigus erythematosus may be associated with myasthenia gravis or thymoma [13,15].

Erythematous, scaly lesions over the nose and cheeks in a butterfly distribution simulate cutaneous lupus erythematosus or seborrhoeic dermatitis. Sunlight may exacerbate the disease. Lesions on the trunk, either localized or generalized, are similar to those in pemphigus foliaceus. Oral mucosa is involved rarely.

Differential diagnosis. Pemphigus foliaceus may resemble seborrhoeic dermatitis or impetigo, but the histological and immunological features are diagnostic. Pemphigus erythematosus needs to be distinguished from both seborrhoeic dermatitis and chronic cutaneous lupus erythematosus. Pemphigus may simulate dermatitis herpetiformis both clinically and histologically, but immunopathological studies differentiate the diseases. Histological features may not be diagnostic in the early stages. Eosinophilic spongiosis may be an early manifestation [16]. Immunofluorescence studies should always be performed if pemphigus is suspected.

Treatment of pemphigus foliaceus and its variants. These superficial forms of pemphigus usually respond to potent topical or intralesional steroids or, if control is inadequate, prednisolone 20–40 mg/day. Azathioprine or cyclophosphamide are effective adjuncts to oral steroids in severe cases. Hydroxychloroquine 200/mg twice per day has also been recommended as adjuvant therapy [17]. Intravenous immunoglobulin has been reported as effective in resistant cases [18,19].

Dapsone 100–300 mg/day may be effective as a monotherapy or given in combination with oral steroids [20]. Dapsone 100–300 mg/day is the treatment of choice for pemphigus with dermatitis herpetiformis-like lesions (pemphigus herpetiformis), but retinoids have been suggested as a second-line therapy in these patients [21,22]. Mycophenolate mofetil has been used as a steroid-sparing agent [23,24].

Nicotinamide 1.5 g/day combined with either tetracycline 500 mg four times per day or minocycline 100 mg/day appeared effective in superficial pemphigus in one uncontrolled study [25] but these results were not substantiated [26]. High-dose intravenous immunoglobulin has been used successfully in severe pemphigus foliaceus, resistant to other therapies [19].

Prognosis of pemphigus foliaceus. Pemphigus foliaceus is generally regarded as a benign disease which responds well to treatment and may remit. However, like pemphigus vulgaris it can also pursue a very chronic course over many years and be subject to repeated relapse [27]. There are rare reports of pemphigus foliaceus evolving both clinically and immunopathologically into pemphigus vulgaris [28–33]. Pemphigus erythematosus may persist as localized disease for years. The clinical course is often similar to pemphigus foliaceus.

References

1 Lever W. *Pemphigus and Pemphigoid*. Springfield: Thomas, 1965.

2 Rocha-Alvarez R, Friedman H, Campbell IT *et al.* Pregnant women with endemic pemphigus foliaceus (Fogo Selvagem) give birth to disease-free babies. *J Invest Dermatol* 1992; **99**: 78–82.

3 Walker DC, Kolar KA, Hebert AA *et al.* Neonatal pemphigus foliaceus. *Arch Dermatol* 1995; **131**: 1308–11.

4 Avalos-Diaz E, Olague-Marchan M, Lopez-Swiderski A *et al.* Transplacental passage of maternal pemphigus foliaceus autoantibodies induces neonatal pemphigus. *J Am Acad Dermatol* 2000; **43**: 1130–4.

5 Jablonska S, Chorzelski TP, Beutner EH *et al.* Herpetiform pemphigus, a variable pattern of pemphigus. *Int J Dermatol* 1975; **14**: 353–9.

6 Robinson ND, Hashimoto T, Amagai M *et al.* The new pemphigus variants. *J Am Acad Dermatol* 1999; **40**: 649–71

7 Santi CG, Maruta CW, Aoki V *et al.* Pemphigus herpetiformis is a rare clinical expression of nonendemic pemphigus foliaceus, fogo selvagem, and pemphigus vulgaris. Cooperative Group on Fogo Selvagem Research. *J Am Acad Dermatol* 1996; **34**: 40–6.

8 Ishii K, Amagai M, Komai A *et al.* Desmoglein 1 and desmoglein 3 are the target autoantigens in herpetiform pemphigus. *Arch Dermatol* 1999; **135**: 943–7.

9 Kubo A, Amagai M, Hashimoto T *et al.* Herpetiform pemphigus showing reactivity with pemphigus vulgaris antigen (desmoglein 3). *Br J Dermatol* 1997; **137**: 109–13.

10 Senear F, Usher B. An unusual type of pemphigus. *Arch Dermatol* 1926; **13**: 761–81.

11 Maize J, Green D, Provost T. Pemphigus foliaceus: a case with serological features of Senear-Usher syndrome and other autoimmune abnormalities. *J Am Acad Dermatol* 1982; **7**: 736–41.

12 American M, Ahmed A. Pemphigus erythematosus. *Int J Dermatol* 1985; **24**: 16–25.
13 Jordon RE. Pemphigus erythematosus. *Arch Dermatol* 1982; **118**: 742.
14 Gomi H, Kawada A, Amagai M *et al.* Pemphigus erythematosus: detection of anti-desmoglein-1 antibodies by ELISA. *Dermatology* 1999; **199**: 188–9.
15 Cruz PD Jr, Coldiron BM, Sontheimer RD. Concurrent features of cutaneous lupus erythematosus and pemphigus erythematosus following myasthenia gravis and thymoma. *J Am Acad Dermatol* 1987; **16**: 472–80.
16 Crotty C, Pittelkow M, Muller SA. Eosinophilic spongiosis: a clinicopathologic review of seventy-one cases. *J Am Acad Dermatol* 1983; **8**: 337–43.
17 Hymes SR, Jordon RE. Pemphigus foliaceus. Use of antimalarial agents as adjuvant therapy. *Arch Dermatol* 1992; **128**: 1462–4.
18 Sami N, Qureshi A, Ahmed AR. Steroid sparing effect of intravenous immunoglobulin therapy in patients with pemphigus foliaceus. *Eur J Dermatol* 2002; **12**: 174–8.
19 Ahmed AR, Sami N. Intravenous immunoglobulin therapy for patients with pemphigus foliaceus unresponsive to conventional therapy. *J Am Acad Dermatol* 2002; **46**: 42–9.
20 Basset N, Guillot B, Michel B *et al.* Dapsone as initial treatment in superficial pemphigus. Report of nine cases. *Arch Dermatol* 1987; **123**: 783–5.
21 Maciejowska E, Jablonska S, Chorzelski T. Is pemphigus herpetiformis an entity? *Int J Dermatol* 1987; **26**: 571–7.
22 Bauer R, Stadler R, Immel C *et al.* [Acantholysis and eosinophilic spongiosis: pemphigus herpetiformis. Successful retinoid therapy]. *Hautarzt* 1983; **34**: 13–7.
23 Katz KH, Marks JG Jr, Helm KF. Pemphigus foliaceus successfully treated with mycophenolate mofetil as a steroid-sparing agent. *J Am Acad Dermatol* 2000; **42**: 514–5.
24 Chams-Davatchi C, Nonahal Azar R, Daneshpazooh M *et al.* [Open trial of mycophenolate mofetil in the treatment of resistant pemphigus vulgaris]. *Ann Dermatol Venereol* 2002; **129**: 23–5.
25 Chaffins ML, Collison D, Fivenson DP. Treatment of pemphigus and linear IgA dermatosis with nicotinamide and tetracycline: a review of 13 cases. *J Am Acad Dermatol* 1993; **28**: 998–1000.
26 Alpsoy E, Yilmaz E, Basaran E *et al.* Is the combination of tetracycline and nicotinamide therapy alone effective in pemphigus? *Arch Dermatol* 1995; **131**: 1339–40.
27 Zaraa I, Mokni M, Hsairi M *et al.* Pemphigus vulgaris and pemphigus foliaceus: similar prognosis? *Int J Dermatol* 2007; **46**: 923–6.
28 Ishii K, Amagai M, Ohata Y *et al.* Development of pemphigus vulgaris in a patient with pemphigus foliaceus: antidesmoglein antibody profile shift confirmed by enzyme-linked immunosorbent assay. *J Am Acad Dermatol* 2000; **42**: 859–61.
29 Tsuji Y, Kawashima T, Yokota K *et al.* Clinical and serological transition from pemphigus vulgaris to pemphigus foliaceus demonstrated by desmoglein ELISA system. *Arch Dermatol* 2002; **138**: 95–6.
30 Harman KE, Gratian MJ, Shirlaw PJ *et al.* The transition of pemphigus vulgaris into pemphigus foliaceus: a reflection of changing desmoglein 1 and 3 autoantibody levels in pemphigus vulgaris. *Br J Dermatol* 2002; **146**: 684–7.
31 Sami N, Bhol KC, Ahmed AR. Diagnostic features of pemphigus vulgaris in patients with pemphigus foliaceus: detection of both autoantibodies, long-term follow-up and treatment responses. *Clin Exp Immunol* 2001; **125**: 492–8.
32 Komai A, Amagai M, Ishii K *et al.* The clinical transition between pemphigus foliaceus and pemphigus vulgaris correlates well with the changes in autoantibody profile assessed by an enzyme-linked immunosorbent assay. *Br J Dermatol* 2001; **144**: 1177–82.
33 Muller E, Kernland K, Caldelari R *et al.* Unusual pemphigus phenotype in the presence of a Dsg1 and Dsg3 autoantibody profile. *J Invest Dermatol* 2002; **118**: 551–5.

Endemic pemphigus foliaceus

Synonyms
- Fogo selvagem (wild fire)
- Brazilian pemphigus foliaceus

One form of pemphigus foliaceus is endemic to certain parts of South America. Histologically and immunopathologically it resembles the non-endemic form and is distinguished from it by its unique epidemiological features, including geographical and temporal and familial clustering of cases, high prevalence in the young, and association with certain HLA haplotypes [1].

Endemic pemphigus foliaceus occurs clustered in certain subtropical states of Brazil [1–4]. For a recent review see Culton *et al.* [5]. Endemic foci have also been reported in Columbia, El Salvador, Paraguay and Peru [1–4,6]. An endemic focus has also been observed in rural Tunisia and Libya [2–4].

Aetiology and pathogenesis. Passive transfer studies demonstrate the pathogenicity of desmoglein-1 antibodies [7] which as in idiopathic pemphigus foliaceus are of IgG4 subclass. Sera recognize epitopes located in the extracellular aminoterminal domain of desmoglein and may be different from those involved in non-endemic disease [8]. Some sera also contain autoantibodies directed against desmoglein-3 [9] and desmocollins-1 and 2 [10,11]. Autoantibodies bind to oral mucosa as well as to skin [12]. Mucosal involvement clinically virtually never occurs but there may be ultrastructural abnormalities, for example widening of the intercellular spaces and desmosomal changes [13].

Using sensitive ELISA techniques, it is now clear that the prevalence of antidesmoglein-1 antibodies is high among normal subjects living in an endemic area. The background prevalence of desmoglein-1 antibodies is 20% in the general population, chiefly comprising non-pathogenic IgG subclasses or targeting a non-pathogenic domain of desmoglein-1 [14,15]. IgM class anti-Dsg1 antibodies are common in FS patients and in unaffected Amerindians in their native environment but are absent in migrants to urban areas [16]. Antidesmoglein-3 IgG has also been detected by ELISA in 43% of patients with fogo selvagem (without mucosal disease) and also in 20% of unaffected Amerindians [17]. The significance of desmoglein-3 antibodies is unknown.

The seroepidemiological evidence suggests that endemic pemphigus foliaceus is precipitated by an environmental factor, possibly a biting insect. The disease is endemic in newly developed jungle areas of Brazil that are being used for agriculture, but endemic foci are eradicated by urbanization. Rural labourers are at greatest risk. The incidence of disease is greatest at the end of the rainy season when insects are most abundant. Black fly (*Simuliidae*) bites are a risk factor for the disease [1]. Desmoglein-1 antibodies are especially prevalent in individuals with insect-transmitted parasitic diseases compared to those with non-insect borne infections. No infectious agent, chemical toxin or pollutant has yet been isolated.

Possibly, exposure to components of insect vector salivary antigens triggers the formation of antibodies which cross-react with human epidermal antigens [18]. In susceptible individuals, the immune response may become pathogenic by epitope spreading to target the pathogenic domains of desmoglein-1 [14] or by IgG subclass switching to produce pathogenic IgG4 [19].

A significant number of cases have an affected family member [1]. In one Brazilian population the susceptibility allele was identified as HLA-DRB1*0102. In two other Brazilian populations different alleles of the HLA-DRB1 gene (DRB1*0404, *1402 or *1406) have been linked to the development of endemic pemphigus foliaceus [6,20]. All alleles involved in predisposition to disease share

the same amino acid sequence in the DRB1 gene. Inheritance of this sequence may determine susceptibility when individuals are exposed to the appropriate environmental agent [1].

Clinical features. Endemic pemphigus foliaceus affects children and young adults, with a peak incidence in the second and third decades, whereas other forms of pemphigus foliaceus affect middle-aged adults [21,22].

Patients present with flaccid bullae which rupture easily leaving superficial erosions. Nikolsky's sign is positive. The head and neck are involved at first. The burnt appearance and burning sensation, particularly on sun exposure, gives the disease its popular name, fogo selvagem, Portuguese for 'wild fire'. The disease slowly spreads acrally and may become generalized. Oral mucosa is usually spared.

Some patients develop widespread bullae with pyrexia, arthralgia and malaise. Generalized erythroderma may supervene. Chronic disease is frequent with disseminated verrucous lesions that simulate prurigo nodularis. Plaques may vegetate. Hyperpigmentation is a feature of inactive disease.

Growth retardation, common in affected children, responds to treatment with oral corticosteroids. Adults who were affected in childhood may have azoospermia. Patients may show signs of chronic depression [21,22].

Although antibodies to desmoglein-1 cross the placenta, the disease is rarely transmitted from affected mothers to the neonate [23], except in rare cases with high titre antibodies [24]. Desmoglein-3 is more highly expressed in neonatal than adult skin and this may be protective [25].

Treatment. Treatment is similar to other forms of pemphigus foliaceus. Topical steroids are effective in localized disease or as an adjunct to systemic treatment. Most patients respond to systemic steroids alone, but verrucous plaques may be resistant to therapy. Immunosuppressive agents, gold and antimalarials have been recommended [22,23].

Prognosis. Before the advent of corticosteroids 40 to 60% of untreated patients died. Now less than 10% die, often as a result of the complications of treatment. Spontaneous remissions have been reported.

References

1 Hans-Filho G, Aoki V, Rivitti E *et al.* Endemic pemphigus foliaceus (fogo selvagem)—1998. The Cooperative Group on Fogo Selvagem Research. *Clin Dermatol* 1999; **17**: 225–35.

2 Morini JP, Jomaa B, Gorgi Y *et al.* Pemphigus foliaceus in young women. An endemic focus in the Sousse area of Tunisia. *Arch Dermatol* 1993; **129**: 69–73.

3 Bastuji-Garin S, Souissi R, Blum L *et al.* Comparative epidemiology of pemphigus in Tunisia and France: unusual incidence of pemphigus foliaceus in young Tunisian women. *J Invest Dermatol* 1995; **104**: 302–5.

4 Joly P, Mokhtar I, Gilbert D *et al.* Immunoblot and immunoelectronmicroscopic analysis of endemic Tunisian pemphigus. *Br J Dermatol* 1999; **140**: 44–9.

5 Culton DA, Qian Y, Li N *et al.* Advances in pemphigus and its endemic pemphigus foliaceus (Fogo Selvagem) phenotype: a paradigm of human autoimmunity. *J Autoimmun* 2008; **31**: 311–24.

6 Moraes ME, Fernandez-Vina M, Lazaro A *et al.* An epitope in the third hypervariable region of the DRB1 gene is involved in the susceptibility to endemic pemphigus foliaceus (fogo selvagem) in three different Brazilian populations. *Tissue Antigens* 1997; **49**: 35–40.

7 Futamura S, Martins C, Rivitti EA *et al.* Ultrastructural studies of acantholysis induced in vivo by passive transfer of IgG from endemic pemphigus foliaceus (Fogo Selvagem). *J Invest Dermatol* 1989; **93**: 480–5.

8 Akiyama M, Hashimoto T, Sugiura M *et al.* Ultrastructural localization of Brazilian pemphigus foliaceus (fogo selvagem) antigens in cultured human squamous cell carcinoma cells. *Br J Dermatol* 1993; **128**: 378–83.

9 Cunha PR, Bystryn JC, Medeiros EP *et al.* Sensitivity of indirect immunofluorescence and ELISA in detecting intercellular antibodies in endemic pemphigus foliaceus (Fogo Selvagem). *Int J Dermatol* 2006; **45**: 914–8.

10 Dmochowski M, Hashimoto T, Garrod DR *et al.* Desmocollins I and II are recognized by certain sera from patients with various types of pemphigus, particularly Brazilian pemphigus foliaceus. *J Invest Dermatol* 1993; **100**: 380–4.

11 Dmochowski M, Hashimoto T, Chidgey MA *et al.* Demonstration of antibodies to bovine desmocollin isoforms in certain pemphigus sera. *Br J Dermatol* 1995; **133**: 519–25.

12 Rivitti EA, Sanches JA, Miyauchi LM *et al.* Pemphigus foliaceus autoantibodies bind both epidermis and squamous mucosal epithelium, but tissue injury is detected only in the epidermis. The Cooperative Group on Fogo Selvagem Research. *J Am Acad Dermatol* 1994; **31**: 954–8.

13 Guedes AC, Rotta O, Leite HV *et al.* Ultrastructural aspects of mucosas in endemic pemphigus foliaceus. *Arch Dermatol* 2002; **138**: 949–54.

14 Warren SJ, Lin MS, Giudice GJ *et al.* The prevalence of antibodies against desmoglein 1 in endemic pemphigus foliaceus in Brazil. Cooperative Group on Fogo Selvagem Research. *N Engl J Med* 2000; **343**: 23–30.

15 Li N, Aoki V, Hans-Filho G *et al.* The role of intramolecular epitope spreading in the pathogenesis of endemic pemphigus foliaceus (fogo selvagem). *J Exp Med* 2003; **197**: 1501–10.

16 Diaz LA, Prisayanh PS, Dasher DA *et al.* The IgM anti-desmoglein 1 response distinguishes Brazilian pemphigus foliaceus (fogo selvagem) from other forms of pemphigus. *J Invest Dermatol* 2008; **128**: 667–75.

17 Hilario-Vargas J, Dasher DA, Li N *et al.* Prevalence of anti-desmoglein-3 antibodies in endemic regions of Fogo selvagem in Brazil. *J Invest Dermatol* 2006; **126**: 2044–8.

18 Diaz LA, Arteaga LA, Hilario-Vargas J *et al.* Anti-desmoglein-1 antibodies in onchocerciasis, leishmaniasis and Chagas disease suggest a possible etiological link to Fogo selvagem. *J Invest Dermatol* 2004; **123**: 1045–51.

19 Warren SJ, Arteaga LA, Rivitti EA *et al.* The role of subclass switching in the pathogenesis of endemic pemphigus foliaceus. *J Invest Dermatol* 2003; **120**: 104–8.

20 Moraes JR, Moraes ME, Fernandez-Vina M *et al.* HLA antigens and risk for development of pemphigus foliaceus (fogo selvagem) in endemic areas of Brazil. *Immunogenetics* 1991; **33**: 388–91.

21 Diaz LA, Sampaio SA, Rivitti EA *et al.* Endemic pemphigus foliaceus (fogo selvagem). I. Clinical features and immunopathology. *J Am Acad Dermatol* 1989; **20**: 657–69.

22 Sampaio SA, Rivitti EA, Aoki V *et al.* Brazilian pemphigus foliaceus, endemic pemphigus foliaceus, or fogo selvagem (wild fire). *Dermatol Clin* 1994; **12**: 765–76.

23 Rocha-Alvarez R, Friedman H, Campbell IT *et al.* Pregnant women with endemic pemphigus foliaceus (Fogo Selvagem) give birth to disease-free babies. *J Invest Dermatol* 1992; **99**: 78–82.

24 Avalos-Diaz E, Olague-Marchan M, Lopez-Swiderski A *et al.* Transplacental passage of maternal pemphigus foliaceus autoantibodies induces neonatal pemphigus. *J Am Acad Dermatol* 2000; **43**: 1130–4.

25 Wu H, Wang ZH, Yan A *et al.* Protection against pemphigus foliaceus by desmoglein 3 in neonates. *N Engl J Med* 2000; **343**: 31–5.

Induced pemphigus

Drugs may exacerbate or induce pemphigus. Drugs containing a sulphydryl group (thiol drugs) such as penicillamine and captopril are the best studied, but pemphigus can also been attributed to non-thiol drugs, including other ACE inhibitors, for example enalapril [1], ramapril [2], fosinopril [3], and the angiotensin II receptor blockers candesartan and telmisartan [4]. Other drugs implicated in pemphigus are nifedipine, the penicillins, cephalo-

sporins, pyrazolon derivatives, chloroquine, hydoxychloroquine, rifampicin, montelukast and interferon [5–8].

Pemphigus vulgaris and foliaceus have been induced by radiotherapy [9–11] and pemphigus vulgaris by thermal burns [12] and electrical injury [13]. Apparently, dietary factors, particularly vegetables of the *Allium* group, have triggered pemphigus [14]. Human herpes virus-8 DNA sequences have been reported in peripheral blood mononuclear cells and skin from pemphigus patients [15,16]. Their significance is disputed [17].

Aetiology and pathogenesis. Alleles of HLA-DR4 predispose to pemphigus vulgaris and a susceptibility allele is also carried by individuals with drug-induced pemphigus [18]. Perhaps drugs act to trigger disease in genetically predisposed individuals. Thiol drugs provoke acantholysis *in vitro*, possibly by increasing the activity of plasminogen activators. An active amide group in the molecule of non-thiol drugs may be responsible for inducing disease [5].

Clinical features. Pemphigus foliaceus or pemphigus erythematosus are the most common patterns of pemphigus induced by drugs. Drug-induced pemphigus vulgaris and pemphigus vegetans are rare. Most patients have circulating autoantibodies with the same antigenic specificities as in other forms of pemphigus [19,20].

Prognosis. Forty to 50% of patients with thiol-drug-induced pemphigus recover spontaneously when the drug is withdrawn [5] with rapid decline in desmoglein antibody levels [21]. Only 15% of the cases induced by non-thiol drugs remit following drug withdrawal [5].

References

1 Kuechle MK, Hutton KP, Muller SA. Angiotensin-converting enzyme inhibitor-induced pemphigus: three case reports and literature review. *Mayo Clin Proc* 1994; **69**: 1166–71.

2 Vignes S, Paul C, Flageul B *et al.* Ramipril-induced superficial pemphigus. *Br J Dermatol* 1996; **135**: 657–8.

3 Ong CS, Cook N, Lee S. Drug-related pemphigus and angiotensin converting enzyme inhibitors. *Australas J Dermatol* 2000; **41**: 242–6.

4 Bae YI, Yun SJ, Lee SC *et al.* Pemphigus foliaceus induced by an angiotensin II receptor blocker. *Clin Exp Dermatol* 2008; **33**: 721–3.

5 Brenner S, Bialy-Golan A, Ruocco V. Drug-induced pemphigus. *Clin Dermatol* 1998; **16**: 393–7.

6 Ghaffarpour G, Jalali MH, Yaghmaii B *et al.* Chloroquine/hydroxychloroquine-induced pemphigus. *Int J Dermatol* 2006; **45**: 1261–3.

7 Fleischmann M, Celerier P, Bernard P *et al.* Long-term interferon-alpha therapy induces autoantibodies against epidermis. *Dermatology* 1996; **192**: 50–5.

8 Cetkovska P, Pizinger K. Childhood pemphigus associated with montelukast administration. *Clin Exp Dermatol* 2003; **28**: 328–9.

9 Low GJ, Keeling JH. Ionizing radiation-induced pemphigus. Case presentations and literature review. *Arch Dermatol* 1990; **126**: 1319–23.

10 Ambay A, Stratman E. Ionizing radiation-induced pemphigus foliaceus. *J Am Acad Dermatol* 2006; **54**: 251–2.

11 Robbins AC, Lazarova Z, Janson MM *et al.* Pemphigus vulgaris presenting in a radiation portal. *J Am Acad Dermatol* 2007; **56**: S82–5.

12 Hogan P. Pemphigus vulgaris following a cutaneous thermal burn. *Int J Dermatol* 1992; **31**: 46–9.

13 Tan SR, McDermott MR, Castillo CJ *et al.* Pemphigus vulgaris induced by electrical injury. *Cutis* 2006; **77**: 161–5.

14 Ruocco V, Brenner S, Ruocco E. Pemphigus and diet: does a link exist? *Int J Dermatol* 2001; **40**: 161–3.

15 Memar OM, Rady PL, Goldblum RM *et al.* Human herpesvirus 8 DNA sequences in blistering skin from patients with pemphigus. *Arch Dermatol* 1997; **133**: 1247–51.

16 Tufano M, Baroni A, Buommino E *et al.* Detection of virus DNA in peripheral blood mononuclear cells and skin lesions of patients with pemphigus by polymerase chain reaction. *Br J Dermatol* 1999; **141**: 1033–9.

17 Dupin N, Marcelin AG, Gorin I *et al.* Prevalence of human herpesvirus 8 infection measured by antibodies to a latent nuclear antigen in patients with various dermatologic diseases. *Arch Dermatol* 1998; **134**: 700–2.

18 Matzner Y, Erlich HA, Brautbar C *et al.* Identical HLA class II alleles predispose to drug-triggered and idiopathic pemphigus vulgaris. *Acta Derm Venereol* 1995; **75**: 12–4.

19 Korman NJ, Eyre RW, Zone J *et al.* Drug-induced pemphigus: autoantibodies directed against the pemphigus antigen complexes are present in penicillamine and captopril-induced pemphigus. *J Invest Dermatol* 1991; **96**: 273–6.

20 Brenner S, Bialy-Golan A, Anhalt GJ. Recognition of pemphigus antigens in drug-induced pemphigus vulgaris and pemphigus foliaceus. *J Am Acad Dermatol* 1997; **36**: 919–23.

21 Nagao K, Tanikawa A, Yamamoto N *et al.* Decline of anti-desmoglein 1 IgG ELISA scores by withdrawal of D-penicillamine in drug-induced pemphigus foliaceus. *Clin Exp Dermatol* 2005; **30**: 43–5.

Intercellular IgA dermatosis and subcorneal pustular dermatosis

These two conditions share clinical and histological features. Immunofluorescence studies were negative in classical subcorneal pustular dermatosis. Although there is overlap, the relationship between the diseases has not been defined, and so they are considered separately here.

Intercellular IgA dermatosis

Synonyms
- IgA pemphigus foliaceus
- Intraepidermal neutrophilic IgA dermatosis
- IgA herpetiform pemphigus
- Intercellular IgA vesiculopustular dermatosis

Over 50 cases have been reported of patients presenting with vesicopustular or vesicobullous eruptions with intraepidermal antikeratinocyte IgA detected in perilesional skin on direct IMF. These comprise a heterogeneous group clinically, histologically and immunologically. Some may be variants of subcorneal pustular dermatosis (see below), others may be a form of pemphigus, but the relationships between these conditions have still to be clarified [1,2].

Pathology. A neutrophil-rich polymorphonuclear infiltrate in the epidermis is observed. Two types are distinguished based on the level of pustule formation and IgA deposition [1]: the subcorneal pustular dermatosis type (subcorneal pustules) and the intraepidermal neutrophilic type (intraepidermal pustules). However, microabscesses at various levels have been observed and may depend on the age of the lesion [2]. Acantholysis is usually sparse or absent but is occasionally pronounced, mimicking either pemphigus vulgaris or pemphigus foliaceus histologically.

Pathogenesis. The hallmark of these disorders is intercellular IgA deposition in the epidermis, either at different levels or throughout. Circulating IgA is either undetectable or present in low titre

[2–4] and a few cases have coexisting IgA and IgG [5]. Desmocollin-1, a desmosomal component located mainly in the upper epidermis, has been identified as the target antigen in cases with subcorneal pustules [6–8] but also occasionally in the intraepidermal neutrophilic type [5]. In an ultrastructural study of antigen localization, cases with subcorneal pustules showed deposits predominantly in the extracellular spaces between keratinocytes at desmosomes, suggesting reactivity with the extracellular domain of desmocollins [9]. One case of subcorneal pustular dermatosis had IgA antibodies to both desmocollin-1 and desmoglein-1 [10].

In patients with intraepidermal neutrophilic pustules, antigens resembling desmogleins-1 [6] or 3 [8,11–13] have been implicated. In other cases the target antigen could not be identified. Standard immunoblotting is frequently negative, probably because the target epitopes are conformation dependent [8,14]. Immunoelectron microscopy in cases with intraepidermal neutrophilic pustules showed deposits mainly in the intercellular spaces in non-desmosomal areas, suggesting that IgA may target a non-desmosomal transmembranous protein [9].

Clinical features. The disease chiefly affects adults, though childhood cases have been reported [1,2]. Patients with both types have flaccid vesicles or pustules arising on either erythematous or normal skin. The lesions may be pruritic and show a circinate or annular configuration with central clearing and evolve to crusted or scaly erythematous macules. The sites of predilection are the axillae and groins. Other sites are elsewhere on the trunk, face, scalp and proximal limbs. In some cases the flaccid pustules resemble those seen in subcorneal pustular dermatosis of Sneddon–Wilkinson. Others may resemble pemphigus foliaceus or pemphigus herpetiformis [15–17]. Flexural, oozing, verrucous plaques mimicking pemphigus vegetans have been described in a child [18]. Nikolsky's sign is usually negative and mucosal involvement is unusual. Most run a chronic, indolent course.

The most frequently reported association is with monoclonal IgA gammopathy in the subcorneal type [19,20], a feature it has in common with classical subcorneal pustular dermatosis. Other cases have been linked with HIV infection, inflammatory bowel disease, gluten sensitive enteropathy [21–25], rheumatoid arthritis [2] and thiol drugs [26].

Treatment. These neutrophilic dermatoses respond well to dapsone [3,4,27] but poorly to steroids [3]. Other reported therapies are etretinate [3,27,28], isotretinoin [29], PUVA [28], immunosuppressives [16], plasmapheresis [30] and colchicine [12,31].

References

1 Robinson ND, Hashimoto T, Amagai M *et al.* The new pemphigus variants. *J Am Acad Dermatol* 1999; **40**: 649–71; quiz 72–3.

2 Ongenae KC, Temmerman LJ, Vermander F *et al.* Intercellular IgA dermatosis. *Eur J Dermatol* 1999; **9**: 85–94.

3 Tagami H, Iwatsuki K, Iwase Y *et al.* Subcorneal pustular dermatosis with vesiculo-bullous eruption. Demonstration of subcorneal IgA deposits and a leukocyte chemotactic factor. *Br J Dermatol* 1983; **109**: 581–7.

4 Huff JC, Golitz LE, Kunke KS. Intraepidermal neutrophilic IgA dermatosis. *N Engl J Med* 1985; **313**: 1643–5.

5 Heng A, Nwaneshiudu A, Hashimoto T *et al.* Intraepidermal neutrophilic IgA/IgG antidesmocollin 1 pemphigus. *Br J Dermatol* 2006; **154**: 1018–20.

6 Hashimoto T, Ebihara T, Nishikawa T. Studies of autoantigens recognized by IgA anti-keratinocyte cell surface antibodies. *J Dermatol Sci* 1996; **12**: 10–7.

7 Yasuda H, Kobayashi H, Hashimoto T *et al.* Subcorneal pustular dermatosis type of IgA pemphigus: demonstration of autoantibodies to desmocollin-1 and clinical review. *Br J Dermatol* 2000; **143**: 144–8.

8 Hashimoto T, Komai A, Futei Y *et al.* Detection of IgA autoantibodies to desmogleins by an enzyme-linked immunosorbent assay: the presence of new minor subtypes of IgA pemphigus. *Arch Dermatol* 2001; **137**: 735–8.

9 Ishii N, Ishida-Yamamoto A, Hashimoto T. Immunolocalization of target autoantigens in IgA pemphigus. *Clin Exp Dermatol* 2004; **29**: 62–6.

10 Kopp T, Sitaru C, Pieczkowski F *et al.* IgA pemphigus—occurrence of anti-desmocollin 1 and anti-desmoglein 1 antibody reactivity in an individual patient. *J Dtsch Dermatol Ges* 2006; **4**: 1045–50.

11 Prost C, Intrator L, Wechsler J *et al.* IgA autoantibodies bind to pemphigus vulgaris antigen in a case of intraepidermal neutrophilic IgA dermatosis. *J Am Acad Dermatol* 1991; **25**: 846–8.

12 Gengoux P, Tennstedt D, Lachapelle JM. Intraepidermal neutrophilic IgA dermatosis: pemphigus-like IgA deposits. *Dermatology* 1992; **185**: 311–3.

13 Wang J, Kwon J, Ding X *et al.* Nonsecretory IgA1 autoantibodies targeting desmosomal component desmoglein 3 in intraepidermal neutrophilic IgA dermatosis. *Am J Pathol* 1997; **150**: 1901–7.

14 Niimi Y, Kawana S, Kusunoki T. IgA pemphigus: a case report and its characteristic clinical features compared with subcorneal pustular dermatosis. *J Am Acad Dermatol* 2000; **43**: 546–9.

15 Wallach D. Intra-epidermal immunoglobulin A pustulosis. *Dermatologica* 1990; **181**: 261–3.

16 Chorzelski TP, Beutner EH, Kowalewski C *et al.* IgA pemphigus foliaceus with a clinical presentation of pemphigus herpetiformis. *J Am Acad Dermatol* 1991; **24**: 839–44.

17 Harman KE, Holmes G, Bhogal BS *et al.* Intercellular IgA dermatosis (IgA pemphigus)—two cases illustrating the clinical heterogeneity of this disorder. *Clin Exp Dermatol* 1999; **24**: 464–6.

18 Weston WL, Friednash M, Hashimoto T *et al.* A novel childhood pemphigus vegetans variant of intraepidermal neutrophilic IgA dermatosis. *J Am Acad Dermatol* 1998; **38**: 635–8.

19 Wallach D. Intraepidermal IgA pustulosis. *J Am Acad Dermatol* 1992; **27**: 993–1000.

20 Takata M, Inaoki M, Shodo M *et al.* Subcorneal pustular dermatosis associated with IgA myeloma and intraepidermal IgA deposits. *Dermatology* 1994; **189** (Suppl. 1): 111–4.

21 Myers SA, Rico MJ. Intraepidermal neutrophilic IgA dermatosis in an HIV-infected patient. *J Am Acad Dermatol* 1994; **31**: 501–4.

22 Muldrow M. Intraepidermal neutrophilic Iga dermatosis in a patient with advanced human immunodeficiency virus infection. *Arch Dermatol* 1997; **133**: 667–8.

23 Barnadas M, Nadal C, Verger G *et al.* Intraepidermal IgA pustulosis with monoclonal IgA gammopathy in an HIV-infected patient. *Dermatology* 1997; **194**: 308–9.

24 Borradori L, Saada V, Rybojad M *et al.* Intraepidermal neutrophilic IgA pustulosis and Crohn's disease. *Br J Dermatol* 1992; **126**: 383–6.

25 Varigos GA. Subcorneal pustulosis with IgA abnormalities in serum and small bowel mucosa: case report. *Aust J Dermatol* 1979; **20**: 75–7.

26 Kishimoto K, Iwatsuki K, Akiba H *et al.* Subcorneal pustular dermatosis-type IgA pemphigus induced by thiol drugs. *Eur J Dermatol* 2001; **11**: 41–4.

27 Hashimoto T, Inamoto N, Nakamura K *et al.* Intercellular IgA dermatosis with clinical features of subcorneal pustular dermatosis. *Arch Dermatol* 1987; **123**: 1062–5.

28 Todd DJ, Bingham EA, Walsh M *et al.* Subcorneal pustular dermatosis and IgA paraproteinaemia: response to both etretinate and PUVA. *Br J Dermatol* 1991; **125**: 387–9.

29 Gruss C, Zillikens D, Hashimoto T *et al.* Rapid response of IgA pemphigus of subcorneal pustular dermatosis type to treatment with isotretinoin. *J Am Acad Dermatol* 2000; **43**: 923–6.

30 Sibley Hash K, Rencic A, Hernandez MI *et al.* Aggressive immunosuppressive therapy for a refractory case of IgA pemphigus. *Arch Dermatol* 2002; **138**: 744–6.

31 Hodak E, Lapidoth M, David M. Effect of colchicine in the subcorneal pustular dermatosis type of IgA pemphigus. *J Am Acad Dermatol* 1999; **40**: 91–4.

Subcorneal pustular dermatosis

Synonym
- Sneddon–Wilkinson disease

Definition. A chronic, relapsing, pustular eruption, mainly involving the trunk, which affects women over 40 years of age. Pustules are subcorneal.

Background. This disorder was separated from bullous impetigo in 1956 [1]. The exact nosological position of subcorneal pustular dermatosis remains controversial. Some cases may be a variant of pustular psoriasis whereas others appear to overlap with the subcorneal pustular variant of IgA pemphigus [2].

Pathogenesis. The pathogenesis is obscure. The salient feature is subcorneal accumulation of neutrophils. Culture of the pustules is sterile. Subcorneal pustular dermatosis has been reported in association with various types of immune dysfunction. Monoclonal gammopathy, usually IgA (occasionally IgG), has been reported often. The paraproteinaemia is usually benign but IgA myeloma also occurs. Other reported associations are pyoderma gangrenosum, inflammatory bowel disease and rheumatoid arthritis [3–7]. The condition has also been observed at the injection site of recombinant human granulocyte–macrophage colony-stimulating factor in a patient with IgA myeloma [8]. Excess production of TNF-α has been implicated in the pathogenesis of neutrophil activation [9].

In classical subcorneal pustular dermatosis, immunofluorescent studies are negative. However, a possible subgroup with identical clinical and histological features to the 'classical' type have intercellular IgA deposition in the upper epidermis [10,11]. Desmocollin-1 is the target antigen in these cases and a study of antigen localization by post-embedding immunoelectron microscopy, showed deposits predominantly in the extracellular spaces between keratinocytes at desmosomes, suggesting reactivity with the extracellular domain of desmocollins [12]. One case of subcorneal pustular dermatosis had IgA targeting both desmocollin-1 and desmoglein-1 [13]. There are also examples of 'classical, immunofluorescence-negative' cases in whom intercellular epidermis IgA deposits were detected on repeat immunofluorescence testing [11], in one case after a latent period of many years [14]. The relationship between the intercellular IgA dermatoses, regarded as part of the pemphigus spectrum, and classic subcorneal pustular dermatosis remains unclear (see above).

Pathology. Biopsies from early lesions show a perivascular inflammatory infiltrate with neutrophils and occasional eosinophils. Neutrophils migrate through the epidermis, without forming spongiform pustules, to collect beneath the stratum corneum in subcorneal pustules. The pustules sit on the surface of the epidermis rather than being an integral part of it. A few acantholytic cells may be found in old lesions [1]. Ultrastructural studies show cytolysis of single cells and invasion by neutrophils [15].

Both direct and indirect immunofluorescent studies are negative in classical cases [16], but recently some cases have been described with clinical features resembling classic subcorneal pustular dermatosis but with intercellular IgA within the epidermis [17–19].



Fig. 40.10 Subcorneal pustular dermatosis. Annular lesions with a scaly margin and surrounding pustules. Pus has accumulated in the lower half of the flaccid pustule leaving clear fluid in the upper half.

Clinical features [1,20,21]. The disease is more common in women than in men and usually affects individuals between 40 and 50 years of age. The eruption occurs mainly in flexures and on the flexor aspect of the limbs. The face is almost never affected, nor are the mucous membranes. The primary lesion is an oval, pea-sized flaccid pustule, which arises on normal skin or a slightly erythematous base. Characteristically, pus accumulates in the lower half of a fully developed pustule, leaving clear fluid in the upper half (Fig. 40.10). Pustules rupture easily and tend to coalesce, forming annular or serpiginous patterns with a scaly edge. The eruption fades to leave faint hyperpigmentation but successive waves of pustules pass across the previously affected areas. The interval between active and quiescent phases varies from several days to several weeks.

Prognosis. The condition is benign but chronic, with an average duration of 5.8 years [1]. The presence of myeloma worsens the outlook.

Diagnosis. The differential diagnosis includes impetigo, pustular psoriasis, pemphigus foliaceus, dermatitis herpetiformis, intercellular IgA dermatosis and acute generalized exanthematic pustulosis.

Pathogenic organisms are cultured from pustules in impetigo and the condition responds to antibiotics.

Pustular psoriasis, either of the acute von Zumbusch type with small pustules or the spreading annular type, may resemble subcorneal pustular dermatosis. Spongiosis is not a feature of subcorneal pustular dermatosis, but spongiform pustules, which are an integral part of the epidermis, are characteristic of pustular psoriasis [22]. Subcorneal pustular dermatosis, unlike pustular psoriasis, responds to dapsone. Some authors consider that subcorneal pustular dermatosis is part of the spectrum of pustular psoriasis [23].

'Atypical cases' reported as examples of subcorneal pustular dermatosis may be unusual presentations of pustular psoriasis.

Biopsies from early lesions of pemphigus foliaceus may show subcorneal pustules with very little acantholysis. Direct immunofluorescence will show intercellular IgG in the epidermis in pemphigus.

Acute generalized exanthematic pustulosis is distinguished by its acute onset in a febrile patient with a history of exposure to a candidate drug. The histology shows spongiform pustules [24].

Treatment. Dapsone 50 to 150 mg daily is the treatment of choice. Though the response to dapsone is slower than in dermatitis herpetiformis, most patients obtain partial, if not complete, relief. Sulphpyridine and sulphamethoxypyridazine have been used as alternatives. Treatment can often be weaned or stopped without relapse. Some cases do respond to potent topical corticosteroids [25] or oral steroids [9] but in general steroids are ineffective even in large doses. Etretinate [6,18,26] and acetretin [27] have been used. Isotretinoin was found ineffective at a dose of 0.5 mg/kg/d [28]. Broad-band UVB [29], narrow-band UVB [30,31], PUVA [18,32] and Re-PUVA have also been reported as effective. Colchicine [33] and topical tacalctiol [34] have been recommended. There are individual cases reports of the use of etanercept [35], combination adalimumab and mycophenolate mofetil [36] and infliximab, which produced rapid but short-lived benefit [37]. In cases associated with myeloma, the skin lesions may improve when the paraprotein is reduced by chemotherapy [19].

References

1 Sneddon I, Wilkinson D. Subcorneal pustular dermatosis. *Br J Dermatol* 1956; **68**: 385–94.
2 Reed J, Wilkinson J. Subcorneal pustular dermatosis. *Clin Dermatol* 2000; **18**: 301–13.
3 Venning VA, Ryan TJ. Subcorneal pustular dermatosis followed by pyoderma gangrenosum. *Br J Dermatol* 1986; **115**: 117–8.
4 Roger H, Thevenet JP, Souteyrand P *et al.* Subcorneal pustular dermatosis associated with rheumatoid arthritis and raised IgA: simultaneous remission of skin and joint involvements with dapsone treatment. *Ann Rheum Dis* 1990; **49**: 190–1.
5 Delaporte E, Colombel JF, Nguyen-Mailfer C *et al.* Subcorneal pustular dermatosis in a patient with Crohn's disease. *Acta Derm Venereol* 1992; **72**: 301–2.
6 Szabo E, Hamm H. Subkorneale pustulose Sneddon-Wilkinson mit IgG lambda-paraproteinamie. *HG Z Hautkrank* 1992; **67**: 792–5.
7 Cartier H, Plantin P, Leroy JP *et al.* [Pyoderma gangrenosum, subcorneal IgA pustulosis and recurrent neutrophilic pleural and pulmonary diseases in a patient with IgA gammopathy]. *Ann Dermatol Venereol* 1995; **122**: 97–101.
8 Lautenschlager S, Itin PH, Hirsbrunner P *et al.* Subcorneal pustular dermatosis at the injection site of recombinant human granulocyte-macrophage colony-stimulating factor in a patient with IgA myeloma. *J Am Acad Dermatol* 1994; **30**: 787–9.
9 Grob JJ, Mege JL, Capo C *et al.* Role of tumor necrosis factor-alpha in Sneddon-Wilkinson subcorneal pustular dermatosis. A model of neutrophil priming in vivo. *J Am Acad Dermatol* 1991; **25**: 944–7.
10 Iwatsuki K, Imaizumi S, Takagi M *et al.* Intercellular IgA deposition in patients with clinical features of subcorneal pustular dermatosis. *Br J Dermatol* 1988; **119**: 545–7.
11 Lutz ME, Daoud MS, McEvoy MT *et al.* Subcorneal pustular dermatosis: a clinical study of ten patients. *Cutis* 1998; **61**: 203–8.
12 Ishii N, Ishida-Yamamoto A, Hashimoto T. Immunolocalization of target autoantigens in IgA pemphigus. *Clin Exp Dermatol* 2004; **29**: 62–6.
13 Kopp T, Sitaru C, Pieczkowski F *et al.* IgA pemphigus—occurrence of anti-desmocollin 1 and anti-desmoglein 1 antibody reactivity in an individual patient. *J Dtsch Dermatol Ges* 2006; **4**: 1045–50.
14 Harman KE, Holmes G, Bhogal BS *et al.* Intercellular IgA dermatosis (IgA pemphigus)—two cases illustrating the clinical heterogeneity of this disorder. *Clin Exp Dermatol* 1999; **24**: 464–6.
15 Metz J, Schropl F. Elektronenmikroskopische Untersucheungen bei subkorneale pustuloser dermatose. *Arch Klin Exp Dermatol* 1970; **236**: 190–206.
16 Sneddon IB. Subcorneal pustular dermatosis. *Int J Dermatol* 1977; **16**: 640–4.
17 Hashimoto T, Inamoto N, Nakamura K *et al.* Intercellular IgA dermatosis with clinical features of subcorneal pustular dermatosis. *Arch Dermatol* 1987; **123**: 1062–5.
18 Todd DJ, Bingham EA, Walsh M *et al.* Subcorneal pustular dermatosis and IgA paraproteinaemia: response to both etretinate and PUVA. *Br J Dermatol* 1991; **125**: 387–9.
19 Takata M, Inaoki M, Shodo M *et al.* Subcorneal pustular dermatosis associated with IgA myeloma and intraepidermal IgA deposits. *Dermatology* 1994; **189** (Suppl. 1): 111–4.
20 Wilkinson D. Pustular dermatoses. *Brit J Dermatol* 1969; **81** (Suppl. 3): 38–45.
21 Sneddon IB, Wilkinson DS. Subcorneal pustular dermatosis. *Br J Dermatol* 1979; **100**: 61–8.
22 Wolff K. Subcorneal pustular dermatosis is not pustular psoriasis. *Am J Dermatopathol* 1981; **3**: 381–2.
23 Sanchez NP, Perry HO, Muller SA *et al.* Subcorneal pustular dermatosis and pustular psoriasis. A clinicopathologic correlation. *Arch Dermatol* 1983; **119**: 715–21.
24 Roujeau JC, Bioulac-Sage P, Bourseau C *et al.* Acute generalized exanthematous pustulosis. Analysis of 63 cases. *Arch Dermatol* 1991; **127**: 1333–8.
25 Walkden V, Roverts A, Wilkinson J. Two cases of subcorneal pustular dermatosis. Response to the use of intermittent topical clobetasol propionate cream. *Eur J Dermatol* 1994; **4**: 44–6.
26 Vaccaro M, Cannavo SP, Guarneri B. Subcorneal pustular dermatosis and IgA lambda myeloma: an uncommon association but probably not coincidental. *Eur J Dermatol* 1999; **9**: 644–6.
27 Marliere V, Beylot-Barry M, Beylot C *et al.* Successful treatment of subcorneal pustular dermatosis (Sneddon-Wilkinson disease) by acitretin: report of a case. *Dermatology* 1999; **199**: 153–5.
28 Rutman AJ, Powles AV, Griffiths CEM *et al.* Failure of isotretinoin to control dermatitis herpetiformis and subcorneal pustular dermatosis. *Br J Dermatol* 1988; **119**: 270–1.
29 Park YK, Park HY, Bang DS *et al.* Subcorneal pustular dermatosis treated with phototherapy. *Int J Dermatol* 1986; **25**: 124–6.
30 Orton DI, George SA. Subcorneal pustular dermatosis responsive to narrowband (TL-01) UVB phototherapy. *Br J Dermatol* 1997; **137**: 149–50.
31 Cameron H, Dawe RS. Subcorneal pustular dermatosis (Sneddon-Wilkinson disease) treated with narrowband (TL-01) UVB phototherapy. *Br J Dermatol* 1997; **137**: 150–1.
32 Bauwens M, De Coninck A, Roseeuw D. Subcorneal pustular dermatosis treated with PUVA therapy. A case report and review of the literature. *Dermatology* 1999; **198**: 203–5.
33 Pavithran K. Subcorneal pustular dermatosis in type 2 lepra reaction. *Int J Lepr Other Mycobact Dis* 1992; **60**: 89–91.
34 Kawaguchi M, Mitsuhashi Y, Kondo S. A case of subcorneal pustular dermatosis treated with tacalcitol (1alpha,24-dihydroxyvitamin D3). *J Dermatol* 2000; **27**: 669–72.
35 Bedi MK. Successful treatment of long-standing, recalcitrant subcorneal pustular dermatosis with etanercept. *Skinmed* 2007; **6**: 245–7.
36 Howell SM, Bessinger GT, Altman CE *et al.* Rapid response of IgA pemphigus of the subcorneal pustular dermatosis subtype to treatment with adalimumab and mycophenolate mofetil. *J Am Acad Dermatol* 2005; **53**: 541–3.
37 Bonifati C, Trento E, Cordiali Fei P *et al.* Early but not lasting improvement of recalcitrant subcorneal pustular dermatosis (Sneddon–Wilkinson disease) after infliximab therapy: relationships with variations in cytokine levels in suction blister fluids. *Clin Exp Dermatol* 2005; **30**: 662–5.

Paraneoplastic pemphigus

A distinctive form of pemphigus has been described in association with a variety of underlying neoplasms [1] most commonly B-cell

lymphoproliferative disorders but also thymoma, sarcomas and carcinomas [2,3]. Some cases have been linked with the use of fludarabine chemotherapy [4,5]. The clinical features overlap with erythema multiforme and lichen planus pemphigoides. Patients have severe mucosal erosions and polymorphous cutaneous signs including blisters, erosions, particularly on the upper body, and palmoplantar target lesions [1,2,6–10]. An exceptional case, associated with thymoma, had no mucosal involvement despite antibodies to cadherin and plakins typical of paraneoplastic pemphigus (PNP). In two-thirds of cases, PNP occurs with an existing neoplasm; in the remainder the neoplasm is detected after the mucocutaneous disease has occurred [2] and in one case no underlying neoplasm was found over 8 years of follow-up [11]. Biopsies show necrosis of keratinocytes or vacuolar interface dermatitis in addition to suprabasal clefting with acantholysis [12], but the specificity of these histological findings has been questioned [13].

Direct immunofluorescence reveals immunoglobulin and/or complement at the basement membrane zone as well as on the surfaces of keratinocytes. Indirect immunofluorescence is positive in both non-stratifying (simple and transitional) epithelia and stratifying epithelia [14].

Antibodies are predominantly antiplakin antibodies of the IgG1 subclass. Their pathogenicity has been established by passive transfer studies. The autoantibodies recognize a complex of antigens on immunoblotting and immunoprecipitation. These are members of the plakin family of proteins and include desmoplakin-1 (250 kD), envoplakin (210 kD), periplakin (190 kD), plectin (500 kDa) and the 230-kDa bullous pemphigoid antigen [1,15–19]. Epitope mapping shows that major antigenic sites recognized by PNP sera lie in linker subdomains of envoplakin and periplakin [20,21]. Antiplakin antibodies are not specific to PNP and have also been detected in patients with severe erythema multiforme [22], toxic epidermal necrolysis [23], bullous pemphigoid [24] and pemphigus foliaceus [25,26]. Antidesmoglein antibodies have been detected in PNP in some [19,27–29] but not all cases [30]. Clinically indistinguishable lichenoid mucocutaneous but seronegative disease has been reported in four patients with lymphoproliferative neoplasms treated with rituximab. These cases suggest that PNP can occur despite blunting the antibody response by rituximab and that cell-mediated effects may also play a role [31]. Paraneoplastic pemphigus is a multisytem disease. Passive transfer of PNP sera to mice produces autoantibody deposits in skin, upper digestive and respiratory tract epithelia, kidney, urinary bladder, and smooth and striated muscle [32]. Predisposing HLA alleles may differ in different populations, HLA-DRB1*03 being associated in French cases [33] and HLA-Cw*14 in Chinese patients [34].

Paraneoplastic pemphigus is generally refractory to all treatments. Oral steroids, azathioprine, ciclosporin, mycophenolate mofetil and plasmaphoresis have been tried [1,2,8,9,35,36]. Most patients deteriorate inexorably, with death usually secondary to sepsis, gastrointestinal bleeding, multiorgan failure or respiratory failure [2,35]. Cases associated with benign or low-grade neoplasia, such as thymoma or Castleman's disease [8,37–39], may remit partially after surgical removal of the neoplasm. One case associated with non-Hodgkin's lymphoma evolved into typical pemphigus vulgaris after a 4-year disease-free interval [40].

References

1 Anhalt GJ, Kim SC, Stanley JR *et al.* Paraneoplastic pemphigus. An autoimmune mucocutaneous disease associated with neoplasia. *N Engl J Med* 1990; **323**: 1729–35.

2 Robinson ND, Hashimoto T, Amagai M *et al.* The new pemphigus variants. *J Am Acad Dermatol* 1999; **40**: 649–71; quiz 72–3.

3 Matz H, Milner Y, Frusic-Zlotkin M *et al.* Paraneoplastic pemphigus associated with pancreatic carcinoma. *Acta Derm Venereol* 1997; **77**: 289–91.

4 Braess J, Reich K, Willert S *et al.* Mucocutaneous autoimmune syndrome following fludarabine therapy for low-grade non-Hodgkin's lymphoma of B-cell type (B-NHL). *Ann Hematol* 1997; **75**: 227–30.

5 Gooptu C, Littlewood TJ, Frith P *et al.* Paraneoplastic pemphigus: an association with fludarabine? *Br J Dermatol* 2001; **144**: 1255–61.

6 Saikia NK. Extraction of pemphigus antibodies from a lymphoid neoplasm and its possible relationship to pemphigus vulgaris. *Br J Dermatol* 1972; **86**: 411–4.

7 Redon J, Sorni G, Gonzalez-Molina A *et al.* Pemphigus associated with giant lymph node hyperplasia. *BMJ (Clin Res Ed)* 1983; **287**: 1761–2.

8 Camisa C, Helm TN, Liu YC *et al.* Paraneoplastic pemphigus: a report of three cases including one long-term survivor. *J Am Acad Dermatol* 1992; **27**: 547–53.

9 Stevens SR, Griffiths CEM, Anhalt GJ *et al.* Paraneoplastic pemphigus presenting as a lichen planus pemphigoides-like eruption. *Arch Dermatol* 1993; **129**: 866–9.

10 Zillikens D, Brocker EB. [Paraneoplastic pemphigus. Induction of autoantibodies against structural proteins in the skin]. *Hautarzt* 1994; **45**: 827–33.

11 Park GT, Lee JH, Yun SJ *et al.* Paraneoplastic pemphigus without an underlying neoplasm. *Br J Dermatol* 2007; **156**: 563–6.

12 Horn TD, Anhalt GJ. Histologic features of paraneoplastic pemphigus. *Arch Dermatol* 1992; **128**: 1091–5.

13 Kanitakis J, Wang YZ, Roche P *et al.* Immunohistopathological study of autoimmune pemphigus. Lack of strictly specific histological and indirect immunofluorescence criteria for paraneoplastic pemphigus. *Dermatology* 1994; **188**: 282–5.

14 Liu AY, Valenzuela R, Helm TN *et al.* Indirect immunofluorescence on rat bladder transitional epithelium: a test with high specificity for paraneoplastic pemphigus. *J Am Acad Dermatol* 1993; **28**: 696–9.

15 Oursler JR, Labib RS, Ariss-Abdo L *et al.* Human autoantibodies against desmoplakins in paraneoplastic pemphigus. *J Clin Invest* 1992; **89**: 1775–82.

16 Joly P, Thomine E, Gilbert D *et al.* Overlapping distribution of autoantibody specificities in paraneoplastic pemphigus and pemphigus vulgaris. *J Invest Dermatol* 1994; **103**: 65–72.

17 Joly P, Gilbert D, Thomine E *et al.* Immunofluorescence and immunoelectron microscopy analyses of a human monoclonal anti-epithelial cell surface antibody that recognizes a 185-kD polypeptide: a component of the paraneoplastic pemphigus antigen complex? *J Invest Dermatol* 1993; **101**: 339–45.

18 Hamada T, Nagata Y, Tomita M *et al.* Bullous pemphigoid sera react specifically with various domains of BP230, most frequently with C-terminal domain, by immunoblot analyses using bacterial recombinant proteins covering the entire molecule. *Exp Dermatol* 2001; **10**: 256–63.

19 Proby C, Fujii Y, Owaribe K *et al.* Human autoantibodies against HD1/plectin in paraneoplastic pemphigus. *J Invest Dermatol* 1999; **112**: 153–6.

20 Mouquet H, Drenovska K, Lartigue A *et al.* Detection and characterization of anti-envoplakin linker autoantibodies in paraneoplastic pemphigus using specific bead-based assay. *Clin Immunol* 2008; **129**: 304–12.

21 Huang Y, Li J, Zhu X. Detection of anti-envoplakin and anti-periplakin autoantibodies by ELISA in patients with paraneoplastic pemphigus. *Arch Dermatol Res* 2008; **301**: 703–9.

22 Foedinger D, Sterniczky B, Elbe A *et al.* Autoantibodies against desmoplakin I and II define a subset of patients with erythema multiforme major. *J Invest Dermatol* 1996; **106**: 1012–6.

23 Park GT, Quan G, Lee JB. Sera from patients with toxic epidermal necrolysis contain autoantibodies to periplakin. *Br J Dermatol* 2006; **155**: 337–43.

24 Okura M, Tatsuno Y, Sato M *et al.* Vesicular pemphigoid with antidesmoplakin autoantibodies. *Br J Dermatol* 1997; **136**: 794–6.

25 Jiao D, Bystryn JC. Antibodies to desmoplakin in a patient with pemphigus foliaceous. *J Eur Acad Dermatol Venereol* 1998; **11**: 169–72.

26 Kazerounian S, Mahoney MG, Uitto J *et al.* Envoplakin and periplakin, the paraneoplastic pemphigus antigens, are also recognized by pemphigus foliaceus autoantibodies. *J Invest Dermatol* 2000; **115**: 505–7.

27 Amagai M, Nishikawa T, Nousari HC *et al.* Antibodies against desmoglein 3 (pemphigus vulgaris antigen) are present in sera from patients with

paraneoplastic pemphigus and cause acantholysis in vivo in neonatal mice. *J Clin Invest* 1998; **102**: 775–82.
28 Bouloc A, Joly P, Saint-Leger E *et al.* Paraneoplastic pemphigus with circulating antibodies directed exclusively against the pemphigus vulgaris antigen desmoglein 3. *J Am Acad Dermatol* 2000; **43**: 714–7.
29 Ohyama M, Amagai M, Hashimoto T *et al.* Clinical phenotype and anti-desmoglein autoantibody profile in paraneoplastic pemphigus. *J Am Acad Dermatol* 2001; **44**: 593–8.
30 Inaoki M, Kodera M, Fujimoto A *et al.* Paraneoplastic pemphigus without anti-desmoglein 3 or antidesmoglein 1 autoantibodies. *Br J Dermatol* 2001; **144**: 610–3.
31 Cummins DL, Mimouni D, Tzu J *et al.* Lichenoid paraneoplastic pemphigus in the absence of detectable antibodies. *J Am Acad Dermatol* 2007; **56**: 153–9.
32 Nguyen VT, Ndoye A, Bassler KD *et al.* Classification, clinical manifestations, and immunopathological mechanisms of the epithelial variant of paraneoplastic autoimmune multiorgan syndrome: a reappraisal of paraneoplastic pemphigus. *Arch Dermatol* 2001; **137**: 193–206.
33 Martel P, Loiseau P, Joly P *et al.* Paraneoplastic pemphigus is associated with the DRB1*03 allele. *J Autoimmun* 2003; **20**: 91–5.
34 Liu Q, Bu DF, Li D *et al.* Genotyping of HLA-I and HLA-II alleles in Chinese patients with paraneoplastic pemphigus. *Br J Dermatol* 2008; **158**: 587–91.
35 Anhalt GJ. Paraneoplastic pemphigus. *Adv Dermatol* 1997; **12**: 77–96; discussion 7.
36 Izaki S, Yoshizawa Y, Kitamura K *et al.* Paraneoplastic pemphigus: potential therapeutic effect of plasmapheresis. *Br J Dermatol* 1996; **134**: 987–9.
37 Plewig G, Jansen T, Jungblut RM *et al.* [Castleman tumor, lichen ruber and pemphigus vulgaris: paraneoplastic association of immunological diseases?]. *Hautarzt* 1990; **41**: 662–70.
38 Gili A, Ngan BY, Lester R. Castleman's disease associated with pemphigus vulgaris. *J Am Acad Dermatol* 1991; **25**: 955–9.
39 Jansen T, Plewig G, Anhalt GJ. Paraneoplastic pemphigus with clinical features of erosive lichen planus associated with Castleman's tumor. *Dermatology* 1995; **190**: 245–50.
40 Ishii N, Hashimoto T. A case of paraneoplastic pemphigus who shifted to pemphigus vulgaris. *J Eur Acad Dermatol Venereol* 2008; **22**: 374–5.

Structure of the dermoepidermal junction

The basal keratinocytes of the epidermis are separated from the underlying dermis by the basement membrane, a two-layered structure on electron microscopy comprising the lamina lucida, the major components of which are laminins and the lamina densa. Above the lamina lucida, straddling the plasma membrane of the epidermal basal cells are discrete, electron-dense structures, the hemidesmosomes. Fine structures, the anchoring filaments, traverse the lamina lucida, particularly in the region of the hemidesmosomes, and appear to terminate in the lamina densa, rich in both laminin 5 and type IV collagen [1]. Beneath the lamina densa and appearing to embed in the upper dermis are curved structures, the anchoring fibrils, composed of type VII collagen (Fig. 40.11) [2]. The laminins are glycoprotein molecules composed of three chains (α, β and γ) bound through disulphide bonds. There are at least 15 different laminin isoforms, which are tissue and development specific. Recently, the nomenclature for the laminin family was revised to assign three-digit numbers to each laminin isoform. For example, the laminin isoform composed of α3β3γ2, formerly known as laminin-5 (also termed kalinin, epiligrin, ladsin or nicein) is now called laminin-332 [3].

The intracellular plaque of the hemidesmosomes contains a 230-kDa polypeptide, a member of the plakin family known as BP230 or BPAg1 as it binds to sera of patients with bullous pemphigoid [4]. Other components of the intracellular plaque are plectin (MW 500 kDa) and the less well characterized antigens HD1, IFAP300 and P200. The intracytoplasmic keratin intermediate filaments (keratins types 5 and 14), organized into tonofilaments, loop down and insert into the hemidesmosomes where they interact with the carboxyterminals of BP230 and plectin.

The transmembrane components of the hemidesmosome include BP180/collagen XVII and α6β4 integrin (see Fig. 40.11). Collagen XVII (MW 180 kD, also known as BP180 as it binds bullous pemphigoid sera) comprises an intracellular globular domain, where its NH_2 terminal interacts with the NH_2 terminal of BP230 [5], with additional stabilizing interactions with both plectin and β4 integrin [6]. The long extracellular collagenous domain of collagen XVII is shed by the physiological action of proteases [7] and interacts both with α6 integrin [6] and with the β3 chain of laminin 5 (laminin-332) in the region of the anchoring filaments. Laminin 5 (laminin-332) also interacts with other laminin isoforms, with both β4 and α6 integrin [8] as well as being the principal ligand for type VII collagen, the main component of the anchoring fibrils. Hence laminin serves as a bridge between the transmembrane hemidesmosomal molecules and the dermal matrix molecules.

These structures collectively form the adhesion complex of the dermoepidermal junction, with continuity running from the keratin filaments within the epidermal cells via the hemidesmosomes, the anchoring filaments and through to the anchoring fibrils embedded in the dermis. In normal skin mechanical stability and adhesion between the epidermis and dermis depends on the integrity of the adhesion complex components. Mutations of these molecules produce skin fragility and blistering, and are considered in Chapter 39. Autoantibody-mediated diseases have been described in relation to BP230, BP180, P200, α6 and β4 integrin, laminin 5 (laminin-332) and type VII collagen, and these are considered in this chapter. There are also case reports of autoimmune bullous disease with antibodies to type IV collagen and plectin.

References

1 Shimizu H. New insights into the immunoultrastructural organization of cutaneous basement membrane zone molecules. *Exp Dermatol* 1998; **7**: 303–13.
2 Borradori L, Sonnenberg A. Structure and function of hemidesmosomes: more than simple adhesion complexes. *J Invest Dermatol* 1999; **112**: 411–8.
3 Sugawara K, Tsuruta D, Ishii M *et al.* Laminin-332 and -511 in skin. *Exp Dermatol* 2008; **17**: 473–80.
4 Stanley J, Hawley-Nelson P, Yuspa S *et al.* Characterization of bullous pemphigoid antigen—a unique basement membrane protein of stratified squamous epithelia. *Cell* 1981; **24**: 897–903.
5 Hopkinson SB, Jones JC. The N terminus of the transmembrane protein BP180 interacts with the N-terminal domain of BP230, thereby mediating keratin cytoskeleton anchorage to the cell surface at the site of the hemidesmosome. *Mol Biol Cell* 2000; **11**: 277–86.
6 Hopkinson SB, Findlay K, deHart GW *et al.* Interaction of BP180 (type XVII collagen) and alpha6 integrin is necessary for stabilization of hemidesmosome structure. *J Invest Dermatol* 1998; **111**: 1015–22.
7 Schacke H, Schumann H, Hammami-Hauasli N *et al.* Two forms of collagen XVII in keratinocytes. A full-length transmembrane protein and a soluble ectodomain. *J Biol Chem* 1998; **273**: 25937–43.
8 Jones JC, Hopkinson SB, Goldfinger LE. Structure and assembly of hemidesmosomes. *Bioessays* 1998; **20**: 488–94.

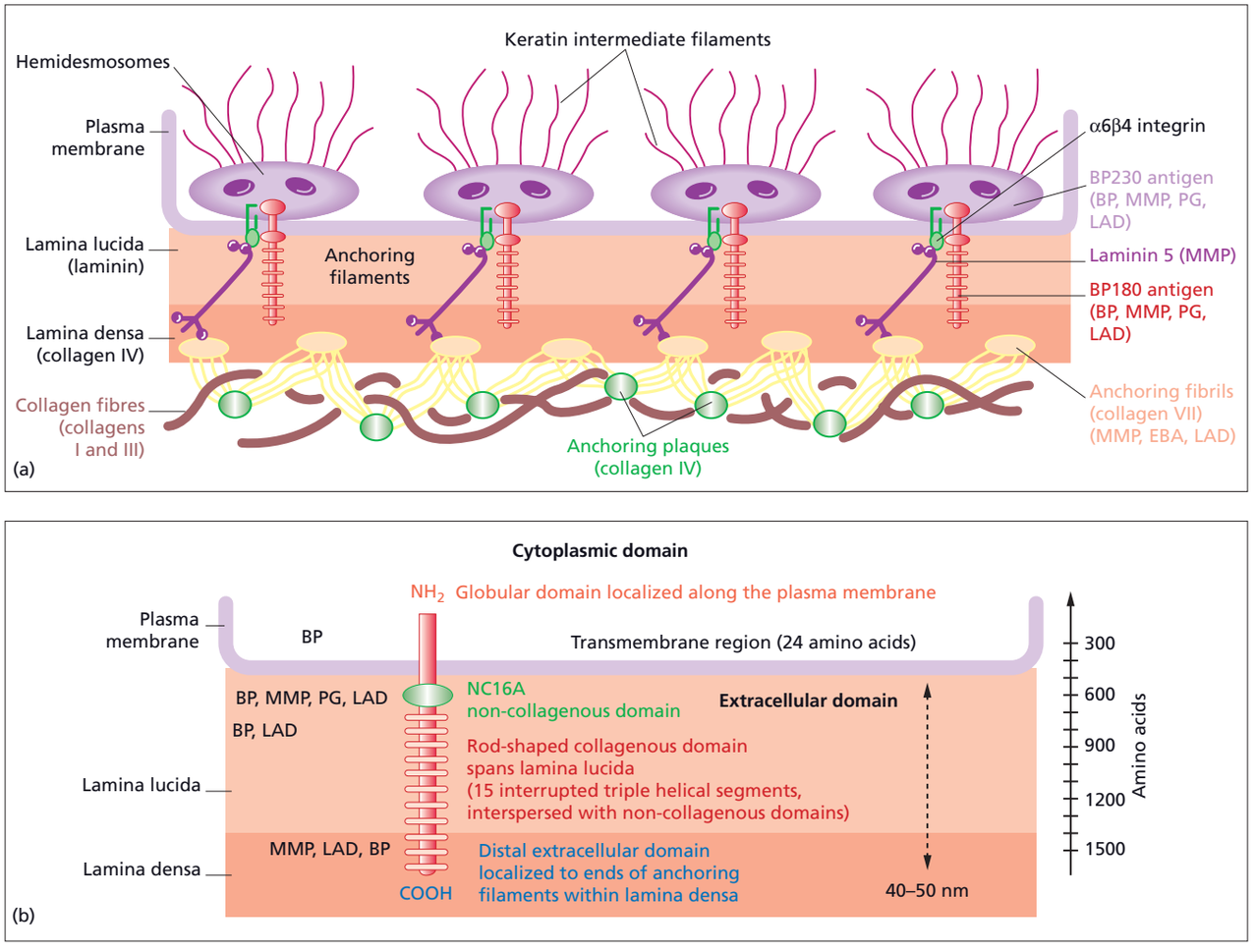


Fig. 40.11 The dermal–epidermal junction. (a) The structure of the adhesion complex of the basement-membrane zone. (b) The structure of BP180/collagen XVII, showing sites of antigen binding. BP, bullous pemphigoid; EBA, epidermolysis bullosa acquisita; LAD, linear IgA disease; MMP, mucous membrane pemphigoid; PG, pemphigoid gestationis. (Courtesy of Dr J. Allen, Oxford Radcliffe Hospital, Oxford, UK.)

Subepidermal immunobullous diseases

These bullous diseases include a number of clinical entities (Table 40.4). However, there is clinical overlap and it is not uncommon for individual patients to be difficult to classify clinically (Fig. 40.12). The histology and immunofluorescence similarly are not always distinctive, and the identification of the target antigens for these diseases has demonstrated that not only are the antigens and their specific epitopes common to many of the entities, they are often multiple within a patient. In addition, new antigens are still being described. It seems likely that many as yet poorly characterized or undiscovered molecules within the anchoring complex of the basement-membrane zone can be the targets for autoantibodies in the subepidermal blistering diseases. The expectation that perhaps the immunogenetic constitution of the individual might determine the disease has been only partially fulfilled. Thus, the clinical overlap is reflected in immunopathological and immunogenetic overlap (Fig. 40.12) and is shown in Tables 40.5 and 40.6.

The subepidermal autoimmune bullous diseases are, with the exception of dermatitis herpetiformis, characterized by autoanti-

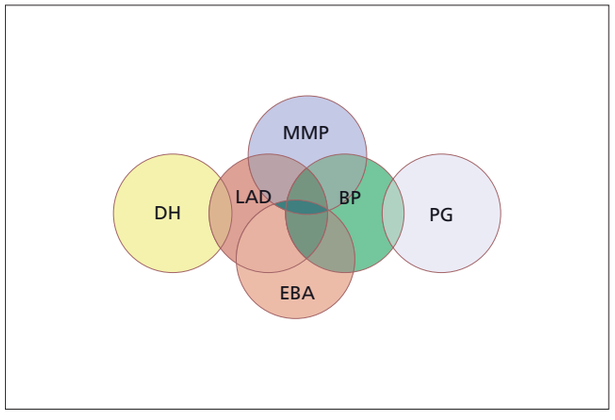


Fig. 40.12 The clinical and immunopathological overlap between the subepidermal blistering diseases. BP, bullous pemphigoid; DH, dermatitis herpetiformis; EBA, epidermolysis bullosa acquisita; LAD, linear IgA disease; MMP, mucous membrane pemphigoid; PG, pemphigoid gestationis.

Table 40.4 The subepidermal immunobullous diseases.

Bullous pemphigoid
variant: pemphigoid nodularis
variant: localized pemphigoid
variant: localized vulvar pemphigoid
variant: pemphigoid vegetans
variant: lichen planus pemphigoides
Mucous membrane pemphigoid
variant: oral pemphigoid
variant: Brunsting–Perry pemphigoid
Pemphigoid gestationis
Linear IgA disease
variant: chronic bullous disease of childhood
variant: linear IgA disease of adults
variant: dermal associated linear IgA disease
variant: linear IgA mucous membrane pemphigoid
variant: mixed immunobullous disease
Epidermolysis bullosa acquisita
variant: IgA epidermolysis bullosa acquisita
variant: epidermolysis bullosa acquisita mucous membrane pemphigoid
Bullous systemic lupus erythematosus
Dermatitis herpetiformis

bodies directed against components of the adhesion complex (see Fig. 40.11). The use of the patient's sera to identify these antigens and their genes has made a major contribution to cell and molecular biology. The mechanisms by which the autoimmune process is initiated and how the combination of antibody with antigen results in blistering are in the process of being elucidated. However, evidence is accumulating that the autoantibodies are pathogenic and animal and other experimental models have demonstrated this with regard to many of the autoantigens, as described below.

Bullous pemphigoid

Synonym
- Pemphigoid

Definition. A blistering disease of elderly people which often starts with pruritus and urticated and erythematous lesions. Later, large, tense blisters develop both on erythematous and on normal skin and there may be mucosal involvement with blisters and erosions. The blisters are subepidermal and intact epidermis forms the roof. Autoantibodies, chiefly IgG, to the epidermal basement-membrane zone are found in the skin and blood [1].

The clinical features, immunopathology and immunogenetics are summarized in Tables 40.5 and 40.6, and see Figs 40.13 and 40.14.

Table 40.5 The subepidermal immunobullous diseases: clinical features.

Disease	Patients	Cutaneous distribution	Mucosal involvement	Lesions	Associations	Treatment	Prognosis
Bullous pemphigoid	Elderly (few infants & children)	Trunk, limbs, flexures	Common, minor	Urticated plaques, tense blisters, (milia)	Neurological disease Psoriasis see text	Steroids, dapsone, immunosuppressives	3–6 years' duration
Mucous membrane pemphigoid	Middle–old age	Infrequent (30%)	Major, severe	Erosions, blisters, gingivitis, milia *Scarring*	Autoimmune disease	Steroids, dapsone, immunosuppressives	Chronic
Pemphigoid gestationis	Pregnant women	Umbilicus, generalized	Minor	Urticated plaques, tense blisters	Autoimmune thyroid disease	Steroids	Remits postpartum
Linear IgA disease chronic bullous disease of childhood	Children	Perineum, face, trunk, limbs	Majority (few severe)	Urticated plaques, annular lesions, tense blisters		Dapsone, sulphonamides	3–4 years' duration (few persist)
adult linear IgA disease	Young adults to elderly	Trunk, limbs	Majority (few severe)	Urticated plaques, tense blisters, papulovesicles	Ulcerative colitis, rare lymphoma	Dapsone, sulphonamides	3–6 years' duration (few persist)
Epidermolysis bullosa acquisita	Adults & children	Generalized, variable	Some (few severe)	Urticated plaques, tense blisters, milia *Scarring*	Inflammatory bowel disease	Steroids, dapsone, immunosuppressives	Persists
Bullous SLE	Adults	Generalized, variable	Minor	Urticated plaques, tense blisters	SLE	Dapsone	Transient
Dermatitis herpetiformis	Young adults (some children and elderly)	Symmetrical, elbows, knees, buttocks	Minor	Papulovesicles	Gluten-sensitive enteropathy, lymphoma	Dapsone, sulphonamides, gluten-free diet	Persists

Table 40.6 The subepidermal immunobullous diseases: immunopathology and immunogenetics.

Disease	BMZ antibodies							Immunogenetics	
	Direct IMF	Isotype	Binding to split skin	Target antigens	Antigens (kDa)	Location	Structure	MHC and class I and II	MHC class III
Bullous pemphigoid	Linear BMZ	IgG (few IgA)	Epidermal (few dermal)	BP230 BP180	230 180 200 Others	Hemidesmosome Transmembrane	Dense plaque Dense plaque	DQ7 (males)	
Mucous membrane pemphigoid		Linear BMZ IgG, IgA	Epidermal	BP180 BP230 α6β4 integrin ?	180 230 120 205 45	Lamina lucida Hemidesmosome Hemidesmosome	Anchoring filament	DQ7	
		few dermal		Laminin 5 Collagen VII	600 290	Lamina lucida Lamina densa	Anchoring filament Anchoring fibril		
Pemphigoid gestationis	Linear BMZ	IgG	Epidermal	BP230 BP180	230 180	Hemidesmosome	Dense plaque	A1, B8, DR3/4	C4 null
Linear IgA disease (CBDC and adult LAD)	Linear BMZ	IgA	Epidermal (majority)	BP180 (shed ectodomain) LAD285 BP230	180 120/97 285 230	Hemidesmosome and lamina lucida Hemidesmosome	Anchoring filament Dense plaque Anchoring fibril	B8, CW7, DR3,	TNF2 (some homozygous)
			Dermal (minority)	Collagen VII Other	Collagen VII 285	Lamina densa			
Epidermolysis bullosa acquisita	Linear BMZ	IgG	Dermal	Collagen VII (anchoring fibril)	290	Lamina densa	Anchoring fibril	DR2	
Bullous SLE	Linear BMZ	IgG, IgA	Dermal	Collagen VII (anchoring fibril) Others	290	Lamina densa Lamina densa	Anchoring fibril	DR2	
Dermatitis herpetiformis	Granular dermal papillae	IgA	Negative	Unknown ?epidermal tissue transglutaminase		Upper dermis		A1, B8, DR3 DQw2	TNF2 TNFB*1

IMF, immunofluorescence; BMZ, basement-membrane zone; MHC, major histocompatibility complex; CBDC, chronic bullous disease of childhood; LAD, linear IgA disease.

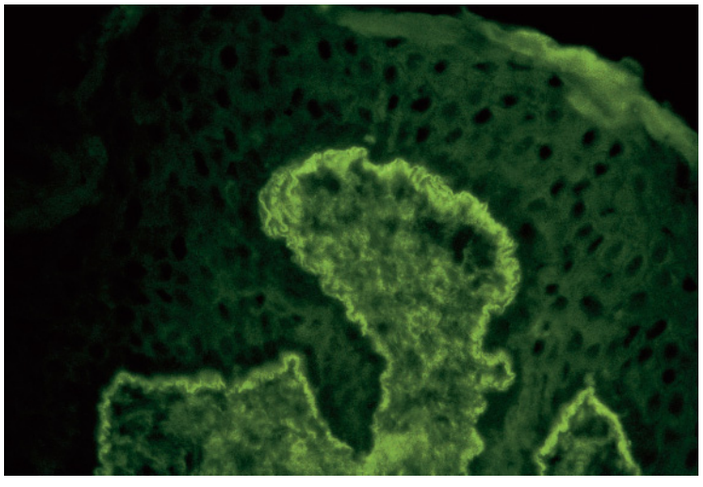


Fig. 40.13 Immunofluorescence showing IgG at the basement-membrane zone in a patient with pemphigoid. (Courtesy of Dr R.J. Pye, Addenbrooke's Hospital, Cambridge, UK.)

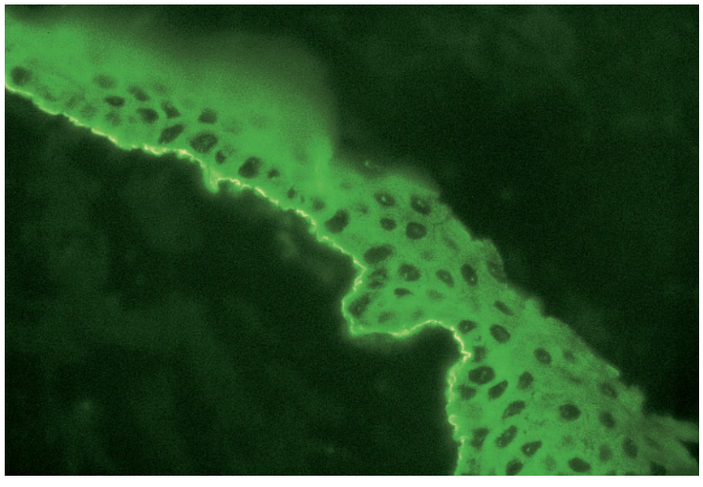


Fig. 40.14 Split-skin substrate with pemphigoid sera showing immunofluorescence of the roof of the split. (Courtesy of Dr J. Allen, Oxford Radcliffe Hospital, Oxford, UK.)

Reference

1 Kirtschig G, Wojnarowska F. Autoimmune blistering diseases: an up-date of diagnostic methods and investigations. *Clin Exp Dermatol* 1994; **19**: 97–112.

Aetiology. Bullous pemphigoid is an affliction of elderly people, with onset usually after 60 years of age, with a mean of 80 years [1], but the condition can occur in the under-forties, and about 80 cases have been described in children, the youngest being 10 weeks or less at onset of their disease [2–6]. The risk of developing bullous pemphigoid increases with age [1,7]. Bullous pemphigoid is the commonest immunobullous disease in Western Europe. In France and Germany, the incidence of bullous pemphigoid is estimated to be six to seven cases per million population per year [8,9] and is similar in Singapore [10]. In the UK, the rates are higher and increasing, being 14 per million in Scotland [11] and 30 per million in central UK [1,12]. However, in other countries of the Middle and Far East bullous pemphigoid appears to be rarer [13], and more likely to develop in Indians than Chinese [10,14,15]. Recent work suggests that in Northern Europeans HLA-DQ7 may be associated with bullous pemphigoid but only in men [16,17]. This association does not exist in either Chinese or Japanese patients [18,19].

References

1 Langan SM, Smeeth L, Hubbard R *et al.* Bullous pemphigoid and pemphigus vulgaris—incidence and mortality in the UK: population based cohort study. *BMJ* 2008; **337**: a180.

2 Oranje AP, Vuzevski VD, van Joost T *et al.* Bullous pemphigoid in children. Report of three cases with special emphasis on therapy. *Int J Dermatol* 1991; **30**: 339–42.

3 Nemeth AJ, Klein AD, Gould EW *et al.* Childhood bullous pemphigoid. Clinical and immunologic features, treatment, and prognosis. *Arch Dermatol* 1991; **127**: 378–86.

4 Kirtschig G, Wojnarowska F, Marsden RA *et al.* Acquired bullous diseases of childhood: re-evaluation of diagnosis by indirect immunofluorescence examination on 1 M NaCl split skin and immunoblotting. *Br J Dermatol* 1994; **130**: 610–6.

5 Amos B, Deng JS, Flynn K *et al.* Bullous pemphigoid in infancy: case report and literature review. *Pediatr Dermatol* 1998; **15**: 108–11.

6 Waisbourd-Zinman O, Ben-Amitai D, Cohen AD *et al.* Bullous pemphigoid in infancy: clinical and epidemiologic characteristics. *J Am Acad Dermatol* 2008; **58**: 41–8.

7 Jung M, Kippes W, Messer G *et al.* Increased risk of bullous pemphigoid in male and very old patients: a population-based study on incidence. *J Am Acad Dermatol* 1999; **41**: 266–8.

8 Bernard P, Vaillant L, Labeille B *et al.* Incidence and distribution of subepidermal autoimmune bullous skin diseases in three French regions. Bullous Diseases French Study Group. *Arch Dermatol* 1995; **131**: 48–52.

9 Zillikens D, Wever S, Roth A *et al.* Incidence of autoimmune subepidermal blistering dermatoses in a region of central Germany. *Arch Dermatol* 1995; **131**: 957–8.

10 Wong SN, Chua SH. Spectrum of subepidermal immunobullous disorders seen at the National Skin Centre, Singapore: a 2-year review. *Br J Dermatol* 2002; **147**: 476–80.

11 Gudi VS, White MI, Cruickshank N *et al.* Annual incidence and mortality of bullous pemphigoid in the Grampian Region of North-east Scotland. *Br J Dermatol* 2005; **153**: 424–7.

12 Reed JR, Wojnarowska F. The Incidence of Bullous Pemphigoid and Other Autoimmune Bullous Diseases in Oxfordshire, England. (Unpublished).

13 Nanda A, Al-Saeid K, Al-Sabah H *et al.* Clinicoepidemiological features and course of 43 cases of bullous pemphigoid in Kuwait. *Clin Exp Dermatol* 2006; **31**: 339–42.

14 Adam BA. Bullous diseases in Malaysia: epidemiology and natural history. *Int J Dermatol* 1992; **31**: 42–5.

15 Jin P, Shao C, Ye G. Chronic bullous dermatoses in China. *Int J Dermatol* 1993; **32**: 89–92.

16 Delgado J, Turbay D, Yunis E *et al.* A common major histocompatibility complex class II allele HLA-DQB1*0301 is present in clinical variants of pemphigoid. *Proc Natl Acad Sci* 1996; **93**: 8569–71.

17 Banfield C, Wojnarowska F, Allen J *et al.* The association of HLA-DQ7 and bullous pemphigoid is restricted to men. *Br J Dermatol* 1998; **138**: 1085–90.

18 Okazaki A, Miyagawa S, Yamashina Y *et al.* Polymorphisms of HLA-DR and -DQ genes in Japanese patients with bullous pemphigoid. *J Dermatol* 2000; **27**: 149–56.

19 Gao XH, Winsey S, Li G *et al.* HLA-DR and DQ polymorphisms in bullous pemphigoid from northern China. *Clin Exp Dermatol* 2002; **27**: 319–21.

Pathogenesis. Bullous pemphigoid provides one of the best models for an autoimmune disease. The disease is characterized by IgG autoantibodies to hemidesmosome-associated proteins within the adhesion complex (see Fig. 40.11). The target antigens have been characterized and their genes cloned (see below). The autoantibodies have been shown to be pathogenic and complement to be necessary for blister formation [1–3]. Current knowledge of the pathophysiology of bullous pemphigoid has recently been summarized [4].

The two major bullous pemphigoid antigens are BP230 and BP180, which are associated with hemidesmosomes (see Fig. 40.11) and are the products of genes located on different chromosomes [5].

BP230, also known as BPAG1, was the first to be characterized and has a molecular weight of 230 kDa [6,7]. BP230 is intracellular and localized to the dense plaque [8]. The gene for BP230 has been cloned and resides on the short arm of chromosome 6 [9,10]. It is known to have isoforms which are differentially expressed in epithelial and neuronal tissue [11]. The portions of BP230 antigen that are the target for the autoantibodies (immunodominant epitopes) are located chiefly at the carboxy terminal end which mediates the interaction of keratin intermediate filaments with hemidesmosome [12,13].

BP180, also known as BPAG2 and collagen type XVII, has a molecular weight of 180 kDa [6,14], and is a transmembrane molecule with collagenous domains and a long extracellular portion, which is shed under physiological conditions (see Fig. 40.11) [15,16]. The gene for BP180 has been cloned and is situated on the long arm of chromosome 10 [5,15]. It is located in the hemidesmosome and the extracellular portion interacts with the anchoring filaments [8,17]. The extracellular region adjacent to the transmembrane portion, the NC16A domain, is the immunodominant epitope, however other epitopes are found in many regions of the molecule, including the intracellular region, the shed collagenous ectodomain and the carboxy terminal (see Fig. 40.11) [8,18–23]. This extracellular location makes it a likely candidate for pathogenic autoantibodies.

There are reports of other target antigens in individual patients, the most common being p200, 200 kDa weight, which is associated with the epidermis and dermis [6,24,25].

After 20 years of research it is still unclear as to which autoantigen is the most important in the pathogenesis of bullous pemphigoid. Two animal models have demonstrated that the BP180 autoantibodies in bullous pemphigoid are pathogenic. In the first

model, injection of bullous pemphigoid autoantibodies into rabbit cornea produced subepidermal blisters and immune deposits of IgG and C3 along the basement-membrane zone [1]. Other attempts were unsuccessful until molecular biology demonstrated that the chief epitope differed in mice and humans. Antibodies were raised to the immunodominant mouse epitope of BP180, and these antibodies produced immunopathological bullous pemphigoid in neonatal mice [2]. Early models for pathogenicity of BP230 were successful only with the use of epidermis damaged by UV [26], but more recently a model similar to that for BP180 has induced bullous pemphigoid in mice [3].

The formation of blisters begins with autoantibody deposition, which binds C3 along the dermoepidermal junction [27]. These antibodies are directed at BP180 and BP230 and are mainly of the IgG subclass, predominantly IgG1 and IgG4 isotypes [28]. There is a change with disease duration and remission in the relative amounts of inflammatory IgG1 and less inflammatory blocking IgG4 [29], although IgG4 can contribute to the inflammatory process [30]. The pivotal role of complement has been demonstrated using the mouse model used previously to deduce the autoimmune basis of bullous pemphigoid [2]. Mice depleted of complement did not develop blisters following the injection of pathogenic rabbit BP180 antibodies, and $F(ab')_2$ fragments of the IgG antibody, which cannot bind complement, did not produce disease when injected into animals [31]. Blister formation in C5 deficient mice could be restored if fragments of C5a were injected with the pathogenic anti-BP180 IgG. C5a fragments are thought to stimulate the recruitment of neutrophils to the site of inflammation [31]. The importance of neutrophil recruitment in the pathogenesis of this disease has been shown using the mouse model. Mice depleted of neutrophils by pre-treatment with an antineutrophil serum become resistant to the pathogenic effects of BP180 antibodies [32], indicating that the inflammatory response in bullous pemphigoid is in part mediated by neutrophils. Macrophages too are essential [33]. The role of proteases in blister formation has been shown using mouse models either genetically deficient for neutrophil elastase or with elastase inhibitors, and by demonstrating that elastase can cleave BP180 *in vitro* and *in vivo* [34]. Eosinophil infiltration occurs [35] and releases a 92 kDa-gelatinase (gelatinase B or MMP-9) at the blister site that can cleave BP180 [36]. Mice genetically deficient for gelatinase B did not produce blisters after infusion with antibodies to BP180, unless reconstituted with neutrophils from normal mice [37].

All these data taken together suggest a mechanism for blister formation. Autoantibodies bind to the bullous pemphigoid antigens and activate complement. Complement components set off an inflammatory cascade attracting leukocytes, degranulating mast cells and releasing inflammatory mediators. The activated inflammatory cells release lysosomal enzymes and proteases, cleaving the target antigens and disrupting the hemidesmosomes, resulting in blister formation.

There is accumulating evidence for the role of T cells, both Th1 and Th2, directly by producing inflammatory cytokines and indirectly by production of the autoantibodies in bullous pemphigoid, most of this work concerns reactivity to BP180 but reactivity to BP230 has also been demonstrated [38–41].

References

1 Anhalt G, Bahn C, Labib R *et al.* Pathogenic effects of bullous pemphigoid autoantibodies on rabbit corneal epithelium. *J Clin Invest* 1981; **68**: 1097–101.

2 Liu Z, Diaz LA, Troy JL *et al.* A passive transfer model of the organ-specific autoimmune disease, bullous pemphigoid, using antibodies generated against the hemidesmosomal antigen, BP180. *J Clin Invest* 1993; **92**: 2480–8.

3 Kiss M, Husz S, Janossy T *et al.* Experimental bullous pemphigoid generated in mice with an antigenic epitope of the human hemidesmosomal protein BP230. *J Autoimmun* 2005; **24**: 1–10.

4 Kasperkiewicz M, Zillikens D. The pathophysiology of bullous pemphigoid. *Clin Rev Allergy Immunol* 2007; **33**: 67–77.

5 Sawamura D, Li K, Uitto J. 230-kDa and 180-kDa bullous pemphigoid antigens are distinct gene products. *J Invest Deramtol* 1992; **98**: 942–3.

6 Labib R, Anhalt G, Patel H *et al.* Molecular heterogeneity of the bullous pemphigoid antigens as detected by immunoblotting. *J Immunol* 1986; **136**: 1231–5.

7 Muller S, Klaus-Kovtun V, Stanley J. A 230-kDa basic protein is the major bullous pemphigoid antigen. *J Invest Dermatol* 1989; **92**: 33–8.

8 Ishiko A, Shimizu H, Ebihara T *et al.* Human autoantibodies against the 230-kD bullous pemphigoid antigen (BPAG1) bind only to the intracellular domain of the hemidesmosome, whereas those against the 180-kD bullous pemphigoid antigen (BPAG2) bind along the plasma membrane of the hemidesmosome in normal human and swine skin. *J Clin Invest* 1993; **91**: 1608–15.

9 Stanley J, Tanaka T, Mueller S *et al.* Isolation of complementary cDNA for bullous pemphigoid antigen by use of patients' autantibodies. *J Clin Invest* 1988; **82**: 1864–70.

10 Sawamura D, Nomura K, Sugita Y *et al.* Bullous pemphigoid antigen (BPAG1): cDNA cloning and mapping of the gene to the short arm of human chromosome 6. *Genomics* 1990; **8**: 722–6.

11 Dowling J, Yang Y, Wollmann R *et al.* Developmental expression of BPAG1-n: insights into the spastic ataxia and gross neurologic degeneration in dystonia musculorum mice. *Dev Biol* 1997; **187**: 131–42.

12 Miller JE, Rico MJ, Hall RP 3rd. IgG antibodies from patients with bullous pemphigoid bind to fusion proteins encoded by BPAg1 cDNA. *J Invest Dermatol* 1993; **101**: 779–82.

13 Skaria M, Jaunin F, Hunziker T *et al.* IgG autoantibodies from bullous pemphigoid patients recognize multiple antigenic reactive sites located predominantly within the B and C subdomains of the COOH-terminus of BP230. *J Invest Dermatol* 2000; **114**: 998–1004.

14 Morrison L, Labib R, Zone J *et al.* Herpes gestationis autoantibodies recognize a 180kD human epidermal antigen. *J Clin Invest* 1988; **81**: 2023–6.

15 Giudice C, Emerty D, Diaz I. Cloning and primary structural analysis of the bullous pemphigoid autoantigen BP180. *J Invest Dermatol* 1992; **99**: 243–50.

16 Schacke H, Schumann H, Hammami-Hauasli N *et al.* Two forms of collagen XVII in keratinocytes. A full-length transmembrane protein and a soluble ectodomain. *J Biol Chem* 1998; **273**: 25937–43.

17 Diaz L, Ratrie H, Saunders W *et al.* Isolation of human epidermal cDNA corresponding to 180-kD autoantigen recognised by bullous pemphigoid and herpes gestationes sera: immunolocalization of this protein to the hemidesmosome. *J Clin Invest* 1990; **86**: 1088–94.

18 Giudice GJ, Emery DJ, Zelickson BD *et al.* Bullous pemphigoid and herpes gestationis autoantibodies recognize a common non-collagenous site on the BP180 ectodomain. *J Immunol* 1993; **151**: 5742–50.

19 Zillikens D, Rose PA, Balding SD *et al.* Tight clustering of extracellular BP180 epitopes recognized by bullous pemphigoid autoantibodies. *J Invest Dermatol* 1997; **109**: 573–9.

20 Perriard J, Jaunin F, Favre B *et al.* IgG autoantibodies from bullous pemphigoid (BP) patients bind antigenic sites on both the extracellular and the intracellular domains of the BP antigen 180. *J Invest Dermatol* 1999; **112**: 141–7.

21 Schumann H, Baetge J, Tasanen K *et al.* The shed ectodomain of collagen XVII/BP180 is targeted by autoantibodies in different blistering skin diseases. *Am J Pathol* 2000; **156**: 685–95.

22 Hofmann S, Thoma-Uszynski S, Hunziker T *et al.* Severity and phenotype of bullous pemphigoid relate to autoantibody profile against the NH2- and COOH-terminal regions of the BP180 ectodomain. *J Invest Dermatol* 2002; **119**: 1065–73.

23 Di Zenzo G, Grosso F, Terracina M *et al.* Characterization of the anti-BP180 autoantibody reactivity profile and epitope mapping in bullous pemphigoid patients. *J Invest Dermatol* 2004; **122**: 103–10.

24 Zillikens D, Kawahara Y, Ishiko A *et al.* A novel subepidermal blistering disease with autoantibodies to a 200-kDa antigen of the basement membrane zone. *J Invest Dermatol* 1996; **106**: 1333–8.
25 Shimanovich I, Rose C, Hirako Y *et al.* [Anti-p200 pemphigoid–a new bullous autoimmune dermatosis]. *J Dtsch Dermatol Ges* 2004; **2**: 7–14.
26 Hall RP 3rd, Murray JC, McCord MM *et al.* Rabbits immunized with a peptide encoded for by the 230-kD bullous pemphigoid antigen cDNA develop an enhanced inflammatory response to UVB irradiation: a potential animal model for bullous pemphigoid. *J Invest Dermatol* 1993; **101**: 9–14.
27 Schmidt-Ullrich B, Rule A, Schaumburg-Lever G *et al.* Ultrastructural localization of in vivo-bound complement in bullous pemphigoid. *J Invest Dermatol* 1975; **65**: 217–9.
28 Bird P, Friedmann P, Ling N *et al.* Subclass distribution of IgG autoantibodies in bullous pemphigoid. *J Invest Dermatol* 1986; **86**: 21–5.
29 Modre B, Allen J, Wojnarowska F. Does class switching contribute to remission in bullous pemphigoid? *Acta Dermato-Venerologica* 1999; **79**: 127–31.
30 Mihai S, Chiriac MT, Herrero-Gonzalez JE *et al.* IgG4 autoantibodies induce dermal-epidermal separation. *J Cell Mol Med* 2007; **11**: 1117–28.
31 Liu Z, Giudice GJ, Swartz SJ *et al.* The role of complement in experimental bullous pemphigoid. *J Clin Invest* 1995; **95**: 1539–44.
32 Liu Z, Giudice GJ, Zhou X *et al.* A major role for neutrophils in experimental bullous pemphigoid. *J Clin Invest* 1997; **100**: 1256–63.
33 Chen R, Fairley JA, Zhao ML *et al.* Macrophages, but not T and B lymphocytes, are critical for subepidermal blister formation in experimental bullous pemphigoid: macrophage-mediated neutrophil infiltration depends on mast cell activation. *J Immunol* 2002; **169**: 3987–92.
34 Liu Z, Shapiro SD, Zhou X *et al.* A critical role for neutrophil elastase in experimental bullous pemphigoid. *J Clin Invest* 2000; **105**: 113–23.
35 Dvorak AM, Mihm MC Jr, Osage JE *et al.* Bullous pemphigoid, an ultrastructural study of the inflammatory response: eosinophil, basophil and mast cell granule changes in multiple biopsies from one patient. *J Invest Dermatol* 1982; **78**: 91–101.
36 Stahle-Backdahl M, Inoue M, Guidice G *et al.* 92-kD gelatinase is produced by eosinophils at the site of blister formation in bullous pemphigoid and cleaves the extracellular domain of recombinant 180-kD bullous pemphigoid and autoantigen. *J Clin Invest* 1994; **93**: 2022–30.
37 Liu Z, Shipley JM, Vu TH *et al.* Gelatinase B-deficient mice are resistant to experimental bullous pemphigoid. *J Exp Med* 1998; **188**: 475–82.
38 Budinger L, Borradori L, Yee C *et al.* Identification and characterization of autoreactive T cell responses to bullous pemphigoid antigen 2 in patients and healthy controls. *J Clin Invest* 1998; **102**: 2082–9.
39 Leyendeckers H, Tasanen K, Bruckner-Tuderman L *et al.* Memory B cells specific for the NC16A domain of the 180 kDa bullous pemphigoid autoantigen can be detected in peripheral blood of bullous pemphigoid patients and induced in vitro to synthesize autoantibodies. *J Invest Dermatol* 2003; **120**: 372–8.
40 Black AP, Seneviratne SL, Jones L *et al.* Rapid effector function of circulating NC16A-specific T cells in individuals with mucous membrane pemphigoid. *Br J Dermatol* 2004; **151**: 1160–4.
41 Thoma-Uszynski S, Uter W, Schwietzke S *et al.* Autoreactive T and B cells from bullous pemphigoid (BP) patients recognize epitopes clustered in distinct regions of BP180 and BP230. *J Immunol* 2006; **176**: 2015–23.

Pathology. The blister in bullous pemphigoid is subepidermal with an intact and often viable epidermis forming the roof. The blisters may contain numerous eosinophils and neutrophils. Biopsies of blisters and from erythematous areas of skin show a dermal inflammatory infiltrate containing many eosinophils and neutrophils with lymphocytes and histiocytes. Eosinophilic spongiosis may also be seen. There are patients with bullous pemphigoid in whom the dermal infiltrate is so intense in the papillae that it cannot be distinguished from dermatitis herpetiformis. Old blisters may demonstrate re-epithelialization along the base giving an artefactual intraepidermal blister. Biopsies taken from apparently normal and non-inflamed skin are non-diagnostic or normal.

The findings with immunofluorescence are summarized in Table 40.6 and in a review [1]. Positive direct or indirect immunofluorescence or ELISA to BP180 [2] and BP230 [3] is essential to confirm the clinical and histological diagnosis.

Direct immunofluorescence studies should not be performed on a blister, as the immunoreactants are often lost from the roof of a blister. They are best performed on a perilesional biopsy (within 2 cm of a lesion). The biopsy for immunofluorescence can also be taken from clinically uninvolved skin, the front of the thigh or flexor forearm, if this is more convenient or there are no active lesions, and from mucosal surfaces [4,5]. A 3–4 mm punch biopsy is ideal, and need not be deep. The biopsy will show either IgG and C3, or C3 alone along the basement-membrane zone (Fig. 40.13); deposition of IgA and IgM may also occur. The patient's biopsy can be split by incubation in 1 mol/L sodium chloride (salt-split skin) to provide additional information as to the localization of the target antigens, as the immune deposits should be associated with the hemidesmosomes, and thus present on the epidermal side of the split (roof of the artificial blister) [1,6]. The raising of a suction blister in the patient can give similar information but is cumbersome [7].

Indirect immunofluorescence can be performed on blood, blister fluid and urine (although less often positive), the latter two being useful substitutes for blood with an uncooperative child or adult [8,9]. About three-quarters of bullous pemphigoid patients have a circulating IgG autoantibody to the basement-membrane zone. False positives are rare, and the finding of circulating antibodies is diagnostic. The circulating autoantibodies in bullous pemphigoid react with the epidermal side of normal human skin that has been split by prolonged incubation with salt or suction (Fig. 40.14) [7,10,11]. The use of salt-split skin increases the sensitivity of autoantibody detection and differentiates patients with bullous pemphigoid from those with epidermolysis bullosa, and is to be recommended as a routine technique [10]. There are rare, dermal-binding bullous pemphigoid patients and these can only be identified with immunoelectron microscopy or immunoblotting [12].

Recently, the use of ELISA techniques to detect antibodies against specific epitopes has begun to be used as a routine diagnostic test in some centres [2,3,13,14].

There is a change with time from inflammatory IgG1 to less inflammatory, blocking IgG4 associated with diminution in disease activity, even though an overall diminution in titre may not be seen [15].

Occasionally, patients with bullous pemphigoid have pemphigus-like antibodies, and the diseases may co-exist. This may relate to the homology between BP230 and desmoplakin [16,17].

Immunoelectron microscopy demonstrates that the autoantibodies are deposited in the lamina lucida *in vivo* [18], but in contrast bind to the target antigens in association with the dense plaque (antibodies to BP230) and hemidesmosome (antibodies to BP180) *in vitro* [19].

Immunoblotting demonstrates that the majority of patients have circulating autoantibodies that react with the BP230 and BP180 antigens. The individual patient may react with either or both [20,21]. There is some suggestion that patients who have autoantibodies to BP180 may have more severe or prolonged disease

[22–24]. A clinical pattern indistinguishable from bullous pemphigoid may be seen with other target antigens.



Fig. 40.15 Bullous pemphigoid. Figurate erythema with large tense bullae. (Courtesy of Dr R.J. Pye, Addenbrooke's Hospital, Cambridge, UK.)

Clinical features. Bullous pemphigoid commonly starts with itching and a non-specific rash on the limbs that may be either urticaria-like or occasionally eczematous and rarely may simulate vesicular eczema. The pruritus may persist for many months. The urticarial prodrome usually lasts 1–3 weeks before blisters occur. The eczematous prodrome may precede the blisters by several months. Severe irritation with a faint, dusky erythema in a figurate pattern may sometimes precede blister formation (Fig. 40.15). These changes may closely resemble erythema multiforme or dermatitis herpetiformis. Sudden generalization of the true eruption of bullous pemphigoid follows the prodromal phase and most of the body may be affected within a week.

Blisters may arise on erythematous and on normal skin and may be associated with dermal oedema. The blisters are tense and dome shaped, obtaining a diameter of many centimetres (Figs 40.15 & 40.16). They appear mainly on the flexural aspects of limbs and on the central abdomen. Their contents are usually clear serous exudate, although occasionally this is bloodstained. The blisters are tough and may remain intact for several days, the contents often becoming jelly-like with coagulated fibrin. In some

References

1 Kirtschig G, Wojnarowska F. Autoimmune blistering diseases: an up-date of diagnostic methods and investigations. *Clin Exp Dermatol* 1994; **19**: 97–112.

2 Zillikens D, Mascaro JM, Rose PA *et al.* A highly sensitive enzyme-linked immunosorbent assay for the detection of circulating anti-BP180 autoantibodies in patients with bullous pemphigoid. *J Invest Dermatol* 1997; **109**: 679–83.

3 Yoshida M, Hamada T, Amagai M *et al.* Enzyme-linked immunosorbent assay using bacterial recombinant proteins of human BP230 as a diagnostic tool for bullous pemphigoid. *J Dermatol Sci* 2006; **41**: 21–30.

4 Venning V, Frith P, Bron A *et al.* Mucosal involvement in bullous and cicatricial pemphigoid. A clinical and immunopathological study. *Br J Dermatol* 1988; **118**: 5–7.

5 Anstey A, Venning V, Wojnarowska F *et al.* Determination of the optimum site for diagnostic biopsy for direct immunofluorescence in bullous pemphigoid. *Clin Exp Dermatol* 1990; **15**: 438–41.

6 Gammon W, Kowalewski C, Chorzelski T *et al.* Direct immunofluorescence studies of sodium chloride-separated skin in the differential diagnosis of bullous pemphigoid and epidermolysis bullosa acquisita. *J Am Acad Dermatol* 1990; **22**: 664–70.

7 Venning V, Allen J, Millard P *et al.* The localization of the bullous pemphigoid and cicatricial pemphigoid antigens: direct and indirect immunofluorescence of suction blisters. *Br J Dermatol* 1989; **120**: 305–15.

8 Zhou S, Wakelin SH, Allen J *et al.* Blister fluid for the diagnosis of subepidermal immunobullous diseases: a comparative study of basement membrane zone autoantibodies detected in blister fluid and serum. *Br J Dermatol* 1998; **139**: 27–32.

9 Allen J, Shears E, Powell J *et al.* Assessment of skin basement membrane zone antibodies in the urine of patients with acquired subepidermal immunobullous diseases. *Br J Dermatol* 2001; **144**: 540–5.

10 Kelly S, Wojnarowska F. The use of chemically split tissue in the detection of circulating anti-basement membrane zone antibodies in bullous pemphigoid and cicatricial pemphigoid. *Br J Dermatol* 1988; **118**: 31–40.

11 Gammon R, Fine J-D, Forbes M *et al.* Immunofluorescence on salt-split skin for the detection and differentiation of basement membrane zone autoantibodies. *J Am Acad Dermatol* 1992; **27**: 79–87.

12 Logan RA, Bhogal B, Das AK. Localisation of bullous pemphigoid antibody: an indirect immunofluorescence study of 228 cases using split skin technique. *Br J Dermatol* 1987; **117**: 471–8.

13 Feng S, Lin L, Jin P *et al.* Role of BP180NC16a-enzyme-linked immunosorbent assay (ELISA) in the diagnosis of bullous pemphigoid in China. *Int J Dermatol* 2008; **47**: 24–8.

14 Patsatsi A, Vyzantiadis TA, Devliotou-Panagiotidou D *et al.* Detection of anti-BP180NC16a and anti-BP230 autoantibodies in blister fluid of patients with bullous pemphigoid: the first survey in Greece. *Clin Exp Dermatol* 2008; **33**: 183–5.

15 Modre B, Allen J, Wojnarowska F. Does class switching contribute to remission in bullous pemphigoid? *Acta Dermato-Venerologica* 1999; **79**: 127–31.

16 Sami N, Ahmed AR. Dual diagnosis of pemphigus and pemphigoid. Retrospective review of thirty cases in the literature. *Dermatology* 2001; **202**: 293–301.

17 Sami N, Bhol KC, Beutner EH *et al.* Diagnostic features of pemphigus vulgaris in patients with bullous pemphigoid. Molecular analysis of autoantibody profile. *Dermatology* 2002; **204**: 108–17.

18 Prost C, Labeille B, Chaussade V. Immunoelectron microscopy in sub-epidermal autoimmune bullous diseases. *J Invest Dermatol* 1987; **89**: 567–73.

19 Ishiko A, Shimizu H, Ebihara T *et al.* Human autoantibodies against the 230-kD bullous pemphigoid antigen (BPAG1) bind only to the intracellular domain of the hemidesmosome, whereas those against the 180-kD bullous pemphigoid antigen (BPAG2) bind along the plasma membrane of the hemidesmosome in normal human and swine skin. *J Clin Invest* 1993; **91**: 1608–15.

20 Labib R, Anhalt G, Patel H *et al.* Molecular heterogeneity of the bullous pemphigoid antigens as detected by immunoblotting. *J Immunol* 1986; **136**: 1231–5.

21 Muller S, Klaus-Kovtun V, Stanley J. A 230-kD basic protein is the major bullous pemphigoid antigen. *J Invest Dermatol* 1989; **92**: 33–8.

22 Tanaka M, Hashimoto T, Dykes P *et al.* Clinical manifestations in 100 Japanese bullous pemphigoid cases in relation to autoantigen profiles. *Clin Exp Dermatol* 1996; **21**: 23–7.

23 Bernard P, Bedane C, Bonnetblanc JM. Anti-BP180 autoantibodies as a marker of poor prognosis in bullous pemphigoid: a cohort analysis of 94 elderly patients. *Br J Dermatol* 1997; **136**: 694–8.

24 Schmidt E, Obe K, Brocker EB *et al.* Serum levels of autoantibodies to BP180 correlate with disease activity in patients with bullous pemphigoid. *Arch Dermatol* 2000; **136**: 174–8.



Fig. 40.16 Bullous pemphigoid. Tense, haemorrhagic bullae. (Courtesy of Dr R.J. Pye, Addenbrooke's Hospital, Cambridge, UK.)



Fig. 40.17 Bullous pemphigoid. Milia at sites of severe blistering. (Courtesy of Dr R.J. Pye, Addenbrooke's Hospital, Cambridge, UK.)

blisters, the fluid is reabsorbed and the epithelium settles back in place like a skin graft. Those that do rupture leave erosions that heal rapidly, leaving mild post-inflammatory changes. Erythema may persist at the sites of previous blisters for many weeks or months. Milia may be profuse during the healing phase (Fig. 40.17). Mucosal lesions occur less frequently and are less severe than in mucous membrane pemphigoid and pemphigus vulgaris and are usually confined to the mouth. The oral lesions consist of small blisters that, like those of the skin, may remain intact and, if they rupture, heal rapidly.

In infants the distribution of the lesions is often acral and in older children involvement of the genital region occurs in almost half [1].

The acute phase is usually accompanied by leukocytosis and eosinophilia, but fever is uncommon, and in spite of extensive blistering (Fig. 40.15) the patients' general condition remains good. Fresh crops of small blisters may continue to occur even after apparent control has been achieved with treatment.

Reference

1 Waisbourd-Zinman O, Ben-Amitai D, Cohen AD *et al.* Bullous pemphigoid in infancy: clinical and epidemiologic characteristics. *J Am Acad Dermatol* 2008; **58**: 41–8.

Induced bullous pemphigoid and associated diseases

There are no well-defined causal agents, although a number of agents have been associated with the development of bullous pemphigoid. Several drugs have been implicated [1], including furosemide [2,3], spironolactone [4], sulphasalazine, penicillins [5–7], penicillamine [8], β-blockers [9] and enaxoparin [10]. These patients tend to have a younger average age than those in the idiopathic group. A case–control study suggests that antipsychotic drugs and aldosterone antagonists are associated with the development of bullous pemphigoid [11]. Whether or not the drugs are exerting a direct effect on the immune system is not yet known.

Local irritation and damage to the skin have all been implicated in the induction of bullous pemphigoid [12]. UV light or PUVA have been described as precipitating or exacerbating bullous pemphigoid [13–17]. Other physical agents, including thermal burns, wounds, localized trauma, skin grafts and radiotherapy, have also been reported to induce bullous pemphigoid in normal skin [12,18]. There have been a number of case reports of bullous pemphigoid associated with radiotherapy for breast cancer [19,20]. Topical 5-fluorouracil has induced bullous pemphigoid, but the role of topical chemical irritants such as anthralin (dithranol) and tar is less clear. Immunization has been reported to induce bullous pemphigoid, especially in children, but there is no association overall with influenza immunization [21–24]. The mechanisms may be alteration or exposure of epitopes of adhesion complex proteins, or a change in the host immunological response.

Bullous pemphigoid is associated with certain other diseases; however, as it occurs in an elderly population these patients often have other disorders at the same time. To determine whether the associations truly exist, prospective age-controlled studies are necessary. There are many individual case reports of bullous pemphigoid in association with autoimmune diseases, although a case–control study did not show an overall association [25]. However, other systemic diseases have been reported in association with bullous pemphigoid. These include diabetes mellitus [26,27], rheumatoid arthritis [28–30] and ulcerative colitis [31–33]. There is an association with multiple sclerosis [34,35] and other neurological diseases, including Parkinson's disease and dementia [36–39]. There are numerous reports of bullous pemphigoid in patients with psoriasis, the blisters may be localized to the plaques of psoriasis or independent of them, and in some instances therapeutic anthralin or UV radiation appeared to be the trigger [14,37,40]. A case–control study suggested an association between psoriasis and bullous pemphigoid [41]. Bullous pemphigoid can occur in the setting of lichen planus (see below and Chapter 41).

There is controversy about the association between bullous pemphigoid and malignancy. Initially, most large series concluded that there is no or only a very small increase in incidence of malignancy in bullous pemphigoid patients compared with age- and sex-matched controls, although the association may exist in individual patients [42]. However, a large series of more than 1000

bullous pemphigoid patients in Japan showed a 5.8% incidence of malignancy (with gastric carcinoma being the commonest), which was significantly higher than that of age-matched controls [43]. A similar incidence was reported in Chinese patients with bullous pemphigoid [44,45] and in Italy [46]. The carcinoma may express the bullous pemphigoid antigens and evoke an immune response.

References

1 Fellner MJ. Drug-induced bullous pemphigoid. *Clin Dermatol* 1993; **11**: 515–20.
2 Koch CA, Mazzaferri EL, Larry JA *et al.* Bullous pemphigoid after treatment with furosemide. *Cutis* 1996; **58**: 340–4.
3 Lee JJ, Downham TF 2nd. Furosemide-induced bullous pemphigoid: case report and review of literature. *J Drugs Dermatol* 2006; **5**: 562–4.
4 Modeste AB, Cordel N, Courville P *et al.* [Bullous pemphigoid induced by spironolactone]. *Ann Dermatol Venereol* 2002; **129**: 56–8.
5 Alcalay J, David M, Ingber A *et al.* Bullous pemphigoid mimicking bullous erythema multiforme: an untoward side effect of penicillins. *J Am Acad Dermatol* 1988; **18**: 345–9.
6 Hodak E, Ben-Shetrit A, Ingber A *et al.* Bullous pemphigoid—an adverse effect of ampicillin. *Clin Exp Dermatol* 1990; **15**: 50–2.
7 Miralles J, Barnadas MA, Baselga E *et al.* Bullous pemphigoid-like lesions induced by amoxicillin. *Int J Dermatol* 1997; **36**: 42–7.
8 Weller R, White M. Bullous pemphigoid and penicillamine. *Clin Exper Dermatol* 1996; **21**: 121–2.
9 Perry A, Sparling JD, Pennington M. Bullous pemphigoid following therapy with an oral beta-blocker. *J Drugs Dermatol* 2005; **4**: 746–8.
10 Dyson SW, Lin C, Jaworsky C. Enoxaparin sodium-induced bullous pemphigoid-like eruption: a report of 2 cases. *J Am Acad Dermatol* 2004; **51**: 141–2.
11 Bastuji-Garin S, Joly P, Picard-Dahan C *et al.* Drugs associated with bullous pemphigoid. A case-control study. *Arch Dermatol* 1996; **132**: 272–6.
12 Venning V, Wojnarowska F. Induced bullous pemphigoid. *Br J Dermatol* 1995; **132**: 831–2.
13 Sacher C, Konig C, Scharffetter-Kochanek K *et al.* Bullous pemphigoid in a patient treated with UVA-1 phototherapy for disseminated morphea. *Dermatology* 2001; **202**: 54–7.
14 Kirtschig G, Chow ET, Venning VA *et al.* Acquired subepidermal bullous diseases associated with psoriasis: a clinical, immunopathological and immunogenetic study. *Br J Dermatol* 1996; **135**: 738–45.
15 Perl S, Rappersberger K, Fodinger D *et al.* Bullous pemphigoid induced by PUVA therapy. *Dermatology* 1996; **193**: 245–7.
16 Pfau A, Hohenleutner U, Hohenleutner S *et al.* UV-A-provoked localized bullous pemphigoid. *Acta Derm Venereol* 1994; **74**: 314–6.
17 Preesman AH, Toonstra J, Van der Putte SC *et al.* UV-B-induced bullous pemphigoid restricted to mycosis fungoides plaques. *Clin Exp Dermatol* 1990; **15**: 363–6.
18 Duschet P, Schwarz T, Gschnait F. Bullous pemphigoid after radiation therapy. *J Am Acad Dermatol* 1988; **18**: 441–4.
19 Cliff S, Harland CC, Fallowfield ME *et al.* Localised bullous pemphigoid following radiotherapy. *Acta Derm Venereol* 1996; **76**: 330–1.
20 Ohata C, Shirabe H, Takagi K *et al.* Localized bullous pemphigoid after radiation therapy: two cases. *Acta Derm Venereol* 1997; **77**: 157.
21 Fournier B, Descamps V, Bouscarat F *et al.* Bullous pemphigoid induced by vaccination. *Br J Dermatol* 1996; **135**: 153–4.
22 Baykal C, Okan G, Sarica R. Childhood bullous pemphigoid developed after the first vaccination. *J Am Acad Dermatol* 2001; **44**: 348–50.
23 Erbagci Z. Childhood bullous pemphigoid following hepatitis B immunization. *J Dermatol* 2002; **29**: 781–5.
24 Garcia-Doval I, Mayo E, Nogueira Farina J *et al.* Bullous pemphigoid triggered by influenza vaccination? Ecological study in Galicia, Spain. *Br J Dermatol* 2006; **155**: 820–3.
25 Taylor G, Venning V, Wojnarowska F *et al.* Bullous pemphigoid and autoimmunity. *J Am Acad Dermatol* 1993; **29**: 181–4.
26 Rosina P, Chieregato C, D'Onghia FS. Bullous pemphigoid and diabetes mellitus. *Acta Derm Venereol* 1996; **76**: 497–8.
27 Chuang TY, Korkij W, Soltani K *et al.* Increased frequency of diabetes mellitus in patients with bullous pemphigoid: a case-control study. *J Am Acad Dermatol* 1984; **11**: 1099–102.
28 Sant SM, O'Loughlin S, Murphy GM. Bullous pemphigoid and rheumatoid arthritis: is there disease association? *Ir J Med Sci* 1997; **166**: 106–7.
29 Hsu VM, Krey PR, Schwartz RA. Bullous pemphigoid and rheumatoid arthritis. *Cutis* 1989; **43**: 30–2.
30 Giannini JM, Callen JP, Gruber GG. Bullous pemphigoid and rheumatoid arthritis. *J Am Acad Dermatol* 1981; **4**: 695–7.
31 Harrison PV, Blewitt RW, Allen J *et al.* Bullous pemphigoid and ulcerative colitis: a report of two cases and description of immunoblot findings. *Br J Dermatol* 1996; **134**: 599–600.
32 Barth JH, Kelly SE, Wojnarowska F *et al.* Pemphigoid and ulcerative colitis. *J Am Acad Dermatol* 1988; **19**: 303–8.
33 Ahmed AR, Kaplan RP, Hardy D *et al.* Bullous pemphigoid and ulcerative colitis. *Int J Dermatol* 1982; **21**: 594–8.
34 Kirtschig G, Walkden VM, Venning VA *et al.* Bullous pemphigoid and multiple sclerosis: a report of three cases and review of the literature. *Clin Exp Dermatol* 1995; **20**: 449–53.
35 Stinco G, Mattighello P, Zanchi M *et al.* Multiple sclerosis and bullous pemphigoid: a casual association or a pathogenetic correlation? *Eur J Dermatol* 2002; **12**: 186–8.
36 Foureur N, Descamps V, Lebrun-Vignes B *et al.* Bullous pemphigoid in a leg affected with hemiparesia: a possible relation of neurological diseases with bullous pemphigoid? *Eur J Dermatol* 2001; **11**: 230–3.
37 Bourdon-Lanoy E, Roujeau JC, Joly P *et al.* [Bullous pemphigoid in young patients: a retrospective study of 74 cases]. *Ann Dermatol Venereol* 2005; **132**: 115–22.
38 Cordel N, Chosidow O, Hellot MF *et al.* Neurological disorders in patients with bullous pemphigoid. *Dermatology* 2007; **215**: 187–91.
39 Stinco G, Codutti R, Scarbolo M *et al.* A retrospective epidemiological study on the association of bullous pemphigoid and neurological diseases. *Acta Derm Venereol* 2005; **85**: 136–9.
40 Kawahara Y, Zillikens D, Yancey KB *et al.* Subepidermal blistering disease with autoantibodies against a novel dermal 200-kDa antigen. *J Dermatol Sci* 2000; **23**: 93–102.
41 Grattan CE. Evidence of an association between bullous pemphigoid and psoriasis. *Br J Dermatol* 1985; **113**: 281–3.
42 Venning V, Wojnarowska F. The association of bullous pemphigoid and malignant disease: a case control study. *Br J Dermatol* 1990; **123**: 439–45.
43 Ogawa H, Sakuma M, Morioka S *et al.* The incidence of internal malignancies in pemphigus and bullous pemphigopid in Japan. *J Derm Science* 1995; **9**: 136–40.
44 Jin P, Shao C, Ye G. Chronic bullous dermatoses in China. *Int J Dermatol* 1993; **32**: 89–92.
45 Chang Y, Liu H, Wong C. Bullous pemphigoid—a report of 86 cases from Taiwan. *Clin Exper Dermatol* 1996; **21**: 21–2.
46 Cozzani E, Parodi A, Rebora A *et al.* Bullous pemphigoid in Liguria: a 2-year survey. *J Eur Acad Dermatol Venereol* 2001; **15**: 317–9.

Pemphigoid nodularis

This entity presents great diagnostic difficulty. The patients present with intensely itchy nodules, suggesting a diagnosis of prurigo nodularis; blisters are rarely reported by the patient or seen, but when present are diagnostic [1]. It may occur in children [2]. The immunopathology and the antigens are the same as in ordinary pemphigoid [3]. The eruption may be generalized or localized to the shins. It is often difficult to treat [1].

References

1 Powell AM, Albert S, Gratian MJ *et al.* Pemphigoid nodularis (non-bullous): a clinicopathological study of five cases. *Br J Dermatol* 2002; **147**: 343–9.
2 Ratnavel RC, Shanks AJ, Grant JW *et al.* Juvenile pemphigoid nodularis. *Br J Dermatol* 1994; **130**: 125–6.
3 Schmidt E, Sitaru C, Schubert B *et al.* Subacute prurigo variant of bullous pemphigoid: autoantibodies show the same specificity compared with classic bullous pemphigoid. *J Am Acad Dermatol* 2002; **47**: 133–6.

Localized disease

An unusual variant of bullous pemphigoid is the localized form of the disease, which occurs in 5 to 30% of patients with bullous pemphigoid, usually limited to the lower extremities, and responding well to treatment [1–3]. Localized disease, of course, may progress to generalized disease.

References

1 Person JR, Rogers RS 3rd, Perry HO. Localized pemphigoid. *Br J Dermatol* 1976; **95**: 531–4.
2 Ahmed A, Maize J, Provost T. Bullous pemphigoid. Clinical and immunologic follow-up after successful therapy. *Arch Dermatol* 1977; **113**: 1043–6.
3 Downham TF 2nd, Chapel TA. Bullous pemphigoid: therapy in patients with and without diabetes mellitus. *Arch Dermatol* 1978; **114**: 1639–42.

Localized vulvar pemphigoid

This rarely reported entity is characterized by recurrent blistering confined to the vulva of young girls, which does not result in scarring [1,2]. A localized desquamative vaginitis has also described [3].

References

1 Kirtschig G, Wojnarowska F, Marsden RA *et al.* Acquired bullous diseases of childhood: re-evaluation of diagnosis by indirect immunofluorescence examination on 1 M NaCl split skin and immunoblotting. *Br J Dermatol* 1994; **130**: 610–6.
2 Farrell AM, Kirtschig G, Dalziel KL *et al.* Childhood vulval pemphigoid: a clinical and immunopathological study of five patients. *Br J Dermatol* 1999; **140**: 308–12.
3 Haustein U-F. Localized nonscarring bullous pemphigoid of the vagina. *Dermatologica* 1988; **176**: 200–1.

Pemphigoid vegetans

This is a rare variant with circumscribed hypertrophic lesions with crusts or erosion, and pustules or vesicles at the periphery. The lesions chiefly affect intertriginous areas [1–3].

References

1 Ogasawara M, Matsuda S, Nishioka K *et al.* Pemphigoid vegetans. *J Am Acad Dermatol* 1994; **30**: 649–50.
2 Chan LS, Dorman MA, Agha A *et al.* Pemphigoid vegetans represents a bullous pemphigoid variant. Patient's IgG autoantibodies identify the major bullous pemphigoid antigen. *J Am Acad Dermatol* 1993; **28**: 331–5.
3 Ueda Y, Nashiro K, Seki Y *et al.* Pemphigoid vegetans. *Br J Dermatol* 1989; **120**: 449–53.

Lichen planus pemphigoides

Bullous pemphigoid can occur in the setting of lichen planus in both adults and children. Tense, subepidermal blisters arise from the lesions of lichen planus and normal skin. The blistering usually responds rapidly to treatment and is short lived [1–5]. The disease is immunopathologically identical to bullous pemphigoid although there are antibodies to a characteristic epitope of BP180 [6] (see Chapter 41).

References

1 Bouloc A, Vignon-Pennamen MD, Caux F *et al.* Lichen planus pemphigoides is a heterogeneous disease: a report of five cases studied by immunoelectron microscopy. *Br J Dermatol* 1998; **138**: 972–80.
2 Davis AL, Bhogal BS, Whitehead P *et al.* Lichen planus pemphigoides: its relationship to bullous pemphigoid. *Br J Dermatol* 1991; **125**: 263–71.
3 Willsteed E, Bhogal BS, Das AK *et al.* Lichen planus pemphigoides: a clinicopathological study of nine cases. *Histopathology* 1991; **19**: 147–54.
4 Flageul B, Hassan F, Pinquier L *et al.* [Lichen pemphigoid associated with developing hepatitis B in a child]. *Ann Dermatol Venereol* 1999; **126**: 604–7.
5 Paige DG, Bhogal BS, Black MM *et al.* Lichen planus pemphigoides in a child—immunopathological findings. *Clin Exp Dermatol* 1993; **18**: 552–4.
6 Zillikens D, Caux F, Mascaro JM *et al.* Autoantibodies in lichen planus pemphigoides react with a novel epitope within the C-terminal NC16A domain of BP180. *J Invest Dermatol* 1999; **113**: 117–21.

Differential diagnosis. It may not be possible to diagnose accurately the early urticaria-like, eczematous and erythematous prodromal eruptions, but the possibility of bullous pemphigoid should always be considered in the elderly patient with irritable, fixed erythematous lesions. The lower leg in elderly people seems particularly prone to develop blisters, and it must be remembered that eczema or oedema at this site may blister.

When blisters have appeared, it is usually possible to differentiate bullous pemphigoid from pemphigus vulgaris on clinical grounds alone. The large, tense, tough blisters of bullous pemphigoid can be distinguished from the smaller, flaccid, more easily broken blisters of pemphigus, and the severe mucosal lesions of pemphigus vulgaris are a further distinguishing feature. Clinically, typical cases of bullous pemphigoid may be found to be linear IgA disease or epidermolysis bullosa acquisita on investigation. More atypical cases of bullous pemphigoid with small or absent blisters and/or annular lesions may resemble dermatitis herpetiformis, linear IgA disease, erythema multiforme and a final differentiation must then be on histological grounds. Direct and indirect immunofluorescence should confirm the diagnosis.

A more difficult task may be separating mucous membrane pemphigoid from bullous pemphigoid. The generalized eruption of mucous membrane pemphigoid may be clinically and histologically indistinguishable from bullous pemphigoid, and bullous pemphigoid may evolve into mucous membrane pemphigoid [1]. However, involvement of the mucous membranes with scarring is characteristic of mucous membrane pemphigoid.

Reference

1 Banfield C, Papadavid E, Frith P *et al.* Bullous pemphigoid evolving into cicatricial pemphigoid? *Clin Exp Dermatol* 1997; **22**: 30–3.

Prognosis. Untreated bullous pemphigoid runs a chronic, self-limiting course over a number of months or years. Remission may occur within a few months or the eruption may continue for many years. The disease duration is usually 3–6 years, with most patients achieving complete remission off treatment. Bullous pemphigoid can be fatal, particularly in the active blistering phase in elderly people, and about one-third of untreated patients died; the results are similar in some recent series [1–3]. Bullous pemphigoid patients have double the risk of death compared to the general population [4]. The features that predict a poor prognosis and mortality are age, generalized disease, low Karnofsky score, low albumin and high doses of steroids [3,5–9]. Localized disease is very responsive to treatment and more of these patients appear to go into remission.

References

1 Colbert RL, Allen DM, Eastwood D *et al.* Mortality rate of bullous pemphigoid in a US medical center. *J Invest Dermatol* 2004; **122**: 1091–5.

2 Gudi VS, White MI, Cruickshank N *et al.* Annual incidence and mortality of bullous pemphigoid in the Grampian region of North-east Scotland. *Br J Dermatol* 2005; **153**: 424–7.
3 Joly P, Benichou J, Lok C *et al.* Prediction of survival for patients with bullous pemphigoid: a prospective study. *Arch Dermatol* 2005; **141**: 691–8.
4 Langan SM, Smeeth L, Hubbard R *et al.* Bullous pemphigoid and pemphigus vulgaris—incidence and mortality in the UK: population based cohort study. *BMJ* 2008; **337**: a180.
5 Savin JA. Some factors affecting prognosis in pemphigus vulgaris and pemphigoid. *Br J Dermatol* 1981; **104**: 415–20.
6 Rzany B, Partscht K, Jung M *et al.* Risk factors for lethal outcome in patients with bullous pemphigoid: low serum albumin level, high dosage of glucocorticosteroids, and old age. *Arch Dermatol* 2002; **138**: 903–8.
7 Roujeau JC, Lok C, Bastuji-Garin S *et al.* High risk of death in elderly patients with extensive bullous pemphigoid. *Arch Dermatol* 1998; **134**: 465–9.
8 Wojnarowska F, Kirtschig G, Highet AS *et al.* Guidelines for the management of bullous pemphigoid. *Br J Dermatol* 2002; **147**: 214–21.
9 Khumalo NP, Murrell DF, Wojnarowska F *et al.* A systematic review of treatments for bullous pemphigoid. *Arch Dermatol* 2002; **138**: 385–9.

Treatment. The aim of treatment is to suppress disease activity with the minimum dose of drugs necessary. Bullous pemphigoid patients are elderly, commonly on many drugs and very susceptible to adverse drug reactions and side effects. During prolonged treatment, it is advisable to aim for the presence of a blister once every few weeks so as to be certain that the patient is not being over treated. The treatment of bullous pemphigoid has recently been the subject of a systematic review and UK guidelines have been produced [1–3].

Topical and systemic steroids are the mainstay of treatment. For localized BP, very potent topical steroids are often sufficient. Topical steroids should be considered in all patients. Intensive topical therapy with potent steroids, clobetasol propionate, applied all over twice daily, can give good control with fewer side effects than high-dose systemic steroids [4]. This is often not practical, however topical steroids can still aid control and may reduce the dose of systemic agents. The recommended initial dose of prednisolone is 20 mg/day or 0.3 mg/kg/day in localized or mild disease, 40 mg/day or 0.6 mg/kg/day in moderate disease, and 50–70 mg/day or 0.75–1 mg/kg/day in severe disease. Measures to prevent osteoporosis should be implemented from the start of systemic steroid therapy, whenever practicable. For mild to moderate disease, tetracyclines and nicotinamide should be considered. Steroid dosage can often be reduced quite quickly over the course of a few weeks to a dose of 15–20 mg/day and thereafter more slowly. The majority can be managed on doses of less than 10 mg/day prednisolone, which can be slowly withdrawn. One reducing regimen is reduction by 1 mg/month once the dose is below 10 mg/day. Immunosuppressants cannot be recommended routinely, but should be considered if the steroid dose cannot be reduced to an acceptable level. Azathioprine is the best established immunosuppressant and ideally thiopurine methyltransferase (TPMT) activity testing should be assessed prior to initiation of treatment to guide dosage. A recent study suggests that mycophenolate mofetil is a useful alternative immunosuppressant [5]. Methotrexate may be considered in patients with additional psoriasis [1]. The role of biological therapies is still unclear. Two successful cases of the use of the TNF blocker, etanercept, in patients with psoriasis and bullous pemphigoid are reported [6,7]; however, those patients treated with negative results are not reported. Rituximab has been reported to be both successful and unhelpful in a few cases [7–9].

There may be occasional flares that will require temporary increases in therapy.

Corticosteroid therapy has lowered the morbidity from the disease considerably and most patients achieve remission off all therapy, but significant mortality of bullous pemphigoid still remains at 15–40%, and is nearly always treatment related or related to the general condition and age of the patients. However, treatment is essential to control this distressing disease.

References

1 Wojnarowska F, Kirtschig G, Highet AS *et al.* Guidelines for the management of bullous pemphigoid. *Br J Dermatol* 2002; **147**: 214–21.
2 Khumalo NP, Murrell DF, Wojnarowska F *et al.* A systematic review of treatments for bullous pemphigoid. *Arch Dermatol* 2002; **138**: 385–9.
3 British Association of Dermatologists. http://www.bad.org.uk
4 Joly P, Roujeau JC, Benichou J *et al.* A comparison of oral and topical corticosteroids in patients with bullous pemphigoid. *N Engl J Med* 2002; **346**: 321–7.
5 Beissert S, Werfel T, Frieling U *et al.* A comparison of oral methylprednisolone plus azathioprine or mycophenolate mofetil for the treatment of bullous pemphigoid. *Arch Dermatol* 2007; **143**: 1536–42.
6 Yamauchi PS, Lowe NJ, Gindi V. Treatment of coexisting bullous pemphigoid and psoriasis with the tumor necrosis factor antagonist etanercept. *J Am Acad Dermatol* 2006; **54**: S121–2.
7 Saraceno R, Citarella L, Spallone G *et al.* A biological approach in a patient with psoriasis and bullous pemphigoid associated with losartan therapy. *Clin Exp Dermatol* 2008; **33**: 154–5.
8 Chee R, Nagendran V, Bansal A *et al.* B-cell targeted therapy alone may not be effective in bullous pemphigoid. *Clin Exp Dermatol* 2007; **32**: 111–2.
9 Schmidt E, Seitz CS, Benoit S *et al.* Rituximab in autoimmune bullous diseases: mixed responses and adverse effects. *Br J Dermatol* 2007; **156**: 352–6.

Mucous membrane pemphigoid

Synonyms
- Cicatricial pemphigoid
- Benign mucosal pemphigoid
- Ocular pemphigus
- Scarring pemphigoid
- Oral pemphigoid
- Brunsting Perry pemphigoid

Definition. A chronic blistering disease of the mucosa that may involve the skin, and usually results in permanent scarring of the affected area, particularly the conjunctiva. This entity is defined on the basis of the clinical picture and was renamed mucous membrane pemphigoid in 2002 [1], having been previously known as cicatricial pemphigoid. The new entity includes patients formerly diagnosed as oral pemphigoid and some linear IgA disease and epidermolysis bullosa acquisita patients, and excludes Brunsting–Perry pemphigoid. Brunsting–Perry pemphigoid will, however, still be discussed in this section as some patients have mucosal involvement and identical cutaneous signs.

The clinical features, immunopathology and immunogenetics are summarized in Tables 40.5 and 40.6, and Figs 40.13 and 40.14.

Reference

1 Chan LS, Ahmed AR, Anhalt GJ *et al.* The first international consensus on mucous membrane pemphigoid: definition, diagnostic criteria, pathogenic factors, medical treatment, and prognostic indicators. *Arch Dermatol* 2002; **138**: 370–9.

Aetiology. Mucous membrane pemphigoid is a disease of late middle to old age [1,2], but can affect children and teenagers and is more common in females [3–5]. The annual incidence in Western Europe is approximately 1–2 per million [3,4,6] and is probably less in China and the East [7,8].

There is an association with HLA-DQB1*0301(DQ7) in all types of mucous membrane pemphigoid [9–18].

References

1 Hardy K, Perry H, Pingree G *et al.* Benign mucous membrane pemphigoid. *Arch Dermatol* 1971; **104**: 467–75.
2 Shklar G, McCarthy P. Oral lesions of mucous membrane pemphigoid. *Arch Otolaryngology* 1971; **93**: 354–64.
3 Bernard P, Vaillant L, Labeille B *et al.* Incidence and distribution of subepidermal autoimmune bullous skin diseases in three French regions. Bullous Diseases French Study Group. *Arch Dermatol* 1995; **131**: 48–52.
4 Zillikens D, Wever S, Roth A *et al.* Incidence of autoimmune subepidermal blistering dermatoses in a region of central Germany. *Arch Dermatol* 1995; **131**: 957–8.
5 Veysey E, McHenry P, Powell J *et al.* Mucous membrane pemphigoid in a series of 7 children and a review of the literature with particular reference to prognostic features and treatment. *Eur J Pediat Dermatol* 2007; **17**: 218–26.
6 Reed JWF. Incidence of subepidermal bullous diseases in Oxford, UK. (Unpublished).
7 Jin P, Shao C, Ye G. Chronic bullous dermatoses in China. *Int J Dermatol* 1993; **32**: 89–92.
8 Wong SN, Chua SH. Spectrum of subepidermal immunobullous disorders seen at the National Skin Centre, Singapore: a 2-year review. *Br J Dermatol* 2002; **147**: 476–80.
9 Mondino BJ, Brown SI, Rabin BS. HLA antigens in ocular cicatricial pemphigoid. *Arch Ophthalmol* 1979; **97**: 479.
10 Zaltas MM, Ahmed R, Foster CS. Association of HLA-DR4 with ocular cicatricial pemphigoid. *Curr Eye Res* 1989; **8**: 189–93.
11 Ahmed AR, Foster S, Zaltas M *et al.* Association of DQw7 (DQB1*0301) with ocular cicatricial pemphigoid. *Proc Natl Acad Sci USA* 1991; **88**: 11579–82.
12 Nayar M, Wojnarowska F, Venning V *et al.* Association of autoimmunity and cicatricial pemphigoid: is there an immunogenetic basis? *J Am Acad Dermatol* 1991; **25**: 1011–5.
13 Yunis JJ, Mobini N, Yunis EJ *et al.* Common major histocompatibility complex class II markers in clinical variants of cicatricial pemphigoid. *Proc Natl Acad Sci USA* 1994; **91**: 7747–51.
14 Delgado JC, Turbay D, Yunis EJ *et al.* A common major histocompatibility complex class II allele HLA-DQB1*0301 is present in clinical variants of pemphigoid. *Proc Natl Acad Sci USA* 1996; **93**: 8569–71.
15 Chan LS, Hammerberg C, Cooper KD. Significantly increased occurrence of HLA-DQB1*0301 allele in patients with ocular cicatricial pemphigoid. *J Invest Dermatol* 1997; **108**: 129–32.
16 Drouet M, Delpuget-Bertin N, Vaillant L *et al.* HLA-DRB1 and HLA-DQB1 genes in susceptibility and resistance to cicatricial pemphigoid in French Caucasians. *Eur J Dermatol* 1998; **8**: 330–3.
17 Carrozzo M, Fasano ME, Broccoletti R *et al.* HLA-DQB1 alleles in Italian patients with mucous membrane pemphigoid predominantly affecting the oral cavity. *Br J Dermatol* 2001; **145**: 805–8.
18 Setterfield J, Theron J, Vaughan RW *et al.* Mucous membrane pemphigoid: HLA-DQB1*0301 is associated with all clinical sites of involvement and may be linked to antibasement membrane IgG production. *Br J Dermatol* 2001; **145**: 406–14.

Pathogenesis. Mucous membrane pemphigoid is assumed to have a pathogenesis similar to bullous pemphigoid. Some but not all patients have circulating autoantibodies, usually of low-titre that recognize proteins in the adhesion complex.

The reasons for the localization of mucous membrane pemphigoid to mucosal areas and limited areas of skin, and the scarring pattern are still not understood (see below). The antigens are identical to those of bullous pemphigoid in many patients, although the binding site of the autoantibodies seems to be associated more with the anchoring filament than the hemidesmosome.

The major autoantigens in mucous membrane pemphigoid are all components of the basement-membrane zone (Fig. 40.11), and are associated with the hemidesmosome, the anchoring filament and the anchoring fibrils (see below). There are experimental models for the pathogenicity of the autoantibodies in mucous membrane pemphigoid. An animal model for laminin 5 (laminin 332 in the new nomenclature), an anchoring filament component, has been developed and complement binding is not required for blister formation [1,2]. There are *in vitro* experimental models of pathogenicity of other antibodies in mucous membrane pemphigoid [3–5].

Immunoblotting and immunoprecipitation have shown multiple target antigens [6,7]. Many patients' autoantibodies target the bullous pemphigoid antigens, BP230 and BP180 [8,9]. BP180 is considered to be the major antigen with numerous different epitopes, including the shed ectodomain and the carboxy terminal which seems to be the major site for autoreactivity in oral pemphigoid (see Fig. 40.11) [10–15].

Some patients' antibodies bind to the α6 or β4 subunits of the α6β4 integrin and there is evidence that these are pathogenic [5,16–18]. There seems to be a correlation with antibodies to the α6 subunit in oral pemphigoid and the β4 subunit and ocular involvement [7,19].

A minority of patients have dermal-binding antibodies with salt-split skin target laminin 5 [20] and the most bind to the α3 subunit of laminin 5 [6,21] and are associated with laryngeal involvement [22–24]. In a few patients with typical mucous membrane pemphigoid the dermal binding antibodies target collagen VII [25].

The autoantibodies in mucous membrane pemphigoid may be IgG and/or IgA, and the presence of a dual antibody response is a marker for more severe disease [26–29]. In children IgA antibodies are associated with a worse prognosis [30]. There is evidence of involvement of T cells and release of γ-interferon and also of TNF [31,32].

The mechanism for the scarring is still unclear. The demonstration of the autoantibodies is more difficult than in bullous pemphigoid, and other mechanisms may be involved. Many patients share target antigens and HLA-DQB1*0301(DQ7) with bullous pemphigoid and thus the scarring cannot be attributed solely to the site of the immune reaction or to differing immunogenetics. The nature of the inflammatory response and the cytokine network activated (see above) is a current focus for investigation, and probably determines the outcome of the lesions.

References

1 Lazarova Z, Hsu R, Briggaman RA *et al.* Fab fragments directed against laminin 5 induce subepidermal blisters in neonatal mice. *Clin Immunol* 2000; **95**: 26–32.
2 Lazarova Z, Yee C, Darling T *et al.* Passive transfer of anti-laminin 5 antibodies induces subepidermal blisters in neonatal mice. *J Clin Invest* 1996; **98**: 1509–18.
3 Chan RY, Bhol K, Tesavibul N *et al.* The role of antibody to human beta4 integrin in conjunctival basement membrane separation: possible in vitro model for ocular cicatricial pemphigoid. *Invest Ophthalmol Vis Sci* 1999; **40**: 2283–90.

4 Colon JE, Bhol KC, Razzaque MS *et al.* In vitro organ culture model for mucous membrane pemphigoid. *Clin Immunol* 2001; **98**: 229–34.
5 Bhol KC, Goss L, Kumari S *et al.* Autoantibodies to human alpha6 integrin in patients with oral pemphigoid. *J Dent Res* 2001; **80**: 1711–5.
6 Chan LS, Ahmed AR, Anhalt GJ *et al.* The first international consensus on mucous membrane pemphigoid: definition, diagnostic criteria, pathogenic factors, medical treatment, and prognostic indicators. *Arch Dermatol* 2002; **138**: 370–9.
7 Oyama N, Setterfield JF, Powell AM *et al.* Bullous pemphigoid antigen II (BP180) and its soluble extracellular domains are major autoantigens in mucous membrane pemphigoid: the pathogenic relevance to HLA class II alleles and disease severity. *Br J Dermatol* 2006; **154**: 90–8.
8 Bernard P, Prost C, Lecerf V *et al.* Studies of cicatricial pemphigoid autoantibodies using direct immunoelectron microscopy and immunoblot analysis. *J Invest Dermatol* 1990; **94**: 630–5.
9 Bedane C, Prost C, Bernard P *et al.* Cicatricial pemphigoid antigen differs from bullous pemphigoid antigen by its exclusive extracellular localization. A study by indirect immunoelectron microscopy. *J Invest Dermatol* 1991; **97**: 3–9.
10 Schumann H, Baetge J, Tasanen K *et al.* The shed ectodomain of collagen XVII/BP180 is targeted by autoantibodies in different blistering skin diseases. *Am J Pathol* 2000; **156**: 685–95.
11 Leverkus M, Bhol K, Hirako Y *et al.* Cicatricial pemphigoid with circulating autoantibodies to beta4 integrin, bullous pemphigoid 180 and bullous pemphigoid 230. *Br J Dermatol* 2001; **145**: 998–1004.
12 Schmidt E, Skrobek C, Kromminga A *et al.* Cicatricial pemphigoid: IgA and IgG autoantibodies target epitopes on both intra- and extracellular domains of bullous pemphigoid antigen 180. *Br J Dermatol* 2001; **145**: 778–83.
13 Kromminga A, Sitaru C, Meyer J *et al.* Cicatricial pemphigoid differs from bullous pemphigoid and pemphigoid gestationis regarding the fine specificity of autoantibodies to the BP180 NC16A domain. *J Dermatol Sci* 2002; **28**: 68–75.
14 Lee JB, Liu Y, Hashimoto T. Cicatricial pemphigoid sera specifically react with the most C-terminal portion of BP180. *J Dermatol Sci* 2003; **32**: 59–64.
15 Calabresi V, Carrozzo M, Cozzani E *et al.* Oral pemphigoid autoantibodies preferentially target BP180 ectodomain. *Clin Immunol* 2007; **122**: 207–13.
16 Tyagi S, Bhol K, Natarajan K *et al.* Ocular cicatricial pemphigoid antigen: partial sequence and biochemical characterization. *Proc Natl Acad Sci USA* 1996; **93**: 14714–9.
17 Bhol KC, Dans MJ, Simmons RK *et al.* The autoantibodies to alpha 6 beta 4 integrin of patients affected by ocular cicatricial pemphigoid recognize predominantly epitopes within the large cytoplasmic domain of human beta 4. *J Immunol* 2000; **165**: 2824–9.
18 Kumari S, Bhol KC, Simmons RK *et al.* Identification of ocular cicatricial pemphigoid antibody binding site(s) in human beta4 integrin. *Invest Ophthalmol Vis Sci* 2001; **42**: 379–85.
19 Rashid KA, Gurcan HM, Ahmed AR. Antigen specificity in subsets of mucous membrane pemphigoid. *J Invest Dermatol* 2006; **126**: 2631–6.
20 Domologe-Hultsch N, Gammon W, Briggaman R *et al.* Epiligrin, the major human keratinocyte ligand, is a target in both an acquired and an inherited subepidermal blistering skin disease. *J Clin Invest* 1992; **90**: 1628–33.
21 Lazarova Z, Hsu R, Yee C *et al.* Antiepiligrin cicatricial pemphigoid represents an autoimmune response to subunits present in laminin 5 (alpha3beta3gamma2). *Br J Dermatol* 1998; **139**: 791–7.
22 Nousari HC, Rencic A, Hsu R *et al.* Anti-epiligrin cicatricial pemphigoid with antibodies against the gamma2 subunit of laminin 5. *Arch Dermatol* 1999; **135**: 173–6.
23 Seo SH, Kye YC, Kim SN *et al.* Antiepiligrin cicatricial pemphigoid with autoantibodies to the beta subunit of laminin 5 and associated with severe laryngeal involvement necessitating tracheostomy. *Dermatology* 2001; **202**: 63–6.
24 Shipman A, Ali I, Murrell D *et al.* Mucous membrane pemphigoid: are laminin 5 antibodies a risk factor for laryngeal involvement? *J Eur Acad Dermatol Venereol* 2008; **23**: 169–170.
25 Luke MC, Darling TN, Hsu R *et al.* Mucosal morbidity in patients with epidermolysis bullosa acquisita. *Arch Dermatol* 1999; **135**: 954–9.
26 Bean S, Waisman M, Michel B *et al.* Cicatricial pemphigoid: immunofluorescent studies. *Arch Dermatol* 1972; **106**: 195–6.
27 Sarret Y, Hall R, Cobo I *et al.* Salt-split human skin substrate for the immunofluorescence screening of serum from patients with cicatricial pemphigoid and a new method of immunoprecipitation with IgA antibodies. *J Am Acad Dermatol* 1991; **24**: 952–8.
28 Bernard P, Prost C, Aucouturier P *et al.* The subclass distribution of IgG autoantibodies in cicatricial pemphigoid and epidermolysis bullosa acquisita. *J Invest Dermat* 1991; **97**: 259–63.
29 Setterfield J, Shirlaw PJ, Kerr-Muir M *et al.* Mucous membrane pemphigoid: a dual circulating antibody response with IgG and IgA signifies a more severe and persistent disease. *Br J Dermatol* 1998; **138**: 602–10.
30 Veysey E, McHenry P, Powell J *et al.* Mucous membrane pemphigoid in a series of 7 children and a review of the literature with particular reference to prognostic features and treatment. *Eur J Pediat Dermatol* 2007; **17**: 218–26.
31 Black AP, Seneviratne SL, Jones L *et al.* Rapid effector function of circulating NC16A-specific T cells in individuals with mucous membrane pemphigoid. *Br J Dermatol* 2004; **151**: 1160–4.
32 Cordero Coma M, Yilmaz T, Foster CS. Tumour necrosis factor-alpha in conjunctivae affected by ocular cicatricial pemphigoid. *Acta Ophthalmol Scand* 2007; **85**: 753–5.

Pathology. Histological examination of a blister is helpful only if the blister is intact and recent. Biopsy of an erosion is rarely helpful. Blisters in the mouth and on the skin show subepithelial or subepidermal blister formation, but often lack distinctive and diagnostic features. There are usually fewer eosinophils present in the cutaneous lymphohistiocytic infiltrate than in bullous pemphigoid. At a later stage there is fibrosis, the distinctive feature of mucous membrane pemphigoid. The conjunctiva shows invasion of the epithelium by inflammatory cells and an appearance of granulation tissue in the submucosa. The corneal epithelium may later be transformed into an epidermis-like structure.

The findings with immunofluorescence are summarized in Table 40.6 and Figs. 40.13 and 40.14, and there is a detailed review [1].

The site for biopsy for direct immunofluorescence often presents a problem. The involvement of mucosal surfaces may mean that there is no perilesional area accessible to the dermatologist. However, it is worth taking a 3–4-mm punch biopsy or shave biopsy from uninvolved skin and from the inner lower lip [2]. The help of other specialities is needed to take biopsies from bulbar conjunctiva and other mucosal surfaces. The direct immunofluorescence findings are of linear basement-membrane zone IgG or C3, and less commonly IgA and IgM [3,4]. Not all patients with the clinical disease have positive immunofluorescence; in one series, the conjunctiva was most frequently positive [2].

Using indirect immunofluorescence, the serum in mucous membrane pemphigoid does not always contain detectable circulating autoantibodies. The use of salt-split skin increases sensitivity and often demonstrates the presence of IgA autoantibodies that are not detected on intact skin [5–7]. The majority of the sera bind to the epidermal aspect of split skin (see Fig. 40.14). However, there are some that bind dermally [5–7], and these usually have circulating antibodies to laminin 5 [8] or rarely collagen VII [7]. The use of intact or salt-split mucosa does not improve the overall sensitivity [9]. ELISA is used in some centres to identify circulating antibodies to the NC16A domain of BP180. IgG autoantibodies are most commonly detected and are usually of the IgG1 and IgG4 isotypes, with IgG4 being present in nearly all cases [10]. IgA autoantibodies are present in a minority of cases and are all IgA1 [5]. ELISA techniques are available in some centres for B180 [11] and laminin 5 [12].

The immunoelectron microscopy data suggest that the antigens of mucous membrane pemphigoid are within the lamina lucida or associated with the lamina densa [13–15]. Thus, the antigens or their epitopes do seem to differ in their location from those of bullous pemphigoid.

There are multiple target antigens including BP180, BP230, α6β4 integrin, laminin 5 and collagen VII [7], explaining the variation in immunofluorescence patterns.

References

1 Kirtschig G, Wojnarowska F. Autoimmune blistering diseases: an up-date of diagnostic methods and investigations. *Clin Exp Dermatol* 1994; **19**: 97–112.

2 Venning V, Frith P, Bron A *et al.* Mucosal involvement in bullous and cicatricial pemphigoid. A clinical and immunopathological study. *Br J Dermatol* 1988; **118**: 5–7.

3 Bean S, Waisman M, Michel B *et al.* Cicatricial pemphigoid: immunofluorescent studies. *Arch Dermatol* 1972; **106**: 195–6.

4 Leonard J, Hobday C, Haffenden G *et al.* Immunofluorescent studies in ocular cicatricial pemphigoid. *Br J Dermatol* 1988; **118**: 209–17.

5 Sarret Y, Hall R, Cobo I *et al.* Salt-split human skin substrate for the immunofluorescence screening of serum from patients with cicatricial pemphigoid and a new method of immunoprecipitation with IgA antibodies. *J Am Acad Dermatol* 1991; **24**: 952–8.

6 Kelly S, Wojnarowska F. The use of chemically split tissue in the detection of circulating anti-basement membrane zone antibodies in bullous pemphigoid and cicatricial pemphigoid. *Br J Dermatol* 1988; **118**: 31–40.

7 Chan LS, Ahmed AR, Anhalt GJ *et al.* The first international consensus on mucous membrane pemphigoid: definition, diagnostic criteria, pathogenic factors, medical treatment, and prognostic indicators. *Arch Dermatol* 2002; **138**: 370–9.

8 Domloge-Hultsch N, Anhalt GJ, Gammon WR. Antiepiligrin cicatricial pemphigoid—a subepidermal bullous disorder. *Arch Dermatol* 1994; **130**: 1521.

9 Powell F, Connolly S, Rogers R III *et al.* Failure of specific human tissue substrates to increase the sensitivity of indirect immunofluorescence testing in cicatricial pemphigoid. *Acta Derm Venereol (Stockh)* 1984; **64**: 540–3.

10 Bernard P, Prost C, Aucouturier P *et al.* The subclass distribution of IgG autoantibodies in cicatricial pemphigoid and epidermolysis bullosa acquisita. *J Invest Dermat* 1991; **97**: 259–63.

11 Zillikens D, Mascaro JM, Rose PA *et al.* A highly sensitive enzyme-linked immunosorbent assay for the detection of circulating anti-BP180 autoantibodies in patients with bullous pemphigoid. *J Invest Dermatol* 1997; **109**: 679–83.

12 Bekou V, Thoma-Uszynski S, Wendler O *et al.* Detection of laminin 5-specific auto-antibodies in mucous membrane and bullous pemphigoid sera by ELISA. *J Invest Dermatol* 2005; **124**: 732–40.

13 Fine J, Neises G, Katz S. Immunofluorescence and immunoelectron microscopic studies in cicatricial pemphigoid. *J Invest Dermatol* 1984; **82**: 39–43.

14 Bernard P, Prost C, Lecerf V *et al.* Studies of cicatricial pemphigoid autoantibodies using direct immunoelectron microscopy and immunoblot analysis. *J Invest Dermatol* 1990; **94**: 630–5.

15 Bedane C, Prost C, Bernard P *et al.* Cicatricial pemphigoid antigen differs from bullous pemphigoid antigen by its exclusive extracellular localization. A study by indirect immunoelectron microscopy. *J Invest Dermatol* 1991; **97**: 3–9.



Fig. 40.18 Mucous membrane pemphigoid. Erosions around the gingival margins. (Courtesy of Dr R.J. Pye, Addenbrooke's Hospital, Cambridge, UK.)



Fig. 40.19 Mucous membrane pemphigoid. Recurrent bullae and ulceration of the penis resulting in some scarring. (Courtesy of Dr R.J. Pye, Addenbrooke's Hospital, Cambridge, UK.)

Clinical features. The striking features are the recurring blisters on either a mucous membrane or an area of skin often near one of the orifices (Fig. 40.18) [1], together with the tendency for scars to form at these sites. The initial site may be any mucous membrane including the conjunctiva, the oral mucosa and those of the nose, larynx, pharynx, oesophagus, penis (Fig. 40.19), vulva, vagina and anus.

Oral lesions occur in the majority of patients [1]. In the mouth, vesicles or small blisters, which remain intact for some time, may be seen and when erosions form they are slow to heal. Persistent, extensive erosions may be present in the buccal mucosa and especially the palate. Desquamative gingivitis with eroded bleeding gums and occasionally blisters is common (Fig. 40.18). Localized oral pemphigoid was the name previously given to patients in whom there were only oral lesions without scarring. Adhesions may develop between the buccal mucosa and the alveolar process and around the uvula and tonsillar fossae. Extension of the disease to the pharynx and oesophagus causes dysphagia and may give rise to strictures that can result in weight loss, often necessitating surgical intervention [2].

The disease can involve the larynx, manifesting with hoarseness and in rare cases may give rise to strictures causing stridor and even asphyxiation requiring surgical intervention [3–5].

Deafness from involvement of the middle ear has been reported [6].

The genitals are involved in half of female patients, with blisters and erosions of the vulva [7]. Scarring leads to obliteration of the vulval architecture with labial fusion, introital shrinkage and end-

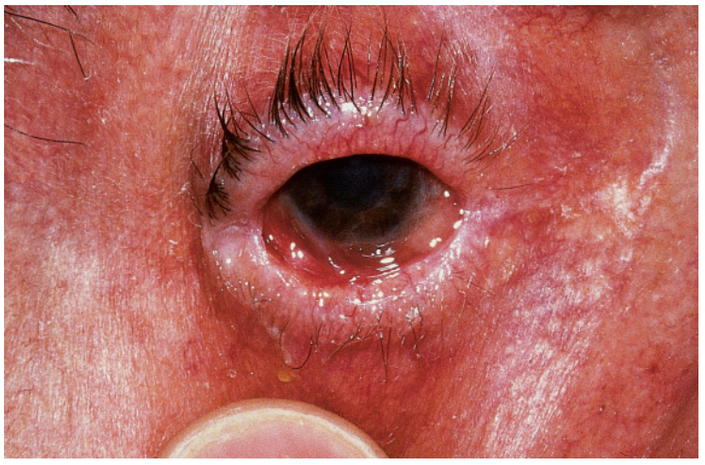


Fig. 40.20 Mucous membrane pemphigoid. Severe scarring and blindness. (Courtesy of Dr R.J. Pye, Addenbrooke's Hospital, Cambridge, UK.)

stage scarring that may be indistinguishable from lichen sclerosus [8]. The penis may be involved with blisters and erosions and adhesions may form between the prepuce and the glans penis.

Conjunctival lesions may start in one eye but will later involve both. At first, there may be a simple conjunctivitis causing redness, soreness and discomfort, and this may last for years, with alternating periods of activity and remission. Occasionally, episodes of blistering may be associated with pain and discomfort, and blisters or erosions may rarely be visible on the tarsal conjunctiva. Scarring can also occur without any preceding symptoms. There is progressive scar tissue formation, with forniceal shrinkage, linear scarring, formation of symblepharon, adhesions between the palpebral and bulbar conjunctiva, and corneal involvement. It becomes difficult to move the eyes. The conjunctive become shrunken and dry and the lower lids become inverted causing entropion (Fig. 40.20). In the final stages, the cornea becomes dry and opaque, the 'statue eye'. The conjunctivae are eventually affected in many patients, but other areas may be involved for several years before the eyes become affected.

Two types of skin lesion may occur, the most common of which is a generalized bullous eruption such that an initial diagnosis of bullous pemphigoid is made [9]. The second type is an localized to erythematous plaque, which becomes the site of the recurring blisters with subsequent scarring and hyperpigmentation. These localized lesions are often near affected mucosal surfaces. The scalp may be involved and the scarring and atrophy produce permanent alopecia. In 1957, Brunsting and Perry [10] described a group of patients who developed subepidermal bullous skin lesions that left scars; these patients apparently did not develop mucous membrane involvement. However, in many such patients mucosal involvement does ensue and they are best regarded as part of mucous membrane pemphigoid.

References

1 Hardy K, Perry H, Pingree G *et al.* Benign mucous membrane pemphigoid. *Arch Dermatol* 1971; **104**: 467–75.

2 Naylor M, MacCarty R, Rogers R III. Barium studies in esophageal cicatricial pemphigoid. *Abdom Imaging* 1995; **20**: 97–100.

3 Gaspar Z, Wojnarowska F. Cicatricial pemphigoid with severe laryngeal involvement necessitating tracheostomy (laryngeal cicatricial pemphigoid). *Clin Exper Dermatol* 1996; **21**: 209–10.

4 Whiteside OJ, Martinez Devesa P, Ali I *et al.* Mucous membrane pemphigoid: nasal and laryngeal manifestations. *J Laryngol Otol* 2003; **117**: 885–8.

5 Alexandre M, Brette MD, Pascal F *et al.* A prospective study of upper aerodigestive tract manifestations of mucous membrane pemphigoid. *Medicine (Baltimore)* 2006; **85**: 239–52.

6 Thomson J, Lang W, Craig JA. Deafness complicating mucous membrane pemphigoid: a case report. *Br J Dermatol* 1975; **93**: 337–9.

7 Marren P, Wojnarowska F, Venning V *et al.* Vulvar involvement in the autoimmune bullous diseases. *J Reprod Med* 1993; **38**: 101–8.

8 Marren P, Walkden V, Mallon E *et al.* Vulval cicatricial pemphigoid may mimic lichen sclerosus. *Br J Dermatol* 1996; **134**: 522–4.

9 Banfield C, Papadavid E, Frith P *et al.* Bullous pemphigoid evolving into cicatricial pemphigoid? *Clin Exp Dermatol* 1997; **22**: 30–3.

10 Brunsting L, Perry H. Benign pemphigoid? A report of seven cases with chronic, scarring, herpetiform plaques about the head and neck. *Arch Dermatol* 1957; **75**: 489–501.

Associated diseases. There is an association with autoimmune disease, both organ and non-organ specific [1] and with lichen sclerosus [2] with which it may share clinical similarities in the genital area as well an association with HLA-DQ7 (DQB1*0301) [3,4].

There is no association with malignancy [5] overall nor in patients with α6β4 integrin subunit antibodies [6,7]. However, there does seem to be an association of laminin 5 antibodies and malignancy (antiepiligrin mucous membrane pemphigoid) [8,9] with several case reports [10–14].

References

1 Nayar M, Wojnarowska F, Venning V *et al.* Association of autoimmunity and cicatricial pemphigoid: is there an immunogenetic basis? *J Am Acad Dermatol* 1991; **25**: 1011–5.

2 Marren P, Neild V, Frith P *et al.* Cicatricial pemphigoid and lichen sclerosus. *J Europ Acad Dermatol Venerol* 1996; **7**: 71–4.

3 Marren P, Yell J, Charnock F *et al.* The association between lichen sclerosus and antigens of the HLA system. *Br J Dermatol* 1995; **132**: 197–203.

4 Powell J, Wojnarowska F. Childhood vulvar lichen sclerosus: an increasingly common problem. *J Am Acad Dermatol* 2001; **44**: 803–6.

5 Nayar M, Wojnarowska F. No association between cicatricial pemphigoid and malignant disease. *Br J Dermatol* 1991; **125**: 193–4.

6 Malik M, Gurcan HM, Christen W *et al.* Relationship between cancer and oral pemphigoid patients with antibodies to alpha6-integrin. *J Oral Pathol Med* 2007; **36**: 1–5.

7 Letko E, Gurcan HM, Papaliodis GN *et al.* Relative risk for cancer in mucous membrane pemphigoid associated with antibodies to the beta4 integrin subunit. *Clin Exp Dermatol* 2007; **32**: 637–41.

8 Egan CA, Lazarova Z, Darling TN *et al.* Anti-epiligrin cicatricial pemphigoid and relative risk for cancer. *Lancet* 2001; **357**: 1850–1.

9 Sadler E, Lazarova Z, Sarasombath P *et al.* A widening perspective regarding the relationship between anti-epiligrin cicatricial pemphigoid and cancer. *J Dermatol Sci* 2007; **47**: 1–7.

10 Uchiyama K, Yamamoto Y, Taniuchi K *et al.* Remission of antiepiligrin (laminin-5) cicatricial pemphigoid after excision of gastric carcinoma. *Cornea* 2000; **19**: 564–6.

11 Setterfield J, Shirlaw PJ, Lazarova Z *et al.* Paraneoplastic cicatricial pemphigoid. *Br J Dermatol* 1999; **141**: 127–31.

12 Chamberlain AJ, Cooper SM, Allen J *et al.* Paraneoplastic immunobullous disease with an epidermolysis bullosa acquisita phenotype: two cases demonstrating remission with treatment of gynaecological malignancy. *Australas J Dermatol* 2004; **45**: 136–9.

13 Fukushima S, Egawa K, Nishi H *et al.* Two cases of anti-epiligrin cicatricial pemphigoid with and without associated malignancy. *Acta Derm Venereol* 2008; **88**: 484–7.

14 Mitsuya J, Hara H, Ito K *et al.* Metastatic ovarian carcinoma-associated subepidermal blistering disease with autoantibodies to both the p200 dermal antigen and the gamma 2 subunit of laminin 5 showing unusual clinical features. *Br J Dermatol* 2008; **158**: 1354–7.

Prognosis. Mucous membrane pemphigoid is a chronic debilitating and mutilating disease. It can affect the general health causing blindness, weight loss, respiratory, sexual and urinary problems. Impairment of vision is the most important complication, with some patients becoming blind in both eyes. Rare cases may die from laryngeal stenosis or complications of treatment. Unlike bullous pemphigoid, it does not appear to be self-limiting, and prolonged remissions are rare [1,2] except in localized oral or skin disease [3]. The disease often extends over many years with periods of activity and extension followed by quiescent phases. Very rarely, carcinoma has arisen in chronic oral lesions and oesophageal lesions [4].

References

1 Hardy K, Perry H, Pingree G *et al.* Benign mucous membrane pemphigoid. *Arch Dermatol* 1971; **104**: 467–75.
2 Person JR, Rogers RS 3rd. Bullous and cicatricial pemphigoid. Clinical, histopathologic, and immunopathologic correlations. *Mayo Clin Proc* 1977; **52**: 54–66.
3 Chan LS, Ahmed AR, Anhalt GJ *et al.* The first international consensus on mucous membrane pemphigoid: definition, diagnostic criteria, pathogenic factors, medical treatment, and prognostic indicators. *Arch Dermatol* 2002; **138**: 370–9.
4 Anstey A, Wojnarowska F, Whitehead P *et al.* Oesophageal webs preceding carcinoma and rupture of the oesophagus in cicatricial pemphigoid. *Clin Exp Dermatol* 1991; **16**: 395–8.

Differential diagnosis. The oral lesions, which may appear first, are difficult to differentiate from pemphigus vulgaris or from erosive lichen planus. Desquamative gingivitis may be a manifestation of local oral pemphigoid, mucous membrane pemphigoid or lichen planus and these diseases may be difficult to distinguish. The clinical signs elsewhere differentiate these conditions, but there are patients in whom initial differentiation may be impossible.

End-stage scarring of the conjunctiva may resemble scarring that can occur as a result of severe infective conjuctivitis, chronic allergy, reactions to topical drugs, erythema multiforme and toxic epidermal necrolysis, or burns. Similarly the end-stage scarring of the genital region may mimic the commoner lichen sclerosus (although both conditions may co-exist) and erosive lichen planus. The history of the mode of onset and the evidence of other active lesions should be helpful. The generalized skin eruption is indistinguishable from that of bullous pemphigoid; however, the presence of mucosal lesions and scarring favour the diagnosis of mucous membrane pemphigoid. Fixed scaly patches near the face and scalp may resemble pemphigus erythematosus.

Histological examination of a recent blister but not an erosion is helpful. Direct immunofluorescence on perilesional or clinically uninvolved mucosa and skin and indirect immunofluorescence are diagnostic if positive.

Treatment. Treatment is difficult and a systematic review has demonstrated how little evidence there is for the treatments used [1,2]. The disease activity fluctuates without treatment, and most treatments modify disease activity rather than totally suppressing it [3]. Treatment approaches have been summarized by an international consensus [4].

Local treatments are crucial and may be sufficient to control the disease to an acceptable level [3,5]. Secondary infection of oral and genital mucosa with candida is common and should be sought and treated with oral fluconazole or equivalent.

Systemic treatments are required for severe mucosal and laryngeal lesions and the control of generalized bullous eruptions, but are not always successful. The best evidence is for the use of cyclophosphamide in severe ocular disease, and for dapsone or sulphonamides in moderate to severe disease [1,2,6–8]. Dapsone and sulfamethoxypyridazine or sulphapyridine may be of value in controlling oral and cutaneous blistering and ocular disease [9,10]. Azathioprine is used but there are no large trials to support its use, similarly there are no large trials to support the use of the alternative mycophenolate mofetil, although there are encouraging reports of its benefit [11,12]. There are recent reports that systemic tetracyclines alone or combined with nicotinamide may be helpful for oral lesions [13]. The use of intravenous immunoglobulins has been advocated, although chiefly by one centre [4,14–16]. There are case reports of success with biological therapies. Several cases have responded to the TNF blockers etanercept [17–19] and infliximab [20,21]. The results with rituximab are not so encouraging; of two patients only one responded [22,23].

The usual approach is to start with the least toxic therapies in mild to moderate disease. In rapidly advancing disease threatening sight or airway more aggressive treatment is needed.

Oral lesions are often helped by local treatment with topical steroids, as mouthwashes, sprays or applications, or tetracycline mouthwashes. The sprays and mouthwashes may also help the pharynx and oesophagus. There are several anecdotal reports of the use of topical tacrolimus [24–27], but our own experience is not as good. Tetracyclines and nicotinamide can be helpful [5]. Oesophageal strictures may necessitate dilatation, which gives excellent results. Tracheotomy, which may need to be permanent, can be life-saving if there is stridor. Intralesional infiltration with mitomycin has been used to prevent recurrent laryngeal scarring [28].

The management of ocular disease needs to be performed by an ophthalmologist with experience in treating mucous membrane pemphigoid, and includes topical steroids and subconjunctival injections of corticosteroid suspension and mitomycin [29], which may be temporarily effective for conjunctival disease, but neither of these treatments nor systemic dapsone, cyclophosphamide, intravenous immunoglobulins, and/or corticosteroids will halt the progress in every case. Surgery to the lashes, division of adhesions and grafting may be required. Some patients will become blind.

Genital lesions may respond to potent topical steroids or to the combination of topical steroid and tetracycline. Vulval adhesions may require surgical division, and a Fenton's procedure to enlarge the introitus may be required in sexually active patients. Circumcision may be required in men.

Persistent skin erosions on the scalp or face can be helped by potent topical steroids.

The role of mucosal grafts is controversial and in the eye may have an adverse effect [30], although autologous stem cell transplantation may be useful in the future [31].

Mucous membrane pemphigoid is frustrating for the patient and the physician, and the patients endure many years of discomfort and morbidity, and rarely mortality from the disease and its treatment.

References

1 Kirtschig G, Murrell D, Wojnarowska F *et al.* Interventions for mucous membrane pemphigoid/cicatricial pemphigoid and epidermolysis bullosa acquisita: a systematic literature review. *Arch Dermatol* 2002; **138**: 380–4.

2 Kirtschig G, Murrell D, Wojnarowska F *et al.* Interventions for mucous membrane pemphigoid and epidermolysis bullosa acquisita (Cochrane Review). *Cochrane Database Syst Rev* 2003: CD004056.

3 Nayar M, Wojnarowska F. Cicatricial pemphigoid: a re-evaluation of therapy. *J Dermatol Treat* 1993; **4**: 89–93.

4 Chan LS, Ahmed AR, Anhalt GJ *et al.* The first international consensus on mucous membrane pemphigoid: definition, diagnostic criteria, pathogenic factors, medical treatment, and prognostic indicators. *Arch Dermatol* 2002; **138**: 370–9.

5 Wojnarowska F, Kirtschig G, Khumalo N. Treatment of subepidermal immunobullous diseases. *Clin Dermatol* 2001; **19**: 768–77.

6 Foster CS, Wilson LA, Ekins MB. Immunosuppressive therapy for progressive ocular cicatricial pemphigoid. *Ophthalmology* 1982; **89**: 340–53.

7 Foster CS. Cicatricial pemphigoid. *Trans Am Ophthalmol Soc* 1986; **84**: 527–663.

8 Tauber J, Sainz de la Maza M, Foster CS. Systemic chemotherapy for ocular cicatricial pemphigoid. *Cornea* 1991; **10**: 185–95.

9 Rogers RS 3rd. Dapsone and sulfapyridine therapy of pemphigoid diseases. *Australas J Dermatol* 1986; **27**: 58–63.

10 McFadden J, Leonard J, Powles A *et al.* Sulphamethoxypyridazine for dermatitis herpetiformis, linear IgA disease and cicatricial pemphigoid. *Br J Dermatol* 1989; **121**: 759–62.

11 Thorne JE, Jabs DA, Qazi FA *et al.* Mycophenolate mofetil therapy for inflammatory eye disease. *Ophthalmology* 2005; **112**: 1472–7.

12 Saw VP, Dart JK, Rauz S *et al.* Immunosuppressive therapy for ocular mucous membrane pemphigoid strategies and outcomes. *Ophthalmology* 2008; **115**: 253–61.

13 Reiche L, Wojnarowska F, Mallon E. Combination therapy with nicotinamide and tetracyclines for cicatrical pemphigoid: further support for efficacy. *Clin Exp Deramtol* 1998; **23**: 254–7.

14 Sami N, Bhol KC, Razzaque Ahmed A. Intravenous immunoglobulin therapy in patients with multiple mucosal involvement in mucous membrane pemphigoid. *Clin Immunol* 2002; **102**: 59–67.

15 Letko E, Miserocchi E, Daoud YJ *et al.* A nonrandomized comparison of the clinical outcome of ocular involvement in patients with mucous membrane (cicatricial) pemphigoid between conventional immunosuppressive and intravenous immunoglobulin therapies. *Clin Immunol* 2004; **111**: 303–10.

16 Sami N, Letko E, Androudi S *et al.* Intravenous immunoglobulin therapy in patients with ocular-cicatricial pemphigoid: a long-term follow-up. *Ophthalmology* 2004; **111**: 1380–2.

17 Canizares MJ, Smith DI, Conners MS *et al.* Successful treatment of mucous membrane pemphigoid with etanercept in 3 patients. *Arch Dermatol* 2006; **142**: 1457–61.

18 Prey S, Robert PY, Drouet M *et al.* Treatment of ocular cicatricial pemphigoid with the tumour necrosis factor alpha antagonist etanercept. *Acta Derm Venereol* 2007; **87**: 74–5.

19 Sacher C, Rubbert A, Konig C *et al.* Treatment of recalcitrant cicatricial pemphigoid with the tumor necrosis factor alpha antagonist etanercept. *J Am Acad Dermatol* 2002; **46**: 113–5.

20 Heffernan MP, Bentley DD. Successful treatment of mucous membrane pemphigoid with infliximab. *Arch Dermatol* 2006; **142**: 1268–70.

21 Veysey E, McHenry P, Powell J *et al.* Mucous membrane pemphigoid in a series of 7 children and a review of the literature with particular reference to prognostic features and treatment. *Eur J Pediat Dermatol* 2007; **17**: 218–26.

22 Schmidt E, Seitz CS, Benoit S *et al.* Rituximab in autoimmune bullous diseases: mixed responses and adverse effects. *Br J Dermatol* 2007; **156**: 352–6.

23 Taverna JA, Lerner A, Bhawan J *et al.* Successful adjuvant treatment of recalcitrant mucous membrane pemphigoid with anti-CD20 antibody rituximab. *J Drugs Dermatol* 2007; **6**: 731–2.

24 Assmann T, Becker J, Ruzicka T *et al.* Topical tacrolimus for oral cicatricial pemphigoid. *Clin Exp Dermatol* 2004; **29**: 674–6.

25 Gunther C, Wozel G, Meurer M *et al.* Topical tacrolimus treatment for cicatricial pemphigoid. *J Am Acad Dermatol* 2004; **50**: 325–6.

26 Hall VC, Liesegang TJ, Kostick DA *et al.* Ocular mucous membrane pemphigoid and ocular pemphigus vulgaris treated topically with tacrolimus ointment. *Arch Dermatol* 2003; **139**: 1083–4.

27 Suresh L, Martinez Calixto LE, Radfar L. Successful treatment of mucous membrane pemphigoid with tacrolimus. *Spec Care Dentist* 2006; **26**: 66–70.

28 Whiteside OJ, Martinez Devesa P, Ali I *et al.* Mucous membrane pemphigoid: nasal and laryngeal manifestations. *J Laryngol Otol* 2003; **117**: 885–8.

29 Donnenfeld ED, Perry HD, Wallerstein A *et al.* Subconjunctival mitomycin C for the treatment of ocular cicatricial pemphigoid. *Ophthalmology* 1999; **106**: 72–8, discussion 9.

30 Heiligenhaus A, Shore JW, Rubin PA *et al.* Long-term results of mucous membrane grafting in ocular cicatricial pemphigoid. Implications for patient selection and surgical considerations. *Ophthalmology* 1993; **100**: 1283–8.

31 Nishida K, Yamato M, Hayashida Y *et al.* Corneal reconstruction with tissue-engineered cell sheets composed of autologous oral mucosal epithelium. *N Engl J Med* 2004; **351**: 1187–96.

Pemphigoid gestationis

Synonym

- Herpes gestationis

Definition. Pemphigoid gestationis is an intensely pruritic, bullous eruption that may develop in association with pregnancy or rarely the trophoblastic tumours, hydatiform mole and choriocarcinoma.

The clinical features, immunopathology and immunogenetics are summarized in Tables 40.5 and 40.6, and Figs 40.13 and 40.14.

Aetiology. Pemphigoid gestationis is a rare condition that may affect from one in 10 000 to one in 60 000 pregnancies [1,2]. In Western Europe, the incidence is approximately 0.5 per million population [3,4]. It has been reported from Tunisia [5,6] and Kuwait [7]. It does occur in Afro-Caribbeans, but is very rare in the Far East [8].

The disease arises only in the presence of paternal-derived tissue, that is the fetus, and rarely hydatiform mole or choriocarcinoma, and thus tissue expressing HLA antigens from the father [9–12]. The fathers are more often HLA-DR2 than the control population [13]. It is considered that an HLA mismatch between mother and fetus triggers an immune response that cross-reacts with the maternal skin. There is clinical evidence of placental insufficiency (see below) and immunohistochemical findings of immune activation in the placenta [14,15], and affected mothers have high titres of antibodies to HLA class 1 antigens [16].

The mothers in the UK and USA frequently manifest the autoimmune haplotype, HLA-B8, -DR3 and -DR4 [9,17,18], and this association has been verified in a Mexican population [19], as has the association with HLA-DR3 in an Arab population [7]. They also have, as predicted for this HLA haplotype, a linkage disequilibrium with certain immune-response genes and thus a high incidence of the C4 null allele, which influences clearing of immune

complexes [20]. The immunogenetics of the mothers increase susceptibility to the development of pemphigoid gestationis.

Pemphigoid gestationis is associated with other autoimmune diseases (see below), implying an autoimmune basis [9,21,22].

The clinical course of pemphigoid gestationis may be modified by changes in oestrogen and progesterone levels; exacerbations may occur with oral contraceptives, and the severity may vary during the menstrual cycle [9,22].

References

1 Kolodny RC. Herpes gestationis. A new assessment of incidence, diagnosis, and fetal prognosis. *Am J Obstet Gynecol* 1969; **104**: 39–45.
2 Shornick JK, Bangert JL, Freeman RG *et al.* Herpes gestationis: clinical and histologic features of twenty-eight cases. *J Am Acad Dermatol* 1983; **8**: 214–24.
3 Bernard P, Vaillant L, Labeille B *et al.* Incidence and distribution of subepidermal autoimmune bullous skin diseases in three French regions. Bullous Diseases French Study Group. *Arch Dermatol* 1995; **131**: 48–52.
4 Zillikens D, Wever S, Roth A *et al.* Incidence of autoimmune subepidermal blistering dermatoses in a region of central Germany. *Arch Dermatol* 1995; **131**: 957–8.
5 Boudaya S, Turki H, Meziou TJ *et al.* [Pemphigoid gestationis: a study of 15 cases]. *J Gynecol Obstet Biol Reprod (Paris)* 2003; **32**: 30–4.
6 Mokni M, Fourati M, Karoui I *et al.* [Pemphigoid gestationis: a study of 20 cases]. *Ann Dermatol Venereol* 2004; **131**: 953–6.
7 Nanda A, Al-Saeed K, Dvorak R *et al.* Clinicopathological features and HLA tissue typing in pemphigoid gestationis patients in Kuwait. *Clin Exp Dermatol* 2003; **28**: 301–6.
8 Jin P, Shao C, Ye G. Chronic bullous dermatoses in China. *Int J Dermatol* 1993; **32**: 89–92.
9 Holmes R, Black M, Jurecka W *et al.* Clues to the aetiology and pathogenesis of herpes gestationis. *Br J Dermatol* 1983; **109**: 131–9.
10 do Valle Chiossi MP, Costa RS, Ferreira Roselino AM. Titration of herpes gestationis factor fixing to C3 in pemphigoid herpes gestationis associated with choriocarcinoma. *Arch Dermatol* 2000; **136**: 129–30.
11 Sinemus K, Zillikens D, Lehmann P. [Pemphigoid gestationis—first sign of metastatic choriocarcinoma]. *J Dtsch Dermatol Ges* 2004; **2**: 851–4.
12 Tindall J, Rea T, Shulman I *et al.* Herpes gestationis in association with hydatidiform mole. *Arch Dermatol* 1981; **117**: 510–2.
13 Shornick J, Stastny P, Gilliam J. Paternal histocompatibility (HLA) antigens and maternal anti-HLA antibodies in herpes gestationis. *J Invest Dermatol* 1983; **81**: 407–9.
14 Borthwick G, Holmes R, Stirrat G. Abnormal expression of Class II MHC antigens in placentae from patients with pemphigoid gestationis: analysis of Class II MHC subregion product expression. *Placenta* 1988; **9**: 81–94.
15 Kelly SE, Fleming S, Bhogal BS *et al.* Immunopathology of the placenta in pemphigoid gestationis and linear IgA disease. *Br J Dermatol* 1989; **120**: 735–43.
16 Shornick JK, Jenkins RE, Briggs DC *et al.* Anti-HLA antibodies in pemphigoid gestationis (herpes gestationis). *Br J Dermatol* 1993; **129**: 257–9.
17 Shornick J, Stasny P, Gilliam J. High frequency of histocompatibility antigens HLA-DR3 and DR4 in herpes gestationis. *J Clin Invest* 1981; **68**: 553–5.
18 Shornick JK, Jenkins RE, Artlett CM *et al.* Class II MHC typing in pemphigoid gestationis. *Clin Exp Dermatol* 1995; **20**: 123–6.
19 Garcia-Gonzalez E, Castro-Llamas J, Karchmer S *et al.* Class II major histocompatibility complex typing across the ethnic barrier in pemphigoid gestationis. A study in Mexicans. *Int J Dermatol* 1999; **38**: 46–51.
20 Shornick J, Artlett C, Jenkins R *et al.* Complement polymorphism in herpes gestationis: association with C4 null allele. *J Am Acad Dermatol* 1993; **29**: 545–9.
21 Shornick J, Black M. Secondary autoimmune diseases in herpes gestationis (pemphigoid gestationis). *J Am Acad Dermatol* 1992; **26**: 563–6.
22 Jenkins RE, Hern S, Black MM. Clinical features and management of 87 patients with pemphigoid gestationis. *Clin Exp Dermatol* 1999; **24**: 255–9.

Pathogenesis. The autoantibodies are directed at the same hemidesmosome target antigens as bullous pemphigoid, BP180 and less commonly BP230 [1,2]. The NC16A domain, the extracellular region of BP180 adjacent to the transmembrane portion (Fig. 40.11), is the immunodominant epitope [3] with the antibody response mostly restricted to this region [4–8]. This extracellular location makes it a likely target for pathogenic autoantibodies. The same epitopes are recognized by the autoantibodies and T cells [5]. There is a report of a target antigen of 200 kDa in an individual patient [9].

An animal model has demonstrated that autoantibodies to BP180 are pathogenic and require complement (see above, bullous pemphigoid) [10,11]. Use of immunosorbent techniques against epitopes within the NC16A domain prevents dermoepidermal separation induced by the antibodies [12].

There is evidence of involvement of T cells and eosinophils in blister formation [13,14].

The autoantibodies react with the basement membrane of amnion placenta from the second trimester on and are found in the fetal skin and cord blood [15–18]. BP180 is expressed in the syncytial and cytotrophoblastic cells of normal placenta and in epithelial cells of amniotic membrane, and may be involved in the invasion of extravillous trophoblasts during placental development as well as the integrity of amniotic basement membrane [19]. Although the exact pathomechanism of pemphigoid gestationis is still largely unknown, the clinical symptoms of pemphigoid gestationis are initiated after the expression of collagen XVII in placenta during the first trimester of pregnancy.

The autoantibodies are IgG antibodies of the IgG1 and IgG3 subclasses [20,21]. These IgG1 antibodies avidly bind C3, and often this binding is detected rather than the IgG antibodies themselves. There is a single case report of IgA antibodies [22].

References

1 Morrison L, Labib R, Zone J *et al.* Herpes gestationis autoantibodies recognize a 180 kD human epidermal antigen. *J Clin Invest* 1988; **81**: 2023–6.
2 Kelly S, Bhogal B, Wojnarowska F *et al.* Western blot analysis of the antigen in pemphigoid gestationis. *Br J Dermatol* 1990; **122**: 445–9.
3 Giudice GJ, Emery DJ, Zelickson BD *et al.* Bullous pemphigoid and herpes gestationis autoantibodies recognize a common non-collagenous site on the BP180 ectodomain. *J Immunol* 1993; **151**: 5742–50.
4 Lin MS, Gharia M, Fu CL *et al.* Molecular mapping of the major epitopes of BP180 recognized by herpes gestationis autoantibodies. *Clin Immunol* 1999; **92**: 285–92.
5 Lin MS, Gharia MA, Swartz SJ *et al.* Identification and characterization of epitopes recognized by T lymphocytes and autoantibodies from patients with herpes gestationis. *J Immunol* 1999; **162**: 4991–7.
6 Kromminga A, Sitaru C, Meyer J *et al.* Cicatricial pemphigoid differs from bullous pemphigoid and pemphigoid gestationis regarding the fine specificity of autoantibodies to the BP180 NC16A domain. *J Dermatol Sci* 2002; **28**: 68–75.
7 Sitaru C, Powell J, Shimanovich I *et al.* Pemphigoid gestationis: maternal sera recognize epitopes restricted to the N-terminal portion of the extracellular domain of BP180 not present on its shed ectodomain. *Br J Dermatol* 2003; **149**: 420–2.
8 Di Zenzo G, Calabresi V, Grosso F *et al.* The intracellular and extracellular domains of BP180 antigen comprise novel epitopes targeted by pemphigoid gestationis autoantibodies. *J Invest Dermatol* 2007; **127**: 864–73.
9 Kirtschig G, Wojnarowska F, Collier P *et al.* Severe case of pemphigoid gestationis with unusual target antigen. *Br J Dermatol* 1994; **131**: 108–11.
10 Liu Z, Diaz LA, Troy JL *et al.* A passive transfer model of the organ-specific autoimmune disease, bullous pemphigoid, using antibodies generated against the hemidesmosomal antigen, BP180. *J Clin Invest* 1993; **92**: 2480–8.
11 Liu Z, Giudice GJ, Swartz SJ *et al.* The role of complement in experimental bullous pemphigoid. *J Clin Invest* 1995; **95**: 1539–44.

12 Herrero-Gonzalez JE, Brauns O, Egner R *et al.* Immunoadsorption against two distinct epitopes on human type XVII collagen abolishes dermal-epidermal separation induced in vitro by autoantibodies from pemphigoid gestationis patients. *Eur J Immunol* 2006; **36**: 1039–48.
13 Fabbri P, Caproni M, Berti S *et al.* The role of T lymphocytes and cytokines in the pathogenesis of pemphigoid gestationis. *Br J Dermatol* 2003; **148**: 1141–8.
14 Gunther C, Wozel G, Dressler J *et al.* Tissue eosinophilia in pemphigoid gestationis: association with eotaxin and upregulated activation markers on transmigrated eosinophils. *Am J Reprod Immunol* 2004; **51**: 32–9.
15 Chorzelski TP, Jablonska S, Beutner EH *et al.* Herpes gestations with identical lesions in the newborn. Passive transfer of the disease? *Arch Dermatol* 1976; **112**: 1129–31.
16 Katz A, Minto JO, Toole JW *et al.* Immunopathologic study of herpes gestationis in mother and infant. *Arch Dermatol* 1977; **113**: 1069–72.
17 Ortonne J, Hsi B-L, Verrando P *et al.* Herpes gestationis factor reacts with amniotic epithelial basement membrane. *Br J Dermatol* 1987; **117**: 147–54.
18 Kelly SE, Fleming S, Bhogal BS *et al.* Immunopathology of the placenta in pemphigoid gestationis and linear IgA disease. *Br J Dermatol* 1989; **120**: 735–43.
19 Huilaja L, Hurskainen T, Autio-Harmainen H *et al.* Pemphigoid gestationis autoantigen, transmembrane collagen XVII, promotes the migration of cytotrophoblastic cells of placenta and is a structural component of fetal membranes. *Matrix Biol* 2008; **27**: 190–200.
20 Kelly SE, Cerio R, Bhogal BS *et al.* The distribution of IgG subclasses in pemphigoid gestationis: PG factor is an IgG1 autoantibody. *J Invest Dermatol* 1989; **92**: 695–8.
21 Chimanovitch I, Schmidt E, Messer G *et al.* IgG1 and IgG3 are the major immunoglobulin subclasses targeting epitopes within the NC16A domain of BP180 in pemphigoid gestationis. *J Invest Dermatol* 1999; **113**: 140–2.
22 Shimanovich I, Skrobek C, Rose C *et al.* Pemphigoid gestationis with predominant involvement of oral mucous membranes and IgA autoantibodies targeting the C-terminus of BP180. *J Am Acad Dermatol* 2002; **47**: 780–4.

Pathology. The histopathology of the early urticated lesions of pemphigoid gestationis shows epidermal and papillary dermal oedema with occasional foci of eosinophilic spongiosis. The bullous lesions are subepidermal and contain numerous eosinophils. The split is through the lamina lucida.

The findings with immunofluorescence are summarized in Table 40.6, and Figs 40.13 and 40.14. Direct immunofluorescence studies show that in all active cases of pemphigoid gestationis there is C3 deposition at the basement-membrane zone. In some cases, IgG is also found. C3 and IgG deposition are found in the placenta and fetal skin [1–4].

Indirect immunofluorescence studies demonstrate binding of C3 to the basement-membrane zone; this serum factor was known as the HG factor. Although conventional immunofluorescence techniques are able to demonstrate IgG in only about 25% of cases, it is now clear that the autoantibody is an IgG of the IgG1 subclass [5,6]. The autoantibodies bind to the epidermal side of salt-split skin [7]. IgG antibodies can be detected by ELISA [8,9].

Immunoelectron microscopic studies have confirmed that IgG is deposited along the basement-membrane zone, chiefly within the lamina lucida and localized to the proximal part of the anchoring filament [10–12].

Immunoblotting and ELISA techniques have shown that the major antigen recognized by the circulating autoantibodies is BP180 [13–15].

There may be evidence of a villitis of the placenta [16].

References

1 Chorzelski TP, Jablonska S, Beutner EH *et al.* Herpes gestations with identical lesions in the newborn. Passive transfer of the disease? *Arch Dermatol* 1976; **112**: 1129–31.
2 Katz A, Minto JO, Toole JW *et al.* Immunopathologic study of herpes gestationis in mother and infant. *Arch Dermatol* 1977; **113**: 1069–72.
3 Ortonne J, Hsi B-L, Verrando P *et al.* Herpes gestationis factor reacts with amniotic epithelial basement membrane. *Br J Dermatol* 1987; **117**: 147–54.
4 Kelly SE, Fleming S, Bhogal BS *et al.* Immunopathology of the placenta in pemphigoid gestationis and linear IgA disease. *Br J Dermatol* 1989; **120**: 735–43.
5 Kelly SE, Cerio R, Bhogal BS *et al.* The distribution of IgG subclasses in pemphigoid gestationis: PG factor is an IgG1 autoantibody. *J Invest Dermatol* 1989; **92**: 695–8.
6 Chimanovitch I, Schmidt E, Messer G *et al.* IgG1 and IgG3 are the major immunoglobulin subclasses targeting epitopes within the NC16A domain of BP180 in pemphigoid gestationis. *J Invest Dermatol* 1999; **113**: 140–2.
7 Kelly SE, Bhogal BS, Wojnarowska F *et al.* Expression of a pemphigoid gestationis-related antigen by human placenta. *Br J Dermatol* 1988; **118**: 605–11.
8 Sitaru C, Powell J, Messer G *et al.* Immunoblotting and enzyme-linked immunosorbent assay for the diagnosis of pemphigoid gestationis. *Obstet Gynecol* 2004; **103**: 757–63.
9 Powell AM, Sakuma-Oyama Y, Oyama N *et al.* Usefulness of BP180 NC16a enzyme-linked immunosorbent assay in the serodiagnosis of pemphigoid gestationis and in differentiating between pemphigoid gestationis and pruritic urticarial papules and plaques of pregnancy. *Arch Dermatol* 2005; **141**: 705–10.
10 Holubar K, Konrad K, Stingl G. Detection by immunoelectron microscopy of immunoglobulin G deposits in skin of immunofluorescence negative herpes gestationis. *Br J Dermatol* 1977; **96**: 569–71.
11 Jurecka W, Holmes R, Black M *et al.* An immunoelectron microscopy study of the relationship between herpes gestationis and polymorphic eruption of pregnancy. *Br J Dermatol* 1983; **108**: 147–51.
12 Boulinguez S, Bedane C, Prost C *et al.* Chronic pemphigoid gestationis: comparative clinical and immunopathological study of 10 patients. *Dermatology* 2003; **206**: 113–9.
13 Morrison L, Labib R, Zone J *et al.* Herpes gestationis autoantibodies recognize a 180 kD human epidermal antigen. *J Clin Invest* 1988; **81**: 2023–6.
14 Kelly S, Bhogal B, Wojnarowska F *et al.* Western blot analysis of the antigen in pemphigoid gestationis. *Br J Dermatol* 1990; **122**: 445–9.
15 Sitaru C, Powell J, Shimanovich I *et al.* Pemphigoid gestationis: maternal sera recognize epitopes restricted to the N-terminal portion of the extracellular domain of BP180 not present on its shed ectodomain. *Br J Dermatol* 2003; **149**: 420–2.
16 Huilaja L, Hurskainen T, Autio-Harmainen H *et al.* Pemphigoid gestationis autoantigen, transmembrane collagen XVII, promotes the migration of cytotrophoblastic cells of placenta and is a structural component of fetal membranes. *Matrix Biol* 2007; **27**: 190–200.

Clinical features. Pemphigoid gestationis may begin at any time between 4 weeks' gestation and 5 weeks postpartum, with the majority presenting in the second and third trimester [1,2]. Almost half of cases develop in the first pregnancy. There is a high risk of recurrence in subsequent pregnancies; the onset is likely to be earlier than in the previous one and the disease may be very different in severity. In many cases, the disease becomes relatively quiescent in late pregnancy, only to flare severely immediately postpartum [1]. Usually, the disease lasts several weeks to months, on average 6 months, but sometimes it can continue for years afterwards [2]. The likelihood of prolonged disease is increased by older age, multiparity and mucosal involvement [3].

Pemphigoid gestationis is intensely itchy. The condition characteristically begins around the umbilicus, and then spreads to the abdomen, thighs, limbs, palms and soles (Figs 40.21 & 40.22). Involvement of the oral cavity is relatively rare. Early in its course, the eruption consists of urticated papules, plaques, target lesions and annular wheals, associated with marked pruritus (Fig. 40.21); subsequently, vesicles and larger blisters appear (Fig. 40.22).

Neonatal pemphigoid gestationis may occur in 3% pregnancies [2], with positive direct immunofluorescence in the neonate [4,5],

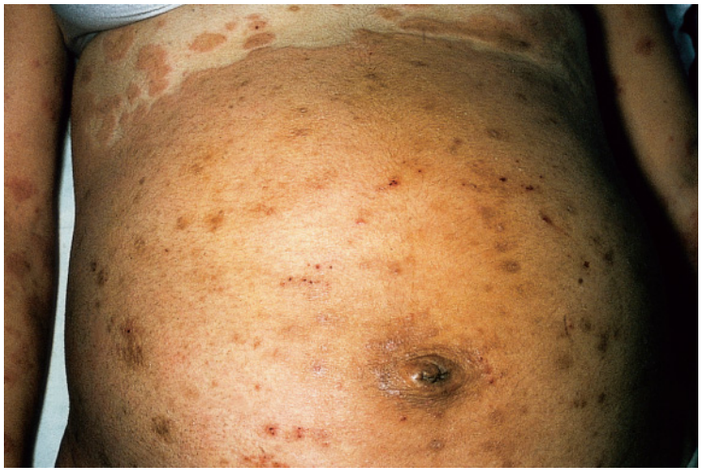


Fig. 40.21 Pemphigoid gestationis. Early pruritic erythematous stage. (Courtesy of Dr P. Hudson, Peterborough Hospital, Peterborough, UK.)



Fig. 40.22 Pemphigoid gestationis. Bullae arising on urticated erythematous skin on the thigh. (Courtesy of Dr P. Hudson, Peterborough Hospital, Peterborough, UK.)

due to transfer of antibodies across the placenta. It usually resolves rapidly without treatment [2,4,5].

References

1 Shornick JK, Bangert JL, Freeman RG *et al.* Herpes gestationis: clinical and histologic features of twenty-eight cases. *J Am Acad Dermatol* 1983; **8**: 214–24.
2 Jenkins RE, Hern S, Black MM. Clinical features and management of 87 patients with pemphigoid gestationis. *Clin Exp Dermatol* 1999; **24**: 255–9.
3 Boulinguez S, Bedane C, Prost C *et al.* Chronic pemphigoid gestationis: comparative clinical and immunopathological study of 10 patients. *Dermatology* 2003; **206**: 113–9.
4 Chorzelski TP, Jablonska S, Beutner EH *et al.* Herpes gestations with identical lesions in the newborn. Passive transfer of the disease? *Arch Dermatol* 1976; **112**: 1129–31.
5 Katz A, Minto JO, Toole JW *et al.* Immunopathologic study of herpes gestationis in mother and infant. *Arch Dermatol* 1977; **113**: 1069–72.

Associated diseases. Pemphigoid gestationis is associated with other autoimmune diseases, 14% in a recent study [1], particularly with Graves' disease (10%), hypothyroidism, vitiligo, alopecia areata and autoimmune thrombocytopenia [1–3].

References

1 Jenkins RE, Hern S, Black MM. Clinical features and management of 87 patients with pemphigoid gestationis. *Clin Exp Dermatol* 1999; **24**: 255–9.
2 Holmes R, Black M, Jurecka W *et al.* Clues to the aetiology and pathogenesis of herpes gestationis. *Br J Dermatol* 1983; **109**: 131–9.
3 Shornick J, Black M. Secondary autoimmune diseases in herpes gestationis (pemphigoid gestationis). *J Am Acad Dermatol* 1992; **26**: 563–6.

Prognosis. Pemphigoid gestationis tends to improve postpartum, but it may be weeks, months or years before there is complete resolution. In rare cases the disease may evolve into bullous pemphigoid [1,2]. There are often flares with menstruation. There are usually dramatic flares with the oral contraceptive, which is contraindicated while the disease is still active, but can often be used subsequently.

There are reports of persistent disease postpartum and these cases are more likely to have previous disease and to be older [1,3].

Once pemphigoid gestationis has occurred, it is likely to recur in subsequent pregnancies, and may be more or less severe. About 8% of subsequent pregnancies are spared [4]. Although a change in partner does not increase the risk of developing pemphigoid gestationis, it is unclear whether it alters the risk of recurrence [4]. Patients should be counselled as to the risk of recurrence, but not advised against having further pregnancies because they have had pemphigoid gestationis.

The modern view is that pemphigoid gestationis is associated with premature delivery and a risk of low birth weight [5–8]. The fetal prognosis is worse when there is early onset of the disease, reflecting more prolonged duration of placental insufficiency, and when there is blistering, perhaps because of more severe microseparation and placental damage [8,9]. Deliveries from mothers with pemphigoid gestationis should take place in departments that have facilities for special care of the newborn.

References

1 Jenkins RE, Jones SA, Black MM. Conversion of pemphigoid gestationis to bullous pemphigoid—two refractory cases highlighting this association. *Br J Dermatol* 1996; **135**: 595–8.
2 Amato L, Mei S, Gallerani I *et al.* A case of chronic herpes gestationis: persistent disease or conversion to bullous pemphigoid? *J Am Acad Dermatol* 2003; **49**: 302–7.
3 Boulinguez S, Bedane C, Prost C *et al.* Chronic pemphigoid gestationis: comparative clinical and immunopathological study of 10 patients. *Dermatology* 2003; **206**: 113–9.
4 Jenkins RE, Hern S, Black MM. Clinical features and management of 87 patients with pemphigoid gestationis. *Clin Exp Dermatol* 1999; **24**: 255–9.
5 Holmes RC, Black MM. The fetal prognosis in pemphigoid gestationis (herpes gestationis). *Br J Dermatol* 1984; **110**: 67–72.
6 Shornick J, Black M. Fetal risks in herpes gestationes. *J Am Acad Dermatol* 1992; **26**: 63–8.
7 Mascaro JM Jr, Lecha M, Mascaro JM. Fetal morbidity in herpes gestationis. *Arch Dermatol* 1995; **131**: 1209–10.
8 Chi C-C, Wang S-H, Charles-Holmes R *et al.* Pemphigoid gestationis: early onset and blister formation are associated with adverse pregnancy outcomes. *Br J Dermatol* 2009; **160**: 1222–8.
9 Huilaja L, Hurskainen T, Autio-Harmainen H *et al.* Pemphigoid gestationis autoantigen, transmembrane collagen XVII, promotes the migration of cytotrophoblastic cells of placenta and is a structural component of fetal membranes. *Matrix Biol* 2008; **27**: 190–200.

Differential diagnosis. The main problem is the differentiation of pemphigoid gestationis from the much more common eruption that begins in later pregnancy, termed polymorphic eruption of pregnancy (see Chapter 8). This usually begins in the stretch marks and almost never blisters. The histopathology often differentiates the two conditions, and immunofluorescence and ELISA is negative in polymorphic eruption of pregnancy.

Treatment. In mild cases of pemphigoid gestationis, topical potent or very potent steroids can be successful, and this was so in almost 20% in recent retrospective studies [1–3]. They are often combined with a systemic antihistamine (using one suitable for use in pregnancy) [1,2]. Once the blisters develop, systemic steroids are usually necessary. Moderate disease responds to 20–30 mg/day of prednisolone, severe disease may need 40–80 mg/day of prednisolone. Prednisolone dose can usually be reduced fairly rapidly to a much lower maintenance dose. The use of systemic steroids does not seem to have an adverse effect on pregnancy outcomes, other than reflecting severe disease [4]. Because postpartum exacerbations are so frequent, it is worth increasing the corticosteroid dose temporarily at the first sign of a flare.

Plasmapheresis can be considered in the most severe cases [5]. The role of dapsone is unclear and the drug can cause haemolytic disease in the neonate [2]. There is only anecdote to support the use of pyridoxine [6].

Postpartum treatment can be a problem if the mother wishes to breastfeed, as the drugs pass into the breast milk. Antihistamines can cause drowsiness in the baby, steroids at high doses (more than prednisolone 40 mg/day) may cause adrenal suppression, and dapsone may cause haemolysis. The paediatricians should therefore be consulted in this situation. In the non-breastfeeding woman there are reports of the successful use of tetracyclines, sometimes with nicotinamide [7–9]. Immunosuppressive treatment, including cyclophosphamide and immunomodulating treatments such as intravenous immunoglobulins [10–13], immunoapheresis [14] and rituximab [15] have also been used, mainly postpartum.

References

1 Jenkins RE, Hern S, Black MM. Clinical features and management of 87 patients with pemphigoid gestationis. *Clin Exp Dermatol* 1999; **24**: 255–9.

2 Boudaya S, Turki H, Meziou TJ *et al.* [Pemphigoid gestationis: a study of 15 cases]. *J Gynecol Obstet Biol Reprod (Paris)* 2003; **32**: 30–4.

3 Mokni M, Fourati M, Karoui I *et al.* [Pemphigoid gestationis: a study of 20 cases]. *Ann Dermatol Venereol* 2004; **131**: 953–6.

4 Chi CC, Wang SH, Charles-Holmes R *et al.* Pemphigoid gestationis: early onset and blister formation are associated with adverse pregnancy outcomes. *Br J Dermatol* 2009; **160**: 1222–8.

5 Van de Wiel A, Hart HC, Flinterman J *et al.* Plasma exchange in herpes gestationis. *BMJ* 1980; **281**: 1041–2.

6 Burkhart CG. Pyridoxine-responsive herpes gestationis. *Arch Dermatol* 1982; **118**: 535.

7 Satoh S, Seishima M, Sawada Y *et al.* The time course of the change in antibody titres in herpes gestationis. *Br J Dermatol* 1999; **140**: 119–23.

8 Loo WJ, Dean D, Wojnarowska F. A severe persistent case of recurrent pemphigoid gestationis successfully treated with minocycline and nicotinamide. *Clin Exp Dermatol* 2001; **26**: 726–7.

9 Amato L, Coronella G, Berti S *et al.* Successful treatment with doxycycline and nicotinamide of two cases of persistent pemphigoid gestationis. *J Dermatolog Treat* 2002; **13**: 143–6.

10 Castle SP, Mather-Mondrey M, Bennion S *et al.* Chronic herpes gestationis and antiphospholipid antibody syndrome successfully treated with cyclophosphamide. *J Am Acad Dermatol* 1996; **34**: 333–6.

11 Hern S, Harman K, Bhogal BS *et al.* A severe persistent case of pemphigoid gestationis treated with intravenous immunoglobulins and cyclosporin. *Clin Exp Dermatol* 1998; **23**: 185–8.

12 Harman KE, Black MM. High-dose intravenous immune globulin for the treatment of autoimmune blistering diseases: an evaluation of its use in 14 cases. *Br J Dermatol* 1999; **140**: 865–74.

13 Kreuter A, Harati A, Breuckmann F *et al.* Intravenous immune globulin in the treatment of persistent pemphigoid gestationis. *J Am Acad Dermatol* 2004; **51**: 1027–8.

14 Wohrl S, Geusau A, Karlhofer F *et al.* Pemphigoid gestationis: treatment with immunoapheresis. *J Dtsch Dermatol Ges* 2003; **1**: 126–30.

15 Cianchini G, Masini C, Lupi F *et al.* Severe persistent pemphigoid gestationis: long-term remission with rituximab. *Br J Dermatol* 2007; **157**: 388–9.

Linear IgA disease

Synonyms

- Chronic bullous disease of childhood
- Juvenile dermatitis herpetiformis
- Juvenile pemphigoid
- Linear dermatitis herpetiformis
- Linear IgA bullous dermatosis

Definition. Linear IgA disease is a chronic, acquired, subepidermal disease of children and adults, with cutaneous and mucosal involvement, characterized by IgA basement-membrane antibodies. The disease responds to dapsone and has a tendency to remit.

Two main clinical syndromes are distinguished, chronic bullous disease of childhood, beginning in childhood, and adult linear IgA disease, beginning any time in adult life. They differ in their age of presentation and to some extent as regards their clinical signs, but there is much overlap, and the immunopathology and immunogenetics are common to both diseases.

The clinical features, immunopathology and immunogenetics are summarized in Tables 40.5 and 40.6.

Aetiology. Linear IgA disease affects all ages from babies of a few months to the elderly. The majority of children present as toddlers or preschool children, although a few have presented as neonates [1,2]. Teenagers and young adults also present with the disease and there is a second peak over 60 years [3]. Linear IgA disease is one of the less common subepidermal blistering diseases in western Europe with an incidence of less than 0.5 per million, chiefly adults [4,5]. It is commoner in China where it is about one third as common as bullous pemphigoid and one-third are children [6]. It has been reported from the Middle East (Kuwait) and South East Asia [7–10]. There seem to be more children with the disease in developing communities, for example China, Malaysia, Sri Lanka, India, Thailand, Tunisia, Kuwait, Mali, Uganda and black children in South Africa than in Western Europe [6,11–20].

The sex incidence is about equal or there may be a slight excess of female patients.

There is a strong association between linear IgA disease and the extended autoimmune haplotype HLA-B8, -CW7, -DR3 in UK and black South African patients and possession of this haplotype is

associated with an early disease onset [14,21]. This extended haplotype is in linkage disequilibrium with a high producing allele of tumour necrosis factor (TNF), and this association exists in linear IgA patients and confers a worse prognosis [21].

References

1 Hruza LL, Mallory SB, Fitzgibbons J *et al.* Linear IgA bullous dermatosis in a neonate. *Pediatr Dermatol* 1993; **10**: 171–6.
2 Kishida Y, Kameyama J, Nei M *et al.* Linear IgA bullous dermatosis of neonatal onset: case report and review of the literature. *Acta Paediatr* 2004; **93**: 850–2.
3 Wojnarowska F, Marsden R, Bhogal B *et al.* Chronic bullous disease of childhood, childhood cicatricial pemphigoid and linear IgA disease of adults, a comparative study demonstrating clinical and immunopathological overlap. *J Am Acad Dermatol* 1988; **19**: 792–805.
4 Bernard P, Vaillant L, Labeille B *et al.* Incidence and distribution of subepidermal autoimmune bullous skin diseases in three French regions. Bullous Diseases French Study Group. *Arch Dermatol* 1995; **131**: 48–52.
5 Zillikens D, Wever S, Roth A *et al.* Incidence of autoimmune subepidermal blistering dermatoses in a region of central Germany. *Arch Dermatol* 1995; **131**: 957–8.
6 Jin P, Shao C, Ye G. Chronic bullous dermatoses in China. *Int J Dermatol* 1993; **32**: 89–92.
7 Adam BA. Bullous diseases in Malaysia: epidemiology and natural history. *Int J Dermatol* 1992; **31**: 42–5.
8 Ratnam KV. IgA dermatosis in an adult Chinese population. A 10-year study of linear IgA and dermatitis herpetiformis in Singapore. *Int J Dermatol* 1988; **27**: 21–4.
9 Wong SN, Chua SH. Spectrum of subepidermal immunobullous disorders seen at the National Skin Centre, Singapore: a 2-year review. *Br J Dermatol* 2002; **147**: 476–80.
10 Nanda A, Dvorak R, Al-Saeed K *et al.* Spectrum of autoimmune bullous diseases in Kuwait. *Int J Dermatol* 2004; **43**: 876–81.
11 Adam BA. Bullous diseases: a 7-year survey of experience with 77 patients. *Ann Acad Med Singapore* 1983; **12**: 19–25.
12 Piamphongsant T, Sirimachan S, Himmunknan P. Juvenile blistering diseases: the problems of diagnosis and treatment. *Asian Pac J Allergy Immunol* 1986; **4**: 133–7.
13 Reid C, Wojnarowska F, Pothupityiyia G *et al.* Chronic bullous dermatosis of childhood around the world. *Br J Dermatol* 1988; **119** (Suppl. 33): 41.
14 Aboobaker J, Wojnarowska F, Bhogal B *et al.* Chronic bullous dermatosis of childhood—clinical and immunological features seen in African patients. *Clin Exp Dermatol* 1991; **16**: 160–4.
15 Denguezli M, Ben Nejma B, Nouira R *et al.* [Iga linear bullous dermatosis in children. A series of 12 Tunisian patients]. *Ann Dermatol Venereol* 1994; **121**: 888–92.
16 Mahe A, Flageul B, Bobin P. [Bullous IgA linear dermatosis of children in Mali]. *Ann Dermatol Venereol* 1996; **123**: 544–8.
17 Ajithkumar K, Kurian S, Jacob M *et al.* Linear IgA bullous dermatosis in south India. *Int J Dermatol* 1997; **36**: 191–3.
18 Kulthanan K, Akaraphanth R, Piamphongsant T *et al.* Linear IgA bullous dermatosis of childhood: a long-term study. *J Med Assoc Thai* 1999; **82**: 707–12.
19 Nanda A, Dvorak R, Al-Sabah H *et al.* Linear IgA bullous disease of childhood: an experience from Kuwait. *Pediatr Dermatol* 2006; **23**: 443–7.
20 Mulyowa GK, Jaeger G, Kabakyenga J *et al.* Autoimmune subepidermal blistering diseases in Uganda: correlation of autoantibody class with age of patients. *Int J Dermatol* 2006; **45**: 1047–52.
21 Collier P, Wojnarowska F, Welsh K *et al.* Adult linear IgA disease and chronic bullous disease of childhood: the association with human leucocyte antigens Cw7, B8, HLA DR3, and tumour necrosis factor influences disease expression. *Br J Dermatol* 1999; **141**: 867–75.

Pathogenesis. The autoantibodies in linear IgA disease are IgA, and this is unusual for an autoimmune disease, and are usually IgA1 and monomeric [1–3]. However, IgG antibodies can also be detected by immunoblotting techniques, although their antigen repertoire is more limited [4–6].

The IgA antibodies are directed at a number of different target antigens within the adhesion complex. The major antigen in linear IgA disease is BP180/collagen XVII and its shed ectodomain, formerly known as LAD1 with molecular weights of 97 and 120 kDa. There are also antibodies to BP230 and a unique antigen LAD285, which has a molecular weight of 285 kDa [5–10]. The autoantibodies recognize many different epitopes on BP180, including the NC16A domain [11–13]. T cell responses to BP180 have been demonstrated [14]. Collagen VII, the anchoring fibril component, is a rare antigen and is almost never associated with a mechanobullous scarring phenotype, unlike classical epidermolysis bullosa acquisita (see below) [15–18]. There are other unidentified dermal antigens [6,19].

There is indirect evidence that the antibodies are pathogenic, in that they cause splitting of skin in culture and binding of neutrophils to the basement-membrane zone [20,21]. An animal model has demonstrated that IgA mouse monoclonal antibodies passively transferred to SCID mice with human skin grafts can produce neutrophil infiltration and basement membrane vesiculation in a third of mice tested [22].

References

1 Leonard J, Haffenden G, Unsworth D *et al.* Evidence that the IgA in patients with linear IgA disease is qualitatively different from that of patients with dermatitis herpetiformis. *Br J Dermatol* 1984; **110**: 315–21.
2 Wojnarowska F, Bhogal G, Black M. Chronic bullous disease of childhood and linear IgA disease of adults are IgA1 mediated diseases. *Br J Dermatol* 1994; **131**: 201–4.
3 Egan CA, Martineau MR, Taylor TB *et al.* IgA antibodies recognizing LABD97 are predominantly IgA1 subclass. *Acta Derm Venereol* 1999; **79**: 343–6.
4 Kromminga A, Scheckenbach C, Georgi M *et al.* Patients with bullous pemphigoid and linear IgA disease show a dual IgA and IgG autoimmune response to BP180. *J Autoimmun* 2000; **15**: 293–300.
5 Allen J, Wojnarowska F. Linear IgA disease: the IgA and IgG response to dermal antigens demonstrates a chiefly IgA response to LAD285 and a dermal 180-kDa protein. *Br J Dermatol* 2003; **149**: 1055–8.
6 Allen J, Wojnarowska F. Linear IgA disease: the IgA and IgG response to the epidermal antigens demonstrates that intermolecular epitope spreading is associated with IgA rather than IgG antibodies, and is more common in adults. *Br J Dermatol* 2003; **149**: 977–85.
7 Zone J, Taylor T, Kadunce D *et al.* Identification of the cutaneous basement membrane zone antigen and isolation of antibody in linear immunglobulin A bullous dermatosis. *J Clin Invest* 1990; **85**: 812–20.
8 Wojnarowska F, Whitehead P, Leigh I *et al.* Identification of the target antigen in chronic bullous disease of childhood and linear IgA disease of adults. *Br J Dermatol* 1991; **124**: 157–62.
9 Marinkovich P, Taylor T, Keene D *et al.* LAD-1, the linear IgA bullous dermatosis autoantigen, is a novel 120 kDa anchoring filament protein synthesized by epidermal cells. *J Invest Dermatol* 1996; **106**: 734–8.
10 Ghohestani R, Nicolas J, Kanitakis J *et al.* Linear IgA bullous dermatosis with IgA autoantibodies exclusively directed against the 180- or 230 kDa epidermal antigens. *J Invest Dermatol* 1997; **108**: 854–8.
11 Zillikens D, Herzele K, Georgi M *et al.* Autoantibodies in a subgroup of patients with linear IgA disease react with the NC16A domain of BP1801. *J Invest Dermatol* 1999; **113**: 947–53.
12 Schumann H, Baetge J, Tasanen K *et al.* The shed ectodomain of collagen XVII/BP180 is targeted by autoantibodies in different blistering skin diseases. *Am J Pathol* 2000; **156**: 685–95.
13 Georgi M, Scheckenbach C, Kromminga A *et al.* Mapping of epitopes on the BP180 ectodomain targeted by IgA and IgG autoantibodies in patients with the lamina lucida-type of linear IgA disease. *Arch Dermatol Res* 2001; **293**: 109–14.
14 Lin MS, Fu CL, Olague-Marchan M *et al.* Autoimmune responses in patients with linear IgA bullous dermatosis: both autoantibodies and T lymphocytes recognize the NC16A domain of the BP180 molecule. *Clin Immunol* 2002; **102**: 310–9.

15 Allen J, Zhou S, Wakelin S *et al.* Linear IgA disease: a report of two dermal binding sera which recognise a pepsin-sensitive epitope (?NC-1 domain) of collagen type VII. *Br J Dermatol* 1997; **137**: 526–33.
16 Caux F, Kirtschig G, Lemarchand-Venencie F *et al.* IgA-epidermolysis bullosa acquisita in a child resulting in blindness. *Br J Dermatol* 1997; **137**: 270–5.
17 Wakelin SH, Allen J, Zhou S *et al.* Drug-induced linear IgA disease with antibodies to collagen VII. *Br J Dermatol* 1998; **138**: 310–4.
18 Harman KE, Bhogal BS, Eady RA *et al.* Defining target antigens in linear IgA disease using skin from subjects with inherited epidermolysis bullosa as a substrate for indirect immunofluorescence microscopy. *Br J Dermatol* 1999; **141**: 475–80.
19 Wojnarowska F, Allen J, Collier PM *et al.* A comparison of the expression of known basement membrane components with the linear IgA disease antigens using the novel substrate cylindroma. *Br J Dermatol* 1999; **141**: 62–70.
20 Niwa Y, Sakane T, Shingu M *et al.* Neutrophil-generated active oxygens in linear IgA bullous dermatosis. *Arch Dermatol* 1985; **121**: 73–8.
21 Hendrix J, Mangum K, Zone J *et al.* Cutaneous IgA deposits in bullous diseases function as ligands to mediate adherence of activated neutrophils. *J Invest Dermatol* 1990; **94**: 667–72.
22 Zone JJ, Egan CA, Taylor TB *et al.* IgA autoimmune disorders: development of a passive transfer mouse model. *J Investig Dermatol Symp Proc* 2004; **9**: 47–51.

Pathology. The histological features are not specific for the condition. The subepidermal vesicles may contain numerous eosinophils suggestive of pemphigoid. In some blisters, neutrophils predominate and dermal capillary microabscesses are seen, suggesting dermatitis herpetiformis. Others show subepidermal blisters with non-specific features. An old blister will give misleading results. In a child, it is not always worthwhile performing a biopsy on a lesion, as the direct immunofluorescence will give the diagnosis and is often easier and less traumatic to perform.

The findings with immunofluorescence are summarized in Table 40.6 and a detailed review has been published [1]. Direct immunofluorescence can be carried out on clinically uninvolved skin, and the back is often convenient (and out of sight) in a child. The forearm is the least satisfactory site [2] and mucosal biopsies from the mouth, but not necessarily the conjunctiva, are also positive [3].

In all cases, there is linear deposition of IgA along the basement-membrane zone. There may also be other immunoreactants, IgG, IgM or C3, on direct immunofluorescence [4,5]. Direct salt splitting of the biopsies or the raising of suction blisters in patients shows that the deposition of the autoantibodies can be associated with the epidermal aspect of the artificial blister, with the dermal aspect or both [6,7].

The significance of the rare, linear, granular pattern of IgA deposition at the basement-membrane zone is still unclear [4]. Some patients with this pattern have true dermatitis herpetiformis and others may have autoantibodies to unusual target antigens.

Indirect immunofluorescence for IgA basement-membrane zone antibodies is more often positive in children (about 80%) than adults (about 30%) [5]. The titres are usually low, of the order of 1:5 or 1:10, but occasionally much higher. The use of normal human skin split through the lamina lucida with suction or more commonly 1 mol/L salt increases the sensitivity and gives additional information as to the site of the target antigen. The majority of sera demonstrate a binding to the epidermis, implying an antigen associated with hemidesmosomes or the upper lamina lucida; a few have a combined pattern, and a larger minority bind to the dermal aspect of the artificial blister, suggesting a lower lamina lucida or dermal antigen [5,6,8].

Blister fluid is an alternative to serum for indirect immunofluorescence and may be easier to obtain in a child [9]. However, urine did not prove a practical alternative [10].

The presence of IgG autoantibodies on direct or indirect immunofluorescence causes problems with disease definition, and has been used to define a further entity, mixed immunobullous disease (see below) [11–13].

Immunoelectron-microscopy studies have shown that the immunoreactants and target antigens are either associated with the hemidesmosomes, within the lamina lucida, in the subbasal lamina zone or in a mirror-image pattern on each side of the lamina densa [14–20].

Immunoblotting studies have demonstrated a variety of target antigens, in keeping with the multiple localizations found with split skin and immunoelectron-microscopy studies. The antigens include both epidermal and dermal associated antigens, and the major one is BP180 (see above).

References

1 Kirtschig G, Wojnarowska F. Autoimmune blistering diseases: an up-date of diagnostic methods and investigations. *Clin Exp Dermatol* 1994; **19**: 97–112.
2 Collier P, Wojnarowska F. Variation in the deposition of the antibodies at different anatomical sites in linear IgA disease of adults and chronic bullous disease of childhood. *Br J Dermatol* 1992; **127**: 482–4.
3 Kelly S, Frith P, Millard P *et al.* A clinico-pathological study of mucosal involvement in linear IgA disease. *Br J Dermatol* 1988; **119**: 161–70.
4 Leonard JN, Haffenden GP, Ring NP *et al.* Linear IgA disease in adults. *Br J Dermatol* 1982; **107**: 301–16.
5 Wojnarowska F, Marsden R, Bhogal B *et al.* Chronic bullous disease of childhood, childhood cicatricial pemphigoid and linear IgA disease of adults, a comparative study demonstrating clinical and immunopathological overlap. *J Am Acad Dermatol* 1988; **19**: 792–805.
6 Aboobaker J, Bhogal B, Black M. The localisation of the binding site of circulating IgA antibodies in linear IgA disease of adults, chronic bullous disease of childhood, and cicatricial pemphigoid. *Br J Dermatol* 1987; **116**: 293–302.
7 Wojnarowska F, Collier P, Allen J *et al.* The localisation of the target antigens and antibodies in linear IgA disease is heterogeneous and dependent on the methods used. *Br J Dermatol* 1995; **132**: 750–7.
8 Willsteed E, Bhogal B, Black M *et al.* Use of 1M NaCl split skin in the indirect immunofluorescence of the linear IgA bullous dermatoses. *J Cutan Pathol* 1990; **17**: 144–8.
9 Zhou S, Wakelin SH, Allen J *et al.* Blister fluid for the diagnosis of subepidermal immunobullous diseases: a comparative study of basement membrane zone autoantibodies detected in blister fluid and serum. *Br J Dermatol* 1998; **139**: 27–32.
10 Allen J, Shears E, Powell J *et al.* Assessment of skin basement membrane zone antibodies in the urine of patients with acquired subepidermal immunobullous diseases. *Br J Dermatol* 2001; **144**: 540–5.
11 Darling TN, Cardenas AA, Beard JS *et al.* A child with antibodies targeting both linear IgA bullous dermatosis and bullous pemphigoid antigens. *Arch Dermatol* 1995; **131**: 1438–42.
12 Sheridan AT, Kirtschig G, Wojnarowska F. Mixed immunobullous disease: is this linear IgA disease? *Australas J Dermatol* 2000; **41**: 219–21.
13 Powell J, Kirtschig G, Allen J *et al.* Mixed immunobullous disease of childhood: a good response to antimicrobials. *Br J Dermatol* 2001; **144**: 769–74.
14 Bhogal B, Wojnarowksa F, Marsden R *et al.* Linear IgA bullous dermatosis of adults and children: an immunoelectronic microscopic study. *Br J Dermatol* 1987; **117**: 289–96.
15 Prost C, De Leca A, Combermale P *et al.* Diagnosis of adult linear IgA disease by immunoelectron microscopy in 16 patients with linear IgA deposits. *J Invest Dermatol* 1989; **92**: 39–45.

16 Bedane C, Prost C, Kowalewski C *et al.* Immunoelectron microscopy in linear IgA dermatosis of adults. In: Ishibashi Y, Nakagawa H, Suzuki H, eds. *Electron Microscopy in Dermatology—Basic and Clinical Researsch*. Amsterdam: Elsevier, 1994.
17 Haftek M, Zone J, Taylor T *et al.* Immunogold localization of the 97-kD antigen of linear IgA bullous dermatosis (LABD) detected with patient serum. *J Invest Dermatol* 1994; **103**: 656–9.
18 Ishiko A, Shimizu H, Masunaga T *et al.* 97-kDa Linear IgA bullous dermatosis (LAD) antigen localizes to the lamina lucida of the epidermal basement membrane. *J Invest Dermatol* 1996; **106**: 739–43.
19 Kowalewski C, Haftek M, Jablonska S *et al.* Ultrastructural localization of binding sites of sera from patients with linear IgA bullous dermatosis. *Arch Dermatol Res* 1995; **287**: 636–40.
20 Zhou S, Ferguson D, Allen J *et al.* The localization of target antigens and antibodies in linear IgA disease is variable: correlation of immunogold electron microscopy and immunoblotting. *Br J Dermatol* 1998; **139**: 591–7.

Clinical features (Figs 40.23 & 40.24). The clinical features of children and adults will be described separately as they are distinctive.



Fig. 40.23 Chronic bullous dermatosis of childhood. Cluster of blisters with new blisters forming around an older lesion (string of pearls). (Courtesy of Dr R.J. Pye, Addenbrooke's Hospital, Cambridge, UK.)



Fig. 40.24 Linear IgA disease. Intact tense bullae on the thigh and annular lesions. (Courtesy of Dr P. Hudson, Peterborough Hospital, Peterborough, UK.)

Chronic bullous disease of childhood. The mean age of onset is under 5 years; it is usually acute and the initial attack more severe than subsequent recurrences. Symptoms vary from absent or mild pruritus to severe burning. The face and perineum are involved, particularly in younger children. The perioral area, the eyelids, ears and scalp may be affected. The involvement of the perineum and vulva (Fig. 40.23) has been mistaken for sexual abuse in some patients. The eruption may spread to the trunk, thighs, limbs, and hands and feet. The lesions comprise urticated plaques and papules, and annular, polycyclic lesions often with blistering around the edge, the string of pearls sign. Large blisters may develop and become very extensive, they are occasionally haemorrhagic, and usually arise on previously normal skin. Papules and vesicles also occur.

Mucosal involvement is common. The mouth may be involved with ulcers and erosions, and hoarseness may indicate pharyngeal involvement. There can be nasal stuffiness and bleeding. The eyes are often sore or gritty and there is conjunctivitis [1]. The children who progressed to conjunctival scarring and blindness are best regarded as having mucous membrane pemphigoid [1–4].

Linear IgA disease of adults. This commences at any age from the postpubertal teenager to the ninth decade, most commonly after the age of 60 years. The onset may be insidious or more usually abrupt. Symptoms vary from mild pruritus to severe pruritus and burning. The trunk is almost always involved, and the limbs, face and scalp, hands and feet are commonly affected. The lesions comprise urticated plaques, papules and vesicles, and blisters. The blisters may arise from normal skin or from urticated plaques (Fig. 40.24) and can be haemorrhagic. The characteristic annular lesions with blistering around the edge are less common than in the children (Fig. 40.23). Milia are almost unknown.

Mucosal involvement is common [1]. The mouth may be involved with ulcers and erosions. Hoarseness indicates pharyngeal involvement. There is often nasal stuffiness, crusting and bleeding. The eyes are often sore or gritty. Involvement of the genitals and also the vagina can occur. Those few patients that progress to scarring, including blindness, are best regarded as having mucous membrane pemphigoid [5–7].

References

1 Wojnarowska F, Marsden R, Bhogal B *et al.* Chronic bullous disease of childhood, childhood cicatricial pemphigoid and linear IgA disease of adults, a comparative study demonstrating clinical and immunopathological overlap. *J Am Acad Dermatol* 1988; **19**: 792–805.
2 Wojnarowska F, Marsden R, Bhogal B *et al.* Childhood cicatricial pemphigoid with linear IgA deposits. *Clin Exp Dermatol* 1984; **9**: 407–15.
3 Langeland T. Childhood cicatricial pemphigoid with linear IgA deposits: a case report. *Acta Derm Venereol (Stockh)* 1985; **65**: 354–5.
4 Caux F, Kirtschig G, Lemarchand-Venencie F *et al.* IgA-epidermolysis bullosa acquisita in a child resulting in blindness. *Br J Dermatol* 1997; **137**: 270–5.
5 Leonard J, Wright P, Williams D *et al.* The relationship between linear IgA disease and benign mucous membrane pemphigoid. *Br J Dermatol* 1984; **110**: 307–14.
6 Zambruno G, Manca V, Kanitakis J *et al.* Linear IgA bullous dermatosis with autoantibodies to a 290 kd antigen of anchoring fibrils. *J Am Acad Dermatol* 1994; **31**: 884–8.
7 Chan LS, Ahmed AR, Anhalt GJ *et al.* The first international consensus on mucous membrane pemphigoid: definition, diagnostic criteria, pathogenic factors, medical treatment, and prognostic indicators. *Arch Dermatol* 2002; **138**: 370–9.

Dermal-associated linear IgA disease

Previous case reports and a study of 17 patients with dermal-binding IgA antibodies found such patients to comprise more than 15% of linear IgA patients, and to be more commonly adult, but otherwise not to have any distinguishing clinical features [1–3]. There does not seem to be a mechanobullous scarring phenotype for linear IgA disease when associated with dermal antigens including collagen VII. Patients with classical scarring mechanobullous IgA epidermolysis bullosa acquisita with antibodies to collagen VII are very rare and both those reported progressed to a mucous membrane pemphigoid-like phenotype [4,5].

References

1 Wakelin SH, Allen J, Zhou S *et al.* Drug-induced linear IgA disease with antibodies to collagen VII. *Br J Dermatol* 1998; **138**: 310–4.
2 Vodegel RM, de Jong MC, Pas HH *et al.* IgA-mediated epidermolysis bullosa acquisita: two cases and review of the literature. *J Am Acad Dermatol* 2002; **47**: 919–25.
3 Lally A, Chamberlain A, Allen J *et al.* Dermal-binding linear IgA disease: an uncommon subset of a rare immunobullous disease. *Clin Exp Dermatol* 2007; **32**: 493–8.
4 Zambruno G, Manca V, Kanitakis J *et al.* Linear IgA bullous dermatosis with autoantibodies to a 290 kd antigen of anchoring fibrils. *J Am Acad Dermatol* 1994; **31**: 884–8.
5 Caux F, Kirtschig G, Lemarchand-Venencie F *et al.* IgA-epidermolysis bullosa acquisita in a child resulting in blindness. *Br J Dermatol* 1997; **137**: 270–5.

Linear IgA mucous membrane pemphigoid

Patients with typical clinical signs of mucous membrane pemphigoid, who have linear IgA on direct immunofluorescence should, following the International Consensus on Mucous Membrane Pemphigoid, be regarded as having mucous membrane pemphigoid [1]. Interestingly, this has been described in several children and some adults, and the case of linear IgA desquamative vaginitis is also best regarded as such [2–8].

References

1 Chan LS, Ahmed AR, Anhalt GJ *et al.* The first international consensus on mucous membrane pemphigoid: definition, diagnostic criteria, pathogenic factors, medical treatment, and prognostic indicators. *Arch Dermatol* 2002; **138**: 370–9.
2 Wojnarowska F, Marsden R, Bhogal B *et al.* Childhood cicatricial pemphigoid with linear IgA deposits. *Clin Exp Dermatol* 1984; **9**: 407–15.
3 Leonard J, Wright P, Williams D *et al.* The relationship between linear IgA disease and benign mucous membrane pemphigoid. *Br J Dermatol* 1984; **110**: 307–14.
4 Langeland T. Childhood cicatricial pemphigoid with linear IgA deposits: a case report. *Acta Derm Venereol (Stockh)* 1985; **65**: 354–5.
5 Wojnarowska F, Marsden R, Bhogal B *et al.* Chronic bullous disease of childhood, childhood cicatricial pemphigoid and linear IgA disease of adults, a comparative study demonstrating clinical and immunopathological overlap. *J Am Acad Dermatol* 1988; **19**: 792–805.
6 Jacobson M, Krumholz B, Franks A. Desquamative inflammatory vaginitis. A case report. *J Reprod Med* 1989; **34**: 647–50.
7 Zambruno G, Manca V, Kanitakis J *et al.* Linear IgA bullous dermatosis with autoantibodies to a 290 kd antigen of anchoring fibrils. *J Am Acad Dermatol* 1994; **31**: 884–8.
8 Caux F, Kirtschig G, Lemarchand-Venencie F *et al.* IgA-epidermolysis bullosa acquisita in a child resulting in blindness. *Br J Dermatol* 1997; **137**: 270–5.

Mixed immunobullous disease

A small number (16) of patients with a dual antibody response of IgA and IgG autoantibodies have been studied. This immunopathological finding was seen in both children [1–3] and adults [4,5]. In most cases the patients had a clinical picture compatible with linear IgA disease and a good response to dapsone or sulphonamides. The exact position of this entity is still unclear, but for practical purposes the patients are best managed as linear IgA disease.

References

1 Darling TN, Cardenas AA, Beard JS *et al.* A child with antibodies targeting both linear IgA bullous dermatosis and bullous pemphigoid antigens. *Arch Dermatol* 1995; **131**: 1438–42.
2 Powell J, Kirtschig G, Allen J *et al.* Mixed immunobullous disease of childhood: a good response to antimicrobials. *Br J Dermatol* 2001; **144**: 769–74.
3 Viglizzo G, Cozzani E, Nozza P *et al.* A case of linear IgA disease in a child with IgA and IgG circulating antibodies directed to BPAg2. *Int J Dermatol* 2007; **46**: 1302–4.
4 Sheridan AT, Kirtschig G, Wojnarowska F. Mixed immunobullous disease: is this linear IgA disease? *Australas J Dermatol* 2000; **41**: 219–21.
5 Metz BJ, Ruggeri SY, Hsu S *et al.* Linear IgA dermatosis with IgA and IgG autoantibodies to the 180 kDa bullous pemphigoid antigen (BP180): evidence for a distinct subtype. *Int J Dermatol* 2004; **43**: 443–6.

Induced linear IgA disease and associated diseases

A number of precipitating factors are observed, namely infection and antibiotics (penicillins) in about a quarter of adults and more children [1,2], and the presence of building work in the home in about half the adult patients and three-quarters of the children [3]. The significance of these findings is unclear. Drug-induced linear IgA disease is commonly reported, vancomycin being the drug most frequently implicated [4–7] and diclofenac and other non-steroidal anti-inflammatory drugs less commonly [8–13]. However, a large range of drugs has been reported [10,14,15]. Local skin trauma has initiated the disease in some cases [1,2,16].

Patients with linear IgA disease were originally thought to have dermatitis herpetiformis, but it is now clear that this is a totally distinct disease and there is no overall association with gluten-sensitive enteropathy [1,17,18]. There is an association with ulcerative colitis and other inflammatory bowel disease in a small number of patients [19–21]. There is no overall association with autoimmune disease, although autoantibodies are common [1]. There is one child reported with an autoimmune lymphoproliferative disorder in association with linear IgA disease [22].

There is an increased incidence of lymphoproliferative disorders in adults with linear IgA disease, which may occur after remission of the skin disease [2,23–26], and a single report in a child [27]. There are a number of case reports of various cancers in association with linear IgA disease, of which bladder and renal cancer are the commonest, but there is no overall increase [2,28,29].

References

1 Wojnarowska F, Marsden R, Bhogal B *et al.* Chronic bullous disease of childhood, childhood cicatricial pemphigoid and linear IgA disease of adults, a comparative study demonstrating clinical and immunopathological overlap. *J Am Acad Dermatol* 1988; **19**: 792–805.
2 Godfrey K, Wojnarowska F, Leonard J. Linear IgA disease of adults: association with lymphoproliferative malignancy and possible role of other triggering factors. *Br J Dermatol* 1990; **123**: 447–52.
3 Collier P, Wojnarowksa F. Linear IgA disease and chronic bullous disease of childhood. *Eur J Dermatol* 1993; **3**: 623–34.
4 Nousari HC, Kimyai-Asadi A, Caeiro JP *et al.* Clinical, demographic, and immunohistologic features of vancomycin-induced linear IgA bullous disease of the

skin. Report of 2 cases and review of the literature. *Medicine (Baltimore)* 1999; **78**: 1–8.
5 Palmer RA, Ogg G, Allen J *et al.* Vancomycin-induced linear IgA disease with autoantibodies to BP180 and LAD285. *Br J Dermatol* 2001; **145**: 816–20.
6 Dellavalle RP, Burch JM, Tayal S *et al.* Vancomycin-associated linear IgA bullous dermatosis mimicking toxic epidermal necrolysis. *J Am Acad Dermatol* 2003; **48**: S56–7.
7 Billet SE, Kortuem KR, Gibson LE *et al.* A morbilliform variant of vancomycin-induced linear IgA bullous dermatosis. *Arch Dermatol* 2008; **144**: 774–8.
8 Gabrielsen TO, Staerfelt F, Thune PO. Drug-induced bullous dermatosis with linear IgA deposits along the basement membrane. *Acta Derm Venereol* 1981; **61**: 439–41.
9 Valsecchi R, Serra M, Tornaghi A *et al.* [Drug-induced bullous dermatosis with linear IgA]. *G Ital Dermatol Venereol* 1982; **117**: 221–3.
10 Paul C, Wolkenstein P, Prost C *et al.* Drug-induced linear IgA disease: target antigens are heterogeneous. *Br J Dermatol* 1997; **136**: 406–11.
11 Camilleri M, Pace JL. Linear IgA bullous dermatosis induced by piroxicam. *J Eur Acad Dermatol Venereol* 1998; **10**: 70–2.
12 Bouldin MB, Clowers-Webb HE, Davis JL *et al.* Naproxen-associated linear IgA bullous dermatosis: case report and review. *Mayo Clin Proc* 2000; **75**: 967–70.
13 Plunkett RW, Chiarello SE, Beutner EH. Linear IgA bullous dermatosis in one of two piroxicam-induced eruptions: a distinct direct immunofluorescence trend revealed by the literature. *J Am Acad Dermatol* 2001; **45**: 691–6.
14 Collier P, Wojnarowska F. Drug-induced linear immunoglobulin A disease. *Clin Dermatol* 1993; **11**: 529–33.
15 Kuechle M, Stegemeir E, Maynard B *et al.* Drug induced linear IgA bullous dermatosis: report of six cases and review of the literature. *J Am Acad Dermatol* 1994; **30**: 187–92.
16 Girao L, Fiadeiro T, Rodrigues JC. Burn-induced linear IgA dermatosis. *J Eur Acad Dermatol Venereol* 2000; **14**: 507–10.
17 Leonard J, Wright P, Williams D *et al.* The relationship between linear IgA disease and benign mucous membrane pemphigoid. *Br J Dermatol* 1984; **110**: 307–14.
18 Leonard J, Griffiths C, Powles A *et al.* Experience with a gluten free diet in the treatment of linear IgA disease. *Acta Dermatol Venerol* 1987; **67**: 145–8.
19 Paige D, Leonard J, Wojnarowska F *et al.* Linear IgA disease and ulcerative colitis. *Br J Dermatol* 1997; **136**: 779–82.
20 Birnie AJ, Perkins W. A case of linear IgA disease occurring in a patient with colonic Crohn's disease. *Br J Dermatol* 2005; **153**: 1050–2.
21 Nanda A, Dvorak R, Al-Sabah H *et al.* Linear IgA bullous disease of childhood: an experience from Kuwait. *Pediatr Dermatol* 2006; **23**: 443–7.
22 Wong CS, Arkwright PD, Rieux-Laucat F *et al.* Childhood linear IgA disease in association with autoimmune lymphoproliferative syndrome. *Br J Dermatol* 2004; **150**: 578–80.
23 McEvoy MT, Connolly SM. Linear IgA dermatosis: association with malignancy. *J Am Acad Dermatol* 1990; **22**: 59–63.
24 Jacyk WK, Nagel GJ, van der Hoven AE. Linear IgA dermatosis and Hodgkin's lymphoma—report of a case in an African and review of the literature. *J Dermatol* 1990; **17**: 633–7.
25 Usmani N, Baxter KF, Child JA *et al.* Linear IgA disease in association with chronic lymphocytic leukaemia. *Br J Dermatol* 2004; **151**: 710–1.
26 Muncaster A, Lewis HM. Linear IgA disease in a patient with Castleman's disease. *Clin Exp Dermatol* 2002; **27**: 24–6.
27 Polat M, Lenk N, Kurekci E *et al.* Chronic bullous disease of childhood in a patient with acute lymphoblastic leukemia: possible induction by a drug. *Am J Clin Dermatol* 2007; **8**: 389–91.
28 Rodenas JM, Herranz MT, Tercedor J *et al.* Linear IgA disease in a patient with bladder carcinoma. *Br J Dermatol* 1997; **136**: 257–9.
29 van der Waal RI, van de Scheur MR, Pas HH *et al.* Linear IgA bullous dermatosis in a patient with renal cell carcinoma. *Br J Dermatol* 2001; **144**: 870–3.

Prognosis. Spontaneous remission occurs in the majority of patients after an average of 3–6 years, the TNF genotype of the patient influencing disease duration [1–3]. Initially, there were no reports of chronic bullous disease of childhood extending beyond puberty, but cases have now been documented [2,4]. Some of these patients are women of childbearing age. In pregnancy, often there is improvement or remission of the disease from the second trimester, and the women may be able to discontinue all drugs, however there is usually a relapse postpartum at about 3 months [5]. There does not seem to be any fetal damage [5].

References

1 Marsden R, McKee P, Bhogal B *et al.* A study of benign chronic bullous dermatosis of childhood, a comparison with dermatitis herpetiformis and bullous pemphigoid occurring in childhood. *Clin Exp Dermatol* 1980; **5**: 159–72.
2 Wojnarowska F, Marsden R, Bhogal B *et al.* Chronic bullous disease of childhood, childhood cicatricial pemphigoid and linear IgA disease of adults, a comparative study demonstrating clinical and immunopathological overlap. *J Am Acad Dermatol* 1988; **19**: 792–805.
3 Collier P, Wojnarowska F, Welsh K *et al.* Adult linear IgA disease and chronic bullous disease of childhood: the association with human leucocyte antigens Cw7, B8, HLA DR3, and tumour necrosis factor influences disease expression. *Br J Dermatol* 1999; **141**: 867–75.
4 Burge S, Wojnarowska F, Marsden A. Chronic bullous dermatosis of childhood persisting into adulthood. *Ped Dermatol* 1988; **5**: 246–9.
5 Collier P, Kelly S, Wojnarowska F. Linear IgA disease and pregnancy. *J Am Acad Dermatol* 1994; **30**: 407–12.

Differential diagnosis. In the young infant, bullous impetigo may resemble the initial lesions, but its response to antibiotics will differentiate it. Genetic epidermolysis bullosa is often present at birth and the family history further differentiates it. Bullous papular urticaria rarely affects the face or genital region and is usually of short duration. Childhood bullous pemphigoid may give a similar clinical picture, but the deposition of IgG and C3 at the basement-membrane zone is diagnostic. The adult disease is frequently confused with atypical erythema multiforme, neurotic excoriations and nodular prurigo, dermatitis herpetiformis and most commonly bullous pemphigoid. Histology is helpful and direct immunofluorescence is essential for diagnosis.

Treatment. A few patients have mild disease and can be controlled with topical steroids alone. The treatment of the children can be difficult, because side effects limit dosage, but the drugs used are identical in children and adults. The favourable reports of erythromycin suggest that this should be tried as first-line treatment in children [1]. Dapsone in doses starting at less than 0.5 mg/kg, which often means giving it as 25 mg on alternate days or less in young children, and 25–50 mg/day in an adult, may be slowly increased to a dose of 1 mg/kg or a little more in a child and 100–150 mg in an adult to keep the patient comfortable and without significant side effects. Too rapid an increase in the dose often results in haemolytic anaemia, which does not reach its maximum for a month. A fall in haemoglobin with a low mean corpuscular volume (MCV) indicates iron deficiency (due to intravascular haemolysis) rather than pure haemolytic anaemia. Patients at risk of glucose-6-phosphate dehydrogenase deficiency should be screened prior to treatment. Methaemoglobinaemia is common, reaching a steady state after about 2 weeks, and may cause cyanosis, breathlessness and angina. Hepatitis, the dapsone syndrome (lymphadenopathy and hepatitis) and agranulocytosis are serious, usually early, complications. Motor neuropathy may occur. Most complications occur in the first 3 months. Sulphonamides are alternatives. Sulfapyridine is often poorly tolerated and may cause an allergic reaction, hepatitis or agranulocytosis,

and is used at doses of 250 mg to 3 g daily, which usually controls the eruption rapidly, but the dose may need frequent adjustment. Sulfamethoxypyridazine (adult dose 250 mg to 1.5 g daily) is an alternative, which is often better tolerated. Dapsone and sulfonamides can be combined. Some patients do not respond to either of these, and corticosteroids may need to be added. Disease in a few patients is very difficult to control and may need azathioprine or ciclosporin [2]; isolated case reports suggest that mycophenolate mofetil may be useful in children and adults [3–5]. Success has been reported in small numbers of patients with other antimicrobials including tetracyclines and nicotinamide/niacinamide [6–8], penicillins [9–11] and erythromycin [1]. Colchicine has been used successfully in children and adults [12–16]. There are case reports of the successful use of intravenous immunoglobulin [17–21]. The association with TNF alleles would predict that TNF antagonists might be helpful, but there are no reports of the use of biologics.

The cutaneous lesions are always much more responsive than the mucosal lesions, which can be treated with topical steroids (see mucous membrane pemphigoid).

In view of the ultimate spontaneous recovery in the majority of patients, attempts should be made to avoid over-treatment and the production of side effects with steroids.

References

1 Cooper SM, Powell J, Wojnarowska F. Linear IgA disease: successful treatment with erythromycin. *Clin Exp Dermatol* 2002; **27**: 677–9.
2 Young HS, Coulson IH. Linear IgA disease: successful treatment with cyclosporin. *Br J Dermatol* 2000; **143**: 204–5.
3 Farley-Li J, Mancini AJ. Treatment of linear IgA bullous dermatosis of childhood with mycophenolate mofetil. *Arch Dermatol* 2003; **139**: 1121–4.
4 Glaser R, Sticherlin M. Successful treatment of linear IgA bullous dermatosis with mycophenolate mofetil. *Acta Derm Venereol* 2002; **82**: 308–9.
5 Talhari C, Mahnke N, Ruzicka T *et al.* Successful treatment of linear IgA disease with mycophenolate mofetil as a corticosteroid sparing agent. *Clin Exp Dermatol* 2005; **30**: 297–8.
6 Peoples D, Fivenson DP. Linear IgA bullous dermatosis: successful treatment with tetracycline and nicotinamide. *J Am Acad Dermatol* 1992; **26**: 498–9.
7 Chaffins ML, Collison D, Fivenson DP. Treatment of pemphigus and linear IgA dermatosis with nicotinamide and tetracycline: a review of 13 cases. *J Am Acad Dermatol* 1993; **28**: 998–1000.
8 Yomada M, Komai A, Hashimato T. Sublamina densa-type linear IgA bullous dermatosis successfully treated with oral tetracycline and niacianamide. *Br J Dermatol* 1999; **141**: 608–9.
9 Denguezli M, Ben Nejma B, Nouira R *et al.* [Iga linear bullous dermatosis in children. A series of 12 Tunisian patients]. *Ann Dermatol Venereol* 1994; **121**: 888–92.
10 Skinner RB Jr, Rotondo CK, Schneider MA *et al.* Treatment of chronic bullous dermatosis of childhood with oral dicloxacillin. *Pediatr Dermatol* 1995; **12**: 65–6.
11 Siegfried EC, Sirawan S. Chronic bullous disease of childhood: successful treatment with dicloxacillin. *J Am Acad Dermatol* 1998; **39**: 797–800.
12 Aram H. Linear IgA bullous dermatosis. Successful treatment with colchicine. *Arch Dermatol* 1984; **120**: 960–1.
13 Banodkar DD, al-Suwaid AR. Colchicine as a novel therapeutic agent in chronic bullous dermatosis of childhood. *Int J Dermatol* 1997; **36**: 213–6.
14 Elling SV, Keane F, O'Sullivan D *et al.* Linear IgA disease—a review of four patients. *Ir Med J* 1998; **91**: 167–8.
15 Ang P, Tay YK. Treatment of linear IgA bullous dermatosis of childhood with colchicine. *Pediatr Dermatol* 1999; **16**: 50–2.
16 Benbenisty KM, Bowman PH, Davis LS. Localized linear IgA disease responding to colchicine. *Int J Dermatol* 2002; **41**: 56–8.
17 Goebeler M, Seitz C, Rose C *et al.* Successful treatment of linear IgA disease with salazosulphapyridine and intravenous immunoglobulins. *Br J Dermatol* 2003; **149**: 912–4.
18 Jolles S. A review of high-dose intravenous immunoglobulin (hdIVIg) in the treatment of the autoimmune blistering disorders. *Clin Exp Dermatol* 2001; **26**: 127–31.
19 Khan IU, Bhol KC, Ahmed AR. Linear IgA bullous dermatosis in a patient with chronic renal failure: response to intravenous immunoglobulin therapy. *J Am Acad Dermatol* 1999; **40**: 485–8.
20 Kroiss MM, Vogt T, Landthaler M *et al.* High-dose intravenous immune globulin is also effective in linear IgA disease. *Br J Dermatol* 2000; **142**: 582.
21 Wetter DA, Davis MD, Yiannias JA *et al.* Effectiveness of intravenous immunoglobulin therapy for skin disease other than toxic epidermal necrolysis: a retrospective review of Mayo Clinic experience. *Mayo Clin Proc* 2005; **80**: 41–7.

Epidermolysis bullosa acquisita

Synonyms
- Acquired epidermolysis bullosa
- Dermolytic pemphigoid

Definition. Epidermolysis bullosa acquisita (EBA) is a rare condition in which patients may have chronic acquired, trauma-induced, subepidermal blistering or a clinical picture indistinguishable from bullous pemphigoid. There is a distinctive immunopathology, and the disease was defined in terms of the target antigen, namely collagen VII. However, patients exist with the same clinical pattern in whom antibodies to collagen VII cannot be identified [1], and antibodies to collagen VII are found in patients with mucous membrane pemphigoid (see above) [2,3]. In addition, there are patients with antibodies to both collagen VII and laminin 5 [4,5]. EBA needs to be redefined to encompass the distinctive clinical features and target antigen. It is interesting that this acquired mechanobullous disease was named for its clinical resemblance to genetic dystrophic epidermolysis bullosa (Chapter 39) and that the molecular basis of both these diseases is collagen VII.

The clinical features, immunopathology and immunogenetics are summarized in Tables 40.5 and 40.6 and Fig. 40.25.

References

1 Wakelin SH, Bhogal B, Black MM *et al.* Epidermolysis bullosa acquisita associated with epidermal-binding circulating antibodies. *Br J Dermatol* 1997; **136**: 604–9.

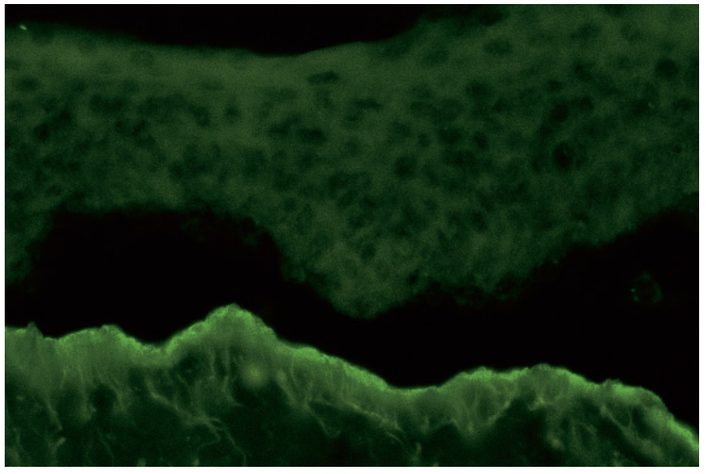


Fig. 40.25 Epidermolysis bullosa acquisita. Indirect immunofluorescence showing dermal binding of autoantibodies to salt-split skin. (Courtesy of Dr J. Allen, Oxford Radcliffe Hospital, Oxford, UK.)

2 Luke MC, Darling TN, Hsu R *et al.* Mucosal morbidity in patients with epidermolysis bullosa acquisita. *Arch Dermatol* 1999; **135**: 954–9.
3 Chan LS, Ahmed AR, Anhalt GJ *et al.* The first international consensus on mucous membrane pemphigoid: definition, diagnostic criteria, pathogenic factors, medical treatment, and prognostic indicators. *Arch Dermatol* 2002; **138**: 370–9.
4 Jonkman MF, Schuur J, Dijk F *et al.* Inflammatory variant of epidermolysis bullosa acquisita with IgG autoantibodies against type VII collagen and laminin alpha3. *Arch Dermatol* 2000; **136**: 227–31.
5 Umemoto N, Demitsu T, Toda S *et al.* A case of nonscarring subepidermal blistering disease associated with autoantibodies reactive with both type VII collagen and laminin 5. *Dermatology* 2003; **207**: 61–4.

Aetiology. EBA can occur at any age. It has been described in children and adults [1–5]. The original reports from the USA included many African-American patients, and it may be more common in African and Oriental races [6–10]. It is one of the rarest subepidermal bullous diseases in Western Europe, with an incidence of about 0.25 per million, but may be more common in the middle and far East [7–9,11–13].

There is an association with HLA-DR2 in the USA [6] but not in Korean patients [14].

References

1 Arpey CJ, Elewski BE, Moritz DK *et al.* Childhood epidermolysis bullosa acquisita. Report of three cases and review of literature. *J Am Acad Dermatol* 1991; **24**: 706–14.
2 Edwards S, Wakelin SH, Wojnarowska F *et al.* Bullous pemphigoid and epidermolysis bullosa acquisita: presentation, prognosis, and immunopathology in 11 children. *Pediatr Dermatol* 1998; **15**: 184–90.
3 Trigo-Guzman FX, Conti A, Aoki V *et al.* Epidermolysis bullosa acquisita in childhood. *J Dermatol* 2003; **30**: 226–9.
4 Roenigk HJ, Ryan J, Bergfeld W. Epidermolysis bullosa acquisita: report of three cases and review of all published cases. *Arch Dermatol* 1971; **103**: 1–10.
5 Gammon WR, Briggaman RA, Woodley DT *et al.* Epidermolysis bullosa acquisita—a pemphigoid-like disease. *J Am Acad Dermatol* 1984; **11**: 820–32.
6 Gammon W, Heise E, Burke W *et al.* Increased frequency of HLA-DR2 in patients with auto-antibodies to epidermolysis bullosa acquisita antigen: evidence that expression of autoimmunity to type VII collagen is HLA class II allele associated. *J Invest Dermatol* 1988; **91**: 228–32.
7 Jin P, Shao C, Ye G. Chronic bullous dermatoses in China. *Int J Dermatol* 1993; **32**: 89–92.
8 Lee CW. Prevalences of subacute cutaneous lupus erythematosus and epidermolysis bullosa acquisita among Korean/Oriental populations. *Dermatology* 1998; **197**: 187.
9 Wong SN, Chua SH. Spectrum of subepidermal immunobullous disorders seen at the National Skin Centre, Singapore: a 2-year review. *Br J Dermatol* 2002; **147**: 476–80.
10 Mulyowa GK, Jaeger G, Kabakyenga J *et al.* Autoimmune subepidermal blistering diseases in Uganda: correlation of autoantibody class with age of patients. *Int J Dermatol* 2006; **45**: 1047–52.
11 Nanda A, Dvorak R, Al-Saeed K *et al.* Spectrum of autoimmune bullous diseases in Kuwait. *Int J Dermatol* 2004; **43**: 876–81.
12 Bernard P, Vaillant L, Labeille B *et al.* Incidence and distribution of subepidermal autoimmune bullous skin diseases in three French regions. Bullous Diseases French Study Group. *Arch Dermatol* 1995; **131**: 48–52.
13 Zillikens D, Wever S, Roth A *et al.* Incidence of autoimmune subepidermal blistering dermatoses in a region of central Germany. *Arch Dermatol* 1995; **131**: 957–8.
14 Lee CW, Kim SC, Han H. Distribution of HLA class II alleles in Korean patients with epidermolysis bullosa acquisita. *Dermatology* 1996; **193**: 328–9.

Pathogenesis. Collagen type VII, the major component of the anchoring fibrils, is the target antigen recognized by autoantibodies from patients with EBA [1]. Collagen type VII is expressed at the dermal aspect of the basement membrane zone, originating and terminating in the lamina densa (Fig. 40.11) and interacts with laminin 5 and the dermal matrix [2]. It comprises a globular amino non-collagenous domain (NC1) and a collagenous triple helix (Col-1), and the gene is located to the short arm of chromosome 3 [3]. The autoantibodies in EBA are directed at epitopes chiefly within the fibronectin-like region at the NC1 domain [4–9] and in particular the N-terminal 227 amino acids (residues 1 to 227), which contains homology with cartilage matrix protein [10]. However, antibodies to Col-1 and non-collagenous 2 domain (NC2) have also been demonstrated [2,9,11,12] and may be more common in childhood cases [13].

The autoantibodies are IgG, and of all IgG isotypes, although the IgG1 and IgG4 isotypes may predominate in the chronic mechanobullous forms [14–16]. Some of the antibodies bind complement [16,17]. There are patients with antibodies to additional antigens, particularly laminin 5 [18,19]. Cases have been described with IgA antibodies, usually without an EBA clinical phenotype [20–24].

There is evidence that the autoantibodies are pathogenic. Complement-binding autoantibodies from patients with EBA bind to skin and attract neutrophils to the basement-membrane zone [25,26] and also induce blistering in the presence of neutrophils in sections of human skin [27]. Animal models in which the clinical, immunopathological and histological features of the disease were induced in neonatal mice using antibodies to collagen VII (both raised against mouse collagen VII and purified human antibodies) have demonstrated that the antibodies are pathogenic [28–31]. Granulocyte-derived elastase and gelatinase B are required for blister formation [32].

References

1 Woodley DT, Briggaman RA, O'Keefe EJ *et al.* Identification of the skin basement-membrane autoantigen in epidermolysis bullosa acquisita. *N Engl J Med* 1984; **310**: 1007–13.
2 McMillan JR, Matsumura T, Hashimoto T *et al.* Immunomapping of EBA sera to multiple epitopes on collagen VII: further evidence that anchoring fibrils originate and terminate in the lamina densa. *Exp Dermatol* 2003; **12**: 261–7.
3 Parente M, Chung L, Ryynanen J *et al.* Human type VII collagen:cDNA cloning and chromosomal mapping of the gene. *Proc Natl Acad Sci* 1991; **88**: 6931–5.
4 Woodley D, Burgeson R, Lunstrum G *et al.* Epidermolysis bullosa acquisita antigen is the globular carboxyl terminus of type VII procollagen. *J Clin Invest* 1988; **81**: 683–7.
5 Gammon WR, Briggaman RA. Bullous SLE: a phenotypically distinctive but immunologically heterogeneous bullous disorder. *J Invest Dermatol* 1993; **100**: 28S–34S.
6 Lapiere JC, Woodley DT, Parente MG *et al.* Epitope mapping of type VII collagen. Identification of discrete peptide sequences recognized by sera from patients with acquired epidermolysis bullosa. *J Clin Invest* 1993; **92**: 1831–9.
7 Tanaka T, Furukawa F, Imamura S. Epitope mapping for epidermolysis bullosa acquisita autoantibody by molecularly cloned cDNA for type VII collagen. *J Invest Dermatol* 1994; **102**: 706–9.
8 Jones DA, Hunt SW 3rd, Prisayanh PS *et al.* Immunodominant autoepitopes of type VII collagen are short, paired peptide sequences within the fibronectin type III homology region of the noncollagenous (NC1) domain. *J Invest Dermatol* 1995; **104**: 231–5.
9 Ishii N, Yoshida M, Hisamatsu Y *et al.* Epidermolysis bullosa acquisita sera react with distinct epitopes on the NC1 and NC2 domains of type VII collagen: study using immunoblotting of domain-specific recombinant proteins and postembedding immunoelectron microscopy. *Br J Dermatol* 2004; **150**: 843–51.

10 Chen M, Doostan A, Bandyopadhyay P *et al.* The cartilage matrix protein subdomain of type VII collagen is pathogenic for epidermolysis bullosa acquisita. *Am J Pathol* 2007; **170**: 2009–18.
11 Tanaka H, Ishida-Yamamoto A, Hashimoto T *et al.* A novel variant of acquired epidermolysis bullosa with autoantibodies against the central triple-helical domain of type VII collagen. *Lab Invest* 1997; **77**: 623–32.
12 Chen M, Keene DR, Costa FK *et al.* The carboxyl terminus of type VII collagen mediates antiparallel dimer formation and constitutes a new antigenic epitope for epidermolysis bullosa acquisita autoantibodies. *J Biol Chem* 2001; **276**: 21649–55.
13 Mayuzumi M, Akiyama M, Nishie W *et al.* Childhood epidermolysis bullosa acquisita with autoantibodies against the noncollagenous 1 and 2 domains of type VII collagen: case report and review of the literature. *Br J Dermatol* 2006; **155**: 1048–52.
14 Mooney E, Gammon W. Heavy and light chain isotypes of immunoglobulin in epidermolysis bullosa acquisita. *J Invest Dermatol* 1990; **95**: 317–9.
15 Bernard P, Prost C, Aucouturier P *et al.* The subclass distribution of IgG autoantibodies in cicatricial pemphigoid and epidermolysis bullosa acquisita. *J Invest Dermat* 1991; **97**: 259–63.
16 Gandhi K, Chen M, Aasi S *et al.* Autoantibodies to type VII collagen have heterogeneous subclass and light chain compositions and their complement-activating capacities do not correlate with the inflammatory clinical phenotype. *J Clin Immunol* 2000; **20**: 416–23.
17 Mooney E, Falk RJ, Gammon WR. Studies on complement deposits in epidermolysis bullosa acquisita and bullous pemphigoid. *Arch Dermatol* 1992; **128**: 58–60.
18 Jonkman MF, Schuur J, Dijk F *et al.* Inflammatory variant of epidermolysis bullosa acquisita with IgG autoantibodies against type VII collagen and laminin alpha3. *Arch Dermatol* 2000; **136**: 227–31.
19 Umemoto N, Demitsu T, Toda S *et al.* A case of nonscarring subepidermal blistering disease associated with autoantibodies reactive with both type VII collagen and laminin 5. *Dermatology* 2003; **207**: 61–4.
20 Mutasim DF, Cummings MP. Linear IgA disease with clinical and immunopathological features of epidermolysis bullosa acquisita. *Pediatr Dermatol* 1997; **14**: 303–6.
21 Vodegel RM, de Jong MC, Pas HH *et al.* IgA-mediated epidermolysis bullosa acquisita: two cases and review of the literature. *J Am Acad Dermatol* 2002; **47**: 919–25.
22 Lally A, Chamberlain A, Allen J *et al.* Dermal-binding linear IgA disease: an uncommon subset of a rare immunobullous disease. *Clin Exp Dermatol* 2007; **32**: 493–8.
23 Caux F, Kirtschig G, Lemarchand-Venencie F *et al.* IgA-epidermolysis bullosa acquisita in a child resulting in blindness. *Br J Dermatol* 1997; **137**: 270–5.
24 Bauer JW, Schaeppi H, Metze D *et al.* Ocular involvement in IgA-epidermolysis bullosa acquisita. *Br J Dermatol* 1999; **141**: 887–92.
25 Gammon WR, Inman AO 3rd, Wheeler CE Jr. Differences in complement-dependent chemotactic activity generated by bullous pemphigoid and epidermolysis bullosa acquisita immune complexes: demonstration by leukocytic attachment and organ culture methods. *J Invest Dermatol* 1984; **83**: 57–61.
26 Gammon W, Yancey K, Mangum K *et al.* Generation of C5-dependent bioactivity by tissue-bound anti-BMZ autoantibodies. *J Invest Dermatol* 1989; **93**: 195–200.
27 Sitaru C, Kromminga A, Hashimoto T *et al.* Autoantibodies to type VII collagen mediate Fcgamma-dependent neutrophil activation and induce dermal-epidermal separation in cryosections of human skin. *Am J Pathol* 2002; **161**: 301–11.
28 Borradori L, Caldwell JB, Briggaman RA *et al.* Passive transfer of autoantibodies from a patient with mutilating epidermolysis bullosa acquisita induces specific alterations in the skin of neonatal mice. *Arch Dermatol* 1995; **131**: 590–5.
29 Sitaru C, Mihai S, Otto C *et al.* Induction of dermal-epidermal separation in mice by passive transfer of antibodies specific to type VII collagen. *J Clin Invest* 2005; **115**: 870–8.
30 Woodley DT, Chang C, Saadat P *et al.* Evidence that anti-type VII collagen antibodies are pathogenic and responsible for the clinical, histological, and immunological features of epidermolysis bullosa acquisita. *J Invest Dermatol* 2005; **124**: 958–64.
31 Woodley DT, Ram R, Doostan A *et al.* Induction of epidermolysis bullosa acquisita in mice by passive transfer of autoantibodies from patients. *J Invest Dermatol* 2006; **126**: 1323–30.
32 Shimanovich I, Mihai S, Oostingh GJ *et al.* Granulocyte-derived elastase and gelatinase B are required for dermal-epidermal separation induced by autoantibodies from patients with epidermolysis bullosa acquisita and bullous pemphigoid. *J Pathol* 2004; **204**: 519–27.

Pathology. The blistering is subepidermal, but the precise histological findings depend on the stage of the disease. In inflammatory disease, there is a heavy predominately neutrophil infiltrate. In the mechanobullous, non-inflammatory phase, there is usually an absent or sparse infiltrate.

The findings with immunofluorescence are summarized in Table 40.6 and shown in Fig. 40.25, and a detailed review has been published [1]. On direct immunofluorescence, linear IgG at the basement-membrane zone is found in all patients, and linear IgA and IgM may also be seen [2]. C3 has been reported in most cases. The basement membrane staining may be broader than that seen in bullous pemphigoid, and a diagnostic U-serrated pattern has been described [3]. Patients' skin split through the lamina lucida with suction (applied *in vivo*) or with 1 mol/L salt demonstrates the IgG antibodies to be bound to the dermal aspect of the blister [4].

Positive indirect immunofluorescence has been demonstrated in approximately half the patients tested, with circulating autoantibodies binding to the basement-membrane zone. However, if skin is separated through the lamina lucida using 1 mol/L sodium chloride, or suction, and then used as substrate, the fluorescence is seen on the dermal aspect of the artificial blister (floor of the split skin) (Fig. 40.25) [5]. EBA serum is negative on toad skin [6,7]. An ELISA technique is more sensitive, but is not in routine use [8].

Electron microscopy has shown dermolysis and cleavage in the upper dermis with preservation of the basal lamina, but no reduction in the number of anchoring fibrils [9]. Amorphous material has been found beneath the basal lamina, sometimes in a band-like distribution [9–11].

Immunoelectron microscopy has shown that the IgG was deposited in the upper dermis beneath the basal lamina and within the sublamina densa zone [9]. Immunogold studies demonstrate that the autoantibodies bind to the non-collagenous ends (NC1 domain) of the anchoring fibrils and elsewhere [12,13].

Immunoblotting and ELISA techniques demonstrate that EBA autoantibodies recognize proteins of 290 kDa and 145 kDa, shown to be collagen VII, and that the immunodominant epitopes are within the NC1 domain, but that other regions are immunogenic (see above) [8].

References

1 Kirtschig G, Wojnarowska F. Autoimmune blistering diseases: an up-date of diagnostic methods and investigations. *Clin Exp Dermatol* 1994; **19**: 97–112.
2 Peters MS, Rogers RS. Clinical correlations of linear IgA deposition at the cutaneous basement membrane zone. *J Am Acad Dermatol* 1989; **20**: 761–70.
3 Vodegel RM, Jonkman MF, Pas HH *et al.* U-serrated immunodeposition pattern differentiates type VII collagen targeting bullous diseases from other subepidermal bullous autoimmune diseases. *Br J Dermatol* 2004; **151**: 112–8.
4 Gammon W, Kowalewski C, Chorzelski T *et al.* Direct immunofluorescence studies of sodium chloride-separated skin in the differential diagnosis of bullous pemphigoid and epidermolysis bullosa acquisita. *J Am Acad Dermatol* 1990; **22**: 664–70.

5 Gammon R, Fine J-D, Forbes M *et al.* Immunofluorescence on salt-split skin for the detection and differentiation of basement membrane zone autoantibodies. *J Am Acad Dermatol* 1992; **27**: 79–87.
6 Paller A, Queen L, Woodley D *et al.* Organ-specific, phylogenetic and ontogenetic distribution of the epidermolysis bullosa acquisita antigen. *J Invest Dermatol* 1986; **86**: 376–9.
7 Pang BK, Lee YS, Ratnam KV. Floor-pattern salt-split skin cannot distinguish bullous pemphigoid from epidermolysis bullosa acquisita. Use of toad skin. *Arch Dermatol* 1993; **129**: 744–6.
8 Chen M, Chan LS, Cai X *et al.* Development of an ELISA for rapid detection of anti-type VII collagen autoantibodies in epidermolysis bullosa acquisita. *J Invest Dermatol* 1997; **108**: 68–72.
9 Yaoita H, Briggaman R, Lawley T *et al.* Epidermolysis bullosa acquisita: ultrastructural and immunological studies. *J Invest Dermatol* 1981; **76**: 288–92.
10 Nieboer C, Boorsma D, Woerdeman M *et al.* Epidermolysis bullosa acquisita: immunofluorescence, electron microscopic and immunoelectron microscopic studies in four patients. *Br J Dermatol* 1980; **102**: 383–92.
11 Bernard P, Prost C, Aucouturier P *et al.* The subclass distribution of IgG autoantibodies in cicatricial pemphigoid and epidermolysis bullosa acquisita. *J Invest Dermat* 1991; **97**: 259–63.
12 Ishiko A, Hashimoto T, Shimizu H *et al.* Epidermolysis bullosa acquisita: report of a case with comparison of immunogold electron microscopy using pre- and postembedding labelling. *Br J Dermatol* 1996; **134**: 147–51.
13 Tanaka H, Ishida-Yamamoto A, Hashimoto T *et al.* A novel variant of acquired epidermolysis bullosa with autoantibodies against the central triple-helical domain of type VII collagen. *Lab Invest* 1997; **77**: 623–32.

Clinical features. There are many reports of EBA in children [1–22]. Early in the disease, clinical manifestations may be very variable and may mimic a number of bullous dermatoses including bullous pemphigoid and linear IgA disease. Blisters may be serous or haemorrhagic, tend to be localized to areas of trauma, especially on the dorsa of the hands, tops of the feet and elbows, and heal with scarring, milia and hyperpigmentation (Fig. 40.26). Nails may be dystrophic but are often normal. Some patients are indistinguishable from bullous pemphigoid, although some of these evolve into a more typical mechanobullous picture [23,24]. Mucosal involvement is variable but both erosions and intact blisters may be present in the mouth, larynx and oesophagus, and may cause dysphagia and laryngeal stenosis, and ocular involvement and blindness have been reported.



Fig. 40.26 Epidermolysis bullosa acquisita. Milia and scarring and dystrophic nails. (Courtesy of Dr S. Wakelin, St John's Dermatology Centre, London, UK.)

References

1 Arpey CJ, Elewski BE, Moritz DK *et al.* Childhood epidermolysis bullosa acquisita. Report of three cases and review of literature. *J Am Acad Dermatol* 1991; **24**: 706–14.
2 Borok M, Heng MC, Ahmed AR. Epidermolysis bullosa acquisita in an 8-year-old girl. *Pediatr Dermatol* 1986; **3**: 315–22.
3 Callot-Mellot C, Bodemer C, Caux F *et al.* Epidermolysis bullosa acquisita in childhood. *Arch Dermatol* 1997; **133**: 1122–6.
4 Chorzelski T, Karczewska K, Dyduch A *et al.* Epidermolysis bullosa acquisita in a 4-year-old boy. *Pediatr Dermatol* 2000; **17**: 157–8.
5 Cozzani E, Verrini A, Parodi A *et al.* Epidermolysis bullosa acquisita in a child: an additional case. *Int J Dermatol* 2005; **44**: 262–3.
6 Edwards S, Wakelin SH, Wojnarowska F *et al.* Bullous pemphigoid and epidermolysis bullosa acquisita: presentation, prognosis, and immunopathology in 11 children. *Pediatr Dermatol* 1998; **15**: 184–90.
7 Feliciani C, Fasciocco D, Franchi A *et al.* Epidermolysis bullosa acquisita in a 10-year-old Albanian boy. *Br J Dermatol* 1997; **137**: 307–8.
8 Fukumoto T, Umekawa T, Higuchi M *et al.* Childhood epidermolysis bullosa acquisita with autoantibodies against all 3 structural domains of type VII collagen. *J Am Acad Dermatol* 2004; **50**: 480–2.
9 Hayashi K, Ueda M, Sakai M *et al.* Epidermolysis bullosa acquisita in a 6-year-old Japanese boy. *Int J Dermatol* 1998; **37**: 612–4.
10 Inauen P, Hunziker T, Gerber H *et al.* Childhood epidermolysis bullosa acquisita. *Br J Dermatol* 1994; **131**: 898–900.
11 Lacour JP, Bernard P, Rostain G *et al.* Childhood acquired epidermolysis bullosa. *Pediatr Dermatol* 1995; **12**: 16–20.
12 Mayuzumi M, Akiyama M, Nishie W *et al.* Childhood epidermolysis bullosa acquisita with autoantibodies against the noncollagenous 1 and 2 domains of type VII collagen: case report and review of the literature. *Br J Dermatol* 2006; **155**: 1048–52.
13 McCuaig CC, Chan LS, Woodley DT *et al.* Epidermolysis bullosa acquisita in childhood. Differentiation from hereditary epidermolysis bullosa. *Arch Dermatol* 1989; **125**: 944–9.
14 Nousari HC, Anhalt GJ. Bullous skin diseases. *Curr Opin Immunol* 1995; **7**: 844–52.
15 Roger H, Machado P, Nicolas JF *et al.* Epidermolysis bullosa acquisita in a 3 1/2-year-old girl. *J Am Acad Dermatol* 1992; **27**: 858–62.
16 Schmidt E, Hopfner B, Chen M *et al.* Childhood epidermolysis bullosa acquisita: a novel variant with reactivity to all three structural domains of type VII collagen. *Br J Dermatol* 2002; **147**: 592–7.
17 Su JC, Varigos GA, Dowling J. Epidermolysis bullosa acquisita in childhood. *Australas J Dermatol* 1998; **39**: 38–41.
18 Tanaka H, Ishida-Yamamoto A, Hashimoto T *et al.* A novel variant of acquired epidermolysis bullosa with autoantibodies against the central triple-helical domain of type VII collagen. *Lab Invest* 1997; **77**: 623–32.
19 Wakelin SH, Bhogal B, Black MM *et al.* Epidermolysis bullosa acquisita associated with epidermal-binding circulating antibodies. *Br J Dermatol* 1997; **136**: 604–9.
20 Wozniak K, Kazama T, Kowalewski C. A practical technique for differentiation of subepidermal bullous diseases: localization of in vivo-bound IgG by laser scanning confocal microscopy. *Arch Dermatol* 2003; **139**: 1007–11.
21 Wozniak K, Kowalewski C, Rosinska-Borkowska D *et al.* Two patients with localized epidermolysis bullosa acquisita: diagnostic value of laser scanning confocal microscopy. *Br J Dermatol* 2007; **156**: 1066–8.
22 Wu JJ, Wagner AM. Epidermolysis bullosa acquisita in an 8-year-old girl. *Pediatr Dermatol* 2002; **19**: 368–71.
23 Gammon WR, Briggaman RA, Woodley DT *et al.* Epidermolysis bullosa acquisita—a pemphigoid-like disease. *J Am Acad Dermatol* 1984; **11**: 820–32.
24 Briggaman R, Gammon W, Woodley D. Epidermolysis bullosa acquisita of the immunopathological type (dermolytic pemphigoid). *J Invest Dermatol* 1985; **85**: 79–84.

EBA mucous membrane pemphigoid. Those patients in whom mucosal symptoms predominate, in particular those with oesophageal strictures, laryngeal stenosis, and ocular scarring and blindness, are now regarded as mucous membrane pemphigoid [1].

Reference

1 Chan LS, Ahmed AR, Anhalt GJ *et al.* The first international consensus on mucous membrane pemphigoid: definition, diagnostic criteria, pathogenic factors, medical treatment, and prognostic indicators. *Arch Dermatol* 2002; **138**: 370–9.

IgA EBA and IgA EBA mucous membrane pemphigoid. A number of patients have been described as IgA EBA, with IgA antibodies to dermal antigens and collagen VII. However, there are two different clinical entities with this immunopathology. There are linear IgA disease patients who are indistinguishable from other linear IgA patients [1–3] and there are patients with a mucous membrane pemphigoid phenotype [4–6].

References

1 Mutasim DF, Cummings MP. Linear IgA disease with clinical and immunopathological features of epidermolysis bullosa acquisita. *Pediatr Dermatol* 1997; **14**: 303–6.
2 Vodegel RM, de Jong MC, Pas HH *et al.* IgA-mediated epidermolysis bullosa acquisita: two cases and review of the literature. *J Am Acad Dermatol* 2002; **47**: 919–25.
3 Lally A, Chamberlain A, Allen J *et al.* Dermal-binding linear IgA disease: an uncommon subset of a rare immunobullous disease. *Clin Exp Dermatol* 2007; **32**: 493–8.
4 Caux F, Kirtschig G, Lemarchand-Venencie F *et al.* IgA-epidermolysis bullosa acquisita in a child resulting in blindness. *Br J Dermatol* 1997; **137**: 270–5.
5 Bauer JW, Schaeppi H, Metze D *et al.* Ocular involvement in IgA-epidermolysis bullosa acquisita. *Br J Dermatol* 1999; **141**: 887–92.
6 Chan LS, Ahmed AR, Anhalt GJ *et al.* The first international consensus on mucous membrane pemphigoid: definition, diagnostic criteria, pathogenic factors, medical treatment, and prognostic indicators. *Arch Dermatol* 2002; **138**: 370–9.

Induced EBA and associated diseases. A number of conditions have been associated with EBA. There is an association with inflammatory bowel disease, both ulcerative colitis and Crohn's disease [1–6]. Collagen VII is expressed in human colon, and autoantibodies to collagen VII react with the epithelial mesenchymal junction, moreover antibodies to collagen VII are present in Crohn's disease and to a lesser extent in ulcerative colitis, suggesting that cross reactivity and epitope spreading may explain this association [7].

There are reports of EBA in association with multiple myeloma, amyloidosis and lymphoma [8–13]. Individual cases have been associated with carcinoma [14–16].

The association with systemic lupus erythematosus is discussed below under bullous systemic lupus erythematosus.

Drug-induced EBA has been described [17]

References

1 Roenigk HH Jr, Ryan JG, Bergfeld WF. Epidermolysis bullosa acquisita. Report of three cases and review of all published cases. *Arch Dermatol* 1971; **103**: 1–10.
2 Metz G, Metz J, Frank H. [Acquired epidermolysis bullosa in Crohn's disease]. *Hautarzt* 1975; **26**: 321–6.
3 Ray TL, Levine JB, Weiss W *et al.* Epidermolysis bullosa acquisita and inflammatory bowel disease. *J Am Acad Dermatol* 1982; **6**: 242–52.
4 Hughes BR, Horne J. Epidermolysis bullosa acquisita and total ulcerative colitis. *J R Soc Med* 1988; **81**: 473–5.
5 Labeille B, Gineston JL, Denoeux JP *et al.* Epidermolysis bullosa acquisita and Crohn's disease. A case report with immunological and electron microscopic studies. *Arch Intern Med* 1988; **148**: 1457–9.
6 Van't Veen AJ, Heule F, Vuzevski VD *et al.* Epidermolysis bullosa acquisita. *Br J Dermatol* 1994; **131**: 724–5.
7 Chen M, O'Toole EA, Sanghavi J *et al.* The epidermolysis bullosa acquisita antigen (type VII collagen) is present in human colon and patients with Crohn's disease have autoantibodies to type VII collagen. *J Invest Dermatol* 2002; **118**: 1059–64.
8 Kanoh T, Tanaka S. [Epidermolysis bullosa acquisita in multiple myeloma associated with skin amyloidosis (author's transl)]. *Nippon Naika Gakkai Zasshi* 1978; **67**: 600–5.
9 Trump DL, Allen H, Olson J *et al.* Epidermolysis bullosa acquisita. Association with amyloidosis and multiple myeloma. *JAMA* 1980; **243**: 1461–2.
10 Shaw M, McKee PH, Gaminara E *et al.* Epidermolysis bullosa acquisita associated with chronic lymphatic leukaemia. *Clin Exp Dermatol* 1985; **10**: 162–8.
11 Baler GR. Epidermolysis bullosa acquisita associated with lymphoma. *J Am Acad Dermatol* 1987; **17**: 856–9.
12 Soria C, Munoz E, Espana A *et al.* [Acquired bullous epidermolysis and multiple myeloma]. *Med Cutan Ibero Lat Am* 1990; **18**: 206–11.
13 Engineer L, Dow EC, Braverman IM *et al.* Epidermolysis bullosa acquisita and multiple myeloma. *J Am Acad Dermatol* 2002; **47**: 943–6.
14 Klein JS, Goldin HM, Keegan C *et al.* Clear-cell carcinoma of the lung in a patient treated with cyclosporine for epidermolysis bullosa acquisita. *J Am Acad Dermatol* 1991; **24**: 297.
15 Bernard P, Bedane C, Taieb A *et al.* [Squamous cell carcinoma complicating acquired bullous epidermolysis]. *Ann Dermatol Venereol* 1992; **119**: 35–6.
16 Etienne A, Ruffieux P, Didierjean L *et al.* [Epidermolysis bullosa acquisita and metastatic cancer of the uterine cervix]. *Ann Dermatol Venereol* 1998; **125**: 321–3.
17 Delbaldo C, Chen M, Friedli A *et al.* Drug-induced epidermolysis bullosa acquisita with antibodies to type VII collagen. *J Am Acad Dermatol* 2002; **46**: S161–4.

Prognosis. The prognosis is very variable. Those patients with a bullous pemphigoid-like picture may go into remission. However, patients with mechanobullous disease or a mucous membrane phenotype tend to have disease that is difficult to suppress and is very prolonged.

Differential diagnosis. Cases of EBA are often confused with dominant dystrophic epidermolysis bullosa, bullous pemphigoid or porphyria cutanea tarda. Clinically, the mechanobullous epidermolysis bullosa acquisita patients most closely resemble mild dominant dystrophic epidermolysis bullosa, but the lack of family history, late onset and positive direct immunofluorescence distinguish them. The lesions on the hands may mimic porphyria cutanea tarda but this can be ruled out by porphyrin studies. Bullous pemphigoid presents the greatest diagnostic problems, because the direct immunofluorescence may be similar in these conditions. The conditions may be separated by using salt-split skin as a substrate for indirect immunofluorescence and the additional finding on electron microscopy of cleavage beneath the basal lamina and the deposition of IgG in the dermis.

Treatment. The rarity of the condition has precluded proper trials but the mechanobullous variant is characterized by resistance to usual treatment modalities. A systematic review identified only 10 reports of studies on two or more patients (20 adults and 11 children) [1]. Much of the information on treatment is anecdotal; corticosteroids, azathioprine, ciclosporin, vitamin E, gold, dapsone, sulfonamides, colchicines and photophoresis have been reported to give inconsistent benefit [2]. Mycophenolate mofetil has been reported as helpful in a few cases [3–5]. Intravenous immunoglobulins and subcutaneous immunoglobulin (by home administration) can improve the condition, however the response is not universal [2,6,7]. Rituximab has been reported to be successful in several case reports [8–12].

Steroids in combination with dapsone or sulfonamides are probably the best first-line treatment, certainly in children [1].

References

1 Kirtschig G, Murrell D, Wojnarowska F *et al.* Interventions for mucous membrane pemphigoid/cicatricial pemphigoid and epidermolysis bullosa acquisita: a systematic literature review. *Arch Dermatol* 2002; **138**: 380–4.
2 Engineer L, Ahmed AR. Emerging treatment for epidermolysis bullosa acquisita. *J Am Acad Dermatol* 2001; **44**: 818–28.
3 Kowalzick L, Suckow S, Ziegler H *et al.* Mycophenolate mofetil in epidermolysis bullosa acquisita. *Dermatology* 2003; **207**: 332–4.
4 Marzano AV, Dassoni F, Caputo R. Treatment of refractory blistering autoimmune diseases with mycophenolic acid. *J Dermatolog Treat* 2006; **17**: 370–6.
5 Trebing D, Ziemer A. [Acquired epidermolysis bullosa with a highly varied clinical picture and successful treatment with mycophenolate mofetil]. *Hautarzt* 2001; **52**: 717–21.
6 Segura S, Iranzo P, Martinez-de Pablo I *et al.* High-dose intravenous immunoglobulins for the treatment of autoimmune mucocutaneous blistering diseases: evaluation of its use in 19 cases. *J Am Acad Dermatol* 2007; **56**: 960–7.
7 Tayal U, Burton J, Dash C *et al.* Subcutaneous immunoglobulin therapy for immunomodulation in a patient with severe epidermolysis bullosa acquisita. *Clin Immunol* 2008; **129**: 518–9.
8 Crichlow SM, Mortimer NJ, Harman KE. A successful therapeutic trial of rituximab in the treatment of a patient with recalcitrant, high-titre epidermolysis bullosa acquisita. *Br J Dermatol* 2007; **156**: 194–6.
9 Niedermeier A, Eming R, Pfutze M *et al.* Clinical response of severe mechanobullous epidermolysis bullosa acquisita to combined treatment with immunoadsorption and rituximab (anti-CD20 monoclonal antibodies). *Arch Dermatol* 2007; **143**: 192–8.
10 Sadler E, Schafleitner B, Lanschuetzer C *et al.* Treatment-resistant classical epidermolysis bullosa acquisita responding to rituximab. *Br J Dermatol* 2007; **157**: 417–9.
11 Schmidt E, Hunzelmann N, Zillikens D *et al.* Rituximab in refractory autoimmune bullous diseases. *Clin Exp Dermatol* 2006; **31**: 503–8.
12 Wallet-Faber N, Franck N, Batteux F *et al.* Epidermolysis bullosa acquisita following bullous pemphigoid, successfully treated with the anti-CD20 monoclonal antibody rituximab. *Dermatology* 2007; **215**: 252–5.

Bullous systemic lupus erythematosus

Synonym

- Vesiculobullous systemic lupus erythematosus

Definition. An autoimmune blistering condition, often transient, that occurs in the setting of systemic lupus erythematosus [1,2]. There is some controversy as to whether the term bullous systemic lupus erythematosus should include all subepidermal autoimmune bullous diseases that arise in patients with systemic lupus erythematosus or should be reserved for those patients with dermal antigens [2–4].

The clinical features, immunopathology and immunogenetics are summarized in Tables 40.5 and 40.6, and Fig. 40.25 and in a review [2].

References

1 Yell JA, Allen J, Wojnarowska F *et al.* Bullous systemic lupus erythematosus: revised criteria for diagnosis. *Br J Dermatol* 1995; **132**: 921–8.
2 Yell JA, Wojnarowska F. Bullous skin disease in lupus erythematosus. *Lupus* 1997; **6**: 112–21.
3 Gammon WR, Briggaman RA. Bullous SLE: a phenotypically distinctive but immunologically heterogeneous bullous disorder. *J Invest Dermatol* 1993; **100**: 28S–34S.
4 Vassileva S. Bullous systemic lupus erythematosus. *Clin Dermatol* 2004; **22**: 129–38.

Aetiology. Bullous systemic lupus erythematosis (BSLE) occurs only in patients with systemic lupus erythematosus. It affects young adults, chiefly women, often of African or Hispanic descent, and has been reported in children [1–3]. It is very rare in Western Europe with an incidence of 0.2 per million [4,5] and has been reported from China and Singapore [6,7]. In the USA, there is an association with HLA-DR2 [8].

References

1 Kettler AH, Bean SF, Duffy JO *et al.* Systemic lupus erythematosus presenting as a bullous eruption in a child. *Arch Dermatol* 1988; **124**: 1083–7.
2 Yung A, Oakley A. Bullous systemic lupus erythematosus. *Australas J Dermatol* 2000; **41**: 234–7.
3 Harris-Stith R, Erickson QL, Elston DM *et al.* Bullous eruption: a manifestation of lupus erythematosus. *Cutis* 2003; **72**: 31–7.
4 Bernard P, Vaillant L, Labeille B *et al.* Incidence and distribution of subepidermal autoimmune bullous skin diseases in three French regions. Bullous Diseases French Study Group. *Arch Dermatol* 1995; **131**: 48–52.
5 Zillikens D, Wever S, Roth A *et al.* Incidence of autoimmune subepidermal blistering dermatoses in a region of central Germany. *Arch Dermatol* 1995; **131**: 957–8.
6 Jin P, Shao C, Ye G. Chronic bullous dermatoses in China. *Int J Dermatol* 1993; **32**: 89–92.
7 Wong SN, Chua SH. Spectrum of subepidermal immunobullous disorders seen at the National Skin Centre, Singapore: a 2-year review. *Br J Dermatol* 2002; **147**: 476–80.
8 Gammon W, Heise E, Burke W *et al.* Increased frequency of HLA-DR2 in patients with auto-antibodies to epidermolysis bullosa acquisita antigen: evidence that expression of autoimmunity to type VII collagen is HLA class II allele associated. *J Invest Dermatol* 1988; **91**: 228–32.

Pathogenesis. The bullous disease is mediated by autoantibodies to the basement-membrane zone, as demonstrated by positive direct immunofluorescence at the basement-membrane zone. The autoantibodies initially were demonstrated to react with collagen and to bind to fibronectin-like domains of the NC1 terminal [1,2] and also the cartilage matrix protein subdomain [3]. However, as more cases have been studied it has become obvious that other dermal and epidermal antigens can also be involved, and in some cases no circulating autoantibodies can be detected [4–8]. Basement-membrane autoantibodies have also been detected in patients with systemic lupus erythematosus without blisters, although other groups have not confirmed this [4,5,9]. Collagen VII antibodies do not seem to contribute to the lupus band in patients without BSLE [10].

Both IgG and IgA autoantibodies are involved [5,6].

The target antigens and immunogenetic susceptibility are, in many patients, shared with EBA, and yet in general they differ in clinical presentation. The reasons for these marked differences in the clinical phenotype are intriguing but unexplained, but do not relate to complement fixing properties [11].

References

1 Gammon WR, Woodley DT, Dole KC *et al.* Evidence that anti-basement membrane zone antibodies in bullous eruption of systemic lupus erythematosus recognize epidermolysis bullosa acquisita autoantigen. *J Invest Dermatol* 1985; **84**: 472–6.
2 Gammon WR, Murrell DF, Jenison MW *et al.* Autoantibodies to type VII collagen recognize epitopes in a fibronectin-like region of the noncollagenous (NC1) domain. *J Invest Dermatol* 1993; **100**: 618–22.

3 Chen M, Doostan A, Bandyopadhyay P *et al.* The cartilage matrix protein subdomain of type VII collagen is pathogenic for epidermolysis bullosa acquisita. *Am J Pathol* 2007; **170**: 2009–18.
4 Burge S, Schomberg K, Wojnarowska F. Bullous eruption of SLE: a case report and investigation of the relationship of antibasement membrane zone antibodies to blistering. *Clin Exp Dermatol* 1991; **16**: 133–8.
5 Gammon WR, Briggaman RA. Bullous SLE: a phenotypically distinctive but immunologically heterogeneous bullous disorder. *J Invest Dermatol* 1993; **100**: 28S–34S.
6 Yell JA, Allen J, Wojnarowska F *et al.* Bullous systemic lupus erythematosus: revised criteria for diagnosis. *Br J Dermatol* 1995; **132**: 921–8.
7 Yell JA, Wojnarowska F. Bullous skin disease in lupus erythematosus. *Lupus* 1997; **6**: 112–21.
8 Chan LS, Lapiere JC, Chen M *et al.* Bullous systemic lupus erythematosus with autoantibodies recognizing multiple skin basement membrane components, bullous pemphigoid antigen 1, laminin-5, laminin-6, and type VII collagen. *Arch Dermatol* 1999; **135**: 569–73.
9 Ishikawa O, Zaw K, Miyachi Y *et al.* The presence of anti-basement membrane zone antibodies in the sera of patients with non-bullous lupus erythematosus. *Br J Dermat* 1997; **136**: 222–6.
10 Alahlafi AM, Wordsworth P, Wojnarowska F. The lupus band: do the autoantibodies target collagen VII? *Br J Dermatol* 2004; **150**: 504–10.
11 Gandhi K, Chen M, Aasi S *et al.* Autoantibodies to type VII collagen have heterogeneous subclass and light chain compositions and their complement-activating capacities do not correlate with the inflammatory clinical phenotype. *J Clin Immunol* 2000; **20**: 416–23.

Pathology. Histologically, the bullae are subepidermal with a neutrophilic infiltrate, occasionally resulting in microabscesses resembling dermatitis herpetiformis.

The findings with immunofluorescence are summarized in Table 40.6. Direct immunofluorescence shows linear bands of IgG, IgA, IgM and C3 in the basement-membrane zone.

With indirect immunofluorescence, circulating antibodies, when present, may bind to the basement-membrane zone and to either the dermal, as shown in Fig. 40.25, or the epidermal aspects of split skin, or may be absent [1,2].

Immunoelectron microscopy studies have demonstrated that circulating IgG autoantibodies bind below the lamina densa [3].

References

1 Yell JA, Allen J, Wojnarowska F *et al.* Bullous systemic lupus erythematosus: revised criteria for diagnosis. *Br J Dermatol* 1995; **132**: 921–8.
2 Gammon WR, Briggaman RA. Bullous SLE: a phenotypically distinctive but immunologically heterogeneous bullous disorder. *J Invest Dermatol* 1993; **100**: 28S–34S.
3 Hall RP, Lawley TJ, Smith HR *et al.* Bullous eruption of systemic lupus erythematosus. Dramatic response to dapsone therapy. *Ann Intern Med* 1982; **97**: 165–70.

Clinical features. The onset of the disease is usually in patients with already established systemic lupus erythematosus. There is widespread blistering, which may include both vesicles and larger tense blisters, and there may be erythematous macules as well. All cutaneous sites may be involved. Mucosal lesions are uncommon. In some patients, the eruption is photosensitive. Post-inflammatory hyperpigmentation may occur. The occurrence of the bullous eruption is not related to flares of the systemic disease, and shows clinical similarities to bullous pemphigoid and dermatitis herpetiformis. The classical epidermolysis bullosa phenotype of a mechanobullous eruption with milia and scarring (see above) is rare [1,2]. In many patients, the disease is transient.

References

1 Yell JA, Allen J, Wojnarowska F *et al.* Bullous systemic lupus erythematosus: revised criteria for diagnosis. *Br J Dermatol* 1995; **132**: 921–8.
2 Eckman JA, Mutasim DF. Bullous systemic lupus erythematosus with milia and calcinosis. *Cutis* 2002; **70**: 31–4.

Associated disease. Bullous systemic lupus erythematosis, by definition, only occurs in the setting of systemic lupus erythematosis. Vesiculobullous skin eruptions are uncommon but well recognized in patients with systemic lupus erythematosus, occurring in less than 10% of SLE patients, whilst true BSLE was reported in 1/73 British and 1/186 Italian patients [1,2]. The classical widespread bullous skin eruption appears to be unrelated to the other systemic manifestations, exacerbations or the severity of the systemic lupus erythematosus [3–6]. There are many reports of other autoimmune diseases, pemphigus, bullous pemphigoid, linear IgA disease, dermatitis herpetiformis and reactive bullous diseases, erythema multiforme and toxic epidermal necrolysis in association with systemic lupus erythematosus, but all the subepidermal ones are best regarded as BSLE [7,8].

References

1 Yell JA, Mbuagbaw J, Burge SM. Cutaneous manifestations of systemic lupus erythematosus. *Br J Dermatol* 1996; **135**: 355–62.
2 Cardinali C, Caproni M, Bernacchi E *et al.* The spectrum of cutaneous manifestations in lupus erythematosus—the Italian experience. *Lupus* 2000; **9**: 417–23.
3 Gammon WR, Briggaman RA. Bullous SLE: a phenotypically distinctive but immunologically heterogeneous bullous disorder. *J Invest Dermatol* 1993; **100**: 28S–34S.
4 Hall RP 3rd, Lawley TJ, Katz SI. Bullous eruption of systemic lupus erythematosus. *J Am Acad Dermatol* 1982; **7**: 797–9.
5 Hall RP, Lawley TJ, Smith HR *et al.* Bullous eruption of systemic lupus erythematosus. Dramatic response to dapsone therapy. *Ann Intern Med* 1982; **97**: 165–70.
6 Malcangi G, Brandozzi G, Giangiacomi M *et al.* Bullous SLE: response to methotrexate and relationship with disease activity. *Lupus* 2003; **12**: 63–6.
7 Yell JA, Wojnarowska F. Bullous skin disease in lupus erythematosus. *Lupus* 1997; **6**: 112–21.
8 Vassileva S. Bullous systemic lupus erythematosus. *Clin Dermatol* 2004; **22**: 129–38.

Prognosis. Most patients have a transient eruption. However, patients with the rare mechanobullous and scarring picture have a poorer prognosis.

Differential diagnosis. The presence of blistering in a patient with systemic lupus erythematosus can be due to photosensitivity, acute lupus or a drug eruption. The histopathology and immunopathology will distinguish bullous systemic lupus erythematosus.

Treatment. Some of these patients appear to have responded to steroids used to control their systemic lupus erythematosus. Dapsone has been shown to be very effective as first-line treatment and also in patients with steroid-resistant blistering [1–9]. Methotrexate has also been reported to be helpful [10]. Rituximab may be useful [11].

References

1 Hall RP, Lawley TJ, Smith HR *et al.* Bullous eruption of systemic lupus erythematosus. Dramatic response to dapsone therapy. *Ann Intern Med* 1982; **97**: 165–70.

2 Camisa C, Sharma H. Vesiculobullous systemic lupus erythematosus. *J Am Acad Dermatol* 1983; **9**: 924–33.
3 Fabbri P, Cardinali C, Giomi B *et al.* Cutaneous lupus erythematosus: diagnosis and management. *Am J Clin Dermatol* 2003; **4**: 449–65.
4 Fujimoto W, Hamada T, Yamada J *et al.* Bullous systemic lupus erythematosus as an initial manifestation of SLE. *J Dermatol* 2005; **32**: 1021–7.
5 Harris-Stith R, Erickson QL, Elston DM *et al.* Bullous eruption: a manifestation of lupus erythematosus. *Cutis* 2003; **72**: 31–7.
6 Kacalak-Rzepka A, Zaluga E, Maleszka R *et al.* Bullous systemic lupus erythematosus with antiphospholipid syndrome. *J Eur Acad Dermatol Venereol* 2004; **18**: 490–4.
7 Kumar S, Agarwal I. Unusual presentation of childhood systemic lupus erythematosus. *Pediatr Rheumatol Online J* 2007; **5**: 20.
8 Ludgate MW, Greig DE. Bullous systemic lupus erythematosus responding to dapsone. *Australas J Dermatol* 2008; **49**: 91–3.
9 Sirka CS, Padhi T, Mohanty P *et al.* Bullous systemic lupus erythematosus: response to dapsone in two patients. *Indian J Dermatol Venereol Leprol* 2005; **71**: 54–6.
10 Malcangi G, Brandozzi G, Giangiacomi M *et al.* Bullous SLE: response to methotrexate and relationship with disease activity. *Lupus* 2003; **12**: 63–6.
11 Schmidt E, Brocker EB, Goebeler M. Rituximab in treatment-resistant autoimmune blistering skin disorders. *Clin Rev Allergy Immunol* 2008; **34**: 56–64.

Dermatitis herpetiformis

Synonym
- Duhring–Brocq disease

Definition. Dermatitis herpetiformis (DH) is a rare, intensely pruritic, chronic, recurrent, papulovesicular disease. The eruption is symmetrical and pleomorphic, consisting of erythematous, urticarial, papular, vesicular or bullous lesions (Fig. 40.27). There is an underlying gluten-sensitive enteropathy that may be asymptomatic. The mechanism by which ingestion of gluten induces granular IgA deposition in the skin and blistering is still obscure (see below).

The characteristic clinical and immunopathological features are shown in Tables 40.5 and 40.6.



Fig. 40.27 Dermatitis herpetiformis. Intact tense bullae on the elbow. (Courtesy of Dr R.J. Pye, Addenbrooke's Hospital, Cambridge, UK.)

Aetiology. Dermatitis herpetiformis is a disease of all ages. In Italy and Hungary it commonly presents in childhood [1–3], in the UK in young and middle-aged adults, with a slight male preponderance, and in southern Sweden it may present in old age [4]. The incidence is more than 3000 per million in Ireland, 200–390 per million in Sweden, 110 per million in Scotland and Finland, and probably less elsewhere in Europe [4,5]. Dermatitis herpetiformis is rare in the Far East.

There is a family history of dermatitis herpetiformis or coeliac disease in 10.5% of patients and it has been reported to be both concordant and discordant in monozygotic twins [6–13].

All patients have an underlying gluten-sensitive enteropathy, although this may be asymptomatic. Others will have been investigated for abdominal pain, and may be misdiagnosed. There is an association with exposure to infection with adenovirus, as has been observed in coeliac disease [14].

HLA studies in patients who on clinical and immunological criteria have dermatitis herpetiformis, have shown identical findings to coeliac disease. There is a very strong association with DR3 and DQw2 [5,15–18].

References

1 Ermacora E, Prampolini L, Tribbia G *et al.* Long term follow-up of dermatitis herpetiformis in children. *J Am Acad Dermatol* 1986; **15**: 24–34.
2 Karpati S, Torok E, Kosnai I. Discrete palmar and plantar symptoms in children with dermatitis herpetiformis Duhring. *Cutis* 1986; **37**: 184–7.
3 Kosnai I, Karpati S, Savilahti E *et al.* Gluten challenge in children with dermatitis herpetiformis: a clinical, morphological and immunohistological study. *Gut* 1986; **27**: 1464–70.
4 Fry L. *Dermatitis herpetiformis*. London: Chapman & Hall Medical, 1990.
5 Fry L. Dermatitis herpetiformis: problems, progress and prospects. *Eur J Dermatol* 2002; **12**: 523–31.
6 Reunala T. Incidence of familial dermatitis herpetiformis. *Br J Dermatol* 1996; **134**: 394–8.
7 Marks J, May SB, Roberts DF. Dermatitis herpetiformis occurring in monozygous twins. *Br J Dermatol* 1971; **84**: 417–9.
8 Jepsen LV, Ullman S. Dermatitis herpetiformis and gluten-sensitive enteropathy in monozygotic twins. *Acta Derm Venereol* 1980; **60**: 353–5.
9 Kosnai I, Karpati S, Torok E *et al.* Dermatitis herpetiformis in monozygous twins: discordance for dermatitis herpetiformis and concordance for gluten-sensitive enteropathy. *Eur J Pediatr* 1985; **144**: 404–5.
10 Green ST, Natarajan S, Connor JM *et al.* Monozygous twins concordant for duodenojejunal villous atrophy and dermatitis herpetiformis. *Gut* 1986; **27**: 970–1.
11 Anstey A, Wilkinson JD, Walshe MM. Dermatitis herpetiformis in monozygous twins—concordance for dermatitis herpetiformis and gluten-sensitive enteropathy. *Clin Exp Dermatol* 1991; **16**: 51–2.
12 Bardella MT, Fredella C, Prampolini L *et al.* Gluten sensitivity in monozygous twins: a long-term follow-up of five pairs. *Am J Gastroenterol* 2000; **95**: 1503–5.
13 Hervonen K, Karell K, Holopainen P *et al.* Concordance of dermatitis herpetiformis and celiac disease in monozygous twins. *J Invest Dermatol* 2000; **115**: 990–3.
14 Lahdeaho ML, Parkkonen P, Reunala T *et al.* Antibodies to E1b protein-derived peptides of enteric adenovirus type 40 are associated with celiac disease and dermatitis herpetiformis. *Clin Immunol Immunopathol* 1993; **69**: 300–5.

15 Hall M, Lanchbury J, Bolsover W *et al.* HLA association with dermatitis herpetiformis is accounted for by a *cis* or *trans* associated DQ heterodimer. *Gut* 1991; **32**: 487–90.
16 Hall RP 3rd, Otley C. Immunogenetics of dermatitis herpetiformis. *Semin Dermatol* 1991; **10**: 240–5.
17 Balas A, Vicario JL, Zambrano A *et al.* Absolute linkage of celiac disease and dermatitis herpetiformis to HLA-DQ. *Tissue Antigens* 1997; **50**: 52–6.
18 Sachs JA, Leonard J, Awad J *et al.* A comparative serological and molecular study of linear IgA disease and dermatitis herpetiformis. *Br J Dermatol* 1988; **118**: 759–64.

Pathogenesis. The characteristic finding is deposition of IgA in a granular pattern in the papillary dermis (Fig. 40.28), although IgM, IgG and C3 may be found. The IgA deposits are gluten dependent, and are slowly cleared from the skin once gluten is removed from the diet [1,2]. The mechanism by which gluten causes the IgA deposition in the skin is still unknown, although non-immunological binding of gliadin to reticulin has been shown [3]. The IgA deposits are often, but not exclusively, associated with the microfibrils [4,5]. The antigen within normal human skin to which IgA antibodies from dermatitis herpetiformis sera bind is still unknown.

The IgA deposits have been shown to be chemoattractant to neutrophils [6]. C3 has been demonstrated in the papillary dermis of both lesional and perilesional skin. Properdin and factor B have been found and support the suggestion that complement is activated via the alternative pathway [7]. C5 and fibrin are often detected in similar sites [8]. The activated fraction, C5a, is highly chemotactic for neutrophils and may contribute to the inflammatory change at the papillary tip. Lymphocytes also play a role, with the neutrophils, in initiating an inflammatory cascade [9].

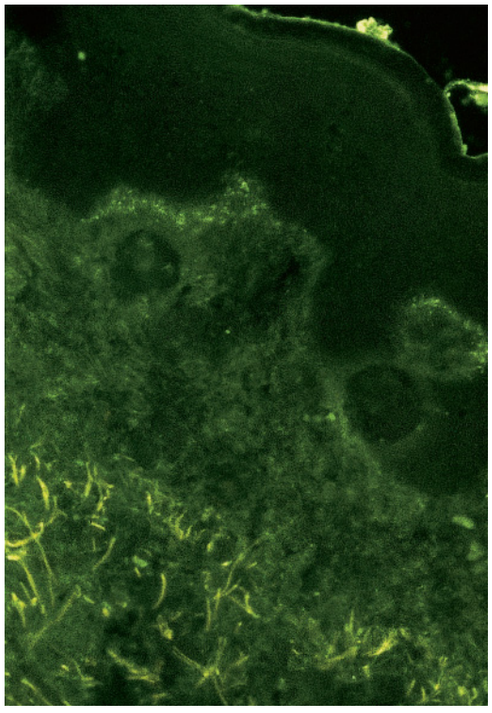


Fig. 40.28 Dermatitis herpetiformis. Direct immunofluorescence demonstrating granular IgA deposition in the dermal papillae. (Courtesy of Dr J. Allen, Oxford Radcliffe Hospital, Oxford, UK.)

Characterization of the IgA deposits has shown the IgA to be almost exclusively IgA1 and to be both monomeric and polymeric, with J chains and secretory components present [10–12]. These data suggest that the IgA is derived from mucosa and serum.

In 1967, the link with gluten sensitive enteropathy (coeliac disease) was established [13]. Further studies showed that the small-bowel changes of villous atrophy were secondary to gluten sensitivity and responded to gluten-free diet [14]. The gluten-sensitive enteropathy is present in all patients though is difficult to demonstrate in some [15]. Patients were found to have antireticulin antibodies and antigluten or antigliadin antibodies [15–19]. IgA endomysial antibodies, directed at smooth muscle, are frequently found in dermatitis herpetiformis and coeliac disease and fall with the introduction of a gluten-free diet [20,21].

One of the most exciting developments of recent years has been the recognition that autoantibodies and T-cell reactions to tissue transglutaminases, and in particular transglutaminase 2, are relevant to the pathogenesis of coeliac disease [22]. These antibodies have been demonstrated in dermatitis herpetiformis [23–25]. In addition, it is now clear that the previously recognized antireticulin and endomysial antibodies, in coeliac disease and dermatitis herpetiformis, are associated with these antibodies [26] and require transglutaminase 2 to bind to tissues [27]. The tissue transglutaminases cleave gliadin into antigenic peptides and this may contribute to their role in pathogenesis [28]. There is a difference in autoantibody profile between dermatitis herpetiformis and coeliac disease, in that IgA antibodies to epidermal transglutaminases (tissue transglutaminase 3) are more common in DH than coeliac disease [29,30]. The IgA precipitates in the dermis contain epidermal transglutaminases [29], and there is co-localization of the granular IgA deposits and the epidermal transglutaminases in the upper dermis and blood vessels, thus DH may be an immune complex disease [31,32]. However, the precise chain of events leading to IgA deposition in the skin and blistering has still to be unravelled [9]. The serum of patients with DH does not contain antibodies that bind either to human skin or to mouse models [33,34]. An animal model using genetically primed DQ8 mice has shown that in a minority gluten can induce blisters with the characteristic histology and granular IgA deposition, however this was not associated with circulating antibodies to skin, endomysium, gluten, gliadin, or tissue transglutaminases, nor with enteropathy [34].

References

1 Harrington CI, Read NW. Dermatitis herpetiformis: effect of gluten-free diet on skin IgA and jejunal structure and function. *BMJ* 1977; **1**: 872–5.
2 Leonard J, Haffenden G, Tucker W *et al.* Gluten challenge in dermatitis herpetiformis. *New Eng J Med* 1983; **308**: 816–9.
3 Unsworth DJ, Leonard JN, Hobday CM *et al.* Gliadins bind to reticulin in a lectin-like manner. *Arch Dermatol Res* 1987; **279**: 232–5.
4 Yaoita H. Identification of IgA binding structures in skin of patients with dermatitis herpetiformis. *J Invest Dermatol* 1978; **71**: 213–6.
5 Karpati S, Meurer M, Stolz W *et al.* Dermatitis herpetiformis. Ultrastructural study on the skin in patients using direct preembedding immunogold labelling. *Arch Dermatol* 1990; **126**: 1469–74.
6 Hendrix J, Mangum K, Zone J *et al.* Cutaneous IgA deposits in bullous diseases function as ligands to mediate adherence of activated neutrophils. *J Invest Dermatol* 1990; **94**: 667–72.

7 Katz SI, Hertz KC, Crawford PS *et al.* Effect of sulfones on complement deposition in dermatitis herpetiformis and on complement-mediated guinea-pig reactions. *J Invest Dermatol* 1976; **67**: 688–90.
8 Mustakallio KK, Blomqvist K, Laiho K. Papillary deposition of fibrin, a characteristic of initial lesions of dermatitis herpetiformis. *Ann Clin Res* 1970; **2**: 13–8.
9 Fry L. Dermatitis herpetiformis: problems, progress and prospects. *Eur J Dermatol* 2002; **12**: 523–31.
10 Unsworth D, Payne A, Leonard J *et al.* IgA in dermatitis herpetiformis is dimeric. *Lancet* 1982; **i**: 478–80.
11 Hall R, Lawley T. Characterization of circulating and cutaneous IgA immune complexes in patients with dermatitis herpetiformis. *J Immunol* 1985; **135**: 1760–5.
12 Wojnarowska F, Bhogal G, Black M. Chronic bullous disease of childhood and linear IgA disease of adults are IgA1 mediated diseases. *Br J Dermatol* 1994; **131**: 201–4.
13 Fry L, Keir P, McMinn R *et al.* Small intestinal structure and function, and haematological changes in dermatitis herpetiformis. *Lancet* 1967; **ii**: 729–34.
14 Fry L, McMinn RM, Cowan JD *et al.* Effect of gluten-free diet on dermatological, intestinal, and haematological manifestations of dermatitis herpetiformis. *Lancet* 1968; **1**: 557–61.
15 Ljunghall K, Loof L, Grimelius L *et al.* Dermatitis herpetiformis: relation between circulating antibodies against reticulin and gluten, small-intestinal mucosal status and absorptive capacity. *Acta Derm Venereol* 1983; **63**: 27–34.
16 Ljunghall K, Scheynius A, Forsum U. Circulating reticulin autoantibodies of IgA class in dermatitis herpetiformis. *Br J Dermatol* 1979; **100**: 173–6.
17 Menzel EJ, Pehamberger H, Holubar K. Demonstration of antibodies to wheat gliadin in dermatitis herpetiformis using 14C-radioimmunoassay. *Clin Immunol Immunopathol* 1978; **10**: 193–201.
18 Huff JC, Weston WL, Zirker DK. Wheat protein antibodies in dermatitis herpetiformis. *J Invest Dermatol* 1979; **73**: 570–4.
19 Kumar PJ, Ferguson A, Lancaster-Smith M *et al.* Food antibodies in patients with dermatitis herpetiformis and adult coeliac disease—relationship to jejunal morphology. *Scand J Gastroenterol* 1976; **11**: 5–9.
20 Chorzelski TP, Beutner EH, Sulej J *et al.* IgA anti-endomysium antibody. A new immunological marker of dermatitis herpetiformis and coeliac disease. *Br J Dermatol* 1984; **111**: 395–402.
21 Beutner EH, Chorzelski TP, Kumar V *et al.* Sensitivity and specificity of IgA-class antiendomysial antibodies for dermatitis herpetiformis and findings relevant to their pathogenic significance. *J Am Acad Dermatol* 1986; **15**: 464–73.
22 Dieterich W, Ehnis T, Bauer M *et al.* Identification of tissue transglutaminase as the autoantigen of celiac disease. *Nat Med* 1997; **3**: 797–801.
23 Rose C, Dieterich W, Brocker EB *et al.* Circulating autoantibodies to tissue transglutaminase differentiate patients with dermatitis herpetiformis from those with linear IgA disease. *J Am Acad Dermatol* 1999; **41**: 957–61.
24 Porter WM, Unsworth DJ, Lock RJ *et al.* Tissue transglutaminase antibodies in dermatitis herpetiformis. *Gastroenterology* 1999; **117**: 749–50.
25 Dieterich W, Laag E, Bruckner-Tuderman L *et al.* Antibodies to tissue transglutaminase as serologic markers in patients with dermatitis herpetiformis. *J Invest Dermatol* 1999; **113**: 133–6.
26 Kumar V, Jarzabek-Chorzelska M, Sulej J *et al.* Tissue transglutaminase and endomysial antibodies—diagnostic markers of gluten-sensitive enteropathy in dermatitis herpetiformis. *Clin Immunol* 2001; **98**: 378–82.
27 Korponay-Szabo IR, Laurila K, Szondy Z *et al.* Missing endomysial and reticulin binding of coeliac antibodies in transglutaminase 2 knockout tissues. *Gut* 2003; **52**: 199–204.
28 Mowat AM. Coeliac disease—a meeting point for genetics, immunology, and protein chemistry. *Lancet* 2003; **361**: 1290–2.
29 Sardy M, Karpati S, Merkl B *et al.* Epidermal transglutaminase (TGase 3) is the autoantigen of dermatitis herpetiformis. *J Exp Med* 2002; **195**: 747–57.
30 Hull CM, Liddle M, Hansen N *et al.* Elevation of IgA anti-epidermal transglutaminase antibodies in dermatitis herpetiformis. *Br J Dermatol* 2008; **159**: 120–4.
31 Cannistraci C, Lesnoni La Parola I, Cardinali G *et al.* Co-localization of IgA and TG3 on healthy skin of coeliac patients. *J Eur Acad Dermatol Venereol* 2007; **21**: 509–14.
32 Karpati S. Dermatitis herpetiformis: close to unravelling a disease. *J Dermatol Sci* 2004; **34**: 83–90.
33 Zone JJ, Egan CA, Taylor TB *et al.* IgA autoimmune disorders: development of a passive transfer mouse model. *J Investig Dermatol Symp Proc* 2004; **9**: 47–51.
34 Marietta E, Black K, Camilleri M *et al.* A new model for dermatitis herpetiformis that uses HLA-DQ8 transgenic NOD mice. *J Clin Invest* 2004; **114**: 1090–7.

Pathology. Diagnostic histological changes are best seen in the vicinity of early blisters or in lesions that have not yet blistered. Neutrophils and eosinophils accumulate within the dermal papillae and form microabscesses. The surrounding collagen is degraded, resulting in detachment of the epidermis and a subepidermal vesicle. Multilocular vesicles may coalesce to form blisters; at that stage the cellular infiltrate is mixed and distinction from pemphigoid may be difficult.

The characteristic immunofluorescence findings are shown in Table 40.6 and Fig. 40.28. Direct immunofluorescence is always positive [1]. However, sometimes when there is a high degree of clinical suspicion, serial sections and multiple biopsies may be necessary to confirm the diagnosis. The biopsy (a 3–4-mm punch biopsy is sufficient) should be taken from clinically normal skin. The forearm or buttock is usually suitable. There are granular deposits of IgA in the dermal papillae (Fig. 40.28). There may also be C3 and IgG.

The diagnostic significance of the rare, linear, granular pattern of IgA deposition at the basement-membrane zone is still unclear [2]. Some patients with this pattern have true dermatitis herpetiformis and others may have autoantibodies to unusual target antigens.

Indirect immunofluorescence is negative for basement-membrane zone or dermal autoantibodies. However, if monkey oesophagus is used, IgA endomysial antibodies may be detected [3]. Immunoblotting studies are negative.

Electron microscopy shows that the blisters are subepidermal and can occur beneath the basal lamina. In the lesions, the basal lamina may be fragmented or lost. However, in adjacent skin the basal lamina may be thickened and reduplicated. The basal cells show cytolysis, but these changes are probably secondary to the effects of the inflammatory cells [4].

Ultrastructurally on immunoelectron microscopy, the IgA deposits appear to be closely associated with the dermal microfibrillar bundles [5,6]. However, immunogold studies have shown that not all of the IgA is associated with any recognizable structure [6].

Gastrointestinal investigations. All the abnormalities found in coeliac disease may be found in dermatitis herpetiformis [7]. A full blood count may reveal anaemia. The additional signs on the blood film depend on whether it is due to iron deficiency or folate deficiency. There may also be Howell–Jolly bodies on the film, indicating splenic atrophy [8]. There may be antireticulin antibodies and antigliadin antibodies as well as antiendomysial antibodies and antibodies to tissue transglutaminases. A jejunal biopsy will demonstrate signs of gluten-sensitive enteropathy in almost all cases; these signs may be a raised intraepithelial lymphocyte count or in more severe cases a flat biopsy.

References

1 Fry L, Seah P. Dermatitis herpetiformis: an evaluation of diagnostic criteria. *Br J Dermatol* 1974; **90**: 301–6.
2 Leonard JN, Haffenden GP, Ring NP *et al.* Linear IgA disease in adults. *Br J Dermatol* 1982; **107**: 301–16.
3 Chorzelski TP, Beutner EH, Sulej J *et al.* IgA anti-endomysium antibody. A new immunological marker of dermatitis herpetiformis and coeliac disease. *Br J Dermatol* 1984; **111**: 395–402.
4 Fry L, Johnson FR. Electron microscopic study of dermatitis herpetiformis. *Br J Dermatol* 1969; **81**: 44–50.
5 Yaoita H. Identification of IgA binding structures in skin of patients with dermatitis herpetiformis. *J Invest Dermatol* 1978; **71**: 213–6.
6 Karpati S, Meurer M, Stolz W *et al.* Dermatitis herpetiformis. Ultrastructural study on the skin in patients using direct preembedding immunogold labelling. *Arch Dermatol* 1990; **126**: 1469–74.
7 Fry L, Keir P, McMinn R *et al.* Small intestinal structure and function, and haematological changes in dermatitis herpetiformis. *Lancet* 1967; **ii**: 729–34.
8 Pettit JE, Hoffbrand AV, Seah PP *et al.* Splenic atrophy in dermatitis herpetiformis. *BMJ* 1972; **2**: 438–40.

Clinical features. Dermatitis herpetiformis presents mainly between the ages of 20 and 55 years, but can present both in childhood and old age. The onset may be acute or gradual, and pruritus is usually the first and predominant symptom. Early lesions on the skin are erythematous papules, urticarial weals or groups of small vesicles often excoriated so rapidly that it may be impossible to find one intact. The vesicles are usually grouped together on plaques of erythema, and rarely blisters 1–2 cm in diameter occur (Fig. 40.27). This happens more frequently in relapses when suppressive treatment has been discontinued. Papules without blistering are not uncommon and eczematous changes that may be lichenified are sometimes seen. Progressive pigmentation of the sites of the skin lesions occurs in some patients. The distribution of the lesions is characteristic. The extensor aspects of the limbs, especially the knees, just below the point of the elbows, buttocks and the natal cleft, are affected in the majority of patients (Fig. 40.27). The axillary folds, shoulders, trunk, face and scalp are all frequently involved. In partially suppressed disease the scalp and chin are often the sited effected. Oral lesions are common but asymptomatic [1].

Provocation or exacerbation by iodides either by mouth or by patch test is not specific for dermatitis herpetiformis and is now considered outmoded as a diagnostic test [2,3]. Skin cleansers containing iodine and iodine-containing preparations must be avoided, as they can exacerbate dermatitis herpetiformis.

There may be a feeling of malaise with the acutely active disease. In addition, constitutional symptoms due to the gluten-sensitive enteropathy can be present. The patient may experience bouts of abdominal pain, constipation and diarrhoea, and be undernourished. A diagnosis of irritable bowel is not uncommon. Patients are often tired and lack a feeling of well-being.

References

1 Fraser NG, Kerr NW, Donald D. Oral lesions in dermatitis herpetiformis. *Br J Dermatol* 1973; **89**: 439–50.
2 Marks JM. Dowling oration 1977. Dogma and dermatitis herpetiformis. *Clin Exp Dermatol* 1977; **2**: 189–207.
3 Haffenden GP, Blenkinsopp WK, Ring NP *et al.* The potassium iodide patch test in the dermatitis herpetiformis in relation to treatment with a gluten-free diet and dapsone. *Br J Dermatol* 1980; **103**: 313–7.

Associated diseases. There are often associated autoimmune diseases, particularly thyroid disease, pernicious anaemia and diabetes [1,2]. There is an association with thyroid disease in up to 30% of patients [3]. A variety of organ-specific and non-organ-specific autoantibodies have been detected in patients with dermatitis herpetiformis, notably thyroid antibodies [4].

Lymphoma is a well-recognized complication of dermatitis herpetiformis, as are other malignancies [5–12], although a recent study contradicts this [13]. Moreover, the protective role of a gluten-free diet for the lymphomas has been established [11,12,14].

References

1 Gawkrodger DJ, Blackwell JN, Gilmour HM *et al.* Dermatitis herpetiformis: diagnosis, diet and demography. *Gut* 1984; **25**: 151–7.
2 Fry L. Dermatitis herpetiformis: problems, progress and prospects. *Eur J Dermatol* 2002; **12**: 523–31.
3 Cunningham MJ, Zone JJ. Thyroid abnormalities in dermatitis herpetiformis. Prevalence of clinical thyroid disease and thyroid autoantibodies. *Ann Intern Med* 1985; **102**: 194–6.
4 Fraser NG. Autoantibodies in dermatitis herpetiformis. *Br J Dermatol* 1970; **83**: 609–13.
5 Reunala T, Helin H, Kuokkanen K *et al.* Lymphoma in dermatitis herpetiformis: report on four cases. *Acta Derm Venereol* 1982; **62**: 343–6.
6 Tucker WF, Leonard JN, Fry L. Increased risk of lymphoma in dermatitis herpetiformis. *J R Soc Med* 1983; **76**: 95–7.
7 Leonard JN, Tucker WF, Fry JS *et al.* Increased incidence of malignancy in dermatitis herpetiformis. *BMJ (Clin Res Ed)* 1983; **286**: 16–8.
8 Swerdlow AJ, Whittaker S, Carpenter LM *et al.* Mortality and cancer incidence in patients with dermatitis herpetiformis: a cohort study. *Br J Dermatol* 1993; **129**: 140–4.
9 Sigurgeirsson B, Agnarsson BA, Lindelof B. Risk of lymphoma in patients with dermatitis herpetiformis. *BMJ* 1994; **308**: 13–5.
10 Collin P, Pukkala E, Reunala T. Malignancy and survival in dermatitis herpetiformis: a comparison with coeliac disease. *Gut* 1996; **38**: 528–30.
11 Askling J, Linet M, Gridley G *et al.* Cancer incidence in a population-based cohort of individuals hospitalized with celiac disease or dermatitis herpetiformis. *Gastroenterology* 2002; **123**: 1428–35.
12 Hervonen K, Vornanen M, Kautiainen H *et al.* Lymphoma in patients with dermatitis herpetiformis and their first-degree relatives. *Br J Dermatol* 2005; **152**: 82–6.
13 Lewis NR, Logan RF, Hubbard RB *et al.* No increase in risk of fracture, malignancy or mortality in dermatitis herpetiformis: a cohort study. *Aliment Pharmacol Ther* 2008; **27**: 1140–7.
14 Lewis HM, Renaula TL, Garioch JJ *et al.* Protective effect of gluten-free diet against development of lymphoma in dermatitis herpetiformis. *Br J Dermatol* 1996; **135**: 363–7.

Prognosis. The disease runs a very long course with exacerbations and remissions [1]. Ten per cent of patients experience remissions. Acute infection and even emotional disturbances may precipitate an attack. A strict gluten-free diet will result in remission of the skin and the gut.

Interestingly, patients with dermatitis herpetiformis on a normal diet or a gluten-free diet do not have a decreased life expectancy, despite the slight increase in mortality from lymphoma, perhaps because of a reduction in ischaemic heart disease [2–6].

References

1 Gawkrodger DJ, Blackwell JN, Gilmour HM *et al.* Dermatitis herpetiformis: diagnosis, diet and demography. *Gut* 1984; **25**: 151–7.

2 Swerdlow AJ, Whittaker S, Carpenter LM *et al.* Mortality and cancer incidence in patients with dermatitis herpetiformis: a cohort study. *Br J Dermatol* 1993; **129**: 140–4.
3 Collin P, Pukkala E, Reunala T. Malignancy and survival in dermatitis herpetiformis: a comparison with coeliac disease. *Gut* 1996; **38**: 528–30.
4 Lear JT, Neary RH, Jones P *et al.* Risk factors for ischaemic heart disease in patients with dermatitis herpetiformis. *J R Soc Med* 1997; **90**: 247–9.
5 Askling J, Linet M, Gridley G *et al.* Cancer incidence in a population-based cohort of individuals hospitalized with celiac disease or dermatitis herpetiformis. *Gastroenterology* 2002; **123**: 1428–35.
6 Viljamaa M, Kaukinen K, Pukkala E *et al.* Malignancies and mortality in patients with coeliac disease and dermatitis herpetiformis: 30-year population-based study. *Dig Liver Dis* 2006; **38**: 374–80.

Differential diagnosis. The diagnosis should be suspected when any persistent, pruritic, symmetrical eruption resists topical treatment. In view of the pruritus and involvement of the axillary folds and buttocks, many patients are thought to have scabies, but the absence of burrows or of contact cases should help with the diagnosis. The most difficult diagnostic problem is the group of patients with chronic exudative eczema, papular urticaria and chronic prurigo, some of whom may be dapsone responsive. The histology and the lack of IgA deposition should help establish the correct diagnosis.

Treatment. The treatment of dermatitis herpetiformis has been reviewed [1]. Dapsone is the most widely used treatment for dermatitis herpetiformis. The dose needed for the average case is 100–200 mg/day but a few may require 400 mg/day. It is wise to start at 25–50 mg/day in an adult and slowly increase to a dose that keeps the patient comfortable and without significant side effects. Too rapid an increase in the dose often results in haemolytic anaemia, which does not reach its maximum for a month. A fall in haemoglobin with a low MCV indicates iron deficiency (due to intravascular haemolysis) rather than pure haemolytic anaemia. Patients at risk of glucose-6-phosphate dehydrogenase deficiency should be screened prior to treatment. Methaemoglobinaemia is common, reaching a steady state after about 2 weeks, and may cause cyanosis, breathlessness and angina. Hepatitis, the dapsone syndrome (lymphadenopathy and hepatitis) and agranulocytosis are serious, usually early complications. Motor neuropathy may occur. Most complications occur in the first 3 months. Sulfapyridine (up to 3 g/day) or sulfamethoxypyridazine 0.5–1.5 g/day is an alternative in patients who cannot tolerate dapsone; side effects include nausea, lethargy, haemolytic anaemia and bone-marrow suppression, their incidence increasing with doses above 1 g/day [2]. Although systemic corticosteroids are in the main ineffective and not indicated, topical steroids may be helpful in lessening symptoms [3]. Heparin, with or without tetracyclines, in combination with nicotinamide/niacinamide are advocated for patients who cannot tolerate dapsone or sulfonamides [4,5].

A gluten-free diet is the treatment of choice in the long term. It has been shown not only to improve the enteropathy, but also to allow discontinuation of drug therapy. The patients put on weight, lose their abdominal symptoms and often feel generally much better. In order to obtain strict adherence to the diet, the patient needs to be highly motivated, intelligent and leading a regular life. Sometimes it may be wise to postpone starting the diet until a more settled period. Wheat must be avoided, but oats certified free of gluten are usually tolerated, although a few patients may have reactions to oat proteins [3,6–8]. Unlike patients with coeliac disease, ingestion of small quantities of gluten does not always precipitate symptoms. The help of a dietician and the Coeliac Society are essential. It is usually many months and sometimes years before patients are able to reduce their dapsone requirements. Often dapsone can be discontinued altogether after 2–3 years on a strict gluten-free diet, but some patients take much longer [9]. Reintroduction of gluten in selected patients produced a relapse in skin lesions [10,11]. The gluten-free diet after 5–10 years protects patients from lymphoma, and this is an additional reason to recommend a gluten-free diet [12].

References

1 Wojnarowska F, Kirtschig G, Khumalo N. Treatment of subepidermal immunobullous diseases. *Clin Dermatol* 2001; **19**: 768–77.
2 McFadden J, Leonard J, Powles A *et al.* Sulphamethoxypyridazine for dermatitis herpetiformis, linear IgA disease and cicatricial pemphigoid. *Br J Dermatol* 1989; **121**: 759–62.
3 Arentz-Hansen H, Fleckenstein B, Molberg O *et al.* The molecular basis for oat intolerance in patients with celiac disease. *PLoS Med* 2004; **1**: e1.
4 Tan CC, Sale JE, Brammer C *et al.* A rare case of dermatitis herpetiformis requiring parenteral heparin for long-term control. *Dermatology* 1996; **192**: 185–6.
5 Shah SA, Ormerod AD. Dermatitis herpetiformis effectively treated with heparin, tetracycline and nicotinamide. *Clin Exp Dermatol* 2000; **25**: 204–5.
6 Hardman CM, Garioch JJ, Leonard JN *et al.* Absence of toxicity of oats in patients with dermatitis herpetiformis. *N Engl J Med* 1997; **337**: 1884–7.
7 Reunala T, Collin P, Holm K *et al.* Tolerance to oats in dermatitis herpetiformis. *Gut* 1998; **43**: 490–3.
8 Rashid M, Butzner D, Burrows V *et al.* Consumption of pure oats by individuals with celiac disease: a position statement by the Canadian Celiac Association. *Can J Gastroenterol* 2007; **21**: 649–51.
9 Garioch JJ, Lewis HM, Sargent SA *et al.* 25 years' experience of a gluten-free diet in the treatment of dermatitis herpetiformis. *Br J Dermatol* 1994; **131**: 541–5.
10 Harrington CI, Read NW. Dermatitis herpetiformis: effect of gluten-free diet on skin IgA and jejunal structure and function. *BMJ* 1977; **1**: 872–5.
11 Leonard J, Haffenden G, Tucker W *et al.* Gluten challenge in dermatitis herpetiformis. *N Engl J Med* 1983; **308**: 816–9.
12 Lewis HM, Renaula TL, Garioch JJ *et al.* Protective effect of gluten-free diet against development of lymphoma in dermatitis herpetiformis. *Br J Dermatol* 1996; **135**: 363–7.

CHAPTER 41
Lichen Planus and Lichenoid Disorders

S.M. Breathnach
St John's Institute of Dermatology, St Thomas' Hospital, London, UK

Definition of lichenoid eruptions, 41.1
Pathogenesis, 41.1
Incidence, 41.4
Histology, 41.4
Clinical features, 41.6
Variants, 41.9
Complications, 41.14
Associated conditions, 41.16
Differential diagnosis, 41.17
Prognosis, 41.17
Treatment, 41.17
'Mixed' LP/discoid lupus erythematosus disease patterns, 41.20
Bullous LP and LP pemphigoides, 41.20
Lichen nitidus, 41.21
Symptomatic lichenoid reactions, 41.23
LP-like contact dermatitis due to contact with colour developing agents and methacrylic acid esters, 41.23
Lichenoid eruptions due to drugs, 41.23
Nékam's disease, 41.27

Definition of lichenoid eruptions

The term 'lichenoid' is used by clinicians to describe a flat-topped, shiny, papular eruption resembling lichen planus (LP), or by histopathologists to describe a type of tissue reaction consisting principally of basal cell liquefaction and a band-like inflammatory cell infiltrate in the papillary dermis [1]. The prototype of all lichenoid eruptions is LP itself but a number of other diseases may develop a lichenoid tissue reaction [2,3] and will be discussed here. Lichenoid aspects of graft-versus-host disease are addressed in Chapters 51 and 62.

References

1 Pinkus H. Lichenoid tissue reactions. *Arch Dermatol* 1973; **107**: 840–6.
2 Weedon D. The lichenoid tissue reaction. *Int J Dermatol* 1982; **21**: 203–6.
3 Boyd AS, Neldner KH. Lichen planus. *J Am Acad Dermatol* 1991; **25**: 593–619.

Pathogenesis

Immunological aspects. LP is thought to be an immunologically mediated disorder [1], not least because a lichenoid eruption may be seen as part of graft-versus-host disease [2–4] (see Chapters 51 and 62). Cloned murine autoreactive T cells produce a lichenoid reaction in recipient animals following injection [5]. T cells, both $CD4^+$ and $CD8^+$, accumulate in the dermis, while $CD8^+$ T cells infiltrate the epidermis, in LP lesions; it has been proposed that $CD8^+$ cytotoxic T cells recognize an antigen (currently unknown) associated with the major histocompatibility complex (MHC) class I on lesional keratinocytes and lyse them [6–10]. T-cell receptor (TCR) repertoires are skewed in tissue samples and in peripheral blood mononuclear cells of patients with oral LP [11].

T cells and keratinocytes express interferon-γ (IFN-γ) and interleukin-6 (IL-6) [6], and T cells also express lymphocyte function associated antigen-1 (LFA-1) [8] and secrete IFN-γ *in vitro* [12]. Mononuclear cells infiltrating the skin, the majority of which are $CD8^+$, as well as basal keratinocytes, express tumour necrosis factor-α (TNF-α) and TNF-R1 [12]. Activated T cells secreting IFN-γ induce keratinocyte expression of human leukocyte antigen (HLA)-DR [13], and the presence of epidermotropic T cells correlates with that of HLA-DR-expressing keratinocytes and Langerhans' cells [14]. NF-kappaB-dependent inflammatory cytokines TNF-α, IL-1-α, IL-6 and IL-8 are detected at increased levels in salivary fluid and serum from patients with oral LP [15,16]. The role of chemokines in the pathophysiology of lichenoid tissue reactions in regard to recruitment and local activation of cytotoxic Th1 cells and plasmacytoid dendritic cells has recently been reviewed [17]. Infiltrating $CD8^+$ T cells, as well as keratinocytes, express a variety of different chemokines [18–20]. RANTES (regulated upon activation, normal T-cell expressed and secreted) secreted by T cells may trigger mast cell degranulation with consequent release of TNF-α, which in turn up-regulates lesional T-cell RANTES secretion; such mechanisms may contribute to chronicity of T-cell infiltration and clinical disease [21]. Lesional type I IFN cytokines produced by plasmacytoid dendritic cells play an important role in LP by recruiting autoreactive cytotoxic $CD8^+$ T lymphocytes via IP10/CXCR3 interactions [22]. Type I IFN-inducible chemokines include CXCL9, the CXCR3 ligand, which is a significant marker for LP [23], and CXCL10, which is expressed exactly where cytotoxic lymphocytes invade the basal epidermis and cause keratinocyte death [24]. IFN-γ, IL-4 and IL-18 gene polymorphisms seem to promote disease susceptibility and progression of oral lichen planus in ethnic Chinese subjects [25,26].

Keratinocytes are also type I IFN producers in LP skin lesions [23]. Keratinocyte cytokines may up-regulate expression of cell surface adhesion molecules on, and migration by, T cells [27–29]. $CD1a^+$ Langerhans' cells and factor $XIIIa^+$ cells are increased in LP [8,30,31] and may be involved in antigen presentation to T cells. Activin A, a transforming growth factor-β (TGF-β) family member induced by pro-inflammatory cytokines and which promotes Langerhans' cell differentiation and activation, is increased in the

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

upper epidermis and dermis in LP [32]. Vascular endothelial expression of the adhesion molecules intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) is also elevated [8]. Mast cell degranulation [33], and T-cell secretion of matrix metalloprotein (MMP) 9 [34], may contribute to basement membrane disruption, enabling migration of $CD8^+$ T cells into the epithelium. Granzyme B^+ T cells have been observed close to apoptotic keratinocytes [35]. Over-expression of bone morphogenic protein (BMP-4), another member of the TGF-β family, may contribute to apoptosis of epithelial cells in oral LP through up-regulation of p53, MMP1 and MMP3 [36]. Over-expression of MMP-2, MT1-MMP, and especially MMP-9, may be involved in malignant transformation in oral lichen planus [37].

References

1 Dutz JP. T-cell-mediated injury to keratinocytes: insights from animal models of the lichenoid tissue reaction. *J Invest Dermatol* 2008; **129**: 309–14.
2 Breathnach SM, Katz SI. Immunopathology of cutaneous graft-versus-host disease. *Am J Dermatopathol* 1987; **9**: 343–8.
3 Liddle BJ, Cowan MA. Lichen planus-like eruption and nail changes in a patient with graft-versus-host disease. *Br J Dermatol* 1990; **122**: 841–3.
4 Garcia F, Villalta MJ, Pascual-Lopez M *et al*. Superficial mucoceles and lichenoid graft-versus-host disease: report of three cases. *Acta Derm Venereol (Stockh)* 2002; **82**: 453–5.
5 Shiohara T. The lichenoid tissue reaction. An immunological perspective. *Am J Dermatopathol* 1988; **10**: 252–6.
6 Fayyazi A, Schweyer S, Soruri A *et al*. T lymphocytes and altered keratinocytes express interferon-γ and interleukin 6 in lichen planus. *Arch Dermatol Res* 1999; **291**: 485–90.
7 Sugerman PB, Satterwhite K, Bigby M. Autocytotoxic T-cell clones in lichen planus. *Br J Dermatol* 2000; **142**: 449–56.
8 Villarroel Dorrego M, Correnti M, Delgado R, Tapia FJ. Oral lichen planus: immunohistology of mucosal lesions. *J Oral Pathol Med* 2002; **31**: 410–4.
9 Kawamura E, Nakamura S, Sasaki M *et al*. Accumulation of oligoclonal T cells in the infiltrating lymphocytes in oral lichen planus. *J Oral Pathol Med* 2003; **32**: 282–9.
10 Sugerman PB, Savage NW, Walsh LJ *et al*. The pathogenesis of oral lichen planus. *Crit Rev Oral Biol Med* 2002; **13**: 350–65.
11 Gotoh A, Hamada Y, Shiobara N *et al*. Skew in T cell receptor usage with polyclonal expansion in lesions of oral lichen planus without hepatitis C virus infection. *Clin Exp Immunol* 2008; **154**: 192–201.
12 Khan A, Farah CS, Savage NW *et al*. Th1 cytokines in oral lichen planus. *J Oral Pathol Med* 2003; **32**: 77–83.
13 Barker JNWN, Navsaria HA, Leigh IM *et al*. Gamma-interferon induced human keratinocyte HLA-DR synthesis: the role of dermal activated T-cells. *Br J Dermatol* 1988; **119**: 567–72.
14 Shiohara T, Moriya N, Tanaka Y *et al*. Immunopathological study of lichenoid skin diseases: correlation between HLA-DR-positive keratinocytes or Langerhans cells and epidermotropic T cells. *J Am Acad Dermatol* 1988; **18**: 67–74.
15 Rhodus NL, Cheng B, Myers S *et al*. A comparison of the pro-inflammatory, NF-kappaB-dependent cytokines: TNF-alpha, IL-1-alpha, IL-6, and IL-8 in different oral fluids from oral lichen planus patients. *Clin Immunol* 2005; **114**: 278–83.
16 Zhang Y, Lin M, Zhang S *et al*. NF-kappaB-dependent cytokines in saliva and serum from patients with oral lichen planus: a study in an ethnic Chinese population. *Cytokine* 2008; **41**: 144–9.
17 Meller S, Gilliet M, Homey B. Chemokines in the pathogenesis of lichenoid tissue reactions. *J Invest Dermatol* 2008; **129**: 315–9.
18 Zhao ZZ, Sugerman PB, Walsh LJ, Savage NW. Expression of RANTES and CCR1 in oral lichen planus and association with mast cell migration. *J Oral Pathol Med* 2002; **31**: 158–62.
19 Iijima W, Ohtani H, Nakayama T *et al*. Infiltrating $CD8^+$ T cells in oral lichen planus predominantly express CCR5 and CXCR3 and carry respective chemokine ligands RANTES/CCL5 and IP-10/CXCL10 in their cytolytic granules: a potential self-recruiting mechanism. *Am J Pathol* 2003; **163**: 261–8.
20 Little MC, Griffiths CE, Watson RE *et al*. Oral mucosal keratinocytes express RANTES and ICAM-1, but not interleukin-8, in oral lichen planus and oral lichenoid reactions induced by amalgam fillings. *Clin Exp Dermatol* 2003; **28**: 64–9.
21 Zhao ZZ, Sugerman PB, Zhou XJ, Walsh LJ, Savage NW. Mast cell degranulation and the role of T cell RANTES in oral lichen planus. *Oral Dis* 2001; **7**: 246–51.
22 Wenzel J, Scheler M, Proelss J *et al*. Type I interferon-associated cytotoxic inflammation in lichen planus. *J Cutan Pathol* 2006; **33**: 672–8.
23 Wenzel J, Peters B, Zahn S *et al*. Gene expression profiling of lichen planus reflects CXCL9+-mediated inflammation and distinguishes this disease from atopic dermatitis and psoriasis. *J Invest Dermatol* 2008; **128**: 67–78.
24 Wenzel J, Tüting T. An IFN-associated cytotoxic cellular immune response against viral, self-, or tumor antigens is a common pathogenetic feature in 'interface dermatitis'. *J Invest Dermatol* 2008; **128**: 2392–402.
25 Bai J, Lin M, Zeng X *et al*. Association of polymorphisms in the human IFN-gamma and IL-4 gene with oral lichen planus: a study in an ethnic Chinese cohort. *J Interferon Cytokine Res* 2008; **28**: 351–8.
26 Bai J, Zhang Y, Lin M *et al*. Interleukin-18 gene polymorphisms and haplotypes in patients with oral lichen planus: a study in an ethnic Chinese cohort. *Tissue Antigens* 2007; **70**: 390–7.
27 Shiohara T, Moriya N, Nagashima M. The lichenoid tissue reaction: a new concept of pathogenesis. *Int J Dermatol* 1988; **27**: 365–74.
28 Yamamoto T, Osaki T. Characteristic cytokines generated by keratinocytes and mononuclear infiltrates in oral lichen planus. *J Invest Dermatol* 1995; **104**: 784–8.
29 Yamamoto T, Nakane T, Osaki T. The mechanism of mononuclear cell infiltration in oral lichen planus: the role of cytokines released from keratinocytes. *J Clin Immunol* 2000; **20**: 294–305.
30 Hasseus B, Jontell M, Brune M *et al*. Langerhans cells and T cells in oral graft-versus-host disease and oral lichen planus. *Scand J Immunol* 2001; **54**: 516–24.
31 Deguchi M, Aiba S, Ohtani H *et al*. Comparison of the distribution and numbers of antigen-presenting cells among T-lymphocyte-mediated dermatoses: $CD1a^+$, factor $XIIIa^+$, and $CD68^+$ cells in eczematous dermatitis, psoriasis, lichen planus and graft-versus-host disease. *Arch Dermatol Res* 2002; **294**: 297–302.
32 Musso T, Scutera S, Vermi W *et al*. Activin A induces Langerhans cell differentiation *in vitro* and in human skin explants. *PLoS ONE* 2008; **3**: e3271.
33 Zhou XJ, Sugerman PB, Savage NW *et al*. Intra-epithelial $CD8^+$ T cells and basement membrane disruption in oral lichen planus. *J Oral Pathol Med* 2002; **31**: 23–7.
34 Zhou XJ, Sugerman PB, Savage NW, Walsh LJ. Matrix metalloproteinases and their inhibitors in oral lichen planus. *J Cutan Pathol* 2001; **28**: 72–82.
35 Ammar M, Mokni M, Boubaker S *et al*. Involvement of granzyme B and granulysin in the cytotoxic response in lichen planus. *J Cutan Pathol* 2008; **35**: 630–4.
36 Kim SG, Chae CH, Cho BO *et al*. Apoptosis of oral epithelial cells in oral lichen planus caused by upregulation of BMP-4. *J Oral Pathol Med* 2006; **35**: 37–45.
37 Chen Y, Zhang W, Geng N *et al*. MMPs, TIMP-2, and TGF-beta1 in the cancerization of oral lichen planus. *Head Neck* 2008; **30**: 1237–45.

Genetics. There may be a genetic susceptibility to idiopathic LP. Familial cases are reported [1–6], and a familial incidence of 10.7% was quoted in one series [4]. LP has also been reported in monozygotic twins [7,8]. An association with HLA-3 and HLA-5 has been documented [9], although others found no such association [10,11], as have associations with HLA-B7 [1], HLA-28 in Jews with LP and carbohydrate intolerance [12], HLA-DR1 [13], HLA-DR10 [14], and HLA-DRB1*0101 [15]. Genetic heterogeneity in LP has led to a suggestion that idiopathic cutaneous, and purely mucosal, LP may each have a different pathogenesis [16].

Viruses. An epidemiological association of LP with hepatitis C virus (HCV) infection has been recorded, especially in patients from Italy, certain parts of France, Spain, Japan and Pakistan [17–24], and HCV RNA has been isolated from lesional skin in patients with LP and chronic HCV infection [25,26]. Thus, an HCV-related

product has been postulated as a possible antigen in LP. However, no association between LP and HCV infection has been noted in patients from Northern Europe including the UK, the USA or Nepal [24,27–31]. It has been suggested that the observed geographical differences with regard to HCV infection and LP could be related to immunogenetic factors such as the HLA-DR6 allele, significantly expressed in Italian patients with oral LP and HCV infection [17,18]. LP has been associated with human herpesvirus type 7 replication [32].

Dental amalgam. Another putative antigen in oral LP is mercury in dental amalgam; 87–97% of patients with oral LP associated with dental amalgam fillings benefit from amalgam removal [33–38], but only 28–39% have positive patch test reactions to amalgam or inorganic mercury. Patients who improve following removal of amalgam, but in whom patch testing is negative, are presumed to have an irritant reaction to amalgam. A recent study reported that the presence of amalgam or of gold is not associated with an increased risk of oral LP, but corrosion of amalgams, and a 'galvanic effect' from dissimilar dental materials in continuous contact with the mucosa (bimetallism) are associated with an elevated risk of oral LP [39].

Miscellaneous. LP has been induced by radiotherapy [40], and has been reported to have been confined to a radiation field [41]. Anxiety and depression [42] and stress [43] may be risk factors for the development of LP.

References

1 Copeman PWM, Tan RSH, Timlin D *et al*. Familial lichen planus. *Br J Dermatol* 1978; **98**: 573–7.
2 Malhotra YK, Kanwar AJ. Familial lichen planus. *Arch Dermatol* 1980; **116**: 622.
3 Grunnet N, Schmidt H. Occurrence of lichen planus in a family. Genetic susceptibility or coincidence? *Clin Exp Dermatol* 1983; **8**: 397–400.
4 Kofoed ML, Lange Wantzin G. Familial lichen planus—more frequent than previously suggested? *J Am Acad Dermatol* 1985; **13**: 50–4.
5 Katzenelson V, Lotem M, Sandbank M. Familial lichen planus. *Dermatologica* 1990; **180**: 166–8.
6 Sandhu K, Handa S, Kanwar AJ. Familial lichen planus. *Pediatr Dermatol* 2003; **20**: 186.
7 Gibstine CF, Esterly NB. Lichen planus in monozygotic twins. *Arch Dermatol* 1984; **120**: 580.
8 Graells J, Notario J, Badia F. Lichen planus in monozygotic twins. *Clin Exp Dermatol* 1998; **23**: 299.
9 Lowe NJ, Cudworth AG, Woodrow JC. HLA antigens in lichen planus. *Br J Dermatol* 1976; **95**: 169–71.
10 Saurat JH, Lemarchand F, Hors J *et al*. HLA markers and lymphocytotoxins in lichen planus. *Arch Dermatol* 1977; **113**: 1719–20.
11 Veien NK, Risum G, Jorgensen HP *et al*. HLA antigens in patients with lichen planus. *Acta Derm Venereol (Stockh)* 1979; **59**: 205–9.
12 Halery S, Feuerman EJ. Abnormal glucose tolerance associated with lichen planus. *Acta Derm Venereol (Stockh)* 1979; **59**: 167–70.
13 Valsecchi R, Bontempelli M, Rossi A *et al*. HLA-DR and DQ antigens in lichen planus. *Acta Derm Venereol (Stockh)* 1988; **68**: 77–80.
14 White AG, Rostom AI. HLA antigens in Arabs with lichen planus. *Clin Exp Dermatol* 1994; **19**: 236–7.
15 Luis-Montoya P, Yamamoto-Furusho JK, Vega-Memije E *et al*. HLA-DRB1*0101 is associated with the genetic susceptibility to develop lichen planus in the Mexican Mestizo population. *Arch Dermatol Res* 2007; **299**: 405–7.
16 Nasa GL, Cottoni F, Mulargia M *et al*. HLA antigen distribution in different clinical subgroups demonstrates genetic heterogeneity in lichen planus. *Br J Dermatol* 1995; **132**: 897–900.
17 Carrozzo M, Francia Di Celle P, Gandolfo S *et al*. Increased frequency of HLA-DR6 allele in Italian patients with hepatitis C virus-associated oral lichen planus. *Br J Dermatol* 2001; **144**: 803–8.
18 Carrozzo M, Gandolfo S. Oral diseases possibly associated with hepatitis C virus. *Crit Rev Oral Biol Med* 2003; **14**: 115–27.
19 Jubert C, Pawlotsky JM, Pouget F. Lichen planus and hepatitis (virus-related chronic active hepatitis). *Arch Dermatol* 1994; **130**: 73–6.
20 Cribier B, Garnier C, Laustriat D, Heid E. Lichen planus and hepatitis C virus infection: an epidemiologic study. *J Am Acad Dermatol* 1994; **31**: 1070–2.
21 Sanchez-Perez J, De Castro M, Buezo GF *et al*. Lichen planus and hepatitis C virus: prevalence and clinical presentation of patients with lichen planus and hepatitis C infection. *Br J Dermatol* 1996; **134**: 715–9.
22 Mahboob A, Haroon TS, Iqbal Z, Iqbal F, Butt AK. Frequency of anti-HCV antibodies in patients with lichen planus. *J Coll Physicians Surg Pak* 2003; **13**: 248–51.
23 Nocente R, Ceccanti M, Bertazzoni G *et al*. HCV infection and extrahepatic manifestations. *Hepatogastroenterology* 2003; **50**: 1149–54.
24 Carrozzo M. Oral diseases associated with hepatitis C virus infection. Part 2: lichen planus and other diseases. *Oral Dis* 2008; **14**: 217–28.
25 Lazaro P, Olalquiaga J, Bartolome J *et al*. Detection of hepatitis C virus RNA and core protein in keratinocytes from patients with cutaneous lichen planus and chronic hepatitis C. *J Invest Dermatol* 2002; **119**: 798–803.
26 Kurokawa M, Hidaka T, Sasaki H *et al*. Analysis of hepatitis C virus (HCV) RNA in the lesions of lichen planus in patients with chronic hepatitis C. Detection of anti-genomic as well as genomic-strand HCV RNAs in lichen planus lesions. *J Dermatol Sci* 2003; **32**: 65–70.
27 Chuang TY, Stitle L, Brashear R, Lewis C. Hepatitis C virus and lichen planus. A case-control study of 340 patients. *J Am Acad Dermatol* 1999; **41**: 787–9.
28 Tucker SC, Coulson IH. Lichen planus is not associated with hepatitis C virus infection in patients from north west England. *Acta Derm Venereol (Stockh)* 1999; **79**: 378–9.
29 Roy KM, Dickson EM, Staines KS, Bagg J. Hepatitis C virus and oral lichen planus/lichenoid reactions: lack of evidence for an association. *Clin Lab* 2000; **46**: 251–4.
30 Eisen D. The clinical features, malignant potential, and systemic associations of oral lichen planus. A study of 723 patients. *J Am Acad Dermatol* 2002; **46**: 207–14.
31 Garg VK, Karki BM, Agrawal S *et al*. A study from Nepal showing no correlation between lichen planus and hepatitis B and C viruses. *J Dermatol* 2002; **29**: 411–3.
32 De Vries HJ, van Marle J, Teunissen MB *et al*. Lichen planus is associated with human herpesvirus type 7 replication and infiltration of plasmacytoid dendritic cells. *Br J Dermatol* 2006; **154**: 361–4.
33 Dunsche A, Kästel A, Terheyden H *et al*. Oral lichenoid reations associated with amalgam: improvement after amalgam removal. *Br J Dermatol* 2003; **148**: 70–6.
34 Dunsche A, Frank MP, Luttges J *et al*. Lichenoid reactions of murine mucosa associated with amalgam. *Br J Dermatol* 2003; **148**: 741–8.
35 Wong L, Freeman S. Oral lichenoid lesions (OLL) and mercury in amalgam fillings. *Contact Dermatitis* 2003; **48**: 74–9.
36 Thornhill MH, Pemberton MN, Simmons RK, Theaker ED. Amalgam contact hypersensitivity lesions and oral lichen planus. *Oral Surg Oral Med Oral Pathol* 2003; **95**: 291–9.
37 Laeijendecker R, Dekker SK, Burger PM *et al*. Oral lichen planus and allergy to dental amalgam restorations. *Arch Dermatol* 2004; **140**: 1434–8.
38 Pezelj-Ribari S, Prpi J, Mileti I *et al*. Association between oral lichenoid reactions and amalgam restorations. *J Eur Acad Dermatol Venereol* 2008; **22**: 1163–7.
39 Martin MD, Broughton S, Drangsholt M. Oral lichen planus and dental materials: a case-control study. *Contact Dermatitis* 2003; **48**: 331–6.
40 Pretel M, España A. Lichen planus induced by radiotherapy. *Clin Exp Dermatol* 2007; **32**: 582–3.
41 Shurman D, Reich HL, James WD. Lichen planus confined to a radiation field: the 'isoradiotopic' response. *J Am Acad Dermatol* 2004; **50**: 482–3.
42 Vallejo MJ, Huerta G, Cerero R, Seoane JM. Anxiety and depression as risk factors for oral lichen planus. *Dermatology* 2001; **203**: 303–7.
43 Manolache L, Seceleanu-Petrescu D, Benea V. Lichen planus patients and stressful events. *J Eur Acad Dermatol Venereol* 2008; **22**: 437–41.

Incidence

LP has a worldwide distribution with no overt racial predisposition. LP represented about 1.2% of all new patients in London [1] and Turin [2], 0.9% in Copenhagen [3] and 0.38% in India [4]. Hypertrophic cases were reportedly common in Nigeria [5]. Both oral and cutaneous LP have rarely been reported in childhood [3,6–13]. Familial cases are recorded (see above). There was an over-representation of South Asians in a series of childhood cases in Birmingham, UK [13].

References

1 Calnan CD, Meara RH. St John's Hospital diagnostic index. *Trans Rep St John's Hosp Derm Soc Lond* 1957; **39**: 56–68.
2 Depaoli M. Lichen ruber planus, clinical and statistical features. *Minerva Dermatol* 1964; **39**: 166–71.
3 Schmidt H. Frequency, duration and localisation of lichen planus. A study based on 181 patients. *Acta Derm Venereol (Stockh)* 1961; **41**: 164–7.
4 Bhattacharya M, Kaur I, Kumar B. Lichen planus: a clinical and epidemiological study. *J Dermatol* 2000; **27**: 576–82.
5 Harman RRM. Letter from Ibadan. *Br J Dermatol* 1962; **74**: 416–20.
6 Kanwar AJ, Handa S, Ghosh S *et al*. Lichen planus in childhood: a report of 17 patients. *Pediatr Dermatol* 1991; **8**: 288–91.
7 Milligan A, Graham Brown RAC. Lichen planus in children—a review of six cases. *Clin Exp Dermatol* 1990; **15**: 340–2.
8 Scully C, de Almeide OP, Welbury R. Oral lichen planus in childhood. *Br J Dermatol* 1994; **130**: 131–3.
9 Sharma R, Maheshwari V. Childhood lichen planus: a report of fifty cases. *Pediatr Dermatol* 1999; **16**: 345–8.
10 Rybojad M, Moraillon I, Cordoliani F *et al*. Lichen planus in the child: 25 cases. Clinical, follow-up and therapeutic aspects. *Ann Dermatol Vénéréol* 2000; **127**: 661.
11 Nanda A, Al-Ajmi HS, Al-Sabah H *et al*. Childhood lichen planus: a report of 23 cases. *Pediatr Dermatol* 2001; **18**: 1–4.
12 Handa S, Sahoo B. Childhood lichen planus. A study of 87 cases. *Int J Dermatol* 2002; **41**: 423–7.
13 Balasubramaniam P, Ogboli M, Moss C. Lichen planus in children: review of 26 cases. *Clin Exp Dermatol* 2008; **33**: 457–9.

Histology [1,2]

The earliest finding is an increase in epidermal Langerhans' cells [1], associated with a superficial perivascular infiltrate of lymphocytes and histiocytes, impinging on the dermal–epidermal junction (DEJ). Mild spongiosis is followed by vacuolar alteration and clefting along the DEJ, with accumulation of necrotic keratinocytes (colloid bodies) [3].

The characteristic histological changes are best seen in biopsies of fully developed LP papules [4] (Fig. 41.1). The centre of the papule shows irregular acanthosis of the epidermis, irregular thickening of the granular layer, and compact hyperkeratosis. The mid-epidermal cells appear larger, flatter and paler than usual [4]. In oral LP, epithelial proliferation is increased [5]. Parakeratosis is rarely found in idiopathic LP, in contrast to some drug-induced lichenoid tissue reactions. A focal increase in thickness of the granular layer and infiltrate corresponds to the presence of Wickham's striae [6]. Degenerating basal epidermal cells are transformed into *colloid bodies* (15–20 μm diameter) which appear singly or in clumps [7–9]. The rete ridges may appear flattened or effaced (*'saw-tooth' appearance*), and focal separation from the dermis may lead to Max Joseph spaces (Fig. 41.2). In older or hypertrophic lesions, the number of colloid bodies is considerably reduced. In 'active' LP, a *band-like infiltrate* of lymphocytes and histiocytes, rarely admixed with plasma cells [10,11], obliterates the DEJ. Epidermal melanocytes are absent or considerably decreased in number [4], while *pigmentary incontinence* with dermal melanophages is characteristic. When the disease is becoming inactive, the infiltrate, with melanophages, becomes sparser and is arranged around papillary blood vessels, which may show ectasia and surrounding fibroplasia.

In hypertrophic LP, the epidermis may show a pseudoepitheliomatous appearance with extreme irregular acanthosis. Follicles

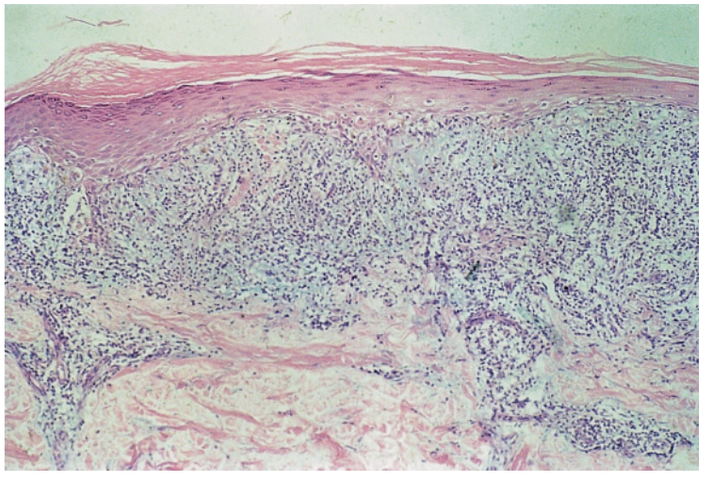


Fig. 41.1 Lichen planus, typical histology. H&E × 40. (Courtesy of St John's Institute of Dermatology, King's College London, UK.)

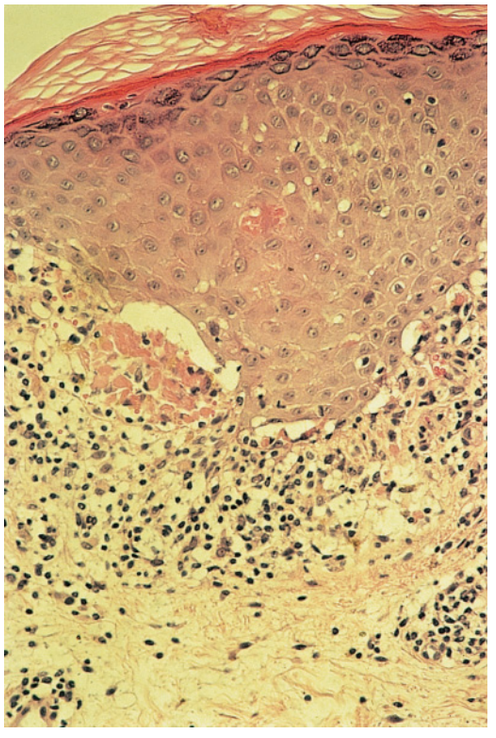


Fig. 41.2 Lichen planus. Photomicrograph to show clumps of cytoid bodies. H&E × 100. (Courtesy of St John's Institute of Dermatology, King's College London, UK.)



Fig. 41.3 Lichen planus. Photomicrograph of follicular lesion. Scanning view. H&E × 20. (Courtesy of St John's Institute of Dermatology, King's College London, UK.)

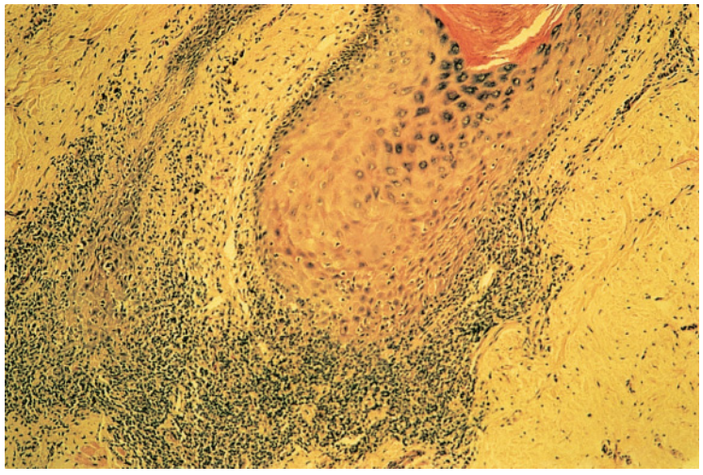


Fig. 41.4 Lichen planus. Photomicrograph of follicular lesion. Higher power, H&E × 40. (Courtesy of St John's Institute of Dermatology, King's College London, UK.)

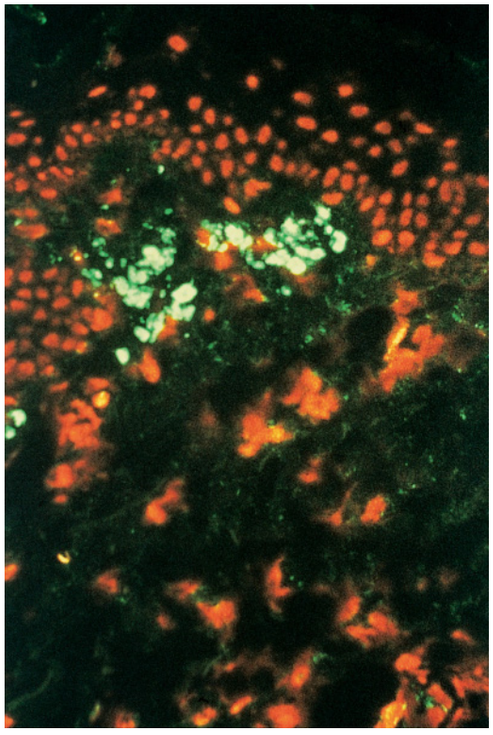


Fig. 41.5 Lichen planus. Photomicrograph of direct immunofluorescence. Bright fluorescence of cytoid bodies with anti-IgM × 100. (Courtesy of St John's Institute of Dermatology, King's College London, UK.)

may be expanded and at times have a 'cyst-like' appearance. The infiltrate may not appear very 'band-like', but serial sections will usually show foci of basal cell liquefaction and colloid body formation, often around the follicular epithelium. Long-standing cases usually demonstrate coexistent dermal fibrosis adjacent to the inflammatory changes.

In atrophic LP, the epidermis may be greatly thinned almost to the level of the granular layer, although relatively compact hyperkeratosis remains. The rete ridges are usually completely effaced with relatively few colloid bodies. The papillary dermis shows fibrosis and loss of elastica.

In follicular lesions (Figs 41.3 & 41.4), an infiltrate extends around, and may permeate, the base of the hair follicle epithelium, with follicular keratin plugging [12,13].

In mucosal LP, the epithelium is usually thinned with parakeratosis, although both types of keratinization may be seen [14]; the epithelium may resemble epidermis from skin, plasma cells may be prominent in the 'band-like' infiltrate, and colloid bodies are fewer than in typical cutaneous papular LP. The erythematous subtype of oral LP is associated with increased cell proliferation compared with the reticular form [15]. Moderate or severe epithelial dysplasia on oral biopsy should probably be regarded as an increased risk for subsequent cancer development [16].

Bullous LP is rare; blister formation takes place predominantly between the basal lamina and cytomembranes of basal keratinocytes (i.e. intrabasal) [7], such that there is a wide separation between the epidermis and infiltrate.

Direct immunofluorescence (IMF) shows globular deposits of IgM (Fig. 41.5), and occasionally IgG and IgA, representing apoptotic keratinocytes, around the DEJ and lower epidermis, with fibrin deposition at the region of the DEJ [17–19]. Direct IMF studies may be useful in differentiating LP from lupus erythematosus or LP pemphigoides [20,21], and can be carried out on routine histological material [22].

A clinicopathological study of lichenoid dermatitis concluded that it was usually possible to provide a specific diagnosis [23]. Occasionally, lichenoid dermatitis can become generalized and

clinically mimic an exfoliative dermatitis; such eruptions are usually triggered by drugs [24].

Benign lichenoid keratoses (BLKs) are usually solitary but may be multiple [25–27], and show characteristic lichenoid infiltrates of lymphocytes, occasional parakeratosis, and apoptotic bodies in the epidermis without nuclear atypia of keratinocytes; rarely, the histology may show features of mycosis fungoides [28]. Malignant melanoma may be associated with a lichenoid tissue reaction [29], and melanoma *in situ* with lichenoid regression may mimic a BLK histologically [30].

References

1 Ragaz A, Ackerman AB. Evolution, maturation and regression of lesions of lichen planus. *Am J Dermatopathol* 1981; **3**: 5–25.
2 Patterson JW. The spectrum of lichenoid dermatitis. *J Cutan Pathol* 1991; **18**: 67–74.
3 Neppelberg E, Johannessen AC, Jonsson R. Apoptosis in oral lichen planus. *Eur J Oral Sci* 2001; **109**: 361–4.
4 Black MM, Wilson Jones E. The role of the epidermis in the histopathogenesis of lichen planus. *Arch Dermatol* 1972; **105**: 81–6.
5 da Silva Fonseca LM, do Carmo MA. Identification of the AgNORs, PCNA and ck16 proteins in oral lichen planus lesions. *Oral Dis* 2001; **7**: 344–8.
6 Summerly R, Wilson Jones E. The micro-architecture of Wickham's striae. *Trans Rep St John's Hosp Derm Soc Lond* 1964; **50**: 157–61.
7 Ebner H, Erlach E, Gebhart W. Untersuchurgen uber die Blasenbildung bein Lichen ruber planus. *Arch Dermatol Forsch* 1973; **247**: 193–205.
8 Ebner H, Gebhart W. Light and electronmicroscopic differentiation of amyloid and colloid and hyaline bodies. *Br J Dermatol* 1975; **92**: 637–45.
9 Ebner H, Gebhart W. Light and electron microscopic studies on colloid and other cytoid bodies. *Clin Exp Dermatol* 1977; **2**: 311–22.
10 Lupton GP, Goette DK. Lichen planus with plasma cell infiltrate. *Arch Dermatol* 1981; **117**: 124–5.
11 Roustan G, Hospital M, Villegas C *et al*. Lichen planus with predominant plasma cell infiltrate. *Am J Dermatopathol* 1994; **16**: 311–4.
12 Horn RT, Goette DK, Odom RB *et al*. Immunofluorescent findings and clinical overlap in two cases of follicular lichen planus. *J Am Acad Dermatol* 1982; **7**: 203–7.
13 Matta M, Kibbi AG, Khattar J *et al*. Lichen planopilaris: a clinicopathologic study. *J Am Acad Dermatol* 1990; **22**: 594–8.
14 Shklar G. Erosive and bullous oral lesions of lichen planus. *Arch Dermatol* 1968; **97**: 411–6.
15 Karatsaidis A, Schreurs O, Helgeland K *et al*. Erythematous and reticular forms of oral lichen planus and oral lichenoid reactions differ in pathological features related to disease activity. *J Oral Pathol Med* 2003; **32**: 275–81.
16 Odukoya O, Gallagher G, Shklar G. A histologic study of epithelial dysplasia in oral lichen planus. *Arch Dermatol* 1985; **121**: 1132–6.
17 Abell E, Presbury DGC, Marks R *et al*. The diagnostic significance of immunoglobulin and fibrin deposition in lichen planus. *Br J Dermatol* 1975; **93**: 17–24.
18 Bergfeld WF, Valenzuela R, Beutner EH. Lichen planus. In: Beutner EH, Chorzelski TP, Kumar V, eds. *Immunopathology of the Skin*, 3rd edn. New York: Churchill Livingstone, 1987: 647–58.
19 Kulthanan K, Jiamton S, Varothai S *et al*. Direct immunofluorescence study in patients with lichen planus. *Int J Dermatol* 2007; **46**: 1237–41.
20 Camisa C, Neff GC, Olsen AG. Use of indirect immunofluorescence in lupus erythematosus/lichen planus overlap syndrome: an additional diagnostic clue. *J Am Acad Dermatol* 1984; **11**: 1050–9.
21 Camisa C, Nesbitt LT Jr, Brantley JB. Lichen planus pemphigoides: clinical and immunofluorescence findings in four cases. *J Am Acad Dermatol* 1983; **8**: 331–6.
22 Kolde G, Wesendahl C, Stein H, Reichart PA. Oral lichen planus: diagnostic immunofluorescence testing on routine histological material. *Br J Dermatol* 2003; **148**: 374–6.
23 Oliver GF, Winkelmann RK, Muller SA. Lichenoid dermatitis. A clinicopathologic and immunopathologic review of sixty-two cases. *J Am Acad Dermatol* 1989; **21**: 284–92.
24 Patterson JW, Berry AD, Darwin BS *et al*. Lichenoid histopathological changes in patients with clinical diagnoses of exfoliative dermatitis. *Am J Dermatopathol* 1991; **13**: 358–64.
25 Jang KA, Kim SH, Choi JH *et al*. Lichenoid keratosis. A clinicopathologic study of 17 patients. *J Am Acad Dermatol* 2000; **43**: 511–6.
26 Morgan MB, Stevens GL, Switlyk S. Benign lichenoid keratosis: a clinical and pathologic reappraisal of 1040 cases. *Am J Dermatopathol* 2005; **27**: 387–92.
27 Toll A, Gilaberte M, Gallardo F *et al*. Multiple and extensive lichen planus-like keratoses: an underestimated cutaneous eruption observed in patients with intense sun damage. *J Eur Acad Dermatol Venereol* 2006; **20**: 472–3.
28 Al-Hoqail IA, Crawford RI. Benign lichenoid keratoses with histologic features of mycosis fungoides: clinicopathologic description of a clinically significant histologic pattern. *J Cutan Pathol* 2002; **29**: 291–4.
29 Dalton SR, Baptista MA, Libow LF, Elston DM. Lichenoid tissue reaction in malignant melanoma: a potential diagnostic pitfall. *Am J Clin Pathol* 2002; **117**: 766–70.
30 Dalton SR, Fillman EP, Altman CE *et al*. Atypical junctional melanocytic proliferations in benign lichenoid keratosis. *Hum Pathol* 2003; **34**: 706–9.

Clinical features

LP is characterized by shiny, violaceous, flat-topped polygonal papules which retain the skin lines, and which vary in size from pinpoint to a centimetre or more across; they may be closely aggregated or widely dispersed. The size of the papules is often fairly uniform in an individual patient, but minute and large papules coexist in some cases. White lines, known as Wickham's striae [1] (Fig. 41.6), may traverse the surface of the papules. Papules can remain discrete or appear in groups, in lines or in circles. Linear lesions often appear along scratch marks or in scars (Koebner phenomenon) (Fig. 41.7), while annular lesions may be formed either by groups of papules arranged in rings or by single, large papules clearing in the centre and leaving an active margin.



Fig. 41.6 Lichen planus. Close up to show Wickham's striae. (Courtesy of St John's Institute of Dermatology, King's College London, UK.)



Fig. 41.7 Lichen planus papules showing Koebner effect. (Courtesy of St John's Institute of Dermatology, King's College London, UK.)



Fig. 41.8 Lichen planus. Annular lesion on shaft of penis. (Courtesy of St John's Institute of Dermatology, King's College London, UK.)

Annular lesions are especially common on the penis (Fig. 41.8) and rarely may be the predominant type of lesion present, leading to atrophy later [2].

A variant in which groups of 'spiny' lesions resembling keratosis pilaris develop around hair follicles (lichen planopilaris) (Fig. 41.9) is not uncommon. Lichen planopilaris more often forms only a minor feature of the disease, but occasionally this type of lesion may predominate.

Although a few cases evolve rapidly and clear within a few weeks, the onset is usually insidious. In most cases, the papules eventually flatten after a few months, often to be replaced by an area of pigmentation that retains the shape of the papule and persists for months or years. There may be a gradual change in colour from pink to blue to black. The residual pigmentation may be intense, especially in dark-skinned races, or almost imperceptible in fair-skinned individuals. New papules may form while others are clearing. Some papules persist much longer, enlarge and thicken, and develop a roughened surface with a prominent violaceous hue, so-called hypertrophic LP. Such lesions may resolve with atrophy or scarring. More warty lesions are seen occasionally. Areas of pigment loss are described in black South Africans [3]. Co-localization of LP and vitiligo has been reported [4].

LP can affect any part of the body surface, but is most often seen on the volar aspect of the wrists (Fig. 41.10), the lumbar region and around the ankles. The ankles and shins are the commonest sites for hypertrophic lesions. When the palms and soles are affected, the lesions tend to be firm and rough with a yellowish hue (Fig. 41.11) [5,6]. A rare, erosive, flexural variant of LP has



Fig. 41.9 Lichen planopilaris. Hyperpigmented follicular 'plugged' lesions in frontal scalp hairline. (Courtesy of St John's Institute of Dermatology, King's College London, UK.)

been described [7]. Isolated lesions of LP have been reported to involve one or both eyelids [8,9] or the lips [10–12]. Milia have been recorded in LP [13], and LP was confined to a radiation therapy site in one patient [14].

Mucous membrane lesions are very common, occurring in 30–70% of cases, and may be present without evidence of skin lesions. They are, however, much less common in black people. The buccal mucosa and tongue are most often involved, but lesions may be found around the anus, on the genitalia, in the larynx and, very



Fig. 41.10 Lichen planus. Classical eruption on volar aspect of wrist. (Courtesy of St John's Institute of Dermatology, King's College London, UK.)



Fig. 41.11 Lichen planus of palm showing hyperkeratosis and a yellow colour. (Courtesy of St John's Institute of Dermatology, King's College London, UK.)

rarely, on the tympanic membrane of the ears or even in the oesophagus. White streaks, often forming a lacework, on the buccal mucosa are highly characteristic (Fig. 41.12). They may be seen on the inner surface of the cheeks, on the gum margins or on the lips. On the tongue, the lesions are usually in the form of fixed, white plaques, often slightly depressed below the surrounding normal mucous membrane, especially on the upper surface and edges (Fig. 41.13). Ulcerative lesions in the mouth are uncommon, but may be the site of epitheliomatous transformation (Fig. 41.14). There may be striking pigmentation of oral LP in darkly



Fig. 41.12 Lichen planus on buccal mucosa showing a lacework of white streaks. (Courtesy of St John's Institute of Dermatology, King's College London, UK.)



Fig. 41.13 Lichen planus of tongue showing irregular, fixed, white plaques. (Courtesy of St John's Institute of Dermatology, King's College London, UK.)

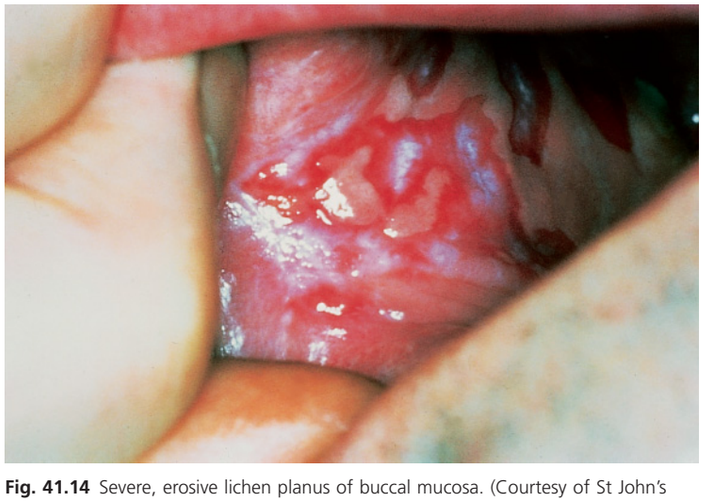


Fig. 41.14 Severe, erosive lichen planus of buccal mucosa. (Courtesy of St John's Institute of Dermatology, King's College London, UK.)

pigmented races [15]. Diabetes is a possible associated disease of oral LP [16,17], and candidiasis may coexist with LP in some patients.

Itching is a fairly consistent feature in LP and ranges from occasional mild irritation to more or less continuous, severe itching, which interferes with sleep and makes life almost intolerable; occasionally, itching is completely absent. Hypertrophic lesions usually itch severely. Paradoxically, there is seldom evidence of scratching, as the patient rubs, rather than scratches, to gain relief. Itching at sites without visible skin lesions can occur. Burning and stinging are less common complaints. In the mouth, the patient may complain of discomfort, stinging or pain; ulcerated lesions are especially painful. Great discomfort may be caused by hot foods and drinks.

References

1 Rivers JK, Jackson R, Orizaga M. Who was Wickham and what are his striae? *Int J Dermatol* 1986; **25**: 611–3.
2 Friedman DB, Hashimoto K. Annular atrophic lichen planus. *J Am Acad Dermatol* 1991; **25**: 392–4.
3 Dogliotti M, Schmaman A. Aspetti clinicoistologici del lichen planus nei negri sudafricani. *G Ital Dermatol* 1975; **110**: 174–82.
4 Anstey A, Marks R. Colocalization of lichen planus and vitiligo. *Br J Dermatol* 1993; **128**: 103–4.
5 Mugoni MG, Monteso MA, Cottoni F. Lichen planus on the palms and soles. *J Eur Acad Dermatol Venereol* 1994; **3**: 535–40.
6 Sánchez-Pérez J, Rios Buceta L, Fraga J, García-Díez A. Lichen planus with lesions on the palms and/or soles. Prevalence and clinicopathological study of 36 patients. *Br J Dermatol* 2000; **142**: 310–4.
7 Higgins CR, Handfield-Jones S, Black MM. Erosive, flexural lichen planus—an uncommon variant. *Clin Exp Dermatol* 1993; **18**: 169–70.
8 Vogel PS, James WD. Lichen planus of the eyelid: an unusual clinical presentation. *J Am Acad Dermatol* 1992; **27**: 638–9.
9 Sharma R, Singhal N. Lichen planus of the eyelids. A report of 5 cases. *Dermatol Online J* 2001; **7**: 5.
10 Itin PH, Schiller P, Gilli L *et al*. Isolated lichen planus of the lip. *Br J Dermatol* 1995; **132**: 1000–2.
11 Cecchi R, Giomi A. Isolated lichen planus of the lip. *Australas J Dermatol* 2002; **43**: 309–10.
12 Yu TC, Kelly SC, Weinberg JM, Scheinfeld NS. Isolated lichen planus of the lower lip. *Cutis* 2003; **71**: 210–2.
13 Lucke T, Fallowfield M, Burden D. Lichen planus associated with milia. *Clin Exp Dermatol* 1999; **24**: 266–9.
14 Kim JH, Krivda SJ. Lichen planus confined to a radiation therapy site. *J Am Acad Dermatol* 2002; **46**: 604–5.
15 Kanwar AJ, Ghosh S, Dhar S *et al*. Oral lesions of lichen planus. *Int J Dermatol* 1993; **32**: 76.
16 Hornstein OP, Stuhler C, Schirner E *et al*. Lichen ruber and diabetes mellitus: pathogenetic relationships. *Hautarzt* 1984; **35**: 287–91.
17 Smith MJA. Oral lichen planus and diabetes mellitus. *J Oral Med* 1977; **32**: 110–2.

Variants

LP principally involving mucous membranes

Lesions confined to the mouth, or with minimal accompanying skin involvement, are not uncommon [1–6], and account for about 15% of all cases [1]. The prevalence of oral LP was 1.5% among the villagers of Kerala in southern India [7], possibly related to chewing tobacco, and ranges between 0.5% and 2.2% of the population in other epidemiological studies [2,8]. The lesions do not differ from those found in connection with skin lesions, but, being confined to the mouth, may lead to great difficulty in diagnosis. They are often referred first to a dental surgeon. Distinct clinical subtypes such as reticular, atrophic, hypertrophic and erosive forms are well recognized; more than one type may be present [2]. On the tongue and buccal mucosa, they are most likely to be mistaken for leukoplakia and on the gum margin for gingivitis or chronic candidiasis, or the latter may coexist. Other conditions that must be excluded are 'smoker's patches', which characteristically involve the palate, and white-sponge naevi, in which the mucous membrane is thickened, irregularly folded and feels soft to the touch. These occur mainly on the floor of the mouth and histologically many of the prickle cells are vacuolated. It is important to bear in mind the possibility of a lichenoid drug reaction in patients with oral lichenoid changes (see below). Oral lichenoid reactions may be asymmetrical on the buccal mucosa and occur adjacent to dental amalgam fillings. If patch testing reveals mercury allergy, changing to another type of filling may prove beneficial [9–14].

Very occasionally, LP lesions extend to the larynx or oesophagus [15–19]. Oesophageal LP may result in dysphagia and the formation of benign strictures.

In young men, the lesions are sometimes restricted to the genitalia and/or the mouth [20,21]. Genital lesions, which are usually characteristic, may be present on the penile shaft (see Fig. 41.8), glans penis, prepuce or scrotum. Ulceration is very unlikely, and syphilis can usually be excluded without difficulty; the presence of buccal mucosal lesions will usually confirm the diagnosis. Circumcision may be helpful [20].

Lesions on the female genitalia are fairly common [22–29]; they may occur alone, be combined with lesions in the mouth only, or be part of widespread involvement. The clinical presentation of LP of the vulva spans a spectrum from subtle, fine, reticulate papules to severe erosive disease accompanied by dyspareunia, scarring and loss of the normal vulvar architecture. The condition should be distinguished from lichen sclerosus or leukoplakia, but this may be difficult when there is coexisting atrophy or vaginal stenosis. The association of erosive LP of the vulva and vagina with desquamative gingivitis has been termed the *vulvovaginal–gingival syndrome* [21,23] (Fig. 41.15). Coexisting vulval lichen sclerosus and lichenoid oral lesions have been described [30].

References

1 Warin RP, Crabb HSM, Darling AI. Lichen planus of the mouth. *BMJ* 1958; **i**: 983–4.
2 Setterfield JF, Black MM, Challacombe SJ. The management of oral lichen planus. *Clin Exp Dermatol* 2000; **25**: 176–82.
3 Alam F, Hamburger J. Oral mucosal lichen planus in children. *Int J Paediatr Dent* 2001; **11**: 209–14.
4 Agarwal R, Saraswat A. Oral lichen planus: an update. *Drugs Today (Barc)* 2002; **38**: 533–47.
5 Eisen D. The clinical manifestations and treatment of oral lichen planus. *Dermatol Clin* 2003; **21**: 79–89.
6 Ismail SB, Kumar SK, Zain RB. Oral lichen planus and lichenoid reactions: etiopathogenesis, diagnosis, management and malignant transformation. *J Oral Sci* 2007; **49**: 89–106.
7 Pindborg JJ, Mehta FS, Draftary DK *et al*. Prevalence of oral lichen planus among 7639 Indian villagers in Kerala, South India. *Acta Derm Venereol (Stockh)* 1972; **52**: 216–20.
8 Saloren L, Axell T, Hellden L. Occurrence of oral mucosal lesions, the influence of tobacco habits and an estimate of treatment time in an adult Swedish population. *J Oral Pathol Med* 1990; **19**: 170–6.



(a)



(b)

Fig. 41.15 Vulvovaginal–gingival syndrome. Showing (a) vulvitis and (b) gingivitis in the same patient. (Courtesy of Dr S. Neill, St John's Institute of Dermatology, King's College London, UK.)

9 Laine J, Kalimo K, Forssell H *et al*. Resolution of oral lichenoid lesions after replacement of amalgam restorations in patients allergic to mercury compounds. *Br J Dermatol* 1992; **126**: 10–5.

10 Ibbotson SH, Speight EL, Macleod RJ *et al*. The relevance and effect of amalgam replacement in subjects with oral lichenoid reactions. *Br J Dermatol* 1996; **134**: 420–3.

11 Dunsche A, Kästel A, Terheyden H *et al*. Oral lichenoid reactions associated with amalgam: improvement after amalgam removal. *Br J Dermatol* 2003; **148**: 70–6.

12 Dunsche A, Frank MP, Luttges J *et al*. Lichenoid reactions of murine mucosa associated with amalgam. *Br J Dermatol* 2003; **148**: 741–8.

13 Wong L, Freeman S. Oral lichenoid lesions (OLL) and mercury in amalgam fillings. *Contact Dermatitis* 2003; **48**: 74–9.

14 Thornhill MH, Pemberton MN, Simmons RK, Theaker ED. Amalgam contact hypersensitivity lesions and oral lichen planus. *Oral Surg Oral Med Oral Pathol* 2003; **95**: 291–9.

15 Menges M, Hohloch K, Pueschel W, Stallmach A. Lichen planus with oesophageal involvement. A case report and review of the literature. *Digestion* 2002; **65**: 184–9.

16 Keate RF, Williams JW, Connolly SM. Lichen planus esophagitis: report of three patients treated with oral tacrolimus or intraesophageal corticosteroid injections or both. *Dis Esophagus* 2003; **16**: 47–53.

17 Chryssostalis A, Gaudric M, Terris B *et al*. Esophageal lichen planus: a series of eight cases including a patient with esophageal verrucous carcinoma. A case series. *Endoscopy* 2008; **40**: 764–8.

18 Chandan VS, Murray JA, Abraham SC. Esophageal lichen planus. *Arch Pathol Lab Med* 2008; **132**: 1026–9.

19 Westbrook R, Riley S. Esophageal lichen planus: case report and literature review. *Dysphagia* 2008; **23**: 331–4.

20 Porter WM, Dinneen M, Hawkins DA, Bunker CB. Erosive penile lichen planus responding to circumcision. *J Eur Acad Dermatol Venereol* 2001; **15**: 266–8.

21 Rogers RS III, Eisen D. Erosive oral lichen planus with genital lesions: the vulvovaginal–gingival syndrome and the peno–gingival syndrome. *Dermatol Clin* 2003; **21**: 91–8.

22 Edwards L. Vulvar lichen planus. *Arch Dermatol* 1989; **125**: 1677–80.

23 Eisen D. The vulvovaginal–gingival syndrome of lichen planus. *Arch Dermatol* 1994; **130**: 1379–82.

24 Lewis FM, Shah M, Harrington CI. Vulval involvement in lichen planus. A study of 37 women. *Br J Dermatol* 1996; **135**: 89–91.

25 Lewis FM. Vulval lichen planus. *Br J Dermatol* 1998; **138**: 569–75.

26 Kirtschig G, Van Der Meulen AJ, Ion Lipan JW, Stoof TJ. Successful treatment of erosive vulvovaginal lichen planus with topical tacrolimus. *Br J Dermatol* 2002; **147**: 625–6.

27 Lotery HE, Galask RP. Erosive lichen planus of the vulva and vagina. *Obstet Gynecol* 2003; **101**: 1121–5.

28 Watsky KL. Erosive perianal lichen planus responsive to tacrolimus. *Int J Dermatol* 2003; **42**: 217–8.

29 Kennedy CM, Galask RP. Erosive vulvar lichen planus: retrospective review of characteristics and outcomes in 113 patients seen in a vulvar specialty clinic. *J Reprod Med* 2007; **52**: 43–7.

30 Marren P, Millard P, Chia Y *et al*. Mucosal lichen sclerosis/lichen planus overlap syndrome. *Br J Dermatol* 1994; **131**: 118–23.

Hypertrophic LP

This usually develops during the course of a subacute attack, but occasionally only hypertrophic or warty lesions are found. They most often occur on the lower limbs, especially around the ankles; venous stasis has been put forwards as an explanation (Fig. 41.16). The development of hypertrophic lesions greatly lengthens the course of the disease, as they may persist for many years. When such lesions eventually clear, an area of pigmentation and scarring may remain and there is often some degree of atrophy. They must be distinguished from lichen simplex chronicus and lichen amyloidosus (papular). Multiple cutaneous horns overlying hypertrophic LP are recorded [1], as are keratoacanthoma [2,3] and malignant transformation [4–6] arising in hypertrophic LP, as well as metastatic squamous cell cancer [7].

References

1 Sharma VK, Achar A, Ramam M, Singh MK. Multiple cutaneous horns overlying lichen planus hypertrophicus. *Br J Dermatol* 2001; **144**: 424–5.

2 Badell A, Marcoval J, Gallego I *et al*. Keratoacanthoma arising in hypertrophic lichen planus. *Br J Dermatol* 2000; **142**: 380–2.

3 Chave TA, Graham-Brown RA. Keratoacanthoma developing in hypertrophic lichen planus. *Br J Dermatol* 2003; **148**: 592.

4 Yesudian P, Rao R. Malignant transformation of hypertrophic lichen planus. *Int J Dermatol* 1985; **24**: 177–8.



Fig. 41.16 Hypertrophic lichen planus of great chronicity occurring on lower leg and ankle. (Courtesy of St John's Institute of Dermatology, King's College London, UK.)



Fig. 41.17 Lichen planus of scalp leading to large areas of cicatricial alopecia. (Courtesy of St John's Institute of Dermatology, King's College London, UK.)

5 Singh SK, Saikia UN, Ajith C, Kumar B. Squamous cell carcinoma arising from hypertrophic lichen planus. *J Eur Acad Dermatol Venereol* 2006; **20**: 745–6.

6 Krasowska D, Bogaczewicz J, Chodorowska G. Development of squamous cell carcinoma within lesions of cutaneous lichen planus. *Eur J Dermatol* 2007; **17**: 447–8.

7 Ardabili M, Gambichler T, Rotterdam S *et al*. Metastatic cutaneous squamous cell carcinoma arising from a previous area of chronic hypertrophic lichen planus. *Dermatol Online J* 2003; **9**: 10.

Follicular LP [1]

Synonym
- Lichen planopilaris

Follicular lesions usually appear during the course of typical LP, but occasionally they predominate and diagnosis may then be difficult. Absence of arrector pili muscles and sebaceous glands, a perivascular and perifollicular lymphocytic infiltrate in the reticular dermis and mucinous perifollicular fibroplasia within the upper dermis with absence of interfollicular mucin, and superficial perifollicular wedge-shaped scarring are characteristic features of the histology [2]. Presentation with alopecia of the trunk is recorded [3]. Follicular lesions occurring in the scalp are accompanied by some scaling and are likely to lead to a scarring alopecia (Fig. 41.17). Very rarely, the scalp alone is involved. The so-called *Graham Little–Piccardi–Lassueur syndrome* comprises the triad of multifocal scalp cicatricial alopecia, non-scarring alopecia of the axillae and/or groin, and keratotic lichenoid follicular papules [4–9]. The clinical, histological and IMF overlap between this syndrome and LP with follicular involvement (lichen planopilaris) suggest that both are variants of LP. Progressive *frontal fibrosing alopecia*, a scalp condition that affects elderly women in particular and which frequently involves the eyebrows, has been regarded by some authors as a clinically distinct variant of lichen planopilaris [10], and is certainly associated with mucocutaneous lichen planus [11]. Onset of lichen planopilaris has been anecdotally associated with etanercept therapy [12].

Follicular LP must be distinguished by biopsy from keratosis pilaris, Darier's disease, follicular mucinosis, lichen scrofulosorum and, in the scalp, from lupus erythematosus.

References

1 Kang H, Alzolibani AA, Otberg N, Shapiro J. Lichen planopilaris. *Dermatol Ther* 2008; **21**: 249–56.

2 Tandon YK, Somani N, Cevasco NC, Bergfeld WF. A histologic review of 27 patients with lichen planopilaris. *J Am Acad Dermatol* 2008; **59**: 91–8.

3 Gupta SN, Palceski D. Lichen planopilaris presenting as truncal alopecia: a case presentation and review of the literature. *Cutis* 2003; **72**: 63–6.

4 Graham Little EG. Folliculitis decalvans et atrophicans. *Br J Dermatol* 1915; **27**: 183–5.

5 Matta M, Kibbi AG, Khattar J *et al*. Lichen planopilaris: a clinicopathologic study. *J Am Acad Dermatol* 1990; **22**: 594–8.

6 Horn RT, Goette DK, Odom RB *et al*. Immunofluorescent findings and clinical overlap in two cases of follicular lichen planus. *J Am Acad Dermatol* 1982; **7**: 203–7.

7 Ghislain PD, Van Eeckhout P, Ghislain E. Lassueur–Graham Little–Piccardi syndrome: a 20-year follow-up. *Dermatology* 2003; **206**: 391–2.

8 Viglizzo G, Verrini A, Rongioletti F. Familial Lassueur–Graham-Little–Piccardi syndrome. *Dermatology* 2004; **208**: 142–4.

9 Abbas O, Chedraoui A, Ghosn S. Frontal fibrosing alopecia presenting with components of Piccardi–Lassueur–Graham-Little syndrome. *J Am Acad Dermatol* 2007; **57** (2 Suppl.): S15–8.

10 Kossard S, Lee MS, Wilkinson B. Postmenopausal frontal fibrosing alopecia: a frontal variant of lichen planopilaris. *J Am Acad Dermatol* 1997; **36**: 59–66.

11 Tan KT, Messenger AG. Frontal fibrosing alopecia: clinical presentations and prognosis. *Br J Dermatol* 2009; **160**: 75–9.



Fig. 41.18 Lichen planus, zosteriform lesion on chest wall. (Courtesy of St John's Institute of Dermatology, King's College London, UK.)

12 Garcovich S, Manco S, Zampetti A *et al*. Onset of lichen planopilaris during treatment with etanercept. *Br J Dermatol* 2008; **158**: 1161–3.

Linear LP

Linear lesions as a Koebner effect are frequently found in LP. Isolated linear lesions, usually made up of small papules in close apposition, sometimes becoming confluent, are rare [1,2]; they are more common in childhood [3]. Linear LP lesions are usually only a few centimetres in length, but long, narrow linear lesions extending the whole length of a limb may occur. Such cases may overlap with epidermal naevi, and the term lichenoid epidermal naevus has been introduced [3]. Multiple linear LP lesions following the lines of Blaschko have been reported [4–6], as has a linear drug eruption to nicergoline [7]. Multiple linear LP was documented in a patient with human immunodeficiency virus (HIV) infection [8]. Segmental LP was co-localized with vitiligo in one case [9]. Zosteriform LP has been described [10–14] (Fig. 41.18). The histology of linear or zosteriform LP is characteristic, and enables distinction from other linear dermatoses such as lichen striatus, linear naevi and linear psoriasis. Interestingly, linear lichenoid lesions may occur in graft-versus-host disease [15–17].

References

1 Hartl C, Steen KH, Wegner H *et al*. Unilateral linear lichen planus with mucous membrane involvement. *Acta Derm Venereol (Stockh)* 1999; **79**: 145–6.
2 Kootiratrakarn T, Masu T, Aiba S, Tagami H. Unilateral lichen planus located on the chest showing a patchy and linear distribution. *Eur J Dermatol* 2003; **13**: 28.
3 Brownstein MH, Silverstein L, Leting W. Lichenoid epidermal nevus: 'Linear lichen planus'. *J Am Acad Dermatol* 1989; **20**: 913–5.
4 Long CC, Finlay AY. Multiple linear lichen planus in the lines of Blaschko. *Br J Dermatol* 1996; **135**: 275–6.
5 Kabbash C, Laude TA, Weinberg JM, Silverberg NB. Lichen planus in the lines of Blaschko. *Pediatr Dermatol* 2002; **19**: 541–5.
6 Ber Rahman S, Ul Bari A, Mumtaz N. Unilateral Blaschkoid lichen planus involving the entire half of the body, a unique presentation. *Dermatol Online J* 2007; **13**: 36.
7 Muñoz MA, Pérez-Bernal AM, Camacho FM. Lichenoid drug eruption following the Blaschko lines. *Dermatology* 1996; **193**: 66–7.
8 Ruiz Villaverde R, Blasco Melguizo J, Naranjo Sintes R *et al*. Multiple linear lichen planus in HIV patient. *J Eur Acad Dermatol Venereol* 2002; **16**: 412–4.



Fig. 41.19 Lichen planus actinicus, showing well-defined, pigmented, nummular patches on face. (Courtesy of St John's Institute of Dermatology, King's College London, UK.)

9 Sardana K, Sharma RC, Koranne RV, Mahajan S. An interesting case of colocalization of segmental lichen planus and vitiligo in a 14-year-old boy. *Int J Dermatol* 2002; **41**: 508–9.
10 Nagy GY, Husz S, Szucs L. Lichen planus zosteriformis. *Z Hautkr* 1978; **53**: 5–9.
11 Shemer A, Weiss G, Trau H. Wolf's isotopic response: a case of zosteriform lichen planus on the site of healed herpes zoster. *J Eur Acad Dermatol Venereol* 2001; **15**: 445–7.
12 Turel A, Ozturkcan S, Sahin MT, Turkdogan P. Wolf's isotopic response: a case of zosteriform lichen planus. *J Dermatol* 2002; **29**: 339–42.
13 Bari AU, Rahman SB. Zosteriform lichen planus. *J Coll Physicians Surg Pak* 2003; **13**: 104–5.
14 Perry D, Fazel N. Zosteriform lichen planus. *Dermatol Online J* 2006; **12**: 3.
15 Freemer CS, Farmer ER, Cerio RL *et al*. Lichenoid chronic graft-versus-host disease occurring in a dermatomal distribution. *Arch Dermatol* 1994; **130**: 70–2.
16 Wilson BB, Lockman DW. Linear lichenoid graft-versus-host disease. *Arch Dermatol* 1994; **130**: 1206–7.
17 Beers B, Kalish RS, Kaye VN *et al*. Unilateral linear lichenoid eruption after bone marrow transplantation: an unmasking of tolerance to an abnormal keratinocyte clone? *J Am Acad Dermatol* 1993; **28**: 888–92.

Actinic LP

Synonym
- Lichen planus subtropicus

'Actinic' or (sub)tropical LP generally occurs in children or young adults with dark skin living in tropical countries; virtually all cases originate from the Middle East, East Africa or India [1–5]. Lesions occur on exposed skin (usually the face) as well-defined annular or discoid patches, which have a deeply hyperpigmented centre surrounded by a striking hypopigmented zone (Fig. 41.19).

Erythematous actinic LP has been associated with oral erosive LP and chronic active hepatitis [6]. Sunlight exposure appears to be central to the pathogenesis of actinic LP [7], although evidence for photo-induction of lesions in actinic LP is still lacking [8]. Actinic LP may mimic melasma [9]. There is a histological spectrum comprising: a form with features of classical idiopathic LP; an intermediate form (lichenoid melanodermatitis) with foci of spongiosis and parakeratosis; and a more overtly eczematous type [10]; all share striking pigmentary incontinence. Some of these 'hybrids' of actinic LP may not be mere variants of LP. Actinic LP has been treated with acitretin and topical corticosteroids [11] and with ciclosporin [12].

References

1 Dilairny M. Lichen planus subtropicus. *Arch Dermatol* 1976; **112**: 1251–5.
2 Singh OP, Kanwar AJ. Lichen planus in India. An appraisal of 441 cases. *Int J Dermatol* 1976; **16**: 752–6.
3 Peretz E, Grunwald MH, Halevy S. Annular plaque on the face. Actinic lichen planus (ALP). *Arch Dermatol* 1999; **135**: 1543–6.
4 Bouassida S, Boudaya S, Turki H *et al*. Actinic lichen planus: 32 cases. *Ann Dermatol Vénéréol* 1998; **125**: 408–13.
5 Meads SB, Kunishige J, Ramos-Caro FA, Hassanein AM. Lichen planus actinicus. *Cutis* 2003; **72**: 377–81.
6 Skowron F, Grezard P, Merle P *et al*. Erythematosus actinic lichen planus: a new clinical form associated with oral erosive lichen planus and chronic active hepatitis B. *Br J Dermatol* 2002; **147**: 1032–4.
7 Isaacson D, Turner ML, Elgart ML. Summertime actinic lichenoid eruption (lichen planus actines). *J Am Acad Dermatol* 1981; **4**: 404–11.
8 Salman SM, Kibbi AG, Zaynoun S. Actinic lichen planus. A clinicopathologic study of 16 patients. *J Am Acad Dermatol* 1989; **20**: 226–31.
9 Salman SM, Khallout R, Zaynoun S. Actinic lichen planus mimicking melasma: a clinical and histopathologic study of three cases. *J Am Acad Dermatol* 1988; **18**: 275–8.
10 Verhagen ARHB, Koten JW. Lichenoid melanodermatitis. *Br J Dermatol* 1979; **101**: 651–8.
11 Jansen T, Gambichler T, von Kobyletzki L, Altmeyer P. Lichen planus actinicus treated with acitretin and topical corticosteroids. *J Eur Acad Dermatol Venereol* 2002; **16**: 174–5.
12 Gallo L, Ayala F, Ayala F. Relapsing lichen actinicus successfully treated with cyclosporin. *J Eur Acad Dermatol Venereol* 2008; **22**: 370–1.

LP pigmentosus [1–3]

This is a pigmentary disorder seen in India or in the Middle East, which may or may not be associated with typical LP papules. The macular hyperpigmentation involves chiefly the face, neck and upper limbs, although it can be more widespread, and varies from slate grey to brownish black; it is mostly diffuse, but reticular, blotchy and perifollicular forms are seen [3]. The duration at presentation ranged from 2 months to 21 years in one series [3]. Occasionally, there is a striking predominance of lesions at intertriginous sites, especially the axillae [4,5]. The mucous membranes, palms and soles are usually not involved, but involvement of mucous membranes has been observed [6]. LP pigmentosus has been anecdotally reported in association with acrokeratosis of Bazex [7].

References

1 Bhutani LK, Bedi TR, Pandi RK *et al*. Lichen planus pigmentosus. *Dermatologica* 1974; **149**: 43–50.
2 Kanwar AJ, Kaur S. Lichen planus pigmentosus. *J Am Acad Dermatol* 1989; **21**: 815.



Fig. 41.20 Annular lichen planus.

3 Kanwar AJ, Dogra S, Handa S *et al*. A study of 124 Indian patients with lichen planus pigmentosus. *Clin Exp Dermatol* 2003; **28**: 481–5.
4 Pock L, Jelinkova L, Drlik L *et al*. Lichen planus pigmentosus-inversus. *J Eur Acad Dermatol Venereol* 2001; **15**: 452–4.
5 Kashima A, Tajiri A, Yamashita A, Asada Y, Setoyama M. Two Japanese cases of lichen planus pigmentosus-inversus. *Int J Dermato*l 2007; **46**: 740–2.
6 Laskaris GC, Papavasilious SS, Bovopoulou OD *et al*. Lichen planus pigmentosus of the oral mucosa: a rare clinical variety. *Dermatologica* 1982; **162**: 61–3.
7 Sassolas B, Zagnoli A, Leroy JP *et al*. Lichen planus pigmentosus associated with acrokeratosis of Bazex. *Clin Exp Dermatol* 1994; **19**: 70–3.

Annular LP [1]

Although small annular lesions are common in LP, cases showing a few large annular lesions only are unusual. They may be widely scattered, and usually have a very narrow rim of activity and a depressed, slightly atrophic, centre (Fig. 41.20). Much less often, the margin is wide, and the central area is quite small. Annular lesions are characteristically found on the penis (see Fig. 41.8), sometimes associated with lesions on the buccal mucosa. The differential diagnosis includes granuloma annulare. A distinct entity termed annular lichenoid dermatitis of youth [2,3] has been described, characterized by persistent asymptomatic erythematous macules and round annular patches with a red-brownish border and central hypopigmentation, mostly distributed on the groin and flanks, in children and adolescents. Histology reveals a lichenoid dermatitis with necrosis/apoptosis of the keratinocytes limited to the tips of rete ridges.

Atrophic LP

Lesions tend to be few in number; the atrophy may be the result of faded annular lesions [4,5], or resolved hypertrophic lesions on the lower legs especially. The histology is likely to be non-specific, but allows lichen sclerosus or guttate morphoea to be excluded.

References

1 Reich HL, Nguyen JT, James WD. Annular lichen planus: a case series of 20 patients. *J Am Acad Dermatol* 2004; **50**: 595–9.
2 Annessi G, Paradisi M, Angelo C *et al*. Annular lichenoid dermatitis of youth. *J Am Acad Dermatol* 2003; **49**: 1029–36.
3 Kleikamp S, Kutzner H, Frosch PJ. Annular lichenoid dermatitis of youth—a further case in a 12-year-old girl. *J Dtsch Dermatol Ges* 2008; **6**: 653–6.



Fig. 41.21 Guttate lichen planus. (Courtesy of St John's Institute of Dermatology, King's College London, UK.)

4 Mseddi M, Bouassida S, Marrakchi S *et al*. Annular atrophic lichen planus. *Dermatology* 2003; **207**: 208–9.
5 Morales-Callaghan A Jr, Martínez G, Aragoneses H *et al*. Annular atrophic lichen planus. *J Am Acad Dermatol* 2005; **52**: 906–8.

Guttate LP

Lesions are widely scattered and remain discrete, may be all small (1–2 mm across), or larger (up to 1 cm) (Fig. 41.21), and individual lesions seldom become chronic. Guttate psoriasis must be differentiated.

Acute and subacute LP with confluence of lesions

In these forms, small lesions are widely distributed; where they become confluent, eczema may be simulated. Colour changes may be marked, with individual lesions initially red but progressing rapidly to black as they fade. Successive crops may occur, such that the total time for clearance may be little different from other forms; a small minority clear in under 3 months. Differential diagnosis includes pityriasis rosea in the earliest phase, and eczema later; drug-induced lichenoid eruptions may present in this fashion.

LP of the palms and soles

Although lesions on the volar aspect of the wrists or at the ankles occur in more than 50% of cases of LP, lesions on the adjacent palms and soles are less common, lack the characteristic shape and colour of lesions elsewhere, and are firm to the touch and yellow in hue [1,2] (see Fig. 41.11). They may be broadly sheeted or show up as punctate keratoses [3]. Vesicle-like papules are recorded [4]. Itching may be absent. When such changes occur in isolation, diagnosis is very difficult; syphilis, psoriasis, callosities and warts must be excluded.

A rare, very chronic, form of LP involves large, painful indolent ulcers on the sole of one or both feet [5], with gradual, permanent loss of toenails; there may be secondary webbing of the toes [6]. The sole may resemble lichenified dermatitis or psoriasis rather than LP before the ulcers appear. The onset is insidious and there may be no other evidence of LP, although cicatricial alopecia has been associated in some cases.

References

1 Mugoni MG, Monteso MA, Cottoni F. Lichen planus on the palms and soles. *J Eur Acad Dermatol Venereol* 1994; **3**: 535–40.
2 Sánchez-Pérez J, Rios Buceta L, Fraga J, García-Díez A. Lichen planus with lesions on the palms and/or soles. Prevalence and clinicopathological study of 36 patients. *Br J Dermatol* 2000; **142**: 310–4.
3 Sait MA, Garg BR. Punctate keratoses of palms in lichen planus. *Int J Dermatol* 1986; **25**: 592–3.
4 Gunduz K, Inanir I, Turkdogan P, Sacar H. Palmoplantar lichen planus presenting with vesicle-like papules. *J Dermatol* 2003; **30**: 337–40.
5 Cram DL, Kierland PR, Winkelmann RK. Ulcerative lichen planus of the feet. *Arch Dermatol* 1966; **93**: 692–701.
6 Sonnex TS, Eady RAJ, Sparrow GP *et al*. Ulcerative lichen planus associated with webbing of the toes. *J R Soc Med* 1986; **79**: 363–5.

Complications

Hair. Alopecia is uncommon in LP, but most often occurs in small areas on the scalp, producing patches of atrophic cicatricial alopecia [1–5] (see Fig. 41.17). It results from follicular destruction by the inflammatory infiltrate, with scarring. Areas of alopecia may continue to appear, or to extend, for months after the skin lesions have faded. The final result is one of pseudopelade [2,5]; this is probably best considered as a clinical entity due to a number of independent conditions, of which LP is only one. Lichen planopilaris is more common in women and about half will develop involvement of glabrous skin, mucous membranes or nails [1]; it may occur in children [3]. Tumid forms of LP follicularis have been described in which clusters of milium cysts and comedones develop [6]. LP pilaris has been reported in association with dermatitis herpetiformis [7].

Nails. Nail involvement occurs in up to 10% of cases, but is usually a minor feature of the disease [8,9]. The majority of cases present during the fifth or sixth decades; long-term permanent damage to the nails is rare [10]. Fingernails are more frequently affected than toenails [10], with initial involvement of two or three fingernails before subsequent involvement of the remaining digits. The most common changes are exaggeration of the longitudinal lines and linear depressions (Fig. 41.22), due to slight thinning of the nail plate. These changes usually occur in the context of severe generalized LP, although skin lesions may not be seen in the vicinity of the affected nail. Elevated ridges may be seen on the nail [9]. Adhesion between the epidermis of the dorsal nail fold and the nail bed may cause partial destruction of the nail (pterygium unguis) (Fig. 41.23). Rarely, the nail is completely shed; there is usually clinical evidence of LP at the base of the nail before shedding. Nails may partially regrow or be permanently lost (Fig. 41.24); the nails of the great toes are the ones most often affected.

LP has been shown to cause childhood idiopathic atrophy of the nails [11]. LP of the nails in childhood is rare [12], but may overlap with the condition of twenty-nail dystrophy of childhood (idiopathic trachyonychia); the exact relationship is unclear [13–18]. The rare variant of LP that causes ulceration of the soles is often accompanied by permanent destruction of several toenails. LP of the nail bed may give rise to longitudinal melanonychia [19], hyperpigmentation, subungual hyperkeratosis or onycholysis [9], or changes mimicking the yellow nail syndrome [20,21].



Fig. 41.22 Lichen planus of thumbnail showing thinning of nail plate and longitudinal lines. (Courtesy of St John's Institute of Dermatology, King's College London, UK.)



Fig. 41.23 Severe lichen planus of fingernails showing involvement of nail fold areas and early pterygium formation. (Courtesy of St John's Institute of Dermatology, King's College London, UK.)

Mucous membranes. Squamous cell cancer developing on mouth lesions is uncommon, but is a potential danger, especially with ulcerated lesions [22–30], although the incidence varies greatly in different series. Lesions may occur on the lip (Fig. 41.25), the buccal mucosa or the gum margin. It has been postulated that high expression of cyclo-oxygenase (COX)-2 reported in oral lichen planus may be of aetiological significance in the development of



Fig. 41.24 Severe, destructive lichen planus of toenails. (Courtesy of St John's Institute of Dermatology, King's College London, UK.)



Fig. 41.25 Squamous carcinoma on lower lip developing at site of lichen planus cheilitis. (Courtesy of St John's Institute of Dermatology, King's College London, UK.)

squamous cell cancer [31]. Squamous cell cancer arising on LP cutaneous lesions [32] and anogenital lesions [33–35] is definitely a rare phenomenon. Cicatricial conjunctivitis [36] and lacrimal canalicular obstruction are recorded [37].

References

1 Mehregan DA, Van Hale HM, Mullen SA. Lichen planopilaris: clinical and pathologic study of 45 patients. *J Am Acad Dermatol* 1992; **27**: 935–42.

2 Annessi G, Lombardo G, Gobello T, Puddu P. A clinicopathologic study of scarring alopecia due to lichen planus. Comparison with scarring alopecia in discoid lupus erythematosus and pseudopelade. *Am J Dermatopathol* 1999; **21**: 324–31.

3 Sehgal VN, Bajaj P, Srivastva G. Lichen planopilaris (cicatricial [scarring] alopecia) in a child. *Int J Dermatol* 2001; **40**: 461–3.

4 Faulkner CF, Wilson NJ, Jones SK. Frontal fibrosing alopecia associated with cutaneous lichen planus in a premenopausal woman. *Australas J Dermatol* 2002; **43**: 65–7.

5 Amato L, Mei S, Massi D *et al*. Cicatricial alopecia; a dermatopathologic and immunopathologic study of 33 patients (pseudopelade of Brocq is not a specific clinico-pathologic entity). *Int J Dermatol* 2002; **41**: 8–15.

6 Vasquez Garcia J, Pérez Oliva N, Peireio Ferreirós MAM *et al*. Lichen planus follicularis tumidus with cysts and comedones. *Clin Exp Dermatol* 1992; **17**: 346–8.

7 Isaac M, McNeely MC. Dermatitis herpetiformis associated with lichen planopilaris. *J Am Acad Dermatol* 1995; **33**: 1050–1.
8 Samman PD. The nails in lichen planus. *Br J Dermatol* 1961; **73**: 288–92.
9 Zaias N. The nail in lichen planus. *Arch Dermatol* 1970; **101**: 264–71.
10 Tosti A, Peluso AM, Fanti PA *et al*. Nail lichen planus: clinical and pathologic study of 24 patients. *J Am Acad Dermatol* 1993; **28**: 724–30.
11 Colver GB, Dawber RPR. Is childhood idiopathic atrophy of the nails due to lichen planus? *Br J Dermatol* 1987; **116**: 709–12.
12 Tosti A, Piraccini BM, Cambiaghi S, Jorizzo M. Nail lichen planus in children. Clinical features, response to treatment, and long-term follow-up. *Arch Dermatol* 2001; **137**: 1027–32.
13 Arias AM, Yung CW, Rendeler S *et al*. Familial severe twenty-nails dystrophy. *J Am Acad Dermatol* 1982; **7**: 349–52.
14 Menni S, Piccinno R, Sala F *et al*. Twenty-nail dystrophy of childhood—two cases in one family. *Clin Exp Dermatol* 1984; **9**: 604–7.
15 Tosti A, Bardazzi F, Piraccini BM *et al*. Idiopathic trachyonychia (twenty nail dystrophy): a pathologic study of 23 patients. *Br J Dermatol* 1994; **131**: 866–72.
16 Taniguchi S, Kusuna H, Tani Y *et al*. Twenty-nail dystrophy (trachyonychia) caused by lichen planus in a patient with alopecia universalis and ichthyosis vulgaris. *J Am Acad Dermatol* 1995; **33**: 903–5.
17 Scheinfeld NS. Trachyonychia. A case report and review of manifestations, associations, and treatments. *Cutis* 2003; **71**: 299–302.
18 Sehgal VN. Twenty nail dystrophy trachyonychia: an overview. *J Dermatol* 2007; **34**: 361–6.
19 Baran R, Jancovici E, Sayag J *et al*. Longitudinal melanonychia in lichen planus. *Br J Dermatol* 1985; **113**: 369–70.
20 Tosti A, Piraccini BM, Cameli N. Nail changes in lichen planus may resemble those of yellow nail syndrome. *Br J Dermatol* 2000; **142**: 848–9.
21 Baran R. Lichen planus of the nails mimicking the yellow nail syndrome. *Br J Dermatol* 2000; **143**: 1117–8.
22 Rode M, Kogoj-Rode M. Malignant potential of the reticular form of oral lichen planus over a 25-year observation period in 55 patients from Slovenia. *J Oral Sci* 2002; **44**: 109–11.
23 Reichart PA. Oral precancerous conditions—an overview. *Mund Kiefer Gesichtschir* 2003; **7**: 201–7.
24 Epstein JB, Wan LS, Gorsky M, Zhang L. Oral lichen planus: progress in understanding its malignant potential and the implications for clinical management. *Oral Surg Oral Med Oral Pathol* 2003; **96**: 32–7.
25 van der Meij EH, Schepman KP, van der Waal I. The possible premalignant character of oral lichen planus and oral lichenoid lesions: a prospective study. *Oral Surg Oral Med Oral Pathol* 2003; **96**: 164–71.
26 Larsson A, Warfvinge G. Malignant transformation of oral lichen planus. *Oral Oncol* 2003; **39**: 630–1.
27 Tomb R, El-Hajj H, Nehme E, Haddad A. Verrucous carcinoma of the tongue occurring on lesions of lichen planus. *Ann Dermatol Vénéréol* 2003; **130**: 55.
28 Warshaw EM, Templeton SF, Washington CV. Verrucous carcinoma occurring in a lesion of oral lichen planus. *Cutis* 2000; **65**: 219–22.
29 Lanfranchi-Tizeira HE, Aguas SC, Sano SM. Malignant transformation of atypical oral lichen planus. A review of 32 cases. *Med Oral* 2003; **8**: 2–9.
30 Mignogna MD, Lo Russo L, Fedele S *et al*. Clinical behaviour of malignant transforming oral lichen planus. *Eur J Surg Oncol* 2002; **28**: 838–43.
31 Lysitsa S, Samson J, Gerber-Wicht C *et al*. COX-2 expression in oral lichen planus. *Dermatology* 2008; **217**: 150–5.
32 Sigurgeirsson B, Lindelöf B. Lichen planus and malignancy: an epidemiologic study of 2071 patients and a review of the literature. *Arch Dermatol* 1991; **127**: 1684–8.
33 Dwyer CM, Kerr REI, Millan DWM. Squamous carcinoma following lichen planus of the vulva. *Clin Exp Dermatol* 1995; **20**: 171–2.
34 Jones RW, Rowan DM, Kirker J, Wilkinson EJ. Vulval lichen planus: progression of pseudoepitheliomatous hyperplasia to invasive vulval carcinomas. *Br J Obstet Gynaecol* 2001; **108**: 665–6.
35 Hoshi A, Usui Y, Terachi T. Penile carcinoma originating from lichen planus on glans penis. *Urology* 2008; **71**: 816–7.
36 Thorne JE, Jabs DA, Nikolskaia OV *et al*. Lichen planus and cicatrizing conjunctivitis: characterization of five cases. *Am J Ophthalmol* 2003; **136**: 239–43.
37 McNab AA. Lacrimal canalicular obstruction in lichen planus. *Orbit* 1998; **17**: 201–2.

Associated conditions

Idiopathic LP has been reported in association with diseases of altered or disturbed immunity, including ulcerative colitis [1–4], alopecia areata [2,4,5], vitiligo [4], dermatomyositis [6], morphoea and lichen sclerosus [7], systemic lupus erythematosus [8,9], pemphigus [8] and paraneoplastic pemphigus [10,11]. In addition, LP has been observed in association with thymoma [5,8,12,13], myasthenia gravis [3,4,13], hypogammaglobulinaemia [5,14], primary biliary cirrhosis [15–17], especially in those treated with penicillamine, and primary sclerosing cholangitis [18]. The literature with regard to LP and HCV infection is reviewed in the section on pathogenesis above. In Italy, possibly because of a higher prevalence of hepatitis B virus (HBV) and HCV infection, patients with LP seem more prone to develop liver disease, including chronic active hepatitis [19–23]. A high prevalence of anticardiolipin antibodies has been documented in patients with HCV-associated oral LP [24]. Elsewhere, the association between LP and chronic active hepatitis or primary biliary cirrhosis is unusual and probably coincidental [25–27]. Overall, the majority of patients with LP live to old age, despite an association with autoimmunity [28].

LP has also been associated with diabetes mellitus [29]. Anecdotally, LP has occurred in patients with Castleman's tumour (giant lymph-node hyperplasia) [30] or with generalized lichen amyloidosus [31]. LP has been described in certain tattoo reactions, particularly in those areas where there is coexisting mercury hypersensitivity to the injected dye [32,33].

References

1 Cox NH, Finlay AY, Watkinson G. Atypical lichen planus associated with ulcerative colitis. *Dermatologica* 1986; **173**: 294–6.
2 Gruppo Italiano Studi Epidemiologici in Dermatologia. Epidemiological evidence of the association between lichen planus and two immune-related diseases: alopecia areata and ulcerative colitis. *Arch Dermatol* 1991; **127**: 688–91.
3 Miller TN. Myasthenia gravis, ulcerative colitis and lichen planus. *Proc R Soc Med* 1971; **64**: 807–8.
4 Tan RSH. Ulcerative colitis, myasthenia gravis, atypical lichen planus, alopecia areata, vitiligo. *Proc R Soc Med* 1974; **67**: 195–6.
5 Tan RSH. Thymoma, acquired hypogammaglobulinaemia, lichen planus, alopecia areata. *Proc R Soc Med* 1974; **67**: 196–8.
6 Al-Najjar A, Reilly GD, Harrington CI. Dermatomyositis and lichen planus: an association or manifestation? *Clin Exp Dermatol* 1985; **10**: 174–8.
7 Connelly MG, Winkelmann RK. Co-existence of lichen sclerosus, morphoea and lichen planus. *J Am Acad Dermatol* 1985; **12**: 844–51.
8 Ng PP, Ng SK, Chng HH. Pemphigus foliaceus and oral lichen planus in a patient with systemic lupus erythematosus and thymoma. *Clin Exp Dermatol* 1998; **23**: 181–4.
9 Koga T, Kubota Y, Kiryu H *et al*. Late onset systemic lupus erythematosus with lichen planus-like eruption and cardiac tamponade. *Eur J Dermatol* 2000; **10**: 620–2.
10 Passeron T, Bahadoran P, Lacour JP *et al*. Paraneoplastic pemphigus presenting as erosive lichen planus. *Br J Dermatol* 1999; **140**: 552–3.
11 Bowen GM, Peters NT, Fivenson DP *et al*. Lichenoid dermatitis in paraneoplastic pemphigus: a pathogenic trigger of epitope spreading? *Arch Dermatol* 2000; **136**: 652–6.
12 Calista D. Oral erosive lichen planus associated with thymoma. *Int J Dermatol* 2001; **40**: 762–4.
13 Aronson IK, Soltani K, Paik KI *et al*. Triad of lichen planus, myasthenia gravis and thymoma. *Arch Dermatol* 1978; **114**: 255–8.
14 Mann RJ, Wallington TB, Warin RP. Lichen planus with late onset hypogammaglobulinaemia: a casual relationship? *Br J Dermatol* 1982; **106**: 357–60.
15 Powell FC, Rogers RS III, Dickson ER. Primary biliary cirrhosis and lichen planus. *J Am Acad Dermatol* 1983; **9**: 540–5.

16 Sarkany I. The skin–liver connection. *Clin Exp Dermatol* 1988; **13**: 151–9.
17 Chu CY, Yang CY, Huang SF *et al*. Lichen planus with xanthomatous change in a patient with primary biliary cirrhosis. *Br J Dermatol* 2000; **142**: 377–8.
18 Tong DC, Ferguson MM. Concurrent oral lichen planus and primary sclerosing cholangitis. *Br J Dermatol* 2002; **147**: 356–8.
19 Rebora A, Rongioletti F. Lichen planus and chronic active hepatitis: a retrospective study. *Acta Derm Venereol (Stockh)* 1984; **64**: 52–6.
20 Cerimele D. Lichen planus and internal medicine. *Ital Gen Rev Dermatol* 1988; **25**: 41–166.
21 Gruppo Italiano Studi Epidemiologici in Dermatologia. Lichen planus and liver diseases: a multicentre case–control study. *BMJ* 1990; **300**: 227–30.
22 Rebora A. Hepatitis viruses and lichen planus. *Arch Dermatol* 1994; **130**: 1328–9.
23 Parodi A, Carla Divano M, Rebora A. Serologic markers of autoimmune chronic hepatitis in patients with lichen planus. *Eur J Dermatol* 1996; **6**: 30–1.
24 Nagao Y, Tsubone K, Kimura R *et al*. High prevalence of anticardiolipin antibodies in patients with HCV-associated oral lichen planus. *Int J Mol Med* 2002; **9**: 293–7.
25 Epstein O. Lichen planus and liver disease. *Br J Dermatol* 1984; **111**: 473–5.
26 Mobacken H, Nilsson LA, Olsson R *et al*. Incidence of liver disease in chronic lichen planus of the mouth. *Acta Derm Venereol (Stockh)* 1984; **64**: 70–3.
27 El-Kabir M, Scully C, Porter S *et al*. Liver function in UK patients with oral lichen planus. *Clin Exp Dermatol* 1993; **18**: 12–6.
28 Anonide AA, Rebora A. What lichen planus patients die of: a retrospective study. *Int J Dermatol* 1989; **28**: 524–6.
29 Romero MA, Seoane J, Varela-Centelles P *et al*. Prevalence of diabetes mellitus amongst oral lichen planus patients. Clinical and pathological characteristics. *Med Oral* 2002; **7**: 121–9.
30 Ashinoff R, Cohen R, Lipkin G. Castleman's tumour and erosive lichen planus: coincidence or association? *J Am Acad Dermatol* 1989; **21**: 1076–80.
31 Hongcharu W, Baldassano M, Gonzalez E. Generalized lichen amyloidosis associated with chronic lichen planus. *J Am Acad Dermatol* 2000; **43**: 346–8.
32 Clarke J, Black MM. Lichenoid tattoo reactions. *Br J Dermatol* 1979; **100**: 451–4.
33 Winkelmann RK, Harris RB. Lichenoid delayed hypersensitivity reactions in tattoos. *J Cutan Pathol* 1979; **6**: 59–65.

Differential diagnosis

Typical cases of LP need be distinguished only from lichenoid eruptions induced by drugs or colour developer. Less typical cases of LP may be mistaken for plane warts, eczematous eruptions with lichenification from scratching [1–3], pityriasis rosea, and other lichenoid eruptions such as papular lichen amyloidosus. Occasional cases of LP without itching must be distinguished from secondary syphilis [4–6], systemic lupus erythematosus [7], atypical mycobacterium infection [8] and sarcoidosis [9].

The differential diagnosis of the special variants has already been mentioned; in case of doubt, a biopsy should establish the diagnosis. Although erythema dyschromicum perstans (ashy dermatosis) has a characteristic clinical appearance, it has been regarded as simply a macular variant of LP (LP pigmentosus) [10–12].

References

1 Patmizi A, Di Lernia V, Ricci G *et al*. Atopic background of recurrent papular eruption of childhood (frictional lichenoid eruption). *Pediatr Dermatol* 1990; **7**: 111–5.
2 Allen HB, Jones NP, Bowen SE. Lichenoid and other clinical presentations of atopic dermatitis in an inner city practice. *J Am Acad Dermatol* 2008; **58**: 503–4.
3 Summey BT, Bowen SE, Allen HB. Lichen planus-like atopic dermatitis: expanding the differential diagnosis of spongiotic dermatitis. *J Cutan Pathol* 2008; **35**: 311–4.
4 Tang MB, Yosipovitch G, Tan SH. Secondary syphilis presenting as a lichen planus-like rash. *J Eur Acad Dermatol Venereol* 2004; **18**: 185–7.
5 Monastirli A, Pasmatzi E, Georgiou S *et al*. Lichen planus-like secondary syphilis in an 83-year-old woman. *Clin Exp Dermatol* 2008; **33**: 780–1.
6 Narang T, De D, Dogra S *et al*. Secondary syphilis presenting as annular lichenoid plaques on the scrotum. *J Cutan Med Surg* 2008; **12**: 114–6.
7 Kobayashi T, Hatamochi A, Kamada N *et al*. Systemic lupus erythematosus with lichen planus-like eruptions associated with pericarditis. *J Dermatol* 2008; **35**: 306–7.
8 Breza TS Jr, Magro CM. Lichenoid and granulomatous dermatitis associated with atypical mycobacterium infections. *J Cutan Pathol* 2006; **33**: 512–5.
9 Garrido-Ruiz MC, Enguita-Valls AB, de Arriba MG *et al*. Lichenoid sarcoidosis: a case with clinical and histopathological lichenoid features. *Am J Dermatopathol* 2008; **30**: 271–3.
10 Miyagawa S, Komatsu M, Okuchi T *et al*. Erythema dyschromicum perstans: immunopathologic studies. *J Am Acad Dermatol* 1989; **20**: 882–6.
11 Bhutani LK. Ashy dermatosis or lichen planus pigmentosus: what is in a name? *Arch Dermatol* 1986; **122**: 133.
12 Torrelo A, Zaballos P, Colmenero I *et al*. Erythema dyschromicum perstans in children: a report of 14 cases. *J Eur Acad Dermatol Venereol* 2005; **19**: 422–6.

Prognosis [1–5]

Occasional cases clear in a few weeks, but skin lesions more usually subside within 9 months in about 50% of cases, and in 85% have cleared within 18 months, unless treated with systemic corticosteroids or potent topical steroids. Itching disappears first, then papules flatten, to be replaced by a corresponding area of post-inflammatory hyperpigmentation.

If hypertrophic patches develop, they are likely to persist for many more months, and occasionally for 20 years or more. The development of large, annular lesions is also a poor prognostic sign. Hair fall is usually permanent. Mucous membrane lesions clear more slowly than those on the skin and may remain visible for years after all evidence of the skin lesions has cleared [5]. Only 13% of patients with oral LP under follow-up in a large series went into remission [6], although mucous membrane lesions in Indian people were reported to be short-lived and without a tendency to malignancy [7]. About one case in five relapses, and frequent attacks occur in a small minority of cases.

References

1 Altman J, Perry HO. The variations and course of lichen planus. *Arch Dermatol* 1961; **84**: 179–91.
2 Hard S, Holmberg P. Spontaneous healing time in lichen ruber planus. *Acta Derm Venereol (Stockh)* 1959; **39**: 324–6.
3 Schmidt H. Frequency, duration and localization of lichen planus. A study based on 181 patients. *Acta Derm Venereol (Stockh)* 1961; **41**: 164–7.
4 Samman PD. Lichen planus. An analysis of 200 cases. *Trans Rep St John's Hosp Derm Soc Lond* 1961; **46**: 36–8.
5 Vincent SD, Fotos PG, Baker KA, Williams TP. Oral lichen planus. Clinical, historical, and therapeutic features of 100 cases. *Oral Surg Oral Med Oral Pathol* 1990; **70**: 165–71.
6 Porter S, Scully C. Management of oral lichen planus. *Br J Dermatol* 2000; **143**: 201.
7 Sehgal VN, Rege VL. Lichen planus. An appraisal of 147 cases. *Ind J Dermatol Venereol* 1974; **40**: 104–7.

Treatment

A large number of different forms of medication have been advocated, without adequate controlled trials [1]. Symptomatic treatment is usually sufficient, and largely consists of the use of the fluorinated topical steroid creams and ointments. These should be of the 'potent' variety (e.g. fluocinonide 0.05%, clobetasol proprionate 0.05%) to have any real chance of being effective. They are

recommended for comparatively small areas, but in a diluted form (e.g. 1 : 4 in white soft paraffin) can cover much larger areas. Oral antihistamines such as promethazine hydrochloride, alimemazine tartrate, chlorphenamine maleate or hydroxyzine hydrochloride may be helpful for pruritus. Hypertrophic lesions may be treated with occlusive dressings of tar or flurandrenolone tape, topical steroid preparations under polythene occlusion, or intralesional steroid injection. Topical tacrolimus is often advocated for mucous membrane LP (see below) and has been reported as effective in ulcerative LP of the sole [2]. Skin grafting has also been used for ulcerative lesions on the soles [3]. Topical calcipotriol is of limited use [4]; topical aloe vera gel was reported as helpful in oral LP [5].

Systemic corticosteroids, either stimulated by injection of adrenocorticotrophic hormone (ACTH) or tetracosactrin (Synacthen®), or administered as prednisolone at 20 mg daily for about 6 weeks and thereafter gradually reduced, may be of great value in treating the 5% of severe cases with marked irritation, ulcerative mucous membrane lesions, or progressive nail destruction or alopecia [6]. Equivalent doses are sufficient to retard growth in children [7]. Some relapse is liable to occur on discontinuation of systemic steroids, but the disease is self-limiting and corticosteroid therapy eases the patient through the worst part of its course.

Other agents used in treating severe cutaneous or erosive LP have included acitretin [8], itraconazole [9], metronidazole [10–12], low-molecular-weight heparin (enoxaparin) [13,14], tetracycline antibiotics [15], sulfasalazine [16], broad or narrow-band ultraviolet B phototherapy [17–19], oral or bath photochemotherapy with psoralen and UVA (PUVA) [19–22], Re-PUVA (retinoids with PUVA; this combination, however, has anecdotally induced dramatic hyperpigmentation) [23], ultraviolet A1 phototherapy [24], cyclophosphamide [25], azathioprine [26–28], methotrexate [29], recombinant IFN-α-2b [30], basiliximab [31], mycophenolate mofetil [32], and systemic ciclosporin (cyclosporin) [33–35]. Topical and systemic ciclosporin have been used to treat ulcerative LP of the feet [36,37]. Systemic ciclosporin [38,39] and thalidomide [40–42] have been helpful in management of lichen planopilaris of the scalp. Efalizumab [43] and alefacept [44,45] have been used for generalized or erosive LP.

Mucous membranes. Treatment of oral lesions has been reviewed [46,47]. Topical lidocaine (lignocaine) gel or diphenhydramine may alleviate discomfort, and topical tetracycline may be useful [48]. Topical corticosteroids, such as triamcinolone in Orabase®, clobetasol propionate as an ointment or a paste [49–52], corticosteroid lozenges (Corlan®), betamethasone (Betnesol®) mouthwashes 0.5 mg three to four times daily [53], or fluticasone propionate spray [53], are often beneficial. Vaginal hydrocortisone suppositories have been advocated [54,55]. The use of silastic prosthetic devices to enhance the delivery of topical corticosteroids to mucosal surfaces (e.g. vagina and oral) has been documented [56]. Intralesional steroid injections may be used but are painful [57]. Reactivation of human papillomavirus may occur at genital sites with topical steroids [58]. Topical ciclosporin for chronic mucosal LP has been of variable benefit and is expensive [59–62]. There has been a spate of papers on the merits of topical tacrolimus or pimecrolimus in oral, genital and perianal mucous membrane LP [63–69].

Extensive ulcerative lesions should be treated with systemic steroid preparations, but the starting dose will need to be higher than for treatment of skin lesions. Oral ciclosporin can be effective [70]. Griseofulvin [71], dapsone [72], hydroxychloroquine [73], retinoids (either topical in the form of retinaldehyde [74], isotretinoin gel (0.1%) [75], or tazarotene [76], or systemic as with etretinate [77], isotretinoin [78] or acitretin [79]), and thalidomide [80], have all had their advocates. The heparinoid sulodexide, given systemically, was judged as effective as topical ciclosporin [81].

Carbon dioxide and Nd : Yag laser therapy [47,82], as well as the 308-nm UVB excimer laser [83], have been utilized in the treatment of oral LP, as have efalizumab [84] and extracorporeal photochemotherapy [85]. Surgical excision of persistent ulcers has been recommended [86], and malignancy demands immediate surgery combined with radiotherapy.

References

1 Chan ES, Thornhill M, Zakrzewska J. Interventions for treating oral lichen planus. *Cochrane Database Syst Rev* 2000; **2**: CD001168.

2 Al-Khenaizan S, Al Mubarak L. Ulcerative lichen planus of the sole: excellent response to topical tacrolimus. *Int J Dermatol* 2008; **47**: 626–8.

3 Zijdenbos LM, Starink TM, Spronk CA. Ulcerative lichen planus with associated sicca syndrome and good therapeutic result of skin grafting. *J Am Acad Dermatol* 1985; **13**: 667–8.

4 Bayramgurler D, Apaydin R, Bilen N. Limited benefit of topical calcipotriol in lichen planus treatment: a preliminary study. *J Dermatolog Treat* 2002; **13**: 129–32.

5 Choonhakarn C, Busaracome P, Sripanidkulchai B, Sarakarn P. The efficacy of aloe vera gel in the treatment of oral lichen planus: a randomized controlled trial. *Br J Dermatol* 2008; **158**: 573–7.

6 Kellet JK, Ead RD. Treatment of lichen planus with short course of oral prednisolone. *Br J Dermatol* 1990; **123**: 550–1.

7 Brice SL, Barr RJ, Rattet JP. Childhood lichen planus, a question of therapy. *J Am Acad Dermatol* 1980; **3**: 370–6.

8 Laurberg G, Geiger JM, Hjorth N *et al*. Treatment of lichen planus with acitretin. *J Am Acad Dermatol* 1991; **24**: 434–7.

9 Libow LF, Coots NV. Treatment of lichen planus and lichen nitidus with itraconazole: reports of six cases. *Cutis* 1998; **62**: 247–8.

10 Shelley WB, Shelley ED. Urinary tract infection as a cause of lichen planus: metronidazole therapy. *J Am Acad Dermatol* 1984; **10**: 905–7.

11 Wahba-Yahav AV. Idiopathic lichen planus: treatment with metronidazole. *J Am Acad Dermatol* 1995; **33**: 301–2.

12 Buyuk AY, Kavala M. Oral metronidazole treatment of lichen planus. *J Am Acad Dermatol* 2000; **43**: 260–2.

13 Stefanidou MP, Ioannidou DJ, Panayiotides JG, Tosca AD. Low molecular weight heparin; a novel alternative therapeutic approach for lichen planus. *Br J Dermatol* 1999; **141**: 1040–5.

14 Pacheco H, Kerdel F. Successful treatment of lichen planus with lowmolecular-weight heparin: a case series of seven patients. *J Dermatolog Treat* 2001; **12**: 123–6.

15 Hantash BM, Kanzler MH. The efficacy of tetracycline antibiotics for treatment of lichen planus: an open-label clinical trial. *Br J Dermatol* 2007; **156**: 758–60.

16 Bauzá A, España A, Gil P *et al*. Successful treatment of lichen planus with sulfasalazine in 20 patients. *Int J Dermatol* 2005; **44**: 158–62.

17 Pavlotsky F, Nathansohn N, Kriger G *et al*. Ultraviolet-B treatment for cutaneous lichen planus: our experience with 50 patients. *Photodermatol Photoimmunol Photomed* 2008; **24**: 83–6.

18 Taneja A, Taylor CR. Narrow-band UVB for lichen planus treatment. *Int J Dermatol* 2002; **41**: 282–3.

19 Wackernagel A, Legat FJ, Hofer A *et al*. Psoralen plus UVA vs. UVB-311 nm for the treatment of lichen planus. *Photodermatol Photoimmunol Photomed* 2007; **23**: 15–9.

20 Gonzalez E, Khosrow Momtaz T, Freedman S. Bilateral comparison of generalized lichen planus treated with psoralens and ultraviolet A. *J Am Acad Dermatol* 1984; **10**: 958–61.

21 Ortonne JP, Thivolet J, Sannwald C. Oral photochemotherapy in the treatment of lichen planus. *Br J Dermatol* 1978; **99**: 77–88.

22 Kerscher M, Volkenandt M, Lehmann P *et al*. PUVA-bath photochemotherapy of lichen planus. *Arch Dermatol* 1995; **131**: 1210–1.

23 Carlin CS, Florell SR, Krueger GG. Induction of dramatic hyperpigmentation in a patient with generalized lichen planus treated with Re-PUVA. *J Cutan Med Surg* 2002; **6**: 125–7.

24 Polderman MC, Wintzen M, van Leeuwen RL *et al*. Ultraviolet A1 in the treatment of generalized lichen planus: a report of 4 cases. *J Am Acad Dermatol* 2004; **50**: 646–7.

25 Paslin DA. Sustained remission of generalized lichen planus induced by cyclophosphamide. *Arch Dermatol* 1985; **121**: 236–9.

26 Lear JT, English JSC. Erosive and generalized lichen planus responsive to azathioprine. *Br J Dermatol* 1996; **21**: 56–7.

27 Verma KK, Sirka CS, Khaitan BK. Generalized severe lichen planus treated with azathioprine. *Acta Derm Venereol (Stockh)* 1999; **79**: 493.

28 Verma KK, Mittal R, Manchanda Y. Azathioprine for the treatment of severe erosive oral and generalized lichen planus. *Acta Derm Venereol (Stockh)* 2001; **81**: 378–9.

29 Nylander Lundqvist E, Wahlin YB, Hofer PA. Methotrexate supplemented with steroid ointments for the treatment of severe erosive lichen ruber. *Acta Derm Venereol (Stockh)* 2002; **82**: 63–4.

30 Hildebrand A, Kolde G, Luger TA *et al*. Successful treatment of generalized lichen planus with recombinant interferon alfa-2b. *J Am Acad Dermatol* 1995; **33**: 880–3.

31 Rebora A, Parodi A, Murialdo G. Basiliximab is effective for erosive lichen planus. *Arch Dermatol* 2002; **138**: 1100–1.

32 Dalmau J, Puig L, Roé E *et al*. Successful treatment of oral erosive lichen planus with mycophenolate mofetil. *J Eur Acad Dermatol Venereol* 2007; **21**: 259–60.

33 Higgins EM, Munro CS, Friedmann PS *et al*. Cyclosporin A in the treatment of lichen planus. *Arch Dermatol* 1989; **125**: 1436.

34 Ho VC, Gupta AK, Ellis CN *et al*. Treatment of severe lichen planus with cyclosporine. *J Am Acad Dermatol* 1990; **22**: 64–8.

35 Levell NJ, Munro CS, Marks JM. Severe lichen planus clears with very low-dose cyclosporin. *Clin Exp Dermatol* 1992; **17**: 66–7.

36 Pacj M, Silva R. Treatment of plantar erosive lichen planus with topical cyclosporin. *J Eur Acad Dermatol Venereol* 2001; **15**: 79–80.

37 Cecchi R, Giomi A, Bartoli L. Cyclosporine A in chronic ulcerative lichen planus of the feet. *Eur J Dermatol* 1994; **4**: 68.

38 Bottoni U, Innocenzi D, Carlesimo M. Treatment of Piccardi–Lassueur–Graham Little syndrome with cyclosporine A. *Eur J Dermatol* 1995; **5**: 216–9.

39 Mirmirani P, Willey A, Price VH. Short course of oral cyclosporine in lichen planopilaris. *J Am Acad Dermatol* 2003; **49**: 667–71.

40 George SJ, Hsu S. Lichen planopilaris treated with thalidomide. *J Am Acad Dermatol* 2001; **45**: 965–6.

41 Boyd AS, King LE Jr. Thalidomide-induced remission of lichen planopilaris. *J Am Acad Dermatol* 2002; **47**: 967–8.

42 Doherty SD, Hsu S. A case series of 48 patients treated with thalidomide. *J Drugs Dermatol* 2008; **7**: 769–73.

43 Böhm M, Luger TA. Lichen planus responding to efalizumab. *J Am Acad Dermatol* 2007; **56** (5 Suppl.): S92–3.

44 Fivenson DP, Mathes B. Treatment of generalized lichen planus with alefacept. *Arch Dermatol* 2006; **142**: 151–2.

45 Chang AL, Badger J, Rehmus W, Kimball AB. Alefacept for erosive lichen planus: a case series. *J Drugs Dermatol* 2008; **7**: 379–83.

46 Scully C, Eisen D, Carrozzo M. Management of oral lichen planus. *Am J Clin Dermatol* 2000; **1**: 287–306.

47 Setterfield JF, Black MM, Challacombe SJ. The management of oral lichen planus. *Clin Exp Dermatol* 2000; **25**: 176–82.

48 Walchner M, Messer G, Salomon N *et al*. Topical tetracycline treatment of erosive oral lichen planus. *Arch Dermatol* 1999; **135**: 92–3.

49 Lo Muzio L, della Valle A, Mignogna MD *et al*. The treatment of oral aphthous ulceration or erosive lichen planus with topical clobetasol propionate in three preparations: a clinical and pilot study on 54 patients. *J Oral Pathol Med* 2001; **30**: 611–7.

50 Gonzalez-Moles MA, Morales P, Rodriguez-Archilla A *et al*. Treatment of severe chronic oral erosive lesions with clobetasol propionate in aqueous solution. *Oral Surg Oral Med Oral Pathol* 2002; **93**: 264–70.

51 Carbone M, Goss E, Carrozzo M *et al*. Systemic and topical corticosteroid treatment of oral lichen planus: a comparative study with long-term follow-up. *J Oral Pathol Med* 2003; **32**: 323–9.

52 Gonzalez-Moles MA, Ruiz-Avila I, Rodriguez-Archilla A *et al*. Treatment of severe erosive gingival lesions by topical application of clobetasol propionate in custom trays. *Oral Surg Oral Med Oral Pathol* 2003; **95**: 688–92.

53 Hegarty AM, Hodgson TA, Lewsey JD, Porter SR. Fluticasone propionate spray and betamethasone sodium phosphate mouthrinse. A randomized crossover study for the treatment of symptomatic oral lichen planus. *J Am Acad Dermatol* 2002; **47**: 271–9.

54 Sobel JD. Treatment of vulvovaginal lichen planus with vaginal hydrocortisone suppositories. *Curr Infect Dis Rep* 2002; **4**: 507–8.

55 Anderson M, Kutzner S, Kaufman RH. Treatment of vulvovaginal lichen planus with vaginal hydrocortisone suppositories. *Obstet Gynecol* 2002; **100**: 359–62.

56 Walsh DS, Dunn CL, Konzelman J *et al*. A vaginal prosthetic device as an aid in treating ulcerative lichen planus of the mucous membrane. *Arch Dermatol* 1995; **131**: 265–7.

57 Keate RF, Williams JW, Connolly SM. Lichen planus esophagitis: report of three patients treated with oral tacrolimus or intraesophageal corticosteroid injections or both. *Dis Esophagus* 2003; **16**: 47–53.

58 von Krogh G, Dahlman-Ghozlan K, Syrjanen S. Potential human papillomavirus reactivation following topical corticosteroid therapy of genital lichen sclerosus and erosive lichen planus. *J Eur Acad Dermatol Venereol* 2002; **16**: 130–3.

59 Sieg P, Von Domarus H, Von Zitzewitz V *et al*. Topical cyclosporin in oral lichen planus: a controlled randomized, prospective trial. *Br J Dermatol* 1995; **132**: 790–4.

60 Demitsu T, Sato T, Inoue T *et al*. Corticosteroid-resistant erosive oral lichen planus successfully treated with topical cyclosporine therapy. *Int J Dermatol* 2000; **39**: 79–80.

61 Feliciani C, Tulli A. Topical cyclosporin in the treatment of dermatologic diseases. *Int J Immunopathol Pharmacol* 2002; **15**: 89–93.

62 Conrotto D, Carbone M, Carrozzo M *et al*. Ciclosporin vs. clobetasol in the topical management of atrophic and erosive oral lichen planus: a double-blind, randomized controlled trial. *Br J Dermatol* 2006; **154**: 139–45.

63 Watsky KL. Erosive perianal lichen planus responsive to tacrolimus. *Int J Dermatol* 2003; **42**: 217–8.

64 Byrd JA, Davis MD, Rogers RS 3rd. Recalcitrant symptomatic vulvar lichen planus: response to topical tacrolimus. *Arch Dermatol* 2004; **140**: 715–20.

65 Byrd JA, Davis MD, Bruce AJ *et al*. Response of oral lichen planus to topical tacrolimus in 37 patients. *Arch Dermatol* 2004; **140**: 1508–12.

66 Donovan JC, Hayes RC, Burgess K *et al*. Refractory erosive oral lichen planus associated with hepatitis C: response to topical tacrolimus ointment. *J Cutan Med Surg* 2005; **9**: 43–6.

67 Meyer S, Burgdorff T, Szeimies RM *et al*. Management of erosive lichen planus with topical tacrolimus and recurrence secondary to metoprolol. *J Eur Acad Dermatol Venereol* 2005; **19**: 236–9.

68 Shichinohe R, Shibaki A, Nishie W *et al*. Successful treatment of severe recalcitrant erosive oral lichen planus with topical tacrolimus. *J Eur Acad Dermatol Venereol* 2006; **20**: 66–8.

69 Volz T, Caroli U, Lüdtke H *et al*. Pimecrolimus cream 1% in erosive oral lichen planus—a prospective randomized double-blind vehicle-controlled study. *Br J Dermatol* 2008; **159**: 936–41.

70 Giomi B, Pestelli E, Massi D *et al*. Vulvar lichen planus associated with ulcerative colitis. A case report. *J Reprod Med* 2003; **48**: 209–12.

71 Bagan JV, Silvestre FJ, Mestre S *et al*. Treatment of lichen planus with griseofulvin: report of seven cases. *Oral Surg Oral Med Oral Pathol* 1985; **60**: 608–10.

72 Falk DK, Lataur DL, King LE Jr. Dapsone in the treatment of erosive lichen planus. *J Am Acad Dermatol* 1985; **12**: 567–70.

73 Eisen D. Hydroxychloroquine sulfate (Plaquenil) improves oral lichen planus: an open trial. *J Am Acad Dermatol* 1993; **28**: 609–12.

74 Boisnic S, Licu D, Ben Slama L *et al*. Topical retinaldehyde treatment in oral lichen planus and leukoplakia. *Int J Tissue React* 2002; **24**: 123–30.

75 Giustina TA, Stewart JCB, Ellis CN *et al*. Topical application of isotretinoin gel improves oral lichen planus. *Arch Dermatol* 1986; **122**: 534–6.

76 Petruzzi M, De Benedittis M, Grassi R *et al*. Oral lichen planus: a preliminary clinical study on treatment with tazarotene. *Oral Dis* 2002; **8**: 291–5.
77 Hersle K, Mobacken H, Sloberg K *et al*. Severe oral lichen planus: treatment with an aromatic retinoid (etretinate). *Br J Dermatol* 1982; **106**: 77–80.
78 Straus ME, Bergfeld WF. Treatment of oral lichen planus with low-dose isotretinoin. *J Am Acad Dermatol* 1984; **11**: 527–8.
79 Laurberg G, Geiger JM, Hjorth N *et al*. Treatment of lichen planus with acitretin. *J Am Acad Dermatol* 1991; **24**: 434–7.
80 Camisa C, Popovsky JL. Effective treatment of oral erosive lichen planus with thalidomide. *Arch Dermatol* 2000; **136**: 1442–3.
81 Femiano F, Gombos F, Scully C. Oral erosive/ulcerative lichen planus: preliminary findings in an open trial of sulodexide compared with cyclosporine (ciclosporin) therapy. *Int J Dermatol* 2003; **42**: 308–11.
82 van der Hem PS, Egges M, van der Wal JE, Roodenburg JL. CO_2 laser evaporation of oral lichen planus. *Int J Oral Maxillofac Surg* 2008; **37**: 630–3.
83 Kollner K, Wimmershoff M, Landthaler M, Hohenleutner U. Treatment of oral lichen planus with the 308-nm UVB excimer laser—early preliminary results in eight patients. *Lasers Surg Med* 2003; **33**: 158–60.
84 Heffernan MP, Smith DI, Bentley D *et al*. A single-center, open-label, prospective pilot study of subcutaneous efalizumab for oral erosive lichen planus. *J Drugs Dermatol* 2007; **6**: 310–4.
85 Guyot AD, Farhi D, Ingen-Housz-Oro S *et al*. Treatment of refractory erosive oral lichen planus with extracorporeal photochemotherapy: 12 cases. *Br J Dermatol* 2007; **156**: 553–6.
86 Hardman FG, Emslie EM. The surgical treatment of oral lichen planus. *Trans Rep St John's Hosp Derm Soc Lond* 1970; **56**: 43–4.

'Mixed' LP/discoid lupus erythematosus disease patterns

Discoid lupus erythematosus (DLE) and LP are usually considered as distinct entities with characteristic clinical, histopathological and immunopathological features, with basement membrane deposition of IgG in DLE [1,2]. However, similarities between LP and DLE have been noted [3]. In addition, there have been several reports of patients showing overlapping features of both disorders [4–12]. Chronic atrophic DLE-like lesions on the head, neck and upper trunk may accompany reticular white lesions in the oral cavity, and combinations of lichenoid or verrucous lesions are seen. Eyelid involvement is recorded [13]. The association of extensive generalized LP with subacute cutaneous DLE has been documented [14]. Both ciclosporin [14] and acitretin [15] can be of benefit in treating LP/DLE overlap syndrome.

References

1 Potts EDA, Rowell NR. Lichen planus: a distinct entity from lupus erythematosus. *Acta Derm Venereol (Stockh)* 1981; **61**: 413–6.
2 Nieboer C. The reliability of immunofluorescence and histopathology in the diagnosis of discoid lupus erythematosus and lichen planus. *Br J Dermatol* 1987; **116**: 189–98.
3 Marren P, De Berker D, Wojnarowska F *et al*. The dermo-epidermal interface in lichen planus and lupus erythematosus. *Eur J Dermatol* 1994; **4**: 58–62.
4 Copeman PWM, Schroeter AL, Kierland RR. An unusual variant of lupus erythematosus or lichen planus. *Br J Dermatol* 1970; **83**: 269–72.
5 Davies MG, Gorkiewicz A, Knight A *et al*. Is there a relationship between lupus erythematosus and lichen planus? *Br J Dermatol* 1977; **96**: 145–54.
6 Nagy E, Szakaly I. Lupus erythematosus discoides oder Lichen planus? *Z Hautkr* 1978; **53**: 599–60.
7 Piamphongsant T, Sawanna Preecha S, Gritiyarangon P *et al*. Mixed lichen planus–lupus erythematosus disease. *J Cutan Pathol* 1978; **5**: 209–15.
8 Romero RW, Nesbitt LT, Reed R. Unusual variant of lupus erythematosus or lichen planus. *Arch Dermatol* 1977; **113**: 741–8.
9 Uitto J, Santa-Cruz DJ, Eisen AZ *et al*. Verrucous lesions in patients with discoid lupus erythematosus: clinical, histopathological and immunofluorescence studies. *Br J Dermatol* 1978; **98**: 507–20.
10 Van der Horst JC, Cirkel PKS, Nieboer C. Mixed lichen planus-lupus erythematosus disease—a distinct entity? Clinical, histopathological and immunopathological studies in six patients. *Clin Exp Dermatol* 1983; **8**: 631–40.
11 Mahler V, Hornstein OP, Meyer S *et al*. Lupus erythematosus/lichen ruber planus overlap syndrome. Five cases in a patient sample of the Erlangen University Dermatology Clinic (1894–1995). *Hautarzt* 1998; **49**: 295–302.
12 Nagao K, Chen KR. A case of lupus erythematosus/lichen planus overlap syndrome. *J Dermatol* 2006; **33**: 187–90.
13 Tursen U, Oz O, Ikizoglu G *et al*. A case of lichen planus–lupus erythematosus overlap syndrome with eyelid involvement. *Eur J Ophthalmol* 2002; **12**: 244–6.
14 Grabbe S, Kalde G. Co-existing lichen planus and subacute cutaneous lupus erythematosus. *Clin Exp Dermatol* 1995; **20**: 249–54.
15 De Jong EM, Van De Kerkhof PC. Coexistence of palmoplantar lichen planus and lupus erythematosus with response to treatment using acitretin. *Br J Dermatol* 1996; **134**: 538–41.

Bullous LP and LP pemphigoides

Lichen ruber pemphigoides was first described by Kaposi in 1892 [1]. Bullous LP and LP pemphigoides were in the past differentiated solely on clinical and histological criteria [2], but can now be differentiated using IMF procedures and immunoelectron-microscopy [3,4]. In bullous LP, blisters arise only on or near the lesions of LP, as a result of severe liquefaction degeneration of the basal cell layer [5]. Histologically, there is subepidermal bulla formation with typical changes of LP, and direct and indirect IMF is negative [3]. The eruption is usually only of short duration [3].

In LP pemphigoides [6–9], the LP tends to be acute and generalized and is followed by the sudden appearance of large bullae on both involved and uninvolved skin (Fig. 41.26). Occasionally, even in LP pemphigoides, blisters may arise only on the lesions of LP [10]. LP pemphigoides has been precipitated by PUVA [11] and has evolved into pemphigoid nodularis [12]. An LP pemphigoides-like eruption has been reported to overlap with paraneoplastic pemphigus [13,14]. In LP pemphigoides, the histology shows



Fig. 41.26 Lichen planus pemphigoides. Large bulla arising on and around vicinity of lichen planus around ankle. (Courtesy of St John's Institute of Dermatology, King's College London, UK.)

a subepidermal bulla with no evidence of associated LP [3]. Direct IMF shows linear basement-membrane-zone deposition of IgG and C3 in perilesional skin [3,9]. Immunoelectron-microscopic studies reveal deposition of IgG and C3 in the base of the bulla and not in the roof as found in bullous pemphigoid [15].

Immunoblotting data have revealed that circulating autoantibodies in LP pemphigoides react with an epitope within the C-terminal NC16A domain of bullous pemphigoid 180-kDa antigen, and also with a 200-kDa antigen detected in bullous pemphigoid [16–21]. It seems that epidermal damage from liquefaction degeneration in LP exposes basement-membrane antigens, and consequent stimulation of autoantibody production.

The mean age of patients with LP pemphigoides is lower than that of those with classical bullous pemphigoid, and the course of the disease also tends to be less severe. Nevertheless, some cases require treatment with systemic steroids or azathioprine and fatalities occur [9]. A combination of corticosteroids and acitretin has been used [21,22].

References

1 Kaposi M. Lichen ruber pemphigoides. *Arch Dermatol Syphilol* 1892; **24**: 343–6.
2 Sarkany I, Caron GA, Jones HH. Lichen planus pemphigoides. *Trans St John's Hosp Derm Soc Lond* 1964; **50**: 50–5.
3 Gawkrodger DJ, Stavropoulos PG, McLaren KM *et al*. Bullous lichen planus and lichen planus pemphigoides—clinico-pathological comparisons. *Clin Exp Dermatol* 1989; **14**: 150–3.
4 Murphy GM, Cronin E. Lichen planus pemphigoides. *Clin Exp Dermatol* 1989; **14**: 322–4.
5 Ebner H, Erlach E, Gebhart W. Untersuchurgen über die Blasenbildung bein Lichen ruber planus. *Arch Dermatol Forsch* 1973; **247**: 193–205.
6 Bouloc A, Vignon-Pennamen MD, Caux F *et al*. Lichen planus pemphigoides is a heterogeneous disease: a report of five cases studied by immunoelectron microscopy. *Br J Dermatol* 1998; **138**: 972–80.
7 Swale VJ, Black MM, Bhogal BS. Lichen planus pemphigoides: two case reports. *Clin Exp Dermatol* 1998; **23**: 132–5.
8 Demircay Z, Baykal C, Demirkesen C. Lichen planus pemphigoides: report of two cases. *Int J Dermatol* 2001; **40**: 757–9.
9 Mora RG, Nesbitt LT, Brantley JB. Lichen planus pemphigoides: clinical and immunofluorescent findings in four cases. *J Am Acad Dermatol* 1983; **8**: 331–6.
10 Archer CB, Cronin E, Smith NP. Diagnosis of lichen planus pemphigoides in the absence of bullae on normal appearing skin. *Clin Exp Dermatol* 1992; **17**: 433–6.
11 Kuramoto N, Kishimoto S, Shibagaki R, Yasuno H. PUVA-induced lichen planus pemphigoides. *Br J Dermatol* 2000; **142**: 509–12.
12 Sakuma-Oyama Y, Powell AM, Albert S *et al*. Lichen planus pemphigoides evolving into pemphigoid nodularis. *Clin Exp Dermatol* 2003; **28**: 613–6.
13 Stevens SR, Griffiths CEM, Anhalt GJ *et al*. Paraneoplastic pemphigus presenting as a lichen planus pemphigoides-like eruption. *Arch Dermatol* 1993; **129**: 866–9.
14 Hsiao CJ, Hsu MM, Lee JY *et al*. Paraneoplastic pemphigus in association with a retroperitoneal Castleman's disease presenting with a lichen planus pemphigoides-like eruption. A case report and review of literature. *Br J Dermatol* 2001; **144**: 372–6.
15 Prost C, Tesserand F, Laroche L *et al*. Lichen planus pemphigoides: an immunoelectron microscopic study. *Br J Dermatol* 1985; **113**: 31–6.
16 Davis A, Wojnarowska F, Bhogal B *et al*. Lichen planus pemphigoides and its relationship to bullous pemphigoid. *Br J Dermatol* 1989; **120**: 296.
17 Tamada Y, Yokochi K, Nitta Y *et al*. Lichen planus pemphigoides: identification of 180 Kd hemidesmosome antigen. *J Am Acad Dermatol* 1995; **32**: 883–7.
18 Zillikens D, Caux F, Mascaro JM *et al*. Autoantibodies in lichen planus pemphigoides react with a novel epitope within the C-terminal NC16A domain of BP180. *J Invest Dermatol* 1999; **113**: 117–21.
19 Skaria M, Salomon D, Jaunin F *et al*. IgG autoantibodies from a lichen planus pemphigoides patient recognize the NC16A domain of the bullous pemphigoid antigen 180. *Dermatology* 1999; **199**: 253–5.
20 Hsu S, Ghohestani RF, Uitto J. Lichen planus pemphigoides with IgG autoantibodies to the 180 kd bullous pemphigoid antigen (type XVII collagen). *J Am Acad Dermatol* 2000; **42**: 136–41.
21 Yoon KH, Kim SC, Kang DS, Lee IJ. Lichen planus pemphigoides with circulating autoantibodies against 200 and 180 kDa epidermal antigens. *Eur J Dermatol* 2000; **10**: 212–4.
22 Kolb-Maurer A, Sitaru C, Rose C *et al*. Treatment of lichen planus pemphigoides with acitretin and pulsed corticosteroids. *Hautarzt* 2003; **54**: 268–73.

Lichen nitidus [1]

Lichen nitidus is a rarer condition than idiopathic LP and is clinically characterized by the presence of pinpoint to pinhead-sized papules, which are usually asymptomatic, flesh coloured, with a flat, shiny surface.

Aetiology. The view that lichen nitidus represents a variant of LP tends to be supported by the fact that early, tiny LP papules may be clinically and histopathologically indistinguishable from lichen nitidus [2,3]. Immunophenotypic studies also reinforce the association between LP and lichen nitidus [4]. However, some authorities favour a separation into two dermatoses, because of histopathological differences, or differences in cytokine expression in lichen nitidus [5]. Surprisingly, direct IMF studies in lichen nitidus have given negative results [6,7]. However, ultrastructural studies have shown identical changes in lichen nitidus and LP [6].

Histology. The histology of a typical papule is characteristic. The papule is formed by an intense infiltrate situated immediately below the epidermis and is well circumscribed. The infiltrate consists of lymphocytes and histiocytes and there are often a few Langhans' giant cells (Fig. 41.27). Sometimes, plasma cells are numerous in the infiltrate [8]. The overlying epidermis is flattened and sometimes there is liquefaction degeneration of the basal cell

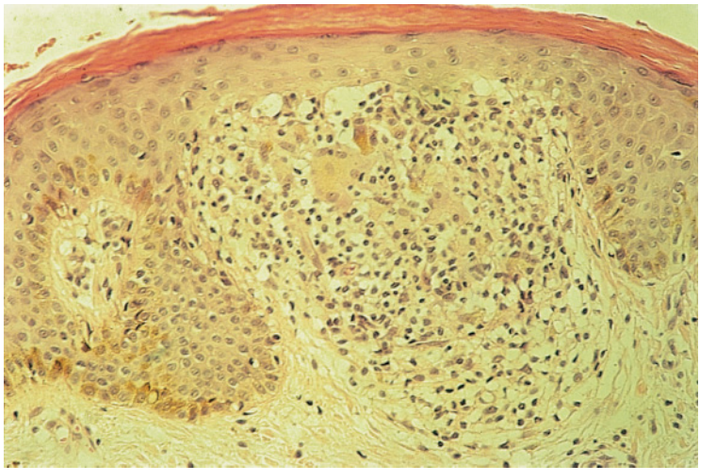


Fig. 41.27 Lichen nitidus. Typical histology showing the focally dense infiltrate containing a few giant cells. H&E × 100. (Courtesy of St John's Institute of Dermatology, King's College London, UK.)



Fig. 41.28 Lichen nitidus. Close-up of aggregated, pinhead-sized papules. (Courtesy of St John's Institute of Dermatology, King's College London, UK.)



Fig. 41.29 Lichen nitidus. Aggregates of pinhead-sized papules on shaft of penis. (Courtesy of St John's Institute of Dermatology, King's College London, UK.)

layer. The rete ridges at the margin of the infiltrate are elongated and tend to encircle it. Although tuberculoid in appearance, there is never true tubercle formation or caseation. The histology of a palmar lesion may show a deep parakeratotic plug, which distinguishes it from the palmar lesions of LP [9]. Perifollicular granulomas can occur in spinous and follicular lichen nitidus, which may simulate lichen scrofulosorum [10]. Perforating lichen nitidus has also been described [11].

Incidence. In its characteristic monomorphic form, lichen nitidus is rare, but lesions of lichen nitidus occurring in association with LP are more common [3]. The age incidence tends to be lower than that of LP. Most cases occur in children or young adults. Familial lichen nitidus has rarely been observed [12].

Natural history. Typical lichen nitidus may clear in a few weeks or last a very long time, and may show little or no response to treatment. There have been no large series reporting the natural history of this disorder. With our present knowledge, its course is unpredictable.

Clinical features. Typical lichen nitidus papules are minute, pinpoint to pinhead sized, and have a flat or dome-shaped, shiny surface. They usually remain discrete, although they may be closely grouped (Fig. 41.28). They are found on any part of the body but the sites of predilection are the forearms, penis (Fig. 41.29), abdomen, chest and buttocks. The eruption is sometimes generalized [13,14]. When the palms or soles are involved, the changes can be those of a confluent hyperkeratosis resembling chronic fissured eczema, or there may be multiple, distinctive, minute papules [15,16]. On the palms, the minute papules can become purpuric [9] and may occasionally resemble pompholyx [17]. Such cases may lack lesions of lichen nitidus elsewhere, so a biopsy is essential to confirm the diagnosis [9,15].

Linear lichen nitidus has been described, but is exceptionally rare [18]. The development of lesions along scratch marks is not uncommon. The lesions are flesh coloured or reddish brown. Although intense pruritus can occur [14], the lesions are generally quite symptomless.

Coexistence with LP is common, and Wilson and Bett [3] claim that lesions clinically identical to those of lichen nitidus can be found in 25–30% of all cases of LP. Nail pitting may coexist with lichen nitidus [19], or the affected nails may appear rough due to increased linear striations and longitudinal ridging [15,20]. An actinic variant has been documented [21].

Mucous membrane lesions occur occasionally and are much rarer than in LP. Krook [22] described a generalized case as having mucosal lesions mainly on the hard palate and maxillary alveolar margins, which consisted of fairly closely grouped, greyish yellow, round, sharply demarcated, discrete papules up to 1 mm in diameter; many were petechial. In other cases, lesions occur that are similar to those in LP.

Lichen nitidus must be distinguished from lichen scrofulosorum [10], where there are grouped follicular papules in small patches on the trunk, and from keratosis pilaris, where there are horny follicular papules mainly on the extensor surface of the limbs. In cases of doubt, a biopsy usually clarifies the diagnosis.

Lichen nitidus has been described in association with Crohn's disease [23], trisomy 21 and congenital megacolon [24].

Treatment. As the disease is often asymptomatic and eventually self-limiting, no treatment is required in most cases, but fluorinated topical steroid preparations may be recommended if treatment is demanded, for example for lesions on the penis, and can be dramatically successful [25]. Clearance of generalized lichen nitidus has been described with sun exposure [26], PUVA [27] or

narrow-band UVB phototherapy [28,29], and astemizole [13,30,31]. Acitretin can lead to a gradual improvement in palmoplantar lichen nitidus [32].

References

1 Pinkus F. Uber eine neue knochtenformige Hauteruption: Lichen nitidus. *Arch Dermatol Syphilol* 1907; **85**: 11–36.
2 Ellis FA, Hill WF. Is lichen nitidus a variant of lichen planus? *Arch Dermatol* 1938; **38**: 569–73.
3 Wilson HTH, Bett DCG. Miliary lesions in lichen planus. *Arch Dermatol* 1961; **83**: 920–3.
4 Wright AL, McVittie E, Hunter JAA. An immunophenotypic study of lichen nitidus. *Clin Exp Dermatol* 1990; **15**: 273–6.
5 Smoller BR, Flynn TC. Immunohistochemical examination of lichen nitidus suggests that it is not a localised papular variant of lichen planus. *J Am Acad Dermatol* 1992; **27**: 232–6.
6 Clausen J, Jacobsen FK, Brandrup F. Lichen nitidus: electron-microscopic and immunofluorescence studies. *Acta Derm Venereol (Stockh)* 1982; **62**: 15–9.
7 Waisman M, Durdon BC, Michel B. Immunofluorescent studies in lichen nitidus. *Arch Dermatol* 1973; **107**: 200–3.
8 Eisen RF, Stenn J, Kahn SM *et al*. Lichen nitidus with plasma cell infiltrate. *Arch Dermatol* 1985; **121**: 1193–4.
9 Coulson IH, Marsden RA, Cook MG. Purpuric palmar lichen nitidus: an unusual though distinctive eruption. *Clin Exp Dermatol* 1988; **13**: 347–9.
10 Madhok R, Winkelmann RK. Spinous, follicular lichen nitidus associated with perifollicular granulomas. *J Cutan Pathol* 1988; **15**: 245–8.
11 Banse-Kupin L, Morales A, Kleinsmith D. Perforating lichen nitidus. *J Am Acad Dermatol* 1983; **9**: 452–6.
12 Kato N. Familial lichen nitidus. *Clin Exp Dermatol* 1995; **20**: 336–8.
13 Ocampo J, Torne R. Generalized lichen nitidus: report of two cases treated with astemizole. *Int J Dermatol* 1989; **28**: 49–51.
14 Wall LM, Heenan PJ, Papadimitriau JM. Generalized lichen nitidus: a case report. *Australas J Dermatol* 1985; **26**: 36–40.
15 Munro CS, Cox NH, Marks JM *et al*. Lichen nitidus presenting as palmoplantar hyperkeratosis and nail dystrophy. *Clin Exp Dermatol* 1993; **18**: 381–3.
16 Weiss RM, Cohen AD. Lichen nitidus of the palms and soles. *Arch Dermatol* 1971; **104**: 538–40.
17 Porter DI, Samman PD. Lichen nitidus. *Br J Dermatol* 1976; **82**: 423–4.
18 Prigent F, Cavelier-Balloy B, Lemarchand-Venencie F *et al*. Lichen nitidus linéaire. *Ann Dermatol Vénéréol* 1989; **116**: 814–5.
19 Kellett JK, Beck MH. Lichen nitidus with distinctive nail changes. *Clin Exp Dermatol* 1984; **9**: 201–6.
20 Natarajan S, Dick DC. Lichen nitidus associated with nail changes. *Int J Dermatol* 1986; **25**: 461–2.
21 Summey BT, Cusack CA. Actinic lichen nitidus. *Cutis* 2008; **81**: 266–8.
22 Krook G. Purpura in lichen nitidus generalisatus. *Acta Derm Venereol (Stockh)* 1959; **39**: 238–46.
23 Kint A, Meysman L, Bugingo G *et al*. Lichen nitidus and Crohn's disease. *Dermatologica* 1982; **164**: 272–7.
24 Patrizi A, Lernia D, Paulazzi P. Lichen nitidus généralisé, trisomie 21 et mégacôlon congenital. *Ann Dermatol Vénéréol* 1991; **118**: 725.
25 Wright S. Successful treatment of lichen nitidus. *Arch Dermatol* 1984; **120**: 155–6.
26 Arizaga A, Gaughan MD, Bang RH. Generalized lichen nitidus. *Clin Exp Dermatol* 2002; **27**: 115–7.
27 Randle HW, Sander HM. Treatment of generalized lichen nitidus with PUVA. *Int J Dermatol* 1986; **25**: 330–1.
28 Kim YC, Shim SD. Two cases of generalized lichen nitidus treated successfully with narrow-band UV-B phototherapy. *Int J Dermatol* 2006; **45**: 615–7.
29 Do MO, Kim MJ, Kim SH *et al*. Generalized lichen nitidus successfully treated with narrow-band UVB phototherapy: two cases report. *J Korean Med Sci* 2007; **22**: 163–6.
30 Thio HB. Lichen nitidus treated with astemizole. *Br J Dermatol* 1993; **129**: 342.
31 Vaughan RY, Graham Smith J Jr. The treatment of lichen nitidus with astemizole. *J Am Acad Dermatol* 1990; **23**: 757–8.
32 Lucker GPH, Koopman RJJ, Steijlen PM *et al*. Treatment of palmoplantar lichen nitidus with acitretin. *Br J Dermatol* 1994; **130**: 791–3.

Symptomatic lichenoid reactions

Lichenoid reactions occur in persons handling developer used in the processing of colour films. Many drugs may produce an eruption identical with or similar to LP.

LP-like contact dermatitis due to contact with colour developing agents and methacrylic acid esters

An LP-type eruption was reported in up to 25% of persons exposed to chemicals in colour developer [1–5]. Lesions began in areas of contact with the developer, but sometimes extended widely; the mucous membranes were usually spared. Resolution was slow, and lesions persisted for months, with residual pigmentation lasting for a year or more. The responsible chemicals were substituted paraphenylene diamines. Current automated equipment minimizes contact with these, and LP-like eruptions due to this source are now rare [5]. Two types of reaction were observed—acute (eczematous) and subacute (lichenoid)—but either evolved into the other. It is not clear why exposure to colour developers caused a spongiotic dermatitis in some patients and a lichenoid dermatitis in others [5]. Patch-test reactions were usually positive to the substituted paraphenylenediamine and were eczematous in nature, but might become lichenoid [4].

LP-like lesions have developed on sites exposed to methacrylic acid esters used in the car industry [6]. As dental devices contain methacrylic acid esters, it is possible that methacrylic acid esters may be one of the causative agents in oral LP [6]. Other inducers of contact lichenoid eruptions include dental restorative materials, musk ambrette, nickel, aminoglycoside antibiotics and gold.

References

1 Buckley WR. Lichenoid eruptions following contact dermatitis. *Arch Dermatol* 1958; **78**: 454–7.
2 Canizares O. Lichen planus-like eruption caused by color developer. *Arch Dermatol* 1959; **80**: 81–6.
3 Fry L. Skin disease from colour developers. *Br J Dermatol* 1965; **77**: 456–61.
4 Liden C. Lichen planus in relation to occupational and non-occupational exposure to chemicals. *Br J Dermatol* 1986; **115**: 23–31.
5 Brancaccio RP, Cockerell CJ, Belsito D *et al*. Allergic contact dermatitis from color film developers: clinical and histologic features. *J Am Acad Dermatol* 1993; **28**: 827–30.
6 Kawamura T, Fukuda S, Ohtake N *et al*. Lichen planus-like contact dermatitis due to methacrylic acid esters. *Br J Dermatol* 1996; **134**: 358–60.

Lichenoid eruptions due to drugs

The reader is also directed to Chapter 75, Table 75.8, as well as to information on individual drugs. The mechanisms by which drugs induce a lichenoid tissue reaction are unknown, but they may develop as a result of autoreactive cytotoxic T-cell clones directed against a drug/class II MHC antigen complex, such that keratinocytes and Langerhans' cells are viewed by the immune system as 'non-self'. Macrophage migration inhibition factor (MIF) assays are significantly increased in lichenoid drug eruptions [1].

Histology. The pattern of an LP-like eruption can be indistinguishable from idiopathic LP, although the cellular infiltrate tends to be more pleomorphic and less dense; helpful histological features indicative of a drug reaction include the following: focal

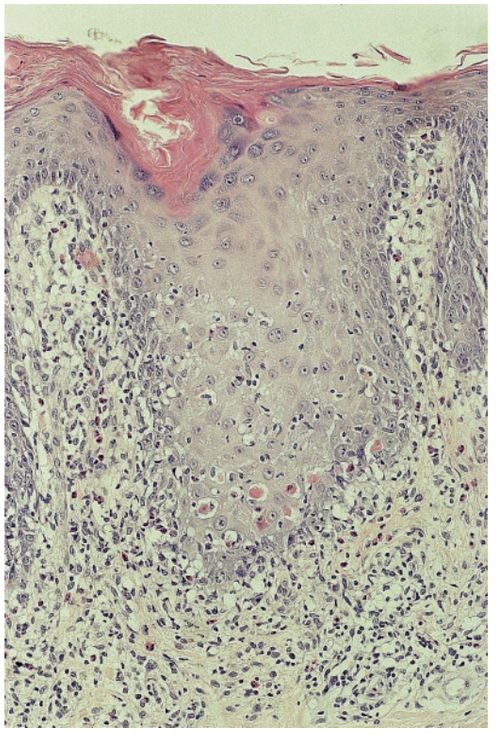


Fig. 41.30 Lichenoid drug eruption (gold). Photomicrograph showing the presence of higher level cytoid bodies with several eosinophils amongst the lichenoid infiltrate. H&E × 20.

parakeratosis; focal interruption of the granular layer (Fig. 41.30); cytoid bodies situated higher in the granular and cornified layers; presence of a few eosinophils; exocytosis of lymphoid cells into the upper epidermis; and a deeper perivascular infiltrate [2]. Later, there may be scarring with destruction of the sweat glands. The histopathology of photodistributed, as opposed to non-photodistributed, lichenoid drug eruptions has been shown to be often indistinguishable from that of idiopathic LP [3]. Occasionally, the degree of lymphoid epidermotropism may simulate mycosis fungoides [4]. The IMF findings in lichenoid drug eruptions are identical to those in idiopathic LP [5].

Clinical features. Lichenoid drug eruptions tend to be extensive, and may develop weeks or months after initiation of therapy; they may progress to an exfoliative dermatitis [6,7]. Lesions may be rather more psoriasiform than in idiopathic LP (Fig. 41.31), and oral involvement is rare. Long-lasting, deep hyperpigmentation, alopecia and skin atrophy with anhidrosis due to sweat gland atrophy may develop. Resolution of the skin eruption may be slow after cessation of therapy, on average from 1 to 4 months, but up to 24 months with gold [8]. Difficulties may arise with antimalarial lichenoid tissue reactions in patients with pre-existing lupus erythematosus [9].



Fig. 41.31 Diffuse psoriasiform lichenoid drug eruption due to β-blocker administration. (Courtesy of St John's Institute of Dermatology, King's College London, UK.)

References

1 Halery S, Sandbank M, Llivni E. Macrophage migration inhibition factor release in lichenoid drug eruption. *J Am Acad Dermatol* 1993; **29**: 263–5.

2 Van Den Haute V, Antoine JL, Lachapelle JM. Histopathological discriminant criteria between lichenoid drug eruption and idiopathic lichen planus: retrospective study on selected samples. *Dermatologica* 1989; **179**: 10–3.

3 West AJ, Berger TG, LeBoit PE. A comparative histopathologic study of photodistributed and nonphotodistributed lichenoid drug eruptions. *J Am Acad Dermatol* 1990; **23**: 689–93.

4 Okun MM, Henner M, Paulson C. A quinine-induced drug reaction of photosensitive distribution with histological features mimicking mycosis fungoides. *Clin Exp Dermatol* 1994; **19**: 246–8.

5 Watnabe C, Hayashi T, Kawada A. Immunofluorescence study of drug-induced lichen planus-like lesions. *J Dermatol* 1981; **8**: 473–7.

6 Almeyda J, Levantine A. Drug reactions XVI. Lichenoid drug eruptions. *Br J Dermatol* 1971; **85**: 604–7.

7 Halevy S, Shai A. Lichenoid drug eruptions. *J Am Acad Dermatol* 1993; **29**: 249–55.

8 Penneys NS, Ackerman AB, Gottlieb NL. Gold dermatitis. *Arch Dermatol* 1974; **109**: 372–6.

9 Geraminejad P, Stone MS, Sontheimer RD. Antimalarial lichenoid tissue reactions in patients with pre-existing lupus erythematosus. *Lupus* 2004; **13**: 473–7.

Causative drugs. The list of drugs causing LP-like eruptions continues to increase steadily. Gold has probably been the most common drug producing an LP-like eruption [1]; oral involvement tends to be rarer in LP-like drug eruptions, but occasionally it can be severe and involve the oesophagus [2]. Mercury-induced lichenoid eruptions are recorded [3], and may be of particular relevance in oral LP (see above). During the Second World War, millions of troops took mepacrine to prevent malaria, and many cases of an LP-like eruption occurred [4]. Mepacrine (quinacrine) lichenoid eruptions may be followed by skin cancers, up to 34 years later. Photodistributed lichenoid lesions [6] may be seen with quinine and quinidine [5–8], demeclocycline [9] and other tetracyclines, thiazide diuretics [10] (Figs 41.32 & 41.33), furosemide (frusemide), diazoxide, amlodipine [11], chlorpromazine, carbamazepine, 5-fluorouracil, pyritinol, ethambutol [12], thioridazine [13], solifenacin [14] and sparfloxacin [15].

Other drugs implicated include: various vaccines [16–23]; streptomycin, isoniazid [24], pyrazinamide [25], cycloserine [26]; pyrimethamine [27]; levopromazine; methyldopa, the α-blocker terazosin [28], and β-blocking agents including propranolol [29], oxprenolol [30], labetalol [31] and nebivolol [32]; sulphydryl drugs such as penicillamine [33], tiopronin [34], captopril [35–37] and enalapril [38]; non-steroidal anti-inflammatory drugs (NSAIDs)



Fig. 41.32 Lichenoid photodermatitis occurring in a patient with a long history of thiazide ingestion. (Courtesy of Dr D.H. McGibbon, St John's Institute of Dermatology, King's College London, UK.)



Fig. 41.33 Close-up of dorsum of finger shown in Fig. 41.32.

[39] including acetylsalicylic acid [40], naproxen [41] and salsalate [42]; levamisole [43]; proton pump inhibitors [44]; the sulfonylureas chlorpropamide and tolazamide [45], glyburide and glimepiride [46,47]; carbamazepine [48]; the statins simvastatin [49], pravastatin [50], and fluvastatin and lovastatin [51]; the antiplatelet drugs clopidogrel [52] and ticlopidine [53]; sildenafil [54,55]; propylthiouracil [56]; interferon and ribavirin treatment of chronic hepatitis C [57,58]; antihistamines [59] including chlorpheniramine [60], roxatidine and ranitidine [61]; isotretinoin [62]; alendronate [63]; PUVA therapy [64]; ursodeoxycholic acid given for neonatal hepatitis [65]; imatinib [66–68]; intravenous immunoglobulin [69]; etanercept [70,71] and adalimumab [72]. Lichenoid reactions have been documented at the sites of injection of granulocyte colony-stimulating factor [73].

Ulcerative lesions may occur with hydroxyurea [74,75], methyldopa, propranolol and lithium carbonate. Oral LP lesions are associated with drugs metabolized by major cytochrome P450-enzymes [76]. Oral involvement may be caused by NSAIDs, gold salts, penicillamine, sulphonylureas, angiotensin-converting enzyme (ACE) inhibitors, methyldopa, allopurinol, ketoconazole, antiretroviral agents including zidovudine [77], clopidogrel [52] and lithium carbonate [78]. Social use of betel nut is relatively common in India and South-East Asia; the product that is chewed, betel quid, is a mixture of substances, including the areca nut and betel leaf, and is associated with oral LP [79,80]. An LP pemphigoides-like eruption has been reported following administration of captopril, cinnarizine [81], simvastatin [82] and oral Chinese herbal therapy [83]. Bullous lesions are recorded with labetalol and tiopronin; LP pigmentosus with gold; and exfoliative dermatitis with nifedipine. Lichenoid photoeruptions have been described in advanced HIV infection; black patients are disproportionately affected and all were taking potential photosensitizing drugs [84]. Hydroxyurea has induced a lichenoid chronic graft-versus-host disease-like acrodermatitis [85].

Treatment. Treatment is to withdraw the drug; with gold eruptions, dimercaprol (BAL) or ethylene diamine tetraacetic acid (EDTA) may be used. Subsequent treatment is symptomatic, but severe cases may require corticosteroid therapy as outlined for idiopathic LP.

References

1 Penneys NS, Ackerman AB, Gottlieb NL. Gold dermatitis. *Arch Dermatol* 1974; **109**: 372–6.

2 Torrelo A, Sonia C, Rocamora A *et al*. Lichen planus-like eruption with esophageal involvement as a result of cyanamide. *J Am Acad Dermatol* 1990; **23**: 1168–9.

3 Kato Y, Hayakawa R, Shiraki R, Ozeki K. A case of lichen planus caused by mercury allergy. *Br J Dermatol* 2003; **148**: 1268–9.

4 Bauer F. Quinacrine hydrochloride drug eruption (tropical lichenoid dermatitis). Its early and late sequelae and its malignant potential. A review. *J Am Acad Dermatol* 1981; **4**: 239–48.

5 Okun MM, Henner M, Paulson C. A quinine-induced drug reaction of photosensitive distribution with histological features mimicking mycosis fungoides. *Clin Exp Dermatol* 1994; **19**: 246–8.

6 Halevy S, Shai A. Lichenoid drug eruptions. *J Am Acad Dermatol* 1993; **29**: 249–55.

7 Meyrick Thomas RH, Munro DD. Lichen planus in photosensitive distribution due to quinine. *Clin Exp Dermatol* 1986; **11**: 97–101.

8 Bonnetblanc JM, Bernard P, Catanzano G *et al*. Quinidine-induced lichenoid photodermatitis. *Ann Dermatol Vénéréol* 1987; **114**: 957–61.

9 Epstein J, Maibach HI, Sams M. Photosensitive lichenoid eruption associated with demeclocycline. *Arch Dermatol* 1974; **109**: 97–8.

10 Johnston GA, Coulson IH. Thiazide-induced lichenoid photosensititity. *Clin Exp Dermatol* 2002; **27**: 670–2.

11 Swale VJ, McGregor JM. Amlodipine-associated lichen planus. *Br J Dermatol* 2001; **144**: 920–1.

12 Grossman ME, Warren K, Mady A *et al*. Lichenoid eruption associated with ethambutol. *J Am Acad Dermatol* 1995; **33**: 675–6.

13 Llambrich A, Lecha M. Photoinduced lichenoid reaction by thioridazine. *Photodermatol Photoimmunol Photomed* 2004; **20**: 10–9.

14 Shalders K, Gach JE. Photodistributed lichenoid drug eruption secondary to solifenacin. *Clin Exp Dermatol* 2008; **33**: 340–1.

15 Hamanaka H, Mizutani H, Shimizu M. Sparfloxacin-induced photosensitivity and the occurrence of a lichenoid tissue reaction after prolonged exposure. *J Am Acad Dermatol* 1998; **38**: 945–9.

16 Pemberton MN, Sloan P, Thakker NS. Oral lichenoid lesions after hepatitis B vaccination. *Oral Surg Oral Med Oral Pathol* 2000; **89**: 717–9.

17 Al-Khenaizan S. Lichen planus occurring after hepatitis B vaccination: a new case. *J Am Acad Dermatol* 2001; **45**: 614–5.

18 Schuh T, Rocken M, Schmoeckel C, Degitz K. Lichen ruber planus after hepatitis B vaccination. *Hautarzt* 2002; **53**: 650–1.

19 Stavrianeas NG, Katoulis AC, Kanelleas A *et al*. Papulonodular lichenoid and pseudolymphomatous reaction at the injection site of hepatitis B virus vaccination. *Dermatology* 2002; **205**: 166–8.

20 Limas C, Limas CJ. Lichen planus in children: a possible complication of hepatitis B vaccines. *Pediatr Dermatol* 2002; **19**: 204–9.

21 Criado PR, de Oliveira Ramos R, Vasconcellos C *et al*. Two case reports of cutaneous adverse reactions following hepatitis B vaccine: lichen planus and granuloma annulare. *J Eur Acad Dermatol Venereol* 2004; **18**: 603–6.

22 Akay BN, Arslan A, Cekirge S *et al*. The first reported case of lichen planus following inactivated influenza vaccination. *J Drugs Dermatol* 2007; **6**: 536–8.

23 Tasanen K, Renko M, Kandelberg P *et al*. Childhood lichen planus after simultaneous measles-mumps-rubella and diphtheria-tetanus-pertussis-polio vaccinations. *Br J Dermatol* 2008; **158**: 646–8.

24 Sharma PK, Gautam RK, Bhardwaj M, Kar HK. Isonicotinic acid hydrazide induced anagen effluvium and associated lichenoid eruption. *J Dermatol* 2001; **28**: 737–41.

25 Choonhakarn C, Janma J. Pyrazinamide-induced lichenoid photodermatitis. *J Am Acad Dermatol* 1999; **40**: 645–6.

26 Shim JH, Kim TY, Kim HO, Kim CW. Cycloserine-induced lichenoid drug eruption. *Dermatology* 1995; **191**: 142–4.

27 Cutler TP. Lichen planus caused by pyrimethamine. *Clin Exp Dermatol* 1980; **5**: 253–6.

28 Koh MJ, Seah PP, Tay YK, Mancer K. Lichenoid drug eruption to terazosin. *Br J Dermatol* 2008; **158**: 426–7.

29 Hawk JLM. Lichenoid drug eruption induced by propranolol. *Clin Exp Dermatol* 1980; **5**: 93–6.

30 Gange RW, Levene GM. A distinctive eruption in patients receiving oxyprenalol. *Clin Exp Dermatol* 1979; **4**: 87–97.

31 Gange RW, Wilson Jones E. Bullous lichen planus caused by labetalol. *BMJ* 1978; **1**: 816–7.

32 Bodmer M, Egger SS, Hohenstein E *et al*. Lichenoid eruption associated with the use of nebivolol. *Ann Pharmacother* 2006; **40**: 1688–90.

33 Powell FC, Roger RS III, Dickson ER. Primary biliary cirrhosis and lichen planus. *J Am Acad Dermatol* 1983; **9**: 540–5.

34 Piérard E, Delaporte E, Flip RM *et al*. Tiopronin-induced lichenoid eruption. *J Am Acad Dermatol* 1994; **31**: 665–7.

35 Bravard P, Barbet M, Eich D *et al*. Captopril induced lichenoid eruption. *Ann Dermatol Vénéréol* 1983; **110**: 433–8.

36 Wong SS, Long CC, Holt PJA. Lichenoid eruption induced by low dose captopril. *Acta Derm Venereol (Stockh)* 1992; **72**: 358–9.

37 Phillips WG, Vaughan-Jones S, Jenkins R *et al*. Captopril-induced lichenoid eruption. *Clin Exp Dermatol* 1994; **19**: 317–20.

38 Ruiz Villaverde R, Blasco Melguizo J, Linares Solano J *et al*. Lichen planus-like eruption due to enalapril. *J Eur Acad Dermatol Venereol* 2003; **17**: 612–4.

39 Potts CJ, Hamberger J, Scully C. The medication of patients with oral lichen planus and the association of non-steroidal anti-inflammatory drugs with erosive lesions. *Oral Surg Oral Med Oral Pathol* 1987; **64**: 541–3.

40 Ruiz Villaverde R, Blasco Melguizo J, Mendoza Guil F *et al*. Generalized lichen planus-like eruption due to acetylsalicylic acid. *J Eur Acad Dermatol Venereol* 2003; **17**: 470–2.

41 Heymann Güne AT, Fetil E, Ilknur T *et al*. Naproxen-induced lichen planus: report of 55 cases. *Int J Dermatol* 2006; **45**: 709–12.

42 Powell ML, Ehrilch A, Belsito DV. Lichenoid drug eruption to salsalate. *J Am Acad Dermatol* 2001; **45**: 616–9.

43 Kirby JD, Black M, McGibbon D. Levamisole induced lichenoid eruptions. *J R Soc Med* 1980; **73**: 208–11.

44 Bong JL, Lucke TW, Douglas WS. Lichenoid drug eruption with proton pump inhibitors. *BMJ* 2000; **320**: 283.

45 Barnett JH, Barnett CM. Lichenoid drug reactions to chlorpropamide and tolazamide. *Cutis* 1984; **34**: 542–4.

46 Fox GN, Harrell CC, Mehregan DR. Extensive lichenoid drug eruption due to glyburide: a case report and review of the literature. *Cutis* 2005; **76**: 41–5.

47 Noakes R. Lichenoid drug eruption as a result of the recently released sulfonylurea glimepiride. *Australas J Dermatol* 2003; **44**: 302–3.

48 Atkin SL, McKenzie TMH, Stevenson CJ. Carbamazepine-induced lichenoid eruption. *Clin Exp Dermatol* 1990; **15**: 382–3.

49 Roger D, Rolle F, Labrousse F *et al*. Simvastatin-induced lichenoid drug eruption. *Clin Exp Dermatol* 1994; **19**: 88–9.

50 Keough Pua VS, Scolyer RA, Barnetson RS. Pravastatin-induced lichenoid drug eruption. *Australas J Dermatol* 2006; **47**: 57–9.

51 Sebök B, Tóth M, Anga B *et al*. Lichenoid drug eruption with HMG-CoA reductase inhibitors (fluvastatin and lovastatin). *Acta Derm Venereol* 2004; **84**: 229–30.

52 Guijarro Guijarro B, Lopez Sanchez AF. Lichenoid reaction caused by Clopidogrel, a new anti-platelet drug. *Med Oral* 2003; **8**: 33–7.

53 Kurokawa I, Umehara M, Nishijima S. Lichen planus-type drug eruption resulting from ticlopidine. *Int J Dermatol* 2005; **44**: 436–7.

54 Goldman BD. Lichenoid drug reaction due to sildenafil. *Cutis* 2000; **65**: 282–3.

55 Antiga E, Melani L, Cardinali C *et al*. A case of lichenoid drug eruption associated with sildenafil citratus. *J Dermatol* 2005; **32**: 972–5.

56 Saito M, Nakamura K, Kaneko F. Lichenoid drug eruption of nails induced by propylthiouracil. *J Dermatol* 2007; **34**: 696–8.

57 Giuliani M, Lajolo C, Sartorio A *et al.* Oral lichenoid lesions in HIV-HCV-coinfected subjects during antiviral therapy: 2 cases and review of the literature. *Am J Dermatopathol* 2008; **30**: 466–71.

58 Grossmann S de M, Teixeira R, de Aguiar MC, do Carmo MA. Exacerbation of oral lichen planus lesions during treatment of chronic hepatitis C with pegylated interferon and ribavirin. *Eur J Gastroenterol Hepatol* 2008; **20**: 702–6.

59 Crowson AN, Magro CM. Lichenoid and subacute cutaneous lupus erythematosus-like dermatitis associated with antihistamine therapy. *J Cutan Pathol* 1999; **26**: 95–9.

60 Kuroda K, Hisanaga Y. The diagnosis of lichen-planus-like contact dermatitis to chlorpheniramine maleate. *Dermatology* 2002; **205**: 281–4.

61 Horiuchi Y, Katagiri T. Lichenoid eruptions due to the H2-receptor antagonists roxatidine and ranitidine. *J Dermatol* 1996; **23**: 510–2.

62 Boyd AS, King LE. Lichenoid drug reaction from isotretinoin therapy. *Cutis* 2001; **68**: 301–3.

63 Lazarov A, Moss K, Plosk N *et al*. Alendronate-induced lichen planus. *Isr Med Assoc J* 2002; **4**: 389–90.

64 Nanda S, Grover C, Reddy BS. PUVA-induced lichen planus. *J Dermatol* 2003; **30**: 151–3.

65 Buyukgebiz B, Arslan N, Ozturk Y *et al*. Drug reaction to ursodeoxycholic acid: lichenoid drug eruption in an infant using ursodeoxycholic acid for neonatal hepatitis. *J Pediatr Gastroenterol Nutr* 2002; **35**: 384–6.

66 Lim DS, Muir J. Oral lichenoid reaction to imatinib (STI 571, Gleevec). *Dermatology* 2002; **205**: 169–71.

67 Ena P, Chiarolini F, Siddi GM, Cossu A. Oral lichenoid eruption secondary to imatinib (Glivec). *J Dermatolog Treat* 2004; **15**: 253–5.

68 Pascual JC, Matarredona J, Miralles J *et al*. Oral and cutaneous lichenoid reaction secondary to imatinib: report of two cases. *Int J Dermatol* 2006; **45**: 1471–3.

69 Smith KJ, Dutka AL, Skelton HG. Lichenoid/interface cutaneous eruptions to IVIg with the primary infusion may be related to the re-regulation of anti-idiotype network. *J Cutan Med Surg* 1998; **3**: 96–101.

70 Bovenschen HJ, Kop EN, Van De Kerkhof PC, Seyger MM. Etanercept-induced lichenoid reaction pattern in psoriasis. *J Dermatolog Treat* 2006; **17**: 381–3.

71 Battistella M, Rivet J, Bachelez H, Lioté F. Lichen planus associated with etanercept. *Br J Dermatol* 2008; **158**: 188–90.

72 De Simone C, Caldarola G, D'Agostino M *et al*. Lichenoid reaction induced by adalimumab. *J Eur Acad Dermatol Venereol* 2008; **22**: 626–7.

73 Viallard AM, Lavenue A, Balme B *et al*. Lichenoid cutaneous drug reaction at injection sites of granulocyte colony-stimulating factor (Filgrastim). *Dermatology* 1999; **198**: 301–3.

74 Rentro L, Kamino H, Raphael B *et al*. Ulcerative lichen planus-like dermatitis associated with hydroxyurea. *J Am Acad Dermatol* 1991; **24**: 143–5.

75 Bohn J, Hansen JP, Menne T. Ulcerative lichen planus-like dermatitis due to long-term hydroxyurea therapy. *J Eur Acad Dermatol Venereol* 1998; **10**: 187–9.

76 Kragelund C, Thomsen CE, Bardow A *et al*. Oral lichen planus and intake of drugs metabolized by polymorphic cytochrome P450 enzymes. *Oral Dis* 2003; **9**: 177–87.

77 Scully C, Diz Dios P. Orofacial effects of antiretroviral therapies. *Oral Dis* 2001; **7**: 205–10.

78 Hogan DJ, Burgess WR, Epstein JD *et al*. Lichenoid stomatitis associated with lithium carbonate. *J Am Acad Dermatol* 1985; **13**: 243–6.

79 Reichart PA, Schmidtberg W, Samaranayake LP, Scheifele C. Betel quid-associated oral lesions and oral *Candida* species in a female Cambodian cohort. *J Oral Pathol Med* 2002; **31**: 468–72.

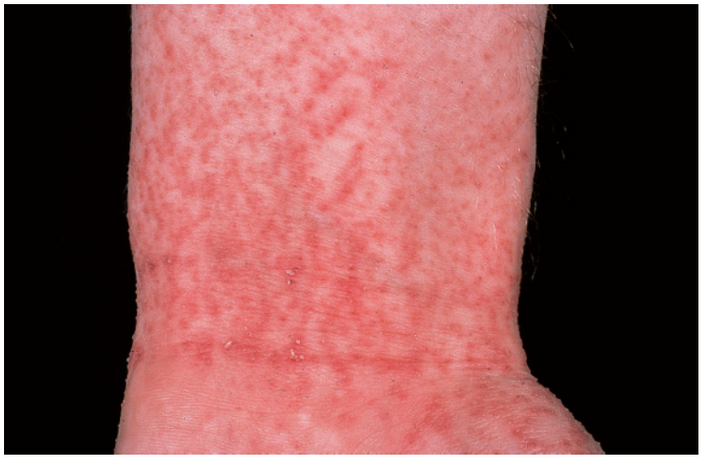


Fig. 41.34 Nékam's disease. Reticulate keratotic erythematous papules on volar aspect of wrist. (Courtesy of St John's Institute of Dermatology, King's College London, UK.)



Fig. 41.35 Nékam's disease. Same patient as shown in Fig. 41.34. Involvement on dorsum of hand. (Courtesy of St John's Institute of Dermatology, King's College London, UK.)

80 Stoopler ET, Parisi E, Sollecito TP. Betel quid-induced oral lichen planus: a case report. *Cutis* 2003; **71**: 307–11.
81 Miyagawa S, Ohi H, Muramatsu T *et al*. Lichen planus pemphigoides-like lesions induced by cinnarizine. *Br J Dermatol* 1985; **112**: 607–13.
82 Stoebner PE, Michot C, Ligeron C *et al*. Simvastatin-induced lichen planus pemphigoides. *Ann Dermatol Vénéréol* 2003; **130**: 187–90.
83 Xu HH, Xiao T, He CD *et al.* Lichen planus pemphigoides associated with Chinese herbs. *Clin Exp Dermatol* 2009; **34**: 329–32.
84 Berger TG, Dhar A. Lichenoid photo-eruptions in human immunodeficiency virus infection. *Arch Dermatol* 1994; **130**: 609–13.
85 Eming SA, Peters T, Hartmann K *et al*. Lichenoid chronic graft-versus-host disease-like acrodermatitis induced by hydroxyurea. *J Am Acad Dermatol* 2001; **45**: 321–3.

Nékam's disease [1–4]

Synonyms
- Keratosis lichenoides chronica
- Orokeratosis striata lichenoides
- Lichen ruber moniliformis
- Lichen verrucosus et reticularis

The variety of synonyms used implies that there is no complete consensus of agreement about this rare disorder. The great majority of cases are adults between the ages of 20 and 40 years [2], although children are occasionally affected [5]. Nékam's disease is characterized by violaceous, papular and nodular lesions typically arranged in a linear and reticulate pattern (Figs 41.34 & 41.35), most marked on the extremities and buttocks, and accompanied by a seborrhoeic dermatitis-like eruption on the face. Nékam's original case was also associated with palmoplantar keratoderma [6]. The individual lesions are erythematous verrucous papules covered by a hyperkeratotic plug that can only be removed with difficulty, revealing irregular indentations and prominent capillary loops [1,7]. In extensive Nékam's disease, the lesions tend to be symmetrical bilaterally, mainly involving the antecubital fossae, extensor forearms, lumbosacral area and buttocks, posterior thighs, popliteal fossae, and less commonly the oral cavity and genitalia. Oral manifestations occur in 50% of patients, recurrent aphthous ulcers, larger chronic ulcers or erythrokeratotic papules being the commonest oral features [2]. The nails can become thickened, longitudinally ridged and prone to paronychia [8]. Cases have followed trauma [9] and erythroderma [10]. A limited variant of Nékam's disease presenting with erythematous hyperkeratotic papules and plaques on the face, clearing in the summer months, has been described in two young siblings [11].

Histologically, changes are often non-specific and consistent with a chronic dermatitis, but lichenoid features can be seen [1,7]. Some authors [1] believe that the condition is an unusual variant of LP, while others [12] consider that it is a distinct entity. A case of Nékam's disease associated with porokeratotic histology and amyloid deposition may also point against the view that Nékam's disease is a subset of LP [13]. A possible association of Nékam's disease with glomerulonephritis and lymphoproliferative disorders has been commented on [2]. The course of the dermatosis is chronic and progressive and very resistant to therapeutic approaches, but has shown a favourable response to photochemotherapy without [14,15] or with [16] acitretin; etretinate [17] and photodynamic therapy [18] have been reported to be helpful.

References

1 Kersey P, Ive FA. Keratosis lichenoides chronica is synonymous with lichen planus. *Clin Exp Dermatol* 1982; **7**: 49–54.
2 Masouyé I, Saurat JM. Keratosis lichenoides chronica. The centenary of another Kaposi's disease. *Dermatology* 1995; **191**: 188–92.
3 Böer A. Keratosis lichenoides chronica: proposal of a concept. *Am J Dermatopathol* 2006; **28**: 260–75.
4 Wozniacka A, Schwartz RA, Omulecki A *et al.* Keratosis lichenoides chronica: a diagnostic and therapeutic challenge. *Clin Exp Dermatol* 2006; **31**: 48–50.
5 Patrizi A, Neri I, Passarim B *et al*. Keratosis lichenoides chronica: a pediatric case. *Dermatology* 1995; **191**: 264–7.
6 Nékam L. Sur la question du lichen moniliformis. *Presse Med* 1938; **46**: 1000.
7 Margolis MH, Cooper GA, Johnson SA. Keratosis lichenoides chronica. *Arch Dermatol* 1972; **105**: 739–43.
8 Baran R, Panizzon R, Goldberg L. The nails in keratosis lichenoides chronica. *Arch Dermatol* 1984; **120**: 1471–4.

9 Haas N, Czaika V, Sterry W. Keratosis lichenoides chronica following trauma. A case report and update of the last literature review. *Hautarzt* 2001; **52**: 629–33.
10 Criado PR, Valente NY, Sittart JA *et al*. Keratosis lichenoides chronica: report of a case developing after erythroderma. *Australas J Dermatol* 2000; **41**: 247–9.
11 Arata J, Seno A, Tada J *et al*. Peculiar facial erythematosquamous lesions in two siblings with cyclical summer improvement and winter relapse: a variant of keratosis lichenoides chronica? *J Am Acad Dermatol* 1993; **28**: 870–3.
12 Braun-Falco O, Bieber T, Heider L. Keratosis lichenoides chronica: a variant or a pathological entity? *Hautarzt* 1989; **40**: 614–22.
13 Stefanato CM, Youssef EAH, Cerio R *et al*. Atypical Nékam's disease—keratosis lichenoides chronica associated with porokeratotic histology and amyloidosis. *Clin Exp Dermatol* 1993; **18**: 274–6.
14 Lang PG. Keratosis lichenoides chronica: successful treatment with psoralen–ultraviolet A therapy. *Arch Dermatol* 1981; **117**: 105–8.
15 Kunte C, Kerschenlohr K, Röcken M, Schirren C. Keratosis lichenoides chronica: treatment with bath-PUVA. *Acta Derm Venereol* 2007; **87**: 182–3.
16 Koseoglu RD, Sezer E, Yuksek J. Keratosis lichenoides chronica treated with acitretin plus narrowband ultraviolet B phototherapy. *J Dermatol* 2008; **35**: 172–4.
17 David M, Filhaber A, Rotem A *et al*. Keratosis lichenoides chronica with prominent telangiectasia: response to etretinate. *J Am Acad Dermatol* 1989; **21**: 1112–4.
18 Lopez-Navarro N, Alcaraz I, Bosch RJ *et al*. Keratosis lichenoides chronica: response to photodynamic therapy. *J Dermatolog Treat* 2008; **19**: 124–5.

CHAPTER 42
Disorders of the Sebaceous Glands

A.M. Layton
Harrogate and District Foundation Trust, Harrogate, North Yorkshire, UK

Structure and distribution, 42.1
Development, 42.3
Ultrastructure, histochemistry and immunocytochemistry of the sebaceous gland and duct, 42.3
Composition and biosynthesis of sebum, 42.5
Functions of sebum, 42.6
Measurement of sebaceous activity and sebum production, 42.7
Endocrine control of sebaceous gland activity, 42.9
Retinoid control of sebaceous gland activity, 42.14
Inhibitors of sebaceous activity, 42.15
Acne vulgaris, 42.17
Aetiology of acne, 42.20
Seborrhoea, 42.20
Comedone formation (comedogenesis), 42.22
Relationship between *P. acnes* and acne, 42.24
The role of inflammation in the pathogenesis of acne, 42.25
Mechanisms inducing acne scarring, 42.26
Resolution of acne, 42.27
Biological significance of acne, sebum and *P. acnes*, 42.27
Clinical features, 42.30
Physiological and environmental factors that influence acne, 42.33
Psychosocial effects of acne, 42.35
Differential diagnosis, 42.36
Treatment, 42.38
General principles of acne treatment, 42.38
Topical acne therapies, 42.39
Oral therapy, 42.46
Side effects of topical treatments and oral antibiotics, 42.49
Hormonal treatments, 42.52
The patient with slow or failed response to treatment, 42.55
Oral isotretinoin, 42.57
Other oral treatments, 42.66
Physical modalities for treating active acne, 42.67
Treatment of scars, 42.68
Uncommon associations with acne, 42.70
Severe acne variants, 42.82
Ectopic sebaceous glands, 42.86
Sebaceous gland hyperplasia, adenoma and carcinoma, 42.86
Sebaceous gland hyperplasia, 42.86
Sebaceous gland tumours, 42.87
'Sebaceous' (epidermoid) cysts and steatocystoma multiplex, 42.88

Structure and distribution

The sebaceous gland (Fig. 42.1) is holocrine [1]; its secretion is formed by the complete disintegration of the glandular cells. The cells are replaced by cell division at the periphery of the lobes or acini of the glands, with the consequence that differentiating cells are displaced towards the centres of each acinus. The average transit time of the cells, from formation to discharge, has been given as 7–25 days in the human gland [2], a figure similar to that estimated for the rat [3,4]. However, the dynamics of the human gland are complicated. The gland consists of a series of lobes, each with a duct lined by a keratinizing squamous epithelium. The lobule ducts converge towards the main sebaceous duct, which normally opens into the pilary canal, whose epithelium is continuous with the surface epidermis.

Within any one glandular unit, the acini vary in differentiation and maturity: some are completely undifferentiated, showing little or no lipid accumulation in any of their cells, and some are full of lipid-laden cells (Fig. 42.2) that extend to the outer periphery of the acinus [5]. New acini can arise from the walls of the ducts, grow into sebaceous units and fuse with adjacent ones. Three proliferative regions were recognized by Plewig *et al.* [6,7] using ^{3}H-thymidine autoradiography. The duct displayed fast cellular migration with a renewal time of 2–4 days. An undifferentiated cell pool, with a renewal time of 4–7 days, could be distinguished from the differentiating lipid-producing cells in the glandular fundus, with a replacement time of between 14 and 25 days [8]. The synthesis and discharge of the lipid contained in the sebaceous cells require more than a week [9].

Sebaceous glands occur over much of the body, although not normally on the palms or soles, and only sparsely on the dorsal surfaces of the hand and foot. Sebaceous glands are largest and most numerous on the face, scalp, upper trunk, in the external auditory meatus and on the anogenital surfaces. On the scalp, forehead, cheeks and chin, for example, there are between 400 and 900 glands/cm^2; elsewhere there are less than 100 glands/cm^2 [10–12].

In a few sites, sebaceous glands open directly to the surface of the skin and are unrelated to hair follicles. Examples of such glands are the Meibomian glands of the eyelids and the Tyson's glands of the prepuce [13]. Free sebaceous glands are also found on the mucocutaneous surfaces of the female genitalia, the areolae of the nipples, and ectopic sites such as the tongue and the cervix uteri [14]. Free sebaceous glands in the margin of the upper lip are often visible to the naked eye as pale-yellow bodies, which vary in size from minute specks to about 1.5 mm in diameter; they are known as Fordyce's spots [15].

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

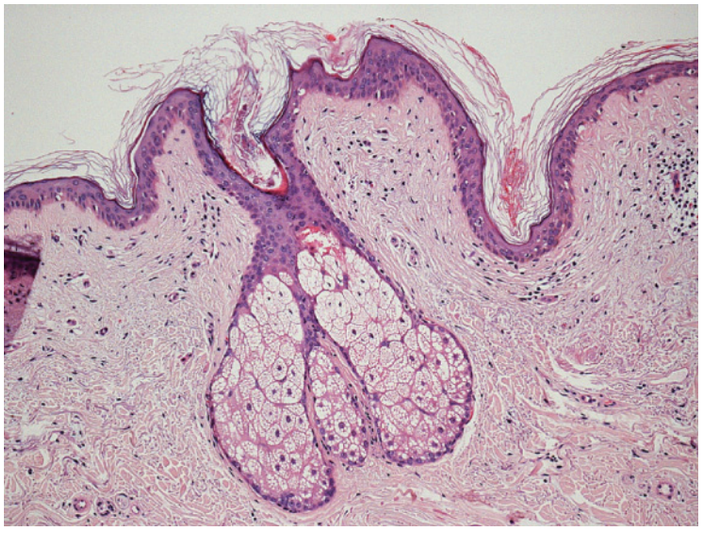


Fig. 42.1 An haematoxylin and eosin stain showing a clinically normal sebaceous gland. (Courtesy of Dr D. Scott, Department of Pathology, Harrogate and District Foundation Trust, Harrogate, North Yorkshire, UK.)

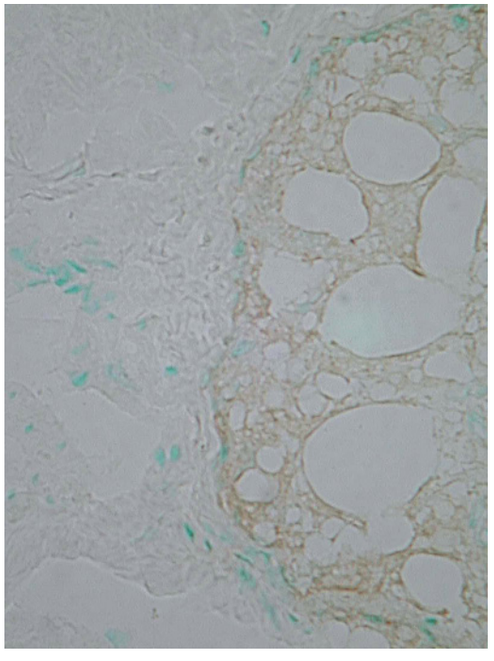


Fig. 42.2 Sebaceous gland edge: non-labelled frozen section of the edge of a sebaceous gland demonstrating the sebocyte's globular nature. Sebocytes filled with lipid as they differentiate and move away from the basal cells at the periphery of the gland. (Courtesy of Dr D. Holland and Dr A. Jeremy, Skin Research Centre, Institute of Molecular and Cellular Biology, Faculty of Biological Sciences, University of Leeds, UK.)

Many mammals have specialized aggregations of sebaceous units that function as scent glands [16–19] and include tubular 'apocrine' units (Chapter 44). Of special interest as possible models for the study of compounds that affect sebaceous activity [20] are the costovertebral organs of the golden hamster [13,20–23], the supracaudal gland of the guinea pig [24,25], the abdominal gland of the gerbil [26] and the preputial glands of many species of rodents [27].

References

1 Strauss JS, Downing DT, Ebling FJ. Sebaceous glands. In: Goldsmith LA, ed. *Biochemistry and Physiology of the Skin*, Vol. 1. New York: Oxford University Press, 1983: 569–95.

2 Epstein EH, Epstein WL. New cell formation in human sebaceous glands. *J Invest Dermatol* 1966; **46**: 453–8.

3 Bertalanffy FD. Mitotic activity and renewal rate of sebaceous gland cells in the rat. *Anat Rec* 1957; **129**: 231–41.

4 Ebling FJ. Hormonal control of sebaceous glands in experimental animals. In: Montagna W, Ellis RA, Silver AF, eds. *Advances in Biology of Skin*, Vol. 4. *The Sebaceous Glands*. Oxford: Pergamon, 1963: 200–19.

5 Montagna W, Parakkal PF. *The Structure and Function of Skin*, 3rd edn. New York: Academic Press, 1974.

6 Plewig G, Christophers E, Braun-Falco O. Proliferative cells in human sebaceous gland. *Acta Derm Venereol (Stockh)* 1971; **51**: 413–22.

7 Plewig G, Christophers E, Braun-Falco O. Cell transition in human sebaceous glands. *Acta Derm Venereol (Stockh)* 1971; **51**: 423–8.

8 Plewig G, Christophers E. Renewal rate of human sebaceous glands. *Acta Derm Venereol (Stockh)* 1974; **54**: 177–82.

9 Downing DI, Strauss JS, Ramasastry P *et al.* Measurement of the time between synthesis and surface excretion of sebaceous lipids in sheep and man. *J Invest Dermatol* 1975; **64**: 215–9.

10 Benfenati A, Brillanti F. Sulla distribuzione delle ghiandole sebacee nella cute del corpo umino. *Arch Ital Dermatol* 1939; **15**: 33–42.

11 Montagna W. The sebaceous glands in man. In: Montagna W, Ellis RA, Silver AF, eds. *Advances in Biology of Skin*, Vol. 4. *Sebaceous Glands*. Oxford: Pergamon, 1963: 19–30.

12 Yamada K. Quantitative Undersuchung der Anhangsorgane der Haut bei den Deutschen. *Folio Anat (Japan)* 1932; **10**: 721–52.

13 Frost P, Gomez EC. Inhibitors of sex hormones: development of experimental models. In: Montagna W, Van Scott EJ, Stoughton RB, eds. *Advances in Biology of Skin*, Vol. 12. *Pharmacology of the Skin*. New York: Appleton–Century–Crofts, 1972: 403–20.

14 Hyman AB, Guiducci AA. Ectopic sebaceous glands. In: Montagna W, Ellis RA, Silver AF, eds. *Advances in Biology of Skin*, Vol. 4. *Sebaceous Glands*. Oxford: Pergamon, 1963: 78–91.

15 Miles AEW. Sebaceous glands in oral and lip mucosa. In: Montagna W, Ellis RA, Silver AF, eds. *Advances in Biology of Skin*, Vol. 4. *Sebaceous Glands*. Oxford: Pergamon, 1963: 46–76.

16 Albone ES. *Mammalian Sociochemistry*. Chichester: John Wiley and Sons, 1984.

17 Doty RL, ed. *Mammalian Olfaction: Reproductive Processes and Behaviour*. New York: Academic Press, 1976.

18 Muller-Schwartze D, Manzell MM, eds. *Chemical Signals in Vertebrates*. New York: Plenum Press, 1977.

19 Strauss JS, Ebling FJ. Control and function of skin glands in mammals. *Mem Soc Endocrinol* 1970; **18**: 341–71.

20 Ebling JL. Hormonal control of mammalian sebaceous glands. In: Muller-Schwartze D, Manzell MM, eds. *Chemical Signals in Vertebrates*. New York: Plenum Press, 1977: 17–33.

21 Burdick KH, Hill R. The topical effect of the antiandrogen chlormadinone acetate and some of its chemical modifications on the hamster costovertebral organ. *Br J Dermatol* 1970; **82** (Suppl. 6): 19–25.

22 Hsia SL, Voigt W. Inhibition of dihydrotestosterone formation: an effective means of blocking androgen action in the hamster sebaceous gland. *J Invest Dermatol* 1974; **62**: 224–7.

23 Voigt W, Hsia SL. The antiandrogenic action of 4-androstene-3-one-17β-carboxylic acid and its methyl ester on the hamster flank organ. *Endocrinology* 1973; **92**: 1216–22.

24 Martan J. Effect of castration and androgen replacement on the supracaudal gland of the male guinea pig. *J Morphol* 1962; **110**: 285–98.

25 Martan J, Price D. Comparative responsiveness of supracaudal and other sebaceous glands in male and female guinea pigs to hormones. *J Morphol* 1967; **121**: 209–22.

26 Thiessen D, Yahr P. *The Gerbil in Behavioral Investigations*. Austin: University of Texas, 1977.
27 Clevedon Brown J, Williams JD. The rodent preputial gland. *Mammal Rev* 1972; **2**: 105–47.

Development

The development of sebaceous glands is closely related to the differentiation of hair follicles and epidermis [1,2]. Around the third week of fetal life, the epidermis consists of a single layer of undifferentiated cells, but by the fourth week an outer periderm and a basal stratum germinativum can be distinguished. Between the 10th and 12th weeks, a stratum intermedium becomes apparent, and at about the same time developing hair germs are quite distinct (Chapter 3). In the following weeks, the follicles extend downwards into the dermis and the rudiments of the sebaceous glands appear on the posterior surfaces of the hair pegs; by 13–15 weeks, the glands are clearly distinguishable.

The cells at first contain glycogen which lingers at the periphery of the gland, but is quickly lost at the centre, where large lipid drops are visible at 17 weeks [3–5].

At the point of their origin from the follicle, centrally positioned cells degenerate to form a lumen, and surrounding cells keratinize to form the sebaceous duct [6]. The glands become multi-acinar by the formation of buds on the peripheral wall.

Sebaceous glands are functional from their formation; sebum is the first demonstrable glandular product of the human body. Their development and function before birth and in the neonatal period appear to be regulated by maternal androgens and by endogenous steroid synthesis by the fetus [7]. Hydroxysteroid dehydrogenases and 5α-reductase, which reduces testosterone to 5′α-dihydrotestosterone (5′α-DHT), are present after 16 weeks [8,9]. The glands reach a peak of activity in the third trimester, and their secretion forms part of the vernix caseosa. The vernix lipids resemble sebum in their content of fatty acids, squalene and wax esters, but also contain sterols and sterol esters [10]. Sebaceous glands remain active in the neonatal period, but then involute and remain quiescent until puberty [11].

References

1 Holbrook KA. Structure and function of the developing human skin. In: Goldsmith LA, ed. *Biochemistry and Physiology of the Skin*. New York: Oxford University Press, 1983: 64–101.
2 Serri F, Huber WM. The development of sebaceous glands in man. In: Montagna W, Ellis RA, Silver AF, eds. *Advances in Biology of Skin*, Vol. 4. *Sebaceous Glands*. Oxford: Pergamon, 1963: 1–18.
3 Breathnach AS. The Herman Beerman Lecture: embryology of human skin. A review of ultrastructural studies. *J Invest Dermatol* 1971; **57**: 133–43.
4 Fujita H, Asagami C, Murota S *et al.* Ultrastructural study of embryonic sebaceous cells especially of their droplet formation. *Acta Derm Venereol (Stockh)* 1972; **52**: 99–115.
5 Sato S, Hiraga K, Nishijima A *et al.* Neonatal sebaceous glands: fine structure of sebaceous and dendritic cells. *Acta Derm Venereol (Stockh)* 1977; **57**: 279–87.
6 Breathnach AS. *An Atlas of the Ultrastructure of Human Skin*. London: Churchill, 1971: 1–30.
7 Solomon LM, Esterley NB. Structure of fetal and neonatal skin. In: *Neonatal Dermatology. Major Problems in Clinical Pediatrics*, Vol. 9. Philadelphia: Saunders, 1973.
8 Sharp F, Calman KC, Milne JA *et al.* The demonstration of hydroxysteroid dehydrogenase activity *in vitro* by human foetal skin in the first 32 weeks of gestation. *Br J Dermatol* 1970; **83**: 177–81.
9 Sharp F, Hay JB, Hodgins MB. Metabolism of androgens *in vitro* by human foetal skin. *J Endocrinol* 1976; **70**: 491–9.
10 Nazzaro-Porro M, Passi S, Boniforti L *et al.* Effects of aging on fatty acids in skin surface lipid. *J Invest Dermatol* 1979; **73**: 112–7.
11 Ramasastry P, Downing DT, Pochi PE *et al.* Chemical composition of human skin surface lipids from birth to puberty. *J Invest Dermatol* 1970; **54**: 139–44.

Ultrastructure, histochemistry and immunocytochemistry of the sebaceous gland and duct

Undifferentiated sebaceous cells at the periphery of the gland are rich in ribonucleoproteins and stain with basic dyes [1]. As the cells move towards the centre of each lobe their lipid content rises and they become progressively acidophilic. All cells have numerous mitochondria appearing as short or wavy rods. The undifferentiated cells contain coarse, osmium-staining particles around the nucleus; as differentiation proceeds, these particles increase in number and size and develop lipid droplets in their centres, which gradually enlarge. This complex corresponds to the Golgi body; at completion of sebaceous synthesis it is no longer recognizable.

In studies with the electron microscope [2–4], the undifferentiated cells at the periphery of the gland can be seen to rest upon a basement membrane, and to be connected with each other by desmosomes. The membranes of the granular endoplasmic reticulum are coated with ribosomes, and there are in addition particles of ribonucleoprotein and glycogen scattered free in the cytoplasm. At this stage, the Golgi zones are usually inconspicuous; the nucleus is relatively very large. Differentiation of the cell becomes evident with the appearance of one or more small sebum vacuoles within it. During the active phase of lipid synthesis, the cytoplasm becomes packed with smooth-surfaced membranes of the endoplasmic reticulum. In some partially differentiated cells, a large Golgi zone becomes apparent; typically, it consists of parallel, smooth-surfaced, thick membranes, slightly dilated cisterns and small vesicles. The Golgi appears to be the centre where lipid aggregates to form sebum vacuoles. At an early stage of sebaceous transformation, one of the cisterns in the Golgi zone becomes more dilated than the others, and forms the centre of the developing sebum vacuole. At a later stage, the smooth membranes of Golgi apparatus and the endoplasmic reticulum become orientated around the edge of the developing vacuole, forming a sort of 'husk'. The fully differentiated cells contain very large sebum vacuoles, which compare in size with the nucleus; the cell may have a complement of more than 60 (Fig. 42.3). In the final stages of differentiation, the mitochondria become widely separated, indicating that their numbers have decreased, and the nucleus becomes irregularly shaped, with clumping of the nucleochromatin and dispersal of the nucleolar material. Lysosomes are prominent in peripheral and other cells in the early stages of differentiation, but are found at all stages [2]. They may be concerned with hydrolysing precursors of sebaceous lipids or the breakdown of mature cells.

The sebaceous cells of prepubertal and hypogonadal males are qualitatively similar to those of normal adults, even though the glands are smaller [1].

Immunocytochemical techniques, supported in some instances by investigating messenger RNA (mRNA) expression of the peptide, performed both on human skin biopsies and on

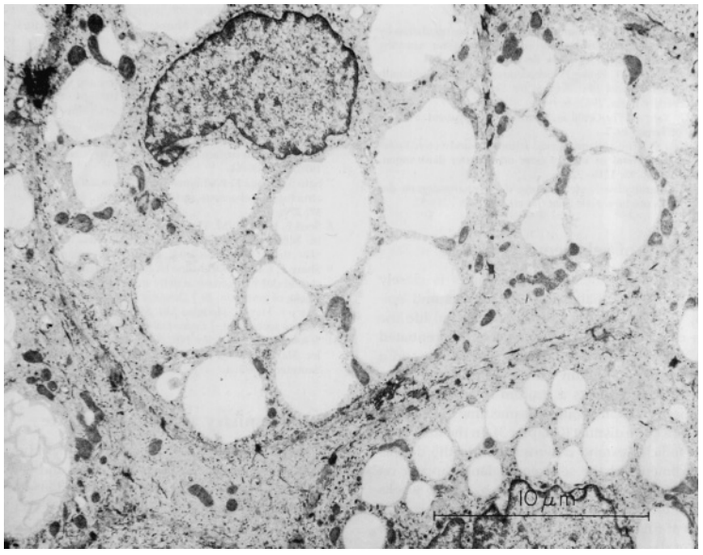


Fig. 42.3 Transverse section of the sebaceous gland of a 24-week fetus. The cytoplasm of the cells is honeycombed with spaces occupied by lipid droplets, which have been leached away during processing. (Courtesy of Professor A.S. Breathnach, St John's Institute of Dermatology, London, UK.)

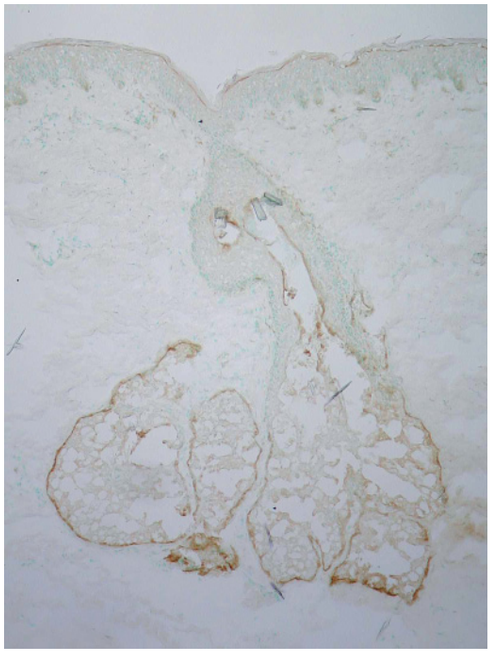


Fig. 42.4 Follicle IL-1RTII: immunohistochemical labelling for IL-1 receptor type II expression exhibited by the basal cells at the periphery of the sebaceous gland and at the tip of some epidermal ridges in a frozen section of a clinically normal pilosebaceous follicle from the back of an acne patient. (Courtesy of Dr D. Holland and Dr A. Jeremy, Skin Research Centre, Institute of Molecular and Cellular Biology, Faculty of Biological Sciences, University of Leeds, UK.)

immortalized sebocytes, have helped our understanding of the hormonal and cytokine control of the sebaceous gland and duct in health and disease [3]. Androgen receptors are present both in the gland and the duct [4].

Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear hormone receptor family that form heterodimers with retinoid X receptors and act as transcriptional regulators of a variety of genes including those involved in lipid metabolism in adipose tissue, liver and skin [5,6].

There are three subtypes (PPAR-α, γ and δ); localization studies on whole specimens of human skin have demonstrated that all subtypes are present in sebaceous glands and pilosebaceous ducts of both acne-involved and non-involved skin as well as healthy skin [7,8]. Each subtype is expressed in the basal layer of the sebaceous gland with PPARγ expression noted in differentiated cells within the gland [9]. The specific identity of endogenous ligands that act on PPARs in the skin is not yet known. Potential ligands include fatty acids, eicosanoids and other lipids found in the skin and sebaceous glands. It has been shown that PPARs play a role in regulating sebum production and that selective modulation of their activity may lead to novel therapies for the treatment of acne [9].

Sebocytes are target cells for several neurohormones. Immunocytochemical studies have shown that human sebocytes express melanocortin MC1 and MC5 receptors and are target cells for α-melanocyte-stimulating hormone (α-MSH) [10]. MC5-R has been shown to correlate with sebocyte differentiation and this suggests a regulatory role for MC5-R in human sebaceous lipid production [11].

The sebaceous gland constitutively expresses other cytokines (Figs 42.4 & 42.5) without any influence of external factors. Interleukin-1 (IL-1) is present in the normal human sebaceous gland [12] and mRNA for IL-1-α, IL-1-β and tumour necrosis factor-α

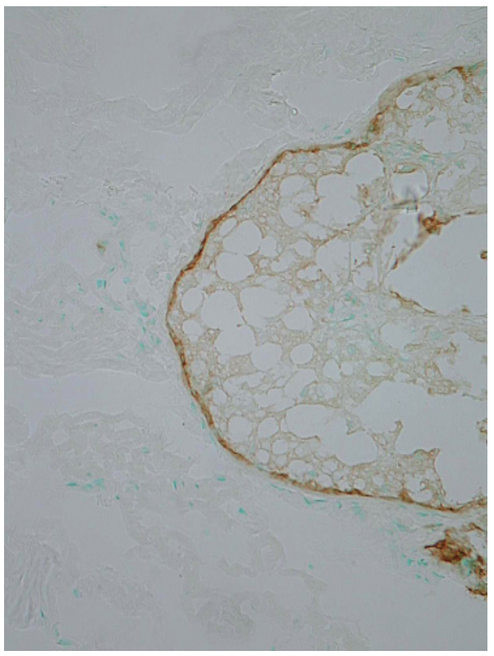


Fig. 42.5 Sebaceous gland edge IL-1RTII: immunohistochemical labelling for interleukin-1 receptor type II expression (brown staining) clearly expressed by the basal cells at the periphery of the sebaceous gland. (Courtesy of Dr D. Holland and Dr A. Jeremy, Skin Research Centre, Institute of Molecular and Cellular Biology, Faculty of Biological Sciences, University of Leeds, UK.)

(TNF-α) are also present in the sebaceous glands. Cultured human sebocytes also express IL-1-α at the mRNA and protein levels. The presence of such cytokines may relate to the development of inflammation [13].

References

1 Montagna W. The sebaceous glands in man. In: Montagna W, Ellis RA, Silver AF, eds. *Advances in Biology of Skin*, Vol. 4. *Sebaceous Glands*. Oxford: Pergamon, 1963: 19–31.
2 Bell M. A comparative study of the ultrastructure of the sebaceous glands of man and other primates. *J Invest Dermatol* 1974; **62**: 132–43.
3 Zouboulis CC, Seltmann H, Neitzel H, Orfanos CE. Establishment and characterisation of an immortalised human sebaceous gland cell line. *J Invest Dermatol* 2001; **113**: 1011–20.
4 Schmidt JB, Spona J, Huber J. Androgen receptors in hirsutism and acne. *Gynecol Obstet Invest* 1986; **22**: 206–11.
5 Ferre P. The biology of peroxisome proliferator-activated receptors: relationship with lipid metabolism and insulin sensitivity. *Diabetes* 2004; **53** (Suppl. 1): S43–S50.
6 Knouff C, Auwerx J. Peroxisome proliferator-activated receptor-gamma calls for activation in moderation: lessons from genetics and pharmacology. *Endocr Rev* 2004; **25**: 899–919.
7 Chen W, Yang C, Sheu H *et al*. Expression of peroxisome proliferator-activated receptors and CCAAT/enhancer binding protein transcription factors in cultured human sebocytes. *J Invest Dermatol* 2003; **121**: 441–7.
8 Alestas T, Ganceviciene R, Fimmel S *et al*. Enzymes involved in the biosynthesis of leukotriene B4 and prostaglandin E2 are active in sebaceous glands. *J Mol Med* 2006; **84**: 75–9.
9 Trivedi N, Cong Z, Nelson A *et al*. Peroxisome proliferator-activated receptors increase human sebum production. *J Invest Dermatol* 2006; **126**: 2002–9.
10 Bohm M, Schiller M, Stander S *et al.* Evidence for expression of melanocortin-1 receptor in human sebocytes *in vitro* and *in situ*. *J Invest Dermatol* 2002; **118**: 533–9.
11 Zhang L, Anthonavage M, Huang Q *et al.* Proopiomelanocortin peptides and sebogenesis. *Ann N Y Sci* 2003; **994**: 154–61.
12 Anttila HS, Reitamo S, Saurat JH. Interleukin 1 immunoreactivity in sebaceous glands. *Br J Dermatol* 1992; **4**: 335–41.
13 Zouboulis CC. Is acne vulgaris a genuine inflammatory disease? *Dermatology* 2001; **203**: 277–9.

Composition and biosynthesis of sebum

Sebum is a complex mixture of lipids, which varies widely from species to species [1–3]. The analysis of human sebum is complicated by several factors. The principal difficulty is that the surface film contains not only sebum, but also lipid from the keratinizing epidermis and possibly from eccrine glands. In addition, the pure sebaceous secretion undergoes degradation as it passes through the ducts or on the skin surface as a result of bacterial lipase activity [4]. Some material, for example hydrocarbons, may also be acquired from environmental sources.

Surface lipid can be collected by simple non-invasive tests, such as wiping the skin with a sponge soaked in an organic solvent such as hexane or ether [5]. However, skin biopsies are necessary to investigate sebum synthesis and the analysis of pure sebum. Incubation of isolated human sebaceous glands showed that acetate and glucose appeared to be equally efficient as substrates for triglycerides but not for squalene [6].

An unusual feature of sebaceous lipogenesis is a partial or complete inhibition of cholesterol biosynthesis at some point in the pathway. Thus, in human and in some other animal glands, there is little or no conversion of squalene to cholesterol and squalene remains a major product.

In vivo studies suggest that the synthesis of some sebaceous lipids is indirect, with newly synthesized fatty acids becoming first incorporated into phospholipids and later recycled into non-polar lipids. In human scalp, the label of intradermally injected ^{14}C acetate is immediately taken up by squalene, wax esters and triglycerides, but as the cells mature the proportion in wax esters increases [7].

Human skin surface lipid consists of glycerides, free fatty acids, wax esters, squalene, cholesterol esters and cholesterol. Lipid production varies according to site, for example 5–10 μg/cm^2 were recovered from the trunk and limbs of subjects who washed 3 h prior to extraction, compared with 150–300 μg/cm^2 from the forehead [8]. When amounts were in the range 5–10 μg/cm^2, the skin surface lipid contained virtually no wax esters or squalene. However, as the quantity of surface lipid increased, so did the proportion of wax esters and squalene, while at the same time the proportions of cholesterol esters decreased. The proportion of each of the constituents became nearly constant when the amount of lipid reached 50–100 μg/cm^2.

These results are consistent with the view that wax esters and squalene are produced by the sebaceous glands only, and not by the epidermis. When the surface lipid is as low as 4–10 μg/cm^2 no sebum is present, and this level of lipid represents that contributed by the epidermis. However, when the surface lipid is greater than 100 μg/cm^2, its composition approximates to that of sebum. The percentage proportions of constituents are shown in Table 42.1. It may be concluded from these figures that the sebaceous glands do not, to any great extent, convert squalene to sterols, whereas in the epidermis squalene synthesized in the lower layers is rapidly and totally converted to sterols, either to precursors of vitamin D or to cholesterol. Squalene is unique to sebum and is virtually unique to humans [2].

Between birth and sexual maturity, surface lipid undergoes two distinct changes [9,10]. Shortly after birth it resembles adult sebum, presumably because maternal hormones have activated the sebaceous glands. Thereafter and up to 8 years of age, the wax esters and squalene remain low, and epidermal lipids, that is cholesterol and its esters, are high. In this age range, sebum constitutes less than half the total surface lipid of the forehead, compared with 95% or more in the adult. Between 8 and 10 years of age, the wax esters and squalene rise to about two-thirds of the adult level, and between 10 and 15 years the composition comes to resemble that of the adult.

Free fatty acids constitute 10–30% of the human skin surface fat [11–13], but occur in only small amounts in the skin lipids of most other animals. This difference is presumably due to the rather

Table 42.1 Comparison between constituents of sebum and epidermal lipid.

Constituents	Sebum (%)	Epidermal lipid (%)
Glycerides (plus free fatty acids)	57.5	65
Wax esters	26.0	—
Squalene	12.0	—
Cholesterol esters	3.0	15
Cholesterol	1.5	20

unique bacterial flora of humans, in particular *Propionibacterium acnes*, and its lipase action on sebaceous triglycerides. Analysis of pure sebum from isolated human sebaceous glands showed the presence of triglycerides, but not free fatty acids, monoglycerides or diglycerides [14,15]. It thus seems that, prior to secretion, all the fatty acids are combined as triglycerides, which are subsequently subjected to lipolytic activity by enzymes present in the sebaceous ducts and on the skin surface. This conclusion is reinforced by the demonstration that the skin surface can hydrolyse triglycerides of exogenous origin; when ^{14}C-labelled tripalmitin was spread on the back, labelled free fatty acids were isolated from the surface fat 3 h later [7].

The fatty acid components [1–3,16] have both odd- and even-numbered carbon chains up to C25 in length, although more than half are C16 and C18 compounds. They are both saturated and unsaturated, and of particular interest is the presence in both classes of unusual branched chains. These are of two kinds, one having an even number of carbons with the methyl group attached to the penultimate (iso series), the other having an odd number of carbons with the methyl group attached to the antepenultimate (antiso series). Such branches are present in the chains of the wax esters, which are virtually limited to 18 carbons and produced only by the sebaceous glands and, in higher proportion, in the longer chains of the sterol esters, which probably arise from both sebaceous glands and epidermis.

It is possible to modulate sebum composition as a result of dietary, hormonal or drug manipulation. Although various effects have been ascribed to diet, there is no evidence from either humans or experimental animals that any components of sebum are directly derived from ingested fats. In humans, most of the unsaturated fatty acids in the surface film are Δ6 compounds, whereas dietary lipids are Δ9 compounds [3]. Prolonged starvation of human subjects [17,18] decreased the rate of sebum synthesis by about 40%, without any decrease in the actual amount of squalene, which thus rose as a proportion of the total surface lipid.

Administered hormones can also influence the composition of the skin surface fat. In rats, testosterone, at the same time as increasing the amount of sebaceous secretion (see below), increases the ratio of palmitate to stearate and the ratio of oleate to stearate; oestrogens and antiandrogens antagonize these effects [19–21]. In female patients prescribed co-cyprindiol (35 μg ethinyl oestradiol and 2 mg cyproterone acetate [CPA]) there is a significant increase in sebaceous linoleate, which might explain in part the anticomedogenic effect of the therapy [22]. A reduced sebaceous linoleate may induce comedogenesis. Oral isotretinoin not only significantly reduces sebum production, but produces a notable change in lipid composition, including a great reduction in sebaceous-related lipids (i.e. squalene, wax esters and fatty acids) [23].

For comprehensive discussions of lipid biosynthesis in the sebaceous glands, the reader is referred to detailed references [3,24].

References

1 Downing DT, Strauss JS. Synthesis and composition of surface lipids of human skin. *J Invest Dermatol* 1974; **62**: 228–44.

2 Nikkari T. Comparative chemistry of sebum. *J Invest Dermatol* 1974; **62**: 257–67.

3 Strauss JS, Downing DT, Ebling FJG *et al.* Sebaceous glands. In: Goldsmith LA, ed. *Biochemistry and Physiology of the Skin*, 2nd edn. New York: Oxford University Press, 1991: 569–95.

4 Marples RR, Downing DT, Kligman AM. Control of free fatty acids in human surface lipids by *Corynebacterium acnes*. *J Invest Dermatol* 1971; **83**: 473–7.

5 Cotterill JA, Cunliffe WJ, Williamson B. A semi-quantitative method for the biochemical analysis of sebum. *Br J Dermatol* 1971; **85**: 35–9.

6 Middleton B, Birdi I, Heffron M *et al.* The substrate determines the rate and pattern of neutral lipid synthesized by isolated human sebaceous glands. *FEBS Lett* 1988; **231**: 59–61.

7 Downing DT, Strauss JS, Norton LA *et al.* The time course of lipid formation in human sebaceous glands. *J Invest Dermatol* 1977; **69**: 407–12.

8 Green RS, Downing DT, Pochi PE *et al.* Anatomical variation in the amount and composition of human skin surface lipid. *J Invest Dermatol* 1970; **54**: 240–7.

9 Ramasastry P, Downing DT, Pochi PE. Chemical composition of human skin surface lipids from birth to puberty. *J Invest Dermatol* 1970; **54**: 138–44.

10 Sansone-Bazzano G, Cummings B, Seeler AK *et al.* Differences in the lipid constituents of sebum from pre-pubertal and pubertal subjects. *Br J Dermatol* 1980; **103**: 131–7.

11 Nicolaides N. Human skin surface lipids—origin, composition and possible function. In: Montagna W, Ellis RA, Silver AF, eds. *Advances in Biology of Skin*, Vol. 4. *Sebaceous Glands*. Oxford: Pergamon, 1963: 167–86.

12 Nicolaides N. Skin lipids: the biological uniqueness. Unlike internal organs the skin biosynthesizes and excretes unusual fat soluble substances. *Science* 1974; **186**: 19–26.

13 Wheatley VR. Problems in the analysis of sebum. In: Montagna W, Ellis RA, Silver AF, eds. *Advances in Biology in Skin*, Vol. 4. *Sebaceous Glands*. Oxford: Pergamon, 1963: 135–47.

14 Kellum RE. Isolation of human sebaceous glands. *Arch Dermatol* 1966; **93**: 610–2.

15 Kellum RE. Human sebaceous gland lipids: analysis by thin-layer chromatography. *Arch Dermatol* 1967; **95**: 218–20.

16 Nicolaides N, Fu HC, Ansari MNA *et al.* The fatty acids of wax esters and sterol esters from vernix caseosa and from human skin surface lipid. *Lipids* 1972; **7**: 506–17.

17 Downing DT, Strauss JS, Pochi PE. Changes in skin surface lipid composition induced by severe caloric restriction in man. *Am J Clin Nutr* 1972; **25**: 365–7.

18 Pochi PE, Downing DT, Strauss JS. Sebaceous gland response in man to prolonged total caloric deprivation. *J Invest Dermatol* 1970; **55**: 303–9.

19 Nikkari T, Valavaara M. Effects of androgens and prolactin on the rate of production and composition of sebum in hypophysectomized female rats. *J Endocrinol* 1970; **48**: 373–8.

20 Nikkari T, Valavaara M. The influence of age, sex, hypophysectomy and various hormones on the composition of the skin surface lipids of the rat. Hormones and sebum composition in the rat. *Br J Dermatol* 1970; **83**: 459–76.

21 Wilde PF, Ebling FJ. Preliminary observations on the composition of skin surface fat from rats treated with testosterone and estradiol. *J Invest Dermatol* 1969; **52**: 362–5.

22 Stewart ME, Greenwood R, Cunliffe WJ *et al.* Effect of cyproterone acetate–ethinyl estradiol treatment on the proportions of linoleic acid in various skin surface lipid classes. *Arch Dermatol Res* 1988; **278**: 481–5.

23 Stewart ME, Benoit AM, Downing DT, Strauss JS. Suppression of sebum secretion with 13-*cis*-retinoic acid: effect on individual skin surface lipids and implications for their anatomic origin. *J Invest Dermatol* 1984; **82**: 74–8.

24 Wheatley VR. The sebaceous glands. In: Jarrett A, ed. *The Physiology and Pathophysiology of the Skin*, Vol. 9. London: Academic Press, 1986: 2705–971.

Functions of sebum

Several functions have been ascribed to sebum, but they are by no means undisputed. In humans, it has been stated that the lipid film both controls moisture loss [1] from the epidermis and protects the skin from fungal and bacterial infection. The colonization of the skin by *P. acnes* may have an immunomodulatory role. Aggregations of holocrine glands play an important part in scent production in many mammals, and components of sebum may possibly contribute to body odour [2].

It was believed that the sebaceous lipids were essential factors for the barrier function of the skin. This is clearly not so. A healthy

prepubertal child who produces no sebum has no impaired barrier function. Certain surface free fatty acids markedly reduce the growth of pathogenic organisms, such as *Staphylococcus aureus*, *in vitro* [3], and suppression of sebaceous gland activity by isotretinoin may be followed by impetigo towards the end of a 4-month course [3]. Circumstantial evidence supports the view that sebum, or at least the product of its hydrolysis, is fungistatic. Fungi causing tinea pedis preferentially colonize areas that are not supplied with sebaceous glands: ringworm of the scalp becomes rare after puberty, when sebum production increases.

Propionibacterium acnes is unique to humans and this fact may equate with the rather unique composition of human sebum. Shuster [4] made the interesting suggestion that the capacity to develop delayed immune hypersensitivity may be augmented and maintained by the *P. acnes*, which colonizes sebaceous glands in adults. A sequel of this may be an enhanced immunoregulatory effect, producing some protection against cancers such as leukaemia and melanoma, which occur less frequently in acne patients [5].

The sebaceous gland has also been shown to secrete vitamin E into the upper layers of facial skin. This mechanism may in part serve to protect skin surface lipid and the upper stratum corneum from harmful oxidation [6].

References

1 Blank IH. Further factors which influence the water content of the stratum corneum. *J Invest Dermatol* 1953; **21**: 259–69.
2 Cohn BA. In search of human pheromones. *Arch Dermatol* 1994; **130**: 1048–51.
3 Leyden JJ, James WD. *Staphylococcus aureus* infection as a complication of isotretinoin therapy. *Arch Dermatol* 1987; **123**: 606–8.
4 Shuster S. Biological purpose of acne. *Lancet* 1976; **i**: 1328–9.
5 Beral V, Evans S, Shaw H. Cutaneous factors related to the risk of malignant melanoma. *Br J Dermatol* 1983; **109**: 165–72.
6 Thiele JJ, Weber SU, Packer L. Sebaceous gland secretion is a major physiological route of vitamin E delivery to the skin. *J Invest Dermatol* 1999; **113**: 1006–10.

Measurement of sebaceous activity and sebum production

Various methods have been used for collecting lipids from human skin, and for measuring their production [1]. They include swabbing by pads soaked in solvent [2], washing lipid solvents over areas of skin circumscribed by rings, caps or apertures of bottles [3–6] and absorption on paper [7,8]. Another method is removal by pressing a ground-glass plate on the skin followed by photometric assessment [9–14]—for both stages an instrument known as a Lipometer®/sebometer has been devised [15]. The rate of sebum production has been calculated from the squalene content of skin biopsies [16]. Analysis of the ratio of wax esters/(cholesterol plus cholesterol esters) may provide an indirect measure of lipid synthesis per sebaceous cell [17–19].

A simple, practical, but time consuming, method for measuring human sebaceous secretion is to place a pad of specially absorbent cigarette papers for 3 h on a delineated area of the forehead, and then to extract the sebum with diethyl ether. In view of circadian changes in secretion [20], the measurement should be carried out between standard times. It does not give the absolute sebum production rate, which is indefinitely sustainable [21], but it is valuable for comparative purposes, and provides more reproducible results than many other methods. The method that follows was originally devised by Strauss and Pochi [7,8].



Fig. 42.6 Patient with a firm but comfortable headband which is holding in place the special absorbent papers for measurement of sebum production.

1 Two areas on either side of the forehead (2.0 × 3.5 cm) are delineated by pre-cut Micropore® tape.
2 A pad of four or five cigarette papers is placed carefully, to avoid creasing, over the forehead and held in place by a gauze pad and a stocking-weave bandage encircling the head (Fig. 42.6).
3 In order to remove the accumulated surface lipids, two or three pads are so applied for 10–15 min and then discarded. After 30–40 min, close examination of the final paper in contact with the forehead will reveal a follicular pattern of sebum emerging from the follicles.
4 A pad of papers of known weight (previously prepared by washing in ether and being allowed to dry) is then applied. At the end of a 3-h collection period, the lipid-containing papers are then reweighed [22].

Control papers must be used to control for variation in environmental factors (such as humidity), which may influence the weight of the papers. Precision in weighing techniques is essential. The weight of sebum multiplied by the time of collection and divided by the area of collection provides a figure, which is referred to as the sebum excretion rate (SER).

The sustainable rate of sebum production on the forehead can be measured by first depleting the follicular reservoir by an application of an aqueous gel of bentonite clay, into which a rectangle of non-woven polyester cloth is pressed. The cloth is removed after 14 h, and the sebum is then collected for 3 h on two discs of clay, each 2 cm in diameter. The lipid is extracted and quantified by thin-layer chromatography [23–25] or by weighing [26]. The

method also makes possible an estimation of the extent of the follicular reservoir [26]. According to Saint-Leger and Cohen [27], the forehead can be defatted with 70% ethanol and the rate of sebum excretion is then linear.

The introduction of a sebum-absorbent tape (Sebutape®) (Figs 42.7 & 42.8) has made it possible to observe the lipid output of individual follicles [28,29]. Computerized image analysis has been used for quantification [30–32].

Several authors have described methods for the isolation, from skin biopsies, of whole human glands [33,34] or sebaceous cells [35], and their cultivation *in vitro* for study of their activity. These techniques reflect reasonably well the *in vitro* situation. In particular, the sebocyte culture system has provided much information on the hormonal and cytokine control of the sebaceous gland [36]. Sebum production in the rat has been measured by total immersion of animals in lipid solvents [37], by changes in hair fat lipid [38,39], or by absorption of lipid on paper from areas denuded of hair [40]. To study responses to hormones, the size of the sebaceous glands has also been estimated from histological sections using planimetry [41]. Mitotic activity, estimated after injecting the rats with colchicine, which arrests mitoses in the metaphase, has also been used as a measure of glandular activity [41]. Other experimental models, such as the preputial glands of rodents [42], which can be dissected out and weighed, or the visible costovertebral glands of the hamster [43,44], to which hormones can be topically applied, have been reviewed by Ebling [1].

When interpreting the results of animal experiments it is important to realize that the reactions of supposed homologues of the sebaceous glands may vary not only from species to species but also within species. Thus, the responses to hormones of the preputial and sebaceous glands of the rat may not be identical. Moreover, because of the miscellaneous parameters involved, it is also important to understand the relationships between the different facets of sebaceous activity. The rate of secretion of sebum depends on two factors: the synthetic capacity of each sebaceous cell and the rate of production of the cells. The size of the glands depends partly on both these things, but also of critical importance is the time taken for each cell to mature and pass through the gland, i.e. the turnover time or cell life. If, for example, the rate of production of cells were doubled, with a consequent increase in sebum production, no alteration in gland size need occur if at the same time cell life were halved. As a general principle, it seems to be true that, the greater the mitotic rate, the lower the turnover time [45]; but in practice the changes do not keep pace with each other, and glands under stimulation do increase in size as well as in rate of secretion.

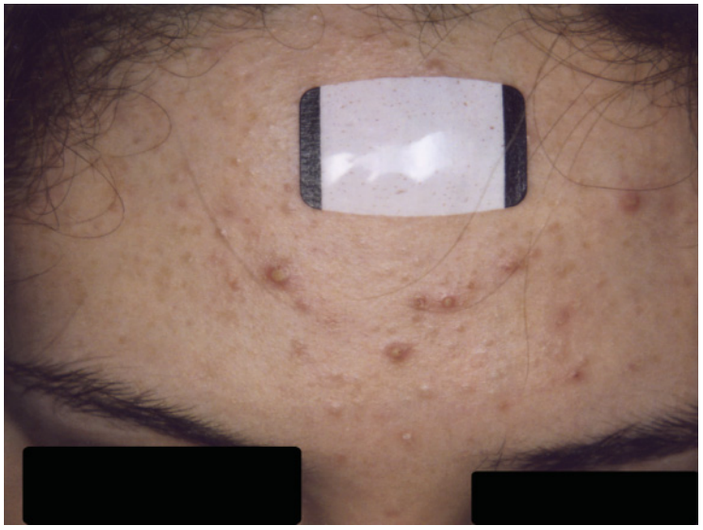
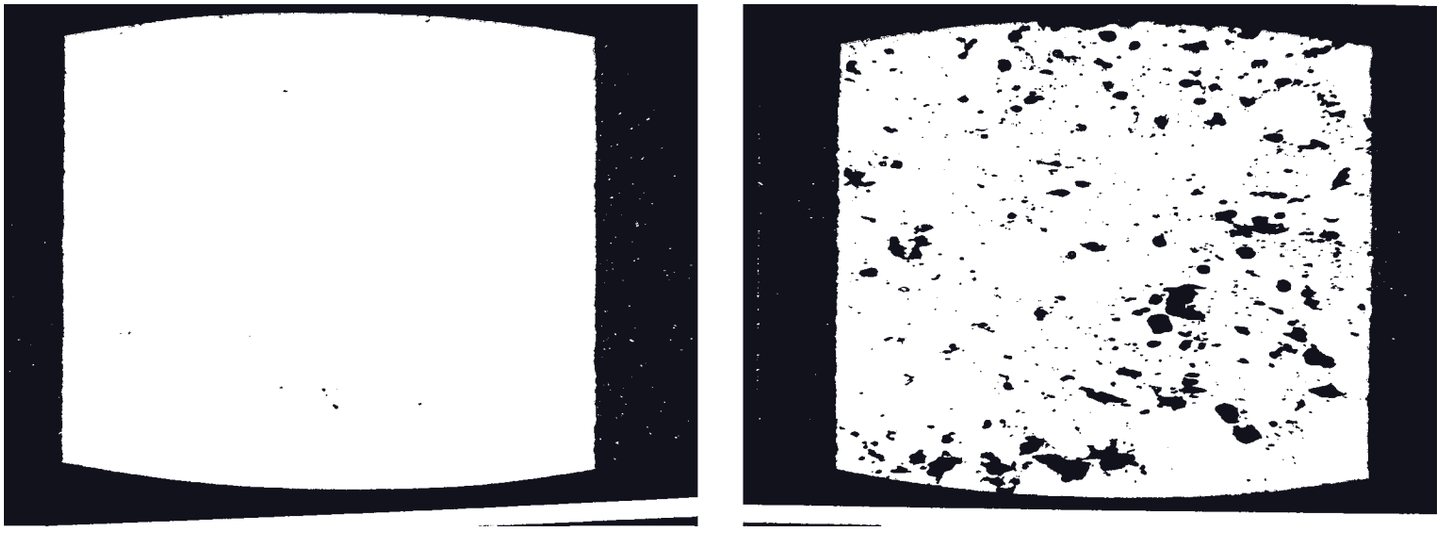


Fig. 42.7 Patient with Sebutape® placed on central forehead.



(a) (b)

Fig. 42.8 A comparison of two Sebutapes® demonstrating the difference between patients with and without acne: (a) from patient with very low sebum production; (b) from patient with high sebum production showing actively secreting sebaceous follicles and heterogeneity. (Courtesy of Dr A. Eady, Department of Microbiology, Leeds University, UK.)

References

1 Ebling FJ. Sebaceous glands. In: Marzulli FN, Maibach HI, eds. *Dermatotoxicology and Pharmacology*. Washington, DC: Hemisphere, 1977: 55–92.
2 Ramasastry P, Downing DT, Pochi PE *et al.* Chemical composition of human skin surface lipids from birth to puberty. *J Invest Dermatol* 1970; **54**: 139–44.
3 Jarrett A. The effects of stilboestrol on the surface sebum and upon acne vulgaris. *Br J Dermatol* 1955; **67**: 165–79.
4 Jarrett A. The effects of progesterone and testosterone on surface sebum and acne vulgaris. *Br J Dermatol* 1959; **71**: 102–16.
5 Downing DT, Strauss JS, Pochi PE. Variability in the chemical composition of human skin surface lipids. *J Invest Dermatol* 1969; **53**: 322–7.
6 Greene RS, Downing DT, Pochi PE *et al.* Anatomical variation in the amount and composition of human skin surface lipid. *J Invest Dermatol* 1970; **54**: 240–7.
7 Strauss JS, Pochi PE. The quantitative gravimetric determination of sebum production. *J Invest Dermatol* 1961; **36**: 293–8.
8 Strauss JS, Pochi PE. The human sebaceous gland: its regulation by steroidal hormones and its use as an end organ for assaying androgenicity *in vivo*. *Recent Prog Horm Res* 1963; **19**: 385–444.
9 Cunliffe WJ, Shuster S. The rate of sebum excretion in man. *Br J Dermatol* 1969; **81**: 697–704.
10 Schaefer H, Kuhn-Bussius H. Methodik zur quantitativen Bestimmung der menschlichen Talgsekretion. *Arch Klin Exp Dermatol* 1970; **238**: 429–35.
11 Schaefer H. The quantitative differentiation of sebum excretion using physical methods. *J Soc Cosmet Chem* 1973; **24**: 331–53.
12 Eberhardt H. The regulation of sebum excretion in man. *Arch Dermatol Forsch* 1974; **51**: 155–64.
13 Simpson NB, Martin AR. A more reliable photometric technique for the measurement of scalp sebum excretion. *Br J Dermatol* 1983; **109**: 647–52.
14 Cunliffe WJ, Kearney JN, Simpson NB. A modified photometric technique for measuring sebum excretion rate. *J Invest Dermatol* 1980; **75**: 394–8.
15 Saint-Leger D, Berrebi C, Duboz C *et al.* The Lipometer®: an easy tool for rapid quantitation of skin surface lipids (SSL) in man. *Arch Dermatol Res* 1979; **265**: 79–89.
16 Downing DT, Stewart ME, Strauss JS. Estimation of sebum production rates in man by measurement of the squalene content of skin biopsies. *J Invest Dermatol* 1981; **77**: 358–60.
17 Stewart ME, Quinn MA, Downing DT. Variability in the fatty acid composition of wax esters from vernix caseosa and its possible relation to sebaceous gland activity. *J Invest Dermatol* 1983; **78**: 291–5.
18 Stewart ME, Grahek MO, Cambier LS *et al.* Dilutional effect of increased sebaceous gland activity on the proportion of linoleic acid in sebaceous wax esters and in epidermal acylceramides. *J Invest Dermatol* 1986; **87**: 733–6.
19 Stewart ME, Steele WA, Downing DT. Changes in the relative amounts of endogenous and exogenous fatty acids in sebaceous lipids during early adolescence. *J Invest Dermatol* 1989; **92**: 371–8.
20 Burton JL, Cunliffe WJ, Shuster S. Circadian rhythm in sebum excretion. *Br J Dermatol* 1970; **82**: 497–501.
21 Downing DT, Stranier AM, Strauss JS. The effect of accumulated lipids on measurements of sebum secretion in human skin. *J Invest Dermatol* 1982; **72**: 226–8.
22 Lookingbill DP, Cunliffe WJ. A direct gravimetric technique for measuring sebum excretion rate. *Br J Dermatol* 1986; **114**: 75–81.
23 Harris HH, Downing DT, Stewart ME *et al.* Sustainable rates of sebum secretion in acne patients and matched normal control subjects. *J Am Acad Dermatol* 1983; **8**: 200–3.
24 Stewart ME, Downing DT. Measurement of sebum secretion rates in young children. *J Invest Dermatol* 1985; **84**: 59–61.
25 Collison DW, Burns TL, Stewart ME *et al.* Evaluation of a method for measuring the sustainable rate of sebaceous wax ester secretion. *Arch Dermatol Res* 1987; **279**: 266–9.
26 Hughes BR, Cunliffe WJ. Measurement of the follicular reservoir using sebum absorption into bentonite clay. In: Marks R, Plewig G, eds. *Acne and Related Disorders*. London: Dunitz, 1989: 43–4.
27 Saint-Leger D, Cohen E. Practical study of qualitative and quantitative sebum excretion on the human forehead. *Br J Dermatol* 1985; **113**: 551–7.
28 Kligman AM, Miller DL, McGinley KJ. Sebutape®: a device for visualizing and measuring human sebaceous secretion. *J Soc Cosmet Chem* 1986; **37**: 369–74.
29 Nordstrom KM, Schmus HG, McGinley KJ *et al.* Measurement of sebum output using a lipid absorbent tape. *J Invest Dermatol* 1986; **87**: 260–3.
30 Pierard G, Pierard-Franchimont C. Sebum excretion rate and density of active sebaceous follicles. *J Invest Dermatol* 1988; **91**: 413 (Abstract).
31 Pierard-Franchimont C, Pierard GE, Saint-Leger D *et al.* Comparison of the kinetics of sebum secretion in young women with and without acne. *Dermatologica* 1991; **183**: 1120–2.
32 Pierard GE, Pierard-Franchimont C, Kligman AM. Kinetics of sebum excretion evaluated by the Sebutape®–chromameter technique. *Skin Pharmacol* 1993; **6**: 28–44.
33 Kealey T, Lee CM, Thody AJ *et al.* The isolation of human sebaceous gland by shearing. *Br J Dermatol* 1986; **114**: 181–8.
34 Xia L, Zouboulis C, Detmar M *et al.* Isolation of human sebaceous glands and cultivation of sebaceous gland-derived cells as an *in vitro* model. *J Invest Dermatol* 1989; **93**: 315–21.
35 Doran TI, Baff R. The inhibition of proliferation of human sebaceous cells *in vitro* as a predictive assay for anti-acne activity. *J Invest Dermatol* 1988; **90**: 554.
36 Zouboulis CC, Seltmann H, Neitzel H, Orfanos CE. Establishment and characterisation of an immortalised human sebaceous gland cell line. *J Invest Dermatol* 2001; **113**: 1011–20.
37 Ebling FJ, Skinner J. The measurement of sebum production in rats treated with testosterone and oestradiol. *Br J Dermatol* 1967; **79**: 386–92.
38 Ebling FJ, Skinner J. The removal and restitution of hair fat in the rat. *Br J Dermatol* 1975; **92**: 321–4.
39 Ebling FJ, Randall VA, Skinner J. Local suppression of sebum secretion in rats by topical cyproterone acetate in ethanol. *J Invest Dermatol* 1981; **77**: 458–63.
40 Haskin D, Lasher N, Rothman W. Some effects of ACTH, cortisone, progesterone and testosterone on sebaceous glands in the white rat. *J Invest Dermatol* 1953; **20**: 207–11.
41 Ebling FJ. Hormonal control of sebaceous glands in experimental animals. In: Montagna W, Ellis RA, Silver AF, eds. *Advances in Biology of Skin*, Vol. 4. *Sebaceous Glands*. Oxford: Pergamon, 1963: 200–19.
42 Clevedon Brown J, Williams JD. The rodent preputial gland. *Mammal Rev* 1972; **2**: 105–47.
43 Burdick KH, Hill R. The topical effect of the antiandrogen chlormadinone acetate and some of its chemical modifications on the hamster costovertebral organ. *Br J Dermatol* 1970; **82** (Suppl. 6): 19–25.
44 Frost P, Geigel JL, Weinstein G *et al.* Biodynamic studies of hamster flank organ growth: hormonal influences. *J Invest Dermatol* 1973; **61**: 159–67.
45 Bullough WS. Mitotic and functional homeostasis: a speculative review. *Cancer Res* 1965; **25**: 1683–727.

Endocrine control of sebaceous gland activity [1]

The link between sebaceous gland activity and puberty has been recognized for many years [1]. Pioneering work was performed on the rat, which has a simple unilobular sebaceous gland, and on the Syrian hamster, whose flank organ is a good model for the human sebaceous gland. The development of techniques to grow human sebocytes and ductal cells in culture [2–4] has confirmed and built on previous observations of human physiological and pathological states. This section will concentrate on the human sebaceous gland, with reference to animal work where the evidence in humans is lacking or uncertain.

Androgens

Androgens are responsible for the development and maintenance of sebum secretion in both sexes. They are without doubt the most important hormones controlling sebaceous gland activity. The level of sebum excretion at birth is similar to that in adults [5]. There is a significant correlation between maternal and neonatal sebum excretion rate (SER) perinatally. This observation suggests an important role for the maternal hormonal environment on the infant's sebaceous glands [6]. The sebaceous glands regress to become minute during the prepubertal period, but undergo vast enlargement at puberty, when the sebum output of males increases

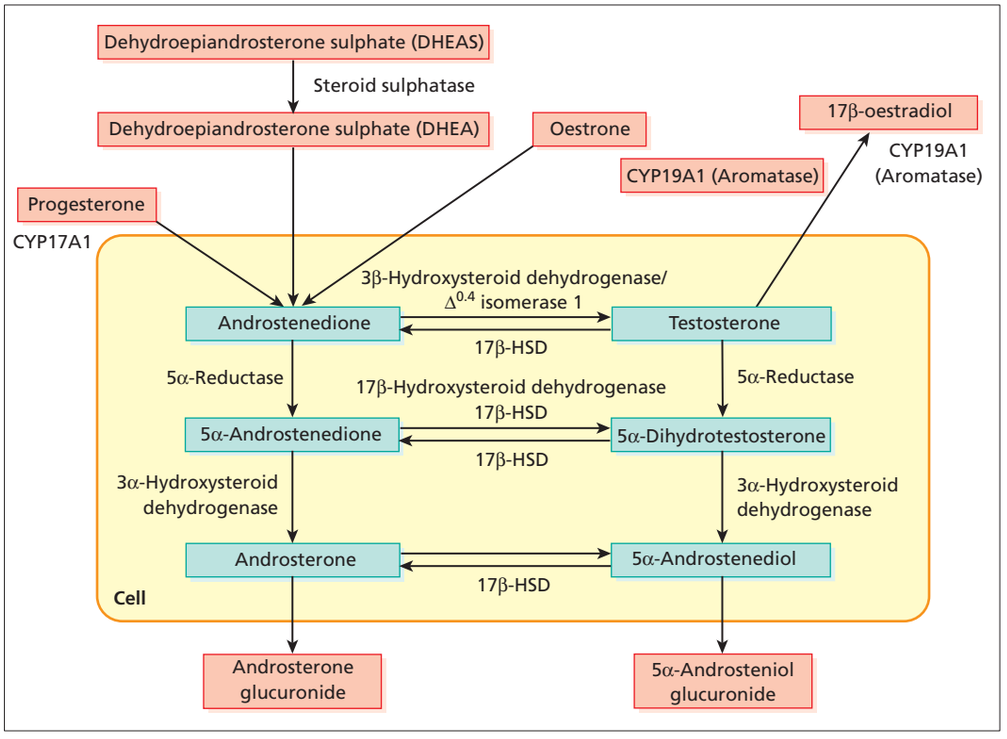


Fig. 42.9 Diagrammatic representation of androgen metabolism in the skin.

more than fivefold [7]. Sebum production remains essentially unchanged in both sexes until around the age of 60 years, when it declines [8]; paradoxically, in old age the sebaceous glands become larger because cell turnover is decreased [9].

The majority of potent androgens are produced by peripheral target tissues. The biological activity of testosterone on the skin is in the main induced by its conversion to 5α-DHT by the enzyme 5α-reductase [10]. Testosterone and 5α-DHT stimulate 5α-reductase mRNA and 5α-reductase activity and exert their effects through binding to androgen receptors identified in the keratinocytes of the basal layer of the sebaceous gland and the outer root sheath of the hair follicle but not keratinocytes elsewhere [11,12]. There are two isoforms of the enzyme 5α-reductase and it is the type-II isoenzyme that is important for most androgen action in sexual organs [13–15]. However, sebocytes [14] and epithelia [16] in the pilosebaceous unit possess the type I isoenzyme, and individuals who are genetically deficient in type II 5α-reductase still develop normal sebaceous glands and suffer from acne [17,18]. There is evidence from cell culture experiments that androgens stimulate the growth of sebocytes and other components of the pilosebaceous unit by action on specific stromal components, and interact with retinoic acid to regulate directly sebocyte differentiation [19,20]. 5α-DHT is 5–10 times more potent than testosterone in its interaction with the androgen receptor but both stimulate proliferation in the target cells. The impact of these androgens on human sebocyte proliferation is site dependent, facial sebocytes being the most affected [21].

Sebaceous glands possess many enzymes for the interconversion of androgens. The enzyme 3β-hydroxysteroid dehydrogenase (3β-HSD) acts on dehydroepiandrosterone (DHEAS) to convert it to androstenedione. There are two isozymes of 3β-HSD; type I is found in the skin [22].

The major isozymes of steroid metabolizing enzymes that are active in human sebaceous glands are illustrated in Fig. 42.9.

17β-hydroxysteroid dehydrogenase (17β-HSD) is a reversible enzyme, of which several types have been cloned, that can oxidize and reduce androgens and oestrogens. It converts androstenedione to the more potent testosterone or oxidizes the latter back to the less potent form. Type II is the most active in sebaceous glands, where it can oxidize testosterone to androstenedione, so possibly protecting the skin from excess testosterone [23]. Administration of testosterone dramatically increases the size of the sebaceous glands and the sebum output of prepubertal boys (Fig. 42.10). In adult males, the glands are almost but not completely maximally stimulated by endogenous androgen [24–27]. Adrenal androgens increase sebum production [27,28] but require conversion to testosterone within the sebaceous gland.

Eunuchs secrete about half as much sebum as normal males, but substantially more than prepubertal boys [29]. Sebum production by eunuchs is quantitatively correlated with the urinary excretion of 17-hydroxycorticoids and 17-oxosteroids [30]; thus, the activity of the sebaceous glands of eunuchs appears to be dependent on adrenal androgens.

The secretion of sebum by adult women is only a little less than that of normal men. Up to the age of 50 years it is greater than in castrated men, but after that age it falls [7]. This, as well as the fact that women generally have less adrenal androgens than men, suggests that sebaceous glands are affected by extra-adrenal sources of androgen. Evidence also implicates secretion or conversion of androgens and oestrogens in the ovary and conversion in the skin

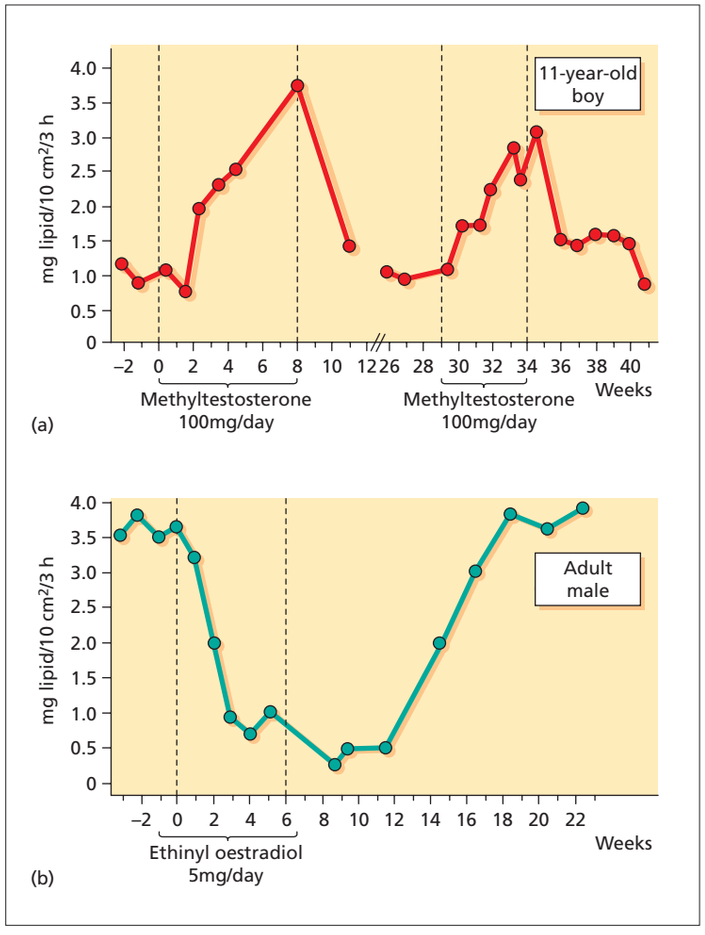


Fig. 42.10 (a) Sebum output of an 11-year-old boy given two courses of methyltestosterone orally (100 mg/day). Sebaceous secretion promptly rose with androgenic stimulation and quickly declined to the original level when the drug was stopped. (b) Suppression of sebum production in an adult male given 5 mg of ethinyl oestradiol orally daily for 6 weeks. In this subject the decrease was readily detectable in 2 weeks and was nearly maximal after 3 weeks. Sebum production returned to pre-oestrogen levels approximately 11–12 weeks after discontinuation of oestrogen. (From Strauss *et al.* [27].)

[31]. However, there is only a small reduction in skin-surface lipid following bilateral oophorectomy [29].

Progesterone

The effect of progesterone on sebaceous glands has been a matter of dispute. The fluctuation of sebum production in women during the menstrual cycle has been blamed on progesterone [32], but this has not been proved experimentally. Progesterone administration can produce acne [33], and when given to elderly women it increases sebum production [34], but no such effect could be demonstrated in young women [35,36]. Progesterone is a competitive inhibitor of 5α-reductase and might be expected to reduce sebaceous gland activity; in humans its sebosuppressive effect is minimal [37–39]. Experiments in the rat showed varied responses, depending upon when progesterone was administered in relation to birth, puberty, castration and oophorectomy [39–43]. The progesterone receptor is only expressed in basal keratinocytes [44].

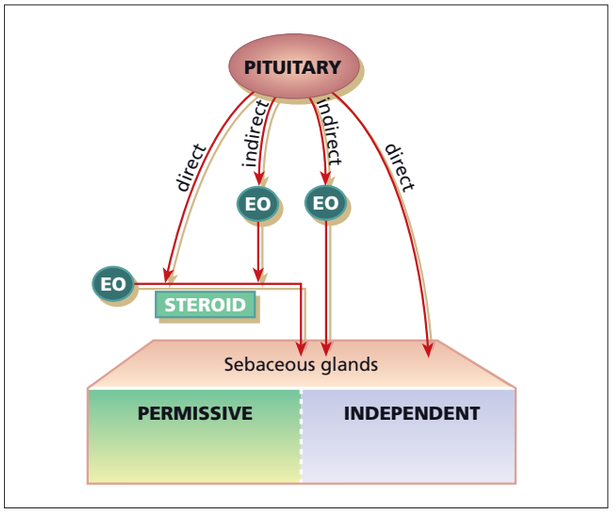


Fig. 42.11 Possible ways in which pituitary hormones may affect the sebaceous glands. The effect may be direct or indirect, and in addition may be either independent or permissive, in the sense that the pituitary hormone facilitates the response of another hormone, for example a steroid. EO, endocrine organ.

Adrenocortical hormones

Sebum production post adrenalectomy for Cushing's syndrome has been shown to fall [28]. Adrenocorticotrophic hormone (ACTH) causes hypertrophy of sebaceous glands in prepubertal human males and postpubertal human females [45], and increases the size of sebaceous glands [41,46] and sebum production [47] in hypophysectomized and gonadectomized rats.

Glucocorticoids stimulate sebocyte proliferation [48]. It has been suggested that glucocorticoids can aggravate sebaceous gland diseases due to their stimulatory effects on proliferation and differentiation in the presence of growth factors [49]. Hydrocortisone given to a prepubertal boy caused enlargement of sebaceous glands [45]. Sebum production is decreased in adrenal insufficiency, but replacement of glucocorticoids has no effect [28,50].

Pituitary hormones

The pituitary has a major effect on sebaceous gland activity (Fig. 42.11). The pituitary acts indirectly through its various target glands, and as a result of a direct action by some of its hormones on sebaceous glands. Gonadotrophins stimulate sebum secretion in the human male [51], but probably do not have any direct independent action on the sebaceous gland.

ACTH has an effect through adrenal androgens. Patients with hypopituitarism and those with isolated growth hormone deficiency have low levels of sebum [52], while patients with acromegaly show increased sebum secretion [53,54]. Growth hormone levels can be raised in prepubertal boys by supplemental testosterone administration, through increased growth hormone-releasing hormone secretion [55].

Growth hormone (GH) is secreted by the pituitary gland and acts on peripheral tissue to stimulate production of insulin-like growth factors (IGFs). There are two forms, IGF-1 and IGF-2; the former is the most prevalent. It has been suggested that GH may be involved in acnegenesis [56], and is likely to be involved

in sebaceous gland development. GH stimulates sebocyte differentiation but not proliferation, and augments the effect of 5α-reductase on sebaceous lipid synthesis [57]. *In vitro* IGF-1 and insulin stimulate sebocyte proliferation and differentiation especially with GH [57]. In addition, IGF-1 is thought to be involved in the induction of 5α-reductase [58].

Acne can be exacerbated by hyperprolactinaemia [59].

Alpha-melanocyte-stimulating hormone (α-MSH) is a member of the propiomelanocortin peptide family, which includes ACTH. α-MSH is an important stimulator of sebaceous gland growth and development in the rat [60,61] and has synergistic action alongside testosterone [42,61,62]. In human sebocytes, *in vitro* α-MSH has been shown to stimulate proliferation through its binding to MC1 and lipid synthesis through binding to MC5 [63]. Slight elevations of plasma concentrations of α-MSH have been found in Cushing's disease [64].

The drug levodopa decreases the seborrhoea of Parkinsonism, but has no effect in normal subjects. Increased sebaceous gland activity in pregnancy [65], lactation [66] and after taking phenothiazine drugs could be due to a pituitary-derived sebotrophic factor [1].

Oestrogens

Oestrogens undoubtedly depress sebaceous activity, especially in pharmacological doses. They decrease the size of sebaceous glands when injected into rats [67–69] or when given orally to adult human males [27], and have also been shown to reduce sebum production in both animals [70–72] and humans [27,73–76]. Oestrogens have also been shown to directly suppress an enhanced sebaceous gland function [77]. On the grounds that it was not possible to demonstrate a local, as distinct from a systemic effect by topical application of oestrogen ointment to the human forehead [27], it has been suggested that oestrogens may act by reducing endogenous androgen production [51]. This view that they suppress gonadotrophin secretion by the pituitary receives support from the finding that sebum-suppressing doses of oestrogen reduced the levels of testosterone in the plasma and urine of normal men [76], although not from the evidence that they suppressed sebum secretion in eunuchs [30].

Evidence from animal experiments favours the hypothesis that oestrogens act peripherally and directly upon the sebaceous glands [48,68,78–82]. The major active oestrogen is oestrodiol, which is produced from testosterone in the ovary adipose tissue and other peripheral tissues. Oestrodiol can be converted to the less potent oestrogen, estrone, by the action of 17β-hydroxysteroid dehydrogenase (17β-HSD) enzyme. Both aromatase and 17β-HSD are present in the skin. Oestrogen receptors of the β-isotope are strongly expressed in many cells of the skin and the α-isotope is found in coenocytes and dermal fibroblasts *in vitro* [83].

Hormonal actions on sebocytes in culture

Data from corneocytes in culture have supported the *in vivo* evidence presented in the previous sections. Several groups [2,48,84–87] have made significant contributions. Zouboulis's group [48,86,87] has established an immortalized human sebaceous gland cell culture system that has been passaged over 50 times; cells have been cloned and show no signs of senescence after 4.5 years *in vitro*, whereas normal human sebocytes can only be grown for three to six passages. These immortalized sebocytes have large cytoplasm profiles with abundant organelles, including vacuoles and myelin figures, which indicate lipid synthesis. The cells express molecules typically associated with human sebocytes such as keratins 7, 13 and 19. Functional studies have revealed that the synthesis of the sebaceous lipids is virtually identical to that of the human sebaceous gland cells. They also showed an increased cell proliferation after the addition of 5α-DHT, and a significant inhibition in the proliferation of these immortalized cells after the addition of retinoids, in particular 13-*cis*-retinoic acid (13-*cis*-RA).

These culture systems have demonstrated that the skin is a factory of androgen metabolism [48,86,87]. Studies on immortalized sebocytes have demonstrated that the four major enzymes involved in the intracellular activation and deactivation of androgens are: (i) 3β-hydroxysteroid dehydrogenase Δ^{4-5} isomerase (Δ^5–3β-HSD), (ii) 17β-hydroxysteroid dehydrogenase (17β-HSD), (iii) 5α-reductase and (iv) 3α-hydroxysteroid dehydrogenase (3α-HSD). Three-beta-hydroxysteroid dehydrogenase Δ^{4-5} isomerase (isotype 1), which converts dihydroepiandrosterone to androstenedione, is almost exclusively located in the sebaceous glands. Sebaceous glands express isoforms 2 and 3 of 17β-HSD, and thus are able to reversibly convert androstenedione to testosterone [88]. Five-alpha-reductase isotype 1, which irreversibly metabolizes testosterone to 5α-DHT, is also predominantly expressed in the sebaceous glands [16]. Zouboulis's group also demonstrated that corticotrophin-releasing hormone (CRH) is a sebaceous gland autocrine hormone, and is a biphasic regulator of lipogenesis in human sebocytes [89]. The evidence was obtained from sebocyte cell culture experiments and suggests that human sebocytes possess a complete CRH/CRH-receptor system. These proteins are expressed at the mRNA and protein level. It may be that stress-related acne could be explained by a local hormonal pathway.

In contrast, keratinocytes have different expression and metabolic rates of some of these enzymes. For example, sebocytes are able to synthesize testosterone from adrenal precursors and to inactivate them in order to maintain androgen homeostasis, whereas keratinocytes are responsible for androgen degradation. These unique expressions of differing androgen activity in different cutaneous cells suggest that there may be differentially programmed duties of skin cell populations for androgen metabolism [48,86–88].

In addition to androgens, other physiological and pharmacological candidates have been reported to control the development of sebocytes and to stimulate the proliferation of human sebocytes. Growth factors such as epidermal growth factor (EGF), transforming growth factor-α (TGF-α) and basic and fibroblast growth factor are paracrine and autocrine mediators of the proliferation and differentiation of a wide variety of cells [90,91]. Studies on hamster sebocytes have shown that these growth factors have mitogenic activity and act as antilipogenic factors [91].

For more detailed information on human skin as a target and endocrine gland the reader is referred to review papers [92,93].

References

1 Thody AJ, Shuster S. Control and function of sebaceous glands. *Physiol Rev* 1989; **69**: 383–416.

2 Zouboulis CC, Seltmann H, Neitzel H, Orfanos CE. Establishment and characterisation of an immortalised human sebaceous gland cell line. *J Invest Dermatol* 2001; **113**: 1011–20.

3 Ridden J, Ferguson D, Kealey T. Organ maintenance of human sebaceous glands: *in vitro* effects of 13-*cis*-retinoic acid and testosterone. *J Cell Sci* 1990; **95**: 125–36.
4 Sanders DA, Philpott MA, Nicolle FV, Kealey T. The isolation and maintenance of the human pilosebaceous unit. *Br J Dermatol* 1994; **131**: 166–76.
5 Agache P, Blanc D, Barrand C, Laurent R. Sebum levels during the first year of life. *Br J Dermatol* 1980; **103**: 643–9.
6 Henderson CA, Taylor J, Cunliffe WJ. Sebum excretion rate in mothers and neonates. *Br J Dermatol* 2000; **42**: 110–1.
7 Pochi PE, Strauss JS, Downing DT. Age-related changes in sebaceous gland activity. *J Invest Dermatol* 1979; **73**: 108–11.
8 Pochi PE, Strauss JS. Endocrinologic control of the development and activity of the human sebaceous gland. *J Invest Dermatol* 1974; **62**: 191–201.
9 Plewig G, Kligman AM. Proliferative activity of the sebaceous glands of the aged. *J Invest Dermatol* 1978; **70**: 314–7.
10 Chen W, Thiboutot D, Zouboulis ChC. Cutaneous androgen metabolism: basic research and clinical perspectives. *J Invest Dermatol* 2002; **119**: 992–1007.
11 Choudhry R, Hodgins MB, Van Der Kwast TH *et al.* Localisation of androgen receptors in human skin by immunohistochemistry: implications for the hormonal regulation of hair growth, sebaceous glands and sweat glands. *J Endocrinol* 1992; **133**: 467–75.
12 Liang T, Hoyer S, Yu R *et al.* Immunocytochemical localization of androgen receptors in human skin using monoclonal antibodies against the androgen receptor. *J Invest Dermatol* 1993; **100**: 663–6.
13 Randall VA. Role of 5α-reductase in health and disease. *Clin Endocrinol Metab* 1994; **8**: 405–31.
14 Thigpen AE, Silver RI, Guileyardo JM *et al.* Tissue distribution and ontogeny of steroid 5α-reductase isoenzyme expression. *J Clin Invest* 1993; **91**: 101–5.
15 Andersson S, Chan HK, Einstein M, Patel S. The molecular genetics of steroid 5α-reductase. *J Endocrinol* 1993; **139** (Suppl.): 6 (Abstract).
16 Thiboutot D, Harris G, Iles V *et al.* Activity of the type 1,5α-reductase activity exhibits regional differences in isolated sebaceous glands of whole skin. *J Invest Dermatol* 1995; **105**: 209–14.
17 Imperato-McGinley J, Miller M, Wilson JD *et al.* A cluster of male pseudohermaphrodites with 5α-reductase deficiency in Papua New Guinea. *Clin Endocrinol (Oxf)* 1991; **34**: 293–8.
18 Imperato-McGinley J, Gautier T, Cai LQ *et al.* The androgen control of sebum production. Studies of subjects with dihydrotestosterone deficiency and complete androgen insensitivity. *J Clin Endocrinol Metab* 1993; **76**: 524–8.
19 Rosenfield RL, Deplewski D. Role of androgens in the developmental biology of the pilosebaceous unit. *Am J Med* 1995; **98** (Suppl. 1A): S80–7.
20 Bläuer M, Vaalasti A, Pauli S-L. Localisation of androgen receptor in human skin. *J Invest Dermatol* 1991; **97**: 264–8.
21 Akamatsu H, Zouboulis ChC, Orfanos CE. Control of human sebocyte proliferation *in vitro* by testosterone and 5-alpha-dihydrotestosterone is dependent on the localization of the sebaceous gland. *J Invest Dermatol* 1992; **99**: 509–11.
22 Mason J. The 3B-hydrosteroid dehydrogenase family of enzymes. *Trends Endocrinol Metab* 1993; **4**: 199–202.
23 Thiboutot D, Martin D, Volikos L *et al*. Oxidative activity of the type 2 isoenzyme 17B-hydroxysteroid dehydrogenase predominates in human sebaceous glands. *J Dermatol* 1998; **111**: 390–5.
24 Hamilton JB. Male hormone substance: a prime factor in acne. *J Clin Endocrinol Metab* 1941; **1**: 264–8
25 Rony HR, Zakon SJ. Effect of androgen on the sebaceous glands of human skin. *Arch Dermatol Syphilol* 1943; **48**: 601–4.
26 Strauss JS, Pochi PE. The quantitative gravimetric determination of sebum production. *J Invest Dermatol* 1961; **36**: 293–8.
27 Strauss JS, Kligman AM, Pochi PE. The effect of androgens and estrogens on human sebaceous glands. *J Invest Dermatol* 1962; **39**: 139–55.
28 Pochi PE, Strauss JS, Mescon H. The role of adrenocortical steroids in the control of human sebaceous gland activity. *J Invest Dermatol* 1963; **41**: 391–9.
29 Hamilton JB, Mestler GE. Low values for sebum in eunuchs and oöphorectomised women. *Proc Soc Exp Biol Med* 1963; **112**: 374–8.
30 Pochi PE, Strauss JS, Mescon H. Sebum secretion and the urinary fractional 17-ketosteroids and total 17-hydroxycorticoid excretion in male castrate. *J Invest Dermatol* 1962; **39**: 475–83.
31 Duffy DM, Legro RS, Chang L *et al.* Metabolism of dihydrotestosterone to 5α-androstane-3α,17β-diol glucuronide is greater in the peripheral compartment than in the splanchnic compartment. *Fertil Steril* 1995; **64**: 736–9.
32 Hodgson-Jones IS, Mackenna RMB, Wheatley VR. The study of human sebaceous activity. *Acta Derm Venereol (Stockh)* 1952; **32** (Suppl. 29): 151–61.
33 Zeligman I, Hubner LF. Experimental production of acne by progesterone. *Arch Dermatol* 1957; **76**: 652–8.
34 Smith JG. The aged human sebaceous gland. The effects of hormone administration and a comparison with adolescent gland function. *Arch Dermatol Syphilol* 1959; **80**: 663–71.
35 Jarrett A. The effects of progesterone and testosterone on surface sebum and acne vulgaris. *Br J Dermatol* 1959; **71**: 102–6.
36 Strauss JS, Kligman AM. The effect of progesterone and progesterone-like compounds on the human sebaceous gland. *J Invest Dermatol* 1961; **36**: 309–18.
37 Simpson NB, Bowden PE, Forster RA *et al.* The effect of topically applied progesterone on sebum excretion rate. *Br J Dermatol* 1979; **100**: 687–92.
38 Cunliffe WJ, Simpson NB. Hormonal control of sebaceous glands with special reference to antiandrogens topically applied. In: Mauvais-Jarvis P, Vickers CFH, Wepierre J, eds. *Percutaneous Absorption of Steroids*. London: Academic Press, 1980: 149–54.
39 Girard J, Barbier A, Latille C. Inhibition of testosterone metabolism and lipogenesis in animal sebaceous glands by progesterone. *Arch Dermatol Res* 1980; **269**: 281–90.
40 Ebling FJ, Ebling E, Skinner J. The influence of the pituitary on the response of the sebaceous and preputial glands of the rat to progesterone. *J Endocrinol* 1969; **45**: 257–63.
41 Haskin D, Lasher N, Rothman W. Some effects of ACTH, cortisone, progesterone and testosterone on sebaceous glands in the white rat. *J Invest Dermatol* 1953; **20**: 207–11.
42 Shuster S, Thody AJ. The control and measurement of sebum secretion. *J Invest Dermatol* 1974; **62**: 172–90.
43 Shuster S, Hinks WM, Thody AJ. Effects of sex and age at gonadectomy on the sebaceous response to progesterone. *J Endocrinol* 1977; **73**: 67–70.
44 Im S, Lee ES, Kim W *et al*. Expression of progesterone receptor on human keratinocytes. *J Korean Med Sci* 2000; **15**: 647–54.
45 Strauss JS, Kligman AM. The effect of ACTH and hydrocortisone on the human sebaceous gland. *J Invest Dermatol* 1959; **33**: 9–14.
46 De Graaf HJ, Kooy R. The effect of ACTH on the sebaceous glands of the rat. *Acta Physiol Pharmacol Néerl* 1955; **4**: 201–6.
47 Ebling FJ, Ebling E, Skinner J, White A. The response of the sebaceous glands of hypophysectomized–castrated male rats to adrenocorticotrophic hormone and to testosterone. *J Endocrinol* 1970; **48**: 73–81.
48 Zouboulis ChC, Xia L, Akamatsu H *et al*. The human sebocytes culture model provides new insights into development and management of seborrhoea and acne. *Dermatology* 1998; **196**: 21–31.
49 Slokinski A, Wortman J, Luger T *et al*. Corticotrophin releasing hormone and propiomelanocortin involvement in the cutaneous response to stress. *Physiol Rev* 2000; **80**: 979–1020.
50 Goolamali SK, Plummer N, Burton JL, Shuster S. Sebum excretion and melanocyte-stimulating hormone in hypoadrenalism. *J Invest Dermatol* 1974; **63**: 253–5.
51 Strauss JS, Pochi PE. Hormonal control of human sebaceous glands. In: Montagna W, Ellis RA, Silver A, eds. *Advances in Biology of Skin*, Vol. 4. *Sebaceous Glands*. Oxford: Pergamon, 1963: 220–54.
52 Goolamali SK, Burton JL, Shuster S. Sebum excretion in hypopituitarism. *Br J Dermatol* 1973; **89**: 21–7.
53 Burton JL, Libman LJ, Cunliffe WJ *et al.* Sebum excretion in acromegaly. *BMJ* 1972; **i**: 406–8.
54 Pochi PE, Strauss JS. Studies on the sebaceous glands in acne and endocrine disorders. *Bull NY Acad Med* 1977; **53**: 359–67.
55 Eakman GD, Dallas JS, Ponder SW, Keenan BS. The effects of testosterone and dihydrotestosterone on hypothalamic regulation of growth hormone secretion. *J Clin Endocrinol Metab* 1996; **81**: 1217–23.
56 Rosenfield RL, Deplewski D. Role of androgens in the development of the pilosebaceous unit. *Am J Med* 1995; **98** (Suppl. 1A): 1A80S–1A88S.
57 Zouboulis CC. Human skin: an independent peripheral endocrine organ. *Horm Res* 2000; **54**: 230–42.

58 Horton R, Pasupuletti V, Antonipillai I. Androgen induction of steroid 5α-reductase may be mediated via insulin-like growth factor-1. *Endocrinology* 1993; **133**: 447–51.
59 Darley CR, Kirby JD, Besser GM *et al.* Circulating testosterone, sex hormone binding globulin and prolactin in women with late onset or persistent acne vulgaris. *Br J Dermatol* 1982; **106**: 517–22.
60 Thody AJ, Shuster S. The control of sebum secretion by the posterior pituitary. *Nature* 1972; **237**: 346–7.
61 Thody AJ, Shuster S. Control of sebaceous gland function in the rat by α-melanocyte-stimulating hormone. *J Endocrinol* 1975; **64**: 503–10.
62 Ebling FJ, Ebling E, Randall V, Skinner J. The synergistic action of α-melanocyte stimulating hormone and testosterone on the sebaceous, prostate, preputial, Harderian and lachrymal glands, seminal vesicles and brown adipose tissue in the hypophysectomized–castrated rat. *J Endocrinol* 1975; **66**: 407–12.
63 Thody AJ, Fisher C, Kendal-Taylor P *et al.* The measurement of immunoreactive α-melanocyte stimulating hormone in human plasma. *Acta Endocrinol* 1985; **110**: 313–8.
64 Bohn M, Schiller M, Stander S *et al.* Evidence for expression of melanocortin-1 receptor in human sebocytes and *in situ*. *J Invest Dermatol* 2002; **118**: 533–9.
65 Burton JL, Cunliffe WJ, Millar DG *et al.* Effect of pregnancy on sebum excretion. *BMJ* 1970; **ii**: 769–71.
66 Burton JL, Shuster S, Cartlidge M *et al.* Lactation, sebum excretion and melanocyte-stimulating hormone. *Nature* 1973; **243**: 249–50.
67 Ebling FJ. Sebaceous glands. 1. The effect of sex hormones on the sebaceous glands of the female albino rat. *J Endocrinol* 1948; **5**: 297–302.
68 Ebling FJ. Sebaceous glands. 2. Changes in the sebaceous glands following the implantation of oestradiol benzoate in the female albino rat. *J Endocrinol* 1951; **7**: 288–98.
69 Ebling FJ. Endocrine factors affecting cell replacement and cell loss in the epidermis and sebaceous glands of the female albino rat. *J Endocrinol* 1955; **12**: 38–49.
70 Ebling FJ. The action of an anti-androgenic steroid, 17α-methyl-αnor-testosterone, on sebum secretion in rats treated with testosterone. *J Endocrinol* 1967; **38**: 181–5.
71 Ebling FJ, Skinner J. The measurement of sebum production in rats treated with testosterone and oestradiol. *Br J Dermatol* 1967; **79**: 386–92.
72 Nikkari T. Composition and secretion of the skin surface lipids of the rat; effects of dietary lipids and hormones. *Scand J Clin Lab Invest* 1965; **17** (Suppl. 85): 1–140.
73 Jarrett A. The effects of stilboestrol on the surface sebum and upon acne vulgaris. *Br J Dermatol* 1955; **67**: 165–79.
74 Pochi PE, Strauss JS. Effect of cyclic administration of conjugated equine estrogens on sebum production in women. *J Invest Dermatol* 1966; **47**: 582–5.
75 Pochi PE, Strauss JS. Sebaceous gland suppression with ethinyl estradiol and diethylstilbestrol. *Arch Dermatol* 1973; **108**: 210–4.
76 Forchielli E, Roa GS, Sarda IR *et al.* Effect of ethinyl oestradiol on plasma testosterone levels and urinary testosterone excretion in man. *Acta Endocrinol* 1965; **50**: 51–4.
77 Guy R, Ridden C, Kealey T. The improved organ maintenance of the human sebaceous gland: modeling *in vitro* the effects of epidermal growth factor, androgens, estrogens, 13-cis retinoic acid and phenol red. *J Invest Dermatol* 1996; **106**: 454–60.
78 Ebling FJ. The action of testosterone and oestradiol on the sebaceous glands and epidermis of the rat. *J Embryol Exp Morphol* 1957; **5**: 74–82.
79 Ebling FJ. Steroid hormones and sebaceous secretion. In: Briggs MH, ed. *Advances in Steroid Biochemistry and Pharmacology*. London: Academic Press, 1970: 1–39.
80 Ebling FJ. The effects of cyproterone acetate and oestradiol upon testosterone stimulated sebaceous activity in the rat. *Acta Endocrinol* 1973; **72**: 361–5.
81 Ebling FJ, Randall VA. Steroid inhibitors of androgen-potentiated actions on skin. *J Steroid Biochem* 1983; **19**: 587–90.
82 Ebling FJ, Skinner J. The local effects of topically applied estradiol, cyproterone acetate, and ethanol on sebaceous secretion in intact male rats. *J Invest Dermatol* 1983; **81**: 448–51.
83 Haczynski J, Tarkowski R, Jarzabek K *et al*. Human cultured fibroblasts express estrogen receptor alpha and beta. *Int J Mol Med* 2002; **10**: 149–53.
84 Rosenfield Rl, Eplewski D, Kentsis A, Ciletti N. Mechanisms of androgen induction of sebocyte differentiation. *Dermatology* 1998; **196**: 43–6.
85 Zouboulis CC, Seltmann H, Neitzel H. Establishment and characterisation of an immortalised human sebaceous gland cell line. *J Invest Dermatol* 1999; **113**: 1011–20.
86 Fritsch M, Orfanos CE, Zouboulis CC. Sebocytes are the key regulators of androgen homeostasis in human skin. *J Invest Dermatol* 2001; **116**: 793–800.
87 Zouboulis CC, Xia L, Akamatsu H *et al.* The human sebocyte culture model provides new insights into development and management of seborrhoea and acne. *Dermatology* 1998; **196**: 21–31.
88 Chen W, Thiboutot D, Zouboulis CC. Cutaneous androgen metabolism: basic research and clinical perspectives. *J Invest Dermatol* 2002; **119**: 992–1007.
89 Zouboulis CC, Seltmann H, Hiroi N *et al.* Corticotrophin-releasing hormone: an autocrine hormone that promotes lipogenesis in human sebocytes. *Proc Natl Acad Sci USA* 2002; **99**: 7148–53.
90 Akimoto N, Sato T, Sakiguchi T *et al.* Cell proliferation and lipid formation in hamster sebaceous gland cells. *Dermatology* 2002; **204**: 118–25.
91 Tavakkol A, Varani J, Zouboulis CC. Maintenance of the human skin in organ culture: the role for insulin-like growth factor-1 receptor and epidermal growth factor receptor. *Arch Dermatol Res* 1999; **291**: 603–51.
92 Zouboulis ChC. The human skin as a target and endocrine gland hormone. *Hormones* 2005; **3**: 9–26.
93 Wollina U, Alohamed A, Ruta G *et al.* Receptors of eccrine, apocrine and holcrine skin glands. *Dermatol Clin* 2007; **25**: 577–88.

Retinoid control of sebaceous gland activity

Interest in retinoid metabolism within sebocytes and the sebaceous gland was stimulated by the excellent clinical effectiveness of 13-*cis*-RA (isotretinoin) in severe acne. Other retinoid drugs including retinoic acid and all-*trans*-RA (tretinoin) have been shown to have a clinical effect in acne. Retinoids exert their effect through cell proliferation, lipid synthesis and keratin expression.

13-*cis*-RA reduces the size of sebaceous glands through prolongation of the maturation of basal sebocytes, suppresses sebum production up to 90% by inhibiting sebaceous lipid synthesis and *in vivo* and *in vitro* inhibits terminal sebocyte differentiation [1]. Despite the superb efficacy of this agent, the molecular basis for the unique sebostatic activity is still not fully understood. Sebocyte proliferation and lipid synthesis are suppressed when cells are cultured in the absence of vitamin A [2] and in an immortalized human sebaceous gland cell line, the addition of retinoids to culture medium significantly reduced sebocyte proliferation [3]. Its stereoisomers tretinoin and al-tretinoin (9-*cis*-retinoic acid) are inferior to isotretinoin in terms of sebum suppression, reducing sebocyte proliferation, and hence efficacy in acne. Pharmacological quantities of 13-*cis*-RA or all-*trans*-RA have also been shown to suppress sebocyte proliferation and lipid synthesis in a dose-dependent manner [4]. The superior effect of 13-*cis*-retinoic acid has been attributed to delayed initiation of retinoid inactivation under incubation of sebocytes with 13-*cis*-RA as this leads to high intracellular levels of tretinoin. 13-*cis*-RA acid down-regulates the expression of keratins 5, 6, 14 and 16 and up-regulates keratin 7, whereas all-*trans*-RA down-regulates keratin 5, 6 and 16 expression and up-regulates the expression of keratin 19 [4]. All-*trans*-RA is thought to be the active metabolite of isotretinoin within cells following enzymic conversion from 13-*cis*-RA. Evidence comes from the preferential binding of all-*trans*-RA to retinoic acid receptors (RARs) [4]. The antiproliferative effect of retinoids on human sebocytes *in vitro* was found to be mediated by RAR [5]. Figure 42.12 illustrates probable interconversion of retinoids within cells.

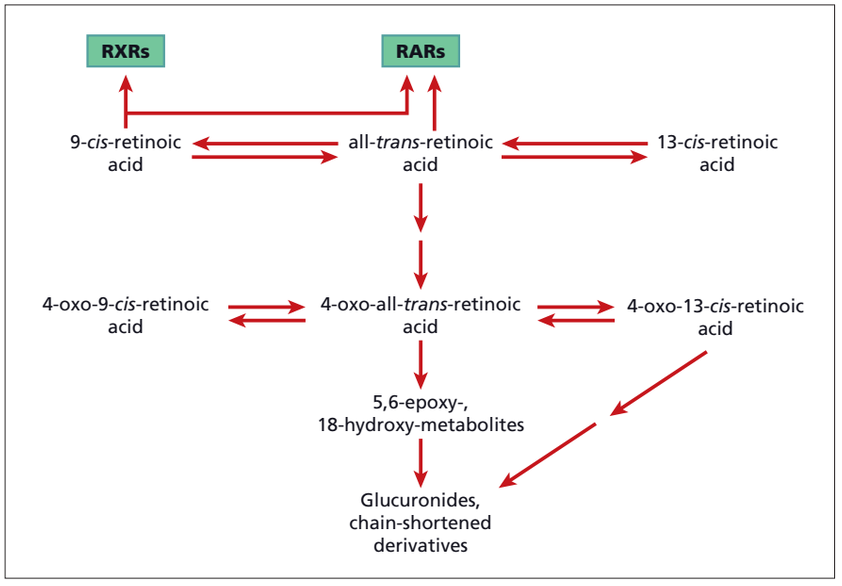


Fig. 42.12 The likely retinoid pathways of isotretinoin metabolism in the sebaceous gland. RAR, retinoic acid receptor; RXR, retinoid X receptor. (Reproduced with the kind permission of Dr U. Wiegand, Roche, Basel.)

Human sebocytes are naturally eliminated by apoptosis on their way to terminal differentiation before their death and holocrine secretion [6]. Nelson *et al*. confirmed that isotretinoin-induced apoptosis was not evident within a 24-h treatment period, but detected marginal apoptosis after 48–72 h; the effect was specific to sebocytes [7]. This process of cell cycle arrest and apoptosis of sebocytes provides an explanation for the significant reduction in size, shape and lipid content of sebaceous glands post treatment with isotretinoin. Terminal differentiation of human sebocytes is associated with increased cell volume, increased lipid synthesis and accumulation of lipid droplets. Skin surface lipids alter post treatment with isotretinoin, demonstrating a marked decrease in wax esters, reduction in squalene and relative increase in cholesterol [1]. This inhibitory effect of 13-*cis*-RA on sebaceous lipids has been attributed to inhibition of terminal sebocyte differentiation [8], and is probably mediated by both RXR and RAR [3,5].

A study has demonstrated the specific and significant presence of CYP26A1 expression in epithelial cells of sebaceous glands of healthy human skin, which may provide new insights into pathogenesis and treatment of conditions affecting the sebaceous follicle [9].

References

1 Zouboulis CC, Orfanos CE. Retinoids. In: Millikan LE, ed. *Drug Therapy in Dermatology*. Marcel Dekker: New York/Basel, 2000: 171–233.

2 Zouboulis CC, Korge BP, Mischke D, Orfanos CE. Altered proliferation, synthetic activity, and differentiation of cultured human sebocytes in the absence of vitamin A and their modulation by synthetic retinoids. *J Invest Dermatol* 1993; **101**: 626–33.

3 Tsukada M, Schröder M, Roos T *et al*. 13-cis retinoic acid exerts its specific activity on human sebocytes through selective intracellular isomerization to all-trans retinoic acid and binding to retinoid acid receptors. *J Invest Dermatol* 2000; **115**: 321–7.

4 Zouboulis CC, Korge B, Akamatsu H *et al*. Effects of 13-*cis*-retinoic acid, all-*trans*-retinoic acid, and acitretin on the proliferation, lipid synthesis and keratin expression of cultured human sebocytes *in vitro*. *J Invest Dermatol* 1991; **96**: 792–7.

5 Kim MJ, Ciletti N, Michel S *et al*. The role of specific retinoid receptors in sebocytes growth and differentiation in culture *J Invest Dermatol* 2000; **114**: 349–531.

6 Wrobel A, Seltmann H, Fimmels S *et al*. Differentiation and apoptosis in human immortalized sebocytes. *J Invest Dermatol* 2003; **120**: 175–81.

7 Nelson AM, Gilliband KL, Cong Z *et al*. Retinoic acid induces apoptosis and cell cycle in human SEB-1 sebocytes. *J Invest Dermatol*; **126**: 2178–89.

8 Zouboulis CC, Krieter A, Gollnick H *et al*. Progressive differentiation of human sebocytes *in vitro* is characterized by increased cell size and altered antigenic expression and is regulated by culture duration and retinoids. *Exp Dermatol* 1994; **3**: 151–5.

9 Heise R, Mey J, Neis M *et al*. Skin retinoid concentrations are modulated by CYP26A1 expression restricted to basal keratinocytes in normal human skin and differentiated 3D models. *J Invest Dermatol* 2006; **126**: 2473–80.

Inhibitors of sebaceous activity

Acne is associated with increased sebum secretion and proliferative activity of sebaceous glands. Much effort has therefore gone into developing treatments for acne that reduce sebaceous gland activity.

Possible mechanisms include reducing the circulating levels of serum androgens through an effect on the pituitary, adrenal or gonads, or by affecting the transport of androgens (Fig. 42.13). Alternatively, the pharmacological/physiological suppression of androgens could be achieved through a direct effect on sebocyte metabolism. Such mechanisms include blocking enzyme activity (5α-reductase type 1, Δ^5–3β-HSD, cytochrome p450), or by blockage of androgen or retinoid receptors.

The effect of topically applied hormones shows a considerable species difference between animals and humans. Some topical therapies significantly reduce sebum excretion in animals but have no effect in the human. The most likely explanation is anatomical, as the animals under investigation have sebaceous glands situated very close to the epidermis, whereas the human sebaceous gland is relatively deep in the dermis and connects to the epidermis via a long pilosebaceous duct, making it more difficult for these topical compounds to reach the gland. Clinical benefit does not occur until sebum suppression achieves a minimum of 30%.

Co-cyprindiol (Dianette® and Estelle 35®), which contains 35 µg ethinyl oestradiol and 2 mg cyproterone acetate (CPA), reduces

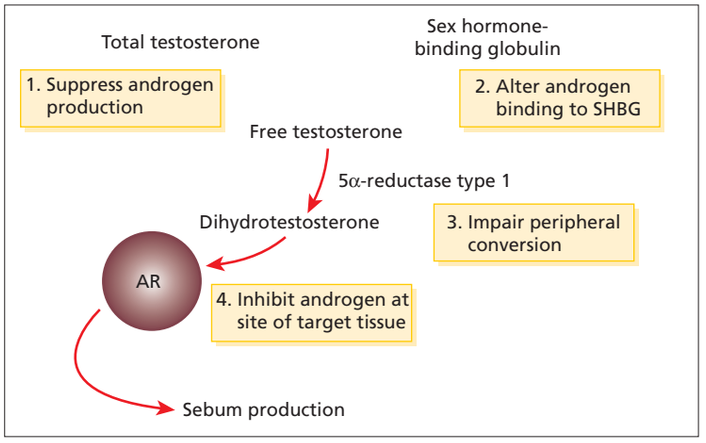


Fig. 42.13 Possible mechanisms for reducing circulating androgens. AR = androgen receptor within the sebaceous gland.

sebum excretion by 28% [1–3]. When combined with additional CPA (100 mg/day) from the fifth to the 14th days of cycle, the sebum suppression rises to 68%.

Topical CPA was ineffective when applied in 50% dimethylsulfoxide (DMSO) or in cetomacrogol [4–5], but did have some effect in an ethanol base [6]. Other topical agents said to be effective [7–12] include 17α-propyltestosterone, 17α-mesterolone and flutamide, but none have been shown to be of clinical benefit in patients with acne. Inocoterone, another non-steroidal receptor blocker, reduces sebaceous gland activity when applied topically to rat and hamster sebaceous glands [13,14], and lacks any systemic effects. However, in adult males topical inocoterone produced a small reduction in sebum excretion and a minor improvement in clinical acne [15]. Seventeen substituted α-chloro and 17β-sulphinyl steroids have been suggested as inhibitors of sebaceous activity [16], but have been disappointing in humans. Spironolactone, given systemically, has been shown to inhibit the hamster flank organ [17], and, given topically, to block androgen activity in sebaceous glands of the hamster pinna [18]. However, there was no effect on sebum excretion when applied topically to humans [19]. In contrast, spironolactone given orally significantly reduces sebum excretion in humans in a dose-dependent manner; there is a reduction of around 30% with 100 mg/day, and a reduction of 60–70% with 200 mg/day [20]. Oral administration of the H_2-receptor antagonists ranitidine and cimetidine reduces sebum excretion in humans [21], but not to a clinically significant level, and these drugs lack effect when applied topically [22].

Substances that inhibit the conversion of testosterone to DHT also reduce sebum production [23]. Topical progesterone, which may achieve a reduction in the rate of sebum excretion [24,25], has a relatively small and temporary sebosuppressive effect in humans, unlikely to be of any clinical benefit to the patient with acne.

Certain derivatives of vitamin A, in particular isotretinoin (13-*cis*-RA), have marked effects on the sebaceous glands when given systemically. They have been shown to reduce the size of the hamster flank organ [26] and human sebaceous glands [27], in which they profoundly inhibit sebum excretion [28–30]. Isotretinoin reduces 5α-reductase activity in human liver and skin [31–33], and has been shown to reduce the binding capacity of the androgen receptor in back skin [33]. Isotretinoin reduces the synthesis of DNA and the incorporation of a lipid precursor ^{14}C-acetate in human sebaceous glands *in vitro* [34,35]. The metabolism of retinoids in the human sebaceous gland has been described above (see also section on oral isotretinoin below). Topical retinoids, in contrast to certain oral retinoids, have no effect in reducing sebum production or excretion.

It has been assumed that topical antibiotics do not influence sebum production or sebum excretion. However, it has been shown that topical erythromycin plus zinc acetate (Zineryt®) reduces SER by about 20% (using Sebutape® technology), in contrast to topical erythromycin alone [36]. The mechanism for this is unclear, but may relate to the drug affecting sebum outflow from the duct and is unlikely to have any impact on clinical efficacy.

References

1 Miller JA, Wojnarowska FT, Dowd PM *et al.* Anti-androgen treatment in women with acne: a controlled trial. *Br J Dermatol* 1986; **114**: 705–16.
2 Burton JL, Laschet U, Shuster S. Reduction of sebum excretion in man by the antiandrogen cyproterone acetate. *Br J Dermatol* 1973; **89**: 487–90.
3 Ebling FJ, Thomas AK, Cooke ID *et al.* Effect of cyproterone acetate on hair growth, sebaceous secretion and endocrine parameters in a hirsute subject. *Br J Dermatol* 1977; **97**: 371–81.
4 Cunliffe WJ, Shuster S, Cassels Smith AJ. The effect of topical cyproterone acetate on sebum secretion in patients with acne. *Br J Dermatol* 1969; **81**: 200–1.
5 Pye RJ, Burton JL, Harris HI. Effect of 1% cyproterone acetate in cetomacrogol cream BPC (Formula A) on sebum excretion rate in patients with acne. *Br J Dermatol* 1976; **95**: 427–8.
6 Bingham KD, Low M, Wyatt EH. Effect of topical cyproterone acetate on sebum excretion in man. *Lancet* 1979; **ii**: 304–5.
7 Ferrari RA, Chakrabarty K, Beyler AL *et al.* Suppression of sebaceous gland development in laboratory animals by 17-α-propyltestosterone. *J Invest Dermatol* 1978; **71**: 320–3.
8 Lyons F, Shuster S. Effect of topical 17α-propylmesterolone in man. *Br J Dermatol* 1981; **104**: 685–6.
9 Schmidt JB, Spona J. Effect of topically applied 17α-propylmesterolone in acne patients. *Endocrinol Exp* 1987; **21**: 71–8.
10 Schmidt JB, Spona J. An effective topical antiandrogen: 17α-propylmesterolone in acne. *Hautarzt* 1987; **38**: 470–3.
11 Lutsky BN, Budak M, Koziol P *et al.* The effects of a nonsteroid antiandrogen, flutamide, on sebaceous gland activity. *J Invest Dermatol* 1975; **64**: 412–7.
12 Lyons F, Shuster S. Sex difference in response of the human sebaceous gland to topical flutamide. *Br J Dermatol* 1982; **107**: 697–9.
13 Bouton MM, Lecaque D, Secchi J, Tournemine C. Effect of a new topically active antiandrogen (RU38882) on the rat sebaceous gland: a comparison with cyproterone acetate. *J Invest Dermatol* 1985; **86**: 163–7.
14 Matias JR, Gaillard M. Local inhibition of sebaceous gland growth by topically applied RU58841. *Ann NY Acad Sci* 1995; **761**: 56–65.
15 Lookingbill DP, Abrams BB, Ellis CN *et al.* Inocoterone and acne: the effect of a topical antiandrogen: results of a multicenter clinical trial. *Arch Dermatol* 1992; **128**: 1197–200.
16 Green MJ, Tiberi R, Draper RW *et al.* Novel 17α-chloro-17β-sulfinyl steroids as specific inhibitors of sebaceous gland activity: potential antiacne agents. *J Med Chem* 1983; **26**: 78–85.
17 Luderschmidt C, Bidlingmaier F, Plewig G. Inhibition of sebaceous gland activity by spironolactone in Syrian hamster. *J Invest Dermatol* 1982; **78**: 253–5.
18 Seki T, Toyomoto T, Morohashi M. Effects of topically applied spironolactone on androgen stimulated sebaceous glands in the hamster pinna. *J Dermatol* 1995; **22**: 233–7.
19 Walton S, Cunliffe WJ, Lookingbill P *et al.* Lack of effect of topical spironolactone on sebum excretion. *Br J Dermatol* 1986; **114**: 261–9.
20 Goodfellow A, Alaghband-Zadeh J, Carter G *et al.* Oral spironolactone improves acne and reduces sebum excretion. *Br J Dermatol* 1984; **111**: 209–14.
21 Gloor M, Wirth H, Swoboda U. Is sebosuppression by cimetidine an antiandrogenic effect? *Acta Derm Venereol (Stockh)* 1981; **61**: 262–4.

22 Lyons F, Shuster S. The suppression of sebaceous gland activity by H_2-receptor antagonists. *Br J Dermatol* 1980; **102**: 730–1.
23 Hsia SL, Voigt W. Inhibition of dihydrotestosterone formation: an effective means of blocking androgen action in hamster sebaceous gland. *J Invest Dermatol* 1974; **62**: 224–7.
24 Cunliffe WJ, Simpson NB. Hormonal control of sebaceous glands with special reference to antiandrogen applied topically. In: Mauvais-Jarvis P, Vickers CFH, Wepierre J, eds. *Percutaneous Absorption of Steroids*. London: Academic Press, 1980: 149–54.
25 Simpson NB, Bowden PE, Forster RA *et al.* The effect of topically applied progesterone on sebum excretion rate. *Br J Dermatol* 1979; **100**: 687–92.
26 Gomez EC. Differential effect of 13-*cis*-retinoic acid and an aromatic retinoid (Ro 10–9359) on the sebaceous glands of the hamster flank organ. *J Invest Dermatol* 1980; **76**: 60–9.
27 Landthaler M, Kummermehr JA, Plewig O. Inhibitory effects of 13-*cis*-retinoic acid on human sebaceous glands. *Arch Dermatol Res* 1980; **269**: 297–309.
28 Goldstein JA, Socha-Szott A, Thomsen RJ *et al.* Comparative effects of isotretinoin and etretinate on acne and sebaceous gland secretion. *J Am Acad Dermatol* 1982; **6**: 760–5.
29 King K, Jones DH, Daltrey DC *et al.* A double-blind study of the effects of 13-*cis*-retinoic acid on acne, sebum excretion rate and microbial population. *Br J Dermatol* 1982; **107**: 583–90.
30 Strauss JS, Stranieri AM, Farrill LN *et al.* The effect of marked inhibition of sebum production with 13-*cis*-retinoic acid on skin surface lipid composition. *J Invest Dermatol* 1980; **74**: 66–7.
31 Rademaker M, Wallace M, Cunliffe WJ, Simpson NB. Isotretinoin treatment alters steroid metabolism in women with acne. *Br J Dermatol* 1991; **124**: 361–4.
32 Boudou P, Chivot M, Vexiau P *et al.* Evidence for decreased androgen 5-α-reduction in skin and liver of men with severe acne after 13-*cis*-retinoic acid treatment. *J Clin Endocrinol Metab* 1994; **78**: 1064–9.
33 Boudou P, Soliman H, Chivot M *et al.* Effect of oral isotretinoin treatment on skin androgen receptor levels in male acneic patients. *J Clin Endocrinol Metab* 1995; **80**: 1158–61.
34 Ridden J, Kealy T. Effect of 13-*cis*-retinoic acid and testosterone on isolated human sebaceous glands. *Br J Dermatol* 1988; **118**: 281–2.
35 Kealey T, Ridden J. Isotretinoin and testosterone regulate the *in vitro* lipogenesis of human sebaceous glands isolated by shearing. *Br J Dermatol* 1989; **121** (Suppl. 34): 30.
36 Pierard GE, Pierard-Franchimont C. Effect of a topical erythromycin-zinc formulation on sebum delivery. Evaluation by combined photometric multi-step samplings with Sebotape®. *Clin Exp Dermatol* 1993; **18**: 410–3.

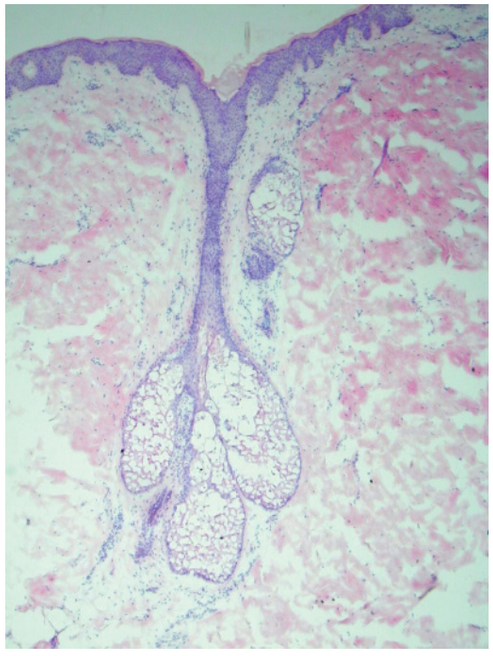


Fig. 42.14 An haematoxylin and eosin stain of a longitudinal frozen section of a clinically normal pilosebaceous follicle from the back of an acne patient. A mild perifollicular infiltrate is present. (Courtesy of Dr A. Jeremy, Skin Research Centre, Institute of Molecular and Cellular Biology, Faculty of Biological Sciences, University of Leeds, UK.)



Fig. 42.15 Mixed non-inflammatory and inflammatory acne lesions.

Acne vulgaris

Definition. Acne is a chronic inflammatory disease of the pilosebaceous units (Fig. 42.14)

It is characterized by seborrhoea, the formation of open and closed comedones, erythematous papules and pustules (Fig. 42.15) and in more severe cases nodules, deep pustules and pseudocysts (Fig. 42.16). In many cases a degree of scarring will ensue.

Four major factors are involved in the pathogenesis: (i) increased sebum production, (ii) hypercornification of the pilosebaceous duct, (iii) abnormality of the microbial flora especially colonization of the duct with *P. acnes*, and (iv) inflammation.

Natural history. The condition usually starts in adolescence and frequently resolves by the mid-twenties [1]. Prevalence data is variable depending on the time of the study and population assessed. In one community based study, acne was noted in 56% of boys and 45% of girls aged between 14 and 16 years and noted to be moderate to severe in 11% [2]. A peak in prevalence and severity occurs between 14 and 17 years in females, when 40% are affected, and 16 and 19 years in males, when 35% are affected [1]. A study from the USA [3] indicated that the prevalence by the mid-teens was virtually 100%. On the other hand, only about 20% of sufferers needed the help of a physician. A study of adolescents in New Zealand identified acne in 91% of male and 79% of female students studied. Severe acne was noted in 6.9% of males and just 1.1% of females [4]. A population-based prevalence study from Australia demonstrated that the overall prevalence rates were 36.1%, ranging from 27.7% in 10–12 year olds to 93.3% in 16–18



Fig. 42.16 Deep-seated inflammation resulting in an acne cyst. (Courtesy of Dr A. Yung, Auckland, New Zealand.)

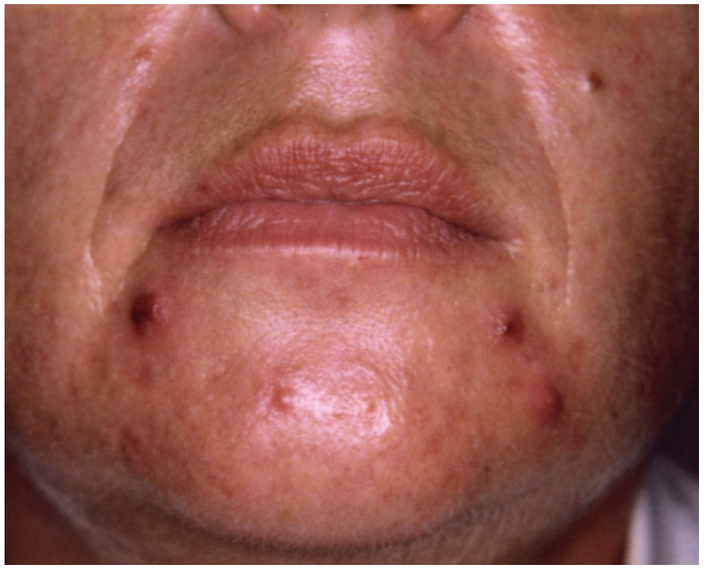


Fig. 42.17 Persistent acne in a mature female demonstrating deep-seated inflammatory lesions with a predilection for the perioral region.

year olds. It was less prevalent in boys between 10 and 12 years, but between 16 and 18 years of age boys were more likely to have acne than girls. Moderate to severe acne was present in 17% of students (24% boys, 11% girls). Comedones, papules and pustules were the most common clinical features and 1:4 cases had scarring [5]. A further study in Portugal confirmed a high prevalence rate of 82.4% in 10–12 year olds and identified that only 44% of cases sought treatment [6].

In those patients with very mild disease the problem is referred to as physiological acne. Acne develops earlier in females than in males [1,7], which may reflect the earlier onset of puberty. Significant prepubertal acne is only rarely found to be a cutaneous marker of an endocrine abnormality but should be considered in early-onset acne (see Table 42.2). Mild, comedonal acne can be the first sign of pubertal maturation; significant comedones usually precede inflammatory lesions by 2–3 years, and early mid-facial comedones are recognized as a marker of subsequent disease [8,9]. Some subjects show small, non-inflamed lesions by the age of 8–9 years [1]. Site of involvement is linked to the age of onset of the disease, with inflammatory lesions in the midline of the face presenting early in sexual maturation [5].

By 20 to 25 years the tendency is for acne to resolve slowly [10]. However, in 7–17% of individuals clinical acne persists beyond the age of 25 years [11] (Fig. 42.17) with physiological acne in females having a prevalence of 24% [12]. A study from Denmark suggested that there has been a decrease in the prevalence of acne in females, and this may relate to the widespread use of oral contraceptives [13]. On the other hand, some clinicians consider that they are now seeing an increase in the number of patients with mature acne. In another study [11], 25% of acne patients referred to an acne clinic had a mean age of 24 years. Most had acne persisting from adolescence, but 8% had late-onset (age over 25 years) acne. This may be a reflection of a more demanding and articulate group of mature acne patients [14]. At the age of 40 years, significant lesions are still present in 1% of males and 5% of females [10]. On the other hand, questionnaire-based studies in France [15] and in the USA [16] have shown that as many as 80% of patients treated for acne have some level of disease activity that persists into the 30 to 40-year age range.

Factors that underlie the resolution of acne are not understood, nor are the relative persistence in females. Recent studies on the natural history of acne are limited, because improved treatment has modified the prevalence, severity and age of presentation to dermatological clinics [17].

Genetic factors. Several studies have shown that genetic factors influence susceptibility to acne [18,19]. A survey in Germany [20] showed that acne had been present in one or both parents of 45% of schoolboys with acne but in only 8% of parents of boys without acne. A genetic influence is confirmed by the very high concordance between monozygotic twins, in whom the SER is virtually identical. Comedone numbers are also similar in identical twins but not in dizygotic twins, which suggests a genetic role in comedone formation [19]. Furthermore, in three pairs of identical twins, severe nodular acne developed at approximately the same time in each pair. On the other hand, in less than half of affected dizygotic twins did both twins have acne [20]. Patients with persistent acne have a strong family history of persistent acne, in contrast to patients with adolescent acne [11]. A correlation between neonatal acne and familial hyperandrogenism has been suggested [21].

The decreased incidence of atopic dermatitis in acne sufferers [22] may be genetically determined, but could be explained by the low sebum excretion in patients with eczema. The association of very severe acne with the XYY syndrome [23,24] has been recorded.

Racial studies provide an insight into genetic and environmental factors. Acne in black Americans is less evident than in white Americans, who, in turn, have more severe acne than Japanese [25]. The incidence of acne is said to be low in Inuits, who eat a diet rich in fish, but increases markedly when they change to a 'Western' (Canadian) diet with more saturated fats. Similar changes have been noted in Japanese people who immigrate to Hawaii and consume an American-style diet [25].

Although evidence of familial clustering exists [26], and to date a few acne candidate genes have been proposed [27], some of them related to androgen and steroid metabolism [28], research is currently limited. Understanding the genetic basis for acne could potentially identify new therapeutic options and help to identify those more prone to scarring. Further research is required in this area.

References

1 Burton JL, Cunliffe WJ, Stafford L *et al.* The prevalence of acne vulgaris in adolescence. *Br J Dermatol* 1971; **85**: 119–26.
2 Smithard A, Glazebrook C, Williams HC. Acne prevalence, knowledge about acne and psychological morbidity in mid-adolescence: a community-based study. *Br J Dermatol* 2001; **145**: 274–9.
3 Stern RS. The prevalence of acne on the basis of physical examination. *J Am Acad Dermatol* 1992; **26**: 931–5.
4 Lello J, Peari A, Arroll B *et al*. Prevalence of acne vulgaris in Auckland senior high school students. *N Z Med J* 1995; **108**: 287–9.
5 Kilkenny M, Merlin K, Plunkett A *et al*. The prevalence of common skin conditions in Australian school students: 3. Acne vulgaris. *Br J Dermatol* 1998; **139**: 840–5.
6 Amado JM, Matos ME, Abreu AM *et al*. The prevalence of acne in the north of Portugal. *J Eur Acad Dermatol Venereol* 2006; **20**: 1287–95.
7 Munro-Ashman D. Acne vulgaris in a public school. *Trans St John's Hosp Dermatol Soc* 1963; **49**: 144–8.
8 Lucky AW, Biro FM, Huster FA *et al.* Acne vulgaris in early adolescent boys: correlations with pubertal maturation and age. *Arch Dermatol* 1991; **172**: 210–6.
9 Lucky AW, Biro FM, Huster GA *et al.* Acne vulgaris in premenarchal girls. *Arch Dermatol* 1994; **130**: 308–14.
10 Cunliffe WJ, Gould DJ. Prevalence of facial acne vulgaris in late adolescence and in adults. *BMJ* 1979; **1**: 1109–10.
11 Goulden V, Clark SM, Cunliffe WJ. Post adolescent acne: a review of clinical features. *Br J Dermatol* 1997; **136**: 66–70.
12 Goulden V, Stables GI, Cunliffe WJ. Prevalence of facial acne in adults. *J Am Acad Dermatol* 1999; **41**: 577–80.
13 Jemec GBE, Linneberg A, Nielsen NH *et al.* Have oral contraceptives reduced the prevalence of acne? A population-based study of acne vulgaris, tobacco smoking and oral contraceptives. *Dermatology* 2002; **204**: 179–84.
14 Healy E, Simpson N. Acne vulgaris. *BMJ* 1994; **308**: 831–3.
15 Poli F, Dreno B, Verschoore M. An epidemiological study of acne in female adults: results of a survey conducted in France. *J Eur Acad Dermatol Venereol* 2001; **15**: 541–5.
16 Shaw JC. Persistent acne in adult women. *Arch Dermatol* 2001; **137**: 1252–3.
17 Rademaker M, Garioch JJ, Simpson NB. Acne in schoolchildren: no longer a concern for dermatologists. *BMJ* 1989; **298**: 1217–9.
18 Palatsi R, Oikarinena A. Hormonal analysis and delayed hypersensitivity in identical twins with severe acne. *Acta Derm Venereol (Stockh)* 1979; **59**: 157–60.
19 Walton S, Wyatt E, Cunliffe WJ. Genetic control of sebum excretion and acne. A twin study. *Br J Dermatol* 1988; **18**: 393–6.
20 Gloor M, Hubscher M, Friederich HL. Untersuchungen zur externen Behandlung der Acne vulgaris mit Tetracyclin und Öestrogen. *Hautarzt* 1974; **25**: 391–4.
21 Bekaert C, Song M, Delvigne A. Acne neonatorum and familial hyperandrogenism. *Dermatology* 1998; **196**: 453–4.
22 Liddell K. A familial study of acne and eczema. *Br J Dermatol* 1976; **94**: 633–7.
23 Funderburk SJ, Landan JW. Acne in a retarded boy with autosomal chromosomal abnormality. *Arch Dermatol* 1976; **112**: 859–61.
24 Voorhees JJ, Wilkins JW Jr, Hayes E *et al.* Nodulocystic acne as a phenotypic feature of the XYY genotype. Report of five cases, review of all known XYY subjects with severe acne, and discussion of XYY cytodiagnosis. *Br J Dermatol* 1972; **105**: 913–9.
25 Hamilton JB, Terada H, Mestler CE. Greater tendency to acne in white American than in Japanese populations. *J Clin Endocrinol Metab* 1964; **24**: 267–72.
26 Bataille V, Sneider H, McGregor A *et al*. The influence of genetics and environmental factors in the pathogenesis of acne: a twin study of acne in women. *J Invest Dermatol* 2002; **119**: 1317–22.
27 Paraskevaidis A, Drakoulis N, Roots I *et al*. Polymorphisms in the human cytochrome P-450 1A1 gene (CYP1A1) as a factor for developing acne. *Dermatolog* 1998; **196**: 171–5.
28 Ostlere LS, Rumsby G, Holownia P *et al*. Carrier status for steroid 21-hydroxylase deficiency is only one factor in the variable phenotype of acne. *Clin Endocrinol (Oxf)* 1998; **48**: 209–15.

The size of the problem [1]. A person is more likely to develop acne than any other disease [2]. The major burden of acne is experienced during the teenage years, but acne may continue as a clinical problem into the twenties and older. Data are more reliable for school-aged children than for those in the later teens or older because of the ease of data capture.

Studies of European schoolchildren in Switzerland in 1931 [3], Newcastle upon Tyne, England, in 1971 [4] and Glasgow, Scotland, in 1989 [2] have shown a consistent level of maximum prevalence, approaching 100% for 16–17-year-old boys and 85–100% in 16-year-old girls. However, the same period has seen a major reduction in severity. In the 1931 study, 57% of boys and 19% of girls had severe acne [3]. These figures had changed to 30% and 20% in 1971 [4] and changed to 35% and 13% respectively in a further study in Newcastle upon Tyne in 1981 [5]. By 1989, the Glasgow study showed no schoolchildren with severe acne, only 1.8% of boys with moderate acne and no girls with worse than mild acne [2]. Only the Newcastle upon Tyne and Glasgow studies were randomized cross-sectional views. Similar prevalence levels were found in New Zealand [6] and Southern Australia [7], but both countries showed significantly larger numbers of school students with the more severe grades of acne than were found in the UK. Unfortunately, most studies have been affected by selection bias due to place of work, educational institution or hospital/surgery attendance. Questionnaire based surveys in the USA and the UK [8,9] have shown a lower prevalence, as might have been expected from the Glasgow study, which found clinical acne in 18% of boys, many of whom denied the presence of spots.

The clinical problem of acne in older patients in their twenties and thirties appears to be increasing [8–12], but better epidemiological data are required.

The size of the problem is also influenced by patients' beliefs and perception [13,14]. Twelve per cent of teenage boys denied the presence of clinical acne [2] and, in another study, 49% of patients believed their acne to be curable within 6 months [13].

References

1 Simpson NB. Acne. In: Williams HC, Strachan D, eds. *The Challenge of Dermato-Epidemiology*. Boca Raton, FL: CRC Press, 1997: 163–72.
2 Rademaker M, Garioch JJ, Simpson NB. Acne in schoolchildren: no longer a concern for dermatologists. *BMJ* 1989; **298**: 1217–9.
3 Bloch B. Metabolism, endocrine glands and skin diseases, with special reference to acne vulgaris and xanthoma. *Br J Dermatol* 1931; **43**: 61–87.
4 Burton JL, Cunliffe WJ, Stafford I, Shuster S. The prevalence of acne in adolescence. *Br J Dermatol* 1971; **85**: 119–26.

5 Fellowes HM, Billewicz WZ, Thomson AM. Is acne a sign of normal puberty? A longitudinal study. *J Biosoc Sci* 1981; **13**: 401–7.
6 Lello J, Pearl A, Arroll B *et al.* Prevalence of acne vulgaris in Auckland senior high school students. *NZ Med J* 1995; **108**: 287–9.
7 Kilkenny M, Merlin K, Plunkett A, Marks R. The prevalence of common skin conditions in Australian school students: 3. Acne vulgaris. *Br J Dermatol* 1998; **139**: 840–5.
8 Stern RS. The prevalence of acne on the basis of physical examination. *J Am Acad Dermatol* 1992; **26**: 931–5.
9 Rea JN, Newhouse ML, Halil T. Skin disease in Lambeth: a community study of prevalence and use of medical care. *Br J Prev Soc Med* 1976; **30**: 107–14.
10 Cunliffe WJ, Gould DG. Prevalence of facial acne vulgaris in late adolescence and in adults. *BMJ* 1979; **i**: 1109–10.
11 Poli F, Dreno B, Verschoore M. An epidemiological study of acne in female adults: results of a survey conducted in France. *J Eur Acad Dermatol Venereol* 2001; **15**: 541–5.
12 Shaw JC. Persistent acne in adult women *Arch Dermatol* 2001; **137**: 1252–3.
13 Tan JKL, Vasey K, Fung KY. Beliefs and perceptions of patients with acne. *J Am Acad Dermatol* 2001; **44**: 439–43.
14 Pearl A, Arroll B, Lello J, Birchall NA. The impact of acne: a study of adolescents' attitudes, perception and knowledge. *NZ Med J* 1998; **111**: 269–71.

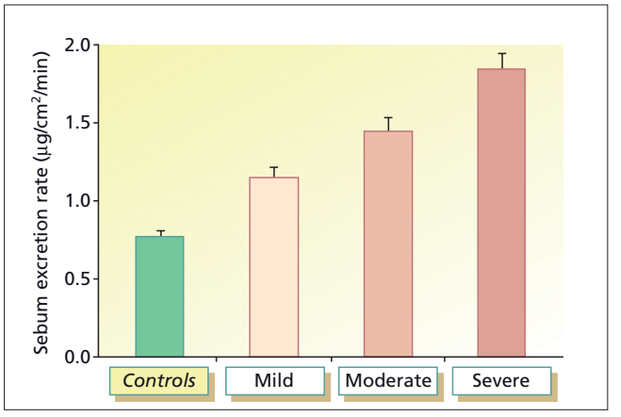


Fig. 42.18 Correlation between acne severity and sebum excretion.

Table 42.2 Outline of mechanisms leading to high sebum production.

Excessive androgen production
Increased availability of free androgen which may be associated with a relative reduction of sex hormone binding globulin (SHBG)
An amplified target response mediated through the conversion of testosterone to more active dihydrotestosterone
An increased capacity of the intracellular receptor to bind androgens

Aetiology of acne

The four major factors involved in the aetiology of acne are:
1 Seborrhoea
2 Comedo formation (comedogenesis)
3 Colonization of the intrafollicular duct with *P. acnes*
4 Inflammation.

Seborrhoea

The most obvious function of the sebaceous glands is to produce sebum and excess sebum production is a prerequisite for the development of acne [1]. The level of sebum secretion correlates reasonably well with the severity of the acne (Fig. 42.18) [2,3].

Sebaceous activity is regulated by androgens of gonadal or adrenal origin [4–6]. Androgen-insensitive subjects lack androgen receptors; they do not produce sebum and do not develop acne [5]. Systemic administration of testosterone and dehydroepiandrosterone (DHEAS) increases the size and secretion of sebaceous glands [6]. These two facts support the essential role of androgens in sebum stimulation. Clinical observations pointing to the importance of androgens in acne include the development of early acne in association with increased levels of DHEAS, a precursor of testosterone. The rise of DHEAS in prepubescent children is associated with an increase in sebum production and development of comedonal acne [7]. Androgens regulate sebaceous gland function through binding to nuclear androgen receptors (ARs) [8]. Immunohistochemistry has demonstrated that sebaceous glands have the highest AR density within the skin [9]. Table 42.2 outlines mechanisms leading to high sebum production.

There is general agreement that plasma testosterone levels are not abnormally high in males with acne [10–12]. In females with acne, the situation is more complicated. Some investigators have found testosterone levels to be normal [13–15], while others have found raised levels [16–18], albeit often lower than in males with no acne whatsoever. Most studies have shown that mean SHBG levels are significantly below normal, with free testosterone consequently above normal. However, results from studies are conflicting, and many of the studies included patients who were older than the modal value for all female acne patients, and not infrequently had other features of endocrine disease, such as significantly irregular menstruation and hirsutism, so fell within the definition of polycystic ovary syndrome (PCOS). Lawrence *et al.* [16] found that only 41% of their acne patients had free testosterone levels above normal. Lucky *et al.* [17] measured a number of androgens and their precursors, as well as SHBG, and found that 52% of non-hirsute women with acne had at least one abnormal hormone level. Cibula *et al.* [19] found that 81% (73 of 90 patients) had an elevation of at least one androgen hormone of the four that they measured. In their study, 21% had hirsutism and 50% had polycystic ovarian syndrome, but there was no correlation between the severity of acne and abnormalities of the sex hormones. Darley *et al.* [20] examined 38 women with acne and found high serum testosterone in 26%, low SHBG in 45% and high prolactin in 45%, but 24% had no hormonal abnormality at all. The majority of potent androgens are produced by peripheral target tissues. This peripheral androgen metabolism is important, for example increased androsterone metabolism has been reported in females with normal circulating androgen levels [21]. Hyperinsulinaemia results in a lowering of SHBG, thereby influencing androgen levels [22]. However, post-meal transient hyperinsulinaemia does not seem to play a role in hyperandrogenaemic acne patients [23].

In conclusion, androgenic hormonal balance may be disturbed to some degree in female acne patients; however, this does not establish a causal link and at least a quarter of all cases remain unexplained. There are no correlations between the severity of

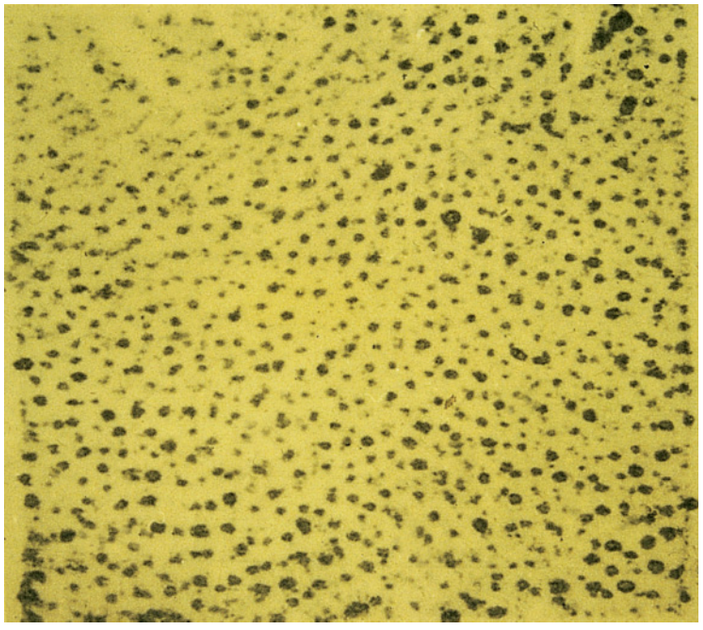


Fig. 42.19 Homogeneous sebaceous outflow in a normal subject.

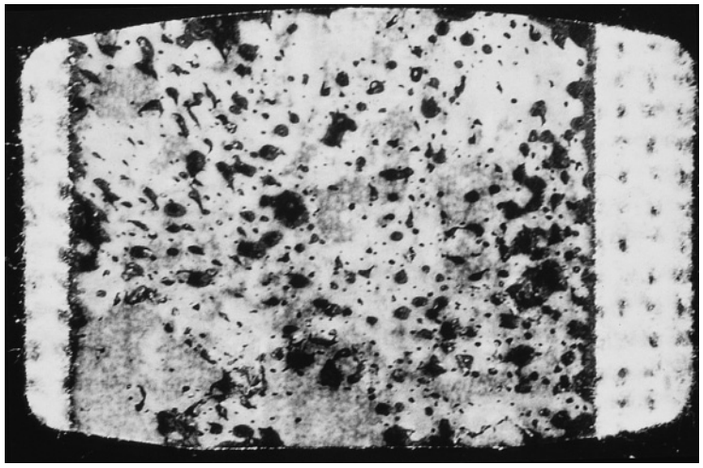


Fig. 42.20 Heterogeneous sebaceous outflow in an acne subject.

Table 42.3 Indications for endocrine evaluation of acne patients.

Reason for investigation:
Severe/sudden acne
Therapy-resistant acne
Rapid significant relapse post isotretinoin
Additional signs of hyperandrogenism
Irregular menses
Hirsutism
Hyperseborrhoea
Unusual clinical presentation
Multiple comedones
Hyperseborrhoea
Mature onset/perioral distribution

acne, hirsutism and menstrual irregularity [24]. Moreover, if the development of acne were simply related to systemic hormone levels, it should have a similar frequency on the face, back and chest, but this is not so. In general, acne patients are not endocrine misfits.

Androgen effects on the pilosebaceous unit are reasonably well characterized although the variability in the response of the pilosebaceous unit is not completely understood [25]. Testosterone and DHT act through a single nuclear androgen receptor, with dihydrotestosterone (DHT) being the most active ligand.

The fact that acne does not occur simultaneously on all susceptible sites correlates with the finding that sebum excretion varies from follicle to follicle (Figs 42.19 & 42.20) [26]. In acne patients, there is marked heterogeneity in individual follicular sebum excretion. This allows us to hypothesize that certain follicles may be prone to acne [27] and that an enhanced peripheral (end organ) response to androgens is a probable factor in many subjects. Weak prohormones (DHEA, DHEAS and androstenedione) only act after conversion to more potent androgens testosterone and 5α-DHT. Sebaceous glands in acne-prone regions show abnormally high 5α-reductase activity *in vitro* [28]. In addition, abnormally high levels of plasma DHT and urinary 5α-androstanediols, considered by some to be biological markers of cutaneous androgen metabolism, have been identified in some female acne patients [13]. Data on androgen receptors in acne suggest that androgen action on the sebaceous gland may be independent of serum hormone levels [29]. There are two forms of 5α-reductase [30]. 5α-reductase type I is the most relevant in acne supported by the fact that finasteride, an inhibitor of type II 5α-reductase, does not reduce sebum production [31] and the fact that patients with a deficiency of type II 5α-reductase have normal sebum levels [31]. Regional differences in the activity of type I 5α-reductase in isolated sebaceous glands from various body sites also support the end-organ hyper-responsiveness theory for acne [32–35].

Unless patients with acne show other features of hyperandrogenism it is not necessary to investigate for an endocrinopathy [36]. An endocrine evaluation may be indicated in adult females. Table 42.3 summarizes the need for investigation.

A medical history and physical examination should be performed before embarking upon relevant blood tests. Polycystic ovarian syndrome (Fig. 42.21) is the most frequently associated hormonal disease [37].

In most acne clinics, the majority of female patients with acne have no other clinical features of the syndrome, which consists of hirsutism, relative infertility or irregular menstruation [37]. There is no correlation between the presence of ovarian cysts and the severity of the acne [38]. Late-onset adrenal hyperplasia due to a partial deficiency of 21-hydroxylase should be considered in patients with persistent problems with their acne [39] and may rarely cause severe acne in boys [40]. It is very rare to find virilizing tumours that present as acne alone. When thought necessary, appropriate initial tests should include measurement of total testosterone, SHBG, androstenedione, dehydroepiandrosterone (DHEA), prolactin, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) [41]. Hormonal levels should ideally be taken early in the menstrual cycle (day 1–3). If late-onset congenital adrenal hyperplasia is suspected, then a 09.00 cortisol and

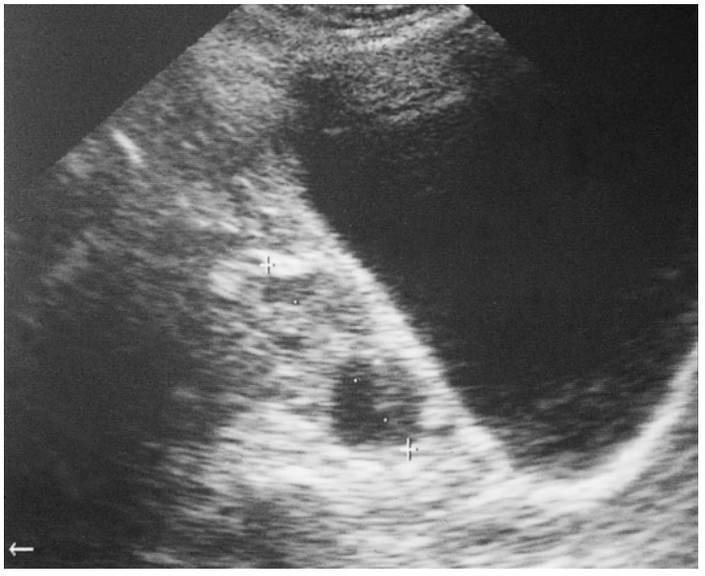


Fig. 42.21 Ultrasound of the pelvis showing polycystic ovaries.

Table 42.4 Investigations required to identify an endocrine problem in acne patients.

Androgen profile: *testosterone, SHBG, 17(OH)—progesterone, DHEAS*
FSH, LH, ± oestradiol
Prolactin/thyroid function tests
Assessment of glucose tolerance/insulin resistance; GTT, lipid profile
Suspected Cushing's: dexamethasone suppression test (will also help to identify congenital adrenal hyperplasia along with DHEAS, 17(OH) progesterone

17α-hydroxyprogesterone measurement should be performed. Either the adrenal gland or the ovary may produce excess androgens. Serum dehydroepiandrosterone sulphate (DHEAS) levels can be used to screen for an adrenal source of excess androgen production, patients with a serum DHEAS greater than 21.7 µmol/L may have an adrenal tumour. Some adrenal tumours may also produce testosterone. Values of DHEAS in the range of 10.8–21.7 µmol/L may be seen with congenital adrenal hyperplasia, which is often associated with a slightly raised cortisol and a 17α-hydroxyprogesterone level of greater than 12.8 µmol/L. An ovarian source of excess androgen can be suspected in cases where the serum total testosterone is elevated. A raised serum testosterone and an increased LH level are seen in patients with polycystic ovarian disease. The LH:FSH ratio is not always elevated in PCOS and is not necessarily a diagnostic measure. Table 42.4 outlines investigations required to identify an endocrine problem.

High elevations in serum testosterone may indicate an ovarian tumour.

The possibility that other hormones may affect the sebaceous glands, either directly or by enhancing their response to androgens, should not be neglected. In acromegaly, the rate of sebum excretion (SER) is high and correlates with skin thickness and growth hormone levels [42]. The SER is low in individuals with isolated growth hormone deficiency, who therefore do not have associated acne [43]. In clinical practice, these endocrinopathies

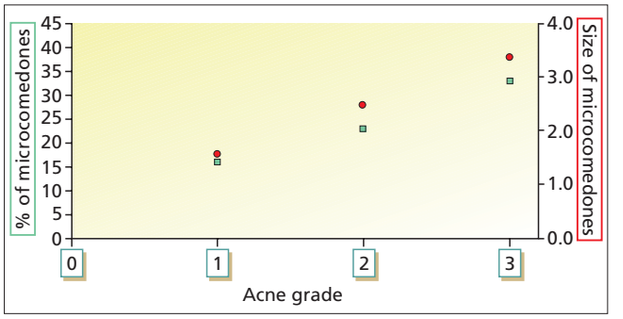


Fig. 42.22 Correlation between the number and size of microcomedones and acne severity.

are rarely encountered as presenting features in the dermatological clinic.

Sebaceous lipid composition

Human sebaceous glands secrete a mixture containing squalene and wax esters as well as cholesterol esters, triglycerides and some free cholesterol [44]. It is recognized that bacterial hydrolases, especially from *P. acnes*, convert the triglycerides to free fatty acids on the skin surface [45]. There is also evidence to suggest that sebaceous glands can synthesize free fatty acids [46]. The role of individual lipid components in causing acne is uncertain. Lipids may be involved in ductal hypercornification, or may be essential to the growth (stimulation and inhibition) of bacteria. Sampling of skin-surface lipids has shown that patients with acne tend to have higher levels of squalene and wax esters, lower levels of fatty acids [47–49], and a more frequent occurrence of particular free fatty acids [50,51]. Linoleic acid is significantly reduced in epidermal and comedonal lipids, and this may relate to ductal hypercornification.

Comedone formation (comedogenesis)

An important feature in the aetiology of acne is the presence of ductal hypercornification, which can be seen histologically as microcomedones, and clinically as blackheads, whiteheads and other forms of comedones such as macrocomedones. There is a significant correlation between the severity of acne and the number and size of follicular casts (microcomedones), the presence of which is a measure of comedogenesis [52] (Fig. 42.22). Follicular casts (microcomedones) can be sampled by applying cyanoacrylate gel to the skin surface, followed by pressing a glass microscopic slide on top for 1 min [53,54]. The sample can be analysed by low-power microscopy or by digital image analysis [46,47] (Fig. 42.23).

Comedones are due to abnormalities in the proliferation and differentiation of ductal keratinocytes. They represent the retention of hyperproliferating ductal keratinocytes/corneocytes in the duct. The hyperproliferation has been confirmed by showing an increase in ^{3}H-thymidine labelling of comedones [55] and increase in the Ki-67 labelling (a marker of cell turnover) of ductal keratinocytes (Fig. 42.24) [56]. Ki-67 labels nuclear antigen expressed by cells in the late G1, S, M and G2 phases of the cell cycle [57]. This technique has also shown an increase in the proliferation of ductal keratinocytes of 'non-affected' follicles, which were biopsied as

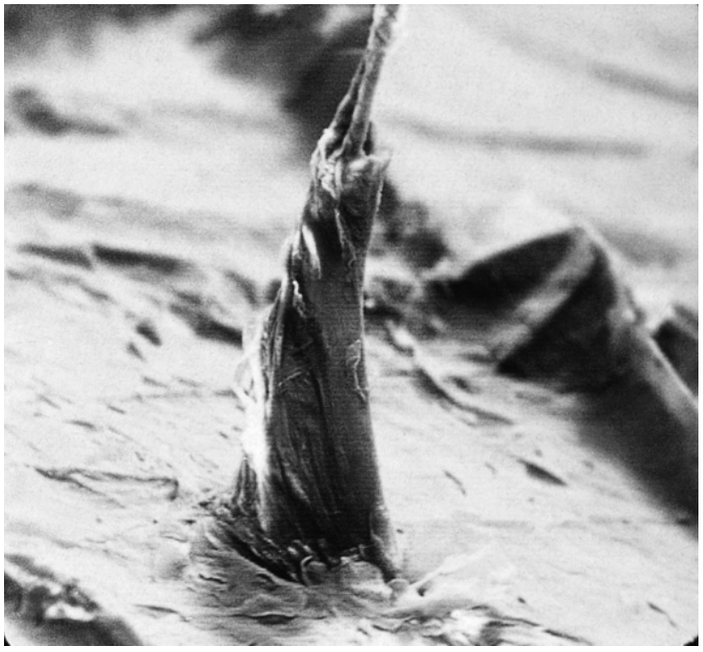


Fig. 42.23 Scanning electron microscopy of a microcomedo that has been sampled from an acne-prone skin using the skin-surface biopsy technique.

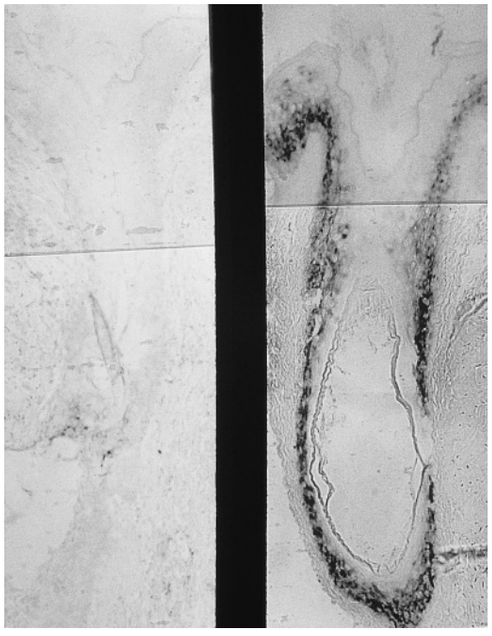


Fig. 42.25 *In situ* hybridization for keratin 6 (a marker of hyperproliferation) demonstrates little activity in a normal follicle (left) and considerable activity in a comedo (right). (Courtesy of Dr D.B. Holland, Department of Microbiology, Leeds General Infirmary, Leeds, UK.)

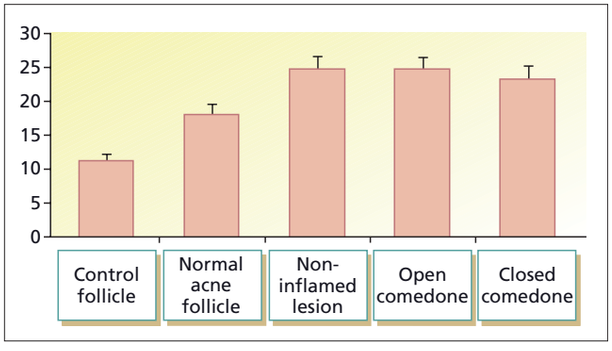


Fig. 42.24 Uptake of Ki-67, a marker of keratinocyte proliferation, in control skin, microcomedones and clinical comedones.

clinically 'normal' follicles from an area affected by acne [56]. This fits with the histological observation of microcomedones being found in 30% of tissue sections of clinically 'normal' skin taken from skin adjacent to acne lesions. Further evidence of ductal hyperproliferation is the presence of keratins 6 and 16 (keratin markers of hyperproliferation) in microcomedones and comedones (Fig. 42.25) [58]. The primary abnormality that gives rise to hypercornification is not related to changes in keratin expression [58,59]. There is as yet no evidence to suggest that comedogenesis may be related to failure of ductal keratinocytes to separate. Studies of involucrin expression and desmosomes, which are features of terminal differentiation, have shown no difference between follicles from acne and control biopsies [60].

Several factors have been implicated in the induction of keratinocyte hyperproliferation, and include sebaceous lipid composition, androgens, local cytokine production and bacteria.

Of the abnormal sebaceous lipids in acne patients, the linoleate levels may be relevant. Examination of polar lipids recovered from comedones shows that the acryl ceramides contain only 6% linoleate among the esterified fatty acids, compared with 45% in normal human epidermis [61,62]. Similarly, linoleic acid is reduced in sebum from acne subjects, but returns to normal with resolution of acne following treatment with isotretinoin [63] and antiandrogens [64]. In animal experiments, a low linoleate produces hypercornification, which may parallel the increased scale found in comedones. In these animals, a low linoleate produced a decreased epidermal barrier function, which might have rendered the comedonal wall more permeable to inflammatory substances. Membrane-coated granules [65–67] are probably more related to barrier permeability than cell separation, and are decreased in comedones, but the significance of this is as yet unclear.

Other lipids have been incriminated; in particular, free fatty acids and squalene have been blamed for inducing comedones [68,69] in the rabbit-ear model [70]. The development of a human model for comedogenesis has, however, suggested that the rabbit model is inappropriately over reactive [71]. Laboratory animals do not develop whiteheads or inflamed acne lesions, even though the rabbit ear readily produces comedones [72]. The rhino mouse is an alternative useful model for comedogenesis [73]. From experiments in the rhino mouse, it has been suggested that comedone formation may be associated with an abnormality in apoptosis (programmed cell death) [74]. Evidence is accumulating to propose that androgens may play an important role in comedogenesis. There is a correlation between comedone numbers in early acne and DHEAS levels [75]. Cells of the pilosebaceous duct have androgen receptors [76], and 5α-reductase type I is also present in these cells both in health and in disease [77–79]. Antiandrogen

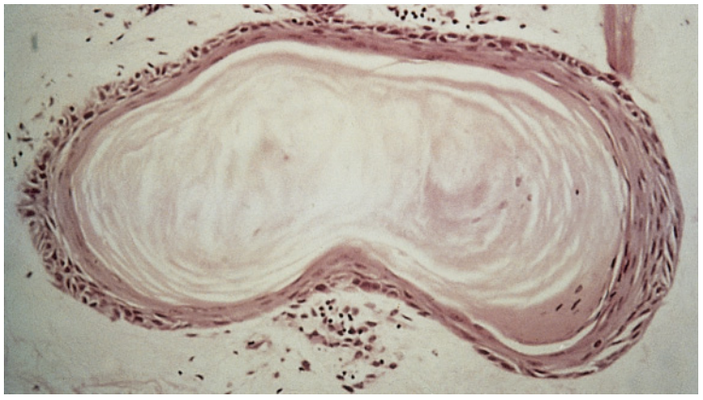


Fig. 42.26 An *in vitro* comedo, induced by interleukin-1-α (IL-1-α). (Courtesy of Dr T. Kealy, Cambridge University, UK.)

drugs, such as cyproterone acetate (CPA) in the drug co-cyprindiol (Dianette® and Estelle 35®), reduce comedones. Co-cyprindiol also increases the sebaceous linoleate concentration [64], and thus antiandrogen therapy could modulate comedogenesis both directly and indirectly by influencing sebaceous lipid.

Cytokine production by ductal keratinocytes is also likely to be important. Kealey and colleagues developed an excellent *in vitro* model for growing and studying the duct [80–82]. IL-1-α is present in many comedones at levels that are likely to be biologically and pathologically relevant [83]; IL-1-α induces comedogenesis (Fig. 42.26). Furthermore, EGF markedly disrupts the duct comedo *in vitro* [82]. Kealey and colleagues have also demonstrated that IL-1-α acts on the fundibular keratinocytes to induce cornification [83] and that EGF and TGF-α inhibit sebum secretion [84].

Bacteria are thought not to be involved in the initiation of comedones. Electron microscopy of early non-inflamed lesions taken from prepubertal and early pubertal individuals has demonstrated few or no bacteria [85]. Mourelatos *et al*. demonstrated a lack of propionibacteria in comedones in a temporal study assessing early acne development in children [86]. Other work quantifying bacteria from comedones suggests that follicular colonization is unrelated to comedogenesis [87]. Biopsy and culture of early non-inflamed lesions has shown that 30% of these are without bacteria [88], suggesting that ductal bacteria are not needed for the initiation of cornification in the development of comedones.

Comedones are temporary structures. Using markers of cell cycling (Ki-67) and keratinocyte proliferation, it has been shown that, like the hair follicle, normal pilosebaceous follicles and comedones undergo cyclical growth [89]. Extracted blackheads refill over 2–6 weeks. Functionally, some comedones are blocked [90], but others can become blocked temporarily following skin hydration [91], and this obstruction is associated with a decrease in outflow of sebum. Such observations could help to explain tropical acne and premenstrual flare of acne [92].

Certain external chemicals may contribute to comedogenesis. These substances include the ingredients of some cosmetics such as isopropyl myristate, propylene glycol, and D and C red dyes [93]. It has been suggested that the excretion of products from the sebaceous gland occurs through an organized acellular tubular conduit—the sebolemmal sheath produced by the sebaceous duct cells; rupture of this sheath may contribute to comedogenesis [94]. However, this concept has yet to be confirmed by others.

Relationship between *P. acnes* and acne

Acne is not an infectious disease in the classical sense; however, inflammatory acne can be viewed as an infection of the blocked pilosebaceous ducts with propionibacteria which are trapped by cornified plugs within the follicular ducts [95]. The three major organisms isolated from the surface of the skin and the pilosebaceous ducts of patients with acne are *P. acnes*, *Staphylococcus epidermidis* and *Malassezia furfur* [96]. There are three major subgroups of the propionibacteria—*P. acnes*, *P. granulosum* and *P. avidum*. Almost certainly *P. acnes* and, to a lesser extent, *P. granulosum* are the most important. Nevertheless, as they live in association with *S. epidermidis* and *M. furfur*, the latter organisms probably have some control over the growth of *P. acnes* [97]. The cornified plug within the pilosebaceous duct obstructs sebum outflow, allowing propionibacteria to multiply but preventing them and their products of metabolism from escaping onto the skin surface. Adolescence and its attendant seborrhoea are associated with a significant increase in *P. acnes* numbers [86,98] but there is little or no relationship between the number of bacteria on the skin surface and the severity of acne [99–101]. There is a much closer relationship between follicular organisms recovered from 4 mm punch biopsies and the severity of the disease [102]. In a study examining the cutaneous microflora from biopsies of 26 papules and 48 normal follicles in patients with persistent and late-onset acne compared with individuals with adolescent acne and normal control volunteers without acne, the microflora consisted in the main of *Propionibacterium*, staphylococci and *Malassezia*, and at all sites there were significantly more *Propionibacterium* spp. than the other two microorganisms. Female facial skin and male back skin showed significantly higher numbers of microorganisms in the upper parts of the follicles when compared with those from control volunteers [102]. There was a bimodal distribution of microbial colonization, with about 90% of normal follicles and about 10% of acne follicles having no detectable viable microorganisms. There were fewer microorganisms in normal follicles than in inflamed lesions. Although the presence of microorganisms, especially *P. acnes*, cannot be deemed to be singularly responsible for the onset of the inflammatory lesion, the significant difference between the number of inflamed lesions, which were colonized, when compared with normal follicles, lends support to the theory that these microorganisms are involved in the inflammatory process at some point. The entrapment of propionibacteria adds to inflammatory processes via a number of mechanisms. Concentrations of powerful hydrolytic enzymes rise to levels at which tissue damage is inevitable. The *P. acnes* genome sequence recently published has demonstrated that the organism produces many more such enzymes than previously thought [103]. Intrafollicular bacteria will also die and lyse *in situ* producing immunologically active intracellular products within the duct. Stress related proteins may increase as a result of the trapped bacteria such as GroEL/HSP60 and DNAκ/HSP70 [104]. It seems plausible that damage to the basement membrane may well ensue, permitting leakage of comedonal contents into the dermis, thereby triggering the adaptive immune response to ductal antigens. The infiltrate around early inflamed

lesions is predominantly comprised of $CD4^+$ T cells and macrophages consistent with a delayed-type hypersensitivity (DTH) reaction [105]. This DTH response may be to an autoantigen or a persistent microbial pathogen. If the dominant antigen is not microbial it may well be that propionibacteria augment the response to the autoantigen by acting as a mitogen [106] or via adjuvant activity [107]. There is also the possibility of cross-reactivity between human and bacterial homologues of stress related proteins.

Recent evidence suggests that antigen-specific responses are secondary to an innate immune reaction which renders healthy-looking follicles in acne-prone skin subclinically inflamed [105]. Microcomedones are absent from these visibly normal-looking follicles. IL-1-α is a key mediator of inflammation and comedogenesis [82,108]; it is not clear what triggers its release from ductal keratinocytes to start the inflammatory cascade. One theory relates to the possible activation of Toll-like receptors either by pathogen-associated molecular patterns (PAMPs) or endogenous ligands. The theory is that *P. acnes* cell walls or a component thereof would act as the PAMP and activate TLR-2 on keratinocytes thereby inducing NF-κB and switching on the production of pro-inflammatory cytokines including IL-1α. *P. acnes* has been shown to activate TLR-2 on keratinocytes [109] and monocytes [110] leading to the production of pro-inflammatory cytokines such as IL-8 and in the case of keratinocytes human-beta-defensin-2 (HBD-2) but significantly not IL-1-α. Other endogenous ligands such as breakdown products of hyaluronan, HBD-2, free fatty acids and heat shock proteins may also activate TLRs on keratinocytes [111,112]. *P. acnes* are not evident in juvenile comedones so this mechanism is not likely to be important as an initial event but may contribute to a second innate response in more established lesions.

The microenvironment within the pilosebaceous unit produced by the bacteria is probably more important than their absolute numbers for the development of acne lesions. *In vitro*, it has been shown that oxygen tension, pH and nutrient supply markedly affect the growth of *P. acnes*, and the bacterial production of active substances such as lipases, proteases, hyaluronate lyase, phosphatase and smooth muscle contracting substances [113–115]. *In vivo*, the pH of blackheads markedly varies between 3.6 and 6.7 [116], and this is likely to affect the bacteria. Oxygen tension is also likely to be important. *Propionibacterium acnes* grows well at low oxygen tensions. In the presence of light at high oxygen concentrations, *P. acnes* grows well, but growth is inhibited because of photodamaging reactions involving excess oxygen and endogenous microbial porphyrins [117]. These factors could determine whether or not a follicle develops into a non-inflamed comedo and, subsequently, into an inflamed lesion.

The role of inflammation in the pathogenesis of acne

The precise sequence of events involved in the initiation, subsequent augmentation and resolution of acne has been a challenge to acne researchers for a number of years.

It was previously thought that hyperproliferation and abnormal differentiation of the ductal keratinocytes initially gave rise to the formation of the microcomedone. It was believed that from the microcomedone further hyperproliferation could occur, leading to accumulation of corneocytes and sebum in the lumen of the intra-follicular duct, so forming a horny plug and developing into a clinically evident comedone. Diffusion of components from the follicle lumen into the dermis with inflammation resulted in the clinically inflamed papule or pustule recognized in acne (Fig. 42.27).

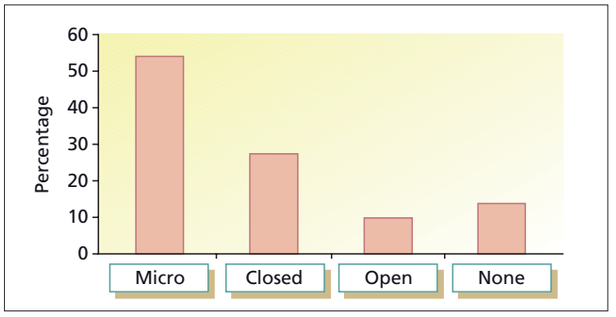


Fig. 42.27 Most, but not all, early inflamed lesions are associated with a microcomedo or clinical comedo.

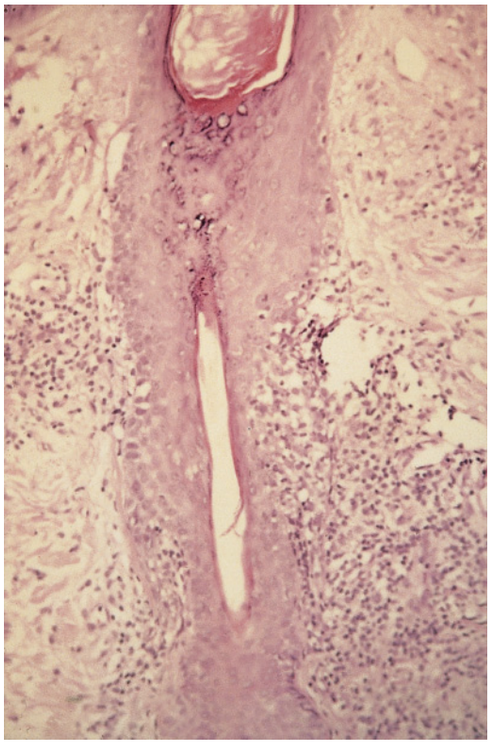


Fig. 42.28 An early inflamed papule (6 h). Note spongiosis and a lymphocytic infiltrate but no obvious rupture of the duct.

However, examination of both non-inflamed and inflamed lesions has led to the conclusion that these are two separate mechanisms affecting the same type of follicle and that many inflamed lesions do not present with a microcomedo within their histological features. Jeremy *et al*. [105] confirmed that inflammation in acne occurs prior to hyperproliferation of the follicular wall (Fig. 42.28). This study demonstrated that inflammation is dominated by $CD4^+$ T helper cells and a macrophage infiltrate, and that these cells were present in clinically normal skin around uninvolved

follicles from acne patients in acne-prone sites. The majority of the T cells were skin homing, memory/effector cells and were abundant in numbers much greater than the level of surveillance T cells found in normal skin. However, macrophage numbers were similar to those of clinically evident inflamed lesions. Despite the increased inflammatory infiltrate, there was no increased amount of cellular HLA-DR expression, suggesting that the cells were not activated. The number of Langerhans' cells in the perifollicular dermis and surrounding epidermis was reduced, indicating migration of these cells to skin-draining lymph nodes. Neutrophils were not observed in the infiltrate, suggesting that the initiation of inflammation by $CD4^+$ T helper cells was a response to antigenic stimulation. The inflammatory processes occurred in the absence of hyperproliferation and abnormal differentiation in the uninvolved follicles which were similar to those of control follicles. This absence of hyperproliferation was supported by the lack of microcomedonal features. In addition, the follicular wall was intact, verified by continuous immunolabelling of laminin and collagen IV along the basement membrane. The data from this study therefore showed that subclinical inflammatory events occur before hyperproliferative events and are the earliest events seen in acne lesion formation.

Transcripts for cytokines IL-12, TNF-β and IFN-γ have been reported as evident in uninvolved follicles from acne prone sites [118]. These cytokines are typically secreted by CD4 type 1 T helper cells which are effectors of the adaptive immune response, suggesting that acne is an inflammatory disorder mediated by a Th1 response.

As outlined previously, there is strong evidence to implicate *P. acnes* as an initiating factor in the adaptive immune response in acne. As the basement membrane of the follicle wall remains intact in uninvolved follicles, a soluble antigen, as yet undiscovered, could be a trigger for inflammation. It is unlikely that *P. acnes* is implicated in this, as the soluble products of *P. acnes* do not stimulate T-cell responses [106]. However, *P. acnes* may be implicated as the lower infra-infundibulum is very thin and the wall consequently very fragile; it could be possible for *P. acnes* to be exposed to Langerhans' cells in this location.

One hypothesis is that linoleic acid, which is known to be deficient in acne, could lead to a change in the integrity of the barrier function within individual follicles [119]. It is possible that the presence of *P. acnes* at this normal point would allow interactions with Langerhans' cells in the follicle wall, which would result in presentation and stimulation of CD4 T helper cells within the skin-draining lymph nodes, and the development of an adaptive immune response.

It is also feasible that inflammation may be driven by an innate immune response. The presence of CD4 memory/effector T cells may be a result of the up-regulation of vascular marker E-selectin which is a receptor for skin homing T-cells, and could result in selective migration of cells into the local tissue.

Interleukin-1-α (IL-1α) could also be an initiating factor, as it can induce the up-regulation of vascular adhesion molecule expression such as ICAM-1, E-selectin and Elam-1. This could result indirectly in monocyte migration into the perifollicular dermis. It is still not clear what factors are responsible for the increase in IL-1-α. The disturbance in barrier function may lead to transepidermal water loss into the follicular lumen so changing the ductal microenvironment, promoting the growth of *P. acnes* and increasing its population. This would lead to a greater opportunity for *P. acnes* and viable keratinocytes to interact in the follicle wall leading to the release of pro-inflammatory cytokines IL-1-α, TNF-γ and granulocyte macrophage colony stimulating factor [104]. In addition, linoleic acid deficiency identified in certain acne follicles [120] can lead to the release of pro-inflammatory cytokines, for example IL-1-α and TNF-γ from epithelial keratinocytes, into the dermis, so stimulating an inflammatory cascade [121].

Leukotriene B4 (LTB4) is a pro-inflammatory mediator synthesized from arachidonic acid. Synthesis of LTB4 is catalysed by 5-lipoxygenase and is increased by inflammatory mediators including complement fragments, TNF-α and interleukins. Leukotriene precursors are synthesized in the sebaceous gland [122]. LTB4 induces recruitment and activation of neutrophils and monocytes. It also stimulates the production of a number of pro-inflammatory cytokines and mediators that augment and prolong tissue inflammation. These events are independent of bacteria. Limited data from pharmacological inhibition studies support a role of LTB4 in the pathogenesis of neutrophil-medicated tissue damage. A preliminary, small-scale clinical study of an oral anti-inflammatory agent that specifically blocks the formation of LTB4 showed a 70% reduction in inflammatory lesions at 3 months in patients with acne [123]. These data support the suggestion that bacterial involvement may not always be necessary for expression of inflammation.

Recent studies have provided new insights into the development of acne lesions and their resolution, and have provided significant evidence for inflammatory events. It would appear that individual sensitivity and tolerance to potential causal antigens, as well as variance in exposure to antigens, may result in differences in the way an individual responds which determine the clinical manifestations. The integrity of the skin and/or ductal barrier function will influence the type of acne lesion that develops. This emphasizes the need to assess clinical lesions carefully, and to tailor medication according to the acne type.

Mechanisms inducing acne scarring

Scarring is a consequence of abnormal resolution or wound healing following the damage that occurs in the sebaceous follicle during acne inflammation (Fig. 42.29).

A cell-mediated immune response has been found to be involved in the inflammatory events in acne; such a response not only contributes to the clearance of antigen but also to tissue damage. Previously, no attention has been paid to the influence that such a response may have on the resolution of acne lesions. The inflammatory response has been implicated as an important component in the development of scars [124]. Holland *et al.* [125] investigated the differences in cell-mediated immune responses in developing and resolving inflamed lesions between those acne patients who were prone to scarring, and those with the same degree of inflamed acne who were not prone to develop scarring. The numbers and activation states of lymphocytes, macrophages and endothelial cells were examined in biopsies of timed inflamed lesions of known duration at less than 6 h, 24 h, 48 h, 72 h and 6/7 days, using standard immunohistochemical methods.



Fig. 42.29 Significant scarring resulting from severe facial acne. (Courtesy of Dr V. Bettoli, University of Ferrara, Italy.)

Clear differences in the cellular infiltrate present in lesions from the two groups of patients were identified. In acne patients who were not prone to scarring, the time course was typical of a type IV delayed hypersensitivity response. In developing lesions there was significant angiogenesis and vascular adhesion molecule expression, with a large influx of activated CD4 T cells, macrophages (CD68) and Langerhans' cells (CD1a). Cell recruitment peaked at 48 h, after which there was a decrease in leukocytes, cellular activation and a return to normal levels of blood vessels and vascular adhesion molecules in resolving lesions. Of the CD4 T cells, 50% were skin homing memory effector cells (CD45RO, CLA) and naïve cells (CD45RA) cells, whilst the remainder were unclassified ($CD45RO^-$, $CD45RA^-$, CLA^-), which suggests that effective resolution occurred by both non-specific/innate and adaptive immune mechanisms.

In lesions from acne patients who were prone to scar, a predominantly adaptive immune response was present, which was persistent and up-regulated in resolving lesions. The number of CD4 T cells was approximately half of those found in lesions of non-scarrers, but a high percentage of these cells were skin homing memory/effector cells, suggesting that these patients were sensitized to the causative antigen(s). In developing lesions, although the numbers of macrophages, blood vessels and vascular adhesion molecules were high and similar to those present in lesions of non-scarrers, the numbers of Langerhans' cells and the level of cellular activation was low, and comparable to levels found in normal skin, indicative of an ineffective response. However, in resolving lesions, there was an up-regulation of the response with greater cellular activation, and a further influx of macrophages and skin homing memory/effector cells. Certainly, the strong macrophage presence represents a dominant force in this response. Thus, it may be interpreted that, in patients prone to scarring, there is a chronic delayed-type hypersensitivity reaction provoked by a persistent antigen which these patients are initially unable to eliminate.

The different inflammatory cell profiles elicited by the two patient groups could explain the different qualities of repair observed. Lymphocytes and macrophages secrete an extensive array of cytokines and growth factors that are known to modulate dermal fibroblast recruitment, proliferation and phenotype, and will affect fibroblast functions such as wound remodelling and contraction, both contributory factors in scarring. This model suggests that the type and magnitude of the inflammatory response in 'resolving' lesions from patients with such a dominant macrophage presence, would lead to abnormal healing and pathological scarring. It is possible that the management of either numbers or activation states of inflammatory cells during the development and resolution stages of acne may help to control scarring.

Resolution of acne

This can be considered in two ways, resolution of individual lesions and resolution of the disease as a whole. The evolution of acne has received considerable attention; its resolution has been largely ignored. Limited studies suggest that the resolution is not related to reduction of sebum production or changes in surface bacteria [97]. The relationships between ductal hypercornification, inflammatory mediators, changes in the host response and resolution are obscure. Pierard [26] has shown that individual sebaceous glands function at different rates in acne patients. Resolution may be associated with specific changes in these acne-prone hypersecreting glands. Resolution of individual lesions could relate to cytokine activity within the pilosebaceous duct. For example, EGF and TGF-α are *in vitro* not only associated with disruption of the follicle but also with inhibition of sebaceous secretion [85]. Could this switch off an acne-prone follicle—albeit temporarily—and convert it into a non-acne-prone follicle?

Biological significance of acne, sebum and *P. acnes*

Activity of the sebaceous glands is unlikely to be essential for healthy skin, because prepubertal skin appears perfect unless severely challenged by soap and water! Yet the ubiquity of both hypersecretion of sebum and the presence of *P. acnes* suggests that their apparent undesirability may be outweighed by some selective advantages: the possible biological role of sebum is discussed above and it has been suggested that *P. acnes*, which enhances immune responses, may provide protection against malignant haematological disease [126], although not against solid tumours [127]. Independent of bacterial colonization, there is now evidence that the sebaceous gland is an immunocompetent organ [128].

References

1 Pochi PE, Strauss JS. Sebum production, casual sebum levels, titratable acidity of sebum and urinary fractional 17-ketosteroid excretion in males with acne. *J Invest Dermatol* 1964; **43**: 383–8.

2 Burton JL, Shuster S. The relationship between seborrhoea and acne vulgaris. *Br J Dermatol* 1971; **84**: 600–1.

3 Cunliffe WJ, Shuster S. Pathogenesis of acne. *Lancet* 1969; **i**: 685–7.

4 Ebling FJ. Hormonal control and methods of measuring sebaceous gland activity. *J Invest Dermatol* 1974; **62**: 161–71.

5 Imperato-McGinley J, Gautier T, Cai LQ *et al*. The androgen control of sebum production: studies of subjects with dihydrotestosterone deficiency and complete androgen insensitivity. *J Clin Endocrin Metabol* 1993; **76**: 524–8.

6 Pochi PE, Strauss JS. Sebaceous gland response in man to the administration of testosterone D4-androstenedione and dehydroandrosterone. *J Invest Dermatol* 1969; **52**: 32–6.
7 Lucky AW, Biro FM, Huster GA *et al*. Acne vulgaris in premenarchal girls. *Arch Dermatol* 1994; **130**: 308–14.
8 Fritsch M, Orfanos CE, Zouboulis CC *et al*. Sebocytes are the key regulators of androgen homeostasis in human skin. *J Invest Dermatol* 2001; **116**: 793–800.
9 Liang T, Hoyer S, Yu R *et al*. Immunohistochemical localization of androgen receptors in the skin using monoclonal antibodies against the androgen receptor. *J Invest Dermatol* 1993; **100**: 663–6.
10 Pochi PE, Strauss JS, Rao CS *et al*. Plasma testosterone and estrogen levels, urine testosterone excretion, and sebum production in males with acne vulgaris. *J Clin Endocrinol Metab* 1965; **25**: 1660–4.
11 Forstrom L, Mustakallio KK, Dessypris A *et al*. Plasma testosterone level and acne. *Acta Derm Venereol (Stockh)* 1974; **54**: 369–71.
12 Lim LS, James VHT. Plasma androgens in acne vulgaris. *Br J Dermatol* 1974; **91**: 135–43.
13 Mauvais-Jarvis P, Charransol G, Bobas-Masson F. Simultaneous determination of urinary androstanediol and testosterone as an evaluation of human androgenicity. *J Clin Endocrinol Metab* 1973; **36**: 452–9.
14 Odlind V, Carlstrom K, Michaelsson C *et al*. Plasma androgenic activity in women with acne vulgaris and in healthy girls before, during and after puberty. *Clin Endocrinol (Oxf)* 1982; **16**: 243–9.
15 Walton S, Cunliffe WJ, Keczkes K *et al*. Clinical, ultrasound and hormonal markers of androgenicity in acne vulgaris. *Br J Dermatol* 1995; **133**: 249–53.
16 Lawrence DM, Katz M, Robinson TW *et al*. Reduced sex hormone binding globulin and derived free testosterone levels in women with severe acne. *J Clin Endocrinol* 1981; **15**: 87–91.
17 Lucky AW, McGuire J, Rosenfield RL *et al*. Plasma androgens in women with acne vulgaris. *J Invest Dermatol* 1983; **81**: 70–4.
18 Schiarone FE, Rietschel RL, Sgoutas D *et al*. Elevated free testosterone levels in women with acne. *Arch Dermatol* 1983; **119**: 799–802.
19 Cibula D, Hill M, Vohradnikova O *et al*. The role of androgens in determining acne severity in adult women. *Br J Dermatol* 2000; **143**: 399–404.
20 Darley CR, Kirby JD, Besser GM *et al*. Circulating testosterone, sex hormone binding globulin and prolactin in women with late onset or persistent acne vulgaris. *Br J Dermatol* 1982; **106**: 517–22.
21 Carmina E, Lobo RA. Evidence for increased androsterone metabolism in some normoandrogenic women with acne. *J Clin Endocrinol Metab* 1993; **76**: 1111–4.
22 Smith S, Ravnikar VA, Barbieri RL. Androgen and insulin response to an oral glucose challenge in hyperandrogenic women. *Fertil Steril* 1987; **48**: 72–7.
23 Aizawa H, Niimura M. Mild insulin resistance during oral glucose tolerance test (OGTT) in women with acne. *J Dermatol* 1996; **23**: 526–9.
24 Sheehan-Dare R, Hughes BR, Cunliffe WJ. Clinical markers of androgenicity in acne patients. *Br J Dermatol* 1988; **119**: 723–30.
25 Rosenfield RL. Hirsutism and the variable response of the pilosebaceous unit to androgen. *J Invest Dermatol Symp* 2005; **10**: 205–8.
26 Pierard GE. Follicle to follicle heterogeneity of sebum excretion. *Dermatologica* 1986; **173**: 61–5.
27 Pierard GE, Pierard-Franchimont C, Kligman AM. Kinetics of sebum excretion evaluated by the Sebutape®–chromameter technique. *Skin Pharmacol* 1993; **6**: 38–44.
28 Sansone G, Reisner RM. Differential rates of conversion of testosterone to dihydrotestosterone in acne and in normal human skin—a possible pathogenic factor in acne. *J Invest Dermatol* 1971; **56**: 366–72.
29 Schmidt JB, Spona J, Huber J. Androgen receptor in hirsutism and acne. *Gynecol Obstet Invest* 1986; **22**: 206–11.
30 Jenkins EP, Andersson S, Imperato-McGinley J *et al*. Genetic and pharmacological evidence for more than one human steroid 5α-reductase. *J Clin Invest* 1992; **89**: 293–300.
31 Imperato-McGinley J, Gautier T, Cai L-Q *et al*. The androgen control of sebum production. Studies of subjects with dihydrotestosterone deficiency and complete androgen insensitivity. *J Clin Endocrinol Metab* 1993; **76**: 524–8.
32 Thiboutot D, Harris G, Iles V *et al*. Activity of the type 1 5α-reductase exhibits regional differences in isolated sebaceous glands and whole skin. *J Invest Dermatol* 1995; **105**: 209–14.
33 Thiboutot D, Gilliland K, Light J *et al*. Androgen metabolism in sebaceous glands from subjects with and without acne. *Arch Dermatol* 1999; **135**: 1041–5.
34 Thiboutot D, Martin P, Volikes L. Oxidative activity of the type 2 isozyme of 17α-hydroxysteroid dehydrogenase predominates in human sebaceous glands. *J Invest Dermatol* 1998; **113**: 395.
35 Thiboutot D. Acne, an overview of clinical research findings. *Dermatol Clin* 1997; **15**: 97–109.
36 Leyden JJ. New understandings of the pathogenesis of acne. *J Am Acad Dermatol* 1995; **32**: S15–25.
37 Bunker CB, Newton JA, Kilbom J *et al*. Most women with acne have polycystic ovaries. *Br J Dermatol* 1989; **121**: 675–80.
38 Peserico A, Angeloni G, Bertoli P *et al*. Prevalence of polycystic ovaries in women with acne. *Arch Dermatol Res* 1989; **281**: 502–3.
39 McLaughlin B, Barrett P, Finch T *et al*. Late onset adrenal hyperplasia in a group of Irish females who presented with hirsutism, irregular menses and/or cystic acne. *Clin Endocrinol (Oxf)* 1990; **32**: 57–64.
40 Placzek M, Degitz K, Schmidth H, Plewig G. Acne fulminans in our patient with late onset congenital adrenal hyperplasia. *Lancet* 1999; **354**: 739–40.
41 Rosenfield RL. Hyperandrogenism in peripubertal girls. *Pediatr Clin North Am* 1990; **37**: 1333–57.
42 Burton JL, Libman LJ, Cunliffe WJ *et al*. Sebum excretion in acromegaly. *BMJ* 1972; **i**: 1006–8.
43 Goolamali SK, Burton JL, Shuster S. Sebum excretion in hypopituitarism. *Br J Dermatol* 1973; **89**: 21–4.
44 Downing DT, Strauss JS, Pochi PE. Variability in the chemical composition of human skin surface lipids. *J Invest Dermatol* 1969; **53**: 322–7.
45 Shalita AR. Genesis of free fatty acids. *J Invest Dermatol* 1974; **62**: 332–5.
46 Zouboulis CC. Is acne vulgaris a genuine inflammatory disease? *Dermatology* 2001; **203**: 277–9.
47 Beveridge GW, Powell EW. Sebum changes in acne vulgaris treated with tetracycline. *Br J Dermatol* 1969; **81**: 525–7.
48 Cotterill JA, Cunliffe WJ, Williamson B *et al*. Further investigations on the pathogenesis of acne. *BMJ* 1972; **ii**: 400–6.
49 Kanaar P. Lipolysis of skin-surface lipids of acne vulgaris patients and healthy controls. *Dermatologica* 1971; **143**: 121–9.
50 Kellum RL, Strangfeld KE. Acne vulgaris: studies in pathogenesis. Fatty acids of human surface triglycerides from patients with and without acne. *J Invest Dermatol* 1972; **58**: 315–8.
51 Morello AM, Downing DT, Strauss JS. Octadecadienoic acids in the skin surface lipids of acne patients and normal subjects. *J Invest Dermatol* 1976; **66**: 319–23.
52 Holmes RL, Williams M, Cunliffe WJ. Pilo-sebaceous duct obstruction and acne. *Br J Dermatol* 1972; **87**: 327–32.
53 Pagnoni A, Kligman AM, el-Gammal S, Stoudemayer T. Determination of density of follicles on various regions of the face by cyanoacrylate biopsy: correlation with sebum output. *Br J Dermatol* 1994; **131**: 862–5.
54 Pierard GE, Pierard-Franchimont C, Goffin V. Digital image analysis of microcomedones. *Dermatology* 1995; **190**: 99–103.
55 Plewig G, Fulton JE, Kligman AM. Cellular dynamics of comedo formation in acne vulgaris. *Arch Dermatol Forsch* 1971; **242**: 12–29.
56 Knaggs HE, Holland DB, Morris C *et al*. Quantification of cellular proliferation in acne using the monoclonal antibody Ki-67. *J Soc Invest Dermatol* 1994; **102**: 89–92.
57 Gerdes J. Growth fractions in breast cancer determined *in situ* with monoclonal antibody Ki-67. *J Clin Pathol* 1986; **39**: 977–80.
58 Hughes BR, Morris C, Cunliffe WJ, Leigh IM. Keratin expression in pilosebaceous epithelia in truncal skin of acne patients. *Br J Dermatol* 1996; **134**: 247–56.
59 Kirokawa I, Mayer de Silva A, Gollnick H, Orfanos CE. Monoclonal antibody labelling for cytokeratins and filaggrin in the human pilosebaceous unit of normal seborrhoeic and acne skin. *J Invest Dermatol* 1988; **91**: 566–71.
60 Knaggs HE, Hughes BR, Morris C *et al*. Immunohistochemical study of desmosomes in acne vulgaris. *Br J Dermatol* 1994; **130**: 731–7.
61 Stewart ME, Wertz PW, Crahek MO. Relationship between sebum secretion rates and the concentration of linoleate in sebum and epidermal lipids. *Clin Res* 1985; **33**: 684–8.
62 Wertz PW, Miethke MC, Long SA *et al*. The composition of the ceramides from human stratum corneum and from comedones. *J Invest Dermatol* 1985; **84**: 410–2.
63 Downing DT, Stewart ME, Wertz PW *et al*. Essential fatty acids and acne. *J Am Acad Dermatol* 1986; **14**: 221–5.

64 Stewart ME, Greenwood R, Cunliffe WJ *et al.* Effect of cyproterone acetate-ethinyl estradiol treatment on the proportion of linoleic and sebaceic acids in various skin surface lipid classes. *Arch Dermatol Res* 1986; **278**: 481–5.
65 Knutson DD. Ultrastructural observations in acne vulgaris: the normal sebaceous follicle and acne lesions. *J Invest Dermatol* 1974; **62**: 288–307.
66 Motoyoshi K. Enhanced comedo formation in rabbit ear skin by squalene and oleic acid peroxides. *Br J Dermatol* 1983; **109**: 191–8.
67 Woo-Sam PC. Cohesion of horny cells during comedo formation. An electron microscope study. *Br J Dermatol* 1977; **97**: 609–15.
68 Kanaar P. Follicular–keratogenic properties of fatty acids in the extemal ear canal of the rabbit. *Dermatologica* 1971; **142**: 14–22.
69 Kligman AM, Katz AC. Pathogenesis of acne vulgaris. I. Comedogenic properties of human sebum in external ear canal of the rabbit. *Arch Dermatol* 1968; **98**: 53–7.
70 Frank SB. Is the rabbit ear test in its present state, prophetic of acnegenicity? *J Am Acad Dermatol* 1982; **6**: 373–7.
71 Mills OH, Kligman AM. A human model for assaying comedolytic substances. *Br J Dermatol* 1982; **107**: 543–8.
72 Tucker SB, Flannigan SA, Dunbar M *et al.* Development of an objective comedogenicity assay. *Arch Dermatol* 1986; **122**: 699–702.
73 Zheng P, Gendimenico GJ, Mezick JA, Kligman AM. Topical all-*trans*-retinoic acid rapidly corrects the follicular abnormalities of the rhino mouse. An ultrastructural study. *Acta Derm Venereol (Stockh)* 1993; **73**: 97–101.
74 Seiberg M, Siock P, Wisniewski S *et al.* The effects of trypsin on apoptosis, utriculi size, and skin elasticity in the rhino mouse. *J Invest Dermatol* 1997; **109**: 370–6.
75 Lucky AW, Biro FM, Huster GA *et al.* Acne vulgaris in premenarchal girls. *Arch Dermatol* 1994; **130**: 310–4.
76 Choudry R, Hodgins MB, Van der Kavast TH *et al.* Localisation of androgen receptors in human skin by immunocytochemistry. *J Endocrinol* 1992; **133**: 467–74.
77 Thiboutot DM, Knaggs H, Gilliland K *et al.* Activity of type 1 5α-reductase is greater in the follicular infra infundibulum compared with the epidermis. *Br J Dermatol* 1997; **136**: 166–71.
78 Thiboutet D, Gilliland K, Light J, Lookingbill D. Androgen metabolism in sebaceous glands from subjects with and without acne. *Arch Dermatol* 1999; **135**: 1041–8.
79 Thiboutot D, Bayne El, Thorne J *et al.* Immunolocalisation of 5α-reductase isozymes in acne lesions and normal skin. *Arch Dermatol* 2000; **136**: 1125–9.
80 Guy R, Ridden C, Barth J, Kealey T. Isolation and maintenance of the human pilosebaceous duct: 13-*cis*-retinoic acid acts directly on the duct *in vitro*. *Br J Dermatol* 1993; **128**: 242–8.
81 Sanders DA, Philpott MP, Nicolle FV, Kealey T. The isolation and maintenance of the human pilosebaceous unit. *Br J Dermatol* 1994; **131**: 166–76.
82 Guy R, Green MR, Kealey T. Modelling acne *in vitro*. *J Invest Dermatol* 1996; **106**: 176–82.
83 Ingham E, Eady A, Goodwin CE *et al.* Pro-inflammatory levels of interleukin 1-α-like bioactivity are present in the majority of open comedones in acne vulgaris. *J Invest Dermatol* 1992; **98**: 895–901.
84 Guy G, Kealey T. The effect of inflammatory cytokines on the isolated human sebaceous infundibulum. *J Invest Dermatol* 1998; **110**: 410–5.
85 Downie MMT, Sanders DA, Kealey T. Modelling the remission of individual acne lesions *in vitro*. *Br J Dermatol* 2002; **147**: 869–78.
86 Mourelatos K, Eady EH, Cunliffe WJ *et al.* Temporal changes in sebum excretion and propionibacterial colonization in preadolescent children with and without acne. *Br J Dermatol* 2007; **156**: 22–31.
87 Lavker RM, Leyden JJ, McCinley KJ. The relationship between bacteria and the abnormal follicular keratinization in acne vulgaris. *J Invest Dermatol* 1981; **77**: 325–30.
88 Leeming JP, Holland KT, Cunliffe WJ. The pathological and ecological significance of microorganisms colonising acne vulgaris comedones. *J Med Microbiol* 1985; **20**: 11–6.
89 Aldana OL, Holland DB, Cunliffe WJ. The theory of comedone cycling. *J Invest Dermatol* 1997; **108**: 384 (Abstract).
90 Simpson NB. Functional blockage of open comedones. *Br J Dermatol* 1987; **117**: 43–7.
91 Williams M, Cunliffe WJ, Gould D. Pilo-sebaceous duct physiology. I. Effect of hydration on pilo-sebaceous duct orifice. *Br J Dermatol* 1974; **90**: 631–5.
92 Williams M, Cunliffe WJ. Explanation for premenstrual acne. *Lancet* 1973; **ii**: 1055–7.
93 O'Donoghue MN. Cosmetics for the elderly. *Dermatol Clin* 1991; **9**: 99–104.
94 Gonzalez-Serva A. Excretion of sebum is channelled by a keratinous envelope from sebaceous duct origin: the sebolemmal sheath. *J Invest Dermatol* 1997; **108**: 376.
95 Eady EA, Cove JH. Is acne an infection of blocked pilosebaceous follicles? Implications for antimicrobial treatment. *Am J Clin Dermatol* 2000; **1**: 201–9.
96 Marples RR. The microflora of the face and acne lesions. *J Invest Dermatol* 1974; **62**: 326–31.
97 Holland KT, Cunliffe WJ, Roberts CD. The role of bacteria in acne vulgaris—a new approach. *Clin Exp Dermatol* 1978; **3**: 253–7.
98 Leyden JL, McGinley KJ, Mills OH *et al. Propionibacterium* levels in patients with and without acne vulgaris. *J Invest Dermatol* 1975; **65**: 382–4.
99 Leyden JL, McGinley KJ, Mills OH *et al.* Age-related changes in the resident bacterial flora of the human face. *J Invest Dermatol* 1975; **65**: 379–81.
100 Cove JH, Holland KT, Cunliffe WJ. An analysis of sebum excretion rate, bacterial population and the production rate of free fatty acids on human skin. *Br J Dermatol* 1980; **103**: 383–6.
101 Leyden JJ. The evolving role of *Propionibacterium acnes* in acne. *Semin Cutan Med Surg* 2001; **20**: 139–41.
102 Till AE, Goulden V, Cunliffe WJ, Holland KT. The cutaneous microflora of adolescent, persistent and late-onset acne patients does not differ. *Br J Dermatol* 2000; **142**: 885–92.
103 Bruggermann H, Henne A, Hoster F *et al.* The complete genome sequence of *Propionibacterium acnes*, a commensal of human skin. *Science* 2004; **305**: 671–3.
104 Graham GM, Farrar MD, Cruse-Sawyer JE *et al.* Proinflammtory cytokine production by human keratinocytes stimulated by *Propionibacteria acnes* and *P. acnes* GroEL. *Br J Dermatol* 2004; **150**: 421–8.
105 Jeremy A, Holland DB, Roberts SG *et al.* Inflammatory events are involved in acne lesion initiation. *J Invest Dermatol* 2003; **121**: 20–7.
106 Jappe U, Ingham E, Henwood J *et al. Propionibacterium acnes* and inflammation in acne: *P. acnes* T-cell mitogenic activity. *Br J Dermatol* 2002; **146**: 202–9.
107 Ingham E. The immunology of *Propionibacterium acnes* and acne. *Curr Opin Infect Dis* 1999; **12**: 191–7.
108 Ingham E, Eady EA, Goodwin CE *et al.* Pro-inflammatory levels of interleukin-1 alpha-like bioactivity are present in the majority of open comedones in acne vulgaris. *J Invest Dermatol* 1992; **98**: 895–901.
109 Nagy I, Pivarsci A, Kroeck A *et al.* Distinct stains of *Propionibacterium acnes* induce selective β-defensin-2 and interleukin-8 expression human keratinocytes through Toll-like receptors. *J Invest Dermatol* 2005; **124**: 931–8.
110 Kim J, Ochoa MT, Krutzik SR *et al.* Activation of Toll-like receptor 2 in acne triggers inflammatory cytokine responses. *J Immunol* 2002; **169**: 1535–41.
111 Lee JY, Plakidas A, Lee WH *et al.* Differential modulation of Toll-like receptors by fatty acids: preferential inhibition by n-3 polyunsaturated fatty acids. *J Lipid Res* 2003; **44**: 479–86.
112 Johnson GB, Brunn GJ, Platt JL. Activation of mammalian Toll-like receptors by endogenous ligands. *Crit Rev Immunol* 2003; **23**: 15–44.
113 Holland KT, Greenman J, Cunliffe WJ. Growth of cutaneous propionibacteria on synthetic medium; growth yields and exoenzyme production. *J Appl Bacteriol* 1979; **47**: 383–94.
114 Ingham E, Holland KT, Gowland C *et al.* Purification and partial characterisation of hyaluronate lyase (EC 4.2.2.1) from *Propionibacterium acnes*. *J Gen Microbiol* 1979; **115**: 411–8.
115 Ingham E, Holland KT, Gowland C *et al.* Studies of the extracellular proteolytic activity produced by *Propionibacterium acnes*. *J Appl Bacteriol* 1983; **54**: 263–71.
116 Holland DB, Cunliffe WJ. Skin surface and open comedone pH in acne patients. *Acta Derm Venereol (Stockh)* 1983; **63**: 155–8.
117 Gribbon EM, Shoesmith JG, Cunliffe WJ, Holland KT. The microaerophily and photosensitivity of *Propionibacterium acnes*. *J Appl Bacteriol* 1994; **77**: 583–90.
118 Holland DB, Jeremy AHT. The role of inflammation in the pathogenesis of acne and acne scarring. *Semin Cutan Med Surg* 2005; **24**: 79–83.
119 Elias PM, Brown BE, Ziboh VA. The permeability barrier in essential fatty acid deficiency: evidence for a direct role for linoleic acid in barrier function. *J Invest Dermatol* 1980; **74**: 230–3.
120 Downing DT, Stewart ME, Wertz PW *et al.* Essential fatty acids and acne. *J Am Acad Dermatol* 1986; **14**: 221–5.

121 Wood LC, Feingold KR, Sequeira-Martin SM *et al*. Barrier function co-ordinately regulates epidermal IL-1 and IL-1 receptor antagonist mRNA levels. *Exp Dermatol* 1994; **3**: 56–60.
122 Zouboulis CC. Is acne vulgaris a genuine inflammatory disease? *Dermatology* 2001; **203**: 277–9.
123 Zouboulis CC, Nestoris S, Adler YD *et al*. A new concept for acne therapy: a pilot study with zileuton, an oral 5-lipoxygenase inhibitor. *Arch Dermatol* 2003; **139**: 668–70.
124 Cowin AJ, Brosman MP, Holmes TM, Ferguson MWJ. Endogenous inflammatory response to dermal wound healing in the fetal and adult mouse. *Dev Dyn* 1998; **212**: 385–93.
125 Holland DB, Jeremy AH, Roberts SG *et al*. Inflammation in acne scarring: a comparison of the responses in lesions from patients prone and not prone to scar. *Br J Dermatol* 2004; **150**: 72–81.
126 Sheehan-Dare R, Cunliffe WJ, Simmons AV *et al*. Acne vulgaris and malignancy. *Br J Dermatol* 1988; **119**: 669–73.
127 Rampen FHJ. Role of *Propionibacterium acnes* in cancer risk. *Br J Dermatol* 1989; **121**: 279–80.
128 Luger T, Bohm M. The sebaceous gland as an immunocompetent organ. *J Invest Dermatol* 1997; **108**: 381.

Clinical features

Acne is a polymorphic, inflammatory disease of the skin which occurs most commonly on the face (in 99% of cases) (Fig. 42.30) and to a lesser extent on the back (60%) and chest (15%) [1]. Seborrhoea is a frequent and distressing feature [2,3]. The clinical picture can vary from very mild comedonal acne, with or without sparse inflammatory lesions, to aggressive fulminant disease with associated systemic upset.

Non-inflamed lesions are the earliest lesions to develop in younger patients [4] and embrace both open (blackheads) and closed (whiteheads) comedones. Open comedones represent dome-shaped papules in which there are dilated follicular outlets filled with keratin. The apparent black colour is thought to be due to melanin deposited within the cellular debris. Comedones frequently appear in a mid-facial distribution and when evident early in the onset of the disease indicate a poor prognosis [4] (Fig. 42.31). Closed comedones or whiteheads are generally 1 mm in diameter, skin coloured and have no visible follicular opening. These lesions are often inconspicuous and require adequate lighting and stretching of the skin to be seen. Most patients have a mixture of lesions [5].

There are also several subtle subtypes of comedones whose presence may influence response to therapy [6]:

- 'Sandpaper' comedones consist of multiple, very small whiteheads, frequently distributed on the forehead (Fig. 42.32), which produce a roughened, gritty feel to the skin.
- 'Macrocomedones' (Fig. 42.33) are large whiteheads or occasionally blackheads greater than 1 mm in diameter. Both mac-



Fig. 42.31 Midfacial comedones correlate with poor prognosis when present early in the course of the disease.



Fig. 42.30 Facial acne showing mixed inflammatory and non-inflammatory lesions.



Fig. 42.32 A patient with sandpaper acne. Note the very small, multiple whiteheads.



Fig. 42.33 Multiple macrocomedones (closed comedones) which are only seen clearly on stretching the skin. (Courtesy of Dr A. Yung, Auckland, New Zealand.)

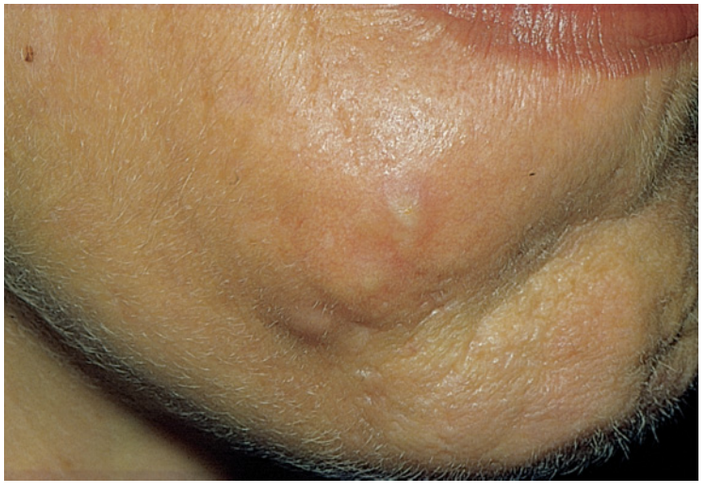


Fig. 42.34 This patient had submarine comedones requiring stretching of the skin in order for them to be detected.

rocomedones and sandpaper comedones respond poorly to conventional topical treatments.

- 'Submarine' comedones are large comedonal structures greater than 0.5 cm in diameter and are resident more deeply in the skin; they are frequently the source of recurrent inflammatory nodular lesions (Fig. 42.34).
- Secondary comedones may be produced after exposure to dioxins (chloracne), pomades (pomade acne), topical steroids and other drugs (drug-induced acne).

Inflammatory lesions arise from the microcomedo or non-inflammatory lesions and can develop into superficial or deep lesions [7]. The superficial lesions are usually papules and pustules (5 mm or less in diameter) (Fig. 42.35), and the deep lesions are deep pustules and nodules (Fig. 42.36). The term nodulo-cystic acne is incorrect. Acne 'cysts' are not true cysts because they are not lined by an epithelium. It is therefore more accurate to describe such lesions as nodules [8].



Fig. 42.35 Multiple superficial papules.



Fig. 42.36 Deep inflammatory nodules.

Nodules are seen more frequently in males and when exudative or haemorrhagic are particularly disfiguring and uncomfortable (Fig. 42.37). Nodules may extend deeply and over large areas showing little surface involvement. Sinus formation (Fig. 42.38) between nodules and/or deep pustules leads to devastating cosmetic effects and inevitable scarring [9,10]. These lesions are frequently very tender, chronic and resistant to treatment and although they usually emerge slowly over a few days, they may occur acutely within a 24-h period. There is usually no obvious reason for an acute episode, although eruptive and severe inflammatory acne has been reported alongside glandular fever [11].



Fig. 42.37 Exudating haemorrhagic lesions.

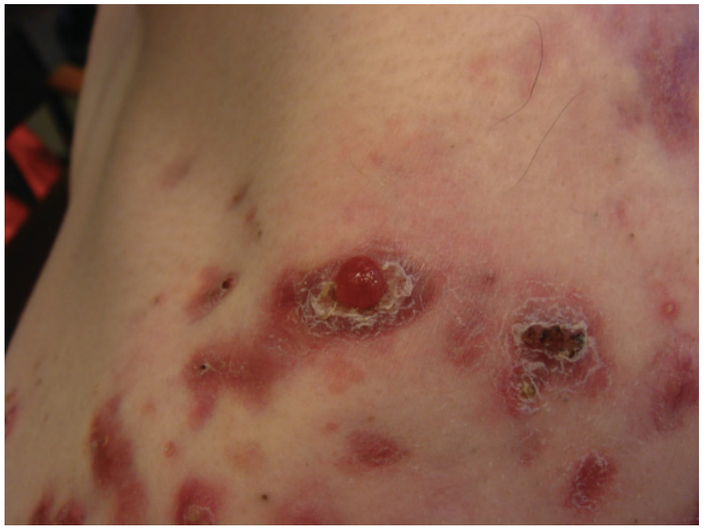


Fig. 42.39 Pyogenic granulomas rarely occur in acne and/or as a result of acne treated with isotretinoin. (Courtesy of Dr V. Bettoli, University of Ferrara, Italy.)



Fig. 42.38 Sinuses and nodules in severe acne. (Courtesy of Dr A. Yung, Auckland, New Zealand.)



Fig. 42.40 Post-acne keloid scar.

Itching is a rare symptom of acne, but may be evident and possibly relates to the release of histamine-like compounds from *P. acnes* [12].

Pyogenic granulomas develop very infrequently [13,14] in patients with very severe disease of the trunk (Fig. 42.39). They can also be precipitated during the early phase of treatment with oral isotretinoin. Inflammatory and haemorrhagic nodules are also a feature of acne conglobata, which is characterized by extensive acne found particularly on the trunk. There are usually many grouped polyporous comedones, which are frequently inflamed and result in scarring. Acne conglobata is characteristically a chronic disorder, and may last up to 40–50 years of age.

Inflammatory macules are often not recognized as a physical sign of acne; these represent regressing lesions that may persist for many weeks and contribute markedly to the general inflammatory appearance [5]. Although the classification of lesions may be helpful in choosing the appropriate management, it must not be forgotten that inflammatory lesions frequently change from one type to another.

Scarring usually follows deep-seated inflammatory lesions, but may also occur as a result of more superficial inflamed lesions in scar-prone patients. Close inspection under a bright light may reveal some scarring, albeit mild, in up to 90% of patients who attend a dermatologist [15]. Scars may show increased collagen (hypertrophic scars and keloids) or be associated with loss of collagen (i.e. ice-pick scars, depressed fibrotic scars, atrophic macules and perifollicular elastolysis). Keloids (Fig. 42.40) by definition extend beyond the extent of original inflammation and are most prevalent on the trunk. Hypertrophic scars in contrast to keloids do not extend beyond the extent of the original inflammation. Atrophic macular scars are frequently multiple, and represent soft distensible lesions. They often retain a vascular hue for many



Fig. 42.41 Ice pick scars on the cheeks. (Courtesy of Dr V. Bettoli, University of Ferrara, Italy.)



Fig. 42.42 Post-inflammatory hyperpigmentation more common in III/IV skin types.

months before becoming white and less conspicuous. Ice-pick scars (Fig. 42.41) are small, jagged, firm atrophic scars, most evident on the cheeks. Ice-pick scarring can result from comedones alone. Perifollicular elastolysis (PFE) is commonly found on the trunk and consists of multiple, follicular, atrophic looking lesions, sometimes seen without evidence of acne [16]. Calcification is a rare complication of scarring [17,18].

Persistent post-inflammatory hyperpigmentation, seen most frequently in pigmented skin (Fig. 42.42) and post-inflammatory erythema are both common and cosmetically disfiguring features of acne. The pigmentary change may take many months to resolve and in some cases can be permanent.

Associated features. Certain diseases that occlude the follicular pores, including hidradenitis suppurativa [19] and dissecting folliculitis (perifolliculitis capitis abscedens et suffodiens) [20], of the scalp may accompany acne, and are classified as the follicular occlusion triad when accompanied by acne conglobata. All conditions have in common a deep, recurrent, chronic folliculitis that results in abscess formation, sinus tract formation and scarring. These diseases are discussed later in this chapter.

References

1 Cunliffe WJ. *The Acnes*. London: Dunitz, 1989.
2 Cunliffe WJ, Shuster S. Pathogenesis of acne. *Lancet* 1969; **i**: 685–7.
3 Beylot C. Seborrhoea and its complications. *Rev Prat* 1993; **43**: 2320–7.
4 Lucky AW, Bifo FN, Hustar EA *et al.* Acne vulgaris in premenarcheal girls. *Arch Dermatol* 1994; **130**: 308–14.
5 Burke BM, Cunliffe WJ. The assessment of acne vulgaris—the Leeds technique. *Br J Dermatol* 1984; **111**: 83–92.
6 Cunliffe WJ, Holland DB, Clark SM, Stables GI. Comedogenesis: some new aetiological, clinical and therapeutic strategies. *Br J Dermatol* 2000; **142**: 1084–91.
7 Orentreich N, Durr NP. The natural evolution of comedones into inflammatory papules and pustules. *J Invest Dermatol* 1974; **62**: 316–20.
8 Pochi PE, Shalita AR, Strauss JS *et al.* Report of the Consensus Conference on Acne Classification, Washington, DC. *J Am Acad Dermatol* 1991; **241**: 495–500.
9 Jansen T, Lindner A, Plewig G. Draining sinus in acne and rosacea. A clinical, histopathological and experimental study. *Hautarzt* 1995; **46**: 417–20.
10 Jansen T, Romiti R, Plewig G *et al.* Disfiguring draining sinus tracks in a female patient. *Pediatr Dermatol* 2000; **17**: 123–5.
11 Jansen T, Romiti R, Woitalla S *et al.* Eruptive acne vulgaris with infectious mononucleosis. *Br J Dermatol* 2000; **142**: 837–8.
12 Yee KC, Cunliffe WJ. Itching in acne—an unusual complication of therapy. *Dermatology* 1994; **189**: 117–9.
13 Hagedorn M, Kirchner S. Multiple granulomata pyogenica bei Acne vulgaris. *Dermatologica* 1979; **158**: 93–8.
14 Mobaven MM, Copeman PWM. Multiple pyogenic granulomas in secondarily infected cystic acne. *Clin Exp Dermatol* 1983; **8**: 107–9.
15 Layton AM, Henderson CA, Cunliffe WJ. A clinical evaluation of acne scarring and its incidence. *Clin Exp Dermatol* 1994; **19**: 303–8.
16 Varadi DP, Saqueton AC. Perifollicular elastolysis. *Br J Dermatol* 1970; **83**: 143–50.
17 Leider M. Osteoma cutis as a result of severe acne vulgaris of long duration. *Arch Dermatol Syphilol* 1950; **62**: 405–7.
18 MacGregor A. Calcification in scars of healed acne vulgaris. *Oral Surg Oral Med Oral Pathol* 1971; **32**: 829–30.
19 Jansen T, Altmeyer P, Plewig G. Acne inversa (alias hidradenitis suppurativa). *J Eur Acad Dermatol Venereol* 2001; **15**: 532–40.
20 Bachynsky T, Antonyshyn OM, Ross JB. Dissecting folliculitis of the scalp. *J Dermatol Surg Oncol* 1992; **18**: 877–80.

Physiological and environmental factors that influence acne

There are many myths about factors that might help or aggravate acne.

Diet

Dietary factors, particularly sweets, chocolate and fat, are frequently regarded by patients and clinicians as a cause or aggravator of acne [1,2]. However, there is still a paucity of scientific evidence to prove a causal relationship between diet and acne. Chocolate has been reported to have no significant influence as a trigger for acne; however, the methodology used in these old studies had significant shortcomings [3–7]. Severe dietary

restriction, resulting in marked weight loss, reduces seborrhoea, but cannot be considered as routine treatment [8]. Acne occurs less frequently in Zambia, Nigeria and Japan [9], where diets differ markedly from those in Western Europe, but the lower incidence could be due to other environmental or genetic factors. A detailed epidemiological study of Kitavan islanders of Papua New Guinea and Aché hunter-gatherers of Paraguay failed to find a single male or female with significant acne [10]. The authors proposed that the absence of acne was due to dietary factors, but these are closed communities in which genetic and environmental factors other than diet must play a very significant part. The authors suggest that the diet in the Western civilization has a high glycaemic index which can lead to hyperinsulinaemia and result in a cascade of endocrine triggers, including increased insulin-like growth factor 1, altered retinoid signalling and increased androgens, thereby mediating acne pathogenesis. These theories would be difficult to test as this would require an experiment such as raising Western children on a strict Papa New Guinea diet.

A further study has demonstrated a correlation between an exacerbation of acne and worsening diet in a group of university students in a pre-examination period. However, the dietary variable was only evaluated by a subjective, self-assessed diet quality measure and the main factor examined was effect of examination stress [11].

The possible effect of nutrition on the age of puberty may be relevant, as acne is more likely after the start of sexual development, and this occurs when the body weight attains about 48 kg [12]. Acne may be an effect of starvation and is seen in patients with anorexia nervosa. Dieting behaviour may be adopted to control acne and this approach has been reported as a risk factor for anorexia nervosa [13]. The trend of increased weight among children and earlier puberty may be reflected in an earlier onset of clinical acne [14].

One study identified a positive association between acne and intake of total milk and skim milk, and suggested that the presence of hormones and bioactive molecules in milk might be linked to this association [15].

A randomized, double-blinded, controlled trial in Australia examined the effect of diet on facial acne in men aged 15 to 25. 27 men who ate a high glycaemic load (HGL) diet were compared with 27 who ate a low glycaemic load (LGL) diet with more complex carbohydrates and protein. Both groups used a mild cleanser to wash and acne medications were avoided during the study. Both groups had fewer acne lesions after 12 weeks but the group taking the LGL diet had significantly fewer lesions. The authors suggest that the LGL diet resulted in less insulin and insulin growth factor production, which theoretically should reduce androgen-mediated acne. However, the LGL diet resulted in significantly more weight reduction than the HGL diet, suggesting that weight loss might be the trigger for this positive effect [16]. There are a number of hypotheses that have been presented in the literature implicating diet in acne pathogenesis [17]. However, to date the debate regarding acne and diet continues, and further robust controlled studies are required to support this concept and provide us with compelling evidence linking nutrition to acnegenesis.

Premenstrual flare

About 70% of women complain of a flare 2–7 days premenstrually [12,14]. It is unlikely that any possible variation in sebum excretion during the menstrual cycle [18] could be substantial enough to explain the flare. Possibly, flaring is related to a premenstrual change in the hydration of the pilosebaceous epithelium [19]. Progesterone and oestrogen also have both pro- and anti-inflammatory effects [20]. Up-regulation of aspects of the inflammatory response would make some teleological sense at this vulnerable time.

Sweating

Up to 15% of acne patients notice that sweating causes a deterioration in their acne, especially if they live or work in a hot humid environment; for example, for a cook, ductal hydration may be the responsible factor [21].

Ultraviolet radiation

Patients and doctors alike accept that natural sunlight often improves acne, but there is no scientific evidence for this belief. The cosmetic effect of tanning may be the entire explanation. Artificial UV radiation appears to be less satisfactory than natural radiation, and psoralen and UVA (PUVA) has been reported to very uncommonly induce acne lesions [22]. Furthermore, UV radiation may enhance the comedogenicity of sebum [23,24].

A recent systematic review examining the direct evidence for a positive effect of sunlight exposure on acne confirmed that evidence was lacking. Although there was some evidence to suggest that various spectra of artificial light may be beneficial this could not be generalized to natural sunlight [25]. Other important considerations for not advocating natural sunlight as treatment for acne relates to the potential long-term sequelae of sun exposure including an increased risk of melanoma and non-melanoma skin cancer, an increased risk of photosensitivity whilst on some acne medications, particularly tetracycline and isotretinoin, and the interesting reported association of acne with decreased risk of melanoma [26].

Occupation

Hydration of the ductal stratum corneum may induce acne in such occupations as catering and steam cleaning. Patients dealing with oil may develop an acneiform oil folliculitis, particularly on their trunks and limbs, but usually need their overalls to be very heavily contaminated. The induction of chloracne by accidental release of halogenated hydrocarbons or other chemicals is discussed elsewhere in this chapter.

Smoking and acne

One cross-sectional study has shown a linear relationship between acne prevalence and the number of cigarettes smoked daily but did include patients over a wide age range [27]. Other studies have not confirmed this association [28,29]. Investigations have revealed that cigarette smoke contains high amounts of arachidonic acid and polycyclic aromatic hydrocarbons, which induce a phospholipasic A2-dependent inflammatory pathway [30]. This effect may further stimulate arachidonic acid synthesis [31]. Smokers have also been shown to have a higher saturated fat and

lower polyunsaturated intake in their diet, principally due to lower linoleic acid intake when compared to non-smokers. [32].

Psychosocial effects of acne

Data from the older literature suggested that it is unlikely that stress alone induces the formation *de novo* of acne lesions [33,34]. However, one study assessed acne grade before and during exams and confirmed that stress can induce acne. In addition, the authors demonstrated that acne itself induces stress, and the 'picking' of spots will aggravate the appearance [35]. This is particularly obvious in young females who present with acne excoriée [36,37]. Corticotrophin-releasing hormone induces the synthesis of sebaceous lipids *in vitro* [38] and adrenocorticotrophic hormone evokes adrenal dehydroepiandrosterone to regulate skin inflammation [39]. These current findings indicate that central [40] or topical stress [31–38] may indeed influence the feedback regulation, thus inducing the development of clinical inflammation in early acne.

There have been many studies over the years investigating the specific psychological effects produced by acne. Studies have shown that many acne patients experience shame (70%), embarrassment and anxiety (63%), lack of confidence (67%), impaired social contact (57%) and a significant problem with unemployment [41,42]. Severe acne may be related to increased anger and anxiety [43]. Clinical depression has been demonstrated in acne patients and the prevalence of active suicidal ideation is higher in acne patients than reported in the general population. Of note, the psychological impairment does not necessarily correlate with the clinical severity of disease [44]. There have been reports of acne patients committing suicide [45].

Appearance is an important factor in social and emotional functioning. Appearance, particularly facial appearance, represents an important aspect of one's perception of body image [46]. From psychosocial research, it is known that physically attractive strangers attribute more positive qualities such as friendliness, intelligence and higher social skill levels to each other, compared with physically unattractive strangers. This effect is strongly reinforced through television commercials and the media, in which a cosmetically acceptable appearance is inherently linked to social success.

Over the last decade, there has been renewed interest in the measurement and identification of disease disability and impact of disease on quality of life; skin disease and acne is no exception. Questionnaires including disease specific, dermatology specific, general health and utility measures have been developed.

Several groups have developed simple questionnaires to better understand the impact of acne in inducing anxiety, depression and impaired quality of life. These questionnaires are very helpful; they take only a few minutes for the patient to complete and assist the physician in quantifying the psychological and social effects of the disease and allow an appreciation of the overall response to therapy. Combinations of generic and dermatology-specific questionnaires are available and have been used with these aims in mind [47–61].

General health measures assess a variety of diseases and include the Sickness Impact Form (SIP) [62], the Short-Form 36 (SF-36) [63] and the General Health Questionnaire (GHQ). These tools have been used in acne and allow comparison between skin diseases and a spectrum of other diseases. The Dermatology Life Quality Index (DLQI) represents a specific measure of disability in skin disease and provides a comprehensive and practical way of assessing the impact of skin disease [57]. Disease-specific questionnaires that relate specifically to acne include the Cardiff Acne Disability Index (CADI), the Assessment of the Psychosocial Effects of Acne (APSEA) from Leeds and the Acne Quality of Life Scale (Acne-QOL) [52,57]. Utility measures assess the hypothetical value that people place on their health. Values may be expressed in financial ways or time frames, for example how much would a patient pay to cure their disease?

Comparisons with other chronic illnesses have shown that acne patients have levels of social, psychological and emotional disability that are similar to those reported by patients with 'more serious' diseases such as asthma, epilepsy, diabetes or arthritis [61]. Acne also affects functional abilities. Patients are prone to embarrassment and social withdrawal, depression, anxiety and anger. There are still many misconceptions held about acne in different communities and cultures and younger acne patients are subject to bullying, teasing and stigmatization from their peers.

The use of quality of life and psychosocial questionnaires is essential to adequately understand just how the disease is affecting a patient, and can aid in assessing the efficacy of therapy. Newton *et al.* [62] demonstrated in 111 patients that treatment with oral isotretinoin or combined oral and topical antibiotics subsequently improved quality of life. Similarly, Kellett and Gawkrodger demonstrated significant psychological and emotional effects of acne which improved with oral isotretinoin [63].

References

1 Brajac I, Bilic-Zulle L, Tkalcic M *et al*. Acne vulgaris: myths and misconceptions among patients and family physicians. *Pat Educ and Couns* 2004; **54**: 21–5.
2 Green J, Sinclair RD. Perceptions of acne vulgaris in final year medical students' written examination answers. *Aust J Dermatol* 2001; **42**: 98–101.
3 Fries JH. Chocolate: a review of published reports of allergic and other deleterious effects, real or presumed. *Ann Allergy* 1978; **41**: 195–207.
4 Fulton JE, Plewig C, Kligman AM. Effect of chocolate on acne vulgaris. *JAMA* 1969; **210**: 2071–4.
5 Grant JD, Anderson PC. Chocolate and acne: a dissenting view. *Missouri Med* 1965; **62**: 459–60.
6 Anderson PC. Foods as the cause of acne. *Am Fam Phys* 1971; **3**: 102–3.
7 Rosenberg WE, Kirk BS. Acne diet reconsidered. *Arch Dermatol* 1981; **117**: 193–5.
8 Pochi PE, Downing DT, Strauss JS. Sebaceous gland response in man to prolonged total caloric deprivation. *J Invest Dermatol* 1970; **55**: 303–9.
9 Ratnam AV, Jayaraju K. Skin diseases in Zambia. *Br J Dermatol* 1979; **101**: 449–53.
10 Cordain L, Lindeberg S, Hurtado M *et al*. Acne vulgaris. A disease of western civilisation. *Arch Dermatol* 2002; **138**: 1584–90.
11 Chiu AC, Chon SY, Kimball AB. The response of skin disease to stress: changes in the severity of acne vulgaris as affected by examination stress. *Arch Dermatol* 2003; **139**: 897–900.
12 Frisch RE. Weight at menarche: similarity for well-nourished and under-nourished girls at differing ages, and evidence for histologic constancy. *Pediatrics* 1972; **50**: 445–50.
13 Lee S, Leung CM, Wing YK *et al*. Acne as a risk factor for anorexia nervosa in Chinese. *Aust N Z J Psych* 1991; **25**: 134–7.
14 Lucky AW, Biro FM, Huster GA *et al*. Acne vulgaris in premenstrual girls. *Arch Dermatol* 1994; **130**: 308–14.
15 Clement AA, Spiegelman D, Danby W *et al*. High school dietary dairy intake and teenage acne. *J Am Acad Dermatol* 2005; **52**: 207–14.

16 Smith RN, Mann NJ, Braue A *et al*. A low-glycaemic load diet improves symptoms in acne vulgaris patients: a randomized controlled trial. *Am J Clin Nutr* 2007; **86**: 107–15.
17 Cordain L. Implications or the role of diet in acne. *Semin Cutan Med and Surg* 2005; **24**: 84–91.
18 Cunliffe WJ, Schaefer H, Kuhn WJ, Cotterill JA. *The Acnes*. London: Saunders, 1975.
19 Williams M, Cunliffe WJ. Explanation for premenstrual acne. *Lancet* 1973; **ii**: 1055–7.
20 Bussius H. Methodik zur quantitativen Bestimmung der menschlichen Talgsekretion. *Arch Klin Exp Dermatol* 1970; **238**: 429–35.
21 Williams M, Cunliffe WJ, Gould D. Pilo-sebaceous duct physiology. I. Effect of hydration on pilo-sebaceous duct orifice. *Br J Dermatol* 1974; **90**: 631–5.
22 Jones C, Bleehen SS. Acne induced by PUVA treatment. *BMJ* 1977; **ii**: 866.
23 Mills OH, Kligman AM. Ultraviolet phototherapy and photochemotherapy of acne vulgaris. *Arch Dermatol* 1978; **114**: 221–3.
24 Mills OH, Porte M, Kligman AM. Enhancement of comedogenic substances by ultraviolet radiation. *Br J Dermatol* 1978; **98**: 145–8.
25 Parker M, Pond D, Smith W *et al*. A systematic review of the evidence for 'myths and misconceptions' in acne management: diet, face-washing and sunlight. *Family Practice* 2005; **22**: 62–70.
26 Beral V, Evans S, Shaw H *et al*. Cutaneous factors related to the risk of malignant melanoma. *Br J Dermatol* 1983; **109**: 165–72.
27 Schafer T, Nienhaus A, Vieluf D *et al*. Epidemiology of acne in the general population: the risk of smoking. *Br J Dermatol* 2001; **45**: 100–4.
28 Jemec GBE, Linneberg A, Neilsen NH *et al*. Have oral contraceptives reduced the prevalence of acne? A population based study of acne vulgaris, tobacco smoking and oral contraceptives. *Dermatology* 2002; **204**: 179–84.
29 Firroz A, Sarhangnejad R, Davoudi S *et al*. Acne and smoking: is there a relationship? *BMC Dermatol* 2005; **5**: 1–3.
30 Tithof PK, Elgayyar H, Cho T *et al*. Polycyclic aromatic hydrocarbons present in cigarette smoke cause endothelial cell apoptosis by a phospholipase A2-dependent mechanism. *FASEB J* 2002; **16**: 1463–4.
31 Zouboulis CC. Human skin: an independent peripheral endocrine organ. *Hormone Res* 2000; **54**: 230–42.
32 Thompson RL, Pyke S, Scott EA *et al*. Cigarette smoking, polyunsaturated fats, and coronary heart disease. *Ann N Y Acad Sci* 1993; **686**: 130–8.
33 Kenyon FE. Psychosomatic aspect of acne. *Br J Dermatol* 1966; **76**: 344–51.
34 Gupta MA, Gupta AK, Schork NJ. Psychosomatic study of self-excoriative behaviour among male acne patients: preliminary observations. *Int J Dermatol* 1994; **33**: 846–8.
35 Chiu A, Chon SY, Kimball AB. The response of skin disease to stress: changes in the severity of acne vulgaris as affected by examination stress. *Arch Dermatol* 2003; **139**: 897–900.
36 Sneddon J, Sneddon I. Acne excoriée—a protective device. *Clin Exp Dermatol* 1983; **8**: 65–8.
37 Bach M, Bach D. Psychiatric and psychometric issues in acne excoriée. *Psychother Psychosom* 1993; **60**: 207–10.
38 Zouboulis CC, Seltmann H, Hiroi N *et al*. Corticotropin-releasing hormone: an autocrine hormone that promotes lipogenesis in human sebocytes. *Proc Nat Acad Sci* 2002; **99**: 7148–53.
39 Alesci S, Bornstein SR. Neuroimmunoregulation of androgens in the adrenal gland and the skin. *Hormone Res* 2000; **54**: 281–6.
40 Slominski AT, Botchkarev V, Choudhry M *et al*. Cutaneous expression of CRH and CRH-R. Is there a 'skin stress' response system? *Ann N Y Acad Sci* 1999; **885**: 287–311.
41 Jowett S, Ryan T. Skin disease and handicap: an analysis of the impact of skin conditions. *Soc Sci Med* 1985; **20**: 425–9.
42 Cunliffe WJ. Unemployment and acne. *Br J Dermatol* 1986; **115**: 386.
43 Wu SF, Kinder BN, Trunnell TN *et al*. Role of anxiety and anger in acne patients: a relationship with the severity of the disorder. *J Am Acad Dermatol* 1988; **18**: 325–33.
44 Gupta MA, Gupta AK. Depression and suicidal ideation in dermatology patients with acne, alopecia areata, atopic dermatitis and psoriasis. *Br J Dermatol* 1998; **139**: 846–50.
45 Cotterill JA, Cunliffe WJ. Suicide in dermatological patients. *Br J Dermatol* 1997; **137**: 246–50.
46 Liveneh H. Body image. *Rehab Literature* 1982; **43**: 338–47.
47 Rubinow DR, Peek GL, Squillace KM *et al*. Reduced anxiety and depression in cystic acne patients after successful treatment with oral isotretinoin. *J Am Acad Dermatol* 1987; **17**: 25–32.
48 Motley RJ, Finlay AY. Practical use of a disability index in the routine management of acne. *Clin Exp Dermatol* 1992; **17**: 1–3.
49 Khan MZ, Naeem A, Mufti KA. Prevalence of mental health problems in acne patients. *J Ayub Med Coll Abbottabad* 2001; **13**: 7–8.
50 Finlay AY. Dermatology patients: what do they really need? *Clin Exp Dermatol* 2000; **35**: 444–50.
51 Finlay AY. Dermatology Life Quality Index: initial experience of a single practical measure. In: Rajagopalan R, Sherertz EF, Anderson RT, eds. *Care Management of Skin Disease: Life Quality and Economic Impact*. Marcel Dekker: New York, 1998: 85–94.
52 Finlay AY. Quality of life assessments in dermatology. *Semin Cutan Med Surg* 1998; **17**: 291–6.
53 Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI): a simple practical measure for routine clinical use. *Clin Exp Dermatol* 1994; **19**: 210–6.
54 Lasek RJ, Chren MM. Acne vulgaris and the quality of life of adult dermatology patients. *Arch Dermatol* 1998; **134**: 454–8.
55 Clark SM, Goulden V, Finlay AY *et al*. The psychological and social impact of acne: a comparison study using three acne disability questionnaires. *Br J Dermatol* 1997; **137** (Suppl. 50): 41 (abstract).
56 Oakley AMM. The Acne Disability Index: usefulness confirmed. *Australas J Dermatol* 1996; **37**: 37–9.
57 Gupta MA, Johnson AM, Gupta AK. The development of an Acne Quality of Life Scale: reliability, validity and relation to the subjective acne severity in mild to moderate acne vulgaris. *Acta Derm Venereol (Stockh)* 1998; **78**: 451–8.
58 Klasson AF, Newton JN, Mallon E. Measuring quality of life in people referred for specialist care of acne: comparing generic and disease specific measures. *J Am Acad Dermatol* 2000; **43**: 229–33.
59 Salek MS. Measuring the quality of life of patients with skin disease. In: Walker SR, Rosser RM, eds. *Quality of Life Assessment; Key Issues in the 1990s*. Lancaster: Kluwer Academic 1993: 355–70.
60 Ware JE, Sherbourne CD. The MOS 36-short item Short-Form Health Survey (SF-36). Conceptual framework and item selection. *Med Care* 1992; **30**: 437–83.
61 Layton AM, Seukaran D, Cunliffe WJ. Scarred for life? *Dermatol* 1997; **195** (Suppl. 1): 15–21, 37, 38.
62 Newton JN, Mallon E, Klassen A *et al*. The effectiveness of acne treatment: an assessment by patients on the outcome of therapy. *Br J Dermatol* 1997; **137**: 563–7.
63 Kellett SC, Gawkrodger DJ. The psychological and emotional impact of acne and the effect of treatment with isotretinoin. *Br J Dermatol* 1999; **140**: 273–82.

Differential diagnosis

Acne is rarely misdiagnosed. The commonest mistaken diagnosis is rosacea, which occurs in older patients and lacks comedones, nodules, cysts or scarring. The presence of facial flushing and specific triggers, including heat, spicy food or alcohol, may indicate rosacea. Rosacea patients may also have ocular involvement, but rarely have truncal lesions. Some patients appear to have features of both diseases and clinical acne may evolve into more typical rosacea later in life.

In females, confusion with perioral dermatitis is possible, but in these patients the lesions itch, the skin is dry and there are no comedones.

Whiteheads (closed comedones) may be confused with milia. Milia represent subepidermal keratin cysts predominantly infraorbital in distribution. They are very common and can occur in association with, although unrelated to, acne.

Folliculitis due to Gram-negative organisms can complicate acne therapy [1], and rarely *Candida* or *S. epidermidis* folliculitis may present as multiple pustules. Demodex folliculitis can also



Fig. 42.43 Acne and keratosis pilaris coexisting on the upper arms.



Fig. 42.44 Typical distribution of *Pityrosporum* folliculitis.

present as non-responsive acne. Plane warts, particularly on the face, can also cause confusion, as can pseudofolliculitis barbae.

Acne may occur on the limbs but occasionally inflammatory keratosis pilaris may coincide or masquerade as acne (Fig. 42.43).

Pityrosporum folliculitis presents on the upper trunk as moderately ill-defined, superficial plaques, among which are scattered many papules or pustules (Fig. 42.44). It is likely, but unproven, to be a host reaction to *M. furfur*, which is a normal skin commensal [2–4].

Rarely, dermatitis herpetiformis may present as a vesicular pustular facial eruption, but it is usually very itchy unlike acne. Linear IgA disease can also present very uncommonly as a papular facial rash without comedones. Biopsy, including immunofluorescence studies, is essential to confirm diagnosis.

Rare diseases that may produce diagnostic difficulties include acne agminata (granulomatous rosacea) and tuberous sclerosis.



Fig. 42.45 A persistent 'acne nodule' due to a dental sinus.

Acne agminata presents as an asymptomatic papulopustular eruption. The lesions are light-brown in colour (somewhat darker in black skin) and on diascopy may reveal an apple jelly colour. There are reports of successful treatment with steroids and isotretinoin in the literature [5,6]. Tuberous sclerosis lesions are relatively monomorphic papules, often with a brownish appearance.

Micropapular sarcoid of the face can occur, and one case report attributed its appearance to selective perifollicular absorption of oils present in certain bubble gums [7].

The severe papulopustular eruption associated with zinc deficiency can be mistaken for marked acne, and several cases have been reported after prolonged intravenous feeding without zinc supplementation [8].

Acne necrotica (varioliformis) is associated with itching and smallpox-like scars, usually on the trunk. Biopsy shows a necrotizing lymphocytic folliculitis [9]. It can be mistaken for severe acne excoriée, but the response to isotretinoin can be excellent [10].

Behçet's disease may produce an acneiform eruption. A dental sinus can be confused with a persistent facial acne nodule (Fig. 42.45). Epidermoid cysts may become inflamed and be mistaken for acne nodules. Of course, acne may coexist alongside one of these alternative diagnoses.

Acneiform drug eruptions are discussed in this chapter and in Chapter 75.

Acne scarring can mimic scarring due to hydroa vacciniforme, ulerytherma oophryogenes, acne keloidalis [11,12], varioliform atrophy and porphyria cutanea tarda.

References

1 Fulton JE, McGinley K, Leyden J *et al.* Gram-negative folliculitis in acne vulgaris. *Arch Dermatol* 1968; **98**: 349–53.

2 Ford CP, Ive FA, Midgley G. *Pityrosporum* folliculitis and ketoconazole. *Br J Dermatol* 1982; **107**: 691–5.

3 Faergemann J. *Pityrosporum* infections. *J Am Acad Dermatol* 1994; **31**: S18–20.

4 Goodfield MJD, Saihan EM. Failure of isotretinoin therapy in *Pityrosporum* folliculitis. *J Am Acad Dermatol* 1988; **18**: 143.

5 Daneshpazhooh M, Ehsani A, Toosi S *et al.* Isotretinoin in acne agminata. *Saudi Med J* 2007; **28**: 1600–2.

6 Uesugi Y, Aiuba S, Usuba M, Tagami H. Oral prednisolone in the treatment of acne agminata. *Br J Dermatol* 1996; **134**: 1098–100.

7 Georgousas K, Kocsard E. Micropapular sarcoidal facial eruption in a child. Gianotti-type perioral dermatitis. *Acta Derm Venereol (Stockh)* 1978; **58**: 433–6.

8 Schlappner OLA, Shelley WB, Ruberg RL, Dudrick SJ. Acute papulopustular acne, associated with prolonged intravenous hyperalimentation. *JAMA* 1972; **219**: 877–80.
9 Kossard S, Collins A, McCrossin I. Necrotizing lymphocytic folliculitis: the early lesion of acne necrotica (varioliformis). *J Am Acad Dermatol* 1987; **16**: 1007–14.
10 Maibach HI. Acne necroticans (varioliformis) versus *Propionibacterium acnes* folliculitis. *J Am Acad Dermatol* 1989; **21**: 323.
11 Conte MS, Lawrence JE. Pseudofolliculitis barbae. No 'pseudo-problem'. *JAMA* 1979; **241**: 53–4.
12 Dinehart SC, Tanner L, Mallory SB *et al.* Acne keloidalis in women. *Cutis* 1989; **44**: 250–2.

Treatment

General principles of acne treatment

Acne management aims to alleviate symptoms, clear existing lesions, limit disease activity so preventing new lesions and scars developing, and avoid negative impact on quality of life. Successful management of acne is dependent on detailed patient discussion and education, and should include a comprehensive assessment including personal and family history, a record of present and previous therapies and response to these treatments, careful physical examination and psychosocial review. Selection of treatment must take into consideration a strategy that the patient can adhere to [1–3]. The cause of the acne should be discussed, as should the goals and expected outcome; patient expectation should also be discussed. Patient leaflets are a very valuable tool. Most cases of acne clear spontaneously as the patient matures through adolescence into adulthood; however, even mild cases can persist for 4–6 years and in severe cases the natural history could be in excess of 12 years. Patients should be reassured that there are treatments available that can significantly limit the disease duration, but should be informed that response is slow and resolution is directly linked to good adherence.

Outcome measures

The severity of clinical acne is assessed visually according to the extent of disease and number of lesions. There are a number of outcome measures that have been utilized in the literature but they can be divided in the main into grading or counting. The evaluation can be further divided into: (i) overall or 'global' assessment; (ii) separate evaluations of individual lesions, for example comedones, papules, pustules, nodules; and/or (iii) evaluation according to the predominant lesion type, that is inflammatory or non-inflammatory.

In the clinic environment, global grading is very useful when assessing. A grading scale similar to that shown in Figs 42.46–42.49 is recommended. Good lighting for examination is essential. The acne can be graded on a scale of 0 to 10 on the face, back and chest. Little practice is required to become reasonably proficient and produce consistent assessments from one time frame to another [4].

Lesion counts are essential for clinical trials but not practical for use in the day-to-day clinic [5]. Other important outcome measures that should be considered in assessment of therapy include patient satisfaction, speed of action and adherence to therapeutic regime, tolerability and adverse effects of therapy, evidence of scarring and impact or changes in quality of life measures.



Fig. 42.46 Mild acne.



Fig. 42.47 Mild to moderate acne.

Choice of therapy

This is largely determined by the severity and extent of the disease but should be tempered by a number of other factors including duration of disease, response to treatments, predisposition to



Fig. 42.48 Moderate acne.



Fig. 42.49 Severe acne.

scarring, post-inflammatory erythema and pigmentation, as well as patient preference and cost. By adopting this approach treatment can be tailored to an individual patient [3].

Patients with mild acne usually receive topical therapy alone; patients with moderate acne receive oral and topical therapies; patients with more severe acne should be started on systemic antibiotic therapy but the need to commence oral isotretinoin should be considered early in the course of their disease and may well be used first line in those patients demonstrating poor prognostic factors which are associated with more severe disease, as outlined in Table 42.5 [6].

Table 42.5 Poor prognostic factors in acne.

Family history
Early onset:
mild facial comedones
early and more severe sebum production
early onset relative to menarche
Hyperseborrhoea
Site of acne:
truncal
Scarring
Persistent

Treatment selection should also be based on a logical understanding of the pathophysiology of acne and impact of therapies on these aetiological factors. A panel of experts with an interest in acne has put together an algorithm based on evidence, where available, and expert opinion in an attempt to improve outcomes in acne, as outlined in Table 42.6.

Topical acne therapies

No single topical agent is able to impact on all of the main aetiological factors implicated in acne pathogenesis and no one agent has a significant sebosuppressive effect (Table 42.7).

The most widely used topical drugs are benzoyl peroxide (BPO), retinoids, antibiotics and azelaic acid, either as monotherapy or in combinations [7–9]. Up until recent years it was suggested that topical retinoids should be limited to the treatment of comedonal lesions because of potential to aggravate inflammatory acne. It has now been shown that topical retinoids have some anti-inflammatory activity and also impact on the microcomedo, which represents the precursor of non-inflammatory and inflammatory lesions [1,7]. As a result of these findings, topical retinoids are now ideally combined with antimicrobials and should be considered in treating acne from the onset of acne management. Topical BPO, antibiotics or azelaic acid have predominantly anti-inflammatory activity in acne and can be used safely in combination with topical retinoids, with the exception of tretinoin which is inactivated if used simultaneously with BPO.

Topical retinoids

Retinoic acid (vitamin A acid) is available in 0.01 up to 0.05% concentrations as either a gel or a cream [10–14]. A newer formulation, the so-called microsponge or polymer formulation, is said to be less irritant than original formulations [11–13]. Isotretinoin 0.05% gel is a second-generation retinoid similar in efficacy to benzoyl peroxide [15] and topical tretinoin [16]. A third-generation retinoid, adapalene 0.1% cream or gel, has significant and rapid anti-inflammatory action and has a greater benefit/risk ratio than tretinoin [17–21]. In the USA and a few other countries, there

Table 42.6 Global Alliance algorithm for improving outcomes in acne. Adapted from Gollnick *et al*. [7].

	Mild		Moderate		Severe
	Comedonal	**Papular/pustular**	**Papular/pustular**	**Nodular†**	**Nodular/conglobate**
1st choice	Topical retinoid	Topical retinoid + topical antimicrobial	Oral antibiotic + topical retinoid ± BPO	Oral antibiotic + topical retinoid ± BPO	Oral isotretinoin‡
Alternatives*	Alt. topical retinoid or azelaic acid§ or salicylic acid	Alt. topical antimicrobial + alt. topical retinoid or azelaic acid§	Alt. oral antibiotic + alt. topical retinoid ± BPO	Oral isotretinoin or Alt. oral antibiotic + alt. topical retinoid ± BPO/azelaic§ acid	High-dose oral antibiotic + topical retinoid + BPO
Alternatives for females	See 1st choice	See 1st choice	Oral antiandrogen + topical retinoid/azelaic acid§ ± topical antimicrobial	Oral antiandrogen + topical retinoid ± oral antibiotic ± alt. antimicrobial	High-dose oral antiandrogen + topical retinoid ± alt. topical antimicrobial
Maintenance therapy	Topical retinoid	Topical retinoid ± BPO			

BPO, benzoyl peroxide; Alt., alternative.
* Consider physical removal of comedones.
† With small nodules (>0.5–1 cm).
‡ Second course in case of relapse.
§ There was not consensus on this alternative recommendation, however in some countries axelaic acid prescribing is appropriate practice.

Table 42.7 Topical preparations available for acne and their impact on pathogenesis.

Agent	Sebum production	Comedogenesis	Antimicrobial activity	Inflammation
Adapalene	✗	✓✓✓	✗	✓✓
All *trans*-retinoic-acid (tretinoin)	✗	✓✓✓	✗	✓
Azelaic acid	✗	✓	✓	✓
Benzoyl peroxide alone	✗	✓	✓✓✓	✓✓
Clindamycin	✗	✓	✓✓✓	✓✓✓
Erythromycin	✗	✓	✓✓✓	✓✓✓
Tetracycline	✗	✓	✓✓✓	✓✓
Nicotinamide	✗	✓	✓	✓

✗ = no effect; ✓ = slight/mild effect; ✓✓ = moderate effect; ✓✓✓ = high effect.

is a fourth-generation retinoid on prescription for acne called tazarotene [22,23].

Vitamin A acid and other retinoids reduce abnormal growth and development of keratinocytes within the pilosebaceous duct. The reversal of hypercornification within the follicular canal as well as the induction of the follicular epithelium helps to 'unplug' the follicle [24]. This also inhibits development of the microcomedo and non-inflamed lesions resulting in less-anaerobic conditions with fewer *P. acnes*, making the microenvironment less favourable for the development of inflammation. In addition, some of the novel retinoids reduce rupture of the comedones into surrounding skin which results in less inflammation [9,25,26]. Tretinoin binds to cytosolic retinoid acid-binding protein (RAR) with high affinity, but adapalene does not bind at all. Tretinoin has high affinity for all nuclear receptors, but adapalene has selective affinity for RAR-α and RAR-β [27]. Some of the actions are receptor modulated. Adapalene also has anti-inflammatory actions, notably against leukotriene [28]. *In vitro*, adapalene and tretinoin down-regulate TLR2 expression and function, which in turn influences the production of pro-inflammatory cytokines [29–33]. These studies concluded that 0.1% adapalene and 0.025% tretinoin are equally effective against total lesion count, with adapalene demonstrating greater activity at 1 week. Percentage reductions in non-inflammatory lesions reached up to 83% with both products at 12 weeks and inflammatory lesions were reduced by up to 70%. Higher concentrations of adapalene were more effective but associated with more irritancy and erythema. All current studies demonstrate that 0.1% adapalene causes less irritation than 0.025% tretinoin but that the rate of irritancy of both agents increases with higher concentrations. The active comedolytic and anti-inflammatory effects of topical retinoids supports their use in the treatment of mild acne and their activity on the microcomedo, recognized as the precursor to non-inflammatory and inflammatory lesions, suggests that they should also be used in moderate to severe acne along with topical and oral antimicrobial therapy. BPO inactivates tretinoin so the two agents should be alternated morning and evening and not used simultaneously. As local irritancy is a recognized adverse effect of all topical retinoids, they should be commenced at lower concentration and duration of application should be gradually increased as tolerated. Due to

potential photosensitivity, topical retinoids are ideally applied in the evening.

Few comparative data for retinoids against other agents are available; studies comparing tretinoin versus BPO are equivocal and confirm a similar side effect profile [34–37]. Isotretinoin 0.05% was less effective in reducing inflammatory and non-inflammatory lesions than 5% BPO and slower to resolve inflammatory lesions in one study [15]. A four-arm, randomized, controlled study of a novel retinoid/BPO combination product available in some countries comparing a once daily application of the combination product 0.1% adapalene plus 2.5% BPO, against 0.1% adapalene or 2.5% BPO as monotherapy or vehicle for inflammatory acne demonstrated that the combination product is superior with a success rate of 27.5% clear or nearly clear against 15.4% for BPO, 15.5% for adapalene and 9.9% for vehicle [37]. This suggests that adapalene 0.1% has similar efficacy to 2.5% BPO in inflammatory acne. Some formulations are available over-the-counter in a number of countries.

Benzoyl peroxide (BPO)

BPO is currently available in a number of different formulations and concentrations (2.5%, 5% and 10%) either alone or in combination with imidazole, hydroxyquinolone, glycolic acid, zinc lactate and in some countries adapalene 0.1% [38–42]. Some formulations are available over-the-counter. BPO is a powerful antimicrobial [40,43] and rapidly destroys both surface and ductal *P. acnes* and yeasts [43]. The lipophilic nature of BPO allows it to penetrate the pilosebaceous duct. Once applied to the skin it decomposes to release free oxygen radicals with potent bactericidal activity in the sebaceous follicles and anti-inflammatory action [32,43,44]. BPO has only mild comedolytic activity but has been shown in randomized controlled trials to reduce the number of non-inflamed lesions [15,34,45,46] by decreasing follicular hyperkeratosis [47]. It does not impact on sebum production [48,49].

Four randomized, controlled trials have examined different concentrations of BPO [34,50–53] and no evidence to date supports a dose–response effect but potential adverse effects, including irritancy and bleaching, are increased with the 10% concentration [34]. A number of randomized, controlled trials have examined BPO combination with antibiotics against the topical antibiotic (clindamycin, erythromycin, meclocycline and metronidazole) alone and found the combination preparations have superior activity to monotherapy against inflammatory and non-inflammatory lesions [53–56]. In studies in which BPO was used as the comparator monotherapy, results were equivocal with some studies suggesting better efficacy with combination treatments and others demonstrating no difference [53–55,57]. BPO combined with 3% erythromycin has greater activity against *P. acnes* and results in better efficacy than 3% erythromycin alone [58].

One randomized, controlled trial demonstrated similar efficacy with 5% BPO when compared to oral tetracycline and minocycline in mild to mild–moderate acne and found it to be extremely cost effective [45]. BPO washes 6–10% may offer a useful approach in patients also utilizing antibiotics for acne as they have the potential to act against fully sensitive bacteria and reduce antibiotic resistant strains of propionibacteria.

Topical antibiotics

Topical antibiotics used in the treatment of acne include clindamycin, erythromycin and tetracycline [59–64]. They are used in concentrations of 1–4%, usually in a cream or lotion base. Topical antibiotics have some effect on the non-inflamed lesions by reducing perifollicular lymphocytes which are involved in comedogenesis [1,9]. They also significantly reduce numbers and function of *P. acnes* [65–67]. Some topical antibiotics also have a direct anti-inflammatory action via an antioxidant effect on leukocytes [68].

A number of randomized, controlled trials have investigated these topical antibiotics against their vehicle [45,69–79]. Most studies used twice daily applications and most were statistically underpowered to conclusively determine differences between the active agent and their vehicle. However, in the larger randomized, controlled trials 55–60% reduction in mean inflammatory lesion count was demonstrated at 12 weeks with little impact on non-inflammatory lesions [32]. Topical clindamycin has been compared to topical erythromycin in mild to severe acne [80–84] with no overall consistent differences in clinical outcome. However, overall improvement in severity has been demonstrated with topical clindamycin when compared to topical tetracycline [85,86]. Combinations of erythromycin with zinc or benzoyl peroxide are superior to single therapies [63,64,87,88]. A randomized controlled trial comparing combination product clindamycin/BPO with zinc/BPO did not show any convincing clinical benefit of one product over another at 12 weeks [89].

Two systematic reviews examining acne management have identified comparative data on the use of oral versus topical antibiotics [32,90]. Other randomized controlled trials have studied the difference between the different routes of administration [57,91–93]. It is clear that oral antibiotics have a delayed onset of activity so shorter studies may bias the study in favour of the topical agent [94]. Many of these studies were underpowered and/or too short making it difficult to draw definitive conclusions. A detailed analysis of 144 clinical trials of topical antimicrobial therapy rejected over 50% because of poor trial design [95]. Adequate conclusions could not be drawn from the remaining data because of the different protocols, but BPO emerged as a successful treatment and was probably similar in effectiveness to topical erythromycin and clindamycin, with topical tetracycline being the least effective. The clinical benefit of topical 3% erythromycin can be improved by combining it with either zinc or 5% benzoyl peroxide [63,64,87,96–98].

One large, randomized, controlled trial in a community care setting showed that topical Benzamycin® and its components given separately (erythromycin and 5% benzoyl peroxide) were more effective than oral tetracycline and minocycline [45].

There has been an alarming increase in worldwide resistance of *P. acnes* to antibiotics [99–102]. There is evidence to show some correlation between *P. acnes* resistance and clinical improvement and with erythromycin clinical failure [45,100,103]. However, the association between colonization and antibiotic resistant strains is complex and it is important to recognize that even if some specific antibiotic resistant strain of *P. acnes* is reported microbiologically it does not necessarily mean that the acne will be clinically resistant to this antibiotic. If the concentration of the antibiotic at the relevant skin site is equal to or greater than the minimal inhibitory

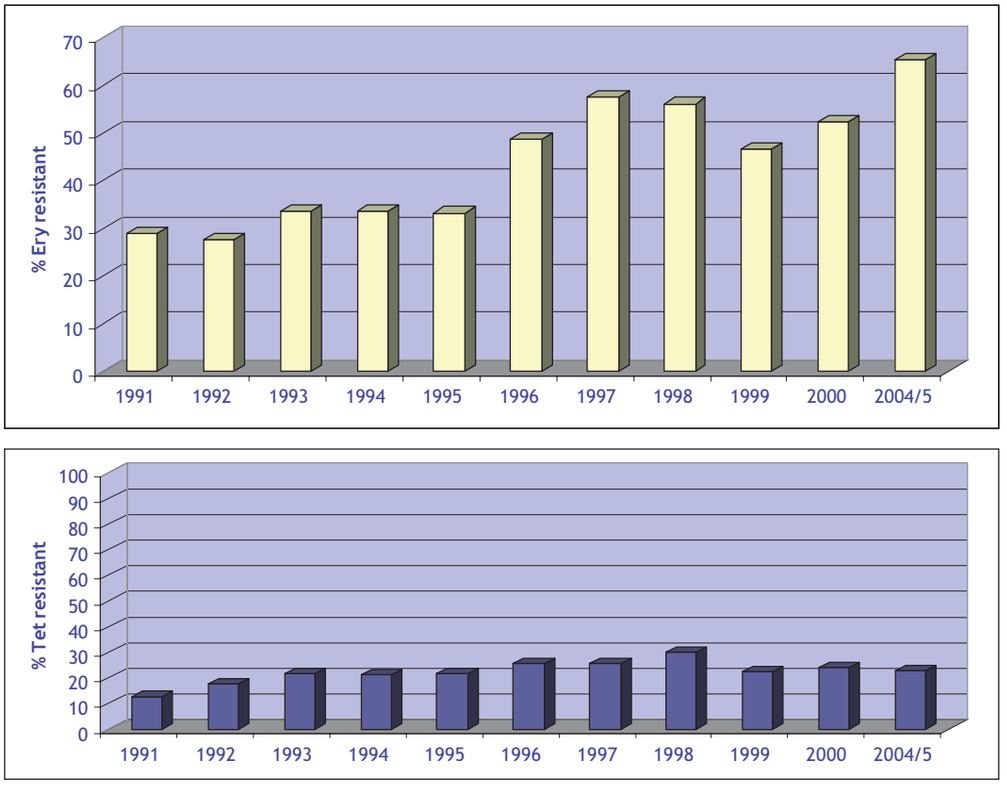


Fig. 42.50 Increase in the prevalence of erythromycin and tetracycline resistant *Propionibacterium acnes* in Leeds, UK. (Courtesy of Dr A. Eady and Dr J. Cove, Department of Microbiology, University of Leeds, UK.)

Table 42.8 Reasons to suspect possible resistance to oral and/or topical antibiotic therapy.

Reasons to suspect possible antibiotic-resistant *P. acnes*	Comments
Failure to respond to antibiotic therapy	Confirm good compliance
Deterioration in acne despite continuing antibiotic therapy	Patients often confirm initial good results
History of poor compliance	This will lend itself to resistance emerging
Multiple courses of oral and topical antibiotics	Particularly when used as monotherapy

Table 42.9 Strategies to avoid antibiotic resistant propionibacteria emerging. (Courtesy of Dr A. Eady, Department of Microbiology, Leeds University, UK.)

Strategy to avoid propionibacterial resistance emerging	Comments
Avoid inappropriate use of topical and systemic antibiotics	Use oral antibiotics for 3 months in the first instance and only continue if clinical improvement continues
If extending the duration of oral antibiotics utilize combination therapy	Combine with an agent that reduces the likelihood of promoting antibiotic propionibacterial resistance e.g. benzoyl peroxide
If repeated courses of antibiotics are required and the initial clinical response was favourable, re-use the same drug	This will avoid multiple resistant strains emerging
Avoid prescribing different oral and topical antibiotics concomitantly	This will avoid multiple resistant strains emerging
Consider using topical retinoids and non-antibiotic antimicrobials wherever possible	These do not promote resistant isolates and when used with antibiotics may achieve more rapid efficacy so reduce the duration of the antibiotic course
Topical benzoyl peroxide (BPO) can be used for 7 days between antibiotic courses	BPO is fully active against sensitive and resistant strains of *P. acnes* and able to eradicate resistant isolates
Remember to check medical adherence	Poor adherence to antibiotic therapies promotes resistance

concentration (MIC) of this *P. acnes* strain, the patient will be clinically responsive. In addition, many antibiotics with antiacne properties achieve efficacy via anti-inflammatory mechanisms of action [104], which can offset problems with antibiotic resistance.

A Health Technology Assessment conducted between 1998 and 2000 in general practice in the UK identified 18% of acne patients with tetracycline-resistant strains of *P. acnes*, 47% with erythromycin-resistant and 41% with clindamycin-resistant strains [45]. Up to 61% of patients referred to specialist acne clinics in Leeds, UK, had resistant *P. acnes* (Fig. 42.50). Resistance is most frequently seen to erythromycin and clindamycin. Resistance to more than one antibiotic is seen in 18% of patients. Table 42.8 outlines possible reasons to suspect resistance to antibiotic therapies. Antibiotic prescribing policies have been advocated in an attempt to control/reduce the levels of resistance (Table 42.9) [105,106].

A systematic review examined the results from clinical trials investigating the use of topical erythromycin and clindamycin for inflammatory acne to establish whether or not there has been a decrease in efficacy since their introduction in the mid 1970s. In 50 eligible trials identified, a gradual reduction in the efficacy of topical erythromycin was identified whilst the efficacy of clindamycin over the same time frame remained stable. The authors postulated that the reduced efficacy of erythromycin probably related to the development of antibiotic resistant propionibacteria [107]. Greater numbers of resistant *P. acnes* have been demonstrated on the skin of close contacts of acne patients using antibiotics compared with controls [108]. In addition clinicians working within the field of acne harbour significantly more resistant propionibacteria than clinicians working in an environment unrelated to acne. Given the fact that the resistance is due to a mutant gene [109], it is likely that *P. acnes* resistance is going to last for many years. BPO is fully active against sensitive and resistant strains of *P. acnes* and combining topical BPO with oral antibiotics or topical erythromycin results in less resistance both *in vitro* and *in vivo* [110].

Azelaic acid

Azaleic acid (1:2 heptanedicarboxylic acid) is available as a 20% cream for acne [111,112]. It is not sebosuppressive and has been reported to reduce the numbers and function of *P. acnes* [113,114], but recent studies have thrown doubt on this observation. Azelaic acid reduces comedones by normalizing the disturbed terminal differentiation of keratinocytes in the follicle infundibulum [115]. A direct anti-inflammatory effect has been demonstrated [116].

A number of randomized controlled trials have compared azelaic acid to placebo, vehicle, BPO, tretinoin and 2% erythromycin [117–121]. In mild to moderate papulopustular acne the studies would suggest that 20% azelaic acid has similar efficacy to 5% BPO, 0.05% tretinoin and 2% topical erythromycin at 5–6 months, with reductions in inflammatory lesions of up to 84%. In comedonal acne 20% azelaic acid had similar activity to 0.05% topical isotretinoin with approximately 80% reduction in comedonal lesion counts at 6 months [119]. Clinical experience with azelaic acid has not delivered the improvement suggested by the original clinical trials.

Topical nicotinamide

Topical nicotinamide 4% has anti-inflammatory actions and does not induce *P. acnes* resistance [122,123]. Double-blind studies have shown it to be better than the vehicle alone against inflamed lesions, although the improvement with the placebo was considerable (32–76%) [124]. A comparison of 4% nicotinamide gel demonstrated it to be similar in efficiency to 1% clindamycin gel [125].

Salicyclic acid

2% Salicylic acid has been shown to be more effective in reducing non-inflammatory and inflammatory acne lesions than alcoholic vehicle at 12 weeks in a randomized controlled trial [126,127].

Topical dapsone

Topical dapsone 5% gel has been shown in two placebo-controlled trials to improve acne severity better than vehicle in the magnitude of 40.8% success for the active preparation compared with 32.8% for vehicle [123,128,129]. Comparative studies against other active agents are required to assess the potential benefit of this novel preparation.

Other topical therapies for acne

The efficacy of other topical treatments has not been established by controlled studies.

- **Sulphur**: a long-standing antiacne therapy, which may be both comedogenic and comedolytic [130–132]. Sulphur is unpopular because of its smell, and is rarely used.
- **Resorcin**: the many formulations of resorcin appear to be totally ineffective [133].
- **Steroids**: a few topical preparations contain weak corticosteroids but proof of their efficacy is lacking. Potent steroids such as clobetasol propionate (Dermovate®) applied twice a day for 5 days can dramatically reduce the inflammation in an active inflammatory nodule [134].
- **Complementary therapies**: data have been published on the potential value of traditional 'herbal' medicines from the eastern hemisphere. So far the clinical benefits of certain plant alkaloids have not been established [135]. A recent systematic review of randomized clinical trials examining tea tree oil (TTO) in dermatological conditions, including acne, concluded there was no compelling evidence to demonstrate that TTO is efficacious in any dermatological conditions, however there were some promising data suggesting that TTO might be effective for acne and further investigation was advocated [136]. A further review examined the empirical evidence for the efficacy of complementary therapies in acne and concluded that many of the therapies were biologically plausible but in general poor methodology had been used in studies. The authors concluded that further rigorously conducted trials were required to define efficacy and adverse effect profiles of currently used complementary therapies for acne [137]. It is very important that all new treatments are validated for safety and efficacy against standard medicines before their release to patients.

Selecting topical therapy

Patients with mixed lesions should be prescribed therapy active against comedones, inflammatory lesions and microcomedones from the outset. Given the fact that the microcomedo is the precursor to inflammatory and non-inflammatory lesions, even patients with predominantly inflammatory acne should be prescribed a topical retinoid as part of their regimen [9]. Topical therapy should be prescribed alone for mild acne, in conjunction with appropriate oral acne therapy for moderate acne, and as maintenance therapy after oral therapy has stopped.

Topical therapy may be necessary for many years. It is also important to stress to the patient that topical therapy should be applied to all areas of skin within the active site and not just visible lesions as clinically normal looking skin in an acne-prone site is likely to have many evolving microcomedones. The concept of acne prevention must be stressed to the patient.

In conclusion, combined topical therapies should be used for patients with mild inflammatory acne. Topical retinoids have anti-inflammatory and comedolytic activity which makes them suitable for treatment of comedonal and mild to moderate inflammatory disease and they should therefore be used at the onset of treatment combined with topical or oral antimicrobials. Topical retinoids are also advocated in conjunction with oral antibiotics in patients with moderate and severe acne [1,9] and as maintenance treatment after cessation of systemic treatment [1,9]. Selecting therapies that work synergistically and impact on as many aetiological factors as possible will enhance treatment success. Products that combine preparations should in theory be more convenient for patients to use and so aid adherence [3].

References

1 Leyden JJ. Therapy for acne vulgaris. *N Engl J Med* 1997; **336**: 1156–62.
2 Cunliffe WJ, Clayden AD, Gould D *et al.* Acne vulgaris—its aetiology and treatment. A review. *Clin Exp Dermatol* 1981; **6**: 461–9.
3 Thiboutot D. New treatment and therapeutic strategies for acne. *Arch Fam Med* 2000; **9**: 179–87.
4 O'Brien SC, Lewis JB, Cunliffe WJ. The Leeds revised acne grading scale. *J Dermatolog Treat* 1998; **9**: 215–20.
5 Lucky AW, Barber BL, Girman CJ *et al.* A multirater validation study to assess the reliability of acne lesion counting. *J Am Acad Dermatol* 1996; **35**: 559–65.
6 Dreno B, Bettoli V, Ochsendorf F *et al.* An expert view on the treatment of acne with systemic antibiotics and/or oral isotretinoin in the light of the new European recommendations. *Eur J Dermatol* 2006; **15**: 565–71.
7 Gollnick H, Cunliffe WJ, Berson D *et al.* Management of acne. Report from a Global Alliance to Improve Outcomes in Acne. *J Am Acad Dermatol* 2003; **49** (Suppl.): S1–37.
8 Berson DS, Shalita AR. The treatment of acne: the role of the combination therapies. *J Am Acad Dermatol* 1995; **32**: 531–41.
9 Lyons RE. Comparative effectiveness of benzoyl peroxide and tretinoin in acne vulgaris. *Int J Dermatol* 1978; **17**: 246–51.
10 Christiansen JV, Gadborg E, Ludvigsen K *et al.* Topical vitamin A acid and systemic oxytetracycline in the treatment of acne vulgaris. *Dermatologica* 1974; **149**: 121–8.
11 Embil K, Nacht S. The microsponge delivery system (MDS): a topical delivery system with reduced irritancy incorporating multiple triggering mechanisms for the release of actives. *J Microencapsul* 1996; **13**: 575–88.
12 Lucky AW, Cullen SI, Funicella T *et al.* Double-blind multicentre comparison of two 0.025% tretinoin creams in patients with acne vulgaris. *J Am Acad Dermatol* 1998; **38**: S24–30.
13 Lucky A, Quigley JW. Comparative efficacy and safety of Avita 0.025% gel, a novel topical tretinoin preparation and Retin-A 0.025% gel: results from a multicentre, double-blind parallel study. *J Am Acad Dermatol* 1998; **38** (Suppl.): S17–23.
14 Chalker DK, Lesher JL, Smith JG *et al.* Efficacy of topical isotretinoin 0.05% gel in acne vulgaris: results of a multicenter, double-blind investigation. *J Am Acad Dermatol* 1987; **17**: 251–4.
15 Hughes BR, Norris JF, Cunliffe WJ. A double-blind evaluation of topical isotretinoin 0.05%, benzoyl peroxide gel 5% and placebo in patients with acne. *Clin Exp Dermatol* 1992; **17**: 165–8.
16 Elbaum DJ. Comparison of the stability of topical isotretinoin and topical tretinoin and their efficacy in acne. *J Am Acad Dermatol* 1988; **19**: 486–91.
17 Caron D, Sorba V, Kerrouche N, Clucas A. Split-face comparison of adapalene 0.1% gel and tretinoin 0.025% gel in acne patients. *J Am Acad Dermatol* 1997; **36**: S110–2.
18 Shalita A, Weiss JS, Chalker DK *et al.* A comparison of the efficacy and safety of adapalene gel 0.1% and tretinoin gel 0.025% in the treatment of acne vulgaris: a multicenter trial. *J Am Acad Dermatol* 1996; **34**: 482–5.
19 Ioannides D, Rigopoulos D, Katsambas A. Topical adapalene gel 0.1% vs isotretinoin gel 0.05% in the treatment of acne vulgaris: a randomized open-label clinical trial. *Br J Dermatol* 2002; **147**: 523–7.
20 Cunliffe WJ, Caputo R, Dreno B *et al.* Clinical efficacy and safety comparison of adapalene gel and tretinoin gel in the treatment of acne vulgaris: Europe and US multicentre trials. *J Am Acad Dermatol* 1997; **36**: S126–34.
21 Grosshans E, Marks R, Mascaro J. Evaluation of clinical efficacy and safety of adapalene 0.1% against tretinoin 0.025% gel in the treatment of acne vulgaris, with particular reference to the onset of action and impact on quality of life. *Br J Dermatol* 1998; **52** (Suppl.): 17–22.
22 Shalita AR, Chalker DK, Griffith RF *et al.* Tazarotene gel is safe and effective in the treatment of acne vulgaris: a multicentre double-blind randomised controlled study. *Cutis* 1999; **63**: 349–53.
23 Webster GF, Berson D, Stein LF *et al.* Efficacy and tolerability of once-daily tazarotene 0.0% gel vs once-daily 0.025% gel in the treatment of facial acne vulgaris: a randomised trial. *Cutis* 2001; **67**: 17–27.
24 Christophers E, Wolfe HH. Effect of vitamin A acid on skin: *in vivo* and *in vitro* studies. *Acta Derm Venereol (Stockh)* 1975; **74**: 42–53.
25 Leyden J, Shallita AR. Rational therapy for acne vulgaris: an update on topical treatment. *J Am Acad Dermatol* 1986; **15**: 907–15.
26 Bouclier M, Chatelus A, Ferracin J *et al.* Quantification of epidermal histological changes induced by topical retinoids and CD271 in the rhino mouse model using a standardized image analysis technique. *Skin Pharmacol* 1991; **4**: 65–73.
27 Charpentier B, Bernard JM, Eustache J *et al.* Synthesis structure function relationships and biological activities of ligands binding to retinoic acid subtypes. *J Med Chem* 1995; **38**: 4993–5006.
28 Hensby CN, Avey D, Bouclier M *et al.* The *in vivo* and *in vitro* anti-inflammatory activity of CD271, a new retinoid-like modulator of cell differentiation. *Skin Pharmacol* 1989; **3**: 160–2.
29 Liu PT, Krutzik SR, Kim J *et al.* Cutting edge: all-*trans* retinoic acid down regulates TLR2 expression and function. *J Immunol* 2005; **174**: 2467–70.
30 Tenaud I, Khamamari A, Dreno B. In vitro modulation of TLR-2, CD1d and IL-10 by adapalene on normal human skin and inflammatory lesions. *Exp Dermatol* 2007; **16**: 500–6.
31 Jones DA. The potential immunomodulatory effects of topical retinoids. *Dermatol Online J* 2005; **11**: 3.
32 Lehman HP, Andrecos JS, Robinson KA. *Management of Acne*. Evidence report/technology assessment no. 17. Agency for Healthcare Research and Quality, 2001.
33 Cunliffe WJ, Poncet M, Loesche C *et al.* A comparison of the efficacy and tolerability of adapalene 0.1% gel versus tretinoin 0.025% gel in patients with acne vulgaris: a meta-analysis of five randomised trials. *Br J Dermatol* 1998; **139** (Suppl. 52): 48–56.
34 Handojo I. The combined use of topical benzoyl peroxide and tretinoin in the treatment of of acne vulgaris. *Int J Dermatol* 1979; **18**: 489–96.
35 Lyons RE. Comparative effectiveness of benzoyl peroxide and tretinoin in acne vulgaris. *Int J Dermatol* 1978; **17**: 246–51.
36 Bucknall JH, Murdoch PN. Comparison of tretinoin solution and benzoyl peroxide lotion in the treatment of acne vulgaris. *Curr Med Res Opin* 1977; **5**: 266–8.
37 Thiboutot DM, Weis J, Bucko A *et al.* Adapalene-benzoyl peroxide, a fixed-dose combination for the treatment of acne vulgaris: results of a multicenter, randomized double-blind, controlled study. *J Am Acad Dermatol* 2007; **57**: 791–9.
38 Bossche HV, Comelissen F, van Cutsem J. Synergism of the antimicrobial agents miconazole and benzoyl peroxide. *Br J Dermatol* 1982; **107**: 343–8.
39 Mesquita-Cuimaraes J, Ramos S, Tavares MR *et al.* A double-blind clinical trial with a lotion containing 5% benzoyl peroxide and 2% miconazole in patients with acne vulgaris. *Clin Exp Dermatol* 1989; **14**: 357–60.
40 Cunliffe WJ, Holland KT. The effect of benzoyl peroxide on acne. *Acta Derm Venereol (Stockh)* 1981; **61**: 267–9.
41 Degreef H, Bussche CV. Double-blind evaluation of a miconazole–benzoyl peroxide combination for the topical treatmentof acne vulgaris. *Dermatologica* 1982; **164**: 201–8.
42 Sklar JL, Jacobson C, Rizer R, Gans EH. Evaluation of Triaz 10% gel and Benzamycin in acne vulgaris. *J Dermatolog Treat* 1996; **7**: 147–52.
43 Bojar RA, Cunliffe WJ, Holland KT. The short-term treatment of acne vulgaris with benzoyl peroxide: effects on the surface and follicular cutaneous microflora. *Br J Dermatol* 1995; **132**: 204–8.
44 Haider A, Shaw JC. Treatment of acne vulgaris. *JAMA* 2004; **292**: 726–35.

45 Ozolins M, Eady EA, Avery A *et al*. A cost-effectiveness rationale for the selection of antimicrobial therapy in acne: a randomized controlled trial. *Br J Dermatol* 2002; **147**: 13–8.

46 Hunt MJ, Barnetson RS. A comparative study of gluconolactone versus benzoyl peroxide in the treatment of acne. *Australas J Dermatol* 1992; **33**: 131–4.

47 Fulton JE, Farzad-Batshandeth A. Studies on the mechanism of action of topical benzoyl peroxide in acne vulgaris. *J Cut Path* 1974; **1**: 194–200.

48 Fanta D, Jurecka W. Autoradiographic investigation on benzoyl peroxide treated skin. *Acta Derm Venereol (Stockh)* 1978; **58**: 361–3.

49 Goldstein JA, Pochi PE. Failure of benzoyl peroxide to decrease sebaceous gland secretion in acne. *Dermatologica* 1981; **162**: 287–91.

50 Mills OH, Kligman AM, Pochi P, Comite H. Coparing 2.5%, 5% and 10% benzoyl peroxide on inflammatory acne vulgaris. *Int J Dermatol* 1986; **25**: 664–7.

51 Yong CC. Benzoyl peroxide gel therapy in acne in Singapore. *Int J Dermatol* 1979; **18**: 485–8.

52 Marsden J. Evidence that the method of use, dose and duration of treatment with benzoyl peroxide and tetracycline determines response of acne. *J R Soc Med* 1985; **78** (Suppl.10): 25–8.

53 Lookingbill DP, Chalker DK, Lind Holm JS *et al.* Treatment of acne with a combination clindamycin/benzoyl peroxide and vehicle gel; combined with results of two double blind investigations. *J Am Acad Dermatol* 1997; **37**: 590–5.

54 Chalker DK, Shalita A, Smith JG, Swann RW. A double-blind study of the effectiveness of a 3% erythromycin and 5% benzoyl peroxide combination in the treatment of acne vulgaris. *J Am Acad Dermatol* 1983; **9**: 933–6.

55 Tucker SB, Tausend R, Cochran R, Flannigan SA. Comparison of topical clindamycin phosphate, benzoyl peroxide and a combination of the two for treatment in acne vulgaris. *Br J Dermatol* 1984; **110**: 487–92.

56 Swinyer LJS, Barker MD, Swinyer TA, Mills OH Jr. A comparative study of benzoyl peroxide and clindamycin phosphate for treating acne vulgaris. *Br J Dermatol* 1988; **119**: 615–22.

57 Borglund E, Kristensen B, Larsson-Stymne B *et al*. Topical meclocycline sulfosalicylate, benzoyl peroxide, and a combination of the two in the treatment of acne vulgaris. *Acta Derm Venereol (Stockh)* 1991; **71**: 175–8.

58 Eady EA, Bojar RA, Jones CE *et al*. The effects of acne treatment with a combination of benzoyl peroxide and erythromycin on skin carriage of erythromycin-resistant propionibacteria. *Br J Dermatol* 1996; **134**: 107–13.

59 Dobson RL, Belknap BS. Topical erythromycin solution in acne: results of a multi-clinic trial. *J Am Acad Dermatol* 1980; **3**: 478–82.

60 Fulton JE, Pablo C. Topical antibacterial therapy for acne—study of the family of erythromycins. *Arch Dermatol* 1974; **110**: 83–6.

61 Gloor M, Kraft H, Franke M. Effectiveness of topically applied antibiotics on anaerobic bacteria in the pilosebaceous duct. *Dermatologica* 1984; **157**: 96–104.

62 Stoughton RB. Topical antibiotics for acne vulgaris. *Arch Dermatol* 1979; **115**: 486–9.

63 Feucht CL, Allen BS, Chalker DK *et al.* Topical erythromycin with zinc in acne. A double-blind controlled study. *J Am Acad Dermatol* 1980; **3**: 483–91.

64 Bojar RA, Eady EA, Jones CE *et al.* Inhibition of erythromycin-resistant propionibacteria on the skin of acne patients by topical erythromycin with and without zinc. *Br J Dermatol* 1994; **18**: 410–3.

65 Norris JF, Hughes BR, Basey AJ, Cunliffe WJ. A comparison of the effectiveness of topical tetracycline, benzoyl peroxide gel and oral oxytetracycline in the treatment of acne. *Clin Exp Dermatol* 1991; **16**: 31–3.

66 Bernstein JE, Shalita AR. Effects of topical erythromycin on aerobic and anaerobic surface flora. *Acta Derm Venereol (Stockh)* 1980; **60**: 537–8.

67 Cratton D, Raymond CP, Guertin-Larochelle S *et al*. Topical clindamycin versus systemic tetracycline in the treatment of acne. Results of a multiclinic trial. *J Am Acad Dermatol* 1982; **1**: 50–3.

68 Basak PY, Gultekin F, Kilinc I *et al.* The effect of benzoyl peroxide and benzoyl peroxide/erythromycin combination on the anti-oxidative defence system in papulo pustular acne. *Eur J Dermatol* 2002; **12**: 53–7.

69 Braathen LR. Topical clindamycin versus oral tetracycline and placebo in acne vulgaris. *Scand J Infect Dis* 1984; **16** (Suppl. 43): 71–5.

70 Gratton D, Raymond GP, Guertin-Larochelle S *et al.* Topical clindamycin versus systemic tetracycline in the treatment of acne. Results of a multiclinic trial. *J Am Acad Dermatol* 1982; **7**: 50–3.

71 Christian JL, Krueger GG. Clindamycin v placebo as adjunctive therapy in moderately severe acne. *Arch Dermatol* 1975; **111**: 997–1000.

72 Lucchina LC, Kollias N, Gillies R *et al.* Fluorescence photography in the evaluation of acne. *J Am Acad Dermatol* 1996; **35**: 58–63.

73 Tomsen RJ, Stranieri A, Knutson D, Strauss JS. Topical clindamycin treatment of acne. Clinical, surface lipid composition, and quantitative surface microbiology response. *Arch Dermatol* 1980; **116**: 1031–4.

74 Becker LE, Bergstresser PR, Whiting DA *et al.* Topical clindamycin therapy for acne vulgaris. A cooperative clinical study. *Arch Dermatol* 1981; **117**: 482–5.

75 Guin JD. Treatment of acne vulgaris with topical clindamycin phosphate: a double blind study. *Int J Dermatol* 1981; **20**: 286–8.

76 Kuhlman DS, Callen JP. A comparison of clindamycin phosphate 1 percent topical lotion and placebo in the treatment of acne vulgaris. *Cutis* 1986; **38**: 203–6.

77 Petersen MJ, Krusinski PA, Krueger GG. Evaluation of 1% clindamycin phosphate lotion in the treatment of acne. *Curr Ther Res* 1986; **40**: 232–8.

78 Ellis CN, Gammon WR, Stone DZ, Heezen-Wehner JL. A comparison of Cleocin T Solution, Cleocin T Gel, and placebo in the treatment of acne vulgaris. *Cutis* 1988; **42**: 245–7.

79 McKenzie MW, Beck DC, Popovich NG. Topical clindamycin formulations for the treatment of acne vulgaris. An evaluation. *Arch Dermatol* 1981; **117**: 630–4.

80 Strauss JS, Stranieri AM. Acne treatment with topical erythromycin and zinc; effect of *Propionibacterium acnes* and free fatty acid composition. *J Am Acad Dermatol* 1984; **11**: 86–9.

81 Henderson TA, Olson WH, Leach AD. A single blind, randomized comparison of erythromycin pledgets and clindamycin lotion in the treatment of mild-to-moderate facial acne vulgaris. *Adv Ther* 1995; **12**: 172–7.

82 Leyden JJ, Shalita AR, Saatjian GD, Sefton J. Erythromycin 2% gel in comparison with clindamycin phosphate 1% solution in acne vulgaris. *J Am Acad Dermatol* 1987; **16**: 822–7.

83 Mills OH, Berger RS, Kligman AM *et al*. A comparative study of Erycette (TM) v Cleocin-T (TM). *Adv Ther* 1992; **9**: 14–20.

84 Thomas DR, Raimer S, Smith EB. Comparison of topical erythromycin 1.5 percent solution versus topical clindamycin phosphate 1.0 percent solution in the treatment of acne vulgaris. *Cutis* 1982; **29**: 624–5.

85 Padilla RS, McCabe JM, Becker LE. Topical tetracycline hydrochloride v. topical clindamycin phosphate in the treatment of acne; a comparative study. *Int J Dermatol* 1981; **20**: 445–8.

86 Robledo AA, Lopez BE, del Pino GJ *et al.* Multicentric comparative study of the efficacy and tolerance of clindamycin phosphate 1% topical solution and tetracycline topical solution for the treatment of acne vulgaris. *Curr Ther Res Clin Exp* 1988; **43**: 23–6.

87 Leyden J, Kaidbey K, Levy SF. The combination formulation of clindamycin 1% plus benzoyl peroxide 5% vs three different formulations of topical clindamycin alone in the reduction of *Propionibacterium acnes*. An *in-vivo* comparative study. *Am J Clin Dermatol* 2001; **2**: 263–6.

88 Leyden JJ, Hickman JG, Jarratt MT *et al.* The efficacy and safety of a combination of benzoyl peroxide/clindamycin topical gel compared with benzoyl peroxide alone and a benzoyl peroxide/erythromycin combination. *J Cutan Med Surg* 2001; **5**: 37–42.

89 Langner A, Sheehan-Dare R, Layton A. A randomized single-blind comparison of topical clindamycin + benzoyl peroxide and adapalene in the treatment of mild to moderate facial acne vulgaris. *Br J Dermatol* 2007; **158**: 122–9.

90 Garner SE, Eady EA, Popescu C *et al*. Minocycline for acne vulgaris; efficacy and safety. In: Cochrane Collaboration. *Cochrane Library.* Issue 2. Oxford: Update Software, 2000.

91 Perez M, Aspiolea D, De Moragas JM. Comparative double-blind study of topical clindamycin phosphate and oral tetracycline in the treatment of acne. [Spanish]. *Met Cutan Ibero Lat Am* 1987; **15**: 173–7.

92 Stoughton RB, Cornell RC, Grange RW, Walter JF. Double-blind comparison of topical 1 percent clindamycin phosphate (Cleocin T) and oral tetracycline 500 mg/day in the treatment of acne vulgaris. *Cutis* 1980; **26**: 424–5.

93 Katsambas A, Towarky AA, Stratigos J. Topical clindamycin phosphate compared with oral tetracycline in the treatment of acne vulgaris. *Br J Dermatol* 1987; **116**: 387–91.

94 Garner SE, Williams H. *Acne Vulgaris Evidence Based Dermatology*. London: BMJ, 2003: 87–114.

95 Eady EA, Cope JH, Jones DN *et al.* Topical antibiotics for the treatment of acne: a critical evaluation of the literature on their clinical benefit and comparative efficacy. *J Dermatolog Treat* 1990; **1**: 215–26.

96 Habbema L, Koopmans B, Menke HE *et al.* A 4% erythromycin and zinc combination (Zineryt®) versus 2% erythromycin (Eryderm) in acne vulgaris: a randomized, double-blind comparative study. *Br J Dermatol* 1989; **121**: 497–502.

97 Schactner L, Pestana A, Kittles C. A clinical trial comparing the safety and efficacy of a topical erythromycin–zinc formulation with a topical clindamycin formulation. *J Am Acad Dermatol* 1990; **22**: 252–60.

98 Strauss JS, Stranieri AM. Acne treatment with topical erythromycin and zinc: effect on *Propionibacterium acnes* and free fatty acid composition. *J Am Acad Dermatol* 1984; **11**: 86–9.

99 Nishijima S, McGinley KH, Leyden JJ. Cutaneous microbiologic profiles of Japanese adults residing in the United States of America. *Nippon Hifuka Gakkai Zasshi* 1990; **100**: 175–83.

100 Eady EA, Cove JH, Holland KT, Cunliffe WJ. Erythromycin resistant propionibacteria in antibiotic treated acne patients: association with therapeutic failure. *Br J Dermatol* 1989; **121**: 51–7.

101 Eady EA, Jones CE, Gardner KJ *et al.* Tetracycline-resistant propionibacteria from acne patients are cross-resistant to doxycycline, but sensitive to minocycline. *Br J Dermatol* 1993; **128**: 556–60.

102 Dreno B, Legallou F, de Sainte Marie I, Richet H. Prevalence of erythromycin resistant propionibacteria and *Staphylococcus epidermidis* in acne patients in France. *J Invest Dermatol* 1997; **108**: 379.

103 Leyden JJ, McGinley KJ, Cavalieri S *et al. Propionibacterium acnes* resistance to antibiotics in acne patients. *J Am Acad Dermatol* 1983; **8**: 41–5.

104 Eady EA, Ingham E, Walters CE *et al.* Modulation of comedonal levels of interleukin-1 in acne patients treated with tetracyclines. *J Invest Dermatol* 1993; **101**: 86–91.

105 Coates P, Vyakrnam S, Eady EA *et al.* Prevalence of antibiotic resistant Propionibacteria on the skin of acne patients: a ten-year surveillance data and snapshot distribution and study. *Br J Dermatol* 2002; **146**: 840–8.

106 Eady EA. Bacterial resistance in acne. *Dermatology* 1998; **196**: 59–66.

107 Simonart T, Dramaix M. Treatment of acne with topical antibiotics: lessons from clinical studies. *Br J Dermatol* 2005; **153**: 395–403.

108 Miller Y, Eady EA, Vyakrnams S *et al.* One or two close contacts of antibiotic-treated acne patients carry resistant propionibacteria on their skin surface. *J Invest Dermatol* 1997; **108**: 379.

109 Ross JI, Eady EA, Ratyal AH *et al.* Resistance to erythromycin and clindamycin in cutaneous propionibacteria is associated with mutations in 23S rRNA. *Dermatology* 1998; **196**: 69–70.

110 Eady EA, Farmery MR, Ross JI *et al.* Effects of benzoyl peroxide and erythromycin alone and in combination against antibiotic-sensitive and -resistant skin bacteria from acne patients. *Br J Dermatol* 1994; **131**: 331–6.

111 Cunliffe WJ. The clinical efficacy of azelaic acid in the treatment of acne. *Rev Contemp Pharmacother* 1993; **4**: 433–9.

112 Cunliffe WJ. Azelaic acid—review of its role in acne. *J Dermatolog Treat* 1993; **4** (Suppl. 1): S12–8.

113 Holland KT, Bojar RA. Antimicrobial effects of azelaic acid. *J Dermatolog Treat* 1993; **4**: S8–11.

114 Leeming JP, Holland KT, Bojar RA. The *in vitro* antimicrobial effect of azelaic acid. *Br J Dermatol* 1986; **115**: 551–6.

115 Silva A, Gollnick H, Detmar M *et al.* Effects of azelaic acid on sebaceous gland, sebum excretion rate and keratinization pattern in human skin. *Acta Derm Venereol (Stockh)* 1989; **143**: 20–30.

116 Kurokawa I, Akamatsu H, Nishijima S *et al.* Clinical and bacteriologic evaluation of OPC-7251 in patients with acne; a double-blind group comparison study versus cream base. *J Am Acad Dermatol* 1991; **25**: 674–81.

117 Cavicchini S, Caputo R. Long-term treatment of acne with 20% azelaic acid cream. *Acta Derm Venereol (Stockh)* 1989: **143**: 40–4.

118 Cunliffe WJ, Holland KT. Clinical and laboratory studies on treatment with 20% azelaic acid cream for acne. *Acta Derm Venereol (Stockh)* 1989; **143** (Suppl.): 31–4.

119 Katsambas A, Graupe K, Stratigos J. Clinical studies of 20% azelaic acid cream in the treatment of acne vulgaris. Comparison with vehicle and topical tretinoin. *Acta Derm Venereol (Stockh) Suppl* 1989; **143**: 35–9.

120 Graupe K, Zaumseil RP. Skinoren—a new local therapeutic agent for the treatment of acne vulgaris. In: Macher E, Kolde G, Bröcker EB, eds. *Jahrbuch De Dermatologie.* Zülpich: Biermann, 1991: 159–69.

121 Graupe K, Cunliffe WJ, Gollnick HP, Zaumseil RP. Efficacy and safety of topical azelaic acid (20 percent cream): an overview of results from European clinical trials and experimental reports. *Cutis* 1996; **57** (Suppl.1): s20–35.

122 Verschoore M, Langner A, Wolska H *et al.* Efficacy and safety of CD271 alcoholic gels in the topical treatment of acne vulgaris. *Br J Dermatol* 1991; **124**: 368–71.

123 Bernstein JE, Lorincz AL. The effects of topical nicotinamide, tetracycline and dapsone and potassium iodide-induced inflammation. *J Invest Dermatol* 1988; **74**: 257–8.

124 Griffiths CEM. Nicotinamide 4% gel for the treatment of inflammatory acne vulgaris. *J Dermatolog Treat* 1995; **6** (Suppl. 1): 8–10.

125 Shalita AR, Smith JG, Parish LC *et al.* A double-blind comparison of topical nicotinamide with clindamycin gel for the treatment of inflammatory acne vulgaris. *Int J Dermatol* 1995; **34**: 34–7.

126 Shalita AR. Treatment of mild and moderate acne vulgaris with salicyclic acid in an alcohol-detergent vehicle. *Cutis* 1981; **28**: 556–8.

127 Eady EA, Burke BM, Pulling K *et al.* The benefit of 2% salicylic acid lotion in acne—a placebo controlled study. *J Dermatolog Treat* 1996; **7**: 93–6.

128 Draelos ZD, Carter E, Maloney JM *et al.* Two randomized studies demonstrate the efficacy and safety of dapsone gel, 5% for the treatment of acne. *J Am Acad Dermatol* 2007; **56**: 439e, 1–10.

129 Lucky AW, Maloney JM, Roberts J *et al.* Dapsone gel 5% for the treatment of acne vulgaris: safety and efficacy of long-term (1 year) treatment. *J Drugs Dermatol* 2007; **6**: 981–7.

130 Mills OH, Kligman AM. Is sulphur helpful or harmful in acne vulgaris? *Br J Dermatol* 1972; **86**: 620–7.

131 Strauss JS, Goldman PH, Nacht S *et al.* A re-examination of the potential comedogenicity of sulfur. *Arch Dermatol* 1978; **114**: 1340–2.

132 Mills OH, Kligman AM. Assay of comedolytic activity in acne patients. *Acta Derm Venereol (Stockh)* 1983; **63**: 68–71.

133 Mills OH, Kligman AM. Drugs that are ineffective in the treatment of acne vulgaris. *Br J Dermatol* 1983; **108**: 371–4.

134 MacDonald-Hull SM, Cunliffe WJ. The use of a corticosteroid cream for immediate reduction in the clinical signs of acne vulgaris. *Acta Derm Venereol (Stockh)* 1989; **69**: 452–3.

135 Higaki S, Nakamura M, Morohashi M *et al.* Anti-lipase activity of Kamkpo formulations, coptidis rhizoma and its alkaloids against *Propionibacterium acnes*. *J Dermatol* 1996; **23**: 310–4.

136 Ernst E, Huntley A. Tea tree oil: a systematic review of randomised trials. *Forsch Komplementarmed Klass Naturheikd* 2000; **7**: 17–20.

137 Magin PJ, Adams J, Pond CD *et al.* Topical and oral CAM in acne: a review of the empirical evidence and consideration of its context. *Complement Therapy Med* 2006; **14**: 62–76.

Oral therapy

Systemic therapy for the treatment of acne includes antibiotics, hormones, isotretinoin and, occasionally, steroids [1]. Other drugs such as dapsone [2], clofazimine and vitamin A acid (10–20 mg/day) [3] are occasionally used but evidence to support their effectiveness is limited. Oral zinc has also been advocated in acne management and is discussed later on in this section.

Oral antibiotics

Oral antibiotics are the most widely prescribed agents in acne and are indicated for severe acne, moderate facial acne not responding to topical therapies and/or extensive truncal acne.

Cyclines (tetracycline, oxytetracycline, doxycycline, lymecycline, minocycline) have excellent efficacy and are the antibiotics of choice [4–10]. The second generation cyclines may aid adherence and of these lymecycline and doxycycline should be used in preference to minocycline [11]. Macrolide (erythromycin, azithro-

mycin or clindamycin) prescribing for acne has increasingly fallen out of favour due to the emergence of antibiotic-resistant strains of *P. acnes* in line with extensive erythromycin usage in the past [11,12]. Erythromycin remains the preferred option in female patients who are, or might become, pregnant or are breastfeeding [13] and in children varying from 8 to 12 years (depending on national licences) when tetracylines are contraindicated due to potential musculoskeletal problems and discoloration of dentition.

Clindamycin is highly lipophilic and very effective in acne but adverse effects including diarrhoea seen in 5–20% of cases and potential pseudomembranous colitis from overgrowth of *Clostridium difficile* have rightly discouraged prescribers from using it [14,15].

Oral azithromycin has been reported to be effective for acne in four open and two investigator-blinded trials. Regimens have varied but intermittent dosing schedules have been advocated (250 mg three times a week) due to the long half-life of 68 h [16,17]. As azithromycin is commonly used to treat a variety of systemic infections its use should also be restricted and discouraged in acne. This philosophy should also apply to cephalosporins and fluoroquinolones although there are documented cases of acne that have improved with these agents [16]. Exceptions to this rule may include short-term use for extremely refractory disease and/or evidence of Gram-negative folliculitis where other agents are not acceptable.

Trimethoprim (400–600 mg/day) has similar efficacy to tetracycline [18] but does not have a licence for acne and is reserved as a third-line antibiotic for acne or for cases where there is proven resistance to other agents. It has been used successfully in cases that have become refractory to first or second-line antibiotics over time [19–21]. Trimethoprim may also be used in young patients in whom tetracyclines are contraindicated. However, as trimethoprim is used for treatment of some potentially serious cutaneous and systemic infections, such as those caused by CA-MRSA, it is advisable to limit use to selected cases [21].

Response to systemic antibiotics is variable. Young males with marked seborrhoea and truncal acne respond less well than females with purely facial acne [10]. Patients who require antibiotics should be given 1 g/day of tetracycline or where indicated erythromycin in divided doses [22]. There is no evidence to support the need for this to be four times a day. The major disadvantage of tetracycline is the prerequisite for it to be taken half an hour before food and not with milk to avoid reduced absorption [23]. Second-generation tetracyclines, doxycycline, lymecycline or minocycline, are less likely to be affected by food [24–26] and can be taken once daily, which may enhance patient adherence. The perception that they are more active as a result of their lipophilicity resulting in greater concentration within the pilosebaceous duct is not supported with good evidence. Table 42.10 outlines dosage regimens for systemic antibiotics recommended for the treatment of acne and considers potential adverse effects.

Many systematic reviews and publications have failed to find any evidence to suggest that there are any clinical benefits between any of the tetracycline antibiotics. In the Western world, minocycline is used very extensively. This may in part have resulted from claims that antibiotic-resistant *P. acnes* is less likely to emerge with minocycline use. However, with the increased use of minocycline there has been an increased trend of minocycline-resistant *P. acnes* emerging [27–30]. A Cochrane review published in 2003 found no evidence to suggest that minocycline should be prescribed in preference to other tetracyclines [31]. Other reviews have confirmed that minocycline should not be used as first-line therapy [32,33]. There are many studies examining the efficacy of individual antibiotics against placebo; however, the methodology and quality of these studies is poor and very few compare one active agent with another. A large randomized, controlled trial conducted in UK community practice demonstrated that oral minocycline and oral tetracycline were of similar efficacy to each other and comparable in terms of efficacy to topical BPO. Hence, given the cost and the increased side-effect profile of oral minocycline, minocycline should not be the first choice of oral antibiotic therapy in acne [34].

Table 42.10 Systemic antibiotics in the treatment of acne vulgaris: dosage and adverse effects.

Antibiotic tetracyclines	Dosage	Adverse effects
Oxytetracycline	500 mg twice daily half hour pre food and not with milk; makes adherence to medication problematic for some	Common: GI upset Rare: onycholysis, photosensitivity, benign intracranial hypertension
Lymecycline (not available in the USA)	300–600 mg daily	As oxytetracycline but tolerated better
Doxycycline	100–200 mg daily	As oxytetracycline Photosensitivity (dose dependent)
Minocycline	100–200 mg daily	Rare but serious: headaches and dizziness associated with benign intracranial hypertension, pigmentary changes, autoimmune hepatitis/LE-like syndrome
Erythromycin	500 mg twice daily	Common: GI upset, nausea, diarrhoea
Trimethoprim	200–300 mg twice daily	Maculopapular rash Rare: hepatic/renal toxicity/agranulocytosis

How long and what dose?

A number of publications have proposed how antibiotics should be administered to achieve optimal therapeutic response whilst avoiding antibiotic resistance [11]. Suggestions include restricting the duration of antibiotics, use of combination regimens from the onset of therapy to expedite response and reduce duration of antibiotic courses, utilization of benzoyl peroxide either to reduce the emergence or to treat antibiotic resistant strains of *P. acnes* and avoidance of using chemically dissimilar antibiotics and regular switching of antibiotics. The question of how long antibiotics should be given in acne has not been adequately researched

in randomized, controlled trials and recommendations made in publications are not backed by hard evidence. It has been stated that 3 weeks is required before any obvious improvement is noted [35,36] and that a minimum of 3 months extending to 6 months in conjunction with topical therapy is required to achieve maximum benefit [11,22]. However, one controlled study comparing five antimicrobial regimes for mild to moderate facial acne in the community suggested that maximum improvement was reached at 6 weeks with both oral antibiotics and topical BPO [34].

There is a paucity of randomized, controlled trials examining different dosages of antibiotics in acne. One non-randomized, controlled study confirmed that patients on oral erythromycin in combination with topical 5% BPO responded better on 1 g compared to 500 mg daily. The relapse rates within 1 year were also significantly lower in the high-dose group [22]. Further reports suggest that higher doses of tetracycline [37,38] and oxytetracycline [39] are more effective in recalcitrant and severe acne. In patients with non-responding disease, minocycline limited dose–response studies have shown that doubling the dose of minocycline to 200 mg/day is more effective than continuing on an average dose of 100 mg where acne has not responded [40]. Daily doses of doxycycline (100 mg), minocycline (100 mg) and lymecycline (408 mg) are said to be equally effective, provided *P. acnes* is not resistant to doxycycline and lymecycline [41–45].

Subtherapeutic doses of doxycycline have been reported as effective in the treatment of moderate acne via non-antimicrobial mechanisms of action [46].

A correlation between sebum excretion rate and degree of improvement was noted in a retrospective study examining 255 patients treated with oral oxytetracycline, erythromycin and minocycline. Interestingly, this correlation was not noted with trimethoprim. The higher the sebum extraction rate the less well the patients responded to their systemic therapy. The authors hypothesized that this may be related to dilution of the antibiotic within the intrafollicular duct and as a result of this suggested that when the sebum excretion rate was greater than 2.5 $\mu g/cm^2$ a higher daily dosage of antibiotics might be required (lymecycline 600 mg, doxycycline and minocycline 200 mg) [47]. When prescribing higher doses of antibiotics patients and physicians should be wary about increased adverse effects [11].

Mechanisms of action

There are several potential mechanisms of action for oral antibiotics; as well as their antibacterial activity, they have anti-inflammatory effects [48–53]. Tetracycline and erythromycin are bacteriostatic, especially in larger doses. In smaller doses oral antibiotics do not reduce the number of organisms, but they do affect their function. The magnitude of reduction of *P. acnes* achieved by oral antibiotics does not correlate well with clinical efficacy [54]. Support for the important role of antibacterial therapy in the management of acne includes the fact that *P. acnes* is integral to the mediation of inflammation in acne, successful treatment with antibiotics is associated with significant reductions in *P. acnes* and colonization of the skin with antibiotic-resistant strains of *P. acnes* is associated with reduced clinical efficacy. Antibiotics can also inhibit various enzyme activities and modulate chemotaxis, lymphocyte function and pro-inflammatory cytokines, in particular TNF-α, IL-1 and IL-6 expression [51–53].

Combining oral antibiotics with topical preparations

Oral antibiotics should not be used as monotherapy in acne and should always be combined with topical agents. Combining BPO with antibiotics results in superior efficacy, this may be in part due to the relative lack of activity when used as monotherapy against non-inflammatory lesions. There is also evidence that such combinations prevent, reduce or eliminate bacterial resistance and can achieve significant clinical improvement in patients already colonized with antibiotic resistant strains of *P. acnes*. Intermittent usage of BPO during extended courses of antibiotics is recommended to eliminate resistant strains [11,55]. Topical retinoids may also be safely combined with antibiotics and are likely to enhance efficacy by acting on the microcomedo and non-inflammatory lesions [55,56]. The use of oral and topical antibiotics does not proffer any benefit and may select for resistant strains if chemically dissimilar preparations are used.

References

1 Stern RS. Acne therapy: medication use and sources of care in office-based practice. *Arch Dermatol* 1996; **132**: 776–80.
2 Ross CM. The treatment of acne vulgaris with dapsone. *Br J Dermatol* 1961; **73**: 367–70.
3 Plewig G, Schill WB, Hofmann C. Orale Behandlung mit Tretinoin, androlgisone, trichologisone, opthalmologisone Befunde und Therapieergeb-nisse bei Akne. *Arch Dermatol Res* 1979; **265**: 37–47.
4 Lane P, Williamson D. Treatment of acne vulgaris with tetracycline hydrochloride; a double-blind trial with 51 patients. *BMJ* 1969; **ii**: 76–9.
5 Olsen TC. Therapy of acne. *Med Clin North Am* 1982; **66**: 851–71.
6 Witowski JA, Simons HM. Objective evaluation of demethylchlorotetracycline hydrochloride in the treatment of acne. *JAMA* 1966; **196**: 397–400.
7 Olafsson JH, Gudgeirsson J, Eggertsdottir GE, Kristjansson F. Doxycycline versus minocycline in the treatment of acne vulgaris: a double-blind study. *J Dermatolog Treat* 1989; **1**: 15–7.
8 Thiboutot D. New treatments and therapeutic strategies for acne. *Arch Fam Med* 2000; **9**: 179–87.
9 Leyden JJ. Therapy for acne vulgaris. *N Engl J Med* 1997; **336**: 1156–62.
10 Thiboutot D. Acne: an overview of clinical research findings. *Dermatol Clin* 1997; **15**: 97–109.
11 Dreno B, Bettoli V, Ochsendorf F *et al*. European recommendations on the use of oral antibiotics for acne. *Eur J Dermatol* 2004; **14**: 391–9.
12 Fernandez-Obregon AC. Azithromycin for the treatment of acne. *Int J Dermatol* 2000; **39**: 45–50.
13 Cunliffe WJ, Clayden AD, Gould D *et al*. Acne vulgaris—its aetiology and treatment. A review. *Clin Exp Dermatol* 1981; **6**: 461–9.
14 Carraso DA, Vander Straten M, Tyring SK. A review of antibiotics in dermatology. *J Cut Med Surg* 2002; **6**: 128–50.
15 Lasson HE, Price AB. Pseudomembranous colitis: presence of clostridial toxin. *Lancet* 1977; **ii**: 1312–4.
16 Amin K, Riddle CC, Aires DJ *et al*. Common and alternative oral therapies for acne vulgaris: a review. *J Drugs Dermatol* 2007; **6**: 873–80.
17 Rafiei R, Yaghoobi R. Azithromycin versus tetracycline in the treatment of acne vulgaris. *J Drugs Dermatol* 2006; **17**: 217–21.
18 Gibson JR, Darley CR, Harvey SG *et al*. Oral trimethoprim versus oxytetracycline in the treatment of inflammatory acne vulgaris. *Br J Dermatol* 1982; **107**: 221–4.
19 Bottomley WW, Cunliffe WJ. Oral trimethoprim as a third-line antibiotic in the management of acne vulgaris. *Dermatology* 1993; **187**: 193–6.
20 Cunliffe WJ, Aldana OL, Goulden V. Oral trimethoprim: a relatively safe and successful third-line treatment for acne vulgaris. *Br J Dermatol* 1999; **141**: 757–8.
21 Bhambri S, Del Rosso JQ, Desai A. Oral trimethoprim in the treatment of acne vulgaris. *Cutis* 2007; **79**: 430–4.

22 Greenwood R, Burke B, Cunliffe WJ. Evaluation of a therapeutic strategy for the treatment of acne vulgaris with conventional therapy. *Br J Dermatol* 1986; **114**: 353–8.
23 Leyden JJ. Absorption of minocycline hydrochloride and tetracycline hydrochloride. *J Am Acad Dermatol* 1985; **12**: 308–12.
24 Chopra I, Hawkey P, Hinton M. Tetracyclines: molecular and clinical aspects. *J Antimicrob Chemoth* 1992; **29**: 245–77.
25 Meyer FP. Minocycline for acne. Food reduces minocycline's bioavailability. *BMJ* 1996; **312**: 1101.
26 Leyden JJ. Absorption of minocycline hydrochloride and tetracycline hydrochloride: effect of food, milk and iron. *J Am Acad Dermatol* 1985; **12**: 308–12.
27 Leyden JJ, Del Rosso JQ, Webster JF. Clinical consideration in the treatment of acne and other inflammatory skin disorders. *Cutis* 2007; **79**: 9–25.
28 Ross JI, Snelling AM, Eady EA *et al*. Phenotypic and genotypic characterizations of antibiotic-resistant *Propionibacterium acnes* isolated from acne patients attending dermatology clinics in Europe, the USA, Japan and Australia. *Br J Dermatol* 2001; **144**: 339–46.
29 Ross JI, Snelling AM, Carnegie E *et al*. Antibiotic resistant acne: lessons from Europe. *Br J Dermatol* 2003; **148**: 467–78.
30 Eady EA, Cove JH, Layton AM. Is antibiotic resistance clinically relevant? Implications of resistance for acne and prescribers. *Am J Dermatol* 2003; **4**: 813–31.
31 Garner SE, Eady EA, Popescu C *et al*. Minocycline for acne vulgaris: efficacy, safety. *Cochrane Database Syst Rev* 2003; **1**: CD002086.
32 Anon. Is minocycline overused in acne? *Drugs and Therapeutic Bulletin* 2006; **44**: 60–4.
33 McManus P, Iheanacho I. Don't use minocycline as first line oral antibiotic in acne. *BMJ* 2007; **334**: 154.
34 Ozolins M, Eady EA, Avery A *et al.* A cost-effectiveness rationale for the selection of antimicrobial therapy in acne: a randomized controlled trial. *Br J Dermatol* 2002; **147**: 13–8.
35 Smith JG Jr, Chalker DK, Wehr RF. The effectiveness of topical and oral tetracyclines for acne. *Southern Med J* 1976; **69**: 695–7.
36 Knaggs HE, Layton AM, Cunliffe WJ. The role of oral minocycline and erythromycin in tetracycline therapy-resistant acne—a retrospective study and a review. *J Dermatolog Treat* 1993; **4**: 53–6.
37 Baer RL, Leshaw SM, Shalita AR. High-dose tetracycline therapy in severe acne. *Arch Dermatol* 1976; **112**: 479–81.
38 Friedman Kein A, Shalita AR, Baer RL. Tetracycline therapy in acne vulgaris. *Arch Dermatol* 1972; **105**: 608.
39 Marsden J. Evidence that the method of use, dose and duration of treatment with benzoyl peroxide and tetracyclines determines response of acne. *J R Soc Med* 1985; **78** (Suppl. 110): 25–8.
40 Goulden V, Glass D, Cunliffe WJ. Safety of long term high dose minocycline in the treatment of acne. *Br J Dermatol* 1996; **134**: 693–5.
41 Harrison PV. A comparison of doxycycline and minocycline in the treatment of acne vulgaris. *Clin Exp Dermatol* 1988; **13**: 242–4.
42 Olafsson JH, Cudgeirsson J, Eggertsdottir CE *et al.* Doxycycline versus minocycline in the treatment of acne vulgaris: a double-blind study. *J Dermatolog Treat* 1989; **1**: 15–7.
43 Dubertret L, Alirezai M, Rostain G. The use of lymecycline in the treatment of moderate to severe acne vulgaris: a comparison of the efficacy and safety of two dosing regimes. *Eur J Dermatol* 2003; **13**: 44–8.
44 Bossuyt L, Bosschaert J, Richert B *et al.* Lymecycline in the treatment of acne: an efficacious, safe and cost-effective alternative to minocycline. *Eur J Dermatol* 2003; **13**: 130–5.
45 Eady EA, Jones CE, Gardner KJ *et al.* Tetracycline-resistant propionibacteria from the acne patients are cross-resistant to doxycycline but sensitive to minocycline. *Br J Dermatol* 1993; **128**: 556–60.
46 Skidmore R, Kovach R, Walker C *et al*. Effects of sub-antimicrobial dose doxycycline in the treatment of moderate acne. *Arch Dermatol* 2003; **139**: 459–64.
47 Layton AM, Hughes BR, Hull SM *et al*. Seborrhoea is an indication of poor response to systemic antibiotics. *Clin Exp Dermatol* 1992; **17**: 173–5.
48 Cunliffe WJ, Forster RA, Greenwood ND *et al.* Tetracycline and acne vulgaris: a clinical and laboratory investigation. *BMJ* 1973; **iv**: 332–5.
49 Cotterill JA, Cunliffe WJ, Williamson B. The effect of trimethoprim–sulphamethoxazole on sebum excretion rate and biochemistry in acne vulgaris. *Br J Dermatol* 1971; **85**: 130–3.
50 Hassing GS. Inhibition of *Corynebacterium acnes* lipase by tetracycline. *J Invest Dermatol* 1971; **56**: 189–92.
51 Webster GF, Leyden JJ, McGinley KJ *et al.* Suppression of polymorphonuclear leukocyte chemotactic factor production in *Propionibacterium acnes* by subminimal inhibitory concentrations of tetracycline, ampicillin, minocycline and erythromycin. *Antimicrob Agents Chemother* 1982; **21**: 770–7.
52 Akamatsu H, Asada M, Komura J *et al.* Effect of doxycycline on the generation of reactive oxygen species: a possible mechanism of action of acne therapy with doxycycline. *Acta Derm Venereol (Stockh)* 1992; **72**: 178–9.
53 Eady EA, Ingham E, Walters CE *et al.* Modulation of comedonal levels of interleukin-1 in acne patients treated with tetracyclines. *J Invest Dermatol* 1993; **101**: 86–91.
54 Leyden JJ, McGinley KJ, Mills OH *et al*. Propionibacterium levels in patients with and without acne vulgaris. *J Invest Dermatol* 1975; **65**: 382–4.
55 Gollnick H, Cunliffe WJ, Berson D *et al*. Management of acne. Report from a Global Alliance to Improve Outcomes in Acne. *J Am Acad Dermatol* 2003; **49** (Suppl.): S1–37.
56 Cunliffe WJ, Meynadier J, Alirezai M *et al*. Is combined oral and topical therapy better than oral therapy alone in patients with moderate to moderately severe acne vulgaris? A comparison of the efficiency and safety of lymecycline plus adapalene gel 0.1% against lymecycline plus gel vehicle. *J Am Acad Dermatol* 2003; **49** (3 Suppl.): S218–26.

Side effects of topical treatments and oral antibiotics

Topical agents. The most common side effect of topical acne products is a primary irritant dermatitis (Fig. 42.51) which often subsides with time and can be managed by reducing frequency of application, using emollients and if severe short-term application of a type I potency topical corticosteroid [1,2]. Some topical therapies have a comparatively lower irritant profile than others. Azelaic acid is relatively non-irritant [3], the novel topical retinoids are less irritant than some of the older established retinoids such as tretinoin and less likely to produce an early treatment flare [4–6]; and the newer formulations of tretinoin (microsponge or polymer based) are said to be less irritating than the early formulations [7–9]. Certain antibiotic/benzoyl peroxide combinations are less irritating than benzoyl peroxide alone [10], possibly explained by the anti-inflammatory action of the antibiotic. Allergic contact dermatitis has been reported with BPO but is rare with other



Fig. 42.51 A typical primary irritant dermatitis from topical anti-acne therapy.

topical agents. From animal studies and much clinical experience there is no evidence to support the claims that benzoyl peroxide and vitamin A acid induce skin carcinomas, and continued use of these two drugs is recommended [11,12]. Benzoyl peroxide bleaches clothes and hair and the patient must be informed of these inconvenient side effects.

Retinoids are associated with teratogenicity but significant absorption of topical retinoids has not been demonstrated [13,14]. In light of the potential hazard of systemic absorption, female patients using topical retinoids should be advised to avoid pregnancy and to discontinue therapy immediately if they do conceive whilst using a retinoid. Patients should also be advised that they will be more susceptible to photosensitivity when using topical retinoids.

Oral antibiotics. All oral antibiotics for acne can produce mild adverse effects but oral tetracycline and erythromycin are both relatively safe [15,16] (Table 42.11). Gastrointestinal effects, especially colic and diarrhoea, may occur in 5% of patients and are seen most commonly with erythromycin and doxycycline [17]. Vaginal candidiasis occurs in up to 6% of female patients.

Uncommon complications of oral tetracycline therapy include onycholysis (Fig. 42.52) [18], oesophagitis with ulceration [19], fixed drug eruptions [20] and photosensitivity (Fig. 42.53), including porphyria-like cutaneous changes [21]. Doxycycline causes a dose-dependent phototoxic rash in up to 3% of patients [22]; appropriate photoprotection should be recommended. Widespread drug eruptions are rare except with trimethoprim, where the incidence is 2.5% [23]. Tetracyclines (reported most commonly on minocycline) may rarely cause headaches as a result of benign intracranial hypertension [24–27]; these generally resolve quickly on drug withdrawal. This side effect is dose dependent and the patient should be carefully informed.

Caution should be adopted when prescribing tetracyclines in children due to the potential problems with permanent discoloration of the teeth.

Minocycline may result in pigmentary changes in the skin and mucosa. The time course of onset and time to resolve is variable although cumulative exposure may correlate with the changes [28]. Pigmentary changes may present in three forms: blue-grey pigmentation in sites of inflamed lesions and scars (acne and non-acne) (Figs 42.54 & 42.55); generalized dark-grey discoloration in

Table 42.11 Suppressive effects of oral drugs on sebum excretion rate at 3 months' treatment.

Drug	Suppression of sebum excretion rate (%)
Dianette®*	28
Dianette®* 50 mg CPA	42
Dianette®* 100 mg CPA	67
Trinordiol	20
Spironolactone 100 mg	35
Spironolactone 200 mg	70
Isotretinoin 0.5–1.0 mg/kg/day	92

CPA, cyproterone acetate.
* Dianette® is 35 μg ethinyl oestradiol 2 mg CPA.



Fig. 42.52 Photo-onycholysis due to doxycycline.



Fig. 42.53 A phototoxic reaction in a patient on doxycycline.

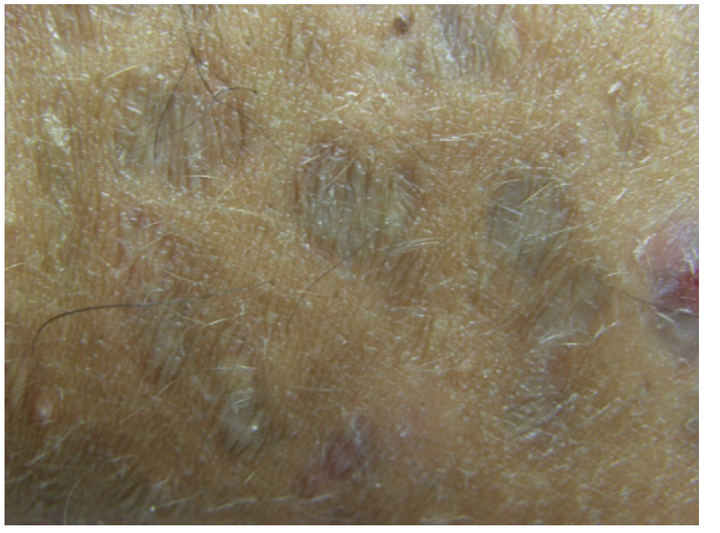


Fig. 42.54 Minocycline pigmentation in acne scars. (Courtesy of Dr V. Bettoli, University of Ferrara, Italy.)

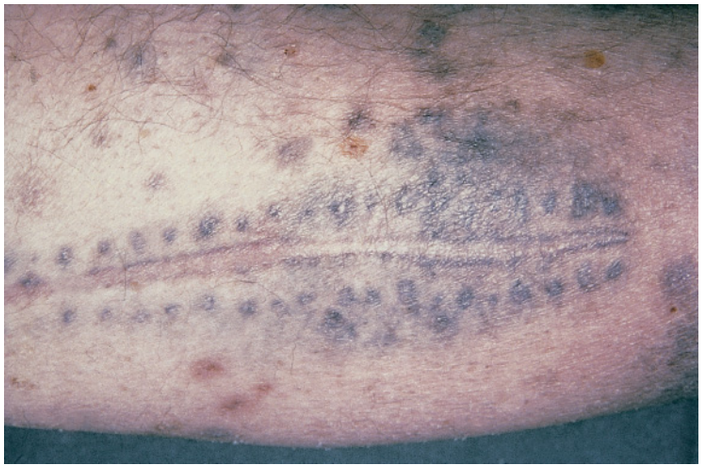


Fig. 42.55 Minocycline pigmentation in non-acne scars.



Fig. 42.56 Minocycline pigmentation in the sclera.

sites unrelated to acne; and pigmentary changes in sun-exposed sites [26,28–35]. The pigmentation is due to a melanin–drug complex and lasts for an average of 8–15 months post therapy. It lasts longer in older patients. If therapy is required, local lesions can be treated reasonably successfully with the Q-switched ruby laser [33]. The brown-grey pigmentation due to minocycline may also occur in the nails, oral mucous membranes [35] and sclera [36] (Fig. 42.56). At these sites, the pigmentation tends to last for longer than it does in the skin. When present in the mucous membranes, only a small percentage of affected patients are aware of its presence [37], particularly if the tongue is affected. Even more uncommon but quite dramatic is black breast milk due to minocycline therapy [38,39].

Minocycline has been used in a large number of acne patients worldwide. Reports of serious systemic minocycline-induced side effects have prompted much debate [40–44]. These serious side effects are all relatively uncommon. Drug hypersensitivity syndrome (DHS) has been reported within 3 months of treatment. This is characterized by fever, malaise, arthralgia and a diffuse exanthematous skin eruption. Systemic involvement may include pulmonary eosinophilia and hepatitis. DHS commonly occurs within 2–6 weeks of commencing the agent and repeat exposure to the causative drug may result in recurrence of DHS within a few days. Early recognition and withdrawal of the agent are mandatory. DHS has also rarely been reported with trimethoprim [45].

A lupus-like reaction has been reported with minocycline, this reaction occurs much later, usually at about 6–48 months of chronic treatment. These patients are usually female and present with fever, malaise and polyarthralgia. A cutaneous rash is not always evident but urticaria, vasculitis and non-specific erythema have all been reported. Some of these patients have concomitant liver disease, which may occur in the absence of joint symptoms. Serology for lupus is evident with a positive antinuclear antibody (ANA), along with positive perinuclear antineutrophilic cytoplasmic antibodies (pANCA), and raised C-reactive protein. Severely deranged hepatic enzymes are also a feature and rarely liver damage is devastating resulting in death or needing liver transplantation [46,47]. Positive antihistone antibodies are rarely identified. The lupus-like reaction is reversible if the drug is withdrawn but the abnormal serology may persist for many months. It is therefore advisable to avoid minocycline in patients with a personal or family history of systemic lupus erythematosus. Before embarking on long-term minocycline it is advisable to check hepatic function and ANA at baseline and to repeat hepatic function, ANA and pANCA every 3–6 months, regardless of whether the patient has signs or symptoms of this condition. Absolute certainty about potential cross-reactivity to tetracyclines is not evident; it is therefore advisable for a patient with any of these iatrogenic side effects to avoid all classes of tetracycline antibiotics.

Pseudomembranous colitis is an exceedingly rare consequence of oral antibiotic therapy, and was a particular problem with long-term oral clindamycin treatment, but oral clindamycin is rarely used in acne management.

Trimethoprim may produce some rare but serious adverse effects [48]. DHS has been discussed previously. Haematological reactions, including agranulocytosis, thromobocytopenia and pancytopenia, have all been reported and the risk of these developing correlates with the use of higher dose regimens and those with folic acid deficiency and/or megaloblastic haematopoiesis characterized with elevated mean corpuscular volume or hypersegmented neutrophils [48,49].

Toxic epidermal necrolysis and Stevens–Johnson syndrome have been reported in the first 2 months of treatment and are associated with significant morbidity and mortality [48].

The possible interaction between oral antibiotics and the contraceptive pill leading to contraceptive failure is reported as a small risk [50,51]. Although a recent review identified rifampicin as the only antibiotic implicated in this problem [52], it is important to discuss this with all sexually active females.

Should therapy be required in pregnancy, oral erythromycin is thought to be safe although there are no data available evaluating chronic use over prolonged periods in pregnancy [53]. The safest therapies in pregnancy are therefore topical benzoyl peroxide and/or topical erythromycin [52].

References

1 Olsen TE. Therapy of acne. *Med Clin North Am* 1982; **66**: 851–77.
2 Sykes NL, Webster GF. Acne: a review of optimum treatment. *Drugs* 1994; **48**: 59–70.
3 Graupe K, Cunliffe WJ, Gollnick HP *et al.* Efficacy and safety of topical azelaic acid. *Cutis* 1996; **57** (Suppl. 1): 20–35.
4 Shalita A, Weiss JS, Chalker DK *et al.* A comparison of the efficacy and safety of adapalene gel 0.1% and tretinoin gel 0.025% in the treatment of acne vulgaris. *J Am Acad Dermatol* 1996; **34**: 482–5.
5 Alirezai M, Meynadier J, Jablonski S *et al.* Étude comparative de l'efficacité de la tolérance des gels d'apalana à 0.1% et 0.03% et d'un gel de trétinoine à 0.025%. *Arch Dermatol Vénéréol* 1996; **123**: 165–70.
6 Shalita A, Weiss JS, Chalker DK *et al.* A comparison of the efficacy and safety of adapalene gel 0.1% and tretinoin gel 0.025% in the treatment of acne vulgaris: a multicenter trial. *J Am Acad Dermatol* 1996; **34**: 482–5.
7 Caron D, Sorba V, Kerrouche N, Clucas A. Split-face comparison of adapalene 0.1% gel and tretinoin 0.025% gel in acne patients. *J Am Acad Dermatol* 1997; **36**: S110–2.
8 Shalita AR, Chalker DK, Griffith RF *et al.* Tazarotene gel is safe and effective in the treatment of acne vulgaris: a multicentre double-blind randomised controlled study. *Cutis* 1999; **63**: 349–53.
9 Webster GF, Berson D, Stein LF *et al.* Efficacy and tolerability of once-daily tazarotene 0.0% gel vs once-daily 0.025% gel in the treatment of facial acne vulgaris: a randomised trial. *Cutis* 2001; **67**: 17–27.
10 Chu A, Huber FJ, Plott RT. The comparative efficacy of benzoyl peroxide, 5% erythromycin gel, 3% gel and erythromycin 4% zinc 1–2% solution in the treatment of acne vulgaris. *Br J Dermatol* 1997; **136**: 235–8.
11 Nelson KG, Slaga TJ. Effects of inhibitors of tumor promotion on 12-*O*tetra-decanoxylphorbol-13-acetate-induced keratin modification in mouse epidermis. *Carcinogenesis* 1982; **3**: 1311–5.
12 Zbinden G. Scientific opinion on the carcinogenic risk due to topical administration of benzoyl peroxide for the treatment of acne vulgaris. *Pharmacol Toxicol* 1988; **63**: 307–9.
13 Elbaum DJ. Comparison of the stability and safety of topical isotretinoin and topical tretinoin and their efficacy in acne. *J Am Acad Dermatol* 1988; **19**: 486–91.
14 Schaefer H. Penetration and percutaneous absorption of topical retinoids. A review. *Skin Pharmacol* 1993; **6**: 17–23.
15 Driscoll MS, Rothe MJ, Abrahamiam L *et al.* Long term oral antibiotics for acne: is laboratory monitoring necessary? *J Am Acad Dermatol* 1993; **28**: 595–602.
16 Cunliffe WJ, Clayden AD, Could D *et al.* Acne vulgaris—its aetiology and treatment. A review. *Clin Exp Dermatol* 1981; **6**: 461–9.
17 Tan AW, Tan HH. A review of antibiotic therapy. *Expert Opin Pharmacother* 2005; **6**: 409–18.
18 Frank SB, Cohen HJ, Minkin W. Photo-onycholysis due to tetracycline hydrochloride and doxycycline. *Arch Dermatol* 1971; **103**: 520–1.
19 Channer KS, Hollander D. Tetracycline-induced oesophageal ulceration. *BMJ* 1981; **282**: 1359–60.
20 Delaney TJ. Tetracycline-induced fixed drug eruptions. *Br J Dermatol* 1970; **83**: 357–8.
21 Epstein HH, Tuffanelli DL, Seibert JS *et al.* Porphyria-like cutaneous changes induced by tetracycline hydrochloride photosensitization. *Arch Dermatol* 1976; **112**: 661–6.
22 Layton AM, Cunliffe WJ. Phototoxic eruptions due to doxycycline—a dose related phenomenon. *Clin Exp Dermatol* 1993; **18**: 425–7.
23 Aldana OL, Goulden V. Oral trimethoprim: a relatively safe and successful third line treatment for acne vulgaris. *Br J Dermatol* 1999; **141**: 757–8.
24 Wright AL, Colver GB. Tetracyclines—how safe are they? *Clin Exp Dermatol* 1988; **13**: 57–61.
25 Meacock DJ, Hewer RL. Tetracycline and benign intracranial hypertension (Letter). *BMJ* 1981; **282**: 1240.
26 Goulden V, Glass D, Cunliffe WJ. Safety of long term high dose minocycline in the treatment of acne. *Br J Dermatol* 1996; **134**: 693–5.
27 Nagarajan L, Lam GC. Tetracycline induced benign intracranial hypertension. *J Paediatr Child Health* 2000; **36**: 82–3.
28 Del Rosso JQ. Systemic therapy for rosacea: focus on oral antibiotic therapy and safety. *Cutis* 2000; **66**: 7–13.
29 Okada N, Moriya K, Nishida K *et al.* Skin pigmentation associated with minocycline therapy. *Br J Dermatol* 1989; **121**: 247–54.
30 Huhg PH, Caldwell JB, James WD. Minocycline-induced hyperpigmentation. *J Fam Pract* 1995; **41**: 183–5.
31 Dwyer CM, Cuddihy AM, Kerr REI *et al.* Skin pigmentation due to minocycline treatment of facial dermatoses. *Br J Dermatol* 1993; **129**: 158–62.
32 Pepine M, Flowers FP, Ramos-Caro FA. Extensive cutaneous hyperpigmentation caused by minocycline. *J Am Acad Dermatol* 1993; **28**: 292–5.
33 Collins P, Cotterill JA. Minocycline-induced pigmentation resolves after treatment with the Q-switched ruby laser. *Br J Dermatol* 1996; **135**: 317–9.
34 Gordon G, Sparano BM, Iatropoulos MJ. Hyperpigmentation of the skin associated with minocycline therapy. *Arch Dermatol* 1985; **121**: 618–23.
35 Chu P, Van SL, Yen TSB, Berger TG. Minocycline hyperpigmentation localized to the lips: an unusual fixed drug reaction? *J Am Acad Dermatol* 1994; **30**: 802–3.
36 Sabroe RA, Archer CB, Harlow D *et al.* Minocycline induced discoloration of the sclera. *Br J Dermatol* 1996; **135**: 314–6.
37 Katz J, Barak S, Shemer J *et al.* Black tongue associated with minocycline therapy. *Arch Dermatol* 1995; **131**: 620.
38 Hunt MJ, Salisbury ELC, Grace J, Armati R. Black breast milk due to minocycline therapy. *Br J Dermatol* 1996; **134**: 943–4.
39 Basler RS, Lynch PJ. Black galactorrhea as a consequence of minocycline and phenothiazine therapy. *Arch Dermatol* 1985; **121**: 417–8.
40 Byrne PAC, Williams BD, Pritchard MH. Minocycline-related lupus. *Br J Rheumatol* 1994; **33**: 674–6.
41 Kaufmann D, Pichler W, Beer JH. Severe episode of high fever with rash, lymphadenopathy, neutropenia and eosinophilia after minocycline therapy for acne. *Arch Intern Med* 1994; **154**: 1983–4.
42 Gough A, Chapman S, Wagstaff K *et al.* Minocycline induced autoimmune hepatitis and systemic lupus erythematosus-like syndrome. *BMJ* 1996; **312**: 169–72.
43 Knowles SR, Shapiro L, Shear NH. Serious adverse reactions induced by minocycline. *Arch Dermatol* 1996; **132**: 934–9.
44 Seukeran D, Eady AE, Cunliffe WJ. Benefit–risk assessment of acne therapies. *Lancet* 1997; **349**: 1251.
45 Knowles SR, Shear SR. Cutaneous drug eruptions associated with systemic features. In: Wolverton SE, ed. *Comprehensive Dermatologic Drug Therapy*, 2nd edn. Philadelphia, PA: Saunders Elsevier, 2007: 977–81.
46 Pohle T, Menzel J, Domschke W. Minocycline and fulminant hepatic failure necessitating liver transplantation. *Am J Gastroenterol* 2000; **95**; 560–1.
47 Knowles SR, Shear SR. Cutaneous drug eruptions associated with systemic features. In: Wolverton SE, ed. *Comprehensive Dermatologic Drug Therapy*, 2nd edn. Philadelphia, PA: Saunders Elsevier, 2007: 982–3.
48 Bhambri S, Del Rosso JQ, Desai A. Oral trimethoprim-sulfamethoxazole in the treatment of acne vulgaris. *Cutis* 2007; **79**: 430–4.
49 Remlinger KA. Haematologic toxicity of drug therapy. In: Wolverton SE, ed. *Comprehensive Dermatologic Drug Therapy*, 2nd edn. Philadelphia, PA: Saunders Elsevier, 2007: 901–3.
50 Fleischer AB, Resnick SD. The effect of antibiotics on the efficacy of oral contraceptives. *Arch Dermatol* 1989; **125**: 1562–4.
51 Hughes BR, Cunliffe WJ. Interactions between the oral contraceptive pill and antibiotics. *Br J Dermatol* 1990; **122**: 717–8.
52 Rothman KF, Pochi PE. Use of oral and topical agents for acne in pregnancy. *J Am Acad Dermatol* 1988; **19**: 431–42.
53 Amin K, Riddle CC, Aires DJ *et al.* Common and alternative oral therapies for acne vulgaris: a review. *J Drugs Dermatol* 2007; **79**: 873–80.

Hormonal treatments

Various systemic hormone preparations are available for acne in female patients. These may be indicated when:

1 Standard antibiotic regimens have failed
2 Menstrual control and/or contraception are required alongside acne therapy
3 Oral isotretinoin is inappropriate or not available.

Topical therapy can and should be prescribed in conjunction with hormonal regimens. Table 42.11 outlines the relative sebosuppressive effects of systemic acne therapy.

Potential hormonal treatments for acne include inhibitors of androgen production by the ovary (oral contraceptives) or adrenal gland (low-dose corticosteroids), androgen receptor blockers, and antiandrogens that block the effect of androgens on the sebaceous gland.

Inhibitors of adrenal androgen production

Low-dose glucocorticoids are used most commonly to manage late-onset congenital adrenal hyperplasia, an inherent defect in the 11-hydroxylase or the 21-hydroxylase enzyme. Low-dose prednisolone 2.5–5 mg/day at bedtime is usually used. Dexamethasone may also be employed but the risk of adrenal suppression is greater with dexamethasone. Low-dose glucocorticosteroids (i.e. 2.5 mg prednisolone on waking and 5 mg on retiring) to suppress adrenal androgens, with or without a contraceptive pill, will reduce sebum production by up to 50% with a concomitant improvement in acne [1]. Cyclical oestrogen (30 μg) with medroxyprogesterone acetate (5 mg for 7 days) is also of benefit [2].

Inhibition of ovarian androgen production

Gonadotrophin releasing agonists block ovulation by interrupting cyclic release of LH and FSH from the pituitary. These products, such as leuprolide, nafarelin and buserelin, are available in nasal spray and injectable forms. However, as well as reducing ovarian androgen production, they will also block the ovarian production of oestrogens, potentially leading to reduced bone mass and menopausal symptoms. As a result, the potential benefit in acne is far outweighed by the potential adverse effects which negate their usage.

Oral contraceptives generally contain oestrogen (most commonly ethinyl oestradiol) and a progestin. Oestrogens act on the liver to increase synthesis of sex hormone binding globulin (SHBG), which binds testosterone and reduces the level of free circulating testosterone, hence all oral contraceptives will potentially improve acne. In addition, oral contraceptives suppress ovulation by inhibiting the production of ovarian androgens which results in reduced serum androgens and lower sebum production. The dosage of oestrogen in oral contraceptives has been reduced over the years and many third-generation combined contraceptives contain 20 μg of ethinyl oestradiol. Progestins in combined oral contraceptives include estranes and gonanes, which are derivatives of 19-nortestosterone, cyproterone acetate and drosperinone. The third-generation progestins (gestodene, desogestrel, norgestimate) are less selective for the androgen and more selective for the progesterone receptor. Drosperinone is a novel progestin derived from 17α-spironolactone and as with the parent compound has antimineralocorticoid and antiandrogenic activity, making it potentially helpful in acne. Yasmin® contains drospirenone 3 mg combined with ethinyl oestradiol 30 μg and Yaz® contains the same dose of drospirenone with 20 μg of ethinyl oestradiol.

The use of oral contraceptives as treatment for acne has been studied extensively. A Cochrane systematic review to determine the effectiveness of combined oral contraceptives (COCs) for the treatment of facial acne compared to placebo or other active therapies confirmed that COCs reduced acne lesion counts, severity grades and self-assessed acne compared to placebo. Limited data suggested that chlormadinone or cyproterone acetate (CPA) achieved better efficacy than levonogestrel, and a COC containing CPA may produce better outcomes than one containing desogestrel, although results from three studies were conflicting. Likewise one study showed slight superiority with levonorgestrel compared to desogestrel but this was not consistent with results from a second comparative study. Limited data were available comparing COCs with other therapies [3]. One company-supported comparative study [4] has shown that Yasmin® is similar to co-cyprindiol in its efficacy against acne.

Androgen receptor blockers

These include CPA, spironolactone and flutamide. Antiandrogens are a logical approach to the treatment of acne, as they suppress sebum production to an extent that depends on the drug and dose prescribed (Table 42.11) [5–9].

The antiandrogen CPA is licensed for acne in most European countries, but not in the USA. It directly inhibits the androgen receptor and serves as a progestogen in oral contraceptives. Co-cyprindiol (Dianette® and Estelle 35®) is an oral contraceptive that ameliorates acne [5–9]. It is as effective as oral tetracycline 1 g/day given over a 6-month period, although it is slower in action [10]. It is also of potential benefit in women with acne resistant to other therapies [7]. In males, 25 mg CPA has been used with success, but it reduces libido and produces gynaecomastia and possible azoospermia. In women, it has been suggested that the side effects of CPA 2 mg with ethinyl oestradiol (35 μg) oestrogen are different from those of conventional contraceptive pills that contain lower amounts of oestrogen. In particular, it has been suggested that there is a greater risk of deep venous thrombosis embolism (VTE) [11] and as a result current recommendation suggests that once the acne is brought under control co-cyprindiol formulations should be replaced by a combined oral contraceptive containing a lower dose of oestrogen. However, a recent article reviewing the evidence for efficacy and adverse effects with co-cyprindiol concluded that the risk of VTE was no greater than with third-generation combined oral contraceptives [12]. Co-cyprindiol reduces sebum production by no more than 30%; it is likely that it also acts by an additional mechanism, such as a direct effect on comedogenesis, which is also androgen-mediated [13]. The clinical efficacy of this combination can be enhanced by giving an extra 50 mg or 100 mg CPA from the fifth to 14th day of the cycle [14]. At this dosage, the reduction in sebum production is 50–67%.

Spironolactone is an effective treatment (it is not a contraceptive) and reduces sebum excretion by 30–75% depending on the dosage used. Its effects are dose dependent, and it is usually prescribed at a dose of 50–100 mg daily with meals, but many women with sporadic outbreaks do well with doses as low as 25 mg daily [15–18]. Although spironolactone is used in this context with clinical success there are a paucity of studies to confirm its effectiveness due to very small sample populations [19]. The main side effects are menstrual irregularity, breast tenderness, occasional fluid retention and, rarely, melasma. A question mark remains over its long-term use because of a theoretical increase in breast cancer, which has been shown in animal but not human studies [20]. Pregnancy should be avoided due to potential abnormalities to the male fetus and serum electrolytes should be monitored in

older females who might have other medical problems due to potential risk of hyperkalaemia. All hormonal regimens should be combined with appropriate topical therapies. Effective hormonal regimens seem to have a dual mechanism of action, suppressing gonadotrophin release and having an additional peripheral effect on the sebaceous gland [21]. A recent study, albeit small, confirmed efficacy and good tolerability in 27 women with severe papular and nodulocystic acne treated with a combination of ethinyl oestradiol 30 μg and drospirenone 3 mg as well as 100 mg spironolactone [22].

Flutamide is a potent antagonist of the androgen steroid. Although most commonly used in the treatments of prostatic conditions flutamide has been shown to be efficacious in a number of androgen-mediated problems, including acne, administered at a dose of 250 mg daily. Fatal hepatotoxicity has been reported and therefore use in acne is not generally advocated [23]. One single randomized, controlled trial showed significant reductions in acne score and hirsutism in 119 women with PCOS treated with three different doses of flutamide plus COC compared to placebo at 6 and 12 months [24]. There are a paucity of good studies comparing hormonal approaches to antibiotics and isotretinoin. Isotretinoin has been shown to be more effective than co-cyprindiol for acne patients [5]. One systematic review of this subject assessed mean weighted effects across different reported variables. Isotretinoin scored 85 ± 10% improvement compared with baseline, whereas tetracyclines and hormonal treatments were less effective, scoring 54 ± 3%, and CPA plus ethinyl oestradiol 65 ± 4% improvement compared with baseline levels [25]. There is concern about the potential reduction in efficacy of oral contraceptives as a result of systemic antibiotics used in conjunction with COCs. The risk is theoretical, based on the hypothesis that broad-spectrum antibiotics reduce bacterial flora in the gut and thus interfere with oestrogen absorption. Pharmacokinetic studies have demonstrated that serum levels of oestrogen are unaffected by tetracycline, doxycycline and others and there have been very few reports in the literature associating pregnancy with the combined use of COCs and antibiotics. The failure rate of COCs when used with tetracycline resulting in pregnancy is reported as 1.2–1.4 pregnancies per 100 woman-years of oral contraceptive use which is no greater than background failure rate of COCs. The only antibiotic which has been shown to reduce COC efficacy is rifampicin [26–29].

Hormonal therapy provides an excellent alternative for women whose acne is not responding to conventional therapy. Signs of hyperandrogenism require investigation and are an indication for hormonal treatment but it is clear that women with normal serum androgen levels also respond well to hormonal therapy. For female patients with intractable moderate or severe acne, and/or in whom antiandrogen therapy is not appropriate, isotretinoin is the treatment of choice.

References

1 Darley CR, Moore JW, Besser GM *et al.* Low dose prednisolone or oestrogen in the treatment of women with late onset or persistent acne vulgaris. *Br J Dermatol* 1983; **108**: 345–53.

2 Pochi PE, Strauss SS. Sebaceous gland suppression with ethinyl estradiol and diethylstilbestrol. *Arch Dermatol* 1973; **108**: 210–4.

3 Arowojolu AO, Gallo MF, Lopez LM *et al*. Combined oral contraceptive pills for the treatment of acne (Review). *Cochrane Database of Sytematic Review* 2007; **1**: CD004425.

4 van Vloten W, van Haselen CW, van Zuuren EJ. The effect of two combined oral contraceptives containing either drospirenone or cyproterone acetate on acne and seborrhoea. *Cutis* 2002; **69**: 1–15.

5 Greenwood R, Jones DH, Brummitt L. Comparison of isotretinoin and cyproterone acetate—a clinical and laboratory study. In: Cunliffe WJ, Miller AJ, eds. *Retinoid Therapy*. Lancaster: MTP Press, 1984: 287–92.

6 Greenwood R, Burke B, Brummitt L *et al.* Cyclic cyproterone/ethinyloestradiol for acne. *Lancet* 1983; **ii**: 796.

7 Hanstead B, Reymann F. Cyproterone acetate in the treatment of acne vulgaris in adult females. *Dermatologica* 1982; **164**: 117–26.

8 Miller JA, Wojnarowska FT, Dowd PM *et al.* Anti-androgen treatment in women with acne: a controlled trial. *Br J Dermatol* 1986; **114**: 705–16.

9 Mugglestone CJ, Rhodes EL. The treatment of acne with an anti-androgen/oestrogen combination. *Clin Exp Dermatol* 1982; **7**: 593–8.

10 Greenwood R, Brummitt L, Burne B *et al.* Acne: double-blind clinical and laboratory trial of tetracycline, oestrogen, cyproterone acetate and combined treatment. *BMJ* 1985; **291**: 1231–5.

11 Vasilakis-Scaramozza C, Jick H. Risk of venous thromboembolism with cyproterone contraceptives. *Lancet* 2001; **358**: 1427–9.

12 Franks S, Layton A, Glasier A. Cyproterone acetate/ethinyl estradiol for acne and hirsutism: time to revise prescribing policy. *Hum Reprod* 2008; **23**: 231–2.

13 Thiboutot DM, Knaggs H, Gilliland K, Hagari S. Activity of type I 5α-reductase is greater in the follicular infrainfundibulum compared with the epidermis. *Br J Dermatol* 1997; **136**: 166–71.

14 Hammerstein J, Cupceancu B. Behandlung des Hirsutismus mit Cyproteronacetat. *Dtsch Med Wochenschr* 1969; **94**: 829–34.

15 Muhlemann MF, Carter GD, Cream JJ *et al.* Oral spironolactone: an effective treatment for acne vulgaris in women. *Br J Dermatol* 1986; **115**: 227–32.

16 Goodfellow A, Alaghband-Zadeh J, Carter C *et al.* Oral spironolactone improves acne vulgaris and reduces sebum excretion. *Br J Dermatol* 1984; **111**: 209–14.

17 Lubbos H, Rose LI. Adverse effects of spironolactone therapy in women with acne. *Arch Dermatol* 1998; **134**: 1162–3.

18 Thiboutot D. Acne: hormonal concepts and therapy. *Clinics in Dermatol* 2004; **22**: 419–28.

19 Farquhar C, Lee O, Toomath R *et al.* Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne. *Cochrane Database of Systematic Reviews* 2003; **4**: CD000194.

20 Loube SD, Quirk RA. Breast cancer associated with administration of spironolactone. *Lancet* 1975; **i**: 1428–9.

21 Prelevic GM, Wurzburger MI, Balint-Peric L *et al.* Effects of a low-dose estrogen-antiandrogen combination on clinical signs of androgenisation, hormone profile and ovarian size in patients with polycystic ovary syndrome. *Gynecol Endocrinol* 1989; **3**: 269–80.

22 Krunic A, Ciurea A, Scheman A. Efficacy and tolerance of acne treated with both spironolactone and a compbined contraceptive containing dropirenone. *J Am Acad Dermatol* 2008; **58**: 60–2.

23 Wysowski D, Freiman J, Tourtelot J *et al.* Fatal and non-fatal hepatotoxicity associated with flutamide. *Ann Int Med* 1993; **118**: 860–4.

24 Calaf J, López E, Millet A, Alcañiz J *et al.* Long-term efficacy and tolerability of flutamide combined with oral contraception in moderate to severe hirsutism: a 12-month, double-blind, parallel clinical trial. *J Clin Endocrinol Metab* 2007; **92**: 3446–52.

25 Larsen TH, Jemec GB. Acne: comparing hormonal approaches to antibiotics and isotretinoin. *Expert Opin Pharmacother* 2003; **4**: 1097–103.

26 Archer J, Archer D. Oral contraceptive efficacy and antibiotic interaction: a myth debunked. *J Am Acad Dermatol* 2002; **46**: 917–23.

27 Weaver K, Glasier A Interaction between broad spectrum antibiotics and the combined oral contraceptive pill. A literature review. *Contraception* 1999; **59**: 71–8.

28 Helms SE, Bredle DL, Zajic J *et al*. Oral contraceptive failure rates and oral antibiotics. *J Am Acad Dermatol* 1997; **36**: 705–10.

29 London BM, Lookingbill DP. Frequency of pregnancy in acne patients taking oral antibiotics and oral contraceptives (Letter). *Arch Dermatol* 1994; **130**: 392–3.

Table 42.12 Reasons for poor response to treatment in acne.

Reason for poor response to therapy	Comments
Poor education of the doctor or patient	Understanding of how to use therapies is mandatory for successful treatment
Poor compliance to therapy	Steadily diminishing compliance may lead to relapse
Presence of relevant antibiotic resistant *P. acnes* in patient complying to therapy	Colonization with resistant isolates from the start results in poor response, subsequent colonization leads to relapse
Development of Gram-negative folliculitis	
Incorrect diagnosis	See section on differential diagnosis
Refractory subtypes of acne	See section on unusual cases
Intolerance to or side effects of treatment	See section on adverse effects
Inadequate dose of antibiotics	Patients of high body weight or marked seborrhoea may require a higher dose

Table 42.13 Factors implicated in affecting medical adherence to acne therapy.

	Improved adherence	Reduced adherence
Demographics of the patient	Older more mature patients Female gender Being married (vs. single)	Smoking Alcohol Unemployment
Patient preferences	Good doctor–patient relationship Shame, embarrassment Satisfaction with treatment	Psychosocial morbidity (anxiety and depression)
Characteristics of medication		
Systemic treatments	Oral isotretinoin (better than other systemics) Once daily formulations (better than divided doses)	Increasing costs (regardless of treatment type)
Topical treatments	Gel formulations Once daily formulations	

The patient with slow or failed response to treatment

There are several reasons why some acne patients show slow, minimal or no response to therapy as outlined in Table 42.12.

Poor medical compliance

Acne represents a chronic disease frequently requiring treatment over many years [1]. It is well recognized that chronic diseases *per se* are associated with poor compliance to treatments and acne is no exception [2]. Medication adherence is integral to therapeutic success as illustrated by a number of studies examining a variety of chronic diseases in which predictable and disappointing responses to treatment frequently resulted from poor adherence [3,4]. These same studies confirmed that adherence is influenced by many variables. One study in students with acne treated with over-the-counter benzoyl peroxide (BPO) demonstrated that compliance to treatment was only 48% despite implementing educational strategies to improve this outcome [5]. A further study confirmed that 44% of dermatological patients did not follow their prescription instructions [6]. In one study utilizing direct (pill count) and indirect (interview) methods, a 65% adherence rate was recorded [2]. As well as not taking therapy acne patients may miss appointments, as demonstrated in a study that determined 19% of patients did not return after their first visit and only 28% kept all four scheduled appointments. The likelihood of keeping appointments related to demographics, including age and race as well as financial aspects [7]. The frequency of medication has been shown to influence adherence such that an orally administered therapy once daily was adhered to in 87% of patients but only 39% of patients treated with a four-times daily regimen complied. In addition, the number of medications and costs of treatment can affect adherence [4]. Demographics have not been shown to be good indicators of medical adherence in many studies but one has linked poor adherence in acne subjects to young age, sex of the patient (females being more adherent than males), and marital status (single persons being less adherent than those that are married). Some social aspects were also linked to poor adherence in this study, including smoking, alcohol and unemployment [2]. Patient satisfaction with therapy as well as with the manner of the prescribing physician both strongly correlate with treatment adherence. Shame and embarrassment also link to better adherence, possibly as these motivate the patient to take their therapy [6]. Psychiatric morbidity correlates negatively with adherence and worse scores on the DQLI have been shown to be associated with poor adherence [2]. Degree of disability of disease in acne but not clinical rating can influence adherence to therapy [6,8]. It is important to recognize that patients with severe disease may not be as motivated to adhere to therapy as the prescribing clinician or parents would expect (Table 42.13) [9].

Education of patients and doctors is paramount to achieve good medical compliance. This should include explanation that acne is a chronic disease which responds slowly and requires a strategic approach to therapy. Utilization of simple therapies that take into account patient preferences and lifestyle are important issues to consider. Support over the treatment period is vital, particularly if patients have had disappointing results to treatment in the past. Assessment of treatments used and how patients have used them is important during the follow-up period. Impact of acne on quality of life and psychosocial morbidity should be routinely assessed as this may impact on adherence [10]. The patient–physician relationship is one of the most important factors influencing adherence in any chronic disease and acne is no exception. Clinicians should be adept in counselling patients regarding their condition and therapy and should provide realistic expectations with written educational material, medication reminders and information on available resources that might help to support the consultation and management of their patients [11].

Propionibacterium acnes resistance

Resistant isolates of *Propionibacterium acnes* to commonly used antibiotics can contribute to inadequate response to therapy in acne patients.

The outcome of antibiotic treatment for acne patients whose skin is colonized by *P. acnes* with reduced susceptibility to a

particular antibiotic depends on many factors, most of which act at the follicular level. Colonization of some follicles by resistant *P. acnes* is likely to produce a diminished response to treatment rather than complete failure, as it is unlikely that all follicles will harbour resistant organisms at any one time. However, it is likely that the more follicles that contain resistant organisms or acquire them during therapy the fewer will respond to treatment [12].

Clinical resistance will occur if the MIC of the resistant isolates of *P. acnes in vitro* exceeds the concentration of the antibiotic in the pilosebaceous duct. The concentration of ductal antibiotics varies considerably [13]. There are several factors that contribute to a less than optimal concentration of the drug in and around the pilosebaceous duct. Poor compliance will reduce drug availability, and a high sebum excretion is likely to dilute an effective drug concentration [14]. A low tissue drug concentration will encourage the acquisition of antibiotic resistant *P. acnes.* Tables 42.8 & 42.9 summarize possible factors that might indicate the presence of antibiotic-resistant *P. acnes* and strategies that might avoid resistance emerging.

Antibiotic-resistant isolates of *P. acnes* have now been identified in Europe, the USA, the Far East and Australasia [12,14–19]. In one UK study, resistance rose dramatically between 1990 and 1997 but has not increased significantly in subsequent years [12]. In 2003, the prevalence rates in a pan-European study [15] were lowest in Hungary (50.8%) and highest in Spain (93.6%). Resistance is seen to tetracycline and doxycycline in 20% of subjects in Europe and 30% in the USA. When present, tetracycline and doxycycline resistance is frequently associated with resistance to erythromycin and clindamycin [12]. One in two acne patients are colonized by strains resistant to erythromycin and clindamycin in European centres.

The incidence of erythromycin- and clindamycin-resistant *P. acnes* in non-antibiotic-treated close contacts is 50% and this may account for the apparent difficulty in treating some of our younger acne patients who have older siblings who have received antibiotic therapy for their acne. Colonization with tetracycline-resistant strains is rare in these contacts [19].

Isolates resistant to trimethoprim have been demonstrated in 12% of cases sampled and isolates resistant to more than one antibiotic are found in 24% of patients. Resistance to minocycline is said to be relatively uncommon [15]. However, there is now some doubt as to which minocycline MICs indicate clinical resistance and it is very likely that isolates of *P. acnes* from the USA which require 16 mg/L of minocycline to inhibit their growth *in vitro* [18] will not be inhibited *in vivo*, as this concentration far exceeds serum levels that can be achieved even using high-dose minocycline at 200 mg daily. It is well recognized that the correlation between microbiological resistance and clinical response is complex. However, there is clinical evidence to suggest that the presence of antibiotic-resistant *P. acnes* will correlate with poor clinical response to antibiotics in some patients. This was originally observed over 20 years ago by Leyden *et al.* who found that the mean MIC of the therapeutic antibiotic for propionibacteria obtained from acne patients receiving long-term therapy with tetracyclines or oral erythromycin exceeded the mean MIC for isolates from untreated patients and controls without acne. This same study confirmed that patients harbouring resistant strains had higher propionibacterial counts and responded less well than their counterparts with susceptible strains [20]. In 1989, one UK study showed that acne outpatients colonized with erythromycin-resistant propionibacteria were significantly less likely to respond adequately than those with fully susceptible strains [21]. A further study has demonstrated that acne patients colonized with tetracycline-resistant propionibacteria respond less well to both tetracycline and minocycline [22]. This suggests that combinations of antibiotics of dissimilar chemical groups should be avoided in an attempt to avoid promotion of multiple resistances.

Molecular studies have demonstrated that the resistance of *P. acnes* to erythromycin and clindamycin is due to a mutation [23]. The same is likely to be the situation with tetracycline [24]. This suggests that resistance will persist even after the selective pressure of any specific antibiotic has been removed and it is clear with mutational resistance that the harder the organisms are hit the more they will retaliate, resulting in higher and higher MICs.

Several studies have confirmed that the therapeutic use of antibiotics for acne drives resistance [16,22]. Hence, clinicians should adhere to treatment strategies that aim to prevent antibiotic resistance emerging and utilize therapies that reduce resistant organisms when present (Table 42.9).

High-dose antibiotics (such as minocycline 200 mg/day or trimethoprim 600 mg/day) have been shown to be successful in overcoming apparent resistance [25]. This may be due to the balance between the antimicrobial and anti-inflammatory activity. High-dose antibiotics will inevitably increase the drug concentration in the intrafollicular duct, where they may act as better antimicrobial agents, but in the dermis the higher dose may enhance the drug's anti-inflammatory action. Oral isotretinoin has also been shown to have a profound effect on *P. acnes* reducing numbers significantly, regardless of whether they are antibiotic sensitive or resistant [26,27].

Gram-negative folliculitis (GNF) can result as a consequence of any long-term topical or oral antibiotic therapy. It results from an overgrowth of Gram-negative organisms including *Klebsiella*, *Escherichia coli*, *Proteus*, *Serratia* or *Pseudomonas* organisms [28]. Clinically two forms of GNF have been described [29]. Type 1 may present with an acute flare of many pustules, predominantly around the nose and chin. Alternatively, an apparent deterioration of ordinary acne may occur and this is characterized by more painful, deep pustules and nodules, some of which may coalesce to form sinus tracts. *Proteus mirabilis* is frequently isolated from this second form. Bacterial swabs should be sampled from the skin and nose of these patients to identify the offending organism. The current antibiotic should be stopped. Alternative antibiotic treatment options include ampicillin 250 mg three times per day or oral trimethoprim 200–300 mg twice a day. However, systemic isotretinoin 0.5–1.0 mg/kg/day is the treatment of choice as relapse after antibiotic therapy is much more frequent.

Certain subtypes of acne are more frequently associated with clinical failure. As discussed above, some patients have specific types of comedones. Patients with sandpaper comedones respond poorly to the more standard antibiotic/topical retinoid therapy and frequently require oral isotretinoin (0.5 mg/kg/day for 4–6 months). Patients with macrocomedones (Fig. 42.57) require physical treatment with gentle cautery under a local anaesthetic (EMLA®) [30,31]. Ill-advised prescription of isotretinoin to patients

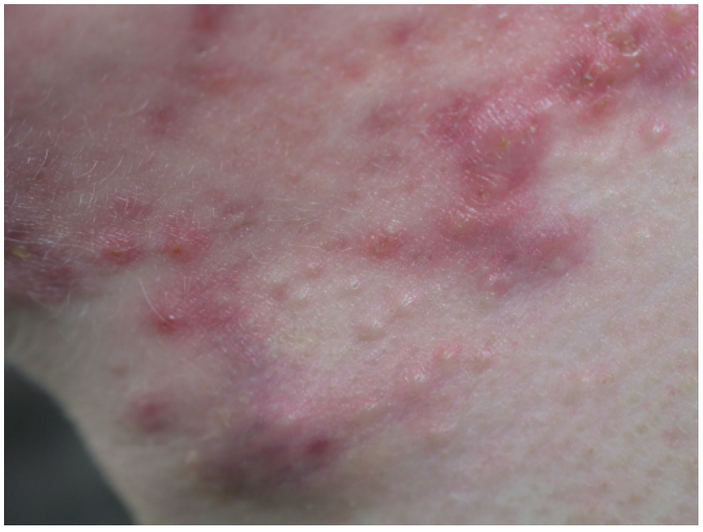


Fig. 42.57 Multiple macrocomedones: a frequent cause of persistent inflammatory acne. (Courtesy of Dr A. Yung, Auckland, New Zealand.)

with multiple macrocomedones may precipitate a bad flare of acne, which may produce significant scarring. This disease flare probably relates to the release of large quantities of inflammatory mediators due to death of *P. acnes* organisms within the duct system. Similar treatment with gentle cautery is also required for patients with submarine comedones, but in contrast to those patients with macrocomedones who respond very well to this physical treatment, only about 50% of patients with submarine comedones show a satisfactory response.

Patients with severe inflammatory acne, such as acne fulminans, acne conglobata and sinus tract disease, also respond badly to standard therapy. Most other non-responding patients will respond successfully to isotretinoin.

References

1 Balkrishnan R, Kulkarni AS, Cayce K *et al*. Predictors of healthcare outcomes and costs related to medication use in patients with acne in the United States. *Cutis* 2006; **77**: 251–5.

2 Zaghoul SS, Cunliffe WJ, Goodfield MJ. Objective assessment of compliance with treatments in acne. *Br J Dermatol* 2005; **152**(5): 1012–21.

3 McDonald HP, Garg AX, Haynes RB. Interventions to enhance patient adherence to medication prescriptions. *JAMA* 2002; **288**: 2868–79.

4 Lee IA, Maibach HI. Pharmionics in dermatology: review of topical medication adherence. *Am J Clin Dermatol* 2006; **7**: 231–6.

5 Flanders P, McNamara JR. Prediction of compliance with an over the counter acne medication. *J Psychol* 1984; **118**: 31–6.

6 Renzi C, Picardi A, Abeni D *et al*. Association of dissatisfaction with care and psychiatric morbidity with poor treatment compliance. *Arch Dermatol* 2002; **138**: 337–42.

7 McEvoy B, Nydegger R, Williams G. Factors related to compliance in the treatment of acne vulgaris. *Int J Dermatol* 2003; **42**: 274–80.

8 Mufleh L, Gonzalez M, Judodihardjo H *et al*. Compliance is high in patients taking oral isotretinoin for acne. *Br J Dermatol* 1999; **141** (Suppl. 55): 87.

9 Krowchuk DP, Stancin T, Keskinen R *et al*. The psychosocial effects of acne on adolescents. *Paed Dermatol* 1991; **8**: 108–15.

10 Oakley AMM. The acne disability index: usefulness confirmed. *Austral J Dermatol* 1996; **37**: 37–9.

11 Thiboutot D, Dreno B, Layton A *et al*. Acne counselling to improve adherence. *Cutis* 2008; **81**: 81–6.

12 Eady AE, Cove HJ, Layton AM. Is antibiotic resistance in cutaneous propionibacteria clinically relevant? *Am J Clin Dermatol* 2003; **4**: 813–31.

13 Gardner KJ, Cunliffe WJ, Eady EA *et al*. Variation in comedonal antibiotic concentrations following applications of topical tetracycline for acne vulgaris. *Br J Dermatol* 1994; **131**: 649–54.

14 Layton AM, Hughes BR, Hull SM *et al*. Seborrhoea is an indication of poor response to systemic antibiotics. *Clin Exp Dermatol* 1992; **17**: 173–5.

15 Coates P, Vyakrnam S, Eady EA *et al*. Prevalence of antibiotic resistant propionibacteria on the skin of acne patients: 10 year surveillance data and snapshot of distribution study. *Br J Dermatol* 2002; **146**: 840–8.

16 Ross JI, Snelling AM, Carnegie E *et al*. Antibiotic resistance: lessons from Europe. *Br J Dermatol* 2003; **148**: 467–78.

17 Eady EA, Gloor M, Leyden JJ. Propionibacterium acnes resistance; a worldwide problem. *Dermatology* 2003; **206**: 54–6.

18 Ross JI, Snelling AM, Eady EA *et al*. Phenotypic and genotypic characterization of antibiotic-resistant Propionibacterium acnes isolated from acne patients attending dermatology clinics in Europe, the USA, Japan and Australia. *Br J Dermatol* 2001; **144**: 339–46.

19 Miller Y, Eady EA, Vyakrnams S *et al*. One or two close contacts of antibiotic-treated acne patients carry resistant propionibacteria on their skin surface. *J Invest Dermatol* 1997; **108**: 379.

20 Leyden JJ, McGinley KJ, Cavalieri S *et al*. *Propionibacterium acnes* resistance to antibiotics in acne patients. *J Am Acad Dermatol* 1983; **8**: 41–5.

21 Eady EA, Cove JH, Holland KT *et al*. Erythromycin resistant propionibacteria in antibiotic treated acne patients: association with therapeutic failure. *Br J Dermatol* 1989; **121**: 51–7.

22 Ozolins M, Eady EA, Avery A *et al*. A cost-effectiveness rationale for the selection of antimicrobial therapy in acne: a randomized controlled trial. *Br J Dermatol* 2002; **147**: 13–8.

23 Ross JI, Eady EA, Cove JH *et al*. Clinical resistance to erythromycin and clindamycin in cutaneous propionibacteria isolated from acne patients in association with mutations in 23S rRNA. *Antimicrob Agents Chemother* 1997; **41**: 1162–5.

24 Ross JI, Eady EA, Cove JH *et al*. 16rRNA mutation associated with tetracycline resistance in a Gram-positive bacterium. *Antimicrob Agents Chemother* 1998; **32**: 1702–5.

25 Goulden V, Glass D, Cunliffe WJ. Safety of long term high dose minocycline in the treatment of acne. *Br J Dermatol* 1996; **134**: 693–5.

26 Coates P, Adams CA, Cunliffe WJ *et al*. Does oral isotretinoin prevent *Propionibacterium acnes* resistance? *Dermatology* 1997; **195** (Suppl. 1): 4–9.

27 Coates P, Vyakrnam S, Ravenscroft JC *et al*. Efficacy of oral isotretinoin in the control of skin and nasal colonization by antibiotic resistant propionibacteria in patients with acne. *Br J Dermatol* 2005; **153**: 1126–36.

28 Fulton JE, McGinley K, Leyden J. Gram negative folliculitis in acne. *Arch Dermatol* 1968; **98**: 349–53.

29 Leyden JJ, Marples RR, Mills OH *et al*. Gram negative folliculitis—a complication of antibiotic therapy in acne vulgaris. *Br J Dermatol* 1973; **88**: 533–8.

30 Pepall LM, Cosgrove MP, Cunliffe WJ. Ablation of whiteheads by cautery under topical anaesthesia. *Br J Dermatol* 1991; **125**: 256–9.

31 Bottomley WW, Yip J, Knaggs H, Cunliffe WJ. Treatment of closed comedones—comparisons of fulguration with topical tretinoin and electrocautery with fulguration. *Dermatology* 1993; **186**: 253–7.

Oral isotretinoin

Oral isotretinoin (13-*cis*-retinoic acid) is a synthetic vitamin A analogue which was first approved by the US Food and Drug Administration (FDA) in 1982 for the treatment of severe recalcitrant acne. Since this introduction, the management of acne has been revolutionized and, over two decades later, isotretinoin remains the most clinically effective antiacne therapy, producing long-term remission or significant improvement in many patients.

Mechanism of action

Isotretinoin is the only treatment that has an effect on all of the major aetiological factors involved in acne, by influencing

cell-cycle progression, cellular differentiation, cell survival and apoptosis [1–6]. It lowers sebum production significantly although the exact mechanism is poorly understood; it reduces comedogenesis as well as surface and ductal *P. acnes* and has anti-inflammatory properties.

Oral isotretinoin is the only oral retinoid known to have a profound effect on sebaceous gland activity. A dose of 0.5–1.0 mg/kg/day dramatically reduces sebum excretion by the order of 90% within 6 weeks. Unlike tretinoin (all-*trans* retinoic acid), isotretinoin has little or no ability to bind to cellular retinol-binding proteins or retinoic acid nuclear receptors (RARs and RXRs) but may act as a pro-drug that is converted intracellularly to metabolites that are agonists for RAR and RXR nuclear receptors [1–4].

Isotretinoin has at least five biologically important metabolites: 4-*oxo*-13-*cis*-retinoic acid (4-*oxo*-isotretinoin), all-*trans*-RA (tretinoin), all-*trans*-4-*oxo*-retinoic acid (4-*oxo*-tretinoin), 9-*cis*-retinoic acid and 4-*oxo*-9-*cis*-retinoic acid (see Fig. 42.12). Studies of SER in sufferers of severe acne have shown that, within 4 weeks, 4-*oxo*-isotretinoin (30–60 mg/day orally) produces a mean reduction of 70% of that achieved by 30–60 mg/day of oral isotretinoin and that isotretinoin is superior to either 9-*cis*-retinoic acid or all-*trans*-retinoic acid for suppression of sebum production and sebaceous gland activity [4,5].

In vitro studies of human sebocyte proliferation in cell culture, keratin 7 induction in pig sebocytes, HL-60 cell differentiation, the limb bud assay and the production of hypervitaminosis A in rats, have shown that isotretinoin and its three main metabolites, tretinoin, 4-*oxo*-isotretinoin and 4-*oxo*-tretinoin, have comparable but not identical activities. In the human sebocyte proliferation assay, all three isotretinoin metabolites inhibit sebocyte proliferation at slightly lower concentrations than isotretinoin. All three metabolites have similar activity in the limb bud assay, which defines teratogenic potential, and in the hypervitaminosis A assay, which predicts the overall side-effect potential. It is reasonable, therefore, to conclude that all three metabolites may contribute to the overall efficacy and safety, and side effects, of isotretinoin. These four compounds activate retinoid receptors RAR-α, RAR-β and RAR-γ in SZ 95 sebocytes, but only tretinoin and 4-*oxo*-tretinoin bind to RAR-γ, which is the receptor that is thought to be important in retinoid treatment of acne. Incubation of SZ 95 human sebocytes with isotretinoin led to significantly higher intracellular concentrations of tretinoin than isotretinoin [6]. The incubation with tretinoin generated very high intracellular concentrations of tretinoin and negligible concentrations of isotretinoin. These data suggest that tretinoin may be the active intracellular form of isotretinoin and prompted Tsukada *et al.* [6] to conclude that isotretinoin should be considered as a pro-drug. Differences in the plasma concentrations of these metabolites could therefore explain the differences in the intensity of the therapeutic response and the severity and/or occurrence of side effects in individual patients. Isotretinoin has been found to induce apoptosis in sebocytes and this effect is independent of RAR receptor activation [7], suggesting that it is sebaceous gland involution resulting from oral isotretinoin which leads to reduced sebum production.

Just how oral isotretinoin influences a significant reduction in comedogenesis by decreasing hyperkeratinization by 50% is uncertain [8–11]. However, research demonstrates that isotretinoin does not affect the metabolic activity of the keratinocytes [12].

Oral isotretinoin has no direct antimicrobial action, but by dramatically reducing SER and the size of the pilosebaceous duct it markedly alters the microenvironment within the duct. The result is a $\log_3$ reduction in *P. acnes*—a suppression much greater than that seen with oral and topical antibiotics. It has also been suggested that like all-*trans*-retinoic acid, isotretinoin might increase host defence mechanisms [13].

Oral isotretinoin also modifies monocyte chemotaxis, which in part explains the anti-inflammatory effects of the drug [14]. The significant reduction in the *P. acnes* population also contributes to the reduction in acne inflammation.

Clinical benefit of oral isotretinoin

Most patients who receive oral isotretinoin will be free of acne by the end of 4–6 months of treatment depending on the dose used. Recent clinical experience suggests that the long-term cure rate may be lower than was initially thought by dermatologists when isotretinoin became prescribable in the mid 1980s [15–20]. One explanation is that isotretinoin is being used to treat patients with less severe acne, who then have high expectations of a totally acne-free life, whereas the initial cohorts of patients had severe disease and were less concerned by the resurgence of a few spots. Furthermore, some of the early reported 'cures' may have been due to the fact that patients had eventually grown out of their acne as they may well have received initial treatments much later on in the course of their disease. There is evidence to suggest that younger patients relapse more readily than older ones [21]. Isotretinoin currently has a licence for treatment of severe acne unresponsive to other combination therapies including antibiotics used for acne (Figs 42.58–42.60) [9–15]. However, over the years



Fig. 42.58 A patient with severe acne before treatment with oral isotretinoin.



Fig. 42.59 The same patient at 3 months of treatment with isotretinoin.



Fig. 42.60 The same patient 3 years after treatment with isotretinoin.

isotretinoin has been used to treat other cases of acne with poor prognostic factors and a number of other clinical conditions with varying degrees of success, as outlined in Table 42.14.

A European directive on prescribing of isotretinoin has recently been introduced [22]. The aims of the directive are to ensure generic prescribing is harmonized and delivered appropriately throughout the European Union and to minimize the risk of adverse effects including pregnancy. Table 42.15 summarizes the recommendations. The regulatory authority in each country has approved a Pregnancy Prevention Programme (PPP). This programme includes advice on education, therapy management and control of distribution of the drug. Education suggests that both patients and prescribers must be fully aware of teratogenicity. The patient should acknowledge the problem by signing a consent form and should accept detailed counselling by the clinician prior to and during treatment. Therapy management includes medically supervised pregnancy testing before, during and 5 weeks after a course of therapy and provides advice on contraception. Distribution control suggests that only 30 days of oral isotretinoin can be supplied at one time to a female patient and the prescription will only be valid for 7 days.

The scope of the PPP suggests that it should include all females of childbearing potential. Clinicians can exercise clinical judgment if they establish that the patient is not currently sexually active, but it is mandatory that clinicians check carefully at each 4-week follow-up visit and record as well as act on any change in circumstance. Pregnancy testing is mandatory pre- and 5 weeks post-therapy. It has been suggested that the initial test can be done up to 2 weeks prior to the start of treatment providing contraception is used in those who require it. In addition, monthly pregnancy testing is recommended throughout the treatment period. The treatment should ideally start on day 3 of the menstrual cycle. The programme suggests that where possible patients should agree to at least one, and preferably two, complementary methods of effective contraception, including a barrier method, before therapy is

Table 42.14 Relative success of isotretinoin in various acne-related conditions.

Diagnosis	Excellent response	Moderate response	Limited response
Severe acne	3		
Moderate acne*	3		
Mild acne*	3		
Acne fulminans*†	3		
Rosacea	3		
Rosacea fulminans*†	3		
Acne conglobata			3
Gram-negative folliculitis		3	
Solid facial oedema			3
Hidradenitis suppurativa			3
Vasculitic acne			3
Dissecting scalp cellulitis			3
Steatocystoma multiplex			3
Oil acne		3	
Fordyce's disease		3	
Chemoprophylaxis of skin cancer		3	
Basal cell naevus syndrome			
Xeroderma pigmentosum			
Eruptive keratoacanthomas			

* Especially if associated with scarring and/or psychological problems.
† Also needs pre-isotretinoin therapy with oral steroids.

Table 42.15 Recommendations from the European Directive on Isotretinoin Prescribing.

	Pre Directive	Post Directive
Dosage	0.5–1.0 mg/kg/day	Start 0.5 mg/kg/day
Indications for use	Isotretinoin recommended as first-line therapy for severe acne (nodular and conglobata) as well as acne not responding to 3 months' systemic antibiotics in combination with topical therapy	The new recommendations suggest isotretinoin should only be used in severe acne (nodular, conglobata) that has or is not responding to appropriate antibiotics and topical therapy; the inference of this being that it should now not be used at all as first-line therapy
Age	Previously no age limit	Not indicated in children <12 years
Monitoring	Liver enzymes and lipids should be checked before treatment and 1 month after the maximum dosage has been used	Baseline investigations as before but at 1 month and 3 monthly throughout the course of treatment
Physical treatments	It was recommended that chemical and physical peeling should be avoided during treatment and for 6 months afterwards and that wax depilation should be avoided during and 6 weeks post-therapy.	All forms of peeling and wax depilation should be avoided during therapy and for 6 months afterwards
Pregnancy prevention programme		See text

initiated. The dispensing restrictions do not apply to males as the process is aimed at ensuring that females do not get extended periods of treatment without pregnancy tests being performed. The responsibility for the assessment of pregnancy tests and the administration of further prescriptions lies with the clinician. Clinical problems relating to the implementation of this approach include difficulties in females with irregular menses, potential lack of continuity of treatment due to potential unavailability of patient and/or health-care workers as well as forgotten tests. These factors may all contribute to early cessation and/or partial treatment, resulting in ineffective management and associated financial burden on health-care systems [22]. Given potential side effects of oral contraceptives, it may not always be appropriate to insist on all patients regardless of pregnancy risk using specific contraceptives.

The recommendations suggest that isotretinoin should no longer be used as first-line therapy and/or should not be used below the age of 12 years. There are many publications advocating the use of isotretinoin for severe acne and scarring acne in the literature, hence delaying this effective therapy in certain cases may go against best and evidence-based practice. With increasing clinical experience, use of the drug has been expanded worldwide to include less severely affected patients who have responded unsatisfactorily to what have been called conventional treatments, including long-term antibiotics and/or appropriate topical antimicrobial or retinoid-like therapies [16–18,23–25].

Failure of conventional treatment may occur for many reasons, including resistance of *P. acnes* to antibiotics [26]. A European review outlines when isotretinoin might be considered in light of the new European directive and identifies poor prognostic factors, as summarized in Table 42.15 [27]. The recommendations to start at 0.5 mg/kg/day and to titrate the dose as tolerated are well received when using isotretinoin for conventional acne. However, some patients with persistent acne, especially in the mature age group, as well as cases where side effects are not tolerated at these recommended doses, will require low-dose and possibly intermittent treatment. This has been advocated for some of these specific cases in the literature [28,29].

The USA has adopted a more rigid programme for pregnancy prevention and monitoring. In 2005, the Food and Drug Administration (FDA) announced that both male and female users of Accutane® (oral isotretinoin) would have to enrol into the National Registry 'iPLEDGE'. If this is not achieved, patients will no longer be able to receive the drug. Women of childbearing age now have to provide two negative pregnancy tests before their initial prescription, show proof of another negative pregnancy test before each monthly repeat prescription, and use two forms of contraception throughout therapy and for 30 days after treatment. They must enter these forms of contraception into the registry. All patients sign a document confirming that they are aware of potential adverse effects including depression and suicidal thoughts. One unfortunate consequence of this strict regimen may be a reduction in the usage of isotretinoin, which could potentially disadvantage patients who require this effective treatment. In addition, the restriction of isotretinoin as a second-line therapy may have consequences on the evolution of acne scarring, and on the quality of life in many acne patients. Expert opinion based on clinical data [17,23,24,27] supports the use of isotretinoin for patients with moderate acne who are failing to respond to conventional therapy, for whatever reason. Acne may produce scars in 30% of patients with moderate disease, and significant psychological morbidity in 12–13%.

The definition of poor response should be made against objective or semiobjective criteria. The use of a clinical acne scoring system [30], as well as quality-of-life and psychosocial assessments [31], should be used when evaluating acne. Physical and psychological severity of acne and local financial pressures will all play a role in the decision whether to prescribe isotretinoin. There is strong evidence to show that isotretinoin significantly reduces the psychological problems associated with acne [32,33].

A small number of patients with mild acne have psychological problems disproportionate to their degree of acne. These patients may have body dysmorphophobic syndrome. There is evidence to suggest these patients respond to isotretinoin but withdrawing the drug may be difficult [34].

Although the European directive suggests isotretinoin should not be used below 12 years of age, up to 0.5 mg/kg/day has been used successfully in a number of neonates or juveniles with acne that have not responded to all appropriate topical or oral therapy [35]. Some pre-adolescent youngsters, even under 10 years of age,

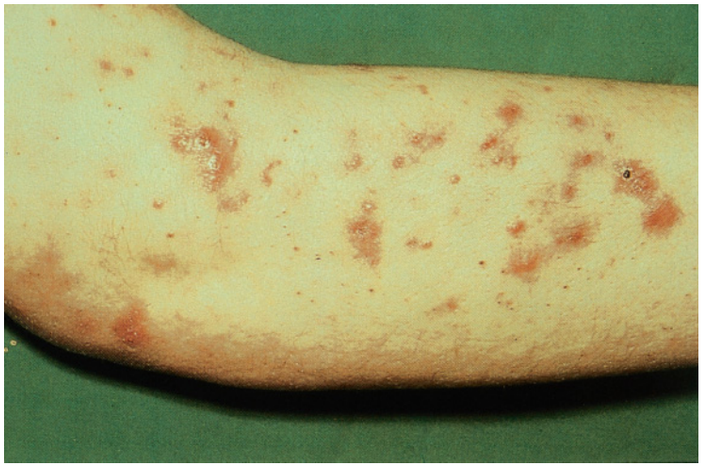


Fig. 42.61 The unusual extent of acne in a patient with Apert's syndrome.



Fig. 42.62 The typical appearance of the fingers of a patient with Apert's syndrome.

develop troublesome acne with scarring. Oral isotretinoin should be considered for paediatric acne patients if there are sufficient clinical indications [36]. Apert's syndrome is a rare disorder associated with a hyperresponse of the epiphyses (Figs 42.61 & 42.62) and sebaceous glands to androgens, which results in premature epiphyseal fusion, particularly of the long bones and skull, and in acne, respectively. These patients, presumably because of the hypersensitivity of the sebaceous glands to androgens, respond poorly to conventional therapy, and are therefore often treated successfully by oral isotretinoin [37].

Most dermatologists are treating increasing numbers of patients with acne that has persisted beyond the age of 25 years. The reasons for this change in the age-referral pattern are unclear, but may reflect increased expectations for cure based on the widely known clinical effectiveness of isotretinoin. Although the acne severity in these cases is not usually as great as when they were 15–25 years old, the persistence of the disease results in an increased risk of scarring and disproportionate psychological distress [38]. Isotretinoin can play an important role in the treatment of this age group. Data from a clinic in Leeds, UK, show that an adult with acne persisting at the age of 30 years is likely to have acne for at least a further 10 years. Small, intermittent-dose isotretinoin therapy (see below) may be appropriate for this subgroup of patients, but relapse often occurs quickly following a successful acne-free interval while on therapy.

Table 42.16 Isotretinoin dose schedules that may be most appropriate for patients with significant systemic disease.

1 Protocol A: standard regimen	2 Protocol B: initially half the standard regimen	3 Protocol C: once-a-week regimen with gradual dose increase
Crohn's disease	Chronic renal failure	Behçet's syndrome
Diabetes mellitus	Renal dialysis	Cerebellar spongiform encephalopathy
Epilepsy	Hypertriglyceridaemia	Idiopathic thrombocytopenic purpura
Spina bifida	Immunosuppression	Leukaemia
Ulcerative colitis	Manic depressive psychosis	Mitochondrial degeneration
	Myalgic encephalopathy	Paroxysmal nocturnal haemoglobinuria
	Motor neurone disease	Polymyalgia rheumatica
	Multiple sclerosis	

Isotretinoin for patients with significant systemic disease

Patients with significant systemic disease have been successfully treated with oral isotretinoin. It has been suggested that these patients fall into three subgroups and therefore three appropriate protocols have been recommended (Table 42.16) aimed at minimizing adverse effects in the associated disorder. In all instances it is necessary that a careful check be made by the dermatologist and/or the relevant physician at monthly intervals to ensure that there are no significant clinical or laboratory changes in the systemic disease [39,40].

1 Patients in Group 1 are those patients for whom there is evidence to show that the full dose of isotretinoin can be safely given.
2 Patients in Group 2 are those patients for whom there is limited information but, on balance, the drug probably does not cause any change in the associated disorder. These patients usually can start on a dose regimen of 0.25–0.5 mg/kg/day. If all is well, the dose can be increased at 2-monthly intervals to 0.5 mg/kg/day, and beyond if required, and therapy usually maintained for 24 weeks.
3 Group 3 includes patients who have rare diseases, or where not much information exists. In these uncommon circumstances, it is recommended that therapy begins at 20 mg isotretinoin/week. The dose is increased by 20 mg each week so that at the end of 7 weeks patients are taking 20 mg/day. The cycle can then be repeated to achieve a higher dose, so that by the end of a further 7 weeks they are taking 20 mg twice a day. In this group of diseases, it is particularly important that the dermatologist links with the appropriate physician so that a very careful clinical and, where appropriate, laboratory measurement is made of the associated disease. The authors recommend publication of these cases to help other similarly affected patients.

Isotretinoin in the treatment of acne variants

These diseases are very rare, and represent a small but essential indication for oral isotretinoin. This group includes patients with acne fulminans, rosacea fulminans, Gram-negative folliculitis, dissecting cellulitis of the scalp, hidradenitis suppurativa and acne conglobata.

Patients with acne fulminans and rosacea fulminans respond to oral isotretinoin [41,42]. The best response in these conditions is obtained by starting with a course of prednisolone 0.5–1.0 mg/kg for 4–6 weeks [41,42]. The steroids can usually be reduced gradually over the following 2 weeks, and isotretinoin can be introduced at a dosage of 0.5 mg/kg body weight/day and this can be increased gradually to 1 mg/kg/day according to the response.

Patients with acne conglobata and Gram-negative folliculitis usually do not require oral steroids, and can be started immediately on oral isotretinoin at a dose of 0.2–0.5 mg/kg/day [43]. Hidradenitis suppurativa is a distressing disease that is difficult to treat. The response to isotretinoin is variable [44,45]. However, oral isotretinoin may achieve some improvement in patients who have not responded to hormonal regimens or long-term high-dose antibiotics such as minocycline. Dissecting cellulitis of the scalp also responds variably to oral isotretinoin, but a 4-month course should be tried [46].

Steatocystoma multiplex does not respond well to isotretinoin and although the inflammatory component of this disease may improve, it may respond equally well to long-term oral antibiotics [47]. Other uncommon diseases related to acne that may respond to isotretinoin are oil acne [48], especially where there is an inflammatory component, and extensive Fordyce's disease [49]. Table 42.14 summarizes the acne-related conditions that have been treated successfully with isotretinoin in the literature.

Recommended doses and duration of therapy

Most physicians to date have prescribed a dose within the range 0.5–1.0 mg/kg body weight/day. There are variations in the way treatment is started [50–53]. According to the European Directive treatment regimens should start with 0.5 mg/kg/day and may be increased to 1.0 mg/kg/day according to tolerance and response. The half life is 22 h and the bioavailability is 25%. Absorption of isotretinoin is markedly affected by the presence of fat and pharmacokinetic studies show that absorption can be doubled by taking isotretinoin with, or after, a meal compared with the fasting state [52]. It is therefore advisable to take the capsules with food at the same time of day. The dose can then be adjusted according to clinical response and presence or absence of side effects.

The duration of therapy varies according to the dose administered over the course of the treatment period. The range is usually 16–30 weeks, and the mean between 16 and 20 weeks, with patients receiving 0.5 mg/kg/day requiring a longer course of therapy to achieve appropriate results. Studies to derive a cumulative dose for maximum benefit and reduced relapse rate [51] have confirmed that there is a definite effect of both dose and duration of therapy but that there is not an *a priori* pharmacokinetic reason to support the concept of accumulation of drug or a cumulative dose effect. Post-therapy relapse is minimized by treatment courses that amount to a total of at least 120 mg/kg, but there is not necessarily any added benefit when 150 mg/kg is exceeded [51]. Typically, this total dose can be achieved by 4–6 months at 0.5–1.0 mg/kg/day. The duration of therapy should be adjusted to give at least 90% clearance of acne based upon initial clinical acne grade scoring techniques followed by 4–8 weeks of consolidation.

Demographic factors, such as age, sex and duration of acne, may also govern the rate of response and relapse. Males with extensive truncal acne, more severe acne, and/or suffering from acne for less than 7 years, fail to respond as well as, and relapse more quickly than, female patients with predominantly facial acne of a less severe grade.

Eighty-five per cent of patients who receive a dose of 0.5–1.0 mg/kg/day are virtually clear of their acne by 16 weeks. Thirteen per cent require 5 or 6 months to clear, and 3% require a longer course. Less than 1% of patients may need up to 12 months of continuous therapy. Low-dose courses of isotretinoin have been used successfully in mature adults with persistent and late-onset acne [28,29]. A typical approach consists of 0.5 mg/kg/day taken 1 week out of 4 for a period of 6 months. Ninety-one per cent will be clear of acne using this regimen [54] but relapse is disappointingly frequent. Furthermore, some patients will not accept even minimal disease and become very dependent on these small doses, expecting to stay on the drug for many years at this lower dosage. It is not clear whether this approach will result in long-term adverse effects and it is important to clarify with the patient that although nothing untoward has been reported to date this is clearly using the drug outside recommended guidelines and is not deemed appropriate for a female of reproductive potential.

What are the reasons for a slow response to isotretinoin?

Analysis of slow responders to isotretinoin shows that the cause is due to the presence of macrocomedones (see Fig. 42.63) in the majority of cases 70% [55], although hyperandrogenism may also play a part in resistance to isotretinoin therapy [56]. An early post-isotretinoin flare, poor absorption, possibly differences in receptor



Fig. 42.63 Macrocomedones may be a reason for acne flare when treated with isotretinoin.

sensitivity, colonization with *Staphylococcus aureus*, severe acne and unusual variants account for 25% of poor responders, and the cause of poor response is unknown in about 5%.

Macrocomedones may be subtle and should be detected under a suitable lamp with the skin stretched. They should be identified before systemic isotretinoin is started as an acute flare of acne may ensue if left untreated before embarking on isotretinoin [57]. Treatment requires light cautery or hyfrecation. A local anaesthetic cream should be applied to the lesions for the requisite time beneath an occlusive dressing and then the lesions touched gently with light cautery [58] or hyfrecation. This procedure should initially be performed on a test area of 10 cm^2, to ensure that the patient does not develop scarring or hypo- or hyperpigmentation.

When macrocomedones are not the cause of poor response, the dosage of isotretinoin should be carefully considered as some patients will suffer a deterioration in their acne at the start of a course of isotretinoin [57]. If the poor response or worsening acne is thought to be due to an early post-isotretinoin flare which is well reported an antibiotic can be used in combination with isotretinoin such as erythromycin 1 g daily or trimethoprim 200–300 mg twice daily. Tetracyclines should be avoided in combination with isotretinoin due to a possible increased risk of benign intracranial hypertension [59,60].

If the acne is very inflammatory, then a significant reduction in the dose of isotretinoin and addition of oral steroids may be required (e.g. 0.5–1.0 mg/kg/day for 2–3 weeks). In other patients it may be appropriate to increase the dose of isotretinoin providing that the side effects are tolerated.

Some patients do not appear to metabolize isotretinoin as well as others and therefore may require higher doses. Adherence to therapy must also be considered. Mucocutaneous side effects, particularly cheilitis, are usually a good measure of absorption.

Unusual variants as discussed elsewhere may lead to slow response and some female patients with hormonal dysfunction, due, for example, to polycystic ovarian syndrome, may need additional treatment with a hormonal preparation such as co-cyprindiol.

Persistent deep pustules in about 1% of patients may be due to *Staphylococcal aureus*, and bacterial swabs should always be examined and appropriate antistaphylococcal therapy prescribed. Some patients have multiple reasons for the slow response.

Further courses of therapy are usually successful when required. There are no reports of cumulative toxicity from using repeat courses and tachyphylaxis has not been noted.

Side effects

Isotretinoin has many side effects but most are predictable and rarely interfere with the patient management [16–18,23,25,47]. The common mucocutaneous side effects are dose dependent and rendered tolerable by modification of the dose and/or additional symptomatic therapy.

Teratogenicity is well recognized and regarded as one of the most serious potential adverse effects [61]. Fifty per cent of pregnancies spontaneously abort, and of the remainder about half of the infants are born with cardiovascular or skeletal deformities. The recently introduced European Directive and iPLEDGE in the USA have addressed the importance of pregnancy prevention as discussed previously. Discussion about the teratogenicity and recognized side effects should be recorded in the notes at each visit, and patients should be given appropriate written information.

Mood changes including depression are common among adolescents and have been reported in acne patients treated with isotretinoin. Two studies that looked at spontaneous reports of side effects for the Food and Drug Administration (FDA) in the USA [62,63] found little or no increase in psychiatric disease including depression and suicide over the background prevalence in the adolescent population. A further study of general practice databases in Canada and the UK showed similar findings [64] as have subsequent studies [65]. A more recent controlled case crossover study demonstrated a relative risk for depression of 2.68 (95% CI = 1.03 to 3.89) for acne patients exposed to oral isotretinoin [66]. This is the first controlled study to find a statistically significant association between isotretinoin and depression. Despite contradictory reports, clinicians have been advised of a potential rare idiosyncratic reaction in some young vulnerable patients which could lead to mood changes and clinical depression during treatment with isotretinoin. It is therefore advisable to specifically enquire about related symptoms at each clinic visit.

A suggested short questionnaire with good stringency is:

Over the past 2 weeks have you consistently . . .

1 Been feeling unusually sad or fed up?
2 Lost interest in things that used to interest you?
3 Felt any more short tempered or irritable than you used to?

If significant depression is identified, then a psychiatric referral may be indicated. Increased aggression has been identified in some male patients and the FDA in the USA has advised clinicians to warn potential patients about this side effect. If there is any doubt, the drug must be stopped.

The mucocutaneous side effects are dose dependent and can usually be controlled with regular use of moisturizers and lip salves. Occasionally retinoid dermatitis, a severe retinoid cheilitis or conjunctivitis occur (Figs 42.64 & 42.65), often complicated by secondary infection with *S. aureus* (Fig. 42.66).



Fig. 42.64 Patient with troublesome cheilitis due to oral isotretinoin.



Fig. 42.65 Patient with troublesome discoid eczema due to oral isotretinoin.



Fig. 42.66 Patient with troublesome facial crusting (and *Staphylococcus aureus* infection) due to oral isotretinoin.

These patients may need treatment with an intermediate-strength steroid ointment combined with an antiseptic. If there is impetiginization, oral antistaphylococcal therapy such as flucloxacillin and/or topical mupirocin 2% ointment may be required [67]. A nasal preparation of mupirocin can be used to eradicate nasal carriage of staphylococci.

Table 42.17 and Table 42.18 outline common and rarer side effects reported with isotretinoin.

Significant systemic effects are uncommon; headaches may uncommonly be an early feature of benign intracranial hypertension and arthralgia is seen most frequently in those patients participating in regular and heavy exercise. Tetracyclines, including doxycycline and minocycline, must not be prescribed with isotretinoin, as both drugs may produce benign intracranial hypertension [60]. Systemic side effects are usually well controlled by dose reduction and concomitant use of non-steroidal anti-inflammatory drugs or aspirin. There is a long list of very uncommon, systemic side effects (Chapter 75); a detailed review of these is beyond the scope of this chapter.

Table 42.17 The most common mucocutaneous problems that may arise from isotretinoin use.

Adverse effect	Incidence (maximum %)
Cheilitis	98
Conjunctivitis/blepharitis	35
Dermatitis	65
Desquamation	20
Facial erythema	65
Epidermal atrophy	25
Epistaxis	35
Fragility of skin	20
Itching	25
Mucositis	40
Vestibulitis	50
Xerosis	50

Table 42.18 Less common but recognized side effects of isotretinoin.

Achilles tendonitis
Acne fulminans
Depression
Diarrhoea/colitis
Elkonyxis
Hair loss
Headaches/benign intracranial hypertension
High-tone deafness
Mood changes
Night blindness
Paronychia
Pyogenic granulomas
Sticky palms
Urticaria
Vasculitis

An acute flare of acne early in a course of isotretinoin is a recognized problem in about 6% cases and is clinically significant in half of these [57]. The physician should inform patients accordingly and provide a fast track follow-up should this problem occur as these flares can be very aggressive producing physical and psychological difficulties. Predisposing risk factors for a flare include the presence of macrocomedones and nodules [57]. If a severe flare occurs oral prednisolone should be given in a dose of 0.5–1.0 mg/kg/day over a period of 2–3 weeks, and the dose slowly decreased over the next 6 weeks. The isotretinoin should either be stopped or reduced to a dosage of 0.25 mg/kg/day depending on the severity of the problem. If stopped, the drug can be slowly reintroduced at a dose of 0.25 mg/kg/day, and then increased or decreased as response dictates.

There has been much debate as to whether liver function tests and lipids should be monitored while on therapy. Elevations in these tests occur in almost all patients and rapidly return to pretreatment levels after therapy has been stopped [15,21,68]. It is,

however, essential to carry out these tests before starting therapy. Published evidence suggests that the laboratory tests need not be repeated except in groups at risk, such as diabetics and patients with known familial hypertriglyceridaemia [24,68]. However, the EU directive is prescriptive in suggesting these investigations should be performed at baseline, 1 month into therapy and 3-monthly throughout treatment. Amichai and Grunwald have published an excellent overview on the many side effects of oral isotretinoin [69].

Cost-effectiveness

Oral isotretinoin is clearly more effective than oral antibiotics in acne of all grades of severity. However, its relative expense and side effects have deterred some physicians from prescribing it. Cost-effectiveness comparisons, prior to the EU directive and iPLEDGE, in the UK [70,71], France [72], New Zealand [73] and Australia [74] have shown that a 4–6-month course of isotretinoin is significantly cheaper than a 3-year therapeutic regimen of rotational courses of antibiotics and topical treatment. In fact, only patients treated with isotretinoin achieved complete clearance of acne when assessed 3–5 years post-treatment [60]. Generic isotretinoin has made the cost-effectiveness more apparent. However, the extra investigations, monitoring and prescription control introduced with the European Directive and iPLEDGE have negatively impacted on this cost-effectiveness.

Drug interactions

Reduced efficacy has been noted when isotretinoin is taken with heavy alcohol intake [75]. Isotretinoin is metabolized by cytochrome P450 enzymes, inducible by ethanol and inhibited by some drugs, for example ketoconazole. Hence, increased drug levels of isotretinoin may occur if combined with imidazole fungistatics. Salicylic acid and indometacin represent acidic drugs with a high affinity for albumin. If present in the blood in high therapeutic concentrations they may displace isotretinoin from protein binding sites, so resulting in an increase in the unbound concentration of the drug [76]. Carbamazepine plasma levels decrease when concurrent isotretinoin is taken, hence careful monitoring should be considered in epileptics on carbamazepine if requiring isotretinoin [77]. Oral tetracyclines in combination with isotretinoin should be avoided, as both can lead to benign intracranial hypertension. These are likely to be rare idiosyncratic reactions attributable to each drug in its own right, but there are reports in the literature suggesting there could theoretically be an additive effect by combining the two [60]. Vitamin supplements containing vitamin A should be avoided alongside isotretinoin, as additive toxic effects could ensue.

References

1 King K, Jones DH, Daltry DC, Cunliffe WJ. A double-blind study of the effects of 13-*cis*-retinoic acid on acne, sebum excretion rate and microbial population. *Br J Dermatol* 1982; **107**: 583–90.

2 Allenby G, Bocquel MT, Saunders M *et al*. Retinoic acid receptors and retinoid X receptors: interactions with endogenous retinoic acids. *Proc Natl Acad Sci USA* 1993; **90**: 30–4.

3 Levin A, Bosakowski T, Kazmer S *et al*. 13-cis retinoic acid does not bind to retinoic acid receptors alpha, beta and gamma. *Toxicologist* 1992; **12**: 181.

4 Ott F, Bollag W, Geiger JM. Oral 9-*cis*-retinoic acid in acne therapy. *Dermatology* 1996; **193**: 124–6.

5 Geiger JM, Hommel L, Harms M *et al*. Oral 13-*cis*-retinoic acid is superior to 9-*cis*-retinoic acid in sebosuppression in human beings. *J Am Acad Dermatol* 1996; **34**: 513–5.

6 Tsukada M, Schröder M, Roos TC *et al*. 13-*cis*-retinoic acid exerts its specific activity on human sebocytes through selective intracellular isomerization to all-*trans*-retinoic acid and binding to retinoid acid receptors. *J Invest Dermatol* 2000; **115**: 321–7.

7 Nelson AM, Gilliland KL, Cong Z *et al*. 13-*cis*-retinoic acid induces apoptosis and cell cycle arrest in human SEB-1 sebocytes. *J Invest Dermatol* 2006; **126**: 2178–89.

8 Knutson DD. Ultrastructural observations in acne vulgaris: the normal sebaceous follicle and lesions. *J Invst Dermatol* 1974; **62**: 228–307.

9 Plewig G, Dressel H, Pfleger M *et al*. Low dose isotretinoin witn tretinoin is effective to correct abnormalities of acne. *J Dtsch Dermatol Ges* 2004; **2**: 31–45.

10 Dalziel K, Barton S, Marks R. The effect of isotretinoin on follicular and sebaceous gland differentiation. *Br J Dermatol* 1987; **117**: 317–23.

11 Coates P, Adams CA, Cunliffe WJ. Does oral isotretinoin prevent *Propionibacterium acnes* resistance? *Dermatology* 1997; **195**: 4–9.

12 Leyden JJ, McGinley KJ. Effect of 13-*cis*-retinoic acid on sebum production and *Propionibacterium acnes* in severe nodulocystic acne. *Arch Dermatol Res* 1982; **272**: 331–7.

13 Seguin-Devaux C, Hanriot D, Dailloux M *et al*. Retinoic acid amplifies the host response to LPS through increased T lymphocyte numbers and LPS binding protein expression. *Mol Cell Endocrinol* 2005; **241**: 67–76.

14 Falcon RH, Lee WJ, Shalita AR *et al*. *In vitro* effect of isotretinoin on monocyte chemotaxis. *J Invest Dermatol* 1986; **86**: 550–2.

15 King K, Jones DH, Daltry DC *et al*. A double blind study of the effects of 13-*cis*-retinoic acid on acne, sebum excretion and microbial population. *Br J Dermatol* 1982; **107**: 583–90.

16 Strauss JA, Rapini RP, Shalita AR *et al*. Isotretinoin therapy for acne: results of a multicentre dose–response study. *J Am Acad Dermatol* 1994; **10**: 490–6.

17 Shalita AR. Acne revisited. *Arch Dermatol* 1994; **130**: 363–4.

18 Layton AM, Knaggs H, Taylor J *et al*. Isotretinoin for acne vulgaris—10 years later: a safe and successful treatment. *Br J Dermatol* 1993; **129**: 292–6.

19 Azoulay L, Oraichi D, Berard A. Isotretinoin therapy and the incidence of acne relapse: a nested case-control study. *Br J Dermatol* 2007; **157**: 1240–8.

20 Leyden JJ. Oral isotretinoin. How can we treat difficult acne patients? *Dermatology* 1997; **195** (Suppl. 1): 29–33.

21 Jones DH, King K, Miller AJ *et al*. A dose response of 13-*cis*-retinoic acid in acne vulgaris. *Br J Dermatol* 1983; **108**: 333–43.

22 Layton AM, Dreno B, Gollnick HPM *et al*. A review of the European Directive for prescribing systemic isotretinoin for acne vulgaris. *J Eur Acad Dermatol Venereol* 2006; **20**: 773–6.

23 Cunliffe WJ, van de Kerkhof P, Caputo R *et al*. Roaccutane treatment guidelines: results of an international survey. *Dermatology* 1997; **194**; 351–7.

24 Gollnick H, Cunliffe WJ, Berson D *et al*. Management of acne. A report from a global alliance to improve outcomes in acne. *J Am Acad Dermatol* 2003; **49**: S1–36.

25 Eady EA, Jones CE, Tipper JL *et al*. Antibiotic resistant propionibacteria in acne: need for policies to modify usage. *BMJ* 1993; **306**: 555–6.

26 Eady EA, Farmery MR, Ross JI *et al*. Effects of benzoyl peroxide and erythromycin alone and in combination against antibiotic-sensitive and -resistant skin bacteria from acne patients. *Br J Dermatol* 1994; **131**: 331–6.

27 Dreno B, Bettoli V, Ochsendorf F *et al*. European recommendations on the use of oral antibiotics for acne. *Eur J Dermatol* 2004; **14**: 391–9.

28 Goulden V, Clark SM, McGeown C, Cunliffe WJ. Treatment of acne with intermittent isotretinoin. *Br J Dermatol* 1997; **137**: 106–8.

29 Akman A, Durusoy C, Senturk M *et al*. Treatment of acne with intermittent and conventional isotretinoin: a randomized, controlled multicenter study. *Arch Dermatol Res* 2007; **299**: 467–73.

30 O'Brien SC, Lewis J, Cunliffe WJ. The Leeds revised acne grading system. *J Dermatolog Treat* 1998; **9**: 215–20.

31 Motley RJ, Finlay AY. Practical use of a disability index in the routine management of acne. *Clin Exp Dermatol* 1992; **17**: 1–3.

32 Rubinow DR, Peck GL, Squillace KM, Gantt GG. Reduced anxiety and depression in cystic acne patients after successful treatment with oral isotretinoin. *J Am Acad Dermatol* 1987; **17**: 25–32.
33 Kellet SC, Gawkrodger DJ. The psychological and emotional impact of acne and the effect of treatment with isotretinoin. *Br J Dermatol* 1999; **140**: 273–82.
34 MacDonald-Hull S, Cunliffe WJ, Hughes BR. Treatment of the depressed and dysmorphophobic acne patient. *Clin Exp Dermatol* 1991; **16**: 210–1.
35 Horne HL, Carmichael AJ. Juvenile nodulocystic acne responding to systemic isotretinoin. *Br J Dermatol* 1997; **136**: 796–7.
36 Clark SM, Cunliffe WJ. The use of isotretinoin in the treatment of acne in children. *Br J Dermatol* 1995; **133** (Suppl. 45): 39.
37 Parker TL, Roth JG, Esterly NB. Isotretinoin for acne in Apert syndrome. *Pediatr Dermatol* 1992; **9**: 298–300.
38 Goulden V, Cunliffe WJ. Post adolescent acne: a review of the clinical features. *Br J Dermatol* 1997; **136**: 66–70.
39 Bunker CB, Rustin MD, Dowd PM. Isotretinoin treatment of severe acne in post-transplant patients taking cyclosporin. *J Am Acad Dermatol* 1990; **22**; 613–4.
40 Cunliffe WJ, Stables G. Optimum use of isotretinoin in acne. *J Cutan Med Surg* 1996; **1** (Suppl. 2): S2–14, S2–25.
41 Plewig C, Jansen T, Kligman A. Pyoderma faciale—a review and report of 20 additional cases: is it rosacea? *Arch Dermatol* 1992; **128**: 1611–7.
42 Karvonen S. Acne fulminans: report of clinical findings and treatment of twenty-four patients. *J Am Acad Dermatol* 1993; **28**: 572–9.
43 Leyden JJ, Marples RR, Mills OH Jr. Gram-negative folliculitis. A complication of antibiotic therapy in acne vulgaris. *Br J Dermatol* 1973; **88**: 553–8.
44 Boer J. Hidradenitis suppurativa or acne inversa: a clinicopathological study. *Br J Dermatol* 1996; **135**: 721–5.
45 Chow ETY, Mortimer PS. Successful treatment of hidradenitis suppurativa and retroauricular acne with etretinate. *Br J Dermatol* 1992; **126**: 415–9.
46 Ketter TA, Post RM, Worthington K. Treatment of perifolliculitis capitis abscendens et suffodiens with isotretinoin. *J Dermatolog Treat* 1992; **3**: 27.
47 Holmes R, Black MM. Steatocystoma multiplex with unusual prominent cysts on the face. *Br J Dermatol* 1980; **102**: 711–3.
48 Finkelstein E, Lazarov A, Cagncana M, Halevy S. Oil acne: successful treatment with isotretinoin. *J Am Acad Dermatol* 1994; **30**: 491–2.
49 Monk BE. Fordyce spots responding to isotretinoin therapy. *Br J Dermatol* 1993; **129**: 355.
50 Layton AM, Stainforth JM, Cunliffe WJ. Ten years' experience of oral isotretinoin for the treatment of acne vulgaris. *J Dermatolog Treat* 1994; **4** (Suppl. 2): S2–5.
51 Harms M, Masooye I, Radeff B. The relapses of cystic acne after isotretinoin treatment are age-related: a long-term follow up study. *Dermatologica* 1986; **172**: 148–53.
52 Colburn WA, Gibson DM, Wiens RE, Hanigan JJ. Food increases the bioavailability of isotretinoin. *J Clin Pharmacol* 1983; **23**: 534–8.
53 Hermes B, Praetel B, Hez BM. Medium dose isotretinoin for the treatment of acne. *J Eur Acad Dermatol Venereol* 1998; **11**: 117–21.
54 Goulden V, Clark SM, Cunliffe WJ. Treatment of adult acne with low dose intermittent isotretinoin. *Br J Dermatol* 1996; **135** (Suppl. 47): 20.
55 Clark SM, Goulden V, Cunliffe WJ. The management of acne patients who respond slowly to oral isotretinoin. *Br J Dermatol* 1996; **135**: 20.
56 Lehucher-Ceyrac D, Salmoniere P, Chastang CL *et al*. Predictive factors for failure of isotretinoin treatment in acne patients: results from a cohort of 237 patients. *Dermatology* 1999; **198**: 278–83.
57 Clark SM, Cunliffe WJ. Acne flare and isotretinoin—incidence and treatment. *Br J Dermatol* 1995; **133** (Suppl. 45): 26.
58 Pepall LM, Cosgrove MP, Cunliffe WJ. Ablation of whiteheads by cautery under topical anaesthesia. *Br J Dermatol* 1991; **125**: 256–9.
59 Griffin JP. A review of the literature on benign intracranial hypertension associated with medication. *Adverse Drug React Toxicol Rev* 1992; **11**: 41–58.
60 Lee AG. Pseudotumor cerebri after treatment with tetracycline and isotretinoin for acne. *Cutis* 1995; **55**: 165–8.
61 Stern RS. When a uniquely effective drug is teratogenic: the case of isotretinoin. *N Engl J Med* 1989; **320**: 1007–9.
62 Jacobs DG, Deutsch NL, Brewer M. Suicide, depression and isotretinoin: is there a causal link? *J Am Acad Dermatol* 2001; **45**: S168–75.
63 Wysowski DK, Pitts M, Beitz J. An analysis of reports of depression and suicide in patients treated with isotretinoin. *J Am Acad Dermatol* 2001; **45**: 515–9.
64 Jick SS, Kremmers HM, Vasilakis-Scaramozza C. Isotretinoin use and risk of depression, psychotic symptoms, suicide and attempted suicide. *Arch Dermatol* 2000; **136**: 1231.
65 Cohen J, Adams S, Patten S. No association found between patients receiving isotretinoin for acne and the development of depression in a Canadian prospective cohort. *Can J Clin Pharmacol* 2007; **14**: s227–33.
66 Azoulay L, Blais L, Koren G *et al*. Isotretinoin and the risk of depression in patients with acne vulgaris: a case crossover study. *J Clin Psych* 2008; **198**: e1–7.
67 Williams REA, Doherty VR, Perkins W *et al*. *Staphylococcus aureus* and intra-nasal mupirocin in patients receiving isotretinoin for acne. *Br J Dermatol* 1992; **126**: 362–6.
68 Altman RS, Altman LJ, Altman JS. A proposed set of new guidelines for routine blood tests during isotretinoin therapy for acne vulgaris. *Dermatology* 2002; **204**: 232–5.
69 Amichai B, Grunwald MH. Isotretinoin in dermatology. *J Dermatolog Treat* 2000; **11**: 219–40.
70 Simpson N. Effect of isotretinoin on the quality of life of patients with acne. *Pharmacoeconomics* 1994; **6**: 108–13.
71 Cunliffe WJ, Gray JA, MacDonald-Hull S *et al.* Cost effectiveness of isotretinoin. *J Dermatolog Treat* 1991; **1**: 285–8.
72 Lafarge H, Levy PE. Évaluation économique d'une innovation médica-menteuse: le traitement de l'acne sévère par Roaccutane. *J Econ Med* 1987; **5**: 117–27.
73 Wishart J, Villiger J. Cost–benefit of isotretinoin (Roaccutane). *NZ Med J* 1991; **104**: 193.
74 Lee ML, Cooper A. Isotretinoin: cost–benefit study. *Australas J Dermatol* 1991; **32**: 17–20.
75 Soria C, Allegue F, Galiana J *et al*. Decreased isotretinoin efficacy during acute alcohol intake. *Dermatologica* 1991; **182**: 203.
76 Tam M, Cooper A. The use of isotretinoin in a renal transplant patient with acne. *Br J Dermatol* 1988; **116**: 463.
77 Kinaly C, Valkamo MH. Renal transplantation and isotretinoin. *Acta Derm Venereol (Stock)* 1990; **70**: 540.

Other oral treatments

Several other oral treatments may occasionally be adopted for management of difficult acne if the newer drugs are contraindicated, unobtainable or ineffective. Oral zinc is of some value [1–6]. Two double-blind studies showed a significant benefit, particularly with zinc gluconate (200 mg/day). Comparison with minocycline 100 mg/day demonstrated the antibiotic improved acne by 63% in contrast to 32% with 30 mg/day of elemental zinc after 3 months, no placebo was included in the study. Certain non-steroidal anti-inflammatory drugs, such as ibuprofen and benoxaprofen, have been shown to reduce inflamed lesions [7]. More recently, a small pilot study using a 5-lipoxygenase inhibitor elicited a reduction in inflamed lesions and seborrhoea but had little effect on comedones [8]. Clofazimine (200 mg three times a week) has been shown to improve acne fulminans [9]. Dapsone (100–300 mg/day for 6 months) has also been tried with varied success [10,11]; it is much less effective than isotretinoin [11].

Oral vitamin A has been used [12,13] but doses of less than 40 mg/day are not effective and in our experience, oral vitamin A proved considerably less effective than 1 g/day of either tetracycline or erythromycin. The side effects of oral vitamin A are similar to oral isotretinoin.

Oral prednisolone (0.5–1.0 mg/kg body weight/day) should be prescribed in patients with severe inflammatory acne vulgaris and in acne fulminans and pyoderma faciale [14]. Oral steroids are also indicated in patients whose acne flares badly while taking oral isotretinoin [14]. If these patients have many macrocomedones,

they should be urgently treated with light cautery under a local anaesthetic cream such as EMLA® [15].

References

1 Cunliffe WJ, Burke B, Dodman B *et al.* A double-blind trial of a zinc sulphate/citrate complex and tetracycline in the treatment of acne vulgaris. *Br J Dermatol* 1979; **101**: 321–5.
2 Dreno B, Amblard P, Agache P *et al.* Low doses of zinc gluconate for inflammatory acne. *Acta Derm Venereol (Stockh)* 1989; **69**: 541–3.
3 Hillstrom L, Pettersson L, Hellbe L *et al.* Comparison of oral treatment with zinc sulphate and placebo in acne vulgaris. *Br J Dermatol* 1977; **97**: 679–84.
4 Michaelsson G, Juhlin L, Ljunghall K. A double-blind study of the effect of zinc and oxytetracycline in acne vulgaris. *Br J Dermatol* 1977; **97**: 561–6.
5 Weimar VM, Puhl SC, Smith WH *et al.* Zinc sulfate in acne vulgaris. *Arch Dermatol* 1978; **114**: 1776–8.
6 Dreno B, Moyse D, Alirezi I *et al.* A multicentre randomised double-blind controlled clinical trial of the safety and efficacy of zinc gluconate against minocycline hydrochloride in the treatment of inflammatory acne vulgaris. *Dermatology* 2001; **203**: 135–40.
7 Hindson C, Lawlor F, Wacks H. Benoxaprofen for nodular acne. *Lancet* 1982; **i**: 1415.
8 Zouboulis CC, Nestoris S, Adler YD *et al.* A new concept for acne therapy: a pilot study with zileuton, an oral 5-lipoxygenase inhibitor. *Arch Dermatol* 2003; **139**: 668–70.
9 Prendiville I, Cream JJ. Clofazimine responsive acne vulgaris. *Br J Dermatol* 1983; **109** (Suppl. 24): 90–1.
10 Ross CM. The treatment of acne vulgaris with dapsone. *Br J Dermatol* 1961; **73**: 367–70.
11 Prendiville JS, Logan RA, Russell-Jones R. A comparison of dapsone with 13-*cis*-retinoic acid in the treatment of nodular cystic acne. *Clin Exp Dermatol* 1988; **13**: 67–71.
12 Kligman AM, Mills OH, Leyden JJ. Acne vulgaris—a treatable disease. *Postgrad Med J* 1974; **55**: 99–105.
13 Schumacher A, Stüttgen G. Vitamin-A-saure bei hyperkeratosen epithelialen Tumoren und Akne. *Dtsch Med Wochenschr* 1971; **96**: 1547–51.
14 Cunliffe WJ, Stables G. Optimal use of isotretinoin. *J Cutan Med Surg* 1996; **1**: 14–25.
15 Peppall L, Cosgrove M, Cunliffe WJ. Ablation of whiteheads by cautery under topical anaesthetic. *Br J Dermatol* 1991; **125**: 256–9.

Physical modalities for treating active acne

Some of the physical modalities used as an adjunct to treatment require considerable skill. The many abrasive materials, usually based on polyethylene and aluminium oxide, are of little or no value. Facial saunas, heat and massage probably worsen the condition by precipitating the development of inflamed lesions. Removal of comedones can be aided by hot compresses. Comedone removal can be surprisingly uncomfortable, and a variety of specially shaped tools, particularly for blackhead removal, are available. Some patients have very visible closed comedones, which often become inflamed. For these lesions, the eccentrically placed pore may be widened with a small blade under a good light, which allows enucleation of the cornified plug with the comedo remover. The limitations of comedonal extraction include incomplete extraction, refilling and the risk of tissue damage. Light cautery or hyfrecation after the application of a local anaesthetic (EMLA®) [1] has been shown to help patients with multiple macrocomedones; these are usually whiteheads but occasionally blackheads (up to 1.5 mm diameter), and chloracne can be improved [1,2]. A topical anaesthetic preparation is applied for the requisite time beneath an occlusive dressing. The cautery or hyfrecation should be set as low as possible to produce little or no pain. The tip of the instrument should be just sufficiently warm to char paper towelling. The aim is to produce very low-grade thermal damage so as to stimulate the body's own defence mechanisms to eradicate the comedo. The actual treatment of each lesion takes seconds and is associated with very little scarring or post-inflammatory pigmentation. This therapy is more effective than topical tretinoin for macrocomedones [3].

Until recently, there has been little objective assessment of treatment by UV radiation. Broad-spectrum sunlamp therapy is probably not as good as natural sunlight; both provide only short-term benefits in acne. Lasers and light-based devices have been available over the last few years, and there has been increasing interest in their use in acne. The mode of action for light therapy relates to destruction of propionibacteria via targeting porphyrins produced by these bacteria. There is a differential cytotoxic effect, in that cutaneous bacteria, including *P. acnes*, are more susceptible to short-term damage from, for example, photodynamic therapy, than keratinocytes [4]. These regimens also significantly suppress a range of comedonal and pro-inflammatory cytokines [5,6].

To date, the evidence in support of the use of lasers and light devices is poor. A significant number of randomized controlled trials (RCTs) embracing light of diverse wavelengths have been conducted, but results from these studies have been contradictory. Many of the studies include small numbers and short follow-up periods, and have not compared these therapies to conventional treatments used for acne. Outcome measures have also been very variable, making comparison between trials and meta-analysis difficult. A systematic review assessing lasers, light sources and photodynamic therapy (PDT) for acne in 16 randomized controlled and three controlled studies confirmed most light sources do help in the short term, with PDT showing the most consistent results (up to 68% improvement, aminolaevulinic acid, methyl aminolaevulinic acid and red light) [7]. One single-blinded RCT of red light in Asian women showed a 66% improvement in acne at 8 weeks [8]. However, the light was self-administered to the randomized side of the face with no treatment given to the other side (not even a conventional topical treatment) and the results were reported as percentage improvements, with no actual figures, so it is difficult to judge whether improvements were clinically significant. A well-conducted RCT of infrared laser therapy versus placebo treatment showed no difference between the laser and placebo for acne, but there was a transient improvement in open comedones or blackheads [9]. An RCT comparing intense pulsed light (IPL) versus benzoyl peroxide in Asian women found that both treatments improved acne, but there was no statistically significant difference between the two treatments [10]. One controlled study demonstrated that blue light improved inflammatory lesions by 76% compared with benzoyl peroxide, which resulted in a 60% improvement, suggesting the benefits of light therapy were only marginal [11]. A small randomized controlled trial of IPL-PDT versus IPL versus control [12], with all subjects using adapalene 0.1% gel at night, showed no significant difference in improvements in acne lesions between the groups, but a statistically significant improvement in comedones in the light treatment groups. However, the confidence intervals for the results were large, reflecting the small numbers of subjects. Laser therapy with the NLite laser, which emits light at 585 nm, has been reported in a small randomized controlled trial to produce a 50% improvement

in acne grade and lesion counts by 12 weeks after a single treatment [13].

Light therapy may cause pain, erythema, crusting, oedema, pigmentary changes and pustular eruptions. The intensity of these problems is more likely when aminolaevulinic acid or methyl-aminolaevulinic acid are employed in the treatment, and frequently leads to the patient not pursuing further therapy. The other concern relates to long-term safety, as sebocytes are necessary for the immune function of the skin and may be permanently damaged by PDT. Topical amino laevulinic acid (ALA) plus broad-band light (550–700 nm) has been shown to produce acute damage to the sebaceous glands, resulting in significant sebum suppression for up to 20 weeks post-therapy; this was associated with a significant decrease in *P. acnes* for many weeks [12].

Patients should be informed of the existing evidence, which indicates that optical treatments today are not included among first-line treatments.

Superficial freezing with liquid nitrogen will hasten the resolution of chronic fluctuant nodular lesions and is comparatively painless [14]. Two freeze–thaw cycles of 15–30 seconds each are recommended, depending on the size of the nodule. It is uncertain how this treatment works, but it probably invokes an inflammatory reaction, so breaking down the indolent tissue surrounding the lesion. Cryotherapy is probably preferred to intralesional steroid injections in the treatment of older (7 or more days) nodular lesions, whereas intralesional steroid is preferred in lesions less than 7 days old [15]. Triamcinolone, 2.5 mg/mL, may be administered from a syringe with a 30-gauge needle [15,16]. Placement too superficially or too deeply may cause atrophy; 0.025–0.1 mL should be injected into the middle of the lesion, causing slight distension. Aspiration before the steroid injection is desirable but not always possible because of the nature of the fluctuant nodular lesions, which are not true cysts. Deep X-ray treatment must not be prescribed because of its carcinogenic risk. Superficial X-ray therapy (no more than 8.1 Gray given in fractionated doses to any one area of skin in a lifetime) has been advocated, but is of questionable benefit.

Chemical peels [17,18]. Some dermatologists in certain countries use light chemical peels to help remove comedones as well as possibly helping superficial scarring and hyperpigmentation. Peeling agents include α-hydroxy acids (glycolic acid), salicylic acid and trichloroacetic acid. A small split-face, double blind randomized controlled trial comparing α-hydroxy and β-hydroxy acid peels in the treatment of mild to moderate acne demonstrated that the glycolic acid and salicyclic acid peels were of similar efficacy. The salicylic acid peel had sustained effectiveness and fewer side effects in this study [19]. Chemical peels are said to promote desquamation which reduces corneocyte cohesion and keratinocyte plugging, so enabling the extrusion of inflammatory contents. There is still limited scientific evidence to support the use of chemical peels, but guidelines and evidence for use have been considered in a recent Japanese review [20].

References

1 Pepall LM, Cosgrove MP, Cunliffe WJ. Ablation of whiteheads by cautery under topical anaesthesia. *Br J Dermatol* 1991; **125**: 256–9.

2 Yip J, Peppall L, Gawkrodger DJ, Cunliffe WJ. Light cautery and EMLA® in the treatment of chloracne lesions. *Br J Dermatol* 1993; **128**: 313–6.

3 Bottomley WW, Yip J, Knaggs H, Cunliffe WJ. Treatment of closed comedones—comparisons of fulguration with topical tretinoin and electrocautery with fulguration. *Dermatology* 1993; **186**: 253–7.

4 Zeina B, Greenman J, Purcell WM *et al.* Killing of cutaneous microbial species by photodynamic therapy. *Br J Dermatol* 2001; **144**: 274–8.

5 Hongcharu W, Taylor CR, Chang Y *et al.* Topical ALA-photodynamic therapy for the treatment of acne vulgaris. *J Invest Dermatol* 2000; **115**: 183–92.

6 Zeina B, Greenman J, Corry D *et al.* Cytotoxic effects of antimicrobial photodynamic therapy on keratinocytes *Br J Dermatol* 2002; **146**: 568–73.

7 Hædersdal M, Togsverd-Bo K, Wulf HC. Evidence-based review of lasers, light sources and photodynamic therapy in the treatment of acne vulgaris. *J Eur Acad Dermatol Venereol* 2008; **22**: 267–78.

8 Na JI, Suh DH. Red light phototherapy alone is effective for acne vulgaris: randomized, single-blinded clinical trial. *Dermatol Surg* 2007; **33**: 1228–33.

9 Orringer JS, Kang S, Maier L *et al.* A randomized, controlled, split-face clinical trial of 1320-nm Nd:YAG laser therapy in the treatment of acne vulgaris. *J Am Acad Dermatol* 2007; **56**: 432–8.

10 Chang SE, Ahn SJ, Rhee DY *et al.* Treatment of facial acne papules and pustules in Korean patients using an intense pulsed light device equipped with a 530- to 750-nm filter. *Dermatol Surg* 2007; **33**: 676–9.

11 Zhong JQ, Xian DH, Chen DY. The clinical efficacy of narrowband blue light in the treatment of acne vulgaris. *J Clin Dermatol* 2007; **36**: 115–6.

12 Yeung CK, Shek SY, Bjerring P *et al.* A comparative study of intense pulsed light alone and its combination with photodynamic therapy for the treatment of facial acne in Asian skin. *Lasers Surg Med* 2007; **39**: 1–6.

13 Seaton E, Charikida A, Mouser PE *et al.* Pulsed dye laser treatment for inflammatory acne vulgaris: a randomised controlled trial. *Lancet* 2003; **362**: 1347–52.

14 Schonberg IL, Litz JZ. Fluro-therapy cryotherapy; an adjuvant in the treatment of acne vulgaris and post-acne scarring. *Ohio Med* 1958; **54**: 1046.

15 Callen JP. Intralesional corticosteroids. *J Am Acad Dermatol* 1981; **4**: 149–51.

16 Levine RM, Rasmussen JE. Intralesional corticosteroids in the treatment of nodulocystic acne. *Arch Dermatol* 1983; **119**: 480–1.

17 Horton CE, Sadove RC. Refinements in combined chemical peel and simultaneous abrasion of the face. *Ann Plast Surg* 1987; **19**: 504–11.

18 Monheit GD. The Jessner's trichloroacetic acid peel. An enhanced medium depth chemical peel. *Dermatol Clin* 1995; **13**: 273–83.

19 Kessler E, Flanagan K, Chia C *et al*. Comparison of α- and β-hydroxy acid chemical peels in the treatment of mild to moderately severe facial acne. *Dermatol Surg* 2008; **34**: 45–51.

20 Furukawa F, Yamamoto Y. Recent advances in chemical peeling in Japan. *J Dermatol* 2006; **33**: 655–61.

Treatment of scars

There is no good evidence available to promote one therapeutic measure over another in the treatment of acne scars. Response to treatment is variable and sometimes not that successful. Some scars will become less conspicuous over time and where possible it is worthwhile adopting a wait and see policy. Recent interest in the pathogenesis of wound healing and scars may pave the way for new oral and topical therapies. The expansion of dermatological surgery and new lasers hold some promise. Surgical/laser therapies for scars should be reserved for patients whose acne is under good control. Treatment of facial scars associated with loss of tissue may include excision, planing and filling techniques. Such techniques are rarely used for scars on the trunk.

Treatment of atrophic scars

Excision of scars. Small, well-defined scars can sometimes be satisfactorily excised via punch excision, sub-cision or punch elevation [1].

Dermabrasion and laser resurfacing [2–7]. These may be of value for depressed scars of even depth, but multiple ice-pick scars of irregular depth respond badly. Dermabrasion involves the use of a high-speed wire brush or diamond fraise to plane the skin under local or general anaesthesia. It is best avoided in summer because of the risk of post-inflammatory hyperpigmentation. Hypopigmentation can also occur in some patients. Postoperative care is very important, and should include the use of a topical sunscreen and in some cases prophylaxis with oral aciclovir to prevent herpes simplex infection. In the past 5 years, laser resurfacing has taken over from dermabrasion [6,7].

A recent review on laser resurfacing for acne scars confirmed that there is lack of good-quality evidence for any conclusions to be drawn about the effectiveness of lasers for treating atrophic or ice-pick acne scars. No randomized, controlled trials where laser treatment was compared to either placebo or a different type of laser were found. Most of the 27 studies uncovered were poor-quality case series with small numbers of acne-scarred patients. The authors therefore concluded that well-designed, randomized controlled comparisons of carbon dioxide versus Erbium:YAG laser are urgently needed [8].

Filling materials. Injections of purified bovine dermal collagen to augment tissue defects are of limited benefit, but have been shown to help soft scars that are easily stretched [9–11]. Deep ice-pick and fibrotic scars show little improvement. Degradable, biosynthetic implants such as hyaluronic acid (Restylane, Perlane) are now being used in preference to collagen as the potential risks of sensitization and foreign body reactions are much lower with these agents.

Recollagenation of acne scars refers to a technique in which an implant of freeze-dried, irradiated human cadaver fascia lata is placed in an intradermal pocket at the site of each scar through a needle hole to elevate the depressed epidermis [12]. A further alternative is the injection of autologous fat into atrophic scars.

Gelatine matrix implant. One or two injections of this preparation have been shown to help scars and the improvement was maintained over 2 years [13].

Chemical peeling. Chemical peeling has been used in the treatment of atrophic acne scars. Expertise is required for such a procedure. Several chemical agents are used, including α-hydroxy acids, glycolic acids and resorcinol. The reader is referred to detailed texts on how, when and why to use chemical peels [14–17].

Multiple treatments. If several approaches are required, it is probably best to excise the larger scars and then re-plane the skin surface using lasers. Filling agents may then be necessary. In older patients with significant loss of tissue, face-lifts may help.

Treatment of hypertrophic and keloids scars

Keloids and hypertrophic scars (Fig. 42.67) also vary in their response to therapy, but several options are worth trying. These include steroids, either potent topical steroid creams or triamcinolone depot injections, excision, cryotherapy or topical application

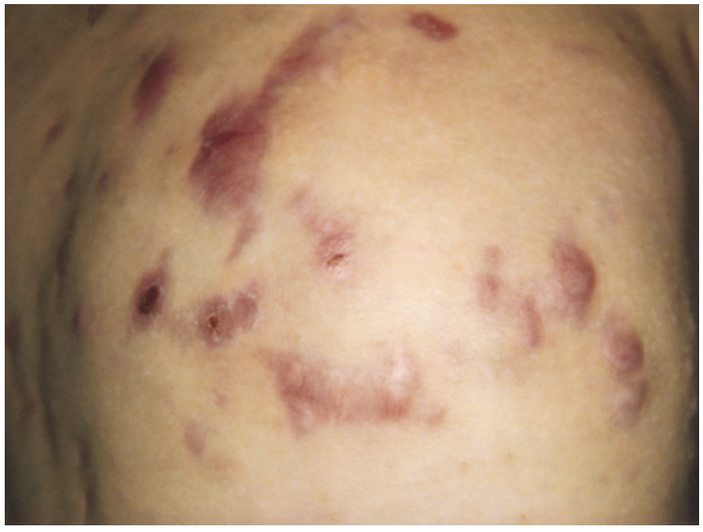


Fig. 42.67 Hypertrophic and keloid scars over the upper trunk.

of silicone gels. There are several papers that testify to both the benefit and pitfalls of such therapy [18,19]. Potent steroids such as clobetasol propionate need to be applied carefully to the scar, usually twice daily, avoiding adjacent skin to prevent atrophy of the perilesional skin. Each treatment should be used initially for 2 months. Intralesional triamcinolone (2.5 mg/mL; 0.05–0.1 mL) injections into the scars can be tried at monthly intervals for a few months and the decision about subsequent therapy based on the response. Excision is frequently followed by recurrence, which may be larger than the original lesion. Double-blind studies are needed to confirm the optimum therapy for hypertrophic and keloid scars. It is important to remember that some scars improve with time and without treatment. Vascular keloids may benefit from therapy with the pulsed tuneable dye laser [20]. Silicone gel sheeting applied for 12/24 h per day for at least 2 months to young hypertrophic and keloid scars has been reported to be of benefit [21]. Such sheets are available without prescription in many countries but adequate trials are lacking.

Many patients have multiple scars, and since multiple treatments are available then different treatments could be used for different scars—perhaps with some not being treated to act as an internal control. This approach might determine the natural resolution of the patient's scars.

Cosmetic camouflage. Although certain cosmetics may induce acne, it is often psychologically necessary for female patients to use some form of cosmetic camouflage. Patients can be advised that they can wear light, non-greasy make-up. In certain countries, professional advice is available, and in the UK these cosmetics are available on prescription. Make-up is often needed for persistent post-inflammatory pigmentation seen most frequently in darker skins. Topical all-*trans*-RA and azaleic acid may be of possible therapeutic benefit in reducing post-inflammatory pigmentation, but therapy has to be continued for many months.

References

1 Orentreich N, Durr NP. Rehabilitation of acne scarring. *Dermatol Clin* 1983; **1**: 405–13.

2 Coleman WP. Dermabrasion and hypertrophic scars. *Int J Dermatol* 1991; **30**: 629–31.
3 Orentreich N, Orentreich DS. Dermabrasion. *Dermatol Clin* 1995; **13**: 313–27.
4 Tsai RY, Want CN, Chan HL. Aluminium oxide crystal microderm abrasion. A new technique for treating facial scarring. *Dermatol Surg* 1995; **21**: 539–42.
5 Goodman G. Dermabrasion using tumescent anaesthesia. *J Dermatol Surg Oncol* 1994; **20**: 802–7.
6 Alster TS, West TB. Resurfacing of atrophic facial acne scars with a high-energy, pulsed carbon dioxide laser. *Dermatol Surg* 1996; **22**: 151–4.
7 Goodman GJ. Facial resurfacing using a high energy, short pulse carbon dioxide laser. *Australas J Dermatol* 1996; **37**: 125–31.
8 Jordan RE, Cummins CL, Burls AJE *et al*. Laser resurfacing for facial acne scars. *Cochrane Database of Systematic Reviews* 2008; **2**: CD001866.
9 Klein AW. Implantation technics for injectable collagen. Two and one-half years of personal clinical experience. *J Am Acad Dermatol* 1983; **9**: 224–8.
10 Stegman SJ, Tromovitch TA. Implantation of collagen for depressed scars. *J Dermatol Surg Oncol* 1980; **6**: 450–3.
11 Varnavides CK, Forster RA, Cunliffe WJ. The role of bovine collagen in the treatment of acne scars. *Br J Dermatol* 1987; **116**: 199–206.
12 Burres SA. Recollagenation of acne scars. *Dermatol Surg* 1996; **22**: 364–7.
13 Millikan L, Alexander AM, Chungi VS *et al.* Long-term safety and efficacy with Fibrel in the treatment of cutaneous scars—results of a multicenter study. *J Dermatol Surg Oncol* 1989; **15**: 837–42.
14 Ghersetich I, Teofoll P, Gantcheva M *et al.* Chemical peeling: how, when, why? *J Eur Acad Dermatol Venereol* 1997; **8**: 1–11.
15 Brody JH. *Chemical Peeling*. St Louis: Mosby Year Book, 1992: 23–31.
16 Rubin MG. Jessner's peels. In: *Manual of Chemical Peels*. Philadelphia: Lippincott, 1995: 79–88.
17 Furukwa F, Yamamoto Y. Recent advances in chemical peeling in Japan. *J Dermatol* 2006; **33**: 655–61.
18 Ernst K, Hundeiker M. Results of cryosurgery in 394 patients with hypertrophic scars and keloids. *Hautarzt* 1995; **46**: 462–6.
19 Layton AM, Yip J, Cunliffe WJ. A comparison of intralesional triamcinolone and cryosurgery in the treatment of acne keloids. *Br J Dermatol* 1994; **130**: 498–501.
20 Alster TS, Williams CM. Treatment of keloid sternotomy scars with 585 nm flashlamp-pumped pulsed-dye laser. *Lancet* 1995; **345**: 1198–200.
21 Chmori S. Effectiveness of silastic sheet coverage in the treatment of scar keloid (hypertrophic scar). *Aesthetic Plast Surg* 1988; **12**: 95–9.

Uncommon associations with acne

A miscellaneous group of either distinct diseases or unusual physical features which may coexist with acne are included in this section. In some, the association is unquestionable, but in others the association is debatable. In many of these clinical situations much more research is required to provide clarity.

Acne excoriée

Synonym
- Acne des jeunes filles

Acne excoriée is considered a subset of neurotic excoriations. It is seen predominantly in adolescent girls and young women (Fig. 42.68) and is regarded as a self-inflicted skin condition in which the sufferer compulsively picks real or imagined acne lesions. The disease can emerge into dermatitis artefacta. There is frequently some personality or psychological problem underlying the condition including obsessive compulsive disorder [1,2]. Evidence of linear erosions is suggestive of self-mutilation, and underlying psychiatric disease should be suspected [3]. An atopic background may be evident and the patient often complains of significant pruritus in the lesions. A contact dermatitis should be considered and excluded [4]. The persistent trauma to lesions can result in significant scarring.

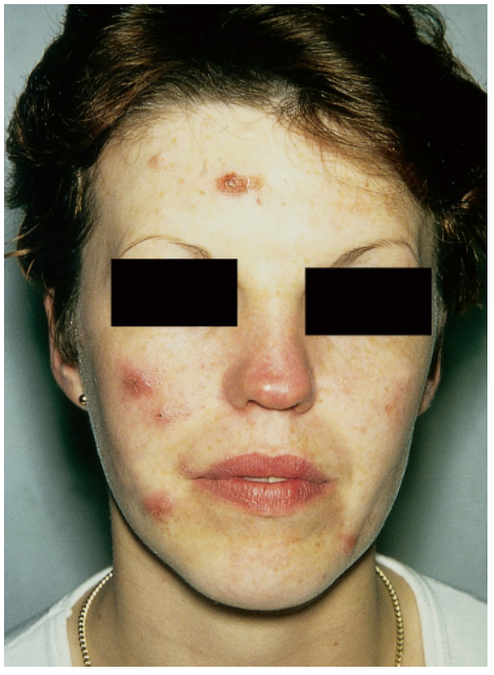


Fig. 42.68 A patient with acne excoriée.

Treatment can be difficult. The importance of not picking needs to be emphasized. If active acne is evident, an aggressive approach to treatment should be utilized. By reducing the number of inflammatory lesions, the regimen leaves the patient with fewer spots to tamper with. Topical treatment has a tendency to irritate the skin and aggravate the problem.

In those with virtually no acne spots, trifluoperazine hydrochloride (5–30 mg/day), pimozide (2 mg twice a day) and olanzapine 2.5–5 mg daily have all been used with some success [5,6] along with psychotherapeutic support. In addition, doxepin as well as selective serotonin re-uptake inhibitors such as fluoxetine have been used, as has sertraline. Hypnosis and habit reversal techniques have also been utilized [7,8]. Treatment for facial scarring and ulceration resulting from acne excoriée has been improved using the 585-nm pulsed dye laser along with cognitive psychotherapy [9].

Apert's syndrome

Synonym
- Acrocephalosyndactyly

Apert's syndrome is a rare congenital type I acrocephalosyndactyly, characterized by craniosynstosis and early epiphyseal closure which results in deformities of the skull, hands and feet. The characteristic facial abnormalities are: hypertelorism, a flattened occiput, proptosis due to shallow orbits, prognathism, a parrot-beaked nose and fused shortened digits. Severely delayed tooth eruption, shovel shaped incisors and malocclusion of teeth occurs.

Abnormalities of the upper and lower respiratory tracts include cleft soft palate and bifid uvula [10]. There is an association between acne and Apert's syndrome [11–12] and most adolescents with this disorder are prone to the development of severe pustular acne which can extend from the usual sites on the trunk and face to forearms and buttocks (see Figs 42.61 & 42.62) [13]. Early epiphyseal closure, like acne, is an androgen-mediated event. No difference in the androgen receptor expression has been demonstrated between patients with Apert's cases compared to controls, suggesting that the underlying problem in Apert's relates to abnormal sensitivity to normal circulating levels of androgens rather than excess numbers of androgen receptors [14–16].

Other cutaneous changes reported in Apert's include seborrhoea, hyperhidrosis, nail dystrophy, hyperkeratosis of plantar surfaces and ocular and cutaneous hypopigmenatation [17]. Apert's syndrome may be inherited as an autosomal dominant, but most mutations are new and of paternal origin, with a 1% risk of a second child being affected. The genetic defect is a missense mutation of the amino acid substitution of serine–proline dipetide in exon 7 of chromosome 10, the fibroblast growth receptor (*FGFR-2*) [18].

The acne responds less well to topical preparations and oral antibiotics in Apert's syndrome and patients frequently require oral isotretinoin [19,20]. Etretinate has also been reported to be beneficial in refractory cases [21].

Body dysmorphic disorder and acne

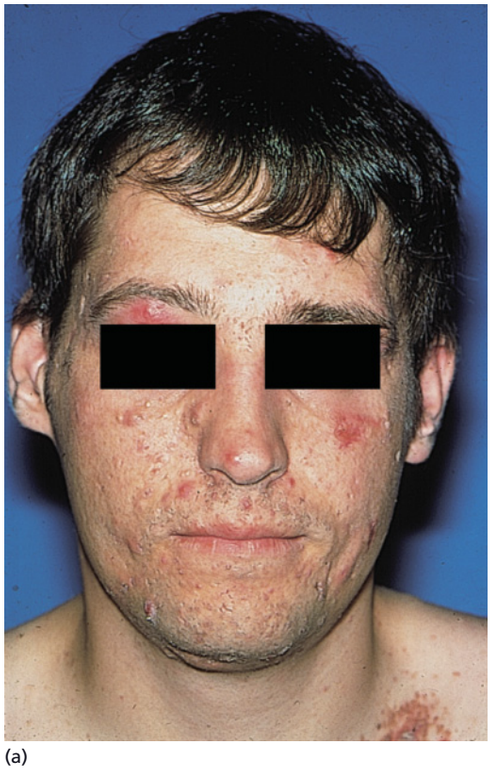
A small number of patients with body dysmorphic disorder have acne as their prime symptom [22]. The acne is usually very mild, and the patient's complaint is out of all proportion to the physical signs. These patients require much support; they are often depressed or obsessional and have a significant risk of suicide [23]. Unfortunately, they usually tolerate psychiatric treatment badly, and the dermatologist must treat the acne aggressively with effective treatment. Isotretinoin given for 4 months is the preferred therapy. The authors consider that 'relapse', either real or perceived, is common and requests for further isotretinoin are also common [24]. This subject is dealt with in greater detail in Chapter 64.

Darier's disease

This disease is discussed in detail in Chapter 19, but it is possibly associated with acne; some patients with Darier's disease have significant nodular acne that can be very difficult to treat with antibiotics, oral isotretinoin or acitretin. The variable penetrance of Darier's disease means that sometimes the clinical features are relatively inconspicuous, such that Darier's disease may be initially missed in patients with severe nodular acne (Fig. 42.69). Two patients with prominent nodular and comedonal lesions on the face and scalp showed histological features of Darier's disease on examination of a comedone [25].

Drug-induced acne/acneiform eruptions

Many drugs have been implicated as possible aggravators or inducers of acne [26–51]. Much of the evidence consists of isolated case reports, and many of the reported reactions are idiosyncratic.



(a)



(b)

Fig. 42.69 (a) A patient with acne conglobata, which can coexist with Darier's disease (b).

Acneiform eruptions account for about 1% of all drug-induced skin eruptions (Table 42.19). Clinically the acne presents as monomorphic inflammatory papules and pustules with little evidence of comedones, contrasting with the heterogeneous morphology usually seen in normal acne. The face and upper trunk are most frequently affected. The interval between the onset of the acneiform eruption and the start of the drug implicated depends very much on the agent provoking the response. Only those substances that definitely induce acne or acneiform eruptions will be discussed.

Table 42.19 Drug classes and types of medication that may exacerbate or cause acne.

Drug class or type	Examples
Corticosteroid:	
topical	Betamethasone
oral	Prednisolone
inhaled	Budesonide
ACTH	ACTH, synthetic ACTH
Anabolic steroid/synthetic androgen	Danazol, nandrolone, stanozolol
Anticonvulsant	Carbamazepine, phenytoin, phenobarbitone, troxidone, gabapentin, topiramate
Antidepressant	Lithium, sertraline
Other neuroleptic/antipsychotic	Pimozide, risperidone
Antitubercular	Isoniazid, pyrazinamid
Antineoplastic/EGFR-antagonists	Dactinomycin, pentostatin, cetuximab
Antiviral	Ritonavir, ganciclovir
Calcium antagonist	Nilvadipine, nimodipine
Halogen	Sodium fluoride, potassium iodine
Human growth hormone	Genetically engineered human growth hormone
Vitamins	Vitamin B_{12}, possibly other B vitamins
Miscellaneous	Buserelin, cabergoline, ciclosporin, clofazimine, dantrolene, disulfuram, famotidine, follitropin alfa, isosorbide mononitrate, medroxyprogesterone, mesalazine, quinine, ramipril, sulphur, thiouracil, thiourea

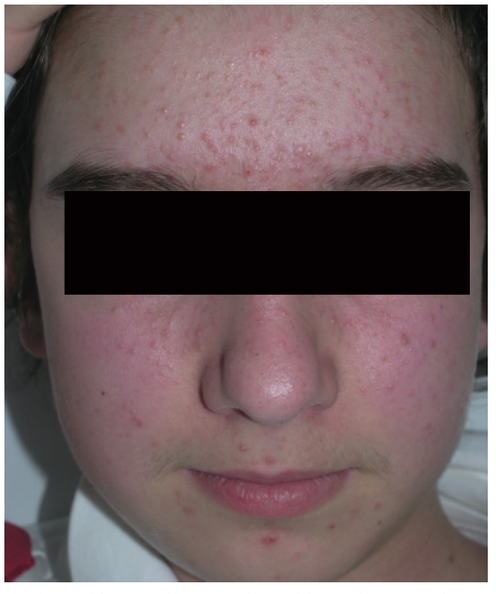


Fig. 42.70 A patient with acne due to oral steroids used to treat dermatomyositis. (Courtesy of Dr V. Bettoli, University of Ferrara, Italy.)

Corticosteroids may provoke an acneiform reaction regardless of their route of administration (Fig. 42.70) [31–36]. The precise mechanism is uncertain. Corticosteroids induce cornification in the upper part of the pilosebaceous duct, but do not affect the number of surface bacteria [31,33]. Steroid acne is usually, but not invariably, more monomorphic than true acne vulgaris; however,



Fig. 42.71 Acneiform rash in a gentleman receiving cetuximab for colonic cancer.

both inflammatory and non-inflammatory lesions may be present on the face, back and chest [50].

Androgens including anabolic steroids and gonadotrophins may precipitate acne, especially in athletes who take performance-enhancing drugs [37–41]. In the former group, both testosterone and stanazolol have been shown to increase sebum excretion and the surface population of *P. acnes* [40]. Acne is said to occur in up to 50% of athletes and body builders that abuse anabolic–androgenic steroids, especially in young men 18–26 years old. Both acne conglobata and acne fulminans may result [41].

Antiepileptic drugs, especially phenytoin, have been incriminated in case reports in the past, but a study of severe epileptics taking several different anticonvulsants showed that they were at no more risk of acne than the normal population, although some patients with severe epilepsy showed features of hypogonadism [42].

Isoniazid, especially in patients who slowly inactivate the drug, provokes an acneiform rash [43]. A small number of patients receiving PUVA treatment have been reported to develop a perioral dermatitis and/or an acneiform eruption on the face [44,45].

An acneiform eruption has also been described in patients taking amineptine [29,46]. Most reported cases have involved adult females. Comedonal lesions are the most prevalent and inflammatory lesions are usually absent or few in number. The causal mechanism is unknown; the drug contains no halogenated substances. The drug should be withdrawn, but the response is variable and oral isotretinoin (0.5–1.0 mg/kg/day) plus physical treatment of the comedones appears to be the most appropriate treatment.

A follicular acneiform eruption (Fig. 42.71) has been reported in cancer patients treated with the anti-EGF receptor inhibitors [47,48]. The consistency of lesion morphology and timing following monotherapy with this antibody suggest a direct biological effect of the antibody. Histological examination of the lesions, which occur within a few weeks of receiving the antibody, has demonstrated a superficial dermal inflammatory cell infiltrate surrounding a dilated follicular infundibulum. A direct correlation



Fig. 42.72 A patient with acne due to lithium. (Courtesy of Dr V.M. Yates, Royal Bolton Hospital, Bolton, UK.)



Fig. 42.73 A patient with pomade acne.

between efficacy to cancer therapy and severity of acneiform reaction has been reported [48].

Iodides and bromides used to be a common cause of follicular pustules that were marked by the rapidity of onset after starting these preparations [49,50]. In contrast to acne vulgaris, all people and all ages were affected. Lithium is currently still an occasional cause of iatrogenic acne (Fig. 42.72).

In all cases, the risks and benefits must be assessed, and the causative drug should be stopped if possible. Clinicians should enquire about use of over-the-counter products, as well as treatments prescribed, when trying to elicit a drug-related cause for acne.

Endocrine acne

The role of the endocrine system in the aetiology of acne is discussed elsewhere in this chapter. Most patients suffering from acne have no underlying endocrinological abnormalities. The term 'endocrine' acne should be reserved for cases associated with clear signs and symptoms of endocrine disease such as Cushing's disease, late-onset congenital adrenogenital syndrome and polycystic ovarian syndrome. The latter is the commonest cause of 'endocrine' acne. The acne is generally more severe, associated with marked seborrhoea, may present abruptly and is frequently more refractory to therapy. Insulin resistance and acanthosis nigricans can occur in the context of hyperandrogenism in the HAIR-AN syndrome. These patients should be monitored carefully as they have an increased risk of cardiovascular disease and type II diabetes. Also reported is the so-called SAHA syndrome (*s*eborrhoea, *a*cne, *h*irsutism and *a*lopecia), which can be associated with polycystic ovarian syndrome, cystic mastitis, obesity and infertility (Orfanos CE *et al*. data presented at Third Teupitzer Colloquium, Berlin 2000). The association of these clinical features should also alert the physician to exclude an androgen-producing tumour.

Externally induced acne

Cosmetic acne

Cosmetics are cited as a cause for acne particularly in adolescent girls and young women. This variant is reported more commonly in the USA [51]. The lesions characteristically occur in the perioral area, and are seen more frequently in those who had acne as an adolescent and in those who have used cosmetics for a long time. The rabbit-ear model, which is oversensitive for humans, has shown that some cosmetics, especially those containing lanolin, petrolatum, certain vegetable oils, butylstearate, lauryl alcohol and oleic acid, are comedogenic. Many cosmetics, especially in the USA, are now screened by the rabbit-ear test and appropriate cosmetics are labelled as being non-comedogenic [52]. Patients should be warned that switching to a non-comedogenic cosmetic does not bring rapid clinical improvement in cosmetic acne. Treatment with topical retinoids or benzoyl peroxide is usually successful.

Pomade acne

Pomades are greasy preparations used to defrizz curly hair used most frequently in Afro-Caribbeans. The rash is similar to cosmetic acne and consists predominantly of many non-inflamed lesions around the forehead and other areas, where greasy pomades may extend onto the hairless skin (Fig. 42.73) [53]. It may also coexist with true acne vulgaris. The rabbit-ear model has shown that certain pomades are comedogenic. Restriction of the

use of pomades is essential, and the treatment of choice is with topical retinoids.

Detergent acne

This uncommon form of acne develops in patients who wash many times each day, in the mistaken hope of improving their existing acne. Trauma and the alkalinity of soap are likely to be involved in the mechanism. Pustular and papular lesions are most noticeable [54]. Several bacteriostatic soaps contain weak acnegenic compounds, such as hexachlorophene.

Folliculitis on the scalp (dissecting cellulitis of the scalp/folliculitis decalvans) and acne

Scalp folliculitis

About 1% of acne patients will complain of, or are found on examination to have, small papules or pustules in the scalp. In patients with moderate and severe acne, it is not unusual to see inflammatory papules, pustules and nodules in and around the hairline in the occipital area. Despite the frequent occurrence of this association, there have been few clinical and research studies.

Follicular pustules in treated acne patients are also seen in subjects with Gram-negative folliculitis. Patients receiving treatment with oral isotretinoin may develop a pustular scalp folliculitis, which is either due to *S. aureus* infection or may arise for unknown reasons and may persist for several weeks after stopping therapy. If due to a *S. aureus* infection, response to therapies such as oral flucloxacillin is very successful. Significant, very persistent scalp folliculitis associated with an acneiform eruption has been recorded in patients with cyclical neutropenia [55].

Folliculitis decalvans

Folliculitis decalvans is a chronically progressive disorder of the hair-bearing areas on the scalp that leads to scarring, alopecia and atrophy [56–58]. The aetiology is unknown, but in some cases *S. aureus* may be identified from lesions, and it has been suggested that folliculitis decalvans may be the result of an abnormal host response to toxins released from *S. aureus*. If *S. aureus* is identified systemic antibiotics are required; oral clindamycin or rifampicin may help by offering better tissue penetration, one case report suggests added benefit by also using topical mupirocin acid [59]. An isolated case report advocates the use of oral clindamycin in combination with oral isotretinoin and steroids [60]. Topical fusidic acid and oral zinc have also been used with some success in one series [61] but the response to any therapy is frequently poor. Radiation therapy and treatment with dapsone have also been reported in isolated cases [62,63]. Areas of tufted folliculitis have been identified in cases of folliculitis decalvans and the histological features embrace hyperkeratosis, follicular plugging and perifollicular inflammation.

Dissecting folliculitis of the scalp

Synonym

- Perifolliculitis capitis abscedens et suffodiens

This condition is more frequently seen in Afro-Caribbean males. It is an uncommon chronic suppurative disorder of the scalp [64–68]. Together with acne conglobata, hidradenitis suppurativa and pilonidal cysts it is a component of the 'follicular occlusion tetrad'. Patients present with multiple, tender, inflammatory nodules and abscesses most commonly on the vertex and occiput of the scalp. Lesions frequently coalesce into sinus tracts. Scarring alopecia frequently results from the chronic suppurative changes.

Follicular hyperkeratosis appears to be the primary feature in pathogenesis but secondary bacterial superinfection frequently occurs. Histology demonstrates a neutrophilic perifolliculitis with follicular destruction, granulomas and fibrosis.

Lesions characteristically last years and are cosmetically disfiguring, painful and foul smelling. It has been reported to occur with marginal keratitis [64]. Response to therapy is poor. Options include high-dose systemic antibiotics used for acne (such as minocycline 100 mg twice daily, trimethoprim 300 mg twice daily). Success has also been reported with oral zinc sulphate, 135 mg three times a day [65] and topical isotretinoin [66]. A prolonged course of oral isotretinoin has been advocated as one of the most effective treatments [67]. Other treatment options include potent topical, intralesional and systemic steroids and widespread surgical excision with skin grafting [68].

Solid facial oedema

This is a rare and disfiguring complication of acne [69] that has been reported in twins [70]. It is also reported as a consequence of rosacea [71] and in Melkersson–Rosenthal syndrome. The solid symmetrical or asymmetrical facial oedema leads to significant distortion of the midline face and cheeks due to soft tissue swelling most likely due to pre-existing hypoplastic lymphatics. The thickened woody changes are often associated with erythema. The disorder is frequently progressive, and the associated acne must be treated aggressively to minimize the swelling, which can become permanent. Successful treatment with oral isotretinoin alone or in combination with clofazamine or ketotifen has been reported [72–74]. Short or intermittent courses of oral steroids may also help the inflammatory component.

Granulomatous acne

Extensive, localized acne may also be due to an extensive granulomatous reaction (Fig. 42.74) to the mediators of acne inflammation. The precise mechanism producing localized granulomatous acne is not known. The clinical picture is usually that of deep, very well-demarcated lesion(s), especially on the cheeks. Response to therapy is slow and sometimes unsatisfactory, and antibiotics and isotretinoin are of limited benefit; oral steroids are also often required.

These patients often have recurrent relapses and therefore long-term follow-up is recommended.

Hidradenitis suppurativa

This entity is described in more detail in Chapter 30. However, given its occasional association with severe nodular acne, often of the conglobate type, a brief note is necessary. There is often a family history and the onset is usually in late adolescence; the disease may persist up to the age of 40 or 50 years [75–78]. There are very occasional reports of early- or late-onset disease. It is a persistent disease that affects the axillae, breasts, and the genital



Fig. 42.74 A patient with granulomatous acne.

and perianal areas, and may sometimes spread extensively on to the buttocks and lower back. There is clinical evidence of comedones (often polyporous), papules, pustules, deep nodules, large abscesses, sinus track formation and scarring. The inflammatory lesions are frequently deep seated, exudative, painful, and malodorous, which often results in significant compromise of daily activities. Thus, the disease produces a high degree of morbidity [76].

It is primarily a disorder of follicular occlusion. It is not a primary disease of the apocrine gland. Aetiological factors such as hyperandrogenism, obesity, smoking and local irritation (e.g. from excessive sitting) are not consistently associated with the disease, but in some patients may be relevant aggravating factors.

Treatment is usually very disappointing. Therapeutic options include long-term antibiotics as used in acne but in high doses, such as minocycline at 100 mg twice daily, trimethoprim 300 mg twice daily; co-cyprindiol plus additional CPA (100 mg/day taken from the fifth to the 14th day of the cycle); topical retinoids; topical antiseptic washes; oral isotretinoin; oral zinc; and potent topical, intralesional and intermittent pulsed oral steroids (the dose of steroid prescribed depending upon the severity of the inflammation). Combinations of such therapy may also be tried. At the moment, there are no good clinical data to indicate which therapy should be prescribed first and in what order. Finasteride 5 mg/day has been reported to be successful [79] and, more recently, infliximab [80].

Childhood acne

Acne can present in the first year of life and early childhood as well as in the classic prepubertal and adolescent age groups [81]. It is usually mild and transient in the neonatal period but can be more severe and persistent in the infant.

Neonatal acne and neonatal cephalic pustulosis

In the neonatal period, acne may present at birth or shortly afterwards as predominantly comedonal lesions of the cheeks with a paucity of inflammatory lesions. The acne usually settles spontaneously and leaves little in the way of scars. The underlying pathogenesis is thought to relate to hyperactivity of the sebaceous glands stimulated by neonatal androgens from the testes in boys and adrenals in girls [82].

Neonatal cephalic pustulosis (NCP) was historically referred to as neonatal acne [83]. This disorder usually presents in the first 3 weeks of life, and affects about 20% of newborns. It is characterized by erythematous papular/pustular lesions especially on the cheeks but also on the chin, eyelids, neck and upper chest. Comedonal lesions are not usually seen. It has been postulated that NCP develops in association with *Malassezia sympodialis* and *Malassezia globosa*; however, the exact aetiological role of *Malassezia* is uncertain, as the organism is part of the normal flora of neonatal skin, and up to 38% of cases had negative smears in one study [84]. Another explanation is that NCP relates to an overgrowth of lipophilic yeasts at birth that results in an inflammatory reaction leading to monomorphic papules and pustules in predisposed neonates with more sebum production. Treatment is often not required for this self-limiting disorder which usually heals without scarring in 1–3 months. If the condition does persist beyond this time and/or is widespread and unsightly, topical ketoconazole cream helps to shorten the duration of lesions [85,86].

Differential diagnosis should include infections, milia, miliaria, transient neonatal pustular melanosis, sebaceous hyperplasia, erythema toxicum neonatorum, bilateral naevus comedonicus, acneiform eruptions relating to topical applications (acne venenata) or systemic maternal medications (steroids, phenytoin, lithium) or a virilizing luteoma in pregnancy [87].

Infantile acne

Infantile acne is much less common and usually presents later than neonatal acne/NCP at 3–6 months of age but has been reported as late as 16 months [86–98]. Male infants are affected more commonly than females and there may be a history of severe acne in one or more parents. Patients present with facial acne between 3 and 24 months, and the acne may persist up to 5 years of age (Fig. 42.75) [86,87,90–97]. The lesions are generally localized to the cheeks. Clinically, comedonal acne is prominent but inflammatory papules, pustules and nodules can occur and may result in scarring (Fig. 42.76). Rarely, conglobate acne can be seen associated with deep-seated, inflammatory nodules and sinus tracts [86–89].

A study of 29 patients with infantile/juvenile acne over a period of 25 years [88] showed that the median age of onset was 9 months; the disease was mild in 24%, moderate in 62% and severe in 14%. In 59% the acne was predominantly inflammatory. Five patients (17%) were left with scarring. It is important to note that this single study was from a specialist acne centre, and therefore the data may not reflect completely the overall clinical pattern of patients with infantile acne. It is thought that infantile/juvenile



Fig. 42.75 A patient with infantile acne.



Fig. 42.76 A patient who has scarring as a consequence of infantile acne.

acne initially results from transplacental stimulation of the adrenal gland, as most sufferers have elevated plasma adrenal androgens [92]. Sebaceous glands are unique, in skin, in having enzymes capable of converting the adrenal androgen dehydroepiandrosterone to androstenedione and testosterone. It is uncertain why the acne should sometimes last for several years. Infantile acne is very rarely associated with other clinical features of androgen excess such as hirsutism or premature closure of epiphyses; very occasionally, there may be transient or more persistent high plasma levels of testosterone, LH and FSH. An associated virilizing tumour or underlying congenital adrenal hyperplasia is extremely rare. If the child is otherwise well and there are no other abnormal features, no endocrine investigations are required. However, such investigations may be appropriate in a patient who develops acne between 5 and 8 years of age. Occasionally, a drug such as phenytoin has been incriminated, but the evidence is weak [93].

The principles of treatment are the same as for patients with adult acne, except that the tetracycline group of drugs is not prescribed because of the risk of damage to developing bones and permanent discoloration of dentition. For mild disease, topical therapies such as topical retinoids and/or topical antimicrobials (not containing tetracycline) are recommended. For moderate disease, a topical retinoid and/or benzoyl peroxide combined with a systemic antibiotic such as erythromycin (as ethyl succinate, 125 mg three times a day) for 6 months is essential until lesions have totally disappeared. Alternatives include oral trimethoprim (100 mg twice daily) [88].

Deep nodules can be injected with a low concentration of intralesional triamcinolone acetonide (2.5 mg/ml). Infantile acne may take several months to resolve—the more severe the disease the longer the disease lasts [88]. Isotretinoin is rarely needed, and only for severe non-responding cases. Successful treatment with isotretinoin has been reported in the literature using doses of 0.36–2 mg/kg/day for 4–6 months in children younger than 5 years [89,99,100]. Patients with infantile acne may develop significant acne as teenagers [86,88,95–98]. Topical retinoids may provide prophylaxis following systemic therapy [98].

Mechanical acne

Synonym
- Acne mechanica

This term reflects acne that occurs at the site of physical trauma due to repeated mechanical and/or frictional obstruction of the pilosebaceous outlet [101–103]. Comedo formation is the result of the trauma or friction. Examples include ‘fiddler’s neck’, which may occur on the neck of violin players, and is characterized by well-defined plaques with the presence of comedones, lichenification and pigmentation. Headbands, tight bra straps, suspenders and collars as well as turtleneck sweaters may cause localized acne in the frictional sites [102]. The mechanism involved in the development of mechanical acne is unclear. Most patients have a tendency to develop acne, and its localization may be caused by an irritant dermatitis of the upper part of the pilosebaceous duct or excessive hydration at that site. Adolescent patients lying in bed for a long time, for example following a fractured femur in the orthopaedic ward, may develop a flare of acne—so-called ‘immobility acne’. Linear areas and geometrically distributed areas of involvement should raise the suspicion of acne mechanica. This is probably due to a change in the environment of the skin, which may enhance bacterial colonization of the duct [103]. Treatment of

these conditions should include elimination of the causative forces and treatments aimed at reducing non-inflammatory and inflammatory lesions as in other forms of acne.

Occupational acne

Oil and tar acne

This acneiform eruption occurs in areas of skin that are in contact with oils and crude tars [104–107]. It is now much less common because of improved working practices. However, outbreaks do still occur. In a controlled study of 55 workers in a tar distillation plant, 18% in the study group, and 4% of the control group, had periorbital comedones [105].

Not surprisingly, men are more often affected than women. The skin may show conspicuous comedones with just the occasional superficial inflammatory lesion. Occupational acne can occur within 6 weeks of exposure on almost any site, but the thighs and lower arms are especially prone. It has been suspected, but not proven, that individuals with acne vulgaris are more likely to develop oil acne. The commonest oils involved are the impure paraffin mixtures used in the engineering industry. Petroleum products can affect oilfield and refinery workers; workers exposed to heavy coal-tar distillates, especially pitch and creosote, may also develop acne. Dichlorodiphenyltrichloroethane (DDT), asbestos and heavy water distillate has caused acne in some patients.

The treatment is removal from the source of the disease and the use of topical retinoids. If significant inflammatory lesions are present, then topical and oral antimicrobials may help. Very infrequently, oral isotretinoin has been successfully prescribed [107].

Chloracne

This term is used to describe occupational acne caused by exposure to chlorinated aromatic hydrocarbons. Chloracne lesions develop after prolonged exposure to the hydrocarbons and consist of multiple comedones; inflammatory lesions are not always evident [108–123]. Lesions are usually located on both sides of the head and neck (Fig. 42.77), especially the temporal retroauricular and mandibular regions but in more severe cases the chloracne may occur on other parts of the body including the axillae, scrotum, extremities, trunk and buttocks. Inflammatory lesions may be evident as cystic papules and nodules. These may heal with significant scarring and outbreaks may persist for many years after exposure to the causal agent.

Other skin lesions may also occur, including pigmentation, hypertrichosis and palmar and plantar hyperhidrosis. Ophthalmic chloracne may occur, due to the Meibomian gland involvement. Systemic abnormalities are less frequent but when present include fatigue, anorexia, neuropathy, impotence, disturbed liver function and hyperlipidaemia. The chloracne and systemic disturbances may last for many years following exposure [113,116,118,124]. Persistent chloracne, goitre, headache, broken teeth, anaemia and arthritis were more prevalent in patients compared to controls in a 14-year follow-up study following exposure to polychlorinated biphenyls and polychlorinated dibenzofurans [124].

Chloracne has been reported following exposure to a number of chemicals (Table 42.20) linked to electrical conductors and insulators, fungicides, pesticides, wood preservatives and herbicides.



Fig. 42.77 A patient with multiple blackheads typical of chloracne.

Table 42.20 Chemicals resulting in chloracne.

Polychlornaphthalenes
Polychlorinated and polybrominated biphenyls:
Polychlorinated dibenzofurans
Polychlorinated dibenzodioxins
Tetrachloroazobenzenes/tetrachloroazoxybenzenes
Chlorophenol contaminants
Trifluoromethyls
Pyrazole derivatives

Contamination may follow an explosion resulting in the uncontrolled liberation of the chemical [110,116,120]. The chloracnegens have been identified in the blood in some cases [117,121,123]. They have not been identified in the pilosebaceous apparatus, but in one instance exposure to dioxin was reported to produce a hyperproliferative reaction of the cutaneous epithelium with squamous metaplasia of the pilosebaceous duct, with subsequent atrophy of the sebaceous gland [121].

The skin lesions are relatively persistent and resistant to treatment. Topical therapy with retinoids such as adapalene and tretinoin are worthy of a therapeutic trial; long-term oral antibiotic therapy may be needed for the inflammatory lesions. Oral isotretinoin does not help. This is not surprising, since the sebaceous gland has already undergone atrophy [121]. Gentle cautery under local anaesthetic cream (EMLA® applied for 60–75 min under polythene occlusion) produces excellent results [124]. Litigation is frequent when the contamination follows an industrial accident.

Osteoma cutis

This term denotes the development of focal ossifications in the subcutaneous and dermal tissue. This uncommon complication of acne is described more commonly in women with long-standing inflammatory acne and usually needs no treatment [125–127]. The calcification presents as small, 2–4 mm persistent papules, which are slightly firm to touch and usually skin or ivory coloured, mimicking macrocomedones and cysts [128]. They are occasionally associated with hyperpigmentation, especially after therapy with minocycline and tetracyclines [129]. A biopsy will reveal calcified trabecular bone formation surrounded by a perivascular proliferation, sometimes with increased fibrous tissue formation.

Treatment modalities are limited. Topical tretinoin has improved some cases by promoting transepidermal elimination of osteomas and is probably only successful in small superficial lesions [130,131]. Surgical ablative therapy is the most effective and reports describe techniques of combined dermabrasion and punch biopsy, scalpel incisions and curettage, extirpation of the small bone fragments after microdissection using a needle followed by a primary closure using steristrip application, as well as laser therapies. The Erbium:YAG laser is said to be associated with minimal thermal injury with better cosmetic results than the carbon dioxide laser [132–136].

Pilosebaceous naevoid disorders

Some of these disorders are only tenuously linked with the pilosebaceous system; they are described in more detail in Chapter 18.

Acne and non-acne naevi

Patients have been described with symmetrical areas of normal skin set in the midst of severe acne on the back [137], or with acne localized to one side of the back [138]. A reduced rate of sebum excretion with a reduction in surface bacteria has been demonstrated in the normal (non-acne) areas.

Comedo naevus

Synonyms
- Naevus comedonicus
- Naevus follicularis
- Naevus unilateralis comedonicus

This uncommon naevus is usually a developmental defect of the hair follicles [139–145]. The associated sebaceous glands may be normal, hypoplastic or hyperplastic. In one case, however, the sweat duct was the origin of the lesions [141]. Lesions usually occur on the scalp, face and trunk, and occasionally at unusual sites such as the penis. The individual lesions consist of keratin-filled pits, often grouped or linear in arrangement (Fig. 42.78). Occasionally, inflammatory acne lesions may be found. Although usually present at birth they often become more prominent at puberty [145]. *FGFR2* mutations have been identified in a comedonal naevus but not in the adjacent normal skin [146]. The symptoms are mainly cosmetic, but at times can be psychologically and physically devastating. An association with epidermolytic hyperkeratosis has been reported [144]. Treatment is usually of only limited success. Topical retinoids are a logical treatment. Twelve per cent aqueous ammonium lactate solution has been reported to be of benefit. Gentle cautery can help the less severe cases [145].



Fig. 42.78 A patient with a comedo naevus (predominantly consisting of blackheads) on the lower abdomen.

Familial comedones

This uncommon genetic disorder shows autosomal inheritance. The earliest lesions are monoporous, but later the face may be extensively involved with polyporous comedones and cysts, and scarring may follow. New lesions may continue into middle age.

Sebaceous naevus

Synonym
- Naevus sebaceus of Jadassohn

This is an organoid naevus, consisting of a mixture of relatively normal-looking epidermis, dermis, sweat and sebaceous glands. It usually presents on the scalp as an area of alopecia associated with a pinkish yellow, fleshy swelling [147–151]. At puberty, the sebaceous glands enlarge and the epidermis becomes verrucous. Co-occurrence with aplasia cutis has been reported [148]. Trichoepithelioma and eccrine syringoadenoma has been reported to develop in naevus sebaceus [150]. Unusual haematopoietic proliferation at birth that spontaneously resolved at 4 months has been documented [151]. Lesions occurring in the midline are often associated with mental subnormality and epilepsy. Excision is usually recommended because of malignant change into a squamous or basal cell carcinoma in later life [149].

Pyogenic granulomas in acne

Pyogenic granulomas are a rare complication of healing severe nodular lesions [152], and this occurs more frequently following isotretinoin therapy [153]. The lesions can either be left alone or, if single, treated with cautery; if multiple, they will usually respond to clobetasol priopionate (Dermovate®) cream topically twice daily applied carefully to the lesions over a 2–3-week period.

Seborrhoea

Excessive grease production is an uncommon reason for referral, but some patients complain bitterly of seborrhoea. Excess sebum can persist after the acne has regressed [154]. Patients with acromegaly or Parkinsonism, especially the post-encephalitic type, often have seborrhoea. Antibiotic and desquamating agents used in the treatment of acne do not influence the seborrhoea, but oral isotretinoin, CPA combined with oestrogen (co-cyprindiol) and spironolactone all significantly reduce the seborrhoea. Physicians have to decide whether the patient's distress justifies the use of these systemic drugs.

(Acne with) solar comedones

Synonyms
- Senile comedones
- Favre–Racouchot syndrome

These are seen in elderly people, especially in the periorbital areas (Fig. 42.79). Most patients have had high exposure to UV radiation, and the solar damage to the supporting dermis allows the pilosebaceous duct to become more easily distended with impacted corneocytes. The clinical presentation is that of multiple, open, and sometimes closed, comedones superimposed on a sun-damaged skin, usually symmetrically affecting the periorbital areas and the cheeks; occasionally the lesions are unilateral [155]. Similar lesions may be seen in pseudoxanthoma elasticum and after radiotherapy. In patients with isolated lesions, the edge of the adjacent skin may be mistaken for the pearly edge of a basal cell carcinoma. The lesions are easily removed with a comedo extractor, but they slowly recur. A topical retinoid to suppress the formation of future comedones may help. Gentle electrocautery can eliminate the smaller comedones [126].

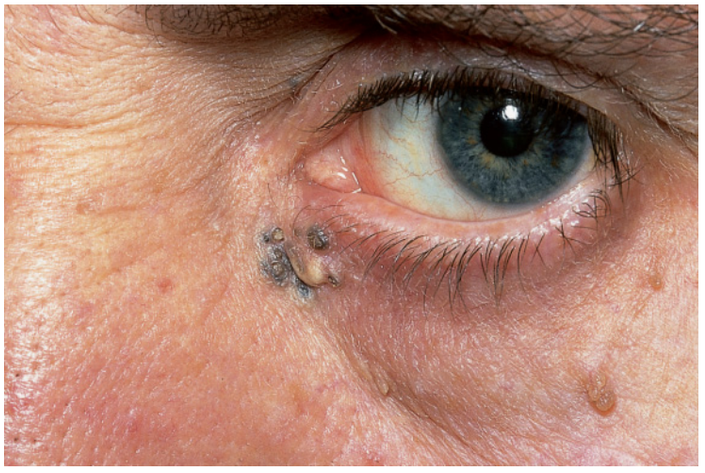


Fig. 42.79 Typical senile comedone seen in a light-exposed area in an elderly patient.

'Tropical' acne (hydration acne)

Troops in the Second World War suffered badly when posted to the Far East, but US Marines in Vietnam were relatively spared, possibly because acne-prone individuals were not selected for service [156]. Certain occupations may aggravate pre-existing acne; for example, workers in a hot, humid environment, such as cooks and pressers, are at risk. It is thought that hydration of the pilosebaceous duct pores may accentuate blockage of the duct and so precipitate inflamed lesions [157]. A similar explanation may apply to 'Mallorca acne', Norwegian acne (Fig. 42.80a & b) in which small, follicular papules appear, especially on the upper trunk, during or after a holiday in a hot, humid environment. Comedogenic sunscreens may also be an exacerbating factor in these patients [158]. Prolonged conventional treatment is often required as the event often precipitates or exacerbates troublesome pre-existing acne.

'Virally' induced acne

Acne can occur at unusual sites and at unusual ages with little involvement of the commonly affected sites. An acneiform rash has been reported at the site of previous herpes zoster infection. Histology revealed follicular occlusion and the disease was quite persistent [159].

A very small number of patients with severe acne and significant glandular fever responded poorly to oral antibiotics and oral isotretinoin. It was proposed that the viral illness in some way played an important role in the poor response [160].

References

1 Sneddon J, Sneddon I. Acne excoriée: a protective device. *Clin Exp Dermatol* 1983; **8**: 65–8.
2 Gupta MA, Gupta AK, Schork NJ. Psychosomatic study of self-excoriative behaviour among male acne patients: preliminary observations. *Int J Dermatol* 1994; **33**: 846–8.
3 Gupta MA, Gupta AK. Psychodermatology; an update. *J Am Acad Dermatol* 1996; **34**: 1030–46.
4 Kranke B, Brabek E, Derhaschnig J *et al.* Acne excoriata—look for allergy! *Dermatology* 2001; **203**: 256–7.
5 Gupta MA, Gupta AK. Olanzapine is effective in the management of some self inflicted dermatoses: three case reports. *Cutis* 2000; **66**: 143–6.
6 Gupta MA, Gupta AK. Olanzapine may be an effective adjunctive therapy in the management of acne excoriee: a case report. *J Cutan Med Surg* 2001; **5**: 25–7.
7 Shenefelt PD. Using hypnosis to facilitate resolution of psychogenic excoriations in acne excoriee. *Am J Clin Hyp* 2004; **46**: 239–45.
8 Kent A, Drummond LM. Acne excoriee—a case report using habit reversal. *Clin Exp Dermatol* 1989; **14**: 163–4.
9 Bowes LE, Alster TS. Treatment of facial scarring and ulceration resulting from acne excoriee with the 585-nm pulsed dye laser irradiation and cognitive psychotherapy. *Dermatol Surg* 2004; **30**: 934–8.
10 Kreiborg S, Cohen MM Jr. The oral manifestations of Apert's syndrome. *J Cranofac Genet Dev Biol* 1992; **12**: 41–8.
11 Atherton DJ, Rebella T. Apert's syndrome with severe acne vulgaris. *Proc R Soc Med* 1976; **69**: 517–8.
12 Cohn MS, Mahon MJ. Apert's syndrome in a patient with hyperhidrosis. *Cutis* 1993; **52**: 205–8.
13 Solomon LM, Fretzin D, Pruzansky S. Pilosebaceous abnormalities in Apert's syndrome. *Arch Dermatol* 1970; **102**: 381–5.



(a) (b)

Fig. 42.80 (a & b) Acne aestivalis papular inflammatory lesions characteristically seen on the upper trunk. (Courtesy of Dr N.K. Veien, Dermatology Clinic, Aalborg, Denmark.)

14 Henderson CA, Knaggs H, Clark A *et al*. Apert's syndrome and androgen receptor staining of the basal cells of sebaceous glands. *Br J Dermatol* 1995; **132**: 139–43.

15 Campanati A, Marconi B, Penna L *et al*. Pronounced and early acne in Apert's syndrome: a case successfully treated with oral isotretinoin. *Eur J Dermatol* 2002; **12**: 496–8.

16 Gilaberte M, Puig L, Alomar A. Isotretinoin treatment of acne in a patient with Apert's syndrome. *Paed Dermatol* 2003; **20**: 443–6.

17 Cohen MM, Kreiborg S. Cutaneous manifestations of Apert's syndrome. *Am J Med Genet* 1995; **58**: 94–6.

18 Oldridge M, Zackai EH, McDonald-McGinn DM *et al*. De novo alu-element insertions in FGFR2 identify a distinct pathological basis for Apert's syndrome. *Am J Hum Genet* 1999; **64**: 446–61.

19 Downs AMR, Condon CA, Tan R. Isotretinoin therapy for antibiotic-refractory acne in Apert's syndrome. *Clin Exp Dermatol* 1999; **24**: 461–3.

20 Cuerda E, Del Pozo J, Rodriguez-Lozano J *et al*. Acne in Apert's syndrome: treatment with isotretinoin. *J Dermatolog Treat* 2003; **14**: 43–5.

21 Steffen C. The acneform eruption of Apert's syndrome is not acne vulgaris. *Am J Dermatopathol* 1984; **6**: 213–20.

22 Cotterill JA. Dermatological non-disease: a common and potentially fatal disturbance of cutaneous body image. *Br J Dermatol* 1981; **104**: 611–9.

23 Cotterill JA, Cunliffe WJ. Suicide in dermatological patients. *Br J Dermatol* 1997; **137**: 246–50.

24 Hull SM, Cunliffe WJ, Hughes BR. Treatment of the depressed and dysmorphophobic acne patient. *Clin Exp Dermatol* 1991; **16**: 210–1.

25 Derrick EK, Darley CR, Burge S. Comedonal Darier's disease. *Br J Dermatol* 1995; **132**: 453–5.

26 Bencini PL, Montagnino G, Sala F *et al*. Cutaneous lesions in 67 cyclosporin treated renal transplant recipients. *Dermatologica* 1986; **172**: 24–30.

27 Burkhart CG. Quinidine-induced acne (Letter). *Arch Dermatol* 1981; **117**: 603–4.

28 Guldager H. Halothane allergy as cause of acne. *Lancet* 1987; **i**: 1211–2.

29 Vexiau P, Gourmel B, Castot A *et al*. Severe acne due to chronic amineptine overdose. *Arch Dermatol Res* 1990; **282**: 103–7.

30 Betti R, Uziel L, Inselvini E *et al*. Severe acne-like lesions in chronic amineptine overdose and Hodgkin's lymphoma. *J Dermatolog Treat* 1994; **5**: 143–4.

31 Plewig G, Kligman AM. Induction of acne by topical steroids. *Arch Dermatol Forsch* 1973; **247**: 29–52.

32 Monk B, Cunliffe WJ, Layton AM, Rhodes DJ. Acne induced by inhaled corticosteroids. *Clin Exp Dermatol* 1993; **18**: 148–50.

33 Daltrey DC, Cunliffe WJ. Effect of betamethasone valerate on the normal facial skin flora. *Acta Derm Venereol (Stockh)* 1983; **63**: 160–2.

34 Bong JL, Connell JM, Lever R. Intranasal betamethasone induced acne and adrenal suppression. *Br J Dermatol* 2000; **142**: 579–80.

35 Fung MA, Berger TG. A prospective study of acute-onset steroid acne associated with administration of intravenous corticosteroids. *Dermatology* 2000; **200**: 43–4.

36 Guillot B. Adverse skin reactions to inhaled steroids. *Expert Opin Drug Saf* 2002; **1**: 325–9.

37 White GL Jr, Tyler LS. Blackmarket steroids complicate acne therapy. *J Fam Pract* 1987; **25**: 214.

38 Scott MJ 3rd, Scott AM. Effect of anabolic–androgenic steroids on the pilosebaceous unit. *Cutis* 1992; **50**: 113–6.

39 Fyrand O, Fiskdaadal HJ, Trygstad O. Acne in pubertal boys undergoing treatment with androgens. *Acta Derm Venereol (Stockh)* 1992; **72**: 148–9.

40 Kiraly CL, Alen M, Korvola J *et al.* The effect of testosterone and anabolic steroids on the skin surface lipids and the population of *Propionibacteria acnes* in young postpubertal men. *Acta Derm Venereol (Stockh)* 1988; **68**: 21–6.

41 Melnik B, Jansen T, Grabbe S. Abuse of anabolic-androgenic steroids and bodybuilding acne: an underestimated health problem. *J Dtsh Dermatol Ges* 2007; **5**: 110–7.

42 Greenwood R, Fenwick PB, Cunliffe WJ. Acne and anti-convulsants. *BMJ* 1983; **287**: 1669–70.

43 Cohen LK, George W, Smith R. Isoniazid-induced acne and pellagra: occurrence in slow inactivators of isoniazid. *Arch Dermatol* 1974; **109**: 377–81.

44 Jones C, Bleehen SS. Acne induced by PUVA treatment. *BMJ* 1977; **ii**: 866.

45 Nielson EB, Thormann J. Acne-like eruptions induced by PUVA treatment. *Acta Derm Venereol (Stockh)* 1978; **58**: 374–5.

46 Aranda MV, Sanches S, Corral A *et al*. Acneiform eruption caused by amineptine. A case report and review of the literature. *J Eur Acad Dermatol Venereol* 2001; **15**: 337–9.

47 Busam KJ, Capodiece P, Motzer R *et al*. Cutaneous side-effects in cancer patients treated with the anti epidermal growth factor receptor antibody C 225. *Br J Dermatol* 2001; **144**: 1169–76.
48 Segaert S, Tabernero J, Chosidow O *et al*. The management of skin reactions in cancer patients receiving epidermal growth factor receptor targeted therapies. *J Dtsch Dermatol Ges* 2005; **3**: 599–606.
49 Papa CM. Acne and hidden iodides (Letter). *Arch Dermatol* 1976; **112**: 555–6.
50 Plewig G, Strzeminski YA. Iodide and skin disease. *Dtsch Med Wochenschr* 1985; **110**: 1266–9.
51 Kligman AM, Mills OH. Acne cosmetica. *Arch Dermatol* 1972; **106**: 843–50.
52 Kligman AM, Katz AG. Comedogenic properties of human sebum in the external ear canal of the rabbit. *Arch Dermatol* 1968; **98**: 53–7.
53 Plewig G, Fulton JE, Kligman AM. Pomade acne. *Arch Dermatol* 1970; **101**: 580–4.
54 Mills OH Jr, Kligman AM. Acne detergicans. *Arch Dermatol* 1975; **111**: 65–8.
55 Hughes BR, Cunliffe WJ. Development of folliculitis and pyoderma gangrenosum in association with abdominal pain in a patient following treatment with isotretinoin. *Br J Dermatol* 1990; **122**: 683–7.
56 Karakuzu A, Erdem, T, Aktas A *et al*. A case of folliculitis decalvans involving the beard, face and nape. *J Dermatol* 2001; **28**: 329–31.
57 Powell JJ, Dawber RPR, Gatter K. Folliculitis decalvans including tufted folliculitis: clinical, histological and therapeutic findings. *Br J Dermatol* 1999; **140**: 328–33.
58 Brooke RC, Griffiths CE. Folliculitis decalvans. *Clin Exp Dermatol* 2001; **26**: 120–2.
59 Kaur S, Kanwar AJ. Folliculitis decalvans: successful treatment with a combination of rifampicin and topical mupirocin. *J Dermatol* 2002; **29**: 180–1.
60 Gemmeke A, Wollina U. Folliculitis decalvans of the scalp: response to triple therapy with isotretinoin, clindamycin and prednisolone. *Acta Dermatovernereol Alp Panonica Adriat* 2006; **15**: 184–6.
61 Abdeck D, Korting HC, Braun-Falco O. Folliculitis decalvans. Long lasting response to combined therapy with fusidic acid and zinc. *Acta Derm Venerol* 1992; **72**: 143–5.
62 Kunte C, Loeser C, Wolff H. Folliculitis spinulosa decalvans: successful treatment with dapsone. *J Am Acad Dermatol* 1998; **39**: 891–3.
63 Smith EP, Hardaway CA, Graham BS *et al*. Folliculitis decalvans treated with radiation therapy. *Cutis* 2006; **78**: 162–4.
64 Sivakumaran S, Meyer P, Burrows NP. Dissecting folliculitis of the scalp with marginal keratitis. *Clin Exp Dermatol* 2001; **26**: 490–2.
65 Kobayashi H, Aiba S, Tagami H. Successful treatment of dissecting cellulitis and acne conglobata with oral zinc. *Br J Dermatol* 1999; **141**: 1137–8.
66 Karpouzis A, Giatromanolaki A, Sivridis E, Kouskoukis C. Perifolliculitis capitis abscedens et suffodiens successfully controlled with topical isotretinoin. *Eur J Dermatol* 2003; **13**: 192–5.
67 Ljubojevic S, Pasic A, Lipozencic J *et al*. Perifolliculitis capitis abscendens et suffodiens. *J Eur Acad Dermatol Venereol* 2005; **19**: 719–21.
68 Scheinfeld NS. A case of dissecting cellulitis and a review of the literature. *Dermatol Online J* 2003; **9**: 8.
69 Camcho-Martinez F, Winkelmann RK. Solid facial edema as a manifestation of acne. *J Am Acad Dermatol* 1990; **22**: 129–30.
70 Tosti A, Guerra L, Bettoli V. Solid facial edema as a complication of acne vulgaris in twins. *J Am Acad Derm* 1987; **17**: 843–4.
71 Uhara H, Kawachi S, Saida T. Solid facial edema in a patient with rosacea. *J Dermatol* 2000; **27**: 214–6.
72 Freidman SJ, Fox BJ, Albert HL. Solid edema as a complication of acne vulgaris: treatment with isotretinoin. *J Am Acad Derm* 1986; **15**: 286–9.
73 Jungfer B, Jansen T, Przbilla G. Solid facial edema of acne: successful treatment with isotretinoin and ketotifen. *Dermatology* 1993; **187**: 34–7.
74 Helander I, Aho HJ. Solid facial edema as a complication of acne vulgaris: treatment with isotretinoin and clofazimine. *Acta Derm Venereol (Stockh)* 1987; **67**: 535–7.
75 Jansen T, Altmeyer P, Plewig G. Acne inversa (alias hidradenitis suppurativa). *J Eur Acad Dermatol Venereol* 2001; **15**: 532–40.
76 Von der Werth JM, Jemec GBE. Morbidity in patients with hidradenitis suppurativa. *Br J Dermatol* 2001; **144**: 809–13.
77 Von der Werth JM, Williams HC, Raeburn JA. The clinical genetics of hidradenitis suppurativa revisited. *Br J Dermatol* 2000; **142**: 947–53.
78 Palmer RA, Keefe M. Early onset hidradenitis suppurativa. *Clin Exp Dermatol* 2001; **26**: 501–3.
79 Farrell AM, Randall VA, Vafee T *et al*. Finasteride as a therapy for hidradenitis suppurativa. *Br J Dermatol* 1999; **141**: 1136–7.
80 Sullivan TP, Welsh E, Kerdel FA. Infliximab for hidradenitis suppurativa. *Br J Dermatol* 2003; **149**: 1046–9.
81 Cantatore-Francis JL, Glick S. Childhood acne: evaluation and management. *Dermatologic Therapy* 2006; **19**: 202–9.
82 Lucky AW. A review of infantile and paediatric acne. *Dermatology* 1998; **196**: 95–7.
83 Bernier V, Weill FX, Hirigoyen V *et al*. Skin colonisation by a *Malassezia* species in neonates; a prospective study in relationship with neonatal cephalis pustulosis. *Arch Dermatol* 2002; **138**: 215–8.
84 Bergman JN, Eichenfeld LF. Neonatal acne and cephalic pustulosis: is *Malassezia* the whole story? *Arch Dermatol* 2002; **138**: 255–7.
85 Niamba P, Weill FX, Sarlangue J *et al*. Is common neonatal cephalic pustulosis (neonatal acne) triggered by *Malassezia synpodialis*? *Arch Dermatol* 1998; **134**: 995–8.
86 Herane MI, Ando I. Acne in infancy and acne genetics. *Dermatology* 2003; **206**: 24–8.
87 Katsambas AD, Katoulis AC, Stavropoulos P. Acne neonatorum: a study of 22 cases. *Int J Dermatol* 1999; **38**: 128–30.
88 Cunliffe WJ, Baron SE, Coulson IH. A clinical and therapeutic study of 29 patients with infantile acne. *Br J Dermatol* 2001; **145**: 463–6.
89 Barnes CJ, Eichenfield LF, Lee J *et al*. A practical approach for the use of oral isotretinoin for infantile acne. *Paed Dermatol* 2005; **22**: 166–9.
90 Janniger CK. Neonatal and infantile acne vulgaris. *Cutis* 1993; **52**: 16.
91 Sigurdsoon V, De Wit RF, De Groot AC. Infantile acne. *Br J Dermatol* 1991; **125**: 285.
92 Bessone L. L'eruzione acneiforme corticotropane e cortisonica nell infanzia. *Chron Dermatol* 1974; **1**: 77.
93 Stankler L, Campbell AGM. Neonatal acne vulgaris: a possible feature of the fetal hydantoin syndrome. *Br J Dermatol* 1980; **103**: 453–5.
94 Arbegast KD, Braddock SW, Lamberty LF, Sawka AR. Treatment of infantile cystic acne with oral isotretinoin: a case report. *Pediatr Dermatol* 1991; **8**: 166–8.
95 Hellier FF. Acneiform eruptions in infancy. *Br J Dermatol* 1954; **66**: 25–9.
96 Chew EW, Bingham A, Burrows D. Incidence of acne vulgaris in patients with infantile acne. *Clin Exp Dermatol* 1990; **15**: 376–7.
97 Dupont C. A study of juvenile acne (Letter). *Clin Exp Dermatol* 1989; **14**: 175–6.
98 Jansen T, Bugdorf WHC, Plewig G. Pathogenesis and treatment of acne in childhood. *Paed Dermatol* 1997; **14**: 17–21.
99 Sarazin F, Dompmartin A, Nivot S *et al*. Treatment of an infantile acne with oral isotretinoin. *Eur J Dermatol* 2004; **14**: 71–2.
100 Torrelo A, Pastor A, Zambrano A. Severe acne infantum successfully treated with isotretinoin. *Paediatr Dermatol* 2005; **22**: 357–9.
101 Peachey RDG, Matthews CNA. 'Fiddler's neck'. *Br J Dermatol* 1978; **98**: 669–74.
102 Goldman L. Turtleneck shirt and sweater acne (Letter). *Arch Dermatol* 1977; **113**: 109.
103 MacGregor AJ, Cunliffe WJ, Tan SG. Acne mechanica. *BMJ* 1976; **i**: 130.
104 Wulf K, Fegeler F. Komedonen und Talgcysten hinter den ohren durch Seifenschauna. *Hautarzt* 1953; **4**: 371–9.
105 Adams BB, Chetty VB, Mutasim DF. Periorbital comedones and their relationship to pitch tar: a cross sectional analysis and a review of the literature. *J Am Acad Dermatol* 2000; **42**: 624–7.
106 Svendson K, Hilt B. Skin disorders in ship's engineers exposed to oils and solvents. *Contact Dermatitis* 1997; **36**: 216–20.
107 Finkelstein E, Lazarov A, Cagnano M, Halevy S. Oil acne: successful treatment with isotretinoin. *J Am Acad Dermatol* 1994; **30**: 491–2.
108 Crow KD. Chloracne. A critical review including a comparison of two series of cases of acne from chlornaphthalene and pitch fumes. *Trans St John's Hosp Dermatol Soc* 1970; **56**: 79–99.
109 Crow KD. Chloracne and its potential clinical implications. *Clin Exp Dermatol* 1981; **6**: 243–57.
110 Caramaschi F, Del Corne G, Favare C *et al*. Chloracne following environmental contamination by TCDD in Seveso, Italy. *Int J Epidemiol* 1982; **10**: 135–43.

111 McDonagh AJ, Gawkrodger DJ, Walker AE. Chloracne—study of an outbreak with new clinical observations. *Clin Exp Dermatol* 1993; **18**: 523–5.
112 McConnell R, Anderson K, Russell W *et al.* Angiosarcoma, porphyria cutanea tarda, and probable chloracne in a worker exposed to waste oil contaminated with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *Br J Ind Med* 1993; **50**: 699–703.
113 Coenraads PJ, Brouwer A, Olie K, Tang N. Chloracne. Some recent issues. *Dermatol Clin* 1994; **12**: 569–76.
114 Jansing PJ, Korff R. Blood levels of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and gamma-globulins in a follow up investigation of employees with chloracne. *J Dermatol Sci* 1994; **8**: 91–5.
115 Hsu MM, Mak CP, Hsu CC. Follow-up of skin manifestations in Yu-Cheng children. *Br J Dermatol* 1995; **132**: 427–32.
116 Scerri L, Zaki I, Millard LG. Severe halogen acne due to a trifluoro-methylpyrazole derivative and its resistance to isotretinoin. *Br J Dermatol* 1995; **132**: 144–8.
117 Dickson LC, Buzik SC. Health risks of 'dioxins': a review of environmental and toxicological considerations. *Vet Hum Toxicol* 1993; **35**: 68–77.
118 Jensen NE, Sneddon IB, Walker AE. Tetrachlorobenzodioxin and chloracne. *Trans St John's Hosp Dermatol Soc* 1972; **58**: 172–6.
119 Caputo R, Monti M, Ermacora E *et al.* Cutaneous manifestations of tetrachlorodibenzo-*p*-dioxin in children and adolescents. *J Am Acad Dermatol* 1988; **19**: 812–9.
120 Cunliffe WJ, Williams M, Edwards JC *et al.* An explanation for chloracne: an industrial hazard. *Acta Derm Venereol (Stockh)* 1975; **55**: 211–4.
121 Passi S, Nazzaro-Porro M, Bonifortic L *et al*. Analysis of lipids and dioxin in chloracne due to tetrachloro-2,3,7,8-*p*-dibenzodioxin. *Br J Dermatol* 1981; **105**: 137–43.
122 Guo YL, Yu ML, Hsu CC *et al*. Chloracne, goiter, arthritis and anaemia after polychlorinated biphenyl poisoning: 14-year follow-up of the Taiwan Yucheng cohort. *Environ Health Perspect* 1999; **107**: 715–9.
123 Moshammer H, Neuberger M. Sex ratio in the children of the Austrian chloracne cohort. *Lancet* 2000; **356**: 1271–2.
124 Yip J, Peppall L, Gawkrodger DJ, Cunliffe WJ. Light cautery and EMLA® in the treatment of chloracne lesions. *Br J Dermatol* 1993; **128**: 313–6.
125 MacGregor AJ. Calcification in scars of healed acne vulgaris. *Oral Surg Oral Med Oral Pathol* 1971; **32**: 829–30.
126 Basler RGW, Taylor WB, Peacor DR. Post-acne osteoma. *Arch Dermatol* 1974; **110**: 113–4.
127 Monteiro M, Koblenzer C. Multiple osteoma cutis lesions associated with acne. *Int J Dermatol* 2000; **39**: 553–4.
128 Cunliffe WJ, Holland DB, Clark SM *et al*. Comedogenesis: some aetiological, clinical and therapeutic strategies. *Dermatology* 2003; **206**: 11–6.
129 Moritz DL, Elewski B. Pigmented post-acne osteoma cutis in a patient treated by minocycline: report and review of the literature. *J Am Acad Dermatol* 1991; **24**: 851–3.
130 Cohen AD, Chetov T, Cagnano E *et al*. Treatment of multiple miliary osteoma cutis of the face with local application of tretinoin (all-trans-retinoic-acid): a case report and review of the literature. *J Dermatol Treat* 2001; **12**: 171–3.
131 Smith CG, Galser DA. Treatment of multiple miliary osteoma cutis with tretinoin gel. *J Am Acad Dermatol* 1999; **41**: 500.
132 Fulton JE Jr. Dermabrasion-Loo-Punch-excision technique for the treatment of acne-induced osteoma cutis. *J Dermatol Surg Oncol* 1987; **13**: 655–9.
133 Altman JF, Nehal KS, Halpern AC *et al*. Treatment of miliary osteoma cutis with incision, curettage and primary closure. *J Am Acad Dermatol* 2001; **44**: 96–9.
134 Baskan EB, Turan H, Tunali S *et al*. Miliary osteoma cutis of the face: treatment with needle microincision-extirpation method. *J Dermatol Treat* 2007; **18**: 252–4.
135 Ochsendorf FR, Kaufmann R. Erbium-YAG laser-assisted treatment of miliary osteoma cutis. *Br J Dermatol* 1998; **138**: 371–2.
136 Ochsendorf FR, Kaufmann R. Erbium-YAG laser ablation for osteoma cutis: modification of approach. *Arch Dermatol* 1999; **135**: 1416.
137 Cunliffe WJ, Ead RD, Perera WHD *et al.* An acne-free naevus. *Br J Dermatol* 1977; **96**: 287–90.
138 Cooper MF, Hay JB, McGibbon D *et al.* Androgen metabolism and sebaceous activity in clonal acne. *J Invest Dermatol* 1976; **66**: 261 (Abstract).
139 Betiman C. Über den Naevus acneiformis. *Arch Dermatol Syphilol* 1906; **80**: 63–6.
140 White CJ. Naevus follicularis keratosus. *J Cutan Dis* 1914; **32**: 187–90.
141 Marsden RA, Fleming K, Dawber RPR. Comedo naevus of the palm—a sweat duct naevus? *Br J Dermatol* 1979; **101**: 717–22.
142 Abdel-Aal H, Abdel-Aziz AHM. Nevus comedonicus: report of three cases localized on glans penis. *Acta Derm Venereol (Stockh)* 1975; **55**: 78–80.
143 Beck MH, Dave VK. Extensive nevus comedonicus. *Arch Dermatol* 1980; **116**: 1048–50.
144 Barsky S, Doyle JA, Winkelmann RK. Nevus comedonicus with epidermolytic hyperkeratosis. A report of four cases. *Arch Dermatol* 1981; **117**: 86–9.
145 Baxter K, Highet A, Cunliffe WJ. An unusual late onset closed-comedone naevus: successful therapy with light cautery and a topical retinoid. *J Dermatolog Treat* 2004; **15**: 58–9.
146 Munro CS, Wilkie AO. Epidermal mosaicism producing localized acne: somatic mutation in FGFR2. *Lancet* 1998; **352**: 704–5.
147 Mehregan AH, Pinkus H. Life history of organouid naevi. Special reference to naevus sebaceus of Jadassohn. *Arch Dermatol* 1965; **91**: 574–88.
148 Lantis S, Leyden JE, Thew M *et al.* Naevus sebaceus of Jadassohn: part of a new neuro cutaneous syndrome? *Arch Dermatol* 1968; **98**: 117–23.
149 Fergin PE, Chu AC, MacDonald DM. Basal cell carcinoma complicating naevus sebaceus. *Clin Exp Dermatol* 1981; **6**: 111–5.
150 Weigl L, Eberlein-Konig B, Ring J. Eccrine syringofibroadenoma developing in a sebaceous naevus. *Br J Dermatol* 2000; **142**: 1049–50.
151 Rendlemann L, Stone MS. An unusual hematopoietic proliferation seen in a nevus sebaceus. *J Am Acad Dermatol* 2000; **42**: 881–2.
152 Mobayen MM, Copeman PWM. Multiple pyogenic granuloma in secondarily infected cystic acne. *Clin Exp Dermatol* 1983; **8**: 107–9.
153 Miller RAW, Ross JB. Multiple granulation tissue lesions occurring in isotretinoin treatment of acne vulgaris. *J Am Acad Dermatol* 1985; **12**: 888–9.
154 Cunliffe WJ, Shuster S. Pathogenesis of acne. *Lancet* 1969; **1**: 685–7.
155 Stefanidou M, Ioannidou D, Tosca A. Unilateral nodular elastosis with cysts and comedones (Favre–Racouchot syndrome). *Dermatology* 2001; **207**: 270–1.
156 Novy FG. Tropical acne. *California Med J* 1946; **115**: 274–6.
157 Williams M, Cunliffe WJ, Gould D. Pilosebaceous duct physiology. I. Effect of hydration on pilosebaceous duct orifice. *Br J Dermatol* 1974; **90**: 631–5.
158 Hjorth N, Sjulin KE, Sylvest B *et al*. Acne aestivalis—Mallorca acne. *Acta Derm Venereol (Stockh)* 1972; **52**: 61–3.
159 Stubbings JM, Goodfield MJD. An unusual distribution of an acneiform rash due to herpes zoster infection. *Clin Exp Dermatol* 1993; **18**: 92–3.
160 Jansen T, Romiti R, Woitalla S *et al*. Eruptive acne vulgaris with infectious mononucleosis. *Br J Dermatol* 2000; **142**: 837–8.

Severe acne variants

Six severe acne variants will be discussed in this section. For ease of reference, they are discussed alphabetically.

Acne conglobata

This is a rare but severe form of acne found most commonly in adult males with no or little systemic upset. Familial cases have been reported. Lesions usually occur on the trunk and upper limbs and frequently extend to the buttocks. In contrast to ordinary acne, facial lesions are not common. The condition often presents in the second to third decade and may persist into the 40s and 50s. Acne conglobata is characterized by multiple inflammatory papules, tender nodules and abscesses which commonly coalesce to form draining sinuses (Figs 42.81 & 42.82). Multiple grouped comedones and extensive disfiguring scarring are also features [1]. Malignancy has been reported in chronic scars [2]. Acne conglobata may occur in the context of hidradenitis suppurativa, folliculitis decalvans—a rare chronic progressive scalp disorder that produces scarring alopecia and atrophy [3]—and pilonidal cysts. An association of severe acne with sterile pyogenic arthritis and pyoderma gangrenosum has been reported (PAPA syndrome) as part of a



Fig. 42.81 A patient with extensive acne conglobata.



Fig. 42.82 Sinus formation in a patient with acne conglobata.

related group of inflammatory disorders including psoriasis, uveitis and inflammatory bowel disease [4]. Familial transmission has been reported with linkage to chromosome 15q24-26 in the region of IL-16 and *CRABPI* genes [5].

Therapy is notoriously difficult; options include long-term high-dose antibiotics, dapsone, ciclosporin and/or colchicine in conjunction with topical retinoids and antimicrobial therapy [6]. Oral isotretinoin (1 mg/kg/day) for 4–6 months is the treatment of choice. Isotretinoin may need to be combined with oral antibiotics such as erythromycin or trimethoprim. Concomitant short, intermittent courses of oral steroids may relieve inflammation during acute exacerbations. Surgery may well be required to lay open abscesses and sinus tracts [1,6,7]. One report has demonstrated the benefit of the carbon dioxide laser in combination with tretinoin to open up cysts and to prevent the emergence of new lesions [8]. In addition, infliximab, an anti-TNF inhibitor, has proved helpful in an isolated case report [9].



Fig. 42.83 A patient with severe truncal acne who had acne fulminans.

Acne fulminans

Acne fulminans represents a rare form of acne presenting in adolescent males, most commonly on the trunk. It was originally described as an acute form of febrile ulcerative acne conglobata. It presents very suddenly, usually in the context of previous mild to moderate acne (Fig. 42.83) [10–37]. Associated features are fever, polyarthropathy, marked leukocytosis (even a leukaemoid reaction), weight loss, anorexia and general malaise. Painful splenomegaly [23], erythema nodosum [24] and bone pain due to aseptic osteolysis have also been reported [21,25]. Bone involvement is common [26]; in a series of 24 patients, 48% had lytic bone lesions on X-ray and 67% showed increased radiolabel uptake; 25% showed destructive lesions resembling osteomyelitis [25,26]. The prognosis for bone lesions is good, and chronic sequelae, if any, are mild, leading to sclerosis and hyperostosis [26]. Blood cultures from the pustular lesions are universally sterile. The aetiology of acne fulminans is uncertain but the presence in some patients of microscopic haematuria, erythema nodosum, increased response to *P. acnes* antigen on skin tests and depressed response to intradermal purified protein derivatives are in favour of an abnormal immunological response. Skin tests with *P. acnes* demonstrate a very extensive, immediate and delayed reaction, the immunohistology of which reveals a type III or type IV hypersensitivity reaction [27]. One case has been reported in a young man with late-onset congenital adrenal hyperplasia [34]. A number of case reports have cited anabolic steroids, testosterone or oral isotretinoin as a trigger for acne fulminans [20,28,29,31]. An acne fulminans-like picture has been reported in association with Epstein–Barr virus infection. Thus, patients with a sudden



Fig. 42.84 A patient with the typical multiple pustules of Gram-negative folliculitis.

exacerbation of previously relatively mild acne should be checked for infectious mononucleosis [30].

Oral prednisolone therapy should be commenced first line (0.5–1.0 mg/kg/day) and decreased slowly over 2–3 months. The acute myalgia, arthralgia and fever can also be helped with oral salicylates or non-steroidal anti-inflammatory drugs and graduated physical exercise. Low-dose oral isotretinoin (0.25–0.5 mg/kg/day) should be cautiously introduced after 3–4 weeks of steroids [32,33,36] and gradually increased as tolerated, according to clinical response. Oral isotretinoin should be used with caution as paradoxically it has been reported to induce acne fulminans in some patients [37]. Topically, crusts need to be removed by soaking the skin with emollient oil, followed by the use of a potent steroid/antimicrobial cream for 2–3 weeks. Isotretinoin in combination with dapsone has been used successfully to treat acne fulminans associated with erythema nodosum [37].

Gram-negative folliculitis

Gram-negative folliculitis can occur as a complication of long-term oral or, less frequently, topical antibiotic therapy used to treat acne [38–40]. Clinical features include a sudden eruption of multiple, small follicular pustules (Fig. 42.84) or occasionally nodular lesions, most frequently localized around the perioral or perinasal regions. This results from overgrowth of Gram-negative organisms including *Klebsiella*, *Escherichia coli*, *Serratia marescens*, *Proteus mirabilis* or *Pseudomonas aeruginosa*. These organisms replace the Gram-positive flora of the facial skin and mucous membranes. As sampling for Gram-negative folliculitis is not routine the incidence of this problem in acne patients is probably underestimated.

Discontinuation of the current antibiotic is required; replacing it with either ampicillin (250 mg four times a day) or trimethoprim (600 mg/day) may effect improvement. However, the response may be slow and relapse is almost inevitable. Isotretinoin is now considered the treatment of choice, relapse following oral isotretinoin being much less likely [41–43].

It has been shown that 1% of treated acne cases with pustular lesions have significantly high counts of *S. epidermidis*, and very occasionally this may cause folliculitis [44]. Therapy usually requires stopping all antibiotics and using topical benzoyl peroxide, which is particularly helpful.

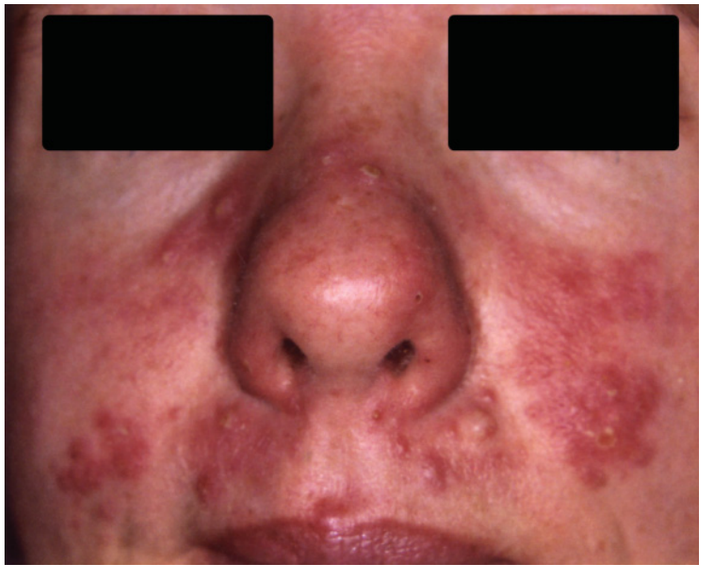


Fig. 42.85 A patient with rosacea fulminans.

Pyoderma faciale

Synonym
- Rosacea fulminans

This was initially believed to be a variant of acne but there has been subsequent debate that it represents rosacea (Chapter 43) [45,46]. Further clinical and basic science research is required to evaluate the underlying pathogenesis of this devastating facial dermatosis. It is rare and seen more commonly in postadolescent women of 20–40 years of age. It is reported to occur in the context of emotional distress and suddenly erupts producing numerous inflammatory pustules and nodules, predominantly on the face, making it particularly visible and distressing (Fig. 42.85). Comedonal lesions are rare. Facial flushing frequently precedes the exacerbation. In contrast to acne fulminans, there are usually no systemic symptoms. The reason for the sudden acute flare is unknown. Rosacea fulminans has been reported in association with Crohn's disease—the significance of which is unclear [47]. The daily ingestion of high-dose vitamin B supplements has also been reported to be associated with the sudden onset of rosacea fulminans [48].

Treatment options include the use of oral tetracyclines plus intralesional steroids or liquid nitrogen to the nodules aimed at reducing inflammation and reducing the nodular component, respectively. However, progress is generally slow with systemic antibiotics and the inflammation can be controlled more quickly using potent topical corticosteroids for a week along with systemic prednisolone (1 mg/kg/day), decreasing slowly over a 4- to 6-week period. Reports recommend the early use of isotretinoin (within a week of starting the steroids) at a dose of 0.5 mg/kg/day gradually increasing to 1 mg/kg/day, for at least 4–6 months

[39–42]. Dapsone has also been used successfully in this condition [49].

The prognosis is difficult to assess, but scarring is infrequent. Recurrence occurs more frequently than was believed some 5 years ago.

SAPHO syndrome

This acronym, first described in 1987, represents a syndrome of pustular dermatoses together with aseptic osteoarticular lesions in the form of *s*ynovitis, *a*cne, *p*ustulosis, *h*yperostosis and *o*steitis [50,51]. In the classic syndrome patients present with sudden-onset haemorrhagic and ulcerative acne on the face and trunk, sterile pustular lesions on the palms and soles with slowly evolving pain, especially on the anterior chest wall. However, the acne and palmoplantar pustulosis may be quite mild and it is believed the condition is under-diagnosed in these cases. The disease may represent an immune reaction to a particular skin or bacterial antigen. *Propionibacteria acnes* have been isolated in a few osteitic bone lesions but this is by no means universal and the bony lesions fail to respond to antibiotics suggesting that the bacteria are not necessarily the primary trigger [52]. Treatment remains empiric as only small groups of patients have been studied in any one series and results are conflicting. Recent reports have suggested that biphosphonates will aid the bony lesions as a result of their osteoclastic activity but they have no impact on the cutaneous manifestations of the syndrome [53].

There is documented evidence of incremented TNF-α in SAPHO, hence TNF-α blockers may be helpful. An isolated case report has demonstrated that prolonged benefit, up to 10 months, can be achieved by using infliximab [54]. However, other authors have suggested that whereas amelioration of the osteoarticular effects may occur the cutaneous manifestations may be exacerbated [55]. Isotretinoin has been used very successfully for the acne but concerns of possible provocation of the articular symptoms have been suggested.

Vasculitic/pyoderma gangrenosum acne

A few patients, who previously had very mild acne, have developed the sudden onset of severe vasculitic, pyoderma gangrenosum-like lesions (Fig. 42.86). Significant scarring is the inevitable consequence (Fig. 42.87). The mechanism of this devastating acne is probably an immunological reaction to *P. acnes*. Such patients appear to be unresponsive to oral isotretinoin alone, but settle to some extent with oral steroids and azathioprine (200 mg/day) over a 3- to 4-month period [56].



Fig. 42.86 A patient with very significant vasculitic acne.



Fig. 42.87 Pyoderma gangrenosum-type scarring in a patient who had suffered from vasculitic acne.

References

1 Patterson WM, Stibich AS, Dobke M *et al.* Mutilating facial acne conglobata. *Dermatol Plast Surg* 2000; **66**: 139–42.

2 Whipp MJ, Harrington CI, Dundas S. Fatal squamous cell carcinoma associated with acne conglobata in a father and daughter. *Br J Dermatol* 1987; **117**: 389–92.

3 Chicarilli N. Follicular occlusion triad: hidradenitis suppurativa, acne conglobata and dissecting cellulites of the scalp. *Ann Plast Surg* 1987; **18**: 230–7.

4 Lindor NM, Arsenault TM, Solomon H *et al*. A new autosomal dominant disorder of pyogenic sterile arthritis, pyoderma gangrenosum and acne: PAPA syndrome. *Mayo Clin Proc* 1997; **72**: 611–5.

5 Yeon HB, Lindon NM, Seidman JG *et al*. Pyogenic arthritis, pyoderma gangrenosum and acne syndrome maps to chromosome 15q. *Am J Hum Gen* 2000; **66**: 1443–8.

6 Jeong SJ, Lee CW. Acne conglobata: treatment with isotretinoin, colchicine and cyclosporin as compared with surgical intervention. *Clin Exp Dermatol* 1996; **21**: 461–8.

7 Weinrauch L, Peled I, Hacham-Zadeh S *et al*. Surgical treatment of severe acne conglobata. *J Dermatol Surg Oncol* 1981; **7**: 492–4.

8 Haregawa T, Matsukura T, Suga Y. One case of acne conglobata treated by the CO_2 laser combined with tretinoin. *J Dermatol* 2007; **34**: 583–5.

9 Shirakam M, Uramoto K, Harad FA. Treatment of acne conglobata with infliximab. *J Am Acad Dermatol* 2006; **55**: 344–6.

10 Plewig G, Jansen T, Kligman AM. Pyoderma faciale. A review and report of 20 additional cases: is it rosacea? *Arch Dermatol* 1992; **128**: 1611–7.

11 Jansen T, Plewig G. An historical note on pyoderma faciale. *Br J Dermatol* 1993; **129**: 594–6.

12 Jansen T, Plewig G, Kligman AM. Diagnosis and treatment of rosacea fulminans. *Dermatology* 1994; **188**: 251–4.

13 Massa MC, Su DWP. Pyoderma faciale: a clinical study of tweny-nine patients. *J Am Acad Dermatol* 1982; **6**: 84–91.

14 Marks VJ, Briggaman RA. Pyoderma faciale: successful treatment with isotretinoin. *J Am Acad Dermatol* 1987; **17**: 1062–3.

15 McHenry PM, Hudson M, Smart LM *et al.* Pyoderma faciale in a patient with Crohn's disease. *Clin Exp Dermatol* 1992; **17**: 460–2.

16 Jansen T, Lindner A, Plewig G. Draining sinus in acne and rosacea. A clinical histopathologic and experimental study. *Hautarzt* 1995; **46**: 417–20.

17 Burns RE, Colville JM. Acne conglobata with septicemia. *Arch Dermatol* 1959; **79**: 361–3.
18 Kelly AP, Burns RE. Acute febrile ulcerative conglobata acne with polyarthralgia. *Arch Dermatol* 1971; **104**: 182–7.
19 Strom S, Thyresson N, Bostrom H. Acute febrile ulcerative conglobate acne with leukaemoid reaction. *Acta Derm Venereol (Stockh)* 1973; **53**: 306–12.
20 Karvonen SL. Acne fulminans: report of clinical findings and treatment of twenty four patients. *J Am Acad Dermatol* 1993; **28**: 572–9.
21 Lane JM, Leyden JJ, Spiegel RJ. Acne arthralgia. *J Bone Joint Surg* 1976; **58**: 673–5.
22 Statham BN, Holt PJA, Pritchard MH. Acne fulminans—report of a case with polyarthritis. *Clin Exp Dermatol* 1983; **8**: 401–4.
23 van Schaardenburg D, Lavrijsen S, Vermeer B-J. Acne fulminans associated with painful splenomegaly. *Arch Dermatol* 1989; **125**: 132–3.
24 Williamson DM, Cunliffe WJ, Gatecliff M *et al.* Acute ulcerative acne conglobata (acne fulminans) with erythema nodosum. *Clin Exp Dermatol* 1977; **2**: 351–4.
25 Siegel D, Strosberg JM, Wiese F *et al.* Acne fulminans with osteolytic bone lesions responsive to dapsone. *J Rheumatol* 1982; **92**: 344–6.
26 Laasonen LS, Karvonen SL, Reunala TL. Bone disease in adolescents with acne fulminans and severe cystic acne: radiologic and scintigraphic findings. *Am J Roentgenol* 1994; **162**: 1161–5.
27 Karvonen SL, Rasanen L, Cunliffe WJ *et al.* Delayed hypersensitivity to *Propionibacterium acnes* in patients with severe nodular acne and acne fulminans. *Dermatology* 1994; **189**: 344–9.
28 Hartmann AA, Burg G. Acne fulminans bei Klinefelter-Syndrom unter Testosteron. *Monatsschr Kinderheilkd* 1989; **137**: 466–7.
29 McFadden N. Testosterone-induced acne fulminans in a patient treated for tall stature. *J Dermatolog Treat* 1989; **1**: 33–4.
30 Jansen T, Romiti R, Woitalla S *et al.* Eruptive acne vulgaris with infectious mononucleosis. *Br J Dermatol* 2000; **142**: 837–8.
31 Melnik B, Jansen T, Grabbe S. Abuse of anabolic-androgenic steroids and bodybuilding acne: an underestimated health problem. *J Dtsch Dermatol Ges* 2007; **5**: 110–7.
32 Choi EH, Bang D. Acne fulminans and 13-*cis*-retinoic acid. *J Dermatol* 1992; **19**: 378–83.
33 Karvonen SL, Vaalasti A, Kautiainen H, Reunala T. Systemic corticosteroid and isotretinoin treatment in cystic acne. *Acta Derm Venereol (Stockh)* 1993; **73**: 452–5.
34 Placzek M, Degitz K, Shmidt H *et al.* Acne fulminans in late-onset congenital adrenal hyperplasia. *Lancet* 1999; **354**: 739–40.
35 Seukeran DC, Cunliffe WJ. The treatment of acne fulminans: a review of 25 cases. *Br J Dermatol* 1999; **141**: 307–9.
36 Jansen T, Plewig G. Acne fulminans. *Int J Dermatol* 1998; **37**: 254–7.
37 Tan BB, Lear JT, Smith AG. Acne fulminans and erythema nodosum during isotretinoin therapy responding to dapsone. *Clin Exp Dermatol* 1997; **22**: 26–7.
38 Fulton JE, McGinley K, Leyden J *et al.* Gram-negative folliculitis in acne vulgaris. *Arch Dermatol* 1968; **98**: 349–53.
39 Leyden JJ, Marples RR, Mills OK. Gram negative folliculitis—a complication of antibiotic therapy in acne vulgaris. *Br J Dermatol* 1973; **88**: 533–8.
40 Leyden JJ, McGinley KJ, Mills OH. *Pseudomonas aeruginosa* Gram negative folliculitis. *Arch Dermatol* 1979; **115**: 1203–4.
41 James WD, Leyden JJ. Treatment of Gram-negative folliculitis with isotretinoin: positive clinical and microbiologic response. *J Am Acad Dermatol* 1985; **12**: 319–24.
42 Plewig C, Nikolowski J, Wolff HH. Action of isotretinoin in acne rosacea and Gram-negative folliculitis. *J Am Acad Dermatol* 1982; **6**: 766–85.
43 Boni R, Nehroff B. Treatment of Gram negative folliculitis in acne patients. *Am J Clin Dermatol* 2003; **4**: 273–6.
44 Lotem M, Ingber A, Filhaber A *et al.* Skin infection provoked by coagulase-negative *Staphylococcus* resembling Gram-negative folliculitis. *Cutis* 1988; **42**: 443–4.
45 Plewig G, Jansen T, Kligman AM. Pyoderma faciale. A review and report of 20 additional cases: is it rosacea? *Arch Dermatol* 1992; **128**: 1611–7.
46 Jansen T, Plewig G. An historical note on pyoderma faciale. *Br J Dermatol* 1993; **129**: 594–6.
47 McHenry PM, Hudson M, Smart LM *et al.* Pyoderma faciale in a patient with Crohn's disease. *Clin Exp Dermatol* 1992; **17**: 460–2.
48 Jansen T, Romiti R, Kreuter A, Altmeyer P. Rosacea fulminans triggered by high-dose vitamins B_6 and B_{12}. *J Eur Acad Dermatol Venereol* 2001; **15**: 484–5.
49 Bormann G, Gaber G, Marsch WC. Dapsone in rosacea fulminans. *J Eur Acad Dermatol Venereol* 2001; **15**: 465–7.
50 Beretta-Piccoli BC, Sauvain MHJ, Gal I *et al.* Synovitis, acne pustulosis, hyperostosic osteitis (SAPHO) syndrome in childhood: a report of 10 cases and review of the literature. *Eur J Pediatr* 2000; **159**: 594–601.
51 Van Doorman S, Barraclough D, McColl G *et al.* SAPHO: rare or just not recognised? *Semin Arthritis Rheum* 2000; **93**: 70–7.
52 Colina M, Lo Monaro A, Khodien M. Propionibacterium acnes and SAPHO: a case report and a literature review. *Clin Exp Rheum* 2007; **25**: 457–60.
53 Olivieri I, Padula A, Palazzi C. Pharmacological management of SAPHO syndrome. *Expert Opin Invest Drugs* 2006; **15**: 1229–33.
54 Iqbal M, Kolodney MS. Acne fulminans and synovitis-acne-pustulosis-hyperostosis-osteitis (SAPHO) syndrome treated with infliximab. *J Am Acad Dermatol* 2005; **52**(5 Suppl.1): S118–20.
55 Massara A, Cavazzini PL, Trotta F. In SAPHO syndrome anti-TNF-alpha therapy may induce persistent amelioration of osteoarticular complaints, but exacerbate cutaneous manifestations. *Rhematology* 2006; **45**: 730–3.
56 Woolfson H. Acne fulminans with circulating immune complexes and leukaemoid reaction treated with steroids and azathioprine. *Clin Exp Dermatol* 1987; **12**: 463–6.

Ectopic sebaceous glands

Synonym
- Fordyce spots

Fordyce spots are heterotopic sebaceous glands that can occur around the vermilion border of the lips or within the oral mucosa. They are commonly multiple, and appear as symmetrical, barely elevated, discrete yellow papules [1]. They are present in 25% of the population over the age of 35 years and are usually asymptomatic. When extensive they can be quite disfiguring, especially if evident on the lips. Oral isotretinoin has been used with some success to treat extensive lesions [2]. However, there are no adequate data that indicate whether or not relapse occurs post-therapy. Carbon dioxide ablative laser therapy has also been used with good effect to treat Fordyce spots [3]. Lesions may also occur on the penile shaft, especially on the ventral surface, and these may become inflamed and can be cause for concern. Other sites occasionally affected include the areolar area of the breast [4].

References

1 Daley TD. Intraoral sebaceous hyperplasia. Diagnostic criteria. *Oral Surg Oral Med Oral Pathol* 1993; **75**: 343–7.
2 Monk BE. Fordyce spots responding to isotretinoin therapy. *Br J Dermatol* 1993; **129**: 355.
3 Ocampo-Candriani J, Villarreal-Rodriquez A, Quinones-Fernandez AG *et al.* Treatment of Fordyce spots with CO_2 laser. *Dermatol Surg* 2003; **29**: 869–71.
4 Tsuji T, Yamauchi R. Areolar sebaceous hyperplasia with a Fordyce's spot-like lesion. *J Dermatol* 1994; **21**: 524–6.

Sebaceous gland hyperplasia, adenoma and carcinoma

Sebaceous gland hyperplasia

This represents a benign proliferation of the sebaceous gland (Fig. 42.88). The sebaceous glands sometimes become prominent in middle-aged or elderly people. In white people they produce numerous yellowish pink papules, each 1–3 mm in diameter. They

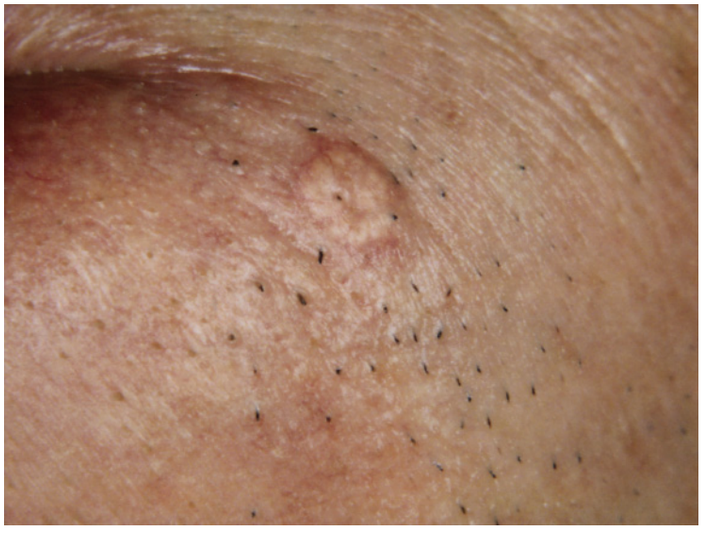


Fig. 42.88 A localized area of sebaceous hyperplasia.

are seen especially on the forehead and temples, and are of no clinical significance. They also are present occasionally on the light-exposed skin of renal transplant patients who are receiving ciclosporin [1]. Treatment is rarely requested, but cosmetic camouflage may be used. If requested and appropriate, some physical treatments such as gentle cautery, cryotherapy, trichloroacetic acid, and carbon dioxide and pulsed dye laser may be used [2,3]. Sometimes, but very uncommonly, the lesions are diffuse, producing a yellowish hue to the skin. In such patients, oral isotretinoin has been reported to be of considerable benefit [4]. Co-cyprindiol (Dianette® and Estelle 35®), with or without additional oral CPA, will also produce regression of sebaceous hyperplasia whilst on therapy. A therapeutic trial of oral isotretinoin may help to differentiate between sebaceous hyperplasia and multiple early basal cell carcinomas in transplant recipients, and may avoid multiple biopsies if there are many lesions. More recently photodynamic therapy using aminolevulinic acid has been used successfully [5].

References

1 De Berker DAR, Taylor AE, Quinn AG *et al.* Sebaceous hyperplasia in organ transplant recipients: shared aspects of hyperplastic and dysplastic processes? *J Am Acad Dermatol* 1996; **35**: 696–9.

2 Ahassi D, Gonzalez E, Anderson RR *et al.* Elucidating the pulsed-dye laser treatment of sebaceous hyperplasia *in vivo* with real-time confocal scanning laser microscopy. *J Am Acad Dermatol* 2000; **43**: 49–53.

3 No D, McClaren M, Chotzen V. Sebaceous hyperplasia treated with a 1450 nm diode laser. *Dermatolog Surg* 2004; **30**: 383–4.

4 Gollnick H, Orfanos CE. Front facial picture of a lady with familial nevoid sebaceous hyperplasia before and after treatment with isotretinoin. In: Wilkinson DS, Mascaro JM, Orfanos CE, eds. *Clinical Dermatology. The CMD Case Collection*. Stuttgart: Schattauer, 1987: 350–2.

5 Richey DF. Aminolevulinic acid photodynamic therapy for sebaceous gland hyperplasia. *Dermatol Clin* 2007; **25**: 59–65.

Sebaceous gland tumours

These are very uncommon. The adenomas in particular may be associated with an internal malignancy and systemic disease.

Sebaceous adenoma

This is a benign tumour composed of incompletely differentiated sebaceous cells. It occurs in both sexes and is seen mainly in elderly patients on the face or scalp [1]. The pink or waxy yellow tumours are round, raised, sessile or pedunculated; they are usually 10 mm or less in size, but may form plaques and ulcerate. Excision is the best treatment, but they are radiosensitive. Very infrequently, sebaceous gland adenomas can be associated with multiple visceral carcinomas. The internal tumours are usually of relatively early onset (45 years). This association is referred to as the Muir–Torré syndrome (MTS). MTS is a rare genodermatosis defined clinically by the occurrence of a sebaceous neoplasm (adenoma, epithelioma or carcinoma) and at least one internal malignancy in the absence of other predisposing factors. Most patients present with sebaceous adenomas but cystic sebaceous neoplasms have been reported as specific markers of MTS. Gastrointestinal and genitourinary malignancies are the most commonly reported with colorectal cancers presenting at or proximal to the splenic flexure contrary to most sporadic colorectal cancers [2,3]. MTS is most frequently found as a variant of the autosomal dominant hereditary disorder non-polyposis colorectal cancer (HNPCC) [4] with tumours demonstrating microsatellite instability and germline mutations in the DNA mismatch repair genes Muts homolog *MSH-2* and *MLH1*. However, the distribution of gene mutations in patients with MTS is slightly different from that seen in all patients with HNPCC and some cases of MTS arise spontaneously [5].

Clinicians should consider a diagnosis of MTS in patients presenting with sebaceous neoplasms and immunohistochemical examination of tumours for MSH2 and MLH1 protein can be used as a screening test for MTS. The neoplasms of MTS tend to follow a more indolent course than the sporadic cases which can be quite aggressive. The role of microsatellite instability in sporadic sebaceous carcinoma has until recently not been demonstrated. Of the nine tumours recently reported, five tumours were from four renal transplant recipients and four were from otherwise healthy individuals [6].

Careful follow-up and active treatment are required for both familial and sporadic cases. Evidence suggests that patients with MTS and HNPCC should undergo colonoscopy every 1–2 years from the age of 25 years or at an age 10 years younger than the family member who originally presented with the disease. Others recommend annual history, physical examination including thorough review of the skin, and urinalysis as well as endometrial sampling and transvaginal ultrasound for females.

Sebaceous carcinoma

This is a very uncommon malignant tumour arising from sebaceous glands. It is commoner in men over the age of 40 years and presents as a solitary, firm tumour, yellow–orange in colour, especially on the face and scalp. Sebaceous carcinomas have a well-recognized association with the Muir–Torré syndrome. The tumour grows slowly, but those arising in the eyelid (from the Meibomian glands) have a greater predilection for metastasizing [7]. Treatment is by excision or radiotherapy [8]. A tumour diameter of 10 mm or greater and/or tumours classified as T4 on the

T classification of the tumour, node, mestastasis staging system are linked to a poor prognosis [9].

References

1 Torré D. Multiple sebaceous tumors. *Arch Dermatol* 1968; **98**: 549–52.
2 Davis DA, Cohen PR. Genitourinary tumors in men with the Muir–Torré syndrome. *J Am Acad Dermatol* 1995; **33**: 909–12.
3 Schwartz RA, Torré DP. The Muir–Torré syndrome: a 25 year retrospect. *J Am Acad Dermatol* 1995; **33**: 90–104.
4 Hall NR, Murday VA, Chapman P *et al*. Genetic linkage in Muir–Torré syndrome to the same chromosomal region as cancer family syndrome. *Eur J Cancer* 1994; **30A**: 180–2.
5 Lachiewicz AM, Wilkinson JM, Groben P *et al*. Muir-Torre Syndrome. *Am J Clin Dermatol* 2007; **8**: 215–9.
6 Kruse R, Rutten A, Schweiger N *et al*. Frequency of microsatellite instability in unselected sebaceous gland neoplasias and hyperplasias. *J Invest Dermatol* 2003; **120**: 858–64.
7 Brauninger GE, Hood CI, Worthen DM. Sebaceous carcinoma of lid margin masquerading as cutaneous horn. *Arch Ophthalmol* 1973; **90**: 380–1.
8 Matsumoto CS, Nakatsuka K, Matsuo K *et al*. Sebaceous carcinoma responds to radiation therapy. *Ophthalmologica* 1995; **209**: 280–3.
9 Saito A, Tsutsumida A. Sebaceous carcinoma of the eyelids—a review of 21 cases. *J Plast Reconst Aesthetic Surg* 2008; **61**: 1328–31.

‘Sebaceous’ (epidermoid) cysts and steatocystoma multiplex

The classical ‘sebaceous’ cyst is an epidermal structure; strictly, it should be referred to as an epidermoid cyst, and it is discussed in Chapter 52. However, true sebaceous cysts occur as so-called steatocystoma multiplex, a naevoid condition that histologically shows a mixture of a keratinizing epithelium and sebaceous lobules attached to the epidermis by a thin epidermal strand [1–3]. A recent clinical and histological study examined 64 sporadic cases with an average age of onset of 26 years. They confirmed the presence of multiple, smooth, elastic, yellow dermal swellings varying from a few millimetres to 20 mm in size (Fig. 42.89) distributed on the arms, chest, neck and axillae and appearing and/or enlarging at puberty. Lesions are known to last indefinitely, and whether they resolve with old age is uncertain. Inflamed lesions due to rupture of the cysts are common and, when extensive, can produce the so-called steatocystoma multiplex suppurativa, which mimics acne conglobata. Steatocystoma multiplex (SM) shares many clinical features and may show overlapping histopathological features with eruptive vellus hair cyst (EVHC). In this series of 64, all cases exhibited eosinophilic cuticle and lack of granular layer, and 17–42% displayed vellus hair, hair follicles, keratin, and smooth muscle components within the cavity, in the wall, or adjacent to it. The results of this study suggest that SM is a hamartomatous condition and that SM and EVHC are variants which originate in the pilosebaceous duct [4].

Steatocystoma multiplex is uncommon, and in some patients is associated with type 2 pachyonychia congenita (PC-2 or Jackson–Lawler syndrome), in which natal teeth are also a feature [5–9]. Histologically, the cysts in PC-2 may be true steatocysts, eruptive vellus hair cysts or keratinous cysts, even in the same family or individual [10–12]. To date, mutations in the Ia domain of keratin 17 (K17) have been found in all cases [12,13]. In some families with clinically and histologically typical steatocystoma multiplex,



Fig. 42.89 A patient with extensive steatocystoma multiplex. (Courtesy of Dr N.K. Veien, Dermatology Clinic, Aalborg, Denmark.)

mutations in the K17 gene are also found [14]. In these families, close inspection shows that some but not all members have nail changes, which are usually but not always milder than those of PC. Familial steatocystoma multiplex has also been associated with natal teeth in the absence of nail dystrophy [14], and it seems likely that these cases are also due to keratin gene mutations. However, in a case of steatocystoma multiplex/eruptive vellus hair cyst (EVHC) and in another of EVHC, mutations in K17 were not found along the Ia domain [13], and hence it is likely that steatocystoma multiplex is genetically heterogeneous.

Treatment is very difficult [1]; excision of the larger cysts is possible, but total removal of all cysts is impractical because of their number. Successful treatment employing a vein hook to locally extract cysts has been reported [15]. One study has also utilized the carbon dioxide laser with some improvement [16]. Topical therapy is of limited benefit. Systemic antibiotics may reduce inflammation and/or suppuration and oral isotretinoin is of some help in reducing inflammation, but does not affect the primary disease process.

References

1 Amerlinck F. Sébocystomatose héréditaire. *Arch Belg Dermatol Syphiligr* 1949; **5**: 187–91.
2 Egbert DM, Price NM, Segal RJ. Steatocystoma multiplex. Report of a florid case and a review. *Arch Dermatol* 1979; **115**: 334–5.
3 Plewig G, Wolff HH, Braun-Falco D. Steatocytoma multiplex: anatomic re-evaluation, electron microscopy, and autoradiography. *Arch Dermatol Res* 1982; **272**: 363–80.
4 Cho S, Chang SE, Choi JH *et al*. Clinical and histological features of 64 cases of steatocystoma multiplex. *J Dermatol* 2002; **29**: 152–6.
5 Murray FA. Congenital anomalies of nails associated with teeth erupted at birth. *Br J Dermatol* 1921; **33**: 409–16.
6 Jackson AD, Lawler SD. Pachyonychia congenita: a report on six cases in one family. *Ann Eugen* 1951; **16**: 142–6.
7 Clementi M, Cardin de Stefani E, Dei Rossi C *et al*. Pachyonychia congenita Jackson–Lawler type: a distinct malformation syndrome. *Br J Dermatol* 1986; **114**: 367–70.
8 OH SW, Kim MY, Lee JS *et al*. Keratin 17 mutation in pachyonychia congenita type 2 with early onset steatocystoma multiplex and Hutchinson-like tooth deformity. *J Dermatol* 2006; **33**: 161–4.

9 McDonald RM, Reed WB. Natal teeth and steatocystoma multiplex complicated by hidradenitis suppurativa. *Arch Dermatol* 1975; **112**: 1132–4.
10 Moon SE, Lee YS, Youn JI. Eruptive vellus hair cyst and steatocystoma multiplex in a patient with pachyonychia congenita. *J Am Acad Dermatol* 1994; **30**: 275–6.
11 McLean WHI, Rugg EL, Lunny DP *et al.* Keratin 16 and keratin 17 mutations cause pachyonychia congenita. *Nat Genet* 1995; **9**: 273–6.
12 Smith FJD, Corden LD, Rugg EL *et al.* Missense mutations in keratin 17 cause either pachyonychia congenita type 2 or a phenotype resembling steatocystoma multiplex. *J Invest Dermatol* 1997; **108**: 220–3.
13 Feng YG, Xiao SX, Ren XR *et al.* Keratin 17 mutation in pachyonychia congenita type 2 with early onset sebaceous cysts. *Br J Dermatol*; **148**: 452–5.
14 King NM, Lee AMP. Natal teeth and steatocystoma multiplex: a newly recognised syndrome. *J Craniofac Genet Dev Biol* 1987; **7**: 311–7.
15 Lee SJ, Choe YS, Park BC *et al.* The vein hook successfully used for eradication of steatocystoma multiplex. *Dermatol Surg* 2007; **33**: 82–6.
16 Rossi R, Cappugi P, Battini M *et al.* CO_2 laser therapy in a case of steatocystoma multiplex with prominent nodules on the face. *Int J Dermatol* 2003; **42**: 302–4.

CHAPTER 43

Rosacea, Perioral Dermatitis and Similar Dermatoses, Flushing and Flushing Syndromes

J. Berth-Jones

Department of Dermatology, University Hospitals Coventry and Warwickshire, Coventry, UK

Rosacea, 43.1
Rhinophyma and other phymas, 43.9
Corticosteroid-induced rosacea, 43.10
Perioral dermatitis, 43.11
Acne agminata, 43.12
Granulomatous perioral dermatitis in children, 43.13
Pyoderma faciale, 43.13
Idiopathic facial aseptic granuloma, 43.14
Flushing and flushing syndromes, 43.14
Physiological flushing, 43.15
Menopausal flushing, 43.15
Flushing caused by drugs, 43.15
Flushing associated with alcohol intake, 43.16
Flushing associated with food, 43.16
Other causes of flushing, 43.16
Carcinoid syndrome, 43.17

This chapter brings together a range of dermatoses presenting with facial eruptions and/or flushing. It includes rosacea, the rosacea-like eruptions and carcinoid syndrome.

Rosacea

Definition. Rosacea is a disease lacking an entirely satisfactory definition. It is a chronic disorder affecting the facial convexities, characterized by frequent flushing, persistent erythema and telangiectasia, interspersed by episodes of inflammation during which swelling, papules and pustules are evident [1]. However, not all cases fit this description since not all features are always present. A recent attempt to define diagnostic criteria [2] concluded that the presence of one or more of the following signs with a central face distribution is indicative of rosacea: flushing, non-transient erythema, papules and pustules, and telangiectasia. Clearly, if all individuals with one or more of these features are to be included, rosacea is a highly heterogeneous entity.

Many authorities have expressed the view that vascular changes, particularly flushing, are the initial and constant feature, followed by progression to inflammatory changes (papulation and pustulation) and that the development of chronic lymphoedema, thickening of affected skin and rhinophyma are late complications. However, many cases do not demonstrate this pattern of evolution.

Nomenclature. The term 'acne rosacea' is used synonymously with rosacea but is better avoided. It reflects the occurrence in both diseases of facial papules and pustules. However, the epidemiology, aetiology and pathology of rosacea are quite distinct from acne vulgaris. The latter is primarily a disorder of pilosebaceous units but it is not clear to what extent the same is true of rosacea.

Epidemiology. Rosacea is a very common disease. It is considered more common in fair-skinned than darker-skinned individuals, although it does occur in all skin types including black people [3] and may just be more noticeable in those with pale skin. Meaningful figures on prevalence are scarce, but in Swedish 'white-collar' workers the figure is probably about one in ten [4], representing about 1–3% of dermatological consultations. In a study from Greece, rosacea accounted for 1.2% of dermatological consultations [5]. Women are more commonly affected than men, especially within the age range 36–50 years [5]. The development of rhinophyma is much more common in men. Rosacea is predominantly a disease of young to middle-aged adults but is seen in patients of all ages, including occasionally in children [6].

Pathogenesis. The cause, or causes, of rosacea remain uncertain. In contrast to acne vulgaris, rosacea is not associated with seborrhoea [7]. Marks [1] has proposed that damage to dermal connective tissue, often caused by solar irradiation, may be the initiating event. This may result in dysfunction of the unsupported facial blood vessels with consequent endothelial damage, leakage, oedema and inflammation.

Others have argued for the central role of abnormal vascular reactivity [8]. The association of rosacea with migraine seems to support this hypothesis [9]. When assessed by laser Doppler studies cutaneous blood flow is increased markedly in papulopustular disease and, perhaps surprisingly, to a lesser degree in erythematotelangiectatic rosacea [10]. Capillaroscopy demonstrates the presence of telangiectasia and neoangiogenesis in erythematotelangiectatic rosacea. These findings are not present in nailfold capillaries, suggesting that the vascular abnormalities associated with rosacea may be confined to the face [11]. Vascular endothelial

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

growth factor (VEGF) receptor expression appears to be increased in the vascular endothelium of the skin in rosacea, suggesting a possible role for VEGF in mediating the vascular and inflammatory changes [12].

Sensitivity to noxious stimuli including heat is increased in involved skin, regardless of whether vascular or inflammatory features predominate [10]. This may explain the burning sensation characteristic of rosacea and lends support to a neurogenic aetiology. It is possible that lowered neural thresholds for reaction to noxious stimuli may result in neurogenic inflammation [10].

Changes in redox status, with reduced levels of superoxide dismutase have been observed in the skin in cases of inflammatory rosacea [13], although it is not clear whether this is the cause or the effect of the inflammation. A role for oxidative stress is further supported by a report of increased malondialdehyde (an indicator of reactive oxygen species activity) and reduced antioxidant potential in peripheral blood of rosacea patients [14]. The therapeutic effect of antibiotics, including tetracyclines, metronidazole and azithromycin, may be explained by their antioxidant properties.

Abnormally high levels of cathelicidin have been demonstrated in the facial skin of patients with rosacea [15]. Cathelicidin is an endogenous antimicrobial peptide which constitutes a component of the innate immune system. In addition to their ability to kill microorganisms, cathelicidin and related peptides trigger inflammation by promoting leukocyte chemotaxis and angiogenesis. The active antimicrobial component of cathelicidin, LL-37, is cleaved off a precursor molecule by serine proteases, including stratum corneum tryptic enzyme. Interestingly, activity of this protease also appears elevated in rosacea. This could potentially result in production of a specific pattern of cathelicidin isoforms which are pro-inflammatory and which may play a central role in the pathogenesis of rosacea.

Because there is usually no associated sweating, it has been argued that flushing in rosacea is mediated by released vasoactive substances rather than a neural reflex mechanism [16] but this cannot yet be taken as established and both mechanisms may play a role. Proposed mediators included serotonin, bradykinin, prostaglandins [17], substance P, opioid peptides and gastrin. Blood levels of substance P were raised in some patients but not consistently [18]. Involvement of opioid peptides has been proposed on the basis of the suppressive action of the opioid antagonist naloxone [19].

It is often stated that rosacea is associated with gastrointestinal symptomatology although there is little evidence to support this [20–22]. No consistent evidence of gastritis was obtained in a controlled endoscopic study [23]. An association between jejunal mucosal atrophy and rosacea has also been proposed [24] but has not been confirmed.

A possible role for *Helicobacter pylori* infection of the gastric mucosa has been the subject of particular controversy. A high prevalence of this infection has been reported in patients with rosacea, reaching up to 100% in one uncontrolled series [25,26]. In controlled studies, prevalence rates have sometimes been similar to controls [27–30] and sometimes higher than controls [22,31–33]. The infection may be more prevalent in patients with papulopustular rosacea than those with erythematotelangiectatic disease [34]. It has been suggested that the prevalence of seropositivity in patients with rosacea might be artificially reduced as a result of antibiotic treatment [22], increasing the difficulty in drawing conclusions from these data.

The role of *H. pylori* in rosacea might be clarified if it could be established that eradication of the organism cured the disease, but the available data are inconclusive in this regard. There are anecdotal reports of impressive responses. A patient who had suffered from rosacea for 9 years cleared and remained free of the disease 2 years later [35]. A case of granulomatous rosacea of 4 years' duration resolved after eradication of *H. pylori* and remained clear 3 years later [36]. Significant improvement was seen in an uncontrolled trial of *H. pylori* eradication studying 22 patients with rosacea and evidence of *H. pylori* infection [30]. In a placebo-controlled trial of *H. pylori* eradication on 44 *H. pylori* infected patients with rosacea, the disease abated in almost all the patients in both treatment groups, although none were cured [37]. There was no significant difference between placebo and active treatment at the 60-day end point, although improvement was somewhat greater in the active limb. In an open-label study comparing the response of rosacea to a helicobacter eradication regimen in groups of patients with and without evidence of helicobacter infection, both groups were improved when assessed at 3 and 6 weeks with a somewhat larger response being seen in those with *H. pylori* [32]. Szlachcic *et al*. [33] treated 53 *H. pylori* infected patients with rosacea with an eradication regimen and reported clearing of rosacea within 2 to 4 weeks in 51 cases. The clinical improvement was accompanied by resolution of gastritis and reduction in serum levels of gastrin, IL-8 and TNF-α, possible mediators of the vascular changes in rosacea.

A range of different eradication regimens were used in these studies but all contained antibiotics known to be effective in rosacea. Antibiotics used in treatment of rosacea are all potentially effective in treatment of *H. pylori*. Whilst these do have anti-inflammatory properties and may therefore work by other mechanisms, it remains an interesting and plausible hypothesis that suppression of *H. pylori* might partially explain their efficacy.

A potential role has often been proposed for the follicle mites *Demodex folliculorum* and *Demodex brevis* in the pathogenesis of rosacea. Infestation with these mites is extremely common in the general population, reaching up to 100% of subjects in some studies [38]. These organisms have traditionally been considered harmless commensals but there is increasing evidence that they are potentially pathogenic, especially when present in very high numbers. Eruptions strongly resembling rosacea and associated with the presence of large numbers of *Demodex folliculorum* have been reported under the title of rosacea-like demodicosis [39,40]. These cases have improved following treatment to eradicate the mite.

Several investigators have reported increased numbers of *Demodex folliculorum* in the facial skin of patients with rosacea relative to controls [38,41–45]. Demodex mites have also been demonstrated in the dermis associated with an inflammatory response and undergoing phagocytosis by multinucleate giant cells. This phenomenon has been observed both in localized and more widespread facial eruptions resembling rosacea [46,47]. Furthermore, *Demodex brevis* is often present in the eyelid in hair

follicles, eyelash follicles and meibomian glands [48,49] and is often reported in association with periocular pathology including blepharitis and meibomianitis [50–52]. These observations would suggest that the presence of *Demodex* mites might also play a role in some of the ophthalmic complications of rosacea. Against a central role for *Demodex* is the relatively infrequent observation of the mites (in 19% or less of the biopsies) in some of the larger histological studies of rosacea [53–55]. However, in a histological study specifically examining the prevalence of mites, these were observed in 51% of patients with rosacea and perifollicular inflammation was observed around infested hair follicles [56].

Further insight into the role of *Demodex* in the pathogenesis of rosacea might be gained by investigating the effects of eradication of this organism but there has been limited formal study of this. A combination of oral ivermectin with topical permethrin has proved helpful in isolated cases [57]. In a small left/right comparative study permethrin cream and topical metronidazole both yielded similar results [58]. In a parallel group study, permethrin was superior to placebo and equivalent to metronidazole in reducing papules and erythema [59]. Some improvement has been reported in an uncontrolled study using crotamiton [44]. Benzyl benzoate reduces mite numbers but seems to be irritant in patients with rosacea [60]. A florid rosacea-like facial eruption associated with *Demodex* and accompanied by dermal inflammatory response and phagocytosis of the mites responded to metronidazole [47]. This is not easy to explain as metronidazole is not considered to be mitocidal. However the mites are associated with bacteria, both in their gut and on their skin [44]. One bacterium found in association with *Demodex* is *Bacillus oleronius*, and proteins from this organism have the potential to induce an immune response in patients with rosacea [61]. These microorganisms therefore provide a potential microbial target for antibiotics.

Recently, rosacea has been reported as a manifestation in the skin of human immunodeficiency virus (HIV) infection [62], and the same is true of rosacea-like demodicosis [40,63].

An important question relating to the pathogenesis of rosacea has been how to link the vascular features and the inflammatory lesions. A possible link is provided by the theory that the inflammatory lesions may develop as a result of the increased skin temperature associated with the vascular features. This may be explained by different behaviour of bacteria [64] or perhaps follicle mites, at a higher skin temperature. Improvement of inflammatory lesions has been reported after effective ablation of telangiectasia and would support this hypothesis [65], although this has not been consistently reported and others have commented on the failure of laser therapy to improve inflammatory lesions [66].

Clinical features. Rosacea is a polymorphic disease with several variants, each of which may require a different approach to treatment. The areas characteristically affected are the central convex areas of the face (nose, forehead, cheeks and chin) (Fig. 43.1). Occasionally, the scalp, upper chest, back and even the limbs may be involved [67]. In cases of rosacea showing the classical pattern of progression, the onset is most often marked by vascular changes, notably episodic flushing usually unaccompanied by sweating. Erythema, which is often accompanied by a burning sensation [10], gradually becomes more persistent, is easily triggered by minor irritants, and is associated with increasingly prominent telangiectasia. More advanced cases show follicular and non-follicular papules and pustules, without comedones, followed by persisting tissue thickening due to oedema, fibrosis and glandular hyperplasia, leading ultimately to a *peau d'orange* appearance and phymas.



Fig. 43.1 Predominantly erythematotelangiectatic rosacea affecting the cheeks and nose. Note conjunctival injection.

Table 43.1 Rosacea: classical pattern of progression.

Early	Episodic flushing
	Mild telangiectasia
	Transient oedema
Progressive	Papules
	Pustules
	Sustained oedema
	Extensive telangiectasia
Late	Induration
	Rhinophyma

Factors which trigger flushing include emotion and stress [68], hot drinks [69], alcohol [19] and other vasodilating drugs, and spicy food. Despite traditional beliefs to the contrary it is the heat, not the caffeine content of hot drinks, which causes flushing [69]. Aggravating factors include the use of topical steroids on those occasions when they are used (usually in error) to treat rosacea. Sun exposure may worsen or improve rosacea [70].

The classical progression of rosacea is summarized in Table 43.1. Many cases do not follow this pattern. Some show predominantly the vascular features (erythematotelangiectatic rosacea, Fig. 43.2), others develop mainly inflammatory lesions (papulopustular rosacea, Fig. 43.3), others develop mainly chronic thickening and induration and still others develop only rhinophyma. Each of these patterns, and also ocular rosacea, may occur in isolation or in any combination.

Complications. Rosacea, usually of long duration, is associated with several important complications.

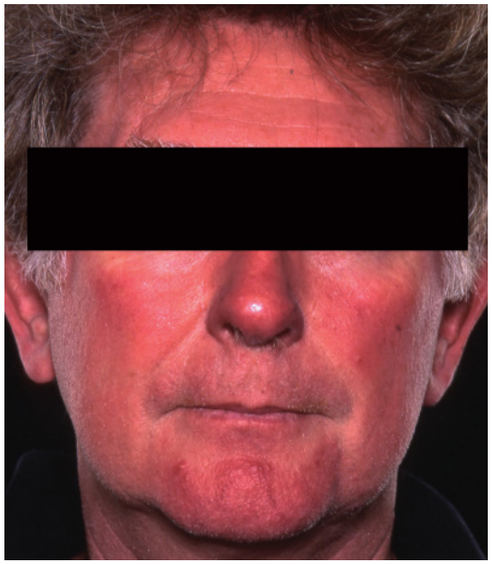


Fig. 43.2 Erythema mainly involving the convex areas of the face in a patient with rosacea.



Fig. 43.3 Inflammatory papulopustular rosacea. (Courtesy of Professor M. Greaves.)

Lymphoedema. This is a relatively rare complication of rosacea which can affect any part of the face and the ears (Fig. 43.4). In time this may develop into a coarsening of the features known as leonine facies. A characteristic pattern of lymphoedema of the upper half of the face developing as a complication of chronic rosacea has been termed chronic upper facial erythematous oedema or Morbihan's disease [71]. The orbital skin is often affected resulting in severe eyelid swelling and sometimes ectropion [72,73]. Histological examination reveals features of lymphoedema and inflammatory cell infiltration of variable intensity.

Eye involvement. Ophthalmological complications are common, although estimates of prevalence vary widely from 6% [74] to over 50% of patients with rosacea [75] although the pathogenesis is still not well understood. These include a sensation of grittiness or irritability of the eyes, often accompanied by visible reddening of the conjunctiva. Blepharitis, episcleritis, chalazion and hordeolum are also common. Rosacea keratitis is a more serious and quite common complication, occurring in 5% of patients including children [76,77]. The conjunctivitis, keratitis and other complications seem likely to be at least partly secondary to reduced tear secretion and Meibomian gland dysfunction, resulting in an unstable tear film [78,79]. Ocular rosacea may be seen in isolation or occur before the onset of cutaneous features, especially in children [80]. The condition may be unilateral or asymmetrical [80]. Interestingly, childhood sty may be indicative of increased risk of developing rosacea in adulthood [81].



Fig. 43.4 Chronic lymphoedema in a patient with a long history of rosacea. (Courtesy of Professor M. Greaves.)

Salivary gland involvement. The well documented reduction in tear secretion associated with ocular rosacea would suggest that involvement of the lacrimal glands is not infrequent. The involvement of salivary glands appears to be a rare event [82].

Histopathology [53,54,56,83,84]. The histological features are predominantly dermal. These tend to reflect the clinical features. Thus telangiectasia is indicated by the presence of dilated superficial capillaries. Lymphatic channels may also be dilated but tend to be located rather deeper in the mid-dermis. Solar elastosis is commonly present and often prominent. The intensity and pattern of inflammation is variable, ranging from a mild perivascular lymphohistiocytic infiltrate in erythematotelangiectatic cases, to more intense infiltration which may be perifollicular, interfollicular and perivascular in papular rosacea (Fig. 43.5). Mast cell density is reported to be increased [85]. Some lesions contain granulomas (Fig. 43.6) which can be epithelioid, elastolytic or pallisaded around altered collagen. Foreign-body type giant cells may be observed. Pustules are evidenced by polymorph accumulation in

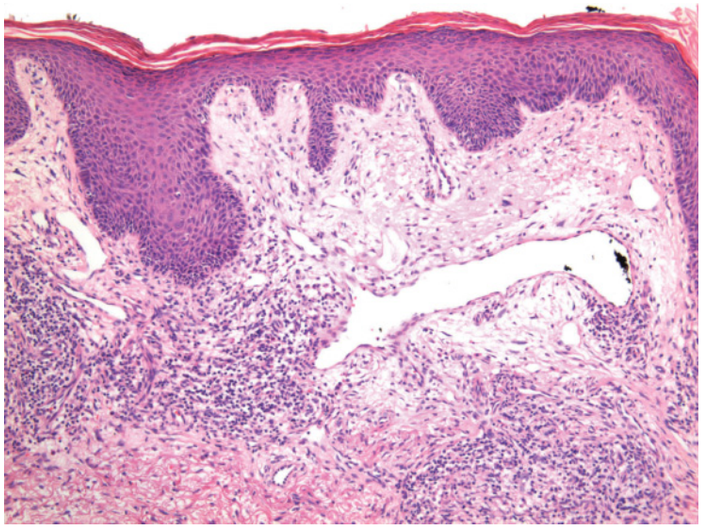


Fig. 43.5 Inflammatory rosacea, H&E × 100. (Courtesy of Dr R.A. Carr.)

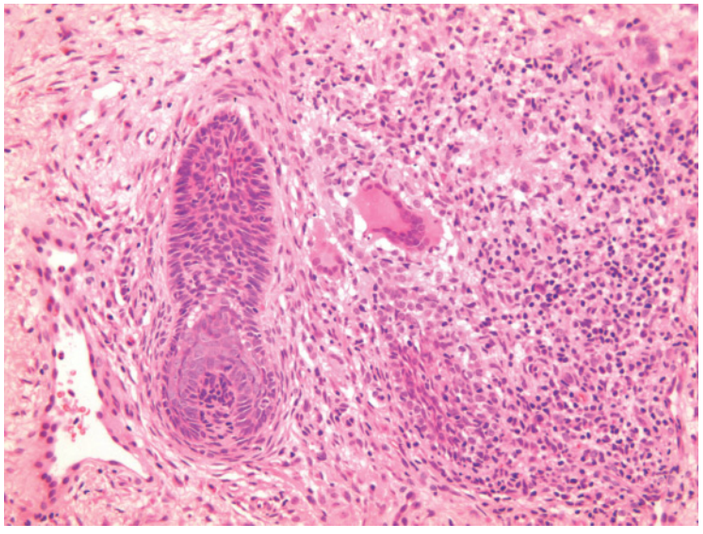


Fig. 43.6 Histological appearance of granulomatous rosacea (H & E × 400). (Courtesy of Dr R.A. Carr.)

the upper parts of hair follicles. Areas of necrosis are occasionally conspicuous, sometimes marking the remnants of inflamed hair follicles. *Demodex folliculorum* has been observed in up to 51% of cases in one series [56] and may densely populate the pilosebaceous follicles. However, the mites have not consistently been associated with inflammation.

Differential diagnosis. Important differential diagnoses include acne vulgaris, lupus erythematosus, perioral dermatitis, seborrhoeic dermatitis and nasal sarcoidosis. Although acne vulgaris and rosacea are quite distinct diseases, there are occasional patients in whom the distinction is difficult. Since both conditions are very common, it is to be expected that, by chance, both will often occur in the same patient. Acne vulgaris affects a younger age group and often has an extensive distribution over the face, neck and trunk whereas extra-facial rosacea is rare. Typical acne vulgaris lacks the redness, telangiectasia and flushing of rosacea whilst rosacea lacks the comedones and seborrhoea characteristic of acne vulgaris [86].

Scarring, scaling and follicular plugging are not features of rosacea and therefore readily distinguish it from facial discoid lupus erythematosus. However, patients are often referred to the dermatology clinic with a 'butterfly' erythema and a tentative diagnosis of systemic lupus erythematosus (SLE). The latter is not pustular and is usually associated with systemic symptoms. In some cases, lupus serology and a skin biopsy for histological and immunofluorescent examination may be necessary.

The pattern of the rash in seborrhoeic dermatitis differs markedly from that of rosacea. The former, but not the latter, characteristically involves the scalp, retroauricular area, eyelids and nasolabial folds. That scaling is not normally a feature of rosacea but is the rule in seborrhoeic dermatitis may also be helpful. However, rosacea and seborrhoeic dermatitis often seem to occur concurrently.

Nasal sarcoidosis (lupus pernio) superficially resembles rhinophymatous rosacea and both are granulomatous. However, sarcoidosis often affects the nasal septum (causing nasal obstruction) and the surface of the thickened nose in lupus pernio, although telangiectatic, is smooth and lacks the rugose *peau d'orange* surface which characterizes rhinophyma. Patients with lupus pernio almost invariably have evidence of multisystem disease.

Demodex folliculitis can clearly mimic rosacea but is generally considered to be a separate entity.

Rosacea may occasionally be induced by carcinoid syndrome [87]. The possibility of carcinoid syndrome should be considered particularly when the symptoms are predominantly vascular and unusually severe (see p. 43.17).

Prognosis. The duration of the disease and eventual outcome are highly variable and difficult to predict. In a follow-up study on 70 patients after 6 months' treatment with tetracycline, two-thirds had relapsed after a mean follow-up period of 2.6 years [88]. In a survey of 92 patients 10 or more years after a diagnosis of rosacea, 48 responded and 25 still had active disease, whilst 23 had cleared [89]. In those patients in whom the rosacea had resolved, the duration of the disease had ranged from 1 to 25 years. There is no evidence that treatment affects the likelihood of resolution. When it persists, rosacea usually follows a fluctuating course. In males and less often females, the persistence of rosacea may result in chronic thickening and induration of the face (leonine facies) and rhinophyma. Eye involvement is usually mild and reversible, though occasionally ocular keratitis can lead to severe scarring and even corneal perforation [90]. Most symptoms of rosacea can usually be successfully controlled (see below) but the flushing is often impossible to suppress.

Treatment. Papulopustular rosacea responds well to treatment in the majority of cases but improvement may be gradual so perseverance is sometimes required. Relapse is often prompt when treatment is discontinued [88]. It is important to avoid irritants such as strong soaps and cosmetic alcohol-based cleansers. Emollients are soothing in some cases. Although many patients say that their rosacea improves in the sun, solar exposure should probably

not be encouraged in view of the marked photodamage often seen in these patients and the possible role of this elastotic change in the pathogenesis.

Papulopustular rosacea. Both topical and systemic modalities can be highly effective and patients often have a particular preference for one route or the other. Effective oral agents include tetracyclines (e.g. tetracycline or oxytetracycline 250 mg twice daily) and erythromycin 250 mg twice daily. Higher doses are often prescribed in the belief that they are more effective although there is little evidence that this is true. More recently developed tetracyclines, such as minocycline, lymecycline and doxycycline, are often used and offer the advantages of once daily administration and lower potential for interaction with dietary calcium, enabling them to be taken with food. Doxycycline appears to be effective at doses as low as 40 mg daily [91]. Ampicillin appears superior to placebo but less effective than tetracycline [92]. Oral metronidazole can also be effective [93], although this can cause peripheral neuropathy if used for more than 3 months. Series of patients and open-label trials have shown efficacy of azithromycin [94]. In one series this drug proved beneficial after 4 weeks at 250 mg/day, for 3 days each week (Monday, Wednesday and Friday) [95]. Ocular symptoms also improved. Development of Gram-negative folliculitis has been reported as a rare complication of broad-spectrum antibiotic treatment of rosacea [96].

Oral isotretinoin (10–60 mg/day) is an alternative in resistant rosacea [97]; it not only reduces inflammatory lesions, but also improves quality of life [98]. This treatment can even improve rhinophyma [99]. This is most often used in relatively low dosage in rosacea, partly due to concern about worsening ocular disease. Treatment may need to continue for several months and particular caution is required with this teratogenic drug in fertile female patients. Isotretinoin may not be suitable for patients with ocular involvement (see below).

Topical treatment with metronidazole 1% cream is effective [100]. A 0.75% gel formulation is also available and is preferred by some patients. Tetracycline and erythromycin are also available in topical formulations although these are lotions developed for treatment of acne vulgaris and they can prove irritant on skin affected by rosacea. Clindamycin gel, also developed for treatment of acne, may be better tolerated. A combined formulation containing 5% benzoyl peroxide and 1% clindamycin has proved effective and well tolerated in a placebo-controlled trial [101].

Topical tacrolimus has been reported to improve erythema, but not inflammatory lesions, in an open-label series of 20 patients [102]. Pimecrolimus cream has been reported to improve erythema and papulopustular lesions in an open study with 12 subjects [103]. In a controlled trial, topical pimecrolimus was no more effective than placebo [104]. Topical tacrolimus and pimecrolimus have both been reported to induce rosacea-like eruptions [105,106].

Additional topical therapies reported as effective include azelaic acid 20% cream and 15% gel, 0.025% retinoic acid, 0.1% adapalene gel, 10% sulphur cream, NADH, methylnicotinamide and 5–10% benzoyl peroxide gel.

Combinations of topical and systemic treatment are often used and may be more effective than either used alone. The addition of low-dose (20 mg) doxycycline has been shown to improve the response to topical metronidazole [107].

There is little point in discontinuing treatment before 3 months and in many cases it is necessary to continue for several years.

Treatments directed at eradication of *Helicobacter pylori* or *Demodex* are discussed above. The final place of these modalities will be determined when the pathogenic role of these organisms has been established or excluded. On current evidence, the author would suggest that these treatments may prove helpful in individual cases where there is reason to believe that these organisms may be playing a role.

A novel approach is the use of photodynamic therapy [108]. A series of 17 patients with rosacea refractory to previous therapy were treated with PDT using 16% methyl aminolevulinic acid (Metvix®) cream applied for 3 h followed by 37 J/cm^2 of red light. Initially, patients received one or two treatments at an interval of 1 week, and up to four treatments were used on each treated area if required. A good response was reported in 10 cases.

Flushing. It is important to explain to patients with papulopustular rosacea that none of the above measures will significantly suppress the troublesome flushing or the burning discomfort which often accompanies this. Flushing and burning are the most difficult features of rosacea to treat. Non-cardioselective β-blockers, such as propranolol 40 mg twice daily or nadolol 40 mg daily [109], are often used but generally provide rather limited benefit. Clonidine 50 μg twice daily and the related but less sedative drug rilmenidine 1 mg daily may also provide some modest improvement, perhaps due to a non-specific vasoconstrictor effect [110]. Two cases of erythematotelangiectatic rosacea have recently been reported to respond to topical oxymetazoline 0.05% applied daily [111]. Both redness and flushing were improved. Treatment of erythema and telangiectasia with vascular lasers or intense pulse light can also be beneficial in reducing flushing and burning.

Cosmetic camouflage may also be helpful for patients with persistent facial redness. The British Red Cross provide cosmetic camouflage clinics free-of-charge throughout the UK in association with hospital dermatology departments (British Red Cross Beauty Care and Camouflage Service, 9 Grosvenor Crescent, London SW1X 7EJ).

Telangiectasia and erythema. Vascular lasers and intense pulsed light sources provide a range of highly effective treatments for ablation of telangiectasia and can also improve erythema [112–114].

Lymphoedema of rosacea. Treatment is far from satisfactory. Reduction of the inflammatory component of rosacea by broad-spectrum antibiotics may slow down progression. Jansen and Plewig have suggested the use of low-dose isotretinoin 0.1–0.2 mg/kg/day over a period of 2–4 months, which may be combined with ketotifen 1–2 mg daily and a potent H_1 antihistamine [71]. Marked reduction in facial swelling was reported in one case from a reducing course of prednisolone, starting at 30 mg daily and metronidazole 400 mg/day over a 4-month period, followed by metronidazole 200 mg/day [115]. For established leonine facies, regular facial massage may help. In cases of severe eyelid oedema

surgical debulking of the tissue [116] and CO_2 laser blepharoplasty [117] have proved helpful.

Ocular rosacea. The keratitis associated with rosacea can be severe and specialist ophthalmological supervision is frequently required.

Symptomatic benefit is often achieved with use of a wide range of 'artificial tears'. These include ophthalmic formulations of liquid paraffin, carbomers (polyacrylic acid), hydroxyethylcellulose, hypromellose, povidone and others.

Systemic tetracyclines are helpful. A comparison of doxycycline 100 mg/day and tetracycline 1 g/day showed improvement in both treatment groups. Tetracycline was significantly more effective at 6 weeks, but the difference between groups was not significant at 3 months [118]. Tetracyclines are thought to act as anti-inflammatory agents and can suppress cytokine secretion [119]. A study on the actions of minocycline has demonstrated changes in the composition of Meibomian gland lipids, suggesting that the treatment reduced lipase activity, which may have been secondary to changes in microbial flora [120]. In another trial, a topical ophthalmic formulation of fusidic acid appeared more effective than systemic oxytetracycline [121]. Retinoids are probably best avoided in patients with eye involvement as they may further impair Meibomian function, exacerbating the sensation of grittiness and the dryness of the eyes.

Eradication of *H. pylori* is reported to improve ocular rosacea [122].

References

1 Marks R. Rosacea: hopeless hypotheses, marvelous myths and dermal disorganization. In: Marks R, Plewig G, eds. *Acne and Related Disorders*. London: Martin Dunitz, 1989: 293–9.
2 Wilkin J, Dahl M, Detmar M *et al*. Standard classification of rosacea: Report of the National Rosacea Society Expert Committee on the Classification and Staging of Rosacea. *J Am Acad Dermatol* 2002; **46**: 584–7.
3 Rosen T, Stone MS. Acne rosacea in blacks. *J Am Acad Dermatol* 1987; **17**: 70–3.
4 Berg M, Liden S. An epidemiological study of rosacea. *Acta Derm Venereol (Stockh)* 1989; **69**: 419–23.
5 Kyriakis KP, Palamaras I, Terzoudi S *et al*. Epidemiologic aspects of rosacea. *J Am Acad Dermatol* 2005; **53**: 918–9.
6 Drolet B, Paller AS. Childhood rosacea. *Pediatr Dermatol* 1992; **9**: 22–6.
7 Burton JL, Pye RJ, Meyrick G, Shuster S. Sebum excretion rate in rosacea. *Br J Dermatol* 1975; **92**: 541–3.
8 Wilkin JK. Rosacea. Pathophysiology and treatment. *Arch Dermatol* 1994; **130**: 359–62.
9 Tan SG, Cunliffe WJ. Rosacea and migraine. *Br Med J* 1976; **i (6000)**: 21.
10 Guzman-Sanchez DA, Ishiuji Y, Patel T *et al*. Enhanced skin blood flow and sensitivity to noxious heat stimuli in papulopustular rosacea. *J Am Acad Dermatol* 2007; **57**: 800–5.
11 Rosina P, Zamperetti MR, Giovannini A *et al*. Videocapillaroscopic alterations in erythematotelangiectatic rosacea. *J Am Acad Dermatol* 2006; **54**: 100–4.
12 Smith JR, Lanier VB, Braziel RM *et al*. Expression of vascular endothelial growth factor and its receptors in rosacea. *Br J Ophthalmol* 2007; **91**: 226–9.
13 Oztas MO, Balk M, Ogüs E *et al*. The role of free oxygen radicals in the aetiopathogenesis of rosacea. *Clin Exp Dermatol* 2003; **28**: 188–92.
14 Baz K, Cimen MY, Kokturk A *et al*. Plasma reactive oxygen species activity and antioxidant potential levels in rosacea patients: correlation with seropositivity to *Helicobacter pylori*. *Int J Dermatol* 2004; **43**: 494–7.
15 Yamasaki K, Di Nardo A, Bardan A *et al*. Increased serine protease activity and cathelicidin promotes skin inflammation in rosacea. *Nat Med* 2007; **13**: 975–80.
16 Anon. Rosacea in hot water. *Lancet* 1981; **i (8221)**: 647.
17 Guarrera M, Parodi A, Cipriani C *et al*. Flushing in rosacea: a possible mechanism. *Arch Dermatol Res* 1982; **272**: 311–6.
18 Powell FC, Corbally N, Powell D. Substance P levels in rosacea. In: Marks R, Plewig G, eds. *Acne and Related Disorders*. London: Martin Dunitz, 1989: 307–10.
19 Bernstein JE, Soltani K. Alcohol-induced rosacea flushing blocked by naloxone. *Br J Dermatol* 1982; **107**: 59–61.
20 Marks R. Concepts in pathogenesis of rosacea. *Br J Dermatol* 1968; **80**: 170–7.
21 Usher B, Young G. Gastroscopic studies in rosacea. *Can Med Assoc J* 1956; **75**: 111–3.
22 Bonamigo RR, Leite CS, Wagner M, Bakos L. Rosacea and *Helicobacter pylori*: interference of systemic antibiotic in the study of possible association. *J Eur Acad Dermatol Venereol* 2000; **14**: 424–5.
23 Fry L, Swann JC. Gastrocamera studies in rosacea. *Br J Dermatol* 1968; **80**: 737–9.
24 Watson WC, Paton E, Murray D. Small bowel disease in rosacea. *Lancet* 1965; **ii**: 47–50.
25 Powell FC, Dawa MA, Duguid C. Positive *Helicobacter pylori* serology in rosacea patients. *Ir J Med Sci* 1992; **161**: S75.
26 Rebora A, Drago F, Parodi A. May helicobacter pylori be important for dermatologists? *Dermatology* 1995; **191**: 6–8.
27 Schneider MA, Skinner RBJ, Rosenberg EW *et al*. Serologic determination of Hp in rosacea patients and controls. *Clin Res* 1992; **40**; 831A.
28 Sharma VK, Lynn A, Kaminski M *et al*. A study of *Helicobacter pylori* infection and other markers of upper gastrointestinal tract disease in patients with rosacea. *Am J Gastroenterol* 1998; **93**: 220–2.
29 Jones MP, Knable AL, White MJ, Durning SJ. *Helicobacter pylori* in rosacea: lack of an association. *Arch Dermatol* 1998; **134**: 511.
30 Utas S, Ozbakir O, Turasan A, Utas C. *Helicobacter pylori* eradication treatment reduces the severity of rosacea. *J Am Acad Dermatol* 1999; **40**: 433–5.
31 Erel A, Oztas N, Ilter N *et al*. *Helicobacter pylori* seroprevalence in patients with acne rosacea. *J Eur Acad Dermatol Venereol* 1995; **5** (Suppl. 1): S151.
32 Son SW, Kim IH, Oh CH, Kim JG. The response of rosacea to eradication of *Helicobacter pylori*. *Br J Dermatol* 1999; **140**: 984–5.
33 Szlachcic A, Sliwowski Z, Karczewska E *et al*. *Helicobacter pylori* and its eradication in rosacea. *J Physiol Pharmacol* 1999; **50**: 777–86.
34 Diaz C, O'Callaghan CJ, Khan A, Ilchyshyn A. Rosacea: a cutaneous marker of *Helicobacter pylori* infection? Results of a pilot study. *Acta Derm Venereol* 2003; **83**: 282–6.
35 Kolibasova K, Tothova I, Baumgartner J, Filo V. Eradication of *Helicobacter pylori* as the only successful treatment in rosacea. *Arch Dermatol* 1996; **132**: 1393.
36 Mayr-Kanhauser S, Kranke B, Kaddu S, Mullegger RR. Resolution of granulomatous rosacea after eradication of *Helicobacter pylori* with clarithromycin, metronidazole and pantoprazole. *Eur J Gastroenterol Hepatol* 2001; **13**: 1379–83.
37 Bamford JL, Tilden RL, Blankush JL, Gangeness DE. The effect of the treatment of Helicobacter pylori infection on rosacea. *Arch Derm* 1999; **135**: 659–63.
38 Forton F, Seys B. Density of *Demodex folliculorum* in rosacea: a case-control study using standardized skin-surface biopsy. *Br J Dermatol* 1993; **128**: 650–9.
39 Forstinger C, Kittler H, Binder M. Treatment of rosacea-like demodicosis with oral ivermectin and topical permethrin cream. *J Am Acad Dermatol* 1999; **41**: 775–7.
40 Jansen T, Kastner U, Kreuter A, Altmeyer P. Rosacea-like demodicosis associated with acquired immunodeficiency syndrome. *Br J Dermatol* 2001; **144**: 139–42.
41 Sibenge S, Gawkrodger DJ. Rosacea: a study of clinical patterns, blood flow and the role of *Demodex folliculorum*. *J Am Acad Dermatol* 1992; **26**: 590–3.
42 Bonnar E, Eustace P, Powell FC. The Demodex mite population in rosacea. *J Am Acad Dermatol* 1993; **28**: 443–8.
43 Georgala S, Katoulis AC, Kylafis GD *et al*. Increased density of *Demodex folliculorum* and evidence of delayed hypersensitivity reaction in subjects with papulopustular rosacea. *J Eur Acad Dermatol Venereol* 2001; **15**: 441–4.
44 Abd-El-Al AM, Bayoumy AM, Abou Salem EA. A study on *Demodex folliculorum* in rosacea. *J Egypt Soc Parasitol* 1997; **27**: 183–95.
45 Erbagci Z, Ozgoztasi O. The significance of *Demodex folliculorum* density in rosacea. *Int J Dermatol* 1998; **37**: 421–5.
46 Pena GP, Andrade Filho JS. Is demodex really non-pathogenic? *Rev Inst Med Trop Sao Paulo* 2000; **42**: 171–3.

47 Hoekzema R, Hulsebosch HJ, Bos JD. Demodicosis or rosacea: what did we treat? *Br J Dermatol* 1995; **133**: 294–9.
48 Roth AM. *Demodex folliculorum* in hair follicles of eyelid skin. *Ann Ophthalmol* 1979; **11**: 37–40.
49 English FP, Nutting WB. Demodicosis of ophthalmic concern. *Am J Ophthalmol* 1981; **91**: 362–72.
50 Ayres S Jr, Mihan R. Rosacea-like demodicosis involving the eyelids. *Arch Dermatol* 1967; **95**: 63–6.
51 Post CF, Juhlin E. *Demodex folliculorum* and blepharitis. *Arch Dermatol* 1963; **88**: 298–302.
52 Kamoun B, Fourati M, Feki J *et al*. Blepharitis due to demodex: myth or reality? *J Fr Ophthalmol* 1999; **22**: 525–7.
53 Marks R, Harcourt-Webster JN. Histopathology of rosacea. *Arch Dermatol* 1969; **100**: 683–91.
54 Ramelet AA, Perroulaz G. Rosacee: etude histopathologique de 75 cas. *Ann Dermatol Venereol* 1988; **115**: 801–6.
55 Ecker RI, Winkelmann RK. Demodex granuloma. *Arch Dermatol* 1979; **115**: 343–4.
56 Roihu T, Kariniemi A-L. Demodex mites in acne rosacea. *J Cutan Pathol* 1998; **25**: 550–2.
57 Allen KJ, Davis CL, Billings SD, Mousdicas N. Recalcitrant papulopustular rosacea in an immunocompetent patient responding to combination therapy with oral ivermectin and topical permethrin. *Cutis* 2007; **80**: 149–51.
58 Signore RJ. A pilot study of 5 percent permethrin cream versus 0.75 percent metronidazole gel in acne rosacea. *Cutis* 1995; **56**: 177–9.
59 Kocak M, Yagli S, Vahapoglu G, Eksioglu M. Permethrin 5% cream versus metronidazole 0.75% gel for the treatment of papulopustular rosacea. A randomized double-blind placebo-controlled study. *Dermatology* 2002; **205**: 265–70.
60 Forton F, Seys B, Marchal J-L, Song M. *Demodex folliculorum* and topical treatment: acaricidal action evaluated by standardized skin surface biopsy. *Br J Dermatol* 1998; **138**: 461–6.
61 Lacey N, Delaney S, Kavanagh K, Powell FC. Mite-related bacterial antigens stimulate inflammatory cells in rosacea. *Br J Dermatol* 2007; **157**: 474–81.
62 Vin-Christian K, Maurer TA, Berger TG. Acne rosacea as a cutaneous manifestation of HIV infection. *J Am Acad Dermatol* 1994; **30**: 139–40.
63 Barrio J, Lecona M, Hernanz JM *et al*. Rosacea-like demodicosis in an HIV-positive child. *Dermatology* 1996; **192**: 143–5.
64 Dahl MV, Ross AJ, Schlievert PM. Temperature regulates bacterial protein production: possible role in rosacea. *J Am Acad Dermatol* 2004; **50**: 266–72.
65 Tan ST, Bialostocki A, Armstrong JR. Pulsed dye laser therapy for rosacea. *Br J Plast Surg* 2004; **57**: 303–10.
66 Berg M, Edström DW. Flashlamp pulsed dye laser (FPDL) did not cure papulopustular rosacea. *Lasers Surg Med* 2004; **34**: 266–8.
67 Marks R, Wilson Jones E. Disseminated rosacea. *Br J Dermatol* 1969; **81**: 16–28.
68 Whitlock FA. Psychosomatic aspects of rosacea. *Br J Dermatol* 1961; **73**: 137–48.
69 Wilkin JK. Oral thermal-induced flushing in erythematotelangiectatic rosacea. *J Invest Dermatol* 1981; **76**: 15–8.
70 Logan RA, Griffiths WAD. Climatic factors and rosacea. In: Marks R, Plewig G, eds. *Acne and Related Disorders*. London: Martin Dunitz, 1989: 311–5.
71 Jansen T, Plewig G. The treatment of rosaceous lymphoedema. *Clin Exp Dermatol* 1997; **22**: 57.
72 Scerri L, Saihan EM. Persistent facial swelling in a patient with rosacea. *Arch Dermatol* 1995; **131**: 1069–74.
73 Bernardini FP, Kersten RC, Khouri LM *et al*. Chronic eyelid lymphedema and acne rosacea. Report of two cases. *Ophthalmology* 2000; **107**: 2220–3.
74 Michel JL, Cabibel F. Frequency, severity and treatment of ocular rosacea during cutaneous rosacea. *Ann Dermatol Venereol* 2003; **130**: 20–4.
75 Starr PAJ, McDonald R. Oculocutaneous aspects of rosacea. *Proc R Soc Med* 1969; **62**: 9–11.
76 Erzurum SA, Feder RS, Greenwald MJ. Acne rosacea with keratitis in childhood. *Arch Ophthalmol* 1993; **111**: 228–30.
77 Chamaillard M, Mortemousque B, Boralevi F *et al*. Cutaneous and ocular signs of childhood rosacea. *Arch Dermatol* 2008; **144**: 167–71.
78 Meschig R, Melnik B, Plewig G. Ophthalmic complications of rosacea. In: Marks R, Plewig G, eds. *Acne and Related Disorders*. London: Martin Dunitz, 1989: 321–5.
79 Gudmundsen KJ, O'Donnell BF, Powell FC. Schirmer testing for dry eyes in patients with rosacea. *J Am Acad Dermatol* 1992; **26**: 211–4.
80 Nazir SA, Murphy S, Siatkowski RM *et al*. Ocular rosacea in childhood. *Am J Ophthalmol* 2004; **137**: 138–44.
81 Bamford JT, Gessert CE, Renier CM *et al*. Childhood stye and adult rosacea. *J Am Acad Dermatol* 2006; **55**: 951–5.
82 Ohata C, Saruban H, Ikegami R. Granulomatous rosacea affecting the lacrimal and salivary glands. *Arch Dermatol* 2004; **140**: 240–2.
83 Helm KF, Menz J, Gibson LE, Dicken CH. A clinical and histopathologic study of granulomatous rosacea. *J Am Acad Dermatol* 1991; **25**: 1038–43.
84 Aroni K, Tsagroni E, Lazaris AC, Patsouris E, Agapitos E. Rosacea: a clinicopathological approach. *Dermatology* 2004; **209**: 177–82.
85 Aroni K, Tsagroni E, Kavantzas N *et al*. A study of the pathogenesis of Rosacea: how angiogenesis and mast cells may participate in a complex multifactorial process. *Arch Dermatol Res* 2008; **300**: 125–31.
86 Lever L, Marks R. Diagnostic discrimination between acne and rosacea. In: Marks R, Plewig G, eds. *Acne and Related Disorders*. London: Martin Dunitz, 1989: 317–20.
87 Bell HK, Poston GJ, Vora J, Wilson NJ. Cutaneous manifestations of the malignant carcinoid syndrome. *Br J Dermatol* 2005; **152**: 71–5.
88 Knight AK, Vickers CFH. A follow up of tetracycline treated rosacea. *Br J Dermatol* 1975; **93**: 577–80.
89 Irvine C, Marks R. Prognosis and prognostic factors in rosacea. In: Marks R, Plewig G, eds. *Acne and Related Disorders*. London: Martin Dunitz, 1989: 331–3.
90 Akpek EK, Merchant A, Pinar V, Foster CS. Ocular rosacea: patient characteristics and follow-up. *Ophthalmology* 1997; **104**: 1863–7.
91 Del Rosso JQ, Webster GF, Jackson M *et al*. Two randomized phase III clinical trials evaluating anti-inflammatory dose doxycycline (40-mg doxycycline, USP capsules) administered once daily for treatment of rosacea. *J Am Acad Dermatol* 2007; **56**: 791–802.
92 Marks R, Ellis J. Comparative effectiveness of tetracycline and ampicillin in rosacea. A controlled trial. *Lancet* 1971; **ii (7733)**: 1049–52.
93 Pye RJ, Burton JL. Treatment of rosacea by metronidazole. *Lancet* 1976; **i (7971)**: 1211–2.
94 Bakar O, Demirçay Z, Gürbüz O. Therapeutic potential of azithromycin in rosacea. *Int J Dermatol* 2004; **43**: 151–4.
95 Fernandez-Obregon A. Oral use of azithromycin for the treatment of acne rosacea. *Arch Dermatol* 2004; **140**: 489–90.
96 Jansen T, Melnik B. Plewig G. Gramnegative Follikulitis als Begleit Komplikation bei Rosazea. *Aktuel Dermatol* 1994; **20**: 381–4.
97 Ertl GA, Levine N, Kligman AM. A comparison of the efficacy of topical tretinoin and low dose oral isotretinoin in rosacea. *Arch Dermatol* 1994; **130**: 319–24.
98 Hofer T. Continuous 'microdose' isotretinoin in adult recalcitrant rosacea. *Clin Exp Dermatol* 2004; **29**: 204–5.
99 Irvine C, Kumar P, Marks R. Isotretinoin in the treatment of rosacea and rhinophyma. In: Marks R, Plewig G, eds. *Acne and Related Disorders*. London: Martin Dunitz, 1989: 301–5.
100 Nielson PG. Treatment of rosacea with 1% metronidazole cream. A double-blind study. *Br J Dermatol* 1983; **108**: 327–32.
101 Breneman D, Savin R, VandePol C *et al*. Double-blind, randomized, vehicle-controlled clinical trial of once-daily benzoyl peroxide/clindamycin topical gel in the treatment of patients with moderate to severe rosacea. *Int J Dermatol* 2004; **43**: 381–7.
102 Bamford JT, Elliott BA, Haller IV. Tacrolimus effect on rosacea. *J Am Acad Dermatol* 2004; **50**: 107–8.
103 Crawford KM, Russ B, Bostrom P. Pimecrolimus for treatment of acne rosacea. *Skinmed* 2005; **4**: 147–50.
104 Weissenbacher S, Merkl J, Hildebrandt B *et al*. Pimecrolimus cream 1% for papulopustular rosacea: a randomized vehicle-controlled double-blind trial. *Br J Dermatol* 2007: **156**: 728–32.
105 Antille C, Saurat JH, Lübbe J. Induction of rosaceiform dermatitis during treatment of facial inflammatory dermatoses with tacrolimus ointment. *Arch Dermatol* 2004; **140**: 457–60.
106 Gorman CR, White SW. Rosaceiform dermatitis as a complication of treatment of facial seborrheic dermatitis with 1% pimecrolimus cream. *Arch Dermatol* 2005; **141**: 1168.

107 Sanchez J, Somolinos AL, Almodovar PI *et al*. A randomized, double-blind, placebo-controlled trial of the combined effect of doxycycline hyclate 20 mg tablets and metronidazole 0.75% topical lotion in the treatment of rosacea. *J Am Acad Dermatol* 2005; **53**: 791–7.
108 Bryld LE, Jemec GB. Photodynamic therapy in a series of rosacea patients. *J Eur Acad Dermatol Venereol* 2007; **21**: 1199–202.
109 Wilkin JK. The effect of nadolol on flushing reactions in rosacea. *J Am Acad Dermatol* 1989; **20**: 202–5.
110 Wilkin JK. Effect of subdepressor clonidine on flushing reactions in rosacea. Change in malar thermal circulation index during provoked flushing reactions. *Arch Dermatol* 1983; **119**: 211–4.
111 Shanler SD, Ondo AL. Successful treatment of the erythema and flushing of rosacea using a topically applied selective alpha1-adrenergic receptor agonist, oxymetazoline. *Arch Dermatol* 2007; **143**: 1369–71.
112 Lowe NJ, Behr KL, Fitzpatrick R *et al*. Flash lamp pumped dye laser for rosacea-associated telangiectasia and erythema. *J Dermatol Surg Oncol* 1991; **17**: 522–5.
113 Clark SM, Lanigan SW, Marks R. Laser treatment of erythema and telangiectasia associated with rosacea. *Lasers Med Sci* 2002; **17**: 26–33.
114 Angermeier MC. Treatment of facial vascular lesions with intense pulsed light. *J Cutan Laser Ther* 1999; **1**: 95–100.
115 Scerri L, Saihan EM. Persistent facial swelling in a patient with rosacea. *Arch Dermatol* 1995; **131**: 1069–74.
116 Bernardini FP, Kersten RC, Khouri LM *et al*. Chronic eyelid lymphedema and acne rosacea. Report of two cases. *Ophthalmology* 2000; **107**: 2220–3.
117 Bechara FG, Jansen T, Losch R *et al*. Morbihan's disease: treatment with CO_2 laser blepharoplasty. *J Dermatol* 2004; **31**: 113–5.
118 Frucht-Pery J, Sagi E, Hemo I, Ever-Hadani P. Efficacy of doxycycline and tetracycline in ocular rosacea. *Am J Ophthalmol* 1993; **116**: 88–92.
119 Bender A, Zapolanski T, Watkins S *et al*. Tetracycline suppresses ATPγS-induced CXCL8 and CXCL1 production by the human dermal microvascular endothelial cell-1 (HMEC-1) cell line and primary human dermal microvascular endothelial cells. *Exp Dermatol* 2008; **17**: 752–60.
120 Shine WE, McCulley JP, Pandya AG. Minocycline effect on meibomian gland lipids in meibomianitis patients. *Exp Eye Res* 2003; **76**: 417–20.
121 Seal DV, Wright P, Ficker L *et al*. Placebo controlled trial of fusidic acid gel and oxytetracycline for recurrent blepharitis and rosacea. *Br J Ophthalmol* 1995; **79**: 42–5.
122 Daković Z, Vesić S, Vuković J *et al*. Ocular rosacea and treatment of symptomatic Helicobacter pylori infection: a case series. *Acta Dermatovenerol Alp Panonica Adriat* 2007; **16**: 83–6.

Rhinophyma and other phymas

The phymas are localized swellings of facial soft tissues due to variable combinations of fibrosis, sebaceous hyperplasia and lymphoedema [1]. They develop predominantly in males. The commonest is rhinophyma, a swelling of the nose which may become grossly distorted in contour (Fig. 43.7). Other areas which may be affected include the forehead (metophyma) (Fig. 43.8), chin (gnathophyma) (Fig. 43.9), eyelids (blepharophyma) and ears (otophyma) [2]. In many cases rhinophyma develops in patients with a long history of other features of rosacea and it is often regarded as a complication or 'end stage' of the disease. However, rhinophyma is sometimes also seen in patients who do not have any history of other manifestations of rosacea. Occasionally, rhinophyma is complicated by the development of a malignancy and this can be difficult to recognize [3]. There have also been examples of various malignancies being misdiagnosed as rhinophyma.

It is likely, but not proved, that active treatment of rosacea may inhibit the development of rhinophyma. Unfortunately, neither systemic nor topical treatments for rosacea have any useful impact on established rhinophyma. One exception is systemic isotretinoin, which can significantly reduce the bulk of rhinophyma although it does not restore normal skin contours [4]. Treatment of rhinophyma and other phymas therefore usually involves surgical removal of excess tissue or other means of physical ablation. Remodelling can often be successfully achieved simply by paring



Fig. 43.7 Rhinophyma. (Courtesy of Dr I. Ahmed, Coventry.)

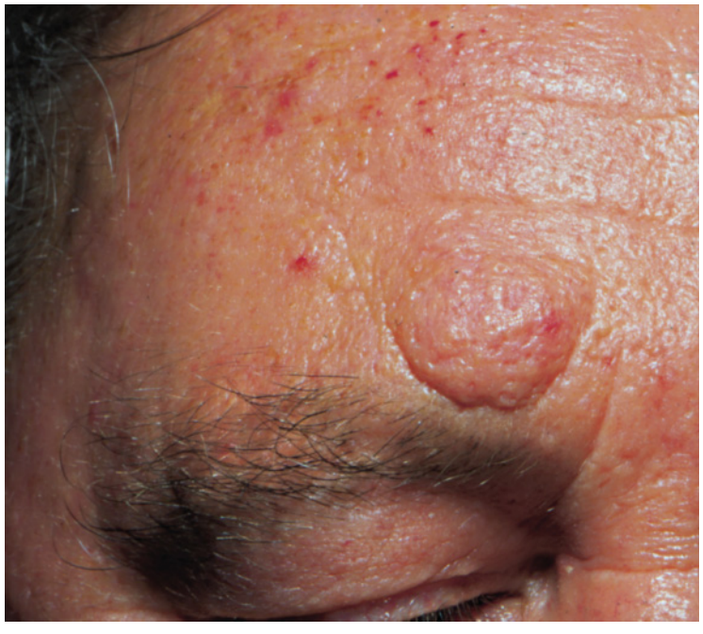


Fig. 43.8 Metophyma.



Fig. 43.9 Gnathophyma. (Courtesy of Dr C.T. Kakihara, Hospitalar Padre Bento de Guarulhos, Guarulhos, Brazil.)

off the excess tissue with a scalpel. Electrosurgery is an inexpensive alternative method. Excision and vaporization with argon, carbon dioxide or Nd : Yag lasers is effective. Other treatments have included cryotherapy and ionizing radiation [5]. The latter approach is probably most useful in cases with coexisting malignancy.

References

1 Marks R, Harcourt-Webster JN. Histopathology of rosacea. *Arch Dermatol* 1969; **100**: 683–91.
2 Gubisch W. Das Otophym-Eine Raritat. *HNO* 1983; **31**: 56–8.
3 Lutz ME, Otley CC. Rhinophyma and coexisting occult skin cancers. *Dermatol Surg* 2001; **27**: 201–2.
4 Irvine C, Kumar P, Marks R. Isotretinoin in the treatment of rosacea and rhinophyma. In: Marks R, Plewig G, eds. *Acne and Related Disorders*. London: Martin Dunitz, 1989: 311–5.
5 Plenk HP. Rhinophyma, associated with carcinoma, treated successfully with radiation. *Plast Reconstr Surg* 1995; **95**: 559–62.

Corticosteroid-induced rosacea

The use of potent topical corticosteroids on the face often results in a papulopustular eruption accompanied by erythema which may closely resemble rosacea (Fig. 43.10) [1,2]. Patients of all age groups and either gender are susceptible although this seems to happen rather more often in females. It is usually necessary to continue treatment for 8 weeks or more before steroid rosacea develops. If application of the steroid continues, fixed erythema and telangiectasia develop, further increasing the similarity to idiopathic rosacea. Patients experience exquisite sensitivity of the involved skin to the slightest irritant; itching, burning and intense redness being major complaints. Whenever the treatment is discontinued, the eruption flares, leading to a state of dependence. Patients affected by steroid rosacea often fail to recognize the causal link between the treatment and the rash. On the contrary, the application of the steroid usually produces prompt, if transient, improvement in the symptoms, creating the illusion of significant benefit.

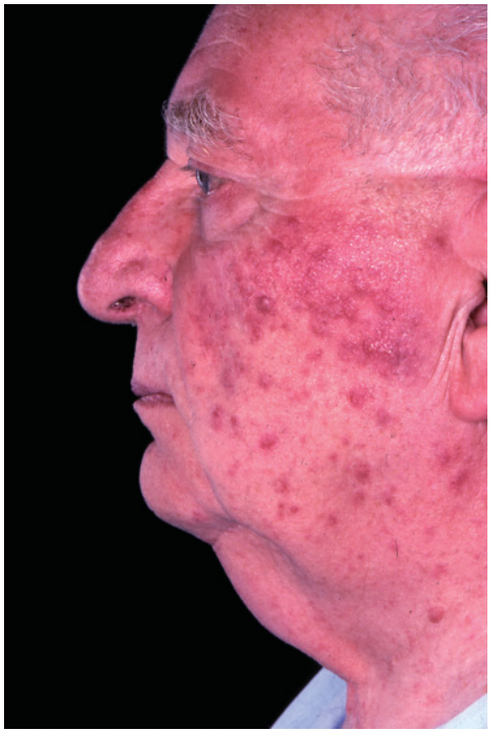


Fig. 43.10 Corticosteroid-induced rosacea.

On occasions, even 1% hydrocortisone may provoke steroid rosacea in children [3]. The use of steroid nasal spray may also be responsible [4]. A granulomatous eruption described as resembling rosacea developed 9 months into therapy with topical tacrolimus 0.1% ointment [5]. This resolved on treatment with doxycycline and did not recur when the tacrolimus was reintroduced.

Treatment. The first and most important step is withdrawal of the causative topical corticosteroid. Patients must be advised to anticipate a flare of the rosacea at this stage. In order to reduce the severity of this flare it is often necessary initially to introduce a less potent steroid. The author has found that a topical or systemic antibiotic, used in the same way as in idiopathic rosacea, can also be very useful in the early stages of steroid withdrawal. Topical application of tacrolimus ointment [6] or pimecrolimus cream [7,8] has proved helpful, although a rosacea-like eruption has also been reported to arise or worsen as a side effect of topical tacrolimus and pimecrolimus therapy (see above). Steroid rosacea may take several weeks or even months to subside but eventually complete resolution can be anticipated.

References

1 Leyden JJ, Thew AM, Kligman AM. Steroid rosacea. *Arch Dermatol* 1974; **110**: 619–22.
2 Ljubojeviae S, Basta-Juzbasiae A, Lipozeneiae J. Steroid dermatitis resembling rosacea: aetiopathogenesis and treatment. *J Eur Acad Dermatol Venereol* 2002; **16**: 121–6.

3 Weston WL, Morelli JG. Steroid rosacea in prepubertal children. *Arch Pediatr Adolesc Med* 2000; **154**: 62–4.
4 Egan CA, Rallis TM, Meadows KP, Krueger GG. Rosacea induced by beclomethasone dipropionate spray. *Int J Dermatol* 1999; **38**: 133–4.
5 Bernard LA, Cunningham BB, Al-Suwaidan S *et al*. A rosacea-like granulomatous eruption in a patient using tacrolimus ointment for atopic dermatitis. *Arch Dermatol* 2003; **139**: 229–31.
6 Goldman D. Tacrolimus ointment for the treatment of steroid-induced rosacea: a preliminary report. *J Am Acad Dermatol* 2001; **44**: 995–8.
7 Chu CY. The use of 1% pimecrolimus cream for the treatment of steroid-induced rosacea. *Br J Dermatol* 2005; **152**: 396–9.
8 Lee DH, Li K, Suh DH. Pimecrolimus 1% cream for the treatment of steroid-induced rosacea: an 8-week split-face clinical trial. *Br J Dermatol* 2008; **158**: 1069–76.

Perioral dermatitis

Definition. Perioral dermatitis is a persistent erythematous eruption, consisting of tiny papules and papulopustules with a distribution primarily around the mouth [1]. A similar eruption involving the eyelids and periorbital skin has been termed periocular dermatitis [2,3].

Epidemiology. First described in the late 1950s and 1960s, it became a commonplace diagnosis in the 1970s [1]. Over the past decade there has been an apparent fall in new cases—possibly attributable to a decline in the use of potent topical steroids on the face. It almost entirely affects young adult females, the age range tending to be somewhat younger than that of rosacea and occurrence in childhood more frequent. It has a worldwide distribution.

Aetiology. Although infectious agents and infestations including *Candida* spp. [4], *Demodex* [5] and fusiform bacteria [6] have been incriminated, none is established as playing a causative role. A variety of primary irritant and allergic contact factors have been proposed but not substantiated, including toothpaste and intimate contact with a partner's beard stubble [2]. A high prevalence of atopy has been reported in patients suffering from perioral dermatitis [7] and these patients were also found to have impaired barrier function of facial skin assessed by measurement of transepidermal water loss. Despite the prevalence among young female adults, there is no evidence to incriminate the oral contraceptive pill. Cosmetic products, especially foundation, may play a role, possibly resulting from an occlusive effect [8]. Topical steroid therapy is known to be an important aetiological factor. Prescribed initially for trivial facial eruptions, regular application of potent topical steroids leads to papulation and pustulation in the 'muzzle' area of the face [9,10]. Even brief exposure may occasionally cause the disease [9]. The more potent the steroid the more likely it is to cause perioral dermatitis although even hydrocortisone may very occasionally be sufficient [11]. The use of inhaled steroids for treating asthma, particularly from nebulizers, may also cause perioral dermatitis [12]. Systemic steroids may be an additional triggering factor [13]. Periocular dermatitis may be caused by steroid eye ointment [3].

Clinical features. Characteristically, the eruption begins abruptly in the nasolabial areas spreading rapidly to the perioral zone but sparing the lip margins (Fig. 43.11). The course of the condition may be continuous, intermittent or remittent. Occasionally it may spread to the forehead, eyelids and glabella, and rarely the lesions may be only periocular. Pruritus, burning and soreness are prominent symptoms. The lesions consist of monomorphic small papules and pustules occurring against a background of redness and variable scaling. The papules may occur in recurrent crops and are usually less substantial than those of rosacea. Strong soaps, sunlight and even contact with water may cause discomfort.



Fig. 43.11 Perioral dermatitis.

Histopathology. There is not a large amount of data published on the histology of perioral dermatitis, probably because of concern over the risk of scarring from facial biopsies. One study of 26 cases [14] showed a perivascular and perifollicular mononuclear cell infiltrate with mild eczematous changes. In another study of 36 patients similar features were observed but in addition to epidermal spongiosis, oedema of the papillary dermis was prominent. There was often perifollicular inflammation and some follicular pustules were observed. Granulomatous infiltration was observed in only two cases and *Demodex* mites were also rarely present [15].

Differential diagnosis. The clinical picture of perioral dermatitis is distinctive. The important differential diagnoses include rosacea, seborrhoeic dermatitis, contact allergic dermatitis, late-onset acne vulgaris, acne agminata and granulomatous perioral dermatitis in children (see below). Unlike rosacea, there is usually no telangiectasia or flushing in perioral dermatitis. Seborrhoeic dermatitis like perioral dermatitis affects the nasolabial area, but is not usually circumoral, and the scalp, ears and eyebrows are commonly involved. Contact dermatitis does not usually spare the immediate perioral area, but may present a problem which can only be resolved by patch testing. Acne vulgaris usually shows evidence of comedones, large papules and cysts in a wider distribution and responds more slowly to treatment than perioral dermatitis. Acne agminata may be difficult to distinguish if confined to the perioral area but can be differentiated histologically, if

necessary, as the lesions are more consistently granulomatous. Similarly, granulomatous perioral dermatitis in children (facial Afro-Caribbean childhood eruption) may be difficult to distinguish when the lesions are predominantly perioral although they do not spare the perilabial skin as in perioral dermatitis and pustules do not occur. This occurs especially in Afro-Caribbean children and unlike perioral dermatitis, seems to occur often in males.

Prognosis. Most patients experience permanent remission after a fairly short course of broad-spectrum antibiotics [16]. Relapses occur in a small minority [17]. However, if untreated and especially if the provoking topical steroids are continued, perioral dermatitis can persist for years [18].

Treatment. The most important measure is usually to discontinue the application of topical corticosteroids. Other applications, including cosmetics, should also be stopped. The patient must be warned that an initial flare may develop after withdrawal of a topical steroid. A 4-week course of oral tetracycline is usually all that is required. Topical tetracycline is also effective [19] as is topical metronidazole cream 1% [20] and topical erythromycin [21]. Response to pimecrolimus 1% cream has been demonstrated in recent clinical trials [22,23]. Photodynamic therapy performed weekly for 4 weeks proved somewhat more effective than clindamycin in a left/right comparative trial with 14 evaluable subjects [24]. Adapalene proved useful in one case [25].

References

1 Sneddon I. Perioral dermatitis. *Br J Dermatol* 1972; **87**: 430–4.
2 Wilkinson DS. What is perioral dermatitis? *Int J Dermatol* 1981; **20**: 485–6.
3 Velangi SS, Humphreys F, Beveridge GW. Periocular dermatitis associated with the prolonged use of a steroid eye ointment. *Clin Exp Dermatol* 1998; **23**: 297–8.
4 Bradford LG, Montes LF. Perioral dermatitis and *Candida albicans*. *Arch Dermatol* 1972; **105**: 892–5.
5 Bendl BJ. Perioral dermatitis: etiology and treatment. *Cutis* 1976; **17**: 903–8.
6 Takiwaki H, Tsuda H, Arase S, Takeichi H. Differences between intrafollicular microorganism profiles in perioral and seborrhoeic dermatitis. *Clin Exp Dermatol* 2003; **28**: 531–4.
7 Dirschka T, Tronnier H, Fölster-Holst R. Epithelial barrier function and atopic diathesis in rosacea and perioral dermatitis. *Br J Dermatol* 2004; **150**: 1136–41.
8 Malik R, Quirk CJ. Topical applications and perioral dermatitis. *Australas J Dermatol* 2000; **41**: 34–8.
9 Weber G. Rosacea like dermatitis. Contraindication or intolerance reaction to strong steroids. *Br J Dermatol* 1972; **86**: 253–9.
10 Cotterill JA. Perioral dermatitis. *Br J Dermatol* 1979; **101**: 259–62.
11 Guin JD. Complications of topical hydrocortisone. *J Am Acad Dermatol* 1981; **4**: 417–22.
12 Dubus JC, Marguet C, Deschildre A *et al*. Local side-effects of inhaled corticosteroids in asthmatic children: influence of drug, dose, age, and device. *Allergy* 2001; **56**: 944–8.
13 Adams SJ. Perioral dermatitis in renal transplant recipients maintained on corticosteroids and immunosuppressive therapy. *Br J Dermatol* 1982; **106**: 589–92.
14 Marks R, Black MM. Perioral dermatitis. A histopathologic study of 26 cases. *Br J Dermatol* 1971; **84**: 242–7.
15 Ramelet AA, Delacretaz J. Histopathological study of perioral dermatitis. *Dermatologica* 1981; **163**: 361–9.
16 Wilkinson DS, Kirton V, Wilkinson JD. Perioral dermatitis: a 12-year review. *Br J Dermatol* 1979; **101**: 245–57.
17 Macdonald A, Feiwel M. Perioral dermatitis: aetiology and treatment with tetracycline. *Br J Dermatol* 1972; **87**: 315–9.
18 Wells K, Brodell RT. Topical corticosteroid 'addiction'. A cause of perioral dermatitis. *Postgrad Med* 1993; **93**: 225–30.
19 Wilson RG. Topical tetracycline in the treatment of perioral dermatitis. *Arch Dermatol* 1979; **115**: 637.
20 Veien NK, Munkvad JM, Nielsen AO *et al*. Topical metronidazole in the treatment of perioral dermatitis. *J Am Acad Dermatol* 1991; **24**: 258–60.
21 Weber K, Thurmayr R, Meisinger A. A topical erythromycin preparation and oral tetracycline for the treatment of perioral dermatitis: a placebo-controlled trial. *J Dermatolog Treat* 1993; **4**: 57–9.
22 Oppel T, Pavicic T, Kamann S *et al*. Pimecrolimus cream (1%) efficacy in perioral dermatitis—results of a randomized, double-blind, vehicle-controlled study in 40 patients. *J Eur Acad Dermatol Venereol* 2007; **21**: 1175–80.
23 Schwarz T, Kreiselmaier I, Bieber T *et al*. A randomized, double-blind, vehicle-controlled study of 1% pimecrolimus cream in adult patients with perioral dermatitis. *J Am Acad Dermatol* 2008; **59**: 34–40.
24 Richey DF, Hopson B. Photodynamic therapy for perioral dermatitis. *J Drugs Dermatol* 2006; **5**: 12–6.
25 Jansen T. Perioral dermatitis successfully treated with topical adapalene. *J Eur Acad Dermatol Venereol* 2002; **16**: 175–7.

Acne agminata

Synonyms
- Lupus miliaris disseminatus faciei
- Acnitis
- Facial idiopathic granulomas with regressive evolution

Acne agminata is seen mainly in young adults and adolescents of either gender although a case has been reported in a 71-year-old Japanese woman [1]. It presents as multiple, monomorphic, symmetrical, reddish-brown papules on the chin, forehead, cheeks and eyelids (Fig. 43.12). The lesions may cluster around the mouth or on the eyelids or eyebrows so that the term 'agminata' is appropriate, although paradoxically, in many cases, the lesions are widely disseminated around the face and the term 'disseminatus' seems more applicable. Diascopy of larger lesions often reveals an apple-jelly nodule-like appearance indicating their granulomatous histology, which also shows central caseation. The lesions are not consistently related to hair follicles [2]. This eruption tends to be self-limiting, resolving completely over a few months or up to 2 years. In some cases there is scarring. There are reports of similar eruptions having an extra-facial distribution but this seems to be very rare [3].



Fig. 43.12 Acne agminata. (Courtesy of Dr S. Charles-Holmes, Nuneaton.)

The clinical picture in classical cases of acne agminata is quite distinctive and does not closely resemble rosacea or acne vulgaris since the other features of these diseases are not present. The synonym 'lupus miliaris dissseminatus' results from a historical classification of this condition as a presentation of tuberculosis. It now seems most unlikely to be tuberculous in aetiology and more likely that this condition is a distinct entity. The recently proposed acronym 'FIGURE' (facial idiopathic granulomas with regressive evolution) is perhaps more appropriate as it avoids linking the condition to acne or tuberculosis [4].

The aetiology remains unknown. It has been considered by some to be a variant of rosacea and may represent a self-limiting variant of the granulomatous form of this disease. Whilst the distribution of lesions is similar, the natural history and the tendency to affect males and females approximately equally argue against this being a form of rosacea. It can be difficult to distinguish from micropapular sarcoidosis.

The response of acne agminata to tetracyclines has been variable as has the response to isotretinoin. Dapsone may be effective [5], and a good response to low-dose prednisolone has been reported [6]. In one case the use of clofazimine 100 mg three times weekly was followed by complete resolution within 8 weeks [7].

References

1 Dekio S, Jidoi J, Imaoka C. Lupus miliaris disseminatus faciei—report of a case in an elderly woman. *Clin Exp Dermatol* 1991; **16**: 295–6.
2 Shitara A. Clinicopathological and immunological studies of lupus miliaris disseminatus faciei. *J Dermatol* 1982; **9**: 383–95.
3 Bedlow AJ, Otter M, Marsden RA. Axillary acne agminata (lupus miliaris disseminatus faciei). *Clin Exp Dermatol* 1998; **23**: 125–8.
4 Skowron F, Causeret AS, Pabion C *et al*. F.I.GU.R.E.: facial idiopathic granulomas with regressive evolution. Is lupus miliaris disseminatus faciei still an acceptable diagnosis in the third millennium? *Dermatology* 2000; **201**: 287–9.
5 Kumano K, Tani M, Mwata Y. Dapsone in the treatment of miliary lupus of the face. *Br J Dermatol* 1983; **109**: 57–62.
6 Uesugi Y, Aiba S, Usuba M, Tagami H. Oral prednisolone in the treatment of acne agminata. *Br J Dermatol* 1996; **134**: 1098–100.
7 Seukeran DC, Stables GI, Cunliffe WJ, Sheehan-Dare RA. The treatment of acne agminata with clofazimine. *Br J Dermatol* 1999; **141**: 596–7.

Granulomatous perioral dermatitis in children

Synonyms

- Facial Afro-Caribbean childhood eruption (FACE)
- Gianotti-type perioral dermatitis
- Granulomatous periorificial dermatitis
- Sarcoid-like granulomatous dermatitis

This eruption, which is seen in prepubertal children, may represent a juvenile form of perioral dermatitis or of acne agminata. It is considered relatively common in Afro-Caribbean children, giving rise to the acronym FACE (Fig. 43.13) [1] (see also Chapter 9).

This is a papular eruption generally confined to the face with lesions clustering around the mouth, eyes and ears [1–4]. In contrast to perioral dermatitis it does not spare the narrow zone bordering the lips and pustules are not seen. The histology has been variously described as showing non-specific inflammation with hyperkeratosis or, more often, as granulomatous, with the inflammatory changes often, but not invariably, being perifollicular. Blepharitis has occasionally been present. A series of cases with typical facial lesions accompanied by more disseminated lesions involving the trunk, limbs and labia majora has been described [5].



Fig. 43.13 Facial Afro-Caribbean childhood eruption. (Courtesy of Professor H.C. Williams.)

Complete resolution usually occurs after a few months, either spontaneously or in response to treatment. In some cases small pitted scars have been reported. Treatment with systemic erythromycin or topical metronidazole seems to have hastened resolution in several cases. A good response has been reported to treatment with minocycline and topical tacrolimus [6].

References

1 Williams HC, Ashworth J, Pembroke AC, Breathnach SM. FACE—Afro-Caribbean childhood eruption. *Clin Exp Dermatol* 1990; **15**: 163–6.
2 Gianotti F, Ermacora E, Bennelli MG, Caputo R. Particuliere dermatite peri-orale infantile: observations sur cinq cas. *Bull Soc Franc Dermatol Syph* 1970; **77**: 341.
3 Marten RH, Presbury DGC, Adamson JE, Cardell BS. An unusual papular and acneiform facial eruption in the negro child. *Br J Dermatol* 1976; **91**: 435–8.
4 Frieden IJ, Prose NS, Fletcher V, Turner ML. Granulomatous perioral dermatitis in children. *Arch Dermatol* 1989; **125**: 369–73.
5 Urbatsch AJ, Frieden I, Williams ML *et al*. Extrafacial and generalized granulomatous periorificial dermatitis. *Arch Dermatol* 2002; **138**: 1354–8.
6 Misago N, Nakafusa J, Narisawa Y. Childhood granulomatous periorificial dermatitis: lupus miliaris disseminatus faciei in children? *J Eur Acad Dermatol Venereol* 2005; **19**: 470–3.

Pyoderma faciale

Synonym

- Rosacea fulminans

Although pyoderma faciale is also known as rosacea fulminans it is not yet clear whether this condition is a variant of rosacea or acne vulgaris or a separate entity.

Pyoderma faciale affects mainly adult females. This is a sudden, severe eruption of pustules and cystic swellings, which may be interconnected by sinuses (Fig. 43.14). Marked erythema and



Fig. 43.14 Pyoderma faciale.

oedema are usually present. Comedones are usually absent or inconspicuous, as are other features of acne vulgaris or rosacea [1,2]. There is often no preceding history of acne. Some cases have developed during pregnancy, suggesting that hormonal factors may play a role. Occasional cases may arise as a side effect of medication, for example interferon α-2B and ribavirin therapy for hepatitis C [3]. As the name implies, the eruption is usually confined to the face, involving the cheeks, chin, nose and forehead. Localized forms may be confined to the cheeks, jaw line or chin. Culture of the purulent discharge or needle aspiration may be sterile or may yield growth of commensal organisms including *Staphylococcus epidermidis* and *Propionibacterium acnes*. This investigation can be helpful in excluding Gram-negative infection. Significant scarring develops in many cases.

In view of the distressing nature of this disease and the risk of severe scarring it is usually treated initially with systemic corticosteroids. In one series, 10 of the 20 cases were hospitalized to commence treatment with prednisolone at 1 mg/kg/day, before adding isotretinoin 0.2–0.5 mg/kg/day. The steroid was tapered off over 2–3 weeks and the isotretinoin continued for 3–4 months [2]. Others have used moderately potent topical corticosteroids combined with systemic isotretinoin [4], application of Vleminckx packs (containing sulphur, calcium polysulphide and calcium thosulphate), UVB, benzoyl peroxide, systemic antibiotics [1] or dapsone [5].

References

1 Massa MC, Su WPD. Pyoderma faciale: a clinical study of twenty-nine patients. *J Am Acad Dermatol* 1982; **6**: 84–91.

2 Plewig G, Jansen T, Kligman AM. Pyoderma faciale: a review and report of 20 additional cases: is it rosacea? *Arch Dermatol* 1992; **128**: 1611–7.

3 Jensen SL, Holmes R. Rosacea fulminans associated with pegylated interferon alpha-2B and ribavirin therapy. *J Drugs Dermatol* 2003; **2**: 554–6.

4 Veraldi S, Scarabelli G, Rizzitelli G, Caputo R. Treatment of rosacea fulminans with isotretinoin and topical alclometasone dipropionate. *Eur J Dermatol* 1996; **6**: 94–6.

5 Bormann G, Gaber G, Fischer M, Marsch WC. Dapsone in rosacea fulminans. *J Eur Acad Dermatol Venereol* 2001; **15**: 465–7.

Idiopathic facial aseptic granuloma

This recently described entity manifests as a benign, painless, inflammatory nodule on the face in children aged 8 months to 13 years [1]. Most cases seem to occur on the cheek and many are solitary, although two or three lesions are sometimes present. Histology shows a dermal lymphohistiocytic granuloma with numerous foreign body type giant cells. The lesions typically persist for 11 months or more.

Reference

1 Boralevi F, Léauté-Labrèze C, Lepreux S; Groupe de Recherche Clinique en Dermatologie Pédiatrique. Idiopathic facial aseptic granuloma: a multicentre prospective study of 30 cases. *Br J Dermatol* 2007; **156**: 705–8.

Flushing and flushing syndromes

Synonyms
- Blushing
- Hot flushes
- Hot flashes

Flushing is intermittent redness, often accompanied by a sensation of warmth or burning due to cutaneous vasodilation. This is usually most evident on the face and neck but less conspicuous changes may occur over the entire body. Flushing may arise from the action of a circulatory vasodilator substance, for example histamine, or it may be caused by changes in the neurological control of the cutaneous vasculature in the affected areas. In the face, neck and upper trunk, where flushing is most apparent, vascular tone is predominantly influenced by autonomic vasodilator nerve fibres rather than by relaxation of vasoconstrictor tone [1]. These fibres are found in somatic nerves supplying the affected skin, including the trigeminal nerve [2]. Since autonomic nerve fibres also supply sweat glands, neurally activated flushing is frequently associated with sweating ('wet flushing') whereas flushing due to circulating vasodilator mediators usually does not involve sweating ('dry flushing'). The presence or absence of sweating has therefore been proposed as a clinical guide to the mechanisms of flushing [3]. This is not entirely reliable in practice and it should be noted, in particular, that severe sweating occurs in some cases of carcinoid syndrome. Causes of flushing are summarized in Table 43.2.

Table 43.2 Causes of flushing.

Cause	Proposed mediator(s)
Physiological	Autonomic
Menopausal	Autonomic
Drug-induced	Various
Alcohol	Acetaldehyde
Chlorpropamide and alcohol	Acetaldehyde
Food	Autonomic
Scombroid fish poisoning	Histamine
Carcinoid syndrome	Serotonin
	Prostaglandins
	Bradykinin
	Histamine
Mastocytosis	Histamine
Thyrotoxicosis	Thyroxine
Medullary carcinoma of the thyroid	Prostaglandins
	Calcitonin
Pancreatic tumours	Vasoactive intestinal peptide
Insulinoma	?
POEMS syndrome	?

Table 43.3 Drugs that cause flushing.

5-HT3 receptor antagonists: ondansetron, ramosetron, tropisetron
ACE inhibitors: captopril, enalapril, lisinopril, perindopril, ramipril
β-3 adrenoceptor agonists: fluvoxamine, mirtazapine
Calcium channel blockers: nifedipine, verapamil
Chlorpropamide*
Disulfiram*
Ethanol
Fumaric acid esters
Hydralazine
Metronidazole*
Nicotinic acid
Nitrates: isosorbine mononitrate/dinitrate, glyceryl trinitrate
Phentolamine
Pilocarpine
Prostacyclin
Prostaglandin E
Sildenafil, tadalafil and vardenafil
Venlafaxine

* With ethanol.

Physiological flushing

Flushing develops as part of the normal thermoregulatory response in a hot environment or following exercise. A similar mechanism is responsible for facial flushing due to hot drinks, which cause a rise in temperature of blood in the oral cavity which in turn leads, by a counter-current heat-exchange process involving the internal jugular vein and internal carotid artery, to a rise in temperature of blood perfusing the hypothalamus [4].

Emotionally triggered flushing due to embarrassment or anger may be a problem in some patients in whom the threshold for this response may be low or the reaction itself unusually intense or extensive. It is often associated with telangiectasia and with sweating and can be a significant social handicap. Such patients are occasionally referred for investigation to exclude an underlying carcinoid tumour.

Explanation, accompanied if necessary by the β-blocker propranolol, may alleviate the symptom, which is essentially due to exaggeration of a normal response. Transthoracic endoscopic sympathectomy can be effective but seems justifiable only in the most severe cases and perhaps those with concurrent severe palmar hyperhidrosis [5,6]. This procedure can result in compensatory hyperhidrosis at other sites, Horner's syndrome and other complications.

Menopausal flushing

About 80% of menopausal women develop troublesome flushing, often associated with sweating. Attacks, which are often preceded by a feeling of heat, may be provoked by emotion, exertion and hot food or drink. The mechanism remains imperfectly understood but it is likely that the endocrine changes associated with the menopause result in a disturbance of thermoregulation and the flushing and sweating represent a hypothalamic response reducing body temperature [7]. A similar syndrome may also occur in men with prostatic cancer receiving treatment by gonadotrophin-releasing hormone analogues such as buserelin [8].

Menopausal flushing usually improves with oral or transdermal oestrogen replacement therapy. Combined oral contraceptives are effective and even the use of progestagens alone may be beneficial. Non-hormonal approaches to management include the use of clonidine 0.05 mg twice daily or selective serotonin reuptake inhibitors (SSRIs) [9].

Flushing caused by drugs

Numerous drugs cause flushing as an unwanted side effect, most frequently those listed in Table 43.3. There seems to be considerable variation between individuals in susceptibility to this side effect. It is not surprising that vasodilating drugs, such as calcium antagonists and sildenafil, may do this. Flushing occurs in an estimated 12% of patients taking sildenafil and may be accompanied by headache [10].

Fumaric acid esters, used in treatment of psoriasis, produce flushing in about one-third of patients [11]. Some state that this regularly occurs 20–60 min after each dose but in others the timing is not consistent. Flushing episodes may be quite severe but are usually very evanescent, lasting for only a couple of minutes. They may be accompanied by headache. Some patients do not notice this flushing at all whilst occasionally it is so severe that they cannot tolerate the drug. The flushing may sometimes be reduced by addition of oxypentifylline, perhaps due to antagonism of TNF-α by the latter drug [12].

Flushing is observed as part of generalized vasodilatation in reactions to gold therapy for rheumatoid disease, which have been termed 'nitritoid reactions' [13]. These occur most commonly with gold sodium aurothiomalate but have also been reported with other formulations. The reaction may develop after several years of regular treatment and may be more severe if angiotensin-converting enzyme (ACE) inhibitors are used simultaneously.

This phenomenon may be accompanied by hypotension and has occasionally been complicated by stroke or myocardial infarction. It is usually quite benign.

A reduction in the normal flushing response induced by systemic or topical nicotinic acid has been proposed as the basis of a diagnostic test for schizophrenia [14].

Flushing associated with alcohol intake

Most information on alcohol-evoked flushing in otherwise healthy individuals has been acquired by study of Japanese, Chinese and Korean volunteers since a majority of these oriental genotypes show extensive flushing in response to low doses of alcohol [15]. This difference with occidentals is associated with higher plasma levels of acetaldehyde, the initial metabolite of ethanol. Acetaldehyde may act partly by causing histamine release from mast cells [16]. Harada *et al*. [17] demonstrated deficiency of an isoenzyme of liver aldehyde dehydrogenase (low Km aldehyde dehydrogenase ALDH-1) in 50% of Japanese and that these, but not other, Japanese developed flushing after alcohol intake. This population can be detected using an ethanol patch test, which shows erythema due to accumulation of acetaldehyde in the ethanol-treated skin [18]. In a Caucasian population, patch testing with acetaldehyde proved more reliable [19]. Symptoms can be alleviated by aspirin [20] and also by antihistamines, H_1 and H_2 antagonists being most effective used in combination [21].

The chlorpropamide–alcohol flush is a special type of alcohol-induced flushing occurring in patients receiving this oral antidiabetic sulphonylurea drug. Even small amounts of alcohol provoke intense flushing within a few minutes of ingestion [22]. There is no associated sweating, and no systemic symptoms. The abnormality is dominantly inherited, associated with familial non-insulin-dependent diabetes and with a low frequency of diabetic complications. The flush is mediated by elevated acetaldehyde plasma levels, but release of prostaglandins is also involved since aspirin and other non-steroidal anti-inflammatory agents block the flush [23].

Flushing associated with food

It is a matter of common experience that eating spicy foods causes facial flushing, usually associated with sweating. This type of flushing, termed gustatory, is due to a nerve reflex involving autonomic neurones carried by the branches of the trigeminal nerve. Sour foods may also cause a similar response which, curiously, may be unilateral, as demonstrated by a child in whom the right (but not the left) side of the face manifested a 'slapped cheek' appearance (without sweating) a few seconds after sucking an acid drop (Fig. 43.15).

Monosodium glutamate has a reputation for causing flushing associated with sweating and faintness ('Chinese restaurant syndrome'). Although first described by Kwok [24], his account did not include flushing which was added to the symptom complex by later authors [25]. A more recent study involving oral challenge of volunteers with and without a history of previous monosodium glutamate reactions, by both monosodium l-glutamate and its cyclized derivate monosodium l-pyroglutamate, failed to provoke flushing over a range of doses although burning and tightness of the skin was noted in some volunteers [26]. Similar negative results have subsequently been reported [27]. Flushing due to monosodium glutamate, if it exists at all, must be an extremely rare occurrence.



Fig. 43.15 Unilateral gustatory flushing. (Courtesy of Professor M. Greaves.)

Scombroid fish poisoning

The scombroid families of edible fish include tuna and mackerel. Non-scombroid fish including dolphin and herring have also occasionally been reported to cause this syndrome [28]. Scombroid fish poisoning, which is the commonest form of ichthyotoxicosis worldwide, is due to ingestion of fish which has 'gone off', usually due to having been left on the fishmonger's counter in a warm atmosphere for several hours. Ingestion of the affected fish causes flushing, heat, sweating, vomiting and diarrhoea. That the symptoms are due to histamine intoxication is indicated by recent studies of the histamine content of affected fish and measurement of urinary histamine excretion in affected individuals [29]. Bacterial biosynthesis (by histidine decarboxylation) is thought to be the source of histamine in the spoiled fish.

Patients poisoned in this way should be treated with a combination of H_1 and H_2 antihistamines. Adrenaline and corticosteroids may be required in severe cases.

Other causes of flushing

Persistent flushing is sometimes observed in thyrotoxicosis as part of a picture of generalized vasodilatation. Mastocytosis is discussed elsewhere (Chapter 22). Medullary carcinoma of the thyroid [30] and certain pancreatic tumours [31] have been found to cause attacks of flushing. There are also single case reports of the association of flushing with an insulinoma [32] and the POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal proteinaemia and skin changes) [33]. These may therefore cause confusion with the carcinoid syndrome, which may also present with flushing (see below).

References

1 Fox RH, Goldsmith P, Kidd DJ. Cutaneous vasomotor control in the human head, neck and upper chest. *J Physiol* 1962; **161**: 298–312.
2 Gonzalez G, Onofrio BM, Kerr FWL. Vasodilator system for the face. *J Neurosurg* 1975; **42**: 696–703.
3 Wilkin JK. Skin changes in the flushing disorders and the carcinoid syndrome. In: Fitzpatrick TB, Eisen AZ, Wolff K *et al*., eds. *Dermatology in General Medicine*, 4th edn. New York: McGraw-Hill, 1993: 2131–6.
4 Wilkin JK. Oral thermal-induced flushing in erythematotelangiectatic rosacea. *J Invest Dermatol* 1981; **76**: 15–8.
5 Drott C, Claes G, Rex L *et al*. Long-term effects after surgery for hand sweating and facial blushing. Patients are satisfied in spite of troublesome side-effects. *Lakartidningen* 2001; **98**: 1766–72.
6 Lardinois D, Ris HB. Minimally invasive video-endoscopic sympathectomy by use of a transaxillary single port approach. *Eur J Cardiothorac Surg* 2002; **21**: 67–70.
7 Wilkin JK. Flushing reactions: consequences and mechanisms. *Ann Intern Med* 1981; **95**: 468–76.
8 Hardiman PJ, Abel PD, Ginsberg J. Peripheral vascular effects of gonadotrophin releasing hormone agonists in men. *J North Am Menopause Soc* 1995; **2**: 159–61.
9 Burstein HJ, Winer EP. Primary care for survivors of breast cancer. *N Engl J Med* 2000; **343**: 1086–94.
10 Fink HA, Mac Donald R, Rutks IR *et al*. Sildenafil for male erectile dysfunction: a systematic review and meta-analysis. *Arch Int Med* 2002; **162**: 1349–60.
11 Mrowietz U, Christophers E, Altmeyer P. Treatment of severe psoriasis with fumaric acid esters: scientific background and guidelines for therapeutic use. *Br J Dermatol* 1999; **141**: 424–9.
12 Friedrich M, Sterry W, Klein A *et al*. Addition of pentoxifylline could reduce the side effects of fumaric acid esters in the treatment of psoriasis. *Acta Derm-Venereol* 2001; **81**: 429–30.
13 Arthur AB, Klinkhoff A, Teufel A. Nitritoid reactions: case reports, review, and recommendations for management. *J Rheumatol* 2001; **28**: 2209–12.
14 Puri BK, Easton T, Das I *et al*. The niacin skin flush test in schizophrenia: a replication study. *Int J Clin Prac* 1997; **55**: 368–70.
15 Wolff PH. Ethnic differences in alcohol sensitivity. *Science* 1972; **175**: 449–50.
16 Koivisto T, Kaihovaara P, Salaspuro M. Acetaldehyde induces histamine release from purified rat peritoneal mast cells. *Life Sciences* 1999; **64**: 183–90.
17 Harada S, Agarawal DP, Goedde HW. Aldehyde dehydrogenase deficiency as a cause of facial flushing reaction to alcohol in Japanese. *Lancet* 1981; **ii**: 982.
18 Higuchi S, Muramatsu T, Saito M *et al*. Ethanol patch test for low Km aldehydrogenase deficiency. *Lancet* 1987; **i**: 629.
19 Ward RJ, McPherson AJS, Chow C *et al*. Identification and characterisation of alcohol-induced flushing in Caucasian subjects. *Alcohol Alcoholism* 1994; **29**: 433–8.
20 Truitt EB, Gaynor CR, Mehl DL. Aspirin attenuation of alcohol-induced flushing and intoxication in Oriental and Occidental subjects. *Alcohol* 1987; Suppl. 1: 595–9.
21 Miller NS, Goodwin DW, Jones FC *et al*. Histamine receptor antagonism of intolerance to alcohol in the Oriental population. *J Nerv Mental Dis* 1987; **175**: 661–7.
22 Wiles PG, Pyke DA. The chlorpropamide alcohol flush. *Clin Sci* 1984; **67**: 375–81.
23 Barnett AH, Spiliopoulos AJ, Pyke DA. Blockade of chlorpropamide alcohol flushing by indomethacin suggests an association between prostaglandin and diabetic vascular complications. *Lancet* 1980; **ii**: 164–6.
24 Kwok RHA. Chinese restaurant syndrome. *N Engl J Med* 1968; **278**: 796.
25 Ghadimi H, Kumar S, Abaci F. Studies on monosodium glutamate ingestion. *Biochem Med* 1971; **5**: 447–56.
26 Wilkin JK. Does monosodium glutamate cause flushing (or merely 'glutamania'). *J Am Acad Dermatol* 1986; **15**: 225–30.
27 Rosenblum I, Bradley JD, Coulston F. Single- and double-blind studies with oral monosodium glutamate in man. *Toxicol Appl Pharmacol* 1971; **18**: 367–73.
28 Kim R. Flushing syndrome due to Mahimahi (scombroid fish) poisoning. *Arch Dermatol* 1979; **115**: 963–5.
29 Morrow JD, Margolies GR, Rowland J, Roberts LJ. Evidence that histamine is the causative toxin of scombroid fish poisoning. *N Engl J Med* 1991; **324**: 716–20.
30 Cunliffe WJ, Black MM, Hall R *et al*. A calcitonin secreting thyroid carcinoma. *Lancet* 1968; **ii**: 63–6.
31 Murray JS, Paton RR, Pope CE. Pancreatic tumor associated with flushing and diarrhea. *N Engl J Med* 1961; **264**: 436–9.
32 Gulledge AD, Kavanaugh GJ, Priestley JT. Cutaneous flushing as a primary manifestation of functioning insulinoma. Report of a case. *Mayo Clin Proc* 1967; **42**: 547–50.
33 Myers BM, Miralles GD, Taylor CA *et al*. POEMS syndrome with idiopathic flushing mimicking carcinoid syndrome. *Am J Med* 1991; **90**: 646–8.

Carcinoid syndrome

The carcinoid syndrome results from secretion of a variable and diverse range of endocrinologically active substances by a malignant carcinoid tumour and its metastases. It may present with cutaneous features alone so it is of particular importance that dermatologists remain alert to this disease.

The term 'Karzinoid' was first used in 1907 to denote an intestinal tumour which behaved less aggressively than the more common adenocarcinoma [1]. A variety of other terms have been used to describe these tumours, which are probably derived from a primitive endocrine stem cell. Some of these reflect staining characteristics (argentaffinoma, enterochromaffinoma), others reflect their functional capacity to secrete a range of hormonally active substances (neuroendocrine tumours, Amine Precursor Uptake and Decarboxylation tumours (APUDomas)).

The tumours are variable in their degree of malignancy and in the pattern of hormones they secrete. Clinical manifestations are also highly dependent on the anatomical situation in which they arise, as their secretory products are substantially metabolized during passage through the liver and lungs when these organs lie downstream of the circulation from the tumour.

Carcinoid tumours are found most commonly in the embryological midgut (appendix, small bowel), especially in the appendix, where they may cause appendicitis. Estimates of the prevalence of appendiceal carcinoids range between 0.03 and 0.69% [2]. Most are asymptomatic and only a minority metastasize. Small bowel carcinoids are also common, whereas foregut (stomach, pancreas, biliary tract) and hindgut (colon and rectum) tumours are relatively rare. Occasionally, carcinoid tumours arise outside the intestinal tract (lung, ovary, testis).

The low levels of endocrine activity associated with most carcinoid tumours are asymptomatic, probably as a result of rapid hepatic metabolism of endocrine products in portal blood. The symptoms of the carcinoid syndrome normally develop as a consequence of liver metastases, although pulmonary carcinoids release hormonal products directly into the systemic circulation and can therefore cause symptoms without metastases. The considerable range of products with potential for endocrine activity known to be produced by carcinoid tumours includes 5-hydroxytryptamine (5-HT, serotonin), 5-hydroxytryptophan, histamine, dopamine, kallikrein, prostaglandins, tachykinins (neuropeptide K, substance P), gastrin, motilin, somatostatin, calcitonin and pancreatic polypeptide [2,3].

Clinical features. The cardinal features of carcinoid syndrome are flushing, diarrhoea, asthma and right sided cardiac dysfunction.

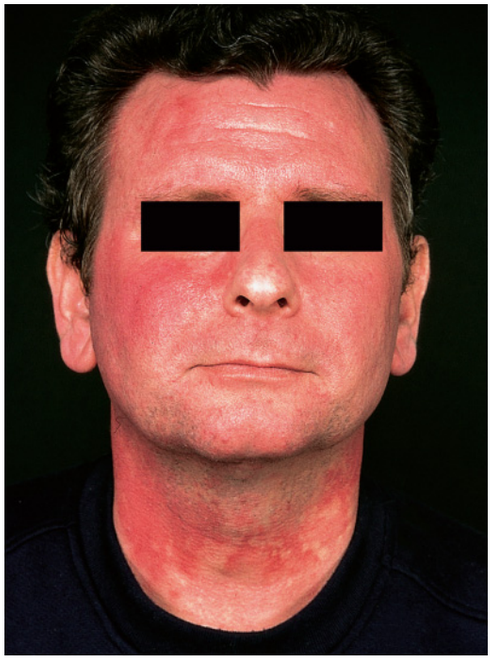


Fig. 43.16 Histamine-evoked 'geographical' pattern of flushing due to foregut carcinoid tumour. (Courtesy of Professor M. Greaves.)

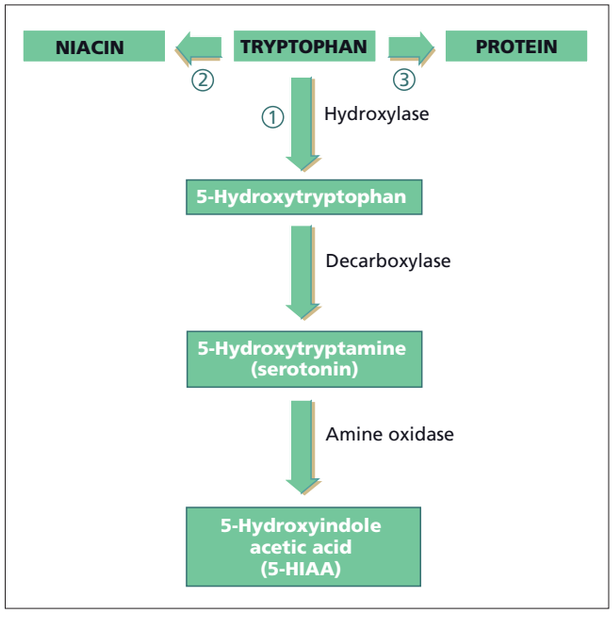


Fig. 43.17 Pathways for transformation of tryptophan to 5-hydroxytryptamine (pathway 1); niacin (pathway 2); and protein (pathway 3).

The relative prominence of these varies considerably between patients. Flushing and diarrhoea are the most common symptoms.

Flushing is observed in 80% of cases and may develop long before other symptoms. This is usually episodic and may be spontaneous or precipitated by exercise, alcohol, stress or meals. Certain foods, especially those containing tyramine or catecholamines (red wine, chocolate, blue cheese) are especially likely to induce flushing.

The character of the flush can vary considerably and seems to depend particularly upon the site of origin of the tumour. Midgut tumours usually produce diffuse, transient flushes of pink to red colour, lasting 2 to 10 min, affecting the face, neck, arms and upper chest. The flush is often mingled with areas of pallor, especially as it resolves [4]. Foregut carcinoids tend to produce slightly more prolonged and violaceous flushes, sometimes associated with a permanent cyanotic hue, facial telangiectasia, watery eyes, and injected conjunctivae [2]. Gastric carcinoids are often associated with increased histamine secretion and bright red, patchy 'geographic' flushing (Fig. 43.16) [5]. Bronchial carcinoids may result in particularly severe episodes of fiery violaceous-red flushing lasting up to 2 weeks and associated with profuse lacrimation, salivation and sweating, nasal congestion, swelling of the salivary glands, facial oedema, tachycardia, increased cardiac output and hypotension [6]. In contrast, rectal carcinoid tumours very rarely result in the carcinoid syndrome, tending to present with local symptoms such as bleeding, pain, constipation or pruritus ani.

The pathophysiology of the flushing is not fully understood. It is likely that histamine plays a major role in the distinctive bright red, geographical flushing associated with foregut (especially stomach) carcinoids [5]. The cause of the more classical flushing of midgut carcinoids is less clear. Serotonin, the major product of these tumours, seems unlikely to be the primary mediator. Serotonin infusions do not consistently induce flushing and flushing is not consistently associated with a rise in serotonin [7]. Serotonin antagonists inhibit the diarrhoea associated with the carcinoid syndrome but not the flushing. It seems more likely that carcinoid tumours may release kallikrein, which may produce flushing by acting on kininogen to release bradykinin [8]. Other proposed mediators of flushing include prostaglandins [9] and substance P [7].

A photosensitive eruption resembling pellagra may occur as part of the carcinoid syndrome and is believed to result from diversion of tryptophan metabolism away from synthesis of niacin (Fig. 43.17). Additional cutaneous manifestations reported in association with carcinoid tumours have included scleroderma [10], pyoderma gangrenosum [11] and pruritus [9]. Fixed facial erythema, telangiectasia and lymphoedema may give rise to an incorrect diagnosis of rosacea [12], and rosacea may develop as a feature of carcinoid syndrome [13].

Gastrointestinal symptoms are common. An estimated 76% of patients develop watery (secretory) diarrhoea [2]. This seems likely to be mediated substantially by serotonin. Abdominal pain is often reported and arises from a range of causes including altered motility, bowel obstruction, intussusception or appendicitis. Cardiac involvement results from the development of right-sided endocardial fibrosis, which may lead to pulmonary stenosis, tricuspid incompetence and congestive cardiac failure. The pathogenesis of the fibrotic changes is unknown. The asthma associated with carcinoid syndrome is a less constant feature than the flushing and the diarrhoea, occurring in about 25% of cases [2]. The episodes of wheezing often coincide with flushing and/or diarrhoea.

Diagnosis. The clinical diagnosis is not difficult in patients with advanced disease who present with flushing, diarrhoea, wheezing, weight loss and a large liver. Early recognition of the carcinoid syndrome is not so easy and some cases have been misdiagnosed for years as suffering from benign causes of flushing. These symptoms may even be dismissed as psychogenic in origin.

The diagnosis is usually confirmed by determining the urinary excretion of 5-hydroxyindole acetic acid (5-HIAA), the major metabolite of serotonin. The normal excretion rate is up to 10 mg (150 µmol) in 24 hours. In carcinoid syndrome, the level often exceeds 40 mg daily and may be much higher, especially after flushing episodes. However, levels can vary considerably from day to day. If attacks are infrequent, it may be helpful to wait until a flushing episode occurs before performing the urine collection. Foods containing serotonin, such as avocados, aubergine, bananas, pineapples, plums, tomatoes and walnuts should be avoided for 3 days before the urine collection is made, in order to avoid false-positive results. The elevation of 5-HIAA due to these is usually only marginal. Various drugs, including bromocriptine, caffeine, L-dopa, paracetamol, phenothiazines and salicylates, may also cause marginal changes in 5-HIAA excretion or interfere with the assay, so the laboratory should be advised about the patient's drug intake.

Further confirmation of the diagnosis may be obtained by induction of the flushing which can usually be provoked by alcohol ingestion (4 ml of 45% ethanol) or the infusion of norepinephrine (noradrenaline) 6 µg. This response to norepinephrine can be blocked by phentolamine (5–15 mg i.v.) [14].

If hepatic involvement is evident by abdominal palpation there is little point in elaborate attempts to locate the primary tumour, unless it is suspected to be causing obstruction. Many imaging techniques have been employed to investigate the extent of liver and lymph node metastases including angiography, ultrasound, endoscopic ultrasound, CT scanning and positron emission tomography [2]. Octreotide receptor imaging using radiolabelled octreotide can be used to localize both primary and secondary tumours [15].

In some cases, further investigation may be indicated to exclude additional neuroendocrine tumours. Carcinoid tumours, especially those of foregut origin, may occur in association with multiple tumours of the pancreas, parathyroid and pituitary as a feature of type I multiple endocrine neoplasia [16]. This condition is inherited as an autosomal dominant trait.

Prognosis. About one-fifth of patients with the carcinoid syndrome undergo a protracted course. In the remainder, deterioration can be rapid. The mean survival in one series was 8 years, the longest survivor living for 20 years [17].

Treatment. Alcohol and foods that may exacerbate symptoms (listed in Table 43.4) should be avoided as should exercise and stress. Nicotinamide supplements are often provided to reduce the risk of pellagra.

A range of pharmacological agents have been employed with variable degrees of success in providing control of symptoms.

Table 43.4 Food items that may cause flushing in carcinoid syndrome.

Alcohol	Pecan nuts
Aubergine	Pineapples
Avocado	Plums
Bananas	Red wine
Chocolate	Spicy foods
Hickory nuts	Tomatoes
Kiwi fruit	Walnuts

Serotonin antagonists such as cyproheptadine, ketanserin and methysergide, and the inhibitor of serotonin synthesis parachlorophenylalanine, can help control the diarrhoea but these are less effective against flushing [18]. Codeine phosphate and loperamide can also be useful for reducing diarrhoea. Clonidine has been reported to suppress flushing at low doses (0.05 mg twice daily) [19] and higher (antihypertensive) doses (0.4 mg/day) [20]. Antihistamines, both H_1 and H_2 [21], are effective in blocking the flush of foregut, especially gastric carcinoids, due to the dominant role of histamine in carcinoids at this location. Corticosteroids can be highly effective in controlling prolonged flushing associated with bronchial carcinoids [6]. α-Adrenoceptor blockers such as phentolamine and phenoxybenzamine have been helpful in improving flushing, diarrhoea and wheezing in some cases [22].

Octreotide, a somatostatin analogue given by subcutaneous injection at total daily dosage of 50–600 µg, lowers plasma levels of serotonin and tachykinins and relieves both flushing and diarrhoea [23]. The requirement for subcutaneous injections two or three times daily has been a disadvantage but a long-acting depot injection is now available and can be used at the dose of 20 mg intramuscularly every 28 days. In some cases, treatment for 6–12 months has resulted in partial or complete tumour regression [24]. Another somatostatin analogue, lanreotide, is also now available in depot formulation.

Surgical excision of carcinoid tumours is performed when possible. In metastatic disease, reduction of tumour mass can be useful in reducing symptoms; a similar effect can often be achieved by hepatic artery ligation or embolization [25]. Some patients have had multiple embolizations over a number of years. This treatment is based upon the dependence of metastatic malignant tissue, but not healthy liver parenchyma, on an intact hepatic arterial blood supply. Chemotherapy with agents such as streptozotocin, dacarbazine, adriamycin and 5-fluorouracil has also been employed [2]. All these 'tumour ablative' interventions run the risk of provoking an acute carcinoid crisis (profound flushing, bronchospasm and shock), due to massive release of mediators. This can be prevented or treated with intravenous octreotide [26]. Interferon-α has also proved helpful in reduction of symptoms and 5-hydroxyindole acetic acid levels in some cases, but side effects include flu-like symptoms and bone-marrow suppression [27].

References

1 Oberndorfer S. Karzinoid Tumoren des Dünndarms. *Frankf Z Pathol* 1907; **1**: 426–9.

2 Memon MA, Nelson H. Gastrointestinal carcinoid tumours: current management strategies. *Dis Colon Rectum* 1997; **40**: 1101–18.

3 Vinik AI, McLeod MK, Fig LM *et al*. Clinical features, diagnosis and localisation of carcinoid tumours and their management. *Gastro Clin N Am* 1989; **18**: 865–96.

4 Wereide K, Neset G. Skin manifestations in carcinoid syndrome. *Acta Derm Venereol (Stockh)* 1961; **41**: 264–76.

5 Oates JA, Sjoredsma A. A unique syndrome associated with secretion of 5-hydroxytryptophan by metastatic gastric carcinoids. *Am J Med* 1962; **32**: 333–42.

6 Melmon KL, Sjoerdsma A, Mason DT. Distinctive clinical and therapeutic aspects of the syndrome associated with bronchial carcinoid tumours. *Am J Med* 1965; **39**: 568–81.

7 Creutzfeldt W, Stockmann F. Carcinoids and carcinoid syndrome. *Am J Med* 1987; **82** (Suppl. 5B): 4–16.

8 Grahame-Smith DG. The carcinoid syndrome. *Am J Cardiol* 1968; **21**: 376–87.

9 Smith AG, Greaves MW. Blood prostaglandin activity associated with noradrenaline-provoked flush in the carcinoid syndrome. *Br J Dermatol* 1974; **90**: 547–51.

10 Fries JF, Lindgren JA, Bull JM. Scleroderma-like lesions and the carcinoid syndrome. *Arch Intern Med* 1973; **131**: 550–3.

11 Lee SS, Biro H, Price E. Pyoderma gangrenosum with carcinoid tumours. *Cutis* 1976; **18**: 791–4.

12 Creamer JD, Whittaker SJ, Griffiths WAD. Multiple endocrine neoplasia type I presenting as rosacea. *Clin Exp Dermatol* 1996; **21**: 170–1.

13 Bell HK, Poston GJ, Vora J, Wilson NJ. Cutaneous manifestations of the malignant carcinoid syndrome. *Br J Dermatol* 2005; **152**: 71–5.

14 Adamson AR, Grahame-Smith DG, Peart WS, Starr M. Pharmacological blockade of carcinoid flushing provoked by catecholamines and alcohol. *Lancet* 1969; **ii**: 293–7.

15 Lamberts SWJ, Bakker WH, Reubi J-C, Krenning EP. Somatostatin receptor imaging in the localization of endocrine tumors. *N Engl J Med* 1990; **323**: 1246–9.

16 Duh QY, Hybarger CP, Geist R *et al*. Carcinoids associated with multiple endocrine neoplasia syndromes. *Am J Surg* 1987; **154**: 142–8.

17 Norheim I, Oberg K, Theodorsson-Norheime E *et al*. Malignant carcinoid tumours. An analysis of 103 patients in relation to tumour localization, hormone production and survival. *Ann Surg* 1987; **206**: 115–26.

18 Engelman K, Lovenberg W, Sjoerdsma A. Inhibition of serotonin synthesis by para-chlorophenylalanine in patients with carcinoid syndrome. *N Engl J Med* 1967; **277**: 1103–8.

19 Wilkin JK, Rountree CB. Blockade of carcinoid flush with cimetidine and clonidine. *Arch Dermatol* 1982; **118**: 109–11.

20 Metz SA, Halter JB, Porte D *et al*. Suppression of plasma catecholamines and flushing by clonidine in man. *J Clin Endocrinol Metab* 1978; **46**: 83–90.

21 Granerus G, Ahlman H. Histamine metabolism in patients with foregut carcinoid tumours. *Agents Actions* 1993; **38**: C165–8.

22 Grahame-Smith DG. The carcinoid syndrome. *Am J Cardiol* 1968; **21**: 376–87.

23 Camisa C. Somatostatin and a long-acting analogue, octreotide acetate. Relevance to dermatology. *Arch Dermatol* 1989; **125**: 407–12.

24 Tomassetti P, Migliori M, Caletti GC *et al*. Treatment of type II gastric carcinoid tumours with somatostatin analogues. *N Engl J Med* 2000; **343**: 551–4.

25 Maton PN, Camilleri M, Griffin G *et al*. Role of hepatic arterial embolisation in the carcinoid syndrome. *Br Med J* 1983; **287**: 932–5.

26 Marsh HM, Martin JK Jr, Kvols LK *et al*. Carcinoid crisis during anaesthesia: a successful treatment with a somatostatin analogue. *Anesthesiology* 1987; **66**: 89–91.

27 Oberg K, Norheim I, Lind E. Treatment of malignant carcinoid tumours with human leukocyte interferon: long term results. *Cancer Treat Rep* 1986; **70**: 1297–304.

CHAPTER 44
Disorders of Sweat Glands

I.H. Coulson
Burnley General Hospital, Burnley, UK

Comparative anatomy and physiology, 44.1
Anatomy and physiology of human eccrine glands, 44.3
Control of eccrine sweating, 44.5
Hyperhidrosis, 44.7
Generalized hyperhidrosis, 44.7
Palmoplantar, axillary and craniofacial ('emotional') hyperhidrosis, 44.7
Localized and asymmetrical hyperhidrosis, 44.8
Gustatory hyperhidrosis, 44.10
Anhidrosis, 44.13
Ross's syndrome, 44.13
Miliaria, 44.15
Disorders associated with abnormal eccrine histology, 44.16
Neutrophilic eccrine hidradenitis, 44.16
Idiopathic recurrent palmoplantar hidradenitis, 44.17
Syringosquamous metaplasia, 44.17
Drugs and eccrine glands, 44.17
Coma-induced eccrine necrosis, 44.18
Radiation-induced eccrine damage, 44.18
Disorders with sweat gland cellular inclusions, 44.18
Granulosis rubra nasi, 44.18
Apocrine sweat glands, 44.18
Anatomy and physiology, 44.18
Abnormal sweat odour (bromhidrosis and osmidrosis), 44.19
Fish odour syndrome (trimethylaminuria), 44.20
Chromhidrosis, 44.20
Fox–Fordyce disease, 44.21

Comparative anatomy and physiology

Sweat glands are described as merocrine; unlike the holocrine sebaceous glands, their cells are not destroyed in the process of secretion. Merocrine glands have been further subdivided into two major types, usually known as apocrine and eccrine. The nomenclature is attributed to Schiefferdecker [1,2], who believed that secretion by apocrine glands involved decapitation of the apical cytoplasm, in contrast with eccrine glands, in which no breakdown of any cellular material occurs. Such a distinction between modes of secretion has been denied [3–5]. However, in the rabbit chin gland [6] and the lemur antebrachial organ [7], large portions of secretory epithelium do appear to be sloughed during secretion. In the axillary organ of humans, although some authors have claimed that decapitation of apical cells can sometimes occur [8], most believe this to be abnormal. The favoured view is that secretion occurs by small portions of apical cytoplasm becoming pinched off [9].

Even though the mechanisms of secretion may be debatable, there are a number of characteristic differences between the two types of gland (Fig. 44.1). The alternative designations of 'epitrichial' (where the sweat duct opens into the hair follicle) for 'apocrine', and 'atrichial' (where the duct does not enter the hair follicle) for 'eccrine', are not entirely satisfactory, because glands that on developmental and histochemical grounds must be classed as apocrine do not invariably open into the hair ducts. On balance, therefore, there is no strong case for abandoning the well-established terms.

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

The terminology has become further complicated by the use of 'apoeccrine' to describe a distinct type of tubule present in the human axilla. The axilla contains not only typical eccrine and apocrine elements, but numbers of large, irregularly shaped glands which cannot be assigned to either category, although they have some characteristics of each [10]. Such glands consistently occur in adults, but not in children, and become apparent between the ages of 8 and 14 years. Whether their precursors are apocrine or eccrine is unclear, but their ducts do not open into hair canals.

Apocrine glands occur in all known orders of mammals except whales, elephants, sea cows and scaly ant-eaters, although in some species only as part of specialized aggregates [11]. When dispersed, their density varies widely, ranging from 20 to 30/cm^2 in the pig to over 2000/cm^2 in Zebu cattle [5].

Eccrine glands occur in the footpads of many mammals; the exceptions again include whales, sea cows, elephants and scaly ant-eaters, with the addition of bats. Such glands probably serve to moisten the surface of the skin to improve grip.

In hairy skin, however, eccrine glands are found only in tree shrews, Old World monkeys, apes and humans. They appear to replace, but not to evolve from, apocrine glands. Only in humans do eccrine glands completely replace apocrine glands over the major areas of hairy skin. In the human embryo, such glands develop later than those on the friction surfaces, and thus should probably be placed in a different category and distinguished from mammalian footpad glands in general.

Specialized glands, that is aggregations of secreting units, are not only widespread among mammalian orders but, in different species, can be found in almost every area of the body, from the head to the rump and the extremities [11]. Some—for example, the chin and anal glands of the rabbit—contain only tubular units [12,13]; others—for example, the supracaudal gland of the guinea

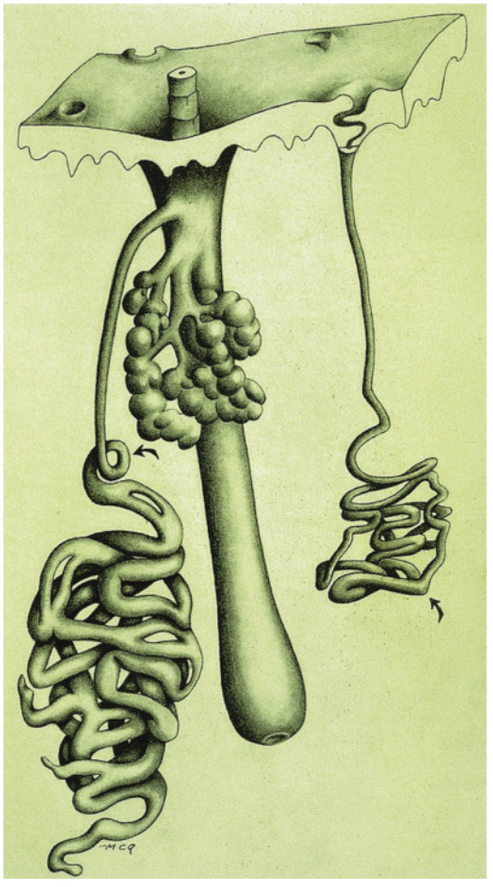


Fig. 44.1 An apocrine, sebaceous and eccrine gland and their relationships to the hair follicle. (Courtesy of Dr W. Montagna.)

pig, the flank organ of the golden hamster, the abdominal gland of the gerbil and the preputial glands of rodents—are purely sebaceous. Both types of unit may be associated, as in the muzzle glands of certain bats [14], the side glands of shrews, in which batteries of tubular glands underlie the sebaceous elements [15], and the inguinal glands of the rabbit, which consist of a discrete pair of each type [16]. Similar glandular aggregations occur in primates [17]. In humans, rudiments of apocrine glands attached to each follicle appear during development, but survive to become functional only in the axillae, the genital area and the areolae.

In animals, two main functions, thermoregulation and odour production, are performed by apocrine glands. The first is carried out by glands dispersed over the general body surface or, in some species, limited to areas such as the scrotum. Odour production is a property of specialized aggregates, although possibly not exclusive to them.

The extent to which the glands respond to environmental heat loads, and the exact nature of the control mechanisms, have been studied mainly in domestic animals. They vary widely. In horses, oxen and camels, the glands secrete in response to a rise in ambient temperature, but in pigs, dogs and deer they do not [18]. Apart from the primates, Equidae and some Bovidae, sweat glands appear to play a minor role in the control of body temperature in warm conditions [5,19], although they may cool local areas, such as the scrotum in sheep [20]. By sympathetic denervation of the skin, it has been shown that sweating is under adrenergic nervous control, even in species that lack a demonstrable nerve supply. In addition, in most species studied, the glands also respond to administration of epinephrine (adrenaline), although in contrast with human eccrine glands they are much less sensitive to acetylcholine. Although various interpretations have been made of the experimental results, it is now accepted that apocrine sweating is, in general, controlled by adrenergic nerves, and that in some species—for example the horse—epinephrine from the adrenal medulla supplements the sweating caused by exercise, although not that caused by heat exposure [18,19].

Odour production is known to occur in 15 out of 29 mammalian orders, but has received detailed study in only a few species. Chemical signals serve a number of social purposes, of which the marking of territory, the maintenance of social hierarchy, alarm signals and individual, group or species recognition are only a few [13,21–23]. They are also concerned with sexual attraction, either of the female by the male, as has been well established, for example, in the boar [24], or of the male by the female, as in the hamster [25] and the rhesus monkey [26,27].

Notwithstanding social pressures to devalue its impact, odour is undoubtedly important in human communication [28], as Havelock Ellis recognized in his comprehensive and entertaining, if almost entirely anecdotal, review in 1905 [29]. The odorous steroids 5-α-androsterone and 5-α-androsterol, known to act as pheromones in pigs, have been found in axillary sweat, as well as in human urine, plasma and fatty tissue [30–34]. The role of odour in human social behaviour is discussed in Chapter 4.

The limited evidence available suggests that at least some of the tubular glands of apocrine type are, like the sebaceous glands, controlled by hormones. In the rabbit, all three sets of apocrine glands are stimulated by androgens and inhibited by oestrogens [35].

It seems likely that the human apocrine glands of the axillary and pubic regions are similarly under some androgenic control [36]. The glands do not become active until puberty, at the same time as the development of the sexual hair with which they are associated.

References

1 Schiefferdecker P. Die Hautdrüsen des Menschen und des Säugetieres, ihre biologische und rassenanatomische Bedeutung, sowie die Muscularis sexualis. *Biol Zbl* 1917; **37**: 534–62.

2 Schiefferdecker P. Die Hautdrüsen des Menschen und des Säugetieres, ihre Bedeutung sowie die Muscularis sexualis. *Zoologica* 1922; **27**: 1–154.

3 Ellis RA. Eccrine, sebaceous and apocrine glands. In: Zelickson AS, ed. *Ultrastructure of Normal and Abnormal Skin*. Philadelphia: Lea & Febiger, 1967: 132–62.

4 Hibbs RG. Electron microscopy of human apocrine sweat glands. *J Invest Dermatol* 1962; **38**: 77–84.

5 Jenkinson DM. Comparative physiology of sweating. *Br J Dermatol* 1973; **88**: 397–406.

6 Kurosumi K, Yamagishi M, Sekine M. Mitochondrial deformation and apocrine secretory mechanism in the rabbit submandibular organ as revealed by electron microscopy. *Z Zellforsch Microsk Anat* 1961; **55**: 297–312.

7 Kneeland JE. Fine structure of the sweat glands of the ante-brachial organ of *Lemur catta*. *Z Zellforsch Microsk Anat* 1966; **73**: 521–33.

8 Hashimoto K, Gross BG, Lever WF. Electron microscopic study of apocrine secretion. *J Invest Dermatol* 1966; **46**: 378–90.

9 Bell M. The ultrastructure of human axillary apocrine glands after epinephrine injection. *J Invest Dermatol* 1974; **63**: 147–59.
10 Sato K, Leidal R, Sato F. Morphology and development of an apoeccrine sweat gland in human axillae. *Am J Physiol* 1987; **252**: R166–80.
11 Gabe M. Le tégument et ses annexes. In: Grassé P, ed. *Traité de Zoologie*, Vol. XVI.1: *Mamifères, Téguments et Squelette*. Paris: Masson, 1967: 1–233.
12 Goodrich BS, Mykytowicz R. Individual and sex differences in the chemical composition of pheromone-like substances from the skin glands of the rabbit, *Oryctolagus cuniculus*. *J Mammal* 1972; **53**: 540–8.
13 Mykytowycz R, Goodrich BS. Skin glands as organs of communication in mammals. *J Invest Dermatol* 1974; **62**: 124–31.
14 Quay WB. Integument and derivatives. In: Wimsatt WA, ed. *Biology of Bats*, Vol. 2. New York: Academic Press, 1970: 1–56.
15 Dryden GL, Conaway CH. The origin and control of scent production in *Suncus murinus*. *J Mammal* 1967; **48**: 420–7.
16 Lyne AG, Molyneux GS, Mykytowycz R *et al*. The development, structure and function of the submandibular cutaneous (chin) glands in the rabbit. *Aust J Zool* 1964; **12**: 341–8.
17 Montagna W, Yun JS. The skin of primates, 10: the skin of the ring-tailed lemur (*Lemur catta*). *Am J Phys Anthropol* 1962; **20**: 95–118.
18 Robertshaw D. Neural and humoral control of apocrine glands. *J Invest Dermatol* 1974; **63**: 160–7.
19 Robertshaw D. Apocrine sweat glands. In: Goldsmith LA, ed. *Biochemistry and Physiology of the Skin*. New York: Oxford University Press, 1983: 642–53.
20 Waites GMH, Voglmayr JK. Apocrine sweat glands of the scrotum of the ram. *Nature* 1962; **196**: 965–7.
21 Albone ES. *Mammalian Semiochemistry*. Chichester: Wiley, 1984.
22 Ebling FJG. The role of odour in mammalian aggression. In: Brain BF, Benton D, eds. *The Biology of Aggression*. Alpen aan den Rijn: Sijthoff and Noordhoff, 1981: 301–21.
23 Müller-Schwarze D, Mozel MM, eds. *Chemical Signals in Vertebrates*. New York: Plenum Press, 1977.
24 Sink JD. Theoretical aspects of sex odour in swine. *J Theor Biol* 1967; **17**: 174–80.
25 Singer AG, Agosta WC, O'Connell RF *et al*. Dimethyl disulphide: an attractant pheromone in hamster vaginal secretions. *Science* 1976; **191**: 948–50.
26 Keverne EB, Michael RP. Sex-attractant properties of ether extracts of vaginal secretions from rhesus monkeys. *J Endocrinol* 1971; **51**: 313–22.
27 Michael RP, Keverne EB, Bonsall RW. Pheromones: isolation of male sex attractants from a female primate. *Science* 1971; **172**: 964–6.
28 Russell MJ. Human olfactory communication. *Nature* 1976; **260**: 520–2.
29 Ellis H. Smell. In: *Studies in the Psychology of Sex*, Vol. IV. *Sexual Selection in Man*. Philadelphia: Davies, 1905: 44–50.
30 Bird S, Gower DB. The validation and use of radioimmunoassay for 5α-androst-16-en-3-one in human axillary collections. *J Steroid Biochem* 1981; **14**: 213–9.
31 Bird S, Gower DB. Axillary 5α-androst-16-en-3-one, cholesterol and squalene in man: preliminary evidence for the 5α-androst-16-en-3-one being a product of bacterial action. *J Steroid Biochem* 1982; **17**: 517–22.
32 Gower DB. 16 unstructured C19 steroids: a review of their chemistry, biochemistry and possible physiological role. *J Steroid Biochem* 1972; **3**: 45–103.
33 Cohn BA. In search of human pheromones. *J Invest Dermatol* 1993; **130**: 1048–51.
34 Claus R, Alsing W. Occurrence of 5-alpha-androst-16-en-3-one, a boar pheromone, in man and its relationship to testosterone. *J Endocrinol* 1976; **68**: 483–4.
35 Strauss JS, Ebling FJ. Control and function of skin glands in mammals. *Mem Soc Endocrinol* 1970; **18**: 341–71.
36 Ebling FJG. Apocrine glands in health and disorder. *Int J Dermatol* 1989; **28**: 508–11.

Anatomy and physiology of human eccrine glands [1–4]

Human eccrine sweat glands have two distinct functions: they allow body cooling by evaporation, and have thus contributed in a major way to adaptation to a hot environment by humans (major illness or death may ensue with sweat gland failure, even in temperate climates); they also moisten the skin on the palms and soles at times of activity, and thus improve their grip.

Eccrine sweat glands are distributed over the whole skin surface, including the glans penis and foreskin, but not on the lips, external ear canal, clitoris or labia minora. The number varies greatly with site, from 620/cm^2 on the soles and about 120/cm^2 on the thighs to 60/cm^2 on the back [5]. The total number on the body surface is between 2 and 5 million, and is the same in black people as in white people. It has been calculated that the weight of the eccrine glands totals 100 g. The glands vary in size from person to person by a factor of five, and this probably accounts for individual as well as regional differences in sweat rate (maximal individual gland secretion rates ranging from 2 to 20 nL/min/gland).

Embryologically, sweat glands are derived from a specialized down-growth of the epidermis at about the third month of intrauterine life on the palms and soles and at about 5 months elsewhere, and they resemble adult glands by 8 months. Sweat glands are morphologically normal at birth, but may not function fully until about 2 years of age. No new eccrine glands develop after birth. Unlike the apocrine glands, they have no developmental relationship with the pilosebaceous follicle, although some glands may eventually come to open into the follicular neck. The gland consists of a secretory coil in the lower dermis and subcutaneous tissue, and a duct leading through the dermis to the intraepidermal sweat duct unit. Apoeccrine glands have features of both eccrine and apocrine glands, but seem to be nearer to eccrine in function. They open onto the surface, and produce a copious watery fluid. Some authors claim that they may account for 10–45% of adult axillary glands [6]; others more recently have studied serial sections of axillary skin and cast doubt on their existence in humans [7].

The *secretory coil* contains three types of cell: large clear cells, which are the main secretory cells, small dark cells, which resemble mucus-secreting cells of other organs but whose function is not known, and myoepithelial cells [7] (Figs 44.2 & 44.3). The large and small cells of the secretory coil, unlike those of the duct, are attached to the basement membrane, although individual sections may at times suggest a double layer. Outside the basement membrane are the longitudinally arranged myoepithelial cells, whose function is probably to support the gland, but they may also help propel the sweat towards the surface. They respond to cholinergic stimuli. The function of the coil is to produce from plasma a watery isotonic secretion which can subsequently be modified by the duct. Ultrastructurally, the large clear cells are characterized by the presence of many mitochondria and by both intricate basal infoldings and intercellular canaliculi. Paranitrophenyl phosphatase activity, which reflects catalytic activity of Na-K-ATPase, is evident in the basal infoldings but not the intercellular canaliculi, suggesting that the basal areas are the sites of active ion transport requisite for sweat secretion. The classical theory suggests that acetylcholine passively increases entry of sodium into the cell, and this is then pumped out by the sodium pump into the intercellular canaliculi rather than directly through the luminal margin. However, there are other theories [4]. Fluid secretion is believed to be mediated osmotically, but

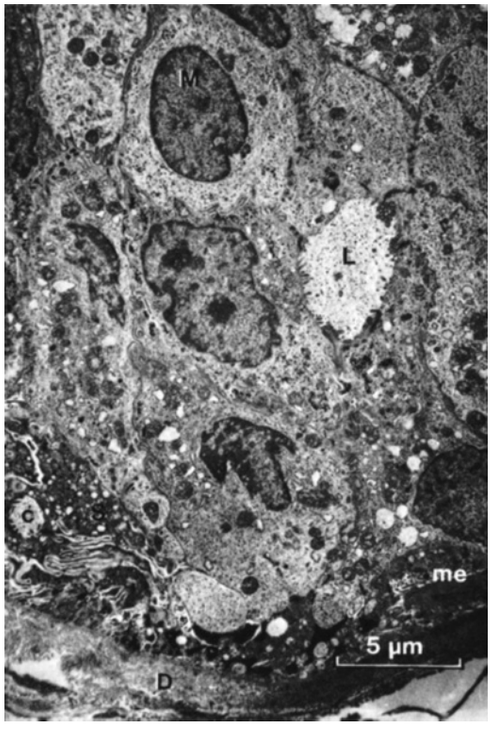


Fig. 44.2 Section of a secretory coil of an eccrine sweat gland stained with osmium. The coil contains three types of cell: (i) serous or clear cells (S) containing finger-like processes and bordering a canaliculus (c); (ii) mucous or dark cells (M); and (iii) myoepithelial cells (me). D, dermis; L, lumen of coil. (Courtesy of the late Professor A.S. Breathnach, St John's Dermatology Centre, London, UK.)

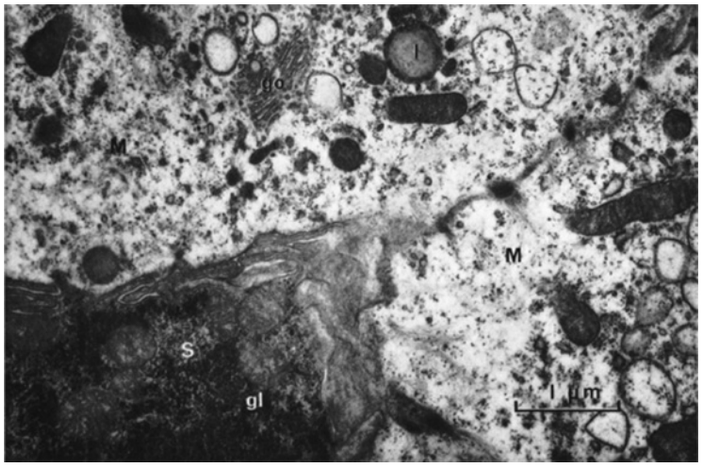


Fig. 44.3 Portions of two mucous (dark) cells (M), showing a Golgi complex (go) and lipid globules (l) and a serous (clear) cell (S) with glycogen granules (gl). (Courtesy of the late Professor A.S. Breathnach, St John's Dermatology Centre, London, UK.)

the mechanism by which water moves has long been obscure. However, recently a membrane protein with water transporting properties has been described in a range of tissues, including the human eccrine sweat gland [8]. The sodium pump in the gland can achieve a pressure up to 500 mmHg [9]. During active secretion, and in certain pathological conditions, well-marked histological changes occur in the gland [10]. Many different monoclonal antibodies can be shown to react with different portions of the sweat glands [11].

The *duct* consists of two or more layers of relatively uniform cuboidal cells. About one-third of the coil has this histology, as well as the uncoiled part passing up to the epidermis. The basal cells are rich in mitochondria and their entire membranes are rich in Na-K-ATPase activity, suggesting that sodium pumping occurs along the entire duct membrane and performs an active part in modifying the secretion produced by the coil.

It has been suggested that sweat glands do not cool the skin only by evaporation of heat from the surface, but also act as heat pipes. According to this theory, evaporation of the fluid at the base of the duct allows water vapour to pass up the duct and condense nearer the surface, and thence return to the deeper parts by capillary action. Such systems are a very effective way of transferring heat quickly [12].

The *intraepidermal sweat unit* is lined by a layer of specialized cells which may sometimes be distinguished only with difficulty from the surrounding epidermis. On the palms and soles, it has a well-developed coil structure that is not so apparent in other sites.

The *techniques for studying the function* of the eccrine sweat glands [12–14] include the following:

1. Collection of sweat in bags or pads at rest, after heat, or after injection or iontophoresis of pilocarpine or other cholinergic agonists.
2. Direct measurement of water loss.
3. Microcannulation of the duct or coil [15].
4. Measurement of electrical potentials and electrical resistance of the skin, which depends on both the sweat present on the epidermis and the column present within the duct [16,17].
5. Visualization of the individual sweat droplets. This may be achieved by direct microscopy, by *in vivo* staining, by forming plastic impressions [18] or by indicators that become coloured on contact with water, such as the starch/iodine technique [19], bromophenol blue [13], quinizarin [20] and the food dye edicol ponceau. The plastic or silicone impression techniques are probably the most reliable, and can produce a permanent record. A simple modification of the starch/iodine test is to dry the skin, paint it with 2% iodine in alcohol, allow it to dry, and then press the skin against a good-quality paper. The starch in the paper reacts with iodine in the presence of water, so that each sweat droplet shows up as a minute dark spot. Alternatively, the starch may be suspended in castor oil (50 g in 100 mL) and painted onto the iodine-treated skin (Fig. 44.4). Special dry starch/iodine powders can be dusted directly onto the skin [21].
6. Isolated glands. Recently, it has become possible to isolate single eccrine glands (and also hair follicles, sebaceous glands and apocrine sweat glands) by the relatively simple technique of shearing tissues with scissors [22,23]. This allows the physiology, biochemistry and tissue culture behaviour to be studied *in vitro*.
7. Cutaneous microdialysis–microperfusion of the skin with perfusate containing various pharmacological agonists and antagonists allows for the study of continuous stimulation of sweat glands [24].



Fig. 44.4 Starch iodine test on the finger, showing individual sweat droplets. (Courtesy of the late Dr R.H. Champion, Addenbrooke's Hospital, Cambridge, UK.)

Control of eccrine sweating [1–4]

Eccrine glands alter their activity in response to thermal, osmotic, mental and gustatory factors. When the core temperature of the body rises above a certain level, termed the temperature set point, eccrine sweating is initiated. Thermosensitive receptors are present in both the preoptic area and the anterior hypothalamus, and, in experimental animals, warming of these areas of the brain activates functions to facilitate cooling, including sweating, panting and vasodilatation. Conversely, cooling the same areas initiates shivering. Different receptors respond to heat and cold. Microelectrode recording has demonstrated that the firing rate of the warm-sensitive receptors is increased not only by the local receptor temperature, but also by a rise in skin temperature, indicating the effect of local skin and spinal thermoreceptors. The effect of core temperature rise is about nine times more efficient than skin temperature in stimulating sweating. The efferent pathways from the hypothalamus involve nerve fibres relaying in the medulla, lateral horn of the spinal cord and sympathetic ganglia [2].

Thermoregulatory sweating occurs especially on the upper trunk and the face [25], but also over the whole body surface, including the palms and soles. The hypothalamic thermal set point is also influenced by alterations in blood osmotic pressure. Hyperosmolarity results in an elevation of the thermal set point and reduced sweating (as sweat is hypotonic, this is a response to conserve further water loss).

The centres and pathways controlling mental sweating are not fully known, but responsible centres within the frontal region of the brain have been identified. Mental stimuli produce sweating, especially on the palms and soles, perhaps to improve the grip at times of activity. Mental activity also produces some general increase in sweating over the body surface. The activity may be emotional or intellectual—for example, mental arithmetic.

Innervation of the eccrine sweat gland

The efferent sudomotor pathway consists of the cerebral cortex to the hypothalamus, hypothalamus to medulla, medulla (mostly crossed) to the lateral horn of the spinal cord, then to the sympathetic ganglia, and finally from the ganglia to the sweat gland as postganglionic non-myelinated fibres.

The functioning of the eccrine sweat gland is dependent on intact non-myelinated C fibres of sympathetic nerves. Glands deprived of their postganglionic nerve supply soon cease to respond to any stimuli, although they remain histologically normal. The main sympathetic nerve supply of sweat glands is unusual in being muscarinic cholinergic. Work in rats has shown that there is a complex interrelationship between the developing sweat glands and peripheral nerves. The glands influence the nerves to produce the appropriate neurotransmitter [26]. Adrenergic agents and nerve stimulation also increase sweat-gland activity [27–29], and a single isolated eccrine gland can respond to both cholinergic and adrenergic stimuli. The ratio of maximal secretory rates for human sweat glands *in vitro* and *in vivo* is 5:1:1 for cholinergic, α-adrenergic and β-adrenergic stimulation, respectively. The adrenergic nerve supply seems to play little part in the normal control of eccrine sweating in humans. Vasoactive intestinal peptide (VIP), calcitonin gene-related peptide, atrial natriuretic peptide and galinin immunoreactivity can be found in human axillary periglandular neurons, but whether physiologically relevant concentrations are present remains to be established [30].

Other factors may modify the quantity and quality of sweat in the presence of an intact sympathetic nerve supply—for example, local temperature [31], hormones, circulatory changes, and axon and spinal reflexes. Sweat coils contain androgen receptors [32], and androgens may be at least partly responsible for the increase in sweating around puberty, and for the greater activity in males. Androgens do not play a significant role in the day-to-day regulation of eccrine sweat gland activity.

By these mechanisms, the quantity and quality of the sweat may be varied greatly. Under basal conditions, there may be few or no impulses passing to the sweat gland. Some insensible perspiration always occurs, partly due to transepidermal water loss and partly to sweat gland activity. Only the latter can be suppressed by atropine. Under maximal stimulation, the body can produce up to 12 L in 24 h, or for short periods 3 L in 1 h; this rate exceeds the ability of humans to drink [33].

The composition of sweat [4,34] varies greatly from person to person, time to time and site to site. It has a basic similarity to the plasma from which it is derived. The sweat duct is largely responsible for the modification in sweat constituent concentration which occurs, and this will therefore vary according to how rapidly the sweat is passing through the duct. The most important constituents are sodium, chloride, potassium, urea and lactate. Sweat is hypotonic and this is largely due to reabsorption of sodium in the duct. At increased sweat rates, the sodium concentration rises, presumably because there is reduced time for ductal reabsorption. The normal sodium concentration is between 10 and 20 mmol/L at low sweat rates, and up to 100 mmol/L at high rates. Ald-

osterone can increase ductal sodium reabsorption and in Addison's disease high sweat sodium can be demonstrated (70–80 mmol/L). Antidiuretic hormone may reduce sweat rates in humans, but it also induces local vasoconstriction.

An increase in sweat electrolytes occurs in cystic fibrosis, and is sufficiently constant to be a most useful diagnostic test [35]. The basic defect seems to be an abnormal, diminished permeability of many cells to chloride ions [36–38]. The gene responsible has been identified [39]. Sweat may be collected after intradermal injection or iontophoresis of pilocarpine or methacholine (Mecholyl), or after heating. In normal children, it is not unusual to have a sweat sodium level above 60 mmol/L, but the majority of children with cystic fibrosis have levels greater than this, often above 90 mmol/L. Sometimes a normal level is present, but the normal fall in sweat sodium concentration after deoxycorticosterone acetate (DOCA) or aldosterone is not seen. In adults, the normal levels are higher, and the test is of much less value. Initial suggestions that partial forms and carriers of cystic fibrosis could be diagnosed in this way have not been substantiated. An increase in sweat potassium has been reported in infants with apparent life-threatening events ('near-miss sudden infant death syndrome') [40].

Lactate is found in a concentration of 4–40 mmol/L, which greatly exceeds the concentration found in plasma. It is formed in the gland from glucose from the blood. It is interesting to speculate whether urea and lactate can act to moisturize the stratum corneum.

Glucose is present in small quantities only (usually 0–3 mg/100 mL, although levels up to 11 mg/100 mL may be found). High sweat glucose may be found in uncontrolled diabetes and this may create a favourable environment for skin infections. The pH is 4–6.8.

The concentration of these substances varies greatly in health and disease. Such changes seldom give rise to any symptoms referable to the skin, but may help in the understanding of disease.

A variety of other substances may be found in sweat, including pharmacologically active substances and inhibitors, antigens, antibodies and drugs [4]. Some of these seem to be excreted, and have no special function; others may have a definite function—for example, a urokinase-type plasminogen activator may play a part in digestion of glycoprotein plugs in sweat pores [41]. Active excretion or secretion of drugs such as griseofulvin and ketoconazole may contribute to their efficacy.

Atopic dermatitis patients often have IgE antibodies against an antigen found in their own sweat. The importance of this in the pathogenesis of the disease is uncertain [42].

References

1 Montagna W, Parakkal PF. *The Structure and Function of Skin*, 3rd edn. London: Academic Press, 1974.

2 Rothman S. *Physiology and Biochemistry of the Skin*. Chicago: University of Chicago Press, 1954.

3 Sato K. The physiology and pharmacology of the eccrine sweat gland. In: Goldsmith LA, ed. *Biochemistry and Physiology of the Skin*. Oxford: Oxford University Press, 1983.

4 Sato K, Kang WH, Saga K *et al*. Biology of sweat glands and their disorders. *J Am Acad Dermatol* 1989; **20**: 537–63, 713–26.

5 Szabo G. The regional anatomy of the human integument with special reference to the distribution of hair follicles, sweat glands and melanocytes. *Philos Trans R Soc Lond Biol* 1967; **252**: 447–85.

6 Sato K, Leidal R, Sato F. Morphology and development of an apoeccrine sweat gland in human axillae. *Am J Physiol* 1987; **252**: R166–80, 181–7.

7 Breathnach AS. *An Atlas of the Ultrastructure of Human Skin*. London: Churchill Livingstone, 1971.

8 Hasegawa H, Lian SC, Finkbeiner WE, Verkman AS. Extrarenal tissue distribution of CHIP28 water channels by *in situ* hybridization and antibody staining. *Am J Physiol* 1994; **266**: C893–903.

9 Bell M. The ultrastructure of human axillary apocrine glands after epinephrine injections. *J Invest Dermatol* 1974; **63**: 147–59.

10 Sargent F, Dobson RL. The effect of acetyl-beta-methylcholine on the structure and function of the eccrine sweat gland. *J Invest Dermatol* 1962; **38**: 305–17.

11 Cotton DWK. Immunohistochemical staining of normal sweat glands. *Br J Dermatol* 1986; **113**: 441–9.

12 Thiele FAJ, Mier PD, Reay DA. Heat transfer across the skin. The role of the 'resting' sweat gland. Thermography, Proceedings of the 1st European Congress, Amsterdam. *Bibl Radiol* 1975; **6**: 140–3.

13 Sulzberger MB, Hermann F. *The Clinical Significance of Disturbances in the Delivery of Sweat*. Springfield, IL: Thomas, 1954.

14 Collins KJ. Measurement of sweating and sweat gland function. In: Greaves MW, Shuster S, eds. *The Pharmacology of the Skin*. Berlin: Springer, 1989.

15 Schulz IJ. Micropuncture studies of the sweat formation in cystic fibrosis patients. *J Clin Invest* 1969; **48**: 1470–7.

16 Montagna W, Ellis RA, Silver AF. *Advances in Biology of Skin*, Vol. 3. *Eccrine Sweat Glands and Eccrine Sweating*. Oxford: Pergamon, 1962.

17 Christie MJ. Electrodermal activity in the 1980s: a review. *J R Soc Med* 1981; **74**: 616–7.

18 Harris DR, Polk BF, Willis I. Evaluating sweat gland activity with imprint techniques. *J Invest Dermatol* 1972; **58**: 78–84.

19 Muller SA, Kierland RR. The use of a modified starch-iodine test for investigating local sweating responses to intradermal injection of methacholine. *J Invest Dermatol* 1959; **32**: 126–8.

20 Guttman I. A demonstration of the study of sweat secretion by the quinizarin method. *Proc R Soc Med* 1941; **35**: 77–89.

21 Sato KT, Richardson A, Sato K. One step iodine starch method for direct investigation of sweating. *Am J Med Sci* 1988; **295**: 528–31.

22 Kealey T, Philpott MP. Human pilosebaceous culture: the background. In: Leigh I, Lane B, Watt F, eds. *The Keratinocyte Handbook*. Cambridge: Cambridge University Press, 1994: 109–29.

23 Kealey T, Philpott M, Guy R, Dove N. Skin gland and appendage epithelial cells. In: Harris A, ed. *Practical Cell Biology Series*. Cambridge: Cambridge University Press, 1996: 147–77.

24 Morgan CJ, Friedmann PS, Church MK, Clough GF. Cutaneous microdialysis as a novel means of continuously stimulating eccrine sweat glands *in vivo*. *J Invest Dermatol* 2006; **126**: 1220–5.

25 Kuno Y. *Human Perspiration*. Springfield, IL: Thomas, 1956.

26 Habecker BA, Landis SC. Noradrenergic regulation of cholinergic differentiation. *Science* 1994; **264**: 1602–4.

27 Randall WC, Kimura KK. The pharmacology of sweating. *Pharmacol Rev* 1955; **7**: 365–97.

28 Warndorff JA, Hamer M. The response of the sweat glands to alphaadrenergic stimulation with isoprenaline. *Br J Dermatol* 1974; **90**: 263–8.

29 Wolf JE, Maibach HI. Palmar eccrine sweating: the role of adrenergic and cholinergic mediators. *Br J Dermatol* 1974; **91**: 439–46.

30 Tainio H. Cytochemical localization of VIP-stimulated adenylate cyclase activity in human sweat glands. *Br J Dermatol* 1987; **116**: 323–8.

31 Van Beaumont W, Bullard RW. Sweating: direct influence of skin temperature. *Science* 1965; **147**: 1465–7.

32 Choudry R, Hodgins MB, Van der Kwast TH *et al*. Localization of androgen receptors in human skin by immunohistochemistry. *J Endocrinol* 1992; **133**: 467–75.

33 Schmidt-Nielsen K. *Desert Animals: Physiological Problems of Heat and Water*. Oxford: Oxford University Press, 1964.

34 Lobitz WC, Dobson RL. Dermatology: the eccrine sweat glands. *Annu Rev Med* 1961; **12**: 289.

35 Report of the Committee for Study of Evaluation of Testing for Cystic Fibrosis. *J Pediatr* 1976; **88**: 711–50.
36 Littlewood JM. The sweat test. *Arch Dis Child* 1986; **61**: 1041–3.
37 Geddes DM, Alton A. Cystic fibrosis: towards the basic defect. *Q J Med* 1988; **69**: 945–7.
38 Towards the biochemical defect in cystic fibrosis [editorial]. *Lancet* 1989; **ii**: 1433–4.
39 Knight RA, Hodson ME. Identification of the cystic fibrosis gene. *BMJ* 1990; **300**: 345–6.
40 Tirosh E, Haddad F, Lanir A *et al*. Relationship of sweat electrolytes to apparent life-threatening events (ALTE): a case control study. *Acta Paediatr Scand* 1994; **83**: 1268–71.
41 Takemura T, Hibinoo T, Sato K. Urokinase-type plasminogen activator in human eccrine sweat. *Br J Dermatol* 1993; **128**: 178–83.
42 Adachi K, Aoki T. IgE antibody to sweat in atopic dermatitis. *Acta Derm Venereol Suppl (Stockh)* 1989; **144**: 83–7.

Hyperhidrosis [1,2]

Hyperhidrosis is the excessive production of sweat, and can be a major inconvenience to sufferers. In theory, when there is over- or underproduction of sweat it should be possible to determine whether the change is in the sweat glands, due to pharmacologically active agents acting on the gland, to abnormal stimulation of the sympathetic pathway between the hypothalamus and the nerve ending, or to overactivity of one of the three different 'centres' responsible for thermoregulatory, mental and gustatory sweating. Any difficult case should be approached from first principles in this way. In practice, most cases of hyperhidrosis fall into the clinical groups outlined below.

Generalized hyperhidrosis

There is marked physiological variation in thermoregulatory sweating from person to person in the absence of disease. An increase in the temperature of blood bathing the hypothalamus increases heat loss by sweating and vasodilatation. Some instability of the sweat regulating centre is caused by many febrile conditions, so that sweating may occur at times when there is no fever. This instability may persist for days, or even months, after the fever has subsided, and in some cases is such a prominent feature that the term 'sweating sickness' has been used [3]. Generalized sweating may occur in disorders of unknown aetiology, which alter the setting of the thermoregulatory centre, and may be associated with episodic hypothermia [1]. Generalized sweating can occur with a wide range of medical and neurological disorders, but seldom in the absence of other neurological symptoms or signs (Table 44.1). Thermoregulatory sweating occurs during or after many infective processes, and may be the presenting manifestation of malaria, tuberculosis, brucellosis, lymphoma, subacute bacterial endocarditis, etc. Night sweats are often part of the clinical picture. A similar mechanism may account for the hyperhidrosis associated with alcohol intoxication or gout, and after vomiting. The mechanism of generalized hyperhidrosis which may be associated with diabetic autonomic neuropathy, hyperthyroidism, hyperpituitarism, hypoglycaemia, obesity, the menopause and malignant disease is unknown. Increased sweating has been documented in some patients with Parkinson's disease, but others have noted the combination of patchy anhidrosis and compensatory hyperhidrosis, suggesting autonomic dysfunction. Paroxysmal sweating, tachycardia and headaches strongly suggests phaeochromocytoma. Hypertension is noted during attacks. Two sisters have been reported who had generalized sweating in a thermal pattern, but induced by cold [4]. Hyperhidrosis is seen in association with peripheral neuropathies, as in familial dysautonomia, or the Riley–Day syndrome, a recessively inherited disorder of Ashkenazi Jews comprising an absent axon reflex flare after histamine injection, pupillary meiosis, diminished tendon reflexes, diminished pain sensation and absent fungiform papillae of the tongue. Excess sweating is thought to be due to sweat centre excitability. Congenital autonomic dysfunction with universal pain loss is similar, but individuals are not Ashkenazi Jews, have complete absence of pain sensation with accidental self-mutilation, corneal opacities and episodic fever. Cold-induced profuse sweating has been reported with a peripheral motor and autonomic neuropathy. Generalized hyperhidrosis may be associated with brain lesions (diencephalic lesions, malformations of the corpus callosum, microgyria) and may be accompanied by episodic hypothermia. Some drugs—for example, fluoxetine—are able to cause generalized hyperhidrosis. In many cases of generalized hyperhidrosis of the thermal type, but with no obvious underlying disease, the aetiology remains unknown, even after extensive investigation.

Table 44.1 Causes of generalized hyperhidrosis.

Febrile infective illnesses
Tuberculosis, malaria, brucellosis, endocarditis, etc.
Metabolic diseases
Diabetes, hyperthyroidism, hyperpituitarism, hypoglycaemia, phaeochromocytoma
Menopause
Underlying solid malignancy and lymphoma
Parkinson's disease
Congestive heart failure
Neurological disorders
Cold-induced sweating syndrome
Peripheral neuropathies
Familial dysautonomia (Riley–Day)
Congenital autonomic dysfunction with universal pain loss
Brain disease
Episodic hypothermia with hyperhidrosis
Generalized hyperhidrosis without hypothermia
Drugs
Fluoxetine

Palmoplantar, axillary and craniofacial ('emotional') hyperhidrosis

Emotional or mental activity increases sweating, especially on the palms, soles, axillae and, to a lesser extent, groin and face. It should be emphasized that mental activity devoid of any clear emotional content may provoke sweating. There may be some generalized increase in sweating. Thermal stimuli and physical effort increase this effect in many cases. Most cases of hyperhidrosis presenting to the dermatologist are of this type, affecting especially the palms, soles and axillae, and may affect up to 1% of the population in the UK. The head, neck and scalp may be affected



Fig. 44.5 Disabling palmar hyperhidrosis.



Fig. 44.6 Symmetrical lividity. Hyperhidrosis of the feet, with cool macerated soles and pitted keratolysis. (Courtesy of the late Dr R.H. Champion, Addenbrooke's Hospital, Cambridge, UK.)

in craniofacial hyperhidrosis in the absence of other areas being affected. Although mental or emotional factors are the usual trigger for this type of sweating, and in some patients deep-seated emotional disturbances may be found, in many there seems to be some facilitation of the nervous pathways causing physiological mental sweating.

The sweating of the palms and soles may be either continuous or phasic [5,6]. When continuous it is worse in the summer, and not so clearly precipitated by mental factors. When phasic, it is usually precipitated by minor emotional or mental activity, and is not markedly different in summer and winter. The hands may be cold, and show a tendency to acrocyanosis. Hyperhidrosis may be associated with Raynaud's phenomenon and reflex sympathetic dystrophy [6], or may follow cold injury.

Hyperhidrosis may be a significant disability, in that sweat drips from the hands onto the floor (Fig. 44.5), rusting of metal objects may be an occupational problem, or clothing may be saturated. This disorder occurs in either sex, and commonly begins in childhood or around puberty. Frequently there is a family history, and it is one component of various syndromes in which palmoplantar keratoderma occurs (Chapter 19). It also occurs with the nail–patella syndrome (Chapter 65). Hyperhidrosis may persist for some years, but there is a tendency to spontaneous improvement of the axillae and hands after the age of 25 years. Apart from the embarrassing nature of the disorder, complications include pompholyx (Chapter 23) and contact dermatitis. Control of plantar hyperhidrosis may reduce the exacerbations of contact dermatitis to footwear constituents.

Sweating affects the hands, feet and axillae in any combination, but only a minority of patients with axillary hyperhidrosis also have involvement of the palms and soles. Troublesome hyperhidrosis of the feet occurs especially in young adult men. When this is associated with vasomotor changes, so that the sodden skin is also cold and cyanotic, the name 'symmetrical lividity' is sometimes applied (Fig. 44.6). The condition of pitted keratolysis (Chapter 30) of the feet, due to infection with *Micrococcus sedentarius*, is associated with hyperhidrosis.

Axillary sweating may be continuous, or more commonly phasic, and may or may not be aggravated by heat or mental activity. It is uncommon before puberty. Axillary sweating on undressing is very common. Axillary hyperhidrosis is due to overactivity of eccrine glands, unlike axillary odour which is mainly apocrine in origin. Craniofacial hyperhidrosis is often phasic, occurs in middle age and may be exacerbated by heat, exercise and eating, but, unlike true gustatory hyperhidrosis, not exclusively so. It may be more persistent and presents at a later age than palmoplantar hyperhidrosis. Sweating sufficient to soak the hair is an additional embarrassment (Fig. 44.7).

Cold-induced sweating syndrome. This is a rare, familial condition in which profuse sweating of the trunk occurs when the skin is cooled to between 7 and 10°C [7]. There are associated physical anomalies including a high arched palate, inability to fully extend the elbows and scoliosis. Chromosomal anomalies have recently been identified [8].

Localized and asymmetrical hyperhidrosis

The causes of localized hyperhidrosis are outlined in Table 44.2. Excessive sweating may be due to neurological lesions involving



Fig. 44.7 Craniofacial hyperhidrosis producing persistent saturation of the hair.



Fig. 44.8 Idiopathic circumscribed hyperhidrosis on the wrist (indicated by edicol ponceau powder, which turns scarlet on hydration). The rest of the patient's sweating and neurological examinations were normal.

Table 44.2 Causes of localized hyperhidrosis.

Spinal cord injury
Hyperhidrosis associated with autonomic dysreflexia
Hyperhidrosis due to orthostatic hypotension
Intrathoracic neoplasia
Gustatory hyperhidrosis
Frey's syndrome
Granulosis rubra nasi
Functional and true sweat gland naevi
Sweating associated with local skin disorders
Glomangioma
Blue rubber bleb naevi
Pachydermoperiostosis
Pretibial myxoedema
POEMS syndrome
Burning feet syndrome
Compensatory
After sympathectomy, or with partial anhidrosis
Idiopathic unilateral circumscribed hyperhidrosis

POEMS, polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes.

any part of the sympathetic pathway from the brain to the nerve ending. It may be the presenting symptom, but it is quite exceptional for this to occur as an isolated phenomenon in the absence of other neurological symptoms or signs. Such lesions may be within the central nervous system [1,7–11] (cortex, basal ganglia or spinal cord), the sympathetic pathway and ganglia, or in the peripheral nerves. It must be remembered that the distribution of the sympathetic nerves does not exactly correspond with sensory dermatomes. One sympathetic grey ramus may supply 10 or more sensory segments, and one white ramus extends over at least five. Asymmetrical sweating may also occur reflexly from visceral disturbances [12], adjacent to an area of anhidrosis or due to axon reflex stimulation, around a leg ulcer, for example [7], or around glomus tumours, blue rubber bleb naevi or sudoriparous angioma [13]. Compensatory hyperhidrosis occurs in normal sweat glands when those elsewhere are not functioning because of neurological or skin disease, or after sympathectomy (see also Ross's syndrome). Functional sweat gland naevi have been reported [14], but must be distinguished from sweat gland hypertrophy associated with local hyperhidrosis of some other aetiology. There are some bizarre cases of hyperhidrosis which cannot be explained in these ways. Areas of skin that may be localized [15] (Fig. 44.8), termed idiopathic circumscribed hyperhidrosis, or as extensive as one-half of the body [16], may sweat continuously, or, more commonly, with mental activity. They may represent functional naevi, where the eccrine glands show increased sensitivity to cholinergic neurotransmitters. Sometimes, some psychological disturbance accounts for the distribution [17], but more often such cases remain a mystery. In the absence of other neurological symptoms or signs, they are seldom a manifestation of a progressive neurological lesion.

References

1 Sato K, Kang WH, Saga K *et al*. Biology of sweat glands and their disorders. *J Am Acad Dermatol* 1989; **20**: 537–63, 713–26.

2 Sulzberger MB, Hermann F. *The Clinical Significance of Disturbances in the Delivery of Sweat*. Springfield, IL: Thomas, 1954.

3 Davison WC. Sweating sickness. *Am J Dis Child* 1960; **100**: 934–5.

4 Sohar E, Udassin R, Shoenfeld Y *et al*. Cold-induced profuse sweating on back and chest. *Lancet* 1978; **ii**: 1073–4.

5 Herxheimer A. Excessive sweating: a review. *Trans St John's Hosp Dermatol Soc* 1958; **40**: 20–5.

6 Paice E. Reflex sympathetic dystrophy. *BMJ* 1995; **310**: 1645–8.

7 Sohar E, Shoenfeld Y, Udassin R *et al*. Cold-induced profuse sweating on back and chest. A new genetic entity? *Lancet* 1978; 18; **ii**: 1073–4.

8 Knappskog PM, Majewski J, Livneh A *et al*. Cold-induced sweating syndrome is caused by mutations in the CRLF1 gene. *Am J Hum Genet* 2003; **72**: 375–83.

9 Rothman S. *Physiology and Biochemistry of the Skin*. Chicago: University of Chicago Press, 1954.

10 Schliack H, Schiffter R. In: *Jadassohns Handbuch der Haut und Geschlechtskrankheiten*. Berlin: Springer, 1979.

11 McCoy BP. Apical pulmonary adenocarcinoma with contralateral hyperhidrosis. *Arch Dermatol* 1981; **117**: 659–61.

12 Korr IM. Skin resistance patterns associated with visceral disease. *Fed Proc Am Soc Exp Biol* 1949; **8**: 87–8.

13 Srinivas CR, Rao PLNG. Sudoriparous angioma: regression following intravascular aethoxysclerol, a sclerosing agent. *Br J Dermatol* 1988; **119**: 111–3.
14 Lapiere S. A propos d'une observation de naevus sudoripare avec hyperidrose. *Dermatologica* 1957; **115**: 293–7.
15 Mellinkoff SM. Localized paroxysmal hyperhidrosis. *Am J Med Sci* 1951; **221**: 86–8.
16 Champion RH, Herxheimer A. Unilateral hyperhidrosis of the trunk. *Acta Med Scand* 1960; **168**: 17–20.
17 Shorvon HJ. Psychiatry and the skin. *Proc R Soc Med* 1950; **43**: 801–4.

Gustatory hyperhidrosis (Table 44.3)

Sweating on the lips, forehead and nose after eating certain foods occurs physiologically in many people. Hot spicy foods are the most likely cause. The central connections of this reflex are not fully known. Gustatory hyperhidrosis also occurs in pathological conditions involving the autonomic nervous system. Localized areas of intense hyperhidrosis may occur on the face [1], and even on the knees [2]. These disorders are very rare, usually start in childhood and are not progressive (Fig. 44.9). Their nature is little understood.

Also uncommon is gustatory hyperhidrosis due to a lesion within the central nervous system [3].

Much the commonest cause is damage to the sympathetic nerves around the head and neck. After damage to sympathetic nerves, regeneration occurs not only from the proximal ends of the damaged sympathetic nerves, but also from damaged or undamaged parasympathetic nerves [4,5]. In this way, abnormal connections are made. Thus, the reflex arcs that normally allow chewing or taste stimulation to cause parotid or gastric secretion may cause sweating in a localized zone corresponding to the area of the skin in which the sympathetic innervation has been damaged. The commonest site is within the distribution of the auriculotemporal nerve, following injury, abscess or operation in the parotid region (auriculotemporal or von Frey's syndrome) [6–8]. Submental gustatory sweating [9,10] follows injuries involving the chorda tympani, and sweating in the distribution of the greater auricular nerve commonly follows radical neck surgery [11]. On the upper arm, fibres from the vagus may cause gustatory sweating after cervical sympathectomy [12].

Gustatory sweating may occur in diabetes as part of a widespread autonomic neuropathy [13,14]. It has also followed herpes zoster [15].

Table 44.3 Classification of gustatory hyperhidrosis.

Idiopathic
Central
Post-herpetic
Post-peripheral nerve injury
Parotid surgery, injury and abscess
Auriculotemporal
Chorda tympani
Greater auricular
Cervical sympathectomy
Peripheral autonomic neuropathy
Diabetes mellitus



Fig. 44.9 Auriculotemporal or von Frey's syndrome without any neurological abnormality and not preceded by surgery or injury. Cheek flushing and sweating was precipitated by eating. (Courtesy of Dr P. Hudson, Peterborough District Hospital, Peterborough, UK.)

Gustatory sweating is by no means uncommon, and occurs in 50–80% of patients subjected to operations on the parotid gland [16,17]. Usually the symptoms appear 4–7 months after operation, and either persist indefinitely or wane after 3–5 years. The stimuli required to initiate the reflex vary, as does the severity. Sometimes chewing, without taste sensation, is the most important stimulus. In many cases, it is merely a curiosity, but in others it can be a significant disability. As well as sweating there is usually vasodilatation, which rarely occurs by itself in the absence of visible sweating.

Treatment of severe cases may require surgical interruption of the parasympathetic pathway—for example, section of the glossopharyngeal nerve within the skull, or tympanic neurectomy [4]. Excision of the auriculotemporal nerve is usually followed by recurrence. Topical therapy with aluminium chloride [18], topical glycopyrronium bromide [19] or botulinum toxin injections may be helpful.

Olfactory hyperhidrosis, in which the trigger stimulus is olfactory in origin, has also been recorded [20].

References

1 Munro PAG. *Sympathectomy*. Oxford: Oxford University Press, 1959.
2 Mellinkoff SM, Mellinkoff MJ. Gustatory hyperhidrosis of the left knee. *JAMA* 1950; **142**: 901–2.
3 Wilson WC. Observations relating to the innervation of the sweat glands of the face. *Clin Sci* 1956; **2**: 273–86.
4 Harrison K, Donaldson I. Frey's syndrome. *J R Soc Med* 1979; **72**: 503–8.
5 Harper KE, Spielvogel RL. Frey's syndrome. *Int J Dermatol* 1986; **25**: 524–6.
6 Linder TE, Huber A, Schmid S. Frey's syndrome after parotidectomy: a retrospective and prospective analysis. *Laryngoscope* 1997; **107**: 1496–501.
7 Burton MJ, Brochwicz-Lewinski M. Lucja Frey and the auriculotemporal nerve syndrome. *J R Soc Med* 1991; **84**: 619–20.

8 Glaister DH, Hearnshaw JR, Haffron PF *et al*. The mechanism of postparotidectomy gustatory sweating (the auriculotemporal syndrome). *BMJ* 1958; **ii**: 942–6.
9 Young AG. Unilateral sweating of the submental region after eating. *BMJ* 1956; **ii**: 976–9.
10 Young AG, Stein GE. A further report on the chorda tympani syndrome. *BMJ* 1960; **i**: 620–1.
11 McGibbon BM, Paletta FX. Further concepts in gustatory sweating. *Plast Reconstr Surg* 1972; **49**: 639–42.
12 Herxheimer A. Gustatory sweating and pilomotion. *BMJ* 1958; **i**: 688–9.
13 Watkins PJ. Facial sweating after food. *BMJ* 1973; **i**: 583–7.
14 Sheehy TW. Diabetic gustatory sweating. *Am J Gastroenterol* 1991; **86**: 1514–7.
15 Drummond PD, Boyce GM, Lance JW. Postherpetic gustatory flushing and sweating. *Ann Neurol* 1987; **21**: 559.
16 Laage-Hellman JE. Gustatory sweating and blushing after conservative parotidectomy. *Acta Otolaryngol* 1957; **48**: 234–52.
17 Moyse P. A propos de 200 tumeurs parotidiennes opérées. *Mem Acad Chir* 1955; **81**: 999–1007.
18 Black MJM, Gunn A. The management of Frey's syndrome with aluminium chloride hexahydrate antiperspirant. *Ann R Coll Surg Engl* 1990; **72**: 49–52.
19 Shaw JE, Abbott CA, Tindle K *et al*. A randomised controlled trial of topical glycopyrrolate, the first specific treatment for diabetic gustatory sweating. *Diabetologia* 1997; **40**: 299–301.
20 Eedy DJ, Corbett JR. Olfactory facial hyperhidrosis responding to amitriptyline. *Clin Exp Dermatol* 1987; **12**: 298–9.

Treatment of hyperhidrosis. In many patients all that is necessary is simple reassurance and explanation of the nature of the disorder, and that it is likely to improve spontaneously, perhaps in several years. Topical and systemic treatments are by no means satisfactory and, at best, only temporarily suppressive.

Topical treatment

Topical anticholinergics. Atropine-like drugs may be absorbed sufficiently to produce a beneficial local effect without associated systemic side effects, but none of those at present available can be relied upon to do so [1]. Poldine methosulphate, 1–4% in alcohol, suppresses experimentally induced sweating, but unfortunately is less valuable on the palms, soles and axillae [2]. Topical 0.5% glycopyrronium bromide cream has been successfully used in gustatory hyperhidrosis in diabetics and 2% aqueous solution has been used in scalp hyperhidrosis.

Eccrine duct blocking agents. These drugs act by impeding the delivery of sweat to the skin surface. Formalin 1% soaks have long been used for treatment of hyperhidrosis of the feet, but are unsuitable for the hands and axillae. Glutaraldehyde 10% in a buffered solution, pH 7.5, swabbed onto the feet three times weekly, has helped some patients [3], but may cause allergic sensitization and stains the skin, so that it is suitable only for the feet. For axillary hyperhidrosis (as opposed to bromhidrosis) the most commonly used topical applications are aluminium (or other metal) salts. Aluminium chloride, the first to be introduced, is in many ways the best, but may be irritant to the skin and damage clothes. Many other salts—for example, the chlorhydrate—are in use in cosmetic preparations [4]. Improved results can be achieved by applying 20% aluminium chloride in absolute ethanol at night, when the axilla is dry, with or without polythene occlusion, at first nightly and later every 1–4 weeks [5,6]. Commercial preparations are available. Mild irritation of the skin from such therapy may be helped by a weak topical steroid. The same treatment can also be tried on the hands and feet, or other localized areas of hyperhidrosis, but usually with rather less success. The mode of action of aluminium salts is uncertain, but they can be shown to affect both the duct and the secretory coil [7].

Iontophoresis. One of the more satisfactory methods of controlling hyperhidrosis of the hands and feet is by iontophoresis, either using tap water or anticholinergic drugs such as glycopyrronium bromide [8–11]. The mode of action of tap water iontophoresis is not known. It is more effective than using saline, and duct occlusion does not occur. Direct current is usually used, with each palm or sole being treated for 30 min with 20 mA, initially three times a week. Once euhidrosis is established, monthly maintenance treatment may be sufficient. Alternating current is less effective, but may usefully be combined with direct current (alternating current offset) to produce a safer, more comfortable treatment [12]. Once control has been achieved, a single treatment may prove effective for some weeks. Minor systemic side effects due to absorption of anticholinergic agents, such as dry mouth and eye symptoms, are not uncommon, and can be avoided if tap water alone is used. The author's practice is to initiate thrice-weekly treatment on a hospital outpatient basis, and if this is successful, a small battery-operated home unit can be purchased for maintenance therapy [13]. Less frequent treatment will then be required. When the sweating is controlled, the associated lividity, coolness and oedema improve. Similar treatment has also been used for the axilla, but is less often needed because topical applications or injections of botulinum toxin are more effective in this site.

Botulinum toxin A injection. This compound produces prolonged blockade of neuronal acetylcholine release at the neuromuscular junction and in cholinergic autonomic neurons, and has been used to treat dystonic conditions for many years. In recent years, intradermal injection has been used to produce marked reduction of sweating in hyperhidrotic areas associated with a variety of conditions [14–17]. Different preparations of botulinum A toxin have different activities, and dose schedules differ for each product; 0.1 mL of appropriately diluted botulinum toxin administered by high intradermal injections can be given to 1 cm^2 areas of skin appropriately anaesthetized—topical eutectic lignocaine/prilocaine is sufficient for axillary skin, but palms and soles require regional nerve blockade. Each axilla usually requires 12 injections, hands 20 and each foot 24–36 injections. It will produce reduction in sweating within 48 h and the benefit will last for up to 8 months in axillary and 6 months in palmar and craniofacial hyperhidrosis [18]. Reinjection seems to be effective, and to date resistance has not been seen in hyperhidrosis, although it eventually occurs in 5% of patients treated intramuscularly for dystonia. Botulinum toxin has been used for idiopathic circumscribed and gustatory hyperhidrosis, including Frey's syndrome, the hyperhidrotic areas in Ross's syndrome, and frontal and craniofacial hyperhidrosis. Slight transient reduction of thenar and hypothenar muscle power is a minor problem after palmar injections [18]. The use of botulinum toxin on the forehead may produce short-lived frown reduction [19].

Systemic drug treatment

Atropine-like drugs have been used to block the effect of acetylcholine on the sweat glands, but their side effects are often more troublesome than the hyperhidrosis itself. These include dryness of the mouth, constipation, urinary retention and disturbances of vision, due to paralysis of accommodation, but more serious side effects, for example glaucoma, hyperthermia and convulsions, can occur. Atropine itself is seldom employed. Propantheline may be prescribed in doses of 15 mg three times daily, increasing, if tolerated, to as much as 150 mg daily [20], but overall the results are disappointing. The oral antimuscarinic agent oxybutinin, usually used to treat bladder instability, has been reported to be effective for generalized hyperhidrosis in a small series of cases [21]. Ganglion-blocking drugs can inhibit sweating, but side effects from hypotension are usually too troublesome. Calcium-channel blockers, such as diltiazem [22], have helped some cases. In cases with a pronounced emotional factor, sedative or tranquillizing drugs are often useful, but psychiatric treatment may be necessary. Both clonazepam [23] and amitriptyline have helped isolated cases of unusual localized hyperhidrosis.

Surgical treatment

Sympathectomy, whether cervical, transaxillary or endoscopic, when complete, causes anhidrosis [24–27]. Sweating may return after a period of some years, due either to regeneration of sympathetic fibres or to fibres that do not pass through the sympathetic ganglia [28]. The open approach has been largely replaced by an endoscopic procedure, which may be successful in treating palmar, axillary and craniofacial hyperhidrosis. A pneumothorax is induced, and an operating endoscope inserted into the thorax via a small axillary incision, allowing visualization of the sympathetic trunk. Interruption of the sympathetic fibres between the second and fourth thoracic ganglia can be achieved by surgical transection, radiofrequency ablation, phenol destruction, cautery or clipping [29] (the latter technique has the potential advantage of partial reversibility). Most surgeons treat both sides at a single session. With both the open and endoscopic approaches, satisfactory reduction of palmar hyperhidrosis is achieved in over 95% of cases; it is a little less successful for axillary hyperhidrosis. In a series of 650 patients treated endoscopically, the initial failure rate was 2%, and there was recurrence in 2%; overall, 98% were satisfied with the result [30]. Large case series using endoscopic techniques in children show it to be an acceptable option, with a low recurrence rate [31]. Complications of sympathectomy include haemothorax, pneumothorax, chylothorax, nipple sensitivity and Horner's syndrome. There are rare instances of transient or permanent bradycardia complicating the technique. Other disadvantages are that the palms or soles may become excessively dry, and irritant eczema after sympathectomy has been reported [32]. Postoperative compensatory hyperhidrosis is a problem, particularly in warmer climates, as it may occur in up to 80% of those treated, affecting the trunk, legs and face, where it may be gustatory. It is usually mild and preferable to severe palmar hyperhidrosis, but rarely is more disabling than the original condition. In five patients who had undergone a clipping procedure and subsequently developed compensatory hyperhidrosis, removal of the clips resulted in return of the palmar sweating and abolition of the compensatory hyperhidrosis [29]. It has been suggested that ablation at the level of the third thoracic ganglion does not produce this side effect. Abolition of severe facial blushing may be a desirable consequence, and resolution of palmar eczema has been reported after endoscopic sympathectomy. In general, only those patients in whom a severe disability is arising from the hands or axillae warrant surgery, and in these selected cases the results can be very gratifying. Endoscopic sympathectomy has been used successfully in the treatment of severe craniofacial hyperhidrosis [33]. Pedal sympathetic denervation requires lumbar sympathectomy; if more cranial lumbar ganglia are removed, ejaculatory impotence may occur. A selective retroperitoneal approach has recently been advocated that has no effect on sexual function in either men or women [34].

Axillary hyperhidrosis may be greatly helped by local excision of the axillary vault [35,36]. Variations of this technique include subcutaneous curettage of the axillary skin [37], directly trimming the eccrine glands after reflection of the axillary skin using only a short incision [38], and tumescent liposuction of the axillae [39].

References

1 McMillan FSK, Reller HH, Snyder FH. Antiperspirant action of topically applied anticholinergics. *J Invest Dermatol* 1964; **43**: 363–7.

2 Grice KA, Bettley FR. Inhibition of sweating by poldine methosulphate (Nacton). *Br J Dermatol* 1966; **78**: 458–64.

3 Juhlin L, Hansson H. Topical glutaraldehyde for plantar hyperhidrosis. *Arch Dermatol* 1968; **97**: 327–30.

4 Jass HE. In: Frost P, Horwitz SN, eds. *Principles of Cosmetics for the Dermatologist*. St Louis: Mosby, 1982.

5 Aluminium chloride for hyperhidrosis. *Drug Ther Bull* 1981; **19**: 101–2.

6 Shelley WB, Hurley HJ. Studies on topical antiperspirant control of axillary hyperhidrosis. *Acta Derm Venereol (Stockh)* 1975; **95**: 241–60.

7 McWilliams SA, Montgomery I, Jenkinson DM *et al*. Effects of topically applied antiperspirant on sweat gland function. *Br J Dermatol* 1987; **117**: 617–26.

8 Levit F. Simple device for treatment of hyperhidrosis by iontophoresis. *Arch Dermatol* 1968; **98**: 505–7.

9 Abell E, Morgan K. The treatment of idiopathic hyperhidrosis with glycopyrronium bromide and tapwater iontophoresis. *Br J Dermatol* 1974; **91**: 87–91.

10 Hölzle E, Alberta N. Long-term efficacy and side-effects of tap water iontophoresis on palmo-plantar hyperhidrosis: the usefulness of home therapy. *Dermatologica* 1987; **175**: 126–35.

11 Stolman LP. Treatment of excessive sweating of the palms by iontophoresis. *Arch Dermatol* 1987; **123**: 895–6.

12 Reinauer S, Neusser A, Schauf G, Holzle E. Iontophoresis with alternating current and direct current offset (AC/DC iontophoresis): a new approach for the treatment of hyperhidrosis. *Br J Dermatol* 1993; **129**: 166–9.

13 Akins DL, Meisenheimer JL, Dobson RL. Efficacy of the Drionic unit in the treatment of hyperhidrosis. *J Am Acad Dermatol* 1987; **16**: 828–32.

14 Heckmann M, Ceballos-Baumann AO, Plewig G. Hyperhidrosis Study Group. Botulinum toxin A for axillary hyperhidrosis (excessive sweating). *N Engl J Med* 2001; **344**: 488–93.

15 Boger A, Herath H, Rompel R, Ferbert A. Botulinum toxin for treatment of craniofacial hyperhidrosis. *J Neurol* 2000; **247**: 857–61.

16 Kinkelin I, Hund M, Naumann M, Hamm H. Effective treatment of frontal hyperhidrosis with botulinum toxin A. *Br J Dermatol* 2000; **143**: 824–7.

17 Schnider P, Moraru E, Kittler H *et al*. Treatment of focal hyperhidrosis with botulinum toxin type A: long-term follow-up in 61 patients. *Br J Dermatol* 2001; **145**: 289–93.

18 Swartling C, Farnstrand C, Abt G *et al*. Side-effects of intradermal injections of botulinum A toxin in the treatment of palmar hyperhidrosis: a neurophysiological study. *Eur J Neurol* 2001; **8**: 451–6.

19 Böger A, Herath H, Rompel R, Ferbert A. Botulinum toxin for treatment of craniofacial hyperhidrosis. *J Neurol* 2000; **247**: 857–61.

20 Canaday BR, Stanford RH. Propantheline bromide in the management of hyperhidrosis associated with spinal cord injury. *Ann Pharmacother* 1995; **29**: 489–92.
21 Tupker RA, Harmsze AM, Deneer VH. Oxybutynin therapy for generalized hyperhidrosis. *Arch Dermatol* 2006; **142**: 1065–6.
22 James WD, Schoomaker EB, Rodman OG. Emotional eccrine sweating. A heritable disorder. *Arch Dermatol* 1987; **23**: 925–9.
23 Takase Y, Tsushimi K, Yamamoto K *et al*. Unilateral localized hyperhidrosis responding to treatment with clonazepam. *Br J Dermatol* 1992; **126**: 416.
24 Ellis H. Surgery of sweat glands. *J R Soc Med* 1982; **75**: 585–7.
25 Gjerris F, Oleson HP. Palmar hyperhidrosis: long-term results following high thoracic sympathectomy. *Acta Neurol Scand* 1975; **51**: 167–72.
26 Malone PS, Cameron AEP, Rennie JA. The surgical treatment of upper limb hyperhidrosis. *Br J Dermatol* 1986; **115**: 81–4.
27 Drott C, Gothberg G, Claes G. Endoscopic transthoracic sympathectomy: an efficient and safe method for the treatment of hyperhidrosis. *J Am Acad Dermatol* 1995; **33**: 78–81.
28 Orteu CH, McGregor JM, Almeyda JR, Rustin MHA. Recurrence of hyperhidrosis after endoscopic transthoracic sympathectomy: case report and review of the literature. *Clin Exp Dermatol* 1995; **20**: 230–3.
29 Lin CC, Mo LR, Lee LS *et al*. Thoracoscopic T2-sympathetic block by clipping: a better and reversible operation for treatment of hyperhidrosis palmaris: experience with 326 cases. *Eur J Surg* 1998; **580** (Suppl.): 13–8.
30 Reisfeld R, Nguyen R, Pnini A. Endoscopic thoracic sympathectomy for treatment of essential hyperhidrosis syndrome: experience with 650 patients. *Surg Laparosc Endosc Percutan Tech* 2000; **10**: 5–10.
31 Imhof M, Zacherl J, Plas EG *et al*. Long-term results of 45 thoracoscopic sympathectomies for primary hyperhidrosis in children. *J Pediatr Surg* 1999; **34**: 1839–42.
32 Hofbauer GF, Nestle FO. Irritant contact dermatitis of the hands following thoracic sympathectomy. *Contact Dermatitis* 2000; **42**: 119–20.
33 Lin TS, Fang HY. Transthoracic endoscopic sympathectomy for craniofacial hyperhidrosis: analysis of 46 cases. *J Laparoendosc Adv Surg Tech* 2000; **10**: 243–7.
34 Rieger R, Pedevilla S. Retroperitoneoscopic lumbar sympathectomy for the treatment of plantar hyperhidrosis: technique and preliminary findings. *Surg Endosc* 2007; **21**: 129–35.
35 Hurley HJ, Shelley WB. Axillary hyperhidrosis. *Br J Dermatol* 1966; **78**: 127–40.
36 Munro DD, Verbov J, Gorman DJ. Axillary hyperhidrosis. *Br J Dermatol* 1974; **90**: 325–9.
37 Rompel R, Scholz S. Subcutaneous curettage vs. injection of botulinum toxin A for treatment of axillary hyperhidrosis. *J Eur Acad Dermatol Venereol* 2001; **15**: 207–11.
38 Lawrence CM, Lonsdale Eccles AA. Selective sweat gland removal with minimal skin excision in the treatment of axillary hyperhidrosis: a retrospective clinical and histological review of 15 patients. *Br J Dermatol* 2006; **155**: 115–18.
39 Swinehart JM. Treatment of axillary hyperhidrosis: combination of the starch-iodine test with the tumescent liposuction technique. *Dermatol Surg* 2000; **26**: 392–6.

Anhidrosis

Anhidrosis is the absence of sweat from the surface of the skin in the presence of an appropriate stimulus. This may be caused by an abnormality of the sweat gland itself, or at any level in the nervous pathway. There are many causes [1], and a number of the more important of these are listed in Table 44.4. A full account of the assessment of sympathetic nerve activity is beyond the scope of this book [2–10].

Extensive anhidrosis may impair heat regulation to such a degree that hyperpyrexia occurs on exposure to heat. It characteristically occurs in anhidrotic ectodermal dysplasia and in otherwise normal premature or full-term infants under the age of 1 month [11]. It may be associated with compensatory hyperhidrosis of the remaining functionally active glands. It has been reported as an isolated finding [12,13]. Cessation of sweating is the cause of heat hyperpyrexia. The anhidrosis associated with ichthyosis may be more apparent than real. Localized areas of anhidrosis are of little clinical importance, except that they may help in the diagnosis of neurological lesions or leprosy. Sweat gland function can be a useful way to assess damage to the sympathetic nervous system—for example, in patients with postural hypotension [2,10,14]. Sweat retention is the cause of miliaria (see below), and plays an important part in producing crises of irritation in patients with atopic dermatitis, eczema and other dermatoses. It also occurs in psoriasis, where sweat duct blockage, and perhaps also impaired ductal absorption, occurs [15]. A rare disorder termed idiopathic acquired anhidrosis results in skin pain during exposure to stimuli that would usually induce sweating. Ductal occlusion by a PAS-positive material thought to emanate from dark cell granules was identified [16].

Table 44.4 Classification of anhidrosis.

Brain lesions
Organic lesion at any level
Hyperthermia
Spinal cord and peripheral nerve lesions
Organic lesions, e.g.:
Syringomyelia
Leprosy
Sympathectomy
Diabetes mellitus
Alcoholism
Congenital sensory neuropathy with anhidrosis
Other causes of autonomic neuropathy
Ross's syndrome
Ganglion-blocking and anticholinergic drugs
Botulism
Sweat gland lesions
Aplasia
Congenital ectodermal dysplasia
Ichthyosis
Any cause of atrophy (e.g. acrodermatitis chronica atrophicans)
Mepacrine eruption
Scleroderma
Myelomatosis
Lymphoma
Sjögren's syndrome
Incontinentia pigmenti
Fabry's disease
Plugging of the eccrine duct
Miliaria
Eczema and atopic dermatitis
Lichen planus
Psoriasis
Uncertain
Neonatal
Sweat gland fatigue
Idiopathic acquired anhidrosis

Ross's syndrome [17]

This rare syndrome consists of widespread hypohidrosis combined with patchy, sometimes very striking, compensatory



(a)



(b)



(c)

Fig. 44.10 Ross's syndrome. (a) There is generalized anhidrosis, with large islands of severe compensatory hyperhidrosis (delineated with edicol ponceau powder, which turns red in the presence of water). (b) The hyperhidrosis is sufficient to soak the underclothes, with consequent embarrassment. (c) An abnormal pupil, showing an irregular outline and meiosis. It responds sluggishly to light.

hyperhidrosis (Fig. 44.10), together with tonic pupils (appearing asymmetrical and irregular in their outline, constricting and dilating slowly to light and dark, respectively) and loss of deep tendon reflexes (Holmes–Adie syndrome). Patients with the Holmes–Adie syndrome often show asymptomatic changes in sweating [18]. The anhidrosis may be quite localized—for example, mainly on one palm, mimicking a *Trichophyton rubrum* infection [19]. When the anhidrosis is extensive, remaining areas of functioning eccrine glands may show compensatory hyperhidrosis. Cardiac sympathetic denervation which may be asymptomatic has been shown to develop [20]. The compensatory hyperhidrosis may be striking and severe enough to require therapy, for example with iontophoresis [21] or botulinum toxin injection [22], although eventually it may be lost as complete anhidrosis develops. The changes are due to selective degeneration of the sympathetic pathways [22].

References

1 Shelley WB, Horvath PN, Pillsbury DM. Anhidrosis. *Medicine* 1950; **29**: 194–224.

2 Bannister R, Mathias CJ. *Autonomic Failure: A Textbook of Clinical Disorders of the Autonomic Nervous System*, 3rd edn. Oxford: Oxford University Press, 1992.

3 Johnson RH, Spalding JMK. *Disorders of the Autonomic Nervous System*. Oxford: Oxford University Press, 1974.

4 Autonomic neuropathy in liver disease [editorial]. *Lancet* 1989; **ii**: 721–2.

5 Ishii N, Kawagachi H, Miyakawa K *et al*. Congenital sensory neuropathy with anhidrosis. *Arch Dermatol* 1988; **124**: 964–6.

6 Domingues JC, Moreno A, Mariano A *et al*. Congenital sensory neuropathy with anhidrosis. *Pediatr Dermatol* 1994; **11**: 231–6.

7 Mitchell J, Greenspan J, Daniels T *et al*. Anhidrosis (hypohidrosis) in Sjögren's syndrome. *J Am Acad Dermatol* 1987; **16**: 233–5.
8 Katayama I, Yokozeki H, Nishioka K. Impaired sweating as an exocrine manifestation in Sjögren's syndrome. *Br J Dermatol* 1995; **133**: 716–20.
9 Kang WH. Generalized anhidrosis associated with Fabry's disease. *J Am Acad Dermatol* 1987; **17**: 883–7.
10 Brown MJ. The measurement of autonomic function in clinical practice. *J R Coll Physicians* 1987; **21**: 206–9.
11 Foster KG, Hey EN, Katz G. Eccrine sweat gland function in the newborn baby. *J Physiol* 1968; **198**: 36–7.
12 Faden AI, Chan P, Mendoza P. Progressive isolated segmental anhidrosis. *Arch Neurol* 1982; **39**: 172–5.
13 Mahloudji M, Livingston KE. Familial and congenital simple anhidrosis. *Am J Dis Child* 1967; **113**: 477–9.
14 Ryder REJ, Marshall R, Johnson K *et al*. Acetylcholine sweatspot test for autonomic denervation. *Lancet* 1988; **i**: 1303–5.
15 Shuster S, Johnson C. The abnormality of sweat duct function in psoriasis. *Br J Dermatol* 1969; **81**: 846–50.
16 Ogino J, Saga K, Kagaya M *et al*. Idiopathic acquired generalized anhidrosis due to occlusion of proximal coiled ducts. *Br J Dermatol* 2004; **150**: 589–93.
17 Heath PD, Moss C, Cartlidge NEF. Ross syndrome and skin changes. *Neurology* 1982; **32**: 1041–2.
18 Bacon PJ, Smith SE. Cardiovascular and sweating dysfunction in patients with Holmes–Adie syndrome. *J Neurol Neurosurg Psychiatry* 1993; **56**: 1096–102.
19 Itin P, Birsbrunner P, Rufli T *et al*. Das Ross-Syndrom. *Hautarzt* 1992; **43**: 359–60.
20 Druschky K, Hilz MJ, Koelsch C *et al*. Cardiac sympathetic denervation in Ross syndrome demonstrated by MIBG-SPECT. *J Auton Nerv Syst* 1999; **28**: 184–7.
21 Reinauer S, Schauf G, Holzle E. Ross syndrome: treatment of segmental compensatory hyperhidrosis with a modified iontophoretic device. *J Am Acad Dermatol* 1993; **28**: 308–11.
22 Sommer C. Selective degeneration of sudomotor fibers in Ross syndrome and successful treatment of compensatory hyperhidrosis with botulinum toxin. *Muscle Nerve* 1998; **21**: 1790–3.

Miliaria

Aetiology and pathology [1–3]. The three forms of miliaria—miliaria crystallina (sudamina), miliaria rubra (prickly heat) and miliaria profunda—occur as a result of either obliteration or disruption of the eccrine sweat duct. They differ in clinical form due to the different levels at which obliteration occurs, although some authorities have suggested that disruption of the duct rather than obliteration is responsible [4]. In miliaria crystallina, the obstruction is very superficial within the stratum corneum and the vesicle is subcorneal. In miliaria rubra, the later changes include keratinization of the intraepidermal part of the sweat duct, with leakage and then formation of a vesicle around the duct. In miliaria profunda, there is rupture of the duct at the level of or below the dermal–epidermal junction.

Miliaria crystallina can easily be produced experimentally by minimal non-specific epidermal injury and profuse sweating [5]. It is often seen in febrile illnesses associated with profuse sweating. It occurs commonly in infants due to a delay in patency developing in the sweat ducts. In a large Japanese study, it was identified in 4.5% of babies, with a peak frequency at 1 week [6].

The incidence of miliaria rubra is highest in hot, humid conditions, but it may occur in desert regions, affecting up to 30% of people exposed to these climatic conditions [7]. It may begin within a few days of arrival in a tropical climate, but is maximal after 2–5 months. There is a striking variation in individual susceptibility. Infants are especially prone. Lesions may be produced experimentally in susceptible subjects by epidermal injury. They can be reproduced regularly by occlusion of the skin under polythene for 3–4 days, following which anhidrosis lasts for about 3 weeks. Prolonged exposure of the skin to sweat achieves the same effect. The first event may be an increase in the skin flora, perhaps with *Staphylococcus epidermidis* being responsible for producing an extracellular polysaccharide substance or slime that blocks the lumen of the sweat duct [1,8]. The parakeratotic plugs which are a notable feature of the later stages of the disease are not the primary cause of the obstruction, but arise in the repair process, and may further aggravate the obstruction. Leakage of sweat into the epidermis is responsible for the final production of the lesions, and for their further aggravation.

Miliaria profunda is due to more severe damage to the sweat duct, and usually follows repeated attacks of miliaria rubra. It may be reproduced by experimental injury [8].

Rarely, miliaria may be associated with pseudohypoaldosteronism; high sweat sodium levels produce damage of the eccrine ducts, causing lesions similar to those seen in miliaria rubra [9].

Clinical features of the three types of miliaria are as follows.

Miliaria crystallina. Clear, thin-walled vesicles, 1–2 mm in diameter, without an inflammatory areola are usually symptomless and develop in crops, mainly on the trunk. In persistent febrile illnesses, recurrent crops may occur. The vesicles soon rupture, and are followed by superficial, branny desquamation.

Miliaria rubra. The typical lesions develop on the body, especially in areas of friction with clothing, and in flexures. They may also commonly be seen after occlusive therapy with polythene. The lesions are uniformly minute erythematous papules, which may be present in very large numbers (Fig. 44.11). Miliaria rubra is common on the trunk in hospitalized patients, who have to be



Fig. 44.11 Miliaria rubra on a baby's cheek. (Courtesy of Dr Richard Logan, Bridgend General Hospital, Bridgend, Mid Glamorgan, UK.)

nursed on their backs on bedding that has waterproof occlusive membranes below the sheets. Characteristically, the lesions produce intense discomfort in the form of an unbearable pricking sensation. Relief is often instantaneous when the stimulus to sweating is abolished by a cool shower. Outbreaks on the legs in miners working in tropical climates have been reported [10]. In infants, lesions commonly appear on the occluded skin of the neck, groins and axillae, but also occur elsewhere.

Miliaria profunda. This nearly always follows repeated attacks of miliaria rubra, and is uncommon except in the tropics. The lesions are easily missed. The affected skin is covered with pale, firm papules 1–3 mm across, especially on the body, but sometimes also on the limbs. There is no itching or discomfort from the lesions.

Patients often wrongly refer to polymorphic light eruption as 'prickly heat', but the relationship of the rash to light, particularly on newly exposed sites, is usually straightforward.

Natural history. The course depends mainly on environmental factors. If continued sweating occurs, recurrent episodes lasting a few days are usual, but discomfort may be continuous. However, after a few months some degree of acclimatization occurs, and the disorder becomes less prevalent.

The most important complications of miliaria are secondary infection and disturbance of heat regulation. Secondary bacterial infection is common and sometimes serious. This may present as impetigo. In other cases, the pustules are more clearly related to sweat ducts, although in *pustular miliaria* factors other than bacterial infection are concerned [11]. Periporitis staphylogenes [12] is the name given to multiple staphylococcal abscesses superimposed on miliaria rubra in young infants. In most cases of miliaria rubra, the changes are reversible if further sweating is avoided, but permanent damage to the sweat duct may occur, especially after miliaria profunda.

Treatment. The only really effective prevention or treatment for miliaria is avoidance of further sweating. Even if this is achieved only for a few hours a day, as in an air-conditioned office or bedroom, considerable relief is experienced. For the very susceptible person, a move away from tropical climates may be essential. Avoidance of excessive clothing, friction from clothing, excessive use of soap and contact of the skin with irritants will reduce the incidence. The large number of treatments advocated for prickly heat is the best indication of their relative ineffectiveness if sweating is not reduced. In the absence of gross secondary sepsis, the effect of topical or systemic antibiotics or other antibacterial preparations on established miliaria is disappointing, but they may have some role in prophylaxis [1]. Oral ascorbic acid 500 mg twice daily was found to diminish the severity of miliaria, as was the degree of subsequent anhidrosis in experimentally-induced disease [13]. Calamine lotion is probably as effective as anything for the relief of discomfort, but because of its drying effect, a bland emollient, for example oily cream, may subsequently be required to prevent further epidermal damage. Isotretinoin was reported to help a recalcitrant case of miliaria profunda [14].

References

1 Holzle E, Kligman AM. The pathogenesis of miliaria rubra. *Br J Dermatol* 1978; **99**: 117–37.
2 Leithead CS, Lind AR. *Heat Stress and Heat Disorders*. London: Cassell, 1964.
3 Sargent F, Slutsky HL. The natural history of the eccrine miliarias. *N Engl J Med* 1957; **256**: 401–8, 451.
4 Shuster S. Duct disruption, a new explanation of miliaria. *Acta Derm Venereol (Stockh)* 1997; **77**: 1–3.
5 Shelley WB, Horvath PN. Experimental miliaria in man, 3. *J Invest Dermatol* 1950; **14**: 193–204.
6 Hidano A, Purwoko R, Jutsukawa K. Statistical survey of skin changes in Japanese neonates. *Pediatr Dermatol* 1986; **3**: 130–4.
7 Mowad CM, McGinley KJ, Foglia A, Leyden JJ. A role of extracellular polysaccharide substance produced by *Staphylococcus epidermidis* in miliaria. *J Am Acad Dermatol* 1995; **33**: 729–33.
8 Lyons RE, Levine R, Auld D. Miliaria rubra. *Arch Dermatol* 1962; **86**: 282–6.
9 Martín JM, Calduch L, Monteagudo C *et al*. Clinico-pathological analysis of the cutaneous lesions of a patient with type I pseudohypoaldosteronism. *J Eur Acad Dermatol Venereol* 2005; **19**: 377–9.
10 Donoghue AM, Sinclair MJ. Miliaria rubra of the lower limbs in underground miners. *Occup Med (Lond)* 2000; **50**: 430–3.
11 Lobitz WC. Pustular miliaria. *JAMA* 1952; **148**: 1097–100.
12 Lubowe II, Perlman HH. Periporitis staphylogenes and other complications of miliaria in infants and children. *Arch Dermatol Syphil* 1954; **69**: 543–53.
13 Hindson TC, Worsley DE. The effects of administration of ascorbic acid in experimentally induced miliaria and hypohidrosis in volunteers. *Br J Dermatol* 1969; **81**: 226–7.
14 Kirk JF, Wilson BB, Chun W, Cooper PH. Miliaria profunda. *J Am Acad Dermatol* 1996; **35**: 54–6.

The role of sweating in some other dermatoses

The role of sweating in pompholyx or dyshidrosis is discussed in Chapter 23, in Grover's disease or transient acantholytic dermatosis in Chapter 40 and in cholinergic urticaria in Chapter 22.

Disorders associated with abnormal eccrine histology

Neutrophilic eccrine hidradenitis

Necrosis of the eccrine epithelium and secretory coil with a dense surrounding neutrophilic infiltrate is seen in a variety of clinical entities (Table 44.5, Fig. 44.12).

Chemotherapy-induced neutrophilic eccrine hidradenitis. The most common variant occurs during cancer chemotherapy [1–3], and has been reported in adults and children. The clinical presentation is of painful erythematous papules and plaques arising on the limbs, neck, face and ears 8–10 days after the start of chemotherapy, often associated with fever and neutropenia. Cases featuring only erythematous swelling of the periorbital areas [4] and the ears [5] have been described. The eruption lasts for about 10

Table 44.5 The classification of neutrophilic eccrine hidradenitis.

Chemotherapy-induced eccrine hidradenitis
Infectious neutrophilic hidradenitis
Palmoplantar hidradenitis
Neutrophilic eccrine hidradenitis with HIV infection and Behçet's disease

HIV, human immunodeficiency virus.



Fig. 44.12 Drug-associated acute neutrophilic eccrine hidradenitis of the palms. (Courtesy of Dr Neil Cox, Cumberland Royal Infirmary.)

days, resolving without therapy, and only rarely recurs at subsequent chemotherapy exposures [6]. No one chemotherapeutic agent has been identified as the culprit; indeed, most cases have arisen after administration of a cocktail of chemotherapeutic agents given for myeloproliferative disorders, lymphomas and solid tumours. It has been reported after granulocyte colony-stimulating factor [7]. The histological changes have been experimentally induced in healthy volunteers given intradermal bleomycin, suggesting that a direct toxic effect of the drug on the eccrine gland is responsible [8]. In a case of recurrent chemotherapy-triggered disease, dapsone prophylaxis was effective [9].

Neutrophilic eccrine hidradenitis (NEH) and other diseases. NEH has recently been associated with Behçet's disease [10], and has been reported in association with human immunodeficiency virus (HIV) infection [11]. Although often reported as a consequence of chemotherapy in leukaemia, it may arise as a paraneoplastic condition with chronic myeloid leukaemia [12].

Infectious neutrophilic eccrine hidradenitis [1]. The eccrine sweat glands are resistant to infection, and there are few reports of bacterial hidradenitis. *Serratia* and staphylococcal hidradenitis have been reported in immunocompromised hosts. Enterococci have been cultured from an otherwise healthy woman with hidradenitis on the trunk.

Idiopathic recurrent palmoplantar hidradenitis

This disorder, first described in 1994, is probably more common than the literature suggests [13]. Tender, erythematous plaques develop on the soles and occasionally the palms of children; it has been reported between the ages of 18 months and 15 years [14]. It may mimic a vasculitis. Attacks, lasting up to 3 weeks, are more frequent in autumn and spring. Resolution occurs spontaneously and, in almost half of the cases, the condition is recurrent. Vigorous exercise has been implicated in initiation of some attacks; exposure to cold, damp footwear was believed to be important in another small series [15]. Histology shows eccrine epithelial necrosis, dense infiltration of the periglandular dermis with neutrophils and sometimes abscess formation. Rest, cool compresses, and topical and oral steroids have been used as symptomatic treatment.

Syringosquamous metaplasia

Syringosquamous metaplasia is a histopathological term describing the transformation of normal cuboidal duct epithelium into cells with an eosinophilic cytoplasm and a larger more irregular nucleus, so that in some areas it seems that ducts appear in islands of squamous epithelium mimicking squamous carcinoma, or as dilated structures reminiscent of syringomas. The eccrine gland coils are not affected [16]. The histological changes may be seen around areas of cutaneous ulceration of diverse causes, such as burns and arterial ulcers, but also adjacent to pyoderma gangrenosum and extravasated chemotherapy sites [17]. It may represent a non-specific reaction pattern.

References

1 Wenzel FG, Horn T. Nonneoplastic disorders of the eccrine glands. *J Am Acad Dermatol* 1998; **38**: 1–17.
2 Harris T, Fine JD, Berman RS *et al*. Neutrophilic eccrine hidradenitis. *Arch Dermatol* 1982; **118**: 268.
3 Bailey DL, Barron D, Lucky AW. Neutrophilic eccrine hidradenitis: case report and review of the literature. *Pediatr Dermatol* 1989; **6**: 33–8.
4 Bardenstein DS, Haluschak J, Gerson S *et al*. Neutrophilic eccrine hidradenitis simulating orbital cellulitis. *Arch Ophthalmol* 1994; **112**: 1460–3.
5 Ostlere LS, Wells J, Stevens HP *et al*. Neutrophilic eccrine hidradenitis with an unusual presentation. *Br J Dermatol* 1993; **128**: 696–8.
6 Bernstein EF, Spielvogel RL, Topolsky DL. Recurrent neutrophilic eccrine hidradenitis. *Br J Dermatol* 1992; **127**: 529–33.
7 Bachmeyer C, Chaibi P, Aractingi S. Neutrophilic eccrine hidradenitis induced by granulocyte colony-stimulating factor. *Br J Dermatol* 1998; **139**: 354–5.
8 Templeton S, Solomon AR, Swerlick RA. Intradermal bleomycin injections into normal human skin: a histopathologic and immunopathologic study. *Arch Dermatol* 1994; **130**: 577–83.
9 Shear NH, Knowles SR, Shapiro L, Poldre P. Dapsone in prevention of recurrent neutrophilic eccrine hidradenitis. *J Am Acad Dermatol* 1996; **35**: 819–22.
10 Krischer J, Rutschmann O, Roten SV *et al*. Neutrophil eccrine hidradenitis in a patient with AIDS. *J Dermatol* 1998; **25**: 199–200.
11 Bilic M, Mutasim DF. Neutrophilic eccrine hidradenitis in a patient with Behçet's disease. *Cutis* 2001; **68**: 107–11.
12 Stahr BJ, Cooper PH, Caputo RV. Idiopathic plantar hidradenitis occurring primarily in children. *J Cutan Pathol* 1994; **21**: 289–96.
13 Simon M Jr, Cremer H, von den Driesch P. Idiopathic recurrent palmoplantar hidradenitis in children: report of 22 cases. *Arch Dermatol* 1998; **134**: 76–9.
14 Gómez Vázquez M, Peteiro C, Toribio J. Neutrophilic eccrine hidradenitis heralding the onset of chronic myelogenous leukaemia. *J Eur Acad Dermatol Venereol* 2003; **17**: 328–30.
15 Naimer SA, Zvulunov A, Ben-Amitai D, Landau M. Plantar hidradenitis in children induced by exposure to wet footwear. *Pediatr Emerg Care* 2000; **16**: 182–3.
16 Bahwan J, Malhorta R. Syringosquamous metaplasia: a distinctive eruption in patients receiving chemotherapy. *Am J Dermatopathol* 1990; **12**: 1–6.
17 Serrano T, Amparo S, Moreno S. Eccrine squamous syringometaplasia. *J Cutan Pathol* 1993; **20**: 61–5.

Drugs and eccrine glands

A number of drugs are concentrated and secreted by eccrine glands, and in part this may account for their therapeutic effect. Drugs known to be secreted include sulfaguanidine, sulfadiazine,

amphetamines, iodides, phenytoin, phenobarbital, carbamazepine, griseofulvin, ketoconazole, fluconazole, ciprofloxacin, diamorphine, cocaine and nicotine. Thiotepa excretion may result in hyperpigmentation of the skin where it is occluded under bandages.

Coma-induced eccrine necrosis

Necrosis of the eccrine glands is the most consistently reported feature of drug-induced coma, whether it be caused by barbiturates, benzodiazepines, narcotics or antidepressants. Similar changes are seen in blisters resulting from coma induced by hypoglycaemia or neurological events, suggesting that the changes are due to pressure rather than the drug *per se*. Areas not usually subject to pressure are the areas that usually show these changes. Early features are necrosis of the secretory coil; later, the duct may be similarly affected. Subsequently, epidermal spongiosis, and subepidermal and intraepidermal blisters form with minimal dermal inflammatory infiltrate.

Radiation-induced eccrine damage

High-dose radiation (>50 Gy) resulting in radiation dermatitis will abolish eccrine function. Lower doses of radiation will reduce eccrine function within 2 weeks of exposure, reaching a nadir at 8 weeks and recovering to a final dose-dependent deficit by 30 weeks. Radiation-induced keratoses have been described that block the eccrine duct, resulting in milia-like lesions. Histologically, dilated eccrine orifices filled with keratin were identified. Resolution occurred a few months after completion of the radiotherapy.

Disorders with sweat gland cellular inclusions

Accumulation of substances within the secretory cells occurs in a number of metabolic conditions, and their identification in skin biopsies can be used diagnostically. In the Hurler and Sanfilippo types of mucopolysaccharidosis, membrane-bound vacuoles may be seen in the secretory cells [1]. Intracytoplasmic lipid occurs in Sandhoff and Niemann–Pick lipid storage disease [2]. Secretory cell inclusions are seen in Fabry's disease, fucosidosis [3] and Kanzaki disease [4], and in amaurotic idiocy, maltase deficiency and adrenoleukodystrophy [5]. Periodic acid–Schiff (PAS)-positive granules in the outer duct cells characterize Lafora's myoclonic epilepsy [6].

References

1 Belchin RW. Ultrastructure and function of eccrine glands in the mucopolysaccharidoses. *Arch Pathol* 1973; **96**: 339–44.

2 Drut R. Eccrine sweat gland involvement in GM gangliosidosis. *J Cutan Pathol* 1978; **5**: 35–40.

3 Nakamura T, Kaneko H, Nishino I. Angiokeratoma corporis diffusum (Fabry disease): ultrastructural studies of the skin. *Acta Derm Venereol (Stockh)* 1981; **61**: 37–41.

4 Kodama K, Kobayashi H, Abe R *et al*. A new case of α-*N*-acetylgalactosaminidase deficiency with angiokeratoma corporis diffusum, with Ménière's syndrome and without mental retardation. *Br J Dermatol* 2001; **144**: 363–8.

5 Martin JJ, Cruterich C. Morphologic study of skin biopsy specimens: a contribution to the diagnosis of metabolic disorders with involvement of the nervous system. *J Neurol Neurosurg Psychiatry* 1978; **41**: 232–6.

6 Carpenter S, Kaepati G. Sweat gland cells in Lafora disease: diagnosis by skin biopsy. *Neurology* 1981; **31**: 1564.

Granulosis rubra nasi [1–3]

The pathogenesis of this rare disease is obscure. Most cases are genetically determined, but the mode of inheritance is uncertain.

The disease usually starts in childhood, from the age of 6 months to 10 years. Excessive sweating may precede other changes by several years. Diffuse erythema first appears on the tip of the nose, gradually extends, and may involve the cheeks, the upper lip and the chin. The erythema is covered by small beads of sweat, which may also be evident over a wider area. Small, red macules and papules, and sometimes vesicles, later form at the sweat duct orifices. The condition usually subsides spontaneously at puberty, but may persist indefinitely. In such cases, telangiectasia becomes a conspicuous feature, and small cysts may be present. Many of those affected have poor peripheral circulation and hyperhidrosis of the palms and soles. Response to treatment is usually disappointing. A single case has been associated with phaeochromocytoma [4].

References

1 Aram H, Mohaghedi AP. Granulosis rubra nasi. *Cutis* 1972; **10**: 463.

2 Maschkilleisson LN, Naradow LA. 33 Fälle von Jadassohns Granulosis rubra nasi. *Dermatol Z* 1935; **71**: 79–84.

3 Veltman G. Über das familiäre Vorkommen der Granulosis rubra nasi. *Arch Klin Exp Dermatol* 1949; **188**: 188–96.

4 Heid E, Samain F, Jelen G, Boivin S. Granulosis rubra nasi and phaeochromocytoma. *Ann Dermatol Venereol* 1996; **123**: 106–8.

Apocrine sweat glands

Anatomy and physiology [1–4]

Apocrine sweat glands derive their name from the way that their secretion appears, on light microscopy, to be derived by pinching off parts of the cytoplasm. They are epidermal appendages, and develop as part of the pilosebaceous follicle in the fourth to fifth month of intrauterine life. In the embryo, they are present over the entire skin surface, but most glands subsequently disappear, so that in the adult the characteristic distribution in the axillae, perianal region and areolae of the breasts is found. So-called ectopic glands may be found elsewhere. The mammary glands and glands in the external auditory meatus are modified apocrine glands. Apocrine glands are poorly developed in childhood, and begin to enlarge with the approach of puberty. The activity of the glands is androgen-dependent, and the glands show marked testosterone 5α-reductase activity [5]. The glands are larger than eccrine glands, and in the dissected specimen are visible to the naked eye. They are situated in the subcutaneous tissue. Each consists of a tubule and a duct. The latter is often quite short, and

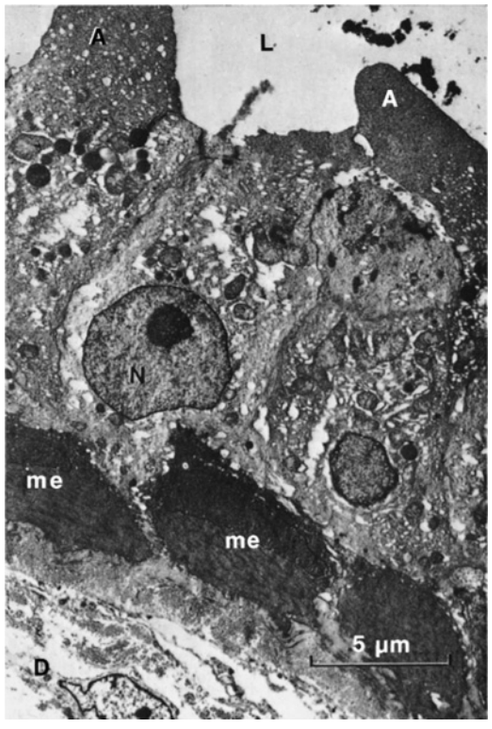


Fig. 44.13 Section of a secretory coil of an apocrine gland from the human axilla; lying next to the basement membrane are myoepithelial cells (me), followed by cuboidal secretory cells, with prominent nuclei (N) and apical caps (A), projecting into the lumen (L). D, dermis. (Courtesy of the late Professor A.S. Breathnach, St John's Dermatology Centre, London, UK.)

opens into the neck of the hair follicle above the sebaceous gland. Despite their embryological origin from the hair follicle, some apocrine glands eventually come to open on the surface of the skin. The secretory coil is a simple convoluted tube. It is lined by a single layer of columnar or cuboidal cells resting on a basement membrane. The free edge of the cells may show the appearance of apocrine secretion. Electron microscopy shows that this may be partly an artefact, but eccrine, apocrine and even holocrine secretion may all be found in places [3,6,7] (Fig. 44.13). The apocrine duct closely resembles the eccrine duct, and consists of a double layer of cuboidal cells. Outside the basement membrane of the gland and duct is a longitudinal layer of myoepithelial cells. Their function is to support the duct and to propel the secretion to the surface, and waves of peristalsis have been seen in them [8]. Where the duct opens into the neck of the hair follicle, there is the equivalent of the acrosyringium of the eccrine duct, although it is less obvious [9].

Apocrine glands secrete very small quantities of an oily fluid, which may be coloured. This secretion is odourless on reaching the surface, and bacterial decomposition is responsible for the characteristic odour; *trans*-3-methyl-2-hexanoic acid, which is water-soluble, is one of the substances which contributes to the odour [10]. The glands have no thermoregulatory function in humans, although they may play some part in human olfactory communication. The epithelium of the secretory coil produces its secretion continuously, with some variation depending on hormonal factors—for example, menstruation and pregnancy. The ducts have an adrenergic sympathetic nerve supply and are also stimulated by circulating epinephrine. Nervous control of secretion is unimportant, and it is even disputed whether the glands have any motor innervation [4,11]. Expulsion of apocrine sweat may occur continuously or be provoked by emotional stimuli. It seems possible that histologically normal apocrine glands may fail to produce any secretion, and that only the axillary glands in humans are important in producing body odour [12].

References

1 Hurley HJ, Shelley WB. *The Human Apocrine Sweat Gland in Health and Disease*. Springfield, IL: Thomas, 1960.
2 Ebling FJG. Apocrine glands in health and disease. *Int J Dermatol* 1989; **28**: 508–11.
3 Montagna W, Parakkal PF. *The Structure and Function of Skin*, 3rd edn. London: Academic Press, 1974.
4 Montagna W. Histology and cytochemistry of human skin, 24: further observations on the axillary organ. *J Invest Dermatol* 1964; **42**: 119–29.
5 Takayasu S, Wakimoto H, Itami S *et al*. Activity of testosterone 5α-reductase in various tissues of human skin. *J Invest Dermatol* 1980; **74**: 187–91.
6 Hashimoto K, Gross BG, Lever WF. Electron-microscopic study of apocrine secretion. *J Invest Dermatol* 1966; **46**: 378–90.
7 Schaumburg-Lever G, Lever WF. Secretion from human apocrine glands. *J Invest Dermatol* 1975; **64**: 38–41.
8 Hurley HJ, Shelley WB. The role of the myoepithelium of the human apocrine sweat gland. *J Invest Dermatol* 1954; **22**: 143–56.
9 Tani M, Yamamoto K, Mishima Y. Apocrine acrosyringeal complex in the human skin. *J Invest Dermatol* 1980; **75**: 431–5.
10 Leyden JJ, Zeng XN, McGinley K *et al*. Characterization of pungent axillary odours [abstract]. *J Invest Dermatol* 1990; **94**: 549.
11 Robertshaw D. Neural and humoral control of apocrine glands. *J Invest Dermatol* 1974; **63**: 160–7.
12 Kligman AM, Shehadek N. Pubic apocrine glands and odour. *Arch Dermatol* 1964; **89**: 461–3.

Abnormal sweat odour (bromhidrosis and osmidrosis) [1–3]

Odour of the skin in humans is, to a large extent, determined by apocrine gland secretion, although there are other sources. Sebaceous secretion has some odour, and decomposition products of keratinization, especially in the presence of hyperhidrosis, produce offensive smells. Eccrine secretion is usually odourless, but various substances may be excreted in it—for example, garlic, drugs, arsenic. Characteristic odours may be associated with various uncommon amino-acidurias (see below). Old textbooks of medicine report that sweat has a characteristic odour in gout, diabetes, scurvy, typhoid and other diseases [4]. Cases of generalized bromhidrosis associated with nasal foreign bodies have been recorded in children [5,6], and the symptom may be a clue to premature puberty. Other patients complaining of body odour may be suffering from paranoia or phobias (monosymptomatic delusions of malodour) or from organic lesions of the central nervous system.

Apocrine secretion is odourless as it reaches the surface, apart from excreted substances such as garlic. Bacterial decomposition liberates fatty acids, etc., with characteristic smells. This process

occurs only after some hours, and frequent removal of apocrine sweat prevents its decomposition. A strong axillary odour tends to be associated with a richer bacterial flora, and especially with more corynebacteria [7,8]. Increased axillary pH may facilitate the overgrowth of these bacteria, and some deodorants may help by acidifying the axillary skin.

There is marked individual and racial variation in body odour, and what is socially acceptable varies greatly with race and social upbringing. Recent studies have demonstrated histological differences between normal and bromhidrotic apocrine glands; in the bromhidrotics, the apocrine glands were larger and more numerous [9]. Elevated activity of type I 5α-reductase activity has been shown in those with bromhidrosis [10].

Treatment of axillary bromhidrosis includes omission of foodstuffs such as garlic from the diet, frequent washing of the axillary regions and local antibacterial substances [2]. There is little evidence that measures used to control axillary eccrine hyperhidrosis—for example, aluminium salts and anticholinergic drugs—have much effect on the apocrine glands, although excessive eccrine excretion may favour the spread of apocrine secretion. Botulinum toxin has been used to treat genital osmidrosis with good effect; the effect on eccrine sweating and rendering the area anhidrotic may prevent bacterial activity and thus have an effect on odour [11]. Surgical excision of axillary subcutaneous tissue by a variety of surgical techniques (axillary shave and subsection of subcutaneous glands, laser ablation, ultrasound ablation and liposuction), which remove both eccrine and apocrine glands, has been performed with good effect in those dissatisfied with conservative measures [12–14].

References

1 Hurley HJ, Shelley WB. *The Human Apocrine Sweat Gland in Health and Disease*. Springfield, IL: Thomas, 1960.
2 Labows JN. In: Frost P, Hörwitz SN, eds. *Principles of Cosmetics for the Dermatologist*. St Louis: Mosby, 1982.
3 Cone TE. Diagnosis and treatment: some diseases, syndromes and conditions associated with an unusual odour. *Pediatrics* 1968; **41**: 993–5.
4 Smith M, Smith LG, Levinson B. The use of smell in differential diagnosis. *Lancet* 1982; **ii**: 1452.
5 Golding IM. An unusual case of bromhidrosis. *Pediatrics* 1965; **36**: 791–2.
6 Lucky AW. Acquired bromhidrosis in an 8-year-old-boy secondary to a nasal foreign body. *Arch Dermatol* 1991; **127**: 129.
7 Leyden JJ, McGinley KJ, Hölzle E *et al*. The microbiology of the human axilla and its relationship to axillary odour. *J Invest Dermatol* 1981; **77**: 413–6.
8 Jackman PJH. Body odour: the role of skin bacteria. *Semin Dermatol* 1982; **1**: 143–8.
9 Bang YH, Kim JH, Paik SW *et al*. Histopathology of apocrine bromhidrosis. *Plast Reconstr Surg* 1996; **98**: 288–92.
10 Sato T, Sonoda T, Itami S, Takayasu S. Predominance of type I 5 alpha-reductase in apocrine sweat glands of patients with excessive or abnormal odour derived from apocrine sweat (osmidrosis). *Br J Dermatol* 1998; **139**: 806–10.
11 Lee JB, Kim BS, Kim MB *et al*. A case of foul genital odor treated with botulinum toxin A. *Dermatol Surg* 2004; **30**: 1233–5.
12 Tung TC, Wei FC. Excision of subcutaneous tissue for the treatment of axillary osmidrosis. *Br J Plast Surg* 1997; **50**: 61–6.
13 Park YJ, Shin MS. What is the best method for treating osmidrosis? *Ann Plast Surg* 2001; **47**: 303–9.
14 Yoo WM, Pae NS, Lee SJ *et al*. Endoscopy-assisted ultrasonic surgical aspiration of axillary osmidrosis: a retrospective review of 896 consecutive patients from 1998 to 2004. *J Plast Reconstr Aesthet Surg* 2006; **59**: 978–82.

Fish odour syndrome (trimethylaminuria)

This disorder results from excessive amounts of the offensively smelling tertiary amine trimethylamine appearing in both eccrine and apocrine sweat, breath and urine, which imparts an unpleasant rotting fish smell to sufferers [1]. Affected individuals are unable to oxidize this substance, which is produced by the intestinal bacterial degradation of choline and carnitine in food to the odourless trimethylamine N-oxide. This can occur as a primary problem, as a result of a mutation in the flavin-containing monooxygenase 3 (*FMO3*) gene [2]. The ability to N-oxidize trimethylamine is distributed polymorphically, and sufferers are homozygous for an allele that determines this impaired reaction. One per cent of the population are heterozygous carriers of the allele. Secondary trimethylaminuria can occur when there is an increased burden of trimethylamine, and is seen when there is an increased production of trimethylamine (TMA) from its precursors by gut bacteria, in conditions such as blind loop syndrome, uraemia and liver disease.

The unpleasant odour, which is often worse after eating seafood, during periods of stress and during menstruation, can be the source of much distress, rejection and resentment. Sufferers are sometimes unaware of their smell, which may be intermittent and may not be detected by physicians when consulted. Trimethylaminuria was found in 7% of a series of individuals who perceived themselves to be malodorous [3]. The condition can be diagnosed by direct estimation of TMA in the urine; both affected individuals and heterozygous carriers have abnormal elevated excretion of TMA after an oral TMA challenge. A diet low in carnitine and choline may help. Short courses of metronidazole or neomycin may temporarily reduce the bacteria that degrade the carnitine and choline in the gut. Charcoal and copper chlorophyllin have been shown to reduce urinary trimethylamine concentrations to normal levels in sufferers [4].

References

1 Humbert JR, Hammond KB, Hathaway WE *et al*. Trimethylaminuria: the fish odour syndrome. *Lancet* 1970; **i**: 770–1.
2 Dolphin CT, Janmohamed A, Smith RL *et al*. Missense mutation in flavin-containing mono-oxygenase 3 gene, *FMO3,* underlies fish-odour syndrome. *Nat Genet* 1997; **17**: 491–4.
3 Ayesh R, Mitchell SC, Zhang A, Smith RL. The fish odour syndrome: biochemical, familial and clinical aspects. *BMJ* 1993; **307**: 655–7.
4 Yamazaki H, Fujieda M, Togashi M *et al*. Effects of the dietary supplements, activated charcoal and copper chlorophyllin, on urinary excretion of trimethylamine in Japanese trimethylaminuria patients. *Life Sci* 2004; **74**: 2739–47.

Chromhidrosis [1,2]

Apocrine sweat may be tinged with a yellow, green or blue hue in up to 10% of the population, but only rarely does it occur to the striking degree that merits the term chromhidrosis (Fig. 44.14). Most commonly blue–black, yellow or green, it results from the secretion of lipofuscins in apocrine sweat, and may be associated with the secretion of coloured breast milk. The more oxidized lipofuscins appear deeper in colour; the lighter-coloured pigments may fluoresce. The diagnosis can be confirmed by finding lipofuscin pigment granules that may fluoresce on fluorescence micros-

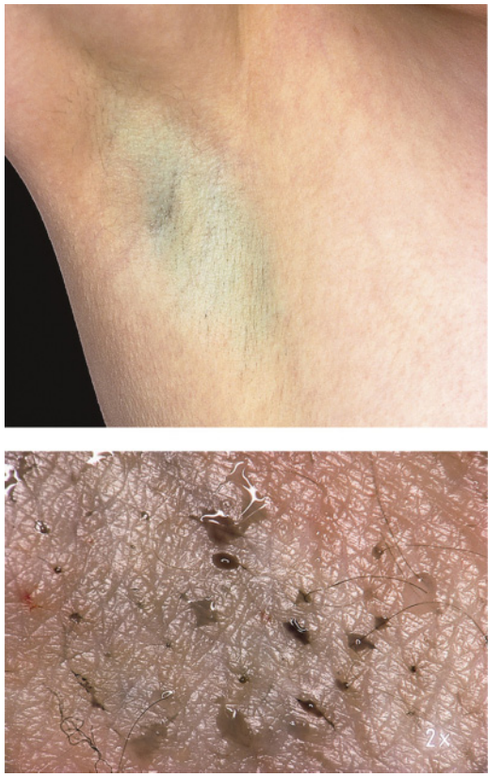


Fig. 44.14 Axillary chromhidrosis. (Courtesy of Dr D. Shuttleworth, Essex County Hospital, Colchester, UK.)



Fig. 44.15 Axillary Fox–Fordyce disease.

copy in the apocrine secretory cells. The secretion of coloured sweat starts at puberty and persists until there is a gradual regression of apocrine function in old age. Coloured sweat may be discharged from the glands in response to exercise and emotional stimuli, and after manipulation of the skin. The axillae are the most frequently affected sites, although facial [3] and areolar chromhidrosis [4] are recorded. Topical capsaicin has satisfactorily reduced facial and nipple chromhidrosis. Botulinum toxin has been used to successfully suppress facial chromhidrosis [5,6].

Pseudochromhidrosis refers to the coloration of otherwise colourless sweat when it reaches the surface of the skin due to dyes, paints or chromogenic or porphyrin-producing bacteria on the skin. Blue pseudochromhidrosis has been reported in workers occupationally exposed to copper salts. An outbreak of red pseudochromhidrosis occurred in a group of flight attendants who had new red-dyed labels put into their uniforms [7]. Erythromycin eradicated a presumed bacterial pseudochromhidrosis of the face in a young girl [8]. Eccrine chromhidrosis is usually due to exogenous dyes and is usually weak in hue. A case of red pseudochromhidrosis resulting in red staining of underwear was attributed to eating excessive quantities of a snack containing a red food dye [9]. Dark perspiration has been reported to occur in alkaptonuria (ochronosis).

References

1 Shelley WB, Hurley HJ. Localized chromhidrosis: a survey. *Arch Dermatol Syphilol* 1954; **69**: 449–71.

2 Hurley HJ, Shelley WB. *The Human Apocrine Sweat Gland in Health and Disease*. Springfield, IL: Thomas, 1960.

3 Marks JG Jr. Treatment of apocrine chromhidrosis with topical capsaicin. *J Am Acad Dermatol* 1989; **21**: 418–20.

4 Saff DM, Owens R, Kahn TA. Apocrine chromhidrosis involving the areolae in a 15-year-old amateur figure skater. *Pediatr Dermatol* 1995; **12**: 48–50.

5 Wu JM, Mamelak AJ, Nussbaum R, McElgunn PS. Botulinum toxin A in the treatment of chromhidrosis. *Dermatol Surg* 2005; **31**: 963–5.

6 Matarasso SL. Treatment of facial chromhidrosis with botulinum toxin type A. *J Am Acad Dermatol* 2005; **52**: 89–91.

7 Poh-Fitzpatrick MB. 'Red sweat.' *J Am Acad Dermatol* 1981; **4**: 481–2.

8 Thami GP, Kanwar AJ. Red facial pseudochromhidrosis. *Br J Dermatol* 2000; **142**: 1219–20.

9 Cilliers J, de Beer C. The case of red lingerie: chromhidrosis revisited. *Dermatology* 1999; **199**: 149–52.

Fox–Fordyce disease

Aetiology and pathology [1]. Fox–Fordyce disease is a disorder of the apocrine glands comparable with prickly heat of the eccrine glands. The aetiology is unknown. Obliteration of the apocrine duct at the infundibulum is felt to be the cause. The earliest visible change histologically is a small vesicle in the apocrine duct [2]; early changes may be seen most easily in transverse histological sections. This progresses to an inflammatory lesion, followed by rupture and plugging of the duct. Apocrine sweat retention therefore follows. Hormonal influences are important, but there is little evidence of a primary hormonal abnormality.

Clinical features. The disease occurs mainly in women soon after puberty, but can be postmenopausal [3]. It can occur in males or in children, and has been reported in females with Turner syndrome and in identical twins [4]. Itching, which may be intense, occurs in the axillae, and to a lesser extent in the anogenital region and around the breasts. Objectively there may be little to see at first, but later skin-coloured, or slightly pigmented, dome-shaped, follicular papules develop (Fig. 44.15). Hair loss in the axillae usually ensues. The itching is often provoked by those emotional stimuli that normally cause apocrine secretion. The disease runs a very prolonged course, and may persist until the menopause. Some remission may occur in pregnancy. A condition resembling Fox–Fordyce disease has been reported due to accumulation of xanthoma cells obliterating the axillary apocrine ducts [5].

Treatment. Response to treatment is unsatisfactory. Topical and intralesional steroids provide some benefit, but their use is limited by atrophy. Topical pimecrolimus may reduce itch and does not have the atrophogenic potential of steroids [6]. Topical clindamycin is reported to have been of help [3]. Treatment with four to six weekly doses of ultraviolet radiation (UVR), sufficient to cause exfoliation, helps some patients [7]. Topical retinoic acid may also be helpful [8], as may oral contraceptive agents [9,10], and oral retinoids [11]. Other cases are sufficiently severe to require electrocautery [12] or surgical excision of the affected skin, or subcutaneous removal of the apocrine glands [13].

References

1 Hurley HJ, Shelley WB. *The Human Apocrine Sweat Gland in Health and Disease*. Springfield, IL: Thomas, 1960.

2 Shelley WR, Levy EJ. Apocrine sweat retention in man. *Arch Dermatol* 1956; **73**: 38–49.

3 Feldmann R, Misouyé I, Chavaz R, Saurat JH. Fox–Fordyce disease: successful treatment with topical clindamycin in alcoholic propylene glycol solution. *Dermatology* 1992; **184**: 310–3.

4 Graham JH, Shafer JC, Helwig EB. Fox–Fordyce disease in male identical twins. *Arch Dermatol* 1960; **82**: 212–21.

5 Kossard S, Dwyer P. Axillary perifollicular xanthomatosis resembling Fox-Fordyce disease. *Australas J Dermatol* 2004; **45**: 146–8.

6 Pock L, Svrcková M, Macháckova R, Hercogová J. Pimecrolimus is effective in Fox-Fordyce disease. *Int J Dermatol* 2006; **45**: 1134–5.

7 Pinkus H. Treatment of Fox–Fordyce disease. *JAMA* 1973; **223**: 924.

8 Giacobetti R, Caro WA, Roenigk HH. Fox–Fordyce disease. *Arch Dermatol* 1979; **115**: 1365–6.

9 Kronthal HL, Pomeranz JR, Sitomer G. Fox–Fordyce disease. *Arch Dermatol* 1965; **91**: 243–5.

10 Leyh F. Morbus Fox–Fordyce: Überlegungen zur Pathogenese. *Hautarzt* 1973; **24**: 482–5.

11 Effendy I, Ossowski B, Happle R. Fox–Fordyce disease in a male patient: response to oral retinoid treatment. *Br J Dermatol* 1994; **19**: 67–9.

12 Pasricha JS, Nayyar KC. Fox–Fordyce disease in the postmenopausal period treated successfully with electrocoagulation. *Dermatologica* 1973; **147**: 271–3.

13 Chevoin JP, Charasson T, Barnard JD. Surgical treatment of areolar hidradenitis suppurativa and Fox–Fordyce disease. *Ann Chir Plast Esthet* 1994; **39**: 233–8.

CHAPTER 45
Disorders of Connective Tissue

N.P. Burrows[1] *& C.R. Lovell*[2]

[1]Department of Dermatology, Addenbrooke's Hospital, Cambridge, UK
[2]Kinghorn Dermatology Unit, Royal United Hospital, Bath, UK

Cutaneous atrophy, 45.2
Generalized cutaneous atrophy, 45.2
Localized cutaneous atrophy, 45.6
Poikiloderma, 45.13
Disorders of elastic fibres, 45.14
Lax skin, 45.14
Generalized cutis laxa, 45.14
Anetoderma, 45.17
Other localized forms of elastolysis, 45.19
Pseudoxanthoma elasticum, 45.21
Acquired PXE-like syndromes, 45.24
Linear focal elastosis, 45.25
Actinic elastosis, 45.26
Digital papular calcific elastosis, 45.28
Actinic granuloma, 45.28
Elastofibroma, 45.29
Elastoderma, 45.29
Marfan's syndrome (MFS), 45.30
Disorders of collagen, 45.31
Ehlers–Danlos syndrome, 45.31
Occipital horn syndrome, 45.39
Prolidase deficiency, 45.39
Osteogenesis imperfecta (OI), 45.40
Pachydermoperiostosis, 45.41
Relapsing polychondritis, 45.42
Fibromatoses, 45.44
Palmar fibromatosis, 45.45
Camptodactyly, 45.46
Plantar fibromatosis, 45.47
Penile fibromatosis, 45.47
Knuckle pads, 45.48
Pachydermodactyly, 45.48
Juvenile fibromatoses, 45.49
Other benign fibrous cutaneous nodules, 45.50
Infantile stiff-skin syndromes, 45.50
Systemic hyalinosis, 45.50
Winchester's syndrome, 45.50
Congenital fascial dystrophy, 45.50
Restrictive dermopathy, 45.51
Other causes of diffuse fibrosis, 45.51
Environmental and drug-induced scleroderma, 45.51
Nephrogenic systemic fibrosis, 45.53
GEMSS syndrome, 45.53
POEMS syndrome, 45.54
Keloids and hypertrophic scars, 45.54
Premature ageing syndromes, 45.56
Pangeria, 45.57
Progeria, 45.58
Acrogeria, 45.59
Laboratory studies, 45.60
Other associated conditions, 45.60
Perforating dermatoses, 45.63
Acquired reactive perforating dermatosis, 45.63
Perforating disease due to exogenous agents, 45.64
Reactive perforating collagenosis, 45.64
Verrucous perforating collagenoma, 45.65
Elastosis perforans serpiginosa, 45.65
Miscellaneous disorders, 45.66
Colloid milium, 45.66
White fibrous papulosis of the neck, 45.67
Papular elastorrhexis, 45.68
Progressive osseous heteroplasia, 45.68
Fascial hernias of the legs, 45.68
Constricting bands of the extremities, 45.69
Heberden's and Bouchard's nodes, 45.70

Introduction

The connective tissue of the normal skin is discussed in Chapter 3.

Diseases that predominantly affect the cutaneous connective tissue (collagen, elastin and ground substance) can be divided into three main groups [1,2]:

1 Genetic abnormalities that affect connective tissue formation or metabolism. Examples include Ehlers–Danlos syndrome (EDS) (which affects collagen), pseudoxanthoma elasticum (PXE) (elastic tissue) and the mucopolysaccharidoses (ground substance).
2 Acquired metabolic or degenerative disorders, such as scurvy and solar elastosis, which are liable to affect people with no genetic defect if the environmental cause is present.
3 Inflammatory 'collagen vascular' or 'connective tissue' diseases, which damage connective tissue as a result of complex immunological reactions involving autogenous antigens. This group includes systemic lupus erythematosus, rheumatic fever, systemic sclerosis and dermatomyositis. Both genetic and acquired factors (including the possibility of infective agents) may play some part in producing these conditions, which are fully discussed in Chapter 51.

The attempt to classify the pathological changes according to whether ground substance, collagen, elastin or cellular components are mainly or wholly involved is not always easy, and may have been inaccurate in the past.

In this chapter, some of the genetic and acquired diseases that affect mainly collagen or elastin are discussed. Disorders of the ground substance are discussed elsewhere (see myxoedema, cutaneous mucinosis and mucopolysaccharidoses).

There are, in addition, many other disorders, including developmental defects, reactive or scarring conditions and benign or malignant neoplasms, that may involve the connective tissue.

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

References

1 Christiano AM, Uitto J. Molecular pathology of the elastic fibers. *J Invest Dermatol* 1994; **103**: S53–7.
2 Prockop DJ, Kivirikko KI. Collagens: molecular biology, diseases, and potentials for therapy. *Annu Rev Biochem* 1995; **64**: 403–34.

Cutaneous atrophy

Atrophy of the skin is a term that is applied to the clinical changes produced by a decrease in the dermal connective tissue. It is characterized by thinning and loss of elasticity. The skin usually appears smooth and finely wrinkled, and it feels soft and dry. Veins or other subcutaneous structures may be unduly conspicuous. There is often associated loss of hair follicles, and telangiectasia may also be present, due to the loss of connective tissue support of the capillaries. There may or may not be an associated atrophy of the epidermis.

Atrophy of the skin occurs in varying degree in a large number of skin conditions, and the underlying histological changes are also variable, because the several components of the connective tissue may be involved to a different degree. Atrophy that includes subcutaneous tissue or even deeper structures is referred to as *panatrophy*.

The main causes of cutaneous atrophy are as follows.

1 Generalized cutaneous thinning:
   (a) ageing
   (b) rheumatoid disease
   (c) glucocorticoids (exogenous or endogenous)
2 Poikiloderma
3 Atrophic scars (striae)
4 Anetoderma (see p. 45.17)
5 Chronic atrophic acrodermatitis (borreliosis)
6 Follicular atrophoderma
7 Vermiculate atrophoderma
8 Atrophoderma of Pasini and Pierini (probably morphoea)
9 Atrophic naevi
10 Panatrophy:
   (a) local panatrophy
   (b) facial hemiatrophy.

Generalized cutaneous atrophy

The skin becomes increasingly thin and atrophic in elderly people, and both the epidermis and the dermis are affected [1] (see Chapter 8 for further details). As a result, the aged skin becomes fragile, translucent, lax and wrinkled, with a tendency to easy bruising. Intrinsic ageing of skin may be compounded by environmental factors, such as chronic sun exposure and smoking. Dermal thickness is considerably decreased in the elderly [1]. Wound healing is delayed in the elderly because of a decrease in the numbers and synthetic capability of fibroblasts [2]. With increasing age, both keratinocytes and fibroblasts show a decreased response to various growth factors [3].

Ageing and wrinkles

Wrinkles may be defined as creases or furrows in the skin surface. They are generally distinguished from the lax pendulous folds of skin which occur in conditions such as PXE and cutis laxa, but the distinction is somewhat arbitrary, because loss of dermal elastic tissue is common to all these conditions. Deepening of the furrows occurs with advancing age [4]. Histologically, there is epidermal thinning, decrease in chondroitin sulphate and deposition of abnormal elastic tissue in the papillary dermis [5].

Wrinkles can be classified into three morphological types [6]:

1 **Crinkles.** This is a very fine wrinkling which occurs in aged skin, even in areas protected from sunlight. These fine wrinkles disappear when the skin is slightly stretched. They are caused by deterioration of elastin, especially the vertical subepidermal fine elastic fibres which keep the epidermis in tight apposition to the dermis [7,8]. Ultrastructural studies have shown that even in normal people the elastic fibres begin to deteriorate from the age of 30 years onwards, regardless of the amount of sun exposure, although sunlight undoubtedly increases the damage [9]. Crinkles are seen in a marked form in mid-dermal elastolysis (see below).
2 **Glyphic wrinkles.** These creases are an accentuation of the normal skin markings. They occur on skin which has been prematurely aged by elastotic degeneration caused by sunlight, for example on the sides and back of the neck (see actinic elastosis).
3 **Linear furrows.** These are long, straight or slightly curved grooves that are usually seen on the faces of elderly people. They include the horizontal frown lines along the forehead, the 'crows' feet' radiating from the lateral canthus of the eye and the creases from the nose to the corners of the mouth.

The facial skin has a remarkably complex and dense intradermal elastic tissue mesh. This sheath of elastin is unique to the face, not being found in such complexity elsewhere. In youth, the linear furrows caused by facial muscle contraction disappear due to elastic recoil, but in older people they become permanent. There is some controversy regarding the histology of these linear furrows. Several groups have claimed that the linear wrinkles cannot be distinguished by light or electron microscopy from the surrounding skin, and Kligman *et al.* [6] claim the furrow is merely a configurational change, like the crease in an old glove. Tsuji *et al.* [8], however, claim that the upper dermis in the furrow shows less elastotic change than the surrounding skin. Other authors [9,10], on the other hand, claim that the trabeculae of the retinacula cutis (which anchors the dermis to the underlying fascia) are broader and much shorter underneath the wrinkles than in the surrounding skin. The hypertrophy of these subcutaneous septa is probably related to repetitive mechanical stimuli generated by the facial muscles over the years.

Wrinkles are a characteristic feature of photodamaged skin (Chapter 29). Cigarette smoking is also a potent, independent cause of wrinkling. The so-called 'cigarette face' is characterized by pale, grey, wrinkled skin with rather gaunt features, so that heavy smokers can often be recognized from their facial appearance alone. Heavy smokers are five times more likely to be wrinkled than non-smokers of the same age, and cigarette smoking probably has at least as much effect on facial wrinkles as sun exposure [11,12]. The pathogenesis of these deleterious effects on facial skin is unknown, but causative factors might include ischaemia due to the vasoconstriction induced by nicotine or sympathetic nerve stimulation, decreased tissue oxygenation, increased tissue carboxyhaemoglobin, increased platelet aggregation, decreased prostacyclin formation and reduced collagen deposition [12]. Both UVA and tobacco smoke may cause wrinkling through additive induction of matrix metalloproteinase-1 (MMP-1) expression [13].

Treatment of wrinkles

See Chapter 80.

References

1 Kligman AM, Lavker RM. Cutaneous aging. The difference between intrinsic aging and photoaging. *J Cutaneous Aging Cosmetic Dermatol* 1988; **1**: 5–12.
2 Bolognia JL. Dermatologic and cosmetic concerns of the older woman. *Clin Geriatr Med* 1993; **9**: 209–29.
3 Gilchrest BA, Yaar M. Ageing and photoageing of the skin: observations at the cellular and molecular level. *Br J Dermatol* 1992; **127** (Suppl. 41): 25–30.
4 Akazaki S, Nakagawa H, Kazama H *et al*. Age-related changes in skin wrinkles assessed by a novel three-dimensional morphometric analysis. *Br J Dermatol* 2002; **147**: 689–95.
5 Contet-Audonneau JL, Jeanmaire C, Pauly G. A histological study of human wrinkle structures. Comparison between sun-exposed areas of the face, with or without wrinkles, and sun-protected areas. *Br J Dermatol* 1999; **140**: 1038–47.
6 Kligman AM, Zheng P, Lavker RM. The anatomy and pathogenesis of wrinkles. *Br J Dermatol* 1985; **113**: 37–42.
7 Lavker RM. Structural alterations in exposed and unexposed skin. *J Invest Dermatol* 1979; **73**: 59–69.
8 Tsuji T, Yorifuji T, Hamarta T *et al*. Light and scanning electron microscopic studies on wrinkles in aged person's skin. *Br J Dermatol* 1986; **114**: 329–35.
9 Braverman IM, Finferko E. Studies in cutaneous ageing. 1. The elastic fiber network. *J Invest Dermatol* 1982; **78**: 434–43.
10 Piérard GE, Lapière CM. The micro-anatomical basis of facial lines. *Arch Dermatol* 1989; **125**: 1090–2.
11 Davis BE, Koh HK. Faces going up in smoke. A dermatologic opportunity for cancer prevention. *Arch Dermatol* 1992; **128**: 1106–7.
12 Smith JB, Fenske NA. Cutaneous manifestations and consequences of smoking. *J Am Acad Dermatol* 1996; **34**: 717–32.
13 Yin L, Morita A, Tsuji T. Skin aging induced by ultraviolet exposure and tobacco smoking: evidence from epidemiological and molecular studies. *Photodermatol Photoimmunol Photomed* 2001; **17**: 178–83.

Atrophic skin with rheumatoid disease

In rheumatoid patients over the age of 60 years, especially women, the skin on the dorsa of the hands may become thin, loose, smooth, inelastic and transparent, so that the details of veins and tendons are clearly seen. The change is generalized but is seldom conspicuous, except on the hands and forearms. Histologically, the dermis is thinned but shows no distinctive changes.

There is a significant association between transparent skin, rheumatoid arthritis and osteoporosis, and it is assumed to form part of a general connective tissue defect [1]. Steroid therapy is not a factor but it will potentiate the problem [2]. Skin collagen is structurally abnormal [3]. A reported association with PXE may be coincidental [4].

References

1 McConkey B. Transparent skin and osteoporosis. A study of patients with rheumatoid disease. *Ann Rheum Dis* 1965; **24**: 219–23.
2 Shuster S, Raffle E, Bottoms E. Skin collagen in rheumatoid arthritis and the effect of corticosteroids. *Lancet* 1967; **i**: 525–7.
3 Adam M, Vitasek R, Deyl Z *et al*. Collagen in rheumatoid arthritis. *Clin Chim Acta* 1976; **70**: 61–9.
4 Praderio L, Marian JF, Baldini V. Pseudoxanthoma elasticum and rheumatoid arthritis. *Arch Intern Med* 1987; **147**: 206–7.

Glucocorticosteroid-induced atrophy [1]

Both systemic and topical steroid therapy can produce cutaneous atrophy by a dose-related pharmacological effect. The effect is more severe with the more potent steroids (as assessed by the vasoconstrictor assay test), but both fluorinated and non-fluorinated topical steroids can cause atrophy. The effect is most marked when potent steroids are applied topically under an occlusive dressing. The skin becomes thin, fragile and transparent, and striae may develop (see below) (Fig. 45.1).

Severe dermal atrophy can follow injection of intralesional steroids, such as triamcinolone acetonide (particularly if the higher concentration of 40 mg/mL is used, instead of the more usual 10 mg/mL, which is less likely to cause atrophy) (Fig. 45.2).



Fig. 45.1 Striae of the legs due to long-term application of a potent topical steroid in a young woman with psoriasis.



Fig. 45.2 Localized atrophy due to injection of a steroid (triamcinolone, 40 mg/mL) into the skin between the second and third metatarsals.

The earliest histological change is marked thinning of the epidermis, with flattening of the rete ridges and decreased corneocyte size [2]. This is followed a few weeks later by thinning of the dermis, which can be measured by skinfold callipers, ultrasonography or a radiographic technique [3–5].

The epidermal thinning probably results from a reduction of mitotic activity in the germinal layer [6], but the mechanism by which dermal thinning is produced is uncertain.

Loss of dermal ground substance leads to a reorganization of the dermal architecture. The spaces between the collagen and elastic fibres become smaller, so that the dermis becomes more compact but thinner [7]. Steroids are known to inhibit the formation of glycosaminoglycans, and hyaluronate and the major cell-surface hyaluronate receptor CD44 are depleted in atrophic skin [8,9]. The fibroblasts become shrunken, although their numbers do not decrease, but the number of mast cells is markedly reduced.

Topical steroids also inhibit the activity of enzymes involved in collagen biosynthesis [10], and they have been shown to depress synthesis of types I and III collagen *in vivo* [11–13]. Type III collagen synthesis is preferentially reduced in fibroblast cultures [14]. They can also depress collagenase production and collagen breakdown [15], and the rate of collagen turnover is probably decreased. Even a weak steroid, such as hydrocortisone, can suppress the stimulatory effect of cyclic nucleotides on collagenase production. Studies of the effect of topical steroids on collagen and elastic fibres *in vivo* have given conflicting results [7,16,17]. Collagen microfibrils may form globular microfibrillar bodies, although the changes are not specific for steroid atrophy [18]. These ultrastructural changes can develop in the early stages before there is clinical or histological evidence of atrophy. Digestion of collagen fibrils in the endocytic vesicles of fibroblasts may be involved in the production of steroid-induced atrophy [15].

Capillaroscopic studies have shown that steroid-induced vasoconstriction involves the superficial capillary network, and prolonged superficial ischaemia could also play a role in producing atrophy [10].

Treatment. It has been suggested that local and oral vitamin C therapy might help restore the normal skin thickness [19]. Concurrent application of retinoic acid may partially prevent the epidermal atrophy due to steroids [20]. Intralesional saline injections can restore surface contour [21]. Hyaluronate fragments are reported to induce skin thickening in corticosteroid-induced atrophy [9].

References

1 Henqqe VR, Ruzicka T, Schwartz RA *et al.* Adverse effects of topical corticosteroids. *J Am Acad Dermatol* 2006; **54**: 1–15.
2 Burton JL, Winter GD. Experimentally induced steroid atrophy in the domestic pig and man. *Br J Dermatol* 1976; **94** (Suppl. 12): 107–9.
3 Dykes PJ, Marks R. Measurements of skin thickness. A comparison of two *in vivo* techniques. *J Invest Dermatol* 1977; **69**: 275–8.
4 Dykes PF, Marks R. An appraisal of the methods used in the assessment of atrophy from topical corticosteroids. *Br J Dermatol* 1979; **101**: 599–609.
5 James MP, Black MH, Sparkes CG. Measurement of dermal atrophy induced by topical steroids using a radiographic technique. *Br J Dermatol* 1977; **96**: 303–5.
6 Marks R, Halprin K, Fukui K *et al.* Topically applied triamcinolone and macromolecular synthesis by human epidermis. *J Invest Dermatol* 1971; **56**: 470–3.
7 Lehmann P, Zheng P, Lavker RM *et al.* Corticosteroid atrophy in human skin. A study of light scanning and transmission electron microscopy. *J Invest Dermatol* 1983; **81**: 169–75.
8 Sarrni H, Hopsu-Havu BK. The decrease of hyaluronate synthesis by anti-inflammatory steroids *in vivo*. *Br J Dermatol* 1978; **98**: 445–9.
9 Kaya G, Tran C, Sorg O *et al.* Hyaluronate fragments reverse skin atrophy by a CD44-dependent mechanism. *PLoS Med* 2006; **3**: e493.
10 Risteli J. Effect of prednisolone on the activities of intracellular enzymes of collagen biosynthesis in rat skin. *Biochem Pharmacol* 1977; **26**: 1295–8.
11 Autio P, Oikarinen A, Melkko J *et al.* Systemic glucocorticoids decrease the synthesis of type I and type III collagen in human skin *in vivo,* whereas isotretinoin has little effect. *Br J Dermatol* 1994; **131**: 660–3.
12 Werth VP, Kligman AM, Shi X *et al.* Lack of correlation of skin thickness with bone density in patients receiving chronic glucocorticoid. *Arch Dermatol Res* 1998; **290**: 388–93.
13 Nuutinen P, Riekki R, Parikka M *et al.* Modulation of collagen synthesis and mRNA by continuous and intermittent use of topical hydrocortisone in human skin. *Br J Dermatol* 2003; **148**: 39–45.
14 Oishi Y, Fu ZW, Ohnuki Y *et al.* Molecular basis of the alteration in skin collagen metabolism in response to *in vivo* dexamethasone treatment: effects on the synthesis of collagen type I and III, collagenase, and tissue inhibitors of metalloproteinases. *Br J Dermatol* 2002; **147**: 859–68.
15 Koob TJ, Jeffrey JJ, Eisen AZ. Regulation of human skin collagenase activity by hydrocortisone and dexamethasone in organ culture. *Biochem Biophys Res Commun* 1974; **61**: 1083–8.
16 Jablonska S, Groniowska M, Dabrowski J. Comparative evaluation of skin atrophy in man produced by topical corticosteroids. *Br J Dermatol* 1979; **100**: 193–206.
17 Stevanovic DV. Corticosteroid-induced atrophy of the skin with telangiectasia. *Br J Dermatol* 1972; **87**: 548–56.
18 Holze E, Plewig G. Effects of dermatitis, stripping and steroids on the morphology of corneocytes. *J Invest Dermatol* 1977; **68**: 350–6.
19 Pinnell S. Management of cutaneous atrophy after corticosteroid injection. *J Am Acad Dermatol* 1987; **17**: 521.
20 McMichael AJ, Griffiths CEM, Talwar HS *et al.* Concurrent application of tretinoin (retinoic acid) partially protects against corticosteroid-induced epidermal atrophy. *Br J Dermatol* 1996; **135**: 60–4.
21 Shumaker PR, Rao J, Goldman MP. Treatment of local, persistent cutaneous atrophy following corticosteroid injection with normal saline infiltration. *Dermatol Surg* 2005; **31**: 1340–3.

Achenbach's syndrome [1–4]

Synonym
- Paroxysmal haematoma of the finger

This syndrome presents with the sudden spontaneous onset of one or more painful haematomas in the fingers, usually in a middle-aged female (Fig. 45.3). It may recur at intervals for several years. The cause is unknown—there is no evidence of vasculitis or amyloid on skin biopsy, and the condition, although troublesome, has a good prognosis. It may be mistaken for easy bruising due to steroid atrophy.

References

1 Achenbach W. Das paroxysmale Handhämatom. *Medizinische* 1958; **52**: 2138–40.
2 Stieler W, Heinze-Werlitz C. Paroxysmales Fingerhämatom (Achenbach Syndrom). *Hautarzt* 1990; **41**: 270–1.
3 Layton AM, Cotterill JA. A case of Achenbach's syndrome. *Clin Exp Dermatol* 1993; **18**: 60–1.
4 Parslew R, Verbov JL. Achenbach syndrome. *Br J Dermatol* 1995; **132**: 319.

Striae

Synonyms
- Striae atrophicans
- Striae distensae
- 'Stretch marks'



Fig. 45.3 Achenbach's syndrome. (Courtesy of Dr J. Verbov, Royal Liverpool University Hospitals, Liverpool, UK.)



Fig. 45.4 Striae due to obesity in a young man.

Definition. Striae are visible, linear scars, which form in areas of dermal damage produced by stretching of the skin. They are characterized histologically by thinning of the overlying epidermis, with fine dermal collagen bundles arranged in straight lines parallel to the surface.

Aetiology. The factors that govern the development of striae are poorly understood. Many authors have suggested that striae develop as a result of stress rupture of the connective tissue framework [1], but others disagree. It has been suggested that they develop more easily in skin that has a critical proportion of rigid cross-linked collagen, as occurs in early adult life [2]. They are common during adolescence [3], and they seem to be associated with rapid increase in size of a particular region. They are very common over the abdomen and breasts in pregnancy, and they may develop on the shoulders in young male weightlifters when their muscle mass rapidly increases [4]. They are a feature of Cushing's disease, and they may be induced by local or systemic steroid therapy [2,5]. The effects of glucocorticoids on the dermal connective tissue are outlined above. Together with other steroid effects, striae have been reported in human immunodeficiency virus (HIV)-positive patients receiving the protease inhibitor, indinavir [6].

The importance of genetic factors in determining susceptibility of connective tissue is emphasized by their presence as one of the (minor) diagnostic criteria for Marfan's syndrome (MFS) [7], but they are commonly absent in pregnancy in EDS.

Pathology. In the early stages, inflammatory changes may be conspicuous; the dermis is oedematous and perivascular lymphocytic cuffing is present. In the later stages, the epidermis is thin and flattened [8]. The dermal collagen is layered in thin eosinophilic bundles, orientated in straight lines parallel to the surface in the direction of the presumed stress. Scanning electron microscopy shows amorphous, sheet-like structures [9,10]. With Luna's stain, the elastic fibres are numerous, close together, fine and straight, in the same direction as the collagen bundles [9]. On scanning electron microscopy, in collagen-free preparations there is an abundance of thin, curled and branched elastic fibres. The histology is that of a scar.

Clinical features. Striae are very common, and occur in most adult women, as they readily develop at puberty or during pregnancy. Adolescent striae may first develop soon after the appearance of pubic hair. The commonest sites are the outer aspect of the thighs and the lumbo-sacral region in boys (Fig. 45.4), and the thighs, buttocks and breasts in girls, but there is considerable variation, and other sites, including the outer aspect of the upper arm, are sometimes affected. Early lesions may be raised and irritable, but they soon become flat, smooth and livid red or bluish in colour. Their surface may be finely wrinkled. They are commonly irregularly linear, several centimetres long and 1–10 mm wide. After some years, they fade and become relatively inconspicuous.

The striae in Cushing's syndrome or those induced by steroid therapy may be larger and more widely distributed, and involve other regions, including sometimes the face. In pregnancy, the striae appear first and are most conspicuous on the abdominal wall, and later on the breasts, but may involve most or all of the pubertal sites [11].

The striae induced by topical steroid therapy occur particularly in the flexures, but may appear in other sites if occlusive plastic films increase absorption [12,13]. They may disappear or become less conspicuous when treatment is stopped.

Usually, striae are only a cosmetic problem, but occasionally, if extensive, they may ulcerate or tear easily should the patient be involved in an accident.

Diagnosis. The diagnosis of striae is usually simple. The possibility of Cushing's syndrome must be considered, although this is rarely the cause. In linear focal elastosis the lesions are yellow and palpable (p. 45.25).

Treatment. In the case of common adolescent striae, the patient may be reassured that in time they will become less conspicuous. Numerous unproven remedies are available from cosmetic companies.

Some cases appear to respond to treatment with topical tretinoin [14]. The erythema of 'younger' striae is claimed to respond to the 585 nm pulsed dye and Nd:YAG lasers [15,16]. Fractional photothermolysis has been used in chronic striae [17].

References

1 Stevanovic DV. Corticosteroid-induced atrophy of the skin with telangiectasia. A clinical and experimental study. *Br J Dermatol* 1972; **87**: 548–56.
2 Shuster S. The cause of striae distensae. *Acta Derm Venereol (Stockh)* 1979; **59** (Suppl. 85): 161–9.
3 Herxheimer H. Cutaneous striae in normal boys. *Lancet* 1953; **ii**: 204.
4 Carr RD, Hamilton JF. Transverse striae of the back. *Arch Dermatol* 1969; **99**: 26–30.
5 Thiers H, Moulin G, Larive M. Les vergetures de la corticothérapie locale. *Ann Dermatol Syphiligr (Paris)* 1969; **96**: 29–36.
6 Darvay A, Acland K, Lynn W *et al.* Striae formation in two HIV-positive persons receiving protease inhibitors. *J Am Acad Dermatol* 1999; **41**: 467–9.
7 De Paepe A, Devereux RB, Dietz HC *et al.* Revised diagnostic criteria for the Marfan syndrome. *Am J Med Genet* 1996; **62**: 417–26.
8 Zheng PS, Lauker RM, Lehmann P *et al.* Morphologic investigations on the rebound phenomenon after corticosteroid-induced atrophy in human skin. *J Invest Dermatol* 1984; **82**: 345–52.
9 Arem AJ, Kischer CW. Analyses of striae. *Plast Reconstr Surg* 1980; **65**: 22–9.
10 Zheng P, Lavker RM, Kligman AM. Anatomy of striae. *Br J Dermatol* 1985; **112**: 185–93.
11 Poidevin LOS. Striae gravidarum. Their relation to adrenal cortical hyperfunction. *Lancet* 1959; **ii**: 436–8.
12 Chernovsky ME, Knox JM. Atrophic striae after occlusive corticosteroid therapy. *Arch Dermatol* 1964; **90**: 15–9.
13 Kikuchi I, Horikawa S. Perilymphatic atrophy of the skin. A side effect of topical corticosteroid injection therapy. *Arch Dermatol* 1974; **109**: 558–9.
14 Elson ML. Treatment of striae distensae with topical tretinoin. *J Dermatol Surg Oncol* 1990; **16**: 267–70.
15 Alster TS. Laser treatment of hypertrophic scars, keloids and striae. *Dermatol Clin* 1997; **15**: 419–29.
16 Goldman A, Rossato F, Prati C. Stretch marks: treatment using the 1,064 nm Nd:YAG laser. *Dermatol Surg* 2008; **34**: 686–92.
17 Kou BJ, Lee DH, Kim MN *et al.* Fractional photothermolysis for the treatment of striae distensae in Asian skin. *Am J Clin Dermatol* 2008: **9**: 33–7.

Congenital reticulate scarring

Three children have been described who presented at birth with vesicles, deep erosions and erythematous patches. The vesicles were generalized, but spared the palms, soles and face, superficially resembling 'scalded skin syndrome'. Healing at around 3 months was followed by fragile reticulate scars; the affected areas were anhidrotic [1]. Two further children with this condition had epilepsy and delayed intellectual and motor milestones [2]. Histological examination showed that the reticular dermis was partially replaced by collagenous scar tissue, and eccrine glands were absent. The differential diagnosis includes Goltz syndrome, Rothmund–Thomson syndrome, acrodermatitis chronica atrophicans and aplasia cutis [1,2].

References

1 Cohen BA, Esterley NB, Nelson PF. Congenital erosive and vesicular dermatitis healing with reticulated supple scarring. *Arch Dermatol* 1985; **121**: 361–7.
2 Gupta AK, Rasmussen JE, Headington JT. Extensive congenital erosions and vesicles healing with reticulate scarring. *J Am Acad Dermatol* 1987; **17**: 369–76.

Localized cutaneous atrophy

Focal facial dermal dysplasia

Scar-like depressions on the face are a feature of this syndrome, which may be a variant of the Setleis syndrome (Chapters 15 & 18) [1,2].

References

1 Kowalski DC, Fenske NA. The focal facial dermal dysplasias: report of a kindred and a proposed new classification. *J Am Acad Dermatol* 1992; **27**: 575–82.
2 Ward KA, Moss C. Evidence for genetic homogeneity of Setleis' syndrome and focal facial dermal hypoplasia. *Br J Dermatol* 1994; **130**: 645–9.

Atrophic scars and pseudoscars

Atrophy may result from the destruction of connective tissue by trauma or by inflammatory changes. The distribution and character of the atrophic lesions may be so distinctive as to betray their origin, and is sometimes of considerable importance in diagnosis. Viral infections, such as varicella, can leave widespread, small, circular, atrophic scars [1]. The scars left by tertiary syphilis, certain tuberculides and some deep mycoses, especially sporotrichosis, are usually completely atrophic. Lupus erythematosus may also leave atrophy without clinical evidence of sclerosis. Lupus vulgaris and the chronic follicular pyodermas, and some cases of lupus erythematosus, leave a combination of atrophy and sclerosis, in which the latter predominates. Lesions that have been treated by intralesional steroid injections may also leave atrophic scars.

Exposure to ionizing radiation gives rise to a very striking combination of atrophy, pigmentation and telangiectasia (Chapter 79).

The wide atrophic scars which follow injuries in EDS (p. 45.31) emphasize the importance of constitutional factors in determining the pattern of dermal response to a known external injury.

Reference

1 Leung AKC, Pinkao C, Suave RS. Scarring resulting from chickenpox. *Pediatr Dermatol* 2001; **18**: 378–80.

Stellate and discoid pseudoscars [1,2]

Stellate pseudoscars are white, irregular or 'star-shaped' atrophic scars (Fig. 45.5). They are common on light-exposed skin, particularly on the extensor aspects of the forearms, often in association with senile purpura. These are seen in 20% of patients aged 70–90 years, and a much less common presenile form occasionally occurs before the age of 50 years. These pseudoscars are secondary to mild trauma, and are probably always preceded by haemorrhage into the dermis.

Stellate scars following trivial trauma can also occur in other conditions that cause fragile skin, for example porphyria cutanea tarda and prolonged use of potent topical steroids.

Brown pseudoscars may also develop over the shins of diabetic patients with no history of trauma (Fig. 45.6).

References

1 Colomb D. Stellate spontaneous pseudoscars. Senile and presenile forms: especially those forms caused by prolonged corticoid therapy. *Arch Dermatol* 1972; **105**: 551–4.
2 Zac FG, Pai SH, Kanshepolsky J. Stellate spontaneous pseudoscars (Colomb). *Arch Dermatol* 1968; **98**: 499–501.



Fig. 45.5 Stellate pseudoscars on the forearm of an elderly woman. There was no history of trauma.



Fig. 45.6 Brown pseudoscars of the legs due to diabetic dermopathy. There was no history of trauma.

Spontaneous atrophic scarring of the cheeks

Synonyms
- Varioliform atrophy
- Atrophia maculosa varioliformis cutis



Fig. 45.7 Spontaneous atrophic scarring of the cheeks (varioliform atrophy). (Courtesy of Dr S. George, Amersham Hospital, Amersham, UK.)

This is a very rare condition in which spontaneous scars develop on the cheeks (Fig. 45.7) in young adults [1,2] or children [3]. The shallow atrophic lesions have sharp margins and may be linear, rectangular or varioliform. They may be preceded by slight erythema and scaling. Histology shows mild loss of collagen or elastic fibres; there may be thickening of the stratum corneum [4]. Familial cases are recorded [1,5]; inheritance is probably autosomal dominant [6]. The differential diagnosis includes vermiculate atrophoderma (p. 45.8), chickenpox scars and artefact.

References

1 Marks VJ, Miller OF. Atrophia maculosa varioliformis cutis. *Br J Dermatol* 1986; **115**: 105–9.
2 McCoriston LR, Roys HC. Atrophia maculosa varioliformis cutis. *Arch Dermatol* 1951; **64**: 59–61.
3 Paradisi M, Angelo C, Conti G *et al.* Atrophia maculosa varioliformis cutis: a pediatric case. *Pediatr Dermatol* 2001; **18**: 478–80.
4 Kolenik SA, Perez MI, Davidson DM *et al.* Atrophia maculosa varioliformis cutis. *J Am Acad Dermatol* 1994; **30**: 837–40.
5 Gordon PM, Doherty VR. Familial atrophia maculosa varioliformis cutis. *Br J Dermatol* 1996; **134**: 982–3.
6 Ou T, Wang B, Fang K. Familial atrophia maculosa varioliformis cutis: case report and pedigree analysis. *Br J Dermatol* 2005; **153**: 821–4.

Atrophoderma

Follicular atrophoderma

In this distinctive syndrome dimple-like depressions at the follicular orifices are present from birth or early life, usually on the backs of hands (Fig. 45.8) and feet and sometimes in the elbow region.



Fig. 45.8 Follicular atrophoderma in Conradi's syndrome. (Courtesy of Dr D.A. Burns, Leicester Royal Infirmary, Leicester, UK.)



Fig. 45.9 Vermiculate atrophoderma on the cheek of a child. (Courtesy of Dr P. Frosch, Heidelberg, Germany.)

Histology shows widened follicular ostia with thickening of the connective tissue sheath of the follicle.

It appears to be due to a variety of genetic defects and it may be associated with the following conditions [1]:

1 Calcifying chondrodysplasia (Conradi's syndrome) (Chapter 19)
2 Bazex syndrome (Chapter 15) [2]
3 Hyperkeratosis palmoplantaris, follicular keratosis or palmoplantar hyperhidrosis.

It may also occur as an isolated defect of limited extent.

References

1 Curth HO. The genetics of follicular atrophoderma. *Arch Dermatol* 1978; **114**: 1479–83.

2 Viksnins P, Berlin A. Follicular atrophoderma and basal cell carcinoma. The Bazex syndrome. *Arch Dermatol* 1977; **113**: 948–51.

Vermiculate atrophoderma

This rare condition has been described under a variety of other names, including atrophoderma reticulatum, folliculitis ulerythematosa reticulata and honeycomb atrophy. It is a characteristic reticulate or 'honeycomb' type of atrophy, which seems to develop as a late reaction to inflammation around horny follicular plugs on the cheeks (Fig. 45.9). The condition is now regarded as part of the keratosis pilaris syndrome, and is further discussed in Chapter 19.

Familial focal facial dermal dysplasia

Atrophic macules occur on the temples in this rare autosomal dominant disease (Chapters 15 & 18).

Hallermann–Streiff syndrome

There may be focal atrophy of the scalp skin in this condition (Chapter 18) [1].

Reference

1 Grattan CEH, Liddle BJ, Willshaw HE. Atrophic alopecia in the Hallermann–Streiff syndrome. *Clin Exp Dermatol* 1989; **14**: 250–2.

Atrophoderma of Pasini and Pierini

Definition. This condition appears to be an atrophic variant of morphoea (Chapter 51) in which one or more patches of skin become bluish and sharply depressed, with no surrounding erythema [1–3].

Aetiology. The cause is unknown. No genetic factor has been reliably incriminated, although familial cases have been reported [4], and morphoea and atrophoderma of Pasini have occurred in siblings with phenylketonuria [5].

Pathology [3]. The histological changes are slight. There may be increased pigmentation of the basal layer. During the earlier stages, the collagen in the lower dermis may be oedematous, and elastic tissue clumped and scanty. There may be a dermal perivascular infiltrate consisting of macrophages and T lymphocytes. Immunofluorescence studies may show IgM and C3 staining in the dermal blood vessels [6]. Later, the oedema subsides and there is some reduction in the total thickness of the dermis. Collagen

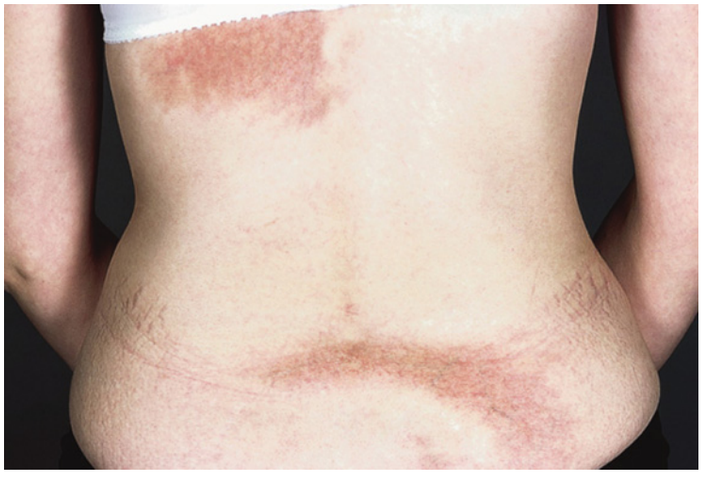


Fig. 45.10 Atrophoderma of Pasini and Pierini. (Courtesy of Dr D.A. Burns, Leicester Royal Infirmary, Leicester, UK.)

bundles appear homogeneous and clumped in the reticular dermis. Eventually there may also be some epidermal atrophy.

Clinical features [3,7,8]. The lesions, which may be single or multiple, range in size from 2 cm to many centimetres in diameter, and are round or oval in shape, but may become confluent to form irregular patches (Fig. 45.10). They are smooth, slate-coloured or violet brown, and are slightly depressed below the level of the entirely normal surrounding skin. The back is almost always involved, the chest and abdomen frequently, and the proximal parts of the limbs occasionally. The patches extend very slowly, increase in number for 10 years or more, and then usually persist unchanged. The eventual development of sclerodermatous changes within the patches has been observed, as has the presence in the same patient of lesions typical of atrophoderma and of morphoea.

Diagnosis. Clinical differentiation from morphoea, possibly an academic exercise, is based on the ivory-white, indurated plaque with an oedematous lilac ring so characteristic of the latter. Histologically, sclerosis may be prominent in morphoea and is usually absent in atrophoderma. Serological tests for *Borrelia burgdorferi* are negative [3].

Treatment. None is of proven efficacy, but psoralen and UVA (PUVA) has helped some patients. Hydroxychloroquine has been used [9].

References

1 Kee CE, Brothers WS, New W. Idiopathic atrophoderma of Pasini and Pierini with co-existent morphea. A case report. *Arch Dermatol* 1960; **82**: 154–7.
2 Miller RF. Idiopathic atrophoderma, report of a case and nosologic study. *Arch Dermatol* 1965; **92**: 653–60.
3 Beuchner SA, Rufli T. Atrophoderma of Pasini and Pierini. *J Am Acad Dermatol* 1994; **30**: 441–6.
4 Barsky S, Ke M. Congenital atrophoderma of the newborn. *Arch Dermatol* 1970; **101**: 374–5.
5 Lasser AE, Schultz BC, Beaff D *et al*. Phenylketonuria and scleroderma. *Arch Dermatol* 1978; **114**: 1215–7.
6 Berman A, Berman GD, Winkelmann RK. Atrophoderma (Pasini–Pierini) findings on direct immunofluorescent, monoclonal antibody and ultra-structural studies. *Int J Dermatol* 1988; **27**: 487–90.
7 Canizares O, Sachs PM, Jaimovich L *et al*. Idiopathic atrophoderma of Pasini and Pierini. *Arch Dermatol* 1958; **77**: 42–60.
8 Jablonska S, ed. *Scleroderma and Pseudoscleroderma*, 2nd edn. Warsaw: Polish Medical Publishers, 1975.
9 Carter JD, Valeriano J, Vasey FB. Hydroxychloroquine as a treatment for atrophoderma of Pasini and Pierini. *Int J Dermatol* 2006; **45**: 1255–6.

Linear atrophoderma

Pigmented atrophic bands follow Blaschko's lines [1] on the trunk, arms and legs. Histologically, collagen bundles are normal or thickened; the apparent atrophy may be due to loss of fat. Leukonychia has been associated [2]. The condition may reflect mosaicism for an autosomal lethal gene [3].

References

1 Moulin G, Hill MP, Guillaud V *et al*. Bandes pigmentées atrophiques acquises suivant les lignes de Blaschko. *Ann Dermatol Vénéréol* 1992; **119**: 729–36.
2 Atasoy M, Aliagaoglu C, Sahin O *et al*. Linear atrophoderma of Moulin together with leuconychia: a case report. *J Eur Acad Dermatol Venereol* 2006; **20**: 337–40.
3 Danarti R, Bittar M, Happle R *et al*. Linear atrophoderma of Moulin: postulation of mosaicism for a predisposing gene. *J Am Acad Dermatol* 2003; **49**: 492–8.

Acrodermatitis chronica atrophicans

Synonyms
- Chronic atrophic acrodermatitis
- Late-phase Lyme borreliosis

Definition. This is a late skin manifestation of Lyme borreliosis (Chapter 30). It is characterized by the insidious onset of painless, dull-red nodules or plaques on the extremities, which slowly extend centrifugally for several months or years, leaving central areas of atrophy.

Aetiology. The condition is due to infection with a spirochaete, *Borrelia burgdorferi sensu lato*, which is transmitted by ticks [1]. The disease occurs mainly in northern or central Europe, Italy and the Iberian Peninsula. Occasional cases occur in other parts of Europe and Africa, but it is very rare in the UK, America, Australia and Asia [2]. These geographical variations are related to different strains of the organism [3–5]. *Borrelia afzelii* is the predominant species associated with acrodermatitis chronica atrophicans. This species is transmitted by ticks in Western Europe, but is rare in the USA, where *Borrelia burgdorferi sensu stricto* predominates.

Pathology [6]. During the early stages, there is non-specific dermal oedema with perivascular inflammatory infiltration. Subsequently, the epidermis becomes atrophic and the epidermal appendages are destroyed. Beneath a subepidermal zone of degenerate connective tissue lies a dense, band-like infiltrate, predominantly consisting of lymphocytes, histiocytes and plasma cells. Ultimately, the infiltrate is reduced to narrow bands between collagen fibres. In some patients, scleroderma-like changes may develop [7,8]. *Borrelia afzelii* has been cultured from the atrophic skin [7] but culture is usually negative. *Borrelia afzelii* can be identified by polymerase chain reaction (PCR). The organism may be

resistant to attack by the complement system and may lurk in immunologically protected areas such as fibroblasts and endothelial cells. Expression of cytokines, such as interferon-γ (IFN-γ), is impaired [9].

Clinical features [10]. Most cases occur in country dwellers between the ages of 30 and 60 years.

The onset is usually insidious, and constitutional symptoms are exceptional. Painless, dull-red or bluish-red nodules or plaques, more or less infiltrated, develop on the feet or legs, and less often on the forearms and hands. The lesions themselves are typically painless, but there may be associated acral pain or paraesthesiae. Erythema chronicum migrans (Chapter 30) may have been present at the same site some years earlier. Extension to the trunk and the greater part of the body, including the face, is sometimes seen. Single or multiple lesions may be present. They slowly extend centrifugally, the active inflammatory stage persisting for months, years or even decades. Marginal extension may continue once the central areas have already entered the atrophic phase, in which the skin is smooth, hairless and tissue-paper-like, dull red, pigmented or poikilodermatous (Fig. 45.11).

Subcutaneous nodules may develop around the knees or elbows, and fibrous bands along the ulnar margin of the forearms. Gaiter-like sclerosis of the lower third of the legs, often accompanied by ulceration, is a further complication. Morphoea of the trunk and lichen sclerosus et atrophicus (both genital and extragenital) have also been reported as associated lesions [2,11], and it is interesting that *Borrelia* antibodies have been found in five of 10 patients with morphoea [12], although others have not confirmed this [13].



Fig. 45.11 Atrophic skin of the knee in acrodermatitis chronica atrophicans. (Courtesy of Dr T. Robinson, University College Hospital, London, UK.)

In some cases, involvement of the joint capsule or bone results in limitation of movement of the joints of the hands and feet, or of the shoulders.

Very rarely, squamous carcinoma has developed in the atrophic skin, and lymphoma has also been reported in the non-affected skin [14,15].

Other late syndromes of Lyme borreliosis (lymphocytoma, neurological, etc.) have been fully reviewed by Steere [1].

Diagnosis. The appearance of erythema chronicum migrans may be similar, but the evolution of the annular lesions establishes the differentiation. In the atrophic stage, diagnosis is usually readily made, and can be confirmed histologically.

Immunoblotting, using *B. afzelii* flagellar antigen (41 kDa) is confirmatory [5]. Serology is used to confirm the diagnosis of Lyme disease, but false-negative and false-positive results are common. In chronic atrophic acrodermatitis, however, the antibody titre is very high. Serology may be positive on enzyme-linked immunosorbent assay (ELISA) but negative on immunoblotting, particularly in patients with neurological disease [16]. A high titre of antibodies may reflect occult central nervous system involvement, when the antibodies can also be demonstrated in colony-stimulating factor [17].

When it occurs on the lower legs, the condition can mimic venous insufficiency [18], with thick, cyanotic, itchy skin.

Treatment. Oral antibiotics should be given for 1 month, for example doxycycline or amoxicillin in standard doses [1]. The improvement occurs gradually, several weeks after the course of treatment, but there may be no response if treatment is delayed until atrophy has developed. If the antibody titre is high, or there are clinical features of systemic disease (e.g. neuroborreliosis), intravenous penicillin G, ceftriaxone or cefotaxime should be given for 3 weeks [17]. There may be a case for chemoprophylaxis or even vaccine development in endemic areas [19].

References

1 Steere AC. Lyme disease. *N Engl J Med* 1989; **321**: 586–96.
2 Coulson IH. Acrodermatitis chronica atrophicans with coexisting morphoea. *Br J Dermatol* 1989; **121**: 263–9.
3 Aberer E, Kersten A, Klade H. Heterogeneity of *Borrelia burgdorferi* in the skin. *Am J Dermatopathol* 1996; **18**: 571–9.
4 Picken RN, Strle F, Picken MM. Identification of three species of *Borrelia burgdorferi sensu lato* among isolates from acrodermatitis chronica atrophicans lesions. *J Invest Dermatol* 1998; **110**: 211–4.
5 Flisiah I, Schwartz RA, Chodynicke B. Clinical features and specific immunological response against *Borrelia afzelii* in patients with acrodermatitis chronica atrophicans. *J Med* 1999; **30**: 267–78.
6 Boehmer-Andersson E, Hovmark A, Asbrink E. Acrodermatitis chronica atrophicans: histopathologic findings and clinical correlation in 111 cases. *Acta Derm Venereol* 1998; **78**: 207–13.
7 Asbrink E, Hovmark A. Successful cultivation of spirochaetes from the skin lesions of patients with erythema chronicum migrans and acrodermatitis chronicum atrophicans. *Acta Pathol Microbiol Immunol Scand (A)* 1985; **93**: 161–3.
8 Asbrink E, Hovmark A. Early and late cutaneous manifestations of *Ixodes* borne borreliosis (Lyme borreliosis). *Ann NY Acad Sci* 1988; **539**: 4–15.
9 Mullegger RR, McHugh G, Ruthazar R. Differential expression of cytokine mRNA in skin specimens from patients with erythema migrans or acrodermatitis chronica atrophicans. *J Invest Dermatol* 2000; **115**: 1115–23.
10 Burgdorf WHC, Worret W, Schultka O. Acrodermatitis chronica atrophicans. *Int J Dermatol* 1979; **18**: 595–601.

11 Ramelet AA. Association of acrodermatitis chronica atrophicans and morphoea. *Dermatologica* 1987; **175**: 253–6.
12 Aberer E, Neumann R, Stanek G. Is localised scleroderma a *Borrelia* infection? *Lancet* 1985; **ii**: 278.
13 Halkier-Sorensen L. Antibodies to the *Borrelia burgdorferi* in patients with scleroderma. *Acta Derm Venereol Suppl (Stockh)* 1989; **69**: 116–9.
14 Goos W, Schwarz-Speck M. Acrodermatitis chronica atrophicans. *Dermatologica* 1972; **145**: 287–90.
15 Garbe C, Stein H, Dienemann D, Orfanos CE. *Borrelia burgdorferi*-associated cutaneous B cell lymphoma. *J Am Acad Dermatol* 1991; **24**: 584–90.
16 Rees DHE, O'Connell S, Brown MM *et al.* The value of serological testing for Lyme disease in the UK. *Br J Rheumatol* 1995; **34**: 132–6.
17 Aberer E, Breier F, Stanek G. Success and failure in the treatment of acrodermatitis chronica atrophicans. *Infection* 1996; **24**: 85–7.
18 Fagrell B, Heiland RA, Howe TR. Acrodermatitis chronica atrophicans can mimic a peripheral vascular disorder. *Acta Med Scand* 1986; **20**: 485–8.
19 Stanek G, Strle F. Lyme borreliosis. *Lancet* 2003; **362**: 1639–47.

Local panatrophy

Definition and aetiology. Local panatrophy is a rare disorder involving partial or total loss of subcutaneous fat and atrophy of overlying skin, sometimes associated with atrophy or impaired growth of muscle or bone. A primary neurogenic disturbance has been postulated but not proved. The syndrome may represent the end result of more than one pathological process, but many cases may be due to a variant of morphoea.

The atrophic areas exhibit a reduced sympathetic response and aberrant production of non-esterified fatty acids after stimulation with norepinephrine (noradrenaline), and it has been suggested that there may be a primary abnormality of the sympathetic nervous system [1].

Two groups of cases can be differentiated:

1 **Panatrophy of Gower:** no scleroderma or other sclerotic process accompanies or follows the loss of subcutaneous tissue. Most cases have occurred in women, usually in the second to fourth decades.
2 **Sclerotic panatrophy:** either typical morphoea or similar sclerotic change in dermal collagen precedes the atrophy [2].

Clinical features of the two groups are as follows.

Panatrophy of Gower [3]. Sharply defined areas of atrophy, irregular in size, shape and distribution, develop over a period of a few weeks, without preceding inflammatory stages. In each affected area, the subcutaneous tissue disappears and the overlying skin appears atrophic but is otherwise normal. There may be a single area of atrophy or two or more. In size they range from 2 to 20 cm across, and in shape they are very variable but are sometimes triangular or quadrangular. Most lesions have occurred on the back, buttocks, thighs or upper arms, but some have involved forearms or lower legs. The atrophy reaches its maximum extent within a few months and then remains unchanged indefinitely.

Sclerotic panatrophy. Atrophy of the subcutis, and sometimes of underlying muscle and bone, may follow clinically and histologically typical morphoea, especially when the process begins in childhood and involves a limb (Chapter 51).

Sclerotic panatrophy may also occur in the absence of morphoea. The sclerosis involves subcutaneous tissue and muscle, and dense, sclerotic, scar-like, linear bands develop along a limb, or encircle the trunk in a metameric distribution, or encircle a limb. These lesions have also usually occurred in childhood. They cease to progress after a few months and, although new areas may be involved, most lesions have been solitary.

It is possible that Gower's panatrophy and linear morphoea are at the ends of a continuous disease spectrum. The histology of linear morphoea reveals thickened bundles of collagen, which appear to be intact on B-scan ultrasound imaging [4].

In the differential diagnosis of panatrophy, the various forms of panniculitis must be excluded. The preceding inflammatory changes are the single most distinctive feature, but they are not always easy to distinguish.

Facial hemiatrophy

Synonym
- Parry–Romberg syndrome

Definition and aetiology. Facial hemiatrophy is an atrophic dysplasia of the superficial facial tissues, but the underlying muscles, cartilage and bone may also be affected. The cause is unknown, but it may be a disorder of the sympathetic nervous system in some cases. Other cases have followed lupus panniculitis [5].

There is no evidence that it is usually genetically determined, but it appears to be hereditary in a few pedigrees. Some cases have been associated with syringomyelia, epilepsy or cerebrovascular disease, but in 90% of cases no such association is demonstrable. The sexes are equally affected.

Clinical features [6–8]. This rare disease usually starts within the first two decades. The first manifestation is usually increased or decreased pigmentation in irregular patches on cheeks, forehead or lower jaw. Occasionally, there may be premonitory muscle spasms or neuralgia. Progressive atrophy gradually develops in the affected sites, involving skin, subcutis, muscle and bone, and may extend in area—and sometimes in depth—for months or years with temporary remissions. The skin becomes dry, thin and atrophic, but may be scar-like and adherent in some areas. When the atrophy is fully developed, the contrast between the sunken, haggard, pigmented affected half of the face and the unaffected half is dramatic. The hair may be lost in the frontoparietal region on the affected side but is often normal; occasionally, localized canities is an early change. A variety of neurological signs have been reported, of which Horner's syndrome is the most frequent. Heterochromia of the iris has developed at the same time as the facial atrophy in about 5% of cases, and retinal changes may also be present [9]. There can be ipsilateral cerebral atrophy [10].

The atrophy may remain limited both in extent and depth. It may be confined to the distribution of one division of the trigeminal nerve or involve the whole of the side of the face, sharply demarcated at the midline. Rarely, it may be bilateral, and very rarely may involve half the body, usually on the same side as the face but exceptionally the opposite side—crossed hemiatrophy. The atrophy may, in such cases, begin on the trunk or a limb and only later involve the face.

The degree of bone atrophy as established radiologically is usually much less than the clinical appearance suggests, and is severe only in some cases of early onset. In such cases, the cerebral cortex may also be affected, and contralateral epilepsy may result.

Localized scleroderma of the 'coup de sabre' paramedian form may be associated with some degree of facial hemiatrophy, especially if it begins early in life. However, it is a more superficial process than progressive facial hemiatrophy. The skin in scleroderma is bound down and adherent, and loss of hair and pigmentary changes are conspicuous. In progressive facial hemiatrophy, the skin may remain mobile and grossly normal. The two processes have been confused frequently in the literature, and may coexist [11].

Diagnosis. When the cutaneous involvement is early and conspicuous, the diagnosis presents few difficulties. Hypoplasia following radiotherapy given in infancy, perhaps in treatment of a naevus in the region of the temporomandibular joint, could cause confusion. If the skin changes are slight, or of later onset, physiological asymmetry, unilateral mandibular agenesis, hemihypertrophy and atrophy secondary to facial paralysis must be excluded. Hemihypertrophy is always congenital. When the limbs are involved, infantile hemiplegia and lipodystrophy must also be considered.

Treatment. Plastic surgery using large, buried pediculated flaps of dermis and fat, or silicone implants, offers some cosmetic benefit [5,11–14].

References

1 Nakano R, Wakamatsu N, Tsujui S. Juvenile Sandhoff disease with local panatrophy. A case report. *Baillieres Clin Neurol* 1989; **29**: 1032–8.
2 Jablonska S, ed. *Scleroderma and Pseudoscleroderma*, 2nd edn. Warsaw: Polish Medical Publishers, 1975.
3 Barnes S. Gower's case of local panatrophy. *Br J Dermatol* 1939; **51**: 377–80.
4 Levy JJ, Gassmuller J, Anding H *et al.* Imaging subcutaneous atrophy in circumscribed scleroderma with 20 Mhz B-scan ultrasound. *Hautarzt* 1993; **44**: 446–51.
5 Moscona R, Bergman R, Friedman-Birnbaum R. Multiple dermal grafts for hemifacial atrophy caused by lupus panniculitis. *J Am Acad Dermatol* 1986; **14**: 840–3.
6 Bramley P, Forbes A. A case of progressive hemiatrophy presenting with spontaneous fractures of the lower jaw. *BMJ* 1960; **i**: 1476–8.
7 Ho KH. Hemifacial atrophy (Romberg's disease). *Br Dent J* 1971; **162**: 182–4.
8 Fry JA, Alvarellos A, Fink CW *et al.* Intracranial findings in progressive facial hemiatrophy. *J Rheumatol* 1992; **19**: 956–8.
9 Theodossiadis PG, Grigoropoulos VG, Emfietzoglou I *et al.* Parry–Romberg syndrome studied by optical coherence tomography. *Ophthalmic Surg Lasers Imaging* 2008; **39**: 78–80.
10 Chang S-E, Huh J, Choi J-H *et al.* Parry–Romberg syndrome with ipsilateral cerebral atrophy of neonatal onset. *Pediatr Dermatol* 1999; **16**: 487–8.
11 Handfield-Jones SE, Peachey RDG, Moss ACH *et al.* Ossification in linear morphoea with hemifacial atrophy—treatment by surgical excision. *Clin Exp Dermatol* 1988; **13**: 385–8.
12 Franz FP, Blocksma R, Brundage SR *et al.* Massive injection of liquid silicone for hemifacial atrophy. *Ann Plast Surg* 1988; **20**: 140–5.
13 Sakamoto T, Oku T, Takigawa M. Gower's local panatrophy. *Eur J Dermatol* 1998; **8**: 116–7.
14 Guerrerosantos JG, Guerrerosantos F, Orozco J. Classification and treatment of facial tissue atrophy in Parry-Romberg disease. *Aesthetic Plast Surg* 2007; **31**: 424–34.

Scleroatrophic syndrome of Huriez

This autosomal dominant congenital syndrome is discussed in more detail in Chapter 19. It comprises a triad of diffuse scleroatrophy of the hands, mild palmoplantar keratoderma and hypoplastic nail changes [1–4]. Scleroatrophy is accentuated on the palms and fingers, which are tapered as in sclerodactyly; however, Huriez syndrome is congenital, and Raynaud's phenomenon is absent. The acral hyperkeratosis is associated with dry skin, resulting in painful fissures in winter months. Nail changes include prominent lunulae, elongated cuticles, longitudinal and transverse ridging, increased longitudinal curvature [5] and V-shaped notches [6]. Squamous carcinoma may develop in the scleroatrophic skin, sometimes as early as the third or fourth decades of life [1,6]; fatal metastases may occur [7].

Histology shows marked orthokeratosis, acanthosis with a prominent granular cell layer, and mild fibrosis of the upper and mid-dermis. Elastic fibres are reduced. Epidermal Langerhans' cells are reduced in number, perhaps contributing to the risk of malignant change [6]. A gene has been identified which maps to chromosome 4q23 [7].

Patients should be followed throughout life, with early excision of suspected malignancies. Acitretin reduces the painful hyperkeratosis [8] and could reduce the incidence of skin cancer.

References

1 Huriez C, Agache P, Bombart M *et al.* Épithéliomes spinocellulaires sur atrophie cutanée congénitale dans deux familles à morbidité cancéreuse élevée. *Bull Soc Fr Dermatol Syphiligr* 1963; **70**: 24–8.
2 Huriez C, Agache P, Souillart F *et al.* Scléroatrophie familiale des extremités avec dégénérescences spinocellulaires multiples. *Bull Soc Fr Dermatol Syphiligr* 1963; **70**: 743–4.
3 Huriez C, Deminatti M, Agache P *et al.* Une Génodysplasie non encore individualisée; la génodermatose scléroatrophiante et kératodermique des extrémités fréquemment dégénérative. *Sem Hôp Paris* 1968; **44**: 481–8.
4 Downs AMR, Kennedy CTC. Scleroatrophic syndrome of Huriez in an infant. *Pediatr Dermatol* 1998; **15**: 207–9.
5 De Berker D, Kavanagh G. Distinctive nail changes in scleroatrophy of Huriez. *Br J Dermatol* 1993; **129** (Suppl. 42): 36 (Abstract).
6 Hamm H, Traupe H, Bröcker E-B *et al.* The scleroatrophic syndrome of Huriez: a cancer-prone genodermatosis. *Br J Dermatol* 1996; **134**: 512–8.
7 Lee YA, Stevens HP, Delaporte E *et al.* A gene for an autosomal scleroatrophic syndrome predisposing to skin cancer (Huriez syndrome) maps to chromosome 4q23. *Am J Hum Genet* 2000; **66**: 326–30.
8 Delaporte E, N'Guyen-Mailfer C, Janin A *et al.* Keratoderma with scleroatrophy of the extremities or sclerotylosis (Huriez syndrome): a reappraisal. *Br J Dermatol* 1995; **133**: 409–16.

Localized abdominal wall atrophy

Congenital cutis laxa (p. 45.14) may rarely be confined to an area such as the abdomen. There may be other associated defects, for example dysplasia of the abdominal muscles, deformity of the thorax or mediastinal hernia. This condition must be distinguished from centrifugal abdominal lipodystrophy (Chapter 46) and the prune belly syndrome, in which wrinkled abdominal skin due to underlying abdominal muscle deficiency is associated with malformation of the urogenital tract [1,2].

References

1 Orvis BR, Bottles K, Kogan BA. Testicular histology in the 'prune belly' syndrome. *J Urol* 1988; **139**: 335–7.

2 Pagon RA, Smith DW, Shepherd TH. Urethral obstruction malformation complex. A cause of abdominal muscle deficiency and the 'prune belly'. *J Pediatr* 1979; **94**: 900–6.

Poikiloderma

Poikiloderma is a descriptive term, often somewhat loosely applied. Atrophy, macular or reticulate pigmentation and telangiectasia are the essential features. Depigmentation, miliary lichenoid papules, fine scaling and small petechial haemorrhages are less constantly present.

Congenital poikiloderma

Poikiloderma may occur as an apparently primary abnormality in certain genetically determined syndromes, including the Rothmund–Thomson syndrome, dyskeratosis congenita (Chapter 15) and the Mendes da Costa syndrome (Chapter 19).

Several other syndromes have been described in which poikiloderma is a prominent feature [1].

Hereditary sclerosing poikiloderma of Weary [2]
This rare, autosomal dominant syndrome was described in a large black family. Generalized poikiloderma, which developed in early childhood, was accompanied by sclerosis of the palms and soles, and linear hyperkeratotic and sclerotic bands developed in the flexures of the arms and legs.

Kindler syndrome [3,4]
This is an autosomal recessive disorder characterized by acral blistering, which is usually present at birth, and early poikiloderma. The poikiloderma is progressive, resulting in thin, wrinkled skin without surface markings. Cutaneous atrophy is most pronounced on the hands and feet. Clinical overlap with epidermolysis bullosa and hereditary acrokeratotic poikiloderma may cause diagnostic confusion. Photosensitivity is common and, like other cutaneous features, tends to improve with time. However, recurrent acral blisters have been described in a 46-year-old Japanese male [5]. Kindler syndrome is caused by loss-of-function mutations in the *KIND1* gene, which encodes kindlin-1. This protein is involved in anchorage of the actin cytoskeleton to the extracellular matrix [6,7].

Hereditary acrokeratotic poikiloderma of Weary [1,8,9]. Weary described an autosomal dominant condition of vesicopustules of the hands and feet, which start at the age of 1–3 months and resolve in childhood. There is also a widespread eczema, and the gradual appearance of poikiloderma, which persists into adult life. Keratotic papules develop in childhood on the hands, feet, knees and elbows, and these also persist indefinitely. Mucosal involvement is frequent. Some cases do not fit clearly into either Weary's or Kindler's syndromes [10].

Diffuse and macular atrophic dermatosis [11]
This rare condition is characterized by the presence from birth of generalized poikilodermatous changes that give the appearance of prematurely sun-damaged skin. The facies, hair and skeleton are normal. Biopsy shows thinning of the epidermis, with large hyaline bodies in the superficial dermal collagen, and these stain positively with periodic acid–Schiff (PAS) and elastin stains. Electron microscopy shows that these globular structures consist of microfibrillar material, and the adjacent fibroblasts may be degenerative.

Degos–Touraine syndrome [12]
In this condition, incontinentia pigmenti is accompanied by poikiloderma of light-exposed areas, often with gastrointestinal symptoms. Both gastrointestinal and skin manifestations are said to disappear following treatment with diiodohydroxyquine. Small bullae on the extremities have been described, but the initial bullae appear on the face. Hyperpigmentation follows a chronic erythrodermatous phase.

Acquired poikiloderma

Poikiloderma may occur as a pattern of cutaneous response to injury by cold, heat or ionizing radiation [13]. So-called poikiloderma of Civatte (Chapter 58) is a similar reaction mediated by photosensitizing chemicals in cosmetics. Some inflammatory dermatoses, such as lichen planus, may also give rise to poikilodermatous changes.

Poikiloderma is also a feature of some inflammatory 'connective tissue' diseases, and is particularly characteristic of dermatomyositis. It is also seen in lupus erythematosus and rarely in systemic sclerosis. Poikiloderma occurs as a manifestation of some lymphomas, especially mycosis fungoides (Fig. 45.12).

References

1 Draznin MB, Esterly NB, Fretzin DF. Congenital poikiloderma with features of hereditary acrokeratotic poikiloderma. *Arch Dermatol* 1978; **114**: 1207–10.
2 Weary PE, Hsu YT, Richardson D. Hereditary sclerosing poikiloderma. Report of two families with an unusual and distinctive genodermatosis. *Arch Dermatol* 1969; **100**: 413–22.
3 Forman AB, Prendiville JS, Esterley NB *et al*. Kindler syndrome: report of two cases and review of the literature. *Pediatr Dermatol* 1989; **6**: 91–101.
4 Kindler T. Congenital poikiloderma with traumatic bulla formation and progressive cutaneous atrophy. *Br J Dermatol* 1954; **66**: 104–11.
5 Ban M, Hosoe H, Yamada T *et al*. Kindler's syndrome with recurrence of bullae in the fifth decade. *Br J Dermatol* 1996; **135**: 503–4.



Fig. 45.12 Poikiloderma in a prelymphomatous eruption. The patient eventually developed cutaneous T-cell lymphoma.

6 Siegel DH, Ashton GH, Penagos HG *et al*. Loss of kindlin-1 a human homolog of the *Caenorhabditis elegans* actin-extracellular-matrix linker protein UNC-112, causes Kindler syndrome. *Am J Hum Genet* 2003; **73**: 174–87.
7 Arita K, Wessagowit V, Inamadar AC *et al*. Unusual molecular findings in Kindler syndrome. *Br J Dermatol* 2007; **157**: 1252–6.
8 Weary PE, Manley WF, Graham GF. Hereditary acrokeratotic poikiloderma. *Arch Dermatol* 1971; **103**: 409–22.
9 Larrègue M, Prigent F, Lorette G *et al*. Acrokeratose poikilodermique bulleuse et hereditaire de Weary–Kindler. *Ann Dermatol Syphiligr (Paris)* 1981; **108**: 69–76.
10 Person JR, Perry HO. Congenital poikiloderma with traumatic bulla formation, anhidrosis and keratoderma. *Acta Derm Venereol Suppl (Stockh)* 1959; **59**: 347–51.
11 Kirby JD. The diffuse and macular atrophic dermatosis. *Clin Exp Dermatol* 1980; **5**: 57–60.
12 Degos R, Touraine R. Incontinentia pigmenti avec état poikilodermique. *Bull Soc Fr Dermatol Syphiligr* 1961; **68**: 6–10.
13 Okazaki M, Kikuchi I. Radiodermatitis. An analysis of 43 cases. *J Dermatol* 1986; **13**: 356–65.

Disorders of elastic fibres

The capacity of the skin to adapt to local or general changes in body size and contour, and to allow for movement of head and limbs and a wide range of facial expression, depends upon its tension, elasticity and tensile strength. These properties may be congenitally defective or modified by ageing or disease [1–3]. Acquired disorders of elastic tissue have been reviewed in detail by Lewis *et al*. [4,5].

Elasticity. Elastic fibres are abundant in the skin, arteries, lungs and ligaments. They provide tissues with resilience and elasticity (the ability to resume its original shape after deforming forces have ceased to act). There is wide individual variation, but a tendency to decrease with age. Several diseases, such as cutis laxa, decrease cutaneous elasticity. Elastic fibres also provide adhesion for cells and play a role in regulating growth factors' (e.g. transforming growth factor-β) availability [2].

Tensile strength. The tensile strength of the skin is the degree to which it can be elongated before it tears. It is greatest in infancy and decreases with age, but is also abnormally low in diseases associated with collagen defects such as EDS and Cushing's syndrome [3].

References
1 Grahame R. A method for measuring human skin elasticity *in vivo* with observations on the effects of age, sex and pregnancy. *Clin Sci* 1970; **39**: 223–9.
2 Kielty CM. Elastic fibres in health and disease. *Expert Rev Mol Med* 2006; **8**: 1–23.
3 Uitto J. Biochemistry of collagen in diseases. *Ann Intern Med* 1986; **105**: 740–56.
4 Lewis KG, Bercovitch L, Dill SW *et al*. Acquired disorders of elastic tissue: Part 1. Increased elastic tissue and solar elastotic syndromes. *J Am Acad Dermatol* 2004; **51**: 1–21.
5 Lewis KG, Bercovitch L, Dill SW *et al*. Acquired disorders of elastic tissue: Part II. Decreased elastic tissue. *J Am Acad Dermatol* 2004; **51**: 165–85.

Lax skin

Increased laxity of the skin due to ageing (accelerated by dermal photodegradation) is of course extremely common, but cutaneous laxity can occasionally be due to marked weight loss (especially after gross obesity) or can follow recovery from severe oedema. Less commonly, the skin may become lax due to localized or generalized defects in elastic tissue resulting from other causes, and these may be grouped as follows.

1 Generalized elastolysis (cutis laxa):
  (a) congenital
  (b) associated with other inherited disorders (PXE, SCARF syndrome (*s*keletal abnormalities, *c*utis laxa, *c*raniostenosis, *a*mbiguous genitalia, *r*etardation and *f*acial abnormalities), de Barsy syndrome, geroderma osteodysplastica)
  (c) acquired (numerous associated disorders, for example inflammatory skin disease, multiple myeloma, systemic lupus erythematosus, hypersensitivity reactions, complement deficiency, penicillamine therapy)
2 Localized elastolysis:
  (a) anetoderma
  (b) blepharochalasis
  (c) chronic atrophic acrodermatitis (due to *Borrelia*)
  (d) granulomatous slack skin (due to lymphoma)
  (e) other localized lesions, including mid-dermal elastolysis, post-inflammatory elastolysis and cutis laxa (PECL), elastic tissue naevi etc.

Generalized cutis laxa [1]

Synonyms
- Generalized elastolysis
- Generalized elastorrhexis
- Generalized dermatochalasis

Definition. Cutis laxa is characterized clinically by lax, pendulous skin and histologically by loss of elastic tissue in the dermis. It is a heterogeneous condition, with several causes and associations, and it may be inherited or acquired.

Aetiology. Cutis laxa may be *inherited*, either as an autosomal dominant or autosomal recessive trait [2]. Occipital horn syndrome was originally described as X-linked recessive cutis laxa and subsequently EDS type IX, but is now classified with Menkes' syndrome as a condition in which secondary changes in connective tissue are caused by abnormal copper metabolism [3–4] (p. 45.15 and Chapter 66).

Since the initial identification of mutations in the elastin gene in autosomal dominant cutis laxa [5,6] only a few similar families have been reported [7]. Abnormalities of the microfibrillary protein, fibulin-5, can also lead to autosomal dominant cutis laxa, indicating genetic heterogeneity [8]. Both fibulin-4 and some fibulin-5 mutations cause the more severe autosomal recessive phenotype [9,10]. Loss-of-function mutations in *ATP6V0A2*, encoding the α2 subunit of the V-type H^+ ATPase, have been identified in several families with autosomal recessive cutis laxa type II, resulting in abnormal glycosylation [11].

Cutis laxa may also be *acquired* following inflammatory skin disease [12], and it has occurred in babies born to women taking penicillamine [13]. An immunological pathogenesis has been suggested in some acquired cases because of the rare associations with drug hypersensitivity, complement deficiency, systemic lupus erythematosus, multiple myelomatosis and coeliac disease [14–18].

Amyloidosis seems to provoke cutis laxa in some cases [19], and it is known that amyloid can coat elastic fibres [20,21]. Cutis laxa may also accompany inherited disorders of connective tissue such as pseudoxanthoma elasticum and Ehlers–Danlos syndrome [22].

Pathology. The skin is of normal thickness, but the elastic fibres are sparse, short, fragmented and clumped, particularly in the upper dermis, and they show granular degeneration [23]. The elastic fibres are deficient in elastin, but their microfibrils appear normal [24,25]. Similar changes in elastic fibres may occur in the lungs and aorta.

Various ultrastructural changes have been described, including separation of the elastin microfibrils from the amorphous matrix, the presence of a 'wood-grain' pattern and aggregation, fragmentation and clumping of the elastic fibres [11,23,24].

Clinical features. In this rare condition, the skin becomes inelastic and hangs in redundant folds. The face and neck are often affected, which produces a 'bloodhound' appearance of premature ageing. The internal elastic tissues may also be affected, and emphysema and cardiovascular abnormalities occur in some types.

Hereditary forms [26] (Table 45.1)

Various clinical types have been described [27,28]. In the *autosomal dominant* form, the skin changes may develop at any age, but tend to present later than in the recessive form. Those presenting in adult life usually have no internal defects, and the life expectancy is normal [28]. When the condition presents in infancy there is intrauterine growth retardation, delayed fontanelle closure and ligamentous laxity [29]. The skin changes may be preceded by episodes of oedema, usually within the first 2 months of life, and the child may look aged by the end of the second year. Affected males may be impotent, with infantile genitalia and scanty body hair. Pulmonary emphysema due to a loss of elastic tissue in the lungs is common [2].

In the commoner, but more severe, *autosomal recessive* form there is a characteristic facies with downward slanting palpebral fissures, a broad flat nose, sagging cheeks and large ears. There are prominent skin folds around the knees, abdomen and thighs [28]. Herniae, diverticula, severe pulmonary emphysema and cor pulmonale are important complications. Death due to respiratory complications is common in the first few years of life. Dental caries, aortic aneurysm and osteoporosis may also occur.

The *de Barsey syndrome* is a rare type in which cutis laxa is accompanied by retarded psychomotor development and corneal clouding due to degeneration of the tunica elastica of the cornea [30–32]. Growth is retarded and there may be pseudoathetoid movements. Congenital cutis laxa has also been associated with SCARF syndrome [33], osteoporosis [34] and geroderma osteodysplastica, which is characterized by skeletal abnormalities, including joint hypermobility, Wormian bones and osteoporosis [35].

Although there are many similarities between the wrinkly skin syndrome and cutis laxa type II, the skin changes in the former are limited mainly to the abdomen, hands and feet. Facial dysmorphism is less pronounced in wrinkly skin syndrome and the large fontanelles have not been described [36].

Table 45.1 Cutis laxa syndromes.

Type	Molecular defect	Major clinical features
Autosomal dominant	*ELN*, *FBLN5*	Symptoms less severe than autosomal recessive types Onset usually childhood/early adult Cutis laxa, gastrointestinal diverticula, herniae, uterine prolapse, aortic dilatations
Autosomal recessive Type I	*FBLN4* and *FBLN5*	Cutis laxa, pulmonary emphysema, gastrointestinal and bladder diverticula, arterial aneurysms, pulmonary artery stenosis, herniae
Autosomal recessive Type II	Loss-of-function mutations *ATP6V0A2*	Cutis laxa, growth and developmental delay, skeletal abnormalities, large fontanelle with delayed closure, oxycephaly, herniae, hip dislocations
Autosomal recessive Type III (de Barsey syndrome)	Unknown	Cutis laxa, corneal opacities, mental retardation, pseudoathetoid movements
Other syndromes with cutis laxa		
X-linked (occipital horn syndrome)	*ATP7A* (allelic with Menkes syndrome)	Bladder diverticulae, inguinal hernias, slight skin laxity and hyperextensibility, joint laxity and coarse hair Skeletal abnormalities, including persistent open anterior fontanelle and occipital exostoses
SCARF syndrome	Unknown X-linked recessive	SCARF acronym: *s*keletal abnormalities, *c*utis laxa/craniostenosis, *a*mbiguous genitalia, *r*etardation, *f*acial abnormalities
Geroderma osteodysplastica	Unknown Autosomal recessive	Dwarfism with premature aged appearance, lax skin, osteoporosis, Wormian bones, mandibular prognathism, malar hypoplasia
Costello's syndrome	*HRAS*	Phenotypic overlap with cardiofaciocutaneous syndrome Characteristic coarse facies, short stature, cutis laxa particularly hands and feet, severe feeding difficulty and failure to thrive, cardiac anomalies, facial warts Often presents in childhood

Acquired forms [37]

Cutis laxa may rarely develop at any age following episodes of urticaria or angio-oedema, extensive inflammatory skin disease (such as systemic lupus erythematosus or erythema multiforme) or febrile illness. It may also follow hypersensitivity reactions such as penicillin allergy [14].

Cutis laxa has also been reported in association with complement deficiency, sarcoidosis, syphilis, multiple myeloma [15,17] and the Klippel–Trenaunay syndrome [24]. Focal elastolysis can also occur in association with lupus erythematosus [38], severe rheumatoid arthritis [39] and coeliac disease [18]. D-Penicillamine disrupts elastic fibre formation and may cause cutis laxa, elastosis perforans serpiginosa and pseudoxanthoma-like changes [40]. Congenital cutis laxa may also occur in offspring of mothers taking penicillamine [13].

There may be widespread, massive folds of lax skin, or the changes may be mild and confined to a limited area, in which case it cannot be distinguished from anetoderma. Purpura may follow slight trauma and fibrotic nodules may form over bony prominences. Organs other than the skin may also be involved. Emphysema, gastric fibromas and tracheobronchomegaly have been reported [41].

In acquired cutis laxa, dermal elastic tissue is markedly reduced, although collagen is normal. Fibroblasts express increased elastolytic activity (cathepsin G). Levels of serum α_1-antitrypsin and elastase inhibition are decreased [42].

Post-inflammatory elastolysis and cutis laxa also appears to develop as a distinctive syndrome in African children, with clinical features intermediate between anetoderma and cutis laxa [43] (p. 45.17). This condition might represent an unusual reaction to an arthropod bite, as the lesions are preceded by urticaria or multiple red papules, which slowly enlarge to form rings 2–10 cm in diameter.

Diagnosis. The diagnosis, which is suggested by finding loose skin that recoils only slowly after stretching, may be confirmed by histology.

In EDS, the skin is hyperextensible but not lax, and it recoils quickly. In PXE, the skin may be lax, but it is yellowish and the face is usually spared. It is distinguished histologically by the presence of calcification. There may be circumscribed folds of lax skin in neurofibromatosis, and loose folded skin may also occur in leprechaunism, Patterson syndrome and trisomy 18, but these conditions are distinguished by their associated features.

In Costello's syndrome there is skin laxity, especially on hands and feet, with joint hyperextensibility, but the elastin fibres are normal under both light and electron microscopy [44]. The other features of this rare syndrome include poor postnatal growth, developmental delay and a distinctive facies with macroglossia, bilateral ptosis, epicanthic folds and posterior rotation of the pinnae, with prominent helices and thickened lobes.

In severe actinic damage, there may be marked skin laxity due to damage to elastic fibres.

Treatment. Plastic surgery ('face-lift') may reduce the cosmetic disability. Investigations for emphysema are indicated, with referral to a pulmonary physician if necessary.

References

1 Goltz RH, Hult AM, Goldfarb M *et al.* Cutis laxa: a manifestation of generalized elastolysis. *Arch Dermatol* 1965; **92**: 373–87.

2 Agha A, Sakati NO, Higginbottom MC *et al.* Two forms of cutis laxa presenting in the newborn. *Acta Paediatr Scand* 1978; **67**: 775–80.

3 Byers PH, Siegel RC, Holbrook K *et al.* X-linked cutis laxa: defective cross-link formation in collagen. *N Engl J Med* 1980; **303**: 61–5.

4 Beighton P, de Paepe A, Hall JG *et al.* Molecular nosology of heritable disorders of connective tissue. *Am J Med Genet* 1992; **42**: 431–8.

5 Tassabehji M, Metcalfe K, Hurst J *et al.* An elastin gene mutation producing abnormal tropoelastin and abnormal elastic fibres in a patient with autosomal dominant cutis laxa. *Hum Mol Genet* 1998; **7**: 1021–8.

6 Zhang MC, He L, Giro M *et al.* Cutis laxa arising from frameshift mutations in exon 30 of the elastin gene (*ELN*). *J Biol Chem* 1999; **274**: 981–6.

7 Rodriguez-Revenga L, Iranzo P, Badenas C *et al.* A novel elastin gene mutation resulting in an autosomal dominant form of cutis laxa. *Arch Dermatol* 2004; **140**: 1135–9.

8 Markova D, Zou Y, Rinpfeil F *et al.* Genetic heterogeneity of cutis laxa: a heterozygous tandem duplication within the fibulin-5 (FBLN5) gene. *Am J Hum Genet* 2003; **72**: 998–1004.

9 Loeys B, Van Maldergem L, Mortier G *et al.* Homozygosity for a missense mutation in fibulin-5 (*FBLN5*) results in a severe form of cutis laxa. *Hum Mol Genet* 2002; **11**: 2113–8.

10 Hucthagowder V, Sausgruber N, Kim KH *et al.* Fibulin-4: a novel gene for an autosomal recessive cutis laxa syndrome. *Am J Hum Genet* 2006; **78**: 1075–80.

11 Kornak U, Reynders E, Dimopoulou A *et al.* Impaired glycosylation and cutis laxa caused by mutations in the vesicular H+-ATPase subunit ATP6V0A2. *Nat Genet* 2008; **40**: 32–4.

12 Nanko H, Jepson LV, Zachariae H *et al.* Acquired cutis laxa (generalised elastolysis): light and electron microscopic studies. *Acta Derm Venereol Suppl (Stockh)* 1979; **59**: 315–24.

13 Harpey J-P. Cutis laxa and low serum zinc after antenatal exposure to penicillamine. *Lancet* 1983; **ii**: 858–9.

14 Kerl H, Burg G. Fatal penicillin-induced generalized post-inflammatory elastolysis (cutis laxa). *Hautarzt* 1975; **26**: 191–8.

15 Tsuji T, Imajo Y, Sawabe M *et al.* Acquired cutis laxa concomitant with nephrotic syndrome. *Arch Dermatol* 1987; **123**: 1211–6.

16 Scott MA, Kauh YC, Luscombe HA. Acquired cutis laxa associated with multiple myelomatosis. *Arch Dermatol* 1976; **112**: 853–5.

17 Ting HC, Foo MH, Wang F. Acquired cutis laxa and multiple myelomatosis. *Br J Dermatol* 1984; **110**: 363–7.

18 García-Patos V, Pujol RM, Barnadas MA *et al.* Generalized acquired cutis laxa associated with coeliac disease: evidence of immunoglobulin A deposits on the dermal elastic fibres. *Br J Dermatol* 1996; **135**: 130–4.

19 Newton JA, McKee PH, Black MM. Cutis laxa associated with amyloidosis. *Clin Exp Dermatol* 1986; **11**: 87–91.

20 Winkelmann RK, Peters MS, Venencie PY. Amyloid elastosis. A new cutaneous and systemic pattern of amyloidosis. *Arch Dermatol* 1985; **121**: 498–502.

21 Yanagihara M, Kato F, Shikano Y. Intimate structural association of amyloid and elastic fibres in systemic and cutaneous amyloidoses. *J Cutan Pathol* 1985; **12**: 110–6.

22 Ostlere LS, Pope FM, Holden CA. Cutis laxa complicating Ehlers–Danlos syndrome type II. *Clin Exp Dermatol* 1996; **21**: 135–7.

23 Hashimoto K, Kanzaki T. Cutis laxa: ultrastructural and biochemical studies. *Arch Dermatol* 1975; **111**: 861–73.

24 Marchase P, Holbrook K, Pinnell SR. A familial cutis laxa syndrome with ultrastructural abnormalities of collagen and elastin. *J Invest Dermatol* 1980; **75**: 399–403.

25 Sephel GC, Byers PH, Holbrook KA *et al.* Heterogeneity of elastin expression in cutis laxa fibroblast strains. *J Invest Dermatol* 1989; **93**: 147–53.

26 Pope FM. Cutis laxa. In: Beighton P, ed. *McKusick's Heritable Disorders of Connective Tissue*, 5th edn. St Louis: Mosby, 1993: 253–79.

27 Fitzsimmons JS, Gilbert G. Variable clinical presentations of cutis laxa. *Clin Genet* 1985; **28**: 284–95.

28 Patton MA, Tolmie J, Ruthnum P *et al.* Congenital cutis laxa with retardation of growth and development. *J Med Genet* 1987; **24**: 556–61.

29 Gardner LI, Sanders-Fay K, Bifano EM *et al.* Congenital cutis laxa syndrome: relation of joint dislocations to oligohydramnios. *Arch Dermatol* 1987; **122**: 1241–3.

30 De Barsey AM. Dwarfism, oligophrenia and degeneration of the elastic tissue in skin and cornea. *Helv Paediatr Acta* 1968; **23**: 305–13.
31 Kunze J. De Barsey syndrome. *Eur J Pediatr* 1985; **144**: 348–54.
32 Pontz BF, Zepp F, Stöss H. Biochemical, morphological and immunological findings in a patient with a cutis laxa-associated inborn disorder (de Barsey syndrome). *Eur J Pediatr* 1986; **145**: 428–34.
33 Koppe R, Kaplan P, Hunter A, MacMurray B. Ambiguous genitalia associated with skeletal abnormalities, cutis laxa, craniostenosis, psychomotor retardation and facial abnormalities (SCARF syndrome). *Am J Med Genet* 1989; **34**: 305–12.
34 Sakati NO, Nyhan WL. Congenital cutis laxa and osteoporosis. *Am J Dis Child* 1983; **137**: 452–4.
35 Lisker R, Hernandez A, Martinez-Lavin M *et al.* Gerodermia osteodysplastica hereditaria: report of three affected brothers and literature review. *Am J Med Genet* 1979; **3**: 389–95.
36 Gupta N, Phadke SR. Cutis laxa type II and wrinkly skin syndrome: distinct phenotypes. *Pediatr Dermatol* 2006; **23**: 225–30.
37 Reed WB, Horowitz RE, Beighton P. Acquired cutis laxa. Primary generalized elastolysis. *Arch Dermatol* 1971; **103**: 661–9.
38 Randle EHW, Muller S. Generalised elastolysis associated with systemic lupus erythematosus. *J Am Acad Dermatol* 1983; **8**: 869–73.
39 Rongioletti F, Cutolo M, Bondavalli P, Rebora A. Acral localized acquired cutis laxa associated with rheumatoid arthritis. *J Am Acad Dermatol* 2002; **46**: 128–30.
40 Hill VA, Seymour CA, Mortimer PS. Penicillamine-induced elastosis perforans serpiginosa and cutis laxa in Wilson's disease. *Br J Dermatol* 2000; **142**: 560–1.
41 Wanderer AA, Ellis EF, Goltz RW *et al.* Tracheobronchomegaly and acquired cutis laxa in a child. *Pediatrics* 1969; **44**: 709–15.
42 Fornieri C, Quaglino D, Lungarella G *et al.* Elastin production and degradation in cutis laxa acquisita. *J Invest Dermatol* 1994; **103**: 583–8.
43 Verhagen AR, Woerdemann MJ. Post-inflammatory elastolysis and cutis laxa. *Br J Dermatol* 1975; **92**: 183–90.
44 Costello JM. A new syndrome. *NZ Med J* 1971; **74**: 397–40.

Anetoderma

Synonym
- Macular atrophy

Definition and nomenclature. The term anetoderma (*anetos* = slack) refers to a circumscribed area of slack skin associated with a loss of dermal substance on palpation and a loss of elastic tissue on histological examination.

'Primary' anetoderma implies that there is no associated, localized, underlying cutaneous disease, whereas 'secondary' anetoderma can be attributed to some associated condition.

In the past, cases of primary anetoderma were divided into the *Jadassohn–Pellizari* type, in which the lesions are preceded by erythema or urticaria, and the *Schweninger–Buzzi* type, in which there are no preceding inflammatory lesions. This is now of historical interest only, because in the same patient some lesions may be preceded by inflammation and others may not, and the prognosis and histology are identical in the two types [1–3].

Primary anetoderma

Aetiology. In a few cases there appears to be an underlying structural defect of connective tissue. Familial cases are reported [4,5] and there is an association with inherited bony or ocular abnormalities. The Blegvad–Haxthausen syndrome comprises anetoderma, blue sclerae and osteogenesis imperfecta (OI) (p. 45.14).

Recently, it has become apparent that 'primary' anetoderma is strongly associated with antiphospholipid antibodies, with or without a prothrombotic state [6,7]. It is probable that these antibodies underlie the association historically noted with syphilis, and more recently with borreliosis [8] and systemic lupus.

The histology of anetoderma suggests that the basic abnormality is focal elastolysis [1,9,10]. This may be secondary to the release of elastase from the inflammatory cells, which are probably always present in the early stages. Metalloproteinases are increased in lesional skin [11].

Complement activation may be involved, as C3 is deposited on the remaining elastic fibres [12]. It has been suggested that decay-accelerating factor (DAF) and vitronectin (an inhibitor of the membrane-attack complex) may protect elastic fibres against this type of damage [13]. Abnormalities in the protective system could play a role in primary anetoderma.

Secondary anetoderma

This arises in association with another identifiable disease, but the atrophic areas do not always develop at the sites of the known inflammatory lesions. They are soft, round or oval areas which occur mainly on the trunk.

Lupus erythematosus. Anetoderma has occurred in association with systemic or chronic discoid lupus erythematosus, not always in relation to the lesions. Biopsy shows a focal loss of elastic tissue, and a perivascular infiltrate with prominent plasma cells [1,2]. Generalized elastolysis (cutis laxa) has also occurred [14]. Anetoderma is also associated with lupus profundus [15,16] and discoid lupus with hereditary complement (C2) deficiency [17].

Some cases of primary anetoderma have direct immunofluorescent findings similar to those of either chronic cutaneous or systemic lupus erythematosus, even though there may be no other features of lupus erythematosus [18,19].

No antibodies have been demonstrated against elastic fibres [19].

Other diseases [2]. Some of the other reported associations may be coincidental, but it is probable that many inflammatory diseases may occasionally be complicated by anetoderma. It has been reported in association with tuberculosis and leprosy [20], urticaria pigmentosa [21], pityriasis versicolor [22], granuloma annulare [23], and B- and T-cell lymphoma [24–26]. Localized anetoderma-like changes on histology have been reported in association with pilomatricoma [27], dermatofibroma [28], juvenile xanthogranuloma [29] and hamartomatous congenital naevi [30]. Penicillamine-induced anetoderma has also been reported [31].

Localized anetoderma may occur in premature infants, possibly due to the application of transcutaneous oxygen monitoring devices [32,33].

Lesions resembling anetoderma occur in post-inflammatory elastolysis and cutis laxa (p. 45.14).

Pathology [2,8]. During the early stages, the dermis is oedematous, and a lymphocytic infiltrate (predominantly helper T cells) surrounds the blood vessels and appendages [1,10]. Plasma cells and histiocytes, with some granuloma formation, may also be seen. Later, the oedema and perivascular infiltrate subside and elastic fibres become scanty. The persistence of fine, irregular or twisted elastic fibres is common. The dermal collagen may also be

diminished, but the fragmentation and disappearance of elastic tissue is the essential change, beginning superficially in the subpapillary zone and extending downwards. Electron microscopy shows phagocytosis of elastic fibres by macrophages [34,35].

Clinical features [2]. This rare disorder occurs mainly in women aged 20–40 years, but is occasionally reported in younger and older patients of both sexes. It is perhaps more frequent in central Europe than elsewhere, which suggests a possible relationship to chronic atrophic acrodermatitis (due to *Borrelia* sp.) in some cases. In the most usual form, crops of round or oval, pink macules 0.5–1.0 cm in diameter develop on the trunk, thighs and upper arms, less commonly on the neck and face and rarely elsewhere. The scalp, palms and soles are usually spared. Each macule extends for a week or two to reach a size of 2–3 cm. Sometimes, there are larger plaques of erythema, and nodules have also been reported as a primary lesion [36]. Slowly, each lesion fades and flattens from the centre outwards to leave a macule of wrinkled, atrophic skin, which yields on pressure, admitting the finger through the surrounding ring of normal skin (Fig. 45.13). The colour varies from skin colour to grey, white or blue. The number of lesions varies widely, from less than five to 100 or more. The lesions remain unchanged throughout life, and new lesions often continue to develop for many years. If the lesions coalesce they form large atrophic areas, which are indistinguishable from acquired cutis laxa [2].

In some cases, the lesions are initially urticarial weals which, after a succession of exacerbations and remissions, perhaps continuing for many weeks, are succeeded by atrophy. They may become confluent, to cover large areas, especially at the roots of the limbs and on the neck.

Diagnosis. The white cicatricial lesions of 'white spot disease' (extragenital lichen sclerosus) (Chapter 51) around the base of the neck and shoulders should not be confused with anetoderma.

Histological examination establishes the diagnosis. Focal dermal hypoplasia and atrophic scars (e.g. following varicella) must also be considered.

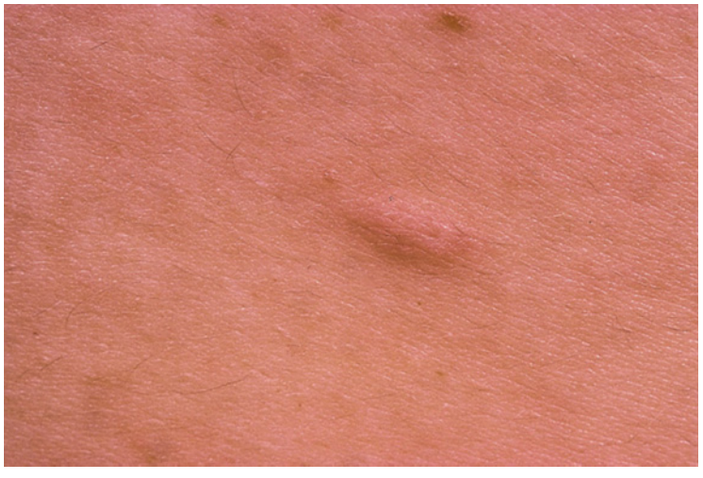


Fig. 45.13 Primary anetoderma. (Courtesy of Dr J. Ellis, Swindon, UK.)

Acquired cutis laxa is probably a variant of anetoderma.

The diagnosis of 'primary' anetoderma can be established only by excluding the presence of any of the diseases known to be associated with 'secondary' atrophy, for example perifollicular elastolysis (p. 45.20).

Treatment. Penicillin and the antifibrinolytic drug ε-aminocaproic acid have been advocated [37], but Venencie *et al.* [2] studied 16 patients and found no treatment was beneficial once the atrophy had developed. Colchicine may prevent some atrophic changes [38]. In patients with primary anetoderma it is important to test for antiphospholipid syndrome and treat appropriately, for example with aspirin.

References

1 Venencie PY, Winkelmann RK. Histopathologic findings in anetoderma. *Arch Dermatol* 1984; **120**: 1040–4.
2 Venencie PY, Winkelmann RK, Moore BA. Anetoderma: clinical findings, associations, and long term follow-up evaluations. *Arch Dermatol* 1984; **120**: 1032–9.
3 Karrer S, Szeimies RM, Stoltz W, Landthaler M. Primary anetoderma in children: report of two cases and literature review. *Pediatr Dermatol* 1996; **13**: 382–5.
4 Peterman A, Scheel M, Sams WM Jr *et al.* Hereditary anetoderma. *J Am Acad Dermatol* 1996; **35**: 999–1000.
5 Zellman GL, Levy ML. Congenital anetoderma in twins. *J Am Acad Dermatol* 1997; **36**: 483–5.
6 Sparsa A, Piette JC, Wechsler B *et al.* Anetoderma and its prothrombotic abnormalities. *J Am Acad Dermatol* 2003; **49**: 1008–12.
7 Hodak E, David M. Primary anetoderma and antiphospholipid antibodies – review of the literature. *Clin Rev Allergy Immunol* 2007; **32**: 162–9.
8 Hofer T, Golderberger D, Itin PH. Anetoderma and borreliosis: is there a pathogenic relationship? *Eur J Dermatol* 2003; **13**: 399–401.
9 Venencie PY, Winkelmann RK, Moore BA. Ultrastructural findings in the skin lesions of patients with anetoderma. *Acta Derm Venereol Suppl (Stockh)* 1984; **64**: 112–20.
10 Venencie PY, Winkelmann RK. Monoclonal antibody studies in the skin lesions of patients with anetoderma. *Arch Dermatol* 1985; **121**: 747–9.
11 Ghomrasseni S, Dridi M, Gogly B *et al.* Anetoderma: an altered balance between metalloproteinases and tissue inhibitors of metalloproteinases. *Am J Dermatopathol* 2002; **24**: 118–29.
12 Kossard S, Kronman KR, Dicken CH *et al.* Inflammatory macular atrophy. Immunofluorescence and ultrastructural findings. *J Am Acad Dermatol* 1979; **1**: 325–34.
13 Werth VP. Decay-accelerating factor in human skin is associated with elastic fibers. *J Invest Dermatol* 1988; **91**: 511–6.
14 Randle HW, Muller S. Generalized elastolysis associated with systemic lupus erythematosus. *J Am Acad Dermatol* 1983; **8**: 869–73.
15 Ryll-Nardzewski C. Remarques sur le lupus érythémate profond et sur l'anetodermie érythématoide. *Ann Dermatol Syphiligr (Paris)* 1960; **87**: 627–36.
16 Schnitzler L, Sayag J. Pseudotumoral lupus anetoderma and infantile chorea. *Ann Dermatol Vénéréol* 1988; **115**: 679–85.
17 De Bracco MM, Bianchi CA, Bianchi O *et al.* Hereditary complement (C2) deficiency with discoid lupus erythematosus and idiopathic anetoderma. *Int J Dermatol* 1979; **18**: 713–5.
18 Bergman R, Friedman-Birnbaum R. An immunofluorescence study of primary anetoderma. *Clin Exp Dermatol* 1990; **15**: 124–30.
19 Hodak E, Shamai-Lubovitz O, David M *et al.* Primary anetoderma associated with a wide-spectrum of autoimmune abnormalities. *J Am Acad Dermatol* 1991; **25**: 415–8.
20 Inemadar AC, Palit A, Athanikar SB *et al.* Generalised anetoderma in a patient with HIV and dual mycobacterial infection. *Lepr Rev* 2003; **74**: 275–8.
21 Kalogeramitros D, Gregoriou S, Makris M *et al.* Secondary anetoderma associated with mastocytosis. *Int Arch Allergy Immunol* 2007; **142**: 86–8.
22 Tatnall F, Rycroft R. Pityriasis versicolor with cutaneous atrophy. *Clin Exp Dermatol* 1985; **10**: 258–61.

23 Ozkan S, Fetil E, Izler F *et al.* Anetoderma secondary to generalized granuloma annulare. *J Am Acad Dermatol* 2000; **42**: 335–8.
24 Jubert C, Cosnes A, Clerici T *et al.* Sjögren's syndrome and cutaneous B cell lymphoma revealed by anetoderma. *Arthritis Rheum* 1993; **36**: 133–4.
25 Sequrado M, Guerra-Tapia A, Zarco C *et al.* Anetoderma secondary to cutaneous B-cell lymphoma. *Clin Exp Dermatol* 2006; **31**: 130–1.
26 Requena L, González-Guerra E, Angulo J *et al.* Anetodermic mycosis fungoides; a new clinicopathological variant of mycosis fungoides. *Br J Dermatol* 2008: **158**: 157–62.
27 Shames BS, Nassif A, Bailey CS *et al.* Secondary anetoderma involving a pilomatrixoma. *Am J Dermatopathol* 1994; **16**: 557–60.
28 Page EH, Assaad M. Atrophic dermatofibroma and dermatofibrosarcoma protuberans. *J Am Acad Dermatol* 1987; **17**: 947–50.
29 Gamo R, Ortiz-Romero P, Sopeno J *et al.* Anetoderma developing in juvenile xanthogranuloma. *Int J Dermatol* 2005; **44**: 503–6.
30 Cockayne SE, Gawkrodger DJ. Hamartomatous congenital naevi showing secondary anetoderma-like changes. *J Am Acad Dermatol* 1998; **39**: 843–5.
31 Davis W. Wilson's disease and penicillamine-induced anetoderma. *Arch Dermatol* 1977; **113**: 976–7.
32 Prizant TL, Lucky AW, Frieden IJ *et al.* Spontaneous atrophic patches in extremely premature infants. Anetoderma of prematurity. *Arch Dermatol* 1996; **132**: 671–4.
33 Cartlidge PH, Fox PE, Rutter N. The scars of newborn intensive care. *Early Hum Dev* 1990; **21**: 1–10.
34 Oikarinen AK, Palatsi R, Adomian GE *et al.* Anetoderma: biochemical and ultrastructural demonstration of an elastin defect in the skin of three patients. *J Am Acad Dermatol* 1984; **11**: 64–72.
35 Zaki I, Scerri C, Nelson H. Primary anetoderma: phagocytosis of elastic fibres by macrophages. *Clin Exp Dermatol* 1994; **19**: 388–90.
36 Indianer L. Anetoderma of Jadassohn. *Arch Dermatol* 1970; **102**: 697–8.
37 Reiss F, Linn E. The therapeutic effect of ε-aminocaproic acid on anetoderma of Jadassohn. *Dermatologica* 1973; **146**: 357–60.
38 Braun RP, Borradori L, Chavaz P *et al.* Treatment of primary anetoderma with colchicine. *J Am Acad Dermatol* 1998; **38**: 1002–3.

Other localized forms of elastolysis

Idiopathic mid-dermal elastolysis

Several cases have been described in which idiopathic loss of the elastic fibres in the mid-dermis has led to widespread wrinkling of the crinkle type in an otherwise healthy, young or middle-aged woman (Fig. 45.14) [1,2]. The exact relationship between this condition and other elastolytic disorders, such as acquired cutis laxa (p. 45.16) and anetoderma (p. 45.17), is uncertain.

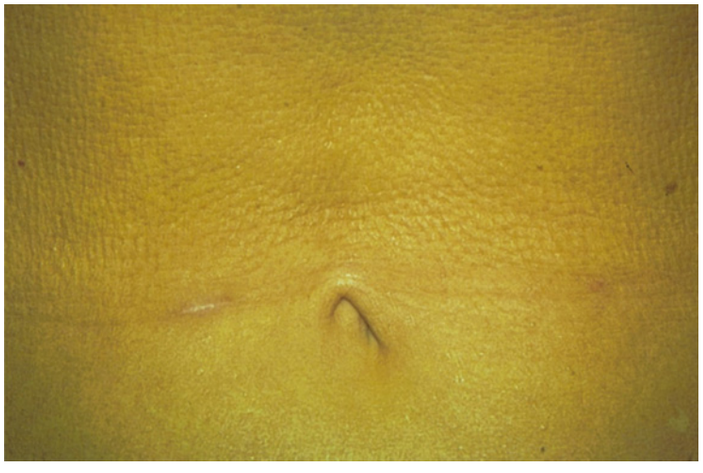


Fig. 45.14 Idiopathic mid-dermal elastolysis. (Courtesy of Dr L. Ostlere, St George's Hospital, London, UK.)

Maghraoui *et al.* [3] have distinguished post-inflammatory elastolysis, with or without features of cutis laxa, from non-inflammatory elastolysis. Inflammatory triggers may include UV radiation, insect bites, borreliosis and acute neutrophilic dermatosis [4]. Localized elastolysis adjacent to varicose veins has also been reported [5].

Ultrastructural studies of mid-dermal elastolysis demonstrate elastic fibres engulfed by macrophages [6]. Immunological studies of affected skin show a non-specific profile of immune activation [7]. Localized areas may clinically resemble PXE, although they are histologically distinct [8,9]. Cultured fibroblasts from lesional dermis exhibit increased elastolytic activity and reduced elastin mRNA compared with normal skin [10].

The histology of idiopathic mid-dermal elastolysis is similar to that of post-inflammatory elastolysis and cutis laxa (PECL), which occurs in young African girls (see below). Those lesions are preceded by inflammatory lesions, but the lesions of idiopathic mid-dermal elastolysis may also occasionally be preceded by erythema, urticaria or a burning sensation, and the two conditions are similar, if not identical.

No definite treatment exists but topical retinoic acid (0.01% gel) produced some cosmetic improvement in one patient [7].

References

1 Brenner W, Schmint FG, Konrad K *et al.* Non-inflammatory dermal elastolysis. *Br J Dermatol* 1978; **99**: 335–8.
2 Rae V, Falanga V. Wrinkling due to mid-dermal elastolysis. *Arch Dermatol* 1989; **125**: 950–1.
3 Maghraoui G, Grossin M, Crickx B *et al.* L'elastolyse acquise du derme moyen. *Ann Dermatol Vénéréol* 1994; **121**: 259–65.
4 Lewis KG, Dill SW, Wilkel CS *et al.* Mid-dermal elastolysis preceded by acute neutrophilic dermatosis. *J Cutan Pathol* 2004; **31**: 72–6.
5 Bayle-Lebey P, Periole B, Daste G *et al.* Acquired localized elastolysis associated with varicose veins. *Clin Exp Dermatol* 1995; **20**: 492–5.
6 Harmon CB, Su WPD, Gagne EJ *et al.* Ultra-structural evaluation of mid-dermal elastolysis. *J Cutan Pathol* 1994; **21**: 233–8.
7 Sterling JC, Coleman N, Pye RJ. Mid-dermal elastolysis. *Br J Dermatol* 1994; **130**: 502–6.
8 El-Charif M, Mousani AM, Rubeiz NG *et al.* Pseudoxanthoma elasticum-like papillary dermal elastolysis: a report of two cases. *J Cutan Pathol* 1994; **21**: 252–5.
9 Rongioletti F, Rebora A. Pseudoxanthoma elasticum-like papillary dermal elastolysis. *J Am Acad Dermatol* 1992; **26**: 648–50.
10 Tajima S, Imazumi T, Kojiya H *et al.* Elastin metabolism in skin fibroblasts explanted from a patient with mid-dermal elastolysis. *Br J Dermatol* 1999; **140**: 752–4.

Upper dermal elastolysis

Selective loss of elastic tissue in the papillary dermis has been described in an otherwise healthy 86-year-old woman, who presented with numerous yellowish papules on the neck and upper trunk, and associated coarse wrinkles [1].

Reference

1 Hashimoto K, Tye MJ. Upper dermal elastolysis: a comparative study with mid-dermal elastolysis. *J Cutan Pathol* 1994; **21**: 533–40.

Post-inflammatory elastolysis and cutis laxa

PECL is a distinctive severe variant of anetoderma (p. 45.17), which occurs predominantly in black girls living in a tropical climate [1–3]. It has a prolonged course, with relapsing inflammatory

phases lasting for months or years. In the acute phase, there are firm, infiltrated plaques or rings, with a collarette of scale, and these progress to leave a diffuse, fine, wrinkled skin with the appearance of premature ageing. In some cases, most of the body surface may be involved. There is no internal involvement, and no preceding infection, such as syphilis or tuberculosis. Histological examination shows destruction of the elastic fibres in the upper and mid-dermis.

It is thought that PECL is a reaction to arthropod bites because some patients have eosinophilia, other family members may suffer from papular urticaria, the lesions show a predilection for exposed parts and no new lesions develop when the patient is in hospital. There is a resemblance to erythema chronicum migrans (Chapter 30).

References

1 O'Brien JP. Is actinic damage the provoking cause of postinflammatory elastolysis and cutis laxa? *Br J Dermatol* 1976; **95**: 105–6.
2 Lewis PG, Hood AF, Barnett NF. Post-inflammatory elastolysis and cutis laxa. *J Am Acad Dermatol* 1990; **22**: 40–8.
3 Verhagen AR, Woerdemann MJ. Post-inflammatory elastolysis and cutis laxa. *Br J Dermatol* 1975; **92**: 183–90.

Perifollicular elastolysis

Anetoderma-like changes in a perifollicular distribution have been described in three women aged 30–40 years [1]. The lesions were small, grey–white, finely wrinkled, round or oval areas, each with a central hair follicle. Some exhibited a balloon-like bulge above the surface. They occurred on the upper trunk, neck, earlobes and arms. Histology showed a non-inflammatory perifollicular loss of elastin fibres, and it was suggested that the lesions might have been caused by an elastase-producing strain of *Staphylococcus epidermidis* [2]. Similar changes are more commonly seen in acne scars (Chapter 42) [3].

References

1 Varadi DP, Saqueton AC. Perifollicular elastolysis. *Br J Dermatol* 1970; **83**: 143–50.
2 Dick GF. Elastolytic activity of *P. acnes* and *Staph. epidermidis* in acne and normal skin. *Acta Derm Venereol Suppl (Stockh)* 1976; **56**: 279–82.
3 Wilson BB, Dent CH, Cooper PH. Papular acne scars. A common cutaneous finding. *Arch Dermatol* 1990; **126**: 797–800.

Granulomatous slack skin

Granulomatous slack skin is a rare disease characterized by the slow development of pendulous folds of lax erythematous skin, which on histological examination contains a dense granulomatous dermal infiltrate, with destruction of dermal elastic tissue. It is now considered to be a type of lymphoma (Chapter 57).

Blepharochalasis [1–3]

Definition. Laxity of the eyelid skin due to a defect in the elastic tissue.

Aetiology. The cause is unknown. Most cases are sporadic, but some pedigrees show autosomal dominant inheritance. Some cases may be a localized form of post-inflammatory elastolysis or follow angio-oedema [4].



Fig. 45.15 Blepharochalasis. (Courtesy of Dr D.A. Burns, Leicester Royal Infirmary, Leicester, UK.)

Pathology [3]. In the early stages there may be a mild dermal lymphocytic infiltrate, and in the later stages the elastic fibres in the lids fragment and decrease. Normal elastin gene expression suggests other factors may be involved in elastic fibre loss [5]. IgA deposition may be detected on fibres, implying an immunopathogenic mechanism may be involved [6]. Disintegration of collagen fibres has also been observed in one case [7].

Clinical features. Blepharochalasis is an uncommon condition that usually develops insidiously around the time of puberty. Repeated, transient attacks of painless swelling of the eyelids lasting for 2 or 3 days are followed by laxity, atrophy, wrinkling and pigmentation, predominantly of the upper eyelids (Fig. 45.15). There may be multiple telangiectases. These changes produce an appearance of tiredness, debauchery or premature ageing.

Reduplication of the mucous membrane of the upper eyelid is associated with blepharochalasis in about 10% of cases, and this may make the eyelids appear thick.

Blepharochalasis is occasionally a manifestation of generalized cutis laxa, and it may form part of Ascher's syndrome (see below). Laxity of the eyelid skin also occurs in EDS, but other features of this syndrome will also be present. Occasionally, laxity particularly affecting the upper eyelid, occurs in otherwise healthy individuals [8].

Diagnosis. The many other causes of eyelid swelling must be excluded (Chapter 67). Ptosis is easily distinguished because the skin appears normal.

Treatment. Plastic surgery can be performed, but the condition may recur [2].

References

1 Brazin SA. Unilateral blepharochalasis. *Arch Dermatol* 1979; **115**: 479–81.
2 Harris WA, Dortzbach RK. Levator tuck. A simplified blepharoptosis procedure. *Ann Ophthalmol* 1975; **7**: 873–8.
3 Tepaszto I, Liszkay L, Vass Z. Some data on the pathogenesis of blepharochalasis. *Acta Ophthalmol (Copenh)* 1963; **41**: 167–75.

4 Jordan DR. Blepharochalasis syndrome: a proposed pathophysiologic mechanism. *Can J Ophthalmol* 1992; **27**: 10–5.
5 Kaneoya K, Momota Y, Hatamochi A *et al.* Elastin gene expression in blepharochalasis. *J Dermatol* 2005; **32**: 26–9.
6 Grasseger A, Romani N, Fritsch P *et al.* Immunoglobulin A (IgA) deposits in lesional skin of a patient with blepharochalasis. *Br J Dermatol* 1996; **135**: 791–5.
7 Dózsa A, Károlyi ZS, Degrell P. Bilateral blepharochalasis. *J Eur Acad Dermatol Venereol* 2005; **19**: 725–8.
8 Shah-Desai S, Sandy C, Collin R. Lax eyelid syndrome or "progeria" of eyelid tissues. *Orbit* 2004; **23**: 3–12.

Ascher's syndrome

Ascher's syndrome is the association of blepharochalasis with progressive enlargement of the upper lip due to hypertrophy and inflammation of the labial salivary glands [1–5]. The lip feels soft and lobulated and there may be excessive salivation. In some cases, the accessory lacrimal glands are also affected, with increased thickness of the eyelids. Enlargement of the thyroid has also been reported.

References

1 Findlay GH. Idiopathic enlargements of the lips: cheilitis granulomatosa, Ascher's syndrome and double lip. *Br J Dermatol* 1954; **66**: 129–38.
2 Papanayotou PH, Hatzoitis JC. Ascher's syndrome: report of a case. *Oral Surg Oral Med Oral Pathol* 1973; **35**: 467–71.
3 Pitanguy I. Ascher's syndrome. *Head Neck Surg* 1988; **10**: 309–10.
4 Halling F, Sandrock D, Merten HA *et al.* Das Ascher syndrome. *Dtsch Z Mund Kiefer Gesichtschir* 1991; **15**: 440–4.
5 Ali K. Ascher syndrome: a case report and review of the literature (epub). *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; **103**: e26–8.

Pseudoxanthoma elasticum

Synonyms
- Systematized elastorrhexis
- Grönblad–Strandberg syndrome

Definition. PXE is an inherited disorder characterized by generalized fragmentation and progressive calcification of elastic tissue in the dermis, blood vessels and Bruch's membrane of the eye. This leads to laxity of the skin, arterial insufficiency and retinal haemorrhage.

Aetiology. Until recently the basic defect was unknown. Because the pathology affects elastic fibres the genes responsible for elastin and microfibrillary proteins were initially studied, but linkage analysis excluded these early candidate genes [1,2]. Positional cloning identified candidate genes on chromosome 16p13.1 and mutations have subsequently been identified in the *MRP6/ABCC6* gene [3–5]. This is a member of the ATP-binding cassette (ABC) family and acts as a transmembrane transporter. Mutations in the gene affect transport of anionic peptides [6]. *ABCC6* is expressed primarily, if not exclusively, in the liver and kidneys and absence of normal *ABCC6* may allow certain metabolic compounds to accumulate, resulting in progressive calcification of elastic fibres. This suggests that PXE may in fact be a primary metabolic disorder with secondary involvement of elastic fibres [7]. Genotype–phenotype analysis has failed to identify any correlation [8].

The inheritance of PXE has been controversial over the past few years, and historically at least five genetic groups have been described [9–11]. With molecular testing it is now apparent that familial inheritance is autosomal recessive and no confirmed autosomal dominant form has yet been shown [12]. Clinical features of PXE can be seen in unambiguously identified heterozygous carriers, and this, as well as pseudodominance, explains some earlier reports of different clinical types and modes of inheritance.

Pathology [13–19]. In the fully developed skin lesions, the elastic fibres in the mid-dermis are clumped, degenerate, fragmented and swollen, and the abnormal fibres stain positively for calcium. The collagen fibres are also abnormal, being split into small fibres.

Similar changes occur in the connective tissue of the media and intima of the blood vessels, Bruch's membrane of the eye, and in the endocardium and pericardium. The heart may occasionally be enlarged, with extensive calcification [20], and pulmonary calcification has been reported [21]. Calcification may occur in other viscera [22].

The vascular involvement may be generalized but may involve predominantly the larger arteries, the mesenteric and visceral arteries, or those of the extremities [23]. Calcification of the internal elastic lamina of the arteries leads to vascular occlusion. Hypertension, angina, myocardial infarction, cerebrovascular accidents and recurrent mucosal haemorrhages may result. The changes in Bruch's membrane give rise to angioid streaks, and rupture of the retinal vessels to haemorrhages and choroiditis.

The complete syndrome consists of the distinctive skin lesions, retinal changes (angioid streaks) and vascular disturbances. The characteristic skin changes and angioid streaks have also been reported as isolated findings, but this is unusual, and in ten patients with angioid streaks but no obvious skin abnormalities, a biopsy of scar tissue, regardless of site, was diagnostic of PXE in six patients, with three also having histological changes in elastic tissue in normal-appearing flexural skin [18]. The relatively low yield from biopsy of normal-looking axillary skin of patients with PXE at other skin sites has also been demonstrated [24].

Skin changes. The skin lesions are characteristic. They consist of small (1–3 mm), yellowish papules in a linear or reticular pattern, in confluent plaques, although the changes are sometimes very subtle. The skin is soft, lax and slightly wrinkled, and may hang in folds, especially in elderly people. There may be a slightly pebbly surface, which has been variously described as a 'cobblestone', 'Moroccan leather' or 'chicken skin' appearance (Fig. 45.16). The sites of predilection are the sides of the neck, below the clavicles, the axillae (Fig. 45.17), abdomen, groins, perineum and thighs. Reticulate pigmentation on the abdomen may occur [25]. Numerous acneiform lesions have been reported [26]. Although usually limited, the eruption may occasionally involve most of the body. It may develop in early childhood, and usually does so before the age of 30 years, but it may also first appear in old age. It usually persists unchanged indefinitely. Similar changes may occur in the soft palate, inside the lips and in the mucous membranes of stomach, rectum and vagina. In the mouth, the lesions may mimic sebaceous glands (Fordyce spots). Rarely, chronic granulomatous nodules have developed in the skin lesions [27].



Fig. 45.16 Pseudoxanthoma elasticum, showing the typical 'chicken skin' appearance involving the neck.



Fig. 45.17 Pseudoxanthoma elasticum of the axilla, showing the characteristic yellow discoloration of the skin and the loose folds. The changes in this condition are often much more subtle than in this patient.

Occasionally, there may be spontaneous perforating lesions, with transepidermal elimination of the fragmented elastic fibres. These present as hyperkeratotic papules, which leave a bleeding surface when dislodged.

The presence of an exaggerated mental (chin) crease has recently been shown to be a sensitive and highly specific finding in patients under the age of 30 years with PXE [28].



Fig. 45.18 Angioid streaks of the retina in pseudoxanthoma elasticum. (Courtesy of Professor D. Easty, Bristol Eye Hospital, Bristol, UK.)

Cardiovascular changes. The arteries throughout the body are affected. There may be intermittent claudication with diminished peripheral pulses, and there is accelerated atheroma, often with hypertension [29]. The circulatory disturbances are detectable by plethysmography or oscillometry, and angiography may show angiomatous malformations, aneurysmal dilatation, and narrowing or occlusion of peripheral or visceral arteries [30]. Signs of arterial degeneration may be seen by the age of 30 years, and death may result from cerebral haemorrhage, coronary occlusion or massive haemorrhage into the gut [31]. Cardiomyopathy has been reported [32,33].

Arterial involvement may not be clinically manifest until adult life, but intermittent claudication and angina have occurred in early childhood. Some patients, however, survive to old age.

Mitral valve prolapse occurs in about 5–8% of the normal population. In one series of 14 patients with PXE, 11 had mitral valve prolapse [34], but these individuals probably had an overlap with Marfanoid features [35].

Ocular changes. Angioid streaks [36,37] of the retina are seen as slate-grey, poorly defined streaks radiating from an incomplete greyish ring surrounding the nerve head (Fig. 45.18). They are bilaterally symmetrical, and usually first appear between the ages of 20 and 40 years. There may be no impairment of vision, but progressive visual failure may occur, and haemorrhages and choroiditis occasionally result in total blindness.

Other associated ocular findings include small, raised, pearly white *drusen*, or punched-out atrophic areas in focal areas of dehiscence of Bruch's membrane [38]. There may also be speckled yellowish mottling at the posterior pole, and this change, which has been called 'leopard spotting', may antedate the angioid streaks [39]. About 50% of patients also have a random scattering of small, round pigment dots throughout the macula and optic nerve [40]. These may resemble a string of pearls in some cases, and they are best seen on fluorescein angiography.

Abnormal visibility of the choroidal vessels has been present in some apparently unaffected members of some families with PXE [41].

Obstetric risk. There is an increased risk of miscarriage in the first trimester, possibly related to failure of placental development [42], and abdominal striae develop during pregnancy in virtually all patients [43]. Opinions differ regarding the risk to the mother. Berde *et al.* [44] reviewed the literature and concluded that there was a serious risk of cardiovascular complications during pregnancy, but Viljoen *et al.* [43] reported 54 pregnancies in which there were no serious maternal complications. Subsequent reports also agree that although skin manifestations may worsen, the risks of pregnancy have been overstated [45].

Associated abnormalities. In most cases of PXE the serum calcium and phosphate levels are normal, but in a few patients the phosphate levels are increased, with mild hypercalcaemia and abnormalities of vitamin D metabolism [22,46]. The biochemical changes resemble those of tumoral calcinosis [47], although the clinical changes are those of PXE. This seems to be a distinctive, rare type of PXE which may be associated with renal failure in other members of the family. Some of these patients also have systemic sclerosis [48].

Other patients have been reported with multiple, calcified cutaneous nodules, with angioid streaks and hyperphosphataemia, but without pseudoxanthoma [49].

Skin changes of PXE and/or angioid streaks are occasionally seen in patients with osteitis deformans (Paget's disease). Pseudoxanthoma elasticum has also been reported in association with osteoectasia, which is characterized by dwarfism, bizarre radiographic changes and elevated serum alkaline phosphatase levels [50].

The development of both clinical and histopathological PXE-like changes, involving skin, eyes and vasculature, in sickle cell disease and β-thalassaemia has been well documented [51]. The abnormalities are most probably acquired and related to the consequences of the primary disease. The clinical features are of later onset and milder than in inherited PXE.

The typical features of PXE have been reported in a patient with true Marfan's syndrome, but it is likely that this is a chance association [52].

A group of patients with PXE-like phenotype with cutis laxa and deficiency of vitamin K-dependent clotting factors has been identified without causal mutations in *ABCC6* or *VKORC1* (vitamin K 2,3 epoxide reductase) [53]. This suggests a separate clinical and genetic entity.

Diagnosis. The clinical and histological changes of PXE are often distinctive, and the diagnosis is usually readily made when skin lesions are present. The disseminated form of dermatofibrosis lenticularis (Buschke–Ollendorff) can be clinically similar, and juvenile elastoma, which is a feature of this condition, shows thickened elastic fibres on histology. If laxity of the involved skin is extreme, other forms of dermatochalasis must be excluded.

In cases without skin lesions the diagnosis may be difficult, and attempts have been made to establish diagnostic criteria [1,19]. These are summarized in Table 45.2. It should be suspected in obliterative arterial disease of early onset and in unexplained gastrointestinal haemorrhage. The presence of angioid streaks or mucosal lesions should be sought. A skin biopsy from the side of the neck may be helpful, even if there are no clinically evident changes, although the characteristic histological changes are not necessarily diagnostic [18,19]. The diagnosis can be difficult in the presence of marked solar elastosis and/or macular degeneration [54]. Soft-tissue or vascular calcification may be detectable radiologically [55], and angiography may be helpful [30]. Ultrasonography can detect early renal parenchymal calcification, although its prognostic significance remains uncertain [56].

Table 45.2 Diagnostic criteria for pseudoxanthoma elasticum (PXE). (From Lebwohl *et al.* [19].)

Major criteria

1 Flexural yellow cobblestone lesions

2 Characteristic histological features of lesional skin, using elastic tissue and calcium stains (e.g. van Gieson and von Kossa)

3 Angioid streaks in the retina

Minor criteria

4 Characteristic histological changes in non-lesional skin

5 Family history of PXE in first-degree relatives

Definitive diagnosis is made by molecular analysis of the *ABCC6* gene. This also provides a means for prenatal and presymptomatic testing in families at risk for recurrence [7,8]. Emerging evidence also suggests that heterozygosity for an *ABCC6* mutation (*R1141X*) confers a fourfold risk of developing coronary artery disease [57].

Treatment. It is important that the condition is accurately diagnosed so that appropriate genetic advice may be given. The most important aspect of treatment is to ensure that complications from vascular involvement are prevented or dealt with speedily by the appropriate specialist. Ophthalmologists will recommend that the patient learns to use an Amsler grid in the early detection of visual loss. Patients should avoid any activity that might cause sudden increase in blood pressure or contact injury to the eyes. Laser photocoagulation may be helpful in preventing further retinal haemorrhage. Cardiovascular risks should be minimized with control of blood pressure and serum lipids, and avoidance of smoking. The cosmetic appearance of the skin lesions may be improved by plastic surgery. Restriction of dietary calcium has been tried, with apparent benefit in some cases [47], but this treatment remains controversial.

References

1 Christiano AM, Lebwohl MG, Boyd CD *et al.* Workshop on pseudoxanthoma elasticum: molecular biology and pathology of the elastic fibres (Jefferson Medical College, Philadelphia). *J Invest Dermatol* 1992; **99**: 660–3.

2 Christiano AM, Uitto J. Molecular pathology of the elastic fibres. *J Invest Dermatol* 1994; **103**: S53–7.

3 Le Saux O, Urban Z, Tschuch C *et al.* Mutations in a gene encoding an ABC transporter cause pseudoxanthoma elasticum. *Nat Genet* 2000; **25**: 223–7.

4 Bergen AAB, Plomp AS, Schuurman EJ *et al.* Mutations in *ABCC6* cause pseudoxanthoma elasticum. *Nat Genet* 2000; **25**: 228–31.

5 Ringpfeil F, Lebwohl MG, Christiano AM *et al.* Pseudoxanthoma elasticum: mutations in the *MRP6* gene encoding a transmembrane ATP binding cassette (ABC) transporter. *Proc Natl Acad Sci USA* 2000; **97**: 6001–6.

6 Ilias A, Urban Z, Seidl TL *et al.* Loss of ATP-dependent transport actvitiy in pseudoxanthoma elasticum-associated mutants of human *ABCC6* (*MRP6*). *J Biol Chem* 2002; **277**: 16860–7.

7 Ringpfeil F, Pulkkinen L, Uitto J. Molecular genetics of pseudoxanthoma elasticum. *Exp Dermatol* 2001; **10**: 221–8.
8 Pfender EG, Vanakker O, Terry SF *et al*. Mutation detection in the *ABCC6* gene and genotype-phenotype analysis in a large international case series affected by pseudoxanthoma elasticum. *J Med Genet* 2007; **44**: 621–8.
9 Pope FM. Historical evidence for the genetic heterogeneity of pseudoxanthoma elasticum. *Br J Dermatol* 1975; **92**: 493–509.
10 Viljoen DL, Beighton P, Mabin T *et al.* Pseudoxanthoma elasticum in South Africa—genetic and clinical implications. *S Afr Med J* 1984; **66**: 813–6.
11 Viljoen DL, Pope FM, Beighton P *et al.* Heterogenicity of pseudoxanthoma elasticum: delineation of a new form? *Clin Genet* 1987; **32**: 100–5.
12 Ringpfeil F, McGuigan K, Fuchsel L *et al*. Pseudoxanthoma elasticum is a recessive disease characterized by compound heterozygosity. *J Invest Dermatol* 2006; **126**: 782–6.
13 Altman LK, Shenhav R, Schaudinischky L. Pseudoxanthoma elasticum. An underdiagnosed genetically heterogeneous disorder with protean manifestations. *Arch Intern Med* 1974; **134**: 1048–54.
14 Eddy DD, Farber EM. Pseudoxanthoma elasticum. Internal manifestations: case-reports and literature review. *Arch Dermatol* 1962; **86**: 729–40.
15 Goodman RM, Smith EW, Paton D *et al.* Pseudoxanthoma elasticum: a clinical and histopathological study. *Medicine* 1963; **42**: 297–334.
16 Gordon SG, Subryan VL, Solomons CC *et al*. *In vitro* uptake of calcium in dermis of patients with pseudoxanthoma elasticum. *J Lab Clin Med* 1975; **86**: 638–40.
17 Pasquali-Ronchetti I, Volpin D, Baccarani CM *et al.* Pseudoxanthoma elasticum. Biochemical and ultrastructural studies. *Dermatologica* 1981; **163**: 307–25.
18 Lebwohl M, Phelps RG, Yannuzzi L *et al.* Diagnosis of pseudoxanthoma elasticum in patients without characteristic skin lesions. *N Engl J Med* 1987; **317**: 347–50.
19 Lebwohl M, Nelder K, Pope FM *et al.* Classification of pseudoxanthoma elasticum. Report of a consensus conference. *J Am Acad Dermatol* 1994; **30**: 103–7.
20 Fang ML, Astarita RN, Steinman H. Cardiac calcifications and yellow papules in a young man. *Arch Dermatol* 1988; **124**: 1559–64.
21 Jackson A, Loh CL. Pulmonary calcification and elastic tissue damage in pseudoxanthoma elasticum. *Histopathology* 1980; **4**: 607–11.
22 Cnudde F, Muller P, Hajjar C *et al.* Pseudoxanthome élastique avec calcifications multiples et hyperphosphoremie. *Ann Dermatol Vénéréol* 1996; **123**: 563–6.
23 Bardsley JL, Ruben-Koehler P. Pseudoxanthoma elasticum: angiographic manifestations in abdominal vessels. *Radiology* 1969; **93**: 559–62.
24 Brown SJ, Talks SJ, Needham SJ *et al*. Pseudoxanthoma elasticum: biopsy of clinically normal skin in the investigation of patients with angioid streaks. *Br J Dermatol* 2007; **157**: 748–51.
25 Li T-H, Tseng C-R, Hsiao G-H. An unusual cutaneous manifestation of pseudoxanthoma elasticum mimicking reticulate pigmentary disorders. *Br J Dermatol* 1966; **134**: 1157–9.
26 Hartman A, Hartman-Visser SR. Pseudoxanthoma elasticum with extensive comedo formation. *Dermatologica* 1977; **154**: 318–9.
27 Heyl T. Pseudoxanthoma elasticum with granulomatous skin lesions. *Arch Dermatol* 1967; **96**: 528–31.
28 Lebwohl M, Lebwohl E, Bercovitch L. Prominent mental (chin) crease: a new sign of pseudoxanthoma elasticum. *J Am Acad Dermatol* 2003; **48**: 620–2.
29 Parker JC, Friedman-Kien AE, Levin S *et al.* Pseudoxanthoma elasticum and hypertension. *N Engl J Med* 1964; **271**: 1204–7.
30 Belli A, Cawthorne S. Visceral angiographic findings in pseudoxanthoma elasticum. *Br J Radiol* 1988; **61**: 368–71.
31 Kundrotas L, Novak J, Kremzier J *et al.* Gastric bleeding in pseudoxanthoma elasticum. *Am J Gastroenterol* 1988; **83**: 868–72.
32 Navarro-Lopez F, Llorian A, Ferrer-Roca O *et al.* Restrictive cardiomyopathy in pseudoxanthoma elasticum. *Chest* 1980; **78**: 113–5.
33 Przybojewski JZ, Hoffman H, de Graaf AS *et al.* Pseudoxanthoma elasticum with cardiac involvement. A case report and review of the literature. *S Afr Med J* 1981; **59**: 268–75.
34 Lebwohl MJ, Distefano D, Prioleau PG. Pseudoxanthoma elasticum and mitral-valve prolapse. *N Engl J Med* 1982; **307**: 228–31.
35 Pyeritz RE, Weiss JL, Rennie W *et al.* Pseudoxanthoma elasticum and mitral valve prolapse. *N Engl J Med* 1982; **307**: 1451–2.
36 Connor PJ, Juergeens JL, Perry HO *et al.* Pseudoxanthoma elasticum and angioid streaks. A review of 106 cases. *Am J Med* 1961; **30**: 537–43.
37 McWilliam RJ. Classification of angioid streaks. *Br J Ophthalmol* 1955; **39**: 298–300.
38 Clarkson JG, Altmann RD. Angioid streaks. *Surv Ophthalmol* 1982; **26**: 235–46.
39 Gills JP, Paton D. Mottled fundus oculi in pseudoxanthoma elasticum. *Arch Ophthalmol* 1963; **73**: 792–5.
40 McDonald HR, Schatz H, Aarberg TM. Reticular-like pigmentary patterns in pseudoxanthoma elasticum. *Ophthalmology* 1988; **95**: 306–11.
41 Berlyne GM, Bulmer MG, Platt R. The genetics of pseudoxanthoma elasticum. *QJM* 1961; **30**: 201–12.
42 Elejalda BR, de Elejalda MM, Samter T *et al*. Manifestations of pseudoxanthoma elasticum during pregnancy: a case report and review of the literature. *Am J Med Genet* 1984; **18**: 755–62.
43 Viljoen DL, Beatty S, Beighton P. The obstetric and gynaecological implications of pseudoxanthoma elasticum. *Br J Obstet Gynaecol* 1987; **94**: 884–8.
44 Berde C, Willis DC, Sandberg EC. Pregnancy in women with pseudoxanthoma elasticum. *Obstet Gynaecol Surg* 1983; **38**: 339–44.
45 Yoles A, Phelps R, Lebwohl M. Pseudoxanthoma elasticum and pregnancy. *Cutis* 1996; **58**: 161–4.
46 Mallette LE, Mechanick JI. Heritable syndrome of pseudoxanthoma elasticum with abnormal phosphorus and vitamin D metabolism. *Am J Med* 1987; **83**: 1157–62.
47 Prince MJ, Schaefer H, Goldsmith RS *et al.* Hyperphosphatemic tumoral calcinosis. *Ann Intern Med* 1982; **96**: 586–91.
48 Pai SH, Zak FG. Concurrence of pseudoxanthoma elasticum, elastosis perforans serpiginosa and systemic sclerosis. *Dermatologica* 1970; **140**: 54–9.
49 McPhaull JJ, Engel FL. Heterotopic calcification, hyperphosphataemia and angioid streaks of the retina. *Am J Med* 1961; **31**: 488–9.
50 Saxe N, Beighton P. Cutaneous manifestations of osteoectasia. *Clin Exp Dermatol* 1982; **7**: 605–9.
51 Aessopos A, Farmakis D, Loukopoulos D. Elastic tissue abnormalities resembling pseudoxanthoma elasticum in β thalassemia and the sickling syndromes. *Blood* 2002; **99**: 30–5.
52 Hidano A, Nakajima S, Shimizu T, Kimata Z. Pseudoxanthoma elasticum associated with Marfan syndrome. *Ann Dermatol Vénéréol* 1979; **106**: 503–5.
53 Vanakker OM, Martin L, Gheduzzi D *et al*. Pseudoxanthoma elasticum-like phenotype with cutis laxa and multiple coagulation factor deficiency represents a separate genetic entity. *J Invest Dermatol* 2007; **127**: 581–7.
54 Christen-Zäch S, Huber M, Lindpainter K *et al*. Pseudoxanthoma elasticum: evaluation of diagnostic criteria based on molecular data. *Br J Dermatol* 2006; **155**: 89–93.
55 James AE, Eaton SB, Blazek JV *et al*. Roentgen findings in pseudoxanthoma elasticum. *Am J Roentgenol* 1969; **106**: 642–4.
56 Crespi G, Derchi LE, Saffioti S. Sonographic detection of renal changes in pseudoxanthoma elasticum. *Urol Radiol* 1992; **13**: 223–5.
57 Trip MD, Smulders YM, Wegman JJ *et al.* Frequent mutation in the *ABCC6* gene (*R1141X*) is associated with a strong increase in the prevalence of coronary artery disease. *Circulation* 2002; **106**: 773–5.

Acquired PXE-like syndromes

Perforating PXE

Synonym
- Perforating calcific elastosis

Transepithelial elimination (TEE) of altered elastic fibres can occasionally occur in generalized hereditary forms of PXE (see above), but it can also occur as a localized, acquired defect in patients who do not have the other features of PXE [1]. These localized lesions usually occur in the periumbilical area in obese, multiparous black women, and it is possible that this represents a response to repeated cutaneous stretching, for example ascites or previous abdominal surgery [2,3]. Similar lesions on the breast have been reported in patients undergoing haemodialysis [4,5].

Clinically, asymptomatic yellow macules and papules coalesce into well-demarcated, hyperpigmented plaques which slowly enlarge. The surface may be atrophic, grooved, fissured or verrucous, and compression of the edge of the lesion may produce a liquid discharge.

It seems likely that most cases previously described as elastosis perforans serpiginosa in association with PXE were really examples of perforating PXE [6]. The histology of the two conditions is similar, but in perforating PXE there is TEE of altered basophilic, calcified, elastic fibres, which are short, fragmented, curled and predominantly in the mid-dermis, whereas in elastosis perforans serpiginosa the fibres are abnormally large, non-calcified, eosinophilic and straight.

Spontaneous resolution has been reported [7].

References

1 Premathala S, Yesudian P, Thambiah AS. Periumbilical pseudoxanthoma elasticum with transepithelial elimination. *Int J Dermatol* 1982; **10**: 604–5.
2 Kazakis AM, Parish WR. Periumbilical perforating pseudoxanthoma elasticum. *J Am Acad Dermatol* 1988; **19**: 384–8.
3 Somarsundaram V, Premathala S, Rao NR *et al.* Periumbilical perforating pseudoxanthoma elasticum. *Int J Dermatol* 1987; **26**: 536–7.
4 Nickoloff BJ, Noodleman FR, Abel EA. Perforating pseudoxanthoma elasticum associated with chronic renal failure and haemodialysis. *Arch Dermatol* 1985; **121**: 1321–2.
5 Kazakis AM, Parish WR. Periumbilical perforating pseudoxanthoma elasticum. *J Am Acad Dermatol* 1988; **19**: 384–8.
6 Lund HZ, Gilbert CF. Perforating pseudoxanthoma elasticum. Its distinction from elastosis perforans serpiginosa. *Arch Pathol Lab Med* 1976; **100**: 544–6.
7 Sueki H, Amemiya M, Watanaba H *et al.* Spontaneous resolution in a case of pseudo-pseudoxanthoma elasticum. *Br J Dermatol* 2001; **144**: 213–5.

Pseudo-PXE

Skin changes which are virtually identical to those of PXE can rarely be produced by penicillamine, although the systemic features do not occur [1]. The skin changes can be explained by the known effect of penicillamine in inhibiting collagen and elastin cross-linking, with the production of vastly increased amounts of abnormal elastin in the dermis [2]. Transepidermal extrusion of elastin has been reported in this condition [3]. Lesions clinically resembling PXE are reported in the eosinophilia–myalgia syndrome; dermal calcification is absent on histology [4]. Yellowish papules and plaques resembling PXE are seen in some patients with amyloidosis; amyloid deposits are seen and, again, dermal calcification is absent [5,6].

References

1 Burge S, Ryan T. Penicillamine-induced pseudo-pseudoxanthoma elasticum in a patient with rheumatoid arthritis. *Clin Exp Dermatol* 1988; **13**: 255–8.
2 Light N, Meyrick-Thomas RH, Stephens A *et al.* Collagen and elastin changes in D-penicillamine-induced pseudoxanthoma elasticum-like skin. *Br J Dermatol* 1986; **114**: 381–8.
3 Meyrick-Thomas RH, Kirby JDT. Elastosis perforans serpiginosa and pseudoxanthoma elasticum-like skin changes due to d-penicillamine. *Clin Exp Dermatol* 1985; **10**: 386–91.
4 Mainetti C, Masouye I, Saurat JH. Pseudoxanthoma elasticum-like lesions in the L-tryptophan- induced eosinophilia-myalgia syndrome. *J Am Acad Dermatol* 1991; **24**: 657–8.
5 Winkelmann RK, Peters MS, Venencie PY. Amyloid elastosis. A new cutaneous and systemic pattern of amyloidosis. *Arch Dermatol* 1985; **121**: 498–502.
6 Vecchietti G, Masouye I, Salomon D *et al.* An unusual form of primary systemic amyloidosis: amyloid elastosis—report of a case treated by haematopoietic cell transplantation. *Br J Dermatol* 2003: **145**: 154–9.

Saltpetre disease [1–3]

A condition which resembles the skin changes of PXE clinically, histologically and ultrastructurally has been described in a group of elderly farmers, who decades earlier had spread a fertilizer containing calcium-ammonium nitrate (Norwegian saltpetre). The patients developed cutaneous ulcers at sites of exposure (including antecubital fossae). These quickly healed to leave yellowish-white papules and plaques. None of the patients had a positive family history or other signs of PXE.

References

1 Christensen OB. An exogenous variety of pseudoxanthoma elasticum in old farmers. *Acta Derm Venereol Suppl (Stockh)* 1978; **58**: 319–22.
2 Neilson AO, Christensen OB, Hentzer B *et al.* Saltpetre-induced dermal changes electron microscopically indistinguishable from pseudoxanthoma elasticum. *Acta Derm Venereol Suppl (Stockh)* 1978; **58**: 323–7.
3 Neri I, Marzaduri S, Berdazzi F *et al.* Exogenous pseudoxanthoma elasticum: a new case in an old farmer. *Acta Derm Venereol* 1993; **78**: 153–4.

Williams–Beuren syndrome

The Williams–Beuren syndrome is a developmental disorder characterized by premature laxity of the skin, congenital heart disease (notably supravalvular aortic stenosis), metabolic abnormalities and dysmorphic facial features, which include baggy connective tissue around the eyes, full cheeks, prominent lips and dental malocclusion [1]. Delayed motor and perceptual development are sometimes masked by above-average language skills allied to a 'cocktail party' personality [2].

In situ hybridization techniques have revealed both inherited and new deletions at the elastin locus on chromosome 7q11.23 [3]. Size heterogeneity of the deletion exists, with multiorgan involvement as a consequence of contiguous gene deletions. At least 24 genes may be involved in the critical region [4]. Only the elastin gene deletion is associated with a specific phenotype (supravalvular aortic stenosis). An 'epidemic' of the Williams' syndrome was reported in the UK following the administration of excessive doses of vitamin D to prevent rickets in pregnant women [5]. Vitamin D is known to downregulate elastin gene expression [6].

References

1 Morris CA, Dilts C, Dempsey SA *et al.* The natural history of Williams syndrome: physical characteristics. *J Pediatr* 1988; **113**: 318–26.
2 Giddins NG, Finley JP, Nanton MA *et al.* The natural course of supravalvular aortic stenosis and peripheral pulmonary artery stenosis in Williams syndrome. *Br Heart J* 1989; **62**: 315–9.
3 Ewart AK, Morris CA, Atkinson D *et al.* Hemizygosity at the elastin locus in a developmental disorder: Williams syndrome. *Nat Genet* 1993; **5**: 11–6.
4 Tassabehji M. Williams-Beuren syndrome: a challenge for genotype-phenotype correlations. *Hum Mol Genet* 2003; **12**: R229–37.
5 Lightwood R, Sheldon W, Harris C *et al.* Hypercalcaemia in infants and vitamin D. *BMJ* 1965; **2**: 149.
6 Christiano AM, Uitto J. Molecular pathology of the elastic fibres. *J Invest Dermatol* 1994; **103** (Suppl.): S53–7.

Linear focal elastosis

Synonym

- Elastotic striae

This condition is characterized by asymptomatic, yellow, linear bands arranged horizontally on the lower back [1–4]. It less commonly occurs on the lower limbs and shoulders. Superficially, the lesions resemble striae distensae, but they are palpable rather than

depressed and yellow rather than purplish or white. Although the two conditions are generally unrelated, linear focal elastosis has been reported adjacent to striae distensae [5], and in one case following potent topical corticosteroids [6]. The condition was originally described in elderly males [1], although it has been reported in a young black male whose father was similarly affected [7]. It may be commoner than is suggested by the paucity of reports. Ultrastructural studies reveal active elastogenesis. The middle and lower dermal collagen is separated by bluish grey, fine, fibrillar material, which is composed of thin, wavy elastic fibres and fragmented elastic fibre bundles. Early lesions may, in contrast, show elastolysis, with decreased elastin and microfibrillar proteins [8]. The elastic fibres are near to, or even in contact with, fibroblasts [9], and elastogenesis may occur in response to local trauma, ultraviolet light or perhaps following the development of striae distensae [10]. However, these mechanisms do not adequately explain the increasing number of cases reported, particularly in the young, and it may be that intrinsic defects of elastic fibre metabolism play a role [4].

References

1 Burket JM, Zelickson AS, Padilla RS. Linear focal elastosis (elastotic striae). *J Am Acad Dermatol* 1989; **20**: 633–6.
2 Vogel PS, Cardenas A, Ross EV *et al.* Linear focal elastosis. *Arch Dermatol* 1995; **131**: 855–6.
3 Kanitakis J, Chouvet B, Dupin M *et al.* Linear focal elastosis. *Eur J Dermatol* 1997; **7**: 300–2.
4 Péc J, Chromej I. Linear focal elastosis: what's new? *J Eur Acad Dermatol Venereol* 2004; **18**: 247–9.
5 White G. Linear focal elastosis: a degenerative or regenerative process of striae distensae. *J Am Acad Dermatol* 1992; **22**: 468.
6 Neve S, Kirtschig G. Elastotic striae associated with striae distensae after application of very potent topical corticosteroids. *Clin Exp Dermatol* 2006; **31**: 452–82.
7 Moiin A, Hashimoto K. Linear focal elastosis in a young black man: a new presentation. *J Am Acad Dermatol* 1994; **30**: 874–7.
8 Choi SW, Lee JH, Woo HJ *et al.* Two cases of linear focal elastosis: different histopathologic findings. *Int J Dermatol* 2000; **39**: 207–9.
9 Hagari Y, Mihara M, Morimura T *et al.* Linear focal elastosis: an ultrastructural study. *Arch Dermatol* 1991; **127**: 1365–8.
10 Hashimoto K. Linear focal elastosis: keloidal repair of striae distensae. *J Am Acad Dermatol* 1998; **39**: 309–13.

Late-onset focal dermal elastosis

Yellowish papules with a *peau d'orange* appearance appear on the flexures. Clinically and histologically the lesions resemble elastomas, but this rare condition has only been reported in elderly Japanese men [1,2].

References

1 Tajima S, Shimizu K, Izumi T *et al.* Late-onset focal dermal elastosis: clinical and histological features. *Br J Dermatol* 1995; **133**: 303–5.
2 Limas C. Late onset focal dermal elastosis: a distinct clinicopathologic entity? *Am J Dermatopathol* 1999; **21**: 381–3.

Actinic elastosis

Synonym
- Solar elastosis

Definition. This is a degenerative change in the dermis caused by prolonged exposure to electromagnetic (usually solar) radiation. It is characterized clinically by yellowish discoloration and histologically by degeneration of elastic fibres.

Aetiology. Actinic elastosis usually results from prolonged exposure to sunlight, but it can also result from infrared (IR) radiation [1,2]. It is related to the cumulative dose of radiation, as it is more common in older people, outdoor workers and in sunny climates. There is, however, considerable variation in susceptibility between individuals. Fair-skinned people are the worst affected, although the condition can occur in black people [3,4]. Severe elastosis may occur in photosensitized skin, for example in porphyria cutanea tarda. UVB wavelengths are the most likely to cause solar elastosis, although UVA and PUVA therapy can also accentuate it [5,6].

Ageing normal skin becomes atrophic, with fewer elastic fibres [3]. In contrast, sun-damaged ('photo-aged') skin exhibits hypertrophy of elastic tissue, secondary to a prolonged inflammatory process [7]. Skin on the back of the neck exposed to chronic UV radiation shows partially degranulated mast cells in close apposition to fibroblasts. Metalloproteinases produced by mast cells and macrophages degrade skin collagen [8].

Pathology [9,10]. At an early stage, there is a perivenular lymphohistiocytic infiltrate, with degranulating mast cells [7,11]. The vessel walls become thickened due to deposition of a basement-membrane-like material [4]. The elastic fibres of the upper and middle dermis then become curled and fibrillar to form thick, irregular masses [12]. At a later stage, the elastotic degeneration becomes more diffuse, forming long, swollen bands of irregular texture, with finely granular elastin and dense microfibrillar masses. Actinic elastosis originates in elastic fibres rather than collagen, as shown by the findings that the abnormal fibres stain with antielastin antibody HB8, disappear with elastase but resist collagenolytic enzymes, and have a high desmosine content.

In the early stages of actinic elastosis, there is also an increase in collagen and in glycosaminoglycans, although ultimately fibrillar (types I and III) procollagens decrease. Anchoring fibrils (collagen type VII) and the fibrillin-rich microfibrils at the dermoepidermal junction are also reduced [13–15]. Collagenolytic enzymes, notably matrix metalloproteinase-I, are increased [16]. Eventually, the fibrous network degenerates into an amorphous, elastotic mass, and the dermal blood vessels become sparse and tortuous [3,4]. Increased dermal glycosaminoglycans are deposited on the elastotic material in the superficial dermis [17].

Clinical features. The condition is more common in later life. In temperate climates, it is rare before the fourth decade, but it starts earlier and is more severe in sunnier climates. The light-exposed areas are affected, particularly the forehead and the back of the neck. Mild degrees of elastosis may not be apparent until the skin is pinched up, when it may assume a wrinkled appearance. Elastosis is usually more advanced in the tissue than the clinical appearance would suggest.

The affected skin is diffusely thickened and yellowish (Fig. 45.19), and on the neck it may be divided by well-defined furrows into an irregular rhomboidal pattern (cutis rhomboidalis nuchae). There may also be more sharply marginated, thickened plaques on the face or neck. These are usually, but not always, symmetrical.

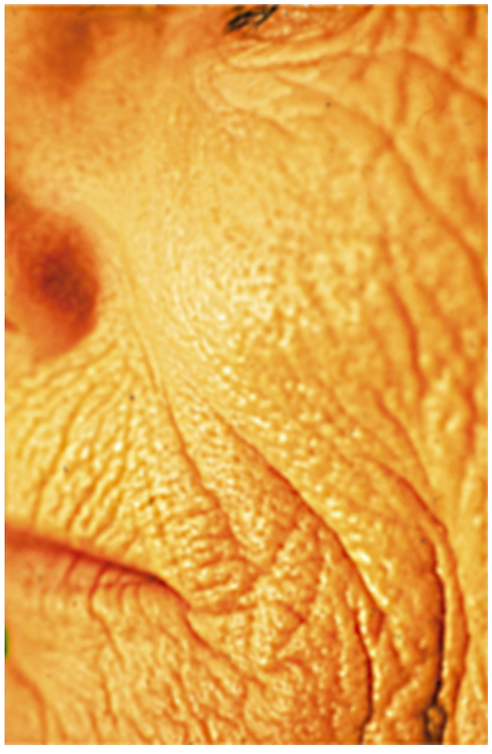


Fig. 45.19 Actinic (solar) elastosis, showing the characteristic yellowish discoloration, thickening and wrinkling of the facial skin.

When the skin around the orbits is affected, it is often studded with numerous comedones, and this has been called the *Favre–Racouchot syndrome* (Fig. 45.20). Favre–Racouchot syndrome is usually confined to facial skin and is bilaterally symmetrical, but unilateral and circumscribed forms have been reported [18]. The term actinic-comedonal plaque has been suggested for similar lesions which can rarely occur on other parts of the body, such as the forearm [19,20].

Skin which is affected by actinic elastosis is likely to develop other signs of sun damage, including irregular pigmentation, wrinkling, scaling, solar keratoses and malignancy. This range of changes due to chronic sun damage has been called *dermatoheliosis* [21].

Actinic elastosis may also be complicated by actinic granuloma (see below).

Photodamage is markedly exacerbated in smokers [22].

Diagnosis. Plane xanthoma, PXE and colloid milium may sometimes cause confusion, but the combination of the clinical and histological features is distinctive.

Treatment. Sunscreens protect against the development of photodamage both in humans and animals [23]. In hairless mice exposed to UVB radiation, synthesis of subepidermal collagen has been demonstrated in animals protected with a sunscreen [24]. Topical application of α-hydroxy acids ('fruit acids'), that is lactic, glycolic and citric acids, led to a modest improvement in photodamaged skin [25]. More impressive results have been obtained with topically applied tretinoin cream [26–28]. A double-blind study [29] demonstrated a decrease in papillary dermal collagen type I in photodamaged skin, and subsequent treatment with 0.1% tretinoin cream for 10–12 months resulted in an 80% increase in dermal collagen. Several studies have shown clinical and histological improvement after prolonged use [23]. Tretinoin may also repair skin changes due to intrinsic ageing [29,30]. Retinoids reduce MMP-1 expression *in vitro*, partially restoring levels of fibrillin-1 and collagens I and VII in the papillary dermis [27,31]. Similar results have been obtained in double-blind trials of topical isotretinoin [32] and tazarotene cream [33]. There has been interest in the use of so-called non-ablative lasers, including the 1320-nm Nd:YAG and 1540-nm erbium glass lasers, which are claimed to wound the upper dermis without epidermal damage [34]. Restoration of fibrillin-I in the microfibrillar network of the papillary dermis may prove a useful 'biomarker' for the efficacy of topical products used in the treatment of actinic elastosis [35,36].

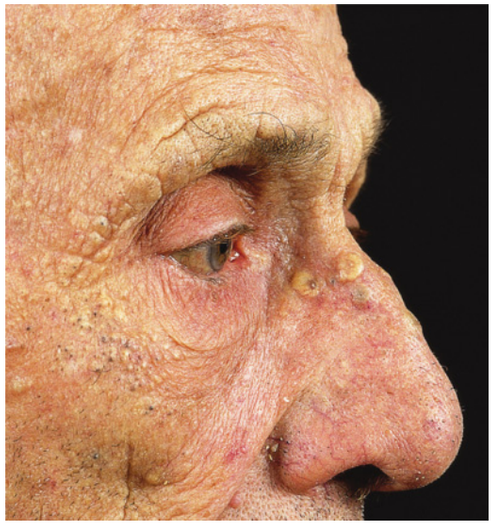


Fig. 45.20 Favre–Racouchot syndrome, showing comedones and actinic elastosis. (Courtesy of Professor R. Marks, St Vincent's Hospital, Melbourne, Victoria, Australia.)

References

1 Finlayson GR, Sams WM Jr, Smith JG. Erythema ab igne: a histopathological study. *J Invest Dermatol* 1966; **46**: 104–8.

2 Kligman AM. Early destructive effects of sunlight on human skin. *J Am Acad Dermatol* 1969; **210**: 2377–80.

3 Braverman IM, Fonferko E. Studies in cutaneous aging. I. The elastic fiber network. *J Invest Dermatol* 1982; **78**: 434–43.

4 Braverman IM, Fonferko E. Studies in cutaneous aging. II. The microvasculature. *J Invest Dermatol* 1982; **78**: 444–8.

5 Kumakiri M, Hashimoto K, Willis I. Biologic changes due to long-wave ultraviolet radiation in human skin. *J Invest Dermatol* 1977; **69**: 392–400.

6 Pfau RG, Hood AF, Morison WL. Photoageing: the role of UVB, solarsimulated UVB and psoralen PUVA. *Br J Dermatol* 1986; **114**: 319–27.

7 Lavker RM, Kligman AM. Chronic heliodermatitis: a morphologic evaluation of chronic actinic dermal damage with emphasis on the role of the mast cells. *J Invest Dermatol* 1988; **90**: 325–30.

8 Fisher GJ, Kang S, Varami J *et al.* Mechanisms of photoaging and chronological skin aging. *Arch Dermatol* 2002; **138**: 1467–70.

9 Carter VH, Constantine VS, Poole WL. Elastotic nodules of the antihelix. *Arch Dermatol* 1969; **100**: 282–5.

10 Mitchell RE. Chronic solar dermatosis: a light and electron microscopic study of the dermis. *J Invest Dermatol* 1967; **48**: 203–20.
11 Lavker RM. Structural alterations in exposed and unexposed aged skin. *J Invest Dermatol* 1979; **73**: 59–66.
12 Bouissou H, Pieraggi M-T, Julian M, Savit T. The elastic tissue of the skin. A comparison of spontaneous and actinic (solar) aging. *Int J Dermatol* 1988; **27**: 327–35.
13 Tolwar HS, Griffiths CEM, Fisher GJ *et al.* Reduced type I and type III procollagen in photodamaged adult human skin. *J Invest Dermatol* 1995; **105**: 285–90.
14 Craven NM, Watson REB, Jones CJP *et al.* Clinical features of photodamaged skin are associated with a reduction in collagen VII. *Br J Dermatol* 1997; **137**: 344–50.
15 Watson REB, Griffiths CEM, Craven NM *et al.* Fibrillin-rich microfibrils are reduced in photoaged skin distribution at the dermal-epidermal junction. *J Invest Dermatol* 1999; **112**: 782–7.
16 Brennan M, Bhatti H, Nerusu KC *et al.* Matrix metalloproteinase-1 is the major collagenolytic enzyme responsible for collagen damage in UV-irradiated human skin. *Photochem Photobiol* 2003; **78**: 43–8.
17 Bernstein EF, Underhill CB, Hahn PJ *et al.* Chronic sun exposure alters both the content and distribution of dermal glycosaminoglycans. *Br J Dermatol* 1996; **135**: 255–62.
18 Wojno T, Tenzel RR. Actinic comedonal plaque of the eye. *Am J Ophthalmol* 1983; **96**: 687–8.
19 Eastern JS, Martin S. Actinic comedonal plaque. *J Am Acad Dermatol* 1988; **3**: 633–6.
20 John SM, Hamm H. Actinic comedonal plaque. A rare ectopic form of the Favre–Racouchot syndrome. *Clin Exp Dermatol* 1993; **18**: 256–8.
21 Sams WM. Sun-induced aging. Clinical and laboratory observations in man. *Dermatol Clin* 1986; **4**: 509–16.
22 Davis BE, Koh HK. Faces going up in smoke. A dermatologic opportunity for cancer prevention. *Arch Dermatol* 1992; **128**: 255–62.
23 Gilchrest BA. A review of skin ageing and its medical therapy. *Br J Dermatol* 1996; **135**: 867–75.
24 Kligman LH. Connective tissue photo-damage in hairless mice is potentially reversible. *J Invest Dermatol* 1987; **88**: S12–7.
25 Moy LS, Murad H, Moy RL. Glycolic acid therapy, evaluation of efficacy and techniques in treatment of photodamaged lesions. *Am J Cosmetic Surg* 1993; **10**: 9–13.
26 Kligman AM, Grove GL, Hirose R *et al.* Topical tretinoin for photoaged skin. *J Am Acad Dermatol* 1986; **15**: 836–59.
27 Griffiths CEM, Russman AN, Majmuder G *et al.* Restoration of collagen formation in photodamaged human skin by tretinoin (retinoic acid). *N Engl J Med* 1993; **329**: 530–5.
28 Singh M, Griffiths CEM. The use of retinoids in the treatment of photoaging. *Dermatol Ther* 2006; **19**: 297–305.
29 Kligman AM, Dogadkina D, Lavker RM. Effects of topical tretinoin on non-sun-exposed protected skin of the elderly. *J Am Acad Dermatol* 1993; **29**: 25–33.
30 Gilchrest BA. Turning back the clock: retinoic acid modifies intrinsic aging changes. *J Clin Invest* 1994; **94**: 1711–2.
31 Lateef H, Stevens MJ, Varani J. All-*trans*-retinoic acid suppresses matrix metalloproteinase activity and increases collagen synthesis in diabetic human skin in organ culture. *Am J Pathol* 2004; **165**: 167–74.
32 Maddin S, Laurharanta J, Agache P *et al.* Isotretinoin improves the appearance of photodamaged skin: results of a 36-week, multicenter, double-blind, placebo-controlled trial. *J Am Acad Dermatol* 2000; **42**: 56–63.
33 Phillips TJ, Gottlieb AB, Leyden JJ *et al.* Efficacy of 0.1% tazarotene cream for the treatment of photodamage. *Arch Dermatol* 2002; **138**: 1486–93.
34 Ang P, Barlow RJ. Non-ablative laser resurfacing: a systematic review of the literature. *Clin Exp Dermatol* 2002; **27**: 630–5.
35 Watson REB, Craven NM, Kang S *et al.* A short-term screening assay, using fibrillin-1 as a reporter molecule for photoageing repair agents. *J Invest Dermatol* 2001; **116**: 672–8.
36 Watson REB, Long SP, Bowden JJ *et al.* Repair of photoaged dermal matrix by topical application of a cosmetic "antiageing" product. *Br J Dermatol* 2008; **158**: 472–7.

Elastotic nodules of the ear

In this variant of actinic elastosis, single or multiple firm papules occur on the anterior crus of the antihelix, usually in middle-aged or elderly males. Sometimes lesions have a pearly edge, clinically suggesting BCC, but histology reveals large aggregates of amorphous elastotic material, sometimes with degradation of underlying cartilage [1,2].

References

1 Carter VH, Constantine VS, Poole WC. Elastotic nodules of the antehelix. *Arch Dermatol* 1969; **100**: 282–5.
2 Weedon D. Elastotic nodules of the ear. *J Cutan Pathol* 1981; **8**: 429–33.

Digital papular calcific elastosis

Synonyms
- Keratoelastoidosis marginalis
- Collagenous and elastotic marginal plaques of the hands

Digital papular calcific elastosis (DPCE) is an acquired papular eruption in which keratoderma is associated with changes in dermal connective tissue. Predominantly it affects the radial aspect of the index finger, first web space and ulnar aspect of the thumb on the dominant hand [1,2]. Histologically there is hyperkeratosis, with sawtoothing of the rete ridges. The dermal collagen fibres are thickened and arranged haphazardly; there are basophilic elastotic masses, often containing calcium, in the upper reticular dermis [3]. Cases are sporadic, unlike the clinically similar disorders acrokeratoelastoidosis and focal acral hyperkeratosis (Chapter 19) [4]. Chronic friction and photodamage have been proposed as aetiological factors; the condition has been reported in manual workers and entirely from geographical areas with high solar irradiation. Digital papular calcific elastosis has been regarded as a variant of actinic elastosis [5], although actinic damage is not always observed clinically [6]. Furthermore, in DPCE, the elastotic process relatively spares the papillary dermis, and the basophilic areas containing calcium differ from the changes in actinic elastosis. Squamous carcinoma has been reported, arising from the lesion [7].

References

1 Burks JW, Wise LJ, Clark WH. Degenerative collagenous plaques of the hands. *Arch Dermatol* 1960; **82**: 362–6.
2 Jordaan HF, Rossouw DJ. Digital papular calcific elastosis: a histopathological, histochemical and ultrastructural study of 20 patients. *J Cutan Pathol* 1990; **17**: 358–70.
3 Menegesha YM, Kayal JD, Swerlick RA. Keratoelastoidosis marginalis. *J Cutan Med Surg* 2002; **6**: 23–5.
4 Rongioletti F, Betti R, Crosti C *et al.* Marginal papular acrokeratodermas: a unified nosology for focal acral hyperkeratosis, acrokeratoelastoidosis and related disorders. *Dermatology* 1994; **188**: 28–31.
5 Calderone DC, Fenske NA. The clinical spectrum of actinic elastotic. *J Am Acad Dermatol* 1995; **32**: 1016–24.
6 Mortimore RJ, Conrad RJ. Collagenous and elastoic marginal plaques of the hands. *Australas J Dermatol* 2001; **42**: 221–3.
7 Todd D, Al-Aboosi M, Hameed O *et al.* The role of UV light in the pathogenesis of digital papular calcific elastosis. *Arch Dermatol* 2001; **137**: 379–81.

Actinic granuloma

Synonym
- O'Brien's granuloma

Definition. This is an annular inflammatory reaction with a giant cell dermal infiltrate, which develops in an area of actinic elastosis. Some authors feel that this is not a specific entity, and the changes could be a feature of granuloma annulare or some other granulomatous disease that happens to occur on light-exposed skin [1]. Others point out that a similar granulomatous reaction to elastotic material can occur in pinguecula of the eye [2]. Histopathological studies support histological distinction of the two conditions [3–7]. There is minimal or no lysozyme activity in the histiocytes in the inflammatory area of actinic granuloma, in contrast with those of granuloma annulare, which exhibit abundant lysozyme activity [4].

The condition is more common in sunny countries, and fair-skinned or freckled subjects are particularly susceptible. It has been associated with doxycycline photosensitivity [8]. A similar condition has been described in dark-skinned people under the name of granuloma multiforme (Chapter 60).

Pathology [3–7]. A biopsy taken radially across the thickened edge of the lesion shows three distinct zones in the dermis. In the external 'normal' skin, there is actinic elastosis. In the thickened annulus, there is a histiocytic and giant cell inflammatory reaction in relation to elastotic fibres, and in the centre, within the annulus, little or no elastic tissue remains. The cellular infiltrate slowly expands outwards, leaving behind a central area from which elastic fibres have been removed by 'elastoclasis'.

The epidermis may be normal or it may show signs of actinic damage.

Clinical features. Lesions develop in the exposed 'weather-beaten' skin of patients after the third decade, particularly in fair-skinned or freckled subjects. They start insidiously as small, pink papules, which progress slowly to form an annulus of firm, superficial, dermal thickening. This is smooth, slightly raised and measures 0.2–0.5 cm in width. The ring may expand up to 6 cm in diameter. The centre may become slightly atrophic, and variable depigmentation may occur. The lesions are usually asymptomatic, but a sunburn reaction may provoke severe erythema and irritation.

Diagnosis. The condition must be distinguished from granuloma multiforme, granuloma annulare, serpiginous perforating elastosis, Miescher's disciform granuloma, sarcoidosis and necrobiosis lipoidica. The lesions of actinic granuloma are confined to light-exposed skin, and the infiltrate lacks the tidy palisaded arrangement that is normally seen with granuloma annulare. Rarely, granuloma annulare can occur in an actinic distribution [9].

Treatment. Infiltration of the annular edge of the lesions with triamcinolone may be effective. Sunscreens should be used to prevent further damage.

Isotretinoin (0.5 mg/kg/day) [10] and acitretin 25 mg/day [11] arrested the development of lesions in elderly males.

References

1 Ragaz A, Ackerman AB. Is actinic granuloma a specific condition? *Am J Dermatopathol* 1979; **1**: 43–50.
2 Dahl M. Is actinic granuloma really granuloma annulare? *Arch Dermatol* 1986; **122**: 39–40.
3 Al-Hoqail IA, Al-Ghamdi AM, Martinka M *et al.* Actinic granuloma is a unique and distinct entity: a comparative study with granuloma annulare. *Am J Dermatopathol* 2002; **24**: 209–12.
4 McGrae JD. Actinic granuloma: a clinical, histopathologic and immunocytochemical study. *Arch Dermatol* 1986; **122**: 43–8.
5 O'Brien JP. Actinic granuloma: an annular connective tissue disorder affecting sun and heat-damaged (elastotic) skin. *Arch Dermatol* 1975; **111**: 460–70.
6 Prendiville J, Griffiths WAD, Russell-Jones R. O'Brien's actinic granuloma. *Br J Dermatol* 1985; **113**: 353–8.
7 Limas C. The spectrum of primary cutaneous elastolytic granulomas and their distinction from granuloma annulare: a clinicopathological analysis. *Histopathology* 2004; **44**: 277–82.
8 Lim DS, Triscott J. O'Brien's granuloma associated with prolonged doxycycline photosensitivity. *Australas J Dermatol* 2003; **44**: 67–70.
9 Barker JNWN, Groves RW, MacDonald DM. Actinic granuloma annulare. *Br J Dermatol* 1991; **125** (Suppl. 38): 79–80.
10 Ratnavel RC, Grant JW, Handfield-Jones SE *et al.* O'Brien's actinic granuloma: response to isotretinoin. *J R Soc Med* 1995; **88**: P528–9.
11 Stefanaki C, Panagiotopoulos A, Kostakis P *et al.* Actinic granuloma successfully treated with acitretin. *Int J Dermatol* 2005; **44**: 163–6.

Elastofibroma [1–5]

Elastofibroma occurs predominantly in elderly women. Most cases are reported from Southern Japan. There may be a history of prolonged manual labour. The painless or slightly tender swelling situated beneath the lower angle of the scapula, and from 2 to 10 cm in diameter, is often discovered fortuitously. It may enlarge slowly, displacing neighbouring structures, and it can be clinically confused with a sarcoma. This is a benign lesion, however, despite the fact that it is poorly circumscribed. The growth is composed of mature fibrous tissue, containing fibres which stain as elastic fibres. The lesions may be solitary or multiple.

Histologically, the lesion contains abundant, large elastic fibres, some broken into irregular masses, and large amounts of relatively acellular collagen. The elastic fibres are composed of true elastin surrounded by a large amount of hydrophilic material forming an orderly array of tubules [4]. It is generally regarded either as a type of reactive hyperplasia, or as a hamartoma, arising either from dermis, subscapular connective tissue or periosteum [6]. It is cured by simple excision [7].

References

1 Nagamine N, Nohara Y, Ito E. Elastofibroma in Okinawa; a clinicopathologic study of 170 cases. *Cancer* 1982; **50**: 1794–805.
2 Fukuda Y. Histogenesis of the unique elastinophilic fibres of elastofibroma. *Hum Pathol* 1987; **18**: 424–9.
3 Kapff PD. Elastofibroma of hand. *J Bone Joint Surg* 1987; **69**: 468–9.
4 Govoni E. Elastofibroma: an *in vivo* model of abnormal elastoneogenesis. *Ultrastruct Pathol* 1988; **12**: 327–39.
5 Gartmann H, Groth W, Kuhn A. Elastofibroma dorsi. *Z Hautkr* 1988; **63**: 525–8.
6 Yamazaki K. An ultrastructural and immunohistochemical study of elastofibroma: CD 34, MEF-2, pronine 2 (CD33), and factor XIIIa- positive proliferating fibroblastic stromal cells connected by Cx43-type gap junctions. *Ultrastruct Pathol* 2007; **31**: 209–19.
7 Mortman KD, Hochheiser GM, Giblin EM *et al.* Elastofibroma dorsi: clinicopathologic review of 6 cases. *Ann Thorac Surg* 2007; **83**: 1894–7.

Elastoderma

Elastoderma is a very rare condition which is due to excessive elastogenesis, as distinct from acquired cutis laxa, where there is a loss of elastic tissue. A young woman developed a localized

defect of the skin of one arm, which became pendulous and lax, but lost its elastic recoil. Histological and biochemical investigation showed this was due to accumulation of excessive elastin, with derangement of elastin fibrillogenesis [1].

In a further case, clinically uninvolved skin showed thin elastic fibres on haematoxylin and eosin staining [2].

References

1 Kornberg RL, Hendler SS, Oikarinen AI *et al.* Elastoderma—disease of elastin accumulation within the skin. *N Engl J Med* 1985; **312**: 771–2.

2 Yen A, Wen J, Grau M *et al.* Elastoderma. *J Am Acad Dermatol* 1995; **33**: 389–92.

Marfan's syndrome (MFS)

Definition. This is an autosomal dominant inherited disorder of connective tissue with variable clinical manifestations, both between and within families, and a prevalence of one in 5000–10 000 [1]. Up to 30% of cases are new mutations [2]. The full syndrome is characterized by aortic dilatation, ectopia lentis and skeletal abnormalities [3].

Aetiology. Mutations in the fibrillin-1 (*FBN1*) gene, located on chromosome 15q21.1, cause Marfan's syndrome [4]. Fibrillin is one component of the elastin-associated microfibrils, which are especially important in the ciliary zonule of the eye (the suspensory ligament of the lens). Patients with MFS show a striking lack of fibrillin in their skin and on culture of their dermal fibroblasts [5,6]. It has recently been recognized that changes in growth factor signalling are critical in MFS. As well as its structural role, fibrillin-1 also binds transforming growth factor β (TGF-β), and abnormal fibrillin leads to a detrimental increased expression of TGF-β [7]. In addition, a number of disorders with phenotypic overlap with MFS, for example Loeys–Dietz syndrome, are caused by mutations in the TGF-β receptor genes, *TGFBR1* and *TGFBR2* [8].

Pathology. The cardiovascular lesions are the most important. Fragmentation and sparsity of elastic fibres, with accumulation of mucinous material, occur in the media of the aorta [9–11]. These changes lead to aortic incompetence, dissecting aneurysm, or rupture of the aorta [12]. Mitral incompetence is common [13]. Dermal elastic fibres are narrower than normal and more resistant to neutrophil elastase [14]. Mild to severe degenerative changes in elastic tissue are also seen in the lungs [15].

Clinical features [3,10,16,17]. Despite recent advances in mutation detection, the diagnosis of MFS is primarily clinical and relies on the Ghent nosology [3]. The full syndrome comprises skeletal, ocular and cardiovascular defects. The patient is often, but not invariably, exceptionally tall, and the skeletal proportions are abnormal. The limbs are long, the excess being greatest distally, giving rise to arachnodactyly, and the length of the hallux is often particularly conspicuous. The skull is dolichocephalic, the paranasal sinuses are large and the palate high and arched [18]. Lax capsules result in unstable or hyperextensible joints, kyphoscoliosis, pectus excavatum and flat foot. Muscles may be underdeveloped and hypotonic, and subcutaneous fat is sparse.

The common ocular abnormalities [19] include ectopia lentis (usually upward), a trembling iris, myopia and retinal detachment; less frequent are blue sclerae and heterochromia of the iris.

Aneurysmal dilatation of the ascending aorta is the most important abnormality of the cardiovascular system, and aortic and mitral incompetence are common. Aortic dilatation may begin in childhood. Mitral valve prolapse occurs in 80% of cases [20].

Skin changes may be under-reported. Serpiginous perforating elastosis may occur [17]. In a recent study [21], striae atrophicae were observed in 7% of children and 35% of adults. Other features include papyraceous scars and skin hyperextensibility [22]. Several patients have been described with concomitant EDS and MFS [23].

Other abnormalities are frequent—nerve deafness occurs in 6%; pulmonary malformations are often reported at autopsy; renal abnormalities are manifest as proteinuria and raised blood urea [16].

The prognosis is related to the severity of the cardiac defects, the localization and progression of which are dependent on haemodynamic stresses [10,24]. Survival beyond the fifth decade is unusual, and some cases die in childhood. The average age at which dissection of the aorta develops is 30 years. Early death from cardiovascular disease may occur, even in apparently mild cases, and the correlation between cardiac and skeletal problems is poor [25–27].

Diagnosis [3,28]. The full syndrome is unmistakable, but diagnostic certainty is impossible in the partial forms. Clinical features are divided into major and minor according to their specificity. To make a diagnosis major criteria must be present in two organs and involvement in a third is required [3].

Simple screening tests that may be helpful include the thumb sign (positive if the thumb when completely opposed in the clenched hand projects beyond the ulnar border), the wrist sign (positive if the thumb and little finger overlap when wrapped around the opposite wrist) and the ratio of the lower segment (pubic ramus to floor) to the upper segment (height minus lower segment), but this ratio varies with age and sex.

Some tall people have high, arched palates and some degree of arachnodactyly. This is probably of no consequence in many cases, although a marfanoid habitus in women may be associated with mitral valve prolapse [20,29].

Joint hypermobility may also be associated with mitral valve prolapse [30]. Other causes of joint hypermobility, such as homocystinuria, may be confused with the partial forms of the syndrome. Homocystinuria should be considered in marfanoid patients with myopia or downward ectopia lentis. Urine screening is unreliable; blood levels of methionine and homocysteine should be measured. Prompt diagnosis and treatment reduce the risk of coronary artery or cerebrovascular thrombosis [31].

The marfanoid habitus has been reported in association with distal pigmentation, neuroma of the eyelids and tongue, medullary carcinoma of the thyroid and phaeochromocytoma [32] (see also multiple endocrine neoplasm syndrome (Chapter 62)).

Congenital contractural arachnodactyly is another fibrillinopathy, which is caused by mutations of the fibrillin-2 gene [33]. It is primarily an orthopaedic condition unrelated to MFS [34,35]. It produces multiple joint contractures, arachnodactyly, kyphoscoli-

osis, distorted pinnae and dolichostenomelia (long, thin limbs), but there are no cardiovascular complications.

Management [28]. Patients should be seen by an ophthalmologist and an orthopaedic surgeon, and they should be reviewed regularly by a cardiologist. Beta-blockers may be used to retard the development of aortic dilatation, and surgical replacement before the diameter exceeds 5.5–6.0 cm is recommended [11,36]. Losartan, an angiotensin II type I receptor antagonist has anti-TGF-β effects and, if administered postnatally to fibrillin-deficient mice, reverses aortic root dilatation [37]. Trials are underway to determine whether similar effects can be observed in young patients with Marfan's syndrome.

Oestrogen therapy has been used to prevent excessive stature in female patients [38].

Pregnancy is inadvisable, because of the 50% risk of inheritance in the fetus, and because of the risk of acceleration of aortic degeneration and vascular rupture. A pregnant patient with no cardiac signs needs monthly checks from the third month. Those with aortic or mitral valvular disease or dilatation of the aortic root are at high risk during pregnancy [39,40].

The majority of *FBN1* mutations are unique to one affected individual or family, but despite this and the presence of sporadic cases, prenatal and preimplantation diagnosis is feasible [2].

References

1 Pyeritz RE, Dietz HC. The Marfan syndrome and other microfibrillary disorders. In: Royce PM, Steinmann B, eds. *Connective Tissue and its Heritable Disorders: Molecular, Genetic and Medical Aspects*, 2nd edn. New York: Wiley–Liss, 2002: 585–626.

2 Toudjarska I, Kilpatrick MW, Lembessis P *et al*. Novel approach to the molecular diagnosis of Marfan syndrome: application to sporadic cases and in prenatal diagnosis. *Am J Med Genet* 2001; **99**: 294–302.

3 De Paepe A, Devereux RB, Dietz HC *et al.* Revised diagnostic criteria for the Marfan syndrome. *Am J Med Genet* 1996; **62**: 417–26.

4 Dietz HC, Cutting GR, Pyeritz RE *et al.* Marfan syndrome caused by a recurrent *de novo* missense mutation in the fibrillin gene. *Nature* 1991; **352**: 337–9.

5 Hollister DW, Godfrey MP, Keene DR *et al.* Immunohistologic abnormalities of the microfibrillar-fiber system in the Marfan syndrome. *N Engl J Med* 1990; **323**: 152–9.

6 Milewicz DM, Pyeritz R, Stanley Crawford E *et al.* Marfan syndrome: defective synthesis, secretion, and extracellular matrix formation of fibrillin by cultured dermal fibroblasts. *J Clin Invest* 1992; **89**: 79–86.

7 Neptune ER, Frischmeyer PA, Arking DE *et al*. Dysregulation of TGF-β activation contributes to pathogenesis in Marfan syndrome. *Nat Genet* 2003; **33**: 407–11.

8 Robinson PN, Arteaga-Solis E, Baldock C *et al*. The molecular genetics of Marfan syndrome and related disorders. *J Med Genet* 2006; **43**: 769–87.

9 Boucek RJ. The Marfan syndrome: a deficiency in chemically stable collagen cross-links. *N Engl J Med* 1981; **305**: 988–90.

10 Bruno L, Tredici S, Mangiavacchi M *et al.* Cardiac, skeletal and ocular abnormalities in patients with Marfan's syndrome and their relatives. *Br Heart J* 1984; **51**: 220–30.

11 Gott VL. Surgical treatment of aneurysms of the ascending aorta in the Marfan syndrome. *N Engl J Med* 1986; **314**: 1070–4.

12 Pyeritz RE. Marfan syndrome and other disorders of fibrillin. In: Rimoin DL, Connor JM, Pyeritz RE, Korf BR, eds. *Principles and Practice of Medical Genetics*, 4th edn. London: Churchill Livingstone, 2002: 3977–4020.

13 Roberts WC. The spectrum of cardiovascular disease in the Marfan syndrome. A clinico-morphologic study of 18 necropsy patients. *Am Heart J* 1982; **104**: 115–35.

14 Berteretche M-V, Hornebeck W, Pellat B *et al.* Histomorphometric parameters and susceptibility to neutrophil elastase degradation of skin elastic fibres from healthy individuals and patients with Marfan syndrome, Ehlers–Danlos type IV, and pseudoxanthoma elasticum. *Br J Dermatol* 1995; **133**: 836–41.

15 Soyers CP, Goltz RW, Mottiaz J. Pulmonary elastic tissue in generalized elastolysis (cutis laxa) and Marfan's syndrome: a light and electron microscopic study. *J Invest Dermatol* 1975; **65**: 451–7.

16 Loughridge LW. Renal abnormalities in the Marfan syndrome. *QJM* 1959; **28**: 531–43.

17 Loveman AB, Gordon AM, Fliegelmann MT. Marfan's syndrome. *Arch Dermatol* 1963; **87**: 428–33.

18 Wilner HJ, Finby N. Skeletal manifestations in Marfan's syndrome. *J Am Acad Dermatol* 1964; **187**: 490–5.

19 Wachtel JG. The ocular pathology of Marfan's syndrome including an explanation of ectopia lentis. *Arch Ophthalmol* 1966; **76**: 512–22.

20 Beighton P. Mitral valve prolapse and a Marfanoid habitus. *BMJ* 1982; **284**: 920.

21 Grahame R, Pyeritz RE. The Marfan syndrome. Joint and skin manifestations are prevalent and correlated. *Br J Rheumatol* 1995; **34**: 126–31.

22 Goodman RM, Allison ML. Observations on the heart in a case of combined Ehlers–Danlos and Marfan syndrome. *Am J Cardiol* 1969; **24**: 734–42.

23 Cunliffe WJ, Ead RD. A case of Marfan's syndrome occurring with Ehlers–Danlos syndrome. *Clin Exp Dermatol* 1977; **2**: 117–20.

24 Halpern B, Char F, Murdoch JL *et al.* A prospectus on the prevention of aortic rupture in the Marfan syndrome with data on survivorship without treatment. *Johns Hopkins Med J* 1971; **129**: 123–9.

25 Come PC. Echocardiographic recognition of silent aortic root dilatation in Marfan's syndrome. *Chest* 1977; **72**: 789–92.

26 Dalgleish R, Hawkins JR, Keston M. Exclusion of the α2 (I) and α1 (III) collagen genes as the mutant loci in a Marfan syndrome family. *J Med Genet* 1987; **24**: 148–51.

27 Marlow N, Gregg JEM, Qureshi SA. Mitral valve disease in Marfan's syndrome. *Arch Dis Child* 1987; **62**: 960–2.

28 Pyeritz RE, McKusick VA. The Marfan syndrome: diagnosis and management. *N Engl J Med* 1979; **300**: 772–7.

29 Schutte JE, Gaffney FA, Blend L *et al.* Distinctive anthropometric characteristics of women with mitral valve prolapse. *Am J Med* 1981; **71**: 533–8.

30 Grahame R, Edwards JC, Pitcher D *et al.* A clinical and echocardiograph study of patients with hypermobility syndrome. *Ann Rheum Dis* 1981; **40**: 451–6.

31 Cruysberg JRM, Boers GHJ, Frans Trijbels JM *et al.* Delay in diagnosis of homocystinuria: retrospective study of consecutive patients. *BMJ* 1996; **313**: 1037–40.

32 Cunliffe WJ, Hudgson P, Fulthorpe JJ *et al.* A calcitonin-secreting medullary thyroid carcinoma with mucosal neuromas, Marfanoid features, myopathy and pigmentation. *Am J Med* 1970; **48**: 121–6.

33 Putnam EA, Zhang H, Ramirez F, Milewicz DM. Fibrillin-2 (*FBN2*) mutations result in the Marfan-like disorder, congenital contractural arachnodactyly. *Nat Genet* 1995; **11**: 456–8.

34 Currarino G, Friedman JM. A severe form of congenital contractural arachnodactyly in two newborn infants. *Am J Med Genet* 1986; **25**: 763–73.

35 Travis RC, Shaw DG. Congenital contractural arachnodactyly. *Br J Radiol* 1985; **58**: 1115–7.

36 McDonald G, Schaff HV, Pyeritz RE. Surgical management of patients with Marfan syndrome and dilatation of the ascending aorta. *J Thorac Cardiovasc Surg* 1981; **81**: 180–6.

37 Habashi JP, Judge DP, Holm TM *et al*. Losartan, an AT1 antagonist, prevents aortic aneurysm in a mouse model of Marfan syndrome. *Science* 2006; **312**: 117–21.

38 Knudtzon J, Aarskog D. Estrogen treatment of excessively tall girls with Marfan's syndrome. *Acta Paediatr Scand* 1988; **77**: 537–41.

39 Mor-Yosef S, Younis J, Granat M *et al.* Marfan's syndrome in pregnancy. *Obstet Gyn Surv* 1988; **43**: 382–5.

40 Pyeritz RE. Maternal and fetal complications of pregnancy in the Marfan syndrome. *Am J Med* 1981; **71**: 784–90.

Disorders of collagen

Ehlers–Danlos syndrome

Synonym

- Cutis hyperelastica

Definition. Ehlers–Danlos syndrome (EDS) is a heterogeneous group of inherited disorders of connective tissue. Estimates of its prevalence vary between 1:560 000 and 1:5000 [1]. For many patients the symptoms are so mild that they may not be recognized. The hallmarks of EDS are fragility of the skin and blood vessels, hyperextensibility of the skin and joint hypermobility [2]. The original classification divided EDS into 11 clinical types; however, in 1986, the International Nosology of Heritable Disorders of Connective Tissue redefined EDS into subtypes I–VIII and X [3]. It is now clear that certain phenotypic subtypes (EDS types I and II) overlap and some patients do not fit neatly into one category. Progress in molecular biology has been rapid in recent years, enabling further subdivision of some types [4].

Aetiology. Specific molecular and biochemical abnormalities have been identified in several types (Table 45.3) [5,6]. Attempts should be made to delineate the clinical, biochemical and, if possible, molecular abnormalities in a patient with EDS in view of the widely differing prognosis between different types. Defects predominantly involve collagen, although a fibronectin defect has been reported in type X [7], and most recently mutations in tenascin-X have been found to cause a newly recognized autosomal recessive form of EDS.

Pathology [8,9]. Skin histology is variable and often within normal limits. Typically, there is a loose, disordered dermal collagen network. Elastic fibres are usually increased and orientated irregularly. The 'pseudotumours' seen in classical EDS (type I) consist of fat and mucoid material in fibrous capsules; they may be calcified. Bone mineralization is decreased, and the collagen fibres are irregular. Adventitial defects of small arteries and inadequate support from the surrounding connective tissue account for the vascular vulnerability in vascular EDS (type IV) [10,11]. Although bruising can be explained on the basis of skin and blood vessel fragility, a few patients also exhibit both ultrastructural and functional platelet defects [12,13]. Clotting factor deficiencies have

Table 45.3 Clinical and molecular subtypes of Ehlers–Danlos syndrome.

EDS type	Synonym	Villefranche classification*	Mode of inheritance	Clinical features	Ultrastructural findings	Molecular defect
I II	Gravis Mitis	Classical	AD	Soft, velvety, hyperextensible skin; easy bruising; atrophic scars; hypermobile joints; pseudotumours	'Cauliflower' fibrils	*COL5A1* & *COL5A2* (& *COL1A1*) mutations
III	Hypermobile	Hypermobility	AD	Hypermobile joints; minimal skin abnormality	As above	?
IV	Acrogeric or ecchymotic	Vascular	AD	Thin skin; easy bruising; small joint hypermobility; vascular and bowel ruptures	Small variable fibrils	*COL3A1* mutations
V	X-linked	Other form	XLR	Resembles mild classical type; bruising more pronounced	—	?
VI	Ocular-scoliotic	Kyphoscoliosis	AR	Soft, hyperextensible skin; hypermobile joints; scoliosis; ocular fragility; keratoconus	Small collagen bundles; fibrils normal or similar to classical type	Lysyl hydroxylase *(PLOD)* mutations
VIIA, B	Arthrochalasis multiplex congenita	Arthrochalasis	AD	Floppy infant; congenital hip dislocation; hypermobile joints; soft skin; normal scarring; short stature	Angular fibrils	A & B: *COL1A1* & *COL1A2* mutations, respectively, result in loss of exon 6 (procollagen *N*-proteinase/ *ADAMTS2* cleavage site)
VIIC	Dermatosparaxis	Dermatosparaxis	AR	Markedly hypermobile joints; very soft and extremely fragile skin; easy bruising	Hieroglyphic fibrils	Procollagen *N*-proteinase (*ADAMTS2*) mutations
VIII	Periodontal	Other form	AD	Severe periodontitis; pigmented pretibial plaques and scarring	Small fibrils in some patients	Occasionally collagen III deficient
X	Fibronectin	Other form	AR	Similar to mild classical type	Large, irregular fibrils	Fibronectin deficiency abnormality
—	Progeroid	Other form	AR	Atrophic scars; lax skin and joints; aged appearance; short stature; osteopenia; mental retardation	—	*XGPT1* mutations
—	Tenascin-X	—	AR	Similar to mild classical type but no scarring	Normal fibrils but reduced density	Tenascin-X mutations

* The Villefranche classification simplifies EDS into six major types. The other types have been provisionally grouped under 'other forms' until more is known about their molecular basis.

AD, autosomal dominant; AR, autosomal recessive; EDS, Ehlers–Danlos syndrome; XLR, X-linked recessive.

been only rarely reported. Electron microscopy of dermal collagen consistently shows irregularities of fibril shape and size, although reliable subclassification of the more common subtypes is not possible [14]. Tenascin-X deficient patients have uniform collagen fibrils which are less densely packed and not as well aligned [15]. In contrast, arthrochalasia type EDS is characterized by angular fibrils in cross-section, and dermatosparaxis by grossly distorted, hieroglyphic fibrils. Biomechanical studies confirm increased skin elasticity and hyperextensibility, particularly in classical EDS (type I) [16,17].

Clinical features. These are summarized in Table 45.3. The india-rubber men and circus contortionists who are affected by EDS turn the syndrome to their advantage. More details are given in the accounts of each type.

Classical type (EDS I/II)

This subgroup, which is inherited as an autosomal dominant, includes both EDS type I (gravis) and II (mitis).

Pathology. Histology may be within normal limits; alternatively there may be thin, weakly polarized, dermal collagen bundles. Elastic fibres may be irregular and relatively increased [8,9]. At ultrastructural level, collagen bundles are of variable size with abnormally large, composite 'cauliflower' fibrils, reflecting abnormal fibrilogenesis [14,18,19]. Linkage to *COL5A1* was originally identified in a British family with EDS II, and analysis of further families subsequently showed that EDS I and II are allelic [20,21]. Up to half of all classical EDS patients have mutations in *COL5A1* or *COL5A2*, which encode the α_1 and α_2 chains of type V collagen, respectively. Although quantitatively minor (approximately 2–5% of dermal collagen), collagen V plays an important role in the regulation of type I collagen diameter [22]. Missense and exon skipping mutations with dominant-negative effects or mutations giving rise to haploinsufficiency may occur [15,23]. Genetic heterogeneity is apparent with reports of classical EDS caused by a mutation in the collagen I gene [24]. Furthermore, knock-out experiments with mice suggest other extracellular matrix components such as decorin, fibromodulin, thrombospondin-2, lumican and biglycan may be important [25,26].

Clinical features. The skin is soft, velvety and hyperextensible (Fig. 45.21) but retains its normal recoil. The skin on the palms and soles may be redundant, like a loose glove. The skin is not usually otherwise lax until later in life, when redundant folds occur on the eyelids (blepharochalasis), face and limbs. Secondary cutis laxa has been described on the lower back of a patient with mild classical EDS [27]. Striae do not develop during pregnancy. Trivial lacerations form gaping wounds that heal very slowly to leave broad, atrophic 'cigarette paper' scars (Figs 45.22 & 45.23). Sutures may tear out repeatedly. Blue-grey, spongy tumours (molluscoid pseudotumours), due to accumulation of connective tissue, may form on the skin, especially in scars or over pressure points. Smaller, firm, subcutaneous nodules (spheroids), which show calcification on X-ray, develop on the shins and forearms in up to a third of patients.

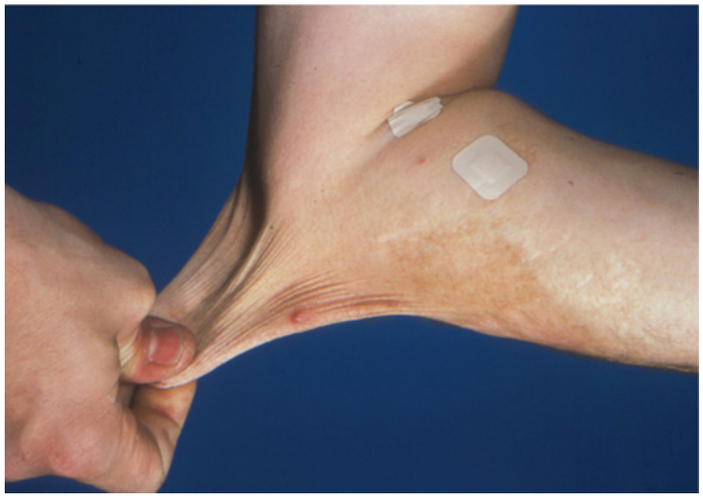


Fig. 45.21 Cutaneous hyperextensibililty in classical Ehlers–Danlos syndrome.



Fig. 45.22 Atrophic scarring of the elbow in classical Ehlers–Danlos syndrome.



Fig. 45.23 Scarring of the forehead in classical Ehlers–Danlos syndrome.

Easy bruising may be the presenting symptom, and pigmentation due to haemosiderin deposition is often found on areas of repeated trauma.

The facies may be distinctive, with widely spaced eyes, a wide nasal bridge, and epicanthic folds. The sclerae are sometimes blue.

There is marked joint hypermobility, which can impair walking, especially during pregnancy. Subluxation of the large joints may occur, and genu recurvatum and kyphoscoliosis are frequent [28]. Muscle tone is often poor, and hernias develop. Pedal piezogenic papules are seen more frequently. Diaphragmatic eventration and gastric torsion have been reported [29]. Symptomatic bladder diverticula may develop [30]. Varicose veins may develop in early life. Prematurity due to ruptured fetal membranes is common.

As physical and mental development are normal, life expectancy is not reduced, hence large family pedigrees are not unusual. A mild variant of classical EDS has been described in 9% of a general dermatology population less than 50 years old, and merges with benign hypermobility syndrome and the normal spectrum [31]. A simple clinical scoring system, based on an assessment of joint hypermobility, skin extensibility and bruising might be useful in predicting which members of the general population are likely to produce poor scars following cutaneous surgery [32].

Hypermobility type (EDS III)

Hypermobile EDS and benign joint hypermobility syndrome (BJHS) are autosomal dominant and considered by some authors to be the same disorder. Revised criteria have been proposed for their diagnosis [33]. The Beighton score (Table 45.4) is a useful, quick method for assessing global joint hypermobility, and an adult score of four or more out of nine either currently or historically is considered hypermobile [34]. Ultimately, molecular analysis will determine whether these two groups are genetically heterogeneous. Haploinsufficiency of tenascin-X results in reduced dermal collagen and may account for 5–10% of hypermobile type EDS, although this has only been found in females [35]. There is one report of a family with hypermobile EDS phenotype due to collagen III deficiency, as occurs in vascular EDS [36]. The ultrastructural changes resemble those in classical EDS. The skin is only minimally affected by scarring and hyperextensibility, whereas joint mobility is markedly increased, and dislocation and joint pains are common [37,38]. A study of a small number of hypermobile patients showed they were resistant to the effects of intradermal or topical local anaesthetic compared with BJHS patients or controls, suggesting that the disorders are distinct [39]. However, the criteria used to diagnose the hypermobile group were not clearly documented. In the authors' experience, patients with classical EDS may also rarely be resistant to local anaesthetic. Symptoms such as syncope, palpitations and fatigue suggest dysautonomia and are significantly more common in joint hypermobility patients, although the mechanisms remain unclear [40].

Table 45.4 Beighton score [34].

Movement	Score
Dorsiflex L and R 5th finger >90°	2
Apposition L and R thumb to forearm	2
Hyperextend L and R elbow >10°	2
Hyperextend L and R knee >10°	2
Palms to floor	1
TOTAL	9

Vascular type (EDS IV)

This very severe form is inherited as an autosomal dominant. Cases previously reported as autosomal recessive inheritance were probably due to sporadic mutations [41–43]. It is rare, the prevalence being between one in 10^5 and one in 10^6 [41].

Pathology. The condition is characterized by an abnormality of the synthesis, secretion or structure of type III collagen due to an abnormality of the collagen III gene (*COL3A1*) [6,44]. Segregation studies using polymorphic restriction sites in the gene may be of use in prenatal diagnosis [45]. The syndrome is biochemically heterogeneous [5]. Several changes have been reported, the most common of which are point mutations (substituting other amino acids for glycine residues in the triple helical domain). Exon-skipping mutations are nearly as common; small genomic deletions within one exon and multiexon deletions have also been described [5,6,46]. It has been suggested that the region of the type III collagen molecule where mutation occurs may be linked with the clinical severity [6], although this has not been found in other studies [46].

These abnormalities all result in abnormal structure, synthesis or secretion of type III procollagen. Often, the skin is reduced to 25% of normal thickness, with small collagen fibre bundles. Fibril diameter is markedly variable in some patients [47]. In many patients, the fibroblasts contain prominent rough endoplasmic reticulum containing abnormal type III procollagen [47,48]. Cell strains from other individuals show markedly reduced extracellular accumulation of procollagen and collagen but without intracellular accumulation, perhaps due to rapid degradation of mutant chains [49]. Bizarre elastic fibres are often abundant.

The condition affects tissues rich in type III collagen, notably arterial media, bowel and uterus. Interestingly, type III collagen production by fibroblasts is decreased in some patients with ruptured cerebral aneurysm, even though they have no other stigmata of EDS [50]. The collagen deficiency in these patients does not appear to arise from *COL3A1* mutations, but may relate to abnormal post-translational modification or altered collagen metabolism [51].

Clinical features. The major clinical features are spontaneous rupture of large arteries, colon and gravid uterus. Dissecting aortic aneurysm is a common cause of sudden death [52]. Spontaneous carotid–cavernous fistula can also occur, resulting in unilateral exophthalmos [53]; it may respond to surgical repair or embolization [54]. Repair of rupture of the colon (usually sigmoid) is complicated by tissue friability and peritoneal contamination [55]. In one series complications of pregnancy led to death in the peripartum period in 12 of 81 women who had a total of 183 pregnancies [46]. Seven died following vessel rupture and five following uterine rupture.



Fig. 45.24 Cutaneous atrophy in vascular (acrogeric) Ehlers–Danlos syndrome.

Other features include prematurity (due to rupture of friable placental membranes), low birth weight, short stature, easy bruising (which may lead to the mistaken accusation of child abuse) [56] and pneumothorax [57,58]. Elastosis perforans serpiginosa is seen more commonly in this EDS subtype.

Two phenotypic groups are recognizable. In the *acrogeric* type, individuals appear prematurely aged with thin, translucent, fragile skin (Fig. 45.24), a hollow-eyed appearance, thin, peaked nose and thin lips. Easy bruising predominates in the *ecchymotic* type, often falsely suggesting a primary disorder of coagulation [13]. Unlike other forms of EDS, the skin is not hyperextensible, and joint hypermobility is chiefly restricted to the small joints of the hands and feet. Surface veins are usually readily visible. There is a tendency to form keloid scars.

The largest case series to date of 220 index cases of vascular EDS patients and 199 affected relatives showed the median survival as 48 years, with 25% of index cases having their first significant complication by 20 years [46]. Most deaths follow arterial dissection or rupture, mainly of the thoracic and abdominal vessels. Milder variants may occur, presenting with cardiac features in later life [59].

Recently a new autosomal dominant aneurismal disorder, Loeys-Dietz syndrome, has been described. The major features of Loeys-Dietz syndrome type I patients overlap clinically with Marfan's syndrome whereas type II patients have a phenotype similar to vascular EDS. In a cohort of 40 patients with a presentation suggestive of vascular EDS, but normal type III collagen, Loeys and colleagues found mutations in the transforming growth factor-beta receptor genes *TGFBR1* and *TGFB2* [60]. Therefore Loeys-Dietz syndrome should be considered in any vascular EDS phenotype with normal collagen III.

X-linked type (EDS V)

Two families have been described as type V EDS. Clinically, it resembles mild classical EDS, but bruising is more marked. However, it is distinguished by X-linked inheritance [61]. The biochemical defect is unknown, and skin collagen cross-links are normal [62]. Lysyl oxidase activity has been reported to be reduced in one family [63], but these patients appear to form a clinically distinct subgroup. In other families, the lysyl oxidase levels have been normal [64]. Until a precise genetic or biochemical abnormality is found, the status of this type must remain in question [5].

Kyphoscoliosis type (EDS VI; ocular-scoliotic)

This autosomal recessive condition was the first true disorder of collagen structure to be described [64–66]. The biochemical abnormality in most, but not all, patients, is a deficiency of lysyl hydroxylase [65]. Different mutations in the lysyl hydroxylase gene (*PLOD*) have been identified in unrelated families. One is homozygous for a stop codon at residue 319 (R319X) [67]. In another, duplication of 180 base pairs in the coding sequence of the complementary DNA resulted in decreased enzyme function [68], and a further family revealed a compound heterozygote combining a three-base pair deletion and an amino acid substitution (G678A) [69].

Deficiency of the enzyme leads to reduced hydroxylation of lysyl residues in types I and III collagen in skin; hydroxylysine-containing cross-links are not formed [70]. Lysine-derived cross-links appear not to be as stable as those derived from hydroxylysine; the former do not mature as rapidly to stable intermolecular cross-links [71]. Types II, IV and V collagens are hydroxylated normally, which suggests that there may be different isoenzymes or different affinities of a single enzyme for specific collagen types [5]. Detection of abnormal pyridinoline cross-links in urine can be used as a diagnostic aid [72].

Clinical features include soft, velvety, hyperextensible skin and increased joint mobility. Scoliosis is common. Eye manifestations include microcornea, glaucoma, keratoconus and ocular fragility. Some patients have a marfanoid habitus. Bleeding may occur from major wounds, and there may be delayed motor development [73].

The kyphoscoliotic type of EDS appears to be rare, with less than two dozen cases reported in the literature [5]. Because it is inherited recessively, after the birth of an affected child there is a 25% risk of recurrence in each successive pregnancy. Measurement of lysyl hydroxylase activity in amniotic fluid enabled the prediction of a phenotypically normal heterozygous infant in a family at risk [74].

Some patients respond to treatment with ascorbic acid, which regulates collagen biosynthesis [75].

Arthrochalasia type (EDS VIIA and B; arthrochalasis multiplex congenita)

This rare autosomal dominant condition, like OI, results from mutations causing defects in type I collagen. Phenotypic overlap therefore occurs.

All or part of exon 6 of the *COL1A1* or *COL1A2* gene is deleted in types A and B, respectively, resulting in a defect in the cleavage sites of the substrate pro-α_1(I) or pro-α_2(I) chains [75–79]. Mutations appear to affect cross-link formation, decreasing tensile strength of tissues rich in type I collagen. Partially processed molecules accumulate in the dermis and other tissues, where they interfere with tissue function without much effect on fibrillar organization [76,80].

Arthrochalasis is characterized clinically by extreme joint hypermobility and multiple dislocations affecting both large and small



Fig. 45.25 Extreme cutaneous fragility and laxity in dermatosparaxis.



Fig. 45.26 Premature periodontal recession in periodontitis type Ehlers–Danlos syndrome (VIII).

joints [27]. Bilateral hip dislocation presents a major surgical problem. Some individuals have a short stature. There may be a chubby facial appearance due to lax facial tissues, and a depressed nasal bridge [80].

Dermatosparaxis type (EDS VIIC)

This very rare autosomal recessive form is characterized by extreme skin fragility (Fig. 45.25), bruising, droopy skin, joint laxity, umbilical hernia and blue sclerae [81–84]. The condition is akin to dermatosparaxis, a disorder causing fragile skin in animals [85–86]. It is caused by homozygous mutations in the gene encoding procollagen I *N*-terminal proteinase (*ADAMTS2*), the enzyme that excises the *N*-propeptide of type I and II procollagens [87]. Collagen fibrils from affected children and animals are small, with a bizarre hieroglyphic-like appearance in cross-section; they are ribbon-like in longitudinal section [5].

Periodontitis type (EDS VIII)

This type has features similar to classical EDS but there is often only moderate small-joint hypermobility. The distinguishing clinical features are premature periodontal recession (Fig. 45.26), resulting in loss of teeth by the third decade, and heavily pigmented, pretibial plaques (Fig. 45.27) [88,89]. Little is known about the biochemical defect, although there is a reduced proportion of type III collagen in skin [89]. Some patients have small collagen fibrils [89]. It is inherited as an autosomal dominant and linkage has been shown to chromosome 12p13 in three out of five families, indicating genetic heterogeneity [91].



Fig. 45.27 Pigmented pretibial plaques in periodontitis type Ehlers–Danlos syndrome (VIII).

EDS IX (occipital horn syndrome)

This is an X-linked recessive disorder allelic to Menkes' syndrome and is no longer considered a variant of EDS [3]. It was formerly known as X-linked cutis laxa or 'occipital horn syndrome' and has been reclassified as a disorder of copper transport (p. 45.39).

Fibronectin-deficient type (EDS X)

Only one family has been identified to date with this autosomal recessive disorder. Skin and joint changes are mild, but bruising occurs readily due to defective platelet aggregation [7]. This defect is reversed *in vitro* by adding purified fibronectin to the assay. Some patients have composite fibrils in the dermal collagen, possibly due to a defect in fibronectin interactions [92].

Progeroid EDS

A rare association of EDS with progeroid facies, short stature, osteopenia and mental retardation is recognized [93]. Patients lack the full phenotype of progeria (p. 45.58) and do not fit in to the more well-defined progeroid syndromes. Galactosyltransferase I activity is reduced in patients' fibroblasts due to mutations in the *XGPT1* gene [94]. This enzyme is involved in the synthesis of glycosaminoglycans, suggesting that they may be involved in the

process of senescence. The phenotype of decorin/ biglycan double knock-out mice is similar to human progeroid EDS and occurs as the result of impaired binding of glycosaminoglycans to decorin and biglycan [25].

Tenascin-X-deficient type EDS

Tenascin-X deficiency causes a recently identified, clinically distinct, autosomal recessive form of EDS [95]. Patients have hyperextensible skin, bruising and joint laxity, but no scarring. The gene for tenascin-X (TNXB) overlaps the steroid 21-hydroxylase gene, and it was originally identified as a candidate gene for EDS in a patient with a contiguous-gene deletion giving rise to both 21-hydroxylase deficiency and EDS [96]. Tenascin-X is the first EDS gene that does not encode a fibrillar collagen or collagen-modifying enzyme. It is a large extracellular matrix protein that appears to be an essential regulator of collagen deposition by dermal fibroblasts [97].

Associated syndromes

Various unclassified forms of EDS overlap with other disorders, such as OI, PXE, MFS [98], renal tubular acidosis and medullary sponge kidney [99], and osteolysis of the terminal phalanges.

Diagnosis. The diagnosis is mainly clinical; a scoring system may be helpful in doubtful cases [100]. Confirmation of the subtype can require a combination of electron microscopy of dermal collagens, protein chemistry analysis from cultured fibroblasts and mutation detection. Immunofluorescent staining of fibroblasts for retained type III collagen may be a faster and cheaper method for the diagnosis of the important type IV EDS [101]. Similarly, the finding of reduced type III procollagen aminopropeptide in the serum of some, but not all, patients with EDS IV may help diagnosis [102]. Chorionic villus sampling may enable prenatal diagnosis of abnormalities of type I (and II) collagen [103]. Measurement of the ratio of urinary lysyl and hydroxylysyl pyridinolines is a non-invasive, reliable diagnostic test for kyphoscoliosis type EDS [72].

EDS should be distinguished from cutis laxa, in which the skin hangs in flaccid redundant folds. In EDS, redundant skin folds may develop in late adult life, but they are usually limited to the elbows and the skin around the eyes. Hyperelastic skin is a feature of Turner's syndrome (Chapter 15), but the dwarfism, cubitus valgus and webbed neck are distinctive. Hyperelastic skin with abnormal elastic fibres in the papillary dermis has been reported in the rare cartilage–hair hypoplasia syndrome [104].

Treatment. All patients should receive genetic counselling. Treatment is highly unsatisfactory, although some features of EDS VI may respond to oral ascorbic acid [74]. Patients with type IV EDS should be advised to avoid pregnancy and trauma, including physical contact sports, and to avoid activities, such as trumpet playing, which raise intracranial pressure by the Valsalva effect. Bleeding should be managed conservatively if at all possible. The fragility of blood vessels makes arteriography and surgical procedures dangerous and difficult. Surgeons must be made aware of the patient's diagnosis prior to surgery. Sutures should be buttressed, and tension avoided. Although re-excision of ugly scars can give a good cosmetic result it is not generally recommended [105].

References

1 Steinmann B, Royce PM, Superti-Furga A. The Ehlers–Danlos syndrome. In: Royce PM, Steinmann B, eds. *Connective Tissue and its Heritable Disorders: Molecular, Genetic and Medical Aspects*. New York: Wiley–Liss, 2002: 431–523.

2 Beighton P, ed. *The Ehlers–Danlos Syndrome*. London: Heinemann, 1970.

3 Beighton P, de Paepe A, Danks A *et al.* International nosology of heritable disorders of connective tissue, Berlin. *Am J Med Genet* 1988; **29**: 581–4.

4 Beighton P, de Paepe A, Steinmann B *et al.* Ehlers–Danlos syndromes: revised nosology, Villefranche, 1997. *Am J Med Genet* 1998; **77**: 31–7.

5 Byers PH. Ehlers–Danlos syndrome: recent advances and current understanding of the clinical and genetic heterogeneity. *J Invest Dermatol* 1994; **103**: S47–52.

6 Pope FM, Narcisi P, Nicholls AC *et al. COL3A1* mutations cause variable clinical phenotypes including acrogeria and vascular rupture. *Br J Dermatol* 1996; **135**: 163–81.

7 Arneson MA, Hammerschmidt DE, Furcht LT *et al.* A new form of Ehlers–Danlos syndrome: fibronectin corrects defective platelet function. *JAMA* 1980; **244**: 144–7.

8 Sulica VI, Cooper PH, Pope M *et al.* Cutaneous histological features in Ehlers–Danlos syndrome: a study of 21 patients. *Arch Dermatol* 1979; **115**: 40–2.

9 Piérard GE, Piérard-Franchimont C, Lapière CM. Histopathological aid in the diagnosis of the Ehlers–Danlos syndrome, gravis and mitis types. *Int J Dermatol* 1993; **22**: 300–4.

10 Bopp P, Hatam K, Busat P *et al.* Cardiovascular aspects of the Ehlers–Danlos syndrome. *Circulation* 1965; **32**: 602–7.

11 Cikrit DF, Miles JH, Silver D. Spontaneous arterial perforation: the Ehlers–Danlos specter. *J Vasc Surg* 1987; **5**: 248–55.

12 Kashiwagi H, Riddle JM, Abraham JP. Functional and ultrastructural abnormalities of platelets in Ehlers–Danlos syndrome. *Ann Intern Med* 1965; **63**: 249–54.

13 Anstey A, Mayne K, Winter K *et al.* Platelet and coagulation studies in Ehlers–Danlos syndrome. *Br J Dermatol* 1991; **125**: 155–63.

14 Holbrook KA, Byers PH. Skin is a window on heritable disorders of connective tissue. *Am J Med Genet* 1989; **34**: 105–21.

15 Mao J-R, Bristow J. The Ehlers–Danlos syndrome. On beyond collagens. *J Clin Invest* 2001; **107**: 1063–9.

16 Grahame R, Beighton P. Physical properties of the Ehlers–Danlos syndrome. *Ann Rheum Dis* 1969; **28**: 246–51.

17 Henry F, Goffin V, Piérard-Franchimont CP *et al.* Mechanical properties of skin in Ehlers–Danlos syndrome types I, II and III. *Pediatr Dermatol* 1996; **13**: 464–7.

18 Piérard GE, Lê T, Piérard-Franchimont C *et al.* Morphometric study of 'cauliflower' fibrils in Ehlers–Danlos syndrome type I. *Coll Relat Res* 1988; **8**: 453–7.

19 Hausser I, Anton-Lamprecht I. Differential ultrastructural aberrations of collagen fibrils in Ehlers–Danlos syndrome type I–IV as a means of diagnostics and classification. *Hum Genet* 1994; **3**: 394–407.

20 Loughlin J, Irven C, Hardwick LJ *et al.* Linkage of the gene that encodes the α_1 chain of type V collagen (*COL5A1*) to type II Ehlers–Danlos syndrome (EDS II). *Hum Mol Genet* 1995; **4**: 1649–51.

21 Burrows NP, Nicholls AC, Yates JWR *et al.* The gene encoding α1 (V) (*COL5A1*) is linked to mixed Ehlers–Danlos syndrome type I/II. *J Invest Dermatol* 1996; **106**: 1273–6.

22 Fichard A, Kleman J-P, Ruggiero F. Another look at collagen V and XI molecules. *Matrix Biol* 1994; **14**: 515–31.

23 Burrows NP. The molecular genetics of the Ehlers–Danlos syndrome. *Clin Exp Dermatol* 1999; **24**: 99–106.

24 Nuytinck L, Freund M, Lagae L *et al.* Classical Ehlers–Danlos syndrome caused by a mutation in type I collagen. *Am J Hum Genet* 2000; **66**: 1398–402.

25 Corsi A, Xu T, Chen X-D *et al.* Phenotypic effects of biglycan deficiency are linked to collagen fibril abnormalities, are synergized by decorin deficiency, and mimic Ehlers–Danlos-like changes in bone and other connective tissues. *J Bone Miner Res* 2002; **17**: 1180–9.

26 Jepsen KJ, Wu F, Peragallo JH *et al.* A syndrome of joint laxity and impaired tendon integrity in lumican- and fibromodulin-deficient mice. *J Biol Chem* 2002; **277**: 532–40.

27 Ostlere LS, Pope FM, Holden CA. Cutis laxa complicating Ehlers–Danlos syndrome type II. *Clin Exp Dermatol* 1996; **21**: 135–7.

28 Beighton P, Grahame R, Bird H. *Hypermobility of Joints*, 3rd edn. London: Springer-Verlag, 1999: 147–77.
29 Phadke JG. Ehlers–Danlos syndrome with surgical repair of penetration of diaphragm and torsion of stomach. *J R Soc Med* 1979; **72**: 781–3.
30 Burrows NP, Monk BE, Harrison JB, Pope FM. Giant bladder diverticulum in Ehlers–Danlos syndrome type I causing outflow obstruction. *Clin Exp Dermatol* 1998; **23**: 109–12.
31 Holzberg M, Hewan-Lowe KO, Olansky AJ. The Ehlers–Danlos syndrome: recognition, characterization, and importance of a milder variant of the classic form. *J Am Acad Dermatol* 1998; **19**: 656–66.
32 Rebora A, Fiallo P, Muzio GF. Prediction of poor outcome of cutaneous surgery. *Lancet* 1989; **ii**: 1109.
33 Grahame R, Bird HA, Child A *et al.* The revised (Brighton 1998) criteria for the diagnosis of benign joint hypermobility syndrome (BJHS). *J Rheumatol* 2000; **27**: 1777–9.
34 Beighton PH, Solomon L, Soskolne CL. Articular mobility in an African population. *Ann Rheum Dis* 1973; **32**: 413–8.
35 Zweirs MC, Bristow J, Steijlen PM et al. Haploinsufficiency of TNXB is associated with hypermobility type of Ehlers-Danlos syndrome. *Am J Hum Genet* 2003; **73**: 214–7.
36 Narcisi P, Richards AJ, Ferguson SD *et al.* A family with Ehlers–Danlos syndrome type III/articular hypermobility syndrome has a glycine 637 to serine in type III collagen. *Hum Mol Genet* 1994; **3**: 1617–20.
37 Kaalund S, Høgsaa B, Grevy C. Coxa saltans in patients with Ehlers–Danlos syndrome type III. *Scand J Rheumatol* 1988; **17**: 229–30.
38 Sacheti A, Szemere J, Bernstein B *et al.* Chronic pain is a manifestation of the Ehlers–Danlos syndrome. *J Pain Symptom Manage* 1997; **14**: 88–93.
39 Arendt-Nielson L, Kaalund S, Hogsaa B *et al.* The response to local anaesthetics (EMLA®) as a clinical test to diagnose between hypermobility and Ehlers–Danlos III syndrome. *Scand J Rheumatol* 1991; **20**: 190–5.
40 Gazit Y, Nahir AM, Grahame R *et al*. Dysautonomia in the joint hypermobility syndrome. *Am J Med* 2003; **115**: 33–40.
41 Pope FM, Nicholls AC, Jones PM *et al.* EDS IV (acrogeria): new autosomal dominant and recessive types. *J R Soc Med* 1980; **73**: 180–6.
42 Sulh HMB, Steinmann B, Rao VH *et al.* Ehlers–Danlos syndrome type IVD. An autosomal recessive disorder. *Clin Genet* 1984; **25**: 278–87.
43 Superti-Furga A, Steinmann B, Byers PH. Type III collagen deficiency. *Lancet* 1989; **i**: 903–4.
44 Superti-Furga A, Gugler E, Gitzelmann R *et al.* Ehlers–Danlos syndrome type IV. A multi-exon deletion in one of the two COL3A1 alleles affecting structure, stability and processing of type III procollagen. *J Biol Chem* 1988; **263**: 6226–32.
45 Tsipouras P, Byers PH, Schwartz RC *et al.* Ehlers–Danlos syndrome type IV. Cosegregation of the phenotype to a COL3A1 allele of type III procollagen. *Hum Genet* 1986; **74**: 41–6.
46 Pepin M, Schwarze U, Superti-Furga A, Byers PH. Clinical and genetic features of Ehlers–Danlos syndrome type IV, the vascular type. *N Engl J Med* 2000; **342**: 673–80.
47 Byers PH, Holbrook KA, McGillivray B *et al.* Clinical and ultrastructural heterogeneity of type IV Ehlers–Danlos syndrome. *Hum Genet* 1979; **47**: 141–50.
48 Laurent R, Agache P. L'acrogéria est-elle une maladie du fibroblasts? *Dermatologica* 1974; **148**: 28–38.
49 Clark JG, Kuhn C III, Uitto J. Lung collagen in type IV Ehlers–Danlos syndrome: ultrastructural and biochemical studies. *Am Rev Respir Dis* 1980; **122**: 971–8.
50 Dwyer NG, Bartlett JR, Nicholls AC *et al.* Collagen deficiency and ruptured cerebral aneurysms. *J Neurosurg* 1983; **59**: 16–20.
51 Kuivaniemi H, Prockop DJ, Wu Y *et al.* Exclusion of mutations in the gene for type III collagen (*COL3A1*) as a common cause of intracranial aneurysms or cervical artery dissections: results from sequence analysis of the coding sequences of type III collagen from 55 unrelated patients. *Neurology* 1993; **43**: 2652–8.
52 Gertsch P, Loup PW, Lochman A *et al.* Changing patterns in the vascular form of Ehlers–Danlos syndrome. *Arch Surg* 1986; **121**: 1061–4.
53 Fox R, Pope FM, Narcisi P *et al.* Spontaneous carotid-cavernous fistula in Ehlers–Danlos syndrome. *J Neurol Neurosurg Psychiatry* 1988; **51**: 984–6.
54 Halbach VV, Higashida RT, Dowd CF *et al.* Treatment of carotid-cavernous fistula in Ehlers–Danlos syndrome. *Neurosurgery* 1990; **26**: 1021–7.
55 Pepin MG, Superti-Furga A, Byers PH. Natural history of Ehlers–Danlos syndrome type IV (EDS type IV): review of 137 cases. *Am J Hum Genet* 1992; **51**: A44.
56 Roberts DLL, Pope FM, Nicholls AL *et al.* Ehlers–Danlos type IV mimicking non-accidental injury in a child. *Br J Dermatol* 1984; **111**: 341–5.
57 Pope FM, Narcisi P, Nicholls AC *et al.* Clinical presentations of Ehlers–Danlos syndrome type IV. *Arch Dis Child* 1988; **63**: 1016–25.
58 Taylor DJ, Wilcox I, Russell JK. Ehlers–Danlos syndrome during pregnancy. A case report and review of the literature. *Obstet Gynecol Surv* 1981; **36**: 277–81.
59 Takahashi T, Koida T, Yamaguchi H *et al.* Ehlers–Danlos syndrome with aortic regurgitation, dilatation of the sinuses of Valsalva, and abnormal dermal collagen fibrils. *Am Heart J* 1992; **123**: 1709–12.
60 Loeys BL, Schwarze U, Holm T *et al.* Aneurysm syndromes caused by mutations in the TGF-beta receptor. *N Engl J Med* 2006; **355**: 788-98.
61 Beighton P, Curtis D. X-linked Ehlers–Danlos syndrome type V. The next generation. *Clin Genet* 1985; **27**: 472–8.
62 Siegel RC, Black CM, Bailey AJ. Cross-linking of collagen in the X-linked Ehlers–Danlos type V. *Biochem Biophys Res Commun* 1979; **88**: 281–7.
63 Di Ferrante N, Leachman RD, Angelini P *et al.* Lysyl oxidase deficiency in Ehlers–Danlos syndrome type V. *Connect Tissue Res* 1975; **3**: 38–53.
64 Ihme A, Krieg T, Nerlich A *et al.* Ehlers–Danlos syndrome type VI. Collagen type specificity of defective lysyl hydroxylation in various tissues. *J Invest Dermatol* 1984; **83**: 161–5.
65 Pinnell SR, Krane SM, Kenzora JE *et al.* A heritable disorder of connective tissue. Hydroxylysine-deficient collagen disease. *N Engl J Med* 1972; **266**: 1013–20.
66 Sussman M, Lichtenstein JR, Nigra TP *et al.* Hydroxylysine-deficient collagen in a patient with a form of the Ehlers–Danlos syndrome. *J Bone Joint Surg Am* 1974; **56**: 1228–34.
67 Hyland J, Ala-Kokko L, Royce P *et al.* A homozygous stop codon in the lysyl hydroxylase gene in two siblings with Ehlers–Danlos syndrome type VI. *Nat Genet* 1992; **2**: 228–31.
68 Hautala T, Keikkinen J, Kivirikko KI *et al.* A large duplication in the gene for lysyl hydroxylase accounts for the type VI variant of the Ehlers–Danlos syndrome in two siblings. *Genomics* 1993; **15**: 399–404.
69 Ha VT, Marshall MK, Elsas LJ *et al.* A patient with Ehlers–Danlos syndrome type VI is a compound heterozygote for mutations in the lysyl hydroxylase gene. *J Clin Invest* 1994; **93**: 1716–21.
70 Chamson A, Berbis P, Fabre JF *et al.* Collagen biosynthesis and isomorphism in a case of Ehlers–Danlos syndrome type VI. *Arch Dermatol Res* 1987; **279**: 303–7.
71 Eyre DR, Glimcher MJ. Reducible cross-links in hydroxylysine-deficient collagens of a heritable disorder of connective tissue. *Proc Natl Acad Sci USA* 1972; **69**: 2594–8.
72 Steinmann B, Eyre DR, Shao P. Urinary pyridinoline cross-links in Ehlers–Danlos syndrome type VI. *Am J Hum Genet* 1995; **57**: 1505–8.
73 Wenstrup RJ, Murad S, Pinnell SR. Ehlers–Danlos syndrome type VI; clinical manifestation of collagen lysyl hydroxylase deficiency. *J Pediatr* 1989; **115**: 405–9.
74 Dembure PP, Priest JH, Snoddy SC *et al.* Genotyping and prenatal assessment of collagen lysyl hydroxylase deficiency in a family with Ehlers–Danlos syndrome, type VI. *Am J Hum Genet* 1984; **36**: 783–90.
75 Dembure PP, Janko AR, Priest JH *et al.* Ascorbate regulation of collagen biosynthesis in Ehlers–Danlos syndrome type VI. *Metabolism* 1987; **36**: 687–91.
76 Steinmann B, Tuderman L, Peltonen L *et al.* Evidence for a structural mutation of procollagen type I in a patient with Ehlers–Danlos syndrome type VII. *J Biol Chem* 1980; **255**: 8887–93.
77 Wirtz MK, Glanville RW, Steinmann B *et al.* Ehlers–Danlos syndrome type VII B. Deletion of 18 amino acids comprising the N-telopeptide region of a proα_2(I) chain. *J Biol Chem* 1987; **262**: 16376–85.
78 Watson RB, Wallis GA, Holmes DF *et al.* Ehlers–Danlos syndrome type VII B. Incomplete cleavage of abnormal type I procollagen by N-proteinase *in vitro* results in the formation of copolymers of collagen and partially cleared pN collagen that are near circular in cross-section. *J Biol Chem* 1992; **267**: 9093–100.
79 D'Alessio M, Ramirez F, Blumberg BD *et al.* Characterization of a *COL1A1* splicing defect in a case of Ehlers–Danlos syndrome type VII. Further evidence of molecular homogeneity. *Am J Hum Genet* 1991; **49**: 400–6.
80 Cole WG, Evans R, Sillence DO. The clinical features of Ehlers–Danlos syndrome type VII due to a deletion of 21 amino acids from the pro-α_1(I) chain of type I procollagen. *J Med Genet* 1987; **24**: 698–701.
81 Smith LT, Wertelecki W, Milstone LM *et al.* Human dermatosparaxis: a form of Ehlers–Danlos syndrome that results from failure to remove the amino-terminal propeptide of type I procollagen. *Am J Hum Genet* 1992; **51**: 235–44.

82 Wertelecki W, Smith LT, Byers PH. Initial observations of human dermatosparaxis: Ehlers–Danlos syndrome type VII C. *J Pediatr* 1992; **121**: 558–64.
83 Nusgens BV, Verellen-Dumoulin C, Hermanns Le T *et al.* Evidence for a relationship between Ehlers–Danlos type VII C in humans and bovine dermatosparaxis. *Nat Genet* 1992; **1**: 214–7.
84 Lehmann HW, Mundlos S, Winterpacht A *et al.* Ehlers–Danlos type VII. Phenotype and genotype. *Arch Dermatol Res* 1994; **286**: 425–8.
85 Becker U, Timpl R. Amino-terminal extensions in skin collagen from sheep with a genetic defect in conversion of procollagen into collagen. *Biochemistry* 1976; **15**: 2853–62.
86 Counts DF, Byers PH, Holbrook KA *et al.* Dermatosparaxis in a Himalayan cat: biochemical studies on dermal collagen. *J Invest Dermatol* 1980; **74**: 96–9.
87 Colige A, Sieron AL, Li S-W *et al.* Human Ehlers–Danlos syndrome type VIIC and bovine dermatosparaxis are caused by mutations in the procollagen I N-proteinase gene. *Am J Hum Genet* 1999; **65**: 308–17.
88 Linch DC, Acton CH. Ehlers–Danlos syndrome presenting with juvenile destructive periodontitis. *Br Dent J* 1979; **147**: 95–6.
89 Stewart RD, Hollister DW, Rimoin DL. A new variant of the Ehlers–Danlos syndrome. An autosomal dominant disorder of fragile skin, abnormal scarring, and generalised periodontitis. *Birth Defects Orig Artic Ser* 1977; **13**: 85–93.
90 Lapière CM, Nusgens BV. Ehlers–Danlos type VIII skin has a reduced proportion of type III collagen. *J Invest Dermatol* 1981; **76**: 422 (Abstract).
91 Rahman N, Dunstan M, Teare MD *et al*. Ehlers-Danlos syndrome with severe early-onset periodontal disease (EDS-VIII) is a distinct, heterogeneous disorder with one predisposition gene at chromosome 12p13. *Am J Hum Genet* 2003; **73**: 198–204.
92 Holbrook KA, Byers PA. Ultrastructural characteristics of the skin in a form of Ehlers–Danlos syndrome. *Lab Invest* 1981; **44**: 342–9.
93 Hernandez A, Aguirre-Negrete MG, Ramirez-Soltero S *et al.* A distinct variant of the Ehlers–Danlos syndrome. *Clin Genet* 1979; **16**: 335–9.
94 Okajima T, Fukumoto S, Furukawa K *et al.* Molecular basis for the progeroid variant of Ehlers–Danlos syndrome. *J Biol Chem* 1999; **274**: 28 841–4.
95 Schalkwijk J, Zweere MC, Steijlen PM *et al.* A recessive form of the Ehlers–Danlos syndrome caused by tenascin-X deficiency. *N Engl J Med* 2001; **345**: 1167–75.
96 Burch GH, Gong Y, Liu W *et al.* Tenascin-X deficiency is associated with Ehlers–Danlos syndrome. *Nat Genet* 1997; **17**: 104–8.
97 Mao JR, Taylor G, Dean WB *et al.* Tenascin-X deficiency mimics Ehlers–Danlos syndrome in mice through alteration of collagen deposition. *Nat Genet* 2002; **30**: 421–5.
98 Cunliffe WJ, Ead RD. A case of Ehlers–Danlos syndrome occurring with Marfan's syndrome. *Clin Exp Dermatol* 1977; **2**: 117–20.
99 Levine AS, Michael AF Jr. Ehlers–Danlos syndrome with renal tubular acidosis and medullary sponge kidney. *J Pediatr* 1967; **71**: 107–13.
100 Holzberg M, Hewan-Lowe KO, Olansky AJ. The Ehlers–Danlos syndrome: recognition, characterization and importance of a milder variant of the classic form. A preliminary study. *J Am Acad Dermatol* 1988; **19**: 656–66.
101 Temple AS, Hinton P, Narcisi P *et al.* Detection of type III collagen in fibroblasts from patients with Ehlers–Danlos syndrome type IV by immunofluorescence. *Br J Dermatol* 1988; **118**: 17–26.
102 Steinmann B, Superti-Furga A, Joller-Jemelka HI *et al.* Ehlers–Danlos syndrome type IV. A subset of patients distinguished by low serum levels of the amino-terminal propeptide of type III procollagen. *Am J Med Genet* 1989; **34**: 68–71.
103 Raghunath M, Steinmann B, Delozier-Blanchet C *et al.* Prenatal diagnosis of collagen disorders by direct biochemical analysis of chorionic villus biopsies. *Pediatr Res* 1994; **36**: 441–8.
104 Brennan TE. Abnormal elastic tissue in cartilage hair hypoplasia. *Arch Dermatol* 1988; **124**: 1411–4.
105 Reidy JP. Cutis hyperelastica (Ehlers–Danlos) and cutis laxa. *Br J Plast Surg* 1963; **16**: 84–94.

Occipital horn syndrome

Synonyms
- X-linked cutis laxa
- Ehlers–Danlos syndrome type IX

In this rare, X-linked, recessive disorder, affected males have a defect in distribution of intracellular copper to copper-dependent enzymes, as in Menkes' syndrome [1]. Lysyl oxidase is a major copper-dependent enzyme, and its activity is markedly decreased in some patients [2], resulting in defective collagen cross-links. Serum copper and caeruloplasmin levels are low [1]. The disorder, like Menkes' syndrome, is caused by mutations in the gene (*ATP7A*) encoding for Cu^{2+}-transporting adenosine triphosphatase (ATPase) α-polypeptide [3,4].

Clinical manifestations include the development of bladder diverticula during childhood, inguinal herniae, mild laxity of skin and skeletal defects such as short humeri and clavicles. Bony occipital horns appear during adolescence [2]. Other features include mild chronic diarrhoea and orthostatic hypotension.

References

1 Peltonen L, Kuivaniemi H, Palotie A *et al.* Alterations in copper metabolism in the Menkes syndrome and a new subtype of Ehlers–Danlos syndrome. *Biochemistry* 1983; **22**: 6156–63.
2 Byers PH, Siegel RC, Holbrook KA *et al.* X-linked cutis laxa. Defective cross-linked formation in collagen due to decreased lysyl oxidase activity. *N Engl J Med* 1980; **303**: 61–5.
3 Levinson B, Gitschier J, Bulpe D *et al.* Are X-linked cutis laxa and Menkes disease allelic? *Nat Genet* 1993; **3**: 6.
4 Levinson B, Conant R, Schnur R *et al.* A repeated element in the regulatory region of the *MNK* gene and its deletion in a patient with occipital horn syndrome. *Hum Mol Genet* 1996; **5**: 1737–42.

Prolidase deficiency

Definition. Prolidase (peptidase D) is involved in the latter stages of degradation of endogenous and dietary proteins and is particularly important in collagen catabolism. Deficiency of prolidase is a rare inborn error of collagen metabolism, associated with chronic skin ulceration, mental retardation and recurrent respiratory infections.

Aetiology. The deficiency is inherited as an autosomal recessive [1,2]. Mutations in the prolidase gene (*PEPD*) result in loss of prolidase activity [3]. Some siblings of patients have the enzyme deficiency without clinical manifestations [4].

Pathology. Light and electron microscopy of cultured fibroblasts from affected patients suggest necrosis-like cell death with abnormal morphology and increased cytosolic vacuolization, and abnormal plasma membranes and mitochondria [3]. Large amounts of imidodipeptides are excreted in the urine [5,6], and the proline/hydroxyproline ratio in collagen is increased.

Abnormal laboratory findings include mild anaemia, thrombocytopenia and hypergammaglobulinaemia.

Clinical features [7]. Most patients are mentally defective, with an abnormal facies, but there is no characteristic or consistent pattern. Skin changes occur in about 85% of cases. The skin may feel spongy, with pitting and scarring, especially on the legs (Fig. 45.28). The skin is fragile and leg ulcers are common. Occasionally, there may be photosensitivity, telangiectasia, purpura, premature greying and lymphoedema.



Fig. 45.28 Pitted skin in prolidase deficiency. (Courtesy of Dr D.A. Burns, Leicester Royal Infirmary, Leicester, UK.)

Splenomegaly, recurrent infections and obesity or a protuberant abdomen occur in about 30% of cases. Families have been described with associated chronic lung disease, resembling cystic fibrosis [8].

Diagnosis. This is confirmed by the finding of massive imidodipeptiduria with prolidase deficiency in the red cells, white cells or cultured fibroblasts. Mutations can be detected in the gene encoding for prolidase [3].

Treatment. Topical proline has been successfully applied to the leg ulcers [9]. Oral proline administration produces no clinical improvement. Enzyme replacement by transfusion of prolidase-containing red cells is a possibility, perhaps using manganese activation of the enzyme before transfusion [10]. Pulsed corticosteroids may help [11]. Apheresis exchange has improved skin ulceration in two patients [12].

References

1 Ogata A, Tanaka S, Tomoda T *et al.* Autosomal recessive prolidase deficiency. *Arch Dermatol* 1981; **117**: 689–97.

2 Powell GF, Kurosky A, Maniscalco RM. Prolidase deficiency: report of a second case with quantification of the excessively excreted amino-acids. *J Pediatr* 1977; **91**: 242–6.

3 Forlina A, Luupi A, Vaghi P *et al.* Mutation analysis of five new patients affected by prolidase deficiency; the lack of enzyme activity causes necrosis-like cell death in cultured fibroblasts. *Hum Genet* 2002; **111**: 3114–22.

4 Isemura M, Hanyu T, Gejyo F *et al.* Prolidase deficiency with imidodipeptiduria. *Clin Chim Acta* 1979; **93**: 401–7.

5 Arata J, Umemura S, Yamamoto Y *et al.* Prolidase deficiency. *Arch Dermatol* 1979; **114**: 62–7.

6 Sheffield LJ, Schlesinger P, Faull K *et al.* Imidopeptiduria, skin ulceration and edema in a boy with prolidase deficiency. *J Pediatr* 1977; **91**: 578–83.

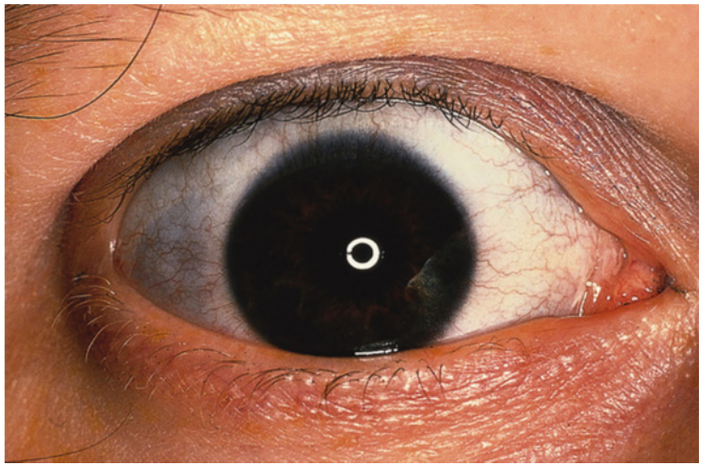


Fig. 45.29 Blue sclera in osteogenesis imperfecta.

7 Milligan A, Graham-Brown RAC, Burns DA *et al.* Prolidase deficiency. A case report and literature review. *Br J Dermatol* 1989; **121**: 405–9.

8 Luder AS, Mandel H, Khyat M *et al.* Chronic lung disease and cystic fibrosis phenotype in prolidase deficiency; a newly recognized association. *J Pediatr* 2007; **150**: 656–8.

9 Arata J, Hatakenaka K, Oono T. Effect of topical application of glycine and proline on recalcitrant leg ulcers of prolidase deficiency. *Arch Dermatol* 1986; **122**: 626–7.

10 Hechtman P, Richter A, Corman N *et al. In situ* activation of human erythrocyte prolidase. Potential for enzyme replacement therapy. *Pediatr Res* 1988; **24**: 709–12.

11 Yasuda K, Ogata K, Kodama H *et al.* Corticosteroid treatment of prolidase deficiency skin lesions by inhibiting iminodipeptide-primed neutrophil superoxide generation. *Br J Dermatol* 1999; **141**: 846–51.

12 Lupi A, Casado B, Soli M *et al.* Therapeutic apheresis exchange in two patients with prolidase deficiency. *Br J Dermatol* 2002; **147**: 1237–40.

Osteogenesis imperfecta (OI)

Definition. This term is applied to a heterogeneous group of heritable disorders characterized by osteoporosis with fractures, due predominantly to type I collagen abnormalities. Patients may also have blue sclerae (Fig. 45.29), deafness, skeletal deformity, abnormal dentine formation (dentinogenesis imperfecta), mild joint hypermobility, hernias, mitral valve prolapse, arterial fragility and thin, fragile skin [1,2].

Aetiology. Approximately 80–90% of patients with OI, who fit into types I–IV, have mutations in one of the type I collagen genes (*COL1A1*, *COL1A2*) [3]. The aetiology of the remainder is unclear. A variety of mutations are seen but very few families share the same mutation. Furthermore, considerable intrafamilial variation of phenotype occurs in type IA [4].

Pathology [5]. The bones are markedly collagen deficient, and often have a distorted architecture. The dermis is thin, with a relative increase of argyrophil and elastic fibres, and a deficiency of adult collagen [6].

Clinical features [1,2,5]. The following broad groups exist, although some patients are difficult to classify.

Type IA: Classic form. This is the commonest form. It is inherited as an autosomal dominant, although sporadic cases also occur [7]. Fractures are common in childhood. The sclerae are blue or grey, and easy bruising and early-onset deafness are common, but skeletal deformity is absent or mild. Joint laxity is common. The incidence of mitral valve prolapse is increased, and the aortic valves are thin and occasionally incompetent [8–10]. A few patients (type IB) have dentinogenesis imperfecta, but this is more common in the type IV group. Most patients have increased skin collagen, with an increased ratio of type I/type III [6]. Other patients have an abnormal α_2 chain, which is unduly susceptible to proteolysis by pepsin [11].

Type II: Lethal perinatal form. This is the rarest form. There are multiple fractures *in utero* and infants rarely survive for more than a few days after birth [12]. Avulsion of the limbs may occur during delivery due to a generalized connective tissue fragility. Radiography shows beaded ribs, crumpled femora and little skull calcification. This form has been subdivided on the basis of rib and limb bone abnormalities [6,13]. Inheritance is usually autosomal dominant. Multiple recurrence of gonadal mosaicism can mimic autosomal recessive inheritance [14].

Type III: Progressively deforming form. In this condition, there are fractures *in utero* or at birth, and the long bones are thin and occasionally cystic. As the child grows older, progressive scoliosis and bowing of long bones cause crippling deformities. The sclerae are blue in childhood but become normal in the adult. The inheritance is uncertain, but the disease may be genetically heterogeneous. Some patients with this form seem unable to synthesize α_2 chains [7,15].

Type IV: Mild form with normal sclerae. This condition is similar to type I in clinical features and inheritance, but the sclerae are not blue, dentinogenesis imperfecta is frequent and deafness is rare.

Diagnosis. Patients with short extremities and a large skull may be confused with achondroplasia, but bone fragility and thin skin do not occur in achondroplasia. Prenatal diagnosis of the more severe forms is possible, using ultrasonography from week 16 [16]. The skin of patients with OI is stiffer and less elastic than normal skin, and these differences in mechanical properties may prove useful in diagnosis and prognosis [17].

Treatment. This is essentially an orthopaedic problem, although many children die of respiratory infections [18]. Bisphosphonates have become standard care for patients with this condition although it is unclear how long therapy should be maintained [2]. Somatic cell therapy, using allogeneic bone marrow and mesenchymal stromal cell transplantation have been used [19,20].

References

1 Sillence DO, Senn A, Danks DM *et al.* Genetic heterogeneity in osteogenesis imperfecta. *J Med Genet* 1979; **16**: 101–16.
2 Glorieux FH. Experience with bisphosphonates in osteogenesis imperfecta. *Pediatrics* 2007; **119**: S163–5.
3 Byers PH, Wallis GA, Willing MC. Osteogenesis imperfecta: translation of mutation to phenotype. *J Med Genet* 1991; **28**: 433–42.
4 Willing MC, Deschenes SP, Scott DA *et al.* Osteogenesis imperfecta type I. Molecular heterogeneity for *COL1A1* null alleles of type I collagen. *Am J Hum Genet* 1994; **55**: 638–47.
5 Smith R. Osteogenesis imperfecta. *BMJ* 1984; **289**: 394–5.
6 Francis MJ, Williams KJ, Sykes BC, Smith R. The relative amounts of the collagen chains alpha 1 (I), alpha 2 and alpha 1 (III) in the skin of 31 patients with osteogenesis imperfecta. *Clin Sci (Lond)* 1981; **60**: 617–23.
7 Pope FM, Nicholls AC. Heterogeneity of osteogenesis imperfecta congenita. *Lancet* 1980; **i**: 820–1.
8 Pentinnen RP, Lichtenstein JR, Martin GR *et al.* Abnormal collagen metabolism in cultured cells in osteogenesis imperfecta. *Proc Natl Acad Sci USA* 1975; **72**: 586–9.
9 Pyeritz RE, Levin LS. Aortic root dilatation and vascular dysfunction in osteogenesis imperfecta. *Circulation* 1981; **64** (Suppl. 4): 311 (Abstract 1193).
10 White NJ, Winearls CG, Smith R *et al.* Cardiovascular abnormalities in osteogenesis imperfecta. *Am Heart J* 1983; **106**: 1416–20.
11 Nicholls AC, Pope FM, Craig D. An abnormal collagen α-chain containing cysteine in autosomal dominant osteogenesis imperfecta. *BMJ* 1983; **288**: 112–3.
12 Trelstad RL, Rubin D, Gross J. Osteogenesis imperfecta. Evidence for a generalized molecular disorder of collagen. *Lab Invest* 1977; **36**: 501–8.
13 Thompson EM, Young ID, Hall CM *et al.* Recurrence risks and prognosis in severe sporadic osteogenesis imperfecta. *J Med Genet* 1987; **24**: 390–405.
14 Byers PH. Brittle bones, fragile molecular disorders of collagen gene structure and expression. *Trends Genet* 1990; **6**: 293–300.
15 Nicholls AC, Pope FM, Schloon H *et al.* Biochemical heterogeneity of osteogenesis imperfecta: new variant. *Lancet* 1979; **i**: 1193–5.
16 Shapiro JE, Phillips JA, Byers PH *et al.* Prenatal diagnosis of lethal osteogenesis imperfecta (OI type II). *J Paediatr* 1982; **100**: 127–33.
17 Hansen B, Jemec GB. The mechanical properties of skin in osteogenesis imperfecta. *Arch Dermatol* 2002; **138**: 909–11.
18 Bleck EE. Non-operative treatment of osteogenesis imperfecta: orthotic and mobility management. *Clin Orthop* 1981; **159**: 111–22.
19 Horwitz EM, Prockop DJ, Gordon PL *et al.* Clinical responses to bone marrow transplantation in children with severe osteogenesis imperfecta. *Blood* 2001; **97**: 1227–31.
20 Horwitz EM, Prockop DJ, Fitzpatrick LA *et al.* Transplantability and therapeutic effects of bone-marrow derived mesenchymal cells in children with osteogenesis imperfecta. *Nat Med* 1999; **5**: 309–13.

Pachydermoperiostosis (see also Chapter 15)

Synonyms
- Primary (idiopathic) hypertrophic pulmonary osteoarthropathy
- Touraine–Solente–Golé syndrome

In this rare condition [1,2], inheritance is autosomal dominant, but autosomal recessive families probably also occur [3]. Digital clubbing is associated with cylindrical thickening of legs and forearms, hypohidrosis, seborrhoea, sebaceous gland hyperplasia and folliculitis. X-rays reveal symmetrical, irregular periosteal ossification, predominantly affecting the distal ends of long bones. Histology shows cutaneous sclerosis and hyalinosis, with perivascular infiltration by lymphoid cells in the dermis [2]. Additional clinical features include carpal and tarsal tunnel syndrome, chronic leg ulceration and calcification of the Achilles tendon [4]. Cultured dermal fibroblasts synthesize increased amounts of collagen and α_1(I) procollagen mRNA, and exhibit up-regulation of transcriptional activity of the α_1(I) procollagen gene promoter [5]. Proteoglycan synthesis is also affected [6].

When conventional treatments fail, intravenous pamidronate may help rheumatological manifestations [7].

References

1 Touraine A, Solente G, Golé L. Un syndrome osteodermopathique; la pachydermie plicaturée avec pachypériostose des extrémités. *Presse Med* 1958; **92**: 1820–4.

2 Matucci-Cerinic M, Lotti T, Jajic I *et al*. The clinical spectrum of primary hypertrophic osteoarthropathy. *Medicine* 1991; **70**: 208–14.
3 Castori M, Sinibaldi L, Mingarelli R *et al*. Pachydermoperiostosis: an update. *Clin Genet* 2005; **68**: 477–86.
4 Cantatore FP, Mancini L, Ingrosso AM *et al*. Pachydermoperiostosis. Dermatological, neurological and radiological observations. *Clin Rheumatol* 1995; **14**: 705–7.
5 Padula SJ, Broketa G, Sampieri A *et al*. Increased collagen synthesis in skin fibroblasts from patients with primary hypertrophic osteoarthropathy. Evidence for trans-activational regulation of collagen transcription. *Arthritis Rheum* 1994; **37**: 1386–94.
6 Wegrowski Y, Gillery P, Serpier H *et al*. Alteration of matrix molecule synthesis by fibroblasts from a patient with pachydermoperiostitis. *J Invest Dermatol* 1996; **106**: 70–4.
7 Guyot-Drouot MH, Solau-Gervais E, Cortet B *et al*. Rheumatologic manifestations of pachydermoperiostosis and preliminary experience with bisphosphonates. *J Rheumatol* 2002; **27**: 2418–23.

Relapsing polychondritis

Synonyms
- Atrophic polychondritis
- Systemic chondromalacia

Definition. In this non-infective condition, focal inflammatory destruction of cartilage is accompanied by fibroblastic regeneration. It is characterized by: (i) recurrent chondritis of the pinnae; (ii) chondritis of nasal cartilage; (iii) inflamed cartilage in the larynx, trachea or respiratory tract; (iv) ocular inflammation; (v) cochlear or vestibular lesions; and (vi) non-erosive arthritis. Three or more of these features are required for the diagnosis [1].

Aetiology. Relapsing polychondritis has been recorded as rare, but recent reports suggest that it is not so uncommon but is easily overlooked. The cause is unknown, but the association with rheumatoid arthritis, lupus erythematosus, vasculitis, Behçet's disease and Hashimoto's disease suggests that autoimmune mechanisms may be concerned (see also MAGIC syndrome, p. 45.44). Other reported associations include ulcerative colitis, Crohn's disease, psoriasis, glomerulonephritis, Sjögren's syndrome, thymoma, ankylosing spondylitis, myeloproliferative disorders and following intravenous injections [2–7]. Cutaneous manifestations have been reported in a patient treated for prostatic adenocarcinoma with goserelin, a luteinizing hormone releasing analogue [8].

Relapsing polychondritis probably overlaps with Wegener's syndrome. Auricular chondritis has been described in some patients with the latter [9], and cANCA, an antibody once regarded as specific for Wegener's syndrome, has been reported in patients with relapsing polychondritis [10].

Antibodies to type II collagen have been detected in the serum in acute polychondritis, and granular deposits of IgG, IgA, IgM and C3 at fibrochondrial junctions have indicated a possible role of immune-complex deposits [11–15]. Antibody production is T-cell dependent and major histocompatibility complex (MHC) restricted; the arthritis in experimental animal models can be suppressed by synthetic type II collagen peptides [16]. The intravenous injection of papain into rabbits produces loss of cartilage rigidity, manifested by floppy ears [17], and it has been suggested that local protease activity may play some part in causing relapsing polychondritis [18]. Cartilage oligomeric matrix protein (COMP) is decreased and cartilage matrix protein (matrilin-1) increased. Both revert to normal levels during successful therapy [19].

Pathology [20]. Areas of damaged cartilage, which have lost the normal basophilic staining, are separated by areas of predominantly lymphocytic infiltration. Later, the fragments of cartilage are surrounded and replaced by abundant granulation tissue and even nascent cartilage. Occasionally there is evidence of vasculitis [21].

Clinical features [1,22–24]. The condition affects both sexes equally and usually begins between the ages of 30 and 50 years. Chondritis ultimately involves three or more sites in most patients but may be limited to one or two for long periods. The following tissues may be involved in decreasing order of frequency: auricular, joint, nasal, ocular, respiratory tract, heart valves and skin [25,26]. During the acute stage, the affected area is swollen, red and tender, and may be mistaken for cellulitis (Fig. 45.30). Sparing of the ear lobe is a useful differentiating sign. Serous otitis media can occur, and there may be loss of hearing even in the absence of chondritis [27]. Involvement of the nasal cartilage leads to obstruction and later to a saddle-nose deformity (Fig. 45.31). Cutaneous and systemic vasculitis, cerebral aneurysms, superficial thrombophlebitis and toxic erythema have been described [1,21,24,28,29].

The joint changes, usually affecting the smaller peripheral joints, may simulate rheumatoid arthritis [30]. Involvement of the larynx, trachea or bronchi produces respiratory embarrassment and recurrent infection. Permanent tracheostomy may be required



Fig. 45.30 Relapsing polychondritis, showing inflammation of the pinna.

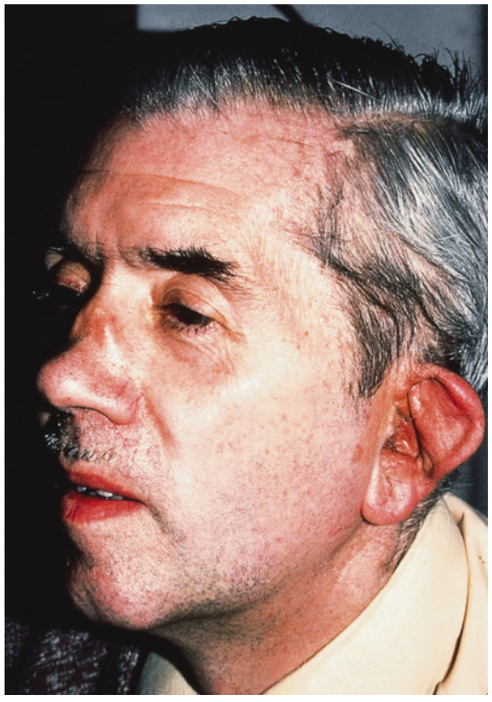


Fig. 45.31 Relapsing polychondritis: late stage, showing damage to the cartilage of the ear and nose. (Courtesy of Dr D.M. Wilkinson, Ackton Hospital, Pontefract, UK.)



Fig. 45.32 Relapsing polychondritis, showing ocular involvement. (Courtesy of Dr N. Cox, Cumberland Royal Infirmary, Carlisle, UK.)

[20,27]. An association with granulomatous lung disease has also been described. Ocular abnormalities are found in some cases—episcleritis, conjunctivitis and iritis (Fig. 45.32), or more rarely keratoconjunctivitis sicca or chorioretinitis. Proptosis occurs in 3% of cases [31,32]. Involvement of the heart valves may cause serious complications, including sudden valve rupture, even in a patient otherwise in remission [1,33,34].

The course of the disease is extremely variable [7]. Relapses are the rule, but they vary in frequency and severity. Some cases continue to relapse for over 20 years, but others become inactive within a short period. Pregnancy does not appear to affect the course of the disease, although complications are more frequent [35]. Deformity of the ears and nose is common, but in general the disease is a source of discomfort and disfigurement rather than a threat to life. Plasma viscosity or erythrocyte sedimentation rate is usually raised and anaemia is frequent. The rheumatoid factor and antinuclear factor are often positive. Leukocytosis is inconstant, but eosinophilia is found in 40% of cases. The characteristic biochemical finding is the increased urinary excretion of acid mucopolysaccharides during each relapse.

Radiological abnormalities are not pathognomonic, but evidence of extensive destruction of joint cartilage without changes in adjacent bone is suggestive. In some cases, the changes are indistinguishable from rheumatoid arthritis.

Diagnosis. Polychondritis may present to the dermatologist as 'chronic otitis externa with cellulitis of the pinna'. The diagnosis is established by biopsy, or by other associated changes, and by the examination of urine for acid mucopolysaccharides. Wegener's granulomatosis and lethal midline granuloma can produce a similar histology, but in these two conditions the involvement is more purely destructive.

Treatment. The progression of the acute relapse can be controlled with corticosteroids. An initial daily dose of 30 mg prednisone can be gradually reduced and finally discontinued as remission develops. Remissions may also be induced with indometacin or dapsone [13]. Colchicine is also helpful in some patients [36]. Immunosuppressive agents such as methotrexate and ciclosporin [15] may have a role. Pulsed intravenous cyclophosphamide has been used for renal disease [37]. Intravenous immunoglobulin [38] and anti-TNF therapies have been successful in a small number of patients [39]. Remission has followed autologous stem cell transplantation [40]. Surgical reconstruction of the nose or larynx is sometimes required.

References

1 McAdam LP, O'Hanlan MA, Bluestone R *et al.* Relapsing polychondritis: prospective review of 23 patients and review of the literature. *Medicine* 1976; **55**: 193–216.

2 Berger R. Polychondritis resulting from i.v. substance abuse. *Am J Med* 1988; **85**: 415–7.

3 Borbujo J, Balsa A, Aguado P *et al.* Relapsing polychondritis associated with psoriasis. *J Am Acad Dermatol* 1989; **20**: 130–2.

4 Conti JA, Colicchio AR, Howard LM *et al.* Thymoma, myasthenia gravis and relapsing polychondritis. *Ann Intern Med* 1988; **109**: 163–4.

5 Nield GH, Cameron JS, Lessof MH *et al.* Relapsing polychondritis with crescentic glomerulonephritis. *BMJ* 1978; **i**: 743–5.

6 Pazirandeh M, Ziran BH, Khandelwal BK *et al.* Relapsing polychondritis and spondyloarthropathies. *J Rheumatol* 1988; **15**: 630–2.

7 Michet CJ, McKenna CH, Luthra HS *et al.* Relapsing polychondritis: survival and predictive role of disease manifestation. *Ann Intern Med* 1986; **104**: 74–8.

8 Labarthe MP, Bayle-Lebey P, Bazex J. Cutaneous manifestations of relapsing polychondritis in a patient receiving goserelin for carcinoma of the prostate. *Dermatology* 1997; **195**: 391–4.

9 Small P, Black M, Davidman M *et al.* Wegener's granulomatosis and relapsing polychondritis: a case-report. *J Rheumatol* 1980; **7**: 915–8.

10 Papo T, Piette J-C, Le Thi Huong DU *et al.* Antineutrophil cytoplasmic antibodies in polychondritis. *Ann Rheum Dis* 1993; **52**: 384–5.

11 Ebringer R, Rook G, Swana GT *et al.* Autoantibodies to cartilage and type II collagen in relapsing polychondritis. *Ann Rheum Dis* 1981; **40**: 473–9.
12 Foidart JM, Abe S, Martin GR *et al.* Antibodies to type II collagen in relapsing polychondritis. *N Engl J Med* 1978; **299**: 1203–7.
13 Ridgeway HB, Hansotia PL, Schorr WF *et al.* Relapsing polychondritis. Unusual neurological features and therapeutic efficacy of dapsone. *Arch Dermatol* 1979; **115**: 43–5.
14 Ueno Y, Chai D, Barnatt EV. Relapsing polychondritis associated with ulcerative colitis: serial determinations of antibodies to cartilage and circulating immune complex by three assays. *J Rheumatol* 1981; **8**: 456–61.
15 Anstey A, Mayou S, Morgan K *et al.* Relapsing polychondritis: autoimmunity to type II collagen and treatment with cyclosporin A. *Br J Dermatol* 1991; **125**: 588–91.
16 Cremer MA, Rosloniec EF, Kang AH. The cartilage collagens: a review of their structure, organization and role in the pathogenesis of experimental arthritis in animals and in human rheumatic disease. *J Mol Med* 1998; **76**: 275–88.
17 McCluskey RT, Thomas L. The removal of cartilage matrix *in vivo* by papain. *J Exp Med* 1958; **108**: 371–84.
18 Gange RW. Relapsing polychondritis. Report of two cases with an immunopathological review. *Clin Exp Dermatol* 1976; **1**: 261–6.
19 Saxne T, Heinegard D. Serum concentrations of two cartilage matrix proteins reflecting different aspects of cartilage turnover in relapsing polychondritis. *Arthritis Rheum* 1995; **38**: 294–6.
20 Kaye RL, Sones DA. Relapsing polychondritis: clinical and pathological features in 14 cases. *Ann Intern Med* 1964; **60**: 653–64.
21 Michet CJ. Vasculitis and relapsing polychondritis. *Rheum Dis Clin North Am* 1990; **16**: 441–4.
22 Damiani J, Levine H. Relapsing polychondritis. Report of 10 cases. *Laryngoscope* 1979; **89**: 929–46.
23 Dolan DL, Lemmon GB, Teitelbaum SL. Relapsing polychondritis. Analytical literature review. *Am J Med* 1966; **41**: 285–99.
24 Hughes RAC, Berry CL, Seifert M *et al.* Relapsing polychondritis. Three cases with a clinicopathological study and literature review. *QJM* 1972; **41**: 363–80.
25 Balsa-Criada A, Garcia-Fernandez F, Roldan I *et al.* Cardiac involvement in relapsing polychondritis. *Int J Cardiol* 1987; **14**: 381–3.
26 Van Decker W, Panidis IP. Relapsing polychondritis and cardiac valvular involvement. *Ann Intern Med* 1988; **109**: 340–1.
27 Moloney JR. Relapsing polychondritis—its otolaryngological manifestations. *J Laryngol Otol* 1978; **92**: 9–14.
28 Meyrick-Thomas RH, Payne CMER, Black MM. Polychondritis as a concomitant feature of polyarteritis nodosa. *Clin Exp Dermatol* 1982; **7**: 519–22.
29 Stewart SS. Cerebral vasculitis in relapsing polychondritis. *Neurology* 1988; **38**: 150–2.
30 Franssen MJ, Boerbooms AM, van de Putt LB. Polychondritis and rheumatoid arthritis, case report and review of the literature. *Clin Rheumatol* 1987; **6**: 453–7.
31 McKay DA, Watson PG, Lyne AJ. Relapsing polychondritis and eye disease. *Br J Ophthalmol* 1974; **58**: 600–5.
32 Crovato F, Nigro A, de Marchi R *et al.* Exophthalmos in relapsing polychondritis. *Arch Dermatol* 1980; **116**: 383–4.
33 Marshall DAS, Jackson R, Rae AP *et al.* Early aortic valve cusp rupture in relapsing polychondritis. *Ann Rheum Dis* 1992; **51**: 413–5.
34 Buckley LM, Ades PA. Progressive aortic valve inflammation occurring despite apparent remission of relapsing polychondritis. *Arthritis Rheum* 1992; **35**: 812–4.
35 Papo T, Wechsler B, Bletry O *et al.* Pregnancy in relapsing polychondritis: twenty-five pregnancies in eleven patients. *Arthritis Rheum* 1997; **40**: 1245–9.
36 Mark KA, Franks AG. Colchicine and indomethacin for the treatment of relapsing polychondritis. *J Am Acad Dermatol* 2002; **46**: S22–4.
37 Stewart KA, Mazanec DJ. Pulsed intravenous cyclophosphamide for kidney disease in relapsing polychondritis. *J Rheumatol* 1992; **19**: 498–500.
38 Temier B, Aouba A, Bienvenu B *et al.* Complete remission in refractory relapsing polychondritis with intravenous immunoglobulin. *Clin Exp Rheumatol* 2008; **26**: 136–8.
39 Seymour MW, Home DM, Williams RO *et al.* Prolonged response to anti-tumour necrosis factor treatment with adalimumab (Humira) in relapsing polychondritis complicated by aortitis. *Rheumatology* 2007; **46**: 1738–9.
40 Rosen O, Thiel A, Massenkeil G *et al.* Autologous stem-cell transplantation in refractory auto-immune diseases after *in vivo* immunoablation and *ex vivo* depletion of mononuclear cells. *Arthritis Res* 2000; **2**: 327–36.

MAGIC syndrome

At least 13 patients have been described with features of both relapsing polychondritis and Behçet's syndrome [1]. The term MAGIC syndrome (*m*outh *a*nd *g*enital ulcers with *i*nflamed *c*artilage) has been used for this overlap syndrome. The underlying immunological defects are still unclear, but circulating immune complexes and autoantibodies to elastic tissue have been suggested as possible factors [1,2].

Aortic valve disease and aneurysmal aortitis have been associated with the syndrome [3,4], and features of the MAGIC syndrome have been described in an HIV-positive individual [5].

References

1 Orme RL, Nordlund JJ, Barich L *et al.* The MAGIC syndrome (mouth and genital ulcers with inflamed cartilage). *Arch Dermatol* 1990; **126**: 940–4.
2 Firestein GS, Gruber HE, Weisman MH *et al.* Mouth and genital ulcers with inflamed cartilage: MAGIC syndrome. *Am J Med* 1985; **79**: 69–72.
3 Le Thi Huong DU, Wechsler B, Piette J-C *et al.* Aortic insufficiency and recurrent valve prosthesis dehiscence in MAGIC syndrome. *J Rheumatol* 1993; **20**: 397–8.
4 Hidalgo Tenorio C, Sabio-Sánchez JM, Linares PJ *et al.* Magic syndrome and true aortic aneurysm. *Clin Rheumatol* 2008; **27**: 115–7.
5 Belzunegui J, Cancio J, Pego JM *et al.* Relapsing polychondritis and Behçet's syndrome in a patient with HIV infection. *Ann Rheum Dis* 1995; **54**: 780.

Fibromatoses

Fibrous overgrowth of dermal and subcutaneous connective tissue occurs most readily in certain sites and at certain ages, and some of the resulting syndromes are clinically and histologically distinctive and well defined. There are some cases, however, that defy precise classification, and others in which histological criteria may be a poor guide to prognosis. Invasiveness and a high local recurrence rate may or may not be associated with a tendency to metastasize. The borderline between simple overgrowth and a benign tumour may be equally difficult to define.

Fibromatosis is a benign, fibrous tissue proliferation, which is intermediate between benign fibroma and metastasizing fibrosarcoma. The lesions of fibromatosis tend to infiltrate and recur when removed, but they do not metastasize. The term should not be applied to reactive fibrous proliferation, or to keloid, which is usually secondary to injury. The lesions in fibromatosis may be single or multiple, and the likelihood of recurrence after surgical removal varies with the location of the lesion and the age of the patient. The fibromatoses occur in two major groups.

1 Superficial fibromatoses (fascial fibromatoses):
   (a) palmar (Dupuytren's)
   (b) plantar
   (c) penile (Peyronie's)
   (d) knuckle pads

2 Deep fibromatoses (non-metastasizing fibrosarcoma). These are rapidly growing tumours that usually involve the musculature or aponeuroses. Their tendon-like consistency accounts for their alternative name of desmoid tumours.

These conditions are discussed in more detail elsewhere (Chapter 56).



Fig. 45.33 Palmar fibromatosis (Dupuytren's contracture). (Courtesy of Dr D.A. Burns, Leicester Royal Infirmary, Leicester, UK.)

Palmar fibromatosis

Synonym
- Dupuytren's contracture

Definition. This is a fibromatous hyperplasia of the palmar aponeurosis, which is characterized by nodular thickening of the fascia with associated flexion contractures of one or more digits (Fig. 45.33).

Aetiology. The condition seems to be due to a reactive proliferation of fibroblasts with no inflammatory component, and the basic cause is obscure. Free radical production secondary to ischaemia may be involved, and the concentration of hypoxanthine substrate capable of releasing free radicals is greatly increased in the affected tissue [1]. Localized ischaemia has been thought to play a part, and in animal studies allopurinol (a competitive inhibitor of xanthine oxidase) has been shown to limit the damage associated with acute ischaemia [2]. High concentrations of free radicals are toxic, but in low concentration they stimulate fibroblast proliferation [1]. The contractures, which are a late complication, appear to follow the conversion of the fibroblasts to contractile myofibroblasts [3].

Palmar fibromatosis is often familial, and may be inherited as an autosomal dominant trait [4].

Some families are described in which there is a predominantly female expression [5]. The prevalence in the general adult population is around 2–6% [6], but it may approach 20% or more in elderly males [7–9], in diabetic patients and in patients with acquired immune deficiency syndrome (AIDS). It is relatively rare in black and oriental races.

Associated disorders. The condition occurs more commonly in patients with alcoholic cirrhosis, epilepsy [10] and diabetes mellitus [9,11], but the prevalence is decreased in rheumatoid arthritis [12].

Palmar fibromatosis is also associated in about 5% of patients with other fibrosing conditions, such as knuckle pads, Peyronie's disease, keloid scarring or plantar fibromatosis [13], and this has been termed the *polyfibromatosis syndrome*. Other conditions which have been less convincingly claimed to be associated with Dupuytren's contracture include periarthritis of the shoulder, chronic lung disease, gout, trauma and ulnar nerve damage [14]. Phenytoin appears to stimulate fibrosis in the polyfibromatosis syndrome [15] and it may also cause gingival hypertrophy by stimulating fibroblasts and increasing collagen production [10,16].

There is one case report of a girl aged 14 years who developed Dupuytren's contracture while receiving growth hormone therapy for hypopituitarism [17].

Pathology [18]. Fibroblasts in Dupuytren's contracture are identical to those in normal palmar fascia. However, there are more of them in Dupuytren's contracture and they tend to be clustered around narrowed microvessels [19]. In the early stages, there are nodules in the subcutaneous tissue, or within the fascia, composed of proliferating fibroblasts with irregular hyperchromatic nuclei, but with no excess of collagen. Later stages are characterized by the presence of myofibroblasts which have a fibrillary ultrastructure in the cytoplasm and seem to have some other properties of smooth muscle. The nuclei are deeply indented, and these constrictions may be related to the contractile properties of the cell. The cell also has surface membrane differentiations which provide attachment to neighbouring cells and stroma. Myofibroblasts have also been identified in the normal aorta and in granulation tissue, hypertrophic scars, keloids, liver fibrosis, dermatofibroma, etc. [3], in which their contractile properties may be important. The advanced stages of Dupuytren's contracture are characterized by dense, fibrous connective tissue with a few elongated cells. An increased concentration of type III collagen is present in the nodules [20]. This may be due to decreased degradation caused by increased levels of tissue inhibitors of metalloproteinases in the lesions [21]. Structural abnormalities of glycosaminoglycans, notably dermatan sulphate, may predispose to abnormal fibrillogenesis [22].

Clinical features. The age of onset is generally between 30 and 50 years, and the disease is less common and progresses more slowly in women [14]. The earliest sign is the development of a palmar nodule, usually in the ulnar half of the hand. There are usually no symptoms, but there may be a dull ache or tingling. Insidious progression of the fibrosis over several years causes flexion contractures of the affected fingers. There is often puckering of the overlying skin. Eventually, the function of the hand becomes impaired due to fixed flexion of one or more digits. If left untreated, there may be some improvement after many years.

Diagnosis. There are few diagnostic difficulties. There may be a histological resemblance to fibrosarcoma, but this is more pleomorphic, with larger nuclei and more mitoses. Juvenile aponeurotic fibroma may produce palmar or plantar nodules, but Dupuytren's contracture does not occur in young children.

Treatment. The advice of an orthopaedic or plastic surgeon should be sought. Complete removal of the palmar aponeurosis is generally recommended [23], although subtotal fasciectomy and direct closure may be an alternative approach [24].

Medical treatments are disappointing. Allopurinol may help by decreasing free-radical production [25], and it has been suggested that vitamin C might prevent progression of the disease by acting as a free-radical scavenger [7]. Many other non-surgical approaches have been tried, including continuous slow skeletal traction, radiotherapy, dimethyl sulfoxide, vitamin E, steroid injections and interferon, although none has been proven to be clinically useful [26]. However, placebo-controlled trials of collagenase injections look very promising [27].

Another suggestion, which has yet to be tested clinically, is the use of immunosuppressive therapy as an adjunct to surgery, on the grounds that the presence of CD3 lymphocytes and the expression of MHC class II proteins in the affected tissue imply that Dupuytren's disease is a T-cell-mediated autoimmune disorder [28].

References

1 Murrell GAC, Francis MJ, Bromley L *et al.* Free radicals and Dupuytren's contracture. *BMJ* 1987; **295**: 1373–5.
2 Granger DN. Superoxide radicals in feline intestinal ischaemia. *Gastroenterology* 1981; **81**: 22–9.
3 James WD, Odom RB. The role of the myofibroblast in Dupuytren's contracture. *Arch Dermatol* 1980; **116**: 807–11.
4 Ling RSM. The genetic factor of Dupuytren's disease. *J Bone Joint Surg* 1963; **45B**: 709–18.
5 Matthews P. Familial Dupuytren's contracture with predominant female expression. *Br J Plast Surg* 1979; **32**: 120–3.
6 Mikkelsen OA. The prevalence of Dupuytren's contracture in Norway. *Acta Chir Scand* 1972; **138**: 695–700.
7 Bower M, Nelson M, Gazzard BG. Dupuytren's contracture in patients infected with HIV. *BMJ* 1990; **300**: 164–5.
8 Evans RA. The aetiology of Dupuytren's disease. *Br J Hosp Med* 1986; **35**: 198–9.
9 Heathcote JG. Fibromatosis and diabetes mellitus. *Lancet* 1981; **i**: 1420.
10 Critchley EM, Vakil SD, Hayward HW *et al.* Dupuytren's disease in epilepsy: result of prolonged administration of anticonvulsants. *J Neurol Neurosurg Psychiatry* 1976; **39**: 498–50.
11 Larkin JG, Frier BM. Limited joint mobility and Dupuytren's contracture in diabetic, hypertensive and normal populations. *BMJ* 1986; **292**: 1494.
12 Arafa M, Steingold RF, Noble J *et al.* The incidence of Dupuytren's disease in patients with rheumatoid arthritis. *J Hand Surg (Am)* 1984; **9B**: 165–6.
13 Wolfe SJ, Summerskill WHJ, Davidson CS. Dupuytren's contracture associated with alcoholism and cirrhosis. *N Engl J Med* 1956; **255**: 559–63.
14 Allen PW. The fibromatoses. A clinicopathologic classification based on 140 cases. *Am J Surg Pathol* 1977; **1**: 255–70.
15 Piérard GE, Lapière CM. Phenytoin dependent fibrosis in polyfibromatosis syndrome. *Br J Dermatol* 1979; **100**: 335–41.
16 Hassell TM, Page RC, Narayanan AS *et al.* Diphenylhydantoin (Dilantin) gingival hyperplasia: drug-induced abnormality of connective tissue. *Proc Natl Acad Sci USA* 1976; **73**: 2909–12.
17 Kiess W, Butenandt O. Development of Dupuytren's contracture during growth hormone therapy. *Lancet* 1993; **342**: 181–2.
18 Gabbiani G, Manjo G. Dupuytren's contracture: fibroblast contraction. An ultrastructural study. *Am J Pathol* 1972; **66**: 131–46.
19 Murrell GA. The role of the fibroblast in Dupuytren's contracture. *Hand Clin* 1991; **7**: 669–80.
20 Bailey AJ, Sims TJ, Gabbiani G *et al.* Collagen of Dupuytren's disease. *Clin Sci Mol Med* 1977; **53**: 499–502.
21 Ulrich D, Hrynyschyn K, Pallua N. Matrix metalloproteinases and tissue inhibitors of metalloproteinases in sera and tissue of patients with Dupuytren's disease. *Plast Reconstr Surg* 2003; **112**: 1279–86.
22 Koźna EM, Glowacki A, Olazyk K *et al.* Dermatan sulphate remodeling associated with advanced Dupuytren's contracture. *Acta Biochim Pol* 2007; **54**: 821–30.
23 Rodrigo JJ, Niebauer JJ, Brown RL *et al.* Treatment of Dupuytren's contracture. Long-term result after fasciotomy and fascial excision. *J Bone Joint Surg Am* 1976; **58**: 380–7.
24 Shaw DL, Wise D, Holms W. Dupuytren's disease treated by palmar fasciectomy and an open palm technique. *J Hand Surg (Am)* 1996; **218**: 484–5.
25 Murrell GAC. Hypothesis for the resolution of Dupuytren's contracture with allopurinol. *Spec Sci Technol* 1987; **10**: 107–12.
26 Hurst LC, Badalamente MA. Nonoperative treatment of Dupuytren's disease. *Hand Clin* 1999; **15**: 97–107.
27 Badalamente MA, Hurst LC, Hentz VR. Collagen as a clinical target: Nonoperative treatment of Dupuytren's disease. *J Hand Surg (Am)* 2002; **27**: 788–98.
28 Baird KS, Alwan WH, Crossan JF, Wojciak B. T-cell mediated response in Dupuytren's disease. *Lancet* 1993; **341**: 1622–3.

Camptodactyly

Camptodactyly is a non-traumatic flexion deformity affecting the proximal interphalangeal joint of one or more fingers [1]. It may be a feature of a variety of syndromes; the molecular defects in several of these have been identified. Congenital camptodactyly is most notably associated with non-inflammatory arthropathy [2]. Additionally, other serous membranes undergo fibrosis, leading to *c*onstricting pericarditis *a*nd *p*leuritis (*CAP syndrome*) [3,4]. Familial camptodactyly of later onset has been described in association with an inflammatory arthritis with erosive changes [5]. *Blau's syndrome* encompasses familial camptodactyly, granulomatous arthritis, uveitis and an erythematous eruption with phenotypic overlap with early onset sarcoidosis [6]. Mutations in *NOD2/CARD15* have been shown to confer susceptibility to several chronic inflammatory disorders, including Crohn's disease, Blau syndrome and early-onset sarcoidosis [7]. In one family, taurinuria was associated [8]. Bilateral camptodactyly is also part of an autosomal recessive disorder (Crisponi syndrome) characterized by muscular contractions of the face, trismus, facial anomalies and death due to fevers. The syndrome is caused by *CRLF1* mutations and is allelic to cold-induced sweating syndrome type I [9].

Microdeletion of 1p36 is a relatively common syndrome, affecting 1:5000 neonates. Clinical features include camptodactyly, facial dysmorphism and low-set ears, cardiac and CNS defects; it is responsible for around 1% of idiopathic mental retardation [10]. Sporadic cases of camptodactyly have been linked with accelerated growth and osseous maturation, unusual facial appearance (including large ears, small mouth, broad forehead and hypertelorism), a hoarse, low-pitched cry and hypertonia (*Weaver's syndrome*) [11]. Other associated features include pectus excavatum and scoliosis.

Treatment, if required, is surgical [1,12,13].

References

1 Engbar WD, Flatt AF. Camptodactyly. An analysis of sixty-six patients and twenty-four operations. *J Hand Surg (Am)* 1977; **2A**: 216–24.
2 Jacobs JC, Downey JA. Juvenile rheumatoid arthritis. In: Downey JH, Low NC, eds. *The Child with Disabling Illness*. Philadelphia: Saunders, 1974: 5–24.
3 Martinez-Lavin M, Buendia A, Delgardo E *et al.* A familial syndrome of pericarditis, arthritis and camptodactyly. *N Engl J Med* 1983; **309**: 224–5.
4 Laxer RM, Cameron BJ, Chaisson D *et al.* The camptodactyly–arthropathy–pericarditis syndrome: case report and literature review. *Arthritis Rheum* 1986; **29**: 439–44.
5 Gigante MC, Santori FS, Zoppini A *et al.* Familial erosive arthritis associated with camptodactyly. *Scand J Rheumatol* 1970; **19**: 239–44.
6 Raphael SA, Blau EB, Zhang WH *et al.* Analysis of a large kindred with Blau syndrome for HLA, autoimmunity and sarcoidosis. *Am J Dis Child* 1993; **147**: 842–8.
7 Le Bourhis L, Benko S, Girardin SE. Nod1 and Nod2 in innate immunity and human inflammatory disorders. *Biochem Soc Trans* 2007; **35**: 1479–84.

8 Nevin NC, Hurwitz LJ, Neill DW. Familial camptodactyly with taurinuria. *J Med Genet* 1966; **3**: 265–8.
9 Dagoneau N, Bellais S, Blanchet P *et al*. Mutations in cytokine receptor-like factor 1 (CRLF1) account for both Crisponi and cold-induced sweating syndromes. *Am J Hum Genet* 2007; **80**: 966–70.
10 Battaglia A, Hayme HE, Dallapiccola B *et al*. Further delineation of deletion 1p36 syndrome in 60 patients: a recognizable phenotype and common cause of developmental delay and mental retardation. *Pediatrics* 2008; **121**: 404–10.
11 Weaver DD, Graham CB, Thomas IT *et al*. A new overgrowth syndrome with accelerated skeletal maturation, unusual facies and camptodactyly. *J Pediatr* 1974; **84**: 547–52.
12 Goffin D, Lenoble E, Marin-Braun F *et al*. Camptodactyly: classification and therapeutic results. *Ann Chir Main* 1994; **13**: 20–5.
13 Foucher G, Loréa P, Khouri RK *et al*. Camptodactyly as a spectrum of congenital deficiencies: a treatment algorithm based on clinical examination. *Plast Reconstr Surg* 2006: **117**; 1897–905.

Streblodactyly

Streblodactyly [1] is inherited as a sex-linked, autosomal, dominant character. The affected females show from birth a flexion deformity at the metacarpophalangeal joints of the thumbs and the proximal interphalangeal joints of the little fingers. Some fingers show swan-neck deformities and hyperextensible metacarpophalangeal joints. In one family there was an abnormal α-amino aciduria.

Reference

1 Parish JG, Horn DB, Thompson M *et al*. Familial streblodactyly with amino-aciduria. *BMJ* 1963; **ii**: 1247–50.

Plantar fibromatosis [1,2]

Synonym
- Ledderhose's disease

This is a much rarer condition than palmar fibromatosis. The lesions, which occur most often on the medial half of the mid-foot, present as one or more nodules, which may become painful and may ulcerate (Fig. 45.34). They rarely produce contractures, but they tend to be locally invasive and to recur. Total excision of the lesion and the entire plantar fascia seems to give the best results, with the lowest incidence of recurrence. The differential diagnosis includes keloid and fibrosarcoma, and in younger patients aggressive infantile fibromatosis and aponeurotic fibroma must also be considered [3]. Similar nodules have been described symmetrically affecting the anteromedial heel pads in children. They are asymptomatic and may resolve spontaneously [4,5]. Surgery is contraindicated.

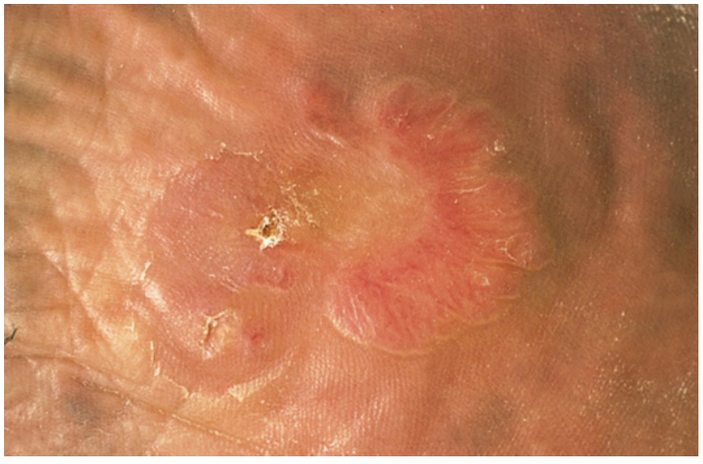


Fig. 45.34 Plantar fibromatosis. (Courtesy of Dr J. Ellis, Princess Margaret Hospital, Swindon, UK.)

References

1 Allen RA, Woolner LB, Ghormley RK *et al*. Soft tissue tumours of the sole with special reference to plantar fibromatosis. *J Bone Joint Surg (Am)* 1995; **37**: 14–26.
2 Warthan TL, Rudolf RI, Gross PR *et al*. Isolated plantar fibromatosis. *Arch Dermatol* 1973; **108**: 823–5.
3 Fleischmajer R, Nedwich A, Reeves JR *et al*. Juvenile fibromatoses. *Arch Dermatol* 1973; **107**: 574–9.
4 Godette A, O'Sullivan M, Menelaus MB. Plantar fibromatosis of the heel in children: a report of 14 cases. *J Pediatr Orthop* 1997; **17**: 16–7.
5 Jacob CI, Kumm RC. Benign anteromedial plantar nodules of childhood: a distinct form of plantar fibromatosis. *Pediatr Dermatol* 2000; **17**: 472–4.

Penile fibromatosis

Synonyms
- Peyronie's disease
- Plastic induration of the penis
- Fibrous sclerosis of the penis

Definition. Penile fibromatosis is characterized by one or more irregular, dense fibrous plaques in the penile shaft.

Aetiology. Penile fibromatosis may occur as an isolated abnormality, or as one component of polyfibromatosis in association with palmoplantar fibromatosis, keloids and knuckle pads. Atheroma predisposes to the condition, and it is now thought that the association with the use of β-adrenoreceptor blocking drugs is probably attributable to concomitant atheroma [1,2]. There may be a genetic factor, but reliable studies of the mode of inheritance are lacking. The condition is rare below the age of 20 years, and the highest incidence is between 40 and 60 years. It is much less common than palmar or plantar fibromatosis.

Pathology [3]. The thickened plaque shows cellular fibroblastic proliferation surrounded by dense masses of collagen. Calcification and ossification may occur. The process appears to begin as a vasculitis in the areolar connective tissue beneath the tunica albuginea, whence it extends to adjacent structures.

Clinical features. The disease presents with painful erections and curvature of the erect penis due to a thickened subcutaneous plaque, rubbery or hard, usually on the dorsal aspect of the penis in its distal third. The erectile deformity may make vaginal penetration impossible, and pain or anxiety about performance may cause secondary impotence. Fibrosis of the underlying cavernous erectile tissue may lead to a constriction or 'waisting' of the penile shaft, leading to flaccidity of the distal portion.

The course is unpredictable [4]. The pain generally subsides within a few months, but the fibrous plaque may resolve, remain unchanged or progress [5].

The severity of the disease and the response to treatment can now be evaluated by high-resolution ultrasonography [6], computed tomography [7] or magnetic resonance imaging of the erect penis [8]. If necessary, an erection can be induced by the intracavernosal injection of papaverine [9].

Treatment. Many treatments have been tried, but there is little evidence that vitamin E, potassium aminobenzoate, orgotein, radiotherapy, ultrasonic therapy or intralesional steroids affect the long-term outcome, although they may relieve the pain [4]. Clostridial collagenase injections have given promising results [10]. Surgery is probably the treatment of choice, using Nisbet's operation, in which ellipses of normal tunica albuginea are excised from the side of the shaft, opposite the point of maximum curvature. An alternative is venous grafting, using the deep dorsal vein [11]. A semirigid penile prosthesis may also be inserted.

References

1 Chilton CP, Castle WM, Westwood CA *et al.* Factors associated in the aetiology of Peyronie's disease. *Br J Urol* 1982; **54**: 748–50.
2 Pryor JP. Association between Peyronie's disease and chronic degenerative arterial disease rather than β-adrenoreceptor blocking agents. *Prog Reprod Biol Med* 1983; **9**: 23–6.
3 Smith BH. Peyronie's disease. *Am J Clin Pathol* 1966; **45**: 670–8.
4 Gingell JC, Desai KM. Peyronie's disease. Treatment should always restore sexual function. *BMJ* 1988; **297**: 1489–90.
5 Williams JL, Thomas GG. The natural history of Peyronie's disease. *J Urol* 1970; **103**: 75–6.
6 Balconi G, Angeli E, Nessi R *et al.* Ultrasonic evaluation of Peyronie's disease. *Urol Radiol* 1988; **10**: 85–8.
7 Rollandi GA, Tentarelli T, Vespier M *et al.* Computed tomographic findings in Peyronie's disease. *Urol Radiol* 1985; **7**: 153–6.
8 Bystrom J, Johansson B, Edgren J *et al.* Induratio penis plastica (Peyronie's disease). Cavernosography in assessment of the disease process. *Scand J Urol Nephrol* 1974; **8**: 155–61.
9 Desai KM, Gingell JC. Outpatient assessment of penile curvature. *Br J Urol* 1987; **60**: 470–1.
10 Gelbard MK, Lindner A, Kaufman JJ *et al.* The use of collagenase in the treatment of Peyronie's disease. *J Urol* 1985; **134**: 280–3.
11 Hsu GC, Chen HS, Hsieh CH *et al.* Long term results of autologous venous grafts for penile morphological reconstruction. *J Androl* 2007; **28**: 186–93.

Knuckle pads [1–4]

Synonym
- Holoderma

Definition. Knuckle pads are circumscribed thickenings overlying the finger joints. The term is a misnomer as most lesions occur over the proximal interphalangeal rather than the metacarpophalangeal joints (knuckles).

Aetiology. The condition is usually sporadic but several pedigrees have shown an autosomal dominant inheritance. The age of onset and the distribution of the lesions tend to be more or less constant in each family, but show interfamily variation. The condition is not rare but the true prevalence is uncertain, as most patients ignore the lesions. Knuckle pads are thought to be idiopathic in children, although they occur at sites prone to picking, chewing or 'knuckle cracking' [4].

Pathology [1]. The epidermis is grossly hyperkeratotic and acanthotic. The dermal connective tissue is hyperplastic and individual collagen fibres may be obviously thickened. Histologically, the changes resemble those of palmar fibromatosis.

Clinical features [2,3]. Flat or convex, smooth, circumscribed keratoses develop slowly and almost imperceptibly over the course of months or years. In some patients they become very much raised and obviously indurated, but in others the dermal component is not clinically apparent. They are most commonly seen over the dorsa of the proximal interphalangeal joints, but occasionally develop over the knuckles or the distal interphalangeal joints. Any single site or combination of sites may be involved. Sites other than the hands are not often affected, but similar lesions on the knees were also present in one family [2].

The age of onset is variable but it is more common after the fourth decade. In some individuals, the lesions may not be conspicuous until they have been present for some years.

An association between Dupuytren's contracture and other fibromatous lesions has been recorded in some families. In one large family, knuckle pads were associated with sensorineural deafness and with leukonychia [5]. Knuckle pads have also been associated with epidermolytic palmoplantar keratoderma in a Chinese family due to keratin 9 mutations [6].

Another family has been described with knuckle pads in association with oesophageal cancer, hyperkeratosis and oral leukoplakia [7].

In differential diagnosis, occupational callosities, Heberden's nodes of osteoarthritis, pachydermodactyly, granuloma annulare, erythema elevatum diutinum and rheumatoid nodules must be excluded.

Treatment. There is no satisfactory treatment. Excision may be followed by keloidal scarring.

References

1 Lagier R, Meineke R. Pathology of knuckle pads. *Virchows Arch* 1975; **365**: 185–91.
2 Morginson WJ. Discrete keratodermas over the knuckle and finger articulations. *Arch Dermatol* 1955; **71**: 349–53.
3 Mikkelson OH. Knuckle pads in Dupuytren's disease. *Hand* 1977; **9**: 301.
4 Peterson CM, Barnes CJ, Davis LS. Knuckle pads: does knuckle cracking play an etiologic role? *Pediatr Dermatol* 2000; **17**: 450–2.
5 Bart RS, Pumphrey RE. Knuckle pads, leukonychia and deafness. *N Engl J Med* 1967; **276**: 202–7.
6 Lu Y, Guo C, Liu Q *et al.* A novel mutation of keratin 9 in epidermolytic palmoplantar keratoderma combined with knuckle pads. *Am J Med Genet* 2003; **120A**: 345–9.
7 Ritter SB, Peterson G. Esophageal cancer, hyperkeratosis and oral leukoplakia. *JAMA* 1976; **235**: 1723.

Pachydermodactyly [1–7]

This is a benign fibromatosis of the fingers that usually affects young adult males (Fig. 45.35). It produces a symmetrical, diffuse swelling of the skin around the dorsal and lateral aspects of the proximal phalanges of the index, ring and middle fingers. Pachydermodactyly has been recently reported in women [4,5] and two young girls, one of whom had tuberous sclerosis and the other EDS [6]. It may be associated with bilateral carpal tunnel



Fig. 45.35 Pachydermodactyly. (Courtesy of Dr A. Chamberlain, Churchill Hospital, Oxford, UK.)

syndrome [2] and varioliform atrophy [8]. A distal variant has been described in an elderly woman, who also presented with nodules over the extensor aspects of the elbows [9]. Affected families have been reported [10].

It has been suggested that repeated rubbing of the fingers or mechanical injury to the joints may contribute to the condition [3,6], but pachydermodactyly must be distinguished from occupational callosities, obsessive 'chewing pads' and true knuckle pads [11,12], although knuckle pads and pachydermodactyly coexisted in one family [13].

Histology shows epidermal hyperplasia and marked dermal thickening, with extension of collagenous fibres into the subcutaneous tissue. Types III and V collagen are increased, and electron microscopy shows increased numbers of fine-diameter collagen fibres.

References

1 Al Hammadi A, Hakim M. Pachydermodactyly: case report and review of the literature. *J Cutan Med Surg* 2007; **11**: 185–7.
2 Verbov J. Pachydermodactyly: a variant of the true knuckle pad. *Arch Dermatol* 1975; **111**: 524.
3 Meunier L, Pailler C, Barneon G, Meynadier J. Pachydermodactyly or acquired digital fibromatosis. *Br J Dermatol* 1994; **131**: 744–6.
4 Draluck JC, Kopf AU, Hodak E. Pachydermodactyly: first report in a woman. *J Am Acad Dermatol* 1992; **27**: 303–5.
5 Bardazzi F, Fanti PA, De Padova MP *et al.* Localized pachydermodactyly in a woman. *Acta Derm Venereol Suppl (Stockh)* 1994; **74**: 152–3.
6 Bardazzi F, Neri I, Fanti PA *et al.* Pachydermodactyly in two young girls. *Pediatr Dermatol* 1996; **13**: 288–91.
7 Curley RK, Hudson PM, Marsden RA. Pachydermodactyly: a rare form of digital fibromatosis—report of four cases. *Clin Exp Dermatol* 1991; **16**: 121–3.
8 Callot V, Wechsler J, Hovanian A *et al.* Pachydermodactyly and atrophia maculosa varioliformis cutis. *Dermatology* 1995; **190**: 56–8.
9 Tompkins SD, McNutt NS, Shea CR. Distal pachydermodactyly. *J Am Acad Dermatol* 1998; **38**: 359–62.
10 Russo F, Rodriguez-Picardo A, Camacho F. Familial pachydermodactyly. *Acta Derm Venereol* 1994; **74**: 386–7.
11 Kopera D, Soyer HP, Kerl H. An update on pachydermodactyly and a report of three additional cases. *Br J Dermatol* 1995; **133**: 433–7.
12 Lautenschlager S, Itin PH, Rufli T. Pachydermodactyly: reflecting obsessive-compulsive behavior? *Arch Dermatol* 1994; **130**: 387.
13 Chamberlain AJ, Venning VA, Wojnarowska F. Pachydermodactyly; a forme fruste of knuckle pads? *Australas J Dermatol* 2003; **44**: 140–3.

Juvenile fibromatoses

The term juvenile fibromatosis has been applied to a group of disorders occurring in infants and children, and characterized by proliferative activity of the fibroblasts [1–6]. There is a tendency to local recurrence but, unlike fibrosarcomas, they do not metastasize. The group includes a number of well-defined clinical entities that affect the skin:

1 infantile myofibromatosis
2 fibrous hamartoma of infancy
3 juvenile hyaline fibromatosis
4 infantile digital fibromatosis
5 calcifying aponeurotic fibroma
6 giant cell fibroblastoma.

These conditions are described in Chapter 56.

Juvenile hyaline fibromatosis

Synonyms
- Systemic hyalinosis
- Puretic syndrome

Definition. This is a disorder of glycosaminoglycan synthesis, which is characterized clinically by skin papules or tumours, gingival enlargement, osteolytic lesions and joint contractures, and histologically by deposition of amorphous hyaline material.

Aetiology. The cause is unknown, but increased chondroitin synthesis has been demonstrated in skin fibroblasts cultured from the tumour tissue [1]. The disease is very rare and occurs sporadically, but it has occurred in siblings.

Pathology [1–4]. The skin lesions contain 'chondroid' cells embedded in amorphous eosinophilic ground substance in the dermis. In the early lesions, this consists of glycosaminoglycans, but in the later lesions the matrix is mainly composed of chondroitin sulphate [5]. The dermal collagen is decreased and the collagen fibrils are fewer and thinner than in normal skin. The hyaline material may also be present in the muscles and bones. Absence of pro-α_2 chains and type III collagen has been demonstrated in affected skin [6].

Clinical features [4,7–10]. Skin lesions are present at birth or develop in early childhood. There may be small, pearly papules or nodules, particularly on the face or neck. Large subcutaneous tumours may also occur, particularly on the scalp. These may be hard or soft, fixed or mobile, and they may ulcerate. Gingival hypertrophy is commonly present, and flexion contractures of the fingers, elbows, hips and knees may develop. Osteolytic lesions can occur in the skull, long bones or phalanges. The musculature is poorly developed. The condition persists into adult life and the joint contractures are disabling. Infantile systemic hyalinosis is probably an extreme variant, leading to death in infancy.

Treatment. This is unsatisfactory. The tumours do not respond to radiotherapy, and they may recur after excision [11]. Joint

contractures may respond to intralesional steroid injections in the early stages and they may also respond to systemic steroids and physiotherapy.

References

1 Iwata S, Horiuchi R, Maeda H *et al.* Systemic hyalinosis or juvenile fibromatosis. Ultrastructural and biochemical study of cultured skin fibroblasts. *Arch Dermatol Res* 1980; **267**: 115–21.
2 Chitale AR, Murthy AK, Maniar JK *et al.* Juvenile hyaline fibromatosis. *Ultrastruct Pathol* 1987; **11**: 771–5.
3 Ishikawa H, Maeda H, Takamatsu H *et al.* Systemic hyalinosis (juvenile hyaline fibromatosis). Ultrastructure of the hyaline with particular reference to the cross-banded structure. *Arch Dermatol Res* 1979; **265**: 195–206.
4 Finlay AY, Ferguson SD, Holt PJA *et al.* Juvenile hyaline fibromatosis. *Br J Dermatol* 1983; **108**: 609–16.
5 Mayer DA, Silva A. Juvenile hyaline fibromatosis. A histologic and histochemical study. *Arch Pathol Lab Med* 1988; **112**: 928–31.
6 Winik B, Boente M, Asail R. Juvenile hyaline fibromatosis: ultrastructural study. *Am J Dermatopathol* 1998; **20**: 372–8.
7 Camarasa JG, Moreno A. Juvenile hyaline fibromatosis. *J Am Acad Dermatol* 1987; **16**: 881–3.
8 Fayad MN, Yacoub A, Salman S *et al.* Juvenile hyaline fibromatosis. Two new cases and a review of the literature. *Am J Med Genet* 1987; **26**: 123–31.
9 Landing BH, Nadorra R. Infantile systemic hyalinosis. *Pediatr Pathol* 1986; **6**: 55–97.
10 Remberger K, Krieg J. Fibromatosis hyalinica multiplex (juvenile hyaline fibromatosis). *Cancer* 1985; **56**: 614–24.
11 Quintal D, Jackson R. Juvenile hyaline fibromatosis. A 15-year follow up. *Arch Dermatol* 1985; **121**: 1062–3.

Other benign fibrous cutaneous nodules

Nodular fasciitis

See Chapter 56. In this condition, there is fibroblastic proliferation of one or more nodules, usually on the limbs or trunk.

Collagenoma

Multiple fibrous dermal nodules with coarse, collagen fibres may develop as sporadic cases (*eruptive collagenoma*) or as a genetic disorder with a dominant inheritance (*familial cutaneous collagenoma*) (Chapter 18).

Collagen naevi

See Chapter 18.

Albopapuloid form of epidermolysis bullosa

Synonym
- Pasini's syndrome

This rare form of epidermolysis bullosa is characterized by the development of ivory-white papules on the trunk, which histologically show connective tissue hyperplasia. Epidermolysis bullosa is discussed in Chapter 39.

Buschke–Ollendorf syndrome

Extensive nodular fibrosis may occur in the Buschke–Ollendorf syndrome (Chapter 18), in association with juvenile elastoma and osteopoikilosis.

Fibrous digital nodules

In addition to giant cell synovioma and infantile digital fibromatosis, fibrous nodules in the digits may be due to acquired digital fibrokeratoma, fibrous papule of the finger, dermatofibroma (Chapter 56) or the Koenen tumour (Chapter 15).

Infantile stiff-skin syndromes

Several rare syndromes have been described in which hard, stiff skin and joint contractures develop in early life.

Systemic hyalinosis

Infantile systemic hyalinosis is an autosomal recessive condition in which the skin becomes diffusely thickened and hard in the first few weeks of life, with limited joint mobility. Other characteristic features include small nodular thickenings of the perianal region, ears or lips, and gingival hypertrophy. There may also be hyperpigmentation, painful swollen joints with contractures, osteopenia, diarrhoea, frequent severe infections and growth failure. The prognosis is poor, and survival beyond the age of 2 years is unlikely [1].

The tissues show widespread deposits of hyaline material with the general staining properties of collagen.

Clinically, this syndrome shares many similarities with juvenile hyaline fibromatosis (see p. 45.49) [2,3]. Mutations in capillary morphogenic protein 2 (*CMG2*) have been found in both conditions, indicating that they are allelic [4,5].

Winchester's syndrome

Diffusely stiff, thickened skin may also occur in Winchester's syndrome [6–8]. This is a rare, autosomal recessive disease of infancy characterized by joint contractures, gingival hypertrophy, dwarfism, osteolysis, arthralgia, corneal opacities and hypertrichosis. The prognosis is relatively good, and many patients survive into adult life.

Previously, similar cases have been described as *hereditary contractures with sclerodermatoid changes of skin* and *stiff-skin syndrome* [9], with increased mucopolysaccharides in the skin.

The skin changes resemble those of scleredema of Buschke but are distinguished by their early onset. The condition must also be distinguished from sclerema neonatorum, but this is a disorder of subcutaneous fat rather than the skin.

Winchester's syndrome is caused by mutations in the matrix metalloproteinase 2 (*MMP2*) gene. The clinical and molecular findings suggest that Winchester's syndrome, nodulosis–arthropathy–osteolysis (NAO) syndrome and Torg (hereditary multicentric osteolysis) syndrome are allelic disorders that form a clinical spectrum [10].

Congenital fascial dystrophy

Synonym
- Stiff-skin syndrome

This hereditary connective tissue disorder is characterized by mild hirsutism, limitation of joint mobility affecting gait and localized areas of stony-hard skin, which are otherwise normal in appearance [11]. It appears in early infancy, and is only slowly progressive. The condition affects the deeper skin and fascia, which is

much thicker than normal, and tends to be most pronounced on the buttocks and legs, with a sharp demarcation of subcutaneous sclerosis at the inguinal canal. Unlike morphoea, no inflammatory changes are seen on histology. Electron microscopy of the skin shows large collagen fibres, and bundles of aggregated microfibrils [11]. Thickening of the thoracic fascia may cause hypoventilation due to thoracic underdevelopment, but there are no other systemic features of this disease.

The condition appears to be analogous to the tight-skin mouse [12].

Restrictive dermopathy

This very rare autosomal recessive laminopathy, also known as tight skin contracture syndrome, presents at birth with a taut, shiny skin, which restricts movement of the joints [13–15]. It is characterized by intrauterine growth retardation and premature birth, due to ruptured fetal membranes. The typical facies is a small, fixed, round, open mouth, micrognathia, small nose, low-set ears and widely spaced cranial sutures. The joints are all fixed in flexion, and gross restriction of the respiratory movements causes death within hours, or at most weeks. The epidermis shows hyperkeratosis and parakeratosis, and the keratohyaline granules are abnormal. The dermal–epidermal junction is flat, with a thin dermis, and a thick layer of subcutaneous fat. The eccrine and pilosebaceous glands are underdeveloped. The collagen bundles appear stretched, and orientated in parallel lines, as they are in a tendon [16].

Mutations have been found in the *LMNA* genes leading to synthesis of mutant prelamin A that cannot be processed into mature lamin A. Mutations in the prelamin A processing enzyme gene (*ZMPSTE24/FACE-1*) also cause abnormal accumulation of the precursor with deleterious effects on nuclear homeostasis [17,18].

References

1 Landing BH, Nadorra R. Infantile systemic hyalinosis: report of four cases of a disease, fatal in infancy, apparently different from juvenile systemic hyalinosis. *Pediatr Pathol* 1986; **6**: 55–79.

2 Nezelof C, Letourneux-Toromanoff B, Griscelli C *et al.* La fibromatose disseminée doloureuse (hyalinose systemique). *Arch Fr Pediatr* 1978; **35**: 1063–74.

3 Puretic S, Puretic B, Fiser-Herman M *et al.* A unique form of mesenchymal dysplasia. *Br J Dermatol* 1962; **74**: 8–19.

4 Dowling O, Difeo A, Ramirez MC *et al*. Mutations in capillary morphogenesis gene-2 result in the allelic disorders juvenile hyaline fibromatosis and infantile systemic hyalinosis. *Am J Hum Genet* 2003; **73**: 957–66.

5 Hanks S, Adams S, Douglas J *et al*. Mutations in the gene encoding capillary morphogenesis protein 2 cause juvenile hyaline fibromatosis and infantile systemic hyalinosis. *Am J Hum Genet* 2003; **73**: 791–800.

6 Winchester P, Grossman H, Lim WN *et al.* A new acid mucopolysaccharidosis with skeletal deformities simulating rheumatoid arthritis. *Am J Roentgenol* 1969; **106**: 121–8.

7 Cohen AH, Hollister DW, Reed WB. The skin in the Winchester syndrome. *Arch Dermatol* 1975; **111**: 230–6.

8 Prapanpoch S, Jorgensen RJ, Langlais RP *et al.* Winchester syndrome: a case report and literature review. *Oral Surg Oral Med Oral Pathol* 1992; **74**: 671–7.

9 Esterley NB, McKusick VA. Stiff skin syndrome. *Pediatrics* 1971; **47**: 360–9.

10 Zankl A, Bonafe L, Calcaterra V *et al*. Winchester syndrome caused by a homozygous mutation affecting the active site of matrix metalloproteinase 2. *Clin Genet* 2005; **67**: 261–6.

11 Jablonska S, Blaszczyk M. Scleroderma-like indurations involving fascias: an abortive form of congenital fascial dystrophy (stiff skin syndrome). *Pediatr Dermatol* 2000; **17**: 105–10.

12 Jiminez SA. Scleroderma-like alterations in collagen metabolism in the tight-skin mouse. *Arthritis Rheum* 1984; **27**: 180–5.

13 Witt DR, Hayden MR, Holbrook KA *et al.* Restrictive dermopathy: a newly recognised autosomal recessive skin dysplasia. *Am J Med Genet* 1986; **24**: 631–48.

14 Welsh KM, Smoller BR, Holbrook KA *et al.* Restrictive dermopathy. Report of two affected siblings and a review of the literature. *Arch Dermatol* 1992; **128**: 228–31.

15 Happle R, Stekhoven JHS, Hamel BCJ *et al.* Restrictive dermopathy in two brothers. *Arch Dermatol* 1992; **128**: 232–5.

16 Holbrook KA, Dale BA, Witt DR *et al.* Arrested epidermal morphogenesis in three newborn infants with a fatal genetic disorder (restrictive dermopathy). *J Invest Dermatol* 1987; **88**: 330–40.

17 Navarro CL, De Sandre-Giovannoli A, Bernard R *et al*. Lamina A and ZMPSTE24 (FACE-1) defects cause nuclear disorganization and identify restrictive dermopathy as a lethal neonatal laminopathy. *Hum Mol Genet* 2004; **13**: 2493–503.

18 Young SG, Meta M, Yang SH *et al*. Prelamin A farnesylaion and progeroid syndromes. *J Biol Chem* 2006; **281**: 39741–5.

Other causes of diffuse fibrosis

Environmental and drug-induced scleroderma

(see also Chapter 51)

A variety of environmental triggers may stimulate a localized or diffuse scleroderma-like reaction in a genetically susceptible host. Important causes are listed in Table 45.5. In most cases, the fibrotic process continues after withdrawal of the external stimulus. Sometimes, the ensuing clinical pattern resembles idiopathic forms of scleroderma (see Chapter 51).

Exposure to *vinyl chloride monomer* occurs in workers involved in polyvinyl chloride (PVC) production. One-third of male

Table 45.5 Cutaneous fibrosis due to chemical exposure.

Vinyl chloride
Silica dust
Organic solvents:
Aromatic hydrocarbons (e.g. toluene, benzene)
Aliphatic hydrocarbons:
Chlorinated (e.g. trichlorethylene, perchlorethylene)
Non-chlorinated (e.g. naphtha-*n*-hexane)
Epoxy resins
Toxic oil syndrome
Urea formaldehyde foam insulation
Breast augmentation (paraffin, silicone)
Drugs:
Reactions to local injection:
Phytomenadione
Pentazocine
Heparin
Reactions to systemic therapy:
Bleomycin
L-tryptophan (eosinophilia–myalgia syndrome)
Carbidopa and L-5-hydroxytryptophan
Penicillamine
Valproate sodium
Cocaine
Appetite suppressants (diethylpropion hydrochloride, amphetamine)
Diltiazem



Fig. 45.36 Vinyl chloride-induced osteolysis affecting fingertips.



Fig. 45.37 Scleroderma and scarring of the face due to porphyria cutanea tarda. (Courtesy of Dr D.A. Burns, Leicester Royal Infirmary, Leicester, UK.)

operatives in a British factory developed a clinical syndrome that included Raynaud's phenomenon, dyspnoea, cutaneous sclerosis, pulp atrophy and radiological evidence of acro-osteolysis (Fig. 45.36) [1]. Genetic marker studies have demonstrated an increased incidence of human leukocyte antigen (HLA)-DR5 in affected individuals; severe disease is linked with B8 and DR3 [2]. A similar syndrome has been reported in gold miners exposed to silica dust [3], and in workers exposed to organic solvents, such as trichlorethylene [4] and perchlorethylene [5], which are structurally similar to vinyl chloride. Exposure to epoxy resin results in an acute syndrome of cutaneous sclerosis, muscle weakness, arthralgia, impotence, lung and oesophageal involvement [6]. The causative agent appears to be a cyclohexylamine. An increased prevalence of autoimmune disorders, including scleroderma, is reported in miners exposed to vermiculite contaminated with tremolite asbestos [7].

Toxic oil syndrome is a multisystem illness, reported in Spain in 1981. Acute fever, severe but transient pulmonary oedema, myalgia, and a pruritic exanthem and eosinophilia were followed after several months by widespread cutaneous sclerosis in 30% of cases [8,9]. The syndrome was probably due to ingestion of imported rapeseed oil mixed with an aniline denaturant, designed to make the oil unfit for human consumption. Toxic oil syndrome bears a striking resemblance to the *eosinophilia–myalgia syndrome* [10–12], linked with consumption of L-tryptophan; this is used as a 'food supplement' to treat insomnia and depression. The offending batches of L-tryptophan contained impurities similar to the contaminants in toxic oil [13,14].

In environmental fibrotic disorders, as in idiopathic scleroderma, subpopulations of fibroblasts appear to be activated to synthesize excess collagen; this property is perpetuated by fibroblasts *in vitro*, indicating that the elevated collagen gene expression is independent of extracellular stimuli [12]. Cytokines appear to stimulate the proliferation of these abnormal clones of fibroblasts; thus, transforming growth factor-β (TGF-β) and platelet-derived growth factor (PDGF) are elevated in the eosinophilia–myalgia syndrome [15].

Numerous drugs have been reported to induce cutaneous sclerosis. Lesions resembling morphoea may follow injections of pentazocine [16], heparin [17] and vitamin K_1 (phytomenadione) [18–20]; in the case of vitamin K_1, the trigger may be a solvent rather than vitamin K_1 itself [21]. Morphoea-like plaques have also been reported in patients taking penicillamine [22] and valproate [23].

Diffuse scleroderma-like changes have been reported following bleomycin therapy [24]. A combination of L-5-hydroxytryptophan and carbidopa induced lesions resembling eosinophilia–myalgia syndrome [25]. Phenytoin and diltiazem both induce gingival hypertrophy [26,27]. A patient on phenytoin developed florid hypertrophic retroauricular folds [28]. Thickened skin on the feet has been reported in a patient taking diltiazem [29].

Alcohol can provoke porphyria cutanea tarda, which can produce a sclerodermatous appearance (Fig. 45.37).

References

1 Ward AM, Udnoon S, Watkins J *et al.* Immunological mechanism in the pathogenesis of vinyl chloride disease. *BMJ* 1976; **i**: 936–8.

2 Black CM, Pereira S, McWhirter A *et al.* Genetic susceptibility to scleroderma-like syndrome in symptomatic and asymptomatic workers exposed to vinyl chloride. *J Rheumatol* 1986; **13**: 1059–62.

3 Sluis-Cremer GK, Hessel PA, Nizdo EH *et al.* Silica, silicosis and progressive systemic sclerosis. *Br J Ind Med* 1985; **42**: 838–43.

4 Saihan EM, Burton JL, Heaton KW. A new syndrome with pigmentation, scleroderma, gynaecomastia, Raynaud's phenomenon and peripheral neuropathy. *Br J Dermatol* 1978; **99**: 437–40.

5 Sparrow GP. A connective tissue disease similar to vinyl chloride disease in a patient exposed to perchlorethylene. *Clin Exp Dermatol* 1977; **2**: 17–22.

6 Yamakage A, Ishikawa H, Saito Y *et al.* Occupational scleroderma-like disorders occurring in men engaged in the polymerization of epoxy resins. *Dermatologica* 1980; **161**: 33–44.

7 Noonan CW, Pfau JC, Carson TC *et al.* Nested case-control study of autoimmune disease in an asbestos-exposed population. *Environ Health Perspect* 2006; **114**: 1243–7.

8 Iglesias JL, De Moragas JM. The cutaneous lesions of the Spanish toxic oil syndrome. *J Am Acad Dermatol* 1983; **9**: 159–60.

9 Phelps RG, Fleishmajer R. Clinical, pathologic, and immunological manifestations of the toxic oil syndrome. *J Am Acad Dermatol* 1988; **18**: 313–24.

10 Kaufman LD, Seidman RJ, Phillips ME *et al.* Cutaneous manifestations of the L-tryptophan-associated eosinophilia–myalgia syndrome: a spectrum of sclerodermatous disease. *J Am Acad Dermatol* 1990; **23**: 1063–9.

11 Kilbourne EM, Posada de la Paz M, Borda IA *et al.* Toxic oil syndrome: a current clinical and epidemiologic summary, including comparisons with the eosinophilia–myalgia syndrome. *J Am Coll Cardiol* 1991; **18**: 711–7.

12 Varga J, Jimenez SA. Chemical exposure-induced cutaneous fibrosis. Lessons from 'experiments of nature'. *Arch Dermatol* 1994; **130**: 97–100.
13 Slutsker L, Hoesly FC, Miller L *et al.* Eosinophilia–myalgia syndrome associated with exposure to tryptophan from a single manufacturer. *JAMA* 1990; **264**: 213–7.
14 Mayeno AN, Belongia EA, Lin F *et al.* 3-(Phenylamino) alanine, a novel aniline-derived amino acid associated with the eosinophilia–myalgia syndrome: a link to the toxic oil syndrome. *Mayo Clin Proc* 1992; **67**: 1134–9.
15 Kaufman LD, Gruber BL, Gomez-Reion JJ. Fibrogenic growth factors in the eosinophilia–myalgia syndrome and the toxic oil syndrome. *Arch Dermatol* 1994; **130**: 41–7.
16 Palestine RF, Millas JL, Spigel GT *et al.* Skin manifestations of pentazocine abuse. *J Am Acad Dermatol* 1980; **2**: 47–55.
17 Barthelemy H, Hermier C, Perrot H. Nécrose cutanée avec évolution sclérodermiforme aprés l'injection souscutanée d'heparinate de calcium. *Ann Dermatol Vénéréol* 1985; **112**: 245–7.
18 Brunskill NJ, Berth-Jones J, Graham-Brown RAC. Pseudosclerodermatous reaction to phytomenadione injection (Texier's syndrome). *Clin Exp Dermatol* 1988; **13**: 276–8.
19 Pujol RM, Puig L, Moreno A. Pseudoscleroderma secondary to phytomenadione (vitamin K_1) injections. *Cutis* 1989; **43**: 365–8.
20 Morel A, Betlloch I. Morphea-like reaction from vitamin K_1. *Int J Dermatol* 1995; **34**: 201–2.
21 Bourrat E, Moraillon I, Vignon-Pennamen MD. Placard sclérodermiforme de la cuisse de l'enfant aprés injection de vitamine K_1 à la naissance. *Ann Dermatol Vénéréol* 1996; **123**: 634–8.
22 Bernstein RM, Hall MA, Gostelow BE. Morphoea-like reaction to D-penicillamine therapy. *Ann Rheum Dis* 1981; **40**: 42–4.
23 Goihman-Yahr M, Leal G, Essenfeld-Yahr E. Generalised morphea: a side effect of valproate sodium? *Arch Dermatol* 1980; **116**: 621.
24 Finch WR, Rodnan GP, Buckingham RB *et al.* Bleomycin-induced scleroderma. *J Rheumatol* 1980; **7**: 651–9.
25 Sternberg EM, van Woert MH, Young SN *et al.* Development of a scleroderma-like illness during therapy with 1-5-hydroxytryptophan and carbidopa. *N Engl J Med* 1980; **303**: 782–7.
26 Hassell TM, Page RC, Narayanan AS *et al.* Diphenylhydantoin (Dilantin) gingival hyperplasia: drug-induced abnormality of connective tissue. *Proc Natl Acad Sci USA* 1976; **73**: 2909–12.
27 Guistiniani S, Robustelli F, Marieni M. Hyperplastic gingivitis during diltiazem therapy. *Int J Cardiol* 1987; **15**: 247–9.
28 Trunnell TN, Waisman M. Hypertrophic retroauricular folds attributable to diphenylhydantoin. *Cutis* 1982; **30**: 207–9.
29 Ilia R, Goldfarb B, Gueron M. Skin thickening and sensory loss of the feet during diltiazem therapy. *Int J Cardiol* 1992; **35**: 115.

Nephrogenic systemic fibrosis

Synonyms
- Scleromyxoedema-like illness of renal disease
- Nephrogenic fibrosing dermopathy

Acute onset of skin thickening has been reported in patients with renal disease undergoing haemodialysis or renal transplant [1]. Irregular erythematous or brownish indurated plaques, with amoeba-like projections and islands of sparing, occur chiefly on the lower trunk and legs. Sometimes the skin has a *peau d'orange* texture, which can mimic carcinoma erysipelatoides [2]. Dermal mucin is detected with Alcian-blue staining, and increased collagen is laid down in haphazard bundles; there are increased numbers of $CD68^+$ histiocytes, dermal dendrocytes and fibroblasts. Inflammatory changes may predominate, including a septal panniculitis [3]. Although initially described as 'scleromyxoedema-like', the lesions have a different distribution and morphology, and there is no associated paraproteinaemia [4]. Initially thought to be restricted to the skin, there are several reports of involvement of internal organs including lungs, myocardium and striated muscle, which contribute to a high mortality [4].

The condition is strongly associated with the prior administration of gadolinium-based magnetic resonance contrast agents, particularly in patients with severe renal disease [5]. Gadolinium chelates stimulate fibroblast growth, synthesis and differentiation into myofibroblasts [6]. High-dose erythropoietin may also be implicated [7].

Usually, the condition is progressive, although it may remit spontaneously, particularly with the correction of renal abnormalities. No treatment is of proven benefit, but thalidomide [8], hydroxychloroquine [9], intravenous sodium thiosulphate and extracorporeal photopheresis [10] have been used empirically. Transient benefit has been reported with the use of the tyrosine kinase inhibitor imatinib mesylate [11].

References

1 Cowper S, Robin H, Steinberg S *et al.* Scleromyxedema-like cutaneous diseases in renal-dialysis patients. *Lancet* 2000; **356**: 1000–1.
2 Solomon GJ, Wu E, Rosen PP. Nephrogenic systemic fibrosis mimicking inflammatory breast carcinoma. *Arch Pathol Lab Med* 2007; **131**: 145–8.
3 Naylor E, Hu S, Robinson-Bostom L. Nephrogenic systemic fibrosis with septal panniculitis mimicking erythema nodosum. *J Am Acad Dermatol* 2008; **58**: 149–50.
4 Swaminathan S, High WA, Ranville J *et al.* Cardiac and vascular metal deposition with high mortality in nephrogenic systemic fibrosis. *Kidney Int* 2008; **73**: 1413–8.
5 Grobner T. Gadolinium—a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? *Nephrol Dial Transplant* 2006; **21**: 1104–8.
6 Edward M, Quinn J, Mukherjee S *et al.* Gadodiamide contrast agent 'activates' fibroblasts: a possible cause for nephrogenic systemic fibrosis. *J Pathol* 2008; **214**: 584–93.
7 Swaminathan S, Ahmed I, McCarthy JT *et al.* Nephrogenic fibrosing dermopathy and high-dose erythropoietin therapy. *Ann Intern Med* 2006; **145**: 234–5.
8 Streams BN, Liu V, Liegois N *et al.* Clinical and pathologic features of nephrogenic fibrosing dermopathy: a report of two cases. *J Am Acad Dermatol* 2003; **48**: 42–7.
9 Kalb RE, Helm TN, Sperry H *et al.* Gadolinium-induced nephrogenic systemic fibrosis in a patient with an acute and transient kidney injury. *Br J Dermatol* 2007; **158**: 607–10.
10 Linfert DR, Schell JO, Fine DM. Treatment of nephrogenic systemic fibrosis: limited options but hope for the future. *Semin Dial* 2008; **21**: 155–9.
11 Kay J, High WA. Imatinib mesylate treatment of nephrogenic systemic fibrosis. *Arthritis Rheum* 2008; **58**: 2543–8.

GEMSS syndrome

This is an autosomal dominant condition, comprising *g*laucoma, lens *e*ctopia, *m*icrospherophakia (small, spherical lens), joint *s*tiffness and *s*hort stature [1]. Affected individuals have a stocky, 'pseudoathletic' build. Associated cutaneous sclerosis notably affects the upper back and limbs but spares the face. Skin histology is reminiscent of systemic sclerosis. Increased synthesis of collagen is reflected by markedly enhanced gene expression of $TGF\beta_1$ [2].

References

1 Verloes A, Hermia JP, Garland A *et al.* Glaucoma–lens ectopia–microspherophakia–stiffness–shortness (GEMSS) syndrome: a dominant disease with manifestations of Weill–Marchesani syndrome. *Am J Med Genet* 1992; **40**: 48–51.
2 Kunz M, Paulus W, Sollberg S *et al.* Sclerosis of skin in the GEMSS syndrome. *Arch Dermatol* 1995; **131**: 1170–4.

POEMS syndrome (see also Chapters 58 & 62)

Synonym
- Crow–Fukase–Takatsuki syndrome

This acronym is derived from *p*olyneuropathy, *o*rganomegaly (of liver, spleen or lymph nodes), *e*ndocrinopathy (often diabetes mellitus), *M* protein (a monoclonal gammopathy) and *s*kin lesions. The skin features include hyperpigmentation, hyperhidrosis, hypertrichosis and diffuse thickening resembling scleroderma [1–3]. Rarer features include angiomas, white fingernails and alopecia [3].

The syndrome appears to be a rare variant of myelomatosis [4], although skeletal X-rays show single or multiple osteosclerotic lesions with areas of bony proliferation rather than the lytic lesions that are more typical of myeloma [5].

Overproduction of vascular endothelial growth factor (VEGF) may explain the microangiopathy, neovascularization and accelerated vasopermeability that occur in this syndrome [6].

High-dose chemotherapy followed by autologous stem cell transplant is a successful treatment, although morbidity is high [7].

References

1 Shelley WB, Shelley ED. The skin changes in the Crow–Fukase (POEMS) syndrome. *Arch Dermatol* 1987; **123**: 85–7.
2 Manning WJ, Goldberger AL, Drews RE *et al.* POEMS syndrome with myocardial infarction: observations concerning pathogenesis and review of the literature. *Semin Arthritis Rheum* 1992; **22**: 151–61.
3 Amicha B, Giryes H, Ariad S *et al.* Alopecia as a rare cutaneous manifestation of the POEMS syndrome. *Br J Dermatol* 1994; **131**: 297–8.
4 Burton JL. Peripheral neuropathy associated with dysproteinaemia, skin changes and endocrinopathy. *BMJ* 1986; **292**: 1415–6.
5 Piette WW. Myeloma, paraproteinaemias and the skin. *Med Clin North Am* 1986; **70**: 155–76.
6 Watanabe O, Maruyama I, Arimura K *et al.* Overproduction of vascular endothelial growth factor/vascular permeability factor is causative in Crow–Fukase (POEMS) syndrome. *Muscle Nerve* 1998; **21**: 1390–7.
7 Dispenzieri A, Lacy MQ, Hayman SR *et al.* Peripheral blood stem cell transplant for POEMS syndrome is associated with high rates of engraftment syndrome. *Eur J Haematol* 2008; **80**: 397–406.

Keloids and hypertrophic scars

Both conditions represent an excessive connective tissue response to injury, which may be trivial. A keloid (cheloid, meaning 'crab claw') is a benign, well-demarcated area of fibrous tissue overgrowth that extends beyond the original defect. A hypertrophic scar is similar, but remains confined to the initial defect and tends to resolve with time [1].

Aetiology. The cause is unknown, although both local and constitutional factors are involved. A scar at any site has the potential to become hypertrophic or keloidal, although the earlobes, chin, neck, shoulders, upper trunk and lower legs are especially vulnerable. Ear piercing is an important cause of earlobe keloids. Burns or scalds and infected lesions predispose to hypertrophy. Another risk factor is the presence of foreign material, either exogenous (e.g. suture material) or endogenous (e.g. embedded hair). Some African tribes introduce foreign bodies into tribal marks to induce scar hypertrophy. Scarring acne, particularly on the trunk, may become keloid-like. Isotretinoin has been reported to delay wound healing and induce keloids in patients who received argon laser or dermabrasion for acne or rosacea [2,3].

Some races, notably Afro-Caribbeans, are more prone to develop keloids than others. A positive family history is obtained in 5–10% of Europeans with keloids, particularly severe lesions [4]. Family studies suggest an autosomal dominant inheritance with incomplete penetrance [5]. There is a genetic association with other 'fibromatoses' such as Dupuytren's contracture [6]. Keloids form readily in acromegalics, and after thyroidectomy in young patients. They have been reported in a boy with Dubowitz's syndrome [7]. Keloids are also recorded in association with EDS, pachydermoperiostosis and Rubinstein–Taybi syndrome [8]. Keloids are rare in infancy and old age, occurring chiefly between puberty and the age of 30 years. Women have a greater predisposition, and keloids may occur or enlarge during pregnancy [9].

Linear keloids have been reported to occur in athletes taking anabolic steroids [10].

Pathology [11–13]. Although the histology may be difficult to distinguish from normal wound healing in the early stages, hypertrophic scars and keloids typically exhibit increased cellularity. In keloids of recent onset, endothelial proliferation is surrounded by increased numbers of fibroblasts, which form large, irregular nodules or whorls of collagen with a peripheral capsule-like band [11]. Mast cells are increased in hypertrophic scars [12]. Mucinous material is deposited focally in keloids but not in hypertrophic scars. The epidermis is normal, or thinned by the underlying lesion.

On electron microscopy, the nodules contain stellate fibroblasts. It is uncertain whether these are [14] or are not [15] myofibroblasts. Scanning electron microscopy of keloids shows more haphazard organization of collagen bundles than in normal skin or mature scars. The collagen filaments are about half the diameter of those of normal skin.

Biochemical studies confirm that collagen and proteoglycan synthesis is increased in keloids and hypertrophic scars. Collagen degradation appears to be normal [16]. Synthesis of both types I and III collagen is increased [17], and hypertrophic scar collagen possesses the reducible keto cross-link, dehydrohydroxylysinonorleucine, normally associated with embryonic skin and granulation tissue [18]. Several growth factors have been studied using keloid fibroblasts *in vitro*. Keloid fibroblasts, unlike those from hypertrophic scar tissue, are hyperresponsive to both TGF-β, which is abundant in healing wounds [19], and PDGF [20]. Keloid fibroblasts also express increased levels of heat shock protein (HSP) 47, another stimulus to collagen synthesis [21].

Keloid fibroblasts secrete increased amounts of collagen and glycosaminoglycans for several passages in tissue culture [22]. It is unclear whether these cells represent a normal subgroup or have undergone transformation. Altered expression of proteoglycans in keloids may affect the three-dimensional organization of collagen fibres [23].

Immunohistochemical studies have shown that neuropeptide-containing nerves are present [24] and opioid receptors are upreg-



Fig. 45.38 Spontaneous keloids of the neck.

ulated [25] in hypertrophic scars but not in non-hypertrophic scars, and these may contribute to the symptoms of discomfort and itching in such scars.

Clinical features. Both hypertrophic scars and keloids become raised and thickened within 3–4 weeks of the provocative stimulus. The lesion becomes a firm, pink or red plaque, which may grow for months or years. Lesions often assume a 'dumb-bell' configuration, but sometimes become bizarre and irregular (Fig. 45.38). Usually, a hypertrophic scar shows signs of regression after a few months. The surface of a keloid becomes smoother and rounder, extending beyond the area of the original lesion. It is often irritable and hypersensitive, and sometimes exquisitely tender. Keloids tend to regress after several years; lesions on the beard area sometimes undergo central suppurative necrosis. Malignant degeneration has been reported [26], although a fibrosarcoma can mimic keloid clinically.

The diagnosis is usually simple if there is a history of trauma or an inflammatory skin lesion. Spontaneous keloids usually develop on the presternal region or upper chest. Lesions that can cause diagnostic difficulty include sclerotic basal cell carcinoma, scar sarcoid or malignancy developing in a scar, and dermatofibrosarcoma. In endemic areas, blastomycosis and lobomycosis cause keloidal reactions.

Prophylaxis and treatment. Although numerous treatments have been advocated with enthusiasm, a cure is rarely achieved [27]. Non-essential surgery should be avoided in the sites of predilection. If surgery is necessary, simple excision, ideally intralesional (core) excision, aiming to minimize skin tension and secondary infection, is preferable to electrocoagulation or caustic chemicals. In an individual at risk, preoperative radiotherapy to the excision site may be useful.

Keloids usually recur following simple excision, although adjuvant therapy, such as radiation, local compression with a custom-made pressure garment [28], particularly on the earlobe, or intralesional steroids may reduce the risk of recurrence. Some lesions respond to pressure alone, or to occlusion with a hydrocolloid dressing. Small keloids can respond to self-adherent silicone sheeting/silicone gel [29,30]. Silicone gel treatment is also effective for hypertrophic scars [29]. Promising results have been obtained using a cream made of 20% silicone oil, applied under occlusion; this may be beneficial for sites where it is impracticable to apply gel-sheeting [31].

Radiotherapy, including superficial X-rays, implantation with iridium-192 wires, or more recently with electron beam may prevent recurrence following surgery [32,33], but electron-beam therapy offers no advantage over orthovoltage [34]. Intralesional triamcinolone (10 mg/mL) is useful, especially in early lesions. Several injections may be necessary at intervals of 3–6 weeks. Prior freezing with liquid nitrogen before the injection causes oedema, which allows the triamcinolone to be injected more readily. Acne keloids respond moderately well to either intralesional triamcinolone or cryotherapy, but the response to the latter is better in early vascular lesions [35].

Topical retinoic acid, applied daily, may be helpful [36,37], although systemic retinoids may enhance keloid formation [3]. Intralesional lathyrogens, such as β-aminoproprionitrile, have been used, but systemic penicillamine is ineffective [38]. Intralesional cytotoxic drugs may cause ulceration, but intralesional 5-fluorouracil and 585-nm flashlamp-pumped pulsed dye laser produced comparable improvement in one study [39]. Flattening and reduced pruritus is claimed to follow intralesional bleomycin, administered through multiple superficial punctures [40]. A preliminary study suggests that topical mitomycin C reduces the risk of recurrence after shave biopsy of keloids [41].

Inhibitory cytokines, such as IFN-α and IFN-γ [42–44] perhaps in conjunction with intralesional triamcinolone [45], and TGF-β analogues [46], show promise. Interferons appear to reduce fibroblast collagen synthesis and increase collagenase activity by reducing the steady-state levels of mRNA [44]. Imiquimod cream can prevent recurrence of earlobe keloids after excision but is of limited value for presternal lesions [47]. Studies of keloid fibroblasts *in vitro* suggest a possible future role for gene therapy [48].

Different modes of laser treatment, for example the pulsed dye, Nd:YAG and carbon dioxide lasers, have a high recurrence rate.

References

1 Köse O, Waseem A. Keloids and hypertrophic scars; are they two different sides of the same coin? *Dermatol Surg* 2008; **34**: 336–46.
2 Rubenstein R, Roenigk H, Stegmann S *et al*. Atypical keloids after dermabrasion of patients taking isotretinoin. *J Am Acad Dermatol* 1986; **15**: 280–5.
3 Zachariae H. Delayed wound healing and keloid formation following argon laser treatment or dermabrasion during isotretinoin treatment. *Br J Dermatol* 1988; **118**: 703–6.
4 Cosman B, Crikelair GF, Ju DMC *et al*. The surgical treatment of keloids. *Plast Reconstr Surg* 1961; **27**: 335–8.
5 Marneros AG, Norris JEC, Olsen BR *et al*. Clinical genetics of familial keloids. *Arch Dermatol* 2001; **137**: 1429–34.
6 González-Martínez R, Marín-Bertolín S, Amorrortu-Velayos J. Association between keloids and Dupuytren's disease: case report. *Br J Plast Surg* 1995; **48**: 47–8.
7 Paradisi M, Angelo C, Conti G *et al*. Dubowitz syndrome with keloidal lesions. *Clin Exp Dermatol* 1994; **19**: 425–7.
8 Kelly AP. Keloids: a review. *Dermatol Clin* 1988; **7**: 130–9.
9 Moustafa MFH, Abdul Fattah AF. Presumptive evidence of the effect of pregnancy oestrogens on keloid growth. *Plast Reconstr Surg* 1975; **56**: 450–3.
10 Scott MH Jr, Scott MJ, Scott AM. Linear keloids resulting from abuse of anabolic androgenic steroid drugs. *Cutis* 1994; **53**: 41–3.

11 Linares HA, Kischer CW, Dobrkovsky M *et al.* The histiotypic organization of the hypertrophic scar in humans. *J Invest Dermatol* 1972; **59**: 323–31.
12 Kischer CW, Bunce H III, Shetlar MR. Mast cell analyses in hypertrophic scars, hypertrophic scars treated with pressure and mature scars. *J Invest Dermatol* 1978; **70**: 355–7.
13 Herlich HP, Desmouliere A, Diegelmann RF *et al.* Morphological and immunochemical differences between keloid and hypertrophic scar. *Am J Pathol* 1994; **145**: 105–13.
14 James WD, Besanceney CD, Odom RB. The ultrastructure of a keloid. *J Am Acad Dermatol* 1980; **3**: 50–7.
15 Mutsuoka LY, Uitto J, Wortsman J *et al.* Ultrastructural characteristics of keloid fibroblasts. *Am J Dermatopathol* 1988; **10**: 505–8.
16 Milsom JP, Craig RDP. Collagen degradation in cultural keloid and hypertrophic scar tissue. *Br J Dermatol* 1973; **89**: 635–44.
17 Zhang K, Garner W, Cohen L *et al.* Increased types I and III collagen and transforming growth factor- β1 mRNA and protein in hypertrophic burn scar. *J Invest Dermatol* 1995; **104**: 750–4.
18 Bailey AJ, Bazin S, Sims TJ *et al.* Characterisation of the collagen of hypertrophic and normal human scars. *Biochem Biophys Acta* 1975; **405**: 412–21.
19 Younai S, Nichter LS, Wellisz T *et al.* Modulation of collagen synthesis by transforming growth factor-β in keloid and hypertrophic scar fibroblasts. *Ann Plast Surg* 1994; **33**: 148–51.
20 Haisa M, Okochi H, Grotendorst GR. Elevated levels of PDGF and receptors in keloid fibroblasts contribute to an enhanced response to PDGF. *J Invest Dermatol* 1994; **103**: 560–3.
21 Chen JJ, Zhao S, Cen Y *et al.* Effect of heat shock protein 47 on collagen accumulation in keloid fibroblast cells. *Br J Dermatol* 2007; **156**: 1188–95.
22 Duncan MR, Hasan A, Berman B. Oncostatin M stimulates collagen and glycosaminoglycan production by cultured normal dermal fibroblasts: insensitivity of sclerodermal and keloidal fibroblasts. *J Invest Dermatol* 1995; **104**: 128–33.
23 Hunzelmann N, Anders S, Sollberg S *et al.* Coordinate induction of collagen type I and biglycan expression in keloids. *Br J Dermatol* 1996; **135**: 394–9.
24 Crowe R, Parkhouse N, McGrouther D, Burnstock G. Neuropeptide-containing nerves in painful hypertrophic human scar tissue. *Br J Dermatol* 1994; **130**: 444–52.
25 Cheng B, Liu H-W, Fu XB *et al.* Coexistence and upregulation of three types of opioid receptor, mu, delta and kappa, in human hypertrophic scars. *Br J Dermatol* 2008; **158**: 713–20.
26 Kanaar P, Oort J. Fibrosarcomas developing in scar tissue. *Dermatologica* 1969; **138**: 312–9.
27 Leventhal D, Furr M, Reiter D. Treatment of keloids and hypertrophic scars: a meta-analysis and review of the literature. *Arch Facial Plast Surg* 2006; **8**: 362–8.
28 Kischer CW, Shetlar MR, Shetlar CL. Alteration of hypertrophic scars induced by mechanical pressure. *Arch Dermatol* 1975; **111**: 60–4.
29 Berman B, Flores F. Comparison of a silicone gel-filled cushion and silicone gel sheeting for the treatment of hypertrophic or keloid scars. *Dermatol Surg* 1999; **25**: 484–6.
30 Berman B, Perez OA, Konda S *et al.* A review of the biologic effects, clinical efficacy and safety of silicone elastomer sheeting for hypertrophic and keloid scar treatment and management. *Dermatol Surg* 2007; **33**: 1291–302.
31 Wong T-W, Chiu H-C, Chen J-S *et al.* Symptomatic keloids in two children: dramatic improvement with silicone cream occlusive dressing. *Arch Dermatol* 1995; **131**: 775–7.
32 Bischof M, Krempien R, Debus J *et al.* Postoperative electron beam radiotherapy for keloids: objective findings and patient satisfaction—self assessment. *Int J Dermatol* 2007; **46**: 971–5.
33 Ogawa R, Miyashita T, Hyakusoku H *et al.* Postoperative radiation protocol for keloids and hypertrophic scars: statistical analysis of 370 sites followed for over 18 months. *Ann Plast Surg* 2007; **59**: 668–91.
34 Klumpar DI, Murray JC, Anscher M. Keloids treated with excision followed by radiation therapy. *J Am Acad Dermatol* 1994; **31**: 225–31.
35 Layton AM, Yip J, Cunliffe WJ. A comparison of intralesional triamcinolone and cryosurgery in the treatment of acne keloids. *Br J Dermatol* 1994; **130**: 498–501.
36 De Limpens J. The local treatment of hypertrophic scars and keloid with topical retinoic acid. *Br J Dermatol* 1982; **103**: 319–23.
37 Panabiere-Castaings MH. Retinoic acid in the treatment of keloids. *J Dermatol Surg Oncol* 1988; **14**: 1275–6.
38 Mayou BJ. Treatment of keloids. *Br J Dermatol* 1981; **105**: 87–9.
39 Manuskiatli W, Fitzpatrick R. Treatment response of keloidal and hypertrophic sternotomy scars. Comparison among intralesional corticosteroid, 5-fluorouracil, and 585-nm flashlamp-pumped pulsed-dye laser treatments. *Arch Dermatol* 2002; **138**: 1149–55.
40 Aggarwal H, Saxena A, Lubana PS *et al.* Treatment of keloids and hypertrophic scars using bleomycin. *J Cosmetic Dermatol* 2008; **7**: 43–9.
41 Bailey JN, Waite AE, Clayton WJ *et al.* Application of topical mitomycin C to the base of shave-removed keloid scars to prevent their recurrence. *Br J Dermatol* 2007; **156**: 682–6.
42 Tredget EE, Shen YJ, Forsyth N *et al.* Regulation of collagen synthesis, intracellular degradation and mRNA levels by interferon α2β in hypertrophic scar fibroblasts. *Wound Repair Regen* 1993; **1**: 156–65.
43 Gransten RD, Rook A, Flotte TJ *et al.* A controlled trial of intralesional recombinant interferon-γ in the treatment of keloidal scarring. Clinical and histologic findings. *Arch Dermatol* 1990; **126**: 1295–302.
44 Harrop AR, Ghahary A, Scott PG *et al.* Regulation of collagen synthesis and mRNA expression in normal and hypertrophic scar fibroblasts *in vitro* by interferon-γ. *J Surg Res* 1995; **58**: 471–7.
45 Lee JH, Kim SE, Lee AY. Effects of interferon-alpha2b on keloid treatment with triamcinolone acetonide intralesional injection. *Int J Dermatol* 2008; **47**: 183–6.
46 Chu Y, Guo F, Li Y *et al.* A novel truncated TGF-beta receptor II down-regulates collagen synthesis and TGF beta 1 secretion of keloid fibroblasts. *Connect Tissue Res* 2008; **49**: 92–8.
47 Malhotra AK, Gupta S, Khaitan BK *et al.* Imiquimod 5% cream for the prevention of recurrence after excision of presternal keloids. *Dermatology* 2007; **215**: 63–5.
48 Xu B, Liu ZZ, Zhu GY *et al.* Efficacy of recombinant adenovirus mediated double suicide gene therapy in human keloid fibroblasts. *Clin Exp Dermatol* 2008; **33**: 322–8.

Premature ageing syndromes [1,2]

Increasing age appears to cause many anatomical and functional changes in human skin, but some of these may be the result of cumulative damage due to sun exposure, etc. To date, no disease has been found to cause a true acceleration of the rate of ageing in all tissues. More than 150 diseases manifest one or more features of apparent premature ageing, but there are discrepancies between this process and true ageing. All the premature ageing syndromes are probably inherited, although the defect may not be obvious in the first few years of life. Cutaneous changes that may be a sign of a premature ageing syndrome include atrophy, loss of cutaneous fat, wrinkling, canities, hair loss, nail dystrophy, defective pigmentation, poikiloderma, sclerosis and ulceration.

The conditions associated with cutaneous signs of premature ageing are shown below.

1 Classical inherited premature ageing syndromes:
  (a) pangeria (Werner's syndrome)
  (b) progeria (Hutchinson–Gilford syndrome)
  (c) acrogeria (Gottron's syndrome)
2 Other congenital progeroid syndromes:
  (a) trisomy 21 (Down's syndrome)
  (b) neonatal pseudohydrocephalic progeroid syndrome (Wiedemann–Rauchenstrauch)
  (c) osteodysplastic geroderma
  (d) wrinkly skin syndrome
  (e) familial mandibulo-acral dysplasia
  (f) progeroid EDS
3 Excessive exposure to irradiation (usually UV)
4 Photosensitivity, especially congenital, for example poikiloderma congenitale, xeroderma pigmentosum, Cockayne's syndrome

5 Diseases causing elastolysis, for example cutis laxa
6 Thickened immobile skin, for example diabetic cheiroarthropathy
7 Fragile skin, for example prolidase deficiency
8 Loss of subcutaneous fat, for example generalized lipodystrophy.

References

1 Beauregard S, Gilchrest BA. Syndromes of premature ageing. *Dermatol Clin* 1987; **5**: 109–21.
2 Martin GM. Syndromes of accelerated ageing. *NCI Monogr* 1982; **60**: 241–7.

Pangeria

Synonyms
- Werner's syndrome
- Adult premature ageing syndrome

Definition. An inherited disorder in which the ageing process is accelerated, starting after puberty. It is characterized by short stature, senile appearance, cataracts, joint contractures, early menopause, premature arteriosclerosis, various skin changes (including scleroderma-like features, premature canities, baldness and ulceration) and an increased risk of malignancy [1]. Werner's syndrome is considered one of the genomic instability syndromes [2].

Aetiology. The syndrome is due to an autosomal recessive gene, with a calculated gene frequency of 1–5 per 1000 population [3].

Numerous abnormalities have been described in this syndrome, including chromosomal aberrations (most noticeably translocations, inversions and deletions), altered connective tissue metabolism, and abnormalities in the immune and endocrine systems [4–14].

Causal mutations have been identified in the RecQ type DNA helicase gene (*RECQL2*, *WRN* gene) [15,16]. Recent biochemical and genetic studies indicate that the *WRN* gene plays significant roles in DNA replication and repair and telomere maintenance [17].

Pathology. Many tissues show premature ageing, but the changes are not uniform. Microsplanchnia and generalized atheroma are usually present. The epidermis is atrophic and some appendages are sparse. The dermis is thickened, with replacement of subcutaneous fat by hyalinized collagen, increased glycosaminoglycans, abnormal elastic fibres, disorganized nerves and vessel changes, which resemble those seen in diabetes mellitus. These abnormalities are more marked in the acral skin than on the trunk [4].

Clinical features [1]. The earliest manifestation of the syndrome is greying at the temples, which usually develops between the ages of 14 and 18 years but may rarely be present as early as 8 years. The greying rapidly becomes uniform and is sometimes associated with progressive alopecia. The first significant changes are usually noticed between 18 and 30 years but may begin earlier. The lower legs, feet, forearms and hands are most severely involved, the face and neck less so; atrophy of the skin and loss of subcutaneous fat results in a tense, shining and adherent appearance of the skin. Thin, spindly legs contrast with the normal or obese trunk, and there is a bird-like facies. The joints become fixed, and there may be sclerodactyly and acral gangrene. Mottled or diffuse pigmentation and telangiectasia are often conspicuous on the limbs, face and neck. Keratoses over pressure points on the feet and ankles separate to leave indolent ulcers. The voice may be high pitched and hoarse from thinning of the cords and fixation of the epiglottis. Intelligence is usually normal.

Most patients are of small stature and hypogonadal, with sparse or absent pubic and axillary hair, but some achieve normal stature and successful pregnancies. Other endocrine deficiencies are sometimes present; frank diabetes mellitus in at least 30% and abnormal glucose tolerance in many others. The diabetes is characterized by relatively low blood glucose levels and peripheral resistance to insulin [18,19].

Cataracts develop between the ages of 20 and 35 years in most cases and are usually posterior and subcapsular. Other ocular defects may occur [20].

The incidence of malignancy is high, especially fibrosarcomas, which occur in 10% of patients [21]. Carcinoma has developed in a chronic leg ulcer [22], but skin cancer is relatively rare. Generally, atheroma develops early. Abnormalities of metabolism are sometimes present but are not of uniform type. Death usually occurs in the fourth to sixth decade, due to myocardial infarction or malignancy [23].

The radiological changes [24] are often striking. There may be calcification of arteries, ligaments, tendons and subcutaneous tissues, with osteoporosis of the extremities, especially the legs.

Diagnosis. The prematurely aged appearance, the physical immaturity, the scleroderma-like changes and the cataracts, in combination, are unmistakable. In the Rothmund–Thomson syndrome, erythema, which is of early onset, is followed by poikilodermatous changes and, although the facies may be superficially similar, there is no sclerosis. In systemic sclerosis, the hands are involved more than the feet and there is no premature ageing; in some advanced cases, confusion is possible but can be resolved by biopsy.

Huriez syndrome may require exclusion (Chapter 19). The differentiation from some of the other ageing syndromes is indicated in Table 45.6.

Mutational analysis of the *WRN* gene is now possible, although diagnosis by immunoblot analysis using a monoclonal antibody directed against the *WRN* gene product is also feasible [25].

Treatment. Only symptomatic measures are available. The management of the recurrent, painful ulceration of the feet and legs is difficult, and amputation may be needed. Cataract surgery should be undertaken with special caution, for it is often complicated by severe degenerative changes of the cornea [20].

References

1 Furuichi Y. Premature aging and predisposition to cancers caused by mutations in RecQ family helicases. *Ann NY Acad Sci* 2001; **928**: 121–31.
2 Martin GM, Oshima J. Lessons from human progeroid syndromes. *Nature* 2000; **408**: 263–6.
3 Epstein CJ, Martin GM, Schultz AL *et al*. Werner's syndrome: a review. *Medicine* 1966; **45**: 177–221.

Table 45.6 Clinical features of the classical premature ageing syndromes.

	Pangeria (Werner's syndrome)	Progeria (Hutchinson-Gilford sndrome)	Acrogeria (Gottron's syndrome)
Stature	Small stature; cessation of growth at 12 years	Small stature	Normal
Facies	Beaked nose; skin of ears atrophic and tightly bound down	Mid-facial cyanosis; bird-like facies; glyphic nasal tip; prominent frontal tuberosities and scalp veins; chin recessed	Micrognathia; atrophy of skin on tip of nose
Skin	Dry atrophic skin; mottled hyperpigmentation; telangiectasia	Dry, thin and wrinkled with mottled pigmentation; may present with scleroderma-like changes on limbs	Atrophic with telangiectasia and mottled hyperpigmentation on extremities
Scalp hair	Premature greying at 20 years; loss of hair at 20–25 years	Hair lost in first 2 years of life	Normal
Eyes	Bilateral juvenile cataracts (20–30 years); keratopathy; glaucoma	Prominent eyes; otherwise normal	Normal
Nails	Normal	Thin and brittle	Dystrophic or thickened
Limbs	Lower limb ulcers; hyperkeratosis over bony prominences; generalized loss of subcutaneous fat	Prominent joints; coxa valga; generalized subcutaneous fat loss; poorly developed muscular system; no acrosclerosis or Raynaud's phenomenon	Atrophy of skin most marked on extremities; no leg ulcers

4 Bauer EA, Uitto J, Tan EM *et al.* Werner's syndrome. Evidence for preferential regional expression of a generalized mesenchymal cell defect. *Arch Dermatol* 1988; **124**: 90–101.
5 Gawkrodger DJ, Priestley GC, Vijayalaxmi *et al.* Werner's syndrome. Biochemical and cytogenetic studies. *Arch Dermatol* 1985; **121**: 636–41.
6 Kieras FJ, Brown WT, Houck GE *et al.* Elevation of urinary hyaluronic acid in Werner's syndrome and progeria. *Biochem Med Metab Biol* 1986; **36**: 276–82.
7 Muratta K. Urinary acidic glycosaminoglycans. *Experientia* 1982; **38**: 313–4.
8 Salk D. Werner's syndrome: a review of recent research. *Hum Genet* 1982; **62**: 1–15.
9 Salk D. *Werner's Syndrome and Human Ageing*. New York: Plenum Press, 1985.
10 Tao LC, Stecker E, Gardner HA *et al.* Werner's syndrome and acute myeloid leukemia. *Can Med Assoc J* 1971; **105**: 951–4.
11 Thompson KVA, Halliday R. Genetic effects on the longevity of human fibroblasts. I. Werner's syndrome. *Gerontology* 1983; **29**: 73–9.
12 Shannon-Danes B. Progeria: a cell culture study on aging. *J Clin Invest* 1971; **50**: 2000–3.
13 Higachi T, Ishikawa O, Hayashi H *et al.* Disaccharide analysis of skin glycosaminoglycans in patients with Werner's syndrome. *Clin Exp Dermatol* 1994; **19**: 487–91.
14 Fleischmajer R, Nedwich A. Werner's syndrome. *Am J Med* 1973; **54**: 111–8.
15 Yu C-E, Oshima J, Fu YH *et al.* Positional cloning of the Werner's syndrome gene. *Science* 1996; **272**: 258–62.
16 Yu C-E, Oshima J, Wijsman EM *et al.* Mutations in the consensus helicase domains of the Werner syndrome gene. *Am J Hum Genet* 1997; **60**: 330–41.
17 Cheng WH, Muftuoglu M, Bohr VA. Werner syndrome protein: functions in the response to DNA damage and replication stress in S-phase. *Exp Gerontol* 2007; **42**: 871–8.
18 Kuzuya H, Imura H. Insulin resistance associated with congenital disorders. Insulin receptors in Werner's syndrome, myotonic dystrophy and type A extreme insulin resistance. *Jpn J Med* 1988; **27**: 219–21.
19 Vannini P, Ciavarella A, Forlani G *et al.* Investigation of insulin resistance associated with Werner's syndrome. *Diabete Metab* 1987; **13**: 81–5.
20 Jonas JB, Ruprecht KW, Schmitz-Valckenbarg P. Ophthalmic surgical complications in Werner's syndrome. *Ophthalmic Surg* 1987; **18**: 760–4.
21 Bjornberg A. Werner's syndrome and malignancy. *Acta Derm Venereol Suppl (Stockh)* 1976; **56**: 149–50.
22 Revuz J, Abensour M, Clérici T *et al.* Squamous cell epithelioma on a leg ulcer in Werner's syndrome. *Ann Dermatol Vénéréol* 1987; **114**: 841–3.
23 Cohen JI, Arnett EN, Kolodny AL *et al.* Cardiovascular features of the Werner syndrome. *Am J Cardiol* 1987; **59**: 493–5.
24 Zucker FD, Rifkin H, Jacobson HG. Werner's syndrome: an analysis of 10 cases. *Geriatrics* 1968; **23**: 124–35.
25 Shimizu T, Tateishi Y, Furuichi Y *et al.* Diagnosis of Werner syndrome by immunoblot analysis. *Clin Exp Dermatol* 2002; **27**: 157–9.

Progeria

Synonym
- Hutchinson–Gilford syndrome

Definition. This is a rare disorder characterized by retarded physical development and abnormal facies, skeletal abnormalities and the onset in early childhood of scleroderma. Although progressive senile degeneration occurs, many of the more common features of ageing, such as cataracts, presbyacusis and presbyopia, are not seen.

Aetiology. It occurs due to *de novo* mutations of the lamin A gene (*LMNA*) which encodes for a major constituent of the inner membrane lamina [1]. Reduced cell proliferation and altered DNA-damage responses are common causal mechanisms in the pathogenesis of both Werner and Hutchinson–Gilford syndromes [2]. Affected families have a high risk of spontaneous abortion.

Various abnormalities of mesodermal tissue have been identified [3]. In tissue culture, progeria fibroblasts have a decreased survival time [4]. The fibroblasts show a threefold increase in the production of hyaluronic acid, and the urinary excretion of hyaluronic acid is increased [4–7]. Animal studies suggest that increased hyaluronic acid in the tissues might produce a reduction in vascularity [5,8]. Tropoelastin production is increased [9], and it has also been suggested that type IV collagen may accumulate due to an interaction between activated T lymphocytes and fibroblasts [10,11]. A preliminary study of cultured fibroblasts from two affected patients suggests mitotic instability [12]. A polymorphism in the galactosyltransferase gene (*B4GALT1*) has been identified in affected cell lines [13].

Fewer than 100 cases have been reported to date, and 97% of patients have been white [8].

Pathology [14]. The major changes are in the skin, bone and cardiovascular tissues.

The skin shows atrophy of epidermis and dermis. There may be progressive hyalinization of dermal collagen and loss of subcutaneous fat. Scanning electron microscopy of hairs from one patient showed unusual longitudinal depressions with minor cuticular defects [11].

The cardiovascular system shows extensive atheroma, and there may be extensive myocardial fibrosis, with extensive lipofuscin ('age pigment') deposition characteristic of elderly adults [15,16].

The bones show a variety of changes including osteolysis, osteoporosis, necrosis, dislocations and poorly healing fractures [17,18].

Clinical features [19]. Affected children usually appear normal at birth, and growth may be only slightly retarded in the first year, but during the second year there is profound growth failure, with reduced subcutaneous fat on the face and limbs [8]. The facial appearance is reminiscent of a fledgling bird, with a disproportionately large cranium with patent fontanelles and frontal bossing, prominent eyes and scalp veins, very sparse, downy scalp hair, sparse or absent eyebrows and eyelashes, centrofacial cyanosis, micrognathia, thin lips and a 'beaked' nose. By the second year, the skin has become thin, taut and shiny in some areas but lax and finely wrinkled in others. Eccrine sweating is decreased. The veins are prominent and there may be easy bruising. After several years, progressive mottled hyperpigmentation develops, most marked on exposed sites, but there is no photosensitivity. Thickened sclerotic areas may be present on the lower trunk or thighs, and in one case multiple keloids developed on the hands and arms [11]. The nails are usually small, thin and dystrophic, and koilonychia and onychogryphosis may occur. Generalized alopecia often begins in the first year of life and the few remaining hairs are pale, fine and 'fuzzy'. The nipples may be hypoplastic.

The dentition is abnormal and delayed, and there may be skeletal abnormalities such as dystrophic clavicles and coxa valga, with joint contractures and a 'horse-riding' stance. Progressive bone resorption may lead to frequent fractures [18]. Sexual maturation is absent but intelligence is normal.

Death usually occurs in the second decade as a result of severe, generalized atheroma.

Diagnosis. The large, bald head with conspicuous veins, the bird-like facies and the well-proportioned little body are distinctive. Bird-headed dwarfism (Chapter 15) is distinguished by the absence of skin atrophy.

Cockayne's syndrome may cause confusion, but progeria is distinguished by the loss of hair, the lack of photosensitivity and ocular changes, and the absence of disproportionately large extremities.

In metageria, sexual maturation and skeletal growth are normal [20].

References

1 Eriksson M, Brown WT, Gordon LB *et al*. Recurrent *de novo* mutations in lamin A cause Hutchinson–Gilford progeria syndrome. *Nature* 2003; **423**: 293–8.

2 Kudlow BA, Kennedy BK, Monnat RJ. Werner and Hutchinson-Gilford progeria syndromes: mechanistic basis of human progeroid diseases. *Nat Rev Mol Cell Biol* 2007; **8**: 394–404.

3 Gracy RW, Chapman ML, Cini JK *et al*. Molecular basis of the accumulation of abnormal proteins in progeria and aging fibroblasts. *Basic Life Sci* 1985; **35**: 427–42.

4 Danes BS. Progeria: a cell culture study of aging. *J Clin Invest* 1971; **50**: 2000–3.

5 Brown WT, Zebrower M, Kieras FJ *et al*. Progeria, a model disease for the study of premature ageing. *Basic Life Sci* 1985; **35**: 375–96.

6 Goldstein S, Moerman E. Heat-labile enzymes in skin fibroblasts in subjects with progeria. *N Engl J Med* 1975; **292**: 1305–9.

7 Zebrower M, Kieras FJ, Brown WT *et al*. Urinary hyaluronic acid elevation in Hutchinson–Gilford progeria syndrome. *Mech Ageing Dev* 1986; **35**: 39–46.

8 Badame AJ. Progeria. *Arch Dermatol* 1989; **125**: 540–4.

9 Sephel GC. Increased elastin production by progeria skin is controlled by steady-state levels of elastin mRNA. *J Invest Dermatol* 1988; **90**: 643–7.

10 Conover CA, Dollar LA, Rosenfeld RG *et al*. Somatomedin C-binding and action in fibroblasts from aged and progeric subjects. *J Clin Endocrinol Metab* 1985; **60**: 685–91.

11 Jimbow K, Kobayashi H, Ishii M *et al*. Scar and keloid like lesions in progeria. An electron microscopic and immunohistochemical study. *Arch Dermatol* 1988; **124**: 1261–6.

12 Ly DH, Lockhart DJ, Lerner RA, Schultz PG. Mitotic misregulation and human ageing. *Science* 2000; **287**: 2486–92.

13 O'Brien ME, Weiss AS. A novel β(1-4)galactosyltransferase gene silent mutation (594C > T) associated with Hutchinson–Gilford progeria. *Hum Mutat* 2001; **17**: 355–7.

14 Fleischmajer R, Nedwich A. Progeria (Hutchinson–Gilford). *Arch Dermatol* 1973; **107**: 253–8.

15 Baker PB, Baba N, Boesel CP. Cardiovascular abnormalities in progeria. *Arch Pathol Lab Med* 1981; **105**: 384–6.

16 Reichel W, Garcia-Bunuel R. Pathologic findings in progeria: myocardial fibrosis and lipofuscin pigment. *Am J Clin Pathol* 1970; **53**: 243–55.

17 Hamer L, Kaplan F, Fallon M *et al*. The musculoskeletal manifestations of progeria. A literature review. *Orthopedics* 1988; **11**: 763–9.

18 Moen C. Orthopedic aspects of progeria. *J Bone Joint Surg Am* 1982; **64**: 542–6.

19 De Busk FL. The Hutchinson–Gilford progeria syndrome. *J Pediatr* 1972; **80**: 697–724.

20 Gilkes JJH, Sharvill DE, Wells RS. The premature ageing syndromes. *Br J Dermatol* 1974; **91**: 243–62.

Acrogeria [1–4]

Synonym
- Gottron's syndrome

Definition. This disorder begins at birth or soon afterwards, and is characterized by cutaneous atrophy and loss of subcutaneous fat, particularly over the distal extremities, but with no tendency to atheroma, diabetes mellitus or decreased life expectancy. The term 'acrogeria' refers to premature ageing of the extremities.

Aetiology. Most cases occur without a family history, but presumed autosomal recessive as well as autosomal dominant inheritance has been reported [1,2]. Most patients have been female. *COL3A1* mutations cause variable phenotype, including Gottron-type acrogeria and vascular EDS [5,6].

Pathology. The subcutaneous fat is absent in the most severely affected regions. The dermis is atrophic, with sparse, thin collagen bundles, but there is abundant elastin, which appears clumped due to the deficiency of collagen.

Clinical features. The changes develop at or soon after birth. The skin becomes dry, thin, transparent and wrinkled, especially over the hands and feet, although the trunk and face may be affected

to a lesser extent. The veins are prominent, and there may be easy bruising, poikiloderma and telangiectasia. The nails may be atrophic or thickened. The face appears 'pinched', with a hollow-cheeked 'owl-eyed' appearance, a beaked nose and thin lips. Micrognathism may be present. The lack of subcutaneous fat accentuates the appearance of premature senility. Some patients have low birth weight and persistent short stature, but the general health and life expectancy are normal. The hands and feet may be very small.

Diagnosis. The normal hair and eyes help to distinguish the condition from progeria and pangeria. Cases are occasionally described which do not fit easily into any of the previously recognized categories and have been termed metageria and acrometageria [7,8]. It is not entirely clear whether these are separate entities.

References

1 Gottron H. Familiäre akrogeria. *Arch Dermatol Syphilol (Berlin)* 1941; **181**: 571–83.
2 De Groot WP, Tafelkruyer J, Woerdemann MJ *et al.* Familial acrogeria (Gottron). *Br J Dermatol* 1980; **103**: 213–23.
3 Venencie PY, Powell FC, Winkelmann RK *et al.* Acrogeria with perforating elastoma and bony abnormalities. *Acta Derm Venereol Suppl (Stockh)* 1984; **64**: 348–51.
4 Ho A, White SJ, Rasmussen JE *et al.* Skeletal abnormalities of acrogeria, a progeroid syndrome. *Skeletal Radiol* 1987; **16**: 463–8.
5 Jansen T, De Paepe A, Luytinck N, Plewig G. *COL3A1* mutations leading to acrogeria (Gottron type). *Br J Dermatol* 2000; **142**: 178–9.
6 Pope FM, Narcisi P, Nicholls AC *et al.* *COL3A1* mutations cause variable clinical phenotypes including acrogeria and vascular rupture. *Br J Dermatol* 1996; **135**: 163–81.
7 Gilkes JJH, Sharvill DE, Wells RS *et al.* The premature ageing syndromes. Reports of eight cases and description of a new entity named metageria. *Br J Dermatol* 1974; **91**: 243–62.
8 Greally JM, Boone LY, Lenkey SG *et al.* Acrometageria: a spectrum of 'premature aging' syndromes. *Am J Med Genet* 1992; **44**: 334–9.

Laboratory studies [1–3]

Fibroblasts from normal human skin have a limited lifespan in culture, which is inversely proportional to the age of the donor, and it seems that the *in vitro* ageing of fibroblasts may serve as a model for the *in vivo* ageing of the whole body. All the premature ageing syndromes studied to date have shown a marked reduction in fibroblast growth potential *in vitro*. These include Werner's syndrome, progeria, poikiloderma congenitale, trisomy 21 and diabetes mellitus. In addition, fibroblasts from progeria patients have shown a decrease in mitotic activity, rate of outgrowth from explants, DNA synthesis and cloning efficiency. Studies on fibroblasts from patients with progeria and Werner's syndrome have also shown enzyme changes consistent with an accelerated ageing process.

In the normal ageing process, there is a threefold increase in the affinity of surface insulin receptors for native insulin between the first and seventh decades. This accounts for the clinical finding of relative insulin resistance in the elderly. Patients with progeria also show increased insulin binding and relative insulin resistance.

Other cellular abnormalities in Werner's syndrome and progeria include a decrease in surface-membrane HLA antigens and a marked increase in the activity of a procoagulant, which may predispose to atheroma.

Post-irradiation DNA repair appears to be normal in progeria and pangeria, although the cultured fibroblasts may have reduced karyotype stability. A reduction in DNA stability might increase the rate of genomic deterioration, and this might accelerate cellular ageing.

References

1 Brown WT, Zebrower M, Kieras FJ *et al.* Progeria, a model disease for the study of accelerated aging. *Basic Life Sci* 1985; **35**: 375–96.
2 Martin GM. The biologic basis for aging: implications for medical genetics. In: Rimoin DC, Connor JM, Pyeritz RE, Korf BR, eds. *Principles and Practice of Medical Genetics*, 4th edn. London: Churchill Livingstone, 2002: 571–89.
3 Goldstein S. Studies on age-related diseases in cultured fibroblasts. *J Invest Dermatol* 1979; **73**: 19–23.

Other associated conditions

Premature ageing with short stature and pigmented naevi

Synonym
- Mulvihill–Smith syndrome

This rare syndrome [1] is characterized by low birth weight, short stature and moderate mental retardation, associated with multiple pigmented naevi and a distinctive bird-like facies. There is a small chin, with broad forehead, and the lack of facial subcutaneous fat gives an appearance of premature ageing. Other features include hypospadias, a high-pitched voice, irregular dentition, fine hair, hepatomegaly and low IgG. The clinical features tend to become more noticeable with increasing age.

Reference

1 de Silva DC, Wheatley DN, Herriot R *et al.* Mulvihill–Smith progeria-like syndrome: a further report with delineation of phenotype, immunologic deficits, and novel observation of fibroblast abnormalities. *Am J Med Genet* 1997; **69**: 56–64.

Neonatal pseudohydrocephalic progeroid syndrome of Wiedemann–Rautenstrauch [1–3]

This rare, autosomal recessive condition is characterized by mental and physical retardation and frontal and lateral bossing of the skull, with small facial bones, a small, beak-shaped nose, low-set ears, small mouth with dysodontia, and ectropion. The scalp hair and eyebrows are long and sparse, the extremities are thin, and the hands are large with long fingers and atrophic nails. The subcutaneous fat is decreased, the skin is thin and wrinkled, and the veins are prominent.

References

1 Devos EA, Leroy JG, Frijns JP *et al.* The Wiedemann–Rautenstrauch or neonatal progeroid syndrome. Report of a patient with consanguineous parents. *Eur J Pediatr* 1981; **136**: 245–8.
2 Snigula F, Rautenstrauch T. A new neonatal progeroid syndrome. *Eur J Pediatr* 1981; **136**: 325–4.
3 Pivnick EK, Angle B, Kaufman RA *et al.* Neonatal progeroid (Wiedemann–Rautenstrauch) syndrome: a report of five new cases and review. *Am J Med Genet* 2000; **90**: 131–40.

Gerodermia osteodysplastica [1]

Stunting of growth from early childhood is associated with senile changes in the skin, with normal scalp hair. Wrinkly, lax skin is

most prominent on the dorsa of the hands and feet. Generalized osteoporosis, multiple fractures, joint laxity and skeletal malformations, including Wormian bones, occur. The face appears sad, with drooping eyelids and jowls, malar hypoplasia and mandibular prognathism. Relatives presenting partial forms of the syndrome showed cutaneous ageing and osteodysplasia without dwarfism. Skin biopsy may show fragmented elastic fibres. Two reports of consanguineous Arabian families showed features overlapping both gerodermia osteodysplastica and wrinkly skin syndrome, suggesting that they may represent variable manifestations of the same disorder [2,3].

References

1 Lisker R, Hernández A, Martinez-Lavin M. Gerodermia osteodysplastica hereditaria: report of three brothers and a literature review. *Am J Med Genet* 1979; **3**: 389–95.

2 Al-Gazali LI, Sztriha L, Skaff F, Haas D. Gerodermia osteodysplastica and wrinkly skin syndrome: are they the same? *Am J Med Genet* 2001; **101**: 213–20.

3 Nanda A, Alsaleh QA, Al-Sabah H *et al*. Gerodermia osteodysplastica/wrinkly skin syndrome: report of three patients and brief review of the literature. *Pediatr Dermatol* 2008; **25**: 66–71.

Wrinkly skin syndrome [1]

This rare, familial condition is characterized by the appearance at birth of dry, wrinkled skin of the hands, feet and ventral surfaces of the trunk. The veins are unduly prominent. There may also be mental retardation, ocular defects and poor muscle tone. The cause is unknown, and the dermal collagen and elastin appear normal on light microscopy. There is some phenotypic overlap with gerodermia osteodysplastica and autosomal recessive cutis laxa type II [2].

References

1 Gazit E, Goodman RM, Katznelson MB *et al*. Wrinkly skin syndrome. *Clin Genet* 1973; **4**: 186–7.

2 Gupta N, Phadke SR. Cutis laxa type II and wrinkly skin syndrome: distinct phenotypes. *Pediatr Dermatol* 2006; **23**: 225–30.

Poikiloderma congenitale

Synonym
- Rothmund–Thomson syndrome

This condition is fully described in Chapter 15. It may be considered as a premature ageing syndrome because of the atrophic hyperpigmented skin, the early onset of cataracts, and the premature greying and loss of hair. The striking poikiloderma is distinctive.

Cockayne's syndrome (Chapter 15)

The atrophic skin with mottled pigmentation and loss of subcutaneous fat on the face produce an appearance of premature senility, and the disease has often been confused with progeria.

Trisomy 21 (Chapter 15)

Synonym
- Down's syndrome

This disorder shows more features of true ageing than the classical premature ageing syndromes [1]. These features include progressive dementia with the neurofibrillary tangle seen in senile dementia, amyloid and lipofuscin deposition in many organs, diabetes mellitus, cataracts, cardiovascular disease, increased incidence of autoimmune disease and malignancy, and a decreased life expectancy [2].

The cutaneous features include dry, lax skin, and premature greying and loss of hair [2].

References

1 Martin GM. The biologic basis for aging: implications for medical genetics. In: Rimoin DC, Connor JM, Pyeritz RE, Korf BR, eds. *Principles and Practice of Medical Genetics*, 4th edn. London: Churchill Livingstone, 2002: 571–89.

2 Pueschel SM. Clinical aspects of Down syndrome from infancy to adulthood. *Am J Med Genet* 1990; **37** (Suppl.): 52–6.

Familial mandibulo-acral dysplasia

Synonym
- Craniomandibular dermatodysostosis

The main features of this rare syndrome are mandibular hypoplasia, delayed cranial suture closure, dysplastic clavicles, abbreviated club-shaped terminal phalanges associated with acro-osteolysis and atrophy of the skin over the hands and feet [1] (Fig. 45.39). Other characteristics may include short stature, multiple Wormian bones, prominent eyes and a sharp nose [2,3]. In one family, the condition was also associated with loss of the lower teeth and alopecia [4]. Two types of body fat distribution patterns, both of which are associated with insulin resistance and its metabolic complications, may be evident; partial lipodystrophy of the extremities (type A) and generalized loss of subcutaneous fat (type B) [5]. Both are autosomal recessive, with mutations in the gene encoding lamin A/C; *LMNA* underlie type A and mutations in the zinc metalloproteinase STE24 gene (*ZMPSTE24*) give rise to type B [6,7].



Fig. 45.39 Familial mandibulo-acral dysplasia, showing the short, club-shaped terminal phalanges, the so-called 'tree-frog' appearance. (Courtesy of Dr A.M. Zina, Turin University, Turin, Italy.)

The cutaneous changes are a milder phenotype of progeria and some cases have been mistakenly diagnosed in the past as acrogeria or Werner's syndrome.

References

1 Danks DM, Mayne V, Wettenhall NB *et al.* Craniomandibular dermato-dysostosis. *Birth Defects Orig Artic Ser* 1974; **X**: 99–105.
2 Tenconi R, Miotti F, Miotti A *et al.* Another Italian family with mandibulo-acral dysplasia. *Am J Med Genet* 1986; **24**: 357–64.
3 Zina AM, Cravario A, Bundino S. Familial mandibulo-acral dysplasia. *Br J Dermatol* 1981; **105**: 719–23.
4 Welsh O. Study of a family with a new progeroid syndrome. *Birth Defects Orig Artic Ser* 1975; **11**: 25–38.
5 Simha V, Garg A. Body fat distribution and metabolic derangements in patients with familial partial lipodystrophy associated with mandibuloacral dysplasia. *J Clin Endocrinol Metab* 2002; **87**: 776–85.
6 Novelli G, Muchir A, Sangiuolo F *et al.* Mandibuloacral dysplasia is caused by a mutation in LMNA-encoding lamin A/C. *Am J Hum Genet* 2002; **71**: 426–31.
7 Agarwal AK, Fryns J-P, Auchus RJ *et al.* Zinc metalloproteinase, ZMPSTE24, is mutated in mandibuloacral dysplasia. *Hum Mol Genet* 2003; **12**: 1995–2001.

Diabetic thick skin [1,2]

Synonym
- Cheiroarthropathy

Diabetes may be classified as a premature ageing syndrome because of the predisposition to cataracts and atheroma and the reduced life expectancy [1,3].

Some patients with diabetes mellitus have thick, tight, waxy skin and limited joint mobility. This combination has been called *cheiroarthropathy* [4]. Affected patients are unable to bring their palms completely together, and their fingers will not bend backwards. The 'prayer sign', in which the patient tries to oppose the two palms, provides an easy screening test [5]. Skin and tendon sheath thickness has also been measured by ultrasound [6,7].

Cheiroarthropathy is present in 30–40% of insulin-dependent diabetics, and in non-insulin-dependent diabetics the figures have varied widely, from 4% to 70%. The changes may even precede the diagnosis of diabetes [8]. The changes are important because affected patients have an increased risk of retinal and renal disease due to microvascular damage [9]. Patients with diabetic cheiroarthropathy also have an increased incidence of frozen shoulder and Dupuytren's contracture [10]. There is often associated thickening of the plantar fascia [11].

The biochemical change is not fully understood, but it seems likely that non-enzymatic glycosylation in diabetic subjects might alter collagen metabolism [1,3]. The lysines in collagen are slowly glycosylated with increasing age, and during this process the glucose attaches to the lysine and undergoes an Amadori rearrangement, thus making the process irreversible [12]. Enzymatic digestion of tendon collagen from young patients who died from diabetes showed that their collagen behaved as if it was from patients who were 50–65 years older than their actual age [13].

Studies of viscoelastic ratio and skin extensibility in patients with type 1 diabetes have shown subclinical stiffness and loss of skin elasticity [14].

The histology of the skin changes resembles systemic sclerosis, but there is a subtle difference, with a predominance of large collagen fibres, thickening of the capillary basement membrane and increased mucin [15].

In some diabetic patients with thick skin, the extensor surfaces of the fingers develop a characteristic, minutely pebbled appearance over or near the knuckles (Huntley's papules). On histology, this shows a papillated epidermal hyperplasia with hyperkeratosis [16].

Because biochemical studies suggest that collagen is 'aged' by increased binding with glucose, it is desirable to maintain tight control of blood glucose levels in diabetic patients [17]. A patient improved with aminobenzoic acid, colchicine and DMSO gel [18].

References

1 Burton JL. Skin and stiff joints in insulin dependent diabetes mellitus. *Br J Dermatol* 1982; **101**: 369–71.
2 Perez MI, Kohn SR. Cutaneous manifestations of diabetes mellitus. *J Am Acad Dermatol* 1994; **30**: 519–31.
3 Monnier VM, Sell DR, Nagaraj RH *et al.* Maillard reaction-mediated molecular damage to extracellular matrix and other tissue proteins in diabetes, aging and uraemia. *Diabetes* 1992; **41** (Suppl. 2): 36–41.
4 Editorial. Diabetic skin, joints and eyes—how are they related? *Lancet* 1987; **ii**: 313–4.
5 Starkman HS, Gleason RE, Rand LI *et al.* Limited joint mobility of the hands in patients with diabetes mellitus. *Ann Rheum Dis* 1986; **45**: 130–5.
6 Collier A, Matthews DM, Kellett HA *et al.* Change in skin thickness associated with cheiroarthropathy in insulin dependent diabetes mellitus. *BMJ* 1986; **292**: 936.
7 Ismail AA, Dasgupta B, Tanqueray AB *et al.* Ultrasonographic features of diabetic cheiroarthropathy. *Br J Rheumatol* 1996; **35**: 676–9.
8 Sherry DD, Rothstein RR, Petty RE *et al.* Joint contracture preceding insulin-dependent diabetes mellitus. *Arthritis Rheum* 1982; **25**: 1362–4.
9 Rosenbloom AL, Silverstein JH. Limited joint mobility in childhood diabetes mellitus. *N Engl J Med* 1981; **305**: 191–4.
10 Moren-Hybbinette I, Moritz U, Schersten B *et al.* The clinical picture of the painful diabetic shoulder. *Acta Med Scand* 1987; **221**: 73–82.
11 Duffin AC, Lam A, Kidd R *et al.* Ultrasonography of plantar soft tissues thickness in young people with diabetes. *Diabet Med* 2002; **19**: 1009–13.
12 Le Pape A, Muh JP, Bailey AJ. Characterisation of N-glycosylated type I collagen in streptozotocin-induced diabetes. *Biochem J* 1981; **197**: 405–12.
13 Hamlin CR, Kohn RR, Luschin JH *et al.* Apparent accelerated ageing of human collagen in diabetes mellitus. *Diabetes* 1975; **24**: 902–4.
14 Nikkels-Tassaudji N, Henry F, Letawe C *et al.* Mechanical properties of the diabetic waxy skin. *Dermatology* 1996; **192**: 19–22.
15 Hanna W, Friesen D, Bombardier C *et al.* Pathologic features of diabetic thick skin. *J Am Acad Dermatol* 1987; **16**: 546–53.
16 Huntley AC. Finger pebbles: a common finding in diabetes mellitus. *J Am Acad Dermatol* 1986; **14**: 612–7.
17 Lieberman LS, Rosenbloom AC, Riley WJ *et al.* Reduced skin thickness with pump administration of insulin. *N Engl J Med* 1980; **303**: 940–1.
18 Gruson LM, Franks A Jr. Scleredema and diabetic sclerodactyly. *Dermatol Online J* 2005; **30**: 3.

Leprechaunism

Synonym
- Donohue's syndrome

Definition. Leprechaunism is a rare and poorly defined syndrome characterized by severe intrauterine and postnatal growth retardation, decreased subcutaneous tissue and muscle mass, and a characteristic facies [1]. Tissue resistance to insulin appears to be an important feature, as hyperinsulinaemia and pancreatic β-cell hyperplasia are frequently present [2,3].

Aetiology. The condition is inherited as an autosomal recessive trait. The basis for the insulin resistance is homozygous or compound heterozygous mutations in the extracellular domain of the insulin receptor, which leads to markedly impaired insulin binding [4]. Mutations that retain significant insulin binding activity cause the less severe phenotype of Rabson–Mendenhall syndrome.

The fibroblasts have a prolonged doubling time *in vitro*. They respond poorly to the metabolic actions of insulin, and to the actions of several other growth factors, such as epidermal growth factor.

Pathology [5]. In the skin, the elastic and collagen fibres are few and fragmented. On the extremities, the horny layer is markedly thickened. The muscles show a proliferation of abnormal connective tissue. In some cases, the ovaries are large and cystic, and there is β-cell hyperplasia of the pancreatic islets.

Clinical features [5–8]. The child is abnormal at birth, with low birth weight. The nose is broad, the ears low set and large, the eyes widely spaced. There is hypertrichosis of the forehead and cheeks. The skin appears too large for the body, is loosely folded at the flexures and may be corrugated, with gyrate folds on the hands and feet, which may be disproportionately large. Muscle wasting, often progressive, is usually present. The breasts and the penis or clitoris may be slightly hypertrophic. The bone age is retarded and there may be metaphyseal and epiphyseal dystrophy.

Growth is generally retarded, the nutritional status remains poor and susceptibility to infection is high. Death by the age of 1 year is usual.

Diagnosis. The cutaneous changes could be confused with cutis laxa, but in leprechaunism the skin, although folded, is thickened and not lax. The diagnosis is confirmed by the associated features and the finding of raised plasma insulin levels.

References

1 Donohue WL, Uchida I. Leprechaunism: a euphemism for a rare familial disorder. *J Pediatr* 1954; **45**: 505–19.

2 Kaplowitz PB, D'Ercole J. Fibroblasts from a patient with leprechaunism are resistant to insulin, epidermal growth factor and somatomedin C. *J Clin Endocrinol Metab* 1982; **55**: 741–8.

3 Taylor SI, Hedo JA. Extreme insulin resistance in association with abnormally high binding affinity of insulin receptors from a patient with leprechaunism: evidence for a defect intrinsic to the receptor. *J Clin Endocrinol Metab* 1982; **55**: 1108–13.

4 Longo N, Wang Y, Smith SA *et al.* Genotype–phenotype correlation in inherited severe insulin resistance. *Hum Mol Genet* 2002; **11**: 1465–75.

5 Patterson JH, Watkins WL. Leprechaunism in a male infant. *J Pediatr* 1962; **60**: 730–9.

6 Kaloustian VM. Leprechaunism: a report of two new cases. *Am J Dis Child* 1971; **122**: 442–5.

7 Hartdegen RG, Dogliotti M, Rabinowitz L *et al.* Leprechaunism: case report in a black African child. *Br J Dermatol* 1975; **93**: 587–91.

8 Joan D, Dimitriu L, Belengeanu V *et al.* Leprechaunism: report of two cases and review. *Endocrinologie* 1988; **26**: 205–9.

Lipoatrophy

The absence of subcutaneous fat may give the appearance of premature ageing if the face is affected. Lipoatrophy is fully discussed in Chapter 46.

Perforating dermatoses

Many dermatoses occasionally exhibit the phenomenon of transepithelial elimination (TEE), in which material from the dermis is extruded through the epidermis to the exterior with little or no disruption of the surrounding structures [1]. The extruded material may include inflammatory cells, red cells, microorganisms and extracellular substances, such as mucin or altered connective tissue components [2,3]. In most of these conditions, the TEE is secondary to some underlying disease, such as granuloma annulare or PXE, but there are four conditions that are regarded as *primary perforating disorders*: Kyrle's disease (Chapter 19), perforating folliculitis (Chapter 30), reactive perforating collagenosis and perforating serpiginous elastosis. It is possible that these primary perforating disorders might be due to defects in the epidermal keratinocytes, hair follicle, collagen and elastic fibres, respectively, with TEE being the final common pathway [2,3].

In acquired reactive perforating dermatosis (see below), the bulk of the coarse granular basophilic material that is extruded by TEE appears to derive from the nuclei of polymorphonuclear leukocytes [4]. It has been suggested that lysosomal enzymes derived from leukocytes might be responsible for the altered staining of collagen fibres, the degradation of elastic fibres and the impairment of keratinocyte adhesion, which allows TEE of dermal components [4].

Acquired reactive perforating dermatosis

Until recently, the four conditions mentioned above were thought to be unrelated, but there have now been numerous reports of these perforating dermatoses occurring in diabetes mellitus or in patients with chronic renal failure, many of whom were undergoing haemodialysis [2,5–9]. An incidence of 11% has been reported, with a particular association with long-standing diabetes [9]. The keratotic lesions in this condition develop on the trunk and limbs, and are usually pruritic, dome-shaped papules with central crusts (Fig. 45.40). They are not related to trauma.

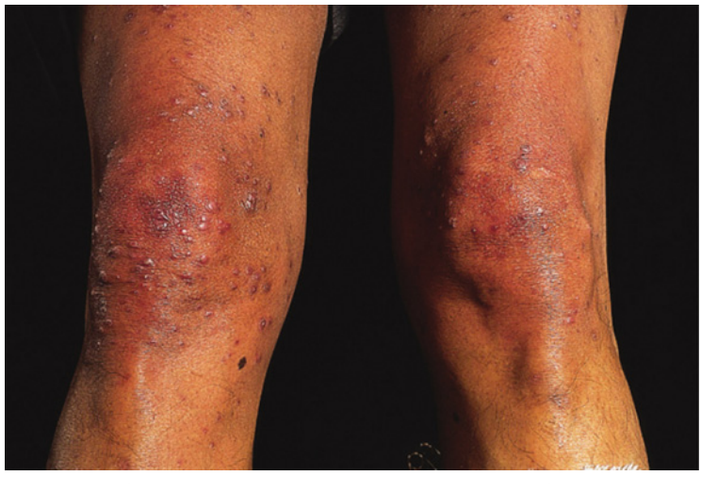


Fig. 45.40 Perforating dermatosis in a diabetic patient with renal failure. (Courtesy of Dr D.A. Burns, Leicester Royal Infirmary, Leicester, UK.)

The distinction between the four dermatoses has not always been clear-cut, and the presence or absence of the Koebner reaction, and the presence or absence of collagen fibres in the epidermis, are not reliable distinguishing features [2,3]. Both collagen and elastic fibres can be extruded in the same patient [7], and it seems likely that at least in the case of haemodialysis patients these conditions may overlap. The name *acquired reactive perforating dermatosis* has been suggested for this skin problem. These four conditions, however, appear to be separate entities when they occur outside the setting of renal failure or diabetes mellitus.

Topical or intralesional steroids or topical retinoids may be helpful, but some patients improve spontaneously [9]. Other reported treatments include rifampicin and allopurinol [10].

References

1 Mehregan RH. Transepithelial elimination. *Curr Probl Dermatol* 1970; **3**: 124–47.
2 Patterson JW. The perforating disorders. *J Am Acad Dermatol* 1984; **10**: 561–81.
3 Patterson JW. Progress in the perforating dermatoses. *Arch Dermatol* 1989; **125**: 1121–3.
4 Zelger B, Hintner H, Aubock J, Fritsch PO. Acquired perforating dermatosis. *Arch Dermatol* 1991; **127**: 695–700.
5 Cochran RJ, Tucker SB, Wilkin JK *et al.* Reactive perforating collagenosis of diabetes mellitus and renal failure. *Cutis* 1983; **31**: 55–8.
6 Poliak SC, Lebwohl MG, Parris A *et al.* Reactive perforating collagenosis associated with diabetes mellitus. *N Engl J Med* 1982; **306**: 81–4.
7 Rapini RP, Herbert AA, Drucker CR *et al.* Acquired perforating dermatosis: evidence of combined transepidermal elimination of both collagen and elastic fibres. *Arch Dermatol* 1989; **125**: 1074–8.
8 Stone RA. Kyrle-like lesions in two patients with renal failure undergoing dialysis. *J Am Acad Dermatol* 1981; **5**: 707–9.
9 Morton CA, Henderson IS, Jones MC *et al.* Acquired perforating dermatosis in a British dialysis population. *Br J Dermatol* 1996; **135**: 671–7.
10 Kruger K, Tebbe B, Krengel S *et al.* Acquired reactive perforating dermatosis. Successful treatment with allopurinol in two cases. *Hautzart* 1999; **50**: 115–20.

Perforating disease due to exogenous agents

Occasionally, a chemical that has been applied to the skin topically or by intradermal injection can be eliminated by the transepidermal route to produce a perforating disorder. Eight cases have been reported following occupational exposure to a caustic drilling fluid used in the petrochemical industry [1]. Each patient noted skin irritation following exposure to the fluid, and 1 or 2 days later developed tender papules with central umbilication, which ulcerated and crusted. Histological examination of the lesions revealed TEE of altered collagen and debris which stained for calcium.

It is possible that the lesions were due to follicular penetration by the calcium present in the drilling mud. The drilling fluids contain many additives, but calcium carbonate or calcium chloride are often present in high concentrations in the mud. Similar cases have been reported following the use of calcium-containing electroencephalography paste [2].

TEE of altered collagen has also been reported following the use of intradermal steroid injections [3,4].

References

1 Knox JM, Knox JM, Dinehart SM *et al.* Acquired perforating disease in oil field workers. *J Am Acad Dermatol* 1986; **14**: 605–11.
2 Shoenfeld RJ, Grekin JN, Mehregan A. Calcium deposition in the skin. A report of four cases following electroencephalography. *Neurology* 1965; **15**: 477–80.
3 Goette DK. Transepidermal elimination of altered collagen after intralesional adrenal steroid injections. *Arch Dermatol* 1984; **120**: 539–40.
4 Katz R, Hood AF. Transepidermal elimination following the use of a topical adrenal steroid. *Arch Dermatol* 1985; **121**: 412–3.

Reactive perforating collagenosis [1–4]

Definition. A rare inherited form of TEE in which collagen is extruded through the epidermis. It is usually precipitated by environmental cold or trauma. The commoner, acquired, form is often referred to as acquired perforating dermatosis (qv) which is typically associated with haemodialysis, although lesions have been recorded with internal neoplasia [4].

Aetiology. The cause is unknown, but the condition is often familial [5,6]. The basic defect seems to be a type of focal damage to collagen, which is then extruded as a result of necrolysis of the overlying epidermis [7].

Pathology [2,7,8]. The lesion originates in the papillary dermis, where collagen is surrounded and engulfed by focal epidermal proliferation. The collagen appears normal on electron microscopy, but gives an abnormal staining pattern with trichrome and phosphotungstic acid haematoxylin. The central crater which develops contains inflammatory cells and keratinous debris. Elastic tissue is typically absent, and the abnormal collagen is eliminated by transepithelial migration.

Clinical features [7]. The inherited form usually starts in early childhood as small papules on the extensor surface of the hands, the elbows and the knees following superficial trauma. Each skin-coloured papule increases to a size of about 6 mm over 3–5 weeks and then becomes umbilicated, with a keratinous plug. The lesions regress spontaneously in 6–8 weeks to leave a hypopigmented area or slight scar, but new lesions may appear. Lesions can be produced experimentally, and Koebner's phenomenon may be present, with linear lesions [9]. The papules can also be provoked by inflamed acne lesions, but deep incisions do not produce the lesions. The condition persists into adult life. In some cases, the disease is associated with intolerance to cold and improves in warm weather.

Diagnosis. The condition may be mistaken clinically for molluscum contagiosum, papular urticaria, perforating serpiginous elastoma, perforating folliculitis, perforating granuloma annulare and Kyrle's disease, but the histology is characteristic [6]. Verrucous perforating collagenoma must also be distinguished (see below). The nosological relationship between reactive perforating collagenosis and the acquired reactive perforating dermatosis of renal failure remains uncertain (see above) [4].

Treatment. Topical retinoic acid may reduce the number of lesions. Other treatments which may help include oral isotretinoin, methotrexate, emollient creams, topical steroids under occlusion [3,4] and PUVA [10].

References

1 Mehregan AH, Schwartz OD. Reactive perforating collagenosis. *Arch Dermatol* 1967; **96**: 277–82.

2 Fretzin DF, Beal DW, Jao W. Light and ultrastructural study of reactive perforating collagenosis. *Arch Dermatol* 1980; **116**: 1054–8.
3 Patterson JW. Progress in the perforating disorders. *Arch Dermatol* 1989; **125**: 1121–3.
4 Chae KS, Park YM, Cho SH *et al.* Reactive perforating collagenosis associated with periampullary carcinoma. *Br J Dermatol* 1998; **139**: 548–50.
5 Kanan MW. Familial reactive perforating collagenosis and intolerance to cold. *Br J Dermatol* 1974; **91**: 405–14.
6 Nair BKH, Sarojini PA, Basheer AM *et al.* Reactive perforating collagenosis. *Br J Dermatol* 1974; **91**: 399–403.
7 Cerio R, Calnan CD, Wilson-Jones E. A clinico-pathological study of reactive perforating collagenosis: report of 10 cases. *Br J Dermatol* 1987; **117** (Suppl. 32): 16–7 (Abstract).
8 Millard PR, Young E, Harrison DE *et al.* Reactive perforating collagenosis: light, ultrastructural and immunohistological studies. *Histopathology* 1986; **10**: 1047–56.
9 Bovenmeyer DA. Reactive perforating collagenosis. Experimental production of the lesion. *Arch Dermatol* 1970; **102**: 313–7.
10 Serrano G, Aliaga A, Lorente M *et al.* Reactive perforating collagenosis responsive to PUVA. *Int J Dermatol* 1988; **27**: 118–9.

Verrucous perforating collagenoma [1,2]

Synonym
- Collagenome perforant verruciforme

In this rare condition, severe (as opposed to superficial) trauma to the skin produces verrucous papules which show TEE of collagen. The eruption occurs as a single episode and is not familial.

References

1 Delacretaz J, Gattlen JM. Verrucous perforating collagenoma. *Dermatologica* 1976; **152**: 65–6.
2 Laugier P, Woringer F. Reflexions au sujet d'une collagenome perforant verruciforme. *Ann Dermatol Syphiligr (Paris)* 1963; **90**: 29–32.

Elastosis perforans serpiginosa

Synonyms
- Perforating elastoma
- Elastoma intrapapillare perforans

Definition. In this reactive perforating dermatosis, the material extruded through the epidermis is derived from elastic fibres in the upper dermis.

Aetiology. The cause is unknown, but a genetically determined defect of elastic tissue may be involved [1]. The altered elastin resembles that seen in experimental animals subjected to lathyrogens or copper deficiency.

It is probable that the primary abnormality is in the dermal elastin, which provokes a cellular response that ultimately leads to extrusion of the abnormal elastic tissue. It may be significant that the lesions are commonly seen in areas subjected to wear and tear. The lesions may follow an abrasion.

Some 40% of reported cases have been associated with connective tissue disorders, such as PXE, EDS, MFS, OI and acrogeria [2,3]. It has also been reported in otherwise healthy individuals and in mental deficiency, especially Down's syndrome [4–6].

It sometimes occurs in patients taking penicillamine, which is known to cause the production of abnormal elastin [7–10].

The relationship to perforating PXE and pseudo-PXE due to penicillamine is discussed on p. 45.25.

Pathology [4,11–13]. The earliest detectable change is the focal development of elastotic staining tissue and basophilic debris in the dermis. This is followed by a reaction of the overlying epidermis, which grows down to engulf the elastotic material. The epidermis surrounding the fully developed lesion is acanthotic and hyperkeratotic. The papule consists of a circumscribed area of epidermal hyperplasia traversed by a channel communicating directly with the dermis and containing a mass of tissue, which projects above the surface. This plug consists of horny material in its upper third and of amorphous debris derived from elastin in its lower two-thirds [11]. In the dermis beneath and around the lesion, there is a foreign-body giant cell reaction. The elastotic material is finally extruded, to leave irregular scarring and warty thickening. Electron microscopy shows an increase in elastic fibres, with fine filaments on the surface similar to those seen in normal embryos. In penicillamine-induced cases the elastic fibres have a characteristic 'bramble bush' or 'lumpy bumpy' morphology [9]. The hydroxylation of dermal collagen is similar to that of newborn skin [12].

Clinical features [14,15]. The age of onset ranges from 6 to 20 years. Males are predominantly affected. Small, horny or umbilicated papules are characteristically arranged in lines, circles or segments of circles in a serpiginous pattern. The individual papules may remain small or may enlarge slightly to assume a crateriform appearance with an elevated edge and a central plug, or further to leave an area of atrophic skin surrounded by smaller papules, each with a horny plug. The rings may reach a diameter of 15–20 cm but are usually smaller (Fig. 45.41). The back and sides of the neck are most commonly affected, but the lesions may also occur on the cheeks or on the arms or thighs, and are sometimes bilaterally symmetrical. They may persist for several years, but eventually involute spontaneously to leave reticulate atrophic scars. Biopsy scars readily become keloidal.



Fig. 45.41 Elastosis perforans serpiginosa in a patient with vascular Ehlers–Danlos syndrome.

Diagnosis. The annular or linear arrangements of the papules and their distribution suggest the diagnosis, which is confirmed by the characteristic histology. Conditions which may cause confusion include porokeratosis of Mibelli, reactive perforating collagenosis and perforating granuloma annulare.

A similar histological appearance can occur in the acquired reactive perforating dermatosis of renal failure (see above) [16].

Treatment. Careful removal of the nodules with a curette under local anaesthesia may give a reasonable cosmetic result. Freezing has been recommended [14,17]. Excision should be avoided, and dermabrasion may make the condition worse [4]. In a child with Down's syndrome and associated vitamin A deficiency, clinical improvement was observed with oral retinoid therapy, even though the treatment produced side effects [6]. Isotretinoin has been used successfully in a patient with penicillamine-induced disease [18]. There are reports of improvement following Sellotape stripping of the surface keratinous material [19], tazarotene [20], imiquimod [21], pulsed dye [22], ultrapulsed carbon dioxide [23] and Er:YAG [24] laser therapies.

References

1 Ayala F, Donofrio P. Elastosis perforans serpiginosa: report of a family. *Dermatologica* 1983; **166**: 32–4.
2 Reed WB, Pidgeon JW. Elastosis perforans serpiginosa with osteogenesis imperfecta. *Arch Dermatol* 1964; **89**: 342–4.
3 Mehta RK, Burrows NP, Payne CM *et al*. Elastosis perforans serpiginosa and associated disorders. *Clin Exp Dermatol* 2001; **26**: 521–4.
4 Patterson JW. The perforating disorders. *J Am Acad Dermatol* 1984; **10**: 561–81.
5 O'Donnell B, Kelly P, Dervan P *et al*. Generalized elastosis perforans serpiginosa in Down's syndrome. *Clin Exp Dermatol* 1992; **17**: 31–3.
6 Jan V, Saugier J, Arbeille B *et al*. Elastome perforant serpigineux avec hypovitaminose A chez une enfant ayant une trisomie 21. *Ann Dermatol Vénéréol* 1996; **123**: 188–90.
7 Pass F, Goldfischer S, Sternlieb I *et al*. Elastosis perforans serpiginosa during penicillamine therapy for Wilson's disease. *Arch Dermatol* 1973; **108**: 713–5.
8 Kirsch N, Hukill PB. Elastosis perforans serpiginosa induced by penicillamine. Electron microscopic observations. *Arch Dermatol* 1977; **113**: 630–5.
9 Bardach H, Gebhart W. Elastic fiber changes induced by penicillamine. *J Am Acad Dermatol* 1982; **6**: 398–9.
10 Light N, Meyrick-Thomas RH, Stephens A *et al*. Collagen and elastin changes in d-penicillamine-induced pseudoxanthoma elasticum-like skin. *Br J Dermatol* 1986; **114**: 381–8.
11 Hashimoto K, Hill WR. Elastosis perforans serpiginosa—histochemical and enzymic digestion studies. *J Invest Dermatol* 1960; **35**: 7–14.
12 Volpin D, Pasquali-Ronchetti I, Castellani I *et al*. Ultrastructural and biochemical studies on a case of elastosis perforans serpiginosa. *Dermatologica* 1978; **156**: 209–23.
13 Bergman R, Friedman-Burnbaum R, Hazaz B. A direct immunofluorescence study in elastosis perforans serpiginosa. *Br J Dermatol* 1985; **113**: 573–9.
14 Mehregan AH. Elastosis perforans serpiginosa. A review of the literature and report of 11 cases. *Arch Dermatol* 1968; **97**: 381–93.
15 Catterall MD, Padley NR. Elastosis perforans serpiginosa. *Clin Exp Dermatol* 1979; **4**: 119–22.
16 Schamroth JM. Elastosis perforans serpiginosa in a patient with renal disease. *Arch Dermatol* 1988; **122**: 82–4.
17 Whyte HJ, Winkelmann RK. Elastosis perforans—the association of congenital anomalies, and salient facts in histology. *J Invest Dermatol* 1960; **35**: 113–22.
18 Ratnavel RC, Norris PG. Penicillamine-induced elastosis perforans serpiginosa treated successfully with isotretinoin. *Dermatology* 1994; **189**: 81–3.
19 Langeveld-Wildschut EG, Toonstra J *et al*. Familial elastosis perforans serpiginosa. *Arch Dermatol* 1993; **129**: 205–7.
20 Outland JD, Brown TS, Callen JP. Tazarotene is an effective therapy for elastosis perforans serpiginosa. *Arch Dermatol* 2002; **138**: 169–71.
21 Kelly SC, Purcell SM. Imiquimod therapy for elastosis perforans serpiginosa. *Arch Dermatol* 2006; **142**: 829–30.
22 Kaufman AJ. Treatment of elastosis perforans serpiginosa with the flashlamp pulsed dye laser. *Dermatol Surg* 2000; **26**: 1060–2.
23 Abdullah A, Colloby PS, Foulds IS, Whitcroft I. Localized idiopathic elastosis perforans serpiginosa effectively treated by the Coherent Ultrapulse 5000°C aesthetic laser. *Int J Dermatol* 2002; **39**: 719–20.
24 Saxena M, Tope WD. Response of elastosis perforans serpiginosa to pulsed CO_2, Er:YAG, and dye lasers. *Dermatol Surg* 2003; **29**: 677–8.

Miscellaneous disorders

Colloid milium

Synonyms
- Colloid pseudomilium
- Colloid degeneration of the skin
- Elastosis colloidalis conglomerata

Definition. Colloid milium is a degenerative change characterized clinically by the development of yellowish, translucent papules or plaques on light-exposed skin, and histologically by the presence of colloid in the dermal papillae.

Aetiology. The cause is uncertain, and the condition may not represent a single entity. The rare juvenile form [1,2], beginning before puberty and often familial, can be distinguished from a non-familial form occurring in later life. Although light appears to play little part in provoking the lesions in the juvenile form, it is certainly implicated in older patients, among whom the incidence is highest in fair-skinned, outdoor workers in sunny climates [1,3,4]. Some authors consider the adult form to be a variant of actinic elastosis [5]. Cases among refinery workers in the tropics suggest that trauma and the photodynamic effects of phenols in oxide fuel (gas oil) may be contributory factors [6]. Cases have also been reported after the long-term application of strong hydroquinone bleaching creams. These patients also had ochronosis [7].

Pathology [7–13]. The earliest histological change is the appearance of colloid globules at the tips of the dermal papillae. Homogeneous fissured masses of colloid occupy the upper dermis, each surrounded by bands of collagen. The colloid is usually eosinophilic but may be basophilic. Within it, small blood vessels and the nuclei of fibroblasts are well preserved. In the larger, plaque-like lesions, the colloid change occurs diffusely throughout the dermis.

In the juvenile form, the colloid masses may also occur in the epidermis, and elastosis is not present, whereas in the adult form the colloid is separated from the epidermis by a band of elastin, and elastosis is present. In the juvenile form, 'immature' Civatte bodies occur in the epidermis.

The source of the colloid material is uncertain. It could be a protein synthesized by fibroblasts or it could be derived from degraded elastic fibres [1,3,9].

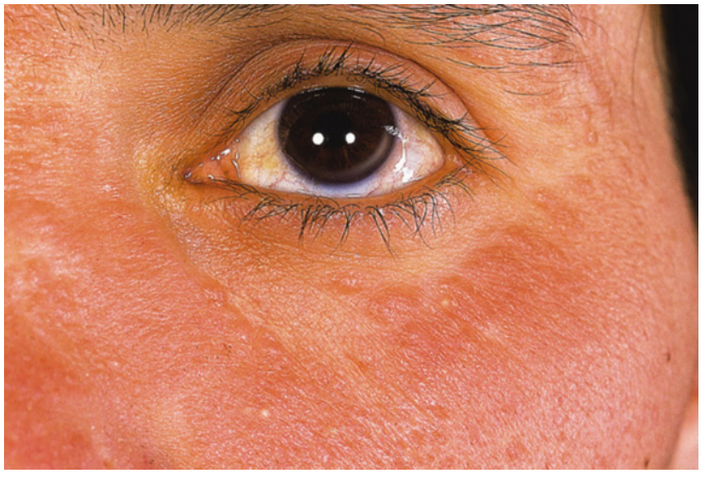


Fig. 45.42 Colloid milium of the infraorbital region. (Courtesy of Dr D.A. Burns, Leicester Royal Infirmary, Leicester, UK.)

The histological changes may be difficult to distinguish from those of amyloidosis, especially lichen amyloid. Electron microscopy may be needed for definitive diagnosis [7,9,13]. In adult colloid milium, the colloid is amorphous, with wavy, branching filaments. In the juvenile form, it is composed of closely packed filaments, which are often in parallel rows, forming whorled fascicles [1,13].

Clinical features. Small dermal papules 1–2 mm in diameter, yellowish brown and sometimes translucent, develop slowly and more or less symmetrically in irregular groups in areas exposed to sunlight (Fig. 45.42). They feel soft and may release their gelatinous contents when punctured. The most frequently involved sites are the face, especially around the orbits, the dorsa of the hands, the back and sides of the neck and the ears. There is some variation in the clinical features according to the age of onset. In young children, the lesions are often confined to the face, with diffuse infiltration surmounted by innumerable small papules, which may appear vesicular. In older patients, the papules are often fewer and larger, and their potential distribution is much wider, although often only one or two sites are involved in each individual. The changes induced by prolonged light exposure are associated to varying degrees. Although colloid milium may become more severe and more extensive over the years, most cases reach their maximum development within 3 years and then remain unchanged.

The juvenile form may be associated with conjunctival and gingival deposits of an amyloid-like homogeneous material [11].

A nodular form has been described in which lesions may be 5–50 mm in size and may be single or multiple [14].

Diagnosis. The histological and clinical findings together are unmistakable, although the former alone may be difficult to differentiate from amyloidosis. Similar papular lesions are seen in severe actinic elastosis [15]. Trichoepithelioma, tuberous sclerosis and hidrocystoma are distinguished by biopsy.

Treatment. Treatments for actinic elastosis have been used in adult patients, including topical retinoids [5]. Improvement has been reported following dermabrasion [15] and ablation with the Er:YAG laser [16]. Destruction of the lesions with the diathermy or with cryotherapy has also been advocated, but the cosmetic result is seldom satisfactory.

References

1 Handfield-Jones SE, Atherton D, Black M. Juvenile colloid milium. *Br J Dermatol* 1991; **125**: 80–1.
2 Chowdhury MMV, Blackford S, Williams S. Juvenile colloid milium. *Br J Dermatol* 1999; **141** (Suppl. 55): 102–7.
3 Innocenzi D, Barduagni F, Cerio R, Wolter M. UV-induced colloid milium. *Clin Exp Dermatol* 1993; **18**: 347–50.
4 Hashimoto K, Kumakiri M. Colloid-amyloid bodies in PUVA-treated human psoriatic patients. *J Invest Dermatol* 1979; **72**: 70–80.
5 Dummer R, Laetsch B, Stutz S *et al.* Elastosis colloidalis conglomerata (adult colloid milium, paracolloid of the skin) a maximal manifestation of actinic elastosis. *Eur J Dermatol* 2006; **16**: 163–6.
6 Findlay GH, Morrison JGL, Simson IW *et al.* Exogenous ochronosis and pigmented colloid milium from hydroquinone bleaching creams. *Br J Dermatol* 1975; **93**: 613–22.
7 Ebner H, Gebhart W. Colloid milium: light and electron microscopic investigations. *Clin Exp Dermatol* 1977; **2**: 217–26.
8 Hashimoto K, Miller F, Bereston ES. Colloid milium: histochemical and electron microscopic studies. *Arch Dermatol* 1972; **105**: 684–94.
9 Hashimoto K, Black M. Colloid milium: a final degeneration product of actinic elastoid. *J Cutan Pathol* 1985; **12**: 147–56.
10 Kobayashi H, Hashimoto K. Colloid and elastic fibre: ultrastructural study on the histogenesis of colloid milium. *J Cutan Pathol* 1983; **10**: 111–22.
11 Oskay T, Erdem C, Anadolu R *et al.* Juvenile colloid milium associated with conjunctival and gingival involvement. *J Am Acad Dermatol* 2003: **49**: 1185–8.
12 Patterson JW, Wilkin JK, Schatzki PF. Nodular colloid degeneration: distinctive histochemical and ultrastructural features. *Cutis* 1985; **10**: 355–8.
13 Hashimoto K, Nakayama H, Chimenti S *et al.* Juvenile colloid milium. Immunohistochemical and ultrastructural studies. *J Cutan Pathol* 1989; **16**: 164–74.
14 Kuittken J. Papular elastosis. *Cutis* 2000; **66**: 81–3.
15 Apfelberg DB, Druker D, Spence B *et al.* Treatment of colloid milium of the hand by dermabrasion. *J Hand Surg (Am)* 1978; **3**: 98–100.
16 Ammiraki CT, Granola JM, Hruza GJ. Adult-onset facial colloid milium successfully treated with the long-pulsed Er:YAG laser. *Dermatol Surg* 2002; **28**: 215–9.

White fibrous papulosis of the neck

Asymptomatic, small, white, fibrous papules around the neck have been described in several Japanese [1,2], Iranian and European patients [3,4]. The number of papules ranges from 10 to 100; middle-aged to elderly men are predominantly affected. The papules are round to oval, clearly marginated and non-follicular (Fig. 45.43). Histology is unremarkable, showing bundles of thickened collagen fibres in the mid-papillary dermis. Although lesions clinically resemble disorders of elastic tissue, such as anetoderma and dermatofibrosis lenticularis disseminata, elastic fibres are morphologically normal on histology. Acquired connective tissue naevi could exhibit similar features, although the late age of onset makes this diagnosis unlikely. The condition appears to have no prognostic significance, and may be under-reported. It may reflect intrinsic or photo-ageing [5].

Recently, it has been suggested that there may be a relationship between fibrous papulosis of the neck and acquired elastolysis of the papillary dermis [6]. These changes are attributed to ageing or photoageing [5,7].

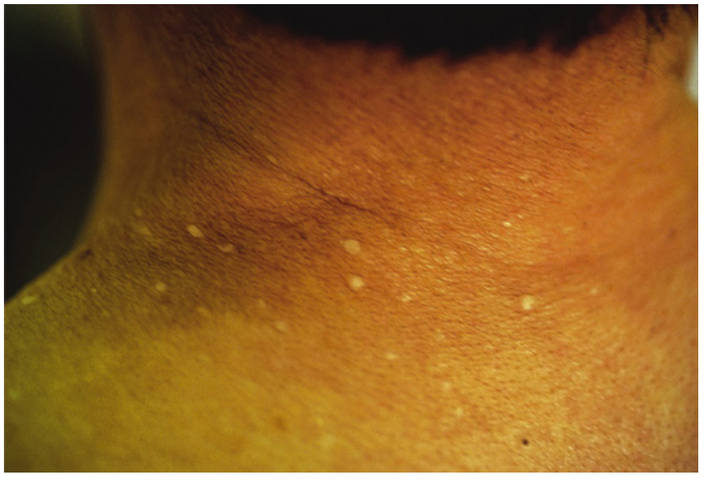


Fig. 45.43 White fibrous papulosis of the neck. (Courtesy of Professor H. Shimizu, Sapporo Hospital, Tokyo, Japan.)

References

1 Shimizu H, Nishikawa T, Kimura S. White fibrous papulosis of the neck: a review of 16 cases. *Jpn J Dermatol B* 1985; **95**: 1077–84.
2 Shimizu H, Kimura S, Harada T *et al.* White fibrous papulosis of the neck: a new clinicopathologic entity? *J Am Acad Dermatol* 1989; **20**: 1073–7.
3 Cerio R, Gold S, Wilson-Jones E. White fibrous papulosis of the neck. *Clin Exp Dermatol* 1991; **16**: 224–5.
4 Redondo P, Vázquez-Doval J, de Alava E. White fibrous papulosis of the neck. *Dermatology* 1993; **186**: 238–9.
5 Balus L, Amanthea A, Donati P *et al.* Fibroelastolytic papulosis of the neck: a report of 20 cases. *Br J Dermatol* 1997; **137**: 461–6.
6 Perrin CH, Castenet J, Lacour J-P *et al.* Papulose blanche du cou. Aspects cliniques de pseudoxanthoma elastique. *Ann Dermatol Vénéréol* 1996; **123**: 114–7.
7 Siragusa M, Schepis C, Palazzo R *et al.* Skin pathology findings in a cohort of 1500 adult and elderly subjects. *Int J Dermatol* 1999; **38**: 361–6.

Papular elastorrhexis

This is a rare variant of connective tissue naevus. Adolescents or young adults present with multiple, non-follicular oval white or yellowish papules on the trunk or limbs; dermal elastic fibres are decreased and fragmented on histology. Most reports are of sporadic cases, with no family history and no extracutaneous manifestations [1–3]. Similar lesions are seen in some patients with Buschke–Ollendorff syndrome (Chapter 18), in which osteopoikilosis is also a feature. To add to the confusion, abortive forms of Buschke–Ollendorff syndrome have been described, lacking osteopoikilosis [4]. A family has been described with this variant [5]. It is possible that papular elastorrhexis is not a separate entity [6]. Intralesional triamcinolone may be beneficial [7].

References

1 Bordas X, Ferrandiz C, Ribera M *et al.* Papular elastorrhexis: a variety of nevus anelasticus? *Arch Dermatol* 1987; **123**: 433–4.
2 Sears JK, Seabury Stone M, Argenyi Z. Papular elastorrhexis: a variant of connective tissue nevus. *J Am Acad Dermatol* 1988; **19**: 409–14.
3 Choonhakarn C, Jirarattanapochai K. Papular elastorrhexis. A distinct variant of connective tissue nevi or an incomplete form of Buschke–Ollendorff syndrome? *Clin Exp Dermatol* 2002; **27**: 454–7.
4 Schorr WF, Opitz JM, Reyes CN. The connective tissue nevus–osteopoikilosis syndrome. *Arch Dermatol* 1992; **106**: 208–14.
5 Schirren H, Schirren CG, Stolz W *et al.* Papular elastorrhexis: a variant of dermatofibrosis lenticularis disseminata (Buschke–Ollendorff syndrome). *Dermatology* 1994; **189**: 368–72.
6 Ryder HF, Antaya RJ. Nevus anelasticus, papular elastorrhexis and eruptive collagenoma: clinically similar entities with focal absence of elastic fibres in childhood. *Pediatr Dermatol* 2005; **22**: 153–7.
7 Lee SH, Park SH, Yoon TJ *et al.* Papular elastorrhexis improved by intralesional injection of triamcinolone. *J Dermatol* 2001; **28**: 569–71.

Progressive osseous heteroplasia [1,2]

This rare condition typically affects female infants and is characterized by ossification of skin and soft tissues. Ossification begins in the dermis, progressing to deeper tissues and to adjacent areas of skin. It is not associated with trauma or infection [3]. Skin lesions begin as groups of small, firm papules resembling rice grains; later, larger ossified nodules may develop. A skin biopsy should include subcutaneous fat. Cancellous and even mature intra-membranous bone is found in the dermis and subcutis. The differential diagnosis includes plate-like osteoma cutis (in which the lesion is solitary) (Chapter 56), Albright hereditary osteodystrophy (which is associated with dysmorphic features, including brachydactyly and short stature, and less severe ossification) and fibrodysplasia ossificans progressiva, in which ossification initially affects muscle or fascia and the great toes are malformed. The disorder is caused by a paternally inherited, inactivating *GNASI* mutation, which is also found in Albright hereditary osteodystrophy [4]. This gene encodes for guanine nucleotide-binding protein Gs alpha, which couples receptors to adenyl cyclases, generating cAMP. Studies in mice indicate that Gs alpha directly regulates the differentiation of growth plate cartilage and suppresses ectopic ossification, without affecting renal function [5,6].

The condition is progressive, and the morbidity depends on the site and the severity of the ossification. There is no effective treatment to prevent the ossification, but lesions that disrupt function or impair movement can sometimes be removed surgically.

References

1 Kaplan FS, Craver R, MacEwen GD *et al.* Progressive osseous heteroplasia: a distinct developmental disorder of heterotopic ossification. *J Bone Joint Surg Am* 1994; **76**: 425–36.
2 Miller ES, Esterly NB, Fairley JA. Progressive osseous heteroplasia. *Arch Dermatol* 1996; **132**: 787–91.
3 Kaplan FS, Shore EM. Progressive osseous heteroplasia. *J Bone Miner Res* 2000; **15**: 2084–94.
4 Shore EM, Ahn J, Jan de Beur S *et al.* Paternally inherited inactivating mutations of the *GNASI* gene in progressive osseous heteroplasia. *New Engl J Med* 2002; **346**: 99–106.
5 Bastepe M, Weinstein LS, Ogata N *et al.* Stimulatory G protein directly regulates hypertrophic differentiation of growth plate cartilage in vivo. *Proc Nat Acad Sci USA* 2004; **101**: 14794–9.
6 Castrop H, Oppermann M, Mizel D *et al.* Skeletal abnormalities and extra-skeletal ossification in mice with restricted Gs alpha deletion caused by a renin promoter–Cre transgene. *Cell Tissue Res* 2007; **330**: 487–501.

Fascial hernias of the legs [1,2]

Small fascial hernias of the lower legs are not uncommon in athletes and heavy manual workers, and may present a problem in differential diagnosis. Herniation of muscle takes place through the hiatus in the deep fascia where it is perforated by communicating veins.

The hernias develop suddenly as nodules on the anterolateral aspect of the lower leg and are usually about 15 cm above the lateral malleolus. The nodules are soft, compressible and 1.5–2.0 cm in diameter. If bilateral, they are strictly symmetrical. No treatment is required, although minimally invasive fasciotomy is claimed to give symptomatic benefit [3].

References

1 Kitchin ID, Richmond DA. Multiple muscle herniae. *BMJ* 1943; **i**: 602–3.
2 Obermayer ME, Wilson JW. Fascial hernias of the legs. *JAMA* 1951; **145**: 548–9.
3 deFijter WM, Scheltingen MB, Luiting MG. Minimally invasive fasciotomy in chronic exertional compartment syndrome and fascial hernias of the anterior lower leg: short and long-term results. *Mil Med* 2006; **171**: 399–403.

Constricting bands of the extremities

Synonym
- Ainhum and pseudo-ainhum

Definition. This is a constricting band around a digit or limb. The band may be shallow, involving only the skin, or it may be deeper, involving fascia or bone, and in some cases amputation may result. The term *ainhum* (an African word meaning 'to saw' [1]) is applied to a specific type in which a painful constriction of the fifth toe occurs in adults, with eventual spontaneous amputation. *Pseudo-ainhum* is the term applied to other constricting bands which are congenital or secondary to another disease.

Ainhum

Synonym
- Dactylolysis spontanea

Aetiology. The condition appears to be due to an abnormal blood supply to the foot in some patients, as arteriography has shown that in these patients the posterior tibial artery is attenuated at the ankle, and the plantar arch and its branches are absent [2]. Mechanical factors, including trauma from walking barefoot, may then precipitate the development of a groove in the ischaemic toe. Chronic fissuring in hyperkeratotic skin also seems to be an important factor. A family history is common, and the disease is more common in certain races. Ainhum is most common in black Africans, but many cases have been reported in black Americans, and it can also occur in other races.

Various tropical infections, including leprosy, tuberculosis and yaws, have been suggested as possible contributory factors, but these conditions are probably coexistent rather than causative [2,3].

Pathology [4]. Fissuring and hyperkeratosis on the medial aspect of the digit is followed by fibrosis, distal degeneration and osteoporosis, ultimately leading to spontaneous amputation. There may be secondary infection and osteomyelitis.

Clinical features. The condition is most common between the ages of 30 and 50 years, but the earliest stages may be seen in childhood. The presenting symptom is usually a painful fissure.



Fig. 45.44 Ainhum, just before shedding of the fifth digit. (Courtesy of Dr D. Burley, Princess Margaret Hospital, Swindon, UK.)

The toe is held dorsiflexed at the metatarsophalangeal joint, and gradually becomes clawed. Rest pain, coolness and cyanosis of the digit distal to the groove suggest that ischaemia is present. Once the constricting band has encircled the toe, the condition tends to progress rapidly. The toe becomes globular, hangs by a thread of fibrous tissue and is eventually shed (Fig. 45.44).

Diagnosis. The condition must be distinguished from pseudo-ainhum.

Treatment. Control of secondary infection and protection from trauma may prevent extension of the scarring process. If symptoms are severe, or the dangling digit is a disability, amputation is indicated.

Pseudo-ainhum

Congenital. Congenital pseudo-ainhum may involve a digit, a limb or even the trunk, and it ranges in severity from a superficial groove to amputation *in utero* [5–8]. The cause is unknown, but familial cases have been reported. Some cases of pseudo-ainhum may be due to amniotic bands [9] or adhesions *in utero*, which may arise as a result of tearing of the amnion some time after the 45th day of pregnancy [10]. Cases have occurred in EDS and after amniocentesis [10,11]. Several cases are reported where raised limb bands develop in the postnatal period, not always associated with amniotic tears; other possible causes include an early teratogenic insult [1,12].

Histology of the affected digit or limb reveals broad, finger-like projections of collagen, and coarse elastic bundles that penetrate deep into the subcutaneous fat [8].

Congenital pseudo-ainhum must be distinguished from: *aplasia* of the limbs with rudimentary digits; *acromelia* (in which part of the limb does not develop); and *hypoplasia* (in which the parts, although formed, are poorly developed).



Fig. 45.45 Vohwinkel's disease with pseudo-ainhum of the fifth digit of the left hand. (Courtesy of Dr F.A. Ive, Durham, UK.)

Acquired. Pseudo-ainhum may be acquired as a result of infection (particularly leprosy), trauma, cold injury, neuropathy (especially congenital sensory neuropathy), systemic sclerosis, etc. [13] and chronic psoriasis [14], and it may occur in association with other hereditary diseases such as palmoplantar keratoderma (particularly Vohwinkel's disease) (Fig. 45.45), pachyonychia congenita, erythropoietic protoporphyria [15,16], and Olmsted's syndrome (Chapter 19). Factitial pseudo-ainhum has also been reported due to the self-application of a rubber tourniquet.

Multiple skin creases resembling constrictions may be seen in the Michelin baby syndrome (Chapter 18) and in 'multiple benign annular creases of the extremity' (Chapter 19).

Treatment. Staged Z-plasty sometimes gives an excellent result [17].

References

1 Meggitt ST, Harper J, Lacour M *et al.* Raised limb bands developing in infancy. *Br J Dermatol* 2002; **147**: 359–63.
2 Dent DM, Fataar S, Rose AG. Ainhum and angiodysplasia. *Lancet* 1981; **ii**: 396–7.
3 Editorial. Ainhum. *Lancet* 1975; **ii**: 19–20.
4 Browne SG. Ainhum. *Int J Dermatol* 1976; **15**: 348–50.
5 Glessner JR. Spontaneous intra-uterine amputation. *J Bone Joint Surg Am* 1963; **45**: 351–5.
6 Petereka ES, Karon IM. Congenital pseudo-ainhum of the finger. *Arch Dermatol* 1964; **90**: 12–4.
7 Raque CJ, Stein KM, Lane JM. Pseudo-ainhum constricting bands of the extremities. *Arch Dermatol* 1972; **105**: 434–8.
8 Rushton DI. Amniotic band syndrome. *BMJ* 1983; **286**: 919–20.
9 Young ID, Lindenbaum RH, Thompson EM *et al.* Amniotic bands in connective tissue disorders. *Arch Dis Child* 1985; **60**: 1061–3.
10 Lockwood C, Ghidini A, Romero R *et al.* Amniotic band syndrome: reevaluation of its pathogenesis. *Am J Obstet Gynecol* 1989; **160**: 1030–3.
11 Moessinger AC. Amniotic band syndrome associated with amniocentesis. *Am J Obstet Gynecol* 1981; **141**: 588–91.
12 Latteo SA, Taylor AE, Meggitt SJ. Raised limb bands developing in infancy. *Br J Dermatol* 2006; **154**: 791–2.
13 Bockers M, Benes P, Bork K *et al.* Persistent skin ulcers, mutilations and acro-osteolysis in hereditary sensory and autonomic neuropathy. *J Am Acad Dermatol* 1989; **21**: 736–9.
14 Almond SL, Curley RK, Feldberg L. Pseudoainhum in chronic psoriasis. *Br J Dermatol* 2003; **149**: 1064–6.
15 Christopher AP, Grattan CEH, Colvan MA. Pseudo-ainhum and erythropoietic protoporphyria. *Br J Dermatol* 1988; **118**: 113–6.
16 Schamroth JM. Mutilating keratoderma. *Int J Dermatol* 1986; **25**: 249–51.
17 Kamalan A. Ainhum trichosporosis Z-plasty. *Dermatologica* 1981; **162**: 372.

Heberden's and Bouchard's nodes

Heberden's nodes [1] are posterolateral bony outgrowths affecting one or more *distal* interphalangeal joints. Similar changes, affecting the *proximal* interphalangeal joints, are termed Bouchard's nodes. Both Heberden's and Bouchard's nodes are strongly associated with osteoarthritis, although they may be inherited independently as an autosomal dominant trait [2,3]. Characteristically, they are asymptomatic and of insidious onset, although tender nodes may develop acutely with a red, swollen joint. The association of multiple symmetrical nodes with distal interphalangeal joint arthritis has been termed 'primary generalized osteoarthritis'. Because this is associated with the tissue types HLA-A1 and B8 and shows a marked female preponderance, it has been postulated to be an autoimmune disorder; increased amounts of immune complexes can be detected in cartilage and synovium [4].

References

1 Kellgren JH, Moore R. Generalised osteoarthritis and Heberden's nodes. *BMJ* 1952; **i**: 181–7.
2 Stecker RM. Heberden's nodes. A clinical description of osteoarthritis of the finger joints. *Ann Rheum Dis* 1953; **48**: 523–7.
3 Irlenbusch U, Dominick G. Investigations into generalized osteoarthritis. Part 1: genetic study of Heberden's nodes. *Osteoarthritis Cartilage* 2006; **14**: 423–7.
4 Doherty M, Pattrick M, Powell RJ. Hypothesis—nodal generalised osteoarthritis is an auto-immune disease. *Ann Rheum Dis* 1990; **49**: 1017–20.

CHAPTER 46
Subcutaneous Fat

D.H. McGibbon
St John's Institute of Dermatology, St Thomas' Hospital, London, UK

Obesity, 46.5
Cellulite, 46.9
General pathology of adipose tissue: panniculitis, 46.10
Inflammatory disorders of subcutaneous fat, 46.12
Septal panniculitis, 46.12
Lobular panniculitis, 46.13
Mixed (septal and lobular) panniculitis, 46.25
Panniculitis with vasculitis, 46.32
Lipodystrophy, 46.34
Localized lipoatrophy, 46.34
Partial or generalized lipoatrophies, 46.37
Lipomas, 46.43
Angiolipoma, 46.44
Frontalis-associated lipoma, 46.45
Fat-storing hamartoma of dermal dendrocytes, 46.45
Hibernoma, 46.45
Lipomatosis, 46.46
Non-symmetrical lipomatosis, 46.46
Multiple symmetrical lipomatosis, 46.46
Congenital diffuse lipomatosis, 46.47
Dercum's disease, 46.47

Introduction

Subcutaneous fat (subcutis) occurs almost universally over the body surface between the skin and the deep fascia, but it is absent from the eyelids and the male genitalia. It varies in thickness with the race, age, sex, endocrine and nutritional status of the individual.

Subcutaneous fat acts as an insulating layer and a protective cushion; it also has an important role in thermogenesis, and as a store of readily available energy. In a normal person, fat constitutes about 10% of body weight, and provides about 40 days' reserve energy [1]. Brown fat has a very important thermoregulatory role and acts by increasing the basal metabolic rate [2]. This is particularly important in infancy, and heat production in response to cold exposure is maximal in neonates, who have large quantities of brown fat.

Fat also provides support and has a cosmetic function, for example in the contours of the face. It also has great social importance. Fat children may be bullied or ostracized at school [3], fat adults may find it harder to get certain jobs, and the contribution of fat to the shape of the breasts and buttocks as a secondary sexual development in the female has been known to influence social behaviour.

In addition to the above functions, the obesity epidemic and the metabolic consequences of abnormal fat distribution have underlined the fact that the subcutaneous fat, comprising as it does innumerable adipocytes secreting a large variety of enzymes, hormones and cytokines, is also a major endocrine organ [4].

Embryology [5,6]

The first fat-containing cell, the pre-adipocyte, appears in the mesenchyme around the 14th week of fetal life. The primitive mesenchymal cell that forms the determined pre-adipocyte is also capable of maturing to form a fibrocyte, a myocyte, a chondrocyte or an osteoblast. Pre-adipocytes can terminally differentiate into either brown adipocytes or white adipocytes.

Brown fat is a special type of granular fat that differs from white fat in its distribution, histology and function. It is multilocular and is metabolically very active with many mitochondria so that it is capable of transferring energy from food to produce heat. As it has a much greater capillary network surrounding it compared to white fat (which is partly responsible for the brown colour), heat can be rapidly transferred into the circulation. It is most prominent in the neck and upper thorax of the fetus, and it may be homologous to the hibernating gland fat found in some animals [7]. Brown fat is now known to persist into adult life [8], and it may have a role in preventing obesity [8]. Warm patches develop in the skin 1 hour after taking ephedrine orally, and these warm patches may indicate the site of thermogenic brown fat. Brown fat adipocyte mitochondria uniquely express uncoupling protein-1 (UCP-1), allowing confirmation that brown fat is present in adult white fat depots in variable amounts, and that transdifferentiation from white to brown adipocytes can occur. Development of brown fat begins at the 20th week of gestation, reaches its maximum at birth and then diminishes so that there are no large collections of brown fat in the adult, though fluorodeoxyglucose positron emission tomography (FDG PET) suggests that some adults have supraclavicular areas of brown fat [9]. Evidence for cold induction of brown fat as an adaptive response in humans is at present equivocal [9].

Histology

White fat adipocytes are the largest connective tissue cells in the body, with a diameter of up to 100 µm. Much of their differentiation occurs soon after birth. The mature fat cell has a characteristic signet-ring appearance, because the flat oval nucleus is displaced to the side by a single, large, intracellular, fat-containing vacuole,

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

which is surrounded by perilipin. Originally thought of as an inert store for emergency supplies of energy when necessary, it is now realized that the white adipocyte has a huge array of functions, secreting factors (adipokines) that affect lipid and glucose metabolism, endocrine functions, blood pressure control, coagulation, fibrinolysis, angiogenesis and inflammation. For a full review the reader is referred to Frühbeck [6]. Groups of lipocytes are arranged in lobules, which are separated by interlobular septa composed of collagen and reticulin fibres. The adipocytes may comprise only 25% of the total cell population of a lobule; the remainder, the stromavascular tissue, being macrophages, fibroblasts, mast cells, pericytes, endothelial cells and pre-adipocytes, allowing for considerable cross-talk between cells with even more factors being produced.

Fat tissue has an abundant blood supply, each individual lobule being supplied by a terminal arteriole from the vascular supply running along the septa, which then breaks up to form capillaries which come into close apposition with the individual fat cells. The subcutaneous fat also contains a rich lymphatic plexus, which receives vessels from the dermis. These lymph vessels traverse the subcutaneous layer parallel to the skin surface for some distance, before eventually penetrating the deep fascia and draining into the regional lymph nodes. The nature of the lipocyte and its relationship to blood vessels and lymphatics has been reviewed in detail by Ryan and Curri [10]. Both white fat and brown fat are innervated by noradrenergic fibres of the sympathetic nervous system and para-sympathetic fibres.

The fat tissue and the fat organ. All fat tissue is composed of lobules of fat cells with their supporting connective and stromavascular tissue. In addition to the subcutaneous fat, approximately 20% of fat tissue occurs internally, in the mediastinal and retroperitoneal tissues, the mesentery and the bone marrow and in and around individual organs, including blood vessels. This tissue, although it is widely scattered throughout the body, forms a true organ as regards both structure and function [1] but in which depot-specific differences occur [11]. For example, increases in subcutaneous upper body and visceral fat are associated with an increased cardiovascular and metabolic risk but increases in gluteofemoral subcutaneous fat are not [12]. In addition, perivascular adipose tissue shows increased angiogenesis compared to subcutaneous fat [13]. The fact that some genetic lipodystrophy patients lose peripheral fat but fat padding for absorption of mechanical pressure is maintained, is further evidence for depot-specific differences.

The combination of the obesity epidemic and the advent of liposuction has rekindled interest in the structure of subcutaneous fat with MRI scanning as the investigative tool [14]. Subcutaneous fat is divided by the superficial fascia into two compartments, superficial and deep. The fat mass in the superficial (areolar) layer is compartmentalized into lobules by vertical and oblique fibrous septal planes and bands, whilst that of the deeper (lamellar) layer has its septae more horizontally positioned. The superficial layer is fairly constant, but the deeper is more variable, with an increase in fat mass accumulating between split horizontal septae. In females, subcutaneous fat is most abundant in the gluteofemoral region and breasts, resulting in the so-called gynoid distribution, whereas in males the android distribution of shoulders and upper arms, neck and lumbosacral area predominates.

Physiology [5,6,15–18]

Traditionally, adipose tissue was regarded as an inert energy store with insulating and padding properties. Whilst storage is still a major function, there is now an appreciation that adipocytes and their stromavascular tissue have many other highly complex and dynamic actions, including energy homeostasis, adipogenesis, insulin sensitivity and influences on immune and inflammatory responses.

Energy homeostasis. A major function of white adipose tissue is to store energy at times of calorie excess and release it when needed, such as during exercise or starvation. The synthesis (anabolism) and catabolism of fat in the subcutaneous depot depends on many factors, including nourishment, endocrine and nervous activity. The role of the autonomic nervous system in regulating fat metabolism is now well established [19], being particularly important for rapid energy need compared to the slower control exerted by neuroendocrine factors [20]. A decrease in parasympathetic activity results in increased lipolysis, as does an increase in sympathetic activity, with the opposites stimulating lipogenesis [21]. Hormones that may affect the energy metabolism of fat cells include insulin, cortisol, norepinephrine (noradrenaline) and several pituitary hormones, including somatotrophin, adrenocorticotrophic hormone (ACTH), thyrotrophin, lipotrophin and natruretic peptide [22].

The fats contained within the lipocytes are predominantly triglycerides (triacylglycerols), especially those of palmitic and stearic acids and the unsaturated oleic acid. All the fatty acids have an even number of carbon atoms, predominantly C16 and C18, with a few C14 and C12. Adipose tissue contains 10–30% of water with a small proportion of lipochromes, and less than 2% cholesterol. Fat-soluble substances are also present in varying amounts. These include fat-soluble vitamins and traces of chlorinated hydrocarbons (e.g. aldrin, dieldrin) ingested with the diet, as well as drugs such as acitretin. Adipose tissue *in vitro* has a metabolic rate similar to that of kidney tissue, and approximately half that of liver. Approximately half the triglyceride in the adipose tissue of rats and mice is catabolized and reconstituted in the course of a week or so.

The fat for storage enters the lipocyte as fatty acids, having been converted from lipoproteins by the extracellular enzyme lipoprotein lipase (Fig. 46.1). The fatty acids combine with coenzyme A, using the energy of adenosine triphosphate (ATP), to form the corresponding acyl coenzyme A compounds. Some of these are then oxidized to provide energy for the regeneration of ATP, but most are converted to triglyceride by combination with glycerol-3-phosphate derived from glucose.

The adipocyte is one of the few cells to express the insulin-dependent glucose transporter receptor 4 (GLUT-4), which mediates the passage of glucose into the cell, as well as leading to further triglyceride formation via *de novo* lipogenesis, the latter providing only a small contribution to the pool. At the same time, insulin inhibits hydrolysis and breakdown of triglyceride, conserving the energy store.

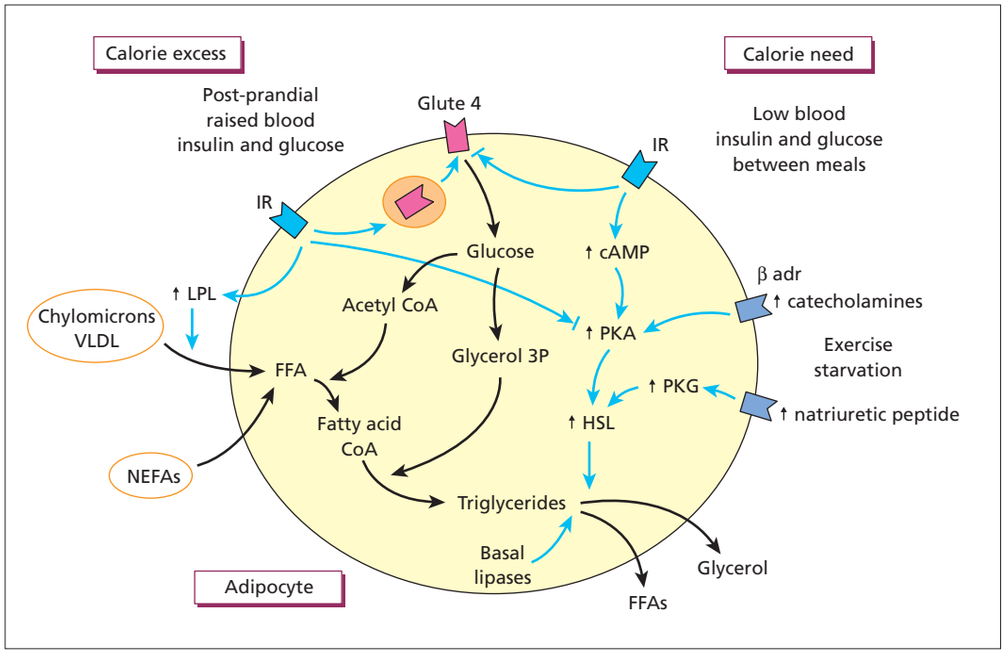


Fig. 46.1 Simplified outline of lipogenesis in an adipocyte during energy excess and lipolysis during calorie need. Effects of hormones and enzymes are in blue. β adr, β-adrenoceptor; cAMP, cyclic andenosine monophosphate; FFA, free fatty acid; Glute 4, insulin-sensitive glucose transporter; HSL, hormone-sensitive lipase; IR, insulin receptor; LPL, lipoprotein lipase; NEFAs, non-esterified fatty acids; PKA, protein kinase A; PKG, protein kinase G; VLDL, very low density lipoproteins.

When the body requires energy, lipolysis occurs. Triglyceride is hydrolysed in the adipocyte, converted to non-esterified fatty acids (NEFA) and glycerol, the rate-limiting enzyme being hormone-sensitive lipase (HSL). The NEFAs are conveyed in the blood to tissues such as liver and muscle, in which fatty acid oxidation readily takes place. In both tissues, the essential part of the process consists of the oxidation in the mitochondria of the long-chain fatty acids. The glycerol of the triglyceride molecule reacts with ATP to form glycerol phosphate, which is oxidized to glyceraldehyde-3-phosphate. This in turn may either be converted to glycogen by reversal of glycolysis, or it may be converted to pyruvate. Skeletal muscle readily oxidizes fatty acids but glucose, if available, is preferentially used. In cardiac muscle, fatty acids are a major source of energy. Lipolysis is regulated predominantly through insulin and catecholamines. The latter, elevated during a sudden energy demand, bind to β-adrenergic receptors on the adipocyte and activate HSL through the classic adenosine monophosphate-protein kinase A (AMP-PKA) pathway.

Leptin [23]. Leptin is an adipokine involved in energy homeostasis which may have evolved to help adaption from the starved to the adequately nourished state rather than to prevent obesity. Leptin, a product of the *ob* gene, is a 16-kDa polypeptide comprising 167 amino acids with a structural homology similar to other cytokine proteins such as TNF-α and interleukin-6. It is secreted by adipocytes predominantly, but also by the stomach, aiding immediate appetite control. Leptin receptors are present in the hypothalamus, on adipocytes, skeletal muscle, liver, pancreatic β-cells, ovary and endometrium. The main effect of leptin is via the satiety centres in the hypothalamus. If excess energy is being stored, rising leptin levels stimulate satiety centres to reduce appetite. Conversely, during starvation low leptin levels stimulate appetite. Circulating levels of leptin correlate with increasing body mass index (BMI), but have little effect on satiety centres, indicating an apparent leptin resistance. Leptin also influences several other functions, including neuroendocrine and reproductive functions, insulin secretion and blood pressure. Patients with congenital leptin deficiency have gross obesity, hyperphagia, delayed pubertal development, abnormal T-cell number and function, and altered thyroid and growth hormone function [24]. In addition, leptin has a role in immune function and inflammation [25]. There is increased expression in chondrocytes and leptin may have a part to play in articular degenerative disease.

Adipogenesis. Adipogenesis refers to the recruitment from multipotent stem cells in the mesenchyme and stromavascular tissue, and proliferation of pre-adipocytes followed by their differentiation into mature fat cells. Culture of cell lines has led to the elucidation of many of the transcriptional factors involved in adipogenesis, the major ones being peroxisome proliferator-activated receptor-γ (PPARγ) and the CCAAT-enhancer-binding proteins (C/EBPs). The precise contribution of adipogenesis towards enlargement of the fat organ at different stages of human development and life changes is uncertain, but it seems maximal before and around birth before diminishing, then possibly continuing at a low rate throughout adult life. Glucocorticoids, growth hormone and insulin stimulate cells to terminal differentiation, but when mature fat cells reach a certain size, recruitment occurs so that the fat organ enlarges through hyperplasia (increased numbers of cells) rather than hypertrophy (increase in size of cells). Control of this hyperplastic response may come from the local adipocyte through paracrine effects involving local growth factors. During adipogenesis the local extracellular matrix also changes, the effects of which might play their own role in differentiation. This is supported by the fact that fat tissue repair is improved if elements of this matrix are included with the donor adipocytes.

Insulin sensitivity. Insulin secretion, stimulated by raised blood glucose levels after meals to reverse hyperglycaemia, has two major effects. It facilitates glucose uptake into most of the body's cells (liver, skeletal muscle and adipocytes) and it suppresses glucose output by the liver. Insulin resistance occurs when a target organ fails to respond normally to insulin, resulting in hyperinsulinaemia. The effect may be incomplete suppression of hepatic glucose output in the liver and/or impaired insulin-mediated glucose uptake in peripheral tissues, including adipocytes. If increased insulin secretion cannot prevent hyperglycaemia, type 2 diabetes mellitus results. Adipocytes secrete many factors, some of which have direct and indirect effects on insulin sensitivity. The effects of dysregulation of some of these factors are discussed under obesity, below.

Adiponectin [26–28]. Adiponectin is a 30-kDa protein comprised of 244 amino acids with some structural similarity to both collagen and complement C_1q. It is thought, at the moment, to be secreted exclusively by adipocytes and has autocrine/paracrine effects within the local adipose tissue and endocrine effects distantly. Locally, it can promote preadipocytes to become mature fat cells which, with increasing size, down-regulate their adiponectin secretion to exert some feedback control. Adiponectin receptors are present in many tissues as well as adipocytes. It is likely that adiponectin receptor-activated AMPK (AMP-activated protein kinase) leads to enhanced insulin signalling and therefore insulin sensitivity. Adiponectin expression is lower in visceral adipose tissue (VAT) adipocytes compared to subcutaneous depots (SAT) if BMI is increased. Serum adiponectin levels are lower with weight gain and higher with weight loss.

Adiponectin also exerts protective anti-inflammatory effects both locally, by inhibiting secretion of interleukin-6, interleukin-8, macrophage inflammatory protein-1 and monocyte chemotactic protein-1, and distantly on monocyte/macrophages, endothelial cells, hepatic and muscle cells directly, and via inhibition of TNF-α production and action. There is an, as yet unexplained, paradox concerning adiponectin and its anti-inflammatory effects. Obesity is associated with macrophages in the visceral adipose tissue that generate factors, particularly TNF-α, that suppress adiponectin secretion. However, low levels of adiponectin promote inflammation, generating a self-sustaining loop; thus in obesity low adiponectin levels negatively correlate with inflammatory markers. In autoimmune states, such as rheumatoid arthritis and systemic lupus erythematosus, adiponectin levels are raised, the level positively correlating with inflammatory markers. To explain this, it has been suggested that the adiponectin system has evolved as a mechanism for adaptation to starvation, a catabolic state [29]. It is therefore raised in other catabolic states such as autoimmune disease and inflammatory bowel disease, and it did not evolve as a protective device against insulin resistance.

Many other adipokines have been described [6,18] and most are still being evaluated for their relevance to human biology. The stromavascular tissue itself is also responsible for a variety of cytokines. Macrophages secrete TNF-α, interleukins 1, 6, 8 and 10, monocyte chemoattractant protein 1, macrophage migration inhibitory factor, angiotensinogen, and endothelial and vascular growth factors. Therefore, as well as affecting energy homeostasis, insulin sensitivity and adipocyte differentiation, the fat organ has influences on inflammation, immune function, vascular inflammation and neo-angiogenesis. All of this lends credence to the concept of the fat organ being an endocrine organ in its own right. Whilst these discoveries are of the utmost importance for worldwide obesity-associated morbidity and mortality, except for lipodystrophy patients, their relevance has not provided much insight about the causation and treatment of classical skin panniculitides.

References

1 Lundgren H, Bengtsson C, Blohme E, Lapidus L. Adiposity and adipose tissue distribution in relation to incidence of diabetes in women. *Int J Obes* 1989; **13**: 413–8.

2 Heaton JM. The distribution of brown adipose tissue in the human. *Anatomy* 1972; **112**: 35–9.

3 Taitz LS. *The Obese Child*. Oxford: Blackwell Scientific Publications, 1983: 21.

4 Bays HE, González-Campoy JM, Henry RR *et al*. The Adiposopathy Working Group. Is adiposopathy (sick fat) an endocrine disease? *Int J Clin Pract* 2008; **62**: 1474–83.

5 Avram AS, Avram MM, James WD. Subcutaneous fat in normal and diseased states: 2. Anatomy and physiology of white and brown adipose tissue. *J Am Acad Dermatol* 2005; **53**: 671–83.

6 Frühbeck G. Overview of adipose tissue and its role in obesity and metabolic disorders. *Methods Mol Biol* 2008; **456**: 1–22.

7 Aherne W, Hull D. The site of heat production in the newborn infant. *Proc R Soc Med* 1964; **57**: 1172–3.

8 Jung RT, Shetty PS. Reduced thermogenesis in obesity. *Nature* 1979; **279**: 322–3.

9 Nedergaard J, Bengtsson T, Cannon B. Unexpected evidence for active brown adipose tissue in adult humans. *Am J Physiol Endocrinol Metab* 2007; **293**: E444–52.

10 Ryan TJ, Curri SB, eds. *Clinics in Dermatology*, Vol. 7. *The Cutaneous Adipose Tissue*. Philadelphia: JB Lippincott, 1989.

11 Giorgino F, Laviola L, Eriksson JW. Regional differences of insulin action in adipose tissue: insights from *in vivo* and *in vitro* studies. *Acta Physiol Scand* 2005; **183**: 13–30.

12 Lafontan M, Berlan M. Do regional differences in adipocyte biology provide new pathophysiological insights? *Trends Pharmacol Sci* 2003; **24**: 276–83.

13 Thalmann S, Meier CA. Local adipose tissue depots as cardiovascular risk factors. *Cardiovasc Res* 2007; **75**: 690–701.

14 Johnson D, Cormack GC, Abrahams PH *et al*. Computed tomographic observations on subcutaneous fat: implications for liposuction. *Plast Reconstr Surg* 1996; **97**: 387–96.

15 Bell GH. *Textbook of Physiology and Biochemistry*. Edinburgh: Churchill Livingstone, 1987.

16 Frayn KN. Adipose tissue metabolism. In: Ryan TJ, Curri SB, eds. *Clinics in Dermatology*, Vol. 7. *The Cutaneous Adipose Tissue*. Philadelphia: JB Lippincott, 1989: 48–61.

17 Avram MM, Avram AS, James WD. Subcutaneous fat in normal and diseased states 3. Adipogenesis: from stem cell to fat cell. *J Am Acad Dermatol* 2007; **56**: 472–92.

18 Wang P, Mariman E, Renes J, Keijer J. The secretory function of adipocytes in the physiology of white adipose tissue. *J Cell Physiol* 2008; **216**: 3–13.

19 Dalziel K. The nervous system and adipose tissue. In: Ryan TJ, Curri SB, eds. *Clinics in Dermatology*, Vol. 7. *The Cutaneous Adipose Tissue*. Philadelphia: JB Lippincott, 1989: 62–77.

20 Boden G, Hoeldtke RD. Nerves, fat, and insulin resistance. *N Engl J Med* 2003; **349**: 1966–7.

21 Romijn JA, Fliers E. Sympathetic and parasympathetic innervation of adipose tissue: metabolic implications. *Curr Opin Clin Nutr Metab Care* 2005; **8**: 440–4.

22 Langin D. Adipose tissue lipolysis as a metabolic pathway to define pharmacological strategies against obesity and the metabolic syndrome. *Pharmacol Res* 2006; **53**: 482–91.

23 Anubhuti, Arora S. Leptin and its metabolic interactions—an update. *Diabetes Obes Metab* 2008; **10**: 973–93.

24 Ranadive SA, Vaisse C. Lessons from extreme human obesity: monogenic disorders. *Endocrinol Metab Clin North Am* 2008; **38**: 733–51.

25 Lago R, Gómez R, Lago F *et al*. Leptin beyond body weight regulation—current concepts concerning its role in immune function and inflammation. *Cell Immunol* 2008; **252**: 139–45.
26 Lara-Castro C, Fu Y, Chung BH *et al*. Adiponectin and the metabolic syndrome: mechanisms mediating risk for metabolic and cardiovascular disease. *Curr Opin Lipidol* 2007; **18**: 263–70.
27 Fantuzzi G. Adiponectin and inflammation: consensus and controversy. *J Allergy Clin Immunol* 2008; **121**: 326–30.
28 Whitehead JP, Richards AA, Hickman IJ *et al*. Adiponectin—a key adipokine in the metabolic syndrome. *Diabetes Obes Metab* 2006; **8**: 264–80.
29 Behre CJ. Adiponectin: saving the starved and the overfed. *Med Hypotheses* 2007; **69**: 1290–2.

Obesity

Obesity is variously defined. Originally it was simply a condition in which there is excessive fat in the body. This has been modified slightly to the more subjective, an unhealthy excess of body fat that leads to an impaired quality of life, or the more specific, an unhealthy excess of body fat that increases the risk of morbidity and premature mortality.

Epidemiology. Body mass index (BMI: body weight in kilograms divided by height in metres squared) is used as a surrogate marker of adiposity. Both the World Health Organization (WHO) and the National Institutes of Health (NIH) classify adults with a BMI 25–29.9 kg/m^2 as overweight, above 30 kg/m^2 as obese and above 40 kg/m^2 as extremely obese [1,2]. For children and adolescents (under 20 years of age) the term obese is not used. 'At risk of overweight' is defined as a BMI for age at or above the sex-specific 85th centile and 'overweight' above the 95th centile. Being overweight as a child is of special significance, because many overweight children are obese as adults. Observations indicate that the prevalence of being overweight in childhood is high where adult obesity is common [3,4].

For adults, morbidity and mortality from hypertension, stroke, coronary artery disease and type 2 diabetes increase as the body mass index rises above 25 kg/m^2 [5], with more of an increase above 30 kg/m^2. These parameters were deduced from data on individuals under 50 years of age and they may not be true for individuals over 65 years with a BMI 25–27 kg/m^2 [6]. Nor does BMI take into account ethnicity [7]. BMI is an index of excess weight rather than excess body fat relative to height. More accurate measurements reveal that, for equivalent BMI levels, Asian people have more body fat, and Black people have less body fat, than do White people. To account for these differences in body fatness, it has been suggested that BMI cut-off points for overweight and obesity be lowered among Asian and increased among Black people. The same is true, but to a lesser extent, for children [7]. The other criticism of BMI is that it measures fatness as a whole and does not distinguish between visceral and subcutaneous adiposity. Visceral adiposity correlates better with morbidity and mortality and also correlates with body trunk measurements [8]. Waist circumference divided by hip circumference (WHR) can be used for this purpose. The waist is measured, after an overnight fast, halfway between the lower costal margin and the iliac crest, and hip circumference is measured over the widest part of the gluteal region [9]. WHR should not exceed 1.0 in men and 0.85 in women—cut-offs based on Scandinavian data [10]. Waist circumference is another reasonable way of assessing obesity. Circumference values that indicate a significant increased relative risk are more than 88 cm for women and more than 102 cm for men [10].

Measurement of skinfold thickness with callipers is another alternative technique, but there are possible variations in the distribution of fat between subcutaneous areas and deep body fat [11]. Computed tomography (CT), magnetic resonance imaging (MRI) and dual-energy X-ray absorptiometry (DEXA) are reserved for the more precise measurement during research rather than routine clinical practice.

The advantage of BMI is that it can be used easily for population screening. In the United States in 2003–4, among children and adolescents aged 2 to 19 years, 17.1% were overweight (above the 95th centile) and 32.2% of adults aged 20 years or older were obese. Sixty-five percent of all adults had a BMI above 25 kg/m^2. The prevalence of extreme obesity among adults was 4.8%. Between 1980 and 2002, obesity prevalence doubled in adults and overweight prevalence tripled in children and adolescents [12]. Between 1999 and 2004, the prevalence of overweight among children and adolescents and obesity among men continued to increase significantly, but no increase was observed among women over this 6-year period. Ethnicity differences remained. Among women, almost 58% of non-Hispanic black women aged 40 to 59 years were obese in 2003–2004 compared with about 38% of non-Hispanic white women of the same age. Among men, however, the prevalence of obesity did not differ by racial/ethnic group [12].

In England in 2006, 14% of 11 year olds were between the 85th and 95th centile and 17% were above the 95th centile [13]. In adults, the prevalence of obesity is much the same as the rest of Europe, with rates of around 20% [13]. Developing countries are now seeing serious increases in obesity, for example in the Caribbean, South America and South-East Asia [14,15], while in Australian Aborigines and Polynesia, figures approaching 80% have been recorded. China, except in poor rural areas, now has similar problems with childhood overweight and obesity approaching the epidemic levels of the USA [16]. It is estimated that globally there are 1 billion adults overweight of which 300 million are obese [17], a medical problem of a size beyond the capacity of even the best health-care system [1].

Obesity is accompanied by complications such as hypertension, non-insulin-dependent diabetes mellitus and atherosclerosis, which in turn cause ischaemic heart disease, stroke and premature death [18–20]. Other complications include hepatic steatosis, polycystic ovary syndrome, sleep apnoea, osteoarthritis, depression and certain malignancies such as prostate cancer. The alarming increase in diabetes is most probably a consequence of the current rapid rise in the prevalence of obesity.

Aetiology [21,22]. Very rarely obesity is monogenic [23]. It may be classified into three groups: due to gene mutations that affect the leptin–melanocortin system, mutations affecting hypothalamic development, or associated with a pleiotropic developmental syndrome such as Prader–Willi syndrome. Typically, these patients present with hyperphagia and very early onset obesity. Therapy

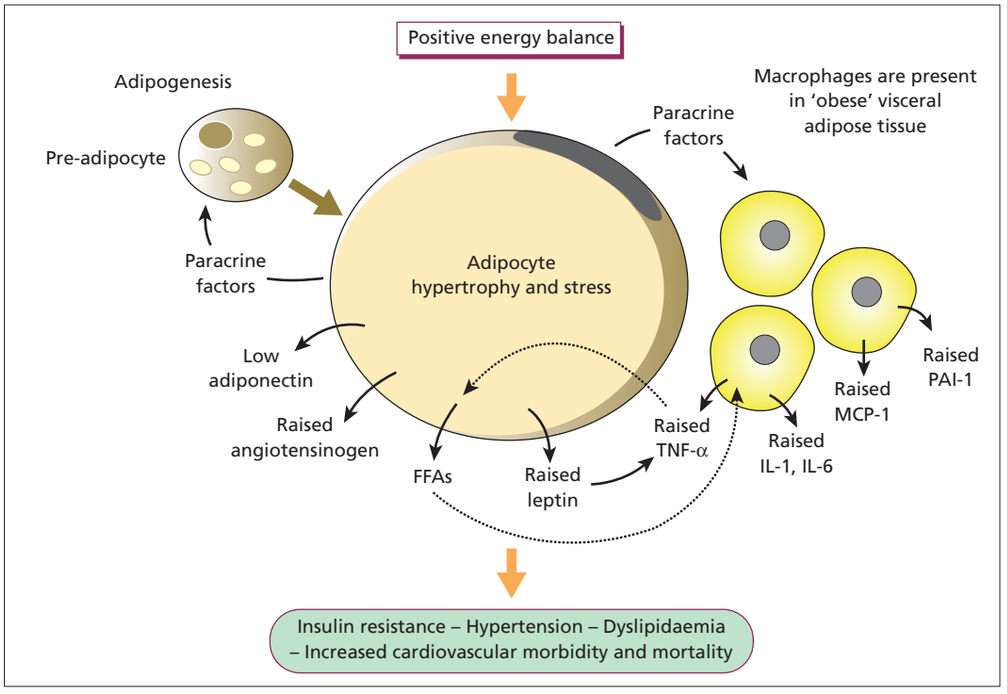


Fig. 46.2 Simplified outline of visceral adipocyte dysfunction in obesity leading to metabolic syndrome. FFAs, free fatty acids; IL-1, interleukin 1; IL-6, interleukin 6; MCP-1, monocyte chemoattractant protein-1; PAI-1, plasminogen activation inhibitor-1; TNF-α, tumour necrosis factor-α.

with leptin has transformed those with leptin deficiency. More frequently, obesity is associated with underlying disease such as polycystic ovary syndrome, hypothyroidism, Cushing's disease and hypothalamic injury, as well as corticosteroid and other drug therapy. By far and away the most frequent cause is common obesity—the result of genetic, behavioural, environmental, physiological, social, psychosocial and cultural factors that cause energy imbalance and promote excessive fat deposition. It has been suggested that inheritable factors contribute 45–75% to obesity. Bouchard *et al*. [24] demonstrated that the amount of body weight and fat gained, as well as the distribution of fat gained in response to overfeeding, had greater similarity within identical twin pairs. It is likely that genetic polymorphisms modify individual susceptibility to environmental factors [25,26]. Nutritional variability during fetal development is one such factor [27]. Maternal underweight before pregnancy [28], fetal under-nourishment and over-nourishment are all predictive of adult obesity, as is rapid weight gain in the first week of life. The pre-pubertal growth phase of early adolescence may be another susceptible time [29].

Obesity is the result of a positive energy balance input that exceeds output. The World Health Organization consultation on obesity [15] concluded that behavioural and environmental factors, such as sedentary lifestyles combined with excessive energy intake, are primarily responsible for the dramatic increase in obesity in the last 10–20 years. Food consumption has changed drastically over the last 30 years [30]. More calories are available to be consumed with a higher proportion of fats and sugar, often through increased snacking and soft drinks as well as increased portion sizes. Disordered eating behaviours, from missing meals such as breakfast, eating outside the home to binge eating, peer pressure and altered mental health may all contribute to an excessive intake. An increase in sedentary behaviour means that this increase in energy intake is not burnt off. Only a small amount of excess daily calorie intake is needed to lead to obesity [31].

Chronic positive energy balance leads to increased storage of triglycerides into fat cells. The increase in fat mass occurs due to adipocyte hypertrophy and hyperplasia. It has been suggested that increased storage occurs at first in the superficial and deep components of subcutaneous tissue until the maximal capacity has been reached [32]. At that time the secondary fat depots, including visceral fat, are filled. The subcutaneous fat shows both hypertrophy and hyperplasia but the visceral depot shows hypertrophy alone [32].

In obese subjects, macrophages are present in subcutaneous fat and they diminish in number after surgery-induced weight loss [33]. They are more numerous in omental than subcutaneous fat [34]. Inflammation associated with these macrophages, whether triggered by dysregulated adipogenesis, excess adipocyte hypertrophy or adipocyte endoplasmic reticulum and mitochondrial stress [22], results in adipocyte insulin resistance and dysfunction (Fig. 46.2). Free fatty acids and triglycerides are released into the circulation, and there is an altered secreted adipokine profile and release of inflammatory mediators. Higher concentrations of circulating free fatty acids and triglycerides are associated with lipid accumulation in multiple tissues, including liver, skeletal muscle, heart, pancreatic β-cells and blood vessels. With the portal vein draining visceral fat tissue products directly into the liver, the effect is accentuated in this organ. Perivascular lipid deposits have a role in atherogenesis [35]. Although the adipocyte secretes many adipokines, leptin and adiponectin have been the best evaluated. Circulating leptin levels correlate with increasing BMI, but the chronic high levels in obesity seem to generate leptin resistance at the hypothalamic level, in that the satiety centres do not respond

by diminishing appetite. Raised leptin levels contribute to hypertension as well as being independently moderately associated with coronary disease. In contrast, circulating adiponectin levels are low in obesity and therefore insulin sensitivity is blunted. TNF-α is an inflammatory marker associated with adiposity and cardiovascular risk factors. It inhibits lipoprotein lipase activity and increases lipolysis and also induces adipocyte apoptosis [36], as well as blunting insulin responsiveness. Increased angiotensinogen from the hypertrophied adipocyte contributes to hypertension. Monocyte chemoattractant protein 1 (MCP-1) plays an important role in atherogenesis, and plasminogen activation inhibitor-1 (PAI-1), a regulator of fibrinolysis, might be important in cardiac events [37]. Both MCP-1 and PAI-1 are produced by the stromavascular tissue.

Metabolic syndrome. The disease consequences of increasing amounts of fat tissue merits the fat being labelled as pathogenic. The traditional label for this has been the metabolic syndrome, though others prefer adiposopathy [38]. Adiposopathy is pathogenic adipose tissue that is promoted by a positive caloric balance and sedentary lifestyle in genetically and environmentally susceptible individuals. Diagnostic criteria for metabolic syndrome include glucose intolerance, elevated blood pressure, dyslipidaemia and measures of central obesity, and increased waist circumference or waist-to-hip ratio. Whilst metabolic syndrome is a convenient key for remembering its components, it may be no better as a predictor of future metabolic disease than assessment of its individual components. Also, there are five slightly different definitions of metabolic syndrome, of which three are given in Table 46.1; the use of these can blur the distinction between health and disease and exclude some individuals from preventive programmes [39,40]. Using the National Cholesterol Education Program (NCEP) metabolic syndrome criteria, the prevalence in adults in the USA is 35%, but it is 40% using criteria of the International Diabetes Federation (IDF) [41]. The prevalence in adolescents (with the IDF criteria) was 4.5% [42]. A global prevalence has been calculated at 16% [43].

Because obesity is associated with hyperinsulinaemia and diabetes, it is difficult to decide whether the skin manifestations seen in these conditions are due to obesity or its effects. Obesity impedes lymphatic flow with consequent lymphoedema. Acanthosis nigricans, the effects of hyperandrogenism, including hirsutism, hidradenitis suppurativa, striae distensae, venous hypertension, intertrigo and skin infections, are all seen more frequently in obese patients [44], as is plantar hyperkeratosis.

Prevention and treatment. The aim of obesity treatment is to achieve and then maintain clinically meaningful weight loss, with the ultimate aim of reducing the risk for, or severity of, obesity-related diseases. Measures directed at improving public health awareness should be given high priority in national efforts. They include: information campaigns, providing opportunities for exercise at school and in the community, making exercise-sparing devices such as escalators less readily available, and establishing bicycle and walking lanes in cities. Despite an increased focus on nutrition, an increased awareness of the energy and fat content of foods, and the availability of various reduced-fat, fat-free and sugar-free food and beverages, obesity continues to increase [45].

Effective therapeutic regimens for treating obesity should incorporate multiple approaches to encourage behavioural change or modification and create strategies to facilitate consistent and long-term follow-through [46]. Numerous options are available [46,47], including reduced-energy diets, physical activity and exercise, behavioural modification, pharmacotherapy and surgery.

The principle for treatment, self-evidently, is to induce a negative energy balance. Short-term weight loss is easy, but long-term weight maintenance after that is unusual [44,48]. The body weight itself is often not the most important problem, unless it is affecting mobility. It is the morbidity associated with the

Table 46.1 Three commonly used sets of criteria for the metabolic syndrome, showing differences.

	WHO	NCEP ATP III	IDF
Required criteria	Insulin resistance or impaired fasting glucose or impaired glucose tolerance or type 2 diabetes plus any 2 of the following:	3 or more of the following:	Central obesity and any 2 of the following:
Central obesity	BMI >30 kg/m^2 or waist to hip ratio >0.9 (men), >0.85 (women)	Waist circumference ≥102 cm (men), ≥88 cm (women)	Waist circumference ≥94 cm (European men), ≥90 cm (Asian men), ≥80 cm (women)
Insulin resistance	Insulin sensitivity < lowest quartile		
Glucose intolerance	Fasting glucose ≥110 mg/dL (6.1 mmol/L) or impaired glucose tolerance or previously diagnosed type 2 diabetes	Fasting glucose ≥110 mg/dL (6.1 mmol/L)	Fasting glucose ≥100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes
Blood pressure	140/90 or above	130/85 or above	130/85 or above
Triglyceride	Triglyceride >150 mg/dL OR	Triglyceride ≥150 mg/dL (1.7 mmol/L)	Triglyceride ≥150 mg/dL (1.7 mmol/L), or specific treatment for this lipid abnormality
HDL cholesterol	HDLc <35 mg/dL (men), and <39 mg/dL (women)	HDLc <40 mg/dL (men), and <50 mg/dL (women)	HDLc <40 mg/dL (1.03 mmol/L) in men and <50 mg/dL (1.29 mmol/L) in women, or specific treatment for this lipid abnormality

WHO, World Health Organization; NCEP, National Cholesterol Education Program; IDF, International Diabetes Federation.

metabolic complications that is of major concern, and this can improve rapidly even after a limited loss of weight. A normal body weight is not necessary, and is often unrealistic in the long term.

Reduced energy intake must be individually tailored to allow normal activities. A deficit of 500–600 kcal (0.210–0.251 mJ) per day is usually well tolerated. Emphasis should be placed on fat intake and on the energy density of food. Involvement of the family is important [49]. A combination of exercise and diet is more effective than either alone [48], and long-term low-intensity exercise such as walking is as effective as high-intensity activities [50]. This is important because most obese patients are unaccustomed to sporting activities and will drop out of vigorous regimens.

Behaviour modification is an important component of all weight loss programmes [51,52]. Frequently, behavioural strategies are targeted toward identifying stimuli that signal unhealthy behaviours such as binge eating, learning about the role of readiness in initiating or continuing positive behaviours [53], and recognizing barriers that may compromise healthy pursuits.

Pharmacological agents may be used in conjunction with diet, exercise and behavioural strategies when non-pharmacological approaches have failed to produce a success. Several appetite-suppressant drugs are approved for weight loss and the reader is referred to authoritative sources on the subject [45]. In general, their use can achieve a weight loss of only 5 kg after 1 year [54]. For overweight children, medications and lifestyle interventions are similarly disappointing [55].

Surgery was once reserved for cases of extreme obesity (BMI over 40 kg/m^2) but is now also being recommended for a BMI over 35 kg/m^2 plus serious obesity-related co-morbid conditions [56]. Vertical gastric banding is the most common procedure. It is the best treatment for long-term weight loss and reduces mortality markedly for diabetes, heart disease and cancer [57].

An excellent review on the aetiology, prevalence and treatment of obesity is by Racette *et al*. [45] and on the particular problems for the adolescent by Jasik and Lustig [29]. With the elucidation of the neuroendocrine regulation of body weight it remains to be seen whether novel molecular compounds might become available in the future, but this should not be at the expense of simple dietary measures and exercise [58].

References

1 Bjorntorp P. Obesity. *Lancet* 1997; **350**: 423–5.

2 National Institutes of Health. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults—the evidence report. *Obes Res* 1998; **6** (Suppl. 2): 51S–209S.

3 Chadwick DJ, Cardew G, eds. *The Origins and Consequences of Obesity*. London: Ciba Foundation/Wiley, 1996.

4 Guillaume M, Lapidus L, Beckers F *et al*. Cardiovascular risk factors in children from the Belgian Luxembourg Province: the Belgian Luxembourg Child Study. *Am J Epidemiol* 1996; **144**: 867–80.

5 Adams KF, Schatzkin A, Harris TB *et al*. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. *N Engl J Med* 2006; **355**: 763–78.

6 Heiat A, Vaccarino V, Krumholz HM. An evidence-based assessment of federal guidelines for overweight and obesity as they apply to elderly persons. *Arch Intern Med* 2001; **161**: 1194–203.

7 Freedman DS, Wang J, Thornton JC *et al*. Racial/ethnic differences in body fatness among children and adolescents. *Obesity (Silver Spring)* 2008; **16**: 1105–11.

8 Bjorntrop P. Visceral obesity: a 'civilisation syndrome'. *Obes Res* 1993; **1**: 206–22.

9 World Health Organization. *Measuring Obesity: Classification and Description of Anthropometric Data* (EUR/ICP/Nut125). Copenhagen: WHO Regional Office for Europe, Nutrition Unit, 1988.

10 Iwao S, Iwao N, Muller DC *et al*. Does waist circumference add to the predictive power of the body mass index for coronary risk? *Obes Res* 2001; **9**: 685–95.

11 Womersley J, Durmin JVGA. A comparison of the skinfold method with extent of 'overweight' and various weight/height relationships in the assessment of obesity. *Br J Nutr* 1977; **38**: 271–84.

12 Ogden CL, Carroll MD, Curtin LR *et al*. Prevalence of overweight and obesity in the United States, 1999–2004. *JAMA* 2006; **295**: 1549–55.

13 Crowther R, Dinsdale H, Rutter H, Kyffin R (South East Public Health Observatory) on behalf of the Association of Public Health Observatories. *Analysis of the National Childhood Obesity Database 2005–06*. Department of Health. http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsStatistics/DH_063565.

14 International Association for the Study of Obesity. *Global prevalence of adult obesity*. http://www.iotf.org/database/documents/GlobalPrevalenceofAdultObesityMay2009pdf.pdf.

15 Prevention and management of the global epidemic of obesity. *Report of the WHO Consultation on Obesity, Geneva, 3–5 June 1997*. Geneva: World Health Organization, 1997.

16 Ji CY, Cheng TO. Prevalence and geographic distribution of childhood obesity in China in 2005. *Int J Cardiol* 2008; **131**: 1–8.

17 World Health Organization. *Global strategy on diet, physical activity and health 2008*. http://www.who.int/dietphysicalactivity/publications/facts/obesity/en/.

18 Flegal KM, Caroll MD, Kuczmarkski RJ *et al*. Over weight and obesity in the United States: prevalence and trends, 1960–94. *Int J Obes* 1998; **22**: 29–47.

19 Kaplan NM. The deadly quartet: upper-body obesity, glucose intolerance, hypertriglyceridemia and hypertension. *Arch Intern Med* 1989; **149**: 1514–20.

20 Bjorntorp P. Metabolic implications of body fat distribution. *Diabetes Care* 1991; **14**: 1132–43.

21 Bays HE, González-Campoy JM, Bray GA *et al*. Pathogenic potential of adipose tissue and metabolic consequences of adipocyte hypertrophy and increased visceral adiposity. *Expert Rev Cardiovasc Ther* 2008; **6**: 343–68.

22 de Ferranti S, Mozaffarian D. The perfect storm: obesity, adipocyte dysfunction, and metabolic consequences. *Clin Chem* 2008; **54**: 945–55.

23 Ranadive SA, Vaisse C. Lessons from extreme human obesity: monogenic disorders. *Endocrinol Metab Clin North Am* 2008; **37**: 733–51.

24 Bouchard C, Tremblay A, Despres JP *et al*. The response to long-term overfeeding in identical twins. *N Engl J Med* 1990; **322**: 1477–82.

25 Barsh GS, Farooqi IS, O'Rahilly S. Genetics of body-weight regulation. *Nature* 2000; **404**: 644–51.

26 Farooqi IS, O'Rahilly S. Genetic factors in human obesity. *Obes Rev* 2007; **8** (Suppl. 1): 37–40.

27 Kuzawa CW, Gluckman PD, Hanson MA. Development perspectives on the origins of obesity. In: Fantuzzi G, Mazzone T, eds. *Adipose Tissue and Adipokines in Health and Disease*. New Jersey: Humana Press, 2007: 207–19.

28 Stettler N, Stallings VA, Troxel AB *et al*. Weight gain in the first week of life and overweight in adulthood: a cohort study of European American subjects fed infant formula. *Circulation* 2005; **111**: 1897–903.

29 Jasik CB, Lustig RH. Adolescent obesity and puberty: the 'perfect storm'. *Ann N Y Acad Sci* 2008; **1135**: 265–79.

30 Diewald L, Dolan MS, Faith MS. Environmental aspects of obesity. In: Fantuzzi G, Mazzone T, eds. *Adipose Tissue and Adipokines in Health and Disease*. New Jersey: Humana Press, 2007: 197–206.

31 Ravussin E. Physiology: a NEAT way to control weight? *Science* 2005; **307**: 530–1.

32 Drolet R, Richard C, Sniderman AD *et al*. Hypertrophy and hyperplasia of abdominal adipose tissues in women. *Int J Obes (Lond)* 2008; **32**: 283–91.

33 Cancello R, Henegar C, Viguerie N *et al*. Reduction of macrophage infiltration and chemoattractant gene expression changes in white adipose tissue of mor-

bidly obese subjects after surgery-induced weight loss. *Diabetes* 2005; **54**: 2277–86.
34 Cancello R, Tordjman J, Poitou C *et al*. Increased infiltration of macrophages in omental adipose tissue is associated with marked hepatic lesions in morbid human obesity. *Diabetes* 2006; **55**: 1554–61.
35 Thalmann S, Meier CA. Local adipose tissue depots as cardiovascular risk factors. *Cardiovasc Res* 2007; **75**: 690–701.
36 Prins JB, Niesler CU, Winterford CM *et al*. Tumor necrosis factor-alpha induces apoptosis of human adipose cells. *Diabetes* 1997; **46**: 1939–44.
37 Sobel BE, Taatjes DJ, Schneider DJ. Intramural plasminogen activator inhibitor type-1 and coronary atherosclerosis. *Arterioscler Thromb Vasc Biol* 2003; **23**: 1979–89.
38 Bays HE, González-Campoy JM, Henry RR *et al*. The Adiposopathy Working Group. Is adiposopathy (sick fat) an endocrine disease? *Int J Clin Pract* 2008; **62**: 1474–83.
39 Sandhofer A, Iglseder B, Paulweber B *et al*. Comparison of different definitions of the metabolic syndrome. *Eur J Clin Invest* 2007; **37**: 109–16.
40 Lee CM, Huxley RR, Woodward M *et al*. Detect-2 Collaboration. Comparisons of metabolic syndrome definitions in four populations of the Asia-Pacific region. *Metab Syndr Relat Disord* 2008; **6**: 37–46.
41 Ford ES. Prevalence of the metabolic syndrome defined by the International Diabetes Federation among adults in the U.S. *Diabetes Care* 2005; **28**: 2745–9.
42 Ford ES, Li C, Zhao G *et al*. Prevalence of the metabolic syndrome among U.S. adolescents using the definition from the International Diabetes Federation. *Diabetes Care* 2008; **31**: 587–9.
43 Wild SH, Byrne CD. The global burden of the metabolic syndrome and its consequences for diabetes and cardiovascular disease. In: Byrne CD, Wild SH, eds. *The Metabolic Syndrome*. Chichester, England: John Wiley & Sons, 2005: 1–43.
44 Yosipovitch G, DeVore A, Dawn A. Obesity and the skin: skin physiology and skin manifestations of obesity. *J Am Acad Dermatol* 2007; **56**: 901–16.
45 Racette SB, Deusinger SS, Deusinger RH. Obesity: an overview of prevalence, etiology, and treatment. *Phys Ther* 2003; **83**: 276–88.
46 National Institute of Health, National Heart, Lung and Blood Institute, North American Association for the Study of Obesity. *The Practical Guide: Identification, Evaluation and Treatment of Overweight and Obesity in Adults.* Bethesda, MD: US Department of Health and Human Services, Public Health Service. National Institute of Health, National Heart, Lung and Blood Institute, 2000.
47 Rosenbaum M, Leibel RL, Hirsch J. Obesity. *N Engl J Med* 1997; **337**: 396–407.
48 Black DR, Threlfall WE. Partner weight status and subject weight loss: implications for cost-effective programs and public health. *Addict Behav* 1989; **14**: 279–89.
49 Skender ML. Comparison of a 2-year weight loss trends in behavioral treatments of obesity: diet, exercise and combination interventions. *J Am Diet Assoc* 1996; **96**: 342–6.
50 Despres JP, Lamarche B. Effects of diet and physical activity on adiposity and body fat distribution: implications for the prevention of cardiovascular disease. *Nutr Res Rev* 1993; **6**: 1–23.
51 Wadden TA, Foster GD. Behavioural treatment of obesity. *Med Clin North Am* 2000; **84**: 4441–61.
52 Brownell KD. Diet, exercise and behavioural intervention: the non-pharmacological approach. *Eur J Clin Invest* 1998; **28**: 19–22.
53 King AC, Frey-Hewitt B, Drecon DM *et al*. Diet against exercise in weight maintenance: effects of minimal intervention strategies and long-term outcomes in man. *Arch Intern Med* 1989; **149**: 2741–6.
54 Li Z, Maglione M, Tu W *et al*. Meta-analysis: pharmacologic treatment of obesity. *Ann Intern Med* 2005; **142**: 532–46.
55 McGovern L, Johnson JN, Paulo R *et al*. Clinical reviews: treatment of pediatric obesity: a systematic review and meta-analysis of randomized trials. *J Clin Endocrinol Metab* 2008; **93**: 4600–5.
56 Bult MJ, van Dalen T, Muller AF. Surgical treatment of obesity. *Eur J Endocrinol* 2008; **158**: 135–45.
57 Adams TD, Gress RE, Smith SC *et al*. Long-term mortality after gastric bypass surgery. *N Engl J Med* 2007; **357**: 753–61.
58 Foster-Schubert KE, Cummings DE. Emerging therapeutic strategies for obesity. *Endocr Rev* 2006; **27**: 779–93.

Cellulite

Cellulite is an alteration of the topography of the skin that occurs mainly in women in the pelvic region, the limbs and abdomen. It is characterized by a dimpled appearance if mild, and lumpy skin if severe, and affects 85% of post-pubescent females [1]. No formal quality of life study has been performed on this, probably normal, secondary sex characteristic but treatment improves self-esteem and the size of the anticellulite market attests to patients' concerns [2].

Many authors confuse cellulite with obesity. However, this is incorrect; in obesity only adipocyte hypertrophy and hyperplasia occurs [3], whereas in cellulite there are several structural alterations in the dermis, in the local microcirculation and within the adipocytes. These may result in further morphological, histochemical and biochemical modifications [4–7].

Cellulite may be classified in at least two ways. One classification divides cellulite into four stages according to the histopathological and clinical changes [3]:

Grade 1. The patient has no symptoms and there are no clinical alterations. Histologically, there may be an increased thickness of the areolar layer, increased capillary permeability and microhaemorrhages.

Grade 2. There are no obvious changes in the skin at rest, but after skin compression or muscular contraction small dimples, local pallor, decreased temperature and decreased elasticity may be evident.

Grade 3. A padded skin or an orange peel appearance is evident at rest, and there is a slight feeling of granularity in the deeper parts of the skin on palpation, which may be associated with some pain. At this stage, there is the beginning histologically of fatty tissue destruction and the formation of micronodules.

Grade 4. This stage is characterized by changes seen in grade 3 but with more visible palpable and painful nodules and an obvious wavy appearance of the skin surface. Histopathologically, the lobular structure of the fatty tissue has disappeared and some nodules are encapsulated by dense connective tissue and there may be much fibrosis.

Cellulite may also be classified by the consistency of the skin—being hard, flaccid, oedematous or mixed [8]. Hard cellulite is observed in young women who perform regular physical activity. The appearance is of compact, firm tissues and is not changed according to position. Flaccid cellulite is characteristically found in inactive women, especially if they have suddenly lost weight. In contrast, oedematous cellulite presents as an increased volume of the entire affected limb, and is associated with depression of the tissue to fingertip palpation, which persists when the finger is removed.

Aetiology. Just what precisely triggers the histopathological and clinical changes of cellulite is poorly understood. Hormonal factors may play a predisposing or aggravating part. Oestrogen is probably the most important hormone. Evidence for oestrogen involvement includes the fact that cellulite predominantly occurs in females, the onset of the disease after puberty, and aggravation of

the condition during pregnancy, menstruation and with oestrogen therapy [9].

A genetic predisposition may also be important. White women tend to be more prone to cellulite than Asian or Black women and Latin women develop cellulite on the hips while Anglo-Saxon women develop cellulite on the abdomen.

Sedentary lifestyle contributes to the aggravation of cellulite as a consequence of a decrease in muscle mass, and the consequent decreased muscular pumping mechanism in the lower limbs inhibiting venous return. Obesity contributes to the problem by increasing the fatty mass. Factors that act as a mechanical barrier to the venous return are also likely to be important; tight clothes and pregnancy may be important in this context.

Traditionally, three major theories have been put forward to explain the abnormalities: oedema in the fat lobules; alterations in the fat microcirculation; and a structural conformation of the subcutaneous tissue that is different in women compared to men. Whilst there is evidence for all three, it is uncertain if these are the effects or the cause. MRI scanning has provided support for the anatomical case [10,11]. 'Pseudoherniation' of fat pushing into the lower layers of dermis is more prevalent in cellulite, perhaps due to a thinner dermis in women compared to men. Women appear to have a different fibrous septal structure in the upper layers of subcutaneous fat, tending to have more vertical bands and pillars than the oblique criss-crossing bands seen in men, which contain smaller fat chambers. In cellulite there would appear to be fewer vertical septal bands with some bands and pillars appearing thickened and some thinned. The histology of some of these thinner bands has appeared similar to the elastic tissue changes seen in cutaneous stretch marks [12]. What is unknown is what role the multifunctioning adipocyte has played in the development of this apparent remodelling process [13].

Treatment. Because of the multifactorial pathogenesis of cellulite, there are numerous therapeutic approaches—especially because many of the treatments are much less than optimal in their success. Treatments include reduction in aggravating factors, pharmacological agents, and the use of physical and mechanical methods, ultrasound and lasers.

Attempts to reduce weight, regular exercise and the use of non-hormonal contraceptives need to be encouraged, but weight loss improves the appearance of cellulite only in those with a high starting BMI and aggravates the appearance in those with a low BMI [14]. Several pharmacological agents have been tried, both topical and injectable (mesotherapy), but adequate double-blind, placebo-controlled studies are lacking [15]. Physical therapies, including thermotherapy, pressotherapy and lymphatic massage, have similar drawbacks. Local surgery, so-called subcision, seems effective and works by destroying the thicker fibrous septal bands using the cutting edge of a needle under local anaesthesia [16]. Focused ultrasound is helpful in dissolving fat in body-contouring and may prove useful for cellulite [17].

More recently, radiofrequency devices, such as low-energy diode laser and infra-red systems, have been reported to be of benefit [18–20]. A unipolar radiofrequency device with the capacity to generate heat 15–20 mm into skin produced dermal fibrosis, which might be responsible for the observed good clinical benefit still present after 6 months [21].

References

1 Draelos ZD, Marenus KD. Cellulite. Etiology and purported treatment. *Dermatol Surg* 1997; **23**: 1177–81.

2 Hexsel D, Hexsel CL. Social impact of cellulite and its impact on quality of life. In: Goldman MP, Bacci PA, Leibaschoff G *et al.*, eds. *Cellulite: Pathophysiology and Treatment*. New York: Taylor & Francis, 2006: 1–5.

3 Bray GA. Obesity: basic considerations and clinical approaches. *Disease-a-Month* 1989; **35**: 451–528.

4 Binazzi M, Papini M. Aspetti clinico histomorfologici. In: Ribuffo A, Bartoletti CA, eds. *La Cellulite*. Rome: Salus, 1983: 7–15.

5 Chimenti S, Pranteda G, Cantaresi F *et al*. Aspetti istochuimci. In: Ribuffo A, Bartoletti CA, eds. *La Cellulite*. Rome: Salus, 1983: 17–22.

6 Curri SB. Aspects morpho-histochimiques et biochimiques du tissue adipeux dans la dermo hypodermose cellulitique. *J Med Esth* 1976; **5**: 183.

7 Curri SB. Aspetti biochimici. In: Ribuffo A, Bartoletti CA, eds. *La Cellulite*. Rome: Salus, 1983: 29–36.

8 Bartoletti CA, Gualtierotti R, Rota M *et al*. Utilizzazione dell'estrato di centella asiatica nel trettomento della 'cellulite' edematosa degli arti inferiori. *La Med Est* 1983; **3**: 97–103.

9 Rossi AB, Vergnanini AL. Cellulite: a review. *J Eur Acad Dermatol Venereol* 2000; **14**: 251–62.

10 Querleux B, Cornillon C, Jolivet O *et al*. Anatomy and physiology of subcutaneous adipose tissue by *in vivo* magnetic resonance imaging and spectroscopy: relationships with sex and presence of cellulite. *Skin Res Technol* 2002; **8**: 118–24.

11 Mirrashed F, Sharp JC, Krause V *et al*. Pilot study of dermal and subcutaneous fat structures by MRI in individuals who differ in gender, BMI, and cellulite grading. *Skin Res Technol* 2004; **10**: 161–8.

12 Quatresooz P, Xhauflaire-Uhoda E, Piérard-Franchimont C *et al*. Cellulite histopathology and related mechanobiology. *Int J Cosmet Sci* 2006; **28**: 207–10.

13 Terranova F, Berardesca E, Maibach H. Cellulite: nature and aetiopathogenesis. *Int J Cosmetic Science* 2006; **28**: 157–67.

14 Smalls LK, Hicks M, Passeretti D *et al*. Effect of weight loss on cellulite: gynoid lipodystrophy. *Plast Reconstr Surg* 2006; **118**: 510–6.

15 Wanner M, Avram M. An evidence-based assessment of treatments for cellulite. *J Drugs Dermatol* 2008; **7**: 341–5.

16 Hexsel DM, Mazzuco R. Subcision: a treatment for cellulite. *Int J Dermatol* 2000; **39**: 539–44.

17 Moreno-Moraga J, Valero-Altés T, Riquelme AM *et al*. Body contouring by non-invasive transdermal focused ultrasound. *Lasers Surg Med* 2007; **39**: 315–23.

18 Alster T, Tanzi EL. Extended experience with a novel combination radiofrequency, infrared light and mechanical tissue manipulation device for the treatment of cellulite. *J Cosmetic Laser Ther* 2005; **7**: 81–5.

19 Sadick NS, Mulholland RS. A prospective clinical study to evaluate the efficacy and safety of cellulite treatment using the combination of optical and RF energies for subcutaneous tissue heating. *Journal Cosmetic Laser Ther* 2004; **6**: 187–90.

20 Nootheti PK, Magpantay A, Yosowitz G *et al*. A single center, randomized, comparative, prospective clinical study to determine the efficacy of the Velasmooth system versus the Triactive system for the treatment of cellulite. *Lasers Surg Med* 2006; **38**: 908–12.

21 Goldberg DJ, Fazeli A, Berlin AL. Clinical, laboratory, and MRI analysis of cellulite treatment with a unipolar radiofrequency device. *Dermatol Surg* 2008; **34**: 204–9.

General pathology of adipose tissue: panniculitis [1–11]

Inflammatory disorders of the subcutaneous fat present an important diagnostic challenge to the dermatologist, because the lesions

often develop as subcutaneous nodules or plaques. An adequate diagnostic biopsy is essential as a prerequisite to accurate diagnosis in almost all instances. A larger scalpel incisional biopsy is preferred, which obviously should extend deeply through the subcutis. Conventional punch biopsies (4 mm or smaller) are totally inadequate, as the tissue tapers down to leave little, if any, subcutaneous tissue. However, trephine punches are adequate and provide acceptable cosmetic results [10]. The pathologist may well need to cut serial sections, as some of the panniculitides are characterized by rather focal or even scattered pathological changes, and to look for evidence of damage to larger blood vessels.

Most panniculitides are persistent, lasting for weeks or months. For diagnostic purposes, the biopsy should be taken from an active earlier lesion: erythematous, indurated and usually tender. Although the fat lobules have a rich capillary blood supply closely applied to fat cells, there are no lymphatics and very little intervening connective tissue [11]. Furthermore, the vasculature in the subcutis area is slow flowing. This renders the subcutaneous fat vulnerable to a variety of noxious insults [9]; for example, cold injury or enzymatic damage.

The sequence of cellular events following injury to the subcutis may take weeks or months to fully evolve, and is usually as follows [1,2]:

Neutrophils (eosinophils)
↓
Lymphocytes
↓
Histiocytes (granulomatous 'foamy macrophages')
↓
Fibroblasts (fibrosis)

The histological changes of the granulomatous stage are not necessarily diagnostic. When fat cells are damaged, the liberated lipid undergoes hydrolysis to glycerol and fatty acids, which usually provoke a foreign-body-type granulomatous reaction. Macrophages are attracted and foam cells are produced. After the phase of reaction to released lipocyte products, there is a period of reconstitution, the ease of repair depending on the extent of the initial lipocyte damage and the efficiency of the local circulation.

Atrophy of subcutaneous tissue (lipoatrophy) is a consequence of some types of inflammation in the fat lobules. In other instances, extensive fibrosis is inevitable after damage to subcutis, resulting in the formation of chronic subcutaneous fibrotic nodules.

In certain types of panniculitis, an ongoing slow chain reaction is set up, in which small foci of fat necrosis provoke a peripheral inflammatory reaction, which in itself leads to further peripheral fat necrosis, thus allowing the lesion to spread centrifugally. It is therefore clear that the histological findings will differ, depending on the age of the lesion biopsied.

In difficult cases of panniculitis, it is helpful to submit more than one biopsy from lesions at different stages of their clinical evolution. Polarization of sections should be routinely performed to look for crystalline material, and in certain clinical situations extra tissue should be submitted for bacterial or fungal culture.

Panniculitis may be classified histologically according to whether it is predominantly septal, mixed, or associated with vasculitis, as in the following [1–4]:

1 Septal panniculitis:
- (a) erythema nodosum (see Chapter 50)
- (b) erythema nodosum migrans (see Chapter 50); (subacute nodular migratory paniniculitis)
- (c) eosinophilic panniculitis (this condition may overlap with lobular or mixed panniculitis)

2 Lobular panniculitis:
- (a) relapsing febrile nodular panniculitis (Weber–Christian syndrome)
- (b) idiopathic nodular panniculitis
- (c) lipoatrophic panniculitis (formerly Rothman–Makai syndrome)
- (d) panniculitis associated with crystal deposition—sclerema neonatorum (see Chapter 17), subcutaneous fat necrosis of newborn (see Chapter 17), gout or factitial panniculitis, poststeroid panniculitis, calciphylaxis
- (e) enzymic (pancreatic) panniculitis
- (f) α_1-antitrypsin deficiency panniculitis
- (g) fat necrosis—cold injury, nodular cystic fat necrosis, lipomembranous
- (h) lymphomatous panniculitis
- (i) cytophagic histiocytic panniculitis

3 Mixed panniculitis:
- (a) lupus erythematosus profundus
- (b) scleroderma (fasciitis with eosinophilia, see Chapter 51)
- (c) connective-tissue panniculitis (overlaps with lipoatrophic panniculitis)
- (d) subcutaneous sarcoidosis (see Chapter 61)
- (e) subcutaneous granuloma annulare (see Chapter 60)
- (f) necrobiosis lipoidica (see Chapter 60)
- (g) infective panniculitis (e.g. opportunistic bacterial or fungal infections)
- (h) physical and factitious panniculitis (e.g. sclerosing lipogranuloma, oil granulomas, eosinophilic sclerosing lipogranuloma)
- (i) sclerosing panniculitis (lipodermatosclerosis)
- (j) fasciitis—panniculitis syndromes

4 Panniculitis with vasculitis (see Chapters 49 and 50):
- (a) small-vessel vasculitis—leukocytoclastic vasculitis
- (b) large-vessel vasculitis—polyarteritis nodosa, thrombophlebitis, nodular vasculitis (erythema induratum)
- (c) neutrophilic panniculitis
- (d) oedematous scarring vasculitic panniculitis: hydroa-like lymphoma.

References

1 Black MM. Panniculitis. *J Cutan Pathol* 1985; **12**: 366–80.

2 Black MM. Panniculitis: problems with diagnosis. *Australas J Dermatol* 1988; **29**: 79–84.

3 Requena L, Sánchez Yus E. Panniculitis. I. Mostly septal panniculitis. *J Am Acad Dermatol* 2001; **45**: 163–83.

4 Requena L, Sánchez Yus E. Panniculitis. II. Mostly lobular panniculitis. *J Am Acad Dermatol* 2001; **45**: 325–61.

5 Doyle IA, Connolly S, Winkelmann RK. Cutaneous and subcutaneous inflammatory sclerosis syndromes. *Arch Dermatol* 1982; **118**: 886–90.
6 Eng AM, Aronson JK. Dermatopathology of panniculitis. *Semin Dermatol* 1984; **3**: 1–9.
7 Patterson JW. New findings in the 'third compartment'. *Arch Dermatol* 1987; **123**: 1615–7.
8 Peters MS, Daniel Su WP. Panniculitis. *Dermatol Clin* 1992; **10**: 37–57.
9 Thiers BH. Panniculitis. *Dermatol Clin* 1983; **1**: 537–51.
10 Tok J, Abrahams I, Ravits MA *et al.* Surgical Pearl: the trephine punch for diagnosing panniculitis. *J Am Acad Dermatol* 1996; **35**: 980–1.
11 Ryan TJ. Panniculitis: its pathogenesis and management. In: Champion RH, Pye RJ, eds. *Recent Advances in Dermatology*, Vol. 9. Edinburgh: Churchill Livingstone, 1992: 17–32.

Inflammatory disorders of subcutaneous fat

Septal panniculitis

Erythema nodosum (see Chapter 50)

Although erythema nodosum is the prototype of a septal panniculitis, the inflammatory changes always involve the overlying dermis. In acute lesions, there is oedema of the septae with transudation of neutrophils, and sometimes eosinophils, into the septae and adjacent margin of fat lobules. In older lesions, the infiltrate becomes lymphohistiocytic and finally granulomatous, before the septae became thickened and finally fibrotic. Radial granulomas (Miescher) are often found in the interlobular septae in erythema nodosum [1]. There is still some debate as to whether *erythema nodosum migrans* (subacute nodular migratory panniculitis) [2–4] and the chronic and granulomatous forms of erythema nodosum [5] are variants of the same pathological process. Erythema nodosum migrans tends to be characterized by markedly thickened and fibrotic septae, marked capillary proliferation and a massive granulomatous reaction (with giant cells) along the borders of the widened septae [6].

Eosinophilic panniculitis

Eosinophilic panniculitis is characterized by a prominent infiltration of subcutaneous fat with eosinophils, and has been identified in patients presenting with a variety of associated clinical conditions [7–14].

The inflammatory infiltrate, including eosinophils, occurs principally within the septae but can involve the lobules. The overlying dermis is often involved, closely resembling eosinophilic cellulitis (Wells' syndrome) [9]. Fragmented eosinophilic granules (flame figures) are occasionally seen (Fig. 46.3). The current view of eosinophilic panniculitis is that it is not a disease entity, but it can be principally considered as a reactive process, often associated with a systemic condition [8].

More common causes of eosinophilic panniculitis include arthropod bites, atopic eczema, erythema nodosum, infectious causes (*Gnathostoma*, *Streptococcus*, *Toxocara*) and leukocytoclastic vasculitis [8]. The condition has also been associated with chronic recurrent parotitis [11], lupus panniculitis, morphoea profundus [12] and *Fasciola hepatica* infection [13]. Fortunately, only very rarely is eosinophilic panniculitis associated with malignancy, either leukaemia [14] or a solid tumour [9]. It has been seen in association with trauma and autoinoculation with farm products [15] but may also arise spontaneously [16]. In a case of subcutaneous fat necrosis of the newborn, eosinophilic granules were seen inside giant cells [17].

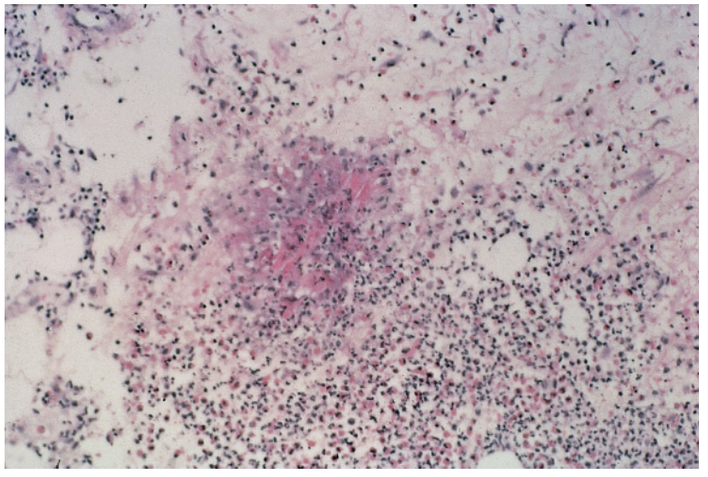


Fig. 46.3 Eosinophilic panniculitis. H&E, × 40.

References

1 Sánchez Yus E, Sanz Vico MD, de Diego V. Miescher's radial granuloma: a characteristic marker of erythema nodosum. *Am J Dermatopathol* 1989; **11**: 434–42.
2 Hannuksela M. Erythema nodosum migrans. *Acta Dermatol Venereol (Stockh)* 1973; **53**: 313–7.
3 Perry HO, Winkelmann RK. Subacute nodular migratory panniculitis. *Arch Dermatol* 1964; **89**: 170–9.
4 Vilanova X, Piñol Aguadé J. Subacute nodular migratory panniculitis. *Br J Dermatol* 1959; **71**: 45–50.
5 Forstrom L, Winkelmann RK. Granulomatous panniculitis in erythema nodosum. *Arch Dermatol* 1975; **111**: 335–46.
6 de Almeida Prestes C, Winkelmann RK, Su WPD. Septal granulomatous panniculitis: comparison of the pathology of erythema nodosum migrans (migratory panniculitis) and chronic erythema nodosum. *J Am Acad Dermatol* 1990; **22**: 477–83.
7 Burket JM, Burket BJ. Eosinophilic panniculitis. *J Am Acad Dermatol* 1985; **12**: 161–4.
8 Peters MS, Su WPD. Panniculitis. *Dermatol Clin* 1992; **10**: 37–57.
9 Winkelmann RK, Frigas E. Eosinophilic panniculitis: a clinicopathologic study. *J Cutan Pathol* 1986; **13**: 1–12.
10 Adame J, Cohen PR. Eosinophilic panniculitis: diagnostic considerations and evaluation. *J Am Acad Dermatol* 1996; **34**: 229–34.
11 Glass LA, Zaghloul AB, Solomon AR. Eosinophilic panniculitis associated with chronic recurrent parotitis. *Am J Dermatopathol* 1989; **11**: 555–9.
12 Peters MS, Su WPD. Eosinophils in lupus panniculitis and morphoea profunda. *J Cutan Pathol* 1991; **18**: 189–92.
13 Perez C, Vives R, Montes M *et al.* Recurrent eosinophilic panniculitis associated with *Fasciola hepatica* infection. *J Am Acad Dermatol* 2000; **42**: 900–2.
14 Marullo S, Dallot A, Carelier-Balloy B *et al.* Subcutaneous eosinophilic necrosis associated with refractory anaemia with an excess of myeloblasts. *J Am Acad Dermatol* 1989; **20**: 320–3.
15 Gómez Rodríguez N, Ortiz-Rey JA, de la Fuente Buceta A *et al.* Auto-induced eosinophilic panniculitis: a diagnostic dilemma. *Ann Med Interne* 2001; **18**: 635–7.
16 Liu Y, Xiao SX, Wang JM *et al.* Eosinophilic panniculitis: report of three cases. *Int J Dermatol* 2006; **45**: 1412–4.
17 Tajirian A, Ross R, Zeikus P *et al.* Subcutaneous fat necrosis of the newborn with eosinophilic granules. *J Cutan Pathol* 2007; **34**: 588–90.

Lobular panniculitis

Relapsing febrile nodular panniculitis

Synonym
- Weber–Christian syndrome

Relapsing febrile nodular panniculitis was first described by Pfeifer in 1892 [1]. The term Weber–Christian syndrome came to be used following the cases reported by Weber [2] and Christian [3]. Weber–Christian syndrome encompasses a febrile disease, characterized by the recurrent formation of single or multiple crops of tender inflammatory nodules in the subcutaneous fat. Because the range of clinical features differed, and the extent of systemic involvement varied, the concept of Weber–Christian syndrome never became popular and the view was put forward that it should not be considered to be a distinct entity [4–6]. The term nodular panniculitis was preferred [5]. Nodular panniculitis is essentially a lobular panniculitis in which fat necrosis develops in the absence of overt vasculitis.

Macrophages ingest fat released from damaged lipocytes, thus producing a characteristic foamy appearance. In some cases, liquefactive nodules appear, which ulcerate and discharge an oily yellow liquid [7]. In others, there is more systemic involvement, which may affect visceral fat or even the myocardium [8].

Nodular panniculitis can affect both adults and children, when it can occur in early infancy [9,10]. However, it must be stressed that nodular panniculitis or Weber–Christian syndrome may not be a distinct disease entity. On further investigation, many cases of nodular panniculitis can be subsequently reclassified depending on their cause; for example, pancreatic panniculitis, α_1-antitrypsin deficiency or cytophagic panniculitis. However, there are undoubtedly some cases of nodular panniculitis, in both children and adults, in which the aetiology remains to be determined.

References

1 Pfeifer V. Über einen Fall von Herdweiser: atrophie des subcutanen Fettgebewes. *Dtsch Arch Klin Med* 1892; **50**: 438–49.
2 Weber FP. A case of relapsing non-suppurative nodular panniculitis showing phagocytosis of subcutaneous fat cells by macrophages. *Br J Dermatol* 1925; **37**: 301–11.
3 Christian HA. Relapsing febrile nodular non-suppurative panniculitis. *Arch Intern Med* 1928; **42**: 338–51.
4 Förström L, Winkelmann RK. Acute panniculitis. *Arch Dermatol* 1977; **113**: 909–17.
5 Macdonald A, Feiwel M. A review of the concept of Weber–Christian panniculitis with a report of five cases. *Br J Dermatol* 1968; **80**: 355–61.
6 White JW, Winkelmann RK. Panniculitis: a review of 30 cases with this diagnosis. *J Am Acad Dermatol* 1998; **39**: 56–62.
7 Hoyas N, Schaffer B, Beerman H. Liquefying nodular panniculitis. *Arch Dermatol* 1965; **94**: 436–9.
8 Wilkinson PJ, Harman RRM, Tribe CR. Systemic nodular panniculitis with cardiac involvement. *J Clin Pathol* 1974; **27**: 808–12.
9 Aronson IK, Zeitz HJ, Variakojir D. Panniculitis in childhood. *Pediatr Dermatol* 1988; **5**: 216–30.
10 Randle SM, Richter MB, Palmer RG *et al.* Panniculitis: a report of four cases and literature review. *Arch Dis Child* 1991; **66**: 1057–60.

Idiopathic nodular panniculitis

An idiopathic condition characterized by recurrent crops of nodular panniculitis. Some cases are accompanied by fever, malaise, abdominal pain and arthritis. As indicated above, the term Weber–Christian syndrome is best avoided. Many cases of nodular panniculitis can now be attributed to specific causes (see below).

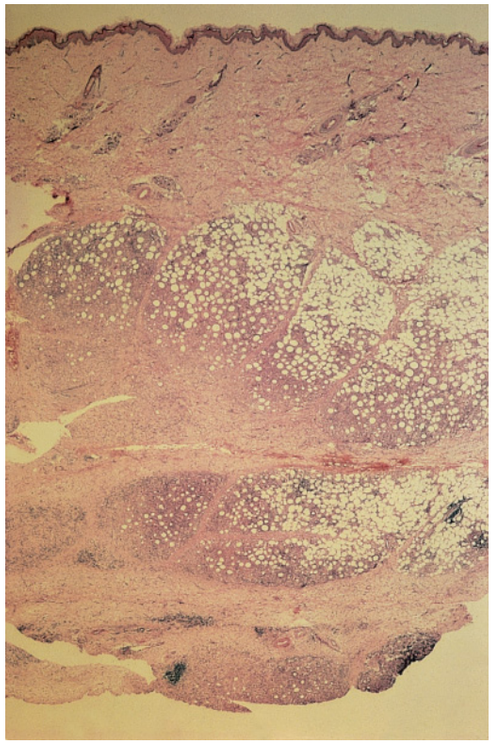


Fig. 46.4 Idiopathic nodular panniculitis. Low-power view showing lobular pattern of panniculitis. H&E, × 2.5.

Pathology. The histological changes are non-specific but the panniculitis is mainly lobular [1] (Fig. 46.4). In the early stages, the fat lobules are infiltrated with acute inflammatory cells, producing a pseudopyogenic reaction. Later, lymphocytes and macrophages appear to ingest the fat released from damaged lipocytes. These lipophages develop a characteristic foamy cytoplasm, producing the typical appearance of a lipophagic granuloma (Fig. 46.5). Healing is by fibrosis, the fibrocytes invading the lobules from the fibrous septae and ultimately producing complete lobular fibrosis.

Clinical features. Approximately 50% of cases of nodular panniculitis are idiopathic [2]. All ages may be affected, but the condition is very rare in childhood [3,4]. The majority of cases are young adult females who develop crops of dull-red, tender, subcutaneous nodules, usually about 1–2 cm in diameter. The lesions tend to be maximal on the lower limbs (Fig. 46.6), although the trunk and face can be affected.

Systemic features including fever, malaise, myalgia, arthralgia and weight loss are often present when there are multiple lesions. Many of the nodules eventually resolve, leaving a pigmented area or an atrophic depression. In a few cases, there may be overlying necrosis with drainage of oily, brownish, serous fluid (Fig. 46.7),

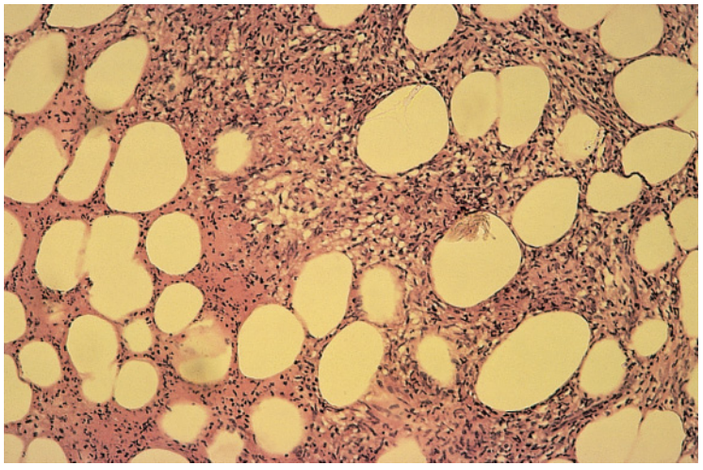


Fig. 46.5 Idiopathic nodular panniculitis: typical appearances of a lipophagic granuloma. H&E, × 40.



Fig. 46.6 Idiopathic nodular panniculitis.

eventually leading to scarring. Rarely, there may be involvement of visceral fat, including the heart, lungs, liver and kidneys, which may lead to death [5]. MRI scanning may disclose inflammation in an internal fat depot such as the retroperitoneum [6].

The laboratory features are non-specific, but there may be anaemia, leukocytosis or leukopenia, thrombocytopenia and a raised erythrocyte sedimentation rate.

Diagnosis. Idiopathic nodular panniculitis has to be distinguished from other forms of panniculitis (see below). It is important to perform repeated laboratory tests for pancreatic disease, autoimmune disease, complement deficiency, α_1-antitrypsin deficiency, and to exclude cytophagic histiocytic panniculitis. The possibility of factitial or infective panniculitis must also be considered.



Fig. 46.7 Idiopathic nodular panniculitis: drainage of serous fluid.

Prognosis. When only subcutaneous fat is involved, the prognosis is good [2]. Some cases recover after a few months, and permanent remission within 2–5 years is usual. Rarely, recurrences may continue for 10 years or longer, but without serious deterioration of the general condition. Exceptionally, the condition can be fatal if there is visceral involvement [5].

Treatment. Once the possibility of systemic disease has been excluded, the treatment is mainly symptomatic. Analgesics may be needed to alleviate pain, and ulceration may need bland aseptic dressings. In severe cases, systemic corticosteroids may be effective, provided adequate dosage (up to 80 mg/day prednisolone) is used for 7–10 days. The dosage should then be slowly tapered over a period of 4–6 weeks. Other treatments that have helped in some cases include antimalarials [7] and thalidomide [8].

Unusual causes of lobular panniculitis resembling idiopathic nodular panniculitis

Increasing numbers of case reports, usually isolated, are appearing that link nodular panniculitis to other illnesses or events. Autoimmune diseases such as Sjögren's syndrome have been linked to a lobular plasma cell panniculitis [9], and ulcerative colitis and myopathy with nodular panniculitis [10].

Infections, for example hepatitis A [11], *Borrelia burgdorferi* [12,13] and brucellosis [14], have also been implicated in the causation of nodular panniculitis. Granulomatous panniculitis has been associated with crescentic glomerulonephritis [15]. Lobular panniculitis has been reported to develop at the site of interleukin-2 injections for treatment of metastatic carcinoma, and to be exacerbated by intravenous use of the same treatment [16]. Delayed expression of an octopus bite [17] and local reaction to glatiramer acetate injection for multiple sclerosis [18] are other causes. Oral administration of the low-calorie artificial sweetener aspartame (Nutra-Sweet®) has been implicated in the causation of lobular panniculitis [19].

References

1 Eng AM, Aronson IK. Dermatopathology of panniculitis. *Semin Dermatol* 1984; **3**: 1–13.

2 Panush RS, Youker RA, Dlesk A *et al.* Weber–Christian disease: analysis of 15 cases and review of the literature. *Medicine* 1985; **64**: 181–91.
3 Aronson IK, Zeitz HJ, Variakojis D. Panniculitis in childhood. *Pediatr Dermatol* 1988; **5**: 216–30.
4 Randle SM, Richter MB, Palmer RG *et al.* Panniculitis: a report of four cases and literature review. *Arch Dis Child* 1991; **66**: 1057–60.
5 Aronson IK, West DP, Variakojis D *et al.* Fatal panniculitis. *J Am Acad Dermatol* 1985; **12**: 535–51.
6 Nakai M, Sato M, Sahara S *et al.* Weber–Christian disease presenting with retroperitoneal panniculitis. *Eur J Radiol Extra* 2006; **60**: 89–92.
7 Sorensen RU, Abramowsky C, Stern RC. Corticosteroid-sparing effect of hydroxychloroquin in a patient with early-onset Weber–Christian syndrome. *J Am Acad Dermatol* 1990; **22**: 1172–4.
8 Eravelly J, Waters MFR. Thalidomide in Weber–Christian disease. *Lancet* 1977; **i**: 251.
9 McGovern TW, Erickson AR, Fitzpatrick JE. Sjögren's syndrome, plasma cell panniculitis and hidradenitis. *J Cutan Pathol* 1996; **23**: 170–4.
10 Nozue M, Ono A, Goto N. Ulcerative colitis associated with Weber–Christian panniculitis and musculitis: a case report. *J Gastroenterol* 1994; **29**: 84–7.
11 Fowler JF Jr, Callen JP. Panniculitis associated with hepatitis. *Cutis* 1983; **32**: 543–7.
12 Haasler D, Zorn J, Zöller L *et al.* Noduläre Panniculitis: eine verlaufsform der Lyme Borreliose? *Hautarzt* 1992; **43**: 134–8.
13 Viljanen MK, Oksi J, Salomaa P *et al.* Cultivation of *Borrelia burgdorferi* from the blood and a subcutaneous lesion of a patient with relapsing febrile nodular nonsuppurative panniculitis. *J Infect Dis* 1992; **160**: 596–7.
14 Tanyel E, Fisgin NT, Yildiz L *et al.* Panniculitis as the initial manifestation of brucellosis: a case report. *Am J Dermatopathol* 2008; **30**: 169–71.
15 Thomashow DF, Huan Z, Sanchez MA *et al.* Granulomatous panniculitis associated with crescentic glomerulonephritis. *Nephron* 1994; **67**: 374–6.
16 Baars JW, Coenen JLLM, Wagstaff J *et al.* Lobular panniculitis after subcutaneous administration of interleukin-2 (IL-2) and its exacerbation during intravenous therapy with IL-2. *Br J Cancer* 1992; **66**: 698–9.
17 Misago N, Inoue T, Narisawa Y. Delayed reaction after an octopus bite showing a giant cell-rich granulomatous dermatitis/panniculitis. *J Cutan Pathol* 2008; **35**: 1068–72.
18 Ball NJ, Cowan BJ, Moore GR *et al.* Lobular panniculitis at the site of glatiramer acetate injections for the treatment of relapsing-remitting multiple sclerosis. A report of two cases. *J Cutan Pathol* 2008; **35**: 407–10.
19 McCauliffe DP, Poitras K. Aspartame-induced lobular panniculitis. *J Am Acad Dermatol* 1991; **24**: 298–300.

Lipoatrophic panniculitis

Synonyms
- Connective tissue panniculitis
- Autoimmune panniculitis

As the name implies, lipoatrophic panniculitis denotes the findings of prominent lipoatrophy. However, the development of lipoatrophy should be considered to be an 'end-stage' process, which is preceded by inflammation in the fat lobules and sometimes the fibrous septae. In the earlier literature, many cases of lipoatrophic panniculitis were considered to have Weber–Christian syndrome or Rothman–Makai syndrome [1]. As the aetiology of lipoatrophic panniculitis is unknown, it is perhaps not surprising that the nomenclature remains confused, and almost certainly there is considerable overlap in these clinical entities. 'Primary' lipophagic panniculitis has been described in adults (Fig. 46.8) [2] and children [3,4], either as an acute benign condition or as a chronic recurrent disabling disease. In children, a granulomatous histopathology can be seen prior to the development of lipoatrophy, for which the term lipophagic panniculitis is used [4]. Connective tissue panniculitis is a rare form of panniculitis, affecting septae and lobules, and leading to prominent lipoatrophy [5] (Fig. 46.9). The condition has been described in female adults and children [6]. Episodes of intense lymphocytic panniculitis lead to lipoatrophy. At various times in the illness, a circulating antinuclear antibody and/or SSB (La) antibodies may be detected [5,6]. The clinical spectrum of lipoatrophic panniculitis is thought to encompass connective tissue panniculitis [7]. Histologically, in connective tissue panniculitis there is no evidence of hyalinization of fat and collagen, which is typical of lupus erythematosus profundus [8]. Various other autoimmune diseases have been reported in association with lipoatrophic panniculitis, including diabetes mellitus, rheumatoid arthritis and Hashimoto's thyroiditis [3]. Lipoatrophic panniculitis has been reported in a very young child with a chromosomal abnormality on chromosome 10q26 [9].



Fig. 46.8 Lipoatrophic panniculitis: recurrent episodes of panniculitis have resolved to leave prominent lipoatrophy on the outer thigh. (Courtesy of St John's Institute of Dermatology, King's College London, UK.)

Treatment. Systemic corticosteroids are effective, but usually only in higher doses. Antimalarial therapy, hydroxychloroquine or chloroquine, is the most effective acceptable treatment [10], but may not be sufficient alone [5,7]. Reconstructive surgery, in the form of vascular pedicles or alloplastic implants, has been successfully used in severe cases of lipoatrophic panniculitis [7].

References

1 Pierini LE, Abulafia J, Wainfeld S. Idiopathic lipogranulomatous hypodermatitis. *Arch Dermatol* 1968; **98**: 290–8.
2 Umbert IJ, Winkelmann RK. Adult lipophagic atrophic panniculitis. *Br J Dermatol* 1991; **124**: 291–5.
3 Billings JK, Milgraum SS, Gupta AK *et al.* Lipoatrophic panniculitis: a possible autoimmune inflammatory disease of fat. *Arch Dermatol* 1987; **123**: 1662–6.

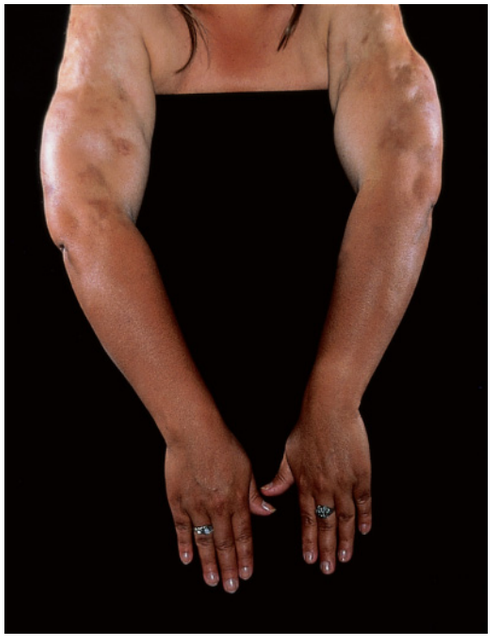


Fig. 46.9 Lipoatrophic (connective tissue) panniculitis: note the dimpled atrophic fat of the upper arms. (Courtesy of Dr M.R. Pittelkow, Mayo Clinic, Rochester, MN, USA.)

4 Winkelmann RK, McEvoy MT, Peters MS. Lipophagic panniculitis of childhood. *J Am Acad Dermatol* 1989; **21**: 971–8.
5 Winkelmann RK, Padilha-Goncalves A. Connective tissue panniculitis. *Arch Dermatol* 1980; **116**: 291–4.
6 Winkelmann RK. Panniculitis in connective tissue disease. *Arch Dermatol* 1983; **119**: 336–44.
7 Handfield-Jones SE, Stephens CJM, Mayou BJ *et al.* The clinical spectrum of lipoatrophic panniculitis encompasses connective tissue panniculitis. *Br J Dermatol* 1993; **129**: 619–24.
8 Sánchez NP, Peters MS, Winkelmann RK. The histopathology of lupus erythematosus panniculitis. *J Am Acad Dermatol* 1981; **5**: 673–80.
9 Martinez A, Malone M, Hoeger P *et al.* Lipoatrophic panniculitis and chromosome 10 abnormality. *Br J Dermatol* 2000; **142**: 1034–9.
10 Shelley WB. Chloroquine-induced remission of nodular panniculitis present for 15 years. *J Am Acad Dermatol* 1981; **5**: 168–70.

Panniculitis associated with crystal deposition

Polarization of skin histology is important in the assessment of any inflammatory or granulomatous type of panniculitis, as it may be the only way to identify crystals readily [1].

Lipid-containing crystals are dissolved out during formalin fixation, but usually leave cleft-like spaces, which often produce a characteristic histology. Needle-shaped clefts are characteristically seen in subcutaneous fat necrosis of the newborn (see Chapter 17), sclerema neonatorum (see Chapter 17) and post-steroid panniculitis. Cholesterol crystals may cause panniculitis, but the crystals are only found in the lumen of smaller blood vessels.

Post-steroid panniculitis [2–5]

Post-steroid panniculitis is now undoubtedly very rare. All the reported cases have been in children, in whom subcutaneous nodules developed 1–13 days after stopping high doses of systemic corticosteroids quickly. The nodules vary in size from 0.5 to 4 cm, and tend to localize in those areas where there is the greatest accumulation of fat from steroid therapy, but typically on the cheeks [6]. Although the nodules appear after the rapid discontinuation of steroids, they are not associated with systemic manifestations of the steroid-withdrawal syndrome. Resolution of the nodules is gradual, occurring over several weeks or months. There is no effective treatment.

The histology of post-steroid panniculitis is very similar to that of subcutaneous fat necrosis of the newborn, in that needle-shaped crystals may be found within lipocytes and histiocytes.

Calcifying panniculitis with renal failure [7]

In patients with chronic renal failure, a chronic alteration of calcium and phosphate metabolism often exists, and secondarily causes hyperparathyroidism. This combination leads to the processes of calciphylaxis and metastatic calcification [8,9]. Whilst calciphylaxis is almost always associated with chronic renal failure patients, many of whom are on long-term dialysis, it is seen in patients with normal renal function [10–12]. Some have, or have had, parathyroid problems, but it has also been reported in association with alcoholic cirrhosis [13] and malignancy, breast cancer and cholangiocarcinoma [14]. The calcification is principally present within smaller and medium-sized arteries. Weenig has suggested that vascular calcification results from the dysregulation of many factors, in particular nuclear factor κ-B (NFκ-B), a key transcription factor in bone mineral homeostasis, activation of which results in bone mineral loss [15]. If this local damage slows blood flow and contributes with other factors such as TNF-α to a local procoagulant state, the addition of a systemic hypercoagulable state, often present in these patients, would result in thrombosis.

Clinical features. The process begins with erythematous tender nodules or plaques that progress to violaceous livedo-like areas, usually located on the thighs (Fig. 46.10), abdomen or buttocks. These lesions tend to increase rapidly in size, progressing to large necrotic ulcers. In the acute stage a necrotic livedo pattern on the upper anterior thigh or lower abdomen in a patient with acute or chronic renal failure is a strong clinical pointer. Any long-term dialysis or chronic renal failure patient with a persisting leg ulcer should be assumed to have calciphylaxis until proved otherwise (Fig. 46.11). One clue is the really severe pain experienced, so extreme that patients cannot keep still. Parathyroid hormone levels are no different from dialysis patients without calciphylaxis, but are often high [16]. Sometimes repeated biopsy is required to find the calcified small vessels. Calcification in vessels is not pathognomonic, as it can be seen incidentally or in arteriopaths. Cutaneous necrosis mimicking calciphylaxis in renal failure has been reported, resulting from oxalate crystal deposition in the vessel wall [17]. Crystals from calcinosis in the fat induced by local heparin injection in renal patients and others are not in the vessel wall [18,19].

Treatment. Treatment should be aimed at preventing the hyperparathyroidism and secondary infection, but usually the disease has a high mortality, in one series only 46% surviving for a year [16]. Intravenous sodium thiosulphate [20] and biphosphonates



Fig. 46.10 Calciphylaxis of the upper thigh in a patient with renal failure.



Fig. 46.11 Calciphylaxis of the lower leg in a patient on long-term dialysis.

have been used with success [21,22] and may prevent the need for parathyroidectomy, which is not always successful in reversing the skin changes.

Gout

Urate crystals are inflammatory, and occasionally lobular panniculitis can be caused by deposition of crystals secondary to hyperuricaemia [23–25] though a raised urate is not always present [26]. Painful, ulcerating nodules on the lower legs is the usual presentation, though only four cases have been described. Crystals may be sampled directly from the chalky ulcer exudate and polarized. Large, pink, amorphous deposits surrounded by a giant cell reaction with little other inflammatory response is seen in the subcutis on histology. One case showed a neutrophilic lobular panniculitis [24]. Urate crystals can be distinguished by their fine, needle-like shape and tendency to form sheaves, but are usually only visible in ethanol-fixed sections.

In a unique case [27] urate crystals were seen intracellularly in adipocytes, mimicking subcutaneous fat necrosis of the newborn and post-steroid panniculitis. They were only visible as tissue had been processed through alcohol. The 6-month-old immunosuppressed patient had a large subcutaneous fungal infection on the cheek caused by fungi of the class *Zygomycetes*. The crystals appeared concomitant with the infection, much as oxalate crystals are seen with *Aspergillus* infections.

Drugs

Lobular panniculitis with crystals can occur following injection of drugs such as meperidine and pentazocine (Fig. 46.12) [28,29].

Crystal-storing histiocytosis

Crystal-storing histiocytosis is a rare condition in which tumorous deposits of histiocytes containing crystalline immunoglobulins are deposited in soft tissue. The condition has been reported to cause panniculitis of Weber–Christian type in a patient with lymphoblastic lymphoma [30].

References

1 Black MM. Panniculitis. *J Cutan Pathol* 1985; **12**: 366–80.
2 Jaffe N, Hann HWL, Vauter GF. Post-steroid panniculitis in acute leukaemia. *N Engl J Med* 1971; **284**: 366–7.
3 Roenigk KH, Haserick JR, Arundell FD. Post-steroid panniculitis. *Arch Dermatol* 1964; **90**: 387–91.
4 Silverman RA, Newman AJ, Le Vine MJ. Post-steroid panniculitis: a case report. *Pediatr Dermatol* 1988; **5**: 92–3.
5 Spagnuolo M, Taranta A. Post-steroid panniculitis. *Ann Intern Med* 1961; **54**: 1181–90.
6 Kwon EJ, Emanuel PO, Gribetz CH *et al*. Poststeroid panniculitis. *J Cutan Pathol* 2007; **34** (Suppl. 1): 64–7.
7 Young DC, Cuozzo DW, Seidman AJ *et al.* Widespread livedo reticularis with painful ulcerations. *Arch Dermatol* 1995; **131**: 786–8.
8 Lowry LR, Tschen JA, Wolf JE *et al.* Calcifying panniculitis and systemic calciphylaxis in an end-stage renal patient. *Cutis* 1993; **51**: 245–7.
9 Lugo-Somolinos A, Sanchez JL, Mendez-Coll J *et al.* Calcifying panniculitis associated with polycystic kidney disease and chronic renal failure. *J Am Acad Dermatol* 1990; **22**: 743–7.
10 Pollock B, Cunliffe WJ, Merchant WJ. Calciphylaxis in the absence of renal failure. *Clin Exp Dermatol* 2000; **25**: 389–92.



Fig. 46.12 Ulceration of the thighs secondary to panniculitis caused by injections of pentazocine. (Courtesy of Dr R.F. Palestine, Mayo Clinic, Rochester, MN, USA.)

11 Goyal S, Huhn KM, Provost TT. Calciphylaxis in a patient without renal failure or elevated parathyroid hormone: possible aetiological role of chemotherapy. *Br J Dermatol* 2000; **143**: 1087–90.

12 Couto FM, Chen H, Blank RD *et al*. Calciphylaxis in the absence of end-stage renal disease. *Endocr Pract* 2006; **12**: 406–10.

13 Ferreres JR, Marcoval J, Bordas X *et al*. Calciphylaxis associated with alcoholic cirrhosis. *J Eur Acad Dermatol Venereol* 2006; **20**: 599–601.

14 Riegert-Johnson DL, Kaur JS, Pfeifer EA. Calciphylaxis associated with cholangiocarcinoma treated with low-molecular-weight heparin and vitamin K. *Mayo Clin Proc* 2001; **76**: 749–52.

15 Weenig RH. Pathogenesis of calciphylaxis: Hans Selye to nuclear factor κ-B. *J Am Acad Derm* 2008; **58**: 458–71.

16 Weenig RH, Sewell LD, Davis MD *et al*. Calciphylaxis: natural history, risk factor analysis, and outcome. *J Am Acad Dermatol* 2007; **56**: 569–79.

17 Somach SC, Davis BR, Paras FA *et al*. Fatal cutaneous necrosis mimicking calciphylaxis in a patient with type I primary hyperoxaluria. *Arch Dermatol* 1995; **131**: 821–3.

18 van Haren FM, Ruiter DJ, Hilbrands LB. Nadroparin-induced calcinosis cutis in renal transplant recipients. *Nephron* 2001; **87**: 279–82.

19 Campanelli A, Kaya G, Masouyé I *et al*. Calcifying panniculitis following subcutaneous injections of nadroparin-calcium in a patient with osteomalacia. *Br J Dermatol* 2005; **153**: 657–60.

20 Subramaniam K, Wallace H, Sinniah R *et al*. Complete resolution of recurrent calciphylaxis with long-term intravenous sodium thiosulfate. *Australas J Dermatol* 2008; **49**: 30–4.

21 Rogers NM, Teubner DJ, Coates PT. Calcific uremic arteriolopathy: advances in pathogenesis and treatment. *Semin Dial* 2007; **20**: 150–7.

22 Hanafusa T, Yamaguchi Y, Tani M *et al*. Intractable wounds caused by calcific uremic arteriolopathy treated with bisphosphonates. *J Am Acad Dermatol* 2007; **57**: 1021–5.

23 Niemi KM. Panniculitis of the legs with urate crystal deposition. *Arch Dermatol* 1977; **113**: 655–6.

24 Le Boit PE, Schneider S. Gout presenting as lobular panniculitis. *Am J Dermatopathol* 1987; **9**: 334–8.

25 Snider AA, Barsky S. Gouty panniculitis: a case report and review of the literature. *Cutis* 2005; **76**: 54–6.

26 Dahiya A, Leach J, Levy H. Gouty panniculitis in a healthy male. *J Am Acad Derm* 2007; **57**: S52–S54.

27 Vernon SE, Dave SP. Cutaneous zygomycosis associated with urate panniculitis. *Am J Dermatopathol* 2006; **28**: 327–30.

28 Forström L, Winkelmann RK. Factitial panniculitis. *Arch Dermatol* 1974; **110**: 747–50.

29 Harisdangkul V. Factitial panniculitis. *Illinois Med J* 1978; **154**: 358–60.

30 Harada M, Shimada M, Fukayama M *et al*. Crystal-storing histiocytosis associated with lymphoplasmacytic lymphoma mimicking Weber–Christian disease: immunohistochemical, ultrastructural and gene-rearrangement studies. *Hum Pathol* 1996; **27**: 84–7.

Enzymic panniculitis

Synonym

- Pancreatic panniculitis [1]

Clinically, enzymic panniculitis overlaps closely with nodular panniculitis (Weber–Christian type) and leads to foci of subcutaneous fat necrosis. Systemic features are quite common, including arthritis, pleural effusions and ascites. The erythematous subcutaneous nodules tend to be present in the distal part of the extremities (often around periarticular areas). In milder cases, the nodule(s) can be single and resolve without ulcerating [2], mimicking erythema nodosum (Fig. 46.13), but usually they evolve into sterile necrotic abscesses, which spontaneously ulcerate and exude a thick, brown, oily material, which represents adipose tissue that has undergone liquefaction necrosis (Fig. 46.14).

Subcutaneous fat necrosis affects 2–3% of all patients with diseases of the pancreas [3]. It appears that all three pancreatic enzymes (lipase, trypsin and amylase) are needed to induce fat necrosis [4]. In 40% of cases associated with pancreatic-induced subcutaneous fat necrosis, the skin lesions were the presenting feature [5]. Monoarticular or oligoarticular arthritic symptoms are common, and may also precede diagnosis of pancreatic disease [6]. The nature of the pancreatic pathology can vary widely. Surgical correction of an anatomical ductal anomaly [7] or pancreatic pseudocyst [8] can result in complete resolution of panniculitis.

The syndrome has been described in post-traumatic pancreatitis [9], acute and chronic pancreatitis [10] and pancreatic carcinoma [1]. CT scanning can be useful in delineating the pancreatic lesion, as well as outlining areas of subcutaneous fat necrosis [11]. Rarely, acute panniculitis can be associated with a high urinary amylase excretion in the absence of overt pancreatic disease [12]. The association of subcutaneous fat necrosis with pancreatic disease has been reported in systemic lupus erythematosus [13].

Pancreatic panniculitis has been reported in association with primary human immunodeficiency virus (HIV) infection and a haemophagocytic syndrome [14], and in pancreatitis associated with hypertriglyceridaemia [15].

The histological changes of pancreatic panniculitis are unique but rarely encountered. Focal fat necrosis in the lobules occurs, which is probably initiated by circulating enzymes (Fig. 46.15). A characteristic coagulative necrosis of lipocytes ensues, which leads to ghosts of lipocytes and varying degrees of calcification [1]. In older lesions, fat necrosis and 'ghost' lipocytes become less prominent, and are replaced by a granulomatous infiltrate with Langhans' giant cells [1] (Fig. 46.16). In the very early stages of pancreatic panniculitis, a septal pattern of inflammatory involvement has been described [16].

The treatment of pancreatic panniculitis is primarily supportive and dependent on the underlying pancreatic pathology. Occasionally, complete resolution of symptoms occurs when gallstones are removed [17] or when an anatomical ductal anomaly has been divided [7]. Usually, the prognosis is gloomy. In a review of 27 patients with pancreatic panniculitis, all eight cases with pancreatic carcinoma and 42% of the 19 patients with pancreatitis died of their disease [18].

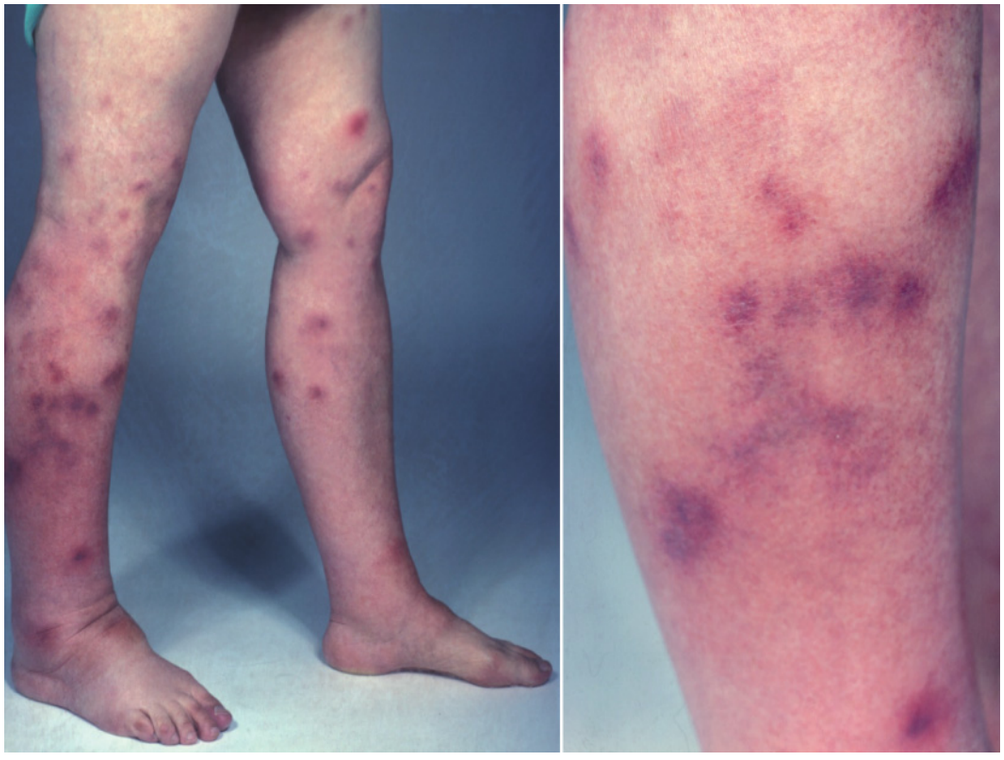


Fig. 46.13 Enzymic (pancreatic) panniculitis: transient nodules after cholecystitis mimicking erythema nodosum.



Fig. 46.14 Enzymic (pancreatic) panniculitis: suppurative nodules occurring around the ankles in a patient with pancreatic carcinoma.

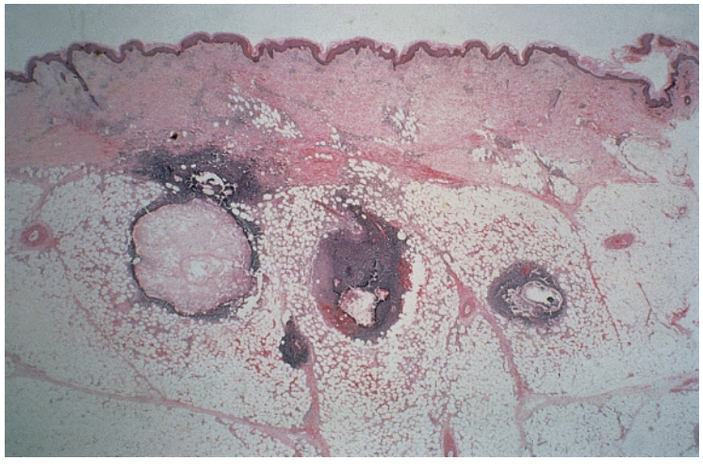


Fig. 46.15 Enzymic (pancreatic) panniculitis: low-power view showing foci of fat necrosis in lobules. H&E, × 4.

References

1 Dahl PR, Su WPD, Cullimore KC *et al.* Pancreatic panniculitis. *J Am Acad Dermatol* 1995; **33**: 413–7.

2 Herrera-Sanchez M, Suarez Fernandez R, Gomez Calcerrada MR. Single-nodule pancreatic panniculitis. *Dermatology* 1996; **193**: 269.

3 Sibrack LA, Goutermann IH. Cutaneous manifestations of pancreatic diseases. *Cutis* 1978; **21**: 763–8.

4 Panabokké RG. An experimental study of fat necrosis. *J Pathol Bacteriol* 1958; **75**: 319–31.

5 Hughes SH, Apisarnthanarax P, Mullins F. Subcutaneous fat necrosis associated with pancreatic disease. *Arch Dermatol* 1975; **111**: 506–10.

6 Saag KG, Niemann TH, Warner CA *et al.* Subcutaneous pancreatic fat necrosis associated with acute arthritis. *J Rheumatol* 1992; **19**: 630–2.

7 Haber RM, Assaad DM. Panniculitis associated with a pancreas division. *J Am Acad Dermatol* 1986; **14**: 331–4.

8 Millns JL, Evans HL, Winkelmann RK. Association of islet cell carcinoma of the pancreas with subcutaneous fat necrosis. *Am J Dermatopathol* 1979; **1**: 273–80.

9 Lee MS, Lowe PM, Nevell DF *et al.* Subcutaneous fat necrosis following traumatic panniculitis. *Australas J Dermatol* 1995; **36**: 196–8.

10 Cheng KS, Stansby G, Law N *et al.* Recurrent panniculitis as the first clinical manifestation of recurrent acute pancreatitis to cholelithiasis. *J R Soc Med* 1996; **89**: 106.

11 Patel JC, Robertson EM. Computed tomography appearances of acute pancreatitis presenting as polyarthropathy with subcutaneous fat necrosis. *Scot Med J* 1993; **38**: 183–4.

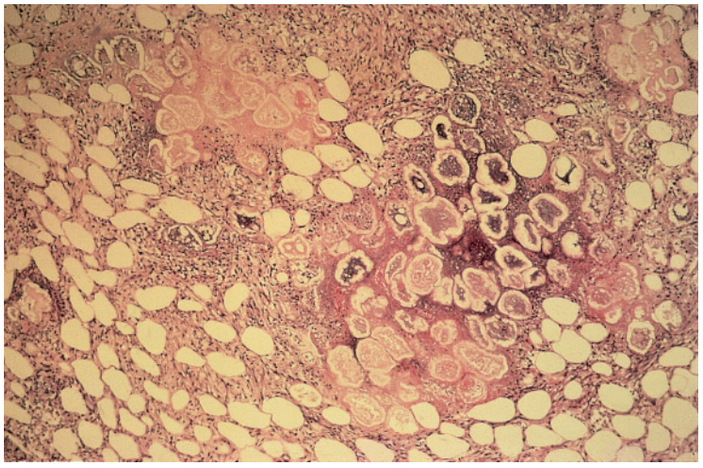


Fig. 46.16 Enzymic (pancreatic) panniculitis: coagulative necrosis of lipocytes, associated with ghosts of lipocytes and focal calcification. H&E, × 40.

12 Förström L, Winkelmann RK. Acute, generalised panniculitis with amylase and lipase in the skin. *Arch Dermatol* 1975; **111**: 497–502.

13 Cutlan RT, Wesche WA, Jenkins SJ III *et al.* A fatal case of pancreatic panniculitis presenting in a young patient with systemic lupus. *J Cutan Pathol* 2000; **27**: 466–71.

14 Martinez-Escribano JA, Pedro F, Sabater V *et al.* Acute exanthem and pancreatic panniculitis in a patient with primary HIV infection and haemophagocytic syndrome. *Br J Dermatol* 1996; **134**: 804–7.

15 Suwattee P, Cham PM, Pope E *et al.* Pancreatic panniculitis in a 4-year-old child with nephrotic syndrome. *Pediatr Dermatol* 2007; **24**: 659–60.

16 Ball NJ, Adams SPA, Marx LH *et al.* Possible origin of pancreatic fat necrosis as a septal panniculitis. *J Am Acad Dermatol* 1996; **34**: 362–4.

17 Riaz AA, Smith F, Phylactides L *et al.* Panniculitis complicating gallstone pancreatitis with subsequent resolution after therapeutic endoscopic retrograde cholangiopancreatography. *Br J Dermatol* 2000; **143**: 1332–3.

18 Potts DE, Mass MF, Iseman MD. Syndrome of pancreatic disease, subcutaneous fat necrosis and polyserositis. *Am J Med* 1975; **58**: 417–23.

α_1-Antitrypsin-deficiency panniculitis (MIM +107400)

Subcutaneous panniculitis simulating Weber–Christian syndrome may be associated with deficiency of α_1-protease inhibitor (α_1-antitrypsin) [1].

Aetiology. Severe deficiency of this important inhibitor in the blood is inherited as the ZZ phenotype, which occurs in about 1 in 2500 people [2]. Severe deficiencies of α_1-antitrypsin can be associated with emphysema, hepatitis, cirrhosis, vasculitis, urticaria, angio-oedema and panniculitis.

The alleles of the gene involved are measured by electrophoretic ability and divided into medium (M), slow (S) and very slow (Z). MM is normal. Homozygous deficiency with phenotype ZZ is most commonly associated with panniculitis, although heterozygous deficiency with phenotype MZ has also been implicated [2,3] as has SS [4]. Patients with the MM phenotype have normal α_1-antitrypsin blood levels, whilst those with ZZ have the lowest.

α_1-Antitrypsin inhibits trypsin activity, but it is also active against neutrophil elastase, pancreatic elastase, serine proteases, collagenase, factor VIII and kallikrein [5].

The exact pathogenesis of the panniculitis is obscure, but deficiency of α_1-antitrypsin could accelerate the activation of lymphocytes and phagocytes, thus producing severe inflammation as well as tissue necrosis secondary to protease action.



Fig. 46.17 Severe suppurative panniculitis secondary to deficiency of α_1-antitrypsin. (Courtesy of Dr M.R. Pittelkow, Mayo Clinic, Rochester, MN, USA.)

Pathology. Characteristically, the panniculitis is severely necrotic and suppurative, involving lobules and septae. Vasculitis, haemorrhage or phlebothrombosis can occur in areas of severe inflammation. The end result can be extensive liquefactive necrosis of the dermis and fibrous septae in the subcutis, leading to transepidermal elimination of necrotic material. Even so, large areas of normal fat can be found adjacent to necrotic lobular and septal areas, which contain abundant polymorphonuclear leukocytes and macrophages [6]. In the earliest stage of inflammation, splaying of neutrophils between collagen bundles in the reticular dermis has been noted [7].

Clinical features. The age of onset of the panniculitis ranges from infancy to old age. Early lesions may resemble a cellulitis, as has been described in Marshall's syndrome (Sweet's syndrome leading to acquired cutis laxa), which has been reported to be associated with α_1-antitrypsin deficiency, and may represent part of the disease spectrum [8]. A clue to the diagnosis of α_1-antitrypsin deficiency is that the ulcerative lesions occur predominantly on the trunk and proximal extremities [2] (Fig. 46.17). The clinical findings of ulcerative panniculitis, combined with the histological findings of acute inflammation, necrosis and haemorrhage, certainly justify investigation of α_1-antitrypsin blood levels. Some of the lesions may be precipitated by trauma, and can be exacerbated by surgical debridement [6]. Even cryosurgery has been implicated [9].

Treatment. Dapsone [10] or doxycycline [11] can be very effective in controlling panniculitis [2,10], while systemic steroids, antimalarials and immunosuppressive drugs often give an inconsistent response. For patients with more severe manifestations of disease (e.g. emphysema, lung fibrosis and liver failure), replacement with weekly intravenous α_1-antitrypsin (Prolastin®) offers a valuable treatment [2]. Each patient requires approximately 10 g/month; the treatment is expensive and not licensed everywhere [12], but may be life-saving even for patients with panniculitis [13].

References

1 Warter J, Storck D, Grosshans E *et al.* Syndrome de Weber–Christian associé à un déficit en α_1-antitrypsine: enquête familiale. *Ann Med Interne (Paris)* 1972; **123**: 877–82.
2 Smith KC, Pittelkow MR, Su WPD. Panniculitis associated with severe α_1-antitrypsin deficiency. *Arch Dermatol* 1987; **123**: 1655–61.
3 Hendrick SJ, Silvermann AK, Solomon AR *et al.* α_1-Antitrypsin deficiency associated with panniculitis. *J Am Acad Dermatol* 1988; **18**: 684–92.
4 Pinto AR, Maciel LS, Carneiro F *et al.* Systemic nodular panniculitis in a patient with alpha-1 antitrypsin deficiency (PiSS phenotype). *Clin Exp Dermatol* 1993; 18: 154–5.
5 Su WPD, Smith KC, Pittelkow MR *et al.* α_1-Antitrypsin deficiency panniculitis: a histopathologic and immunopathologic study of four cases. *Am J Dermatol* 1987; **9**: 483–90.
6 Smith KC, Su WPD, Pittelkow MR *et al.* Clinical and pathologic correlations in 96 patients with panniculitis, including 15 patients with deficient levels of α_1-antitrypsin. *J Am Acad Dermatol* 1989; **21**: 1192–6.
7 Geller JD, Su WPD. A subtle clue to the histopathologic diagnosis of early α_1-antitrypsin deficiency panniculitis. *J Am Acad Dermatol* 1994; **31**: 241–5.
8 Hwang ST, Williams ML, McCalmont TH *et al.* Sweet's syndrome leading to acquired cutis laxa (Marshall's syndrome) in an infant with α_1-antitrypsin deficiency. *Arch Dermatol* 1995; **131**: 1175–7.
9 Linares-Barnios M, Conejo-Min JS, Artola Igarza JL *et al.* Panniculitis due to α_1-antitrypsin deficiency induced by cryosurgery. *Br J Dermatol* 1998; **138**: 552–3.
10 Irvine C, Neild V, Stephens C *et al.* α_1-Antitrypsin deficiency panniculitis. *J R Soc Med* 1990; **83**: 743–4.
11 Chng WJ, Henderson CA. Suppurative panniculitis associated with α_1-antitrypsin deficiency (PiSZ phenotype) treated with doxycycline. *Br J Dermatol* 2001; **144**: 1282–3.
12 Ortiz PG, Skov BG, Benfeldt E. Alpha1-antitrypsin deficiency-associated panniculitis: case report and review of treatment options. *J Eur Acad Dermatol Venereol* 2005; **19**: 487–90.
13 Chowdhury MM, Williams EJ, Morris JS *et al.* Severe panniculitis caused by homozygous ZZ alpha1-antitrypsin deficiency treated successfully with human purified enzyme (Prolastin). *Br J Dermatol* 2002; **147**: 1258–61.

Fat necrosis

Fat necrosis is often an important accompanying feature in panniculitis, and can be prominent enough and sufficiently distinctive to merit separate description. Insults to the fat, including cold injury [1] or trauma [2], are well known to cause fat necrosis, often when there is accompanying venous insufficiency in the lower legs.

Cold panniculitis

Synonym
- Adiponecrosis e frigore (Haxthausen's disease) [1]

Cold panniculitis is a form of localized panniculitis that results from cold injury to subcutaneous fat.

Aetiology. The condition has been reported in neonates [2], children [1,3] and adults, notably as a consequence of ice cubes [4], ice packs [2] or exposure to mountain rivers [4,5] or freezing air temperatures, particularly in adults with a chilblain-type of circulation [6]. Cold panniculitis of the thighs or buttocks may occur in skiers or horse riders who wear inadequate clothing [6], although in this situation perniosis is more common than true panniculitis histologically [7]. Children sucking ice lollies (popsicles) can induce cold panniculitis in the facial subcutaneous tissues [8].



Fig. 46.18 Cold panniculitis: erythematous nodular area on the malar region of a 6-month-old infant which developed after exposure to a very cold wind. (Courtesy of Dr D.J. Atherton, St John's Institute of Dermatology, King's College London, UK.)

Pathology. The early features show a perivascular lymphohistiocytic infiltrate at the dermal–subcutaneous junction with established lesions showing a lobular panniculitis with a mixed infiltrate [5].

Clinical features. Some 48–72 h after cold exposure, the affected areas become indurated with an ill-defined margin. The inflamed skin may be red or bluish, but the diagnostic test is that the area is cold to the touch (Fig. 46.18). The subject may complain of a cold sensation or a dull ache. If the area is kept warm, the subcutaneous plaques slowly soften and resolve over weeks without scarring.

Differential diagnosis. The clinical appearances may resemble other forms of panniculitis (especially erythema induratum) but can usually be distinguished by the location, history of prior cold exposure and being cold to the touch.

Treatment. Cold panniculitis resolves spontaneously if further exposure to cold injury is avoided. In horse riders, tight jeans should be replaced by several layers of looser and thicker clothing. If the limb becomes thoroughly chilled, rapid rewarming should be avoided. Vasodilators tend not to be helpful [9]. One case had a dramatic response to tetracycline which was also effective prophylactically [10].

References

1 Haxthausen H. Adiponecrosis e frigore. *Br J Dermatol* 1941; **53**: 83–9.
2 Ter Poorten JC, Hebert AA, Ilkiw R. Cold panniculitis in a neonate. *J Am Acad Dermatol* 1995; **33**: 383–5.
3 Baruchin AM, Scharf S. Cold panniculitis in children (Haxthausen's disease). *Burns Incl Thermal Injury* 1988; **14**: 51–2.
4 Price RD, Murdoch DR. Perniosis (chilblains) of the thigh: report of five cases, including four following river crossings. *High Alt Med Biol* 2001; **2**: 535–8.
5 Solomon LM, Beerman H. Cold panniculitis. *Arch Dermatol* 1963; **88**: 897–900.
6 Beacham BE, Cooper PH, Buchanan S *et al.* Equestrian cold panniculitis in women. *Arch Dermatol* 1980; **116**: 1025–7.
7 Wall JM, Smith NP. Perniosis: a histopathological review. *Clin Exp Dermatol* 1981; **6**: 263–71.

8 Day S, Klein BL. Popsicle panniculitis. *Pediatr Emerg Care* 1992; **8**: 91–3.
9 Dowd PM. Cold-related disorders. *Prog Dermatol* 1986; **20**: 1–8.
10 Aroni K, Aivaliotis M, Tsele E *et al*. An unusual panniculitis appearing in the winter with good response to tetracycline. *J Dermatol* 1998; **25**: 677–81.

Nodular cystic fat necrosis [1]

Synonym
- Encapsulated fat necrosis [2]

The term denotes a characteristic form of encapsulated subcutaneous fat necrosis that presents as solitary or multiple subcutaneous nodules.

Aetiology. Early lesions begin as lobules of adipose tissue, which, because of compromised blood supply, often following trauma, become separated from the surrounding tissue [3]. These lobules subsequently become surrounded by thin fibrous tissue, and remain as encapsulated necrotic tissue or later undergo dystrophic calcification.

Pathology. The lesions are totally or nearly totally encapsulated, showing massive fat necrosis with preservation of the outlines of non-nucleated adipocytes, usually with little in the way of inflammatory changes. Fibrous septae within the lesion, and dystrophic calcification, tend to be seen in older lesions. Focal or extensive lipomembranous changes may coexist [4,5].

Clinical features. The painless lesions occur often on the lower legs of healthy adolescent boys or middle-aged women. The lesions can be solitary or multiple, often mobile, and varying from 2 to 35 mm in diameter, though 'giant-sized' cases 15–18 cm have been reported [4,6]. Multiple lesions have been described in both systemic lupus erythematosus and systemic sclerosis [7,8]. Preceding trauma is present in about 30% of cases. The nodules may be present for several weeks to years before excision. During surgical removal, a smooth-walled cyst within the subcutaneous fat containing solitary or multiple, free-floating or attached nodules is usually found. Nodular cystic fat necrosis is probably not uncommon, but not readily recognized. Similar changes in the fat have been reported within the abdominal cavity [9] or within the abdominal wall [10]. Some authors take the view that encapsulated angiolipomas and encapsulated lipomas are variants of nodular cystic fat necrosis, with a variable degree of vascularity [2,11].

Differential diagnosis. This includes lipoma, angiolipoma, pancreatic fat necrosis and membranous fat necrosis.

References

1 Przyjemski CJ, Schuster SR. Nodular-cystic fat necrosis. *J Pediatr* 1977; **91**: 605–7.
2 Kiryu H, Rikihisa W, Furue M. Encapsulated fat necrosis: a clinicopathological study of eight cases and a literature review. *J Cutan Pathol* 2000; **27**: 19–23.
3 Hurt MA, Santa Cruz DJ. Nodular-cystic fat necrosis. *J Am Acad Dermatol* 1989; **21**: 493–8.
4 Felipo F, Vaquero M, del Agua C. Pseudotumoral encapsulated fat necrosis with diffuse pseudomembranous degeneration. *J Cutan Pathol* 2004; **31**: 565–7.
5 Pujol RM, Wang CY, Gibson LE *et al*. Lipomembranous changes in nodular-cystic fat necrosis. *J Cutan Pathol* 1995; **22**: 551–5.
6 Sonmez E, Safak T, Kecik A. Giant nodular cystic fat necrosis: a report of a rare case. *J Plast Reconstr Aesthet Surg* 2009; **62**: 152–4.
7 Demitsu T, Yoneda K, Iida E *et al*. A case of nodular cystic fat necrosis with systemic lupus erythematosus presenting the multiple subcutaneous nodules on the extremities. *J Eur Acad Dermatol Venereol* 2008; **22**: 885–6.
8 Toritsugi M, Yamamoto T, Nishioka K. Nodular cystic fat necrosis with systemic sclerosis. *Eur J Dermatol* 2004; **14**: 353–5.
9 Lynn TE, Dockerty MB, Waugh JM. A clinicopathological study of the epiploic appendages. *Surg Gynecol Obstet* 1956; **103**: 423–33.
10 Herbert DC, DeGeus J. Post-traumatic lipomas on the abdominal wall. *Br J Plast Surg* 1975; **28**: 303–6.
11 Sahl WJ Jr. Mobile encapsulated lipomas: formerly called encapsulated angiolipomas. *Arch Dermatol* 1978; **114**: 1684–6.

Lipomembranous fat necrosis [1]

Synonym
- Membranocystic fat necrosis

Lipomembranous fat necrosis is a striking and distinctive alteration in adipose tissue that was first described in Nasu–Hakola disease, a genetic disorder characterized by profound membranocystic degeneration of long bones and systemic adipose tissue, with associated progressive sudanophilic leukodystrophy of the brain [2]. Cystic areas of fat necrosis are lined by wavy hyaline acidophilic membranes (Fig. 46.19). Convoluted projections and arabesques of the membranes into the interior of the cysts are prominent [3]. The membranous structures stain brightly with periodic acid–Schiff but are resistant to diastase. Ultrastructurally, the membranes consist of two layers [4].

Changes of lipomembranous fat necrosis can occur as a non-specific reaction pattern in a wide range of autoimmune diseases, including lupus erythematosus [3], diabetes mellitus [3], morphoea [5] and dermatomyositis [6]. It may also be seen in panniculitis induced by chemotherapy [7]. In a clinical and pathological correlation of 1806 biopsies of panniculitis, lipomembranous fat necrosis was only identified in 13 cases [3]. It is now clear that venous stasis and ischaemia are important co-factors [1,3,8,9] in

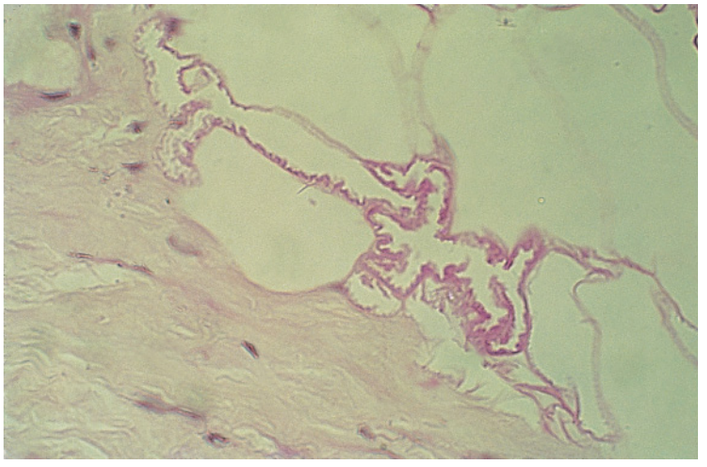


Fig. 46.19 Lipomembranous fat necrosis: the cystic areas are lined by wavy hyaline membranes. Periodic acid–Schiff (PAS) stain, × 25.

the development of lipomembranous fat necrosis. Most cases are seen in middle-aged, obese women who develop venous stasis-associated chronic sclerotic plaques on the lower legs and ankles [1]. The condition therefore overlaps with, or is a part of, sclerosing panniculitis [10], lipodermatosclerosis; some consider it to be a non-specific finding [11].

References

1 Snow JL, Su WPD. Lipomembranous (membrano-cystic) fat necrosis. *Am J Dermatopathol* 1996; **18**: 151–5.
2 Nasu T, Tsukahara Y, Terayama K. A lipid metabolic disease 'membranous lipodystrophy': an autopsy case demonstrating numerous peculiar membrane structures composed of compound lipid in bone and bone marrow and various adipose tissues. *Acta Pathol Jpn* 1973; **23**: 539–58.
3 Alegre VA, Winkelmann RK, Aliaga A. Lipomembranous changes in chronic panniculitis. *J Am Acad Dermatol* 1988; **19**: 39–46.
4 Sueki H, Shinura Y, Fujisawa R *et al*. Ultrastructural study of the histogenesis of membranocystic lesions (Nasu) in diabetes. *J Cutan Pathol* 1986; **13**: 390–401.
5 Snow JL, Su WPD, Gibson LE. Lipomembranous (membranocystic) changes associated with morphoea: a clinicopathologic study of three cases. *J Am Acad Dermatol* 1994; **31**: 246–50.
6 Ishikawa O, Tamura A, Ryuzaki K *et al*. Membranocystic changes in the panniculitis of dermatomyositis. *Br J Dermatol* 1996; **134**: 773–6.
7 Akay OM, Urer SM, Oner U *et al*. Lipomembranous panniculitis in a patient with acute leukemia induced by chemotherapy. *Leuk Res* 2008; **32**: 669–71.
8 Ahn S, Yoo M, Lee S. A clinical and histopathological study of 22 patients with membranous lipodystrophy. *Clin Exp Dermatol* 1996; **21**: 269–72.
9 Machinami R. Incidence of membranous lipodystrophy-like change among patients with limb necrosis caused by chronic arterial obstruction. *Arch Pathol Lab Med* 1984; **108**: 823–6.
10 Jorizzo JL, White WL, Zanolli MD *et al*. Sclerosing panniculitis: a clinicopathologic assessment. *Arch Dermatol* 1991; **127**: 554–8.
11 Fernandoz-López E, Peñá-Peñabad C, Garcia Silva J *et al*. Membranous fat necrosis: a non-specific histological finding. *Eur J Dermatol* 2002; **12**: 82–4.

Panniculitis caused by cellular proliferative disease

Subcutaneous T-cell lymphoma is a rare type of peripheral T-cell lymphoma, which clinically and histologically may mimic benign forms of panniculitis [1]. Erythematous subcutaneous nodules localized to the extremities appear in crops, often accompanied by fever and malaise [1,2]. The lymphoma may behave indolently for months to years, but in most cases it enters an acute aggressive phase in which the majority of patients develop fatal haemophagocytic syndrome [3] or sometimes acute leukaemia [4].

Although low-power histological appearances may resemble benign panniculitis, high-power examination reveals cytological atypia of the malignant lymphoid cells, and immunochemistry studies confirm the T-cell lineage [5]. Angiocentric lymphoma can also cause lobular granulomatous panniculitis [6,7].

Cytophagic histiocytic panniculitis [1,2]

Cytophagic histiocytic panniculitis is the term commonly used to refer to the specific cutaneous manifestation of haemophagocytic syndrome (HPS) [3].

In HPS, there is a histiocytic proliferation throughout the reticuloendothelial system. The proliferation and phagocytic activity of histiocytes in HPS is associated with a proliferation of lymphocytes [3]. Indeed, the primary abnormality in cytophagic histiocytic panniculitis may be a clonal T-cell proliferation [8], though in familial HPS the genetic defect leads to an inability of natural killer cells to kill target cells, allowing lymphocytes and macrophages to proliferate [9].

Aetiology. The proliferation of lymphocytes and histiocytes in HPS may be secondary to microbial, particularly viral, infections (e.g. Epstein–Barr virus [10], cytomegalovirus), may be associated with autoimmune disease such as lupus erythematosus [11,12], or neoplastic in origin [2]. Cytophagic histiocytic panniculitis has been reported as a late complication of allogeneic bone marrow transplantation [13]. HPS has a higher rate of mortality when it is associated with a state of known immunosuppression, and has been reported in HIV-1 infections [2]. Indeed, lymphoma and infection may act as co-factors in the development of HPS. It has been postulated that in HPS cytokine production by the proliferating lymphocytes is important as a stimulus to activate macrophages [2]. In the light of a new classification of subcutaneous T-cell lymphoma [14], and case reviews [15], the histological picture of cytophagic histiocytic panniculitis may be thought of as occurring against a background of infection, in association with other diseases, particularly autoimmune, or in association with malignancy. Malignancy is further subdivided into subcutaneous panniculitis-like T-cell lymphoma of α/β T-cell phenotype (SPTL-AB) and SPTL with a γ/δ T-cell phenotype (SPTL-GD) [14]. Only 20% of SPTL-AB patients exhibit haemophagocytosis in the skin, compared to all SPTL-GD ones. Many SPTL-AB patients also have autoimmune diseases. SPTL-GD patients are now included in the cutaneous γ/δ T-cell lymphoma group (CGD-TCL) because of their poor prognosis.

Pathology [16]. Cytophagic histiocytic panniculitis may begin as a type of regional histiocytosis that primarily involves the subcutis. In most cases, the condition spreads to involve the bone marrow, lymph nodes and reticuloendothelial system. The affected tissues are gradually replaced by a syncytium of histiocytic cells with associated T lymphocytes and plasma cells. The histiocytes are actively cytophagic, so that they become stuffed with white blood cells, red cells, nuclear fragments and platelets, thus giving them a characteristic 'bean-bag' appearance (Fig. 46.20).

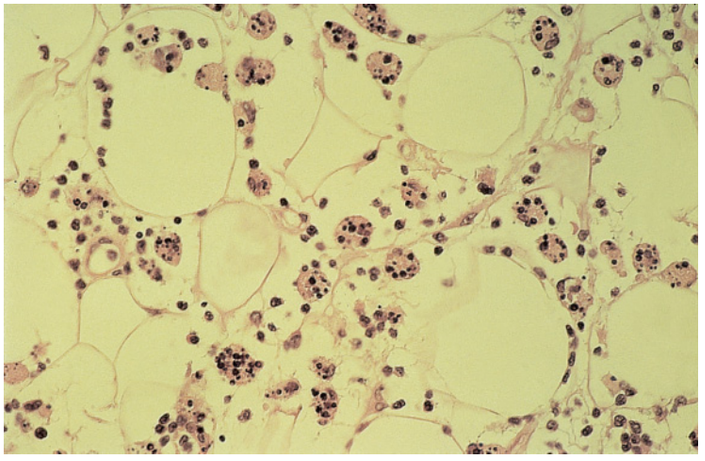


Fig. 46.20 Cytophagic histiocytic panniculitis: many histiocytes are present in the fat lobule, showing the characteristic 'bean-bag' appearance. H&E, × 25.



Fig. 46.21 Cytophagic histiocytic panniculitis: early stage with recurrent crops of lesions. (Courtesy of the Mayo Clinic, Rochester, MN, USA.)



Fig. 46.22 Cytophagic histiocytic panniculitis: note the haemorrhagic nature of this early lesion on the thigh. (Courtesy of St John's Institute of Dermatology, King's College London, UK.)

The histiocytic proliferation is accompanied by lobular panniculitis with areas of fat necrosis, together with massive hyaline necrosis, oedema and haemorrhage [16]. Immunohistochemical studies tend to show that the histiocytic population is benign, whereas the lymphoid element, whether benign or malignant, is composed primarily of T cells [2]. SPTL-AB lymphoma shows a lobular panniculitis with a lymphocytic infiltrate showing cells of variable size and irregularity. Rimming of individual adipocytes by neoplastic T cells is common. The presence of plasma cells points to the possibility of lupus erythematosus profundus being associated, whose gene rearrangement is polyclonal. The immunophenotype of SPTL-AB lymphoma is $CD3^+$, $CD8^+$ and $CD4^-$. Conversely, the infiltrate in SPTL-GD is more extensive and diffuse, and involves the overlying dermis as well as the lobules; there is less rimming, it is more angioinvasive, and is comprised of more medium–large, irregular lymphocytes. The immunophenotype is $CD3^+$, $CD8^-$ and $CD4^-$ and very often $CD56^+$. *In-situ* hybridization for Epstein–Barr virus is negative in both. The diagnosis is confirmed by the presence of the appropriate clonal gene rearrangement [14].

Clinical features. This is a rare condition, which in the past has probably been labelled as systemic nodular panniculitis (Weber–Christian syndrome) [17,18]. The condition begins with crops of red tender nodules, associated with fever (Fig. 46.21). The nodules often develop a purpuric or bruised appearance (Fig. 46.22). The condition can be acute, or chronic with a febrile course associated with anaemia and pancytopenia. More severe cases tend to display weight loss, thrombocytopenia, raised liver enzymes, serosal effusions and hepatosplenomegaly [17–19].

Most patients have a progressive form of the disease, which is ultimately fatal. The fatal progression is usually determined by the development of severe anaemia, thrombocytopenia and coagulation defects provoking bleeding, hypocalcaemia and liver failure [18,19]. At this stage, the development of terminal T-cell lymphoma [20,21], B-cell lymphoma [22,23], histiocytic lymphomas [24] or sinus histiocytosis with massive lymphadenopathy (Rosai–Dorfman) [25] may also be evident. The complex coagulation defects are not fully understood. There may be a combination of thrombocytopenia or thrombocytosis, decreased factor VIII and fibrinogen levels, and an increase in excretion of fibrin degradation products. It has been suggested that these abnormalities in coagulation may be caused by a circulating proteolytic enzyme other than thrombin, which may originate from proliferating lymphocytes [26].

However, prolonged survival after combination-type chemotherapy has been reported, even in cases where the clinical features indicate a poor prognosis [11,27]. Monitoring of phagocytic activity may be of value in assessing disease activity [11].

Treatment. Many cases are ultimately fatal, and for the progressive forms combination cytotoxic chemotherapy should be tried [10,19]. Prolonged survival or even complete remission have been reported with this type of treatment schedule [27,28]. Ciclosporin has been reported to be effective in cytophagic histiocytic panniculitis [29], presumably by suppression of the abnormal T-cell activation and proliferation. Combinations of systemic corticosteroids and azathioprine have been reported to be effective [30], as has the use of intravenous immunoglobulins [31]. The prognosis appears to depend on the presence or absence of systemic features of HPS and, if T-cell lymphoma is present, whether it is SPTL-AB or SPTL-GD in type. If systemic features of HPS are present (fever, unexplained cytopenia in two out of three lineages of the peripheral blood, hyperferritinaemia and histological evidence of

haemophagocytosis in bone marrow or lymph node), then treatment should be directed there, but prognosis is poor [9]. SPTL-AB lymphoma may need only systemic steroids or immunosuppressive agents, whereas SPTL-GD lymphoma needs aggressive chemotherapy [14].

References

1 Marzano AV, Berti E, Paulli M *et al.* Cytophagic histiocytic panniculitis and subcutaneous panniculitis-like T-cell lymphoma. *Arch Dermatol* 2000; **136**: 889–96.
2 Wick MR, Patterson JW. Cytophagic histiocytic panniculitis: a critical reappraisal. *Arch Dermatol* 2000; **136**: 922–4.
3 Smith KJ, Skelton HG, Yeager J *et al.* Cutaneous histopathologic, immunohistochemical, and clinical manifestations in patients with haemophagocytic syndrome. *Arch Dermatol* 1992; **128**: 193–200.
4 Romero LS, Goltz RW, Nagi C *et al.* Subcutaneous T-cell lymphoma with associated haemophagocytic syndrome and terminal leukemic transformation. *J Am Acad Dermatol* 1996; **34**: 904–10.
5 Monterroso V, Bujan W, Jaramillo O. Subcutaneous tissue involvement by T-cell lymphoma. *Arch Dermatol* 1996; **132**: 1345–50.
6 Takeshita M, Akamatso M, Oshima K *et al.* Angiocentric immunoproliferative lesions of the skin show lobular panniculitis and are mainly disorders of large granular lymphocytes. *Hum Pathol* 1995; **26**: 1321–8.
7 Takeshita M, Kimura N, Suzumiya J *et al.* Angiocentric lymphoma with granulomatous panniculitis in the skin expressing natural killer cell and large granular T-cell phenotypes. *Virchows Arch* 1994; **425**: 499–504.
8 Hytiroglou P, Phelps RG, Wattenberg DJ *et al.* Histiocytic cytophagic panniculitis: molecular evidence for a clonal T-cell disorder. *J Am Acad Dermatol* 1992; **27**: 333–6.
9 Arceci RJ. When T cells and macrophages do not talk: the hemophagocytic syndromes. *Curr Opin Hematol* 2008; **15**: 359–67.
10 Harada H, Iwatsuki K, Kaneko F. Detection of Epstein–Barr virus genes in malignant lymphoma with clinical and histologic features of cytophagic histiocytic panniculitis. *J Am Acad Dermatol* 1994; **31**: 379–83.
11 Zollner TM, Podda M, Ochsendorf FR *et al*. Monitoring of phagocytic activity in histiocytic cytophagic panniculitis. *J Am Acad Dermatol* 2001; **44**: 120–3.
12 Tsukahara T, Horiuchi Y, Iidaka K. Cytophagic histiocytic panniculitis in systemic lupus erythematosus. *Hiroshima J Med Sci* 1995; **44**: 13–6.
13 Galande J, Vazquez ML, Almeida J *et al.* Histiocytic cytophagic panniculitis: a rare late complication of allogeneic bone marrow transplantation. *Bone Marrow Transplant* 1994; **14**: 637–9.
14 Willemze R, Jansen PM, Cerroni L *et al*; EORTC Cutaneous Lymphoma Group. Subcutaneous panniculitis-like T-cell lymphoma: definition, classification, and prognostic factors: an EORTC Cutaneous Lymphoma Group Study of 83 cases. *Blood* 2008; **111**: 838–45.
15 Craig AJ, Cualing H, Thomas G *et al.* Cytophagic histiocytic panniculitis – a syndrome associated with benign and malignant panniculitis: case comparison and review of the literature. *J Am Acad Dermatol* 1998; **39**: 721–36.
16 Alegre VA, Winkelmann RK. Histiocytic cytophagic panniculitis. *J Am Acad Dermatol* 1989; **20**: 177–85.
17 White JW Jr, Winkelmann RK. Cytophagic histiocytic panniculitis is not always fatal. *J Cutan Pathol* 1989; **16**: 137–44.
18 Crotty CP, Winkelmann RK. Cytophagic histiocytic panniculitis with fever, cytopenia, liver failure and terminal haemorrhagic diathesis. *J Am Acad Dermatol* 1981; **4**: 181–94.
19 Winkelmann RK, Walter Bowie EJ. Haemorrhagic diathesis associated with benign, histiocytic, cytophagic panniculitis and systemic histiocytosis. *Arch Intern Med* 1980; **140**: 1460–3.
20 Coupe M, Foroni L, Stamp G *et al.* Clonal rearrangement of the T-cell receptor γ gene associated with a bizarre lymphoproliferation syndrome. *Eur J Haematol* 1988; **41**: 289–94.
21 Avinoach I, Halery S, Argou S *et al.* Gamma/Delta T-cell lymphoma involving the subcutaneous tissue and associated with a haemophagocytic syndrome. *Am J Dermatopathol* 1994; **16**: 426–33.
22 Ando I, Okitsu H, Kukita A *et al.* A case of haemophagocytic syndrome associated with B-cell lymphoma. *J Eur Acad Dermatol Venereol* 1995; **4**: 77–81.
23 Peters MS, Winkelmann RK. Cytophagic panniculitis and B-cell lymphoma. *J Am Acad Dermatol* 1985; **13**: 882–5.
24 Jaffe ES, Costa J, Fauci AS *et al.* Malignant lymphoma and erythrophagocytosis simulating malignant histiocytosis. *Am J Med* 1983; **75**: 741–8.
25 Suster S, Cartagena N, Cabello-Inchausti B *et al.* Histiocytic lymphophagocytic panniculitis: an unusual extranodal presentation of sinus histiocytes with massive lymphadenopathy (Rosai–Dorfman disease). *Arch Dermatol* 1988; **124**: 1246–9.
26 Henriksson P. Generalised proteolysis in a young woman with Weber–Christian disease. *Scand J Haematol* 1975; **14**: 355–60.
27 Alegre VA, Fortea JM, Camps C *et al.* Cytophagic histiocytic panniculitis: case report with resolution after treatment. *J Am Acad Dermatol* 1989; **20**: 875–8.
28 Masue K, Itoh M, Tsukuda K *et al.* Successful treatment of cytophagic histiocytic panniculitis with modified CHOP-E. *Am J Clin Oncol* 1994; **17**: 470–4.
29 Royle G, Blacklock H, Miller M. Treatment of cytophagic panniculitis with cyclosporine A. *Am J Med* 1992; **92**: 704–5.
30 Pettersson T, Kariniemi AL, Tervonen S *et al.* Cytophagic histiocytic panniculitis: a report of four cases. *Br J Dermatol* 1992; **127**: 635–40.
31 Gill DS, Spencer A, Cobcroft RG. High-dose gammaglobulin therapy in the reactive haemophagocytic syndrome. *Br J Haematol* 1994; **88**: 204–6.

Mixed (septal and lobular) panniculitis

Lupus panniculitis

Synonym
- Le profundus

Lupus panniculitis is a rare condition in which the inflammatory changes primarily affect the deep dermis and subcutaneous fat. The overlying skin may be associated with discoid lupus erythematosus (LE) in 20% of cases [1,2]. The serum antinuclear antibody is usually positive in approximately 70% of cases, but only 25–50% fulfil the American Rheumatism Association criteria for systemic LE [1,2]. However, there are a significant number of cases of lupus panniculitis that never meet the criteria for systemic LE, and some have no extracutaneous manifestations [3]. Many patients with lupus panniculitis tend to have a relatively mild but usually chronic disease course [3]. Lupus panniculitis is seen predominantly in females [1–4], usually young adults, though childhood [5–7] and neonatal [8] cases do occur. It arises spontaneously but can be triggered by injury such as immunization [7] (Fig. 46.23). Local injections of glatiramer acetate for multiple sclerosis have induced lupus panniculitis-like histology in some instances [9]. Hepatitis B vaccination has reactivated old lesions of lupus profundus [10], whilst interferon-beta has induced new ones [11]. Some cases have been associated with complement deficiencies [7] which might have made the disease more extensive [12].

Clinical features. The lesions begin with subcutaneous nodules or plaques, where the overlying skin may appear normal, erythematous or may show changes characteristic of discoid LE [2]. The lesions can be painful and may ulcerate, leading to atrophy and scarring after healing [13], even giving an anetoderma-like appearance [14].

Common sites for nodules include thighs, buttocks, arms, breasts and face (Fig. 46.24). When breast tissue is involved (lupus mastitis), there may be difficulty in distinguishing lupus mastitis from breast carcinoma, even on mammography [15]. Indeed, lupus mastitis may account for 10% of all patients with lupus



Fig. 46.23 Lupus panniculitis originally triggered by immunization. (Courtesy of St John's Institute of Dermatology, King's College London, UK.)



Fig. 46.24 Lupus panniculitis. (Courtesy of St John's Institute of Dermatology, King's College London, UK.)

panniculitis [16]. In black patients, peri-orbital oedema may be the initial presentation [4]. Many cases of lupus panniculitis may have only mild extracutaneous features, but the coexistence of photosensitivity, arthritis, pericarditis, renal involvement [3] and even neuropsychiatric manifestations has been reported [16].

Perhaps not surprisingly, lupus panniculitis can overlap with morphoea-like lesions [17], dermatomyositis [18] or other forms of connective tissue panniculitis [4]. Linear variants have been described [19,20].

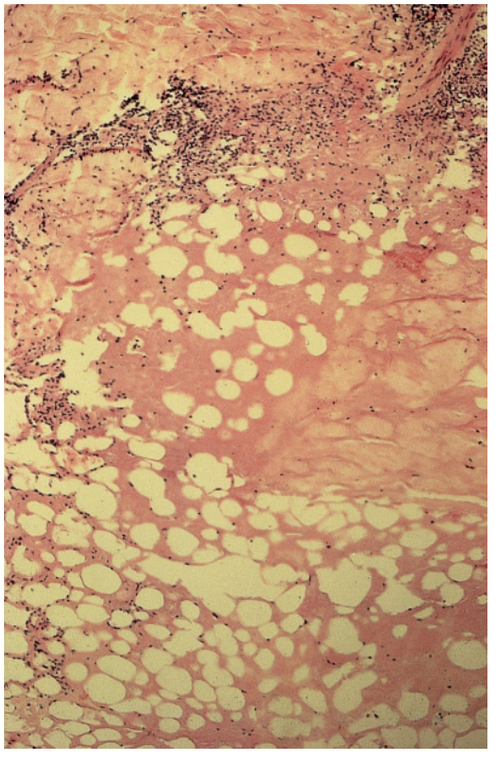


Fig. 46.25 Lupus panniculitis: extensive hyaline necrosis of fat with overlying lymphocytic aggregates are shown. H&E, × 4.

Pathology. The major histological criteria needed for a diagnosis of lupus panniculitis include hyaline necrosis of fat, lymphocytic aggregates or lymphoid follicle formation, periseptal or lobular lymphocytic panniculitis, and calcification [1] (Fig. 46.25). Minor changes (not necessary for diagnosis) include overlying changes of discoid LE, hyalinization of the subepidermal zone, mucin deposition, lymphocytic vascular inflammation and collections of plasma cells and eosinophils [21]. Karyorrhexis from lymphocyte nuclear dust is common and a strong pointer [1,22]. The main differential diagnosis is subcutaneous panniculitis-like T-cell lymphoma (SPTL), where the presence of atypical CD8+ve T lymphocytes and the absence of septal fibrosis, B-cell follicles, and plasma cells are major clues [22]. Rimming of adipocytes by lymphocytes is common in lupus profundus and not diagnostic of SPTL. A lupus band on immunofluorescence is positive in most cases, even in the absence of epidermal changes on routine histopathology [1].

Treatment. Treatment can be difficult in chronic forms of lupus panniculitis. Local treatment in the form of potent corticosteroids under hydrocolloid dressings [23] or intralesional triamcinolone can be of benefit. Dapsone [24], oral hydroxychloroquine [4,5] and corticosteroids [4,15] can be effective in the management of lupus panniculitis. Low-dose thalidomide can be effective for antimalarial drug-resistant cases of discoid LE and LE profundus [7,25].

References

1 Sánchez NP, Peters MS, Winkelmann RK. The histopathology of lupus erythematosus panniculitis. *J Am Acad Dermatol* 1981; **5**: 673–80.

2 Tuffanelli DL. Lupus erythematosus panniculitis (profundus): clinical and immunologic studies. *Arch Dermatol* 1971; **103**: 231–42.
3 Watanabe T, Tsuchida T. Lupus erythematosus profundus: a cutaneous marker for a distinct clinical subset? *Br J Dermatol* 1996; **134**: 123–5.
4 Jacyk WK, Bhana KN. Lupus erythematosus profundus in black South Africans. *Int J Dermatol* 2006; **45**: 717–21.
5 Fox JN, Klapman MH, Rowe L. Lupus profundus in children: treatment with hydroxychloroquine. *J Am Acad Dermatol* 1987; **16**: 839–44.
6 Wimmershoff MB, Hohenleutner, M, Landthaler M. Discoid lupus erythematosus and lupus profundus in childhood: A report of two cases. *Pediatr Dermatol* 2003; **20**: 140–5.
7 Burrows NP, Walport MJ, Hammond AH *et al*. Lupus erythematosus profundus with partial C4 deficiency responding to thalidomide. *Br J Dermatol* 1991; **125**: 62–7.
8 Nitta Y. Lupus erythematosus profundus associated with neonatal lupus erythematosus. *Br J Dermatol* 1997; **136**: 112–4.
9 Ball NJ, Cowan BJ, Moore GR, Hashimoto SA. Lobular panniculitis at the site of glatiramer acetate injections for the treatment of relapsing-remitting multiple sclerosis. A report of two cases. *J Cutan Pathol* 2008; **35**: 407–10.
10 Choffray A, Pinquier L, Bachelez H. Exacerbation of lupus panniculitis following anti-hepatitis-B vaccination. *Dermatology* 2007; **215**: 152–4.
11 Gono T, Matsuda M, Shimojima Y *et al*. Lupus erythematosus profundus (lupus panniculitis) induced by interferon-beta in a multiple sclerosis patient. *J Clin Neurosci* 2007; **14**: 997–1000.
12 Nousari HC, Kimyai-Asadi A, Provost TT. Generalized lupus erythematosus profundus in a patient with genetic partial deficiency of C4. *J Am Acad Dermatol* 1999; **41**: 362–4.
13 Winkelmann RK. Panniculitis in connective tissue disease. *Arch Dermatol* 1983; **119**: 61–4.
14 Marzano A, Vanotti M, Alessi E. Anetodermic lupus panniculitis and antiphospholipid antibodies: report of three cases. *Acta Derm Venereol* 2004; **84**: 385–8.
15 Cernea SS, Kihara SM, Sotto MN *et al*. Lupus mastitis. *J Am Acad Dermatol* 1993; **29**: 343–6.
16 Biedermann T, Schirren CG, Meurer M *et al*. Lupus erythematosus profundus: Kaposi–Irgang. *Eur J Dermatol* 1996; **6**: 519–22.
17 Stork J, Vosmik F. Lupus erythematosus panniculitis with morphoea-like lesions. *Clin Exp Dermatol* 1994; **19**: 79–82.
18 Yoo JY, Jo SJ, Cho KH. Lupus panniculitis with combined features of dermatomyositis resulting in severe lipoatrophy. *J Dermatol* 2004; **31**: 552–5.
19 Tada J, Arata J, Katayama H. Linear lupus erythematosus in a child. *J Am Acad Dermatol* 1991; **24**: 871–4.
20 Marzano AV, Tanzi C, Caputo R *et al*. Sclerodermic linear lupus panniculitis: report of two cases. *Dermatology* 2005; **210**: 329–32.
21 Peters MS, Su WPD. Eosinophils in lupus panniculitis and morphoea profunda. *J Cutan Pathol* 1991; **18**: 189–92.
22 Massone C, Kodama K, Salmhofer W *et al*. Lupus erythematosus panniculitis (lupus profundus): clinical, histopathological, and molecular analysis of nine cases. *J Cutan Pathol* 2005; **32**: 396–404.
23 Yell JA, Burge SM. Lupus erythematosus profundus treated with clobetasol propionate under hydrocolloid dressings. *Br J Dermatol* 1993; **128**: 103.
24 Yamada Y, Dekio S, Jidai J *et al*. Lupus erythematosus profundus: report of a case treated with dapsone. *J Dermatol* 1989; **16**: 379–82.
25 Housman TS, Jorizzo JL, McCarty MA *et al*. Low dose thalidomide therapy for refractory cutaneous lesions of lupus erythematosus. *Arch Dermatol* 2003; **139**: 50–4.

Panniculitis with complement deficiency

Although complement deficiencies are perhaps better known for their association with lupus erythematosus and partial lipoatrophy syndromes [1], they have also been reported in lobular panniculitis. The association of an immunoglobulin E (IgE) paraproteinaemia and severe acquired depletion of C1-esterase inhibitor with episodes of nodular panniculitis and hepatitis has been reported [2]. Nodular panniculitis has also been associated with a low serum complement, together with a systemic LE-like disease and circulating IgM immune complexes [3].

References

1 Wayte J, Bird G, Wilkinson JD. The clinical significance of partial lipoatrophy and C3 hypocomplementaemia: a report of two cases. *Clin Exp Dermatol* 1996; **21**: 131–4.
2 Pascual M, Widmann JJ, Schifferli JA. Recurrent febrile panniculitis and hepatitis in two patients with acquired complement deficiency and paraproteinaemia. *Am J Med* 1987; **8**: 959–62.
3 Caldwell J, Cusumano C, Ludwig F. Circulating 7S IgM immune complexes and low serum complement in a patient with systemic Weber–Christian disease. *Clin Res* 1974; **22**: 416 (Abstract).

Infective panniculitis

Infective panniculitis (either through direct inoculation or as a manifestation of sepsis) is becoming an increasingly important cause of panniculitis [1]. This is particularly so for any immunocompromised patient, either as a result of steroid or immunosuppressive therapy [2] or brought about by HIV infection [3]. An association of acquired immune deficiency syndrome (AIDS) with cutaneous aspergillosis is developing, and some patients present with subcutaneous nodules [4].

Granulomatous panniculitis on the legs caused by *Candida albicans* has been reported in a diabetic who had not received immunosuppressive treatment [5]. Other occasional cases with infective panniculitis are not overtly immunosuppressed [1].

Clinical features [1]. Most cases of infectious panniculitis appear as inflamed subcutaneous nodules, plaques or ulcers [4] on the lower extremities. Other sites include the shoulders, arms, fingers, abdominal wall and gluteal region. The differential diagnosis includes erythema nodosum, abscess or other type of panniculitis.

A wide variety of organisms have been identified in infective panniculitis. These particularly include Gram-negative [3] and Gram-positive [1] bacteria, *Histoplasma* [2,6], *Mycobacterium tuberculosis* [7], atypical mycobacteria [8,9], *Actinomyces* and *Nocardia* species [1], *Candida* [4] and various fungi [1]. Occasionally, the diagnosis of infective panniculitis has been missed because the infection has occurred in a clinical setting where a non-infective panniculitis was expected [10]. Conversely the situation whereby the patient's clinical setting has suggested that the panniculitis should be infective but tissue staining, culture or PCR was not confirmatory has been labelled panniculitic bacterid [11].

Histology. Classically, in infective panniculitis there is a mixed pattern of septal and lobular involvement. Neutrophilic involvement of the fibrous septae can occur [1], a feature that can rarely overlap with acute erythema nodosum [12]. Indeed, neutrophilic involvement in infective panniculitis can also overlap with other neutrophilic dermatoses (neutrophilic vasculitis and panniculitis) [13]. Certain morphological changes are found in infective panniculitis, whatever the identity of the infective organism. Epidermal involvement is common, as is papillary dermal oedema with diffuse neutrophilic infiltrate, vascular proliferation and haemorrhage [1]. Focal necrosis of sweat glands and discrete microabscess formation may be noted [1].

It is important to stress that infection should be suspected in virtually any case of panniculitis when it is known that the patient is immunocompromised. Extra biopsy material submitted for

tissue culture is highly desirable, if not essential [3], as special stains may fail to demonstrate the organisms [1].

References

1 Patterson JW, Brown PC, Broecker AH. Infection-induced panniculitis. *J Cutan Pathol* 1989; **16**: 183–93.
2 Silvermann AK, Gilbert SC, Watkins D *et al.* Panniculitis in an immunocompromised patient. *J Am Acad Dermatol* 1991; **24**: 912–4.
3 Smith RA, Ross JS, Branfoot C *et al.* Panniculitis with *Pseudomonas* septicaemia in AIDS. *J Eur Acad Dermatol Venereol* 1995; **4**: 166–9.
4 Murakawe GJ, Harvell JD, Lubitz P *et al.* Cutaneous aspergillosis and acquired immunodeficiency syndrome. *Arch Dermatol* 2000; **136**: 365–9.
5 Ginter G, Rieger E, Soyer P *et al.* Granulomatous panniculitis caused by *Candida albicans*: a case presenting with multiple leg ulcers. *J Am Acad Dermatol* 1993; **28**: 315–7.
6 Abildgaard WH, Hargrave RH, Kalivas J. *Histoplasma* panniculitis. *Arch Dermatol* 1985; **121**: 914–6.
7 Langenberg A, Egbert B. Neutrophilic tuberculosis panniculitis in a patient with polymyositis. *J Cutan Pathol* 1993; **20**: 177–9.
8 Drabick JJ, Duffy PE, Samlaska CP *et al.* Subspecies cheloniae infection with cutaneous and osseous manifestations. *Arch Dermatol* 1990; **126**: 1064–7.
9 Santa Cruz DJ, Strayer DS. The histologic spectrum of the cutaneous mycobacterioses. *Hum Pathol* 1982; **13**: 485–95.
10 Leung YY, Choi KW, Ho KM, Kun EW. Disseminated cutaneous infection with *Mycobacterium chelonae* mimicking panniculitis in a patient with dermatomyositis. *Hong Kong Med J* 2005; **11**: 515–9.
11 Magro CM, Dyrsen ME, Crowson AN. Acute infectious id panniculitis/panniculitic bacterid: a distinctive form of neutrophilic lobular panniculitis. *J Cutan Pathol* 2008; **35**: 941–6.
12 Forstrom L, Winkelmann RK. Acute panniculitis: a clinical and histopathologic study of 34 cases. *Arch Dermatol* 1977; **113**: 909–17.
13 Jorizzo JL, Solomon AR, Zanolli MD *et al.* Neutrophilic vascular reactions. *J Am Acad Dermatol* 1988; **19**: 983–1005.

Factitial panniculitis [1]

Factitial panniculitis is a rare condition in which the panniculitis is self-inflicted. Its importance lies in the fact that some cases may masquerade as systemic disease or idiopathic Weber–Christian syndrome. The causes and clinical features of factitial panniculitis may vary widely depending on the type of insult to the subcutaneous fat. Factitial panniculitis may result from blunt trauma to the skin, usually on the forearm and hand (l'oedème bleu) [2]. Histologically, such cases may show an organizing haematoma in the fat, together with haemosiderin and amorphous polysaccharide masses [2]. Cupping and acupuncture techniques for relief of pain may rarely lead to factitial panniculitis on the limbs [3]. More commonly, however, factitial panniculitis is induced by injected materials (e.g. drugs and silicone materials). Injected drugs such as morphine, pentazocine, meperidine or tetanus toxoid can all cause chronic ulcerative panniculitis on the thighs and buttocks, associated with 'woody-hard' fibrotic induration (see Fig. 46.12) [4,5]. Silicone injections (used by some patients to augment the size of breasts or genitalia) can cause panniculitis [6], as can the accidental injection of various oily vehicles for therapeutic agents. Povidine, a synthetic polymer used as a dispersing or suspending agent for drugs, has also been reported to cause panniculitis associated with fever [7]. The injection of mineral oil into tissues may induce a granulomatous foreign body reaction (sclerosing lipogranuloma) or 'paraffinoma' [8]. Histologically, paraffinomas show multiple 'Swiss-cheese-like' pseudocystic spaces (Fig. 46.26), which are surrounded by fibrosis and inflammation. Most paraffinomas occur on the head and neck area in women who have the injections for cosmetic reasons [9] (Fig. 46.27).

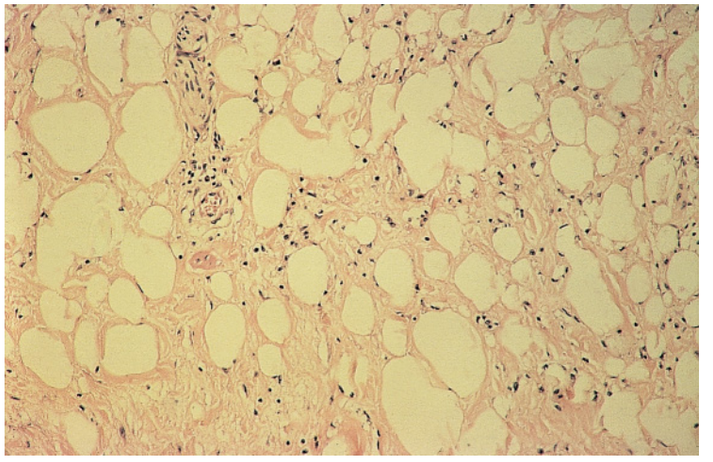


Fig. 46.26 Paraffinoma: showing typical 'Swiss-cheese'-like pseudocystic spaces. H&E, × 25.



Fig. 46.27 Paraffinoma: firm indurated areas present on the malar areas, following paraffin oil injections many years before for cosmetic purposes. (Courtesy of St John's Institute of Dermatology, King's College London, UK.)

Rarely, however, paraffinomas are not factitial in origin. The development of orbital and palpebral paraffinoma has been reported to ensue after ethmoidectomy for chronic sinusitis, when the nasal cavity was packed with gauze containing a petrolatum-based antibiotic ointment [10]. Mentally disturbed patients have been known to inject milk or faeces, which produces a severe cellulitis or suppurative panniculitis.

Factitial panniculitis simulating pyoderma gangrenosum has also been reported in Münchausen syndrome [11] and eosinophilic panniculitis was triggered by autoinjection of several farming products [12].

Histology. The histology will obviously vary according to the type of noxious injury to the fat. Blunt trauma tends to produce deeper haematomas [2]. Polarization is essential to reveal the possibility of injected crystals [4,5]. The presence of vacuoles or

pseudocystic spaces favours the injection of silicone [6] or paraffin [9,10].

The use of scanning electron microscopy or energy-dispersive spectroscopy techniques can aid in the identification of injected materials [6]. In general, factitial panniculitis is a mixed septal and lobular panniculitis that is associated with a prominent degree of inflammatory or granulomatous infiltrate, with fibrosis ensuing.

Differential diagnosis. The diagnosis may be suggested by the personality of the patient, the chronic and recurrent nature of the panniculitis and by its focal or bizarre site. In some cases, there may be fever or systemic symptoms and the condition may then be mistaken for systemic nodular panniculitis (Weber–Christian syndrome).

References

1 Forstrom L, Winkelmann RK. Factitial panniculitis. *Arch Dermatol* 1974; **110**: 747–50.
2 Winkelmann RK, Barker SM. Factitial traumatic panniculitis. *J Am Acad Dermatol* 1985; **13**: 988–94.
3 Lee JS, Ahn SK, Lee SH. Factitial panniculitis induced by cupping and acupuncture. *Cutis* 1995; **55**: 217–8.
4 Palestine RF, Millus JL, Spigel GT *et al*. Skin manifestations of pentazocine abuse. *J Am Acad Dermatol* 1980; **2**: 47–55.
5 Parks DL, Perry HO, Muller SA. Cutaneous complications of pentazocine injections. *Arch Dermatol* 1971; **104**: 231–5.
6 Rae V, Pardo RJ, Blackwelder PL, Falanga V. Leg ulcers following subcutaneous injection of a liquid silicone preparation. *Arch Dermatol* 1989; **125**: 1283–4.
7 Kossard S, Ecker RI, Dicken CH. Povidone panniculitis (polyvinylpyrrolidone panniculitis). *Arch Dermatol* 1980; **116**: 704–6.
8 Goldwyn RM. The paraffin story. *Plast Reconstr Surg* 1980; **65**: 517–24.
9 Bloem JJ, Van der Waal J. Paraffinoma of the face. *Oral Surg* 1974; **38**: 675–80.
10 Feldmann R, Harms M, Chavaz P *et al*. Orbital and palpebral paraffinoma. *J Am Acad Dermatol* 1992; **26**: 833–5.
11 Parent DJ, Krafft T, Noel JC *et al*. Cutaneous Münchausen syndrome with presentation simulating pyoderma gangrenosum. *J Am Acad Dermatol* 1994; **31**: 1072–4.
12 Gómez Rodríguez N, Ortiz-Rey JA, de la Fuente Buceta A *et al*. Auto-induced eosinophilic panniculitis: a diagnostic dilemma. *Ann Med Interne* 2001; **18**: 635–7.

Oil granuloma

Synonyms
- Oleogranuloma
- Oleoma
- Paraffinoma
- Sclerosing lipogranuloma

Definition. A granulomatous reaction to the injection of a relatively bulky oily fluid into the tissues. In many cases the condition overlaps with that of factitial panniculitis, but in some cases it may represent an industrial injury.

Aetiology. Many years ago, mineral oils, particularly liquid paraffin and soft paraffin, were in vogue for improving the contour of the body (breasts, face, genitalia) [1]. Oil granulomas are now less common since the development of less toxic silicones and bovine collagen for tissue replacement, or the use of liposuction techniques, but they still occur [2–4].

Grease-gun injuries can cause sclerosing lipogranulomas [5].

Histology. A massive injection of oil tends to provoke an initial acute inflammatory response, but some mineral oils will remain in the tissue for a considerable time without producing any marked inflammatory reaction. Larger oil droplets become encysted by fibrosis ('onion-skin cysts'). The classical 'paraffinoma' shows multiple, small cystic areas ('Swiss-cheese effect') associated with very little inflammatory change but a prominent degree of fibrosis. Certain animal fats produce a tuberculoid granuloma, whereas vegetable oils, by virtue of irritant substances liberated by hydrolysis, often provoke inflammatory changes and lipophagic granuloma.

Differential diagnosis of a mineral oil granuloma from idiopathic sclerosing lipogranuloma may be very difficult, although the use of scanning electron microscopy and energy-dispersive spectroscopy techniques can be of help [6].

Clinical features. The nodules or plaques usually appear several months after injection, but their onset can be delayed for up to 42 years [7]. Once initiated, the lesions tend to persist indefinitely. Firm, non-tender nodules or plaques form, which may be fixed to both skin and deeper fascia. Ulceration occasionally occurs. The common sites following cosmetic procedures are the face and breasts of women. Nodules on the thighs and buttocks are the result of injections of therapeutic agents in oily vehicles. It is not rare for some patients to strenuously deny any history of earlier injections for cosmetic or therapeutic purposes.

The grease-gun injury characteristically affects the dorsum of the left hand and appears as a nodule, plaque or sinus [2,8]. The onset is more rapid, the patient usually being unaware of the injury, but there may be an anaesthetic period before the gradual onset of swelling, pain and ischaemia. Rapid referral to a plastic surgeon or hand specialist is necessary. Perianal oil granulomas have been reported to follow injections for haemorrhoids [9]. Factitial panniculitis (dermatitis artefacta) can be caused by self-injection of mineral oils or silicones. An analysis of the lipid content in 23 cases of sclerosing lipogranuloma of the male genitalia demonstrated the presence of paraffin hydrocarbons in all specimens [10].

Prognosis. In chronic cases, the lesions remain essentially unchanged almost indefinitely, although the coexistence of squamous cell carcinoma [11,12] and sarcoma has been reported [13]. With acute grease-gun injuries, ischaemic changes may rapidly develop.

Treatment. MRI scanning can be diagnostic and show the extent of the problem [14]. Decompression and clearing of the affected area are needed in grease-gun injuries [2]. Tetanus toxoid may be needed along with high-dose systemic steroids if there has been a delay in diagnosis of grease-gun injuries [2]. If there is any doubt about the diagnosis of chronic oil granuloma, a deep surgical biopsy should be performed. No effective treatment exists other than complete excision.

Idiopathic sclerosing lipogranuloma (eosinophilic sclerosing lipogranuloma)

An idiopathic form of sclerosing lipogranuloma has also been reported [15]. Whilst it is possible that this really represents an oil granuloma in which the history is concealed [8,9], it is a real entity in Japan specifically involving the male genitalia [16,17] and other cases continue to be reported where there is no history of injury or injection [18,19]. Idiopathic lesions are more likely to involve the scrotum rather than penis and to be painless rather than painful. On examination there is usually a Y-shaped, string-like mass in the scrotum at the base of the penis. Peripheral eosinophilia is often present and the histology is also characterized by an eosinophil-rich granulomatous infiltrate with some lipid vacuoles and lipomembranous changes. MRI scanning can contribute to the diagnosis. Spontaneous remission does occur. Trauma and cold injury have been implicated in causation, but eosinophilic sclerosing lipogranuloma is often spontaneous. The diagnostic clue is the tissue and peripheral eosinophilia, which seems not to occur in secondary lipogranulomas.

References

1 Goldwyn RM. The paraffin story. *Plast Reconstr Surg* 1980; **65**: 517–24.
2 D'costa GF, Hastak MS, Agale SV *et al*. Self-inflicted, bilateral oleogranuloma of the breast: report of a bizarre case. *Indian J Pathol Microbiol* 2007; **50**: 373–5.
3 Zickerman PM, Ratanawong C. Penile oleogranuloma among Wisconsin Hmong. *WMJ* 2007; **106**: 270–4.
4 De Gado F, Mazzocchi M, Chiummariello S *et al*. Johnson's baby oil, a new type of filler? *Acta Chir Plast* 2006; **48**: 123–6.
5 Macaulay JC. Occupational high-pressure injection injury. *Br J Dermatol* 1986; **115**: 379–81.
6 Rae V, Pardo RJ, Blackwelder PL *et al.* Leg ulcers following subcutaneous injection of a liquid silicone preparation. *Arch Dermatol* 1989; **125**: 670–3.
7 Klein JA, Cole G, Barr RJ *et al.* Paraffinomas of the scalp. *Arch Dermatol* 1985; **121**: 382–5.
8 Smith MGH. Grease-gun injury. *BMJ* 1964; **ii**: 918–20.
9 Symmers WC. Simulation of cancer by oil granulomas of therapeutic origin. *BMJ* 1955; **ii**: 1536–9.
10 Oertel YC, Johnson FB. Sclerosing lipogranuloma of male genitalia. *Arch Pathol Lab Med* 1977; **101**: 321–6.
11 Ciancio SJ, Coburn M. Penile salvage for squamous cell carcinoma associated with mineral oil injection. *J Urol* 2000; **164**: 1650.
12 Ko CJ, Sarantopoulos GP, Bhuta S *et al*. Scalp paraffinoma underlying squamous cell carcinoma. *Arch Pathol Lab Med* 2004; **128**: 1171–2.
13 Colomb D. L'avenir des paraffinomes. *Ann Dermatol Syphiligr* 1962; **89**: 36–46.
14 Motoori K, Takano H, Ueda T *et al.* Sclerosing lipogranuloma of male genitalia: CT and MR images. *J Comput Assist Tomogr* 2002; **26**: 138–40.
15 Smetana HF, Bernhard WG. Sclerosing lipogranuloma. *Am J Pathol* 1948; **24**: 675–7.
16 Matsuda T, Shichiri Y, Hida S *et al*. Eosinophilic sclerosing lipogranuloma of the male genitalia not caused by exogenous lipids. *J Urol* 1988; **140**: 1021–4.
17 Kojima Y, Inoue H, Adachi Y *et al*. Sclerosing lipogranuloma of the male genitalia: report of 2 cases–review of 72 cases reported in Japan. *Hinyokika Kiyo* 1992; **38**: 93–7.
18 Bussey LA, Norman RW, Gupta R. Sclerosing lipogranuloma: an unusual scrotal mass. *Can J Urol* 2002; **9**: 1464–9.
19 Lim HK, Byun JH, Yoon SE *et al.* Primary sclerosing lipogranuloma of the rectum: CT findings. *Br J Radiol* 2006; **79**: e190–2.

Sclerosing panniculitis [1–4]

Synonyms
- Lipodermatosclerosis [3]
- Hypodermatitis sclerodermaformis [3]

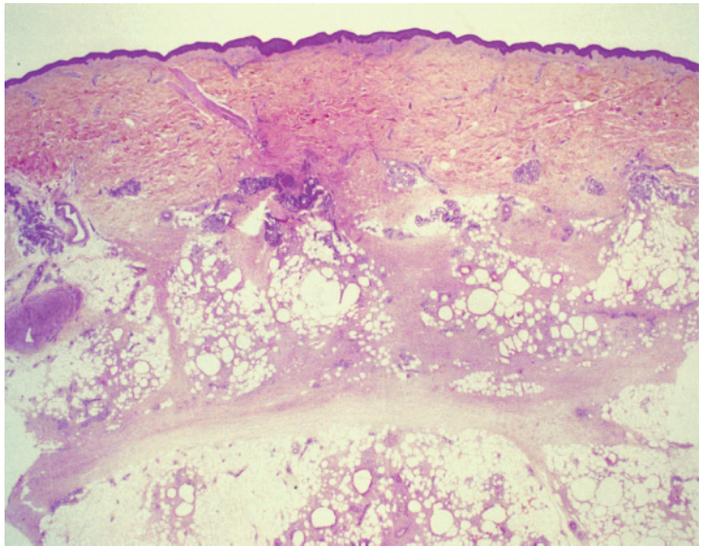


Fig. 46.28 Lipodermatosclerosis with thickened septa, lobular panniculitis and lipomembranous changes.

There is growing evidence that the term sclerosing panniculitis encompasses both lipodermatosclerosis and hypodermatitis sclerodermaformis, perhaps appearing in different stages [2]. The term lipodermatosclerosis was coined to describe the effects in the skin of chronic venous hypertension [5]. It is likely that its pathogenesis is multifactorial [6,7] but usually initiated by increased ambulatory venous pressure unrelieved by exercise. The original concept of physical obstruction to oxygen transport by pericapillary fibrin cuffs, slower capillary blood flow, white cell trapping and activation and highly convoluted capillaries, has been superseded by the realization that the changes probably result from highly complex interactions occurring in and around the endothelial cell, involving a huge variety of cytokines and growth factors [8] as well as matrix metalloproteinases [9]. The precise mechanism has yet to be elucidated. Not all cases are overtly associated with chronic venous hypertension [3]. It has been postulated that there may be overlap in the pathogenesis between lipodermatosclerosis and eosinophilic fasciitis [10] and that infective cellulitis may also have a role in exacerbating lipodermatosclerosis [11].

Histologically, there is a combination of fat necrosis and a lobular panniculitis, ultimately leading to fibrous thickening of the fascia and fibrous septae in the subcutis. Lipomembranous changes can coexist [12] (Fig. 46.28).

The patients, usually women in middle age with a high body mass index, gradually develop well-circumscribed, indurated plaques around the lower extremities, usually but not always on the medial aspect. In acute lipodermatosclerosis [3,13] (Fig. 46.29) the plaques are erythematous, painful and tender, simulating cellulitis. In the commoner chronic lipodermatosclerosis the indurated areas are skin coloured, with haemosiderin staining, eventually resulting in fibrotic narrowing of the lower leg.

Standard treatment is weight loss, elevation of legs and use of elastic compression stockings [2], but stockings cannot be tolerated in the acute situation. Stanazolol has been reported to be

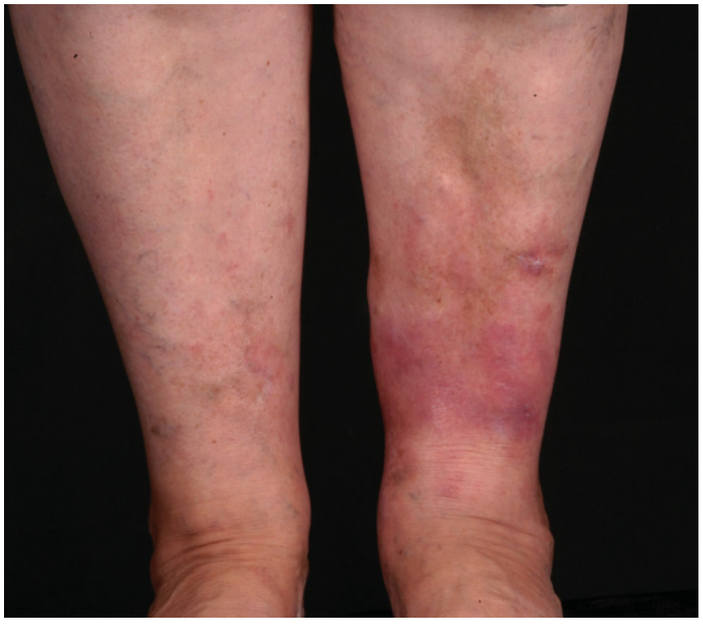


Fig. 46.29 Acute lipodermatosclerosis on the front of the left leg.

effective in both acute [14] and chronic stages [2]. Topical capsaicin is reported to have been of help in the acute stage [15].

References

1 Jorizzo JL, White WL, Zanolli MD *et al.* Sclerosing panniculitis: a clinicopathologic assessment. *Arch Dermatol* 1991; **127**: 554–8.
2 Kirsner RS, Pardes JB, Eaglestein WH *et al.* The clinical spectrum of lipodermatosclerosis. *J Am Acad Dermatol* 1993; **28**: 623–7.
3 Bruce AJ, Bennett DD, Lohse CM *et al.* Lipodermatosclerosis: a review of cases evaluated at Mayo Clinic. *J Am Acad Dermatol* 2002; **46**: 187–92.
4 Huriez C, Legache G, Desmons F *et al.* Ulcères de jambes et troubles trophiques d'origine veineuse (donnés tirées de l'étude d'un millier d'ulcéreux hospitalisés). *Rev Pract* 1955; **5**: 2703–21.
5 Browse NL, Burnand KG. The cause of venous ulceration. *Lancet* 1982; **2**: 243–5.
6 Naschitz JE, Yeshurun D, Misselvrich I *et al.* The pathogenesis of lipodermatosclerosis: facts, uncertainties and theories. *J Eur Acad Dermatol Venereol* 1997; **9**: 209–14.
7 Valencia IC, Falabella A, Kirsner RS *et al.* Chronic venous insufficiency and venous leg ulceration. *J Am Acad Dermatol* 2001; **44**: 401–21.
8 Smith PC. The causes of skin damage and leg ulceration in chronic venous disease. *Int J Low Extrem Wounds* 2006; **5**: 160–8.
9 Herony Y, May AE, Pornschlegel G *et al.* Lipodermatosclerosis is characterised by elevated expression and activation of matrix metalloproteinases: implications for venous ulcer formation. *J Invest Dermatol* 1998; **111**: 822–7.
10 Naschitz JE, Yeshurun D, Schwartz H *et al.* Pathogenesis of lipodermato-sclerosis of venous disease: the lesson learned from eosinophilic fasciitis. *Cardiovasc Surg* 1993; **1**: 524–9.
11 Naschitz JE, Yeshurun D, Zuckermann E *et al.* The fasciitis–panniculitis syndrome: clinical spectrum and therapeutic response to treatment with cimetidine. *Semin Arthritis Rheum* 1992; **21**: 211–20.
12 Alegre VA, Winkelmann RK, Aliaga A. Lipomembranous changes in chronic panniculitis. *J Am Acad Dermatol* 1988; **19**: 39–46.
13 Greenberg AS, Hasan A, Montalvo BM *et al.* Acute lipodermatosclerosis is associated with venous insufficiency. *J Am Acad Dermatol* 1996; **35**: 566–8.
14 Vesić S, Vuković J, Medenica LJ *et al.* Acute lipodermatosclerosis: an open clinical trial of stanozolol in patients unable to sustain compression therapy. *Dermatol Online J* 2008; **14**: 1.
15 Yosipovitch G, Mengesha Y, Facliaru D *et al.* Topical capsaicin for the treatment of acute lipodermatosclerosis and lobular panniculitis. *J Dermatolog Treat* 2005; **16**: 178–80.

Fasciitis–panniculitis syndromes [1]

In eosinophilic fasciitis and related syndromes, the inflammation often extends to involve the fibrous septae and fat lobules, the subcutaneous fascia which becomes thickened, and the underlying perimysium, resulting in thickened fascia around smaller muscle bundles [1]. It has become increasingly recognized that a histological picture similar to eosinophilic fasciitis, involving the subcutaneous fat, can occur in a variety of diseases, including morphoea profunda [1], lupus panniculitis [1], toxic oil syndrome [2], L-tryptophan-induced eosinophilia–myalgia syndrome [3], graft-versus-host reaction [4], post-irradiation injury [5], infections [6] and cancer-related (paraneoplastic) syndromes [7,8]. The term fasciitis–panniculitis syndromes [1] was coined to draw attention to the fact that any of the above diseases might present with either a plaque or, if on a limb, a sleeve of indurated bound-down skin, unilateral or bilateral, and which had the histology of chronic inflammation with extensive scarring.

References

1 Naschitz JE, Boss JH, Misselvich I *et al.* The fasciitis–panniculitis syndromes: clinical and pathological features. *Medicine* 1996; **75**: 6–16.
2 Alonso-Ruiz A, Zea-Mendoza AC, Salazar-Vallines JM *et al.* Toxic oil syndrome: a syndrome with features overlapping those of various forms of scleroderma. *Semin Arthritis Rheum* 1986; **15**: 200–12.
3 Freundlich B, Werth VP, Rook AH *et al.* L-Tryptophane injection associated with eosinophilic fasciitis but not progressive systemic sclerosis. *Ann Intern Med* 1990; **112**: 758–62.
4 Janin A, Socie G, Devergie A *et al.* Fasciitis in chronic graft-versus-host disease. *Ann Intern Med* 1994; **120**: 993–8.
5 Winkelmann RK, Grado GL, Quimby SR. Pseudosclerodermatous panniculitis after irradiation: an unusual complication of megavoltage treatment of breast carcinoma. *Mayo Clin Proc* 1993; **68**: 122–7.
6 Zuckerman E, Naschitz J, Yeshurun D *et al.* Fasciitis–panniculitis in acute brucellosis. *Int J Dermatol* 1994; **33**: 57–9.
7 Cox NH, Ramsay B, Dobson C *et al.* Woody hands in a patient with pancreatic carcinoma: a variant of cancer-associated fasciitis–panniculitis syndrome. *Br J Dermatol* 1996; **135**: 995–8.
8 Naschitz JE, Yeshurun D, Zuckerman E *et al.* Cancer-associated fasciitis panniculitis. *Cancer* 1994; **73**: 231–5.

Panniculitis in other connective tissue diseases

As already indicated, panniculitis in connective tissue diseases may overlap with lupus panniculitis [1] and also lipoatrophic panniculitis [2]. Deep morphoea (morphoea profunda) may show lipoatrophy, scleroderma-like lesions and deeper subcutaneous nodules or plaques. They may also share some histological features, notably lymphocytic panniculitis, lymphoid nodular areas in the fat, widening of the fibrous septae and lymphocytic vasculitis [3–5].

The association of panniculitis with dermatomyositis is very rare but well documented [6–9]. The parallel course of panniculitis and muscular involvement, and their response to treatment, suggest that panniculitis may be an inherent part of dermatomyositis [6–9]. Subcutaneous nodules or plaques develop on the arms, buttocks, thighs and abdomen, or features of multifocal lipoatrophy may be present [10]. Partial lipoatrophy may also coexist with

dermatomyositis [11,12]. The association of panniculitis and dermatomyositis has been reported to respond to a combination of low-dose methotrexate and prednisolone [10], or high-dose intravenous immunoglobulins [13].

References

1 Winkelmann RK. Panniculitis in connective tissue disease. *Arch Dermatol* 1993; **119**: 336–44.
2 Handfield-Jones SE, Stephens CJM, Mayou BJ *et al.* The clinical spectrum of lipoatrophic panniculitis encompasses connective tissue panniculitis. *Br J Dermatol* 1993; **129**: 619–24.
3 Person JR, Su WPD. Subcutaneous morphoea: a clinical study of 16 cases. *Br J Dermatol* 1979; **100**: 371–9.
4 Su WPD, Person JR. Morphoea profunda: a new concept and a histopathologic study of 23 cases. *Am J Dermatopathol* 1981; **3**: 251–60.
5 Whittaker SJ, Smith NP, Jones RR. Solitary morphoea profunda. *Br J Dermatol* 1989; **120**: 431–40.
6 Fusade T, Belanyi P, Joly P *et al.* Subcutaneous changes in dermatomyositis. *Br J Dermatol* 1993; **128**: 451–3.
7 Neidenbach PJ, Sahn EE, Helton J. Panniculitis in juvenile dermatomyositis. *J Am Acad Dermatol* 1995; **33**: 305–7.
8 Winkelmann WJ, Billick RC, Srolovitz H. Dermatomyositis presenting as panniculitis. *J Am Acad Dermatol* 1990; **23**: 127–8.
9 Chao YY, Yang LJ. Dermatomyositis presenting as panniculitis. *Int J Dermatol* 2000; **39**: 141–4.
10 Commens C, O'Neill P, Walker G. Dermatomyositis associated with multifocal lipoatrophy. *J Am Acad Dermatol* 1990; **22**: 966–9.
11 Kavanagh GM, Colaco CB, Kennedy CTC. Juvenile dermatomyositis associated with partial lipoatrophy. *J Am Acad Dermatol* 1993; **28**: 348–51.
12 Torrelo A, España A, Boixeda P *et al.* Partial lipodystrophy and dermatomyositis. *Arch Dermatol* 1991; **127**: 1846–7.
13 Sabroe RA, Wallington TB, Kennedy CTC. Dermatomyositis treated with high-dose intravenous immunoglobulins and associated with panniculitis. *Clin Exp Dermatol* 1995; **20**: 164–7.

Panniculitis with vasculitis

Because the vasculature of the subcutis is 'housed' in the fibrous septae that divide up fat lobules, it is obvious that most deep vasculitis syndromes (particularly large-vessel vasculitis) begin as a septal panniculitis and involve the fat lobules later.

Nearly all cases of leukocytoclastic vasculitis in the subcutis zone also affect the overlying dermis. Nodular forms of vasculitis affecting the fat are primarily dealt with in Chapter 50, together with larger vessel vasculitis syndromes (e.g. polyarteritis nodosa).

This section covers a series of miscellaneous entities that may overlap with vasculitis, or may in some way be associated with them.

Panniculitis has rarely been reported in association with relapsing polychondritis, and histologically was characterized by septal and lobular involvement with vasculitis [1,2]. The association of granulomatous lipophagic panniculitis with temporal arteritis and chronic active hepatitis has been reported, and perhaps represents three-organ manifestations of an underlying aberration of the immune defence mechanism [3].

Unusual forms of vasculitis-associated panniculitis include that resulting from the complications of jejunoileal bypass surgery for obesity (Fig. 46.30) [4,5].



Fig. 46.30 Scarring of lower abdominal folds secondary to panniculitis and/or vasculitis following jejunoileal bypass for gross obesity.

Neutrophilic panniculitis

Subcutaneous neutrophilic infiltrates are a rare accompaniment in atypical Sweet's syndrome and bullous pyoderma gangrenosum [6]. Recent case reports have highlighted the association of neutrophilic panniculitis with myelodysplastic syndromes [7,8] and sometimes administration of granulocyte colony-stimulating factor (GCSF) [9]. The neutrophilic infiltrates spread out from the septa to the lobules, without evidence of necrotizing panniculitis. It has been postulated that neutrophilic panniculitis belongs to the spectrum of atypical neutrophilic dermatoses associated with myelodysplastic syndromes [7] and inflammatory bowel disease. Septal forms of neutrophilic panniculitis can occur in classical Sweet's syndrome, and may present as erythema nodosum-like eruptions [10]. All-*trans*-retinoic acid chemotherapy triggered a pure lobular neutrophilic panniculitis in a patient with acute promyelocytic leukaemia [11].

A pustular neutrophilic form of panniculitis has been associated with rheumatoid arthritis, both adult [12] and juvenile [13]. Neutrophilic panniculitis is also seen in α_1-antitrypsin deficiency and factitious panniculitis, and it is necessary to exclude an infective organism, particularly in an immunocompromised patient [14]. Occasionally, a neutrophilic panniculitis is seen where infection is expected from the clinical setting but nothing found from the tissue. The term acute infectious id panniculitis or panniculitic bacterid has been coined for this situation [15].

Oedematous scarring vasculitic panniculitis: hydroa-like lymphoma

A condition termed oedematous scarring vasculitic panniculitis has been identified in children, which is described as a novel multisystemic disease with a mortality rate of 35.7% [16]. The cutaneous lesions may initially resemble hydroa vacciniforme, but later disfiguring involvement affects both covered and sun-exposed areas. The lesions develop as oedematous vesicles, which progress to deep ulcerations and varicelliform scars. Histologically, panniculitis and vasculitis coexist with a heavy nodular lymphohistiocytic infiltrate. In cases with systemic involvement, malaise, fever, failure to thrive, leukopenia, thrombocytopenia, hepatosplenomegaly and increased levels of serum C3 have been frequently observed [16]. Several of the patients ultimately developed cutaneous lymphoma, after an interval of 5–8 years, though

others wax and wane not unlike lymphomatoid papulosis. Other patients with 'hydroa vacciniforme' have also been reported to develop malignant lymphoma [17–19]. Thirty-one cases of this syndrome have now been reported, and it is likely that the entity is an evolutionary process in the development of malignant lymphoma in children, namely hydroa-like lymphoma. Most cases are CD4 or CD8 positive, but two cases with the natural killer cell phenotype CD56 have been reported [20].

References

1 Disdier P, Andrac L, Swiaden L *et al.* Cutaneous panniculitis and relapsing polychondritis: two cases. *Dermatology* 1996; **193**: 266–8.
2 Smith CR, Sawicka EH, Sheffield E *et al.* Relapsing polychondritis and Weber–Christian disease. *Br J Rheumatol* 1988; **27**: 486–9.
3 Naschitz JE, Yeshurun D, Barth J *et al.* Granulomatous lipophagic panniculitis and temporal arteritis in a patient with cryptogenic chronic active hepatitis. *Ann Rheum Dis* 1992; **51**: 812–4.
4 Kennedy CTC. The spectrum of inflammatory skin disease following jejuno-ileal bypass for morbid obesity. *Br J Dermatol* 1981; **105**: 425–35.
5 Williams HJ, Samuelson CO, Zone JJ. Nodular non-suppurative panniculitis associated with jejuno-ileal bypass surgery. *Arch Dermatol* 1979; **115**: 1091–3.
6 Cooper PH, Frierson HF, Greer KE. Subcutaneous neutrophilic infiltrates in acute febrile neutrophilic dermatosis. *Arch Dermatol* 1983; **119**: 610–1.
7 Matsumara Y, Tanabe H, Wada Y *et al.* Neutrophilic panniculitis associated with myelodysplastic syndromes. *Br J Dermatol* 1997; **136**: 142–4.
8 Suzuki Y, Kuroda K, Kojima T *et al.* Unusual cutaneous manifestations of myelodysplastic syndrome. *Br J Dermatol* 1995; **133**: 483–6.
9 Prendiville J, Thiessen P, Mallory SB. Neutrophilic dermatoses in two children with idiopathic neutropenia: association with granulocyte colony-stimulating factor (G-CSF) therapy. *Pediatr Dermatol* 2001; **18**: 417–21.
10 Blaustein A, Moreno A, Noguera J *et al.* Septal panniculitis in Sweet's disease. *Arch Dermatol* 1985; **121**: 785–8.
11 Jagdeo J, Campbell R, Long T *et al.* Sweet's syndrome-like neutrophilic lobular panniculitis associated with all-trans-retinoic acid chemotherapy in a patient with acute promyelocytic leukemia. *J Am Acad Dermatol* 2007; **56**: 690–3.
12 Anstey A, Wilkinson JD, Wojnarowska F *et al.* Pustular panniculitis in rheumatoid arthritis. *J R Soc Med* 1991; **84**: 307–8.
13 Dyer JA, Guitart J, Klein-Gitelman M *et al.* Neutrophilic panniculitis in infancy: a cutaneous manifestation of juvenile rheumatoid arthritis. *J Am Acad Dermatol* 2007; **57**: S65–8.
14 Patterson JW, Brown PC, Broecker AH. Infection-induced panniculitis. *J Cutan Pathol* 1989; **16**: 183–93.
15 Magro CM, Dyrsen ME, Crowson AN. Acute infectious id panniculitis/panniculitic bacterid: a distinctive form of neutrophilic lobular panniculitis. *J Cutan Pathol* 2008; **35**: 941–6.
16 Ruiz-Maldonado R, Parrilla FM, Orozco-Covarrubias ML *et al.* Oedematous, scarring vasculitic panniculitis: a new multisystemic disease with malignant potential. *J Am Acad Dermatol* 1995; **32**: 37–44.
17 Ibarra-Durán G, Rodriguez-Jurado R, Rodriguez-Moguel L *et al.* Linforma T cutáneo angiocèntrico en niña con hidroa vacciniforme. *Dermatol Rev Mex* 1991; **35**: 344–8.
18 Oono T, Arata J, Masuda T *et al.* Coexistence of hydroa vacciniforme and malignant lymphoma. *Arch Dermatol* 1986; **122**: 1306–9.
19 Steger GG, Dittrich C, Honigsmann H *et al.* Permanent cure of hydroa vacciniforme after chemotherapy for Hodgkin's disease (Letter). *Br J Dermatol* 1988; **119**: 684–5.
20 Doeden K, Molina-Kirsch H, Perez E *et al.* Hydroa-like lymphoma with CD56 expression. *J Cutan Pathol* 2008; **35**: 488–94.

Wells' syndrome [1–4]

Synonyms
- Eosinophilic cellulitis
- Recurrent granulomatous dermatitis with eosinophilia

Definition. This is a syndrome with an impressive and distinctive clinical picture resembling cellulitis, and with a typical histology characterized by tissue eosinophilia, oedema and 'flame' figures.

Aetiology. The syndrome can arise spontaneously or be apparently triggered by a particular stimulus, or be seen in association with other diseases. As such it may represent an allergic hypersensitivity response, with eosinophils playing a dominant role; the mechanism is unknown, but interleukin-5 may be involved [5,6]. Drugs [7] including cladribine for lymphoproliferative disease [8] and adalimumab [9], infection (HIV, herpetic, parasitic and fungal) and insect bites have all been incriminated. In one report, antiviral therapy led to a complete remission of the eosinophilic cellulitis associated with recurrent *Herpes simplex* virus type 2 infection [10]. Reactions to other triggers, such as thiomersal after immunization, can also occur [11]. More recently angioimmunoblastic lymphadenopathy, malignancy and inflammatory bowel disease have been added to the list [12–14]. Eosinophilic fasciitis [6], eosinophilic pustular folliculitis [15], Churg–Strauss syndrome [16] and immunobullous disease are other associations. Rarely, eosinophilic cellulitis is the first presentation of hypereosinophilic syndrome [17] and rarer still it is familial [18].

Pathology. Early on, there is an infiltrate of polymorphs and especially of eosinophils, with considerable oedema. Flame figures are noteworthy—clusters of eosinophils and histiocytes around a core of collagen and eosinophilic debris. The flame figures may disappear after the acute stage with the granulomatous infiltrate becoming more obvious. In bullous lesions, eosinophil-rich subepidermal and intraepidermal vesicles are found, but the dermal changes still dominate. Blood eosinophilia is usual but not invariable.

Clinical features. Wells' syndrome is rare. It can affect either sex, usually in adult life, but some congenital [18], neonatal [19] or childhood cases [20] have occurred. Any site may be involved, with single or multiple lesions. The disease evolves over a few weeks, and recurrences are common. Initially, the lesions are itchy erythematous plaques with features resembling both urticaria and cellulitis, sometimes evolving into a greenish morphoea-like plaque. Any pattern can occur, including unusual nodular variants [21] and lesions that follow the lines of Blaschko [22]. Vesicles and bullae may be dominant [15,16]. After a week or two, the lesions become flatter, and sometimes go through a greenish colour change before resolving without scarring. The general health is usually unimpaired, but fever has been reported, as has arthralgia and mild hepatic dysfunction.

Differential diagnosis. Clinically, erysipelas, cellulitis, urticaria and contact dermatitis are the main differential diagnoses. Multiple lesions in an atypical pattern far apart is a strong clinical pointer. *Toxocara* infections may be similar, both clinically and histologically. Infections such as ascariasis and onchocerciasis need to be excluded. Flame figures can be found in many other diseases, including insect-bite reactions, dermatophyte ide eruptions and pemphigoid; that is wherever the dermal infiltrate is

eosinophil rich. The histology in Sweet's syndrome is neutrophil rich, and extra-facial Kimura's disease shows lymphoid follicles. In general, the presence of systemic features, especially if severe, makes the diagnosis of Wells' syndrome unlikely and drug eruption with eosinophilia and systemic symptoms (DRESS) should be excluded, as should hypereosinophilic syndrome or other associated disease.

Treatment. Often no specific treatment is needed. Low-dose systemic steroids can provide symptomatic relief in severe cases [23]. Cetirizine, interferon-α and ciclosporin have all proved effective [24–26].

References

1 Wells GC. Recurrent granulomatous dermatitis with eosinophilia. *Trans St John's Hosp Dermatol Soc* 1971; **57**: 46–56.
2 Wells GC, Smith NP. Eosinophilic cellulitis. *Br J Dermatol* 1979; **100**: 101–9.
3 Aberer W, Konrad K, Wolff K. Wells' syndrome is a distinctive disease entity and not a histological diagnosis. *J Am Acad Dermatol* 1988; **18**: 105–14.
4 Steffen C, Wells GC. Eosinophilic cellulitis (Wells' syndrome). *Am J Dermatopathol* 2002; **24**: 164–5.
5 Espana A, Sanz ML, Sola J *et al.* Wells' syndrome (eosinophilic cellulitis): correlation between clinical activity, eosinophil levels, eosinophil cation protein and interleukin-5. *Br J Dermatol* 1999; 140: 127–30.
6 French LE, Shapiro M, Junkins-Hopkins JM *et al*. Eosinophilic fasciitis and eosinophilic cellulitis in a patient with abnormal circulating clonal T cells: increased production of interleukin 5 and inhibition by interferon alfa. *J Am Acad Dermatol* 2003; **49**: 1170–4.
7 Seçkin D, Demirhan B. Drugs and Wells' syndrome: a possible causal relationship? *Int J Dermatol* 2001; **40**: 138–40.
8 Rossini MS, de Souza EM, Cintra ML *et al*. Cutaneous adverse reaction to 2-chlorodeoxyadenosine with histological flame figures in patients with chronic lymphocytic leukaemia. *J Eur Acad Dermatol Venereol* 2004; **18**: 538–42.
9 Boura P, Sarantopoulos A, Lefaki I, Skendros P *et al*. Eosinophilic cellulitis (Wells' syndrome) as a cutaneous reaction to the administration of adalimumab. *Ann Rheum Dis* 2006; **65**: 839–40.
10 Ludwig RJ, Grundmann-Kollmann M, Holtmeir W *et al.* Herpes simplex virus type 2-associated eosinophilic cellulitis (Wells' syndrome). *J Am Acad Dermatol* 2003; **48**: 560–1.
11 Koh KJ, Warren L, Moore L *et al.* Wells' syndrome following thiomersal-containing vaccinations. *Australas J Dermatol* 2003; **44**: 199–202.
12 Renner R, Kauer F, Treudler R *et al*. Eosinophilic cellulitis (Wells' syndrome) in association with angioimmunoblastic lymphadenopathy. *Acta Derm Venereol* 2007; **87**: 525–8.
13 Farrar CW, Guerin DM, Wilson NJE. Eosinophilic cellulitis associated with squamous cell carcinoma of the bronchus. *Br J Dermatol* 2001; **145**: 668–9.
14 Sakaria SS, Ravi A, Swerlick R *et al*. Wells' syndrome associated with ulcerative colitis: a case report and literature review. *J Gastroenterol* 2007; **42**: 250–2.
15 Arca E, Köse O, Karslioğlu Y *et al*. Bullous eosinophilic cellulitis succession with eosinophilic pustular folliculitis without eosinophilia. *J Dermatol* 2007; **34**: 80–5.
16 Schuttelaar ML, Jonkman MF. Bullous eosinophilic cellulitis (Wells' syndrome) associated with Churg–Strauss syndrome. *J Eur Acad Dermatol Venereol* 2003; **17**: 91–3.
17 Bogenrieder T, Griese DP, Schiffner R *et al.* Wells' syndrome associated with idiopathic hypereosinophilic syndrome. *Br J Dermatol* 1997; **137**: 978–82.
18 Davis MPD, Brown AC, Blackston RD *et al.* Familial eosinophilic cellulitis, dysmorphic habitus, and mental retardation. *J Am Acad Dermatol* 1998; **38**: 919–28.
19 Kuwahara RT, Randall MB, Eisner MG. Eosinophilic cellulitis in a newborn. *Pediatr Dermatol* 2001; **18**: 89–90.
20 Anderson CR, Jenkins D, Tron V *et al.* Wells' syndrome in childhood: case report and review of the literature. *J Am Acad Dermatol* 1995; **33**: 857–64.
21 Holme SA, McHenry P. Nodular presentation of eosinophilic cellulitis (Wells' syndrome). *Clin Exp Dermatol* 2001; **26**: 677–9.
22 Sommer S, Wilkinson SM, Merchant WJ. Eosinophilic cellulitis following the lines of Blaschko. *Clin Exp Dermatol* 1999; **24**: 449–51.
23 Coldiron BM, Robinson JK. Low dose alternate-day prednisone for persistent Wells' syndrome. *Arch Dermatol* 1989; **125**: 1625–6.
24 Aroni K, Aivaliotis M, Liossi A *et al*. Eosinophilic cellulitis in a child successfully treated with cetirizine. *Acta Derm Venereol* 1999; **79**: 332.
25 Husak R, Goerdt S, Orfanos CE. Interferon alfa treatment of a patient with eosinophilic cellulitis and HIV infection. *N Engl J Med* 1997; **337**: 641–2.
26 Karabudak O, Dogan B, Taskapan O *et al*. Eosinophilic cellulitis presented with semicircular pattern. *J Dermatol* 2006; **33**: 798–801.

Lipodystrophy

The terms lipoatrophy and lipodystrophy are sometimes used interchangeably and without precise definition. Perhaps it is best to define lipodystrophy as an abnormality of fat that is usually associated with atrophy (lipoatrophy), or infrequently hypertrophy of the adipose tissue. Lipoatrophy refers specifically to loss of fat. However, the lipoatrophy may be part of a local panatrophy affecting all mesodermal layers [1]. Lipodystrophies are a rare and heterogeneous group of disorders characterized by selective and variable reduction in and, more often, loss of adipose tissue from different parts of the body; in all but the more very localized varieties they are often associated with metabolic complications of insulin resistance, in particular insulin-resistant diabetes mellitus [2]. Over the last 5 years, there has been a much better understanding of the aetiology of these disorders. The loss of adipose tissue can have a genetic, immunological, infectious or drug-associated aetiology [3]. The age of onset may also determine the nomenclature of the disease. Some patients may develop the disease very early on in life—such patients are then sometimes referred to as having congenital lipodystrophy. In other patients, the disease occurs later on in life—so-called acquired lipodystrophy. The lipodystrophies can also be classified according to the extent of the disease into three major clinical entities: localized, partial-body and whole-body distribution. The atrophy may be localized (e.g. to the thighs); it can be widespread, involving the upper part of the trunk (partial lipodystrophy); or it may affect the whole body (generalized lipodystrophy).

Nevertheless, the aetiology and clinical presentation are not always clear-cut. For example, cases of partial lipoatrophy have been reported that have evolved into generalized lipoatrophy, suggesting some common link between these uncommon disorders.

References

1 Serup J, Weismann K, Kobayasi T *et al.* Local panatrophy with linear distribution. *Acta Derm Venereol (Stockh)* 1982; **62**: 101–5.
2 Reitman ML, Arioglu E, Gavrilova O, Taylor SI. Lipoatrophy revisited. *Trends Endocrionol Metab* 2000; **11**: 410–6.
3 Shalev A. Discovery of a lipodystrophy gene: one answer, 100 questions. *Eur J Endocrinol* 2000; **143**: 565–7.

Localized lipoatrophy

Localized atrophy may be seen following injection of medications, for example in insulin-dependent diabetics, induced by insulin [1–9]; following certain inflammatory conditions, such as panniculitis and morphoea; or as primary idiopathic lipoatrophy. The list of medications inducing atrophy includes corticosteroids, antibiotics, heparin, growth hormone and glatiramer [10]. The

mechanism is uncertain and has been attributed directly to the medication, but localized lipoatrophy has been reported following acupuncture alone [11]. In many of these situations, spontaneous healing has occurred over the next month or two. Failure to perform a biopsy in the early phases of the atrophy may explain why some of the cases are labelled as idiopathic in origin. It has been suggested that many cases may be preceded by an inflammatory reaction in the fat (see also lipoatrophic panniculitis) [1].

Insulin lipodystrophies

This is a cosmetically distressing complication of insulin administration. Both atrophy and hypertrophy of the fat tissue can occur. It occurs in various degrees in up to 37% of insulin-dependent diabetics [2].

Aetiology. Insulin lipoatrophy is usually seen in women and children, rarely in men. The mechanism remains speculative but local changes induced by insulin or impurities are probably important [3] as are antibodies to insulin [4]. Most cases are associated with high levels of insulin requirement and/or an increased insulin-binding capacity.

Cross-reaction of insulin antibodies with cells thus changed could result in further damage [5]. It was thought that the introduction of highly purified insulin would make a significant impact in reducing the frequency of this disorder. There is evidence to support this view, because the subcutaneous damage is reduced if highly purified insulins are used, resulting in clinical improvement and a reduction in insulin requirements and insulin-binding capacity [5–7]. However, localized lipodystrophies in insulin-requiring patients are still very common, affecting up to 40% of patients.

A recent publication investigated a cross-sectional study of 112 children and adolescents with type 1 diabetes mellitus and related the presence of insulin antibodies to the clinical features of insulin lipodystrophies [4]. The antibodies against insulin increased significantly after diabetes manifestations and initiation of insulin treatment, while β-cell-specific antibodies did not. Severe lipohypertrophy was seen in four children, severe lipohypertrophy in 18 and moderate lipohypertrophy in 27 children. Among clinical and immunological parameters investigated, insulin antibodies were significantly associated with hypertrophy or atrophy of injection sites. It was concluded that lipodystrophies in diabetics are significantly associated with insulin antibodies, and that these may have a role in the development of the disease.

Histopathology. There is a loss of fat tissue and inflammatory changes are conspicuously absent. In lipohypertrophy, there may be replacement of mid-dermal collagen by hypertrophic fat cells.

Clinical features. Although both features can occur in the same patient, recent publications suggest that insulin fat hypertrophy is more common than atrophic changes [4]. Most cases present 6 months to 2 years after the start of insulin administration. Lesions may vary from only a small dimple to an extensive, disfiguring area with much local loss of fat or firm fatty induration. The changes are usually found only at the sites of injection, but loss of fat may occur elsewhere. There is a definite tendency to spontaneous recovery at the involved site when the site of injection is changed.

Treatment. A change to a purified insulin, particularly the new human insulin, is not necessarily curative [8]. Prevention is either by constant alteration of the site of injection, so that no two injections are given in exactly the same area more frequently than once a month, or by the use of the more purified insulins [5,9]. Alternatively, injection at the edge of the atrophy or combination with dexamethasone may help [12]. Liposuction may help the hypertrophic variety [13]. In one very resistant case of progressive lipoatrophy, continuous subcutaneous infusion with human insulin was required to control the atrophy [9] but continuous infusion itself may provoke the same reaction [14].

Localized lipohypertrophy has also been reported in a 51-year-old female patient with panhypopituitism during growth hormone replacement therapy [15].

References

1 Peters MS, Winkelmann RK. Localized lipoatrophy (atrophic connective tissue disease panniculitis). *Arch Dermatol* 1980; **116**: 1363–8.
2 Kakourou T, Dacou-Voutetakis C, Kavadias G *et al*. Limited joint mobility and lipodystrophy in children and adolescents with insulin-dependent diabetes mellitus. *Pediatr Dermatol* 1994; **11**: 310–4.
3 Eisert J. Diabetes and diseases of the skin. *Med Clin North Am* 1965; **49**: 621–32.
4 Raile K, Noelle V, Landgraf R, Schwarz HP. Insulin antibodies are associated with lipatrophy but also with lipohypertrophy in children and adolescents with type 1 diabetes. *Exp Clin Endocrinol Diabetes* 2001; **109**: 393–6.
5 Daggett P, Mustaffa BE, Nabarro JDN. Improvements in skin reactions to insulin produced by a highly purified preparation. *Br J Dermatol* 1977; **96**: 439–43.
6 Kristensen JS, Falhott K. Human monocomponent insulin in the treatment of insulin allergic diabetics. *Diabetes* 1983; **32** (Suppl. 1): 66.
7 Tantillo JJ, Karam JH, Burrill KC. Immunogenicity of 'single peak' beef–pork insulin in diabetic subjects. *Diabetes* 1974; **23**: 276–81.
8 Galloway JA, Bressler R. Insulin treatment in diabetes. *Med Clin North Am* 1978; **62**: 663–80.
9 Chantelau E, Reuter M, Scholes S *et al*. A case of lipoatrophy with human insulin therapy. *Exp Clin Endocrinol* 1993; **101**: 194–6.
10 Soos N, Shakery K, Mrowietz U. Localized panniculitis and subsequent lipoatrophy with subcutaneous glatiramer acetate (Copaxone) injection for the treatment of multiple sclerosis. *Am J Clin Dermatol* 2004; **5**: 357–9.
11 Drago F, Rongioletti F, Battifoglio ML, Rebora A. Localised lipoatrophy after acupuncture. *Lancet* 1996; **347**: 1484.
12 Richardson T, Kerr D. Skin-related complications of insulin therapy: epidemiology and emerging management strategies. *Am J Clin Dermatol* 2003; **4**: 661–7.
13 Field LM. Successful treatment of lipohypertrophic insulin lipodystrophy with liposuction surgery. *J Am Acad Dermatol* 1988; **19**: 570.
14 Radermecker RP, Piérard GE, Scheen AJ. Lipodystrophy reactions to insulin: effects of continuous insulin infusion and new insulin analogs. *Am J Clin Dermatol* 2007; **8**: 21–8.
15 Mersebach H, Feldt-Rasmussen UF. Localised liphypertrophy during growth hormone therapy. *Ugeskr Laeger* 2002; **164**: 1930–2.

Localized 'idiopathic' lipoatrophy

This group of disorders predominantly affects the thighs, ankles or abdomen, and all cases may possibly be variants of the same process.

Histopathology. Two histological subsets exist: involutional and inflammatory [1]. Sixty percent can be termed involutional; the adipocytes are small and embedded in hyaline connective tissue with many capillaries. Such patients usually have a single lesion,



Fig. 46.31 Extensive lipoatrophy of the legs.

and only one-third show immunoreactants. Forty per cent can be classed as inflammatory [2]; the lipocytes are normal and there is a sparse infiltrate of lymphocytes, histiocytes and plasma cells; all show immunoreactants [1]. The epidermis is normal. The appearance should not be confused with the striking lipomembranous (membranocystic) changes seen occasionally in morphoea, panniculitis and other inflammatory dermatoses.

Clinical features. Two clinical groups, based on the localization of the atrophy, have been described.

Lipoatrophia semicircularis [3–5]. These patients show lesions on the anterolateral aspects of the thighs, characterized by a band-like circular depression, 2–4 cm in width. Patients have also been described with lipoatrophy of the ankles which can extend up the legs (Fig. 46.31) [6]. The overlying skin is normal. An association with osteodystrophy of the hands and feet has also been reported [7].

The loss of fat develops rapidly within several weeks, usually without associated symptoms, although rheumatic-like pains within the involved areas were reported by two women. Trauma is a possible triggering mechanism—a series of seven cases has been reported in individuals working in the same office. The exact position of the indentations corresponding to the height of the desks strongly supports the hypothesis that in some patients this condition is caused by repetitive trauma to the upper thighs [8].

Primary inflammatory vascular changes in the subcutaneous tissue have been demonstrated in these patients, and also during the early period of other lipoatrophies [9]. There is no treatment, but considerable improvement may occur after the activity of the disease settles.

Centrifugal lipodystrophy. Lipodystrophia centrifugalis abdominalis infantalis is rare, and has been seen predominantly in Japanese children [10–14], affecting the subcutaneous fat, usually of the abdomen and upper groin. Patients of Chinese and English ancestry have been reported [15]. The condition spreads in a centrifugal fashion, with a central, large, bluish depressed area and slight erythema of the edge. Further experience has shown that the original name is inappropriate, because the condition may affect other areas, and may occur outside infancy and not affecting the abdomen [16,17]. The condition may be strikingly unilateral [18,19]. One case is reported to have lasted over 40 years, and was associated with angioblastoma, which occurred at the same site at the age of 46 years [11]. Regional lymphadenopathy may occur [13]. A 10-year-old boy with a centrifugal lipodystrophy also developed serpiginous erythema of the scalp with scarring alopecia [20]. Ulceration may also be a complication [21].

Histology shows a decrease in the subcutaneous fat, with an inflammatory infiltrate in the lower dermis and subcutis. Immunocytochemistry has more recently suggested the possible involvement of apoptosis as a factor responsible for fatty tissue degeneration [22]. A patient has been reported who showed characteristics of both centrifugal and progressive lipodystrophy [17].

Treatment. Treatment is disappointing, although after the disease activity has ceased there seems to be regrowth of fat in 75% of cases. Some improvement has been reported in most cases treated with oral and topical corticosteroids [10].

References

1 Peters MS, Winkelmann RK. The histopathology of localized lipoatrophy. *Br J Dermatol* 1986; **114**: 27–36.
2 Rongioletti F, Rebora A. Annular and semicircular lipoatrophies: three cases and review of the literature. *J Am Acad Dermatol* 1989; **20**: 433–6.
3 Bloch PH, Runne U. Lipotrophia semicircularis beim Mann: Zusammentreffen von Arterienvariet und Mikrotraumata als mögliche Krankheitsursache. *Hautarzt* 1978; **29**: 270–2.
4 Gschwandter WR, Munzberger H. Lipoatrophia semicircularis. *Wien Klin Wochenschr* 1975; **87**: 164–8.
5 Karkaritas C, Miller JA, Kirby JD. Semicircular lipoatrophy. *Br J Dermatol* 1981; **105**: 591–3.
6 Jablonska S, Szczepanski A, Gorkiewicz A. Lipoatrophy of the ankles and its relation to other lipoatrophies. *Acta Derm Venereol (Stockh)* 1975; **55**: 135–40.
7 Masala MV, Tedde G, Cottoni F. Annular atrophy of the ankles: an unusual case associated with bone abnormality. *Dermatology* 2001; **203**: 81–2.
8 Gruber PC, Fuller LC. Lipoatrophy semicircularis induced by trauma. *Clin Exp Dermatol* 2001; **26**: 269–71.
9 Peters MS, Winkelmann RK. Localized lipoatrophy (atrophic connective tissue disease panniculitis). *Arch Dermatol* 1980; **116**: 1363–8.
10 Imamura S, Yamada M. Lipodystrophia centrifugalis abdominalis infantilis. *Br J Dermatol* 1977; **96**: 96.
11 Hiraiwa A, Takai K, Fukui Y *et al.* Non-regressing lipodystrophia centrifugalis abdominalis with angioblastoma (Nakagawa). *Arch Dermatol* 1990; **126**: 206–9.
12 Imamura S, Yamada M, Yamamoto K. Lipodystrophia centrifugalis abdominalis infantilis: a follow-up study. *J Am Acad Dermatol* 1984; **11**: 203–9.
13 Imamura S, Yamada M, Yamamoto K *et al.* Lipodystrophia centrifugalis abdominalis infantilis. *Hautarzt* 1979; **30**: 360–4.
14 Makino K, Inone T, Shimao S. Lipodystrophia centrifugalis abdominalis infantilis. *Arch Dermatol* 1972; **106**: 899–900.

15 Mak K-H, Ho H-F, Chan L-V, Chong L-Y. Lipodystrophia centrifugalis abdominalis infantalis: two cases from China. *J Dermatol* 2001; **28**: 320–3.
16 Hagari Y, Sasaoka R, Nishiura S *et al*. Centrifugal lipodystrophy of the face mimicking progressive lipodystrophy. *Br J Dermatol* 1992; **127**: 407–10.
17 Higuchi T, Yamakage A, Tamuea T *et al*. Lipodystrophia centrifugalis abdominalis infantilis occurring in the neck. *Dermatology* 1994; **188**: 142–4.
18 Franks A, Verbov JL. Unilateral localised idiopathic lipoatrophy. *Clin Exp Dermatol* 1993; **18**: 468–9.
19 Zachary CB, Wells RS. Centrifugal lipodystrophy. *Br J Dermatol* 1984; **110**: 107–10.
20 Hagari Y, Ikehara A, Nuno K, Mihara M. Centrifugal lipodystrophy presenting with serpiginous erythema and alopecia. *Cutis* 2002; **69**: 281–3.
21 Aoki E, Kawana S. Lipodystrophia centrifugalis abnominalis infantilis with ulceration. *Dermatology* 2000; **200**: 280–1.
22 Okita H, Ohtsuka T, Yamakage A, Yamazaki S. Lipodystrophia centrifugalis abdominalis infantilis: immunohistochemical demonstration of an apoptotic process in the degenerating fatty tissue. *Dermatology* 2000; **201**: 370–2.

Partial or generalized lipoatrophies [1–3]

HIV-associated lipodystrophy syndrome has become by far and away the commonest. The remainder are rare syndromes where there is extensive absence, or progressive loss, of subcutaneous fat. Several syndromes are described: congenital generalized lipodystrophy, acquired generalized lipodystrophy, partial (cephalothoracic) lipodystrophy and partial face-sparing lipodystrophy [4]. Genetic explanations for these diseases are increasingly being reported [5].

Congenital generalized lipodystrophy

Synonyms
- Lipoatrophic diabetes
- Berardinelli–Seip syndrome (MIM 608694; MIM269700)

A rare congenital generalized lipoatrophy, autosomal recessive, with loss of the subcutaneous and visceral fat, hepatomegaly, increased bone growth, hyperlipaemia and, later, diabetes mellitus [1,3,6–8].

Aetiology. Two gene abnormalities on different chromosomes have been described, but some phenotypically similar pedigrees have an as yet undetermined genetic abnormality [9]. Congenital generalized lipodystrophy type I (CGL1) was mapped to chromosome 9q34 and CGL2 to chromosome 11q13. CGL1 is caused by mutations in the *AGPAT2* gene [10]. AGPAT enzymes are involved in triglyceride and glycerophospholipid biosynthesis. How the abnormality is converted into lipoatrophy is undetermined. CGL2 is caused by mutations in the *BSCL2* gene encoding a protein, seipin, expressed in neural tissue as well as adipocytes [11]. Again the effect of the abnormality is unknown. The phenotypic expression of both types is much the same, but CGL2 would appear to cause more morbidity than CGL1, with a higher incidence of premature death, more severe fat loss, including that in mechanical areas, more severe cardiomyopathy and more severe intellectual impairment [12]. CGL2 patients have higher insulin levels and earlier onset diabetes [13]. Lipodystrophy with cystic angiomatosis (Brunzell syndrome) demonstrates an *AGPAT2* mutation [14].

Histopathology. There is complete loss of subcutaneous and visceral fat.

Clinical features. There is complete loss of subcutaneous and other fat, present at birth or before the age of 2 years. As such, the musculature appears more defined and prominent. The children have an elevated metabolic rate accompanied by an excessive appetite and accelerated growth, sometimes producing an acromegaloid appearance. They are tall for their age; the somatic musculature is increased and the abdomen markedly protuberant, often with an umbilical hernia. There is often generalized hypertrichosis, even at birth, and the scalp hair becomes abundant and often curly with the onset of disease. Acanthosis nigricans starts in childhood, becoming more severe through adolescence. There is precocious enlargement of the genitalia, and in females marked enlargement of the clitoris. Affected men have normal fertility, but females are prone to oligomenorhoea, polycystic ovary and infertility. Hepatic steatosis leads to hepatomegaly, splenomegaly and cirrhosis. Younger patients show glycosuria only when given large amounts of glucose. Hyperglycaemia with excessive thirst and polyuria usually develop only after the age of 10 years, the evolving diabetes becoming markedly insulin resistant. Hypertriglyceridaemia, sometimes triggering pancreatitis, and low HDL cholesterol are other metabolic features.

Detailed metabolic and radiological studies have shown poor metabolically active adipose tissue, whereas mechanical adipose tissue may be well preserved [15]. X-rays show focal bone lesions which on MRI can be shown to be caused by absence of marrow fat [16].

Differential diagnosis. The main differential diagnosis of congenital generalized lipodystrophy is Donohue syndrome (leprechaunism) due to an insulin receptor defect [17]. Acanthosis nigricans and hypertrichosis may be present, as well as the generalized decrease in fat. However, the elfin facial appearance is a major difference. In SHORT syndrome (short stature, hyperextensibility of joints, ocular depression, Rieger anomaly and delay of dental eruption), an apparent autosomal dominant disorder, the lipodystrophy shows relative sparing on the legs [18]. Neonatal progeroid syndrome expresses fat loss confined to the face, distal extremities, and possibly the paravertebral and lateral gluteal regions [19]. Fat loss with mandibuloacral dysplasia is usually confined to the extremities though may be generalized [20].

Acquired generalized lipodystrophy [21]

Selective loss of body fat from large regions of the body occurs after birth, usually before adolescence.

Aetiology. The development of molecular genetics has allowed re-evaluation of the lipodystrophies, resulting in new diagnostic criteria for acquired generalized lipodystrophy (AGL), albeit still a heterogeneous mix. Individuals with a known or likely genetic abnormality are automatically excluded, as are patients with diminished subcutaneous fat in association with thyrotoxicosis, malabsorption, malnutrition and cachexia. Patients are then further divided into three groups: type 1, AGL with panniculitis

(25%); type 2, AGL with autoimmune disease (25%); and type 3, idiopathic (50%).

Histopathology. Type I AGL histology reveals a lobular panniculitis without vasculitis.

Clinical features. AGL is a disease of childhood and adolescence, with a female to male ratio of 3:1. The panniculitic type is expressed as a nodular inflammatory process occurring anywhere, but healing with a depressed area which might gradually enlarge without inflammation. More widespread, uninflamed fat loss might then occur, the whole evolving over several years. Some of these patients might have an autoimmune disease, but the true autoimmune AGL group do not have a clinical inflammatory panniculitis preceding the lipodystrophy. Juvenile dermatomyositis seems particularly associated with type 2 AGL [22]. The idiopathic group has neither of the features of type 1 or 2 AGL, and arises spontaneously or occasionally after a febrile illness. The degree of fat loss is less than the congenital counterpart; with variable preservation of visceral and mechanical fat pads but complete preservation of retro-orbital and bone marrow fat. Type 1 patients have less extensive fat loss, which may correlate with the less severe expression of anabolic and metabolic features. After fat loss, hepatomegaly from asteatosis is the commonest clinical feature, followed by acanthosis nigricans and hirsutism. Xanthomas are present in 50% of the type 3 group, but less in the other two. Excessive appetite and increased growth emphasize the overlap with the congenital type. Hyperinsulinaemia, diabetes mellitus, hypertriglyceridaemia, and low serum leptin and adiponectin levels are similarly present. Menstrual irregularities and polycystic ovary syndrome are less frequent than in the congenital type, as is hirsutism. Curly hair may still occur.

MRI imaging has provided a major advance in assessment of fat loss and fat hypertrophy, whether subcutaneous, visceral or mechanical [23]. Whether a simple MRI screening test of thigh fat will be a strong discriminator between normal and abnormal remains to be confirmed [23].

Patients with hepatomegaly may progress to cirrhosis, but the consequence of accelerated atherosclerosis seems a more important prognostic factor.

Differential diagnosis. In CGL fat loss is absent from birth. Other later-onset genetic lipodystrophies need to be excluded through clinical means, MRI scanning and confirmation of mutations. Cushing's syndrome, diabetes mellitus and thyrotoxicosis need to be excluded, as does any cachetic state such as HIV infection, malabsorption and malignancy. Localized lipoatrophy is focal and usually obvious from the history or distribution.

Treatment. Apart from genetic counselling, the management of CGL and AGL shows much overlap, with the emphasis placed on lessening the risk from glycaemic and dyslipidaemic metabolic consequences using standard management. If leptin deficiency and diabetes is present, CGL, AGL and partial lipodystrophic patients can have their insulin resistance and dyslipidaemia reversed if given continuing recombinant leptin therapy [24–27]. Diabetic complications and other features such as voracious appetite, hepatic steatosis, acanthosis nigricans and amenorrhoea can also be reversed, but not the subcutaneous fat loss. Surgical intervention for specific anatomical defects, such as the repair of severe buttock deformities with bilateral gluteus maximus muscle flap advancements [28], may be helpful.

References

1 Garg A. Acquired and inherited lipodystrophies. *N Engl J Med* 2004; **350**: 1220–34.
2 Hegele RA, Joy TR, Al-Attar SA *et al*. Thematic review series: adipocyte biology. Lipodystrophies: windows on adipose biology and metabolism. *J Lipid Res* 2007; **48**: 1433–44.
3 Seip M, Trygstad O. Generalized lipodystrophy. *Arch Dis Child* 1963; **38**: 447–53.
4 Mamalaki E, Katsantounis J, Papavasiliou S *et al*. A case of partial face sparing lipodystrophy combining features of generalised lipodystrophy. *J Am Acad Dermatol* 1995; **32**: 130–3.
5 Agarwal AK, Garg A. Genetic basis of lipodystrophies and management of metabolic complications. *Ann Rev Med* 2006; **57**: 297–311.
6 Berardinelli W. An undiagnosed endocrinometabolic syndrome: report of 2 cases. *J Clin Endocrinol Metab* 1954; **14**: 193–204.
7 Brunzell JD, Shankle SW, Bethune JE. Congenital generalized lipodystrophy accompanied by cystic angiomatosis. *Ann Intern Med* 1968; **69**: 501–16.
8 Reed WB, Dexter R, Corley C *et al*. Congenital lipodystrophic diabetes with acanthosis nigricans. *Arch Dermatol* 1965; **91**: 326–34.
9 Rajab A, Heathcote K, Joshi S *et al*. Heterogeneity for congenital generalized lipodystrophy in seventeen patients from Oman. *Am J Med Genet* 2002; **110**: 219–25.
10 Agarwal AK, Arioglu E, De Almeida S *et al*. AGPAT2 is mutated in congenital generalized lipodystrophy linked to chromosome 9q34. *Nat Genet* 2002; **31**: 21–3.
11 Magre J, Delepine M, Khallouf E *et al*. Identification of the gene altered in Berardinelli–Seip congenital lipodystrophy on chromosome 11q13. *Nat Genet* 2001; **28**: 365–70.
12 Van Maldergem L, Magre J, Khallouf TE *et al*. Genotype–phenotype relationships in Berardinelli–Seip congenital lipodystrophy. *J Med Genet* 2002; **39**: 722–33.
13 Fu M, Kazlauskaite R, Baracho Mde F *et al*. Mutations in Gng3lg and AGPAT2 in Berardinelli–Seip congenital lipodystrophy and Brunzell syndrome: phenotype variability suggests important modifier effects. *J Clin Endocrinol Metab* 2004; **89**: 2916–22.
14 Gomes KB, Pardini VC, Ferreira AC, Fernandes AP. Phenotypic heterogeneity in biochemical parameters correlates with mutations in AGPAT2 or Seipin genes among Berardinelli–Seip congenital lipodystrophy patients. *J Inherit Metab Dis* 2005; **28**: 1123–31.
15 Garg A, Fleckenstein JL, Peshock RM *et al*. Peculiar distribution of adipose tissue in patients with congenital generalized lipodystrophy. *J Clin Endocrinol Metab* 1992; **75**: 358–9.
16 Fleckenstein JL, Garg A, Bonte FJ *et al*. The skeleton in congenital, generalized lipodystrophy: evaluation using whole-body radiographic surveys, magnetic resonance imaging and technetium-99m bone scintigraphy. *Skeletal Radiol* 1992; **21**: 381–6.
17 Elsas LJ, Endo F, Strumlauf E *et al*. Leprechaunism: an inherited defect in a high-affinity insulin receptor. *Am J Hum Genet* 1985; **37**: 73–88.
18 Koenig R, Brendel L, Fuchs S. SHORT syndrome. *Clin Dysmorphol* 2003; **12**: 45–9.
19 O'Neill B, Simha V, Kotha V *et al*. Body fat distribution and metabolic variables in patients with neonatal progeroid syndrome. *Am J Med Genet A* 2007; **143A**: 1421–30.
20 Simha V, Garg A. Body fat distribution and metabolic derangements in patients with familial partial lipodystrophy associated with mandibuloacral dysplasia. *J Clin Endocrinol Metab* 2002; **87**: 776–85.
21 Misra A, Garg A. Clinical features and metabolic derangements in acquired generalized lipodystrophy: case reports and review of the literature. *Medicine (Baltimore)* 2003; **82**: 129–46.
22 Bingham A, Mamyrova G, Rother KI *et al*. Predictors of acquired lipodystrophy in juvenile-onset dermatomyositis and a gradient of severity. *Medicine (Baltimore)* 2008; **87**: 70–86.

23 Al-Attar SA, Pollex RL, Robinson JF *et al*. Quantitative and qualitative differences in subcutaneous adipose tissue stores across lipodystrophy types shown by magnetic resonance imaging. *BMC Med Imaging* 2007; **7**: 3.
24 Oral EA, Simha V, Ruiz E *et al*. Leptin-replacement therapy for lipodystrophy. *N Engl J Med* 2002; **346**: 570–8.
25 Moran SA, Patten N, Young JR *et al*. Changes in body composition in patients with severe lipodystrophy after leptin replacement therapy. *Metabolism* 2004; **53**: 513–9.
26 Ebihara K, Kusakabe T, Hirata M *et al*. Efficacy and safety of leptin-replacement therapy and possible mechanisms of leptin actions in patients with generalized lipodystrophy. *J Clin Endocrinol Metab* 2007; **92**: 532–41.
27 Park JY, Chong AY, Cochran EK *et al*. Type 1 diabetes associated with acquired generalized lipodystrophy and insulin resistance: the effect of long-term leptin therapy. *J Clin Endocrinol Metab* 2008; **93**: 26–31.
28 Okada E, Iwahira Y, Maruyama Y. Buttock deformity repair for congenital generalized lipodystrophy. *Plastic Reconstr Surg* 1995; **95**: 744–5.

Partial lipoatrophy [1,2]

Synonyms
- Partial lipodystrophy
- Barraquer–Simons disease
- Progressive lipodystrophy (MIM 608709)

This rare lipoatrophy occurs either in childhood or in young adults as an incidental part of a widespread mesodermal atrophy. The partial lipodystrophy locus has been mapped to chromosome 1q with no evidence of genetic heterogeneity [3].



Fig. 46.32 The typical cadaveric facies of a patient with partial lipodystrophy. She also has melasma.

Aetiology. Most patients are children or young adults when the disorder begins, but onset in the first year and in middle age is reported. Females are affected four or five times more frequently than males [4], and the condition is sometimes familial. It may follow an acute specific fever such as measles, but the common occurrence of non-specific fevers makes proof of this observation difficult. Facial hemiatrophy associated with loss of subcutaneous fat in borreliosis has been reported [5]. Partial lipodystrophy has followed damage to the region of the mid-brain or diencephalon [6]. The association of lipodystrophy with immunologically related renal disease [4,7–10], systemic sclerosis [11], systemic lupus erythematosus [12] and high titres of thyroid antibodies, supports the view of lipodystrophy being an immunological disorder in some patients [13], but one that requires more investigation.

It is difficult to explain the abnormal distribution of adipose tissue in partial lipodystrophy. Fatty tissue autotransplanted to an atrophic site lost fat, while atrophic tissue autotransplanted to a fatty site accumulated it, suggesting that local factors determine the distributions of fat [14]. The local factor may be neuronally mediated, as suggested by observations that there may be symmetrical segmental loss of fat, and the line demarcating dystrophic and normal tissue in partial lipodystrophy may correspond to a dermatome. Jensen [15] described increased adrenergic activity in a patient with partial lipodystrophy, and proposed that this was of significance, as adipocytes in the upper body are sensitive to the lipolytic effects of epinephrine (adrenaline) and those in the lower body are not. Alternatively, the pattern of disease may be related to complement factor D expression, a serine protease expressed in the kidney, but also by adipocytes. Activation of the alternative complement pathway by C3 nephritic factor (see below) however, could lead to complement-dependent lysis of adipocytes [16]. But the finding of mutations in the *LMNB2* gene in some patients with acquired partial lipodystrophy [17] suggests that a simple autoimmune process involving C3 nephritic factor is only part of the story.

Histopathology. There is usually complete loss of adipose tissue over the affected areas.

Clinical features. The disease is characterized by the relatively slow, symmetrical disappearance of the facial fat, producing a cadaverous appearance (Fig. 46.32) and complete loss of the subcutaneous fat in the upper half of the body (Weir–Mitchell type). In some cases, there is a coincidental hypertrophy of the subcutaneous fat of the lower part of the body (Laignel–Lavastine and Viard type) [3]. Ten per cent may have 'hemilipodystrophy' involving half of the face or body. Up to 90% can develop progressive membranous mesangiocapillary glomerulonephritis [3,18,19] and this can be precipitated by the contraceptive pill, pregnancy (especially in the third trimester) or the use of ergot derivatives [4]. A successful outcome in pregnancy is uncommon [20]. Thus, such patients should be observed by a renal physician during pregnancy, and oral contraceptives are prohibited.

The association of hypocomplementaemia and mesangiocapillary glomerulonephritis is now well established [7,8]. Approximately half of the patients with this form of glomerulonephritis have a persistently low plasma concentration of the third component of complement (C3), while the concentration of the fourth component (C4) is normal. This is accompanied by the presence

of a factor in serum that is capable of activating C3 without activation of the earlier components. This material has been termed 'C3 nephritic factor' or C3NeF [21,22]. Lupus, C3 nephritic factor and partial lipodystrophy are perhaps not as rare as previously thought [21,22]. Juvenile dermatomyositis is also a rare association [23].

The relationship between C3NeF, persistently low C3 and mesangiocapillary glomerulonephritis is not clear. It has been suggested that C3NeF predisposes the glomerulus to the development of mesangiocapillary glomerulonephritis in response to some other agent. In a series of 12 patients, four died from renal failure 10–25 years after the onset of the partial lipoatrophy [4]. Transplantation in one case resulted in normalization of C3 and the disappearance of C3NeF [18].

Insulin-dependent diabetes mellitus develops in one-third of patients with partial lipodystrophy. Retinitis pigmentosa, acanthosis nigricans and hepatomegaly are rare associated features [2]. Chronic purpura resulting from leukocytoclastic vasculitis has been reported [24]. This patient had extensive and moderate hypertrophy of the subcutaneous fatty tissue, macroglossia, polyarthralgia and mononeuritis. Myopathy associated with muscle weakness has rarely been reported, and is caused by fat droplets between the myofibrils [25]. Mammography in patients with partial lipodystrophy reveals unusually dense breasts with homogeneous opacities and ectopic fat depositions. These changes are possibly diagnostic, but confusing to the ill-informed radiologist [26]. Extrinsic allergic alveolitis has been reported in association with partial lipodystrophy, but with an acral distribution as opposed to the more usual facial involvement [27].

Treatment. There is little effective treatment, other than the prevention and treatment of kidney disease. New plastic surgical techniques, including free radial forearm adipofascial flaps, can markedly improve the facial appearance [28,29].

References

1 Poley JR, Stickler GB. Progressive lipodystrophy. *Am J Dis Child* 1963; **106**: 356–63.
2 Senior B, Gellis SS. The syndromes of total lipodystrophy and of partial lipodystrophy. *Pediatrics* 1964; **33**: 593–612.
3 Eisinger AJ, Shortland JR, Moorhead PJ. Renal disease in partial lipodystrophy. *QJM* 1972; **41**: 343–54.
4 Simpson NB, Cunliffe WJ, Davison A. Partial lipodystrophy, glomerulonephritis and hypocomplementaemia. *Br J Dermatol* 1979; **101** (Suppl. 17): 11.
5 Abele DC, Bedingfield RB, Chandler FW *et al.* Progressive facial hemiatrophy (Romberg syndrome) and borreliosis. *J Am Acad Dermatol* 1990; **22**: 531–5.
6 Hawes CR, Johnson FC, Palmer HD. Progressive hypothalamic dysfunction. *J Pediatr* 1954; **45**: 393–400.
7 Ipp MM, Minta JO, Gelfand EW. Disorders of the complement system in lipodystrophy. *Immunol Immunopathol* 1976; **7**: 281–7.
8 Sissons JGP, West RJ, Fallows J *et al*. The complement abnormalities of lipodystrophy. *N Engl J Med* 1976; **294**: 461–5.
9 Mehmet B, Ozlem E, Gulay D *et al*. Acute pancreatitis in a patient with partial lipodystrophy and membranoproliferative glomerulonephritis. *Nephrol Dial Transplant* 2001; **16**: 1930–1.
10 Levy Y, George J, Yona E, Shoenfeld Y. Partial lipodystrophy, mesangiocapillary glomerulonephritis, and complement dysregulation: an autoimmune phenomenon. *Immunol Res* 1998; **18**: 55–60.
11 Hall WS, Gillespie JJ, Tenczynski TE. Generalized lipodystrophy, scleroderma and Hodgkin's disease. *Arch Intern Med* 1978; **138**: 1303–4.
12 Ishiguro N, Kanazawa H, Ishibashi M, Kawashima M. Partial lipodystrophy in a patient with systemic lupus erythematosus. *Dermatology* 2002; **204**: 298–300.
13 Wilson WA, Sissons JGP, Morgan OS. Multiple autoimmune diseases with bilateral optic atrophy and lipodystrophy. *Ann Intern Med* 1978; **89**: 72–3.
14 Langhof H, Zabel R. Zür lipodystrophia progressiva. *Arch Klin Exp Dermatol* 1960; **210**: 313–21.
15 Jensen MD. Adrenergic regulation of lipolysis with lipoatrophy of the upper body. *Mayo Clin Proc* 1991; **66**: 704–10.
16 Mathieson PW, Peters DK. Lipodystrophy in MCGN type II: the clue to links between the adipocyte and the complement system. *Nephrol Dial Transplant* 1997; **12**: 1804–6.
17 Hegele RA, Cao H, Liu DM *et al*. Sequencing of the reannotated LMNB2 gene reveals novel mutations in patients with acquired partial lipodystrophy. *Am J Hum Genet* 2006; **79**: 383–9.
18 Ljunghall S, Fjellstrom KE, Wibell L. Partial lipodystrophy and chronic hypocomplementaemic glomerulonephritis. *Acta Med Scand* 1974; **195**: 493–7.
19 Peters DK, Charlesworth JA, Sissons JGP *et al.* Mesangiocapillary nephritis, partial lipodystrophy and hypocomplementaemia. *Lancet* 1973; **ii**: 535–8.
20 Akhter J, Quereshi R. Partial lipodystrophy and successful pregnancy outcome. *J Pak Med Assoc* 1995; **45**: 24–7.
21 Cronin CC, Higgins T, Molloy M. Lupus, C3 nephritic factor and partial lipodystrophy. *QJM* 1995; **88**: 298–9.
22 Walport MJ, Davies KA, Botto M *et al.* C3 nephritis factor and SLE: report of four cases and review of the literature. *QJM* 1994; **87**: 609–15.
23 Kavanagh GM, Colaco CB, Kennedy CTC. Juvenile dermatomyositis associated with partial lipoatrophy. *J Am Acad Dermatol* 1993; **28**: 348–51.
24 Perrot H, Delaup J-P, Chouvet B. Partial lipodystrophy, complement abnormalities and cutaneous leukocytoclastic vasculitis. *Ann Dermatol Vénéréol* 1987; **114**: 1083–91.
25 Orrell RW, Peatfield RC, Collins CE *et al.* Myopathy in acquired partial lipodystrophy. *Clin Neurol Neurosurg* 1995; **97**: 181–6.
26 Citagy OS, Benitez RP, Farzaneh NK *et al.* Unusual mammographic findings in a patient with partial lipodystrophy. *Am J Roentgen* 1993; **160**: 417–22.
27 Winhoven SM, Hafejee A, Coulson IH. An unusual case of an acquired acral partial lipodystrophy (Barraquer–Simons syndrome) in a patient with extrinsic allergic alveolitis. *Clin Exp Dermatol* 2006; **31**: 594–6.
28 Coessens BC, Van Geertrudyen JP. Simultaneous bilateral facial reconstruction of a Barraque–Simons lipodystrophy with free TRAM flaps. *Plast Reconstr Surg* 1995; **95**: 911–5.
29 Koshy CE, Evans J. Facial contour reconstruction in localised lipodystrophy using free radial forearm adipofascial flaps. *Br J Plast Surg* 1998; **51**: 499–502.

Partial face-sparing lipodystrophy

Synonym
- Kobberling–Dunnigan syndrome

This even rarer form is a genetically heterogeneous set of disorders characterized by a widespread but partial absence of subcutaneous fat usually sparing the face and neck; it can be easily missed because of the normal facial appearance [1]. Onset is usually during adolescence and the condition is often familial. With the development of molecular genetics this phenotype has been superseded by an evolving genetic classification into three groups: familial partial lipodystrophy (FPLD) one, two and three [2].

FPLD1. FPLD1 (Kobberling type; MIM 608600) at present has no known molecular genetic basis. Kobberling *et al.* described three patients [3], the proband, her mother and her sister, with the same clinical appearance of complete absence of subcutaneous fat of arms and legs but with well-developed adipose tissue on the trunk and face. His patient also had hyperlipidaemia, eruptive xanthoma and insulin-resistant diabetes. Herbst *et al.* [4] described a further 13 patients having this phenotype of peripheral lipodystrophy

with normal or increased central obesity and absence of the FDLP1 and FDLP2 genotype, emphasizing the benefit of measuring the ratio of skinfold thickness from abdomen to thigh, which was significantly higher than normal. Patients also had components of the metabolic syndrome, including hypertension, insulin resistance and severe hypertriglyceridaemia resulting in pancreatitis. Premature coronary artery disease was present in 31%.

FPLD2. FPLD2 (Dunnigan type; MIM 151660) results from heterozygous mutations in the *LMNA* gene encoding nuclear lamin A/C usually of an autosomal dominant pattern, but rarely sex-linked recessive. Lamins are a class of intermediate filaments forming the inner membrane of a nucleus. The precise mechanism, structural or otherwise, whereby the gene defect leads to lipodystrophy is unknown, but as lamins are ubiquitous in human cells, different mutations allow lipodystrophy to be associated with other phenotypes, including Hutchinson–Gilford progeria syndrome (HGPS), atypical Werner syndrome, Emery–Dreifuss muscular dystrophy, limb-girdle muscular dystrophy, mandibuloacral dysplasia (MAD), cardiomyopathies, cardiac conduction defects and Charcot–Marie–Tooth disease [2].

Dunnigan [5] described two families with an autosomal dominant disorder appearing in adolescence, and manifesting as loss of subcutaneous fat on the limbs so that the underlying musculature and superficial veins were more defined. The face appeared fuller than normal and moderate genital hypertrophy was noted. Acanthosis nigricans, tuberoeruptive xanthomata and insulin resistance were commonly associated. With increasing numbers of mutations being described, phenotypic heterogeneity is becoming apparent [6]. Patients with abnormalities in the lamin A gene only may demonstrate mild loss of limb fat, no gluteal loss and little of the features of insulin resistance. Those patients with lamin A/C abnormalities are more likely to express more extensive loss of fat, hypertriglyceridaemia, diabetes mellitus, insulin resistance, acanthosis nigricans, hirsutism and polycystic ovary syndrome. Individuals with *LMNA* mutations are recognized as having premature atherosclerosis and early coronary heart disease [7].

FPLD3. FPLD3 (MIM 604637) is associated with many different heterozygous mutations in the *PPARG* gene encoding peroxisome proliferator-activated receptor-γ (PPARγ). The PPAR protein is a nuclear transcription factor important in adipocyte differentiation, and the precise mechanism of effect for the gene abnormality is uncertain [2]. The peripheral fat loss is not as pronounced as FPLD2, but metabolic changes may be more severe. Severe hypertension is a feature [8].

Because the overall distribution of fat loss in FLPD is peripheral with facial sparing, the differential diagnosis includes Cushing's syndrome. Some patients have increased fat deposition on the chin, face and neck, and a buffalo hump, to confuse things further. Truncal obesity, lipomatosis and HIV lipodystrophy also need to be excluded.

Treatment. Management involves genetic counselling, attention to metabolic consequences and exclusion of associated syndromes. Treatment of the metabolic effects with thiazolidinediones, which attach to PPARγ, has been of some benefit in patients with and without defined gene defects [9]. They have increased subcutaneous fat in some subjects, but their use is of still uncertain benefit [10,11].

References

1 Mamalaki E, Katsantonis J, Papavasiliou S *et al*. A case of partial face-sparing lipodystrophy combining features of generalized lipodystrophy. *J Am Acad Dermatol* 1995; **32**: 130–3.

2 Hegele RA, Joy TR, Al-Attar SA *et al*. Thematic review series: adipocyte biology. Lipodystrophies: windows on adipose biology and metabolism. *J Lipid Res* 2007; **48**: 1433–44.

3 Kobberling J, Willms B, Kattermann R *et al*. Lipodystrophy of the extremities: a dominantly inherited syndrome associated with lipoatrophic diabetes. *Humangenetik* 1975; **29**: 111–20.

4 Herbst KL, Tannock LR, Deeb SS *et al*. Kobberling type of familial partial lipodystrophy: an underrecognized syndrome. *Diabetes Care* 2003; **26**: 1819–24.

5 Dunnigan MG, Cochrane M, Kelly A *et al*. Familial lipoatrophic diabetes with dominant transmission: a new syndrome. *QJM* 1974; **43**: 33–48.

6 Garg A, Vinaitheerthan M, Weatherall PT *et al*. Phenotypic heterogeneity in patients with familial partial lipodystrophy (Dunnigan variety) related to the site of missense mutations in lamin a/c gene. *J Clin Endocrinol Metab* 2001; **86**: 59–65.

7 Hegele RA. Premature atherosclerosis associated with monogenic insulin resistance. *Circulation* 2001; **103**: 2225–9.

8 Barroso I, Gurnell M, Crowley VEF *et al*. Dominant negative mutations in human PPAR-gamma associated with severe insulin resistance, diabetes mellitus and hypertension. *Nature* 1999; **402**: 880–3.

9 Sleilati GG, Leff T, Bonnett JW *et al*. Efficacy and safety of pioglitazone in treatment of a patient with an atypical partial lipodystrophy syndrome. *Endocr Pract* 2007; **13**: 656–61.

10 Arioglu E, Duncan-Morin J, Sebring N *et al*. Efficacy and safety of troglitazone in the treatment of lipodystrophy syndromes. *Ann Intern Med* 2000; **133**: 263–74.

11 Owen KR, Donohoe M, Ellard S *et al*. Response to treatment with rosiglitazone in familial partial lipodystrophy due to a mutation in the LMNA gene. *Diabet Med* 2003; **20**: 823–7.

HIV-associated lipodystrophy syndrome

Patterns of fat atrophy and hypertrophy with metabolic changes in HIV patients taking highly active antiretroviral therapy (HAART) are described below [1–3].

Aetiology. Since the syndrome was described in 1998 [1], evolving research continues to uncover different patterns, mechanisms and risk factors [4]. Three patterns are described: lipoatrophy, lipohypertrophy and mixed (lipoatrophy and lipohypertrophy), though one group has found no association between peripheral lipoatrophy and visceral hypertrophy [5,6]. Lipoatrophy may be peripheral subcutaneous (face, limbs and buttocks), central subcutaneous (trunk and neck) and/or visceral (omental, mesenteric and perinephric). Lipohypertrophy may occur at central subcutaneous sites, especially dorsocervical (buffalo hump) and chin, and/or viscerally. Intrathoracic fat may also be increased [7]. Patients with lipohypertrophy are at present classed as having the HIV-associated adipose redistribution syndrome (HARS), which may or may not be associated with lipoatrophy [8]. The prevalence of lipodystrophy in HIV is difficult to ascertain because of problems with diagnostic criteria, but may be 17% in adults treated with protease inhibitor-containing therapy for less than 1 year, and around 40% in those treated for 1 year or more [2,9] though it may be as high as 53% [10]. Significant risk factors include

CD4-positive count, viral load, duration of therapy and age. Patients with fat loss are more likely to have taken an older thymidine analogue nucleoside reverse transcriptase inhibitor (NRTI), particularly stavudine or zidovudine, and be of white race. Patients showing hypertrophy are more likely to have taken an older protease inhibitor (PI) (indinavir or nelfinavir), and be of female sex [11]. Rarely, lipoatrophy is seen in patients who have not been exposed to HAART. The syndrome also occurs in children but less so if they received a lower dose of the protease inhibitor [12]. Another childhood study showed a prevalence of lipodystrophy of 9%, 47% and 65% at 48, 96 and 144 weeks after HAART initiation respectively [13]. At week 144, central lipohypertrophy (46%) was most frequent, with peripheral lipoatrophy (20%), and combined type (34%) less frequent. This variety of patterns of fat atrophy and hypertrophy suggests different mechanisms dependent on drug combinations, viral effects and host factors, such as genetic polymorphisms, interacting to result in a particular phenotype [4].

Pathogenesis. The mechanisms of HIV lipodystrophy are complex [11,14]. Lipoatrophy is associated with impaired adipocyte differentiation and increased apoptosis, insulin resistance and increased lipolysis, altered adipocyte cytokine expression and mitochondrial toxicity. Both PIs and NRTIs can inhibit adipocyte differentiation. Both alter adipocytokine secretion (reduced adiponectin and normal or increased leptin) and adipocyte TNF-α secretion (increased). NRTIs seem mainly responsible for mitochondrial toxicity. Buffalo hump lipohypertrophy [15] shows unaltered expression of marker genes of adipogenesis, but altered gene expression for enhanced cell proliferation plus features of a brown-versus-white fat phenotype. TNF-α secretion is not increased. Cortisol-induced new adipogenesis may be responsible for visceral fat hypertrophy combined with a need for disposal of free fatty acids, generated by lipolysis [11].

Histopathology. There is a diminution in the volume of subcutaneous fat, with the lobules containing adipocytes of varying size, interspersed with increased capillaries. Foci of lymphoid infiltrates and lipogranulomas are seen [3]. Scattered apoptotic adipocytes may also be present [16]. Ultrastructurally, buffalo hump lipohypertrophy shows adipocytes intermediate between those in brown and white fat [17].

Clinical features. Females (28%) are affected by lipoatrophy less than males (38%) [5,6]. The loss is most apparent in the face. Loss of buccal, parotid and pre-auricular fat pads produces a prominent cheekbone, and melolabial folds emphasized by the sunken cheeks and sometimes enlarged parotid glands. Loss of retro-orbital fat produces sunken eyes. Limb fat loss allows superficial veins and muscle to appear more defined. Central subcutaneous fat accumulation may be present on the upper back, neck (buffalo hump), on the breasts, suprapubic area [18], below the jaw, in the supraclavicular region or as multiple lipomas. Omental fat accumulation produces a protuberant abdomen and an increased waist to hip circumference ratio, sometimes provoking symptomatology such as abdominal distension, gastroesophageal reflux and sleep disturbances.

Lipoatrophy of the face is so recognizable that the altered appearance, indicating potential HIV-positivity, can be devastating for the patient [19]. Erosion of self-esteem, diminished desirability, attractiveness and sexual function, anxiety and depression may lead to discontinuation of therapy, though non-adherence is disputed [20]. Patients' subjective reporting of lipodystrophy correlates better with diminished quality of life than physician evaluation [19], and the absence of universally accepted clinical measurement criteria for lipodystrophy is still a handicap. Objective measurement of body fat may be performed with ultrasonography, dual-energy X-ray absorptiometry (DEXA), CT and MRI scanning, though DEXA scans do not distinguish between visceral fat compartments [21]. Anthropometry, such as waist and hip circumference and ratio [22], perhaps combined with ultrasonography [23], may provide the simplest and cheapest clinical method of evaluation, particularly for metabolic risk factors, with MRI remaining the gold standard [24].

Metabolic changes do not appear to be as severe in the HIV lipodystrophy group as in CGL [25], with acanthosis nigricans, hypertrichosis and PCOS almost never being seen. This may be related to the fact that insulin resistance is less frequent. Abnormalities in glucose homeostasis occur in 23%, and in hyperlipidaemia in 74%, of patients [26]. In a study of 614 patients, 20 months after initiation of protease inhibitor therapy, a cross-sectional study demonstrated that 23% had abnormal glucose metabolism, 20% had hypertriglyceridaemia and 57% hypercholesterolaemia [27]. In children at 144 weeks, fasting hypertriglyceridaemia was detected in 12%, hypercholesterolaemia in 11%, and increased plasma glucose in 4% [13]. Insulin resistance is related to increased fat in the liver rather than visceral adiposity [28]. Hyperlactataemia may be seen. However, the prevalence of the metabolic syndrome in HIV patients without lipodystrophy is disputed. One study from the USA found a prevalence of 14–18%, compared to a control prevalence of 24% for a non-HIV-positive adult population [29]. In another study of female HIV-positive patients only, prevalence was 33% versus 22% in controls [30], while a third study found no difference between HIV positive and negative patients [31]. Where obvious lipoatrophy and an increased waist circumference is present, patients often have insulin resistance [25].

Differential diagnosis. HIV lipodystrophy can be differentiated from HIV-wasting syndrome in that it is seen in patients responding to HAART, and lean body mass is preserved.

Management. Prevention and delay of progression/reversal of lipodystrophy, treatment of metabolic effects, and surgical interventions provide the mainstay of treatment [32]. Choosing the right combination of newer HAART drugs, and avoiding stavudine and zidovudine, reduces the risk of developing lipoatrophy. Delaying the timing of treatment, employing treatment interruptions, and treatment switching may all help. The addition of a thiazolidinedione (pioglitazone) may be beneficial in lipoatrophy. Diet and exercise may reduce visceral adiposity, as may the use of growth hormone and metformin; possibly at the cost of aggravating subcutaneous lipoatrophy. Management of traditional risk factors, rather than HIV treatment-associated ones, may be more important for lessening cardiovascular disease from the metabolic

syndrome [31]. Stopping smoking, diet and exercise to achieve an appropriate BMI should be the first line approaches. If lipid levels remain high after lifestyle changes and HAART switching, a statin, or fibrate if triglyceride levels are high as well as cholesterol, should be introduced. Likewise, if lifestyle changes have not achieved strict glycaemic control, metformin should be introduced for an overweight patient and pioglitazone for a lipoatrophic one. Hypertension, if present, should be addressed.

Surgical interventions for lipoatrophy include autologous fat injection, flaps and injection of fillers such as polylactic acid [33]. Fat injections may need to be repeated but can provide a satisfactory result [34], provided the source is not the brown fat in a buffalo hump. Polylactic acid, a synthetic polymer, may need to be injected repeatedly in severe facial wasting, but is safe, and effective, with good patient acceptance [35]. Liposuction is helpful for buffalo humps despite the fibrous septa and the high risk of recurrence [36]. Simple lipectomy treats gynaecomastia and lipomas.

References

1 Carr A, Samaras K, Burton S *et al*. A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. *AIDS* 1998; **12**: F51–8.

2 Chen D, Misra A, Garg A. Clinical review 153: Lipodystrophy in human immunodeficiency virus-infected patients. *J Clin Endocrinol Metab* 2002; **87**: 4845–56.

3 Pujol RM, Domingo P, Xavier-Matias-Guiu *et al*. HIV-1 protease inhibitor-associated partial lipodystrophy: clinicopathologic review of 14 cases. *J Am Acad Dermatol* 2000; **42**: 193–8.

4 Lichtenstein KA. Redefining lipodystrophy syndrome: risks and impact on clinical decision making. *J Acquir Immune Defic Syndr* 2005; **39**: 395–400.

5 Bacchetti P, Gripshover B, Grunfeld C *et al*. Study of fat redistribution and metabolic change in HIV infection (FRAM). Fat distribution in men with HIV infection. *J Acquir Immune Defic Syndr* 2005; **40**: 121–31.

6 Study of Fat Redistribution and Metabolic Change in HIV Infection (FRAM). Fat distribution in women with HIV infection. *J Acquir Immune Defic Syndr* 2006; **42**: 562–71.

7 Blanco JL, Biglia A, Martinez E *et al*. Intrathoracic fat in HIV-infected patients. *HIV Med* 2006; **7**: 213–7.

8 Lichtenstein K, Balasubramanyam A, Sekhar R *et al*. HIV-associated adipose redistribution syndrome (HARS): definition, epidemiology and clinical impact. *AIDS Res Ther* 2007; **4**: 16.

9 Thiébaut R, Daucourt V, Mercié P *et al*. Lipodystrophy, metabolic disorders, and human immunodeficiency virus infection: Aquitaine Cohort, France, 1999. Groupe d'Epidémiologie Clinique du Syndrome d'Immunodéficience Acquise en Aquitaine. *Clin Infect Dis* 2000; **31**: 1482–7.

10 Miller J, Carr A, Emery S *et al*. HIV lipodystrophy: prevalence, severity and correlates of risk in Australia. *HIV Med* 2003; **4**: 293–301.

11 Lichtenstein K, Balasubramanyam A, Sekhar R *et al*. HIV-associated adipose redistribution syndrome (HARS): etiology and pathophysiological mechanisms. *AIDS Res Ther* 2007; **4**: 14.

12 Amaya RA, Kozinetz CA, McMeans A *et al*. Lipodystrophy syndrome in human immunodeficiency virus-infected children. *Pediatr Infect Dis J* 2002; **21**: 405–10.

13 Aurpibul L, Puthanakit T, Lee B *et al*. Lipodystrophy and metabolic changes in HIV-infected children on non-nucleoside reverse transcriptase inhibitor-based antiretroviral therapy. *Antivir Ther* 2007; **12**: 1247–54.

14 Mallewa JE, Wilkins E, Vilar J *et al*. HIV-associated lipodystrophy: a review of underlying mechanisms and therapeutic options. *J Antimicrob Chemother* 2008; **62**: 648–60.

15 Guallar JP, Gallego-Escuredo JM, Domingo JC *et al*. Differential gene expression indicates that 'buffalo hump' is a distinct adipose tissue disturbance in HIV-1-associated lipodystrophy. *AIDS* 2008; **22**: 575–84.

16 Domingo P, Matias-Guiu X, Pujol RM *et al*. Subcutaneous adipocyte apoptosis in HIV-1 protease inhibitor-associated lipodystrophy. *AIDS* 1999; **13**: 2261–7.

17 Fessel WJ, Follansbee SB, Barker B. Ultrastructural findings consistent with brown adipocytes in buffalo humps of HIV-positive patients with fat redistribution syndrome. *Antivir Ther* 2000; **3** (Suppl. 5): 25.

18 Guaraldi G, Orlando G, Squillace N *et al*. Prevalence of and risk factors for pubic lipoma development in HIV-infected persons. *J Acquir Immune Defic Syndr* 2007; **45**: 72–6.

19 Guaraldi G, Murri R, Orlando G *et al*. Severity of lipodystrophy is associated with decreased health-related quality of life. *AIDS Patient Care STDS* 2008; **22**: 577–85.

20 Collins EJ, Burgoyne RW, Wagner CA *et al*. Lipodystrophy severity does not contribute to HAART nonadherence. *AIDS Behav* 2006; **10**: 273–7.

21 Baril JG, Junod P, Leblanc R *et al*. HIV-associated lipodystrophy syndrome: A review of clinical aspects. *Can J Infect Dis Med Microbiol* 2005; **16**: 233–43.

22 Scherzer R, Shen W, Bacchetti P *et al*. Study of Fat Redistribution Metabolic Change in HIV Infection (FRAM). Simple anthropometric measures correlate with metabolic risk indicators as strongly as magnetic resonance imaging-measured adipose tissue depots in both HIV-infected and control subjects. *Am J Clin Nutr* 2008; **87**: 1809–17.

23 Padilla S, Gallego JA, Masiá M *et al*. Ultrasonography and anthropometry for measuring regional body fat in HIV-infected patients. *Curr HIV Res* 2007; **5**: 459–66.

24 Dinges WL, Chen D, Snell PG *et al*. Regional body fat distribution in HIV-infected patients with lipodystrophy. *J Investig Med* 2005; **53**: 15–25.

25 Leow MK, Addy CL, Mantzoros CS. Clinical review 159: Human immunodeficiency virus/highly active antiretroviral therapy-associated metabolic syndrome: clinical presentation, pathophysiology, and therapeutic strategies. *J Clin Endocrinol Metab* 2003; **88**: 1961–76.

26 Carr A, Samaras K, Thorisdottir A *et al*. Diagnosis, prediction, and natural course of HIV-1 protease-inhibitor-associated lipodystrophy, hyperlipidaemia, and diabetes mellitus: a cohort study. *Lancet* 1999; **353**: 2093–9.

27 Saves M, Raffi F, Capeau J *et al*. Factors related to lipodystrophy and metabolic alterations in patients with human immunodeficiency virus infection receiving highly active antiretroviral therapy. *Clin Infect Dis* 2002; **34**: 1396–405.

28 Sutinen J, Hakkinen AM, Westerbacka J *et al*. Increased fat accumulation in the liver in HIV-infected patients with antiretroviral therapy-associated lipodystrophy. *AIDS* 2002; **16**: 2183–93.

29 Samaras K, Wand H, Law M *et al*. Prevalence of metabolic syndrome in HIV-infected patients receiving highly active antiretroviral therapy using International Diabetes Foundation and Adult Treatment Panel III criteria: associations with insulin resistance, disturbed body fat compartmentalization, elevated C-reactive protein, and [corrected] hypoadiponectinemia. *Diabetes Care* 2007; **30**: 113–9.

30 Sobieszczyk ME, Hoover DR, Anastos K *et al*. Prevalence and predictors of metabolic syndrome among HIV-infected and HIV-uninfected women in the Women's Interagency HIV Study. *J Acquir Immune Defic Syndr* 2008; **48**: 272–80.

31 Mondy K, Overton ET, Grubb J *et al*. Metabolic syndrome in HIV-infected patients from an urban, midwestern US outpatient population. *Clin Infect Dis* 2007; **44**: 726–34.

32 Lundgren JD, Battegay M, Behrens G *et al*. EACS Executive Committee. European AIDS Clinical Society (EACS) guidelines on the prevention and management of metabolic diseases in HIV. *HIV Med* 2008; **9**: 72–81.

33 Nelson L, Stewart KJ. Plastic surgical options for HIV-associated lipodystrophy. *J Plast Reconstr Aesthet Surg* 2008; **61**: 359–65.

34 Burnouf M, Buffet M, Schwarzinger M *et al*. Evaluation of Coleman lipostructure for treatment of facial lipoatrophy in patients with human immunodeficiency virus and parameters associated with the efficiency of this technique. *Arch Dermatol* 2005; **141**: 1220–4.

35 Valantin MC, Aubron-Olivier C, Ghosn J *et al*. Polylactic acid implants (Newfill)® to correct facial lipoatrophy in HIV-infected patients: results of the open-label study VEGA. *AIDS* 2003; **17**: 2471–7.

36 Davison SP, Timpone J Jr, Hannan CM. Surgical algorithm for management of HIV lipodystrophy. *Plast Reconstr Surg* 2007; **120**: 1843–58.

Lipomas

Lipomas are benign tumours composed of mature fat cells. They are found in the subcutaneous tissue and less commonly in internal organs.

Aetiology. The metabolic changes associated with benign tumours are varied, but include fundamental defects responsible for the altered growth properties of the tumour. It has been demonstrated that loss of negative-feedback control regulatory enzymes (by citrate or phosphofructokinase) may be an early feature in the development of lipoma [1].

Histopathology. Fat cells in groups slightly larger than the normal lobule are typically enclosed within a capsule of connective tissue, but the capsule may be deficient and the tumour then appears locally invasive. Relatively large blood vessels are seen traversing the connective tissue septa. Primitive fat cells may be found in clinically benign lipomas in children [2]. Xanthomatous and mucinous changes appear in many lipomas. Lipomas exhibit, like many other solid tumours, distinctive cytogenic abnormalities (karyotypic aberrations affecting mainly 12q, 6p, 13q). Such distinctive changes may be of help in histologically borderline or difficult cases [3]. Variants of lipoma with large areas of normal fat cells such as spindle cell lipoma/pleomorphic lipoma and atypical lipomatous tumour are discussed in Chapter 56. For other rare lipomatous-like tumours the reader is referred to specialized texts [4].

Clinical features. A lipoma is a subcutaneous nodule, often lobulated, with a characteristic soft, putty-like consistency. The overlying skin is normal and moves freely over the tumour, and feels cooler than the surrounding skin. The tumour grows very slowly to reach a diameter that is usually between 2 and 10 cm but may be considerably greater. The most common sites are the neck, shoulders and upper arms, back and thighs. There are rarely any subjective symptoms, but pain from pressure on the nerves is sometimes experienced. Another rare event is infiltration of adjacent tissues, in a particular muscle [5]. In these patients, there is a high recurrence rate after surgical intervention because of its diffuse infiltration; thus complete surgical excision is often impossible [6]. Fat necrosis may cause enlargement, pain and tenderness. A large lipoma on the exposed skin of the lower legs is susceptible to nodular perniosis.

There may be only one lipoma, or large numbers [7] may develop at intervals over a period of years. Seven per cent of patients with lipoma have multiple lesions [8,9]. Such lipomas may be randomly distributed, or more or less confined to one region of the body. In most patients, the presence of multiple lipomas appears to have no special significance [2]. They may, however, be associated with neurofibromatosis, or with visceral lipomas in the respiratory, alimentary or genitourinary tract. Tendon sheath lipomas are rare and are usually associated with a mild discomfort [10]. They are an inconstant feature of Gardner's syndrome, in which they are associated with multiple sebaceous cysts, osteomas and polyposis of the colon. Multiple lipomas may also be a pointer to Proteus syndrome, Cowden's disease and Bannayan's syndrome. In addition to multiple lipomas, the latter exhibits macrocephaly, lymphangiomas and haemangiomas (see Congenital diffuse lipomatosis, below) [11].

Diagnosis. The diagnosis is usually easy, but in cases of doubt a biopsy should be performed. Angiolipomas are morphologically similar to lipomas, but are intermittently painful. Lipofascial herniae in the natal or perianal region simulate lipomas. Excision and suture are required to prevent recurrence. Mobile encapsulated lipomas are literally very mobile and can be moved from side to side over a range of up to 8 cm [12].

An epidermoid cyst can mimic a lipoma. However, the presence of the central punctum gives a clue to the correct diagnosis. The possibility of hibernoma should be considered when tumours appear in the thigh, neck and scapular region.

Treatment. This usually depends on the patient's desire for the lipoma to be surgically removed. Lipoma of the lumbar region may be associated with underlying spina bifida occulta, and removal of the tumour is dangerous without simultaneous exploration of the cauda equina. An MRI scan is essential in such patients; the spinal cord involvement is more frequent in girls than in boys, and is significantly associated with bladder dysfunction [13].

References

1 Atkinson JNC, Galton DJ, Gilbert C. Regulatory defect of glycolysis in human lipoma. *BMJ* 1974; **i**: 101–2.
2 Wakeley C, Somerville P. Lipomas. *Lancet* 1952; **ii**: 995–9.
3 Fletcher CDM, Akerman M, Dal Cin P *et al*. Correlation between clinicopathological features and karyotype in lipomatous tumours. *Am J Pathol* 1996; **148**: 623–6.
4 Mentzel T. Cutaneous lipomatous neoplasms. *Semin Diagn Pathol* 2001; **18**: 250–7.
5 Mattel SF, Persky MS. Infiltrating lipoma of the sternocleidomastoid muscle. *Laryngoscope* 1983; **93**: 205–7.
6 Chen CM, Lo LJ, Wong HF. Congenital infiltrating lipomatosis of the face: case report and literature review. *Chang Gung Med J* 2002; **25**: 194–200.
7 Adam BA, Chan YS. Congenital diffuse lipomatosis with diabetes mellitus. *Br J Clin Pract* 1974; **28**: 101–2.
8 Osment LS. Cutaneous lipomas and lipomatosis. *Surg Gynecol Obstet* 1968; **127**: 129–32.
9 Von Knoth W. Über Naevus lipomatosus cutaneous superficialis Hoffmann–Zurhelle und über Naevus naevocellularis partial lipomatoses. *Dermatologica* 1962; **125**: 161–73.
10 Sullivan CR, Dahlin DC, Bryan RS. Lipoma of the tendon sheath. *J Bone Joint Surg* 1956; **38**: 1275–80.
11 Bannayan GA. Lipomatosis, angiomatosis and macroencephalia. *Arch Pathol* 1971; **92**: 1–5.
12 Trapp CF, Baker EJ. Mobile encapsulated lipomas. *Cutis* 1992; **49**: 63–4.
13 Dorward NL, Scatliff JH, Hayward RD. Congenital lumbosacral lipomas: pitfalls in analysing the result of prophylactic surgery. *Childs Nerv Syst* 2002; **18**: 326–32.

Angiolipoma

Angiolipomas are benign encapsulated lobulated tumours, differing from a lipoma in the excessive degree of vascular (capillary) proliferation histologically and in the possession of a normal karyotype cytogenetically. Approximately 10% of all lipomatous lesions examined pathologically are angiolipomas [1]. The degree of vascularity varies and there is no agreed parameter to distinguish between a lipoma and a poorly-vascularized angiolipoma. Fibrin thrombi are common. The age of onset is relatively young, and in one series of 288 patients averaged 17 years. Clinically, the lesions are from 0.5 to 5 cm in diameter and closely resemble lipomas. They are usually painful and tender and are sometimes bluish in colour [2]. The degree of pain varies with the degree of

vascularization. They occur most frequently on the arms, legs and abdomen, and are often multiple [3].

Angiolipomas are categorized into two groups: infiltrating and non-infiltrating [3]. The non-infiltrating angiolipoma is typically a soft, well-encapsulated, subcutaneous nodule. The non-infiltrating type occurs in younger individuals and is usually painful, often multiple and occasionally familial. Compression of nerve fibres that accompany the vascular channels may cause pain, which is usually dull. The infiltrating type, which is the less common type of angiolipoma, is solitary, has a more aggressive behaviour, and can infiltrate osseous, muscular, neural and fibrocollagenous tissues. It may cause signs and symptoms that can simulate malignant neoplasms. The infiltrating type has the propensity to recur following local surgical excision; therefore the treatment for infiltrating angiolipoma is wide excision to include normal tissue surrounding the tumour. Associated features are rare; the association of multiple angiolipomas, multiple cerebral aneurysms and multiple meningomas has been reported [4].

Three cases of HIV-1 infected patients have been described who developed symptomatic angiolipomas shortly after starting antiretroviral therapy, including protease inhibitors [5].

Painful lesions can be excised if single. Conventional analgesics usually do not help. Multiple lesions have been shown to respond to β-blockade with atenolol (50 mg/day). Pain relief was evident after 24 h. Therapy should be continued for a pain-free period of 2–3 months [6]. A double-blind study proved the benefit of intravenous lidocaine (lignocaine) (5 mg/kg) in saline given over 45 min. The pain disappeared after 1–2 days but reappeared 3 weeks later [7]. Infiltrating angiolipomas need wide excision [8]. Liposuction has been successfully used in one patient [9].

References

1 Howard WR, Helwig EB. Angiolipoma. *Arch Dermatol* 1960; **82**: 924–31.
2 Klem KK. Multiple angiolipomas. *Acta Chir* 1949; **97**: 527–32.
3 Dixon AY, McGregor DH, Lee SH. Angiolipomas: an ultrastructural and clinicopathological study. *Hum Pathol* 1981; **12**: 739–47.
4 Stevenson JC, Choksey MS, McMahon J *et al.* Multiple cerebral aneurysms, multiple meningiomas and multiple subcutaneous angiolipomas: a case report. *Br J Neurosurg* 1994; **8**: 477–81.
5 Dank JP, Colven R. Protease inhibitor-associated angiolipomatosis. *J Am Acad Dermatol* 2000; **42**: 129–31.
6 Goodfield MJD, Rowell NR. The clinical presentation of cutaneous angiolipomata and the response to β-blockade. *Clin Exp Dermatol* 1988; **13**: 190–2.
7 Fogh H, Agner T, Agner E. Multiple angiolipomata treated with intravenous infusions of lignocaine. *Clin Exp Dermatol* 1990; **15**: 63–4.
8 Tighe C, Lynn JA. Angiolipomas of the foot. *J Am Pediatr Med Assoc* 1994; **84**: 85–9.
9 Kaneko T, Tokushige H, Kimura N *et al.* Treatment of multiple angiolipomas by liposuction surgery. *J Dermatol Surg Oncol* 1994; **20**: 690–2.

Frontalis-associated lipoma [1,2]

This is a deeply placed lipoma of the forehead, which deserves special mention because it is often mistaken for an epidermoid cyst. The lipoma presents a smooth, doughy, dome-shaped mass, which appears relatively immobile and the skin glides over it. It arises either within the frontalis muscle or between the undersurface of the muscle and its deep fascia, and its removal requires greater surgical skill than is required for removing an epidermoid cyst or lipoma. A layered closure is essential to repair the severed frontalis muscle, and a pressure dressing is advisable to close the 'dead space'.

References

1 Grosshams E, Fersing J, Marescaux J. Le lipome sous-aponeurotique frontal. *Ann Dermatol Vénéréol* 1987; **114**: 335–40.
2 Salasche SJ, McCollough ML, Angeloni VL *et al.* Frontalis-associated lipoma of the forehead. *J Am Acad Dermatol* 1989; **20**: 462–8.

Fat-storing hamartoma of dermal dendrocytes

One patient has been described with a congenital reddish-brown plaque over the lumbosacral area, which was composed of dermal dendrocytes that had phagocytosed lipid droplets [1]. There were no fat cells in the lesion and no associated metabolic abnormalities.

Reference

1 Bork K, Gabbert H, Knop K. Fat-storing hamartoma of dermal dendrocytes. *Arch Dermatol* 1990; **126**: 794–6.

Hibernoma [1–4]

Synonym
- Granular cell lipoma

This is a rare benign tumour, comprising primitive fetal brown fat cells in which an increasing variety of structural abnormalities for the chromosomal band 11q13 are being found [5]. In the Armed Forces Institute of Pathology series of 170 cases [4] the mean age was 38 years, with the site of predilection being the thigh, then the shoulder, back and neck. The average size was 9.3 cm. Whilst the histology is characteristic, showing masses of distinctive cells with fine granules and a solitary central nucleus [1–3], myxoid, spindle cell and lipoma-like variants are also seen [4]. Hibernoma presents as a firm, non-tender nodule, with vascular dilatation of the overlying skin. CT and MRI imaging may be helpful but is not diagnostic [6,7]. Surgical excision is the only treatment. Local recurrence at excision is unusual, the tumour being multilobular but encapsulated [4,8].

References

1 Angervall L, Nilsson L, Stener B. Microangiographic and histological studies in two cases of hibernoma. *Cancer* 1964; **17**: 685–92.
2 Jennings RC, Behr G. Hibernoma. *J Clin Pathol* 1955; **8**: 310–2.
3 Novy FG, Wilson JW. Hibernomas: brown fat tumors. *Arch Dermatol* 1956; **73**: 149–57.
4 Furlong MA, Fanburg-Smith JC, Miettinen M. The morphologic spectrum of hibernoma: a clinicopathologic study of 170 cases. *Am J Surg Pathol* 2001; **25**: 809–14.
5 Maire G, Forus A, Foa C *et al*. 11q13 alterations in two cases of hibernoma: large heterozygous deletions and rearrangement breakpoints near GARP in 11q13.5. *Genes Chromosomes Canc* 2003; **37**: 389–95.
6 Lee JC, Gupta A, Saifuddin A *et al*. Hibernoma: MRI features in eight consecutive cases. *Clinical Radiology* 2006; **61**: 1029–34.
7 Dursun M, Agayev A, Bakir B *et al*. CT and MR characteristics of hibernoma: six cases. *Clinical Imaging* 2008; **32**: 42–7.
8 Lele SM, Chundru S, Chaljub G *et al*. Hibernoma. *Arch Pathol Lab Med* 2002; **126**: 975–8.

Lipomatosis

Lipomatosis is diffuse infiltration of structures with non-encapsulated adipose tissue. Several different types of lipomatosis have been described.

1 Multiple symmetrical lipomatosis, characterized by a symmetric formation of fatty tumours, associated with signs of mediastinal location and neuropathy
2 Pelvic lipomatosis, characterized by fat accumulation in the pelvic cavity with vesical and ureteral displacement, compression and occlusion
3 Mediastinoabdominal lipomatosis, characterized by intrathoracic and intra-abdominal accumulation of fat, mimicking respiratory disease or ascites
4 Mediastinal lipomatosis, frequently associated with long-term oral steroid exposure
5 Renal sinus and perirenal lipomatosis, characterized by a tumour-like accumulation of fat in the renal and perirenal space inside the renal capsule
6 Adiposis dolorosa, or Dercum's disease, a disease affecting women, characterized by the formation of painful para-articular lipomatous masses.

The cutaneous lipomatoses [1,2] are well-defined but rare syndromes of which two major types are identified: the symmetrical and non-symmetrical varieties. Both produce marked disfigurement. Except in the rare cases when they compress a vital structure, they usually present no physical threat to the patient. Both are benign and non-encapsulated, and represent progressive growth and extension of mature adipose tissue far beyond its normal proportions. The fat accumulation is caused by an increase in cell number rather than cell size by a zonal differentiation of adipoblasts into mature adipocytes [3].

Non-symmetrical lipomatosis

The most common, albeit rare, form of localized lipomatosis is the non-symmetrical subcutaneous lipomatosis. It is a benign entity and normally has no clinical significance except for the cosmetic disability. A localized form affecting the shoulder girdle [4,5] may infiltrate the deeper structures and produce distal symptoms. A case has been reported with tuberous sclerosis, but the association may be fortuitous [6]. It is not usually the result of any metabolic disturbance, and is not usually associated with abnormalities of lipid metabolism; in one case there was familial hyperlipidaemia, the mode of inheritance suggesting an autosomal dominant trait [7]. Other associations include ipsilateral cranial and facial asymmetry, cranial and ocular manifestations, alopecia, spasticity and mental retardation. These associations occur with what is called encephalocraniocutaneous lipomatosis—a very rare syndrome [8,9]. It has been suggested that this syndrome is a variety of Proteus syndrome, in which such patients have hyperostoses of the skull, cutaneous lipomas outside the skull and visceral lipomatoses [10]. Co-occurrence with neurocutaneous melanosis has recently been described [11].

Multiple symmetrical lipomatosis

By contrast, multiple symmetrical lipomatosis (Fig. 46.33) is characterized by large, symmetrical masses of fat, mainly in the neck and shoulder region in a horse-collar distribution. MRI can be used to characterize the nature and extent of disease [12,13]. It may be associated with mild hypertriglyceridaemia, elevated high-density lipoprotein cholesterol [14], hyperuricaemia, impaired glucose tolerance and renal tubular acidosis. The lipomatous tissue in these patients has been shown to have enhanced lipoprotein lipase activity [15], a possible explanation for the elevated high-density lipoprotein cholesterol levels displayed by these patients. The inheritance in this type is autosomal dominant. Specific chromosomal abnormalities have been reported [16]. Mitochondrial dysfunction is common in multiple symmetrical lipomatosis and may be based on identifiable defects in the mitochondrial genome [17].

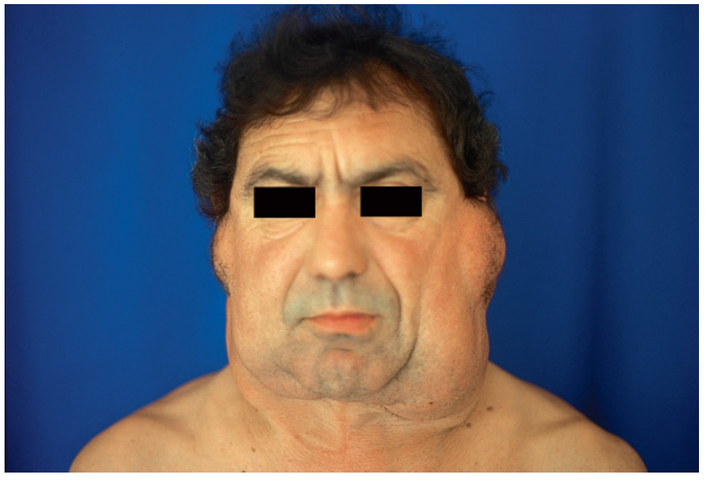


Fig. 46.33 Multiple symmetrical lipomatosis. (Courtesy of M.C. Rodrîguez-Cerdeira, R. Trillo and X.C. Brana, Meixoerio Hospital, Vigo, Spain.)

These patients may also have severe peripheral and autonomic neuropathies [18], often alcoholism, and mediastinal lipomas producing space-occupying symptoms [19]. Sebaceous naevus of Jadassohn has been reported in association with mediastinal lipomatosis [20]. Fifty per cent have a history of high alcohol intake with most of the remainder having a moderate intake or previous alcohol problems [2,21]. The male to female ratio is of the order of 6:1, with the distribution in female patients being proximal arms and legs and not the sub-mental neck pattern seen in men [21]. An unusual patient had benign symmetrical lipomatoses and giant rhinophyma producing a grotesque appearance [22]. Madelung's neck, probably the same condition, is a diffuse multilobular lipomatosis involving the back of the neck and the shoulders in a cape-like distribution. It classically afflicts wine porters and brewery workers. The disease may infrequently be sited in the upper thighs and lower abdomen [23]. Localization to the soles has been reported [24]. Localization of the symmetrical lipomatoses to the tongue results in macroglossia. Therapy is partial glossectomy [25].

The prominent fat deposits over the buttocks that constitute the steatopyga of the Bushmen and Hottentots may be regarded as a racial form of physiological lipomatosis. A distal form of acquired symmetrical lipomatosis of the hands has been reported in a chronic alcoholic Bantu male [26].

Treatment of lipomatosis is difficult. It includes classical lipectomy [27,28] but recurrence is common. Liposuction [29–31] has been reported to help considerably. Fenofibrate has been beneficial [32]. Unlike obesity there is no increase in cardiac mortality and the frequency of diabetes mellitus is the same as the normal population [33], but patients may have problems with autonomic neuropathy [34].

References

1 Shafar J, Behr G. Tumorous abnormalities of adipose tissue. *Postgrad Med J* 1965; **41**: 15–7.
2 Enzi G. Multiple symmetric lipomatosis: an updated clinical report. *Medicine* 1984; **63**: 56–64.
3 Anderson WAD. *Synopsis of Pathology*, 6th edn. New York: Mosby, 1964: 236–7.
4 Enzi G, Carraro R, Alfieri P *et al.* Shoulder girdle lipomatosis. *Ann Intern Med* 1992; **117**: 749–52.
5 McEachern A, Janzen DL, O'Connell JX. Shoulder girdle lipomatosis. *Skeletal Radiol* 1995; **24**: 471–3.
6 Klein JA, Barr RJ. Diffuse lipomatosis and tuberous sclerosis. *Arch Dermatol* 1986; **122**: 1298–302.
7 Rubinstein A, Goor Y, Gazit E *et al.* Non-symmetric subcutaneous lipomatosis associated with familial combined hyperlipidaemia. *Br J Dermatol* 1989; **120**: 689–94.
8 Nosti-Martinex D, del Castillo V, Duran-McKinster C *et al.* Encephalocraniocutaneous lipomatosis: an uncommon neurocutaneous syndrome. *J Am Acad Dermatol* 1995; **32**: 387–93.
9 Grimalt R, Ermacora D, Mistura L *et al.* Encephalocraniocutaneous lipomatosis: case report and review of literature. *Pediatr Dermatol* 1993; **10**: 164–8.
10 Rizzo R, Pavone L, Micali G *et al.* Encephalocraniocutaneous lipomatosis, Proteus syndrome and somatic mosaicism. *Am J Med Genet* 1993; **47**: 653–5.
11 Ahmed I, Tope WD, Young TL *et al*. Neurocutaneous melanosis in association with encephalocraniocutaneous lipomatosis. *J Am Acad Dermatol* 2002; **47**: S196–S200.
12 Martin DS, Sharafuddin M, Boozan J *et al*. Multiple symmetric lipomatosis (Madelung's disease). *Skeletal Radiol* 1995; **24**: 72–3.
13 Hermans R, Verellen S, Vergote G *et al.* Benign symmetric lipomatosis of the neck or Madelung–Launois–Bensaude syndrome, also known as Madelung's neck: CT findings in two cases. *Rofo-Fortschr Rontg* 1994; **161**: 248–50.
14 Deina L, Giovanni MP, Carru C *et al.* Extremely high HDL levels in a patient with multiple symmetric lipomatosis. *Clin Chim Acta* 1993; **223**: 143–7.
15 Enzi G, Favaretto L, Martini S *et al.* Metabolic abnormalities in multiple symmetric lipomatosis: elevated lipoprotein lipase activity in adipose tissue with hyper-alphalipoproteinemia. *J Lipid Res* 1983; **24**: 566–74.
16 Morelli A, Falchetti A, Weinstein L. RFLP analysis of human chromosome 11 region q13 in multiple symmetric lipomatosis and multiple endocrine neoplasia type-1 associated lipomas. *Biophys Res Comm* 1995; **207**: 363–8.
17 Klopstock T, Naumann M, Schalke B *et al.* Multiple symmetric lipomatosis: abnormalities in complex IV and multiple deletions in mitochondrial DNA. *Neurology* 1994; **44**: 862–9.
18 Teplitsky V, Huminer D, Dux S *et al.* Multiple symmetric lipomatosis presenting with polyneuropathy. *Israel J Med Sci* 1995; **31**: 693–5.
19 Munoz-Fernandez C, Aladro Y, Conde MA *et al*. Multiple symmetrical lipomatosis with familial polyneuropathy. *Rev Neurol* 2001; **32**: 1107–11.
20 Taboada E, Moledo E, Alvarez A *et al.* Sebaceous naevus of Jadassohn and primary mediastinal lipomatosis. *Br J Plast Surg* 1993; **46**: 264–5.
21 Busetto L, Strater D, Enzi G. Differential clinical expression of multiple symmetric lipomatosis in men and women. *Int J Obes* 2003; **27**: 1419–22.
22 Izu R, Gardeazabal J, Bejar J *et al.* A case of the elephant man phenotype with giant rhinophyma and benign symmetric lipomatosis. *Clin Exp Dermatol* 1994; **19**: 531–3.
23 Hacker SM, Ramos-Caro FA. An uncommon presentation of multiple symmetric lipomatosis. *Int J Dermatol* 1993; **32**: 594–7.
24 Requera L, Hasson A, Arias D *et al*. Acquired symmetric lipomatosis of the soles. *J Am Acad Dermatol* 1992; **26**: 860–2.
25 Katou F, Nabukazu S, Motegi K *et al.* Symmetrical lipomatosis of the tongue presenting as macroglossia. *J Cranio Maxillo Facial Surg* 1993; **21**: 298–301.
26 Findlay GH, Duvenage M. Acquired symmetrical lipomatosis of the hands: a distal form of the Madelung–Launois–Bensaude syndrome. *Clin Exp Dermatol* 1989; **14**: 58–9.
27 Boozan JA, Maves MD, Schuller DE. Surgical management of massive benign symmetric lipomatosis. *Laryngoscope* 1992; **102**: 94–7.
28 Ujpal M, Nemeth ZS, Reichwein A, Szabo GY. Long-term results following surgical treatment of benign symmetric lipomatosis (BSL). *Int J Oral Maxillofac Surg* 2001; **30**: 479–83.
29 Carlin MC, Ratz JL. Multiple symmetric lipomatosis: treatment with liposuction. *J Am Acad Dermatol* 1988; **18**: 359–62.
30 Basse P, Lohmann M, Hagard C *et al.* Multiple symmetric lipomatosis; combined surgical treatment and liposuction. *Scand J Plast Recons* 1992; **26**: 111–2.
31 Coleman WP, Glogau RG, Klein JA *et al*. Guidelines of care for liposuction. *Am Acad Dermatol* 2001; **45**: 438–47.
32 Heike Z, Gudrun UM, Frank RD *et al*. Multiple benign symmetric lipomatosis—a differential diagnosis of obesity: is there a rationale for fibrate treatment? *Obes Surg* 2008; **18**: 240–2.
33 Enzi G, Busetto L, Ceschin E *et al*. Multiple symmetric lipomatosis: clinical aspects and outcome in a long-term longitudinal study. *Int J Obes Relat Metab Disord* 2002; **26**: 253–61.
34 Nisoli E, Regianini L, Briscini L *et al*. Multiple symmetric lipomatosis may be the consequence of defective noradrenergic modulation of proliferation and differentiation of brown fat cells. *J Pathol* 2002; **198**: 378–87.

Congenital diffuse lipomatosis [1–4]

This has been infrequently recorded. Several syndromes that may involve a neuroectodermal defect have been described, in conjunction with various types of haemangioma or lymphangioma. Congenital lipomatosis may be associated with angiomatosis and macroencephalia (Bannayan's syndrome) [5]. The Proteus syndrome is very rare; the clinical features include hemihypertrophy, macrodactyly, exostoses, epidermal naevi, characteristic cerebriform masses involving the plantar or palmar surfaces, a variety of subcutaneous masses and scoliosis [6]. Histological examination of the subcutaneous masses has identified a variety of lipomatous and angiomatous tumours and hamartomas.

Treatment. Treatment is difficult but liposuction may help.

References

1 Baker AB, Adam JM. Lipomatosis of the central nervous system. *Am J Cancer* 1938; **34**: 214–9.
2 Cameron AH, McMillan DH. Lipomatosis of skeletal muscle in Maffucci's syndrome. *J Bone Joint Surg Br* 1956; **38**: 692–8.
3 Schlicht D. Recurrent lipomatosis in a child. *Med J Aust* 1965; **2**: 959–62.
4 Wising PJ. Hereditary multiple symmetric lipomatosis. *Nord Med* 1954; **51**: 279–81.
5 Bannayan GA. Lipomatosis, angiomatosis and macroencephalia. *Arch Pathol* 1971; **92**: 1–5.
6 Samlaska CP, Levin SW, James WD *et al.* Proteus syndrome. *Arch Dermatol* 1989; **125**: 1109–14.

Dercum's disease

Synonym
- Adiposis dolorosa

Dercum's disease is a rare, progressive disease characterized by localized overgrowth of fat with painful subcutaneous plaques and ecchymoses.

Aetiology. The mechanism of Dercum's disease is not known [1]. It most commonly affects menopausal women; they are usually



Fig. 46.34 Dercum's disease. (Courtesy of Dr R. Motley, University of Wales College of Medicine, Cardiff, UK.)

obese at the time of onset of the disorder and severe emotional disturbance is common. A recent report implies that the disease is a severe expression of multiple painful lipomas [2] but clinical experience of patients in Sweden [3], where the disease appears to be more common, underlines the concept of, at present, a more heterogeneous group, divided into three types. In type I or juxta-articular type, painful folds of fat were seen on the inside of the knees and/or the hips. In type II, the diffuse type, there was widespread pain from increased fatty tissue. In type III, the nodular type, there was intense pain in and around multiple lipomas. In some families there is a dominant inheritance [4].

Histopathology. Histology in the nodular type reveals features of a lipoma or angiolipoma [1].

Clinical features [5,6]. Dercum [7] coined the term 'adiposis dolorosa' to describe three cases of a syndrome characterized by painful deposits of adipose tissue occurring over multiple areas of the body (Figs 46.34 & 46.35). Adiposis dolorosa occurs predominantly in postmenopausal women (female : male ratio of up to 30 : 1) and is associated with weakness, fatigue and, frequently, emotional disturbances. Obesity is almost always present initially, but patients may lose weight and become asthenic as the syndrome progresses. The painful areas of fat may occur as subcutaneous 'lumps', which feel like a 'bag of worms' on palpation, or may be diffuse in a localized or generalized pattern. The juxta-articular areas are the most commonly involved site [8], but painful areas have been described over virtually all areas of the body. The



Fig. 46.35 Dercum's disease showing much improvement after liposuction. (Courtesy of Dr R. Motley, University of Wales College of Medicine, Cardiff, UK.)

pain occurs with palpation of the involved fat, but may also occur spontaneously, often with a fibromyalgia pattern and quality. The disease usually begins gradually with only mild discomfort, but may progress to exquisite pain, particularly with movement, so that the patient is effectively immobilized. The pain tends to be cyclical with constant mild to moderate discomfort punctuated by episodes of severe pain, which is unresponsive to many or all analgesic agents.

Psychiatric disturbances are frequently observed, ranging from mild irritability to dementia. Depression, failure of memory and hypochondriacal complaints are quite common.

Diagnosis. This is not difficult when the classical triad is present: painful plaques, ecchymoses and obesity, appearing in women with amenorrhoea and neurotic symptoms.

Cushing's disease with diffuse deposition of fat, plethora and hirsutes must be distinguished from Dercum's disease. Amenorrhoea and ecchymoses are common to both disorders.

Treatment. Weight reduction and surgical excision of individual tumours may be helpful [8]. The pain is usually unresponsive to conventional therapy but several cases have been shown to respond to intravenous lidocaine [5,9–13]. Two studies were placebo controlled. The pain relief was from 3 to 52 weeks, and repeat therapy was associated with increasing duration of benefit [5,12]. The lidocaine effect is very specific, as other types of pain (e.g. headaches) continued; the mechanism of action is unknown. Topical lidocaine may be an adequate alternative [14]. Some response to mexiletine 150–750 mg orally has been reported [15].

References

1 Wortham NC, Tomlinson IP. Dercum's disease. *Skinmed* 2005; **4**: 157–62.

2 Campen R, Mankin H, Louis DN *et al*. Familial occurrence of adiposis dolorosa. *J Am Acad Dermatol* 2001; **44**: 132–6.

3 Brorson H, Fagher B. Dercum's disease. Fatty tissue rheumatism caused by immune defense reaction? *Lakartidningen* 1996; **10**(93): 1433–6.

4 Lynch HT, Harlan WL. Hereditary factors in adiposis dolorosa (Dercum's disease). *Am J Hum Genet* 1963; **15**: 184–90.

5 Atkinson RL. Intravenous lidocaine for the treatment of intractable pain of adiposis dolorosa. *Int J Obesity* 1982; **6**: 351–7.

6 Palmer ED. Dercum's disease: adiposis dolorosa. *Am Fam Physician* 1981; **24**: 155–7.
7 Dercum FX. Three cases of a hitherto unclassified affliction resembling in its grosser aspects obesity, but associated with special nervous symptoms: adiposis dolorosa. *Am J Med Sci* 1892; **104**: 521–35.
8 Nahir AH, Schapira O, Scharf Y. Juxta-articular adiposis dolorosa: a neglected disease. *Isr J Med Sci* 1983; **19**: 858–9.
9 Juhlin L. Long-standing pain relief of adiposis dolorosa (Dercum's disease) after intravenous infusion of lidocaine. *J Am Acad Dermatol* 1986; **15**: 383–5.
10 Petersen P, Kastrup J. Treating the pain of Dercum's disease. *BMJ* 1984; **288**: 1880.
11 Petersen P, Kastrup J. Dercum's disease (adiposis dolorosa): treatment of the severe pain with intravenous lidocaine. *Pain* 1987; **28**: 77–80.
12 Atkinson RL. Intravenous lidocaine for the treatment of intractable pain of adiposis dolorosa. *Int J Obesity* 1982; **6**: 351–7.
13 Devillers AC, Oranje AP. Treatment of pain in adiposis dolorosa (Dercum's disease) with intravenous lidocaine: a case report with 10 year follow-up. *Clin Exp Dermatol* 1999; **24**: 240–1.
14 Desai MJ, Siriki R, Wang D. Treatment of pain in Dercum's disease with Lidoderm® (lidocaine 5% patch): A case report. *Pain Med* 2008; **9**: 1224–6.
15 Steiner J, Schiltz K, Heidenreich F, Weissenborn K. Lipomatosis dolorosa: a frequently overlooked disease picture. *Nervenarzt* 2002; **73**: 183–7.

CHAPTER 47

Diseases of the Veins and Arteries: Leg Ulcers

P.S. Mortimer[1], *K.G. Burnand*[2] *& H.A.M. Neumann*[3]

[1]St George's, University of London, London, UK
[2]Academic Department of Surgery, St Thomas' Hospital, London, UK
[3]Erasmus Medical Center, Rotterdam, The Netherlands

Arterial and arteriolar disorders, 47.1
Vasculogenesis, angiogenesis and arteriogenesis, 47.1
Arterial disease and peripheral ischaemic disorders, 47.1
Neurovascular disorders of the extremities, 47.9
Telangiectases, 47.12
Development of telangiectasia, 47.12
Secondary telangiectasia and dilatation of pre-existing vessels, 47.13
Primary telangiectasia, 47.16
Treatment of telangiectasia, 47.20
Malformations, 47.21
Arteriovenous shunts, 47.21
Arteriovenous fistulae, 47.21
Arteriovenous malformations, 47.21
Venous malformations, 47.23
Capillary malformations, 47.25
Venous disorders, 47.25
Anatomy, 47.25
Physiology/pathophysiology, 47.25
Venous thrombosis, 47.28
Chronic venous insufficiency, 47.32
Varicose veins, 47.37
Post-thrombotic syndrome, 47.40
Deep vein incompetence, 47.41
Leg ulcers, 47.41
Leg ulceration, 47.41
Venous ulceration of the leg, 47.41
Arterial ulceration, 47.52
Other causes of leg ulceration, 47.54
Diabetic foot ulcers, 47.57

Arterial and arteriolar disorders

Vasculogenesis, angiogenesis and arteriogenesis

Vasculogenesis is the first step in the development of blood vessels and is the process by which endothelial cells differentiate from their mesodermal precursors. Vasculogenesis leads to the formation of a primary capillary plexus and occurs mainly in embryonal development [1]. Angiogenesis is the process by which new capillaries are formed from existing vessels by sprouting, expanding and remodelling [2]. Vasculogenesis precedes angiogenesis but the two processes continue in parallel during early development. The skin, being of ectodermal origin, is vascularized mainly by angiogenesis. The establishment and remodelling of blood vessels requires a complex orchestration of molecular regulators. First, the extracellular matrix is degraded by local tissue proteases. This permits migration of budding endothelial cells under the influence of angiogenic stimuli, particularly the family of vascular endothelial growth factors (vascular endothelial growth factors A, B, C, D and E (viral homologues) plus placental growth factor) and their tyrosine kinase receptors, VEGFR-1, VEGFR-2 and VEGFR-3. Stabilization and maintenance of newly formed vessels occur mainly as a consequence of the angiopoietins and the tie-receptors [3].

Differentiation into arteries, veins and capillaries is the responsibility of angiogenesis. Neoangiogenesis is an important cause of recurrent varicose veins after stripping [4]. Arteriogenesis produces rapid circumferential growth in the pre-existing collateral vessels, which are less perfused under normal flow conditions. While local tissue ischaemia or hypoxia stimulates angiogenesis, arteriogenesis is mainly induced by inflammation and shear stress [5].

References

1 Risau W. Mechanisms of angiogenesis. *Nature* 1997; **386**: 671–4.
2 Carmeliet P. Angiogenesis in health and disease. *Nat Med* 2003; **9**: 677–84.
3 Cohen MM Jr. Vascular update: morphogenesis, tumors, malformations and molecular dimensions. *Am J Med Genet Part A* 2006; **140A**: 2013–38.
4 De Maeseneer MG, Vandenbroeck CP, Lauwers PR *et al*. Early and late complications of silicone patch saphenoplasty at the saphenofemoral junction. *J Vasc Surg* 2006; **44**: 1285–90.
5 Simons M. Angiogenesis. *Circulation* 2005; **111**: 1556–66.

Arterial disease and peripheral ischaemic disorders

Arterial disease

Current concepts on the aetiology of arterial disease, atherosclerosis and peripheral ischaemia

The mechanisms that initiate arterial disease are still poorly understood. Recent research has shown that inflammation plays a key role in atherosclerosis [1]. Early atherosclerotic lesions are dominated by immune cells (macrophages) and their effector molecules accelerate the progression of the lesions. Evidence suggests that cardiovascular risk factors induce endothelial injury and endothelial dysfunction. Endothelial progenitor cells derived from circulating mononuclear cells may protect against atherosclerosis and cardiovascular disease [2]. Atherosclerosis is a patchy accumulation of lipid, mostly in the form of cholesterol, within the intima of the vessel wall. Atheromatous plaques eventually ulcerate through the endothelial lining, exposing a highly thrombogenic surface [3]. Platelets adhere to the ulcerated plaque and platelet

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

aggregates (platelet thrombi) may embolize distally or may initiate local thrombosis. Inadequate collaterals, or occlusion by thrombosis or embolism, will lead to tissue infarction (e.g. peripheral gangrene).

Atherosclerosis is responsible for more than 90% of all arterial disease in the Western world. It affects 5% of men over the age of 50 years, of which 10% may develop critical limb ischaemia; this increases to 20% if diabetic patients are included [4]. Apart from diabetes, tobacco smoking is one of the most important risk factors for arterial disease. A family history and hypercholesterolism are two other factors that are associated with atherosclerosis.

Atherosclerosis of the lower limb vessels

Many patients initially present with claudication (cramping pain on walking, which is usually experienced in the posterior calf muscles and is relieved by rest). The presence of persistent pain in the foot at night indicates the onset of critical ischaemia, which will lead to gangrene or ulceration if left untreated.

In the past, arteriosclerosis (hardening of the vessels) had been classified as a disease, but most authorities would now regard this as a physiological response to ageing. Thickening of the arterial wall, with an increase in collagen and calcium deposition, causes loss of elasticity and increased tortuosity of the vessels in the elderly [3]. Similar changes are seen in the vessels of younger patients with hypertension.

Clinical features [3–6]. All aspects of the patient's history and lifestyle are relevant, with particular attention being paid to risk factors such as cigarette smoking, hypertension, diabetes, diet, dyslipidaemia, hyperhomocysteinaemia, lack of exercise, obesity, occupation and a family history of cardiovascular disease [7]. In 1992, an examination of WHO epidemiological data from Toulouse (France) indicated that in spite of the population having a high saturated fat consumption, comparable serum cholesterol levels and other similar risks, there was a considerably lower incidence of death from coronary heart disease compared with other Western countries. Although the specific mechanism behind this 'French paradox' has not been identified, the flavonoid components in red wine are thought to have antioxidant activity which could contribute to cardiovascular benefits [8].

Most patients present with intermittent claudication, but ischaemic ulceration and skin infarction are more likely to be the presenting features in patients sent to the dermatologist (Fig. 47.1). Rest pain occurs if the disease progresses. This is experienced in the foot, and occurs predominantly at night. Altered skin colour (pallor or deep erythema) indicates ischaemia, and may be accompanied by other trophic skin changes such as dryness, scaling, loss of hair and thickened nails (Fig. 47.2).

A full general examination is essential. Particular attention should be paid to signs of anaemia, polycythaemia, xanthelasma and other xanthomatous deposits. Genetic disorders such as pseudoxanthoma elasticum, Ehlers–Danlos syndrome and Marfan's syndrome should be considered if an aneurysm is present. Cardiac examination should focus on dysrhythmias, particularly atrial fibrillation, murmurs and signs of heart failure.

Abdominal examination should detect the presence of a pulsatile mass, indicative of an abdominal aortic aneurysm. The fundi



Fig. 47.1 An ischaemic hallux with pregangrene; the rest of the foot has an ischaemic erythema.



Fig. 47.2 An ischaemic foot showing patchy areas of gangrene and rubor. The skin is flaky and the nails are brittle.

should be examined for evidence of diabetic and hypertensive retinopathy. The blood pressure should be taken in both arms; a marked difference suggesting a stenosis or occlusion of the subclavian artery (although ischaemic disorders of the upper limbs are unusual).

The skin of the legs may have an erythematous or dusky mottled hue. When the ischaemia is marked, limb elevation causes pallor of the foot while dependency results in delayed but exaggerated hyperaemia, best observed on the dorsum of the foot (Buerger's sign) (Fig. 47.3) [9]. Inspection may reveal ulceration at sites of pressure (Fig. 47.4); small cracks may appear over the sole of the foot or heel (Fig. 47.5). Platelet emboli lodging in the plantar and digital vessels cause areas of discoloration, which are often present over many toes or on the sole of the foot (Fig. 47.6). They often look like ecchymoses initially and may be confused with vasculitis. The aortic, femoral, popliteal, dorsalis pedis and posterior tibial pulses must be carefully palpated. Abnormally situated pulsations may indicate a collateral circulation or a congenital arteriovenous fistula. Auscultation over the course of the arteries may reveal the presence of a bruit indicative of turbulent flow. This is



Fig. 47.3 Buerger's test showing postural colour change in an ischaemic foot—white when the foot is elevated (right) and red when lowered (left).



Fig. 47.4 An ischaemic ulcer on the dorsum of the foot with an ulcer arising in the first interdigital space. Pressure between the toes is a common consequence of tight bandages or footwear.

commonly caused by an up-stream stenosis or by an arteriovenous fistula (which usually causes a 'machinery' murmur, present throughout systole and diastole). It should be noted that significant arterial disease demanding further investigation is uncommon when the foot pulses are easily palpable.

Investigations. Confirmation of the arterial disease of the lower limb can be obtained by measuring the ankle–brachial Doppler pressure index if peripheral pulses are reduced or absent or a bruit is heard [10]. After the Doppler ultrasound probe has been used to locate the dorsalis pedis or posterior tibial vessel a sphygmomanometer cuff is placed around the limb above the ankle and inflated (Fig. 47.7). The red cells flowing past the tip of the ultrasound probe deflect the beam, creating an audible noise. As the cuff is inflated above systolic pressure, flow in the artery ceases and the noise disappears. This ankle–brachial systolic gradient is normally unity, that is 1.0. A fall in ankle pressure results in a reduction of the pressure index: a ratio of 0.71 to 0.90 indicates the presence of mild peripheral arterial disease, an ankle–brachial index of 0.41 to 0.70 indicates moderate disease, and a ratio of 0.40 or less indicates severe disease. Pain at rest or severe occlusive disease typically occurs when an ankle–brachial index is less than 0.50. Ischaemic or gangrenous extremities are associated with an index of less than 0.20 [11]. Falsely high indices may be obtained in some limbs if the vessels are very calcified and fail to compress at systolic pressure. This is especially true for diabetic limbs. In such circumstances a more accurate means of assessment is to measure the Doppler pressures at the toe. Measurement of the transcutaneous Po_2 using a heated (Clark's) electrode applied to the skin of the lower limbs and compared with a reference site on



Fig. 47.5 An ischaemic 'crack' developing as a consequence of nutritional changes seen in hyperkeratosis and loss of suppleness of the skin of the heel.



Fig. 47.6 Multiple platelet emboli into the skin of the foot.



Fig. 47.7 Measurement of the ankle Doppler pressure using a sphygmomanometer cuff. The pressure at which the Doppler signal disappears in the leg is compared with the brachial pressure to give an index of blood supply.

the chest wall [12,13] can also be used to assess limb ischaemia. This usually fails to increase with inhalation of oxygen. Patients with severe venous incompetence can also have hypoxic extremities [14]. Isotope washout studies (which estimate clearance of an inert isotope from a tissue injection) can also be obtained [15].

Investigations in patients suspected of having peripheral arterial disease or critical leg ischaemia [4] should include: a full blood count to exclude anaemia or polycythaemia; electrolytes and creatinine to monitor renal function; and an electrocardiogram (often repeated after exercise) to detect rhythm abnormalities or cardiac ischaemia. A chest radiograph provides an assessment of cardiac size and excludes a coincidental bronchogenic carcinoma, which is common in smokers. Diabetes should be excluded, and plasma cholesterol, homocysteine and fasting triglycerides should be measured. Markers of inflammation, particularly C-reactive protein, have been associated with peripheral arterial disease. Raised haematocrit levels and hyperviscosity have all been reported in patients with peripheral arterial disease [7].

When surgery is contemplated, a detailed assessment of the anatomy of the arterial tree is also required. Duplex ultrasound scanning is often the initial investigation, and is used as a screening test to confirm the major sites of stenosis or occlusion in the vascular tree [16,17]. A duplex ultrasound scan provides both a B-mode image of the artery and a measurement of blood velocity; these can be combined to provide a map of stenoses and occlusions within the arterial tree from the aorta to the crural (calf) vessels. The greater the velocity, the tighter the stenosis. Most surgeons also obtain an arteriogram before angioplasty or bypass surgery is performed. Arteriography is performed by injection of non-ionic contrast media into the vascular tree, usually through a retrograde catheter inserted into the common femoral artery at the groin over a guide wire (Seldinger-type retrograde aortography), or from an intravenous or intra-arterial injection using digital subtraction equipment or computed tomography to enhance picture quality [18]. Each of these methods has its proponents, but retrograde aortography performed as an outpatient, or a combination of intravenous digital subtraction arteriography of the aorta, iliac and femoral vessels with femoral arteriography of the distal vessels, provide equivalent information. Thus invasive digital subtraction angiography remains the final investigation which is used if endovascular intervention is planned. Magnetic resonance angiography (MRA) of the extremities is sometimes useful to diagnose the anatomic location and degree of stenosis in peripheral arterial disease if patients are allergic to contrast. Computed tomography angiography is an alternative if patients have contraindications for MRA [7].

The further management of arterial disease is discussed under the heading of the individual diseases, and usually requires referral to an appropriately experienced surgeon and interventional radiologist.

References

1 Hansson GK. Mechanisms of disease: inflammation, atherosclerosis and coronary artery disease. *N Engl J Med* 2005; **352**: 1685–95.
2 Hill JM, Zalos G, Halcox JPJ *et al.* Circulating endothelial progenitor cells, vascular function and cardiovascular risk. *N Engl J Med* 2003; **348**: 593–600.
3 Woolf N, ed. *Pathology of Atherosclerosis.* London: Butterworth, 1982.
4 Dormandy JA, Stock G, eds. *Critical Leg Ischaemia: its Pathology and Management.* Berlin: Springer-Verlag, 1990.
5 Browse NL, Burnand KG, Irvine AJ, Wilson NM. *Diseases of the Veins,* 2nd edn. London: Arnold, 1999.
6 Rutherford RB, ed. *Vascular Surgery.* Philadelphia: Elsevier Saunders, 2005.
7 Norgren L, Hiatt WR *et al.* Inter-society consensus for the management of peripheral arterial disease (TASC II). *Eur J Endovasc Surg* 2007; **33** (Suppl.): 5–75.
8 Kar P, Laight D, Shaw KM, Cummings MH. Flavonoid-rich grapeseed extracts: a new approach in high cardiovascular rich patients? *Int J Clin Pract* 2006; **60**: 1484–92.
9 Insall RL, Davies RJ, Prout WG. Significance of Buerger's test in the assessment of lower limb ischaemia. *J R Soc Med* 1989; **82**: 729–31.
10 Summer SD, Strandness DE. The relationship between calf blood flow and ankle blood pressure in patients with intermittent claudication. *Surgery* 1969; **65**: 763–5.
11 Khan NA, Rahim SA, Anand SS, Simel DL, Panju A. Does the clinical examination predict lower extremity peripheral arterial disease? *JAMA* 2006; **295**: 536–46.
12 Clyne CAC, Ramsden WH, Chant ADB *et al.* Oxygen tension on the skin of the gaiter area of limbs with venous disease. *Br J Surg* 1985; **72**: 644–7.
13 Franzeck UK, Talke P, Bernstein EF *et al.* Transcutaneous Po_2 measurements in health and peripheral arterial occlusive disease. *Surgery* 1982; **91**: 156–63.
14 Neumann HA, Van den Broek MJ, Boersma IH, Veraart JC. Transcutaneous oxygen tension in patients with and without pericapillary fibrin cuffs in chronic venous insufficiency, porphoria cutanea tarda and non-venous leg ulcers. *Vasa* 1996; **25**: 127–33.
15 Alpert JS, Garcia del Rio H, Lassen NA. Diagnostic use of radioactive xenon clearance and a standardised walking test in obliterative arterial disease of the legs. *Circulation* 1966; **34**: 849–55.
16 Koelemay MJW, Den Hartog D, Prins MH *et al.* Diagnosis of arterial disease of the lower extremities with duplex ultrasonography. *Br J Surg* 1996; **83**: 404–9.
17 Legemate DA, Teeuwen C, Hoeneveld H *et al.* The potential of duplex scanning to replace aorto-iliac and femoro-popliteal angiography. *Eur J Vasc Surg* 1989; **3**: 49–54.
18 Friedman SG, Moccio CG. A prospective comparison of intra-arterial digital subtraction and conventional angiography prior to lower extremity revascularisation. *J Cardiovasc Surg* 1989; **30**: 462–6.

Differential diagnosis. Thromboangiitis obliterans (Buerger's disease, p. 47.6–7) may be very difficult to distinguish from atherosclerosis. Preservation of the proximal femoral and popliteal pulses and the early age at first presentation usually indicates the possibility of this condition. Associated venous thromboses and

characteristic histological changes on vessel biopsy make the diagnosis more secure. A skin biopsy can sometimes be helpful in diagnosing Buerger's disease [1]. Arteriography in Buerger's disease shows characteristic 'corkscrew collaterals' [1].

In patients with acute limb ischaemia it is important to exclude the possibility of embolism, which may be suggested by a recent myocardial infarction or the presence of atrial fibrillation. Transthoracic or transoesophageal echocardiography can demonstrate intracardiac thrombus and structural abnormalities, especially of the valves and, in the case of transoesophageal echocardiography, with great accuracy [2].

Rarer causes of ischaemia include external arterial compression (popliteal entrapment or a cervical rib), dissecting or thrombosed aneurysms, ergot alkaloid poisoning, intra-arterial injections of noxious substances, traumatic disruption of the arterial wall, coagulation disorders, particularly polycythaemia and thrombocytosis, and various forms of vasculitis. Diabetes must always be considered as a potentiating condition, even in patients with atherosclerotic disease.

Claudication pain may be mimicked by arthritic conditions of the hip, such as osteoarthritis or rheumatoid arthritis. Pain in the leg may also result from referred pain arising in the lumbosacral spine, and spinal claudication is sometimes very difficult to differentiate from arterial claudication. Occasionally, venous claudication may also be misdiagnosed. Ischaemic rest pain may have to be differentiated from other painful conditions of the feet and toes, such as gout, interdigital neuromas, glomangiomas, ingrowing toenails, flat feet, calcanial bursitis and plantar fasciitis. Other causes of gangrene may need to be excluded (e.g. clostridial infection, diabetes, other causes of vascular obstruction, vasculitis and coagulation disorders).

Prognosis. Patients with atherosclerotic disease of the lower limb vessels usually have other arteries affected. Coronary artery disease was found to be present in 90% of a group of patients with peripheral arterial disease [3]. The extent of the atheroma in the coronary and carotid arteries determines the life expectancy of the patient, although antiplatelet agents [4], lipid-lowering agents and bypass surgery may improve the patient's prognosis as well as their symptoms of ischaemia. Silent myocardial infarction is present in about one-third of those who presented with intermittent claudication.

Treatment. Treatment options differ for patients presenting with claudication, rest pain or gangrene and acute limb ischaemia.

Claudication. The indications for intervention in a patient with claudication are always relative and must be weighed against the risks of the procedure and the fact that the condition normally has a very benign course [5]. Only 5% of all patients with claudication progress each year to develop rest pain or gangrene; a far greater proportion die every year from other causes, such as myocardial infarction. Patients with intermittent claudication are therefore usually managed conservatively at first, as collateral vessels may develop with an associated improvement in the symptoms.

Smoking cessation has been shown to reduce the risk of progression in patients with lower extremity peripheral arterial disease presenting with claudication. Nicotine replacement has been shown to be a safe and effective method of aiding smoking cessation [6].

Patients should be encouraged to walk through the pain as this tends to stimulate the development of a collateral circulation, to recruit capillaries and to increase the claudication distance. There are a number of studies demonstrating that supervised exercise programmes are as effective as therapeutic intervention in alleviating claudication, although the benefits of supervised exercise may not persist [7].

Patients with peripheral arterial disease should have their blood pressure maintained below 130/85 mmHg [8], but antihypertensive treatment should not be instituted in patients with claudication whose lower limb systolic pressures are lower than 80 mmHg.

Pharmacological interventions comprise the following. Antiplatelet agents must be considered in patients with claudication. Based on the available evidence, the first-line antiplatelet therapy should be aspirin or clopidogrel [6]. Aspirin has not been shown to improve claudication itself, but patients with claudication treated by antiplatelet agents have a 25% reduction in subsequent serious cardiovascular events. Statins modify lipid levels and reduce the risks of disease progression. Statins reduce LDL-cholesterol levels causing a significant reduction in the all-cause mortality [6,8]. Diabetes mellitus is closely associated with peripheral arterial disease and its progression, and rigorous control of blood glucose in patients with diabetes reduces microvascular complications. Although intensive therapy (achieving a HbA_{1c} of below 7%) had no effect on the risk of death or amputation in patients with peripheral arterial disease, there was a trend in favour of a reduced risk of non-fatal cardiovascular events [6,8].

Further investigation is indicated if the claudication distance remains unacceptable despite the patient having stopped smoking and after a reasonable period of conservative treatment. Stenotic lesions confirmed by arteriography can be treated by balloon dilatation (angioplasty), using specially designed coaxial balloon catheters that are constructed to withstand high external pressures [9]. This technique works best on stenoses in large proximal vessels, and least well on long occlusions of the distal arterial tree. Potential complications include arterial rupture, aneurysm formation, thrombosis and dissection. Additionally, the results of angioplasty in the femoropopliteal segment remain disappointing with a 30% restenosis rate at 1 year. The role of primary stent placement in revascularization of the superficial femoral artery remains controversial, mainly because of the high restenosis rate. Chemically treated slow-release stents may overcome 'restenosis' in the future, although so far several randomized trials have failed to confirm this. Stents placed in the superficial femoral artery can undergo fracture, which has been linked to restenosis. A randomized trial by Schillinger *et al.*, involving 104 patients with severe claudication, showed significantly higher patency rates at 1 year for lesions in the superficial femoral artery that were treated with stent placement than for lesions treated with angioplasty with a stent only being placed if there was a suboptimal result [10]. Long-term results are not, however, available.

Surgical endarterectomy or bypass remains the treatment of choice for extensive occlusions longer than 10 cm, or for occlusion of the popliteal or tibial–peroneal vessels [11]. Aortofemoral

bypass has an excellent 5-year patency (90–95%), but the operative mortality varies between 1 and 5% [10]. Femoropopliteal vein bypass grafting has a lower 5-year patency (60–70%) but a lower operative mortality (usually less than 1%) [12]. Distal bypass surgery (the lower anastomoses being below the popliteal artery into one of the three crural vessels) has no part to play in the treatment of claudication, although this procedure is of considerable value in patients with rest pain and early gangrene (see below) [13]. Operative or chemical lumbar sympathectomy do not help to relieve claudication [14] and are mainly of value in patients with ischaemic ulcers or Buerger's disease.

Rest pain or gangrene. Once rest pain or early gangrene has developed the situation changes, for if this state is left untreated amputation will be necessary to relieve pain and preserve life. Patients with rest pain or gangrene must be rapidly admitted and investigated, because successful revascularization can avert limb loss [7]. Any anaemia or polycythaemia should be corrected, and if diabetes is found this should be brought under control. Dehydration and infection must be treated.

The increasing use of more distal surgery with bypasses to the dorsal pedis, posterior tibial, peroneal and even plantar vessels has saved many limbs that in the past would have been amputated [13,15]. Angioplasty, stenting and surgery to the proximal vessels are, of course, still of value as these arteries are the main sites of disease.

In patients without evidence of frank ischaemia, chemical sympathectomy may alleviate rest pain [16]. Prostacyclin, prostaglandin E_1 and prostacyclin analogues, such as iloprost, are being tried in patients in whom a bypass cannot be constructed. These compounds may preserve a small proportion of threatened limbs [17]. A meta-analysis of seven randomized trials involving 643 patients with ischaemic limbs showed a small but significant effect of prostaglandin E_1 on ulcer healing and/or pain reduction and on the combined end points of major amputation or death [18].

Therapeutic angiogenesis using gene therapy has been tried but clinical trials have not shown any benefit to date. A phase 1 study on plasmid transfer of vascular endothelial growth factor in nine patients with severe peripheral arterial disease has, however, shown that this technology is possible. Many other studies are under way to assess the utility of gene therapy in patients with severe peripheral arterial disease [18].

The immediate amputation rate can be lowered by a policy of aggressive reconstruction, but this probably comes at the cost of a few higher amputations and some increased loss of life when graft failure is associated with a continued ischaemia and consequent amputation [19].

Acute limb ischaemia. Patients presenting with acute limb ischaemia should be rapidly assessed and, unless there is unequivocal evidence of an embolus (suggested, for example, by normal vessels in the other limb, atrial fibrillation or recent myocardial infarction), the patient should have urgent angiography to confirm the diagnosis and to assess the cause of the occlusion. This should be followed by infusion of a tissue plasminogen activator into the thrombus or embolus via the catheter unless the state of the limb demands urgent revascularization or amputation [20]. Repeat angiography, to confirm continuing or successful thrombolysis, is required at frequent intervals, and residual stenoses responsible for the thrombosis may require angioplasty, stenting or surgery. When vessel patency has been restored by thrombolysis, patients must remain on anticoagulants.

Balloon-catheter embolectomy should be reserved for embolic occlusions. When platelet emboli are suspected, antiplatelet agents may be prescribed before a definitive surgical or radiological intervention to remove the source of the emboli.

Amputation remains the final option in all types of ischaemic disease of the lower limbs where revascularization is impossible or ineffective. The value of preserving the knee joint for subsequent mobility is well recognized. The mortality of amputation stays stubbornly high (15–20%).

References

1 Olin JW, Shih A. Thromboangiitis obliterans (Buerger's disease). *Curr Opin Rheumatol* 2006; **18**: 18–24.
2 Lagattolla NRF, Burnand KG, Stewart A. Role of transoesophageal echocardiography in determining the source of peripheral arterial embolism. *Br J Surg* 1995; **82**: 1651–4.
3 Golomb BA, Dang TT, Criqui MH. Peripheral arterial disease: morbidity and mortality implications. *Circulation* 2006; **114**: 688–99.
4 Canadian Cooperative Study Group. A randomised trial of aspirin and sulphinpyrazone in threatened stroke. *N Engl J Med* 1978; **299**: 53–9.
5 Imparato AM, Kim GE, Davison T *et al.* Intermittent claudication: its natural course. *Surgery* 1975; **119**: 75–8.
6 Bendermacher BLW, Willigendael EM, Teijink JAW, Prins MH. Medical management of peripheral arterial disease. *J Thromb Haemost* 2005; **3**: 1628–37.
7 Dormandy JA, Stock G, eds. *Critical Leg Ischaemia: its Pathology and Management.* Berlin: Springer-Verlag, 1990.
8 Hankey GJ, Norman PE, Eikelboom JW. Medical treatment of peripheral arterial disease. *JAMA* 2006; **295**: 547–53.
9 Grüntzig A, Kumpe DA. Technique of percutaneous transluminal angioplasty with Grüntzig balloon catheter. *Am J Roentgenol* 1979; **132**: 547–52.
10 Schillinger M, Sabeti S, Loewe C *et al.* Balloon angioplasty versus implantation of nitinol stents in the superficial femoral artery. *N Eng J Med* 2006; **354**: 1879–88.
11 White C. Intermittent claudication. *N Engl J Med* 2007; **356**: 1241–50.
12 De Weese JA, Rob CG. Autogenous venous bypass grafts 5 years later. *Ann Surg* 1971; **174**: 346–56.
13 Tyson RR, Reichle FA. Femorotibial bypass. *Ann Surg* 1969; **170**: 429–34.
14 Haxton HA. Chemical sympathectomy. *BMJ* 1949; **1**: 1026–8.
15 Veith FJ, Gupta SK, Samson RH *et al.* Progress in limb salvage by reconstructive arterial surgery combined with new or improved adjunctive procedures. *Ann Surg* 1981; **194**: 386–401.
16 Cotton LT, Cross FW. Lumbar sympathectomy for arterial disease. *Br J Surg* 1985; **72**: 678–83.
17 Norgren L, Alwmark A, Angqvist KA *et al.* A stable prostacyclin analogue (iloprost) in the treatment of ischaemic ulcers of the lower limb: a Scandinavian-Polish placebo controlled randomised multicenter study. *Eur J Vasc Surg* 1990; **4**: 463–7.
18 Federman DG, Kravetz JD. Peripheral arterial disease: diagnosis, treatment, and systemic implications. *Clin Dermatol* 2007; **25**: 93–100.
19 Burnand KG, Layer G, Whitehead S *et al.* Critical ischaemia of the lower limb: can we save more limbs from amputation? *J Cardiovasc Surg* 1990; **31** (Suppl.): 77 (Abstract).
20 Ouriel K, Shortell CK, De Weese JA *et al.* A comparison of thrombolytic therapy with operative revascularization in the initial treatment of acute peripheral arterial ischaemia. *J Vasc Surg* 1994; **19**: 1021–30.

Thromboangiitis obliterans [1,2]

Synonym
- Buerger's disease

Definition. This appears to be a distinct condition separate from other forms of vascular occlusion [2,3], with differences in the pathological appearance of the vessel wall, and in the population affected, compared with other arterial diseases [2].

This condition was first recognized as an obliterative disorder of peripheral arteries of young males by Leo Buerger in New York [1]. The affected young men were all heavy smokers and the disorder involved the small vessels of the upper limb much more commonly than in atherosclerosis. While originally thought to occur only in men, there are increased reports of women with thromboangiitis obliterans, possibly as a consequence of the increasing use of cigarettes among women in the 20th century [4]. It is common in the Middle and Far East, and in the Indian subcontinent.

Aetiology [2]. The aetiology of the condition is unknown, although tobacco addiction is invariably a major contributing factor, and a failure to overcome this addiction is associated with progressive occlusion of the vessels. Autoantibodies have been found within the blood [5]. In particular, antiendothelial cell antibodies are present in high titre in active disease. They may be used to monitor disease activity and may have a pathogenic role [2].

Pathology [2,6]. The full thickness of the vessel wall is invaded by lymphocytes, eosinophils, plasma cells and monocytes, especially disrupting the internal elastic lamina, and there is luminal occlusion as a result of highly cellular thrombosis. Accompanying nerves and veins may become involved in the inflammatory process. All changes are segmental or focal. At a later stage in the disease, fibrosis occurs, which spreads to involve surrounding structures.

Clinical features. Pain is the main presenting symptom and may be of several types: intermittent claudication; rest pain, more severe at night; pain associated with ischaemic neuropathy, ulceration or superficial venous thrombosis. Sensitivity to cold is a frequent complaint. Claudication in the arch of the foot is especially characteristic [7].

Ulceration or gangrene may develop early in the disease, particularly following trauma, and often starts around the sides of the nails or tips of the digits (Fig. 47.8). Trophic changes, superficial venous thrombosis and oedema are also often present. Red or cyanotic acral colour changes are often unilateral, asymmetrical and may affect isolated digits.

Recurrent venous thrombosis is a frequent problem and may take the form of superficial red streaks and cords of 0.5–3 cm [2] or deep-vein thrombosis presenting with pain and swelling. Erythema nodosum may also develop.

Ischaemic areas are found on the tips of the fingers and toes and may initially present as chronic painful paronychia. The proximal pulses are usually present, but the dorsalis pedis, posterior tibial and brachial pulses are lost at an early stage.

Diagnosis. There are no specific laboratory tests to aid in the diagnosis of thromboangiitis obliterans [4]. The erythrocyte sedimentation rate (ESR) is often elevated and antiendothelial cell autoantibodies may be detected. An arteriogram should be obtained and may suggest the diagnosis, if there are many 'corkscrew' collaterals [8] (Fig. 47.9). The proximal vessels are usually entirely normal while the distal arteries are diffusely affected with multiple stenoses and occlusions.



Fig. 47.8 Ischaemic toes in Buerger's disease.

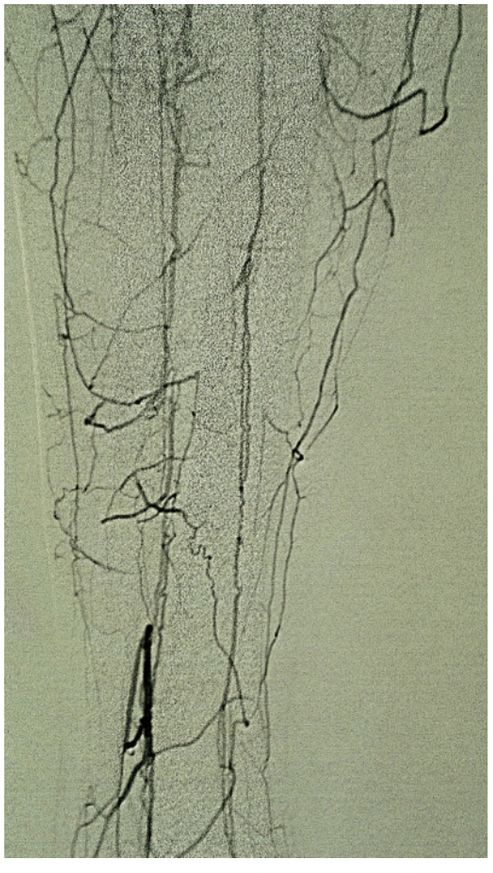


Fig. 47.9 An arteriogram in a patient with Buerger's disease. No major vessels are seen, just multiple collateral arteries.

The differential diagnosis is wide. It includes atypical 'young onset' atherosclerosis, diabetic vasculopathy and rheumatoid arthritis. Collagen-vascular diseases, such as scleroderma and systemic lupus erythematosus, must also be considered in the differential diagnosis. Multiple emboli derived from a proximal source may pose real diagnostic difficulty, and ergotism, abuse of cocaine, amphetamines and cannabis must not be forgotten. Hypercoagulable states (Chapter 49) should be excluded. In mild cases, acrocyanosis, livedo reticularis and erythromelalgia may be considered.

Treatment and prognosis. The dermatologist may be faced with the problem of a patient referred for ulceration or erythema of the foot and toes. Once the diagnosis is established, the matter is best dealt with by the vascular surgeon, whose advice should be sought. Collateral development can be expected to occur during phases of inactivity of the disease. The essential requirement for successful outcome is the complete discontinuation of tobacco use. Bed rest and antibiotics are other facets of conservative treatment. Surgical or chemical sympathectomy is usually helpful and prostacyclin infusions may buy time and minimize ablative surgery [9]. In a double-blind study of a chemically stable prostacyclin analogue, 85% of patients treated showed ulcer healing or relief of pain compared with 17% of an aspirin-treated group [10].

Arterial reconstructive surgery has little part to play in the management of this condition because of the distal nature of the disease. After sympathectomy, every effort should be made to avoid major amputations by the use of antibiotics and, when necessary, toe excisions. Below-knee amputation may eventually be required, particularly if gangrene extends to the foot. It should not be unreasonably delayed. There are an increasing number of reports on the use of an implantable spinal cord stimulator in patients with Buerger's disease; this can produce a marked improvement in regional perfusion, thereby avoiding amputation. The limb survival rate was 93.1% [11].

The prognosis is poor in patients who continue to smoke; hands and feet may be lost.

References

1 Buerger L. Thromboangiitis obliterans: a study of the vascular lesions leading to presenile spontaneous gangrene. *Am J Med Sci* 1908; **136**: 567–80.

2 Totemchokchyakarn K. Thromboangiitis obliterans (Buerger's disease). In: Ball GV, Bridges SL, eds. *Vasculitis*. Oxford: Oxford University Press, 2002: 460–6.

3 Wessler S. Buerger's disease revisited. *Surg Clin North Am* 1969; **49**: 703–13.

4 Olin JW, Smith A. Thromboangiitis obliterans (Buerger's disease). *Curr Opin Rheumatol* 2006; **18**: 18–24.

5 Adar R, Papa MJ, Halpern Z *et al*. Cellular sensitivity to collagen in thromboangiitis obliterans. *N Engl J Med* 1983; **308**: 1113–6.

6 Shionoya S. Pathology of Buerger's disease, clinico-pathico-angiographic correlation. *Pathol Microbiol* 1975; **43**: 163–6.

7 Puéchal X, Fiessinger J-N. Thromboangiitis obliterans or Buerger's disease: challenges for the rheumatologist. *Rheumatology* 2007; **46**: 192–9.

8 Lazarides MK, Georgiadis GS, Papas TT, Nikolopoulos ES. Diagnostic criteria and treatment of Buerger's disease: a review. *Int J Low Extrem Wounds* 2006; **5**: 89–95.

9 Ohta T, Shionoya S. Fate of the ischaemic limb in Buerger's disease. *Br J Surg* 1988; **75**: 259–62.

10 Fiessinger JN, Schäfer M. Trial of iloprost versus aspirin treatment for critical limb ischaemia of thromboangiitis. *Lancet* 1990; **i**: 555–7.

11 Donas KP, Schulte S, Ktenidis K, Horsch S. The role of epidural spinal cord stimulation in the treatment of Buerger's disease. *J Vasc Surg* 2005; **41**: 830–6.



Fig. 47.10 Ulceration associated with calcification of arteries in secondary hyperparathyroidism.

Small vessel calcification and calcific uraemic arteriolopathy (calciphylaxis) [1,2]

Arterial calcification is a common and usually asymptomatic complication of chronic renal failure. Occasionally, especially when associated with hyperparathyroidism, it can cause complete vascular occlusion and infarction of the skin. This condition, calcific uraemic arteriolopathy (previously termed calciphylaxis), may begin as a small area of redness and tenderness or with a broad livedo reticularis pattern, evolving into intense erythema. This may progress to violaceous indurated plaques and nodules in the skin, attributable to fat necrosis [3]. The sites of predilection are the proximal extremities, especially the thighs, abdomen and buttocks (Fig. 47.10) [4]. Plain radiographs demonstrate small and large vessel calcification. The pathogenesis is unknown, and the condition is probably the result of a number of comorbid factors. The condition occurs in an estimated 1–4% of patients with terminal renal insufficiency and is much more common in women [3]. Uraemia and hyperphosphataemia are often more obvious than hypercalcaemia. The exact role of hyperparathyroidism is debated, but an elevated serum parathyroid hormone level is noted in most patients. The role of protein C and S remains to be determined, but a relative hypercoagulable state is present [3,4]. Histology usually confirms arterial medial calcification, intimal hyperplasia, fibrosis and vascular thrombosis and necrosis of the overlying epidermis [3].

The differential diagnosis of calcific uraemic arteriolopathy is extensive (Table 47.1) [3,4]. Treatment is unsatisfactory and the prognosis is poor, with sepsis as the main cause of death. Uraemia, and a raised serum calcium and phosphorus may be treated by dialysis; the mechanisms of the process, and medical treatments, are discussed in more detail in Chapter 49. Other important measures include pain control, wound management, sepsis prevention and avoidance of certain medications [3,4]. Parathyroidectomy is only indicated when there is evidence of hyperparathyroidism.

References

1 Chan YL, Mahony JF, Turner JJ, Posen S. The vascular lesions associated with skin necrosis in renal disease. *Br J Dermatol* 1983; **109**: 85–95.

Table 47.1 Differential diagnosis of calcific uraemic arteriolopathy (calciphylaxis).

Vascular causes
Peripheral arterial occlusive disease
Chronic venous insufficiency
Infections
Subacute bacterial endocarditis
Necrotizing fasciitis
Deep fungal infections
Erysipelas
Cellulitis
Immune mediated
Vasculitis
Cryoglobulinaemia
Lobular panniculitis (e.g. pancreatic)
Connective tissue disorders
Bullous pemphigoid
Erythema nodosum
Coagulopathy
Warfarin/coumarin necrosis
Embolic phenomena
Disseminated intravascular coagulation
Antiphospholipid syndrome
Miscellaneous
Porphyria cutanea tarda
Neoplastic causes
Calcinosis cutis

2 Ross CN, Cassidy MJD, Thompson M *et al*. Proximal cutaneous necrosis associated with small vessel calcification in renal failure. *QJM* 1991; **79**: 443–50.
3 Guldbakke KK, Khachemoune A. Calciphylaxis. *Int J Dermatol* 2007; **46**: 231–8.
4 Meissner M, Gille J, Kaufmann R. Calciphylaxis: no therapeutic concepts for a poorly understood syndrome? *J Dtsch Dermatol Ges* 2006; **4**: 1037–44.

Neurovascular disorders of the extremities

Erythromelalgia [1]

Definition [2]. This is a condition of painful, red extremities in which a sensation of burning is associated with small vessel vasodilatation in the affected skin. The synonyms erythermalgia [3] and erythralgia are confusing. There are three types of erythromelalgia:

Type 1: This is associated with thrombocythaemia and is relieved by aspirin.

Type 2 (Weir Mitchell's disease): This is a primary or idiopathic disorder which is usually congenital and is provoked by exercise or exposure to warmth.

Type 3: This is secondary to inflammatory or degenerative peripheral vascular disease.

However, the simpler division into primary (type 2) and secondary erythromelalgia may be preferred.

Pathogenesis. Type 1 is the result of thrombocythaemia and is seen in polycythaemia and myelofibrosis. It may be unilateral or even affect one finger or toe [4–7]. There is fibromuscular proliferation of the intima which leads to occlusive thrombosis of the digital arterioles and arteries [8].

Type 2 is confined to the lower legs and does not progress to ischaemia [9]. Primary erythromelalgia is often familial and is inherited in an autosomal dominant manner with the causative gene being located at chromosome 2q24 [10–12]. A prospective study by Davis *et al*. showed that most patients with erythromelalgia had a small-fibre neuropathy [13]. Primary erythromelalgia is the first inherited painful neuropathy to be understood at a molecular level, being due to mutations in the gene *SCN9A*, which encodes the voltage-gated channel Nav 1.7. *SCN9A* is preferentially expressed in most nocicepetive neurones and in sympathetic ganglia. Mutations cause a gain of function and a lower threshold for the influx of sodium ions in response to a stimulus such as increased temperature. Consequently, pain signalling increases in response to heat [14]. Families with erythromelalgia have been described in which inheritance is dominant although heterozygous mutations in Nav 1.7 are not always found. Mice homozygous for the mutation do not appear to feel pain. Nav 1.7 might not have a major role in post-traumatic neuropathic pain, but it does appear to have a role in inflammatory pain [12].

Pain has a direct relationship to the temperature of the limb; when this reaches a 'critical point', which normally lies between 32 and 36°C and which is constant for each individual, then pain will occur [14]. Pain is not a direct result of vasodilatation as it can be induced or maintained by warming the limb while its blood supply is occluded by a cuff. The pain is made worse by making the limb dependent, irrespective of its temperature. Pain may also be induced by obstructing the venous return. The involvement of small nerve fibres in primary erythromelalgia is likely as such manoeuvres do not cause pain or distress in normal subjects [15,16].

Type 3 erythromelalgia can occur in patients with connective tissue disorders and other inflammatory states. Certain drugs and peripheral vascular disease can also give rise to erythromelalgia and this can involve acral sites other than the hands and feet. Females are more often affected [17–22]. In types 1 and 3, the hands and feet are usually involved but sometimes only a part of one extremity is affected. The principal feature of erythromelalgia of all types is that attacks are precipitated by exercise or heat, such as a warm bed, and are relieved by rapid cooling, such as immersion in iced water. The patient complains of intense burning associated with erythema and increased warmth of the extremity. Attacks last from a few minutes to several hours. A warm climate and fever may increase the distress. Ulceration and trophic changes may result from cold immersion injury produced by attempts to relieve pain.

Diagnosis. The fully developed characteristics of the syndrome and the description given by the patient seldom leave doubt about the correct diagnosis. However, there are some important differential diagnoses and disease associations. Complex regional pain syndrome (reflex sympathetic dystrophy) following trauma can produce a similar clinical pattern. The effect of dependency, and the bizarre measures by which the patient may attempt to obtain relief, are also indicative of the diagnosis.

Disease associations include hypertension, diabetes, rheumatoid arthritis, lupus erythematosus, thromboangiitis obliterans, gout and vasculitis. The most important association of secondary erythromelalgia is with myeloproliferative disorders, for example polycythaemia rubra vera or thrombocythaemia. It may be a presenting and premonitory symptom of these conditions, often being present several years before they develop. Vasoactive drugs, such as nicardipine, have been incriminated as a cause [21].

Treatment and prognosis. No treatment is consistently effective and there is a dearth of adequate clinical trials. There is a significant decrease in survival compared to the general population, and most cases get worse over time [20].

Management consists of avoiding exacerbating factors, and controlling secondary and underlying factors [23]. Thrombocythaemia, or causes of inflammatory vascular disease, must be treated where possible. Small doses of aspirin give considerable relief in some patients—presumably by preventing platelet aggregation—and clopidogrel may be the most effective antiplatelet agent [5,24]. Patients with vasodilatation and warmth in their affected painful extremities prefer immersion in cold water. Elevation also provides some relief by decreasing oedema. Some have claimed relief of erythromelalgia with benoxybenzamine hydrochloride or propranolol [25]. Amitriptyline and neuropathic pain treatments such as gabapentin can help, and selective serotonin reuptake inhibitors have been used with success. Pain has been totally controlled by inserting an epidural block for up to 3 weeks, which allows healing of ulceration. The response of one family to pizotifen has been reported as spectacular [26]. Recombinant growth hormone therapy immediately relieved pain and healed cutaneous ulcers in a child with erythromelalgia and a growth hormone deficiency [27]. More recently, relief of pain was achieved in 18 out of 33 patients using a 5% lidocaine patch [28].

References

1 Brown GF. Erythromelalgia and other disturbances of the extremities accompanied by vasodilatation and burning. *Am J Med Sci* 1932; **183**: 468–85.
2 Mitchell SW. A rare vasomotor neurosis of the extremities and on maladies with which it may be confounded. *Am J Med Sci* 1878; **76**: 2–36.
3 Smith LA, Allen FV. Erythermalgia (erythromelalgia) of the extremities: a syndrome characterized by redness, heat and pain. *Am Heart J* 1938; **16**: 136–41.
4 Alarcon-Segovia D, Bag RR, Fairbain JF *et al.* Erythermalgia: a clue to early diagnosis of myeloproliferative disorders. *Arch Intern Med* 1966; **117**: 511–5.
5 Michiels JJ, Abels J, Steketee J *et al.* Erythromelalgia caused by platelet-mediated arteriolar inflammation and thrombosis. *Ann Intern Med* 1985; **102**: 466–71.
6 Michiels JJ, Van Joost T. Erythromelalgia and thrombocythemia: a causal relation. *J Am Acad Dermatol* 1990; **22**: 107–11.
7 Redding KG. Thrombocythaemia as a cause of erythermalgia. *Arch Dermatol* 1977; **113**: 448–71.
8 Michiels JJ, Van Joost TH, Vuzevski VD *et al.* Histopathology of erythromelalgia in thrombocythaemia. *Histopathology* 1984; **8**: 669–78.
9 Michiels JJ, Van Joost TH, Vuzevski VD. Idiopathic erythermalgia: a congenital disorder. *J Am Acad Dermatol* 1989; **21**: 1128–30.
10 Drenth JP, Finley WH, Breedveld GJ *et al.* The primary erythermalgia: susceptibility gene is located on chromosome 2q 31–2. *Am J Hum Genet* 2001; **68**: 1277–82.
11 Waxman SG, Dib-Hajj SD. Erythromelalgia: a hereditary pain syndrome enters the molecular era. *Ann Neurol* 2005; **57**: 785–8.
12 Waxman SG, Dib-Hajj SD. Molecular basis for an inherited pain syndrome. *Trends Mol Med* 2005; **11**: 555–62.
13 Davis MDP, Sandroni P, Rooke TW, Low PA. Erythromelalgia: vasculopathy, neuropathy, or both? A prospective study of vascular and neurophysiologic studies in erythromelalgia. *Arch Dermatol* 2003; **139**: 1337–43.
14 Han C, Lampert A, Rush AM *et al.* Temperature dependence of erythromelalgia mutation L858F in sodium channel Nav 1.7. *Mol Pain* 2007; **3**: 3.
15 Babb RR, Alarcon-Segovia D, Fairbain JF. Erythermalgia: review of 51 cases. *Circulation* 1964; **29**: 136–41.
16 Ørstavik K, Mørk C, Kvernebo K, Jørum E. Pain in primary erythromelalgia—a neuropathic component? *Pain* 2004; **110**: 531–8.
17 Davis MD, Fallon WM, Rogers RS III *et al.* Natural history of erythromelalgia: presentation and outcome of 168 patients. *Arch Dermatol* 2000; **136**: 330–6.
18 Alarcon-Segovia D, Diaz-Jouananen E. Erythermalgia in systemic lupus erythematosus. *Am J Med Sci* 1973; **266**: 149–51.
19 Ratz JI, Berfield WF, Steck WD. Erythermalgia with vasculitis. *J Am Acad Dermatol* 1979; **1**: 433–50.
20 Sandroni P, Davis MDP, Harper CM Jr *et al.* Neurophysiologic and vascular studies in erythromelalgia: a retrospective analysis. *J Clin Neuromusc Dis* 1999; **1**: 57–63.
21 Drenth JPH. Erythromelalgia induced by nicardipine. *BMJ* 1989; **298**: 1582.
22 Levesque H, Moore N, Wolf LM *et al.* Erythromelalgia induced by nicardipine (inverse Raynaud's phenomenon). *BMJ* 1989; **298**: 1252–3.
23 Davis MD, Rooke T. Erythromelalgia. *Curr Treat Options Cardiovasc Med* 2006; **8**: 153–65.
24 Michiels JJ, Lindemans J, Van Vliet HHDM *et al.* Survival kinetics of platelets and fibrinogen in thrombocythaemia related to erythromelalgia. *Br J Haematol* 1982; **50**: 690–1.
25 Bada SL. Treatment of erythromelalgia with propranolol. *Lancet* 1977; **ii**: 412.
26 Le Noach E, Guillet MH, Sassolas B *et al.* Erythromelalgie familiale; une observation traitée avec succes par pizotifene. *Ann Dermatol Vénéréol* 1994; **121** (Suppl. 1): 563.
27 Cimaz R, Rusconi R, Fossali E *et al.* Unexpected healing of cutaneous ulcers in a short child. *Lancet* 2001; **358**: 211–2.
28 Davis MDP, Sandroni P. Lidocaine patch for pain of erythromelalgia: follow-up of 34 patients. *Arch Dermatol* 2005; **141**: 1320–1.

Complex regional pain syndrome

Synonyms
- Complex regional pain syndrome types I and II
- Reflex sympathetic dystrophy
- Causalgia
- Sudeck's atrophy

Definition. Complex regional pain syndrome (CRPS) is the name now given to a syndrome of chronic pain and hyperalgesia, associated with sensory, motor, autonomic and dystrophic disturbances, usually in a limb. Two types can be distinguished:

CRPS 1: also known as reflex sympathetic dystrophy, typically develops after minor trauma with no obvious small nerve lesion

CRPS 2: also known as causalgia, in which there is clear evidence of nerve injury [1].

Pathogenesis. There is evidence to suggest that CRPS represents a spectrum of changes in the inflammatory, neural, vascular and musculoskeletal systems. Several mechanisms have been suggested, but none of them has so far explained the exact pathophysiology of this disease. Peripheral nerves or C and A-δ fibre terminals are injured in the autonomic and motor systems as well as in the pain fibres [2].

Clinical features. Patients typically describe pain, swelling and difficulty in using the affected limb. The pain has a burning or deep aching quality and is aggravated by movement. Consequently there is a tendency to avoid using the limb, and hyperalgesia encourages limb protection. The skin takes on a deep red to blue colour, suggesting that vasodilatation is occurring, and is initially warmer than the unaffected contralateral limb becoming cooler in the latter stages. Oedema may result from disuse and dependency, and the muscles atrophy (Sudeck's atrophy).

Diagnosis. CRPS is a clinical diagnosis and there is no simple diagnostic test. In 20% of the patients there are changes in the skin and less commonly in the nails and hair. There is a temperature and colour asymmetry in half the patients. Early hyperhidrosis, and later anhidrosis, may be demonstrated by starch-iodine testing. A decreased range of motion, weakness, dystonia and tremor may also be noted [3]. Increased blood flow is an important diagnostic feature of early CRPS [4]. It is clearly demonstrated by a three-phase bone scan [5]; the delayed phase of this scan is very sensitive, and a segmental diffuse increase in the uptake of radionuclide is very specific. Later the bone scan returns to normal and there are radiographic features of rapid bone loss including visible demineralization with patchy, subchondral or periosteal osteoporosis, metaphyseal banding and profound bone loss [6].

Treatment. The aim of treatment is to reduce pain and restore function of the affected limb as soon as possible. First-line treatment consists of physical therapy in combination with drugs. Medications that may improve neuropathic pain, including tricyclic antidepressants, anticonvulsants and opioid analgesia, are commonly used to treat patients with CRPS [7]. Although not well tolerated by most patients, compression bandaging is one of the mainstays of complex regional pain syndrome treatment, especially in reducing oedema and enhancing the circulation.

Free radical scavengers have been used in both the treatment and prevention of complex regional pain syndrome, based on the assumption that complex regional pain syndrome is induced by an exaggerated inflammatory response to tissue injury, mediated by excessive production of toxic oxygen radicals [8]. Promising results have been reported with dimethylsulfoxide and *N*-acetylcysteine [9].

Severe cases may require regional anaesthetic blockade. A meta-analysis by Hassantash *et al.* [10] found that 88% of 822 patients with CRPS 2 had a beneficial response to sympathetic blocks of the involved extremity. The same literature review demonstrated that 91% of 791 patients who were treated by sympathectomy had a relief of their symptoms after one procedure and 94% after a second procedure. In selected patients with severe chronic pain, electrical spinal cord stimulation can induce pain relief and improve the patient's quality of life.

References

1 Eisenberg E, Geller R, Brill S. Pharmacotherapy options for complex regional pain syndrome. *Expert Rev Neurother* 2007; **5**: 521–31.

2 Jänig W, Baron R. Complex regional pain syndrome: mystery explained? *Lancet Neurol* 2003; **2**: 687–97.

3 Harden RN, Bruehl SP. Diagnosis of complex regional pain syndrome: signs, symptoms, and new empirically derived diagnostic criteria. *Clin J Pain* 2006; **22**: 415–9.

4 Wasner G, Schattschneider J, Heckmann K *et al.* Vascular abnormalities in the reflex sympathetic dystrophy (CRPS 1): mechanisms and diagnostic value. *Brain* 2001; **124**: 587–99.

5 Driessens M, Dijs H, Verheyen G, Blockx P. What is reflex sympathetic dystrophy? *Acta Orthop Belg* 1999; **65**: 202–17.

6 Atkins RM. Aspects of current management: complex regional pain syndrome. *J Bone Joint Surg* 2003; **85-B**: 1100–6.

7 Sharma A, Williams K, Raja SN. Advances in treatment of complex regional pain syndrome: recent insights on a perplexing disease. *Curr Opin Anaesthesiol* 2006; **19**: 566–72.

8 Perez RSGM, Zuurmond WWA, Bezemer PD *et al.* The treatment of complex regional pain syndrome type I with free radical scavengers: a randomized controlled study. *Pain* 2003; **102**: 297–307.

9 Warltier DC. Preventing the development of complex regional pain syndrome after surgery. *Anesthesiology* 2004; **101**: 1215–24.

10 Hassantash SA, Afrakhteh M, Maier RV. Causalgia. A meta-analysis of the literature. *Arch Surg* 2003; **138**: 1226–31.

Angiodyskinesia

Paraesthesiae, painful burning sensations combined with redness or pallor of the legs after prolonged walking or dancing, has been described in young people [1,2] and it has been suggested that these were a consequence of abnormal functioning of the arteriovenous communications. The term 'angiodyskinesia' has been applied to this condition [3].

Under this title, Ryan and Wilkinson described a blotchy erythema of the legs in a 14-year-old boy [4]. His condition developed at the same time as osteochondritis dissecans. The erythematous areas were 2–3°C warmer than the adjoining skin, and disappeared when the patient was recumbent, reappearing and becoming uncomfortable when he was standing. These features suggest failure of the normal vasoconstriction that occurs when a limb is lowered. The condition was more marked in warmer conditions and after a bath.

References

1 Khobreh MT, Roy P. Functional circulatory disorders of the lower extremities due to regional hemokinetic imbalance: a new clinical and angiographic concept. *Surgery* 1967; **61**: 880–90.

2 Malan E. Vascular syndromes from dilatation of arteriovenous communications of the sole of the foot. *Arch Surg* 1958; **77**: 783–95.

3 Amir-Jahed AK. Angiodyskinesia. *Surg Gynaecol Obstet* 1968; **127**: 609–31.

4 Ryan TJ, Wilkinson DS. Angiodyskinesia and osteochondritis dissecans. *Proc R Soc Med* 1974; **67**: 1242–3.

Restless legs syndrome

Definition. Restless legs syndrome is a sensorimotor disorder characterized by an uncomfortable feeling in the legs that urges movement [1].

Pathophysiology. Restless legs syndrome can occur as a primary or a secondary disorder.

In the primary form there is no apparent cause other than a possible genetic predisposition [2]. Under the assumption of a recessive and dominant mode of inheritance, three loci for restless legs have been found on chromosomes 9p, 12q and 14q [3].

Restless legs syndrome occurring as a secondary condition is related to iron deficiency, pregnancy and end-stage renal disease. Clinical evidence suggests that restless legs syndrome is associated with decreased dopaminergic neurotransmission. The symptoms are worse at night when dopamine levels fall [2]. Restless legs syndrome is not associated with chronic venous insufficiency.

Clinical features. The core feature of this syndrome is a distressing, irresistible urge to move the legs (akathisia). This often coexists with an uncomfortable, hard to describe, sensation deep within the legs. The prevalence in the general population lies between 2.5–15%, increasing with age and being more common in women. A family history is often present in patients whose symptoms appear before 40 years of age [4].

Four essential criteria have been established for the diagnosis to be upheld:

1. An urge to move legs that is usually accompanied or caused by uncomfortable or unpleasant sensations in the legs
2. An urge to move or an unpleasant sensation that begins or worsens during periods of rest or inactivity
3. An urge to move or an unpleasant sensation that is partially or totally relieved by movement as long as the activity continues
4. An urge to move or an unpleasant sensation that is worse in the evening or at night rather than during the day or that only occurs during the evening or at night [1].

Diagnosis. The diagnosis is made from the criteria listed above; the most important aspect is to identify any treatable underlying cause and to exclude other disorders that have some clinical similarities. End-stage renal failure is probably the most obvious and best investigated secondary condition associated with restless legs syndrome. Several studies have shown an association between restless legs syndrome and pregnancy. After delivery, the prevalence of restless legs syndrome decreases to values found in the normal population. Disorders in iron regulation may be involved in primary forms of restless legs syndrome. Correcting iron status in patients with iron deficiency has been found to reduce symptoms in patients with restless legs syndrome. An association between Parkinson's disease and restless legs syndrome has been made because of the response to dopaminergic treatment in both disorders [5].

The differential diagnosis of restless legs syndrome includes both movement and sleep disorders. Most of these conditions typically do not have a circadian pattern, nor does movement relieve the symptoms [1]. Although restless legs syndrome may be triggered by radiculopathy, neuropathic pain syndromes or peripheral neuropathy, a distinction should be made between these conditions [6]. Restless legs syndrome should be differentiated from drug-induced akathisia (e.g. antiemetics, neuroleptics, antipsychotics, serotonin reuptake inhibitors and tricyclic antidepressants), positional discomfort and arthritis. Other disorders such as nocturnal leg cramps, restless insomnia and vascular insufficiency should also be distinguished from restless legs syndrome.

Treatment. Treatment of restless legs syndrome begins with an assessment of potential factors that may aggravate the symptoms. Medications that can aggravate the symptoms of restless legs syndrome, such as dopamine-blocking agents, antiemetics, antihistamines and antidepressants, should be avoided. Other non-pharmacologic approaches consist of good sleep 'hygiene', behavioural interventions (for example a brief walk before bedtime and a hot bath) and avoidance of alcohol, nicotine and caffeine, especially in the evening [7].

Iron deficiency, confirmed by a low ferritin level, should be treated, as it has been reported that iron supplementation improves the symptoms of restless legs syndrome [4]. When drug management is required, dopaminergic agents are considered the first line of treatment in idiopathic restless legs syndrome. Other agents that have been shown to improve the symptoms of restless legs syndrome are opiates, benzodiazepines and anticonvulsant agents.

References

1 Kushida CA. Clinical presentation, diagnosis, and quality of life issues in restless legs syndrome. *Am J Med* 2007; **120** (Suppl. 1A): 4–12.
2 Allen RP. Controversies and challenges in defining the etiology and pathophysiology of restless legs syndrome. *Am J Med* 2007; **120** (Suppl. 1A): 13–21.
3 Winkelmann J, Ferini-Strambi L. Genetics of restless legs syndrome. *Sleep Med Rev* 2006; **10**: 179–83.
4 Earley CJ. Restless legs syndrome. *N Engl J Med* 2003; **348**: 2103–9.
5 Trenkwalder C, Paulus W, Walters AS. The restless legs syndrome. *Lancet Neurol* 2005; **4**: 464–75.
6 Garcia-Borreguero D, Egatz R, Winkelmann J, Berger K. Epidemiology of restless legs syndrome: the current status. *Sleep Med Rev* 2006; **10**: 153–67.
7 Hening WA. Current guidelines and strategies of practice for restless legs syndrome. *Am J Med* 2007; **120** (Suppl. 1A): 22–7.

Telangiectases

Definition. Telangiectases (Latin: tel, end + Greek: angos, vessel + ectasis from Greek: ektasis, expansion) are chronically dilated capillaries or venules. They appear on the skin and mucous membranes as small, dull red, linear, stellate or punctate markings. Telangiectases (telangiectasia) represent dilatations (expansion, stretching) of pre-existing vessels without any apparently new vessel growth (angiogenesis) occurring. As such, telangiectases can be bracketed with spider angioma (spider naevi) and capillary aneurysm–venous lakes, whereas vascular malformations represent anomalies of embryological development (disturbances in vasculogenesis or angiogenesis). Hamartomas include proliferation of other tissue elements, for example melanocytic or eccrine cells, and are not solely vascular [1].

Telangiectasia can also be part of chronic venous insufficiency. The red lesions have a higher oxygen content than the blue lesions, suggesting a different origin in the capillary bed [2].

Development of telangiectasia [3]

The common telangiectases can be explained by abnormalities in the organization and ultrastructure of the small vessels rather than by neovascularization (angiogenesis) or random anastomoses.

The *macular telangiectases* seen in scleroderma, generalized essential telangiectasia and naevus flammeus are produced by dilatation of the postcapillary venules of the upper horizontal (subpapillary) plexus.

Cherry angiomas are produced by spherical and tubular dilatations of capillary loops in the dermal papillae with tortuous cross-connections between individual loops.

Telangiectasia macularis eruptiva perstans is a rare form of cutaneous mastocytosis. Clinically, there are tan-to-brown macules with patchy erythema associated with telangiectases that usually involve the trunk. Histologically, there may be only subtle alterations in mast cell numbers. The cells tend to be fusiform and loosely arranged around the dilated vessels of the superficial plexus. Eosinophils are usually absent [4].

Angiokeratomas of Fabry and Fordyce have the ultrastructure of collecting venules that contain valves and appear to represent the ectopic development of small valve-containing collecting veins.

The cutaneous lesions of hereditary haemorrhagic telangiectasia (HHT) represent microvascular arteriovenous anastomoses.

The development of telangiectases is a complex dynamic process with different mechanisms likely to be involved. In HHT, for example, where arteriovenous anastomoses cause focal dilatations of postcapillary venules, different genetic mutations (discussed on p. 47.17) interfere with integral membrane proteins on vascular endothelial cells responsible for binding transforming growth factor-β (TGF-β). TGF-β signalling mediates vascular remodelling through effects on extracellular matrix production [5]. Disruption of this latter maturation phase of angiogenesis seems to be important in the development of HHT [6].

References

1 Requena L, Sangueza OP. Cutaneous vascular anomalies. Part I. Hamartomas, malformations and dilation of pre-existing vessels. *J Am Acad Dermatol* 1997; **37**: 523–49.

2 Sommer A, Van Mierlo PLHMJ, Kessels AGH, Neumann HAM. Red and blue telangiectasias. Differences in oxygenation? *Dermatol Surg* 1997; **23**: 55–9.

3 Braverman IM. Ultrastructure and organisation of the cutaneous microvasculature in normal and pathologic state. *J Invest Dermatol* 1989; **93** (Suppl. 2): 25–95.

4 Weedon D. Cutaneous infiltrates—non-lymphoid. In: Weedon D, ed. *Skin Pathology,* 2nd edn. London: Churchill Livingstone, 2002: 1057–93.

5 Fernàndez-L A, Sanz-Rodriguez F, Blanco FJ *et al*. Hereditary hemorrhagic telangiectasia, a vascular dysplasia affecting the TGF-β signaling pathway. *Clin Med Res* 2006; **1**: 66–78.

6 Lamouile S, Mallet C, Feige JJ, Bailly S. Activin receptor-like kinase 1 is implicated in the maturation phase of angiogenesis. *Blood* 2002; **100**: 4495–501.

Secondary telangiectasia and dilatation of pre-existing vessels

Telangiectases commonly represent the effect of wear and tear on the skin, and are particularly frequent in ageing, on light-exposed skin, or following trauma or X-irradiation, and in some skin diseases such as lupus erythematosus and dermatomyositis. In fact, they are found in most processes that cause atrophy of the skin, whatever their aetiology; they are prominent, for example, in poikiloderma. Smoking and UV-radiation are known to have a detrimental effect on human skin, characterized by elastosis and telangiectasia. The association between increasing age, sun exposure and the amount of telangiectasia is strong in men but less apparent in women. Similarly, smoking is associated with elastosis in both sexes but only with telangiectasia in men [1].

Prolonged vasodilatation may be followed by permanent telangiectases, for example, in rosacea. Varicose veins are frequently the cause of telangiectases on the legs, where they may produce a type of arborescent telangiectasia. Telangiectasias associated with chronic venous disease are assumed to be the result of a rise in venous pressure, which stretches the vulnerable venous end of the capillary or draining venule [2]. The significance of telangiectases of the lower limbs must not be underestimated. Considered a 'cosmetic' problem, their presence is often indicative of early or established abnormalities in the main leg veins. Telangiectases may be individual or they can arise in sheets or have an arborizing appearance. The colour of the telangiectasia depends on the calibre of the dilated venule. Large dilatations (<1 mm) are dark blue and often palpable. The smallest (0.1 mm), most superficial, telangiectases are red and barely empty when the leg is raised. Telangiectasias have been classified by Duffy (Table 47.2) [3]; some of the more important causes are listed in Table 47.3.

Table 47.2 Vessel classification (Duffy, 1988 [3]).

Type I	Spider veins, 0.1–1 mm diameter telangiectatic matting <0.2 mm diameter
Type II	Venulectasia 1–2 mm
Type III	Reticular veins 2–4 mm diameter feeder veins
Type IV	Non-saphenous varicose veins, 3–8 mm
Type V	Saphenous varicose veins

Table 47.3 Some causes of telangiectasia.

Secondary telangiectasia
Prolonged vasodilatation (rosacea, varicose veins)
Prolonged exposure to sunlight, tar, etc.
Post-traumatic
Radiodermatitis
Xeroderma pigmentosum
Atrophy, e.g. poikiloderma, topical corticosteroids
Raynaud's disease
Lupus erythematosus
Dermatomyositis
Systemic sclerosis
Morphoea
Mastocytosis (telangiectasia macularis eruptiva perstans)
Acquired immune deficiency syndrome
Primary telangiectasia
Vascular naevi
Angiomas and angiokeratomas
Angioma serpiginosum
Hereditary haemorrhagic telangiectasia
Ataxia–telangiectasia
Generalized essential telangiectasia
Unilateral naevoid telangiectasia syndrome
Hereditary benign telangiectasia
Spider telangiectases
Bloom's syndrome
Morquio's syndrome
Angiotropic lymphoma
Mycosis fungoides
Naevus anaemicus with telangiectatic vessels
Cutis marmorata telangiectatica
Solitary plaque-like telangiectatic glomangioma

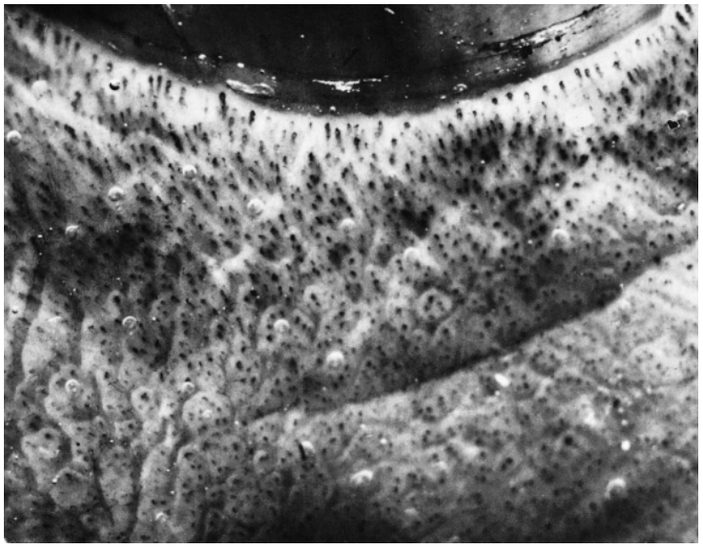


Fig. 47.11 Normal nail-fold capillaries. (Courtesy of Dr H.R. Maricq, Lyons, NJ, USA.)

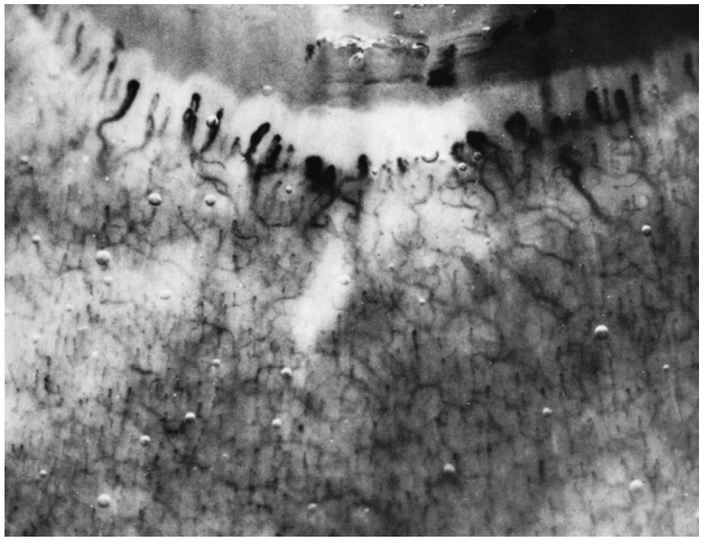


Fig. 47.12 Nail-fold capillaries in scleroderma. (Courtesy of Dr H.R. Maricq, Lyons, NJ, USA.)

The term *corona phlebectatica paraplantans* (venous ankle flare) [4] is used to describe perimalleolar and paraplantar venous telangiectasia that is always associated with venous hypertension. In contrast, telangiectases around the lower border of the ribs ('costal fringe') are virtually physiological in old age.

Telangiectases may be an important diagnostic sign in certain systemic disorders, especially in lupus erythematosus, dermatomyositis and scleroderma, or in association with Raynaud's phenomenon.

Capillary microscopy of nail-fold telangiectases may help in the differential diagnosis (Figs 47.11 & 47.12). Usually, the distribution and associated abnormalities leave little doubt about the diagnosis, but occasionally telangiectases may be the presenting or only sign, or may be the result of an otherwise burnt-out process. Patients with scleroderma, especially of the so-called Thibierge–Weissenbach or CREST type, may present with telangiectases that closely mimic HHT, and that may even cause severe bleeding. Patients with dermatomyositis may have telangiectases on the eyelids, hands or elsewhere. Localized areas of telangiectases on the face may be a manifestation of discoid lupus erythematosus. Telangiectases of the face and also of the mucous membranes are a common feature of Raynaud's phenomenon without other evidence of scleroderma. Telangiectases may be a manifestation of neonatal lupus erythematosus, with or without any other eruption [5].

Unusual mat-like telangiectases, especially on the upper back, have been reported in men working in an aluminium plant [6]. Telangiectases on the chest wall [7] and other sites [8] have been reported in patients with AIDS. Telangiectasias are also described in other conditions, including cutaneous mastocytosis (telangiectasia macularis eruptiva perstans) and angiotrophic (intravascular) lymphoma [9].

References

1 Kennedy C, Bastiaens MT, Bajdik CD *et al*. Effect of smoking and sun on the ageing skin. *J Invest Dermatol* 2003; **120**: 548–54.

2 Bergan JJ, Goldman MP. *Varicose Veins and Telangiectasias*. St. Louis: Quality Medical Publishing, 1993.

3 Duffy DM. Small vessel sclerotherapy: an overview. In: Callen JP. *et al.*, eds. *Advances in Dermatology*, Vol. 3. Chicago: Year Book Medical Publishers, 1988: 221.

4 Van der Molen HR. Die Corona Phlebectatica Paraplantaris. *Der Fuss*, 1982: 154–74.

5 Thornton CM, Eichenfield LF, Shinall EA *et al*. Cutaneous telangiectases in neonatal lupus erythematosus. *J Am Acad Dermatol* 1995; **33**: 19–25.

6 Thériault G, Cordier S, Harvey R. Skin telangiectases in workers at an aluminium plant. *N Engl J Med* 1980; **303**: 1278–81.

7 Fallo T, Abell E, Kingsley L *et al*. Telangiectasias of the anterior chest in homosexual men. *Ann Intern Med* 1986; **105**: 679–82.

8 Ruiz-Avila P, Tercedor J. Painful periungual telangiectasias in a patient with acquired immunodeficiency syndrome. *Int J Dermatol* 1995; **34**: 199–200.

9 Ozguroglu E, Buyulbabani N, Ozguroglu M *et al*. Generalised telangiectasia as the major manifestation of angiotropic (intravascular) lymphoma. *Br J Dermatol* 1997; **137**: 422–5.

Spider telangiectases

Synonyms
- Arterial spider
- Spider naevus
- Naevus araneus
- Spider angioma

Aetiology and pathology. Spider telangiectases occur in up to 15% of completely normal persons, and more frequently in children [1,2]. They occur in large numbers during pregnancy—one or more spider naevi are found in two-thirds of all pregnant women [1]. They may appear in the first few months, but tend to increase in number until term; they usually disappear within 6 weeks of delivery but may persist or recur in the same sites in subsequent pregnancies. They are also characteristically found in patients with liver disease, when they can be a presenting sign [3]. A relationship to oestrogens has been suggested on this clinical evidence. Palmar erythema may be associated with spider naevi, with or without liver disease or pregnancy.



Fig. 47.13 Spider telangiectasis.

The main vessel of the spider telangiectasis is an arteriole. The blood flows from this to the periphery, and then passes into a capillary network [4]. The pressure in spider telangiectases rises to 40 mmHg. The lesions consist of a central, ascending, spiral, thick-walled arteriole which ends in a thin-walled ampulla just beneath the epidermis. From the ampulla, thin-walled branching channels radiate peripherally in the papillary dermis. Glomus cells have been described in the wall of the central arteriole [5]. Therefore these lesions actually resemble microarteriovenous malformations.

Clinical features. Spider naevi vary in size and shape, and may be up to 1.5 cm across. The central body may be raised, and is usually pulsatile on diascopy. The radiating vessels are just visible to the naked eye (Fig. 47.13). They occur on the upper half of the body, especially the face, neck and hands. They are frequently solitary, but may be multiple, even in health. Liver disease is seldom found, but should be suspected at any age when lesions are numerous. They may develop at sites of trauma and may be unilateral [6]. Similar lesions occur on the mucous membranes of the lips and nose. Here, the typical morphology is less apparent and the differentiation from HHT may be difficult.

The majority of lesions that occur in pregnancy disappear spontaneously, but some may persist. Lesions appearing in otherwise healthy children tend to persist indefinitely, but a small proportion regress spontaneously.

Diagnosis. The typical morphology, with a central pulsating vessel, does not occur in other conditions. In HHT, the telangiectases are macular, punctate or linear; when they are stellate they do not pulsate.

References

1 Bean WB. *Vascular Spiders and Related Lesions of the Skin.* Springfield: Thomas, 1958.
2 Wenzl JE, Burgess EO. The spider nevus in infancy and childhood. *Pediatrics* 1964; **33**: 227–32.
3 Whiting DA, Kallmeyer JC, Simson IW. Widespread arterial spiders in a case of latent hepatitis, with resolution after therapy. *Br J Dermatol* 1970; **82**: 32–6.
4 Martini GA, Staubesand J. Zur Morphologie des Gefässpinnen ('vascular spiders') in der Haut Leberkranker. *Virchows Arch Path Anat Physiol* 1953; **324**: 147–64.
5 Weedon D. Vascular tumors. In: Weedon D, ed. *Skin Pathology*, 2nd edn. London: Churchill Livingstone, 2002.
6 Cunliffe WJ, Dodman B, Butterworth MJ. Unilateral spider naevi. *Br J Dermatol* 1972; **87**: 51–2.

Cherry angiomas

Synonym
- Campbell de Morgan spots

These are particularly common on the trunk of middle-aged or elderly people. They disappear in extreme old age. Increased numbers have been recorded in diabetics [1], but this association is of doubtful significance. Ultrastructural examination has shown that they have reduplicated basement membranes with fenestrations of the endothelium [2,3].

When fully developed they are readily recognized. Tiny lesions, which may be very numerous (sometimes termed 'multiple minute Campbell de Morgan spots'), can resemble either petechiae or other types of telangiectases. They cannot always be made to blanch with pressure, and may need to be observed repeatedly to distinguish them from petechiae, although they are readily identifiable if magnified. Larger lesions can be excised or treated with a vascular laser under local anaesthetic if they are unsightly.

Angiokeratomas

Angiokeratomas are rare lesions that appear as dark red papules and plaques arranged either discretely or in clusters. Five different types can be distinguished from their morphology and location. Angiokeratomas are probably not vascular neoplasms but acquired telangiectases of pre-existing blood vessels of the papillary dermis, although some types of venular malformation cannot be excluded. All varieties of angiokeratomas are histologically similar and they possess the ultrastructure of collecting venules with valves [4].

References

1 Bean WB. *Vascular Spiders and Related Lesions of the Skin.* Springfield: Thomas, 1958.
2 Stehbens WE, Ludatscher RM. Fine structure of senile angiomas of human skin. *Angiology* 1968; **19**: 581–92.
3 Braverman IM. Ultrastructure and organisation of the cutaneous microvasculature in normal and pathologic states. *J Invest Dermatol* 1989; **93** (Suppl. 2): 25–95.
4 Mittal R, Aggarwal A, Srivastava G. Angiokeratoma circumscriptum: a case report and review of the literature. *Int J Dermatol* 2005; **44**: 1031–4.

Telangiectasia with calcium channel blocking drugs

There have been increasing numbers of reports associating telangiectasia with calcium channel blockers [1–3], particularly in sun-exposed sites. The aetiology of this disorder is not fully understood. Usually, the telangiectasias resolve within 3 to 6 months after discontinuation of the drug [4]. In a study of renal transplant recipients the grade of photodamage was strongly associated with the use of calcium channel blockers [5].

References

1 Basarab T, Yu R, Jones RR. Calcium antagonist-induced photo-exposed telangiectasia. *Br J Dermatol* 1997; **136**: 974–5.

2 Karonen T, Stubb S, Keski-Oja J. Truncal telangiectases coinciding with felodipine. *Dermatology* 1998; **196**: 272–3.
3 Grabczynska S, Cowley N. Amlodipine induced-photosensitivity presenting as telangiectasia. *Br J Dermatol* 2000; **142**: 1255–6.
4 Ioulios P, Charalampos M, Efrossini T. The spectrum of cutaneous reactions with calcium antagonists: a review of the literature and the possible etiopathogenic mechanisms. *Dermatology Online J* 2003; **5**: 6.
5 Cooper SM, Wojnarowska F. Photo-damage in Northern European renal transplant recipients is associated with use of calcium channel blockers. *Clin Exp Dermatol* 2003; **28**: 588–91.

Venous lakes [1]

A form of senile angioma found on the face, lips and ears of elderly patients. Histologically, they consist of greatly dilated, thin-walled venules without the proliferation of vascular tissue found in the true angioma. There is degeneration of the supporting connective tissue [2]. Treatment consists of primary excision of the lesion rather than laser therapy.

References

1 Bean WB, Walsh JR. Venous lakes. *Arch Dermatol* 1956; **74**: 459–63.
2 Kocsard E, Ofner F, D'Abrera VS *et al*. The phlebectasis of old age—incidence and diagnostic importance. *J Am Geriatr Soc* 1970; **18**: 31–8.

Hand varices

Small varicosities of the palms and fingers, particularly on the palmar phalangeal creases, are much more common than generally is known in elderly people [1]. They can be treated, like other varicose veins, with sclerotherapy [2] or with the Müller technique of phlebectomy [3].

References

1 Clark ANG, Melcher DH, Hall-Smith P. Palmar and finger varicosities of the aged. *Br J Dermatol* 1974; **91**: 305–14.
2 Duffy DM, Garcia C, Clark RE. The role of sclerotherapy in abnormal varicose hand veins. *Plast Reconstr Surg* 1999; **104**: 1474–9.
3 Ramelet AA. Phlebectomy. Technique, indications and complications. *Int Angiol* 2002; **21** (Suppl. 1): 46–51.

Primary telangiectasia

Angioma serpiginosum [1–4]

Angioma serpiginosum is a rare naevoid disorder affecting the small vessels of the upper dermis. Histology shows that the affected papillae are distended by a large, single, ectatic capillary, lined by flattened endothelial cells of normal appearance. Inflammatory changes are not present. The disease occurs predominantly in females (90%), and usually starts in childhood. Most cases are sporadic, but a family history suggesting X-linked dominant inheritance has been reported [5].

The commonly affected sites are the lower limbs and buttocks, but it can be more widespread (Fig. 47.14). It is often unilateral initially. Characteristically, there are red or purple puncta up to 1 mm in diameter. These are grouped in areas a few centimetres across, or sometimes form large sheets. Irregular lesions may arise, and commonly there is livedoid patterning of the puncta. Frequently, there is a background of more diffuse erythema. The lesions may not blanch completely on pressure, but, like multiple minute Campbell de Morgan angiomas, they have been confused with purpura [6]; that they consist of a cluster of small vessels rather than purpura can readily be distinguished by appropriate magnification [7].



(a)



(b)

Fig. 47.14 Angioma serpiginosum. (a) Grouped lesions. (b) Close-up appearance.

The condition starts as one or more small lesions, and usually ceases, but may recommence in adult life. Individual puncta often disappear spontaneously, and complete regression of the eruption may occur, or traces may persist indefinitely. There are no symptoms, and no other changes in the skin, although slight atrophy has been reported [8].

The dilated capillaries are easy to see under the capillary microscope. The background erythema is the result of dilatation of the subpapillary venous plexus. Epiluminescence microscopy can be helpful in diagnosis by demonstrating 'red lagoons'. Histologically, dilated and tortuous capillaries are observed in

the papillary dermis but without any inflammation or red cell extravasation.

The differential diagnosis includes angiokeratoma corporis diffusum, angiokeratoma circumscriptum naeviforme and forms of capillaritis. Treatment with vascular laser, such as pulsed dye laser and intense pulsed light source, improves the disorder, but is not always necessary [9].

References

1 Barker IP, Sachs PM. Angioma serpiginosum. *Arch Dermatol* 1965; **92**: 613–20.
2 Frain-Bell W. Angioma serpiginosum. *Br J Dermatol* 1957; **69**: 251–68.
3 Yaffee HS. Angioma serpiginosum. *Arch Dermatol* 1967; **95**: 667.
4 Kumakiri M, Katoh H, Mitura Y *et al.* Angioma serpiginosum. *J Cut Pathol* 1980; **7**: 410–21.
5 Marriott PJ, Munro DD, Ryan T. Angioma serpiginosum—familial incidence. *Br J Dermatol* 1975; **93**: 701–6.
6 Cox NH, Paterson WD. Angioma serpiginosum: a simulator of purpura. *Postgrad Medl J* 1991; **67**: 1065–6.
7 Ohnishi T, Nagayama T, Morita T *et al.* Angioma serpiginosum: a report of 2 cases identified using epiluminescence microscopy. *Arch Dermatol* 1999; **135**: 1366–8.
8 Gautier-Smith PC, Sanders MD, Sanderson KV. Ocular and nervous system involvement in angioma serpiginosum. *Br J Ophthalmol* 1971; **55**: 433–43.
9 Long CC. Treatment of angioma serpiginosum using a pulsed tunable dye laser. *Br J Dermatol* 1997; **136**: 631–2.

Hereditary haemorrhagic telangiectasia [1]

Synonym
- Osler–Rendu–Weber syndrome

Hereditary haemorrhagic telangiectasia (HHT) is an autosomal dominant disorder characterized by epistaxis, cutaneous telangiectasia and visceral arteriovenous malformations (AVMs). HHT is more prevalent than previously estimated [1]. The clinical diagnosis is made on the basis of: (i) epistaxis—spontaneous, recurrent nose bleeds; (ii) telangiectases—multiple, at characteristic sites (lips, oral cavity, fingers, nose); (iii) visceral lesions—such as gastrointestinal telangiectasia (with or without bleeding), pulmonary AVMs, hepatic AVMs, cerebral AVMs, spinal AVMs; and (iv) a family history—a first-degree relative with HHT. Three criteria indicate a definite diagnosis of the disorder; two a possible or suspected case [2].

Aetiology and pathogenesis. HHT has an autosomal dominant inheritance pattern associated with mutations in at least two genes. Mutations in the endoglin (*ENG*) gene on chromosome 9q34 are responsible for HHT1, while mutations in the activin receptor-like kinase 1 (*ACVRL1*) gene on chromosome 12q are responsible for HHT2. The corresponding proteins, endoglin and ALK-1, are specific endothelial receptors of transforming growth factor β (TGF-β) [3]. TGF-β signalling is essential during angiogenesis and can activate ALK-1 and ALK-5 in endothelial cells, each one leading to opposite effects on endothelial cell proliferation and migration [4]. In HHT there is decreased endoglin expression and impaired ALK-1. HHT1 families have a higher prevalence of pulmonary AVMs than HHT2 families, who generally have a milder phenotype and later onset. Mice lacking the *ENG* or *ACVRL1* genes develop age-dependent vascular lesions of the skin of the extremities, oral cavity and internal organs in a phenotype very similar to the human condition [5].



Fig. 47.15 Hereditary haemorrhagic telangiectasia.

Clinical features. Recurrent epistaxis is usually the presenting symptom. It may begin in childhood or even in infancy, but far more commonly begins at puberty or in early adult life. Telangiectasia of the skin is not often seen before puberty, and usually appears in the third or fourth decade, but it may be extensive in early childhood. The individual lesions are punctate or linear. On the rare occasions when they are spider naevus-like, they do not pulsate. Nodular lesions may be present but are sparse in comparison with the smaller lesions, which may be numerous. Lesions may occur anywhere, but especially on the upper half of the body—face, lips, ears, conjunctivae, trunk, forearms, hands and fingers (Fig. 47.15). They are often conspicuous in the nail beds. The soles and toes may also be affected. The skin lesions seldom bleed.

The mucous membranes are almost invariably involved. Lesions occur on the nasal septum, in the mouth, nasopharynx, and throughout the gastrointestinal tract [2,6,7], where they may be demonstrated by endoscopy or arteriography. They may also be found in many other organs, including the retina. The lesions on the tongue have a characteristic and perhaps diagnostic appearance on capillary microscopy. Within a fungiform papilla there is a single, very dilated vessel, which may cause the papilla to be expanded [8]. Haemorrhages may occur from any site, and their severity and frequency determine the clinical manifestations and course of the disorder. Pulmonary arteriovenous fistulae are present in some cases, and occur particularly in some families [9,10]. They reveal their presence by dyspnoea, cyanosis and

clubbing of the fingers in adolescence. They can be demonstrated radiologically. Paradoxical embolization to the systemic circulation may occur. This disease is the commonest cause of pulmonary arteriovenous anastomoses. Cerebral vascular malformations occur in 10% of patients with HHT [11]. Hepatic arteriovenous anastomoses have been reported, and liver enlargement and cirrhosis also occur [9,11]. Aneurysms of other vessels, including the aortic arch and splenic artery [6], have been reported. Lesions of the eye [12] are uncommon.

Diagnosis. The history, family history and morphology of the individual lesions are usually sufficient to establish the diagnosis. The lesions do not have the characteristic morphology of a spider naevus. Other causes of telangiectasia have to be excluded. Epistaxis and the family history taken together usually permit the detection of patients potentially affected by HHT. The patients with known genetic mutations or clinically suspected familial HHT are then subjected to complete clinical screening. Screening programs are aimed at pre-symptomatic detection of AVMs in the brain or lung and should be recommended for all HHT patients and their relatives at risk [13].

It is recommended that patients with HHT have a complete blood count and haematocrit, evaluation of faeces for occult blood, brain MRI with and without gadolinium to screen for cerebral AVMs, and contrast echocardiography to screen for pulmonary shunting. Chest CT is done to characterize pulmonary AVMs if shunting is found. Screening for liver involvement is not currently performed on a routine basis [2].

Treatment. In mild cases, no treatment is needed. Anaemia from recurrent nosebleeds or gastrointestinal bleeding can be controlled with oral or parenteral iron, and sometimes blood transfusions are necessary for some patients. Laser therapy or intense pulsed light source (IPLS) treatment of telangiectasia of the skin and mucosae can be considered, if lesions bleed or for cosmetic reasons.

Epistaxis is the most common emergency, as it can be massive. Photocoagulation laser or septal mucosal dermoplasty is recommended if administration of tranexamic acid at high doses or combined oestrogen–progesterone preparations does not have any effect. Pulmonary AVMs are safely treated using transcatheter embolization. Although most neurological symptoms in HHT are treated by transcatheter embolization, stereotactic resection or stereotactic radiosurgery are occasionally necessary. Liver involvement may be silent, as the majority of patients remain symptomless throughout their lifetime. Organ transplant remains the treatment of choice when hepatic fistulae cause complications or if very severe liver insufficiency develops. Gastrointestinal bleeding can be treated medically by iron therapy and combined oestrogen–progesterone preparations [2,13].

The disease does not usually shorten life. The mortality rate is less than 10%.

References

1 Guttmacher AE, Marchuk DA, White RI Jr. Hereditary haemorrhagic telangiectasia. *N Engl J Med* 1995; **333**: 918–24.

2 Bayrak-Toydemir P, Mao R, Lewin S, McDonald J. Hereditary hemorrhagic telangiectasia: an overview of diagnosis and management in the molecular era for clinicians. *Genet Med* 2004; **6**: 175–91.

3 Abdalla SA, Letarte M. Hereditary haemorrhagic telangiectasia: current views on genetics and mechanisms of disease. *J Med Genet* 2006; **43**: 97–110.

4 Fernàndez LA, Sanz-Rodriquez F, Blanco FJ *et al*. Hereditary hemorrhagic telangiectasia, a vascular dysplasia affecting the TGF-β signaling pathway. *Clin Med Res* 2006; **4**: 66–78.

5 Urness LD, Sorensen LK, Li DY. Arteriovenous malformations in mice lacking activin receptor-like kinase-1. *Nat Gen* 2000; **26**: 328–31.

6 Muggia FM. Osler's disease with an aortic arch aneurysm. *Arch Intern Med* 1964; **114**: 307–10.

7 Williams GA, Brick IB. Gastrointestinal bleeding in hereditary hemorrhagic telangiectasia. *Arch Intern Med* 1955; **95**: 41–51.

8 Harders H. The micromorphology and biomicroscopical diagnosis of Osler's disease. *Bibl Anat* 1965; **7**: 523–9.

9 Peery WH. Clinical spectrum of hereditary hemorrhagic telangiectasia (Osler–Weber–Rendu disease). *Am J Med* 1987; **82**: 989–97.

10 Purriel P, Muras O. Aneurisms arteriovenosus de pulmòn. *Thorax* 1957; **6**: 101–58.

11 Begbie ME, Wallace GMF, Shovlin CL. Hereditary haemorrhagic telangiectasia (Osler–Weber–Rendu syndrome): a view from the 21st century. *Postgrad J Med* 2003; **79**: 18–24.

12 Landau J, Nelken E, Davis E. Hereditary haemorrhagic telangiectasia with retinal and conjunctival lesions. *Lancet* 1956; **ii**: 230–1.

13 Sabbà C. A rare and misdiagnosed bleeding disorder: hereditary hemorrhagic telangiectasia. *J Thromb Haemost* 2005; **3**: 2201–10.

Ataxia–telangiectasia

Synonym
- Louis–Bar syndrome

Ataxia–telangiectasia [1] is a rare, autosomal recessive disease with pleiotropic involvement of the nervous and lymphoid systems, caused by homozygous mutations in the ataxia–telangiectasia mutated (*ATM*) gene (OMIM: 208900, gene map locus 11q22.3) [2]. Defective repair of DNA damaged by UV-light, gamma or X-rays is responsible for its development. Most mutations are frameshift and nonsense mutations that are predicted to cause truncation of the ataxia–telangiectasia protein; the less common mutations are missense, splicing and there is one in-frame deletion [3]. Mutation of ATM causes defective cell cycle checkpoint activation, a reduced capacity for repair of DNA double strand breaks and abnormal apoptosis, all of which contribute to the major features of ataxia–telangiectasia, including genomic instability, increased cancer risk and neurodegeneration [4].

The syndrome manifests with telangiectases, progressive cerebellar ataxia, combined immunodeficiency and marked susceptibility to cancer, particularly lymphoma and leukaemia [2]. A diminished level of, or an absence of, IgA is characteristic of the condition but there may be a reduction in other immunoglobulins. Defects of T and B cell function may also be present.

Affected children, who are usually small, are apparently normal until the second year of life when they are noticed to be clumsy, and the ataxia becomes progressive, so that by the age of 12 years they are unable to walk without assistance. Other signs of cerebellar disease, such as nystagmus and slurred speech, and mental deterioration may be observed. Neurological symptoms may not begin before the age of 6 years. Telangiectases may be present as early as the second year of life, but usually develop between the ages of 3 and 5 years. They first appear on the bulbar conjunctiva, and subsequently involve the ears, eyelids and the butterfly area



Fig. 47.16 Ataxia–telangiectasia. (Courtesy of Dr P.W.M. Copeman.)

of the cheeks and limbs (Fig. 47.16). Not all sites are affected in every case and bleeding is very uncommon. There may be some associated skin atrophy and dryness. The hair goes prematurely grey. Disturbances of pigmentation and eczematous lesions may also be present [5], as may granulomas [6]. Recurrent sinus and pulmonary infections are frequent, and may dominate the clinical picture; they are not infrequently fatal. Ovarian agenesis is not uncommon.

Ataxia–telangiectasia needs to be distinguished from other neurological disorders with similar features, including the ataxia–telangiectasia-like disorders ataxia oculomotor apraxia 1 and 2 [7].

The laboratory diagnosis currently relies on the measurement of serum alphafetoprotein (AFP), which is elevated in patients with ataxia–telangiectasia, and on demonstrating cellular sensitivity to ionizing radiation. Improved diagnostic testing by immunoblotting of nuclear lysates from lymphoid cell lines for ATM has been described [8]. After the age of 10 years, magnetic resonance imaging (MRI) shows cerebellar atrophy. These patients should have as few ionizing radiological investigations as possible.

Management is discussed in Chapter 15.

References

1 Perlman S, Becker-Catania S, Gatti RA. Ataxia-telangiectasia: diagnosis and treatment. *Semin Pediatr Neurol* 2003; **10**: 173–82.

2 McKinnon PJ. ATM and ataxia telangiectasia. *EMBO* 2004; **5**: 772–6.

3 Li A, Swift M. Mutations at the ataxia–telangiectasia locus and clinical phenotypes of A–T patients. *Am J Med Genet* 2000; **92**: 170–7.

4 Lavin MF, Kozlov S. ATM activation and DNA damage response. *Cell Cycle* 2007; **6**: 931–42.

5 Cohen LE, Tanner DJ, Schaeber HG *et al.* Common and uncommon cutaneous findings in patients with ataxia telangiectasia. *J Am Acad Dermatol* 1984; **10**: 431–8.

6 Joshi AK, Al Asiri RH, Haleem A *et al.* Cutaneous granuloma with ataxia telangiectasia—a case report and review of the literature. *Clin Exp Dermatol* 1993; **18**: 458–61.

7 Taylor AMR, Byrd PJ. Molecular pathology of ataxia telangiectasia. *J Clin Pathol* 2005; **58**: 1009–15.

8 Chun HH, Sun X, Nahas S *et al.* Improved diagnostic testing for ataxia telangiectasia by immunoblotting of nuclear lysates for ATM protein expression. *Mol Genet Metab* 2003; **80**: 437–43.

Generalized essential telangiectasia

Generalized essential telangiectasia [1–3] is a condition that is not as rare as the paucity of reported cases suggests. Many cases may be misdiagnosed as atypical HHT. The heading 'essential telangiectasia' probably includes more than one disease.

The condition occurs more frequently in females, and commonly starts in late childhood or early adult life. Generalized essential telangiectasia is characterized by a widespread cutaneous distribution with extensive sheets of telangiectases on the limbs or body (Fig. 47.17). The lesions may progress and become permanent when they are accentuated by dependency. There is an absence of coexisting epidermal or dermal changes [4]. The telangiectases are usually linear, but small angiomas may be present. Recurrent haemorrhages from the skin and mucous membranes or into the eye may produce incapacity, but in the majority of cases, the disease is only of cosmetic importance.

The diagnosis is made by excluding other causes of telangiectases. HHT is distinguished clinically by the distribution of the lesions, their presence in large and sometimes asymmetrical sheets, and by the absence of haemorrhages associated with generalized essential telangiectasia. High-energy, long-pulsed, frequency-doubled Nd:YAG laser treatment may be helpful but lesions tend to recur [5].

References

1 Bean WB, Rathe J. Universal angiomatosis. *Arch Int Med* 1963; **112**: 869–74.

2 Fox TC. A case of bilateral telangiectasis of the trunk, with a history of marked epistaxis in childhood and recent rectal haemorrhage. *Br J Dermatol* 1908; **20**: 145–62.

3 McGrae JD, Winkelmann RK. Generalised essential telangiectasia. *JAMA* 1963; **185**: 909–13.

4 Checketts SR, Burton PS, Bjorkman DJ, Kadunce DP. Generalized essential telangiectasia in the presence of gastrointestinal bleeding. *J Am Acad Dermatol* 1997; **37**: 321–5.

5 Gamblichler T, Avermaete A, Wilmert M *et al.* Generalised essential telangiectasia successfully treated with high-energy, long-pulse, frequency-doubled Nd:YAG laser. *Dermatol Surg* 2001; **27**: 355–7.

Unilateral naevoid telangiectasia syndrome

Unilateral naevoid telangiectasia can be congenital or acquired. There have been reports that suggest an increase in oestrogen and progesterone receptors in the skin. When this syndrome is acquired, it arises almost exclusively during periods of relatively increased oestrogen levels such as during pregnancy or puberty or in association with alcoholic cirrhosis or hepatitis C infection [1]. Polymorphic light eruption has been described confined to an area of acquired naevoid telangiectasia [2].

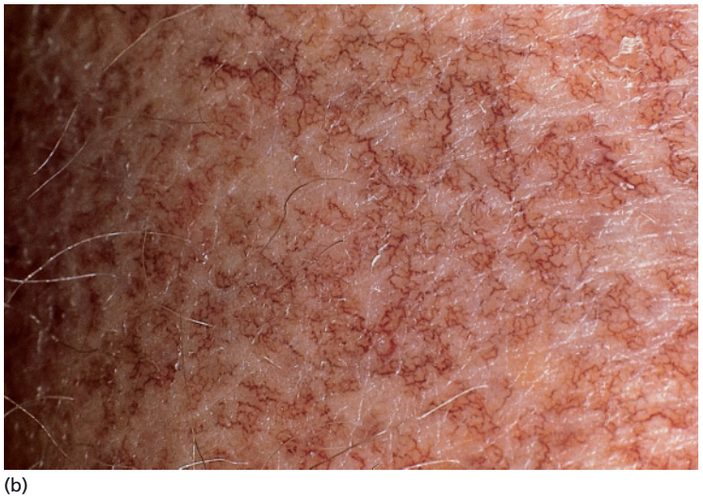
References

1 Hynes LR, Shenefelt PD. Unilateral nevoid telangiectasia: occurrence in two patients with hepatitis C. *J Am Acad Dermatol* 1997; **36**: 819–22.

2 Creamer D, Clement M, McGregor JM, Hawk JL. Polymorphic light eruption occurring solely on an area of naevoid telangiectasia. *Clin Exp Dermatol* 1999; **24**: 202–3.



(a)



(b)

Fig. 47.17 Essential telangiectasia. (a) Arborizing pattern. (b) Close-up appearance.

Hereditary benign telangiectasia

This disorder probably has a dominant inheritance [1] and is characterized by the presence of extensive telangiectases resembling generalized essential telangiectasia, starting in childhood and without other systemic lesions [2,3]. Less commonly, the telangiectases may be present at birth [4]. They tend to occur more in light-exposed skin. Histology and electron microscopy have been used to distinguish this condition from HHT [5]. Distinction from HHT is dependent on the lack of bleeding, although lesions do appear related to arteriovenous anastomoses as in HHT [6].

References

1 Zahorcsek Z, Schneider I. Hereditary benign telangiectasia. *Dermatology* 1994; **189**: 286–8.

2 Gold MH, Eramo L, Prendiville JS. Hereditary benign telangiectasia. *Pediatr Dermatol* 1989; **6**: 194–7.

3 Ryan TJ, Wells RS. Hereditary benign telangiectasia. *Trans St John's Hospital Dermatol Soc* 1971; **57**: 148–56.

4 Watanebe M, Tomita, Y, Tagami H. Hereditary benign telangiectasia—a congenital type. *Dermatologica* 1990; **181**: 152–3.

5 Tsianakas P, Teillac-Hamel D, Fraitag S *et al.* Etude ultrastructurale des telangiectases héréditaires bénignes. *Ann Dermatol* 1995; **122**: 517–21.

6 Onishi Y, Ohara K, Shikida Y, Satomi H. Hereditary benign telangiectasia: image analysis of hitherto unknown association with arteriovenous malformation. *Br J Dermatol* 2001; **145**: 641–5.

Naevus anaemicus with telangiectatic vessels [1]

Following dermabrasion of the epidermis over a naevus anaemicus, enlarged telangiectatic vessels were observed within the previously pale area. The area was transplanted with thin epidermal grafts but 1 year later the naevus anaemicus looked the same as before grafting. The explanation proposed for a naevus anaemicus and port-wine stain coexisting was vascular twin spotting, but the primary abnormality could be telangiectasia with surrounding skin blanched through a 'steal' effect of blood flow.

Reference

1 Juhlin L, Olsson MJ. Naevus anaemicus with telangiectatic vessels. *Eur J Dermatol* 2001; **11**: 518–20.

Solitary plaque-like telangiectatic glomangioma [1]

A painful, solitary telangiectatic plaque revealed ectatic vascular lumens in the upper dermis surrounded by glomus cells on biopsy.

Reference

1 Requena L, Galvan C, Sanchez Yus E. Solitary plaque-like telangiectatic glomangioma. *Br J Dermatol* 1998; **139**: 902–5.

Treatment of telangiectasia [1,2]

The central vessel of a spider naevus can be destroyed with electrolysis or pin-point 'hyfrecation' without anaesthetic. A significant proportion of such lesions recur, which may be related to the origin of the lesions; that is mini-arteriolovenular malformations with relative high pressure. Larger, isolated angiomas can be treated by complete excision. Treatment of extensive small lesions is unsatisfactory. Various types of lasers have been recommended [3]. (Long-)pulsed Nd:YAG laser at 1064 nm, intense pulsed light source (IPLS) and the 585 nm flashlamp pulsed dye laser (PDL) all have shown a beneficial effect on telangiectasia [4–6]. IPLS is preferred because of the excellent cosmetic results without scarring. Spider naevi are also well treated by IPLS [5]. Cryotherapy is disappointing. Injection with sclerosants is a good treatment for venous telangiectasia [1–3,7]. Cosmetic camouflage is possible if no intervention is desired.

References

1 Goldman MP, Bennett RG. Treatment of telangiectases: a review. *J Am Acad Dermatol* 1987; **17**: 167–82.

2 Bergen JJ, Goldman MP. *Varicose Veins and Telangiectases.* St Louis: Quality Medical Publising, 1993.

3 Gonzales E, Gange RW, Montaz KT. Treatment of telangiectases and other benign vascular lesions with the 577 nm pulsed dye laser. *J Am Acad Dermatol* 1992; **27**: 220–6.

4 Railan D, Parlatte EC, Uebelhoer NS, Rohrer TE. Laser treatment of vascular lesions. *Clin Dermatol* 2006; **24**: 8–15.
5 Landthaler M, Hohenleutner U. Laser therapy of vascular lesions. *Photodermatol Photoimmunol Photomed* 2006; **22**: 324–32.
6 Schroeter CA, Wilder D, Reineke T *et al*. Clincal significance of an Intense Pulsed Light Source on leg telangiectasias of up to 1 mm diameter. *Eur J Dermatol* 1997; **7**: 38–42.
7 Norris MJ, Carlin MC, Ratz JL. Treatment of essential telangiectasia: effect of increasing concentrations of polidocanol. *J Am Acad Dermatol* 1989; **20**: 683–9.

Malformations

It is convenient to consider the following separately:
1 Arteriovenous shunts
2 Arteriovenous aneurysms ('fistulae')
  i congenital
  ii acquired
3 Arteriovenous malformations.

Arteriovenous shunts

Arteriovenous shunts form an alternative peripheral system of blood flow and are an integral part of a compensating mechanism at times of capillary stress and injury. Although the pathophysiology of arteriovenous shunting has not been entirely elucidated, prolonged and diffuse patency of arteriovenous shunts may result in a syndrome of local venous dilatation and some degree of tissue ischaemia [1]. Their presence can be demonstrated by finding high oxygen saturation in venous blood and a reduced circulation time [2]. They are active in venous hypertension, varicose veins [3] and in leg ulcers [4]. They can be found in association with atherosclerosis [5] and perhaps with the hormonal changes of pregnancy [6]. Arteriovenous shunting in varicose veins appears to be a secondary rather than an initiating cause [7]. They are also active in psoriasis, in neoplasms [8] and in skin flaps. They may be responsible for the postural changes seen in angiodyskinesia, and are a feature of arborizing telangiectasia [8].

Arteriovenous fistulae

Arteriovenous fistulae [9] consist of direct connections between larger arteries and veins and are always pathological. Their various congenital and acquired forms have been given a large number of descriptive titles (cirsoid aneurysm, aneurysmal varix, pulsating angioma, etc.) but are best described here simply as congenital and acquired. Localized and pulsating, they may present as red nodules with overlying telangiectasis, like a giant spider naevus. While most common on acral sites, they also occur in the head and neck and on the trunk.

Congenital. These are discussed fully elsewhere (Chapter 18). They result from failure of embryological differentiation into an artery and vein [9]. The many clinical varieties that affect the skin and visceral organs have been grouped together under the term congenital dysplastic angiopathy [6]. When such congenital fistulae involve the limb vessels they often give rise to distinctive physical signs, described below.

Acquired. Apart from iatrogenic arteriovenous fistulae (usually for haemodialysis), acquired fistulae are almost always traumatic; they are often large, and may therefore cause significant cardiovascular effects. Early diagnosis is important. Treatment is entirely within the province of the interventional surgeon or radiologist, who should be consulted if there is suspicion of the existence of such a fistula. Treatment is by inserting a covered stent to close off the opening from 'within', or by open surgical closure.

Signs and effects of arteriovenous fistulae [10,11]

Traumatic fistulae following penetrating wounds (classically a shell splinter, or occasionally an operation) can occur anywhere in the body. They should be suspected whenever venous varicosity is unilateral or when signs of venous insufficiency develop unexpectedly after an injury. Increased warmth of a limb and the finding of a machinery-like constant murmur or a palpable thrill establish the diagnosis.

Congenital fistulae commonly affect the limbs and are often multiple. They should be suspected when unilateral varicosities present early in life without a genetic background. The limb is warmer and may be larger than the contralateral limb. Slowing of the pulse produced by inflation of a proximal tourniquet at the root (Branham's sign) is indicative of a large shunt. Duplex ultrasound or arteriography confirms the site of the fistula and indicates the size of the communications.

The effects of arteriovenous aneurysms depend on their size and the volume of blood flow through the fistula rather than its site. No cardiovascular changes may be evident when small, although there will inevitably be some permanent diversion of blood from the capillary bed. Larger fistulae cause dilatation in the superficial veins distal to the site, with a varying degree of impairment of the arterial circulation. The cardiac output increases, often considerably; the heart is dilated and the diastolic blood pressure is reduced, increasing the pulse pressure.

Embolization under angiographic control is the most effective therapy. An alternative is to mobilize the vessel and ligate all the branches (skeletonization). It is also possible to insert a covered stent to block off a localized fistula and this is the treatment of choice in a traumatic fistula in an inaccessible location. Amputation may occasionally be necessary if congestive cardiac failure is a problem.

Arteriovenous malformations

Definition. Arteriovenous malformations are fast-flow vascular lesions composed of malformed arterial and venous vessels connected directly to one another without an intervening capillary bed [12].

Pathogenesis. Arteriovenous malformations may arise during early fetal development because of a failure of regression of arteriovenous channels in the primitive plexus. Although most cases of arteriovenous malformations are sporadic, there are a few inherited syndromes whose molecular genetics have been elucidated. A mutation in the gene *RASA1* has been identified on chromosome 5q in families with capillary malformations associated with arteriovenous malformations [13]. Although the pathogenesis of sporadic lesions still has to be clarified, it may involve an aberration in the TGF-β signalling pathway [14].

Clinical features. In patients with arteriovenous malformations, 40–60% are visible at birth and a further 30% become apparent during childhood. The lesions are more common in the head and neck area than in other locations. Excessive warmth, unusual pain and bleeding episodes provide clues but can occur in other conditions. Auscultation of the lesion should detect a machinery murmur. Duplex scans are helpful screening tools. Arteriovenous malformations may progress through four different stages [15,16].

Stage I. These lesions are in the quiescent phase, are asymptomatic and usually last from birth until adolescence. During this stage, the arteriovenous malformation may either not be apparent, or may have the appearance of a port-wine stain or involuting haemangioma.

Stage II. This is the progressive stage and most commonly begins during adolescence. In this stage, which is characterized by expansion, the vascular lesions enlarge, and darken, deforming the integument and invading deep structures. On examination, the local temperature is increased, a pulse or thrill can be palpated, and a continuous murmur is heard on auscultation. Puberty, trauma and pregnancy induce progression to this stage.

Stage III. This mimics stage II; deep destruction occurs with spontaneous necrosis, chronic ulceration, pain and haemorrhage.

Stage IV. This is defined by cardiac decompensation. High-output cardiac failure may result from increased blood flow through large arteriovenous malformations.

Diagnosis. Arteriovenous malformations are diagnosed by the clinical findings and confirmed by duplex ultrasound, which also allows assessment of the flow characteristics [12]. Other vascular malformations, vascular neoplasms and other neoplasms should be excluded. Radiological evaluation is needed to confirm the diagnosis, and angiography is used to assess the extent of the lesions.

Treatment. The treatment of arteriovenous malformations can be difficult. Extreme pain, ulceration, bleeding and extensive enlargement of the malformations are indications for treatment. Multimodal treatment, including preoperative embolization and complete surgical resection, is usually necessary for the management of localized arteriovenous malformations. Complete surgical resection of the lesions may be difficult, because of their widespread nature and the risk of bleeding. Palliative embolization may be used to treat symptomatic lesions when combination treatment cannot be performed [17]. This can be repeated on many occasions.

References

1 Haimovici H. Abnormal arteriovenous shunts associated with chronic venous insufficiency. *J Cardiovasc Surg* 1976; **17**: 473–82.
2 Piulachs P, Vidal-Barraquer F. Pathogenic study of varicose veins. *Angiology* 1953; **4**: 59–100.
3 Haimovici H, Steinman C, Caplan LH. Role of arteriovenous anastomoses in vascular diseases of the lower extremity. *Ann Surg* 1966; **164**: 990–1002.
4 Myers MB, Cherry C. Pathophysiology and treatment of stasis ulcers of the leg. *Am Surg* 1971; **37**: 167–74.
5 Ryan TJ. Arteriovenous pathways. In: Jarrett A, ed. *The Physiology and Pathophysiology of the Skin*. London: Academic Press, 1973: 586–91.
6 Bean WB, ed. *Vascular Spiders and Related Lesions of the Skin*. Springfield: Thomas, 1958.
7 Haimovici H. Role of A-V shunting in varicose veins: therapeutic implications. *J Cardiovasc Surg* 1995; **36**: 109–15.
8 Urbach F. The blood supply of tumors. In: Morgagna W, Ellis R, eds. *Advances in Biology of Skin*, Vol. 2. Oxford: Pergamon, 1961: 123–49.
9 Fairbairn JF II, Bernatz PF. Arteriovenous fistulas. In: Fairbairn JF II, Juergens JL, Spittell JA Jr, eds. *Peripheral Vascular Diseases*, 4th edn. Philadelphia: Saunders, 1972: 303–26.
10 Elkin DC, Warren JV. Arteriovenous fistulas: their effects on the circulation. *JAMA* 1947; **134**: 1524–8.
11 Holman E, ed. *Abnormal Arterivenous Communications: Peripheral and Intracardiac, Acquired and Congenital*. Springfield: Thomas, 1968.
12 Garzon MC, Huang JT, Enjolras O, Frieden IJ. Vascular malformations: Part 1. *J Am Acad Dermatol* 2007; **56**: 353–62.
13 Eerola I, Boon LM, Mulliken JB *et al*. Capillary malformation-arteriovenous malformation, a new clinical and genetic disorder caused by RASA1 mutations. *Am J Hum Genet* 2003; **73**: 1240–9.
14 Vikkula M, Boon LM, Mulliken JB, Olsen BR. Molecular basis of vascular anomalies. *Trends Cardiovasc Med* 1998; **8**: 281–92.
15 Enjolras O, Logeart I, Gelbert F *et al*. Malformations artérioveineuses: étude de 200 cas. *Ann Dermatol Venereol* 1999; **127**: 17–22.
16 Kohout MP, Hansen M, Pribaz JJ, Mulliken JB. Arteriovenous malformations of the head and neck: natural history and management. *Plast Reconstr Surg* 1998; **102**: 643–54.
17 Komiyama M, Khosla VK, Yamamoto Y, Toyota N. Embolization in high-flow arteriovenous malformations of the face. *Ann Plast Surg* 1992; **28**: 575–83.

Acroangiodermatitis of Mali (pseudo-Kaposi's sarcoma)

A pigmented, purpuric eruption occurring around the malleolae and in the skin of the dorsal forefoot (particularly the base of the second toe) suggests acroangiodermatitis. Brown to plum-red papules coalescing into plaques resemble Kaposi's sarcoma clinically. The term acroangiodermatitis was introduced by Mali *et al*. in 1965 [1]. Histologically, there is marked benign capillary proliferation, plump endothelium and red cell extravasation. Rashkovsky *et al*. [2] described five possible causes:

1 Chronic venous hypertension
2 Arteriovenous malformations
3 Iatrogenic arteriovenous shunts in haemodialysis patients
4 Paralysed limbs
5 Amputation stumps.

Stewart–Bluefarb syndrome

In 1967, Stewart [3] and Bluefarb and Adams [4] independently described similar lesions on the legs of patients with arteriovenous malformations; in these cases the findings are usually unilateral and a palpable thrill may be noted. The condition can lead to ulceration of the toes and forefoot, in which case an arteriovenous shunt is the more likely underlying cause.

References

1 Mali JWH, Kuiper JP, Hamers AA. Acroangiodermatitis of the foot. *Arch Dermatol* 1965; **92**: 515–8.
2 Rashkovsky I, Gilead L, Schamroth J, Leibovici V. Acro-angiodermatitis: review of the literature and report of a case. *Acta Derm Venereol Suppl (Stockh)* 1995; **75**: 475–8.
3 Stewart WM. Fausse angiosarcomatose de Kaposi par fistules arteriovenulaire multiples. *Bull Soc Fr Dermatol Syphil* 1967; **74**: 664–5.

4 Bluefarb SM, Adams LA. Arteriovenous malformations with angiodermatitis. *Arch Dermatol* 1967; **96**: 176–81.

Venous malformations

Solitary venous malformations

Definition. Venous malformations are slow-flow, non-proliferating vascular birthmarks. They are composed of anomalous ectatic venous channels [1].

Pathogenesis. The histopathology of venous malformations reveals poorly circumscribed lesions composed of irregular, endothelial-lined vascular channels, with thin lumen walls that are deficient in smooth muscle cells [2]. This supports the theory that vascular malformations result from aberrant vascular development. Most cases of venous malformations are sporadic, but familial venous malformations can occur and are inherited in an autosomal dominant manner [3,4].

Clinical features. Venous malformations are present at birth, but typically become more prominent as the patient ages. The lesions usually present as soft, compressible blue masses that enlarge when the affected area is in a dependent position or with physical activity. The blue colour is pathognomonic and is caused by the presence of ectatic anomalous venous channels within the dermis. Venous malformations on the extremities are usually localized or segmental, although extensive deep involvement is common. Extensive, pure venous malformations of the extremities may extend into the skeletal muscles and joints and may be associated with either diminished girth or slight hypertrophy of the affected limb. Pain is a common complaint in extremity lesions and other complications include bleeding and phlebolith formation [1].

Diagnosis. The diagnosis of a venous malformation can be confirmed with MRI, which is also helpful in delineating the extent of the involvement of the lesion using the STIR sequence [5]. A coagulation profile, including D-dimer and fibrin, should be obtained to exclude an underlying coagulopathy. Localized intravascular coagulation within a venous malformation may result in abnormal coagulation profiles (consumptive coagulopathy) and may lead to episodes of bleeding and/or thrombosis.

Treatment. A multidisciplinary approach is essential for management of venous malformations. The general goals of therapy are to limit or avoid distortion of the facial features, limit bone deformation, preserve function and minimize painful swelling. Venous malformations may be treated with foam sclerotherapy [6] or surgery, or a combination of both. Large lesions, especially those extending into muscles and joints, are usually treated conservatively. Compression helps to decrease the discomfort caused by the venous malformations by reducing the volume, protecting the overlying skin, limiting swelling and improving localized intravascular coagulation.

Disorders associated with venous malformations

Klippel–Trenaunay syndrome

Definition. Klippel–Trenaunay syndrome (KTS) was first described in 1900, when Maurice Klippel and Paul Trenaunay reported two patients with a capillary malformation, varicosities and hypertrophy of soft tissue and bone in their lower limb [7]. In 1907, Frederick Parkes-Weber independently reported several cases similar to those described by Klippel and Trenaunay, though his cases were caused by multiple congenital arteriovenous malformations [7]. KTS is characterized by a capillary malformation (port-wine stain) of the skin associated with a soft tissue and bone overgrowth hypertrophy of the affected limb, in combination with varicose veins with or without deep venous and lymphatic abnormalities [8].

Pathogenesis. There are many theories on the aetiology of KTS and the genetic component is being defined. The disease may be best explained by either a paradominant disorder with autosomal lethal genes surviving only in the mosaic state, or as an autosomal dominant condition with incomplete penetrance (OMIM: gene map locus 8q22.3) [9,10]. KTS may be caused by a somatic mutation in a factor critical to vasculogenesis and angiogenesis during embryonic development [9].

Clinical features. The condition is characterized by the triad of: capillary malformations (port-wine stain/naevus flammeus), venous malformations (abnormal varicosities, persistent embryonal veins, and sometimes agenesis of deep veins or avalvulosis), with disproportionate limb growth of soft tissue and/or bone. It usually presents soon after birth. The naevus usually appears first; 95% of KTS patients exhibit a capillary malformation (port-wine stain), usually involving only the affected limb but sometimes extending beyond [11]. It usually has a metameric distribution. Limb hypertrophy develops later in childhood. Venous abnormalities may not be evident until adolescence. Lymphatic abnormalities frequently coexist, and affected children may present with a swollen limb. The surface veins are large and extensive with an abnormal distribution. A characteristic feature is a large ectatic 'primitive' vein in the lateral thigh. Varicosities may extend into the pelvis as well as down the leg. Superficial and deep-vein thrombosis is not uncommon, even in children. The bones may overgrow, resulting in increased leg length. Soft-tissue hypertrophy often occurs but may be difficult to distinguish from swelling caused by oedema or engorged veins or lymphatics. Pain is a significant and debilitating problem in KTS patients and has various causes [12].

Skin changes occur because of venous hypertension and abnormalities of lymphatic drainage. Other abnormalities associated with the syndrome include lymphangiectasia (cutaneous vesicles that leak lymph).

The abnormal veins (varicosity) lead to a significant increase in venous volume with age. As a consequence, the flow diminishes and the risk of deep and/or superficial thrombosis rises. There is also some evidence for a coexisting coagulopathy. These factors explain the high incidence of thrombosis in KTS patients. An acquired post-thrombotic syndrome aggravates the severity of KTS.

Diagnosis. The diagnosis is largely clinical. Physical examination should include auscultation and palpation of the involved area to assess for the presence of an arteriovenous malformation to rule out Parkes-Weber syndrome [8]. Duplex ultrasound scanning is the study of choice to evaluate for superficial and deep venous anomalies, and can also be used in differentiating vascular tumours from vascular malformations and arteriovenous fistulae [8,9]. MRI scans are effective for visualizing the extent of tissue overgrowth of lesions and infiltration of deeper tissues. X-rays may show increased thickness or abnormal density of the affected soft tissue as well as phleboliths [9]. Venograms may be required to delineate the venous abnormality and to exclude deep vein agenesis.

The differential diagnosis consists of other diseases associated with limb enlargement combined with a vascular lesion, for example Proteus syndrome, Parkes-Weber syndrome, Servelle–Martorell syndrome and hemihypertrophy with multiple lipomas. Other disorders that should be excluded are infantile haemangioma, kaposiform haemangioendothelioma and tufted angioma [8].

Treatment. Most patients with KTS can be managed conservatively with medical elastic compression stockings (MECS) to control venous hypertension, although patients with atresia of the deep venous system may complain of pain with compression [8]. Anticoagulants are administered to adults with thrombosis and anticoagulant prophylaxis is recommended after surgery, but long-term prophylaxis is not normally necessary, unless the patient is exposed to long periods of immobilization, for example long-term bed rest or air travel. Oral contraceptives should be avoided in women with KTS [9]. In treating varicose veins, (echo-guided) sclerotherapy is the treatment of first choice. Venous stripping, ligation or sclerosis can result in favourable outcomes in carefully evaluated and selected patients with symptomatic superficial varicose veins. If necessary, cutaneous lesions can be treated with vascular lasers or IPLS. Large limb-length discrepancies have been treated by osteotomy or epiphyseodesis as well as by epiphyseal stapling (which can be removed if further growth is required) [9,13].

Parkes-Weber syndrome

This syndrome was first described by Sir Fredrick Parkes-Weber in 1907. He reported a case involving arteriovenous fistula, together with varicosities and hypertrophy of the affected extremity. This syndrome is caused by congenital multiple arteriovenous fistulae, but can manifest with varicose veins and limb overgrowth as in KTS. There is no associated vascular naevus. Limb overgrowth gets progressively worse in Parkes-Weber syndrome, whereas in KTS leg-length disparity rarely increases after the age of 10 years [14]. Parkes-Weber syndrome more commonly affects the lower extremities, and lymphatic anomalies and lymphoedema can be present [8]. An obvious pulsatile swelling may be visible with discoloration of the overlying skin and large veins radiating from it. Duplex ultrasound demonstrates high blood flow and abnormal enlargement of the arteries [14]. During childhood, duplex ultrasound often shows enlarged arteries and patchy areas of hypervascularization; arteriovenous fistulae usually develop around puberty or after trauma. This disease may be complicated by cardiac enlargement and high-output congestive cardiac failure [8].

Conservative management consists of medical elastic compression stockings to prevent venous hypertension. Congestive cardiac failure requires active treatment. Repeated embolization under angiographic control is the most effective therapy. An alternative is to mobilize the vessel and ligate all the branches (skeletonization). Very occasionally, amputation may be necessary.

Genuine diffuse phlebectasia

Synonym
- Bockenheimer's syndrome

Phlebectasia is the term used to describe enlarged and irregular, superficial and deep veins. Histology of the phlebectasia shows a decrease in elastin in the wall of the ectatic veins. Thrombosis and calcification are often present [15]. Phlebangiomatosis involves cavernous angiomas, which manifest with cutaneous angiomas that extend into deeper layers including bone. Both conditions resemble KTS and Parkes-Weber syndrome but without an associated vascular naevus, bone overgrowth and arteriovenous fistula.

Servelle–Martorell syndrome [16]

This syndrome describes the association of a venous, and rarely arterial, malformation with skeletal abnormalities. Unlike KTS and Parkes-Weber syndrome, the intraosseous involvement leads to hypotrophy and therefore shortening of the limb bones. Deformation of the medullary cavity and thinning of the bone cortex can result in joint destruction. Otherwise the syndrome is similar, with ectasia and aneurysmal dilatation of superficial veins resulting in gross deformity of the extremity. The deep veins may be abnormally located or be hypoplastic with absent valves. Servelle–Martorell syndrome is considered to be an inverse form of KTS [17].

References

1 Garzon MC, Huang JT, Enjolras O, Frieden IJ. Vascular malformations: Part I. *J Am Ac Dermatol* 2007; **56**: 353–62.

2 Mulliken JB, Glowacki J. Hemangiomas and vascular malformations in infants and children: a classification based on endothelial characteristics. *Plast Reconstr Surg* 1982; **69**: 412–20.

3 Gallione CJ, Pasyk KA, Boon LM *et al*. A gene for familial venous malformations maps to chromosome 9p in a second large kindred. *Med Genet* 1995; **32**: 197–9.

4 Calvert JT, Riney TJ, Kontos CD *et al*. Allelic and locus heterogeneity in inherited venous malformations. *Hum Mol Genet* 1999; **8**: 1279–89.

5 Dubois J, Garel L. Imaging and therapeutic approach of hemangiomas and vascular malformations in the pediatric age group. *Pediatr Radiol* 1999; **29**: 879–93.

6 Pascarella L, Bergan JJ, Yamada C, Mekenas L. Venous angiomata: treatment with sclerosant foam. *Ann Vasc Surg* 2005; **19**: 457–64.

7 Parkes-Weber F. Angioma formation in connection with hypertrophy of limbs and hemihypertrophy. *Br J Dermatol* 1907; **19**: 231–5.

8 Garzon MC, Huang JT, Enjolras O, Frieden IJ. Vascular malformations: Part II. *J Am Acad Dermatol* 2007; **56**: 541–64.

9 Kihiczak GG, Meine JG, Schwartz RA, Janniger CK. Klippel–Trenaunay syndrome: a multisystem disorder possibly resulting from a pathogenic gene for vascular and tissue overgrowth. *Int J Dermatol* 2006; **45**: 883–90.

10 Tian X-L, Kadaba R, You S-A *et al.* Identification of an angiogenic factor that when mutated causes susceptibility to Klippel–Trenaunay syndrome. *Nature* 2004; **427**: 640–5.
11 Gloviczki P, Stanson AW, Stickler AW *et al.* Klippel–Trenaunay syndrome: the risks and benefits of vascular interventions. *Surgery* 1991; **110**: 469–79.
12 Lee A, Driscoll D, Gloviczki P *et al.* Evaluation and management of pain in patients with Klippel–Trenaunay syndrome: a review. *Pediatrics* 2005; **115**: 744–9.
13 Samuel M, Spitz L. Klippel–Trenaunay syndrome: clinical features, complications and management in children. *Br J Surg* 1995; **82**: 757–61.
14 Browse NL, Burnand KG, Irvine AT, Wilson NM, eds. *Diseases of the Veins*, 2nd edn. London: Arnold, 1999.
15 Van Geest AJ, Veraart JC, de Haan M, Neumann HA. Bockenheimer's syndrome. *J Eur Acad Dermatol Venereol* 1999; **12**: 165–8.
16 Weiss T, Madler U, Oberwittler H *et al.* Peripheral vascular malformation (Servelle–Martorell). *Circulation* 2000; **101**: e82–3.
17 Danarti R, Konig A, Bittar M, Happle R. Inverse Klippel–Trenaunay syndrome: review of cases showing deficient growth. *Dermatology* 2007; **214**: 130–2.

Capillary malformations

Capillary malformations are among the most common vascular malformations of the skin. They include telangiectases (p. 47.12) and port-wine stains (p. 47.23).

Venous disorders

Anatomy [1–7]

Most veins contain semilunar valves; these are usually in pairs, but some veins only contain one valve leaflet and sometimes three (tricuspid) valve leaflets are present. These valves are lined by endothelium and are found especially in the smaller veins and at the junction of these veins with larger branches. They prevent the reflux of blood and are particularly important in the leg, where their integrity, and that of the calf muscle pump (the venous heart), counters the gravitational hydrostatic pressure.

There are three systems: the deep veins, the superficial veins, and the perforating veins (or perforators). The perforating veins are numerous and inconstant, and connect the other two systems. During muscular activity, blood is directed from the superficial to the deep system, up from the foot to the thigh and thence to the abdomen, before venous blood returns towards the heart. Bicuspid valves are found in all three systems. The smallest veins to contain valves lie at the dermal subcutaneous junctions [4] and the valves are extremely variable. Valves may become damaged, thickened or degenerate with age [5]. Thrombosis also causes valvular destruction and a re-canalized post-thrombotic vein is valveless, anatomically distorted and functionally inefficient [5]. The most important perforating veins are considered to be on the medial side of the calf. Incompetence of the valves in these veins has been thought to be important in the causation of venous ulceration [5].

The superficial venous system of the leg begins from the veins on the dorsum of the foot, which join the greater saphenous vein (GSV) (originally called the long saphenous vein) and the short saphenous vein (SSV). They form a dorsal arch, which connects the territory of the SSV with that of the GSV. On the plantar side of the foot the same venous network joins to a plantar venous arch that also joins both saphenous veins [6,7].

References
1 Browse NL, Burnand KC, Irvine AT, Wilson NM, eds. *Diseases of the Veins*, 2nd edn. London: Arnold, 1999.
2 Tibbs D. *Varicose Veins and Related Disorders*. Oxford: Butterworth-Heinemann, 1992.
3 Gillot C. *Anatomical Atlas of the Lower Limb Superficial Venous Network*. St Gallen: Ganzoni & Cie AG, 2004.
4 Braverman IM, Keh-Yen A. Ultrastructure of the human dermal microcirculation. IV. Valve-containing collecting veins at the dermal-subcutaneous junction. *J Invest Dermatol* 1983; **81**: 438–42.
5 Chant ADB, Jones HO, Townsend JCF *et al*. Radiological demonstration of the relationship between calf varices and saphenofemoral incompetence. *Clin Radiol* 1972; **23**: 519–23.
6 Caggiati A, Bergan JJ, Glovicki P *et al*. Nomenclature of the veins of the lower limb: extensions, refinements and clinical application. *J Vasc Surg* 2005; **41**: 19–24.
7 Weiss MA, Weiss RA, Feied CF, eds. *Vein Diagnosis and Treatment: A Comprehensive Approach*. New York: McGraw-Hill Professional Publishing, 2001.

Physiology/pathophysiology

The venous macrocirculation [1,2]

Veins act as the capacitance vessels of the circulation. The 'venous return' is the blood returning to the heart via the great veins. Venous return from the lower limbs is achieved by the pumping action of the foot and calf muscles associated with competent valves that prevent backflow [1].

The venous system of the legs contains a volume of 300 to 350 mL in a healthy standing subject. The venous wall contracts in response to filling, and its function is called 'venous tone'. This acts as counter-pressure and automatically changes to attempt to maintain venous pressure at a constant level. The superficial veins drain through the communicating (perforating) veins into the deep system, and only 10% of the venous blood flow from the lower limb passes through the saphenofemoral junction (SFJ).

The deep veins are compressed by each muscle contraction shifting the blood column towards the heart against the pressure of gravity. The venous valves prevent backflow during muscle relaxation. This mechanism is the 'calf muscle pump'. Other muscle groups such as those of the foot also compress veins and aid venous return, but the calf muscle pump is the most important muscle pump of the leg.

References
1 Browse NL, Burnand KG, Lea Thomas M. Physiology and functional anatomy. In: Browse NL, Burnand KG, Lea Thomas M, eds. *Diseases of the Veins. Pathology, Diagnosis and Treatment*. London: Edward Arnold, 1988; 53–69.
2 Summer DS, Zierler RE. Vascular physiology: Essential hemodynamic principles. In: Rutherford RB, ed. *Vascular Surgery*. Philadelphia: Elsevier Saunders, 2005.

Venous reflux

Venous reflux is thought to be the major cause of venous disorders [1]. Reflux is the presence of retrograde flow in a vein in response to a stimulus such as a calf squeeze. It occurs during standing when the valves are incompetent [2]. It can occur in the superficial, deep and perforating veins of the lower extremity.

Venous pressure falls during calf muscle pump activity in healthy subjects and is known as normal lowering of ambulatory venous pressure [3,4]. An elevated and sustained ambulatory venous pressure (venous hypertension) is indicative of chronic

venous insufficiency (CVI). This may be caused by valvular incompetence or venous outflow obstruction [5]. Venous outflow obstruction occurs in some patients after a deep-vein thrombosis (DVT), a situation known as the post-thrombotic leg. Obstruction is more serious than reflux and more difficult to treat. In this situation, when the leg muscles contract the venous pressure increases, rather than the usual lowering of venous pressure that occurs during ambulation when the vein is not obstructed. Such heightened pressure is transmitted distally as far as the capillary system of the skin, causing capillary hypertension, and eventually leading to destruction of the nutritive capillaries [6].

References

1 Reček Č. The venous reflux. *Angiology* 2004; **55**: 541–8.
2 Sarin S, Scurr JH, Coleridge Smith PD. Assessment of stripping the long saphenous vein in the treatment of primary varicose veins. *Br J Surg* 1992; **79**: 889–93.
3 Reček Č. Conception of the venous hemodynamics in the lower extremity. *Angiology* 2006; **57**: 556–63.
4 Summer DS, Zierler RE. Vascular physiology: essential hemodynamic principles. In: Rutherford RB, ed. *Vascular Surgery*. Philadelphia: Elsevier Saunders, 2005: 75–123.
5 Mendes RR, Marston WA. Physiologic assessment of the venous system. In: Rutherford RB, ed. *Vascular Surgery*. Philadelphia: Elsevier Saunders, 2005.
6 Jünger M, Hahn M, Klyscz T, Sterus A. Role of microangiopathy in the development of venous leg ulcers. *Prog Appl Microcirc* 1999; **23**: 180–3.

The venous microcirculation

Disturbances of the venous microcirculation account for almost all the clinical signs of chronic venous disease. The raised ambulatory venous pressure is transmitted directly to the venular side of the capillary bed. The capillaries in the skin of the lower leg are the most affected. Five theories have been developed to explain the mechanism for the microcirculatory disturbances in venous disease.

1 Capillary stasis. Homans postulated that 'stasis' of venous blood in patients with post-thrombotic syndrome gave rise to the development of anoxia which he thought caused venous ulcers [1]. Initially, when the oxygen content of blood samples taken from varicose veins was measured, lower values were found than in blood taken from healthy individuals [2]. One year later, however, Blalock produced completely different results. He reported that the oxygen content of the femoral venous blood of patients with varicose veins was higher than in healthy persons [3]. He concluded that the blood flow through the leg of patients with a venous ulcer was higher than that of healthy persons. Blalock's findings were subsequently confirmed by several investigators [4]. Only one study carried out in 1971 produced conflicting results [5].

When a contrast agent was injected into the femoral artery of patients with varicose veins it entered their veins faster than the veins of healthy controls [6,7]. The flow velocity may, however, be markedly decreased in certain locations in the venous system, for example in certain capillary beds. This decreased flow might be responsible for focal hypoxia [8], despite the overall increase in venous flow through the whole system.

It was shown that the transcutaneous oxygen tension ($tcPO_2$) was significantly lower in patients with CVI [9–11]. Low $tcPO_2$ values in patients with CVI cannot be fully explained at present. Morphological changes develop in the microcirculation in response to prolonged CVI and these may also play a role in the lower $tcPO_2$ value.

Microangiopathy is a prominent sign of CVI [12] and was first reported by Bollinger *et al*., who combined intravital capillaroscopy and fluorescence angiography with videodensitometry [13]. Bollinger's group measured the transcapillary and interstitial diffusion of a colorant (Na-fluorescein) into the skin of healthy volunteers. These results were then compared to results from patients with CVI. Reduced diffusion was present in the skin areas of patients with CVI that had a reduced capillary density. The density of fluorescein does not, of course, equate to oxygen diffusion. The capillary microscopy showed stagnant blood flow in some capillaries, leading to intracapillary coagulation. It was felt that capillary thrombosis might account for the disappearance of capillaries. The $tcPO_2$ value and cutaneous capillary density appear to be related [14]. The $tcPO_2$ value in capillary plexi with a low density approaches 0 mmHg at a distance of 100 µm or more between the capillaries.

References

1 Homans J. The etiology and treatment of varicose ulcer of the leg. *Surg Gynecol Obstet* 1917; **24**: 300–11.
2 De Takats G, Quint H, Tillotsen BI, Crittenden PJ. The impairment of the circulation in the varicose extremity. *Arch Surg* 1929; **18**: 671–86.
3 Blalock A. Oxygen content of blood in patients with varicose veins. *Arch Surg* 1929; **19**: 898–905.
4 Fagrell B. Local microcirculation in chronic venous incompetence and leg ulcers. *Vasc Surg* 1979; **13**: 217–25.
5 McEwan AJ, McArdle CS. Effect of hydroxyethylrutosides on blood oxygen levels and venous insufficiency symptoms in varicose veins. *BMJ* 1971; **2**: 138–41.
6 Piulachs P, Vidal-Barraquer F. Pathogenic study of varicose veins. *Angiology* 1953; **4**: 39.
7 Haimovici H. Abnormal arteriovenous shunts associated with chronic venous insufficiency. *J Cardiovasc Surg* 1976; **17**: 473–82.
8 Michiels C, Arnould T, Thibaut-Vercruyssen R *et al.* Perfused human saphenous veins for the study of the origin of varicose veins: role of the endothelium and of hypoxia. *Int Angiol* 1997; **16**: 134–41.
9 Neumann HAM, van Leeuwen M, van den Broek MJTB, Berretty PJM. Transcutaneous oxygen tension in chronic venous insufficiency syndrome. *VASA* 1984; **13**: 213–9.
10 Clyne CAC, Ramsden WH, Chant ADB, Webster JH. Oxygen tension of the skin of the gaiter area of limbs with venous disease. *Br J Surg* 1985; **72**: 644–7.
11 Stacey MC, Burnand KG, Layer GT, Pattison M. Transcutaneous oxygen tensions in assessing the treatment of venous ulcers. *Br J Surg* 1990; **97**: 1050–4.
12 Leu AJ, Yanar A, Pfister G *et al*. Mikroangiopathie bei chronischer venösen Insuffizienz. *Dtsch Med Wschr* 1991; **116**: 447–53.
13 Bollinger A, Jäger K, Geser A *et al*. Transcapillary and interstitial diffusion of NA-fluorescein in chronic venous insufficiency with atrophy. *Int J Microcirc Clin Exp* 1982; **1**: 5–17.
14 Huch A, Franzeck UK, Huch R, Bollinger A. A transparent transcutaneous electrode for simultaneous studies of skin capillary morphology, flow dynamics and oxygenation. *Int J Microcirc Clin Exp* 1983; **2**: 103–8.

2 Fibrin cuff-theory. Browse and Burnand postulated that venous ulceration could be the result of deposition of pericapillary fibrin [1]. This theory was later named the 'fibrin cuff-theory' [2]. The leakage of large molecules such as fibrinogen through the pericapillary space was caused by the high venous pressure associated with CVI. Fibrinogen was thought to polymerize to insoluble fibrin in the interstitium to form a pericapillary fibrin 'cuff'. This cuff might then function as a oxygen diffusion barrier. A signifi-

cant increase in the collagen IV layer has also been found in and around the capillaries [3]. The authors suggested that fibrin could function as a matrix for collagen formation. The role of fibrin as a diffusion barrier was never conclusively proven and theoretical objections were put forward to its ability to reduce oxygen transfer [4]. In porphyria cutanea tarda (PCT) patients, where pericapillary fibrin deposits (cuffs) are present, normal tcPO_2 values exist [5]. The fibrin deposition appears to be an indicator of microcirculatory disturbance rather than the cause of a lower tcPO_2 value.

References

1 Burnand KG, Whimster I, Naidoo A, Browse NL. Pericapillary fibrin in the ulcer-bearing skin of the leg: the cause of lipodermatosclerosis and venous ulceration. *BJM* 1982; **285**: 1071–7.
2 Browse NL, Burnand KG. The cause of venous ulceration. *Lancet* 1982; **2**: 243–5.
3 Neumann HAM, van den Broek MJTB. Increased collagen IV layer in the basal membrane area of the capillaries in severe chronic venous insufficiency. *VASA* 1991; **20**: 26–9.
4 Michel CC. Oxygen diffusion in edematous tissue and through pericapillary cuffs. *Phlebology* 1990; **5**: 223–30.
5 Neumann HAM, van den Broek MJTB, Boersma IH, Veraart JCJM. Transcutaneous oxygen tension in patients with and without pericapillary fibrin cuffs in chronic venous insufficiency, porphyria cutanea tarda and non-venous leg ulcers. *VASA* 1996; **25**: 127–33.

3 White cell trapping. In patients with lipodermatosclerosis, white blood cells disappear from the venous blood when the leg is in a dependent position [1]. Coleridge Smith *et al.* formulated a new theory for the aetiology of venous ulcers on the basis of these observations [2]. They suggested that the leukocytes may become trapped in the capillaries, obstructing flow and thereby leading to ischaemic ulceration. Adhesion molecules are over expressed and may play an important role by causing continuous leukocyte migration to the dermis [3,4].

References

1 Thomas PRS, Nash GB, Dormandy JA. White cell accumulation in the dependent legs of patients with venous hypertension. A possible mechanism for trophic changes in the skin. *BJM* 1988; **296**: 1693–5.
2 Coleridge Smith PD, Thomas P, Scurr JH, Dormandy JA. Causes of venous ulceration: a new hypothesis. *BJM* 1988; **296**: 1726–7.
3 Veraart JCJM, Verhaegh MEJM, Neumann HAM *et al.* Adhesion molecule expression in venous leg ulcers. *VASA* 1993; **22**: 213–8.
4 Peschen M, Lahaye T, Hennig B *et al.* Expression of the adhesion of molecules ICAM-1, VCAM-1, LFA-1 and VLA-4 in the skin is modulated in progressing stages of chronic venous insufficiency with and without atrophie blanche. In: Maessen-Visch MB. *Atrophie Blanche* (Thesis). Nijmegen: Drukkerij Hendrix Volharding, 1999: 77–87.

4 Trapping growth factors. Falanga and Eaglestein hypothesized that the pericapillary fibrin cuffs, which included α2-macroglobulin, interfere with growth factor transport, making them biologically unavailable in patients with severe CVI. They felt that this might also account for delayed healing of ulcers [1]. The lack of availability of growth factors is controversial. Clinical research using topical epidermal growth factor (EGF), TGF-β and fibroblast growth factor (FGF) has failed to improve the healing of venous ulcers. The addition of a single growth factor has therefore not been able to restore the process of disturbed wound healing in patients with chronic venous ulcers.

Reference

1 Falanga V, Eaglestein WH. The 'trap' hypothesis of venous ulceration. *Lancet* 1993; **341**: 1006–8.

5 Multicausal model: the Maastricht model. A dynamic conceptual model has been proposed by researchers at the University Hospital of Maastricht in the Netherlands [1,2]. They suggest that a raised pressure in the capillaries acts mainly on the venular side of the dermal microcirculation. The raised microcirculatory pressure is a consequence of elevated ambulatory venous pressure. The continuously elevated pressure leads to alterations in the structure of the capillary wall, in which the interendothelial space broadens and the collagen IV layer disintegrates. The capillary wall becomes thicker [3], and the structural changes interfere with capillary exchange [4]. Collagen IV disintegrates and the interendothelial space enlarges, in turn increasing the capillary filtration fraction.

In the first instance water diffusion is affected, causing oedema [5]; later, larger molecules escape into the tissues. Accumulation of these molecules leads to halo formation [6–8]. The fibrin/fibrinogen cuffs demonstrated by immunofluorescence studies are a sensitive sign of decompensating capillaries in the skin. The fibrin cuffs do not act simply as a diffusion barrier for oxygen; the presence of fibrin also serves as a stimulus for collagen formation. Collagen IV is laid down around the capillaries and collagens I and III in the dermis. α2-macroglobulin is also laid down and this binds molecules such as TGF-β, leading to decreased biological availability of various growth factors.

Widened capillaries have a lower flow velocity. White cells marginate and adhere to the capillary walls, sometimes blocking the circulation and leading to the formation of microthrombi. The escape of plasma proteins into the tissues enhances the inflammatory response, while the escape of leukocytes into the tissues releases proteolytic enzymes causing free radical damage. This is seen clinically as the changes of lipodermatosclerosis (LDS) [9].

There is evidence of continuous collagen degradation resulting from the increased action of the proteolytically active matrix metalloproteinase-1 (MMP-1) and matrix metalloproteinase-2 (MMP-2). Evidence of increased proteolytic activity has been found in patients with LDS who have decreased fibrinolytic activity [10]. It is attractive to assume that elevated proteolytic MMP-2 expression is a consequence of plasminogen activation in LDS which might cause an elevated matrix turnover [9]. This would be responsible for structural changes in the dermis and subcutaneous tissue which could then easily ulcerate.

Clotting and fibrinolytic disturbances play a role in the development of atrophie blanche [11]. The capillaries are obliterated in the affected areas leading to local hypoxia. Minimal trauma then leads to ulceration.

References

1 Neumann HAM, Tazelaar DJ. Compression therapy. In: Bergan JJ, Goldman MP, eds. *Varicose Veins and Telangiectasias, Diagnosis and Treatment*. St. Louis: Quality Medical Publishing Inc., 1993: 103–22.
2 Neumann HAM. Measurement of microcirculation. In: Altmeyer P. *et al.*, eds. *Wound Healing and Skin Physiology*. Berlin/Heidelberg: Springer Verlag, 1995: 115–26.
3 Neumann HAM, van den Broek MJTB. Increased collagen IV layer in the basal membrane area of the capillaries in severe chronic venous insuficiency. *VASA* 1991; **20**: 20–9.

4 Leu HJ. The prognostic significance of cutaneous and microvascular changes in venous leg ulcers. *Vasc Dis* 1965; **2**: 77–80.
5 Roztocil K, Prerovsky I, Olivia I. The effect of hydroxy-ethylrutosides on capillary filtration rate in the lower limb of man. *Eur J Clin Pharmacol* 1997; **11**: 435–8.
6 Neumann HAM, van den Broek MJTB, Boersma IH, Veraart JCJM. Transcutaneous oxygen tension in patients with and without pericapillary fibrin cuffs in chronic venous insufficiency, porphyria cutanea tarda and non-venous leg ulcers. *VASA* 1996; **25**: 127–33.
7 Fagrell B. Microcirculatory disturbances—the final cause for leg ulcers? *VASA* 1982; **11**: 101–3.
8 Burnand KG, Whimster I, Naidoo A, Browse NL. Pericapillary fibrin in the ulcer-bearing skin of the leg: the cause of lipodermatosclerosis and venous ulceration. *BJM* 1982; **285**: 1071–7.
9 Herouy Y, May AE, Pornschlegel G *et al*. Lipodermatosclerosis is characterized by elevated expression and activation of matrix metalloproteinases: implications for venous ulcer formation. *J Invest Dermatol* 1998; **111**: 822–7.
10 Jarrett PE, Burnand KG, Morland M, Browse NL. Fibrinolysis and fat necrosis in the lower leg. *Br J Surg* 1976; **63**: 157.
11 Maessen-Visch MB, Koedam MI, Hamulyák K, Neumann HAM. Atrophie blanche, a review. *Int J Dermatol* 1999; **38**: 161–72.

Venous thrombosis

Deep-vein thrombosis

Epidemiology. Deep-vein thrombosis (DVT) has an annual incidence of 0.2% in the urban population [1]. The disease is rare in children under 15 years old, but its frequency increases with age, with an incidence of 1.8 per 1000 person-years between 65 and 69 years and 3.1 per 1000 person-years between 85 and 89 years of age [2]. First episodes of DVT account for two-thirds of cases. The prevalence of DVT is highest in Caucasian adults and is low in Asian populations. The risk of a DVT seems to be slightly higher in men than in women, and the risk of recurrent venous thromboembolism is about 60% greater in men compared to women [3].

Aetiology and pathogenesis. In 1856, Virchow postulated that the main causes of thrombus formation were damage to the vessel wall, alterations in blood flow and hypercoagulability [2]. This is called 'Virchow's triad' and is still valid today. Risk factors for DVT include cancer, immobility, surgery and thrombophlebitis.

The maintenance of the fluidity and circulation of the blood and its ability to thrombose are essential for the maintenance of life and are governed by extremely complex homeostatic mechanisms. Thrombosis is a protective mechanism which prevents loss of blood and seals off damaged blood vessels. Fibrinolysis counteracts or stabilizes the thrombosis. Alterations in blood coagulability and platelet numbers, with associated changes in blood flow and endothelial damage, are the precursors of deep-vein thrombosis. The loss of normal vascular endothelial function is probably of primary importance [4].

Factor V Leiden, a pro-coagulant mutation, is present in 8% of patients with thrombosis. Anticardiolipin antibodies are also now recognized as an important cause of thrombosis [5,6]. A number of other hereditary and acquired conditions that predispose to thrombosis (thrombophilia) have also been recognized. These include protein C and S deficiency, antithrombin deficiency, the prothrombin 20210A gene mutation and activated protein C resistance (which is usually associated with the factor V Leiden genetic abnormality). Screening for thrombophilia, and for anticardiolipin antibodies, should be performed in patients presenting with a sporadic or recurrent thrombosis [7]. Surgical operations and pregnancy remain important triggers of thrombosis. Prolonged immobility (e.g. long-haul flights) and the contraceptive pill are also well-documented risk factors (Table 47.4).

Table 47.4 Risk factors for deep-vein thrombosis [2,8].

Advancing age
Obesity
Previous venous thromboembolism
Family history of venous thromboembolism
Surgery, especially procedures lasting more than 30 min.
Trauma, especially of the spine or legs
Malignant tumours
Acute medical illnesses, e.g. acute myocardial infarction, heart failure, respiratory failure, infection
Inflammatory bowel disease
Antiphospholipid syndrome
Dyslipoproteinaemia
Nephrotic syndrome
Paroxysmal nocturnal haemoglobinuria
Myeloproliferative diseases
Behçet's syndrome
Varicose veins
Superficial vein thrombosis
Congenital venous malformation
Pulmonary embolism
May–Thurner syndrome
Long-distance travel
Prolonged bed rest or sitting
Immobilization
Hospitalization
Limb paralysis
Pregnancy/puerperium
Oral contraceptives
Hormone replacement therapy
Other drugs
Chemotherapy
Tamoxifen
Thalidomide
Antipsychotics
Central venous catheter
Vena cava filter
Intravenous drug use

Clinical features. The onset of a deep-vein thrombosis is often 'silent' and may remain so. It commonly occurs about 7 to 10 days after a surgical operation, childbirth or the onset of an acute infection. It is often associated with a rise in the platelet count and an increase in young 'sticky' platelets. Between one-third and two-thirds of patients complain of some swelling and pain in the leg, usually in the calf [4]. An iliac thrombosis should be suspected if the whole leg is swollen and dusky. There may be a pink or

Table 47.5 Clinical score list for predicting pretest probability for having a proximal deep vein thrombosis [11].

Clinical feature:
Active cancer treatment ongoing or within previous 6 months or palliative
Paralysis, paresis, or recent plaster immobilization of the lower leg(s)
Recent immobilization for more than 3 days or major surgery within last 4 weeks
Localized tenderness/pain along the distribution of the deep venous system
Entire leg swollen
Calf swelling by more than 2 cm when compared with the asymptomatic leg (measured 10 cm below tibial tuberosity)
Pitting oedema greater in the symptomatic leg
Collateral superficial veins (non-varicose)

Each factor scores 1; maximum score 8; see text for grading of risk according to score.

cyanotic hue to the leg and evidence of superficial venous dilatation. The temperature of the leg may be raised, and pitting oedema of one ankle is an important physical sign.

Diagnosis. Pain and tenderness in the calf and popliteal fossa may occur in other conditions such as a ruptured Baker's cyst, a haematoma, or muscle tears or pulls. Infection (e.g. cellulitis) and lipodermatosclerosis should also be differentiated from a DVT. These can usually be distinguished clinically.

Assessment should include a clinical score and a D-dimer test, as a negative D-dimer test, in combination with a low-risk clinical score, avoids the need for compression ultrasound (CUS) in every patient with a painful or swollen leg [9]. The clinical score, based on medical history and physical examination, divides patients into low, moderate and high-risk categories for having a DVT (Table 47.5). A score of 0 (asymptomatic) means a low probability, a score of 1 or 2 a moderate probability, and a score of 3 or more a high probability, for DVT.

D-Dimer is a degradation product of a cross-linked fibrin clot. A negative test is useful for ruling out a DVT because the test has high sensitivity, but its specificity is low; it can be raised in various other conditions, such as post-surgery, inflammation of various causes, pregnancy and cancer. A moderate or high clinical probability, or a low clinical probability in combination with a high D-dimer, should therefore be followed by CUS of the legs (Fig. 47.18). The sensitivity of CUS is 97% for proximal and 73% for distal vein thrombosis compared with phlebography. CUS has many advantages over phlebography. It is non-invasive, simple, easy to repeat, relatively inexpensive and free of complications.

There are, however, two main disadvantages of CUS. Calf vein thrombosis can be missed, especially when the examination is limited to the popliteal and femoral veins, and small isolated thrombi in the iliac and superficial femoral veins or within the adductor canal can be difficult to detect and therefore easily overlooked [10].

CUS should be repeated after 1 week if the D-dimer is high and the CUS was negative but there is still a moderate or high probability of DVT on clinical grounds. The newer investigations of CT venography and MRI imaging appear to have advantages in certain circumstances, but at present their cost and availability limit their application.

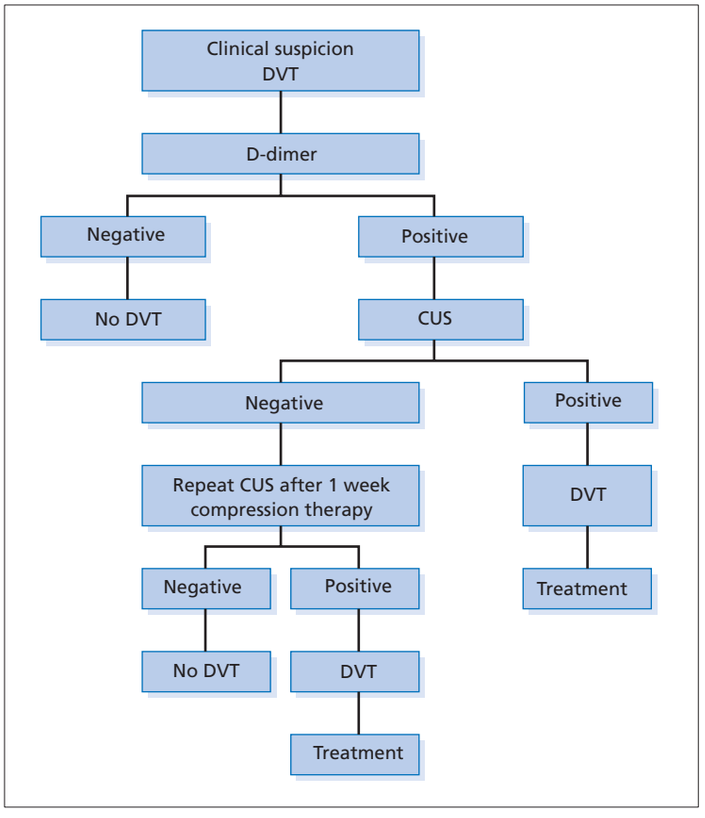


Fig. 47.18 Procedure to safely exclude deep vein thrombosis.

Treatment. Treatment includes the immediate therapy, awareness and prevention of complications and prevention of further episodes. Pulmonary embolism, post-thrombotic syndrome (PTS) and recurrent thrombosis are the main complications of DVT. About 10–30% of patients with DVT develop PTS. DVT has a recurrence rate of about 20% after 5 years, but the rate varies depending on the presence of risk factors [12]. Preventive measures should therefore be undertaken in every patient who has an increased risk of developing venous thromboembolism. Low-molecular-weight heparins (LMWH), intermittent pneumatic compression and medical elastic compression stockings (MECS) should be used as prophylaxis [13].

Active treatment is as follows. Initially a LMWH is given subcutaneously (150 to 200 IU/kg once daily). It can be given as an outpatient without the need for monitoring. It only needs to be given once daily and the risk of heparin-induced thrombocytopenia (Chapter 49) is negligible with LMWH compared with standard heparin preparations [2]. Vitamin K antagonists such as warfarin should be added to the LMWH at 24 or 48 hours unless contraindicated. Monitoring of anticoagulation is done by the prothrombin time, expressed in terms of the international normalized ratio (INR). A ratio between 2.0 and 3.0 should be achieved for adequate anticoagulation with a low risk of bleeding. LMWH can be discontinued when the correct INR has been attained [2]. Idiopathic venous thromboembolism is generally treated for 6 months, but anticoagulation may be for life if the condition recurs or a high risk exists [14].

LMWH and oral anticoagulants should be combined with compression stockings. Once oedema has reduced, class II MECS are prescribed to be worn for life. Class III MECS can be prescribed if the oedema remains a problem [15]. MECS significantly reduce the development of post-thrombotic syndrome.

References

1 Nordstrøm M, Lindblad B, Bergqvist D, Kjellstrom T. A prospective study of the incidence of deep-vein thrombosis within a defined urban population. *J Intern Med* 1992; **232**: 155–60.
2 Kyrle PA. Deep vein thrombosis. *Lancet* 2005; **365**: 1163–74.
3 McRae S, Tran H, Schulman S *et al*. Effect of patient's sex on risk of recurrent venous thromboembolism: a meta-analysis. *Lancet* 2006; **368**: 371–8.
4 Browse NL, Burnand KC, Irvine AT, Wilson NM, eds. *Disease of the Veins*, 2nd edn. London: Arnold, 1999.
5 Boey ML, Colaco CB, Chavari AE *et al*. Thrombosis in systemic lupus erythematosus: striking association with the presence of circulating antcoagulants. *BMJ* 1983; **287**: 289.
6 Mueh JR, Herbst KD, Rapaport SI. Thrombosis in patients with the lupus coagulant. *Ann Intern Med* 1980; **92**: 156–9.
7 Dahlback B. Physiological anticoagulation. *J Clin Invest* 1994; **94**: 923.
8 Cushman M. Epidemiology and risk factors for venous thrombosis. *Semin Hematol* 2007; **44**: 62–9.
9 Stein PD, Hull RD, Patel KC *et al*. D-Dimer for the exclusion of acute venous thromboembolism and pulmonary embolism. *Ann Intern Med* 2004; **140**: 589–602.
10 Michiels JJ, Gadisseur A, van der Planken M *et al*. A critical appraisal of non-invasive diagnosis and exclusion of deep vein thrombosis and pulmonary embolism in outpatients with suspected deep vein thrombosis or pulmonary embolism: how many tests do we need? *Int Angiol* 2005; **24**: 27–39.
11 Michiels JJ, Gadisseur A, van der Planken M *et al.* Screening for deep vein thrombosis and pulmonary embolism in outpatients with suspected DVT or PE by sequential use of clinical score: a sensitive quantitative D-dimer test and non-invasive diagnostic tools. *Semin Vasc Med* 2005; **5**: 351–64.
12 Segal JB, Streiff MB, Hofmann LV *et al*. Management of venous thromboembolism: a systematic review for a practice guideline. *Ann Intern Med* 2007; **146**: 211–22.
13 Pini M, Spyropoulos AC. Prevention of venous thromboemolism. *Semin Thromb Hemost* 2006; **32**: 755–66.
14 Blann AD, Lip GYH. Venous thromboembolism. *BMJ* 2006; **332**: 215–9.
15 Wentel TD, Neumann HAM. Management of the postthrombotic syndrome: the Rotterdam approach. *Semin Thromb Hemost* 2006; **32**: 814–21.

Superficial venous thrombosis

Synonym
- Superficial thrombophlebitis

Incidence. Most studies report a female preponderance (female proportion between 55 and 70%) and a mean age of onset of 60 years [1].

Aetiology and pathogenesis. Several studies have described an association between superficial venous thrombosis and venous thromboembolism. Superficial venous thrombosis located in the main trunk of the saphenous vein has the strongest association with venous thromboembolism [2,3].

Predisposing risk factors for superficial venous thrombosis are similar to those for deep-vein thrombosis [3]. Superficial venous thrombosis usually develops in the lower limbs. In 60–80% of cases the greater saphenous vein (GSV) system is involved, and in 10–20% the short saphenous (SSV) system [4]. The main cause of superficial venous thrombosis of the lower limbs is varicose veins, which are present in 70% of cases [5]. The main cause of superficial venous thrombosis in the upper limb is iatrogenic, for example intravenous catheters or infusion of drugs such as chemotherapy or heroin. Mondor's disease may also be a form of superficial venous thrombosis.

Clinical features. The patient usually presents with pain and a reddened, warm, tender cord extending along the vein. The overlying skin may show signs of erythema and oedema. The differential diagnosis includes cellulitis, panniculitis, erythema nodosum, insect bites and lymphangitis [5].

Diagnosis. Duplex ultrasound can be used to confirm the diagnosis [1,4,5], and to exclude a coexisting deep-vein thrombosis. Patients should be further investigated if they have idiopathic or recurrent superficial venous thrombosis or if they have a superficial venous thrombosis without varicose veins [5].

Treatment. LMWH and non-steroidal anti-inflammatory drugs (NSAIDs) appear to be the best treatments for superficial venous thrombosis of the leg veins [3]. Sclerotherapy and stripping of any varicose veins should only be performed some months after the acute superficial venous thrombosis has settled. When a thrombus is found in or near the saphenofemoral junction or saphenopopliteal junction, especially if it extends as free-floating thrombus extending into the common femoral vein or popliteal veins, it should be treated by surgical removal, combined with ligation and stripping. The patient can receive a 3-month therapeutic course of LMWH [4]. The thrombus can be squeezed out of the vein through a needle puncture. This should be followed by application of compression bandages or stockings.

References

1 Marchiori A, Mosena L, Prandoni P. Superficial vein thrombosis: risk factors, diagnosis, and treatment. *Semin Thromb Hemost* 2006; **32**: 737–43.
2 Wichers IM, Di Nisio M, Büller HR, Middelkoop S. Treatment of superficial vein thrombosis to prevent deep vein thrombosis and pulmonary embolism: a systematic review. *Haematologica* 2005; **90**: 672–7.
3 Di Nisio M, Wichers IM, Middelkoop S. Treatment for superficial thrombophlebitis of the leg. *Cochrane Database Syst Rev* 2007; **18**: CD004982.
4 Leon L, Giannoukas AD, Dodd D *et al*. Clinical significance of superficial vein thrombosis. *Eur J Vasc Endovasc Surg* 2005; **29**: 10–7.
5 Decousus H, Epinat M, Guillot K *et al*. Superficial venous thrombosis: risk factors, diagnosis, and treatment. *Curr Opin Pulm Med* 2003; **9**: 393–7.

Thrombophlebitis migrans [1–4]

Recurrent migratory thrombophlebitis is an uncommon condition that affects large and small veins throughout the body. The superficial veins of the lower extremities, abdominal wall, flank, arms or elsewhere undergo segmental thrombosis, causing crops of tender, linear or oval subcutaneous lumps or streaks. This is a pattern seen in Behçet's disease (Chapter 50) [5,6]. Fazeli *et al.* [7] also found an association between thrombophlebitis migrans and Buerger's disease in 65.4% of 86 patients, though others have put this percentage lower.

Much of the literature regarding migratory thrombophlebitis is concerned with the link with underlying malignancy, termed

Trousseau's syndrome (Chapter 62). This association was carefully reviewed by Sack *et al.* [8] and by Samlaska *et al.* [9], who suggested that migratory thrombophlebitis is a chronic disorder of disseminated intravascular coagulation.

Clues to a primary hypercoagulable state include a family history, recurrent thrombosis, an unusual anatomical site, an early age of onset and resistance to conventional anticoagulation. Secondary hypercoagulable states are a consequence of malignancy, infection, pregnancy, the contraceptive pill, nephritis or liver disease [3,4,9].

A follow-up study of 4399 patients who had venography for suspected DVT recorded that 150 of 1383 with proven DVT and 182 of 2412 without thrombosis developed cancer; although the overall difference was not significant, there were significantly more cancers in the DVT group (66 cancers) than in the non-DVT group (37 cancers) in the first 6 months after the venography [10]. A more severe type of thrombophlebitis is associated with malignant disease. In 1500 cases of thrombophlebitis, 31 of 77 occurring in association with malignancy were of a migratory type [2]. Carcinomas of the lung and pancreas were the most common sites for the primary tumours, although carcinomas of the breast, colon and stomach were also reported.

Treatment. Malignancy must be carefully excluded in patients with migratory thrombophlebitis. It may be difficult to locate, especially if the patient has a pancreatic carcinoma. Computed tomography (CT) scanning, ultrasound, MRI and even positron emission tomographic (PET) scans of the abdomen may be necessary. Treatment is generally conservative, and patients should be treated with adequate anticoagulation. Lowering triglycerides may be advisable and exercise is good prophylaxis. Medical elastic compression stockings or bandages may alleviate symptoms. Stripping of the saphenous system has been advocated [1]. Earlier observations on the good effects of oral fibrinolytic agents [11,12] in Behçet's disease have not been substantiated by some later case reports [13].

References

1 Cruikshrank AH. Venous thrombosis in the internal organs associated with thrombosis of the leg veins. *J Pathol Bacteriol* 1956; **71**: 383–6.
2 Lieberman JS, Borrero J, Urdanetta E *et al.* Thromboembolism associated with neoplasm: review of 77 cases. *Circulation* 1960; **22**: 780.
3 Samlaska CP, James WD. Superficial thrombophlebitis. I. Primary hypercoagulable states. *J Am Acad Dermatol* 1990; **22**: 974–89.
4 Samlaska CP, James WD. Superficial thrombophlebitis. II. Secondary hypercoagulable states. *J Am Acad Dermatol* 1990; **23**: 1–18.
5 Bollinger A, Leu HJ. Thrombophlebitis saltans. *Deutsch Med Wochenschr* 1974; **99**: 1433–6.
6 Forman L. Thrombophlebitis and arteritis in the pathology of Behçet's syndrome. *Hautarzt* 1960; **11**: 363–6.
7 Fazeli B, Modaghegh H, Ravrai H, Kazemzadeh G. Thrombophlebitis migrans as a footprint of Buerger's disease: a prospective-descriptive study in north-east of Iran. *Clin Rheumatol* 2008; **27**: 55–7
8 Sack C, Levin J, Bell WR. Trousseau's syndrome and other manifestations of chronic disseminated coagulopathy in patients with neoplasms: clinical, pathophysiologic and therapeutic features. *Medicine* 1977; **56**: 1–37.
9 Samlaska CP, Jones WD, Simel DL. Superficial migratory thrombophlebitis and factor XII deficiency. *J Am Acad Dermatol* 1990; **22**: 939–43.
10 Nordstrom M, Lindblad B, Anderson H *et al.* Deep vein thrombosis and occult malignancy: epidemiological study. *BMJ* 1994; **308**: 891–4.
11 Chajek T, Fainaru M. Behçet's disease with decreased fibrinolysis and superior vena cava occlusion. *BMJ* 1973; **1**: 782.
12 Cunliffe WJ, Roberts BE, Dodman B. Behçet's disease syndrome and oral fibrinolytic therapy. *BMJ* 1973; **2**: 486–7.
13 Graham-Brown RAC, Sarkany I. Failure of colchicine and fibrinolytic therapy in Behçet's disease. *Clin Exp Dermatol* 1980; **5**: 87–92.

Mondor's disease

The classic Mondor's disease is located in the chest wall and affects veins that include the lateral thoracic vein, the superior epigastric vein and the thoracoepigastric vein [1,2]. Similar cases have been reported in the antecubital fossa, inguinal area, axilla, penis [3], abdomen and lower limbs. The aetiology of the disorder is unknown.

Pathogenesis. A venous thrombosis which may partially or totally occlude the vein is followed by re-canalization. Fibromuscular hyperplasia develops in the vessel wall with infiltration and fibrosis of the surrounding subcutaneous cellular tissue [2]. Trauma or friction causes a sclerosing phlebitis of the affected vein and aggravates the course of the disease.

Clinical features. Women account for 75% of those affected, generally between the second and fifth decade of life [2]. Sudden, localized chest pain is the main presenting symptom, and is accompanied by the appearance of grooved, hardened 'cords' that are visible and palpable on the chest wall where they resemble wires. These cord-like structures attach to the overlying skin before retracting, with the formation of characteristic linear grooves. Patients may have fever and significant regional inflammation in the acute phase. As the disorder is self-limiting [2], relief of pain follows with complete resolution of the symptoms in about 2 to 8 weeks. Mondor's disease has been associated with primary or metastatic mammary carcinoma in up to 12% of cases [4].

Treatment. Mondor's disease is a self-limiting disease which nearly always resolves spontaneously. Anti-inflammatory agents (e.g. ibuprofen) and 75 mg salicylic acetic acid per day are recommended, plus local application of heat and physiotherapy involving gentle stretching of the cords where possible. Neither anticoagulation nor antibiotics are indicated. Resection of thrombotic vessels can be considered to treat the patient and confirm the diagnosis when symptoms are intractable.

References

1 Mondor H. Tronculite sous-cutanee subaigue de la paroi thoracigue antero-laterale. *Mem Acad Chir* 1939; **65**: 1271–8.
2 De Godoy JM, Godoy MF, Batigália F, Braile DM. The association of Mondor's disease with protein S deficiency: case report and review of literature. *J Thromb Thrombolysis* 2002; **93**: 187–9.
3 Al-Mwalad M, Loertzer H, Wicht A, Fornara P. Subcutaneous penile vein thrombosis (penile Mondor's disease): pathogenesis, diagnosis, and therapy. *Urology* 2006; **67**: 586–8.
4 Catania S, Zurrida S, Veronesi P *et al*. Mondor's disease and breast cancer. *Cancer* 1992; **69**: 2267–70.

Axillary web syndrome

Axillary web syndrome (AWS) follows axillary lymphadenectomy for breast cancer and manifests with palpable cords which

'bowstring' across the axilla, creating a web of skin [1,2]. The cords are painful and restrict shoulder movement. They can extend into the ipsilateral arm, even forearm, and can create a linear groove somewhat like those seen in Mondor's disease. Indeed, it is probably a site-specific variant of this condition, and probably has a traumatic cause; it has also been reported after skin surgery [3]. The cause is unclear but the condition usually resolves over 6 months.

References

1 Moskovitz AH, Anderson BO, Yeung RS *et al*. Axillary web syndrome after axillary dissection. *Am J Surg* 2001; **181**: 434–9.
2 Leidenius M, Leppänen E, Krogerus L, von Smitten K. Motion restriction and axillary web syndrome after sentinal node biopsy and axillary clearance in breast cancer. *Am J Surg* 2003; **185**: 127–30.
3 Craythorne EE, Roberts J, Higgins EM, Macfarlane CS. 'Axillary web syndrome' or 'cording': an unusual postsurgical complication and localized variant of Mondor's disease. *Br J Dermatol* 2008; **159** (Suppl. 1): 109.

Deep-vein obstruction [1]

The most common cause of chronic deep-vein obstruction is a previous DVT. Non-thrombotic causes include malignant disease or other pelvic masses compressing the iliac veins. Retroperitoneal fibrosis can obstruct the iliac veins and the inferior vena cava. The iliac compression syndrome (Cockett's or May–Thurner syndrome) is present when the left common iliac vein is compressed by the right common iliac artery crossing its course to the inferior vena cava [2]. Flow alterations do not usually cause problems unless thrombosis takes place. Large tumours (e.g. soft-tissue sarcomas) or aneurysms in the thigh may compress the deep femoral vein. In the popliteal fossa an aneurysm or a Baker's cyst can compress the popliteal vein. Primary tumours of the vein wall (leiomyosarcoma) are rare but are found more often in the lower limb. Ligation of deep veins may be unavoidable when removing a malignancy or when repairing vein damage from accidental trauma.

References

1 Browse NL, Burnand KG, Irvine NM. *Disease of the Veins*, 2nd edn. London: Arnold, 1999: 409–25.
2 Cockett FB, Thomas ML. The iliac compression syndrome. *Br J Surg* 1965; **52**: 816–21.

Chronic venous insufficiency

Classification

Several classifications have been used to describe the severity of chronic venous insufficiency (CVI), of which the classifications by Widmer *et al.* (Table 47.6) [1] and the CEAP classification (Clinical status, Etiology, Anatomy, Pathophysiology) (Table 47.7) [2,3] are the best known. The CEAP classification is a well-recognized classification for varicose veins, despite its deficiencies. In 2000, the Venous Clinical Severity Score (VCSS) was developed, which provides a slightly more detailed description of the factors contributing to CVI (Table 47.8) [4].

References

1 Widmer LK, Plechl SC, Leu HJ *et al*. Venenkrankungen bei 1800 Berufstätigen. Basel Studie II. *Schweiz Med Wochensch* 1967; **97**: 107–10.
2 Porter JM, Moneta GL. Reporting standard in venous disease: an update. International Consensus Committee on Chronic Venous Disease. *J Vasc Surg* 1995; **21**: 635–45.
3 Eklof B, Rutherford RB, Bergan J *et al*. Revision of the CEAP classification for chronic venous disorders: consensus statement. *J Vasc Surg* 2004; **40**: 1248–52.
4 Rutherford RB, Padberg FT Jr, Comerota AJ *et al*. Venous severity scoring: an adjunct to venous outcome assessment. *J Vasc Surg* 2000; **31**: 1307–12.

Chronic venous insufficiency/reflux

Chronic venous insufficiency may be classified anatomically into three categories (Fig. 47.19).

Superficial vein insufficiency. This is actually indicated by the presence of visible, tortuous, truncal varicose veins. It arises from

Table 47.6 The Widmer classification of chronic venous insufficiency [1].

Classification	Symptom
I	Corona phlebectatica paraplantaris, mild oedema
II	Hyperpigmentation, lipodermatosclerosis (LDS), atrophie blanche, oedema, eczema
III	Healed or active ulcer

Table 47.7 The CEAP (Clinical status, Etiology, Anatomy, Pathophysiology) classification [2,3].

C Clinical status	E Etiology	A Anatomy	P Pathophysiology
C0 no visible disorder			
C1 telangiectases or reticular veins	Ec congenital	As superficial	Pr reflux
C2 varicose veins	Ep primary	Ap perforating	Po obstruction
C3 oedema	Es secondary (post-thrombotic)	Ad deep	Pr,o combination
C4a pigmentation, oedema	En no known venous etiology	An no known venous location	Pn no known venous pathophysiology
C4b lipo- et dermatosclerosis, white atrophy			
C5 healed ulcer			
C6 active, venous ulcer			
S symptomatic			
A asymptomatic			

Table 47.8 The VCSS (Venous Clinical Severity Score) classification of factors contributing to chronic venous insufficiency [4].

Attribute	Absent = 0	Mild = 1	Moderate = 2	Severe = 3
Pain	None	Occasional, not restricting activity or requiring analgesics	Daily, moderate activity limitation, occasional analgesics	Daily, severe limiting activities or requiring regular use of analgesics
Varicose veins	None	Few, scattered: branch varicose veins	Multiple: GSV varicose veins confined to calf or thigh	Extensive: thigh and calf or GSV and SSV distribution
Venous oedema	None	Evening ankle oedema only	Afternoon oedema, above ankle	Morning oedema above ankle and requiring activity change, elevation
Skin pigmentation	None or focal, low intensity (tan)	Diffuse, but limited in area and old (brown)	Diffuse over most of gaiter distribution (lower 1/3) or recent pigmentation (purple)	Wider distribution (above lower 1/3) and recent pigmentation
Inflammation	None	Mild cellulitis, limited to marginal area around ulcer	Moderate cellulitis, involves most of gaiter area (lower 1/3)	Entire lower third of leg or more
No. of active ulcers	0	1	>2	>2
Active ulceration, duration	None	<3 months	>3 months, <1 year	Not healed >1 year
Active ulcer, size	None	<2 cm diameter	2 to 6 cm diameter	>6 cm diameter
Compressive therapy	Not used or not compliant	Intermittent use of stockings	Wears stockings most days	Full compliance: stockings + elevation

GSV, greater saphenous vein; SSV, short saphenous vein.

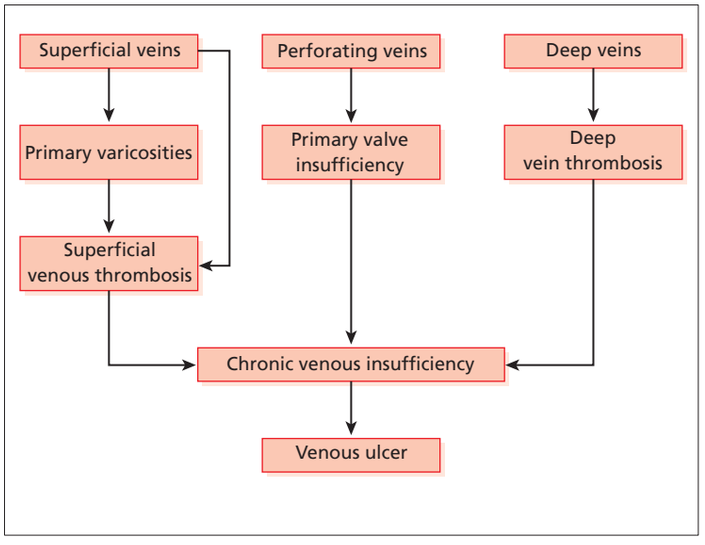


Fig. 47.19 Schematic presentation of the development of chronic venous insufficiency.

primary valve failure or when the superficial veins become distended, causing the valves to become secondarily incompetent.

Perforating vein insufficiency. This is a rare condition in isolation, when it is caused by primary valve insufficiency. Secondary perforating vein insufficiency often occurs in combination with deep vein insufficiency (post-thrombotic limb).

Deep vein insufficiency. Reflux is the most common type of abnormality, but in about 10% of cases a functional obstruction from thrombosis (non-recanalized thrombosis) will be present, in which case it is likely to be associated with the post-thrombotic syndrome. Avalvulosis is rare unless associated with a mutation of the *FOXC2* gene [1].

Reference

1 Mellor RH, Brice G, Stanton AW *et al*. Mutations in *FOXC2* are strongly associated with primary valve failure in veins of the lower limb. *Circulation* 2007; **115**: 1912–20.

Clinical signs of chronic venous insufficiency

Pitting oedema. Pitting oedema as a result of venous incompetence is worst at the end of the day and usually disappears at night. Patients may complain of a tight feeling in the oedematous leg and night cramps. The capillary filtration rate increases as a consequence of the increased ambulatory venous (and consequently capillary) pressure and overwhelms lymph drainage. This oedema always has a low protein content and pits easily, being mainly present around the ankle.

Corona phlebectatica paraplantaris (ankle flare). An ankle flare (the corona phlebectatica) is an early and important clinical sign of CVI and is a direct consequence of increased capillary pressure, which causes these vessels to expand.

Hyperpigmentation. Pigmentation in the 'gaiter skin' associated with CVI is invariably the result of haemosiderin accumulation after extravasation of erythrocytes (red cells). The pinpoint or patchy pigmentation may be minimal but may also extend over large indurated skin areas. In some cases pigmentation caused by melanin occurs as a secondary effect (post-inflammatory melanosis). Pigmentation begins modestly in the 'gaiter' area above the ankle and progresses to induration and inflammation, which indicates that lipodermatosclerosis has developed.

Pressure erythema. This is a direct result of elevated capillary pressure. Grouped, confluent, very small telangiectasiae develop. They are often found near incompetent perforating veins. Pressure erythema is often one of the first signs of evolving venous insufficiency.

Eczema. Several types can be recognized:

1 *Eczema as a result of venous disturbances* (synonyms: stasis dermatitis, hypostatic eczema, venous eczema, dermatitis venseuse). Usually this type of eczema starts round varicosities at the medial ankle, in the region of the Cockett perforating veins in the lower one-third of the leg. The eczema is relatively sharply demarcated and somewhat infiltrated with papules and vesicles, which may also extend beyond the main area of eczematous skin. Scaling and itching develops. Chronic lichenified eczema may develop with time. The aetiology is not completely clear. Homing of activated T-lymphocytes appears to be the most reasonable explanation.
2 *Allergic contact dermatitis*. This form of eczema is typically well demarcated but often with secondary involvement of adjacent or even distant non-contact sites. The most common sensitizing agents are locally applied drugs. Patch testing should be performed to exclude a contact allergic dermatitis. Patients with leg ulcers become more easily sensitized than healthy individuals [1,2], and therefore potential sensitizing agents should be avoided in these patients. Patients treated by MECS may develop an allergic contact dermatitis from the rubber constituents that provide elasticity, or from dyes that are used to give the stockings their colour.
3 *Asteatotic dermatitis* (synonym: eczema craquelé). Frequent washing may cause extreme dehydration of the skin. A morphologically similar eczema with a 'crazy paving' appearance occurs in some patients who develop rapid, lower leg oedema [3]. Patients who routinely wear MECS may develop an itching, dry and desquamating eczema. Application of a bland emollient at night will usually improve their symptoms.
4 *Impetiginization of eczematous dermatitis* (synonym: infected dermatitis). Wet eczema of the lower leg is often extensively colonized with bacteria, yeasts and fungi. Even after the infectious agent has been treated, an eczematous dermatitis may persist.
5 *Secondary spread ('id' eruption, 'autosensitization' eczema)*. Varicose dermatitis and allergic contact dermatitis may cause secondary spread onto adjacent and distant non-contact sites. Itching may develop at any site including the palms and soles.

Lipodermatosclerosis (LDS). This is a specific skin disorder that is pathognomonic of venous and lymphatic hypertension. It is a consequence of an increased matrix turnover caused by a chronic inflammatory reaction in response to escaped plasma constituents. LDS is known to be associated with an increased risk of leg ulcer development [4]. As a rule, the skin and subcutaneous tissues feel hard on palpation. At an early stage LDS may feel a little indurated and often has an inflamed, erythematous appearance. It is also quite often tender and painful. It is often confused with erysipelas, superficial venous thrombosis or even deep-vein thrombosis. In long-standing LDS the skin surface becomes pigmented (Fig. 47.20). It is often found just above the medial malleolus, at the level of the Cockett perforating veins, which are usually incompetent, as is the great saphenous vein. When the small saphenous vein is incompetent, the lipodermatosclerosis often affects the lateral side of the calf. The most characteristic histological findings are dermal and subcutaneous fibrosis, with fat degeneration.



Fig. 47.20 A venous ulcer on the medial side of the leg surrounded by pigmented sclerotic skin (lipodermatosclerosis).

White atrophy (atrophie blanche). This is the result of decreased capillary density caused by microthrombi and matrix degradation causing hypoxia. White atrophy is seen as an atrophic, ivory-white, depressed skin lesion often located on the lower legs (Fig. 47.21). The lesions have a diameter that varies from 0.5 to 15 cm and are almost always multiple. The lesions often contain many centrally enlarged capillaries that are visible as red dots. White atrophy is characterized histologically by an atrophic epidermis and a thickened and scleroderma-like dermis with proliferative, dilated capillaries. One or more capillaries are often occluded with fibrinoid material [5]. White atrophy does not cause clinical symptoms, but the associated ulcers are very painful. White atrophy does not respond well to treatment but antiplatelet agents and fibrinolytic-enhancing drugs have been tried with some success. White atrophy may also be seen in association with other disorders including lupus erythematosus, scleroderma, vasculitides, cryoglobulinaemia, polycythaemia and leukaemia. Summer ulceration is an idiopathic form of white atrophy in which ulcers develop on legs that show no evidence of chronic venous disease. The pathogenesis is largely unknown. Probably, the capillaries occlude as a consequence of microthrombosis during the 'summer' months.

Livedoid vasculopathy (livedo vasculitis). Livedoid vasculopathy is an occlusive thrombotic disease that affects superficial small blood vessels of the lower extremities (see also p. 47.55 and Chapter 49).



Fig. 47.21 Atrophie blanche: white scars with a central ischaemic ulcer and telangiectasia at the edge of the white areas.

Varicosities. Varicosities represent dilated and tortuous veins. In about the half of the patients CVI is the result of primary varicosities. In the 'post-thrombotic syndrome', venous hypertension often induces incompetence of the superficial venous system, and may lead to secondary varicosities [6].

Venous ulcer (ulcus cruris). This is an end stage of CVI.

Secondary (high output) lymphoedema. This may develop in patients with long-lasting CVI. Secondary lymphoedema develops when the previously healthy local lymphatic system fails in the face of an overwhelming filtration load, with eventual structural obliteration of lymphatic routes.

References

1 Malten LE, Kuiper JP, van der Staak WBJM. Contact allergic investigations in 100 patients with ulcus cruris. *Dermatologica* 1973; **147**: 241–5.
2 Perrenoud D, Ramelet AA. Chronic leg ulcers and eczema. *Curr Probl Dermatol* 1999; **27**: 165–9.
3 Bhushan M, Cox NH, Chalmers R. Eczema craquele due to oedema. *Br J Dermatol* 2001; **145**: 355–7.
4 Burnand KG, Whimster I, Naidoo A, Browse NL. Pericapillary fibrin in the ulcer-bearing skin of the leg: the cause of lipodermatosclerosis and venous ulceration. *BMJ* 1982; **285**: 1071–7.
5 Maessen-Visch MB, Koedam MI, Hamulyak K, Neumann HAM. Atrophie blanche, a review. *Int J Dermatol* 1999; **38**: 161–72.
6 Janssen MC, Haenen JH, Asten WN *et al.* Clinical and haemodynamic sequelae of deep venous thrombosis: retrospective evaluation after 7–13 years. *Clin Sci* 1997; **93**: 7–12.

Investigations of chronic venous insufficiency

Duplex ultrasound

Colour Doppler duplex ultrasound has become the first choice investigation for most venous problems. Duplex gives excellent information on venous anatomy and reflux. Reflux does not always indicate a functional defect, because muscle pump capacity can compensate for reflux. It is not easy to diagnose venous obstruction with Duplex scanning. Colour imaging allows the direction of flow to be clearly seen. Duplex ultrasound is very 'operator dependent' and requires considerable experience and a detailed knowledge of venous anatomy.

Technique. A 7.5-MHz high-frequency linear array transducer (probe) is usually satisfactory for venous examination. A probe of 7.5 to 13 MHz is appropriate to obtain good quality images of the superficial veins of the lower limbs. For very large or oedematous legs a curvilinear array transducer of 3.5 to 5 MHz may be useful [1].

Examination of the superficial veins should be performed with the patient standing erect as the detection of reflux and assessment of the vein diameter is inaccurate when the patient is supine. Both transverse and longitudinal views of the veins should be obtained. The investigation should be performed in a warm environment, to encourage venous dilatation.

When compression is applied distal to the probe antegrade (forward) flow is elicited. Reflux (backward or retrograde flow) may subsequently occur when the manual compression is abruptly released. This retrograde flow (reflux) is the result of gravity. A small amount of retrograde flow occurs in normal veins to produce valve closure. Venous reflux is considered to be normal when it lasts less than 0.5 s [2]. Reflux may be elicited by manual compression of varices, of the saphenous trunks or by squeezing the feet. It can also be stimulated by pneumatic calf cuff deflation [3], the Valsalva manoeuvre or by active foot dorsiflexion and relaxation.

Duplex ultrasound allows the communications between the deep and superficial veins to be directly assessed [4].

Indications. The most important indications for venous duplex are: (recurrent) varicose veins, signs of deep vein pathology, analyzing the veins of the popliteal fossa, analyzing the perforating veins, preoperative marking of varicose veins, assessing venous malformations, surveillance after treatment, duplex-guided sclerotherapy, evaluation before endovenous interventions, diagnosing (deep-vein) thrombosis and follow-up after treatment [2].

References

1 Coleridge-Smith P, Labropoulos N, Partsch H *et al*. Duplex ultrasound investigation of veins in chronic venous disease of the lower limbs—UIP consensus document. Part I. Basic principles. *Eur J Vasc Endovasc Surg* 2006; **31**: 83–92.
2 Lagatolla NR, Donald A, Lockhart S, Burnand K. Retrograde flow in the deep veins of subjects with normal venous function. *Br J Surg* 1997; **84**: 36–9.
3 van Bemmelen PS, Mattos MA, Hogdson KJ *et al.* Does air plethysmography correlate with duplex scanning in patients with chronic venous insufficiency? *J Vasc Surg* 1993; **18**: 796–807.
4 Ricci S, Georgiev M. Ultrasound anatomy of the superficial veins of the lower limb. *J Vasc Technol* 2002; **26**: 183–99.

Venous pressure measurement

At the beginning of the 20th century, Von Recklinghausen (1906) measured the venous pressure, followed by Roulson (1911) and Beecher (1936) [1]. The technique that is still used, and remains the gold standard for investigation of venous hypertension, was introduced in 1925 by Barber and Shatara [2], who demonstrated that venous pressure decreases during calf movement. The venous pressure drop during walking is less in patients with varicosities than in healthy individuals [3,4]. Arnoldi demonstrated that the pressure in the superficial venous system and the deep venous system was similar [4]. A correlation exists between calf muscle function and venous pressure [5].

Technique. A vein in the foot is cannulated and the patient stands on tiptoe 10 times. The venous pressure drops and the pressure drop is measured. This is defined as the ambulatory venous pressure. The patient stands still until the pressure returns; the time taken for the pressure to return is defined as the venous refill time.

Interpretation. The venous pressure is between 5 and 10 mmHg in the supine position. During standing the venous pressure is defined by the hydrostatic pressure being dependent on the subject's height. The distance between the right atrium and the puncture location determine the standing venous pressure. This value is between 80 and 100 mmHg in the average European. During the exercise, the pressure should drop to below 40 mmHg (or reach at least 50% of the standing venous pressure). Healthy individuals usually reach an ambulant venous pressure of around 20 mmHg, with a venous refill time of over 25 s.

References

1 Beecher HK, Field ME, Krogh A. Effect of walking on venous pressure at the ankle. *Skand Arch Physiol* 1936; **73**: 133–9.
2 Barber RF, Shatara FI. The varicose disease. *NY State J Med* 1925; **31**: 574–80.
3 Pollack AA, Wood EH. Venous pressure in the saphenous vein in ankle in men during exercise and changes in posture. *J Appl Physiol* 1949; **1**: 649–53.
4 Arnoldi CC. Venous pressure: the function of the venous pump in chronic venous insufficiency. *J Cardiovasc Surg (Torino)* 1961; **2**: 116–27.
5 Kuiper JP. Venous pressure determination (direct method). *Dermatologica* 1966; **132**: 206–17.

Plethysmography

Plethysmography records volume changes in the limb. It was first described by Brodie and Russel in 1905 [1].

Photoplethysmography. Photoplethysmography (PPG) is the most commonly used non-invasive technique. Hertzman in 1938 [2] was the first to describe a photoelectric plethysmographic method of measuring the skin circulation. The intensity of light reflected from the skin red cells correlated with the blood volume in the skin [3]. Venous refill time after a standardized exercise is obtained with the PPG. The venous refill time should not be confused with venous pressure, although there is a relationship between the two [4]. Bays *et al.* found a positive predictive value of venous refill time examined with PPG of 77% and a negative predictive value of 100% [5].

References

1 Brodie TG, Russel AE. On the determination of the rate of blood flow through an organ. *J Physiol* 1905; **32**: 47.
2 Hertzman AB. The blood supply of various skin areas as estimated by the photoelectric plethysmography. *Am J Physiol* 1938; **124**: 328–40.
3 Abramowitz HB, Queral LA, Flinn WR. The use of photoplethysmography in the assessment of venous insufficiency. A comparison to venous pressure measurements. *Surgery* 1979; **86**: 434–41.
4 Wienert V, Blazek V. New method for non-invasive measurement of venous pressure. *Hautarzt* 1982; **33**: 498–9.
5 Bays RA, Healy DA, Atnip RG, Neumyer M, Thiele BL. Validation of air plethysmography, photoplethysmography, and duplex ultrasonography in the evaluation of severe venous stasis. *J Vasc Surg* 1994; **20**: 721–7.

Light reflection rheography and digital photoplethysmography. The technique of light-reflection rheography (LRR) is based on the technique of PPG and was developed by Wienert and Blazek in the 1980s [1]. Digital photoplethysmography (DPPG) is a further development of LRR (second generation LRR) [2]. The results of LRR and DPPG have been compared and show a high degree of correlation, particularly in patients with venous disorders [3,4]. The correlation from LRR to ambulatory venous pressure is 0.73 for venous return and 0.93 for expelled volume [5].

References

1 Wienert V, Blazek V. Eine neue Methode zur unblutigen dynamischen Venendruckmessung. *Hautarzt* 1982; **33**: 498–9.
2 Blazek V, Schmitt HJ, Schultz-Ehrenberg U. Digitale Photoplethysmographie: Ein neues mikroprozessorgesteuertes Messsystem für die Beinvenendiagnostiek. *Biomed Tch* 1988; **33**: 307–8.
3 Kerner J, Schultz-Ehrenberg U, Blazek V. Digitale Photoplethysmographie (D-PPG)—klinische Eignung der neuen Messmethode zur venosen Funktionsdiagnostik. *Phlebol Proktol* 1989; **18**: 98–103.
4 Veraart JCJM, van der Kley AMJ, Neumann HAM. Digital photoplethysmography and light reflection rheography. *J Dermatol Surg Oncol* 1994; **20**: 470–3.
5 O'Donnell TF, McEnroe CS, Heggerick P. Chronic venous insufficiency. *Surg Clin North Am* 1990; **70**: 159–80.

Phlebography

Water-soluble contrast media have lowered the risk of causing DVT to nearly zero.

Ascending phlebography. The objective of the examination is to visualize the deep venous system from the foot to the lower inferior vena cava. Contrast injected into a foot vein is driven into the deep veins by an ankle tourniquet.

Varicography. This is a variant of ascending phlebography. Varicography is performed by directly injecting contrast into a varicose vein or veins. It determines the route of 'drainage' from the varicose veins through communicating veins in the deep venous system and defines the anatomical extent of the varicosities [1]. It indicates the major point of the origin of the reflux, and is very useful for investigating patients with recurrent varicose veins.

Descending phlebography. This has nowadays been replaced by duplex ultrasound.

Reference

1 Lea Thomas M, ed. *Phlebography of the Lower Limbs*. New York: Churchill Livingstone, 1982.

Varicose veins

Synonym
- Venous varicosity

This is the name given when there is visible, tortuous elongation and dilatation of the larger superficial venous trunks and their tributaries. Leg varicosities seldom develop before adolescence in women. Other types of venous dilatation are often incorrectly included within the category of 'varicose veins'. Capillary telangiectasias (diameter 0.1–0.4 mm) are predominantly red and intradermal. The colour of telangiectasias depends upon the calibre of the dilated venule; large dilatations are dark blue and often palpable (although still less than 1 mm in diameter). Reticular varicose veins are subcutaneous (2–4 mm in diameter) and arise from a blue leash of small veins.

Prevalence. The prevalence of varicose veins in the Western population is estimated to be between 10 and 50% although the higher figure is of dubious validity. The prevalence of varicose veins increases with age. By 20 years it is 10%; by the age of 40 years it is 40% in women and 25% in men, and varicose veins are present in about 70% of 80-year-old women and 60% of 80-year-old men. Women that give birth to several children have an increased risk of developing varicose veins [1]. A population-based cross-sectional survey in Germany of 3072 participants found that the prevalence of varicose veins was twice as high in an urban population as in a rural population [2].

Classification. Varicose veins are either primary or secondary.

Primary varicose veins have no obvious underlying cause. The superficial veins dilate and become tortuous with an associated valvular incompetence. The mechanisms for these changes are still not clearly defined. Biochemical abnormalities in the vein wall, genetic predisposition and haemodynamic factors may all affect the development of varicose veins. Haemodynamic changes do not seem to be of major importance in reticular and branch varicosities. Disorders of the endothelium and the extracellular matrix may account for the development of these minor varicosities. The recent report of venous reflux in 100% of patients with mutations in the *FOXC2* gene strongly suggests that at least some forms of varicose veins have a genetic basis which is the result of primary venous valve failure [3]. Similarly, the presence of varicose veins in congenital syndromes such as Klippel–Trenaunay syndrome indicate a genetic basis, although the fault may be in the vein wall as much as the valve.

Secondary varicose veins are the result of raised endoluminal venous pressure (venous hypertension) for which post-thrombotic damage is the most important cause. The deep venous system should be evaluated in all patients in whom secondary varicose veins are suspected to avoid operating on surface veins unnecessarily when prescription of elastic support stockings would be preferable.

References

1 Krijnen RMA, de Boer EM, Bruyunzeel DP. Epidemiology of venous disorders in the general and occupational population. *Epidemiol Rev* 1997; **19**: 294–309.

2 Rabe E, Pannier-Fischer F, Bromen K *et al*. Bonner Venenstudie der Deutschen Gesellschaft für Phlebologie—epidemiologische Untersuchung zur Frage der Häufigkeit und Ausprägung von chronischen Venenkrankheiten in der städtischen und ländlichen Wohnbevölkerung. *Phlebologie* 2003; **32**: 1–14.

3 Mellor RH, Brice G, Stanton AW *et al*. Mutations in *FOXC2* are strongly associated with primary valve failure in veins of the lower limb. *Circulation* 2007; **115**: 1912–20.

Clinical features. Varicose veins may be a purely cosmetic problem but many patients also complain of aching pain, which tends to be worse on prolonged standing at the end of the day, and which is relieved by leg elevation or compression. Symptoms such as itching, ankle swelling, and ultimately the development of lipodermatosclerosis or ulceration indicate haemodynamic failure and the need for investigation.

Complications of varicose veins, such as haemorrhage and thrombophlebitis, result from the varicose veins themselves whereas oedema, haemosiderin pigmentation, varicose eczema, atrophie blanche, lipodermatosclerosis and venous ulceration result from venous hypertension.

Diagnosis. Colour duplex Doppler ultrasound scanning is increasingly being used to investigate all patients with varicose veins, and is the investigation of choice for detecting deep-vein reflux. Duplex scanning is also essential to investigate patients with skin changes attributed to venous hypertension. There is some evidence that the incidence of recurrent varicose veins is lower after duplex assessment has been used to plan surgery.

Treatment of truncal varicose veins. The recognition of the skin changes which are associated with varicose veins is important because of the likely risk of progression to venous ulceration. Causes of secondary varicose veins should be sought, including DVT and intra-abdominal pathology.

Only varicose veins (superficial venous reflux) that are associated with cutaneous complications demand treatment. Many patients, especially women, present for treatment of varicose veins or telangiectases for cosmetic reasons. At present there is no means of assessing which limbs will progress to develop chronic venous insufficiency.

Several types of treatment for varicose veins are discussed [1–7] and the most common complications of these treatments are shown in Table 47.9.

References

1 Munavalli GS, Weiss RA. Complications of sclerotherapy. *Semin Cutan Med Surg* 2007; **26**: 22–8.

2 van den Bos R, Arends L, Kockaert M *et al*. Endovenous therapies of lower extremity varicosities: a meta-analysis. *J Vasc Surg* 2009; **49**: 230–9.

3 Iafrati MD. Subfascial endoscopic perforator vein surgery. *Semin Cutan Med Surg* 2005; **24**: 209–15.

4 De Roos KP, Nieman FHM, Neumann HAM. Ambulatory phlebectomy versus compression sclerotherapy: results of a randomized controlled trial. *Dermatol Surg* 2003; **29**: 221–6.

5 van den Bos RR, Kockaert MA, Neumann HAM, Nijsten T. Technical review of endovenous laser therapy for varicose veins. *Eur J Vasc Endovasc Surg* 2008; **35**: 88–95.

6 Mussa FF, Peden EK, Zhou W, Lin PH *et al*. Iliac vein stenting for chronic venous insufficiency. *Tex Heart Inst J* 2007; **34**: 60–6.

7 Apfelberg DB, Smith T, Maser MR. Study of three laser systems for treatment of superficial varicosities of the lower extremity. *Lasers Surg Med* 1987; **7**: 219–23.

Table 47.9 Important complications of the treatment of varicose veins [1–7].

Treatment	Complications
Sclerotherapy	Skin necrosis, hyperpigmentation, DVT (rare), superficial venous thrombosis, arterial thrombosis (very rare), allergic reactions [1]
Surgical therapy	
Stripping	Nerve damage, haematoma, infection, DVT, lymphocele, hypertrophic scarring, lymphoedema
SEPS	DVT, haematoma [2]
Phlebectomy	DVT, neuralgia, haematoma, infection [3] Haematoma, phlebitis [4]
Endovascular treatment	
Laser	Vein perforation, DVT, ecchymoses, skin burns, superficial venous thrombosis [5]
Foam sclerosant	DVT, allergic reactions, stroke, transient blindness
Stenting	Thrombosis [6]
Lasers	
IPLS	(Temporary) hyperpigmentation [7]
Nd : YAG	(Temporary) hyperpigmentation, scar formation [7]

DVT, deep vein thrombosis. IPLS, intense pulsed light source. SEPS, subfascial endoscopic perforator surgery.

Sclerotherapy

Sclero (compression) therapy is indicated for leg telangiectasias (thread veins), reticular veins, minor tributary veins, varicosities, and recurrent varicose veins following surgery (see Telangiectasia, p. 47.20). The aim of treatment is to obliterate the lumen of the injected veins. The most frequently used sclerosants are sodium tetradecyl sulphate (STD), polidocanol (aethoxysclerol), 23.4% saline, and a combination of 25% dextrose with 10% saline [1]. Several randomized controlled trials have shown that sclerosant choice, dose, local pressure dressing, degree and length of compression have no significant effect on the efficacy of sclerotherapy for varicose veins [2].

References

1 Zimmet SE. Sclerotherapy treatment of telangiectasias and varicose veins. *Tech Vasc Interv Radiol* 2003; **6**: 116–20.

2 Tisi PV, Beverley C, Rees A. Injection sclerotherapy for varicose veins. *Cochrane Database Syst Rev* 2006; **4**: CD001732.

Compression therapy

Graduated elastic compression stockings are classified by the European Standardization Commission into four categories, which have different uses [1,2]:

Class I, 15–21 mmHg: thrombosis prophylaxis

Class II, 23–32 mmHg: mild/moderate oedema, mild CVI, after sclerotherapy, pregnancy

Class III, 34–46 mmHg: severe CVI, severe oedema, lymphoedema, post-thrombotic syndrome

Class IV, >46 mmHg: severe lymphoedema.

Class II or III should be chosen, depending on the severity of the venous hypertension. It is of the utmost importance that stockings are carefully fitted and that patients are instructed about how to put them on and take them off. An applicator may need to be purchased. Hosiery is not usually worn overnight, but this may be ignored if patients find stockings difficult to apply. At least two pairs of stockings should be provided, to allow for daily changing and washing. Washing is necessary to retain the elastic property of Lycra-containing hosiery. Two stockings per leg should last 6 months before compression is lost and replacements are required [3]. Patients should be encouraged to wear elastic compression stockings for the rest of their lives. A healthy lifestyle with regular daily exercise, for example walking, and maintaining an ideal weight is to be encouraged.

Stockings can be below-knee (A–D stockings), thigh length (also named A–F), or tights. Graduated compression stockings may improve the short-term haemodynamics in patients with varicose veins, thereby relieving symptoms [4,5]. There are no data on their long-term benefits. Wearing class II stockings may reduce venous reflux but they do not appear to prevent the development of superficial varicose veins [6]. Wearing class II below-knee stockings is an alternative treatment for patients with severe varicose veins who do not wish to have invasive treatment.

References

1 Neumann HAM. Compression therapy with medical elastic compression stockings for venous diseases. *Dermatol Surg* 1998; **24**: 765–70.

2 Comité European de Normalisation, adopted European prestandard. *Medical Compression Hosiery*. ENV 12718. Brussels: Comité Européen de Normalisation, 2001.

3 Veraart JC, Daamen E, de Vet HC *et al*. Elastic compression stockings: durability of pressure in daily practice. *Vasa* 1997; **26**: 282–6.

4 Anderson JA *et al.* Paroven and graduated compression hosiery for superficial venous insufficiency. *Phlebology* 1990; **5**: 271–6.

5 Labropoulos N, Leon M, Volteas N, Nicolaides AN. Acute and long-term effects of elastic stockings in patients with varicose veins. *Int Angiol* 1994; **13**: 119–23.

6 Thaler E, Huch R, Huch A, Zimmermann R. Compression stockings prophylaxis of emergent varicose veins in pregnancy: a prospective randomised controlled study. *Swiss Med Wkly* 2001; **131**: 659–62.

Surgical therapy

Venous surgery is potentially curative for refluxing superficial veins when the deep veins are competent. Conversely, surgery should be avoided in patients in whom the superficial veins may be acting as collaterals, which are the major route for venous return, in a severely post-thrombotic limb.

Flush ligation and stripping. For more than 100 years saphenous incompetence has been treated by flush ligation and stripping [1]. Although the technique varies, the results are the same. Most surgeons no longer strip the great saphenous vein (GSV) to the ankle. Damage to the saphenous nerve is avoided if the vein is stripped to the knee The short strip appears to be as effective as the long strip, but it does not influence the venous haemodynamics in the lower leg. Veins in the calf can be subsequently treated with foam sclerotherapy [2]. The results of surgical stripping are slightly disappointing, with a success rate of only 79.7% 1 year after treatment [3]. The recurrence of varicose veins is often the result of neovascularization, which will occur in 20 to 30% [4]. However, high saphenous ligation with stripping of the GSV remains the most commonly performed intervention for varicose veins in the world.

Ligation and stripping of the short saphenous vein (SSV) is technically more demanding than stripping of the GSV, which explains why more and more incompetent SSVs are treated by endovenous techniques or by foam sclerotherapy.

References

1 Keller WL. A new method of extirpating the internal saphenous and similar veins in varicose conditions: a preliminary report. *NY Med J* 1905; **82**: 385–6.
2 Ceulen RPM, Kessels A, Veraart JCJM, van Neer PAFA. Lateral venous ulceration and incompetence of the small saphenous vein. *Dermatol Surg* 2007; **33**: 727–30.
3 van den Bos R, Arends L, Kockaert M *et al*. Endovenous therapies of lower extremity varicosities: a meta-analysis. *J Vasc Surg* 2009; **49**: 230–9.
4 De Maeseneer MG, Van Schil PE, Philippe MM *et al*. Is recurrence of varicose veins after surgery unavoidable? *Acta Chir Belg* 1995; **95**: 21–6.

Subfascial endoscopic perforator surgery (SEPS). Incompetent perforating veins of the lower limb have been correlated with leg ulceration. Linton's and Cockett's operations to ligate these veins became discredited partly because the post-operative complication rate was high [1], and there was little evidence that this form of surgery was efficacious in preventing recurrent ulceration. A minimally invasive approach (SEPS) was introduced by Hauer in 1985 [2], but in a prospective randomized controlled trial Van Gent *et al*. showed that this procedure did not prevent recurrent venous ulceration [3].

References

1 Kalra M, Gloviczki P. Subfascial endoscopic perforator vein surgery: who benefits? *Semin Vasc Surg* 2002; **15**: 39–49.
2 Hauer G. The endoscopic subfascial division of the perforating veins—preliminary report. *Vasa* 1985; **14**: 59–61.
3 Van Gent WB, Hop WC, Van Praag MC *et al*. Conservative versus surgical treatment of venous leg ulcers: a prospective, randomized, multicenter trial. *J Vasc Surg* 2006; **44**: 563–71.

Phlebectomy (Muller technique). Removing tributary veins through small incisions has been around for many years, but in 1966 Robert Muller re-described a minimal invasive surgical technique [1]. He used stab avulsions (microincisions) and fine hooks to extract the varicose vein tributaries. This technique is time-consuming but gives excellent cosmetic results. This means of treating varicose tributaries is significantly better than sclerotherapy [2].

References

1 Muller R. Traitement des varices par la phlébectomie ambulatoire. *Phlébologie* 1966; **19**: 277–9.
2 De Roos KP, Nieman FH, Neumann HAM. Ambulatory phlebectomy versus compression sclerotherapy: results of a randomized controlled trial. *Dermatol Surg* 2003; **29**: 221–6.

Endovascular treatment [1,2]

Endovascular treatments do not disconnect the GSV from the femoral vein, which may explain the absence of neovascularization. Endovascular laser treatment (EVLT) was introduced in the late 1990s and has become tremendously popular, especially for the treatment of GSV incompetence. Radiofrequency ablation (RFA) is probably equivalent to EVLT and both types of endovenous treatment appear to have early benefits in pain and return to work. The wavelengths of the laser can be varied in absorption spectra of haemoglobin (e.g. 840 or 940 nm) or water (1320 or 1499 nm). It is not yet known which is the best wavelength. Damage to the vein wall and surrounding tissues may lead to pain and pigmentation.

References

1 van den Bos R, Arends L, Kockaert M *et al*. Endovenous therapies of lower extremity varicosities: a meta-analysis and meta-regression of case series and randomized clinical trials. *J Vasc Surg* 2009; **49**: 230–9.
2 Van den Bos RR, Kockaert MA, Neumann HAM, Nijsten T. Technical review of endovenous laser therapy for varicose veins. *Eur J Vasc Endovasc Surg* 2008; **35**: 88–95.

Foam sclerosant treatment. Tessari introduced a technique in which air and a sclerosing agent are mixed [1]. Both polidocanol and sodium tetradecyl sulphate (STD) are detergents, and mixing them with air results in a firm foam. This foam is stable for a couple of minutes and can be injected directly into the vein under Duplex imaging. The foam allows this to be visualized [2]. This is now being used to obliterate saphenous systems. Comparisons against other techniques are, however, essential.

References

1 Tessari L, Cavezzi A, Frullini A. Preliminary experience with a new sclerosing foam in the treatment of varicose veins. *Dermatol Surg* 2001; **27**: 58–60.
2 O'Hare JL, Earnshaw JJ. The use of foam sclerotherapy for varicose veins: a survey of the members of the Vascular Society of Great Britain and Ireland. *Eur J Vasc Endovasc Surg* 2007; **34**: 232–5.

Stenting. A small group of patients with post-thrombotic syndrome may benefit from this treatment when the iliac vein compression syndrome is present [1,2].

References

1 Neglén P, Berry MA, Raju S. Endovascular surgery in the treatment of chronic primary and post-thrombotic iliac vein obstruction. *Eur J Vasc Endovasc Surg* 2000; **20**: 560–71.
2 Neglén P, Raju S. Proximal lower extremity chronic venous outflow obstruction: recognition and treatment. *J Vasc Surg* 2002; **15**: 57–64.

Lasers for treatment of cosmetic reticular veins and venous telangiectasia. The neodymium : YAG laser (1064 nm, long pulses >40 msec, high energy system) or an intense pulsed light source (IPLS) may be used to treat reticular veins or telangiectases (Fig. 47.22). Several studies have shown that IPLS is more effective in the treatment of veins with a diameter up to 1 mm, while 1064 nm Nd:YAG is more effective in veins from 1 to 4 mm in diameter [1–3].

References

1 Schroeter CA, Wilder D, Reineke T *et al*. Clinical significance of an Intense Pulsed Light Source on leg telangiectasias of up to 1 mm diameter. *Eur J Dermatol* 1997; **7**: 38–42.
2 Sadick NS. A dual wavelength approach for laser/intense pulsed light source treatment of lower extremity veins. *J Am Acad Dermatol* 2002; **46**: 66–72.
3 Fodor L, Ramon Y, Fodor A *et al*. A side-by-side prospective study of intense pulsed light and Nd: YAG laser treatment for vascular lesions. *Ann Plast Surg* 2006; **56**: 164–70.

Pharmacological treatment. There is little to no place for drugs in treating varicose veins, although some drugs may relieve the symptoms of chronic venous insufficiency [1]. Rutoside



Fig. 47.22 'Sunburst veins'.

derivatives diminish capillary filtration rate and may improve aching pain, although there is a marked placebo effect [2].

References

1 Martinez MJ, Bonfill X, Moreno RM, Vargas E, Capellà D. Phlebotonics for venous insufficiency. *Cochrane Database Syst Rev* 2005; CD003229.

2 Pulvertaft TB. General practice treatment of symptoms of venous insufficiency with oxerutins. Results of a 660 patients multicentre study in the UK. *Vasa* 1983; **12**: 373–6.

Post-thrombotic syndrome

Synonym

- Post-phlebitic syndrome

Definition. The post-thrombotic syndrome (PTS) is a chronic condition of the deep venous system in patients with a documented history of deep-vein thrombosis (DVT) [1].

Incidence. DVT has an annual incidence of 0.2% and about one-third of affected patients develop PTS within 5 years [2,3]. The incidence of PTS is about 10% 1 year after an episode of DVT, and increases to about 50% over a period of 5 to 8 years. The only clear, identified risk factor is recurrent DVT, which increases the risk of PTS as much as six-fold [4].

Pathophysiology. Venous hypertension plays a key role in the pathophysiology of PTS [1,5] and is the result of valvular incompetence, outflow obstruction and dysfunction of the calf muscle pump. After the initial thrombosis, resolution of the thrombus may start but propagation of the thrombus can also occur. The two processes can also occur simultaneously.

Loss of valve function leads to overloading of the venous system, which in turn leads to dilatation of the veins and to an increase in the venous volume. If this surpasses the capacity of the calf muscle pump, ambulatory venous hypertension results; this in turn causes further distension of the veins, leading to more valvular incompetence and the development of secondary varicose veins. When there is residual venous obstruction, the venous resistance and the venous pressure increases, which also leads to an increase in venous volume. In general, reflux causes more problems if it occurs in the distal part of the venous system and obstruction causes more problems when it occurs proximally.

Clinical features. The clinical symptoms of PTS are similar to those of CVI. They are, however, often more pronounced but may vary considerably from scarcely visible skin changes to pigmentation, lipodermatosclerosis, venous dilatation, oedema and ulceration. In the early stages of PTS, clinical signs do not correlate with the severity of disturbed venous haemodynamics [1]. Patients experience pain, heaviness, swelling, cramps, itching or tingling in the affected limb. Symptoms may be present in various combinations and may be persistent or intermittent. Typically, symptoms are aggravated by standing or walking and improve with rest and leg elevation, particularly lying down [4,6].

Diagnosis. The severity of PTS is often scored by the Villalta–Prandoni scale [7], which combines objective and subjective assessments. The simple Widmer score is also useful for PTS [8]. Duplex ultrasound provides information on reflux in both the deep and superficial venous systems. Non- or partially recanalized veins can usually be detected using this technique, although considerable interobserver variability is present. Phlebography is still necessary when the duplex scan is equivocal or direct deep venous surgery is being considered.

The range of movement in the ankle and knee joints should be tested because impaired movement in the lower leg reduces the effectiveness of the calf muscle pump [1].

Treatment. Prevention is an important part of treatment. Patients diagnosed with a DVT should be treated with a LMWH and oral anticoagulants. Once the oedema has settled, class II graduated elastic compression stockings are prescribed [3,9]. Patients should be reviewed annually after a DVT. A stent [10] or a Palma procedure [11] can be considered when there is evidence of venous obstruction. Graduated compression stockings should be worn for life.

References

1 Wentel TD, Neumann HAM. Management of the postthrombotic syndrome: the Rotterdam approach. *Semin Thromb Hemost* 2006; **32**: 814–21.

2 Kolbach DN, Sandbrink MWC, Neumann HAM, Prins MH. Compression therapy for treating stage I and II (Widmer) post-thrombotic syndrome. *Cochrane Database Syst Rev* 2003; **4**: CD004177.

3 Kolbach DN, Sandbrink MWC, Hamulyak K *et al*. Non-pharmaceutical management for prevention of post-thrombotic syndrome. *Cochrane Database Syst Rev* 2004; **1**: CD004174.

4 Kahn SR. The post-thrombotic syndrome: The forgotten morbidity of deep venous thrombosis. *J Thromb Thrombolysis* 2006; **21**: 41–8.

5 Neumann HAM, Veraart JCJM. Morphological and functional skin changes in postthrombotic syndrome. *Wien Med Wschr* 1994; **144**: 204–6.
6 Kahn SR. The post-thrombotic syndrome: progress and pitfalls. *Br J Haematol* 2006; **134**: 357–65.
7 Villalta S, Bagatella P, Piccioli A *et al*. Assessment of validity and reproducibility of a clinical scale for the post-thrombotic syndrome. *Haemostasis* 1994; **24** (Suppl. 1): 57a (abstract).
8 Kolbach DN, Neumann HAM, Prins MH. Definition of the post-thrombotic syndrome, differences between existing classifications. *Eur J Vasc Endovasc Surg* 2005; **30**: 404–14.
9 Prandoni P, Lensing AWA, Prins MH *et al*. Below-knee elastic compression stockings to prevent the post-thrombotic syndrome. A randomized controlled trial. *Ann Intern Med* 2004; **141**: 249–56.
10 Neglén P, Raju S. Proximal lower extremity chronic venous outflow obstruction: recognition and treatment. *Semin Vasc Surg* 2002; **15**: 57–64.
11 Palma EC, Esperon R. Vein transplants and grafts in the surgical treatment of the postphlebitic syndrome. *J Cardiovasc Surg* 1960; **1**: 94–107.

Deep vein incompetence

Secondary venous incompetence

All patients with varicose veins should have a colour Doppler duplex ultrasound of their deep venous system. DVT often permanently damages deep veins and their valves leading to deep vein incompetence with the superficial veins then acting as collateral drainage routes; for example, when the popliteal vein is occluded the superficial veins are the major outflow tracts from the limb. Because superficial varicose veins serve as necessary collateral drainage in these circumstances, surgery to ablate varicose veins is contraindicated and graduated compression stockings should be worn instead.

Primary deep vein incompetence

Congenital absence of venous valves is extremely rare [1]. It can affect only the lower limb veins or the whole body. Kistner has described a group of patients with floppy valves [2]. This abnormality is an enlarged valve cusp with a long, free edge that allows the cusp to prolapse when subjected to retrograde flow. Whether this is a congenital or an acquired abnormality is not known.

Mutations in the *FOXC2* gene, the cause of lymphoedema–distichiasis syndrome, has been shown to cause deep venous reflux in one-third of cases [3].

References

1 Basmajian JW. The distribution of valves in the femoral, external iliac and common iliac vein and their relationship to varicose veins. *Surg Gynec Obstet* 1952; **95**: 537.
2 Kistner RL. Surgical repair of the incompetent femoral vein valve. *Arch Surg* 1975; **110**: 1336.
3 Mellor RH, Brice G, Stanton AW *et al*. Mutations in *FOXC2* are strongly associated with primary valve failure in veins of the lower limb. *Circulation* 2007; **115**: 1912–20.

Leg ulcers

Leg ulceration

Definitions and epidemiology. Leg ulcers represent a break of the skin, sometimes extending through the dermis or deeper. Causes are listed in Table 47.10. A chronic ulcer is defined as one lasting more than 6 weeks [1]. Healed and active ulcers of the lower limb affect 1% of the adult population and 3.6% of people older than 65 years [2]. The main causes are venous hypertension, arterial disease and diabetes, but many factors may contribute (Table 47.10). Venous disease is the single most common cause, but gravitational and venous influences may contribute to the development of other pathologies in the lower leg (e.g. vasculitis).

Table 47.10 Causes of lower limb ulceration.

Venous hypertension	Varicose veins, deep-vein thrombosis, venous obstruction, congenital vascular malformations, Klippel–Trenaunay syndrome
Arterial disease	Atherosclerosis, diabetes, hypertension, embolism, calcific uraemic arteriolopathy (calciphylaxis)
Skin cancer	Basal and squamous cell carcinoma, melanoma or any fungating tumour
Vasculitis	Connective tissue diseases, e.g. systemic lupus erythematosus, rheumatoid disease, progressive systemic sclerosis, necrotizing leukocytoclastic vasculitis, ANCA-associated disorders, polyarteritis nodosa
	Livedoid vasculopathy, cryoglobulinaemia
Haematological disorders	Coagulation states, e.g. factor V Leiden, protein S or C deficiency, hyperhomocysteinaemia, antithrombin III deficiency, sickle cell disease, thalassaemia, spherocytosis, antiphospholipid syndrome, myeloproliferative disorders, e.g. polycythaemia rubra vera, thrombocythaemia
Emboli	Cholesterol, platelets, tumour cells, infective
Loss of sensation	Leprosy, diabetes, spina bifida
Infections	Diabetes, osteomyelitis, Buruli ulcer, fungal infections, syphilis, mycobacteria, leishmaniasis, acute 'desert' sore, necrotizing fasciitis and cellulitis
Trauma	Physical, e.g. pressure sore, chemical or thermal (e.g. burns or cold injury)
	Self-harm
	Intravenous drug use
Drugs/therapy	Radiation
	Hydroxycarbamide, ergotamine
	Iododerma
Skin conditions	Pyoderma gangrenosum
	Necrobiosis lipoidica
	Scleroderma
	Graft-versus-host disease
	Blistering disorders (e.g. pemphigoid)
	Bites and stings: insects, snake, scorpion
Genetic	Prolidase deficiency
	Klinefelter's syndrome

Venous ulceration of the leg [3,4]

Definition. Ulceration of the lower leg occurring as the result of persistently elevated venous pressure and its secondary effects on the microvascular system. Nearly half of all venous ulcers are associated with deep-vein valvular incompetence or post-thrombotic damage, while the remainder result from incompetence of the superficial or communicating veins.

Epidemiology [5–7]. Community surveys suggest an overall incidence of about 0.2% [5]. It is an age-related disease, mainly

affecting older women. Women are two to three times more often affected than men; 2% of all those over the age of 80 years suffer with ulceration. About half of the ulcers heal within 4 months but approximately 20% have not healed after 1 year and about 8% have not healed after 5 years. The annual recurrence rate is 6 to 15% and most ulcers recur more than once.

Venous ulceration is a common disease of all Western communities [7]. It appears to be associated with a sedentary and physiologically unnatural mode of life and is comparatively rare in African people, although the incidence may be underrated [8–10].

A study of 4422 healthy working adults in Basle found 'chronic venous insufficiency' in 19% of men and in 25% of women [11]. Ulceration was present in 1.1 and 1.4%, respectively. Figures from other surveys are similar. It has been emphasized that up to one-third of ulcers in elderly people have coexisting arterial insufficiency as one factor contributing to their failure to heal. A family history of leg ulcers is found in over half of those affected [12]; this applies about equally to those who have suffered a known thrombosis and to those who have not. The significance of this is not known, although inheritance of coagulation defects may be one factor.

Venous disease accounts for 1–2% of the health-care budgets of European countries [13].

Pathogenesis. Venous ulcers are the end result of superficial venous insufficiency or the post-thrombotic syndrome (PTS) described above. The consequent ambulatory venous hypertension causes alterations in the microvasculature and interstitium which make the skin more liable to break down, or to fail to repair, following minor episodes of trauma. The fundamental fault is a sustained capillary hypertension resulting from persistently raised venous pressure. A failure to reduce venous pressure satisfactorily when the lower limb is dependent is consequent upon a failure of venous valves (allowing reflux) and poor calf muscle pump function. The lack of skin viability must reflect local hypoxia but the exact mechanism is not understood. The pathogenesis of the microvascular damage from the venous hypertension is discussed on p. 47.26.

A history of deep leg-vein thrombosis is obtained from a significant proportion of patients. In Anning's carefully documented series [12], a story of prior thrombosis was obtained in 75% of the patients. Leg injuries, particularly fractures, are frequently followed by thrombosis [14]. Other relatively common causes include hip replacements, pelvic and lower abdominal operations, medical illnesses and prolonged recumbency from any cause. In one study, 12 of 46 patients admitted to hospital with leg ulcers demonstrated resistance to activated protein C [15], a finding that has been observed in 20–40% of patients known to have had a previous DVT. Patients with chronic venous ulcers have a 41% prevalence rate of thrombophilia, which is 30 times higher than the general population [16]. Interestingly, thrombophilia does not necessarily appear to be related to past DVT [17]. Subjects with Klinefelter's syndrome have an increased risk of leg ulceration through an abnormality in platelet aggregability and fibrinolysis associated with elevated levels of plasminogen activator inhibitor-1 [18].

Up to 60% of patients with venous ulcers have isolated superficial vein incompetence with normal deep veins [19]. The concept of a primary defect in collagen or elastic tissue has been revised by the recognition of ulceration consequent on prolidase deficiency (p. 47.54). Congenital absence of venous valves as a cause of leg ulcers is probably rare [20].

Clinical features. The ulcer may be preceded by patchy erythema or discoloration of an intense bluish red colour, in which ischaemia of the skin finally leads to necrosis, often following a minor episode of trauma. This intense bluish colour can be seen by capillary microscopy to be caused by capillary congestion [21].

The ulcer is characteristically situated on the medial lower aspect of the leg, the 'gaiter' region, which is drained on the medial side by three large pairs of perforating veins. Venous ulcers do not usually develop initially below the level of the malleoli or in the foot unless complicated by livedoid vasculitis or arterial disease.

Two events may lead to a break in the continuity of surface epithelium. The first is capillary thrombosis, when the complete outline of the capillary can be seen to be filled with broken-up thrombus, which does not disperse on pressure. The second is a small bleed from the peak of the capillary; this separates the epidermis from its blood supply. These changes in the capillaries supplying the epidermis are frequently induced by small knocks, scratching or epidermal pathology such as dermatitis. The skin around an ulcer is frequently irritated by exudate, and inflamed varicose or medicament dermatitis may contribute to preventing healing and extending the ulcer size. Other signs of venous hypertension are usually present, for example lipodermatosclerosis, varicose veins (corona phlebectasia), varicose eczema or oedema; sometimes a nearby perforator vein may be evident by a palpable depression in the subcutaneous fat.

Ulcers often show pseudoepitheliomatous hyperplasia at their edge, which may be mistaken for a squamous cell carcinoma. The ulcer is covered with yellowish exudate over granulation tissue [22].

Healing ulcers have a shallow sloping edge with healthy granulation in their base and little slough. Epithelial islands may become scattered over the surface of a well-vascularized bed, and quickly enlarge (Fig. 47.23). The pink lip of the epithelium at the edge of an ulcer is uniform and supplied by relatively uncongested capillaries. The overall appearance is like a normal nail fold and cuticle. By contrast, a non-healing ulcer resembles a severe paronychia, being boggy, undermined and congested from oedema. The base is often white and very fibrous.

The coexistence of arterial disease can contribute to the progression of a venous ulcer, so symptoms and signs of peripheral ischaemia should be sought in all patients with leg ulceration. Rest pain can occur in the absence of arterial disease. Patients develop typical ischaemic pain on elevation of the ulcerated leg, which is oedematous. To relieve this pain, the patient keeps the leg in a dependent position, especially at night; this exacerbates the underlying pathogenesis.

After excluding arterial disease, a period of enforced elevation, necessitating strong analgesia, results in disappearance of the oedema with subsequent relief of the venous rest pain. Occasion-



Fig. 47.23 A healing venous ulcer. There are multiple islands of reforming epithelium spreading over healthy granulation tissue.

ally, venous ulceration occurs at other sites in the limb, but other aetiologies should be suspected in such instances, especially if ulcers are present over the foot or just below the knee. Hyperkeratosis and papillomatosis around an ulcerated area or along the border of the foot, particularly below the malleoli, is a result of impaired local lymphatic drainage.

References

1 Reichenberg J, Davis M. Venous ulcers. *Semin Cutan Surg* 2005; **24**: 216–61.
2 Ruckley CV. Caring for patients with chronic leg ulcer. *BMJ* 1998; **3316**: 407–8.
3 Valencia IC, Falabella A, Kirsner RS *et al*. Chronic venous insufficiency and venous leg ulceration. *J Am Acad Dermatol* 2001; **44**: 401–21.
4 Bergan JJ, Schmid-Schonbein GW, Coleridge Smith PD *et al*. Mechanisms of disease: chronic venous disease. *N Eng J Med* 2006; **355**: 288–98.
5 Cornwall JV, Dore CJ, Lewis JD. Leg ulcers: epidemiology and aetiology. *Br J Surg* 1986; **73**: 693–6.
6 Callum MJ, Ruckley CV, Harper DR *et al*. Chronic ulceration of the leg: extent of the problem and provision of care. *BMJ* 1985; **290**: 1855–6.
7 Nelzen O, Bergquist D, Lindhagen A. Venous and non-venous leg ulcers: clinical history and appearance in a population study. *Br J Surg* 1994; **81**: 182–7.
8 Schulz EJ, Findlay GH, Scott FP. Skin disease in the Bantu: a survey of 4000 cases from the Transvaal and Orange Free State. *S Afr Med J* 1962; **36**: 199–202.
9 Shrank AB, Harman RRM. The incidence of skin disease in a Nigerian teaching hospital dermatological clinic. *Br J Dermatol* 1966; **78**: 235–41.
10 Doglietti M. Skin disorders in the Bantu: a survey of 2000 cases from Baragwanath Hospital. *S Afr Med J* 1970; **44**: 670–2.
11 Borschberg E, ed. *The Prevalence of Varicose Veins of the Lower Extremities*. Basle: Karger, 1967.
12 Anning ST, ed. *Leg Ulcers: Their Causes and Treatment*. London: Churchill, 1954.
13 Ruckley CV. Socioeconomic impact of chronic venous insufficiency and leg ulcers. *Angiology* 1997; **48**: 67–9.
14 Hjelmstedt A, Bergvall U. Incidence of thrombosis in patients with tibial fractures. *Acta Chir Scand* 1967; **134**: 1–10.
15 Munkvad S, Jørgensen M. Resistance to activated protein C: a common anticoagulant deficiency in patients with venous leg ulceration. *Br J Dermatol* 1996; **134**: 296–8.
16 Maessen-Visch MB, Hamulyak K, Tazelaar DJ *et al*. The prevalence of factor V Leiden mutation in patients with leg ulcers and venous insufficiency. *Arch Dermatol* 1999; **135**: 41–4.
17 Mackenzie RK, Ludlam CA, Ruckley CV *et al*. The prevalence of thrombophilia in patients with chronic venous ulceration. *J Vasc Surg* 2002; **35**: 718–22.
18 Zollner TM, Veraart JC, Wolter M *et al*. Leg ulcers in Klinefelter's syndrome—further evidence for an involvement of plasminogen activator inhibitor-1. *Br J Dermatol* 1997; **136**: 341–4.
19 Scriven JM, Hartshorne T, Bell PRF *et al*. Single visit venous ulcer assessment clinic: the first year. *Br J Surg* 1997; **84**: 334–6.
20 Lodin A, Lindvall N, Gentele H. Congenital absence of venous valves as a cause of leg ulcers. *Acta Chir Scand* 1959; **116**: 256–70.
21 Ryan TJ. The epidermis and its blood supply in venous disorders of the leg. *Trans St John's Hosp Dermatol Soc* 1969; **55**: 51–65.
22 Grey JE, Enoch S, Harding KG. Venous and arterial leg ulceration. *BMJ* 2006; **52**: 593–603.

Associations and complications of venous leg ulcers

The main conditions associated with venous ulceration are anaemia and malnutrition (especially in elderly people living alone), and these must be assessed and corrected as far as possible.

General disease [1–3]. Coincidental obesity and hypertension are common. The relationship of these to the presence of the ulcer is uncertain, but they are undoubtedly perpetuating causes. Increased intra-abdominal pressure, for example from obesity, can increase cardiac filling pressures, femoral venous pressures, renal vein pressure, systemic blood pressure and vascular resistance [4]. Cardiovascular disease is common and heart failure can be a major contributor to venous ulceration through its effect on: (i) further raising venous pressure; (ii) creating peripheral oedema; and (iii) encouraging long periods of sitting. Joint disease, peripheral arterial disease and neurological disease can obviously impair the already precarious nutrition of the skin and the action of the muscle pump. Severe rheumatoid disease or long-standing poliomyelitis also reduce the effectiveness of the muscle pump and encourage recurrence.

Anaemia and hypoproteinaemia. Sickle cell anaemia [5] can cause ulceration, and the presence of marked anaemia, for example due to iron-deficiency anaemia or thalassaemia, may prevent other ulcers from healing by reducing peripheral oxygenation. Repeated infection or chronic inflammation arising from the ulcer may itself cause a normochromic normocytic anaemia. A poor diet, combined with continuous seepage of protein and blood from an untreated ulcer, relatively commonly leads to anaemia and hypoalbuminaemia.

Diabetes. Diabetes is common, and will compound any venous ulcer through arterial disease, infection and neuropathy.

Personal attitudes and habits: sociology [6]. Patients with long-standing ulcers commonly develop a number of complications that stem from the personality, domestic and social situation of the patient. Walking has long been abandoned and substituted by more damaging motionless sitting. The ankle can become fixed in equinus and the foot inverted leading to an irreversible condition. The leg becomes transformed into a useless and deformed peg and the calf muscles atrophy. Apathy, often with depression and apparent acceptance of the condition, is frequent. Affected patients may become chairbound with decreasing mobility and malnourishment, but potentially receiving much attention and sympathy from family members. Many such patients never go to bed but sit motionless in the chair all night. In a few cases, it is clear that any real attempt to cure the ulcer will be resisted unless this can be

accompanied by a vigorous social and psychological rehabilitation. Lonely patients may find that an ulcer is their only means of obtaining a visitor, be it district nurse or doctor.

Zinc depletion. This has received considerable attention [7–14], following the observation that zinc deficiency in rats impairs wound healing. Low plasma zinc levels have been found in patients with venous ulceration, and accelerated healing of such ulcers after oral zinc sulphate therapy has been reported. It is, however, the tissue levels of zinc that are of most importance in ulcer healing, and these have never been shown to be low in patients with leg ulcers. Analysis of six randomized trials indicates that oral zinc does not aid healing of leg ulcers, except possibly in patients with low serum zinc [15].

References

1 Browse NL, Burnand K, Irvine AT, Wilson NM. *Diseases of the Veins*, 2nd edn. London: Arnold, 1999.
2 Ryan TJ, ed. *Management of Leg Ulcers*. Oxford: Oxford University Press, 1987.
3 Stevens AE, Ball KP. General disease among leg ulcer patients. *Trans St John's Hosp Dermatol Soc* 1964; **50**: 43–7.
4 Sugerman HJ. Effects of increased abdominal pressure in severe obesity. *Surg Clin North Am* 2001; **81**: 1063–75.
5 Koshy M, Entsuah R, Koranda A *et al*. Leg ulcers in patients with sickle cell disease. *Blood* 1989; **74**: 1403–8.
6 Wilkinson DS. *Nursing and Management of Skin Diseases*, 4th edn. London: Faber and Faber, 1977.
7 Greaves M, Boyde TRC. Plasma-zinc concentrations in patients with psoriasis, other dermatoses and venous leg ulceration. *Lancet* 1967; **ii**: 1019–20.
8 Greaves MW, Ive FA. Double-blind trial of zinc sulphate in the treatment of chronic venous leg ulceration. *Br J Dermatol* 1972; **87**: 632–4.
9 Greaves MW, Skillen AW. Effects of long-continued ingestion of zinc sulphate in patients with venous leg ulceration. *Lancet* 1970; **ii**: 889–91.
10 Myers MB, Cherry G. Zinc and the healing of chronic leg ulcers. *Am J Surg* 1970; **120**: 77–81.
11 Serjeant GR, Galloway RE, Gueri MC. Oral zinc sulphate in sickle-cell ulcers. *Lancet* 1970; **ii**: 891–2.
12 Pories WJ, Henzel JH, Rob CG *et al*. Acceleration of wound healing in man with zinc sulphate given by mouth. *Lancet* 1967; **i**: 121–4.
13 Hallböök T, Lanner E. Serum-zinc and healing of venous ulcers. *Lancet* 1972; **ii**: 780–2.
14 Husain SL. Oral zinc sulphate in leg ulcers. *Lancet* 1969; **i**: 1069–71.
15 Wilkinson EA, Hawke CI. Oral zinc for arterial and venous leg ulcers. *Cochrane Database Syst Rev* 2000; CD001273.

Infection [1]. The role of antisepsis in the healing of leg ulcers is much debated [2–4]. Pathogenic organisms are commonly found in leg ulcers of all types [3]. The bacterial flora is often profuse and usually mixed, but *Staphylococcus aureus* predominates. There is still insufficient evidence to determine to what extent such a flora influences the rate of healing, but quantitative bacteriology has indicated that fewer than 100 000 organisms per square centimetre of surface area or per gram of tissue does not delay repair [5]. Certain pathogens are, however, traditionally taken seriously; for example, the group A β-haemolytic *Streptococcus* or a heavy growth of *Pseudomonas* spp. Unimpeded resolution of uncomplicated leg ulcers under occlusive compressive bandaging is frequently accompanied by considerable pus formation, but healing is not necessarily impaired. Sometimes lakes of pus develop in an atrophic skin that readily breaks down. Referred to as erosive pustular dermatosis of the leg, the pus is sterile and the condition responds to intermittent use of potent topical steroids [6].

Fungi vary in extent and importance. Some authors have found *Candida albicans* only rarely [7], but it can be a common commensal organism, perhaps because of the widespread use of specific antibiotics. Ointment-impregnated bandages without preservatives were blamed for candidal overgrowth in one study [8]. Moist wound healing using contemporary occlusive dressings seems not to encourage infection [9].

Penicillin- and tetracycline-resistant staphylococci, and *Pseudomonas aeruginosa*, are very common in hospital-treated patients, and cross-contamination is very common in leg ulcer clinics [10]. *Proteus vulgaris* and other Gram-negative organisms are probably of little importance. The role of non-clostridial anaerobic organisms such as *Bacteroides* spp. in delaying ulcer healing has probably been underestimated. As with other types of infection, large controlled trials are required to measure healing after the ulcer surface has been sterilized. This information is not currently available to provide advice on the value of infection control. Venous ulcers are less likely to develop infection than arterial or diabetic ulcers [11]. All the antibiotic trials on ulcer healing that have been carried out have failed to show benefit.

Contact dermatitis. The skin around an ulcer frequently becomes red and sore, caused predominantly by the irritant effect of exudate (Fig. 47.24). Small pustules and superficial ulcers may develop, especially in the presence of β-haemolytic streptococci. Eczema may be responsible for further compromising skin viability, and



Fig. 47.24 Redness caused by exudate localized to the site of an overlying dressing, often confused with a contact allergy to the dressing.

Table 47.11 Leg ulcer allergens.

Ointment bases and preservatives
Wool alcohols (lanolins)
Parabens
Propylene glycol
Chlorocresol
Ethylenediamine
Cetostearyl alcohols
Additives in bandages
Ester gum resin
Azo disperse (dyes)
Colophony (adhesives)
Additives that prevent rubber and elastic from perishing
Antibacterial agents
Sodium fusidate
Gentamicin sulphate
Neomycin
Framycetin
Quinoline mix (Vioform, Chinoform)
Self-medication
Caine mix (local anaesthetics)
Antihistamine creams
Chlorxylenol (Dettol)
Germolene



Fig. 47.25 A sensitivity reaction to strapping showing blistering.

so increasing the size of an ulcer. In most cases, the eczema is the result of local treatment (Table 47.11) and sensitivity can be demonstrated by patch testing. Patients with venous ulcers appear to become sensitized easily (Fig. 47.25) [12], often to several medicaments including lanolin and rubber [13–15]. The components of paste bandages may be responsible [16]. True medicament sensitivity is a frequent complication of therapy (Fig. 47.26) [17].

It is unfortunately not widely appreciated that the effect of potent topical corticosteroids on leg ulcers may inhibit healing for several weeks by producing an indolent 'arterial-type' ulcer with a deep adherent slough, 'steroid ulcer' (p. 47.56).

Haemorrhage [18,19]. Spontaneous haemorrhage occasionally occurs, especially from large ulcers [19]. This may be severe and can cause death if the patient faints and is held in the vertical position. First-aid measures include immediately lying the patient on the floor and elevating the limb while applying firm direct pressure to the bleeding point in the base of the ulcer. Occasionally, a suture will be required, but a tight bandage and elevation usually prevents further bleeding.

Lymphoedema (Chapter 48). The superficial lymphatics are absent in and around ulcers and their distortion or obliteration contributes to hyperkeratosis, papillomatosis, dermal fibrosis and oedema. An inadequacy of the lymphatic drainage predisposes to attacks of cellulitis [20], and with each episode of infection damage is compounded and chronic lymphoedema delays ulcer healing.

Malignant change [21]. Primary malignancies of the leg presenting as ulcers are increasingly common in an ageing population or



Fig. 47.26 Patch testing: 72-h reading showing multiple sensitivities, typical of patients with a long history of ulcer therapy.

those with sun exposure or transplantation-associated immunosuppression. Malignant change in an established ulcer is much rarer but carries a worse prognosis. Squamous epitheliomas may be difficult to distinguish from pseudoepitheliomatous hyperplasia, but if missed because of a failed diagnosis will often metastasize [22]. Biopsy should be considered if the diagnosis is in doubt [23]; multiple biopsies have been recommended as features may vary throughout the ulcer-associated tumour [24]. The edge becomes progressively heaped up (Fig. 47.27), vegetating and cauliflower-like and does not flatten with compressive therapy. Basal cell carcinomas may remain quite flat and undetected (Fig. 47.28).



Fig. 47.27 Heaped-up squamous epithelioma.

Suspicion may be aroused when the ulcer fails to respond to compression therapy. A distinction should be made between the rarity of malignant change in a chronic ulcer associated with disorders of the venous system, and the common primary malignancy occurring in the skin of legs that have had prolonged exposure to sunlight.

Subcutaneous calcification (post-phlebitis subcutaneous calcinosis) [25]. This is often widespread. It occurs in up to 10% of patients with chronic venous insufficiency [25]. It may cause nonhealing of an ulcer or be found incidentally. The calcification, which is sometimes osteoid, occurs around areas of fat necrosis and fibrosis [26]. Radiography reveals a coarse network of calcification, the edges of individual plaques impinging on the dermis. Other causes of calcification include phleboliths, atherosclerotic calcification, cysticercosis and a heterotopic form of dystrophic calcification (in which the serum calcium and phosphorus levels are normal). Calcium deposits act as a foreign body nidus for organisms and delay healing, particularly when they are extruded through the skin as a foreign body.

Bone changes. Periostitis is commonly seen beneath a chronic ulcer. Osteoporosis is often present in the later stages because of disuse atrophy. Osteoarthritis is a common concomitant condition in the affected or unaffected leg, especially the knee. Fibrous ankylosis of the ankle occurs also from disuse.



Fig. 47.28 A flat basal cell carcinoma complicating lipodermatosclerosis.

References

1 Kontiainen S, Rinne E. Bacteria in ulcera crurum. *Acta Derm Venereol (Stockh)* 1988; **68**: 240–4.

2 Alinovi A, Bassini P, Pini M. Systemic administration of antibiotics in the management of venous ulcers. *J Am Acad Dermatol* 1986; **15**: 186–91.

3 Phillips TJ, Dover JS. Leg ulcers. *J Am Acad Dermatol* 1991; **25**: 965–89.

4 Rodehaver G. Controversies in topical wound management. *Wounds* 1989; **1**: 19–27.

5 Lookingbill DP, Miller SH, Knowles RC. Bacteriology of chronic leg ulcers. *Arch Dermatol* 1978; **114**: 1765–8.

6 Bull RH, Mortimer PS. Erosive pustular dermatosis of the leg. *Br J Dermatol* 1995; **132**: 279–82.

7 English MP, Smith RJ, Harman RRM. The fungal flora of ulcerated legs. *Br J Dermatol* 1971; **84**: 567–81.

8 Hanson C, Faergemann J, Swanbeck E. Fungal infections occurring under bandages in leg ulcer patients. *Acta Derm Venereol (Stockh)* 1987; **67**: 341–5.

9 Mertz PM, Eaglstein WH. The effect of occlusive dressing on the microbial population in superficial wounds. *Arch Surg* 1984; **119**: 287–9.

10 Mitchell AAB, Pettigrew JB, MacGillvray D. Varicose ulcers as reservoirs of hospital strains of *Staph. aureus* and *Pseudomonas pyocyanea*. *Br J Clin Pract* 1970; **24**: 223–6.

11 Schmidt K, Debus ES, Jessberger ST *et al*. Bacterial population of chronic crural ulcers: is there a difference between the diabetic, the venous and the arterial ulcer? *Vasa* 2000; **29**: 62–70.

12 Tavadia S, Bianchi J, Dawe RS *et al*. Allergic contact dermatitis in venous leg ulcer patients. *Contact Dermatitis* 2003; **48**: 261–5.

13 Angelini G, Rantuccio F, Meneghini CL. Contact dermatitis in patients with leg ulcers. *Contact Dermatitis* 1975; **1**: 81–7.

14 Kulozik M, Powell S, Cherry GW *et al*. Contact sensitivity in community-based leg ulcers. *Clin Exp Dermatol* 1988; **13**: 82–4.

15 Wilson CL, Cameron J, Powell SM *et al*. High incidence of contact dermatitis in leg ulcer patients: implications for management. *Clin Exp Dermatol* 1991; **16**: 250–3.

16 Hardie RA, Benton EC, Hunter JAA. Adverse reactions to paste bandages. *Clin Exp Dermatol* 1982; **7**: 135–42.

17 Jankićević J, Vesić S, Vukićević J *et al*. Contact sensitivity in patients with venous leg ulcers in Serbia: comparison with contact dermatitis patients and relationship to ulcer duration. *Contact Dermatitis* 2008; **58**: 32–6.

18 Harman RRM. Haemorrhage from varicose veins. *Lancet* 1974; **i**: 363.

19 Evans CA, Evans DMD, Seal RME *et al*. Spontaneous fatal haemorrhage caused by varicose veins. *Lancet* 1973; **ii**: 1359–61.

20 Dupuy A, Benchikhi H, Roujeau JC *et al*. Risk factors for erysipelas of the leg (cellulitis): case–control study. *BMJ* 1999; **318**: 1591–4.

21 Pennel TC, Hightower F. Malignant changes in post-phlebitic ulcers. *South Med J* 1965; **58**: 779–81.

22 Baldursson BT, Hedblad MA, Beitner H *et al*. Squamous cell carcinoma complicating chronic venous leg ulceration: a study of the histopathology, course and survival in 25 patients. *Br J Dermatol* 1999; **140**: 1148–52.

23 Lagattolla NRF, Burnand KG. Chronic venous disease may delay the diagnosis of malignant ulceration of the leg. *Phlebology* 1994; **9**: 167–9.

24 Cox NH, Long ED. Pseudoangiosarcomatous squamous cell carcinoma of skin. *Histopathology* 1993; **22**: 295–6.
25 Sarkany I, Kreel L. Subcutaneous ossification of the legs in chronic venous statis. *BMJ* 1966; **ii**: 27–8.
26 Lippman HI, Goldin RR. Subcutaneous ossification of the legs in chronic venous insufficiency. *Radiology* 1960; **74**: 279–81.

Diagnosis of venous ulceration. This is essentially clinical; based on finding ulceration in the gaiter area with the presence of signs of venous hypertension (p. 47.33). A past history of venous thrombosis, treatment for varicose veins or a family history of venous disease is supportive evidence. Arterial disease must be excluded and the ulcer should respond to compression therapy. Colour Doppler duplex ultrasound should be performed, not just to confirm venous reflux but also to see if superficial venous incompetence is responsible, in which case venous surgery may be an option if the deep veins are competent [1]. The preference is to wait for ulceration to heal before fully assessing the venous system. Plethysmography may be useful to investigate calf muscle pump function when venous duplex ultrasound is normal [2].

An ankle–brachial pressure index should be performed if foot pulses are not easily palpable, although the diagnosis of arterial disease does not exclude the possibility of an ulcer predominantly caused by venous disease (mixed origin). Arterial duplex Doppler scanning or arteriography should be undertaken if doubts remain regarding the presence of arterial ischaemia. A skin biopsy does not help in the diagnosis and may not heal in the presence of venous hypertension but is indicated if alternative causes such as skin malignancy [3] or vasculitis are possibilities. Signs of a peripheral neuropathy should be excluded and the range of hip, knee and particularly ankle movement should be tested.

References

1 Grabs AJ, Wakely MC, Nyamekye I *et al*. Colour duplex ultrasonography in the rational management of chronic venous leg ulcers. *Br J Surg* 1996; **83**: 1380–2.
2 Reichenberg J, Davis M. Venous ulcers. *Semin Cutan Med Surg* 2005; **24**: 216–26.
3 Lagattolla NRF, Burnard KG. Chronic venous disease may delay the diagnosis of malignant ulceration of the leg. *Phlebology* 1994; **9**: 167–9.

Management of venous ulcers [1–4]

General management

Most venous ulcers are cared for in the community by appropriately trained nurses and general practitioners. First-line therapy for venous ulcers is compression bandaging. The concept is to reduce venous pressure, particularly during walking, by improving calf muscle pump function and by opposing gravitational venous reflux. Exercise and movement are to be encouraged, while long periods spent sitting and standing should be discouraged. When resting, the legs should be elevated, ideally with the ulcer just above the level of the heart to ensure the maximum reduction in venous pressure. Thus, lying is always preferable to sitting with the leg elevated. Patients should always be instructed to sleep in a bed; this might sound obvious but it is remarkable how many patients with venous ulcers fall asleep and remain in chairs with dependent legs both day and night, so exacerbating venous ulcers (despite bandaging) because of limited reduction in venous pressure.

Obesity is often a problem that becomes worse with immobility, boredom and social isolation. Weight control is therefore essential, but malnourishment with anaemia and poor protein intake can coexist with obesity. Frail, elderly patients are at risk of malnutrition. Adequate intake of essential vitamins and minerals in a balanced diet is essential for wound healing [5]. The contribution of other medical conditions, particularly heart and chest problems, needs to be considered. Heart failure exacerbates venous hypertension, while the need to sit upright in bed or in a chair to alleviate dyspnoea will fail to reduce leg venous pressures. Smoking should be stopped and excessive alcohol intake should be curtailed as both compromise wound healing [6,7].

Intravenous drug users that have used lower limb veins are at increased risk of venous leg ulcers. Management must consider any HIV or hepatitis risk to both the patient and the health-care professional (through wound fluids).

Assessment. After taking a full and detailed history clinical examination should include identifying signs of venous disease, palpation of the peripheral pulses, testing for any loss of cutaneous sensation and for the range of hip, knee and particularly ankle movement. The patient should be observed walking to identify any reasons preventing a normal heel to toe gait. Signs of heart failure should be carefully looked for and any sleep-apnoea syndrome considered, particularly in the obese.

Investigations. Blood tests should seek to exclude significant anaemia (a mild normochromic normocytic anaemia is to expected secondary to the ulcer), infection (indicated by neutrophilia and raised CRP), and hypoalbuminaemia (which will discourage healing and exacerbate oedema). A fasting glucose (plus a HbA_{1c} level in known diabetic individuals), as well as renal and liver function, should be measured [8]. A sickle cell test should be undertaken when sickle cell disease is a possibility. Patients with a history of recurrent thrombosis or family history of thrombosis should be investigated for a thrombophilia [9].

An ankle–brachial pressure index should be performed if foot pulses are not easily palpable. Arterial duplex Doppler scanning or arteriography should be undertaken if doubts remain regarding the presence of arterial ischaemia. Colour duplex Doppler ultrasound should be performed at some stage to see if superficial venous incompetence is responsible, in which case surgery may be indicated.

Compression therapy [10]. Compression therapy is the mainstay of treatment. In addition to stimulating fibrinolytic activity and reducing discomfort and oedema, compression therapy counteracts venous hypertension by facilitating venous return, improving calf muscle pump function and lymph drainage [11]. Many methods of compression are available, for example non-elastic (short stretch) wraps, elastic (long stretch) wraps and pneumatic compression devices. Compression may be administered in the form of single layer bandages, multilayer bandages, compression stockings or a combination of stockings and bandages. Any of these should exert 30–40 mm Hg of pressure at the ankle for effective compression. Compression increases ulcer healing rates compared with no compression. Multilayered systems are more effective than single-layered systems. High compression is more effective than low compression but there are no clear differences

in the effectiveness of different types of high compression. Graduated multilayer high compression bandage regimens capable of sustaining compression for a week at a time should be the first line of treatment for uncomplicated venous ulcers with an ankle–brachial pressure index above 0.8 [12].

When leg ulcer clinics have promoted compression treatment, healing rates have generally improved when compared with usual care given by community nurses [13]. Enthusiasm by professionals and a defined strategy, however, may explain the improvement.

In the UK, elastic (long-stretch) bandages are mainly used, whereas in Europe short-stretch bandages are preferred. Elastic bandages sustain compression for longer, whereas short-stretch bandages produce high 'venous' pumping pressures during exercise but lower resting pressures [14]. Multilayer bandaging has gained popularity owing to the high healing rate success reported in one study [15]. Unfortunately, all large ulcers were excluded and grafted in this study, and others have had difficulty in reproducing these results. Nevertheless, multilayer bandaging provides good conforming properties for a graduated distribution and sustainability of pressures.

Adequate training is essential for good results [16]. Incorrectly applied bandages can be harmful. Although compression therapy for the treatment of leg ulcers is in general performed with bandages, new medical elastic compression stockings were recently introduced for this treatment. A comparative study shows that this type of medical elastic compression stocking is more effective in daily practice than standard compression therapy with bandages [17].

Dermatological assessment. The condition of the ulcer and of the surrounding skin influences treatment outcome. If eczema is present, exudation and scratching will jeopardize the integrity of the surrounding skin. Consideration must be given to the underlying cause of the eczema which may be: (i) varicose; (ii) contact allergy; or (iii) contact irritant (e.g. caused by maceration from soaked dressings, see p. 47.44). A topical steroid is indicated to treat eczema, whereas emollients alone are sufficient for non-inflamed skin. Fragile oedematous skin needs careful application of compression bandages (but not necessarily less compression).

Cleansing and debridement. Management of the leg ulcer itself is important but should only be addressed once the patient's general health and venous hypertension have been considered. Cleansing of the ulcer should be kept simple [17,18]. Irrigation of the ulcer with warmed tap water or sterile saline is usually sufficient [19,20].

Any dressing technique should be clean and aimed at preventing cross-infection. Strict antisepsis is unnecessary. It is customary to remove slough, eschar and bacterial biofilms from the ulcer bed by debridement, as this improves wound healing [21]. Sharp debridement using scalpel, scissors or curette is most rapid and precise [22–23]. Autolytic or enzymatic debridement can be undertaken using moisture-donating dressings or protease preparations, respectively, but both are slow [24]. Debridement can also be achieved by topical negative pressure or vacuum-assisted closure (V.A.C.®) [25]. Maggots are used in some clinics for debridement but have never been compared with surgical debridement [26]. An ultrasound debriding instrument was very acceptable to patients and has provided some promising early results [27].



Fig. 47.29 A hydrocolloid dressing applied to an ulcer provides comfort and stimulus to healing. The centre of the dressing dissolves and contributes to odour and exudates on removal.

Dressings and topical therapies [28–30]. Dressings should keep the ulcers moist but not wet. Dressings should be simple, low adherent, inexpensive and safe. There is no evidence that any particular dressing or dressing type is more effective in healing venous leg ulcers. 'It's not what you do with the ulcer that is important, it is what you do with the leg' is a good axiom, reflecting the fact that the most important aspect of treatment is reversing the venous hypertension, not the choice of wound dressing.

Ideally, a dressing should be left undisturbed for as long as possible so the ulcer can get on with the job of healing. Changes of dressing only disrupt new fragile epithelium. Conversely, a wet, soaked dressing and bandage tends to produce maceration of surrounding skin and encourage infection. 'Strike-through' of exudate to the outside of a bandage is usually an indication for a dressing change.

First-line primary dressings include a knitted viscose primary dressing (e.g. N-A Dressing®) with a superimposed absorbent pad (secondary dressing). Tulle dressings impregnated with paraffin (e.g. Jelonet®) can increase maceration; medicated tulle dressings are not generally recommended unless infection is likely [31]. An absorptive dressing may be valuable in a highly exuding wound (e.g. foam, alginate or hydrofibre). Hydrocolloid dressings can be helpful in dry, sloughy wounds to reduce pain but are not recommended if there is much exudate (Fig. 47.29). In malodorous wounds foam, alginate, hydrocolloid and charcoal are recommended [9]. Zinc paste bandages (e.g. Steripaste®) can be applied directly to the wound base and to the intact skin from the base of toes to knee, with a covering compression bandage in one or two layers (Fig. 47.30). These dressings have been shown to increase the speed of ulcer healing in one controlled study where four-layer bandages were used as the comparator [32]. Patients can develop allergies after using a product for some time [33]. Patch testing should be considered if dermatitis develops or is difficult to control.



(a)



(b)

Fig. 47.30 Applying a past bandage to an ulcer, avoiding a tourniquet effect by frequent: (a) cutting; (b) folding.

Skin and substitutes. Three different types of transplants can be used in ulcer management; these are autologous, donor skin and allogeneic transplants. The autologous transplants consist of three main techniques, namely split-skin grafts, punch grafts and cultured autologous keratinocytes. Donor skin may be cadaver or pig skin. Allogeneic techniques involve a bilayered skin substitute, which consists of allogeneic keratinocytes and fibroblasts in a collagen gel. The disadvantage of this technique is that it is expensive and has shown only minor improvements in healing in certain subgroups [34].

Microbiology [35]. Chronic leg ulcers are usually colonized by microorganisms but whether this affects healing is debatable [36,37]. Routine wound swabs for bacteriology are unnecessary unless there is evidence of clinical infection such as: (i) surrounding inflammation; (ii) increased pain; (iii) heavy or purulent exudate; (iv) a rapid deterioration of the ulcer; or (v) fever. The identification of group A haemolytic *Streptococcus* should prompt use of a course of penicillin, but otherwise antibiotics should not be used too readily. The use of topical antibiotics is discouraged because of the risks of contact allergy and antibiotic resistance.



Fig. 47.31 Tracing around the margins of an ulcer to ensure the healing is occurring.

Pain relief. Most patients with venous ulcers suffer moderate to severe pain [33]. Pain can result in reduced mobility, particularly of the range of joint movement, leading to a poor calf muscle pump. Pain may also indicate other pathology such as arterial insufficiency, malignancy or infection. Analgesia is recommended if compression and elevation fail to resolve pain from a venous ulcer. Opioids may be necessary in some cases. Some deep pain is mediated by the autonomic nervous system and may be helped by amitriptyline, gabapentin or a guanethidine block [38,39]. Quinine is a useful therapy for night cramp [40].

Measurement [41]. It is unwise to recommend any agent for the healing of ulcers that has not been subjected to a properly controlled trial. The only measurement that matters is the time taken for total healing of a large number of ulcers, which would, if possible, be stratified by initial ulcer size. The size influences the time taken for total healing to occur [42]. Large ulcers generally take significantly longer to heal than small ones. The healing rate is a poor measure; however, it is of value in monitoring the progress of individual ulcers (Fig. 47.31).

Systemic therapy. Systemic antibiotics have not been shown to improve the healing rates of venous ulcers and should be reserved for ulcers with clear evidence of infection [43].

The effectiveness of pentoxifylline in healing venous leg ulcers may be because of its fibrinolytic action and a reduction in leukocyte adhesion. Although randomized trials have reported both positive and negative results, a systematic review was positive [44]. A dose of 800 mg three times daily may be better than 400 mg three times daily as conventionally used.

An increased rate of venous ulcer healing with the use of oral enteric-coated aspirin (300 mg) daily was reported in one randomized trial [45]. Mixtures of flavonoid drugs (e.g. oxerutins) are licensed for use in venous disease. Daflon 500 accelerated healing of small ulcers in a randomized trial [46].

Stanozolol, an androgenic steroid with fibrinolytic properties, is helpful in improving lipodermatosclerosis [47] but no studies have demonstrated improved ulcer healing.

Complications. Cellulitis (erysipelas) frequently complicates leg ulcers and in deep, long-standing ulcers osteomyelitis has to be considered [48]. Malignant transformation in a non-healing ulcer is significant, with a relative risk of 5.80 in one study [49].

References

1 Browse NL, Burnand KG, Irvine AT, Wilson NM. *Diseases of the Veins*, 2nd edn. London: Arnold, 1999.
2 Ryan TJ, ed. *The Management of Leg Ulcers*, 2nd edn. Oxford: Oxford University Press, 1987.
3 Callam MJ, Ruckley CV, Harper DR, Dale JJ. Chronic ulceration of the leg: extent and provision of care. *BMJ* 1985; **290**: 1855–6.
4 Freak L, Simon D, Kinsella A *et al*. Leg ulcer care: an audit of cost effectiveness. *Health Trends* 1995; **27**: 133–6.
5 Mathus-Vliegen EM. Old age, malnutrition and pressure sores; an ill-fated alliance. *J Gerontol A Biol Sci Med Sci* 2004; **59**: 355–60.
6 Freiman A, Bird G, Metelitsa AL *et al*. Cutaneous effects of smoking. *J Cutan Med Surg* 2004; **8**: 415–23.
7 Benveniste K, Thut P. The effect of chronic alcoholism on wound healing. *Proc Soc Exp Biol Med* 1981; **166**: 568–75.
8 Hess CT, Trent JT. Incorporating laboratory values in chronic wound management. *Adv Skin Wound Care* 2004; **17**: 378–86.
9 Etufugh CN, Philips TJ. Venous ulcers. *Clin Dermatol* 2007; **25**: 121–30.
10 Fletcher A, Cullum N, Sheldon TA. A systematic review of compression treatment for venous leg ulcers. *BMJ* 1997; **325**: 576–80.
11 Cullum N, Fletcher A, Nelson E, Sheldon T. Compression for venous leg ulcers. *Cochrane Database Syst Rev* 2001; **2**: CD000265.
12 Van Gent WB, Hop WC, van Praag MC *et al*. Conservative versus surgical treatment of venous leg ulcers: a prospective, randomized, multicenter trial. *J Vasc Surg* 2006; **44**: 563–71.
13 Morrell CJ, Walters SJ, Dixon S *et al*. Cost effectiveness of community leg ulcer clinics: randomised controlled trial. *BMJ* 1998; **316**: 1487–91.
14 Thomas S. Bandages and bandaging: the science behind the art. *Care Sci Pract* 1990; **8**: 61–2.
15 Blair SD, Wright DDT, Backhouse CM *et al*. Sustained compression and healing of chronic venous ulcers. *BMJ* 1988; **297**: 1159–61.
16 Nelson EA, Ruckley CV, Barbenel JC. Improvements in bandaging technique following training. *J Wound Care* 1995; **4**: 181–4.
17 Jünger M, Wollina U, Kohnen R, Rabe E. Efficacy and tolerability of an ulcer compression stocking for the therapy of chronic venous ulcer compared with a below-knee compression bandage: results from a prospective, randomized, multicentre trial. *Curr Med Res Opin* 2004; **20**: 1613–23.
18 Lucaroth ME, Morgan AP, Leaper DT. The effect of antiseptics and the moist wound environment on ulcer healing: an experimental and biochemical study. *Phlebology* 1990; **5**: 173–9.
19 Svedman P. Irrigation treatment of leg ulcers. *Lancet* 1983; **ii**: 532–4.
20 Angeras HM, Brandberg A, Falk A, Seeman T. Comparison between sterile saline and tap water for the cleansing of acute soft tissue wounds. *Eur J Surg* 1992; **158**: 347–50.
21 Bradley M, Cullum N, Sheldon T. The debridement of chronic wounds: a systematic review. *Health Technol Assess* 1999; **3**: 1–78.
22 Steed DL. Debridement. *Am J Surg* 2004; **187**: S71–4.
23 Williams D, Enoch S, Miller D *et al*. Effect of sharp debridement using curette on recalcitrant venous ulcers: a concurrently controlled, prospective cohort study. *Wound Rep Reg* 2005; **13**: 131–7.
24 Konig M, Vanscheidt W, Augustin M *et al*. Enzymatic versus autolytic debridement of chronic leg ulcers: a prospective randomized trial. *J Wound Care* 2005; **14**: 320–3
25 Vuerstaek JD, Vainas T, Wuite J *et al*. State-of-the-art treatment of chronic leg ulcers: a randomized controlled trial comparing vacuum-assisted closure (V.A.C.) with modern wound dressings. *J Vasc Surg* 2006; **44**: 1029–37.
26 Sherman RA, Tran JM, Sullivan R. Maggot therapy for venous stasis ulcers. *Arch Dermatol* 1996; **132**: 254–6.
27 Tan J, Abisi S, Smith A, Burnand KG. A painless method of ultrasonically assisted debridement of chronic leg ulcers: a pilot study. *Eur J Vasc Endovasc Surg* 2007; **33**: 234–8.
28 Thomas S. *Wound Management and Dressings*. London: Pharmaceutical Press, 1990.
29 Fonder MA, Lazarus GS, Cowan DA *et al*. Treating the chronic wound: a practical approach to the care of non-healing wounds and wound care dressings. *J Am Acad Dermatol* 2008; **58**: 185–206.
30 Palfreyman S, Nelson EA, Michaels JA. Dressings for venous leg ulcers: systematic review and meta-analysis. *BMJ* 2007; **335**: 244.
31 British Medical Association and Royal Pharmaceutical Society of Great Britain. *British National Formulary* 2002; **44**: 745–57.
32 Mayer W, Jochmann W, Partsch H. Varicose ulcer: healing in conservative therapy. A prospective study. *Wien Med Wochenschr* 1994; **144**: 250–2.
33 Siegel DM. Contact sensitivity and recalcitrant wounds. *Ostomy Wound Manage* 2000; **46**: S65–74.
34 Falanga V, Margolis D, Alvarez O *et al*. Rapid healing of venous ulcers and lack of clinical rejection with an allogenic cultured human skin equivalent. *Arch Dermatol* 1998; **134**: 293–300.
35 O'Meara S, Al-Kurdi D, Ovington L. Antibiotics and antiseptics for venous leg ulcers. *Cochrane Database Syst Rev* 2008; **1**: CD003557.
36 Skene AI, Smith JM, Dore CJ *et al*. Venous leg ulcers: a prognostic index to predict time to healing. *BMJ* 1992; **305**: 1119–21.
37 Trengove NJ, Stacey MC, McGechie DF *et al*. Qualitative bacteriology and leg ulcer healing. *J Wound Care* 1996; **5**: 277–80.
38 Hofman D, Ryan TJ, Arnold F *et al*. Pain in venous leg ulcers. *J Wound Care* 1997; **6**: 222–4.
39 Hannington-Kiff JG. Pharmacological target blocks in painful dystrophic limbs. In: Wall PD, Melzack R, eds. *Textbook of Pain*. Edinburgh: Churchill Livingstone, 1989: 754–66.
40 Young JB, Javid M, George J. Rest cramps in the elderly. *J R Coll Phys (Lond)* 1989; **23**: 103–5.
41 Erikssen G, Eklund A, Liden S *et al*. Comparison of different treatments of venous leg ulcers: a controlled study using stereophotogrammetry. *Curr Ther Res* 1984; **35**: 678–84.
42 Stacey MC, Burnand KG, Layer FT *et al*. Measurement of the healing of venous ulcers. *Aust N Z J Surg* 1991; **61**: 844–8.
43 Alinovi A, Bassissi P, Pini M. Systemic administration of antibiotics in the management of venous ulcers: a randomized clinical trial. *J Am Acad Dermatol* 1986; **15**: 186–91.
44 Jull A, Arroll B, Parag V, Waters J. Pentoxifylline for treating venous leg ulcer. *Cochrane Database Syst Rev* 2007; **3**: CD001733.
45 Layton AM, Ibbotson SH, Davies JA *et al*. Randomised trial of oval aspirin for chronic venous leg ulcers. *Lancet* 1994; **344**: 164–5.
46 Guilhou JJ, Dereure O, Marzin L *et al*. Efficacy of Daflon 500 mg in venous leg ulcer healing: a double blind randomized controlled versus placebo trial in 107 patients. *Angiology* 1997; **48**: 77–85.
47 Burnand K, Clemenson S, Morland M *et al*. Venous lipodermatosclerosis: treatment by fibrinolytic enhancement and elastic compression. *BMJ* 1980; **280**: 7–11.
48 Fernandes Abbade LP, Lastoria S. Venous ulcer: epidemiology, physiopathology, diagnosis and treatment. *Int J Dermatol* 2005; **44**: 449–56.
49 Baldursson B, Sigurgeirsson B, Lindelof B. Venous leg ulcers and squamous cell carcinoma: a large-scale epidemiological study. *Br J Dermatol* 1995; **133**: 571–4.

Recurrent ulcers and their prevention

Once their ulcer is healed, patients should be transferred from a bandage regimen to compression hosiery [1,2].

Many recurrences are the result of poor follow-up and inadequate or worn-out elastic stockings. Indeed, the 50% overall recurrence rate over 5–7 years has been shown to be higher in those prescribed stockings and is an indication of poor supervision [3]. Some recurrences are the result of superimposed arterial disease causing tissue ischaemia and skin necrosis. Many ulcers are precipitated by minor trauma, in which case a foam or felt pad should be worn over or under the stocking over vulnerable areas. Despite this, a considerable proportion of well-treated, formerly ulcerated limbs develop recurrences from time to time, often for no obvious



(a) (b)

Fig. 47.32 A large ulcer (a) before and (b) after skin grafting.

reason. These recurrences are more likely in post-thrombotic limbs. Obsessional attention to detail in stocking use, avoidance of minor trauma and early vigorous treatment of any breakdown should reduce the period of re-ulceration to a minimum.

Surgical ligation of the saphenous veins and of incompetent communicating veins appears no better than stanozolol and stockings in preventing ulcer breakdown. Ablation of venous reflux by conventional surgery or endovenous treatment (plus compression hosiery) can reduce the risk of ulcer recurrence [4].

References

1 Anon. Compression hosiery for stasis disorders. *Drug Ther Bull* 1982; **20**: 81–4.

2 Thomas S. Bandages and bandaging: the science behind the art. *Care Sci Pract* 1990; **8**: 61–2.

3 Browse NL, Burnand KG, Irvine AT *et al.*, eds. *Diseases of the Veins: Pathology, Diagnosis and Treatment*, 2nd edn. London: Arnold, 1999.

4 Neumann HAM Compression therapy with medical elastic stockings for venous disease. *Dermatol Surg* 1998; **24**: 765–70.

Surgical treatment [1]

Surgical removal of the superficial incompetent varicose veins in patients with normal deep veins does not improve ulcer healing but significantly reduces the incidence of ulcer recurrence (Effects of Surgery and Compression on Healing and Recurrence (ESCHAR) trial) [2]. Recurrence rates of 30–50% after different surgical manoeuvres have been reported within 5 years [3–5]. Ligation and stripping of the saphenous veins and compressive sclerotherapy are the procedures most frequently undertaken, although with endovenous treatments the same results should be obtained. Complete extirpation of the communicating veins 'feeding' the ulcer is a logical approach but has failed to show any benefit in the only controlled trial that has been reported [6].

It would appear that surgical eradication of superficial incompetent veins is effective in preventing recurrence in patients without post-thrombotic damage but has little place in preventing recurrent ulceration in patients with damage to the deep venous system [7]. The newer procedures of deep-vein bypass, valvuloplasty and brachial valve transplant have still not been subjected to rigorous assessment by independent centres concerned with treating large numbers of patients with post-thrombotic limbs and venous ulcers. The value of these techniques in preventing ulcer recurrence in post-thrombotic limbs is therefore unknown. Elastic stockings must be worn for life and renewed at 6-monthly intervals if recurrence is to be prevented, and even these are not totally effective [8].

Shave therapy, a method of excision of ulcer and surrounding lipodermatosclerosis followed by meshed split-skin graft, healed 88% of ulcers in 18 patients [9]. The long-term results of this therapy show that 50% of the ulcers remain healed at 5 years [10].

Skin grafting on the lower legs is a means of considerably reducing the time taken for the ulcers to heal. It is usually performed on in-patients but can be carried out as an outpatient ambulatory procedure [11]. Pinch grafting provides small quantities of dermis as well as epidermis but leaves unsightly donor sites; large ulcers usually require split-skin grafts, which must be placed on surgically debrided beds. The application of mesh grafts has proved very effective when combined with ulcer excision (Fig. 47.32) [12,13]. Recurrence rates depend on patient selection. Those with many underlying medical or social problems are likely to have

ulcer recurrence within a few weeks or months of grafting. Many studies of skin grown *in vitro* have indicated that keratinocytes will stimulate healing with the repopulation of host tissues even though the grafts may not themselves survive. Mechanisms underlying growth stimulation by cytokines have led to a growth-factor industry [12]. No cytokine, however, can be relied upon to promote healing unless most of the above-mentioned management factors are first attended to. If the underlying causes of ulceration are well managed, healing rates are excellent and added cytokines are not necessary [14].

Surgical options to correct venous reflux, such as endovenous procedures (foam sclerotherapy and endovenous laser), perforator interruption (SEPS), deep venous reconstruction and ligation and stripping of incompetent superficial veins, have not been shown to improve ulcer healing [15,16]. A randomized, controlled trial demonstrated that compression therapy alone did not differ from surgical correction of superficial venous reflux in combination with compression therapy in healing of venous ulcers [2]. Correction of confirmed superficial vein incompetence should be considered once healing is complete.

References

1 Tibbs D. *Varicose Veins and Related Disorders*, 2nd edn. Oxford: Butterworth–Heinemann, 1997.
2 Gohel MS, Barwell JR, Taylor M *et al*. Long term results of compression therapy alone versus compression plus surgery in chronic venous ulceration (ESCHAR): randomised controlled trial. *BMJ* 2007; **335**: 83–8.
3 Fegan WG. *Varicose Veins and Compression Sclerotherapy*. London: Heinemann, 1971.
4 Lofgren KA, Lauvstad WA, Bonnemaison MFE. Surgical treatment of large stasis ulcer: review of 129 cases. *Mayo Clin Proc* 1965; **40**: 560–3.
5 Silver D, Gileysteen JJ, Rhodes GR *et al*. Surgical treatment of refractory post-phlebitic ulcer. *Arch Surg* 1971; **103**: 554–60.
6 Padberg FT Jr. Surgical intervention in venous ulceration. *Cardiovasc Surg* 1999; **7**: 83–90.
7 Burnand K, Thomas ML, O'Donnell T *et al*. Relation between post-phlebitic changes in the deep veins and results of surgical treatment of venous ulcers. *Lancet* 1976; **i**: 936–8.
8 Anon. Compression hosiery for stasis disorders. *Drug Ther Bull* 1982; **20**: 81–4.
9 Schmeller W, Gaber Y, Gehl HB. Shave therapy is a simple effective treatment of persistent venous ulcers. *J Am Acad Dermatol* 1998; **39**: 232–8.
10 Abisi S, Tan J, Burnand KG. Excision and meshed skin grafting for leg ulcers resistant to compression therapy. *Br J Surg* 2007; **94**: 194–7
11 Dahl MGC. Skin grafting on the lower leg as an outpatient ambulatory procedure. *Br J Dermatol* 1985; **113** (Suppl. 29): 14.
12 Harrison PV. Split skin grafting of varicose leg ulcers: a survey and the importance of assessment of risk factors in predicting outcome from the procedure. *Clin Exp Dermatol* 1987; **13**: 4–6.
13 Phillips TJ, Bhawan J, Leigh IM *et al*. Cultured epidermal autografts and allografts: a study of differentiation and allograft survival. *J Am Acad Dermatol* 1990; **23**: 189–98.
14 Nanninga PB, Mekkes JR, De Vries HJC *et al*. Grafting techniques. In: Westerhoff W, ed. *Leg Ulcers: Diagnosis and Management*. Amsterdam: Elsevier, 1993: 335–55.
15 Welch HJ. Surgical options for the treatment of venous ulcers. *Vasc Endovasc Surg* 2004; **38**: 195–202.
16 Van Gent WB, Hop WC, Van Praag *et al*. Conservative versus surgical treatment of venous leg ulcers: a prospective, randomized, multicentre trial. *J Vasc Surg* 2006; **44**: 563–71.

Arterial ulceration

Death of the skin automatically follows occlusion of its arterial blood supply unless this occurs slowly enough to allow a collateral circulation to be established. Arterial or arteriolar occlusion, if present, also complicates the treatment and prognosis of ulcers that are primarily venous in origin. A study of 600 patients with leg ulcers in the Lothian and Forth Valley, Scotland, revealed evidence of arterial disease in slightly less than one-quarter of those affected [1].

Atheroma of the abdominal and limb vessels is the single most common cause of ischaemic ulceration likely to be seen by the dermatologist involved in the care of patients with leg ulcers. Many other pathological states may, however, cause arterial occlusion, and not all can be defined with accuracy on clinical grounds. A useful empirical approach to the diagnosis of clinically ischaemic ulcers is to consider the causes in three main groups:

1 Extramural 'strangulation'
2 Mural thickening or accretion
3 Intramural restriction of blood flow.

There is often considerable overlap, and the exact pathology cannot always be well defined.

Extramural causes. Scar tissue and radiodermatitis cause a fibrotic strangulation of the arterioles and may give rise to small but persistent ulcers. Ulceration occurs in a number of diseases associated with dermal sclerosis, including scleroderma and progeria (Werner's syndrome; Chapter 15). Compression by tumours may also obstruct arterial flow.

Mural causes. Ulceration depends on the speed with which changes take place in the vessel wall. In vasculitis this is often sudden, but in hypertension it is slower and is preceded by pain, erythema and tenderness. In atherosclerosis the accretion of intimal plaques may proceed with a reduced flow until thrombosis, embolism or infection precipitate complete closure.

Intramural causes. Microvascular occlusion caused by changes in blood viscosity and clotting mechanisms is discussed in Chapter 49.

Clinical features [2]. The general symptoms and signs exhibited by the patient with advancing ischaemic disease of the limbs have already been described (p. 47.1). Arterial ulcers frequently arise in the pretibial area, the foot or on the toes, whereas venous ulcers favour the gaiter region.

Severe pain is usual, but is not a reliable discriminator from venous ulceration, which can also be very painful. Pain is as marked in small ischaemic ulcers as in large ulcers. The edges of the ulcers are sharply defined and the ulcer itself is often punched out.

There is often no pigmentation or lipodermatosclerosis in the surrounding skin, unlike the changes around venous ulcers, but the two can coexist. Usually, exudation from arterial ulcers is minimal. The base is often pale and covered with a slough which may have bare tendons in its base (Fig. 47.33). When smaller arteries and arterioles are occluded, the ulceration may have an irregular outline with strands of infarction extending along a vascular pattern in the skin. The condition is often indolent, healing only when the blood supply is improved and the ulcer base is excised and grafted.



Fig. 47.33 An ischaemic ulcer with slough and exposed tendons.

Treatment. Legs with severe arterial disease (APBI < 0.5) should be considered for immediate revascularization after assessment by arterial duplex ultrasound or angiography. Those with moderate arterial compromise (APBI > 0.5 but < 0.85) should be treated with modified compression, for example short stretch bandages that convey low resting pressures. Revascularization should be considered in ulcers that do not heal [3,4]. Limb salvage can be achieved in most patients but those failing the interventions described above, or who are unsuitable for revascularization, may require amputation. There is weak evidence that intermittent pneumatic compression is of benefit [5]. There is insufficient evidence to determine whether the choice of a topical agent or dressing affects the healing of arterial leg ulcers [6].

References

1 Callam MJ, Harper DR, Dale JJ *et al*. Arterial disease in chronic leg ulceration: an underestimated hazard? Lothian and Forth Valley leg ulcer study. *BMJ* 1987; **294**: 929–31.

2 Browse NL. Diseases of the heart and blood vessels: ischaemia of the lower limbs. *BMJ* 1996; **ii**: 157–9.

3 Humphreys ML, Stewart AH, Gohel MS *et al*. Management of mixed arterial and venous ulcers *Br J Surg* 2007; **94**: 1104–7.

4 Hafner J, Schaad I, Schneider E *et al*. Leg ulcers in peripheral arterial disease (arterial leg ulcers): impaired wound healing above the threshold of chronic critical limb ischemia. *J Am Acad Dermatol* 2000; **43**: 1001–8.

5 Kavros SJ, Delis KT, Turner NS *et al*. Improving limb salvage in critical ischaemia with intermittent pneumatic compression: a controlled study with 18-month follow-up. *J Vasc Surg* 2008; **47**: 543–9.

6 Nelson EA, Bradley MD. Dressings and topical agents for arterial leg ulcers. *Cochrane Database Sys Rev* 2007; CD001836.



Fig. 47.34 A Martorell ulcer. High blood pressure causes vessel wall hypertrophy or vasospasm. Pain and ulceration with a livid reticulate edge but no lipodermatosclerosis is diagnostic. It is usually more proximal than a venous ulcer.

Hypertensive ulcer

Synonym
- Martorell's ulcer

Hypertensive leg ulcers are a unique form of lower extremity ischaemic leg ulcer. First described by Martorell, and by Hines and Farber in the 1940s [1,2], these ulcers are defined by pain disproportionate to the size of the ulcer, specific location on the lower extremity, female-to-male predominance, association with long-standing, often poorly controlled, hypertension, and healing response to specific antihypertensive agents [3].

Hypertensive ulceration tends to be bilateral and produces superficial ulceration yet the peripheral pulses are always present, distinguishing the condition from atherosclerosis. It is often initiated by trauma, and the ischaemia may be a consequence of a failure to meet the demands for repair. Whether it truly represents a specific disease has been questioned [4].

On biopsy there is increased thickening of the arteriolar walls with luminal narrowing by subendothelial hyalin degeneration. Smooth-muscle hyperplasia is most marked in the media and is most easily recognized by an increase in the number of smooth-muscle nuclei. It is later replaced by collagen fibres.

The ulcer is initially preceded by a small macular cyanotic lesion present on the anterior external aspect of the leg at a point between the middle and lower thirds of the limb. It is usually extremely painful, and this may be alleviated by holding the leg in the dependent position. The livid edge is a characteristic feature (Fig. 47.34).

The blood pressure should be controlled, and the leg should be placed in a position to prevent oedema but not so high as to promote further ischaemia. A firm non-elastic (short stretch) support bandage, without compression, is the most helpful treatment. At this site on the leg, the blood supply is difficult to re-establish, and several weeks may pass before the ischaemic necrotic tissue separates and granulation tissue begins to form. Smoking should be stopped and β-blockers avoided. Excision of the ulcerated area with grafting has been advised.



Fig. 47.35 Multiple ulcers with unusual distribution associated with prolidase deficiency.

References

1 Martorell F. Hypertensive ulcer of the leg. *Angiology* 1950; **1**: 133–40.
2 Alberti JMZ. Hypertensive ulcers: Martorell's ulcer. *Phlebology* 1988; **3**: 139–42.
3 Graves JW, Morris JC, Sheps SG. Martorell's hypertensive leg ulcer: case report and concise review of the literature. *J Hum Hypertens* 2001; **15**: 279–83.
4 Leu HJ. Hypertensive ischaemic leg ulcer (Martorell's ulcer): a specific disease entity? *Int Angiol* 1992; **11**: 132–6.

Other causes of leg ulceration

Prolidase deficiency

Prolidase deficiency is transmitted as an autosomal recessive condition and has a European incidence of less than 5 : 10 000 people [1]. This rare disease is caused by a defect in the prolidase (PEPD, iminodipeptidase) gene on chromosome 19cen-q13.11. Prolidase is one of the enzymes that degrade collagen to iminodipeptides, it cleaves dipeptides with hydroxyproline or proline at the C-terminus [2]. Decreased activity of prolidase causes excretion of large amounts of proline and hydroxyproline, bound to amino acids as iminodipeptides in the urine, resulting in a depletion of the total pool of proline [3].

Prolidase deficiency is a multisystem disorder and the skin is its primary target organ. Clinical symptoms commence before the age of 12 years [3]. Ninety per cent of patients have dermatological features. Recurrent, multiple ulcers of the lower extremities are seen in over 50% of patients (Fig. 47.35). The development of a squamous cell carcinoma in the ulcer is an uncommon complication. Fragility of the skin, resulting in breakdown at the site of injury, is often preceded by purpura or bruising. Fine scarring, telangiectasia and eczematous lesions may be a feature. The facies are characteristic, consisting of hypertelorism with a saddle nose, and patients are mentally retarded. Other associations, not present in all cases, are dental caries, splenomegaly, hyperextensibility of ligaments, osteoporosis, respiratory infections, corneal opacities, amblyopia and optic atrophy. The skin may have a doughy consistency as in other collagen diseases [4].

The diagnosis is ascertained by iminodipeptiduria greater than 5 mmol/24 h [5]. In the blood a decreased prolidase activity is found. Laboratory abnormalities associated with prolidase deficiency consist of thrombocytopenia, hypergammaglobulinaemia and iron-deficiency anaemia [2]. Skin biopsy is almost normal in prolidase deficiency, although fragmentation of collagen fibres with impaired aggregation or a decrease in the size of collagen fibres may be found.

A characteristic feature of the disorder is absolute resistance to all forms of treatment, including rejection of skin grafts. Using topical antibiotics may control infections, and developing infections should be treated with oral or intravenous antibiotics [2]. Because co-factors of prolidase are ascorbic acid and manganese, these have been recommended therapies, as has diphenylhydantoin [6]. Japanese investigators recommend an ointment containing 5% glycine and 5% proline [7], and this was confirmed to be effective by Jemec and Moe [6]. Apheresis exchange was successful in two patients [8] and the combination of topical and systemic growth hormone resulted in transient healed recalcitrant leg ulcers in a 13-year-old boy [9].

References

1 Viglio S, Annovazzi L, Conti B *et al*. The role of emerging techniques in the investigation of prolidase deficiency: from diagnosis to the development of a possible therapeutical approach. *J Chromatogr B* 2006; **832**: 1–8.
2 Trent J, Kirsner RS. Leg ulcers secondary to prolidase deficiency. *Adv Skin Wound Care* 2004; **17**: 468–72.
3 Kokturk A, Kaya TI, Ikizoglu G, Koca A. Prolidase deficiency. *Int J Dermatol* 2002; **41**: 46–8.
4 Milligan A, Graham-Brown RAC, Burns DA *et al*. Prolidase deficiency: a case report and literature review. *Br J Dermatol* 1989; **121**: 405–9.
5 Buist NRM, Strandholm JJ, Bellinger JF *et al*. Further studies on a patient with iminodipeptiduria: a probable case of prolidase deficiency. *Metabolism* 1972; **21**: 1113–23.
6 Jemec, GBE, Moe ATT. Topical treatment of skin ulcers in prolidase deficiency. *Pediatr Dermatol* 1996; **13**: 58–60.
7 Arata J, Hatakenaka K, Oono T. Effect of topical application of glycine and proline on recalcitrant leg ulcers of prolidase deficiency. *Arch Dermatol* 1986; **122**: 626–7.
8 Lupi A, Casado B, Soli M *et al*. Therapeutic apheresis exchange in two patients with prolidase deficiency. *Br J Dermatol* 2002; **147**: 1237–40.
9 Monafo V, Marseglia GL, Maghnie M *et al*. Transient beneficial effect of GH replacement therapy and topical GH application on skin ulcers in a boy with prolidase deficiency. *Pediatr Dermatol* 2000; **17**: 227–30.

Hydroxycarbamide (hydroxyurea) therapy

Hydroxycarbamide (formerly hydroxyurea) is a chemotherapeutic agent that acts during cellular replication and inhibits DNA synthesis without affecting RNA synthesis [1]. It is currently the drug of choice for treatment of chronic myelo- and certain lymphoproliferative disorders, for example chronic myeloid leukaemia, chronic lymphocytic leukaemia, polycythaemia vera and essential thrombocythaemia [2]. It is also used in the treatment of sickle cell anaemia. Dermatological adverse effects have been well documented. In a study by Vassallo *et al*., all 158 patients using

hydroxycarbamide for the treatment of chronic myeloid leukaemia suffered cutaneous xerosis and mild stomatitis [3]. Other adverse effects include hyperpigmentation, brown nail discoloration, acral erythema, scaling of the face, hands and feet, dermatomyositis-like eruptions, partial alopecia, atrophy of the skin and subcutaneous tissue, and leg ulcers.

In a prospective study, leg ulceration was reported to occur in 9% of patients taking hydroxycarbamide [4]. In three-quarters of patients, the ulcers are located on or near the malleoli [2]. The ulcers usually develop after at least 1 year of treatment. The lesions are generally very painful and resemble atrophie blanche. Hydroxycarbamide therapy is associated with leg ulceration in a dose-dependent fashion; with higher doses, wound size increases and healing is usually observed after withdrawal of hydroxycarbamide.

Several pathogenetic mechanisms have been postulated, but currently it is unclear how hydroxycarbamide induces leg ulcers. Histological examination shows non-specific changes [5].

Differential diagnosis includes cutaneous leukocytoclastic vasculitis, cryoglobulinaemia and pyoderma gangrenosum, and these diseases should be ruled out.

After withdrawal of hydroxycarbamide, 85% of ulcers spontaneously heal in 1–9 months [2]. In most other patients, a reduction in ulcer size is observed. A split skin graft, preceded by surgical debridement, may be performed in cases without spontaneous resolution. Many patients will develop new ulcers after restarting hydroxycarbamide therapy, so this should be avoided if an alternate agent can be prescribed.

References

1 Sirieix M-E, Debure C, Baudot N *et al*. Leg ulcers and hydroxyurea. *Arch Dermatol* 1999; **135**: 818–20.

2 Bader U, Banyai M, Burg G, Hafner J. Leg ulcers in patients with myeloproliferative disorders: disease- or treatment-related? *Dermatology* 2000; **200**: 45–8.

3 Vassallo C, Passamonti F, Merante S *et al*. Mucocutaneous changes during long-term therapy with hydroxyurea in chronic myeloid leukemia. *Clin Exp Dermatol* 2001; **26**: 141–8.

4 Najean Y, Rain JD. Treatment of polycythemia vera: the use of hydroxyurea and pipobroman in 292 patients under the age of 65 years. *Blood* 1997; **90**: 3370–7.

5 Best PJ, Daoud MS, Pittelkow MR, Petitt RM. Hydroxyurea-induced leg ulceration in 14 patients. *Ann Intern Med* 1998; **128**: 29–32.

Vasculitis/vasculopathy

Most acute forms of vasculitis, and some subacute and chronic forms, are likely to cause ulceration. Vasculitic lesions are usually, but not always, multiple. Palpable purpura is characteristic but vasculitis may be polymorphous, even pustular.

Rheumatoid disease [1]. Leg ulceration in rheumatoid arthritis is common and the causes can be multifactorial. Poor joint movement impairs the calf muscle pump and immobility increases the risk of DVT. True 'rheumatoid ulcers' occur as a manifestation of rheumatoid arteritis. Ulcers are often situated in the gaiter region and have a sloughy base with poor granulation. The absence of surrounding lipodermatosclerosis or of other signs of venous disease, the presence of a positive rheumatoid factor (particularly if at high titre) and demonstration of normal Doppler pressures and venous duplex studies suggest that the ulcer is truly 'rheumatoid'. Biopsy may be helpful but is not always confirmatory and the site may not heal. Ulceration of rheumatoid nodules is uncommon except at pressure sites in bedridden patients. Thinned skin because of long-term corticosteroid treatment, and the use of methotrexate, both increase the risk of ulceration. Healing can be very impaired, particularly in the presence of muscle atrophy, immobility and oedema but patients should be treated with immunosuppression to control the vasculitic component.

Other autoimmune disease. Leg ulceration in patients with lupus erythematosus is well recognized [2]. In Felty's syndrome and Still's disease, multiple painful ulcers occur on the legs and feet and are difficult to heal. Ulcers also occur in polyostotic fibrous dysplasia (Jaffe–Lichtenstein disease), in which a diffuse mesenchymal abnormality is present. Ulceration occurs over large areas of subcutaneous or muscular calcinosis, especially around the knee.

Sarcoidosis. Sarcoidosis can rarely result in leg ulceration due to granulomatous vasculitis [3].

Livedo reticularis. Livedo reticularis, a fixed but broken pattern of mottling, may result from vasculitis but also occurs with intravascular thrombosis caused by cryoproteinaemias [4], antiphospholipid syndrome and Sneddon's syndrome (Chapter 49).

Livedoid vasculopathy (livedo vasculitis). This condition is a more specific form of occlusive vasculopathy limited to the gaiter skin and often extending onto the dorsum of the foot. Ulcers are small, painful and heal with ivory-white scars (atrophie blanche). The mechanism appears to be more to do with hyalinization and thrombosis of the microvasculature with scarce inflammatory infiltrate unlike a leukocytoclastic vasculitis; therefore immunosuppression treatment is not so effective and consideration needs to be given to hypercoagulable states and their treatment [5]. Livedo with summer ulceration is a variant of the same condition (Chapter 49).

Cutaneous polyarteritis nodosa may rarely present with ulcerating atrophie blanche. Associated sensory loss (mononeuritis multiplex) and medium vessel vasculitis may be the only positive findings [6].

Treatment of leg ulceration secondary to vasculitis or vasculopathy involves control of any underlying condition combined with compression, as gravitational forces largely determine the localization of ulceration to the gaiter region.

References

1 Allison JH, Bettley FR. Rheumatoid arthritis with chronic leg ulceration. *Lancet* 1957; **i**: 288–90.

2 Goslen JB. Autoimmune ulceration of the leg. *Clin Dermatol* 1990; **8**: 92–117.

3 Poonawalla T, Colome-Grimmer MI, Kelly B. Ulcerative sarcoidosis in the legs with granulomatous vasculitis. *Clin Exp Dermatol* 2008; **33**: 282–6.

4 Williamson AE, Cone LA, Huard GS. Spontaneous necrosis of the skin associated with cryofibrinogenaemia, cryoglobulinaemia and homocysteinaemia. *Ann Vasc Surg* 1996; **10**: 365–9.

5 Hairston BR, Davis MD, Pittelkow MR, Ahmed I. Livedoid vasculopathy: further evidence for procoagulant pathogenesis. *Arch Dermatol* 2006; **142**: 1413–8.

6 Mimouni D, Ng PP, Rencic A *et al*. Cutaneous polyarteritis nodosa in patients presenting with atrophie blanche. *Br J Dermatol* 2003; **148**: 789–94.



Fig. 47.36 Sickle cell ulcer.



Fig. 47.37 'Steroid ulcer' with totally suppressed granulation tissue.

Haematological disorders

Indolent non-healing ulcers on the leg are a feature of sickle cell anaemia (Fig. 47.36), hereditary spherocytosis and other haemolytic anaemias [1]. Sickle cell ulcers were reported in 2.5% of over 2000 patients with sickle cell anaemia aged 10 or over and were more common in patients with sickle cell anaemia and thalassaemia genotypes [2]. There is a high incidence of venous reflux in sickle cell disease, indicating the need for compression therapy as well as treatment for the sickle cell anaemia itself [3]. Other haemolytic anaemias also predispose to leg ulceration [4].

Myeloproliferative disorders may contribute to leg ulceration if cell size compromises capillary perfusion or if thrombosis develops, but it can be difficult to distinguish between disease-related and treatment-related (e.g. hydroxycarbamide) ulceration.

References

1 Pascher F, Keen R. Ulcers of the leg in Cooley's anemia. *N Engl J Med* 1957; **256**: 1220–2.
2 Koshy M, Entsuah R, Koranda A *et al*. Leg ulcers in patients with sickle cell disease. *Blood* 1989; **74**: 1403–8.
3 Clare A, Fitzhenley M, Harris J *et al*. Chronic leg ulceration in homozygous sickle cell disease: the role of venous incompetence. *Br J Haematol* 2002; **119**: 567–71.
4 Sawhney H, Weedon J, Gillette P *et al*. Predilection of haemolytic anaemia-associated leg ulcers for the medial malleolus. *Vasa* 2002; **31**: 191–3.

'Steroid ulcers'

Intralesional steroid injections, especially if made in areas with an already impoverished blood supply, may cause an indolent ulcer with a characteristic greyish slough (Fig. 47.37) [1]. This condition is most commonly seen when strong topical corticosteroids are applied to venous or other ulcers of the lower leg and ankle. Long-term use of potent topical steroids on the shins can also lead to poor wound healing after traumatic injury.

Reference

1 Bjornberg A, Hellgren L. Necrosis in leg ulcers: probable role of fluocinolone acetonide. *Arch Dermatol* 1965; **92**: 52–3.



Fig. 47.38 Meleny's spreading gangrene.

Infection

Infection may lead to ulceration, which is often slow to heal because of associated oedema, cellulitis, thrombophlebitis, diabetes or underlying vascular disease. Primary uncomplicated pyococcal ulceration is rare; ecthyma is an example. Meleney's ulcer (bacterial synergistic gangrene) extends rapidly and has a burrowing, bluish, undermined and painful edge (Fig. 47.38). Tuberculous ulcers occur in erythema induratum (Bazin's disease) and are chronic, often on the back of the calves. They usually have undermined edges and considerable surrounding inflammation (Chapter 31). Other mycobacterial infections may be more common than suspected (Chapter 31). Ulcers in leprosy are usually on the foot, especially the dorsum, and on the proximal phalanx of the great toe, but can occur occasionally on the leg. The 'classical' appearances of the ulceronodular form of tertiary syphilis are well known, but this is extremely rare. Multiple tissue-paper scars on the legs occur typically in yaws (Chapter 34). The so-called 'desert' or 'veldt' sore is shallow and crusted; the role of *Corynebacterium*

diphtheriae is uncertain. The 'tropical' ulcer is a variety of phagedenic ulcer with a mixed symbiotic infection and rapid spread. Leishmaniasis, relatively uncommon on the legs, should be remembered as a possible cause of an indolent granulomatous ulcer. Among other uncommon infective causes of ulceration are glanders, tularaemia, brucellosis and cat scratch fever.

Pyoderma gangrenosum (Chapter 50)

This causes rapidly spreading and often bizarre and extensive ulceration, which may mimic an artefact, particularly when it precedes obvious ulcerative colitis. Underlying systemic disease such as inflammatory bowel disease, rheumatoid arthritis and haematological malignancies are found in some 70% of cases [1,2].

References

1 Callen JP. Pyoderma gangrenosum. *Lancet* 1998; **351**: 581–5.

2 Su WP, Davis MD, Weenig RH *et al*. Pyoderma gangrenosum: clinicopathologic correlation and proposed diagnostic criteria. *Int J Dermatol* 2004; **30**: 790–800.

Necrobiosis lipoidica and granulomatous diseases

Necrobiosis lipoidica may ulcerate following trauma, is extremely indolent, and should be regarded as ischaemic. Similarly, any granulomatous lesion may ulcerate if its blood supply is inadequate or if the vessels are involved in the granulomatous process, as may occur in sarcoidosis.

Decubitus and neuropathic ulceration

Pressure sores occur easily and with little warning on the heels and ankles of elderly people, especially in those who are comatose or have neurological disease. Pressure, including from bandages, may cause ulceration in those with compromised blood supply or reduced cutaneous sensation. In all cases where ulceration is protracted in the absence of venous, arterial or other obvious disease, artefact must be considered; interference with ulcers already present may also occur, even through bandages [1].

Neuropathic ulceration of the foot benefits from protection from shearing forces [2] by the use of a plaster cast or 'Scotchcast boot'. If this fails to achieve healing, the pressure must be taken off the foot and the base of the ulcer excised before being grafted. Split skin, rotation flaps or pedicle flaps may be used to cure the defect. It may be simpler to excise the toe and most of the first metatarsal to achieve rapid healing if the ulcer is situated over the ball of the foot. Patient education is of prime importance to avoid recurrent, inadvertent self-trauma.

References

1 Chan CL, Meyer FJ, Hay RJ *et al*. The ulceration associated with compression bandaging: observational study. *BMJ* 2001; **323**: 1099.

2 Burden AC, Jones CR, Jones R *et al*. Use of the 'Scotchcast boot' in treating diabetic foot ulcers. *BMJ* 1983; **286**: 1555–7.

Diabetic foot ulcers

Diabetic foot ulceration is a common, yet in many cases an eminently preventable, complication that affects 1 in 20 patients with diabetes. Risk factors for ulceration include reduced sensation (secondary to somatic neuropathy), high foot pressures, callus formation (a consequence of sympathetic neuropathy and high foot pressures), deformities (such as claw feet, prominent metatarsal heads, etc.), peripheral vascular disease, and, most importantly, a past history of ulceration [1].



Fig. 47.39 Neuropathic–ischaemic ulcers over the base of the foot (diabetic).

The natural history in the development of the diabetic foot can be divided into five stages: stage 1, a normal foot; stage 2, a high risk foot; stage 3, an ulcerated foot; stage 4, an infected foot; and stage 5, a necrotic foot. This covers the entire spectrum of foot disease but emphasizes the development of the foot ulcer as a pivotal event in stage 3, which demands urgent and aggressive management. An important prelude to diabetic foot treatment is the differing diagnosis of neuropathic and neuroischaemic foot. In the neuropathic foot, ulcers commonly develop on the plantar surface of the foot and the toes (Fig. 47.39), and are associated with neglected callus and high plantar pressures. In the neuroischaemic foot, ulcers are commonly seen around the edges of the foot, including the tips of the toes and the back of the heel, and are associated with trauma or wearing unsuitable shoes. Ulcers in stage 3 need relief of pressure (mechanical control), sharp debridement and dressings (wound control), and neuroischaemic foot ulcers may need vascular intervention (vascular control). In stage 4, microbiological control is crucial; severe infections need intravenous antibacterial therapy, and urgent assessment of the need for surgical drainage and debridement. Without urgent treatment, severe infections will progress to necrosis. In stage 5, necrosis can be divided into wet and dry necrosis. Wet necrosis in neuropathic feet requires intravenous antibacterials and surgical debridement, and wet necrosis in neuroischaemic feet also needs vascular reconstruction [2].

Infection is most often a consequence of foot ulcerations, which typically follows trauma to a neuropathic foot. Tissue specimens are strongly preferred to wound swabs for wound cultures. Gram-positive bacteria are the sole causative pathogens for most mild and moderate infections. These infections can usually be treated with culture-based narrow-spectrum antibacterials along with appropriate surgical debridement in an outpatient setting. In contrast, severe infections are often polymicrobial, requiring hospitalization and treatment with broad-spectrum antibacterials along with appropriate medical and surgical interventions. The initial

empirical antibacterial regimen may be tailored based on the results of culture and sensitivity tests from properly obtained specimens [3].

Diabetic foot care in all stages needs multidisciplinary management to control mechanical, wound, microbiological, vascular, metabolic and educational aspects. Achieving good metabolic control of blood glucose, lipids and blood pressure is important in each stage, as is education to teach proper foot care appropriate for each stage. In the management of neuropathic ulcers, pressure relief is of the utmost importance, and total contact casting remains the 'gold standard' means of achieving such pressure redistribution. Alleviation of the mechanical load on ulcers (off-loading) should always be a part of treatment. Neuropathic ulcers typically heal in 6 weeks with total contact casting, because it effectively relieves pressure at the ulcer site and enforces patient compliance [4].

An ulcer that does not heal for many months has a high probability of leading to osteomyelitis, for which treatment with antibiotics is not useful and which usually requires a surgical procedure. Charcot neuroarthropathy is a particular complication of neuropathy, which may lead to fragmentation or destruction of joints and bones.

Osteomyelitic bones in the foot must be excised and diabetic ischaemic ulceration treated by revascularization and split skin grafting with mesh where appropriate.

References

1 Boulton AJ. Pressure and the diabetic foot: clinical science and offloading techniques. *Am J Surg* 2004; **187**: 17S–24S.

2 Edmonds M. Diabetic foot ulcers: practical treatment recommendations. *Drugs* 2006; **66**: 913–29.

3 Rao N, Lipsky BA. Optimising antimicrobial therapy in diabetic foot infections. *Drugs* 2007; **67**: 195–214.

4 Cavanagh PR, Lipsky BA, Bradbury AW, Botek G. Treatment for diabetic foot ulcers. *Lancet* 2005; **366**: 1725–35.

CHAPTER 48
Disorders of Lymphatic Vessels

P.S. Mortimer
St George's Hospital, University of London, London, UK

Lymphatic development, 48.1
Anatomy, 48.3
Structure and function, 48.3
Chronic oedema, 48.7
Lymphoedema, 48.7
Epidemiology, 48.7
Pathophysiology, 48.8
Aetiology and classification, 48.9
Primary lymphoedema, 48.9
Secondary lymphoedema, 48.12
Clinical diagnosis of lymphoedema, 48.14
Complications, 48.15
Midline lymphoedema, 48.16
Localized lymphoedema, 48.17
Investigations, 48.17
Differential diagnosis of the swollen limb, 48.19
Management of lymphoedema, 48.21
Assessment, 48.21
Physical therapy (decongestive lymphatic therapy, combined decongestive treatment), 48.21
Prevention and treatment of infection, 48.24
Drug therapy, 48.24
Surgery, 48.25
Lymphatic malformations, lymphangioma and lymphangiectasia, 48.25
Lymphatic malformations (lymphangioma), 48.25
Lymphangioma circumscriptum, 48.26
Macrocystic lymphatic malformations, 48.26
Diffuse lymphangiomatosis, 48.27
Chylous reflux, intestinal lymphangiectasia, 48.27
Cutaneous lymphangiectasia (lymphangiectasis, acquired lymphangioma, benign lymphangiomatous papules), 48.28
Acquired lymphatic abnormalities, 48.29
Lymphangitis, 48.29
Recurrent cellulitis, 48.29
Lymphangiothrombosis, 48.29
Mondor's disease, axillary web syndrome, 48.29
'Seroma', 48.29
Lymphatic tumours, 48.30
Acquired progressive lymphangioma, 48.30
Lymphangiomyomatosis, 48.30
Kaposi's sarcoma, 48.30
Maffucci's syndrome, 48.31
Atypical post-radiation vascular proliferation, 48.31
Lymphangiosarcoma, 48.31
Carcinoma erysipeloides, 48.31

Introduction

The lymphatic system comprises the lymph, lymphatic vessels, lymph nodes and other organs containing lymphoid tissue, especially the spleen and bone marrow. A close developmental and working relationship exists between the lymphatic vessels and the blood circulation, particularly the veins. Although not a true circulation like the blood vascular system, the lymphatic system does provide an important 'limb' to the microcirculation, particularly in the skin, and, with the blood vessels, caters for the constant recirculation of protein and cells. While lymph drainage serves a predominantly 'plumbing' role, the lymphatic system does possess important immunological responsibilities. The lymphatic vessels are essential for the continual drainage from the tissues of the body of both plasma proteins and lymph-borne cells, for example lymphocytes and macrophages [1].

While technology has advanced our knowledge of the lymphatic system at the cellular and molecular level, our understanding of whole-body physiology lags behind. Nevertheless, the importance of the lymphatic vessel in disease is demonstrated by recent evidence implicating it in the pathogenesis of several conditions including cancer metastasis [2], asthma and airways obstruction [3], atherosclerosis [4], Crohn's disease [5], arthritis [6] and renal transplant rejection [7].

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

References

1 Yoffey JM, Courtice JM. *Lymphatics, Lymph and the Lymphomyeloid Complex*. New York: Academic Press, 1970.
2 Harrell MI, Iritani BM, Ruddell A. Tumor-induced sentinel lymph node lymphangiogenesis and increased lymph flow precede melanoma metastasis. *Am J Pathol* 2007; **170**: 774–86.
3 Baluk P, Tammela T, Ator E *et al*. Pathogenesis of persistent lymphatic vessel hyperplasia in chronic airway inflammation. *J Clin Invest* 2005; **115**: 247–57.
4 Xu X, Lin H, Lv H *et al*. Adventitial lymphatic vessels—an important role in atherosclerosis. *Med Hypotheses* 2007; **69**: 1238–41.
5 Pedica F, Ligorio C, Tonelli P *et al*. Lymphangiogenesis in Crohn's disease: an immunohistochemical study using monoclonal antibody D2-40. *Virchows Arch* 2008; **452**: 57–63.
6 Polzer K, Baeten D, Soleiman A *et al*. TNF blockade increases lymphangiogenesis in murine and human arthritic joints. *Ann Rheum Dis* 2008; **67**: 1610–6.
7 Kerjaschki D, Huttary N, Raab I *et al*. Lymphatic endothelial progenitor cells contribute to de novo lymphangiogenesis in human renal transplants. *Nat Med* 2006; **12**: 230–4.

Lymphatic development

The embryonic origin of the lymphatic system has long been uncertain, but its close development with the venous system is not in doubt. In 1902, Sabin proposed that early in fetal development isolated primitive lymph sacs originate by endothelial cell budding from embryonic veins [1,2] and that the skin lymphatic vessels develop by endothelial sprouting from these primary lymph sacs (centrifugal development). Alternatively, it has been suggested that initial lymph sacs develop from precursor cells, 'lymphangioblasts', in the mesenchyme (centripetal development)

[3]. Recent work indicates that lymphangioblasts are located in the confluence of the cranial and caudal cardinal veins, where the jugular lymph sac (JLS) forms. Cell lineage studies show that the JLS is of venous origin. In contrast, the lymphatic vessels of the dermis are derived from mesenchymal lymphangioblasts, suggesting a dual origin of lymphatic endothelial cells (LECs), both central and peripheral, although the primary source of embryonic LECs probably resides in specific embryonic veins [4].

Lymphvasculogenesis and lymphangiogenesis

Lymphvasculogenesis is the *de novo* production of LECs. It may occur in the embryo from specific veins and possibly in the adult from bone-marrow derived progenitor cells [5]. It is essential for establishing the lymphatic system initially.

Lymphangiogenesis is the production of new lymphatic vessels by splitting and splicing of existing LECs, and occurs both in the embryo and the adult.

Vascular endothelial growth factor (VEGF)

In 1995, the first specific growth factor receptor of lymphatic vessels was identified and termed FLT-4 [6]. It is now termed vascular endothelial growth factor receptor-3 (VEGFR-3). The family of vascular endothelial growth factor receptors and their ligands are central to the development of blood and lymph vessels [6]. In embryos, VEGFR-3 is initially expressed in all vasculature, but during development its expression in blood vessels (veins not arteries) becomes restricted to the developing lymphatic vessels. In embryos, therefore, VEGFR-3 is important for cardiovascular development, but in adults it is responsible for the regulation of the lymphatic vessels [7].

Lymphatic development requires the activation of the transcription factor PROX1 [8], which acts as the LEC master control gene and then regulates the expression of VEGFR-3, a receptor for VEGF-C and -D. LECs expressing VEGFR-3 bud off and migrate away from the embryonic cardinal vein in response to a gradient of VEGF-C produced by the nearby mesenchymal cells [9]. The migrating LECs assemble into lymph sacs which extend through sprouting to lay down the lymphatic network.

Post-natal lymphangiogenesis

Lymphatic vessel growth is regulated by several lymphangiogenic factors, including members of the vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), hepatocyte growth factor (HGF) and angiopoietin families. VEGF-C and -D are the main ligands for VEGFR-3, which is lymphatic-specific, and therefore specific for lymphangiogenesis. The most potent inducer of lymphatic sprouting is VEGF-C. Over-expression of VEGF-C in skin keratinocytes leads to dermal lymphatic hyperplasia [10].

While lymphangiogenesis is mediated mainly via VEGF-C and -D binding to VEGFR-3, lymphangiogenic responses can occur through VEGFR-2 and VEGFR-3. In addition to VEGF-C and -D, VEGF-A (also called vascular permeability factor) is able to stimulate lymphangiogenesis. VEGFR-2 has been detected on endothelial cells of the lymphatic vessels, suggesting its direct role in the stimulation of lymphangiogenesis [11]. Alternatively, VEGF-A might recruit inflammatory cells that indirectly stimulate lymphangiogenesis through the secretion of cytokines and growth factors [12].

Recently, VEGFR-1, in response to VEGF-A binding, has been shown to promote lymphangiogenesis, as well as angiogenesis, via bone marrow-derived macrophage recruitment, but probably only in pathological states. For example, progenitor cells have been shown to participate in lymphangiogenesis in chronic renal transplant rejection [13]. VEGFR-1 is expressed not only on vascular and lymphatic endothelium but also on monocytes/macrophages. VEGFR-1 could be involved in lymphangiogenesis in one of three ways: firstly, VEGFR-1 contributes to vascular permeability, and resulting exudates induce lymph vessel dilatation and lymphangiogenesis; secondly, VEGF-A recruits bone marrow-derived macrophages in a VEGFR-1 signal-dependent manner; and thirdly, recruited macrophages express VEGF-C which binds to VEGFR-3 [14]. It is still unclear how physiological lymphangiogenesis is regulated.

Vascular separation

The separation of lymphatic vessels from blood vessels is important for their independent functioning. Syk and SLP-76 deficiency leads to arteriovenous shunting and lymphovenous connections [15]. These proteins and those of the Spred/Sprouty family may have implications in mixed vascular malformations where blood-filled lymphatic vessels can occur.

Lymphatic remodelling

After the initial lymphatic vasculature is established, it is then remodelled into a functioning network comprising lymphatic capillaries/initial lymphatics and collecting lymphatics possessing smooth muscle. FOXC2, EphrinB2 and Angiopoietin-2 play important roles in the remodelling process, including recruitment of smooth muscle cells and formation of valves [16].

References

1 Sabin FR. On the origin of the lymphatic system from the veins and the development of lymph hearts and thoracic duct in the pig. *Am J Anat* 1902; **i**: 3671.

2 Sabin FR. On the development of the superficial lymphatics in the skin of the pig. *Am J Anat* 1904; **9**: 43–91.

3 Huntington GS, McClure CFW. The anatomy and development of the jugular lymph sacs in the domestic cat. *Am J Anat* 1908; **22**: 1–19.

4 Buttler K, Ezaki T, Wilting J. Proliferating mesodermal cells in murine embryos exhibiting macrophage and lymphendothelial characteristics. *BMC Dev Biol* 2008; **8**: 43.

5 Religa P, Cao R, Bjorndahl M *et al*. Presence of bone marrow-derived circulating progenitor endothelial cells in the newly formed lymphatic vessels. *Blood* 2005; **106**: 4184–90.

6 Kaipainen A, Korhonen J, Mustonen T *et al*. Expression of the fms-like tyrosine kinase FLT4 gene becomes restricted to lymphatic endothelium during development. *Proc Natl Acad Sci* 1995; **92**: 3566–70.

7 Jussila L, Alitalo K. Vascular growth factors and lymphangiogenesis. *Physiol Rev* 2002; **82**: 673–700.

8 Wigle JT, Oliver G. Prox-1 function is required for the development of the murine lymphatic system. *Cell* 1999; **98**: 769–78.

9 Olsson AK, Dimberg A, Kreuger J, Claesson-Welsh L. VEGF receptor signaling-in control of vascular function. *Nat Rev Mol Cell Biol* 2006; **7**: 359–71.

10 Saaristo A, Veikkola T, Tammela T *et al*. Lymphangiogenic gene therapy with minimal blood vascular side effects. *J Exp Med* 2002; **196**: 719–30.

11 Nagy JA, Vasile E, Feng D *et al*. Vascular permeability factor/vascular endothelial growth factor induces lymphangiogenesis as well as angiogenesis. *J Exp Med* 2002; **196**: 1497–506.

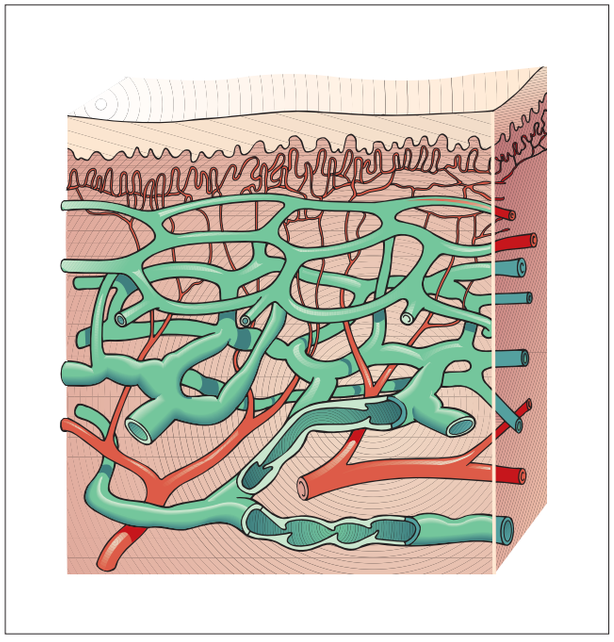


Fig. 48.1 Diagram of superficial and deep initial lymphatic vessels in the skin. Lymph vessels are coloured green, blood vessels are coloured red. (From Kubik and Manestar [1], with permission.)

12 Cursiefen C, Chen L, Borges LP *et al*. VEGF-A stimulates lymphangiogenesis and hemangiogenesis in inflammatory neovascularization via macrophage recruitment. *J Clin Invest* 2004; **113**: 1040–50.

13 Kerjaschki D, Huttary N, Raab I *et al*. Lymphatic endothelial progenitor cells contribute to de novo lymphangiogenesis in human renal transplants. *Nat Med* 2006; **12**: 230–4.

14 Murakami M, Zheng Y, Hirashima M *et al*. VEGFR1 tyrosine kinase signaling promotes lymphangiogenesis as well as angiogenesis indirectly via macrophage recruitment. *Arterioscler Thromb Vasc Biol* 2008; **28**: 658–64.

15 Abtahian F, Guerriero A, Sebzda E *et al*. Regulation of blood and lymphatic vascular separation by signaling proteins SLP-76 and Syk. *Science* 2003; **299**: 247–51.

16 Hosking B, Makinen T. Lymphatic vasculature: a molecular perspective. *Bioessays* 2007; **29**: 1192–202.

Anatomy

In the skin, lymphatic vessels form two horizontally running networks, a narrow-meshed, superficial network lying subepidermally and a deeper, wide-meshed network. The networks are connected to each other through obliquely-running vessels (Fig. 48.1). Although fewer in number than blood vessels, lymphatics are potentially larger at capillary level. Lymphatics are essentially of two types:

1 Smaller, non-contractile, initial lymphatics (these used to be called terminal lymphatics), which commence or 'initiate' the drainage process within the tissues
2 Larger, contractile, lymphatic collectors, into which the initial lymphatics drain [1].

Afferent collectors drain to lymph nodes and efferent collectors (trunks) drain from lymph nodes. Lymphatic capillaries originate as blind-ending, endothelial-lined tubes in the subpapillary region, and are rarely seen within dermal papillae except in certain disease states—for example, in psoriasis [2,3]. From the superficial lymphatic plexus in the upper dermis, lymph drains through a series of enlarging precollectors into the contractile collecting trunks close to the dermosubcutaneous junction [1]. The lobules of adipose tissue have lymphatics only in their periphery, and clearance of lymph from the centre of the lobule is slow [4].

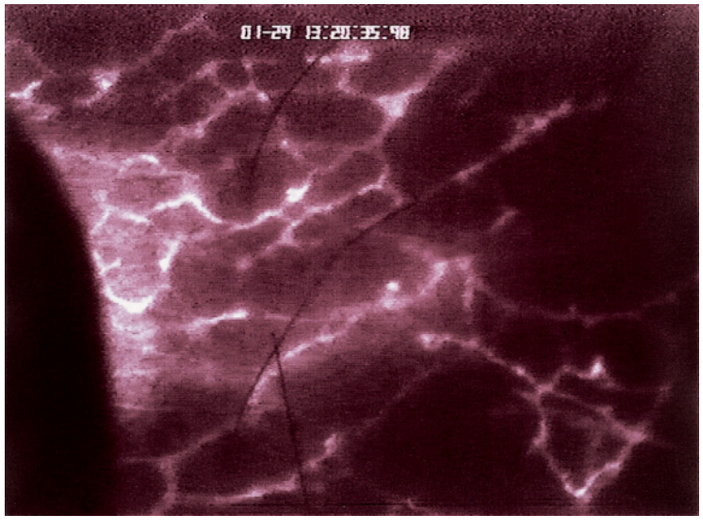


Fig. 48.2 Superficial network of dermal lymphatic vessels as viewed *in vivo* using fluorescence microlymphography.

Initial lymphatics in the skin are arranged in loosely constructed polygonal meshes (Fig. 48.2) high in the dermis [1,5]. Territories of skin are drained by these meshes into the vertically draining precollectors. A series of luminal valves ensure that flow is unidirectional. Such is the capacity of initial lymphatics for dilatation that the valves can become incompetent. Obstruction to deeper lymphatic routes leads to re-routing of lymph and results in 'dermal backflow', as witnessed both on conventional X-ray lymphography and lymphoscintigraphy. In this way, the initial lymphatic network of the skin provides collateralization by which lymph can escape to other (more) normally draining areas [6].

References

1 Kubik S, Manestar M. Anatomy of the lymph capillaries and precollectors of the skin. In: Bollinger A, Partsch H, Wolfe JJN, eds. *The Initial Lymphatics*. Stuttgart: Thieme, 1985: 66–74.

2 Braverman I. The role of blood vessels and lymphatics in cutaneous inflammatory processes: an overview. *Br J Dermatol* 1983; **109** (Suppl. 25): 89–98.

3 Braverman IM. Ultrastructure and organisation of the cutaneous microvasculature in normal and pathologic states. *J Invest Dermatol* 1989; **93**: 25–95.

4 Ryan TJ. Lymphatics and adipose tissue. *Clin Dermatol* 1995; **13**: 493–8.

5 Bollinger A, Jager K, Spier F, Seglias J. Fluorescence microlymphography. *Circulation* 1981; **64**: 1195–200.

6 Tiedjen KU, Knorz S, Heimann KD. The skin: lymphatic collateral organ? *Scope Phlebol Lymphol* 1994; **1**: 7–12.

Structure and function

Description

Initial lymphatics/lymphatic capillaries

The lymphatic capillary is lined by a fine endothelium which is more attenuated than that of blood capillaries (Fig. 48.3). Potentially larger than blood capillaries, lymphatics are frequently not visualized in histological sections, because they are collapsed. A

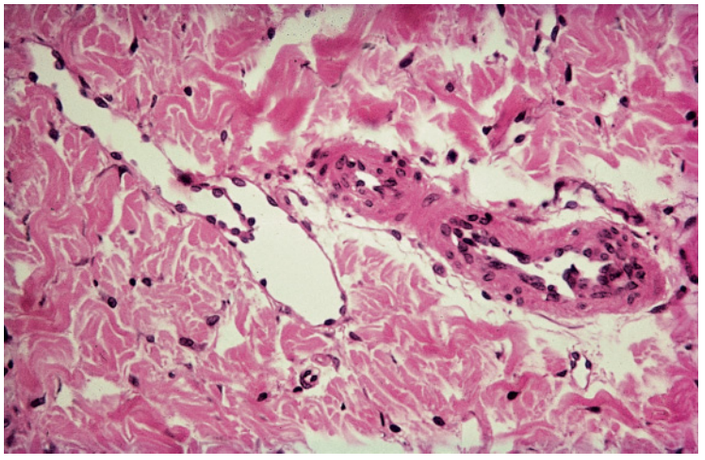


Fig. 48.3 Mid-dermal vessels showing the typical appearance of a mid-dermal blood capillary with plump endothelium compared with adjacent lymphatic vessels with attenuated endothelium and a valve. Such valves are not present in blood vessels high in the dermis.

distended lymphatic exhibits characteristically thin, attenuated walls with nuclei bulging into the lumen. On electron microscopy, the gaps between overlapping endothelial cells are much larger than in the blood capillary. These 'open junctions' act as primary (mural) valves and serve as the entry point for macromolecules [1]. Initial (dermal) lymphatics have little in the way of a basement membrane or pericytes [2]. The lymphatic endothelium contains very few pinocytotic vesicles and lacks Weibel–Palade bodies and fenestrae [3]. Attached to the outside of the endothelium are anchoring filaments which attach the lymphatic to surrounding collagen and elastic fibres [4]. The main molecular component of the anchoring filaments is fibrillin [5]. The elastic fibres form a partial envelope around the dermal lymphatics [6]. In addition to the flap valves in the lymphatic wall are bileaflet intraluminal valves [7].

Lymphatic–vasculature function critically depends on extracellular matrix (ECM) and on its connections with LECs. EMILIN1, an elastic microfibril-associated protein, is highly expressed by LECs *in vitro* and colocalizes with lymphatic vessels in several mouse tissues. The phenotype displayed by *Emilin1*(−/−) mice is the first abnormal lymphatic phenotype associated with the deficiency of an ECM protein and identifies EMILIN1 as a novel local regulator of lymphangiogenesis [8].

Contractile collecting lymphatics

Contractile lymphatics are endowed with a basement membrane and are covered by mural cells, both pericytes and smooth muscle cells. They contain a regularly spaced chain of lumenal valves that prevent retrograde flow even at high pressures. Segments of lymphatic collecting vessel, between one valve and the next, act as active pumps called lymphangions. They are innervated and respond to vasoactive mediators including nitric oxide [9].

References

1 Trzewik J, Mallipattu SK, Artmann GM *et al*. Evidence for a second valve system in lymphatics: endothelial microvalves. *FASEB* 200; **15**: 1711–7.

2 Barsky SH, Baker A, Siegal GP *et al*. Use of anti-basement membrane antibodies to distinguish blood vessel capillaries from lymphatic capillaries. *Am J Surg Pathol* 1983; **7**: 667–77.

3 Ryan TJ. Structure and function of lymphatics. *J Invest Dermatol* 1989; **93**: 18–24.

4 Leak LV, Burke JF. Ultrastructural studies on the lymphatic anchoring filaments. *J Cell Biol* 1968; **36**: 129–49.

5 Weber E, Rossi A, Solito R *et al*. The pattern of fibrillin deposition correlates with microfibril-associated glycoprotein 1 (MAGP-1) expression in cultured blood and lymphatic endothelial cells. *Lymphology* 2004; **37**: 116–26.

6 Mortimer PS, Cherry GW, Jones RL *et al*. The importance of elastic fibres in skin lymphatics. *Br J Dermatol* 1983; **108**: 561–6.

7 Daroczy J. *The Dermal Lymphatic Capillaries*. Berlin: Springer, 1988.

8 Danussi C, Spessotto P, Petrucco A *et al*. Emilin1 deficiency causes structural and functional defects of lymphatic vasculature. *Mol Cell Biol* 2008; **28**: 4026–39.

9 Hagendoorn J, Padera TP, Kashiwagi S. Endothelial nitric oxide synthase regulates microlymphatic flow via collecting lymphatics. *Circ Res* 2004; **95**: 204–9.

Identification of skin lymphatics—molecular markers

The recent discovery of specific markers for lymphatic endothelium has contributed greatly to the identification of skin lymphatics in tissue sections. Previously, the only certain way of distinguishing a lymphatic from a blood vessel was by electron microscopy. Intramural valves between overlapping endothelial cells are pathognomonic of skin lymphatic vessels [1]. If large skin biopsies are fixed in an expanded condition by stretching the specimen in different directions, as would be the case *in vivo*, lymphatic vessels become visible for both light and transmission electron microscopy [2].

A number of markers are available for labelling endothelial cells, but the majority stain both blood and lymph vessels (e.g. factor VIII-related antigen, CD31 (PECAM-1)). Because initial lymphatics lack a continuous basement membrane, immunocytochemistry for the extracellular matrix components type IV collagen and laminin has been used to distinguish them from blood capillaries [3]. Pal-E monoclonal antibody is consistently negative in lymphatic vessels but positive in venules and small veins, the vessels most likely to be mistaken for lymphatics [4].

Of the newer molecular markers, VEGFR-3 was the first to be documented to be expressed in lymphatic endothelium, but it can also be found in a subset of blood vessels and in angiogenic vessels in certain pathological conditions. LYVE-1 (lymphatic vessel hyaluronan receptor-1) is a homolog of hyaluronan receptor CD44 [5] (Fig. 48.4). It is present in initial lymphatics but not in the larger contractile lymphatics. LYVE-1 is also present in activated macrophages in skin and is frequently down-regulated on lymphatics in inflammation.

Podoplanin is a glomerular podocyte membrane mucoprotein which is highly expressed in lymphatic endothelial cells [6]. It is also expressed in keratinocytes but is very specific for dermal lymphatics. Studies in cultured endothelial cells indicate that T1α/podoplanin promotes cell adhesion, migration and tube formation, whereas small interfering RNA-mediated inhibition of T1α/podoplanin expression decreased lymphatic endothelial cell adhesion [7].

Other markers reported to be positive in lymphatic, but not in blood, vessels include Prox-1 which is a nuclear stain [8]. CCL21 is produced by lymphatic endothelium and directs homing of cells such as lymphocytes possessing CC receptors [9]. It is unlikely that any one marker will be totally specific, particularly

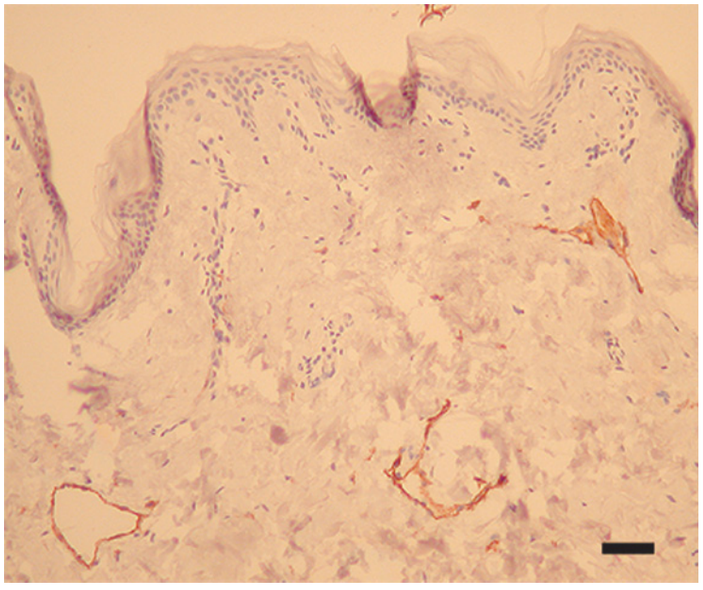


Fig. 48.4 LYVE-1 antibody marker for lymphatic endothelium. (Courtesy of Dr D.G. Jackson.)

Table 48.1 Markers for lymphatic vessels. (Adapted from [10].)

Molecule	Protein class	Biological effect
VEGFR-3	Receptor tyrosine kinase on endothelial cell	Lymphangiogenesis
LYVE-1	Receptor for extracellular matrix glycosaminoglycan	Transport of HA from tissues to lymph nodes
Prox-1	Transcription factor	Lymphvasculogenesis
Podoplanin (D2-40)	Integral membrane protein	Lymphatic morphogenesis
CCL21	Chemokine	T-cell trafficking

HA, hyaluronan; LYVE-1, lymphatic vessel endothelial HA receptor; VEGFR-3, vascular endothelial growth factor receptor-3; CC, chemokine with two adjacent cysteine residues.

in disease states, and the use of several markers is recommended (Table 48.1).

References

1 Braverman IM. Ultrastructure and organization of the cutaneous micro-vasculature in normal and pathologic states. *J Invest Dermatol* 1989; **93**: 25–95.

2 Lubach D, Wawrzyniak-Schulz A, Neukam D, Nissen S. The extension technique: a new method of demonstrating initial lymph vessels in excised human skin. *Br J Dermatol* 1990; **123**: 179–85.

3 Barsky SH, Baker A, Siegal GP *et al*. Use of anti-basement membrane antibodies to distinguish blood vessel capillaries from lymphatic capillaries. *Am J Surg Pathol* 1983; **7**: 667–77.

4 Schlingemann RO, Rietweld FJ, Kwaspen F *et al*. Differential expression of markers for endothelial cells, pericytes and basal lamina in the microvasculature of tumours and granulation tissue. *Am J Pathol* 1991; **138**: 1335–42.

5 Banerji S, Ni J, Wang SX *et al*. LYVE-1, a new homologue of the CD44 glycoprotein, is a lymph specific receptor for hyaluronan. *J Cell Biol* 1999; **144**: 789–801.

6 Breiteneder-Geleff S, Soleman A, Kowalski H *et al*. Angiosarcomas express mixed endothelial phenotypes of blood and lymphatic capillaries: podoplanin as a specific marker for lymphatic endothelium. *Am J Pathol* 1999; **154**: 385–94.

7 Schacht V, Ramirez MI, Hong YK *et al*. T1alpha/podoplanin deficiency disrupts normal lymphatic vasculature formation and causes lymphedema. *EMBO J* 2003; **22**: 3546–56.

8 Wigle JT, Oliver G. Prox-1 function is required for the development of the murine lymphatic system. *Cell* 1999; **98**: 769–78.

9 Shields JD, Emmett MS, Dunn DB *et al*. Chemokine-mediated migration of melanoma cells towards lymphatics—a mechanism contributing to metastasis. *Oncogene* 2007; **26**: 2997–3005.

10 Jussila L, Alitalo K. Vascular growth factors and lymphangiogenesis. *Physiol Rev* 2002; **82**: 673–700.

Purpose of lymphatics

Lymphatic vessels are primarily concerned with draining, from the tissue spaces, materials which cannot directly return to the bloodstream. While the bloodstream essentially supplies the tissues, the lymphatic system essentially drains them. This includes proteins as well as cells—extravasated erythrocytes, dendritic cells, macrophages, lymphocytes and, of course, malignant cells.

Contrary to traditional teaching, the lymphatic is the main drainage route for fluid. Only transiently is fluid reabsorbed by venous capillaries. It is important to understand this role of the lymphatic acting as a 'safety valve' or buffer against fluid overload, because it means that every form of oedema indicates some degree of lymphatic failure [1].

Lymphatics carry foreign material that has penetrated the dermis, including microorganisms, injected vaccines, solvents of skin cosmetics, inorganic material such as silica and stains from tattoos [2]. Bacterial and other microorganisms are channelled through lymphatics as a protective mechanism to prevent noxious agents from directly entering the bloodstream. Presumably this failure to 'police' infection is the reason why cellulitis/erysipelas can cause rapid systemic illness in lymphoedema before local signs are evident.

Snake envenomation causes a dose-dependent contraction of collecting lymphatic vessels, resulting in a reduction of their lumen and in a halting of lymph flow so venom remains contained within the lymphatics following a bite [3].

References

1 Mortimer PS, Levick JR. Chronic peripheral oedema: the critical role of the lymphatic system. *Clin Med* 2004; **4**: 448–53.

2 Ikomi F, Schmid-Schonbein GW. Lymph transport in the skin. *Clin Dermatol* 1995; **13**: 419–27.

3 Mora J, Mora R, Lomonte B, Gutiérrez JM. Effects of *Bothrops asper* snake venom on lymphatic vessels: insights into a hidden aspect of envenomation. *PLoS Negl Trop Dis* 2008; **2**: e318.

Lymph transport

After filtration from the microvasculature, interstitial fluid enters a series of passive initial lymphatics and is then propelled within the collecting trunks through a series of intervalvular pumping segments (lymph hearts) to the lymph nodes before eventually returning to the venous system at the thoracic duct. Transport of fluid and other materials (prelymph) across the interstitial space towards initial lymphatics is a passive process, dependent upon changes in local pressures (convective flow) [1,2]. Deformation or movement of the dermis by surface pressure and underlying muscle contractions and by dermal components, such as arterioles, causes expansion or compression of the initial lymphatics. The process of expansion is likely to result from pulling of the anchoring filaments on the abluminal surface of the lymphatic [3]. These probably act to prevent lymphatic collapse when interstitial

pressure is high, as in oedema [4]. Negative fluid pressure inside the initial lymphatics serves to open the interendothelial junctions (flap valves) and to permit inflow of interstitial fluid. After filling and equilibration of pressure the flap valves close. Compression of the filled lymphatic then moves lymph downstream, that is towards bigger lymphatics; the valves within the lymphatic vessels ensure that flow is in one direction. Recoil of the initial lymphatic occurs when the compression wave (squeezing) of the lymphatic ceases and the cycle repeats itself. Cardiac arrest leads to cessation of lymph flow, but lymph flow can be maintained with active skin massage even after the arrest of the heart.

Lymph does not passively 'drain downstream' through the collecting lymphatic vessels because the net pressure gradients oppose flow. Instead, the collecting vessels must act as both the conduits, that direct and regulate lymph flow, and the pumps that generate the lymph flow. The regulation of lymphatic muscle contractions is thought to occur via the interaction of cell calcium with regulatory and contractile proteins. This is almost certainly one of the mechanisms whereby calcium channel blocking agents cause peripheral oedema. However, our knowledge of this regulation of lymphatic contractile function is far from complete [5].

References

1 Ikomi F, Schmid-Schonbein GW. Lymph transport in the skin. *Clin Dermatol* 1995; **13**: 419–27.
2 Levick JR, McHale N. The physiology of lymph production and propulsion. In: Browse NL, Burnand KG, Mortimer PS, eds. *Diseases of the Lymphatics*. London: Arnold, 2003: 44–64.
3 Leak LV. Ultrastructure and function of the interstitial–lymphatic interface. In: Staub NC, Hogg JC, Hargens ASR, eds. *Interstitial–Lymphatic Liquid and Solute Movement*. Basel: Karger, 1986: 1–14.
4 Castenholz A. Functional microanatomy of initial lymphatics with special consideration of the extracellular matrix. *Lymphology* 1998; **31**: 101–18.
5 Muthuchamy M, Zawieja D. Molecular regulation of lymphatic contractility. *Ann N Y Acad Sci* 2008; **1131**: 89–99.

Immune functions

The principal immune function of the afferent lymphatics is to bear antigens and leukocytes from peripheral tissues to the draining lymph nodes. Recent research has shown that passage of leukocytes into the afferent lymphatic capillaries is far from an indolent process; rather it is carefully orchestrated by an array of adhesion molecules, as well as by chemokines and their receptors [1].

Lymphocytes and mononuclear phagocytes constantly patrol the skin, leaving via the afferent lymphatic vessels for the lymph nodes. Epidermal (e.g. Langerhans' cells) and dermal dendritic cells screen the skin for invading antigens. They migrate from the skin to regional nodes where a primary immune response is initiated [2]. Dendritic cells enter dermal lymphatics by transmigration through intercellular spaces of adjacent endothelial cells, frequently carrying material such as melanosomes and apoptotic bodies [3].

Under normal physiological conditions immature dendritic cells migrate constitutively and continuously from skin to lymph nodes via afferent lymphatics, undertaking immune surveillance [4]. Subsequent to inflammation the number of dendritic cells increases dramatically and they change from phagocytes into professional antigen-presenting cells [5]. Receptors on lymphatic endothelial cells facilitate migration of proteins and cells to, and within, lymphatics. CCL21 is a chemokine that is produced constitutively by lymphatic endothelial cells in the skin [6]. Disruption of the CCR7 gene, which prevents expression of CCL21, thereby prevents migration of dendritic cells from tissue to regional nodes. CCR7-deficient mice lack contact sensitivity due to a failure of translymphatic migration of epidermal dendritic cells [7]. CCR7 and its ligands (CCL21 and 19) are also important in regulating lymphatic trafficking of T cells [8].

Without intact lymphatics a primary immune response cannot develop. In the case of allogeneic skin grafts, removal of the lymph drainage channels causes cessation of the cellular reactions in the lymph nodes until lymphatic pathways are re-established [9,10]. Rejection is delayed in grafted skin sites where all draining lymphatics are severed [11]. Studies in lymphoedema following curative breast cancer treatment demonstrated an impaired response to dinitrochlorobenzene testing in the swollen limb but not in the contralateral control limb [12]. Similar results were reported in lymphoedema associated with Kaposi's sarcoma [13].

Bacteria, viruses, fungi and toxins which penetrate the skin are absorbed by lymphatics and not by blood capillaries [14,15]. Virulent haemolytic streptococci, tubercle bacilli and many types of soluble or particulate antigens injected intradermally readily reach the regional lymph node [9].

References

1 Johnson LA, Jackson DG. Cell traffic and the lymphatic endothelium. *Ann N Y Acad Sci* 2008; **1131**: 119–33.
2 Silverberg-Sinakin I, Thorbecke GJ, Baer RL *et al*. Antigen-bearing Langerhans cells in skin, dermal lymphatics and in lymph nodes. *Cell Immunol* 1976; **25**: 137–51.
3 Stoitzner P, Pfaller K, Stossel H, Romani N. A close-up view of migrating Langerhans cells in the skin. *J Invest Dermatol* 2002; **118**: 117–25.
4 Smith JB, McIntosh GH, Morris B. The traffic of cells through tissues; a study of peripheral lymph in sheep. *J Anat* 1970; **107**: 87–100.
5 Steinman RM, Hawiger D, Nussenzweig MC. Tolerogenic dendritic cells. *Annu Rev Immunol* 2003; **21**: 685–711.
6 Saeki H, Moore AM, Brown MJ, Hwang ST. Cutting edge: secondary lymphoid tissue chemokine (SLC) and cc chemokine receptor 7 (CCR7) participate in the emigration pathway of mature dendritic cells from the skin to regional lymph nodes. *J Immunol* 1999; **162**: 2472–5.
7 Ohl L, Mohaupt M, Czeloth N *et al*. CCR7 governs skin dendritic cell migration under inflammatory and steady-state conditions. *Immunity* 2004; **21**: 279–88.
8 Worbs T, Mempel TR, Bölter J *et al*. CCR7 ligands stimulate the intranodal motility of T lymphocytes in vivo. *J Exp Med* 2007; **204**: 489–95.
9 Yoffey JM, Courtice JM. *Lymphatics, Lymph and the Lymphomyeloid Complex*. New York: Academic Press, 1970.
10 Lambert PB, Frank HA, Bellman S, Farnsworth D. The role of the lymph trunks in the response to allogeneic skin transplants. *Transplantation* 1965; **3**: 62–73.
11 Tilney NL, Gowans JL. The sensitisation of rats by allografts transplanted to alymphatic pedicles of skin. *J Exp Med* 1971; **133**: 951–62.
12 Mallon E, Powell S, Mortimer PS, Ryan TJ. Evidence for altered cell mediated immunity in postmastectomy lymphoedema. *Br J Dermatol* 1997; **137**: 928–33.
13 Ruocco V, Satriano RA, Astarita C. Anomalies régionales des voies lymphatiques et de la réponse au DNCB dans le sarcoma de Kaposi classique. *Ann Dermatol Vénéréol* 1985; **112**: 283–6.
14 Barnes JM, Trueta J. Absorption of bacteria, toxins and snake venoms from the tissues. *Lancet* 1941; **i**: 623–6.
15 De Long TG, Simmons RL. Role of lymphatic vessels in bacterial clearance from early soft tissue infection. *Arch Surg* 1982; **117**: 123–8.

Table 48.2 Causes of oedema.

Increased capillary filtration
Increased capillary pressure
Increased venous pressure, e.g. right heart failure, DVT, obstructing malignancy, overtransfusion
Increased blood flow, e.g. inflammation, arteriovenous fistula
Reduced plasma proteins
Increased loss, e.g. nephrotic syndrome, protein-losing enteropathy
Reduced synthesis, e.g. cirrhosis, advanced cancer
Malabsorption, malnutrition
Increased capillary permeability
Inflammation, e.g. varicose eczema, psoriasis, urticaria and angioedema
Reduced lymph drainage
Primary lymphatic insufficiency
Genetic (and inherited)
Milroy's disease (onset at or soon after birth)
Lymphoedema, distichiasis (postpubertal)
Meige's disease (postpubertal)
Constitutive (presumed genetic)
Secondary lymphatic insufficiency
Iatrogenic interruption to drainage routes, e.g. surgery, radiotherapy
Cancer (particularly relapsed)
Infection, e.g. filariasis, cellulitis
Accidental trauma
Dysfunctional lymphatics
Dependency syndrome
Loss of mobility
High output failure, e.g. venous disease
Deep-vein thrombosis

Chronic oedema

Oedema is an excess of interstitial fluid. Interstitial fluid volume must increase by over 100% before oedema is clinically detectable. Dermal oedema manifests as 'peau d'orange' due to expansion of the interfollicular dermis, whereas subcutaneous oedema gives rise to pitting.

Any oedema, whatever the cause, is due to capillary filtration overwhelming the lymph drainage for a sufficient period of time [1]. Interstitial fluid is reabsorbed almost entirely by the lymphatics. Contrary to popular belief, venous reabsorption of interstitial fluid cannot be maintained for any length of time except in certain vascular beds, for example that of the kidney [1]. The causes of oedema formation are listed in Table 48.2. Most chronic oedemas arise from increased capillary filtration overwhelming lymph drainage. To some extent, therefore, any chronic oedema incriminates the lymphatic system through its failure to keep up with demand. Lymphoedema, however, is oedema arising principally from a failure in lymph drainage.

Therefore any chronic oedema indicates lymphatic failure. It is best not to approach a lower limb chronic oedema clinically by trying to pigeon-hole the diagnosis into 'heart failure', 'venous oedema', 'lymphoedema' etc. A far better approach is to consider if the oedema represents pure lymphatic failure, or, as is most common, lymphatic failure due to lymph drainage being overwhelmed by increased capillary filtration. Most cases of chronic oedema have more than one factor contributing to impaired lymph drainage and increased capillary filtration. Therefore terms such as lymphoedema (predominantly lymph drainage failure) or a filtration oedema (predominantly increased capillary filtration) are suggested [2] (Table 48.2).

References

1 Levick JR. *An Introduction to Cardiovascular Physiology*, 4th edn. London: Arnold, 2003.
2 Mortimer PS, Levick JR. Chronic peripheral oedema: the critical role of the lymphatic system. *Clin Med* 2004; **4**: 448–53.

Lymphoedema

Definition. Swelling due to the excess accumulation of lymph in the tissues caused by inadequate lymph drainage. Lymphoedema differs clinically from other forms of chronic oedema by its altered skin texture and the brawny quality of the subcutaneous tissues, which limit pitting. There may be no distinguishing features, particularly in the early stages of swelling. A more precise definition would be 'a swelling of soft tissues which is the result of accumulation of protein-rich interstitial fluid caused by a low output failure of lymph' [1].

Primary lymphoedema implies a genetic or constitutive cause whereby there is an intrinsic fault in lymph drainage determined by a lymphatic maldevelopment or functional weakness. Secondary lymphoedema implies an acquired failure of previously normal lymph drainage due to an identifiable cause extrinsic to the lymphatic system.

Epidemiology

Lymphoedema *per se* is perceived as uncommon, yet lymphatic insufficiency is a major contributing cause of chronic ankle oedema, which is considered common (particularly in the elderly) [2]. Because lymphoedema can be a difficult diagnosis, particularly if mild or in the early stages, it is frequently underdiagnosed. One survey, which determined the problem of chronic oedema (as a surrogate for lymphoedema) in the community, ascertained 823 patients in a catchment area of 619 000 in south-west London. This estimated the overall prevalence of chronic oedema as 1.33/1000 population; the prevalence increased with age and was 5.4/1000 in subjects aged over 65 years. In only a quarter did the oedema arise from cancer treatment. Twenty-nine per cent had experienced at least one attack of cellulitis over the previous year. Ten per cent of subjects had lost, or had had to change, employment as a result of their chronic oedema. Chronic oedema that was likely to be lymphatic in origin is common in the community and often goes unrecognized [3].

Primary types of lymphoedema tend to affect females more frequently (70–80% of patients are female). In less than 10% of cases is swelling present at birth; most cases present at or soon after puberty. It is estimated that 80% will present before the age of 35 years (lymphoedema praecox) and 10% after the age of 35 years (lymphoedema tarda) [4]. Data on prevalence of lymphoedema are few, and a figure for overall prevalence of primary lymphoedema is not available. However, a study of 1000 young

adults showed that 8% of women demonstrated signs of lymphoedema in the lower limb [5].

Secondary types of lymphoedema are more common than primary. In developed countries cancer treatment dominates as a cause whereas in tropical climates infection dominates [6].

Breast cancer-related lymphoedema (BCRL). The cumulative prevalence of swelling following breast cancer treatment in women is 28% [7]. The introduction of sentinel lymph node biopsy (SLNB), used as a staging investigation for cancer, has not necessarily reduced the incidence of lymphoedema as was hoped. While the incidence of BCRL following SLNB has reduced to 5–7%, the need for axillary clearance in the 30% who are node-positive can lead to an incidence of up to 45% in that group.

Pelvic malignancy. The incidence of lower limb lymphoedema following radical hysterectomy alone is estimated at 5–10% [8] but can be as high as 49% by 10 years of follow up in patients who have also received adjuvant radiation treatment [9]. The incidence after vulval cancer is reported at 28% [10]. Following prostate cancer the incidence has been reported at 3–8% [6], and after penile cancer 23–33% [11].

Melanoma. The incidence after lymphadenectomy can be up to 44% after therapeutic groin dissection for palpable disease [12], but the incidence following sentinel lymph node biopsy is much less [13]. Patients undergoing an inguinal lymph node dissection (ILND) for a positive SLN have a significantly lower risk of postoperative complication or lymphoedema than do patients undergoing ILND for clinically palpable disease [14].

Pathophysiology

Physiologically, there are only a limited number of ways lymphatics may fail. They may be reduced in number, obliterated, obstructed or simply fail to function. A lack of sensitive methods for investigation makes it difficult to distinguish between these mechanisms (Table 48.3).

A reduction in lymphatics may be due to hypoplasia such as the reduction of skin lymphatics in Milroy's disease. In the commonest form of primary lymphoedema, that presenting at or soon after puberty with distal leg swelling, lymphangiograms usually demonstrate a reduction in the size and number of superficial leg lymphatic collectors. It is often assumed that the lymphatics have been abnormal since birth but it is always possible that the lymph vessels have undergone an accelerated atrophy or ageing process. The congenitally determined abnormality may not therefore be an underdevelopment of lymphatics from birth, but rather a failure of growth/regeneration or function following damage or injury. This would explain the latent period before swelling manifests, particularly in those forms presenting later in life (lymphoedema tarda). In truth, we do not know and these possibilities are speculative.

An obliterative process, where there is permanent obliteration of the lymphatic lumen and consequently of the vessel itself, probably develops through lymphangiothrombosis or lymphangitis in the same way as for veins. Obliterative lymphangitis is probably the mechanism following infection or longstanding hand eczema.

Obstruction will cause increased outflow or downstream resistance and lead to re-routing via collateral pathways. Whether lymphoedema develops is dependent on the efficiency of such collaterals to accommodate the lymph load.

Reflux results from incompetence of intraluminal lymphatic valves. This is seen in lymphoedema–distichiasis syndrome, where there appears to be genetically-determined valve maldevelopment affecting both lymphatic and venous valves [15].

Table 48.3 Possible causes of lymph drainage failure.

Mechanism	Causes
Reduced lymph-conducting pathways	Hypoplasia of whole vessel, reduced numbers of vessels (initial or collecting) May be developmental failure or acquired obliteration of lymphatic lumen (e.g. lymphangiothrombosis, lymphangitis)
Poorly functioning lymphatics	May be physiological due to lack of movement or structural, e.g. pump (contractility) failure
Obstructed lymphatics	'Scarring' from lymphadenectomy, radiotherapy or infection
Lymph reflux	Megalymphatics, lymph vessel hyperplasia

Pathology. Decreased transport of lymph from the skin leads to an increase in protein-rich interstitial fluid. In circumstances other than where dermal lymphatics are congenitally absent (for example, Milroy's disease) or are destroyed (for example, post-erysipelas/cellulitis), interstitial pressure consequently rises and lymphatics dilate. Temporal changes observed in experimental lymphoedema indicate that the collagen fibres initially become swollen and separated [16]. Mononuclear cells are seen around the lymphatic and blood vessels [17]. Lymphatic walls thicken and fibrose. The muscular elements of the collecting trunks atrophy. Macrophages, fibroblasts and lymphocytes accumulate. Overgrowth of the interstitial connective tissue gradually transforms the soft stage of lymphoedema into the hard late-stage form [18]. The simple excess of protein seems to be the cause of the fibrosis [19,20]. The number of blood vessels greatly increases.

In human skin, the epidermis overlying an area of lymphoedema becomes acanthotic, with reduplication of the epidermodermal basement membrane. In the dermis, there is an increase in collagen, but the elastic fibres, including anchoring filaments, disappear. Ultrastructurally, the basal lamina of the dermal lymphatics thickens, but remains discontinuous, connective tissue microfilaments are increased, myofibroblasts appear and the connective tissue ground substance becomes hyalinized [21]. Inflammatory cells are conspicuous in the dermis. In the infiltrate, mast cells, macrophages, plasma cells and lymphocytes can be observed. Extravasated erythrocytes are often seen and large amounts of fibrin become deposited. Well-characterized morphological changes develop in the blood vessels (lymphostatic vasculopathy). In the upper dermis, numerous newly formed vessels can be seen. Angiogenesis results in a highly vascularized dermis.

Table 48.4 Causes of primary lymphoedema.

Congenital onset		Postpubertal onset	
Familial	**Sporadic**	**Familial**	**Sporadic**
Milroy's disease: below knee and bilateral	Turner's syndrome, Noonan's syndrome: can be transient; other phenotype abnormalities Neurofibromatosis, Proteus syndrome Pure or mixed vascular lymphatic malformations, lymphangiomatosis, Klippel–Trenaunay syndrome, Maffucci's syndrome: usually unilateral Amniotic bands: associated with autoamputation	Distichiasis–lymphoedema, Meige's disease: below knee and bilateral	Distal hypoplasia, lymph reflux: bilateral foot and lower leg swelling Ilioinguinal node sclerosis: whole limb and unilateral Yellow nail syndrome: bilateral, widespread oedema

References

1 Földi M. Insufficiency of lymph flow. In: Földi M, Casley-Smith JR, eds. *Lymphangiology.* Stuttgart: Schattauer, 1983: 195–213.
2 Bull RH, Gane JN, Evans J *et al.* Abnormal lymph drainage in patients with chronic venous leg ulcers. *J Am Acad Dermatol* 1993; **28**: 585–90.
3 Moffatt CJ, Franks PJ, Doherty DC *et al.* Lymphoedema: an underestimated health problem [abstract]. *Br J Dermatol* 2002; **147** (Suppl. 62): 8.
4 Dale RF. The inheritance of primary lymphoedema. *J Med Genet* 1985; **22**: 274–8.
5 Scharz U. Die Häufigkeit des primären Lymphödems. Eine epidemiologische Studie an über 1000 Probanden. *Med Lymph* 1990; **1**: 29–34.
6 Rockson SG, Rivera KK. Estimating the population burden of lymphedema. *Ann N Y Acad Sci* 2008; **1131**: 147–54.
7 Mortimer PS, Bates DO, Brassington HD *et al.* The prevalence of arm swelling following breast cancer treatment. *QJM* 1996; **89**: 377–80.
8 Snijders-Keilholz A, Hellebrekers BW, Zwinderman AH *et al*. Adjuvant radiotherapy following radical hysterectomy for patients with early-stage cervical carcinoma (1984–1996). *Radiother Oncol* 1999; **51**: 161–7.
9 Chatani M, Nose T, Masaki N, Inoue T. Adjuvant radiotherapy after radical hysterectomy of the cervical cancer. Prognostic factors and complications. *Strahlenther Onkol* 1998; **174**: 504–9.
10 Gaarenstroom KN, Kenter GG, Trimbos JB *et al*. Postoperative complications after vulvectomy and inguinofemoral lymphadenectomy using separate groin incisions. *Int J Gynecol Cancer* 2003; **13**: 522–7.
11 Bevan-Thomas R, Slaton JW, Pettaway CA. Contemporary morbidity from lymphadenectomy for penile squamous cell carcinoma: the M.D. Anderson Cancer Center Experience. *J Urol* 2002; **167**: 1638–42.
12 Allan CP, Hayes AJ, Thomas JM. Ilioinguinal lymph node dissection for palpable metastatic melanoma to the groin. *Aust NZ J Surg* 2008; **78**: 982–6.
13 Wrone DA, Tanabe KK, Cosimi AB *et al*. Lymphedema after sentinel lymph node biopsy for cutaneous melanoma: a report of 5 cases. *Arch Dermatol* 2000; **136**: 511–4.
14 Sabel MS, Griffith KA, Arora A *et al*. Inguinal node dissection for melanoma in the era of sentinel lymph node biopsy. *Surgery* 2007; **141**: 728–35.
15 Mellor RH, Brice G, Stanton AW *et al*. Lymphoedema Research Consortium. Mutations in FOXC2 are strongly associated with primary valve failure in veins of the lower limb. *Circulation* 2007; **115**: 1912–20.
16 Altorfer JL, Clodius L. Chronic experimental lymphedema of the extremities: pathological changes. *Experientia* 1976; **32**: 823–5.
17 Olszewski WL. Pathophysiological and clinical observations of obstructive lymphedema of the limbs. In: Clodius L, ed. *Lymphedema*. Stuttgart: Thieme, 1977: 79–102.
18 Drinker CK, Field ME, Homans J. The experimental production of oedema and elephantiasis as a result of lymphatic obstruction. *Am J Physiol* 1934; **108**: 509–20.
19 Willoughby DA, DiRosa M. A unifying concept for inflammation: a new appraisal of some old mediators. *Excerpta Med* 1970; **229**: 28–38.
20 Casley-Smith JR, Gaffney RM. Excess plasma proteins as a cause of chronic inflammation. *J Pathol* 1981; **133**: 227–72.
21 Daroczy J. Pathology of lymphedema. *Clin Dermatol* 1995; **13**: 433–44.

Aetiology and classification

Lymphoedema may be primary (see Table 48.4), secondary (see Table 48.5), dysfunctional or cancer-related.

Primary lymphoedema

Lymphoedema arising from an intrinsic abnormality of the lymph-conducting pathways is referred to as primary lymphoedema [1] (Table 48.4). A simple classification by age of onset without reference to aetiology or other clinical features is into the following subdivisions: congenital (present at or very soon after birth), praecox (presenting before age 35 years) and tarda (presenting after age 35 years). The development of lymphangiography in the 1950s resulted in a radiological classification: aplasia (no formed lymph pathways found), hypoplasia (lymphatics smaller or fewer than normal) and hyperplasia (lymphatics larger and more numerous). Aplasia, hypoplasia and hyperplasia refer to abnormalities in the main (leg) conducting lymph vessels as opacified on lymphangiography, and not to the initial lymphatics, which are not imaged with this method. Further investigation revealed types of lymphoedema where few, if any, lymph conducting vessels could be identified in the foot, but vessels were found to be normal further up the limb [2].

An increasing understanding of the genetic basis of primary lymphoedema has further changed classification and to some extent made the praecox and tarda categories redundant. For example in lymphoedema–distichiasis syndrome (LDS), the onset of lower-limb oedema can range from puberty to 40 years old despite the same cause, namely a mutation in the *FOXC2* gene [3]. Conversely, LDS and Meige forms of primary lymphoedema can both present at puberty with similar lower lymphoedema but have different genotypes and different mechanisms; LDS is associated with hyperplasia and valve reflux of collecting lymphatics whereas Meige's disease is associated with hypoplasia of collecting vessels. In the future, classification of lymphoedema is likely to be based on phenotype, unless the genotype is known.

Inherited forms of lymphoedema where the gene is known

1 *Milroy's disease* (primary congenital lymphoedema, hereditary lymphoedema type 1; MIM 153100). Milroy first described the disease in 1892 but published definitively on it in 1928. He

described a large pedigree with lymphoedema beginning at or soon after birth [4]. Although the same condition was described earlier by Nonne [5], it was Milroy who gave the most complete description, and the eponym 'Milroy's disease' is universally accepted. Milroy's disease is often considered synonymous with primary lymphoedema, but the term should be restricted to cases of congenital lymphoedema with linkage to chromosome 5 or mutations in the *VEGFR-3* gene [6–8]. A failure of lymphangiogenesis due to inactivation of *VEGFR-3* appears to be responsible for the autosomal dominant inheritance of Milroy's disease [8]. Genotype–phenotype correlation demonstrates swelling which is confined to below the knee, and which is often brawny in the extreme with little pitting. Hydrocoele can be an additional feature, as can superficial vein incompetence but, much as Milroy described, there appear to be no other manifestations.

2 *Lymphoedema–distichiasis syndrome* (LDS; MIM 153400). Distichiasis is a congenital anomaly in which accessory eyelashes occur along the posterior border of the lid margins in the position of the Meibomian glands. It causes symptoms of corneal irritation, conjunctivitis and photophobia and occurs from birth. Lymphoedema in this syndrome, however, does not develop before puberty and may be delayed in onset until the fifth decade. Other features of this syndrome include ptosis, congenital heart defects and varicose veins [3]. The lymphatic abnormality appears to be lymph reflux with an increased number of lower-limb lymph vessels [9]. LDS shows an autosomal-dominant pattern of inheritance with variable expression and has been mapped to 16q24.3 [10]. Mutations in *FOXC2* (*MFH-1*), a forkhead family transcription factor, are now known to be responsible for this condition [11].

3 *Hypotrichosis–lymphoedema–telangiectasia syndrome* is a rare inherited disorder caused by mutations in *SOX18* transcription factor and manifesting with bilateral lymphoedema of the legs, hypotrichosis, telangiectases and angiomata limited to acral regions [12]. SOX18 acts as a molecular switch to induce differentiation of lymphatic endothelial cells early in development [13].

4 *Incontentia pigmenti* (MIM 308300). Incontentia pigmenti (IP) is not usually associated with lymphoedema in surviving females. The second liveborn male to be reported recently led to the identification of a *NEMO* (NFκB essential modulator) stop codon mutation in the affected child and in his mother, who had classical IP [14]. He had features of hypohidrotic ectodermal dysplasia with immune deficiency, recurrent infections and lower-limb lymphoedema which developed at a few weeks of age. A lymphoscintigram showed severe lymphatic obstruction. MRI suggested a lymphangiomatous malformation. Cutaneous capillary angiomas and possible mixed vascular/lymphatic malformations coexisted in the gut [15].

Other germline forms of lymphoedema

1 *Meige's disease* (Kinmonth's lymphoedema praecox, hereditary lymphoedema type II; MIM #153200). In 1898, Meige described the pedigree of a family with a distinct history of lymphoedema appearing at puberty [16]. The eponym Meige's disease has therefore come to be associated with this, the commonest variety of primary lymphoedema, which predominantly affects adolescent females. Swelling is usually mild, rarely extends above the knee and is generally bilateral. Lymphography demonstrates a reduced number of distal lymphatics (hypoplasia) with proximal collectors remaining patent. The term Meige's disease should be reserved for familial lymphoedema developing at or soon after puberty in which there are no associated abnormalities, for example distichiasis.

2 *Turner's syndrome.* This well-known abnormality is due to the absence of one X chromosome. Early spontaneous abortion occurs in over 95% of fetuses. Severely affected fetuses who survive to the second trimester can be detected on ultrasonography, which may reveal cystic hygroma, chylothorax, ascites and hydrops fetalis. The diagnosis may be suggested in the newborn by redundant neck skin and peripheral oedema. Surviving children have webbed necks and may exhibit peripheral oedema which often diminishes with age. Conversely oedema may present later in life. Chromosomal testing should always be undertaken in neonates or young children with primary lymphoedema.

3 *Noonan's syndrome* (MIM #163950). Noonan's syndrome is a multiple congenital anomaly syndrome for which mutations in *PTPN11* have been discovered to be the cause [17]. Lymphoedema is usually present at birth but the age of onset may vary from the prenatal period to adulthood. Phenotypic characteristics include short stature, ptosis, low-set ears and posterior hairline, neck webbing and congenital cardiac anomalies (typically pulmonary stenosis).

4 *Hennekam lymphangiectasia–lymphoedema syndrome* (MIM *235510). A syndrome of intestinal lymphangiectasia with severe lymphoedema of the limbs, genitalia and face, with mental retardation [18]. The intestinal lymphangiectasia causes hypoproteinaemia, hypogammaglobulinaemia and lymphopenia. Facial anomalies are characteristic and look somewhat oriental, with flat face, flat nasal bridge, epicanthic folds, hypertelorism, tooth abnormalities and small ears. Onset of lymphoedema is between birth and 12 years, with probable autosomal-recessive inheritance.

5 *Cholestasis–lymphoedema syndrome* (Aagenaes's syndrome; MIM *214900). Jaundice becomes evident soon after birth and recurs throughout life. Oedema of the leg, due to hypoplasia of the lymph vessels, begins at school age and progresses [19].

6 *Microcephaly lymphoedema–chorioretinal dysplasia* (MIM *152950). An autosomal dominant syndrome [20] in which microcephaly and lymphoedema are linked to chorioretinopathy.

7 *Pes cavus and lymphoedema.* Lymphangiography has revealed hypoplasia of leg lymphatics in this disease association [21].

8 *Yellow nail syndrome* (YNS; MIM #153300). The evidence that YNS is inherited is unsubstantiated, only one report describing YNS with familial primary hypoplasia of leg lymphatics [22].

Other genetic forms of lymphoedema

A number of sporadic forms of lymphoedema occur, usually presenting at birth or during childhood. The defect in such cases is likely to be due to a somatic rather than a germ-line mutation.

Klippel–Trenaunay syndrome (MIM 149000) is the commonest type, in which lymphoedema may be the presenting abnormality.

Subsequently, more characteristic features such as limb overgrowth, cutaneous angiomas and venous disease may develop.

Proteus syndrome (MIM 176920) is a very rare syndrome manifesting with many varied (protean) abnormalities. Characteristic features are asymmetrical overgrowth of almost any part of the body, macrodactyly, and rugose or cerebriform overgrowth of the palmar and plantar soft tissue. Verrucous epidermal naevi, angiomas and lymphangiomatous swelling also occur. Germ-line mutations in *PTEN* have been proposed but are not often found [23].

Amniotic bands: another poorly understood form of congenital lymphoedema is that associated with amniotic bands. These bands, which allegedly wrap around digits or limbs, cause circumferential fibrosis and scarring. This can lead to amputation of digits or lymphoedema distal to the band [24].

Maffucci's syndrome (dyschondroplasia with haemangioma, MIM #166000) usually manifests with venous cavernous malformations in infancy, but cavernous lymphangiomas are also often seen, and may be the sole manifestation, giving rise to limb swelling. Hard nodules arise from the bones, especially of the fingers and toes; these are pathologically enchondromas and are radiologically translucent. The malignant potential of the syndrome is high [25].



Fig. 48.5 The commonest form of primary lymphoedema: distal hypoplasia of peripheral lymphatic vessels presenting with asymmetrical but usually bilateral swelling of feet and lower legs.

References

1 Browse NL, Stewart G. Lymphoedema: pathophysiology and classification. *J Cardiovasc Surg* 1985; **6**: 91–106.
2 Browse NL. The diagnosis and management of primary lymphoedema. *J Vasc Surg* 1996; **3**: 181–4.
3 Brice G, Mansour S, Bell R *et al.* Analysis of the phenotypic abnormalities in lymphoedema distichiasis syndrome in 74 patients with FOXC-2 mutations or linkage to 16q.24. *J Med Genet* 2002; **39**: 478–83.
4 Milroy WF. Chronic hereditary oedema: Milroy's disease. *JAMA* 1928; **91**: 1172–5.
5 Nonne M. Vier Fälle von Elephantiasis congenita hereditaria. *Virchows Arch* 1891; **125**: 189–96.
6 Ferrell RE, Levinson KL, Esman JH *et al.* Hereditary lymphoedema: evidence for linkage and genetic heterogeneity. *Hum Mol Genet* 1998; **7**: 2073–8.
7 Evans AL, Brice G, Sotirova V *et al.* Mapping of primary congenital lymphoedema to the 5q.35.3 region. *Am J Hum Genet* 1999; **64**: 547–55.
8 Karkkainen MJ, Ferrell RE, Lawrence EC *et al.* Missense mutations interfere with VEGFR-3 signalling in primary lymphoedema. *Nat Genet* 2000; **25**: 153–9.
9 Dale RF. Primary lymphoedema when found with distichiasis is of the type defined as bilateral hyperplasia by lymphography. *J Med Genet* 1987; **24**: 170–1.
10 Mangion J, Rahman N, Mansour S *et al.* A gene for lymphedema-distichiasis maps to 16q 24.3. *Am J Hum Genet* 1999; **65**: 427–32.
11 Fang J, Dagenais SL, Erickson RP *et al.* Mutations in FOXC-2 (MFH-1) a forkhead family transcription factor are responsible for hereditary lymphedema–distichiasis syndrome. *Am J Hum Genet* 2000; **67**: 1382–8.
12 François M, Caprini A, Hosking B *et al.* Sox18 induces development of the lymphatic vasculature in mice. *Nature* 2008; **456**: 643–7.
13 Irrthum A, Devriendt K, Chitayat D *et al.* Mutations in the transcription factor gene SOX18 underlie recessive and dominant forms of hypotrichosis-lymphedema-telangiectasia. *Am J Hum Genet* 2003; **72**: 1470–8.
14 Smahi A, Courtois G, Vabres P *et al.* Genomic rearrangement in NEMO impairs NFκB activation and is a cause of incontinentia pigmenti. *Nature* 2000; **405**: 466–72.
15 Mansour S, Woffendin H, Mitton S *et al.* Incontentia pigmenti in a surviving male is accompanied by hypohidrotic ectodermal dysplasia and recurrent infection. *Am J Med Genet* 2001; **99**: 172–7.
16 Meige H. Dystrophie oedemateuse héréditaire. *Presse Méd* 1898; **6**: 341–3.
17 Tartaglia M, Mehler EL, Godberg R *et al.* Mutations in PTPN11, encoding the protein tyrosine phosphatase SHP-2, cause Noonan syndrome. *Nat Genet* 2001; **29**: 465–8.
18 Hennekam RCM, Geerdink RA, Hamel BCJ *et al.* Autosomal recessive intestinal lymphangiectasia and lymphedema with facial anomalies and mental retardation. *Am J Med Genet* 1989; **34**: 593–600.
19 Aagenaes O. Hereditary cholestasis with lymphoedema (Aagenaes syndrome): new cases and follow-up from infancy to adult age. *Scand J Gastroent* 1998; **33**: 335–45.
20 Jarmas AL, Weaver DD, Ellis FD, Davis A. Microcephaly, microphthalmia, falciform retinal folds and blindness: a new syndrome. *Am J Dis Child* 1981; **135**: 930–3.
21 Jackson BT, Kinmonth JB. Pes cavus and lymphoedema. *J Bone Joint Surg* 1970; **52**: 518–20.
22 Wells GC. Yellow nail syndrome with familial primary hypoplasia of lymphatics, manifest late in life. *Proc R Soc Med* 1966; **59**: 447.
23 Zhou XP, Hampel H, Thiele H *et al.* Association of germline mutation in the PTEN tumour suppressor gene and Proteus and Proteus-like syndrome. *Lancet* 2001; **358**: 210–1.
24 Coady MS, Moore MH, Wallis K. Amniotic band syndrome: the association between rare facial clefts and limb ring constrictions. *Plast Reconstr Surg* 1998; **101**: 640–9.
25 Carlton A, St. Elkington JC, Greenfield JG *et al.* Maffucci's syndrome. *QJM* 1942; **11**: 203–8.

Phenotypes of primary lymphoedema

Lower limb

1 *Distal hypoplasia.* The most common presentation, contributing about 80% of all cases of primary lymphoedema, is that of mild oedema of both feet and ankles. Patients are usually female with onset at puberty. The swelling is often asymmetrical and deteriorates slowly. Extension above the knee is uncommon and mild (Fig. 48.5). The cause is a paucity of distal lymph vessels.

2 *Proximal obstruction.* This variety is unilateral in 85% of cases. It usually involves the whole limb and develops rapidly. There is no family history. It is of paramount importance to exclude pelvic causes of venous or lymphatic obstruction—for example, tumour or thrombosis. The cause in primary lymphoedema is

fibrosis within ilioinguinal lymph nodes or obliteration of proximal lymph vessels [1].

3 *Bilateral whole-limb swelling*. Reflux of lymph due to gravitational forces and gross incompetence of valves leads to huge dilatation of lymphatic collectors (megalymphatics) in a manner similar to venous reflux and varicose veins. Chylous reflux may coexist.

Progressive distal failure of lymphatic collectors, the so-called 'die-back' phenomenon, occurs with time as a result of proximal obstruction or reflux [2].

Upper limb

Upper limb lymphoedema, if primary in type, usually presents at birth. It may be unisegmental, affecting one limb and the root of that limb, or may be multisegmental in which case it can be associated with lower limb, facial, genital or systemic involvement. Upper limb lymphoedema may form part of a syndrome with overgrowth, for example in Klippel–Trenaunay syndrome.

Genital lymphoedema

Lymphoedema is rarely confined just to the genitalia and is usually associated with intestinal lymphangiectasia/chylous reflux or lower limb swelling.

Facial lymphoedema

If primary facial lymphoedema occurs it is invariably present at birth and improves over time. It is usually asymmetrical and associated with lymphoedema elsewhere. Head and neck oedema occurring *in utero* may regress by birth but leave signs such as prominent medial epicanthic folds or neck webbing.

Secondary lymphoedema

Secondary lymphoedema refers to those forms of lymphoedema resulting from acquired obstruction or obliteration of lymph-conducting pathways due to some identifiable pathological process arising extrinsic to the lymphatic system (Table 48.5). These processes include infection, inflammation, trauma (including surgery and radiation) and malignant disease. No form of lymphoedema is mutually exclusive, and frequently a number of factors combine to produce swelling. For example, lymphoedema may become clinically obvious only when the lymphatic load is increased through higher fluid filtration exhausting lymph drainage capacity.

Table 48.5 Causes of secondary lymphoedema.

Cancer
Treatment
Surgery
Radiotherapy
Tumour
Kaposi's sarcoma
Infiltrative cancer
Lymphoma
Relapsed tumour
Infection
Filariasis
Lymphangitis, lymphadenitis
Cellulitis
Tuberculosis
Lymphogranuloma inguinale
Lice
Inflammation
Lymphatic occlusion
Podoconiosis
Pretibial myxoedema
Dermatitis, e.g. hand eczema
Rheumatoid arthritis
Psoriasis
Rosacea/acne
Granulomatous disease
Orofacial granulomatosis
Crohn's disease
Sarcoidosis
Vascular
Venous disease
Post-thrombotic syndrome
Venous leg ulcers
Trauma
Surgery
Lymphadenectomy
Vein harvesting
Femoropopliteal bypass
Self-harm
Tourniquet application
Intravenous drug abuse
Accident
Degloving injury
Burns

Lymphoedema associated with infection

Infection may cause progressive damage to lymph drainage routes by intraluminal obliteration of lymphatic vessels through processes such as lymphangitis and lymphangiothrombosis.

In recurrent cellulitis or erysipelas, the damage to lymphatics may ultimately lead to formation of lymphoedema, which itself predisposes to further episodes of infection, so exacerbating the lymphoedema [3,4].

Lymphatic filariasis is concentrated in the tropics and subtropics and is the most common cause of lymphoedema worldwide, with an estimated 90 million people affected [5]. Infection is transmitted by mosquitoes, which introduce microfilariae into the skin. These larvae migrate to the lymphatics, where they mature into adult worms. Progressive and permanent damage to the infested lymphatics causes lymphoedema. It has been established in animal studies that, within days of infection, vigorous movement by adult worms directly impacts on the endothelial lining of the lymphatic trunks and indirectly distorts the local lymph-node architecture. Dilated lymphatics with thickened walls and valves, thrombus formation and perilymphangitis result [6].

Lymphogranuloma inguinale and tuberculous node infection can cause lower limb lymphoedema [7]. Lymphoedema of the ear lobe has been described following infestation with head lice [8].

Lymphoedema associated with inflammation

Circumstances exist in which chronic inflammation without evidence of infection is associated with the development of lymph-

oedema. It is assumed that the inflammation progressively damages lymph drainage routes.

Facial lymphoedema may result from rosacea or even acne vulgaris. Skin or subcutaneous initial lymphatics fail rather than main regional collecting trunks. Telangiectasia and inflammation contribute to oedema through increased fluid filtration. In rosacea (Morbihan's disease, solid facial oedema) epithelioid granulomas are often seen with dilated dermal lymphatics [9].

Upper limb swelling may occur following chronic hand dermatitis, with or without documented episodes of lymphangitis [10]. Like other forms of lymphoedema, once established it tends to be permanent, irrespective of remission of the skin disease.

Podoconiosis (non-filarial elephantiasis) is a form of lymphoedema caused by particles of silica dust, present in certain soils, which penetrate the skin of the foot during barefoot walking. The microparticles are taken up by the lymphatics, causing damage. Soils rich in these substances determine the geographical distribution of the condition [11].

Studies with quantitative lymphoscintigraphy and fluorescence microlymphography have confirmed functional and structural changes to lymph drainage in pretibial myxoedema. It is likely that mucin deposition in the dermis impairs initial lymphatic function, resulting in the clinical appearance which resembles lymphoedema [12].

A small number of patients with rheumatoid arthritis develop lymphoedema, predominantly of the upper limbs. A study in rheumatoid arthritis found impaired lymph drainage only in patients with lymphoedema [13]. This suggested that inflammatory arthritis alone does not directly impair lymphatic drainage. Similar findings have been described in psoriatic arthritis [14].

Granulomatous diseases such as Crohn's disease, sarcoidosis, orofacial and anogenital granulomatosis and foreign body reactions from cosmetic procedures [15,16] cause inflammatory changes in local skin and subcutaneous lymphatics, leading to lymphoedematous swelling.

Panniculitis that is extensive enough to cause severe fibrosis may produce lymphoedema. This has been described following idiopathic retroperitoneal fibrosis [17].

Lymphoedema secondary to trauma

Trauma to lymphatics, either from elective surgery or by accident, usually needs to be extensive to induce lymphoedema. Indeed, the experimental production of lymphoedema is extremely difficult to achieve owing to the excellent regenerative powers of lymphatics [18]. It is possibly the failure of lymphatics to regenerate and re-anastomose satisfactorily through scarred or irradiated tissue which is responsible for lymphoedema following cancer treatment. Surgical excision of axillary or ilioinguinal lymph nodes will not uncommonly produce limb lymphoedema. The puzzles are why such intervention in animal models rarely produces chronic swelling and why there can be such a delay—up to 20 years—before lymphoedema manifests [19]. Radiotherapy to lymph nodes can be as much a risk factor towards lymphoedema as surgery [20]. The incidence of lymphoedema following varicose vein surgery is estimated to be 0.5% [21].



Fig. 48.6 Lymphoedema associated with chronic venous disease.

Accidental trauma, such as a degloving injury to a limb, will produce lymphoedema distal to the injury if widespread circumferential scarring occurs.

Self-inflicted injury, such as the repeated application of a tourniquet, will eventually cause permanent lymphatic damage and chronic swelling (Secrétan's syndrome) [22]. The abrupt termination of the swelling often coincides with a depression due to subcutaneous atrophy caused by a tight constricting band. Skin pigmentation may also coexist at the site.

Intravenous drug abuse may cause lymphoedema due to a combination of infection and associated venous damage.

Lymphoedema and venous disease (phlebolymphoedema)

Oedema is a common complication of venous insufficiency. It is assumed that venous oedema is the sole consequence of increased capillary filtration from venous hypertension. As lymph drainage is the main buffer against oedema, it is in fact the failure of local lymphatics to compensate for the increased lymph load from filtration that leads to oedema. Thrombosis of the major veins and deep vein incompetence does not generally affect the main collecting lymphatics but the small initial and precollecting lymphatics of the skin and subcutaneous tissues of the lower leg are damaged by prolonged venous hypertension. Lymphoedema develops with chronic lipodermatosclerosis, with or without venous ulceration. Lymphoscintigraphy has shown impaired limb lymph drainage [23] while fluorescence microlymphography has revealed damaged skin lymphatics [24]. Lymphoedema associated with venous disease can give rise to the most gross swelling and skin changes owing to the combined effect of impaired lymph drainage in the face of increased lymph load (capillary filtration) (Fig. 48.6).

Malignancy-related lymphoedema

Lymph flow is remarkably well maintained through malignant nodes, therefore cancer does not usually present with swelling. The few exceptions to this general rule are lymphophilic tumours, such as malignant eccrine poroma or Kaposi's sarcoma, as well as advanced cancers where other factors such as venous obstruction and hypoproteinaemia will contribute to oedema formation. Recurrent cancer, however, should always be considered as a cause of limb swelling, particularly if associated with pain. Full staging investigations should always be undertaken in such circumstances. Therefore, in general, malignancy-related lymphoedema usually results from cancer therapy, that is surgery, radiotherapy or a combination of the two, or from recurrent tumour directly infiltrating collateral drainage routes.

Kaposi's sarcoma may present with lymphoedema, sometimes years before tumour is evident. The association with lymphoedema [25] supports the view that in Kaposi's sarcoma the endothelial cell phenotype is lymphatic [26].

Lymphoedema arising from dysfunctional lymphatics

Lymph drainage, unlike blood flow, requires intermittent changes in local tissue pressure generated by movement and exercise in order to produce initial lymphatic transport. Consequently, immobility tends to encourage swelling, particularly if gravitational forces (dependency syndrome) encourage ongoing fluid filtration. A common scenario is 'armchair legs', a term coined by Sneddon and Church [27], where patients sit in a chair day and night with their legs dependent (otherwise known as elephantiasis verrucosis nostras, because of the severe lymphoedema skin changes that ensue). No premorbid abnormalities of lymphatics exist, but the immobility results in minimal lymph drainage and a functional lymphoedema due to a lack of movement or exercise to stimulate normal lymph drainage. Dependency of the limb compounds the problem by increasing capillary filtration. The syndrome is not confined to the legs, but can affect any chronically dependent and immobile part, as demonstrated in the pendulous abdomen [28]. With time, pathological changes within the failing lymphatics occur and an irreversible lymphoedema develops.

References

1 Kinmonth JB, Wolfe JH. Fibrosis of the lymph nodes in primary lymphoedema. *Br J Surg* 1966; **53**: 917–25.

2 Fyfe NCM, Wolfe JHN, Kinmonth JB. 'Die-back' in primary lymphoedema. *Lymphology* 1982; **15**: 66–9.

3 Damstra RJ, van Steensel MA, Boomsma JH *et al*. Erysipelas as a sign of subclinical primary lymphoedema: a prospective quantitative scintigraphic study of 40 patients with unilateral erysipelas of the leg. *Br J Dermatol* 2008; **158**: 1210–5.

4 Cox NH. Oedema as a risk factor for multiple episodes of cellulitis/erysipelas of the lower leg: a series with community follow-up. *Br J Dermatol* 2006; **155**: 947–50.

5 Jamal S. Dramatic manifestations of filarial infection. *Lymphology* 1985; **18**: 148–68.

6 Case T, Leis B, Witte M *et al.* Vascular abnormalities in experimental and human lymphatic filariasis. *Lymphology* 1991; **24**: 174–83.

7 Ngu V, Konstam PG. Chronic lymphoedema in Western Nigeria. *Br J Surg* 1964; **51**: 101–10.

8 Manzoon S, Azadeh B. Elephantiasis of external ear: a rare manifestation of pediculosis capitis. *Acta Derm Venereol (Stockh)* 1983; **63**: 363–5.

9 Nagasaka T, Koyama T, Matsumura K, Chen KR. Persistent lymphoedema in Morbihan disease: formation of perilymphatic epithelioid cell granulomas as a possible pathogenesis. *Clin Exp Dermatol* 2008; **33**: 764–7.

10 Worm AM, Staberg B, Thomsen K. Persistent oedema in allergic contact dermatitis. *Contact Dermatitis* 1983; **9**: 517–8.

11 Price EW. *Podoconiosis, Non-Filarial Elephantiasis*. Oxford: Oxford University Press, 1990.

12 Bull RH, Coburn PR, Mortimer PS. Pre-tibial myxoedema: a manifestation of lymphoedema? *Lancet* 1993; **341**: 403–4.

13 Kiely PD, Bland JM, Joseph AE *et al.* Upper limb lymphatic function in inflammatory arthritis. *J Rheumatol* 1995; **22**: 214–7.

14 Mulherin DM, Fitzgerald O, Bresnihan B. Lymphoedema of the upper limb in patients with psoriatic arthritis. *Semin Arthritis Rheum* 1993; **22**: 350–6.

15 Murphy MJ, Kogan B, Carlson JA. Granulomatous lymphangitis of the scrotum and penis. Report of a case and review of the literature of genital swelling with sarcoidal granulomatous inflammation. *J Cutan Pathol* 2001; **28**: 419–24.

16 Salles AG, Lotierzo PH, Gemperli R *et al*. Complications after polymethylmethacrylate injections: report of 32 cases. *Plast Reconstr Surg* 2008; **121**: 1811–20.

17 Mahoney EM, Edwards EA. Spontaneous regression of leg edema and hydronephrosis following idiopathic retroperitoneal fibrosis. *Am J Surg* 1962; **103**: 514–7.

18 Danese C, Bower R, Howard JM. Experimental anastomoses of lymphatics. *Arch Surg* 1962; **84**: 6–9.

19 Stanton AW, Modi S, Bennett Britton TM *et al*. Lymphatic drainage in the muscle and subcutis of the arm after breast cancer treatment. *Breast Cancer Res Treat* 2009; **7**: 29–45.

20 Kissin MW, della Rovere GO, Easton D *et al.* Risk of lymphoedema following the treatment of breast cancer. *Br J Surg* 1986; **73**: 580–4.

21 Ouvry PA, Guenneguez H. Lymphatic complications from variceal surgery. *Phlebologie* 1993; **46**: 563–8.

22 Reading G. Secrétan's syndrome: hard edema of the dorsum of the hand. *Plast Reconstr Surg* 1980; **65**: 182–7.

23 Bull RH, Gane JN, Evans J *et al.* Abnormal lymph drainage in patients with chronic venous leg ulcers. *J Am Acad Dermatol* 1993; **28**: 585–90.

24 Bollinger A, Isrensing G, Franzeck U. Lymphatic microangiopathy: a complication of chronic venous insufficiency. *Lymphology* 1982; **15**: 60–5.

25 Bossuyt L, Van Den Oord JJ, Degreef H. Lymphangioma like variant of AIDS-associated Kaposi's sarcoma with pronounced oedema formation. *Dermatology* 1995; **190**: 324–6.

26 Cueni LN, Detmar M. New insights into the molecular control of the lymphatic vascular system and its role in disease. *J Invest Dermatol* 2006; **126**: 2167–77 [Review].

27 Sneddon I, Church R. *Practical Dermatology*, 4th edn. London: Arnold, 1983: 166.

28 Bull RH, Mortimer PS. Acute lipodermatosclerosis in a pendulous abdomen. *Clin Exp Dermatol* 1993; **18**: 164–6.

Clinical diagnosis of lymphoedema

Lymphoedema most commonly affects the extremities. This predilection for the limbs is due, at least in part, to the limited collateral drainage available at the root of a limb. Careful examination often reveals extension of the swelling to the associated quadrant of the trunk because the lymph drainage routes are shared with the limb.

The major clinical changes of lymphoedema take place in the skin and subcutaneous tissues; such changes are of value in diagnosis. Lymphoedema differs from all other oedemas (in which increased capillary filtration is the major factor) in that cells, proteins, lipids and debris accumulate in addition to water. This results in a 'solid' as well as a 'fluid' component to the swelling, so giving rise to the brawny nature of the oedema which does not readily pit [1]. The lack of pitting is an unreliable sign in lymphoedema, however, because easy displacement of tissue fluid on pressure can often be demonstrated, particularly in the early stages.



Fig. 48.7 The Kaposi–Stemmer sign: inability to pinch or pick up a fold of skin at the base of the second toe indicates lymphoedema.

Lymphoedema does not usually respond to elevation or diuretics, except in the early stages or when it is compounded by increased capillary filtration. Chronic oedema that does not reduce significantly after overnight elevation is likely to be lymphatic in origin. The symptoms accompanying uncomplicated lymphoedema are few. Swelling frequently develops rapidly, for example overnight. In the distal hypoplastic type, one ankle may swell. Pain may feature initially, prompting diagnoses including deep-vein thrombosis or soft-tissue injury. Oedema is often intermittent before becoming permanent, and is often painless although discomfort, aching and tightness are commonly reported symptoms. Eventually both legs swell. In proximal obstructive lymphoedema, swelling usually develops in the thigh and progresses distally.

Although swelling occurs most in the subcutaneous layer, the skin exhibits most changes. It becomes thicker, as demonstrated by the Kaposi–Stemmer sign (inability to pick or pinch a fold of skin at the base of the second toe) (Fig. 48.7) [2]. Skin creases become enhanced and hyperkeratosis develops. Dilatation of upper dermal lymphatics with consequent organization and fibrosis gives rise to papillomatosis. As dermal lymph stasis progresses these skin changes become more marked and are referred to as elephantiasis. Occasionally, the tissue fibrosis and thickening may become so marked in the later stages of lymphoedema that pitting is absent.

Complications

Complications of lymphoedema are mainly due to swelling and infection.

Swelling. Limb swelling leads to discomfort, limb heaviness, reduced mobility and, on occasions, impaired function. The size and weight of affected limbs can result in secondary musculoskeletal complications such as back pain and joint problems. Thickening of the skin causes pseudoscleroderma and consequently impairs small-joint mobility. The difficulty in finding clothes or shoes to fit creates social problems. Poor footwear will further compound the swelling by discouraging a normal gait or enough exercise.

Leakage of lymph through the skin (lymphorrhoea) may occur from engorged dermal lymphatics (lymphangiectasia).

Infection. Episodes of secondary infection, particularly cellulitis or erysipelas, are a characteristic feature of lymphoedema. Patients with lymphoedema irrespective of cause are liable to these attacks, which reflect a failure of immune surveillance. Constitutional symptoms such as fever, rigors, headache or vomiting can be profound and sudden in onset. Within 24 h, redness appears within the lymphoedematous area but without the advancing border. Pain and heat also feature. Recurrent episodes may be frequent and further impair lymph drainage, so exacerbating the lymphoedema. Thus, a vicious cycle is established. Haemolytic streptococci of group A, B or G have been demonstrated [3], although the bacterial aetiology has been brought into question [4]. Indeed, it is not unusual for patients to comment that attacks of cellulitis can be induced by strenuous exercise or long car journeys. This suggests a mechanism not dissimilar to herpes simplex where the microorganism is always present but becomes reactivated.

Fungal infections, particularly tinea pedis, are difficult to avoid because of web-space skin maceration from swollen toes. Local immune deficiency is likely to be a contributing factor, as illustrated by a case of cryptococcosis complicating congenital lymphoedema [5].

Malignancy. A rare but important complication of chronic lymphoedema is the development of cutaneous malignancy. Although the best-known associated malignancy is lymphangiosarcoma [6], other tumours have been recorded and include basal cell carcinoma [7], squamous cell carcinoma, lymphoma [8–11], melanoma [12,13], malignant fibrous histiocytoma [14] and Kaposi's sarcoma [15]. The Stewart–Treves syndrome describes lymphangiosarcoma developing from well-established postmastectomy oedema. However, lymphangiosarcoma is now described as occurring with lymphoedema of any cause. The favoured theory for these associations is altered immune surveillance in the lymphoedematous region [16].

Miscellaneous conditions. A range of other cutaneous conditions have been reported as occurring preferentially at sites of lymphoedematous involvement. These include xanthomatous deposits [17], atypical pemphigoid [18], toxic epidermal necrolysis [19], atypical neutrophilic dermatosis [20] and severe necrotizing fasciitis [21].

References

1 Mortimer PS. Managing lymphoedema. *Clin Exp Dermatol* 1995; **20**: 98–106.
2 Stemmer R. Ein klinisches Zeichen zur Früh- und Differentialdiagnose des Lymphödems. *Vasa* 1976; **5**: 261–2.
3 Baddour LM, Bisno AL. Non-group A β-haemolytic streptococcal cellulitis: association with venous and lymphatic compromise. *Am J Med* 1985; **79**: 155–9.
4 Edwards EA. Recurrent febrile episodes and lymphoedema. *JAMA* 1963; **184**: 858–62.
5 Krywonis N, Kaye VN, Lynch PJ. Cryptococcal cellulitis in congenital lymphoedema. *Int J Dermatol* 1990; **29**: 41–4.

6 Stewart FW, Treves N. Lymphangiosarcoma in postmastectomy lymphoedema. *Cancer* 1948; **1**: 64–81.
7 Benson PM, Pessoa CM, Lupton GP *et al*. Basal cell carcinomas arising in chronic lymphoedema. *J Dermatol Surg Oncol* 1988; **14**: 781–3.
8 Epstein JL, Mendelsohn G. Squamous carcinoma of the foot arising in association with longstanding verrucous hyperplasia in a patient with congenital lymphoedema. *Cancer* 1984; **54**: 943–7.
9 Waxman M, Fatteh S, Elias JM *et al*. Malignant lymphoma of skin associated with postmastectomy lymphoedema. *Arch Pathol Laboratory Med* 1984; **108**: 206–8.
10 Tatnall FM, Mann BS. Non-Hodgkin's lymphoma of the skin associated with chronic limb lymphoedema. *Br J Dermatol* 1985; **113**: 751–6.
11 Hills RJ, Ive FA. Cutaneous secondary follicular centre cell lymphoma in association with lymphoedema praecox. *Br J Dermatol* 1993; **129**: 186–9.
12 Sarkany I. Malignant melanomas in lymphoedematous arm following radical mastectomy for breast carcinoma. *J R Soc Med* 1972; **65**: 253–4.
13 Bartal AH, Pinsky CM. Malignant melanoma appearing in a postmastectomy lymphoedematous arm: a novel association of double primary tumours. *J Surg Oncol* 1985; **30**: 16–8.
14 Fergusson CM, Copeland SA, Horton L. Unusual sarcoma arising in lymphoedema. *J R Soc Med* 1985; **78**: 1497–8.
15 Merimsky O, Chaitchik S. Kaposi's sarcoma on a lymphoedematous arm following radical mastectomy. *Tumori* 1992; **78**: 407–8.
16 Shreiber H, Barry FM, Russell WC *et al*. Stewart–Treves syndrome: a lethal complication of post mastectomy lymphoedema and regional immune deficiency. *Arch Surg* 1979; **114**: 82.
17 Tatnall FM, Sarkany I. Primary focal lymphoedema with xanthoma. *J R Soc Med* 1988; **81**: 113–4.
18 Callens A, Vaillant L, Machet MC *et al*. Localized atypical pemphigoid on lymphoedema following radiotherapy. *Acta Derm Venereol (Stockh)* 1993; **73**: 461–4.
19 Wilkinson SM, Heagarty AH, Smith AG. Toxic epidermal necrolysis localized to an area of lymphoedema. *Clin Exp Dermatol* 1991; **17**: 456–7.
20 Demitsu T, Tadaki T. Atypical neutrophilic dermatosis on the upper extremity affected by post-mastectomy lymphoedema: report of 2 cases. *Dermatologica* 1991; **183**: 230–3.
21 Kaier T, Larsen J. Necrotizing fasciitis in congenital lymphoedema. *Int J Dermatol* 1990; **29**: 41–4.

Midline lymphoedema

Lymphoedema localized to central regions such as the head and neck, trunk or external genitalia is uncommon, presumably because bilateral drainage routes operate and cross-flow from one region to another prevents swelling. Midline lymphoedema therefore usually develops when the lymphatics of the skin or subcutaneous tissue rather than the regional lymphatics fail.

Head and neck lymphoedema

Facial swelling can coexist with obvious primary lymphoedema of one or more limbs, suggesting that there is widespread congenitally determined lymphatic insufficiency. More commonly, the problem occurs later in life secondary to a variety of inflammatory or traumatic mechanisms. Rosacea, and less commonly acne [1,2], are the commonest causes of facial lymphoedema when it is known as Morbihan's disease or solid facial oedema. Swelling affects the central forehead, periocular skin and cheeks where it may be surprisingly asymmetrical. In rosacea, erythema is always present, but inflammatory pustules and papules may be conspicuous by their absence.

Chronic oedema of the eyelids is common and may be quite simply due to acquired lax skin from photo-ageing and other processes which have undermined tissue compliance, such as blepharochalasis [3]. Congenital eyelid lymphoedema may be associated with conjunctival oedema. Medical conditions to be considered with periocular oedema are dermatomyositis, thyroid or renal disease. Contact allergy or angio-oedema, if persistent or recurrent, may slowly compromise lymphatic function. Equally, one severe attack of facial erysipelas or cellulitis may damage lymphatics sufficiently to cause lymphoedema. Angiosarcoma or Kaposi's sarcoma may infiltrate local lymph drainage, and manifest with eyelid oedema.

Redness and swelling of one or both ears may indicate lymphoedema. Rosacea is the most frequent cause [4] but eczema, psoriasis, infection, pediculosis, trauma (cauliflower ears), pediculosis or congenital lymphoedema may also be responsible.

Oedema of the upper or lower lip (or both) may be congenital or result from recurrent angioedema, orofacial granulomatosis (OFG) or from administration of lip fillers for cosmetic purposes. OFG starts with intermittent bouts of swelling resembling angio-oedema, but with time the condition may become persistent. Extension of oedema within the mouth is common and is the reason for the rugose changes on buccal mucosae and tongue (scrotal tongue). Biopsy may or may not reveal the presence of granulomas. If present, a diagnosis of orofacial granulomatosis (granulomatous cheilitis, Melkersson–Rosenthal syndrome) is made, but it remains unclear if the granulomas are cause or effect [5]. It is possible that granulomatous inflammation in isolation can cause orofacial granulomatosis but a thorough search for gastrointestinal Crohn's or systemic sarcoidosis should be made. Despite negative investigations, Crohn's disease of the bowel can become apparent some time later.

Genital lymphoedema

Genital lymphoedema is more common in the male and may develop from lymphatic obstruction due to advanced pelvic/abdominal cancer or its treatment. Bilateral inguinal lymph node biopsy or infiltration of dermal lymphatics from tumour may also cause genital lymphoedema. Genital swelling may be precipitated by compression therapy to one or both lymphoedematous legs by forcing fluid into the adjoining trunk.

Infection may compromise local lymphatics. Recurrent cellulitis is frequently associated and may antedate the swelling.

Granulomatous inflammation from Crohn's disease, hidradenitis suppurativa or sarcoidosis may manifest only with oedema of the penis or scrotum. As with orofacial granulomatosis, anogenital granulomatosis may occur in isolation without associated granulomatous disease elsewhere.

Primary lymphoedema may involve the genitalia but usually in association with leg swelling. In these circumstances vulval lymphoedema may develop into a swollen fold which can extend from a pedicle and become a polyp [6].

References

1 Connelly MG, Winkelmann RK. Solid facial edema as a complication of acne vulgaris. *Arch Dermatol* 1985; **121**: 87–90.
2 Nagasaka T, Koyama T, Matsumura K, Chen KR. Persistent lymphoedema in Morbihan disease: formation of perilymphatic epithelioid cell granulomas as a possible pathogenesis. *Clin Exp Dermatol* 2008; **33**: 764–7.
3 Dozsa A, Karoli ZS, Degrell P. Bilateral blepharochalasis. *J Eur Acad Dermatol Venereol* 2005; **19**: 725–8.
4 Carlson JA, Mazza J, Kircher K, Tran TA. Otophyma: a case report and review of the literature of lymphoedema (elephantiasis) of the ear. *Am J Dermatopathol* 2008; **30**: 67–72.

5 Nozicka Z. Endovasal granulomatous lymphangitis as a pathogenetic factor in cheilitis granulomatosa. *J Oral Pathol* 1985; **14**: 363–5.
6 Orosz Z, Lehoczky O, Szoke J, Pulay T. Recurrent giant fibroepithelial stromal polyp of the vulva associated with congenital lymphedema. *Gynecol Oncol* 2005; **98**: 168–71.

Localized lymphoedema

Breast lymphoedema

As changes to breast cancer treatment have led to more breast-conserving surgery and increased use of therapeutic radiation, so the incidence of lymphoedema localized to the breast has risen [1]. The risk is higher in the obese and in women with larger breasts; the more pendulous the breast, the greater the risk. Inflammation is generally present, resulting in a red, painful swollen breast. Pitting and peau d'orange are most noticeable on the undersurface of the breast. Cellulitis can coexist and is difficult to distinguish from post-radiation changes, as often the only systemic sign of chronic infection is tiredness. Low-dose antibiotics, for example phenoxymethylpenicillin 1 g/day for 6 weeks, may be the only means of proving infection.

Massive localized lymphoedema

Lymphoedema typically affects a region such as a limb but uncommonly it can present as a localized mass resembling a tumour. It is not unusual for an area of lymphoedema on the lower inner thigh or inguinal region to hypertrophy into an enlarged fold and then, under the influence of gravity, progress into a pendulous swelling (Fig. 48.8). Solid or papillomatous plaques can mimic tumours but biopsy will reveal typical features of lymphoedema (elephantiasis), namely: oedema, dilated lymphatics, fibrosis, fat, epidermal acanthosis and hyperkeratosis, and inflammatory dermal infiltrate. Obesity and localized tissue damage increase risk [2,3].



Fig. 48.8 Massive localized lymphoedema.

Scar lymphoedema

Swelling within a scar and adjacent tissues, such as a flap, is common. Impaired lymph drainage contributes to raised and swollen tissues abutting a U-shaped scar because lymphatic pathways do not always re-establish drainage across scars [4].

References
1 Goffman TE, Laronga C, Wilson L, Elkins D. Lymphedema of the arm and breast in irradiated breast cancer patients: risks in an era of dramatically changing axillary surgery. *Breast J* 2004; **10**: 405–11.
2 Farshid G, Weiss SW. Massive localized lymphedema in the morbidly obese: a histologically distinct reactive lesion simulating liposarcoma. *Am J Surg Pathol* 1998; **22**: 1277–83.
3 Lu S, Tran Ta, Jones DM *et al*. Localized lymphedema (elephantiasis): a case series and review of the literature. *J Cutan Pathol* 2008; **36**: 1–20.
4 Warren Ag, Slavin SA. Scar lymphedema: fact or fiction? *Ann Plast Surg* 2007; **59**: 41–5.

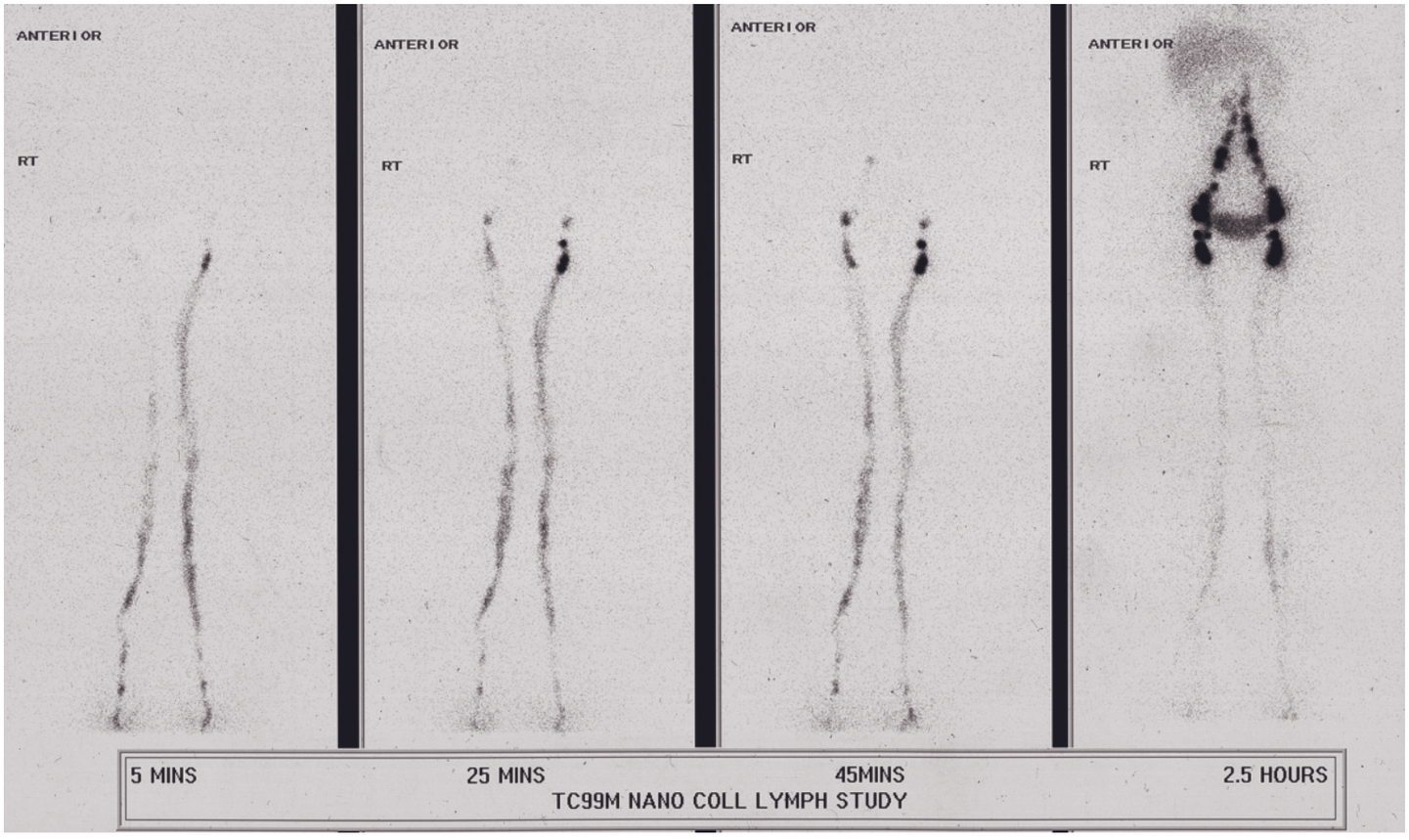
Investigations

Swollen limb

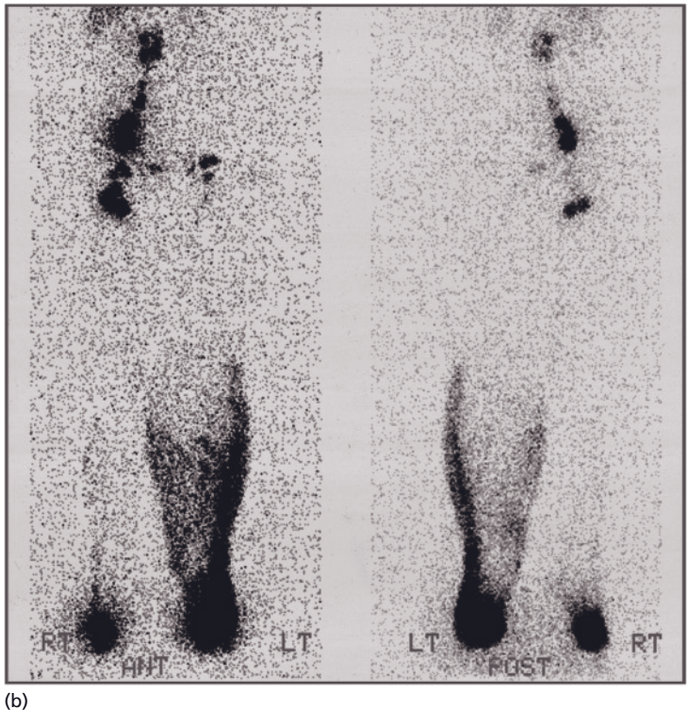
There are limited methods available that permit reliable investigation of lymphatics. Lymphoscintigraphy (isotope lymphography) involves the interstitial (dermis or subcutis) injection of a radiolabelled protein or colloid. Radioactivity, measured using a wide field-of-view γ-camera, is determined over the injection site depot and at regions of interest over vessels or nodes. Measurement of transit times and time activity curves permit quantitative analysis of lymph drainage [1]. Measurement of tracer uptake within axillary or inguinofemoral lymph nodes at a specified time following a standardized exercise routine will discriminate lymphoedema from oedema of non-lymphatic origin [2] (Fig. 48.9).

Computed tomography (CT) of lymphoedematous limbs has demonstrated a characteristic 'honeycomb' pattern in the subcutaneous compartment which other oedemas do not show [3]. CT not only provides information through cross-sectional area of volume change to a limb, but will also identify the compartment in which that change takes place. Whereas in post-thrombotic syndrome the muscle compartment deep to the fascia is enlarged, in lymphoedema it is unchanged or may even show some reduction in size. Thickening of the skin is also a characteristic feature of lymphoedema, although not specific. Magnetic resonance imaging (MRI) is potentially better than CT for distinguishing types of oedema [4].

X-ray contrast lymphography remains the gold standard for demonstrating lymphatic collecting trunks and nodes [5]. The technique is invasive and difficult to perform in the presence of oedema. It involves first of all the interstitial subcutaneous injection of a vital dye—for example, patent blue—to visualize the lymphatic for cannulation. The oily contrast medium Lipiodol is then administered directly into the peripheral lymphatic identified, usually on the dorsum of the foot. The failure to opacify subcutaneous collectors with the vital dye and its persistence in



(a)



(b)

Fig. 48.9 (a) Normal lymphoscintigraphy. Images show patent lymph routes draining tracer from feet to ilio-inguinal nodes. (Courtesy of Professor A.M. Peters.) (b) Obstruction of lymph drainage at the groin leads to re-routing of tracer through skin collaterals (dermal backflow).

the tissues for days afterwards are sufficient evidence for a diagnosis of lymphoedema. If there is lymphatic obstruction, the dye will often flow retrogradely into the dermal network—so-called 'dermal backflow'. Lymphography has been used to confirm lymphoedema less often since the advent of lymphoscintigraphy.

MR lymphangiography (MRL) has recently been introduced to overcome the invasive nature of X-ray lymphography. MRL involves the interstitial injection of paramagnetic contrast agent which delineates the collecting lymphatic vessels of the limb as well as regional lymph nodes and any re-routing such as collateral dermal backflow [6,7].

Initial lymphatics

In vivo visualization of lymphatic vessels (lymphangiography) was first achieved using vital dyes—for example, patent blue—to delineate intradermal and subcutaneous lymphatics. Some classic studies were undertaken in this way [8]. Fluorescence microlymphangiography enables the superficial lymphatic network of the skin to be seen under the vital microscope by means of fluorescing molecules (FITC-Dextran, Sigma) which, when injected subepidermally, are taken up by the initial lymphatics. Information regarding the morphology of functional initial lymphatics and the extent of tracer propagation within the dermal lymphatic network can be recorded on video for analysis [9].

Indirect lymphography involves the intracutaneous injection of a water-soluble contrast medium. Using an infusion pump, the contrast medium is administered over 10 min to create a depot of approximately 3 mL. Intradermal and subcutaneous lymphatics can be opacified by X-ray using the mammography film method, sometimes as far as the first lymph node [10,11]. The advantages over conventional lymphography are the convenience of the interstitial injection without recourse to direct access into the lymphatics, and the ease of application to multiple sites.

Skin biopsy

The distinction between lymphatic and blood vessels in skin biopsy sections has been made more straightforward by specific lymphatic markers. D2-40 (Podoplanin) is considered the most robust as it stains initial lymphatics, pre-collectors and collecting vessels but not blood vessels. LYVE-1 stains initial lymphatics but also macrophages and is down-regulated by inflammation. Prox-1 and VEGFR3 are also lymphatic-specific and stain larger vessels. A panel of markers is recommended, particularly in vascular malformations where differentiation between venous and lymphatic phenotypes may not be clear-cut [12].

CD31 and CD34 stain both lymphatic and blood vascular endothelium.

References

1 Stewart G, Gaunt J, Croft DN *et al.* Isotope lymphography: a new method of investigating the role of lymphatics. *Br J Surg* 1985; **72**: 906–9.

2 Proby CM, Gane JN, Joseph AE *et al.* Investigation of the swollen limb with isotope lymphography. *Br J Dermatol* 1990; **123**: 29–38.

3 Vaughan BF. CT of swollen legs. *Clin Rad* 1990; **41**: 24–30.

4 Duewell S, Hagspiel KD, Zuber J *et al.* Swollen limb extremity: role of MR imaging. *Radiology* 1992; **184**: 227–31.

5 Kinmonth JB. Lymphangiography in man. *Clin Sci* 1952; **11**: 13–20.

6 Lohrmann C, Felmerer G, Foeldi E *et al*. MR lymphangiography for the assessment of the lymphatic system in patients undergoing microsurgical reconstruction of lymphatic vessels. *Microvasc Res* 2008; **76**: 42–5.

7 Lu Q, Xu J, Liu N. Chronic lower extremity lymphedema: a comparative study of high-resolution interstitial MR lymphangiography and heavily T2-weighted MRI. *Eur J Radiol* 2008. (Epub ahead of print.)

8 Hudack SS, McMaster PD. Lymphatic participation in human cutaneous phenomena. *J Exp Med* 1933; **57**: 751–74.

9 Bollinger A, Jager K, Spier F, Seglias J. Fluorescence microlymphography. *Circulation* 1981; **64**: 1195–200.

10 Partsch HT, Urbanek A, Wenzel-Hora B. The dermal lymphatics in lymphoedema visualized by indirect lymphography. *Br J Dermatol* 1984; **110**: 431–8.

11 Partsch H, Stoberl CL, Urbanek A *et al.* Clinical use of indirect lymphography in different forms of leg oedema. *Lymphology* 1988; **21**: 152–60.

12 Costa da Cunha Castro E, Galambos C. Prox-1 and VEGFR3 antibodies are superior to D2-40 in identifying endothelial cells of lymphatic malformations—a proposal of a new immunohistochemical panel to differentiate lymphatic from other vascular malformations. *Pediatr Dev Pathol* 2009; **12**: 187–94.

Differential diagnosis of the swollen limb (Table 48.6)

Swelling of a limb may be caused by oedema, in which case pitting should be evident to some degree, or it may be caused by an increase in volume of other tissue elements, for example bone, muscle or fat. MRI scanning is useful in circumstances where the nature of the swelling is uncertain. One must remember also that a patient may perceive one leg to be swollen when in fact the other leg has become smaller, for example through atrophy of muscle or fat.

Obvious lymphoedema with characteristic skin changes is not usually a difficult diagnosis but such cases are relatively uncommon. Milder cases frequently go unrecognized. Chronic non-inflammatory, and in particular asymmetrical, limb oedema should always suggest lymphoedema. In such cases lymphoscintigraphy is the investigation of choice.

Systemic causes of oedema including cardiac disease, renal disease or hypoproteinaemia should always be considered, particularly if bilateral leg swelling is present. Calcium channel blocking agents cause peripheral oedema in 50% of cases.

Lipoedema

A condition frequently misdiagnosed as lymphoedema is lipoedema (lipidosis, lipodystrophy) in which a 'fatty', non-pitting swelling is confined to the legs, thighs, hips and sometimes arms overlying the triceps [1,2]. Lipoedema is peculiar to females and is usually dismissed as a variant of normality in women with chunky legs and a 'bottom-heavy' weight distribution. Features of importance in recognition include: (i) onset at puberty or times of hormonal change, for example oral contraception, pregnancy or menopause; (ii) bilateral and symmetrical involvement of the lower limbs with sparing of the feet resulting in an 'inverse shouldering' effect at the malleoli (Fig. 48.10); (iii) tenderness and easy bruising; (iv) absence of pitting and lack of benefit from elevation; and (v) lack of benefit from dieting (dieting tends to result in weight loss from body sites other than those affected by lipoedema). Lymph drainage within main leg lymphatics is relatively normal [3] until the later stages when foot oedema develops—the so-called lipoedema–lymphoedema syndrome.

Table 48.6 Causes of a swollen limb.

Congenitally determined
Vascular
Vascular malformation
Diffuse phlebectasia
Klippel–Trenaunay syndrome
Parkes-Weber syndrome
Maffucci's syndrome
Lymphatic
Lymphoedema
Lymphatic malformation (Lymphangioma)
Other
Fat hypertrophy
Lipoedema
Plexiform neurofibroma
Proteus syndrome
Muscle hamartoma
Gigantism
Tissue hypertrophy/hemihypertrophy
Acquired
Vascular
Deep venous thrombosis
Post-thrombotic syndrome
Chronic venous reflux
Venous outflow obstruction
Thrombophlebitis
Venous injury, e.g. intravenous drug abuse
Idiopathic oedema of women
Acute arterial ischaemia
Reflex sympathetic dystrophy
Lymphatic
Lymphoedema
Dependency syndrome/elephantiasis/armchair legs
Trauma
Reconstructive surgery
Femoropopliteal bypass
Vein harvesting
Factitial (tourniquet)
Pretibial myxoedema
Inflammatory
Cellulitis/erysipelas
Varicose eczema
Asteatotic eczema
Psoriasis
Musculoskeletal
Rheumatoid arthritis
Joint effusion
Ruptured Baker's cyst
Haematoma
Torn muscle
Pathological fracture
Achilles tendonitis
Myositis ossificans
Paget's disease
Tumours
Lymphoma
Sarcoma
Metastases



Fig. 48.10 Lipoedema.

Patients with lipoedema gain weight easily and often prefer to be fat than to diet furiously and suffer the embarrassment of thin torso, face and neck while retaining huge legs.

Liposuction performed with tumescent local anaesthesia and using vibrating microcannulae has proved to be a new effective treatment. A targeted and permanent reduction of the fat tissue leads to an increased quality of life due to an improved appearance, reduced tendency to swelling and less pain [4].

Males are very rarely involved and only when there is an underlying hormonal problem such as testosterone deficiency or oestrogen excess with chronic liver disease.

Dercum's disease (adiposis dolorosa, lipomatosis dolorosa, morbus Dercum) is a rare disorder resulting in painful fatty deposits around the upper legs, trunk and upper arms [5]. When pain is a significant symptom with lipoedema it is known as the painful fat syndrome and indistinguishable from Dercum's disease.

Obesity and lymphoedema

Obesity is a significant risk factor for lymphoedema in the arms as well as the legs. Obesity increases the risk of breast cancer-related lymphoedema [6]. Furthermore, dieting improves arm swelling beyond that possible through loss of subcutaneous fat from weight loss [7], irrespective of the diet used [8].

The pathophysiology of lower-limb lymphoedema can be complex. Increased abdominal girth and intra-abdominal pressure impair venous return, particularly when sitting, with the abdominal apron compressing the thighs. Higher venous pressures will increase fluid filtration into the legs so increasing lymph load. However, lymph drainage may also be compromised in the same sitting position, and is certainly decreased as a result of the reduced

exercise associated with obesity [9]. Severely obese patients suffering from sleep apnoea will tend to retain fluid for complex hormonal and autonomic reasons, while sleeping in a chair causes 'armchair legs' as described earlier.

Limb overgrowth (hypertrophy)

Limb hypertrophy (overgrowth) may be mistaken for lymphoedema but also be associated with it. Occasionally, lymphoedema coexists with complete hemihypertrophy, Klippel–Trenaunay syndrome, Parkes-Weber syndrome (multiple arteriovenous anastomoses) or proteus syndrome. Elephantiasis neurofibromatosa is a diffuse neurofibromatosis of nerve trunks with overgrowth of the subcutaneous tissue and of the skin, producing considerable enlargement of that region.

Yellow nail syndrome

YNS is associated with peripheral oedema, but the clinical features rarely resemble classical lymphoedema. Lymphangiogram abnormalities have been described [10], although a lymphoscintigraphic study demonstrated that a primary lymphatic abnormality is unlikely [11].

References

1 Wold LE, Hines EA, Allen EV. Lipoedema of the legs. *Ann Intern Med* 1949; **34**: 1243–50.
2 Kröger K. Lymphoedema and lipoedema of the extremities. *VASA* 2008; **37**: 39–51.
3 Harwood CA, Bull RH, Evans J *et al*. Lymphatic and venous function in lipoedema. *Br J Dermatol* 1996; **134**: 1–6.
4 Schmeller W, Meier-Vollrath I. Tumescent liposuction: a new and successful therapy for lipedema. *J Cutan Med Surg* 2006; **10**: 7–10.
5 Wortham NC, Tomlinson IP. Dercum's disease. *Skinmed* 2005; **4**: 157–62.
6 Hayes SB, Freedman GM, Li T *et al*. Does axillary boost increase lymphedema compared with supraclavicular radiation alone after breast conservation? *Int J Radiat Oncol Biol Phys* 2008; **72**: 1449–55.
7 Shaw C, Mortimer P, Judd PA. A randomized controlled trial of weight reduction as a treatment for breast cancer-related lymphedema. *Cancer* 2007; **110**: 1868–74.
8 Shaw C, Mortimer P, Judd PA. Randomized controlled trial comparing a low-fat diet with a weight-reduction diet in breast cancer-related lymphedema. *Cancer* 2007; **109**: 1949–56.
9 Mortimer PS, Levick JR. Chronic peripheral oedema: the critical role of the lymphatic system. *Clin Med* 2004; **4**: 448–53.
10 Emerson PA. Yellow nails, lymphoedema and pleural effusions. *Thorax* 1966; **21**: 247–53.
11 Bull RH, Fenton DA, Mortimer PS. Lymphatic function in the yellow nail syndrome. *Br J Dermatol* 1996; **134**: 307–12.

Management of lymphoedema

Lymphatic failure results in the accumulation of protein as well as water within the swollen tissues. Treatment is difficult because of the presence of the 'solid' component in the swelling. The management of lymphoedema varies greatly around the world. In developed countries, the emphasis is more on physical forms of therapy involving massage, exercise and compression designed to stimulate lymph drainage, whereas in poorer, hotter countries where hosiery and appropriate bandages are too costly and uncomfortable, surgery may be the mainstay of treatment. Two particular problems need to be overcome with lymphoedema: the swelling and the predisposition to infections, particularly recurrent cellulitis.

There is limited research to inform evidence-based guidelines on the treatment of lymphoedema. Nevertheless, robust guidelines developed through consensus by experts do exist [1, 2].

References

1 Medical Education Partnership. *Best Practice for the Management of Lymphoedema: International Consensus*. London: MEP Ltd, 2006. www.library.nhs.uk
2 Clinical Resource Efficiency Support Team. *Guidelines on the Diagnosis, Assessment and Management of Lymphoedema*, 2008. www.crestni.org.uk

Assessment

Medical

Medical assessment aims to identify and exclude other causes of peripheral oedema. In circumstances where systemic causes for peripheral oedema, for example heart failure, have led to, or coexist with, the lymphoedema, then treatment of the internal medical condition must be undertaken before embarking on specific lymphoedema therapy. Where necessary, appropriate investigations should be performed to confirm lymphoedema and to identify treatable underlying causes (e.g. active cancer) or comorbidities (e.g. superficial venous incompetence).

Lymphoedema therapy

All patients with a diagnosis of lymphoedema should be referred to the local trained lymphoedema therapist. A list of trained therapists can usually be accessed through the national professional body for lymphoedema, for example the British Lymphology Society (http://www.thebls.com/directory); the National Lymphedema Network (USA) (http://www.lymphnet.org); and the Lymphoedema Association of Australia (http://www.lymphoedema.org.au).

Best practice for management will focus on the needs of each individual patient. This may include: (i) risk reduction, for example breast cancer patients; (ii) swelling reduction and improvement of shape; (iii) treatment and prevention of infection; (iv) treating skin problems such as elephantiasis, lymphorrhoea and wounds as well as discouraging tissue fibrosis; (v) restoring functional independence and correcting posture imbalance; and (vi) pain and psychosocial management. Therapy assessment will also include setting the benchmarks against which improvement can be judged, for example limb volume measurement, mobility and functional assessments. A treatment plan will depend on the site and severity of the lymphoedema and the need to engage other services, for example leg ulcer, oncology, vascular etc.

Physical therapy (decongestive lymphatic therapy, combined decongestive treatment)

Physical methods of treating lymphoedema have been practised in Europe for many years [1]. Therapy essentially aims to control lymph formation (capillary filtration), including treatment of inflammatory causes or of venous hypertension, and to improve lymph drainage through existing lymphatics and collateral routes by applying normal physiological procedures that stimulate lymph flow. Physical treatment can, in the majority of cases,



Fig. 48.11 Reduction of swelling in lymphoedema following 3 weeks' intensive therapy with multilayer bandaging and an exercise programme (the same patient as in Fig. 48.5).

improve quality of life considerably (Fig. 48.11). Central to management is getting patients to understand their condition and know what they can do for themselves [2]. Only then can a high level of motivation and compliance with treatment be generated.

It is important to explain to patients that, unlike the blood, which is propelled by the heart, lymph drainage relies on local changes in tissue pressure generated by exercise and movement. Physical treatment exploits these principles, enhancing lymph flow as much as possible within the limits of a compromised drainage. It should be appreciated that lymph flow still exists in lymphoedema, otherwise swelling would be a relentlessly progressive process.

Cornerstones of physical therapy

1 Care of the skin and prevention of infection

Elephantiasis skin changes are not only unsightly but lead to problems including infection, odour, lymphorrhoea, restricted movement from fibrosis (pseudoscleroderma) and possibly poor wound healing. Such problems can be particularly troublesome where fibrosis has become excessive—for example after trauma or surgery. Regular application of an emollient is important for hydrating the hardened skin so making it more supple and discouraging hyperkeratosis. Tinea pedis is almost invariable because of the closely apposed swollen toes, circumstances not improved by elastic hosiery. Modern antifungal creams unfortunately macerate skin further and therefore it is suggested that terbinafine cream is applied for 2 weeks followed by an alcohol wipe (assuming the skin is not broken). For deep cracks and crevices which bacteria may readily colonize, regular toilet is necessary followed by an antiseptic soak, for example potassium permanganate. Hyperkeratosis can often be improved through the regular application of 5% salicylic acid ointment, but the best treatment to reverse elephantiasis skin changes is long-term compression. Areas that constantly seep lymph should also respond to sustained compression.

Prevention of infection, particularly lymphangitis/cellulitis, is crucial to the control of lymphoedema. Care of the skin, good hygiene, control of tinea pedis and good antisepsis following abrasions and minor wounds are important to reduce risk of cellulitis.

2 Exercise

Exercise and movement are crucial to lymph drainage [3,4]. Dynamic muscle contractions (isotonic exercises) encourage both passive (movement of lymph along tissue planes or through non-contractile lymphatics) and active (increased contractility and therefore propulsion of lymph within contractile lymphatics) phases of lymph drainage. Overexertion and excessive static (isometric, e.g. gripping) exercise increase blood flow, which therefore tends to increase oedema.

3 External compression (hosiery, bandage or pneumatic compression)

External compression complements the exercise programme. Such compression is not intended to 'squeeze' oedema but to act as a counterforce to striated muscle activity and so generate higher tissue pressures during contractions. This provides the most powerful stimulus to lymph drainage. Compression also limits capillary filtration by opposing capillary pressure. Without exercise compression is much less effective.

Multilayer bandaging can be used for limb reduction, but also has the advantage of restoring limb shape so that subsequent use of compression garments (hosiery) is more effective at controlling swelling [5]. Bandaging may be the only method suitable for huge misshapen limbs and for controlling lymphorrhoea. Layers of strong, non-elastic (short-stretch) bandages are applied to generate a high pressure during muscular contractions but low pressure at rest. The use of foam or soft padding helps to distribute pressure more evenly and to protect the skin. The digits are also bandaged to control swelling of fingers and toes. The strategic positioning of rubber pads 'irons out' pockets of swelling and deep skin folds. Multilayer bandaging is a skill that takes time to learn and should not be undertaken by any professional without appropriate training. The compression administered may have to be modified in circumstances such as cancer requiring palliative treatment, moderate limb ischaemia, or if there is any neurological deficit.

Hosiery (below-knee or full-length stockings, half or full tights, sleeves) usually requires high compression and double hoses may occasionally be required. Most garments last no more than 6 months. Two garments (or pairs) should be provided, one to wear and one for the wash. Washing is necessary to maintain the compression properties of the garment. The patient's technique for application, removal and care of garments are crucial for a successful outcome.

Pneumatic compression therapy (intermittent/sequential pneumatic compression) should not be used in preference to exercise and compression but can be useful in mixed lympho-

venous oedema and in infirm patients [6]. An inflatable boot, legging or sleeve is connected to a motor-driven pump and lymph is displaced towards the root of the limb. If hosiery is not fitted immediately following compression therapy, the swelling readily recurs. Pneumatic compression softens the tissues and reduces limb volume during treatment, but it is doubtful that any long-term benefit is gained over hosiery and exercise alone.

4 Massage (manual lymphatic drainage therapy)
Massage is an important component of treatment, particularly for midline lymphoedema where there are few alternatives [1]. The problem is that there are different forms of massage, used mostly for increasing blood flow and therefore of vigorous nature. Tissue movement, if gentle, is a stimulus to lymph flow without increasing blood flow [7]. Indeed, in the absence of lymphatic contractility, massaging of filled lymphatics by muscle exercise or surface massage may be the major stimulus to lymph flow, just as it is with blood flow during cardiac arrest [4]. The skin lymphatic network is the likely route for collateral drainage to areas which have normal lymph drainage [8]. The practice that encourages such flow, referred to as manual lymphatic drainage therapy (MLD), is directed at normally draining lymph node regions; this 'siphons' or 'milks' lymph away from congested lymphoedematous areas, so complementing attempts to improve drainage 'upstream' by exercise and external compression. Continuous MLD delivered by a therapist is expensive and few health care providers will fund this long term. Simple lymphatic drainage (SLD) is a best alternative to MLD, and can be delivered by a partner or carer trained in the technique.

5 Breathing, postural exercise, elevation and rest
Breathing and postural exercises are also important, particularly for clearance of lymph from the thorax and abdomen. Without the dispersal of truncal lymph, more peripheral limb oedema will not drain. Elevation *per se* does nothing to improve lymph drainage, but lowering venous pressure (and therefore filtration) can help to reduce swelling. Rest and elevation alone, however, are not the correct treatment for lymphoedema!

Additional therapies

1 Weight loss. Many patients with lymphoedema are overweight, because of morbid obesity as well as fluid retention. Excessive weight gain is likely to impair lymph drainage in the same way as it impairs venous drainage, and obesity reduces mobility (and therefore exercise). Control of weight in combination with physical treatment may be sufficient to resolve oedema completely in some patients. Weight loss irrespective of type of diet has been shown to reduce arm volume over and above what would be expected from fat loss alone in breast cancer related lymphoedema [9,10].

2 Hyperbaric oxygen (HBO), low-level laser therapy (LLLT) and Kinesiotaping. There are some data recommending the use of HBO and LLLT independently in breast cancer related lymphoedema [11–13]. Kinesiotaping has been shown to increase lymph flow [14].

Intensive and maintenance treatment

Patients with mild limb lymphoedema, no fibrosis and no shape distortion can be started on maintenance treatment with compression hosiery. Intensive therapy, comprising a 2- to 4-week course of daily skin care, MLD, multi-layer bandaging and exercises, is indicated for patients with moderate to severe limb swelling, poor limb shape or tissue changes such as fibrosis, elephantiasis or lymphorrhoea. Once intensive treatment is complete, maintenance treatment is started.

Evidence of efficacy

While decongestive lymphatic therapy has become accepted first-line therapy [15], evidence for best treatment is weak. Using limb volume change as the main outcome measure, bandaging plus hosiery was significantly more effective at 6 months than hosiery alone [5]; hosiery was more effective than no hosiery [16]; MLD was more effective than SLD [17], although effects on total arm volume can be small [18]. Pneumatic compression therapy was no better than no treatment [19].

Management of midline lymphoedema

Management of lymphoedema of the head and neck, trunk, breast or genitalia can be challenging.

Truncal lymphoedema implies involvement of a body quadrant, for example a forequarter or hindquarter, and is usually associated with swelling of the adjoining limb. Lymphatic obstruction at the root of the limb, for example from tumour, should always be considered with truncal oedema. Clearance of the trunk, usually with MLD, is necessary before improvement of the limb can be expected.

Breast lymphoedema generally follows cancer treatment and is usually associated with inflammation from radiation or infection. Infection may be extremely difficult to control in these circumstances, requiring low-dose antibiotics, for example phenoxymethylpenicillin 500 mg twice daily for many weeks. Dependency is a contributing factor to oedema formation, particularly in a large breast, and a firm supportive bra, day and night, is recommended. Only then should MLD be introduced.

Genital lymphoedema can occur in the male or female but is more severe in the penis and scrotum due to a combination of dependency and limited drainage outlet routes. Genital lymphoedema is associated with lower-limb swelling when oedema creeps up to involve the lower trunk, such as following surgery or radiotherapy to ilioinguinal lymph nodes, in heart failure and sometimes with genetic forms of lymphoedema. Sadly, genital swelling may appear for the first time when lower limb oedema is forced up into the trunk by over-vigorous leg compression. When lymphoedema is limited to the male genitalia then underlying inflammation from granulomatous disease (Crohn's disease, sarcoidosis, hidradenitis suppurativa or anogenital granulomatosis) or due to infection have to be considered before embarking on specific lymphoedema treatment. MLD and innovative ways of applying compression [20] are most widely used but surgery can be considered at an early stage.

Lymphoedema of the head and neck is often a complication of cancer or its treatment. Facial lymphoedema (solid facial oedema) is most frequently caused by rosacea or acne but a differential diagnosis includes dermatomyositis, thyroid disease, lymphoma and (lymph)angiosarcoma. Periorbital oedema may result from loose eyelid skin, for example blepharochalasia (floppy eyelid

syndrome), where low compliance encourages oedema [21]. Once underlying conditions have been treated or excluded, MLD and SLD are introduced. Raising the head of the bed with blocks can be invaluable for preventing reaccumulation of oedema overnight.

References

1 Foldi E, Foldi M, Weissleder H. Conservative treatment of lymphoedema of the limbs. *Angiology* 1985; **36**: 171–80.
2 Mortimer P, Todd J. *Lymphoedema: Advice on Self-management and Treatment*, 3rd edn. Beaconsfield: Beaconsfield Publishers, 2007.
3 Ikomi F, Schmid-Schonbein GW. Lymph transport in skin. *Clin Dermatol* 1995; **13**: 419–27.
4 Roddie IC. Lymph transport mechanisms in peripheral lymphatics. *News Physiol Sci* 1990; **5**: 85–9.
5 Badger CMA, Peacock JL, Mortimer PS. A randomized, controlled, parallel group clinical trial comparing multi-layer bandaging followed by hosiery versus hosiery alone in the treatment of patients with lymphedema of the limb. *Cancer* 2000; **88**: 2832–7.
6 Anonymous. Compression for lymphoedema. *Lancet* 1986; **i**: 896.
7 Mortimer PS, Simmonds R, Rezvani M *et al*. Measurement of skin lymph flow by an isotope clearance technique: reliability, reproducibility effect of injection dynamics and lymph flow enhancement. *J Invest Dermatol* 1990; **95**: 677–82.
8 Tiedjen KU, Knorz S, Heimann KD. The skin: lymphatic collateral organ? *Scope Phlebol Lymphol* 1994; **1**: 7–12.
9 Shaw C, Mortimer P, Judd PA. A randomised controlled trial of weight reduction as a treatment for breast cancer-related lymphedema. *Cancer* 2007; **110**: 1868–74.
10 Shaw C, Mortimer P, Judd PA. Randomised controlled trial comparing a low-fat diet with a weight-reduction diet in breast cancer-related lymphedema. *Cancer* 2007; **109**: 1949–56.
11 Gothard L, Stanton A, MacLaren J *et al*. Non-randomised phase II trial of hyperbaric oxygen therapy in patients with chronic arm lymphoedema and tissue fibrosis after radiotherapy for early breast cancer. *Radiother Oncol* 2004; **70**: 217–24.
12 Carati CJ, Anderson SN, Gannon BJ, Piller NB. Treatment of postmastectomy lymphedema with low-level laser therapy: a double blind, placebo-controlled trial. *Cancer* 2003; **98**: 1114–22. [Erratum *Cancer* 2003; **98**: 2742.]
13 Kozanoglu E, Basaran S, Paydas S, Sarpel T. Efficacy of pneumatic compression and low-level laser therapy in the treatment of postmastectomy lymphoedema: a randomized controlled trial. *Clin Rehabil* 2009; **23**: 117–24.
14 Tsai HJ, Hung HC, Yang JL *et al*. Could Kinesio tape replace the bandage in decongestive lymphatic therapy for breast-cancer-related lymphedema? A pilot study. *Support Care Cancer* 2009. [Epub ahead of print.]
15 Rockson S, Miller L, Senie R. Workshop III: diagnosis and management of lymphedema. *Cancer* 1998; **83** (Suppl.): 282–5.
16 Hornsby R. The use of compression to treat lymphoedema. *Prof Nurse* 1995; **11**: 127–8.
17 Williams AF, Vadgama A, Franks P, Mortimer PS. A randomized controlled cross-over study of manual lymphatic drainage therapy in women with breast cancer-related lympoedema. *Eur J Cancer Care* 2002; **11**: 254–61.
18 Andersen L, Hojris I, Erlandsen M, Andersen J. Treatment of breast-cancer related lymphoedema with or without manual lymph drainage: a randomized study. *Acta Oncol* 2000; **39**: 399–405.
19 Dini D, Del Mastro L, Gozza A *et al*. The role of pneumatic compression in the treatment of postmastectomy lymphedema: a randomized phase III study. *Ann Oncol* 1998; **9**: 187–90.
20 Whitaker J. Best practice in managing scrotal lymphoedema. *Br J Community Nurs* 2007; **12** (Suppl.): S17–21.
21 Collin JR. Blepharochalasis. A review of 30 cases. *Ophthal Plast Reconstr Surg* 1991; **7**: 153–7.

Prevention and treatment of infection

Infections are common with lymphoedema because of the compromised immune status of the swollen tissues. The recommendations for management are born more out of consensus than robust research [1,2]. Skin care is the first priority as maintenance of skin integrity and an effective barrier will reduce entry of microorganisms.

Acute cellulitis (erysipelas)

Cellulitis is probably more likely to result from a pre-existent lymphatic insufficiency than to be a primary cause of lymphoedema. Nevertheless, it is not unusual for cellulitis to manifest lymphoedema without any prior knowledge of a lymph drainage weakness.

Administration of antibiotics at the time of an attack of cellulitis must be prompt, otherwise they do not significantly influence the course of the illness. Therefore, patients need to carry a supply of antibiotics—for example, co-amoxiclav or amoxicillin—with them at all times [3].

Recurrent cellulitis

For attacks recurring more than once a year, prophylactic antibiotics are the recommended treatment [3]. Phenoxymethyl penicillin 500 mg daily is as effective as any broad-spectrum antibiotic. Long-term prophylaxis is often necessary [4]. Control of the oedema and diabetic-type skin care may help reduce antibiotic requirements.

The only trials investigating prophylaxis against infection in lymphoedema were undertaken in filarial lymphoedema and compared the efficacy of diethylcarbamazine (DEC), ivermectin and skin care in preventing lymphangitis/adenitis [5]. The authors concluded that a foot care programme alone can drastically reduce the number of attacks of acute adenolymphangitis. In a second study [6], the same group compared oral penicillin, diethylcarbamazine and antibiotic cream. Both the penicillin group and the DEC group had significantly reduced frequency of attacks of lymphangitis compared with patients treated with placebo. The authors concluded that antifilarial drugs do not have a role in reducing acute inflammatory attacks (lymphangitis, cellulitis), but that penicillin does contribute significantly to a reduction in attacks when combined with foot care.

References

1 Medical Education Partnership. *Best Practice for the Management of Lymphoedema: International Consensus*. London: MEP Ltd, 2006. http://www.library.nhs.uk
2 Clinical Resource Efficiency Support Team. *Guidelines on the Diagnosis, Assessment and Management of Lymphoedema*, 2008. http://www.crestni.org.uk
3 British Lymphology Society. *Consensus Document on the Management of Cellulitis in Lymphoedema*. http://www.thebls.com/concensus.php
4 Vignes S, Dupuy A. Recurrence of lymphoedema-associated cellulitis (erysipelas) under prophylactic antibiotherapy: a retrospective cohort study. *J Eur Acad Dermatol Venereol* 2006; **20**: 818–22.
5 Shenoy RK, Suma TK, Rajan K *et al*. Prevention of acute adenolymphangitis in brugian filariasis: comparison of the efficacy of ivermectin and diethylcarbamazine each combined with local treatment of the affected limb. *Ann Trop Med Parasit* 1998; **92**: 587–94.
6 Shenoy RK, Kumaraswami V, Suma TK *et al*. A double blind placebo controlled study of the efficacy of oral penicillin, diethylcarbamazine or local treatment of the affected limb in preventing acute adenolymphangitis in lymphoedema caused by brugian filariasis. *Ann Trop Med Parasit* 1999; **93**: 367–77.

Drug therapy

Drug therapy is generally disappointing. Diuretics remain the most commonly used treatment because most doctors consider

oedema to be an indication for such drugs. Diuretics alone have little benefit in lymphoedema because their main mode of action is to limit capillary filtration by reducing circulating blood volume. Improvement with diuretics suggests that the predominant cause of the oedema is not lymphatic.

The benzopyrone group of drugs have been advocated as treatment for lymphoedema, but their clinical effect seems to be small. In the UK, the only available oral prescription medication in this class (although only actually licensed for venous disease) is oxerutins (Paroven®). Three randomized and placebo-controlled trials have been published, all demonstrating a marginal significant effect on limb volume but of little clinical benefit [1]. Other benzopyrone drugs investigated include Daflon® and coumarin (5,6-benzo-α-pyrone) and, while most trials claim significant volume reduction, the poor reporting means a meta-analysis is not possible. One robust trial concluded that there was no difference in effect between coumarin and placebo, and reported serious liver toxicity from coumarin [2].

References

1 Mortimer PS, Badger C, Clarke I, Pallett J. A double blind, randomized, parallel group, placebo-controlled trial of *O*-(-β hydroxyethyl)-rutosides in chronic arm oedema resulting from breast cancer treatment. *Phlebology* 1995; **10**: 51–5.

2 Loprinzi CL, Kugler JW, Sloan JA *et al*. Lack of effect of coumarin in women with lymphoedema after treatment for breast cancer. *N Eng J Med* 1999; **340**: 346–50.

Surgery

Surgery has a specific role in the management of lymphoedema [1]. It is of value in limb lymphoedema in a few patients in whom, even after conservative treatment, the size and weight of a limb inhibit its use or interfere with mobility. Surgery involves either removing excessive tissue or bypassing local lymphatic defects. Lifelong non-surgical measures—for example, hosiery—must be continued postoperatively.

Reduction (excisional) operations remove a longitudinal ellipse of skin and the underlying abnormal subcutaneous tissue down to the deep fascia in a 'melon slice' that permits primary closure of skin edges (Sistrunk procedure). Undercutting of the skin allows removal of additional tissue (Homans' procedure). This procedure is preferred to circumferential excision and skin grafting (Charles' procedure) or to the addition of in-rolling of a skin flap (Thompson buried dermis flap operation). Procedures involving surgery both above and below the knee or the elbow are usually undertaken one region at a time, because blood loss can be extensive.

A new, less invasive, form of debulking has been successfully employed using liposuction but necessitates compression garments 24 hours a day [2].

Reduction/debulking surgery is used sooner rather than later for genital [3] and eyelid lymphoedema.

Bypass operations involve either bridging an area of defective lymphatics with tissue containing lymphatics or with a vessel graft. If the lymphoedema results from excision of, or damage to, a local group of lymph nodes (e.g. in the axilla or groin) the area can be bridged with omentum or with an isolated and opened-out segment of gut. Lymph node-to-venous and direct lymph vessel-to-venous shunts have been undertaken but long-term patency is doubtful [4]. Lymph vessel transplantation, where autologous lymphatics are removed from an unaffected part of the body and anastomosed end-to-end with other unaffected collectors proximal and distal to the obstruction, has been shown to improve lymph transport [5]. Two to three microsurgical lymphaticovenous anastomoses (small subdermal venules joined to local lymphatics) are claimed to be sufficient to reduce limb volume [6].

References

1 Browse NL, Burnand KG, Mortimer PS. *Diseases of the Lymphatics*. London, Arnold, 2003.

2 Brorson H, Ohlin K, Olsson G *et al*. Controlled compression and liposuction treatment for lower extremity lymphedema. *Lymphology* 2008; **41**: 52–63.

3 Garaffa G, Christopher N, Ralph DJ. The management of genital lymphoedema. *BJU Int* 2008; **102**: 480–4.

4 Campisi C. Use of autologous interposition vein graft in management of lymphedema: preliminary experimental and clinical observations. *Lymphology* 1991; **24**: 71–6.

5 Baumeister RG, Siuda S. Treatment of lymphedema by microsurgical lymphatic grafting: what is proved? *Plast Reconstr Surg* 1990; **85**: 75–6.

6 Nagase T, Gonda K, Inoue K *et al*. Treatment of lymphedema with lymphaticovenular anastomoses. *Int J Clin Oncol* 2005; **10**: 304–10.

Lymphatic malformations, lymphangioma and lymphangiectasia

The reclassification of vascular anomalies into vascular tumours and vascular malformations should apply to lymphangioma and lymphatic disorders [1].

Lymphatic malformations represent a failure of lymphatic development and often exist in isolation with no communication with otherwise normal lymph drainage pathways (extratruncular) or with some sort of communication as seen on lymphoscintigraphy (truncular) [2]. It is best to consider lymphatic malformations as genetically determined structural anomalies with normal endothelial cell turnover, rather than as tumours which are proliferative with endothelial hyperplasia. Malformations increase in size by distension or hypertrophy, not through increased cell division.

The term lymphangioma should only be used if progression through proliferation occurs, otherwise lymphatic malformation is to be preferred. Unfortunately, like haemangioma, the term lymphangioma, implying tumour, is often inappropriately used in clinical dermatology. Nevertheless some lymphatic malformations progress on a lethal, inexorably expanding, unalleviated course making distinction from lymphangioma (tumour process) impossible [1].

Acquired simple sustained dilatation of otherwise normal lymphatic vessels is referred to as lymphangiectasia [3].

References

1 Enjolras O, Wassef M, Chapot R. *Color Atlas of Vascular Tumors and Vascular Malformations*. Cambridge: Cambridge University Press, 2007.

2 Lee BB, Kim YW, Seo JM *et al*. Current concepts in lymphatic malformation. *Vasc Endovasc Surg* 2005; **39**: 67–81.

3 Blei F. Congenital lymphatic malformations. *Ann N Y Acad Sci* 2008; **1131**: 185–94.

Lymphatic malformations (lymphangioma)

Localized congenital lymphatic malformations (LMs) are frequently referred to as 'lymphangioma' and can be divided into

macrocystic, or deep, and microcystic, or superficial, lesions. Lymphatic malformations that appear microcystic, localized and superficial within the skin are called 'lymphangioma circumscriptum', but the term is a misnomer because there is frequently communication with a more extensive deeper malformation (particularly if the lesion is at the root of a limb). Macrocystic LMs are usually visible at birth in the neck and are referred to as cystic hygroma. Distinction between the two types is important because treatment and prognosis can differ [1]. Nevertheless, LMs can have both microcystic and macrocystic components.

The most important feature of congenital LMs is that they can be isolated from the normal lymph conducting system (extratruncal). When connected to the main collecting system they are referred to as truncal lymphatic malformations and can then be associated with lymphoedema. There have been attempts to classify LMs into localized or diffuse, with diffuse indicating that there will be associated lymphoedema, but lymphoedema in general is not due to LMs.

LMs are usually congenital but may not be apparent at birth. They may enlarge if infected or traumatized and only then become symptomatic. No evidence for inheritance exists, suggesting a somatic mutation in a restricted area of the lymphatic network as the mechanism for development [2].

LMs/lymphangiomas are classified according to their morphology as seen histologically or by imaging (e.g. using ultrasound), into macrocystic, microcystic and combined lymphangioma [3]. LMs/lymphangiomas have to be distinguished from true lymphatic neoplasms such as acquired progressive lymphangioma (lymphangioendothelioma) and lymphangiomatosis. LMs/lymphangiomas at least partially and temporarily depend on active lymphangiogenesis, and possibly on active angiogenesis, during the course of development or progression [4].

References

1 Garzon M, Huang J, Enjolras O, Frieden I. Vascular malformations, part I. *J Am Acad Dermatol* 2007; **56**: 353–70.

2 Brouillard P, Vikkula M. Genetic causes of vascular malformations. *Hum Mol Genet* 2007; **16**: 140–9.

3 Marler J, Mulliken J. Current management of hemangiomas and vascular malformations. *Clin Plast Surg* 2005; **32**: 99–116.

4 Wiegand S, Eivazi B, Barth P *et al*. Pathogenesis of lymphangioma. *Virchows Arch* 2008; **453**: 1–8.

Lymphangioma circumscriptum

Lymphangioma circumscriptum is a term best reserved for a lymphatic malformation that is localized to an area of skin, subcutaneous tissue and sometimes muscle [1]. Clinically, the condition manifests with fluid-filled vesicles ('lymph blisters') which bulge on the skin surface (Fig. 48.12). The vesicles may be well defined and discrete, or may be grouped into structures resembling frogspawn. They may be translucent when the overlying epidermis is very thin, or they may vary in colour from red to blue-black when they contain blood, a frequent occurrence. The most common symptom is recurrent oozing, usually of clear fluid (lymph), known as lymphorrhoea. Alternatively, the surface of the lymphangiomas may appear extremely warty and the lesions may be mistaken for viral warts. Complications include ulceration, bleeding and secondary infection. Squamous cell carcinoma is described arising within lymphangioma circumscriptum [2].



Fig. 48.12 Lymphangioma circumscriptum: fluid-filled vesicles resembling frogspawn. At times the vesicles can contain blood, weep clear fluid (lymphorrhoea) or become warty.

There may or may not be swelling of the underlying tissues, depending on the presence and size of enlarged, abnormal, anastomosing lymphatic channels beneath the skin or how compromised lymph drainage is, that is where there is a contribution of lymphoedema. It has been postulated that the original malformation arises from deep contractile lymphatics which are malformed and not in continuity with the normal lymph-conducting pathways. Tissue drainage into these abnormal lymphatics results in their gradual dilatation into lymphatic cisterns, contraction of which results in retrograde flow into the skin initial lymphatics [3]. Only by identifying the limits of the subcutaneous cisterns prior to wide excision will there be any chance of cure.

Lymphangioma circumscriptum may present at any age but is usually noted at birth or appears during childhood. The commonest sites are the axillary folds, shoulders, flanks, proximal parts of the limbs and perineum. Doppler ultrasound will distinguish macrocystic from microcystic lesions as well as excluding any high flow and therefore vascular component. MRI is the best for delineating the extent of the lesion [4].

The treatment of choice for lymphangioma circumscriptum is radical surgery [5]. However, inadequate surgical excision of the visible lymphangioma frequently results in further development of surface vesicles, indicating the presence of a more widespread subcutaneous malformation. Therefore a stable, asymptomatic 'lymphangioma' may be better left alone. Bacterial superinfection is common, particularly with weeping lesions, and manifests with pain, systemic upset or cellulitis. Palliation for lymphorrhoea or to improve the appearance of vesicles can be achieved through intralesional administration of a sclerosant—for example, doxycycline [6], picibanil (OK-432) [7] or hypertonic saline [8]. Simple electrocautery and vaporization with carbon dioxide laser can be of palliative benefit, and superficial X-rays have been used successfully [9].

Macrocystic lymphatic malformations

Lymphangiomas with few but large macrocystic swellings containing clear lymph are called cystic hygromas (hygroma = moist

or watery tumour). Most occur in the neck, but they frequently extend into the upper mediastinum. The term tends to be reserved for those congenital lymphatic malformations that present at birth or are diagnosed by prenatal ultrasound. In the neck they presumably arise from an embryonic jugular lymph sac. Individuals with Turner's syndrome are particularly prone to both hydrops and cystic hygroma. Exceptionally, a cystic hygroma occurs in the groin, presumably from an embryonic iliac lymph sac. Fetal cystic hygroma can give rise to severe abnormalities, leading to fetal death [10].

Deeper, larger and cavernous lymphangiomas (LMs) are best called macrocystic LMs. Surface pressure with a digit will result in an indentation but a cavernous LM will rapidly refill, unlike the situation in pitting oedema where it takes many seconds for the interstitial fluid to redistribute when the pressure is released (like a sponge). They may be an isolated entity, part of a mixed vascular malformation (combined lymphatic–venous or capillary malformation) or associated with vascular syndromes such as Klippel–Trenaunay or proteus syndromes [11,12]. Cervicofacial LMs may cause airways obstruction, difficulty with feeding and speech development. Periorbital and skeletal hypertrophy are other complications of head and neck LMs [13].

References

1 Peachey RC, Lim CC, Whimster IM. Lymphangiomas of the skin. *Br J Dermatol* 1970; **83**: 519–27.
2 Wilson GR, Cox NH, McLean NR *et al.* Squamous cell carcinoma arising within lymphangioma circumscriptum. *Br J Dermatol* 1993; **129**: 337–9.
3 Whimster I. The pathology of lymphangioma circumscriptum. *Br J Dermatol* 1976; **94**: 473–86.
4 McAlvanny JP, Jorizzo JL, Zanoll D *et al.* Magnetic resonance imaging in the evaluation of lymphangioma circumscriptum. *Arch Dermatol* 1993; **129**: 194–7.
5 Browse NL, Whimster I, Stewart G *et al.* Surgical management of 'lymphangioma circumscriptum'. *Br J Surg* 1986; **73**: 585–8.
6 Molitch HL, Unger ES, Witte CL *et al.* Percutaneous sclerotherapy of lymphangiomas. *Radiology* 1995; **194**: 343–7.
7 Mikhail M, Kennedy R, Cramer B *et al.* Sclerosing of recurrent lymphangioma using OK-432. *J Pediatr Surg* 1995; **30**: 1159–60.
8 Bikowski J, Dumont M. Lymphangioma circumscriptum: treatment with hypertonic saline sclerotherapy. *J Am Acad Dermatol* 2005; **53**: 442–4.
9 O'Cathail S, Rostom AY, Johnson ML. Successful control of lymphangioma circumscriptum by superficial x-rays. *Br J Dermatol* 1985; **113**: 611–5.
10 Chervanak FA, Isaacson G, Blakemore KJ *et al.* Fetal cystic hygroma, cause and natural history. *N Engl J Med* 1983; **309**: 822–5.
11 Irvine AD, Sweeney L, Corbett J. Lymphangioma circumscriptum associated with paravesical cystic retroperitoneal lymphangioma. *Br J Dermatol* 1996; **134**: 1135–7.
12 Blei F. Congenital lymphatic malformations. *Ann N Y Acad Sci* 2008; **1131**: 185–94.
13 Greene A, Burrows P, Smith L, Mulliken J. Periorbital lymphatic malformation: clinical course and management in 42 patients. *Plast Reconstr Surg* 2005; **115**: 22–30.

Diffuse lymphangiomatosis

There is no clear distinction between lymphatic malformations and lymphangiomatosis. The difference may depend solely on the extent of the malformation. Most LMs are stable and run a completely benign course. Conversely, some visceral thoracic and abdominal LMs can relentlessly progress, infiltrating vital organs with fatal outcome and making distinction from frank neoplasia difficult; for example multifocal lymphangioendotheliomatosis with thrombocytopenia [1]. The CNS seems to be spared, presumably because of its lack of lymphatic vessels. Thoracic involvement leads to pleural and pericardial effusions and severe pulmonary infections [2]. Disseminated intravascular coagulation can give rise to thrombosis and haemorrhage [3]. Gorham's disease (Gorham–Stout disease; disappearing/vanishing bone disease) is characterized by proliferation of lymphatic vessels resulting in progressive destruction and resorption of osseous matrix. Skin 'lymphangiomas' may be the clue to the underlying diagnosis [1,4]. The outcome in diffuse lymphangiomatosis is poor, despite reports of successful use of interferon [5].

References

1 North P, Kahn T, Cordisco M *et al.* Multifocal lymphangioendotheliomatosis with thrombocytopenia: a newly recognized clinico-pathological entity. *Arch Dermatol* 2004; **140**: 599–606.
2 Alvarez O, Kjellin I, Zuppan C. Thoracic lymphangiomatosis in a child. *J Pediatr Hematol Oncol* 2004; **26**: 136–41.
3 Mazreeuw-Hautier J, Syed S, Leisner R, Harper J. Extensive venous/lymphatic malformations causing life-threatening haematological complications. *Br J Dermatol* 2007; **157**: 558–63.
4 Bruch-Gerharz D, Gerharz C, Stege H *et al.* Cutaneous lymphatic malformations in disappearing bone (Gorham-Stout) disease: a novel clue to the pathogenesis of a rare syndrome. *J Am Acad Dermatol* 2007; **56** (Suppl. 2): S21–5.
5 Ozeki M, Ito M, Teramoto T *et al.* Clinical improvement of difuse lymphangiomatosis with pegylated interferon alpha-2b therapy. *J Pediatr Hematol Oncol* 2007; **24**: 513–24.

Chylous reflux, intestinal lymphangiectasia

Chyle is a 'milky lymph' which flows from the lacteals of the gut through the cisterna chyli and even through the thoracic duct. Incompetence of valves within main abdominal lymphatic trunks results in gross reflux of chyle. This can include reflux to the skin below the waist [1]; the most commonly affected sites are the genitalia, perineum and thigh. Chylous reflux is often associated with truncular lymphatic malformations in which case lymphoedema may be present, but the characteristic symptom is oozing of milky fluid through the skin, usually from visibly dilated chylous vesicles (chylous lymphangiectasia or 'lymphangioma'). Rupture of such vesicles may result in a spurt of chyle under pressure, or chronic leakage may give rise to warty plaques of a cream-yellow colour.

Chylous reflux is often associated with intestinal lymphangiectasia, which can lead to hypoalbuminaemia, hypogammaglobulinaemia and lymphopenia due to protein and cell loss through the gut. Capsule endoscopy is the investigation of choice [2]. Dietary replacement of fat with medium chain triglycerides (MCTs) is recommended as MCTs are absorbed and directed to the portal venous system rather than to the intestinal lacteals [3].

While intestinal lymphangiectasia is usually considered primary and therefore genetic in origin, for example Hennekam's syndrome [4], it can occur secondary to a range of gut pathologies where intestinal lymph drainage is altered [5].

References

1 Browse NL. Management of lymph and chyle reflux. In: Browse NL, Burnand KG, Mortimer PS, eds. *Diseases of the Lymphatics*. London: Arnold, 2003: 259–92.
2 Lee J, Kong MS. Primary intestinal lymphangiectasia diagnosed by endoscopy following the intake of a high-fat meal. *Eur J Pediatr* 2008; **167**: 237–9.

3 Bliss CM, Schroy PC III. Primary intestinal lymphangiectasia. *Curr Treat Options Gastroenterol* 2004; **7**: 3–6.
4 Van Balkom ID, Alders M, Allanson J *et al*. Lymphedema-lymphangiectasia-mental retardation (Hennekam) syndrome: a review. *Am J Med Genet* 2002; **112**: 412–21.
5 Safatle-Ribeiro AV, Iriya K, Couto DS *et al*. Secondary lymphangiectasia of the small bowel: utility of double balloon enteroscopy for diagnosis and management. *Dig Dis* 2008; **26**: 383–6.

Cutaneous lymphangiectasia (lymphangiectasis, acquired lymphangioma, benign lymphangiomatous papules)

The surface 'lymph blisters' seen in cutaneous lymphangiectasia are not necessarily structurally or histologically any different from those seen in 'lymphangioma'; both represent distended, otherwise normal, dermal lymphatics engorged with lymph due to a failure of downstream drainage.

Lymphangiectasia can be seen as translucent, almost flat, papules or vesicles in the skin, which may ooze lymph spontaneously or after trauma. Acquired or secondary lymphangioma is an alternative term, but confusing as there is no tumour or proliferative component. Benign lymphangiomatous papules represent the same process [1,2].

The clinical appearance of lymphangiectases/acquired lymphangiomas may vary greatly, ranging from clear fluid-filled blisters to smooth flesh-coloured papules or nodules.

Histologically, the latter show oedematous polypoid nodules within which are dilated lymphatics. Lesions may be solitary but scattered throughout a lymphoedematous limb, or they may be grouped, as seen in lymphangioma circumscriptum.

Lymphangiectases arise following damage to previously normal, deep lymphatic vessels [3]. The mechanism by which they form is identical to congenitally determined lymphatic malformations (lymphangiomas), that is obstruction to drainage leads to backpressure and dermal backflow, with subsequent dilatation of upper dermal lymphatics. Lymphangiectases are not true neoplasms or hamartomas, but represent simple expansion and engorgement (lymphangiectasia) of lymphatic vessels.

Lower-limb lesions usually arise in association with lymphoedema following either ilioinguinal block dissection or pelvic surgery and radiotherapy for gynaecological cancer. Lymphangiectasias/acquired lymphangiomas have been described in association with scarring processes, including recurrent or chronic infections (such as the scrofuloderma variant of tuberculosis), radiotherapy, scleroderma, keloid, tumour and repeated trauma [4]. They may also occur as a consequence of defective collagen or elastin, as documented in a report of penicillamine dermopathy [5].

Genital skin is particularly prone to lymphangiectasia. Lymph blisters of the penis or scrotum (and less commonly vulva), leaking lymph or chyle, may be seen in primary lymphoedema. In such circumstances the lymphangiectasia represents reflux of lymph or chyle from incompetent pelvic lymphatics and is usually associated with lymphoedema of one or both lower limbs.

Lymphangiectasia/acquired lymphangioma of the vulva or scrotum is described following cancer treatment, tuberculous inguinal lymphadenitis and genital involvement with Crohn's disease. Clinically, the most common pattern is that of circumscribed groups of tense, thin-walled vesicles. However, a hyperkeratotic appearance may make distinction from viral warts difficult [6] (Fig. 48.13). Recognition and appropriate treatment of vulval lymphangiectasia is important primarily because the lesions may act as portals of entry for infection. In addition, persistent leakage of lymphatic fluid may be mistaken for urinary incontinence.

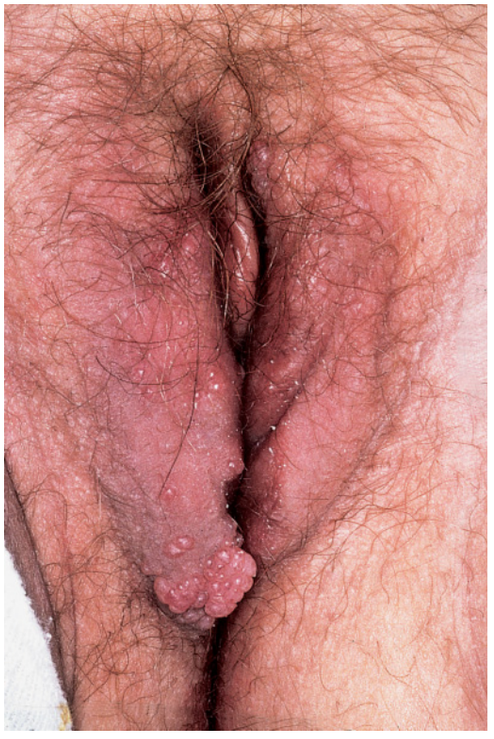


Fig. 48.13 Acquired lymphangiomas (lymphangiectasias) following cervical cancer treatment. The lymphangiomas were mistaken for genital warts.

Treatment of lymphangiectasia/acquired lymphangiomas is essentially the reduction of underlying lymphoedema and control of infection. This may be relatively straightforward on the leg, but is not so easy on the genitalia, where compression is not possible. Destruction of the 'lymph blisters' by laser or diathermy is helpful palliative treatment [7].

Lymphangiectasia/acquired lymphangiomas may be widespread and problematic in palliative circumstances where advanced cancer produces profound oedema of lower limbs, genitalia and lower trunk. In these circumstances copious lymph may weep. Opposing intralymphatic pressure with equivalent surface compression is the only way of controlling the lymphorrhoea unless the lymphatic obstruction can be relieved.

References

1 Diaz-Cascajo C, Borghi S, Weyers W *et al*. Benign lymphangiomatous papules of the skin following radiotherapy: a report of five new cases and review of the literature. *Histopathology* 1999; **35**: 319–27.
2 Gengler C, Coindre JM, Leroux A *et al*. Vascular proliferations of the skin after radiation therapy for breast cancer: clinicopathologic analysis of a series in favor of a benign process: a study from the French Sarcoma Group. *Cancer* 2007; **109**: 1584–98.
3 Mallett RB, Curley RK, Mortimer PS. Acquired lymphangiomata: report of four cases and a discussion of the pathogenesis. *Br J Dermatol* 1992; **126**: 380–2.

4 El Sayed F, Basex J, Bouissou X *et al*. Acquired cutaneous lymphangiectasia mimicking plantar warts. *Br J Dermatol* 1996; **132**: 1014–6.
5 Goldstein JB, McNatt NS, Hambrick GW. Penicillamine dermopathy with lymphangiectases. *Arch Dermatol* 1989; **125**: 92–7.
6 Harwood CA, Mortimer PS. Acquired vulval lymphangiomata mimicking genital warts. *Br J Dermatol* 1993; **129**: 334–6.
7 Makh DS, Mortimer P, Powell B. A review of the surgical treatment of vulval lymphangioma and lymphangiectasia: four case reviews. *J Plast Reconstr Aesthet Surg* 2006; **59**: 1442–5.

Acquired lymphatic abnormalities

Lymphangitis

In theory, the lymphatic system has evolved in humans as a host defence mechanism. Noxious agents and predators such as bacteria, if not dealt with at the point of entry to the host, access the lymphatic system. Lymphatic vessels, together with adjoining lymph nodes, effectively act as the second line of defence, hopefully preventing further onward spread and so limiting systemic involvement. In some circumstances, the inflammatory response may be profound, perhaps due to a heavy infection load, and either an overt lymphangitis or lymphadenitis, or both, arise. Lymphangitis represents inflammation of the lymphatic collectors and is clinically seen as tender red streaks up the limb corresponding to the inflamed vessels. In the lower limb, oedema is so often an accompanying feature that red streaks, such as are seen with lymphangitis of the arm, are rarely seen. A more diffuse erythema is seen extending up the medial side of the leg and thigh. Distinction from an ascending cellulitis becomes difficult.

Infection is usually limited by the lymph nodes, and in the lower limb lymphadenitis may give rise to painful swelling in the groin. Occasionally, infection bypasses a group of lymph nodes and affects those at a higher level. Constitutional upset can be severe and is greater the more proximally the infection has extended.

Lymphangitis may occur without any demonstrable inflammation or may be recurrent, for example following relapsing herpes simplex infection. Permanent obliteration of lymphatic collectors may follow severe or recurrent lymphangitis. In such cases, if reserve lymphatic capacity is limited, permanent swelling (lymphoedema) can result.

Recurrent cellulitis

Synonyms
- Recurrent inflammatory episodes
- Erysipelas
- Lymphangitis

Where lymphatic insufficiency exists and the local lymphoid tissue/lymphatic system fails in its host defence duty, recurrent infection can occur. Clinically, this manifests as recurrent cellulitis/erysipelas. Indeed, any patient who presents with even one attack of cellulitis in one leg may have a compromised lymph drainage in that leg, whether overt lymphoedema is present or not [1]. In most cases, however, subtle signs of lymphoedema are evident, particularly in the skin over the toes and forefoot. Because there is no localization of infection by the lymphatics, the first sign of illness will be constitutional upset with fever, rigors or vomiting. Only later may redness and tenderness appear in the leg and the diagnosis become clear.

Lymphangitis, as witnessed by red streaks up the leg, is generally not seen, presumably because the infection, uncontrolled by the lymphatic system, has spread through tissue planes (cellulitis) with rapid dissemination into the circulation. However, inflammation following the line of lymphatic channels can sometimes be apparent at the proximal border of a cellulitic area in patients with lymphoedema [2].

Treatment for recurrent cellulitis should first of all address predisposing factors such as tinea pedis, foot dermatitis, leg ulcers, etc. [3]. If no portal of entry or cause can be identified, then long-term prophylactic antibiotics may be necessary if the debilitating attacks are to be controlled but even that may fail to control attacks [4].

References

1 Damstra RJ, van Steensel MA, Boomsma JH *et al*. Erysipelas as a sign of subclinical primary lymphoedema: a prospective quantitative scintigraphic study of 40 patients with unilateral erysipelas of the leg. *Br J Dermatol* 2008; **158**: 1210–5.
2 Cox NH. Streptococcal cellulitis in reticulate lymphoedema selectively affects the lymphoedematous herniations. *Br J Dermatol* 1998; **139**: 358–9.
3 British Lymphology Society. *Consensus Document on the Management of Cellulitis in Lymphoedema.* http://www.thebls.com/concensus.php
4 Vignes S, Dupuy A. Recurrence of lymphoedema-associated cellulitis (erysipelas) under prophylactic antibiotherapy: a retrospective cohort study. *J Eur Acad Dermatol Venereol* 2006; **20**: 818–22.

Lymphangiothrombosis

Lymph is capable of clotting, but the circumstances in which this happens, and what pathological effect lymph thrombosis has, are totally unknown. Extrapolating from knowledge about venous thrombosis would suggest that lymph thrombosis is likely to impair the function of lymphatic valves and the contractility of lymph-collecting vessels.

Mondor's disease, axillary web syndrome

Mondor's disease is alleged to be a superficial thrombophlebitis of the breast and chest wall [1] (see Chapter 47). A similar process, whereby cords or threads like violin strings extend down the inner arm, is frequently seen following axillary lymphadenectomy [2]. The manner in which the cords 'bowstring' across the axilla with the arm abducted, their diameter and the fact that the cords can snap between finger and thumb suggests that lymph thrombosis may be a more likely explanation than phlebothrombosis/thrombophlebitis. An equivalent condition may well exist in the lower limb but be mistaken for thrombophlebitis.

'Seroma'

Synonyms
- Lymphocoele
- Lymphocyst

Following lymphadenectomy, it is not unusual for a localized swelling containing clear fluid to develop. Often referred to as a

'seroma', the fluid is not serum, but lymph which has drained from the cut ends of the lymphatic collectors, so filling the space originally occupied by the nodes. The wall of lymphocoeles is 'false', in that no endothelial lining exists and instead a dense network of fibrin with lymphocytes is present [3]. Aspirated fluid is indistinguishable from lymph. Repeat aspiration is often necessary until a collateral lymph drainage forms. A 'seroma', particularly if infected, may herald the onset of lymphoedema if alternative drainage routes are not established.

References

1 Marsch W, Haas N, Stuttgen G. Mondor's phlebitis: a lymphovascular process. *Dermatologica* 1986; **172**: 133–8.

2 Moskovitz AH, Anderson BO, Yeung RS *et al*. Axillary web syndrome after axillary dissection. *Am J Surg* 2001; **181**: 434–9.

3 Ferguson JH, Maclure JG. Lymphocele following lymphadenectomy. *Am J Obstet Gynecol* 1961; **82**: 783–92.

Lymphatic tumours

Tumours of lymphatic vessels allegedly make up only a small group of vascular neoplasms but the use of specific lymphatic markers may change this view or make us realize that venous and lymphatic phenotypes can coexist within one tumour type, for example Kaposi's sarcoma and papillary intralymphatic angioendothelioma (Dabska's tumour) [1].

Reference

1 Goh S, Calonje E. Cutaneous vascular tumours: an update. *Histopathology* 2008; **52**: 661–73.

Acquired progressive lymphangioma

Synonym

- Benign lymphangioendothelioma

This benign tumour differs from simple 'acquired lymphangioma' or simple cutaneous lymphangiectasia by its clinical behaviour and histopathology [1]. Acquired progressive lymphangioma presents as reddish or bruise-like plaques which are usually located on the abdominal wall, thigh or calf. Typically, the condition affects young adolescents but may also arise in adults. It is usually localized, flat and grows slowly. Considered to originate from lymphatic endothelium, the histopathological appearance can mimic a low-grade sarcoma or Kaposi's sarcoma [2]. Anastomosing dilated channels, with a tendency to dissect the collagen bundles, are lined by swollen endothelial cells but without cellular atypia. It usually runs a long and benign course.

References

1 Wilson Jones E, Winkelmann RK, Zachary CB *et al.* Benign lymphangio-endothelioma. *J Am Acad Dermatol* 1990; **23**: 229–34.

2 Guillou L, Fletcher CD. Benign lymphangioendothelioma (acquired progressive lymphangioma): a lesion not to be confused with well-differentiated angiosarcoma and patch stage Kaposi's sarcoma: clinicopathologic analysis of a series. *Am J Surg Pathol* 2000; **24**: 1047–57.

Lymphangiomyomatosis

Synonym

- Lymphangiopericytoma

This condition affects primarily pre-menopausal women, and presents with central lymphatic problems, typically progressive dyspnoea associated with chylous effusions and a chest X-ray which reveals honeycombing of the lungs [1]. Masses of spindle cells proliferate in and around the walls of lymph vessels, particularly in retroperitoneal tissues and in the mediastinum. These cells (lymphangiomyomatosis cells, LAMs) have a smooth muscle phenotype and have mutations in one of the tuberous sclerosis complex genes (*TSC1* or *TCS2*). Skin involvement, with facial angiofibromas, forehead plaques and periungual fibromas, can occur in lymphangiomyomatosis [2]. Lymphoedema of one or both legs can develop due to infiltration of LAM cells in the walls of main lymphatic trunks, and sometimes beyond this into surrounding adipose tissue. Suppression of mTOR signalling might constitute an ameliorative treatment in patients with the tuberous sclerosis complex or sporadic lymphangioleiomyomatosis [3].

References

1 Joliat G, Stalder H, Kapanci Y. Lymphangiomyomatosis: a clinico-anatomical entity. *Cancer* 1973; **31**: 455–61.

2 Glasgow C, Taveiro-Dasilva A, Darling T, Moss J. Lymphatic involvement in lymphangiomyomatosis. *Ann N Y Acad Sci* 2008; **1131**: 206–14.

3 Bissler JJ, McCormack FX, Young LR *et al*. Sirolimus for angiomyolipoma in tuberous sclerosis complex or lymphangioleiomyomatosis. *N Engl J Med* 2008; **358**: 140–51.

Kaposi's sarcoma

There is increasing evidence that Kaposi's sarcoma (KS) may arise from lymphatic rather than from vascular endothelium, although its origins may lie with transdifferentiation from blood vascular to lymphatic phenotype [1,2].

The classical form of the disease, as described by Kaposi, presents with dark-blue or purple lesions, usually on the feet. Initially, lesions may be flat; when they become tumid, diascopy may produce partial blanching to reveal a brown tinge from extravasated blood. Individual tumours enlarge to a diameter of 10–30 mm and stop growing, whereupon adjacent areas fuse to form a plaque or tumour. New lesions appear proximally alongside a superficial vessel. Unlike the situation in patients with lymphangiosarcoma, lymphoedema may not be evident at the time the first lesions appear, but otherwise the morphology is similar. KS, however, is characteristically multifocal and, in time, symmetrical, affecting both lower limbs. Brawny oedema resembling lymphoedema develops with advanced KS.

In the African and Mediterranean types of KS, oedema is often the first sign with lymph nodes as the main tissue involved.

KS associated with immunodeficiency, whether HIV-induced or not, produces subtle lesions which are often widely scattered and quite dissimilar from the classical type.

KS can cause lymphoedema but can also follow lymphoedema. Presumably the local immunodeficiency derived from the lymphatic insufficiency promotes the development and progression

of KS in the same way that lymphoedema encourages infection and skin cancer.

Treatment is dependent on the type of KS. In AIDS-related KS, treatment of HIV is paramount and both KS and lymphoedema may regress. In endemic African-type KS, staging of nodal involvement is necessary before consideration of chemotherapy with or without radiotherapy. For localized disease, radiotherapy is the treatment of choice.

References

1 Skobe M, Brown LF, Tognazzi K *et al.* Vascular endothelial growth factor (VEGF-C) and its receptor KDR and flt-4 are expressed in AIDS-associated Kaposi's sarcoma. *J Invest Dermatol* 1999; **113**: 1047–53.

2 Cueni LN, Detmar M. New insights into the molecular control of the lymphatic vascular system and its role in disease. *J Invest Dermatol* 2006; **126**: 2167–77.

Maffucci's syndrome

Maffucci's syndrome consists of diffuse haemolymphangiomatosis accompanied by severe, widespread deformities of bone and cartilage, notably enchondromas of the digits [1]. The lymphangiomas do not appear, on lymphography, to communicate with the main lymphatic pathways and often possess both blood vascular and lymphatic elements. Bony deformity may be gross and slowly uniting pathological fractures are common. The disease has high malignant potential including lymphangiosarcoma.

Reference

1 Carlton A, St Elkington JC, Greenfield JG *et al.* Maffucci's syndrome. *QJM* 1942; **11**: 203–28.

Atypical post-radiation vascular proliferation

Cutaneous vascular proliferations that occur within the field of prior radiotherapy include angiosarcoma and small cutaneous solitary or multiple papules with a pseudosarcomatous pattern which resemble angiosarcoma (post-radiotherapy vascular proliferations, post-radiotherapy atypical vascular lesions). Clinical and histological distinction can be difficult but atypical vascular proliferations appear to have a benign prognosis [1].

Reference

1 Gengler C, Coindre J-M, Leroux A. Vascular proliferations of the skin after radiation therapy for breast cancer: clinicopathologic analysis of a series in favor of a benign process. *Cancer* 2007; **109**: 1584–98.

Lymphangiosarcoma

This is a rare but well-recognized complication of any chronic lymphoedema, irrespective of cause. Red–brown or purple discoloration, like a bruise, appears in the skin of the lymphoedematous limb. Nodules or raised plaques may appear later. As the tumours proliferate, the oedema may increase and older lesions may ulcerate. The tumour metastasizes early and has a poor prognosis.

The tumour is best described in the upper limb following breast cancer treatment (Stewart–Treves syndrome) [1], but it is well reported in the lower limb in association with lymphoedema, usually of many years' duration [2]. Radical amputation, if performed early enough, may offer hope of cure. Isolated limb perfusion has been reported for non-resectable limb tumour [3].

References

1 Stewart FW, Treves N. Lymphangiosarcoma in postmastectomy lymphoedema. *Cancer* 1948; **1**: 64–81.

2 Eby CS, Brennan MJ, Fine G. Lymphangiosarcoma: lethal complication of chronic lymphedema: report of two cases and review of the literature. *Arch Surg* 1967; **94**: 223–30.

3 Lans TE, de Wilt JH, van Geel AN, Eggermont AM. Isolated limb perfusion with tumor necrosis factor and melphalan for nonresectable Sewart-Treves lymphangiosarcoma. *Ann Surg Oncol* 2002; **9**: 1004–9.

Carcinoma erysipeloides

Synonym

- Carcinoma telangiectatica

Carcinoma erysipeloides manifests clinically with a fixed erythematous patch or plaque resembling cellulitis/erysipelas, but without fever [1]. The inflamed area may show a distinct raised periphery and oedema secondary to lymphatic obstruction. Histology reveals plugging of superficial and deep dermal lymphatics by adenocarcinoma, usually carcinoma of the breast, but the condition has been described with melanoma, lung, ovarian, colonic and pancreatic tumours [2]. The redness appears to be a consequence of the dermal lymphatic plugging with tumour, presumably through the release of cytokines. The term carcinoma telangiectatica refers to the presence of purpuric plaques, papules and vesicles where only the more superficial lymphatics are involved. 'Inflammatory breast carcinoma' has been suggested as an alternative term to 'carcinoma erysipeloides', but oncologists already classify inflammatory breast carcinoma as a subtype of cancer within the breast.

References

1 Finkel LJ, Griffiths CEM. Inflammatory breast carcinoma (carcinoma erysipeloides), an easily overlooked diagnosis. *Br J Dermatol* 1993; **129**: 324–6.

2 Marneros AG, Blanco F, Husain S *et al.* Classification of cutaneous intravascular breast cancer metastases based on immunolabeling for blood and lymph vessels. *J Am Acad Dermatol* 2009; **60**: 633–8.

CHAPTER 49
Purpura and Microvascular Occlusion

N.H. Cox[1] *& W.W. Piette*[2]

[1]Department of Dermatology, Cumberland Infirmary, Carlisle, UK
[2]John H Stroger Jr Hospital of Cook County, Division of Dermatology, Chicago, IL, USA

Definition of purpura, 49.2
Classification and investigation of purpura, 49.2
Diagnosis and pathophysiology of simple macular haemorrhage, 49.4
Laboratory tests, 49.5
Purpura due to thrombocytopenia or platelet defects, 49.7
Thrombocytopenia, 49.8
Abnormalities of platelet function, 49.12
Thrombocytosis, 49.14
Non-thrombocytopenic vascular causes of purpura and syndromes of primarily ecchymotic haemorrhage, 49.14
Purpura due to raised intravascular pressure, 49.14
Purpura due to abnormal blood vessels or decreased support of blood vessels, 49.14
Easy bruising syndrome and purpura simplex, 49.15
Physical and artefactual causes of purpura, 49.16
Paroxysmal finger haematoma, 49.16
Autoerythrocyte sensitization syndrome, 49.16
Stigmata, 49.16
Purpura in other dermatoses, 49.17
Multifactorial purpura associated with systemic diseases, 49.18
Exercise-induced purpura/vasculitis, 49.18
Inflammatory haemorrhage: Henoch–Schönlein purpura and acute haemorrhagic oedema of childhood, 49.18
Dysproteinaemic purpura and Waldenström's hypergammaglobulinaemic purpura, 49.19
Purpura associated with infection, 49.20
Non-thrombocytopenic toxin- and drug-induced purpura, 49.21
Contact purpura, 49.21
Pigmented purpuric dermatoses, 49.22
Secondary pigmented purpuric dermatoses and systemic causes, 49.23
Schamberg's disease, 49.24
Itching purpura, 49.24
Pigmented purpuric lichenoid dermatosis of Gougerot and Blum, 49.25
Lichen aureus, 49.25
Purpura annularis telangiectodes, 49.25
Granulomatous pigmented purpuric dermatosis, 49.25
Familial pigmented purpuric eruption, 49.25
Linear and quadrantic pigmented purpuric dermatoses, 49.25
Treatment of pigmented purpuric dermatoses, 49.26
Disorders of cutaneous microvascular occlusion, 49.26
Occlusion due to platelet plugs, 49.27
Occlusion due to cryogelling, 49.32
Occlusion due to vessel-invasive organisms, 49.34
Occlusion due to embolus, 49.36
Systemic coagulopathies with cutaneous predilection, 49.38
Occlusion due to vascular coagulopathies, 49.42
Occlusion due to reticulocytes, 49.47
Occlusion due to other mechanisms, 49.47
Specific clinical presentations, 49.48
Livedo, 49.48
Cutaneous necrosis, 49.49
Neonatal purpura, 49.49

Introduction

Purpura and bruising, the main terms used to describe bleeding into the skin, may occur as isolated phenomena or as part of a systemic disorder. Purpura is the hallmark of vasculitis affecting the (usually smaller vessels of the) skin, and may be the dominant feature or a minor part of a systemic vasculitis (see Chapter 50). However, it may occur as a result of other non-vasculitic abnormalities of the blood vessel wall and, overall, much the commonest causes (although largely not seen by dermatologists) are haematological conditions due to platelet and coagulation disorders. Vasculitis typically causes other cutaneous lesions, including urticarial lesions, nodules, ulcers, livedo and frank necrosis, which have a purpuric component due to vessel wall damage. Several of these also occur in disorders in which vessels are occluded, as discussed later in this chapter. An appreciation of the morphology and associated features is of great value in the diagnostic approach [1].

Patients with purpura may require management involving one or more of several disciplines, including haematology, general medicine, nephrology and rheumatology, as well as dermatology; multidisciplinary management is often appropriate as each specialty sees a different range of clinical manifestations and has different areas of expertise.

Classification of purpura is difficult, as no single approach is satisfactory. The same clinical pattern may arise from many different causes, both vasculitic and non-vasculitic, and the aetiology of either purpura or vasculitis may be impossible to determine. Classifications based on morphology or aetiology therefore have limitations. For example, clinically non-specific capillaritis may be idiopathic, drug-induced or a manifestation of cutaneous T-cell lymphoma. Even within frank haematological causes of purpura, idiopathic thrombocytopenic purpura is not only viewed as a mixture of diseases but varies in its definitions and clinical descriptions [2]. Furthermore, intravascular events such as microvascular occlusion may give rise to palpable lesions and inflammation as a secondary component, thereby mimicking vasculitis and confusing both the clinical and histopathological picture.

Despite these limitations, as a practical matter the initial approach to a patient with purpura must typically start with a

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

differential diagnosis based on morphology [1], as few patients present with a known aetiology of their lesions. In practice, overt haematological causes (thrombocytopenia and clotting factor abnormalities) can be rapidly and easily evaluated by full blood count and laboratory measures of clotting times. Beyond this, diagnostically more complex haematological disorders (e.g. thrombophilias or abnormal platelet function), vessel wall defects (both structural and others) [3], infections, immunological disorders and thrombotic microvascular occlusion disorders may all need to be considered. The importance of trying to differentiate between disorders causing primarily inflammatory or non-inflammatory lesions is clear [4,5].

This chapter addresses purpura that is not primarily of vasculitic causation; Chapter 50 deals with disorders in which a primary vasculitis is involved.

References

1 Piette WW. The differential diagnosis of purpura from a morphologic perspective. *Adv Dermatol* 1994; **9**: 3–23.
2 Marco R, Fortuna S, Rodeghiero F. Heterogeneity of terminology and clinical definitions in adult idiopathic thrombocytopenic purpura: a critical appraisal from a systematic review of the literature. *Haematologica* 2008; **93**: 98–103.
3 Bick R. Vascular thrombohemorrhagic disorders: hereditary and acquired. *Clin Appl Thrombosis Hemostasis* 2001; **7**: 178–94.
4 Piette WW. Primary systemic vasculitis. In: Sontheimer RD, Provost TT, eds. *Cutaneous Manifestations of Rheumatic Diseases*. Baltimore: Williams & Wilkins, 1996: 177–232.
5 Jones A, Walling H. Retiform purpura in plaques: a morphological approach to diagnosis. *Clin Exp Dermatol* 2007; **32**: 596–602.

Definition of purpura

Purpura is discoloration of the skin or mucous membranes due to extravasation of red blood cells. *Petechiae* are small purpuric lesions usually 1–2 mm (occasionally up to 4 mm) across, often occurring in crops. *Ecchymoses* or *bruises* are larger extravasations of blood. The many causes of petechiae and ecchymoses overlap, for example thrombocytopenia usually causes petechiae but more extensive bleeding may occur at lower levels of platelet count. In contrast, coagulation disorders usually cause ecchymoses rather than petechiae [1–4]. For example, haemophilias usually present as bleeding from the umbilical cord or gingivae, or as haematomas or haemarthroses—although dermatologists need to be aware that haemorrhagic subcutaneous nodules may be the first sign of an inherited haemophilia [5]. Gingival bleeding, epistaxis or internal bleeding may occur with platelet or coagulation disorders.

The sequence of colour changes in a bruise can help to identify it as such, should doubt exist, and can also help to establish its duration. Extravasated blood is broken down to various other pigments derived from haem, usually within 2 or 3 weeks. The characteristic colour changes [6–8] include red, blue and purple in the first 5 days (although these colours can occur at other times, particularly red), green after 5–7 days and yellow after 7–14 days (never less than 18 h). Many factors, both intrinsic to the individual (age, sex, skin colour, body site) and related to the injury (amount of blood extravasated, depth of bruising, medications that alter bruise dispersion), influence the timescale of colour changes [9]. In smaller and more superficial purpuric lesions, orange or brown colours due to residual haemosiderin may predominate. Assessment of traumatic ecchymotic lesions is not a major part of routine dermatological practice, but may be important in suspected child abuse [9].

Unlike purpura, increased intravascular blood in the skin, whether as diffuse erythema or within telangiectatic vessels, can be blanched by pressure, typically using the technique of diascopy (see Chapter 5). However, not all telangiectatic lesions can be emptied in this way. Small angiomas (e.g. in angioma serpiginosum or the multiple minute variant of Campbell de Morgan spots) and angiokeratomas may cause particular confusion [10]. Sometimes, observation over several days is necessary. Capillary microscopy or, more recently, dermoscopy may also be helpful in determining whether blood is intravascular or extravascular.

References

1 Lichtman MA, Buetler E, Kaushansky K *et al*., eds. *Williams' Hematology*, 7th edn. New York: McGraw-Hill, 2005.
2 Greer JP, Foerster J, Lukens JN *et al*., eds. *Wintrobe's Clinical Hematology*, 12th edn. Philadelphia: Lippincott, Williams & Wilkins, 2008.
3 Hoffbrand AV, Catovsky D, Tuddenham EGD, eds. *Postgraduate Haematology*, 5th edn. Oxford: John Wiley and Sons Ltd, 2008.
4 Harmening DM, ed. *Clinical Hematology and Fundamentals of Hemostasis*, 5th edn. Philadelphia: F.A. Davis Company, 2008.
5 Davis G, Butler DF, Greene J. Hemorrhagic subcutaneous nodules: an initial sign of hemophilia A. *Pediatr Dermatol* 2007; **24**: 121–4.
6 Schwartz AJ, Ricci LR. How accurately can bruises be aged in abused children? Literature review and synthesis. *Pediatrics* 1996; **97**: 254–7.
7 Langlois NE, Gresham GA. The ageing of bruises: a review and study of the colour changes with time. *Forensic Sci Int* 1991; **50**: 227–38.
8 Stephenson T. Ageing of bruising in children. *J R Soc Med* 1997; **90**: 312–4.
9 Pride HB. Child abuse and mimickers of child abuse. *Adv Dermatol* 1999; **14**: 417–55.
10 Cox NH, Paterson WD. Angioma serpiginosum: a simulator of purpura. *Postgrad Med J* 1991; **67**: 1065–6.

Classification and investigation of purpura

An aetiological classification of purpura is provided in Table 49.1. However, for clinical purposes, correlations can be made between the clinical features and the mechanism of purpura. Purpura occurs as a result of one or more of the following main mechanisms in cutaneous vessels:

1 Simple haemorrhage
2 Inflammatory haemorrhage
3 Occlusion/ischaemia.

Characteristics of lesions, including size, number, distribution pattern, and presence or absence of palpability and erythema, can be very useful in focusing on the most likely mechanisms of haemorrhage within these subsets.

In general, simple haemorrhage presents as macules without erythema (Table 49.2), although sufficient haemorrhage into subcutaneous tissue becomes palpable as a haematoma. The size of the macules has diagnostic importance. Inflammatory causes of haemorrhagic lesions usually evolve with increasing erythema in the first 24–36 h, along with increasing purpura. Such lesions are frequently, but not invariably, palpable. A subset of palpable purpura syndromes may uncommonly also produce lesions with retiform or stellate patterning, with accompanying early erythema

Table 49.1 Causes of purpura and ecchymosis.

Platelet disorders (see also Table 49.3)
Thrombocytopenia
Abnormal platelet function
Thrombocytosis

Coagulation disorders
Inherited, e.g. haemophilia or acquired factor deficiency or dysfunction (e.g. antibody inhibitor)
Drugs, e.g. anticoagulants
Localized, e.g. heparin injection sites, some insect bites
Metabolic, e.g. vitamin K deficiency, hepatic failure (decreased synthesis of clotting factors)
Thrombophilias, e.g. protein C deficiency, protein S deficiency
Disseminated intravascular coagulopathy and purpura fulminans
Secondary to systemic disease (often multifactorial, e.g. macrophage activation syndrome)

Other intravascular causes of purpura/microvascular occlusion
Dysproteinaemias, e.g. hypergammaglobulinaemic purpura (Waldenström), Sjögren's syndrome
Cryoproteinaemias
Emboli: crystal, fat, myxoma, infective

Mechanical vascular causes of purpura
Raised intravascular pressure
  Coughing, vomiting, Valsalva manoeuvre, tourniquet
  Stasis
Decreased support
  Actinic ('senile') purpura
  Corticosteroid purpura
  Scurvy
  Amyloidosis
Inherited disorders of connective tissue (pseudoxanthoma elasticum, Ehlers–Danlos syndromes)
Abnormal vasculature
Purpura around vascular lesions, e.g. targetoid haemosiderotic haemangioma, tufted angioma, aneurysmal fibrous histiocytoma

Purpura with inflammation
Non-thrombocytopenic toxin- and drug-induced purpura
Contact purpura
Purpura associated with infections
Capillaritis (pigmented purpuric dermatoses)
  Idiopathic
  Drug-induced
  Pre-mycotic
Inflammatory purpura/vasculitis (see Chapter 50), e.g. Henoch–Schönlein purpura, acute haemorrhagic oedema
Associated with other inflammatory dermatoses that are not usually purpuric
Solar purpura

External and other causes of purpura or ecchymosis
Physical and artefactual causes
Easy bruising syndrome and purpura simplex
Paroxysmal finger haematoma (Achenbach's syndrome)
Painful bruising (autoerythrocyte sensitization, Gardner–Diamond) syndrome
Stigmata

Table 49.2 Diagnosis of macular non-retiform haemorrhage/petechiae/ecchymosis by size.

Lesions <4 mm
  Thrombocytopenia
    Immune thrombocytopenic purpura
    Thrombotic thrombocytopenic purpura
    Disseminated intravascular coagulation (DIC)
    Other causes (see Table 49.3)
  Abnormal platelet function
    Congenital/hereditary
    Acquired: drug, systemic disease
    In myeloproliferative disease
    Other causes (see Table 49.3)
  With normal platelets
    Raised intravascular pressure
    Trauma
    Scurvy (perifollicular pattern)
    Hypergammaglobulinaemic purpura (Waldenström)

Intermediate-sized lesions
  Hypergammaglobulinaemic purpura (Waldenström)
  Infection in patients with thrombocytopenia or immune compromise
  Early lesions of vasculitis (sometimes)

Lesions >1 cm (all causes involve a degree of minor trauma)
  Procoagulant defect
    Anticoagulation
    Liver failure
    Vitamin K deficiency
    DIC (some)
  Poor dermal support
    Actinic and corticosteroid purpura
    Scurvy
    Hereditary: Ehlers–Danlos syndrome
    Amyloidosis
  Platelet deficiency or functional defect
  Other causes
    Hypergammaglobulinaemic purpura (Waldenström)
    Capillaritis
    Easy bruising syndrome; purpura simplex
    Physical and artefactual causes
    Gardner–Diamond syndrome
    Stigmata

and palpability (inflammatory retiform purpura). By 48 h, erythema and palpability begin fading in both types of lesions, although the purpura may persist for several days. In contrast, lesions of occlusion/ischaemia usually begin with minimal or no erythema, and may show minimal palpability unless eschar forms, but may develop erythema if sufficient necrosis occurs to induce a wound healing response. Occlusive syndromes tend to manifest retiform or branching patterns of purpura (non-inflammatory retiform purpura), sometimes with accompanying localized livedo reticularis, or as necrotic plaques with minimal erythema.

Non-inflammatory purpura is generally due to haematological causes and detailed discussion is outside the remit of this chapter; specialized haematology texts [1–7] and online review resources [8] can be consulted. Similarly, structural and non-inflammatory

vessel wall changes that allow extravasation of blood are discussed in other chapters of this text, and reviewed elsewhere [9].

References

1 Lichtman MA, Buetler E, Kaushansky K *et al.*, eds. *Williams' Hematology*, 7th edn. New York: McGraw-Hill, 2005.
2 Hoffman R, Furie B, McGlave P *et al.*, eds. *Haematology. Basic Principles and Practice*, 5th edn. Edinburgh: Churchill Livingstone, 2008.
3 Greer JP, Foerster J, Lukens JN *et al.*, eds. *Wintrobe's Clinical Hematology*, 12th edn. Philadelphia: Lippincott, Williams & Wilkins, 2008.
4 Hoffbrand AV, Catovsky D, Tuddenham EGD, eds. *Postgraduate Haematology*, 5th edn. Oxford: John Wiley and Sons Ltd, 2008.
5 Colman RW, Marder VJ, Clowes AW *et al.*, eds. *Hemostasis and Thrombosis: Basic Principles and Clinical Practice*, 5th edn. Philadelphia: Lippincott, 2005.
6 Harmening DM, ed. *Clinical Hematology and Fundamentals of Hemostasis*, 5th edn. Philadelphia: F.A. Davis Company, 2008.
7 O'Shaughnessy D, Makris M, Lillicrap D, eds. *Practical Hemostasis and Thrombosis*. Oxford: Wiley Blackwell, 2005.
8 http://asheducationbook.hematologylibrary.org
9 Bick R. Vascular thrombohemorrhagic disorders: hereditary and acquired. *Clin Appl Thrombosis Hemostasis* 2001; **7**: 178–94.

Diagnosis and pathophysiology of simple macular haemorrhage [1–6]

Purpura due to simple haemorrhage is suggested by the presence of purpura that is macular (non-palpable) and that has no blanching component in newly developed lesions (Table 49.2). Palpable lesions, or a blanching component, suggest that there is associated inflammation (which may occur as a secondary effect, hence the emphasis that evaluation must concentrate on new lesions). It should be noted that pale (not blanching) areas often appear in a perifollicular or blotchy pattern in older ecchymosis as extravasated blood is resorbed. The size of lesions, clinical patterns and body sites affected may all be diagnostically useful.

Size of lesions

Petechiae are often defined as lesions of 2 mm or less in diameter, although non-palpable, non-blanching lesions up to 4 mm usually suggest the same process. The main mechanisms of simple haemorrhage are:

1 Thrombocytopenia (platelet count always $<50 \times 10^9$/L, usually $<10 \times 10^9$/L)
2 Platelet dysfunction (uncommonly a cause of clinical purpura, although some degree of platelet dysfunction occurs in many systemic diseases or due to a variety of drugs)
3 Regional or localized increased intravascular pressure
4 Abnormal vascular support/vessel fragility
5 Many forms of capillaritis (pigmented purpura).

In contrast, macular lesions of 1 cm or greater in diameter (ecchymoses) usually result from disorders of the cascade coagulation system (especially acquired), platelet dysfunction or poor dermal vascular support. Such lesions are usually provoked by minor trauma. This results in two important clinical clues. The first is that lesions tend to localize to areas prone to frequent minor trauma, such as the extensor forearm and dorsal hand, lateral thigh and anterior lower leg. The second finding is a linear or geometric shape of individual lesions, because such lesions typically result from a frictional injury or extension of blunt trauma. Finally, as photodamage of fair skin is a very common cause of poor dermal support, ecchymotic haemorrhage is very commonly found on areas with chronic exposure to both sun and trauma, for example the extensor forearm and dorsal hand.

It is evident that some aetiologies can cause purpuric lesions of variable size. For example, scurvy (a disorder in which the collagen of vessels and dermis is altered) may cause small perifollicular petechiae or large sheets of bruising with significant induration. Drug-induced platelet dysfunction may cause small petechiae, capillaritis-type areas of discoloration, or frank bleeding. Moderately severe thrombocytopenia (platelet count around $10–20 \times 10^9$/L) may cause petechiae or broad ecchymoses.

Clinical patterns of purpura

The clinical pattern may help to determine which patients require investigation, and may suggest the most likely major pathophysiological mechanisms. Tiny purpuric spots on the lower legs, for example, are not uncommon in the elderly, in patients taking antiplatelet drugs, or in the context of an inflammatory dermatosis; investigation of such lesions in these settings is seldom needed. Similarly, larger lesions that are macular, purple, stellate or blotchy, and confined to photo-aged skin on the dorsum of hands or forearms are generally diagnosed clinically as a consequence of actinic damage (although the same process on the face may produce smaller or more linear lesions, clinically resembling amyloidosis, and more widely distributed lesions of this morphology occur in Cushing's syndrome). Some degree of purpura is not uncommon in inflammatory skin disease of several types, but investigation is likely to be aimed at the disease process rather than the purpuric component *per se*.

Features that suggest a need for further investigation include:

- Larger or variably sized lesions, particularly when not in sun-damaged skin
- Numerous or widespread lesions
- Lesions occurring in crops
- Palpable lesions
- Lesions forming reticulate patterns (livedo, retiform pattern)
- Associated features such as pustules, necrosis, nodules, splinter haemorrhages, etc.
- Evidence of bleeding from other sites, e.g. haematuria
- Associated general symptoms, e.g. fever, malaise, arthralgia.

Diagnosis of purpura at various body sites

Gravitational change has a major influence on the distribution of purpuric lesions, as discussed elsewhere in this section. Other body sites of specific importance include the following.

- Eyelids: purpura due to increased venous pressure—classically due to performing the Valsalva manoeuvre, but in practice more likely after severe coughing or vomiting, and also described after endoscopy, etc. (also affects the cheeks; Fig. 49.1); purpura or ecchymosis in amyloidosis (panda sign), due to abnormal vessels and supporting dermis; ecchymosis related to neuroblastoma.
- Ears: purpura due to cryoglobulinaemia and other hyperviscosity disorders; purpura due to some drugs, e.g. antineutrophil cytoplasm antibody (ANCA)-positive propylthiouracil reaction, levamisole
- Face, ears and acral: acute haemorrhagic oedema of childhood (Chapter 50); cryoglobulinaemia



Fig. 49.1 Purpura on the face due to the raised intravascular pressure that occurs during vomiting. The lesions are small, non-palpable and all of the same age.

- Acral: purpura due to cryoglobulinaemia and other hyperviscosity disorders; embolic causes of purpura; rickettsial infection
- Friction sites: clothing contact purpura; some cases of capillaritis; Henoch–Schönlein purpura and other small-vessel vasculitis; ecchymosis of Ehlers–Danlos syndrome
- Intraoral: thrombocytopenia; amyloidosis; myelomonocytic leukaemia; angina bullosa haemorrhagica.

Laboratory tests

Platelet count and function [1–4,7–9]

This is the most important investigation in patients with non-palpable petechiae. The normal count is 150–400 $\times$ 10^9/L. It varies greatly from person to person, and from time to time in the same person. It may be affected by numerous exogenous factors such as infections, and by internal factors such as hormonal changes. Purpura due to thrombocytopenia seldom occurs with a platelet count above 50 $\times$ 10^9/L, and significant spontaneous bleeding is unlikely unless the count is less than 20 $\times$ 10^9/L. Thrombocytosis may also be a cause of bleeding. As well as variation in number, variation in function of platelets may need to be assessed by specialized *in vitro* tests. A full blood count should always be undertaken in the investigation of purpura; in general, especially for milder bleeding problems, a staged approach to diagnostic testing is appropriate depending on the results of initial tests and the clinical suspicions [10].

Tests of occult bleeding

Simple tests to detect other sites of bleeding, whether in vasculitis or in haematological causes of purpura, include fundoscopy, urinalysis and faecal occult blood tests. Haematuria may occasionally occur in disorders that are felt to be essentially dermatological but non-vasculitic, such as drug-induced pigmented purpuric dermatoses [11,12].

Histology

Histological examination of non-palpable, non-blanching, small purpuric lesions is usually unhelpful; it is essential, however, to consider whether lesions are palpable or partially blanching. If there are palpable or partially blanching lesions, then vasculitis should be considered and biopsy is likely to be informative. If lesions are larger but not palpable, and platelet parameters are normal, then biopsy of the skin is appropriate, for example to assess disease of the vessel wall or surrounding tissues.

Capillary resistance and fragility [13–16]

If the pressure difference between the tissues and the capillaries is sufficiently increased, leakage of blood cells occurs. This is the basis of a variety of semi-quantitative tests for capillary fragility. However, the integrity of the capillary endothelium itself, and also the ability of platelets to fill any gaps which may arise in it, contribute to this type of bleeding. Abnormal results may therefore occur in conditions where there is thrombocytopenia, abnormal platelet function or intravascular coagulopathy, as well as in conditions where there is a vessel wall defect. Indeed, the precise aetiology may be mixed; for example, some types of Ehlers–Danlos syndrome (EDS IV) have abnormal vessel wall collagen, abnormal perivascular support, and may occasionally have associated platelet dysfunction, and several defects of haemostasis occur in hereditary haemorrhagic telangiectasia (HHT) as well as the vascular abnormalities [16].

Sometimes capillary leakage is discovered accidentally due to development of a shower of purpura on the arm distal to a blood pressure cuff immediately after the pressure has been released (Rumpel–Leede sign). More commonly, tests are performed to provoke purpura; the simplest clinical test, which essentially performs the same process, is the Hess test. A standardized increase in capillary pressure is produced by inflating a sphygmomanometer cuff around the upper arm to a constant pressure of 80 mmHg (or less if this approaches the systolic blood pressure) for 5 min. Petechiae develop over the next few minutes and can be counted in a measured area of 5 cm diameter just below the antecubital fossa; up to five may be considered normal. However, our experience is that the greatest density of purpura provoked by a Hess test is usually in the 'snuff-box' area over the space between the thumb and index finger metacarpals on the dorsum of the hand.

'Negative-pressure' tests require some simple apparatus to apply negative pressure to an area of skin usually 1–2 cm across. This technique is suitable for repeated tests in the same subject. The application of such a negative pressure at the rim of a cup may only be acting as a local venous tourniquet. Using these techniques capillary resistance is found to vary greatly, as does the platelet count, from individual to individual and with site and numerous other factors.

Bleeding time [4,17–20]

This is the time taken for bleeding to cease after a standardized tiny incision, usually in the skin of the forearm. This type of bleeding normally ceases because of contraction of the small vessels aided by production of a platelet plug. Techniques can be standardized in various ways, for example with a sphygmomanometer cuff at 40 mmHg the bleeding time is usually 4–10 min. The bleeding time is usually prolonged in thrombocytopenia where the platelet count is below 80 $\times$ 10^9/L and becomes progressively prolonged as the count falls, being 30 min at counts less than

10×10^9/L. It may be prolonged in von Willebrand's disease, other disorders of platelet function, severe anaemia, and in patients taking aspirin or receiving heparin, as well as being affected by age and skin laxity. Although often stated to be normal in disorders of coagulation, it may be prolonged in severe haemophilia. It is a rather insensitive test whose wide range of normal values makes it of limited use, even as a screening test. The bleeding time does not accurately predict internal surgical bleeding [19], although it has been used to investigate the effect of aspirin and non-steroidal anti-inflammatory drugs (NSAIDs), which may be relevant as a cause of bleeding during skin surgery [20].

Platelet function analysers (PFA), measuring the PFA closure time, may be more useful, but may vary in sensitivity and specificity according to the disorder being examined, the PFA being more accurate than the bleeding time for diagnosis of type I von Willebrand disease [21]. A study of the combined PFA closure times for ADP and epinephrine in normal subjects (the PFA-100) showed a false-positive rate of almost 16% and, of those who did have a platelet function abnormality, the specificity was 79% compared with 91% for the bleeding time [22]. Current techniques such as the PFA-100, even if less specific, do have the advantage of simplicity, are *in vitro* and therefore less invasive, and are more reproducible than the bleeding time. Although clinical experience with this technique is recent, this and similar methods (such as the Thrombostat 4000) are largely replacing the bleeding time in many clinical haematology laboratories.

Coagulation screen

Major coagulation defects can be excluded by a clotting screen including measurement of prothrombin time, kaolin cephalin clotting time, thrombin clotting time and fibrinogen levels. Clinical considerations and the results of the screening tests may suggest further laboratory tests, for example levels of individual clotting factors [10] or antiphospholipid antibodies. Discussion of how these tests are performed is beyond the scope of this book, but they are described in detail in other publications [23–25].

Capillary microscopy

Direct microscopic examination of capillaries is disappointing in the elucidation of haemorrhagic and purpuric diseases, although it is useful to determine whether small punctate lesions are actually petechial or small convoluted but intact capillaries. Purpura may at times be seen in the nail fold capillaries when not present elsewhere in the skin. Extravasation of blood may occur at the junction of the precapillary arteriole with the capillary, at the tip of the capillary or more usually at the venous end. Capillary microscopy is discussed further in Chapter 47 and, in relation to nailfolds in collagen vascular diseases, in Chapter 51.

Other haematological, biochemical and immunological tests

A number of other haematological tests may be indicated, depending on the likely diagnostic area. As a simple example, a blood film, bone marrow examination, and tests for antiplatelet antibodies may all contribute in distinguishing between thrombocytopenia due to decreased production versus peripheral destruction. This is the province of the haematologist, and is addressed in major haematological texts [1,2]. It is worth being aware that abnormalities predisposing to bleeding may coexist, and may require a wider range of tests than usual for the presumed diagnosis; examples include abnormal platelet function (relatively common), fibrinolytic defects and low-grade disseminated intravascular coagulopathy (DIC) (possibly in 50% of patients) in HHT [16], platelet dysfunction in Ehlers–Danlos syndrome [16], acquired factor X (sometimes IX and X) in systemic amyloidosis [16], bone marrow necrosis in antiphospholipid syndrome [26], thrombocythaemia with antiphospholipid syndrome [27], heparin-induced thrombocytopenia with the antiphospholipid syndrome [28], and the multiple causes of bleeding in acute promyelocytic leukaemia (DIC, fibrinolysis, and proteolysis of fibrinogen and von Willebrand factor) [29]. Some of these are discussed in more detail later in the chapter.

Hyperferritinaemia is a well documented feature of some inflammatory disorders. Ferritin is produced by phagocytic macrophages, and high levels occur in disorders where there is histiocytic proliferation and haemophagocytosis. This occurs in a little known disorder termed the *macrophage activation syndrome* (also termed autoimmune disease-associated reactive haemophagocytic lymphohistiocytosis), a complication mainly occurring in systemic onset juvenile idiopathic arthritis (Still's disease) and sometimes in juvenile systemic lupus erythematosus; it has also been documented in adult-onset Still's disease, and may be triggered by infections or by drugs. Purpura, bruising and mucosal bleeding occur due to a combination of thrombocytopenia and coagulopathy (prolonged prothrombin time and partial thromboplastin time, with fibrin degradation products and hypofibrinogenaemia) [30,31]. Other biochemical abnormalities include low sodium levels, and elevation of triglycerides, lactose dehydrogenase and transaminases.

Although not routinely performed, a variety of serological tests can give an indication of vascular damage; these include levels of thromboxane, endothelin, prostacyclin, soluble thrombomodulin, platelet activating factor, e-selectin and von Willebrand factor. Antibodies against platelets, clotting factors and others are sometimes measured. Emergent antibodies, but still of uncertain clinical application, include those against annexins II and V, which are important in fibrinolysis in acute promyelocytic leukaemia and in the antiphospholipid syndrome, respectively [32]. β_2-glycoprotein I is discussed later in relation to antiphospholipid syndrome.

Genetic tests

Although rarely the first approach, many causes of bleeding and thrombosis are now well characterized at a genetic level; appropriate tests may be used to confirm a diagnosis, and in some cases to estimate prognosis or suitability for specific treatment options. Some examples of relevance in evaluation of purpura and bleeding include cytogenetic testing (for example, demonstrating a high risk of bleeding in patients with acute promyelocytic leukaemia who have t(15:17) translocation), documentation of activated protein C resistance (factor V Leiden; pp. 49.38–39) and genetic tests such as identifying different types of Ehlers–Danlos syndrome (type IV, associated with severe bleeding due to vascular rupture, being due to mutations in the *COL3A1* gene), confirming different types and zygosity in homocystinaemia, distinguishing

between HHT I (endogulin gene mutations) versus HHT II (*ALK1* gene) in hereditary haemorrhagic telangiectasia, and demonstrating ADAMTS13 deficiency in thrombotic thrombocytopenic purpura [33].

Summary

To avoid performing every type of investigation in all cases of purpura, the following broad generalizations may be made.

1. Purpura of mild degree on the lower legs alone is commonly hydrostatic, especially in the elderly, in those with other evidence of venous disease, or in the distribution of other skin diseases, and seldom requires extensive investigation.
2. Coagulation defects usually present as large ecchymoses and external or internal bleeding but not as petechiae; inherited types may present as gingival bleeding. Capillary fragility tests are normal unless there is severe deficiency of clotting factors.
3. Thrombocytopenia is often associated with petechiae but there may also be external or internal haemorrhages and bruising.
4. External bleeding and large ecchymoses are due to coagulation or platelet defects, or to diseases of connective tissue such as Ehlers–Danlos syndrome.
5. Petechiae are due to platelet defects or capillary changes.
6. Dysproteinaemias may cause lesions of simple haemorrhage, inflammatory haemorrhage or occlusion, depending on the properties of individual abnormal proteins.
7. Thrombophilias may present with livedoid change, retiform purpura or usually non-inflammatory cutaneous necrosis.
8. An initial retiform pattern without blanchable erythema or palpable lesions is generally indicative of microvascular occlusion.
9. Inflammatory lesions of the vessels are seldom the cause of external bleeding or ecchymoses, but are the most common cause of persistent and localized purpura. A blanchable erythematous inflammatory component is often present in early lesions.
10. Inflammatory purpuric lesions are due to vascular changes rather than simple haemorrhage.
11. Splinter haemorrhages of the nails are due to purpura of the nail bed, are most commonly due to trauma and are not diagnostic of any one condition (see Chapter 65).

References

1 Lichtman MA, Buetler E, Kaushansky K *et al.*, eds. *Williams' Hematology*, 7th edn. New York: McGraw-Hill, 2005.
2 Greer JP, Foerster J, Lukens JN *et al.*, eds. *Wintrobe's Clinical Hematology*, 12th edn. Philadelphia: Lippincott, Williams & Wilkins, 2008.
3 Taylor RE, Blatt PM. Clinical evaluation of the patient with bruising and bleeding. *J Am Acad Dermatol* 1981; **4**: 348–68.
4 Hardisty RM. Platelet disorders. In: Hoffbrand AV, Lewis SM, eds. *Postgraduate Haematology*, 3rd edn. Oxford: Heinemann, 1989: 598–626.
5 Lowe GDO. Vascular disease and vasculitis. In: Ratnoff OD, Forbes CD, eds. *Disorders of Haemostasis*, 3rd edn. London: Saunders, 1996.
6 Piette WW. The differential diagnosis of purpura from a morphologic perspective. *Adv Dermatol* 1994; **9**: 3–23.
7 Seegmiller A, Sarode R. Laboratory evaluation of platelet function. *Haematol Oncol Clin North Am* 2007; **21**: 731–42.
8 Shen-Yu MP, Frenkel EP. Acquired platelet dysfunction. *Haematol Oncol Clin North Am* 2007; **21**: 647–71.
9 Visentin GP, Liu CY. Drug-induced thrombocytopenia. *Haematol Oncol Clin North Am* 2007; **21**: 685–96.
10 Hayward CPM. Diagnosis and management of mild bleeding disorders. *Hematology Am Soc Hematol Educ Program* 2005: 423–8.
11 Crowson AN, Magro CM, Zahorchak R. Atypical pigmentary purpura: a clinical, histopathologic, and genotypic study. *Hum Pathol* 1999; **30**: 1004–12.
12 Cox NH, Walsh ML, Robson RH. Purpura and bleeding due to calcium channel blockers: an underestimated problem? Case reports and a pilot study. *Clin Exp Dermatol* 2009; **34**: 487–91.
13 Gough KR. Capillary resistance to suction in hypertension. *BMJ* 1962; **i**: 21–4.
14 Kramar J. The determination and evaluation of capillary resistance. *Blood* 1962; **20**: 83–93.
15 Peck SM. Diagnosis and treatment of skin manifestations of capillary fragility. *N Engl J Med* 1946; **235**: 900–6.
16 Bick R. Vascular thrombohemorrhagic disorders: hereditary and acquired. *Clin Appl Thrombosis Hemostasis* 2001; **7**: 178–94.
17 Anonymous. What about the bleeding time? *BMJ* 1985; **291**: 91.
18 Lind SE. Prolonged bleeding time. *Am J Med* 1984; **77**: 305–12.
19 Lind SE. The bleeding time does not predict surgical bleeding. *Blood* 1991; **77**: 2547–52.
20 Lawrence C, Sakuntabhai A, Tiling-Grosse S. Effect of aspirin and nonsteroidal antiinflammatory drug therapy on bleeding complications in dermatologic surgical patients. *J Am Acad Dermatol* 1994; **31**: 988–92.
21 Hassan AA, Kroll MH. Acquired disorders of platelet function. *Hematology Am Soc Hematol Educ Program* 2005: 403–8.
22 Posan E, McBane RD, Grill DE *et al*. Comparison of PFA-100 testing and bleeding time for detecting platelet hypofunction and von Willebrand disease in clinical practice. *Thromb Haemost* 2003; **90**: 892–8.
23 Helbert M, Bodger S, Cavenagh J *et al*. Optimising testing for phospholipid antibodies. *J Clin Pathol* 2001; **54**: 693–8.
24 Pierangeli SS, Harris EN. Clinical laboratory testing for the antiphospholipid syndrome. *Clin Chim Acta* 2005; **357**: 17–33.
25 Hoppensteadt DA, Fabbrini N, Bick RL *et al*. Laboratory evaluation of the antiphospholipid syndrome. *Haematol Oncol Clin North Am* 2008; **22**: 19–32.
26 Paydas S, Koçak R, Zorludemir S, Baslamisli F. Bone marrow necrosis in antiphospholipid syndrome. *J Clin Pathol* 1997; **50**: 261–2.
27 Harrison CN, Machin SJ. Antiphospholipid antibodies and essential thrombocythemia. *Am J Med* 1997; **102**: 317–8.
28 Hoppensteadt DA, Walenga JM. The relationship between the antiphospholipid syndrome and heparin-induced thrombocytopenia. *Haematol Oncol Clin North Am* 2008; **22**: 1–18.
29 Tallman MS, Abutalib SA, Altman JK. The double hazard of thrombophilia and bleeding in acute promyelocytic leukaemia. *Semin Thromb Hemost* 2007; **33**: 330–8.
30 Kelly A, Ramanan AV. Recognition and management of macrophage activation syndrome I juvenile arthritis. *Curr Opin Rheumatol* 2007; **19**: 477–81.
31 Castillo L, Carcillo J. Secondary hemophagocytic lymphohistiocytosis and severe sepsis/systemic inflammatory response syndrome/multiorgan dysfunction syndrome/macrophage activation syndrome share common intermediate phenotypes on a spectrum of inflammation. *Pediatr Crit Care Med* 2009; **10**: 387–92.
32 Rand JH. 'Annexinopathies'—a new class of diseases. *N Engl J Med* 1999; **340**: 1035–6.
33 Kobaashi T, Wada H, Nishioka N *et al*. ADAMTS13 related markers and von Willebrand factor in plasma from patients with thrombotic microangiopathy (TMA). *Thromb Res* 2007; **121**: 849–54.

Purpura due to thrombocytopenia or platelet defects

Platelets are an essential component of the haemostatic process. Thrombocytopenia or abnormal platelet function from any cause may therefore produce purpura or a bleeding tendency, as discussed in the general haematology texts previously listed and in references listed below [1–7].

Table 49.3 Platelet disorders causing purpura.

Thrombocytopenia
Defective platelet production
  Bone marrow abnormality
    Aplasia: toxic, immunological, idiopathic
    Neoplasia: leukaemia, myeloma, carcinomatosis
    Replacement: myelofibrosis, radiation damage, sarcoidosis
Other impaired production: Wiskott–Aldrich syndrome, vitamin B_{12} or folate deficiency
  Metabolic: uraemia, alcohol, drugs
  Infections
Diminished platelet survival
  Platelet alloantibodies
    Neonatal
    Post-transfusion
    Antilymphocyte globulin
  Platelet autoantibodies
    Idiopathic (immune) thrombocytopenic purpura
    Marrow transplant
    Antiphospholipid antibodies
    Systemic lupus erythematosus
Mechanical: prosthetic heart valves
Drugs and vaccines
Infections, sepsis syndrome
Excessive platelet consumption
  Disseminated intravascular coagulation
  Haemangioma (Kasabach–Merritt)
  Hereditary haemorrhagic telangiectasia ('mini-Kasabach–Merritt')
  Thrombotic microangiopathies
    Haemolytic–uraemic syndrome
    Thrombotic thrombocytopenic purpura
Sequestration
  Splenomegaly
  Hypothermia

Abnormal platelet function
Inherited and congenital
  Von Willebrand disease and defects of the platelet von Willebrand factor receptor
  Hereditary haemorrhagic telangiectasia (often have platelet dysfunction also)
  Bernard–Soulier disease (GpIb/IX/V receptor defect with low platelet count)
  GpIa deficiency
  Glanzmann's thrombasthenia (GpIIb/IIIa deficiency)
  MYH9-related disorders (e.g. May–Hegglin abnormality)
  α-granule disorders
  Dense granule (δ-granule) disorders (Hermansky–Pudlak syndrome, Chediak–Higashi syndrome, storage pool disease)
  Abnormalities of signal-transduction pathways
  Membrane phospholipids abnormalities (e.g. Scott syndrome)
  Wiskott–Aldrich syndrome (δ-granule abnormality) and X-linked thrombocytopenia (WASP gene mutations)
Drug-induced
Uraemia
Cardiac bypass
Platelet antibodies
  Idiopathic (immune) thrombocytopenic purpura
  Systemic lupus erythematosus/antiphospholipid syndrome
Myeloproliferative disorders
Dysproteinaemias (especially IgA myeloma and macroglobulinaemia)
Cold-stored (blood bank) platelets

Thrombocytosis
Essential thrombocythaemia
Other myeloproliferative syndromes
Medical diseases and other causes
  Blood loss, trauma, burns
  Post-splenectomy
  Malignant disease
  Tuberculosis
  Sarcoidosis

Platelets exposed to damaged endothelium adhere to one another and to collagen and other subendothelial components. Numerous complex interactions occur, involving von Willebrand factor and its glycoprotein receptor, various integrin adhesion molecules, thrombospondin, fibronectin, laminin, phospholipases and ADP released from damaged cells, as well as collagen and platelets. Platelet activation causes release of serotonin and thromboxane A_2, both of which cause vasoconstriction, and increase platelet adhesiveness and aggregation leading to formation of a platelet plug. This process is aided further by the presence of plasma fibrinogen and by thrombin. Production of prostacyclin, a powerful vasodilator and inhibitor of platelet aggregation, is decreased as a result of endothelial damage. Developing platelet plugs are reinforced by fibrin strands formed as a result of activation of the plasma clotting system by platelet factor 3, when this is exposed by alterations in the surface characteristics of the aggregated platelets.

Purpura due to platelet defects can be divided into three groups:

- Thrombocytopenia, i.e. decreased platelet numbers
- Abnormalities of platelet function
- Thrombocytosis, i.e. increased platelet numbers.

Thrombocytopenia

The platelet count at which purpura occurs is extremely variable. Purpura due to platelet deficiency usually occurs with a count below 20×10^9/L and is seldom observed with a count above 50×10^9/L. The main causes of thrombocytopenia are listed in Table 49.3.

References

1 McCrae KR, Bussel JB, Mannucci PM *et al*. Platelets: an update on diagnosis and management of thrombocytopenic disorders. *Hematology Am Soc Hematol Educ Program* 2001: 282–305.
2 Handin RI. Inherited platelet disorders. *Hematology Am Soc Hematol Educ Program* 2005: 396–402.
3 Cines DB, Bussel JB, McMillan RB, Zehnder JL. Congenital and acquired thrombocytopenia. *Hematology Am Soc Hematol Educ Program* 2004: 390–406.
4 Hayward CPM. Diagnosis and management of mild bleeding disorders. *Hematology Am Soc Hematol Educ Program* 2005: 423–8.
5 Bussel JB, Kunicki TJ, Michelson AD. Platelets: new understanding of platelet glycoproteins and their role in disease. *Hematology Am Soc Hematol Educ Program* 2000: 222–40.
6 George JN, Shattil SJ. The clinical importance of acquired abnormalities of platelet function. *N Engl J Med* 1991; **324**: 27–39.
7 Hassan AA, Kroll MH. Acquired disorders of platelet function. *Hematology Am Soc Hematol Educ Program* 2005: 403–8.

Idiopathic (immune) thrombocytopenic purpura [1–9]

Synonyms
- Autoimmune thrombocytopenic purpura (ATP)
- Werlhof's disease

Idiopathic immune thrombocytopenic purpura (ITP) results from immune destruction of platelets; transient ITP has been documented in children born to affected mothers, and passive transfer has been demonstrated. The prevalence is about 1/10 000 population per year, and it is about twice as common in women, except in childhood where males predominate [10]. Half of cases occur in children [4] (two-thirds before age 21 years), and it may occur in 0.1–0.2% of pregnancies. Familial and twin cases have occurred, some populations show an association with HLA-DRw2 or DRB1*0410 alleles, and a genetic predisposition appears likely [11]. There is an association with other autoimmune diseases, such as celiac disease [12] and thyroid disease [13]; other predisposing factors include certain immunodeficiencies, complement C2 or C4 deficiency, and abnormalities of the Fas pathway [1]. The onset may be gradual or, especially in children, acute, and the overall course may be self-limiting (especially in children) or long-term. Chronic ITP is usually autoimmune and apparently idiopathic.

The autoantibodies often show specificity for the platelet membrane glycoproteins IIb/IIIa (integrin αIIbβ3) and Ib/IX [5], and less often for Ia/IIa, IV or V. It is unclear why these develop but there is a Th1 cytokine profile and T cells may drive the process by stimulating antibody synthesis after being exposed to fragments of glycoprotein IIb/IIIa, but not to the intact native protein; such fragments may arise from destruction of platelets within antigen-presenting cells or by other mechanisms [5,8]. A current theory suggests that there is upregulation of CD40 ligand (CD40L, CD154) on T cells, which causes co-stimulatory B cell activation and ongoing antibody production. Viral antigen–antibody reactions may be demonstrated in acute forms of the disease, usually in children following an acute viral illness such as rubella, varicella, parvovirus B19, Epstein–Barr virus, echoviruses and others. Vaccines to prevent viral illness have also been implicated, including recently the combined measles, mumps and rubella (MMR) vaccine. Chronic infections that can provoke chronic (mainly adult) ITP include HIV, hepatitis C virus and possibly *Helicobacter pylori* [1,13].

Some cases are drug-induced (see later) or are associated with systemic lupus erythematosus (SLE) and other autoimmune connective tissue diseases, with agammaglobulinaemia, or with lymphoproliferative disease (e.g. chronic lymphocytic leukaemia, lymphomas) or with myelodysplasia. ITP may also coexist with other haematological abnormalities, for example the combination of ATP and neutrophilia, which presents as mucosal bleeding with infections; the platelet deficiency tends to be chronic. Of greater dermatological importance is Evans' syndrome, which comprises Coombs-positive haemolytic anaemia with ITP; this is also associated with collagen vascular disorders, usually SLE or scleroderma but occasionally dermatomyositis [14,15].

From the haematology perspective, the platelet count falls below 50×10^9/L and may even be zero. Usually the only symptom is a tendency to bleed from gingivae after brushing teeth, or into the skin to produce crops of petechiae or larger haemorrhages (Fig. 49.2). Bleeding may occur in any organ but joint involvement is unusual. The spleen may be slightly enlarged but gross splenomegaly should suggest an alternative diagnosis. Intracranial haemorrhage occurs in about 0.2% of children and is often fatal, but is very unlikely unless the platelet count is less than 10×10^9/L.

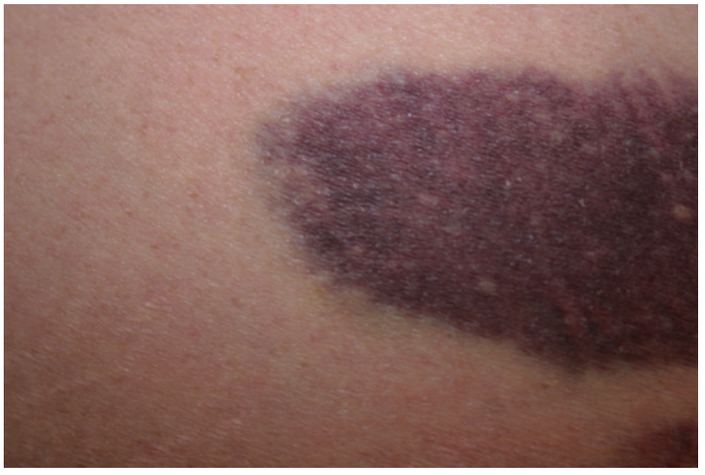


Fig. 49.2 Spontaneous bruising in drug-induced idiopathic thrombocytopenic purpura.

Lupus erythematosus develops in a small proportion of cases [16], although there are differences in immunopathogenesis between the thrombocytopenia of SLE and that of ITP [17]. About 20% of adult patients with immune thrombocytopenia have associated features of the primary antiphospholipid antibody syndrome (APLS), with a prolonged activated partial thromboplastin time (aPTT), lupus anticoagulant and anticardiolipin antibodies. The immune thrombocytopenia associated with APLS is rarely severe [18].

The diagnosis is established by the clinical picture, low platelet count, exclusion of other causes of thrombocytopenia and the mainly negative bone marrow findings (megakaryocytes are present in normal or increased numbers in the bone marrow, but bone marrow examination is not routinely performed, especially in younger subjects without other abnormal findings); ITP has historically been largely a diagnosis of exclusion. Various methods of demonstrating platelet antibodies have been used, but are largely of little help; they are sensitive but non-specific as they detect non-pathological antibodies. Antibodies bound to platelet glycoproteins have been felt to be pathological and more suitable for assay [19], with a positive predictive value of about 80% [4]. Their lack of specificity, and the variability of commercial assays, means that they are of limited value [1,8], although patients with antiplatelet glycoprotein antibodies tend to need more intensive therapy [8]. Elevated levels of caeruloplasmin may help to identify chronic ITP compared with other causes of thrombocytopenia [20]. New biomarkers of the autoimmune reaction (leptin, cell-bound antiplatelet antibodies, specific B cells) and of thrombopoiesis (thrombopoietin, glycocalicin, reticulated platelets) may advance diagnosis in the future [21]. The differential diagnosis is

wide but especially includes SLE, drug-induced purpura, disseminated intravascular coagulation (DIC) and renal failure.

Spontaneous remission often occurs in acute attacks (most children have spontaneous improvement within a month or two, and the disorder resolves in about two-thirds within 2–4 months [9]), but spontaneous remission is rare in chronic cases of more than 3 months' duration, where a continuous or fluctuating course may occur. A variety of treatments have been used [1,3–6,8,9,22–25], the aim being prevention of serious bleeding rather than normalization of the platelet count. In children, observation alone is often satisfactory unless there is bleeding, but in adults severe thrombocytopenia is an indication for treatment even in the absence of serious bleeding. A platelet count of below 30×10^9/L is usually the threshold for intervention. Corticosteroid therapy (prednisolone 1 mg/kg/day) is most commonly used but other regimens, such as a 4-day course of high-dose dexamethasone, may achieve better remission rates; about 50% of adults treated with corticosteroids achieve complete remission but platelet counts often fall as the treatment is tapered. Splenectomy is beneficial in at least two-thirds of chronic cases and in acute cases in which a spontaneous or steroid-induced remission cannot be achieved, but carries some risk. After splenectomy the platelet count tends to remain low but the purpura tends to cease. Immunosuppressive therapy or other treatments are indicated in cases that fail to respond to splenectomy and steroids, or where splenectomy is contraindicated; treatments that have been used in patients with refractory ITP include danazol, azathioprine, vincristine, interferon-α, ciclosporin, mycophenolate mofetil, Fc receptor blockade using intravenous immunoglobulin (IVIG) or intravenous anti-D antiserum (antiD), plasma exchange, various monoclonal antibodies and biological agents such as rituximab (anti-CD20), Campath-1-H (anti-CD52), second generation thrombopoietic agents [24,26,27], pegylated recombinant megakaryocyte-derived growth factor [8], and, rarely, autologous stem cell transplantation. AntiD only works in patients who are Rhesus D-positive and who have a spleen, but in such individuals there is typically a very rapid improvement in platelet count; IVIG is useful in achieving rapid responses, although its mechanism involves upregulation of FcRIIb rather than the competitive binding to FcRIII that occurs with antiD [1], and it also appears to be active in ITP caused by viruses such as parvovirus B19 and Epstein–Barr virus. In view of the possible link between *H. pylori* and ITP (especially in adults), appropriate testing and eradication, if indicated, would appear appropriate before using more toxic therapies. Similarly, hepatitis C infection should be treated if present. Beyond the standards of steroids and splenectomy, for rapid response, IVIG may be the best current agent, for remission rituximab (33% durable remission) and for the future non-thrombopoietin-like thrombopoietic agents and anti-CD154 antibodies.

Various measures have been used to predict and monitor outcome and treatment response in ITP, in addition to the platelet count [4,28–30]. Other than young age, which is associated with a shorter disease course (but which does not predict response to corticosteroids if used), the most useful clinical aspect is that splenectomy is most successful in those who responded initially to steroids, and who get a rapid improvement in platelet count after splenectomy. HLA-DRB1*14 and DRB1*0410 are associated with good prognosis and good response to common interventions, and HLA-DRB1*13 and DR4 with poor prognosis or therapeutic resistance. Serum IL-2 is a good prognostic marker in ITP, relapse is lower in children treated with corticosteroids, and platelet-associated IgGs are a useful monitoring parameter.

References

1 McCrae KR, Bussel JB, Mannucci PM *et al*. Platelets: an update on diagnosis and management of thrombocytopenic disorders. *Hematology Am Soc Hematol Educ Program* 2001: 282–305.

2 Cines DB, Bussel JB, McMillan RB, Zehnder JL. Congenital and acquired thrombocytopenia. *Hematology Am Soc Hematol Educ Program* 2004: 390–406.

3 Kelton JG, Bussel JB, eds. Idiopathic thrombocytopenic purpura. *Semin Hematol* 2000; **37**: 219–314.

4 Cines DB, Blanchette VS. Immune thrombocytopenic purpura. *N Engl J Med* 2002; **346**: 995–1008.

5 McMillan R. The pathogenesis of chronic immune thrombocytopenic purpura. *Semin Hematol* 2007; **44** (Suppl. 5): S3–11.

6 Psaila B, Bussel JB. Immune thrombocytopenic purpura. *Haematol Oncol Clin North Am* 2007; **21**: 743–59.

7 Bussel JB, Kunicki TJ, Michelson AD. Platelets: new understanding of platelet glycoproteins and their role in disease. *Hematology Am Soc Hematol Educ Program* 2000: 222–40.

8 Beardsley DS. ITP in the 21st century. *Hematology Am Soc Hematol Educ Program* 2006: 402–7.

9 Nugent DJ. Immune thrombocytopenic purpura of childhood. *Hematology Am Soc Hematol Educ Program* 2006: 97–103.

10 Segal JB, Powe NR. Prevalence of immune thrombocytopenia: analyses of administrative data. *J Thromb Haemost* 2006; **4**: 2377–83.

11 Rischewski JR, Imbach P, Paulussen M, Kühne T. Idiopathic thrombocytopenic purpura (ITP): is there a genetic predisposition? *Pediatr Blood Cancer* 2006; **47** (5 Suppl.): 678–80.

12 Olén O, Montgomery SM, Elinder G *et al*. Increased risk of immune thrombocytopenic purpura among patients with celiac disease. *Scand J Gastroenterol* 2008; **43**: 416–22.

13 Liebman H. Other immune thrombocytopenias. *Semin Hematol* 2007; **44** (Suppl. 5): S24–34.

14 Fong KY, Loizou S, Boey ML, Walport MJ. Anticardiolipin antibodies, haemolytic anaemia and thrombocytopenia in systemic lupus erythematosus. *Br J Rheumatol* 1992; **31**: 453–5.

15 Chang DK, Yoo DH, Kim TH *et al*. Induction of remission with intravenous immunoglobulin and cyclophosphamide in steroid-resistant Evans' syndrome associated with dermatomyositis. *Clin Rheumatol* 2001; **20**: 63–6.

16 Hepburn MJ, English JC, Keeling JH. Autoimmune idiopathic thrombocytopenic purpura with the subsequent occurrence of systemic lupus erythematosus. *Cutis* 1997; **60**: 185–7.

17 Lazarus AH, Ellis J, Semple JW *et al*. Comparison of platelet immunity in patients with SLE and ITP. *Transfusion Sci* 2000; **22**: 19–27.

18 Cuadrado MJ, Hughes GRV. Hughes (antiphospholipid) syndrome. Clinical features. *Rheum Dis Clin N Am* 2001; **27**: 507–24.

19 Warner M, Kelton JG. Laboratory investigation of immune thrombocytopenia. *J Clin Pathol* 1997; **50**: 5–12.

20 Chousa M, Hiroyasu I, Kuniaki S *et al*. The measurement of serum ceruloplasmin is useful for diagnostic differentiation of immune thrombocytopenic purpura. *Clin Chim Acta* 2008; **389**: 132–8.

21 Sachs UJH. Diagnosis of idiopathic thrombocytopenic purpura. *Haemostaseologie* 2008; **28**: 72–6.

22 Stasi R, Provan D. Management of immune thrombocytopenic purpura in adults. *Mayo Clin Proc* 2004; **79**: 504–22.

23 George JN, Vesely SK. Immune thrombocytopenic purpura—let the treatment fit the patient. *N Engl J Med* 2003; **349**: 903–5.

24 Bromberg ME. Immune thrombocytopenic purpura—the changing therapeutic landscape. *N Engl J Med* 2006; **355**: 1643–5.

25 Arnold DM, Kelton JG. Current options for the treatment of idiopathic thrombocytopenic purpura. *Semin Hematol* 2007; **44** (Suppl. 5): S12–23.

26 Andemariam B, Psaila B, Bussel JB. Novel thrombopoietic agents. *Hematology Am Soc Hematol Educ Program* 2007: 106–13.

27 Newland A. Thrombopoietin mimetic agents in the management of immune thrombocytopenic purpura. *Semin Hematol* 2007; **44** (Suppl. 5): S35–45.
28 Leung AY, Chim CS, Kwong YL *et al.* Clinicopathologic and prognostic features of chronic idiopathic thrombocytopenic purpura in adult Chinese patients: an analysis of 220 cases. *Ann Haematol* 2001; **80**: 384–6.
29 Syed-Naveen N, Adil-Salman N, Sajid S *et al*. Chronic ITP: analysis of various factors at presentation which predict failure to first line treatment and the response to second line therapy. *J Pak Med Assoc* 2007; **57**: 126–9.
30 Tag LM, Ezz-Eldeen AM, Mahmoud MS *et al*. Serum IL-2 and platelet-associated immunoglobulins are good prognostic markers in immune thrombocytopenic purpura. *Egypt J Immunol* 2004; **1**: 121–32.

Secondary or symptomatic thrombocytopenia

Drugs and toxins [1]

Drug- or toxin-induced purpura may occur as a result of thrombocytopenia, altered platelet function or vascular damage. Each of these may be caused by many different mechanisms. The last two are considered later. The main causes of drug- or toxin-induced thrombocytopenia are:

- Direct bone marrow toxicity, e.g. benzol, nitrogen mustard, or general myelotoxicity (e.g. chemotherapeutic agents)
- Immunological bone marrow damage, e.g. chloramphenicol
- Destruction of formed platelets, via either immunological (e.g. apronalide (Sedormid), quinidine, quinine, sulphonamides) or non-immunological mechanisms (e.g. bleomycin).

The immunological mechanisms have been divided into [1]:

- Hapten-induced antibody (e.g. penicillins)
- Drug-dependent (compound or conformational) antibody (e.g. quinine, quinidine, NSAIDs, anticonvulsants, antibiotics and many others)
- Inhibitors of the platelet glycoprotein GIIb/IIIa—further divided into four known or probable mechanisms (ligand mimetic, drug-specific antibody, drug-induced antibody and immune complex-mediated).

Some of these are of interest as they relate to new types of drug, for example the chimeric Fab fragment of abciximab induces antibody specific for murine sequences that control GIIb/IIIa (with onset sometimes within hours of exposure). However, the most important mechanism, in that it is pertinent to most drug-induced thrombocytopenia, is that where a drug-specific antibody is created by the drug (or metabolite) binding to a platelet glycoprotein to create either an antibody-inducing drug–glycoprotein epitope or a conformational change elsewhere in the target glycoprotein for which the antibody is specific. The mechanisms for many drugs, and certainly the binding sites, are often uncertain; some drugs may cause thrombocytopenia by more than one mechanism (e.g. thiazides may cause selective inhibition of megakaryocyte production as well as immunological peripheral destruction).

It has been suggested that at least 200 drugs cause thrombocytopenia. The most common are cytotoxic/chemotherapeutic drugs, quinine, quinidine, gold salts, heparin, sulphonamides, penicillins, thiazides and furosemide (frusemide), procainamide, indometacin (indomethacin) and other NSAIDs, thiouracils and carbimazole, bismuth, arsenicals, rifampicin and isoniazid, acetazolamide, acetylsalicylic acid, imipramine, interferon, various sedatives, and anticonvulsants such as phenytoin, carbamazepine and sodium valproate [2–4]. Recently implicated drugs include tirofiban, roxifiban, eptifibatide and abciximab. Various biological agents used in dermatology, such as efalizumab [5], have also been implicated as a cause of drug-induced thrombocytopenia.

Onset of thrombocytopenia is usually after a week with first exposure but can be within 2–3 days on re-exposure [1]; improvement is usually within 10 days of stopping the culprit drug. However, the duration of thrombocytopenia after stopping the drug is too long to be explained on the basis of either drug clearance or platelet lifespan in some cases, particularly with quinidine or quinine, suggesting that true autoantibodies may be produced [6]. The severity of thrombocytopenia does not necessarily correlate with the implicated drug, mechanism, or specific glycoprotein to which the drug may bind.

Heparin-induced thrombocytopenia (HIT) [7–13] is discussed in more detail later. It may present as isolated thrombocytopenia (which may be severe but can be of modest severity compared with other drug-induced causes), but may also cause platelet-rich clot formation leading to venous thrombosis, limb ischaemia, injection site necrosis, adrenal crisis due to adrenal vein necrosis, and severe systemic post-bolus injection reactions. The risks are greater in females, in surgical settings and with unfractionated heparins; it occurs in about 2% of subjects exposed to heparin, but in up to 40% after cardiac surgery. It is important as it can be confused with post-transfusion purpura in early stages, but the greatest importance (which also helps to distinguish it from other drug-induced thrombocytopenias) is the association with arterial or venous thrombosis (heparin-associated thrombocytopenia and thrombosis syndrome), which occurs in about a third of patients with HIT, and with heparin-induced skin necrosis, as discussed later. A crucial issue in such instances is to avoid coumarins, which will not work (they may in fact worsen thrombosis by depleting protein C, and coumarin-induced thrombosis is about 100-fold more likely if HIT is present than if it is not). Treatment is therefore with agents that directly inhibit thrombin or its generation [11]. It is due to formation of antibodies against an immunogenic complex involving heparin and platelet factor 4 (PF4), the antibody reaction causing platelet aggregation; there are also high levels of thrombin–antithrombin complexes.

Other toxic causes of thrombocytopenia include alcohol, snake venoms and, rarely, foods and food additives.

Infections

Thrombocytopenia may occur with a wide variety of infections, often with associated capillary damage. Infections that may be associated with thrombocytopenia include septicaemia of many aetiologies, typhoid, typhus, tuberculosis, smallpox, chickenpox, vaccinia, scarlet fever, influenza, measles, rubella, cat-scratch disease, infective hepatitis, subacute bacterial endocarditis, glandular fever, malaria, dengue fever, human immunodeficiency virus (HIV), hepatitis C and other virus infections.

Bone marrow diseases

Bone marrow diseases, for example leukaemia or aplastic anaemia, are the commonest causes of thrombocytopenia (see Table 49.3). In addition to the abnormal platelet production, there may be platelet antibodies formed in patients with lymphoma or leukaemia. Splenomegaly of many different aetiologies causes

sequestration of platelets in the splenic sinuses but rarely produces a platelet count low enough to cause purpura. Purpura and ecchymosis are among the commoner cutaneous features of the haemophagocytic syndrome.

Pregnancy

Numerous reasons may explain thrombocytopenia in pregnancy [13]. The commonest cause is termed gestational or incidental thrombocytopenia, and accounts for three-quarters of cases, but does not cause platelet counts low enough to cause purpura. Thus, if purpura is present, other more significant disorders should be considered. ITP accounts for 5% of cases, occurring in 0.1% of pregnancies, and thrombotic thrombocytopenic purpura, drug-induced and infection-induced thrombocytopenia may all occur. The last-mentioned is of dermatological importance, as the likely infections include HIV and cytomegalovirus, both of which may cause congenital infection in the neonate. Pregnancy-specific thrombocytopenias include those due to pre-eclampsia, HELLP (haemolysis, elevated liver function tests, low platelets; discussed on p. 49.31) or fatty liver. There are also potential systemic disease associations, including SLE, antiphospholipid syndrome and disseminated intravascular coagulation, as well as various conditions of bone marrow failure and nutritional deficiencies.

Platelet consumption and the thrombotic microangiopathies (thrombotic thrombocytopenic purpura and haemolytic–uraemic syndrome)

Thrombocytopenia may be associated with haemangiomas (Kasabach–Merritt syndrome, see Chapter 18). This is caused by ongoing chronic consumption and there is often compensated subacute or chronic DIC. Relevant haemangiomas are usually large and have undergone an increase in size and become tender when the thrombocytopenia develops, but a low-grade version can occur in hereditary haemorrhagic telangiectasia.

Thrombotic thrombocytopenic purpura (TTP, Moschowitz's syndrome) [13–20] in adults and haemolytic–uraemic syndrome (HUS) in children are rare forms of thrombotic microangiopathy in which thrombocytopenic purpura and bleeding are associated with fever, haemolytic anaemia and renal and neurological symptoms. HUS has recently been shown to involve a severe prothrombotic coagulation disturbance before onset of clinical features; the main clinically apparent feature is bloody diarrhoea due to Shiga toxin from *Escherichia coli* (mainly serotype 0157:H7). TTP is multifactorial, and may occur due to neoplasia, drugs, infections or organ transplantation, but many cases are due to an acquired autoimmune deficiency of ADAMTS13 (a metalloprotease). Platelets adhere to 'ultra-large' von Willebrand factor (ULVWF) multimers that are secreted from endothelial cells, and are normally cleaved by ADAMTS13; failure of this control mechanism leads to platelet-rich thrombotic microvascular plugging. Schistocytes (fragmented erythrocytes) are seen on blood films. Microvascular injury and intraluminal platelet thrombosis, and platelet plugging in myeloproliferative disorders, are discussed in more detail on p. 49.27.

References

1 Visentin GP, Liu CY. Drug-induced thrombocytopenia. *Haematol Oncol Clin N Am* 2007; **21**: 685–96.

2 George JN, Shattil SJ. The clinical importance of acquired abnormalities of platelet function. *N Engl J Med* 1991; **324**: 27–39.

3 Bruinsma W. *A Guide to Drug Eruptions*. Amsterdam: Excerpta Medica, 1973: 55–8.

4 Bork K. *Cutaneous Side-effects of Drugs*. Philadelphia: Saunders, 1988: 191.

5 Hostetler SG, Zirwas M, Bechtel MA. Efalizumab-associated thrombocytopenia. *J Am Acad Dermatol* 2007; **57**: 707–10.

6 Aster RH. Can drugs cause autoimmune thrombocytopenic purpura? *Semin Hematol* 2000; **37**: 229–38.

7 Fabris F, Luzzatto G, Stefani PM *et al.* Heparin-induced thrombocytopenia. *Haematologica* 2000; **85**: 72–81.

8 Warkentin TE. Heparin-induced thrombocytopenia. *Haematol Oncol Clin N Am* 2007; **21**: 589–607.

9 Stricker H, Lämmle B, Furlan M, Sulzer I. Heparin-dependent in vitro aggregation of normal platelets by plasma of a patient with heparin-induced skin necrosis: specific diagnostic test for a rare side-effect. *Am J Med* 1988; **85**: 721–4.

10 Arnold DM, Kelton JG. Heparin-induced thrombocytopenia: an iceberg rising. *Mayo Clin Proc* 2005; **80**: 988–90.

11 Warkentin TE. Think of HIT. *Hematology Am Soc Hematol Educ Program* 2006: 408–14.

12 Hoppensteadt DA, Walenga JM. The relationship between the antiphospholipid syndrome and heparin-induced thrombocytopenia. *Haematol Oncol Clin N Am* 2007; **21**: 1–18.

13 McCrae KR, Bussel JB, Mannucci PM *et al*. Platelets: an update on diagnosis and management of thrombocytopenic disorders. *Hematology Am Soc Hematol Educ Program* 2001: 282–305.

14 Moake JL. Thrombotic microangiopathies. *N Engl J Med* 2002; **347**: 589–600.

15 Elliott MA, Nichols WL. Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. *Mayo Clin Proc* 2001; **76**: 1154–62.

16 Grabowski EF. The hemolytic-uremic syndrome—toxin, thrombin and thrombosis. *N Engl J Med* 2002; **346**: 58–61.

17 Chandler WL, Jelacic S, Boster DR *et al.* Prothrombotic coagulation abnormalities preceding the hemolytic–uremic syndrome. *N Engl J Med* 2002; **346**: 23–32.

18 Sadler JE, Moake JL, Miyata T, George JN. Recent advances in thrombotic thrombocytopenic purpura. *Hematology Am Soc Hematol Educ Program* 2004: 407–23.

19 Sadler JE. Thrombotic thrombocytopenic purpura: a moving target. *Hematology Am Soc Hematol Educ Program* 2006: 415–20.

20 Tsai H-M. Thrombotic thrombocytopenic purpura: a thrombotic disorder caused by ADAMTS13 deficiency. *Hematol Oncol Clin N Am* 2007; **21**: 1773–7.

Abnormalities of platelet function

Several haemorrhagic syndromes have become recognized in which platelet function is abnormal although the total count may be normal [1–5] (Table 49.3). Such changes may be inherited, idiopathic or secondary to drugs or many other illnesses. These syndromes include thrombopathia, thrombasthenia, von Willebrand's disease, severe anaemia, chronic renal failure and fibrinogen defects. Hermansky–Pudlak syndrome consists of a bleeding disorder due to storage pool disorder, with oculocutaneous albinism and pigment-containing cells in the bone marrow (see Chapter 58). Laboratory testing of platelet function is of limited direct relevance to dermatologists but is reviewed in [6].

Drugs that may cause abnormal platelet function with clinical bleeding include aspirin, NSAIDs, some penicillin and β-lactam antibiotics (especially high-dose penicillin), alteplase and other antifibrinolytic drugs, prostacyclin, thienopyridines (ticlopidine and clopidogrel), glycoprotein IIb/IIIa antagonists (see below), cardiovascular drugs (nitrates, calcium channel blockers and quinidine), antidepressants and phenothiazines, and some chemotherapeutic agents such as mitomycin and daunorubicin [3–5]. Volume expanders such as dextran or hydroxyethylstarch, and radiocontrast media, are often forgotten as a cause of platelet dysfunction but can be particularly important in intensive care



Fig. 49.3 Purpura due to a calcium channel antagonist, an effect probably caused by platelet dysfunction.

situations, as can fibrinolytic agents such as streptokinase, and agents that increase platelet cAMP levels such as iloprost or prostacyclin. Natural and herbal remedy agents that can cause platelet dysfunction include fish oil, garlic, cumin, turmeric, *Gingko biloba* and black tree fungus [5]. In some instances, the mechanisms are well-understood but in others they are obscure. Aspirin causes irreversible acetylation of platelet cyclo-oxygenase-1 (COX-1), thereby inhibiting thromboxane A_2 (TXA_2) synthesis. NSAIDs also inhibit COX-1 but reversibly, such that platelet function recovers quickly once the agents are stopped [2]. COX-II inhibitors have no direct effect on platelets, which do not express COX-II; they may in fact increase thrombosis by an indirect effect as they block prostacyclin production, and prostacyclin has an inhibitory effect on platelet function. Clopidogrel (like ticlopidine) irreversibly binds to platelet purinergic receptor $P2Y_{12}$, blocking response to intrinsic platelet-generated and extrinsic ADP, with a biological half-life of about 3 days. Antagonists of the platelet glycoprotein IIb/IIIa (integrin αIIβ3), such as abciximab, tirofiban and eptifibatide, are strong inhibitors of platelet function, used in coronary artery surgery. Purpura, as provoked by Hess testing, sometimes with clinical bleeding but with normal platelet numbers, appears to be a class effect of calcium channel blockers [7] (Fig. 49.3); although the vasodilating action of such drugs cannot be excluded as a contributory cause, a platelet function abnormality seems most likely. Many other drugs may cause abnormal platelet aggregation *in vitro*, sometimes with abnormal bleeding time, but not necessarily with clinical bleeding [3–5].

Drug-induced platelet function abnormalities are of potential relevance to dermatologists because of issues regarding bleeding during skin surgery. Aspirin, NSAIDs, clopidogrel and calcium channel blockers have all been implicated in bleeding related to skin (and other) surgery, and whether to transiently discontinue such medications needs to be considered, as well as considering anticoagulant monitoring results, as part of the pre-operative management [7–11]. A questionnaire study suggested that stopping warfarin or aspirin before dermatological surgery might cause a thrombotic risk (1/6219 operations for warfarin and 1/21 448 operations for aspirin), but only a third of surveyed surgeons responded, there was no control population considered and no contemporaneous estimate of recalled significant bleeding [12]. Recent studies still conflict to some extent; some feel that the risks of operative bleeding due to aspirin [13], warfarin (with an international normalized ratio (INR) below 3.5) [14], or either drug [15], does not warrant stopping these treatments provided that careful attention is paid to haemostasis. However, there is some evidence that being on two or more different antithrombotic agents does increase the risk of bleeding after skin surgery [16], warfarin has been shown to increase risk of surgical bleeding in dermatology, an INR in the normal range being a poor predictor of this complication [17], and the combination of diltiazem and aspirin in normal subjects has a partially additive effect on platelet function (causing a bleeding time of over 15 min in two of five patients in one study [18]). These medications should probably be continued, but the risk of postoperative bleeding needs to be explained, particularly for difficult closures and body sites where application of pressure is awkward; the need for antithrombotic therapy (especially multiple therapies) and the risk to the patient of stopping treatment may need to be considered, and careful perioperative haemostasis should be performed.

Causes of abnormal platelet function may overlap with causes of thrombocytopenia. For example, both may occur in chronic renal failure (in which the abnormality of function is most important) or in myeloproliferative disorders (in which thrombocytopenia is usually paramount). Patients with Waldenström's macroglobulinaemia often have abnormal platelet function, less commonly those with IgA myeloma or benign monoclonal gammopathy, but bleeding in these conditions is usually due to hyperviscosity rather than to the platelet function defect. The platelet function defect is usually due to non-specific binding of immunoglobulin to platelets, but in some of these disorders other mechanisms may also be pertinent, including thrombocytopenia, inhibition or increased clearance of clotting factors and the hyperviscosity component.

Skin diseases in themselves may also alter platelet function in diverse ways, for example in eczemas, urticaria and psoriasis, potentially influencing expression of immune system inflammatory mediators [19].

References

1 Handin RI. Inherited platelet disorders. *Hematology Am Soc Hematol Educ Program* 2005: 396–402.

2 Neunert CE, Journeycake JM. Congenital platelet disorders. *Hematol Oncol Clin N Am* 2007; **21**: 663–84.

3 George JN, Shattil SJ. The clinical importance of acquired abnormalities of platelet function. *N Engl J Med* 1991; **324**: 27–39.

4 Hassan AA, Kroll MH. Acquired disorders of platelet function. *Hematology Am Soc Hematol Educ Program* 2005: 403–8.

5 Shen Y-MP, Frenkel EP. Acquired platelet dysfunction. *Hematol Oncol Clin N Am* 2007; **21**: 647–61.

6 Seegmiller A, Sarode R. Laboratory evaluation of platelet function. *Hematol Oncol Clin N Am* 2007; **21**: 731–42.

7 Cox NH, Walsh ML, Robson RH. Purpura and bleeding due to calcium channel blockers: an underestimated problem? Case reports and a pilot study. *Clin Exp Dermatol* 2009; **34**: 487–91.

8 Wagenknecht LE, Furberg CD, Hammon JW *et al*. Surgical bleeding: unexpected effect of a calcium antagonist. *BMJ* 1995; **310**: 776–7.

9 Yesudian PD, Velangi SS, Velangi MR *et al*. Postoperative bleeding in a patient on diltiazem. *Br J Dermatol* 2001; **145** (Suppl. 59): 87.

10 Stables G, Lawrence CM. Management of patients taking anticoagulant, nonsteroidal anti-inflammatory and other anti-platelet drugs undergoing dermatological surgery. *Clin Exp Dermatol* 2002; **27**: 632–5.
11 Lawrence C, Sakuntabhai A, Tiling-Grosse S. Effect of aspirin and nonsteroidal antiinflammatory drug therapy on bleeding complications in dermatologic surgical patients. *J Am Acad Dermatol* 1994; **31**: 988–92.
12 Kovich O, Otley OC. Thrombotic complications related to discontinuation of warfarin and aspirin therapy perioperatively for cutaneous operation. *J Am Acad Dermatol* 2003; **48**: 233–7.
13 Fijnheer R, Urbanus RT, Nieuwenhuis HK. Withdrawing the use of acetylsalicylic acid prior to an operation is usually not necessary. *Ned Tijdschr Geneeskd* 2003; **147**: 31–5.
14 Ah-Weng A, Natarajan S, Velangi S, Langtry JAA. Preoperative monitoring of warfarin in cutaneous surgery. *Br J Dermatol* 2003; **149**: 386–9.
15 Shalom A, Klein D, Friedman T, Westreich M. Lack of complications in minor skin lesion excisions in patients taking aspirin or warfarin products. *Am Surg* 2008; **74**: 354–7.
16 Shimizu I, Jellinek NJ, Dufresne RG *et al*. Multiple antithrombotic agents increase the risk of postoperative hemorrhage in dermatologic surgery. *J Am Acad Dermatol* 2008; **58**: 810–6.
17 Blasdale C, Lawrence CM. Perioperative international normalized ratio level is a poor predictor of postoperative bleeding complications in dermatological surgery patients taking warfarin. *Br J Dermatol* 2008; **158**: 522–6.
18 Ring ME, Corrigan JJ Jr, Fenster PE. Effects of oral diltiazem on platelet function: alone and in combination with 'low dose' aspirin. *Thromb Res* 1986; **44**: 391–400.
19 Kasperska-Zajac A, Brzoza Z, Rogala B. Platelet function in cutaneous diseases. *Platelets* 2008; **19**: 317–21.

Thrombocytosis

Abnormally high platelet counts may occur as a result of essential thrombocythaemia or other myeloproliferative disorders, or secondary to a variety of other disease processes (see Table 49.3). This may lead to a tendency to platelet plugging and thrombosis or, paradoxically, to a bleeding tendency (particularly when the platelet count exceeds 1000×10^9/L with a clonal platelet defect such as an acquired form of storage pool disease). Many cases of thrombocytosis do not achieve this high platelet count and are unlikely to cause purpura unless there are additional reasons related to the causative disorder (such as lymphoma or other malignant disease).

Dermatological manifestations and associations of thrombocythaemia include purpura with or without necrosis, livedo reticularis, acrocyanosis, purple (blue) toe syndrome, Raynaud's phenomenon, erythromelalgia, other vascular symptoms including gangrene, and associated disorders such as pyoderma gangrenosum [1–9]. The last-mentioned is relatively uncommon in pure thrombocythaemia [7] (the patient described in [7] subsequently developed further myeloproliferative features; cited in [8]). In one large study, 22% of patients with essential thrombocythaemia had skin lesions; 41% of these had haematomas, ecchymosis, petechiae or purpura, and 26% had erythromelalgia [9]. Many of these presentations are also seen in other hyperviscosity and dysproteinaemic conditions.

Platelet hyper-reactivity is not usually a dermatological consideration, but it is a factor in peripheral arterial disease and thrombotic emboli [10]. It is more common in females, linked with higher mean platelet volume and higher fibrinogen levels, and is partly genetically determined (especially associated with integrin α2 and β3 mutations that lead to high platelet glycoprotein IIb/IIIa levels).

References

1 Champion RH, Rook A. Idiopathic thrombocythemia: cutaneous manifestations. *Arch Dermatol* 1963; **87**: 302–5.
2 Amblard P, Lèques B, Seigneurin D *et al*. Manifestations cutanées des thrombocytémies. *Ann Dermatol Vénéréol* 1977; **104**: 115–20.
3 Singh AK, Wetherley-Mein G. Microvascular lesions in primary thrombocythaemia. *Br J Haematol* 1977; **36**: 553–64.
4 Preston FE, Emmanuel IG, Winfield DA, Malia RG. Essential thrombocythaemia and peripheral gangrene. *BMJ* 1974; **ii**: 548–52.
5 Martin EA, Lavin PJ, Thompson AJ. Painful extremities and neurological disorder in essential thrombocythaemia. *J R Soc Med* 1984; **77**: 372–4.
6 Hachulla E, Rose C, Trillot N *et al*. What vascular events suggest a myeloproliferative disorder? *J Mal Vasc* 2000; **25**: 382–7.
7 Shepherd P, Liddell K. Pyoderma gangrenosum associated with primary thrombocythaemia. *BMJ* 1982; **285**: 837–8.
8 Cox NH, White SI, Walton S *et al*. Pyoderma gangrenosum associated with polycythaemia rubra vera. *Clin Exp Dermatol* 1987; **12**: 375–7.
9 Itin PH, Winkelmann RK. Cutaneous manifestations in patients with essential thrombocythemia. *J Am Acad Dermatol* 1991; **24**: 59–63.
10 Bray PF. Platelet hyperreactivity: predictive and intrinsic properties. *Hematol Oncol Clin N Am* 2007; **21**: 633–45.

Non-thrombocytopenic vascular causes of purpura and syndromes of primarily ecchymotic haemorrhage

A number of disorders cause purpura or ecchymosis due to vascular fragility/poor dermal support, intravascular pressure increase, platelet dysfunction (see also earlier), thrombocytosis (above) or coagulation cascade defects (Table 49.4). Minor trauma is often the precipitant of lesions. Disorders in which inflammation around vessels leads to purpura are discussed separately; these include the pigmented purpuric dermatoses and several conditions in which there is non-specific inflammation.

Purpura due to raised intravascular pressure

Raised intravascular pressure may cause purpura in the absence of any other disease. Crops of petechiae after prolonged coughing or vomiting occur, especially on the relatively loose tissues of the face and neck (see Fig. 49.1). They are of no significance other than causing concern if their cause is not appreciated.

Gravity and venous stasis are the most important causes of this type of purpura. Many purpuric eruptions are maximal on, or even restricted to, the lower leg. Likewise, many erythematous eruptions on the lower legs, especially in the elderly or those with leg oedema, show some degree of purpura that can usually be ignored. Bizarre patterns of purpura should always suggest the possibility of artefact.

Deaths from asphyxia are said to be associated with facial and conjunctival petechiae but the mechanism is probably due to vascular occlusion causing raised intravascular pressure rather than to hypoxia *per se* [1].

Purpura due to abnormal blood vessels or decreased support of blood vessels

Several disorders are associated with abnormal collagen, elastic or other structural proteins, leading to abnormal vessels or poor dermal support or both (Table 49.4). Conditions such as Ehlers–Danlos syndrome (collagen), pseudoxanthoma elasticum (elastic)

Table 49.4 Some dermatologically-relevant non-thrombocytopenic causes of purpura, easy bruising or cutaneous bleeding.

Type of disorder	Examples
Inherited defects affecting structural components of the dermis and/or vascular wall	Ehlers–Danlos syndrome*
	Marfan syndrome*
	Osteogenesis imperfecta
	Pseudoxanthoma elasticum
Acquired defects affecting structural components of the dermis and/or vascular wall	Deposition disorders, e.g. amyloidosis†
	Solar damage (solar/actinic purpura)
	Scurvy
Haemangiomatous disorders	Cavernous haemangioma†
	Hereditary haemorrhagic telangiectasia*†
Clotting factor and related inherited or acquired deficiencies	Haemophilias
	Von Willebrand disease
	Vitamin K deficiency
	Other nutritional deficiencies (often mixed)
Non-thrombocytopenic platelet abnormalities	See Table 49.3
Biochemical (congenital or acquired)	Homocystinuria
	Hyperhomocystinaemia*†
	Diabetes mellitus
	Cushing's syndrome
Collagen vascular disorders	Systemic sclerosis
	Dermatomyositis
Paraproteinaemias and hyperviscosity	Waldenström's macroglobulinaemia*
	Other paraproteinaemias*
Intra- or perivascular inflammation	Capillaropathies (see p. 49.22)
	Vasculitides (Chapter 50)
	Behçet's disease (Chapter 50)
	Many inflammatory dermatoses
Microvascular occlusion	See p. 49.26
Infection	See p. 49.20
Increased pressure within vessels	Valsalva manoeuvre
	Cough purpura
	Distal to a sphygmomanometer cuff
Physical	Simple trauma
	Venous rupture (Achenbach's syndrome)
	Artefactual
	Chemical and mechanical contact irritants (p. 49.21)
Drugs	Drugs altering vascular permeability or causing direct endothelial damage (p. 49.21)
	Antiangiogenic drugs
Others	Malignant hypertension
	Autoerythrocyte sensitization

* May also have platelet dysfunction.
† May also have clotting factor abnormalities.

and amyloidosis (abnormal protein) are discussed in more detail elsewhere. Facial or periorbital purpura ('panda sign') occurs in 15% of patients with primary amyloidosis [2]. In osteogenesis imperfecta, bruising tends to occur rather than purpura; both occur in Ehlers–Danlos and Marfan syndromes and in osteogenesis imperfecta [3] (as well as frank bleeding in Ehlers–Danlos syndrome and osteogenesis imperfecta). In hereditary haemorrhagic telangiectasia (Chapter 47) there may be bleeding from telangiectasias; the structural vascular defects may be accompanied by platelet and other haemostatic defects. Paraproteins act in various ways, causing coating of endothelial cells, occlusion of vasa vasora, and also causing platelet dysfunction as discussed earlier. In Cushing's syndrome, loss of dermal mucopolysaccharides that normally support the vessels, and of elastic tissue from the dermis and from vessels, may be the explanation for purpura; deposition of fibrin leading to thrombosis and 'downstream' capillary stasis is thought to explain purpura in malignant hypertension, diabetes mellitus and chronological ageing.

Scurvy is discussed in more detail in Chapter 59. Altered collagenous support for the blood vessels is manifest by either petechiae, especially on the legs, or by small or large bruises on the limbs following mild or inapparent trauma. Large deep bruises may lead to woody induration, usually of the legs. Perifollicular purpura is typical but is not diagnostic and is frequently absent. Diagnosis is established by the associated symptoms and signs (twisted 'corkscrew' hairs, gingival bleeding), dietary history, laboratory tests and therapeutic response.

Actinic purpura (*Bateman's purpura, 'senile' purpura*) and *corticosteroid purpura* [4,5] are the commonest patterns of purpura due to lack of support of the blood vessels. They occur most commonly in skin altered by both age and solar radiation, but may occur in premature ageing syndromes. Corticosteroid purpura has the same pattern whether due to topical, oral, endogenous (Cushing's syndrome) or even inhaled [6] corticosteroids. The precipitating factor is a shearing stress. Patients who develop this type of purpura with ageing, in association with rheumatoid arthritis or with corticosteroids, are more liable to develop osteoporosis of the spine than patients without this sign [7]. The purpura occurs mainly in atrophic skin on exposed parts of the hands and forearms, or on the legs. Lesions appear after minor trauma or apparently spontaneously. They are usually asymptomatic and vary in size from a few millimetres to several centimetres across. They are often arranged linearly, and may show a linear or geometric shape. The appearance of the lesions is characteristic, with irregular areas, usually not palpable, that show little inflammatory reaction and which are usually dark purple rather than having the sequential colour changes of a normal bruise. They may persist for several weeks. Treatment is usually not necessary or possible.

References

1 Ely SF, Hirsch CS. Asphyxial deaths and petechiae: a review. *J Forensic Sci* 2000; **45**: 1274–7.
2 Kyle RA, Gertz MA. Primary systemic amyloidosis: clinical and laboratory features in 474 cases. *Semin Hematol* 1995; **32**: 45–59.
3 Bick R. Vascular thrombohemorrhagic disorders: hereditary and acquired. *Clin Appl Thrombosis Hemostasis* 2001; **7**: 178–94.
4 Feinstein RJ, Halprin KM, Penneys NS *et al*. Senile purpura. *Arch Dermatol* 1973; **108**: 229–32.
5 Shuster S, Scarborough H. Senile purpura. *QJM* 1961; **30**: 33–40.
6 Capewell S, Reynolds S, Shuttleworth D *et al*. Purpura and dermal thinning associated with high dose inhaled corticosteroids. *BMJ* 1990; **300**: 1548–51.
7 McConkey B, Fraser GM, Bligh AS. Osteoporosis and purpura in rheumatoid disease: prevalence and relation to treatment with corticosteroids. *QJM* 1962; **31**: 419–27.

Easy bruising syndrome and purpura simplex

The term 'easy bruising syndrome' has been used in various ways, usually for a mild purpura for which no cause has been detected,

especially on the thighs of women ('devil's pinches'). It has been used to include those cases of a mild bleeding tendency in which changes in the morphology of capillaries may be seen by capillary microscopy, and in some of which variable but slight changes in coagulation factors have also been found. There are significant limitations in deciding what constitutes 'abnormal' or excessive bleeding [1]. The term 'purpura simplex' has also been used for any inflammatory purpura without vasculitis, including disorders with the morphology of the pigmented purpuric dermatoses [2,3], and this term is therefore also of uncertain value. Autosomal dominant inheritance of purpura simplex has been reported [4] and presumably represents a subtle haemostatic defect; in one family, purpura simplex was coinherited with ptosis [5].

References

1 George JN, Shattil SJ. The clinical importance of acquired abnormalities of platelet function. *N Engl J Med* 1991; **324**: 27–39.
2 Lee GR, Bithell TC, Foerster J *et al.*, eds. *Wintrobe's Clinical Hematology*, 9th edn. Philadelphia: Lea & Febiger, 1993.
3 Ratnam KV, Daniel Su WP. Purpura simplex (inflammatory purpura without vasculitis): a clinicopathologic study of 174 cases. *J Am Acad Dermatol* 1991; **25**: 642–7.
4 Davis E. Hereditary familial purpura simplex. *Lancet* 1941; **i**: 145–6.
5 Fisher B, Zuckerman GH, Douglas RC. Combined inheritance of purpura simplex and ptosis in 4 generations of one family. *Blood* 1954; **9**: 1199–204.

Physical and artefactual causes of purpura

Bruising due to trauma seldom causes diagnostic problems, as there is usually a clear history, except when it occurs as an artefact or in child abuse. Bizarre patterns of purpura may be caused by suction, for example vacuum extractors in the neonate, electrocardiogram leads or around the mouth after sucking out the air from a glass [1]. Cultural remedies such as cupping, coin rubbing (Cao Gio) and spooning (Quat sha) may also produce unusual patterns of purpura that are usually obviously extrinsic in causation [2]. Black heel (talon noire) is a form of purpura due to frictional shearing of vessels, and is considered in Chapter 28.

Paroxysmal finger haematoma [3–5]

Synonym
- Achenbach's syndrome

In this syndrome there are recurrent episodes of painful bruising on the palms and palmar aspects of the fingers (Fig. 49.4). It seems likely that it represents venous rupture, as frictional trauma may be reported, such as turning on a tap or twisting the top off a jar. It is probably more common than the number of reported cases would suggest. Its importance is that it may be confused with Raynaud's phenomenon or acute connective tissue diseases and investigated unnecessarily.

Autoerythrocyte sensitization syndrome [6–9]

Synonyms
- Painful bruising syndrome
- Gardner–Diamond syndrome



Fig. 49.4 Achenbach's syndrome; acute bruising of the entire finger, presumably due to venous rupture after minor trauma.

This is a distinctive but rare clinical entity apparently due, in many cases, to allergic sensitivity to red cells in the tissues. Minor extravasations of blood, for example those so common on the thighs of women, are followed by an intense inflammatory reaction. The disease occurs most frequently in young adult and middle-aged females, who are nearly always psychiatrically abnormal. They present with recurrent, painful erythematous and purpuric lesions on the thighs and elsewhere. The diagnosis may be confirmed by intradermal injections of red cells or their washed stroma, or of phosphatidylcholine. This reaction occurs even in some subjects in whom a psychological cause is suspected and whose disease responds to psychological intervention [10,11].

Sensitivity to DNA [12,13] or to exogenous antigens attached to red cells [14] may present a similar picture. The condition is usually chronic, seldom disabling or associated with other abnormalities and is unresponsive to treatment. Plasmapheresis has been used successfully in isolated cases [15] and antimalarials are said to be effective in DNA sensitivity [16]. Dermatitis artefacta may produce a similar clinical picture, and is believed by some to account for all such cases [8,11,17].

Stigmata

In this very rare disorder there is exudation of apparently fresh blood through the unbroken skin of the hands, feet and side. The mechanism is obscure but, as with the previous syndrome, many if not all cases may have a traumatic origin [8,18].

References

1 Metzker A, Merlob P. Suction purpura. *Arch Dermatol* 1992; **128**: 822–4.
2 Pride HB. Child abuse and mimickers of child abuse. *Adv Dermatol* 1999; **14**: 417–55.
3 Layton AM, Cotterill JA. A case of Achenbach's syndrome. *Clin Exp Dermatol* 1993; **18**: 60–1.
4 Parslew R, Verbov JL. Achenbach syndrome. *Br J Dermatol* 1995; **132**: 319.
5 Stieler W, Heinze-Werlitz C. Paroxysmal finger hematoma (Achenbach syndrome). *Hautarzt* 1990; **41**: 270–1.
6 Gardner FH, Diamond LK. Auto-erythrocyte sensitisation. *Blood* 1955; **10**: 675–90.
7 Hersle K, Mobacken H. Auto-erythrocyte sensitisation syndrome (painful bruising syndrome). *Br J Dermatol* 1969; **81**: 574–87.

8 Ratnoff OD. The psychogenic purpuras: a review of autoerythrocyte sensitisation, autosensitisation to DNA, 'hysterical' and factitial bleeding and the religious stigmata. *Semin Hematol* 1980; **17**: 192–213.
9 Berman DA, Roenigk HH, Green D. Autoerythrocyte sensitization syndrome (psychogenic purpura). *J Am Acad Dermatol* 1992; **27**: 829–32.
10 Uthman IW, Moukarbel GV, Salman SM *et al.* Autoerythrocyte sensitization (Gardner–Diamond) syndrome. *Eur J Haematol* 2000; **65**: 144–7.
11 Cox NH, Wilkinson DS. Dermatitis artefacta as the presenting feature of autoerythrocyte sensitization syndrome and naproxen-induced pseudoporphyria in a single patient. *Br J Dermatol* 1992; **126**: 86–9.
12 Little AS, Bell HE. Painful subcutaneous haemorrhages of the extremities with unusual reaction to injected deoxyribonucleic acid. *Ann Intern Med* 1964; **60**: 886–91.
13 Chandler D, Nalbandian RM. DNA autosensitivity. *Am J Med Sci* 1966; **251**: 145–9.
14 Shelley WB, Florence R. Chronic urticaria due to mold hypersensitivity. *Arch Dermatol* 1961; **83**: 549–58.
15 Hamblin TJ, Hart S, Mufti GJ. Plasmapheresis and a placebo procedure in autoerythrocyte sensitisation. *BMJ* 1981; **81**: 1575–6.
16 Sams WM Jr. Macular purpuras. In: Sams WM Jr, Lynch P, eds. *Principles and Practice of Dermatology*, 2nd edn. New York: Churchill Livingstone, 1996: 559–64.
17 Stefanini M, Blumgart ET. Purpura factitia. *Arch Dermatol* 1972; **106**: 238–41.
18 Simpson CJ. The stigmata: pathology or miracle? *BMJ* 1984; **289**: 1746–8.

Purpura in other dermatoses

Many eruptions on the lower leg, especially in the elderly, tend to become purpuric due to a combination of gravitational changes with vascular damage caused by the dermatosis. Rapid development of lower leg oedema may cause an eczematous eruption in which purpura may be prominent [1].

Even without the gravitational component, many dermatoses may be sufficiently intense to cause purpura. Sometimes this is physically due to scratching, but some disorders such as lichen planus, lichen nitidus and Langerhans' cell histiocytosis are not infrequently purpuric. Purpuric erythema annulare centrifugum, dermatitis herpetiformis, pemphigoid, pityriasis rosea and eczemas (especially of discoid type) may all occur. Purpura may be present in lymphomas and lupus erythematosus, either because of platelet deficiency or, more commonly, because of vascular abnormalities.

Lichen sclerosus often has a haemorrhagic component due to loss of collagenous support for the vessels.

Some insect bite reactions have a purpuric centre due to inoculation of the skin with anticoagulant chemicals in the bite (purpura pulicosa, maculae ceruleae).

Purpura may also occur around localized lesions with a strong vascular component if there are fragile vessels, for example targetoid haemosiderotic haemangioma or aneurysmal fibrous histiocytoma.

A rather characteristic disorder of children under the age of 1 year has been termed the *persistent acrovasculopathy syndrome*. Lesions occur on the ears, cheeks and extremities and are scaly and erosive; they may be purpuric, and there may be local lipoatrophy and distal phalangeal osteopenia.

Most of these conditions are discussed in more detail in other chapters; two disorders are specifically described here.

Solar purpura [2–5]

This condition is distinct from the actinic purpura discussed previously which is a manifestation of cumulative sunlight-induced ageing of the skin. The term 'solar purpura' is used to describe rapid development of purpuric lesions after exposure to sunlight. The precise nature of this disorder is uncertain. Some view it as a variant of polymorphic light eruption. It is distinct from erythropoietic protoporphyria, although purpura clearly occurs in this dermatosis in some patients (Fig. 49.5). Some cases may simply be a variation of purpura in dermatoses that are not usually purpuric, but where profound inflammation has allowed purpura to develop.



Fig. 49.5 Erythropoietic protoporphyria: marked purpura with sharp cut-off after sunlight exposure.

Acroangiodermatitis (of Mali) [6–8]

Synonyms
- Dermite ocre of Favre
- Gravitational purpura
- Pseudo-Kaposi's sarcoma

This chronic dermatosis is associated with venous insufficiency or with vascular anomalies such as Klippel–Trenaunay syndrome [9], and there are several reports of it occurring as a stump dermatosis in amputees [10]. It has been reported in a patient with a thrombophilic prothrombin mutation [11]. It may mimic a pigmented purpuric dermatosis (p. 49.22) but is discussed here as the purpura is due to abnormal vasculature rather than to capillaritis. It occurs more often in men than in women.

The lesions occur especially on the lower legs but may extend on to the dorsa of the feet and toes, and up the leg, especially over dilated varicosities. Individual lesions are minute purpuric macules that coalesce to form irregular plaques, which may be several centimetres in diameter. Follicular lesions may occur. The colour of the lesions is not usually the purple colour of fresh purpura but varying shades of yellow (ochre) and brown from haemosiderin and other breakdown products. The epidermis may be normal or show mild eczematous changes. Oedema, sclerosis, ulceration and other signs of venous insufficiency may be associated, but may be entirely absent even in cases of long duration.

Differential diagnosis includes ordinary gravitational dermatitis, Schamberg's disease and Kaposi's sarcoma; the last mentioned can be distinguished by the staining pattern with CD34 antigen, which stains perivascular spindle cells in Kaposi's sarcoma but only the endothelial cells in acroangiodermatitis [12]. Treatment is unsatisfactory but support hosiery seems logical.

References

1 Bhushan M, Cox NH, Chalmers R. Eczema craquélé due to oedema. *Br J Dermatol* 2001; **145**: 355–7.
2 Leung AKC. Purpura associated with exposure to sunlight. *J R Soc Med* 1986; **79**: 423–4.
3 Kalivas J, Kalivas L. Solar purpura appearing in a patient with polymorphous light reaction. *Photodermatol Photoimmunol Photomed* 1995; **11**: 31–2.
4 Guarrera M, Parodi A, Rebora A. Solar purpura is not related to polymorphous light eruption. *Photodermatol* 1989; **6**: 293–4.
5 Torinuki W, Miura T. Erythropoietic protoporphyria showing solar purpura. *Dermatologica* 1983; **167**: 220–2.
6 Favre M. Angiodermite pigmentée et purpurique des membres inferieurs. In: Darier J, Sabouraud R, Gougerot H *et al. Nouvelle Pratique Dermatologie*, Vol. 5. Paris: Masson, 1936: 413–40.
7 Mali JWH, Kuiper JP, Hamers AA. Acro-angiodermatitis of the foot. *Arch Dermatol* 1965; **92**: 515–8.
8 Rao B, Unis M, Poulos E. Acroangiodermatitis: a study of ten cases. *Int J Dermatol* 1994; **33**: 179–83.
9 Lyle WG, Given KS. Acroangiodermatitis (pseudo-Kaposi's sarcoma) associated with Klippel–Trenaunay syndrome. *Ann Plast Surg* 1996; **37**: 654–6.
10 Badell A, Marcoval J, Graells J *et al*. Kaposi-like acroangiodermatitis induced by a suction-socket prosthesis. *Br J Dermatol* 1994; **131**: 915–7.
11 Martin L, MacHet L, Michalak S *et al.* Acroangiodermatitis in a carrier of the thrombophilic 20210A mutation in the prothrombin gene. *Br J Dermatol* 1999; **141**: 752.
12 Kanitakis J, Narvaez D, Claudy A. Expression of the CD34 antigen distinguishes Kaposi's sarcoma from pseudo-Kaposi's sarcoma (acroangiodermatitis). *Br J Dermatol* 1996; **134**: 44–6.

Multifactorial purpura associated with systemic diseases

Non-thrombocytopenic purpura may be caused by a variety of systemic diseases. Many of these have already been discussed, but in some cases there may be mixed mechanisms of purpura or easy bruising. Of these, renal disease is perhaps the most important; petechiae, ecchymoses or mucosal bleeding are common in end-stage renal failure [1]. Platelet dysfunction is probably the major factor [2], but there may also be frank thrombocytopenia. Diabetes, severe anaemia, liver disease, haemochromatosis and carcinomatosis may also cause purpura.

In amyloidosis, with or without myelomatosis, purpura may be due to infiltration of the capillaries and perivascular tissue with amyloid, but platelet changes and liver disease may also contribute.

Purpura occurs in patients with malnutrition. It seems probable that changes in coagulation, platelets and capillaries all play their part. For example, in cystic fibrosis there may be dysproteinaemia, vasculitis and vitamin K deficiency.

Purpura has been associated with ovarian and other endocrine abnormalities [3], for example Cushing's disease, and may vary with the menstrual cycle.

References

1 Remazzi G. Bleeding in renal failure. *Lancet* 1988; **i**: 1205–8.
2 George JN, Shattil SJ. The clinical importance of acquired abnormalities of platelet function. *N Engl J Med* 1991; **324**: 27–39.
3 Wells R. Haemorrhagic diathesis due to increased capillary fragility secondary to ovarian deficiency. *Lancet* 1958; **i**: 886–7.

Exercise-induced purpura/vasculitis

This is probably an underestimated condition, and histologically is a form of leukocytoclastic vasculitis [1,2]. It is therefore discussed in more detail in Chapter 50. The typical presentation is with purpuric lesions on the lower legs after prolonged walking (many descriptions are in golfers, marathon runners or long-distance walkers), usually in hot weather. Lesions may be urticarial. Patients are generally middle-aged, and otherwise well with no evidence of venous disease. Compression stockings may reduce its occurrence. It is discussed here as it can present as a pigmented purpuric dermatosis related to exercise [3], and has also been described in a child with recurrent purpura on the trunk after vigorous exercise [4].

References

1 Prins M, Veraart JC, Vermeulen AH *et al*. Leucocytoclastic vasculitis induced by prolonged exercise. *Br J Dermatol* 1996; **134**: 915–8.
2 Ramelet AA. Exercise-induced purpura. *Dermatology (Basel)* 2004; **208**: 293–6.
3 Allan SJR, Humphreys F, Buxton PK. Annular purpura and step aerobics. *Clin Exp Dermatol* 1994; **19**: 418.
4 Leung AK, Grant RM, Truscott R. Exercise-induced purpura. *J Sports Med Phys Fitness* 1990; **30**: 329–30.

Inflammatory haemorrhage: Henoch–Schönlein purpura and acute haemorrhagic oedema of childhood

Vessel damage with inflammation may lead to haemorrhage, typically manifest as palpable purpuric lesions. This is usually caused by one of the types of antigen–antibody reaction discussed in Chapter 13 but may be due to a direct toxic effect. The antigen in the allergic mechanism may be a component of the vessel itself or of surrounding tissues or, more commonly, an exogenous substance bound to the blood vessel or other tissues. Such substances include drugs, bacterial products and food additives; they may reach the blood vessel via the bloodstream or from the skin surface. The antigen–antibody reaction may occur on the surface of the endothelial cells or in adjacent tissues, or the vessels may be damaged by soluble complexes. The localization of many such lesions will be determined by local factors, for example changes due to gravity, cold and trauma. This inflammatory process is therefore a vasculitis, and is discussed in Chapter 50. Two conditions of this type are briefly discussed here, one because it carries the name purpura (Henoch–Schönlein purpura) and the other because it may present with striking haemorrhagic lesions (acute haemorrhagic oedema of childhood).

Henoch–Schönlein purpura (HSP, anaphylactoid purpura) is a vasculitic process due to IgA-immune complex deposition in the walls of arterioles and venules that gives rise to palpable inflammatory lesions; these are often purpuric as well as erythematous and may vary in size from 0.5 to 1 cm or more. However, minor lesions of HSP may sometimes be confused clinically with other types of purpura.

Acute haemorrhagic oedema of childhood is a small vessel cutaneous vasculitis; it has been proposed to be a variant of HSP, but IgA immune complexes often cannot be demonstrated. It has also been

described as cocarde purpura, Seidlmayer's syndrome and Finkelstein's disease. Most cases have been reported from continental Europe [1,2], but English [3] and American [4] cases are also reported. It may be overtly haemorrhagic, but can present as arciform or annular brown lesions that are of acute onset but which have some morphological similarity to pigmented purpuric dermatoses.

References

1 Lambert D, Laurent R, Bouilly D *et al.* Oedème aigu hémorrhagique du nourisson. Données immunologiques et ultrastructurales. *Ann Dermatol Vénéréol* 1979; **106**: 975–87.

2 Legrain V, Lejean S, Täieb A *et al.* Infantile acute haemorrhagic edema of the skin: study of ten cases. *J Am Acad Dermatol* 1991; **24**: 17–22.

3 Cox NH. Seidlmayer's syndrome: postinfectious cockade purpura of early childhood. *J Am Acad Dermatol* 1992; **26**: 275.

4 Cunningham BB, Caro WA, Eramo LR. Neonatal acute hemorrhagic edema of childhood: case report and review of the English-language literature. *Pediatr Dermatol* 1996; **13**: 39–44.



Fig. 49.6 Waldenström's hypergammaglobulinaemic purpura: lower leg lesions, in this patient usually provoked by prolonged standing or heat.

Dysproteinaemic purpura and Waldenström's hypergammaglobulinaemic purpura

Purpura may be the presenting and sometimes the only symptom of disturbances in plasma proteins. It may occur at exposed skin sites in cryoproteinaemia (see Chapter 28 and p. 49.32) and may occur due to monoclonal hypergammaglobulinaemia in myeloma. In such instances there may be platelet dysfunction, but clinical bleeding is usually related to the hyperviscosity syndrome rather than to the altered platelet function. Cutaneous features of paraproteinaemia include various patterns of vasculitis and neutrophilic dermatosis (see Chapter 50), cryoglobulinaemia (see below), urticaria and systemic capillary leak syndrome, abnormalities of lipid metabolism (notably diffuse plane xanthomatosis), subcorneal pustular dermatosis, lichen myxoedematosus and sclero-myxoedema, amyloidosis, and features due to hyperviscosity (purpura, mucous membrane bleeding, retinopathy and neurological disturbance) [1,2]. Haemorrhagic features are particularly seen in Waldenström's macroglobulinaemia.

Waldenström's hypergammaglobulinaemic purpura is generally taken to imply an idiopathic phenomenon but in fact two of Waldenström's three cases had sicca symptoms, one with sarcoidosis [3]. Hypergammaglobulinaemic purpura is usually a polyclonal disorder most commonly linked with sarcoidosis, lupus erythematosus, Sjögren's syndrome and other autoimmune conditions [4–10]. The majority of patients have positive antinuclear antibody and anti-SSA (Ro) or anti-SSB (La) antibodies [6–10]. Other features that have been associated include arthropathy (not uncommon), renal tubular acidosis, chest infections, lymphopenia and immune hypersensitivity pneumonitis. Most patients are female [11].

Clinically the pattern of purpura is often non-specific, usually consisting of crops of small erythematous macular or palpable purpuric spots on the lower leg (Fig. 49.6) [3–10], but unusual patterns with reticulate lesions may occur [12]. Prolonged walking, standing or sitting with the legs dependent, or other increase in venous pressure, may be an obvious provocative factor [9,10]. Itch or a burning sensation may occur. It is likely that this disorder is an immune complex vasculitis: immune complexes can be detected, histology may show vasculitic change, and direct immunofluorescence may show immunoglobulin in blood vessel walls [8,12,13]. Hyperviscosity leading to stasis and endothelial damage plays some part. There may be an abnormal ratio of IgG subclasses, with low IgG1/IgG2 ratio [14].

Lesions usually resolve in about a week but may become confluent and permanent. Treatment is often not required, although prednisolone, NSAIDs, hydroxychloroquine and etamsylate (ethamsylate) have been used.

A similar pattern has been reported in association with cystic fibrosis, due to either hypergammaglobulinaemia or cryoglobulinaemia [15,16]. It may appear suddenly, affects the lower legs mainly, and is exacerbated by prolonged standing or by tight garments or footwear. It is associated with severe lung disease and poor prognosis; a high antigenic load due to chronic lung infection may be the cause.

References

1 Russell Jones R. The cutaneous manifestations of paraproteinaemia. I. *Br J Dermatol* 1980; **103**: 335–45.

2 Russell Jones R. The cutaneous manifestations of paraproteinaemia. II. *Br J Dermatol* 1981; **104**: 209–20.

3 Waldenström J. Three new cases of purpura hyperglobulinaemica. A study of a long-standing benign increase in serum globulin. *Acta Med Scand* 1952; **266** (Suppl.): 931–46.

4 Carr RD, Heisel EB. Purpura hyperglobulinemia. *Arch Dermatol* 1966; **94**: 536–41.

5 Kyle RA, Gleich GJ, Bayrd ED *et al.* Benign hypergammaglobulinemic purpura of Waldenström. *Medicine (Baltimore)* 1971; **50**: 113–23.

6 Finder KA, McCollough ML, Dixon SL *et al.* Hyperglobulinemic purpura of Waldenström. *J Am Acad Dermatol* 1990; **23**: 669–76.

7 Miyagawa S, Fukumoto T, Kanauchi M *et al.* Hypergammaglobulinaemic purpura of Waldenström and Ro/SSA autoantibodies. *Br J Dermatol* 1996; **134**: 919–23.

8 Sugai S, Shimizu S, Tachibana J *et al.* Hypergammaglobulinemic purpura in patients with Sjögren's syndrome: a report of nine cases and a review of the Japanese literature. *Jpn J Med* 1989; **28**: 148–55.

9 Malaviya AN, Kaushik P, Budhiraja S *et al.* Hypergammaglobulinaemic purpura of Waldenström: report of 3 cases with a short review. *Clin Exp Rheumatol* 2000; **18**: 518–22.

10 Senecal JL, Chartier S, Rothfield N. Hypergammaglobulinaemic purpura in systemic autoimmune rheumatic disease: predictive value of anti-Ro (SSA) and

anti-La (SSB) antibodies and treatment with indomethacin and hydroxychloroquine. *J Rheumatol* 1995; **22**: 868–75.
11 Olmstead AD, Zone JJ, La Salle B *et al*. Immune complexes in the pathogenesis of hypergammaglobulinemic purpura. *J Am Acad Dermatol* 1980; **3**: 174–9.
12 Tan E, Ng SK, Tan SH, Wong GC. Hypergammaglobulinaemic purpura presenting as reticulate purpura. *Clin Exp Dermatol* 1999; **24**: 469–72.
13 Lopez LR, Schocket AL, Carr RI, Kohler PF. Lymphocytotoxic antibodies and intermediate immune complexes in hypergammaglobulinaemic purpura of Waldenström. *Ann Allergy* 1988; **61**: 93–6.
14 Eriksson P, Almroth G, Denneberg T, Lindstrom FD. IgG2 deficiency in primary Sjögren's syndrome and hypergammaglobulinaemic purpura. *Clin Immunol Immunopathol* 1994; **70**: 60–5.
15 Garty BZ, Scanlin T, Goldsmith DP *et al*. Cutaneous manifestations of cystic fibrosis: possible role of cryoglobulins. *Br J Dermatol* 1989; **121**: 655–8.
16 Schidlow DV, Panitch HB, Zaeri N *et al*. Purpuric rashes in cystic fibrosis. *Am J Dis Child* 1989; **143**: 1030–2.

Purpura associated with infection

Purpuric skin lesions associated with infection [1] may be due to numerous mechanisms, more than one of which may be operative, including:

- Thrombocytopenia (discussed above)
- Localized or disseminated intravascular coagulation (discussed above)
- Direct vascular damage (invasion or occlusion by organisms)
- Vascular effects of toxins
- Immunological vascular damage (vasculitis, immune complex deposition)
- Emboli.

Purpura is a characteristic feature of certain bacterial infections, for example meningococcal or other septicaemias and bacterial endocarditis, and of many viral and rickettsial infections, for example typhus, Rocky Mountain spotted fever, dengue fever and the viral haemorrhagic fevers (see Chapters 30 and 33) [2–9]. Acral purpuric lesions are typical of Rocky Mountain spotted fever [3]; the histological features include a lymphohistiocytic capillaritis and venulitis with variable leukocytoclastic vasculitis, fibrin thrombi, capillary wall necrosis and immunofluorescent evidence of organisms within endothelial cells, suggesting that it is therefore a type of septic vasculitis. In typhus, however, acral sites are generally spared. Dengue fever has three subtypes, dengue fever, dengue haemorrhagic fever (DHF) and dengue septic shock (DSS); in DHF there may be petechiae of acral sites, face, soft palate and axillae, with larger purpuric lesions, epistaxis, gingival bleeding and more serious bleeding (gastrointestinal bleeding, menorrhagia) in some subjects, due to thrombocytopenia. Haemoconcentration is also a feature in DHS and DSS. In hantavirus infection, thrombocytopenia is a typical part of the hantavirus pulmonary syndrome (HPS); skin haemorrhages, gingival bleeding, epistaxis, haematuria and gastrointestinal bleeding are mainly due to thrombocytopenia, but coagulopathy can occur.

Skin lesions are the presenting feature in 70–90% of patients with meningococcaemia and are purpuric in 50%, often stellate in shape and tender. In some cases of meningococcal septicaemia, organisms can be seen on blood smears taken from scraped skin lesions [10]. There may be a leukocytoclastic vasculitis with thrombi and meningococci within endothelial cells or leukocytes, typically resulting in a clinical lesion of classical palpable purpura, ranging in size from 2 to 8 mm in diameter. Lesions may progress to purpura fulminans due to microvascular occlusion, with lesions typically enlarging and often developing stellate or retiform features with minimal to no erythema (discussed above). The mechanism of coagulopathy in severe meningococcal sepsis is probably multifactorial, sharing some features with other conditions of severe sepsis and potentially leading to large vessel thrombosis with digital or limb infarction. Levels of protein C, protein S and antithrombin antigen are reduced, thrombocytopenia and haemophagocytosis occur, and fibrinolysis is reduced. Critically, there is dysfunction of the protein C activation pathway such that the prothrombotic activity of thrombin escapes its usual regulation, and a procoagulant state results [11]; it is now routine for patients with severe sepsis, including that due to meningococcal disease, to be treated with activated protein C [12].

Various congenital infections may cause neonatal purpura (p. 49.49). Purpura may appear in the prodromal period of many infections, for example measles, in which case it is often a sign of a severe infection. When it occurs at the height of the infection it is of less serious importance. A large number of infections may cause purpuric lesions in children [13]. In neonates, congenital infections may cause 'blueberry muffin syndrome' with dermal erythropoiesis, originally described in congenital rubella with thrombocytopenia. There are several non-infectious causes, but the most important infections are those covered by the acronym TORCH (toxoplasmosis, other infections, rubella, cytomegalovirus and herpesviruses). The 'other infection' group that should be screened includes syphilis, coxsackieviruses (especially B2) and HIV [14].

The petechial gloves and socks syndrome, or papular–purpuric gloves and socks syndrome, is a distinctive syndrome that has been attributed to parvovirus B19 infection [15,16] or to other viruses such as measles, hepatitis B, coxsackievirus B6 and cytomegalovirus [13,17] (see also Chapter 33). Purpura may also occur in the laterothoracic eruption, which may have an infectious aetiology (often parvovirus B19), and a genital or 'bathing trunk' distribution of purpura has also been described due to parvovirus B19 [18].

Other infections may be associated with characteristic distributions of purpura, for example *Strongyloides* causes 'thumb-print' periumbilical purpuric lesions [19]. Based on six patients with cancer, immunosuppressed by disease or treatment, this feature was felt to be associated with septic shock and death [20].

References

1 Kingston ME, Mackey D. Skin clues in the diagnosis of life-threatening infections. *Rev Infect Dis* 1986; **8**: 1–11.
2 Anonymous. Viral haemorrhagic fevers. *Lancet* 1981; **ii**: 182–3.
3 Kao GF, Evancho CD, Ioffe O *et al*. Cutaneous histopathology of Rocky Mountain spotted fever. *J Cutan Pathol* 1997; **24**: 604–10.
4 Suresh V. The enigmatic haemorrhagic fevers. *J R Soc Med* 1997; **90**: 622–4.
5 Lupi O, Tyring SK. Old-World haemorrhagic fevers. In: Tyring SK, Lupi O, Hengge UR. *Tropical Dermatology*. London: Elsevier, 2006: 125–32.
6 Glass GE. Hantaviruses. *Curr Opin Infect Dis* 1997; **10**: 362–6.
7 Lupi O, Semenovitch I. New-World haemorrhagic fevers. In: Tyring SK, Lupi O, Hengge UR. *Tropical Dermatology*. London: Elsevier, 2006: 133–6.
8 World Health Organization. *Dengue Haemorrhagic Fever. Diagnosis, Treatment, Prevention and Control*, 2nd edn. Geneva: WHO, 1997.
9 Lupi O, Kouri G, Guzman MG. Dengue. In: Tyring SK, Lupi O, Hengge UR. *Tropical Dermatology*. London: Elsevier, 2006: 136–41.

10 Taylor MR, Keane CT, Periappuram M. Skin scraping is a useful investigation in meningococcal disease. *BMJ* 1997; **314**: 831–2.
11 Faust SN, Levin M, Harrison OB *et al*. Dysfunction of endothelial protein C activation in severe meningococcal sepsis. *N Engl J Med* 2001; **345**: 408–16.
12 Parillo JE. Severe sepsis and therapy with activated protein C. *N Engl J Med* 2005; **353**: 1398–400.
13 Baselga E, Drolet BA, Esterley NB. Purpura in infants and children. *J Am Acad Dermatol* 1997; **37**: 673–705.
14 Hoeger PH. Cutaneous manifestations of congenital infections. In: Harper J, Oranje A, Prose N. *Textbook of Pediatric Dermatology*, 2nd edn. Oxford: Blackwell Publishing, 2006: 72–8.
15 Harmes M, Feldman R, Saurat JH. Papulo-purpuric 'gloves and socks syndrome'. *J Am Acad Dermatol* 1990; **23**: 850–4.
16 Halasz CLG, Den Cormier DM. Petechial glove and sock syndrome caused by parvovirus B19. *J Am Acad Dermatol* 1992; **27**: 835–8.
17 Vargas-Diez E, Buezo GF. Papular–purpuric glove-and-sock syndrome. *Int J Dermatol* 1996; **35**: 626–32.
18 Krankimel N, LeClerc-Mercier S, Rozenberg F *et al*. An adult presenting with a bathing-trunk eruption associated with primary infection to human parvovirus B19. *Br J Dermatol* 2007; **158**: 407.
19 Bank DE, Grossman ME, Kohn SR, Rabinowitz AD. The thumbprint sign: rapid diagnosis of disseminated strongyloidiasis. *J Am Acad Dermatol* 1990; **23**: 324–6.
20 Salluh JIF, Bozza FA, Pinto TS *et al*. Cutaneous periumbilical purpura in disseminated strongyloidiasis in cancer patients: a pathognomonic feature of potentially lethal disease? *Braz J Infect Dis* 2006; **9**: 419–24.

Non-thrombocytopenic toxin- and drug-induced purpura [1–6]

Many agents may lead to purpura by causing thrombocytopenia (discussed above). There are also many substances capable of causing capillary damage with or without any change in platelets, either by direct toxicity or through an allergic reaction. The purpura varies in degree from a few petechiae to massive extravasation of blood. Sometimes there is obvious evidence of inflammatory lesions, as well as purpura, implying a frankly vasculitic process [7]. Exposure may be industrial, accidental or therapeutic. Some drugs may cause thrombocytopenia and either vascular purpura and/or frank vasculitis; the thrombocytopenia in such cases may be caused by a direct effect on platelets or by endothelial damage leading to platelet aggregation.

Substances capable of causing capillary damage include acetylsalicylic acid, allopurinol, *p*-aminosalicylic acid, arsenic, atropine, barbiturates, bismuth, carbimazole, carbromal, chloramphenicol, chlordiazepoxide, chlorothiazide, chlorpromazine, diethylstilbestrol, furosemide, gold, hair dye, indometacin, iodides, isoniazid, menthol, meprobamate, methyldopa, piperazine, quinidine, quinine, reserpine, snake venoms, sodium salicylate, sulphonamides, tartrazine and other food additives, thiouracil, tolbutamide and glyceryl trinitrate.

Carbromal is one of the few drugs that caused a rather distinctive pattern of purpura. The widespread areas of capillary leakage combined with erythema produced a picture which resembled itching purpura and Schamberg's disease. Drug-induced pigmented purpuric dermatoses are considered elsewhere.

Trimethoprim–sulfamethoxazole has been reported to cause an acral purpuric eruption, proven by rechallenge, that resembled the purpuric 'gloves and socks' syndrome more commonly caused by parvovirus B19 [8].

A diagnosis of toxin- and drug-induced purpura usually depends on circumstantial evidence. Unfortunately, laboratory tests are mainly unhelpful, although some drugs that cause purpuric reactions will produce a purpuric reaction when patch tested. Rechallenge may be dangerous; generally the diagnosis is made by careful history taking.

Drug-induced vasculitis or livedo are also discussed in Chapter 75; drugs that cause skin necrosis are considered later in the present chapter (see Table 49.9, p. 49.50).

References

1 Bruinsma W. *A Guide to Drug Eruptions*. Amsterdam: Excerpta Medica, 1973: 55–8.
2 Lee GR, Bithell TC, Foerster J *et al.*, eds. *Wintrobe's Clinical Hematology*, 9th edn. Philadelphia: Lea & Febiger, 1993.
3 Breathnach SB, Hintner H. *Adverse Drug Reactions and the Skin*. London: Blackwell Scientific Publications, 1992: 45–7.
4 Litt JZ. *Drug Eruption Reference Manual 2001*. New York: Parthenon Publishing, 2001.
5 Dowd PM, Champion RH. Purpura. In: Champion RH, Burton JL, Burns DA, Breathnach SM, eds. *Textbook of Dermatology*, 6th edn. Oxford: Blackwell Science, 1998: 2141–54.
6 Michaelsson G, Petterson L, Juhlin L. Purpura caused by food and drug additives. *Arch Dermatol* 1974; **109**: 49–52.
7 Dubost J-J, Souteyrand P, Sauvezie B. Drug-induced vasculitides. *Bailliere's Clin Rheumatol* 1991; **5**: 119–38.
8 van Rooijen MM, Brand CU, Ballmer-Weber BK *et al*. Drug-induced papular–purpuric gloves and socks syndrome. *Hautarzt* 1999; **50**: 280–3.

Contact purpura [1]

Purpura may occur as an irritant reaction to mechanical friction from abrasive agents such as woollen clothing or fibreglass. Some topical medications may rarely cause purpura that appears to be of irritant or toxic causation, such as clioquinol (at flexural sites), benzoyl peroxide or EMLA local anaesthetic [2,3]. Textile and rubber chemicals [4–6] are particular causes of contact purpura that may have little or no eczematous component, although itch or lichenoid morphology may be prominent in some instances. Such reactions may be widespread, the distribution corresponding only approximately with the distribution of contact, and may therefore be confused with idiopathic pigmented purpuras.

Purpura around the acrosyringium may occur at patch-test sites to cobalt, and purpuric patch tests to apronalide and quinidine have been reported in subjects with a purpuric rash after systemic administration of these agents.

The main groups of chemicals that have been reported to cause contact purpura are:

- Dyes and textile agents: azo dyes, paraphenylenediamine, optical whiteners
- Rubber antioxidants: IPPD, isopropylaminodiphenylamine
- Resins: urea formaldehyde compounds, epoxy resin
- Plants: *Rhus*, *Agave*
- Others: topical medicaments, balsam of Peru, mercury.

References

1 Rietschel RL, Fowlet JF. *Fisher's Contact Dermatitis*. Philadelphia: Lippincott, Williams & Wilkins, 2001: 73–5.
2 van Joost T, van Ulsen J, Vuzevski VD *et al*. Purpuric contact dermatitis to benzoyl peroxide. *J Am Acad Dermatol* 1990; **22**: 358–61.
3 de Waard-van der Spek FB, Oranje JP. Purpura caused by EMLA is of toxic origin. *Contact Dermatitis* 1997; **36**: 11–3.
4 Calnan CD, Peachey RDG. Allergic contact purpura. *Clin Allergy* 1971; **1**: 287–90.

5 Roed-Petersen J, Clemmensen OJ, Menne T, Larsen E. Purpuric contact dermatitis from black rubber chemicals. *Contact Dermatitis* 1988; **18**: 166–8.
6 Lazarov A, Cordoba M. Purpuric contact dermatitis in patients with allergic reaction to textile dyes and resins. *J Eur Acad Dermatol Venereol* 2000; **14**: 101–5.

Pigmented purpuric dermatoses

Synonyms
- Capillaritis
- Purpura progressiva pigmentosa

Capillaritis is the generic term for a variety of chronic conditions that share certain histological features. The term 'purpura simplex' has also been applied to this group of disorders, on the basis of the common histological aspects. However, the same term has been applied to other mild and unexplained but morphologically different patterns of purpura such as easy bruising, and it is therefore potentially confusing. The term 'pigmented purpuric dermatoses' may be preferred, at least at present, as it conveys the message of a component beyond simple transient purpura.

The sometimes striking morphological patterns of the pigmented purpuric dermatoses have given rise to a wide range of descriptive and eponymous names [1–8]. Typical examples of the various eponymous diseases are sufficiently distinctive to warrant separate description but in many cases the clinical features may not be characteristic of any one of the eponymous variants. As their aetiology is unknown, and no clear distinction has been established between the different patterns other than on clinical morphological grounds, classification remains clinical. Identification of pigmented purpuric dermatoses secondary to a systemic cause is potentially important and is discussed below. Gravity and increased venous pressure are important localizing factors in many cases. Exercise may be a provoking factor. Most are chronic but two-thirds may improve or clear eventually [5]. Adults are mainly affected but there are several series of cases in childhood [9,10].

Most authors would accept five different morphological variants of idiopathic pigmented purpuric dermatosis, each of which will be discussed separately, namely:

1 Schamberg's disease (about half of cases)
2 Itching purpura (eczematid-like purpura of Doucas and Kapetanakis) (about 10%)
3 Pigmented purpuric lichenoid dermatosis of Gougerot and Blum (about 5%)
4 Lichen aureus (about 10%)
5 Purpura annularis telangiectodes (Majocchi's disease) (about 5%).

A further variant, termed Favre-Chaix's purpura, occurs on the lower leg and comprises purpura and pigmentation associated with oedema, cyanosis and sclerosis; it would appear to be simply a manifestation of venous disease and is not considered further here. However, additional types (such as granulomatous), or subtypes (e.g. segmental variants of the above list) also warrant mention as they may in time prove to be aetiologically distinct; furthermore, about 20% of cases are unclassifiable [5] and many drugs, systemic diseases or local conditions of the skin may lead to localized, mild purpura with haemosiderin deposition and secondary melanin pigmentation [11]. These are summarized briefly before considering the idiopathic variants, and will be discussed in differential diagnosis of the named disorders in this group.

Pathologically, these disorders are characterized by narrowing of the lumen and endothelial swelling of superficial small vessels, accompanied by perivascular T-lymphocytic infiltration, extravasation of erythrocytes and haemosiderin deposits in macrophages. An appearance termed 'ectasizing endocapillaritis' has been reported, in a study in which the authors divided 22 cases into those that were papular (with an upper dermal band-like infiltrate), macular (with a perivascular infiltrate) or eczematous (with exocytosis and spongiosis) [11], but this has not led to any fundamental advance in understanding these diseases. The cellular infiltrate in all types contains $CD4^+$ T cells in close contact with $CD1a^+$ Langerhans' cells [12,13], suggesting that a cell-mediated immune reaction is operative. Strong expression of endothelial cell adhesion receptors ICAM-1 and ELAM-1 may determine the pattern of the infiltrate [13]. Immune complex deposition has also been reported but direct immunofluorescence is often negative. An IgA-associated lymphocytic vasculopathy has been described in eight patients, in six of whom the clinical and histological features were those of a pigmented purpuric dermatosis [14]; the significance of this is unclear but it is notable that many of the subjects had a preceding or associated condition, including viral infection, Henoch–Schönlein purpura, undifferentiated connective tissue disease, lupus erythematosus profundus, Degos' disease and Buerger's disease.

References

1 Randall SJ, Kierland RR, Montgomery H. Pigmented purpuric eruptions. *Arch Dermatol Syphilol* 1951; **64**: 177–91.
2 Farrokhzad S, Champion RH. Pigmented purpuric dermatoses. *Dermatologica* 1970; **140**: 45–53.
3 Touraine A. Le purpura annulaire telangiectasique de Majocchi et ses parentés. *Presse Med* 1949; **57**: 934–6.
4 Tristani-Firouzi P, Meadows KP, Vanderhooft S. Pigmented purpuric eruptions of childhood: a series of cases and review of literature. *Pediatr Dermatol* 2001; **18**: 299–304.
5 Ratnam KV, Su WPD, Peters MS. Purpura simplex (inflammatory purpura without vasculitis): a clinicopathologic study of 174 cases. *J Am Acad Dermatol* 1991; **25**: 642–7.
6 Rabinowitz LG. Pigmented purpuras. In: Harper J, Oranje AP, Prose N, eds. *Textbook of Pediatric Dermatology,* 2nd edn. Oxford: Blackwell Science, 2006: 1927–32.
7 Baselga E, Drolet BA, Esterley NB. Purpura in infants and children. *J Am Acad Dermatol* 1997; **37**: 673–705.
8 Sardana K, Sarkar R, Seghal VN. Pigmented purpuric dermatoses: an overview. *Int J Dermatol* 2004; **43**: 482–8.
9 Tristani FP, Meadows KP, Vanderhooft S. Pigmented purpuric eruptions of childhood: a series of cases and review of literature. *Pediatr Dermatol* 2001; **18**: 299–304.
10 Torrel A, Requena C, Mediero IG, Zambrano A. Schamberg's purpura in children: a review of 13 cases. *J Am Acad Dermatol* 2003; **48**: 31–3.
11 Petruzzellis V, Vadala' P, Inverardi D *et al*. Idiopathic chronic pigmentary purpura. Findings in 22 cases and proposal of a new classification. *VASA* 1994; **23**: 114–9.
12 Aiba S, Takami H. Immunohistological studies in Schamberg's disease. *Arch Dermatol* 1988; **124**: 1058–62.
13 Ghersetich I, Lotti T, Bacci S *et al*. Cell infiltrate in progressive pigmented purpura (Schamberg's disease): immunophenotype, adhesion receptors and intercellular relationships. *Int J Dermatol* 1995; **34**: 846–50.

14 Crowson AN, Magro CM, Usmani A, McNutt NS. Immunoglobulin A-associated lymphocytic vasculopathy: a clinicopathologic study of eight patients. *J Cutan Pathol* 2002; **29**: 596–601.

Secondary pigmented purpuric dermatoses and systemic causes

Many underlying causes have been proven or suggested for the various patterns of pigmented purpuric dermatosis, although with limited specificity [1,2]. Most cases in which a cause is found either resemble Schamberg's disease or are unclassifiable (similar to 70% of idiopathic cases) and drugs have been documented as a cause in all of the main clinical patterns. The apparently idiopathic variants of pigmented purpuric dermatosis, while much the commonest cause, are therefore a diagnosis made by exclusion. The most important underlying conditions are listed below.

Drugs and food additives [1,3–6]. Drugs caused 14% of cases in one large series [1]. Drugs reported to cause capillaritis resembling a pigmented purpuric dermatosis include calcium channel antagonists [6], β-blockers, angiotensin-converting enzyme inhibitors, nitrites, furosemide and other diuretics, antihistamines, antidepressants, chlordiazepoxide, carbamazepine, analgesics such as paracetamol, non-steroidal anti-inflammatory agents, glipizide, bezafibrate, medroxyprogesterone acetate, raloxifene, pseudoephedrine, vitamin B_1 derivatives, interferon-α (in hepatitis C infection), antibiotics including ampicillin and cotrimoxazole, polyvinyl pyrrolidone and topical 5-fluorouracil [2–6]. Amongst food additives and related agents, tartrazine and creatine supplements have been implicated. Minocycline has been reported to selectively pigment areas of pre-existing capillaritis [7], and minocycline-induced ITP has mimicked Schamberg's disease, but it does not seem to be a specific cause of pigmented purpuric dermatoses.

External contact agents. Both contact irritants and allergens, especially clothing dyes, have been implicated as a cause of pigmented purpuric dermatoses [8–10]; these are discussed separately above (p. 49.21). Patch testing at the lesional site has been suggested.

Infections. β-haemolytic streptococci, toxoplasma and rickettsiae have been linked to development of pigmented purpuric dermatoses. More recently, a case has been made for hepatitis viruses being associated with pigmented purpuric dermatoses; in a series of 10 patients, five had hepatitis C antibodies and two had hepatitis B antibodies, although no random controls were tested [11]. One case was reported in association with cryoglobulinaemia, hepatitis C and rheumatoid arthritis (which itself has been linked with pigmented purpuric dermatoses, below) and one with interferon treatment for hepatitis C (above). In five patients, a chronic pigmented purpuric dermatosis (Schamberg pattern in four and itching purpura in one) resolved after treatment of dental infections, either periodontitis or pulpitis [12].

Neoplasia. There are many reported instances in which an apparent pigmented purpuric dermatosis has been a manifestation (sometimes the only manifestation) of mycosis fungoides [4,13–15]. In one instance, pigmented purpuric dermatosis preceded the diagnosis of mycosis fungoides by 24 years [16]. Some have linked this subtle presentation of mycosis fungoides predominantly with the lichenoid patterns of pigmented purpuric dermatosis [17,18], but many cases are of lichen aureus, Schamberg or non-specific capillaritis pattern. Monoclonality, demonstrated by T-cell receptor-gamma [17,18] or beta [19,20] gene rearrangement studies, has been demonstrated in some cases, occurring in almost half of cases in one series [19], although it may also occur in collagen vascular disease and drug reactions as well as representing cutaneous T-cell lymphoma, and some reported cases with clonality have had a benign behaviour [18]. In one series of 23 cases of lichen aureus, half had T-cell monoclonality but none showed progression to mycosis fungoides and over half had no evidence of skin disease after a mean follow-up of over 8 years [21]. Cases with monoclonality thus account for a small minority of pigmented purpuric dermatoses, but it seems prudent to suggest a skin biopsy in cases that are atypical in age-group, site, extent or morphology, or that are progressive or recurrent in behaviour. Other malignancies have been linked with development of pigmented purpuric dermatoses, including neoplasms of breast, bladder, intestine and lung, as well as leukaemia and Hodgkin's disease, but the strength of such associations is unclear.

Collagen vascular disorders. Both lupus erythematosus and rheumatoid disease [22] have been reported in association with pigmented purpuric dermatoses.

Vascular and haematological diseases. Stasis dermatitis commonly includes a component of pigmented purpuric dermatosis, either around the ankle or overlying varicosities. There is a single case of association with spherocytosis. Apparent 'venous' pigmented purpuric dermatosis in younger patients, without overt varicosities, should raise suspicion of a thrombophilia (Fig. 49.7).



Fig. 49.7 A pigmented purpuric dermatosis suggestive of venous disease but occurring in a young male without varicose veins; thrombophilia screening documented a lupus anticoagulant.

Miscellaneous. Diabetes, thyroid disease, liver disease and obesity have all been reported in association with pigmented purpuric dermatoses although causative relationships are not clear in these cases.

References

1 Ratnam KV, Su WPD, Peters MS. Purpura simplex (inflammatory purpura without vasculitis): a clinicopathologic study of 174 cases. *J Am Acad Dermatol* 1991; **25**: 642–7.
2 Petruzzellis V, Vadala' P, Inverardi D *et al*. Idiopathic chronic pigmentary purpura. Findings in 22 cases and proposal of a new classification. *VASA* 1994; **23**: 114–9.
3 Nishioka K, Katayama I, Masuzawa M *et al*. Drug-induced chronic pigmented purpura. *J Dermatol* 1989; **16**: 220–2.
4 Crowson AN, Magro CM, Zahorchak R. Atypical pigmentary purpura: a clinical, histopathologic, and genotypic study. *Hum Pathol* 1999; **30**: 1004–12.
5 Kalinke DU, Wuthrich B. Purpura pigmentosa progressiva in type III cryoglobulinaemia and tartrazine intolerance. A follow-up over 20 years. *Hautarzt* 1999; **50**: 47–51.
6 Cox NH, Walsh ML, Robson RH. Purpura and bleeding due to calcium channel blockers: an underestimated problem? Case reports and a pilot study. *Clin Exp Dermatol* 2009; **34**: 487–91.
7 Madan V, Lear JT. Minocycline-induced pigmentation of pre-existing capillaritis. *Br J Dermatol* 2007; **156**: 590–1.
8 Shah SA, Ormerod AD. Pigmented purpuric clothing dermatitis due to disperse dyes. *Contact Dermatitis* 2000; **43**: 360.
9 Komericki P, Aberer W, Arbab E, Kovacevic Z, Kränke B. Pigmented purpuric contact dermatitis from Disperse Blue 106 and 124 dyes. *J Am Acad Dermatol* 2001; **45**: 456–8.
10 Engin B, Ozdemir M, Kaplan M, Mevlitoglu I. Patch test results in patients with progressive pigmented purpuric dermatosis. *J Eur Acad Dermatol Venereol* 2009; **23**: 209.
11 Dessoukey MW, Abdel-Dayem H, Omar MF, Al-Suweidi NE. Pigmented purpuric dermatosis and hepatitis profile: a report on 10 patients. *Int J Dermatol* 2005; **44**: 486–8.
12 Satoh T, Yokozeki H, Nishioka K. Chronic pigmented purpura associated with odontogenic infection. *J Am Acad Dermatol* 2002; **46**: 942–4.
13 Barnhill RL, Braverman IM. Progression of pigmented purpura-like eruptions to mycosis fungoides: report of three cases. *J Am Acad Dermatol* 1988; **19**: 25–31.
14 Lipsker D, Cribier B, Heid E, Grosshans E. Cutaneous lymphoma masquerading as pigmented purpuric capillaritis. *Acta Derm Venereol (Stockh)* 1999; **126**: 321–6.
15 Ameen M, Darvay A, Black MM *et al*. CD8-positive mycosis fungoides presenting as capillaritis. *Br J Dermatol* 2000; **142**: 564–7.
16 Viseux V, Schoenlaub P, Cnudde F *et al*. Pigmented purpuric dermatitis preceding the diagnosis of mycosis fungoides by 24 years. *Dermatology Basel* 2003; **207**: 331–2.
17 Toro JR, Sander CA, LeBoit PE. Persistent pigmented purpuric dermatitis and mycosis fungoides: stimulant, precursor, or both? A study by light microscopy and molecular methods. *Am J Dermatopathol* 1997; **19**: 108–18.
18 Lor P, Krueger U, Kempf W, Burg G, Nestle FO. Monoclonal rearrangement ot the T cell receptor gamma-chain in lichenoid pigmented purpuric dermatitis of Gougerot-Blum responding to topical corticosteroid therapy. *Dermatology Basel* 2002; **205**: 191–3.
19 Magro CM, Schaefer JT, Crowson NA *et al*. Pigmented purpuric dermatosis: classification by phenotypic and molecular profiles. *Am J Clin Pathol* 2007; **128**: 218–29.
20 Plaza JA, Morrison C, Magro CM. Assessment of TCR-beta clonality in a diverse group of cutaneous T-cell infiltrates. *J Cutan Pathol* 2008; **35**: 358–65.
21 Fink-Puches R, Wolf P, Kerl H, Cerroni L. Lichen aureus. Clinicopathologic features, natural history, and relationship to mycosis fungoides. *Arch Dermatol* 2008; **144**: 1169–73.
22 Wilkinson SM, Smith AG, Davis M, Dawes PT. Capillaritis: a manifestation of rheumatoid disease. *Clin Rheumatol* 1993; **12**: 53–6.

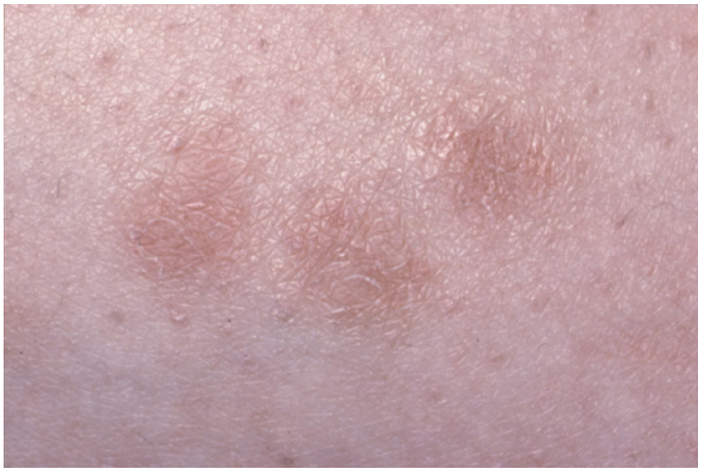


Fig. 49.8 Schamberg's disease.

Schamberg's disease [1,2]

Synonym
- Progressive pigmented purpuric dermatosis

This uncommon eruption is most common in young adult males but may occur at any age including childhood. Familial incidence has been reported [3]. The lesions are most frequent on the legs but may occur anywhere on the body, including the palms [4], and may be few in number or very extensive. They consist of irregular plaques of orange or brown pigmentation due to haemosiderin, with characteristic 'cayenne pepper' spots appearing within and at the edge of old lesions (Fig. 49.8). Slight changes in the epidermis may occur. There are usually no symptoms, although there may be some slight itching. The eruption is characteristically very chronic and may persist for many years. The pattern of the eruption changes, with slow extension and often some clearing of the original lesions. Spontaneous cure may occur eventually. Many patients have an eruption with features both of this disease and of the other pigmented purpuric dermatoses. An annular configuration may occur and there may be small lichenoid papules.

Itching purpura is a disorder that may be similar to Schamberg's disease, but the intensity of itch serves to distinguish the two.

Itching purpura [5–7]

Synonyms
- Eczematide-like purpura (of Doucas and Kapetanakis)
- Disseminated pruriginous angiodermatitis

This condition has many similarities to Schamberg's disease but is generally more extensive, develops more rapidly and is characterized by persistent, intense itch. It occurs most frequently in adult men and is of unknown aetiology. Purpuric lesions usually commence around the ankles and in a few weeks spread to involve the whole legs, sometimes the lower part of the body, and even elsewhere. They are more pronounced at sites of friction with clothing. The lesions consist of erythematous and purpuric macules that may become confluent. The eruption often has a

rather characteristic orange colour. The dermal perivascular changes are those seen generally in the pigmented purpuric dermatoses and there are variable changes in the overlying epidermis, including spongiosis. Spontaneous improvement after a few months is usual, but recurrences may occur and a fluctuating but chronic course is frequent. The itching may respond to topical corticosteroids and oral antihistamines.

An almost identical picture occurs with carbromal sensitivity, and less commonly with other drugs such as meprobamate, carbamazepine and perhaps even some foods. Clothing or rubber dermatitis may produce a similar picture, and may explain many cases of itching purpura.

Pigmented purpuric lichenoid dermatosis of Gougerot and Blum [8]

This eruption occurs especially in men aged between 40 and 60 years. It usually affects the legs, but lesions may occur elsewhere. The characteristic clinical feature of the dermatosis is the presence of lichenoid papules in association with purpuric lesions similar to those of Schamberg's disease, and this may simply be a variation of the same disorder. This clinical pattern has been found in association with porphyria [9] and a similar pattern of eruption may occur in the oral mucosa [10].

Lichen aureus [11,12]

Synonym
- Lichen purpuricus

This is a more localized, more intensely purpuric but often asymptomatic eruption that may have rather lichenoid morphology. Young adults and children are often affected, on body, limbs or even face. The lesions are often solitary and may be yellowish, golden, rust-coloured or purple. They may resemble a bruise, and hence must be distinguished from non-accidental injury in children, but may persist for a few years. Histologically, lichen aureus is distinguished from other pigmented purpuric dermatoses by a lack of epidermal component and in some cases a Grenz zone.

Purpura annularis telangiectodes [13,14]

Synonym
- Majocchi's disease

This eruption occurs especially in adolescents and young adults of either sex but may occur at any age, and may be familial [15]. Exercise may have been a provoking factor in one case [16]. The clinical features are distinctive and described in its name. Lesions occur at any site, often in the absence of venous stasis, and may be few in number or very numerous. They consist of small plaques 1–3 cm across that are usually annular from their onset (Fig. 49.9). Lesions consist of telangiectases and haemosiderin staining of the skin. They may be purple, yellow or brown, and may contain 'cayenne pepper' spots. Individual lesions persist unchanged for many months or years, or there may be slow centrifugal extension with development of slight central atrophy. Sometimes the lesions disappear and are replaced by similar lesions nearby. Treatment is usually ineffective. A variant termed *purpura telangiectatica arciformis (Touraine)* consists of fewer, larger and irregularly arciform lesions [17].



Fig. 49.9 Majocchi's purpura annularis telangiectodes.

Granulomatous pigmented purpuric dermatosis

An uncommon variant of pigmented purpuric dermatosis has been reported in which there is granulomatous histology [18,19]. In a series of four Asian cases, three had hyperlipidaemia, suggesting that this is worthy of evaluation in this rare variant of pigmented purpuric dermatosis [20].

Familial pigmented purpuric eruption

There are rare reported instances of the familial occurrence of Schamberg's disease [3,21] and of purpura annularis telangiectodes [14]. A distinctive pigmented purpuric eruption has been observed in several members of a family in which it was probably determined by an autosomal dominant gene [22]. Discrete reddish-brown spots developed in childhood or adolescence. The individual macules were larger than in Schamberg's disease and were arranged in a mosaic pattern. The lesions gradually covered a larger area and involved new sites, mainly on the limbs and in the larger flexures, but without any symptoms. Another family has been reported in which three generations were affected, supporting an autosomal dominant inheritance pattern [23].

Linear and quadrantic pigmented purpuric dermatoses

Various morphological types of pigmented purpuric eruption may occur in a linear or zosteriform distribution [24–28], or less commonly may diffusely involve a single quadrant of the body [29]. Linear lesions affect the legs more often than the arms. Individual lesions usually resemble lichen aureus or Schamberg's disease. In one case, trauma-induced linear pigmented purpuric dermatosis evolved into linear morphoea [30].

References

1 Schamberg JF. A peculiar progressive pigmentary disease of the skin. *Br J Dermatol* 1901; **13**: 1–5.

2 Schamberg JF. Report of 3 cases of progressive pigmentary dermatosis with particular reference to the blood cholesterol. *Br J Dermatol* 1927; **39**: 389–93.
3 Baden HP. Familial Schamberg's disease. *Arch Dermatol* 1964; **90**: 400.
4 Moyer DG, Chernita SA. Capillaritis of the palms. *Arch Dermatol* 1969; **99**: 591–2.
5 Doucas C, Kapetanakis J. Eczematid-like purpura. *Dermatologica* 1953; **106**: 86–95.
6 Loewenthal LJA. Itching purpura. *Br J Dermatol* 1954; **66**: 95–103.
7 Mosto SJ, Casala AM. Disseminated pruriginous angiodermatitis (itching purpura). *Arch Dermatol* 1965; **91**: 351–6.
8 Gougerot H, Blum P. Purpura angiosclereux prurigineux aux elements lichenoides. *Bull Soc Fr Dermatol Syphiligr* 1925; **32**: 161.
9 Ippen H, Goerz G, Bruster H. Purpura porphyrica. *Arch Klin Exp Derm* 1965; **223**: 128–35.
10 Scully C, Eveson JW. Pigmented purpuric stomatitis. *Oral Surg Oral Med Oral Pathol* 1992; **74**: 780–2.
11 Kanitakis C, Tsoitis G. Lichen purpurique. *Ann Dermatol Vénéréol* 1982; **109**: 445–52.
12 Price ML, Wilson Jones E, Calnan CD *et al.* Lichen aureus: a localised persistent form of pigmented purpuric dermatosis. *Br J Dermatol* 1984; **112**: 307–14.
13 Majocchi D. Sopra una dermatosi telangiectode non ancora descritta: purpura annularis. *G Ital Mal Vener Pelle* 1896; **31**: 263–4.
14 Mackee GM. Purpura annularis telangiectodes. *J Cutan Genitourin Dis* 1915; **33**: 129–41.
15 Borelli G. Purpura annularis teleangectoides: tre casi familiari. *Arch Ital Derm Sif Vener* 1953; **25**: 259–71.
16 Allan SJR, Humphreys F, Buxton PK. Annular purpura and step aerobics. *Clin Exp Dermatol* 1994; **19**: 418.
17 Brehm G. Zur purpura telangiectatica arciformis (Touraine). *Z Haut Geschlechtskr* 1957; **17**: 331–6.
18 Wong WR, Kuo TT, Chen MJ, Chan HL. Granulomatous variant of chronic pigmented purpuric dermatosis: report of two cases. *Br J Dermatol* 2001; **145**: 162–4.
19 Saito R, Matsuoka Y. Granulomatous pigmented purpuric dermatosis. *J Dermatol* 1996; **23**: 551–5.
20 Li WL, Kuo TT, Shih PY *et al*. Granulomatous variant of chronic pigmented purpuric dermatosis: report of four new cases and an association with hyperlipidaemia. *Clin Exp Dermatol* 2007; **32**: 513–5.
21 Kanwar AJ, Thami GP. Familial Schamberg's disease. *Dermatology* 1999; **198**: 175–6.
22 Gould WM, Farber EM. A familial pigmented purpuric eruption. *Dermatologica* 1966; **132**: 400–8.
23 Sethuraman G, Sugandhan S, Bansal A *et al*. Familial pigmented purpuric dermatoses. *J Dermatol* 2006; **33**: 639–41.
24 Braun-Falco O, Abeck O, Betke M *et al.* Lichen aureus zosteriformis. *Hautarzt* 1989; **40**: 373–5.
25 Riordan CA, Darley C, Markey AC *et al*. Unilateral linear capillaritis. *Clin Exp Dermatol* 1992; **17**: 182–5.
26 Filo V, Galbavy S, Filova A *et al*. Unilateral progressive pigmented capillaropathy (Schamberg's disease) of the arm. *Br J Dermatol* 2001; **144**: 190–1.
27 Hamada T, Inoue Y, Nakama T, Hashimoto T. A case of zosteriform pigmented purpuric dermatosis. *Arch Dermatol* 2007; **143**: 1599–600.
28 Ma-Hui JZhao G, Liu W, Dang YP, Li-Dong G. Unilateral linear capillaritis: two unusual Chinese cases. *Eur J Dermatol* 2007; **17**: 160–3.
29 Higgins EM, Cox NH. A case of quadrantic capillaropathy. *Dermatologica* 1990; **180**: 93–5.
30 Bell HK, Dobson CM, Jackson SP, King CM. Localized morphoea preceded by a pigmented purpuric dermatosis. *Clin Exp Dermatol* 2003; **28**: 369–71.

Treatment of pigmented purpuric dermatoses

These disorders may persist for many years [1–3] and are very resistant to any form of therapy; explanation without active intervention, or simply support hosiery, is often the most appropriate approach. Topical steroids may be of some help, especially for itch, but very prolonged use is best avoided. Emollients can be used as necessary. A rapid response of lichen aureus to topical pimecrolimus has been reported [4]. Psoralen and UVA (PUVA) [5–7] has proven effective in treating capillaritis of Schamberg, Gougerot–Blum and lichen aureus patterns, and TL01 UVB has been reported as effective in Schamberg's disease [8] and in Gougerot–Blum pigmented purpuric lichenoid dermatitis [9]. Ciclosporin [10] and griseofulvin [11] have also been effective in individual reports; calcium dobesilate has been suggested as first-line therapy as nine treated patients stopped developing new lesions within 2 weeks, but as the improvement at 12 months was graded as moderate in one patient, mild in six and none in two, it is not clear that this agent has much useful benefit [12].

References

1 Ratnam KV, Su WPD, Peters MS. Purpura simplex (inflammatory purpura without vasculitis): a clinicopathologic study of 174 cases. *J Am Acad Dermatol* 1991; **25**: 642–7.
2 Rabinowitz LG. Pigmented purpuras. In: Harper J, Oranje AP, Prose N, eds. *Textbook of Pediatric Dermatology,* 2nd edn. Oxford: Blackwell Science, 2006: 1927–32.
3 Price ML, Wilson Jones E, Calnan CD *et al.* Lichen aureus: a localised persistent form of pigmented purpuric dermatosis. *Br J Dermatol* 1984; **112**: 307–14.
4 Böhm M, Bonsmann G, Luger T. Resolution of lichen aureus in a 10-year-old child after topical pimecrolimus. *Br J Dermatol* 2004; **150**: 519–20.
5 Wong WK, Ratnam KV. A report of two cases of pigmented purpuric dermatosis treated with PUVA therapy. *Acta Derm Venereol (Stockh)* 1991; **71**: 68–70.
6 Ling TC, Goulden V, Goodfield MJD. PUVA therapy in lichen aureus. *J Am Acad Dermatol* 2001; **45**: 145–6.
7 Seckin D, Yazici Z, Senol A, Demircay Z. A case of Schamberg's disease responding dramatically to PUVA treatment. *Photodermatol Photoimmunol Photomed* 2008; **24**: 95–6.
8 Gudi VS, White GI. Progressive pigmented purpura (Schamberg's disease) responding to TL-01 ultraviolet B therapy. *Clin Exp Dermatol* 2004; **29**: 683–4.
9 Kocaturk E, Kavala M, Zindanci I *et al*. Narrowband UVB treatment of pigmented purpuric lichenoid dermatitis (Gougerot-Blum). *Photodermatol Photoimmunol Photomed* 2009; **25**: 55–6.
10 Okada K, Ishikawa O, Miyachi Y. Purpura pigmentosa chronica successfully treated with oral cyclosporin A. *Br J Dermatol* 1995; **134**: 180–1.
11 Tamaki K, Yasaka N, Osada A *et al.* Successful treatment of pigmented purpuric dermatosis with griseofulvin. *Br J Dermatol* 1995; **132**: 159–60.
12 Agrawal SK, Gandhi V, Bhattacharya SN. Calcium dobesilate in pigmented purpuric dermatosis (PPD): a pilot evaluation. *J Dermatol* 2004; **31**: 98–103.

Disorders of cutaneous microvascular occlusion

Numerous conditions may cause microvascular occlusion (Table 49.5). This process may involve abnormal coagulation (e.g. DIC, APLS), platelet plugging (e.g. heparin necrosis), emboli or crystal deposition (e.g. cholesterol emboli), abnormal erythrocytes (e.g. sickle cell disease) or abnormal proteins (e.g. cryoproteinaemia). Many of these conditions may cause purpura as one of their manifestations; many cause an initial non-inflammatory purpuric process that can be diagnostically helpful in differentiation from vasculitis. Morphological features that suggest this category of disease as an aetiology for early lesions include purpura without erythema, eschar without erythema, branching or fingering extension of the margins, or lesions that show purpuric, non-erythematous retiform, branching, or stellate configurations.

Table 49.5 Disorders of cutaneous microvascular occlusion: differential diagnosis by pathophysiological mechanism.*

Occlusion due to platelet plugs
Heparin-induced thrombocytopenia
Myeloproliferative disorders
Paroxysmal nocturnal haemoglobinuria
Thrombotic thrombocytopenic purpura (TTP)/haemolytic–uraemic syndrome (HUS)†

Occlusion due to cryogelling
Cryoglobulinaemia
Cryofibrinogenaemia
Cold-agglutinin-related occlusion

Occlusion due to vessel-invasive organisms
Ecthyma gangrenosum
Lucio phenomenon
Vessel-invasive fungi
Disseminated strongyloidiasis

Occlusion due to embolus
Cholesterol embolus
Oxalate crystal embolus
Atrial myxoma
Cardiac sterile thrombi
Septic emboli
Fat emboli‡

Occlusion due to systemic coagulopathies with cutaneous manifestations
Protein C/S/thrombomodulin pathway anomalies
  Neonatal purpura fulminans
  Coumadin necrosis
  Sepsis-related purpura fulminans
  Post-infectious purpura fulminans
Antiphospholipid antibody syndrome

Occlusion due to vascular coagulopathies§
Sneddon's syndrome
Livedoid vasculopathy/atrophie blanche
Malignant atrophic papulosis

Occlusion due to reticulocyte occlusion¶
Sickle cell disease
Other severe haemolytic anaemias

Occlusion due to unknown or controversial mechanisms
Cutaneous calciphylaxis
Some insect bites, especially *Loxosceles* (brown recluse spider)
Some snake bite syndromes**

* Most of these disorders present with purpura or necrosis with minimal inflammation, and frequently show retiform (stellate, branching) morphologies.
† TTP/HUS is usually occlusive in visceral vessels, but skin lesions are most often non-palpable petechiae, and not due to occlusion.
‡ Fat emboli typically cause occlusion in viscera, especially lungs; cutaneous lesions are rare and typically petechial, due to minute fat particle occlusion.
§ Sneddon's syndrome typically presents with pathological livedo reticularis; livedoid vasculopathy may have retiform purpura morphologies, however, atrophie blanche and malignant atrophic papulosis are often not purpuric, but heal with a characteristic atrophic scar with surrounding telangiectasia.
¶ Syndromes involving reticulocyte occlusion often heal with lesions mimicking atrophie blanche, and are seldom purpuric or retiform.
** Most snake bites cause haemorrhage; if fulminant disseminated intravascular coagulation results, some lesions might be occlusive.

Occlusion due to platelet plugs

Heparin-induced thrombocytopenia and heparin necrosis [1,2]

Aetiology and pathogenesis. The syndrome of heparin-induced thrombocytopenia (HIT) is an uncommon paradoxical response to heparin, with some female predominance [1]. This syndrome can be defined as any clinical event best explained by PF4/heparin-reactive antibodies (HIT antibodies) in a patient who is receiving, or who has recently received, heparin [1]. Although IgA and IgM class antibodies may play a role, IgG antibody is most closely associated with this syndrome [3]. The antibody that causes HIT is not simply an antiheparin antibody. Heparin and certain other polyanions, when bound to PF4, can induce conformational changes in tetrameric PF4, exposing new epitopes on PF4. This may trigger antibody production to these newly exposed regions. When antiheparin/PF4 antibody binds with heparin/PF4 complexes on the surface of platelets, platelet activation and aggregation results. Not all heparin/PF4 antibodies appear to be pathogenic, and some antibodies responsible for HIT do not bind to heparin/PF4 complexes but to chemokines or cytokines, such as neutrophil activating peptide-2 (NAP-2) and interleukin-8, somehow activating platelets [1–3].

Unfractionated heparin is three times more likely to be associated with HIT following orthopaedic surgery compared with low-molecular-weight heparin [1]. HIT is more likely to be induced by bovine-derived unfractionated heparin than the porcine-derived variety, consistent with the hypothesis that longer and more flexible heparins bind to PF4 tetramers in ways that induce more conformational change and more exposure of neoepitopes. This may also explain the lower risk of HIT with low-molecular-weight heparins. HIT is even less likely to be triggered by fondaparinux, a pentasaccharide anticoagulant modelled after the antithrombin binding region of heparin [1]. The risk of HIT is highest in post-surgical patients, less so in medical patients requiring heparin and lowest in obstetric settings [1].

Clinical features. Patients with HIT usually develop absolute or relative thrombocytopenia (90%), often followed by evidence of venous or arterial thromboses or of heparin necrosis in the skin [1]. A proportional drop of over 50% in platelet number from the pre-treatment count may be a better indication of early heparin-induced platelet aggregation than an absolute thrombocytopenia of 100–150 $\times 10^9$/L [1]. This may occur immediately after heparin administration if the patient has been previously sensitized and has received heparin within the past 100 days. In two-thirds of patients, the fall in platelet count begins between days 5 and 10 of heparin administration, although significant thrombocytopenia may take 7–14 days to develop [1,4,5]. Uncommonly, patients may develop HIT several days after stopping heparin (delayed-onset HIT); this is attributed to the presence of high-titre antibodies that can recognize PF4 neoepitopes even in the absence of heparin binding, perhaps binding instead to chondroitin sulphate [1]. A history of HIT is not predictive of a second episode if the patient last received heparin more than 100 days previously. Although essential to thrombosis, HIT-IgG antibodies are not sufficient

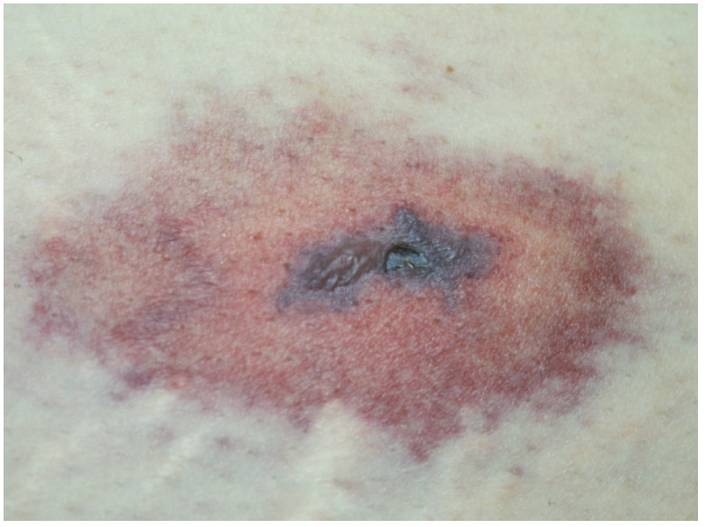
alone to produce thrombosis. Only 5–30% of patients who form HIT-IgG will develop clinical HIT [1]. Only half of antibody-positive patients produce IgG class antibodies, and only half of the IgG class group show biological activity.

Accumulating reports of catastrophic thrombotic episodes, typically venous limb gangrene, suggest that there may be a synergistic thrombophilic state in patients with HIT also treated with warfarin, presumably through both HIT and protein C-depletion pathways [1].

Heparin administration commonly induces cutaneous findings of simple haemorrhage with ecchymoses, and occasionally triggers urticaria or infiltrated plaques [6–8]. Uncommonly, the syndrome of heparin necrosis results as a cutaneous microvascular occlusion subset of HIT. Purpuric, tender, sharply demarcated plaques develop; retiform extensions that sometimes develop at the lesional margins are characteristic of heparin necrosis. Erythema may sometimes accompany such lesions, and necrosis is frequent. Lesions are most common at subcutaneous injection sites but can occur elsewhere [9–11] (Fig. 49.10). Interestingly, as few as one-third of patients with skin lesions of heparin necrosis may develop absolute thrombocytopenia, even when HIT antibodies are detected [1]. Haemorrhagic adrenal infarction has been reported in such cases. Histological examination of lesions reveals 'white clots', representing platelet–fibrin thrombi, in the cutaneous microvasculature [5,12].



(a)



(b)

Fig. 49.10 (a) Heparin necrosis at sites of subcutaneous heparin injection. (b) Close-up of a 15-cm lesion on left abdomen. Lesion is a non-palpable haemorrhage with retiform margins, minimal erythema and central retiform intense haemorrhage, early necrosis and bullae formation. (From Robson K, Piette W. The presentation and differential diagnosis of cutaneous vascular occlusion syndromes. *Adv Dermatol* 1999; **15**: 153–82, with permission from Mosby.)

Treatment. Treatment of HIT and heparin necrosis continues to evolve. The correct diagnosis is important, because many patients on heparin develop thrombocytopenia for reasons other than the development of HIT antibodies; conversely, patients may develop the arterial or venous thromboses, or especially heparin necrosis, without manifesting thrombocytopenia [1]. Stopping heparin is important, although some patients do not worsen if heparin is continued whereas others may progress despite stopping heparin. Although replacing heparin with coumadin was previously thought to be effective in treating HIT and heparin necrosis, coumadin substitution is not only ineffective but may in fact induce venous limb gangrene [1]. Low-molecular-weight heparin is much less likely to cause HIT, but it is contraindicated for treatment of patients with HIT due to other types of heparin. Surprisingly, heparin is the appropriate treatment for cardiac surgery patients with a previous history of HIT, but whose antibodies have disappeared (beyond 100 days). The anticoagulants currently used to treat patients with HIT are danaparoid (a heparinoid) and two thrombin inhibitors, lepirudin and argatroban [1]. Even with treatment with one of these agents, there is a 5–20% frequency of new thromboses. Major bleeding in HIT patients has occurred in 3.1% of those treated with argatroban, and in 5.9–14.4% of those treated with lepirudin. Danaparoid is available in many countries, including the UK, but not currently in the United States.

References

1 Kelton JG, Warkentin TE. Heparin-induced thrombocytopenia: a historical perspective. *Blood* 2008; **112**: 2607–15.

2 Arepally GM, Ortel TL. Heparin-induced thrombocytopenia. *N Engl J Med* 2006; **355**: 809–17.

3 Untch B, Ahmad S, Jeske W *et al.* Prevalence, isotype, and functionality of anti-heparin–platelet factor 4 antibodies in patients treated with heparin and clinically suspected for heparin-induced thrombocytopenia. The pathogenic role of IgG. *Thromb Res* 2002; **105**: 117–23.

4 Sallah S, Thomas D, Roberts H. Warfarin and heparin-induced skin necrosis and the purple toe syndrome: infrequent complications of anticoagulant treatment. *Thromb Haemost* 1997; **78**: 785–90.

5 Gross A, Thompson F, Arzbiaga M *et al.* Heparin-associated thrombocytopenia and thrombosis (HATT) presenting with livedo reticularis. *Int J Dermatol* 1993; **32**: 276–9.

6 Tuneu A, Moreno A, de Moragas J. Cutaneous reactions secondary to heparin injections. *J Am Acad Dermatol* 1985; **12**: 1072–7.

7 Klein G, Kofler H, Wolf H *et al.* Eczema-like, erythematous, infiltrated plaques: a common side effect of subcutaneous heparin therapy. *J Am Acad Dermatol* 1989; **21**: 703–7.

8 Rose GA, Spencer H. Polyarteritis nodosa. *QJM* 1957; **27**: 43.

9 Levine L, Bernstein J, Soltani K *et al.* Heparin-induced cutaneous necrosis unrelated to injection sites: a sign of potentially lethal complications. *Arch Dermatol* 1983; **7**: 674–7.

10 Santamaria A, Romani J, Souto J *et al.* Skin necrosis at the injection site induced by low-molecular-weight heparin: case report and review. *Dermatology* 1998; **196**: 264–5.
11 Tietge U, Schmidt H, Jackel E *et al.* Low molecular weight heparin-induced skin necrosis occurring distant from injection sites and without thrombocytopenia. *J Intern Med* 1998; **243**: 313–5.
12 Chang J. White clot syndrome associated with heparin-induced thrombocytopenia: a review of 23 cases. *Heart Lung* 1987; **16**: 403–7.

Myeloproliferative disorders

Cutaneous lesions are common in thrombocythaemia and other myeloproliferative disorders (see also Chapter 62). Paradoxically, patients with myeloproliferative thrombocytosis may both bleed and clot abnormally. Skin lesions were documented in 22% of 268 patients with essential thrombocythaemia [1], and included urticaria, livedo reticularis, petechiae, ecchymoses, haematomas, erythromelalgia, Raynaud's phenomenon, recurrent superficial thrombophlebitis, necrotizing vasculitis, leg ulceration and gangrene. Biopsy findings were variable, but some livedo reticularis and acral infarcts were associated with evidence of microvascular occlusion. Additionally, tender erythematous facial plaques and palmar violet macules and papules were reported as manifestations of platelet plugging in a patient with atypical chronic myeloproliferative disease and a history of Budd–Chiari syndrome, another known thrombotic complication of myeloproliferative disease [2]. This patient's cutaneous lesions were unresponsive to coumadin, but cleared within 24 h of aspirin administration following identification of platelet plugs as the cause of previously identified microvascular occlusion.

Essential thrombocytosis and polycythaemia vera, although rare, are the first and second most common causes of elevated platelet counts, with an increased frequency of thrombotic events and of erythromelalgia [3]. A recent study of 605 patients with essential thrombocythaemia found a 10-year risk of thrombosis of 14% [4]. These diseases are more common at younger ages and in women. However, reactive or post-splenectomy thrombocytosis at any level is not associated with occlusion, suggesting that thrombosis in the setting of myeloproliferative disease is not a function of thrombocytosis alone. Multiple studies have shown that a specific mutation in the JAK2 tyrosine kinase (JAK2V617F) is found in many patients with essential thrombocytosis, polycythaemia vera, and primary myelofibrosis, and a gain-of-function mutation in the thrombopoietin receptor (MPL) in a subset of patients with essential thrombocytosis but who are JAK2V617-negative [5]. The mechanisms for ischaemic or occlusive syndromes in myeloproliferative disease must therefore depend on more than platelet number alone; the following factors may be relevant. Acquired von Willebrand factors in myeloproliferative disease have been associated with both bleeding and thrombotic complications. Anticardiolipin antibodies, factor V Leiden mutations, abnormal endothelial cell function, and decreased levels of protein C and protein S may be synergistic for thrombosis in chronic myeloproliferative diseases [6,7]. In addition to high platelet counts, abnormal platelet function occurs in myeloproliferative or myelodysplastic disease, although whether this can lead to vascular occlusion at platelet counts less than 1000×10^9/L is controversial. Thrombotic events have been reported at platelet counts below 600×10^9/L in patients with essential thrombocytosis, including some events at normal platelet counts [8]. In a study of 56 consecutive patients with essential thrombocytosis, 46 developed complications mostly related to thrombosis [8]. In these 46 patients, severe complications occurred in 22% at platelet counts lower than 600×10^9/L, in 15% at counts lower than 500×10^9/L, and in 4% at counts lower than 400×10^9/L. In a cohort of 1063 patients with essential thrombocythaemia, a paradoxical finding reported was that a platelet count greater than 1000×10^9/L was associated with a lower risk of thrombocytosis, and if combined with a leukocyte count less than 11×10^9/L pointed to a 'low-risk' category of thrombosis [9].

Erythromelalgia (erythralgia) can occur as a primary or secondary syndrome. This intensely uncomfortable burning associated with paroxysmal erythema of the distal extremities is frequently triggered by skin contact with a warm surface. Although erythromelalgia has been seen in many different settings, the association of purpuric or necrotic areas on hands and feet with the dysaesthetic erythema is exclusively seen with myeloproliferative or myelodysplastic thrombocytosis [10]. Because of the platelet origin of occlusion and vascular symptoms in the myeloproliferative subset of erythromelalgia, aspirin administration is notably effective in clearing lesions and alleviating symptoms, whereas it is much less effective in primary and other secondary forms of erythromelalgia.

Splenomegaly may be seen in all forms of myeloproliferative syndromes. Ruddy cyanosis is characteristic of polycythaemia vera, as is elevation of haemoglobin, haematocrit and red cell mass. All syndromes may show elevations in white count, but this is most characteristic of chronic granulocytic leukaemia, especially in association with elevated eosinophil and basophil counts. Anaemia and altered red cell morphology can occur over time in all patients, and all these diseases have some risk of transition to dyspoiesis and severe anaemia, leukaemia or myelofibrosis.

Many therapies previously used for myeloproliferative thrombocytosis increase the risk of leukaemic transformation and of complications in fertility and pregnancy. Low-dose aspirin has been widely accepted as effective thrombosis prophylaxis, although definitive proof of its efficacy is lacking. Its dramatic reversal of signs and symptoms in erythromelalgia provides some clinical evidence for its usefulness in thrombocythaemic complications. Hydroxycarbamide is the drug of choice for prevention of transient ischaemic attacks, but may not be effective in preventing venous thrombosis, and anagrelide treatment may reduce the risk of venous thrombosis but appears to dramatically increase the risk for arterial thrombosis and haemorrhage. Anagrelide has become an important therapeutic agent, acting to both inhibit platelet activity and decrease the platelet count [11,12]. The JAK2 mutations seem to correlate with leukocyte and platelet proliferation, but the role for the JAK2 and MPL mutations in enhancing thromboses is less clear [5,13]. Multiple studies suggest that the presence of the JAK2V617F mutation translates into activation of haemostasis, at least in part through increase in platelet-associated tissue factor microparticles and increased platelet–neutrophil aggregates [14].

References

1 Itin P, Winkelmann R. Cutaneous manifestations in patients with essential thrombocythemia. *J Am Acad Dermatol* 1991; **24**: 59–63.

2 Stone M, Robson K, Piette W. Erythematous plaques due to platelet plugging: a clue to underlying myeloproliferative disorder. *J Am Acad Dermatol* 2000; **43**: 355–7.
3 Tefferi A, La S, Silverstein M. A clinical update in polycythemia vera and essential thrombocythemia. *Am J Med* 2000; **109**: 141–9.
4 Passominti F, Rumi E, Arcaini L *et al*. Prognostic factors for thrombosis, myelofibrosis, and leukemia in essential thrombocythemia: a study of 605 patients. *Haematologica* 2008; **93**: 1645–51.
5 Levine RL, Heaney M. New advances in the pathogenesis and therapy of essential thrombocythemia. *Hematology Am Soc Hematol Educ Program* 2008: 76–82.
6 Sanchez-Luceros A, Meschengieser S, Woods A *et al*. Acquired von Willebrand factor abnormalities in myeloproliferative disorders and other hematologic diseases: a retrospective analysis by a single institution. *Haematologica* 2002; **87**: 264–70.
7 Jensen M, Brown P, Thorsen S, Hasselbalch H. Frequent occurrence of anticardiolipin antibodies, Factor V Leiden mutation, and perturbed endothelial function in chronic myeloproliferative disorders. *Am J Hematol* 2002; **69**: 185–91.
8 Regev A, Stark P, Blickstein D, Lahav M. Thrombotic complications in essential thrombocythemia with relatively low platelet counts. *Am J Hematol* 1997; **56**: 168–72.
9 Carrobio A, Finazzi G, Antioneli E *et al*. Thrombocytosis and leukocytosis interaction in vascular complications of essential thrombocythemia. *Blood* 2008; **112**: 3134–7. (Comment in *Blood* 2008; **112**: 3526; author reply 3526–7.)
10 Michiels J, ten Kate F. Erythromelalgia in thrombocythemia of various myeloproliferative disorders. *Am J Hematol* 1992; **39**: 131–6.
11 Tefferi A, Silverstein M, Petitt R *et al*. Anagrelide as a new platelet-lowering agent in essential thrombocythemia: mechanism of action, efficacy, toxicity, current indications. *Sem Thromb Hemost* 1997; **23**: 379–83.
12 Emadi A, Spivak JL. Anagrelide: 20 years later. *Expert Rev Anticancer Ther* 2009; **9**: 37–50.
13 Austin SK, Lambert JR. The JAK2 617F mutation and thrombosis. *Br J Haematol* 2008; **143**: 307–20.
14 Falanga A, Barbui T, Rickles FR. Hypercoagulability and tissue factor gene upregulation in hematologic malignancies. *Semin Thromb Hemost* 2008; **34**: 204–10.

Paroxysmal nocturnal haemoglobinuria

Paroxysmal nocturnal haemoglobinuria (PNH) is an acquired clonal blood disorder associated with deficient haematopoiesis, intravascular haemolysis and venous thrombosis [1,2]. Episodic haemoglobinuria is the characteristic result of nocturnal haemolysis, although it is the presenting feature in only 26% of patients [1,2]. The sleep-associated haemoglobinuria is secondary to an abnormally increased sensitivity of red blood cells to lysis by serum complement [1]. This increased sensitivity to complement lysis is related to abnormal regulation at two different points of the complement cascade, and this abnormal regulation is due in turn to the partial to complete deficiency of two membrane-associated inhibitors of the complement cascade, decay-accelerating factor (DAF) and membrane inhibitor of reactive lysis (MIRL, also known as CD59). DAF inhibits the activity of classic complement pathway C3 convertase and of alternative pathway C3 convertase, and MIRL/CD59 regulates the activity of the complement membrane attack complex on red cells. These two inhibitors are part of a group of roughly 20 red cell membrane proteins that share a common post-translational modification in the glycosylphosphatidylinositol (GPI) anchor. In PNH, a somatic mutation in the phosphatidylinositol glycan class A gene (*PIG-A*) on the X chromosome alters the ability of proteins sharing the GPI anchor to bind to the membrane [1–3]. Whereas previous diagnostic tests for PNH relied on the haemolytic sensitivity of PNH red blood cells, current tests rely on detection of loss of CD59 and/or CD55 on red cells, loss of CD59, CD24, CD16, or other GPI-anchored proteins on granulocytes, or lack of FLAER (Fluorescently Labelled inactive toxin AERolysin) binding to granulocytes, which also depends on binding to GPI anchors [4].

This complex pathophysiology explains the haemolysis and haemoglobinuria in PNH, but does not yet completely explain other manifestations of this disease such as thrombosis. Although 10–15% of patients may show spontaneous remission, the median survival is 10–15 years [4]. Thrombosis is a major morbidity; 40% of patients develop venous thrombosis [2], and this is the most frequent cause of death [4]. At least some of the thrombotic tendency may be related to complement-mediated activation of platelets or to platelet–leukocyte complexes, which share the defect in GPI-anchored proteins. Budd–Chiari syndrome (hepatic vein thrombosis) is common, as are thromboses in unusual sites such as cerebral, dermal, hepatic and portal, mesenteric and splanchnic veins [1]. This unusual localization may also favour a role of platelets in the thrombophilic state. The most likely pathway for this appears to be the development of microparticles from complement-damaged red cells and platelets, leading to an increase of phospholipid membrane surface area in blood. Episodes of thrombosis often follow haemolytic episodes, also suggesting that haemolysis-associated changes, such as nitric oxide depletion by released haemoglobin, may play an important role in thrombogenesis [4]. This same pathway is implicated in the vascular occlusion seen in sickle cell disease, another haemolytic anaemia. Clinical dermatological features of PNH include pyoderma gangrenosum, haemorrhagic bullae, cutaneous venous thrombosis and DIC [4,5].

Anticoagulants, corticosteroids and thrombolytic therapy may be effective in treating thrombotic episodes; the role of antiplatelet therapy is unclear [6]. More recently, the use of the humanized monoclonal antibody eculizumab, directed against the C5 component of complement, to reduce haemolysis, has also resulted in reduction in thromboses from 7.37 per 100 patient years to 1.07 per hundred patient years in PNH. This supports the hypothesis that haemolysis induces a thrombophilic state, either through nitric oxide reduction by free haemoglobin or inhibition of membrane damage which might otherwise lead to microparticle formation [7,8]. The only observed risk for infection from this therapy appears to be an increase in the risk of infection by *Neisseria meningitidis* or by *N. gonorrhoeae* (0.5 cases per 100 patient years with eculizumab). Although the antibody-induced equivalent of a late complement component deficiency may lead to an increased risk of infection, the complications from such an infection appear to be less than anticipated, as in patients with inherited terminal complement deficiency. The risk of infection can also be reduced by vaccination with tetravalent meningococcal vaccine, and by counselling of patients to promote early recognition and treatment of possible meningococcal infection [7].

References

1 Parker CJ. Historical aspects of paroxysmal nocturnal haemoglobinuria: 'defining the disease'. *Br J Haematol* 2002; **117**: 3–22.
2 Rosse W, Bunn H. Hemolytic anemias and acute blood loss. In: Fauci A, Braunwald E, Isselbacher K *et al*., eds. *Harrison's Principles of Internal Medicine*. New York: McGraw-Hill, 1998: 659–71.

3 Maceijewski J, Young N, Yu M *et al*. Analysis of the expression of glycosylphosphatidylinositol anchored proteins on platelets from patients with paroxysmal nocturnal hemoglobinuria. *Thromb Res* 1996; **83**: 433–47.
4 Bessler M, Hiken J. The pathophysiology of disease in patients with paroxysmal nocturnal hemoglobinuria. *Hematology Am Soc Hematol Education Program* 2008: 104–10.
5 Rietschel RL, Lewis CW, Simmons RA, Phyliky RL. Skin lesions in paroxysmal nocturnal hemoglobinuria. *Arch Dermatol* 1978; **114**: 560–3.
6 Beutler E. Paroxysmal nocturnal hemoglobinuria. In: Beutler E, Coller B, Lichtman M *et al*., eds. *Williams' Hematology*, 6th edn. New York: McGraw-Hill, 2001: 419–24.
7 Hillmen P. The role of complement inhibition in PNH. *Hematology Am Soc Hematol Educ Program* 2008: 116–23.
8 Hillmen P, Muus P, Duhrsen U *et al*. Effect of the complement inhibitor eculizumab on thromboembolism in patients with paroxysmal nocturnal hemoglobinuria. *Blood* 2007; **110**: 4123–8.

Thrombotic thrombocytopenic purpura/haemolytic–uraemic syndrome

Thrombotic thrombocytopenic purpura (TTP) was first reported by Moschowitz in 1924 as an acquired syndrome, and subsequently as a congenital syndrome by Schulman (Upshaw–Schulman syndrome) in 1960 [1]. For many years, criteria for the diagnosis of TTP included thrombocytopenic purpura, microangiopathic haemolytic anaemia, renal dysfunction or failure, neurological abnormalities and fever, with a fatal outcome in 90% of patients [2]. Once plasma exchange proved at least sometimes effective in treating this disorder, criteria for diagnosis were pared to include only thrombocytopenia and microangiopathic haemolytic anaemia. Haemolytic–uraemic syndrome (HUS) was originally described in children with acute renal failure, microangiopathic haemolytic anaemia and, usually, thrombocytopenia, but no purpura, neurological findings or fever. Current diagnostic criteria do not distinguish between TTP and HUS. However, childhood HUS is distinguished clinically because most cases are related to enteric infection with *Escherichia coli* O157:H7, HUS developing about 1 week after diarrhoea due to this agent; most children survive without plasma exchange [2]. Epidemic forms of HUS are most common, associated with prodromal diarrhoea and with verotoxin (shigatoxin S1 or S2)-producing organisms, usually the *E. coli* strain mentioned previously, or enterococcus [3]. *Mycoplasma* can also provoke TTP. Pregnancy can induce TTP/HUS, as well as *HELLP* syndrome (haemolysis, elevated liver enzymes, low platelet count), as a complication of pre-eclampsia and eclampsia, and these may be difficult to distinguish [3]. TTP/HUS has been reported secondary to drugs (especially mitomycin C, ciclosporin, ticlopidine and quinine), after allogeneic bone marrow transplantation, and associated with autoimmune connective tissue disease (lupus erythematosus, scleroderma), vasculitis (polyarteritis nodosa), APLS [4], Sjögren's syndrome or metastatic carcinoma.

The molecular basis of TTP is a severe deficiency of a protease (ADAMTS13, 'A Disintegrin-like And Metalloprotease with Thrombospondin repeats' family of metalloproteases) that cleaves von Willebrand factor, resulting in persistence in plasma of ultralarge von Willebrand multimers secreted by endothelial cells [1–3]. Persistence of such large multimers in the circulation leads to formation of microvascular platelet thrombi. Congenital deficiency of ADAMTS13 leads to lifelong, recurrent episodes of TTP; mechanisms for acquired ADAMTS13 are still unclear, but can include acquired autoantibody. Some regard ADAMTS13 deficiency as a diagnostic feature of TTP (congenital and idiopathic), although ADAMTS13 levels are reported to be normal in most patients with secondary TTP/HUS [1,5,6]. Von Willebrand factor protease is deficient in hereditary, intermittent relapsing, intermittent acute, ticlodipine-induced and clopidogrel-induced TTP, but is normal in HUS and in transplantation-related thrombotic microangiopathy. However, not all patients with deficient von Willebrand factor protease have active TTP. ADAMTS13 deficiency rarely if ever occurs in the diarrhoea-associated HUS (D+ HUS) caused by shigatoxin-producing *E. coli*. HUS without antecedent diarrhoea is termed 'atypical HUS'; it also is typically not associated with ADAMTS13 deficiency, but frequently has alternate complement pathway abnormalities due to mutations in complement factor H, I, B, or in membrane cofactor protein [1].

Treatment options include plasma exchange with fresh frozen whole plasma or parts of plasma (e.g. cryoprecipitate-reduced plasma, high-molecular-weight fraction); corticosteroids, vincristine and antiplatelet drugs may also have a role. Outcome is usually good in childhood but less so in familial forms. As a practical matter, the response of patients to plasma exchange treatment in TTP or HUS is independent of whether they have deficient or normal levels of ADAMTS13 [7].

Microvascular platelet thrombi are characteristically seen in patients with TTP, especially in the renal and cerebral circulation [2]. Some have reported that HUS patients more often have fibrin-rich thrombi and more limited visceral vessel involvement [8]. Purpuric skin lesions are frequently mentioned in reports and reviews of TTP, but histological characterization of such cutaneous lesions is very sparse. Hyaline microthrombi composed of platelets and fibrin have been reported [9]. It seems likely from evaluation of lesional photographs that many, if not most, of the skin lesions in TTP are related to thrombocytopenia and simple haemorrhage rather than to microvascular platelet plugs as seen in the cerebral and renal vessels.

References

1 Sadler JE. Von Willebrand factor, ADAMTS13, and thrombotic thrombocytopenic purpura. *Blood* 2008; **112**: 11–8.
2 George J, Vesely S. Thrombotic thrombocytopenic purpura: from the bench to the bedside, but not yet to the community. *Ann Intern Med* 2003; **138**: 152–4.
3 Allford S, Hunt B, Rose P, Machin S. Guidelines on the diagnosis and management of the thrombotic microangiopathic haemolytic anaemias. *Br J Haematol* 2003; **120**: 556–73.
4 George J, Rizvi M. Thrombocytopenia. In: Beutler E, Lichtman M, Coller B *et al*., eds. *Williams' Hematology*, 6th edn. New York: McGraw-Hill, 2001: 1495–539.
5 Moake J. Thrombotic microangiopathies. *N Engl J Med* 2002; **347**: 589–600.
6 Veyradier A, Obert B, Houllier A *et al*. Specific von Willebrand factor-cleaving protease in thrombotic microangiopathies: a study of 111 cases. *Blood* 2001; **98**: 1765–72.
7 Vesely S, George J, Lammle B *et al.* ADAMTS13 activity in thrombotic thrombocytopenic purpura–hemolytic uremic syndrome: relation to presenting features and clinical outcomes in a prospective cohort of 142 patients. *Blood* 2003; **102**: 60–8.
8 Hosler G, Cusumano A, Hutchins G. Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome are distinct pathologic entities: a review of 56 autopsy cases. *Arch Pathol Lab Med* 2003; **127**: 834–9.
9 Zucker-Franklin D. Cutaneous manifestations of hematologic disorders. In: Fitzpatrick J, Eisen A, Wolff K *et al.*, eds. *Dermatology in General Medicine*. New York: McGraw-Hill, 1993: 1993–2003.

Occlusion due to cryogelling

Common clinical features

Occlusion syndromes triggered by cold exposure are suggested by an acral distribution of lesions of necrosis or purpura, often with retiform features, and sometimes associated with acral livedo reticularis. An acral distribution must be distinguished from a dependent distribution of lesions. Both patterns may involve hands and feet, but with a dependent pattern there are typically many more lesions on the feet and legs than on the hands. A dependent distribution of lesions suggests immune complex-mediated disease, and usually presents as classical palpable purpura or occasionally as inflammatory retiform purpura, not as bland or non-inflammatory purpura or pauci-erythematous necrosis. An acral distribution of lesions is also characteristic of erythema multiforme. However, erythema multiforme presents with target lesions, atypical target lesions or classical palpable purpura, rather than non-inflammatory retiform purpura or necrosis, and it is not associated with livedo reticularis. In addition, the acral distribution of cryo-occlusion syndromes often includes the ears and nose, sites usually unaffected by erythema multiforme. Although ill patients with immune complex vasculitis may develop dependent lesions on the posterior portions of the ears if supine due to their illness, their other lesions are typically in dependent areas as well, and there is usually no history of cold exposure as the precipitating factor. A biopsy of early lesions, before necrosis has had time to trigger a secondary vasculitic histology, should show non-inflammatory occlusion of dermal vessels with cryoprotein or agglutinated red cells.

Careful handling of serum and plasma is necessary to allow identification of cryogelling proteins, because those most likely to cause disease are those that gel at temperatures very close to normal body temperature. Likewise, identification of cryoproteins or cryoagglutinins does not prove a cryo-occlusion syndrome, because these may either gel at temperatures that are not relevant to typical cold exposure or may simply represent incidental findings. The latter is especially true of cryofibrinogens and cold agglutinins.

Cryoglobulins

Cryoglobulins, immunoglobulins that reversibly precipitate or gel in the cold, were first reported in 1933 and were named cryoglobulins in 1947 [1–4]. In 1974, Brouet *et al*. [1] proposed the now standard subset classification of cryoglobulins into types I, II and III. In the 1990s, a large proportion of cases were found to be associated with hepatitis C. Although precipitation of cryoglobulins is primarily related to reversible cold-induced denaturation of protein, other factors such as cryoglobulin concentration in the microvascular environment, pH and non-covalent binding factors also influence the likelihood and intensity of precipitation.

Type I (single molecule) cryoglobulins are single monoclonal immunoglobulins, usually IgG or IgM, less commonly IgA, and rarely Bence–Jones protein. Accounting for 10–15% of cryoglobulins, they are often associated with an underlying lymphoproliferative disorder, especially multiple myeloma or Waldenström's macroglobulinaemia [5]. As type I cryoglobulins are single proteins and are neither immune complexes nor proven to activate complement, if they are to cause vascular injury or occlusion they can do so only by cryogelling and not by immune complex vasculitis.

Types II and III, termed mixed cryoglobulins, are multiple molecule proteins, typically immune complexes, that gel under laboratory conditions (2–4°C). Unless they gel at temperatures close to body temperature, they are much more likely to cause disease as immune complexes than as cryoproteins, but they can cause disease through either or both mechanisms in any given patient. Rheumatoid factor activity (defined by anti-Fc binding) is detectable in the sera of 87–100% of patients with mixed cryoglobulinaemia [3]. Type II cryoglobulins are composed of monoclonal proteins of IgM, IgG or occasionally IgA class that bind to an antigen present in the blood, most commonly the Fc portion of polyclonal IgG molecules. Those that bind immunoglobulin (usually IgG) by anti-Fc affinity are also, by definition, rheumatoid factors, although only the IgM/anti-IgG rheumatoid factors are recognized by standard rheumatoid factor testing. In up to 95% of type II cryoglobulins with IgM as the antirheumatoid factor immunoglobulin, the IgM contains a κ light chain, which would not be expected by chance alone [3,6]. Type III mixed cryoglobulins are also most commonly rheumatoid factors, but the IgM, IgG or IgA anti-Fc antibodies in this group are polyclonal rather than monoclonal. In patients with mixed type II or III cryoglobulins, complement levels are usually reduced, especially the C4 component.

Antibodies to hepatitis C virus (HCV) have been found in more than 50% (42–98%) of patients with type II and III cryoglobulins [2–4]. Conversely, 13–54% of patients with HCV have mixed cryoglobulins detected in the laboratory, and the majority of these are type III cryoglobulins (67–91%). Of HCV-infected individuals with cryoglobulins, only 27% had clinical signs consistent with the syndrome of cryoglobulinaemia [2]. The reasons why only a fraction of HCV-infected and cryoglobulin-positive patients develop symptomatic cryoglobulinaemia are unknown.

In a multicentre Italian cooperative study of 913 patients with cryoglobulinaemia, 8.9% of all patients with symptomatic cryoglobulinaemia had lymphoproliferative disease at diagnosis [2]. Of this subset of patients, 27% had type I, 68% had type II and 5% had type III cryoglobulins. Although type I cryoglobulinaemia is usually associated with lymphoproliferative disease, it is a much less common type than types II and III; the latter two types therefore accounted for the majority of cryoglobulinaemia-associated lymphoproliferative disease in this study from a region with a high endemic rate of HCV and mixed cryoglobulinaemia.

Other syndromes are also associated with cryoglobulins detectable in serum. Patients with connective tissue disease also have higher rates of cryoglobulinaemia: it occurs in up to 25% of patients with SLE, 12.5% of patients with systemic sclerosis, 46% of patients with active rheumatoid arthritis and 17–37% of patients with Sjögren's syndrome [2]. In addition to HCV, other chronic infections such as Lyme disease, subacute bacterial endocarditis (up to 90%), Q fever, hepatitis A and B, hantavirus, cytomegalovirus, human T-cell leukaemia virus I and HIV have been reported [2,7]. Chronic inflammatory disease, such as liver cirrhosis from any cause, is also associated with a higher than expected rate of detectable cryoglobulins. The presence of cryoglobulins in serum does

not invariably predict disease; cryoglobulins were present at low titre in as high as 51% of normal individuals in one study [8]. In fact, despite detectable serum cryoglobulins in the patient groups mentioned, most will not develop symptomatic cryoglobulinaemia [2].

There are only two known ways in which cryoglobulins can result in disease. The first is by precipitation within the vascular lumen, typically cold-induced, with hyaline plug formation and minimal early-phase inflammation. Typical clinical lesions would be minimally inflammatory cutaneous infarction with or without associated livedo reticularis, or non-inflammatory retiform purpura. Since there is little evidence that cryogelling of monoclonal antibody induces complement activation, cryogelling is the only known mechanism for vascular lesions for type I cryoglobulins [5]. The second mechanism is that of immune complex vasculitis. As nearly all type II and III cryoglobulins are immune complexes, they should all be capable of inducing an immune complex vasculitis, although many do not. If they cryoprecipitate near body temperature, they could also cause vascular injury by simple occlusion, although most appear to gel at temperatures well below 37°C.

The median age at diagnosis of cryoglobulinaemia is early to middle sixth decade, with a female to male ratio of 2:1 [2]. Recurrent showers of dependent palpable purpura, sometimes with burning or itching, frequently associated with arthritis or arthralgia, is the classic presentation of mixed (type II and III) cryoglobulinaemia (the combination of purpura, asthenia and arthralgia has been termed Meltzer's triad). Patients with symptomatic cryoglobulinaemia of any type most often present with cutaneous lesions, usually purpura (in 55–100%, especially if HCV-associated) [2–4,9]. Ulceration, haemorrhagic crusts or cutaneous infarction are seen in 10–25% of patients, most often with type I cryoglobulins. Cold-induced acrocyanosis of acral areas, and non-inflammatory retiform purpura are also more typical of type I cryoglobulinaemia. Other reported cutaneous findings include acral cyanosis, Raynaud's phenomenon, urticarial lesions, ulceration and livedo reticularis [4,10,11]. Histological demonstration of non-inflammatory hyaline thrombosis is more common in patients with type I cryoglobulinaemia, but some such patients have also been reported to have cutaneous vasculitis [9]. A prospective study of biopsies of only new lesions (duration <48 h) of purpura in type I cryoglobulin patients has not been published. This leaves unresolved the issue of whether all reports of vasculitis in type I disease are those of vasculitis secondary to occlusive necrosis or ulceration. Non-cutaneous clinical findings most frequently include involvement of the joints (35–92%), peripheral nerves (17–56%), kidneys (21–29%) and liver [2–4].

Confirmation of cryoglobulins in sera requires careful handling of specimens to prevent cryoprecipitation before they can be detected. Collection of 10–20 mL of blood is suggested, and this must be kept warm and allowed to clot at 37°C for 30–60 min before centrifugation. The serum supernatant is left at 4°C for up to 7 days, with types I and II most likely to precipitate by 24 h [2,3,12]. A true cryoglobulin should once again be soluble if the sample is reheated to 37°C. Cryocrit measurements represent the percentage of the precipitate compared with the serum supernatant. Despite the presence of monoclonal protein, polyclonal gammopathy is the most frequent finding on serum protein electrophoresis of serum samples (not cryoprecipitate specimens) in patients with type II cryoglobulinaemia [2]. A more sensitive technique, such as immunofixation, is needed to identify the presence of a clonal protein.

Treatment of cryoglobulinaemia is often problematic, and prospective or controlled trials are rare [3,4]. If symptoms are mild, no treatment may be needed. If symptoms of acral lesions are precipitated by cold, then protection of affected areas may be sufficient. Measures to reduce the concentration of a type I cryoglobulin, such as plasmapheresis, plasma exchange or cytotoxic therapy, are occasionally effective, although unfortunately usually only in the short term. For immune complex-related disease, corticosteroids, cytotoxic agents or plasmapheresis may be effective, but relapse is typical once therapy is stopped. Interferon-α has been used to treat HCV-associated cryoglobulinaemia, with or without ribavarin [3,4,11]. Treatment with these agents has resulted in partial or complete remissions of vasculitic findings, but relapse often follows cessation of therapy. The therapy itself has occasionally been implicated in triggering the onset of vasculitis. In patients with mixed cryoglobulinaemia troubled primarily by recurrent cutaneous vasculitic lesions, colchicine or dapsone therapy may be of some help in reducing the frequency and severity of episodes.

Cryofibrinogenaemia

Cryofibrinogen deposits consist of a complex of fibrinogen, fibrin and fibronectin that forms on cold exposure [13]. Since cryofibrinogens can be cleaved to form fibrin, plasma rather than serum must be tested to detect these cryogelling proteins. Cryoglobulins should be present in both plasma and sera [13,14].

Cryofibrinogenaemia is common as a laboratory abnormality but is a rare cause of symptomatic clinical disease. One study found an incidence of 3% in a random sample of hospital patients, usually as an incidental finding [15]. Therefore, clinicopathological correlation is important. Cryofibrinogenaemia may be idiopathic or can be associated with malignant disorders (especially haematological), thromboembolic disease, IgA nephropathy or various inflammatory, connective tissue or infectious syndromes [16,17].

Acquired dysfibrinogenaemia very rarely may mimic a cryofibrinogen syndrome by acral occlusion, including gangrene. Interestingly, this subset of dysfibrinogenaemia appears to act by greatly increasing red cell aggregation, mimicking occlusion-inducing cold agglutinins. Blood smear preparations show marked rouleaux formation.

The most common cutaneous findings are cold intolerance, purpura, necrosis, livedo reticularis, gangrene and ulceration (Fig. 49.11) [14,16,17]. The purpura or necrosis typically has a non-inflammatory retiform purpura morphology. Biopsy specimens from skin lesions typically show thrombi in small vessels with dermal necrosis [16]. Leukocytoclastic vasculitis has been reported, but is probably due to ischaemic necrosis rather than being a cause [17]. Fibronectin may be a major component of vascular plugs in patients with cryofibrinogenaemia alone, whereas vascular occlusion in patients with both cryofibrinogens and cryoglobulins shows a predominance of cryoglobulin deposition [17]. Treatment



(a)



(b)

Fig. 49.11 Cold-induced lesions due to cryofibrinogenaemia, (a) on the ear and (b) on the foot. Acral location is typical for cryogelling. Foot lesion shows minimal erythema, retiform bullae and haemorrhage with necrosis.

of cryofibrinogenaemia should be aimed at the underlying disease, where possible, and at protecting areas from cold exposure [18]. Stanozolol, an androgenic steroid with fibrinolysis-enhancing effects, has also been used for treatment of cryofibrinogenaemia, as have other fibrinolytic agents [19].

Cold agglutinin-related cutaneous occlusion

Cold agglutinins are immunoglobulins that are able to agglutinate red blood cells below normal body temperatures. As agglutination of red blood cells depends on binding of antibody to more than one cell at a time, pentavalent IgM is almost exclusively responsible for this phenomenon. Just as with cryoglobulins, there are both monoclonal and polyclonal cold agglutinins, usually directed at I, i or Pr antigens of erythrocytes [20,21]. Monoclonal cold agglutinins are idiopathic or secondary to malignant lymphoproliferative diseases. Polyclonal cold agglutinins are usually associated with infection, especially due to *Mycoplasma pneumoniae*, less often HCV, parvovirus B19 or leptospiral infections.

Just as with many cryoglobulins and most cryofibrinogens, cold agglutinins are most likely to be asymptomatic. When responsible for disease, reversible acrocyanosis secondary to cold-induced acral agglutination is most common. Livedo reticularis, Raynaud's phenomenon, cold urticaria and rarely cutaneous necrosis may occur. In addition to acral lesions on environmental cold exposure, cold intravenous infusions can also trigger localized cutaneous necrosis [20]. Cold agglutinins can induce complement activation after cold-induced binding to red blood cells, followed by lysis and haemolytic anaemia, independent of occlusive syndromes from agglutination.

Patients with cold-induced agglutination syndromes must avoid cold exposure. Therapies such as corticosteroids, cytotoxic agents, danazol, rituxan or interferon-α have been occasionally beneficial [21].

References

1 Brouet JC, Clauvel JP, Danon F *et al*. Biologic and clinical significance of cryoglobulins: a report of 86 cases. *Am J Med* 1974; **57**: 775–88.
2 Dispenzieri A, Gorevic P. Cryoglobulinemia. *Hematol Oncol Clin North Am* 1999; **13**: 1315–49.
3 Dammacco F, Sansonno D, Piccoli C *et al*. The cryoglobulins: an overview. *Eur J Clin Invest* 2001; **31**: 628–38.
4 Rieu V, Cohen P, Andre M *et al*. Characteristics and outcome of 49 patients with symptomatic cryoglobulinaemia. *Rheumatology* 2002; **41**: 290–300.
5 Davis M, Su W. Cryoglobulinemia: recent findings in cutaneous and extracutaneous manifestations. *Int J Dermatol* 1996; **35**: 240–8.
6 Grey H, Kohler P. Cryoimmunoglobulins. *Semin Hematol* 1973; **10**: 87.
7 Bonnet F, Pineau J, Taupin J *et al*. Prevalence of cryoglobulinemia and serological markers of autoimmunity in human immunodeficiency virus infected individuals: a cross-sectional study of 97 patients. *J Rheumatol* 2003; **30**: 2005–10.
8 Cream J. Cryoglobulins in vasculitis. *Clin Exp Immunol* 1972; **10**: 117.
9 Cohen SJ, Pittelkow MR, Su WPD. Cutaneous manifestations of cryoglobulinemia: clinical and histopathologic study of seventy-two patients. *J Am Acad Dermatol* 1991; **25**: 21–7.
10 Speight E, Lawrence C. Reticulate purpura, cryoglobulinaemia and livedo reticularis. *Br J Dermatol* 1993; **129**: 319–23.
11 Burke E, Humphrey R, Horn T. Nonhealing ulcers on the extremities: cryoglobulinemia. *Arch Dermatol* 1997; **133**: 911–4.
12 Kallemuchikkal U, Gorevic P. Evaluation of cryoglobulins. *Arch Pathol Lab Med* 1999; **123**: 119–25.
13 Beightler E, Diven D, Sanchez R *et al*. Thrombotic vasculopathy associated with cryofibrinogenemia. *J Am Acad Dermatol* 1991; **24**: 342–5.
14 Williamson A, Cone L, Huard G. Spontaneous necrosis of the skin associated with cryofibrinogenemia, cryoglobulinemia, and homocystinuria. *Ann Vasc Surg* 1996; **10**: 365–9.
15 Smith A, Arkin C. Cryofibrinogenemia: incidence, clinical correlations, and a review of the literature. *Am J Clin Pathol* 1972; **58**: 524–30.
16 Jantunen E, Soppi E, Neittaanmaki H *et al*. Essential cryofibrinogenaemia, leukocytoclastic vasculitis and chronic purpura. *J Intern Med* 1993; **234**: 331–4.
17 Blain H, Cacoub P, Musset L *et al*. Cryofibrinogenaemia: a study of 49 patients. *Clin Exp Immunol* 2000; **120**: 253–60.
18 Kwaan H, Bongu A. The hyperviscosity syndromes. *Semin Thromb Hemost* 1999; **25**: 199–208.
19 Falanga V, Kirsner R, Eaglstein W *et al*. Stanozolol in treatment of leg ulcers due to cryofibrinogenaemia. *Lancet* 1991; **338**: 347–8.
20 Stone MS, Piette WW, Davey WP. Cutaneous necrosis at sites of transfusion: cold agglutinin disease (letter). *J Am Acad Dermatol* 1988; **19**: 356–7.
21 Lauchli S, Widmer L, Lautenschlager S. Cold agglutinin disease: the importance of cutaneous signs. *Dermatology* 2001; **202**: 356–8.

Occlusion due to vessel-invasive organisms

Ecthyma gangrenosum

Ecthyma gangrenosum is a cutaneous syndrome characterized by usually painless, minimally erythematous macules or thin papules or plaques that typically progress to bullous lesions, followed by haemorrhage and necrosis, often with retiform extensions from lesional margins [1]. The anogenital area is a frequent site of involvement, but lesions can develop anywhere and at widespread

cutaneous sites [2,3]. Patients are almost invariably immunocompromised, and the infectious agent is usually *Pseudomonas aeruginosa*.

In a small series of cases of ecythma gangrenosum, all eight patients had haematological disease and were receiving immunosuppressive medications [4]. All had positive blood cultures, seven of which were *Ps. aeruginosa*. Biopsies of ecthyma gangrenosum reveal minimal vascular neutrophilic infiltration despite necrotizing vessel injury, and special stains show extensive bacillary infiltration of the perivascular region, the adventitia and the media of larger subcutaneous arterioles, with sparing of the lumen and intima [3–5]. Other bacterial-induced vasculitides tend to show bacterial invasion of the vessel lumen and fibrin thrombi.

Prompt recognition of this syndrome is critical, because prognosis correlates partly with delay in instituting effective intravenous antipseudomonal therapy. Other factors correlating with poor prognosis include multiple lesions and neutropenia [4]. Other organisms that may induce ecthyma gangrenosum-like lesions include *Ps. cepacia* and *Ps. maltophilia*, *Serratia marcescens*, *Aeromonas hydrophila*, *Klebsiella pneumoniae*, *E. coli*, *Vibrio vulnificus*, *Morganella morganii*, *Staphylococcus aureus*, *Mucor*, *Aspergillus fumigatus*, *Fusarium*, *Scytalidium dimidiatum*, *Candida albicans* and *Moraxella* [6,7].

Lucio's phenomenon

Lucio's phenomenon (erythema necroticans) is a rare syndrome almost exclusively limited to leprosy patients from Mexico and Central America, but is rarely reported from Cuba, South America, the USA, India, Polynesia, South Africa and South-East Asia [8–10]. It is a type 2 reaction that may be fatal, despite being the presenting feature of leprosy for many patients who develop this reaction. Lesions may be recurrent and sometimes cyclical over periods of 2 months to 10 years, most often on the legs, but occasionally on the arms and trunk [9]. Lesions usually begin as painful purpuric macules, plaques or vesicles, often ulcerate and heal with atrophic scars. Unlike erythema nodosum leprosum, it is restricted to patients with diffuse non-nodular lepromatous leprosy, is not associated with fever, leukocytosis or tenderness, and fails to respond to thalidomide.

At least in some reports, some lesions appear to induce non-inflammatory retiform purpura, eschar or ulceration [8,9]. Ulceration of lesions is common. Histological findings include either leukocytoclastic vasculitis or endothelial proliferation and thrombus formation in dermal or subcutaneous vessels, with a sparse lymphocytic infiltrate [8–10]. How often vasculitic change is secondary to necrosis or ulceration is unclear, but at least in some cases an occlusive mechanism for purpura and necrosis seems likely. Aggregates of bacilli within proliferating cells are evident on acid-fast stain of biopsy material [9,10].

Treatment includes the standard multidrug therapy for lepromatous leprosy (rifampicin, clofazimine and dapsone). Control of infection and attention to fluid and electrolyte balance are important. Prednisone, thalidomide and clofazimine may all be required to control the reaction. Response to treatment is often reported as poor, with severe morbidity and frequent deaths, but numbers of reported cases are small.

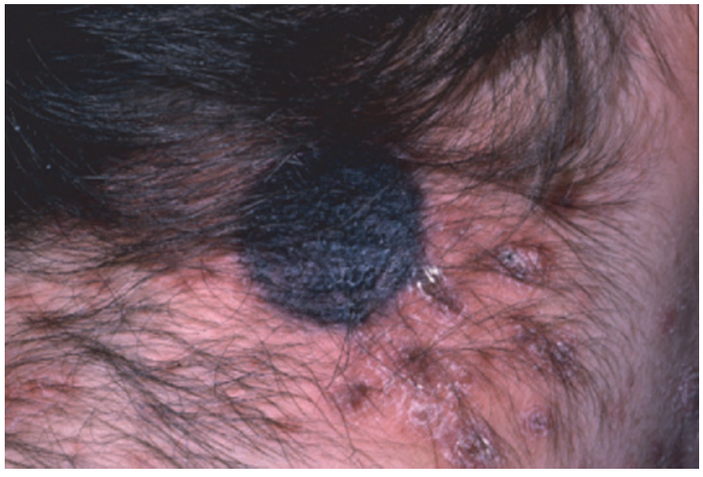


Fig. 49.12 Necrotic cutaneous lesion due to zygomycosis: invasion of vessel walls was apparent histologically.

Vessel-invasive fungi

As alluded to in the ecythema gangrenosum section, fungi may cause overwhelming infections in immunocompromised patients, often with cutaneous lesions, some of which may become purpuric or necrotic due to vessel-invasive organisms and thrombosis. *Aspergillus* and *Mucor* are two of the most commonly reported fungal groups to cause such vessel-invasive lesions.

Cutaneous lesions of *Aspergillus* may be either primary or secondary from haematogenous dissemination. Primary lesions typically occur at intravenous infusion sites, tubing sites secured by tape, or in skin in chronic contact with a colonized intravenous board [11,12]. Primary cutaneous aspergillosis can occur in immunocompetent patients, as well as in patients with burns or surgical wounds. Cutaneous lesions from systemic involvement have been divided into five categories: (i) a solitary necrotizing plaque; (ii) a subcutaneous abscess or granuloma; (iii) eruptive maculopapules with suppurative, vegetating or necrobiotic features; (iv) erythematous or exanthem-like reactions; and (v) progressive confluent granulomas [12,13]. Organisms in lesions appear as septate hyphae with acute-angle branching, invading blood vessels and surrounding tissues, often with minimal inflammation [13]. *Aspergillus fumigatus* is the most common cause of colonization and of disseminated infection by the *Aspergillus* group of fungi. *Fusarium* infections are increasing in frequency in patients with haematological malignancy; 72–91% of patients with this infection have skin lesions, which may be either metastatic or primary [14]. Metastatic skin lesions are described as either subcutaneous nodules, usually painful, or ecthyma gangrenosum-like.

The class Zygomycetes includes *Mucor*, *Absidia* and *Rhizopus* organisms, which can cause identical clinical manifestations (Fig. 49.12) [11]. Lesions may be either primary or secondary to disseminated disease, and include superficial vesiculopustules, ulcerating gangrenous lesions, purpuric nodules, cellulitis and necrotic ulcers. These organisms easily invade the epidermis and spread rapidly in the dermis, with vessel invasion by very large and long non-septate hyphae, resulting in thrombosis and infarction [15].

Response to therapy in these types of infection is relatively refractory. With *Fusarium* infections, for example, response rates are 30–48% with current therapies and support measures [14].

Disseminated strongyloidiasis

Strongyloides stercoralis is the nematode responsible for the human parasitic infestation known as strongyloidiasis. Affecting 100 million people worldwide, it is endemic in tropical or subtropical soil that is contaminated by faeces, in some temperate-zone areas such as the rural south-east and Appalachia of the USA, or in closed communities such as immigrant populations, close-quartered military personnel or institutions [16]. Filiform larvae from contaminated soil penetrate the skin, enter the blood vessels, exit through the lungs and migrate to the glottis, where they are swallowed [16–18]. They mature and reproduce in the upper small bowel, with hatching of non-infective (rhabditiform) larvae. Transformation of these into infective larvae can lead to autoinfection through penetration of intestinal mucosa or perianal skin [18]. Skin lesions with simple infection include papules or erythematous serpiginous tracts, which can extend several centimetres per hour and represent cutaneous migration of the larvae (larva currens).

In immunocompromised patients, including those on corticosteroids, hyperinfection and dissemination of organisms can occur [16]. In this setting, the diagnosis is usually made through examination of stool samples, and skin lesions are uncommon. However, with such overwhelming infection, petechiae, purpura and reticulated purpuric skin lesions have been described [16,17,19,20]. These lesions may be widespread but may cluster, particularly in the periumbilical region where they are said to have a thumb-print appearance. Biopsy of purpuric lesions has shown larvae within capillaries and between collagen bundles in the dermis, with extravasated red cells [20].

Mortality in disseminated strongyloidiasis is high, up to 70–90% [16]. Treatment is with oral thiabendazole, and may need to be prolonged in immunocompromised patients [17,18].

References

1 Robson K, Piette W. The presentation and differential diagnosis of cutaneous vascular occlusion syndromes. *Adv Dermatol* 1999; **15**: 153–82.

2 Boisseau A, Sarlangue J, Perel Y *et al.* Perineal ecthyma gangrenosum in infancy and early childhood: septicemic and nonsepticemic forms. *J Am Acad Dermatol* 1992; **27**: 415–8.

3 Song W, Kim Y, Park H, Cinn Y. Ecthyma gangrenosum without bacteremia in a leukemic patient. *Clin Exp Dermatol* 2001; **26**: 395–7.

4 Greene S, Su W, Muller S. Ecthyma gangrenosum: report of clinical, histopathologic, and bacteriologic aspects of eight cases. *J Am Acad Dermatol* 1984; **11**: 781–7.

5 Lucas S. Bacterial disease. In: Elder D, Elenitsas R, Jaworsky C, Johnson B Jr, eds. *Lever's Histopathology of the Skin*, 8th edn. Philadelphia: Lippincott-Raven, 1997: 465.

6 Prins C, Chavaz P, Tamm K *et al.* Ecthyma gangrenosum-like lesions: a sign of disseminated *Fusarium* infection in the neutropenic patient. *Clin Exp Immunol* 1995; **20**: 428–30.

7 Del Pozo J, Garcia-Silva J, Almagro M *et al.* Ecthyma gangrenosum-like eruption associated with *Morganella morganii* infection. *Br J Dermatol* 1998; **139**: 520–1.

8 Ang P, Tay Y, Ng S, Seow C. Fatal Lucio's phenomenon in 2 patients with previously undiagnosed leprosy. *J Am Acad Dermatol* 2003; **48**: 958–61.

9 Rea T, Levan N. Lucio's phenomenon and diffuse nonnodular lepromatous leprosy. *Arch Dermatol* 1978; **114**: 1023–8.

10 Pursley T, Jacobson R, Apisarnthanarax P. Lucio's phenomenon. *Arch Dermatol* 1980; **116**: 201–4.

11 Elewski B, Radentz W, Gupta A. Opportunistic mycoses. In: Elewski B, ed. *Cutaneous Fungal Infections*. Malden, MA: Blackwell Science, 1998: 225–59.

12 Prystowsky S, Vogelstein B, Ettinger D *et al.* Invasive aspergillosis. *N Engl J Med* 1976; **295**: 655–8.

13 Galimberti R, Kowalczuk A, Hidalgo Parra I *et al.* Cutaneous aspergillosis: a report of six cases. *Br J Dermatol* 1998; **139**: 522–6.

14 Boutati E, Anaissie E. *Fusarium*, a significant emerging pathogen in patients with hematologic malignancy. Ten years' experience at a cancer center and implications for management. *Blood* 1997; **90**: 999–1008.

15 Meyer R, Kaplan M, Ong M *et al.* Cutaneous lesions in disseminated mucormycosis. *JAMA* 1973; **225**: 737–8.

16 Ly M, Bethel S, Usmani A, Lambert D. Cutaneous *Strongyloides stercoralis* infection: an unusual presentation. *J Am Acad Dermatol* 2003; **49**: S157–S160.

17 Kalb R, Grossman M. Periumbilical purpura in disseminated strongyloidiasis. *JAMA* 1986; **256**: 1170–1.

18 Kalter D, Meinking T, Garcia E *et al.* Parasitic diseases. In: Arndt K, Leboit P, Robinson J *et al.*, eds. *Cutaneous Medicine and Surgery: an Integrated Program in Dermatology.* Philadelphia: Saunders, 1996: 1172–89.

19 Purvis R, Beightler E, Diven D *et al. Strongyloides* hyperinfection presenting with petechiae and purpura. *Int J Dermatol* 1992; **31**: 169–71.

20 Ronan S, Reddy R, Manaligod J *et al.* Disseminated strongyloidiasis presenting as purpura. *J Am Acad Dermatol* 1989; **21**: 1123–5.

Occlusion due to embolus

Cholesterol embolus

Aetiology. The most commonly diagnosed cutaneous embolic syndrome is cholesterol embolus, which occurs secondary to fragmentation of ulcerated arteriosclerotic plaques, with distal cutaneous and visceral vessel obstruction. As it occurs secondary to atheromatous plaques, it is no surprise that cholesterol embolus is a syndrome reported primarily in men aged 50 years or older, and is associated with peripheral vascular disease and the known risk factors for atherosclerosis such as diabetes, hypertension and smoking [1,2]. Although cholesterol embolus may be spontaneous, known triggers include angiography, angioplasty, vascular surgery, intra-aortic pump placement, cardiopulmonary resuscitation (all inducing traumatic rupture of plaques, usually within hours or days), thrombolytic therapy (acute clot lysis in plaque with release of friable plaque within hours or days) and anticoagulation (slow reduction of clot with release of plaque fragments, usually after at least 2 months of therapy) [2,3]. Blue toe syndrome associated with coumadin use is a syndrome of cholesterol embolus and not of coumadin necrosis.

Clinical features. There are two 'classic' clinical triads of cholesterol embolus. The first comprises leg or foot pain, livedo reticularis and preservation of good peripheral pulses [3]. The second comprises livedo reticularis, renal insufficiency and eosinophilia [4]. Cutaneous findings are frequent in patients recognized as experiencing episodes of cholesterol embolus. Reported in 35% of patients in one series, findings include livedo reticularis (49%), gangrene (35%), cyanosis (28%), ulceration (17%), nodules (10%) and purpura (9%) [1]. Additional clinical findings include fever, myalgia, altered mental status, sudden-onset arterial hypertension, gastrointestinal ulceration and renal insufficiency that may progress to renal failure [3,4].

The incidence of cholesterol embolization syndrome (CES) following vascular procedures has ranged from 0.15% to 30%, with large retrospective studies reporting figures of 0.6–0.9% [5–7]. Autopsy studies have shown cholesterol emboli in 77% of patients who underwent aortic aneurysm resection [6]. A prospective study of 1786 consecutive patients aged over 40 years who underwent left-heart catheterization found an incidence of cholesterol embolus of 1.4%, with nearly half having definite CES and the remainder having possible CES with primarily renal abnormalities [5]. Patients with cutaneous findings (livedo reticularis, blue toe syndrome or digital gangrene) were considered to have definite CES and comprised 48% of the total. In-hospital mortality was 16% and was associated with progressive renal dysfunction.

Investigation. Eosinophilia is a frequent finding in CES, occurring in up to 80% of patients, and may be related to generation of the C5 component of complement [5,8]. Pre-procedure elevation in serum levels of C-reactive protein has been associated with an increased risk of post-procedure CES [5]. Additional laboratory findings may include leukocytosis, thrombocytopenia, pyuria, eosinophiluria, blood-positive urine or stool, elevated values of red cell sedimentation rate, creatinine, urea and amylase, and decreased serum levels of complement [1,2,8].

The traditional recommendation for cutaneous biopsy of livedo reticularis has been elliptical excisions centred on normal skin areas within rings of livedo reticularis, deep enough to include an ample specimen of subcutaneous fat. However, our experience is that careful examination of the livedo reticularis reveals that many patients will have retiform purpura, and such areas are high-yield biopsy sites for demonstrating the diagnostic cholesterol crystals on histological examination. On histological examination, the arteriole involved in the skin is usually at the dermosubcutaneous junction, with elongated clefts within small-vessel lumina along with thrombi [9]. The clefts result from fixation-related dissolving of cholesterol crystals. In experimentally produced cholesterol embolus, a mixed inflammatory infiltrate may be seen in arterial walls within 24–48 h, followed by multinucleated histiocytes within 3–6 days, and subsequent occasional intimal fibrosis.

Treatment. Treatment of cholesterol emboli involves trying to minimize the risk of further embolization (removal of remaining plaque or perhaps stenting of an atheromatous segment of a major vessel), minimizing damage to end organs, and preventive therapies aimed at slowing progression of atheromatous disease. Statins, iloprost (prostacyclin analogue), pentoxifylline (oxpentifylline) and steroids have been reported as having limited success in therapeutic interventions to minimize organ damage [6,10]. As anticoagulant use may precipitate cholesterol emboli, avoidance of these agents in patients with known CES seems prudent [3,7]. However, some types of cardiac surgery that may precipitate CES may also require post-operative anticoagulation, for example valvular prostheses [3,7].

Oxalate crystal embolus

Oxalate crystals are a rare cause of symptomatic emboli, but can mimic the cutaneous findings of cholesterol embolism. Although primary hyperoxaluria is rare, it is the most common cause of oxalate crystal embolus. Two enzyme defects are associated with primary hyperoxaluria: type I hyperoxaluria (glycolic aciduria) is due to deficiency of the hepatic peroxisomal enzyme alanine: glyoxylate aminotransferase; type II hyperoxaluria (L-glyceric aciduria) is due to diminished activity of D-glyceric acid dehydrogenase [11,12]. Absorptive hyperoxaluria is also reported due to idiopathic intestinal hyperabsorption of oxalate. Secondary hyperoxaluria can be due to excessive intake of oxalate or its precursors (ethylene glycol, methoxyflurane anaesthesia, very-high-dose ascorbic acid), pyridoxine deficiency, ileal resection, some intestinal diseases or long-term haemodialysis [11,13].

Type I hyperoxaluria is the most common and has three forms. The infantile form has no history of nephrolithiasis but has rapidly progressive renal failure. The juvenile form is the common type I subset. In this group, recurrent calcium oxalate nephrolithiasis precedes renal failure. Patients with the adult form typically present with renal failure and later develop complications of oxalate tissue deposition.

Cutaneous manifestations of primary hyperoxaluria are primarily those of oxalate crystal embolization: livedo reticularis, acrocyanosis, and peripheral gangrene, purpura or ulcerations [12,13]. Secondary hyperoxaluria, especially when due to long-term dialysis, is more likely to lead to extravascular cutaneous deposits of oxalate, producing calcified cutaneous nodules, or firm miliary papules that tend to form on the palmar aspect of the fingers [14].

Cardiac sources of embolization

Atrial myxomas, marantic endocarditis and septic endocarditis can be associated with cutaneous embolic phenomena. Although rare, atrial myxomas are the most common benign cardiac tumour, with an estimated incidence of 0.03% [15] and onset usually between the third and sixth decades [16]. The left atrium is the most frequent tumour site. Symptoms may partly mimic those of infectious endocarditis, connective tissue disease, vasculitis or rheumatic fever, with constitutional symptoms such as fever, malaise, arthralgia or weight loss. Obstruction of intracardiac blood flow mimicking valvular disease or embolic phenomena may also occur. Lentigines may be a cutaneous finding in the hereditary NAME or LAMB syndrome, which is associated with cardiac myxomas. Cutaneous findings of myxomatous emboli include livedo reticularis, splinter haemorrhages, Raynaud's phenomenon, an acral papular eruption with claudication, serpiginous or annular purpuric lesions of the fingertips, red–violet malar flush, petechiae of hands and feet, or toe necrosis [16–18]. Histology can confirm myxomatous emboli, but finding the emboli may require serial sectioning and multiple biopsies [16,19]. An echocardiogram is useful in evaluating patients with a history or physical examination compatible with emboli. Atrial myxomas require surgical treatment.

Marantic endocarditis results in the attachment of fibrin vegetations to heart valve leaflets, similar to those seen in acute rheumatic endocarditis and Libman–Sacks (APLS) valve disease, and these vegetations can embolize [19]. Infective endocarditis can also produce emboli from vegetations, but these are usually associated with acute bacterial endocarditis. Lesions in subacute bacterial

endocarditis may be from either emboli or immune complex-related vasculitis. Idiopathic hypereosinophilic syndrome is associated with intracardiac mural thrombi, which can also produce emboli [20,21]. Documentation of cutaneous emboli is limited, with clinical lesions described as splinter haemorrhages, non-blanching livedoid discoloration, or necrotic, blistering or purpuric lesions [22–24].

Crystal globulin vasculopathy is a rare syndrome, usually associated with IgG or light-chain paraproteins, that can produce intravascular occlusion by spontaneous crystallization [25,26]. This syndrome results in rapidly progressive renal failure, polyarthropathy, peripheral neuropathy and skin lesions. Cutaneous lesions include ulcerations, petechiae and ecchymoses, with intravascular thrombus and crystalline deposits [27].

Other emboli

Petechiae, which may be few or very numerous, are an important sign of fat embolism [28,29]. They occur particularly on the upper part of the body 2–3 days after a major injury and are an important clue to this diagnosis. Minute fat emboli have been found within the vessels at the sites of the petechiae.

Emboli may also occur from tumours at sites other than the cardiac myxomas discussed above.

References

1 Falanga V, Fine M, Kapoor W. The cutaneous manifestations of cholesterol crystal embolization. *Arch Dermatol* 1986; **122**: 1194–8.
2 Chandrashekariah R, Fresko O, Lynfield Y. Cholesterol embolism: a case report and review of the literature. *Cutis* 2001; **68**: 263–7.
3 Pennington M, Yeager J, Skelton H, Smith K. Cholesterol embolization syndrome: cutaneous histopathological features and the variable onset of symptoms in patients with different risk factors. *Br J Dermatol* 2002; **146**: 511–7.
4 Mieszczanska H, Lazar J, Marzo K, Cunha B. Cholesterol emboli mimicking acute bacterial endocarditis. *Heart Lung J Acute Crit Care* 2002; **31**: 452–4.
5 Fukumoto Y, Tsutsui H, Tsuchihashi M *et al*. The incidence and risk factors of cholesterol embolization syndrome, a complication of cardiac catheterization: a prospective study. *J Am Coll Cardiol* 2003; **42**: 211–6.
6 Bashore T, Gehrig T. Cholesterol emboli after invasive cardiac procedures. *J Am Coll Cardiol* 2003; **42**: 217–8.
7 Doty J, Wilentz R, Salazar J *et al*. Atheroembolism in cardiac surgery. *Ann Thorac Surg* 2003; **75**: 1221–6.
8 Lawson J. Cholesterol crystal embolization: more common than we thought? *Am J Gastroenterol* 2001; **96**: 3230–2.
9 Kang K, Botella R, White C Jr. Subtle clues to the diagnosis of cholesterol embolism. *Am J Dermatopathol* 1996; **18**: 380–4.
10 Elinav E, Chajek-Shaul T, Stern M. Improvement in cholesterol emboli syndrome after iloprost therapy. *BMJ* 2002; **324**: 268–9.
11 Bogle M, Teller C, Tschen J *et al*. Primary hyperoxaluria in a 27-year-old woman. *J Am Acad Dermatol* 2003; **49**: 725–8.
12 Marconi V, Mofid M, McCall C *et al*. Primary hyperoxaluria: report of a patient with livedo reticularis and digital infarcts. *J Am Acad Dermatol* 2002; **46**: S16–S18.
13 Greer KE, Cooper PH, Campbell F *et al*. Primary oxalosis with livedo reticularis. *Arch Dermatol* 1980; **116**: 213–4.
14 Ohtake N, Uchiyama H, Furue M, Tamaki K. Secondary cutaneous oxalosis: cutaneous deposition of calcium oxalate dihydrate after long-term hemodialysis. *J Am Acad Dermatol* 1994; **31**: 368–72.
15 Reed R, Utz M, Terezakis N. Embolic and metastatic cardiac myxoma. *Am J Dermatopathol* 1989; **11**: 157–65.
16 Greeson D, Wright J, Zanolli M. Cutaneous findings associated with cardiac myxomas. *Cutis* 1998; **62**: 275–80.
17 Feldman A, Keeling J. Cutaneous manifestation of atrial myxoma. *J Am Acad Dermatol* 1989; **21**: 1080–4.
18 Abraham Z, Rozenbaum M, Rosner I *et al*. Cutaneous eruption in a patient with cardiac myxoma. *J Dermatol* 1995; **22**: 276–8.
19 Young R, Zalneraitis E. Marantic endocarditis in children and young adults: clinical and pathological findings. *Stroke* 1981; **12**: 635–9.
20 Ommen S, Seward J, Tajik A. Clinical and echocardiographic features of hypereosinophilic syndromes. *Am J Cardiol* 2000; **86**: 110–3.
21 Bishop G, Bergin J, Kramer C. Hypereosinophilic syndrome and restrictive cardiomyopathy due to apical thrombi. *Circulation* 2001; **104**: E3–E4.
22 Fitzpatrick J, Johnson C, Simon P, Owenby J. Cutaneous microthrombi: a histologic clue to the diagnosis of hypereosinophilic syndrome. *Am J Dermatopathol* 1987; **9**: 419–22.
23 Sanchez J, Padilla M. Hypereosinophilic syndrome. *Cutis* 1982; **29**: 490–4.
24 Weller P, Bubley G. The idiopathic hypereosinophilic syndrome. *Blood* 1994; **83**: 2759–79.
25 Stone G, Wall B, Oppliger I *et al*. A vasculopathy with deposition of lambda light chain crystals. *Ann Intern Med* 1989; **110**: 275–8.
26 Hasegawa H, Ozawa T, Tada N *et al*. Multiple myeloma-associated systemic vasculopathy due to crystalglobulin or polyarteritis nodosa. *Arthritis Rheum* 1996; **39**: 330–4.
27 Ball N, Wickert W, Marx L *et al*. Crystalglobulinemia syndrome: a manifestation of multiple myeloma. *Cancer* 1993; **71**: 1231–4.
28 Sevitt S. The significance and classification of fat-embolism. *Lancet* 1960; **ii**: 825–8.
29 Mellor A, Soni N. Fat embolism. *Anaesthesia* 2001; **56**: 145–54.

Systemic coagulopathies with cutaneous predilection

There are several systemic coagulopathies that have a predilection for the cutaneous microvasculature. Cutaneous lesions may occasionally be a minor feature of a multiorgan syndrome, the most prominent findings of multiorgan involvement or sometimes the sole target of occlusion. The importance of recognizing these syndromes is critical in order to begin early, and sometimes syndrome-specific, therapy. There are two natural anticoagulant pathways that exist in humans. The most well known, the antithrombin III–heparin/heparan pathway, is important for primarily venous large-vessel thrombosis. The only cutaneous lesions related to antithrombin III disorders are stasis ulcers secondary to recurrent venous thrombosis with venous insufficiency. In contrast, disorders of the thrombomodulin–protein C/S anticoagulant pathway are important causes of severe cutaneous occlusion syndromes.

An understanding of this pathway is important in diagnosing and treating these syndromes. The end point of the coagulation cascade is conversion of prothrombin to thrombin, which rapidly catalyses the conversion of fibrinogen to fibrin and clot formation. The procoagulant role of thrombin is well known; less well known is its critical role in anticoagulation. When thrombin fails to bind to procoagulant sites on membranes and binds instead to the membrane protein receptor thrombomodulin, this powerful prothrombotic molecule undergoes a remarkable transformation. Bound to thrombomodulin, thrombin becomes ineffective at binding and activating clotting factors, and instead rapidly converts protein C in the plasma to activated protein C. Activated protein C, stabilized by certain phospholipids and by protein S, down-regulates clotting by cleaving circulating activated clotting factors, including factor VIIIa and most importantly factor Va. It thus exerts an anticoagulant effect; deficiency of protein C, or of its co-factor protein S, therefore creates a procoagulant tendency. The factor V Leiden mutation renders the factor V Leiden molecule much less sensitive to cleavage by activated protein C (APC

resistance); about 5% of the UK and Caucasian North American population are heterozygous for this mutation (reported incidence is highest in Cyprus, Sweden and Turkey at 10–15%, and lowest incidence in Asia and Africa, and in populations of those ethnicities). This protection from cleavage means that activated factor V Leiden remains longer in the plasma and continues to enhance coagulation. It would be expected then that factor V Leiden mutation should be synergistic with deficiencies in the thrombomodulin–protein C pathway. In fact, in some kindreds of protein C-deficient families, the presence of the factor V Leiden mutation appears to be an important predictor for who will develop large-vessel thrombosis in individuals with similar levels of protein C deficiency.

Another major cluster of systemic coagulopathies with cutaneous microvascular occlusion are those related to lupus anticoagulant activity and APLS. The mechanisms for clotting in this group are less well understood, and will be addressed following discussion of protein C/S-related syndromes.

Protein C/protein S-related disease

Neonatal purpura fulminans: homozygous protein C or protein S deficiency

Protein C and S deficiencies can be inherited autosomally with variable penetrance. Patients who are heterozygous for deficiency may develop repeated venous thrombosis or pulmonary embolism early in adult life, or may be asymptomatic [1,2]. One variable affecting the likelihood of thrombosis in these individuals is known—the previously mentioned co-inheritance of homozygous or heterozygous factor V Leiden mutations [3,4]. The frequency of homozygous protein C deficiency is estimated at 1 in 250 000–500 000 births [1]. Homozygous deficiency of either protein C or protein S is associated with neonatal purpura fulminans as well as with cerebral and ophthalmic vessel thrombosis. Retiform (stellate) purpura and necrosis is the most typical cutaneous finding that results from thrombosis within the cutaneous microvasculature. Skin lesions typically begin within a few hours to 5 days after birth, and are most commonly distributed on the extremities, abdomen, buttocks and scalp; they may localize to sites of pressure or previous trauma [1,5,6]. Laboratory findings are consistent with DIC, with evidence of consumption of clotting factors (prolonged partial thromboplastin time, PTT), clot lysis (elevated fibrin split products) and often thrombocytopenia. In the absence of appropriate therapy, lesions invariably progress to full-thickness cutaneous necrosis.

Traditional treatment included fresh frozen plasma to try to replace deficient protein C or S, or oral anticoagulants to reduce procoagulant factors. More recently, protein C and activated protein C concentrates have been used for treatment of both acute disease and as prophylaxis against subsequent episodes [7,8].

Coumadin (coumarin, warfarin) necrosis: severe acquired protein C dysfunction

Coumadin necrosis usually presents as the sudden onset of pain within affected areas 3–5 days after beginning coumadin therapy, followed by well-demarcated erythema progressing to haemorrhage, necrosis and often haemorrhagic bullae or eschar [9]. Although coumadin necrosis may rarely involve acral areas, acral cutaneous purpura in patients on coumadin is more likely to be due to cholesterol embolus—so-called purple (blue) toe syndrome. The risk of coumadin necrosis is increased if loading doses (10 mg or more) of warfarin are used and if a second form of anticoagulation such as heparin therapy is not used to cover the initial phase of anticoagulant therapy [10,11]. Warfarin (coumadin) necrosis is more likely to occur in areas with abundant fatty subcutis, such as breast, hip, buttocks and thigh [9,10]. The peak incidence is between the sixth and seventh decades, and is four times higher in women.

The therapeutic effect of coumadin is due to inhibition of γ-carboxylation of the vitamin K-dependent coagulant factors II, VII, IX and X. Although these factors are still produced and may be antigenically detected within the plasma, without γ-carboxylation they are dysfunctional. Importantly, protein C and protein S are also vitamin K-dependent plasma factors, and their inhibition can lead to a prothrombotic state. Protein C and factor VII, with half-lives of roughly 5 h, are particularly vulnerable to early inhibition, whereas protein S and the remaining procoagulant factors with much longer half-lives remain active for a considerably longer period [11,12]. There is thus a period, after the early inhibition phase, when the anticoagulant effect of protein C has been inhibited but there is an excess of uninhibited procoagulant clotting factors. Although up to one-third of patients with coumadin-induced skin necrosis may have partial protein C deficiency, the majority of cases appear unrelated to inherited deficiencies of protein C [10]. As coumadin action mimics that of vitamin K deficiency, it would be expected that depletion of vitamin K should result in coumadin necrosis-like findings, but this has not been documented.

Restoration of protein C activity can be accomplished through protein C concentrates, and presumably also through the use of activated protein C. If these are not available, heparin therapy has been recommended.

Sepsis-related purpura fulminans (bland retiform purpura) with DIC: acquired severe protein C deficiency

The term ‘purpura fulminans’ is used by physicians for many different situations. It was originally coined in 1887 to describe a syndrome occurring days to a few weeks after some preceding infection, especially varicella zoster or streptococcal infections (now termed ‘post-infectious purpura fulminans’) [13]. The term ‘purpura fulminans’ has subsequently been used for widespread cutaneous haemorrhage in patients with sepsis, including infection with *Neisseria meningitidis*, *Staphylococcus aureus*, groups A and B β-haemolytic streptococci, *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Haemophilus aegyptius* [14]. However, haemorrhage in patients with DIC may be due to septic vasculitis, simple bleeding or microvascular thrombosis. The patterns of cutaneous haemorrhage for each of these different mechanisms are distinctive, and can be a guide to pathophysiology and therapy [15]. Cutaneous microvascular occlusion in sepsis with DIC presents clinically as non-inflammatory (bland) haemorrhage, usually with a retiform, stellate or branching configuration, with rapid transition to necrosis and eschar [16,17]. In a small study, early biopsy of retiform purpuric lesions showed microvascular occlusion with fibrin, and perivascular haemorrhage with minimal to

no inflammation; these findings correlated with severe protein C deficiency [17]. This was not true of other forms of purpura in sepsis with DIC. The protein C pathway is increasingly recognized as critically important in bacterial sepsis, acting to inhibit both coagulation and inflammation [18]. The use of activated protein C concentrate in sepsis appears to be beneficial, especially in severe cases, although whether all patients with sepsis should receive this is not clear [19–22]. In patients with sepsis, DIC and retiform (occlusion) purpura, it seems reasonable to assume severe protein C deficiency in the acute setting and to treat appropriately. Protein C concentrates and plasma exchange have also been successfully used to replace protein C in purpura fulminans [23].

Post-infectious purpura fulminans: acquired severe protein S dysfunction

As mentioned previously, post-infectious purpura fulminans occurs primarily in children as rapidly progressive purpura a few days to weeks after a febrile illness [14,24,25]. The most common associated infections are varicella zoster and streptococci. This syndrome has been associated with lupus anticoagulant activity and with autoantibodies to protein S [14,25,26]. Replacement of protein S activity is difficult, presumably because this condition is not due to simple clearing of protein S but rather to inhibition of protein S function by an antibody. Such antibody-mediated dysfunction is difficult to overcome by replacement of factor, and concentrated sources of protein S are unavailable.

Antiphospholipid antibody/lupus anticoagulant syndrome

From the original description as recurrent venous or arterial thrombosis, repeated fetal loss and thrombocytopenia to consensus statement criteria, APLS continues to be redefined [27–29], most recently by the addition of β_2-glycoprotein I (β_2-GPI) antibodies to the laboratory criteria for diagnosis (Table 49.6) [30].

A variety of serological markers exist, usually detected as antibody against phospholipids (especially cardiolipin) in combination with antigens from a co-factor molecule (e.g. β_2-GPI, prothrombin, annexin V, plasmin, tissue plasminogen activator, thrombin), or as an inhibitor of an *in vitro* coagulation test. Detection of antiphospholipid antibodies is roughly five times more common than detection of lupus anticoagulant [31].

APLS may occur as a primary or secondary disorder. In one large study, primary APLS comprised 53% of cases, lupus-associated APLS 36%, lupus-like APLS 5% and other disease associations with APLS 6%, with catastrophic APLS occurring in 0.8% [32]. Compared with primary syndrome patients, lupus patients with APLS were more likely to have arthritis, livedo reticularis, thrombocytopenia or leukopenia. The mean age was 42 ± 14 years at study entry, onset of symptoms was most often in young to middle-aged patients (2.8% before age 15 years, 12.7% after age 50), and there was a strong female predominance (82%).

Mechanisms of coagulation in APLS are only partially understood. These antibodies were first detected in 1906 in patients with syphilis, and measured as false-positive serological tests for syphilis in 1952 [29]. However, today they are most often detected as β_2-GPI antibodies, lupus anticoagulants or antiphospholipid antibodies. The lupus anticoagulant activity is detected, often incidentally, by prolongation of the activated partial thromboplastin time (aPTT), the dilute Russell's viper venom time (dRVVT), or the kaolin clotting time [33]. Both a test of activation of the intrinsic pathway (either aPTT or kaolin clotting time) and direct activation of Factor X (dRVVT) is recommended. The presence of an inhibitor is determined by 1 : 1 mixing studies with normal plasma. As such mixing guarantees at least 50% levels of all clotting factors, failure to correct the clotting test indicates the presence of an inhibitor. The proof of phospholipid dependency for this inhibitor is often done by the platelet neutralization procedure, in which washed platelets are used to provide enough phospholipid surface to bind the interfering antibodies while still providing excess phospholipid to support the clotting reaction. Although prolongation of these tests would seem to predict a tendency towards bleeding, individuals with lupus anticoagulant activity very rarely bleed abnormally, but may be paradoxically predisposed to clot formation.

Antiphospholipid antibody activity is detected by one of several antibody assays, the most common being ELISA screens for IgG or IgM antibody affinity for cardiolipin, a negatively charged phospholipid molecule found in mitochondrial membranes. Although anticardiolipin antibodies can be detected in the absence of binding to a co-factor such as β_2-GPI, antiphospholipid antibodies which bind to phospholipid alone without a coactor molecule are not usually physiologically relevant in inducing thrombosis. Studies have shown that in patients with both lupus anticoagulant activity and anticardiolipin activity, there may be little or no cross-reaction between antibodies which bind to each. Both the lupus anticoagulant test and the various antiphospholipid antibody assays can be positive in a great many patients who never develop any thrombosis. Likewise, until the mechanisms responsible for thrombosis in patients with these antibodies are understood, it is possible that some patients with thrombosis may test negative with current assays, and yet ultimately be found to have disease mediated by antibodies interfering with physiological pathways responsible for clinical APLS.

Table 49.6 International consensus statement preliminary criteria for antiphospholipid antibody syndrome (definitive diagnosis requires at least one clinical and one laboratory criterion) [30].

Clinical criteria
Vascular thrombosis
One or more clinical episodes of arterial, venous or small-vessel thrombosis
Complications of pregnancy
One or more unexplained deaths of morphologically normal fetuses at or after 10 weeks of pregnancy or
One or more premature births of morphologically normal neonates at or before 34 weeks of gestation or
Three or more unexplained consecutive spontaneous abortions before 10 weeks of gestation
Laboratory criteria
Anticardiolipin antibodies, IgG or IgM, present at moderate or high levels on two or more occasions at least 6 weeks apart
Lupus anticoagulant antibodies on two or more occasions at least 6 weeks apart
β_2-Glycoprotein I antibodies on two or more occasions at least 6 weeks apart

The most important autoantigen in APLS appears to be β_2-GPI (apolipoprotein H), which binds anionic phospholipids as part of physiological disposal of apoptotic cells [34]. β_2-GPI is composed of five complement control modules, domains I to V. Infections may trigger β_2-GPI antibodies (e.g. leprosy, leishmaniasis and leptospirosis), as may childhood atopic dermatitis. These antibodies may differ from those that trigger thrombosis by binding to domain V of the β_2-GPI molecule, rather than to the domain I region which appears to be characteristic of the thrombogenic subset [35]. Infection-related antibodies, especially in leprosy, are more often IgM than IgG type. In general, IgM β_2-GPI antibodies are seldom implicated in thrombotic events, except perhaps in cerebral stroke. IgG antibodies to β_2-GPI, especially the IgG_2 subset, are the most likely to be thrombogenic [33]. The binding of the glycoprotein to negatively-charged phospholipid or *in vitro* to an irradiated negatively-charged plastic plate induces a conformational change in β_2-GPI, leading to exposure of a cryptic epitope in domain I and, in some cases, to autoantibody formation. *In vivo*, the usual binding sites for β_2-GPI which induce the conformational change are membrane phospholipids, especially phosphatidyl serine, which is expressed by agonist stimulation of platelets, for example, with flipping of membrane bilayer phospholipids that are normally on the inner surface to the outer membrane layer [35].

Multiple pathways have been implicated by which antiphospholipid antibodies may promote thrombosis: promotion of procoagulant reactions (interfering with protective membrane proteins such as β_2-GPI or annexin V), interference with anticoagulant pathways (inhibition of protein C/S and antithrombin III pathways), activation of platelets by membrane binding, interference with prostacyclin production and release by endothelium, or interference with fibrinolytic pathways (inhibition of endothelial plasminogen activator or kallikrein activation) [29,36–38]. However, current investigation points to β_2-GPI antibodies being the likely prothrombotic pathway in most patients. The mechanism of thrombosis with antibody-bound β_2-GPI is thought to occur predominantly through disruption of a crystal shield of annexin V which covers the membrane and ordinarily prevents binding of procoagulant molecules [39]. An important physiological role for β_2-GPI is believed to be inhibition of atherosclerosis by preventing scavenger receptor-mediated uptake of oxLDL by macrophages, but β_2-GPI antibodies binding to β_2-GPI-oxLDL mediates atherosclerosis by promoting phagocytosis of the oxLDL complex by macrophages via Fc receptors. This suggests that in addition to potential thrombogenesis, β_2-GPI antibody complexes may also be atherogenic.

Although thrombocytopenia was frequently mentioned in early descriptions of the APLS, this is no longer a diagnostic criterion for the syndrome. Mechanisms for thrombocytopenia or a role for APL antibodies have been difficult to find, but recently it has been shown that β_2-GPI may inhibit both von Willebrand factor-mediated platelet aggregation and binding of platelets to a von Willebrand factor-coated surface, and that antibodies to β_2-GPI reduce the ability of β_2-GPI to inhibit these activities [40]. If this is true, then a role for platelet-mediated vascular occlusion may exist in some patients with antibodies to β_2-GPI.

Investigators have shown that β_2-GPI-oxLDL complexes can frequently be detected in sera from patients with APLS and/or systemic lupus erythematosus, but not in healthy individuals [41]. Furthermore, patients with APS have been shown to have autoreactive $CD4^+$ T cells responsive to β_2-GPI in patients with APLS, and which can promote pathogenic IgG anti-β_2-GPI antibody production by autologous B cells. These T cells do not respond to native β_2-GPI, but will respond to chemically reduced or bacterially expressed recombinant β_2-GPI, further supporting the hypothesis that it is a cryptic epitope that is responsible for pathological β_2-GPI antibodies. This insight leads to the possibility of future therapies targeted at depleting or blocking binding domain I-directed β_2-GPI antibodies, or inhibiting their production through elimination or inhibition of the pathological autoreactive $CD4^+$ T-cell subset [41].

Table 49.7 Cutaneous findings in antiphospholipid antibody syndrome.

Livedo reticularis, with or without retiform purpura or retiform necrosis
Sneddon's syndrome
Livedoid vasculopathy/atrophie blanche
Raynaud's phenomenon
Anetoderma-like lesions with thrombosis
Behçet's-like lesions
Nailfold ulcers
Widespread cutaneous necrosis (catastrophic antiphospholipid antibody syndrome)
Leg ulcers, secondary to recurrent thrombosis with stasis, or from conditions in this table
Cholesterol embolus-like proximal livedo reticularis, with or without distal retiform purpura
Acral livedo
Degos (malignant atrophic papulosis)-like lesions
Pseudo-Kaposi's sarcoma
Vasculitis-like lesions
Pyoderma gangrenosum-like ulcers
Splinter haemorrhages
Superficial thrombophlebitis migrans

Clinically, APLS can present with a variety of cutaneous findings (Table 49.7) [42]. Livedo is one of the most common, but least specific as this and retiform purpura or necrosis occur in other microvascular occlusion disorders [42]. In one large study the frequency of these findings was livedo reticularis 24%, leg ulcers 5.5%, pseudovasculitis 3.9%, digital gangrene 3.3%, cutaneous necrosis 2.1% and splinter haemorrhages 0.7% [32]. Catastrophic APLS is an uncommon but disastrous variant in which patients typically present with widespread cutaneous necrosis and multiorgan failure, especially renal and pulmonary. Precipitating factors include infections, surgical procedures, drugs and discontinuation of anticoagulation. The most common extracutaneous manifestations of non-catastrophic APLS include deep-vein thrombosis, pulmonary embolus and central nervous system abnormalities.

Specific therapy in APLS awaits an understanding of the mechanism by which thrombosis occurs in individual patients, and thus the capability to use tailored therapies to specifically oppose that pathway in a particular individual. As alluded to previously, investigation of the role of autoreactive $CD4^+$ T cells driving B-cell production of pathogenic β_2-GPI antibodies may provide more effective therapies in the future. For now, treatment is empirical. Antiplatelet therapy is of uncertain benefit; most therapy depends

on acute and often chronic anticoagulation, either with standard or low-molecular-weight heparin initially followed by coumadin [34]. Antimalarial therapy may be of some benefit for atrophie blanche-like or Degos-like syndromes in lupus patients; evidence suggests a protective effect in lupus patients against arterial or venous thromboses [29]. There is evidence that hydroxychloroquine may interfere with the binding of IgG-β_2-GPI complexes on phospholipid bilayers or to a line of cultured human monocytic leukaemia cells, which may provide some rationale for possible prophylactic benefit in APLS patients [43].

References

1 Marlar RA, Montgomery RR, Broekmans AW. Diagnosis and treatment of homozygous protein C deficiency. Report of the Working Party on homozygous protein C deficiency of the subcommittee on protein C and protein S, International Committee on Thrombosis and Haemostasis. *J Pediatr* 1989; **114**: 528–34.

2 Comp P, Nixon R, Cooper M *et al.* Familial protein S deficiency is associated with recurrent thrombosis. *J Clin Invest* 1984; **74**: 2082–8.

3 Koeleman BP, van Rumpt D, Hamulyák K *et al*. Factor V Leiden: an additional risk factor for thrombosis in protein S deficient families? *Thromb Haemost* 1995; **74**: 580–3.

4 Simioni P, Sanson B, Prandoni P *et al.* Incidence of venous thromboembolism in families with inherited thrombophilia. *Thromb Haemost* 1999; **81**: 198–202.

5 Marlar RA, Neumann A. Neonatal purpura fulminans due to homozygous protein C or protein S deficiencies. *Semin Thromb Hemost* 1990; **16**: 333–40.

6 Ezer U, Misirlioglu E, Colba V *et al*. Neonatal purpura fulminans due to homozygous protein C deficiency. *Pediatr Hematol Oncol* 2001; **18**: 453–8.

7 Dreyfus M, Magny JF, Bridey F *et al.* Treatment of homozygous protein C deficiency and neonatal purpura fulminans with a purified protein C concentrate. *N Engl J Med* 1991; **325**: 1565–8.

8 Nakayama T, Matsushita T, Hidano H *et al.* A case of purpura fulminans is caused by homozygous delta8857 mutation (protein C-nagoya) and successfully treated with activated protein C concentrate. *Br J Haematol* 2000; **110**: 727–30.

9 Comp P, Elrod J, Karzenski S. Warfarin-induced skin necrosis. *Semin Thromb Hemost* 1990; **16**: 293–8.

10 Griffin J. Anticoagulants and skin necrosis. *Adverse Drug React Toxicol Rev* 1994; **13**: 157–67.

11 Sallah S, Thomas D, Roberts H. Warfarin and heparin-induced skin necrosis and the purple toe syndrome: infrequent complications of anticoagulant treatment. *Thromb Haemost* 1997; **78**: 785–90.

12 O'Brien A, Tate G, Shiach C. Evaluation of protein C and protein S levels during oral anticoagulant therapy. *Clin Lab Haematol* 1998; **20**: 245–52.

13 Hjort PF, Rapaport SI, Jorgensen I. Purpura fulminans: report of a case successfully treated with heparin and hydrocortisone. Review of 50 cases from the literature. *Scand J Haematol* 1964; **1**: 169.

14 Levin M, Eley B, Louis J *et al.* Postinfectious purpura fulminans caused by an autoantibody directed against protein S. *J Pediatr* 1995; **127**: 355–63.

15 Piette WW. The differential diagnosis of purpura from a morphologic perspective. *Adv Dermatol* 1994; **9**: 3–24.

16 Robson K, Piette W. The presentation and differential diagnosis of cutaneous vascular occlusion syndromes. *Adv Dermatol* 1999; **15**: 153–82.

17 Piette W, Shasby DM, Kealey P, Olson J. Retiform purpura is a sign of severe acquired protein C deficiency and risk of progression to purpura fulminans in sepsis and disseminated intravascular coagulation. *Clin Res* 1993; **41**: 253A.

18 Esmon C. Protein C pathways in sepsis. *Ann Med* 2002; **34**: 598–605.

19 Warren H, Suffredini A, Eichacker P, Munford R. Risks and benefits of activated protein C treatment for severe sepsis. *N Engl J Med* 2002; **347**: 1027–30.

20 Manns B, Lee H, Doig C *et al*. An economic evaluation of activated protein C treatment for severe sepsis. *N Engl J Med* 2002; **347**: 993–1000.

21 Siegel J. Assessing the use of activated protein C in the treatment of severe sepsis. *N Engl J Med* 2002; **347**: 1030–4.

22 Ely E, Bernard G, Vincent J. Activated protein C for severe sepsis. *N Engl J Med* 2002; **347**: 1035–6.

23 Hodgson A, Ryan T, Moriarty J *et al*. Plasma exchange as a source of protein C for acute onset protein C pathway failure. *Br J Haematol* 2002; **116**: 905–8.

24 Frances RB Jr. Acquired purpura fulminans. *Semin Thromb Hemost* 1990; **16**: 310–25.

25 Manco-Johnson M, Nuss R, Key N *et al*. Lupus anticoagulant and protein S deficiency in children with postvaricella purpura fulminans or thrombosis. *J Pediatr* 1996; **128**: 319–23.

26 van Ommen C, van Wijnen M, de Groot F *et al*. Postvaricella purpura fulminans caused by acquired protein S deficiency resulting from antiprotein S antibodies: search for the epitopes. *J Pediatr Hematol Oncol* 2002; **24**: 413–6.

27 Lockshin M. Antiphospholipid antibody syndrome. *JAMA* 1992; **268**: 1451–3.

28 Kampe C. Clinical syndromes associated with lupus anticoagulants. *Semin Thromb Hemost* 1994; **20**: 16–26.

29 Levine J, Branch D, Rauch J. The antiphospholipid syndrome. *N Engl J Med* 2002; **346**: 752–63.

30 Miyakis S, Lockshin MD, Atsumi T *et al*. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost* 2006; **4**: 295–306.

31 Gibson G, Su P, Pittelkow M. Antiphospholipid syndrome and the skin. *J Am Acad Dermatol* 1997; **36**: 970–82.

32 Cervera R, Piette J, Font J *et al*. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. *Arthritis Rheum* 2002; **46**: 1019–27.

33 Giannakopoulos B, Passam F, Ioannou Y, Krilis SA. How we diagnose the antiphospholipid syndrome. *Blood* 2009; **113**: 985–94.

34 Lockshin M, Erkan D. Treatment of the antiphospholipid syndrome. *N Engl J Med* 2003; **349**: 1177–9.

35 Giannakopoulo B, Passam F, Rahgozar S, Krilis SA. Current concepts on the pathogenesis of the antiphospholipid syndrome. *Blood* 2007; **109**: 422–30.

36 Angles-Cano E, Guillin M. Antiphospholipid antibodies and the coagulation cascade. *Rheum Dis Clin North Am* 2001; **27**: 573–86.

37 Nojima J, Kuratsune H, Suehisa E *et al.* Acquired activated protein C resistance is associated with the co-existence of anti-prothrombin antibodies and lupus anticoagulant activity in patients with systemic lupus erythematosus. *Br J Haematol* 2002; **118**: 577–83.

38 Izumi T, Pound M, Su Z *et al*. Anti-beta$_2$-glycoprotein I antibody-mediated inhibition of activated protein C requires binding of beta$_2$-glycoprotein I to phospholipids. *Thromb Haemost* 2002; **88**: 620–6.

39 De Laat B, Wu XX, van Lummerl M *et al*. Correlation between antiphospholipid antibodies that recognize domain I of β2-glycoprotein I and a reduction in the anticoagulant activity of annexin A5. *Blood* 2007; **109**: 1490–4.

40 Hulstein JJ, Lenting PJ, de Laat B *et al*. β2-glycoprotein I inhibits von Willebrand factor dependent platelet adhesion and aggregation. *Blood* 2007; **110**: 1483–91.

41 Yamaguchi Y, Seta N, Kaburaki J *et al*. Excessive exposure to anionic surfaces maintains autoantibody response to β2-glycoprotein I in patients with antiphospholipid syndrome. *Blood* 2007; **110**: 4312–8.

42 Weinstein S, Piette WW. Cutaneous manifestations of antiphospholipid antibody syndrome. *Haematol Oncol Clin North Am* 2008; **22**: 67–77.

43 Rand JH, Wu XX, Quinn AS *et al*. Hydroxychloroquine directly reduces the binding of antiphospholipid antibody-β2-glycoprotein I complexes to phospholipid bilayers. *Blood* 2008; **112**: 1687–95.

Occlusion due to vascular coagulopathies

Sneddon's syndrome

Definition. This syndrome comprises generalized livedo racemosa or livedo reticularis with cerebrovascular lesions that cause focal neurological symptoms or signs [1–5]. Livedo racemosa is usually the first manifestation, initially affecting the lower trunk and proximal part of the legs but becoming more generalized. It typically has a broad network pattern (Fig. 49.13). Associated Raynaud's phenomenon or acrocyanosis may occur, and may be the presenting feature.

Incidence. This has been estimated as four cases per million population per year [5]. Sneddon's syndrome is twice as common in

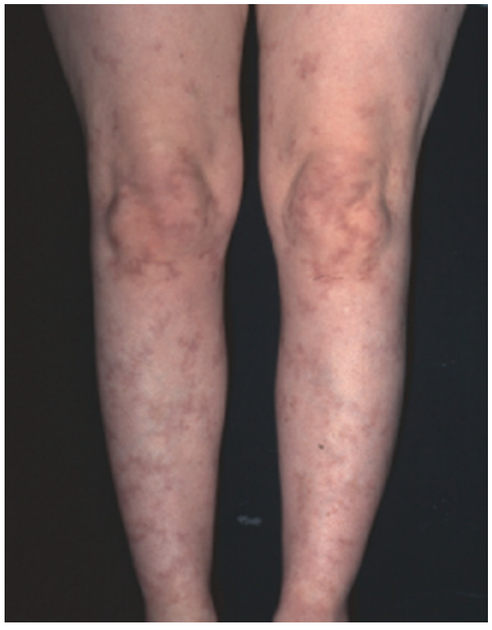


Fig. 49.13 Sneddon's syndrome showing a typical broad racemose livedo patterning.

women as in men, and typically presents in the fourth or fifth decade of life. It is usually sporadic, although familial Sneddon's syndrome has been reported.

Pathogenesis. Several authors have reported the presence of antinuclear antibodies or of antiphospholipid antibodies/lupus anticoagulant (reviewed in [6]), but others would only accept the diagnosis of Sneddon's syndrome if these antibodies were absent. Differences have been documented between the clinical features of patients with Sneddon's syndrome depending on the presence or absence of antiphospholipid antibodies; those without antiphospholipid antibodies typically have a larger-sized livedo pattern, whereas those with antiphospholipid antibodies have a higher risk of seizures, mitral regurgitation and thrombocytopenia [7]. It is likely that there is a spectrum of disease from APLS to SLE that includes the preferential arteriolar pattern of Sneddon's syndrome. Antiprothrombin antibodies were demonstrated in 57% of 46 patients in one series [8], and there are reports of platelet activation in a patient with persistently elevated levels of circulating PF4 [9], of increased levels of antithrombin III [10], of factor V Leiden mutation [11] and of activated protein C resistance [12].

Histopathology. Biopsies may show an endarteritis of dermal arterioles. It has been demonstrated that the most informative biopsies are from the clinically normal centre of any network area rather than from the peripheral 'watershed' area of livedo, and that taking multiple biopsies increases the sensitivity [13]. Initial changes are endothelial swelling with a mixed inflammatory infiltrate, progressing to vascular plugging, subendothelial proliferation and eventual vascular occlusion, fibrosis and disappearance of the inflammatory component [14]. It is possible, if not likely, that the histological findings in patients with antiphospholipid antibodies, especially in association with lupus or lupus-like disease, would be more typical of non-inflammatory occlusion.

Clinical features. In addition to the cutaneous livedo, there may be non-specific neurological prodromal symptoms such as headache, migraine, dizziness or vertigo. Later neurological features include focal paresis or hemiparesis, focal sensory or hemisensory symptoms, fits and visual defects, and later cognitive changes. Transient ischaemic attacks are commoner than completed stroke [15]. Peripheral nerves may also be affected. Hypertension may be present and confers a worse prognosis if untreated; hypertension and the neurological aspects are sometimes aggravated by pregnancy or use of oral contraceptives. There may be renal or cardiac involvement, including valve defects such as mitral regurgitation, although internal organ involvement other than neurological is often asymptomatic [5]. Other features such as shortened digits have rarely been reported.

The differential diagnosis is wide, from both the cutaneous and the neurological perspective. In particular, other causes of livedo and microvascular occlusion syndromes discussed in this chapter need to be considered as well as vasculitic causes (e.g. polyarteritis nodosa). However, it should be noted that other patterns of livedo with anticardiolipin antibodies may be associated with evidence of cerebral microthrombosis, for example livedo with summer ulceration or livedo with pyoderma gangrenosum-like lesions [16].

Magnetic resonance imaging (MRI), electroencephalography and arteriography may help to confirm the neurological component; skin biopsy (as above) and exclusion of other causes of livedo are necessary. Patients with positive antiphospholipid antibodies more commonly have infarcts in the distribution of the main cerebral arteries on MRI, whereas those with negative antibodies have small lacunar infarcts [17] and progressive leukoencephalopathy [15].

Treatment. There is generally no very effective treatment, reflecting the non-inflammatory nature of the disease. Corticosteroids may have some benefit but this is variable and often difficult to assess due to the intermittent nature of the neurological disease; other immunosuppressive agents are often disappointing. Avoidance of smoking and oral contraceptives, and treatment of hypertension and hyperlipidaemia (both of which are commonly present), are important. Thrombolytic agents and vasodilators have been used in the acute situation, and antiplatelet agents appear to be effective in the longer term [7]. In patients with antiphospholipid antibodies or lupus anticoagulants, maintenance of anticoagulation at an international normalized ratio (INR) of 2–3 seems warranted.

References

1 Sneddon IB. Cerebro-vascular lesions and livedo reticularis. *Br J Dermatol* 1965; **77**: 180–5.

2 Daoud MS, Wilmoth GJ, Su WPD, Pittelkow MR. Sneddon syndrome. *Semin Dermatol* 1995; **14**: 166–72.

3 Alegre VA, Winkelmann RK, Gastineau DA. Cutaneous thrombosis, cerebrovascular thrombosis, and lupus anticoagulant: the Sneddon syndrome. Report of 10 cases. *Int J Dermatol* 1990; **29**: 45–9.

4 Lubach D, Schwabe C, Weissenborn K *et al.* Livedo racemosa generalisata: an evaluation of thirty-four cases. *J Am Acad Dermatol* 1990; **22**: 633–9.

5 Zelger B, Sepp N, Stockhammer G *et al.* Sneddon's syndrome: a long-term follow-up of 21 patients. *Arch Dermatol* 1993; **129**: 437–47.

6 Frances C, Piette JC. The mystery of Sneddon syndrome: relationship with antiphospholipid syndrome and systemic lupus erythematosus. *J Autoimmun* 2000; **15**: 139–43.
7 Frances C, Papo T, Wechsler B *et al.* Sneddon syndrome with or without antiphospholipid antibodies. A comparative study in 46 patients. *Medicine (Baltimore)* 1999; **78**: 209–19.
8 Kalashnikova LA, Korczyn AD, Shavit S *et al.* Antibodies to prothrombin in patients with Sneddon's syndrome. *Neurology* 1999; **53**: 223–5.
9 Matsumura Y, Tomimoto H, Yamamoto M *et al.* Sneddon syndrome with multiple cerebral infarctions 12 years after the onset of livedo vasculitis: a possible involvement of platelet activation. *J Dermatol* 2001; **28**: 508–10.
10 Bolayir E, Kececi H, Akyol M *et al.* Sneddon's syndrome and antithrombin III. *J Dermatol* 1999; **26**: 532–4.
11 Besnier R, Francès C, Ankri A *et al.* Factor V Leiden mutation in Sneddon syndrome. *Lupus* 2003; **12**: 406–8.
12 Gualtieri RJ, Walton GD. Activated protein C resistance and Sneddon's syndrome. *Am J Med* 1999; **107**: 293.
13 Wohlrab J, Fischer M, Wolter M, Marsch WC. Diagnostic impact and sensitivity of skin biopsies in Sneddon's syndrome: a report of 15 cases. *Br J Dermatol* 2001; **145**: 285–8.
14 Zelger B, Sepp N, Schmid KW *et al.* Life history of cutaneous vascular lesions in Sneddon's syndrome. *Hum Pathol* 1992; **23**: 668–75.
15 Boesch SM, Plörer AL, Auer AJ *et al.* The natural course of Sneddon syndrome: clinical and magnetic resonance imaging findings in a prospective six year observation study. *J Neurol Neurosurg Psychiatry* 2003; **74**: 542–4.
16 Suzuki Y, Otoyama K, Katayama I *et al.* Livedo with cerebrovascular thrombosis: correlation between clinical features, anti-cardiolipin antibodies, and cerebral microinfarction. *Jpn J Dermatol* 1990; **100**: 1437–44.
17 Fetoni V, Grisoli M, Salmaggi A *et al.* Clinical and neuroradiological aspects of Sneddon's syndrome and primary antiphospholipid antibody syndrome: a follow-up study. *Neurol Sci* 2000; **21**: 157–64.

Livedoid vasculopathy; atrophie blanche

Synonyms
- Livedo reticularis with summer ulceration
- Segmental hyalinizing vasculitis

This syndrome is most common in young to middle-aged women as either an idiopathic or secondary syndrome [1]. One of the most commonly noted associations is with chronic venous hypertension and varicosities, although the atrophic scarring in this setting is not usually preceded by small painful ulcerations, nor with surrounding livedo reticularis. It would seem appropriate to separate venous stasis-related atrophie blanche from more typical forms of the syndrome.

Pathogenesis. The pathogenesis of livedoid vasculopathy is unknown. Clearly, APLS, with or without a lupus association, can produce this clinical syndrome [2]. Multiple pathophysiological abnormalities have been implicated, including platelet activation, factor V Leiden, altered fibrinolysis, antiphospholipid antibodies and hyperhomocystinaemia [1–4]. In one series of 32 patients, heterozygous factor V Leiden mutation was found in two of nine tested (22%), decreased protein C or protein S activity in two of 15 (13%), prothrombin G20210A mutation in one of 12 (8%), lupus anticoagulant in five of 28 (18%), anticardiolipin antibodies in eight of 29 (29%) and elevated homocysteine levels in three of 21 (14%) [5].

Histology. The most characteristic histological findings in this syndrome are some thickening or hyaline changes in the walls of superficial dermal vessels, and luminal fibrin deposition [1,6]. Red cell extravasation and perivascular lymphocytic infiltrates are expected findings. In a series of 45 skin biopsies from 32 patients, all but one showed intraluminal thrombus and direct immunofluorescence was positive in 86% [5].

Clinical features. Persistent, very painful and often punched-out ulcerations of the legs, especially around the malleoli, in women are typical of atrophie blanche [6]. The disease is bilateral in most cases. When accompanied by surrounding livedo reticularis, the term 'livedoid vasculitis' is more likely to be applied. Retiform or stellate purpura or ulcer extension can occur; healing results in a porcelain-white scar, frequently surrounded by telangiectasia. Besides venous hypertension and antiphospholipid antibody-related syndromes, sickle cell ulcers can show the same porcelain-white scar of atrophie blanche.

Treatment. Antiplatelet, anticoagulant and fibrinolytic therapies have been reported to be helpful in this syndrome, as well as anabolic steroids such as danazol and stanozolol [2]. PUVA therapy has been reported as effective in some cases [7]. In patients with lupus and atrophie blanche-like lesions, antimalarial therapy may be effective. Rapid relief of pain has been reported with use of intravenous immunoglobulins [8], postulated to be due to inhibition of the vasoconstrictor chemicals thromboxane A_2 and endothelin which thereby improves perfusion. Lipoprostaglandin E_1 has been used with good response in a patient with livedoid vasculitis and essential cryoglobulinaemia [9], but this may have been mediated by an effect on the cryoprotein levels, which fell dramatically; there are anecdotal reports of response to tetracyclines [10], and dapsone has also been used in patients with underlying myeloproliferative syndromes.

References

1 Maessen-Visch M, Koedam M, Hamulyak K, Neumann H. Atrophie blanche. *Int J Dermatol* 1999; **38**: 161–72.
2 Acland K, Darvay A, Wakelin S, Russell-Jones R. Livedoid vasculitis: a manifestation of the antiphospholipid syndrome? *Br J Dermatol* 1999; **140**: 131–5.
3 Calamia K, Balabanova M, Perniciaro C, Walsh J. Livedo (livedoid) vasculitis and the factor V Leiden mutation: additional evidence for abnormal coagulation. *J Am Acad Dermatol* 2002; **46**: 133–7.
4 Anavekar NS, Kelly R. Heterozygous prothrombin gene mutation associated with livedoid vasculopathy. *Australas J Dermatol* 2007; **48**: 120–5.
5 Hairston BR, Davis MPD, Pittelkow MR, Ahmed I. Livedoid vasculopathy: further evidence for procoagulant pathogenesis. *Arch Dermatol* 2006; **142**: 1413–8.
6 Robson K, Piette W. The presentation and differential diagnosis of cutaneous vascular occlusion syndromes. *Adv Dermatol* 1999; **15**: 153–82.
7 Lee J, Choi H, Kim S *et al*. Livedoid vasculitis responding to PUVA therapy. *Int J Dermatol* 2001; **40**: 153–7.
8 Kreuter A, Gamblicher T, Breukermann F *et al*. Pulsed intravenous immunoglobulin therapy in livedoid vasculitis: an open trial evaluating 9 consecutive patients. *J Am Acad Dermatol* 2004; **51**: 574–9.
9 Kawakami T, Kawasaki K, Mizoguchi M, Soma Y. Therapeutic effect of lipoprostaglandin E_1 on livedoid vasculitis associated with essential cryoglobulinaemia. *Br J Dermatol* 2007; **157**: 1051–3.
10 Webster G, del Rosso JQ. Anti-inflammatory activity of tetracyclines. *Dermatol Clin* 2007; **25**: 133–5.

Malignant atrophic papulosis

Synonyms
- Degos' disease
- Kohlmeier–Degos' disease
- Lethal cutaneous and gastrointestinal arteriolar thrombosis

Definition. Malignant atrophic papulosis is a progressive vasculopathy causing occlusion of small and medium-sized arteries [1–6]. Originally reported separately by Kohlmeier [7] and Degos [8], it was also described as lethal cutaneous and gastrointestinal arteriolar thrombosis [9]. It is characterized by skin and gastrointestinal lesions, but neurological features are also frequent and post-mortem studies show widespread organ involvement. The skin lesions are usually the first feature, and may be the only manifestation over many years [2]; whether this represents a truly 'benign' variant is uncertain.

Incidence. It is rare; a review in 1995 suggested that about 120 cases had been reported [4]. It is mainly reported in white people, has a slight male predominance and is mainly a disease that presents in young adults, although it can affect any age group [3,5]. Familial cases have been reported [10].

Pathogenesis [3,5]. The pathogenesis probably involves abnormal coagulation, although the precise mechanism is uncertain. Platelet and fibrin thrombi are apparent in dermal, mesenteric and nervous system blood vessels, and both abnormal platelet aggregation and inhibition of fibrinolysis have been reported [3,5,11–14]. However, most patients have no clear evidence of a systemic coagulopathy, suggesting that the thrombotic tendency is at the microvascular level. Antiphospholipid antibodies have been documented in a small number of patients, usually in the context of SLE, although they may also occur even in the benign cutaneous variant [15].

There is also some support for a mechanism involving vascular inflammation. An autoimmune mechanism is suggested by the occurrence of lesions resembling malignant atrophic papulosis in some patients with SLE, rheumatoid arthritis, scleroderma or dermatomyositis [16–19]; antiendothelial antibodies have also been demonstrated but are probably not the cause of the disease [5]. Circulating immune complexes, or deposition of immune complexes or complement, are not usually demonstrated [2,20]. Although there can be a prominent lymphocytic infiltrate in later lesions, especially around venules, true arteritis and leukocytoclasis are not found [3,5,21].

Abnormal mucin deposits, which may be thrombogenic, occur even in early lesions although they tend to be more apparent in later lesions [3,5,21]. It is possible that they may be induced by activated T cells.

A viral aetiology was proposed on the basis of electron microscopic demonstration of interwoven tuboreticular structures resembling viral inclusions within endothelial cells [22], but these are seen in other disorders, including SLE, and can be induced by interferon [5]. Cases have been reported with HIV infection but a causal association is unproven.

Histopathology [2–6]. The histological picture in Degos' disease depends upon the duration of the lesion biopsied. Early lesions show a superficial and deep perivascular, perineural and periappendageal chronic inflammatory cell infiltrate [21]. Deep dermal vessels show endovascular inflammation, proliferation and thickening with thrombosis [23]. Mucin deposition is seen at all stages [2–4,21,24], and fibrin deposition may be demonstrated; fibrinoid necrosis of vessel walls may occur [23]. Immunofluorescence is occasionally positive for IgG or C3. From a histopathological perspective, the presence of lymphocytes, which may be seen within the damaged vessel wall, is viewed as abnormal and has led to classification of Degos' disease as a lymphocytic vasculitis [25] although it is not documented that this is a primary abnormality. Later lesions show a classical 'wedge-shaped' pattern of sclerotic change in the dermis, which is usually only sparsely cellular. Between these stages there is a phase with neutrophilic and eosinophilic infiltrate around adnexae and a dense perivascular lymphocytic infiltrate [21]. The epidermis, initially showing a mild vacuolar reaction, becomes atrophic with slight scaling, resembling that seen in lichen sclerosus and corresponding with the typical 'porcelain-white' colour seen clinically. There may be some associated pigmentary incontinence.

Panniculitis resembling that seen in lupus profundus has recently been reported [26]. Similar changes occur in the intestinal wall, particularly the submucosa. The muscularis mucosae is intact. Blood vessels are thickened and disorganized, with fibrinoid degeneration; platelet–fibrin thrombi are more prominent than in skin biopsy material.

Microaneurysms of the bulbar conjunctival vessels have been described. Renal changes include thickening of the afferent glomerular arterioles and of the capillary basement membrane.

Clinical features [1–8]. Cutaneous lesions usually precede systemic manifestations by months to years. They develop as crops over a period of time and are usually asymptomatic, although they may be preceded by slight burning. Skin lesions affect any site, mainly the trunk and proximal limbs; the face, palms and soles are generally spared. Although they may evolve gradually, and the number of lesions may vary considerably, about 30–40 active lesions are usually present [4]. Oral mucosal lesions are rare but penile lesions may occur [27]; the bulbar conjunctiva is often affected by lesions, which appear as sharply demarcated avascular areas [4]. Peristomal lesions have been reported.

Early skin lesions are pink or red, dome-shaped papules, usually 2–5 mm in size but sometimes up to about 15 mm. Papules soon become necrotic and umbilicated with central 'porcelain-white' pallor and scaling, and the pink oedematous border becomes telangiectatic. Most heal rather slowly to leave a small white scar, often surrounded by telangiectases as in atrophie blanche. Urticaria-like, ulceropustular and gumma-like nodules have been reported. New crops of lesions may continue for several years.

Similar lesions occur in many organs. Gastrointestinal lesions are the most important, as perforation of the gut is a cause of death. Neurological symptoms are also relatively common. The features in different systems include the following [4].

- Gastrointestinal: dyspepsia, abdominal pain or distension, bleeding, perforation, peritonitis, fistulae (enteroenteral or enterocutaneous), obstruction, pancreatitis
- Neurological: cerebral infarction (causing headache, aphasia, dementia, focal epilepsy, hemiparesis, pseudobulbar palsy), cord infarction (paraplegia/quadriplegia, transverse myelopathy), peripheral nerve (cauda equina syndrome, mononeuritis multiplex), various sites (sensory disturbance)
- Ocular: ptosis, diplopia, nystagmus, ophthalmoplegia, optic neuritis, papilloedema, visual field loss, pupillary reaction defects, conjunctival avascular lesions, posterior subcapsular cataract
- Cardiovascular: renal artery occlusion, pericardial effusion, constrictive pericarditis, ventricular wall defects
- Pulmonary: pleuritis.

Differential diagnosis. There is sometimes a resemblance to atrophie blanche or to guttate lichen sclerosus, although the evolution of lesions is different. Identical lesions have been described in cases of various connective tissue diseases [16–19] and in a patient with Crohn's disease [28]. The characteristic features can scarcely be confused. A disorder termed 'cutaneous–intestinal syndrome with oropharyngeal ulceration' [29] included a combination of macular, blistering and crusting lesions of the skin, with oropharyngeal ulceration and death from perforation of one of many intestinal ulcers. This differed both clinically and histologically from Degos' disease. Patients in whom systemic disease precedes skin lesions may cause particular diagnostic problems.

Prognosis [4]. Although possibly overestimated by reporting bias, and acknowledging that there does appear to be a benign cutaneous ('skin-limited') variant, mortality of 50–60% within 2–5 years is anticipated. Prognosis in males appears to be worse than in females.

Treatment. There is no consistently effective treatment [2–4]. Steroids do not help, although some benefit in neurological symptoms has been suggested. Aspirin, antiplatelet agents, fibrinolytic agents and pentoxifylline, alone or in combination, may lead to remission and are perhaps most effective in the cutaneous disease [2–6,11,15,30–32]; phenylbutazone has been reported to be effective. Heparin may produce short-term benefit. There is one report of a good response to transdermal nicotine patches [33]. Warfarin, dextrans, chloroquine, immunosuppressive agents and plasma exchange have all been tried. Surgery to treat intestinal perforation may resolve the acute situation but is difficult as there are usually multiple lesions, and there is no long-term benefit from this approach.

References

1 Degos R. Malignant atrophic papulosis. *Br J Dermatol* 1979; **100**: 21–36.
2 Su WPD, Schroeter AL, Lee DA *et al.* Clinical and histologic findings in Degos' syndrome (malignant atrophic papulosis). *Cutis* 1985; **35**: 131–8.
3 Magrinat G, Kerwin KS, Gabriel DA. The clinical manifestations of Degos' syndrome. *Arch Pathol Lab Med* 1989; **113**: 354–62.
4 Snow JL, Muller SA. Degos syndrome: malignant atrophic papulosis. *Semin Dermatol* 1995; **14**: 99–105.
5 Chatham WW. Miscellaneous forms of vasculitis. In: Ball GV, Bridges SL Jr, eds. *Vasculitis*. Oxford: Oxford University Press, 2002: 513–32.
6 Assier-Bonnet H, Chosidow O, Frances C. Degos disease. *Ann Dermatol Vénéréol* 1997; **124**: 273–9.
7 Kohlmeier W. Multiple Hautnelnosen bei Thromboangiitis obliterans. *Arch Dermatol Syphilol* 1941; **181**: 783–4.
8 Degos R, Delort J, Tricot R. Dermatite papulosquamose atrophiante. *Bull Soc Fr Dermatol Syphil* 1942; **49**: 148–50.
9 Sidi E, Reinberg A, Spinasse JB *et al.* Lethal cutaneous and gastrointestinal arteriolar thrombosis. *JAMA* 1960; **174**: 1170–3.
10 Katz SK, Mudd LJ, Roenigk HH Jr. Malignant atrophic papulosis (Degos' disease) involving three generations of a family. *J Am Acad Dermatol* 1997; **37**: 480–4.
11 Drucker CR. Malignant atrophic papulosis: response to antiplatelet therapy. *Dermatologica* 1990; **180**: 90–2.
12 Aizawa H, Takase Y, Inoue K *et al*. An autopsy case of Degos disease with neurological symptoms: neuropathological observations and increased platelet aggregation. *Rinsho Shinkeigaku* 1992; **32**: 23–9.
13 Black MM, Nishioka K, Levene GM. The role of dermal blood vessels in the pathogenesis of malignant atrophic papulosis (Degos' disease). *Br J Dermatol* 1973; **88**: 213–9.
14 Caux F, Aractingi S, Scrobohaci ML *et al*. Abnormal fibrinolysis in Degos disease. A study of 3 cases. *Ann Dermatol Vénéréol* 1994; **121**: 537–42.
15 Farrell AM, Moss J, Costello C *et al.* Benign cutaneous Degos' disease. *Br J Dermatol* 1998; **139**: 708–12.
16 Black MM, Hudson PM. Atrophie blanche lesions closely resembling malignant atrophic papulosis (Degos' disease) in systemic lupus erythematosus. *Br J Dermatol* 1976; **95**: 649–52.
17 Durie BGM, Stroud JD, Kahn JA. Progressive systemic sclerosis with malignant atrophic papulosis. *Arch Dermatol* 1969; **100**: 575–81.
18 Demitsu T, Kakurai M, Marata S *et al.* Degos' disease associated with rheumatoid arthritis. *J Dermatol* 1997; **24**: 488–90.
19 Tsao H, Busam K, Barnhill RL, Haynes HA. Lesions resembling malignant atrophic papulosis in a patient with dermatomyositis. *J Am Acad Dermatol* 1997; **36**: 317–9.
20 Tribble K, Archer ME, Jorizzo JL *et al.* Malignant atrophic papulosis: absence of circulating immune complexes or vasculosis. *J Am Acad Dermatol* 1986; **15**: 365–9.
21 Harvell JD, Williford PL, White WL. Benign cutaneous Degos' disease: a case report with emphasis on histopathology as papules chronologically evolve. *Am J Dermatopathol* 2001; **23**: 116–23.
22 Bleehen SS. Intraendothelial tubular aggregates in malignant atrophic papulosis (Degos' disease). *Clin Exp Dermatol* 1977; **2**: 73–4.
23 Soter NA, Murphy GF, Mihm MC Jr. Lymphocytes and necrosis of the cutaneous microvasculature in malignant atrophic papulosis. A refined light microscopy study. *J Am Acad Dermatol* 1982; **7**: 620–30.
24 Feuerman EJ, Dollberg L, Salvador O. Malignant atrophic papulosis with mucin in the dermis. *Arch Pathol* 1970; **90**: 310–5.
25 Carlson JA, Chen K-R. Cutaneous vasculitis update: neutrophilic muscular vessel and eosinophilic, granulomatous, and lymphocytic vasculitis syndromes. *Am J Dermatopathol* 2007; **29**: 32–43.
26 Grilli R, Soriano ML, Izquierdo MJ *et al.* Panniculitis mimicking lupus erythematosus profundus: a new histopathologic finding in malignant atrophic papulosis (Degos disease). *Am J Dermatopathol* 1999; **21**: 365–8.
27 Thomson KF, Highet AS. Penile ulceration in fatal malignant atrophic papulosis (Degos' disease). *Br J Dermatol* 2000; **143**: 1320–2.
28 Castenet J, Lacour J-P, Perrin C *et al.* Cutaneous vasculitis with lesions mimicking Degos' disease and revealing Crohn's disease. *Acta Derm Venereol (Stockh)* 1995; **75**: 408–9.
29 Bettley FR. A fatal cutaneo-intestinal syndrome. *Br J Dermatol* 1960; **72**: 423–6.
30 Stahl D, Thomsen K, Hou-Jensen K. Malignant atrophic papulosis. *Arch Dermatol* 1978; **114**: 1687–9.
31 Torrelo A, Sevilla J, Medeiro IG *et al.* Malignant atrophic papulosis in an infant. *Br J Dermatol* 2002; **146**: 916–8.

32 Vicktor C, Schultz-Ehrenburg U. Malignant atrophic papulosis (Kohlmeier–Degos): diagnosis, therapy and course. *Hautarzt* 2001; **52**: 734–7.
33 Kanekura T, Uchino Y, Kanzaki T. A case of malignant atrophic papulosis successfully treated with nicotine patches. *Br J Dermatol* 2003; **149**: 660–2.

Occlusion due to reticulocytes

Patients with sickle cell anaemia may develop leg ulcers, which in tropical climates typically progress rapidly due to secondary bacterial infection [1]. However, in temperate climates the lesions are often perimalleolar, quite painful, and may heal with a porcelain-white scar, often mimicking atrophie blanche. Although this ulceration might be attributed solely to sickling of erythrocytes with microvascular occlusion, similar ulcers have been reported in other instances of severe chronic haemolytic anaemia, such as thalassaemia or antibody-mediated haemolysis, where sickling is not possible [2]. Multiple studies of possible occlusive mechanisms in sickle cell disease have shown that both young and old red cells have abnormally sticky membranes. In addition, abnormal leukocyte adhesion may initiate occlusion episodes, followed by adhesion of erythrocytes to these leukocytes, with a drop in tissue perfusion, followed by hypoxia and sickling with propagation of occlusion [3]. A number of platelet, procoagulant, anticoagulant and fibrinolytic abnormalities have been noted in sickle cell disease [3–5]. These might more properly be considered consequences of sickle cell disease vasculopathy [6]. A central mechanism for this vasculopathy seems to be haemolysis-associated reduction in the bioavailability of nitric oxide. Consequences of this reduction include endothelial cell activation, upregulation of the vasoconstrictor endothelin-1, vasoconstriction, platelet activation, increased tissue factor, and coagulation activation. Some of these mechanisms may be operative in other haemolytic anaemias, such as paroxysmal nocturnal haemoglobinuria (see previously) and thalassaemia [7]. Patients with sickle cell disease who are treated with hydroxycarbamide (hydroxyurea) appear to have a higher rate of ulcer development than other patients treated with hydroxycarbamide [7]. Although the mechanism is unclear, macroerythrocytes may play a role in initiation of hydoxyurea-induced leg ulcers and also in syndromes of severe haemolytic anaemia with high reticulocyte count and very early reticulocytes, but without sickling [2]. Whatever studies eventually prove, it seems that erythrocytes or their lysis may play an active role in some occlusive syndromes.

References

1 Piette W. Hematologic associations of leg ulcers. *Clin Dermatol* 1990; **8**: 66–85.
2 Velez A, Garcia-Aranda J, Moreno J. Hydroxyurea-induced leg ulcers: is macroerythrocytosis a pathogenic factor? *J Eur Acad Dermatol Venereol* 1999; **12**: 243–4.
3 Ataga K, Orringer E. Hypercoagulability in sickle cell disease: a curious paradox. *Am J Med* 2003; **115**: 721–8.
4 Shet A, Aras O, Gupta K *et al*. Sickle blood contains tissue factor-positive microparticles derived from endothelial cells and monocytes. *Blood* 2003; **102**: 2678–83.
5 Okpala I. The intriguing contribution of white blood cells to sickle cell disease, a red cell disorder. *Blood Rev* 2004; **18**: 65–73.
6 Morris CM. Mechanisms of vasculopathy in sickle cell disease and thalassemia. *Hematology Am Soc Hematol Education Program* 2008: 177–85.
7 Chaine B, Neonato M, Girot R, Aractingi S. Cutaneous adverse reactions to hydroxyurea in patients with sickle cell disease. *Arch Dermatol* 2001; **137**: 467–70.

Occlusion due to other mechanisms

Calcific uraemic arteriolopathy

Synonym
- Cutaneous calciphylaxis

Calcific uraemic arteriolopathy is a rare, but increasingly frequent, complication of renal failure and dialysis [1–4]. It may very rarely occur in other situations, such as alcoholic liver disease, and occasionally after chemotherapy, in patients with normal renal function. Women are most at risk, accounting for over 80% of cases, mainly in the sixth decade, and even in non-dialysed subjects about a third have diabetes [2]. One large institutional study showed that, compared with other patients on dialysis, risk factors included obesity, liver disease, corticosteroid use, elevated calcium-phosphate product and elevated aluminium levels [2]. Hypoalbuminuria (or albumin infusions), recent rapid weight loss, protein C or protein S deficiency, warfarin treatment and hypotension have also been implicated as risk factors. The original term ‘calciphylaxis’ referred to an experimental situation of systemic necrosis in rats that were hypercalcaemic due to treatment with vitamin D or with parathyroid hormone, but did not specifically relate to vascular calcification, hence the change in terminology [3].

Early lesions tend to present as painful plaques, often with a retiform or stellate pattern, and may show central necrosis. They may resemble the lesions of hyperoxaluria. Some may become semiconfluent as a ‘broken’ livedo. The abdomen, thigh and hips are typical sites but the breasts may be involved, in some patients the disease is mainly acral, and uncommon sites include the penis and the tongue [5,6] as well as muscles and internal organs [3]. Woody induration with extending ulcer and eschar formation typically develops.

Pathologically, there is calcification in the medial layer of the wall of small subcutaneous vessels, with necrosis of overlying tissue [1–4]. Some calcification may occur in dermal vessels, in septae within the subcutaneous fat, and in adipocytes themselves. Thrombosed vessels are seen occasionally, presumably as a secondary effect as the calcification of small-vessel walls extends more widely than the thrombotic change or the extravascular calcification [4]. Dermal inflammation may occur without ulceration, and bullae sometimes occur.

Most patients have secondary or tertiary hyperparathyroidism, although the disorder can rarely occur in some with primary hyperparathyroidism. An elevated calcium–phosphorus product is generally expected, but some authors have suggested that this may be present in only a third of cases. Use of vitamin D, or of calcium carbonate (used as a phosphate binder in chronic renal failure), are risk factors. Relevant aspects of calcium homeostasis are discussed in [3]. Vascular calcification induces a phenotypic switch of the vascular myofibroblast to one of an osteoprogenitor. Local (paracrine) pro-mineralization chemicals that are involved include osteopontin (itself stimulated by high glucose levels), bone morphogenetic protein-2 (BMP-2) and Pit-1, as well as matrix metalloproteinases that are stimulated by a catabolic state.

Inhibitors of mineralization include parathormone-related peptide (which is inhibited by vitamin D) and matrix Gla protein (which is inhibited by warfarin); fetuin A inhibits calcification but is inhibited by vitamin D. Thus vitamin D, a commonly used treatment (often as the precursor alpha-calcidol) in chronic renal failure, and warfarin, may both provoke this process, although vitamin D is also used as therapy in patients with hyperparathyroidism who are not considered suitable for parathyroidectomy. It is felt that tensile stress and vascular stasis within calcified areas may also play a part by creating tissue ischaemia.

Parathyroidectomy has been cited as effective, but there is clearly bias in patient selection for this procedure towards those who can tolerate the procedure and are therefore a relatively healthy subgroup. Reduction of the calcium–phosphorus product when elevated is recommended (using low calcium dialysate fluids, and non-calcium oral phosphate binders), as is good wound care and attention to possible accompanying infection, which is a common cause of death. Hyperbaric oxygen, pamidronate, and tissue plasminogen activator have all been used in treatment. Newer treatments that may influence the outcome of this disorder include sodium thiosulphate [7,8], which increases solubility of calcium deposits and has an antioxidant function that may improve endothelial cell function, and cinacalcet hydrochloride [9], which is a calcimimetic therapy that suppresses levels of parathyroid hormone. Logically, cinacalcet should be most useful in patients with hyperparathyroidism and sodium thiosulphate in those without (or in whom it is controlled). Insufficient numbers of patients have been treated with these agents to determine their overall effect on outcome; the prognosis is generally considered poor, with mortality of 50–80%, although there are occasional reports of a more benign course [1,10].

References

1 Oh D, Eulau D, Tokugawa D *et al*. Five cases of calciphylaxis and a review of the literature. *J Am Acad Dermatol* 2000; **40**: 979–87.

2 Weenig RH, Sewell LD, Davis MPD *et al*. Calciphylaxis: natural history, risk factor analysis, and outcome. *J Am Acad Dermatol* 2007; **56**: 569–79.

3 Somach SC. Calciphylaxis (calcific uremic arteriolopathy). In: Morgan MB, Smoller BR, Somach SC, eds. *Deadly Dermatologic Diseases. Clinicopathologic Atlas and Text*. New York: Springer, 2007: 167–72.

4 Au S, Crawford R. Three-dimensional analysis of a calciphylaxis plaque: clues to pathogenesis. *J Am Acad Dermatol* 2002; **47**: 53–7.

5 Rifkin BS, Perazella MA. Calcific uremic arteriolopathy (calciphylaxis). *Mayo Clin Proc* 2006; **81**: 9.

6 Bedoya RM, Gutierrez JL, Mayorga F. Calciphylaxis causing localized tongue necrosis: a case report. *J Oral Maxillofac Surg* 1997; **55**: 193–6.

7 Baker BL, Fitzgibbons CA, Buescher LS. Calciphylaxis responding to sodium thiosulphate therapy. *Arch Dermatol* 2007; **143**: 269–70.

8 Ackerman F, Levy A, Daugas E *et al*. Sodium thiosulphate as first-line treatment for calciphylaxis. *Arch Dermatol* 2007; **143**: 1336–7.

9 Robinson MR, Augustine JJ, Korman NJ. Cinacalcet for the treatment of calciphylaxis. *Arch Dermatol* 2007; **143**: 152–4.

10 Kalajian AH, Malhotra PS, Callen JP, Parker LP. Calciphylaxis with normal renal and parathyroid function: not as rare as previously believed. *Arch Dermatol* 2009; **145**: 451–8.

Specific clinical presentations

This section briefly discusses clinical presentations that are common to a number of occlusive, embolic or vasculitis disorders, in order to allow an approach to the differential diagnosis.

Livedo [1,2]

Livedo describes a reticulate pattern of slow blood flow, with resultant desaturation of blood and bluish discoloration of the skin, which should be completely blanchable if vessels and the blood are normal. Livedo has been divided into two patterns.

Livedo reticularis tends to develop as a tight, net-like pattern of discoloration, often symmetrically distributed, and is more likely to be associated with general disturbances of blood flow such as cold-induced cutaneous vasoconstriction or vascular flow disturbances such as seen in polycythaemia or some cryogelling syndromes. Cutis marmorata in infancy is a perfect example of this pattern. Cutis marmorata telangiectatica congenita is a condition that causes a similar livid reticulate pattern because of telangiectasia.

Livedo racemosa typically has breaks in the tight, net-like pattern, resulting in larger, irregular rings ('broken livedo') than seen in livedo reticularis. It is seldom symmetrical. Livedo racemosa may be more indicative of focal impairment of blood flow, such as with vasculitis, and seems to be the pattern of livedo most often described in European cases of Sneddon's syndrome. The distinction between livedo reticularis and racemosa may be important, but frequently the term 'livedo reticularis' is used to describe both patterns, so careful documentation of the clinical usefulness of this distinction is limited. Finally, lesions of a variety of vascular occlusion syndromes have sometimes been described as lesions of livedo (as discussed above). Although livedo reticularis or racemosa may accompany or surround lesions of retiform purpura, the presence of purpura provides a more specific finding to aid in diagnosis. Whether such conditions frequently present with livedo alone is unclear as these terms have often been used interchangeably in the dermatological literature, and also because semiconfluent retiform lesions may sometimes resemble a broken livedo.

Localized lower extremity livedo (livedoid vasculopathy) is discussed further on p. 49.44.

Conditions that may present as livedo are listed in Table 49.8. It should be noted that more than one factor may apply in some patients, suggesting that a background abnormality has been 'exposed' by an additional event; examples include a patient with antiphospholipid syndrome and fibromuscular dysplasia of peripheral arteries, who developed livedo racemosa and digital necrosis [3]. The same applies in other retiform purpuras, such as phenylephedrine treatment causing microvascular occlusion syndrome in a patient with factor V Leiden [4], and the same applies in purpura fulminans (p. 49.39) in which, for example, meningococcal septicaemia causing thrombosis is strongly linked with background protein C or protein S abnormalities.

References

1 Fleischer AB Jr, Resnick SD. Livedo reticularis. *Dermatol Clin* 1990; **8**: 347–54.

2 Picascia DD, Pellegrini JR. Livedo reticularis. *Cutis* 1987; **39**: 429–32.

3 Eisendle K, Jaschke W, Sepp N. Livedo racemosa and digital necrosis in a patient with primary seronegative antiphospholipid syndrome and fibromuscular dysplasia of peripheral arteries. *Br J Dermatol* 2007; **157**: 389–91.

4 Kalajian AH, Turpen KB, Donovan KO *et al*. Phenylephedrine-induced microvascular occlusion syndrome in a patient with a heterozygous factor V Leiden mutation. *Arch Dermatol* 2007; **143**: 1314–7.

Table 49.8 Acquired livedo reticularis, non-physiological.

Vascular disease-associated
Vasculitis, especially microscopic polyangiitis, cutaneous periarteritis nodosa, rheumatic vasculitides, mixed cryoglobulinaemia, temporal arteritis, Sneddon's syndrome, livedoid vasculitis, arteriosclerosis
Rheumatic diseases
Lupus erythematosus, dermatomyositis, scleroderma, Sjögren's syndrome, antiphospholipid syndrome
Increased blood viscosity, decreased blood flow
Polycythaemia rubra vera, thrombocytosis, cryoglobulinaemia, cryofibrinogenaemia, cold agglutinaemia, monoclonal gammopathy, hypergammaglobulinaemia
Embolic and hypercoagulable disorders
Cholesterol emboli, thrombotic emboli (secondary to cardiac valvular disease, vascular stenosis or aneurysms, etc.), oxalate emboli, decompression sickness with nitrogen bubble embolization, ventilator gas embolization, antiphospholipid antibody syndrome, thrombophilias
Infection
Some reports of livedo with infection may be secondary to emboli (e.g. endocarditis), angiitis (rickettsial) or purpura fulminans-related occlusion (meningococcal); syphilis, tuberculosis and viral diseases are also important
Endocrine
Hyperparathyroidism, pseudohyperparathyroidism, hypothyroidism, Cushing's disease, carcinoid syndrome, phaeochromocytoma
Nutritional
Pellagra
Iatrogenic
Bismuth (intra-arterial), catecholamines/phenylephedrine, amantadine, quinidine (with drug-induced lupus syndrome), arsphenamine

Cutaneous necrosis

Necrosis of the skin occurs in numerous diverse conditions and may present a diagnostic and therapeutic dilemma. Many of the conditions leading to skin necrosis are discussed elsewhere in this chapter or in Chapter 50; vasculitis and vascular occlusion disorders comprise a significant proportion of such cases, but other disorders are briefly considered here [1–9]. Table 49.9 lists some of the more important causes of cutaneous necrosis. It is not intended to be comprehensive, and the disorders listed are those that either commonly cause cutaneous necrosis or in which cutaneous necrosis is a significant risk. The table therefore lists the most important diagnoses to consider, such as vasculitides or sepsis (Fig. 49.14). Not uncommonly, more than one cause may be present, for example in patients with HIV treated for HCV infection with interferon, or use of anticoagulants or chemotherapy in patients subsequently found to have protein C deficiency.

In some instances, the cause is uncertain; localized skin necrosis at injection or vaccination sites (embolia cutis medicamentosa, Nicolau syndrome) may in different cases be due to arterial spasm, thrombosis due to intra-arterial injection of the drug or arterial occlusion due to inflammation.

In some cases cutaneous necrosis may have predictive value, for example it has been suggested to be linked with the presence of underlying malignancy in patients with dermatomyositis [2].



Fig. 49.14 Acral necrosis due to sepsis; treatment with activated protein C may prevent vascular thrombosis in some patients.

References

1 Baker WF Jr, Bick RL. Treatment of hereditary and acquired thrombophilic disorders. *Semin Thromb Hemost* 1999; **25**: 387–406.
2 Basset-Seguin N, Roujeau JC, Gherardi R *et al*. Prognostic factors and predictive signs of malignancy in adult dermatomyositis. A study of 32 cases. *Arch Dermatol* 1990; **126**: 633–7.
3 Bronza JP. Shwartzmann reaction. *Semin Thromb Hemost* 1990; **16**: 326–32.
4 Oh DH, Eulau D, Tokugawa DA *et al*. Five cases of calciphylaxis and a review of the literature. *J Am Acad Dermatol* 1999; **40**: 979–87.
5 Dubost J-J, Souteyrand P, Suavezie B. Drug-induced vasculitides. *Baillière's Clin Rheumatol* 1991; **5**: 119–38.
6 Clark SM, Lanigan SW. Acute necrotic skin reaction to intramuscular Depo-Provera. *Br J Dermatol* 2000; **143**: 1356–7.
7 Merkel PA. Drugs associated with vasculitis. *Curr Opin Rheumatol* 1998; **10**: 45–50.
8 Chan YC, Valenti D, Mansfield AO, Stansby G. Warfarin induced skin necrosis. *Br J Surg* 2000; **87**: 266–72.
9 Allee JE, Saria EA, Rosenblum D *et al*. Intrauterine epidermal necrosis. *J Cutan Pathol* 2001; **28**: 383–6.

Neonatal purpura [1]

The differential diagnosis of purpura or bleeding in neonates includes most of the causes of purpura. However, it is discussed as a separate entity due to the diagnostic dilemmas that may arise. The main causes are listed below.

- Deficiency of clotting factors and coagulation disorders (including purpura fulminans and vitamin K deficiency)
- Thrombocytopenia: congenital, maternal antibodies (ITP, SLE, others)
- Extramedullary erythropoiesis ('blueberry muffin' baby)
- Infections, e.g. TORCH syndrome, which comprises *t*oxoplasmosis, *o*ther infections (syphilis and viral), *r*ubella, *c*ytomegalovirus and *h*erpes simplex, may cause blueberry muffin baby; other infectious causes include HIV, parvovirus B19 and sepsis
- Congenital/inherited conditions, e.g. Wiskott–Aldrich syndrome
- Maternal antibody-mediated: autoimmune (ITP, SLE, drug) or alloimmune (isoimmune) due to fetomaternal incompatibility
- Associated with haemangiomas

Table 49.9 Some causes of cutaneous necrosis.

Coagulation defects [1]
Purpura fulminans, disseminated intravascular coagulopathy
Protein C or S deficiency, antithrombin III deficiency, prothrombin 20210A mutations

Vasculitis
Most vasculitides may cause skin necrosis, e.g. polyarteritis nodosa, Behçet's disease, Wegener's granulomatosis, Churg–Strauss disease, Henoch–Schönlein purpura (see Chapter 50)

Connective tissue disease (see Chapter 51)
Antiphospholipid syndrome/lupus anticoagulant, dermatomyositis [2], relapsing polychondritis, systemic lupus erythematosus, systemic sclerosis

Immunological
Shwartzmann reaction [3]

Hyperviscosity
Cryoglobulinaemia, cryofibrinogenaemia, cold agglutinins, paraproteinaemia, POEMS syndrome

Embolic
Cholesterol emboli, cardiac myxoma, bacterial endocarditis/septic emboli, emboli from arterial aneurysms, neoplasms, emboli through patent foramen ovale (thrombus, infective) from venous cannulae

Metabolic (see Chapter 59)
Diabetes, hyperhomocystinaemia, oxalosis, calciphylaxis [4], subcutaneous calcification

Arterial occlusion or spasm, neurovascular disease
Arteritis (e.g. temporal arteritis, Buerger's disease), Degos' disease, thrombosis, intra-arterial cocaine, aneurysm, anastomosis, compartment syndrome, embolia cutis medicamentosa (Nicolau syndrome), complex regional pain syndrome (reflex sympathetic dystrophy)

Infections (see Chapters 30–36)
Bacterial, e.g. necrotizing fasciitis, cellulitis, streptococci, clostridia, meningococcus, pseudomonas (ecthyma gangrenosum), leprosy (Lucio's reaction), sepsis (any cause) (Fig. 49.14)
Viral, e.g. HIV, cytomegalovirus, hepatitis B or C, herpes zoster
Fungal, e.g. deep/disseminated fungal infection (especially *Aspergillus*, *Mucor*, *Rhizopus, Histoplasma*)

Venoms
Snake bites, spider bites, stings (e.g. scorpion, stingray)

Drugs and toxins (see also Chapter 75) [5–8]
Systemic
- Anticoagulants, e.g. warfarin (coumadin), heparin
- Vasoactive drugs, e.g. vasopressin, norepinephrine, dopamine, metaraminol, β-blockers
- Chemotherapeutic drugs, e.g. methotrexate, bleomycin, cyclophosphamide, vincristine
- Cytokines and growth factors, e.g. tumour necrosis factor, interferons, interleukin-3, G-CSF, GM-CSF
- Antimicrobials, e.g. penicillins, sulphonamides, aciclovir, levamisole
- Antithyroid, e.g. thiouracils, carbimazole
- Toxins, e.g. carbon monoxide poisoning
- Illicit drugs, e.g. cocaine
- Miscellaneous, e.g. penicillamine, iodides, bromides, phenytoin

Topical
- Glutaraldehyde, cetrimide, calcium chloride, mustard gas, hydrofluoric acid, phosphorus

Injection sites
- Calcium salts, interferon, aminoglycosides, collagen, silicone, hydrocarbons, vaccines (DTP, BCG), iron dextran, chemotherapy extravasation, Depo-Provera, several illicit drugs, intra-arterial injections

Malignant disease
Leukaemia, lymphoma (especially angiotropic types), mycosis fungoides, lymphomatoid granulomatosis, hypereosinophilic syndrome, myelodysplastic syndrome, Langerhans' cell histiocytosis
Phaeochromocytoma (localized or acral necrosis)
Paraneoplastic thrombosis, paraneoplastic acral vasculopathy (Chapter 62)

Physical damage
Burns, radiation, trauma, factitious ulcer, sclerotherapy, liposuction

Inflammatory dermatoses
Sarcoidosis, pityriasis lichenoides acuta, febrile necrotic Mucha–Haberman disease, pyoderma gangrenosum and neutrophilic dermatoses, panniculitides

Miscellaneous
Intrauterine epidermal necrosis [9]

BCG, bacillus Calmette–Guérin; DTP, diphtheria–tetanus–pertussis; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte–macrophage colony-stimulating factor; HIV, human immunodeficiency virus; POEMS, polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes

- Traumatic: caput succedaneum and facial petechiae (prolonged vertex delivery)
- Others, e.g. vascular purpura, non-accidental injury (both rare in this age group).

The three most important groups for dermatologists are purpura fulminans, blueberry muffin baby and infections [1]. Purpura fulminans in the neonate is an important manifestation of protein S or protein C deficiency (discussed on p. 49.39). Skin lesions in blueberry muffin baby are distinguished from purpura as they are palpably firm and elevated, but non-palpable purpura may coexist. The TORCH group of infections may cause this condition, but haemolysis (such as rhesus incompatibility), hereditary spherocytosis and twin transfusion syndrome may also be associated with extramedullary erythropoiesis.

Haemorrhagic disease of the newborn is due to accentuation of the normal fall of prothrombin within the first week of life but is now uncommon due to routine vitamin K prophylaxis. An early form, within the first 24 h of life, may occur if there is maternal intake of drugs that interfere with vitamin K (such as oral anticoagulants), and a late form (1–12 months) occurs in children with impaired gastrointestinal absorption and may cause deep nodular ecchymoses. Haemophilia and other coagulation factor deficiencies only rarely cause bleeding at this age.

Of the many causes of purpura fulminans [2], the following are most likely in neonates or young infants:

- Acute infectious: usually bacterial sepsis [3], including meningococcus, streptococcus, *Haemophilus* and other infections
- Post-infectious: varicella, streptococcus and others (usually 7–10 days post-infection)
- Congenital protein C or S deficiency; factor V Leiden mutation
- Acquired protein C or S deficiency: coumarins, hepatic cholestasis, nephrotic syndrome, renal dialysis, marrow transplantation
- Heparin-induced skin necrosis (most cases are related to local skin injection).

In older children, additional causes include:

- Antiphospholipid syndrome
- Vasculitis: polyarteritis nodosa, Henoch–Schönlein purpura, others
- Thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome, paroxysmal nocturnal haemoglobinuria
- Toxins and poisons: snake and spider bites (usually maximal purpura at the inoculation site).

Antiphospholipid syndrome (APLS) is rare in children although low-titre antiphospholipid antibodies, possibly provoked by infection, are relatively frequent (being found in about 10% of healthy children) [4]. Transplacental transfer of anticardiolipin antibodies occurs in neonates born to mothers with APLS but does not appear to result in thrombotic complications, despite the fact that antithrombin III levels are low in neonates and theoretically would represent a further risk factor. When APLS is associated with purpura fulminans, this is termed the 'catastrophic antiphospholipid antibody syndrome'; patients may have a preceding infection, rarely associated SLE, but do not tend to have protein C or protein S abnormalities [5].

It should be noted that the term purpura fulminans has been used either as a broad term for widespread cutaneous purpura of any type, or more specifically for disorders in which cutaneous microvascular occlusion is the known cause of widespread cutaneous purpura. Especially in neonates, in whom (in the absence of a clotting factor deficiency) infection and/or congenital thrombophilic states are the most likely associated causes of widespread purpura, it is prudent to assume that there may be a protein C or protein S abnormality.

References

1 Baselga E, Drolet BA, Esterley NB. Purpura in infants and children. *J Am Acad Dermatol* 1997; **37**: 673–705.

2 Levin M, Eley B, Faust SN. Purpura fulminans. In: Harper J, Oranje AP, Prose N, eds. *Textbook of Pediatric Dermatology*, 2nd edn. Oxford: Blackwell Science, 2006: 1902–16.

3 Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. *N Engl J Med* 2003; **348**: 138–50.

4 Cimaz R, Descloux E. Pediatric antiphospholipid syndrome. *Rheum Dis Clin N Am* 2006; **32**: 559–73.

5 Cervera R, Asherson RA, Font J. Catastrophic antiphospholipid syndrome. *Rheum Dis Clin N Am* 2006; **32**: 575–90.

CHAPTER 50

Vasculitis, Neutrophilic Dermatoses and Related Disorders

N.H. Cox[1], J.L. Jorizzo[2], J.F. Bourke[3] & C.O.S. Savage[4]

[1]Department of Dermatology, Cumberland Infirmary, Carlisle, UK
[2]Department of Dermatology, Wake Forest University School of Medicine, Winston-Salem, NC, USA
[3]Department of Dermatology, South Infirmary–Victoria Hospital, Cork, Ireland
[4]Division of Immunity and Infection, University of Birmingham, UK

Vasculitis, 50.1
Introduction, 50.1
Classification and nomenclature, 50.1
Pathogenesis of vasculitis, 50.3
Evaluation of the patient with suspected vasculitis, 50.12
Cutaneous small vessel vasculitis, 50.13
Drug-induced vasculitis, 50.17
Henoch–Schönlein purpura, 50.19
Urticarial vasculitis, 50.21
Exercise-induced vasculitis, 50.23
Cryoglobulinaemic vasculitis, 50.23
Erythema elevatum diutinum, 50.25
Eosinophilic vasculitis, 50.27
Granuloma faciale, 50.28
Acute haemorrhagic oedema of childhood, 50.30
Nodular vasculitis, 50.31
Polyarteritis nodosa, 50.33
Microscopic polyangiitis, 50.35
Cutaneous polyarteritis nodosa, 50.37
Wegener's granulomatosis, 50.39
Churg–Strauss syndrome, 50.41
Giant cell arteritis, 50.43
Takayasu's arteritis, 50.44
Other vasculitides and mimics of vasculitis, 50.45
Kawasaki disease, 50.45
Cerebral vasculitis and mimics, 50.46
Lymphocytic vasculitis, 50.47
Pityriasis lichenoides, 50.50
Macular arteritis, 50.51
Lymphocytic thrombophilic arteritis, 50.51
Palisaded neutrophilic and granulomatous dermatitis, 50.52
Vasculitis as a component of other systemic diseases, 50.52
Microvascular occlusion disorders, 50.54
Infections, 50.55
Behçet's disease, 50.56
Neutrophilic dermatoses, 50.62
Introduction, 50.62
Classification, 50.62
Pyoderma gangrenosum, 50.64
Sweet's syndrome, 50.74
Extracutaneous neutrophilic dermatoses, 50.81
Erythema nodosum, 50.82
Bowel-associated dermatosis–arthritis syndrome, 50.87
Pustular neutrophilic dermatoses, 50.88
Other neutrophilic dermatoses and overlapping or associated variants, 50.90

Vasculitis

Introduction

Vasculitis is a term applied to inflammation and necrosis of blood vessels, whether they be arteries, veins or both. Vasculitis may be local or systemic, and may be primary or secondary to another disease process. Small vessels (such as capillaries, arterioles and venules), medium-sized vessels (such as visceral vasculature, including renal, coronary or hepatic arteries) and large vessels (the aorta and its great vessels) may be affected. Many vasculitides have a cutaneous component. A dermatologist can provide invaluable assistance in the clinicopathological diagnosis of vasculitis and by guiding patient evaluation and treatment.

Because of the wide range of organ systems affected by vasculitis of blood vessels of various sizes, the clinical presentation of the many vasculitides is varied. However, classic cutaneous manifestations, such as palpable purpura in dependent areas, typically the ankles and lower legs, characterizes smaller vessel involvement, whereas necrotizing livedo reticularis or multiple sites of peripheral gangrene characterize larger vessel vasculitis. It is also important to note that vasculitides may be present without any cutaneous signs or symptoms, especially in the case of cerebral vasculitis.

Infiltration of inflammatory cells with subsequent destruction of blood vessel walls is classically demonstrated in nearly all vasculitides. However, specific histopathological features are dependent on the type and size of the affected blood vessel.

Many vasculitides are triggered by various antigenic agents, such as infection or medication, or are related to underlying disease such as connective tissue, vascular or inflammatory bowel disease, myelodysplastic or other malignancies. However, a single trigger may be associated with several distinct vasculitides, implying that different and more specific mechanisms of inflammation apply in different disorders. Pathogenetic factors in vasculitis are discussed below.

Classification and nomenclature

The classification of vasculitides has been a confusing and debate-provoking topic over the last half century. The first attempt at a

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

Table 50.1 1990 American College of Rheumatology criteria for hypersensitivity vasculitis (traditional format) [5].

1	Age at disease onset >16 years
2	Medication at disease onset
3	Palpable purpura
4	Maculopapular rash
5	Biopsy including arteriole and venule with histological changes showing granulocytes in a perivascular or extravascular location

At least three of the five criteria must be present. The presence of three criteria was associated with a specificity of 83.9% and a sensitivity of 71.0% [5].

classification was by Zeek in 1952 [1]. In her classification of necrotizing vasculitis, she incorporated a clinicopathological evaluation based on the size of the blood vessel involved in the inflammatory process. Zeek differentiated five types of necrotizing angiitis: periarteritis nodosa, hypersensitivity arteritis, rheumatic arteritis, allergic granulomatous angiitis and temporal arteritis [2].

Other factors that may be considered in the classification of vasculitis were discussed by Winkelmann [3]. He incorporated clinical classification, systemic versus cutaneous involvement, muscular vessel versus small vessel disease, and histopathological features in his schema. He also discussed 'laboratory vasculitis', which reviewed the laboratory findings of patients with vasculitis as part of a classification scheme, as well as aetiological factors of various vasculitides [3].

In 1976, James Gilliam [4] proposed a classification of necrotizing vasculitis as part of Medical Grand Rounds at the University of Texas Southwestern Medical Center.

The American College of Rheumatology published classification criteria for vasculitis in 1990 [5]. However, several problems exist with this classification scheme, which is shown in Table 50.1. Particular problems with the criteria include an attempt to codify histological findings of small vessel ('hypersensitivity') vasculitis using 14 biopsy criteria. Furthermore, the use of such terms as 'maculopapular rash', 'medication at onset' and 'eosinophils on biopsy', as well as the separate classification of Henoch–Schönlein purpura, seem inappropriate to most dermatologists.

In 1994, the Chapel Hill Consensus Conference [6] addressed the nomenclature problems relating to primary systemic vasculitides, aiming to create a standardized nomenclature (which is depicted in Table 50.2). This system divided the vasculitides into small, medium and large vessel types, but specifically did not aim to determine clinical criteria for classification or diagnosis of individual patients.

A further attempt to classify vasculitides based on an updated version of Gilliam's 1976 scheme is presented in Table 50.3.

Classifications based on histopathology features are described in [7,8]. Additional classifications have been proposed but have yet to stand the test of time; examples are described in [9–11] and discussed in [12]. Classifications that include, or are based on, serological markers such as antineutrophil cytoplasm antibodies (ANCA) are increasingly important, but the emphasis is often on primary systemic vasculitides and not all suggested classifications translate easily to understanding vasculitis of the skin. Thus, despite numerous attempts over 50 years, the development of a clinically relevant and easy-to-use classification system for vasculitis that incorporates clinical features, vessel size, histopathological and laboratory features, and aetiologies, is a goal that has not yet been fully achieved.

Despite the obstacles, various groups continue to incorporate current knowledge into revised classifications. As an example, the recent consensus criteria for the classification of childhood vasculitides produced by the European League against Rheumatism (EULAR) and the Paediatric Rheumatology European Society (PReS) have deleted the ACR age criterion for diagnosis of HSP, and have added the fact that skin or renal biopsy should show predominant IgA deposition [9] (the criteria state that there must be palpable purpura with at least one of four other criteria—

Table 50.2 Chapel Hill Consensus Conference classification of vasculitis [6].

I	*Large vessel vasculitis*
A	Giant cell arteritis
B	Takayasu's arteritis
II	*Medium-sized vessel vasculitis*
A	Classic polyarteritis nodosa
B	Kawasaki disease
III	*Small vessel vasculitis*
A	Wegener's granulomatosis
B	Churg–Strauss syndrome
C	Microscopic polyangiitis (polyarteritis)
D	Henoch–Schönlein purpura
E	Essential cryoglobulinaemia
F	Cutaneous leukocytoclastic vasculitis

Table 50.3 Proposed working classification of vasculitis.

Small vessel vasculitis
Cutaneous small vessel vasculitis—not further classified
Henoch–Schönlein purpura
Essential mixed cryoglobulinaemia (Chapter 49)
Waldenström's hypergammaglobulinaemic purpura (Chapter 49)
Associated with collagen vascular disease (Chapter 51)
Urticarial vasculitis
Erythema elevatum diutinum
Eosinophilic vasculitis
Rheumatoid nodules (Chapter 51)
Reactive leprosy (Chapter 32)
Septic vasculitis
Larger vessel vasculitis
Polyarteritis nodosa
• Microscopic polyarteritis
• Cutaneous form
• Systemic form
Granulomatous vasculitis
• Wegener's granulomatosis
• Allergic granulomatosis of Churg and Strauss
• Lymphomatoid granulomatosis (Chapter 57)
Giant cell arteritis
• Temporal arteritis
• Takayasu's arteritis
Larger vessel vasculitis with collagen vascular disease
Nodular vasculitis

diffuse abdominal pain, biopsy with predominant IgA deposition, acute arthritis or arthralgia and renal involvement).

The situation is further complicated by a number of disorders that appear to overlap with vasculitis, in that they may, in at least some cases, include vasculitis. A large group of 'neutrophilic dermatoses' come into this category; although we previously considered these as neutrophilic vascular reactions, the accepted spectrum of such disorders has widened, and histological evidence of vasculitis has been reported sufficiently often that, even though it may be a secondary effect, it is appropriate to discuss this group of conditions here (although epidermal neutrophilic dermatoses, such as neutrophilic IgA pemphigus, are discussed elsewhere). Indeed, in the case of Sweet's syndrome, one of the best accepted neutrophilic dermatoses, histological evidence of vasculitis was once considered inconsistent with the diagnosis but has recently been described as being present in 74% of 31 cases studied [13].

Similarly, the more aggressive forms of pityriasis lichenoides have a vasculitic component and are included here.

Between the extremes of pure vasculitis and pure neutrophilic dermatoses or vascular reactions, Behçet's disease may have pustules similar to bowel-associated dermatitis–arthritis syndrome, pathergy similar to pyoderma gangrenosum, and vasculitis of various sizes and types of blood vessel. The vasculitis of Behçet's disease arguably has features that separate it from other vasculitides, the associated aphthous ulceration of mucosae differs from the main vasculitides or neutrophilic dermatoses, and we have therefore discussed this as a separate entity with mixed features between vasculitis and neutrophilic dermatoses.

References

1 Zeek PM. Periarteritis nodosa: a critical review. *Am J Clin Path* 1952; **22**: 777–90.

2 Zeek PM. Periarteritis nodosa and other forms of necrotizing angiitis. *N Engl J Med* 1953; **248**: 764–72.

3 Winkelmann RK. Classification of vasculitis. In: Wolff K, Winkelmann RK, eds. *Vasculitis*. Philadelphia: Saunders, 1980: 322–32.

4 Gilliam JN, Smiley JD. Cutaneous necrotizing vasculitis and related disorders. *Ann Allergy* 1976; **37**: 328–9.

5 Hunder GG, Arend WP, Block DA *et al*. The American College of Rheumatology 1990 Criteria for the Classification of Vasculitis. *Arthritis Rheum* 1990; **33**: 1065–136.

6 Jennette JC, Falk RG, Andrassy K *et al*. Nomenclature of systemic vasculitides: proposal of an international consensus conference. *Arthritis Rheum* 1994; **37**: 187–92.

7 Carlson JA, Chen K-R. Cutaneous vasculitis update: small vessel neutrophilic vasculitis syndromes. *Am J Dermatopathol* 2006; **28**: 486–506.

8 Carlson JA, Chen K-R. Cutaneous vasculitis update: neutrophilic muscular vessel and eosinophilic, granulomatous, and lymphocytic vasculitis syndromes. *Am J Dermatopathol* 2007; **29**: 32–43.

9 Ozen S, Ruperto N, Dillon MJ *et al*. EULAR/PReS endorsed consensus criteria for the classification of childhood vasculitides. *Ann Rheum Dis* 2006; **65**: 936–41.

10 Watts R, Lane S, Hanslik T *et al*. Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies. *Ann Rheum Dis* 2006; **66**: 222–7.

11 Hogan SL, Falk RJ, Nachman PH, Jennette JC. Various forms of life in antineutrophil cytoplasmic antibody-associated vasculitis. *Ann Intern Med* 2006; **144**: 377–8.

12 Jenette JC, Falk RJ. Nosology of primary vasculitis. *Curr Opin Rheumatol* 2007; **19**: 10–16.

13 Ratzinger G, Burgdorf W, Zelger BG, Zelger B. Acute febrile neutrophilic dermatosis: a histopathologic study of 31 cases with review of literature. *Am J Dermatopathol* 2007; **29**: 125–33.

Pathogenesis of vasculitis

The pathogenesis of vasculitis is a complex subject, not least because there are likely to be many different pathogeneses reflecting the many different causes and pathological entities. This brief overview describes some of the major mechanisms and systems involved, with emphasis on those that have clinical importance (such as the diagnostic potential of ANCA). More detailed recent reviews can be consulted [1–9]; factors pertaining to specific vasculitides are summarized, with more specific references, in the relevant sections discussing specific types of vasculitis.

Histopathologically, cutaneous necrotizing vasculitis may be leukocytoclastic with a neutrophilic infiltrate and a presumed immune complex pathogenesis, or may be lymphomonocytic and pauci-immune; however, this is not always helpful diagnostically as the change from the former to the latter occurs as part of a dynamic sequence, leukocytoclastic vasculitis generating a secondary cell-mediated immune response. Factors that play a part in the pathogenesis of vasculitis include antigen–antibody related mechanisms (including autoantibodies and immune complex diseases), inflammatory cells and their lysosomal content, complement, cytokines, chemokines, adhesion molecules, vascular and cellular growth factors, genetic influences, pro-coagulant factors and the fibrinolytic system, as well as direct vessel wall damage (e.g. by some infectious organisms). Local blood flow influences the development of the vasculitis lesion, as evidenced by lesions occurring at areas of constriction by tight clothing, and local release of histamine also has a role. It is apparent that none of these factors operates in isolation—for example, endothelial damage will cause expression of cell-surface adhesion molecules, production of cytokines and influx of pro-inflammatory cells—so there is inevitably some overlap between the following sections, which address some of the more important and better documented factors involved in vasculitic inflammation.

References

1 Ball GV, Bridges SL. Pathogenesis of vasculitis. In: Ball GV, Bridges SL, eds. *Vasculitis*. Oxford: Oxford University Press, 2002: 34–52.

2 Piette WW. Primary systemic vasculitis. In: Sontheimer RD, Provost TT, eds. *Cutaneous Manifestations of Rheumatic Diseases*. Baltimore: Williams & Wilkins, 1995: 177–232.

3 Kallenberg CGM. Laboratory findings in the vasculitides. *Baillières Clin Rheumatol* 1997; **11**: 395–421.

4 Nowack R, Flores-Suárez LF, van der Woude FJ. New developments in pathogenesis of systemic vasculitis. *Curr Opin Rheumatol* 1998; **10**: 3–11.

5 Savage COS. The evolving pathogenesis of systemic vasculitis. *Clin Med* 2002; **2**: 458–64.

6 Lotti T, Ghersetich I, Comacchi C, Jorizzo JL. Cutaneous small-vessel vasculitis. *J Am Acad Dermatol* 1998; **39**: 667–87.

7 Klippel JH, Dieppe PA. *Rheumatology*, 2nd edn. London: Mosby, 1998: 7.19.1–8.

8 Sneller MC, Fauci AS. Pathogenesis of vasculitis syndromes. *Med Clin N Am* 1997; **81**: 221–42.

9 Jenette JC, Falk RJ. New insight into the pathogenesis of vasculitis associated with antineutrophil cytoplasmic antibodies. *Curr Opin Rheumatol* 2008; **20**: 55–60.

Table 50.4 Theory of pathogenesis of cutaneous small vessel vasculitis. (Modified from [4].)

- Immune complexes interact with the complement system to generate C3a and C5a anaphylatoxins, which stimulate:
  - production of chemotactic factors which initiate chemotaxis of neutrophils
  - release of vasoactive amines (such as histamine), which cause endothelial cell retraction
  - release of proinflammatory cytokines (e.g. IL-1, TNF-α) which induce the expression of adhesion molecules (ICAM-1, VCAM-1, P- and E-selectin) in endothelial cells
  - adhesion molecules (ICAM-1, VCAM-1, P- and E-selectin) in endothelial cells
- Activation of the membrane attack complex of complement directly damages membrane integrity of endothelial cells
- Immune complexes deposit in vascular walls after histamine-induced endothelial retraction which increases selectin expression in endothelial cells
- Attracted neutrophils produce lysosomal enzymes in an attempt to engulf deposited immune complexes
- Neutrophils are activated through Fc binding and degranulate, and also produce reactive oxygen species
- Ultimate inflammation and 'bystander' fibrinoid necrosis of blood vessel wall

Antigens, immune complexes and complement

Antigenic triggers of immunological responses targeted at components of blood vessel walls elicit most vasculitides. The importance of circulating immune complexes has long been recognized in studies of serum sickness [1], and the deposition of immune complexes in blood vessel walls is the best characterized mechanism for the vascular injury associated with vasculitis [2]. This mechanism appears to be particularly important in leukocytoclastic necrotizing cutaneous small vessel vasculitis; potential antigens of relevance include bacteria, viruses, drugs and other chemicals. Most evidence for an immune complex-mediated pathogenesis is circumstantial (e.g. the demonstration of immunoglobulins in skin lesions) and is better documented for cutaneous small vessel vasculitis than for systemic vasculitides. It is generally accepted that immune complexes have a role in Henoch–Schönlein purpura (HSP), serum sickness, hepatitis B and C virus-induced vasculitis, urticarial vasculitis and cryoglobulinaemic vasculitis.

A theory about the pathogenesis of cutaneous small vessel vasculitis is described below and depicted in Table 50.4 [3,4]. The circulating immune complexes mediating vasculitis interact with the complement system to generate C3a and C5a anaphylatoxins which degranulate mast cells. They stimulate the production of chemotactic factors and subsequent chemotaxis, the release of vasoactive amines (such as histamine) and the release of proinflammatory cytokines which induce the subsequent expression of adhesion molecules. Circulating immune complexes may also be bound by myelomonocytic cells (via the Fcγ receptor) and by endothelial cells (via FcγRIIa (CD32)) [5]. Immune complexes with a sedimentation coefficient greater than 19S are deposited in vessel walls, a process that is strongly influenced by platelet-derived vasoactive amines. Endothelial cell retraction and detachment occur due to altered membrane integrity that is induced by vasoactive amines and probably by the membrane attack complex of complement [6]. Secreted cytokines, including interleukin-1 (IL-1), gamma-interferon (IFN-γ) and tumour necrosis factor-alpha (TNF-α), cause increased expression of adhesion molecules (ICAM-1, E-selectin and VCAM-1) and HLA-DR (the 'adhesion cascade') by endothelial cells, which recruit neutrophils [5]. The CD40 ligand, which is structurally similar to TNF-α and which is present on stimulated $CD4^+$ T cells, mast cells and platelets, may also activate secretion of cytokines and expression of adhesion molecules by endothelial cells. Neutrophils that are attracted to the site of immune complex deposition are activated *in situ* through binding of the fragment crystallizable (Fc) portion of the antibody, and release lysosomal enzymes in a teleological attempt to engulf the deposited immune complexes. This causes degranulation and destruction of the neutrophils (visible histologically as leukocytoclasis) with release of collagenase and elastase, and generation of reactive oxygen species, ultimately resulting in inflammation and 'bystander' fibrinoid necrosis of vessel walls. It is of practical importance to appreciate that neutrophils degrade immune complexes within 24–48 h after they are deposited [7], usually within 24 h; hence, direct immunofluorescence of vasculitis lesions older than 3–12 h will generally yield negative results [3,8]. Eosinophils are also attracted in some situations, and also contain cytotoxic lysosomal enzymes. Survival of neutrophils or eosinophils at sites of inflammation may be aided by the antiapoptotic effect of colony stimulating factors (this is discussed with relation to TNF-related apoptosis-induced ligand-3 (TRAIL3) and death receptors in the section on Churg–Strauss syndrome).

Immune complexes may also activate endothelial cells to produce tissue plasminogen activator (t-PA) and thus alter local fibrinolysis and vascular permeability [3]. There are therefore many complex and dynamic changes that occur.

Paraneoplastic vasculitis is thought to be caused by tumour antigens stimulating cell-mediated immunity or forming tumour antigen immune complexes, although direct vessel wall damage or occlusion can occur as a result of emboli. Haematological malignancies are the most common to be associated with vasculitis [9].

Antiphospholipid antibodies are important as a cause of microvascular thrombosis (Chapter 49). However, they also bind to endothelial cells and have numerous effects; they are proinflammatory, induce monocyte activation, stimulate cytokine and vascular adhesion factor expression, and result in a thrombophilic state [10]. In autoimmune conditions, binding requires plasma $\beta_2$glycoprotein-I (β_2-GP-I), which itself binds to endothelial cells and complexes with phospholipids.

Superantigens have also been implicated in development of vasculitis; this is discussed in more detail in the next section.

Complement activation leads to the adherence of C3b to immune complexes, such that they remain soluble and are cleared by macrophages. Immune complexes that have bound C3b also bind to erythrocytes via the complement receptor type 1 (CR1), about 90–95% of which is located on the surface of erythrocytes, leading to clearance of immune complexes from the reticuloendothelial system and preventing interaction with endothelial cells and other structures. Complement deposition is documented in skin lesions (e.g. in HSP) and genetic deficiency of complement is associated with immune complex diseases. However, IgA immune complexes in patients with HSP do not appear to activate the classical

complement pathway, although activation of the alternative pathway by IgA1 (the main IgA subclass in HSP) may allow complexes to be made soluble.

References

1 Lawley TJ, Bielory L, Gascon P *et al*. Prospective clinical and immunologic analysis of patients with serum sickness. *N Engl J Med* 1984; **311**: 1407–13.
2 Dixon FJ, Cochrane CG. The pathogenicity of antigen–antibody complexes. *Pathol Annu* 1970; **5**: 355–79.
3 Lotti T, Ghersetich I, Comacchi C, Jorizzo JL. Cutaneous small-vessel vasculitis. *J Am Acad Dermatol* 1998; **39**: 667–87.
4 Klippel JH, Dieppe PA. *Rheumatology*, 2nd edn. London: Mosby, 1998: 7.19.1–8.
5 Witort-Serraglini E, del Rosso M, Lotti TM, Matucci-Cerinic M. Endothelial injury in vasculitides. *Clin Dermatol* 1999; **17**: 587–90.
6 Kawana S. The membrane attack complex of complement alters the membrane integrity of cultured endothelial cells: a possible pathophysiology for immune complex vasculitis. *Acta Derm Venereol (Stockh)* 1996; **76**: 13–6.
7 Cochrane CG, Weigle WO, Dixon FJ. The role of polymorphonuclear leukocytes in the initiation and cessation of the Arthus vasculitis. *J Exp Med* 1959; **110**: 481–94.
8 Yancey KB, Lawley TJ. Circulating immune complexes: their immunochemistry, biology and detection in selected dermatologic and systemic diseases. *J Am Acad Dermatol* 1984; **10**: 711–31.
9 Paydas S, Zorludemir S, Sabin B. Vasculitis and leukaemia. *Leuk Lymphoma* 2000; **40**: 105–12.
10 Meroni PL, Raschi E, Testoni C *et al*. Antiphospholipid antibodies and the endothelium. *Rheum Dis Clin North Am* 2001; **27**: 587–602.

The role of infections [1–4]

Infections appear to provoke some vasculitides, particularly those relevant to dermatologists; the role of specific infections and the strength of such associations is discussed in sections relating to specific entities such as Henoch–Schönlein purpura (HSP) (in which a role for infective triggers is well documented) and large vessel vasculitides. Vaccinations have also been implicated in some vasculitides, notably acute haemorrhagic oedema of childhood and occasionally in cutaneous small vessel vasculitis. Conditions that mimic vasculitis, such as bacterial or fungal emboli, are not discussed here other than in terms of their potential to damage vessels. This section discusses mechanisms by which infections may be involved in pathogenesis of vasculitis, some of which may apply to other causes as well. There is evidence in most of the 'primary' vasculitides that at least some cases can be linked to one or another form of action of infective organisms [3]; the problems are that studies have produced conflicting evidence, that more than one infection may be linked with any particular pattern of vasculitis, and that the pathogenetic mechanisms have often not been elucidated. Several potential mechanisms, one or more of which may apply in some situations, have been proposed, as below. It must be stressed that this attempt to explain possible mechanisms is probably over-simplistic as they may not occur in isolation—for example, immune complexes may be formed in relation to an antigenic component of a circulating organism, to exposed antigens of an organism that has become intracellular, or to self antigens exposed by cellular infection. Equally, activation of cytokines may be a response to pathogens themselves, or be triggered by cellular damage consequent to an infection. Pathogens themselves may provoke a variety of different responses—for example, cytomegalovirus (a major cause of vascular morbidity in immunosuppressed individuals) infects and damages endothelial cells, causes ischaemia and thrombosis, and expresses antigens that may stimulate an immune response [5]. Thus, one or more of the following may occur as a result of infection:

1 Immune complex reactions (Gell and Coombs type 3 reaction): this has been discussed above as a major mechanism in vasculitis, due to several triggers (e.g. drugs) as well as in response to infections. Immune complexes may be formed between antibodies and an entire organism or specific antigenic components, and may become trapped in vessels, stimulating a cascade of reactions as described above. The pustular vasculitis of gonococcal infection and much of the vasculitis in subacute bacterial endocarditis probably occur due to immune complex formation, and circulating or tissue deposits of immune complexes have been found in hepatitis B, hepatitis C and human immunodeficiency virus (HIV) infections. Immune complexes related to infectious agents may be formed in the circulation or *in situ* in infected vascular cells.

2 Direct activation of complement by infectious organisms: as well as activating the classical complement pathway via formation of immune complexes, some microbial products directly activate the alternative pathway of complement. These include polysaccharides (e.g. from *Candida* spp.) as well as various parts of both Gram-positive and Gram-negative bacteria [1].

3 Direct activation of other pro-inflammatory mechanisms: bacterial lipopolysaccharides, as well as heat shock proteins from several organisms, induce tumour necrosis factor-alpha (TNF-α) production by macrophages, which in turn stimulates vascular endothelial cells to express cell adhesion molecules. Lipopolysaccharides and heat shock proteins also stimulate production of interleukins IL-1 and IL-6 from endothelial cells, and may directly stimulate secretion of matrix metalloproteinases.

4 Molecular mimicry hypothesis: if endothelial cells or other cells comprising vessel walls share epitopes with an infective organism, then humoral and cell-mediated responses to infection will also target the host cells that carry the same epitope. There is some evidence for this mechanism in, for example, renal involvement in HSP; group A β-haemolytic streptococci are implicated as a trigger in about a third of affected subjects, and renal glomerular vessels express nephritis-associated plasmin receptor (NAPlr) which is a streptococcal antigen [6]. Heat shock proteins, which are expressed by endothelial cells following stress, and which have considerable homology with some antigens of infective organisms, have been implicated in such a process but this is not a proven mechanism of autoimmunity in humans.

5 Superantigen hypothesis: superantigens directly activate T cells, without the need for antigen-presenting cells, by interaction with Vβ segments of the T cell receptor (TCR); they may also stimulate B cells. Analysis of Vβ sequences of the TCR of circulating T cells, or the V_H repertoire of B cells in lesional biopsies can be used to demonstrate patterns consistent with superantigen-induced proliferation. A role for superantigens of *Staphylococcus aureus* is a factor in atopic dermatitis (Chapter 24); in the vasculitides, most evidence for a role of staphylococcal superantigens has been documented in Kawasaki disease and in Wegener's granulomatosis (WG) [3]. In Kawasaki disease,

strains of *S. aureus* expressing the toxic shock syndrome toxin-1 (TSST-1) antigen have been implicated in causation. In WG, the evidence for a role of staphylococcal superantigens in disease perpetuation is better than for disease causation (and is supported by benefit from prophylactic treatment with cotrimoxazole). However, other infections have also been linked with both of these conditions [3], such as New Haven coronavirus in Kawasaki disease, so this hypothesis may not be the only pathogenetic factor.

6 Direct non-specific vessel wall or perivascular invasion and damage (also termed the bystander activation hypothesis), especially by vasculotropic viruses such as cytomegalovirus and human herpes-virus HHV-6; this causes both direct and indirect mechanisms of damage:
   i Direct damage: the infection may cause endothelial cell dysfunction, as well as generating cytokines and chemoattractants that augment the initial damage and attract pro-inflammatory cells that further extend the damage. Infected endothelial cells may express cell wall molecules that make them more procoagulant, more prone to oxidative damage, more able to bind inflammatory cells and less able to vasodilate. Infection may also alter other cells of the vessel wall, as discussed below.
   ii Indirect damage: it has been suggested that an additional effect of damage to the vascular cells is that it exposes sequestered autoantigens, thereby generating an autoimmune response. Additionally, some infections, via increased production of TNF-α and IL-1, may cause upregulation of cell surface expression of proteinase 3 (PR3) and myeloperoxidase (MPO) on endothelial cells and inflammatory cells. These proteins are the main targets for antineutrophil cytoplasm antibodies (ANCA), which, when bound to the PR3 or MPO, produce degranulation of neutrophils and a sequence of ongoing vascular damage and cytokine production. ANCA are discussed further below.

7 Altered self hypothesis: in this hypothesis the infective organism interacts directly with vessel proteins to create neo-antigens that in turn will activate the immune system.

8 Alterations of vessel wall components: various organisms may produce an increase in smooth muscle cells of the vessel walls, both by stimulation of the proliferation and migration of these cells and by inhibiting normal apoptosis [4]. Such processes may be important in medium and large vessel vasculitides.

9 Autoantigen complementarity hypothesis: this hypothesis has particularly been proposed in relation to ANCA-associated vasculitides [3,7]. In this hypothesis, the proposed immunogens are 'complementary' to parts of the PR3 and MPO ANCA autoantigens, that is are homologous with the amino acid sequence of the antisense RNA of the non-coding strand of the ANCA autoantigen gene. Such proteins could induce production of antibodies which react with the autoantigen. In support of this, many microbial and fungal proteins have sequences that show homology with the protein product of the middle portion of the antisense RNA of PR3. Thus, these infective agents could trigger production of ANCA-associated vasculitis.

Specific infections that have been implicated in individual vasculitis patterns or syndromes are discussed where appropriate in the relevant disease sections later, and a list of infections that have been documented as causes of vasculitis is provided on p. 50.55.

References

1 Millikan LE, Flynn TC. Infectious etiologies of cutaneous vasculitis. *Clin Dermatol* 1999; **17**: 509–14.
2 Mandell BF, Calabrese LH. Infections and systemic vasculitis. *Curr Opin Rheumatol* 1998; **10**: 51–7.
3 Rodríguez-Pla A, Stone JH. Vasculitis and systemic infections. *Curr Opin Rheumatol* 2006; **18**: 39–47.
4 Yang Y-H, Chuang Y-H, Wang L-C *et al*. The immunobiology of Henoch–Schönlein purpura. *Autoimm Rev* 2008; **7**: 179–84.
5 Golden MP, Hammer SM, Wanke CA, Albrecht MA. Cytomegalovirus vasculitis. *Medicine (Baltimore)* 1994; **73**: 246–55.
6 Masuda M, Nakanishi K, Yoshizawa N *et al*. Group A streptococcal antigen in the glomeruli of children with Henoch-Schönlein nephritis. *Am J Kidney Dis* 2003; **41**: 366–70.
7 Pendergraft WF III, Pressler BM, Jenette JC *et al*. Autoantigen complementarity: a new theory implicating complementary proteins as initiators of autoimmune disease. *J Mol Med* 2005; **83**: 12–25.

Effector cells: T lymphocytes and polymorphonuclear leukocytes

T lymphocytes are found in the inflammatory infiltrate in all vasculitis. In some types of vasculitis, lymphocytes and monocytes appear to be predominant, but this may also relate to the stage at which a biopsy is taken, many vasculitides characterized by neutrophils developing an increase in the proportion of mononuclears with the passage of time. $CD4^+$ T helper (T_H) cells secrete cytokines, notably IL-1, INF-γ and TNF-α, and cause recruitment of $CD8^+$ (cytotoxic) T cells, B cells and natural killer (NK) cells. The cytokines produced not only induce expression of major histocompatibility MHC 1 antigens, which can be presented to $CD8^+$ cells, but also upregulate expression of adhesion molecules by endothelial cells.

A role for γ/δ T lymphocytes ($CD3^+$, $CD4^-$, $CD8^-$) has been proposed in vasculitis. These cells are cytotoxic against various cells but also exhibit some T_H functions; they secrete many cytokines, including interleukins IL-2 and IL-4, granulocyte–monocyte colony stimulating factor (GMCSF) and INF-γ. They are thought to recognize portions of the major histocompatibility complex and peptide antigens within these structures, without the full antigen processing that is required to cause proliferation of α/β T cells, and also recognize human heat shock proteins, notably HSP65. They are found in significant numbers in the later stages of leukocytoclastic vasculitis, and are especially associated with infective causes of vasculitis [1,2].

A population of T lymphocytes that express CXCL8 appear to be important in chemoattraction of neutrophils in Behçet's disease and in pustular drug eruptions; their role in leukocytoclastic vasculitis and neutrophilic dermatoses is less certain [3].

Neutrophils and eosinophils are the predominant cells in many vasculitides, including most that are related to infections, drugs, foods, collagen vascular diseases, type II or III cryoglobulins, IgA-mediated, and many others [4,5]. They are recruited in response to infection; the other main pathogenetic processes that attract them to the skin have been summarized as vasculitis, antibody and complement, mast cell release and T-cell-mediated neutrophil

activation [6]. Neutrophil adhesion mainly occurs in small vessels, in a process that is induced by several factors, including stimulation by TNF-α or ANCA (MPO-ANCA being more potent than PR3-ANCA), although ANCA also accelerate polymorphonuclear cell apoptosis. The role of immune complexes has been discussed, but is still not fully understood. The interaction between ANCA, their antigens, and endothelial cells, in binding polymorphonuclear cells is discussed later, as ANCA play an important role in leukocyte–endothelial interaction. Binding and activation of neutrophils or eosinophils causes release of toxic enzymes and generation of reactive oxygen species, leading to tissue damage. This process seems to require the presence of CD18, as injected polymorphonuclear cells in CD18-deficient mice will gather around perivascular immune complexes but without causing vessel damage [7]. Interestingly, several single nucleotide polymorphisms (SNP) have been associated with MPO–ANCA+ vasculitis [8]. This suggests that some CD18 polymorphisms may facilitate polymorphonuclear cell adhesion, degranulation and respiratory burst, predisposing to vasculitis.

The mechanism by which leukocytoclasis occurs in vasculitis is also not fully understood; it also occurs in neutrophilic dermatoses in which vasculitis is an inconstant feature. The usual expectation would be for late apoptotic polymorphonuclear cells to be phagocytosed by macrophages; electron microscopy immuno-gold methods in anaphylactoid purpura have demonstrated that apoptotic polymorphonuclear cell removal may be incomplete, many polymorphonuclear cells in fully developed leukocytoclastic vasculitis having relatively intact nuclei but disintegration of plasma organelles and cell membrane [9]. One explanation for this relates to the prototypical tissue pentraxin PTX3, which inhibits the anticipated phagocytosis of late-stage apoptotic polymorphonuclear cells by macrophages. This has been demonstrated to be upregulated at sites of leukocytoclastic vasculitis infiltrates, with levels paralleling vasculitis activity; it may therefore permit accumulation of leukocytoclastic debris by inhibition of phagocytosis [10].

References

1 Lotti T, Ghersetich I, Comacchi C, Jorizzo JL. Cutaneous small-vessel vasculitis. *J Am Acad Dermatol* 1998; **39**: 667–87.

2 Comacchi C, Ghersetich I, Katsambas A, Lotti TM. γ/δ T lymphocytes and infection: pathogenesis of cutaneous necrotizing vasculitis. *Clin Dermatol* 1999; **17**: 603–7.

3 Keller M, Spanou Z, Schaerli P *et al*. T cell-regulated neutrophilic inflammation in autoinflammatory diseases. *J Immunol* 2005; **175**: 7678–86.

4 Magro CM, Crowson NA. The cutaneous neutrophilic vascular injury syndromes: a review. *Semin Diag Pathol* 2001; **18**: 47–58.

5 Carlson JA, Chen K-R. Cutaneous vasculitis update: small vessel neutrophilic vasculitis syndromes. *Am J Dermatopathol* 2006; **28**: 486–506.

6 von den Driesch P. Polymorphonuclears: structure, function and mechanisms of involvement in skin diseases. *Clin Dermatol* 2000; **18**: 233–44.

7 Sindrilaru A, Seeliger S, Ehrchen JM *et al*. Site of blood vessel damage and relevance of CD18 in a murine model of immune complex-mediated vasculitis. *J Invest Dermatol* 2006; **127**: 447–54.

8 Meller S, Jagiello P, Borgmann S *et al*. Novel SNPs in the CD18 gene validate the association with MPO–ANCA+ vasculitis. *Genes Immun* 2001; **2**: 269–72.

9 Yamamoto T, Kaburagi T, Izaki S *et al*. Leukocytoclasis: ultrastructural in situ nick end labeling study in anaphylactoid purpura. *J Dermatol Sci* 2000; **24**: 158–65.

10 van Rossum AP, Pas HH, Fazzini F *et al*. Abundance of the long pentraxin PTX3 at sites of leukocytoclastic lesions in patients with small-vessel vasculitis. *Arthritis Rheum* 2006; **54**: 986–91.

Antiendothelial cell antibodies and endothelial cell dysfunction in vessel wall injury

Antiendothelial cell antibodies (AECA) are of uncertain importance in the pathogenesis of vasculitis [1–4]. They can be identified at high titre in most patients with Takayasu's arteritis or with active thromboangiitis obliterans, and are variably demonstrated in patients with Wegener's granulomatosis (WG), microscopic polyangiitis, Kawasaki disease, hepatitis B-associated polyarteritis nodosa, Henoch–Schönlein purpura, Behçet's disease and systemic lupus erythematosus (SLE)-associated vasculitis. They are also found in several other connective tissue diseases and in haemolytic uraemic syndrome/thrombotic thrombocytopenic purpura, IgA nephropathy, ulcerative colitis and diabetes mellitus, as well as in some normal individuals. Some studies correlate their titre with disease activity in medium or large vessel arteritis, but whether this reflects a pathogenic role or vascular damage is unclear. The fact that they bind preferentially to endothelium of mesenteric vessels supports the possibility of a pathogenetic role in visceral arteritis [5].

Mechanisms by which AECA might have a pathogenetic role in vasculitis include those listed below [4], although it should be acknowledged that no target antigens of AECA are specifically expressed by endothelial cells, and also that endothelial cell-specific target antigens of AECA remain unidentified in systemic vasculitides [4]:

1 Direct activation, or indirect induction of activation, of endothelial cells: activation of endothelial cells leads to up-regulation of adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and E-selectin [6,7]; this may be mediated by nuclear factor (NF)-κB [8]. Increased neutrophil cytotoxicity results. E-selectin is a promoter of endothelial cell activation and of leukocyte–endothelial cell interaction, being expressed on cytokine-activated endothelial cells, and might therefore have an active role in the pathogenesis of vasculitis; however, E-selectin levels in a variety of systemic vasculitides do not correlate with disease activity [9]. Identification of AECA with specificity for α-enolase, expressed by endothelial cells, and the possibility of this having an infectious trigger, is discussed in the section on pathogenesis of Behçet's disease. More recently, it has been shown that AECA upregulated expression of two inflammatory molecules, vascular adhesion protein-1 (VAP-1) and MHC class I-related antigen A (MICA) on renal endothelial cells in Wegener's granulomatosis, in turn leading to phosphorylation of stress activated protein kinase (SAPK)/c-Jun N-terminal kinase (JNK), activation of NFκB, and production of the chemoattractant cytokines monocyte chemoattractant protein-1 and granulocyte chemotactic protein-2; blocking SAPK/JNK significantly reduced the chemokine production and decreased expression of MICA, confirming that AECA have a role in generating pro-inflammatory endothelial cell responses [10].

2 Cytotoxicity, which may be direct, complement-dependent or indirect due to complement-independent antibody-dependent cytotoxicity: such cytotoxicity has been demonstrated in mice immunized with purified IgG AECA from a patient with Wegener's granulomatosis, and which subsequently developed

endogenous AECA with renal and pulmonary lymphoid infiltrates [11].

3 Induction of coagulation: von Willebrand factor, factor VIII and soluble thrombomodulin levels may all be increased in vasculitis, possibly due to AECA, although other evidence suggests that these changes are probably a secondary effect resulting from vascular damage. Soluble thrombomodulin levels have been shown to be related to disease activity in WG [9], although this is also increased in disseminated intravascular coagulopathy, thrombotic thrombocytopenic purpura, sepsis, malaria, diabetic microangiopathy and various other disorders in which there is damage to vessels.

4 Induction of apoptosis, for example by binding of phospholipids or of heat shock protein 60.

Several cytokines that may be involved in vasculitis are discussed later. Some cytokine events that are related to the interaction of endothelial cells and AECA have also been discussed above. Again, many of these effects are probably non-specific. For example, high levels of soluble VCAM-1 are found in Kawasaki disease but were even higher in febrile controls [6], and this finding is therefore presumably also a non-specific result of vascular injury. Similarly, nitric oxide production is also increased in some vasculitides but is not specific to an individual vasculitis syndrome; neutrophil-derived nitric oxide is known to be damaging to endothelial cells [12] (see above for a discussion of neutrophils).

Endothelial cell dysfunction has been recognized as a common event and active contributor in systemic vasculitis and connective tissue disease-associated vasculitis, rather than purely occurring as an uninvolved consequence of injury [13]. Endothelial cell dysfunction occurs at sites distant from active vasculitis in several primary small and medium vasculitides, independent of ANCA status or renal involvement (itself a cause of endothelial cell dysfunction), and with improvement correlating with disease suppression in some instances [13]. In Kawasaki disease, impaired endothelial cell function appears to persist for years after the clinical disease, with impaired fibrinolytic activity, and abnormal coronary blood flow, unrelated to the presence or absence of early-stage coronary artery aneurysms, after cold pressor testing [14]. Although this abnormality is prolonged in nature, it can be reversed by ascorbate. Circulating endothelial cell microparticles that can cause endothelial cell injury and apoptosis have been demonstrated in Kawasaki disease, as well as in some primary vasculitides, correlating with other markers of disease activity, and supporting a role of endothelial cell damage in the pathogenesis of these disorders [15]. Endothelial cell dysfunction has been related to either depressed release, or increased breakdown, of nitric oxide; polymorphisms of endothelial nitric oxide synthase (eNOS) have been related to risk of giant cell arteritis and Behçet's disease (discussed further in the section on Behçet's disease).

References

1 Ball GV, Bridges SL. Pathogenesis of vasculitis. In: Ball GV, Bridges SL, eds. *Vasculitis*. Oxford: Oxford University Press, 2002: 34–52.

2 Piette WW. Primary systemic vasculitis. In: Sontheimer RD, Provost TT, eds. *Cutaneous Manifestations of Rheumatic Diseases*. Baltimore: Williams & Wilkins, 1995: 177–232.

3 Goeken JA. Antineutrophil cytoplasmic and antiendothelial cell antibodies: new mechanisms for vasculitis. *Curr Opin Dermatol* 1995; **2**: 75–82.

4 Guilpain P, Mouthon L. Antiendothelial cell antibodies in vasculitis-associated systemic diseases. *Clin Rev Allergy Immunol* 2008; **35**: 59–65.

5 Brasile L, Kremer JM, Clarke JL, Cerilli J. Identification of an autoantibody to vascular endothelial cell-specific antigens in patients with systemic vasculitis. *Am J Med* 1989; **87**: 74–80.

6 Kallenberg CGM. Laboratory findings in the vasculitides. *Baillières Clin Rheumatol* 1997; **11**: 395–421.

7 Carvalho D, Savage CO, Isenberg D, Pearson JD. IgG anti-endothelial cell autoantibodies from patients with systemic lupus erythematosus or systemic vasculitis stimulate the release of two endothelial cell-derived mediators, which enhance adhesion molecule expression and leukocyte adhesion in an autocrine fashion. *Arthritis Rheum* 1999; **42**: 631–40.

8 Blank M, Krause I, Goldkorn T *et al*. Monoclonal anti-endothelial cell antibodies from a patient with Takayasu arteritis activate endothelial cells from large vessels. *Arthritis Rheum* 1999; **42**: 1421–32.

9 Boehme MWJ, Schmitt WH, Youinou P *et al*. Clinical relevance of elevated serum thrombomodulin and soluble E-selectin in patients with Wegener's granulomatosis and other systemic vasculitides. *Am J Med* 1996; **101**: 387–94.

10 Holmén C, Elsheikh E, Christensson M *et al*. Anti-endothelial cell autoantibodies selectively activate SAPK/JNK signaling in Wegener's granulomatosis. *J Am Soc Nephrol* 2007; **18**: 2424–6.

11 Davianovich M, Gilburd B, George J *et al*. Pathogenic role of antiendothelial cell antibodies in vasculitis: an idiotypic experimental model. *J Immunol* 1996; **156**: 4946–51.

12 Bratt J, Palmblad J. Cytokine-induced neutrophil-mediated injury of human endothelial cells. *J Immunol* 1997; **159**: 912–8.

13 Bacon PA. Endothelial cell dysfunction in systemic vasculitis: new developments and therapeutic prospects. *Curr Opin Rheumatol* 2004; **17**: 49–55.

14 Furuyama H, Odagawa Y, Katoh C *et al*. Altered myocardial flow reserve and endothelial function late after Kawasaki disease. *J Pediatr* 2003; **142**: 149–52.

15 Brogan PA, Shah V, Brachet C *et al*. Endothelial and platelet microparticles in vasculitis of the young. *Arthritis Rheum* 2004; **50**: 927–36.

Antineutrophil cytoplasm antibodies

In comparison with other pathogenetic factors, many of which are either not routinely measurable or are of uncertain relevance to pathogenesis, antineutrophil cytoplasm antibodies (ANCA) have diagnostic value as well as an important role in the pathogenesis of vasculitis [1–13].

ANCA are classified, according to their indirect immunofluorescence (IIF) pattern on ethanol-fixed neutrophils, into C-ANCA (granular cytoplasmic staining with accentuation between the nuclear lobes), P-ANCA (perinuclear and/or nuclear staining) and atypical ANCA (various patterns, including diffuse cytoplasmic and 'very perinuclear'; atypical ANCA are also termed X-ANCA, snowdrift-ANCA or more recently a-ANCA) [3,7,9]. These patterns correlate with varying degrees of specificity to specific neutrophil granule contents (Table 50.5). ANCA are usually of IgG type but may be IgM or IgA. In addition to systemic vasculitides, ANCA may be positive in various infections (malaria, human immunodeficiency virus infection; HIV), connective tissue disorders (SLE, rheumatoid arthritis) and gastrointestinal diseases (inflammatory bowel disease, chronic autoimmune liver and biliary tract disease), as well as occasionally in some apparently healthy individuals.

In most disorders other than vasculitides, the types of ANCA identified are of P-ANCA or atypical ANCA type, and in most of these disorders there is no consistent ANCA specificity or correlation with disease activity. However, there are some exceptions, such as the association of cathepsin G-ANCA with malaria [14].

Table 50.5 Antigenic specificity and clinical correlates of antineutrophil cytoplasm antibodies.

Antigen	Usual ANCA pattern on IIF	Most commonly associated diseases
PR3	C-ANCA	WG, MPA, CSS, necrotizing and crescentic GN
MPO	P-ANCA	Idiopathic progressive GN, MPA, CSS, WG, SLE, ANCA-positive drug-induced systemic vasculitis, thromboangiitis obliterans
Cathepsin G	P-ANCA	IBD, especially ulcerative colitis, PSC, malaria
BPI (= CAP 57)	C-ANCA	Systemic vasculitis, SLE, IBD, PSC, cystic fibrosis, chronic airway infections, other chronic infections
Azurocidin (= CAP 37)	P-ANCA or C-ANCA	Systemic vasculitis, drug-induced systemic vasculitis
Lactoferrin	P-ANCA or atypical ANCA	Rheumatoid arthritis, SLE especially with serositis or livedo reticularis, systemic vasculitis, ulcerative colitis, PSC, hydralazine-related vasculitis, thromboangiitis obliterans
HLE	P-ANCA	WG, propylthiouracil-related systemic vasculitis, some other drug-induced vasculitides, HIV infection
β-glucuronidase	P-ANCA	IBD
Lysozyme	P-ANCA	SLE, IBD, HIV infection
h-lamp-2	P-ANCA	Necrotizing and crescentic GN, pyoderma gangrenosum
Others: actin, catalase, α-enolase, high mobility group protein	Anti-actin is C-ANCA, others P-ANCA or atypical	Mainly present in autoimmune hepatitis, primary biliary cirrhosis, inflammatory bowel disease

BPI, bactericidal permeability-increasing protein; C-ANCA, cytoplasmic antineutrophil cytoplasm antibody; CSS, Churg–Strauss syndrome; GN, glomerulonephritis; HIV, human immunodeficiency virus; h-lamp-2, human lysosome-associated membrane protein-2; HLE, human leukocyte elastase (also termed human neutrophil elastase, or simply elastase); IBD, inflammatory bowel disease; MPA, microscopic polyangiitis; MPO, myeloperoxidase; P-ANCA, perinuclear antineutrophil cytoplasm antibody; PBC, primary biliary cirrhosis; PR3, proteinase-3; PSC, primary sclerosing cholangitis; SLE, systemic lupus erythematosus; WG, Wegener's granulomatosis.

The presence of P-ANCA in SLE, although originally felt not to have any particular link with disease pattern [15], has been associated with serositis, livedo reticularis, venous thrombosis, anticardiolipin and anti-SSA/Ro positivity, and periodontal disease [16,17]; in particular, lactoferrin-ANCA is strongly linked with livedo reticularis [14]. Bactericidal/permeability increasing protein (BPI) ANCA and proteinase 3 (PR3) ANCA have also been linked with serositis in patients with SLE. Anti-dsDNA and anti-SSA/Ro antibodies may resemble P-ANCA, depending on fixation methods [18]. Human lysosome-associated membrane protein-2 (h-lamp-2) ANCA has been linked with pyoderma gangrenosum.

Generally, the P-ANCA pattern is relatively non-specific, having various (often undetermined) antigen specificities and often no link with disease activity. In contrast, the C-ANCA pattern almost always corresponds with antibodies against PR3, a 29-kDa neutral serine protease, and clinically with WG or other systemic vasculitis. In the context of systemic vasculitis, the important P-ANCA groups are those with antibodies against myeloperoxidase (MPO). It is therefore important to confirm MPO or PR3 antibodies, usually by enzyme-linked immunosorbent assay (ELISA), in the context of a positive ANCA test identified by IIF screening, and to refer to the more specific result where possible (e.g. as PR3-ANCA) [9]. Immunofluorescence is more sensitive, and ELISA more specific, so combining the two tests is most useful if clinical suspicion of an ANCA-associated systemic vasculitis is high. Other solid-phase assays such as immunodot and multiplex assay are also used.

A positive C-ANCA has a sensitivity of 66% (91% if only considering active disease) and specificity of 98% for WG [19], but may be positive in about one-third of patients with microscopic polyangiitis or with necrotizing crescentic glomerulonephritis, and in about 20% with Churg–Strauss syndrome (CSS). Patients with WG who are negative for C-ANCA/anti-PR3 usually have positive P-ANCA/anti-MPO. In addition, anti-MPO are found in about 65% with progressive idiopathic glomerulonephritis, in about 50% with microscopic polyangiitis or CSS, and may be found in SLE or in ANCA-associated drug reactions (notably to propylthiouracil or hydralazine). If ANCA are present in drug-induced systemic vasculitis the pattern is usually P-ANCA or atypical ANCA. It is important to be aware that 10–20% of patients with Wegener's granulomatosis, and 40–50% with Churg–Strauss syndrome, will have negative tests for ANCA (or may develop a positive test later in the disease). Of interest, patients with Churg–Strauss syndrome who are ANCA-positive are much more likely to have associated necrotizing vasculitis and, particularly, necrotizing and crescentic glomerulonephritis, than those who are ANCA-negative [20], suggesting the possibility that the vasculitic component of the disease may be ANCA mediated but that other manifestations may have a different pathogenesis [12]. A pathogenetic role for drug-induced ANCA is best documented in relation to propylthiouracil, but the ANCA response may be heterogeneous in comparison with the situation in primary vasculitides; of 19 patients with propylthiouracil-induced ANCA-positive vasculitis, all 15 with renal disease had MPO-ANCA but many other specificities were demonstrated in this group, over half of them having ANCA directed against cathepsin G and/or leukocyte elastase, and between a quarter and half having ANCA against one or more of lactoferrin, azurocidin and PR3 [21]. Production of ANCA requires competent T-cell and B-cell function; this may explain why anti-B cell treatments (such as the monoclonal antibody rituximab) can be effective in ANCA-associated systemic vasculitis such as Wegener's granulomatosis.

Numerous studies suggest a pathogenetic role for at least anti-PR3 and anti-MPO antibodies in systemic vasculitides. Both clinical and *in vitro* evidence for pathogenicity have been reviewed [12]. In particular, the IgG3 subclass of PR3 is implicated, a rise in titres in WG being predictive of relapse [3]; this subclass is a particularly strong activator of neutrophils. The role of ANCA in the

pathogenesis of vasculitis is multifactorial. ANCA cause activation of neutrophils primed by TNF-α (or by lipopolysaccharide), leading to production of reactive oxygen species, nitric oxide and cytokines such as IL-1 and IL-8 (a neutrophil chemoattractant), as well as enhancing degranulation with release of proteolytic enzymes. Neutrophils activated by ANCA up-regulate adhesion molecules, adhere to platelet monolayers or to TNF-activated endothelial cells *in vitro* rather than their usual behaviour of 'rolling', and develop pseudopodia [5]. ANCA also up-regulate expression of adhesion molecules (ICAM-1, E-selectin and VCAM-1; the adhesion cascade) and IL-6 production by endothelial cells, which in turn causes neutrophil adhesion, transmigration and tissue damage. The subject of endothelial cell adhesion and recruitment of neutrophils is discussed in detail in [22]. ANCA also stimulate monocytes to produce reactive oxygen species and to produce IL-8; monocyte activation may also be important in non-ANCA-associated vasculitides such as Behçet's disease [4].

Elastase is one of the main tissue-damaging enzymes released by neutrophil degranulation. It is potentially important that elastase stimulates release of tissue factor from cultured endothelial cells (human umbilical vein endothelial cells; HUVEC), as this may be relevant in development of microthrombi *in vivo* (PR3, but not MPO, also stimulates production of tissue factor from HUVEC) [23]. It is also of interest that autoantibodies to elastase enhance rather than decrease elastase activity, thus leading to tissue damage [24]; this might be a pathogenetic mechanism of injury by human leukocyte elastase (HLE)-ANCA.

References

1 Ball GV, Bridges SL. Pathogenesis of vasculitis. In: Ball GV, Bridges SL, eds. *Vasculitis*. Oxford: Oxford University Press, 2002: 34–52.

2 Piette WW. Primary systemic vasculitis. In: Sontheimer RD, Provost TT, eds. *Cutaneous Manifestations of Rheumatic Diseases*. Baltimore: Williams & Wilkins, 1995: 177–232.

3 Kallenberg CGM. Laboratory findings in the vasculitides. *Baillières Clin Rheumatol* 1997; **11**: 395–421.

4 Nowack R, Flores-Suárez LF, van der Woude FJ. New developments in pathogenesis of systemic vasculitis. *Curr Opin Rheumatol* 1998; **10**: 3–11.

5 Savage COS. The evolving pathogenesis of systemic vasculitis. *Clin Med* 2002; **2**: 458–64.

6 Lotti T, Ghersetich I, Comacchi C, Jorizzo JL. Cutaneous small-vessel vasculitis. *J Am Acad Dermatol* 1998; **39**: 667–87.

7 Radice A, Sinico RA. Antineutrophil cytoplasmic antibodies. *Autoimmunity* 2005; **38**: 93–103.

8 Goeken JA. Antineutrophil cytoplasmic and antiendothelial cell antibodies: new mechanisms for vasculitis. *Curr Opin Dermatol* 1995; **2**: 75–82.

9 Bajema IM, Hagen EC. Evolving concepts about the role of antineutrophil cytoplasm autoantibodies in systemic vasculitis. *Curr Opin Rheumatol* 1999; **11**: 34–40.

10 Salama AD. Pathogenesis and treatment of ANCA-associated systemic vasculitis. *J R Soc Med* 1999; **92**: 456–91.

11 Savage COS, Harper L, Holland M. New findings in pathogenesis of antineutrophil cytoplasm antibody-associated vasculitis. *Curr Opin Rheumatol* 2002; **14**: 15–22.

12 Jennette JC, Falk RJ. New insight into the pathogenesis of vasculitis associated with antineutrophil cytoplasmic autoantibodies. *Curr Opin Rheumatol* 2008; **20**: 55–60.

13 Kluth DC, Hughes J. ANCA-associated systemic vasculitis (AASV). *J R Coll Physicians Edin* 2007; **37**: 128–34.

14 Yahya TM, Benedict S, Shalabi A, Bayoumi R. Anti-neutrophil cytoplasmic antibody (ANCA) in malaria is directed against cathepsin G. *Clin Exp Immunol* 1997; **110**: 41–4.

15 Schnabel A, Csernok E, Isenberg DA *et al*. Antineutrophil cytoplasmic antibodies in systemic lupus erythematosus: prevalence, specificities and clinical significance. *Arthritis Rheum* 1995; **38**: 633–7.

16 Galeazzi M, Morrozi G, Sebastiani GD *et al*. Anti-neutrophil cytoplasmic antibodies in 566 European patients with systemic lupus erythematosus: prevalence, clinical associations and correlation with other autoantibodies. *Clin Exp Rheumatol* 1998; **16**: 541–6.

17 Novo E, Garcia-McGregor E, Viera N *et al*. Periodontitis and anti-neutrophil cytoplasmic antibodies in systemic lupus erythematosus and rheumatoid arthritis: a comparative study. *J Periodontol* 1999; **70**: 185–8.

18 Savige JA, Paspaliaris B, Silvestrini R *et al*. A review of immunofluorescent patterns associated with antineutrophil cytoplasmic antibodies (ANCA) and their differentiation from other antibodies. *J Clin Pathol* 1998; **51**: 568–75.

19 Rao JK, Weinberger M, Oddone EZ *et al*. The role of antineutrophil cytoplasmic antibody testing in the diagnosis of Wegener granulomatosis. *Ann Intern Med* 1995; **123**: 925–32.

20 Sinico RA, Di Toma L, Maggiore U *et al*. Renal involvement in Churg–Strauss syndrome. *Am J Kidney Dis* 2006; **47**: 770–9.

21 Yu F, Chen M, Gao Y *et al*. Clinical and pathological features of renal involvement in propylthiouracil-associated ANCA-positive vasculitis. *Am J Kidney Dis* 2007; **49**: 607–14.

22 Kluger MS. Vascular endothelial cell adhesion and signaling during leukocyte recruitment. *Adv Dermatol* 2004; **20**: 163–94.

23 Haubitz M, Gerlach M, Kruse HJ, Brunkhorst R. Endothelial tissue factor stimulation by proteinase 3 and elastase. *Clin Exp Immunol* 2001; **126**: 584–8.

24 Morcos M, Zimmermann F, Radsak M *et al*. Autoantibodies to polymorphonuclear neutrophil elastase do not inhibit but enhance elastase activity. *Am J Kidney Dis Online* 1998; **31**: 978–85.

Other cytokines and chemokines, and the cellular response [1–3]

Numerous cytokines have been implicated in vasculitis; some have already been discussed. Many are released as part of an acute phase response or because of upregulation of production by peripheral blood neutrophils or monocytes, such as IL-1, IL-2, IL-6, IL-8, interferon (IFN) and TNF-α. These may therefore be non-specifically elevated in vasculitis, but may play a part in ongoing damage. TNF-α is important for priming endothelial cells to express E- and P-selectin, ICAM-1 and 2, and VCAM-1 (see above), and also primes neutrophils to produce reactive oxygen species and to degranulate after exposure to ANCA. IL-8 is a potent neutrophil chemoattractant that is expressed by endothelial cells after stimulation by ANCA, and after non-cytotoxic binding of AECA. IL-6 has been studied especially in giant cell arteritis and Takayasu's arteritis, in which it appears to reflect disease activity. Increased levels of soluble TNF receptor have been demonstrated in ANCA-positive vasculitides.

Other chemokines that have enhanced tissue expression in vasculitis include monocyte chemotactic protein-1 (MCP-1), macrophage inflammatory protein-1α and -1β and RANTES (regulated upon activation, normal T-cell expressed and secreted) [4]. Expression of MAC-1 by neutrophils is up-regulated by ANCA.

Based on a mouse model in which genetic deficiency of IL-1 receptor antagonist (IL-1Ra) is associated with arterial inflammation, it has been suggested that IL-1Ra has a significant role in vasculitis and that a recombinant IL-1Ra might be a useful treatment [5].

T cells, monocytes and macrophages play a part in vasculitis injury, in addition to the role of neutrophils discussed above. Both $CD4^+$ and $CD8^+$ T cells accumulate at the site of injury. In WG there is a Th1 cytokine profile, with increased IFN-γ, TNF and IL-12 but

not IL-4, IL-5 or IL-10 [4], and CD28 expression; however, some studies have suggested a Th2 response in nasal mucosa, which may be of importance as nasal staphylococcal infection is associated with relapses in WG. Monocytes from patients with systemic necrotizing vasculitis produce more superoxide and MPO than monocytes from controls, and they can also be induced to express PR3 and to release IL-8 when exposed to ANCA [6]. However, monocyte activation also occurs in Behçet's disease, which is not ANCA-related. Defective macrophage apoptosis may lead to persistence and ongoing damage at the vasculitic site, as occurs with neutrophils [3].

References

1 Ball GV, Bridges SL. Pathogenesis of vasculitis. In: Ball GV, Bridges SL, eds. *Vasculitis*. Oxford: Oxford University Press, 2002: 34–52.
2 Kallenberg CGM. Laboratory findings in the vasculitides. *Baillières Clin Rheumatol* 1997; **11**: 395–421.
3 Nowack R, Flores-Suárez LF, van der Woude FJ. New developments in pathogenesis of systemic vasculitis. *Curr Opin Rheumatol* 1998; **10**: 3–11.
4 Savage COS, Harper L, Holland M. New findings in pathogenesis of antineutrophil cytoplasm antibody-associated vasculitis. *Curr Opin Rheumatol* 2002; **14**: 15–22.
5 Nicklin MJ, Hughes DE, Barton JL, Ure JM, Duff GW. Arterial inflammation in mice lacking the interleukin 1 receptor antagonist gene. *J Exp Med* 2000; **191**: 303–12.
6 Savage COS. The evolving pathogenesis of systemic vasculitis. *Clin Med* 2002; **2**: 458–64.

Genetic factors

Familial clustering has been documented in some vasculitides such as WG, although this is uncommon [1,2]. Various explanations have been proposed, including the occurrence of TNF gene polymorphisms, genetic heterogeneity of ANCA antigens or their expression, and neutrophil Fcγ receptor polymorphisms. For example, expression of PR3 on resting neutrophils shows marked individual variation, the proportion of neutrophils expressing PR3 varying from approximately 10 to 80%, but being quite stable in any individual [1,3] This is now known to be genetically determined [4], and high expression has been associated with a higher risk of WG. Severe renal disease in WG has been linked with expression of the neutrophil receptor FcγRIIIb-NA1, although this is disputed [2,5]. The genetic region for elastase, azurocidin and PR3 is highly polymorphous, but no apparent associations with clinical disease have been identified [1]. Further polymorphisms are increasingly being documented; the association between some CD18 polymorphisms and Wegener's granulomatosis has been referred to earlier, and numerous polymorphisms have been linked with Behçet's disease (and are discussed in the relevant disease section). In particular, a predilection associated with various cytokine and inflammatory mediator alleles and polymorphisms, including polymorphisms in endothelial nitric oxide synthase (eNOS), in interleukin-10 (IL-10), IL-8, and CD28 genes, and presence of the antitumour necrosis factor-alpha (TNF-α) 1031C allele, are all associated with Behçet's disease susceptibility [6].

α_1-Antitrypsin (α_1AT) is a natural inhibitor of PR3 and elastase in neutrophil alpha-granules (as is caeruloplasmin for MPO). Deficiency of α_1AT may be genetic or may be acquired by the formation of α_1AT–PR3 complexes by anti-PR3 ANCA. An association between the α_1AT-deficient PiZZ phenotype and ANCA-positive vasculitis has been described, and PiZ heterozygosity has been linked with poor prognosis in ANCA-positive systemic vasculitis [7,8]. However, a large study of PiZZ-deficient sera showed an association with antibodies against elastase but not against PR3, MPO or lactoferrin, and α_1AT deficiency is not in itself sufficient to induce ANCA-associated vasculitis [5,9]. An α_1 protease inhibitor has been used with dramatic response in the treatment of chronic vasculitis in a patient with α_1AT deficiency [10].

In Kawasaki disease, the G2350A polymorphism in the angiotensin converting enzyme (ACE) gene has been associated with risk of the condition (but not with risk of coronary artery aneurysms) [11]; however, the itpkc_3 polymorphism in the inositol 1,4,5-triphosphate 3-kinase C (*IKPKC*) gene (a negative regulator of T cell activation) seems to be linked to immune hyper-reactivity and is associated with increased risk of Kawasaki disease itself and of coronary artery aneurysms [12]. There are also reported polymorphisms in chemokine receptor genes within the *CCR3-CCR2-CCR5* gene cluster, and polymorphisms in genes for some matrix metalloproteinases (a possible explanation for the variable risk of development of aneurysms).

In Henoch–Schönlein purpura (HSP), there have been reported associations with HLA class 1 alleles; HLA A2, A11 and B35 having an association with increased risk of HSP and HLA A1, B49 and B50 being associated with decreased risk [13]. These alleles did not appear to alter risk of renal disease, whereas some vascular endothelial growth factor polymorphisms may increase, or protect against, the risk of nephritis in HSP [14].

It is likely that advances in genetics will identify many polymorphisms that may alter susceptibility, severity or specific features of different vasculitides, quite possibly in a hierarchical or polygenic fashion [15].

References

1 Nowack R, Flores-Suárez LF, van der Woude FJ. New developments in pathogenesis of systemic vasculitis. *Curr Opin Rheumatol* 1998; **10**: 3–11.
2 Gross WL, Csernok E, Trabandt A. Wegener's granulomatosis: pathogenesis. In: Ball GV, Bridges SL, eds. *Vasculitis*. Oxford: Oxford University Press, 2002: 340–56.
3 Halbwachs-Mecarelli L, Bessou G, Lesavre P *et al*. Bimodal distribution of proteinase 3 (Pr3) surface expression reflects a constitutive heterogeneity in the polymorphonuclear neutrophil pool. *FEBS Lett* 1995; **374**: 29–33.
4 Schreiber A, Busjahn A, Luft FC, Kettritz R. Membrane expression of proteinase 3 is genetically determined. *J Am Soc Nephrol* 2003; **14**: 68–75.
5 Savage COS, Harper L, Holland M. New findings in pathogenesis of antineutrophil cytoplasm antibody-associated vasculitis. *Curr Opin Rheumatol* 2002; **14**: 15–22.
6 Krause I, Weinberger A. Behçet's disease. *Curr Opin Rheumatol* 2008; **20**: 82–7.
7 Ball GV, Bridges SL. Pathogenesis of vasculitis. In: Ball GV, Bridges SL, eds. *Vasculitis*. Oxford: Oxford University Press, 2002: 34–52.
8 Griffith ME, Lovegrove JU, Gaskin G *et al*. C-antineutrophil cytoplasmic antibody positivity in vasculitis patients is associated with the Z phenotype of alpha-1-antitrypsin, and P-antineutrophil cytoplasmic antibody positivity with the S allele. *Nephrol Dial Transplant* 1996; **11**: 438–43.
9 Audrain MAP, Sesboüé R, Baranger TAR *et al*. Analysis of anti-neutrophil cytoplasmic antibodies (ANCA): frequency and specificity in a sample of 191 homozygous (PiZZ) alpha-1-antitrypsin-deficient subjects. *Nephrol Dial Transplant* 2001; **16**: 39–44.
10 Dowd SK, Rodgers GC, Callen JP. Effective treatment with α_1 protease inhibitor of chronic cutaneous vasculitis associated with α_1-antitrypsin deficiency. *J Am Acad Dermatol* 1995; **33**: 913–6.
11 Wu SF, Chang JS, Peng CT *et al*. Polymorphism of angiotensin-1 converting enzyme gene and Kawasaki disease. *Pediatr Cardiol* 2004; **25**: 529–33.

12 Yoshihiro O, Tomohiko G, Burns JC *et al*. ITPKC functional polymorphism associated with Kawasaki disease susceptibility and formation of coronary artery aneurysms. *Nat Genet* 2008; **40**: 35–42.
13 Peru H, Soylemezoglu O, Gonen S *et al*. HLA class 1 associations in Henoch Schönlein purpura: increased and decreased frequencies. *Clin Rheumatol* 2008; **27**: 5–10.
14 Blanca R, Perez AC, Lopez SL *et al*. Association between functional haplotypes of vascular endothelial growth factor and renal complications in Henoch-Schönlein purpura. *J Rheumatol* 2006; **33**: 69–73.
15 Nose M. A proposal concept of a polygene network in systemic vasculitis: lessons from MRL mouse models. *Allergy Int* 2007; **56**: 79–86.

Evaluation of the patient with suspected vasculitis

The essential aspects in the approach to a patient with suspected vasculitis, from a clinical dermatological perspective, have been described in various publications [1–14], some providing either flowchart [2,3,5,8,12] or algorithm approaches [7,11]. Additional approaches and classifications directed by histopathological features are also useful [15–17].

In broad terms, the evaluation of a patient with suspected vasculitis involves histopathological confirmation of the clinical diagnosis, an assessment of the extent of the disease (both the degree of skin damage, and the involvement of internal organs) and an attempt to establish an underlying aetiology. Clinical patterns that may suggest a vasculitis, other than the overtly vasculitic lesions discussed in this chapter, include cutaneous livedo, cutaneous necrosis, non-specific purpura and purple (blue) toe syndrome; these patterns can also occur in non-vasculitic microvascular occlusion disorders, and their significance and likely causes are discussed in Chapter 49.

Histopathological confirmation of suspected small vessel vasculitides is best performed by taking a punch biopsy of the lesions at the appropriate stage, recognizing that lesions represent various chronological stages of the disease process. Deeper, elliptical incisional biopsies should be performed for suspected larger vessel vasculitides. Processing part of the biopsy, or a separate biopsy, for direct immunofluorescence is potentially important. This initial investigative step usually confirms the presence of a vasculitis (or may show evidence of a vasculitis mimic, such as a vasculopathy). It also helps to define the type of vasculitis, based on vessel type and size, type of reaction (e.g. segmental arteritis in polyarteritis nodosa), infiltrating cells (e.g. prominently eosinophilic infiltrate in some drug-induced vasculitides), extent of infiltrate (e.g. pan-dermal small vessel disease in a patient with fever suggests possible sepsis) and may define a specific vasculitis process (e.g. CSVV with vascular IgA deposits in Henoch–Schönlein purpura).

In attempting to assess the extent of the disease, it is important to consider where circulating immune complexes may deposit. Specifically, the following systems should be evaluated, especially but not exclusively for the features listed:

- **General.** Myalgia, arthralgia, fever
- **Renal.** Proteinuria, haematuria
- **Nervous system.** Central or peripheral, diffuse or localized findings
- **Musculoskeletal.** Non-erosive polyarthritis
- **Gastrointestinal.** Abdominal pain, gastrointestinal bleeding
- **Pulmonary.** Pleural effusion, pleuritis, pneumonitis
- **Cardiac.** Pericardial effusion, pericarditis
- **Other systems.** Upper respiratory tract (larger vessel vasculitides), eyes (Behçet's disease, larger vessel vasculitides), larger vessels

The overall clinical pattern needs to be taken into account when evaluating internal disease, for example the combination of respiratory symptoms and mononeuritis multiplex would suggest possible Churg–Strauss syndrome.

Additional investigations should be performed to try to determine the aetiology of the vasculitis. It may be helpful to screen for medications, infections or diseases associated with immune complexes (connective tissue vascular diseases, malignancy, inflammatory bowel disease, etc.). Although 'directed' sequential blood tests are ideal, depending on the clinical picture and results of simpler tests, from a pragmatic perspective it is often the case that a 'vasculitis screen' is performed. Reasonable initial tests might include:

- Full blood count with differential white cell count
- Markers of inflammation: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)
- Electrolytes and hepatic transaminases, glucose
- Urinalysis for protein and blood
- Blood cultures (if pyrexial)
- Serology—ANA (+/− antibodies to extractable nuclear antigens; dsDNA if ANA positive), ANCA, complement C3 and C4, antistreptolysin-O titre, viral titres (e.g. hepatitis B and hepatitis C, possibly HIV, CMV, parvovirus B19 and others if recent infection), others if indicated or to exclude differentials (e.g. rheumatoid factor, electrophoresis, immune complexes)
- cryoglobulins
- chest radiograph (if symptoms, signs, ANCA-positive or suspected larger vessel disease)
- additional organ-directed investigations as necessary (renal, nerve, bone marrow biopsy; arteriography; etc.).

As well as being important for investigation of causes of vasculitis, blood tests requested should also include markers of severity (e.g. C-reactive protein, erythrocyte sedimentation rate), tests to determine the systemic effect of vasculitis (e.g. renal function) and baseline tests for possible corticosteroid or immunosuppressive therapy (glucose, thiopurine methylytransferase (azathioprine), G-6-PD status (dapsone), etc.).

The extent of additional investigation may depend on initial findings, severity of vasculitis and of general symptoms, and on response to therapy. It is important to remember, for example, that investigations for cutaneous small vessel vasculitis fail to demonstrate a cause in up to 50% of cases, and to consider the need for further investigation in a patient in whom the disorder is resolving. It is also often helpful to work with a colleague in internal medicine or paediatrics when evaluating the patient, particularly if larger vessel disease is suspected, as additional investigations might include biopsies of artery, kidney, lung or nerve, radiology studies such as arteriography of aortic arch or visceral vessels, etc. Even if the cutaneous vasculitis has resolved, it is appropriate to perform urinalysis and blood pressure monitoring subsequently (perhaps monthly and 3-monthly respectively, for 6 months) as delayed effects of concurrent renal involvement may become

apparent. In those who do have renal involvement, this may persist as renal impairment later in life [18] so there is an argument for annual tests of renal function in such individuals.

The information in the following sections discusses the definition, history, aetiology, pathogenesis, histopathology, clinical features, diagnosis and treatment of various vasculitides affecting small, medium and large blood vessels.

References

1 Lotti T, Ghersetich I, Comacchi C, Jorizzo JL. Cutaneous small-vessel vasculitis. *J Am Acad Dermatol* 1998; **39**: 667–87.
2 Callen JP. A clinical approach to the vasculitis patient in the dermatologic office. *Clin Dermatol* 1999; **17**: 549–53.
3 Gibson LE. Cutaneous vasculitis update. *Dermatol Clin* 2001; **19**: 603–15.
4 Stone JH, Nousari HC. 'Essential' cutaneous vasculitis: what every rheumatologist should know about vasculitis of the skin. *Curr Opin Rheumatol* 2001; **13**: 23–34.
5 Cohen MD, Conn DL. An approach to the adult with suspected vasculitis. In: Ball GV, Bridges SL, eds. *Vasculitis*. Oxford: Oxford University Press, 2002: 227–33.
6 Goldmuntz EA, White PH. An approach to the child with suspected vasculitis. In: Ball GV, Bridges SL, eds. *Vasculitis*. Oxford: Oxford University Press, 2002: 234–45.
7 Fiorentino DF. Cutaneous vasculitis. *J Am Acad Dermatol* 2003; **48**: 311–40.
8 Gonzalez-Gay MA, Garcia-Porrua C, Pujol RM. Clinical approach to cutaneous vasculitis. *Curr Opin Rheumatol* 2005; **17**: 56–61.
9 Schmidt WA, Gromnica-Ihle E. What is the best approach to diagnosing large-vessel vasculitis? *Clin Rheumatol* 2005; **19**: 223–42.
10 Ozen S, Ruperto N, Dillon MJ *et al*. EULAR/PReS endorsed consensus criteria for the classification of childhood vasculitides. *Ann Rheum Dis* 2006; **65**: 936–41.
11 Watts R, Lane S, Hanslik T *et al*. Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies. *Ann Rheum Dis* 2006; **66**: 222–7.
12 Jenette JC, Falk RJ. Nosology of primary vasculitis. *Curr Opin Rheumatol* 2007; **19**: 10–16.
13 Chen K-R, Carlson AJ. Clinical approach to cutaneous vasculitis. *Am J Clin Dermatol* 2008; **9**: 71–92.
14 Russell JP, Gibson LE. Primary cutaneous small vessel vasculitis: approach to diagnosis and management. *Int J Dermatol* 2006; **45**: 3–13.
15 Crowson AN, Mihm MC Jr, Magro CM. Cutaneous vasculitis: a review. *J Cutan Pathol* 2003; **30**: 161–73.
16 Carlson JA, Chen K-R. Cutaneous vasculitis update: small vessel neutrophilic vasculitis syndromes. *Am J Dermatopathol* 2006; **28**: 486–506.
17 Carlson JA, Chen K-R. Cutaneous vasculitis update: neutrophilic muscular vessel and eosinophilic, granulomatous, and lymphocytic vasculitis syndromes. *Am J Dermatopathol* 2007; **29**: 32–43.
18 Ronkainen J, Nuutinen M, Koskimies O. The adult kidney 24 years after childhood Henoch-Schönlein purpura: a retrospective cohort study. *Lancet* 2002; **360**: 666–70.

Cutaneous small vessel vasculitis

Synonyms

- Cutaneous leukocytoclastic vasculitis
- Hypersensitivity angiitis/vasculitis variants confined to skin
- Cutaneous necrotizing venulitis (necrotizing variant involving predominantly venules)

Definition. Affecting mainly cutaneous post-capillary venules, cutaneous small vessel vasculitis (CSVV) is the most common type of vasculitis in dermatology. Features of CSVV include palpable purpura, urticaria or ulcers on the legs. It affects both children and adults, and is seen more commonly in women. Extracutaneous manifestations of CSVV are by definition relatively uncommon and should prompt a search for other pathology such as Henoch–Schönlein purpura (HSP).

History and nomenclature. In the 1950s, Zeek described small vessel vasculitis related to drug exposure as a separate entity from large vessel vasculitis, and termed the small vessel vasculitis 'hypersensitivity angiitis'. Because of ambiguity, the term hypersensitivity angiitis was redefined by the Chapel Hill Consensus Conference in 1994 to describe patients with a small vessel vasculitis with primarily cutaneous involvement [1].

Aetiology and pathogenesis. A history of drug exposure or recent infection is frequently present in cases of CSVV, and circulating immune complexes can be identified in a large percentage of patients. It is important to be aware that CSVV can occur as part of microscopic polyangiitis or Wegener's granulomatosis, and that some patients with HSP may be erroneously thought to have 'simple' CSVV if renal involvement is delayed or if skin biopsy fails to show IgA deposits (as occurs in biopsy of older lesions). A detailed review suggested that about 50% of cases of cutaneous vasculitis are 'idiopathic', 15–20% due to infection, 15–20% related to inflammatory diseases (such as collagen vascular disorders), 10–15% due to medications and other drugs, and less than 5% are associated with malignancy [2]. CSVV is therefore a term delineating the extent of vasculitis, usually of leukocytoclastic type, but is really a diagnosis of exclusion, as discussed in more detail below.

Histopathology. Leukocytoclastic vasculitis with segmental inflammation in an angiocentric pattern, swelling of the endothelium, fibrinoid necrosis of vessel walls, extravasation of erythrocytes, and an infiltrate of neutrophils with karyorrhexis of nuclei (i.e. leukocytoclasia) are major features of CSVV (Figs 50.1 & 50.2).

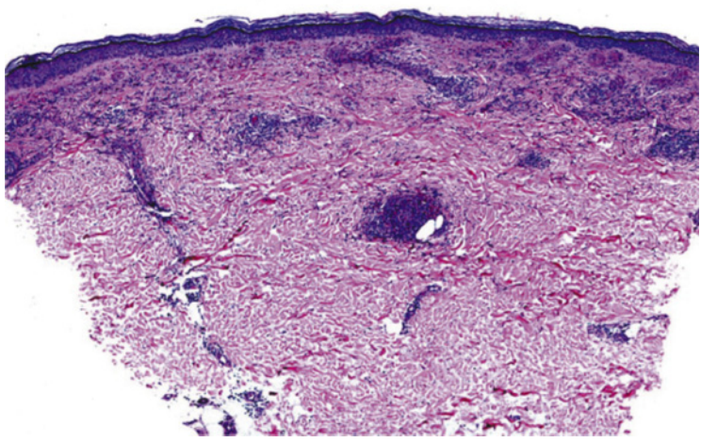


Fig. 50.1 Leukocytoclastic vasculitis. Low power photomicrograph showing perivascular infiltrates and fibrinoid deposits within the vessels of the upper dermis. (Courtesy of Dr Omar Sangueza, Wake Forest University School of Medicine, Winston-Salem, NC, USA.)

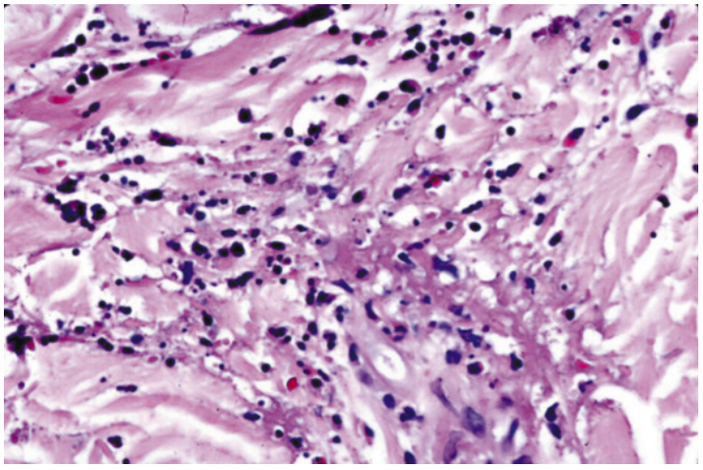


Fig. 50.2 Leukocytoclastic vasculitis. Higher magnification demonstrates nuclear dust, fibrinoid deposits, vascular alteration and collagen degeneration. (Courtesy of Dr Omar Sangueza, Wake Forest University School of Medicine, Winston-Salem, NC, USA.)

In superficial dermal papillary vessels, IgM or complement C3 perivascular deposits are demonstrated in over 80% of fresh lesions [3]. Some studies state lower proportions, but this may depend on timing of biopsy and also because IgM is relatively poor at fixing complement. IgG is found less often.

Clinical features [2,4–13]. The skin lesions of CSVV typically arise as a simultaneous 'crop', resulting from the exposure to an inciting stimulus. They usually resolve within several weeks or a few months although, anecdotally, approximately 10% of patients will have recurrent disease at intervals up to years. In one retrospective analysis, a quarter of patients with cutaneous leukocytoclastic vasculitis had either a chronic course (over 3 months) or recurrent symptoms, including all those with hepatitis C-associated vasculitis and five of nine with a streptococcal aetiology [11]. The major cutaneous manifestation of CSVV is palpable purpura, ranging in size from 1 mm to several centimetres (Figs 50.3–50.5). Sometimes macular in the early stages, such purpura may progress to a wide array of lesions including papules, nodules, vesicles, plaques, bullae or pustules, with secondary findings of ulceration, necrosis and post-inflammatory hyperpigmentation. Other cutaneous findings include oedema, livedo reticularis and urticaria. The presence of the latter two should prompt consideration of cutaneous polyarteritis nodosa and urticarial vasculitis, respectively (see pp. 50.33 and 50.21). Lesions typically occur in areas prone to stasis, commonly including the ankles and lower legs [2,4–10], and typically sparing intertriginous regions. Although often asymptomatic, pruritus, pain or burning may be experienced, as well as systemic symptoms including fever, arthralgia, myalgia and anorexia. The presence of symptoms affecting other organ systems should raise the suspicion of other vasculitides such as HSP, mixed cryoglobulinaemia, or CSVV associated with polyarteritis nodosa (PAN) or with WG.

Diagnosis. A thorough history and physical examination is essential for correct diagnosis of CSVV, with screening for infections, connective tissue disease, medication usage and cancer. Vasculitides with systemic manifestations must be ruled out, as CSVV is diagnosed by exclusion. Table 50.6 describes the evaluation of a patient with a suspected CSVV (see also the preceding section 'Evaluation of the patient with suspected vasculitis', p. 50.12, and [2,8–10]). The differential diagnosis of CSVV includes many more specifically defined disorders, which are discussed in this chapter and listed in [2,3,9–13].

As indicated, a diagnosis of CSVV should be treated with some caution, not only because of the extensive differential diagnosis of the pathological features but also because other features may become apparent and make the diagnosis of CSVV, or of



Fig. 50.3 Cutaneous small vessel vasculitis on the thighs. There was similar involvement on the lower legs.



Fig. 50.4 Cutaneous small vessel vasculitis progressing to blistering.



(a)



(b)

Fig. 50.5 Vasculitis due to sepsis, in a patient with impaired level of consciousness. The necrotic lesion in (a) and the reticulate pattern on the leg in (b) are clues to involvement of deeper vessels. Histologically, vasculitis due to infection may involve vessels at all levels of the dermis.

Table 50.6 Evaluation of a patient with suspected cutaneous small vessel vasculitis.

Confirm the clinical diagnosis histopathologically
- Punch biopsy of lesion at the appropriate stage
- Direct immunofluorescence
- Incisional biopsy for suspected larger vessel vasculitis

Assess the extent of the disease

General
- Myalgia
- Arthralgia
- Fever

Renal involvement
- Proteinuria
- Haematuria

Nervous system
- Central or peripheral
- Diffuse or local findings

Musculoskeletal involvement
- Non-erosive polyarthritis

Gastrointestinal system
- Abdominal pain
- Gastrointestinal bleeding

Pulmonary involvement
- Pleural effusion
- Pleuritis

Pericardial involvement
- Pericardial effusion

Attempt to establish the aetiology (idiopathic in 50%)
- Drugs
- Infections
- Diseases associated with immune complexes
- Connective tissue vascular diseases
- Malignancy
- Inflammatory bowel disease
- Chronic active hepatitis

Idiopathic (50%)

idiopathic CSVV, insecure. The frequency of this occurrence is difficult to ascertain as some retrospective analyses exclude patients with associated collagen vascular disease, infection, etc. Two retrospective reviews of patients diagnosed as having cutaneous vasculitis or CSVV suggest that about a third of patients may have a more specific diagnosis or evidence of internal disease. In one study of 90 patients with CSVV, renal involvement was documented in 39 (43%); in 29 of these, renal biopsy was performed and led to reclassification as HSP (10 patients), microscopic polyangiitis (MPA) (13 patients) or WG (six patients) [14]. In a review of 93 patients, 57 were felt to have 'hypersensitivity vasculitis', the remainder having more specific diagnoses including HSP (11), urticarial vasculitis (six), types of polyangiitis (microscopic polyangiitis, five; classic PAN, one; cutaneous PAN, three), WG (two) and others; 20/93 had renal involvement, comprising six each with hypersensitivity vasculitis and HSP, and four each with microscopic polyangiitis and septic vasculitis [11]. In this study, 44% were classed as idiopathic.

Treatment. Treatment of CSVV is typically unnecessary, as the disease is usually self-limiting. The evidence for efficacy of any therapy in the management of vasculitis is derived from clinical experience rather than controlled trials. However, if any triggering agents are identified, such as a drug or infection, they should be removed or treated. Efforts to minimize stasis, such as use of compression hosiery and elevation of dependent areas, as well as the use of non-steroidal anti-inflammatory drugs (NSAIDs) and antihistamines, typically produce a decrease in symptoms [10], although there is little reason to suppose that they alter the course of the disease. Furthermore, oral corticosteroids at a dosage of 30–80 mg once daily, tapered over 2–3 weeks, often give effective symptom control, although no controlled trials have been carried out to evaluate the treatment of CSVV with oral corticosteroids. Corticosteroid use may be of particular benefit in cases with painful progressive cutaneous lesions, and they prevent glomerulonephritis in patients who actually have HSP. No data support

Table 50.7 Therapeutic ladder for patients with cutaneous small vessel vasculitis.

Symptomatic relief
Supportive therapy (3)
Antihistamines (3)
Non-steroidal anti-inflammatory drugs (2)
Skin lesions alone
Pentoxiphylline (3)
Colchicine (2)
Dapsone (2)
Ulcerative skin lesions alone
Thalidomide (3)
Low-dose weekly methotrexate (3)
Prednisolone (2)
Systemic disease
Prednisolone (2)
Azathioprine (2)
Cyclophosphamide (2)
Mycophenolate mofetil (3)
Ciclosporin (3)
Interferon-α (if hepatitis C-associated) (1)
Intravenous gammaglobulin (3)
Extracorporeal immunomodulation (3)
Infliximab (3)
Rituximab (3)

1, double-blind studies; 2, case series; 3, case reports.

the use of topical corticosteroids or antibiotics in CSVV, although such therapies are commonly used. Colchicine given at a dose of 0.6 mg twice daily has been shown to be of benefit by anecdotal evidence and open-label studies [15–17]. Similarly, the use of dapsone is based only on anecdotal or small case series, yet some believe that the use of dapsone along with colchicine may be advantageous in the treatment of CSVV [18–21]. In patients with disease refractory to the above therapies, cytotoxic agents may be considered. Such agents include azathioprine (typically at a dosage of 2 mg/kg/day; see also Chapter 74), methotrexate at a low dose of less than 25 mg/week, ciclosporin and cyclophosphamide [22–26]. Table 50.7 describes a therapeutic ladder for patients with CSVV. A therapeutic ladder based on individual diagnostic entities is provided in [2].

More recently, biological agents have shown some promise in the treatment of vasculitis, although they are rarely required for CSVV; infliximab, which blocks TNF-α, and rituximab, by blocking CD20 and thus inhibiting B-cell antibody production, appear to be the most promising [27,28]. Paradoxically, both of these agents have also been reported to cause vasculitis [29,30].

In some cases, ulceration, particularly of the lower legs, may prove difficult to heal despite apparently appropriate interventions. Although the cause(s) may be those that impair healing of the lower leg in any situation, such as obesity, diabetes, arterial disease, etc. (Chapter 47) (Fig. 50.6) it is also pertinent to note that hypercoagulability conditions (Chapter 49) may also impair healing; in a study of 13 patients with refractory leg ulcers following leukocytoclastic vasculitis, seven (53%) had either factor V Leiden or a lupus anticoagulant [31].



Fig. 50.6 Prolonged leg ulceration in a patient with cutaneous small vessel vasculitis, without systemic involvement; the main factor impairing healing was diabetic arterial disease.

References

1 Jennette JC, Falk RG, Andrassy K *et al*. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. *Arthritis Rheum* 1994; **37**: 187–92.
2 Fiorentino DF. Cutaneous vasculitis. *J Am Acad Dermatol* 2003; **48**: 311–40.
3 Carlson JA, Chen K-R. Cutaneous vasculitis update: small vessel neutrophilic vasculitis syndromes. *Am J Dermatopathol* 2006; **28**: 486–506.
4 Blanco R, Martinez-Taboada VM, Rodriguez-Valverde V, Garcia-Fuentes M. Cutaneous vasculitis in children and adults: associated diseases and aetiologic factors in 303 patients. *Medicine* 1998; **77**: 403–18.
5 Ekenstam E, Callen JP. Cutaneous leukocytoclastic vasculitis: clinical and laboratory features of 82 patients seen in private practice. *Arch Dermatol* 1984; **120**: 484–9.
6 Martinez-Taboada VM, Blanco R, Garcia-Fuentes M, Rodriguez-Valverde V. Clinical features and outcome of 95 patients with hypersensitivity vasculitis. *Am J Med* 1997; **102**: 186–91.
7 Sais G, Vidaller A, Jucgla A *et al*. Prognostic factors in leukocytoclastic vasculitis: a clinicopathologic study of 160 patients. *Arch Dermatol* 1998; **134**: 309–15.
8 Gonzalez-Gay MA, Garcia-Porrua C, Pujol RM. Clinical approach to cutaneous vasculitis. *Curr Opin Rheumatol* 2005; **17**: 56–61.
9 Chen K-R, Carlson AJ. Clinical approach to cutaneous vasculitis. *Am J Clin Dermatol* 2008; **9**: 71–92.
10 Lotti T, Ghersetich I, Comacchi C, Jorizzo JL. Cutaneous small-vessel vasculitis. *J Am Acad Dermatol* 1998; **39**: 667–87; quiz 688–90.
11 Tai YJ, Chong AH, Williams RA *et al*. Retrospective analysis of adult patients with cutaneous leukocytoclastic vasculitis. *Australas J Dermatol* 2006; **47**: 92–6.
12 Magro CM, Crowson AN. The cutaneous neutrophilic vascular injury syndromes: a review. *Semin Diag Pathol* 2001; **18**: 47–58.
13 Crowson AN, Mihm MC Jr, Magro CM. Cutaneous vasculitis: a review. *J Cutan Pathol* 2003; **30**: 161–73.
14 Ioannidou DJ, Krasagakis Sotsiou F, Tosca AD. Cutaneous small vessel vasculitis: an entity with frequent renal involvement. *Arch Dermatol* 2002; **138**: 413–4.
15 Hazen PG, Michel B. Management of necrotizing vasculitis with colchicine: improvement in patients with cutaneous lesions and Behçet's syndrome. *Arch Dermatol* 1979; **115**: 1303–6.
16 Plotnick S, Huppert AS, Kantor G. Colchicine and leukocytoclastic vasculitis. *Arthritis Rheum* 1989; **32**: 1489–90.
17 Callen JP. Colchicine is effective in controlling chronic cutaneous leukocytoclastic vasculitis. *J Am Acad Dermatol* 1985; **13**: 193–200.
18 Callen JP. A clinical approach to the vasculitis patient in the dermatologic office. *Clin Dermatol* 1999; **17**: 549–53.
19 Wells GC. Allergic vasculitis (tri-symptom of Gougerot) treated with dapsone. *Proc R Soc Med* 1969; **62**: 665–6.
20 Asghar SS, Westerhof W, Das PK *et al*. Treatment of vasculitis with chlorpromazine and dapsone. *Arch Dermatol Res* 1985; **277**: 504–6.

21 Fredenberg MF, Malkinson FD. Sulfone therapy in the treatment of leukocytoclastic vasculitis: report of three cases. *J Am Acad Dermatol* 1987; **16**: 772–8.
22 Jorizzo JL, White WL, Wise CM *et al*. Low-dose weekly methotrexate for unusual neutrophilic vascular reactions: cutaneous polyarteritis nodosa and Behçet's disease. *J Am Acad Dermatol* 1991; **24**: 973–8.
23 Heurkens AH, Westedt ML, Breedveld FC. Prednisone plus azathioprine treatment in patients with rheumatoid arthritis complicated by vasculitis. *Arch Intern Med* 1991; **151**: 2249–54.
24 Boehm I, Bauer R. Low dose methotrexate controls a severe form of polyarteritis nodosa. *Arch Dermatol* 2000; **136**: 167–9.
25 Vena GA, Cassano N. Immunosuppressive therapy in cutaneous vasculitis. *Clin Dermatol* 1999; **17**: 633–40.
26 Callen JP, Spencer LV, Burruss JB, Holtman J. Azathioprine: an effective, corticosteroid-sparing therapy for patients with recalcitrant cutaneous lupus erythematosus or with recalcitrant cutaneous leukocytoclastic vasculitis. *Arch Dermatol* 1991; **127**: 515–22.
27 Uthman IW, Touma Z, Sayyad J, Salman S. Response of deep cutaneous vasculitis to infliximab. *J Am Acad Dermatol* 2005; **53**: 353–4.
28 Chung L, Funke AA, Chakravarty EF *et al*. Successful use of rituximab for cutaneous vasculitis. *Arch Dermatol* 2006; **142**: 1407–10.
29 Anandacoomarasamy A, Kannangara S, Barnsley L. Cutaneous vasculitis associated with infliximab in the treatment of rheumatoid arthritis. *Intern Med J* 2005; **35**: 638–40.
30 Kandula P, Kouides PA. Rituximab-induced leukocytoclastic vasculitis: a case report. *Arch Dermatol* 2006; **142**: 246–7.
31 Mekkes JR, Loots MA, van der Wal AC, Bos JD. Increased incidence of hypercoagulability in patients with leg ulcers caused by leukocytoclastic vasculitis. *J Am Acad Dermatol* 2004; **50**: 104–7.

Drug-induced vasculitis

Definition. Vasculitis of various morphological types can be caused by drug ingestion. This is briefly discussed as a discrete topic as it is always important to consider medications and other ingested drugs as a possible cause of vasculitis. The clinical pattern is usually that of a superficial small vessel cutaneous leukocytoclastic vasculitis but other patterns, including systemic vasculitis, occur. Drug-induced vasculitis is also considered in Chapter 75 with emphasis on causative agents.

Causes. Many drugs may cause vasculitis, and are listed in several reference sources [1–6]. The validity and importance of some reports of drug-induced vasculitis is uncertain as not all are histologically confirmed, the frequency in relation to the number of patients treated with any specific causative drug is often unknown, and most surveillance systems rely on spontaneous reporting. About 200 drug causes of vasculitis are listed by Litt [5]; even allowing for uncertainty in some cases, it seems likely that over 100 drugs are implicated as causes of drug-induced vasculitis or the closely related drug-induced lupus-like syndrome [7], although the actual frequency of drug-induced vasculitis is very low [6], possibly 1/100 000 people. However, it is also clear that, for any drug, vasculitis is one of the rarer reaction patterns that occurs (typically accounting for <1% of reactions to any individual drug). Some of the more important drugs that can cause vasculitis are also listed in Table 50.8. Those most frequently implicated are penicillins, sulphonamides, quinolones, analgesics (including non-steroidal anti-inflammatory drugs), thiazides and other diuretics, anticonvulsants, phenothiazines, allopurinol, and colony-stimulating factors [1–9]. Less commonly used drugs, but with a significant risk of causing vasculitis, include hydralazine, quinidine, thiouracils and various biological agents.

Drugs that may cause skin necrosis or drug-induced purpura are discussed in Chapter 49. It is important to be aware that illicit drugs (especially cocaine and sympathomimetics, such as ephedrine or amphetamines), drug excipients, vaccines (especially influenza and hepatitis B), herbal remedies [10] and food additives can all cause vasculitis, as these may otherwise be overlooked as possible triggers. Cannabis tends to cause an atherosclerosis-like arterial occlusion, mimicking severe peripheral arterial disease [11]. It has been suggested that routine influenza vaccination may lead to an increased number of cases of vasculitis in the target groups for immunization; when this does occur, the vasculitis may be cutaneous or systemic, usually occurs about 2 weeks after the vaccination, and is usually in patients who have had a previous uneventful influenza vaccination [12].

It is always important to consider the possibility of vasculitis in relation to newer drugs, as such reactions may only become apparent during wider use than in clinical trials. This is particularly difficult as some are used for systemic diseases where it may be difficult to distinguish drug-induced vasculitis from vasculitis due to the underlying disease or to other mechanisms (such as infection). Relatively new, or increasingly used, classes of drugs that can cause vasculitis include interferons, retinoids (mainly isotretinoin), leukotriene inhibitors, anti-TNF agents and other monoclonals, and colony stimulating factors. Bortezomib, a proteosome inhibitor used in treatment of haematological malignancies, has been associated with both a Sweet's syndrome-like neutrophilic dermatosis and with leukocytoclastic vasculitis [13]; occurrence of this eruption appears to be associated with a better treatment outcome than in patients who do not develop a rash. Dermatologists need to be aware that anti-TNF agents are not an uncommon cause of skin or systemic vasculitis; one study reported 39 cases during 1 year in France [14].

Mechanisms. Most drug-induced vasculitis is of hypersensitivity type and presumed to be immune complex-mediated; it probably accounts for 10–20% of small vessel cutaneous vasculitis [4]. The evidence for this assumption is often indirect, although sulphonamide crystals have been observed in blood vessel walls [15]. This pattern is provoked by various antibiotics, diuretics, NSAIDs, anticonvulsants, antipsychotics, cardiac drugs such as diltiazem, and others [3,4]. Relatively recent drugs that can cause this pattern include zidovudine, various haemopoietic growth factors and etanercept.

True serum sickness, originally related to use of hyperimmune sera, is rarely seen, although it does occur with protein drugs such as streptokinase and antithymocyte globulin; a serum sickness-like pattern of eruption is more commonly seen, occurring in relation to penicillins or sulphonamides, and less commonly with drugs such as thiouracil, phenytoin (hydantoin) or phenylbutazone.

Any of the other classical Gell and Coombs mechanisms for vasculitis may occur, although the mechanism by which drugs provoke systemic vasculitis is often less clear than in the immune complex pattern. In some instances, such as leukotriene antagonists administered for asthma 'causing' CSS (Chapter 62), there is

Table 50.8 Some causes of drug-induced vasculitis and the patterns of vasculitis they most commonly provoke.

Type of drug or organ targeted	Examples
Antibiotics/anti-infection	Penicillins, sulphonamides, quinolones, cephalosporins, minocycline, clindamycin, vancomycin, macrolides, rifampicin, isoniazid, imidazoles, griseofulvin, zidovudine, didanosine, efavirenz, mefloquine (all usually cause CLV ± SV; penicillins are also the commonest cause of SSLR; cephalosporins may also cause HSP or AASV; ciprofloxacin may also cause AASV; minocycline can cause CLV, AASV/C-PAN and LELS)
Antithyroid	Propylthiouracil; less frequently carbimazole or methimazole (LCV, AASV/MPA)
Rheumatological	NSAIDs (including cycloxygenase-2 inhibitors) (CLV, SV) Allopurinol (CLV, AASV) Penicillamine (AASV); sulphasalazine (CLV, AASV)
Cardiac	Anticoagulant/antiplatelet: aspirin (CLV); streptokinase (SS, CLV); warfarin (coumadin)(CLV ± SV); heparin (CLV) Diuretics (thiazides, furosemide, metolazone) (CLV ± SV; thiazides can cause AASV) Antiarrhythmics: amiodarone (CLV), quinidine (CLV ± SV) Antihypertensives: hydralazine (CLV, AASV, LELS); calcium channel blockers (CLV, SV); beta-blockers (CLV ± SV)
Neurological and psychiatry	Anticonvulsants: hydantoins, carbamazepine, most others (CLV ± SV; phenytoin reported to cause AASV) Phenothiazines, several antidepressants (CLV ± SV)
Oncology	Cytarabine, dacarbazine, gemcitabine, others (CLV ± SV)
Immunosuppressives and related agents	Ciclosporin (AASV, CV); azathioprine, methotrexate, busulphan, cyclophosphamide, melphalan, gold, tacrolimus, dapsone (all CLV ± SV)
Monoclonals	Anti-TNF agents (CLV, SV, HSP, AASV); rituximab (CVL,SV), bortezomib (CLV); colony stimulating factors (CLV); interferons (CLV, AASV, LELS); omalizumab (CSS)
Illicit drugs	Amphetamines/ecstasy, ephedrine, cocaine, heroin (CLV; cocaine causes AASV; cannabis causes atherosclerosis-like arterial occlusion; many may cause cerebral vasospasm or frank CV also)
Vaccines	Influenza (most cases), hepatitis B, hepatitis A, rubella, measles, MMR, pneumococcus, BCG, tetanus/DPT, rabies, smallpox (mostly CLV ± SV; influenza vaccine may also cause MPA; rabies vaccine may cause SS; hepatitis B vaccine may cause AASV/PAN/C-PAN, HSP, UV, CryoV, KD)
Miscellaneous	Warfarin (coumadin), quinine, potassium iodide and iodinated radiocontrast media (all CLV ± SV) Leukotriene inhibitors (AASV, CSS) Retinoids (CLV ± SV; PAN; AASV; pulmonary capillaritis)

AASV, ANCA-associated systemic vasculitis; CLV, cutaneous leukocytoclastic vasculitis; C-PAN, cutaneous polyarteritis nodosa; CryoV, cryoglobulinaemic vasculitis; CSS, Churg–Strauss syndrome; CV, cerebral vasculitis; DPT, diphtheria–pertussis–tetanus; HSP, Henoch–Schönlein purpura; KD, Kawasaki disease; LELS, LE-like syndrome; MMR, mumps–measles–rubella; MPA, microscopic polyangiitis; NSAIDs, non-steroidal anti-inflammatory drugs; PAN, polyarteritis nodosa; SS, serum sickness; SSLR, serum sickness-like reaction; SV, systemic vasculitis.

an argument that the asthma may simply have been an early feature of CSS and that the drug is not relevant. However, ANCA-positive (particularly MPO-positive) vasculitis has been convincingly linked with drugs such as hydralazine (which may also cause small vessel leukocytoclastic vasculitis) and thiouracils, and less commonly with penicillamine, allopurinol, minocycline and sulfasalazine [16–18]. Glomerulonephritis may occur related to propylthiouracil-induced ANCA-positive vasculitis, although in general internal involvement is relatively mild in ANCA-positive drug-induced vasculitis.

Drug-induced lupus erythematosus is discussed in Chapter 51; drug-induced neutrophilic dermatoses are discussed later in this chapter.

Pathology. A small vessel vasculitis with a lymphocytic infiltrate and little leukocytoclasia, or the presence of some degree of tissue eosinophilia, are suggestive of the possibility of drug-induced vasculitis. Although none of these is sensitive or specific, tissue eosinophilia was significantly greater in drug-induced cases of CSVV than in non-drug-related cases [19] and should arouse suspicion of a drug-induced vasculitis, especially in the absence of systemic symptoms and if ANCA are negative. Serum complement levels are generally normal. ANCA may be positive (see above).

Clinical features. Drug-induced leukocytoclastic vasculitis presents with palpable purpura, petechiae, necrosis and urticarial lesions, indistinguishable from other causes of this pattern of vasculitis.

In the serum sickness-like reaction, the initial rash may be acral, with urticaria or purpura, followed by more generalized annular urticarial lesions. There may be fever, arthralgia, haematuria or proteinuria, lymphadenopathy and decreased complement levels.

Medium and large vessel vasculitides mimic the patterns described elsewhere in this chapter, although there may be atypical features such as eosinophilia or the fact that all lesions appear to be of similar duration. Some drug-induced cases resembling CSS have relatively minor respiratory symptoms compared with the idiopathic condition.

Diagnosis. Generally, drug-induced vasculitis is indistinguishable clinically from the same clinical picture occurring due to other causes. This is particularly the case in CSVV or leukocytoclastic

vasculitis with systemic involvement. Timing of the eruption in relation to starting a new drug may be informative, especially if the drug is only administered once (such as vasculitis due to streptokinase, which occurs early after administration). However, in some instances, such as vasculitis due to diuretics, onset may be delayed for several months.

Eosinophilia may be a useful guide. Blood eosinophilia is found in almost 80% of patients with drug-induced systemic vasculitis, but in less than a quarter in whom the reaction is CSVV alone [20]; tissue eosinophilia is also more likely in drug-induced CSVV [19].

ANCA-associated vasculitides generally mimic the primary disease but with less systemic disease, although the differential diagnosis may be difficult, particularly if the cause is concealed, for example when illicit drugs are involved. Cocaine, in particular, is recognized as a cause of systemic vasculitis (notably including cerebral vasculitis), but may also cause facial midline destructive lesions that mimic WG and that cause particular diagnostic problems as over 80% have a positive ANCA (usually P-ANCA, but the pattern may vary even within one individual); a useful distinction is that most ANCA in Wegener's granulomatosis is directed against PR3 and sometimes MPO, whereas patients with cocaine-induced midline destructive lesions do not have MPO-ANCA, and even if they also have a PR3-ANCA, they have ANCA against human neutrophil elastase (human leukocyte elastase, HLE) which is not a specificity seen in WG [21,22]. Drug causes for ANCA-associated systemic vasculitides should be considered if there are multiple ANCA specificities or anti-HLE, rather than the more usual anti-MPO or anti-PR3 ANCA of the main differential diagnoses; for example, minocycline has been linked with MPO, HLE, cathepsin G, bactericidal permeability-increasing protein ANCA as well as with antihistone and anticardiolipin antibodies [7].

Treatment. Stopping any suspect drug is important and may be all that is required for cutaneous vasculitis. In cases with systemic disease, corticosteroids and even other immunosuppressive agents may be necessary. Supportive treatment such as compression hosiery may be required as in other forms of small vessel vasculitis. Renal function and urinalysis should be monitored.

In most instances, the causative drug should not be used again. It is also important to be aware of possible cross-reactions (notably between diuretics) when substituting a different drug.

References

1 Bruinsma W. *A Guide to Drug Eruptions*. Amsterdam: Excerpta Medica, 1973: 51–4.
2 Bork K. *Cutaneous Side-Effects of Drugs*. Philadelphia: Saunders, 1988: 152–5.
3 Ball GV, Bridges SL. Pathogenesis of vasculitis. In: Ball GV, Bridges SL, eds. *Vasculitis*. Oxford: Oxford University Press, 2002: 34–52.
4 Dubost JJ, Souteyrand P, Sauvezie B. Drug-induced vasculitides. *Baillières Clin Rheumatol* 1991; **5**: 119–38.
5 Litt JZ. *Drug Eruption Reference Manual*, 12th edn. London: Taylor and Francis, 2006: 655–6.
6 Merkel PA. Drug-induced vasculitis. *Rheum Dis Clin N Am* 2001; **27**: 849–62.
7 Wiik A. Drug-induced vasculitis. *Curr Opin Rheumatol* 2008; **20**: 35–9.
8 Doyle MK, Cuellar ML. Drug-induced vasculitis. *Expert Opin Drug Saf* 2003; **2**: 401–9.
9 Del Rosso A, Generini S, Pignone A, Matucci-Cerinic M. Vasculitides secondary to systemic diseases. *Clin Dermatol* 1999; **17**: 533–47.
10 Ingraffea A, Donohue K, Wilkel C, Falanga V. Cutaneous vasculitis in two patients taking an herbal supplement containing black cohosh. *J Am Acad Dermatol* 2007; **56**: S124–6.
11 Noel B, Ruf I, Pannizon RG. Cannabis arteritis. *J Am Acad Dermatol* 2008; **58** (Suppl. 1): S65–7.
12 Tavadia S, Drummond A, Evans CD, Wainwright HJ. Leukocytoclastic vasculitis and influenza vaccination. *Clin Exp Dermatol*; **28**: 154–6.
13 Garcia-Navarro X, Puig L, Fernández-Figueras MT *et al*. Bortezomib-associated cutaneous vasculitis. *Br J Dermatol* 2007; **157**: 799–801.
14 Saint Marcoux B, de Bandt M. Vasculitides induced by TNF alpha antagonists: a study in 39 patients in France. *Joint Bone Spine* 2006; **73**: 710–3.
15 Mullick FG, McAllister HA, Wagner BM, Fenoglio JJ. Drug related vasculitis: clinicopathologic correlations in 30 patients. *Hum Pathol* 1979; **10**: 313–25.
16 Choi HK, Merkel PA, Walker AM, Niles JL. Drug-associated antineutrophil cytoplasmic antibody-positive vasculitis: prevalence among patients with high titers of antimyeloperoxidase antibodies. *Arthritis Rheum* 2000; **43**: 405–13.
17 Merkel PA. Drugs associated with vasculitis. *Curr Opin Rheumatol* 1998; **10**: 45–50.
18 Aloush V, Litinsky I, Caspi D, Elkayam O. Propylthiouracil-induced autoimmune syndromes: two distinct clinical presentations with different course and management. *Semin Arthritis Rheum* 2006; **36**: 4–9.
19 Bahrami S, Malone JC, Webb KG, Callen JP. Tissue eosinophilia as an indicator of drug-induced cutaneous small-vessel vasculitis. *Arch Dermatol* 2006; **142**: 155–61.
20 Fiorentino DF. Cutaneous vasculitis. *J Am Acad Dermatol* 2003; **48**: 311–40.
21 Molloy ES, Langford CA. Vasculitis mimics. *Curr Opin Rheumatol* 2008; **20**: 29–34.
22 Wiesner O, Russell KA, Lee AS *et al*. Antineutrophil cytoplasmic antibodies reacting with human neutrophil elastase as a diagnostic marker for cocaine-induced midline destructive lesions but not autoimmune vasculitis. *Arthritis Rheum* 2004; **50**: 2954–65.

Henoch–Schönlein purpura

Synonyms

- IgA immune complex vasculitis
- Anaphylactoid purpura
- Purpura rheumatoide

Definition. Originally described as a tetrad of palpable purpura, arthritis, gastrointestinal involvement and renal glomerular involvement [1,2], HSP is defined by the Chapel Hill Consensus Conference as a vasculitis affecting small vessels, involving deposition of IgA immune complexes, that characteristically involves the skin, gastrointestinal system and glomeruli with or without arthralgia or arthritis [3]. Unfortunately, many literature reports have previously assumed that all cutaneous small vessel vasculitis in children is HSP, rather than insisting on confirmed presence of IgA immune complexes, which causes great confusion. This has been addressed by the EULAR/PReS consensus [4], although some cases are acceptable in which IgA is not demonstrated (presumed to reflect delayed biopsy with destruction of immunoreactants). Although it can occur in adults, HSP is much more common in childhood; 75% of cases occur in children under 6 years old and 90% in children under 10 years old [5–9]. Furthermore, HSP occurs in various racial and ethnic groups [9–11].

History and nomenclature. Heberden first described HSP in 1801, in a young boy with abdominal pain, emesis, bloody stools,

arthritis and a purpuric eruption. The eponymous term Henoch–Schönlein purpura was later applied after Johann Schönlein and Eduard Henoch described features of the vasculitis in the mid-19th century.

Aetiology and pathogenesis [9,12]. Some infections, such as those caused by Group A β-haemolytic streptococci, are implicated in the cause of HSP, although evidence for streptococcal infection is only found in approximately 30% of children [8] (the range from different studies is about 20–50% [12]). Additionally, although other pathogens have been implicated (including *Bartonella henselae*, parvovirus B19, *Staphylococcus aureus*, coxsackieviruses, adenovirus, hepatitis A and B viruses), a triggering pathogen is not found in the majority of cases. Seasonal outbreaks have been described. The demonstration of nephritis-associated plasmin receptor NAPlr, a Group A streptococcal antigen, in renal mesangial vessels of children with HSP-associated nephritis (discussed earlier, p. 50.5) suggests a causative role for streptococci in at least some cases.

IgA is thought to play a pivotal part in the pathogenesis of HSP, as increased levels of IgA in the serum (in 50% with active disease), increased circulating immune complexes containing IgA, and increased deposition of IgA in blood vessel walls and in the renal mesangium are associated with HSP. In patients with HSP, IgA1 rather than IgA2 is the main IgA subclass deposited in the skin lesions [12,13]. Diminished glycosylation of the proline-rich hinge region of the IgA1 heavy chain is thought to be an important factor in allowing the IgA to be deposited in the mesangium and to activate the alternative pathway of complement in IgA, as it makes such IgA1 molecules more prone to forming macromolecular complexes [8,9].

Other IgA antibodies that occur in HSP include IgA ANCA, although this finding is very variable between studies. IgA rheumatoid factor and IgA anticardiolipin antibodies are also sometimes present, as are IgA AECA.

Activation of several cytokines is documented, although it is difficult to determine if any are a primary cause. TNF-α levels are increased, and TNF-α can be detected in skin lesions; IL-6, IL-8, transforming growth factor-beta (TGF-β) and vascular endothelial growth factor (VEGF) levels are all increased in active HSP. TGF-β is of particular interest as blood levels of T cells that produce this cytokine are increased in HSP, and it is known to enhance IgA1 responses. Neutrophil activation, elevated nitric oxide levels, reactive oxygen species and increased urinary leukotriene are all documented.

Familial clustering has been reported, which may support an infectious aetiology; however, various polymorphisms that either increase risk of HSP or are associated with more severe renal disease have been described and would also explain familial HSP (examples include polymorphisms in TGF-β, IL-1β, IL-8 and VEGF).

Histopathology. Biopsy specimens of the purpuric lesions demonstrate leukocytoclastic vasculitis affecting capillaries and post-capillary venules. Direct immunofluorescence microscopy of lesional and perilesional skin reveals deposition of IgA, C3 and fibrin in dermal blood vessel walls.



Fig. 50.7 Henoch-Schönlein purpura, with typical retiform pattern.

Clinical features. Most commonly, HSP manifests at the outset with the classic findings of purpura, arthralgia and abdominal pain [8–10]. The cutaneous findings are typically erythematous urticarial papules, which may evolve within 24 h into palpable purpura with haemorrhage. Furthermore, urticaria, vesicles, bullae and necrotic ulcers may develop. A retiform pattern within lesions is characteristic, but not necessarily present (Fig. 50.7). Typically involving the extensor aspects of the limbs (especially elbows and knees) and buttocks in a symmetrical fashion, HSP may also affect the trunk and face. Usually fading within 5–7 days, crops of lesions can recur for a few weeks to several months. Although HSP is chronic in 5–10% of patients, the cutaneous involvement usually lasts between 6 and 16 weeks and then subsides. Rarely, gastrointestinal involvement and arthritis can occur in the absence of skin disease. Renal involvement with HSP is common, occurring in approximately 40–50% of patients; 25% have gross haematuria and the remainder microscopic haematuria [9]. Proteinuria occurs in 60% of these, but is uncommon in the absence of haematuria. Only 1–3% of these patients progress to end-stage renal disease, although one-third to half of patients have renal abnormalities on long-term follow-up [9,14]. Furthermore, gastrointestinal involvement is common (65%), with frank gastrointestinal bleeding in 30% of patients with HSP [9]. Painful arthritis is seen in about 75% of patients, most frequently affecting the knees and ankles. Less common manifestations of HSP include orchitis (in 10–20% of boys), intussusception, pancreatitis, neurological abnormalities, uveitis, carditis and pulmonary haemorrhage [9].

Diagnosis. HSP is a clinical diagnosis, with confirmation by direct immunofluorescence and routine histology. Perivascular IgA deposits are characteristic of HSP and can help to distinguish it from other vasculitides including CSVV, WG, CSS and MPA. IgA immune complexes are not specific to HSP, but can be seen in a variety of patients including those with SLE, endocarditis, dermatitis herpetiformis, alcoholism, IgA nephropathy, inflammatory bowel disease, ankylosing spondylitis, Sjögren's syndrome,

rheumatoid arthritis, some cancers and in some drug hypersensitivity reactions [15–18]. No laboratory tests are specific for HSP.

Treatment. HSP is frequently self-limiting, the majority of patients fully recovering within several weeks or months, so treatment is mainly supportive. Although no data demonstrate the effectiveness of systemic corticosteroids in treating purpura, shortening the duration of HSP or decreasing the frequency of recurrences, they have been shown in a randomized controlled study to be effective in the treatment of abdominal pain and arthritis, and accelerated resolution of mild nephritis [19] (the dose was 1 mg/kg/day for 2 weeks, tapering over a further 2 weeks).

Dapsone (100 mg once daily) seems to shorten the duration of HSP as well as having a beneficial effect on the cutaneous lesions [6]. One trial proposed that factor XIII replacement may be useful in the treatment of abdominal pain and gastrointestinal bleeding associated with HSP [20], and another small trial demonstrated a decrease in the duration and severity of abdominal pain, as well as a decreased bleeding risk, with the use of ranitidine [21].

The presence of renal disease is the major factor determining the long-term morbidity and mortality associated with HSP [7,9]. Although no controlled trials have been conducted, data from several studies, as well as a case series, suggest a benefit from high-dose corticosteroids, either alone [19,22] or with cyclophosphamide and dipyridamole [23–25] in patients with progressive renal involvement associated with HSP. Ciclosporin and azathioprine have both been used [9], and case reports suggest that gastrointestinal involvement and cutaneous disease may be lessened, and rapidly progressive nephritis may be halted, by the use of intravenous immunoglobulin [26,27]. Patients with severe nephritis, including nephritic syndrome, have poor short-term and long-term outlook compared with those with milder disease; severe nephritis is typically treated with high-dose methylprednisolone at a dosage of 30 mg/kg once daily for 3 days followed by oral corticosteroids and an immunosuppressive drug such as azathioprine or cyclophosphamide [6]. NSAIDs have minimal, if any, benefit in the treatment of HSP, and should not be used in patients with renal involvement. For the cutaneous lesions, the therapeutic ladder presented for cutaneous small vessel vasculitis is also applicable for patients with HSP.

References

1 Henoch E. Uber ein eigentümliche Form von Purpura. *Berl Munch Tierarztl Wochenschr* 1874; **11**: 641–3.
2 Schönlein H. *Allgemeine und Specielle Pathologie und Therapie*, 3rd edn. Wurzburg: Herisau, 1837.
3 Jennette JC, Falk RG, Andrassy K *et al*. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. *Arthritis Rheum* 1994; **37**: 187–92.
4 Ozen S, Ruperto N, Dillon MJ *et al*. EULAR/PReS endorsed consensus criteria for the classification of childhood vasculitides. *Ann Rheum Dis* 2006; **65**: 936–41.
5 Blanco R, Martinez-Taboada VM, Rodriguez-Valverde V, Garcia-Fuentes M. Cutaneous vasculitis in children and adults: associated diseases and aetiologic factors in 303 patients. *Medicine* 1998; **77**: 403–18.
6 Saulsbury FT. Henoch–Schönlein purpura in children: report of 100 patients and review of the literature. *Medicine* 1999; **78**: 395–409.
7 Calvino MC, Llorca J, Garcia-Porrua C *et al*. Henoch–Schönlein purpura in children from northwestern Spain: a 20-year epidemiologic and clinical study. *Medicine* 2001; **80**: 279–90.
8 Trapani S, Micheli A, Grisolia F *et al*. Henoch–Schonlein purpura in childhood: epidemiological and clinical analysis of 150 cases over a 5-year period and review of literature. *Semin Arthritis Rheum* 2005; **35**: 143–53.
9 Saulsbury FT. Clinical update: Henoch–Schönlein purpura. *Lancet* 2007; **369**: 976–8.
10 Blanco R, Martinez-Taboada VM, Rodriguez-Valverde V *et al*. Henoch–Schönlein purpura in adulthood and childhood: two different expressions of the same syndrome. *Arthritis Rheum* 1997; **40**: 859–64.
11 Mills JA, Michel BA, Bloch DA *et al*. The American College of Rheumatology 1990 criteria for the classification of Henoch–Schönlein purpura. *Arthritis Rheum* 1990; **33**: 1114–21.
12 Yang Y-H, Chuang Y-H, Wang L-C *et al*. The immunobiology of Henoch–Schönlein purpura. *Autoimm Rev* 2008; **7**: 179–84.
13 Egan CA, Taylor TB, Meyer LJ *et al*. IgA1 is the major IgA subclass in cutaneous blood vessels in Henoch–Schönlein purpura. *Br J Dermatol* 1999; **141**: 859–62.
14 Ronkainen J, Nuutinen M, Koskimies O. The adult kidney 24 years after childhood Henoch-Schönlein purpura: a retrospective cohort study. *Lancet* 2002; **360**: 666–70.
15 Saklayen MG, Schroeter AL, Nafz MA, Jalil K. IgA deposition in the skin of patients with alcoholic liver disease. *J Cutan Pathol* 1996; **23**: 12–8.
16 Swerdlow MA, Chowdhury LN, Mishra V, Kavin H. IgA deposits in the skin in alcoholic liver disease. *J Am Acad Dermatol* 1983; **9**: 232–6.
17 Thompson AJ, Chan YL, Woodroffe AJ *et al*. Vascular IgA deposits in clinically normal skin of patients with renal disease. *Pathology* 1980; **12**: 407–13.
18 Magro CM, Crowson AN. The cutaneous neutrophilic vascular injury syndromes: a review. *Semin Diagn Pathol* 2001; **18**: 47–58.
19 Ronkainen J, Koskimies O, Ala-Houhala M *et al*. Early prednisone therapy in Henoch-Schönlein purpura: a randomized, double–blind, placebo-controlled trial. *J Pediatr* 2006; **149**: 241–7.
20 Fukui H, Kamitsuji H, Nagao T *et al*. Clinical evaluation of a pasteurized factor XIII concentrate administration in Henoch–Schönlein purpura. *Jpn Pediatr Group* 1989; **56**: 667–75.
21 Narin N, Akcoral A, Aslin MI, Elmastas H. Ranitidine administration in Henoch–Schönlein vasculitis. *Acta Paediatr Jpn* 1995; **37**: 37–9.
22 Niaudet P, Habib R. Methylprednisolone pulse therapy in the treatment of severe forms of Schönlein–Henoch purpura nephritis. *Pediatr Nephrol* 1995; **12**: 238–43.
23 Oner A, Tinaztepe K, Erdogan O. The effect of triple therapy on rapidly progressive type of Henoch–Schönlein nephritis. *Pediatr Nephrol* 1995; **9**: 6–10.
24 Iijima K, Ito-Kariya S, Nakamura H, Yoshikawa N. Multiple combined therapy for severe Henoch–Schönlein nephritis in children. *Pediatr Nephrol* 1998; **12**: 244–8.
25 Flynn JT, Smoyer WE, Bunchman TE *et al*. Treatment of Henoch–Schönlein purpura glomerulonephritis in children with high-dose corticosteroids plus cyclophosphamide. *Am J Nephrol* 2001; **21**: 128–33.
26 Lamireau T, Rebouissoux L, Hehunstre JP. Intravenous immunoglobulin therapy for severe digestive manifestations of Henoch–Schönlein purpura. *Acta Paediatr* 2001; **90**: 1081–2.
27 Rostoker G, Desvaux-Belghiti D, Pilatte Y *et al*. High dose immunoglobulin therapy for severe IgA nephropathy and Henoch–Schönlein purpura. *Ann Intern Med* 1994; **120**: 476–84.

Urticarial vasculitis

Synonyms
- Chronic urticarial lesions as a manifestation of venulitis
- Unusual systemic lupus erythematosus-like syndrome
- Hypocomplementaemic vasculitis
- Hypocomplementaemic–urticaria–vasculitis syndrome (HUVS)

Definition. Of patients with chronic urticaria, roughly 5–10% have urticarial vasculitis (UV) [1,2]. This is a chronic disease, which presents as urticarial lesions that most often occur on the trunk or proximal limbs, frequently with associated angio-oedema

[3]. Lesions differ from those of simple urticaria in that individual lesions persist for greater than 24 h, often demonstrate purpura and post-inflammatory pigmentation, and cause symptoms of burning. Two types of UV have been described: UV associated with hypocomplementaemia, and UV without associated hypocomplementaemia (normocomplementaemic UV). Hypocomplementaemic UV is defined by the presence of anti-C1q precipitin and/or a decrease in the level of C1 [2,4]. Although all patients with hypocomplementaemic UV have these antibodies, this process must be distinguished from SLE, which can show similar laboratory findings [5,6]. Urticarial vasculitis may be described as a continuum starting with patients who have only skin lesions, progressing to patients with skin lesions and hypocomplementaemia, and finally to those who meet the criteria for SLE. UV without hypocomplementaemia has a slight female predominance, whereas hypocomplementaemic UV is seen almost exclusively in female patients.



Fig. 50.8 Urticarial vasculitis.

History and nomenclature. Agnello *et al*. [7] first discussed UV, which was later described as a syndrome consisting of hypocomplementaemia, cutaneous vasculitis and arthritis by McDuffie *et al*. [8].

Aetiology and pathogenesis. UV is strongly associated with some connective tissue diseases, having a prevalence of 32% in patients with Sjögren's syndrome and 20% in patients with SLE [1]. Other associations include physical urticarias, hepatitis B or C, IgM or IgA gammopathies, serum sickness, colonic cancer and drug ingestion. Some cases of UV have been reported in association with exercise or with exposure to ultraviolet light and cold. UV is thought to represent a type III hypersensitivity reaction, as circulating immune complexes may be demonstrated in up to 75% of patients [9]. Complement and immunoreactant deposition in vessel walls, with complement cascade activation in patients with UV [10], further supports this theory. Additionally, removal of immune complexes via plasmapheresis has been shown to briefly alleviate some symptoms of UV [11]. In hypocomplementaemic UV, autoantibodies are directed against the collagen-like region of C1q, resulting in a reduction of C1q in the serum with subsequent activation of the complement pathway [12].

Histopathology [13–16]. Lesions of UV are typically viewed as showing a leukocytoclastic vasculitis; hypocomplementaemic UV shows a large number of interstitial neutrophils, rather than eosinophils, and may therefore be distinguished from normocomplementaemic UV [13,14]. However, a recent prospective study of 22 patients suggested that a leukocytoclastic vasculitis was only present in the minority, most having a lymphocyte-predominant infiltrate with an admixture of eosinophils [17]. The neutrophilic group had more resistant disease, and had a statistical association with leukocytoclasis, fibrin deposition, hypocomplementaemia and anaemia. The significance of this is uncertain—many collagen vascular diseases (with which UV is associated) may cause cutaneous lymphocytic vasculitis (p. 50.47), and the general view that UV is characterized by leukocytoclastic vasculitis may reflect a group of patients with more systemic features and greater likelihood of having a skin biopsy. However, it appears that some cases, especially of normocomplementaemic type, may have a lymphocytic vasculitis.

Clinical features. Cutaneous lesions of both the hypocomplementaemic and normocomplementaemic forms of UV are erythematous indurated weals that may contain purpuric foci (Fig. 50.8). Angio-oedema and macular erythema may also occur; livedo reticularis, nodules and bullae may be evident, and may also contain purpuric foci. Patients with the hypocomplementaemic form may have constitutional symptoms such as fever, malaise and myalgia, as well as other symptoms and signs including lymphadenopathy, hepatosplenomegaly, abdominal pain with or without nausea and/or diarrhoea, laryngeal oedema, dyspnoea, chronic obstructive pulmonary disease (COPD), glomerulonephritis, conjunctivitis, uveitis and episcleritis. Although hypocomplementaemic UV has features similar to SLE, signs such as ocular inflammation, angio-oedema and COPD distinguish the two processes.

Diagnosis. If urticarial lesions last for longer than 24 h (which can be determined by drawing around their margin), then by definition they are not ordinary urticaria and a skin biopsy should be performed. Pain rather than itch, or the presence of purpura, also suggest UV. History, physical examination and laboratory studies, including C3, C4 and antinuclear antibody (ANA), should help to establish the extent of disease and to exclude underlying disease (e.g. hepatitis C), and to evaluate for SLE. Some patients may demonstrate an elevated erythrocyte sedimentation rate (ESR), hypocomplementaemia, a low-titre positive ANA and haematuria. A biopsy must be performed to confirm the diagnosis and to exclude other disorders such as atypical erythema multiforme.

Treatment. Although no single treatment is effective for all cases of UV, the majority of patients respond to systemic corticosteroids. However, other agents should be considered as steroid-sparing therapies [15,16,18]. Drugs that have been shown to be effective for the treatment of UV include dapsone (100–200 mg once daily),

colchicine (0.6 mg twice to three times daily) and hydroxychloroquine (200 mg once to twice daily) [19–23]. Dapsone plus pentoxifylline (400 mg three times daily) has been used in one patient [24], and mycophenolate mofetil (2 g once daily) has been successfully tried as a maintenance therapy in two other patients [25]. Some patients require oral antihistamines for control of angio-oedema and urticaria-like lesions, in addition to the aforementioned therapies directed at the vasculitis.

References

1 Black AK. Urticarial vasculitis. *Clin Dermatol* 1999; **17**: 565–9.
2 Wisnieski JJ. Urticarial vasculitis. *Curr Opin Rheumatol* 2000; **12**: 24–31.
3 Stone JH, Nousari HC. 'Essential' cutaneous vasculitis: what every rheumatologist should know about vasculitis of the skin. *Curr Opin Rheumatol* 2001; **13**: 23–34.
4 Wisnieski JJ, Baer AN, Christensen J *et al*. Hypocomplementemic urticarial vasculitis syndrome: clinical and serologic findings in 18 patients. *Medicine* 1995; **74**: 24–41.
5 Wisnieski JJ, Jones SM. IgG autoantibody to the collagen-like region of C1q in hypocomplementemic urticarial vasculitis syndrome, systemic lupus erythematosus, and six other musculoskeletal or rheumatic diseases. *J Rheumatol* 1992; **19**: 884–8.
6 Wener MH, Uwatoko S, Mannik M. Antibodies to the collagen-like region of C1q in sera of patients with autoimmune rheumatic diseases. *Arthritis Rheum* 1989; **32**: 544–51.
7 Agnello B, Koffler D, Eisenberg JW *et al*. C1q precipitins in the sera of patients with systemic lupus erythematosus and other hypocomplementemic states: characterization of high and low molecular weight types. *J Exp Med* 1971; **134** (Suppl.): 228S.
8 McDuffie FC, Sams WM Jr, Maldonado JE. Hypocomplementemia with cutaneous vasculitis and arthritis: possible immune complex syndrome. *Mayo Clin Proc* 1973; **48**: 340–8.
9 Berg RE, Kantor GR, Bergfeld WF. Urticarial vasculitis. *Int J Dermatol* 1988; **27**: 468–72.
10 Mehregan DR, Gibson LE. Pathophysiology of urticarial vasculitis. *Arch Dermatol* 1998; **134**: 88–9.
11 Russell Jones R, Bhogal B, Dash A, Schifferli J. Urticaria and vasculitis: a continuum of histopathological and immunological changes. *Br J Dermatol* 1983; **108**: 695–703.
12 Wisnieski JJ, Jones SM. Comparison of autoantibodies to the collagen-like region of C1q in hypocomplementemic urticarial vasculitis syndrome and systemic lupus erythematosus. *J Immunol* 1992; **148**: 1396–403.
13 Sanchez NP, Van Hale HM, Su WP. Clinical and histopathologic spectrum of necrotizing vasculitis: report of findings in 101 cases. *Arch Dermatol* 1985; **121**: 220–4.
14 Davis MD, Daoud MS, Kirby B, Gibson LE, Rogers RS III. Clinicopathologic correlation of hypocomplementemic and normocomplementaemic urticarial vasculitis. *J Am Acad Dermatol* 1998; **38**: 899–905.
15 Mehregan DR, Hall MJ, Gibson LE. Urticarial vasculitis: a histopathologic and clinical review of 72 cases. *J Am Acad Dermatol* 1992; **26**: 441–8.
16 Sanchez NP, Winkelmann RK, Schroeter AL, Dicken CH. The clinical and histopathologic spectrums of urticarial vasculitis: study of 40 cases. *J Am Acad Dermatol* 1982; **7**: 599–605.
17 Lee JSS, Loh TH, Seow SC, Tat SH. Prolonged urticaria with purpura: the spectrum of clinical and histopathologic features in a prospective series of 22 patients exhibiting the clinical features of urticarial vasculitis. *J Am Acad Dermatol* 2007; **56**: 994–1005.
18 Worm M, Muche M, Schulze P *et al*. Hypocomplementaemic urticarial vasculitis: successful treatment with cyclophosphamide-dexamethasone pulse therapy. *Br J Dermatol* 1998; **139**: 704–7.
19 Fortson JS, Zone JJ, Hammond ME, Groggel GC. Hypocomplementemic urticarial vasculitis syndrome response to dapsone. *J Am Acad Dermatol* 1986; **15**: 1137–42.
20 Eiser AR, Singh P, Shanies HM. Sustained dapsone-induced remission of hypocomplementemic urticarial vasculitis: a case report. *Angiology* 1997; **48**: 1019–22.
21 Wiles JC, Hansen RC, Lynch PJ. Urticarial vasculitis treated with colchicine. *Arch Dermatol* 1985; **121**: 802–5.
22 Werni R, Schwarz T, Gschnait G. Colchicine treatment of urticarial vasculitis. *Dermatologica* 1986; **172**: 36–40.
23 Lopez LR, Davis KC, Kohler PF, Schocket AL. The hypocomplementemic urticarial–vasculitis syndrome: therapeutic response to hydroxychloroquine. *J Allergy Clin Immunol* 1984; **73**: 600–3.
24 Nurnberg W, Grabbe J, Czarnetzki BM. Urticarial vasculitis syndrome effectively treated with dapsone and pentoxifylline. *Acta Derm Venereol* 1995; **75**: 54–6.
25 Worm M, Sterry W, Kolde G. Mycophenolate mofetil is effective for maintenance therapy of hypocomplementaemic urticarial vasculitis [letter; comment]. *Br J Dermatol* 2000; **143**: 1324.

Exercise-induced vasculitis

This is probably an underestimated condition, several series of ten or more cases having been reported [1–3]. Although also described as exercise-induced purpura [4], the histological features are those of a leukocytoclastic vasculitis with variable deposition of IgM and complement C3 [1]. The typical presentation is with purpuric lesions on the lower legs after prolonged walking (many descriptions are in golfers, marathon runners or long-distance walkers), usually in hot weather. Lesions may be urticarial, plaques, palpable purpura or petechial. Compressed areas, such as the tops of socks, may be spared [4]. Patients are generally middle-aged, and otherwise well with no evidence of venous disease; there is a strong female predominance.

Extrinsic causes such as insect bites, reactions to socks or allergies to grass or ground plants may be suspected if the condition is not known. The disorder has a relapsing course, but patients may prevent it occurring as some know how much walking is likely to provoke the eruption. Treatments have included compression hosiery, manual lymphatic drainage, diuretics, or steroids (local or systemic) [4].

In cases with urticarial vasculitis provoked by exercise, eosinophils predominate in early lesions, with a neutrophilic infiltrate and leukocytoclastic vasculitis subsequently [5]. As CSVV of several aetiologies, and HSP, are often aggravated by exercise, it has been suggested that the pathogenesis of exercise-induced urticarial vasculitis lesions might be extrapolated to other leukocytoclastic vasculitides [6].

References

1 Prins M, Veraart JC, Vermeulen AH *et al*. Leucocytoclastic vasculitis induced by prolonged exercise. *Br J Dermatol* 1996; **134**: 915–8.
2 Kelly RI, Opie J, Nixon R. Golfer's vasculitis. *Australas J Dermatol* 2005; **46**: 11–4.
3 Ramelet AA. Exercise-induced vasculitis. *J Eur Acad Dermatol Venereol* 2006; **20**: 423–7.
4 Ramelet AA. Exercise-induced purpura. *Dermatology (Basel)* 2004; **208**: 293–6.
5 Kano Y, Orihara M, Shiohara T. Cellular and molecular dynamics in exercise-induced urticarial vasculitis lesions. *Arch Dermatol* 1998; **134**: 62–7.
6 Sais G, Vidaller A. Pathogenesis of exercise-induced urticarial vasculitis lesions: can the changes be extrapolated to all leukocytoclastic vasculitis lesions? *Arch Dermatol* 1999; **135**: 87–9.

Cryoglobulinaemic vasculitis

Definition. A form of vasculitis due to cryoglobulins deposited as immune complexes in types II and III cryoglobulinaemia. Small and medium sized vessels are affected, mainly in skin and kidneys. Not all cryoglobulinaemia is associated with symptoms. Type I

cryoglobulinaemia is monoclonal rather than forming immune complexes (therefore causes cryogelling rather than vasculitis), and types II and III cryoglobulinaemia may cause cryogelling as well as an immune complex vasculitis; details of the history, aetiology and pathogenesis of cryoglobulin-associated disease are therefore provided in Chapter 49 and only a brief outline of these aspects is provided here.

Aetiology and pathogenesis. Cryoglobulinaemia as a cause of vasculitis and vascular occlusion is an increasingly recognized condition, largely due to the association between types II and III cryoglobulinaemia with hepatitis C virus infection. Cryoglobulins may be divided into three main subtypes:

I Monoclonal immunoglobulin, usually IgG or IgM, and usually associated with lymphoproliferative disease, especially multiple myeloma or Waldenström's macroglobulinaemia; accounts for about 10–25% of cases. This is discussed in Chapter 49 and is not considered further here.

II Mixed polyclonal (usually IgG) immunoglobulin and monoclonal (usually IgMκ) immunoglobulin, the latter having rheumatoid factor activity; accounts for about 25% of cases.

III Polyclonal IgM with rheumatoid factor activity and polyclonal IgG with antigenic activity; accounts for about 50–65% of cases.

The causes of cryoglobulinaemia include myeloproliferative disorders, systemic lupus erythematosus and chronic infections; all disease associations are discussed in more detail in Chapter 49, and a more detailed summary of the pathogenesis is provided in [1]. Immune complex vasculitis is limited to types II and III (together termed 'mixed' cryoglobulinaemia). The strongest aetiological factor in mixed cryoglobulinaemia is hepatitis C virus (HCV) infection, which accounts for about 80–90% of cases of what was previously termed 'essential' mixed cryoglobulinaemia; hepatitis G may coexist in about 30% of such cases [2]. However, although mixed cryoglobulinaemia can be detected in about 50% of subjects with HCV, immune complex vasculitis occurs in less than 5% [3]. There is also a strong link between mixed cryoglobulinaemia and connective tissue disorders, especially Sjögren's syndrome, in which cryocrit measurements of cryoglobulins may be indistinguishable from those of patients with HCV [1], and a 35-fold increased frequency of non-Hodgkin's lymphoma [3]. Chronic antigenic stimulation (by hepatitis C or other antigens) is felt to lead to B-cell proliferation, production of IgM with rheumatoid factor activity, mainly monoclonal cryoglobulin production and, in some cases, progression to B-cell non-Hodgkin's lymphoma [1–5]. Various factors are involved in the B-cell stimulation [1]. Especially in type II cryoglobulinaemia there may be t(14:18) translocations in peripheral blood lymphocytes; these activate the proto-oncogene Bcl-2, which increases B-cell survival by inhibiting apoptosis. Additionally, the E2 protein of the HCV envelope binds to CD81 on lymphocytes (and hepatocytes), complexing with CD21, CD19 and Leu 13, again causing B-cell activation [1].

HCV causes both cytotoxic and autoimmune hepatitis, and clonal B-cell expansion occurs in both blood and liver. HCV virions bind to IgG and are then complexed with monoclonal IgM which are deposited in vessel walls as an immune complex, causing complement-mediated vascular damage; HCV RNA sequences have been detected in vessel walls [2]. HCV-related mixed cryoglobulinaemia and/or vasculitis has been linked with HLA-B8, DR3 and DRB1*11 [1,4], and some HCV genotypes are predominant (1, 2, 2A/III) [2].

Histopathology [6]. Mixed cryoglobulinaemia affects capillaries, arterioles and venules, producing a pan-dermal leukocytoclastic vasculitis that may extend into the subcutis. Eosinophilic, PAS-positive, globular cryoglobulin deposits are seen, as well as (PAS-negative) intraluminal and fibrin deposition. More chronic lesions develop a mononuclear-predominant infiltrate and may become granulomatous. Changes in other organs include membranoproliferative glomerulonephritis (in a third of cases), and deposition of immune complexes in lung alveolar vessels (leading to lung fibrosis) and in vasa vasora of nerves (causing peripheral neuropathy).

In the liver, chronic HCV is one of several infections that cause a histological pattern termed a fibrin ring granuloma; it has been suggested that this may be a manifestation of endothelial injury related to immune complex deposition [7].

Clinical features [1,7,8]. Features of immune complex vasculitis predominate over those that relate mainly to cryogelling. Palpable purpura, especially of the lower legs but potentially including the buttocks and trunk, occurs in 60–90% and urticated lesions are common, reminiscent of the skin vasculitis seen in HSP. Worsening of skin lesions after prolonged standing is common, and symptoms are often intermittent initially. Polyarteritis-like dermal nodules may occur in 20%. Raynaud's phenomenon, and cold-aggravation of the vasculitis lesions, are each present in about a third of subjects. Livedo, bullae, necrosis and ulceration are all less common.

Associated glomerulonephritis is common and important. Arthralgia, or migratory myalgia, occurs in most patients. Overt lung involvement is uncommon, but may present as dyspnoea or haemoptysis. Peripheral neuropathy, if present, is predominantly sensory and usually mild.

Diagnosis. It is important to distinguish cryoglobulinaemic vasculitis from other causes of CSVV because corticosteroid therapy, although sometimes necessary short-term, will in the longer term worsen the underlying infection that is present in the majority of cases. Most other causes of leukocytoclastic vasculitis cause a more superficial vasculitis on biopsy specimens, and if cryoglobulin deposits are seen histologically then the diagnosis is usually suspected (although this is much commoner in type I cryoglobulinaemia).

Clinically, head and neck involvement, significant livedo, acrocyanosis, Raynaud's phenomenon or larger vessel occlusion, are all more suggestive of type I cryoglobulinaemia.

Blood tests may be helpful in suggesting this diagnosis [9]. A low complement C4 level is found in 90%, rheumatoid factor is positive in 70% and ANA in 20%, elevated transaminases are found in a third, and some patients (with type II cryoglobulinaemia) will have a monoclonal band on electrophoresis. Obtaining samples for identification of cryoproteins is discussed in Chapter 49. Testing for antibodies to HCV should always be performed.

These factors combined with the clinical picture have been gathered to create possible diagnostic criteria [1]; major criteria include mixed cryoglobulins, purpura and leukocytoclastic vasculitis, with minor clinical features including chronic hepatitis, membranoproliferative glomerulonephritis, peripheral neuropathy and skin ulcers, and minor pathology/serology features including positive rheumatoid factor, HCV or HBV, and clonal B-cell infiltrate of liver or bone marrow.

Treatment. Treatment will depend on the underlying cause. Although most cases of mixed cryoglobulinaemia are HCV-associated, SLE and other autoimmune conditions need to be considered and treated appropriately, and other infections need to be considered as alternative (or, especially in the case of HIV, as coexisting) infections that may also require specific therapy.

The treatment of HCV-associated mixed cryoglobulinaemic vasculitis has recently been reviewed [1,3]. Pegylated interferon-α with ribavirin is the usual initial choice for patients with relatively mild symptoms (purpura, arthralgia, proteinuria without haematuria or casts or abnormal renal function, mild neuropathy); in such patients, immunosuppressive agents can be avoided, or relatively non-aggressive therapy can be used (low-dose corticosteroids, or colchicine). There is some logic in also adding rituximab, as this combination targets the causative HCV infection and the cryoglobulin-producing B cells; using rituximab with antiviral therapy is recommended for those with more severe disease or those with an associated B-cell non-Hodgkin's lymphoma [1]. Treatments with corticosteroids, other immunosuppressive agents (cyclophosphamide, azathioprine, mycophenolate mofetil) and plasmapheresis all have a role in patients with severe membranoproliferative glomerulonephritis, severe (especially motor) neuropathy, significant skin necrosis, lung disease or, as occurs in some cases, widespread multiorgan life-threatening vasculitis. Plasmapheresis is recommended if there are features of hyperviscosity, although it also produces rapid response of other complications by removal of immune complexes and inflammatory mediators; if used for its speed of action in severe disease, it must be combined with immunosuppression in order to prevent a rebound flare of activity. Ciclosporin, melphalan and intravenous immunoglobulin have all been used with anecdotal success.

In general, the response of cutaneous vasculitis and arthralgia is quicker than that of renal or neurological disease, where (despite a rapid reduction in viral load) the response to antiviral therapy is slow; thus, immunosuppressives may need to be used whilst awaiting response to the antiviral regimen. Older age (especially age over 60 years), long duration of infection, high cryoglobulinaemia level and renal involvement all infer a poor prognosis, although the response of cryoglobulin levels does not always correlate with overall therapeutic benefit. Response of skin and joint symptoms is expected in over 80%, whereas response of nephropathy and cryoglobulinaemia may be less than 50% and 65% respectively, and mortality at 5 years may be as high as 50% in those with severe renal involvement. Antiviral treatment should be continued for at least 12 months [3]; some genotypes of HCV may be relatively resistant, but an early (3 months) complete virological response is associated with a better prognosis.

References

1 Ferri C, Mascia MT. Cryoglobulinemic vasculitis. *Curr Opin Rheumatol* 2006; **18**: 1854–63.
2 Del Rosso A, Generini S, Pignone A, Matucci-Cerinic M. Vasculitides secondary to systemic diseases. *Clin Dermatol* 1999; **17**: 533–47.
3 Saadoun D, Delluc A, Piette JC, Cacoub P. Treatment of hepatitis C-associated mixed cryoglobulinaemic vasculitis. *Curr Opin Rheumatol* 2008; **20**: 23–8.
4 Saadoun D, Sellam J, Ghillani-Dalbin P *et al*. Increased risks of lymphoma and death among patients with nonhepatitis C virus-related mixed cryoglobulinaemia. *Arch Intern Med* 2006; **166**: 2101–8.
5 González-Gay MA, García-Porrúa C. Epidemiology of the vasculitides. *Rheum Dis Clin N Am* 2001; **27**: 729–46.
6 Magro CM, Crowson AN. The cutaneous neutrophilic vascular injury syndromes: a review. *Semin Diagn Pathol* 2001; **18**: 47–58.
7 Glazer E, Ejaz A, Coley CJ 2nd *et al*. Fibrin ring granuloma in chronic hepatitis C: virus-related vasculitis and/or immune complex disease? *Semin Liver Dis* 2007; **27**: 227–30.
8 Trejo O, Ramos-Casals M, Garcia-Carrasco M *et al*. Cryoglobulinaemia: study of etiologic factors and clinical and immunological features in 443 patients from a single center. *Medicine* 2001; **80**: 252–62.
9 Fiorentino DF. Cutaneous vasculitis. *J Am Acad Dermatol* 2003; **48**: 311–40.

Erythema elevatum diutinum

Definition. Erythema elevatum diutinum (EED) is a rare, chronic, cutaneous eruption that is most commonly seen in the adult population. The first description of EED was by Hutchinson and Bury in the 1880s, and the condition was later named in 1894 by Radcliffe-Crocker and Williams. EED is characterized by fibrosing plaques with histological evidence of leukocytoclastic vasculitis. In addition to the characteristic polymorphonuclear fragmentation, endothelial swelling, extravasation of erythrocytes and fibrinoid necrosis of vessel walls, dermal nodules of EED contain spindle cells and fibrosis [1].

Aetiology and pathogenesis. Although EED is thought to be related to an Arthus-type reaction with immune complex deposition and subsequent inflammation, the exact aetiology is unknown. It has been associated with autoimmune diseases such as rheumatoid arthritis, coeliac disease, inflammatory bowel disease, and type I diabetes mellitus. Associations with infections, including streptococcus, hepatitis and syphilis, have also been suggested [2–11]. Lesions characteristic of EED have been induced by injection of streptococcal antigen into the dermis [12–15], and have occurred at sites of mosquito bites [10]. Erythema elevatum diutinum has also been associated with human immunodeficiency virus (HIV) infection, as lesions of EED have responded to antiretroviral and dapsone treatment in HIV-positive patients [16–22]. EED is now recognized as one of the defined reactive dermatoses associated with HIV [23]. In addition, EED has been associated with hypergammaglobulinaemia and IgA monoclonal gammopathies, as well as with myelodysplasia, pyoderma gangrenosum, and relapsing polychondritis. The association with haematological abnormalities, such as multiple myeloma, is strong; however, EED may precede the haematological disease by several years [24].

Histopathology (Figs 50.9 & 50.10). Acutely, lesions of EED demonstrate leukocytoclastic vasculitis, with little fibrin deposition. Eosinophils may also be present in the upper and mid-dermis.

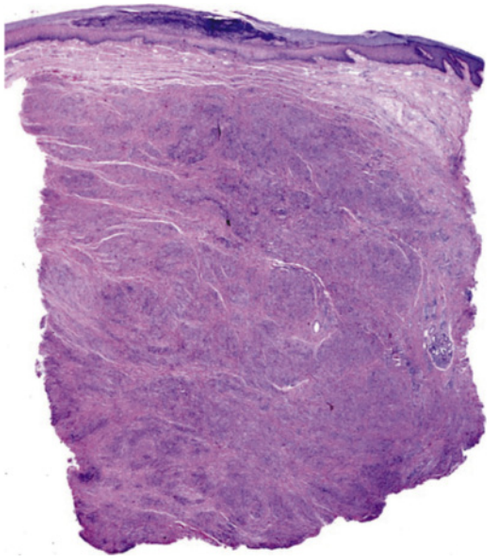


Fig. 50.9 Erythema elevatum diutinum. Low-power photomicrograph shows diffuse infiltrates throughout the entire dermis and areas of fibrosis. (Courtesy of Dr Omar Sangueza, Wake Forest University School of Medicine, Winston-Salem, NC, USA.)

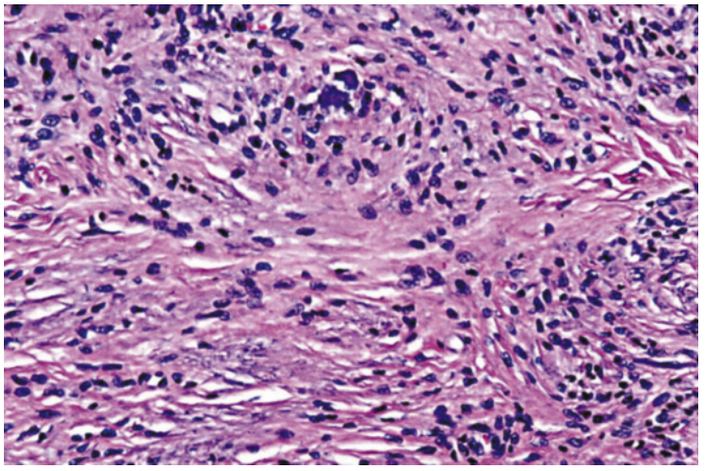


Fig. 50.10 Erythema elevatum diutinum. At higher magnification there is evidence of marked fibrosis and an inflammatory infiltrate composed of lymphocytes, histiocytes, neutrophils and nuclear dust. (Courtesy of Dr Omar Sangueza, Wake Forest University School of Medicine, Winston-Salem, NC, USA.)

Depending on the degree of oedema and infiltration into the dermis, unaffected collagen may be present just under the epidermis. Chronically, lesions demonstrate angiocentric eosinophilic fibrosis, capillary proliferation, and infiltration of macrophages, plasma cells, and lymphocytes. Cholesterol deposits in histiocytes and in the extracellular tissue (the latter corresponding to a pattern that has been termed 'extracellular cholesterolosis') may be present in older lesions [25].

Clinical features. Patients are usually adult, although occasional childhood cases are reported [26]. Lesions of EED most commonly appear chronically in a symmetrical fashion over the dorsa of the hands, the knees, buttocks and Achilles tendons (Fig. 50.11). They



Fig. 50.11 Early non-fibrotic lesions of erythema elevatum diutinum at a typical site on the knee. This patient also had EED on the hands, and pyoderma gangrenosum.

are red-violaceous, red-brown or yellowish papules, plaques or nodules. Occasionally, the face and ears are also affected by EED. Initially, the lesions are soft, but eventually they fibrose, and later leave atrophic scars. Although they may be asymptomatic, the lesions of EED may also be painful. EED may last from 5 to 35 years, with crops of new lesions developing every few weeks to months.

Diagnosis. Although EED may be difficult to distinguish from cutaneous small vessel vasculitis histologically, the clinical presentation differs from that of other chronic small vessel vasculitis syndromes, allowing for an accurate diagnosis. EED and Sweet's syndrome are both described as neutrophilic dermatoses. However, EED differs from Sweet's syndrome by the character of the lesions and their distribution, as well as by histopathological features. The classic assumption that lesions from patients with Sweet's syndrome universally lack histopathological fibrinoid necrosis of vessel walls has been challenged; in one series, 29% of patients had biopsy specimens showing leukocytoclastic vasculitis [27], although it was felt that frank vasculitis was a consequence of neutrophil metabolites and occurred in older lesions. Clinically, the lesions in Sweet's syndrome are acute, more often asymmetrical and located on the arms, face and neck [28]. In contrast, EED lesions are chronic, symmetrical and classically located over the dorsum of the hands and knees, buttocks, and Achilles tendon. Although leukocytoclastic vasculitis has now been reported as a possible feature of Sweet's lesions [2], it is not always present and the fibrosis seen in lesions of EED correlates with the clinical chronicity.

The demonstration of IgA ANCA (with various specificities) in 6/10 cases of EED has been suggested to be of some diagnostic

value [29]; in this series, seven of the ten patients had raised IgA levels (monoclonal in three).

Treatment. Several medications have been used in the treatment of EED. Dapsone has a remarkable effect on EED [15], although stopping it is often followed by swift return of the lesions. Niacinamide has also been used with good effect [30]. High potency topical, or intralesional, corticosteroids may minimize the size of lesions in patients with limited disease. Treatment of an associated disorder such as HIV infection or paraproteinaemia [31] may be effective. Other therapies used for cutaneous small vessel vasculitis may also be effective in treating patients with EED.

References

1 Shanks JH, Banerjee SS, Bishop PW *et al*. Nodular erythema elevatum diutinum mimicking cutaneous neoplasms. *Histopathology* 1997; **31**: 91–6.
2 Collier PM, Neill SM, Branfoot AC *et al*. Erythema elevatum diutinum—a solitary lesion in a patient with rheumatoid arthritis. *Clin Exp Dermatol* 1990; **15**: 394–5.
3 Buahene K, Hudson M, Mowat A *et al*. Erythema elevatum diutinum—an unusual association with ulcerative colitis. *Clin Exp Dermatol* 1991; **16**: 204–6.
4 Walker KD, Badame AJ. Erythema elevatum diutinum in a patient with Crohn's disease. *J Am Acad Dermatol* 1990; **22**: 948–52.
5 Bernard P, Bedane C, Delrous JL *et al*. Erythema elevatum diutinum in a patient with relapsing polychondritis. *J Am Acad Dermatol* 1992; **26**: 312–5.
6 Planagumá M, Puig L, Alomar A *et al*. Pyoderma gangrenosum in association with erythema elevatum diutinum: report of two cases. *Cutis* 1992; **49**: 201–6.
7 Cordier JF, Faure M, Hermier C *et al*. Pleural effusions in an overlap syndrome of idiopathic hypereosinophilic syndrome and erythema elevatum diutinum. *Eur Respir J* 1990; **3**: 115–8.
8 Creus L, Salleras M, Sola MA *et al*. Erythema elevatum diutinum associated with pulmonary infiltrate. *Br J Dermatol* 1997; **137**: 652–3.
9 Tasanen K, Raudasoja R, Kallioinen M *et al*. Erythema elevatum diutinum in association with coeliac disease. *Br J Dermatol* 1997; **136**: 624–7.
10 Sangüeza OP, Pilcher B, Sangüeza JM. Erythema elevatum diutinum: a clinicopathological study of eight cases. *Am J Dermatopathol* 1997; **19**: 214–22.
11 Orteu C, McGregor JM, Whittaker SJ *et al*. Erythema elevatum diutinum and Crohn disease: a common pathogenic role for measles virus? *Arch Dermatol* 1996; **132**: 1523–5.
12 Weidman FD, Bensacçon JH. Erythema elevatum diutinum. Role of streptococci and relationship to other rheumatic dermatoses. *Arch Dermatol Syphilol* 1929; **20**: 593–620.
13 Wolff HH, Scherer R, Maciejewski W *et al*. Erythema elevatum diutinum. II. Immunelekroneumikroskopische Untersuchung der leukocytocklastishew vaskulitis in einer Intrakutanreaktion mit Streptokokkenantigen. *Arch Dermatol Res* 1978; **261**: 17–26.
14 Cream JJ, Leven GM, Calnan CD. Erythema elevatum diutinum: an unusual reaction to streptococcal antigen and response to dapsone. *Br J Dermatol* 1971; **84**: 393–9.
15 Katz SI, Gallin JI, Hertz KC *et al*. Erythema elevatum diutinum: skin and systemic manifestation, immunologic studies, and successful treatment with dapsone. *Medicine* 1977; **56**: 443–55.
16 Cockerell CJ. Noninfectious inflammatory skin diseases in HIV-infected individuals. *Dermatol Clin* 1991; **9**: 531–41.
17 Da Cunha Bang F, Weismann K, Ralfkiaer E *et al*. Erythema elevatum diutinum and pre-AIDS. *Acta Derm Venereol* (Stockh) 1986; **66**: 272–4.
18 Dronda F, González-López A, Lecona M *et al*. Erythema elevatum diutinum in human immunodeficiency virus-infected patients—report of a case and review of the literature. *Clin Exp Dermatol* 1996; **21**: 222–5.
19 Shanks JH, Banerjee SS, Bishop PW *et al*. Nodular erythema elevatum diutinum mimicking cutaneous neoplasms. *Histopathology* 1997; **31**: 91–6.
20 Revenga FM, Vera A, Munoz A *et al*. Erythema elevatum diutinum and AIDS: are they related? *Clin Exp Dermatol* 1997; **22**: 250–6.
21 Suárez J, Miguélez M, Villalba R. Nodular erythema elevatum diutinum in an HIV-1 infected woman: response to dapsone and antiretroviral therapy. *Br J Dermatol* 1998; **138**: 706–23.
22 Hon Pak CPT, Montemarano AD, Berger T. Purpuric nodules and macules on the extremities of a young woman. *Arch Dermatol* 1998; **134**: 232–3.
23 Rover PA, Bittencourt C, Discacciati MP *et al*. Erythema elevatum diutinum as a first clinical manifestation for diagnosing HIV infection: case history. *Sao Paulo Med J* 2005; **123**: 201–3.
24 Yiannias JA, el-Azhary RA, Gibson LE. Erythema elevatum diutinum: a clinical and histopathologic study of 13 patients. *J Am Acad Dermatol* 1992; **26**: 38–44.
25 LeBoit PE, Yen TS, Wintroub B. The evolution of lesions in erythema elevatum diutinum. *Am J Dermatopathol* 1986; **8**: 392–402.
26 Tomasini C, Seia Z, Dapavo P *et al*. Infantile erythema elevatum diutinum: report of a vesiculo-bullous case. *Eur J Dermatol* 2006; **16**: 683–6.
27 Malone JC, Slone SP, Wills-Frank LA *et al*. Vascular inflammation (vasculitis) in Sweet syndrome: a clinicopathologic study of 28 biopsy specimens from 21 patients. *Arch Dermatol* 2002; **138**: 345–9.
28 Cohen PR. Sweet's syndrome—a comprehensive review of an acute febrile neutrophilic dermatosis. *Orphanet J Rare Dis* 2007; **2**: 34.
29 Ayoub N, Charuel J-L, Diemerte M-C *et al*. Antineutrophil cytoplasmic antibodies of IgA class in neutrophilic dermatoses with emphasis on erythema elevatum diutinum. *Arch Dermatol* 2004; **140**: 931–6.
30 Kohler IK, Lorincz AL. Erythema elevatum diutinum treated with niacinamide and tetracycline. *Arch Dermatol* 1980; **116**: 693–5.
31 Chow RKP, Benny WB, Coupe RL *et al*. Erythema elevatum diutinum associated with IgA paraproteinaemia successfully controlled with intermittent plasma exchange. *Arch Dermatol* 1996; **132**: 1360–4.

Eosinophilic vasculitis

Synonym

- Recurrent cutaneous eosinophilic necrotizing vasculitis [1,2]

Definition. A relatively recently described and rare vasculitis consisting of a predominantly centripetal purpuric papular rash, angio-oedema, peripheral blood eosinophilia and an eosinophilic necrotizing vasculitis of small vessels.

History. This condition was recently distinguished from other eosinophilic vasculitides that affect medium to large vessels (CSS; see later in this chapter) and from eosinophilic disorders in which pruritic papules and/or angio-oedema may occur, such as hypereosinophilic syndrome, episodic angio-oedema with eosinophilia, dermatitis herpetiformis, Wells' syndrome, polymorphic eruption of pregnancy or drug eruptions. Association with connective tissue diseases and with rheumatoid arthritis has been reported [3,4].

Aetiology and pathogenesis. The cause is unknown. As in other strongly eosinophilic disorders, eosinophil cytokines such as IL-5, and toxic eosinophil granule proteins such as the major basic protein, have been demonstrated in serum and tissues, respectively, and presumably play a part in the tissue damage. Neutrophil elastase is prominent around vessels, and mast cell degranulation occurs. Eosinophilic vasculitis has also been reported in a patient with the hypereosinophilic syndrome; in this patient, CD40 (a glycoprotein of the TNF receptor family) was considered to be important in pathogenesis [5].

Histopathology. Shows fibrinoid deposition and necrosis of small dermal vessels with an infiltrate of eosinophils and absent or

minimal leukocytoclasis. Small epidermal vesicles containing eosinophils may be present. Immunoglobulin deposition is not a feature. This eosinophilic small vessel vasculitis is distinct from other vasculitides such as CSS, in which medium to large vessels are affected, and from most drug-induced vasculitis in which eosinophils are generally less prominent.

Clinical features. Recurrent pruritic papules and urticarial lesions occur at any site, especially the head and neck, with angio-oedema of the face and extremities. Either sex and any age group may be affected. The course is long and recurrent but fever, arthralgia and visceral involvement are absent. Digital occlusions manifest as Raynaud's phenomenon or digital gangrene have been reported in patients with cutaneous eosinophilic vasculitis associated with the hypereosinophilic syndrome [5,6], but they can also occur in the hypereosinophilic syndrome in the absence of cutaneous eosinophilic vasculitis [7,8].

An eosinophilic vasculitis, typically with hypocomplementaemia, also occurs in connective tissue diseases [9].

Treatment. Oral corticosteroids, intermittently or as prolonged maintenance therapy depending on response, appear to be effective.

References

1 Chen K-R, Su WPD, Pittelkow MR, Leiferman KM. Eosinophilic vasculitis syndrome: recurrent cutaneous eosinophilic necrotizing vasculitis. *Semin Dermatol* 1995; **14**: 106–10.

2 Chen KR, Pittelkow MR, Su D *et al*. Recurrent cutaneous eosinophilic necrotizing vasculitis: a novel eosinophil-mediated syndrome. *Arch Dermatol* 1994; **130**: 1159–66.

3 Chen K-R, Su WPD, Pittelkow MR *et al*. Eosinophilic vasculitis in connective tissue disease. *J Am Acad Dermatol* 1996; **35**: 173–82.

4 Yomoda M, Inoue M, Nakama T *et al*. Cutaneous eosinophilic vasculitis associated with rheumatoid arthritis. *Br J Dermatol* 1999; **140**: 754–5.

5 Jang KA, Lim YS, Choi JH *et al*. Hypereosinophilic syndrome presenting as cutaneous necrotizing eosinophilic vasculitis and Raynaud's phenomenon complicated by digital gangrene. *Br J Dermatol* 2000; **143**: 641–4.

6 Kim SH, Kim TB, Yun YS *et al*. Hypereosinophilia presenting as eosinophilic vasculitis and multiple peripheral artery occlusions without organ involvement. *J Korean Med Sci* 2005; **20**: 677–9.

7 Oppliger R, Gay-Crosier F, Dayer E, Hauser C. Digital necrosis in a patient with hypereosinophilic syndrome in the absence of cutaneous eosinophilic vasculitis. *Br J Dermatol* 2001; **144**: 1087–90.

8 Hamada T, Kimura Y, Hayashi S *et al*. Hypereosinophilic syndrome with peripheral circulatory insufficiency and cutaneous microthrombi. *Arch Dermatol* 2007; **143**: 812–3.

9 Chen KR, Su WP, Pittelko MR *et al*. Eosinophilic vasculitis in connective tissue disease. *J Am Acad Dermatol* 1996; **35**: 173–82.

Granuloma faciale

Definition. Granuloma faciale (GF) is an uncommon condition typified by asymptomatic cutaneous nodules occurring primarily on the face, with occasional extrafacial involvement. Granuloma faciale is limited to the skin, without any systemic manifestations. It is most common in males [1], typically in white people, although cases have been observed in populations of African or oriental ancestry [1,2]. Wigley [3] first described GF in 1945 as a type of eosinophilic granuloma, although it was distinguished from other eosinophilic granulomas by Lever and Leeper in 1950 [4]. Pinkus recommended the present name in 1952 [5].

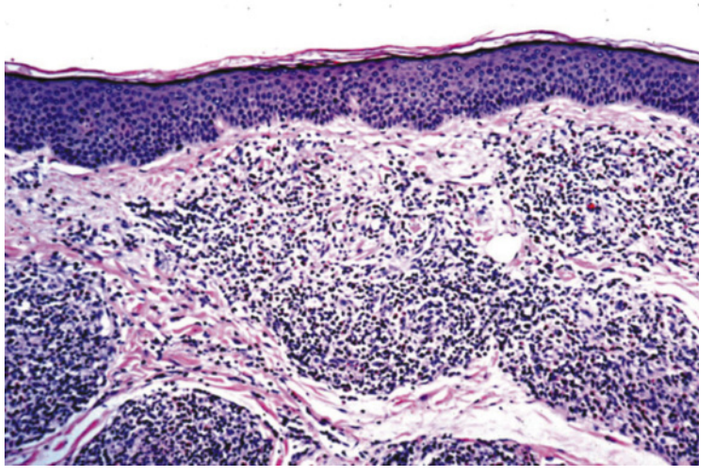


Fig. 50.12 Granuloma faciale. Low-power view shows perivascular nodular infiltrates within the dermis. (Courtesy of Dr Omar Sangueza, Wake Forest University School of Medicine, Winston-Salem, NC, USA.)

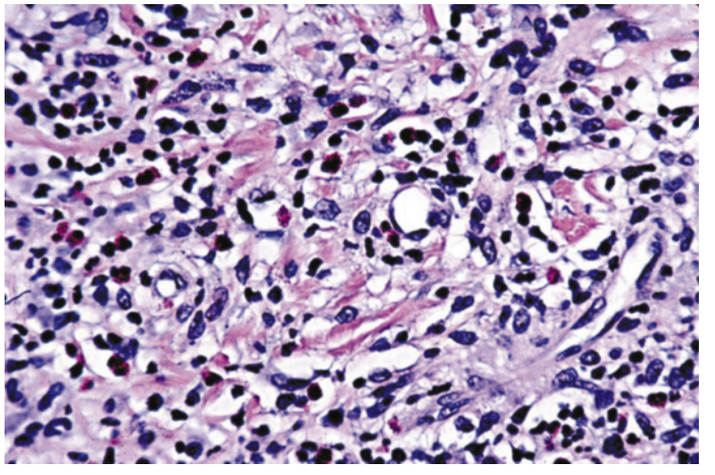


Fig. 50.13 Granuloma faciale. At higher magnification the infiltrate shows lymphocytes, eosinophils and a few neutrophils. (Courtesy of Dr Omar Sangueza, Wake Forest University School of Medicine, Winston-Salem, NC, USA.)

Aetiology and pathogenesis. Although the aetiology is somewhat unclear, GF is considered to be a histological variant of leukocytoclastic vasculitis with a prominent eosinophilic infiltrate, and confined to the skin [6]. Deposition of IgG in and around dermal vasculature has been demonstrated, lending some support to the idea that GF is immune complex-mediated [7]. Clonal expansion of T cells producing IL-5, a powerful eosinophil chemoattractant, has been described within GF lesions [8].

Histopathology [9,10]. GF is characterized by a mixed inflammatory infiltrate with a predominance of neutrophils and eosinophils, although the latter is not constant [10], mainly in the upper half of the dermis but with occasional spread into the lower dermis and subcutaneous tissue (Figs 50.12 & 50.13). A band of normal

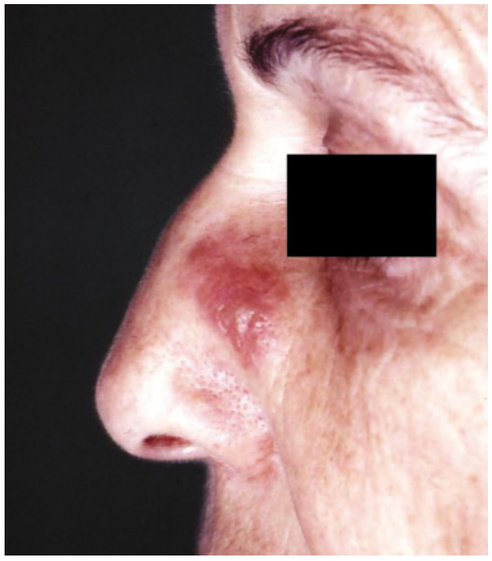


Fig. 50.14 Granuloma faciale. A reddish-brown plaque on the nose. (Courtesy of Dr G. Dawn, Monklands Hospital, UK.)

collagen referred to as a 'Grenz' zone typically separates the inflammatory infiltrate from the epidermis and pilosebaceous appendages. Nuclear dust (fragmented neutrophil nuclei) may be observed near capillaries. Vasculitis, with fibrinoid deposits near and within vessel walls, as well as haemorrhage, may be noted, and even frank vascular necrosis. Immune complexes have been documented either around vessels or at the dermoepidermal junction in several studies, but were lacking in many cases in a large series of patients [10].

Clinical features [10]. Lesions of GF are soft, brown-red nodules or plaques that most commonly occur on the face (Fig. 50.14); multiple lesions are present in about a third of cases but extrafacial involvement is uncommon, occurring in five of 66 patients in one study [10]. The nodules or plaques are smooth, with prominent follicular orifices and telangiectatic surface changes or scaling. Lesions of GF never ulcerate. They are almost always asymptomatic, although some patients may describe itching, burning or pain associated with the lesions [11].

In a review of 14 patients with extrafacial GF, nearly all lesions coexisted with facial lesions, mainly occurring after the facial lesions, and there was a male predominance [12].

An additional rare diagnosis in this category is eosinophilic angiocentric fibrosis, which is a mucosal variant of GF that may occur in nasal passages or upper airways, and which may be associated with skin lesions of GF [13,14].

Diagnosis. A definitive diagnosis of GF requires clinically consistent lesions and a confirmatory biopsy. Although most laboratory studies are normal, mild peripheral blood eosinophilia may be present [10].

Treatment. GF typically follows a chronic course with intermittent acute flares, and is often refractory to treatment. As a result, a wide variety of treatment methods, both surgical and medical, have been used to treat this condition. Examples include topical, intralesional or systemic corticosteroid, dermabrasion [15], laser treatments of various types [15–17], electrosurgery [15], cryosurgery [18], psoralen with ultraviolet A (PUVA) [19], and other systemic treatments including dapsone [11,20], clofazimine [21] and antimalarials [22]. Some cases have been treated with surgical excision [22]. More recently, topical tacrolimus has been reported to be effective, but in reports to date has required regular use for 2 months, then gradual reduction with ongoing once weekly use for many months to maintain remission [17,23]. A therapeutic ladder for GF is depicted in Table 50.9.

Table 50.9 Therapeutic ladder for granuloma faciale.

Topical corticosteroids
Topical tacrolimus (3)
Intralesional corticosteroids (3)
Cryosurgery ± intralesional corticosteroids (3)
Clofazimine (3)
Dapsone (3)
Surgery (3)
Laser (3)

1, double-blind studies; 2, case series; 3, case reports.

References

1 Black C. Granuloma faciale. *Cutis* 1977; **20**: 66–8.
2 Koplon BS, Wood MG. Granuloma faciale: first reported case in a negro. *Arch Dermatol* 1967; **96**: 188–92.
3 Wigley JEM. Sarcoid of Boeck? Eosinophilic granuloma. *Br J Dermatol* 1945; **57**: 68–9.
4 Lever WF, Leeper RW. Eosinophilic granuloma of the skin: report of cases representing two different diseases described as eosinophilic granuloma. *Arch Derm Syph* 1950; **62**: 85–96.
5 Pinkus H. Granuloma faciale. *Dermatologica* 1952; **105**: 85–8.
6 Lever WF, Schaumburg-Lever G, eds. Granuloma faciale. In: *Histopathology of the Skin*. New York: Lippincott, 1990: 193–5.
7 Nieboer C, Kalsbeek GL. Immunofluorescence studies in granuloma eosinophilicum faciale. *J Cutan Pathol* 1978; **5**: 68–75.
8 Gauger A, Ronet C, Schnopp C *et al*. High local interleukin 5 production in granuloma faciale (eosinophilicum): role of clonally expanded skin-specific $CD4^+$ cells. *Br J Dermatol* 2005; **153**: 454–7.
9 Crowson AN, Mihm MC Jr, Magro CM. Cutaneous vasculitis: a review. *J Cutan Pathol* 2003; **30**: 161–73.
10 Ortonne N, Wechsler J, Bagot M *et al*. Granuloma faciale: a clinicopathologic study of 66 patients. *J Am Acad Dermatol* 2005; **53**: 1002–9.
11 Guill MA, Aton JK. Facial granuloma responsive to dapsone therapy. *Arch Dermatol* 1982; **118**: 332–5.
12 Inanir I, Alvur Y. Granuloma faciale with extrafacial lesions. *Br J Dermatol* 2001; **145**: 360–1.
13 Yung A, Wachsmuth R, Ramnath R *et al*. Eosinophilic angiocentric fibrosis – a rare mucosal variant of granuloma faciale which may present to the dermatologist. *Br J Dermatol* 2005; **152**: 574–6.
14 Holme SA, Laidler P, Holt PJA. Concurrent granuloma faciale and eosinophilic angiocentric fibrosis. *Br J Dermatol* 2005; **153**: 851–3.
15 Dinehart SM, Gross DJ, Davis CM, Herzberg AJ. Granuloma faciale: comparison of different treatment modalities. *Arch Otolaryngol Head Neck Surg* 1990; **116**: 849–51.
16 Apfelberg DB, Maser MR, Lash H *et al*. Expanded role of the argon laser in plastic surgery. *J Dermatol Surg Oncol* 1983; **9**: 145–51.
17 Ludwig E, Allam J-P, Bieber T, Noval N. New treatment modalities for granuloma faciale. *Br J Dermatol* 2003; **149**: 634–7.
18 Zacarian S. Cryosurgery effective for granuloma faciale. *J Dermatol Surg Oncol* 1985; **11**: 11–2.

19 Hudson LD. Granuloma faciale: treatment with topical psoralen and UVA. *J Am Acad Dermatol* 1983; **8**: 559–61.
20 Van de Kerkhof PC. On the efficacy of dapsone in granuloma faciale. *Acta Derm Venereol* 1994; **74**: 61–2.
21 Jacyk WK. Facial granuloma in a patient treated with clofazimine. *Arch Dermatol* 1981; **117**: 597–8.
22 Phillips DK, Hymes SR. Recurrent facial plaques following full-thickness grafting: granuloma faciale. *Arch Dermatol* 1994; **130**: 1436–7.
23 Marcoval J, Moreno A, Bordas X, Peyri J. Granuloma faciale: treatment with topical tacrolimus. *J Am Acad Dermatol* 2006; **55** (Suppl.): S110–1.

Acute haemorrhagic oedema of childhood [1]

Synonyms
- Haemorrhagic oedema of childhood
- Acute haemorrhagic oedema of infancy
- Finkelstein's disease
- Seidlmayer's syndrome
- Purpura en cocarde avec oedeme
- Post-infectious cockade purpura

Definition. Acute haemorrhagic oedema of childhood (AHEC) is a rare disorder, whose manifestations are almost exclusively cutaneous. It occurs in children under 2 years old, and rarely outside this age group. There is often a history of a recent upper respiratory infection and/or treatment with antibiotics. Clinical features include petechiae and ecchymoses of the head and distal extremities. Snow first described AHEC in 1913 in the United States. In 1938 in Europe, Finkelstein published his paper on the disease.

Aetiology and pathogenesis. Infections (usually respiratory tract or urinary, e.g. streptococcal, staphylococcal, *Escherichia coli*, cytomegalovirus, adenovirus, coxsackievirus, or rotavirus infections), drugs, or vaccines may trigger AHEC, which may be a variant of childhood cutaneous small vessel vasculitis [1–4]. The age group, body sites affected, lesion morphology, rare renal or gastrointestinal involvement, and inconstant demonstration of IgA deposition in biopsies all serve to distinguish AHEC from HSP.

Histopathology. Leukocytoclastic vasculitis is evident in lesions of AHEC. As in cutaneous small vessel vasculitis (CSVV), the features include: karyorrhexis of neutrophils, endothelial swelling and extravasation of erythrocytes. Lesions of AHEC may show more prominent dermal oedema than lesions of CSVV.

Clinical features. Non-tender facial oedema may be the presenting sign of AHEC lesions, which are often asymmetrical. AHEC is characterized by sudden development of tender, oedematous lesions with petechiae and ecchymoses on the head and distal extremities. Large annular, arciform, coin-shaped or targetoid lesions (Fig. 50.15), that may later develop into bullae or necrotizing lesions, are typical. Lesions of AHEC start distally and progress proximally, sometimes involving the scrotum in males. Clinically, patients with AHEC are typically medically stable, although they may be febrile. Less dramatic presentations, in which the preceding infection and post-inflammatory pigmentation of annular and arciform skin lesions are dominant, may be mistaken for a drug rash or exanthem [5]. Although AHEC may rarely involve joints, the gastrointestinal tract, or the kidneys with vasculitic manifestations, it typically follows a benign course, lasting 1 to 3 weeks and with no persistent adverse effects following resolution [1–3]. Intussusception, classically associated with HSP, has also been reported with AHEC [6].



Fig. 50.15 Early discoid erythematosus lesions in acute haemorrhagic oedema of childhood.

Diagnosis. AHEC may be diagnosed only after meningococcaemia, erythema multiforme, UV, Sweet's syndrome, cutaneous small vessel vasculitis and Kawasaki disease have been ruled out.

Treatment. Supportive care is the only treatment usually necessary for patients with AHEC, although other treatments used in infants with CSVV or HSP may be appropriate in more severely affected patients.

References

1 Taïeb A, Legrain V. Acute haemorrhagic oedema of the skin in infancy. In: Harper J, Oranje A, Prose N. *Textbook of Pediatric Dermatology*, 2nd edn. Oxford: Blackwell Publishing, 2006: 1897–901.
2 Cunningham BB, Caro WA, Eramo LR. Neonatal acute hemorrhagic edema of childhood: case report and review of the English-language literature. *Pediatr Dermatol* 1996; **13**: 39–44.
3 Legrain B, Lejean S, Taïeb A *et al*. Infantile acute hemorrhagic edema of the skin: study of ten cases. *J Am Acad Dermatol* 1991; **24**: 17–22.
4 Kuroda K, Yabunami H, Hisanaga Y. Acute haemorrhagic oedema of infancy associated with cytomegalovirus infection. *Br J Dermatol* 2002; **147**: 1254–7.
5 Cox NH. Seidlmayer's syndrome: post-infectious cockade purpura. *J Am Acad Dermatol* 1992; **26**: 275.
6 Yu JE, Mancini AJ, Miller ML. Intussusception in an infant with acute hemorrhagic edema of infancy. *Pediatr Dermatol* 2007; **24**: 61–4.

Nodular vasculitis

Synonyms
- Lobular panniculitis with vasculitis
- Erythema induratum of Bazin and of Whitfield

Definition. Nodular vasculitis (NV) is a chronic relapsing lobular panniculitis with septal vasculitis. It is characterized by a vasculitis of subcutaneous arteries and veins, with subsequent ischaemia of subcutaneous tissue, which results in clinical suppuration. The cause may be a hypersensitivity reaction to an antigenic trigger such as a bacterial infection. It occurs primarily in middle-aged women, and is manifest as tender nodules or plaques on the legs that may later progress to ulceration.

History and nomenclature. Erythema induratum of Bazin was initially described by Bazin in 1861 as indurated plaques on the legs of women of middle age [1]. In 1900, French dermatologists described an association between erythema induratum and tuberculosis [2], although British physicians reported similar patients without evidence of tuberculosis at approximately the same time, a pattern which was later designated 'Whitfield's erythema induratum' [3–5]. In the middle of the 20th century, American physicians suggested the term nodular vasculitis for Whitfield's erythema induratum, which was thought to be distinct from erythema induratum of Bazin [6]. There remains controversy about whether erythema induratum of Bazin and nodular vasculitis should viewed as distinct, or as the same entity but with tuberculosis as just one cause. Many authors combine these entities [7], some view them as simply different names for the same condition [8], whereas others refer to them as nodular vasculitis/ erythema induratum (or vice versa) [9,10], reflecting some uncertainty. Others have used the term erythema induratum, but qualify it as Bazin-type if due to tuberculosis and Whitfield type if not [11]. A similar debate surrounds the putative role of tuberculosis as the cause; hyperreactivity to purified protein derivative, *Mycobacterium tuberculosis* DNA sequences in lesions, and response to antituberculous therapy all suggest that tuberculosis has a causal role in some cases, yet other convincing causative associations (medications, other infections) are recorded and negative results on investigation for tuberculosis in other cases. Even in terms of detection of *M. tuberculosis* DNA, studies differ; in one study 77% of 50 biopsy specimens were positive (with no obvious clinical or histopathological differences between those with positive or negative results) [10], whereas a more recent study found no positive results in 10 cases [9]. The latter study also had negative PCR results for DNA of several non-tuberculosis mycobacteria. Both studies used retrospective cases, so it is uncertain whether the archived diagnosis might have been influenced by the nosology of nodular vasculitis at the time the specimens were reported. We recommend using the term nodular vasculitis, as it then does not presuppose a single aetiology, but being aware that tuberculosis must be excluded in patients with lesions that fit this clinicopathological pattern, and that there are no histological features that reliably distinguish a tuberculous from a non-tuberculous aetiology.

Aetiology and pathogenesis. Several antigenic triggers have been implicated as the source for the hypersensitivity reactions with resultant subcutaneous vasculitis and lobular panniculitis in NV, as alluded to above. These include bacterial infections, such as streptococcal or mycobacterial infections, viral infections such as hepatitis C virus [12], and drugs such as propylthiouracil. NV has also been reported as occurring repeatedly in association with flares of autoimmune colitis [13], and related to colonic carcinoma [14]. The pathogenesis may be similar to that of cutaneous small vessel vasculitis, probably being immune complex-mediated, but causing a persistent delayed hypersensitivity or Arthus-type reaction [11] and with septal vessels in the panniculus as the target. Similar lesions may occur in rheumatoid disease.

Histopathology. Controversy exists as to whether arteries, veins or both are affected in NV. Regardless of the type of vessel involved, the early changes are of leukocytoclastic (sometimes lymphocytic or granulomatous [8]) vasculitis of vessels in the subcutaneous tissue leading to ischaemic changes, followed by inflammation and injury to lipocytes [7–11]. It has been suggested that the lesions can be classified on pathological grounds into type I (focal panniculitis with central neutrophilic muscular vasculitis, resembling PAN), and type II (diffuse panniculitis with multiple foci of neutrophilic small and muscular vessel vasculitis) [8]. C-PAN can usually be distinguished, as inflammation does not extend beyond the adventitia of arteries. In both histopathological types, there is coagulation and some caseation necrosis, the resulting occlusion leading to ischaemia and necrosis of fat lobules that may eventually involve the overlying dermis. Early in the disease process, the necrotic subcutaneous fat demonstrates fat cysts bordered by a finely granular eosinophilic substance with pyknotic nuclei. Later, foamy histiocytes encircle the necrotic areas, creating granulomatous inflammation (consistent with an additional name that has been used, lobular granulomatous panniculitis) (Figs 50.16 & 50.17).

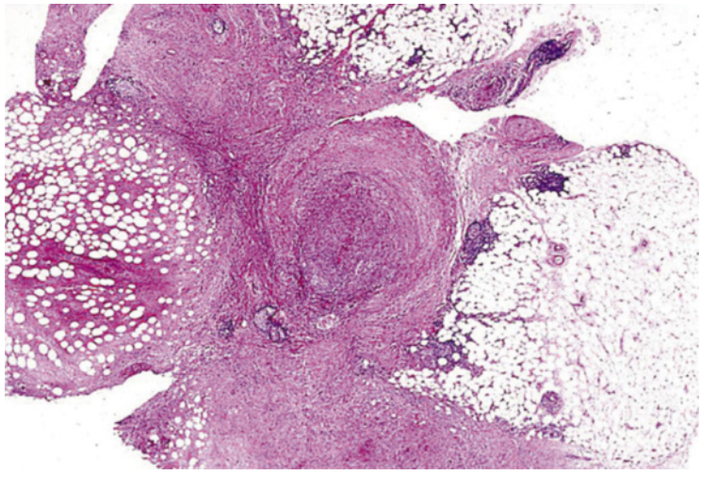


Fig. 50.16 Nodular vasculitis. Lobular panniculitis with prominent inflammation. Note the alteration of a vascular structure in the middle of the photograph. (Courtesy of Dr Omar Sangueza, Wake Forest University School of Medicine, Winston-Salem, NC, USA.)

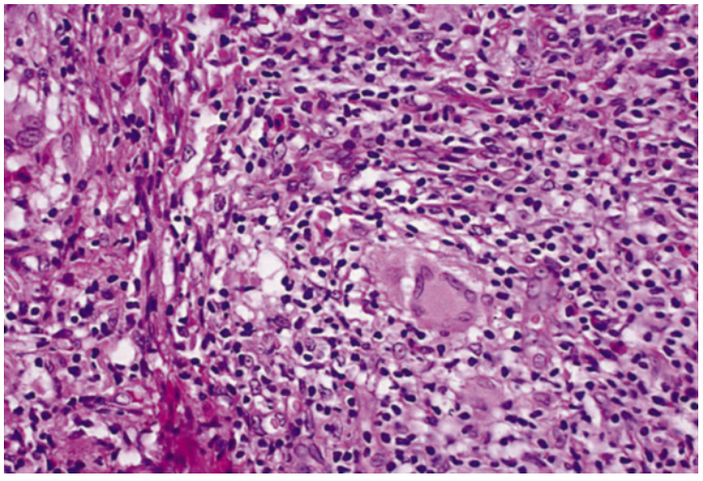


Fig. 50.17 Nodular vasculitis: the inflammatory infiltrate within the vessel wall is composed of lymphocytes and histiocytes, some of them multinucleated. (Courtesy of Dr Omar Sangueza, Wake Forest University School of Medicine, Winston-Salem, NC, USA.)



Fig. 50.18 Bazin's disease on the lower legs.

Clinical features. NV is manifest as tender, dusky, often suppurative, nodules or plaques on the posterolateral aspect of the legs (Fig. 50.18). It is typically seen in healthy, middle-aged, sometimes obese, women who may have venous stasis. Patients often have 'thick' calves with erythrocyanosis and perifollicular erythema. Lesions may be unilateral, are often inflamed and may progress to ulceration. The lesions of NV heal slowly, sometimes leaving an atrophic scar. The course of NV is chronic, with relapses typically occurring over several years. Nodular vasculitis may sometimes be seen in men, with unilateral nodules or plaques involving the anterior aspect of the thighs and legs, and other locations.

Lesions that have previously been termed 'erythrocyanosis with nodules' may have been examples of NV, or alternatively a pattern of perniosis.

Diagnosis. NV is a clinicopathological diagnosis, which requires deep incisional biopsy of active lesions. Lesions may resemble other panniculitides, erythema nodosum, perniosis, pyoderma gangrenosum, skin infections and the cutaneous lesions of polyarteritis nodosa (p. 50.33) or Takayasu's arteritis (p. 50.44). In cases where a tuberculous aetiology is suspected, a tuberculin skin test and chest X-ray should be performed. The recently developed ELISpot, which detects peripheral blood IFN-γ-secreting T cells, may also be useful [15]. Other tests for tuberculosis are discussed in Chapter 31. Evaluation is otherwise similar to that for patients with cutaneous small vessel vasculitis.

Table 50.10 Treatment of nodular vasculitis.

Tuberculosis present
Triple-agent antituberculosis therapy for a minimum of 9 months
Tuberculosis not present
Palliative treatments
• Compression hosiery
• Bed rest
• Non-steroidal anti-inflammatory drugs
Systemic corticosteroids
Potassium iodide
Other treatments used to treat patients with small vessel vasculitis (Table 50.7)

Treatment. In patients in whom tuberculosis is demonstrated, at least a 9-month course of triple-agent antituberculosis therapy should be given (Chapter 31) [16,17]. In non-tubercular cases, supportive measures, such as compression hosiery, bed rest and NSAIDs are recommended. Systemic corticosteroids may also be considered, as well as potassium iodide, which has been reported as an effective treatment of NV [18,19]. Other treatments outlined for patients with small vessel vasculitis might also be appropriate for patients with NV. Mycophenolate mofetil has been used in one case [20]. The treatment of NV is shown in Table 50.10.

References

1 Bazin E. *Leçons Théoriques et Cliniques Sur la Scrofule*, 2nd edn. Paris: Delahaye, 1861: 146.
2 Cribier B, Grosshans E. Erythéme induré de Bazin: concept et terminologie obsolétes. *Ann Dermatol Venereol* 1990; **117**: 937–43.
3 Galloway J. A probable case of Bazin's disease. *Br J Dermatol* 1899; **11**: 206–7.
4 Whitfield A. On the nature of the disease known as erythema induratum scrofulosorum. *Br J Dermatol* 1901; **13**: 386–7.
5 Whitfield A. A further contribution to our knowledge of erythema induratum. *Br J Dermatol* 1905; **15**: 241–7.
6 Montgomery H, O'Leary PA, Barker NW. Nodular vascular diseases of the legs: erythema induratum and allied conditions. *JAMA* 1945; **128**: 335–45.
7 Requena L, Sánchez Yus E. Panniculitis, Part II. Mostly lobular panniculitis. *J Am Acad Dermatol* 2001; **45**: 325–61.
8 Carlsson AJ, Chen K-R. Cutaneous vasculitis update: neutrophilic muscular vessel and eosinophilic, granulomatous and lymphocytic vasculitis. *Am J Dermatopathol* 2007; **29**: 32–43.
9 Bayer-Garner IB, Cox MD, Scott MA, Smoller BR. Mycobacteria other than *Mycobacterium tuberculosis* are not present in erythema induratum / nodular vasculitis: a case series and literature review of the clinical and histologic findings. *J Cutan Pathol* 2005; **32**: 220–6.
10 Baselga E, Margall N, Barnadas MA *et al*. Detection of *Mycobacterium tuberculosis* DNA in lobular granulomatous panniculitis (erythema induratum–nodular vasculitis). *Arch Dermatol* 1997; **133**: 457–62.
11 Weedon D. *Skin Pathology*, 2nd edn. London: Churchill Livingstone, 2002: 521–41.

12 Ural I, Erel A, Ozenirler S *et al*. Nodular vasculitis associated with chronic hepatitis C. *J Eur Acad Dermatol Venereol* 2002; **16**: 298–9.
13 Pozdnyakova O, Garg A, Mahalingam M. Nodular vasculitis—a new cutaneous manifestation of autoimmune colitis. *J Cutan Pathol* 2008; **35**: 315–9.
14 Khachemoune A, Longo MI, Phillips TJ. Nodular vasculitis as a paraneoplastic presentation? *Int J Dermatol* 2003; **42**: 639–42.
15 Clayton R, Grabczynska S, Wilkinson JD. Nodular vasculitis: an indicator for ELISpot screening for tuberculosis? *Clin Exp Dermatol* 2007; **32**: 761–2.
16 Anderson S. Erythema indutatum (Bazin) treated with isoniazid. *Acta Derm Venereol (Stockh)* 1970; **50**: 65–8.
17 Rademaker M, Lowe DG, Munro DD. Erythema induratum (Bazin's disease). *J Am Acad Dermatol* 1989; **21**: 740–5.
18 Schulz EJ, Whiting DA. Treatment of erythema nodosum and nodular vasculitis with potassium iodide. *Br J Dermatol* 1976; **94**: 75–8.
19 Hoti H, Imamura S, Danno K, Ofuji S. Potassium iodide in the treatment of erythema nodosum and nodular vasculitis. *Arch Dermatol* 1981; **117**: 29–31.
20 Taverna JA, Radfar A, Pentland A *et al*. Case reports: nodular vasculitis responsive to mycophenolate mofetil. *J Drugs Dermatol* 2006; **5**: 992–3.

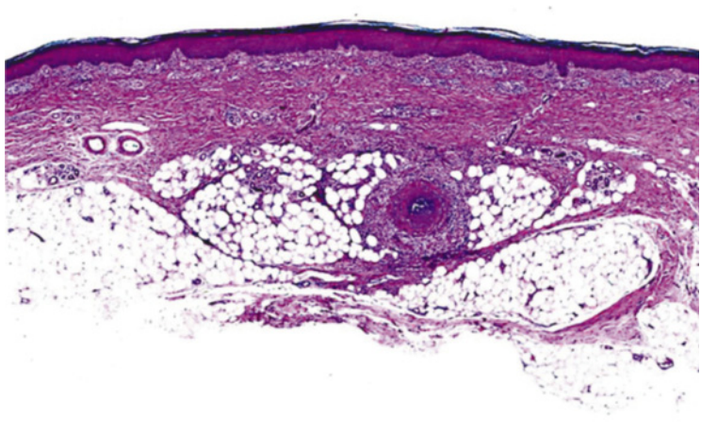


Fig. 50.19 Polyarteritis nodosa. Note the characteristic targetoid alteration of a vascular structure within the subcutaneous tissue. (Courtesy of Dr Omar Sangueza, Wake Forest University School of Medicine, Winston-Salem, NC, USA.)

Polyarteritis nodosa

Synonyms
- Classic polyarteritis nodosa
- Periarteritis nodosa

Definition. Polyarteritis nodosa (PAN) constitutes a necrotizing inflammation of medium-sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries or venules [1]. It was originally described by Kussmaul and Maier in 1866 [2] as 'periarteritis nodosa', and was renamed 'polyarteritis nodosa' in 1903 after Ferrari recognized its multivessel involvement as well as its transmural inflammation. Segmental involvement of medium-sized arteries is usual. Affected patients may have several signs and symptoms involving multiple organ systems. Ischaemia, infarcts and haemorrhage result from the vasculitis and lead to end-organ damage in patients with PAN. It has been described in all racial groups [3–5], with an incidence of 4.6–9 per million per year [6]; in populations with a low incidence of hepatitis B, its incidence is less than 5 per million population, but where hepatitis B is hyperendemic, the incidence rises dramatically (for example 77 per million in an Alaskan Eskimo population [7]). There may be an equal sex incidence or male predominance.

Aetiology and pathogenesis. Immune complexes are most commonly implicated in development of PAN. Immune complexes may activate complement with subsequent recruitment of neutrophils to the vessel wall. Progression of the inflammatory and immune response leads to recruitment of T lymphocytes, particularly $CD8^+$ T cells, and macrophages. Antiendothelial cell antibodies have also been proposed as a pathogenic mechanism, but specific antigens have not been identified and such antibodies are not specific to PAN [8]. The occurrence of nodose lesions and aneurysms at arterial branch points has also led to theories that the increased shear stress at these areas causes up-regulation of endothelial inflammatory factors [9–12], and that there may also be a greater number of macrophages in the tunica intima at these stress points [13,14], adding to the susceptibility of endothelial cells to inflammatory activity.

In cases of PAN associated with hepatitis B virus infection, HbsAg is thought to be the triggering antigen; typically this applies to 5–7% of patients with PAN, although incidences of associated hepatitis B as high as 10–54% have been reported [6]. Rarely, other viruses have been associated with PAN, including hepatitis C, parvovirus B19, human immunodeficiency virus and herpes zoster virus, as well as streptococcal infection. PAN has been described in association with malignancies, particularly hairy cell leukaemia [15], as well as with inflammatory conditions such as SLE, inflammatory bowel disease, familial Mediterranean fever and Cogan's syndrome. Minocycline has been implicated in a minority of individuals [16].

Histopathology. PAN affects small and medium-size muscular arteries and sometimes arterioles [6,17]. Lesions often develop at branch points, where there is a focal necrotizing arteritis; the inflammatory infiltrate is neutrophil-rich initially but subsequently mononuclear cells are predominant. There may be focal panniculitis; granulomata are absent. The vasculitis causes nodose swellings and may cause development of microaneurysms as blood vessel walls become weak and potentially necrotic. The most severely affected arterial branch points of vessels may rupture, leading to luminal thrombosis and obliteration, thus resulting in widespread distal tissue ischaemia and ultimately necrosis (Figs 50.19 & 50.20). Lesions heal by fibrosis. In patients with hepatitis B-associated PAN, HbsAg may be present within the lesions.

Clinical features. Patients with PAN usually have constitutional upset, including fever, weight loss, arthralgia and malaise. Organs commonly targeted comprise kidneys (infarctions and ischaemic nephropathy lead to hypertension and renal failure), heart (angina, myocardial infarction), gut (ischaemia, bleeding, perforation or infarction, presenting as abdominal pain) and peripheral nerves (mononeuritis multiplex) [8]. Rupture of an aneurysm may cause acute haemorrhage within the affected organ. In males, orchitis is a characteristic feature. Importantly for differential diagnosis, PAN does not affect the lung parenchyma and does not cause glomerulonephritis—patients in whom glomerulonephritis is a

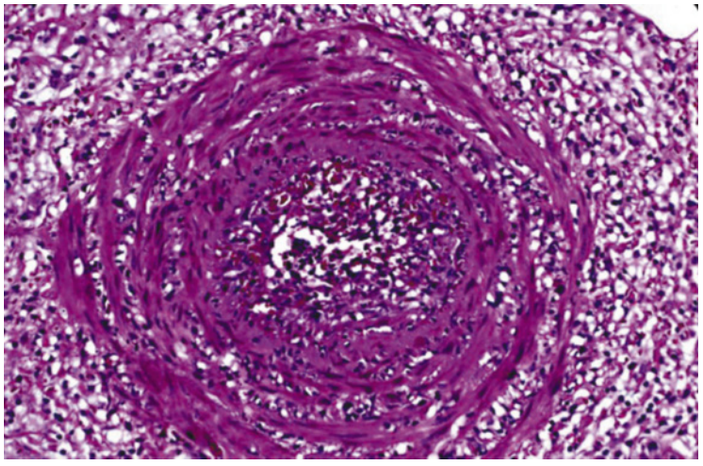


Fig. 50.20 Polyarteritis nodosa. Higher magnification demonstrates the partial destruction of the vessel wall and the inflammatory infiltrate composed of lymphocytes and neutrophils. (Courtesy of Dr Omar Sangueza, Wake Forest University School of Medicine, Winston-Salem, NC, USA.)



Fig. 50.21 Polyarteritis nodosa. Note the location of the lesion on the patient's foot.

dominant feature are more likely to have microscopic polyangiitis. Patients with hepatitis B virus-associated PAN may have features of hepatitis.

Skin features of PAN are common, occurring in about half of patients depending on the series, although early reports included patients with microscopic polyangiitis where small vessel involvement with purpuric manifestations may have confused the picture [8]. In PAN, a subcutaneous nodule or group of nodules ranging from 0.5–2 cm (mostly 5–10 mm) may develop, predominantly on the lower limbs and often in proximity to vessels. Typical sites are around the knee, anterior lower leg and dorsum of the foot. Nodules may be tender, pulsatile or secondarily ulcerated, with either normal or erythematous overlying skin. Livedo reticularis may occur, with or without ulceration. Ulcers have a 'punched-out' appearance. Ulceration and gangrene of the digits or penis may develop. Cutaneous lesions in patients with PAN are depicted in Figs 50.21 and 50.22.



Fig. 50.22 Polyarteritis nodosa. Multiple lesions on the fingers.

Diagnosis. Conventional angiography of hepatitic, renal, splanchnic and splenic circulations remains the most reliable method of demonstrating the aneurysms, stenoses and abnormal vessels in PAN [18], although they are not specific to this disorder. Tissue biopsy of affected muscle or nerve may confirm the presence of vasculitic lesions [19]; sensitivities of muscle and sural nerve biopsy specimens are 60% and 70%, respectively, in cases of symptomatic muscle involvement and nerve involvement demonstrated electrophysiologically [20,21]. Renal biopsy specimens (when urinalysis is abnormal) and angiography and/or aortography demonstrating pathognomonic aneurysmal dilatation of vessel walls may also be used to help establish a diagnosis of PAN. Although very sensitive, skin biopsy is not specific, and is usually not sufficient to establish the diagnosis of PAN. A study of 29 patients with skin ulcers due to PAN (fulfilling both American College of Rheumatology and Chapel Hill Consensus Conference criteria) showed that the highest yield was achieved by biopsying both the peripheral area of the ulcer and the central area (the rationale being that the central area would represent the apex of a wedge-shaped infarct); 26 diagnoses were confirmed but biopsies needed to contain subcutaneous tissue, 9/26 confirmed cases required multiple biopsies and diagnosis could not be achieved from the skin ulcers in the other three [22].

During acute disease, the ESR and CRP will be elevated and there may be other non-specific laboratory abnormalities such as leukocytosis with neutrophilia, thrombocytosis, normocytic anaemia, hypergammaglobulinaemia and cryoglobulinaemia, as well as haematuria, proteinuria. Antineutrophil cytoplasm antibodies are negative; although P-ANCA has been said to be positive in 20% of cases of PAN, it is more commonly seen in MPA or CSS (suggesting that some cases may have been misclassified), whereas a positive C-ANCA is typically associated with WG, CSS or MPA but not with PAN. Patients who test positive for hepatitis B will all be HbsAg-positive and most will be hepatitis B early antigen-positive.

Treatment. Patients who do not have hepatitis B-associated disease benefit from high-dose corticosteroids, commencing at 1 mg/kg/day and tapering over 1 year to 5–10 mg/day; the ESR is useful for monitoring disease activity. Such treatment has improved the 5-year survival from about 10% to over 50% [23]. In patients with severe disease, three daily pulses of methylprednisolone, 500–1000 mg, may be considered although there is no evidence to suggest that this is any better than daily oral prednisolone. Severe disease is indicated by the presence of renal (renal insufficiency, proteinuria >1 g/day), gut, cardiac or central nervous system involvement [24].

It is possible that cyclophosphamide may be useful in achieving remission in patients with severe disease [22]; one recommendation is for 12 pulses of cyclophosphamide, given at 0.6 g/m^2 every 2 weeks for the first three pulses and thereafter monthly [25], although it is worth pointing out that the trial from which these recommendations stem included patients with both PAN and microscopic polyangiitis; patients with PAN were in the minority. Plasma exchange does not appear to have any additional benefit in patients with non-hepatitis B-associated PAN.

Patients with hepatitis B-associated PAN appear to benefit from a combination of antiviral and immune suppressing drugs [26]. Corticosteroids should only be used short-term because of the possibility of increased viral replication; one regimen involves corticosteroids for 2 weeks, followed by the antiviral lamivudine combined with plasma exchanges. Relapses are rare and do not occur once viral replication has ceased and seroconversion has been obtained.

Treatment for hypertension and pain are important. Surgery may be needed for complications.

References

1 Jennette JC, Falk RJ, Andrassy K *et al*. Nomenclature of systemic vasculitides: the proposal of an International Consensus Conference. *Arthritis Rheum* 1994; **37**: 187–92.

2 Kussmaul AMR. Uber eine bisher beschreinbene eigentumliche Arterienenerkrankung (perarteritis nodosa) die mit Morbus Birghitii un rapid fortschreitender allgemeinen Muskellahmung einhergeht. *Arch Klin Med* 1866; **1**: 484–518.

3 Watts RA, Gonzalez-Gay MA, Lane SE *et al*. Geoepidemiology of systemic vasculitis: comparison of the incidence in two regions of Europe. *Ann Rheum Dis* 2001; **60**: 170–2.

4 Watts RA, Lane SE, Bentham G. Epidemiology of systemic vasculitis: a 10-year study in the United Kingdom. *Arthritis Rheum* 2000; **43**: 414–9.

5 Bonsib SM. Polyarteritis nodosa. *Semin Diag Pathol* 2001; **18**: 14–23.

6 Lhote F, Cohen P, Guillevin L. Polyarteritis nodosa, microscopic polyangiitis and Churg–Strauss syndrome. *Lupus* 1998; **7**: 238–58.

7 McMahon BJ, Heyward WL, Templin DW *et al*. Hepatitis B-associated polyarteritis nodosa in Alaskan Eskimos: clinical and epidemiologic features and long-term follow-up. *Hepatology* 1989; **9**: 97–101.

8 Guillevin L. Polyarteritis nodosa and microscopic polyangiitis. In: Ball GV, Bridges SL, eds, *Vasculitis*. Oxford: Oxford University Press, 2002: 300–20.

9 Morigi M, Zoja C, Figliuzzi M *et al*. Fluid shear stress modulates surface expression of adhesion molecules by endothelial cells. *Blood* 1995; **85**: 1696–703.

10 Nagel T, Resnick N, Dewey CF, Gimbrone MA. Vascular endothelial cells respond to spatial gradients in fluid shear stress by enhanced activation of transcription factors. *Arterioscler Thromb Vasc Biol* 1999; **19**: 1825–34.

11 Iiyama K, Hajra L, Iiyama M *et al*. Patterns of vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 expression in rabbit and mouse atherosclerotic lesions and at sites predisposed to lesion formation. *Circ Res* 1999; **85**: 199–207.

12 Cybulsky MI, Lichtman AH, Hajra L, Iiyama K. Leukocyte adhesion molecules in atherogenesis. *Clin Chim Acta* 1999; **286**: 207–18.

13 Malinauskas RA, Herrmann RA, Truskey GA. The distribution of intimal white blood cells in the normal rabbit aorta. *Atherosclerosis* 1995; **115**: 147–63.

14 Stary HC. Macrophages, macrophage foam cells, and eccentric intimal thickening in the coronary arteries of young children. *Atherosclerosis* 1987; **64**: 91–108.

15 Hasler P, Kistler H, Gerber H. Vasculitides in hairy cell leukemia. *Semin Arthritis Rheum* 1995; **25**: 134–42.

16 Schrodt BJ, Callen JP. Polyarteritis nodosa attributable to minocycline treatment of acne vulgaris. *Pediatrics* 1999; **103**: 503–4.

17 Churg J, Churg A. Idiopathic and secondary vasculitis: a review. *Modern Pathol* 1989; **2**: 144–60.

18 Stanson AW, Friese JL, Johnson CM *et al*. Polyarteritis nodosa: spectrum of angiographic findings. *Radiographics* 2001; **21**: 151–9.

19 Churg A, Churg J. *Systemic Vasculitides*. New York: Igaku-Shoin, 1991.

20 Albert DA, Rimon D, Silverstein MD. The diagnosis of polyarteritis nodosa. I. A literature-based decision analysis approach. *Arthritis Rheum* 1988; **31**: 1117–27.

21 Lightfoot RW Jr, Michel BA, Bloch DA *et al*. The American College of Rheumatology 1990 criteria for the classification of polyarteritis nodosa. *Arthritis Rheum* 1990; **33**: 1088–93.

22 Ricotti C, Kowalcyzk JP, Gherst M, Nousari CH. The diagnostic yield of histopathologic sampling techniques in PAN-associated cutaneous ulcers. *Arch Dermatol* 2007; **143**: 1335–6.

23 Gayraud M, Guillevin L, le Toumelin P *et al*. Long-term follow up of polyarteritis nodosa, microscopic polyangiitis, and Churg–Strauss syndrome: analysis of four prospective trials including 278 patients. *Arthritis Rheum* 2001; **44**: 666–75.

24 Guillevin L, Lhote F, Gayraud M *et al*. Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome. *Medicine* 1996; **75**: 17–28.

25 Guillevin L, Cohen P, Mahr A *et al*. Treatment of polyarteritis nodosa and microscopic polyangiitis with poor prognosis factors: a prospective trial comparing glucocorticoids and six or twelve cyclophosphamide pulses in sixty-five patients. *Arthritis Rheum* 2003; **49**: 93–100.

26 Guillevin L, Mahr A, Callard P *et al*. Hepatitis B virus-associated polyarteritis nodosa: clinical characteristics, outcome, and impact of treatment in 115 patients. *Medicine (Baltimore)* 2005; **84**: 313–22.

Microscopic polyangiitis

Synonyms

- Microscopic polyarteritis nodosa
- Microscopic polyarteritis

Definition. Microscopic polyangiitis (MPA) is a systemic vasculitis affecting blood vessels ranging in size from capillaries to medium-sized arteries. In some instances, there is only venous involvement in histopathological specimens from lesions in patients with MPA. MPA is strongly associated with lung involvement (primarily alveolar haemorrhage) and with crescentic glomerulonephritis [1]. The incidence of MPA is six to eight per million per year [2].

Patients demonstrating signs of PAN without cutaneous nodules were first described by Wohlwill in 1923, and then by Arkin in 1930. In 1948, articles were published that distinguished MPA from PAN. In 1994, MPA was termed microscopic polyangiitis instead of microscopic polyarteritis by a consensus conference because of the lack of arterial involvement in some patients and the involvement of vessels other than arteries [1].

Aetiology and pathogenesis. The exact pathogenesis of MPA is poorly understood, although it is considered a pauci-immune vasculitis because of the relative absence of immunoglobulins or

complement in affected vessel walls [3–7]. P-ANCA may have a role in the aetiology by activating neutrophils and monocytes via interactions with enzymes on the surface of or directly around endothelial cells [8], initially causing direct injury to the vessel endothelium. This is demonstrated in early findings of pauci-immune small vessel vasculitides in which there is fibrin accumulation in the subendothelium [7,9] as well as lysis of leukocytes within the vascular space [9] associated with endothelial injury. Products from neutrophils and monocytes (such as serine proteinases and metalloproteinases) may be inactivated at distant sites [10], accounting for the large degree of local tissue injury in lesions of MPA. Direct interactions between these cells and the endothelium may also explain the predilection of the disease for small rather than larger sized vessels. In some patients, there is a relationship between MPA and infection with either hepatitis B or C viruses [11,12]. Recent evidence suggests that antimyeloperoxidase (MPO) antibodies, present in 70% of MPA patients, may play a role in the damage to blood vessels by activating an oxidative burst [13].

Histopathology. Histological specimens from MPA lesions demonstrate segmental vascular necrosis. Neutrophils and monocytes permeate vessel walls, causing leukocytoclasia, accumulation of fibrin and haemorrhage. Biopsy specimens from lesions of palpable purpura demonstrate leukocytoclastic vasculitis.

Clinical features. Many patients with MPA initially experience constitutional symptoms, including fever, weight loss, myalgia and arthralgia. These may be present for several years before the onset of the pulmonary and renal disease that often occurs in patients with MPA. Between 79 and 90% of patients with MPA have necrotizing glomerulonephritis, and 25–50% have lung involvement, sometimes leading to pulmonary–renal syndrome [14], and leading to pulmonary haemorrhage in up to 29% of patients [15–17]. Although less common than in patients with PAN, symmetrical peripheral neuropathies or mononeuritis multiplex may occur in patients with MPA. Gastrointestinal (GI) manifestations are present in half of MPA patients. Although GI disease in MPA is usually mild at presentation, there has been a report of initial presentation with extensive colonic ulcerations and haemorrhage, characterized by a crypt abscess [18]. Nearly half of patients have palpable purpura on dependent skin sites upon presentation [19], but the presence of nodules should raise the suspicion of PAN, Wegener's granulomatosis (WG), or Churg–Strauss syndrome (CSS).

Diagnosis. MPA must be clinically distinguished from other vasculitides such as WG, CSS, CSVV, or PAN. In patients with MPA, positive P-ANCA and rheumatoid factor tests are common, unlike in patients with PAN. Some authors claim that small vessel vasculitis in the skin can distinguish MPA from PAN, stating that cutaneous small vessel vasculitis lesions do not typically occur in patients with PAN, although this is controversial. When palpable purpuric lesions are present in the absence of constitutional symptoms or the systemic features of MPA, patients most probably have CSVV rather than MPA. Small vessel vasculitis in the absence of granulomatous inflammation or asthma suggests MPA instead of CSS or WG [1].

Treatment. The management of MPA has recently been reviewed [20]. The approaches needed for induction, maintenance and long-term follow-up all differ. A preceding 'identification' phase may be associated with delay in treatment, especially if renal disease is absent or ANCA is negative. Initially, patients with MPA should be treated with high-dose corticosteroids and immunosuppressive treatment; cyclophosphamide has been used for some decades and, although strong evidence-based support, such as that supporting its use in patients with WG, is lacking, this combination leads to remission in 75–90% of patients at 6 months [20]. This regimen remains the mainstay of treatment for MPA associated with pulmonary haemorrhage or rapidly progressive glomerulonephritis. Methotrexate achieves similar early results but with a much higher relapse rate. Plasma exchange, or plasma filtration, are used for those with severe renal disease and, although associated with high early disease-related mortality, does appear to reduce longer-term need for dialysis. Intravenous immunoglobulin has also been used with benefit. For those who may not tolerate a steroid–cyclophosphamide regimen, such as the elderly, gabexate mesilate has been employed as an alternative treatment [21]. Based on evidence of an anti-MPO antibody-mediated oxidative burst, a compound such as *N*-acetylcysteine (NAC) may show promise for future therapy; NAC is an antioxidant that blocks HOCl production during the oxidative burst and thus avoids endothelial lysis [13]. Anti-TNF agents have been used but have given rise to concerns about malignancy in the context of vasculitis; additionally, other damaging cytokines (such as IL-18) are not affected by TNF blockade [20]. Selective blockade of different TNF receptors in glomerular vessels may be future targets for therapy. Rituximab has been used in a small number of cases with good results, especially as those treated had refractory disease [20].

The course of MPA is characterized by relapses, in contrast with that of PAN [20,22]. The prognosis is worst in older age, in those with low glomerular filtration rate, and in those with more glomeruli affected, or with extra-glomerular arteritis, on renal biopsy. Long-term follow-up is necessary, with monitoring of renal parameters and ANCA.

References

1 Jennette JC, Thomas DB, Falk RJ. Microscopic polyangiitis (microscopic polyarteritis). *Semin Diag Pathol* 2001; **18**: 3–13.

2 Scott DG, Watts RA. Systemic vasculitis: epidemiology, classification and environmental factors. *Ann Rheum Dis* 2000; **59**: 161–3.

3 Jennette JC, Falk RG, Andrassy K *et al*. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. *Arthritis Rheum* 1994; **37**: 187–92.

4 Savage CO, Winearls CG, Evans DG *et al*. Microscopic polyarteritis: presentation, pathology and prognosis. *QJM* 1985; **56**: 467–83.

5 Jennette JC, Falk RJ. Small vessel vasculitis. *N Engl J Med* 1997; **337**: 1512–23.

6 Jennette JC, Falk RJ. The pathology of vasculitis involving the kidney. *Am J Kidney Dis* 1994; **24**: 130–41.

7 D'Agati V, Chander P, Nash M *et al*. Idiopathic microscopic polyarteritis nodosa: ultrastructural observations on the renal vascular and glomerular lesions. *Am J Kidney Dis* 1986; **7**: 95–110.

8 Jennette JC, Falk RJ. Pathogenesis of the vascular and glomerular damage in ANCA-positive vasculitis. *Nephrol Dial Transplant* 1998; **13** (Suppl. 1): 16–20.

9 Donald KJ, Edwards RL, McEvoy JDS. An ultrastructural study of the pathogenesis of tissue injury in limited Wegener's granulomatosis. *Pathology* 1976; **8**: 161–9.
10 Weiss SJ. Tissue destruction by neutrophils. *N Engl J Med* 1989; **320**: 365–76.
11 Harper L, Savage CO. Pathogenesis of ANCA-associated systemic vasculitis. *J Pathol* 2000; **190**: 349–59.
12 Franssen CF, Stegeman CA, Kallenberg CG *et al*. Antiproteinase 3- and antimyeloperoxidase-associated vasculitis. *Kidney Int* 2000; **57**: 2195–206.
13 Guilpain P, Servettaz A, Goulvestre C *et al*. Pathogenic effects of antimyeloperoxidase antibodies in patients with microscopic polyangiitis. *Arthritis Rheum* 2007; **56**: 2455–63.
14 Niles J, Bottinger E, Saurina G *et al*. The syndrome of lung hemorrhage and nephritis is usually an ANCA-associated condition. *Arch Intern Med* 1996; **156**: 440.
15 Savige J, Davies D, Falk RJ *et al*. Antineutrophil cytoplasmic antibodies and associated diseases: a review of the clinical and laboratory features. *Kidney Int* 2000; **57**: 846–62.
16 Guillevin L, Lhote F. Treatment of polyarteritis nodosa and microscopic polyangiitis. *Arthritis Rheum* 1998; **41**: 2100–5.
17 Lauque D, Cadranel J, Lazor R *et al*. Microscopic polyangiitis with alveolar hemorrhage. A study of 20 cases and review of the literature. Groupe d'Etudes et de Recherche sur les Maladies 'Orphelines' Pulmonaires (GERM'O'P). *Medicine (Baltimore)* 2000; **79**: 222–33.
18 Tsai C-N, Chang C-M, Chuang C-H *et al*. Extended colonic ulcerations in a patient with microscopic polyangiitis. *Ann Rheum Dis* 2004; **63**: 1521–2.
19 Burrows NP, Lockwood CM. Antineutrophil cytoplasmic antibodies and their relevance to the dermatologist. *Br J Dermatol* 1995; **132**: 173–81.
20 Jayne D. Challenges in the management of microscopic polyangiitis: past, present and future. *Curr Opin Rheumatol* 2008; **20**: 3–9.
21 Miyawaki K, Shiraishi J, Tsutsumi Y *et al*. Beneficial effect of gabexate mesilate on microscopic polyangiitis with renal dysfunction and pulmonary hemorrhage: a case report. *Angiology* 2006; **57**: 522–5.
22 Gayraud M, Guillevin L, le Toumelin P *et al*. Long-term follow-up of polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: analysis of four prospective trials including 278 patients. *Arthritis Rheum* 2001; **44**: 666–75.

Cutaneous polyarteritis nodosa

Synonym
- Benign cutaneous periarteritis nodosa

Definition. Cutaneous polyarteritis nodosa (C-PAN) is a variant of PAN that is limited primarily to the skin. It was first described by Lindberg in 1931 [1] as a more benign variant of systemic PAN that did not have visceral involvement, although controversy exists over whether or not it simply represents an early or more limited form of PAN [2,3]. Thus, C-PAN can only be diagnosed by exclusion of findings that would alter the diagnosis to that of classic PAN. The course of C-PAN is typically benign and relapsing, despite the presence of moderate constitutional symptoms and mild nerve and muscle involvement in some patients [4,5].

Aetiology and pathogenesis. Infections such as streptococcus (particularly in children), parvovirus B19, HIV, and hepatitis B, as well as inflammatory bowel disease (IBD), have been associated with C-PAN [6], although the exact aetiology is unknown. Medications including minocycline, prescribed for acne, have also been reported to induce C-PAN [7–9]. Immunological mechanisms are thought by some authors to be involved only in the pathogenesis of systemic polyarteritis nodosa, and not in the development of C-PAN [10]. Whether C-PAN is part of the disease progression of systemic polyarteritis nodosa or should remain a separate clinical entity remains a topic of debate. Evidence suggests that C-PAN should remain separate from PAN as it rarely progresses into PAN and, unlike PAN, it rarely exhibits systemic involvement and has a good prognosis [10–14].



Fig. 50.23 Cutaneous polyarteritis nodosa. Erythematous lesions on the leg.

Histopathology. Early in the course of C-PAN, there is a predominantly neutrophilic inflammatory infiltrate in the walls of medium-sized arteries and arterioles of septae in the upper portions of the subcutaneous fat. The involved vessels classically demonstrate a target-like appearance resulting from an eosinophilic ring of fibrinoid necrosis. Later in the disease process the infiltrate becomes less neutrophilic, consisting predominantly of lymphocytes and histiocytes. Complement and IgM deposits in vessel walls of lesions of C-PAN from some patients may be demonstrated by direct immunofluorescence [15]. Unlike those of systemic PAN, lesions of C-PAN do not typically involve arterial bifurcations.

Clinical features. Although some patients with C-PAN may report constitutional symptoms as well as chronic, mild involvement of both muscles and nerves [4,5], cutaneous manifestations are the most striking feature of the disease. Dermal or subcutaneous nodules are most commonly located on the distal lower extremities near the malleoli (Fig. 50.23) and may extend proximally to the thighs, buttock, arms or hands. Patients may report tenderness associated with the nodules, which may ulcerate (Fig. 50.24) or more commonly demonstrate necrotizing livedo reticularis, also referred to as retiform purpura. Gangrene of the digits can ultimately occur, most commonly in children with C-PAN, but this finding should trigger an aggressive search to exclude systemic PAN [16,17]. Recurrent spiking fevers, polyarthralgia and macular upper extremity cutaneous eruption, symptoms shared by both C-PAN and adult-onset Still's disease (AOSD), sometimes create a challenge when diagnosing C-PAN. The presence of livedo reticularis (Fig. 50.25) and the finding of a characteristic skin biopsy appearance with C-PAN help to differentiate it from AOSD [18].

Diagnosis. Patients with necrotizing lesions of livedo reticularis must be evaluated for vasculitis or vasculopathy (e.g.



Fig. 50.24 Cutaneous polyarteritis nodosa. Nodules and ulceration.



Fig. 50.25 Cutaneous polyarteritis nodosa. Livedo of legs.

antiphospholipid antibody syndrome, cholesterol emboli or other factors that can produce non-vasculitic vessel occlusion; see Chapter 49). If nodules are present, they should be biopsied by incisional biopsy methods to assess for a panarteritis of muscular arteries which would confirm a diagnosis of C-PAN. The distinction from systemic PAN requires patient evaluation by history, physical examination, screening laboratory tests and ongoing follow-up. In addition, rheumatological consultation is often appropriate.

Treatment. Although no double-blind prospective trials have been performed, several reports suggest that non-steroidal anti-inflammatory drugs and salicylates can be an effective treatment for symptoms of C-PAN [19]. High-dose corticosteroids followed by tapering of the dosage may occasionally be necessary for some patients [20,21]. Also without evidence from controlled trials, but based on the strong association with streptococcal infection, penicillin is often used for treatment and prophylaxis in children with C-PAN. Screening for recent streptococcal infection with anti-DNAse B or other tests may guide this decision. Other treatments documented in anecdotal reports include dipyridamole, sulfapyridine, pentoxifylline and dapsone in patients with C-PAN. Low-dose weekly methotrexate (7.5–20 mg/week) has been successful in some patients with skin lesions unresponsive to corticosteroids given topically, intralesionally and orally [22]. In addition, chronic leg ulcers resistant to treatment with high-dose corticosteroids have recently been successfully treated with granulocyte-macrophage colony stimulating factor (GM-CSF) which has been shown to improve wound healing [23]. GM-CSF improves the clearance of bacteria and debris through the local attraction of neutrophils, promotes neovascularization and enhancement of keratinization, and induces acceleration of the formation of new tissue [23]. However, low-dose weekly methotrexate therapy and gradient support hosiery are anecdotally adequate therapy for the majority of patients with C-PAN [22].

References

1 Lindberg K. Ein Beitrag zur Kenntnis der Periarteritis nodosa. *Acta Med Scan* 1931; **76**: 183–225.
2 Thomas RH, Black MM. The wide clinical spectrum of polyarteritis nodosa with cutaneous involvement. *Clin Exp Dermatol* 1983; **8**: 47–59.
3 Minkowitz G, Smoller BR, McNutt NS. Benign cutaneous polyarteritis nodosa. Relationship to systemic polyarteritis nodosa and to hepatitis B infection. *Arch Dermatol* 1991; **127**: 1520–3.
4 Borrie P. Cutaneous polyarteritis nodosa. *Br J Dermatol* 1972; **87**: 87–95.
5 Khoo BP, Ng SK. Cutaneous polyarteritis nodosa: a case report and literature review. *Ann Med Assoc Singapore* 1998; **27**: 868–72.
6 Mat C, Yurdakul S, Tuzuner N, Tuzun Y. Small vessel vasculitis and vasculitis confined to skin. *Baillières Clin Rheumatol* 1997; **11**: 237–57.
7 Tehrani R, Nash-Goelitz A, Adams E *et al*. Minocycline-induced cutaneous polyarteritis nodosa. *J Clin Rheumatol* 2007; **13**: 146–9.
8 Culver B, Itkin A, Pischel K. Case report and review of minocycline-induced cutaneous polyarteritis nodosa. *Arthritis Rheum* 2005; **53**: 468–70.
9 Abad S, Kambouchner M, Nejjari M *et al*. Additional case of minocycline-induced cutaneous polyarteritis nodosa: comment on the article by Culver *et al*. *Arthritis Rheum* 2006; **55**: 831, author reply 832.
10 Daoud MS, Hutton KP, Gibson LE. Cutaneous periarteritis nodosa: a clinicopathological study of 79 cases. *Br J Dermatol* 1997; **136**: 706–13.
11 Choi SW, Lew S, Cho SD *et al*. Cutaneous polyarteritis nodosa presented with digital gangrene: a case report. *J Korean Med Sci* 2006; **21**: 371–3.
12 Gushi A, Hashiguchi T, Fukumaru K *et al*. Three cases of polyarteritis nodosa cutanea and a review of the literature. *J Dermatol* 2000; **27**: 778–81.
13 Bauza A, Espana A, Idoate M. Cutaneous polyarteritis nodosa. *Br J Dermatol* 2002; **146**: 694–9.
14 Misago N, Mochizuki Y, Sekiyama-Kodera H *et al*. Cutaneous polyarteritis nodosa: therapy and clinical course in four cases. *J Dermatol* 2001; **28**: 719–27.
15 Diaz Perez JL, Schroeter AL, Winkelmann RK. Cutaneous periarteritis nodosa: immunofluorescence studies. *Arch Dermatol* 1980; **116**: 56–8.
16 Kumar L, Thapa BR, Sarkar B. Benign cutaneous polyarteritis nodosa in children below 10 years of age—a clinical experience. *Ann Rheum Dis* 1995; **54**: 134–6.
17 Stone MS, Olson RR, Weismann DN *et al*. Cutaneous vasculitis in the newborn of a mother with cutaneous polyarteritis nodosa. *J Am Acad Dermatol* 1993; **28**: 101–5.
18 Kato T, Fujii K, Wakabayashi T *et al*. A case of cutaneous polyarteritis nodosa manifested by spiking high fever, arthralgia and macular eruption like adult-onset Still's disease. *Clin Rheumatol* 2006; **25**: 419–21.
19 Diaz Perez JL, Winkelmann RK. Cutaneous periarteritis nodosa: a study of 33 cases. In: Wolff K, Winkelmann RK, eds. *Vasculitis*. London: Lloyd-Luke, 1980: 273–84.

20 Sheth AP, Olson JC, Esterly NB. Cutaneous polyarteritis nodosa of childhood. *J Am Acad Dermatol* 1994; **31**: 561–6.
21 Siberry GK, Cohen BA, Johnson B. Cutaneous polyarteritis nodosa. Reports of two cases in children and review of the literature. *Arch Dermatol* 1994; **130**: 884–9.
22 Jorizzo JL, White WL, Wise CM *et al*. Low-dose weekly methotrexate for unusual neutrophilic vascular reactions: cutaneous polyarteritis nodosa and Behçet's disease. *J Am Acad Dermatol* 1991; **24**: 973–8.
23 Tursen U, Api H, Kaya TI *et al*. Rapid healing of chronic leg ulcers during perilesional injections of granulocyte-macrophage colony-stimulating factor therapy in a patient with cutaneous polyarteritis nodosa. *J Eur Acad Dermatol Venereol* 2006; **20**: 1341–3.

Wegener's granulomatosis

Definition. WG is classically described as a triad consisting of systemic small vessel vasculitis, necrotizing granulomatous inflammation of both the upper and lower respiratory tracts, and glomerulonephritis. The first description of a patient with WG was by Klinger in 1931, but the disease was later defined in 1936 by Wegener who described three patients. It is a potentially severe disease which, if not treated, can lead to end-organ damage and/or death. Affecting males and females equally, the incidence of WG is 5–10 per million per year, with the majority of cases occurring in Caucasians [1–3]. The average age at onset is 40 years [4].

Aetiology and pathogenesis. Although the pathogenesis of WG is not well understood, it is believed that it may involve an amplified immune response to an antigenic stimulus, such as an infection. Clinical observation points to *Staphylococcus aureus* as a potential trigger in some patients. The incidence of chronic nasal carriage of *S. aureus* is significantly higher in patients with Wegener's granulomatosis compared with healthy individuals [5]. One theory regarding the pathogenesis of WG is that neutrophils are activated via cytokines or apoptosis and degranulate, expressing cytosolic proteins on their surfaces and releasing harmful oxygen radicals as well as chemoattractants [6–9]. This enables ANCA to form against complementary peptide sequences to proteinase-3, otherwise known as the 'Wegener's autoantigen' [10,11]. Wegener's autoantigen may be introduced by a pathogen, specifically *S. aureus*, which exhibits a protein with a peptide sequence that mimics that of antisense PR3 [11]. The cytoplasmic antinuclear cytoplasmic antibodies (C-ANCA) are directed at antisense PR3 sequences which then cross-react with PR3 peptide sequences, thereby functioning as autoantibodies [11]. The perinuclear antineutrophil cytoplasmic antibodies (P-ANCA) are directed at myeloperoxidase (MPO). PR3 induces dendritic cell maturation via the protease activated receptor (PAR)-2, which in turn induces a strong Th1-type T-cell response. The PR3-induced T-cell response in WG is stronger than in healthy and disease controls [10,12]. In addition, activated neutrophils then attract additional neutrophils and damage vascular endothelium by attaching to blood vessel walls [13–15]. Another theory about the role of ANCA in the pathogenesis of WG is that activated neutrophils located at damaged blood vessels release antigens, causing a secondary ANCA response [16].

Histopathology. Although most biopsy specimens taken from patients with WG show perivascular lymphocytic infiltrates, such non-specific infiltrates may not be related to the pathogenesis of the disease [17]. More specific findings such as leukocytoclastic vasculitis and/or granulomatous inflammation may be present in up to 50% of skin biopsy specimens (Figs 50.26 & 50.27), although granulomatous inflammation around vessels or palisading necrotizing granulomas are uncommonly demonstrated in skin lesions.

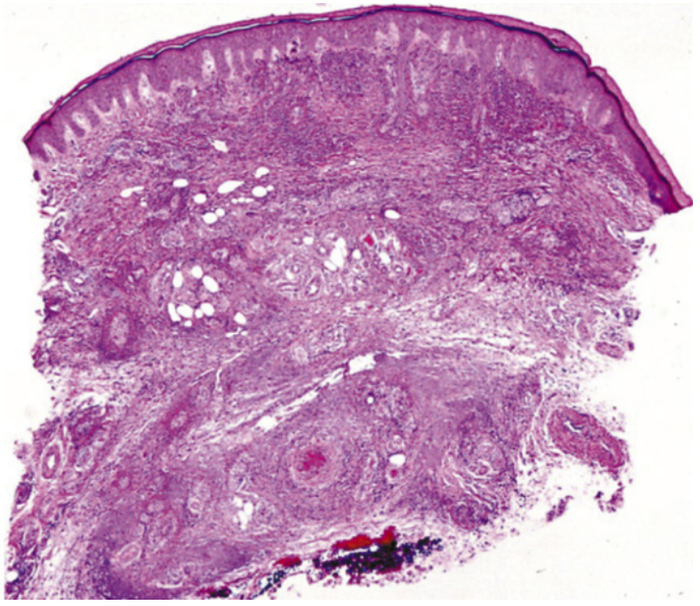


Fig. 50.26 Wegener's granulomatosis. There is extensive leukocytoclastic vasculitis involving the entire dermis. (Courtesy of Dr Omar Sangueza, Wake Forest University School of Medicine, Winston-Salem, NC, USA.)

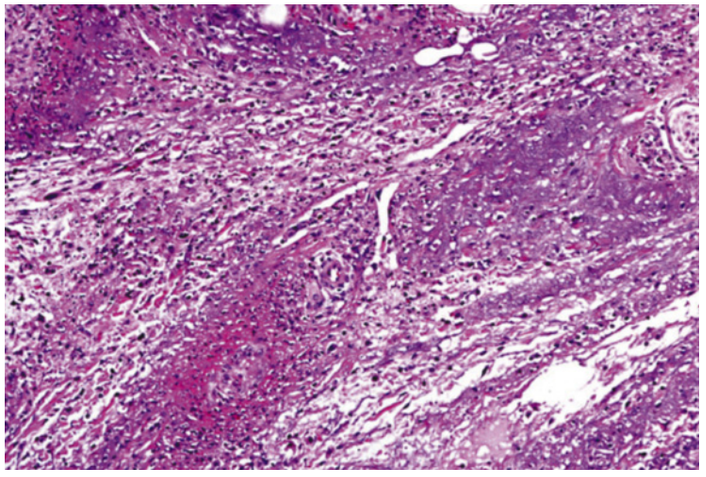


Fig. 50.27 Wegener's granulomatosis. Note the extensive area of collagen degeneration, destruction of vessels and mixed inflammatory infiltrate. (Courtesy of Dr Omar Sangueza, Wake Forest University School of Medicine, Winston-Salem, NC, USA.)

Clinical features. Features of the classic triad of WG are not always present early in the course of the disease, making the diagnosis sometimes difficult. Furthermore, presentation without involvement of the classical sites, including skin, respiratory tract



Fig. 50.28 Wegener's granulomatosis. Ulcerated lesions of cutaneous small vessel vasculitis.



Fig. 50.29 Wegener's granulomatosis. Larger ulcerated lesions with background vasculitis.

and kidneys, can occur. However, in up to 80% of patients, symptoms involving the upper or lower respiratory tract are present [18], and at presentation approximately 73% of patients will have nasal, sinus, tracheal or ear involvement. Less than half of all patients with WG present with pulmonary infiltrates or nodules. Renal disease is initially present in only 18% of patients, although approximately 77% will eventually develop glomerulonephritis [19]. Although 40% of patients with WG will eventually manifest skin findings, cutaneous manifestations and oral ulcers are only found in 13% and 6% of patients at initial presentation, respectively [19]. The most common cutaneous manifestation of WG is palpable purpura on dependent skin sites; other skin lesions include tender subcutaneous nodules, papules, vesicles and petechiae, as well as non-specific ulcers or pyoderma gangrenosum-like lesions. It is thought that patients previously diagnosed as having 'malignant pyoderma' may actually have had lesions secondary to WG. Nodular, or even papulonecrotic, lesions most commonly occur on the extremities but may also occur on the face and scalp. These non-specific lesions (also found in patients with CSS, rheumatoid arthritis, SLE, inflammatory bowel disease and some infectious states) may be differentiated from rheumatoid nodules in that they ulcerate, whereas rheumatoid nodules do not [20–22]. Oral ulcers are the second most common mucocutaneous sign of WG. The upper respiratory tract is most commonly affected by WG, with otitis, epistaxis, rhinorrhea and sinusitis as common presenting signs and symptoms. A saddle nose deformity may result from necrotizing granulomas of the nasal mucosa. Lower respiratory signs and symptoms include cough, dyspnoea, chest pain and haemoptysis. Ulcerative lesions in WG are shown in Figs 50.28–50.30.



Fig. 50.30 Wegener's granulomatosis, presenting with two deep skin ulcers and nasal symptoms.

Diagnosis. Wegener's granulomatosis must be differentiated from CSS. Important differences in these vasculitis syndromes are the lack of upper respiratory involvement and lack of severe glomerulonephritis in CSS, as well as the presence of asthma and eosinophilia in CSS but not in WG. Laboratory findings in WG include elevated ESR and CRP, anaemia, leukocytosis and positive rheumatoid factor [2,3]. Although a small percentage of patients will have a positive P-ANCA, or no ANCA reactivity, up to 80% of patients will have a positive C-ANCA (with anti-PR3 specificity) [23]. Those few patients with no ANCA reactivity may well have localized WG and a better prognosis when compared with those who are ANCA-positive [24,25]. Nodular densities from necrotizing granulomatous inflammation of lung tissue and pulmonary haemorrhage may be present on chest radiography; almost any chest X-ray change may represent WG, with the exception of hilar adenopathy [26].

Treatment. Inducing remission in patients with Wegener's granulomatosis is most successfully accomplished using a combination of corticosteroids and cytotoxic agents, such as cyclophosphamide. This combination of therapy results in a significant resolu-

tion of symptoms in greater than 90% of patients, with remission in 75%, and 87% surviving between 6 months and 24 years [19]. However, oral cyclophosphamide has significant toxicity and therefore other drugs, such as methotrexate, have been studied. Recent data suggest that, in patients with normal renal function, a methotrexate and prednisone regimen shows remission rates similar to the traditional cyclophosphamide and prednisone regimen. However, preliminary data suggest that the methotrexate plus prednisone regimen shows higher relapse rates, and therefore this regimen is suggested for inducing remission in a milder form of WG, such as head- and neck-limited disease [27]. The median survival for untreated WG remains only 5 months, and this prognosis is not appreciably altered by treatment with corticosteroids given as a monotherapy. Long-term treatment with trimethoprim–sulfamethoxazole (co-trimoxazole) has been documented to reduce the incidence of relapses, although side effects are relatively common [5]. Treatment options for refractory WG include anti-TNF-α agents such as infliximab or etanercept, and antilymphocyte antibodies such as rituximab. Rituximab is a monoclonal antibody that targets $CD20^+$ B-cells. It is currently used in the treatment of non-Hodgkin's lymphoma and rheumatoid arthritis but is also under investigation as a treatment option for refractory WG and other autoimmune diseases [28]. Impressive results can be seen, but development of antibodies to rituximab (due to its murine component) may limit long-term use.

References

1 Scott DG, Watts RA. Systemic vasculitis: epidemiology, classification and environmental factors. *Ann Rheum Dis* 2000; **59**: 161–3.
2 Stegeman CA, Kallenberg CG. Clinical aspects of primary vasculitis. *Springer Semin Immunopathol* 2001; **23**: 231–51.
3 Yi ES, Colby TV. Wegener's granulomatosis. *Semin Diag Pathol* 2001; **18**: 34–46.
4 Cotch MF, Hoffman GS, Yerg DE *et al*. The epidemiology of Wegener's granulomatosis. Estimates of the five-year period prevalence, annual mortality, and geographic diseases distribution from population-based data sources. *Arthritis Rheum* 1996; **39**: 87–92.
5 Popa ER, Tervaert JW. The relation between *Staphylococcus aureus* and Wegener's granulomatosis: current knowledge and future directions. *Intern Med* 2003; **42**: 771–80.
6 Falk RJ, Terrell RS, Charles LA, Jennette JC. Anti-neutrophil cytoplasmic autoantibodies induce neutrophils to degranulate and produce oxygen radicals in vitro. *Proc Natl Acad Sci USA* 1990; **87**: 4115–9.
7 Brouwer E, Huitema MG, Mulder L *et al*. Neutrophil activation in vitro and in vivo in Wegener's granulomatosis. *Kidney Int* 1994; **45**: 1120–31.
8 Cockwell P, Brooks CJ, Adu D, Savage CO. Interleukin-8: a pathogenetic role in antineutrophil cytoplasmic autoantibody-associated glomerulonephritis. *Kidney Int* 1999; **55**: 852–63.
9 Kettritz R, Choi M, Butt W *et al*. Phosphatidylinositol 3-kinase controls antineutrophil cytoplasmic antibodies-induced respiratory burst in human neutrophils. *J Am Soc Nephrol* 2002; **13**: 1740–9.
10 Lamprecht P, Gross WL, Kabelitz D. T cell alterations and lymphoid neogenesis favoring autoimmunity in Wegener's granulomatosis. *Arthritis Rheum* 2007; **56**: 1725–7.
11 Erickson VR, Hwang PH. Wegener's granulomatosis: current trends in diagnosis and management. *Curr Opin Otolaryngol Head Neck Surg* 2007; **15**: 170–6.
12 Csernok E, Ai M, Gross WL *et al*. Wegener autoantigen induces maturation of dendritic cells and licenses them for Th1 priming via the protease-activated receptor-2 pathway. *Blood* 2006; **107**: 4440–8.
13 Ewert BH, Jennette JC, Falk RJ. Anti-myeloperoxidase antibodies stimulate neutrophils to damage human endothelial cell. *Kidney Int* 1992; **41**: 375–83.
14 Yang JJ, Falk RJ, Jennette JC, Preston GA. Apoptosis of human endothelial cells induced by the neutrophil serine proteases proteinase 3 and elastase. *J Am Soc Nephrol* 1997; **8**: 431A.
15 Salant DJ. ANCA: Fuel for the fire or the spark that ignites the flame (editorial)? *Kidney Int* 1999; **55**: 1125–7.
16 Johnson RJ. The mystery of the antineutrophil cytoplasmic antibodies (editorial). *Am J Dis* 1995; **26**: 57.
17 Lie JT. Wegener's granulomatosis: histological documentation of common and uncommon manifestations in 216 patients. *Vasa* 1997; **26**: 261–70.
18 Lauque D, Cadranel J, Lazor R *et al*. Microscopic polyangiitis with alveolar hemorrhage. A study of 20 cases and review of the literature. Groupe d'Etudes et de Recherche sur les Maladies 'Orphelines' Pulmonaires (GERM'O'P). *Medicine (Baltimore)* 2000; **79**: 222–33.
19 Hoffman GS, Kerr GS, Leavitt RY *et al*. Wegener granulomatosis: an analysis of 158 patients. *Ann Intern Med* 1992; **116**: 488–98.
20 Magro CM, Crowson AN. The cutaneous neutrophilic vascular injury syndromes: a review. *Semin Diagn Pathol* 2001; **18**: 47–58.
21 Finan M. Rheumatoid papule, cutaneous extravascular necrotizing granuloma, and Churg–Strauss granuloma: are they the same entity? *J Am Acad Dermatol* 1990; **22**: 142–3.
22 Finan M, Winkelmann R. The cutaneous extravascular necrotizing granuloma (Churg–Strauss granuloma) and systemic disease: a review of 27 cases. *Medicine (Baltimore)* 1983; **62**: 142–58.
23 Jennette JC, Falk RJ. Small vessel vasculitis. *N Engl J Med* 1997; **337**: 1512–23.
24 Homer RJ. Antineutrophil cytoplasmic antibodies as markers for systemic autoimmune disease. *Clin Chest Med* 1998; **19**: 627–39.
25 Specks U, Wheatley C, McDonald T *et al*. Anticytoplasmic autoantibodies in the diagnosis and follow-up of Wegener's granulomatosis. *Mayo Clin Proc* 1989; **64**: 28–36.
26 Stone JH, Calabrese LH, Hoffman GS *et al*. Vasculitis. A collection of pearls and myths. *Rheum Dis Clin North Am* 2001; **27**: 677–728.
27 Belmont HM. Treatment of ANCA-associated systemic vasculitis. *Bull NYU Hosp Jt Dis* 2006; **64**: 60–6.
28 Antoniu SA. Treatment options for refractory Wegener's granulomatosis: a role for rituximab? *Curr Opin Investig Drugs* 2007; **8**: 927–32.

Churg–Strauss syndrome

Synonyms
- Allergic granulomatosis
- Vasculitis of Churg and Strauss

Definition. CSS is a rare vasculitis affecting multiple organ systems. The majority of patients demonstrate cutaneous findings while in the active phase of the disease. The disease is characterized by asthma, peripheral blood eosinophilia and necrotizing vasculitis with extravascular granulomas. Originally described by Rackermann and Greene in 1939, as an allergic disease not classified as periarteritis nodosa, Churg and Strauss later described the syndrome and its histopathological characteristics in 1951.

Aetiology and pathogenesis. The aetiology of CSS is unknown, although vaccination, desensitization and rapid discontinuation of corticosteroids have been associated with the onset of symptoms of CSS [1]. In the past it was believed that leukotriene antagonists were associated with the onset of CSS; however, new research suggests that, after adjustment for other asthma drugs, there is not a strong association [2]. Leukotriene antagonists are a marker for more severe asthma and severe asthma is thought to be a risk factor for CSS [3]. The pathogenesis of CSS is not completely understood. Immune complex deposition was once thought to be the mechanism of vasculitis in CSS, although eosinophils, mediated by a Th-2 response, are now thought to be the effector cells in the disease [4].

There is growing evidence for increased eosinophil survival in blood and tissues in CSS [5], possibly due to decreased apoptosis. Recent research has documented increased expression of TRAIL receptor 3 on eosinophils in patients with CSS [6]. TRAIL is a member of the tumour necrosis factor superfamily (TNF-Related Apoptosis-Induced Ligand) that normally binds to two 'death receptors' and two decoy receptors (TRAIL receptors 3 and 4); these decoy receptors are expressed on eosinophils and have an antiapoptotic function, as they cannot transduce the death signal that is activated when TRAIL binds to death receptors. Thus increased expression of TRAIL receptor 3 would be expected to compete with death receptors for TRAIL binding, leading to prolonged eosinophil survival. Eosinophils secrete several highly toxic cytokines such as eosinophil major basic protein, eosinophil cationic protein (ECP), and eosinophil-derived neurotoxin, all of which cause tissue damage. Serum levels of ECP, which is a marker of eosinophil activation, often correspond with disease activity in CSS [7] and may be used to predict relapse [8].

Histopathology. Churg–Strauss syndrome is characterized by three key histopathological features: eosinophilic infiltration of tissue, formation of extravascular granulomas of the visceral and cutaneous tissue and vasculitis involving both arteries and veins. A biopsy specimen of a cutaneous lesion from a patient with CSS may demonstrate any one, if not all, of these features [9]. The granulomas of CSS contain necrotic polymorphonuclear leukocytes, eosinophils, severe fibrinoid and fibrillar collagen degeneration, and a proliferation of granulomatous tissue.

Clinical features [1,5,9]. Three phases of CSS have been described. The first phase, which may continue for years, consists of allergic rhinitis, nasal polyps, asthma and peripheral blood eosinophilia. The asthma component of this phase typically begins in adulthood, in contrast with allergic asthma. The second phase of CSS is vasculitis; this phase is characterized by disease affecting almost all organ systems, including cardiac, pulmonary, nervous, gastrointestinal, renal, genitourinary and musculoskeletal systems. Cardiac involvement is the primary cause of death in patients who do not respond to conventional corticosteroid therapy [10]. In this vasculitic phase, 70% of patients have skin lesions (Fig. 50.31). The third stage of CSS is characterized by allergic rhinitis, asthma, hypertension due to damage to the kidneys that occurred in the second phase, and peripheral neuropathies. There is typically complete resolution of damage to other organ systems. Nearly half of patients in all phases of the disease have cutaneous manifestations of the disease [1,9], with approximately 5% demonstrating cutaneous vasculitis [9]. Palpable purpura and infiltrated nodules (typically located on the scalp or limbs) [11] are the most common skin manifestations, but livedo reticularis, necrotizing livedo (i.e. retiform purpura), migratory erythema, new-onset Raynaud's phenomenon, aseptic pustules or vesicles, or infiltrated papules may also be present.

Diagnosis. The American College of Rheumatology 1990 criteria for the classification of Churg–Strauss syndrome are as follows: asthma, eosinophilia greater than 10% on differential white blood cell count, mononeuropathy (including multiplex) or polyneuropathy, non-fixed pulmonary infiltrates on roentgenography, paranasal sinus abnormality, and biopsy containing a blood vessel with extravascular eosinophils [12]. The manifestations of CSS may be easily confused with lesions of Wegener's granulomatosis (WG), although CSS is strongly associated with both asthma and involvement of the gastrointestinal tract, spleen and heart, in contrast with the strong association with renal disease in patients with WG. The triad of asthma, eosinophilia and extravascular granulomas may also be used to distinguish CSS from other disease processes.



Fig. 50.31 Relatively subtle vasculitis on the legs in Churg–Strauss syndrome; the patient also had eosinophilia and rapidly developed mononeuritis multiplex.

Treatment. Corticosteroids alone have been shown to be an effective treatment of CSS [5], with clinical remission achieved in over 90% of patients. However, the addition of cytotoxic agents, especially cyclophosphamide in severely affected patients, or therapy such as intravenous immunoglobulin (IVIG), may be useful in patients with recalcitrant disease or those with poor prognostic factors such as cardiac, GI, renal or CNS involvement [10], although no double-blind, prospective trials have been done to establish their use.

References

1 Guillevin L, Cohen P, Gayraud M *et al*. Churg–Strauss syndrome. Clinical study and long-term follow-up of 96 patients. *Medicine (Baltimore)* 1999; **78**: 26–37.

2 Harrold LR, Patterson MK, Andrade SE *et al*. Asthma drug use and the development of Churg–Strauss syndrome. *Pharmacoepidemiol Drug Saf* 2007; **16**: 620–6.

3 Lilly CM, Churg A, Lazarovich M *et al*. Asthma therapies and Churg–Strauss syndrome. *J Allergy Clin Immunol* 2002; **109**: S1–19.

4 Kiene M, Csernok E, Muller A *et al*. Elevated interleukin-4 and interleukin-13 production by T cell lines from patients with Churg–Strauss syndrome. *Arthritis Rheum* 2001; **44**: 469–73.

5 Noth I, Strek ME, Leff AR. Churg–Strauss syndrome. *Lancet* 2003; **361**: 587–94.

6 Mitsuyama H, Matsuyama W, Watanabe M *et al*. Increased expression of TRAIL receptor 3 on eosinophils in Churg–Strauss syndrome. *Arthritis Rheum* 2007; **56**: 662–73.

7 Schmitt WH, Csernok E, Kobayashi S *et al*. Churg–Strauss syndrome: serum markers of lymphocyte activation and endothelial damage. *Arthritis Rheum* 1998; **41**: 445–52.

8 Hurst S, Chizzolini C, Dayer JM *et al*. Usefulness of serum eosinophil cationic protein (ECP) in predicting relapse of Churg and Strauss vasculitis. *Clin Exp Rheumatol* 2000; **18**: 784–5.
9 Davis MD, Daoud MS, McEvoy MT, Su WP. Cutaneous manifestations of Churg–Strauss syndrome: a clinicopathologic correlation. *J Am Acad Dermatol* 1997; **37**: 199–203.
10 Taniguchi M, Tsurikisawa N, Higashi N *et al*. Treatment for Churg–Strauss syndrome: induction of remission and efficacy of intravenous immunoglobulin therapy. *Allergol Int* 2007; **56**: 97–103.
11 Lhote F, Cohen P, Guillevin L. Polyarteritis nodosa, microscopic polyangiitis and Churg–Strauss syndrome. *Lupus* 1998; **7**: 238–58.
12 Masi AT, Hunder GG, Lie JT *et al*. The American College of Rheumatology 1990 criteria for the classification of Churg–Strauss syndrome (allergic granulomatosis and angiitis). *Arthritis Rheum* 1990; **33**: 1094–100.

Giant cell arteritis

Synonyms
- Temporal arteritis
- Cranial arteritis

Definition. The definition provided by an International Consensus Conference for giant cell arteritis (GCA) was of a granulomatous arteritis of the aorta and its major branches, with a predilection for the extracranial branches of the carotid artery [1]. It often involves the temporal artery, usually occurs in patients older than 50 years and is often associated with polymyalgia rheumatica (PMR), a syndrome comprising aching and morning stiffness of the shoulder or pelvic girdle muscles that may precede or accompany GCA. However, the similar histopathological findings between GCA, PMR and Takayasu's arteritis have led some investigators to question whether they are separate entities or represent a continuum of disease [2,3]. The matter is not wholly settled.

Epidemiology. GCA is considered a disease that particularly targets Caucasians of European origin, being less common in African Americans, native Americans and Asians. The disease is about three times more common in women than men. The incidence appears to differ with geographical area, being commoner in more northern climes, but overall the worldwide incidence is about 1/50 000/year. The incidence may be increasing, particularly amongst women.

Aetiology and pathogenesis. Ethnic and geographical observations suggest that genetic factors probably contribute to development of GCA. Several studies have indicated an over-representation of HLA-DR4; recent associations have included HLA-class I and MICA and HLA-B polymorphisms [4]. It is suggested that the pathogenesis of GCA, as with many diseases, represents an aberrant response to an infectious agent and that the immune system appears to have a central role in the pathogenesis. The arterial adventitia contains dendritic cells, in close proximity with vasa vasorum, that are in an immature state in normal arterioles but that have a mature and activated phenotype in GCA, so that they are capable of triggering antigen-specific T cells [5]. Activated $CD4^+$ T cells that have undergone clonal expansion are also present in the adventitia and produce large quantities of IFN-γ [6]. In turn, IFN-γ can modify effector functions of macrophages and multinucleated giant cells that locate at the junction between the tunica intima and tunica media, setting up a vicious cycle with further production of proliferative and pro-inflammatory mediators. Distinct subsets of macrophages are present with non-overlapping functions that lead to production of proinflammatory cytokines, the release of reactive oxygen radicals, production of growth and angiogenic factors such as platelet-derived growth factor (PDGF) and vascular endothelial cell growth factor (VEGF), and production of nitric oxide synthase. The intimal hyperplasia and neovascularization that occurs in GCA, and which is largely responsible for the vascular occlusion and ischaemia, is probably driven by oxidative and nitrosactive stress within the medial smooth muscle cell layer. Intimal hyperplasia is also associated with the increased production of IFN-γ and formation of multinucleate giant cells.

Interestingly, in PMR, the arterial wall dendritic cells are in an activated state but there is aborted recruitment of $CD4^+$ T cells and macrophages, suggesting that PMR may be a *forme fruste* of GCA [6].

Histopathology. Almost any artery can be affected in GCA. Indeed, an exhaustive autopsy study by Ostberg in 1972, in which the entire aorta and its major branches were removed and sectioned, suggested that involvement of aortic branch vessels was common [7]. The affected artery demonstrates lymphocytic and macrophage infiltrates in the tunica media that can extend from the tunica intima to the adventitia. The internal elastic lamina is fragmented and concentric intimal thickening develops, leading to occlusion of the vessel lumen. Giant cells can be present but are not required for the diagnosis. Granulomas and fibrinoid necrosis are seen infrequently.

Clinical features. The symptoms and signs of GCA result from the inflammation and occlusion of affected arteries. The disease appears to target those arteries that contain an internal elastic lamina, that is extracranial vessels, sparing intracranial vessels.

Constitutional upset occurs in many patients with fever and weight loss, and GCA is associated with PMR in about half of individuals. Headache is common and may be localized to the area of the affected artery, that is temporal with temporal arteritis, or occipital with vertebrobasilar arteritis. The headache may start abruptly and may be associated with tender arteries that may be pulseless or nodular. Facial pain may occur on chewing due to claudication of jaw muscles. A feared complication is sudden, permanent visual loss related to ocular or orbital artery involvement. Transient monocular loss of vision (amaurosis fugax) may precede permanent loss in some individuals. Vertebrobasilar artery involvement may cause ataxia, vertigo or deafness.

Involvement of the aorta or of its main branches is common. In one longitudinal cohort study that used vascular imaging, 72% of patients had large artery involvement, usually of the aorta, axillary and subclavian arteries [8]. Aortic involvement can cause aortic arch syndrome with absent pulses and upper arm claudication, and aortic aneurysms can lead to life-threatening dissection.

Less common features include cerebrovascular accidents, neuropsychiatric manifestations, angina or myocardial infarction, bowel angina or infarction, leg claudication and renal

involvement. Unilateral or bilateral scalp ulceration, with or without necrosis, may occur. Rarely, tongue ulceration or infarction, or corneal ulceration, develops.

Diagnosis. The gold standard is histological diagnosis following biopsy of an affected artery, usually a temporal artery. The biopsy should ideally comprise a 2 cm length of vessel and, for the greatest chance of obtaining a tissue diagnosis, the biopsy should be performed within 24 h of commencing corticosteroid therapy. A negative biopsy does not exclude the diagnosis, because timing is important and the disease may be quite focal.

Imaging is playing an increasing role in diagnosis. Superficial temporal arteries and axillary arteries may be amenable to duplex ultrasound, and fluorodeoxy-glucose-positron emission tomography and magnetic resonance angiography are increasingly being used for evaluation of disease activity and extent [9,10].

The acute inflammatory response can be measured by C-reactive protein (CRP) levels and erythrocyte sedimentation rate (ESR). Interleukin-6 levels may be a more sensitive biomarker of disease activity than the ESR [11]. A normochromic, normocytic anaemia, thrombocytosis and raised alkaline phosphatase may all be present.

Treatment. Suspected PMR responds well to oral corticosteroids such as prednisolone, 15–20 mg daily. The dose can usually be reduced slowly in small steps every month, providing that the CRP/ESR levels remain controlled. Treatment is usually for 2–3 years. Higher doses of corticosteroids, for example prednisolone 40–60 mg daily, are needed for GCA. Treatment should be started as soon as the diagnosis is suspected in order to avoid the potential for the complications discussed earlier; if the diagnosis turns out to be incorrect, the corticosteroids can be quickly withdrawn. There is some evidence that initial high-dose methylprednisolone may allow for more rapid tapering of oral corticosteroids and may be associated with a greater number of patients experiencing long-term remission after discontinuation of treatment [12]. Intravenous methylprednisolone 500–1000 mg daily for 3 days, followed by oral prednisolone, may be particularly beneficial in those with visual loss. Unfortunately, if visual loss has already occurred, this may be permanent, but it is important to preserve residual vision and prevent further strokes. The dose of prednisolone can be reduced to 10–20 mg/day by 6 months, and then in small increments with discontinuation by 2–3 years, depending on ESR/CRP/interleukin-6 responses. Sometimes additional immunosuppressive therapy, such as azathioprine, mycophenolate mofetil or methotrexate, is required; some patients require treatment for many years. Aspirin is recommended providing there are no contraindications. Carotid artery stenoses may require angioplasty to improve perfusion.

References

1 Jennette JC, Falk RJ, Andrassy K *et al*. Nomenclature of systemic vasculitides: the proposal of an International Consensus Conference. *Arthritis Rheum* 1994; **37**: 187–92.

2 Gonzalez-Gay MA. Giant cell arteritis and polymyalgia rheumatica: two different but often overlapping conditions. *Semin Arthritis Rheum* 2004; **33**: 289–93.

3 Maksimowicz-McKinnon K, Hoffman GS. Large vessel vasculitis. *Clin Exp Rheumatol* 2007; **25** (Suppl. 44): S58–9.

4 Gonzalez-Gay MA, Rueda B, Vilchez JR *et al*. Contribution of MHC class I region to genetic susceptibility for giant cell arteritis. *Rheumatology (Oxford)* 2007; **46**: 431–4.

5 Ma-Krupa W, Jeon MS, Spoerl S *et al*. Activation of arterial wall dendritic cells and breakdown of self tolerance in giant cell arteritis. *J Exp Med* 2004; **199**: 173–83.

6 Weyand CM, Ma-Krupa W, Goronzy JJ. Immunopathways in giant cell arteritis and polymyalgia rheumatica. *Autoimmun Rev* 2004; **3**: 46–53.

7 Ostberg G. Morphological changes in the large arteries in polymyalgia arteritica. *Acta Med Scand* 1972; Suppl. 533: 135–59.

8 Maksimowicz-McKinnon K, Clark T, Hoffman GS. The prevalence of signs and symptoms of polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) in Takayasu's arteritis. *Arthritis Rheum* 2004; **50**: S1072.

9 Dasgupta B, Hassan N. Giant cell arteritis: recent advances and guidelines for management. *Clin Exp Rheumatol* 2007; **25** (Suppl.): S62–3.

10 Bley TA. Imaging studies in the diagnosis of large vessel vasculitis. *Clin Exp Rheumatol* 2007; **25** (Suppl.): S60–1.

11 Weyand CM, Fulbright JW, Hunder GG *et al*. Treatment of giant cell arteritis: interleukin-6 as a biologic marker of disease activity. *Arthritis Rheum* 2000; **43**: 1041–8.

12 Mazlumzadeh M, Hunder GG, Easley KA *et al*. Treatment of giant cell arteritis using induction therapy with high-dose glucocorticoids: a double-blind, placebo-controlled, randomized prospective clinical trial. *Arthritis Rheum* 2006; **54**: 3310–8.

Takayasu's arteritis

Synonyms

- Takayasu's disease
- Takayasu's syndrome
- Aortic arch syndrome
- Pulseless disease
- Occlusive thromboarteriopathy
- Aortitis syndrome

Definition. Takayasu's arteritis (TA) is a granulomatous inflammation of the aorta and its major branches that usually occurs in patients aged younger than 50 years [1]. Although it is most common in individuals less than 40–50 years of age, it may occasionally be diagnosed in older people.

Epidemiology. The disorder is often described as affecting young females of Oriental origin and, indeed, it appears to be a relatively common cause of renovascular hypertension in the Far East, although it does have a worldwide distribution and racial heterogeneity.

Aetiology and pathogenesis. TA is associated with an acute inflammatory response, and the histopathology of acute lesions is similar to that described in GCA, so inflammatory and immune mechanisms appear to be necessary for pathogenesis. Genetic, infectious and environmental triggers have been sought but none has been associated conclusively with the disease. Various HLA associations have been described depending on the population under study, and susceptibility has been linked to polymorphisms around the HLA-B and MICA genes [2]. Tubercle bacilli have been scrutinized as a possible precipitant, but patients generally respond to immunosuppression without development of overt tuberculosis.

Histopathology. The aorta and its branches are targeted and skip lesions can occur [3]. During the acute phase, a pan-arteritis is present. The inflammatory infiltrate may be predominantly around the vasa vasorum. Fibrosis gradually replaces inflammatory infiltrates. The vessel lumen may be narrowed secondary to the fibrosing stenotic lesions and/or by intraluminal thrombosis. In older patients there may be superimposed atherosclerosis, and calcification in the wall may occur as a late feature.

Clinical features. The symptoms and signs of TA result from inflammation, ischaemia and aneurysm formation within the aorta and its branches [4]. There may be overlap in features of TA with those of GCA [5]. Hypertension is a common presenting feature in Asian and Far Eastern patients and the blood pressure should be recorded in all four limbs. Renal artery stenosis, increased arterial stiffness and increased sensitivity of the carotid sinus reflex, all contribute to hypertension. Involvement of the renal arteries can also cause renal dysfunction, and abdominal pain, bleeding or perforation may result from ischaemia or infarction of a viscus. Involvement of the aortic arch and its branches can lead to 'aortic arch syndrome' with arm claudication, absent radial or brachial pulses (hence 'pulseless disease') or subclavian artery bruits. Aortic regurgitation, coronary artery ischaemia with angina or myocardial infarction, pulmonary hypertension, stroke, syncope and visual disturbances can occur.

Skin lesions have been reported in up to a third of cases and may comprise erythema nodosum, erythema induratum and pyoderma gangrenosum [6], as well as ulcerated subacute nodular lesions, papulonecrotic eruptions, papular erythematous lesions of the hands and fingers, facial lupus-like rashes and panniculitis [7]. Cutaneous necrotizing vasculitis has been described resembling nodular vasculitis/erythema induratum, suggesting that Takayasu's arteritis may occasionally involve small blood vessels [8]. The skin lesions do not appear to relate to the distribution of vascular involvement in any way.

Diagnosis. TA is best diagnosed using imaging techniques [9]. Angiography and magnetic resonance angiography may demonstrate stenotic lesions of the aorta or its branches. Increasingly, enhanced magnetic resonance perfusion imaging, duplex ultrasonography and positron emission tomography are being used [10].

In the early stages of the disease, inflammatory markers such as CRP and ESR may be elevated. However, if disease presentation occurs late, features of an acute inflammatory response may be absent. A normochromic normocytic anaemia is often present.

Treatment. The acute phase of TA is managed in a similar way to GCA. The response is usually less dramatic than in GCA and secondary immunosuppressant medication is often required. However, once arterial damage has occurred and the inflammatory component has settled, immunosuppression is unlikely to be helpful. Stenotic lesions may require treatment with angioplasty or stenting. Hypertension requires aggressive management. Smoking should be discouraged and, as there is an increased risk of premature atherosclerosis, cardiac risk factors should be sought and dealt with.

References

1 Jennette JC, Falk RJ, Andrassy K *et al*. Nomenclature of systemic vasculitides: the proposal of an International Consensus Conference. *Arthritis Rheum* 1994; **37**: 187–92.
2 Kimura A, Ota M, Katsuyama Y *et al*. Mapping of the HLA-linked genes controlling the susceptibility to Takayasu's arteritis. *Int J Cardiol* 2000; **75** (Suppl. 1): S105–10.
3 Lie JT. Takayasu's arteritis. In: Churg A, Churg J, eds. *Systemic Vasculitides*. New York: Igaku-Shoin, 1991: 159–79.
4 Sharma BK, Jain S. Takayasu's arteritis. In: Ball GV, Bridges SL, eds. *Vasculitis*. Oxford: Oxford University Press, 2002: 278–89.
5 Maksimowicz-McKinnon K, Clark T, Hoffman GS. The prevalence of signs and symptoms of polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) in Takayasu's arteritis. *Arthritis Rheum* 2004; **50**: S1072.
6 Pascual-Lopez M, Hernandez-Nunez A, Aragues-Montanes M *et al*. Takayasu's disease with cutaneous involvement. *Dermatology* 2004; **208**: 10–15.
7 Boisnic F, Bletry O, Dallot A *et al*. Cutaneous manifestations of Takayasu arteritis. A retrospective study of 80 patients. *Dermatologica* 1990; **181**: 266–72.
8 Skaria AM, Ruffieux P, Piletta P *et al*. Takayasu arteritis and cutaneous necrotizing vasculitis. *Dermatology* 2000; **200**: 139–43.
9 Rizzi R, Bruno S, Stellaci C, Dammacco R. Takayasu's arteritis: a cell-mediated large-vessel vasculitis. *Int J Clin Res* 1999; **29**: 8–13.
10 Bley TA. Imaging studies in the diagnosis of large vessel vasculitis. *Clin Exp Rheumatol* 2007; **25** (Suppl.): S60–1.

Other vasculitides and mimics of vasculitis

Kawasaki disease [1]

This eponymous disease is a mucocutaneous lymph node syndrome, predominantly affecting young children, although recurrent disease in adults and adult-onset disease can occur. It is discussed briefly here as the systemic component includes a multisystem vasculitis; however, the exanthem it causes is not vasculitic. It is discussed in more detail in Chapter 30 (Bacterial infections) because it occurs in epidemics and there is some evidence to suggest an infective aetiology, possibly involving *Staphylococcus aureus*, *Streptococcus pyogenes* or *Yersinia pseudotuberculosis*. Bacterial superantigens, notably staphylococcal toxic shock syndrome toxin type-1 (STSS-1) and streptococcal pyrogenic exotoxins B and C, have particularly been implicated, although evidence to support this is poor [2]. More recently, an IgA response to cytoplasmic inclusion bodies has been documented as a possible cause [3].

At a pathogenetic level, many factors common to medium and larger vessel vasculitides can be found, including activated T cells, B cells and monocyte/macrophages, as well as elevated TNF-α, IFN-γ, IL-1, IL-2, IL-6, IL-12 and ICAM-1 [1]; antiendothelial cell antibodies are also present. Elevated levels of anti-α-enolase antibodies have been demonstrated and suggested to have a pathogenetic role [4]. The elastolytic role of matrix metalloproteinases is also thought to be involved; MMP-1, MMP-2, MMP-9 and MMP-13 have all been implicated, but high circulating levels of MMP-2 and MMP-9 were shown not to be significantly associated with coronary outcome after adjusting for demographic, clinical and laboratory features in patients or in a mouse model [5]. However, a genetic polymorphism in MMP-13 has been proven to occur with a significant difference in frequency in patients with Kawasaki disease with coronary artery lesions than in those without such lesions [6].

The angiitis of Kawasaki disease affects nearly all organs, with a very high frequency of cardiac involvement, which follows four stages [1]. Initially, there is perivasculitis and vasculitis of small vessels (capillaries, small veins and arteries, including those of the vasa vasora of the main coronary arteries); as the stages progress there is a gradual decrease in the small vessel vasculitis but development of focal panvasculitis of medium-size arteries, especially of the heart, with a mixed inflammatory infiltrate. During this phase (stage 2), aneurysms, thrombosis and stenoses of medium-size arteries develop, with gradual scarring and loss of acute vasculitis by stage 4. Deaths may occur due to myocarditis, dysrhythmias, pericarditis, rupture of aneurysms and occlusion of coronary arteries; there is also an increased risk of atherosclerosis due to endothelial cell dysfunction. Coronary aneurysms are demonstrated in almost 20% of patients (and in 90% of those who die); some will regress (potentially with stenosis) but giant aneurysms (>8 mm) rarely regress, carry a high risk of death and may require bypass surgery. Clinical factors that predict a higher risk of coronary artery arteritic lesions or aneurysms, or that predict a poor response to treatment, include age below 1 year, low serum albumin, low haemoglobin, high CRP, abnormal liver function and, especially, duration of fever before treatment [7–10]; peripheral blood eosinophilia (>4%) after treatment is also associated with treatment resistance [10].

The angiitis of Kawasaki disease can be divided into that which affects medium- and large-size arteries outside organs (mainly the coronary arteries, in 90%, also the iliac and other arteries), arteritis within organs (also mainly cardiac, but also the skin, kidneys, gastrointestinal tract and others), and venulitis. Thrombotic disease, which may be triggered by tissue factor [11], is probably important as a cause of morbidity and mortality; gangrene of the legs and disseminated intravascular coagulopathy (DIC) have both been reported [12,13]. Clinically, the skin lesions are polymorphous, including urticarial, morbilliform, maculopapular, erythema-multiforme-like patterns, and less commonly aseptic pustules on knees or buttocks, or a scarlatina-like erythroderma. Hands and feet become swollen, with palmoplantar erythema and subsequent desquamation.

Treatment is with intravenous immunoglobulin (IVIG) and aspirin, which reduce fever and development of aneurysms. There is conflicting evidence regarding the benefits of additionally using pulsed corticosteroid therapy. Other cardiac medications or surgery may be required; formal high-dose anticoagulation is needed for those with large coronary aneurysms. In those in whom IVIG fails (based on echocardiological assessment for aneurysms), re-treatment may be tried, plasma exchange may be successful, and infliximab has also been used. Diagnosis and treatment, with an emphasis on long-term treatment and cardiac disease, have been documented in detail by an expert consensus committee [14].

References

1 Kawasaki T. Kawasaki disease. In: Harper J, Oranje A, Prose N, eds. *Textbook of Pediatric Dermatology*, 2nd edn. Oxford: Blackwell Publishing, 2006: 1953–63.

2 Komatsu H, Fujisawa T. Kawasaki disease and infection. *Nippon Rinsho* 2008; **66**: 278–82.

3 Rowley AH, Baker SC, Orenstein JM, Shulman ST. Searching for the cause of Kawasaki disease—cytoplasmic inclusion bodies provide new insight. *Nat Rev Microbiol* 2008; **6**: 394–401.

4 Chun JK, Lee TJ, Choi KM *et al*. Elevated anti-alpha-enolase antibody levels in Kawasaki disease. *Scand J Rheumatol* 2008; **37**: 48–52.

5 Lau AC, Rosenberg H, Duong TT *et al*. Elastolytic matrix metalloproteinases and coronary outcome in children with Kawasaki disease. *Pediatr Res* 2007; **61**: 710–5.

6 Ikeda K, Ihara K, Yamaguchi K *et al*. Genetic analysis of MMP gene polymorphisms in patients with Kawasaki disease. *Pediatr Res* 2008; **63**: 182–5.

7 Honkanen VEA, McCrindle BW, Laxer RM *et al*. Clinical relevance of the risk factors for coronary artery inflammation in Kawasaki disease. *Pediatr Cardiol* 2003; **24**: 122–6.

8 Zhan W, Li Q, Zhao X-D *et al*. Clinical analysis of 942 cases of Kawasaki disease. *Zhonghua Er Ke Za Zhi* 2006; **44**: 324–8.

9 Sano T, Kurotobi K, Kouji M *et al*. Prediction of non-responsiveness to standard high-dose gamma-globulin therapy in patients with Kawasaki disease before starting initial treatment. *Eur J Pediatr* 2007; **166**: 131–7.

10 Kuo-Ho C, Yang KD, Liang CD *et al*. The relationship of eosinophilia to intravenous immunoglobulin treatment failure in Kawasaki disease. *Pediatr Allergy Immunol* 2007; **18**: 354–9.

11 Pucci A, Martino S, Celeste A *et al*. Angiogenesis, tumor necrosis factor-alpha and procoagulant factors in coronary artery giant aneurysm of a fatal infantile Kawasaki disease. *Cardiovasc Pathol* 2008; **17**: 186–9.

12 Dogan OF, Kara A, Devrim I *et al*. Peripheral gangrene associated with Kawasaki disease and successful management using prostacycline analogue: a case report. *Heart Surg Forum* 2007; **10**: E70–2.

13 Parvathy VK, Manuel AD, Criton S, Rajesh G. Kawasaki disease with DIC as a complication. *Indian J Pediatr* 2007; **74**: 1049.

14 Newburger JW, Takahashi M, Gerber MA *et al*. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the committee on rheumatic fever, endocarditis, and Kawasaki disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Pediatr* 2004; **114**: 1708–33.

Cerebral vasculitis and mimics

Some of the primary vasculitides discussed earlier have cerebral vasculitis as a possible component. There are also various infections, tumours, autoimmune disorders (such as antiphospholipid syndrome), collagen vascular disorders and other systemic diseases (such as sarcoidosis) that may combine neurological and cutaneous lesions and for which vasculitis might be considered in the differential diagnosis. Hypercoagulable states, sickle cell disease, thrombi (e.g. myxoma), Sneddon's syndrome (Chapter 49) and Fabry disease (Chapter 59) may all have both central nervous system and cutaneous features. Although vasculitides with predominantly cerebral features will not present to dermatologists, a few disorders warrant specific mention in the differential diagnosis of cerebral vasculitis as they may have skin manifestations that might suggest a vasculitis, thrombotic or microvascular occlusive process.

Intravascular lymphoma (intravascular lymphomatosis, angiotropic lymphoma, malignant angioendotheliomatosis) is caused by proliferation of clonal lymphocytes (usually B cells) within small vessels, and most commonly affects the central nervous system (CNS) and the skin. Cerebral vasculitis is often in the differential diagnosis of CNS involvement, both clinically and radiologically, and some of the cerebral pathology is due to thrombosis. Skin lesions occur in 40%, and may be the only site affected in 25%; they include localized or generalized telangiectasia, and tender indurated dermal or subcutaneous plaques or nodules with a blue to red colour, mainly on the lower legs, with associated painful swelling. The physical signs may mimic erythema nodosum, thrombophlebitis, adult Still's disease or cellulitis [1,2]. Gangrene of the lower extremities has been reported, and a vasculitis-like

illness with dementia [3]. One case has been reported with systemic lupus erythematosus (SLE) [4]; however, significantly raised serum ANA levels may be found in the absence of other features of SLE [3,5,6], erroneously suggesting a possible diagnosis of connective tissue disease-related vasculitis.

CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is a rare disorder that often presents as a form of dementia. It is due to a mutation in *NOTCH3* on chromosome 19 and is characterized histologically by granular osmiophilic material in the media of arterioles and small arteries, although this also occurs in non-muscular vessels including veins and capillaries [7]. Although the skin is not usually involved clinically, it is at a microscopic level, vessel walls being thickened by PAS-positive material. Additionally, haemorrhagic macular lesions with strong positive direct immunofluorescence for immunoglobulins, complement and fibrin, have been reported in CADASIL [8]. The neurological presentations include transient ischaemic attacks, which, if occurring in combination with haemorrhagic skin lesions, would mean that embolic or vasculitic processes might easily be suspected. Electron microscopy or NOTCH3 immunostaining [9] of skin biopsies may be useful, but gene analysis is more precise.

Leukoencephalopathies [10]. Two such disorders have particular relevance to dermatologists. *Progressive multifocal leukoencephalopathy* is caused by reactivation of the JC polyoma virus. It is particularly linked with systemic lupus erythematosus (SLE) and other collagen vascular diseases or vasculitides, even in patients on mild immunosuppressive regimens, suggesting that immune dysregulation may play a part in viral reactivation. It should be considered if cerebral symptoms are thought to be due to the underlying connective tissue disorder but fail to respond to increased immunosuppression; the importance is that it is progressive and usually fatal, and immunosuppressive treatment should be discontinued rather than increased. *Reversible posterior leukoencephalopathy syndrome* has also been associated with immunosuppressive therapy, usually more intensive treatment of renal disease or accelerated hypertension in SLE or Wegener's granulomatosis.

In tertiary referral practice, cerebral vasculitis occurs as a primary disorder (about 10% of cases), or is part of PAN (15%), MPA (10%), adult HSP (10–15%), WG (15–20%), SLE (15%) or cutaneous vasculitis (4%) [11]. The course and outcome of primary angiitis of the central nervous system (PACNS) appears to be related to the size of vessel involved, small-vessel disease being responsive to immunosuppression but having a relapsing recurrent course with severe brain injury, whereas medium-vessel disease tends to occur as isolated episodes with few relapses after treatment is discontinued. Therapy is recommended for at least 5 years for those with small-vessel disease, which may represent a limited form of PAN [11].

References

1 Röglin J, Böer A. Skin manifestations of intravascular lymphoma mimic inflammatory diseases of the skin. *Br J Dermatol* 2007; **157**: 16–25.

2 Kiyohara T, Kumakiri M, Kobayashi H *et al*. A case of intravascular large B-cell lymphoma mimicking erythema nodosum: the importance of multiple skin biopsies. *J Cutan Pathol* 2000; **27**: 413–8.

3 Demirer T, Dail DH, Aboulafia DM. Four varied cases of intravascular lymphomatosis and a literature review. *Cancer* 1994; **73**: 1338–45.

4 Sánchez CD, Callejas RJL, Vilanova MA *et al*. Intravascular lymphoma in a patient with systemic lupus erythematosus: a case report. *Lupus* 2007; **16**: 525–8.

5 Carter DK, Batts KP, de Groen PC, Kurtin PJ. Angiotropic large cell lymphoma (intravascular lymphomatosis) occurring after follicular small cleaved cell lymphoma. *Mayo Clin Proc* 1996; **71**: 869–73.

6 Scully RE, Mark EJ, McNeely WF, Ebeling SH. Case records of the Massachusetts General Hospital. Case 30–1996. *N Engl J Med* 1996; **335**: 952–9.

7 Rafalowska J, Fidzianska A, Dziewulska D *et al*. CADASIL or CADVaSIL? *Neuropathology* 2004; **24**: 16–20.

8 Ratzinger G, Ramsmayr G, Romani N, Zelger B. CADaSIL—an unusual manifestation with prominent cutaneous involvement. *Br J Dermatol* 2005; **152**: 346–9.

9 Lesnik-Oberstein SAJ, van Duinen SG, van den Boom R *et al*. Evaluation of diagnostic NOTCH3 immunostaining in CADASIL. *Acta Neuropathol (Berlin)* 2003; **106**: 107–11.

10 Molloy ES, Langford CA. Vasculitis mimics. *Curr Opin Rheumatol* 2008; **20**: 29–34.

11 MacLaren K, Gillespie J, Shestha S *et al*. Primary angiitis of the central nervous system: emerging variants. *QJM* 2005; **98**: 643–54.

Lymphocytic vasculitis

Lymphocytic vasculitis does not neatly fit into classifications of vasculitis, except perhaps those based mainly on histopathological features [1–4]. Suggested classifications [3] have never really crossed from pathological to clinical practice, even though some skin disorders (e.g. graft-versus-host disease, Chapter 62) are good examples of lymphocytic vascular damage. To aid understanding of this area, the optimum terminology for lymphocytic vasculitis may need to be slightly different from that of leukocytoclastic vasculitides; for example, the use of terms such as lymphocytic endovasculitis, angiodestructive lymphocytic vasculitis, lichenoid lymphocytic vasculitis, lymphocytic granulomatous vasculitis and lichenoid dermatitis with granulomatous lymphocytic vasculitis, has been proposed [1,4].

It has been suggested that clinicians may try to adapt lymphocytic vasculitis into their working concept of neutrophilic vasculitis and its causes, possibly to the detriment of understanding of lymphocytic vasculitis. This perhaps occurs in part because many of the disorders already discussed may have a lymphocyte-predominant infiltrate at some point in their evolution (typically in more chronic lesions, thereby detracting from the possibility of acute lymphocytic vasculitis), partly because karyorrhexis (nuclear fragmentation) is more associated with polymorphonuclear cells (leukocytoclasis) than with lymphocytes, and also because other identifying features of vasculitis, such as fibrin deposition, are less constant in lymphocytic disease. Probably, some lymphocytic 'vasculopathies' actually represent lymphocytic vasculitis. Additionally, for the clinician, a histopathology report of a lymphocytic vasculitis often indicates that finding a cause will be difficult and that treatment may be difficult, even though lymphocytic vasculitis confined to the skin is often more indolent than its leukocytoclastic counterpart. An additional issue that makes lymphocytic vasculitis more difficult to understand is that, whereas neutrophils in vessel walls may be innocent (undergoing diapedesis) or harmful, lymphocytes in the wall of a muscular vessel are abnormal [3]. Fibrin deposition does occur, as with leukocytoclastic vasculitis, but in many respects the histopathological techniques necessary to understand lymphocytic vasculitis are less advanced than for leukocytoclastic disease. The benefits

of anti-TNF agents and of rituximab in vasculitides point to an important role of both T and B lymphocytes.

This section discusses some of the causes of vasculitis that are particularly associated with a lymphocyte-predominant (but not granulomatous) infiltrate. A histopathological classification (noting that different pathological patterns may coexist) can be summarized as [4]:

1 angiodestructive lymphocytic vasculitis—rare, usually seen in angiodestructive lymphomas or lymphomatoid granulomatosis, but occurs in some patterns of lupus erythematosus and in Behçet's disease
2 lichenoid lymphocytic vasculitis—the most common pattern, which may occur in viral infections, drug reactions, erythema multiforme, lupus erythematosus, graft-versus-host disease, pityriasis lichenoides, lymphomatoid papulosis, lichenoid mycosis fungoides and Degos' disease; a granulomatous component may also occur in some cases of lichenoid and granulomatous mycosis fungoides [5], as well as in mycobacterial infection and in patients with associated hepatobiliary disease [6]
3 lymphocytic endovasculitis—this affects medium size vessels causing intimal hyperplasia and vessel wall mucinosis, or causes segmental hyalinization of smaller vessels with thrombosis; examples include chronic graft-versus-host disease, scleroderma, lupus erythematosus profundus, some livedoid vasculopathy and Degos' disease.

A clinically orientated summary, based on aetiology, is suggested in Table 50.11; disorders discussed elsewhere in this section are cross-referenced from the table.

Leukocytoclastic vasculitis of many types may, in older lesions, have lymphocyte predominance. Examples include GF (in which the mononuclear infiltrate may appear pseudolymphomatous in late lesions, although plasma cells are also present as well as angiocentric fibrosis [1]), EED (although the infiltrate of older lesions also usually contains lipid-laden histiocytes and plasma cells, and exhibits fibrosis), C-PAN (histiocytes also present) and GCA (mixed infiltrate). In *urticarial vasculitis*, a recent study has suggested that the majority of cases have a lymphocyte-predominant infiltrate with an admixture of eosinophils, and that a neutrophilic infiltrate with leukocytoclasis is present in the minority [7], although in the past a leukocytoclastic vasculitis has usually been described; this issue is discussed on p. 50.22. *Macular arteritis* is discussed below (p. 50.51); its infiltrate is typically lymphocytic.

Collagen vascular disorders such as *systemic lupus erythematosus* (SLE), *rheumatoid disease*, *dermatomyositis* and *sclerodermas* may exhibit a type II immune response leading to either a pauci-inflammatory thrombogenic vasculopathy and/or a lymphocytic vasculitis [1], although SLE and rheumatoid disease in particular can also be associated with neutrophilic leukocytoclastic vasculitis. In rheumatoid disease, this may vary from superficial neutrophilic lesions (occasionally pustular or Sweet's syndrome-like) to palisaded neutrophilic granulomatous dermatitis (discussed below, p. 50.52). SLE is associated predominantly with thrombotic infarction, but a lymphocytic vasculitis may affect any organ; in the skin it is often pan-dermal rather than the more superficial leukocytoclastic pattern. Numerous skin lesions are associated with rheumatoid disease (Chapter 51), including various forms of vasculitis, but a thrombotic and lymphocytic vasculitis may affect vessels of all sizes. Less commonly, an eosinophilic vasculitis may also occur in collagen vascular diseases [8]. Vasculitis occurring with *relapsing polychondritis* is usually leukocytoclastic but in a small proportion of cases it may be lymphocytic. The vasculitis

Table 50.11 An aetiological classification of lymphocytic vasculitis*.

Type of process	Examples
Inherited	X-linked lymphoproliferative syndrome Autosomal dominant cutaneous small vessel lymphocytic vasculitis
Collagen vascular diseases	Systemic lupus erythematosus Rheumatoid disease Sclerodermas Dermatomyositis Sjögren's syndrome
Other autoimmune conditions	Lichen sclerosus Diabetic mastopathy
Vasculitides, vasculopathies and microvascular occlusion disorders	Older lesions of several leukocytoclastic vasculitides (see text) Urticarial vasculitis (some cases) (p. 50.21) Polyarteritis nodosa (classic and cutaneous types) Nodular vasculitis Behçet's disease (some lesions) (p. 50.56) Pyoderma gangrenosum (some cases) Degos' disease and Sneddon's syndrome (Chapter 49) Buerger's disease and Mondor's disease Macular arteritis (p. 50.51) Lymphocytic thrombophilic arteritis (p. 50.51) Pityriasis lichenoides et varioliformis acuta (p. 50.50) IgA-associated lymphocytic vasculitis Pigmented purpuric dermatosis (some) Kawasaki disease
Infections	Viral, especially: Epstein-Barr virus varicella-zoster virus (may also be granulomatous) cytomegalovirus Rickettsial
Drugs and vaccinations	Anti-TNF monoclonals Interferon Bortezomib Other systemic drugs, various Topical NSAIDs Imiquimod Various vaccines
Malignancy and paraneoplastic	Chronic lymphocytic leukaemia Lymphomas (especially angiocentric T-cell lymphomas) Myeloproliferative disorders and leukaemia (some) Paraneoplastic vasculitis (some)
Miscellaneous	Perniosis Graft-versus-host disease Some arthropod bites

* Note that other patterns of vasculitis, or thrombotic vasculopathy, may also occur in many of the disorders listed.

that may occur in *Sjögren's syndrome* is immune complex mediated, due to increased immunoglobulin production as a result of B-cell hyperreactivity, and is almost always neutrophilic.

Lupus erythematosus panniculitis may have features of lymphocytic vasculitis in a third of cases [9]; this, combined with the demographics (usually young females), site (usually upper arm or trunk), hyalinization of fat [4] and deposition of mucin in many cases, help to distinguish it from other causes of panniculitis. Similarly, scleroderma profunda is associated with a lymphocytic pattern of vasculitis [4,10].

Behçet's disease is discussed in detail later (p. 50.56). Numerous patterns of vascular injury occur including neutrophilic infiltrates with or without vasculitis, lymphocytic vasculitis, thrombotic lesions which may cause secondary vascular injury, histiocytic panniculitis (erythema nodosum-like lesions), and others [1,11]. Lymphocytic vasculitis is common in the erythema nodosum-like lesions [1,12,13], occurs in acral papular lesions, and is even present in nearly 30% of pustular lesions [14]. Lymphocytic vasculitis has also occasionally been reported in some cases of *pyoderma gangrenosum* [15,16], although leukocytoclastic vasculitis is more common in those cases that have a vasculitic component.

Viral and occasionally other infections are an important cause of lymphocytic vasculitis. Those most commonly implicated are Epstein–Barr virus (EBV), varicella-zoster virus and cytomegalovirus [17–21]. These viruses all have an affinity for endothelial cells, and can all generate clonal T-cell expansion, although the relationship between cutaneous and peripheral T-cell expansion does not appear to be straightforward [16]. EBV may also play a role in the lymphocytic vasculitis of X-linked lymphoproliferative disorder (discussed below). In some cases, viral inclusion bodies are seen in endothelial cells, but in others there is no PCR evidence of viral DNA in the infiltrating cells, so the precise mechanisms of the lymphocytic vasculitis are not fully explained. A lymphocytic vasculitis and perineuritis was documented in a case of parvovirus B19 infection [22]. Rickettsiae also infect endothelial cells and may cause lymphocytic vasculitis [2], and lymphocytic vasculitis has also been reported in dengue fever.

Drugs of many types may cause vasculitis of different types (see p. 50.17). Amongst the most important to recognize is the lymphocytic vasculitis that occurs due to *anti-TNF agents* [23,24]. This may be diagnostically difficult if the drugs are being used in patients with a vasculitis-prone disorder (such as rheumatoid disease), or indeed to treat vasculitis; notable features are that the vasculitis due to these drugs may be aggravated by a change to a different agent, and may relapse at intervals for several years after exposure [24]. Another new drug that can cause a cutaneous lymphocytic vasculitis is *bortezomib*, a proteosome inhibitor used in treatment of non-Hodgkin's lymphoma; patients who develop vasculitis also appear to have a better response to treatment [25]. Several drug causes of lichenoid and granulomatous dermatitis are listed in [6]; in some cases, granulomatous lymphocytic vasculitis was documented.

Topical drugs may also be associated with vasculitis; cases due to non-steroidal anti-inflammatory drugs may have a leukocytoclastic or a lymphocytic vasculitis [26], and lymphocytic vasculitis has been reported due to imiquimod [27]. Vaccination reactions may also cause lymphocytic vasculitis. This has been reported with anthrax vaccine [28] and with tetanus toxoid, the latter case progressing to membranous fat necrosis [29].

Vasculitis mimics such as Degos' disease (a form of microvascular occlusion; Chapter 49) [4] and pityriasis lichenoides may exhibit an element of lymphocytic vasculitis (in the latter case, in its pityriasis lichenoides et varioliformis acuta form; p. 50.50) [4]. Pigmented purpuric dermatoses typically have a mild capillaritis (Chapter 49) but in some instances a lymphocytic vasculitis has been suggested; one possible variant which clinically resembled a pigmented purpuric dermatosis was documented as *IgA-associated lymphocytic vasculitis* [30]. In the cases reported, preceding diseases included HSP, undifferentiated connective tissue disease (known to be associated with lymphocytic vasculitis [31]), lupus erythematosus profundus (see above), Degos' disease, Buerger's disease and viral infection. An immune complex pathogenesis was proposed.

Paraneoplastic vasculitis may sometimes cause a vasculitis of lymphocytic type. The most frequent is that associated with chronic lymphocytic leukaemia (CLL) [32,33] although other lymphomas, hairy cell leukaemia and myeloproliferative disorders may all be associated with a lymphocytic pattern of vasculitis. Rarely, CLL has been associated with an ANCA-positive systemic vasculitis.

Lichen sclerosus (LS; Chapters 51 and 71) is generally viewed as an autoimmune condition with a lymphocytic lichenoid infiltrate histologically. However, a large study of both vulval and penile LS biopsies found that both a perivascular lymphocytic infiltrate without vascular damage and a frank lymphocytic vasculitis were common; the latter had a concentric pattern around vascular adventitiae mainly in penile LS, and subendothelial infiltration with occasional fibrin deposition which was most common in vulval LS [34]. Larger muscular vessel wall infiltration was also documented in some cases, and a granulomatous component in some cases (including one patient with LS and hepatitis C, although the changes in this patient were superficial and lichenoid and not documented as prominently vasculitic [6]).

Diabetic mastopathy [35] is a rare condition but could present to dermatologists. It occurs mostly in type I diabetes, and presents as a unilateral (about 75%) or bilateral (25%) discrete mass or diffuse nodularity, predominantly of the subareolar region. Histologically there is a lymphocytic ductitis and lobulitis, with vasculitis in some cases. Recurrence, or involvement of the contralateral breast, occurs in a third of cases. The specificity of this disorder is uncertain as it also occurs in type 2 diabetes, occasionally in non-diabetic subjects, and in males.

Inherited lymphocytic vasculitis is rare [36,37]. In X-linked lymphoproliferative syndrome, the cause has been felt to be an abnormal response to EBV infection; however, a recent study failed to demonstrate EBV genomic sequences in lesions, so this pathogenetic mechanism is uncertain.

References

1 Crowson AN, Mihm MC, Magro CM. Cutaneous vasculitis: a review. *J Cutan Pathol* 2003; **30**: 161–73.

2 Carlson JA, Chen K-R. Cutaneous vasculitis update: neutrophilic muscular vessel and eosinophilic, granulomatous, and lymphocytic vasculitis syndromes. *Am J Dermatopathol* 2007; **29**: 32–43.

3 Carlson JA, Mihm MC Jr, LeBoit PE. Cutaneous lymphocytic vasculitis: a definition, a review, and a proposed classification. *Semin Diagn Pathol* 1996; **13**: 72–90.
4 Kossard S. Defining lymphocytic vasculitis. *Australas J Dermatol* 2000; **41**: 149–55.
5 Shapiro PE, Pinto FJ. The histologic spectrum of mycosis fungoides / Sézary syndrome (cutaneous T-cell lymphoma): a review of 222 biopsies, including newly described patterns and the earliest pathologic changes. *Am J Surg Pathol* 1994; **18**: 645–67.
6 Magro CM, Crowson AN. Lichenoid and granulomatous dermatitis. *Int J Dermatol* 2000; **39**: 126–33.
7 Lee JSS, Loh TH, Seow SC, Tat SH. Prolonged urticaria with purpura: the spectrum of clinical and histopathologic features in a prospective series of 22 patients exhibiting the clinical features of urticarial vasculitis. *J Am Acad Dermatol* 2007; **56**: 994–1005.
8 Chen KR, Su WP, Pittelkow MR *et al*. Eosinophilic vasculitis in connective tissue disease. *J Am Acad Dermatol* 1996; **35**: 173–82.
9 Ng PPL, Tat SH, Tan T. Lupus erythematosus panniculitis: a clinicopathologic study. *Int J Dermatol* 2002; **41**: 488–90.
10 Balabanova M, Obreshkova E. Scleroderma profunda. Clinicopathological studies. *Adv Exp Med Biol* 1999; **455**: 105–9.
11 Chen K-R, Kawahara Y, Miyakawa S, Nishikawa T. Cutaneous vasculitis in Behçet's disease: a clinical and histopathologic study of 20 patients. *J Am Acad Dermatol* 1997; **36**: 689–96.
12 Kim B, LeBoit PE. Histopathologic features of erythema nodosum-like lesions in Behçet's disease: a comparison with erythema nodosum focusing on the role of vasculitis. *Am J Dermatopathol* 2000; **22**: 379–90.
13 Yi SW, Kim EH, Kang HY *et al*. Erythema nodosum: clinicopathologic correlations and their use in differential diagnosis. *Yonsei Med J* 2007; **48**: 601–8.
14 Ilknur T, Pabuççuogle U, Akin C *et al*. Histopathologic and direct immunofluorescence findings in the papulopustular lesions in Behçet's disease. *Eur J Dermatol* 2006; **16**: 146–50.
15 Mika RB, Riahi I, Fenniche S *et al*. Pyoderma gangrenosum: a report of 21 cases. *Int J Dermatol* 2002; **41**: 65–8.
16 von den Driesch P. Pyoderma gangrenosum: a report of 44 cases with follow-up. *Br J Dermatol* 1997; **137**: 1000–5.
17 Nakagawa A, Ito M, Saga S. Fatal T-cell proliferation in chronic active Epstein-Barr virus infection in childhood. *Am J Clin Pathol* 2002; **117**: 283–90.
18 Gallot G, Hamidou MA, Clémeceau B *et al*. T cell repertoire and Epstein-Barr virus-specific T cell response in chronic active Epstein-Barr virus infection: a case study. *Clin Immunol* 2006; **119**: 79–86.
19 Aram G, Rohwedder A, Nazeer T *et al*. Varicella-zoster-virus folliculitis promoted clonal cutaneous lymphoid hyperplasia. *Am J Dermatopathol* 2005; **27**: 411–7.
20 Uhoda I, Piérard-Franchimont C, Piérard G. Varicella-zoster virus vasculitis: a case of recurrent varicella without epidermal involvement. *Dermatology (Basel)* 2000; **200**: 173–5.
21 Golden MP, Hammer SM, Wanke CA, Albrecht MA. Cytomegalovirus vasculitis. Case reports and review of the literature. *Medicine (Baltimore)* 1994; **73**: 246–55.
22 Aquilar BM, Bassa VJ, Torné-Gutiérrez JI *et al*. Presence of perineuritis in a case of papular purpuric gloves and socks syndrome associated with mononeuritis multiplex attributable to B19 parvovirus. *J Am Acad Dermatol* 2006; **54**: 896–9.
23 Srivastava MD, Alexander F, Tuthill RJ. Immunology of cutaneous vasculitis associated with both etanercept and infliximab. *Scand J Immunol* 2005; **61**: 329–36.
24 Clemente RE. Demyelinating disease and cutaneous lymphocytic vasculitis after etanercept therapy in a patient with rheumatoid arthritis. *Scand J Rheumatol* 2007; **36**: 244–5.
25 Gerecitano J, Goy A, Wright J *et al*. Drug-induced cutaneous vasculitis in patients with non-Hodgkin lymphoma treated with the novel proteosome inhibitor bortezomib: a possible surrogate marker of response? *Br J Haematol* 2006; **134**: 391–8.
26 Delbarre M, Joly P, Balguerie X *et al*. Contact vasculitis caused by topical agents with non-steroidal anti-inflammatory agents or analgesics. *Ann Dermatol Venereol* 1997; **124**: 841–4.
27 Treviño J, Prieto VG, Hearne R *et al*. Atypical lymphocytic reaction with epidermotropism and lymphocytic vasculopathic reaction (lymphocytic vasculitis) after treatment with imiquimod. *J Am Acad Dermatol* 2006; **55** (Suppl.): S123–5.
28 Muñiz AE. Lymphocytic vasculitis associated with anthrax vaccine: case report and review of anthrax vaccination. *J Emerg Med* 2003; **25**: 271–6.
29 Ramdial PK, Chetty R. Vasculitis-induced membranous fat necrosis. *J Cutan Pathol* 1999; **26**: 405–10.
30 Crowson NA, Magro CM, Usmani A, McNutt NS. Immunoglobulin A-associated lymphocytic vasculopathy: a clinicopathologic study of eight patients. *J Cutan Pathol* 2002; **29**: 596–601.
31 Oh C-W, Lee S-H, Heo-Eun P. A case suggesting lymphocytic vasculitis as a presenting sign of early undifferentiated connective tissue disease. *Am J Dermatopathol* 2003; **25**: 423–7.
32 Robak E, Robak T. Skin lesions in chronic lymphocytic leukaemia. *Leuk Lymphoma* 2007; **48**: 855–65.
33 Cabuk M, Inanir I, Türkdogan P *et al*. Cyclic lymphocytic vasculitis associated with chronic lymphocytic leukaemia. *Leuk Lymphoma* 2004; **45**: 811–3.
34 Regauer S, Liegl B, Reich O, Beham-Schmid C. Vasculitis in lichen sclerosus: an under-recognized feature? *Histopathology* 2004; **45**: 237–44.
35 Ely KA, Tse G, Simpson JF *et al*. Diabetic mastopathy. A clinicopathologic review. *Am J Clin Pathol* 2000; **113**: 541–5.
36 Sellick GS, Coleman RJ, Webb EL *et al*. Dominantly inherited cutaneous small vessel lymphocytic vasculitis maps to chromosome 6q26-q27. *Hum Genet* 2005; **118**: 82–6.
37 Kanegane H, Ito Y, Ohshima K *et al*. X-linked lymphoproliferative syndrome presenting with systemic lymphocytic vasculitis. *Am J Hematol* 2005; **78**: 130–3.

Pityriasis lichenoides (Chapter 57)

Although an overlap with vasculitis and an immune complex-mediated pathogenesis has been suggested, there is increasing evidence that the three entities that make up pityriasis lichenoides represent a cytotoxic $CD8^+$ T cell proliferation that may occur in different settings [1,2], at least some cases having convincing evidence of an infective trigger [3,4]. The clinically milder and smaller lesions of pityriasis lichenoides chronica (PLC) are unlikely to be confused with a vasculitis, but the more severe and sometimes necrotic lesions of pityriasis lichenoides et varioliformis acuta (PLEVA, Mucha–Habermann disease) may resemble a vasculitis, pyoderma gangrenosum or lymphomatoid papulosis. Vasculitic features are prominent in the much rarer and aggressive form, febrile ulceronecrotic Mucha–Habermann disease (FUMHD) [3–8] (Fig. 50.32). In contrast with PLC and PLEVA, which occur mainly in childhood and which may coexist, FUMHD usually occurs in



Fig. 50.32 Febrile ulcerative Mucha–Habermann disease, a disorder with pronounced systemic features that may mimic a vasculitis. (Courtesy of Drs I. Helbling and V. Yates, Hope Hospital, Salford, UK).

males in the second or third decade of life [3], and, although it can evolve from PLC or PLEVA [4], it usually occurs in isolation without more recognizable, milder pityriasis lichenoides lesions.

The lesions of PLEVA are oedematous papules and nodules that undergo central vesiculation (sometimes forming larger bullae) and haemorrhagic necrosis, eventually healing with varioliform scarring. In FUMHD, there are abundant, large necrotic lesions. Additional clinical features that might suggest a vasculitis include constitutional symptoms such as fever, headache, malaise and arthralgia that may precede or accompany the onset of PLEVA; in FUHMD there is high fever, general malaise, weakness, myalgia, neuropsychiatric symptoms and lymphadenopathy, with non-specific serological markers of inflammation such as raised ESR and C-reactive protein, and a fulminating course that may even be fatal [8].

Histological features that may suggest vasculitis in inflammatory or necrotic lesions include extravasation of erythrocytes and endothelial proliferation, although in PLEVA the infiltrate (comprised mainly of CD8 lymphocytes) may be deep, dense and wedge-shaped rather than predominantly perivascular. Immunofluorescence studies have variably demonstrated IgM, C3 or fibrin in vessel walls of fresh (usually purpuric) lesions, or at the dermoepidermal junction, and some studies have documented circulating immune complexes, all features that might be consistent with an immune complex-mediated vasculitic pathogenesis [3]. Indeed, in FUMHD there may be marked fibrinoid necrosis of deep vessels with luminal thrombi, partial necrosis of follicles and complete necrosis of eccrine glands [5], which may not be histologically distinguishable from other forms of acute necrosis of the skin.

Treatment options in aggressive PLEVA or FUMHD include systemic corticosteroids, methotrexate, dapsone, ciclosporin and intravenous immunoglobulin. Investigation for possible infection, with appropriate treatment, is also potentially important; serological evidence of associated herpes varicella-zoster [2] and cytomegalovirus [9] infections has been recorded in FUMHD.

References

1 Wenzel J, Gütgemann I, Distelmaier U *et al*. The role of cytotoxic skin-homing $CD8^+$ lymphocytes in cutaneous cytotoxic T-cell lymphoma and pityriasis lichenoides. *J Am Acad Dermatol* 2005; **53**: 422–7.

2 Helmbold P, Gaisbauer G, Fielder E *et al*. Self-limited variant of febrile ulceronecrotic Mucha–Habermann disease with polyclonal T-cell receptor rearrangement. *J Am Acad Dermatol* 2006; **54**: 1113–4.

3 Bowers S, Warshaw EM. Pityriasis lichenoides and its subtypes. *J Am Acad Dermatol* 2006; **55**: 557–72.

4 Khachemoune A, Blyumin ML. Pityriasis lichenoides. Pathophysiology, classification, and treatment. *Am J Clin Dermatol* 2007; **8**: 29–36.

5 Tsuji T, Kasamatsu M, Yokota M *et al*. Mucha–Habermann disease and its febrile ulceronecrotic variant. *Cutis* 1996; **58**: 123–31.

6 Degos R, Duperrat B, Daniel F. Le parapsoriasis ulcero-necrotique hyperthermique. *Ann Dermatol Syphiligr* 1966; **93**: 481–96.

7 De Cuyper C, Hindryckx P, Deroo N. Febrile ulceronecrotic pityriasis lichenoides et varioliformis acuta. *Dermatology* 1994; **189** (Suppl. 2): 50–3.

8 Puddu P, Cianchini G, Colonna L *et al*. Febrile ulceronecrotic Mucha–Habermann's disease with fatal outcome. *Int J Dermatol* 1997; **36**: 691–4.

9 Tsai KS, Hsieh HJ, Chow KC *et al*. Detection of cytomegalovirus infection in a patient with febrile ulceronecrotic Mucha–Habermann's disease. *Int J Dermatol* 2001; **40**: 694–8.

Macular arteritis [1–3]

This recently described disorder is of uncertain causation. The clinical presentation is development of multiple asymptomatic or mildly pruritic, hyperpigmented macules on the trunk or, most commonly, the limbs; the lesions may have slight induration and sometimes have a degree of linearity or reticulation. Histology shows a deeply situated perivascular lymphocytic infiltrate or lymphocytic vasculitis affecting small arteries, which may be in the subcutaneous fat. An admixture of plasma cells is present in some cases. Fibrinoid necrosis of the vascular adventitia may occur, with luminal narrowing and eventual obliteration, but the tunica elastica is intact. There is no leukocytoclasis, no granuloma formation and no haemosiderin or melanin incontinence to explain the pigmentation (which is presumed to be epidermal). Patients are systemically well, do not have renal involvement, have negative ANCA and usually have no other serological abnormality.

Although earlier descriptions distinguished this disorder from C-PAN because the primary lesion is a pigmented macule, and there is no associated livedo, no ulceration, no non-pigmented dermal nodules and no tenderness of lesions [1,2], a recent pathological evaluation of biopsies from a patient with lesions on the instep of one foot led to the suggestion that this might be a latent, non-nodule forming variant of C-PAN [3].

References

1 Fein H, Sheth AP, Mutasim DF. Cutaneous arteritis presenting with hyperpigmented macules: macular arteritis. *J Am Acad Dermatol* 2003; **49**: 519–22.

2 Matsuoka Y, Takai I, Noda M, Kubota Y. Macular arteritis in Japanese patients. *J Am Acad Dermatol* 2005; **52**: 364–6.

3 Al Daraji W, Gregory AN, Carlson JA. Macular arteritis: a latent form of cutaneous polyarteritis nodosa? *Am J Dermatopathol* 2008; **30**: 145–9.

Lymphocytic thrombophilic arteritis [1,2]

This is a very recently described, medium-size vessel arteritis, reported in five young women; all had gradually progressing patchy and reticulate pigmentation, subtle (more marked in one case) subcutaneous indurated areas, with livedo racemosa of the lower limbs [1]. Pain was a feature in one patient, and Raynaud's phenomenon in another. Histologically, there was a predominantly lymphocytic infiltrate in the muscular wall of small arteries of the deep dermis and superficial subcutis, with a ring of fibrin deposition concentrically situated at the periphery of all affected vascular lumina. Granulocytes were scanty or absent, and inflammation was tightly confined within the panniculus in the vicinity of affected vessels. Four of the patients had antiphospholipid antibodies, one also having factor V Leiden; three had positive antinuclear antibodies (but this was negative in two cases on retesting) and three had modestly elevated erythrocyte sedimentation rate. The combined features of lymphocytic vascular inflammation and thrombophilic endovasculitis suggested that the term lymphocytic thrombophilic arteritis was appropriate.

The nosology of this condition has been discussed by LeBoit [2], and it may represent the same condition as the macular arteritis described above. Clinically, polyarteritis nodosa is probably the most likely differential diagnosis, or collagen vascular diseases with livedo and antiphospholipid antibodies.

References
1 Lee JS-S, Kossard S, McGrath MA. Lymphocytic thrombophilic arteritis. A newly described medium-sized vessel arteritis of the skin. *Arch Dermatol* 2008; **144**: 1175–82.
2 LeBoit PE. The enigma of lymphocytic vasculitis. *Arch Dermatol* 2008; **144**: 1215–6.

Palisaded neutrophilic and granulomatous dermatitis [1–4]

Churg–Strauss granulomas were originally described by Churg and Strauss as a histological feature of skin lesions in allergic granulomatosis, later known as Churg–Strauss syndrome. Winkelmann and colleagues described similar lesions in Wegener's granulomatosis, rheumatoid disease and systemic lupus erythematosus, and further delineated the histological features of what they termed the *cutaneous extravascular necrotizing granuloma* [2]. These lesions combine: (1) an interstitial (and variably perivascular) granuloma annulare-like or necrotizing extravascular granulomatous process with basophilic degenerate collagen; (2) intense tissue neutrophilia, leukocytoclasis, small vessel leukocytoclastic vasculitis (in about 50%) and sometimes an admixture with eosinophils; (3) positive direct immunofluorescence for complement, fibrin and immunoglobulins in vessel walls; and (4) associated circulating immune complexes in some cases [1–4]. Similar lesions were subsequently described as *rheumatoid papules*, and have also been documented in Behçet's disease, Takayasu's aortitis and other vasculitides, connective tissue, autoimmune and inflammatory disorders (including inflammatory bowel disease). LeBoit's group suggested that these features could be grouped together as '*palisaded neutrophilic and granulomatous dermatitis of immune complex diseases*' [3]. Other terms that have been applied include *interstitial granulomatous dermatitis with plaques*, *linear rheumatoid nodule*, and *interstitial granulomatous dermatitis with cutaneous cords and arthritis* [1,5–7]. Although it has been suggested that *palisaded neutrophilic granulomatous dermatitis* (PNGD) and interstitial granulomatous dermatitis (IGD) are separate, it is increasingly generally accepted that these are part of a spectrum (at least when associated with a connective tissue or immune complex-mediated disease); drug-induced IGD should probably be distinguished.

Clinical features include: erythematous urticated plaques or papules; firm, violaceous or waxy plaques; skin-coloured or erythematous papular or nodular lesions, sometimes annular and sometimes with ulceration or crusting; tender subcutaneous nodules; and firm linear subcutaneous cords or bands. The most typical presentation is as smooth, asymptomatic or tender papules, nodules or plaques on the forearms and dorsal hands, or on the buttocks and lower legs. Later lesions are usually more centripetal; cord-like lesions may be flexural. Sangueza and colleagues demonstrated a spectrum of clinical disease; earlier lesions are more urticated, whereas older lesions comprise firmer nodules and bands [7]. This would be consistent with the suggestion that the lesions start as leukocytoclastic vasculitis but progress to form palisaded granulomas and dermal fibrosis [1].

Treatment options may be dictated in part by the background disease (most commonly rheumatoid arthritis, in 40%), and include corticosteroids (topical or oral), colchicine, hydroxychloroquine, dapsone, ciclosporin and cyclophosphamide. It is important to be aware that TNF-α inhibitors, increasingly used in treatment of rheumatoid disease, can cause IGD [8]; distinction between disease-associated and drug-induced lesions may be difficult other than by withdrawal of treatment.

Other conditions that may rarely produce a cutaneous granulomatous vasculitis are herpes virus infections (herpes simplex and herpes varicella-zoster) and hepatitis C virus infection [9].

References
1 Draft KS, Wiser EB, Elenitsas R. Dermatopathology update of newer manifestations of systemic disease. *Adv Dermatol* 2001; **21**: 101–32.
2 Finan MC, Winkelmann RK. The cutaneous extravascular necrotizing granuloma (Churg–Strauss granuloma) and systemic disease: a review of 27 cases. *Medicine* 1983; **62**: 142–58.
3 Chu P, Connolly MK, LeBoit PE. The histopathologic spectrum of palisaded neutrophilic and granulomatous dermatitis in patients with collagen vascular disease. *Arch Dermatol* 1994; **130**: 1278–83.
4 Magro CM, Crowson AN. The spectrum of cutaneous lesions in rheumatoid vasculitis: a clinical and pathological study of 43 patients. *J Cutan Pathol* 2003; **30**: 1–10.
5 Gottlieb GB, Duve RS, Ackerman AB. Interstitial granulomatous dermatitis with cutaneous cords and arthritis: linear subcutaneous bands in rheumatoid arthritis revisited. *Dermatopathol: Pract Concept* 1995; **1**: 3–6.
6 Tomasini C, Pippione M. Interstitial granulomatous dermatitis with plaques. *J Am Acad Dermatol* 2002; **46**: 892–9.
7 Sangueza OP, Caudell MD, Mengesha YM *et al*. Palisaded neutrophilic granulomatous dermatitis in rheumatoid arthritis. *J Am Acad Dermatol* 2002; **47**: 251–7.
8 Deng A, Harvey V, Sina B *et al*. Interstitial granulomatous dermatitis associated with use of tumor necrosis factor α inhibitors. *Arch Dermatol* 2006; **142**: 198–202.
9 Pagnoux C, Kluger N, Francès C, Guillevin L. Cutaneous granulomatous vasculitis and extravascular granulomas. *Expert Rev Dermatol* 2006; **1**: 315–26.

Vasculitis as a component of other systemic diseases

Vasculitis is a feature of many systemic diseases that are mainly discussed in other chapters; a representative list is given in Table 50.12. They include collagen vascular diseases (Chapter 51) and disorders such as sarcoidosis (Chapter 61) in which there may be either a large vessel granulomatous vasculitis or an immune complex-associated small vessel cutaneous vasculitis. *Necrotizing sarcoid granulomatosis* is a variant of nodular sarcoidosis that is in the differential diagnosis of Wegener's granulomatosis of the lung [1]; although it is unlikely to present to dermatologists, the occurrence of extrapulmonary lesions is common, and skin involvement has been reported [2].

Sjögren's syndrome is associated with purpuric lesions similar to those of Waldenström's hypergammaglobulinaemic purpura, and with vasculitis that often has an urticarial or urticated component and predominantly affects the lower limbs [3–5]. Pathologically, the vasculitis covers a wide spectrum; one study of 558 patients with Sjögren's syndrome documented 52 patients (51 being female) with vasculitis that was classified as urticarial in 11, cryoglobulinaemic in 14 and CSSV in the remainder. Of 38 patients biopsied, 36 had a leukocytoclastic vasculitis and two had a medium-size vessel necrotizing vasculitis [5]. Vasculitis in these patients had a statistically significant association with the presence of arthritis (occurring in 50%), peripheral neuropathy (31%), Raynaud's phenomenon (40%), renal involvement (10%), antinuclear antibodies (88%), anti-Ro/SSA antibodies (70%) and rheumatoid factor (78%) [5]. Cutaneous livedo, subacute cutaneous lupus erythematosus, erythema nodosum and cytopenias also occur; 10–20% have

Table 50.12 Some systemic diseases in which vasculitis may occur (excluding those in this chapter).

Type of disease	Examples
Collagen vascular and rheumatological diseases	Lupus erythematosus (including drug-induced) Rheumatoid disease Sjögren's disease Dermatomyositis Scleroderma/progressive systemic sclerosis Mixed connective tissue disease Relapsing polychondritis Still's disease Reiter's disease
Gastrointestinal	Inflammatory bowel disease Bowel bypass (see p. 50.87) Primary biliary cirrhosis Peritoneal fibrosis
Granulomatous	Sarcoidosis
Periodic fevers/ autoinflammatory syndromes	Familial Mediterranean fever Hyper-IgD syndrome PFAPA syndrome
Haematological and malignancy	Lymphomas Hairy cell leukaemia Other leukaemias and myeloproliferative disorders Myeloma Hypereosinophilic syndrome Autoerythrocyte sensitization syndrome Wiskott–Aldrich syndrome Solid organ-specific tumours (Chapter 62)
Miscellaneous	Goodpasture's syndrome Cystic fibrosis α_1-antitrypsin deficiency Kikuchi disease (necrotizing lymphadenitis)

PFAPA, periodic fever, aphthous stomatitis, pharyngitis, adenitis.

positive antiphospholipid antibodies or ANCA, but less than 10% of these have vasculitis [4]. High parotid scintigraphy scores and low complement C4 levels are both associated with vasculitis and are predictive that it is likely to occur [6]. Vasculitis, cryoglobulinaemia and hypocomplementaemia are all independently associated with risk of death [6]; 70% with Sjögren's syndrome and cutaneous vasculitis develop peripheral or central nervous system involvement, which is felt to be due to vasculopathy [3]. Hypocomplementaemia is associated with cryoglobulinaemia, systemic disease, lymphoma and death [7]. Less dramatic but of direct dermatological interest, dry skin is also a feature of Sjögren's syndrome; in one patient with cryoglobulinaemia, cutaneous vasculitis and generalized hypohidrosis, a skin biopsy showed dense peri-eccrine lymphocytic infiltration with glandular shrinkage [8], which was presumably distinct from the vasculitis process.

Cystic fibrosis is a cause of episodic vasculitis, especially in more severe cases; purpuric and vasculitis lesions may occur, most commonly on the lower limbs. Bullae and urticarial vasculitis have been reported, but the overall pattern in most cases suggests an immune complex-mediated leukocytoclastic vasculitis [9]. There is often associated arthralgia, and neurological and renal involvement occur. Immune complexes have been demonstrated in the circulation; skin biopsies show leukocytoclastic vasculitis, fibrin deposition and may have positive direct immunofluorescence for complement C3. The episodic nature (usually lasting about 2 weeks) and the link with respiratory symptoms suggests that the antigen in many cases may be from bacteria (or antibiotic treatments). However, cryoglobulins and positive rheumatoid factor have also been documented in some cases.

Hypereosinophilic syndrome (HES; Gleich syndrome; Chapter 62) is an uncommon entity, which may include more than one form of haematological malignancy [10]. In some instances, there is a clonal T-cell production of interleukin IL-5, a major controlling cytokine in production, release and differentiation of eosinophils. In other cases, there is clonal expansion of eosinophils with hepatosplenomegaly and thrombocytopenia; this condition appears to be due to a cytogenetic defect t(9;22)(q34;q11) in which there is chromosomal breakage and reciprocal exchange of chromosomal fragments that leads to formation of a fusion tyrosine kinase FIP1L1–PDGFRα. Various skin lesions have been reported in HES, including eosinophilic vasculitis with gangrene [11] and thrombotic damage with dense perivascular eosinophilic infiltrate but without vasculitis [12,13]. Although these cases were treated with steroids, newer treatments combined with identification of the causative abnormality may allow targeted therapy; imatinib mesylate, used mainly in treatment of chronic myelogenous leukaemia, targets the platelet-derived growth factor receptor (PDGFR) in the fusion tyrosine kinase of HES [14], described above, and mepolizumab, an anti-IL-5 monoclonal antibody, has also been used recently to treat HES [15].

Alpha$_1$-antitrypsin (AAT) deficiency is discussed in Chapter 46 in relation to panniculitis. It may also be associated with systemic necrotizing vasculitis; in a series of eight patients, six had an MPA pattern of vasculitis, one had WG and one had HSP [16]. These authors reviewed additional cases; all had cutaneous vasculitis and either renal or joint involvement, and two-thirds died (mainly due to renal failure).

Autoinflammatory diseases (including the disorders previously termed hereditary fever syndromes or periodic fevers, such as *familial Mediterranean fever* (FMF), *hyperimmunoglobulinaemia D with periodic fever syndrome* and others), are also a potential cause of vasculitis, as well as causing multiple other symptoms (see also Chapter 62). The evolution of understanding of this group of disorders, which also includes cryopyrin-associated periodic syndromes (CAPS), tumour necrosis factor receptor-associated periodic syndrome (TRAPS), PAPA (pyogenic arthritis, pyoderma gangrenosum and acne), Schnitzler syndrome (Chapter 22) and CINCA syndrome (chronic infantile neurologic, cutaneous, articular syndrome; also termed neonatal-onset multisystem inflammatory disease, NOMID), is summarized in recent reviews [17–19]. It is important to consider FMF as a cause of vasculitis in children with apparent HSP in areas where FMF is prevalent, as HSP is much more common in families with FMF compared with the general population [20]; diagnostic delay is common. Tests for faecal occult blood are often positive during acute attacks of FMF. Other vasculitic features in FMF include purpura, subcutaneous nodules and associated PAN (which occurs in about 1% of patients);

in particular, perirenal haematoma is usually associated with PAN secondary to FMF [20]. Both circulating IgD immune complexes and IgD deposits on direct immunofluorescence of the skin have been identified in hyperimmunoglobulinaemia D syndrome [21], and HSP has been reported in this condition [22]. Lymphocytic vasculitis was reported in a child with *PFAPA syndrome* (Periodic Fever, Aphthous stomatitis, Pharyngitis, Adenitis) [23].

Paraneoplastic vasculitis (Chapter 62) is particularly associated with haematological malignancies; mechanisms include vasculitis related to paraproteins, cryoglobulins or to the presence of antinuclear antibodies. Hairy cell leukaemia appears to be especially associated with vasculitis, which may be of leukocytoclastic, lymphocytic or polyarteritis nodosa pattern.

Vasculitis may also be a feature of *Wiskott–Aldrich syndrome* (Chapter 15), usually leukocytoclastic small vessel vasculitis but aortitis and mesenteric or renal arteritis may occur [24].

Several forms of vasculitis have been associated with *relapsing polychondritis*, discussed on p. 50.91.

Autoerythrocyte sensitization syndrome (Chapters 49 and 64) has also been reported with cutaneous vasculitis [25].

References

1 Quaden C, Tillie-Leblond I, Delobbe A *et al*. Necrotising sarcoid granulomatosis: clinical, functional, endoscopical and radiographical evaluations. *Eur Respir J* 2005; **26**: 778–85.

2 Shirodaria CC, Nicholson AG, Hansell DM *et al*. Lesson of the month: Necrotising sarcoid granulomatosis with skin involvement. *Histopathology* 2003; **43**: 91–3.

3 Alexander E, Provost TT. Sjögren's syndrome. Association of cutaneous vasculitis with central nervous system disease. *Arch Dermatol* 1987; **123**: 801–10.

4 Ramos-Casals M, Brito-Zerón P, Font J. The overlap of Sjögren's syndrome with other systemic autoimmune diseases. *Semin Arthritis Rheum* 2007; **36**: 246–55.

5 Ramos-Casals M, Anaya JM, García-Carrasco M *et al*. Cutaneous vasculitis in primary Sjögren syndrome: classification and clinical significance of 52 patients. *Medicine (Baltimore)* 2004; **83**: 96–106.

6 Brito-Zerón P, Ramos-Casals M, Bove A *et al*. Predicting adverse outcomes in Sjögren's syndrome: identification of prognostic factors. *Rheumatology (Oxford)* 2007; **46**: 1359–62.

7 Ramos-Casals M, Brito-Zerón P, Yăgue J *et al*. Hypocomplementaemia as an immunological marker of morbidity and mortality in patients with primary Sjögren's syndrome. *Rheumatology (Oxford)* 2005; **44**: 89–94.

8 Sais G, Admella C, Fantova MJ, Montero JC. Lymphocytic autoimmune hidradenitis, cutaneous leukocytoclastic vasculitis and primary Sjögren's syndrome. *Br J Dermatol* 1998; **139**: 1073–6.

9 Bernstein ML, McCusker MM, Grant-Kels JM. Cutaneous manifestations of cystic fibrosis. *Pediatr Dermatol* 2008; **25**: 150–7.

10 Schwartz RS. The hypereosinophilic syndrome and the biology of cancer. *N Engl J Med* 2003; **348**: 1199–200.

11 Jang K-A, Lim Y-S, Choi J-H *et al*. Hypereosinophilic syndrome presenting as cutaneous necrotizing eosinophilic vasculitis and Raynaud's phenomenon complicated by digital gangrene. *Br J Dermatol* 2000; **143**: 641–4.

12 Hamada T, Kimura Y, Hayashi S *et al*. Hypereosinophilic syndrome with peripheral circulatory insufficiency and cutaneous microthrombi. *Arch Dermatol* 2007; **143**: 812–3.

13 Oppliger R, Gay-Crosier F, Dayer E, Hauser C. Digital necrosis in a patient with hypereosinophilic syndrome in the absence of cutaneous eosinophilic vasculitis. *Br J Dermatol* 2001; **144**: 1087–90.

14 Cools J, DeAngelo DJ, Gotlib J *et al*. A tyrosine kinase created by fusion of the PDGFRA and FIP1L1 genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. *N Engl J Med* 2003; **348**: 1201–14.

15 Rothenberg ME, Klion AD, Roufosse FE *et al*. Treatment of patients with the hypereosinophilic syndrome with mepolizumab. *N Engl J Med* 2008; **358**: 1215–28.

16 Mazodier P, Elzouki A-NY, Segelmark M, Eriksson S. Systemic necrotizing vasculitides in severe alpha$_1$-antitrypsin deficiency. *QJM* 1996; **89**: 599–611.

17 Rose CD, Martin TM. Caspase recruitment domain 15 mutations and rheumatic diseases. *Curr Opin Rheumatol* 2005; **17**: 579–85.

18 Shinkai K, Kilcline C, Connolly MK, Frieden IJ. The pyrin family of fever genes. Unmasking genetic determinants of autoinflammatory disease. *Arch Dermatol* 2005; **141**: 242–7.

19 Ryan JG, Goldbach-Mansky R. The spectrum of autoinflammatory diseases: recent bench to bedside observations. *Curr Opin Rheumatol* 2008; **20**: 66–75.

20 Hamuryudan V, Özdogun H, Yazici H. Other forms of vasculitis and pseudovasculitis. *Baillières Clin Rheumatol* 1997; **11**: 335–55.

21 Boom BW, Daha MR, Vermeer BJ, van der Meer JW. IgD immune complex vasculitis in a patient with hyperimmunoglobulinaemia D and periodic fever. *Arch Dermatol* 1990; **126**: 1621–4.

22 Wickiser J, Saulsbury FT. Henoch-Schönlein purpura in a child with hyperimmunoglobulinemia D and periodic fever syndrome. *Pediatr Dermatol* 2005; **22**: 138–41.

23 Lee WI, Yang MH, Lee KF *et al*. PFAPA syndrome (Periodic Fever, Aphthous stomatitis, Pharyngitis, Adenitis). *Clin Rheumatol* 1999; **18**: 207–13.

24 McCluggage WG, Armstrong DJ, Maxwell RJ *et al*. Systemic vasculitis and aneurysm formation in the Wiskott-Aldrich syndrome. *J Clin Pathol* 1999; **52**: 390–2.

25 Cansu D, Kasifoglu T, Pasaoglu O, Korkmaz C. Autoerythrocyte sensitization syndrome (Gardner-Diamond syndrome) associated with cutaneous vasculitis. *Joint Bone Spine* 2008; **75**: 721–4.

Microvascular occlusion disorders (Chapter 49)

It is important in the differential diagnosis of vasculitis to be aware of disorders that may present with livedo or infarcted lesions, such as *cryoglobulinaemic vasculitis*, *cholesterol embolization*, *cardiac myxoma emboli*, *Sneddon's disease* and *malignant atrophic papulosis* (*Degos' disease*). The major pathology in these is either initially occlusive, or is probably mediated by antiphospholipid antibodies (in Sneddon's syndrome), and so they are all discussed in the section on microvascular occlusion in Chapter 49. Other disorders associated with antiphospholipid antibodies are also discussed. In *calcific uraemic arteriolopathy* (*calciphylaxis)* (Chapter 49), the earliest event is vessel wall calcification [1], therefore this also is discussed in the section on microvascular occlusion rather than as a primarily vasculitic disorder. *Hyperoxaluria* may cause acrocyanosis, gangrene and livedo reticularis. *Hyperhomocysteinaemia*, typically in homozygotes for methyl tetrahydrofolate reductase mutation C677T, also predisposes to endothelial damage and vasculopathy. Vessel wall deposition disorders such as *amyloidosis*, or vessel leakage in *scurvy* or some *pigmented purpuric dermatoses*, may also mimic vasculitis, but histology demonstrates erythrocyte leakage without vasculitis. Thrombotic thrombocytopenic purpura, leukaemias and lymphomas may all occasionally mimic vasculitis.

Thromboangiitis obliterans (*Buerger's disease*) [2] is a disorder of small or medium-sized arteries (less commonly veins) in which there is an inflammatory non-suppurative panarteritis or panphlebitis with thrombosis. Antiendothelial cell antibodies may be significantly elevated in active disease and have a role in monitoring the disease [3]. This disorder is discussed in more detail in Chapter 47.

Other arterial thrombotic disorders that may mimic vasculitis include hypothenar hammer syndrome (Chapter 28), thrombosis resulting from polyvinyl chloride haemodialysis tubing [4], vessel wall invasion by tumour or organisms and sickle cell anaemia. Amyloid infiltration of the vessel wall may cause occlusion. Drugs such as ergot, amphetamines or epinephrine (adrenaline) typically

cause vasospasm but there may be histological evidence of vasculitis.

References

1 Au S, Crawford RI. Three-dimensional analysis of a calciphylaxis plaque: clues to pathogenesis. *J Am Acad Dermatol* 2002; **47**: 53–7.
2 Totemchokchyakarn K. Thromboangiitis obliterans (Buerger's disease). In: Ball GV, Bridges SL, eds. *Vasculitis*. Oxford: Oxford University Press, 2002: 460–6.
3 Eichhorn J, Sima D, Lindschau C, Turowski A. Antiendothelial cell antibodies in thromboangiitis obliterans. *Am J Med Sci* 1998; **315**: 17–23.
4 Bommer J, Ritz E, Andrassay K. Necrotizing dermatitis resulting from haemodialysis with polyvinylchloride tubing. *Ann Intern Med* 1979; **91**: 869–70.

Infections [1–4]

Mechanisms by which infections may cause vasculitis have been discussed on p. 50.5. Several infections are implicated in the pathogenesis of vasculitides, such as streptococci in HSP, hepatitis C in mixed cryoglobulinaemic vasculitis (an immune complex-mediated process p. 50.23) or hepatitis B in PAN. These have been discussed in relation to specific vasculitides earlier. This brief section summarizes some of the preceding discussion of infections, and notes some infections that mimic vasculitis. Lists of infections linked with vasculitis are provided in many texts and references [3,4]; a summary of the most important is provided in Table 50.13.

Table 50.13 Some infections that have been documented to cause vasculitis.

Type of infection	Examples
Bacteria	Streptococci Staphylococci *Neisseria* spp.: *N. meningitidis, N. gonorrhoea* Spirochaetes: *Borrelia burgdorferi, Treponema pallidum* *Yersinia* *Salmonella* *Helicobacter pylori* *Pseudomonas* spp. *Mycobacterium* spp.
Viruses	Herpesviruses: herpes simplex, varicella-zoster, cytomegalovirus Hepatitis viruses: A, B and C Epstein–Barr virus Immune deficiency: HIV, HTLV-1 Parvovirus B19 Influenza and parainfluenza Other common viruses: adenovirus, rubella Hantavirus
Fungi	*Candida* *Aspergillus*
Others	Rickettsia *Mycoplasma* spp. *Toxoplasma* *Pneumocystis carinii* (in HIV infection)
Vaccinations (see Table 50.8)	Influenza Hepatitis B, hepatitis A Rubella/measles/mumps–measles–rubella (MMR) BCG

Kawasaki disease is discussed in Chapter 30, but a brief summary of the vasculitis-related aspects is provided below.

Vasculitis in patients with subacute bacterial endocarditis or with gonococcal infection is mainly immune complex-mediated, although bacterial emboli can also occur; this may also be a feature of mycotic aneurysms, which potentially mimic medium vessel vasculitis. Other infections may cause a vasculitis by direct infection of endothelial cells, notably in rickettsial or cytomegalovirus (CMV) infection. CMV has a particular affinity for endothelial cells, especially those of allografts, and may also provoke thrombosis; infections in immunocompromised patients may respond to intravenous ganciclovir but there is still significant mortality [5].

Some apparent associations, such as that of *Staphylococcus aureus* with Wegener's granulomatosis (p. 50.39) are less well understood. Herpesvirus infections and HIV may also cause or mimic vasculitis. HIV has been associated with numerous patterns of vasculitis including leukocytoclastic and necrotizing vasculitides, HSP, EED, C-PAN, CSS and eosinophilic vasculitis, cerebral vasculitis and others; however, in some instances, HIV-associated vasculitis may be due to therapy (especially zidovudine and didanosine) or to secondary infections such as cytomegalovirus [4].

Vaccines have been implicated as causes of vasculitis. The two that are most frequently reported as causes of different vasculitis syndromes are influenza and hepatitis B. Influenza vaccine has been linked with CSVV, systemic leukocytoclastic vasculitis (LCV), and MPA; hepatitis B vaccine has been linked with development of CSVV, LCV with systemic involvement, Kawasaki disease, HSP, CSS and Takayasu's arteritis.

However, infections may also mimic vasculitis, particularly by embolization or by direct invasion of vessel walls. Zygomycosis is an important cause, occurring especially in immunosuppressed subjects; cutaneous infarction by zygomycosis has been described as having a targetoid 'bull's-eye' appearance [6] but may just cause a necrotic discoid lesion (Chapter 49). Other important examples are *Salmonella* spp. causing aortitis, embolic lesions of *S. aureus* infections, and *Nocardia* infections mimicking Wegener's granulomatosis [7]. Disseminated candidosis has been reported as resembling leukocytoclastic vasculitis [8]. Such infections may occur in subjects who are being treated with immunosuppressive agents, and may be mistaken for a disease flare with the consequent risk of immunosuppressive treatment being increased. Even serological tests may be misleading in such situations—ANCA positivity has been documented in endocarditis, septic shock and others [9,10]. It is important to consider infection in the differential diagnosis of vasculitis (especially if clinically atypical) or as a cause of unexpected disease flares, to ensure that any pustular lesions are sterile, and to carefully investigate fever in patients with vasculitis.

References

1 Somer T, Finegold SM. Vasculitides associated with infections, immunization, and antimicrobial drugs. *Clin Infect Dis* 1995; **20**: 1010–36.
2 Mandell BF, Calabrese LH. Infections and systemic vasculitis. *Curr Opin Rheumatol* 1998; **10**: 51–7.
3 Chatham WW. Miscellaneous forms of vasculitis. In: Ball GV, Bridges SL, eds. *Vasculitis*. Oxford: Oxford University Press, 2002: 513–32.

4 Del Rosso A, Generini S, Pignone A, Matucci-Cerinic M. Vasculitides secondary to systemic diseases. *Clin Dermatol* 1999; **17**: 533–47.
5 Golden MP, Hammer SM, Wanke CA, Albrecht MA. Cytomegalovirus vasculitis. Case reports and review of the literature. *Medicine (Baltimore)* 1994; **73**: 246–55.
6 Rubin AI, Grossman ME. Bull's-eye cutaneous infarct of zygomycosis: a bedside diagnosis confirmed by touch preparation. *J Am Acad Dermatol* 2004; **51**: 996–1001.
7 Gibb W, Williams A. Nocardiosis mimicking Wegener's granulomatosis. *Scand J Infect Dis* 1986; **18**: 583–5.
8 Glaich AS, Krathen RA, Smith MJ, Hsu S. Disseminated candidiasis mimicking leukocytoclastic vasculitis. *J Am Acad Dermatol* 2005; **53**: 544–6.
9 Sato A, Jorgensen C, Oksman F *et al*. Endocarditis accociated with ANCA. *Clin Exp Rheumatol* 1994; **12**: 203–4.
10 Mege JL, Escallier JC, Capo C *et al*. Anti-neutrophil cytoplasmic antibodies (ANCA) and infection. In: Gross WL, ed. *ANCA-Associated Vasculitides: Immunological and Clinical Aspects*. New York: Plenum Press, 1993: 353–6.

Behçet's disease

Synonym
- Adamantiades–Behçet's disease

Definition. Behçet's disease, named after the Turkish dermatologist who first described the condition, is a multisystem disease that is defined by the presence of oral aphthosis with at least two of the following: genital aphthae, synovitis, posterior uveitis, cutaneous pustular vasculitis or meningoencephalitis, in the absence of IBD or autoimmune diseases [1–3]. With respect to classification, it is something of an enigma; it is viewed by some as a neutrophilic dermatosis [4], or as a neutrophilic dermatosis that can be associated with leukocytoclastic vasculitis [5], but by others as a true neutrophilic [6,7] or lymphocytic [8] vasculitis. It is also associated with thrombotic arterial or venous disease [9], and has been described as a pauci-inflammatory thrombogenic vasculopathy. Indeed, it has been suggested that it is unique in being a primary vasculitis with predominant venous involvement [10]. However, it has also been reported to occur in association with other 'classical' neutrophilic dermatoses such as pyoderma gangrenosum and Sweet's syndrome. These apparently conflicting or overlapping features are discussed in subsequent sections, but all of the above processes occur in different lesion types and stages.

Because of these classification difficulties, we have specifically discussed this entity between the sections on vasculitis and neutrophilic dermatoses, the two main groups of disorders comprising this chapter. As a generalization, skin and mucous membrane lesions in Behçet's disease mainly represent a neutrophilic dermatosis, cerebral involvement also represents a vasculopathy rather than vasculitis, but other lesions are vasculitic or thrombotic.

It typically affects young adults, but can occur in children [11]. It is uncommon in northern Europe and the USA, but is common in Middle Eastern and Japanese (i.e. 'silk route') populations [12]. In Arab populations, males are affected about four times as often as females, but in many other populations the sex ratio is approximately equal.

Aetiology and pathogenesis. Although the exact cause of Behçet's disease is unknown, a genetic component of the disease is suggested by its association with HLA-B51 [2,13]. However, this only accounts for a minority of sibling risk, and at least 16 genetic loci have been linked with Behçet's disease [10]. The HLA-B51 association is less strong in populations with a lower frequency of Behçet's disease, where a link with HLA-C*15 and HLA-C*16 may be more apparent. More recent studies have also shown a predilection associated with various cytokine and inflammatory mediator alleles and polymorphisms, including polymorphisms in endothelial nitric oxide synthase (eNOS), in interleukin-10 (IL-10), IL-8, and CD28 genes, and presence of the antitumour necrosis factor-alpha (TNF-α) 1031C allele are all associated with Behçet's disease susceptibility [14]. Several of these have only been found in certain ethnic groups, for example Glu298Asp polymorphisms of eNOS in Turks.

At least during disease flares, there is a Th1-predominant immune reaction. Specific triggering of certain subsets of γδT cells has been documented [15,16], for example Vγ9Vδ2 T cells in the intraocular fluid of patients with uveitis. The cytokine IL-12, serum levels of which correlate with disease activity, not only promotes a Th1 response, but also causes proliferation of γδT cells, suggesting that this is important in pathogenesis.

The possibility that infections may stimulate an abnormal immune response in persons susceptible to Behçet's disease has some support; IL-12B heterozygosity is associated with susceptibility, and plays a part in Th1 antistreptococcal activity [14], and demonstration of altered expression and function of Toll-like receptor 6 on granulocytes and monocytes in Behçet's disease (lower than in controls at basal levels, but enhanced after stimulation with heat shock protein or streptococcal extracts) support a role for microorganisms in the pathogenesis [17]. Further, antibodies to heat shock protein 60 (a streptococcal protein) have been demonstrated, increased serum levels of HSP60 occur but do not seem to correlate with disease activity [18], and the 336–351 sequence of HSP60 induces uveitis in a rat model. Antibodies against *Saccharomyces cerevisiae*, also found in Crohn's disease, are significantly more common in patients with intestinal Behçet's disease (and in their relatives) compared with those without gastrointestinal involvement [14], but a causal relationship has not been established. Parvovirus B19 DNA was detected significantly more often in skin of 40 patients with Behçet's disease than in controls [19].

Altered expression of various adhesion molecules, such as VCAM-1, CD44, CD86, CD58 and CD54, as well as changes in various cytokines and apoptotic markers, has been demonstrated in the oral ulcers in Behçet's disease [20], but, although relevant to cell and matrix interactions at the site of lesions, has not elucidated the pathogenesis. Serum VEGF is elevated, and may be a risk factor for ocular disease [18]. Increased levels of IL-23 p19 subunit (measured by RNA expression) have been demonstrated in the erythema nodosum-like lesions of Behçet's disease [21], but its role is unclear. Acting via CXCR-1 and CXCR-2 receptors, IL-8 is a neutrophil chemoattractant whose serum levels have some correlation with Behçet's disease activity [16]. IL-8 also activates endothelium, creating a pro-thrombotic environment [16].

Homozygosity of the T allele of the methylenetetrahydrofolate reductase (MTHFR) gene is more common in Behçet's disease; it is associated with low thiolactonase activity and high homocysteine levels, creating a pro-thrombotic situation [22]. Increased

platelet activation has also been suggested as an explanation for the thrombotic component of the disease. Neutrophil chemotaxis, activation and production of reactive oxygen species is also a feature; recent studies have shown that a subset of T cells producing CXCL8 may be relevant in this and other neutrophilic dermatoses [23], and also that patients with active Behçet's disease (and those with Sweet's syndrome) have elevated levels of granulocyte colony-stimulating factor (GCSF), which suppresses neutrophil apoptosis [24].

Autoantibodies such as ANCA and anticardiolipin antibodies do not appear to have a pathogenic role in Behçet's disease. Although anticardiolipin/antiphospholipid antibodies have been described in up to 50% of cases, most studies suggest that they are not present, or only in a small proportion, and their presence does not appear to correlate with specific events or overall disease activity [25], although higher serum levels have been reported in patients with thromboses [18]. Other antibodies that have been demonstrated include antiribosomal phosphoprotein and antiphosphatidylserine antibodies; the latter have a role in apoptosis and may be implicated in the development of vasculitis [26]. Antiendothelial cell antibodies (AECA), as in many vasculitides, are found but are of uncertain relevance; a more specific role is suggested by the identification of IgM AECA directed against α-enolase in the vascular wall [27]. Further supporting the possibility that an immune response to microorganisms may be involved in the aetiopathogenesis of Behçet's disease, α-enolase-like molecules are found in the cell wall of streptococci and many fungi [16]. Thus several microorganisms, rather than one specific infection, might cause the same complex immune response, generating anti-α-enolase antibodies that can bind to endothelium, thereby increasing IL-8 production and activating neutrophils.

High prevalences of procoagulant mutations such as factor V Leiden (factor V gene mutation G1691A) [28] and prothrombin gene mutation G20210A [29] have been reported in patients with Behçet's disease in whom thrombotic events occur; each was found in a third of patients with Behçet's disease and thrombosis, compared with those without thrombosis in whom the expected background prevalence (each about 1–5%) is observed. In a study of 64 patients with Behçet's disease (32 with thrombosis and 32 without), over half of those with thrombosis had one or both mutations [29]. Other prothrombotic tendencies therefore seem to augment the thrombotic tendency in this disease.

References

1 Jorizzo JL, Hudson RD, Schmalstieg FC *et al*. Behçet's syndrome: immune regulation, circulating immune complexes, neutrophil migration, and colchicine therapy. *J Am Acad Dermatol* 1984; **10**: 205–14.
2 Jorizzo JL. Behçet's disease: an update based on the 1985 international conference in London. *Arch Dermatol* 1986; **122**: 556–8.
3 O'Duffy JD, Carney JA, Deodhar S. Behçet's disease: report of 10 cases, three with new manifestation. *Ann Intern Med* 1971; **75**: 561–70.
4 Callen JP. Neutrophilic dermatoses. *Dermatol Clin* 2002; **20**: 409–19.
5 Fiorentino D. Cutaneous vasculitis. *J Am Acad Dermatol* 2003; **48**: 311–40.
6 Sams HH, Sams WM. Cutaneous leukocytoclastic vasculitis. In: Ball GV, Bridges SL, eds. *Vasculitis*. Oxford: Oxford University Press, 2002: 467–75.
7 Carlson JA, Chen KR. Cutaneous vasculitis update: small vessel neutrophilic vasculitis syndromes. *Am J Dermatopathol* 2006; **28**: 486–506.
8 Gibson LE. Cutaneous vasculitis update. *Dermatol Clin* 2002; **19**: 603–15.
9 Fessler BJ. Thrombotic syndromes and autoimmune disease. *Rheum Dis Clin N Am* 1997; **23**: 461–79.
10 Melikoglu M, Kural-Seyahi E, Tascilar K, Yaziei I. The unique features of vasculitis in Behçet's syndrome. *Clin Rev Allerg Immunol* 2008; **35**: 40–6.
11 Amman AJ, Johnson A, Fyfe GA *et al*. Behçet's syndrome. *J Pediatr* 1985; **107**: 41–3.
12 James DG. Silk route disease. *Postgrad Med J* 1986; **62**: 151–3.
13 Baricordi OR, Sensi A, Pivetti-Pezzi P *et al*. Behçet's disease associated with HLA-B51 and DRw52 antigens in Italians. *Hum Immunol* 1986; **17**: 297–301.
14 Krause I, Weinberger A. Behçet's disease. *Curr Opin Rheumatol* 2008; **20**: 82–7.
15 Yurdakul S, Hamuryudan V, Yazici H. Behçet's disease. *Curr Opin Rheumatol* 2003; **16**: 38–42.
16 Kalayciyan A, Zouboulis CC. An update on Behçet's disease. *J Eur Acad Dermatol Venereol* 2007; **21**: 1–10.
17 Yavuz S, Elbir Y, Tulunay A *et al*. Differential expression of toll-like receptor 6 on granulocytes and monocytes in Behçet's disease etiopathogenesis. *Rheumatol Int* 2008; **28**: 401–6.
18 Shaker O, Ay El-Deen MA, El Haddidi H *et al*. The role of heat shock protein 60, vascular endothelial growth factor and antiphospholipid antibodies in Behçet disease. *Br J Dermatol* 2007; **156**: 32–7.
19 Baskan EB, Yilmaz E, Saricaoglu H *et al*. Detection of parvovirus B19 DNA in the lesional skin of patients with Behçet's disease. *Clin Exp Dermatol* 2007; **32**: 186–90.
20 Kose O, Stewart J, Waseem A *et al*. Expression of cytokeratins, adhesion and activation molecules in oral ulcers of Behçet's disease. *Clin Exp Dermatol* 2007; **33**: 62–9.
21 Lew W, Chang JY, Jung JY, Bang D. Increased expression of interleukin-23 p19 mRNA in erythema nodosum-like lesions of Behçet's disease. *Br J Dermatol* 2008; **158**: 505–11.
22 Koubaa N, Hammami S, Nakbi A *et al*. Relationship between thiolactonase activity and hyperhomocysteinaemia according to MTHFR gene polymorphism in Tunisian Behçet's disease patients. *Clin Chem Lab Med* 2008; **46**: 187–92.
23 Keller M, Spanou Z, Schaerli P *et al*. T cell-regulated neutrophilic inflammation in autoinflammatory disease. *J Immunol* 2005; **175**: 7678–86.
24 Kawakami T, Ohashi S, Kawa Y *et al*. Elevated serum granulocyte colony-stimulating factor levels in patients with active phase of Sweet syndrome and patients with active Behçet's disease. Implication in neutrophil apoptosis dysfunction. *Arch Dermatol* 2004; **140**: 570–4.
25 Fessler BJ. Thrombotic syndromes and autoimmune diseases. *Rheum Dis Clin N Am* 1997; **23**: 461–79.
26 Berlit P, Stueper B, Fink I *et al*. Behçet's disease is associated with increased concentrations of antibodies against phosphatidylserine and ribosomal phosphoproteins. *VASA* 2005; **34**: 176–80.
27 Lee KH, Chung HS, Kim HS *et al*. Human alpha-enolase from endothelial cells as a target antigen of the anti-endothelial cell antibody in Behçet's disease. *Arthritis Rheum* 2003; **48**: 2025–35.
28 Gül A, Özbek U, Öztürk C *et al*. Coagulation factor V gene mutation increases the risk of venous thrombosis in Behçet's disease. *Br J Rheumatol* 1996; **35**: 1178–80.
29 Gül A, Aslantas AB, Tekinay T *et al*. Procoagulant mutations and venous thrombosis in Behçet's disease. *Rheumatology (Oxford)* 1999; **38**: 1298–9.

Histopathology. As discussed above, the type of reaction (vasculitic or not) and infiltrate (neutrophilic, lymphocytic or pauci-inflammatory) viewed as most characteristic of Behçet's disease is controversial. Even the predominant size of vessels involved (a frequently applied method to classify vasculitides) varies between authors, some classifying Behçet's disease as a primary vasculitis affecting predominantly large vessels (but may also involve small and medium vessels) [1], and others viewing it as predominantly a disease of small and medium-sized vessels [2].

It is probably best viewed as a systemic vasculitis that can affect any vessel size, any organ, and in which individual lesions may have vasculopathic/vasculitic or thrombogenic aetiology, with variable cellular infiltrate in both type and degree [3,4]. As a general rule, larger vessel involvement tends to be thrombotic or aneurysmal [3]. The mucosal and some skin lesions often have

features of a neutrophilic vascular reaction rather than of frank vasculitis, although a leukocytoclastic vasculitis can occur [3–9]; later lesions are lymphocytic, and primary lymphocytic vasculitis occurs in erythema nodosum-like lesions (described below). Pustular lesions are sterile and, even though they may be inflammatory and appear to have clinical features of pustular vasculitis, histologically they may have a neutrophilic infiltrate and leukocytoclasis without vasculitis, resembling the lesions of Sweet's syndrome, bowel-associated dermatitis-arthritis syndrome or rheumatoid neutrophilic dermatosis. Erythema nodosum-like lesions usually contain at least focal lymphocytic or neutrophilic vasculitis, unlike erythema nodosum from other causes, and may have microabscesses, phlebitis or arteriolitis [10]. The tendency of erythema nodosum-like lesions to develop necrosis may reflect a component of thrombophlebitis, coexistence with small vessel vasculitis, or indicate that the panniculitis is occurring due to a medium-size vessel vasculitis; these lesions also tend to scar or heal with hyperpigmentation; neither ulceration, pigmentation nor scarring are typical of 'ordinary' erythema nodosum.

Using pathergy reactions, the initial inflammatory response consists of neutrophils, monocyte/macrophages and $CD11c^+$ dendritic cells followed by an exaggerated Th1 immune response [11].

A review of the pathological features of vasculitides described three main types of reaction in Behçet's disease [4], namely:

1 Vascular, including:
   (a) a lymphocytic or granulomatous vasculitis with or without thrombosis, necrosis and fibrinoid deposition
   (b) a pauci-cellular thrombogenic vasculopathy
   (c) a neutrophilic vascular reaction that may affect capillaries as well as arteries or veins of any size, and that includes a leukocytoclastic vasculitis and a Sweet's syndrome-like reaction

2 Extravascular with or without vasculopathy, including a mononuclear cell- or neutrophil-predominant inflammation of the dermis and/or panniculus, or a histiocytic panniculitis

3 A suppurative or mixed suppurative/granulomatous folliculitis comprising acneiform lesions

According to these authors [4], additional patterns include acral purpuric papulonodules characterized by a lymphocytic interface and perivascular reaction, and the oral or genital aphthae which have a central dense neutrophilic infiltrate with necrosis, but a dense lymphocytic infiltrate in the submucosa.

The acneiform lesions are debated; other authors have described pustules as non-follicular and representing a neutrophilic pustular vasculitis. Non-follicular papulopustular lesions are useful for diagnosis, as they usually have features of a leukocytoclastic vasculitis (sometimes a neutrophilic infiltrate without vasculitis, occasionally a lymphocytic vasculitis), often with positive direct immunofluorescence (especially IgM in vessels) [12].

References

1 Saleh A, Stone JA. Classification and diagnostic criteria in systemic vasculitis. *Clin Rheumatol* 2005; **19**: 209–21.

2 Carlson JA, Chen KR. Cutaneous vasculitis update: small vessel neutrophilic vasculitis syndromes. *Am J Dermatopathol* 2006; **28**: 486–506.

3 Melikoglu M, Kural-Seyahi E, Tascilar K, Yaziei I. The unique features of vasculitis in Behçet's syndrome. *Clin Rev Allerg Immunol* 2008; **35**: 40–6.

4 Crowson AN, Mihm MC, Magro CM. Cutaneous vasculitis: a review. *J Cutan Pathol* 2003; **30**: 161–73.

5 Jorizzo JL, Hudson RD, Schmalstieg FC *et al*. Behçet's syndrome: immune regulation, circulating immune complexes, neutrophil migration, and colchicine therapy. *J Am Acad Dermatol* 1984; **10**: 205–14.

6 Chajek T, Fainaru M. Behçet's disease: report of 41 cases and a review of the literature. *Medicine* 1975; **54**: 179–96.

7 Nazarro P. Cutaneous manifestations of Behçet's disease. In: Monacelli M, Nazzaro P, eds. *International Symposium on Behçet's Disease in Rome*. Basel: Karger, 1966: 15–41.

8 Jorizzo JL, Solomon AR, Cavallo T. Behçet's syndrome: immunopathologic and histopathologic assessment of pathergy lesions is useful in diagnosis and follow-up. *Arch Pathol Lab Med* 1985; **109**: 747–51.

9 Muller W, Lehner T. Quantitative electron microscopical analysis of leukocyte infiltration in oral ulcers of Behçet's syndrome. *Br J Dermatol* 1982; **106**: 535–44.

10 Kim B, LeBoit PE. Histopathologic features of erythema nodosum-like lesions in Behçet disease: a comparison with erythema nodosum focusing on the role of vasculitis. *Am J Dermatopathol* 2000; **22**: 379–90.

11 Melikoglu M, Uysal S, Kreuger JG *et al*. Characterization of the divergent wound-healing responses occurring in the pathergy reaction and normal healthy volunteers. *J Immunol* 2006; **177**: 6415–21.

12 Alpsoy E, Uzun S, Akman A *et al*. Histological and immunofluorescence findings of non-follicular papulopustular lesions in patients with Behçet's disease. *J Eur Acad Dermatol Venereol* 2003; **17**: 521–4.

Clinical features. The clinical course of Behçet's disease is highly variable, although patients typically have oral aphthae with any combination of genital aphthae, cutaneous pustular vasculitis, ocular lesions or arthritis. The International Study Group criteria for the diagnosis of Behçet's disease [1] are depicted in Table 50.14. Two large series of 387 and 661 patients provide a basis for giving an approximate frequency of the various findings [2,3], although it should be noted that both were from areas with a high frequency of Behçet's disease, and some features may have a different incidence in other parts of the world.

Oral and genital lesions (Figs 50.33 & 50.34). Oral ulceration is a defining criterion for Behçet's disease, and therefore is present in 100%, but is not a very sensitive feature for diagnosis as it is common in the general population. Genital ulcers, present in about 90% of subjects [2,3], are possibly slightly more common in

Table 50.14 International Study Group criteria for the diagnosis of Behçet's disease [1] (applicable only in the absence of other explanations for the clinical findings).

Recurrent oral ulceration	Minor aphthous, major aphthous, or herpetiform ulceration observed by physician or patient that recurred at least 3 times in one 12-month period
Plus two of the following criteria:	
Recurrent genital ulceration	Aphthous ulceration or scarring observed by physician or patient
Eye lesions	Anterior uveitis, posterior uveitis, or cells in vitreous on slit-lamp examination; *or* retinal vasculitis observed by ophthalmologist
Skin lesions	Erythema nodosum observed by physician or patient, pseudofolliculitis or papulopustular lesions; *or* acneiform nodules observed by physician in post-adolescent patients not receiving corticosteroid treatment
Positive pathergy test	Read by physician at 24–48 h



Fig. 50.33 Behçet's disease. This patient demonstrates oral aphthosis.



Fig. 50.34 Behçet's disease. An aphtha is present on the penis.



Fig. 50.35 Behçet's disease. Non-follicular pustules on the upper arm.

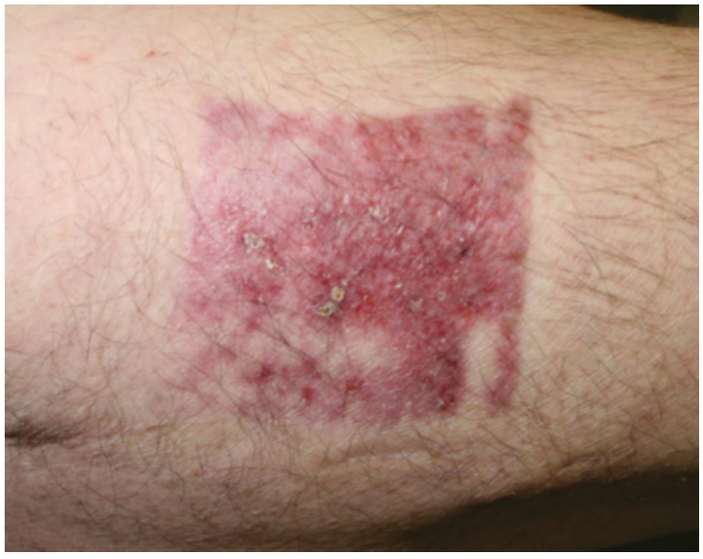


Fig. 50.36 Behçet's disease. An unusual manifestation—the patient had a skin graft site that had failed to heal after 9 months (pathergic pyoderma gangrenosum).

males than in females; they usually occur on the shaft of the penis or on the scrotum in males, and on the labia majora or minora in females. Residual scarring is common.

Skin lesions (Figs 50.35 & 50.36). Other than mucosal ulcers, skin lesions are the most common manifestation of Behçet's disease. Of the possible skin lesions, only pustular vasculitis (present in 55–83% of subjects, more often in males than in females [2,3]) and erythema nodosum-like nodules (44–62% of subjects, more common in females) should be used to satisfy diagnostic criteria when considering Behçet's disease. A wide range of additional cutaneous findings includes Sweet's syndrome-like and pyoderma gangrenosum-like lesions, abscesses, palpable purpura/leukocytoclastic vasculitis, acral purpuric papulonodules, and panniculitis [4–9].

Pathergy, the triggering of a significant inflammatory response by minor injuries such as venepuncture, is a feature of Behçet's disease that is sufficiently specific and frequent (occurring in about 40%, more often in males than females [3]) that it is considered to be a diagnostic criterion; however, it also occurs in several neutrophilic dermatoses, such as pyoderma gangrenosum. Several mechanisms may be involved, including HLA-B51-related hyperreactivity of neutrophils. It typically develops within 48 h, either after specific provocation by needle-prick [6] or following venepuncture or other venous access, and may evolve to form larger lesions inseparable from pyoderma gangrenosum [10].

Other organ systems. Uveitis (usually posterior or pan-uveitis) is the main ocular feature of Behçet's disease, occurring in about 30–45% of subjects, rather more common in males than in females.

The posterior uveitis observed in Behçet's disease is a consequence of retinal vasculitis and may result in blindness, a feared complication of Behçet's disease. Hypopyon uveitis is associated with severe retinal vasculitis and is very suggestive of Behçet's disease, although it is rare [6]. Episcleritis may occur but is not very specific.

Vascular involvement in Behçet's disease may affect arteries and veins, leading to aneurysms or occlusions that are sometimes fatal [6,11,12]. The frequency of vascular disease rises from about 30% at initial presentation, to approaching 50% during the course of the disease, and is most common in males. Venous thromboses are most frequent (seven times more common than arterial occlusion [13]), especially lower limb deep vein thrombosis or superficial thrombophlebitis of extremities. Patients with thrombophlebitis are at greater risk of developing deep venous thrombosis. Other sites of venous thrombosis include the vena cava, hepatic veins (Budd–Chiari syndrome), and cerebral venous sinuses. Arterial lesions include inflammatory stenoses, thrombosis, and, especially, true or false aneurysms of the abdominal aorta, pulmonary or peripheral arteries (with a strong male predominance), in contrast with large vessel vasculitides which tend to affect the aortic arch, renal or mesenteric vessels [6]. Vascular complications should always be borne in mind in patients with known Behçet's disease, particularly pulmonary artery aneurysm as a cause of haemoptysis (the presence of haemoptysis and deep-vein thrombosis may erroneously suggest pulmonary embolism, which is relatively uncommon in Behçet's disease); pulmonary artery aneurysm may occur in isolation (described as the Hughes–Stovin syndrome, but probably part of the spectrum of Behçet's disease). Vessels may show an arteritis, particularly of the vasa vasora, but the aneurysms and thrombosis are not necessarily a consequence of vasculitis, and therefore may not respond to medical therapies for vasculitis. Endovascular control of bleeding aneurysms has been described [13].

Many neurological manifestations may be present in patients with Behçet's disease, including parenchymal and dural sinus thromboses and meningoencephalitis [6,14], but only occur in about 3% of patients. A particular problem of this 'neuro-Behçet's disease' is distinguishing it from central nervous system involvement in Sweet's syndrome (neuro-Sweet's syndrome). Peripheral neuropathies are rare, although brainstem or spinal cord involvement may occur. An asymmetrical, migratory, non-erosive oligoarthritis that may mimic rheumatoid arthritis occurs in 30–40% [3,4,6,15]. Gastrointestinal involvement is uncommon; when it occurs, it consists of mucosal ulceration, especially in the terminal ileum or colon, mimicking inflammatory bowel disease. In contrast with Crohn's disease, which is the most frequent differential diagnosis, anal lesions are rare, and inflammatory markers such as CRP are usually modestly elevated in comparison with active Crohn's disease. Renal involvement is rare, a useful distinction from many vasculitides.

Diagnosis. The diagnosis of Behçet's disease should be suspected in any patient with recurrent and extensive oral aphthosis. However, in these persons, other causes of aphthosis such as inflammatory bowel disease, as well as lesions that mimic aphthae such as herpes simplex infection, must be excluded before a diagnosis of Behçet's disease can be made. Papulopustular lesions, especially outside the normal body site distribution for acne, and with a neutrophilic vascular reaction histologically, suggest Behçet's disease, as do erythema nodosum-like lesions with ulceration, scarring, residual pigmentation or a medium-size vessel vasculitis histologically. The diagnosis should be considered in young patients with deep-vein thrombosis, especially in males or in the absence of other risk factors or thrombophilia. Anterior chamber uveitis with severe retinal vasculitis is not a feature of other vasculitides [6] and therefore suggests a diagnosis of Behçet's disease; similarly, dural sinus thrombosis, aortic or peripheral arterial aneurysms in a young male, or aneurysm(s) of the pulmonary artery or its main branches, strongly suggest this diagnosis. A clinical picture suggesting a medium or large vessel vasculitis, but lacking supporting features such as renal or mesenteric involvement, a positive ANCA, peripheral neuropathy or granulomatous histology, suggests the possibility of Behçet's disease. A positive pathergy provocation test may further support the diagnosis. Ophthalmology, neurology and rheumatology consultations may be beneficial when evaluating a patient with suspected Behçet's disease.

Some patients are encountered in whom recurrent, severe aphthous ulceration dominates the clinical picture; although not fulfilling diagnostic criteria for Behçet's disease they may represent a *forme fruste* of the disorder [16]. Along similar lines, clinical experience also reveals some individuals with severe, non-infective genital ulceration, either in isolation or sometimes with a neutrophilic dermatosis or other features of Behçet's disease, but who deny oral ulceration, and in whom classification is difficult as they appear to have Behçet's disease but in the absence of the main disease-defining criterion. In general, the diagnostic criteria are most reliable in areas of higher prevalence.

References

1 International Study Group for Behçet's disease. Criteria for diagnosis of Behçet's disease. *Lancet* 1990; **335**: 1078–80.

2 Kural-Seyahi E, Fresko I, Seyahi N *et al*. The long-term mortality and morbidity of Behçet syndrome: a 2-decade outcome survey of 387 patients followed at a dedicated center. *Medicine (Baltimore)* 2003; **82**: 60–76.

3 Alpsoy E, Donmez L, Onder M *et al*. Clinical features and natural course of Behçet's disease in 661 cases: a multicentre study. *Br J Dermatol* 2007; **157**: 901–6.

4 Jorizzo JL. Behçet's disease: an update based on the 1985 international conference in London. *Arch Dermatol* 1986; **122**: 556–8.

5 Nazarro P. Cutaneous manifestations of Behçet's disease. In: Monacelli M, Nazzaro P, eds. *International Symposium on Behçet's Disease in Rome*. Basel: Karger, 1966: 15–41.

6 Melikoglu M, Kural-Seyahi E, Tascilar K, Yaziei I. The unique features of vasculitis in Behçet's syndrome. *Clin Rev Allerg Immunol* 2008; **35**: 40–6.

7 Callen JP. Pustular eruptions in systemic disease. *Clin Dermatol* 2000; **18**: 349–53.

8 Jorizzo JL, Solomon AR, Zanolli MD, Leshin B. Neutrophilic vascular reactions. *J Am Acad Dermatol* 1988; **19**: 983–1005.

9 Crowson AN, Mihm MC, Magro CM. Cutaneous vasculitis: a review. *J Cutan Pathol* 2003; **30**: 161–73.

10 Munro CS, Cox NH. Pyoderma gangrenosum associated with Behçet's syndrome—response to thalidomide. *Clin Exp Dermatol* 1988; **13**: 408–10.

11 Shimizu T, Ehrlich GE, Goro I *et al*. Behçet's disease. *Semin Arthritis Rheum* 1979; **8**: 223–60.

12 Shimizu T. Vascular lesions in Behçet's disease. *Cardioangiology* 1977; **1**: 124–9.

13 Cantasdemir M, Kantarci F, Adaletli I *et al*. Emergency intravascular management of pulmonary artery aneurysms in Behçet's disease: report of 2 cases and review of the literature. *Cardiovasc Intervent Radiol* 2002; **25**: 533–7.

Table 50.15 Medical treatments for Behçet's disease.

Palliative treatment of aphthae
Topical corticosteroids/corticosteroid mouthwash
Intralesional corticosteroids
Topical sucralfate
Topical tacrolimus
Nicotine patches
Topical viscous lidocaine (lignocaine)
Topical granulocyte colony-stimulating factor
Mucocutaneous manifestations
Colchicine
Dapsone
Dapsone and colchicine
Systemic involvement
Systemic corticosteroids
Immunosuppressants, cytokines and related agents for most severe disease
• Azathioprine
• Methotrexate
• Ciclosporin
• Cyclophosphamide
• Chlorambucil
• Thalidomide
• Interferon-α
• Anti-TNF agents (infliximab, etanercept)

14 O'Duffy JD, Goldstein NP. Neurologic involvement in seven patients with Behçet's disease. *Am J Med* 1976; **61**: 171–8.
15 Yurkakul S, Yuzici H, Tuzun Y *et al*. The arthritis of Behçet's disease: a prospective study. *Ann Rheum Dis* 1983; **42**: 505–15.
16 Jorizzo JL, Taylor RS, Schmalstieg FC *et al*. Complex aphthosis: a forme fruste of Behçet's syndrome? *J Am Acad Dermatol* 1985; **13**: 80–4.

Treatment (Table 50.15). Oral or genital ulcers may be treated symptomatically with topical or intralesional corticosteroids, topical sucralfate gel, topical tacrolimus and/or viscous lidocaine (lignocaine) applied to individual lesions [1,2]. Nicotine patches applied to oral aphthae have been reported to have rapid benefit [3]. Topical application of granulocyte colony-stimulating factor has been demonstrated to be effective but is expensive [4]. Betamethasone used as a mouthwash is a practical treatment if there are several ulcers. Rebamipide (a mucosal protective agent used in some countries) may also be useful for oral aphthae [5]. Colchicine (0.6 mg two to three times daily) may also be used to treat mucocutaneous manifestations, including aphthae, papulopustules and erythema nodosum-like lesions, although this treatment option is limited by gastrointestinal intolerance and requires monitoring for neutropenia [6–8]. Dapsone alone has demonstrated efficacy in treating Behçet's disease [9], and anecdotally has been effective in combination with colchicine.

Behçet's disease that has manifestations other than mucocutaneous involvement may be treated with systemic corticosteroids, although such treatment may not control severe ocular, neurological or non-vasculitic vascular disease [10–14]. Immunosuppressive agents such as azathioprine, methotrexate or ciclosporin may be used in the treatment of patients with severe Behçet's disease [10,15]. There is a potential concern that ciclosporin can cause neurotoxicity that appears very similar to neuro-Behçet's disease (some feel that it actually provokes neuro-Behçet's disease), so, although useful for treating uveitis, a degree of caution is warranted. Cytokines such as interferon-α are useful (alone or with azathioprine) [5,16], and thalidomide can be effective [1,17] but requires careful monitoring for neurological toxicity. Anecdotal reports suggest use of intravenous immunoglobulin (IVIG) with aspirin, and granulocyte and monocyte adsorption apheresis.

Increasingly, anti-TNF agents such as infliximab or etanercept have been documented to be effective [5,16], especially for uveitis or for severe oral aphthae (although dapsone is a more effective inhibitor of the pathergic response than is etanercept). Novel treatments under investigation for Behçet's disease include induction of tolerance using oral administration of the 336–351 sequence of HSP60 linked to recombinant cholera B-toxin B-subunit [16]. Surgical treatments for large-vessel disease are outside the remit of dermatologists but are summarized in [18].

There is an increasing case for early and aggressive treatment of Behçet's disease, especially in those with, or at risk of, severe symptoms. The highest risk of serious ocular, pulmonary artery or neurological involvement is in males, especially those with disease onset below age 40 years [19]. In general, the risk of complications gradually decreases with increasing age.

References

1 Ghate JV, Jorizzo JL. Behçet's disease and complex aphthosis. *J Am Acad Dermatol* 1999; **40**: 1–18.
2 Alpsoy E, Er H, Durusoy C, Yilmaz E. The use of sucralfate suspension in the treatment of oral and genital ulceration of Behçet disease. *Arch Dermatol* 1999; **135**: 529–32.
3 Scheid P, Bohadana A, Martinet Y. Nicotine patches for aphthous ulcers due to Behçet's syndrome. *N Engl J Med* 2000; **343**: 1816–7.
4 Bacanli A, Yerebakan Dicle O, Parmaksizoglu B *et al*. Topical granulocyte colony-stimulating factor for the treatment of oral and genital ulcers of patients with Behçet's disease. *J Eur Acad Dermatol Venereol* 2006; **20**: 931–5.
5 Yurdakul S, Hamuryudan V, Yazici H. Behçet's disease. *Curr Opin Rheumatol* 2003; **16**: 38–42.
6 Jorizzo JL, Hudson RD, Schmalstieg FC *et al*. Behçet's syndrome: immune regulation, circulating immune complexes, neutrophil migration, and colchicine therapy. *J Am Acad Dermatol* 1984; **10**: 205–14.
7 Mizushima Y, Matsumura N, Mori M. Chemotaxis of leukocytes and colchicine treatment in Behçet's disease. *J Rheumatol* 1979; **6**: 108–10.
8 Miyachi Y, Taniguchi S, Ozaki M, Horio T. Colchicine in the treatment of the cutaneous manifestations of Behçet's disease. *Br J Dermatol* 1981; **104**: 67–9.
9 Sharquie KE, Najim RA, Abu-Raghif AR. Dapsone in Behçet's disease: a double-blind, placebo-controlled, cross-over study. *J Dermatol* 2002; **29**: 267–79.
10 Jorizzo JL. Behçet's disease: an update based on the 1985 international conference in London. *Arch Dermatol* 1986; **122**: 556–8.
11 O'Duffy JD, Carney JA, Deodhar S. Behçet's disease: report of 10 cases, three with new manifestation. *Ann Intern Med* 1971; **75**: 561–70.
12 Chajek T, Fainaru M. Behçet's disease: report of 41 cases and a review of the literature. *Medicine* 1975; **54**: 179–96.
13 Chamberlain MA. Behçet's syndrome in 32 patients in Yorkshire. *Ann Rheum Dis* 1977; **36**: 491–9.
14 Oshima Y, Shimuzu T, Yokohari R *et al*. Clinical studies on Behçet's syndrome. *Ann Rheum Dis* 1963; **22**: 36–45.
15 Wong VG. Immunosuppressive therapy of ocular inflammatory disease. *Arch Ophthalmol* 1969; **81**: 628–37.
16 Pipitone N, Olivien I, Cantini F *et al*. New approaches in the treatment of Adamantiades-Behçet's disease. *Curr Opin Rheumatol* 2006; **18**: 3–9.
17 Munro CS, Cox NH. Pyoderma gangrenosum associated with Behçet's syndrome—response to thalidomide. *Clin Exp Dermatol* 1988; **13**: 408–10.
18 Calamia KT, Schirmer M, Melikoglu M. Major vessel involvement in Behçet disease. *Curr Opin Rheumatol* 2004; **17**: 1–8.

19 Alpsoy E, Donmez L, Onder M *et al*. Clinical features and natural course of Behçet's disease in 661 cases: a multicentre study. *Br J Dermatol* 2007; **157**: 901–6.

Neutrophilic dermatoses

Introduction

The spectrum of disorders currently considered as 'neutrophilic dermatoses' has widened hugely over the last two decades [1–6]. The common features in most of these entities can be summarized as follows:

1 the histological features are dominated by a neutrophilic vascular reaction that typically (although variably) falls short of vasculitis
2 within any diagnostic entity a significant proportion of cases can be demonstrated to have a reactive cause or systemic association (mainly haematological or gastrointestinal diseases, or drug-induced aetiology)
3 many of these disorders may coexist or occur in sequence in an affected individual, and
4 the neutrophilic process itself may in some cases cause systemic disease.

Epidermal neutrophilic dermatoses are not discussed here, other than where they are part of a disease overlap spectrum or where they share a common aetiology with neutrophilic dermatoses affecting the dermis or subcutaneous fat.

The following sections define and discuss the history, aetiology, pathogenesis, histopathology, clinical features, diagnosis and treatment of the major neutrophilic dermatoses, as well as briefly addressing histopathological overlaps, internal (systemic) neutrophilic dermatoses, and identifying areas of controversy. The conditions discussed are characterized by a neutrophilic infiltrate and blood vessel damage, probably as a result of immune complex deposition as well as involving neutrophil-induced injury. Increasingly, different types of infiltrate (lymphocytic, or early myeloid cells), and the presence of at least some features of vasculitis, are being accepted within the spectrum of neutrophilic dermatoses, although in some instances these variations may be secondary and reflect the timing of obtaining histopathology specimens. Some mechanisms of involvement of neutrophils in this group of dermatoses, and of their chemoattraction to tissues, have been discussed in [7–10].

References

1 Jorizzo J, Solomon AR, Zanolli MD, Leshin B. Neutrophilic vascular reactions. *J Am Acad Dermatol* 1988; **19**: 983–1005.
2 de Moragos JM, Pujol RM. Neutrophilic dermatoses. *Curr Opin Dermatol* 1997; **4**: 13–20.
3 Huang W, McNeely MC. Neutrophilic tissue reactions. *Adv Dermatol* 1998; **13**: 33–63.
4 Wallach D. Neutrophilic dermatoses: an overview. *Clin Dermatol* 2000; **18**: 229–31.
5 Callen JP. Neutrophilic dermatoses. *Dermatol Clin* 2002; **20**: 409–19.
6 Wallach D, Vignon-Pennamen M-D. From acute febrile neutrophilic dermatosis to neutrophilic disease: forty years of clinical research. *J Am Acad Dermatol* 2006; **55**: 1066–71.
7 von den Driesch P. Polymorphonuclears: structure, function, and mechanisms of involvement in skin diseases. *Clin Dermatol* 2000; **18**: 233–44.
8 Schröder J-M. Chemoattractants as mediators of neutrophilic tissue recruitment. *Clin Dermatol* 2000; **18**: 245–63.
9 Kluger MS. Vascular endothelial cell adhesion and signaling during leukocyte recruitment. *Adv Dermatol* 2004; **20**: 163–94.
10 Schaerli P, Britschgi M, Keller M *et al*. Characterization of human T cells that regulate neutrophilic skin inflammation. *J Immunol* 2004; **173**: 2151–8.

Classification

A suggested classification of neutrophilic dermatoses is shown in Table 50.16. It should be noted that frank vasculitides, neutrophilic vascular reactions secondary to primary microvascular occlusion (Chapter 49), and infective causes of neutrophilic vasculopathy are not normally included in such classifications.

We have not included, or have listed but will not discuss, additional disorders in which the neutrophilic infiltrate is primarily epidermal such as *subcorneal pustular dermatosis*, *pustular psoriasis*, *Reiter's syndrome*, *intraepidermal neutrophilic IgA dermatosis*, *infantile acropustulosis* and *drug-induced pustular eruptions*, although one might also term these neutrophilic in type of infiltrate. Some authors have also suggested the inclusion of *Rosai–Dorfman disease with neutrophilic predominance* and of *congenital erosive and vesicular dermatosis with reticulated supple scarring*, based on histopathological similarity, but these conditions do not share the disease associations or behaviour of more accepted dermal neutrophilic dermatoses. All of these are discussed in other chapters.

There remain some areas of overlap or uncertainty. Some disorders, notably *Behçet's disease*, have features of vasculitis, pustular vasculitis and thrombosis, and therefore exhibit overlap between neutrophilic dermatosis and vasculitis, as discussed earlier (p. 50.56). *Erythema elevatum diutinum* (EED) is variably classified as a vasculitis or as a neutrophilic dermatosis; we have elected to discuss it as a vasculitis (p. 50.25). *Neutrophilic eccrine hidradenitis* (NEH) appears to have different aetiologies (physical/cold in children, often related to cytotoxic or other drugs and/or haematological malignancies in adults) and is neutrophilic but not primarily vascular; it is also discussed in Chapter 44. *Subcorneal pustular dermatosis* is not a vascular reaction but does share aetiological factors (notably monoclonal gammopathy) with disorders such as pyoderma gangrenosum and EED, and may coexist with them (especially in patients with myelodysplastic disorders), so is included in the classification but is discussed in Chapter 40. Some histological issues that influence classification (e.g. early lymphocytic rather than neutrophilic infiltrates) are discussed in relation to specific conditions below.

Neutrophilic sebaceous adenitis [1,2] is very rare, and how to classify it is unclear. Clinically it presents as annular plaques and papules, spreading from the face to the body and having some resemblance to Sweet's syndrome; histologically it is characterized by a sterile, neutrophilic and sometimes suppurative infiltrate around sebaceous lobules (although cases with a myelomonocytic [3] or granulomatous infiltrate are also reported [2]). It usually has a short, self-limiting course or responds to topical corticosteroids. An autoimmune aetiology has been proposed but it is tempting to suggest that this could be a sebaceous equivalent of neutrophilic eccrine hidradenitis (NEH), as the distribution, morphology, duration and neutrophilic infiltrate, in the presence of necrotic sebocytes without infection, would parallel several aspects of NEH. We have therefore very tentatively suggested that it may belong

Table 50.16 Neutrophilic dermatoses: an aetiological classification.

'Classical' neutrophilic dermatoses
- Pyoderma gangrenosum (various subtypes)
- Sweet's syndrome/acute febrile neutrophilic dermatosis (and possible variants: neutrophilic dermatosis of the dorsal hands; chronic recurrent [annular] neutrophilic dermatosis)

Overlap with vasculitis
- Behçet's disease
- Erythema elevatum diutinum

Specific link with gastrointestinal disease*
- Neutrophilic vascular reaction in bowel-associated dermatosis arthritis syndrome (BADAS)
- Pustular vasculitis/neutrophilic pustulosis (many cases represent pustular pyoderma gangrenosum)
- Aseptic abscesses in Crohn's disease
- Pyodermatitis–pyostomatitis vegetans (?)
- Peristomal pyoderma gangrenosum

Associated with acne or pustulosis†
- Synovitis, acne, pustulosis, hyperostosis, osteomyelitis (SAPHO)
- Pyogenic arthritis, pyoderma gangrenosum, acne (PAPA)

Associated with connective tissue disease or immune complex disease
- Rheumatoid neutrophilic dermatitis/dermatosis
- Palisaded neutrophilic and granulomatous dermatitis
- Relapsing polychondritis
- Sweet's syndrome-like, erythema gyratum repens-like, and figurate neutrophilic infiltrate, in systemic lupus erythematosus

Paraneoplastic or typically chemotherapy-associated
- Paraneoplastic neutrophilic figurate erythema
- Neutrophilic eccrine hidradenitis

Systemic neutrophilic dermatoses
- Neuro-Sweet's syndrome
- Other internal sites: myositis, pulmonary, pericarditis, osteitis (deep to pyoderma gangrenosum, or distant), lymph nodes, other sites of aseptic neutrophilic abscesses (often splenic or visceral), etc.

Other extra-cutaneous neutrophilic disease
- Peripheral ulcerative keratitis
- Neutrophilic panniculitis

Autoinflammatory diseases‡
- Familial Mediterranean fever
- Hyper-IgD syndrome

Non-vessel centred and miscellaneous
- Subcorneal pustular dermatosis (Sneddon–Wilkinson disease)
- Intraepidermal neutrophilic IgA dermatosis
- Neutrophilic urticaria
- Neutrophilic spongiosis?
- Neutrophilic sebaceous adenitis?

* Many of the neutrophilic dermatoses have a strong association with gastrointestinal disease, but this link is especially strong in the disorders listed.

† Pustules are also a feature in many of the other patterns listed, such as Behçet's disease, Sweet's syndrome, BADAS and others.

‡ Autoinflammatory diseases are increasingly classified on the basis of genetic findings, but Sweet's syndrome-like lesions and aseptic pustules, with leukocytosis, are often described.

in the neutrophilic dermatosis spectrum. *Neutrophilic spongiosis*, a disorder of uncertain classification, is discussed in the section on neutrophilic pustular disorders.

Aseptic and TORCH-screen negative pustular eruptions in children, with some features reminiscent of Sweet's syndrome, should be viewed with some suspicion. Paediatric Sweet's syndrome and PG may both occur, but a perforating neutrophilic and granulomatous dermatitis of the newborn was described in two children with immunodeficiency [4], and children with Down's syndrome are prone to transient myeloproliferative disorders, leukaemoid reactions and leukaemia cutis; the lesions may contain immature blast-like immature haemopoietic cells and, like neutrophilic dermatoses, may exhibit pathergy [5,6].

Lupus erythematosus has also been linked with Sweet's syndrome or other neutrophilic dermatoses; earlier reports were those in which hydralazine was implicated [7], but there are other reports where this was not the case [8] and there are increasing reports of neutrophilic dermatoses as the presenting feature of lupus erythematosus [9,10]. Sweet's syndrome, PG (8 years before lupus erythematosus [11]), and figurate and erythema gyratum repens-like patterns [12] of neutrophilic dermatosis have all been reported, as well as other potentially related conditions such as neutrophilic urticaria/urticarial erythema with neutrophilic infiltration [13,14], neutrophilic eccrine hidradenitis (after cyclophosphamide treatment [15]) and palisaded neutrophilic and granulomatous dermatitis. It has been recommended that lupus erythematosus should be considered in the differential diagnosis of neutrophilic dermatoses [10].

References

1 Renfro L, Kopf AW, Gutterman A *et al*. Neutrophilic sebaceous adenitis. *Arch Dermatol* 1993; **129**: 910–1.
2 Newman J, Jacobsom M, Sicari M, Hayman R. Neutrophilic sebaceous adenitis: a report of two cases. *J Clin Pathol* 2007; **34**: 78 [Abstract].
3 Martins C, Tellechea O, Mariano A, Baptista AP. Sebaceous adenitis. *J Am Acad Dermatol* 1997; **36**: 845–6.
4 Torrelo A, Vera A, Portugués M *et al*. Perforating neutrophilic and granulomatous dermatitis of the newborn—a clue to immunodeficiency. *Pediatr Dermatol* 2007; **24**: 211–5.
5 Burch JM, Weston WL, Rogers M, Morelli JG. Cutaneous pustular leukaemoid reactions in trisomy 21. *Pediatr Dermatol* 2003; **20**: 232–7.
6 Nijhawan A, Baselga E, Gonzalez-Ensenat A *et al*. Vesicopustular eruptions in Down syndrome neonates with myeloproliferative disorders. *Arch Dermatol* 2001; **137**: 760–3.
7 Ramsay-Goldman R, Franz T, Solano FX, Medsger TA Jr. Hydralazine induced lupus and Sweet's syndrome. Report and review of the literature. *J Rheumatol* 1990; **17**: 682–4.
8 Goette DK. Sweet's syndrome in subacute cutaneous lupus erythematosus. *Arch Dermatol* 1985; **121**: 789–91.
9 Hou TY, Chang DM, Gao HW *et al*. Sweet's syndrome as an initial presentation in systemic lupus erythematosus: a case report and review of the literature. *Lupus* 2005; **14**: 399–402.
10 Gleason BC, Zembowicz A, Granter SR. Non-bullous neutrophilic dermatosis: an uncommon dermatologic manifestation in patients with lupus erythematosus. *J Cutan Pathol* 2006; **33**: 721–5.
11 Waldman MA, Callen JP. Pyoderma gangrenosum preceding the diagnosis of systemic lupus erythematosus. *Dermatology (Basel)* 2005; **210**: 64–7.
12 Khan DB, Andrassy K, Hartschuh W. Neutrophilic dermatosis with an erythema gyratum repens-like pattern in systemic lupus erythematosus. *Acta Derm Venereol* 2005; **85**: 455–6.
13 Kawana S, Nishioka K, Nishiyama S. Urticarial erythema with neutrophilic infiltration—correlation of cutaneous vascular changes with clinical severity. *Nippon Hifuka Gakkai Zasshi* 1991; **101**: 951–7.

14 Davis MD, Daoud MS, Kirby B *et al*. Clinicopathologic correlation of hypocomplementemic and normocomplementemic urticarial vasculitis. *J Am Acad Dermatol* 1998; **38**: 899–905.
15 Lienesch DW, Mutasin DF, Singh RR. Neutrophilic eccrine hidradenitis mimicking cutaneous vasculitis in a lupus patient: a complication of cyclophosphamide. *Lupus* 2003; **12**: 707–9.

Pyoderma gangrenosum

Definition. Pyoderma gangrenosum (PG) is a rare, non-infectious neutrophilic dermatosis commonly associated with underlying systemic disease. Diagnosis is based on typical clinical features and exclusion of other cutaneous ulcerating diseases, as described in several reviews [1–10].

History and nomenclature. Brocq first described PG in 1916 [11]. It was later described in 1930 by Brunsting *et al*. [12]. The prevalence of PG in inflammatory bowel disease (IBD) was discussed by Greenstein *et al*. in 1976 [13]. Several clinical variants of PG have been described (Table 50.17), diagnostic criteria have been published [3], and PG at unusual sites or with specific triggers, such as pathergy, have also been reviewed [4]. The significance of the different variants described is unclear. There is some evidence that the pustular type may be mainly associated with IBD, the bullous type with haematological malignancies, and that the vegetative type is usually not associated with underlying disease [2,3]. Others describe lesions on the hands, arms and face as being associated with haematological diseases (and thus potentially overlapping with Sweet's syndrome, and with neutrophilic dermatosis of the dorsal hands) [8]. The peristomal pattern, unsurprisingly, is mainly but not exclusively associated with IBD. However, different morphologies may coexist with each other or with other neutrophilic dermatoses or pustular vasculitis [14] (although the vegetative pattern of PG is usually not accompanied by other lesions), or may evolve from one form to another [15], and none of the morphologies is consistently or exclusively associated with any specific cause; such classifications are, however, convenient for discussion and for initiation of the potentially most rewarding investigations. The different patterns are discussed in more detail below. As a guide, about 50–70% of patients will have an underlying disease, approximately equally divided between IBD, arthritides and haematological causes; conversely, about 2% of patients with IBD will develop PG.

Table 50.17 The main variants of pyoderma gangrenosum in selected reviews.

Authors (reference)	Main variants
Powell *et al*. [2,3] Wollina [9] De Moragas & Pujol [16]	Ulcerative Pustular Bullous Vegetative (= superficial granulomatous pyoderma)
Callen [4]	Typical (classical) Atypical (more superficial) Pustular eruption of ulcerative colitis Peristomal Vulvar Pyostomatitis vegetans Malignant pyoderma Bullous
Ahmadi & Powell [6]	*Main classification*: Ulcerative Pustular Bullous Vegetative *Unusual presentations*: Pathergic Peristomal Dorsal hand Head and neck (malignant pyoderma) Multisystem Paraneoplastic
Callen & Jackson [8,10]	Classic (usually on the legs) Atypical (hands, arms, face) Peristomal Other sites not specifically viewed as distinct (vulva, penis and oropharynx [pyostomatitis vegetans])
Present text (an arbitrary division according to morphology and/or site, where these factors influence diagnostic aspects, likely disease associations or therapy)	Classic/ulcerative Atypical forms: Pustular Bullous Upper limbs/trunk Superficial (vegetative) Peristomal Other specific sites that influence diagnostic aspects, disease associations or therapy (face/scalp, breast, genital, mucosal, etc) Pyostomatitis vegetans (?) Neutrophilic dermatosis of dorsal hands (? Sweet's syndrome or pyoderma gangrenosum)

References

1 Callen JP. Pyoderma gangrenosum and related disorders. *Dermatol Clin* 1990; **7**: 1249–59.
2 Powell FC, Su WPD. Pyoderma gangrenosum: classification and management. *J Am Acad Dermatol* 1996; **34**: 395–409.
3 Powell FC, Collins C. Pyoderma gangrenosum. *Clin Dermatol* 2000; **18**: 283–93.
4 Callen JP. Neutrophilic dermatoses. *Dermatol Clin* 2002; **20**: 409–19.
5 Su WPD, Davis MD, Weenig RH *et al*. Pyoderma gangrenosum: clinicopathologic correlation and proposed diagnostic criteria. *Int J Dermatol* 2004; **43**: 790–800.
6 Ahmadi S, Powell FC. Pyoderma gangrenosum: uncommon presentations. *Clin Dermatol* 2005; **23**: 612–20.
7 Provost TT, Harris ML. Pyoderma gangrenosum. In: Provost TT, Flynn JA, eds. *Cutaneous Medicine: Cutaneous Manifestations of Systemic Disease*. Hamilton, Ontario: Decker, 2001: 464–72.
8 Jackson JM, Callen JP. Pyoderma gangrenosum: an expert commentary. *Expert Rev Dermatol* 2006; **1**: 391–400.
9 Wollina U. Pyoderma gangrenosum—a review. *Orphanet J Rare Dis* 2007; **2**: 19.
10 Callen JP, Jackson JM. Pyoderma gangrenosum: an update. *Rheum Dis Clin N Am* 2007; **33**: 787–802.
11 Brocq L. Nouvelle contribution à l'étude du phagedeniome geometrique. *Ann Dermatol Syphiligr (Paris)* 1916; **6**: 1–39.
12 Brunsting LA, Goeckerman WH, O'Leary PA. Pyoderma gangrenosum: clinical and experimental observations in five cases occurring in adults. *Arch Dermatol* 1930; **22**: 655–80.
13 Greenstein AJ, Janowitz HD, Sachar DB. The extra-intestinal complications of Crohn's disease and ulcerative colitis: a study of 700 patients. *Medicine (Baltimore)* 1976; **55**: 401–12.

Table 50.18 Diseases associated with pyoderma gangrenosum.

Category	Examples*
Gastrointestinal	Ulcerative colitis, Crohn's disease, collagenous colitis, gastritis, gastroduodenal ulcers, intestinal polyps
Arthritides	Rheumatoid arthritis, seronegative arthritis (sometimes with IBD), osteoarthritis
Haematological	Leukaemias (especially myelogenous, hairy cell), myelofibrosis, myelodysplastic syndromes/polycythaemia vera, paraproteinaemia including (usually IgA) monoclonal gammopathy, Waldenström's macroglobulinaemia, paroxysmal nocturnal haemoglobinuria, splenomegaly, T-cell lymphomas (less commonly)
Hepatic	Chronic active hepatitis, primary biliary cirrhosis, sclerosing cholangitis
Other vasculitides, collagen vascular and related disorders	Wegener's granulomatosis, Takayasu's arteritis, Behçet's disease, systemic lupus erythematosus, systemic sclerosis
Acne and related disorders	Acne conglobata, acne fulminans, hidradenitis suppurativa, PAPA (recurrent familial arthritis)
Other dermatoses	Many other neutrophilic dermatoses, relapsing polychondritis, pustular vasculitis (this chapter) Psoriasis
Autoimmune	Thyroid disease, diabetes mellitus
Drugs	Colony-stimulating factors† (several), gefinib (epidermal growth factor receptor inhibitor), interferon†, propylthiouracil, isotretinoin, several others (with apparently unrelated structures/activities)
Solid organ tumours	Colon, pancreas, breast, bronchus, carcinoid
Miscellaneous	Sarcoidosis Infections, including HIV, hepatitis C Chronic lung disease Immunological: congenital hypergammaglobulinaemia, autoimmune neutropenia in infancy, immunosuppression, complement deficiencies (C2, C4, C7 deficiency all described) Familial

PAPA: pyogenic arthritis, pyoderma gangrenosum, acne.

* It is not certain that all conditions listed represent true or causal associations.

† Have also been used therapeutically.

14 Wilson DM, John GR, Callen JP. Peripheral ulcerative keratitis—an extracutaneous neutrophilic disorder: report of a patient with rheumatoid arthritis, pustular vasculitis, pyoderma gangrenosum, and Sweet's syndrome with an excellent response to cyclosporine therapy. *J Am Acad Dermatol* 1999; **40**: 331–4.

15 Marzano AV, Tourlaki A, Alessi E, Caputo R. Widespread idiopathic pyoderma gangrenosum evolved from ulcerative to vegetative type: a 10-year history with a recent response to infliximab. *Clin Exp Dermatol* 2007; **33**: 156–9.

16 de Moragos JM, Pujol RM. Neutrophilic dermatoses. *Curr Opin Dermatol* 1997; **4**: 13–20.

Aetiology and pathogenesis. Although the pathogenesis of PG is not fully understood, an immune-mediated process is thought to have an important role. Rather more than 50% of patients with PG have an associated systemic disease [1–3]. Common associations include IBD (in about 15–20% of cases with an associated disease), arthritis of several types, haematological malignancies and monoclonal gammopathies (Table 50.18). The strength of the different associations shows some variation with clinical pattern (see Clinical features section), but some associations may have pathogenetic importance (discussed below).

Both humoral and cell-mediated abnormalities have been associated with PG. Humoral defects reported include autoantibodies against skin and bowel, a dermonecrotic factor present in the serum that produces necrosis when injected into the subject's own skin, and a serum factor present in patients with PG that produces PG-like lesions when injected into guinea pigs [4,5]. Other studies have suggested the mechanism underlying PG is consistent with the Arthus and Schwartzmann reactions in which circulating immune complexes are deposited in vessels leading to activation of the classical and alternative complement pathways [4,6,7]. Direct immunofluorescence staining studies to detect immunoglobulins, complement and fibrin deposits in post-capillary venules have yielded inconsistent results [8,9]. The possibility of cross-reactivity between bacterial and cutaneous antigens has been suspected for many years [10], and treatment to decrease bowel bacteria has shown some benefit in therapy of PG [11], with *Escherichia coli* particularly implicated. Recent support for this possibility was documented in a study in which heat-killed *E. coli* were injected subcutaneously into clinically normal skin; in normal volunteers inflammation peaks at 24 h and fades by 48 h, but in some patients with ulcerative colitis (although in none with Crohn's disease) the inflammation persists; one patient went on to develop PG-like bullous lesions with very high IL-8 levels [12,13] (IL-8 being a very potent neutrophil chemoattractant, discussed further below). The patient had had a previous florid response to an infected wound on the foot, but did not have pathergy at needle injury sites. The authors suggest that this represents an abnormal reaction to bacteria, rather than being a form of pathergy, and suggest a local failure to terminate IL-8 production, resulting in

marked neutrophilic infiltration. However, a study of Crohn's disease lesions found intracellular consensus bacterial 16S rRNA in most bowel biopsies but in no lesions of PG, neutrophilic folliculitis and other skin lesions, including skin lesions from three patients with Crohn's disease and associated skin lesions [14]. The role of bacterial antigens warrants further study.

Cell-mediated defects found include cutaneous anergy to *Candida*, streptokinase and purified protein derivative, as well as altered production of macrophage inhibition factor by lymphocytes [15]. The association with inflammatory bowel disease and various arthritides, in which T cells play a part in the pathogenesis, prompted investigation of clonal T-cell responses in patients with PG. In five patients (three with classical and two with peristomal PG), all patients had evidence of expanded T-cell clones in peripheral blood, and four of them also had clonality identified in the skin at the leading edge of the PG lesions, some of the clones in each of these cases being shared between the skin and the blood (including one patient without underlying IBD) [16]. These results were interpreted as confirming an oligoclonal T-cell response due to an antigenic stimulus, and trafficking between the skin and blood (and, therefore, potentially to other organs also). Clonal gamma and beta T-cell receptor rearrangements have also been demonstrated in PG associated with haematological disease (including splenomegaly) [17], but a recent study (including patients with Sweet's syndrome or PG) found that clonal restriction of neutrophils was present not only in over half of patients with myeloid disorders but also in a rather higher proportion of controls (one of whom later developed myelodysplasia) [18]. Thus, clonality of both T cells and of neutrophils has been demonstrated in different studies, and neither appears to be specifically related to any particular associated disease entity.

Additional reports have described decreased neutrophil chemotaxis and impaired monocyte phagocytosis in association with PG [19]. These leukocyte abnormalities may contribute to the pathergic phenomenon that occurs in up to 50% of PG patients, whereby new lesions can be induced at sites of minor skin trauma including venepuncture, vaccination and surgical procedures [1–3], and also for occurrence of the Koebner reaction in some patients with PG [20]. Various studies support the importance of IL-8 as a neutrophil chemoattractant involved in the pathogenesis of PG. Overexpression of IL-8 induced in immunodeficient mice bearing human skin xenografts caused PG-like ulceration [21], high IL-8 levels in blood have been documented in PG [22], and high IL-8 levels have been demonstrated in fibroblasts from PG ulcers [21,22]; in cultured PG ulcer fibroblasts from one patient, the initially elevated IL-8 production fell over a few weeks to the same undetectable levels as demonstrated throughout the culture period in fibroblasts from normal skin in the same patient [22]. Thus the IL-8 production (which also occurs in IBD) is induced rather than constitutive, suggesting a potential role for cytokines that stimulate its production, such as IL-1 or TNF-α.

Early reports of PG emphasized the association with ulcerative colitis (UC) but, although UC remains more commonly associated with PG than is Crohn's disease, the latter became increasingly recognized as having an association with PG; both classic and peristomal PG have been reported with UC, Crohn's disease and collagenous colitis. Three areas of interest regarding the association of IBD with PG are the different immunopathogenesis of the UC (a Th2-type enteritis) and Crohn's disease (Th1-type), the role of cigarette smoking, and the role of bacteria, especially *E. coli* (discussed above). The possible protective role of smoking in UC has been uncertain, but a recent meta-analysis documented that smoking is protective against UC, is associated with less complications once UC has developed and with disease flares if smoking is discontinued, whereas the opposite (for all these aspects) applies to Crohn's disease [23]. A possible mechanism for the benefit of smoking on UC is that nicotine upregulates the lamina propria nicotinic acetylcholine receptor and could alter the bowel mucosal immune balance towards a Th1 pattern [24]. However, smoking is a significant factor favouring development of extraintestinal manifestations of UC, including PG and erythema nodosum [25]. Combined with the fact that PG may develop up to a decade after panproctocolectomy for UC [26], this dissociation of effect of smoking on the bowel and skin lesions suggests that the UC phenotype may be more important than the presence of colonic mucosa.

PG is not usually associated with vasculitis, but cases with positive tests for either C-ANCA or P-ANCA are occasionally reported (some in the context of drug-induced PG, typically with thiouracils). Patients with PG and other ANCA specificities are of some interest with regard to possible disease mechanisms. A patient who clinically had bullous and ulcerative PG on the legs, with polyarthritis, was found to have lung cysts and a novel ANCA to azurocidin [26]; the patient later developed a lesion on the ankle resembling blastomycosis-like pyoderma that was associated with autoantibodies to BPI. Azurocidin and BPI are antimicrobial components of neutrophil azurophilic granules (see discussion of ANCA in vasculitis, p. 50.8); antibodies to these proteins could potentially interfere with their antibacterial activity, thereby reducing innate immunity. Autoantibodies to azurocidin have also been associated with systemic and cutaneous vasculitis as well as with hydralazine-induced vasculitis [27]. More recently, a patient with PG and C-ANCA specific for h-lamp-2 has been reported [28].

Despite the evidence for cellular and cytokine responses being induced (presumably by antigenic stimuli), some cases may have a constitutive component. Several families with inherited PG have been described [29,30]; although cases have presented at any age in some kindreds, this should be noted as a possible explanation for neonatal PG which is generally rare [31]. There is also a predisposition to PG in patients with a mutation in caspase recruitment domain 15, leading to the autosomal dominant autoinflammatory syndrome of pyogenic arthritis, pyoderma gangrenosum and acne (PAPA); the relevant mutations affect CD2-binding protein 1 (CD2BP1, also known as PSTPIP1), a protein that is involved in cytoskeletal organization and that also reacts with pyrin, mutations in PAPA being predominantly expressed in granulocytes [32]. Other mutations in the same gene are the cause of some of the autoinflammatory (periodic fever) syndromes, some cases of Crohn's disease, familial granulomatous arthritis, and others [33,34].

References

1 Von den Driesch P. Pyoderma gangrenosum: a report of 44 cases with follow-up. *Br J Dermatol* 1997; **137**: 1000–5.

2 Jackson JM, Callen JP. Pyoderma gangrenosum: an expert commentary. *Expert Rev Dermatol* 2006; **1**: 391–400.
3 Wollina U. Pyoderma gangrenosum—a review. *Orphanet J Rare Dis* 2007; **2**: 19.
4 Samitz MH. Cutaneous vasculitis in association with ulcerative colitis. *Cutis* 1966; **2**: 383–7.
5 Ebringer A, Doyles AE, Harris GS. Dermonecrotic factor I: nature and properties of a dermonecrotic factor to guinea pig skin found in human serum. *Br J Exp Pathol* 1969; **50**: 559–65.
6 Samitz MH, Dana AS, Rosemberg P. Cutaneous vasculitis in association with Crohn's disease: review of statistics of skin complications. *Cutis* 1970; **6**: 51–6.
7 Lotti T, Ghersetich I, Comacchi C *et al*. Cutaneous small-vessel vasculitis. *J Am Acad Dermatol* 1998; **39**: 667–87.
8 Ullman S, Halberg P, Howitz J. Deposits of complement and immunoglobulins in vessel walls in pyoderma gangrenosum. *Acta Derm Venereol (Stockh)* 1982; **62**: 340–1.
9 Powell FC, Schroeter AL, Perry HO *et al*. Direct immunofluorescence in pyoderma gangrenosum. *Br J Dermatol* 1983; **108**: 287–93.
10 Samitz MH. Cutaneous vasculitis in association with ulcerative colitis. *Cutis* 1966; **2**: 383–7.
11 Driessen LHHM, Van Saene HKF. A novel treatment of pyoderma gangrenosum by intestinal decontamination. *Br J Dermatol* 1983; **108**: 108 [Abstract].
12 Marks DJ, Harbord MW, MacAllister R *et al*. Defective acute inflammation in Crohn's disease: a clinical investigation. *Lancet* 2006; **367**: 668–78.
13 Marks DJB, Rahman FZ, Novelli M *et al*. An exuberant inflammatory response to *E. coli*: implications for the pathogenesis of ulcerative colitis and pyoderma gangrenosum. *Gut* 2006; **55**: 1662–3.
14 Crowson NA, Nuovo GJ, Mihm MC Jr, Magro C. Cutaneous manifestations of Crohn's disease, its spectrum, and its pathogenesis: intracellular consensus bacterial 16S rRNA is associated with the gastrointestinal but not the cutaneous manifestations of Crohn's disease. *Hum Pathol* 2003; **34**: 1185–92.
15 Lazarus GS, Goldsmith LA, Rocklin RE *et al*. Pyoderma gangrenosum, altered delayed hypersensitivity, and polyarthritis. *Arch Dermatol* 1972; **105**: 46–51.
16 Brooklyn TN, Williams AN, Dunnill MGS, Probert CS. T-cell receptor repertoire in pyoderma gangrenosum: evidence for clonal expansions and trafficking. *Br J Dermatol* 2007; **157**: 960–6.
17 Mittal S, Milner BJ, Vickers MA. Pyoderma gangrenosum as a cause of splenomegaly and association with a T-cell clone. *Clin Lab Haematol* 2005; **6**: 402–4.
18 Magro CM, Kiani B, Li J, Crowson AN. Clonality in the setting of Sweet's syndrome and pyoderma gangrenosum is not limited to underlying myeloproliferative disease. *J Cutan Pathol* 2007; **34**: 526–34.
19 Nerella P, Daniela A, Guido M *et al*. Leukocyte chemotaxis and pyoderma gangrenosum. *Int J Dermatol* 1985; **24**: 45–7.
20 Papi M, Didona B, Chinni LM *et al*. Koebner phenomenon in an ANCA-positive patient with pyoderma gangrenosum. *J Dermatol* 1997; **9**: 583–6.
21 Oka M, Berking C, Nesbit M *et al*. Interleukin-8 overexpression is present in pyoderma gangrenosum ulcers and leads to ulcer formation in human skin xenografts. *Lab Invest* 2000; **80**: 595–604.
22 Oka M. Pyoderma gangrenosum and interleukin-8. *Br J Dermatol* 2007; **157**: 1279–81.
23 Latakos PL, Szamosi T, Latakos L. Smoking in inflammatory bowel disease: good, bad or ugly? *World J Gastroenterol* 2007; **13**: 6134–9.
24 Kikuchi H, Itoh J, Fukada S. Chronic nicotine stimulation modulates the immune response of mucosal T cells to Th1-dominant pattern by upregulation of Th1-specific transcriptional factor. *Neurosci Lett* 2008; **432**: 217–21.
25 Manguso F, Sanges M, Staiano T *et al*. Cigarette smoking and appendectomy are risk factors for extraintestinal manifestations in ulcerative colitis. *Am J Gastroenterol* 2004; **99**: 327–34.
26 Grattan CEH, McCann BG, Lockwood CM. Pyoderma gangrenosum, polyarthritis and lung cysts with novel antineutrophil cytoplasmic antibodies to azurocidin. *Br J Dermatol* 1998; **139**: 340–61.
27 Zhao MH, Lockwood CM. Azurocidin is a novel antigen for anti-neutrophil cytoplasmic autoantibodies (ANCA) in systemic vasculitis. *Clin Exp Immunol* 1996; **103**: 397–402.
28 Hoffman MD. Pyoderma gangrenosum associated with c-ANCA (h-lamp-2). *Int J Dermatol* 2001; **40**: 135–7.
29 Alberts JH, Sams HH, Miller JL. Familial ulcerative pyoderma gangrenosum: a report of two kindreds. *Cutis* 2002; **69**: 427–30.
30 Khandpur S, Mehta S, Reddy BS. Pyoderma gangrenosum in two siblings: a familial predisposition. *Pediatr Dermatol* 2001; **18**: 308–12.
31 al Rimawi HS, Abuekteish FM, Daoud AS, Oboosi MM. Familial pyoderma gangrenosum presenting in infancy. *Eur J Pediatr* 1996; **155**: 759–62.
32 Shoham NG, Centola M, Mansfield E *et al*. Pyrin binds the PSTPIP1/CD2BP1 protein, defining familial Mediterranean fever and PAPA syndrome as disorders in the same pathway. *Proc Natl Acad Sci USA* 2003; **100**: 13501–6.
33 Rose CD, Martin TM. Caspase recruitment domain 15 mutations and rheumatic diseases. *Curr Opin Rheum* 2005; **17**: 579–85.
34 Farasat S, Aksentijevich I, Toro JR. Autoinflammatory diseases: clinical and genetic advances. *Arch Dermatol* 2008; **144**: 392–402.

Histopathology. Although the histopathological findings of PG are often variable and non-specific, they can be useful in excluding other possible aetiologies. Several variables must be considered when evaluating the histopathology, including the type of lesion, the site of the lesion from which the biopsy is obtained, the site within the lesion (biopsy of the edge reduces potentially misleading features that may occur in any chronic ulcerating lesions), the stage of evolution of the lesion, and therapy [1]. Typical findings include central necrosis and ulceration of the epidermis and dermis surrounded by an intense, acute inflammatory cell infiltrate, with a more peripheral mixed to chronic inflammatory cell infiltrate [2–4]. Each clinical variant has additional, more specific, histopathological findings. In the ulcerative variant of PG, there is massive dermal–epidermal neutrophilic infiltrate with suppuration/abscess formation; in pustular PG, a perifollicular neutrophilic infiltrate with subcorneal pustule formation; the bullous variant shows a neutrophilic infiltrate with intraepidermal vesicle formation; and in vegetative PG, there is a granulomatous reaction with peripheral palisading histiocytes and giant cells [4,5]. Otherwise, the presence of giant cells appears to be linked with IBD, especially Crohn's disease (and thus with peristomal PG, but distinct from stomal involvement by Crohn's disease) [6]. Although of different importance between countries, and depending on immune status/associated haematological malignancy, culture and staining of biopsy tissue for fungi, mycobacteria and other organisms is advisable—especially if any granulomas are present in the absence of IBD.

The presence of vasculitis in PG is an area of debate. Many investigators have reported findings consistent with a neutrophilic vascular reaction or leukocytoclastic vasculitis, fibrinoid necrosis, segmental necrotizing vasculitis, granulomatous vasculitis and lymphocytic vasculitis [2–4,7–10], although this is not supported by all studies [11]. True vasculitides and infective causes should be carefully excluded if vasculitis is evident.

References

1 Powell FC, Su WPD. Pyoderma gangrenosum: classification and management. *J Am Acad Dermatol* 1996; **34**: 395–409.
2 Su WPD, Schoeter AL, Perry AL *et al*. Histopathologic and immunopathologic study of pyoderma gangrenosum. *J Cutan Pathol* 1996; **13**: 323–30.
3 Crowson NA, Mihm MC Jr, Magro C. Pyoderma gangrenosum: a review. *J Cutan Pathol* 2003; **30**: 97–107.
4 Benci M, Menchini G, Lotti TM. Pyoderma gangrenosum, an unusual aspect of cutaneous vasculitis. *Clin Dermatol* 1999; **17**: 581–5.
5 Callen JP. Pyoderma gangrenosum. *Lancet* 1998; **351**: 581–5.
6 Sanders S, Tahan SR, Kwan T, Magro CM. Giant cells in pyoderma gangrenosum. *J Cutan Pathol* 2001; **28**: 97–100.

7 Stolman LP, Rosenthal D, Yaworsky R *et al*. Pyoderma gangrenosum and rheumatoid arthritis. *Arch Dermatol* 1975; **111**: 1020–3.
8 Bishopric GA, Bracken JS. Pyoderma gangrenosum as the presenting sign of regional enteritis. *South Med J* 1964; **57**: 675.
9 Dantzig PI. Pyoderma gangrenosum. *N Engl J Med* 1975; **292**: 47–8.
10 Meler F, Berner D, Scherwitz C *et al*. An unusual case of pyoderma gangrenosum with necrotizing granulomatous dermatitis. *J Dtsch Dermatol Ges* 2003; **1**: 302–5.
11 Bennett ML, Jackson JM, Jorizzo JL *et al*. Pyoderma gangrenosum: a comparison of typical and atypical forms with an emphasis on time to remission. *Medicine* 2000; **79**: 37–46.

Clinical features. PG can have a variety of clinical presentations. Extracutaneous involvement is discussed separately later. Diagnostic criteria have been proposed for the cutaneous lesions of classic ulcerative PG [1], with various amendments suggested [2,8], and, although not formally validated, can be summarized as:

Major criteria (both required)

1 Rapid (usually >1 cm/day) progression of painful, necrolytic ulceration with an irregular, undermined, violaceous border—usually with a preceding papule, pustule or bulla, and pain out of proportion to the size of the ulcerated area
2 Exclusion of other causes of ulceration.

Minor criteria (at least two required)

1 (a) history of pathergy, or (b) presence of cribriform scarring
2 Presence of a disease known to be associated with PG (usually listed as IBD, polyarthritis, myelodysplasia or leukaemia, but monoclonal gammopathy should be added to this list; overall about 50% have an associated systemic disease)
3 Appropriate histopathological findings (again, specifically excluding infective causes)
4 Rapid response to oral corticosteroid therapy (usually interpreted as at least 50% reduction in size using 1–2 mg/kg/day).

As described above, for pragmatic reasons of diagnosis, disease association or therapy (below) we have divided the types of PG as follows:

Classic/ulcerative PG [2–9]. This is the commonest and best recognized variant of PG, presenting with small, tender, red–blue papules, plaques or pustules that evolve into painful ulcers with characteristic violaceous undermined edges (Fig. 50.37). There may be granulation tissue, necrosis or purulent exudate at the ulcer base. Lesions may be solitary or multiple, and occur most commonly on the legs (in 70%), but may affect any body site. Pathergy occurs in 25% (usually defined as following minor injuries such as venesection, but numerous reports of PG at operation sites, especially after breast surgery, are also reported, and other forms of skin injury such as scalds or varicella may also act as a pathergic trigger). Healing usually occurs with an atrophic cribriform scar. Associated symptoms include fever, malaise, myalgia and arthralgia. Frequent disease associations include IBD, arthritis, monoclonal gammopathy or internal malignancy; over 70% have one of these [4]. Genital and mucosal involvement (other than pyostomatitis vegetans) are generally considered to be within this category, but are discussed separately below as they raise additional diagnostic issues.



Fig. 50.37 Pyoderma gangrenosum. Classic type, showing a deep ulcer with inflammatory border.

Atypical forms. The term 'atypical PG' has been used in several rather different contexts, and it may be useful to subdivide them. At one time bullous PG, possibly overlapping with bullous Sweet's disease (and being strongly linked with haematological malignancy), was the main 'atypical' form. It is now more common for atypical PG to mean a pattern that is relatively superficial, may be pustular and Sweet's syndrome-like or may be ulcerated, tends to occur on hands, arms and face or upper trunk, and is linked with myeloproliferative disorders and gammopathies (usually IgA) [2,8]; it overlaps with neutrophilic dermatosis of the dorsal hands, discussed separately later. However, others view peristomal or genital PG as also being 'atypical'—to bridge this gap between terminologies, and to help explain the patterns, we have subdivided the 'atypical' forms of PG into three morphological types and some site-specific variants.

Atypical form: (a) pustular PG. Pustular PG is a variant, noted two decades ago [4], that often occurs during acute exacerbations of IBD. Discrete painful pustules, with a surrounding halo of erythema, develop on normal skin [4,9]. These pustules commonly arise with a scattered distribution on the extensor aspects of the limbs. Nomenclature for these lesions varies somewhat, including pustular vasculitis and neutrophilic pustules, as well as pustular PG. This diagnostic area is discussed later with some other pustular neutrophilic dermatoses. Pustular PG lesions often resolve with control of IBD (in some cases using treatments appropriate for both PG and for IBD, discussed later) but some may evolve to form ulcerated classic PG.

Atypical form: (b) bullous PG. This pattern has also traditionally been termed 'atypical' PG. It presents with rapidly arising, superficial, haemorrhagic bullae, often located on the arms [4,6].



Fig. 50.38 Pyoderma gangrenosum. Superficial granulomatous type; the breast is a common site.



Fig 50.39 Pyoderma gangrenosum. Peristomal type, with additional pathergic involvement of surgical wounds. Systemic therapy was contraindicated by pelvic sepsis but the lesion healed with very potent topical corticosteroid treatment. Opiate analgesia and nitrous oxide for severe local pain was able to be discontinued by using topical instillation of amethocaine-prilocaine cream for an hour before dressing changes.

It shares clinical and histopathological findings with Sweet's syndrome, but typically ulcerates and heals with scarring. Bullous PG is especially associated with myeloproliferative disorders [1,4,7,9,10]; if it occurs with IBD it is usually in patients with a significant disease flare.

Atypical form: (c) upper limbs/trunk/face. The pattern of PG that is now often simply referred to as 'atypical PG' [2,8] is a more superficial variant than classic PG. It can occur at any site but most commonly on the arms or face. It can be bullous, and it may be difficult to differentiate from Sweet's syndrome. It is viewed as including neutrophilic dermatosis of the dorsal hands (discussed separately below to explain nomenclature and histological features in more detail; p. 50.80 and Fig. 50.42). The importance of this pattern is that the strongest link with internal disease is with myelogenous leukaemias, myeloproliferative disorders or IgA gammopathies.

Superficial (vegetative) PG (synonym superficial granulomatous pyoderma) presents as a superficial ulcer, usually on the trunk (Fig. 50.38) or sometimes the face, although it can occur at other sites. It has a non-purulent base and generally lacks the violaceous, undermined border of classic PG [4,9,11]. It is often a solitary, slowly progressing, relatively non-painful, variant that resolves with less aggressive treatment [12] and is not usually associated with any systemic disease [13]. Infections are the commonest differential diagnosis. The confusingly similarly-named, morphologically similar, but pathogenetically quite different disorder pyoderma vegetans is discussed on p. 50.89.

Peristomal PG [2,7–9,14] is currently a relatively common pattern of PG, perhaps accounting for about 15% of cases, and sometimes coexisting with pustular vasculitis or PG at other sites (Fig. 50.39). It has several notable features: it is almost always associated with IBD, biopsy may show giant cells or bacteria (the latter mainly due to contamination/colonization of ulcerated skin), there is a significant risk of the area being treated as an infected or broken-down surgical wound, and therapy may be very difficult (see later). Other associations of peristomal PG include diverticular disease, bowel carcinoma, perforated bowel and neurogenic bladder in one series [14], as well as recent reports of collagenous colitis [15] and systemic sclerosis [16].

Other specific sites of PG that influence diagnostic aspects, disease associations or therapy

(a) **PG of the face, lips, orbital adnexae or upper trunk** has already been discussed as these are sites that should give rise to suspicion of associated myeloproliferative disease. However, PG at these areas also causes differential diagnostic problems that may be a lesser consideration at other sites; orbital cellulitis, destructive lymphomas and factitious disease (discussed later) cause particular problems. Ulcerated neoplasms that have been concealed also need to be considered. Another difficult differential diagnosis is a condition termed malignant pyoderma (MP), first described by Perry *et al*. in 1968 [17] as a rapidly progressive ulcerative disease localized to the head, neck and upper trunk. Controversy exists as to whether MP represents a head and neck variant of PG or a cutaneous manifestation of WG. PG and WG may have similar clinical and histopathological findings, and both have been the reported cause of MP in some cases [18–22]. Interestingly, two of the original three reported cases of MP are now believed to represent WG. The presence of C-ANCA, which is highly specific for WG, should mean that it is now easier to distinguish PG from WG. However, some patients with WG may have negative C-ANCA test results, and thus close follow-up is war-

ranted for possible pulmonary or renal lesions that may develop in WG [21–23]. Because of the uncertainty regarding the nosology of MP, it has been suggested that this term should not be used as a final diagnosis [21].

(b) **PG of the genitalia** includes both penile [24] and vulval involvement. There is no reason to suppose that these sites of involvement represent a different form of PG (except perhaps in children, as perianal and genital involvement appears to be over-represented in the first decade of life [25]), or have specific disease associations, but differential diagnosis (below) may be difficult and PG may not be suspected.

(c) **PG of the breast** is also not a specific entity—most cases are either vegetative PG, or the breast is affected with the face or arms in the haematological disease-associated atypical variety. However, there are again specific differential diagnosis issues, one that has caused some problems in recent publications being that of factitial disease (discussed below). PG after breast surgery has been reported on many occasions [26,27].

(d) **PG of oral, pharyngeal, laryngeal, nasal, respiratory tract and ocular mucosae** [28–34] does have some reasons to be discussed separately. Diagnosis and treatment may be difficult, and respiratory involvement may have a predilection for children [33,34]. Ocular lesions are documented in Table 50.18, the most specific being peripheral ulcerative keratitis [28] and possibly nodular episcleritis. Pyostomatitis vegetans is an oral mucosal disease that in some instances appears to be related to PG, having a very strong link with IBD, but is less certain in other instances—it is briefly discussed separately below. Other oral lesions may be aphthous, pustular, frank extensive PG [29,30] or occur within the spectrum of Behçet's disease [31]. Nasal mucosal involvement may occur [29,32], even septal perforation [32], as well as tracheal [33] or respiratory tract involvement [34], either of these having a differential diagnosis of WG as discussed above for 'malignant pyoderma'.

(e) Systemic disease (affecting lung, bone, etc.) is discussed separately on p. 50.81.

Pyostomatitis vegetans [35–38] is nosologically an enigmatic disorder. It is a disorder in which there is oral mucosal thickening with multiple pustules and 'snail track' ulcers on an erythematous base (at any site, although the tongue is less affected). The oral lesions have a very strong link with IBD, especially active ulcerative colitis; this, combined with the presence of Sweet's syndrome-like or PG-like skin lesions in some cases, has led several reviewers to consider this disorder as a manifestation of PG. However, several factors argue against this. Although deeper tissues have a mixed infiltrate including neutrophils, early and superficial lesions have a preponderance of eosinophils and often associated peripheral blood eosinophilia. The skin lesions (perhaps best termed pyodermatitis vegetans, and discussed later in the differential diagnosis of pustular eruptions, p. 50.89) are often flexural and (although clearly distinguished by histology and direct immunofluorescence) are clinically more suggestive of pemphigus vegetans. The various terminologies are used interchangeably, which does not enhance understanding. On present evidence, it is probably best to view this as a predominantly IBD-associated eruption but not as a form of PG.

Diagnosis. There are two facets to diagnosis in PG; one is distinguishing PG from several possible alternatives, and the other is evaluation for underlying causes (of which arthritis and IBD are generally apparent, but haematological causes may not be). PG is often a diagnosis of exclusion as laboratory and histopathological findings are variable and non-specific; some of the more important differential diagnoses are enumerated in Table 50.19 [7–9,39,40]. Patient evaluation should include a detailed history, physical examination and skin biopsies for histopathology and culture (including unusual fungi, atypical mycobacteria and opportunistic infections, in the majority of cases), as well as appropriate laboratory tests to help rule out other possible aetiologies. Sweet's syndrome can often be distinguished by its rather sudden onset of non-ulcerating lesions that generally heal without scarring, although both share some aetiologies, both may coexist, and (especially associated with haematological malignancy) a clinical picture with features of both may occur (typically bullous, and variably termed atypical Sweet's syndrome or atypical PG). Syndromes with vasculitis such as WG, Behçet's disease and SLE can also be confused with PG; however, leukocytoclastic vasculitis is not a feature of PG.

There are examples of both factitious disease or other causes of ulceration being erroneously diagnosed as PG [40,41], and PG has also been misdiagnosed as factitial [42]; both situations are hugely important due to the extensive tissue destruction that may occur, so, provided infection is excluded, a trial of corticosteroid therapy is appropriate as PG is likely to respond. However, this should be limited in duration and other diagnoses considered if response is poor. In one study of 95 patients with ulcers resembling PG, 64 had been treated on this basis for 3–180 (median 10) months, 23 (36%) without response and eight (12%) with deterioration; final diagnoses included vascular occlusion, venous disease, vasculitis, neoplasia, various forms of tissue injury (five had factitial disease) and other inflammatory disorders [40].

In evaluation of associated diseases, it should be noted that the course of PG does not necessarily parallel that of IBD, but that PG in haematological disorders (unless provoked by a neutrophil-increasing therapy, such as colony-stimulating factors) may be an indicator of transformation to a higher grade malignancy [43–45]. Thus careful re-evaluation is appropriate. It is also worth considering re-evaluation of patients with ulcerative colitis who develop peristomal PG, as some will prove to have Crohn's disease.

References

1 Su WPD, Davis MD, Weenig RH *et al*. Pyoderma gangrenosum: clinicopathologic correlation and proposed diagnostic criteria. *Int J Dermatol* 2004; **43**: 790–800.

2 Callen JP, Jackson JM. Pyoderma gangrenosum: an update. *Rheum Dis Clin N Am* 2007; **33**: 787–802.

3 Callen JP. Pyoderma gangrenosum and related disorders. *Dermatol Clin* 1990; **7**: 1249–59.

4 Powell FC, Su WPD. Pyoderma gangrenosum: classification and management. *J Am Acad Dermatol* 1996; **34**: 395–409.

5 Powell FC, Schroeter AL, Su WPD *et al*. Pyoderma gangrenosum: a review of 86 patients. *QJM* 1985; **55**: 173–86.

6 Bennett ML, Jackson JM, Jorizzo JL *et al*. Pyoderma gangrenosum: a comparison of typical and atypical forms with an emphasis on time to remission. *Medicine* 2000; **79**: 37–46.

7 Wollina U. Pyoderma gangrenosum—a review. *Orphanet J Rare Dis* 2007; **2**: 19.

Table 50.19 Some differential diagnoses of pyoderma gangrenosum.

Category	Examples	Comment
Infection	Bacterial: ecthyma, mycobacteria, syphilis, tropical ulcer, necrotizing fasciitis; folliculitis, gonococcaemia and other pustular infections may also mimic pustular PG Fungi: blastomycosis, sporotrichosis, cryptococcosis, zygomycoses, alternaria, *Penicillium marneffei* Viral: herpes simplex Other: amoebiasis	Consider infections especially in instances where 'pathergy' may have actually represented inoculation, and in immunosuppressed subjects (including therapeutic immunosuppression for IBD or arthritis, haematology disease-related immune compromise)
Vascular disease	Arterial disease, venous disease Occlusive angiopathic disorders (cryogelling, livedoid vasculopathy, antiphospholipid syndrome, calcific uraemic arteriolopathy, etc. (Chapter 49) Others: sickle cell disease, thalassaemia/haemoglobinopathies	
Vasculitis	Wegener's granulomatosis (WG), leukocytoclastic vasculitis, polyarteritis nodosa, mixed cryoglobulinaemia, Takayasu's arteritis	The differential diagnosis of WG may be difficult at head and neck sites, or if there is internal neutrophilic dermatosis
Neoplasia	Lymphoma (especially aggressive angiocentric T-cell lymphomas, anaplastic large cell lymphoma, bullous mycosis fungoides) Leukaemia cutis Langerhans' cell histiocytosis	Both a differential diagnosis and a possible cause of PG
Drugs	Halides: e.g. bromoderma Ulceration due to hydroxycarbamide Drug-induced lupus erythematosus	Check ANCA, often positive in thiouracil-induced PG or vasculitis; note that drugs may cause true PG rather than simulators Ulceration due to hydroxycarbamide particularly needs to be considered in patients being treated with this for a known haematological disorder
Other tissue injury	Necrotic bite reations: spiders, others Factitious injury (including panniculitis due to infective or toxic agents); intravenous drug abuse (± secondary infection); cocaine ulceration	Beware of cases without a response to corticosteroids
Medical disorders	Amyloidosis (especially bullous) Ulcerative sarcoidosis Cutaneous (metastatic) Crohn's disease Other neutrophilic disorders Necrobiosis lipoidica Pyodermatitis–pyostomatitis vegetans (see text)	Many of these have also been described as causes of PG

8 Jackson JM, Callen JP. Pyoderma gangrenosum: an expert commentary. *Expert Rev Dermatol* 2006; **1**: 391–400.
9 Ahmadi S, Powell FC. Pyoderma gangrenosum: uncommon presentations. *Clin Dermatol* 2005; **23**: 612–20.
10 Perry HO, Winkelmann RK. Bullous pyoderma gangrenosum and leukaemia. *Arch Dermatol* 1972; **106**: 901–5.
11 Wilson-Jones E, Winkelmann RK. Superficial granulomatous pyoderma: a localized vegetative form of pyoderma gangrenosum. *J Am Acad Dermatol* 1988; **18**: 511–21.
12 Lichter MD, Welykyj SE, Gradini R *et al*. Superficial granulomatous pyoderma. *Int J Dermatol* 1991; **30**: 418–21.
13 Quimby SR, Gibson LE, Winkelmann RK. Superficial granulomatous pyoderma: clinicopathologic spectrum. *Mayo Clin Proc* 1989; **64**: 37–43.
14 Lyon CC, Smith AJ, Beck MH *et al*. Parastomal pyoderma gangrenosum: clinical features and management. *J Am Acad Dermatol* 2000; **42**: 992–1002.
15 Davis MPD, Holderness Nakamura KJ. Peristomal pyoderma gangrenosum associated with collagenous colitis. *Arch Dermatol* 2007; **143**: 669–70.
16 Fujikura M, Ohtsuka T, Oyamada Y. Systemic sclerosis in association with peristomal pyoderma gangrenosum. *Br J Dermatol* 2007; **157**: 618–9.
17 Perry HO, Winkelmann RK, Muller SA *et al*. Malignant pyodermas. *Arch Dermatol* 1968; **98**: 561–74.
18 Malkinson FD. Pyoderma gangrenosum vs. malignant pyoderma: lumpers vs. splitters. *Arch Dermatol* 1987; **123**: 333–7.
19 Erdi H, Anadolu R, Piskin G *et al*. Malignant pyoderma: a clinical variant of pyoderma gangrenosum. *Int J Dermatol* 1996; **35**: 811–3.
20 Spenatto N, Viraben R. Malignant pyoderma. *J Eur Acad Dermatol Venereol* 1999; **12**: 275–6.
21 Gibson LE, Daoud MS, Perry HO. Malignant pyodermas revisited. *Mayo Clin Proc* 1997; **72**: 734–6.
22 Cone LA, Annunsiata GM, Gebhart RN *et al*. Malignant pyoderma and Wegener's granulomatosis. *Mayo Clin Proc* 1998; **73**: 390–1.
23 Jayne DRW, Rasmussen N (European Community Systemic Vasculitis Clinical Trials Study Group (ECSYSVASTRIAL)). Treatment of antineutrophil cytoplasm autoantibody-associated systemic vasculitis: initiatives of the European Community Systemic Vasculitis Trials Study Group. *Mayo Clin Proc* 1997; **72**: 737–47.
24 OLally A, Hollowood K, Bunker CB, Turner R. Penile pyoderma gangrenosum treated with topical tacrolimus. *Arch Dermatol* 2005; **141**: 1175–6.
25 Graham JA, Hansen KK, Rabinowitz LG, Esterley NB. Pyoderma gangrenosum in infants and children. *Pediatr Dermatol* 1994; **11**: 10–17.
26 van Pouke S, Jorens PG, Peeters R *et al*. Pyoderma gangrenosum: a challenging complication of bilateral mastopexy. *Int Wound J* 2004; **1**: 207–13.
27 Davis MPD, Alexander JL, Prawer SE. Pyoderma gangrenosum of the breasts precipitated by breast surgery. *J Am Acad Dermatol* 2006; **55**: 317–20.
28 Wilson DM, John JR, Callen PR. Peripheral ulcerative keratitis: an extracutaneous neutrophilic disorder. Report of a patient with rheumatoid arthritis, pustular

vasculitis, pyoderma gangrenosum, and Sweet's syndrome with an excellent response to cyclosporine therapy. *J Am Acad Dermatol* 1999; **40**: 331–4.
29 Kennedy KS, Prendergast ML, Sooy CD. Pyoderma gangrenosum of the oral cavity, nose and larynx. *Otolaryngology* 1987; **97**: 487–90.
30 Setterfield JF, Shirlaw PJ, Challacombe SJ, Black MM. Pyoderma gangrenosum associated with severe oropharyngeal involvement and IgA paraproteinaemia. *Br J Dermatol* 2001; **144**: 402–5.
31 Munro CS, Cox NH. Pyoderma gangrenosum associated with Behçet's syndrome: response to thalidomide. *Clin Exp Dermatol* 1988; **13**: 408–10.
32 Somura I, Miyawaki S, Morita A. Pyoderma gangrenosum associated with nasal septal perforation, oropharyngeal ulcers and IgA paraproteinaemia. *J Dermatol* 2005; **32**: 193–8.
33 Merke DP, Honig PJ, Potsic WP. Pyoderma gangrenosum of the skin and trachea in a 9-month-old boy. *J Am Acad Dermatol* 1996; **34**: 681–2.
34 Takeuchi K, Kyoko H, Hachiya M *et al*. Pyoderma gangrenosum of the skin and respiratory tract in a 5-year-old girl. *Eur J Pediatr* 2003; **162**: 344–5.
35 Storwick GS, Prihoda MB, Fulton RJ, Wood WS. Pyoderma—pyostomatitis vegetans: a specific marker for inflammatory bowel disease. *J Am Acad Dermatol* 1994; **31**: 336–41.
36 Mehravaran M, Kemény L, Husz S *et al*. Pyoderma–pyostomatitis vegetans. *Br J Dermatol* 1997; **137**: 266–9.
37 Nigen S, Poulin Y, Rochette L *et al*. Pyoderma–pyostomatitis vegetans. Two cases and a review of the literature. *J Cutan Med Surg* 2003; **7**: 250–5.
38 Hegarty AM, Barrett AW, Scully C. Pyostomatitis vegetans. *Clin Exp Dermatol* 2003; **29**: 1–7
39 Powell FC, Collins S. Pyoderma gangrenosum. *Clin Dermatol* 2000; **18**: 283–93.
40 Weenig RH, Davis MPD, Dahl PR, Su WPD. Skin ulcers misdiagnosed as pyoderma gangrenosum. *N Engl J Med* 2002; **347**: 1412–8.
41 Oh CCY, McKenna DB, McLaren KM, Tidman MJ. Factitious panniculitis masquerading as pyoderma gangrenosum. *Clin Exp Dermatol* 2005; **30**: 253–5.
42 Harries MJ, McMullen E, Griffiths CEM. Pyoderma gangrenosum masquerading as dermatitis artefacta. *Arch Dermatol* 2006; **142**: 1509–10.
43 Sheps M, Shapero H, Ramsay C. Bullous pyoderma gangrenosum and acute leukaemia. *Arch Dermatol* 1978; **114**: 1842–3.
44 Cox NH, White SI, Walton S *et al*. Pyoderma gangrenosum associated with polycythaemia rubra vera. *Clin Exp Dermatol* 1987; **12**: 375–7.
45 Grob JJ, Mege JL, Frax AM *et al*. Disseminated pustular dermatosis in polycythemia vera. *J Am Acad Dermatol* 1988; **18**: 1212–8.

Treatment. Many effective treatment strategies have been reported, and have been the subject of extensive review articles [1–6], some evidence-based from literature on large numbers of patients [5], some giving doses and hints for use [4] and others addressing specific patterns of PG [6].

Choice of treatment generally depends on disease severity as well as on the presence of associated disease. For early or mild lesions, topical therapy may be sufficient [1]. This includes wet compresses, hydrophilic occlusive dressings, antimicrobial agents and topical corticosteroids. Topical tacrolimus is also useful for treatment of early PG lesions [7], and intralesional corticosteroids are another therapeutic option of reported benefit [8]. Indeed there may be situations, for example if there is a post-surgical infection which precludes use of systemic immunosuppressive therapy, where analgesia and topical treatment of PG is the most appropriate option (Fig. 50.39). Other topical agents, such as benzoyl peroxide, 5-aminosalicylic acid, nitrogen mustard (20% aqueous), cromoglycate preparations, platelet-derived growth factor, and intralesional therapy with ciclosporin, all have only anecdotal or small series data [5]. Topical nicotine cream was not considered in [5], but a recent (two patient) report supported previous suggestions of efficacy [9].

For more severe disease, or for PG resistant to topical therapy, oral corticosteroids have been the mainstay of therapy. Pulsed intravenous corticosteroid therapy has been reported to be effective in some cases refractory to oral corticosteroids; it has been recommended in PG refractory to other forms of treatment [10]. Evidence for benefit from sulphones and other antimicrobials such as dapsone, clofazimine and minocycline, which may have anti-inflammatory effects or modulate neutrophil function, is anecdotal [5]; however, these are widely used alone or with corticosteroids. Dapsone is probably most frequently used, although low-dose colchicine was recently advocated in a report of two patients [11]. Various immunosuppressant agents (Table 50.20) have been found to be useful in corticosteroid-unresponsive PG, either alone or as corticosteroid-sparing agents. Assessing their individual benefit is difficult as many have been used with other therapy, such as corticosteroids; because of the risk of severe adverse effects such as bone marrow suppression, use of these agents has usually been limited to severe or refractory PG. Ciclosporin was widely used due to rapid action [2] and several case series were published [5], but is not ideal long term. Cyclophosphamide, chlorambucil, intravenous tacrolimus, mycophenolate mofetil and thalidomide have all been effective in a limited number of patients reported [1–6,12–20]; although not providing high-quality evidence, use of these agents has often been in patients refractory to less complex therapies. Ideally, it is best to choose a treatment that will also address any underlying disease, such as melphalan in the case of patients with paraproteinaemia [21], or methotrexate in those with underlying arthritis or IBD [22]. In peristomal PG [6], there are two main issues that are slightly different from treatment of PG at other sites; one of these is that topical therapies (typically corticosteroids or tacrolimus) need to be formulated in a way that neither irritates unduly nor interferes with adhesion of appliances, the other is that, because of the strong link with IBD, there may be a lower threshold to consider systemic therapies (especially those that may be beneficial for both the PG and the bowel disease). Intralesional corticosteroids may avoid some of these problems. Achieving analgesia at this site, where activity of the stoma and need for adhesive appliances in close proximity to the PG both potentially add to discomfort, may be difficult.

In many of these situations, biologically engineered TNF-α inhibitors are now being used in preference to older agents, especially where there is associated IBD or inflammatory arthritis which is also likely to respond; there are several reports of benefit to etanercept, adalimumab and infliximab [23–29]. These reports include one randomized, controlled trial of infliximab (with benefit unrelated to underlying disease) [25], a report of benefit from adalimumab after failure of etanercept [24], reports of benefit of infliximab in vegetative PG [26] and in PG as part of PAPA syndrome [27], and a report of use of infliximab and adalimumab in systemic PG (aseptic abscesses of psoas muscle and spleen) [28]. However, these agents are expensive, and are contraindicated in the presence of malignancy or infection, but may be the most appropriate choice for severe PG with associated active IBD [29].

Other treatments that have been effective in small studies include plasmapheresis [14], leukocytapheresis/granulocytapheresis [30,31] and intravenous immunoglobulin (IVIG) [32–34]. In a retrospective review of ten therapy-resistant patients treated with IVIG, seven cleared, six maintaining benefit with ongoing

Table 50.20 Therapeutic ladder for pyoderma gangrenosum.

Topical:
Topical or intralesional corticosteroids (2)
Tacrolimus (2)
Nicotine (3)
Cromolyn sodium/disodium cromoglycate (3)
Platelet-derived growth factor (3)
Systemic:
Prednisolone (oral or pulsed intravenous) (2)
Dapsone (2), sulphapyridine (3), sulphamethoxypyridazine (3)
Minocycline (3)
Clofazimine (2)
Colchicine (3)
Potassium iodide (3)
Sulfasalazine (2)
Infliximab (1)
Etanercept (3)
Adalimumab (3)
Thalidomide (3)
Methotrexate (weekly pulse) (3)
Ciclosporin (2)
Azathioprine (3)
Cyclophosphamide (3)
Mycophenolate mofetil (3)
Intravenous immunoglobulins (2)
Colony-stimulating factors (perilesional injection) (3)
Interferon-α (3; a patient with hepatitis C)
Other (physical and non-drug therapies):
Skin grafting, flap repairs etc. (3)
Bioengineered skin equivalents, cultured keratinocyte sheets and other keratinocyte delivery systems (3)
Hyperbaric oxygen (3)
Low pressure dressings (3)
Leukocytapheresis/granulocytapheresis (3)
Radiotherapy (3; probably not beneficial)

1, double-blind studies; 2, case series (> just 2 or 3 cases); 3, case reports.

intermittent infusions [33]; one study reported rapid relief of pain after IVIG [34]. Aggressive surgical debridement is contraindicated because of possible exacerbation of PG by the pathergic response. However, split-skin grafts and cultured keratinocyte autografting have been demonstrated to be effective if performed while the pathergic response is minimized using prolonged courses of immunosuppressants, and a variety of bioengineered dressings or keratinocyte delivery systems have been tried [5,35–37]. Low-pressure dressings, and hyperbaric oxygen therapy, have been reported as beneficial in single cases. Gradient support hosiery is probably beneficial for leg lesions.

Therapy decisions depend on an assessment of the degree of active inflammation as opposed to simple wound healing requirements in refractory ulcers. Treatment of PG is usually discontinued after complete healing of lesions. Recurrences may occur but are unpredictable and therefore do not justify prolonged maintenance therapy [2]. A summary of therapeutic options for PG is depicted in Table 50.20; in general, initial treatment for localized disease comprises topical or intralesional corticosteroid or topical tacrolimus, for resistant localized or more widespread PG comprises systemic corticosteroids with possible addition of one of the less toxic steroid-sparing agents (usually dapsone, mycophenolate mofetil, medium-term ciclosporin), and for more severe disease, or where there is an associated disease requiring concurrent therapy, an appropriate systemic agent (increasingly, an anti-TNF monoclonal agent).

References

1 Powell FC, Su WPD. Pyoderma gangrenosum: classification and management. *J Am Acad Dermatol* 1996; **34**: 395–409.
2 Chow RKP, Ho VC. Treatment of pyoderma gangrenosum. *J Am Acad Dermatol* 1996; **34**: 1047–60.
3 Ahmadi S, Powell FC. Pyoderma gangrenosum: uncommon presentations. *Clin Dermatol* 2005; **23**: 612–20.
4 Jackson JM, Callen JP. Pyoderma gangrenosum: an expert commentary. *Expert Rev Dermatol* 2006; **1**: 391–400.
5 Reichrath J, Bens G, Bonowitz A, Tilgen W. Treatment recommendations for pyoderma gangrenosum: an evidence-based review of the literature based on more than 350 patients. *J Am Acad Dermatol* 2005; **53**: 273–83.
6 Lyon CC, Smith AJ, Beck MH *et al*. Parastomal pyoderma gangrenosum: clinical features and management. *J Am Acad Dermatol* 2000; **42**: 992–1002.
7 Petering H, Kiehl P, Breuer C *et al*. Pyoderma gangrenosum: successful topical therapy with tacrolimus (FK506). *Hautarzt* 2001; **52**: 47–50.
8 Gardner LW, Acker DW. Triamcinolone and pyoderma gangrenosum. *Arch Dermatol* 1972; **106**: 559–60.
9 Patel GK, Rhodes JR, Evans B, Holt PJA. Successful treatment of pyoderma gangrenosum with topical 0.5% nicotine cream. *J Dermatol Treat* 2004; **15**: 122–5.
10 Johnson RB, Lazarus GS. Pulse therapy: therapeutic efficacy in the treatment of pyoderma gangrenosum. *Arch Dermatol* 1982; **118**: 76–84.
11 Kontochristopoulos GJ, Stavropoulos PG, Gregoriou S *et al*. Treatment of pyoderma gangrenosum with low-dose colchicine. *Dermatology* 2004; **209**: 233–6.
12 Callen JP, Case JD, Sager D. Chlorambucil: an effective corticosteroid sparing therapy for pyoderma gangrenosum. *J Am Acad Dermatol* 1989; **21**: 515–9.
13 Newell LM, Malkinson FD. Pyoderma gangrenosum: response to cyclophosphamide therapy. *Arch Dermatol* 1983; **119**: 495–7.
14 Kaminska R, Ikaheimo R, Hollmen A. Plasmapheresis and cyclophosphamide as successful treatments for pyoderma gangrenosum. *Clin Exp Dermatol* 1999; **24**: 81–5.
15 Ackerman D, Abu-Elmagd K, Venkataramanan K *et al*. Recalcitrant psoriasis and pyoderma gangrenosum treated with FK506. *J Invest Dermatol* 1991; **96**: 536.
16 Munro CS, Cox NH. Pyoderma gangrenosum associated with Behçet's syndrome: response to thalidomide. *Clin Exp Dermatol* 1988; **13**: 408–10.
17 Federman GL, Federman DG. Recalcitrant pyoderma gangrenosum treated with thalidomide. *Mayo Clin Proc* 2000; **75**: 842–4.
18 Daniels LH, Callen JP. Mycophenolate mofetil is an effective treatment for peristomal pyoderma gangrenosum. *Arch Dermatol* 2004; **140**: 1427–9.
19 Cox NH, Palmer JG. Bowel-associated dermatitis-arthritis syndrome associated with ileo-anal pouch anastamosis, and treatment with mycophenolate mofetil. *Br J Dermatol* 2003; **149**: 1296–7.
20 Lee MR, Cooper MJ. Mycophenolate mofetil in pyoderma gangrenosum. *J Dermatol Treat* 2004; **15**: 303–7.
21 Moller H, Waldenstrom JG, Kettervall O. Pyoderma gangrenosum (dermatitis ulcerosa) and monoclonal (IgA) globulin healed after melphalan treatment. *Acta Med Scand* 1978; **203**: 293–6.
22 Bennett ML, Jackson JM, Jorizzo JL *et al*. Pyoderma gangrenosum: a comparison of typical and atypical forms with an emphasis on time to remission. *Medicine* 2000; **79**: 37–46.
23 Pastor N, Betlloch I, Pascua JC *et al*. Pyoderma gangrenosum treated with anti-TNF alpha therapy (etanercept). *Clin Exp Dermatol* 2005; **31**: 152–3.
24 Pomerantz RG, Husni ME, Mody E, Qureshi AA. Adalimumab for treatment of pyoderma gangrenosum. *Br J Dermatol* 2007; **157**: 1274–5.
25 Brooklyn TN, Dunnill MSG, Shetty A *et al*. Infliximab for the treatment of pyoderma gangrenosum: a randomized, double blind, placebo controlled trial. *Gut* 2006; **55**: 505–9.

26 Marzano AV, Tourlaki A, Alessi E, Caputo R. Widespread idiopathic pyoderma gangrenosum evolved from ulcerative to vegetative type: a 10-year history with a recent response to infliximab. *Clin Exp Dermatol* 2007; **33**: 156–9.
27 Stichweh DS, Punaro M, Pascual V. Dramatic improvement of pyoderma gangrenosum with infliximab in a patient with PAPA syndrome. *Pediatr Dermatol* 2005; **22**: 262–5.
28 Hubbard VG, Friedmann AC, Goldsmith P. Systemic pyoderma gangrenosum responding to infliximab and adalimumab. *Br J Dermatol* 2005; **152**: 1059–61.
29 Reguiaï Z, Grange F. The role of anti-tumor necrosis factor-alpha therapy in pyoderma gangrenosum associated with inflammatory bowel disease. *Am J Clin Dermatol* 2007; **8**: 767–77.
30 Fujimoto E, Fujimoto N, Kuroda K, Tajima S. Leukocytapheresis treatment for pyoderma gangrenosum. *Br J Dermatol* 2004; **151**: 1090–2.
31 Okuma K, Mitsuishi K, Hasegawa T *et al*. A case report of steroid and immunosuppressant-resistant pyoderma gangrenosum successfully treated by granulocytapheresis. *Therap Apher Dial* 2007; **11**: 387–90.
32 Dirschka T, Kastner U, Behrens S *et al*. Successful treatment of pyoderma gangrenosum with intravenous human immunoglobulin. *J Am Acad Dermatol* 1998; **39**: 789–90.
33 Cummins DL, Anhalt GJ, Monahan T, Meyerle JH. Treatment of pyoderma gangrenosum with intravenous immunoglobulin. *Br J Dermatol* 2007; **157**: 1235–9.
34 Kreuter A, Reich-Schupke S, Stücker M *et al*. Intravenous immunoglobulin for pyoderma gangrenosum. *Br J Dermatol* 2008; **158**: 856–7.
35 Cliff S, Holden CA, Thomas PR *et al*. Split skin grafts in the treatment of pyoderma gangrenosum. *Ann Plast Surg* 2001; **46**: 23–8.
36 Limova M, Mauro T. Treatment of pyoderma gangrenosum with cultured keratinocyte autografts. *J Dermatol Surg Oncol* 1994; **20**: 833–6.
37 de Imus G, Golomb C, Wilkel C *et al*. Accelerated healing of pyoderma gangrenosum treated with bioengineered skin and concomitant immunosuppression. *J Am Acad Dermatol* 2001; **44**: 61–6.

Sweet's syndrome

Synonyms
- Acute febrile neutrophilic dermatosis
- Gomm–Button disease

Definition. Sweet's syndrome is characterized by fever, peripheral neutrophil leukocytosis, acute onset of painful, erythematous papules, plaques or nodules and histological findings of a dense neutrophilic infiltrate without evidence of primary vasculitis [1]. Sweet's syndrome can be subdivided into three groups, depending on the clinical setting:

1 classical or idiopathic (classical may be the better term, as upper respiratory and other infections, IBD and pregnancy are all well documented triggers; thus the condition is not really idiopathic in such cases)
2 malignancy-associated
3 drug-induced [2].

Diagnostic criteria have been proposed for Sweet's syndrome [3,4] and also specifically for drug-induced cases [5]. The subject has been reviewed on many occasions, including two recent and comprehensive reviews [6,7]. It is also now acknowledged to have systemic manifestations, discussed separately (p. 50.81).

History and nomenclature. Sweet first described eight women with a 'distinctive and fairly severe illness' in 1964 [1]. The name Gomm–Button disease referred to initial patients with the condition. In retrospect, a patient described by Costello [8] probably had the same condition and was thus the first malignancy-associated case, having acute myelogenous leukaemia [8]. Sweet's syndrome is now considered the prototype of the wider spectrum of neutrophilic dermatoses discussed earlier.

References

1 Sweet RD. An acute febrile neutrophilic dermatosis. *Br J Dermatol* 1964; **76**: 349–56.
2 Cohen PR, Kurzrock R. Sweet's syndrome: a neutrophilic dermatosis classically associated with acute onset and fever. *Clin Dermatol* 2000; **18**: 265–82.
3 Su WPD, Liu H-NH. Diagnostic criteria for Sweet's syndrome. *Cutis* 1986; **37**: 167–74.
4 von den Driesch P. Sweet's syndrome: acute febrile neutrophilic dermatosis. *J Am Acad Dermatol* 1994; **31**: 535–56.
5 Walker DC, Cohen PR. Trimethoprim-sulfamethoxazole-associated acute febrile neutrophilic dermatosis: case report and review of drug induced Sweet's syndrome. *J Am Acad Dermatol* 1996; **34**: 918–23.
6 Cohen PR, Kurzrock R. Sweet's syndrome revisited: a review of disease concepts. *Int J Dermatol* 2003; **42**: 761–78.
7 Cohen PR. Sweet's syndrome—a comprehensive review of an acute febrile neutrophilic dermatosis. *Orphanet J Rare Dis* 2007; **2**: 34.
8 Costello MJ, Canizares O, Montague M III *et al*. Cutaneous manifestations of myelogenous leukaemia. *Arch Dermatol* 1955; **71**: 605–14.

Aetiology and pathogenesis. Sweet's syndrome is associated with underlying disease in approximately 50% of cases (Table 50.21) [1–6].

Classical or idiopathic Sweet's syndrome typically affects women in the third to fifth decade and has been associated with infection (streptococcal upper respiratory infections and yersinial gastrointestinal infections), IBD (ulcerative colitis and Crohn's disease) [1–6] and pregnancy [7].

Malignancy-associated Sweet's syndrome is estimated to comprise 20–25% [1,3,4,8–10]; in this situation, men and women are equally affected [3,10]. Most tumours are haematological malignancies, especially acute myelogenous leukaemia. However, solid tumours, most commonly of genitourinary organs, breast and gastrointestinal tract, are present in about 15% [8,9]. Sweet's syndrome may be the initial manifestation of malignancy or may precede the diagnosis by months to years, making close follow-up essential. In addition, recurrent episodes of Sweet's syndrome may be an indication of cancer recurrence [2,10].

Drug-induced Sweet's syndrome most commonly occurs in patients receiving granulocyte colony-stimulating factor (G-CSF) therapy [11,12], including recent pegylated types and other newer preparations [13,14]. Additional drugs implicated include all-*trans*-retinoic acid [15,16], minocycline [17,18], trimethoprim–sulfamethoxazole [19], carbamazepine [5] and oral contraceptives [20]; other drug associations (some possibly being coincidental) are listed in [3,21].

Other conditions reported in association with Sweet's syndrome include Behçet's disease [22], erythema nodosum [23], sarcoidosis [24–26], rheumatoid arthritis [4,27] and thyroid disease [28]; again, some reports may represent coincidental occurrences rather than true disease associations. The most reported, or most logical, are listed in Table 50.21. Triggering by various different types of trauma, although possibly only relevant if there is an existing systemic stimulus, are discussed in the section on clinical features. There may be some familial tendency; sibling cases have been described [29] and an association with HLA-type Bw54 (discussed

Table 50.21 Conditions that have been associated with Sweet's syndrome/neutrophilic dermatosis.

Category	Examples	Comment
Infections	Streptococcal and upper respiratory tract Gastrointestinal (especially *Salmonella*, *Yersinia*) Mycobacterial infections (including vaccinations) Many others	Upper respiratory tract infections; *Salmonella* and *Yersinia* are well documented causes of 'classical' Sweet's syndrome See also text for discussion of human granulocytic anaplasmosis
Inflammatory bowel disease	Ulcerative colitis Crohn's disease	Well documented causes of 'classical' Sweet's syndrome
Endocrine	Pregnancy Autoimmune thyroid disease	Pregnancy and thyroid disease are relatively well documented
Immunological disorders	Collagen vascular disorders: lupus erythematosus, Sjögren's syndrome, others Others: autoimmune thrombocytopenic purpura, pemphigus	
Haematological malignancy and related conditions, immunodeficiencies	Acute myelogenous leukaemias Myelodysplastic conditions, polycythaemia Aplastic anaemia Fanconi's anaemia Monoclonal gammopathy Lymphomas (various, less common) Chronic granulomatous disease Congenital deficiencies: neutropenia, T-cell immunodeficiency, complement deficiency	Strong evidence linking leukaemias and myelodysplastic disorders Some series suggest a significant association with paraproteinaemias; chronic granulomatous disease, see text
Other malignancies	Genitourinary Breast Gastrointestinal Prostate Larynx Many others	No specific site-association apparent other than the haematological group
Other medical conditions	Sarcoidosis Rheumatoid arthritis Still's disease SAPHO	Many reports of sarcoidosis
Medications	Numerous; the most consistently associated agents are: • Colony-stimulating factors (including recent pegylated types) • Neutrophil-maturation drugs (all-*trans* retinoic acid) • Other haematological treatments (imatinib mesylate, bortezomib) • contraceptives • propylthiouracil Physical treatments for haematological malignancy have also been implicated, in a patient having splenic irradiation	Although most colony-stimulating factor-related Sweet's syndrome has been reported in patients with haematological malignancy, there are also several reports of the same phenomenon in other contexts (e.g. congenital immunodeficiencies) As with vasculitis, there may be positive ANCA with thiouracils
Other neutrophilic dermatoses and related conditions	Pyoderma gangrenosum Neutrophilic dermatosis of the dorsal hands Erythema elevatum diutinum Relapsing polychondritis Neutrophilic eccrine hidradenitis Subcorneal pustular dermatosis Erythema nodosum Behçet's disease Vasculitis (various)	In some cases, several are associated either concurrently or sequentially
Mucosal manifestations of Sweet's syndrome	Oral or genital mucosa ulceration Ocular inflammation especially conjunctivitis, also nodular episcleritis	Oral lesions especially in cases with haematological malignancy; conjunctivitis mainly in classical Sweet's syndrome
Systemic manifestations of neutrophilic dermatoses, and deeper variants	Bone, muscle, tendons, neuro-Sweet's, heart, lung, liver, intestine, spleen, kidney, subcutaneous (Sweet's panniculitis)	Summarized on p. 50.80
Unusual consequences of Sweet's syndrome	Acquired cutis laxa, mid-dermal elastolysis, elastophagocytosis	Several cases of acquired cutis laxa

SAPHO: synovitis, acne, pustulosis, hyperostosis, osteomyelitis.

in more detail in the differentiation between neuro-Sweet's syndrome and neuro-Behçet's disease, p. 50.82).

As with the other neutrophilic dermatoses, the pathogenesis of Sweet's syndrome is unknown, but it is thought to be related to altered immunological reactivity. A hypersensitivity reaction to bacterial, viral, drug or tumour antigens has been suggested as a possible aetiology. This hypothesis is supported by the frequent association of Sweet's syndrome with infection, drugs or malignancy, along with the clinical improvement of symptoms and lesions with corticosteroid treatment. Circulating autoantibodies [30], immune complexes [31] and cytokines have also been proposed to play a part in the pathogenesis of Sweet's syndrome. Atypical ANCA have been found in a few cases of Sweet's syndrome but not in others [30]; in ten patients with Sweet's syndrome, two had C-ANCA of IgA class (both with BPI specificity) but these could only be demonstrated on ethanol-fixed neutrophils, and formaldehyde fixation gave uniformly negative results [32]. Interleukin IL-1 has been suspected of playing a role for some years [33], but IL-3, IL-6, IL-8 and colony stimulating factors are also probably relevant [4]. Cytokine dysregulation has been a favoured theory in the pathogenesis of Sweet's syndrome, an imbalance of cytokine secretion from helper T cells (Th) being implicated. Th1 cytokines (IL-2 and IFN-γ) rather than Th2 cytokines (IL-4) are the proposed mediators, which in turn may stimulate the cytokine cascade leading to activation of neutrophils and release of toxic metabolites [34]; however, an integral role for colony-stimulating factors would appear to have more support.

Elevated serum levels of granulocyte colony-stimulating factor were demonstrated in patients with active Sweet's syndrome, and were associated with reduced neutrophil apoptosis; furthermore, incubation of autologous neutrophils with patient serum caused reduced apoptosis [35], and would account for accumulation of neutrophils which are the hallmark of this condition. Increased superoxide anion generation, a potential consequence of tissue neutrophilia (and for which prednisolone is a potent inhibitor), has been documented in leukaemia- and myelodysplasia-associated Sweet's syndrome [36], and various diverse tumours produce granulocyte colony-stimulating factor [4,37].

There are some issues of interest in relation to the involvement of neutrophils in Sweet's syndrome, that extend the recognized fact that neutrophilic dermatoses can occur during granulocytopenia [38]. The occurrence of other cell types is discussed in the section on histology. First, Sweet's syndrome has been reported in a patient with *chronic granulomatous disease*, a condition in which defects in NADPH-oxidase lead to failure of neutrophil intracellular oxidative killing; thus, this mechanism does not have to be functional in order to develop Sweet's syndrome [39]. Second, there is an interesting case of Sweet's syndrome in a patient with *human granulocytic anaplasmosis* (formerly human granulocytotropic ehrlichiosis) [40]. The causative organism, *Anaplasma phagocytophilum*, is an intracellular infection that infects, multiplies in and disrupts neutrophil function. Whether this means that human granulocytic anaplasmosis is a true cause of Sweet's syndrome is uncertain but, again, it documents that Sweet's syndrome can occur when there is impairment of normal neutrophil function. Third, a patient with congenital neutropenia developed Sweet's syndrome when he was treated with *pegfilgrastim*, a pegylated granulocyte colony-stimulating factor, despite many uneventful treatments both before and subsequently with standard granulocyte colony-stimulating factor [14]. The observation was made that pegfilgrastim has a half-life of 33 h in comparison with 3.4 h for the parent drug, filgrastim; furthermore, filgrastim is largely renally-excreted whereas pegfilgrastim is too large to be eliminated in this fashion, and it is actually removed from the circulation by neutrophil receptor-mediated clearance (binding to the neutrophil G-CSF receptor ligand) and therefore stimulating production of (potentially abnormally functional) neutrophils. Finally, there are reported cases of Sweet's syndrome associated with specific (6:9) translocations in myelodysplastic syndromes [41,42]; it has been suggested that these patients may have clonal neutrophils that could perhaps be more susceptible to the stimuli such as colony-stimulating factors, or exhibit an enhanced skin tropism to account for associated Sweet's syndrome.

Other aspects relating to pathogenesis that have been examined include immunohistochemical studies to detect immune complex deposition in blood vessels. These have yielded inconsistent results, some investigators reporting immunoglobulins and complement within vessel walls [43–45] but others not confirming this [1,46]. Additional studies have found perivascular IgG, IgM, C3 and fibrin, thought to represent non-specific leakage from damaged vessels [47].

References

1 von den Driesch P. Sweet's syndrome: acute febrile neutrophilic dermatosis. *J Am Acad Dermatol* 1994; **31**: 535–56.
2 Su WPD, Liu H-NH. Diagnostic criteria for Sweet's syndrome. *Cutis* 1986; **37**: 167–74.
3 Cohen PR, Kurzrock R. Sweet's syndrome revisited: a review of disease concepts. *Int J Dermatol* 2003; **42**: 761–78.
4 Cohen PR. Sweet's syndrome—a comprehensive review of an acute febrile neutrophilic dermatosis. *Orphanet J Rare Dis* 2007; **2**: 34.
5 Cohen PR, Kurzrock R. Sweet's syndrome: a neutrophilic dermatosis classically associated with acute onset and fever. *Clin Dermatol* 2000; **18**: 265–82.
6 Kemmett D, Hunter JAA. Sweet's syndrome: a clinicopathologic review of 29 cases. *J Am Acad Dermatol* 1990; **23**: 503–7.
7 Cohen PR. Pregnancy-associated Sweet's syndrome: world literature review. *Obstet Gynecol Surv* 1993; **48**: 584–7.
8 Cohen PR, Talpaz M, Kurzrock R. Malignancy-associated Sweet's syndrome: review of the world literature. *J Clin Oncol* 1988; **6**: 1887–97.
9 Cohen PR, Holder WR, Tucker SB *et al*. Sweet syndrome in patients with solid tumors. *Cancer* 1993; **72**: 2723–31.
10 Cohen PR, Kurzrock R. Sweet's syndrome and cancer. *Clin Dermatol* 1993; **11**: 149–57.
11 Paydas S, Berksoy S, Seyrek E *et al*. Sweet's syndrome associated with G-CSF. *Br J Haematol* 1993; **85**: 191–2.
12 Park JW, Mehrotra B, Barnett BO *et al*. The Sweet syndrome during therapy with granulocyte-colony stimulating factor. *Ann Intern Med* 1992; **116**: 996–8.
13 Kumar G, Bernstein JM, Waibel JS, Baumann MA. Sweet's syndrome associated with sargramostin (granulocyte-macrophage colony-stimulating factor). *Am J Hematol* 2004; **76**: 283–5.
14 Draper BK, Robbins JB, Stricklin PG. Bullous Sweet's syndrome in congenital neutropenia: association with pegfilgrastim. *J Am Acad Dermatol* 2005; **52**: 901–5.
15 Cox NH, O'Brien HAW. Sweet's syndrome associated with *trans*-retinoic acid treatment in acute promyelocytic leukemia. *Clin Exp Dermatol* 1994; **19**: 51–2.
16 Piette WW, Trapp JF, O'Donnell MJ *et al*. Acute neutrophilic dermatosis with myeloblastic infiltrate in a leukemia patient receiving all-*trans*-retinoic acid therapy. *J Am Acad Dermatol* 1994; **30**: 293–7.
17 Mensing H, Kowalzick L. Acute febrile neutrophilic dermatosis (Sweet's syndrome) caused by minocycline. *Dermatologica* 1991; **182**: 43–6.

18 Thibault MJ, Billick RC, Srolovitz H. Minocycline-induced Sweet's syndrome. *J Am Acad Dermatol* 1992; **27**: 801–4.
19 Walker DC, Cohen PR. Trimethoprim-sulfamethoxazole-associated acute febrile neutrophilic dermatosis: case report and review of drug-induced Sweet's syndrome. *J Am Acad Dermatol* 1996; **34**: 918–23.
20 Tefany FJ, Georgouras K. A neutrophilic reaction of Sweet's syndrome type associated with the oral contraceptive. *Australas J Dermatol* 1991; **32**: 55–9.
21 Thompson DF, Montarella KE. Drug-induced Sweet's syndrome. *Ann Pharmacother* 2007; **41**: 802–11.
22 Lee MS, Barnetson R. Sweet's syndrome associated with Behçet's disease. *Australas J Dermatol* 1996; **37**: 99–101.
23 Waltz KM, Long D, Marks JG *et al*. Sweet's syndrome and erythema nodosum: the simultaneous occurrence of two reactive dermatoses. *Arch Dermatol* 1999; **135**: 62–6.
24 Gillott TJ, Whallett AJ, Struthers GR *et al*. Concurrent Sweet's syndrome (acute febrile neutrophilic dermatosis), erythema nodosum, and sarcoidosis (letter). *Clin Exp Dermatol* 1996; **22**: 54–6.
25 Pouchot J, Bourgeots-Droin C, Vinceneu P *et al*. Sweet's syndrome and mediastinal lymphadenopathy due to sarcoidosis: three cases of a new association. *Arch Dermatol* 1993; **129**: 1062–4.
26 Wilkinson SM, Heagerty AHM, English JSC. Acute febrile neutrophilic dermatosis in association with erythema nodosum and sarcoidosis. *Clin Exp Dermatol* 1993; **18**: 47–9.
27 Wilson DM, John JR, Callen PR. Peripheral ulcerative keratitis: an extracutaneous neutrophilic disorder. Report of a patient with rheumatoid arthritis, pustular vasculitis, pyoderma gangrenosum, and Sweet's syndrome with an excellent response to cyclosporine therapy. *J Am Acad Dermatol* 1999; **40**: 331–4.
28 O'Brien TJ, Darling JA. Sweet's syndrome and hypothyroidism. *Australas J Dermatol* 1994; **35**: 91–2.
29 Parsapour K, Reep MD, Gohar K *et al*. Familial Sweet's syndrome in 2 brothers, both seen in the first 2 weeks of life. *J Am Acad Dermatol* 2003; **49**: 132–8.
30 Kemmett D, Harrison DJ, Hunter JAA. Antibodies to neutrophil cytoplasmic antigens: a serologic marker for Sweet's syndrome. *J Am Acad Dermatol* 1991; **24**: 967–9.
31 Behm FG, Kay S, Aportela R. Febrile neutrophilic dermatoses associated with acute leukemia. *Am J Clin Pathol* 1981; **76**: 344–7.
32 Ayoub N, Charuel J-L, Diemerte M-C *et al*. Antineutrophil cytoplasmic antibodies of IgA class in neutrophilic dermatoses with emphasis on erythema elevatum diutinum. *Arch Dermatol* 2004; **140**: 931–6.
33 Bourke JF, Jones JL, Fletcher A, Graham-Brown RAC. An immunohistochemical study of the dermal infiltrate and epidermal staining for interleukin-1 in 12 cases of Sweet's syndrome. *Br J Dermatol* 1996; **134**: 705–9.
34 Giasuddin ASM, El-Orfi AHAM, Ziu MM, El-Barnawi NY. Sweet's syndrome: is the pathogenesis mediated by helper T cell type 1 cytokines? *J Am Acad Dermatol* 1998; **39**: 940–3.
35 Kawakami T, Ohashi S, Kawa Y *et al*. Elevated serum granulocyte colony-stimulating factor levels in patients with active phase of Sweet syndrome and patients with active Behçet disease. Implication in neutrophil apoptosis dysfunction. *Arch Dermatol* 2004; **140**: 570–4.
36 Komiya I, Tanoue K, Kakinuma K *et al*. Superoxide anion hyperproduction by neutrophils in a case of myelodysplastic syndrome. Association with Sweet's syndrome and interstitial pneumonia. *Cancer* 1991; **67**: 237–41.
37 Shinojima Y, Toma Y, Terui T. Sweet syndrome associated with intrahepatic cholangiocarcinoma producing granulocyte colony-stimulating factor. *Br J Dermatol* 2006; **154**: 1103–4.
38 Aractingi S, Mallet V, Pnquier L *et al*. Neutrophilic dermatoses during granulocytopenia. *Arch Dermatol* 1995; **131**: 1141–5.
39 Lyon CC, Griffiths CEM. Chronic granulomatous disease and acute neutrophilic dermatosis. *Clin Exp Dermatol* 1999; **24**: 368–71.
40 Halasz CLG, Niedt GW, Kurtz CP *et al*. A case of Sweet syndrome associated with human granulocytic anaplasmosis. *Arch Dermatol* 2005: **141**: 887–90.
41 Soekarman M, Von Lindern M, Daenen S *et al*. The translocation (6:9) (p23:q34) shows consistent rearrangement of two genes and defines a myeloproliferative disorder with specific clinical features. *Blood* 1992; **79**: 2990–7.
42 Mégarbane B, Bodemer C, Valensi F *et al*. Association of acute neutrophilic dermatosis and myelodysplastic syndrome with (6:9) chromosome translocation: a case report and review of the literature. *Br J Dermatol* 2000; **143**: 1327–9.
43 Nunzi E, Crovato F, Dallegri R *et al*. Immunopathological studies on a case of Sweet's syndrome. *Dermatologica* 1981; **163**: 393–400.
44 Takeuchi S, Mashiko T, Ingarashi M. A case of Sweet's disease with deposition of immunoglobulins and complement. *Rinsho Hifuka* 1982; **36**: 557–62.
45 Maekawa Y, Kageshita T, Nagata T. A case of acute febrile neutrophilic dermatosis (Sweet's syndrome): a demonstration of IgM and C3 deposits. *J Dermatol* 1984; **11**: 560–4.
46 Malone JC, Slone SP, Wills-Frank LA *et al*. Vascular inflammation (vasculitis) in Sweet syndrome. *Arch Dermatol* 2002; **138**: 345–9.
47 Going JJ, Going SM, Myskow MW *et al*. Sweet's syndrome: histological and immunohistochemical study of 15 cases. *J Clin Pathol* 1987; **40**: 175–9.

Histopathology. The diagnostic histopathological features of Sweet's syndrome include a dense, predominantly neutrophilic, infiltrate located in the superficial dermis, and prominent papillary dermal oedema which may occasionally lead to subepidermal vesiculation [1–4]. Lymphocytes, eosinophils and 'histiocytes' may be present (discussed below). The infiltrate often occurs in a diffuse pattern, but may be perivascular or have an upper dermal band-like distribution [5]. Neutrophil karyorrhexis (fragmented neutrophil nuclei; nuclear dust) is a common finding [2]. The epidermis is often normal, but spongiosis may be present, and rarely neutrophils may extend into the epidermis to form subcorneal pustules [6]. There are two major histopathological controversies in Sweet's syndrome, one being the role of different cell types in the infiltrate, and the other being whether or not vasculitis occurs; these will be briefly discussed.

In most instances, the main cell type present is the neutrophil. Several studies suggest that there may be an admixture of lymphocytes and/or eosinophils, either of which can be prominent in some cases [2,3]. Several small case series have documented a lymphocytic infiltrate over many months, typically in patients who then develop a haematological malignancy [7,8]. There has been debate about whether frankly malignant myeloid cells might be present in some cases, but it seems unreasonable that a skin infiltrate in a patient with circulating leukaemic cells might not have some abnormal myeloid series cells present [9–11], as documented in some reports [9] prior to the claimed 'first' demonstration of this feature [10]. It has also now been clearly documented that 'histiocytoid' cells in the infiltrate actually represent myeloblast-like immature neutrophil granulocytes [12]; although the histiocytoid cells in 41 patients stained positively with monocyte-histiocyte markers, they also stained strongly with myeloperoxidase, and a variety of measures, including fluorescent *in situ* hybridization studies in 14 patients to exclude *bcr/abl* gene fusion, confirmed that these cells did not represent a leukaemic infiltrate.

Historically, the presence of vasculitis excluded the diagnosis of Sweet's syndrome, but recent studies have reported histopathological features consistent with leukocytoclastic vasculitis. These findings include fibrinoid necrosis along with the presence of inflammatory cells within vessel walls. Additional evidence of vessel wall damage includes extravasated erythrocytes and intraluminal thrombi. However, multiple immunofluorescence studies have failed to consistently demonstrate immune complex-mediated injury, further supporting the theory of secondary vessel damage rather than a primary vasculitis. It has been proposed that toxic metabolites released by activated neutrophils may have a

role in the secondary vessel wall injury [1–3,5,13,14]. In a recent study, 74% of biopsies showed all criteria for a diagnosis of leukocytoclastic vasculitis (vessel disruption by neutrophils, leukocytoclasis and fibrin in or around vessels walls [2]), and nearly two-thirds also had erythrocyte extravasation.

References

1 von den Driesch P. Sweet's syndrome: acute febrile neutrophilic dermatosis. *J Am Acad Dermatol* 1994; **31**: 535–56.
2 Ratzinger G, Burgdorf W, Zelger BG, Zelger B. Acute febrile neutrophilic dermatosis: a histopathologic study of 31 cases with review of literature. *Am J Dermatopathol* 2007; **29**: 125–33.
3 Jordaan HF. Acute febrile neutrophilic dermatosis: a histopathological study of 37 cases and a review of the literature. *Am J Dermatopathol* 1989; **11**: 99–111.
4 Kemmett D, Hunter JAA. Sweet's syndrome: a clinicopathologic review of 29 cases. *J Am Acad Dermatol* 1990; **23**: 503–7.
5 Malone JC, Slone SP, Wills-Frank LA *et al*. Vascular inflammation (vasculitis) in Sweet syndrome. A clinicopathologic study of 28 biopsy specimens from 21 patients. *Arch Dermatol* 2002; **138**: 345–9.
6 Wallach D. Maladie neutrophilique. *Rev Prat* 1999; **49**: 356–8.
7 Evans AV, Sabroe RA, Liddell K, Russell-Jones R. Lymphocytic infiltrates as a presenting feature of Sweet's syndrome with myelodysplasia and response to cyclophosphamide. *Br J Dermatol* 2002; **146**: 1087–90.
8 Vignon-Pennamen M-D, Juillard C, Rybojad M *et al*. Chronic recurrent lymphocytic Sweet syndrome as a predictive marker of myelodysplasia. A report of 9 cases. *Arch Dermatol* 2006; **142**: 1170–6.
9 Cox NH, O'Brien HAW. Sweet's syndrome associated with *trans*-retinoic acid treatment in acute promyelocytic leukemia. *Clin Exp Dermatol* 1994; **19**: 51–2.
10 Urano Y, Miyaoka Y, Kosaka M *et al*. Sweet's syndrome associated with chronic myelogenous leukaemia: demonstration of leukaemic cells within a skin lesion. *J Am Acad Dermatol* 1999; **40**: 275–9.
11 Morgan KW, Callen JP. Sweet's syndrome in acute myelogenous leukaemia presenting as periorbital cellulitis with an infiltrate of leukaemic cells. *J Am Acad Dermatol* 2001; **45**: 590–5.
12 Requena L, Kutzner H, Palmedo G *et al*. Histiocytoid Sweet syndrome. A dermal infiltration of immature neutrophil granulocytes. *Arch Dermatol* 2005; **141**: 834–42.
13 Malone JC, Slone SP. Sweet syndrome. A disease in histologic evolution? *Arch Dermatol* 2005; **141**: 893–5.
14 von den Driesch P. Sweet's syndrome and vasculitis. *J Am Acad Dermatol* 1996; **34**: 539.

Clinical features. The clinical presentation of Sweet's syndrome is usually distinctive. The patient typically appears ill, with a persistent high fever, neutrophilia and an elevated ESR. The cutaneous manifestations consist of erythematous to violaceous tender papules or nodules that often coalesce to form irregular plaques (Figs 50.40 & 50.41) [1–6]. The lesions typically involve the arms, face and neck, but may occur anywhere, and are usually multiple but may be solitary. Later lesions may appear pseudovesicular because of the prominent dermal oedema [1,2,7], and may be studded with tiny pustules resulting from neutrophil migration into the epidermis; in some cases frank bullae develop [8]. The plaques may develop central yellowish discoloration, producing a targetoid appearance [1]. The distribution may be localized, particularly on the face [1–6], or widespread, as may occur in malignancy-associated cases [9]. Several unusual body site distributions have been reported, including localization to recent wounds (Koebner response) [10], localization to old scars [11], localization to an area of lymphoedema (in a patient receiving colony-stimulating factor) [12] and localization to an area of radiotherapy [13]. Photoaggravated and photoinduced Sweet's syndrome have also been reported [14]. Healing usually occurs without scarring, although this can occur, particularly on the hands where it may have a reticulated appearance (see Fig. 50.43).



Fig. 50.40 Sweet's syndrome. The face is often affected.



Fig. 50.41 Sweet's syndrome. Multiple, large erythematous lesions on the legs.

Associated features typically, but not always, include fever and malaise; fever is the most common but may be absent, especially in malignancy-associated Sweet's syndrome [9]. Ocular manifestations are often found, most commonly conjunctivitis or episcleritis. Oral lesions are uncommon in the classical pattern but are more strongly linked with underlying haematological disorders [9]; genital lesions also occur. Subungual erythema has been reported [15]. A variety of systemic manifestations can occur, arthralgia, myalgia and arthritis also occurring frequently. Systemic manifestations of neutrophilic dermatoses are discussed on p. 50.80.

Diagnosis. The proposed diagnostic criteria for Sweet's syndrome state that patients must meet both of the two major criteria and two of the four minor criteria for the diagnosis [16,17].

Major criteria:

1 Acute onset of typical skin lesions

2 Histopathological findings consistent with Sweet's syndrome

Minor criteria:

1 Fever >38°C or general malaise

2 Association with malignancy, inflammatory disorder or pregnancy, or antecedent respiratory or gastrointestinal infection

3 Excellent response to systemic corticosteroids or potassium iodide (KI)

4 Abnormal laboratory values at presentation (three of four required: ESR >20 mm; leukocytes >8000; neutrophils >70%; positive C-reactive protein).

For drug-induced Sweet's syndrome, both major criteria and fever >38°C are required, together with two proposed additional criteria: (i) a temporal relationship between drug administration and clinical presentation; and (ii) a temporal relationship between drug withdrawal and disease resolution [18].

Otherwise, the differential diagnosis is wide. It includes infections (cellulitis/erysipelas, herpes virus infections, viral and bacterial exanthems), inflammatory dermatoses (erythema multiforme, urticaria, erythema nodosum, rosacea, pyoderma faciale, lupus erythematosus, drug eruptions, halogenodermas), tumours (especially leukaemia cutis), and other neutrophilic dermatoses and vasculitides.

References

1 von den Driesch P. Sweet's syndrome: acute febrile neutrophilic dermatosis. *J Am Acad Dermatol* 1994; **31**: 535–56.

2 Cohen PR. Sweet's syndrome—a comprehensive review of an acute febrile neutrophilic dermatosis. *Orphanet J Rare Dis* 2007; **2**: 34.

3 Cohen PR, Kurzrock R. Sweet's syndrome: a neutrophilic dermatosis classically associated with acute onset and fever. *Clin Dermatol* 2000; **18**: 265–82.

4 Callen JP. Neutrophilic dermatoses. *Dermatol Clin* 2002; **20**: 409–19.

5 Whittle CH, Beck GA, Champion RH. Recurrent neutrophilic dermatosis of the face: a variant of Sweet's syndrome. *Br J Dermatol* 1968; **80**: 806–10.

6 Bulengo-Ransby SM, Brown MD, Dubin HV *et al*. Sweet's syndrome presenting as an unusual periorbital eruption. *J Am Acad Dermatol* 1991; **24**: 140–1.

7 Honigsmann H, Kempter R, Wolff K. Acute febrile neutrophile dermatose. *Wien Klin Wochenschr* 1979; **91**: 842–7.

8 Neoh CY, Tan AWH, Ng SK. Sweet's syndrome: a spectrum of unusual clinical presentations and associations. *Br J Dermatol* 2007; **156**: 480–5.

9 Cohen PR, Kurzrock R. Sweet's syndrome and cancer. *Clin Dermatol* 1993; **11**: 149–57.

10 Tavadia SMB, Smith G, Herd RM, Zuk RJ. Sweet's syndrome associated with oral squamous cell carcinoma and exhibiting the Koebner phenomenon. *Br J Dermatol* 1999; **141**: 169–70.

11 Atzori L, Ferreli C, Pinna AL *et al*. P07.16. Sweet's syndrome lesions within pre-existing scars. *J Eur Acad Dermatol Venereol* 2004; **18** (Suppl.): 363.

12 Petit T, Francès C, Marinho E *et al*. Lymphoedema-area-restricted Sweet syndrome during G-CSF treatment. *Lancet* 1996; **347**: 690.

13 Vergara G, Vargas-Machuca I, Pastor MA *et al*. Localization of Sweet's syndrome in radiation-induced locus minoris resistentae. *J Am Acad Dermatol* 2003; **49**: 907–9.

14 Bessis D, Dereure O, Peyron J-L *et al*. Photoinduced Sweet syndrome. *Arch Dermatol* 2003; **137**: 1106–8.

15 Viseux V, Boulenger A, Jestin B, Plantin P. Transient subungual erythema in a patient with idiopathic Sweet's syndrome. *J Am Acad Dermatol* 2003; **49**: 554–5.

16 Su WPD, Liu H-NH. Diagnostic criteria for Sweet's syndrome. *Cutis* 1986; **37**: 167–74.

17 von den Driesch P. Sweet's syndrome: acute febrile neutrophilic dermatosis. *J Am Acad Dermatol* 1994; **31**: 535–56.

18 Walker DC, Cohen PR. Trimethoprim-sulfamethoxazole-associated acute febrile neutrophilic dermatosis: case report and review of drug-induced Sweet's syndrome. *J Am Acad Dermatol* 1996; **34**: 918–23.

Treatment. Treatments used in Sweet's syndrome have been summarized in [1–3]; further comprehensive details of the therapies discussed below are provided. Therapies for Sweet's syndrome are depicted in Table 50.22.

Systemic corticosteroids are a standard and effective therapy for Sweet's syndrome. A 4- to 6-week course of prednisone is generally sufficient to resolve cutaneous and systemic symptoms and signs, but occasionally prolonged low-dosage treatment may be required to prevent recurrences. In addition, topical and intralesional corticosteroids may be used alone or as adjuvant therapy for localized lesions [4].

Many corticosteroid-sparing agents have been reported to be effective in the treatment of Sweet's syndrome. Oral therapy with potassium iodide and colchicine has led to rapid regression of lesions and symptoms. These agents may be reasonable first-line therapy in patients with milder disease [5–9]. Indometacin and clofazimine have been used with success but appear to be less effective than corticosteroids, potassium iodide and colchicine [1–3,10]. Dapsone and ciclosporin have also been reported to be effective therapeutic agents, but require laboratory monitoring because of their potentially serious adverse effects [1–3,11–15].

Table 50.22 Treatment of Sweet's syndrome.

Corticosteroids
Systemic for 4–6 weeks
Adjuvant therapy for localized lesions
Topical
Intralesional
Corticosteroid-sparing agents
Potassium iodide
Colchicine
Dapsone
Indometacin
Clofazimine
Ciclosporin
Cyclophosphamide
Acitretin
Thalidomide
Intravenous immunoglobulin
Interferon-α

Small studies have reported clinical improvement in Sweet's syndrome using etretinate or IFN-γ [4,16,17]. Thalidomide [18], cyclophosphamide [19] and intravenous immunoglobulins [20] have also been used; more toxic agents obviously have a greater place if treatment of an underlying haematological disorder is needed. In one patient, with Sweet's syndrome due to myelodysplasia, and refractory to numerous therapies (including several of the above, plus azathioprine, mycophenolate mofetil and plasmapheresis), use of rabbit-antithymocyte-globulin caused remission of the myelodysplasia and the associated skin lesions. Looking forward, it will be interesting to see the effect of repertaxin, which inhibits chemokine receptors CXCR1 and CXCR2 [21], thereby inhibiting responses of IL-8 (CXCL8) which is a major activator of neutrophils; such approaches may be particularly valuable in those with systemic neutrophilic dermatoses. Other avenues of exploration include development of further inhibitors of IL-8 activated neutrophil chemotaxis, such as thapsigargin [22].

References

1 Cohen PR. Sweet's syndrome—a comprehensive review of an acute febrile neutrophilic dermatosis. *Orphanet J Rare Dis* 2007; **2**: 34.
2 Cohen PR, Kurzrock R. Sweet's syndrome. A review of current treatment options. *Am J Clin Dermatol* 2002; **3**: 117–31.
3 Cohen PR, Kurzrock R. Sweet's syndrome revisited: a review of disease concepts. *Int J Dermatol* 2003; **42**: 761–78.
4 Brodkin RH, Schwartz RA. Sweet's syndrome with myelofibrosis and leukemia: partial response to interferon. *Dermatology* 1995; **190**: 160–3.
5 Hommel L, Harms M, Saurat JH. The incidence of Sweet's syndrome in Geneva: a retrospective study of 29 cases. *Dermatology* 1993; **187**: 303–5.
6 Myatt AE, Baker DJ, Byfield DM. Sweet's syndrome: a report on the use of potassium iodide. *Clin Exp Dermatol* 1987; **12**: 345–9.
7 Smith HR, Ashton RE, Beer TW *et al*. Neutrophil-poor Sweet's syndrome with response to potassium iodide. *Br J Dermatol* 1998; **139**: 555–6.
8 Maillard H, Leclech C, Peria P *et al*. Colchicine for Sweet's syndrome: a study of 20 cases. *Br J Dermatol* 1999; **140**: 565–6.
9 Ritter S, George R, Serwatka LM *et al*. Long-term suppression of chronic Sweet's syndrome with colchicine. *J Am Acad Dermatol* 2002; **47**: 323–4.
10 Jeanfils S, Joly P, Young P *et al*. Indomethacin treatment of 18 patients with Sweet's syndrome. *J Am Acad Dermatol* 1997; **36**: 436–9.
11 Aram H. Acute febrile neutrophilic dermatosis (Sweet's syndrome): response to dapsone. *Arch Dermatol* 1984; **120**: 245–7.
12 Sharpe GR, Leggat HM. A case of Sweet's syndrome and myelodysplasia: response to cyclosporin. *Br J Dermatol* 1992; **127**: 538–9.
13 von den Driesch P, Steffan C, Zobe A *et al*. Sweet's syndrome: therapy with cyclosporin. *Clin Exp Dermatol* 1994; **19**: 274–7.
14 Bourke JF, Berth-Jones J, Graham-Brown RA. Sweet's syndrome responding to cyclosporine. *Br J Dermatol* 1992; **127**: 36–8.
15 Wilson DM, John JR, Callen PR. Peripheral ulcerative keratitis: an extracutaneous neutrophilic disorder. Report of a patient with rheumatoid arthritis, pustular vasculitis, pyoderma gangrenosum, and Sweet's syndrome with an excellent response to cyclosporine therapy. *J Am Acad Dermatol* 1999; **40**: 331–4.
16 Altomare G, Capella GL, Frigerio E. Sweet's syndrome in a patient with idiopathic myelofibrosis and thymoma–myasthenia gravis immunodeficiency complex: efficacy of treatment with etretinate. *Haematologica (Pavia)* 1996; **81**: 54–8.
17 Bianchi L, Masi M, Hagman JH *et al*. Systemic interferon-γ treatment for idiopathic Sweet's syndrome. *Clin Exp Dermatol* 1999; **24**: 443–5.
18 Browning CE, Dixon JE, Malone JC, Callen JP. Thalidomide in the treatment of recalcitrant Sweet's syndrome associated with myelodysplasia. *J Am Acad Dermatol* 2005; **53**: S135–8.
19 Evans AV, Sabroe RA, Liddell K, Russell-Jones R. Lymphocytic infiltrates as a presenting feature of Sweet's syndrome with myelodysplasia and response to cyclophosphamide. *Br J Dermatol* 2002; **146**: 1087–90.
20 Haliasos E, Soder B, Rubenstein DS *et al*. Pediatric Sweet syndrome and immunodeficiency successfully treated with intravenous immunoglobulin. *Pediatr Dermatol* 2005; **22**: 530–5.
21 Casilli F, Bianchini A, Gloaguen I *et al*. Inhibition of interleukin-8 (CXCL8 / IL-8) responses by repertaxin, a new inhibitor of the chemokine receptors CXCR1 and CXCR2. *Biochem Pharmacol* 2005; **69**: 385–94.
22 Elferik JG, de Koster BM. Inhibition of interleukin-8-activated human neutrophil chemotaxis by thapsigargin in a calcium- and cyclic AMP-dependent way. *Biochem Pharmacol* 2000; **59**: 369–75.

Neutrophilic dermatosis of the (dorsal) hands

Synonyms
- Pustular vasculitis of the (dorsal) hands
- Acral Sweet's syndrome
- Atypical pyoderma gangrenosum

Several case series [1–5] and individual reports have helped to define this disorder (Figs 50.42 & 50.43). An early case series described lesions that morphologically and histologically resembled Sweet's syndrome, but had additional histological features of vessel wall necrosis and deposition of fibrin around vessels, thereby constituting a vasculitis [1]. The presence of vasculitic change in this pattern of disease has varied in subsequent reports [2,6], but most reports do not suggest a primarily angiocentric angiodestructive process [7] and, as in Sweet's syndrome [8], the presence of vasculitis in neutrophilic dermatosis of the dorsal hands is probably a consequence of intense inflammation [9].

Thus, although it has been suggested that this entity might be a vasculitic process in the spectrum of EED [10], a site-variant of Sweet's syndrome, or a, usually superficial, variant of pyoderma gangrenosum, maintaining the term 'neutrophilic dermatosis of the dorsal hands' acknowledges the disease spectrum in a way that pustular vasculitis does not. Reviewing the disease associations of this entity reveals a very similar list to that of Sweet's syndrome, including streptococcal infections/pharyngitis [5], gastroenteritis [5], monoclonal gammopathy [5], IBD [4], myelodysplasia [3], lymphoma [4] or solid organ cancers [3,4]. Additional causes include other infections [11], sarcoidosis [11], medications [12] and SAPHO [13], all associated with Sweet's



Fig. 50.42 Neutrophilic dermatosis of the dorsal hands.



Fig. 50.43 Healing of neutrophilic dermatosis of the dorsal hands (without any associated disease) with reticulated scarring.

syndrome. Additionally, nearly 50% have lesions of Sweet's syndrome at other body sites [9], fever and leukocytosis occur in about 50% [1,2], the disorder can occur as an isolated event [5] or as a recurrent process [2], and treatments with corticosteroids or dapsone are usually effective [9].

In the review of Weenig *et al.* in 2004 [3], 25% of reported cases had had a myelodysplastic syndrome or leukaemia, supporting the view that this is an important association with neutrophilic dermatosis/atypical PG of the dorsal hands [7,14] (and often only becoming apparent after the cutaneous eruption). Indeed, review of dorsal hand lesions published earlier as either Sweet's syndrome or PG [15–18] reveals, for example, cases of newly diagnosed polycythaemia as a result of the dorsal hand lesion (termed PG) [15], of worsening myelofibrosis requiring splenectomy (PG) [16], of postpolycythaemic myeloid metaplasia progressing to leukaemia (Sweet's syndrome) [17] and of leukaemia diagnosed due to the hand lesions (Case 2; neutrophilic dermatosis) [18]. The term neutrophilic dermatosis of the dorsal hands thus lies closest to Sweet's syndrome nosologically, but includes lesions indistinguishable from PG, and has a stronger link with haematological malignancy than does 'ordinary' Sweet's syndrome, justifying retention of this terminology.

Streptococcal infection [19], other infections, neutrophilic eccrine hidradenitis, EED and other differential diagnoses for Sweet's syndrome are all in the clinical differential diagnosis; treatment is as for Sweet's syndrome or as determined by an underlying disorder.

References

1 Strutton G, Weedon D, Robertson I. Pustular vasculitis of the hands. *J Am Acad Dermatol* 1995; **32**: 192–8.

2 DiCaudo DJ, Connolly SM. Neutrophilic dermatosis (pustular vasculitis) of the dorsal hands: a report of seven cases and review of the literature. *Arch Dermatol* 2002; **138**: 361–5.

3 Weenig RH, Bruce AJ, McEvoy MT *et al*. Neutrophilic dermatosis of the hands: four new cases and review of the literature. *Int J Dermatol* 2004; **43**: 95–102.

4 Walling HW, Snipes CJ, Gerami P, Piette WW. The relationship between neutrophilic dermatosis (pustular vasculitis) of the dorsal hands and Sweet syndrome. Report of 9 cases and comparison to atypical pyoderma gangrenosum. *Arch Dermatol* 2006; **142**: 57–63.

5 Del Pozo J, Sácristan F, Martínez W *et al*. Neutrophilic dermatosis of the hands: presentation of eight cases and review of the literature. *J Dermatol* 2007; **34**: 243–7.

6 Galaria NA, Junkins-Hopkins JM, Kligman D, James WD. Neutrophilic dermatosis of the dorsal hands: pustular vasculitis revisited. *J Am Acad Dermatol* 2000; **43**: 870–4.

7 James WD. Newer neutrophilic dermatoses. *Arch Dermatol* 2003; **139**: 101–2.

8 Malone JC, Slone SP, Wills-Frank LA *et al*. Vascular inflammation (vasculitis) in Sweet syndrome: a clinicopathologic study of 28 biopsy specimens from 21 patients. *Arch Dermatol* 2002; **138**: 345–9.

9 Cohen PR. Skin lesions of Sweet syndrome and its dorsal hand variant contain vasculitis: an oxymoron or an epiphenomenon? *Arch Dermatol* 2002; **138**: 400–3.

10 Ayoub N, Tomb R. Neutrophilic dermatosis of the dorsal hands: a variant of erythema elevatum diutinum? *Arch Dermatol* 2003; **139**: 102.

11 Baz K, Yazici AC, Kaya TI *et al*. Neutrophilic dermatosis of the hands (localized Sweet's syndrome) in association with chronic hepatitis C and sarcoidosis. *Clin Exp Dermatol* 2003; **28**: 377–9.

12 Hoverson AR, Davis MPD, Weenig RH, Wolanskyj AP. Neutrophilic dermatosis (Sweet syndrome) of the hands associated with lenalidomide. *Arch Dermatol* 2006; **142**: 1070–1.

13 Bachmeyer C, Begon E, Blum L *et al*. Overlapping neutrophilic dermatosis in a patient with SAPHO syndrome. *Arch Dermatol* 2007; **143**: 275–6.

14 Callen JP, Jackson JM. Pyoderma gangrenosum: an update. *Rheum Dis Clin N Am* 2007; **33**: 787–802

15 Cox NH, Leggat H. Sweet's syndrome associated with polycythaemia rubra vera. *J Am Acad Dermatol* 1990; **23**: 1171–2.

16 Young VL, Fernando B, Tabas M *et al*. A case study of pyoderma gangrenosum. *J Hand Surg* 1988; **13A**: 259–62.

17 Horan MP, Redmond J, Gehle D *et al*. Postpolycythemic myeloid metaplasia, Sweet's syndrome, and acute myeloid leukaemia. *J Am Acad Dermatol* 1987; **16**: 458–62.

18 Gibson LE, Dicken CH, Flach DB. Neutrophilic dermatoses and myeloproliferative disease; report of two cases. *Mayo Clin Proc* 1985; **60**: 735–40.

19 Yung A, Merchant W, Sheehan-Dare R. *Streptococcus* induced pustular vasculitis affecting the hands resembling pustular vasculitis of the hands—first reported case. *Clin Exp Dermatol* 2005; **30**: 366–8.

Extracutaneous neutrophilic dermatoses

A number of extracutaneous internal manifestations of neutrophilic dermatoses have been described, separate from internal features of an underlying cause (haematological, inflammatory bowel disease, etc.). These are different from the systemic features (fever, malaise, myalgia, arthralgia, conjunctivitis, scleritis, etc.) that commonly occur in patients with Sweet's syndrome, in that they affect a small minority of patients. Inevitably, they all cause diagnostic problems; most will require involvement of other relevant disciplines for investigation. The main patterns of involvement are listed in Table 50.23 and reviewed in [1,2]. In most instances, 'internal' neutrophilic dermatoses are most common with Sweet's syndrome but several reports also include PG [3–7].

Lung lesions have been described in many reports [1,2]; they have been associated with PG, Sweet's syndrome, subcorneal pustular dermatosis and EED. Clinical features include fever, cough, dyspnoea and pleuritis. About half of the patients reported have had an associated underlying cause, most commonly haematological malignancies, and about a quarter have died despite treatment with corticosteroids as well as specific therapy for the underlying cause. Infection (including fungal infection, in the context of haematological malignancies) must be excluded; bronchial biopsies show sterile, densely neutrophilic and sometimes suppurative masses.

Table 50.23 Some examples of systemic disease associated with neutrophilic dermatoses.

Body system	Clinical features
Lung	Bronchial inflammation/pustules, infiltrates (patchy, lobar or diffuse interstitial), bronchiolitis obliterans organizing pneumonia, effusion, localized (sometimes cavitating) masses
Heart	Aortitis ± stenosis or dilatation, cardiac infiltrate, pericarditis, cardiomegaly, coronary artery occlusion
Bowel	Neutrophilic infiltrate (diffuse, ileal, pan-colitis); visceral abscesses
Liver	Hepatomegaly, elevated transaminases
Spleen	Splenomegaly, aseptic abscesses
Kidney and genitourinary tract	Mesangiocapillary glomerulonephritis, proteinuria, haematuria Prostatic PG with infarction of the urinary sphincter Sterile pyosalpinx
Muscle and tendon	Myalgia, myositis, fasciitis, tendonitis (usually symptomatic in Sweet's syndrome, may be due to exposed tendons in PG)
Bone and joint	Arthralgia, osteitis (may underlie pyoderma gangrenosum, or affect distant scattered sites), chronic recurrent multifocal osteomyelitis, SAPHO, sterile arthritis
Neurological	Neuro-Sweet's syndrome (mainly menigoencephalitis), headache, consciousness disturbance, convulsions, pareses, psychiatric symptoms, brainstem disease, Guillain–Barré disease, bilateral progressive deafness, polyneuropathy, retinal vasculitis
Ocular	Conjunctivitis, scleritis, iritis, uveitis (all non-specific); nodular episcleritis, peripheral ulcerative keratitis
Subcutaneous	Neutrophilic panniculitis, subcutaneous Sweet's disease (see p. 50.90)

SAPHO, synovitis, acne, pustulosis, hyperostosis, osteomyelitis.

Joint disease includes monoarthritis, seronegative polyarthritis and a destructive axial and peripheral polyarthritis. Bone disease is most common in children, as a chronic multifocal osteomyelitis. However, bone involvement may occur underlying ulcerative pyoderma gangrenosum. In one case, retrosternal cavitation due to pyoderma gangrenosum was successfully treated with local infusion of corticosteroids [7]. Myalgia in Sweet's syndrome is a non-specific finding, but rare cases of true myositis have been reported [1,8]; this seems to be particularly associated with use of all-*trans*-retinoic acid for acute promyelocytic leukaemia [8] (a drug also reported to cause cutaneous Sweet's syndrome [9]).

Neurological involvement is uncommon, but causes particular diagnostic problems due to the range of symptoms that can occur (Table 50.23) [1,2,10,11]. Encephalitis and meningitis are the most common patterns. One of the most difficult differential diagnoses is from neuro-Behçet's disease; the presence of HLA-Cw1 (and HLA-B54 in Japanese patients) rather than HLA-B51 is helpful, as is the absence of other features of Behçet's disease (p. 50.56). In the cerebrospinal fluid, neutrophil counts correlate well with levels of the chemoattractant IL-8 [12]. A prompt response to corticosteroids is expected [11], although recurrences may occur; indometacin, dapsone, colchicine and potassium iodide have also been used, especially in recurrent disease. Diagnostic criteria are listed in [11].

Aseptic neutrophilic abscesses are viewed as part of the spectrum of neutrophilic disorders. They may be solitary, but are usually multifocal [1,2,13]. The most common sites of involvement are the spleen, intra-abdominal lymph nodes, around abdominal viscera, liver, lung, pancreas and others. In some cases the skin or subcutaneous tissues may also be involved [1,14,15]. Most cases are associated with inflammatory bowel disease [13,14]; associated neutrophilic dermatoses include Sweet's syndrome (most frequently), PG, relapsing polychondritis, subcorneal pustular dermatosis and intraepidermal IgA pustulosis.

References

1 Vignon-Pennamen MD. The extracutaneous involvement in the neutrophilic dermatoses. *Clin Dermatol* 2000; **18**: 339–47.
2 Rodot S, Lacour JP, van Elslande L *et al*. Manifestations extra-cutanées des dermatoses neutrophiliques. *Ann Dermatol Venereol* 1996; **123**: 129–34.
3 Brown TS, Marshall GS, Callen JP. Cavitating pulmonary infiltrate in an adolescent with pyoderma gangrenosum: a rarely recognized extracutaneous manifestation of a neutrophilic dermatosis. *J Am Acad Dermatol* 2000; **43**: 108–12.
4 Urano S, Kodama K, Nogura K. Pyoderma gangrenosum with systemic involvement. *J Dermatol* 1995; **22**: 515–9.
5 Vignon-Pennamen MD, Wallach D. Neutrophilic disease: a review of extracutaneous manifestations. *Eur J Dermatol* 1995; **5**: 449–55.
6 Vignon-Pennamen MD, Zelinsky-Gurung A, Janssen F *et al*. Pyoderma gangrenosum with pulmonary involvement. *Arch Dermatol* 1989; **125**: 1239–42.
7 Tallon B, Rademaker M, Parkinson G, *et al*. Cavitary pyoderma gangrenosum treated with local infusion of corticosteroid. *J Am Acad Dermatol* 2007; **56**: 696–9.
8 Christ E, Linka A, Jacky E *et al*. Sweet's syndrome involving the musculoskeletal system during treatment of promyelocytic leukaemia with all-trans-retinoic acid. *Leukaemia* 1996; **10**: 731–4.
9 Cox NH, O'Brien HAW. Sweet's syndrome associated with *trans*-retinoic acid treatment in acute promyelocytic leukemia. *Clin Exp Dermatol* 1994; **19**: 51–2.
10 Nobeyama Y, Kamide R. Sweet's syndrome with neurologic manifestation: case report and literature review. *Int J Dermatol* 2003; **42**: 438–43.
11 Hisanaga K, Iwasaki Y, Itoyama Y *et al*. Neuro-Sweet disease. Clinical manifestations and criteria for diagnosis. *Neurology* 2005; **64**: 1756–61.
12 Kimura A, Sakurai T, Koumura A *et al*. Longitudinal analysis of cytokines and chemokines in the cerebrospinal fluid of a patient with neuro-Sweet disease presenting with recurrent meningoencephalitis. *Intern Med* 2008; **47**: 135–41.
13 André MFC, Piette JC, Kémény JL *et al*. Aseptic abscesses: a study of 30 patients with or without inflammatory bowel disease and review of the literature. *Medicine Baltimore* 2007; **86**: 145–61.
14 André M, Aumaître O, Papo T *et al*. Disseminated aseptic abscesses associated with Crohn's disease. A new entity? *Dig Dis Sci* 1998; **43**: 420–8.
15 Carvalho P, Cordel N, Courville P *et al*. Cutaneous aseptic abscesses, manifestations of neutrophilic diseases. *Ann Dermatol Venereol* 2001; **128**: 641–3.

Erythema nodosum

Synonyms
- Erythema nodosum migrans
- Subacute nodular migratory panniculitis
- Chronic erythema nodosum

Definition. Erythema nodosum (EN) is characterized by painful erythematous, and sometimes ecchymotic, nodules on the anterior surface of the legs. The condition may be idiopathic or secondary to various internal diseases or treatments. The incidence of EN is 1–5 in 100 000 population per year, with women accounting for

about 80% of cases, and mainly affecting subjects aged 15 to 40 years [1–5].

History and nomenclature. EN was initially described by Willan in 1798 [6] and was further discussed by Wilson in 1842, who believed it to be a type of erythema multiforme. In 1860, Hebra further described the clinical manifestations of the condition, and suggested 'dermatitis contusiformis' as a name for the disorder [7]. A more chronic variant was described almost a century later, and has been termed 'erythema nodosum migrans', 'chronic erythema nodosum' or 'subacute nodular migratory panniculitis' [8–10].

References

1 MacPherson P. A survey of erythema nodosum in a rural community between 1954 and 1968. *Tubercle* 1970; **51**: 324–7.
2 Erez A, Horowitz J, Sukenik S. Erythema nodosum in the Negev area: a survey of 50 patients. *Isr J Med Sci* 1987; **23**: 1228–31.
3 Cribier B, Caille A, Heid E, Grosshans E. Erythema nodosum and associated diseases: a study of 129 cases. *Int J Dermatol* 1998; **37**: 667–72.
4 Hannuksela M. Erythema nodosum. *Ann Clin Res* 1971; **3** (Suppl. 7): 4.
5 Garcia-Porrua C, Gonzalez-Gay MA, Vazquez-Caruncho M *et al*. Erythema nodosum: aetiologic and predictive factors in a defined population. *Arthritis Rheum* 2000; **43**: 584–92.
6 Willan R. *On Cutaneous Diseases*, Vol. 1. London: J. Johnson, St Paul's Church-Yard, 1798.
7 Hebra F. *Diseases of the Skin*, Vol. 1. London: New Sydenham Society, 1860.
8 Bäfverstedt B. Erythema nodosum migrans. *Acta Derm Venereol (Stockh)* 1954; **34**: 181–93.
9 Fine RM, Meltzer HD. Chronic erythema nodosum. *Arch Dermatol* 1969; **100**: 33–8.
10 Perry HO, Winkelmann RK. Subacute nodular migratory panniculitis. *Arch Dermatol* 1964; **89**: 170–9.

Aetiology and pathogenesis. EN is thought to be a hypersensitivity reaction that may be triggered by antigens usually associated with infections, typically group A β-haemolytic *Streptococcus*. There are several large patient series [1–9], and some smaller series in paediatric patients [10,11], as well as detailed reviews [12,13], that document presumed aetiological triggers and coexisting diseases. A list of drugs that have been implicated is provided in [14]. The most frequent underlying causes vary somewhat depending on the country, age group, and specialty of the authors. In children, infections predominate as the trigger—typically upper respiratory tract (mainly streptococcal), but *Yersinia* and tuberculosis can be found [10,11]. In adults, streptococcal infection usually accounts for about 10–30% of cases, other infections for 5–10%, sarcoidosis for 10–35%, rheumatological and autoimmune diseases for about 5%, inflammatory bowel diseases for 2–3%, medications for about 5–15% (including oral contraceptives), pregnancy for 2% and malignancies rarely [1–9,12,13]; streptococcal infections, and especially tuberculosis, are less prominent in more recent studies, in which sarcoidosis tends to be a more important trigger. EN is also common in sarcoidosis; in a series of patients with respiratory sarcoidosis who had skin lesions, 20% had EN [15]. In about a third (25–50%) of patients with EN, the cause is unknown.

Triggers of the chronic EN variant are generally unknown, although pregnancy and oral contraceptives have been implicated [9,12,13,16,17]; overall, about a third of cases of EN have no cause identified, and nearly a third of these have lesions that continue for over 6 months [5]. In one study with long-term follow-up, over 62% of patients with idiopathic EN had annual recurrences, but such a course was only seen in one patient with a known cause (Behçet's disease) [7]. Another study reported 56 of 438 patients (12%) to have a chronic form; nearly all were women, half had no obvious trigger (pregnancy was implicated in 40% with a possible identifiable cause) and mean duration was 4.5 months [9]. In some cases of chronic EN, the prolonged course may be determined by the course of an underlying condition, a feature particularly noted with non-Hodgkin's lymphoma [5]. In one case, chronic erythema nodosum in a child resolved when she was found to have coeliac disease and was treated with a gluten-free diet [18]. In some cases the course of erythema nodosum is marked by episodic exacerbations rather than by constant lesions, as in a patient who developed EN in the first half of each of four pregnancies and whenever she used oral contraceptives [17].

The exact pathogenesis of EN is not understood, although it is thought that it may be the result of deposition of immune complexes in the venules of the septae of subcutaneous fat, causing a neutrophilic panniculitis. A study of ten patients with EN showed that they had a fourfold higher percentage of 'primed' neutrophils, assessed by production of reactive oxygen intermediates, in comparison with healthy controls [19]; there was also a correlation with disease activity, but it is not clear whether this is a cause or an effect. There may also be a genetic predisposition to EN; in a study that examined genetic polymorphisms associated with high TNF-α production in a group of patients with EN, with or without sarcoidosis, there was a strong correlation of sarcoidosis-associated EN with TNF AII allele [20]. Erythema nodosum was a frequent finding in a series of patients with fever, arthralgia, mucosal ulcers, erythema multiforme-like and Sweet's syndrome-like lesions, in whom a form of superantigen-induced id reaction was proposed as the mechanism [21]; implicated infections included streptococcus, parvovirus B19, cytomegalovirus, mycoplasma, *Klebsiella* and *Borrelia burgdorferi*. A more detailed list of causes, especially of infectious aetiologies, is provided in Table 50.24 [1–17,21–64].

Drug-induced erythema nodosum is well recorded [1–9,12–14]. In the case of antibiotics, it may be difficult to separate infection-induced from drug-induced EN, but penicillins and sulphonamides have been implicated in several series of patients with EN. Oral contraceptives are a fairly convincing cause; in one series, use of oral contraceptives was 2.5-fold the expected level compared with overall national sales figures [9]. Hepatitis B vaccine has been implicated as a cause in several reports [56,57]. Isotretinoin is of some interest as patients with EN have often had acne fulminans, and some have had immune complexes demonstrated [58,59]; this does create some uncertainty about whether antigens due to inflammatory acne, or *Propionibacterium acnes* itself [60], is actually the cause. Acne fulminans has also been documented as a cause of erythema nodosum migrans [61]. Glatiramer acetate-induced EN is also of interest in having a likely immunological explanation; this drug is a polymer that mimics major basic protein (MBP) and is used to treat multiple sclerosis, in which situation it is known to generate polyclonal antibodies that cross-react with MBP epitopes and that have been implicated in anaphylaxis,

Table 50.24 Causes of erythema nodosum [1–18,21–64].

Idiopathic [1–12]

Medical causes, excluding infections

- Sarcoidosis [1–9,12,13,15] and other granulomatous disease (granulomatous mastitis [20])
- Inflammatory bowel disease (see also Chapter 62) [1–9,11–13,23,24] and diverticulitis [13]
- Rheumatological and autoimmune disease, including lupus erythematosus, Reiter's syndrome, Sjögren's syndrome, Behçet's disease, coeliac disease, autoimmune hepatitis [1–9,12,13,18]
- Malignancy (uncommon, mainly haematological but others are recorded including lung, pancreas, renal, stomach, colon, uterus, cervix and others) [1–9,11–13,25–28]
- Haematological stem cell transplantation [29]
- Pregnancy [1–9,12,13]
- Acne fulminans (sometimes with isotretinoin) [58–61]

Infections [1–13,21]

1 Bacterial

- Group A β-haemolytic *Streptococcus* [1–13,21], uncommonly Group C streptococci
- Other bacterial upper respiratory infections, e.g. *Moraxella* [30], meningococcus
- *Staphylococcus aureus* (uncommon) [1–3]; also breast abscesses, probably staphylococcal [31]
- Tuberculosis (uncommon but over 10% in some geographical areas) [1–9,11–13]
- Leprosy (see Chapter 32) [32]; erythema nodosum leprosum may be chronic [33]
- Atypical mycobacterial infection [12]
- *Yersinia* (up to 15% in children) [10,34]
- Gastrointestinal infections: *Salmonella* [35], *Shigella* [36], *Klebsiella* [21], *Campylobacter* [37,38]
- *Escherichia coli* [2]
- Brucellosis [39,40]
- Cat scratch fever [41]
- *Borrelia burgdorferi* [21]
- Mycoplasma [1, 21]
- Genitourinary: syphilis, gonorrhoea, lymphogranuloma venereum, chancroid [13]
- Others: Q fever, tularaemia, *Pasteurella pseudotuberculosis*, leptospirosis, rickettsiae [12,13]

2 Other infections

- Unspecified upper respiratory infections
- *Chlamydia* (including psittacosis) [40–44]
- Coccidioidomycosis [45]
- Histoplasmosis [46]
- Blastomycosis [47]
- Dermatophytes [48]
- Hepatitis B [1,49] and C [50]
- Parvovirus B19 [13,21,51]
- Cytomegalovirus [21]
- Toxoplasmosis [8,52]
- Visceral larva migrans [53]
- Others: amoebiasis/giardiasis (both in the same individual), herpes simplex, varicella-zoster, HIV, infectious mononucleosis, measles, aspergillosis, trichomonas, ascariasis [12,13]

Medications

- Sulphonamides, penicillins [1–9,14]
- Halides [1–9,14]
- Oral contraceptive pill [1–9,12,13,17]
- Hepatitis B vaccine [56,57]
- Isotretinoin [58,59]
- Imatinib mesylate [64]
- Others (see text and [12–14])

livedo-like dermatitis and lymphocytic infiltration [62]. Amongst more recently-introduced drugs causing EN, selective serotonin reuptake inhibitors should be noted as they are so widely used [63]. Imatinib mesylate, a now standard drug in treatment of chronic myeloid leukaemia, causes many skin reactions, but amongst these are several neutrophilic dermatoses including Sweet's syndrome, neutrophilic eccrine hidradenitis and EN [64]. Dermatologists also need to be aware of azathioprine as a possible cause of EN, which may cause diagnostic difficulty as it is also used to treat EN in EN leprosum or in inflammatory bowel disease [65].

References

1 Cribier B, Caille A, Heid E, Grosshans E. Erythema nodosum and associated diseases: a study of 129 cases. *Int J Dermatol* 1998; **37**: 667–72.

2 Garcia-Porrua C, Gonzalez-Gay MA, Vazquez-Caruncho M *et al*. Erythema nodosum: aetiologic and predictive factors in a defined population. *Arthritis Rheum* 2000; **43**: 584–92.

3 Psychos DN, Voulgari PV, Skopouli FN *et al*. Erythema nodosum: the underlying conditions. *Clin Rheumatol* 2000; **19**: 212–6.

4 El-Zawahry M. Erythema nodosum: a study of 60 cases. *Int J Dermatol* 1971; **10**: 145–50.

5 Bohn S, Buchner S, Itin P. Erythema nodosum: 112 cases. Epidemiology, clinical aspects and histopathology. *Schweiz Med Wochenschr* 1997; **127**: 1168–76.

6 Tantisirin O, Puavilia S. Long-term follow-up of erythema nodosum. *J Med Assoc Thai* 2003; **86**: 1095–100.

7 Mert A, Kumbasar H, Ozaras R *et al*. Erythema nodosum: an evaluation of 100 cases. *Clin Exp Rheumatol* 2007; **25**: 563–70.

8 Atanes A, Gómez N, Aspe B *et al*. Erythema nodosum: a study of 160 cases. *Med Clin Barc* 1991; **96**: 169–72.

9 Hannuksela M. Erythema nodosum migrans. *Acta Dern Venereol* 1973; **53**: 313–7.

10 Labbé L, Perel Y, Maleville J, Taïeb A. Erythema nodosum in children: a study of 27 patients. *Pediatr Dermatol* 1996; **13**: 447–50.

11 Kakourou T, Drosatou P, Psychou F *et al*. Erythema nodosum in children: a prospective study. *J Am Acad Dermatol* 2001; **44**: 17–21.

12 White JM Jr. Erythema nodosum. *Dermatol Clin* 1985; **3**: 119–27.

13 Requena L, Sánchez Yus E. Erythema nodosum. *Semin Cutan Med Surg* 2007; **26**: 114–25.

14 Litt JZ. *Drug Eruption Reference Manual*, 12th edn. London: Taylor and Francis, 2006: 619.

15 Yanardag H, Pamuk ON, Karayel T. Cutaneous involvement in sarcoidosis: analysis of the features in 170 patients. *Respir Med* 2003; **97**: 978–82.

16 Förström L, Winkelmann RK. Granulomatous panniculitis in erythema nodosum. *Arch Dermatol* 1975; **111**: 335–40.

17 Bombardieri S, Munno OD, Di Punzio C, Pasero G. Erythema nodosum associated with pregnancy and oral contraceptives. *BMJ* 1977; **i**: 1509–10.

18 Bartyik K, Várkonyi Á, Kirschner Á *et al*. Erythema nodosum in association with celiac disease. *Pediatr Dermatol* 2004; **21**: 227–30.

19 Kunz M, Beutel S, Bröcker E-B. Leukocyte activation in erythema nodosum. *Clin Exp Dermatol* 1999; **24**: 396–401.

20 Labunski S, Posern G, Ludwig S *et al*. Tumour necrosis factor-alpha promoter polymorphism in erythema nodosum. *Acta Derm Venereol* 2001; **81**: 18–21.

21 Magro CM, Crowson AN. A distinctive cutaneous reaction pattern indicative of infection by reactive arthropathy-associated microbial pathogens: the superantigen id reaction. *J Cutan Pathol* 1998; **10**: 538–44.

22 Al-Khaffaf BH, Shanks JH, Bundred N. Erythema nodosum—an extramammary manifestation of granulomatous mastitis. *Breast J* 2006; **12**: 696–70.

23 Kethu SR. Extraintestinal manifestations of inflammatory bowel diseases. *J Clin Gastroenterol* 2006; **40**: 567–75.

24 Trost LB, McDonnell JK. Important cutaneous manifestations of inflammatory bowel disease. *Postgrad Med J* 2005; **81**: 580–5.

25 La Spina M, Russo G. Presentation of childhood myeloid leukaemia with erythema nodosum. *J Clin Oncol* 2007; **25**: 4011–2.

26 Maxit MJ, Paz RA. Diffuse plane xanthoma with arthritis, serositis, erythema nodosum, vasculitis and myelomonocytic leukaemia. *Medicina B Aires* 2001; **61**: 187–90.
27 Almoznino SD, Dotan E, Sandbank J *et al*. Unusual manifestations of myelofibrosis in a patient with congenital asplenia. *Acta Haematol* 2007: **118**: 226–30.
28 Perez NB, Bernad B, Narváez J, Valverde J. Erythema nodosum and lung cancer. *Joint Bone Spine* 2006; **73**: 336–7.
29 Canninga-van-Dijk MR, Sanders CJ, Verdonck LF *et al*. Differential diagnosis of skin lesions after allogeneic haematological stem cell transplantation. *Histopathology* 2003; **42**: 313–30.
30 Periyakoil V, Krasner C. *Moraxella catarrhalis* bacteremia as a cause of erythema nodosum. *Clin Infect Dis* 1996; **23**: 650–1.
31 Ujiie H, Swamura D, Yokata K *et al*. Intractable erythema nodosum associated with breast abscesses: report of two cases. *Clin Exp Dermatol* 2005; **30**: 584–5.
32 Van Brakel WH, Khawas IB, Lucas SB. Reactions in leprosy: an epidemiological study of 386 patients in west Nepal. *Lepr Rev* 1994; **65**: 190–203.
33 Walker SL, Waters MFR, Lockwood DNJ. The role of thalidomide in the treatment of erythema nodosum leprosum. *Lepr Rev* 2007; **78**: 197–215.
34 Mygind N, Thulin H. *Yersinia enterocolitica*: a new cause of erythema nodosum. *Br J Dermatol* 1970; **82**: 351–4.
35 Scott BB. *Salmonella* gastroenteritis: another cause of erythema nodosum. *Br J Dermatol* 1980; **102**: 339–40.
36 Eastmond CJ. Gram-negative bacteria and B27 disease. *Br J Rheumatol* 1983; **22** (4 Suppl. 2): 67.
37 Lambert M, Marion E, Coche E *et al*. *Campylobacter enteritis* and erythema nodosum. *Lancet* 1982; **1**: 1409.
38 Galeazzi M, Palombi L, Mancinelli S *et al*. *Campylobacter* infections and erythema nodosum. *Eur J Epidemiol* 1986; **2**: 80–1.
39 Tanyel E, Fisgin NT, Yildiz L *et al*. Panniculitis as the initial manifestation of brucellosis: a case report. *Am J Dermatopathol* 2008; **30**: 169–71.
40 Akcali C, Savas L, Baba M *et al*. Cutaneous manifestations in brucellosis: a prospective study. *Adv Ther* 2007; **24**: 706–11.
41 Ridder GJ, Boedeker CC, Technau IK, Sander A. Cat scratch disease: otolaryngologic manifestations and management. *Otolaryngol Head Neck Surg* 2005; **132**: 353–8.
42 Sarner M, Wilson RJ. Erythema nodosum and psittacosis: report of five cases. *BMJ* 1965; **2**: 1469.
43 Sharma OP. Erythema nodosum and psittacosis pneumonia: a report of unusual clinical association. *Indian J Dermatol* 1970; **16**: 7 passim.
44 Kousa M, Saikku P, Kanerva L. Erythema nodosum in chlamydial infections. *Acta Derm Venereol* 1980; **60**: 319–22.
45 Erntell M, Ljunggren K, Gadd T *et al*. Erythema nodosum: a manifestation of chlamydial pneumoniae (strain TWAR) infection. *Scand J Infect Dis* 1989; **21**: 693–6.
46 Sundelof B, Gnarpe H, Gnarpe H. An unusual manifestation of *Chlamydia pneumoniae* infection: meningitis, hepatitis, iritis and atypical erythema nodosum. *Scand J Infect Dis* 1993; **25**: 259–61.
47 Blair JE. State-of-the-art treatment of coccidioidomycosis: skin and soft tissue infections. *Ann N Y Acad Sci* 2007; **1111**: 411–21.
48 Ozols II, Wheat LJ. Erythema nodosum in an epidemic of histoplasmosis in Indianapolis. *Arch Dermatol* 1981; **117**: 709–12.
49 Miller DD, Davies SF, Sarosi GA. Erythema nodosum and blastomycosis. *Arch Intern Med* 1982; **142**: 1839.
50 Hicks JH. Erythema nodosum in patients with tinea pedis and onychomycosis. *South Med J* 1977; **70**: 27–8.
51 Maggiore G, Grifeo S, Marzani MD. Erythema nodosum and hepatitis B virus (HBV) infection. *J Am Acad Dermatol* 1983; **9**: 602–3.
52 Calista D, Landi G. Lichen planus, erythema nodosum, and erythema multiforme in a patient with chronic hepatitis C. *Cutis* 2001; **67**: 454–6.
53 Katta R. Parvovirus B19: a review. *Dermatol Clin* 2002; **20**: 333–42.
54 Longmore HJ. Toxoplasmosis and erythema nodosum. *BMJ* 1977; **i**: 490.
55 Hartleb M, Januszewski K. Severe hepatic involvement in visceral larva migrans. *Eur J Gastroenterol Hepatol* 2001; **13**: 1245–9.
56 Rogerson SJ, Nye FJ. Hepatitis B vaccine associated with erythema nodosum and polyarthritis. *BMJ* 1990; **301**: 345.
57 Goolsby PL. Erythema nodosum after Recombivax hepatitis B vaccine. *N Engl J Med* 1989; **321**: 1198–9.
58 Kellet JK, Beck MH, Chalmers RJ. Erythema nodosum and circulating immune complexes in acne fulminans after treatment with isotretinoin. *BMJ* 1985; **290**: 820.
59 Tan BB, Lear JT, Smith AG. Acne fulminans and erythema nodosum during isotretinoin therapy responding to dapsone. *Clin Exp Dermatol* 1997; **22**: 26–7.
60 Williamson DM, Cunliffe WJ, Gatecliff M *et al*. Acute ulcerative acne (acne fulminans) with erythema nodosum. *Clin Exp Dermatol* 1977; **2**: 351–4.
61 Reizis Z, Trattner A, Hodak E *et al*. Acne fulminans with hepatosplenomegaly and erythema nodosum migrans. *J Am Acad Dermatol* 1991; **24**: 886–8.
62 Thouvenot E, Hillaire-Buys D, Bos-Thompson MA *et al*. Erythema nodosum and glatiramer acetate treatment in relapsing-remitting multiple scerosis. *Mult Scler* 2007; **13**: 941–4.
63 Krasowska D, Szymanek M, Schwartz RA, Myslinski W. Cutaneous effects of the most commonly used antidepressant medication, the selective serotonin reuptake inhibitors. *J Am Acad Dermatol* 2007; **56**: 848–53.
64 Scheinfeld N. Imatinib mesylate and dermatology. Part 2: a review of the cutaneous side effects of imatinib mesylate. *J Drugs Dermatol* 2006; **5**: 228–31.
65 de Fonclare AL, Khosrotehrani K, Sélim A *et al*. Erythema nodosum-like eruption as a manifestation of azathioprine hypersensitivity in patients with inflammatory bowel disease. *Arch Dermatol* 2007; **143**: 744–8.

Histopathology. The histopathology of EN is quite varied and more than one biopsy may be required if there is diagnostic uncertainty. The classical picture is of a septal panniculitis without vasculitis [1–4]. Early lesions of EN demonstrate septal oedema and a lymphohistiocytic infiltrate, with an admixture of neutrophils and eosinophils. The inflammation is typically concentrated at the periphery of the septae and spreads into surrounding fat lobules between adipocytes. Miescher's radial granulomata, which are clusters of macrophages around small vessels or a slit-like space, are also seen in these lesions [1–6]; although characteristic of EN, they are also seen in other disorders that might clinically resemble EN, such as erythema induratum, nodular lesions in systemic fibrosing dermopathy, Sweet's syndrome and Behçet's disease. Finally, there may be oedema and lymphocytic infiltration of the walls of veins, although the amount of vascular involvement is variable [1–4]. Pathologists are divided on whether vasculitis within EN is consistent with the diagnosis; some would say that vasculitis does not occur [2], whereas others describe small vessel vasculitis, and even medium vessel arteritis, in at least some vessels [4]. It is probably reasonable to accept the possibility of some vasculitis at sites of severe inflammation where it may be secondary; in contrast, the erythema nodosum-like lesions of Behçet's disease may have foci of leukocytoclastic vasculitis, lymphocytic vasculitis, arteritis or venulitis scattered throughout lesions [7]. Ulceration should suggest that the diagnosis is not one of ordinary EN.

Many of the varied features of EN pathologically are explained by the chronology of lesions [8]. Older lesions of EN demonstrate widened septae with peripheral fibrosis, and inflammation extending into peripheral regions of fat lobules. There are fewer vascular changes and a shift from a primarily neutrophilic infiltrate to one of primarily lipid-rich macrophages with a 'foam-cell' appearance; in some cases, this lymphohistiocytic lobular infiltrate may predominate [4]. Macrophages without phagocytosed lipid surround multinucleated giant cells, forming granulomas. Histologically, chronic EN has similar features to the later findings in lesions of acute EN. However, vascular proliferation is accompanied by endothelial thickening and extravasation of red blood cells [9],

along with more marked formation of granulomas and lipogranulomas.

Histopathologically, the differential diagnosis includes other causes of septal panniculitis [1–4], although many are distinguished by longer duration (lipodermatosclerosis, localized morphoea), a different clinical picture (eosinophilic fasciitis), or associated features (Behçet's disease). Early lesions of erythema induratum have a greater vasculitic component. Infective causes of panniculitis may be difficult to distinguish. Subcutaneous variants of neutrophilic dermatoses, such as Sweet's disease, cause particular difficulty, especially as some of the aetiologies of these disorders are the same as for EN (and, indeed, the two conditions occasionally coexist [10]); a septal neutrophilic infiltrate in some cases of Sweet's syndrome, and even the presence of Miescher's radial granulomas [11], make the histopathological differential diagnosis difficult.



Fig. 50.44 Erythema nodosum. Note the location of the plaques on the anterior aspect of the lower leg.

References

1 Requena L, Sánchez Yus E. Panniculitis. Part II. Mostly septal panniculitis. *J Am Acad Dermatol* 2001; **45**: 163–83.
2 Ter Poorten MC, Thiers BH. Panniculitis. *Dermatol Clin* 2002; **20**: 421–33.
3 Requena L, Sánchez Yus E. Erythema nodosum. *Semin Cutan Med Surg* 2007; **26**: 114–25.
4 Thurber S, Kohler S. Histopathologic spectrum of erythema nodosum. *J Cutan Pathol* 2006; **33**: 18–26.
5 Miescher G. Zur histology des erythema nodosum. *Acta Derm Venereol (Stockh)* 1947; **27**: 447.
6 Sánchez Yus E, Sanz V, de Diego V. Miescher's radial granuloma: a characteristic marker of erythema nodosum. *Am J Dermatopathol* 1989; **11**: 434–42.
7 Kim B, LeBoit PE. Histopathologic features of erythema nodosum-like lesions in Behçet's disease: a comparison with erythema nodosum focusing on the role of vasculitis. *Am J Dermatopathol* 2000; **22**: 379–90.
8 White WL, Hitchcock MG. Diagnosis: erythema nodosum or not? *Semin Cutan Med Surg* 1999; **18**: 47–55.
9 Winkelmann RK, Förström L. New observations in the histopathology of erythema nodosum. *J Invest Dermatol* 1975; **65**: 441–6.
10 Waltz KM, Long D, Marks JG Jr, Billingsley EM. Sweet's syndrome and erythema nodosum: the simultaneous occurrence of 2 reactive dermatoses. *Arch Dermatol* 1999; **135**: 62–6.
11 Blaustein A, Moreno A, Noguera J, de Moragas JM. Septal granulomatous panniculitis in Sweet's syndrome. Report of two cases. *Arch Dermatol* 1985; **121**: 785–8.

Clinical features [1–3]. EN is typically manifest by the sudden onset of painful, erythematous, warm nodules and plaques, typically on the shins, knees and ankles. Lesions may occur at any body site, even the face, but are less common than on the lower legs. The lesions are often more easily palpated than visualized, and are typically bilateral and symmetrical, ranging between 1 and 5 cm in diameter. The nodules may coalesce to form plaques (Fig. 50.44). After several days, the erythematous nodules often flatten and become ecchymotic in colour, finally taking on a yellow-green appearance (similar to an old ecchymosis), sometimes referred to as 'erythema contusiformis'. This transformation is characteristic of EN, making retrospective diagnosis possible. Lesions of EN never ulcerate, atrophy or scar. Lesions erupt and are usually present for 3–6 weeks. In addition to cutaneous manifestations of EN, constitutional signs and symptoms may also be present. Fever, fatigue, malaise, gastrointestinal upset, headache and arthralgia may accompany the characteristic lesions of EN, as may ocular manifestations such as conjunctivitis; laboratory markers of inflammation such as ESR and CRP may be elevated. All of these factors should raise suspicion of secondary rather than primary (idiopathic) EN [4]. A relapsing course appears to be most common in idiopathic cases or those associated with upper respiratory infections.

In the chronic EN variant, lesions may be solitary or few, usually on the lateral part of the lower leg. They are initially nodular but become broader and flatter, vaguely circular or arciform in shape, and often last several months.

Diagnosis. The diagnosis of EN is clinical, although histopathological evaluation may sometimes be necessary to support the diagnosis. Other forms of panniculitis are the main diagnostic consideration on the legs, and primary infective processes must be considered at any body site. In atypical cases of suspected EN (such as the absence of lesions on the legs, persistence or ulceration of the lesions), a deep elliptical biopsy of an active lesion should be performed. A medication history should be considered and a search should be performed for an underlying cause. A chest X-ray, tuberculin skin test and antistreptolysin (ASO) titre may be obtained in such instances to exclude causes such as sarcoidosis, tuberculosis or streptococcal infection.

Treatment. If there is a treatable, or removable (e.g. medication), cause then this should be addressed, as rapid resolution is anticipated. Even without specific therapy for a causative condition, EN typically resolves without treatment, therefore symptomatic support may be all that is necessary for the majority of patients. NSAIDs may also be used [1,2,5], as may potassium iodide 360–900 mg/day [6–9]. The concept that potassium iodide causes release of heparin from mast cells, and that this suppresses delayed hypersensitivity reactions, suggested the use of topical heparinoids [1]. Dapsone can be effective in some cases, as can colchicine. Hydroxychloroquine has been used in chronic erythema

Table 50.25 Therapeutic ladder for erythema nodosum.

Non-steroidal anti-inflammatory drugs (3)
Intralesional corticosteroid (3)
Heparinoid ointment under occlusion (3)
Potassium iodide (2)
Colchicine (3)
Hydroxychloroquine (3)
Dapsone (3)
Methotrexate (3)
Thalidomide (3)
Prednisone (3)
Anti-TNF monoclonal antibodies (3)

1, double-blind studies; 2, case series; 3, case reports.

nodosum. Systemic corticosteroids are infrequently required for the treatment of EN and may worsen underlying disease such as tuberculosis; intralesional steroids may be beneficial. Recent reports include use of anti-TNF biological agents [10,11], but these are contraindicated in the presence of infections (in particular, in the context of EN, tuberculosis must be excluded); they may have a place in cases due to inflammatory bowel disease as they could treat this and EN together [11]. A therapeutic ladder for EN is depicted in Table 50.25.

References

1 Requena L, Sánchez Yus E. Erythema nodosum. *Semin Cutan Med Surg* 2007; **26**: 114–25.
2 Mana J, Marcoval J. Erythema nodosum. *Clin Dermatol* 2007; **25**: 288–94.
3 Bohn S, Buchner S, Itin P. Erythema nodosum: 112 cases. Epidemiology, clinical aspects and histopathology. *Schweiz Med Wochenschr* 1997; **127**: 1168–76.
4 Mert A, Kumbasar H, Ozaras R *et al*. Erythema nodosum: an evaluation of 100 cases. *Clin Exp Rheumatol* 2007; **25**: 563–70.
5 Ubogy Z, Persellin RH. Suppression of erythema nodosum by indometacin. *Acta Derm Venereol* 1982; **62**: 265–6.
6 Schulz EJ, Whiting DA. Treatment of erythema nodosum and nodular vasculitis with potassium iodide. *Br J Dermatol* 1976; **94**: 75–8.
7 Marshall JK, Irvine EJ. Successful therapy of refractory erythema nodosum associated with Crohn's disease using potassium iodide. *Can J Gastroenterol* 1997; **11**: 501–2.
8 Horio T, Imamura S, Danno K *et al*. Potassium iodide in the treatment of erythema nodosum and nodular vasculitis. *Arch Dermatol* 1981; **117**: 29–31.
9 Horio T, Danno K, Okamoto H *et al*. Potassium iodide in erythema nodosum and other erythematous dermatoses. *J Am Acad Dermatol* 1983; **9**: 77–81.
10 Boyd AS. Etanercept treatment of erythema nodosum. *Skinmed* 2007; **6**: 197–9.
11 Quin A, Kane S, Ulitsky O. A case of fistulizing Crohn's disease and erythema nodosum managed with adalimumab. *Nat Clin Pract Gastroenterol Hepatol* 2008; **5**: 278–81.

Bowel-associated dermatosis–arthritis syndrome
(see also Chapter 62)

Definition. Bowel-associated dermatosis–arthritis syndrome (BADAS) is defined by the presence of pustular vasculitic lesions associated with blind loops of bowel or other causes of stasis of bowel content.

History and nomenclature. BADAS was first described in 1971 as pustular vasculitis, cutaneous lesions and serum sickness-like reactions in patients who had undergone jejunoileal bypass surgery for morbid obesity [1–4]. The term has been extended to include the same syndrome in patients with IBD, those who have had creation of a blind loop following surgery for peptic ulcer disease [5,6], or with other causes of stasis of bowel content, such as in achalasia or related to a defunctioning colostomy.

Aetiology and pathogenesis. Blood vessel damage secondary to bowel flora antigen-associated circulating immune complexes is thought to be the pathogenesis of the cutaneous lesions. In these patients, peptidoglycans from gastrointestinal flora may be the antigenic trigger for immune complex-mediated vessel damage [4]. Therapeutic response to antimicrobials in some cases supports this concept, and immune complexes have been demonstrated [5,7]. The various underlying conditions can be divided into two main categories:

1 Related to surgery: jejunoileal bypass [1–4,8], gastric resection [5], blind loops (Bilroth II or Roux-en-Y [5,6]), defunctioning ileoanal pouch procedures [9], biliopancreatic diversion [10] and others
2 Related to bowel disease: ulcerative colitis [5,11], Crohn's disease [5,12], diverticulitis of colon [13], jejunal diverticula [14], appendicitis [15] and achalasia of the cardia [16].

In some cases there are combined causes (e.g. surgery for inflammatory bowel disease). In most instances related to surgery, the loop of bypassed bowel, or a blind loop, is in continuity with the intestine, but may be separated as a defunctioning bowel segment [9].

Histopathology. The changes noted in dermal blood vessels from early lesions of pustular vasculitis in patients with BADAS are similar to those in biopsies from patients with Sweet's syndrome [4–8] and Behçet's disease. Several cases have both clinical and pathological overlap with other neutrophilic dermatoses.

Clinical features. The cutaneous manifestations of BADAS begin as small macular lesions that progress into papules and later pustules on a purpuric base, most often on the arms and other areas of the upper body (Fig. 50.45). These pustules measure 0.5–1.5 cm in diameter and typically occur in crops, with each crop lasting up to 2 weeks, and recurring at intervals of several months [4,5,8].



Fig. 50.45 Bowel-associated dermatosis–arthritis syndrome, showing a papule on an erythematous base.

Larger, erythema nodosum-like, lesions also occur, and sometimes larger pyoderma gangrenosum-like pustular lesions. Like Behçet's disease and pyoderma gangrenosum, pathergy seems to have a role in the distribution of the lesions. The cutaneous lesions may be preceded by constitutional signs and symptoms such as fever, flu-like symptoms or myalgia, or by gastrointestinal upset. Arthralgia or non-erosive polyarthritis affecting hands, wrists and other peripheral joints are common; ocular symptoms such as episcleritis [12], and haematuria or proteinuria [8,15] may also occur. Rarely, severe skin lesions and marked systemic manifestations may occur [17].

Diagnosis. It is important to distinguish between BADAS and Behçet's disease, as both may include oral aphthosis and lesions of pustular vasculitis. In order to distinguish between these two disease processes, an evaluation of the bowel, which may include barium studies as well as endoscopy, should follow a thorough patient history and physical examination. Clinicopathological evaluation of skin lesions is required but does not exclude lesions of Behçet's disease or early lesions of either PG or Sweet's syndrome; some patients appear to exhibit a spectrum of neutrophilic dermatoses [12], and a patient with previous pyoderma gangrenosum developed BADAS due to a defunctioning bowel segment after surgery for her ulcerative colitis [9]. Sweet's syndrome is associated with inflammatory bowel disease (p. 50.74) but has also been described with diverticular disease [18], supporting an overlap of diseases.

It is advisable to perform urinalysis in patients with BADAS as, unlike classical Sweet's syndrome, there may be haematuria or proteinuria, possibly representing an immune complex-initiated glomerulonephritis [8].

Treatment. For patients with BADAS following bowel bypass surgery, surgical correction of bowel anatomy often eliminates the signs and symptoms. In other cases, such as patients with blind loops (whether surgically created or due to bowel disease), surgical correction may be difficult and resolution of symptoms is therefore less likely. Manifestations of BADAS may be effectively controlled by the use of systemic tetracycline, metronidazole, ciprofloxacin or erythromycin [4,5,10,19]. Systemic corticosteroids are typically unnecessary for the treatment of BADAS but may be justified either depending on the degree of skin, joint or systemic symptoms, or to concurrently treat inflammatory bowel disease. Other treatments outlined for patients with cutaneous small vessel vasculitis, especially oral colchicine, dapsone or thalidomide have been used (Table 50.26); systemic drugs with an immunosuppressive action may need to be combined with an appropriate antibiotic.

Table 50.26 Treatment of bowel-associated dermatosis–arthritis syndrome.

Surgical correction of bowel anatomy if possible (may not eliminate symptoms if following blind loop)
Symptoms not secondary to or correctable by surgery, or temporary treatment prior to surgical correction
Systemic tetracycline
Systemic metronidazole
Systemic erythromycin
Other systemic treatments that may be used depending on severity of symptoms and associated bowel condition
Corticosteroids
Colchicine
Dapsone
Mycophenolate mofetil
Thalidomide

References

1 Shagrin JW, Frame B, Duncan H. Polyarthritis in obese patients with intestinal bypass. *Ann Intern Med* 1971; **75**: 377–80.

2 Drenick EJ, Ament MR, Finegold SM *et al*. Bypass enteropathy: intestinal and systemic manifestations following small bowel bypass. *JAMA* 1976; **236**: 269–72.

3 Campbell JM, Hunt TK, Karam JH, Forsham PH. Jejunoileal bypass as a treatment for morbid obesity. *Arch Intern Med* 1977; **137**: 602–10.

4 Ely PH. The bowel bypass syndrome: a response to bacterial peptidoglycans. *J Am Acad Dermatol* 1980; **2**: 473–87.

5 Jorizzo JL, Apisarnthanarax P, Subrt P *et al*. Bowel-bypass syndrome without bowel bypass: bowel-associated dermatosis–arthritis syndrome. *Arch Intern Med* 1983; **143**: 457–61.

6 Dicken CH. Bowel-associated dermatosis–arthritis syndrome: bowel bypass syndrome without bowel bypass. *Mayo Clinic Proc* 1984; **59**: 43–6.

7 Jorizzo JL, Schmalstieg FC, Dinehart SM *et al*. Bowel-associated dermatosis–arthritis syndrome: immune complex-mediated vessel damage and increased neutrophil migration. *Arch Intern Med* 1984; **144**: 738–40.

8 Gamble CN, Kinchi A, Depner TA, Christensen D. Immune complex glomerulonephritis and dermal vasculitis following intestinal bypass for morbid obesity. *Am J Clin Pathol* 1982; **77**: 347–52.

9 Cox NH, Palmer JG. Bowel-associated dermatitis-arthritis syndrome associated with ileo-anal pouch anastamosis, and treatment with mycophenolate mofetil. *Br J Dermatol* 2003; **149**: 1296–7.

10 Slater GH, Kerlin P, Beorghiou PR, Fielding GA. Bowel-associated dermatosis-arthritis syndrome after biliopancreatic diversion. *Obes Surg* 2004; **14**: 133–5.

11 Vázquez J, Almagro M, del Pozo J, Fonseca A. Neutrophilic pustulosis and ulcerative colitis. *J Eur Acad Dermatol Venereol* 2003; **17**: 77–9.

12 Mendoza JL, García-Paredes J, Peña AS *et al*. A continuous spectrum of neutrophilic dermatoses in Crohn's disease. *Rev Esp Enferm Dig* 2003; **95**: 233–6.

13 Brouard MC, Chavez P, Borradori L. Acute pustulosis of the legs in diverticulitis with sigmoid stenosis: an overlap between bowel-associated dermatosis-arthritis syndrome and pustular pyoderma gangrenosum. *J Eur Acad Dermatol Venereol* 2004; **18**: 89–92.

14 Fairris GM, Ashworth J, Cotterill JA. A dermatosis associated with bacterial overgrowth in jejunal diverticula. *Br J Dermatol* 1985; **112**: 709–13.

15 Prpic ML, Kastelan M, Brajac I *et al*. Bowel-associated dermatosis-arthritis syndrome in a patient with appendicitis. *Med Sci Monit* 2007; **13**: CS97–100.

16 Tucker SC, Chalmers RJG, Andrew SM, Odom NJ. Pustular vasculitis secondary to achalasia of the cardia. *Br J Dermatol* 2000; **142**: 373–4.

17 Kawakami A, Saga K, Hida T *et al*. Fulminant bowel-associated dermatosis-arthritis syndrome that clinically showed necrotizing fasciitis-like skin and systemic manifestations. *J Eur Acad Dermatol Venereol* 2006; **20**: 751–3.

18 Rosati E, Aracri N, Bottone A *et al*. Sweet syndrome in a female patient with multiple intestinal lipomas and diverticular disease of the colon. *Recent Prog Med* 2001; **92**: 599–601.

19 Geary RJ, Long LL, Mutasim DF. Bowel bypass syndrome without bowel bypass. *Cutis* 1999; **63**: 17–20.

Pustular neutrophilic dermatoses

This is not a specific entity, but aims to draw together some overlapping disorders and to consider their differential diagnoses. It should be accepted that some of these are probably synonymous terms (Table 50.27) although whether they are viewed as part of Sweet's syndrome, pustular PG [1,2] or simply viewed as

Table 50.27 Nomenclature of some pustular eruptions in the spectrum of neutrophilic dermatoses.

Term	Comment
Pustular PG	Discussed above
Pustular vasculitis/neutrophilic pustulosis	In Behçet's disease, bowel-associated dermatosis-arthritis syndrome; less commonly in systemic lupus erythematosus, primary biliary cirrhosis
Diffuse pustular eruption of ulcerative colitis Vesicopustular eruption of ulcerative colitis Neutrophilic pustulosis in ulcerative colitis [3–7]	Synonymous disorders, appearances vary from Sweet's syndrome to pustular PG Often associated with disease flare, pyrexia, malaise
Vesicopustular eruption associated with hepatobiliary disease [8]	Also viewed as pustular PG Lesions are often necrotizing, although some lesions resemble Sweet's syndrome Associated diseases include autoimmune hepatitis, sclerosing cholangitis, primary biliary cirrhosis and others [8]
Disseminated pustular dermatosis of polycythaemia rubra vera (PRV) [9]	Sweet's syndrome variant with response to dapsone Scattered pustules but also semiconfluent acral grouping and facial plaques, with pustular glossitis, stomatitis and nail dystrophy
Palmar, plantar or vulval pustulosis in Sweet's syndrome [10,11]	May be a presenting feature; distinct from the dorsal hand eruption
Neutrophilic spongiosis (synonym granulocytic spongiotic papulovesiculosis) [12,13]	Intermittent eruption of neutrophilic vesicles, mainly facial and mucosal (see text)
Pyostomatitis vegetans	Oral lesions, 50% with skin involvement: oral lesions may be IBD-associated variant of pustular PG, discussed earlier

unspecified neutrophilic dermatoses is less relevant than recognizing the occurrence of pustular lesions within this spectrum.

Pustular eruptions that are likely to enter the differential diagnosis of the above conditions are numerous. Localized infections such as mycobacterial or fungal infections have been discussed in the differential diagnosis of localized PG. Infections (e.g. streptococcal), folliculitis (sterile or infective), pustular psoriasis, impetigo herpetiformis and acute generalized eruptive pustulosis (AGEP) are all generalized eruptions that may be considered. Non-spongiform pustules have been described due to chronic internal infection, and related to tobacco smoking. At acral sites in infants, scabies and infantile acropustulosis are considerations, and in adults Reiter's syndrome, acropustulosis of Hallopeau or idiopathic acral pustulosis. Both generalized and palmoplantar pustular lesions have been reported in Kawasaki disease [14,15]. Other disorders that fall into the vasculitis or neutrophilic dermatosis spectrum may resemble or coexist with lesions listed in Table 50.27, including intraepidermal neutrophilic IgA dermatosis, subcorneal pustular dermatosis and CSVV.

Some disorders require special consideration as differential diagnoses, either because of close clinical similarity to neutrophilic dermatoses or because their systemic disease associations may require interpretation.

Pyoderma vegetans/blastomycosis-like pyoderma (has also been termed mycosis-like pyoderma, pyostomatitis vegetans and pyodermatitis-pyostomatitis vegetans) [16–19]. This may resemble PG, especially of vegetans type, as a verrucous plaque studded with pustules, and having pseudoepitheliomatous hyperplasia and neutrophilic microabscesses on histology. To further mimic PG, it may occur at sites of injection or tattooing (resembling a pathergic reaction), and, although not exclusively, most patients are immunosuppressed, malnourished or have diseases that have been associated with PG (including IBD (especially ulcerative colitis), leukaemias, lymphoma, diabetes, acne conglobata, hidradenitis suppurativa and dissecting cellulitis of the scalp). However, it can occur in young and fit patients. Oral lesions (which may be the only feature) may occur, especially in those with IBD (the nosology of this 'pyostomatitis vegetans' pattern, and its relationship to PG is discussed on p. 50.70); dorsal hand lesions that are morphologically very similar to neutrophilic dermatosis of the dorsal hands [19] also occur, and a rash very reminiscent of Sweet's syndrome [20]. Various bacteria (not fungi) have been reported as a cause, and the disorder may represent an abnormal response to such organisms. Antimicrobials, rather than corticosteroids or antineutrophil therapies, are indicated if the cause is uncertain, although they do not always eradicate it; the oral disease may respond to topical corticosteroids or tacrolimus, and Crohn's disease-associated cases have been treated with methotrexate and infliximab. Possible diagnostic clues include some cases with raised IgE level, and eosinophilia which is present in 50–90%.

Erosive pustular dermatitis of the leg. Although likely to be suspected when it occurs on the scalp, the commonest site, erosive pustular dermatitis of the leg is a rare condition and may resemble PG. Skin atrophy is typical and may suggest this diagnosis rather than PG; additionally, most patients are aged over 65 years, whereas most PG occurs in younger subjects, but this is not reliable. Several cases (reviewed in [21]) have had bowel problems, some with ostomies, further raising the possibility of PG (although

the underlying condition in such cases has been mainly diverticular disease), and the histology shows neutrophilic spongiosis and an upper dermal neutrophilic or mixed neutrophilic and lymphocytic infiltrate. Reported responses to oral or topical corticosteroids, topical tacrolimus and colchicine, and recurrence around skin grafts as an attempted treatment, also suggest the possibility of PG. As occurs in *amicrobial pustulosis* (below), zinc deficiency, and therapeutic response to zinc, may be a feature [22].

Amicrobial pustulosis associated with autoimmune diseases (APAD; also termed amicrobial pustulosis, follicular impetigo or pyodermatitis vegetans associated with lupus erythematosus or other autoimmune diseases). This is a condition of rapidly evolving, small, semi-confluent pustules that predominantly affects the face, scalp (causing alopecia) and flexures, reviewed in [23]. There is neutrophilic epidermal and ostial exocytosis and spongiform pustules; positive direct immunofluorescence for IgM, C3 and less often IgG is variable and may be vascular or a lupus band. Most cases are in patients with systemic lupus erythematosus, but coeliac disease and other autoimmune conditions occur; corticosteroids or dapsone may be effective, and oral zinc was effective in two cases [23].

Localized reaction to granulocyte colony-stimulating factor (GCF). Colony-stimulating factors are a well-documented triggering factor for neutrophilic dermatoses of different types [24]. A localized form at injection sites may be less recognized. Histology may be Sweet's syndrome-like, a necrotizing vasculitis or predominantly eosinophilic [25].

Neutrophilic spongiosis [12] (originally described as granulocytic spongiotic papulovesiculosis [13]). This was described two decades ago but never fully explained. The cases described had intermittent outbreaks of myriad, semi-confluent, small vesicopustules, predominantly on the face, neck or upper trunk but sometimes at other sites such as axillae. In one case, severe mucosal involvement occurred with significant malaise. One case had dermoepidermal IgA (distinguishing it from intraepidermal neutrophilic IgA dermatosis, which is usually flexural, with annular lesions, no mucosal disease, and intercellular IgA), the other had negative immunofluorescence but did have an admixture of eosinophils in the infiltrate. Neither case had a consistent relationship with medications, making acute, generalized, exanthematous pustulosis unlikely, and neither had any evolution suggesting early spongiotic changes of pemphigus. The illustrated morphology, epidermal neutrophilic disease and extent of mucosal disease were not typical for Sweet's disease, but this might be considered.

References

1 Powell FC, Su WPD. Pyoderma gangrenosum: classification and management. *J Am Acad Dermatol* 1996; **34**: 395–409.
2 Ahmadi S, Powell FC. Pyoderma gangrenosum: uncommon presentations. *Clin Dermatol* 2005; **23**: 612–20.
3 O'Loughlin S, Perry HO. A diffuse pustular eruption associated with ulcerative colitis. *Arch Dermatol* 1978; **114**: 1061–4.
4 Fenske NA, Gern JE, Pierce D *et al*. Vesicopustular eruption of ulcerative colitis. *Arch Dermatol* 1983; **119**: 664–9.
5 Callen JP, Woo TY. Vesicopustular eruption in a patient with ulcerative colitis. *Arch Dermatol* 1985; **121**: 399.
6 Sarkany RPE, Burrows NP, Grant JW *et al*. The pustular eruption of ulcerative colitis. A variant of Sweet's syndrome? *Br J Dermatol* 1998; **138**: 365–6.
7 Váquez J, Almaro M, del Pozo J, Fonseca E. Neutrophilic pustulosis and ulcerative colitis. *J Eur Acad Dermatol Venereol* 2003; **17**: 77–9.
8 Magro CM, Crowson NA. A distinctive vesicopustular eruption associated with hepatobiliary disease. *Int J Dermatol* 1997; **36**: 837–44.
9 Grob JJ, Mege JL, Prax AM, Bonerandi JJ. Disseminated pustular dermatosis in polycythaemia rubra vera. Relationship with neutrophilic dermatosis of myeloproliferative disorders: study of neutrophil function. *J Am Acad Dermatol* 1988; **18**: 1212–8.
10 Keefe M, Wakeel RA, Kerr REI. Sweet's syndrome, plantar pustulosis and vulval pustules. *Clin Exp Dermatol* 1988; **13**: 344–6.
11 Sommer S, Wilkinson SM, Merchant WM, Goulden V. Sweet's syndrome presenting as palmoplantar pustulosis. *J Am Acad Dermatol* 2000; **42**: 32–4.
12 Sayami S, Tagami H. Granulocytic spongiotic papulovesiculosis. A new entity? *Br J Dermatol* 1984; **110**: 504–6.
13 Batista G, Santos ANC, Sampáio SAP. Neutrophilic spongiosis. A new entity? *Br J Dermatol* 1986; **114**: 131–4.
14 Ulloa-Gutierrez R, Acón-Rojas F, Camancho-Badilla K, Soriano-Fallas A. Pustular rash in Kawasaki syndrome. *Pediatr Infect Dis J* 2007; **26**: 1163–5.
15 Mizuno Y, Suga Y, Muramatsu S *et al*. Psoriasiform and palmoplantar pustular lesions induced after Kawasaki disease. *Int J Dermatol* 2006; **45**: 1080–2.
16 Su WPD, Duncan SC, Perry HO. Blastomycosis-like pyoderma. *Arch Dermatol* 1979; **115**: 170–3.
17 Papadopoulos AJ, Schwarz RA, Kapila R *et al.* Pyoderma vegetans. *J Cutan Med Surg* 2001; **5**: 223–7.
18 Magee KH, Pollack BP, Raugi GJ. Pustule-studded plaques after abrasion injury (blastomycosis-like pyoderma). *Arch Dermatol* 2006; **142**: 1643–8.
19 Sodemoto K, Kinbara T, Kitagawa T *et al*. Multiple pustulogranulomatous plaques in the elderly (Pyoderma vegetans). *Clin Exp Dermatol* 2006; **31**: 489–90.
20 Mehravaran M, Kemény L, Husz S *et al*. Pyoderma—pyostomatitis vegetans. *Br J Dermatol* 1997; **137**: 266–9.
21 Brouard MC, Prins C, Chavaz P *et al*. Erosive pustular dermatosis of the leg: report of three cases. *Br J Dermatol* 2002; **147**: 765–9.
22 Salavert M, Franck F, Amarger S *et al*. Erosive pustular dermatosis of the leg: role of zinc deficiency? *Ann Dermatol Venereol* 2006; **133**: 975–8.
23 Bénéton N, Wolkenstein P, Bagot M *et al*. Amicrobial pustulosis associated with autoimmune diseases: healing with zinc supplementation. *Br J Dermatol* 2000; **143**: 1311–5.
24 Johnson ML, Grimwood RE. Leukocyte colony-stimulating factors. A review of associated neutrophilic dermatoses and vasculitides. *Arch Dermatol* 1994; **130**: 77–81.
25 Samlaska CP, Noyes DK. Localized reactions to granulocyte colony-stimulating factor. *Arch Dermatol* 1993; **129**: 645–6.

Other neutrophilic dermatoses and overlapping or associated variants

Subcutaneous Sweet's syndrome and neutrophilic panniculitis

These relatively rare disorders represent a further part of the spectrum of neutrophilic dermatoses that histologically resemble Sweet's syndrome. Terminology varies between authors. Sutra-Loubet and colleagues reviewed these conditions and suggested a classification of neutrophilic dermatoses, in which 'neutrophilic panniculitis' was distinguished by affecting the fat lobules, whereas 'Sweet's syndrome with subcutaneous involvement' was the term applied if there was involvement of the septae [1]. Lesions that extend more deeply from the fat, or that are non-cutaneous, were termed aseptic neutrophilic abscesses (p. 50.82). However, Cohen [2] preferred to use 'subcutaneous Sweet's syndrome' to describe any variant in which there is neutrophilic panniculitis affecting the lobules, septae or both, with or without associated

dermal involvement, suggesting that neutrophilic lobular panniculitis is best viewed as a descriptive term of which subcutaneous Sweet's syndrome is one cause. Whichever term is preferred, the typical pathological pattern, as in Sweet's syndrome, is dominated by neutrophils, without vasculitis, and the involvement of fat is primary rather than simply deep extension of a dermal lesion [1–4]. Immature myeloid cells may be predominant [5]; the septal variant may be granulomatous [6].

Subcutaneous involvement can occur in patients with Sweet's syndrome or pyoderma gangrenosum, but is increasingly recognized in isolation; dermal/subcutaneous aseptic abscesses can occur in conjunction with abscesses at other sites, or combined with various neutrophilic dermatoses. Subcutaneous Sweet's syndrome is predominantly associated with myelodysplasia [1–4]; as in standard Sweet's syndrome, provocation by all-*trans*-retinoic acid [7] and by colony-stimulating factors [8] have been reported, although in one case it is likely that disease progression rather than granulocyte colony-stimulating factor (used uneventfully for the preceding year) was the cause of subcutaneous Sweet's syndrome [9]. A case related to breast carcinoma has also been reported, and some cases have had preceding viral infections.

Clinically, lesions present as subcutaneous nodules, infiltrated plaques or erythema nodosum-like lesions, at any body site, with or without more typical Sweet's syndrome lesions or occasionally pustules [10]. Fever, malaise, arthralgia, and peripheral blood eosinophilia are all common.

Important differential diagnoses, clinically and/or pathologically, include infections (especially in patients with myelodysplasia), α-1-antitrypsin deficiency, and hepatitis C infection [11]; neutrophilic lobular panniculitis also occurs in rheumatoid disease [12].

References

1 Sutra-Loubet C, Carlotti A, Guillemette J, Wallach D. Neutrophilic panniculitis. *J Am Acad Dermatol* 2004; **50**: 280–5.

2 Cohen PR. Subcutaneous Sweet's syndrome: a variant of acute febrile neutrophilic dermatosis that is included in the histopathological differential diagnosis of neutrophilic panniculitis. *J Am Acad Dermatol* 2005; **52**: 927–8.

3 Jordaan HF. Acute febrile neutrophilic dermatosis: a histopathological study of 37 patients and a review of the literature. *Am J Dermatopathol* 1989; **11**: 99–111.

4 Matsumura Y, Tanabe H, Wada Y *et al*. Neutrophilic panniculitis associated with myelodysplastic syndromes. *Br J Dermatol* 1997; **136**: 142–3.

5 Chow S, Pasternak S, Green P *et al*. Histiocytoid neutrophilic dermatoses and panniculitides: variations on a theme. *Am J Dermatopathol* 2007; **29**: 334–41.

6 Blaustein A, Moreno A, Noguera J, de Moragas JM. Septal granulomatous panniculitis in Sweet's syndrome. Report of two cases. *Arch Dermatol* 1985; **121**: 785–8.

7 Jagdea J, Campbell R, Long T *et al*. Sweet's syndrome-like neutrophilic lobular panniculitis associated with all-*trans*-retinoic acid chemotherapy in a patient with acute promyelocytic leukaemia. *J Am Acad Dermatol* 2007; **56**: 690–3.

8 Hasegawa M, Sato S, Nakada M *et al*. Sweet's syndrome associated with granulocyte colony-stimulating factor. *Eur J Dermatol* 1988; **8**: 503–5.

9 Raj K, Ho A, Creamer JD *et al*. Complete response of deep neutrophilic dermatosis associated with myelodysplastic syndrome to 5-azacytidine. *Br J Dermatol* 2007; **156**: 1039–41.

10 Chen HC, Kao WY, Chang DM *et al*. Neutrophilic panniculitis with myelodysplastic syndromes presenting as pustulosis: case report and review of the literature. *Am J Hematol* 2004; **76**: 61–5.

11 Crowson AN, Nuovo G, Ferri C, Magro CM. The dermatopathologic manifestations of hepatitis C infection: a clinical, histological, and molecular assessment of 35 cases. *Hum Pathol* 2003; **34**: 573–9.

12 Tran TA, DuPree M, Carlson JA. Neutrophilic lobular (pustular) panniculitis associated with rheumatoid arthritis: a case report and review of the literature. *Am J Dermatopathol* 1999; **21**: 247–52.

Relapsing polychondritis

Relapsing polychondritis is an inflammatory condition associated with antibodies against type II collagen, which is predominant in cartilage. The nose, ears, larynx, trachea, bronchi, joints and eyes are the most obvious sites affected, often with general malaise or fever during episodes of inflammation. Neurological (headache, nerve palsies, hemiplegia and others), cardiovascular (valvular regurgitation, aortic aneurysm, myocarditis, pericarditis, conduction defects and myocardial infarction) and renal (various forms of nephritis) features are also a consequence [1]. Issues regarding the pathogenesis and effects of the disease, and its treatment, are discussed in Chapter 51. However, features that link it with vasculitides and neutrophilic dermatoses are discussed here; in particular, it both occurs with, and has many disease associations in common with, paraneoplastic vasculitis and with neutrophilic dermatoses, and may appropriately be classified as a neutrophilic dermatosis [2], particularly given the view that neutrophilic dermatoses are a continuum of disease with vasculitides.

Some of the diseases that are associated with relapsing polychondritis as well as with vasculitis or neutrophilic dermatoses are listed in Table 50.28; vasculitides and neutrophilic dermatoses that have been reported in association with relapsing polychondritis are listed in Table 50.29. Myelodysplastic syndromes are an important association [1,3–5], possibly associated in a quarter of cases [4] although others suggest around 10% [6,7]; both Hodgkin's and non-Hodgkin's lymphomas are also reported [1,3], as well as a patient who developed paraneoplastic relapsing polychondritis associated with chemotherapy-induced erythroleukaemia after treatment for Hodgkin's disease [8]. Patients

Table 50.28 Diseases that are associated with both relapsing polychondritis and with vasculitis or neutrophilic dermatoses [1,5,7].

Disease category	Examples
Haematological malignancies	Myelodysplastic syndromes (most) Leukaemia Aplastic anaemia Lymphoma Multiple myeloma (usually IgA)
Collagen vascular disorders and autoimmune	Rheumatoid disease Systemic lupus erythematosus Dermatomyositis Sjögren's syndrome Still's disease Crohn's disease Autoimmune thyroid disease
Infections	Hepatitis C virus infection HIV infection
Other neoplasms [5]	Carcinomas of bladder (in a patient with Sweet's syndrome), breast, pancreas, lung/bronchus, colon/rectum, larynx; sarcomas (rarely)

Table 50.29 Vasculitides, neutrophilic dermatoses and associated clinical cutaneous findings that have been associated with relapsing polychondritis.

Disease category	Examples
Vasculitis	Wegener's granulomatosis Churg–Strauss syndrome Takayasu's arteritis Erythema elevatum diutinum Behçet's disease Temporal arteritis Leukocytoclastic vasculitis Lymphocytic vasculitis Pustular vasculitis
Neutrophilic dermatoses	Sweet's syndrome Erythema nodosum Neutrophilic panniculitis
Clinical findings	Oral and genital aphthae Non-follicular sterile pustules Thrombophlebitis Purpura Livedo reticularis Digital infarcts and necrosis Acral erythema nodosum-like nodules Subcutaneous nodules (representing thromboses and various panniculitides)

with an underlying myelodysplastic syndrome were statistically more likely to be male, older and to have additional skin findings in a large case series [7]. Cutaneous features other than those directly related to underlying inflammation of cartilage (e.g. auricular inflammation sparing the lobe, nasal inflammation and saddle nose) are documented in reviews and large case series [1,5,7], and are listed in Table 50.29. In one large series, over a third had dermatological findings in addition to those directly due to associated disorders (such as haematological or collagen vascular disorders); these features occurred with or separate from episodes of chondritis in approximately equal numbers (each about 10%), and 10% had cutaneous vasculitis (90% leukocytoclastic) [7].

Of the associated neutrophilic dermatoses, Sweet's syndrome has particularly been reported [9–11]; erythema nodosum, acral erythema nodosum-like nodules, neutrophilic panniculitis, non-follicular sterile pustules, and oral and genital aphthae occur and are part of the same spectrum [1,5,7]. Other neutrophilic disorders reported with relapsing polychondritis include pyoderma gangrenosum [12,13], aseptic abscesses [14], and erythema elevatum diutinum [15] (which we would classify as a vasculitis rather than a neutrophilic dermatosis, but which is viewed by some authors as a neutrophilic dermatosis [2]).

References

1 Somach SC. Relapsing polychondritis. In: Morgan MB, Smoller BR, Somach SC. *Deadly Dermatologic Diseases. Clinicopathologic Atlas And Text*. New York: Springer, 2007: 161–4.

2 de Moragos JM, Pujol RM. Neutrophilic dermatoses. *Curr Opin Dermatol* 1997; **4**: 13–20.

3 Cohen PR. Granuloma annulare, relapsing polychondritis, sarcoidosis, and systemic lupus erythematosus: conditions whose dermatologic manifestations may occur as hematologic malignancy-associated mucocutaneous paraneoplastic syndromes. *Int J Dermatol* 2006; **45**: 70–80.

4 Hall R, Hopkinson N, Hamblin T. Relapsing polychondritis, smouldering non-secretory myeloma and early myelodsplastic syndrome in the same patient: three difficult diagnoses produce a life threatening illness. *Leuk Res* 2000; **24**: 91–3.

5 Zeuner M, Straub RH, Rauh G *et al*. Relapsing polychondritis: clinical and immunogenetic analysis of 62 patients. *J Rheumatol* 1997; **24**: 96–101.

6 Provost TT, Flynn JA. Relapsing polychondritis. In: Provost TT, Flynn JA, eds. *Cutaneous Medicine: Cutaneous Manifestations of Systemic Disease*. Hamilton, Ontario: Decker, 2001: 158–64.

7 Francès C, el-Rassi R, Laporte JL *et al*. Dermatologic manifestations of relapsing polychondritis. A study of 200 cases at a single center. *Medicine (Baltimore)* 2001; **80**: 173–9.

8 Scully RE, Mark EJ, McNeely WF *et al*. Case Records of the Massachusetts General Hospital. Case 38–1997. *N Engl J Med* 1997; **337**: 1753–60.

9 Fujimoto N, Tajima S, Ishibashi A *et al*. Acute febrile neutrophilic dermatosis (Sweet's syndrome) in a patient with relapsing polychondritis. *Br J Dermatol* 1998; **139**: 930–1.

10 Astudillo L, Launay F, Lamant L *et al*. Sweet's syndrome revealing relapsing polychondritis. *Int J Dermatol* 2004; **43**: 720–2.

11 Vignon-Pennamen MD, Juillard C, Rybojad M *et al*. Chronic recurrent lymphocytic Sweet syndrome as a predictive marker of myelodysplasia: a report of 9 cases. *Arch Dermatol* 2006; **142**: 1170–6.

12 Check IJ, Ellington EP, Moreland A, McKay M. T helper-suppressor cell imbalance in pyoderma gangrenosum, with relapsing polychondritis and corneal keratolysis. *Am J Clin Pathol* 1983; **80**: 396–9.

13 Tsanadis GD, Chouliara ST, Voulgari PV *et al*. Outcome of pregnancy in a patient with relapsing polychondritis and pyoderma gangrenosum. *Clin Rheumatol* 2002; **21**: 538.

14 André MFC, Piette JC, Kémény JL *et al*. Aseptic abscesses: a study of 30 patients with or without inflammatory bowel disease and review of the literature. *Medicine (Baltimore)* 2007; **86**: 145–61.

15 Bernard P, Bedane C, Delrous JL *et al*. Erythema elevatum diutinum in a patient with relapsing polychondritis. *J Am Acad Dermatol* 1992; **26**: 312–5.

Rheumatoid neutrophilic dermatosis [1–6]

Rheumatoid neutrophilic dermatosis was described by Ackerman in 1978 [3], and a number of cases have been described subsequently, although it is an uncommon disorder. It is thought likely to be immune complex-mediated, and tends to occur in patients with severe, active rheumatoid disease. A significantly elevated rheumatoid factor may be found, but several patients with seronegative disease have been reported [4,7], including patients with rheumatoid nodules and rheumatoid papules [8]. Lesions occur at any site, mainly the limbs and face, and may consist of papules, nodules or plaques, sometimes with an annular morphology (Fig. 50.46). Urticated, vesicular, crusted and ulcerated lesions may all occur. Rarely, lesions may be bullous [9]. Sweet's syndrome may be difficult to distinguish, and coexistence of the two entities has been reported [7,10], as well as rheumatoid neutrophilic dermatosis associated with pyoderma gangrenosum [11].

Histologically, there is a dense neutrophilic infiltrate that may extend into the epidermis or deeply into the subcutaneous fat; papillary microabscesses may be present [1]. Vasculitis is not seen but leukocytoclasis may occur. The picture is similar to that of Sweet's syndrome, but the latter usually has more prominent dermal oedema and less admixture with other cell types (some eosinophils, plasma cells and lymphocytes may be present in rheumatoid neutrophilic dermatosis) [4].



Fig. 50.46 Rheumatoid neutrophilic dermatosis affecting the hands.

Lesions may resolve spontaneously or as a result of treatment of the rheumatoid disease with immunosuppressive agents. Some plaques may be chronic over a period of months [6]. Topical or oral corticosteroids, dapsone and hydroxychloroquine have all been used with benefit.

A disorder termed 'neutrophilic lobular panniculitis associated with rheumatoid arthritis' is of uncertain aetiology, and has been classified as a lobular panniculitis with vasculitis. Histologically, it is in the differential diagnosis of subcutaneous Sweet's syndrome, discussed above. The few cases reported had a perivascular neutrophilic infiltrate and leukocytoclasis without fibrinoid change or definite vasculitis, although one had associated leukocytoclastic vasculitis in the upper dermis [12].

References

1 Huang W, McNeely MC. Neutrophilic tissue reactions. *Adv Dermatol* 1998; **13**: 33–63.

2 Mashek HA, Pham CT, Helm TN, Klaus M. Rheumatoid neutrophilic dermatitis. *Arch Dermatol* 1997; **133**: 757–60.

3 Ackerman AB. *Histologic Diagnosis of Skin Diseases: A Method by Pattern Analysis.* Philadelphia: Lea & Febiger, 1978: 449–51.

4 Sayah A, English JC 3rd. Rheumatoid arthritis: a review of the cutaneous manifestations. *J Am Acad Dermatol* 2005; **53**: 191–209.

5 Lowe L, Kornfeld B, Clayman J, Golitz LE. Rheumatoid neutrophilic dermatitis. *J Cutan Pathol* 1992; **19**: 48–53.

6 Scherbenske JM, Benson PM, Lupton GP, Samlaska CP. Rheumatoid neutrophilic dermatosis. *Arch Dermatol* 1989; **125**: 1105–8.

7 Gay-Crosier F, Dayer JM, Chavaz P, Hauser C. Rheumatoid neutrophilic dermatitis / Sweet's syndrome in a patient with seronegative rheumatoid arthritis. *Dermatology* 2000; **201**: 185–7.

8 Yamamoto T, Matsunaga T, Nishioka K. Rheumatoid neutrophilic dermatitis, rheumatoid papules, and rheumatoid nodules in a patient with seronegative rheumatoid arthritis. *J Am Acad Dermatol* 2003; **48**: 634–5.

9 Kreuter A, Rose C, Zillikens D, Altmeyer P. Bullous rheumatoid neutrophilic dermatitis. *J Am Acad Dermatol* 2005; **52**: 916–8.

10 Wilson DM, John GR, Callen JP. Peripheral ulcerative keratitis—an extracutaneous neutrophilic disorder: report of a patient with rheumatoid arthritis, pustular vasculitis, pyoderma gangrenosum, and Sweet's syndrome with an excellent response to cyclosporine therapy. *J Am Acad Dermatol* 1999; **40**: 331–4.

11 MacAya A, Servitje O, Jucglà A, Peyri J. Rheumatoid neutrophilic dermatosis associated with pyoderma gangrenosum. *Br J Dermatol* 2000; **142**: 1246–8.

12 Requena L, Sánchez Yus E. Panniculitis Part II. Mostly lobular panniculitis. *J Am Acad Dermatol* 2001; **45**: 325–61.

Neutrophilic eccrine hidradenitis

Neutrophilic eccrine hidradenitis (NEH) has been reviewed in detail in [1,2]. It is characterized by a neutrophilic infiltrate that is centred on and extends into the eccrine coils. Typically, the eccrine apparatus shows vacuolar degeneration or necrosis, and there may be mucinous degeneration around eccrine glands and squamous metaplasia of eccrine ducts. There is usually, but not always, a neutrophilic infiltrate that surrounds the eccrine coil and ducts, forms focal dermal abscesses and may surround vessels, without vasculitis. Oedema and/or haemorrhage may be present [2].

Early reports [3,4] implicated chemotherapeutic agents as the cause, and approximately 90% of cases still occur in the setting of leukaemia (usually acute myeloid type) undergoing induction chemotherapy with cytarabine and anthracyclines. However, other causes have subsequently been recorded, and in some of the patients with leukaemia the eruption precedes the diagnosis or treatment. Most cases occur in the setting of neutropenia; in neutropenia associated with acute myelogenous leukaemia (AML), 2–3% of patients may develop a neutrophilic dermatosis [5]. NEH may occur more frequently in AML subtypes FAB 4 and 5 in which leukaemia cutis and skin tropism of blast cells is more common [6]. In some cases, NEH recurs during successive cycles of chemotherapy, and it can also occur recurrently during chemotherapy for relapses of leukaemia, but not in association with consolidation chemotherapy to maintain remission; it is unclear whether this represents altered type or dose of drug therapy, or an altered drug–disease interaction. Thus, NEH represents a reaction pattern with several causes. Nevertheless, cytotoxicity of drugs on the eccrine coil remains the likely explanation for this dermatosis in most cases. The causes can be summarized into a few main groups (Table 50.30).

Clinically, lesions may resemble those of Sweet's syndrome. They may affect predominantly the head (especially the periorbital regions), neck and upper trunk; in some cases they may be generalized, but in others they are limited (for example, to the limbs, face or ears, or, in one case, around the breasts). The palms or dorsa of the hands are occasionally affected, and lesions have been reported at injection sites as a pathergic phenomenon [5]. If recurrent, they may affect similar sites to those previously affected. Lesions may be plaques, papules, nodules, erythema multiforme-like, or urticated, and may be grouped. Annular lesions have been reported on the dorsa of the hands [7]. Pustules, vesicles and occasionally purpura may be present. The lesions may be painful or tender, but can be asymptomatic, and associated fever is common. Most chemotherapy-related cases occur about 2 weeks after starting treatment, and resolve spontaneously after 2–3 weeks. Associated neutrophilic abscess formation occurred in a patient whose cultures grew 'slight' *Staphylococcus aureus* but in whom the lesions all responded to corticosteroids and not to antibiotics [8].

Treatment options, if required, include topical or systemic corticosteroids and non-steroidal anti-inflammatory agents [1]. Dapsone was used to prevent recurrent episodes in a patient receiving lomustine; it was started 2 days before the chemotherapy and

Table 50.30 Causes of neutrophilic eccrine hidradenitis [see also 1,2]*.

Type of process	Specific group	Examples
Malignant disease	Haematological malignancy	Leukaemias (especially acute myelogenous; also acute myelomonocytic, acute lymphoblastic, chronic lymphocytic, others)
		Hodgkin's lymphoma
		Non-Hodgkin's lymphoma
	Other malignant disease	Testicular carcinoma
		Osteosarcoma
		Wilm's tumour
		Breast carcinoma
		Lung carcinoma
Drugs	Chemotherapy agents	Cytosine arabinoside
		Anthracyclines (daunorubicin, doxorubicin)
		Vincristine, vinblastine
		Bleomycin
		Lomustine
		Mitoxantrone
		Cisplatin
		Dacarbazine
		Etoposide
		6-Thioguanine
		Cyclophosphamide
		Chlorambucil
		Methotrexate
		5-Fluorouracil
		Topotecan
		Imatinib mesylate
	Other drugs	Paracetamol (acetaminophen)
		Zidovudine
		Granulocyte colony-stimulating factor
		Amoxycillin
		Minocycline
Other diseases	Infections	*Serratia marcescens*
		Enterobacter cloacae
		Staphylococcus aureus
		Streptococcal endocarditis
		HIV infection (includes untreated cases)
		Hepatitis C
		Nocardiasis
	Other	Idiopathic neutropenia
		Behçet's disease
		Actinic reticuloid (methotrexate treatment)
No apparent disease association		Rare

*It should be noted that many cases have occurred in the setting of haematological malignancy and multiple-drug schedules, so interpretation of a specific cause is difficult in some instances.

continued for 14 days [9]. It was also successful in a patient with chronic NEH associated with Behçet's disease [10]. Colchicine was effective in a patient with apparently idiopathic, persistent, NEH [11].

A paediatric variant of neutrophilic hidradenitis, variously termed 'idiopathic plantar hidradenitis' or 'recurrent palmoplantar hidradenitis' [1], is discussed in Chapter 44. These disorders are not discussed further here as they are primarily neutrophilic eccrine rather than neutrophilic vascular reactions.

References

1 Huang W, McNeely MC. Neutrophilic tissue reactions. *Adv Dermatol* 1998; **13**: 33–63.

2 Bachmeyer C, Aractingi S. Neutrophilic eccrine hidradenitis. *Clin Dermatol* 2000; **18**: 319–30.

3 Flynn TC, Harrist TJ, Murphy GF *et al*. Neutrophilic eccrine hidradenitis: a distinctive rash associated with cytarabine therapy and acute leukaemia. *J Am Acad Dermatol* 1984; **11**: 584–90.

4 Scallan PJ, Kettler AH, Levy ML, Tschen JA. Neutrophilic eccrine hidradenitis. Evidence implicating bleomycin as a causative agent. *Cancer* 1988; **62**: 2532–6.

5 Aractingi S, Mallet V, Pinquier L *et al*. Neutrophilic dermatoses during granulocytopenia. *Arch Dermatol* 1995; **131**: 1141–5.
6 Cancelas-Perez JA, Perez de Oteyza J, Megido M *et al*. Chemotherapy-induced neutrophilic eccrine hidradenitis in acute myelogenous leukaemia. *Acta Haematol* 1992; **87**: 167–8.
7 Scong VY, Appell ML, Omura EF *et al*. Annular plaques on the dorsa of the hands. *Arch Dermatol* 1991; **127**: 1398–1402.
8 Horiguchi Y, Lee SG, Matsumoto I *et al*. Abscess-forming neutrophilic dermatosis: report of three cases associated with hemoglobinopathies. *Dermatology (Basel)* 1998; **197**: 174–7.
9 Shear NH, Knowles SR, Shapiro L, Poldre P. Dapsone in prevention of recurrent neutrophilic eccrine hidradenitis. *J Am Acad Dermatol* 1996; **35**: 819–22.
10 Nijsten TEC, Meuleman L, Lambert J. Chronic pruritic neutrophil eccrine hidradenitis in a patient with Behçet's disease. *Br J Dermatol* 2002; **147**: 797–800.
11 Belot V, Perrinaud A, Corven C *et al*. Adult idiopathic neutrophil eccrine hidradenitis treated with colchicines. *Presse Med* 2006; **35**: 1475–8.

Subcorneal pustular dermatosis and neutrophilic bullous disorders

Subcorneal pustular dermatosis is a rare neutrophilic dermatosis that is associated with monoclonal gammopathy, multiple myeloma, lymphomas, pyoderma gangrenosum, connective tissue disease and IBD [1,2]. Intraepidermal (neutrophilic) IgA pustulosis has some similarities, and has also been linked with monoclonal gammopathy (in 20% of cases) and with lymphomas. These disorders are bullous and are not discussed further here as they do not include a neutrophilic vascular reaction.

References

1 Reed J, Wilkinson J. Subcorneal pustular dermatosis. *Clin Dermatol* 2000; **18**: 301–13.
2 Cheng S, Edmonds E, Ben-Gashir M, Yu RC. Subcorneal pustular dermatosis: 50 years on. *Clin Exp Dermatol* 2008; **33**: 229–33.

CHAPTER 51

The 'Connective Tissue Diseases'

M.J.D. Goodfield[1], *S.K. Jones*[2] *& D.J. Veale*[3]

[1]Department of Dermatology, Leeds General Infirmary, Leeds, UK
[2]Department of Dermatology, Clatterbridge Hospital, Wirral, UK
[3]St Vincent's University Hospital, Dublin, Ireland

Lupus erythematosus, 51.2
Discoid lupus erythematosus, 51.4
Subacute cutaneous lupus erythematosus, 51.22
Systemic lupus erythematosus, 51.27
Neonatal lupus erythematosus, 51.49
The lupus anticoagulant, anticardiolipin antibodies and the antiphospholipid antibody syndrome, 51.63
Scleroderma, 51.64
Localized morphoea, 51.64
Generalized morphoea, 51.76
Pseudoscleroderma, 51.79
Metabolic disorders, 51.79
Deposition disorders, 51.79
Genetic disorders, 51.79
Occupational causes, 51.80
Exogenous/iatrogenic scleroderma, 51.81
Graft-versus-host disease, 51.83
Eosinophilic fasciitis, 51.86
Systemic sclerosis, 51.87
Mixed connective tissue disease, 51.110
Cold, flexed fingers, 51.112
Lichen sclerosus, 51.112
Scleroedema, 51.118
Dermatomyositis, 51.120
Dermatological manifestations of rheumatoid disease, 51.130
Rheumatoid nodules, 51.130
Vascular lesions in rheumatoid arthritis, 51.132
Fibroblastic rheumatism, 51.133
Still's disease, 51.133
Sjögren's syndrome, 51.134
Rheumatic fever, 51.138

Introduction

Many single diseases can produce pathology in one or multiple organ systems. However, not all of the conditions that can affect multiple organ systems are related to each other, so what is it that determines the classification of diseases as 'connective tissue diseases'? We recognize that there are certain features common to all of them—the existence of autoimmunity in the form of autoantibody production or disordered cell-mediated immunity, vascular abnormalities characterized by Raynaud's phenomenon, occlusive vascular disease and vasculitis (although the pathology is not entirely a result of vascular inflammation), arthritis or arthralgia, and skin disease. However, dependence on clinical patterning is unreliable because similar patterns of disease may be seen with widely different pathologies. For instance, the primary vasculitides such as Wegener's granulomatosis or polyarteritis nodosa may share many systemic features of the connective tissue disorders, but so may sarcoidosis with a granulomatous pathology but without autoantibody production.

Despite this problem, it is still true that those disorders contained within the umbrella of the 'connective tissue diseases' share many clinical and pathological features. Indeed, it was this pathological similarity that first suggested that abnormalities of the connective tissue might be the common factor linking these conditions. In 1933, Klinge [1] was the first to propose that rheumatic fever and rheumatoid arthritis were disorders of the entire connective tissue. The changes in the intercellular components of the connective tissue, the presence of fibrinoid necrosis in collagenous tissue and the myxomatous swelling of ground substance were similar to those seen in experimental animals made hypersensitive to foreign protein, and for these reasons he concluded that the rheumatic diseases were caused by hypersensitivity. He included other conditions in which fibrinoid necrosis was a feature, such as polyarteritis nodosa, dermatomyositis and malignant hypertension. The presence of widespread fibrinoid change in the vessels led to the inclusion of systemic sclerosis by Masugi and Yä-Shu [2], and also of systemic lupus erythematosus. However, Klemperer *et al.* [3], with whose work the term 'collagen disease' is associated, struck a note of caution by pointing out that fibrinoid necrosis could be seen in the absence of hypersensitivity mechanisms, for example, in the base of peptic ulcers. It has been stated [4] that the presence of fibrinoid degeneration does not warrant the grouping of the conditions showing this change, nor does it imply an allergic mechanism. It is now recognized that there are various types of fibrinoid with somewhat similar staining properties. They have multiple origins from the degeneration of collagen, from ground substance, muscle, fibrin and other plasma proteins.

In 1950, Klemperer [5] stated: 'The term diffuse collagen disease was originally applied to acute and chronic maladies which are characterized anatomically by generalized alterations of the connective tissue, particularly by abnormalities of its extracellular components. In this case the term can include rheumatic fever, rheumatoid arthritis, polyarteritis nodosa, acute lupus erythematosus, generalized scleroderma and dermatomyositis'. Klemperer disliked the widespread indiscriminate use of the term 'collagen

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

disease' for disorders with unusual clinical or pathological features. He confirmed that his sole intention was to put forward the concept that, 'in certain diseases anatomical investigations reveal conspicuous alterations in the intermediary substances of the connective tissue in a systemic manner'. It is now realized that the connective tissue is not the only tissue involved in these disorders.

It has been customary to consider that systemic and discoid lupus erythematosus (SLE and DLE), systemic sclerosis, localized and generalized morphoea, dermatomyositis, rheumatoid arthritis and Sjögren's syndrome should be grouped together, and this has been supported by evidence of clinical, pathological and immunological overlap. The primary vasculitides, such as polyarteritis nodosa, Wegener's granulomatosis and giant cell arteritis, are sufficiently distinct to be considered separately, although there is much clinical overlap with these diseases too. However, these groupings may not be justified and may even hamper our understanding of these diseases. On the other hand, certain patients with evidence of clinical overlap can be distinguished by characteristic immunological abnormalities, associated with differences in outcome and response to therapy. With the passage of time, other conditions, sometimes newly described, such as eosinophilic fasciitis [6], may have to be added to the group.

When adequate criteria and modern investigative techniques are used, it is apparent that each disorder can usually be distinguished as a separate entity. For example, evidence has been produced that DLE is a separate disorder and not a benign variant of SLE [7–9]. Often, subsets can be distinguished clinically, pathologically or immunologically. Immunological subgroupings are becoming more numerous and complex with the identification of new antigens and the reacting autoantibodies. Specific antibodies may be strongly associated with particular disease patterns, such as the antibody to extractable nuclear antigen found in mixed connective disease or anti-Ro or anti-La antibodies in a clinically distinctive type of lupus erythematosus called subacute cutaneous lupus erythematosus (SCLE; see p. 51.22). Moreover, certain diseases that appear clinically homogeneous may be genetically heterogeneous. The separate genotypes in DLE related to age of onset [8,9], the clinical subsets in SLE and the severity of disease in systemic sclerosis related to HLA-B8 [10] are good examples.

Despite these improvements in investigational techniques, diagnosis of these disorders is sometimes far from easy. Results have to be interpreted in the context of the clinical presentation. Patients are not helped by a diagnosis of 'collagen vascular disease' or 'collagenosis' when suffering from an illness with obscure symptoms and signs, possibly associated with an elevated plasma viscosity, and a weakly positive antinuclear antibody. There is, however, often an early stage in the history of a patient's illness when the full pattern has not evolved. These patients may be said to have an 'undifferentiated connective tissue disease', but the disease usually reveals itself and it is usually ultimately possible to make a precise diagnosis. This is very important for the patient and critical for research, both epidemiological and therapeutic. It is more than an academic exercise as, in the future, specific therapy may well depend on the precision of diagnosis.

Accurate naming of diseases is important for patients, but is also relevant to this chapter. Is the term 'the connective tissue diseases' [11] the most appropriate title for this contribution? We believe that it is because there seems to be no better alternative. Some authorities prefer the older term, 'collagen disease'; others [12] apply it to all inherited or acquired disorders of the connective tissue system. 'Collagen disease' is incorrect because there is no evidence that collagen is primarily at fault. 'Collagen vascular disease' conveys a little more detail, but is still incorrect. The increasing emphasis on immunological abnormalities in these conditions has brought the terms 'autoimmune disease' [13] and 'immunological disease' [14] some popularity, but both are over-inclusive. To avoid the premature coining of a confusing new term we have preferred to continue to refer to 'connective tissue disease' wherever the use of a collective term is unavoidable.

References

1 Klinge F. Der rheumatismus pathologisch-anatomische und experimentell-pathologische tatsachen und ihre auswertung für das ärztliche rheumaproblem. *Ergebed Allg Path Path Anat* 1933; **27**: 1–336.
2 Masugi M, Yä-Shu. Die diffuse Sklerodermie und ihre Gefäss-veränderung. *Virchows Arch Path Anat Physiol* 1938; **302**: 39–62.
3 Klemperer P, Pollack AD, Bachr G. Diffuse collagen disease: acute lupus erythematosus and diffuse scleroderma. *JAMA* 1942; **119**: 331–2.
4 Baehr G, Pollack AD. Disseminated lupus erythematosus and diffuse scleroderma. *JAMA* 1947; **134**: 1169–74.
5 Klemperer P. The concept of collagen diseases. *Am J Pathol* 1950; **26**: 505–19.
6 Shulman LE. Diffuse fasciitis with hypergammaglobulinaemia and eosinophilia: a new syndrome? *J Rheumatol* 1974; **1** (Suppl. 1): 82.
7 Beck JS, Rowell NR. Discoid lupus erythematosus. *QJM* 1966; **35**: 119–36.
8 Burch PRJ, Rowell NR. Lupus erythematosus: analysis of the sex- and age-distribution of the discoid and systemic forms of the disease in different countries. *Acta Derm Venereol (Stockh)* 1966; **50**: 293–301.
9 Millard LG, Rowell NR, Rajah SM. Histocompatibility antigens in discoid and systemic lupus erythematosus. *Br J Dermatol* 1977; **96**: 139–44.
10 Hughes P, Gelsthorpe K, Doughty RW *et al.* The association of HLA-B8 with visceral disease in systemic sclerosis. *Clin Exp Immunol* 1978; **31**: 351–6.
11 Hughes GRV. *Connective Tissue Diseases*. Oxford: Blackwell Scientific Publications, 1978.
12 Gardner DL. *Pathology of the Connective Tissue Diseases*. London: Arnold, 1965.
13 Mackay IR, Burnet FM. *Autoimmune Diseases*. Springfield: Thomas, 1963.
14 Samter M, Alexander HL, eds. *Immunological Diseases*. London: Churchill, 1965.

Lupus erythematosus [1,2]

Lupus erythematosus (LE) is usually divided into two main types: DLE and SLE (defined on pp. 51.4 and 51.27 respectively). Although some authors [3] would prefer the term cutaneous LE to DLE, we are continuing to use the term DLE in view of the long usage and to avoid confusion with SCLE. Others [4] suggest classifying LE into three groups—cutaneous LE, intermediate LE and SLE, but this is still controversial. DLE can be subdivided into a localized form in which lesions are confined to the face above the chin, the scalp and the ears, and a disseminated form in which lesions also occur elsewhere on the body [5,6]. Although haematological and serological abnormalities occur slightly more frequently in the disseminated form, the natural history of the two subgroups is similar, and it is likely that they are subsets of the same disorder. SCLE has been described as a subset intermediate between DLE and SLE [7].

Table 51.1 Comparison of data on a series of patients with discoid and systemic lupus erythematosus seen by the authors.

	Discoid lupus erythematosus (*n* 120) (%)	Systemic lupus erythematosus (*n* 40) (%)
Rash	100	80
Joint pains	23	70
Fever	0	40
Raynaud's phenomenon	14	35
Chilblains	22	22
Poor peripheral circulation	26	32
ESR > 20 mm/h	20	85
Serum globulin >3 g (%)	29	76
LE cells	1.7	83
Antinuclear factor(s)	35	87
Homogeneous	24	74
Speckled	11	26
Nucleolar	0	5.4
Precipitating autoantibodies	4	42
WR positive	5	22
Rheumatoid factor positive	15	37
Direct Coombs' test positive	2.5	15
Leukopenia	12.5	37
Thrombocytopenia	5	21

ESR, erythrocyte sedimentation rate; LE, lupus erythematosus; WR, Wassermann reaction.

The more controversial point is whether DLE and SLE are variants of the same disease. The evidence in favour of this may be summarized as follows:

1 The cutaneous lesions of SLE and DLE may be clinically and histologically indistinguishable.
2 Certain clinical features are found in both conditions (Table 51.1).
3 Similar haematological, biochemical and immunohistochemical abnormalities can be demonstrated in both conditions (Table 51.1), although the incidence of abnormalities is lower in DLE.
4 Patients with DLE occasionally develop evidence of overt SLE.
5 Patients with SLE may develop typical lesions of DLE in the chronic phase of their disease [8].
6 Conditions such as lupus panniculitis, a recognizable clinical and pathological entity, occur in both DLE and SLE.

This seems to be formidable evidence, but the following observations require explanation.

1 The risk of a patient with DLE developing overt SLE is small. It varies from 1.3% [9] to about 6.5% [2,10]. The risk is higher in patients with disseminated DLE (22%) than in DLE confined to the head and neck (1.2%) [10]. In some series [11], such conversion was not encountered despite follow-up for nearly 30 years. A retrospective study [12] of 127 patients with SLE showed that eight patients had had discoid lesions from 2 to 29 years.
2 The presence of laboratory abnormalities in DLE does not in itself appear to predispose to the development of SLE [13], although they are common in disseminated DLE [10,14]. The same prognosis was found in a subgroup intermediate between discoid and SLE as in patients with uncomplicated LE [11].
3 Immunoglobulins and complement are present in uninvolved skin of patients with SLE and absent in patients with DLE [15].
4 Most patients with DLE exposed to UV radiation, stress, trauma, etc., do not develop the systemic disease.
5 The age and sex distribution of SLE [16] is strikingly different from that of DLE [17]. It has been proposed [2,18] that both SLE and DLE are initiated by the occurrence of somatic mutations in lymphocytic stem cells of predisposed individuals, and that they are genetically distinct. There are at least three genotypes related to age of onset in DLE [19] and the female/male ratios found in each disease suggest that there is only one X-linked allele involved in genotype 2 and two in genotype 3. On the simplest interpretation, three 'forbidden clones' [20] of lymphocytes synthesizing cellular autoantibodies develop in SLE, whereas only one 'forbidden clone' is involved in DLE. Autosomal predisposing alleles are probably also present in all the genotypes in both SLE and DLE. The nature of these somatic mutations and the predisposing alleles remain unknown, but almost certainly include polymorphisms of genes determining the production of inflammatory cytokines [21].
6 Further evidence that DLE and SLE are genetically different disorders is now available from studies of histocompatibility antigens in the two diseases [22]. There is a significant difference in the incidence of HLA-B8 in female patients developing each disease between the ages of 15 and 39 years. It is considered that patients may have the predisposition to SLE, DLE or both. Those patients who 'convert' from DLE to SLE, and those patients with SLE who have discoid skin lesions, must be genetically predisposed to both conditions. Those patients with only a genotype for DLE will never convert, even when subjected to environmental factors, such as drugs, bacterial or viral infections, UV radiation and stress. More recent molecular genetic data give further support to this concept [23].

At present, it is not possible to determine the genetic pattern of individual patients or to predict accurately the small proportion of patients with DLE-like lesions who will develop SLE, although the link with HLA-B8 has already been discussed [22]. Humoral autoantibodies are not the primary pathogen in these diseases [24], but they probably reflect the underlying cell-bound autoimmunity that causes the disease. Nevertheless, they may enhance tissue damage [25], and specific antibodies may be responsible for certain features such as the risk of neonatal LE (anti-Ro) and for thrombosis (the lupus anticoagulant). The ability to synthesize particular antinuclear antibodies may depend on additional genetic factors, and this could account for the absence of such antibodies in certain patients with active disease. If the possession of a serological abnormality in DLE implies a predisposition to transformation into systemic disease, we would expect the sex ratio of this group to be similar to that for SLE. This is not the case. The sex ratio in patients with DLE and laboratory abnormalities is not significantly different from the sex ratio in patients without abnormalities.

From consideration of the clinical features, the natural history, the age and sex distribution, and studies of histocompatibility antigens, it is concluded that patients with DLE and haematological and serological abnormalities are not cases of SLE in disguise, but are cases of DLE, which is a separate entity from SLE, and has a different genetic background. Each of these entities, however, consists of several subsets, also genetically determined.

References

1 Rowell NR. Some historical aspects of skin disease in lupus erythematosus. *Lupus* 1997; **6**: 76–83.
2 Rowell NR. The natural history of lupus erythematosus. *Clin Exp Dermatol* 1984; **9**: 217–31.
3 Provost T. The relationship between discoid and systemic lupus erythematosus. *Arch Dermatol* 1994; **130**: 1308–9.
4 Halmi BH, Dileomondo M, Jacoby RA. Classification of lupus erythematosus. *Int J Dermatol* 1993; **32**: 643–4.
5 Dubois EL, ed. *Lupus Erythematosus*, 2nd edn. Berkeley, CA: University of Southern California Press, 1976: 446.
6 Kierland RR. Classification of cutaneous manifestations of lupus erythematosus. *Proc Staff Meet Mayo Clin* 1940; **15**: 674.
7 Sontheimer RD, Thomas JR, Gilliam JN. Subacute cutaneous lupus erythematosus. *Arch Dermatol* 1979; **115**: 1409–15.
8 Ganor S, Sagher F. Systemic lupus erythematosus changing to the chronic discoid type. *Dermatologica* 1962; **125**: 81–92.
9 Cannon EF, Curtis AC. A survey of lupus erythematosus in the University of Michigan Hospital since 1948. *Arch Dermatol* 1958; **78**: 196–9.
10 Millard LG, Rowell NR. Abnormal laboratory test results and their relationship to prognosis in discoid lupus erythematosus. *Arch Dermatol* 1979; **115**: 1055–8.
11 Shrank AB, Doniach D. Discoid lupus erythematosus. *Arch Dermatol* 1963; **87**: 677–85.
12 Rothfield N, March CH, Miescher P *et al.* Chronic discoid lupus erythematosus: study of 65 patients and 65 controls. *N Engl J Med* 1963; **269**: 1155–61.
13 Rowell NR. Laboratory abnormalities in the diagnosis and management of lupus erythematosus. *Br J Dermatol* 1971; **84**: 210–6.
14 Healy E, Kieran E, Rogers S. Cutaneous lupus erythematosus—a study of clinical and laboratory prognostic factors in 65 patients. *Ir J Med Sci* 1995; **164**: 113–5.
15 Tuffanelli DL. Cutaneous immunopathology: recent observations. *J Invest Dermatol* 1975; **65**: 143–53.
16 Burch PRJ, Rowell NR. Systemic lupus erythematosus. *Am J Med* 1965; **38**: 793–801.
17 Burch PRJ, Rowell NR. Autoimmunity: aetiological aspects of chronic discoid and systemic lupus erythematosus, systemic sclerosis and Hashimoto's thyroiditis. *Lancet* 1963; **ii**: 507–13.
18 Burch PRJ, Rowell NR. The sex and age-distribution of chronic discoid lupus erythematosus in four countries. *Acta Derm Venereol (Stockh)* 1968; **48**: 33–46.
19 Burch PRJ, Rowell NR. Lupus erythematosus. Analysis of the sex- and age-distributions of the discoid and systemic forms of the disease in different countries. *Acta Derm Venereol (Stockh)* 1970; **50**: 293–301.
20 Burnet FM. *The Clonal Selection Theory of Acquired Immunity*. Nashville, TN: Vanderbilt University Press, 1959.
21 Tsuchiya N, Ohashi J, Tokunaga K. Variations in immune response genes and their associations with multifactorial immune disorders. *Immunol Rev* 2002; **190**: 169–81.
22 Millard LG, Rowell NR, Rajah SM. Histocompatibility antigens in discoid and systemic lupus erythematosus. *Br J Dermatol* 1977; **96**: 139–44.
23 van der Linden MW, van der Slik AR, Zanelli E *et al*. Six microsatellite markers on the short arm of chromosome 6 in relation to HLA-DR3 and TNF-308A in systemic lupus erythematosus. *Genes Immun* 2001; **2**: 373–80.
24 Beck JS, Oakley CL, Rowell NR. Transplacental passage of anti-nuclear antibody. *Arch Dermatol* 1966; **93**: 656–63.
25 Hughes P, Rowell NR. Aggravation of turpentine-induced pleurisy in rats by 'homogeneous' and 'speckled' antinuclear antibodies. *J Pathol* 1970; **101**: 141–55.

Discoid lupus erythematosus

Synonyms
- Cutaneous lupus erythematosus
- Chronic discoid lupus erythematosus

Definition. DLE is a benign disorder of the skin, most frequently involving the face, and characterized by well-defined, red scaly patches of variable size, which heal with atrophy, scarring and pigmentary changes. The histology is characteristic. There are haematological and serological changes in approximately half of patients, and these changes, with other evidence, suggest an autoimmune aetiology.

Aetiology. This disorder has a characteristic age and sex pattern. The disease affects twice as many females as males, with a peak age of onset in the fourth decade in females and slightly later in males, although it can occur at any age. In a series of 1045 cases, 3% began under 15 years of age and 2.5% at over 70 years [1].

Genetic factors. Familial cases of DLE do occur. A family history was found in 4% of one series [2]. Steagall *et al.* [3] reported the condition in identical twin sisters, and listed 25 families with two or more members who had DLE or SLE. Studies also indicated a striking relationship between polymorphic light eruption and DLE, first in twins [4] and then in a large cohort of patients and their relatives, suggesting a common genetic background for these disorders [5]. Differences in the incidence of histocompatibility antigens [6–8] have supported the concept of multiple genotypes. Positive associations with HLA-B7, -B8, -Cw7, -DR2, -DR3 and -DQw1 are reported [9], but not always confirmed. The relative risk is increased with certain combinations of antigens—HLA-Cw7, -DR3 and -DQw1 and for HLA-B7, -Cw7 and -DR3. The extended haplotype—HLA*01, B*08, DRB1*0301—is associated with both SCLE and DLE, and the A*03, B*07, DRB1*15 haplotype has been associated with DLE alone [9]. Patients of both sexes developing lesions between the ages of 15 and 39 years have an increased incidence of HLA-B7, and females over the age of 40 years of HLA-B8, compared with controls [7].

Before the modern understanding of lymphocyte function [10], it was proposed that genetic factors, including somatic mutations, are implicated in the pathogenesis of the disease [11,12]. These studies suggested that there are at least three. The initiation of the disease may result from the occurrence of random events, either related to somatic mutation or to environmental factors. The model suggests that: (i) three mutations affecting autosomal genes; (ii) four mutations (one of which affects an X-linked gene); or (iii) five mutations (one involving an X-linked gene) could explain the three genotypes. The mutations interfere with control of lymphocytes; after a latent period of approximately 4 years in females and 2 years in males, clinical signs of the disease become manifest. Normally, an endogenous defence mechanism would control lymphocyte function and prevent self-harm. Environmental factors, by interfering with this defence mechanism, can precipitate or exacerbate the disease (Table 51.2). Supporting this view, DLE-like lesions have occurred after allogeneic bone marrow transplantation [13].

Table 51.2 Environmental factors associated with the onset or exacerbation of discoid lupus erythematosus [14–24].

Environmental factors	Frequency
Trauma (including X rays, diathermy, chemical burns)	11%
Stress	12%
Ultraviolet exposure (including PUVA and laser light)	5%
Infection (including herpes zoster and old smallpox vaccination)	3%
Drugs (including isoniazid, penicillamine, griseofulvin, dapsone)	Unknown
Seasonal exacerbation	Winter 10% Summer 50%
Cold exposure	2% (17% disease exacerbation)
Pregnancy	1% (onset)
Pre-menstrual	13% (disease flare)
Hormone replacement therapy	Unknown

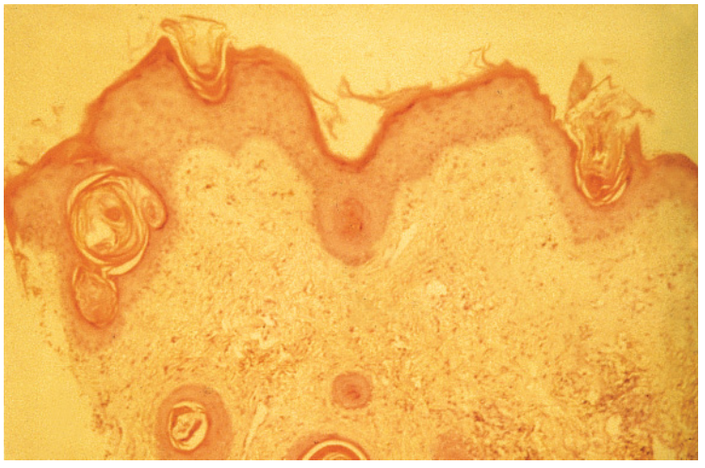


Fig. 51.1 Discoid lupus erythematosus: there is atrophy of the epidermis, keratotic plugging, liquefaction degeneration of the basal layer, oedema and hyalinization of the connective tissue below the epidermis and a marked inflammatory infiltrate.

Ultraviolet light and disease exacerbation [25]. In 120 patients at Leeds, UK a history of exacerbations with sunlight was found in 68%. In those with photo-aggravated disease, both wavelengths shorter than 329 nm and the whole range through UVB, UVA and visible light can produce lesions under experimental conditions. Skin lesions clinically and histologically compatible with lupus erythematosus (LE) were induced by UVB and UVA radiation in 42% of patients with DLE, 64% of patients with SCLE and 25% of patients with SLE.

Viruses. The finding of antibodies to reovirus RNA in 42% of patients suggests that viruses may have a role in DLE [20].

References

1 Damm J, Sonnischsen N. Clinical examinations of chronic lupus erythematosus. *Dermatol Wochenschr* 1964; **150**: 268.
2 Bielsa I, Herrero C, Ercilla G *et al.* Immunogenetic findings in cutaneous lupus erythematosus. *J Am Acad Dermatol* 1991; **25**: 251–7.
3 Steagall RW, Ash HT, Fentanco LB. Familial lupus erythematosus. *Arch Dermatol* 1962; **85**: 394–6.
4 Wojnarowska F. Simultaneous occurrence in identical twins of discoid lupus erythematosus and polymorphic light eruption. *J R Soc Med* 1983; **76**: 791–2.
5 Millard TP, Lewis CM, Khamashta MA *et al.* Familial clustering of polymorphic light eruption in relatives of patients with lupus erythematosus: evidence of a shared pathogenesis. *Br J Dermatol* 2001; **144**: 334–8.
6 Fowler JF, Callen JP, Stelzer FT *et al.* Human histocompatibility antigen associations in patients with chronic cutaneous lupus erythematosus. *J Am Acad Dermatol* 1985; **12**: 73–7.
7 Millard LG, Rowell NR, Rajah SM. Histocompatibility antigens in discoid and systemic lupus erythematosus. *Br J Dermatol* 1977; **96**: 139.
8 Tongio MM, Fersing J, Hauptmann G *et al.* HLA antigens in discoid lupus erythematosus. *Acta Derm Venereol (Stockh)* 1982; **62**: 155–7.
9 Millard TP, Kondeatis E, Vaughan RW *et al.* Polymorphic light eruption and the HLA DRB1*0301 extended haplotype are independent risk factors for cutaneous lupus erythematosus. *Lupus* 2001; **10**: 473–9.
10 Bock G, Goode J, eds. *Generation and Effector Functions of Regulatory Lymphocytes*. Chichester: John Wiley & Sons, 2004.
11 Burch PRJ, Rowell NR. The sex- and age-distributions of chronic discoid lupus erythematosus in four countries. *Acta Derm Venereol (Stockh)* 1968; **48**: 33–46.
12 Burch PRJ, Rowell NR. Lupus erythematosus: analysis of the sex- and age-distributions of the discoid and systemic forms of the disease in different countries. *Acta Derm Venereol (Stockh)* 1970; **50**: 293–301.
13 Gratwhol AA, Haralampos M, Moutsopoulos M *et al.* Sjögren-type syndrome after allogenic bone-marrow transplantation. *Ann Intern Med* 1977; **87**: 703–6.
14 Lodin A. Discoid lupus erythematosus and trauma. *Acta Derm Venereol (Stockh)* 1963; **43**: 142.
15 Lupton GP. Discoid lupus erythematosus occurring in a smallpox vaccination scar. *J Am Acad Dermatol* 1987; **89**: 688–90.
16 Eedy DJ, Corbett JR. Discoid lupus erythematosus exacerbated by X-ray irradiation. *Clin Exp Dermatol* 1988; **13**: 202–3.
17 Schmitt CL, Silverman A. Discoid lupus erythematosus in an arc welder. *Cutis* 1971; **8**: 476–7.
18 Domke HF, Ludwigsen E, Thormann J. Discoid lupus erythematosus possibly due to photochemotherapy. *Arch Dermatol* 1979; **115**: 642.
19 Wolfe JT, Weinberg JM, Elenitses R *et al.* Cutaneous lupus erythematosus following laser-induced thermal injury. *Arch Dermatol* 1997; **133**: 392–3.
20 Grundwald M, David M, Feuerman EJ. Appearance of lupus erythematosus in a patient with lichen planus treated by isoniazid. *Dermatologica* 1982; **162**: 172–7.
21 Burns DA, Sarkany I. Penicillamine-induced discoid lupus erythematosus. *Clin Exp Dermatol* 1979; **4**: 389–92.
22 Alexander S. Lupus erythematosus in two patients after griseofulvin treatment of *Trichophyton rubrum* infection. *Br J Dermatol* 1962; **74**: 72–4.
23 Shlepakov VM. Effect of gestation in the course of chronic lupus erythematosus. *Soviet Med* 1969; **32**: 111–6.
24 Yell JA, Burge SM. The effect of hormonal changes on cutaneous disease in lupus erythematosus. *Br J Dermatol* 1993; **129**: 18–22.
25 Bijl M, Kallenberg CG. Ultraviolet light and cutaneous lupus. *Lupus* 2006; **15**: 724–7.

Pathology [1]. The various clinical types of LE show an essentially similar histological picture (Figs 51.1 & 51.2), and the subsets of LE cannot be easily distinguished histologically [2]. The salient features are as follows:

1 Liquefaction degeneration of the basal cell layer of the epidermis
2 Degenerative changes in the connective tissue, consisting of hyalinization, oedema and fibrinoid change, most marked immediately below the epidermis

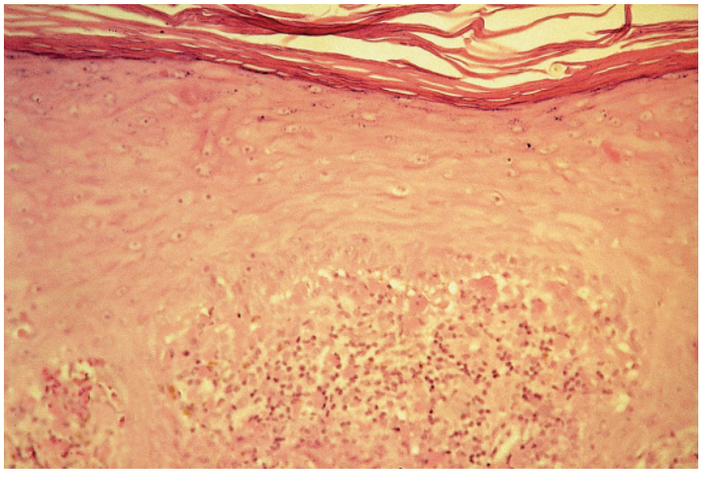


Fig. 51.2 Discoid lupus erythematosus: the degeneration of the basal layer and predominantly lymphocytic infiltration are well shown.

3 A patchy dermal lymphocytic infiltrate with a few plasma cells and histiocytes, particularly around the appendages, which may be atrophic.

The presence of at least two of these is essential to the histological diagnosis of LE. The following changes may also be found, but are less important:

1 Epidermal atrophy with relative hyperkeratosis and plugging of the follicular mouths, associated with pilosebaceous atrophy
2 Thickening of the basement membrane of the epidermis and sometimes of small vessels
3 Premature elastotic degeneration of collagen in light-exposed areas.

In more acute forms there is less hyperkeratosis and dermal infiltration, but more dermal oedema, liquefaction necrosis and atrophy. Disruption of the elastic lamina and, rarely, endothelial proliferation and thrombosis of the deeper vessels of the dermis have been reported [3]. Biopsy material from lesions on the palms stained for alkaline phosphatase activity shows irregular capillary loops with branching, 'dead end' spurs and coiling [4]. In SLE, similar changes are found in involved and uninvolved skin. In tumid lesions the dermal infiltrate can be very dense, and sometimes almost granulomatous. Dermal deposits of mucin occur [5], which may be diffuse or localized, and form nodular lesions. Deposits may be very gross [6]. Occasionally, irregular hyperplasia of the epidermis occurs, and there may be clefts, or even bullae, between the dermis and epidermis. Although keratotic plugs are usually found in the openings of the hair follicles, they may also block the sweat ducts or occur independently of either structure. Sometimes, the hair follicles contain concentric layers of keratin instead of hairs. Atrophy of the prickle cell layer occurs to a variable extent, and sometimes there may be acanthosis. Melanin may be found in the upper dermis as the result of pigmentary incontinence. Blood vessels are dilated and the upper dermis is oedematous.

Immunopathology. Immunohistology [7] shows the presence of immunoglobulins IgG, IgA, IgM and complement at the dermal–epidermal junction, in skin lesions present for 6 weeks or more, in approximately 80% of patients [8]. Homogeneous, granular or thready patterns occur, but the deposition is usually homogeneous in older lesions. They are more frequent on the face and in untreated lesions, but are rare on the trunk [9], and decrease after treatment with topical corticosteroids. They do not occur in uninvolved skin, unlike the majority of cases of SLE. For the diagnosis of DLE lesions, light microscopy is most valuable and should be carried out before direct immunofluorescence [10]. Immunoreactants are also found in oral mucosa and the conjunctiva [11]. C1q deposits are found in 29% of patients with immunofluorescent-positive DLE, compared with 90% in SLE, and the presence of such deposits implies an increased risk of eventual systemic disease [12]. Deposits at the dermal–epidermal junction are not specific to LE and have been found in many other circumstances (Table 51.3). However, in these diseases the deposits are less prominent at the dermal–epidermal junction and are more striking in the blood vessel walls. In LE, the deposits are heavy and contain several immunoglobulin classes, whereas in the other diseases only a single immunoglobulin class is usually present. In scarring alopecia caused by LE, the deposits occur around hair follicles, a feature not seen in other types of scarring alopecia [13].

Properdin, indicating complement activation, has been demonstrated at the dermal–epidermal junction in 70% of lesions, usually in association with deposition of immunoglobulin, C3 and C4 [14]. It may also be found in non-lesional skin. Serum properdin levels are raised in DLE and SLE [14].

Table 51.3 Diseases associated with the presence of immunoreactants at the dermal–epidermal junction that may be confused with lupus erythematosus.

Mixed connective tissue disease
Systemic sclerosis
Dermatomyositis
Sjögren's syndrome
Myasthenia gravis
Porphyrias
Granuloma annulare
Necrobiosis lipoidica
Amyloidosis
Graft-versus-host disease
Psoriasis
Pyoderma gangrenosum
Sarcoidosis
Leprosy
Erythema multiforme
Pityriasis lichenoides acuta
Granuloma faciale
Keratoacanthoma
Scabies
Facial telangiectases
Bullous pemphigoid

References

1 Montgomery H. Pathology of lupus erythematosus. *J Invest Dermatol* 1939; **2**: 343–59.
2 Jerdan MS, Hood AF, Moore GW, Callen JP. Histopathologic comparison of the subsets of lupus erythematosus. *Arch Dermatol* 1990; **126**: 52–5.

3 Panja RK, Sengupta KP, Aikat BK. Vascular changes in the cutaneous lesions of lupus erythematosus and scleroderma. *Br J Dermatol* 1966; **78**: 34–42.
4 Kurban AK, Farah FS, Chaglassian HT. Capillary changes in some connective tissue diseases. *Dermatologica* 1964; **129**: 257–65.
5 Lee WS, Chung J, Ahn SK. Mucinous alopecia associated with papulonodular mucinosis as a new manifestation of lupus erythematosus. *Int J Dermatol* 1996; **35**: 72–3.
6 Weigand DA, Bungdorf HC, Gregg LJ. Dermal mucinosis in discoid lupus erythematosus. *Arch Dermatol* 1981; **117**: 735–8.
7 Rowell NR, Scott DG. Immunohistological studies with anti-connective tissue and anti-immunoglobulin antisera of the skin in lupus erythematosus and scleroderma. *Br J Dermatol* 1975; **93**: 431–41.
8 Prystowsky SD, Gilliam JN. Discoid lupus erythematosus as part of a larger disease spectrum: correlation of clinical features with laboratory findings in lupus erythematosus. *Arch Dermatol* 1975; **111**: 1448–52.
9 Weigand DA. Lupus band test: anatomic regional variations in discoid lupus erythematosus. *J Am Acad Dermatol* 1981; **14**: 426–8.
10 Williams REA, MacKie RM, O'Keefe R *et al.* The contribution of direct immunofluorescence to the diagnosis of lupus erythematosus. *J Cutan Pathol* 1989; **16**: 122–5.
11 Burge SM, Frith PA, Millard PR *et al.* The lupus band test in oral mucosa, conjunctiva and skin. *Br J Dermatol* 1989; **121**: 743–52.
12 Leibowitch M, Droz D, Noel LH *et al.* C1q deposits at the dermoepidermal junction: a marker discriminating for discoid and systemic lupus erythematosus. *J Clin Immunol* 1981; **2**: 119–24.
13 Amato L, Mei S, Massi D *et al*. Cicatricial alopecia: a dermatopathologic and immunopathologic study of 33 patients (pseudopelade of Brocq is not a specific clinicopathologic entity). *Int J Dermatol* 2002; **41**: 8–15.
14 Schrager MA, Rothfield NF. Pathways of complement activation in chronic discoid lupus. *Arthritis Rheum* 1977; **20**: 637–45.

Immunocytochemistry. The majority of infiltrating lymphocytes are T lymphocytes and express Ia-like antigens, as well as the γδ T-cell receptor. There is some evidence of clonal selection of T-cell receptors, suggesting an antigen driven response in the skin. Infiltrating cells are a mixture of $CD4^+$, $CD8^+$ and HLA-DR^+ cells in all types of cutaneous LE, with $CD4^+$ cells slightly predominating [1]. There are also populations of mainly $CD45RO^+$ memory cells, with few activated $CD45RA^+$ differentiated effector cells [2]. In addition, there is evidence of vascular activation with up-regulation of ICAM-1, vascular adhesion molecule-1, E-selectin and P-selectin [3].

The description of the presence of skin-homing cytotoxic lymphocytes, expressing granzyme B, in association with a Th1 pattern of cytokine expression, and targeting the epidermal adnexal structures, is an important step in our understanding of the process of inflammation and scarring in cutaneous LE [4]. Although the pattern of cytokine expression may be variable, with interleukins 2 (IL-2) and -4 absent, and IL-5 and IL-10 variably present, the expression of predominantly type 1 interferons is likely to induce auto-reactive cytotoxic lymphocytes as indicated by Wenzel *et al.* [5].

Identification of the target antigen that drives this response is urgently needed to understand the pathogenesis of the discoid pattern of cutaneous lupus. Information on the interplay of the genetic control of cytokine profiles also gives important clues to the pathogenesis of the various sub-types of cutaneous lupus, particularly the role of TNF-α and IL-10 and their balance [6].

References

1 Volcplatzer B, Alpetz B, Milota S *et al*. Accumulation of gammadelta T-cells in chronic cutaneous lupus erythematosus. *J Invest Dermatol* 1993; **100**: S84–S91.
2 Kohchiyama A, Oka D, Ueki H. T cell subsets in lesions of systemic and discoid lupus erythematosus. *J Cutan Pathol* 1985; **12**: 493–9.
3 Kuhn A, Sonntag M, Lehmann P *et al*. Characterization of the inflammatory infiltrate and expression of endothelial cell adhesion molecules in lupus erythematosus tumidus. *Arch Dermatol Res* 2002; **294**: 6–13.
4 Stein LF, Saed GM, Finerson DP. T cell cytokine network in cutaneous lupus erythematosus. *J Am Acad Dermatol* 1997; **36**: 191–6.
5 Wenzel J, Uerlich E, Worrenkamper S *et al*. Scarring skin lesions of discoid lupus erythematosus are characterised by high numbers of skin-homing cytotoxic lymphocytes associated with strong expression of the type 1 interferon-induced protein MxA. *Br J Dermatol* 2005; **153**: 1011–7.
6 Suarez A, Lopez P, Mozo L, Gutierrez C. Differential effect of IL10 and TNFα genotypes on determining susceptibility to discoid and systemic lupus erythematosus. *Ann Rheum Dis* 2005; **64**: 1605–10.

Histopathological differential diagnosis. Chronic DLE must be differentiated from other conditions in which lymphocytic infiltrations of the dermis occur.

1 In Jessner's lymphocytic infiltration [1], the dermis shows large circumscribed aggregations of lymphocytes, often concentrated round the dermal appendages and blood vessels, with a normal epidermis. Sometimes, the infiltrate may extend into the fat of the subcutaneous tissues. Immunohistochemical studies show that the cells are predominantly T lymphocytes [2], as they are in DLE and SLE [3]. Monoclonal antibody studies show an increase in natural killer (NK) cells and activated cytotoxic T lymphocytes in Jessner's lymphocytic infiltration [4].

2 In polymorphic light eruption (PLE), the infiltrate is less prominent and more likely to occur around blood vessels than cutaneous appendages. Liquefaction degeneration is infrequent but, if present, it may be difficult to distinguish from that of DLE. There may be spongiotic changes in the epidermis and parakeratosis (the histology has some features of eczema, but the dermal infiltrate is usually denser). Lever and Schaumburg-Lever [5] believe that most cases of Jessner's lymphocytic infiltration and the plaque-type of PLE represent variants of chronic DLE, but immunoglobulin does not occur at the dermal–epidermal junction in either of the first two conditions [6,7].

3 Scattered patches of lymphocytes occur in the dermis in lymphocytic lymphoma, but there are no epidermal changes.

4 The infiltrate in lymphocytoma cutis (Spiegler–Fendt sarcoid; see Chapter 57) is usually separated from the normal epidermis by a band of normal collagen, and consists of lymphocytes and a few histiocytes. Sometimes, a follicular arrangement is present, with lymphocytes surrounding islands of histiocytes resembling lymph node follicles.

5 In benign lymphocytic infiltration, polyclonal T and B cells form aggregates in the dermis.

Sometimes, patients show clinical, histopathological and immunofluorescence overlap between DLE and lichen planus. In such cases, a definite diagnosis cannot always be made, and it is likely that such patients have both diseases [8].

References

1 Jessner M, Kanof NB. Lymphocytic infiltration of the skin. *Arch Dermatol Syphilol* 1953; **68**: 447–9.
2 Willemze R, Dijkstra A, Meijer CJLM. Lymphocytic infiltration of the skin (Jessner): a T-cell lymphoproliferative disease. *Br J Dermatol* 1983; **110**: 523–8.
3 Konttinen YT, Reitamo S, Ranki A *et al*. T-lymphocytes and monoclonal phagocytes in the skin infiltrate of systemic and discoid lupus erythematosus and Jessner's lymphocytic infiltrate. *Br J Dermatol* 1981; **104**: 141–5.

4 Viljaranta S, Ranki A, Kariniemi A-L *et al.* Distribution of natural killer cells and lymphocyte subclasses in Jessner's lymphocytic infiltration of the skin and in cutaneous lesions of discoid and systemic lupus erythematosus. *Br J Dermatol* 1987; **116**: 831–8.
5 Lever WF, Schaumburg-Lever G. *Histopathology of the Skin*, 6th edn. Philadelphia: Lippincott, 1983: 457.
6 Fisher DA, Epstein JH, Kay DN *et al.* Polymorphous light eruption and lupus erythematosus. *Arch Dermatol* 1970; **101**: 458–61.
7 Ten Have-Opbroek AAW. On the differential diagnosis between chronic discoid lupus erythematosus and lymphocytic infiltration of the skin (Jessner) with emphasis on fluorescence microscopy. *Dermatologica* 1966; **132**: 109–14.
8 Potts EDA, Rowell NR. Lichen planus: a distinct entity from lupus erythematosus. *Acta Derm Venereol (Stockh)* 1981; **61**: 413–6.

Incidence. Because the condition is persistent, DLE appears to be more common than it really is. The incidence among new patients in the Department of Dermatology at Leeds is approximately 4 or 5 in 1000. It is said that it is only half as frequent in black people [1], although the distribution is worldwide.

Reference

1 Cummer CL. Aetiology of lupus erythematosus. *Arch Dermatol Syphilol* 1936; **33**: 434–45.

Clinical features

Symptoms. The patient usually presents with a rash, but on questioning a history of Raynaud's phenomenon, chilblains or poor peripheral circulation is often obtained. In 120 patients at Leeds, 14% had Raynaud's phenomenon and 22% had chilblains; a poor peripheral circulation, without a definite story of Raynaud's phenomenon, was noted in a further 26% of patients. Joint pains are complained of by approximately one-quarter of patients, but this is similar to the incidence in controls [1]. Most patients have no symptoms of systemic upset, even with widespread cutaneous disease, although fatigue is not uncommon in those with severe disease.

Most patients have disease limited to the head and neck (localized DLE), but a few have much more extensive disease, potentially affecting any area of the skin (disseminated DLE).

Localized disease. The face is most commonly affected, and the scalp, ears, nose, arms, legs and trunk to a lesser extent. The circumscribed or discoid type is the most frequent (Fig. 51.3), and occurs particularly on the cheeks, the bridge of the nose, the ears, the side of the neck and the scalp. Lesions may be bilateral, although not necessarily symmetrical, or unilateral. Alopecia occurs in the scalp lesions in approximately one-third of patients [2], and is usually permanent (Fig. 51.4). The eyebrows may be sparse, with erythema of the eyebrow skin. Usually, lesions occur as well-defined erythematous patches, varying in size from a few millimetres to 10–15 cm. There is adherent scale in many cases, and when this is removed its undersurface shows horny plugs which have occupied dilated pilosebaceous canals. This so-called 'tin-tack' sign can sometimes also be seen in localized pemphigus foliaceus [3]. When not obscured by scaling, these horny plugs can be seen on direct examination. The surface may present a dirty brownish yellow appearance that is rough to the touch, because of the follicular plugging. If hyperkeratosis is marked, a warty lesion with a red, slightly raised edge results. This warty type of LE is most commonly seen on the nose, temples, ears and scalp, but may also occur on the palms and soles and causes difficulty with walking (Fig. 51.5) [4].



Fig. 51.3 Discoid lupus erythematosus: the typical scaling is well shown.



Fig. 51.4 Discoid lupus erythematosus of the scalp: note the follicular plugging.

Non-itching hyperkeratotic papulonodular lesions on the arms and hands, resembling keratoacanthoma, hypertrophic lichen planus or nodular prurigo, also occur [5]. Sometimes, the appearance resembles psoriasis. In other cases, there may be very little hyperkeratosis. Lesions then present as reddish, well-defined, almost smooth plaques with little or no scaling. Sometimes, these plaques may show prominent flattening in the centre, giving rise to annular lesions. Over the course of some months, particularly



Fig. 51.5 Warty lesions of the feet in chronic lupus erythematosus.



Fig. 51.7 Cribriform scarring in discoid lupus erythematosus.



Fig. 51.6 Discoid lupus erythematosus: the pre-auricular type with pigmentation around the scarred area.



Fig. 51.8 Typical lesions in the ear.

if treated, lesions flatten and may clear completely without much scarring. More frequently, a thin white scarred area, often with a slightly raised, red border or zone of hyperpigmentation, remains (Fig. 51.6). Localized cribriform scarring occurs, particularly on the face (Fig. 51.7). Wide follicular pits, sometimes containing scale or blackheads, occur mainly in the concha or triangular fossa of the ear (Fig. 51.8). They occur in up to one-third of cases [6] of DLE but they also occur in SLE. In approximately 7.5% of patients, the lesions on the face resemble rosacea, and differentiation from true rosacea can be difficult, particularly as in approximately 15% of cases patients with true rosacea show exacerbation by sunlight. Low titre ANA also occurs in rosacea, complicating assessment, but has no clinical relevance [7]. LE of this rosaceous type presents with reddish nodular lesions on the nose, cheeks, forehead and sometimes chin, and is associated with a diffuse erythema of the face and easy flushing. Usually, unlike true rosacea, there are no pustules (Fig. 51.9) [8]. Biopsy is required to distinguish between LE and rosacea.



Fig. 51.9 Discoid lupus erythematosus: a rosaceous pattern seen in 7.5% of patients.



Fig. 51.10 Discoid lupus erythematosus: tumid lesions of the face.

Tumid lesions may occur, in which the tissues are swollen, brawny, warm and tense (Fig. 51.10). The surface shows a reddish, mottled appearance resulting from scarring. This type of lesion may be many centimetres in diameter and involve the whole of one cheek, or even the whole of a limb. Another clinical type of DLE results in annular atrophic plaques [8] on the face, neck and behind the ears. The centre of the plaques is depressed and sclerotic, and the lesions resemble morphoea, lichen sclerosus or 'annular atrophic plaques' [9]. Early lesions show IgG and complement at the dermal–epidermal junction [8], but repeated biopsies may be necessary to confirm the diagnosis.

Scarring. Pigmentary disturbances are common, especially in dark-skinned people, and there is some evidence that DLE is more severe in black people (Figs 51.11 & 51.12) [10]. Patches of leukoderma may be interspersed with hyperpigmented areas. If relapse occurs, it usually starts in the reddish zone surrounding the scar. Calcification may occur in the plaques [11]. Lesions on the ear lead to considerable atrophy and scarring (Fig. 51.13).

Disseminated DLE (DDLE). Characteristic lesions of DLE may occur in a widespread pattern on the trunk and limbs, or may be localized to other body sites. This occurs almost always in women, and they are usually cigarette smokers. The appearance may be indistinguishable from the papulosquamous type of SCLE (see p. 51.23), but scarring occurs in most patients. This variety tends to be persistent, resistant to therapy and associated with severe psychological upset. Lesions on the dorsa of the hands (Fig. 51.14),



Fig. 51.11 Discoid lupus erythematosus in a black person.

palms [4] or toes (Fig. 51.15) [12] occurred in 6% of patients at Leeds. Purplish plaques may occur on the front of the knees and on the back of the heels. Another disseminated variety results in a reticulate telangiectasia, usually seen on the arms, legs and the back of the calves. This type of telangiectasia is probably similar to 'lupus erythematosus telangiectoides', first described by Crocker [13]. The appearances are characterized by a persistent, blotchy, reticulate telangiectasia, which occurs on the face, neck, ears, dorsa of the hands, breasts, heels and on the sides of the feet (Fig. 51.16). Healing occurs with punctate atrophic scarring. The histology of this type of lesion shows an atrophic epidermis, with dilata-



Fig. 51.12 Discoid lupus erythematosus in an Asian patient, showing marked hyperpigmentation at the border of the affected area.



Fig. 51.13 Discoid lupus erythematosus of the ear with scarring and atrophy.



Fig. 51.14 Discoid lupus erythematosus: plaques on the back of the hands.



Fig. 51.15 Discoid lupus erythematosus: characteristic redness and scaling of the toes.

tion of the superficial vessels of the skin and slight infiltration of the papillary part of the corium. A further, more annular variant has been called 'lupus erythematosus gyratus repens' and consists of a migratory gyrate annular erythema with the histological features of LE (Fig. 51.17), although the lupus band test is negative [14]. There may be an underlying carcinoma. A pruritic, chronic, discrete, umbilicated papular eruption may occur on the back, and results in acneiform hypertrophic follicular scars [15].

Occasionally, one or more fingers may show a curious atrophic spindling, sometimes with hyperextension of the terminal phalanges and dystrophy of the nails (Fig. 51.18). The fingers and toes may become markedly atrophic, with patchy erythema and tuft resorption on X-ray. Rarely, bullous lesions [16] may occur. Arteritic lesions resembling those of Degos' syndrome or disseminated atrophie blanche occasionally occur, and linear lesions following Blaschko's lines have been reported [17].

'Chilblain lupus' (Fig. 51.19) [18]. Approximately 6% of patients, predominantly female, develop chilblain-like lesions chiefly on the toes and fingers, but also on the heels, calves, knees, knuckles,



Fig. 51.16 Telangiectatic lupus erythematosus of the cheek.



Fig. 51.17 Gyrate erythema in lupus.

elbows, nose and ears. Usually, but not always, the chilblain lesions occur some years after the development of discoid lesions on the face. It can be precipitated by pregnancy [19]. When the discoid lesions remit with treatment, the chilblains persist. Less commonly, discoid and perniotic lesions start simultaneously, and sometimes perniotic lesions occur alone. Histology and immunohistology is that of DLE, and the non-lesional skin gives a negative fluorescent band test. Some patients may have cryofibrinogenaemia or cold agglutinins. Patients are usually Ro antibody-positive [20]. They are also either smokers, or have markedly abnormal peripheral circulation with low resting blood flow. Approximately 15% of patients develop SLE, and this occurs more frequently in those who develop both forms of cutaneous LE simultaneously and in those with the erythema multiforme syndrome.



Fig. 51.18 Unusual spindling of the fingers and hyperextension of the distal phalanges in discoid lupus erythematosus.



Fig. 51.19 'Chilblain' lesions in a patient with Ro-positive systemic lupus erythematosus.

Nail changes. Subungual hyperkeratosis is more common than the red-blue colouring of the nail plate with longitudinal striae and crumbling away of the nail [21]. The changes may respond to chloroquine.

Mucous membranes [22]. These are involved in approximately 24% of patients. Nasal mucosal lesions occur in 9% and hyperkeratotic lichen planus-like plaques on the buccal mucosa and palate in a similar number. The lips show slight thickening and roughness and redness, sometimes with superficial ulceration and crusting. Healing occurs with some scarring. Erythematous patches



Fig. 51.20 Discoid lupus erythematosus of the perianal area.

with a depressed centre and superficial ulceration occur on the inner cheeks, tongue and on the palate. Oral lesions may resemble leukoplakia [23]. Erythematous lesions occur on the vulva in 5%, or around the anus (Fig. 51.20) [24].

Eye lesions. Velvety oedema and marked redness of the conjunctiva may occur. Palpebral lesions have been reported without lesions elsewhere on the face [25]. The eyelids are red, especially peripherally, and are slightly infiltrated and always scaly. Lesions are most common on the lower eyelids, especially on the outer third. The free edge is rarely completely involved. Erythematous plaques on the lower eyelids occur in 6%, and may be associated with conjunctival scarring (Fig. 51.21), and symblepharon [26]. The lesions may itch, and are exacerbated by trauma and sunlight. Corneal involvement is rare. Superficial punctate keratopathy and stromal keratitis have been reported [27]. Acute mucinosis of the eyelids and periorbital skin can occur [28].

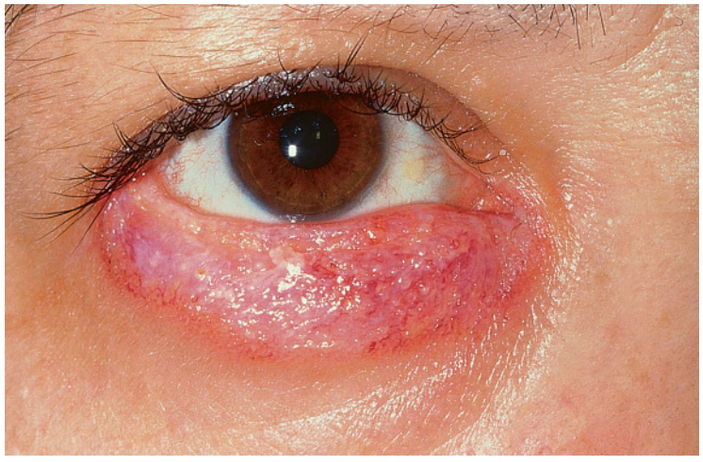


Fig. 51.21 Discoid lupus erythematosus of the lower eyelid.

References

1 Rothfield N, March CH, Miescher P *et al.* Chronic discoid lupus erythematosus. *N Engl J Med* 1963; **269**: 1155–61.
2 Wilson CL, Burge SM, Dean D *et al.* Scarring alopecia in discoid lupus erythematosus. *Br J Dermatol* 1992; **126**: 307–14.
3 Paramsothy Y, Lawrence CM. 'Tin-tack' sign in localized pemphigus foliaceus. *Br J Dermatol* 1987; **116**: 127–9.
4 Parish LC, Kennedy RJ, Hurley HJ. Palmar lesions in lupus erythematosus. *Arch Dermatol* 1967; **96**: 273–6.
5 Uitto J, Santa-Cruz DJ, Eisen AZ *et al.* Verrucous lesions in patients with discoid lupus erythematosus. *Br J Dermatol* 1978; **98**: 507–20.
6 Shuster S. A simple sign of discoid lupus erythematosus. *Br J Dermatol* 1981; **104**: 350–1.
7 Black AA, McCauliffe DP, Sontheimer RD. Prevalence of acne rosacea in a rheumatic skin disease subspeciality unit. *Lupus* 1992; **1**: 222–37.
8 Chorzelski TP, Jablonska S, Blaszczyk M *et al.* Annular atrophic plaques of the face. *Arch Dermatol* 1976; **112**: 1143–5.
9 Christiansen HB, Mitchell WT. Annular atrophic plaques of the face. *Arch Dermatol* 1969; **100**: 703–16.
10 Prystowsky SD, Hernadon JH, Gilliam JN. Chronic cutaneous lupus erythematosus (DLE). *Medicine* 1975; **55**: 183–91.
11 Kabin DI, Malkinson FD. Lupus erythematosus and calcinosis cutis. *Arch Dermatol* 1969; **100**: 17–22.
12 Pramatarov K. Discoid lupus erythematosus of the soles. *J Dermatol* 1989; **16**: 511.
13 Crocker HR. *Diseases of the Skin: Their Description, Pathology, Diagnosis and Treatment*. Philadelphia: Blakiston, 1888.
14 Blanc D, Kienzler JL. Lupus erythematosus gyratus repens: report of a case associated with a lung carcinoma. *Clin Exp Dermatol* 1982; **7**: 129.
15 Haroon TS, Fleming KA. An unusual presentation of discoid lupus erythematosus. *Br J Dermatol* 1972; **87**: 642–9.
16 Nagy E, Balogh E. Bullous form of chronic discoid erythematodes accompanied by LE-cell symptoms. *Dermatologica* 1961; **122**: 6–10.
17 Green JJ, Baker DJ. Linear childhood discoid lupus erythematosus following the lines of Blaschko: a case report with review of the linear manifestations of lupus erythematosus. *Pediatr Dermatol* 1999; **16**: 128–33.
18 Millard LG, Rowell NR. Chilblain lupus erythematosus (Hutchinson). *Br J Dermatol* 1978; **98**: 497–506.
19 Stainforth J, Goodfield MJD, Taylor PV. Pregnancy-induced chilblain lupus erythematosus. *Clin Exp Dermatol* 1992; **18**: 449–51.
20 Aoki T, Ishizawa T, Hozumi Y *et al.* Chilblain lupus erythematosus of Hutchinson responding to surgical treatment: a report of two patients with anti-Ro/SS-A antibodies. *Br J Dermatol* 1996; **134**: 533–7.
21 Kint A, van Herpe L. Ungual anomalies in lupus erythematosus discoides. *Dermatologica* 1976; **153**: 298–302.
22 Burge SM, Frith PA, Juniper RP *et al.* Mucosal involvement in systemic and chronic cutaneous lupus erythematosus. *Br J Dermatol* 1989; **121**: 727–41.
23 Schidt M, Anderson L, Shear M *et al.* Leukoplakia-like lesions developing in patients with oral discoid lupus erythematosus. *Acta Odontol Scand* 1981; **39**: 209–16.
24 Roundtree J, Weigand D, Burgdorf W. Lupus erythematosus with oral and perianal mucous membrane involvement. *Arch Dermatol* 1982; **118**: 55–6.
25 Tosti A, Tosti G, Giovannini A. Discoid lupus erythematosus solely involving the eyelids: report of three cases. *J Am Acad Dermatol* 1987; **16**: 1259–60.
26 Frith P, Burge SM, Millard PR, Wojnarowska F. External ocular findings in lupus erythematosus: a clinical and immunopathological study. *Br J Ophthalmol* 1990; **74**: 163–7.
27 Raizman MB, Baum J. Discoid lupus keratitis. *Arch Ophthalmol* 1989; **107**: 545–7.
28 Williams WL, Ramos-Caro FA. Acute periorbital mucinosis in discoid lupus erythematosus. *J Am Acad Dermatol* 1999; **41**: 871–3.



Fig. 51.22 Annular lesions of discoid lupus erythematosus resembling erythema multiforme and associated with characteristic immunological abnormalities (Rowell's syndrome).



Fig. 51.23 Lupus erythematosus profundus.

Lupus erythematosus and erythema multiforme-like syndrome [1,2]

Synonym
- Rowell's syndrome

The distinctive syndrome of cutaneous LE, either discoid or systemic, occurring with lesions resembling erythema multiforme on the face, neck, hands, chest and in the mouth (Fig. 51.22) was first described by Rowell in 1963 in patients with discoid LE, but may be seen in both subacute and systemic disease. Characteristically, it lasts from a few days to over a month, but episodes may occur at intervals over a period of 20 years. No precipitating factor can be elicited. The lesions are at first papular, but later a ring forms and the edge becomes vesicular. Bullae, necrosis and ulceration may develop if the reaction is intense, although sometimes healing occurs without scarring. Patients with this syndrome also frequently have perniotic lesions [3]. They show a characteristic pattern of serological abnormality, in that the speckled type of antinuclear factor is associated with rheumatoid factor and the same precipitating antibody to saline extract of human tissues (anti-SjT). Anti-SjT is now thought to be identical to anti-La (SS-B). The syndrome has been reported in identical twin sisters, one of whom had DLE and the other SLE [4]. In patients with SLE, the homogeneous type of antinuclear antibody may also be present in the serum. When the syndrome occurs in DLE, the dermal–epidermal band test is positive in the discoid lesions and negative in the erythema multiforme lesions. If the LE is systemic, the bullous lesions show positive findings comparable with those seen in the uninvolved skin of patients with SLE [5]. The syndrome may be confused with patients showing coincidental LE and erythema multiforme [6]. In one case, anti-SS-B antibody and rheumatoid factor only developed after the erythema multiforme-like lesions appeared, suggesting that these factors are not just incidental findings but may have a role in the clinical presentation [7].

References

1 Rowell NR, Swanson-Beck J, Anderson JR. Lupus erythematosus and erythema multiforme-like lesions. *Arch Dermatol* 1963; **88**: 176–80.
2 Aydogan K, Karadogan S, Balaban AS, Tunali S. Lupus erythematosus associated with erythema multiforme: report of two cases and review of the literature. *Eur J Dermatol Venereol* 2005; **19**: 621–7.
3 Millard LG, Rowell NR. Chilblain lupus erythematosus, Hutchinson. *Br J Dermatol* 1978; **98**: 497–506.
4 Parodi A, Drago F, Varaldo G, *et al*. Rowell's syndrome. *J Am Acad Dermatol* 1989; **21**: 374–7.
5 Jablonska S, Blaszcyk M, Chorzelski T. Syndrome de Rowell: Lupus erythemateux avec les lesions coexistentes de type erytheme polymorphe bulleux. *Med Hyg* 1972; **1026**: 1390–3.
6 Lawrence CM, Marshall TL, Byrne JPH. Lupus erythematosus associated with erythema multiforme-like lesions in identical twins. *Br J Dermatol* 1982; **107**: 349–56.
7 Fiallo P, Tagliapetra A-G, Santaro G. Rowell's syndrome. *Int J Dermatol* 1995; **34**: 635–6.

Childhood DLE [1]

DLE is uncommon in childhood. There appears to be no female preponderance, there is less photosensitivity and the frequency of progression to systemic disease is higher. The other clinical features are similar to those in adults.

Reference

1 George PM, Tunnessen WW. Childhood discoid lupus erythematosus. *Arch Dermatol* 1993; **129**: 613–7.

Lupus erythematosus profundus (panniculitis) (Fig. 51.23) [1]

This is an unusual clinical variety of LE in which the cutaneous infiltrate occurs primarily (but not always exclusively) in deeper portions of the corium, with only microscopic epidermal changes, giving rise to firm, sharply defined nodules from one to several centimetres in diameter, lying beneath clinically normal skin [2]. The histopathology is sufficiently characteristic to establish the diagnosis in the absence of other cutaneous or systemic lesions of LE [1]. Clinical LE profundus occurred in 3–5% of patients with DLE [3,4], but histological disease may be found in up to 30% [5]. It can occur at any age and has been described in childhood [6].

The age and sex distribution of published cases is similar to that of DLE [7], and the disease may occur in childhood [8]. Familial cases have been reported [2,9].

Kaposi first described subcutaneous nodules in LE in 1883 [10], but Irgang [11] first used the term 'lupus erythematosus profundus' in 1940. Some authors [12] have considered the lesions to be sarcoid, but it is now usually accepted as a variant of LE [13], related more to DLE than SLE [14]. It was initially considered that it was different from 'lupus erythematosus hypertrophicus et profundus' described by Behçet [5], but the only difference is the involvement of the overlying skin in the version described by Behçet. Serological abnormalities occur when panniculitis is associated with SLE [15].

Histopathology. Microscopically [1], there may be epidermal atrophy, hydropic degeneration of the basal layer, follicular plugging and necrosis of the dermal collagen, suggesting LE. Collections of lymphocytes may occur around skin appendages and vessels in the mid-dermis. There is a striking lower dermal and subcutaneous necrobiosis, with some vasculitis and little cellular response. The collagen fibres in the lower dermis, in the septa and between the fat cells are swollen and poorly stained, and in some areas homogeneous masses and amorphous eosinophilic material replace the collagen. It is very important to exclude subcutaneous panniculitis-like T-cell lymphoma and this may require immunocytochemical investigation [16]. Immunofluorescence microscopy frequently shows linear staining at the basement-membrane zone [17]. Immune complexes can be demonstrated by direct fluorescence in small deep vessels in the dermis [18].

Clinical features. The nodular lesions are of varying size, but are usually one to several centimetres in diameter. They are usually firm, rubbery, sharply defined and persistent. The overlying skin usually appears normal, although histologically there are changes at the dermal–epidermal junction in two-thirds [1]. Typical lesions of DLE may be found elsewhere, most frequently on the cheeks. Healing usually leads to the development of depressed areas, and rarely to soft, slightly pink areas of anetoderma (Fig. 51.24) up to 4 cm in diameter. Cutis laxa followed one case [19]. Lupus profundus confined to the breast has been called lupus mastitis and may herald SLE. It may be confused with carcinoma [20]. LE profundus may affect the periorbital tissues and cause severe localized oedema [21]. It may occur with eyelid plaques [22]. Wherever it occurs, the nodules are persistent, and lesions in the cheeks may lead to marked disfigurement.



Fig. 51.24 Anetoderma secondary to lupus erythematosus profundus.

LE hypertrophicus et profundus starts as a violaceous, scaly, tender lesion, which rapidly enlarges, developing a warty hypertrophic surface with coarse adherent scales, which form a hard brown-black tar-like plaque [18]. Patients with LE hypertrophicus et profundus may have extensive serological abnormalities [18], and antibodies to extractable nuclear antigen (ENA) may sometimes be present [23]. On the legs, it may initially resemble thrombophlebitis [24]. Calcification can occur, and may be extensive, with the extrusion of thick, yellowish white material through ulcerated areas.

Associated diseases. LE profundus followed thrombocytopenic purpura in one case [15]. Lesions can occur after trauma or surgical biopsy [18], and have been precipitated by electromyography [25]. Monoclonal gammopathy has been reported in LE profundus [26].

Treatment. Clobetasol propionate cream (Dermovate) under a hydrocolloid occlusive dressing (Granuflex) is worth trying [27]. Antimalarial drugs are helpful [2,3,7], including in children [28]. Intralesional injections of triamcinolone (5 mg/mL) may be helpful [29]. Oral thalidomide has resolved resistant lesions, and this has been confirmed in a patient with associated partial C4 deficiency [30].

References

1 Ng PP, Tan SH, Tan T. Lupus erythematosus panniculitis: a clinicopathologic study. *Int J Dermatol* 2002; **41**: 488–90.
2 Arnold HL. Lupus erythematosus profundus. *Arch Dermatol* 1956; **73**: 15–33.
3 Tuffanelli DL. Lupus erythematosus panniculitis (profundus). *Arch Dermatol* 1971; **103**: 231–42.
4 de Berker D, Dissaneyeka M, Burge S. The sequelae of chronic cutaneous lupus erythematosus. *Lupus* 1992; **1**: 181–6.
5 Behçet PE. Lupus erythematosus hypertrophicus et profundus. *Arch Dermatol Syphilol* 1950; **61**: 495–8.
6 Marks R, Levene GM. Discoid lupus erythematosus and lupus erythematosus profundus in a child. *Clin Exp Dermatol* 1976; **1**: 187.
7 Thurston CS, Curtis AC. Lupus erythematosus profundus (Kaposi–Irgang). *Arch Dermatol* 1966; **93**: 577–82.
8 Kind P, Schreier-Rometh U, Wahn V *et al.* Lupus panniculitis: lupus erythematodesus profundus. *Gfr Klin Padiatr* 1986; **198**: 62–4.
9 Reed WB, Bergeron RF, Tuffanelli D *et al.* Hereditary inflammatory vasculitis with persistent nodules. *Br J Dermatol* 1972; **87**: 299–307.
10 Kaposi M. *Pathologie und Therapie der Hautkrankheiten*, 2nd edn. Vienna: Urban & Schwarzenberg, 1883: 642.
11 Irgang S. Lupus erythematosus profundus. *Arch Dermatol Syphilol* 1940; **42**: 97–102.
12 Pautrier LM. Apropos du pseudo-lupus erythemateux profond (Kaposi–Irgang). *Ann Dermatol Syphilol* 1953; **80**: 233–53.
13 Pascher F, Sims CF, Pensky N. Lupus erythematosus (Kaposi–Irgang). Reprint of case including comparative study of histopathology with that of chronic discoid lupus erythematosus. *J Invest Dermatol* 1955; **25**: 347–62.
14 Watanabe T, Tsuchida T. Lupus erythematosus profundus: a cutaneous marker for a distinct clinical subset? *Br J Dermatol* 1996; **134**: 123–5.

15 Zweiman B, Tomar RH, Gross PR. Lupus erythematosus profundus following thrombocytopenic purpura. *Arch Dermatol* 1975; **111**: 347–51.
16 Massone C, Kodama K, Salmhofer K *et al*. Lupus erythematosus panniculitis (lupus profundus): clinical, histopathological, and molecular analysis of nine cases. *J Cutan Pathol* 2005; **32**: 396–404.
17 Dammert K. Lupus erythematosus hypertrophicus et profundus. *Acta Derm Venereol (Stockh)* 1971; **51**: 315–20.
18 Otani A. Lupus erythematosus hypertrophicus et profundus. *Br J Dermatol* 1977; **96**: 75–8.
19 Delisee BR, Schanne R, Gilbert M. Cutis laxa generalisée post-inflammatoire associée a une panniculite lupique. *Ann Dermatol Vénéréol* 1990; **117**: 841–4.
20 de Bandt M, Meyer O, Grossin M *et al*. Lupus mastitis heralding systemic lupus erythematosus with anti-phospholipid syndrome. *J Rheumatol* 1993; **20**: 1217–20.
21 Sheehan-Dare RA, Cunliffe WJ. Severe periorbital oedema in association with lupus erythematosus profundus. *Clin Exp Dermatol* 1988; **13**: 406–7.
22 Inuzuka, M, Tomita K, Tokura K, Takigawa M. Lupus erythematosus profundus with unusual skin manifestation: subcutaneous nodules coexisting with eyelid plaques. *J Dermatol* 2001; **28**: 437–41.
23 Spann CR, Callen JP, Klein JB *et al*. Clinical, serologic and immunogenetic studies in patients with chronic cutaneous (discoid) lupus erythematosus who have verrucous and/or hypertrophic skin lesions. *J Rheumatol* 1988; **15**: 256–61.
24 Yeung M, Wood, MS, Grondin C, Chalmers A. Lupus profundus presenting as thrombophlebitis. *J Rheumatol* 1989; **16**: 625–6.
25 Fahrner L, Duvic M. Lupus panniculitis. *Arch Dematol* 1986; **122**: 625–6.
26 Fuerman EJ, Halevy S. Lupus erythematosus profundus (Kaposi–Irgang) with monoclonal gammopathy. *Br J Dermatol* 1977; **96**: 79–82.
27 Yell JA, Burge SM. Lupus erythematosus profundus treated with clobetasol propionate under a hydrocolloid dressing. *Br J Dermatol* 1993; **128**: 103.
28 Fox JN, Klapman MH, Rowe L. Lupus profundus in children: treatment with hydroxychloroquine. *J Am Acad Dermatol* 1987; **16**: 839–44.
29 Rowell NR. Treatment of chronic discoid lupus erythematosus with intralesional triamcinolone. *Br J Dermatol* 1962; **74**: 354–7.
30 Burrows NP, Walport MJ, Hammond AH *et al*. Lupus erythematosus profundus with partial C4 deficiency responding to thalidomide. *Br J Dermatol* 1991; **125**: 62–7.

Associated features. Small telangiectases on the face occur in approximately 20% of patients. These dilated vessels may sometimes resemble spider naevi, but are usually small capillaries of irregular size and distribution, particularly on the cheeks. Dilated nail fold capillaries, similar to those seen in SLE and dermatomyositis, may be visible with the naked eye in 3%, and sometimes there may be erythema of the pulps of the fingers. More than half of patients state that they have a dry skin. Very occasionally, mild diffuse alopecia may occur, similar to that found in SLE, and alopecia areata has occurred in 10% of one series of DLE and mild SLE [1].

Bilateral enlargement of the parotids has been reported [2]. Histologically, there is lymphocytic infiltration of the parotid, which is said to be like that of LE profundus [2]. The parotid swelling may increase with exposure to sunlight and decrease during treatment with antimalarials and corticosteroids [2].

Livedo reticularis on the legs has been reported in DLE, and in one case cryoglobulins were intermittently demonstrated in the serum [3]. Table 51.4 lists the other conditions associated with DLE.

Table 51.4 Diseases reported in association with lupus erythematosus [4–14].

Porphyria
Cutanea tarda
Variegate
Acute intermittent
Erythropoietic protoporphyria
Pemphigus
Myasthenia gravis
Thymoma
Chronic lymphocytic leukaemia
Macroglobulinaemia
Benign monoclonal gammopathy
Multiple myeloma
Polychondritis
Thyroiditis
Carpal tunnel syndrome
Polymorphic light eruption
Sheehan's syndrome

Chronic granulomatous disease. Two siblings showing an autosomal form of chronic granulomatous disease with DLE-like lesions have been reported [1]. An illness resembling LE, especially of the discoid type, occurs in mothers of boys with X-linked chronic granulomatous disease. In these maternal carriers, a population of defective leukocytes can be demonstrated. Photosensitivity, chilblain LE of the fingers and toes, rosaceous lesions on the face, LE profundus and Jessner's lymphocytic infiltration-like lesions and stomatitis occur [2,3].

References

1 Werth VP, White WL, Sanchez MR. Incidence of alopecia areata in lupus erythematosus. *Arch Dermatol* 1992; **128**: 368–71.
2 Trapl J, Sabatova M. Lupus erythematosus and parotitis. *Dermatol Wochenschr* 1960; **142**: 817–9.
3 Nelson CT. Discoid lupus, reticulate livedo of legs, cryoglobulinemia. *Arch Dermatol* 1959; **80**: 497–8.
4 Callen JP, Ross L. Subacute cutaneous lupus erythematosus and porphyria cutanea tarda. *J Am Acad Dermatol* 1981; **5**: 269–73.
5 Cram DL, Epstein JH, Tuffanelli DL. Lupus erythematosus and porphyria. *Arch Dermatol* 1973; **108**: 779–84.
6 O'Reilly FM, O'Loughlin S, Murphy GM. Discoid lupus erythematosus and porphyria cutanea tarda. *J R Soc Med* 1996; **89**: 523–4.
7 Mutasim DF, Pelc NJ. Erythropoietic protoporphyria and lupus erythematosus: case report and review of the literature. *Arch Dermatol* 1994; **130**: 1330–2.
8 Cruz PD Jr, Coldiron BM, Sontheimer RD. Concurrent features of cutaneous lupus erythematosus and pemphigus erythematosus following myasthenia gravis and thymoma. *J Am Acad Dermatol* 1987; **16**: 472–80.
9 Abdou NL, Abdou NI. Discoid lupus erythematosus with macroglobulinemia. *Am J Med* 1974; **57**: 631–7.
10 Hughes RAC, Berry CL, Seifert M *et al*. Relapsing polychondritis. *QJM* 1972; **41**: 363–80.
11 Van der Meer-Roosen CH, Maes EPJ, Faber WR. Cutaneous lupus erythematosus and autoimmune thyroiditis. *Br J Dermatol* 1979; **101**: 91–2.
12 Winkelmann RK, Connolly SM, Doyle JA. Carpal tunnel syndrome in cutaneous connective tissue disease: generalized morphoea, lichen sclerosus, fasciitis, discoid lupus erythematosus and lupus panniculitis. *J Am Acad Dermatol* 1982; **7**: 94.
13 Wojnarowska F. Simultaneous occurrence in identical twins of discoid lupus erythematosus and polymorphic light eruption. *J R Soc Med* 1983; **76**: 791–2.
14 Green S, Trattner A, Weingarten MW. Discoid lupus erythematosus coexistent with Sheehan's syndrome. *Int J Dermatol* 1992; **31**: 182–3.

References

1 Stalder JF, Dreno B, Bureau B *et al*. Discoid lupus erythematosus-like lesions in an autosomal form of chronic granulomatous disease. *Br J Dermatol* 1986; **114**: 251–4.

2 Garioch JJ, Sampson JR, Seywright M *et al.* Dermatoses in five related female carriers of X-linked chronic granulomatous disease. *Br J Dermatol* 1989; **121**: 391–6.
3 Smitt JHS, Weening RS, Krieg SR *et al.* Discoid lupus erythematosus-like lesions in carriers of X-linked chronic granulomatous disease. *Br J Dermatol* 1990; **122**: 643–50.

Complement abnormalities associated with DLE. Hereditary C2 deficiency occurs in association with skin lesions resembling the discoid lesion of SLE [1]. Homozygous C2 deficiency in females is the most common association, but DLE has also been reported in heterozygous C2 deficiency [2]. Low levels of C4 have been demonstrated in two sisters [3]. Hereditary deficiency of the third [4] and of the fifth component of complement has also been associated with a lupus-like syndrome [5]. DLE has also occurred with C1q deficiency [6]. Identical twin boys have been reported with DLE skin lesions, immunological abnormalities of SLE and hereditary angio-oedema with low C1-esterase inhibitor and C4 [7]. DLE is associated with classical hereditary angio-oedema with reduced levels of C1-esterase inhibitor [8]. Approximately 2% of patients with hereditary angio-oedema have LE-like disease [9].

References

1 Stern R, Fu SM, Fotino M *et al.* Hereditary C2 deficiency: association with skin lesions resembling the discoid lesion of systemic lupus erythematosus. *Arthritis Rheum* 1976; **19**: 517–22.
2 Belin CD, Bordwell BJ, Einarson ME *et al.* Familial discoid lupus erythematosus and C2 deficiency. *Arthritis Rheum* 1980; **23**: 898–903.
3 Voigtlander V, Bahmer F, Hauptmann G. Familial discoid lupus erythematosus associated with heterozygous C4 deficiency. *Acta Derm Venereol (Stockh)* 1984; **64**: 552–4.
4 Boom BW, Daha MR. Inherited deficiency of the third component of complement, associated with cutaneous lupus erythematosus. *Br J Dermatol* 1989; **121**: 809–12.
5 Rosenfeld SI, Kelly ME, Leddy JP. Hereditary deficiency of the fifth component of complement in man. *J Clin Invest* 1976; **57**: 1626–34.
6 Uenaka A, Akimoto T, Aoki T *et al.* A complete selective C1q deficiency in a patient with discoid lupus erythematosus (DLE). *Clin Exp Immunol* 1982; **48**: 353–8.
7 Kohler PF, Percy J, Campion WM *et al.* Hereditary angioedema and 'familial' lupus erythematosus in identical twin boys. *Am J Med* 1974; **56**: 406–11.
8 Duhra P, Holmes J, Porter DI. Discoid lupus erythematosus associated with hereditary angioneurotic oedema. *Br J Dermatol* 1990; **123**: 241–4.
9 Donaldson VH, Hess EV, McAdams AJ. Lupus erythematosus-like disease in three unrelated women with hereditary angioneurotic oedema. *Ann Intern Med* 1977; **86**: 312–3.

Laboratory abnormalities in DLE. The incidence of laboratory abnormalities in 120 patients is shown in Table 51.5 [1]. Abnormalities were found in 55% of patients. T-cell counts are significantly lower than in controls, although B cells are not reduced [2]. Kidney biopsy has shown silent lupus nephritis in patients with hypocomplementaemia [3].

Table 51.5 Laboratory abnormalities in discoid lupus erythematosus.

Laboratory abnormalities	Frequency (%)
Anaemia, leukopenia or thrombocytopenia	30
Raised erythrocyte sedimentation rate (ESR)	20
Raised serum globulin	29
Positive Coombs' test	2.5
Positive cryoglobulins	<1
Positive cold agglutinins	<1
False-positive syphilis serology	26
Positive anticardiolipin antibodies (mainly IgM)	15
Positive LE cell test	1.7
Positive rheumatoid factor	17

Autoantibodies. Antinuclear antibodies are found in between 5 and 60% of cases depending on patient selection and laboratory techniques: the 'homogeneous' type of antinuclear factor being twice as frequent as the 'speckled' type. Antinuclear antibodies (ANA) are more common in older patients, in those who have had the disease for a long time and when there is extensive skin involvement. They are also more common in patients with chilblains, Raynaud's phenomenon and joint pains [4–7]. The incidence of anti-DNA antibodies varies from 0% [5,8] to 27% [9]. In the latter series, patients did not show any evidence of systemic involvement, and follow-up 3 years later showed no evidence of SLE [10], although progression has been reported [11]. Antibodies to single-stranded DNA (IgM in 20% [8]) occur in nearly one-fifth and may indicate widespread and progressive disease [12]. DNA antibody titres fall with chloroquine therapy. One-fifth of patients have IgM antibodies to single-stranded DNA [8]. Low-titre anti-Ro antibodies are found in 10% of patients with DLE, but are not related to photosensitivity and do not imply an increased risk of developing SCLE [13]. Antibody to extractable nuclear antigen is not found, but lymphocytotoxic antibodies have been demonstrated in 23% of patients in one series [14], but not found in another [5]. Precipitating autoantibodies are found in approximately 4% of patients. The SjT type of antibody (anti-La [SS-B]) is associated with 'speckled' antinuclear factor and rheumatoid factor in those patients with DLE and erythema multiforme [15]. Soluble IL-2 receptors may be found [16].

A high incidence of antithyroid antibodies has been found in DLE, particularly in females [17], and gastric parietal cell cytoplasmic antibodies occur in 13% of patients [17], but this incidence may not be higher than in controls.

References

1 Rowell NR. Laboratory abnormalities in the diagnosis and management of lupus erythematosus. *Br J Dermatol* 1971; **84**: 210–6.
2 Von Vlasin Z, Kratochvil F, Rozprimova V. Spiegel der Immunoglobuline IgG, IgM, und IgA im Serum von Kranken mit einem chronischen Diskoiden erythematodes. *Dermatol Monatsschr* 1961; **159**: 886–91.
3 Powell FC, Greipp PR, Su WP. Discoid lupus erythematosus and monoclonal gammopathy. *Br J Dermatol* 1983; **109**: 355–60.
4 Beck JS, Rowell NR. Discoid lupus erythematosus. *QJM* 1966; **35**: 119–36.
5 Prystowsky SD, Gilliam JN. Discoid lupus erythematosus as part of a larger disease spectrum. *Arch Dermatol* 1975; **111**: 1448–52.
6 Doeglas HMG. Follow-up of patients with chronic discoid lupus erythematosus. *Dermatologica* 1963; **127**: 211–5.
7 Peterson WC, Fusaro RM. Antinuclear factor in light sensitivity and lupus erythematosus. *Arch Dermatol* 1963; **87**: 563–5.
8 Kulick KB, Provost TT, Reichlin M. Antibodies to single-stranded DNA in patients with discoid lupus erythematosus. *Arthritis Rheum* 1982; **25**: 639–46.
9 Davis P, Atkins B, Hughes GRV. Antibodies to native DNA in discoid lupus erythematosus. *Br J Dermatol* 1974; **91**: 175–81.
10 Bresnihan B, Hughes GRV. Anti-DNA antibodies in discoid lupus erythematosus. *Ann Rheum Dis* 1977; **36**: 476–7.
11 Mandel MJ, Carr RI, Weston WL *et al.* Anti-native DNA antibodies in discoid lupus erythematosus. *Arch Dermatol* 1972; **106**: 668–70.
12 Callen JP, Fowler JF, Kulick KB. Serologic and clinical features of patients with discoid lupus erythematosus: relationship of antibodies to single-stranded

deoxyribonucleic acid and of other anti-nuclear antibody subsets to clinical manifestations. *J Am Acad Dermatol* 1985; **13**: 748–55.
13 Lee LA, Roberts CM, Frank MB *et al*. The antibody response to Ro/SSA in cutaneous lupus erythematosus. *Arch Dermatol* 1994; **130**: 1262–8.
14 Stenszky V, Nagy E, Szerze P. Examination of HLA antigens and lymphocytotoxic antibodies in discoid lupus erythematosus. *Acta Derm Venereol (Stockh)* 1975; **55**: 131–3.
15 Rowell NR, Swanson Beck J, Anderson JR. Lupus erythematosus and erythema multiforme-like lesions. *Arch Dermatol* 1963; **88**: 176–80.
16 Blum C, Zillikens D, Tony HP *et al*. Soluble interleukin-2 receptor as a parameter for disease activity in the serum of systemic and discoid lupus erythematosus. *Hautarzt* 1993; **44**: 290–5.
17 Shrank AB, Doniach D. Discoid lupus erythematosus. *Arch Dermatol* 1963; **87**: 677–85.

Differential diagnosis. The relationship of DLE to SLE has been discussed elsewhere (see p. 51.2). The cutaneous lesions may be very similar, although patients with DLE of the face usually show more scaling, pigmentary disturbances, atrophy and scarring. In those with extensive DDLE, positive antibodies and mild systemic symptoms, it can be difficult to fit the patient into a precise diagnostic category, but patients may fulfil the ARA criteria for the diagnosis of SLE (see p. 51.27), so discussion of 'progression of disease' in these patients is often unhelpful.

The annular atrophic plaque variety of DLE may resemble morphoea or lichen sclerosus [1]. Jessner's lymphocytic infiltration may be confused with the more acute localized oedematous lesions of LE, but the marked histological lymphocytic infiltration in the former should help to distinguish it from the latter, and immunoglobulin deposition does not occur at the dermal–epidermal junction in Jessner's infiltration [2]. Evidence has been produced from a study of 100 patients that Jessner's lymphocytic infiltration is a distinct entity, which does not seem to proceed to DLE, PLE or lymphoma [3], and studies of lymphoid infiltrates using the monoclonal antibody Leu-8 tend to confirm the difference between DLE and Jessner's lymphocytic infiltrate [4]; however, there is still disagreement on the relationship between DLE and Jessner's infiltrate, and others believe the latter to be a precursor of classical cutaneous lupus [5]. Benign lymphocytic infiltration of the skin may be a further form of cutaneous LE as indicated by phototesting [6]. Reticular erythematous mucinosis (REM) syndrome (see Chapter 59), which can show clinical and histological features similar to DLE, may also be induced by ultraviolet radiation, but is a discrete clinical entity.

The history and the presence of lesions elsewhere should exclude contact eczema, seborrhoeic eczema and psoriasis. Lupus vulgaris may resemble DLE, but the lesions of the former usually occur at an early age, are rarely symmetrical, may be ulcerated and usually show characteristic 'apple-jelly nodules'. Necrobiosis lipoidica can give facial lesions like DLE. The rosaceous type of LE can usually be differentiated from true rosacea by the absence of pustules and the histology.

Chronic DLE has been found in 12% of patients diagnosed as having scarring alopecia of the pseudopelade type [7]. Lesions on the lips, tongue, scalp and buccal mucosa may be confused with lichen planus, and the skin of some patients may show clinical, histological and immunological features of both diseases [8,9]. Overlap cases, in addition to LE-like lesions, have lichenoid papules, verrucous lesions, anonychia, and oral and vulval lesions resembling lichen planus. Patients with lichen planus do not have features of LE immunopathologically or by HLA typing [10]. Overlap cases either have both diseases or are variants of LE. In favour of the latter, the verrucous lesions show immunofluorescent findings of LE, and electron microscopy reveals tubuloreticular inclusions in endothelial cells of dermal blood vessels—which are found in LE but not in lichen planus [11].

LE of the legs and feet may resemble chilblains. Plaques of sarcoidosis and lesions of eosinophilic granuloma may cause diagnostic difficulties that can only be resolved histologically. Occasionally, lesions resembling DLE are caused by dermatophytes [12].

The distinction from PLE may be difficult, but the absence of antinuclear factor from the serum [13] and of dermal–epidermal immunoglobulin deposits [14] in PLE may be helpful. PLE and DLE may coexist, or PLE may precede DLE by many years [15]. PLE is more common in the relatives of patients with LE; as many as 65% of patients with cutaneous LE have symptoms indistinguishable from those of PLE [16].

Infants may show sharply marginated, erythematous, finely scaling plaques on the cheeks and bridge of the nose, sometimes exacerbated by the sun [17], or a transitory rash with telangiectases on the face, particularly around the eyes, which clinically and histologically resembles LE [18]. These rashes probably are part of so-called neonatal LE (see p. 51.49). The annular erythemas of infancy have been reviewed [15].

An LE-like rash on the face with sun sensitivity occurs in Bloom's syndrome (see Chapter 15), which is thought to be caused by an autosomal recessive gene. A congenital telangiectatic erythema occurs in well-proportioned dwarfs, who look alike because of their bird-like facial appearance. The skin changes occur in infancy and may be associated with ectodermal and mesodermal defects.

References

1 Chorzelski TP, Jablonska S, Blaszczyk M *et al*. Annular atrophic plaques of the face. *Arch Dermatol* 1976; **112**: 1143–5.
2 Ten Have-Opbroek AAW. On the differential diagnosis between chronic discoid lupus erythematodes and lymphocytic infiltration of the skin (Jessner) with emphasis on fluorescence microscopy. *Dermatologica* 1966; **132**: 109.
3 Toonstra J, Wildschut A, Boer J *et al*. Jessner's lymphocytic infiltration of the skin. *Arch Dermatol* 1989; **125**: 1525–30.
4 Ashworth J, Turbitt M, MacKie R. A comparison of the dermal lymphoid infiltrates in discoid lupus erythematosus and Jessner's lymphocytic infiltrate of the skin using the monoclonal antibody Leu 8. *J Cutan Pathol* 1987; **14**: 198–201.
5 Lipsker D, Mitschler A, Grosshans E, Cribier B. Could Jessner's lymphocytic infiltrate of the skin be a dermal variant of lupus erythematosus? An analysis of 210 cases. *Dermatology* 2006; **213**: 15–22.
6 Adamski H, Labrousse AL, Sparsa A *et al*. Positive photobiological investigation in Jessner's lymphocytic infiltration of the skin. *Ann Dermatol Vénéréol* 2002; **129**: 1370–3.
7 Braun-Falco O, Bergner T, Heilgemier GP. Pseudopelade alopecia. *Hautarzt* 1989; **40**: 77–83.
8 Davies MG, Gorkiewicz A, Knight A *et al*. Is there a relationship between lupus erythematosus and lichen planus? *Br J Dermatol* 1977; **96**: 145–54.
9 Van der Horst JC, Cirkel PKS, Nieboer C. Mixed lichen planus/lupus erythematosus disease: a distinct entity? Clinical, histopathological and immunopathological studies in six patients. *Clin Exp Dermatol* 1983; **8**: 631–40.
10 Potts EDA, Rowell NR. Lichen planus: a distinct entity from lupus erythematosus. *Arch Dermatol* 1981; **61**: 413–6.

11 Santa Cruz DJ, Uitto J, Eisen AZ *et al.* Verrucous lupus erythematosus: ultrastructural studies on a distinct variant of chronic discoid lupus erythematosus. *J Am Acad Dermatol* 1983; **9**: 82–90.
12 Shanon J, Raubitschek F. Tinea faciei simulating chronic discoid lupus erythematosus. *Arch Dermatol* 1960; **82**: 268–71.
13 Ive FA, Sanderson KV. A lupus erythematosus-like eruption in infants. *Trans St John's Hosp Dermatol Soc* 1964; **50**: 144.
14 Vonderheid EC, Koblenzer PJ, Ming PML *et al.* Neonatal lupus erythematosus. *Arch Dermatol* 1976; **112**: 698–705.
15 Cox NH, McQueen A, Evans TJ *et al.* An annular erythema of infancy. *Arch Dermatol* 1987; **123**: 510–3.
16 Peterson WC, Fusaro RM. Antinuclear factor in light sensitivity and lupus erythematosus. *Arch Dermatol* 1963; **87**: 563–5.
17 Fisher DA, Epstein JH, Kay DN *et al.* Polymorphous light eruption and lupus erythematosus. *Arch Dermatol* 1970; **101**: 458–61.
18 Nyberg F, Hasan T, Puska P *et al.* Occurrence of polymorphic light eruption in lupus erythematosus. *Br J Dermatol* 1997; **136**: 217–21.

Prognosis [1]. The untreated skin lesions of DLE tend to be persistent. With treatment, the more tumid lesions with little scaling may clear completely in the course of a month or two. Lesions of longer standing with much scaling and some scarring are slower to remit. Ultimately, scarring is found in 57%, with scarring alopecia in 35%; 35% also have pigmentary abnormalities [2]. Areas of activity at the edge of such scars may take years to settle. Twenty per cent of female patients notice a premenstrual flare, but there is no evidence of a deterioration of the condition on hormone replacement therapy [3]. Complete remission in the course of years can be expected in over 50% [1]. Long duration and lack of remission are related to Raynaud's phenomenon, scalp involvement and chilblain-like lesions [4]. Relapses occurring with sunlight, cold, trauma or mental stress after months or years of remission are not infrequent. In spite of the chronic and relapsing nature of the condition, the patient usually remains in good health.

Despite the fact that over half of patients have haematological and serological abnormalities, the risk of developing overt SLE is only approximately 6.5% [4,5]. The risk is higher in patients with disseminated DLE (22%) than in DLE confined to the head and neck (1.2%). Females developing DLE before the age of 40 years, with HLA-B8 in their histocompatibility type, have an increased risk of 'converting' to SLE [6]. Neither immunological nor biochemical abnormalities appear to alter the patient's progress [5,7]. Patients with active discoid skin lesions rarely have severe renal disease [8]. Patients with DLE showing signs of nephropathy, arthralgia and ANA titres of 1:320 or more should be carefully monitored [9].

References

1 Rowell NR. The natural history of lupus erythematosus. *Clin Exp Dermatol* 1984; **9**: 217–31.
2 de Berker D, Burge S, Dissaneyeka M. The sequelae of chronic cutaneous lupus erythematosus. *Lupus* 1992; **1**: 181–6.
3 Yell SA, Burge SM. The effect of hormonal changes on cutaneous disease in lupus erythematosus. *Br J Dermatol* 1993; **129**: 18–22.
4 Millard LG, Rowell NR. Abnormal laboratory test results and their relationship to prognosis in discoid lupus erythematosus. *Arch Dermatol* 1979; **115**: 1055–8.
5 Rowell NR. Laboratory abnormalities in the diagnosis and management of lupus erythematosus. *Br J Dermatol* 1971; **84**: 210–6.
6 Millard LG, Rowell NR, Rajah SM. Histocompatibility antigens in discoid and systemic lupus erythematosus. *Br J Dermatol* 1977; **96**: 139–44.
7 Beck JS, Rowell NR. Discoid lupus erythematosus. *QJM* 1966; **35**: 119–36.
8 Prystowsky SD, Gilliam JN. Discoid lupus erythematosus as part of a larger spectrum. *Arch Dermatol* 1975; **111**: 1448–52.
9 Tebbe B, Mansmann U, Wollina U *et al.* Markers in cutaneous lupus erythematosus indicating systemic involvement: a multicentre study of 296 patients. *Acta Derm Venereol (Stockh)* 1997; **77**: 305–8.

Neoplastic change in DLE. Squamous cell and, less commonly, basal cell carcinomas occasionally occur in the scars of DLE, particularly on the scalp, ears, lips and nose. An incidence of 3.3% has been noted in a series of 120 white patients with DLE [1]. They are said to be more common in middle-aged males [2], but in either sex occur only in cases of 20 years' duration or more. Black people with DLE may also develop carcinoma [3,4], especially of the lip. Death may occur from multiple metastases [1,5]. Keratoacanthoma [6], malignant fibrous histiocytoma [7] and atypical fibroxanthoma [8] in lesions have been reported.

References

1 Millard LG, Barker DJ. Development of squamous cell carcinoma in chronic DLE. *Clin Exp Dermatol* 1978; **3**: 161.
2 Epstein JH, Tuffanelli DL. In: Dubois EL, ed. *Lupus Erythematosus*. New York: McGraw-Hill, 1966: 124.
3 Caruso WR, Stewart ML, Nanda VK *et al.* Squamous cell carcinoma of the skin in black patients with discoid lupus erythematosus. *J Rheumatol* 1987; **14**: 156–9.
4 Keith WD, Kelly AP, Sumrall AJ *et al.* Squamous cell carcinoma arising in lesions of discoid lupus erythematosus in black persons. *Arch Dermatol* 1980; **116**: 315–7.
5 Martin S, Rosen T, Locker E. Metastatic squamous cell carcinoma of the lip. *Arch Dermatol* 1979; **115**: 1214.
6 Fanti PA, Tosti A, Peluso AM *et al.* Multiple keratoacanthoma in discoid lupus erythematosus. *J Am Acad Dermatol* 1989; **21**: 809–10.
7 Farber JN, Koh HK. Malignant fibrous histiocytoma arising from discoid lupus erythematosus. *Arch Dermatol* 1988; **124**: 114–6.
8 de Berker D, Burge S, Dissaneyeka M. The sequelae of chronic cutaneous lupus erythematosus. *Lupus* 1992; **1**: 181–6.

Treatment [1]. It is important to carry out a complete medical survey of the patient at the first attendance. Such a survey should establish a diagnosis of the sub-type of DLE, a likely prognosis and a baseline by which later progress may be judged. From the outset, general measures play a large part in successful management. Overwork, mental stress and fatigue are often factors in deteriorating disease, and patients with facial scarring often suffer severe psychological upset and depression [2]. Effective forms of camouflage by covering creams are available and help morale. Patients should be warned against excessive exposure to sunlight and they should be advised to wear a broad-brimmed hat, and avoid short-sleeved shirts and shorts. A sunscreen cream or lotion should be prescribed, and a preparation with a UVB protection factor of at least 15 is required; UVA protection is at least as important. Application should be frequent—probably every 2–3 h in bright sunlight. There are many suitable preparations, and patient acceptability is an important element in the choice of agent [3]. It is important that patients understand the preventative action of these preparations.

The management of cutaneous lupus has been well reviewed [1], as has that of 'resistant' disease [4]. Topical therapy can frequently control and sometimes clear lesions without systemic treatment. In one series [5], 43 out of 59 patients could be

Table 51.6 Oral agents useful in discoid lupus erythematosus.

Drug	Daily dosage	Response rate (%) (as first-line treatment)	Response rate (%) (as second-line treatment)	Side effects
Hydroxychloroquine	200–400 mg	60–75	20	See Table 51.7
Chloroquine	200–400 mg	60–75	20	See Table 51.7
Acitretin [21,22]	25–100 mg	50–75	15–20	Dry skin, hair loss, liver or lipid abnormalities, bony ankylosis
Auranofin [23]	3–9 mg	50	15–20	GI upset, haematological, renal or liver abnormality
Dapsone [24]	50–150 mg	25–50	10–20	Rash, haemolysis, dapsone syndrome
Methotrexate [25]	5–30 mg	–	25–50	GI upset, hepatitis, hepatic fibrosis, pulmonary fibrosis
Ciclosporin [26]	2.5–5 mg/kg	–	30–50	Hypertension, renal function abnormalities
Sulfasalazine [27]	1.5 g	–	5–15	
Isotretinoin [28,29]	20–80 mg	–	15–20	
Thalidomide [30–32]	50–150 mg	80–90	40–50	Drowsiness, constipation, teratogenicity, polyneuropathy
Clofazimine [33]	50–150 mg	40–60	5–15	
Phenytoin [34]	200–300 mg	–	–	
Azathioprine [35]	75–200 mg	–	20–30	
Cyclophosphamide [36]	50–200 mg	–	–	
Interferon α2a [37]		–		

controlled by applications of 0.025% fluocinolone cream, and 0.1% betamethasone 17-valerate cream alone was effective in 68 out of 78 patients without inducing epidermal atrophy [6]. There are few data supporting the use of one topical steroid over another, although more potent agents appear generally more effective. The efficacy in resistant cases may be enhanced by applications of steroid creams under plastic occlusion, using a self-adherent plastic dressing (e.g. Tegaderm [7]), or a moulded plastic prosthesis for more difficult anatomical areas such as the ears [8]. Fludroxycortide (Haelan) tape (in which steroid is impregnated onto the tacky side of polythene tape) can be cut to size and stuck on individual lesions.

Intralesional corticosteroid injections are helpful in resistant cases [9], even on lips, mouth and ears. Multiple and repeated injections may be required. Reversible, and occasionally irreversible, atrophy may result. Intralesional therapy is sometimes surprisingly effective in lesions on the nose and ears and it may also help resistant lesions on the palms and soles [10]. Intralesional chloroquine [11] has been tried with limited success. There can be considerable local pain and inflammation. Interferon-α (IFN-α) has also been used intralesionally with success [12]. Among other local measures, cryotherapy, surgical excision [13], painting small lesions with trichloracetic acid and local laser therapy may be helpful. The carbon dioxide laser, and both the pulsed-dye and argon lasers may be valuable for telangiectatic LE [14].

Oral therapy (Table 51.6). Most patients referred to hospital will need oral therapy in addition to local and general methods. In addition, vasodilator drugs, particularly calcium-channel blockers such as nifedipine, are helpful in those with Raynaud's phenomenon and chilblain lesions, and intravenous prostacyclin may be very helpful in winter, and used before intensive oral therapy in these patients.

For patients with severe, extensive or scarring disease, particularly affecting the scalp, oral prednisolone is often the most helpful initial treatment. A dosage of 0.5 mg/kg, rapidly tapered over 6 weeks, is quickly effective, minimizes scarring, and allows the slower acting agents such as antimalarials to work. Long-term therapy with oral steroids is best avoided because of side effects, but may be necessary in a small number of patients resistant to other maintenance therapy. In such circumstances, patients should also receive bone protection with bi-phosphonates or related drugs to avoid osteoporosis. Methylprednisolone 500–1000 mg/day for 2 or 3 days, given as intravenous pulse therapy, may help resistant lesions.

Table 51.7 Side effects of antimalarials.

Mild
Nausea, vomiting, abdominal pain
Severe
Corneal deposits
Retinopathy
Pigmentation of palate, nails and legs
Bleaching of hair
Exfoliative dermatitis
Lichenoid rashes
Myasthenia
Myopathy
Extrapyramidal involuntary movements
Neuropathy
Psychiatric syndromes

There is little doubt that in most cases first-line oral treatment should be with one of the antimalarials (see Chapter 74). Most would start therapy with hydroxychloroquine, initially at 200 mg twice daily, reducing to 200 mg/day once a response is achieved. Chloroquine sulphate is equally effective, usually at a dosage of 200 mg twice daily, but hydroxychloroquine is used first by most prescribers because side effects (Table 51.7), particularly eye toxicity, are less likely provided that the dosage limitations of 6.5 mg/kg lean body weight are adhered to [15]. The comparable safe daily dosage for chloroquine is unclear, but is probably around

2.5 mg/kg/day of chloroquine base. Cumulative toxicity is rarely a problem with hydroxychloroquine, although it can occur with chloroquine [16]. For this reason, courses of treatment lasting approximately 6 months are preferred, but this may not be possible in the most severely affected patients who will require ongoing therapy. Mepacrine is also useful, and is safe from an ophthalmological point of view [16], but it is often reserved for later use (because of skin pigmentation). It may be used alone, or as part of a combination of antimalarials, which may be more effective than the equivalent amount of each drug given individually [17].

The response to therapy varies; usually, the more tumid, less scaly lesions responding more rapidly than chronic, atrophic and scarring lesions. Most patients who are going to respond to antimalarials usually do so within 6 weeks.

The occurrence of side effects with one agent does not necessarily mean that they will occur with another antimalarial, so it is always worth trying an alternative drug. Taking an ophthalmological history and arranging for an examination by an optician before treatment in any patient with symptoms not corrected by spectacles may help in avoidance of the ocular manifestations. Monitoring during therapy should include taking an ophthalmic history, and testing reading ability with appropriate charts [15]. More elaborate tests, such as the electro-oculogram and electroretinogram, are no longer believed to be helpful [15].

Approximately 60–75% of all patients are helped by antimalarials. Cigarette smoking reduces the efficacy of treatment with antimalarials, probably by modifying metabolism [18]. Of those who respond, approximately 50% relapse within 6 months of stopping treatment, and repeated courses of therapy are usually required. Nevertheless, over the course of several years, most cases treated with intermittent oral antimalarials and topical corticosteroids tend to improve, and some clear completely. There is no evidence that the continuation of antimalarials after clearance prevents relapses. Hydroxychloroquine appears to be safe in pregnancy [19]. Responses to all other agents are very limited once topical therapy and antimalarials have failed [20].

For cases not responding to topical steroids, antimalarials and sunscreens, oral thalidomide has proved remarkably effective in suppressing lesions [30], and also in the treatment of chilblain LE. The originally employed dosages of 400 mg/day [31] are unnecessary, and 100 mg/day seems to be equally effective. If used as initial therapy, response rates of 80–90% may be achieved, but when used as second-line treatment the response rate is nearer 50% [20,32]. Short courses are preferable because of the risk of polyneuropathy and the teratogenic effects. The prescription of thalidomide is tightly regulated, with prescribers, dispensers and patients all having to be registered in a pregnancy prevention programme: patients are allowed only monthly amounts of drug, and all potentially fertile women should be using double contraception and require monthly pregnancy tests.

When all of the above have failed in patients with severe and persistent disease, other forms of systemic treatment may be used. Intravenous pulses of cyclophosphamide may be used, usually at a dosage of 10 mg/kg, at 3–4 weekly intervals. It is usually given in combination with intravenous methylprednisolone [36]. Most recently, the biological agents aimed at specific cytokine molecules have been used, with benefit following use of efalizumab [38].

Excision of oral lesions also may be practicable [39]. The carbon dioxide [40] and argon lasers [41] may produce improvement of disfiguring LE, although the latter may precipitate DLE [42]. Dermabrasion may help cribriform scarring of the face [43], as may carbon dioxide laser-brasion. Excision without grafting was successful in a case of verrucous LE following a burn [44].

References

1 Callen JP. Update on the management of cutaneous lupus erythematosus. *Br J Dermatol* 2004; **151**: 731–6.

2 Johnson P, Goodfield MJD. The psychological consequences of discoid lupus erythematosus. *Br J Dermatol* 2001; **145** (Suppl. 59): 71.

3 Hawk JLM, Challoner AVJ, Chaddock L. The efficacy of sunscreening agents: protection factors and transmission spectra. *Clin Exp Dermatol* 1982; **7**: 21–31.

4 Callen JP. Management of 'refractory' skin disease in patients with lupus erythematosus. *Baillieres Best Pract Res Clin Rhematol* 2005; **19**: 767–84.

5 Jansen GT, Villaha CJ, Honeycutt WM. Discoid lupus erythematosus. *Arch Dermatol* 1965; **82**: 283–5.

6 Reymann E. Treatment of discoid lupus erythematosus with betametasone valerate cream 1%. *Dermatologica* 1974; **149**: 65–8.

7 Doeglas HMG. Chronic discoid lupus erythematosus treated with triamcinolone and plastic occlusion. *Dermatologica* 1964; **128**: 384.

8 Stevenson JR, Harman LE. Occlusive therapy of the ears in discoid lupus erythematosus. *Arch Dermatol* 1964; **89**: 391–2.

9 Rowell NR. Treatment of chronic discoid lupus erythematosus with intralesional triamcinolone. *Br J Dermatol* 1962; **74**: 354–7.

10 Callen JP. Intralesional triamcinolone is effective for discoid lupus erythematosus of the palms and soles. *J Rheumatol* 1985; **12**: 630–3.

11 Pelzig A, Witten VH, Sulzberger MB. Chloroquine for chronic discoid lupus erythematosus. *Arch Dermatol* 1961; **83**: 146–8.

12 Martinez J, De Misa RF, Torrelo A, Ledo A. Low dose intralesional interferon-α for discoid lupus erythematosus. *J Am Acad Dermatol* 1992; **26**: 494–6.

13 Ronchese F. Chronic discoid lupus erythematosus treated by plastic surgery. *Chron Dermatol* 1971; **2**: 105–6.

14 Zachariae H, Bjerring P, Cramers M. Argon laser treatment of cutaneous vascular lesions in connective tissue disease. *Acta Derm Venereol (Stockh)* 1988; **68**: 179–82.

15 Fielder A, Graham E, Jones SK *et al*. Royal College of Ophthalmologists guidelines: ocular toxicity and hydroxychloroquine. *Eye* 1998; **12**: 907–9.

16 Aylward JM. Hydroxychloroquine and chloroquine: assessing the risk of retinal toxicity. *J Am Optom Assoc* 1993; **64**: 787–97.

17 Feldmann R, Saloan D, Saurat JH. The association of the two antimalarials chloroquine and quinacrine for treatment resistant chronic and sub-acute cutaneous lupus erythematosus. *Dermatology* 1994; **189**: 425–7.

18 Jewell ML, McCauliffe DP. Patients with cutaneous lupus erythematosus who smoke are less responsive to antimalarial therapy. *J Am Acad Dermatol* 2000; **42**: 983–7.

19 Buchanan NMM, Toubi E, Khamashta MA *et al*. Hydroxychloroquine and lupus pregnancy: review of a series of 36 cases. *Ann Rheum Dis* 1996; **55**: 486–8.

20 Sommer S, Hoye NA, Goodfield MJD. Therapy of discoid lupus erythematosus (DLE)—a retrospective study of therapeutic benefit and risk factors. *Br J Dermatol* 2000; **142** (Suppl.): 64.

21 Ruzicka T, Meurer M, Bieber T. Efficiency of acitretin in the treatment of cutaneous lupus erythematosus. *Arch Dermatol* 1988; **124**: 897–902.

22 Ruzicka T, Sommerburg C, Goerz G *et al*. Treatment of cutaneous lupus erythematosus with acitretin and hydroxychloroquine. *Br J Dermatol* 1992; **127**: 513–8.

23 Dalziel K, Going S, Cartwright PH *et al*. Treatment of chronic discoid lupus erythematosus with an oral gold compound (auranofin). *Br J Dermatol* 1986; **115**: 211–6.

24 Coburn PR, Shuster S. Dapsone and discoid lupus erythematosus. *Br J Dermatol* 1982; **106**: 105–6.

25 Bottomley WW, Goodfield MJD. Methotrexate for the treatment of discoid lupus erythematosus. *Br J Dermatol* 1995; **133**: 655–6.

26 Yell JA, Burge SM. Cyclosporin and discoid lupus erythematosus. *Br J Dermatol* 1994; **131**: 132–3.
27 Delaporte E, Catteau B, Sabbagh N *et al.* Treatment of discoid lupus erythematosus with sulfasalazine: 11 cases. *Ann Dermatol Venereol* 1997; **124**: 151–6.
28 Shornick JK, Formica N, Parke AL. Isotretinoin for refractory lupus erythematosus. *J Am Acad Dermatol* 1991; **24**: 49–52.
29 Green SG, Piette WW. Successful treatment of hypertrophic lupus erythematosus with isotretinoin. *J Am Acad Dermatol* 1987; **17**: 364–8.
30 Knop J, Bonomann G, Happle R *et al.* Thalidomide in the treatment of 60 cases of chronic discoid lupus erythematosus. *Br J Dermatol* 1983; **108**: 461–6.
31 Stevens RJ, Andujar C, Edwards CJ *et al.* Thalidomide in the treatment of cutaneous manifestations of lupus erythematosus: experience in 16 consecutive patients. *Br J Rheumatol* 1997; **36**: 353–9.
32 Housman TS, Jorizzo JL, McCarty MA *et al.* Low-dose thalidomide therapy for refractory cutaneous lesions of lupus erythematosus. *Arch Dermatol* 2003; **139**: 50–4.
33 Mackey JP, Barnes J. Clofazimine in the treatment of discoid lupus erythematosus. *Br J Dermatol* 1974; **91**: 93–6.
34 Rodriguez-Castellanos MA, Rubio JB, Gomez JFB, Mendoza AG. Phenytoin in the treatment of discoid lupus erythematosus. *Arch Dermatol* 1995; **131**: 620–1.
35 Callen JP, Spencer LV, Burrows JB, Holtman J. Azathioprine: an effective corticosteroid-sparing therapy for patients with recalcitrant cutaneous lupus erythematosus or with recalcitrant cutaneous leukocytoclastic vasculitis. *Arch Dermatol* 1991; **127**: 515–22.
36 Schulz EJ, Menter MA. Treatment of discoid and subacute lupus erythematosus with cyclophosphamide. *Br J Dermatol* 1971; **85**: 60–5.
37 Thivolet J, Nicolas JF, Kanitakis J *et al.* Recombinant interferon-α2a is effective in the treatment of discoid and subacute cutaneous lupus erythematosus. *Br J Dermatol* 1990; **122**: 405–9.
38 Usmani N, Goodfield M. Efalizumab in the treatment of discoid lupus erythematosus. *Arch Dermatol* 2007; **143**: 873–7.
39 Schioidt M. Local excision in the treatment of oral discoid lupus erythematosus. *Acta Derm Venereol (Stockh)* 1978; **58**: 274–6.
40 Henderson DL, Odom JC. Laser treatment of discoid lupus erythematosus. *Lasers Surg Med* 1986; **6**: 12–5.
41 Zachariae H, Bjering P, Cramers M. Argon laser treatment of cutaneous vascular lesions in connective tissue disease. *Acta Derm Venereol (Stockh)* 1988; **68**: 175–82.
42 Wolfe JT, Weinberg JM, Elenitsas R, Uberti-Benz M. Cutaneous lupus erythematosus following laser-induced thermal injury. *Arch Dermatol* 1997; **133**: 392–3.
43 Ratner D, Skouge JW. Discoid lupus erythematosus scarring and dermabrasion: a case report and discussion. *J Am Acad Dermatol* 1990; **2**: 314–6.
44 Eskreis BD, Eng AM, Furey NL. Surgical excision of trauma-induced verrucous lupus erythematosus. *J Dermatol Surg Oncol* 1988; **14**: 1296–9.

Subacute cutaneous lupus erythematosus

Definition. Subacute cutaneous lupus erythematosus (SCLE) is a specific 'subset' of lupus first described by Sontheimer *et al.* in 1979 [1]. Patients exhibit mainly cutaneous disease and usually have a good prognosis. Antibodies to the Ro/SS-A antigen are closely associated with this subgroup.

Aetiology. Antibodies to the Ro/SS-A antigen are an almost universal finding in this subset of lupus. That these antibodies may be pathogenic was first suggested by LeFeber *et al.* [2], who demonstrated that sublethal doses of ultraviolet light (UVL) induced the synthesis of Ro/SS-A antigen by cultured human keratinocytes. In addition, they also showed that UVL promoted the expression of Ro/SS-A antigens on the surface of cultured human keratinocytes where they might bind antibodies. In 1988, Ro/SS-A antigen was identified in both adult and neonatal epidermis *in vivo* [3], and subsequent studies have confirmed that UVL increases Ro/SS-A antigen expression on the surface of keratinocytes [2,4,5] and that this is increased by oestrogen [6–8]. Thus, it has been postulated that in photosensitive lupus, UVL exposure leads to increased synthesis and subsequent expression of Ro/SS-A antigen on the surface of keratinocytes where it binds antibody and initiates disease [9,10]. Further support for this hypothesis comes from a study which showed that photosensitivity and the titre of Ro/SS-A antibodies correlated with the expression of Ro/SS-A in skin specimens of patients with LE [11].

Although attractive, this hypothesis does not explain why other patients with Ro/SS-A antibodies (e.g. patients with Sjögren's syndrome) do not exhibit photosensitivity and why in the clinical setting Ro/SS-A titres rarely reflect disease activity [12], although one study has suggested that titres of Ro/SS-A are higher in SCLE patients with systemic involvement than in those without [13].

HLA antigen status may have a role in disease susceptibility. The most common haplotype in SCLE is HLA-DR3 and B8, -DR3 being most commonly associated with the annular phenotype and the expression of Ro/SS-A antibodies [14]. A more recent study has suggested an association with HLA-A1, B8, DR3, DQ2, DRw2 and C4 null haplotype [15]. DR2 has been associated with an older age of disease onset and papulosquamous lesions [16]. Complement genes are located in the HLA region and patients with SCLE have been reported to have deficiencies in the 2nd [17], 3rd [18] and 4th components [19]. A single nucleotide polymorphism leading to decreased levels of C1q antigen has been reported in patients with SCLE, the only genetic association of SCLE that lies outside the HLA region [20]. In addition, the expression of the human leukocyte antigen-DR and CD25 on circulating T cells in cutaneous lupus has been reported to correlate with disease activity [21].

Two studies [22,23] have reported an association of SCLE with the tumour necrosis factor-α (TNF-α) 308A polymorphism, which may be pathogenic or act as a marker for the HLA A1, B8, DRB1*0301 haplotype associated with other autoimmune conditions. Studies of Ro60 exons to see whether sequence alterations might be associated with SCLE have not shown differences between patients with SCLE, DLE or controls [24].

Autoantibody status. SCLE was originally labelled ANA-negative lupus, as these patients often exhibited negative autoantibody screens. This was probably because of the use of test substrates that did not contain suitable antigens for the antibodies found in this group of patients. Using human cell lines as substrates, homogeneous antinuclear antibodies are found in approximately 60% and anti-Ro/SS-A antibodies in approximately 80% of patients [1], rising to higher levels in females [25]. Anticardiolipin antibodies occur in 16% [26].

Histopathology. Histopathologically, SCLE can be differentiated from DLE by the presence of more epidermal atrophy and less hyperkeratosis, basement-membrane thickening, follicular plugging and inflammatory infiltration [27,28]. Colloid bodies and epidermal necrosis are present in more than 50%, especially in those with Ro/SS-A antibodies [29]. Dust-like particles of inter- and intracellular IgG in the basement layers of the epidermis may be a specific feature [30]. It has been suggested that pilosebaceous atrophy is the only significant predictor of DLE versus SCLE



Fig. 51.25 Subacute cutaneous lupus erythematosus.



Fig. 51.26 Subacute cutaneous lupus erythematosus, showing annular polycyclic lesions.

[29,31]. Lesional subepidermal immunoglobulin is found in approximately 60%, and is more frequent in papulosquamous (88%) than annular lesions (29%) [1]. Recent studies have shown significant numbers of chemokine receptor CCR4 and cytotoxic T cells in the basal layers of the epidermis where keratinocytes showed apoptotic death [32] and strongly positive staining for TNF-α in involved skin [33].

Clinical features. This subset [1,34,35], which comprises approximately 10% of patients with LE, have either non-scarring papulosquamous (two-thirds) or annular polycyclic (one-third) lesions. The disease predominantly affects adults, although SCLE has been reported in a child [36,37]. Lesions usually occur above the waist and particularly around the neck, on the trunk and on the outer aspects of the arms (Figs. 51.25 & 51.26) and have been reported to occur along the lines of Blaschko [38]. The borders may show vesiculation and crusting and occasionally bullae [39,40] which may be associated with co-existent porphyria cutanea tarda [41]. Follicular plugging and hyperkeratosis are not prominent, and the lesions resolve leaving grey-white hypopigmentation and telangiectases. The pigmentary changes usually resolve completely. Diffuse non-scarring alopecia and photosensitivity occur in approximately half of patients, and other features include mouth ulceration (especially of the palate), reticular livedo, periungual telangiectasia and Raynaud's phenomenon. Presentation with pityriasiform lesions [2], erythroderma [42] and poikilodermatous lesions [43,44] has been described. Morphoea [45] and dystrophic calcinosis cutis [46] have followed SCLE. Some develop lesions related to mucin deposition [47].

Approximately half of patients fulfil the criteria for SLE of the American Rheumatism Association (ARA) [48], with arthritis the most frequent feature. Fever, malaise and central nervous system involvement occur, but renal disease is mild and infrequent, although a recent study suggested that the latter may occur in up to 16% of patients, a similar frequency to that seen in those with SLE in their series [49]. Urticarial vasculitis has been reported [50]. Chronic interstitial pneumonitis has been reported [51], as has hypokalaemic tetraparesis [52]. Occasionally, the annular lesions may resemble the lesions of Rowell's syndrome or the gyrate erythema secondary to occult malignancy [53]. Some patients also have Sjögren's syndrome [54], rheumatoid arthritis, Sweet's syndrome [55], Crohn's disease [56], lichen planus [57], psoriasis [58,59], hereditary angio-oedema [60,61], porphyria cutanea tarda [62], gluten-sensitive enteropathy [63], toxic epidermal necrolysis [64], inclusion body myositis [65] or calcifying lupus panniculitis [66] and Kikuchi's disease (necrotizing lymphadenitis) [67].

A number of drugs have been reported to precipitate or exacerbate SCLE and these are listed in Table 51.8.

SCLE may occur in the course of PUVA treatment of psoriasis [107], radiation therapy [108] and IFN-β1a therapy [109]. There have been occasional reports of associations with cancer, namely breast carcinoma [110], meningioma [111], hepatocellular carcinoma [112], Hodgkin's disease [113], lung cancer [114], prostate cancer [115] and squamous carcinoma of the head and neck [116]. Occasional patients develop overt SLE with severe visceral disease [117].

Treatment. The condition in most patients is controlled by sunscreens [118,119], topical or intralesional corticosteroids [120–122] or the macrolides pimecrolimus [123] and tacrolimus [124–128]. In those not responding to these agents, antimalarial drugs are often helpful [129]. These can be used as either hydroxychloroquine or chloroquine base, although the former is safer from the ophthalmological point of view and requires less ophthalmological monitoring [130]. The antimalarial mepacrine (quinacrine) does not have ocular side effects but does induce yellow discoloration of the skin. There is evidence that a combination of antimalarials may be more effective than either alone [131] and that they are less effective in smokers [132]. Patients not responding to antimalarials

Table 51.8 Drugs associated with subacute cutaneous lupus erythematosus.

Thiazide diuretics [68–72]
Griseofulvin [73]
Terbinafine [74–77]
Calcium channel blockers [78–81]
Tamoxifen [82]
Acebutalol [83]
Lansoprazole [84]
Statins [85]
ACE inhibitors [86–88]
Etanercept [89]
Efalizumab [90]
Infliximab [91]
Leflunomide [92–94]
Carbamazepine [95,96]
Cinnarizine [97]
Inhaled tiotropium bromide [98]
Bupropion [99,100]
Docetaxel (Taxotere) [101]
Ticlopidine [102]
Gold [103]
Naproxen [104]
Aldactone [105]
Fertilizer- and pesticide-containing hay [106]

may respond to oral corticosteroids or methylprednisolone [133], etretinate [134], acitretin [135], isotretinoin [136,137], dapsone [138], oral, intravenous and subcutaneous methotrexate [139–142], thalidomide [143–147], UVA [148], IFN-α [149], long-term cefuroxime axetil [150], mycophenolate mofetil [151], intravenous immunoglobulin [152,153], etanercept [154] and efalizumab [155].

References

1 Sontheimer RD, Thomas JR, Gilliam JN. Subacute cutaneous lupus erythematosus: a cutaneous marker for a distinct lupus erythematosus subset. *Arch Dermatol* 1979; **115**: 1409–15.

2 LeFeber WP, Norris DA, Ryan SR *et al.* Ultraviolet light induces binding of antibodies to selected nuclear antigens on cultured human keratinocytes. *J Clin Invest* 1984; **74**: 1545–51.

3 Jones SK, Coulter S, Harmon C *et al.* Ro/SSA antigen in human epidermis. *Br J Dermatol* 1988; **118**: 363–7.

4 Furukawa F, Kashihara-Sawami M, Lyons MB *et al*. Binding of antibodies to the extractable nuclear antigens SSA/Ro and SSB/La is induced on the surface of human keratinocytes by ultraviolet light (UVL): implications for the pathogenesis of photosensitive cutaneous lupus. *J Invest Dermatol* 1990; **94**: 77–85.

5 Jones SK. Ultraviolet radiation (UVR) induces cell-surface Ro/SSA antigen expression by human keratinocytes *in vitro*: a possible mechanism for the UVR induction of cutaneous lupus lesions. *Br J Dermatol* 1992; **126**: 546–53.

6 Furukawa F, Lyons MB, Lee LA *et al*. Estradiol enhances binding to cultured human keratinocytes of antibodies specific for SS-A/Ro and SS-B/La; another possible mechanism for estradiol influence of lupus erythematosus. *J Immunol* 1988; **141**: 1480–8.

7 Jones SK. The effects of hormonal and other stimuli on cell-surface Ro/SSA antigen expression by human keratinocytes *in vitro*: their possible role in the induction of cutaneous lupus lesions. *Br J Dermatol* 1992; **126**: 554–60.

8 Wang D, Chan EKL. 17β-Estradiol increases expression of 52-kDa and 60-kDa SS-A/Ro autoantigens in human keratinocytes and breast cancer cell line MCF-7. *J Invest Dermatol* 1996; **107**: 610–4.

9 Norris DA. Pathomechanisms of photosensitive lupus erythematosus. *J Invest Dermatol* 1993; **100**: 58S–68S.

10 Mellers S, Winterberg F, Gilliet M *et al.* Ultraviolet radiation-induced injury, chemokines and leukocyte recruitment. *Arthritis Rheum* 2005; **52**: 1504–16.

11 Ioannides D, Golden BD, Buyon JP *et al*. Expression of SS-A/Ro and SS-B/La antigens in skin biopsy specimens of patients with photosensitive forms of lupus erythematosus. *Arch Dermatol* 2000; **136**: 340–6.

12 Purcell SM, Lieu TS, Davis BM *et al*. Relationship between circulating anti-Ro/SS-A antibody levels and skin disease activity in subacute cutaneous lupus erythematosus. *Br J Dermatol* 1987; **117**: 277–87.

13 Popovic K, Brauner S, Ek M *et al.* Fine specificity of the Ro/SSA autoantibody response in relation to serological and clinical findings in 96 patients with self-reported cutaneous symptoms induced by sun. *Lupus* 2007; **16**: 10–7.

14 Sontheimer RD, Stastny P, Gilliam JN. Human histocompatibility antigen associations in subacute cutaneous lupus erythematosus. *J Clin Invest* 1981; **67**: 312–6.

15 Millard TP, McGregor JM. Molecular genetics of cutaneous lupus erythematosus. *Clin Exp Dermatol* 2001; **26**: 184–91.

16 Johansson-Stephansson E, Koskimies S, Partanen J *et al*. Subacute cutaneous lupus erythematosus: genetic markers and clinical and immunological findings in patients. *Arch Dermatol* 1989; **125**: 791–6.

17 Callen JP, Hodge SJ, Kulick KB *et al*. Subacute cutaneous lupus erythematosus in multiple members of a family with C2 deficiency. *Arch Dermatol* 1987; **123**: 66–70.

18 Van Hees CLM, Boom BW, Vermeer BJ *et al*. Subacute lupus erythematosus in a patient with inherited deficiency of the third component of complement. *Arch Dermatol* 1992; **128**: 700–1.

19 Partanen J, Koskimies S, Johansson E. C4 null phenotypes among lupus erythematosus patients are predominantly the result of deletions covering C4 and closely linked 21-hydroxylase A genes. *J Med Genet* 1988; **25**: 387–91.

20 Sontheimer RD. Subacute cutaneous lupus: a 25 year evolution of a prototypic subset (subphenotype) of lupus erythematosus defined by characteristic cutaneous, pathological, immunological and genetic findings. *Autoimmun Rev* 2005; **4**: 253–63.

21 Wenzel J, Henze S, Brahler S *et al.* The expression of human leukocyte antigen-DR and CD25 on circulating T cells in cutaneous lupus erythematosus and correlation with disease activity. *Exp Dermatol* 2005; **14**: 454–9.

22 Werth VP, Zhang W, Dortzbach K *et al*. Association of a promotor polymorphism of tumor necrosis factor-α with subacute cutaneous lupus erythematosus and distinct photoregulation of transcription. *J Invest Dermatol* 2000; **115**: 726–30.

23 Millard TP, Kondeatis E, Cox A *et al.* A candidate gene analysis of three photosensitivity disorders: cutaneous lupus erythematosus, polymorphic light eruption and actinic prurigo. *Br J Dermatol* 2001; **145**: 229–36.

24 Millard, TP, Ashton GHS, Kondeatis E *et al.* Human Ro60 (SSA2) genomic organization and sequence alterations, examined in cutaneous lupus erythematosus. *Br J Dermatol* 2002; **146**: 210–5.

25 Provost TT, Watson RM. Anti-Ro (SSA), HLA DR3-positive females: the interrelationship between some ANA negative, SS, SCLE, and NLE mothers and SS/LE overlap female patients. *J Invest Dermatol* 1993; **100**: 14S–20S.

26 Fonseca E, Alvarez R, Gonzalez MR *et al*. Prevalence of anticardiolipin antibodies in subacute cutaneous lupus erythematosus. *Lupus* 1992; **1**: 265–8.

27 Bangert JL, Freeman RG, Sontheimer RD *et al*. Subacute cutaneous lupus erythematosus and discoid lupus erythematosus. *Arch Dermatol* 1984; **120**: 332–7.

28 David-Bajar KM, Bennion SD, DeSpain JD *et al*. Clinical, histological and immunofluorescent distinctions between subacute cutaneous lupus erythematosus and discoid lupus erythematosus. *J Invest Dermatol* 1992; **99**: 251–7.

29 Bielsa I, Herrero C, Collado A *et al*. Histopathologic findings in cutaneous lupus erythematosus. *Arch Dermatol* 1994; **130**: 54–8.

30 Nieboer C, Tak-Diamand Z, Van Leeuwen-Wallau HE. Dust-like particles: a specific direct immunofluorescence pattern in subacute cutaneous lupus erythematosus. *Br J Dermatol* 1988; **118**: 725–9.

31 Jerdan MS, Hood AF, Moore GW *et al*. Histopathologic comparison of the subsets of lupus erythematosus. *Arch Dermatol* 1990; **126**: 52–5.

32 Wenzel J, Henze S, Worenkamper E *et al.* Role of the chemokine receptor CCR4 and its ligand thymus- and activation-regulated chemokine/CCL17 for lymphocyte recruitment in cutaneous lupus erythematosus. *J Invest Dermatol* 2005; **124**: 1241–8.

33 Zampieri S, Alaibac M, Iaccarino L *et al.* Tumour necrosis factor α is expressed in refractory skin lesions from patients with subacute cutaneous lupus erythematosus. *Ann Rheum Dis* 2006; **65**: 545–8.
34 Sontheimer RD. Subacute cutaneous lupus erythematosus: a decade's perspective. *Med Clin North Am* 1989; **73**: 1073–90.
35 David-Bajar KM. Subacute cutaneous lupus syndromes. *J Invest Dermatol* 1993; **100**: 2S–8S.
36 Ciconte A, Mills AE, Shipley A, Marks R. Subacute cutaneous lupus presenting in a child. *Australas J Dermatol* 2002; **43**: 62–4.
37 Amato L, Coronella G, Berti S *et al.* Subacute cutaneous lupus erythematosus in childhood. *Paediatr Dermatol* 2003; **20**: 31–4.
38 Rockmann H, Feller G, Schadenforf D *et al.* Subacute cutaneous lupus on the lines of Blaschko. *Eur J Dermatol* 2006; **16**: 302–6.
39 Perera GK, Black MM, McGibbon DH. Bullous subacute cutaneous lupus erythematosus. *Clin Exp Dermatol* 2004; **29**: 265–7.
40 Mutasim DF. Severe subacute cutaneous lupus erythematosus presenting with generalized erythroderma and bullae. *J Am Acad Dermatol* 2003; **48**: 947–9.
41 Peitsch WK, Lorentz K, Goebeler M *et al.* Subacute cutaneous lupus erythematosus with bullae associated with porphyria cutanea tarda. *J Dtsch Dermatol Ges* 2007; **5**: 220–2.
42 De Spain J, Clark DP. Subacute cutaneous lupus erythematosus presenting as erythroderma. *J Am Acad Dermatol* 1988; **19**: 388–92.
43 Pramatarov K, Vassileva S, Miteva L. Subacute cutaneous lupus erythematosus presenting with generalized poikiloderma. *J Am Acad Dermatol* 2000; **42**: 286–8.
44 Marzano AV, Facchetti M, Alessi E. Poikilodermatous subacute cutaneous lupus erythematosus. *Dermatol* 2003; **207**: 285–90.
45 Rao BK, Coldiron BM, Freeman RF *et al.* Subacute lupus erythematosus lesions progressing to morphoea. *J Am Acad Dermatol* 1990; **23**: 1019–22.
46 Marzano AV, Kolesnikova LV, Gasparini G *et al.* Dystrophic calcinosis cutis in subacute lupus. *Dermatology* 1999; **198**: 90–2.
47 Sonntag M, Lehmann P, Megahed M *et al.* Papulonodular mucinosis associated with subacute cutaneous lupus erythematosus. *Dermatology* 2003; **206**: 326–9.
48 Callen JP, Klein J. Subacute cutaneous lupus erythematosus: clinical, serologic, immunogenetic, and therapeutic considerations in 72 patients. *Arthritis Rheum* 1988; **31**: 1007–13.
49 Black DR, Hornung CA, Schneider PD *et al.* Frequency and severity of systemic disease in patients with subacute cutaneous lupus erythematosus. *Arch Dermatol* 2002; **138**: 1175–8.
50 Berti S, Moretti S, Lucin C *et al.* Urticarial vasculitis and subacute cutaneous lupus erythematosus. *Lupus* 2005; **14**: 489–92.
51 Heymann WR, Manders SM, Gottlieb GJ *et al.* Subacute cutaneous lupus erythematosus associated with chronic interstitial pneumonitis. *Int J Dermatol* 1995; **34**: 354–6.
52 De-Silva BD, Plant W, Kemmett D. Subacute cutaneous lupus erythematosus and life-threatening hypokalaemic tetraparesis: a rare complication. *Br J Dermatol* 2001; **144**: 622–4.
53 Kreft B, Marsch WC. Lupus erythematosus gyratum repens. *Eur J Dermatol* 2007; **17**: 79–82.
54 Provost TT, Talal N, Harley JB *et al.* The relationship between anti-Ro (SS-A) antibody-positive Sjögren's syndrome and anti-Ro (SS-A) antibody-positive lupus erythematosus. *Arch Dermatol* 1988; **124**: 63–71.
55 Goette DK. Sweet's syndrome in subacute cutaneous lupus erythematosus. *Arch Dermatol* 1985; **121**: 789–91.
56 Ashworth J. Subacute cutaneous lupus erythematosus in a patient with Crohn's disease. *Clin Exp Dermatol* 1992; **17**: 135–6.
57 Grabbe S, Kolde G. Coexisting lichen planus and subacute lupus erythematosus. *Clin Exp Dermatol* 1995; **20**: 249–56.
58 Kontochristopoulos GK, Giannadaki M, Doulaveri G *et al.* Psoriasis co-existing with subacute cutaneous lupus erythematosus. *Eur Acad Dermatol Venereol* 2004; **18**: 385–6.
59 Ferahbas A, Utas S, Canoz O *et al.* The co-existence of subacute cutaneous lupus erythematosus and psoriasis. *Eur Acad Dermatol Venereol* 2004; **18**: 390–1.
60 Gudat W, Bork K. Hereditary angioedema associated with subacute cutaneous lupus erythematosus. *Dermatologica* 1989; **179**: 211–3.
61 Guillet G, Sassolas B, Plantin P *et al.* Anti-Ro-positive lupus and hereditary angioneurotic oedema. *Dermatologica* 1988; **177**: 370–5.
62 Camp PB, Davis LS. Coexistence of subacute cutaneous lupus erythematosus and porphyria cutanea tarda: a case report. *Cutis* 1997; **59**: 216E.
63 Roberts DL. Subacute cutaneous lupus erythematosus and gluten sensitive enteropathy. *Br J Dermatol* 1988; **118**: 731–2.
64 Bielsa I, Herrero C, Font J *et al*. Lupus erythematosus and toxic epidermal necrolysis. *J Am Acad Dermatol* 1987; **16**: 1265–7.
65 Wenzel J, Uerlich M, Gerdsen R *et al*. Association of inclusion body myositis with subacute cutaneous lupus erythematosus. *Rheumatol Int* 2001; **21**: 75–7.
66 Morgan KW, Callen JP. Calcifying lupus panniculitis in a patient with subacute cutaneous lupus erythematosus: response to diltiazem and chloroquine. *J Rheumatol* 2001; **28**: 2129–32.
67 Toll A, Gilaberte M, Matias-Guiu X *et al.* Kikuchi's disease (necrotizing lymphadenitis) with cutaneous involvement associated with subacute cutaneous lupus erythematosus. *Clin Exp Dermatol* 2004; **29**: 240–3.
68 Brown C, Deng J. Thiazide diuretic induces cutaneous lupus-like cutaneous reaction. *J Toxicol Clin Toxicol* 1995; **33**: 729–33.
69 Reed BR, Huff JC, Jones SK *et al.* Subacute cutaneous lupus erythematosus associated with hydrochlorothiazide therapy. *Ann Intern Med* 1985; **103**: 49–51.
70 Parodi A, Romagnoli M, Rebora A. Subacute cutaneous lupus erythematosus-like eruption caused by hydrochlorothiazide. *Photodermatol* 1989; **6**: 100–2.
71 Wollenberg A, Meurer M. Thiazide diuretic induced subacute cutaneous lupus. *Hautarzt* 1991; **42**: 709–12.
72 Darken M, McBurney E. Subacute cutaneous lupus erythematosus-like drug eruption due to combination diuretic hydrochlorothiazide and triamterine. *J Am Acad Dermatol* 1988; **18**: 38–42.
73 Miyagawa S, Okuchi T, Shiomi Y *et al*. Subacute cutaneous lupus erythematosus lesions precipitated by griseofulvin. *J Am Acad Dermatol* 1989; **21**: 343–6.
74 Callen JP, Hughes AP, Kulp-Shorten C. Subacute cutaneous lupus erythematosus induced or exacerbated by terbinafine. *Arch Dermatol* 2001; **137**: 1196–8.
75 Bonsmann G, Schiller M, Luger TA *et al*. Terbinafine-induced subacute cutaneous lupus erythematosus. *J Am Acad Dermatol* 2001; **44**: 925–31.
76 McKellar G, Porter D, Burden D. Terbinafine as a cause of cutaneous lupus erythematosus. *Rheumatology (Oxford)* 2004; **43**: 249.
77 Farhi D, Viguier M, Cosnes A *et al.* Terbinafine-induced subacute cutaneous lupus erythematosus. *Dermatology* 2006; **212**: 59–65.
78 Crowson AN, Magro CM. Subacute cutaneous lupus erythematosus arising in the setting of calcium channel blocker therapy. *Hum Pathol* 1997; **28**: 67–73.
79 Gubinelli E, Cocuroccia B, Girolomoni G. Subacute cutaneous lupus erythematosus induced by nifedipine. *J Cutan Med Surg* 2003; **7**: 243–6.
80 Marzano AV, Borghi A, Mercogliano M *et al.* Nitrendipine-induced subacute cutaneous lupus erythematosus. *Eur J Dermatology* 2003; **13**: 213–6.
81 Kurtis B, Larson MJ, Hoang MP *et al.* Verapamil-induced subacute cutaneous lupus erythematosus. *J Drugs Dermatol* 2005; **4**: 506–8.
82 Fumal I, Danchin A, Cosserat F *et al.* Subacute cutaneous lupus erythematosus associated with tamoxifen therapy: two cases. *Dermatology* 2005; **210**: 251–2.
83 Fenniche S, Dhaoui A, Amma FB *et al.* Acebutalol-induced subacute cutaneous lupus erythematosus. *Skin Pharmacol Physiol* 2005; **18**: 230–3.
84 Bracke A, Nijsten T, Vandermaesen J *et al.* Lansoprazole-induced subacute cutaneous lupus erythematosus: two cases. *Acta Derm Venereol* 2005; **85**: 353–4.
85 Noel B. Lupus erythematosus and other autoimmune diseases related to statin therapy: a systematic review. *J Eur Acad Dermatol Venereol* 2007; **21**: 17–24.
86 Srivastava M, Rencic A, Diglio G *et al.* Drug induced Ro/SSA positive cutaneous lupus erythematosus. *Arch Dermatol* 2003; **139**: 45–9.
87 Patri P, Nigro A, Rebora A. Lupus erythematosus like eruption from captopril. *Acta Derm Venereol* 1985; **65**: 447–8.
88 Fernandez-Diaz M, Herranz P, Suarez-Marrero M *et al.* Subacute cutaneous lupus erythematosus associated with cilazapril. *Lancet* 1995; **345**: 398.
89 Bleumink GS, Ter-Borg EJ, Ramselaar CG *et al*. Etanercept-induced subacute cutaneous lupus. *Rheumatology* 2001; **40**: 1317–9.
90 Bentley DD, Graves JE, Smith DI *et al.* Efalizumab-induced subacute cutaneous lupus erythematosus. *J Am Acad Dermatol* 2006; **54**: S242–3.
91 High WA, Muldrow ME, Fitzpatrick JE *et al.* Cutaneous lupus erythematosus induced by infliximab. *J Am Acad Dermatol* 2005; **52**: e7–8.
92 Gensburger D, Kawashima M, Marotte H *et al.* Lupus erythematosus with leflunomide: induction or reactivation? *Ann Rheum Dis* 2005; **64**: 153–5.

93 Chan SK, Hazleman BL, Burrows NP. Subacute cutaneous lupus erythematosus precipitated by leflunomide. *Clin Exp Dermatol* 2005; **30**: 724–5.
94 Goeb V, Bertholet JM, Joly P *et al.* Leflunomide-induced subacute cutaneous lupus erythematosus. *Rheumatol* 2005; **44**: 823–4.
95 Capponi A, De Simone C, Guerriero C *et al.* Ro/SSA Positive cutaneous lupus erythematosus induced by carbamazepine. *Arch Dermatol* 2005; **141**: 103–4.
96 Ameio P, Innocente C, Feliciani C *et al.* Drug-induced cutaneous lupus erythematosus after 5 years of treatment with carbamazepine. *Eur J Dermatol* 2006; **16**: 281–3.
97 Toll A, Campo-Pisa P, Gonzalez-Castro J *et al.* Subacute cutaneous lupus erythematosus associated with cinnarizine and thiethylperazine therapy. *Lupus* 1998; **7**: 364–6.
98 Pham HC, Saurat JH. Inhalation route inducing subacute cutaneous lupus erythematosus with tiotropium. *Arch Dermatol* 2005; **141**: 911–2.
99 Cassis TB, Callen JP. Bupropion induced subacute cutaneous lupus erythematosus. *Australas J Dermatol* 2005; **46**: 266–9.
100 Jumez N, Dereure O, Bessis D *et al.* Flare of cutaneous lupus erythematosus induced by bupropion (Zyban). *Dermatology* 2004; **208**: 362.
101 Chen M, Crowson AN, Woofter M *et al.* Docetaxel (taxotere) induced subacute cutaneous lupus erythematosus: report of 4 cases. *J Rheumatol* 2004; **31**: 818–20.
102 Reich A, Bialynick-Birula R, Szepietowski JC. Drug-induced subacute cutaneous lupus erythematosus resulting from ticlopidine. *Int J Dermatol* 2006; **45**: 1112–4.
103 Balsa A, Bernad M, de Miguel E *et al.* Lupus eritematoso cutanoe subagudo por la crisoterapia en una arthritis reumatoide. *Rev Clin Esp* 1988; **182**: 505–6.
104 Parodi A, Rivara G, Guarrera M. Possible naproxen induced relapse of subacute cutaneous lupus erythematosus. *JAMA* 1992; **268**: 51–2.
105 Leroy D, Dompmartin A, Le Jean S *et al.* Dermatitis caused by aldactone of a lupic annular erythema type. *Ann Dermatol Venereol* 1987; **114**: 1237–40.
106 Shapiro M, Sosis AC, Junkins-Hopkins JM *et al.* Lupus erythematosus induced by medications, ultraviolet radiation, and other exogenous agents: a review, with special focus on the development of subacute cutaneous lupus erythematosus in a genetically predisposed individual. *Int J Dermatol* 2004; **43**: 87–94.
107 Dowdy MJ, Nigra TP, Barth WF. Subacute cutaneous lupus erythematosus during PUVA therapy for psoriasis: case report and review of the literature. *Arthritis Rheum* 1989; **32**: 343–6.
108 Balabanova MB, Botev IN, Michailova JI. Subacute cutaneous lupus induced by radiation therapy. *Br J Dermatol* 1997; **137**: 648–9.
109 Nousari HC, Kimyai-Asadi A, Tausk FA. Subacute cutaneous lupus erythematosus associated with interferon-β1a. *Lancet* 1998; **352**: 1825–6.
110 Schewach-Millet M, Shpiro D, Ziv R *et al*. Subacute cutaneous lupus erythematosus associated with breast carcinoma. *J Am Acad Dermatol* 1988; **19**: 406–8.
111 Richardson TT, Cohen PR. Subacute cutaneous lupus erythematosus: report of a patient who subsequently developed a meningioma and whose skin lesions were treated with isotretinoin. *Cutis* 2000; **66**: 183–8.
112 Ho C, Shumack SP, Morris D. Subacute cutaneous lupus erythematosus associated with hepatocellular carcinoma. *Australas J Dermatol* 2001; **42**: 110–3.
113 Castenet J, Taillan B, Lacour JP *et al.* Subacute cutaneous lupus erythematosus associated with Hodgkin's disease. *Clin Rheumatol* 1995; **14**: 692–4.
114 Brenner S, Golan H, Gat A *et al*. Paraneoplastic subacute cutaneous lupus erythematosus: report of a case associated with cancer of the lung. *Dermatology* 1997; **194**: 172–4.
115 Vogt T, Coras B, Hafner C *et al.* Antiangiogenic therapy in metastatic prostate carcinoma complicated by cutaneous lupus erythematosus. *Lancet Oncol* 2006; **7**: 695–7.
116 Chaudry SI, Murphy LA, White IR. Subacute cutaneous lupus: a paraneoplastic dermatosis. *Clin Exp Dermatol* 2005; **30**: 655–8.
117 Weinstein CL, Littlejohn GO, Thomson NM *et al*. Severe visceral disease in subacute cutaneous lupus erythematosus. *Arch Dermatol* 1987; **123**: 638–40.
118 Callen JP, Roth DE, McGrath C *et al*. Safety and efficacy of a broad-spectrum sunscreen in patients with discoid or subacute cutaneous lupus erythematosus. *Cutis* 1991; **47**: 130–6.
119 Herzinger T, Plewig G, Rocken M. Use of sunscreens to protect against ultraviolet induced lupus erythematosus. *Arthritis Rheum* 2004; **50**: 3045–8.
120 Drake LA, Dinehart SM, Farmer ER *et al.* Guidelines of care for cutaneous lupus erythematosus. *J Am Acad Dermatol* 1996; **34**: 830–6.
121 Heath M, Raugi GJ. Evidence-based evaluation of immunomodulatory therapy for the cutaneous manifestations of lupus. *Adv Dermatol* 2004; **20**: 257–91.
122 Callen JP. Cutaneous lupus erythematosus: a personal approach to management. *Australas J Dermatol* 2006; **47**: 13–27.
123 Kreuter A, Gambichler T, Breukmann F *et al.* Pimecrolimus 1% cream for cutaneous lupus erythematosus. *J Am Acad Dermatol* 2004; **51**: 407–10.
124 Bohm M, Gaubitz M, Luger TA *et al.* Topical tacrolimus as a therapeutic adjunct in patients with cutaneous lupus erythematosus. *Dermatology* 2003; **207**: 381–5.
125 Lampropoulos CE, Sangle S, Harrison P *et al.* Topical tacrolimus therapy of resistant cutaneous lesions in lupus erythematosus: a possible alternative. *Rheumatology* 2004; **43**: 1383–5.
126 Tzung TY, Liu YS, Chang HW. Tacrolimus vs clobetasol proprionate in the treatment of facial lupus erythematosus: a randomized, double blind, bilateral comparison study. *Br J Dermatol* 2007; **156**: 191–2.
127 Von Pelchrzim R, Schmook T, Friedrich M *et al.* Efficacy of topical tacrolimus in the treatment of various cutaneous manifestations of lupus erythematosus. *Int J Dermatol* 2006; **45**: 84–5.
128 Druke A, Gambichler T, Altmeyer P *et al*. 0.1% tacrolimus ointment in a patient with subacute cutaneous lupus erythematosus. *J Dermatolog Treat* 2004; **15**: 63–4.
129 Wozniacka A, Carter A, McCauliffe DP. Antimalarials in cutaneous lupus erythematosus: mechanisms of therapeutic benefit. *Lupus* 2002; **11**: 71–81.
130 Fielder A, Graham E, Jones SK *et al*. Royal College of Ophthalmologists guidelines: ocular toxicity and hydroxychloroquine. *Eye* 1998; **12**: 907–9.
131 Feldmann R, Salomon D, Saurat JH. The association of the two antimalarials chloroquine and quinacrine for treatment-resistant chronic and subacute cutaneous lupus erythematosus. *Dermatology* 1994; **189**: 425–7.
132 Jewell ML, McCauliffe DP. Patients with cutaneous lupus erythematosus who smoke are less responsive to antimalarial therapy. *J Am Acad Dermatol* 2000; **42**: 983–7.
133 Goldberg JW, Lidsky MD. Pulse methylprednisolone therapy for persistent subacute cutaneous lupus. *Arthritis Rheum* 1984; **27**: 837–8.
134 Ruzicka T, Meurer M, Braun-Falco O. Treatment of cutaneous lupus erythematosus with etretinate. *Acta Derm Venereol (Stockh)* 1985; **65**: 324–9.
135 Ruzicka T, Meurer M, Bieber T. Efficiency of acitretin in the treatment of cutaneous lupus erythematosus. *Arch Dermatol* 1988; **124**: 897–902.
136 Newton RC, Jorizzo JL, Solomon AR *et al.* Mechanism-oriented assessment of isotretinoin in chronic or subacute cutaneous lupus erythematosus. *Arch Dermatol* 1986; **122**: 170–6.
137 Richardson TT, Cohen PR. Subacute cutaneous lupus erythematosus: report of a patient who subsequently developed a meningioma and whose skin lesions were treated with isotretinoin. *Cutis* 2000; **66**: 183–8.
138 Tsutsui K, Imai T, Hatta N *et al.* Widespread pruritic plaques in a patient with subacute cutaneous lupus erythematosus and hypocomplementaemia: response to dapsone therapy. *J Am Acad Dermatol* 1996; **35**: 313–5.
139 Bohm L, Uerlich M, Bauer R. Rapid improvement of subacute cutaneous lupus erythematosus with low-dose methotrexate. *Dermatology* 1997; **194**: 307–8.
140 Kuhn A, Specker C, Ruzicka T *et al*. Methotrexate treatment for refractory subacute cutaneous lupus erythematosus. *J Am Acad Dermatol* 2002; **46**: 600–3.
141 Wenzel J, Brahler S, Bauer R *et al.* Efficacy and safety of methotrexate in recalcitrant cutaneous lupus erythematosus: results of a retrospective study in 43 patients. *Br J Dermatol* 2005; **153**: 157–62.
142 Huber A, Tuting T, Bauer R *et al.* Methotrexate treatment in cutaneous lupus erythematosus: subcutaneous application is as effective as intravenous administration. *Br J Dermatol* 2006; **155**: 861–2.
143 Stevens RJ, Andujar C, Edwards CJ *et al.* Thalidomide in the treatment of the cutaneous manifestations of lupus erythematosus: experience in 16 consecutive patients. *Br J Rheumatol* 1997; **36**: 353–9.
144 Ordi-Ros J, Cortes F, Cucurull E *et al.* Thalidomide in the treatment of cutaneous lupus refractory to conventional therapy. *Rheumatol* 2000; **27**: 1429–33.
145 Bohmeyer J, Achenbach A, Westenberger M *et al*. Thalidomide therapy of cutaneous lupus erythematosus. *Hautarzt* 2002; **53**: 744–8.
146 Housman TS, Jorizzo JL, McCarty MA *et al.* Low-dose thalidomide therapy for refractory cutaneous lesions of lupus erythematosus. *Arch Dermatol* 2003; **139**: 50–4.

147 Cuadrado MJ, Karim Y, Sanna G *et al*. Thalidomide for the treatment of resistant cutaneous lupus: efficacy and safety of different therapeutic regimes. *Am J Med* 2005; **118**: 246–50.
148 Sonnichsen N, Meffert H, Kunzelmann V *et al*. UVA-1 Therapie bei subakut-kutanem Lupus Erythematodes. *Hautarzt* 1993; **44**: 723–5.
149 Nicolas JF, Thivolet J. Interferon-α therapy in severe unresponsive subacute cutaneous lupus erythematosus. *N Engl J Med* 1989; **321**: 1550–1.
150 Rudnicka L, Szymanska E, Walecka I *et al*. Long-term cefuroxime axetil in subacute cutaneous lupus erythematosus: a report of three cases. *Dermatology* 2000; **200**: 129–31.
151 Schanz S, Ulmer A, Rassner G *et al*. Successful treatment of subacute cutaneous lupus erythematosus with mycophenolate mofetil. *Br J Dermatol* 2002; **147**: 174–8.
152 Goodfield, MJD, Davison K, Bowden K. Intravenous immunoglobulin (IVIg) for therapy-resistant cutaneous lupus erythematosus. *J Dermatolog Treat* 2004; **15**: 46–50.
153 Kreuter A, Hyun J, Altmeyer P *et al*. Intravenous immunoglobulin for recalcitrant subacute cutaneous lupus erythematosus. *Acta Derm Venereol* 2005; **85**: 545–7.
154 Fautrel B, Foltz V, Frances C *et al*. Regression of subacute cutaneous lupus erythematosus in a patient with rheumatoid arthritis treated with a biologic tumour necrosis factor α blocking agent: comment on the article by Pisetsky and the letter from Aringer. *Arthritis Rheum* 2002; **46**: 1408–9.
155 Layton TH, Ogden S, Goodfield MJG. Treatment of refractory subacute cutaneous lupus erythematosus with efalizumab. *J Am Acad Dermatol* 2005; **54**: 892–5.

Systemic lupus erythematosus [1,2]

Definition. A systemic disease characterized by multisystem organ inflammation, most commonly the skin, joints and vasculature, and associated immunological abnormalities. The main clinical features include fever, rashes and arthritis, but renal, pulmonary, cardiac and neurological involvement may occur, with increased mortality. For any individual patient, the ARA criteria may be used as an aid to diagnosis (Table 51.9).

Incidence. SLE is an uncommon disease [3–9], with incidence estimated at 1–12.5 in 100 000 per year at Leeds General Infirmary; for every case of SLE there are six cases of pernicious anaemia and 10 of leukaemia. The condition is universal, but is three times more common in black people than in white people [3]. Younger black American females are particularly predisposed to the disease [4], although it is rare in native Africans. It is also common in the Chinese and in New Zealand Polynesians [5]. The pattern of disease appears to be different in such ethnic subgroups, with black Americans and Hispanics having the highest rate of internal organ damage [6]. A study in Hawaii gave similar racial variation, with the prevalence in those of Chinese origin being 24.1 in 100 000, whereas that in whites was 5.8 in 100 000 [7]. The incidence of newly diagnosed cases in New York is 10–14 per million population [8]. The prevalence varies from less than 1 in 1000 for black females in New York [9] to approximately 1 in 2000 white females in San Francisco, and figures for England and Wales suggest a prevalence of 12.5 in 100 000 women, although this is an underestimate [10]. The observed annual incidence increased from 25 per million in 1955 to 50 per million in 1959 [11]. In Hong Kong, in 1987, the incidence was 2.4 in 100 000 [11], and in Baltimore, in 1985, it was 4.6 in 100 000, a twofold increase over the preceding 15 years. Self-reported physician-diagnosed SLE occurred in 124 in 100 000 in the USA [12]. This suggests that the disorder may be more common than it used to be, but it may also represent better awareness and earlier diagnosis. An epidemiological survey in New York showed that morbidity and mortality rates were highest among black people, followed in descending order by Puerto Ricans and then other white people. Racial differences were independent of housing, overcrowding and migration, but were associated with racial variation in normal gammaglobulin levels, which were higher in black people [6]. A more recent study from England confirms the increased risk of SLE in Afro-Caribbeans and Asians, irrespective of their place of birth [13]. Familial cases occur in approximately 10% [14,15]; relatives of patients with SLE also have an increased incidence of SLE and DLE, rheumatoid arthritis, rheumatic fever, polyarteritis nodosa, dermatomyositis and poikiloderma atrophicans vasculare [16].

The condition tends to occur in early adult life, and the peak age of onset of the first symptom or sign in females is approximately 38 years (35.5 in black women, and 40.7 in white women); it is 44.2 in men [17]. The incidence of the disease is the same in all age ranges, although serositis and Sjögren's syndrome are more common disease manifestations in the elderly [18]. Most authors agree that females outnumber males by a ratio of approximately 8:1, but the features in males are the same as in females [19].

Table 51.9 American Rheumatism Association criteria for diagnosis of systemic lupus erythematosus.

1	Malar rash
2	Discoid rash
3	Photosensitivity
4	Oral ulcers
5	Non-erosive arthritis
6	Serositis—pleurisy or pericarditis
7	Renal disorder—persistent proteinuria (>0.5 g/day) or cellular casts
8	Neurological disorder—seizures or psychosis
9	Haematological disorder—haemolytic anaemia or leukopenia (<4000/mm) or lymphopenia (<1500/mm) or thrombocytopenia (<100 000/mm)
10	Immunological disorder—LE cells or anti-DNA antibody or anti-Sm antibody or false-positive serology for syphilis (longer than 6 months)
11	Antinuclear antibodies

LE, lupus erythematosus.

References

1 Wallace DJ, Hahn BH, eds. *Dubois' Lupus Erythematosus*, 4th edn. Philadelphia: Lee and Febiger, 1993.
2 Rowell NR. The natural history of lupus erythematosus. *Clin Exp Dermatol* 1984; **9**: 217–31.
3 Siegel M, Holley HL, Lee SL. Epidemiologic studies on systemic lupus erythematosus. *Arthritis Rheum* 1970; **13**: 802–11.
4 Ballou SP, Khan MA, Kushner I. Clinical features of systemic lupus erythematosus. *Arthritis Rheum* 1982; **25**: 55–60.
5 Hart HH, Grigor RR, Caughey DE. Ethnic difference in the prevalence of systemic lupus erythematosus. *Ann Rheum Dis* 1983; **42**: 529–32.
6 Segel M, Seelenfreund M. Racial and social factors in systemic lupus erythematosus. *JAMA* 1965; **191**: 77–80.
7 Serdula MK, Rhoads GG. The frequency of systemic lupus erythematosus in different groups in Hawaii. *Arthritis Rheum* 1979; **22**: 328–33.
8 Siegel M, Reilly EB, Lee SL *et al*. Epidemiology of systemic lupus erythematosus: time trend and racial differences. *Am J Public Health* 1964; **54**: 33–43.

9 Siegal M, Lees SL. The epidemiology of systemic lupus erythematosus. *Semin Arthritis Rheum* 1973; **3**: 1–54.
10 Hochberg MC. Prevalence of systemic lupus erythematosus in England and Wales, 1981–2. *Ann Rheum Dis* 1987; **46**: 664–6.
11 Woo J, Wong RWS, Wang SWS *et al.* Patterns of rheumatoid arthritis and systemic lupus erythematosus in Hong Kong. *Ann Rheum Dis* 1987; **46**: 644–5.
12 Hochberg MC, Perlmutter DL, Medsger TA *et al.* Prevalence of self-reported physician diagnosed systemic lupus erythematosus in the USA. *Lupus* 1995; **4**: 454–6.
13 Johnson AE, Gordon C, Palmer RG *et al.* The prevalence and incidence of systemic lupus erythematosus in Birmingham, England. *Arthritis Rheum* 1995; **38**: 551–8.
14 Arnett FC, Shulman LE. Studies in familial systemic lupus erythematosus. *Medicine* 1976; **55**: 313–22.
15 Reveille JD, Bias WB, Winkelstein JA *et al.* Familial lupus erythematosus: immunogenetic studies in eight families. *Medicine* 1983; **62**: 21–35.
16 Tuffanelli DL, Dubois EL. Cutaneous manifestations of systemic lupus erythematosus. *Arch Dermatol* 1964; **90**: 377–86.
17 Hochberg MC. The incidence of systemic lupus erythematosus in Baltimore, Maryland, 1970–77. *Arthritis Rheum* 1985; **28**: 80–6.
18 Jonsson H, Nived O, Sturfelt G. The effect of age on clinical and serological manifestations in unselected patients with systemic lupus erythematosus. *J Rheumatol* 1988; **15**: 505–9.
19 Miller MH, Urowitz MB, Gladman DD. Systemic lupus erythematosus in males. *Medicine* 1983; **62**: 327–34.

Aetiology. The aetiology of SLE remains unknown. Aetiological theories must account for the known variations in the incidence of the disease, the marked immune dysfunction, known precipitating factors and the clear familial predisposition.

Genetic factors. There is considerable evidence to suggest that genetic factors play a part in the pathogenesis [1]. The condition has been reported in identical twins [2,3], with a concordance rate of 65% [2]. Of all cases, 4% are familial [4], with marked concordance of disease expression between parents and offspring. The onset of SLE in identical twins occurred within 2 years, compared with an interval of 9 years between siblings and 20 years between parents and offspring [5]. However, the onset of disease in siblings is temporally rather than age-related, indicating a possible environmental factor [6]. Occasionally, identical twins may be discordant for SLE. In this case, the non-affected twin does not have abnormalities of helper and suppressor T-cell numbers and activity, and has different cellular immune responses [7,8]. The incidence of SLE is probably higher in XXY males with Klinefelter's syndrome [9]. Relatives of patients with SLE have a higher incidence of connective tissue disease, hyperglobulinaemia and antinuclear factor than the relatives of matched controls [10,11]. They may also show increased incidence of anti-RNA and lymphocytotoxic antibodies, specific anti-DNA antibody idiotypes [12], anticardiolipin antibodies [13] and impaired suppressor T-lymphocyte function [14], although these are not related to disease expression [15].

Studies of histocompatibility antigens further support a genetic predisposition. White people with SLE have increased frequencies of HLA-B8 [16], -DR3, -A1 and -DR2 [17]. Similar associations have been confirmed in black people [18,19], as has an association with immunoglobulin allotypes Gm 1 and 17 [20]. HLA-DQ antigens may be even more closely related to the risk of developing the disease, and different alleles may be implicated in the risk of developing the disease from those that influence its expression [21]. There is evidence of linkage disequilibrium between B8-DR3 and alleles at the DQ locus, which is prevalent in patients who express anti-Ro antibodies [22].

Eighty per cent of patients (compared with 40% of controls) have null complement alleles [23], mainly at the C4A or B locus [24]. HLA-DR2 and the C4A null allele are independent and additive risk factors in SLE [25]. Deficiency of complement factors C5–9 is relatively common in familial cases of SLE. Genetic factors other than HLA and complement component deficiencies may also be involved [26]. The results of genome scanning of family pedigrees multiplex for SLE, including over 400 sib pairs and 175 affected relatives, suggest an epistatic interaction between chromosome 14p16–15.2 and chromosome 5p15 in European American families [27].

References

1 Criswell LA. The genetic contribution to systemic lupus erythematosus. *Bull NYU Hosp Jt Dis* 2008; **66**: 176–83.
2 Block SR, Winfield JB, Lockshin MD *et al.* Studies of twins with systemic lupus erythematosus. *Am J Med* 1975; **59**: 533–52.
3 Block SR, Lockshin MD, Winfield JB *et al.* Immunologic observations on nine sets of twins either concordant or discordant for SLE. *Arthritis Rheum* 1976; **19**: 545–54.
4 Estes D, Christian CL. The natural history of systemic lupus erythematosus by prospective analysis. *Medicine* 1971; **50**: 85–95.
5 Alvarellos A, Ahearn JM, Provost TT *et al.* Relationships of HLA-DR and MT antigens to autoantibody expression in systemic lupus erythematosus. *Arthritis Rheum* 1983; **26**: 1533–4.
6 Kaplan D. The onset of disease in twins and siblings with systemic lupus erythematosus. *J Rheumatol* 1984; **11**: 648–52.
7 Brunner CM, Horwitz DA, Shan MK *et al.* Clinical and immunologic studies in identical twins discordant for systemic lupus erythematosus. *Am J Med* 1973; **55**: 249–54.
8 Soppi E, Eskola J, Lehtonen A. Evidence against HLA and immunological dependence of disease outbreak in SLE: immunological characterization of identical twins clinically discordant for SLE. *Ann Rheum Dis* 1985; **44**: 45–9.
9 Burch PRJ, Rowell NR. Systemic lupus erythematosus and Klinefelter's syndrome. *Lancet* 1976; **i**: 1021.
10 Leonhardt T. Family studies in systemic lupus erythematosus. *Acta Med Scand* 1964: **176** (Suppl.): 416.
11 Lowenstein MB, Rothfield NF. Family study of systemic lupus erythematosus. *Arthritis Rheum* 1977; **20**: 1293–303.
12 Isenberg DA, Shoenfeld Y, Walport M *et al.* Detection of crossreactive anti-DNA antibody idiotypes in the serum of systemic lupus erythematosus patients and of their relatives. *Arthritis Rheum* 1985; **28**: 999–1007.
13 Mackworth-Young C, Chan J, Harris N *et al.* High incidence of anticardiolipin antibodies in relatives of patients with systemic lupus erythematosus. *J Rheumatol* 1987; **14**: 723–6.
14 Miller KB, Schwartz RS. Familial abnormalities of suppressor-cell function in systemic lupus erythematosus. *N Engl J Med* 1979; **301**: 803–9.
15 Dudeney C, Shoenfeld Y, Rauch J *et al.* A study of anti-poly (ADP-ribose) antibodies and an anti-DNA antibody idiotype and other immunological abnormalities in lupus family members. *Ann Rheum Dis* 1986; **45**: 502–7.
16 Millard LG, Rowell NR, Rajah SM. Histocompatibility antigens in discoid and systemic lupus erythematosus. *Br J Dermatol* 1977; **96**: 139–44.
17 Walport MJ, Black CM, Batchelor JR. The immunogenetics of SLE. *Clin Rheum Dis* 1982; **8**: 3–21.
18 Goldberg MA, Arnett FC, Bias WB *et al.* Histocompatibility antigens in systemic lupus erythematosus. *Arthritis Rheum* 1976; **19**: 129–32.
19 Kachru RAJB, Sequeira W, Mittal KK *et al.* A significant increase of HLA-DR3 and DR2 in systemic lupus erythematosus among Blacks. *J Rheumatol* 1984; **11**: 471–4.
20 Fielder AHL, Walport MJ, Batchelor JR *et al.* Family study of the major histocompatibility complex in patients with systemic lupus erythematosus: import-

ance of null alleles of C4A and C4B in determining disease susceptibility. *BMJ* 1983; **286**: 425–8.
21 Harley JB, Sestak AL, Willis LG *et al.* A model for disease heterogeneity in systemic lupus erythematosus. *Arthritis Rheum* 1989; **32**: 826–36.
22 Reveille JD, Macleod MJ, Whittington K *et al.* Specific amino acid residues in the second hypervariable region of HLA-DQA1 and DQB1 chain genes promote the Ro (SS-A)/La autoantibody responses. *J Immunol* 1991; **146**: 3871–6.
23 Foad B, Litwin A, Zimmer H *et al.* Acetylator phenotype in systemic lupus erythematosus. *Arthritis Rheum* 1977; **20**: 815–8.
24 Fedrick JA, Pardey JP, Chen Z *et al.* Gm allotypes in blacks with systemic lupus erythematosus. *Hum Immunol* 1983; **8**: 177–81.
25 Howard PF, Hochberg MC, Bias WB *et al.* Relationship between C4 null genes, HLA-D region antigens, and genetic susceptibility to systemic lupus erythematosus in caucasian and black Americans. *Am J Med* 1986; **81**: 187–93.
26 Reveille JD, Bias WB, Winkelstein JA *et al.* Familial systemic lupus erythematosus: immunogenetic studies in eight families. *Medicine* 1983; **62**: 21–35.
27 Gray-McGuire C, Moser KL, Gaffney PM *et al.* Genome scan of human systemic lupus erythematosus by regression modeling: evidence of linkage and epistasis at 4p16–15.2. *Am J Hum Genet* 2000; **67**: 1460–9.

Autoantibodies [1,2]. Non-organ-specific humoral autoantibodies are the hallmark of SLE. A range of autoantibodies may be present in the disease, although some are more disease-specific (anti-double-stranded DNA and anti-Sm antibodies), and some are much more commonly found (antinuclear and anti-Ro antibodies). The disease could be produced by the development of such antibodies against tissue antigens to which tolerance has been lost by failure of homeostatic immunological mechanisms. This could occur either because of polyclonal B-cell activation or specific antigenic drive. There is evidence for both mechanisms of production of autoantibodies [3]. There is also considerable evidence that such non-organ-specific autoantibodies are not the primary pathogens: they are not specific to any disease, they are not present in all cases, their titres are independent of the activity of the disease, they are transmitted across the placenta without apparently harming the fetus [4] and they can be transfused into human volunteers without causing any apparent disease. In animal models, however, antinuclear antibodies can intensify experimental inflammatory lesions [5]; there is also evidence for involvement of immune complexes containing antinuclear antibody (either deposited or formed *in situ*) in the renal lesion of SLE as well as in tissue damage in other sites [6]. Recent evidence suggests that these antibodies may be formed against DNA-containing debris which is packaged into a vesicle after cells have undergone apoptosis, so-called 'apoptotic bodies' [7,8]. Anti-DNA antibodies bind the DNA receptor on white blood cells and block the binding and sequestration of free DNA by mononuclear cells [9]. These antibodies also produce the release of IFN-γ from mononuclear cells, enhancing immunological and inflammatory reactions [10]. Anti-Ro or closely related antibodies are implicated in the development of the rash and heart block found in neonatal LE (see p. 51.49), and possibly in other childhood SLE. The antiphospholipid antibodies, including the so-called lupus anticoagulant, are linked to thrombosis and abortion in patients with SLE (see p. 51.48). Conversely, neurofilament autoantibodies occur in 21% of patients with SLE, but do not correlate with neurological involvement [11]. Antiribosomal P proteins are highly specific for lupus psychosis [12]. Recent evidence suggests that there is switching of antibody types between the active and quiescent stages of the disease, with low-affinity IgM antibodies present when the disease is controlled, and high-affinity IgG, often directed against endothelial cells, being present when the disease is active [13]. Antiendothelial cell antibodies are associated with renal and vascular complications [14].

Idiotypes and anti-idiotypes [15]. Idiotypes are the antigenic determinants of immunoglobulin molecules and are found in the variable region of these molecules and the T-cell receptor. Antibodies to these antigens develop (anti-idiotype antibodies), and are themselves capable of stimulating anti-anti-idiotype antibodies. Thus, complicated networks of antibodies develop, which are involved in the mechanisms of autoimmunity and self-recognition. Anti-idiotype antibodies may have some of the capabilities of the original antigen, and may also cross-react with other self-antigens, interfering with the development of tolerance produced by the removal of self-reactive T cells. This interference would allow the development of the 'forbidden clones' originally predicted by Burch and Rowell [16]. Cross-reaction between self-antigens and those derived from extraneous sources such as infection or other environmental agents may provide the original source of anti-idiotype antibodies [17].

References

1 Alarcón-Segoviá D. The pathogenesis of immune dysregulation in systemic lupus erythematosus. A Troika. *J Rheumatol* 1984; **11**: 588–90.
2 Beck JS, Rowell NR. Discoid lupus erythematosus: a study of the clinical features and biochemcial and serological abnormalities in 120 patients with observations on the relationship of this disease to systemic lupus erythematosus. *QJM* 1966; **35**: 119–36.
3 Hardin JA. The lupus autoantigens and the pathogenesis of systemic lupus erythematosus. *Arthritis Rheum* 1986; **29**: 457–60.
4 Beck JS, Oakley CL, Rowell NR. Transplacental passage of antinuclear antibody. *Arch Dermatol* 1966; **93**: 656–63.
5 Hughes P, Rowell NR. Aggravation of turpentine-induced pleurisy in rats by 'homogeneous' and 'speckled' antinuclear antibodies. *J Pathol* 1970; **101**: 141–55.
6 Brentjens J, Ossie E, Albini B *et al.* Disseminated immune deposits in lupus erythematosus. *Arthritis Rheum* 1977; **20**: 962–8.
7 Lorenz HM, Herrmann M, Winkler T *et al.* Role of apoptosis in autoimmunity. *Apoptosis* 2000; **5**: 443–9.
8 Schmidt-Acevedo S, Perez-Romano B, Ruiz-Arguelles A. 'LE cells' result from phagocytosis of apoptotic bodies induced by antinuclear antibodies. *J Autoimmun* 2000; **15**: 15–20.
9 Bennett RM, Peller JS, Merritt MM. Defective DNA-receptor function in systemic lupus erythematosus and related diseases: evidence for an autoantibody influencing cell physiology. *Lancet* 1986; **i**: 186–8.
10 Ramirez F, Williams RC, Sibbitt WL *et al.* Immunoglobulin from systemic lupus erythematosus serum induces interferon release by normal mononuclear cells. *Arthritis Rheum* 1986; **29**: 326–36.
11 Kurki P, Helve T, Dahl D *et al.* Neurofilament autoantibodies in systemic lupus erythematosus. *J Rheumatol* 1986; **13**: 69–73.
12 Teh LS, Isenberg DA. Antiribosomal P protein antibodies in systemic lupus erythematosus: a reappraisal. *Arthritis Rheum* 1994; **37**: 307–15.
13 Ehrenstein M, Longhurst C, Isenberg DA. Production and analysis of IgG monoclonal anti-DNA antibodies from systemic lupus erythematosus (SLE) patients. *Clin Exp Immunol* 1993; **92**: 39–45.
14 Cervera R, Khamashta MA, Font J *et al.* Endothelial anticellular antibodies in systemic lupus erythematosus: association with vascular and kidney lesions. *Med Clin (Barc)* 1992; **99**: 605–8.
15 Jerne NK. Towards a network theory of the immune system. *Ann Immunol (Paris)* 1974; **125c**: 373–89.
16 Burch PRJ, Rowell NR. Systemic lupus erythematosus: aetiological aspects. *Am J Med* 1965; **38**: 793–801.
17 George J, Shoenfeld Y. Infection, idiotypes and SLE. *Lupus* 1995; **4**: 333–5.

Other immune factors. Cell-mediated immunity is abnormal in SLE [1]. Lymphocyte transformation responses to common antigens [2] and decreased skin-test responses to purified protein derivative, candidin and streptokinase-dornase [3] are related to disease activity [4]. T-cell counts are diminished [5] and null cells are increased [6] in active disease. It would appear that there is an imbalance between T and B lymphocytes in the disease, with depressed cellular immunity and an overactive humoral antibody response, possibly related to a relative lack of suppressor and/or inducer T cells, although all T-cell types are reduced, and their function is impaired. IL-2 production by peripheral blood leukocytes is impaired, reducing the inhibitory effects of T cells on activated B cells [7].

There is a reduction in activated B cells, but hyperactive B cells are increased in SLE [8], and their differentiation abnormally stimulated by monocytes [9]. There is some evidence that in remission there is a return of immunological suppressor function despite a persisting impairment of T-lymphocyte reactivity [10]. Antibody-dependent cellular cytotoxicity may be another pathogenic factor, and antibodies directed against lymphocyte membranes are found in SLE. Serum-induced cytotoxicity occurs to T cells [11], and immune complexes may be implicated [12]. Circulating immune complexes occur in approximately half of patients, especially those with active and extensive disease [13]. Killer cell activity is increased [14], and complement activation occurs, and the anaphylatoxins C3a and C5a are increased during disease exacerbations, possibly contributing to the pathogenesis of the vascular lesions [15].

References

1 Rönnblom L, Pascual V. The innate immune system in SLE: type I interferons and dendritic cells. *Lupus* 2008; **17**: 394–9.
2 Hughes P, Holt S, Rowell NR *et al.* Relationship of phytohaemagglutinin-induced lymphocyte transformation to disease activity in systemic lupus erythematosus. *Ann Rheum Dis* 1976; **35**: 97–105.
3 Paty JG Jr, Sienknecht CW, Townes AS *et al.* Impaired cell-mediated immunity in systemic lupus erythematosus (SLE): a controlled study of 23 untreated patients. *Am J Med* 1975; **59**: 769–79.
4 Horwitz DA, Cousar JB. A relationship between impaired cellular immunity, humoral suppression of lymphocyte function and severity of systemic lupus erythematosus. *Am J Med* 1975; **58**: 829–35.
5 Hughes P, Holt S, Rowell NR *et al.* Thymus-dependent (T) lymphocyte deficiency in progressive systemic sclerosis. *Br J Dermatol* 1976; **95**: 469–73.
6 Scheinberg MA, Cathcart ES, Goldstein AL. Thymosin-induced reduction of 'null cells' in peripheral-blood lymphocytes of patients with systemic lupus erythematosus. *Lancet* 1975; **i**: 424–6.
7 McKenna RM, Wilkins JA, Warrington RJ. Lymphokine production in rheumatoid arthritis and systemic lupus erythematosus. *J Rheumatol* 1988; **15**: 1639–42.
8 Sakane T, Suzuki N, Takeda S *et al.* B cell hyperactivity and its relation to distinct clinical features and the degree of disease activity in patients with systemic lupus erythematosus. *Arthritis Rheum* 1988; **31**: 80–7.
9 Jandl RC, Adirein TA. Stimulation of B cell differentiation by adherent mononuclear cells in systemic lupus erythematosus. *Arthritis Rheum* 1987; **30**: 861–8.
10 Breshihan B, Jasin HE. Suppressor function of peripheral blood mononuclear cells in normal individuals and in patients with SLE. *J Clin Invest* 1977; **59**: 106–16.
11 Kumagai S, Steinberg AD, Green I. Antibodies to T cells in patients with systemic lupus erythematosus can induce antibody dependent cell-mediated cytotoxicity against human T cells. *J Clin Invest* 1981; **67**: 605–14.
12 Penning CA, Hughes P, Rowell NR. The production of antibody dependent cellular cytotoxicity by immune complexes in systemic lupus erythematosus. *J Clin Lab Immunol* 1984; **13**: 123–7.
13 Hughes P, Cunningham J, Day M *et al.* Immune complexes in systemic sclerosis; detection by C1q binding k-cell inhibition and raji cell radioimmunoassays. *J Clin Lab Immunol* 1983; **10**: 133–8.
14 Blasczyk M, Majewski S, Wasik N *et al.* Natural killer cell activity of peripheral blood mononuclear cells from patients with various forms of lupus erythematosus. *Br J Dermatol* 1987; **117**: 709–14.
15 Belmont MH, Hopkins P, Edelson HS *et al.* Complement activation during systemic lupus erythematosus. *Arthritis Rheum* 1986; **29**: 1085–9.

UV radiation. This may precipitate the onset or exacerbate the course of SLE in up to 60% of patients [1]. Phototesting to UVB and UVA [2] shows reduced minimal erythema doses and the development of skin lesions in patients with LE. The mechanism of action of UV radiation in SLE remains unknown, although antibodies to UV radiation-denatured DNA can be demonstrated. There is no defect of DNA repair in SLE [3], and the antibodies to denatured DNA have no clinical or immunological correlations [4]. The expression of Ro antibody can be induced on cultured keratinocytes by UV radiation [5], and this antibody is commonly found in photosensitive patients. However, there is no relationship between absolute levels of Ro and disease activity [6].

References

1 Werth VP. Cutaneous lupus: insights into pathogenesis and disease classification. *Bull NYU Hosp Jt Dis* 2007; **65**: 200–4.
2 Lehmann P, Holzle E, Kind P *et al.* Experimental reproduction of skin lesions in lupus erythematosus by UVA and UVB radiation. *J Am Acad Dermatol* 1990; **22**: 181–7.
3 Palmer RG, Smith-Burchnell CA, Dore CJ *et al.* Sensitivity of lymphocytes from patients with systemic lupus erythematosus to the induction of sister chromatid exchanges by alkylating agents and bromodeoxyuridine. *Ann Rheum Dis* 1987; **46**: 110–3.
4 Davis P. Antibodies to UV DNA and photosensitivity. *Br J Dermatol* 1977; **97**: 197–200.
5 Le Feber WP, Norris DA, Ryan SS *et al.* Ultraviolet light induces expression of selected nuclear antigens in cultured human keratinocytes. *Clin Invest* 1984; **74**: 1545–51.
6 Purcell SM, Lien JS, Davis BM *et al.* Relationship between circulating anti Ro/SSA antibody levels and skin disease activity in subacute cutaneous lupus erythematosus. *Br J Dermatol* 1987; **117**: 277–87.

Environmental factors. Lupus-like disorders have been reported in association with a variety of environmental factors [1]. Although early reports suggested that silicone breast implants are more frequently associated with connective tissue diseases including lupus-like syndromes, scleroderma, fibrositis, inflammatory myopathy and autoimmune thyroid disease [2], later studies show that the incidence is no higher than in control populations [3]. Haemolytic anaemia with high titres of antinuclear and anti-dsDNA antibodies has followed the ingestion of sprouts, seeds and dietary supplements of alfalfa, which contains the amino acid L-canavanine [4]. Heavy metals including cadmium, mercury and gold have also been associated with autoimmunity [5]. Other industrial factors include silica [6,7] and trichlorethylene [8].

References

1 Love LA. New environmental agents associated with lupus-like disorders. *Lupus* 1994; **3**: 467–71.
2 Sanchez-Guerrero J, Schur PH, Sergent JS *et al.* Silicone breast implants and rheumatic disease: clinical, immunological and epidemiological studies. *Arthritis Rheum* 1994; **37**: 158–68.

3 Edworthy SM, Martin L, Barr SG *et al.* A clinical study of the relationship between silicone breast implants and connective tissue disease. *J Rheumatol* 1998; **25**: 254–60.
4 Montanaro A, Bardana EJ. Dietary amino-acid-induced lupus erythematosus. *Rheum Dis Clin North Am* 1991; **17**: 323–32.
5 Bigazzi PE. Auto-immunity and heavy metals. *Lupus* 1994; **3**: 449–52.
6 Sanchez-Roman J, Wichmann I, Salaberri J *et al.* Multiple clinical and biological autoimmune manifestations in 50 workers after occupational exposure to silica. *Ann Rheum Dis* 1993; **52**: 534–8.
7 Conrad K, Mehlhoin J, Luthke K *et al.* Systemic lupus erythematosus after heavy exposure to quartz dust in uranium mines: clinical and serological characteristics. *Lupus* 1996; **5**: 62–9.
8 Kilburn KH, Warshaw RH. Prevalence of symptoms of systemic lupus erythematosus (SLE) and of fluorescent antinuclear antibodies associated with chronic exposure to trichlorethylene and other chemicals in well waters. *Environ Res* 1992; **57**: 1–9.

Infections, stress, hormonal factors. Other factors may precipitate the onset of SLE, and these include bacterial infection and mental or physical stress. A role for antigens derived from infecting organisms in the generation of anti-idiotype antigens [1] has been suggested, and microbial superantigens may stimulate abnormal T- and B-cell interactions, resulting in the state of autoimmunity found in SLE [2]. Infection is more common in SLE than in those not affected, and depressed generation of serum chemotactic factors may contribute to this increase [3]. Initial phagocytosis by polymorphonuclear neutrophils and macrophages is reduced [4].

As markedly more females than males are affected in early adult life, it has been suggested that endocrine factors may be involved [5]. In addition, 20% of female patients have premenstrual flares of skin disease, and a small number present after initiation of oestrogen-containing contraceptive therapy [6]. Levels of circulating androgens are reduced in women with SLE compared with normal controls [7], and men with SLE have reduced testosterone levels [8], indeed hypogonadism from whatever cause may be an aetiological factor in SLE [9]. Prolactin is an immunoregulator, and is secreted by immunologically active cells, suggesting an autocrine effect [10]. Normal humoral and cellular immune responses are greater in females than in males, but this may be a result of the influence of oestrogen on gene expression, rather than on immune responses [11]. A late menarche is associated with an increased risk of SLE in Japanese patients [12]. There is some evidence that neuroendocrine factors play a part in immunity, which could to some extent explain the influence of stress factors in the disease [13].

References

1 George J, Shoenfeld Y. Infection, idiotypes and SLE. *Lupus* 1995; **4**: 333–5.
2 Friedman SM, Posnett DN, Tumang JR *et al.* A potential role for microbial superantigens in the pathogenesis of systemic autoimmune disease. *Arthritis Rheum* 1991; **34**: 468–80.
3 Clark RA, Kimball HR, Decker JL. Neutrophil chemotaxis in systemic lupus erythematosus. *Ann Rheum Dis* 1974; **33**: 167–72.
4 Landry M. Phagocyte function and cell-mediated immunity in systemic lupus erythematosus. *Arch Dermatol* 1977; **113**: 147–54.
5 Talal N. Sex hormones and modulation of immune response in SLE. *Clin Rheum Dis* 1982; **8**: 23–8.
6 Yell JA, Burge SM. The effect of hormonal changes on cutaneous disease in lupus erythematosus. *Br J Dermatol* 1993; **129**: 18–22.
7 Lahita RG, Bradlow HL, Ginzler E *et al.* Low plasma androgens in women with systemic lupus erythematosus. *Arthritis Rheum* 1987; **30**: 241–8.
8 Lahita RG, Bucala R, Bradlow HL *et al.* Determination of 16α-hydroxyestrone by radioimmunoassay in systemic lupus erythematosus. *Arthritis Rheum* 1985; **28**: 1122–7.
9 Jimenez-Balderas FJ, Tapia-Serrano R, Fonseca ME *et al.* High frequency of association of rheumatic/autoimmune diseases and untreated male hypogonadism with severe testicular dysfunction. *Arthritis Res* 2001; **3**: 362–7.
10 Gutierrez MA, Molina JF, Jara LJ *et al.* Prolactin and systemic lupus erythematosus: prolactin secretion by SLE lymphocytes and proliferative (autocrine) activity. *Lupus* 1995; **4**: 348–52.
11 Denman AM. Sex hormones, auto-immune diseases, and immune responses. *BMJ* 1991; **303**: 2–3.
12 Nagata C, Fujita S, Iwata H *et al.* Systemic lupus erythematosus: a case–control epidemiologic study in Japan. *Int J Dermatol* 1995; **34**: 333–7.
13 Rogers MP, Dubey D, Reich P. The influence of the psyche and the brain on immunity and disease susceptibility: a critical review. *Psychosom Med* 1979; **41**: 147–64.

Viruses. An infective cause for SLE has long been postulated, and the role of acute viral infection has been reviewed recently [1]. The high incidence of antibodies to reovirus double-stranded RNA (70%) [2] and raised titres of antibody to measles and rubella antigens [3], suggest potential viral involvement, but this may be only an expression of T-cell suppression in this disease. There is no evidence of retrovirus infection in SLE [4], but endogenous retroviral DNA sequences are found [5].

References

1 Ramos-Casals M, Cuadrado MJ, Alba P *et al.* Acute viral infections in patients with systemic lupus erythematosus: description of 23 cases and review of the literature. *Medicine (Baltimore)* 2008; **87**: 311–8.
2 Sylvester RA, Attias M, Talal N *et al.* Antibodies to viral and synthetic double-stranded RNA in discoid lupus erythematosus. *Arthritis Rheum* 1973; **16**: 383–7.
3 Laitinen O, Vaheri A. Very high measles and rubella virus antibody titres associated with hepatitis, systemic lupus erythematosus and infectious mononucleosis. *Lancet* 1974; **i**: 194–8.
4 Pelton BK, North M, Palmer RG *et al.* A search for retrovirus infection in systemic lupus erythematosus and rheumatoid arthritis. *Ann Rheum Dis* 1988; **47**: 206–9.
5 Walchner M, Leibmosch C, Messer G, Kind P. Endogenous retroviral sequences as a pathogenic factor in systemic lupus erythematosus. *Hautarzt* 1996; **47**: 502–9.

Drugs. The precipitation of SLE by drugs [1,2], especially the antihypertensive hydralazine, is well known. However, there are features to suggest that drug-induced SLE differs from the spontaneous disease: it is uncommon in black people, it occurs in an older age group, renal and central nervous system involvement are infrequent, antihistone antibodies are frequent, anti-DNA antibodies are absent and serum complement is normal. Hydralazine is known to inhibit binding of complement component C4, and this action, with subsequent lack of control of complement activity, may explain the development of lupus-like syndromes.

Cutaneous involvement in drug-induced SLE may be vasculitic, bullous, erythema multiforme-like or resemble pyoderma gangrenosum. Cases have been reported of hydralazine-induced lupus with Sweet's syndrome [3]. It was thought that the clinical manifestations of drug-induced lupus resolved when the drug was withdrawn, but this is not necessarily so, and patients with hydralazine-induced syndromes may have hyperglobulinaemia and other abnormalities before the administration of hydralazine [4]. Patients who develop antinuclear antibodies during drug treatment need not have the drug stopped unless they have

Table 51.10 Drugs inducing systemic lupus erythematosus-like syndromes.

Acebutolol	Oral contraceptives, including:
Allopurinol	Chlormadinone
Aminoglutethimide	Ethinylestradiol
p-Aminosalicylic acid	Etynodiol diacetate
Atenolol	Medroxyprogesterone
Captopril	Mestranol
Carbamazepine	Norethindrone
Chlorpromazine	Norethisterone
Clobazam	Norethynodrel
Clofibrate	Oxyphenisatin
Co-trimoxazole	Oxprenolol
Diphenylhydantoin	Penicillamine
Ethosuximide	Penicillin
Gold salts	Phenothiazine
Griseofulvin	Phenylbutazone
Guanoxan	Phenytoin
Hydralazine	Pindolol
Hydrochlorothiazide	Piroxicam
Hydroxyurea (hydroxycarbamide)	Practolol
Ibuprofen	Primidone
Infliximab	Procainamide
Interferon	Propranolol
Isonicotinic acid hydrazide	Propylthiouracil
Isoquinazepon	Quinine
Labetalol	Recombinant interferon
Leuprolide acetate	Streptomycin
Lithium carbonate	Sulfasalazine
Methyldopa	Sulphonamides
Methylphenylethylhydantoin	Tertalol
Methylthiouracil	Tetracycline
Methysergide	Timolol eye drops
Minocycline	Trimethadione
Minoxidil	Valproate
Nitrofurantoin	Venocuran
	Vostatin/simvastatin

features of the lupus syndrome [5]. Twenty-four cases of lupus induced by minocycline [6] have been reported. It usually occurs after 2 years of therapy. Patients who require more than 1 year's therapy should have ANA and liver function tests monitored. Other drugs, particularly certain anticonvulsants, are known to precipitate SLE-like syndromes (Table 51.10). The biological agents targeting TNF-α are now well known to produce ANF, and occasionally clinical manifestations of lupus.

Drugs have been implicated in precipitating or activating SLE in 3–12% of cases [7]. There is an increased incidence of HLA-DR4 in drug-induced SLE [8] and the ratio of females to males is 4:1, indicating a possible genetic predisposition. It appears that individuals who are slow acetylators are more likely to develop drug-induced LE or LE-like syndromes [9]. The determination of acetylator type and DR typing may enable susceptible patients to be identified. In spontaneous SLE, however, there appears to be a preponderance of slow acetylators [10], although this is disputed [11].

Antihistone antibodies are not drug-specific, although different drugs do induce antibodies to different histone epitopes, and the antibodies are often present well before clinical manifestations occur [12]. Indeed, 50% of procainamide-treated patients develop immunological abnormalities, whereas only 20% develop clinical disease [13]. Of patients with drug-induced lupus syndromes, 82% have antihistone antibodies, compared with 32% of those with serological changes only [12].

References

1 Vedove CD, Del Giglio M, Schena D, Girolomoni G. Drug-induced lupus erythematosus. *Arch Dermatol Res* 2009; **301**: 99–105.
2 Borchers AT, Keen CL, Gershwin ME. Drug-induced lupus. *Ann N Y Acad Sci* 2007; **1108**: 166–82.
3 Ramsay-Goldman R, Franz T, Solano FX *et al*. Hydralazine induced lupus and Sweet's syndrome. *J Rheumatol* 1990; **17**: 682–4.
4 Blumenkrantz N, Christiansen AH, Ullman S, Asboe-Hansen G. Hydralazine-induced lupoid syndrome. *Acta Med Scand* 1974; **195**: 443–9.
5 Mansilla-Tinoco R, Harland SJ, Ryan PJ *et al*. Hydralazine, antinuclear antibodies and the lupus syndrome. *BMJ* 1982; **284**: 936–9.
6 Knowles SR, Shapiro L, Shear NH. Serious adverse reactions induced by minocycline. *Arch Dermatol* 1996; **132**: 934–9.
7 Lee SL, Rivero I, Siegel M. Activation of systemic lupus erythematosus by drugs. *Arch Intern Med* 1966; **117**: 620–6.
8 Batchelor JR, Welsh KI, Tinoco RM *et al*. Hydralazine-induced systemic lupus erythematosus: influence of HLA-DR and sex on susceptibility. *Lancet* 1980; **i**: 1107–9.
9 Godeau P, Aubert M, Imbert JC *et al*. Lupus erythemateux dissemine et taux d'isoniazide actif: étude de 47 observations. *Ann Intern Med* 1973; **124**: 181–6.
10 Larsson R, Karlsson E, Molin L. Spontaneous systemic lupus erythematosus and acetylator phenotype. *Acta Med Scand* 1977; **201**: 223–6.
11 Harland SJ, Facchini V, Timbrell JA. Hydralazine-induced lupus erythematosus-like syndrome in a patient of the rapid acetylator phenotype. *BMJ* 1980; **281**: 273–4.
12 Rubin RL, Nusinow SR, Johnson AD *et al*. Serological changes during induction of lupus-like disease by procainamide. *Am J Med* 1986; **80**: 999–1002.
13 Blamgren SE. Drug-induced lupus erythematosus. *Semin Hematol* 1973; **10**: 345–9.

Relationship of genetic and environmental factors and autoimmunity [1]. The relationship of genetic factors, possible virus infection and depression of cell-mediated immunity has led to the suggestion that genetic factors might allow virus replication in the thymus and in T cells, inducing damage to these cells and hence defective cellular immunity. The age pattern of the disease and its female predominance suggest that these abnormalities appear to affect only a specific susceptible genotype, involving three dominant X-linked alleles. Phenotypic expression then depends on accumulated randomly occurring changes in lymphoid stem cells, with three 'forbidden' clones of lymphocytes developing [2], and with hyperglobulinaemia and autoantibody formation from hyperactive B cells and the lack of T-cell suppression following. Normal defence mechanisms, which are more effective in females, prevent these changes persisting, but may be impaired by infections, drugs, UV radiation and stress, thus precipitating the disease. Organ involvement is determined by genetically controlled antigenic expression in target tissues. Such a concept would explain the sex differences, the occurrence of clinical and subclinical autoimmune disease and antibodies in the relatives of patients, the apparent spontaneous onset in many cases, and the precipitation and exacerbation of clinical manifestations by factors impairing the defence mechanisms.

Table 51.11 Pathological features of systemic lupus erythematosus.

Macroscopic
Pleurisy
Pericarditis
Libman–Sacks endocarditis
Lymphadenopathy
Splenomegaly
May be none
Microscopic
Immunoglobulins and complement at the dermal–epidermal junction in skin lesions (90%) and uninvolved skin (60%)
Haematoxylin bodies in the endocardium, renal glomeruli and elsewhere
Periarterial fibrosis of the spleen
Wire loop lesions in the kidneys

References

1 Jönsen A, Bengtsson AA, Nived O *et al*. Gene–environment interactions in the aetiology of systemic lupus erythematosus. *Autoimmunity* 2007; **40**: 613–7.

2 Burch PRJ, Rowell NR. Lupus erythematosus: analysis of the sex- and age-distribution of the discoid and systemic forms of the disease in different countries. *Acta Derm Venereol (Stockh)* 1970; **50**: 293–301.

Pathology (Table 51.11). The pathological changes of SLE have been well described. The primary lesions of SLE are fibrinoid necrosis, collagen sclerosis, necrosis and basophilic body formation, and vascular endothelial thickening. The basophilic (haematoxylin) bodies are aggregates of homogeneous material staining blue with haematoxylin and staining positively for DNA by the Feulgen technique. This material is similar to that of the homogeneous nuclear material of the LE cell.

Macroscopic appearances. Despite the widespread clinical manifestations and fatal outcome, it is often disappointing to find no macroscopic changes at autopsy. Sometimes, terminal changes and infection obscure the picture. Frequent macroscopic findings include pleurisy with adhesions and effusion, and pericarditis, especially if the patient has died with uraemia. The verrucose vegetations of Libman–Sacks endocarditis are diagnostic (Fig. 51.27) [1]. These are small firm warty deposits, up to 0.5 cm in diameter, adherent to the valves of both sides of the heart and adjacent endocardium of the ventricles, chordae tendinae and on the papillary muscles. Sometimes, lesions of subacute bacterial endocarditis may be superimposed on the warty lesions.

Microscopic appearances. Usually, pathological diagnosis requires histology, but in some cases histological changes can be demonstrated only by immunohistological techniques (Fig. 51.28) [2]. Immunohistology is also useful in diagnosing SLE in patients with a rash.

Skin. There is no single diagnostic pathological feature in the skin, but a combination of features aids diagnosis [3]. Some changes, such as hyperkeratosis without parakeratosis, and keratotic plugging of the hair follicles and glandular orifices, are similar to those found in chronic DLE. There may also be some atrophy or acanthosis of the prickle cell layer. Liquefaction degeneration of the basal cell layer is common. Epidermal necrolysis has been reported [4]. The dermal tissues may be oedematous, and sometimes vesicle formation occurs at the dermal–epidermal junction, with dilatation of the superficial vessels and perivascular lymphocytic infiltration. Occasionally, dermal mucinosis occurs, especially in papular lesions [5] and in areas of alopecia [6]. Pigment-containing chromatophores may occur in the infiltrate. Sometimes, the infiltrate is widely distributed in the upper portion of the dermis, being most pronounced in the more chronic type of lesions. Using monoclonal antibodies, the infiltrate is shown to consist of abundant T cells and Ia-positive cells, with rather fewer B cells and macrophages. Helper or inducer T cells and suppressor or cytotoxic T cells occur in equal numbers [7]. Fragmentation, splintering and oedema of the elastic tissue occur. Changes in the



Fig. 51.27 Libman–Sacks endocarditis. Note the warty vegetations on the heart valves.

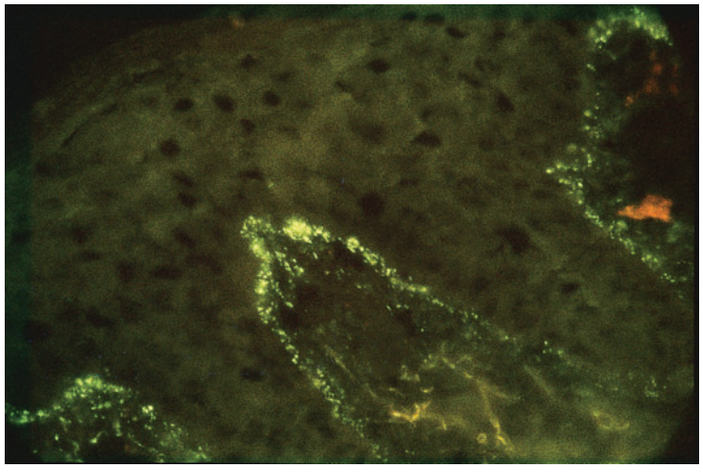


Fig. 51.28 Immunoglobulin at the dermal–epidermal junction in systemic lupus erythematosus.

walls of blood vessels are relatively infrequent, but hyaline changes and fibrinoid degeneration occur.

Immunohistology [8,9]. Immunoglobulins, predominantly IgG, but less frequently IgM and IgA, together with complement (C1, C3) can be demonstrated at the dermal–epidermal junction by immunofluorescence techniques [10,11]. They occur in more than 80% of skin lesions of DLE and SLE, and may be preceded by basement membrane abnormalities in erythematous and purpuric lesions [12]. Deposits occur more frequently in light-exposed areas and are invariably present in acute lesions, although in early and late stages the test may be negative. If IgG, IgM and IgA are all present, the diagnosis of SLE is likely, and the more common combination of IgG and IgM is also suggestive. Single immunoglobulins favour another diagnosis (see DLE). The basement-membrane phenomenon can also be demonstrated in the uninvolved skin in three-quarters of active cases of SLE if the biopsy specimens are taken from the exposed skin, preferably from the dorsum of the wrist or forearm. Biopsy specimens from the unexposed skin are positive in only approximately 50% of cases, which may or may not have more severe renal disease and decreased long-term survival [13,14]. Variability in the presence of immunoglobulins and complement in adjacent sites of both light-exposed and light-protected areas probably accounts for differences between series. Biopsy specimens taken from oedematous areas may be negative. The presence of IgG in unexposed normal skin rarely occurs without SLE, and indicates a poorer prognosis than the presence of IgM or the absence of deposits. An IgM band may be found in other diseases, and without other evidence is not sufficient to make a diagnosis of LE [15]. IgM can be found in 80% of lesion-free sun-exposed skin in patients with actinic keratoses [16]. Deposits also occur in patients without rashes or may be present before other features of LE develop. Positive tests may come and go depending on activity, and decrease after treatment or in remission. Deposits in uninvolved skin may occasionally occur in systemic sclerosis, mixed connective tissue disease, dermatomyositis, anaphylactoid purpura, hypocomplementaemic vasculitis, rheumatoid arthritis, pemphigoid and dermatitis herpetiformis. This basement-membrane phenomenon can also be demonstrated in the uninvolved skin in patients with the so-called transitory type of DLE [17]. This is a subgroup of DLE, described by Baart De La Faille-Kuyper [18], with cutaneous lesions of DLE and immunoglobulins at the dermal–epidermal junction in uninvolved skin, as in SLE, but no definite clinical or serological evidence of the latter. The basement-membrane phenomenon is negative in uninvolved skin in other cases of DLE. The staining may be homogeneous or granular, or there may be larger aggregates under the dermal–epidermal zone [19]. Burnham and Fine describe homogeneous, thready and stippled patterns [20], which are different from the 'tubular' band of bullous pemphigoid [21]. The stippled band occurs in uninvolved skin, thready bands in new lesions and homogeneous bands in older chronic lesions. The band type depends on the type of skin lesion and does not distinguish between DLE and SLE. The presence of complement at the dermal–epidermal junction in patients with widespread SLE without renal disease may be associated with a lowering of the serum complement [22]. Both fibrin and properdin have been demonstrated in the lesions of SLE [23]. Properdin deposition in normal skin appears to correlate with disease activity [24]. The presence of properdin suggests that the alternative pathway of complement activation is involved, but nevertheless the classical pathway is the primary complement pathway involved in SLE. In drug-induced SLE, deposits of IgG, IgM and C3 at the dermal–epidermal junction may disappear when clinical symptoms regress [25].

Epidermal nuclear deposits, usually giving a speckled IgG pattern, occur in the basal epidermal nuclei and cells of the lower epidermis in nearly one-third of patients [26]. Immunoglobulin (IgG, IgA and IgM), with or without complement, can be found in the walls of blood vessels in skin lesions and uninvolved skin. There may be homogeneous fluorescence of the subendothelial part of the vessel wall, or intramural or perivascular granular fluorescence, and these changes are present in discoid, transitory and systemic LE. Homogeneous staining occurs in the uninvolved skin of 20% of patients with DLE and over 80% of patients with transitory or systemic LE. Electron microscopy of involved and uninvolved skin has shown deposits of proteins on the dermal side of the dermal–epidermal junction and in small blood vessels, resembling morphologically those present in 'wire-loop' lesions in the kidney [27].

Internal organs. The characteristic microscopic features in the internal organs include haematoxylin bodies in the heart valves and elsewhere, periarterial fibrosis of the spleen, and the so-called 'wire-loop' lesions in the kidneys. In the heart, microscopic changes, including fibrinoid necrosis, may occur in normal-looking valves. The vegetations of Libman–Sacks endocarditis [1] occur in 50% of cases coming to autopsy [28], and arise from proliferation of ground substance and connective tissue cells [29], which raise the endothelium. Focal necrosis occurs in these areas, and basophilic bodies are frequently seen. Later, infiltration with inflammatory cells occurs, together with fibrosis. Focal atrophy and fibrosis occur in the myocardium, but myocarditis is unusual.

The lungs frequently show pulmonary oedema and infective changes, but specific abnormalities are uncommon. Pulmonary parenchymal lesions or pleuritis occurred in 18% of one series [30], and other findings included interstitial fibrosis, pulmonary vasculitis, haematoxylin bodies and pneumonitis. A mucinous basophilic oedema of the alveolar walls occurs, with a hyaline alveolar lining membrane similar to hyaline membrane disease of the newborn. Alveolar wall thickening and vascular changes similar to those of Hamman–Rich syndrome may be found.

The liver may show infiltration of the portal tracts with lymphocytes, histiocytes and plasma cells. The so-called 'onion skin' appearance in the spleen is caused by concentric periarterial fibrosis around central and penicilliary arteries.

The lymph-node enlargement is usually associated with retention of normal architecture, but sometimes necrosis and haematoxylin bodies may be found.

The so-called 'wire-loop' appearance in the kidneys is caused by thickening and hyalinization of the capillary basement membrane of the glomerular tufts. Although this change may be seen in other diseases such as systemic sclerosis, chronic glomerulone-

phritis and malignant nephrosclerosis, the changes in SLE are more likely to be localized to one part of the glomerulus. Thickening of the glomerular capillary basement membrane and alterations in reticular tissue in the media of arterioles are associated with deposits of IgG and C3 [31]. Lupus nephritis has been divided into three types [32]: focal proliferative (lupus glomerulitis) and membranous, which are relatively benign, and diffuse proliferative (lupus) glomerulonephritis, which has a poor prognosis. In focal proliferative nephritis, a mild proliferation is confined to parts of some of the glomeruli and electron microscopy shows no electron-dense material. In membranous lupus nephropathy, there is irregular thickening of the glomerular basement membrane with epimembranous deposition of electron-dense material. The most common renal disorder is diffuse proliferative nephritis, in which there is irregular endothelial cell proliferation, fibrinoid necrosis, hyaline thrombi and interstitial inflammatory changes. Electron-dense deposits are seen on electron microscopy in subendothelial, subepithelial and mesangial areas. Heavy proteinuria with large numbers of red and white cells and casts in the urine suggests glomerulonephritis [33]. Although most cases of the nephrotic syndrome and renal vein thrombosis show membranous glomerulonephritis, focal proliferative glomerulonephritis has also been reported [34].

Germinal centres in the thymus are frequently increased [35]. Abnormal epithelial hyperplasia in the thymus is said to occur in all cases of SLE, but the change is not specific [36].

There may be evidence of widespread vasculitis in other organs and in the central nervous system. Although the vasculitis in the nervous system is usually mild, it can be florid [37]. Gammaglobulin deposits and complement have been found in the choroid plexus when immunohistology of the cerebrum, cerebellum and brainstem has shown no abnormality [38]. This, together with the finding of low cerebrospinal fluid complement levels [39], suggests an immune-complex pathogenesis for the involvement of the central nervous system.

References

1 Libman E, Sacks B. A hitherto undescribed form of valvular and mural endocarditis. *Arch Intern Med* 1924; **33**: 701–38.
2 Rowell NR. Laboratory abnormalities in the diagnosis and management of lupus erythematosus. *Br J Dermatol* 1971; **84**: 210–6.
3 McCreight WG, Montgomery H. Cutaneous changes in lupus erythematosus. *Arch Dermatol Syphilol* 1950; **61**: 1–11.
4 Pinol-Aguadé J, Palou J, Lecha M, Castel T. Focal epidermal necrolysis: a variation of lupus erythematosus or a new disease? *Med Cutan Ibero Lat Am* 1977; **5**: 1–11.
5 Revier J, Kienzler JL, Blanc D *et al.* Mucinose papuleuse et lupus erythemateux. *Ann Dermatol Vénéréol* 1982; **109**: 331–8.
6 Lee WS, Chung J, Ahn SK. Mucinous lupus alopecia associated with papulonodular mucinosis as a new manifestation of lupus erythematosus (Letter). *Int J Dermatol* 1996; **35**: 72–3.
7 Synkowksi DR, Provost TT. Characterization of the inflammatory infiltrate in lupus erythematosus lesions using monoclonal antibodies. *J Rheumatol* 1983; **10**: 920–4.
8 Dahl MV. Usefulness of direct immunofluorescence in patients with lupus erythematosus. *Arch Dermatol* 1983; **119**: 1010–7.
9 Monroe EW. Lupus band test. *Arch Dermatol* 1977; **113**: 830–4.
10 Co-operative study. Uses for immunofluorescence tests of skin and sera. *Arch Dermatol* 1975; **111**: 371–81.
11 Tuffanelli DL. Cutaneous immunopathology. *J Invest Dermatol* 1975; **65**: 143–53.
12 Rowell NR, Scott DG. Immunohistological studies, with anti-connective tissue and anti-immunoglobulin antisera, of the skin in lupus erythematosus and scleroderma. *Br J Dermatol* 1975; **93**: 431–41.
13 Davis BM, Gilliam JN. Prognostic significance of subepidermal immune deposits in uninvolved skin of patients with systemic lupus erythematosus: a 10-year longitudinal study. *J Invest Dermatol* 1984; **83**: 242–7.
14 Wertheimer D, Barland P. Clinical significance of immune deposits in the skin in SLE. *Arthritis Rheum* 1976; **19**: 1249–55.
15 Wojnarowska F, Bhogal B, Black MM. The significance of an IgM band at the dermo-epidermal junction. *J Cutan Pathol* 1986; **13**: 359–62.
16 Gruschwitz M, Keller J, Hornstein OP. Deposits of immunoglobulins at the dermo-epidermal junction in chronic light-exposed skin: what is the value of the lupus band test? *Clin Exp Dermatol* 1988; **13**: 303–8.
17 Baart De La Faille-Kuyper EH. *Grafisch Bedriff*. Utrecht: Schotanus, Jens, 1969.
18 Baart De La Faille-Kuyper EH. *In vivo* nuclear localization of immunoglobulins in clinically normal skin in systemic and procainamide-induced LE. *Neth J Med* 1974; **17**: 58.
19 Tuffanelli DL. Dermal-epidermal junction in lupus erythematosus. *Arch Dermatol* 1969; **99**: 652–62.
20 Burnham TK, Fine G. The immunofluorescent 'band' test for lupus erythematosus. I. Morphologic variations of the band of localized immunoglobulins at the dermal-epidermal junction in lupus erythematosus. *Arch Dermatol* 1969; **99**: 413–20.
21 Burnham TK, Fine G. The immunofluorescent 'band' test for lupus erythematosus. 3. Employing clinically normal skin. *Arch Dermatol* 1971; **103**: 24–32.
22 Marshall DA, Nesbitt LT, Biundo JJ. Serum complement related to skin lesions of SLE. *South Med J* 1974; **67**: 1275–9.
23 Jordon RE, Schroeter AL, Winkelmann RK. Dermal-epidermal deposition of complement components and properdin in systemic lupus erythematosus. *Br J Dermatol* 1975; **92**: 263–71.
24 Schrager MA, Rothfield NF. Clinical significance of serum properdin level and properdin deposition in the dermal–epidermal junction in systemic lupus erythematosus. *J Clin Invest* 1976; **57**: 212–21.
25 Ullman S, Wiik A, Kobayasi T *et al.* Drug-induced lupus erythematosus syndrome. *Acta Derm Venereol (Stockh)* 1974; **54**: 387–90.
26 Ze-Yi Chen, Dobson RL, Ainsworth SK *et al.* Epidermal nuclear immunofluorescence: serological correlations supporting an *in vivo* reaction. *Br J Dermatol* 1985; **112**: 15–22.
27 Grishman E, Churg J. Ultrastructure of dermal lesions in systemic lupus erythematosus. *Lab Invest* 1970; **22**: 189–97.
28 Bulkley BH, Roberts WC. The heart in systemic lupus erythematosus and the changes induced in it by corticosteroid therapy. *Am J Med* 1975; **58**: 243–64.
29 Gardner DL. *Pathology of the Connective Tissues*. London: Arnold, 1965.
30 Haupt HM, Moore GW, Hutchins GH. The lung in systemic lupus erythematosus. *Am J Med* 1981; **71**: 791–8.
31 Scott DG, Rowell NR. Immunohistological studies of the kidney in systemic lupus erythematosus and systemic sclerosis using antisera to IgG, C3 fibrin and human renal glomeruli. *Ann Rheum Dis* 1974; **33**: 473–81.
32 Baldwin DS, Lowenstein J, Rothfield NF *et al.* The clinical course of proliferative and membranous forms of lupus nephritis. *Ann Intern Med* 1970; **73**: 929–42.
33 Pollak VE, Pirani CL. Renal histologic findings in systemic lupus erythematosus. *Mayo Clin Proc* 1969; **44**: 630–44.
34 Millet VG, Usera G, Alcazardelaossa JM *et al.* Renal vein thrombosis, nephrotic syndrome and focal lupus glomerulonephritis. *BMJ* 1978; **i**: 24–5.
35 Mackay IR, Degail P. Thymic 'germinal centres' and plasma cells in systemic lupus erythematosus. *Lancet* 1963; **ii**: 667.
36 Hutchins GM, Harvey AM. The thymus in systemic lupus erythematosus. *Bull Johns Hopkins Hosp* 1964; **115**: 355–78.
37 Bunning RD, Laureno R, Barth WF. Florid central nervous system vasculitis in a fatal case of systemic lupus erythematosus. *J Rheumatol* 1982; **9**: 735–8.
38 Gershwin ME, Hyman LR, Steinberg AD. The choroid plexus in CNS involvement of systemic lupus erythematosus. *J Pediatr* 1975; **87**: 588–90.
39 Petz LW, Sharp GC, Cooper NR *et al.* Serum and cerebral spinal fluid complement and serum autoantibodies in systemic lupus erythematosus. *Medicine* 1971; **50**: 259–75.

Clinical features. See Table 51.12 for an analysis of the clinical features of several series.

Table 51.12 Clinical features of systemic lupus erythematosus.

Clinical feature	Percentage
Fever	90
Arthritis and arthralgia	90
Skin lesions	80
Renal involvement	67
Lymphadenopathy	50
Pleurisy	40
Raynaud's phenomenon	35
Pericarditis	25
Hepatomegaly	25
Central nervous system involvement	25
Abdominal symptoms	20
Splenomegaly	15

Presenting symptoms. The disease may affect many systems of the body, and the presentation and course are by no means uniform. Large series of cases have been reported [1–8], including one from the Far East [9]. The subject has been reviewed [8,10]. Despite the female sex predominance, clinical gender differences are not found, although men may be more liable to fits and renal failure [11].

The initial manifestations vary. In one series of 200 cases, the first changes were articular in 58% and cutaneous in 13.5% [12]. Presentation with renal abnormalities, psychiatric disturbances, pericarditis, pleurisy, abdominal pain and pyrexia of uncertain origin are less common.

In fulminating cases, there is usually marked constitutional disturbance, with fever, loss of weight, anorexia, malaise and joint pains; the skin may be involved later, if at all. On the other hand, the evolution can be gradual, starting with localized skin lesions and systemic involvement developing later. Fatigue is a prominent symptom, both at presentation and subsequently [13]. The diagnosis in many cases is made only by considering the condition in a patient with an obscure illness. As most cases are females, sex is an important diagnostic point. Although weight loss is a feature in nearly 50% of the cases, some patients may gain weight, and 18% actually did so in the Leeds series, which included several patients with long histories. Menstruation is irregular in 18% and absent in 75%. The onset in 15% of females is after the menopause. Sometimes, there is a previous history of sensitivity to drugs such as penicillin, gold or sulphonamides. Raynaud's phenomenon occurs in the course of the illness in approximately 35% of patients, and others frequently have chilblains and a poor peripheral circulation. Approximately 2% of patients with Raynaud's phenomenon eventually develop SLE. Sometimes, there may be other apparent precipitating factors, such as exposure to the sun, stress, trauma and infection. Rarely, hypothermia may occur, often precipitated by therapy [14].

References

1 Dubois EL, Tuffanelli DL. Clinical manifestations of systemic lupus erythematosus. *JAMA* 1964; **190**: 104–11.

2 Fries JF, Holman HR. Systemic lupus erythematosus: a clinical analysis. *J Invest Dermatol* 1976; **67**: 554–5.

Table 51.13 Cutaneous features of systemic lupus erythematosus in 73 patients. (From Yell *et al.* [2].)

Cutaneous feature	Percentage
Butterfly rash	51
Facial oedema	4
Subacute cutaneous LE	7
Chronic discoid LE	25
Scarring DLE alopecia	14
Non-scarring alopecia	40
Chilblain lupus	20
Mouth ulceration	31
Bullous eruptions	8
Photosensitivity	63
Raynaud's phenomenon	60
Chronic urticaria (>36 h)	44
Cutaneous vasculitis	11
Livedo reticularis	4
Episcleritis	4
Cheilitis	4

DLE, discoid lupus erythematosus; LE, lupus erythematosus.

3 Grigor R, Edmonds J, Lewkonia R *et al.* Systemic lupus erythematosus: a prospective analysis. *Ann Rheum Dis* 1978; **37**: 121–8.

4 Harvey AM, Shulman LE, Tumulty PA *et al.* Systemic lupus erythematosus: review of the literature and clinical analysis of 138 cases. *Medicine* 1954; **33**: 291–437.

5 Larson DL. *Systemic Lupus Erythematosus*. London: Churchill, 1961.

6 Lee P, Urowitz MB, Bookman AAM *et al.* Systemic lupus erythematosus: a review of 110 cases with references to nephritis, the nervous system, infections, aseptic necrosis and prognosis. *QJM* 1977; **46**: 1–32.

7 Ropes MW. *Systemic Lupus Erythematosus*. Cambridge, MA: Harvard University Press, 1976.

8 Wallace DJ, Hahn BH, Quismorio FP, Klinenberg JR, eds. *Dubois' Lupus Erythematosus*, 7th edn. Philadelphia: Lippincott Williams & Wilkins, 2007.

9 Tay CH, Khoo OT. Neurological involvement in systemic lupus erythematosus. *Singapore Med J* 1971; **12**: 18–23.

10 Klippel JH, ed. Systemic lupus erythematosus. *Rheum Dis Clin North Am* 1988; **14**: 1.

11 Ward MM, Studenski S. Systemic lupus erythematosus in men: a multivariate analysis of gender differences in clinical manifestations. *J Rheumatol* 1990; **17**: 220–4.

12 Smolen JS, Zielinski CC. *Systemic Lupus Erythematosus*. Berlin: Springer-Verlag, 1987.

13 Krupp LB, LaRocca NG, Muir J, Steinberg AD. A study of fatigue in systemic lupus erythematosus. *J Rheumatol* 1990; **17**: 1450–2.

14 Kugler SL, Costakos DT, Aron AM, Spiera H. Hypothermia and systemic lupus erythematosus. *J Rheumatol* 1990; **17**: 680–1.

Skin. Approximately 80% of cases have a rash at some stage, and in up to 25% it is the presenting sign [1]. The prevalence varies between series. Findings from a typical UK population are shown in Table 51.13 [2].

The cutaneous changes may be broadly divided between: (i) those specific for LE, and showing the characteristic histopathological appearances of LE; and (ii) those that are less specific in their origin and not showing LE histological changes. Many of these are also seen in the other connective tissue diseases.

Specific changes. Cutaneous erythema is the most common feature, particularly on light-exposed areas (Fig. 51.29). A butterfly



Fig. 51.29 Systemic lupus erythematosus: typical symmetrical slightly scaling erythema of the face and neck.



Fig. 51.30 Systemic lupus erythematosus of the dorsa of hands and forearms. Identical changes may occur in discoid lupus erythematosus. Note the chloroquine pigmentation of the distal part of the nails.

blush or discrete maculopapular eruption with fine scaling on the butterfly area of the cheeks or elsewhere is also frequently found (Fig. 51.30). Photoaggravation occurs in approximately 33% of patients at Leeds, but up to 73% has been reported from America [3]. This may relate to the amount of sunlight. UV radiation such as that found in discos [4], fluorescent lighting [5] and UVA from photocopiers [6] may also cause exacerbations. Oedema, especially of the face, may resemble contact dermatitis, seborrhoeic eczema, dermatomyositis or erysipelas, and can follow tooth extraction [7]. Occasionally, more acute lesions with bullae may follow exposure to the sun (Fig. 51.31), and bullae may be haemorrhagic [8,9].

Epidermal necrosis may give an appearance resembling toxic epidermal necrolysis [10]. In other cases, lesions are like those of erythema multiforme (Rowell's syndrome; see p. 51.14). Very rarely, the skin may show centrifugal annular erythema like that of SCLE. Lesions resembling chronic discoid lesions are initial manifestations in approximately 10% of patients and occur in the course of the disease in approximately 33%; they may be more common in men [11].



Fig. 51.31 Systemic lupus erythematosus: gross involvement of the back.

References

1 Tuffanelli DL, Dubois EL. Cutaneous manifestations of systemic lupus erythematosus. *Arch Dermatol* 1964; **90**: 377–86.

2 Yell JA, Mbuagbaw J, Burge SM. Cutaneous manifestations of systemic lupus erythematosus. *Br J Dermatol* 1996; **135**: 355–62.

3 Wysenbeek AJ, Block DA, Fries JF. Prevalence and expression of photosensitivity in systemic lupus erythematosus. *Ann Rheum Dis* 1989; **48**: 461–3.



Fig. 51.32 Necrosis of the nail fold in systemic lupus erythematosus.



Fig. 51.33 White nail and ragged cuticle in systemic lupus erythematosus.

4 Seibold JR, Lynch CJ. Disco lupus: a new disease syndrome. *Arthritis Rheum* 1980; **23**: 962–3.
5 Martin L, Chalmers IM. Photosensitivity to fluorescent light in a patient with lupus erythematosus. *J Rheumatol* 1983; **10**: 811–2.
6 Klein LR, Elmers CA, Callen JP. Photoexacerbation of cutaneous lupus erythematosus due to ultraviolet A emissions from a photocopier. *Arthritis Rheum* 1995; **38**: 1152–6.
7 Lóescher A, Edmondson HD. Lupus erythematosus: a case of facial swelling. *Br J Oral Maxillofac Surg* 1988; **26**: 129–42.
8 Patcharee B, Sunthonpalin PB, MacGuire HC. Blister fluid in bullous systemic lupus erythematosus. *Br J Dermatol* 1970; **82**: 125–8.
9 Tromovitch TA, Hyman AB. Systemic lupus erythematosus with hemorrhagic bullae. *Arch Dermatol* 1961; **83**: 910–4.
10 Gilliam JN, Sontheimer RD. Skin manifestations of SLE. *Clin Rheum Dis* 1982; **8**: 207.
11 Font J, Pallares L, Cervera R *et al.* Systemic lupus erythematosus: clinical and immunological study of 300 patients. *Med Clinica 100* 1993; **16**: 601–5.

Non-specific changes. Sometimes, lesions may be minimal. This is particularly so in the case of the reticulate telangiectatic erythema seen on the thenar and hypothenar eminences of the palms, on the pulps and dorsum of the fingers and, to a lesser extent, on the toes and over the lateral borders of the feet and heels. The lesions on the palms may be confused with the palmar erythema of liver disease. They are bluish red and may show small whitish areas of scarring. The changes occur particularly on the dorsa of the distal phalanges and between the joints, but sometimes there may be small vascular necroses on the tips of the fingers and alongside the nails (Fig. 51.32). The nail folds may show hyperkeratotic and ragged cuticles (Fig. 51.33). Splinter haemorrhages may sometimes be seen in the nails [1], and other changes include pitting, ridging, onycholysis, striate leukonychia [2] and red lunulae [3]. Nail changes occur in approximately 25% of patients [4]. Recurrent Osler's nodes may occur in the absence of infective endocarditis [5]. Clubbing has been reported [6]. Dilatation of the nail fold capillaries also occurs, but this is seen in other conditions. Biopsies from the nails and from areas of palmar erythema show marked dilatation of superficial capillaries [7].

References

1 Mintz G, Fraga A. Arteritis in systemic lupus erythematosus. *Arch Intern Med* 1965; **116**: 55–66.
2 Friedman SJ. Leukonychia striata associated with systemic lupus erythematosus. *J Am Acad Dermatol* 1986; **15**: 536–8.
3 Garcia-Patos V, Bartralot R, Ordi J *et al.* Systemic lupus erythematosus presenting with red lunulae. *J Am Acad Dermatol* 1997; **36**: 834–6.
4 Urowitz MB, Gladman DD, Chalmers A *et al.* Nail lesions in systemic lupus erythematosus. *J Rheumatol* 1978; **5**: 441–7.
5 Rudusky BM. Recurrent Osler's nodes in systemic lupus erythematosus. *Angiology* 1969; **20**: 33–7.
6 MacKie RM. Lupus erythematosus in association with finger-clubbing. *Br J Dermatol* 1973; **89**: 533–5.
7 Smith EW, Kurban A. Capillary alterations in lupus erythematosus. *Bull Johns Hopkins Hosp* 1962; **110**: 202–11.

Hair changes. Alopecia occurs in over 50% of patients, especially in the active phase of the disease. This takes the form of diffuse loss of hair with a reddish scalp or, less frequently, permanent scarring alopecia, similar to that found in DLE. The hair is usually coarse, dry and fragile, especially on the frontal margin. This leads to an unruly appearance with short, broken-off hair, the so-called 'lupus hair' (Fig. 51.34) [1]. This occurs in 30% of patients, predominantly females [2]. The hair recovers as the disease becomes inactive, but 'lupus hair' usually persists longer than alopecia. The shortened hairs are unbroken and are probably brought about by slowed anagen growth.

References

1 Armas-Cruz R, Harnecker J, Ducach G *et al.* Clinical diagnosis of systemic lupus erythematosus. *Am J Med* 1958; **25**: 409–19.
2 Alarcon-Segovia D, Cetina JA. Lupus hair. *Am J Med Sci* 1974; **267**: 241–2.

Urticarial lesions and vasculitis. Persistent non-itching urticaria-like weals are common, and may respond to dapsone if associated with C1q deficiency. Urticarial lesions occurred in 7% of one series, but in 20% of patients at Leeds, and were considered to be brought about by immune-complex deposition [1]. SLE may present as hypocomplementaemic urticarial vasculitis [2]. Widespread purpura, resulting from thrombocytopenia or cutaneous vasculitis, is a common finding. Leukocytoclastic vasculitis may lead to purpuric macules, up to 1 cm in diameter, and in certain cases



Fig. 51.34 Unruly 'lupus hair' with diffuse alopecia.



Fig. 51.35 Necrotic crusted leg ulcers in systemic lupus erythematosus.

purpuric urticarial lesions may be found. Purpura can also be a result of corticosteroid therapy. Livedo reticularis, a mottled or bluish red discoloration, which blanches on pressure and is not affected by temperature changes, may develop, especially on the outer aspects of the arms. It occurs most frequently in patients who later develop central nervous system lupus [3]. The appearance of livedo reticularis in association with flares of cerebral vasculitis has been noted [4]. Superficial ulceration can occur in areas of livedo. Atrophie blanche [5] and lesions similar to those of malignant atrophic papulosis (Degos' disease) [6] are other features of vasculitis. Patients with the perniotic lesions of 'chilblain lupus' (see p. 51.11) may go on to develop SLE. These lesions may ulcerate, as may the hyperkeratotic keratodermatous skin sometimes found. A subset has been described in which perniotic lesions on the dorsum of the knuckles and toes, fingers and the pulps and palmar and plantar surfaces is associated with anti-Ro antibody [7]. Chronic pyoderma gangrenosum occurs, and has been the presenting feature of hydralazine-induced SLE [8]. Follicular pyoderma resulting from infection has also been described [9].

References

1 Provost TT, Zone JJ, Synkowski D *et al.* Unusual cutaneous manifestations of systemic lupus erythematosus. *J Invest Dermatol* 1980; **75**: 495–9.

2 Coca A, Font J, Herrero C *et al.* Hypocomplementaemic vasculitis and systemic lupus erythematosus. *J Rheumatol* 1987; **14**: 854–5.

3 Yasue T. Livedoid vasculitis and central nervous system involvement in systemic lupus erythematosus. *Arch Dermatol* 1986; **122**: 66–70.

4 Grigor R, Edmonds J, Lewkonia R *et al.* Systemic lupus erythematosus. *Ann Rheum Dis* 1978; **37**: 121–8.

5 Stevanovicà DV. Atrophie blanche. *Arch Dermatol* 1974; **109**: 858–62.

6 Török L. Symptomatic atrophic papulosis in a patient with systemic lupus erythematosus. *Clin Exp Dermatol* 1996; **21**: 390–2.

7 Bottomley W, Goodfield M. A distinctive form of peripheral cutaneous involvement in Ro antibody positive systemic lupus erythematosus. *Lupus* 1995; **4** (Suppl. 2): 154.

8 Peterson LL. Hydralazine-induced systemic lupus erythematosus presenting as pyoderma gangrenosum-like ulcers. *J Am Acad Dermatol* 1984; **10**: 379–84.

9 Lazzari T, Parodi A, Rebora A. Follicular impetigo as a presenting sign of systemic lupus erythematosus. *Dermatologica* 1991; **182**: 233–4.

Large vessel disease. Gangrene of the tips of the fingers and toes [1] may develop insidiously. At first the digits become blue and cold and may be painful. Radiography of the fingers in cases with peripheral ischaemia shows absorption of the distal part of the terminal phalanges, as in systemic sclerosis. Later, the phalanges may become exposed, and spontaneous separation of the tips of the fingers may occur. Amputation of digits may be required. Occlusion of large- and medium-sized arteries can occur suddenly and result in gangrene requiring amputation of a limb [2,3]. This may be the result of vasculitis or thrombosis. Patients with thrombosis frequently have antiphospholipid antibodies [3]. Major vessel occlusion can occur in childhood [4]. Leg ulcers (Fig. 51.35) occur in approximately 10% of patients, usually near the malleoli but sometimes on the feet and elsewhere, from breakdown in reticular livedo and in areas of cutaneous vasculitis. Erythromelalgia (pain in the feet aggravated by heat and dependence and relieved by cooling and elevation) may be a presenting feature [5].

References

1 Dubois EL, Arterberry JD. Gangrene as a manifestation of systemic lupus erythematosus. *JAMA* 1962; **181**: 366–74.
2 Alarcón-Segoviá D, Cardiel MH, Reyes E. Antiphospholipid arterial vasculopathy. *J Rheumatol* 1989; **16**: 762–7.
3 Asherson RA, Derksen RHWM, Harris EN *et al.* Large vessel occlusion and gangrene in systemic lupus erythematosus and 'lupus-like' disease: a report of six cases. *J Rheumatol* 1986; **13**: 740–7.
4 Kaufman JL, Bancilla E, Slade J. Lupus vasculitis with tibial artery thrombosis and gangrene. *Arthritis Rheum* 1986; **29**: 1291–2.
5 Alarcón-Segoviá D, Rabb RR, Fairbairn JF. Systemic lupus erythematosus with erythromelalgia. *Arch Dermatol* 1963; **112**: 688–92.

Mucinosis. Although mucin deposition is a common and often prominent histological feature of cutaneous lupus, specific clinical patterns of mucinosis also occur. Papular or nodular lesions resulting from mucinous deposits in the dermis without microscopic features of LE have been reported [1], and form a distinct entity which may be the presenting feature of LE [2]. Multiple firm nontender dermal papules and nodules, between 5 and 15 mm in diameter, occur on the upper part of the body and extremities [3–6]. The overlying epidermis appeared normal. Hyperpigmented acral papular mucinosis has also occurred in one patient with total alopecia [6].

References

1 Rongioletti F, Parodi A, Rebora A. Papular and nodular mucinosis as a sign of LE. *Dermatologica* 1990; **180**: 221–3.
2 Sonntag M, Lehmann P, Megahed M *et al.* Papulonodular mucinosis associated with subacute cutaneous lupus erythematosus. *Dermatology* 2003; **206**: 326–9.
3 Fowler JF Jr, Callen JP. Cutaneous mucinosis associated with lupus erythematosus. *J Rheumatol* 1984; **11**: 280–3.
4 Gammon WR, Caro I, Long JC *et al.* Secondary cutaneous mucinosis with systemic lupus erythematosus. *Arch Dermatol* 1978; **114**: 432–5.
5 Gold SC. An unusual papular eruption associated with lupus erythematosus. *Br J Dermatol* 1954; **66**: 429–33.
6 Lacour JP, Juhlin L, Blaze PE *et al.* Hyperpigmented acral papular mucinosis, systemic lupus erythematosus and universal alopecia. *Acta Derm Venereol (Stockh)* 1989; **69**: 212–6.

Connective tissue changes. Hardening, binding-down and pigmentation of the skin of the face and limbs may resemble systemic sclerosis, although the typical mat-like telangiectases of the latter are usually absent. Calcinosis is rare [1], but occasionally widespread and large palpable deposits may develop [2] or be found radiologically [3]. Subcutaneous nodules occur in approximately 5% of patients [4]. They resemble rheumatoid nodules, although there may be no evidence of arthritis. They occur mainly over the backs of the proximal phalangeal joints and wrists, but are also found on the elbows, knees, occiput and the flexor aspects of the fingers. They may respond to hydroxychloroquine [5]. Some are histologically identical with classic rheumatoid nodules [6], others are probably caused by vasculitis and thrombosis [7]. Panniculitis, similar to LE profundus, can occur in the course of the disease or can be the presenting sign [8–10]. Lesions may break down, resolve with oral corticosteroids or require surgery and grafting. Relapsing nasal and auricular chondritis have been described [11]. The nose and ears are tender, warm, swollen and red, but cartilage collapse does not occur as in polychondritis. Treatment with corticosteroids is effective.

References

1 Tay CH. Cutaneous manifestation of systemic lupus erythematosus: a clinical study from Singapore. *Australas J Dermatol* 1970; **11**: 30–41.
2 Nomura M, Okada N, Okada M, Yoshikawa K. Large subcutaneous calcification in systemic lupus erythematosus. *Arch Dermatol* 1990; **126**: 1057–9.
3 Rothe MJ, Grant-Kels JM, Rothfield NF. Extensive calcinosis cutis with systemic lupus erythematosus. *Arch Dermatol* 1990; **126**: 1060–3.
4 Hahn BH, Yardley JH, Stevens MB. 'Rheumatoid' nodules in systemic lupus erythematosus. *Arch Dermatol* 1970; **72**: 49–58.
5 Schofield JK, Cerio R, Grice K. Systemic lupus erythematosus presenting with 'rheumatoid nodules'. *Clin Exp Dermatol* 1992; **17**: 53–5.
6 Dubois EL, Friou GJ, Chandor S. Rheumatoid nodules and rheumatoid granulomas in systemic lupus erythematosus. *JAMA* 1972; **220**: 515–8.
7 Bywaters EGL, Glynn LE, Zeldis A. Subcutaneous nodules of Still's disease. *Ann Rheum Dis* 1958; **17**: 278–85.
8 Diaz-Jouanen E, DeHoratius RJ, Alarcón-Segoviá D *et al.* Systemic lupus erythematosus presenting as panniculitis. *Ann Intern Med* 1975; **82**: 376–9.
9 Tuffanelli DL. Lupus erythematosus panniculitis (profundus). *Arch Dermatol* 1971; **103**: 231–42.
10 Winkelmann RK. Panniculitis and systemic lupus erythematosus. *JAMA* 1970; **211**: 472–5.
11 Kitridou RC, Wittmann AL, Quismorio FP Jr. Chondritis in systemic lupus erythematosus: clinical and immunopathologic studies. *Clin Exp Rheumatol* 1987; **5**: 349–53.

Pigmentary changes. Pigmentary disturbances are not uncommon. Whole areas can show hypopigmentation. A bluish black pigmentation of the skin results from antimalarial therapy [1].

Other cutaneous changes. In the Chinese, hyperkeratotic follicular erythematous papules, sometimes becoming pigmented or confluent, occur on the trunk and limbs. Psoriasiform lesions and hyperkeratosis of the palms and soles are found [2,3]. Widespread ichthyosis and warty excrescences on knees and elbows may occur [4]. Eruptive dermatofibromas have been reported [5]. Acanthosis nigricans has been reported in lupoid hepatitis [6]. Herpes zoster is more frequent than expected in SLE [7], and scabies is more severe and may be of the crusted type [8].

References

1 Wallace DJ. Management and prognosis of systemic lupus erythematosus. In: Wallace DJ, Hahn B, Dubois EL, eds. *Dubois' Lupus Erythematosus*, 4th edn. Philadelphia: Lea and Febiger, 1993: 521–3.
2 Issacs P. Myasthenia with systemic lupus and palmoplantar keratosis. *BMJ* 1971; **iv**: 339–40.
3 Wong KO. Systemic lupus erythematosus: a report of 45 cases with unusual clinical and immunological features. *Br J Dermatol* 1969; **81**: 186–90.
4 Buck DC, Dodd HJ, Sarkany I. Hypertrophic lupus erythematosus. *Br J Dermatol* 1988; **119**: 72–4.
5 Kravitz P. Dermatofibromas and systemic lupus erythematosus. *Arch Dermatol* 1980; **116**: 1347.
6 Tuffanelli DL. Acanthosis nigricans with lupoid hepatitis. *JAMA* 1964; **189**: 584–5.
7 Moutsopoulos HM, Gallagher JD, Decker JL *et al.* Herpes zoster in patients with systemic lupus erythematosus. *Arthritis Rheum* 1978; **21**: 798–802.
8 Ting HC, Wang F. Scabies and systemic lupus erythematosus. *Int J Dermatol* 1983; **22**: 473–6.

Bullous SLE (Fig. 51.36) [1]. Blistering is uncommon in SLE. In the classic disease, separation of the epidermis and dermis occurs as a result of severe liquefaction degeneration of the basal layer and dermal oedema. A separate subset called bullous SLE has been defined, with distinct clinical and histopathological features, the



Fig. 51.36 Bullous lupus erythematosus of the face and neck.

latter resembling dermatitis herpetiformis [2]. Subepidermal vesicles contain neutrophils with microabscesses, and nuclear 'dust' and fibrin at the tips of dermal papillae. Immunohistology, however, shows linear deposition of IgA, IgG and IgM and, to a lesser extent, C3 at the basement membrane, resembling bullous pemphigoid and unlike the IgA seen in the dermal papillae in dermatitis herpetiformis. Electron microscopy shows the immunoreactants to be in the sublamina densa [3] and not in the lamina lucida as in pemphigoid, although the immunopathological changes are variable and may indicate that a number of basement-membrane antigens can act as targets [4]. This has subsequently been confirmed [5]. In particular, a form resembling epidermolysis bullosa acquisita (EBA) has been described [6]. The target antigen in some patients is type VII collagen, but other antigens may be involved in bulla formation [7].

Clinically, the bullous lesions are predominantly on the face, neck and upper trunk, but may be more widespread, and may heal with milia formation. One-third have mouth lesions. Photosensitivity may occur. The patient may initially present with lesions resembling erythema multiforme [8]. Glomerulonephritis is common, and associated with hypocomplementaemia and anti-DNA antibodies. Circulating antibasement-zone antibodies have many features of EBA antibodies. The demonstration of such antibodies may precede the development of SLE by many years [9]. It is not yet established whether patients with EBA antibodies are a unique subset of bullous LE or whether they represent the coexistence of two separate diseases, although it has been suggested that the spectrum of bullous LE should include all cases of bullous disease occurring in patients with SLE [1]. Rarely, drugs, including hydralazine [10] and IFN-α [11], may precipitate bullous SLE. Dapsone alone or in combination with prednisone is the treatment of choice. It is not always successful and may even exacerbate the disease [7]. The authors have used thalidomide successfully in these resistant cases.

References

1 Yell JA, Allen J, Wojnarowska F, Kirtschig G, Burge SM. Bullous systemic lupus erythematosus: revised criteria for diagnosis. *Br J Dermatol* 1995; **132**: 921–8.
2 Camisa C. Vesiculobullous systemic lupus erythematosus. *J Am Acad Dermatol* 1988; **18**: 93–100.
3 Rappersberger K, Tschachler E, Tani M *et al.* Bullous disease in systemic lupus erythematosus. *J Am Acad Dermatol* 1989; **21**: 745–52.
4 Burge S, Schomberg K, Wojnarowska F. Bullous eruption of SLE: a case report and investigation of the relationship of anti-basement-membrane zone antibodies to blistering. *Clin Exp Dermatol* 1991; **16**: 133–8.
5 Chan LS, Lapiere JC, Chen M *et al.* Bullous systemic lupus erythematosus with autoantibodies recognizing multiple skin basement membrane components, bullous pemphigoid antigen 1, laminin 5, laminin 6, and type VII collagen. *Arch Dermatol* 1999; **135**: 569–73.
6 Burrows NP, Bhogal BS, Black MM *et al.* Bullous eruption of systemic lupus erythematosus: a clinicopathological study of four cases. *Br J Dermatol* 1993; **128**: 332–8.
7 Yell JA, Wojnarowska F, Allen J, Burge SM. Bullous systemic lupus erythematosus: a variable disease. *Lupus* 1993; **2**: 383–5.
8 Barton DD, Fine J-D, Gammon WR *et al.* Bullous systemic lupus erythematosus: an unusual clinical course and detectable circulating autoantibodies to the epidermolysis bullosa acquisita antigen. *J Am Acad Dermatol* 1986; **15**: 369–73.
9 Boh E, Roberts LJ, Lieu TS *et al.* Epidermolysis bullosa acquisita preceding the development of systemic lupus erythematosus. *J Am Acad Dermatol* 1990; **22**: 587–93.
10 Fleming MG, Bergfeld WF, Tomecki KJ *et al.* Bullous systemic lupus erythematosus. *Int J Dermatol* 1989; **28**: 321–6.
11 Pouthier D, Theissen F, Humbel RL. Lupus syndrome, hypothyroidism and bullous skin lesions after interferon-α for hepatitis C in a haemodialysis patient. *Nephrol Dial Transplant* 2002; **17**: 174.

Pemphigus erythematosus [1]. Erythematous, scaly, hyperkeratotic or crusted lesions, sometimes adversely affected by the sun, occur in a butterfly distribution on the cheeks and in a seborrhoeic distribution on the trunk of patients with Senear–Usher syndrome (see Chapter 40). This combines the immunological features of pemphigus and LE. Direct immunofluorescence shows immunoglobulin and complement in the intercellular substance and at the dermal–epidermal junction of perilesional and, to a lesser extent, of light-exposed and non-exposed skin. Circulating pemphigus-like antibodies and antinuclear factor occur in 80–100%, but anti-DNA and ENA antibodies are not found. Antidesmoglein antibodies have also been demonstrated [2]. The condition occurs spontaneously, but has been induced by penicillamine, propranolol, captopril, pyritinolol and thiopronine. Topical steroids alone may control the condition, but systemic steroids, immunosuppressives or dapsone may be required.

References

1 Amerian ML, Ahmed RA. Pemphigus erythematosus: presentation of four cases and review of literature. *J Am Acad Dermatol* 1984; **10**: 215–22.
2 Gomi H, Kawada A, Amajai M, Matsuo I. Pemphigus erythematosus: detection of anti-desmoglein-1 antibodies by ELISA. *Dermatology* 1999; **199**: 188–99.

Mucous membrane lesions [1–3]. Mucous membrane lesions occur in 26% of cases, usually on the palate (82%) (Fig. 51.37),



Fig. 51.37 Systemic lupus erythematosus involving the palate.

buccal mucosa or gums, in active phases of the disease [3]. Lesions start as small erythematous or purpuric areas, which break down to form shallow and sometimes painful ulcers, with a dirty yellow base and surrounding reddish halo. There may be difficulty in swallowing. Histology and immunohistology show changes similar to those in the skin. Light microscopy can usually distinguish between LE and lichen planus [4]. Immunofluorescence is usually positive [5]. Repeated sore throats and oral ulceration may be presenting features [6]. The appearances can resemble a *Candida* infection, and sometimes *Candida* is present as a secondary infection. The lips may become cracked, oedematous and crusted in acute cases. Infarction of the tongue, with anticardiolipin antibodies, was the presenting feature in one case [7]. Cheilitis occurs in approximately 6%, the lips having a silvery appearance, with erythema, scaling and blurring of the vermilion border [1]. The larynx is occasionally involved. Ulceration of the mucosa of the nasal septum occurs in approximately 5%. Perforation of the nasal septum is a complication of exacerbations and presents with epistaxis [8]. Erythema of the vulva and perianal area occurs and vulval ulceration may develop, but is less common than oral ulcers. Patients may present with vulval and vaginal ulceration. Orogenital ulceration has been reported with hydralazine-induced lupus [9].

References

1 Burge SM, Frith PA, Juniper RP *et al.* Mucosal involvement in systemic and chronic cutaneous lupus erythematosus. *Br J Dermatol* 1989; **121**: 727–41.
2 Schiodt M. Oral manifestations of lupus erythematosus. *Int J Oral Surg* 1984; **13**: 101–47.
3 Urman JD, Lowenstein MB, Abeles M *et al.* Oral mucosal ulceration in systemic lupus erythematosus. *Arthritis Rheum* 1978; **21**: 58–61.
4 Karjalainen TK, Tomich CE. A histopathologic study of oral mucosal lupus erythematosus. *Oral Surg Oral Med Oral Pathol* 1989; **67**: 547–54.
5 Jonsson R, Heyden G, Gunnar Westberg N *et al.* Oral mucosal lesions in systemic lupus erythematosus. *J Rheumatol* 1984; **11**: 38–42.
6 O'Neill SM, Thomson J, Strong AMM *et al.* Systemic lupus erythematosus presenting as a recurrent sore throat and oral ulceration: a case report. *Br J Dermatol* 1977; **96**: 211–3.
7 Korn S, Huppert A, Spitzer S *et al.* Systemic lupus erythematosus presenting with lingual infarction. *J Rheumatol* 1988; **15**: 1281–3.
8 Synder GG, McCarthy RE, Toomey JM *et al.* Nasal septal perforation in systemic lupus erythematosus. *Arch Otolaryngol* 1974; **99**: 456–7.

Table 51.14 Features distinguishing systemic lupus erythematosus (SLE) from rheumatoid arthritis (RA).

Distinguishing feature	SLE (%)	RA (%)
Deforming arthritis	25	Common
Subcutaneous nodules	5	25
Radiological erosions	Rare	Common
Involvement of kidneys	Common	Rare
Positive LE cell test	80	15
Positive ANA test	90	20
Rheumatoid factor present	40	80

ANA, antinuclear antibody; LE, lupus erythematosus.

9 Neville E, Graham PY, Brewis RAL. Orogenital ulcers, SLE and hydralazine. *Postgrad Med J* 1981; **57**: 378–9.

Arthritis [1]. Involvement of the joints occurs at some time in approximately 90% of patients, arthralgia being more common than arthritis. A rheumatoid-like deformity is present in approximately 25% of cases, with marked soft-tissue swelling, especially of the dorsa of the fingers, hands and wrists, although joint erosions on X-ray are not a feature. The deformity is usually less, but the soft-tissue swelling is more marked than in rheumatoid arthritis [2]. Jaccoud's syndrome, severe deformity of the hands with ulnar deviation and swan-neck configuration, often with little pain and good function, occurred in 13% and fixed flexion contractures of the elbows in 11% in one series [3]. Arthritis mutilans of the distal interphalangeal joints of the hands can occur [4]. The elbows, shoulders, knees and feet may also be involved and soft-tissue nodules may occur, usually indicating calcinosis. Temporomandibular joint involvement may be indicated by locking or dislocation, tenderness and pain on mastication [5]. Features distinguishing SLE from rheumatoid arthritis are shown in Table 51.14. Migratory polyarthritis with inflammation, effusion and erythema occur less frequently. Sacroiliitis occurs in male patients [6]. SLE may rarely present with polymyalgia rheumatica [7]. *Salmonella* infections occur in patients with SLE, and may be associated with septic arthritis [8,9].

References

1 Labowitz R, Schumacher HR Jr. Articular manifestations of systemic lupus erythematosus. *Ann Intern Med* 1971; **74**: 911–21.
2 Russell AS, Percy JS, Rigal MM *et al.* Deforming arthropathy in systemic lupus erythematosus. *Ann Rheum Dis* 1974; **33**: 204–9.
3 Esdaile JM, Danoff D, Rosenthall L *et al.* Deforming arthritis in systemic lupus erythematosus. *Ann Rheum Dis* 1981; **40**: 124–6.
4 Martinez-Cordero E, Lopez Zepeda J, Andrade-Ortega L *et al.* Mutilans arthropathy in systemic lupus erythematosus. *Clin Exp Rheumatol* 1989; **7**: 427–9.
5 Jonsson R, Lindvall AM, Nyberg G. Temporomandibular joint involvement in systemic lupus erythematosus. *Arthritis Rheum* 1983; **26**: 1506–10.
6 Nassonova VA, Alekberova ZS, Folomeyev MY *et al.* Sacroiliitis in male systemic lupus erythematosus. *Scand J Rheumatol* 1983; **52**: 23–9.
7 Foley J. Systemic lupus erythematosus presenting as polymyalgia rheumatica. *Ann Rheum Dis* 1987; **46**: 351.
8 Medina F, Fraga A, Lavalle C. Salmonella septic arthritis in systemic lupus erythematosus: the importance of chronic carrier state. *J Rheumatol* 1989; **16**: 203–8.
9 Van De Laar MAFJ, Meenhorst PL, Van Soesbergen RM *et al.* Polyarticular salmonella bacterial arthritis in a patient with systemic lupus erythematosus. *J Rheumatol* 1989; **16**: 231–4.

Heart. Cardiac involvement in SLE is common, and increases with the duration of the disease [1]. Pericarditis is the most frequent cardiac manifestation, but the incidence of 87% in one review [2] must have been the result of selection. Fibrinous pericarditis is frequently found, but sometimes a large effusion may occur and reabsorb on adequate corticosteroid therapy. Rarely, a large effusion can develop within hours, giving rise to cardiac tamponade [3] and requiring aspiration. The incidence of classic endocardial lesions (Libman–Sacks endocarditis) is difficult to estimate, but the diagnosis is rarely made clinically. Lesions were found at autopsy in only four out of 30 patients in one series [4] and in 50% of patients in another [5]. The valves on the left side of the heart are commonly involved. Both systolic and diastolic murmurs may be found depending upon the site of the lesion, and bacterial endocarditis can occur on the damaged heart valves. Aortic incompetence may occur without involvement of the mitral valve [6] at an early stage of the disease before steroids are used, or when the condition is well controlled. Tricuspid regurgitation has been reported [7]. Echocardiography is helpful in diagnosis [8], and valve replacement has been successful [9].

Coronary arteritis results in myocardial infarction [10]. Infarction may also result from atherosclerosis in young patients [11]. Antiphospholipid antibodies may be demonstrated in such patients [12]. The myocardium may also be affected and results in cardiac failure [13]. The diagnosis can be confirmed by endomyocardial biopsy [14]. Alterations in rhythm include atrial fibrillation and heart block of all types. This may be associated with both Ro and U_1-RNP antibodies [15].

Hypertension occurs in approximately 35% of patients. Alterations in the electrocardiogram (ECG) in the course of the illness may be helpful in diagnosing or in confirming the presence of cardiac involvement. There is some evidence that treatment with corticosteroids increases the incidence and degree of hypertension, coronary atherosclerosis and heart failure [5]. Reduced exercise tolerance occurs and may be caused by abnormal myocardial dynamics on exercise [16].

References

1 Giunta A, Picillo U, Maione S *et al.* Spectrum of cardiac involvement in systemic lupus erythematosus: echocardiographic, echo-Doppler observations and immunological investigation. *Acta Cardiol* 1993; **48**: 183–97.

2 Brigden W, Bywaters EGL, Lessof MH *et al.* The heart in systemic lupus erythematosus. *Br Heart J* 1960; **22**: 1–16.

3 Zashin SJ, Lipsky PE. Pericardial tamponade complicating systemic lupus erythematosus. *J Rheumatol* 1989; **16**: 374–7.

4 Kong TQ, Kellum RE, Haserick JR. Clinical diagnosis of cardiac involvement in systemic lupus erythematosus. *Circulation* 1962; **26**: 7–11.

5 Bulkley BH, Roberts WC. The heart in systemic lupus erythematosus and the changes induced in it by corticosteroid therapy. *Am J Med* 1975; **58**: 243–64.

6 El-Ghobarey A, Grennan DM, Hadidi T *et al.* Aortic incompetence in systemic lupus erythematosus. *BMJ* 1976; **ii**: 915–6.

7 Laufer J, Frand M, Milo S. Valve replacement for severe tricuspid regurgitation caused by Libman–Sacks endocarditis. *Br Heart J* 1982; **48**: 294–7.

8 Kalke S, Balakrishanan C, Mangat G *et al.* Echocardiography in systemic lupus erythematosus. *Lupus* 1998; **7**: 540–4.

9 Isaacs AJ. Aortic incompetence in systemic lupus erythematosus. *BMJ* 1976; **ii**: 1260.

10 Bonfiglio TA, Botti RE, Hagstrom JWC. Coronary arteritis and myocardial infarction due to lupus erythematosus. *Am Heart J* 1972; **83**: 153–8.

11 Spiera H, Rothenberg RR. Myocardial infarction in four young patients with SLE. *J Rheumatol* 1983; **10**: 464–6.

12 Asherson RA, Khamashta MA, Baguley E *et al.* Myocardial infarction and antiphospholipid antibodies in SLE and related disorders. *QJM* 1989; **272**: 1103–15.

13 Gur H, Keren G, Averbuch M *et al.* Severe congestive lupus cardiomyopathy complicated by an intracavitary thrombus: a clinical and echocardiographic follow-up. *J Rheumatol* 1988; **15**: 1278–83.

14 Fairfax MJ, Osborn TG, Williams GA *et al.* Endomyocardial biopsy in patients with systemic lupus erythematosus. *J Rheumatol* 1988; **15**: 593–6.

15 Fonseca E, Crespo M, Sobrino JA. Complete heart block in an adult with systemic lupus erythematosus. *Lupus* 1994; **3**: 129–31.

16 Winslow TM, Ossipov M, Redberg RF *et al.* Exercise capacity and haemodynamics in systemic lupus erythematosus: a Doppler echocardiographic exercise study. *Am Heart J* 1993; **126**: 410–4.

Lungs [1]. The incidence of involvement of the pulmonary system varies between series, and the radiological changes [2] depend on the stage of the disease. Transient pleurisy is the most common feature, and in approximately two-thirds of these cases some fluid develops, occasionally haemorrhagic. Pleural thickening can be shown radiographically. Involvement of the lungs is less frequent, and is shown mainly as transient infiltration, sometimes with mottling and reticulation (Fig. 51.38) [3]. Acute pneumonitis with severe dyspnoea and fever may be a presenting manifestation of SLE [4], and cases have been reported with disseminated intravascular coagulation [5]. There is a high incidence of anti-Ro antibodies in pneumonitis [6]. Diffuse fibrosis, like that occurring in systemic sclerosis, is not found [1]. Shrinking lung syndrome is probably caused by diaphragmatic fibrosis [7]. Pulmonary hypertension occurs [8], and pulmonary haemorrhage can be dangerous [9]. When dyspnoea, pleuritic pain and fever occur with linear shadows on radiography, recurrent pulmonary infarction may be simulated. Fibrosing alveolitis has been reported, as well as haemopneumothorax [10]. Hilar lymphadenopathy may cause confusion with other diseases [11]. Unlike those of systemic sclerosis, the pulmonary changes may resolve with steroid therapy.



Fig. 51.38 Pulmonary infiltration in systemic lupus erythematosus. This cleared in approximately 2 years on treatment with corticosteroids.

Impairment of pulmonary diffusion (transfer factor) occurred in 42–80% [12], and is more common than reduction in lung volumes [13]. Function of the diaphragm may also be deficient [12], and bilateral elevation of the diaphragm with linear shadows over the lower zones is characteristic of SLE. *Pneumocystis carinii* infections should be considered in all steroid-treated patients who present with respiratory distress and pulmonary infiltration [14]. Nocardial infection with lung abscesses [15] and Legionnaires' disease [16] have been reported. Laryngeal involvement is rare and indicated by stridor and hoarseness, and may be life-threatening. It can occur in inactive disease, and may be complicated by nocardiosis [17].

References

1 Memet B, Ginzler EM. Pulmonary manifestations of systemic lupus erythematosus. *Semin Respir Crit Care Med* 2007; **28**: 441–50.
2 Swigris JJ, Fischer A, Gillis J *et al*. Pulmonary and thrombotic manifestations of systemic lupus erythematosus. *Chest* 2008; **133**: 271–80.
3 Eisenberg H, Dubois EL, Sherwin RP *et al.* Diffuse interstitial lung disease in systemic lupus erythematosus. *Ann Intern Med* 1973; **79**: 37–45.
4 Matthay RA, Schwarz ML, Petty TL. Pulmonary manifestations of systemic lupus erythematosus. *Medicine* 1974; **54**: 397–409.
5 Chellingsworth M, Scott DGI. Acute systemic lupus erythematosus with fatal pneumonitis and disseminated intravascular coagulation. *Ann Rheum Dis* 1985; **44**: 67–9.
6 Boulware DW, Hedgpeth MT. Lupus pneumonitis and anti-SSA (Ro) antibodies. *J Rheumatol* 1989; **16**: 479–81.
7 Rubin LA, Urowitz MB. Shrinking lung syndrome in SLE: a clinical pathologic study. *J Rheumatol* 1983; **10**: 973–6.
8 Simonson JS, Schiller NB, Petri M *et al.* Pulmonary hypertension in systemic lupus erythematosus. *J Rheumatol* 1989; **16**: 918–25.
9 Onomura K, Nakata H, Tanaka Y, Tsuda T. Pulmonary hemorrhage in patients with systemic lupus erythematosus. *J Thorac Imaging* 1991; **6**: 57–61.
10 Passero FC, Myers AR. Hemopneumothorax in systemic lupus erythematosus. *J Rheumatol* 1980; **7**: 183–6.
11 Kassan SS, Moss ML, Reddick RL. Progressive hilar and mediastinal lymphadenopathy in systemic lupus erythematosus on corticosteroid therapy. *N Engl J Med* 1976; **294**: 1382–3.
12 Gibson GJ, Edmonds JP, Hughes GRU. Diaphragm function and lung involvement in systemic lupus erythematosus. *Am J Med* 1977; **63**: 926–32.
13 Silberstein SL, Barland P, Grayzel AI *et al.* Pulmonary dysfunction in systemic lupus erythematosus: prevalence, classification and correlation with other organ involvement. *J Rheumatol* 1980; **7**: 187–95.
14 Lee P, Urowitz MB, Brookman AAM *et al.* Systemic lupus erythematosus. *QJM* 1977; **46**: 1–32.
15 Gorevic PD, Katler EI, Agus B. Pulmonary nocardiosis. *Arch Intern Med* 1980; **140**: 361–3.
16 Jacox RF, Stuard ID. Legionnaires' disease in a patient with systemic lupus erythematosus. *Arthritis Rheum* 1978; **21**: 975–7.
17 Petri M, Katzenstein P, Hellmann D. Laryngeal infection in lupus: report of nocardiosis and review of laryngeal involvement in lupus. *J Rheumatol* 1988; **15**: 1014–5.

Renal changes. The renal changes [1] in SLE are very important in assessing the prognosis (see p. 51.60). Most patients will have renal involvement, as histological evidence of nephritis may occur without proteinuria or microscopic urinary abnormality and with normal renal function [2]. Sometimes, proteinuria and casts may occur transiently with febrile exacerbations. Renal disease in lupus accounts for 3% of end-stage renal failure, and is an important cause of mortality in SLE [3]. The need for regular screening by urinalysis, blood pressure monitoring, assessment of renal function and early renal biopsy is critical. Usually, renal exacerbations are associated with high titres of antinuclear factor, elevated DNA binding and low serum complement, but occasionally these features may revert to normal in severe relapse [4]. Impaired renal tubular potassium secretion can lead to persistent hyperkalaemia [5].

The course is variable, and albuminuria and casts may persist for years without marked deterioration in renal function. Kidney damage, if this is going to develop, usually appears early (within the first 3 years) and is more frequent and severe in younger patients [1]. However, renal involvement may appear as long as 34 years after diagnosis of SLE [6]. A relatively benign course is associated with membranous lupus nephropathy. This occurs in approximately 8% of patients with SLE. Clinically, proteinuria and microscopic haematuria occur some years after other evidence of the disease. Prednisone treatment does not seem to influence proteinuria or renal function in this type [7].

Some cases develop typical signs of the nephrotic syndrome, and renal vein thrombosis has been reported. The development of pleuritic pain in a patient with SLE and the nephrotic syndrome should alert the clinician to the possibility of renal vein thrombosis and pulmonary emboli [8]. Cystitis with reduction of bladder capacity and thickening of the bladder wall may be a primary manifestation of SLE [9]. A strong correlation between lupus cystitis and gastrointestinal involvement has been noted [10].

References

1 Sauter M, Anders HJ. Lupus nephritis. *Minerva Med* 2007; **98**: 749–58.
2 Pollak VE, Pirani CL, Schwartz FD. The natural history of the renal manifestations of systemic lupus erythematosus. *J Lab Clin Med* 1964; **63**: 537–50.
3 Austin HA, Klippel JH, Balow JE *et al*. Therapy of lupus nephritis: controlled trial of prednisolone and cytotoxic drugs. *N Engl J Med* 1991; **314**: 614–9.
4 White NJ, Winearls CG, Ledingham JGG. Systemic lupus erythematosus and nephritis: severe relapse with disappearance of antinuclear antibodies. *BMJ* 1980; **ii**: 194–5.
5 Defronze RA, Cooke CR, Goldberg M *et al.* Impaired renal tubular potassium secretion in systemic lupus erythematosus. *Ann Intern Med* 1977; **86**: 268–71.
6 Adelman DC, Wallace DJ, Klinenberg JR. Thirty-four year delayed-onset lupus nephritis: a case report. *Arthritis Rheum* 1987; **30**: 479–80.
7 Marks SD, Tullus K, Sebire NJ. Current issues in pediatric lupus nephritis: role of revised histopathological classification. *Fetal Pediatr Pathol* 2006; **25**: 297–309.
8 Appel GB, Williams GS, Meltzer JI *et al*. Renal vein thrombosis, nephrotic syndrome and systemic lupus erythematosus. *Ann Intern Med* 1966; **85**: 310–7.
9 Orth RW, Weisman MH, Cohen AH *et al.* Lupus cystitis: primary bladder manifestations of systemic lupus erythematosus. *Ann Intern Med* 1983; **98**: 323–6.
10 Moriuchi J, Ichikawa Y, Takaya M *et al.* Lupus cystitis and perforation of the small bowel in a patient with systemic lupus erythematosus and overlapping syndrome. *Clin Exp Rheumatol* 1989; **7**: 533–6.

Gastrointestinal tract [1]. Anorexia, nausea and vomiting sometimes occur, and impairment of oesophageal motility has been reported [2], especially in patients with Raynaud's phenomenon. Motility studies show absent or impaired contractions in one-third of patients [3]. Abnormalities may occur in any part of the oesophagus but particularly in the upper third, and such dysfunction is not related to activity of the disease. Fewer patients complain of dysphagia or show radiological abnormalities. Pain, vomiting, diarrhoea, malabsorption [4,5], gluten-sensitive enteropathy [6] and protein-losing enteropathy [7], or evidence of obstruction or bleeding, result from intestinal involvement. Pneumatosis cystoides intestinalis and spontaneous pneumoperitoneum are rare [8],

but have been reported in a patient with antinuclear-negative SLE [9]. Patients with arteritis may present as an acute surgical emergency, and this complication may be fatal [10]. Small intestinal ulceration occurs in patients with antiphospholipid antibodies [11]. Mesenteric arteriography may be helpful in showing irregularities of the small intestinal arteries [12]. Pancreatitis [13] occurs in both children and adults and is often fatal. It can be associated with subcutaneous fat necrosis and calcinosis cutis [14]. Ulcerative colitis [15] and colonic perforation [16] also occur. Mesenteric lymphadenopathy may be associated with hilar lymphadenopathy [17].

Lymphangiographical changes can resemble those seen in early malignant lymphoma [18]. Painless ascites, in the absence of the nephrotic syndrome, congestive heart failure or hepatic cirrhosis, may be the presenting feature [19]. It is presumably a result of peritoneal serositis. Infarction of the tongue can be another presentation [20].

References

1 Alarcón-Segoviá D, Cardiel MA. Connective tissue disorders and the bowel. *Baillière's Clin Rheumatol* 1989; **3**: 371–92.

2 Stevens MB, Hookman P, Siegel CI *et al.* Aperistalsis of the oesophagus in patients with connective tissue disorders and Raynaud's phenomenon. *N Engl J Med* 1964; **270**: 1218–22.

3 Ramirez-Mata M, Reyes PA, Alarcón-Segoviá D *et al.* Oesophageal motility in systemic lupus erythematosus. *Am J Dig Dis* 1974; **19**: 132–6.

4 Bazinet P, Marin GA. Malabsorption in systemic lupus erythematosus. *Am J Dig Dis* 1971; **16**: 460–6.

5 Siurala M, Julkunen H, Toivonen S *et al.* Digestive tract in collagen diseases. *Acta Med Scand* 1965; **178**: 13–25.

6 Rustgi AK, Peppercorn MA. Gluten-sensitive enteropathy and systemic lupus erythematosus. *Arch Intern Med* 1988; **148**: 1583–4.

7 Wood ML, Foulds IS, French MA. Protein losing enteropathy due to systemic lupus erythematosus. *Gut* 1984; **25**: 1013–5.

8 Laing TJ. Gastrointestinal vasculitis and pneumatosis intestinalis due to systemic lupus erythematosus: successful treatment with pulse intravenous cyclophosphamide. *Am J Med* 1988; **85**: 555–8.

9 Pruitt RE, Tumminello VV, Reveille JD. Pneumatosis cystoides intestinalis and benign pneumoperitoneum in a patient with antinuclear antibody-negative systemic lupus erythematosus. *J Rheumatol* 1988; **15**: 1575–7.

10 Zizic TM, Classen JN, Stevens MB. Acute abdominal complications of systemic lupus erythematosus and polyarteritis nodosa. *Am J Med* 1982; **73**: 525–31.

11 Sasamura H, Nakamoto H, Ryuzaki M *et al.* Repeated intestinal ulcerations in a patient with systemic lupus erythematosus and high serum anti-phospholipid antibody levels. *South Med J* 1991; **84**: 515–7.

12 Phillips JC, Howland WJ. Mesenteric arteritis in systemic lupus erythematosus. *JAMA* 1968; **206**: 1569–70.

13 Wolman R, De Gara C, Isenberg D. Acute pancreatitis in systemic lupus erythematosus: report of a case unrelated to drug therapy. *Ann Rheum Dis* 1988; **47**: 77–9.

14 Simons-Ling N, Schachner L, Penneys N *et al.* Childhood systemic lupus erythematosus. *Arch Dermatol* 1983; **119**: 491–4.

15 Alarcón-Segoviá D, Herskovic T, Dearing WH *et al.* Lupus erythematosus cell phenomenon in patients with chronic ulcerative colitis. *Gut* 1965; **6**: 39–47.

16 Zizic TM, Shulma LE, Stevens MB. Colonic perforations in systemic lupus erythematosus. *Medicine* 1975; **54**: 411–26.

17 Kassan SS, Moss ML, Reddick RL. Progressive hilar and mediastinal lymphadenopathy in systemic lupus erythematosus on corticosteroid therapy. *N Engl J Med* 1976; **294**: 1382–3.

18 Wiljasalo M, Ikkala E. Lymphography in systemic lupus erythematosus. *Ann Clin Res* 1964; **3**: 231–5.

19 Averbuch M, Levo Y. Long-standing intractable ascites as the initial and predominant manifestation of systemic lupus erythematosus. *J Rheumatol* 1986; **13**: 442–3.

20 Korn S, Huppert A, Spitzer S *et al.* Systemic lupus erythematosus presenting with lingual infarction. *J Rheumatol* 1988; **15**: 1281–3.

Hepatic lesions [1]. These may be more common than previously recognized. Liver disease is present in approximately one-third of patients, but it is usually mild and often asymptomatic. Histology usually shows steatosis or mild hepatitis. Lesions include granulomatous hepatitis, chronic active hepatitis, cirrhosis, death from liver failure and hepatic infarction. The role of hepatitis C infection has been reviewed [2]. Nodular regenerative hyperplasia occurs [3], and hepatic veno-occlusive disease has been reported [4]. Subclinical liver disease indicated by mild transaminase elevation occurs in approximately 10%. LE cells are sometimes found in hepatitis. The condition, inappropriately named 'lupoid hepatitis', involves mainly young females who have a benign cirrhosis and evidence of adrenal overactivity such as acne, hirsutism, pigmentation, amenorrhoea and abdominal striae. Other features include febrile upsets, polyarthritis, hyperglobulinaemia and other protein abnormalities. Smooth muscle and mitochondrial antibodies may be demonstrated. Patients with chronic active hepatitis may show extensive purplish telangiectasia [5].

Thyroid disease. Both hyperthyroidism and hypothyroidism occur in SLE, and there is a high frequency of abnormal thyroid function tests and thyroid autoantibodies in patients without diagnosed thyroid disease [6].

Nervous system [7,8]. Approximately 50% develop neuropsychiatric features from the disease itself [8]. There is no direct correlation between neurological and psychiatric disease and clinical or laboratory indices of disease activity. Livedoid vasculitis of the skin may be an important prodromal sign of central nervous system (CNS) lupus [9]. Anticardiolipin antibodies may or may not be present. Migraine can be a feature [10]. Epilepsy, resulting from small thromboses in cerebral vessels affected by vasculitis, can be the presenting manifestation of SLE, particularly in patients with high titres of anticardiolipin antibodies. The incidence of epilepsy is difficult to evaluate, owing to selection of cases in series from special clinics. Peripheral sensorimotor [11] and autonomic neuropathy occurs [12], brought about by vasculitis in the vasa nervorum. It is important to distinguish this from the neuropathy induced by chloroquine [13]. Trigeminal neuropathy, with numbness and pain in the face [14], deafness [15], transverse myelitis [16], optic neuritis [17], aseptic meningitis [18], Guillain–Barré syndrome, and a case presenting as disseminated encephalomyelitis, have been reported [19]. Patients may present with clinical features of multiple sclerosis, and in this variant there is a high incidence of chronic biological false-positive Wassermann reactions and mitochondrial antibodies [20]. Occasionally, a single cranial nerve may be involved. Sometimes, signs simulate an intracranial mass [21], and pseudotumour cerebri because of raised intracranial pressure occurs [22]. Subarachnoid haemorrhage [23] and massive spontaneous subdural haematoma have been reported [24]. Parkinsonism is rare [25]. The association of chorea with SLE has been reviewed [26]: two cases of chorea were reported in a series of 175 patients with SLE [27], and the authors have seen this association in two girls aged 3 and 16 years. Chorea

gravidarum also occurs [28]. SLE may also cause psychiatric symptoms, including anxiety, hypomania, emotional lability, memory defects and depression. Psychiatric symptoms are found in approximately 20–30% [29]. Patients may respond to the disease with hypochondriasis, depression and hysteria, and pseudocyesis has been reported [30].

The electroencephalogram (EEG), conventional CT scanning, MRI scanning and oxygen-15 brain scanning may be helpful in the diagnosis of cerebral LE, and abnormalities are related to clinical progress [31]. Cranial computed tomography (CT) may show focal areas of infarction and cerebral atrophy or calcification [31]. The former may be caused by steroid therapy rather than the disease. Autoantibodies to neuronal antigens can be demonstrated in approximately 20% of patients with SLE, especially in those with neuropsychiatric features [32,33]. Antiribosomal P protein antibodies seem to be associated with psychosis [34]. Patients with multiple strokes followed by dementia are likely to have antiphospholipid antibodies [35]. Depressed levels of C4 in the cerebrospinal fluid (CSF) are found in patients with CNS involvement, but not in patients with active SLE without CNS manifestations [36].

Toxoplasmosis of the brain may occur as an opportunistic infection in patients with SLE and the manifestations resemble cerebral lupus [37].

References

1 Leggett BA. The liver in systemic lupus erythematosus. *J Gastroenterol Hepatol* 1993; **8**: 84–8.
2 Lormeau C, Falgarone G, Roulot D, Boissier MC. Rheumatologic manifestations of chronic hepatitis C infection. *Joint Bone Spine* 2006; **73**: 633–8.
3 Klemp P, Timme AH, Sayers GM. Systemic lupus erythematosus and nodular regenerative hyperplasia of the liver. *Ann Rheum Dis* 1986; **45**: 167–70.
4 Pappas SC, Malone DG, Rabin L *et al.* Hepatic veno-occlusive disease in a patient with systemic lupus erythematosus. *Arthritis Rheum* 1984; **27**: 104–8.
5 Green T, Champion RH. Extensive telangiectasia with chronic active hepatitis and systemic lupus erythematosus. *Br J Dermatol* 1989; **121**: 116.
6 Miller FW, Moore GF, Weintraub BD *et al.* Prevalence of thyroid disease and abnormal thyroid function test results in patients with systemic lupus erythematosus. *Arthritis Rheum* 1987; **30**: 1124–31.
7 Moskowitz N. Systemic lupus erythematosus of the central nervous system. I. Classification, epidemiology, pathology, diagnosis and therapy. *Mount Sinai J Med* 1988; **55**: 147–53.
8 Rhiannon JJ. Systemic lupus erythematosus involving the nervous system: presentation, pathogenesis, and management. *Clin Rev Allergy Immunol* 2008; **34**: 356–60.
9 Yasue T. Livedoid vasculitis and central nervous system involvement in systemic lupus erythematosus. *Arch Dermatol* 1986; **122**: 66–70.
10 Isenberg DA, Meyrick-Thomas D, Snaith ML *et al.* A study of migraine in systemic lupus erythematosus. *Ann Rheum Dis* 1982; **41**: 30–2.
11 McCombe PA, McLeod JG, Pollard JD *et al.* Peripheral sensorimotor and autonomic neuropathy associated with systemic lupus erythematosus. *Brain* 1987; **110**: 533–49.
12 Hirohata S, Iwamoto S, Miyamoto T *et al.* Acute autonomic neuropathy in association with systemic lupus erythematosus. *Ann Rheum Dis* 1985; **44**: 420–4.
13 Whisnant JP, Espinosa RE, Kierland RR *et al.* Chloroquine neuromyopathy. *Proc Staff Meetings Mayo Clin* 1963; **38**: 501–13.
14 Bailey A, Sayre GP, Clark EC. Neuritis associated with systemic lupus erythematosus. *Arch Neurol Psychiatr* 1956; **75**: 251–9.
15 Hamblin TJ, Mufti GJ, Bracewell A. Severe deafness in systemic lupus erythematosus: its immediate relief by plasma exchange. *BMJ* 1982; **284**: 1374.
16 Propper DJ, Bucknall RC. Acute transverse myelopathy complicating systemic lupus erythematosus. *Ann Rheum Dis* 1989; **48**: 512–5.
17 Kenik JG, Krohn K, Kelly RB *et al.* Transverse myelitis and optic neuritis in systemic lupus erythematosus: a case report with magnetic resonance imaging findings. *Arthritis Rheum* 1987; **30**: 947–50.
18 Canoso JJ, Cohen AS. Aseptic meningitis in systemic lupus erythematosus. *Arthritis Rheum* 1975; **18**: 369–74.
19 Vejjajiva A. Systemic lupus erythematosus presenting as acute disseminated encephalomyelitis. *Lancet* 1965; **i**: 352.
20 Fulford KWM, Catterall RD, Delhanty JJ *et al.* A collagen disorder of the nervous system presenting as multiple sclerosis. *Brain* 1972; **95**: 373–86.
21 Meagher JN, McCoy F, Rossel C. Disseminated lupus erythematosus simulating intracranial mass lesion: report of an unusual case. *Neurology* 1961; **11**: 862.
22 Li EK, Ho PCP. Pseudotumor cerebri in systemic lupus erythematosus. *J Rheumatol* 1989; **16**: 113–6.
23 Casey EB, Symon L. Systemic lupus erythematosus presenting as subarachnoid haemorrhage and space occupying lesion. *Br J Dermatol* 1971; **84**: 157–60.
24 Futran J, Shore A, Urowitz MB *et al.* Subdural hematoma in systemic lupus erythematosus: report and review of the literature. *J Rheumatol* 1987; **14**: 378–81.
25 Miyoshi Y, Atsumi T, Kitagowa H *et al.* Parkinsonism-like symptoms as a manifestation of systemic lupus erythematosus. *Lupus* 1993; **2**: 199–201.
26 Lusins JO, Szilagyi PA. Clinical features of chorea associated with systemic lupus erythematosus. *Am J Med* 1974; **58**: 857–61.
27 Lessof MH. Sydenham's chorea. *Guy's Hosp Rep* 1958; **107**: 185.
28 Wolf RE, McBeath JG. Chorea gravidarum in systemic lupus erythematosus. *J Rheumatol* 1985; **12**: 992–3.
29 Stojanovich L, Zandman-Goddard G, Pavlovich S, Sikanich N. Psychiatric manifestations in systemic lupus erythematosus. *Autoimmun Rev* 2007; **6**: 421–6.
30 Rodriguez IH, Morreno MJ, Morano LE *et al.* Systemic lupus erythematosus presenting as pseudocyesis. *Br J Rheumatol* 1994; **33**: 400–2.
31 Castellino G, Govoni M, Giacuzzo S, Trotta F. Optimizing clinical monitoring of central nervous system involvement in SLE. *Autoimmun Rev* 2008; **7**: 297–304.
32 Appenzeller S, Pike GB, Clarke AE. Magnetic resonance imaging in the evaluation of central nervous system manifestations in systemic lupus erythematosus. *Clin Rev Allergy Immunol* 2008; **34**: 361–6.
33 Kelly MC, Denburg JA. Cerebrospinal fluid immunoglobulins and neuronal antibodies in neuropsychiatric systemic lupus erythematosus and related conditions. *J Rheumatol* 1987; **14**: 740–4.
34 Isshi K, Hirohata S. Association of anti-ribosomal P protein antibodies with neuropsychiatric systemic lupus erythematosus. *Arthritis Rheum* 1996; **39**: 1483–90.
35 Asherson RA, Khamashta MA, Gil A *et al.* Cerebrovascular disease and antiphospholipid antibodies in systemic lupus erythematosus, lupus-like disease, and the primary antiphospholipid syndrome. *Am J Med* 1989; **86**: 391–9.
36 Petz LD, Sharp GC, Cooper NR *et al.* Serum and cerebral spinal fluid complement and serum autoantibodies in systemic lupus erythematosus. *Medicine* 1971; **50**: 259–75.
37 Deleze M, Mintz G, Del Carmen Mejia M. *Toxoplasma gondii* encephalitis in systemic lupus erythematosus: a neglected cause of treatable nervous system infection. *J Rheumatol* 1985; **12**: 994–6.

Involvement of the eyes. Eye changes in SLE are not uncommon [1]. They include lid oedema, conjunctivitis and subconjunctival haemorrhages, lacrimal hyposecretion, episcleritis, scleritis, anterior and posterior uveitis, retinal cytoid bodies, retinal haemorrhages and branch- and main-trunk arterial and venous occlusions. Optic neuritis is uncommon but may be the presenting feature, causing confusion with multiple sclerosis [2]. The retinal cytoid bodies—oval, whitish areas alongside arteries and veins—are not specific to SLE, and are thought to be brought about by damage to the endothelium of capillaries, which allows the passage of plasma and red cells into the nerve fibre layer. Depigmentation of the retina may be present. Retinal lesions rarely cause visual impairment, but blindness can occur [3]. Lupus retinopathy was found in approximately 8% in one large series and was associated with active disease and lupus cerebritis, and was a marker for poor prognosis [4]. Retinal changes can be demonstrated in nearly

one-third of patients by fluorescein angiography, and are associated with active disease [5]. Visual impairment may be the presenting symptom of SLE [6]. Symptoms of corneal involvement occur in more than half of patients, and 88% have corneal staining with fluorescein [7].

References

1 Lessell S. Some ophthalmological and neurological aspects of systemic lupus erythematosus. *J Rheumatol* 1980; **7**: 398–404.
2 Smith CA, Pinals RS. Optic neuritis in systemic lupus erythematosus. *J Rheumatol* 1982; **9**: 963–6.
3 Bishko F. Retinopathy in systemic lupus erythematosus. *Arthritis Rheum* 1972; **15**: 57–63.
4 Stafford-Brady FJ, Urowitz MB, Gladman DD *et al.* Lupus retinopathy. *Arthritis Rheum* 1988; **31**: 1105–10.
5 Lanham JG, Barrie T, Kohner EM *et al.* SLE retinopathy: evaluation by fluorescein angiography. *Ann Rheum Dis* 1982; **41**: 473–8.
6 Wong K, Ai E, Jones JV *et al.* Visual loss as the initial symptom of systemic lupus erythematosus. *Am J Ophthalmol* 1981; **92**: 238–44.
7 Spaeth GL. Corneal staining in systemic lupus erythematosus. *N Engl J Med* 1967; **21**: 1168–71.

Involvement of the ears. Sudden bilateral loss of hearing, presumably because of vasculitis of the arteries of the cochlea, may be dramatic and permanent. One patient's hearing responded to plasma exchange [1].

Reference

1 Hamblin TJ, Mufti GJ, Bracewell A. Severe deafness in systemic lupus erythematosus: its immediate relief by plasma exchange. *BMJ* 1982; **284**: 1374.

Muscle changes. Muscle pain occurs in approximately 50% of patients, and this may be confused with the pain of arthritis. Muscle weakness is a less common feature. Electromyographic abnormalities correlate better with weakness than myalgia. The serum aldolase level is frequently raised but the serum creatine phosphokinase is usually normal [1]. A vacuolar myopathy is considered to be specific [2]. Calcinosis may occasionally occur [3]. Very rarely, there may be a myasthenic reaction and SLE can follow, or be associated with myasthenia gravis [4]. A thymoma may sometimes be found [5].

References

1 Tsokos GC, Moutsopoulos HM, Steinberg AD. Muscle involvement in systemic lupus erythematosus. *JAMA* 1981; **246**: 766–7.
2 Lang PA, Smith GH, Green WO. Vacuolar myopathy in lupus erythematosus. *JAMA* 1965; **191**: 49–51.
3 Quismorio FP, Dubois EL, Chandon SB. Soft tissue calcification in systemic lupus erythematosus. *Arch Dermatol* 1975; **111**: 352–6.
4 Makela TE, Ruosteenoja R, Wager O *et al.* Myasthenia gravis and systemic lupus erythematosus. *Acta Med Scand* 1964; **175**: 777–80.
5 Funkhouser JW. Thymoma associated with myocarditis and the LE-cell phenomenon. *N Engl J Med* 1961; **264**: 34–6.

Involvement of tendons [1]. Tendon rupture is rare, and involves particularly the weight-bearing tendons such as the patellar, quadriceps and Achilles tendons, but it may occur in any tendon [2,3]. Tendinous laxity may precede rupture and be partly attributable to hyperparathyroidism secondary to chronic renal failure [4], although long-term corticosteroid therapy may be relevant. Abnormalities of the feet with clawing of the toes and flexion contractures have been designated 'lupus foot' [5].

References

1 Potasman I, Bass HM. Multiple tendon rupture in systemic lupus erythematosus: case report and review of the literature. *Ann Rheum Dis* 1984; **43**: 347–8.
2 Lotem J, Maor P, Levi M. Rupture of the extensor tendons of the hand in lupus erythematosus disseminatus. *Ann Rheum Dis* 1973; **32**: 457–9.
3 Hanley JG, Urowitz MB. Tendon rupture in systemic lupus erythematosus. *Ann Rheum Dis* 1986; **45**: 349.
4 Babini SM, Maldonado Cocco JA, De La Sota M *et al.* Tendinous laxity and Jaccoud's syndrome in patients with systemic lupus erythematosus: possible role of secondary hyperparathyroidism. *J Rheumatol* 1989; **16**: 494–8.
5 Morley KD, Leung A, Rynes RI. Lupus foot. *BMJ* 1984; **284**: 557–8.

Calcification. Calcification may occasionally occur. Nine patients in one series of 130 cases had calcification [1]. This is more frequent in the legs, and may be bilateral and diffuse in the skin or deeper soft tissues, or be unilateral and localized. Sometimes, there are large deposits or nodules in the subcutaneous tissues [2]. It can occur without preceding local inflammation or ulceration, and may antedate other manifestations of SLE by as long as 7 years [3]. Periarticular calcification in the hand has been reported [1]. Calcification of the arteries of the legs may occur in early adult life. The myopathy of SLE may result in calcification [4]. A case of SLE with hypercalcaemia has been reported [5]. The serum calcium returned to normal when the patient had responded to treatment with corticosteroids and intravenous pulse cyclophosphamide.

References

1 Budin JA, Feldman F. Soft tissue calcifications in systemic lupus erythematosus. *Am J Roentgenol* 1975; **124**: 358–64.
2 Nomura M, Okada N, Okada M, Yoshikawa K. Large subcutaneous calcification in systemic lupus erythematosus. *Arch Dermatol* 1990; **126**: 1057–9.
3 Kabir DI, Malkinson FD. Lupus erythematosus and calcinosis cutis. *Arch Dermatol* 1969; **100**: 17–25.
4 Quismorio FP, Dubois EL, Chandor SB. Soft tissue calcification in systemic lupus erythematosus. *Arch Dermatol* 1975; **111**: 352–6.
5 Deftos LJ, Burton DW, Baird SM *et al.* Hypercalcaemia and systemic lupus erythematosus. *Arthritis Rheum* 1996; **39**: 2066–9.

Bone changes. Avascular bone necrosis [1] occurs in 5–7% or more of patients and is considered to be part of the disease, although it may be exacerbated by corticosteroid treatment [2], especially in high doses. It may be more frequent in patients with the lupus anticoagulant [3]. It may occur in relatively mild cases of SLE [4], but the risk is increased in patients with Raynaud's phenomenon [5]. The femoral head or condyle is most frequently involved [6], but the condition also may involve the knees, ankles, humerus, metatarsals and the carpal bones causing wrist pain [7]. It is commonly bilateral, with involvement of multiple joints. It is rarely crippling, although it may proceed to destruction of the joint. X-rays may be normal, but the diagnosis is often clear on MRI [8]. The condition is thought to be associated with increased pressure in the bone marrow because of altered venous drainage, and core decompression may be successful [9]. Total hip replacement may be required if it fails, or in the late stages. There may be patchy sclerosis and cystic changes in the bones of the hands and feet, and metacarpophalangeal and metatarsophalangeal joints may rarely show subcondylar erosions and adjacent sclerosis [10]. Osteonecrosis, possibly resulting from infarction, has been found in as many as 13 joints during corticosteroid treatment [11].

Other manifestations of systemic involvement include lymphadenopathy, which occurs in more than 50% of cases, and splenomegaly. Swelling of the parotid, submaxillary and lacrimal glands sometimes develops. Some features of Sjögren's syndrome have been found in practically all cases of SLE on detailed investigation [12].

References

1 Dubois EL, Cozen L. Avascular (aseptic) bone necrosis associated with systemic lupus erythematosus. *JAMA* 1960; **174**: 966–71.
2 Kalla AA, Learmonth ID, Klemp P. Early treatment of avascular necrosis in systemic lupus erythematosus. *Ann Rheum Dis* 1986; **45**: 649–52.
3 Migliaresi S, Picillo U, Ambrosone L. Avascular osteonecrosis in patients with SLE: relation to corticosteroid therapy and anti-cardiolipin antibodies. *Lupus* 1994; **3**: 37–41.
4 Siemsen JK, Brook J, Meister L. Lupus erythematosus and avascular bone necrosis: a clinical study of three cases and review of the literature. *Arthritis Rheum* 1962; **5**: 492–501.
5 Zizic TM, Hungerford DS, Stevens MB. Ischaemic bone necrosis in systemic lupus erythematosus. *Medicine* 1980; **59**: 134–42.
6 Klipper AR, Stevens MB, Zizic TM *et al.* Ischaemic necrosis of bone in systemic lupus erythematosus. *Medicine* 1976; **55**: 251–7.
7 Urman JD, Abeles M, Houghton AN *et al.* Aseptic necrosis presenting as wrist pain in SLE. *Arthritis Rheum* 1977; **20**: 825–8.
8 Halland AM, Klemp P, Botes D *et al.* Avascular necrosis of the hip in systemic lupus erythematosus: the role of magnetic resonance imaging. *Br J Rheumatol* 1993; **32**: 972–6.
9 Hungerford DS, Zizic TM. The treatment of ischemic necrosis of bone in systemic lupus erythematosus. *Medicine* 1980; **59**: 143–8.
10 Green N, Osmer JC. Small bone changes secondary to systemic lupus erythematosus. *Radiology* 1968; **90**: 118–23.
11 Fishel B, Caspi D, Eventov I *et al.* Multiple osteonecrotic lesions in systemic lupus erythematosus. *J Rheumatol* 1987; **14**: 601–4.
12 Alarcón-Segoviá D, Ibanez G, Velazquez-Forero F *et al.* Sjögren's syndrome in systemic lupus erythematosus: clinical and subclinical manifestations. *Ann Intern Med* 1974; **81**: 577–83.

SLE in childhood [1]. The clinical picture, course and treatment are similar to the disorder in adults, but on the whole children have more severe disease [2]. The earliest age of onset reported is 3 months [3]. Bullous SLE may resemble chronic bullous disease of childhood [4]. In one series [5], 30% had CNS involvement and 87% had renal disease (diffuse proliferative lupus nephritis, 34%). Overall survival was 85% at 10 years and 77% at 15 years after onset. Children with CNS lupus did no worse than other patients, and this has been noted by others [6]. The prognosis of patients with renal disease is now better than earlier reports suggested. Enlargement of the liver, spleen and lymph nodes is more common in childhood cases. Pancreatitis associated with cutaneous panniculitis and calcinosis has been reported [7]. Prolonged therapy with high-dose steroids may increase disease-related damage; this may be avoided by judicious use of immunosuppressives [8]. Autologous stem cell transplantation has been used successfully [9].

SLE in the elderly [10]. The onset of disease over 60 years occurs in nearly 20% of patients and is often insidious. There is an increased incidence of lung disease and Sjögren's syndrome, and a lower incidence of renal disease and mesenteric vasculitis [11], and antibodies to Ro and La are frequent. There appears to be an association with HLA-DR3.

References

1 Tucker LB. Making the diagnosis of systemic lupus erythematosus in children and adolescents. *Lupus* 2007; **16**: 546–9.
2 Tucker LB, Menon S, Schally JG *et al.* Adult and childhood onset systemic lupus erythematosus: a comparison of onset, clinical features, serology and outcome. *Br J Rheumatol* 1995; **34**: 866–72.
3 Cummings NP, Hansen J, Hollister JR. Systemic lupus erythematosus in a premature infant. *Arthritis Rheum* 1985; **28**: 573–5.
4 Kettler AH, Bean SF, Duffy JO *et al.* Systemic lupus erythematosus presenting as a bullous eruption in a child. *Arch Dermatol* 1988; **124**: 1083–7.
5 Plat JL, Burke BA, Fish AJ *et al.* Systemic lupus erythematosus in the first two decades of life. *Am J Kidney Dis* 1982; **2** (Suppl. 1): 212–22.
6 Yancey CL, Doughty RA, Athneya BH. Central nervous system involvement in childhood systemic lupus erythematosus. *JAMA* 1981; **24**: 1389–95.
7 Simons-Ling N, Schachner L, Penneys N *et al.* Childhood systemic lupus erythematosus. *Arch Dermatol* 1983; **119**: 491–4.
8 Brunner HI, Silverman ED, To T *et al.* Risk factors for damage in childhood-onset systemic lupus erythematosus: cumulative disease activity and medication use predict disease damage. *Arthritis Rheum* 2002; **46**: 436–44.
9 Wulffraat NM, Sanders EA, Kamphuis SS *et al.* Prolonged remission without treatment after autologous stem cell transplantation for refractory childhood systemic lupus erythematosus. *Arthritis Rheum* 2001; **44**: 728–31.
10 Maddison PJ. Systemic lupus erythematosus in the elderly. *J Rheumatol* 1987; **13**: 182–7.
11 Hochberg MC, Boyd RE, Ahearn JM *et al.* Systemic lupus erythematosus: a review of clinico-laboratory features and immunogenetic markers in 150 patients with emphasis on demographic subsets. *Medicine* 1985; **64**: 285–95.

SLE in pregnancy [1,2]. Fertility is normal if renal function is good. Worsening of SLE is uncommon in pregnancy, especially in those on immunosuppressive therapy [3]. Clinical remission for 6 months before conception should indicate an uncomplicated pregnancy and a live birth [4]. The outcome with renal involvement is comparable with those whose kidneys are not affected [5]. There is a higher risk of premature delivery, fetal loss and perinatal mortality in all patients. Abortion occurred in 8% and perinatal mortality was 13% in one series [6]. The increased risk of fetal death may be because of immune complex deposition on the trophoblast basement membrane [7], or the transplacental passage of antiphospholipid antibodies. Anticardiolipin antibodies, especially of the IgG isotype [8] or the lupus anticoagulant, are associated with a markedly increased fetal loss in all stages of pregnancy, but the presence of these antibodies without a previous history of fetal loss or thrombosis is not an indication for treatment [1]. With a history of recurrent fetal loss, treatment with prednisone and aspirin may be effective [9]. With good obstetric care, close follow-up, and treatment with low-dose aspirin if antiphospholipid antibody is present, a success rate of 71% has been reported [10]. The authors have seen successful pregnancies following *in vitro* fertilization in patients with SLE and the lupus anticoagulant.

Therapeutic abortion is not indicated and only causes added stress, nor is caesarean section required. It is important to avoid excessive trauma, haemorrhage or shock. The dosage of corticosteroids should be temporarily increased at the time of delivery and postpartum. Corticosteroids do not appear to cause impairment of growth or malformation in the fetus, but high-dose steroids during early pregnancy can cause cleft palate. Babies of mothers with untreated SLE are usually smaller than expected, and corticosteroids may assist growth of the fetus *in utero* [5]. If the patient is on azathioprine, this should be continued as there is no evidence of an increase in the malformation rate [11].

Oestrogen-containing contraceptives, even at low dosage, should be avoided in women with SLE. If mechanical methods of contraception or intrauterine devices are not possible, pure progestogens may be an alternative [12]. Breastfeeding is probably safe if the patient is on aspirin or low-dose steroids, but should probably be avoided if other immunosuppressives are used.

References

1 Clowse ME. Lupus activity in pregnancy. *Rheum Dis Clin North Am* 2007; **33**: 237–52.
2 Petri M. The Hopkins Lupus Pregnancy Center: ten key issues in management. *Rheum Dis Clin North Am* 2007; **33**: 227–35.
3 Meehan RT, Dorsey JK. Pregnancy among patients with systemic lupus erythematosus receiving immunosuppressive therapy. *J Rheumatol* 1987; **14**: 252–8.
4 Hayslett JP. Effect of pregnancy in patients with SLE. *Am J Kidney Dis* 1982; **2** (Suppl. 1): 223–8.
5 Oviasu E, Hicks J, Cameron JS. The outcome of pregnancy in women with lupus nephritis. *Lupus* 1991; **1**: 19–25.
6 Varner MW, Meehan RT, Syrop CH *et al.* Pregnancy in patients with systemic lupus erythematosus. *Am J Obstet Gynecol* 1983; **145**: 1025–40.
7 Grennan DM, McCormick JN, Wojtacha D *et al.* Immunological studies of the placenta in systemic lupus erythematosus. *Ann Rheum Dis* 1978; **37**: 129–34.
8 Deleze M, Alarcón-Segoviá D, Valdes-Macho E *et al.* Relationship between antiphospholipid antibodies and recurrent fetal loss in patients with systemic lupus erythematosus and apparently healthy women. *J Rheumatol* 1989; **16**: 768–72.
9 Ordi J, Barquinero J, Vilardell M *et al.* Fetal loss treatment in patients with antiphospholipid antibodies. *Ann Rheum Dis* 1989; **48**: 798–802.
10 Derksen RHWM, Bruinse HW, de Groot PG *et al.* Pregnancy in systemic lupus erythematosus: a prospective study. *Lupus* 1994; **3**: 149–55.
11 Martinez-Ruada JO, Arce-Salinas CA, Kraus A *et al.* Factors associated with foetal losses in severe systemic lupus erythematosus. *Lupus* 1996; **5**: 113–9.
12 Jungers P, Dougados M, Pélissier C *et al.* Influence of oral contraceptive therapy on the activity of systemic lupus erythematosus. *Arthritis Rheum* 1982; **25**: 618–23.

Neonatal lupus erythematosus

Definition. Neonatal lupus erythematosus (NLE) is a disorder thought to be caused by the transplacental passage of maternal antibodies. The most frequent clinical manifestations are cutaneous lesions and congenital heart block (CHB).

Aetiology. Aylward [1] was the first to report CHB in the siblings of a mother with Mikulicz's disease (Sjögren's syndrome) in 1928. McCuiston and Schoch [2], however, were the first to suggest that the association of NLE and maternal systemic lupus may be related to the transplacental transfer of 'a transmittable aetiological agent' (maternal antibodies). This suggestion subsequently gained credence from the fact that the NLE skin lesions resolve as maternal antibodies are cleared from the infant's serum [3].

The first associated antibody described [4] and the serological marker most commonly associated with NLE is the Ro/SS-A antibody. This has been reported to be present in between 82% of infants and 92% of mothers [5] and 100% of NLE patients [6–8]. Two main Ro/SS-A proteins exist (52 and 60 kDa), and studies have suggested that the former is more frequently found in CHB [9,10], whereas the latter is more frequently associated with cutaneous disease [11], although this is by no means a universal finding [12]. It has been claimed that the aa200–239 (p200) locus on the 52-kDa Ro/SS-A protein is a more specific predictor of CHB [13], but a further study found this occurred with a similar frequency in children without CHB [14]. La/SS-B antibodies are less frequently found, one study detecting these in approximately 50% of NLE infants and 60% of mothers (usually in association with Ro/SS-A antibodies) [5]. A further study suggested that 50-kDa La/SS-B antibodies were associated with cutaneous disease [15], and another suggested that anti-idiotype antibodies to La/SS-B antibodies were protective against the development of NLE [16]. U_1-RNP antibodies are much less frequently found but have been reported as the only antibody in some patients with cutaneous NLE [17,18]. In this and subsequent reports, U_1-RNP antibodies have not been associated with CHB.

Evidence that these antibodies may be pathogenic comes from the studies of Lee *et al.* [19] who showed that purified Ro antibody bound to human skin grafted onto nude mice, in a pattern similar to that found in typical LE lesions. In addition, Ro/SS-A antigen is present in neonatal skin [20]. These antibodies have also been shown to bind to Ro/SS-A and La/SS-B antigen in human fetal cardiac conducting tissue [21–23] where they can cause conduction abnormalities [24,25]. A sequence of apoptosis, opsonization and fibrosis has been proposed [26].

It is unlikely that these antibodies represent the whole story, however, as they are non-specific for NLE, occurring in Sjögren's syndrome and SCLE. They are also found in approximately 0.5–2% of the normal population when assessed by immunodiffusion and in 5–11% when assessed by enzyme-linked immunoabsorbent assay (ELISA) [5]. Some studies have suggested that disease expression may be related to HLA status, the HLA-DR3 haplotype (especially when associated with DQA1 and DQB1) having been associated with the immune response to Ro/SS-A [27,28]. These, and a previous study [8], suggest that the HLA haplotype is important for antigen production in the mother but not necessarily relevant in the infants. Other workers argue that these antibodies are only indirectly related to disease, the disease process being caused by either: (i) the 52-kDa Ro/SS-A showing homology with the 5-HT_4 serotoninergic receptor, binding to which then mediates cardiac damage [10]; (ii) the presence of antibodies to a completely separate 57-kDa protein [29]; (iii) the prescience of the TNF-α 308A allele (associated with high TNF-α production), HLA-DRQB1*02, HLA DRB1*03 and TGF-β polymorphisms [30]; or (iv) via maternal microchimerisms [31,32]. A single case report has implicated α-interferon therapy in the aetiology of neonatal lupus [33].

Clinical features

Cutaneous. Approximately half of NLE infants manifest skin lesions [5], which may be present at birth or occur in the first few weeks of life. The most common finding is an erythematous, slightly scaly eruption on the face and periorbital skin (raccoon sign/owl-eye/eye mask) (Fig. 51.39), with the scalp, trunk, extremities, neck and intertriginous areas involved in decreasing order of frequency [34]. The eruption can be exacerbated by UV exposure and there are reports of the rash being precipitated by phototherapy for neonatal jaundice [35,36], although the rash is sometimes present at birth, which would make it difficult to implicate UV exposure in the aetiology [37]. Other manifestations include a vitiligo-like eruption in a black infant [38], morphoea-like lesions [39] and papules on the feet [40].



Fig. 51.39 Typical 'raccoon' eyelid lesions in neonatal lupus erythematosus.

The rash improves over the first few months of life and has usually resolved without scarring by 12 months of age. Occasional patients exhibit residual telangiectasiae [41], dyspigmentation or atrophy [34] and atrophic scarring [42].

Cardiac. Complete heart block occurs in approximately 60% of white patients [5], although it may be less common in Japanese patients [43]. Associated features may also include pericardial effusions, pleural effusions, ascites, intrauterine growth retardation and hydrops fetalis [44]. Up to 50% will require pacing in the neonatal period and others will require a pacemaker at a later date [45]. Dilated cardiomyopathy occurs in up to 20%, and has a significant mortality in the first year of life [45].

Haematological. Thrombocytopenia may occur in up to 20% of cases [41,46], is transient and does not usually require treatment, although it has been associated with petechial and purpuric lesions. Neutropenia, haemolytic anaemia and aplastic anaemia have also been reported [47,48].

Hepatic. Hepatomegaly and splenomegaly have been reported in NLE [49], with histological changes of 'neonatal hepatitis' and, on occasions, fibrosis. Cholestasis has been reported [49,50], as has cholestatic hepatitis [51,52]. A recent study showed hepatobiliary disease in 19 of 219 patients with NLE, and in three this was the only finding [53].

Miscellaneous. Case reports have associated NLE with pneumonitis [6], haemochromatosis [54], aseptic meningitis [55], myelopathy [56], transient myasthenia gravis [57], spastic paraparesis [41,58] and chondrodysplasia punctata [59]. One study demonstrated brain CT abnormalities in 10 of 11 infants with NLE although there was no clinical evidence of neurological disease, the authors emphasizing that it is important to be aware of these findings to avoid misdiagnosis of congenital viral infection in a newborn with multisystem NLE [60]. Hydrocephalus has been reported [61], affecting 8% of NLE infants in one study [62].

Treatment

Cutaneous lesions. Skin disease is often mild and requires no treatment. Sun avoidance should be advised and low-potency topical steroids may be of benefit [5,45]. Persistent telangiectasiae have been reported to respond to the tunable dye laser [63].

Cardiac. Up to 50% may require pacing in the newborn period, and others may require pacemaker insertion at a later date [44]. There is little information with regard to whether CHB and its consequences can be prevented or treated *in utero*. One study reviewed outcomes in pregnancies of mothers with Ro antibodies who had received systemic steroids during pregnancy [64]. When steroids had been given during the first 16 weeks of pregnancy, no conduction defects occurred, suggesting that they may have possibly suppressed disease initiation during this period of gestation. Corticosteroids administered after the first 16 weeks, however, were not beneficial and did not reverse established complete heart block. Another study compared outcome in fetuses whose mothers were treated with oral corticosteroids at various stages during pregnancy. Although there was no improvement in established complete heart block, the treated group showed less progression from first- to second-degree block to complete block and some improvement in pleural effusions, ascites and hydrops [43]. Anecdotally, a mother with the HLA-DR3 phenotype, high titres of Ro/SS-A and La/SS-B antibodies and an existing child with neonatal lupus, delivered a healthy infant after plasmapheresis three times weekly and systemic steroids during gestation [55].

The role of 'placenta crossing' steroids such as dexamethasone in at-risk infants is unclear at present, although a treatment algorithm has been suggested [26] and the results of a multicentre, prospective trial are awaited.

Haematological. Most resolve spontaneously without treatment, although prednisolone at a dose of 2 mg/kg/day for 14 days resulted in a dramatic improvement in thrombocytopenia in one patient [51].

Hepatic. Most resolve spontaneously without treatment.

Pregnancy. A pregnant patient who is known to have Ro/SS-A or La/SS-B antibodies should be made aware of the possible problems, and their obstetrician alerted. The risk of NLE in a Ro/SS-A positive mother without connective tissue disease or a previous history of NLE is probably low, perhaps about 2%. The risk may or may not be higher for symptomatic Ro/SS-A positive mothers, but for women who have already had a baby with NLE, the estimated risk of having another affected child ranges widely between studies, but is probably about 25% [65]. Perhaps in this latter group, the recommendation of serial fetal echocardiography by an experienced paediatric cardiologist [26] should be considered.

Although Ro/SS-A and La/SS-B antibodies have been demonstrated in human breast milk, a large study found no evidence to suggest that they had any pathological consequences. However, in the unusual circumstances of a worsening rash or developing cardiomyopathy, the authors suggested considering discontinuation of breastfeeding [66].

Prognosis

Infant. Although follow-up data are limited, some children have gone on to develop autoimmune disease, even in childhood [65], and one child developed a CNS vasculopathy at the age of 17 years [67]. Follow-up is therefore advised.

Mother. Although mothers are often asymptomatic at the time of the birth, long-term follow-up studies by several groups have shown that many develop signs and symptoms of autoimmune disease, especially Sjögren's syndrome, systemic lupus erythematosus and undifferentiated connective tissue disease [65]. Follow-up is therefore advised.

References

1 Aylward RD. Congenital heart block. *BMJ* 1928; **1**: 943.
2 McCuiston CH, Schoch EP. Possible discoid lupus erythematosus in newborn infant: report of a case with subsequent development of acute systemic lupus erythematosus in mother. *Arch Dermatol* 1954; **70**: 782–5.
3 McCauliff DP. Neonatal lupus erythematosus: a transplacentally acquired autoimmune disorder. *Semin Dermatol* 1995; **1**: 47–53.
4 Franco HL, Weston WL, Tan E *et al.* Association of antibodies to sicca syndrome antigens in newborns with lupus erythematosus and their mothers. *Clin Res* 1980; **28**: 134A.
5 Petri M, Watson R, Hochberg MC. Anti-Ro antibodies and neonatal lupus. *Rheum Dis Clin North Am* 1989; **15**: 335–60.
6 Watson RM, Lane AT, Barnett NK *et al*. Neonatal lupus erythematosus: a clinical, serological and immunogenetic study with review of the literature. *Medicine* 1984; **63**: 362–78.
7 Taylor PV, Taylor KF, Norman A *et al*. Prevalence of maternal Ro (SS-A) and La (SS-B) autoantibodies in relation to congenital heart block. *Br J Rheumatol* 1988; **27**: 128–32.
8 Lee LA, Weston WL. New findings in neonatal lupus syndrome. *Am J Dis Child* 1984; **138**: 233–6.
9 Viana VST, Garcia S, Nascimento JHM *et al.* Induction of *in vitro* heart block is not restricted to affinity purified anti-52 kDa Ro/SSA antibody from mothers of children with neonatal lupus. *Lupus* 1998; **7**: 141–7.
10 Eftekhari P, Salle L, Lezoualch F *et al.* Anti-SSA/Ro52 autoantibodies blocking the cardiac 5-HT_4 serotoninergic receptor could explain neonatal lupus congenital heart block. *Eur J Immunol* 2000; **30**: 2782–90.
11 Lee LA, Frank MB, McCubbin VR *et al*. Autoantibodies of neonatal lupus erythematosus. *J Invest Dermatol* 1994; **102**: 963–6.
12 Gordon P, Khamashta MA, Rosenthal E *et al*. Anti-52kDa Ro, anti-60 kDa Ro, and anti-La antibody profiles in neonatal lupus. *J Rheumatol* 2004; **31**: 2480–7.
13 Salomonsson S, Dorner T, Theander E *et al.* A serologic marker for fetal risk of congenital heart block. *Arthritis Rheum* 2002; **46**: 1233–41.
14 Clancy RM, Buyon JP, Ikeda K *et al.* Maternal antibody responses to the 52-kd SSA/Ro p200 peptide and the development of fetal conduction defects. *Arthritis Rheum* 2005; **52**: 3079–86.
15 Yukiko N. Immune responses to SS-A 52-kDa and 60-kDa proteins and to SS-B 50-kDa protein in mothers of infants with neonatal lupus erythematosus. *Br J Dermatol* 2000; **142**: 908–12.
16 Stea-Eleni A, Routsias JG, Clancy RM *et al.* Anti-La/SSB anti-idiotypic antibodies in maternal serum: a marker of low risk for neonatal lupus in an offspring. *Arthritis Rheum* 2006; **54**: 2228–34.
17 Provost TT, Watson R, Gammon WR *et al.* The neonatal lupus syndrome associated with U_1-RNP (nRNP) antibodies. *N Engl J Med* 1987; **316**: 1135–8.
18 Su CT, Huang CB, Chung MY. Neonatal lupus erythematosus in association with an anti-RNP antibody: a case report. *Am J Perinatol* 2001; **18**: 421–6.
19 Lee LA, Gaither KK, Coulter SN *et al*. Pattern of cutaneous immunoglobulin G deposits in subacute cutaneous lupus erythematosus reproduced by infusing purified anti-Ro (SSA) autoantibodies into human skin-grafted mice. *J Clin Invest* 1989; **83**: 1556–62.
20 Jones SK, Coulter S, Harmon C *et al.* Ro/SSA antigen in human epidermis. *Br J Dermatol* 1988; **118**: 363–7.
21 Deng JS, Blair LW, Shen-Schwartz S *et al*. Localization of Ro (SS-A) antigen in the cardiac conduction system. *Arthritis Rheum* 1987; **30**: 1232–8.
22 Horsfall AC, Venables PJW, Taylor PV *et al*. Ro and La antigens and maternal anti-La idiotype on the surface of myocardial fibres in congenital heart block. *J Autoimmun* 1991; **4**: 165–76.
23 Reichlin M, Brucato A, Frank MB *et al*. Concentration of autoantibodies to native 60-kD Ro/SS-A and denatured 52 kD Ro/SS-A in eluates from the heart of a child who died with congenital complete heart block. *Arthritis Rheum* 1994; **37**: 1698–703.
24 Alexander E, Buyon JP, Provost TT *et al*. Anti-Ro/SS-A antibodies in the pathophysiology of congenital heart block in neonatal lupus syndrome: an experimental model. *Arthritis Rheum* 1992; **35**: 176–89.
25 Garcia S, Nascimento JHM, Bonfa E *et al*. Cellular mechanism of the conduction abnormalities induced by serum from anti-Ro/SSA-positive patients in rabbit hearts. *J Clin Invest* 1994; **93**: 718–24.
26 Buyon JP, Clancy RM. Neonatal lupus: basic research and clinical perspectives. *Rheum Dis Clin N Am* 2005; **31**: 299–313.
27 Stephens HAF, McHugh NJ, Maddison PJ *et al.* HLA class II restriction of autoantibody production in patients with systemic lupus erythematosus. *Immunogenetics* 1991; **33**: 276–80.
28 Reveille JD, Macloed MJ, Whittington K *et al*. Specific amino acid residues in the second hypervariable region of HLA-DQA1 and DQB1 chain genes promote the Ro(SSA)/La(SSB) autoantibody responses. *J Immunol* 1991; **146**: 3871–6.
29 Maddison PJ, Lee L, Reichlin M *et al.* Anti-P57: a novel association with neonatal lupus. *Clin Exp Immunol* 1995; **99**: 42–8.
30 Clancy RM, Backer CB, Yin X *et al*. Genetic association of cutaneous neonatal lupus with HLA class II and tumor necrosis factor α. Implications for pathogenesis. *Arthritis Rheum* 2004; **50**: 2598–603.
31 Stevens AM, Hermes HM, Rutledge JC *et al*. Myocardial-tissue—specific phenotype of maternal microchimerism in neonatal lupus congenital heart block. *Lancet* 2003; **362**: 1617–23.
32 Stevens AM, Hermes HM, Lambert NC *et al*. Maternal and sibling microchimerism in twins and triplets discordant for neonatal lupus syndrome-congenital heart block. *Rheumatology* 2004; **44**: 187–91.
33 Fritz M, Vats K, Goyal RK. Neonatal lupus and IUGR following alpha-interferon therapy during pregnancy. *J Perinatol* 2005; **25**: 552–4.
34 Weston WL, Morelli JG, Lee LA. The clinical spectrum of anti-Ro positive neonatal lupus erythematosus. *J Am Acad Dermatol* 1999; **40**: 675–81.
35 Gawkrodger DJ, Beveridge GW. Neonatal lupus erythematosus in four successive siblings born to a mother with discoid lupus erythematosus. *Br J Dermatol* 1984; **111**: 683–7.
36 Luo SF, Huang CC, Wang JW. Neonatal lupus erythematosus: report of a case. *J Formos Med Assoc* 1989; **88**: 832–5.
37 Cimaz R, Biggioggero M, Catelli L *et al*. Ultraviolet light exposure is not a requirement for the development of cutaneous neonatal lupus. *Lupus* 2002; **11**: 257–60.
38 Jenkins RE, Kurwa AR, Atherton DJ *et al*. Neonatal lupus erythematosus. *Clin Exp Dermatol* 1994; **19**: 409–11.
39 Ohtaki N, Miyamoto C, Orita M *et al*. Concurrent multiple morphea and neonatal lupus erythematosus in an infant boy born to a mother with SLE. *Br J Dermatol* 1986; **115**: 85–90.
40 See A, Wargon O, Lim A *et al*. Neonatal lupus presenting as papules on the feet. *Australas J Dermatol* 2005; **46**: 172–6.
41 Bourke JF, Burns DA. Neonatal lupus erythematosus with persistent telangiectasia and spastic paraparesis. *Clin Exp Dermatol* 1993; **18**: 271–3.
42 High WA, Costner MI. Persistent scarring, atrophy, and dyspigmentation in a preteen girl with neonatal lupus erythematosus. *J Am Acad Dermatol* 2003; **48**: 626–8.
43 Kaneko F, Tanji O, Hasegawa T *et al*. Neonatal lupus erythematosus in Japan. *J Am Acad Dermatol* 1992; **26**: 397–403.
44 Saleeb S, Copel J, Friedman D *et al*. Comparison of treatment with fluorinated glucocorticoids to the natural history of autoantibody-associated congenital heart block: retrospective review of the research registry for neonatal lupus. *Arthitis Rheum* 1999; **42**: 2335–45.
45 Eronen M, Siren MK, Ekblad H *et al*. Short- and long-term outcome of children with congenital complete heart block diagnosed *in utero* or as a newborn. *Paediatrics* 2000; **106**: 86–91.

46 Provost TT, Watson R, Gaither KK *et al*. The neonatal lupus erythematosus syndrome. *J Rheumatol* 1987; **14** (Suppl. 13): 199–205.
47 Watson R, Kang JE, May M *et al*. Thrombocytopaenia in the neonatal lupus syndrome. *Arch Dermatol* 1988; **124**: 560–3.
48 Wolach B, Choc L, Pomeranz A *et al*. Aplastic anaemia in neonatal lupus erythematosus. *Am J Dis Child* 1993; **147**: 941–4.
49 Laxer RM, Roberts EA, Gross KR *et al*. Liver disease in neonatal lupus erythematosus. *J Paediatr* 1990; **116**: 238–42.
50 Rosh JR, Silvermann ED, Groisman G *et al*. Intrahepatic cholestasis in neonatal lupus erythematosus. *J Paediatr Gastroenterol Nutr* 1993; **17**: 310–2.
51 Lin SC, Shyur SD, Huang LH *et al*. Neonatal lupus erythematosus with cholestatic hepatitis. *J Microbiol Immunol Infect* 2004; **37**: 131–4.
52 Erbey F, Cuhaci A, Incecik F *et al*. Neonatal lupus erythematosus presenting with cholestatic hepatitis: a case report and review of the literature. *Turk J Paediatr* 2005; **47**: 63–6.
53 Lee LA, Sokol R, Buyon JP. Hepatobiliary disease in neonatal lupus: prevalence and clinical characteristics in cases enrolled in a national registry. *Pediatrics* 2002; **109**: E11.
54 Schoenlebe J, Buyon JP, Zitelli BJ *et al*. Neonatal haemochromatosis associated with maternal antibodies against Ro/SS-A and La/SS-B ribonucleoprotein. *Am J Dis Child* 1993; **147**: 1072–5.
55 Buyon JP, Roubey R, Swersky S *et al*. Complete congenital heart block: risk of occurrence and therapeutic approach to prevention. *J Rheum* 1998; **15**: 1104–8.
56 Kaye EM, Butler IJ, Conley S. Myelopathy in neonatal and infantile lupus erythematosus. *J Neurol Neurosurg Psychiatry* 1987; **50**: 923.
57 Rider LG, Sherry DD, Glass ST. Neonatal lupus erythematosus simulating transient myasthenia gravis at presentation. *J Paediatr* 1991; **118**: 417–9.
58 Besson-Leaud L, Fontan D, Billeaud C *et al*. Lupus neonatal et atteinte neurologique: une association fortuite? *Arch Pediatr* 2002; **9**: 503–5.
59 Austin-Ward E, Castillo S, Cuchacovich M *et al*. Neonatal lupus syndrome: a case with chondrodysplasia punctata and other unusual features. *J Med Genet* 1998; **35**: 695–7.
60 Prendivill JS, Cabal DA, Poskitt KJ *et al*. Central nervous system involvement in neonatal lupus erythematosus. *Paediatr Dermatol* 2003; **20**: 60–7.
61 Nakayama-Furukawa F, Takigawa M, Iwatsuki K *et al*. Hydrocephalus in two female siblings with neonatal lupus erythematosus. *Arch Dermatol* 1994; **130**: 1210–2.
62 Boros CA, Spence D, Blaser S *et al*. Hydrocephalus and macrocephaly: new manifestations of neonatal lupus erythematosus. *Arthritis Rheum* 2007; **57**: 261–6.
63 Thornton CM, Eichenfield LF, Shinall EA *et al*. Cutaneous telangiectases in neonatal lupus erythematosus. *J Am Acad Dermatol* 1995; **33**: 19–25.
64 Shinohara K, Miyagawa S, Fujita T *et al*. Neonatal lupus erythematosus: results of maternal corticosteroid therapy. *Obstet Gynaecol* 1999; **93**: 952–7.
65 Lee LA. Transient autoimmunity related to maternal autoantibodies: neonatal lupus. *Autoimmun Rev* 2005; **4**: 207–13.
66 Askanase AD, Miranda-Carus ME, Tang X *et al*. The presence of IgG antibodies reactive with components of the SSA/Ro-SSB/La complex in human breast milk: implications in neonatal lupus. *Arthritis Rheum* 2002; **46**: 269–71.
67 Inoue K, Fukushige J, Ohno T *et al*. Central nervous system vasculopathy associated with neonatal lupus. *Pediatr Neurol* 2002; **26**: 68–70.

Laboratory investigations [1]. Laboratory investigations are frequently necessary to confirm the diagnosis, although even after extensive investigations it may be impossible to be entirely dogmatic, in view of the overlap of the manifestations of connective tissue diseases. Anaemia, of some degree, is found in approximately 75% of patients and is brought about by deficiency of iron, haemolysis or renal failure. The serum iron is usually low and may rise after corticosteroid therapy [2]. A positive Coombs' test can occur in the absence of haemolytic anaemia, and was present in 15% in a series of cases seen by the authors. Pure red cell aplasia has been reported [3]. Although leukopenia, specifically a lymphopenia, is a characteristic feature of the condition, and a white cell count of below 5000/mm^2 occurs in more than 33% of patients, leukocytosis may occasionally be found. The platelet count is reduced in approximately 20% of cases and is usually below 40 000/mm^2 in patients presenting with thrombocytopenic purpura. Thrombocytopenia may appear only during exacerbations or be a mild persisting feature [4]. Hyposplenism may occur [5]. The ESR is raised at some time in nearly 90% of patients; the C-reactive protein (CRP) is usually normal in the absence of infection, but some patients have a normal ESR throughout. The plasma viscosity may be raised, although initially thought unreliable, a more consistent assay is now being more widely used as an indicator of activity [6]. Serum globulins are frequently raised, with a rise in the gammaglobulin usually, although α_2-globulin may be elevated and the albumin decreased. IgE antibodies may be raised [7,8], particularly in patients with arthritis. False-positive serological tests for syphilis are found in approximately 25% of patients [9] and an atypical 'beaded' pattern of fluorescence of the *Treponema pallidum* antigen occurs when sera from certain patients are tested in the fluorescent treponemal antibody absorption (FTA-ABS) test [10]. Rheumatoid factor occurs in approximately 40%. Thrombosis occurs with the lupus anticoagulant (see p. 51.63), but occasionally haemorrhage results from other haematological abnormalities [11]. The lupus anticoagulant is one of a number of antiphospholipid antibodies that may be found in up to 50% of patients with SLE. As well as thrombosis, CNS disease is strongly related to the presence of these antibodies [12].

The LE cell phenomenon, first described by Hargraves *et al*. [13], is the basis for the LE cell test, which is positive in over 80% of patients. LE cells are polymorphonuclear leukocytes which have ingested nuclear material from degenerative white cells, in the presence of an antibody to deoxyribonucleoprotein (the LE cell factor) (Fig. 51.40). Sometimes, large masses of nuclear material are found extracellularly and, with surrounding leukocytes, form rosettes. LE cells, if present in large numbers, are highly suggestive of SLE, but the occasional LE cell is sometimes demonstrated in other conditions, including chronic DLE, systemic sclerosis and rheumatoid arthritis [14]. A positive LE cell test is a feature of drug-induced LE; LE cells were demonstrated in 60 out of 66

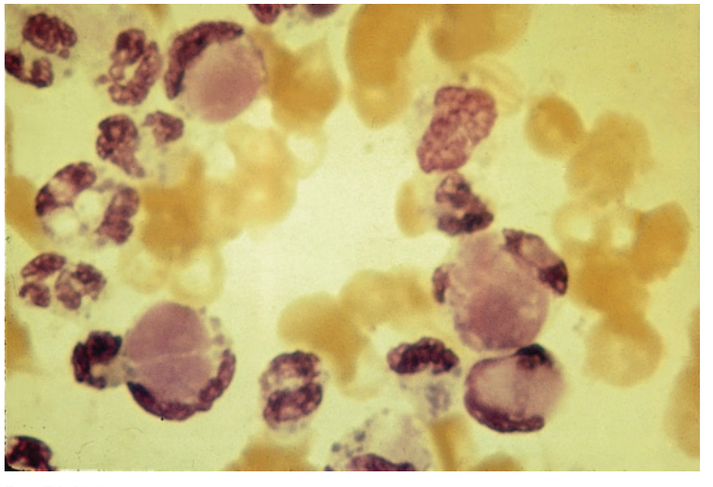


Fig. 51.40 Lupus erythematosus cells: the phagocytosed nuclear material is homogeneous and displaces the polymorph nucleus to one side.

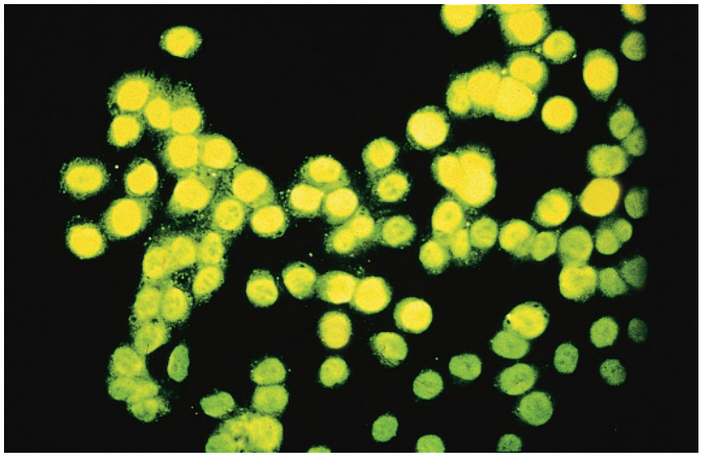


Fig. 51.41 Homogeneous type of antinuclear factor demonstrated on Hep-2 cells.

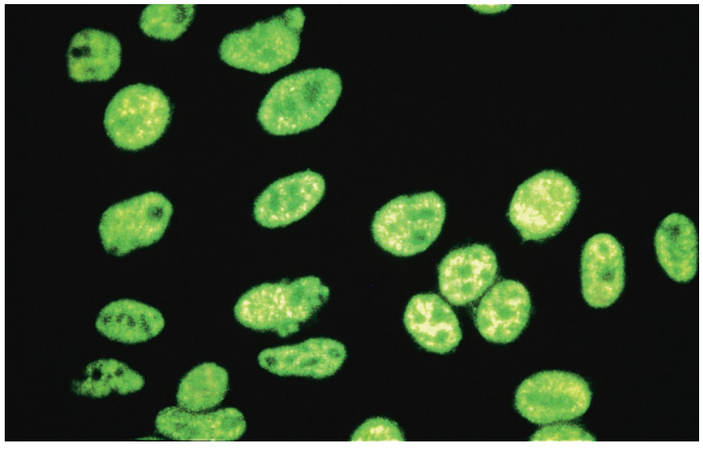


Fig. 51.43 Speckled type of antinuclear factor demonstrated on Hep-2 cells.

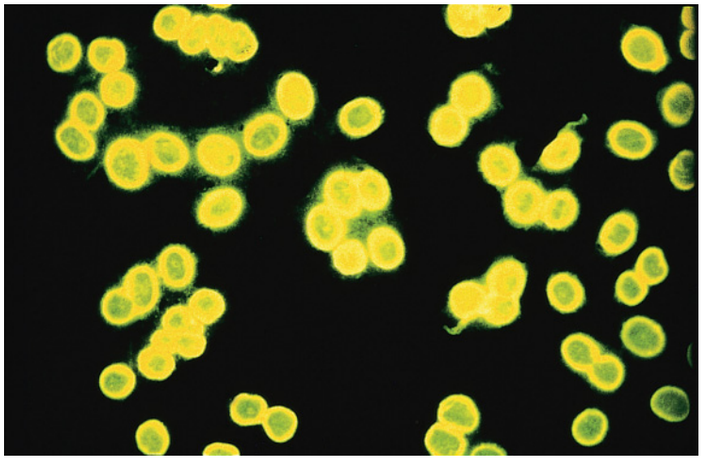


Fig. 51.42 Peripheral type of antinuclear factor demonstrated on Hep-2 cells.

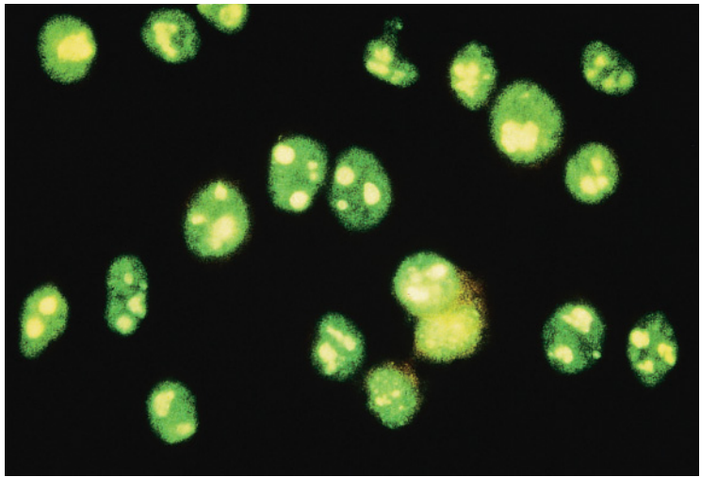


Fig. 51.44 Nucleolar type of antinuclear factor demonstrated on Hep-2 cells.

patients with procainamide-induced lupus [15]. The LE cell test has now been superseded by tests for antinuclear factors and anti-DNA antibodies.

One or more antinuclear antibodies can be detected by fluorescent antibody techniques in over 80% of cases. The incidence depends on the substrate used. Most British laboratories now use human cell lines for antibody testing, particularly Hep-2 cells derived from a human laryngeal cell line. This produces a reduction in the proportion of patients said to be antinuclear factor negative. Previously, the standard substrate was rat or mouse liver. Using rat liver, four staining patterns can be demonstrated [16], representing four systems of antinuclear antibodies (Figs 51.41–51.44).

1 In the *homogeneous pattern*, produced by antinucleohistone, the nuclei are stained all over.
2 The *speckled pattern* shows minute points of fluorescence scattered all over the nucleus, the antigens being saline-soluble proteins.
3 The *nucleolar pattern* shows uniform staining of each nucleolus.
4 Sera containing anti-DNA antibody give rise to the fourth *peripheral or membranous pattern* [16,17], in which staining occurs at the periphery of the nucleus.

These staining patterns are produced by separate antibodies, but more than one antibody may be present in a single serum, usually in different titres. No particular antibody is specific for any disease. Discrepancies in the incidence between series probably depend on differences in techniques and the substrate used.

Homogeneous antinuclear factor (which is the same factor as the LE cell factor, although the fluorescent antibody test is more sensitive than the LE cell test) is more than twice as common as the speckled factor, but antinucleolar antibody is only occasionally found. The peripheral factor is present in high titre in more than 50% in the active phase of the disease [18], and is infrequent in other diseases. The so-called shrunken peripheral pattern is thought to be associated with a poor prognosis and a high incidence of renal disease [19]. It may appear 10–15 days before an exacerbation of the disease and be associated with a fall in serum complement [20]. In a series of 63 cases of SLE seen by the authors, one or more antinuclear factors were demonstrated in 55 patients

(87%). Homogeneous staining was present in 46 cases, speckled staining in 18 and nucleolar staining in five. Titres up to 1:32 000 occur, but the titre frequently bears no relation to the activity, progress or duration of the disease. A high titre (over 1:64) of antinuclear factor(s), in a patient with symptoms and signs of a multiple system disorder, suggests the possibility of SLE or systemic sclerosis, and almost certainly excludes polyarteritis nodosa or cutaneous vasculitis. Any person in apparently good health found to have a high titre of antinuclear factor should be followed-up for years, as there is a considerable likelihood of developing LE or systemic sclerosis. A low titre (less than 1:16), in the absence of clinical symptoms and signs, can be ignored [21].

When Hep-2 cells are used as substrate, as well as being more sensitive to the presence of antinuclear antibody, further patterns can be identified [22]. These include centromere staining (see p. 51.103) associated with the CREST syndrome and in 6% of patients with SLE, homogeneous, peripheral (specific to SLE), fine and coarse speckles and a ground-glass appearance produced by Scl-70 antibody (see p. 51.103) found in systemic sclerosis. There are also several patterns of nucleolar staining: homogeneous, speckled and clumpy. The full clinical association of these antibodies has not been determined.

Circulating antibodies to DNA are almost always present in active disease [23,14] and may occur in the absence of antinuclear factors [24], although this is very uncommon using Hep-2 cells. Their demonstration by the Farr technique is the most specific aid to diagnosis, and levels often correlate with disease activity, although DNA antibodies should not be the only criterion [25]. Radiolabelled DNA is incubated with the test serum and any DNA–anti-DNA complexes formed are precipitated by 50% ammonium sulphate. Comparison of the radioactivity in the supernatant and precipitate gives the so-called DNA-binding activity. Values above 30% are abnormal. The level was raised in 83% of patients with SLE and in 100% of those with active disease. A rise in the index may precede an exacerbation of the disease, and levels fall with remission [26]. Normal values are found in drug-induced LE and in other disorders in which antinuclear antibodies occur. A high binding capacity is associated with poor prognosis and renal disorder [16]. The peripheral staining pattern of antinuclear antibody does not correlate with anti-DNA antibodies or with disease activity [27].

Several other antibodies occur in patients with SLE. Patients with antihistone antibodies have a lower incidence of renal and CNS disease, alopecia, anaemia and decreased complement [28]. Antibodies to soluble cellular antigens include anti-Sm antibody, which is found in 15–25% of patients and appears to be specific for the disease, occurring particularly in patients with renal disease, CNS disease and vasculitis. Anti-RNP antibodies occur in 25% of patients [29], but are characteristic of mixed connective tissue disease (see p. 51.111). It has been reported that titres correlate with disease activity [30].

Anti-Ro [31] antibody occurs in 30% of patients who have an increased tendency to photosensitivity [32,33], renal disease, Sjögren's syndrome and rheumatoid factor, as well as being a marker for neonatal lupus (see p. 51.49). It is also found in SCLE (see p. 51.22). Anti-Ro is an antibody to an RNP derived from RNA polymerase III-transcribed hY RNAs with a protein component that appears to be the main target. Two different proteins, one of 60 kDa and another of 52 kDa, react with most positive sera. The 60-kDa protein predominates in SLE, the 52-kDa in Sjögren's syndrome [34]. Patients with anti-Ro antibodies are more likely to have HLA-B8 and -DRw3 [35]. Anti-La, an antibody to another RNP product of RNA polymerase III, is present in 10–15% of patients, often with Sjögren's syndrome and with anti-Ro antibody. Although several different antibodies occur in the same patient, they fluctuate independently, and the antibody profile may alter over the years. The only characteristic pattern of antibody appears to occur in the LE–erythema multiforme syndrome [36], in which there is speckled type of antinuclear factor, a specific precipitating antibody (originally designated SjT but now thought to be anti-La) and rheumatoid factor. This syndrome is occasionally found in cases of systemic as well as DLE, in which it was originally described (see p. 51.14). In cases associated with SLE, homogeneous antinuclear factor is also usually present.

Cryoglobulins may be found in 11% of patients. Cryoglobulinaemia may precede the manifestations of SLE by many years [37]. Cold agglutinins occur in 6%. Serum complement is frequently low [38], especially in patients with active nephritis. A decrease in levels may precede clinical evidence of an exacerbation of disease, and return to normal with remission but, in general, estimations of CH50, C3, C4 and circulating immune complexes are rarely helpful in assessing disease activity [39]. Other possible indicators of disease activity include β_2-macroglobulin [40] and serum IFN [41]. Increased levels of plasma anaphylatoxins (C3a) may predict exacerbations [42]. The intracutaneous injection of DNA solution, which has been advocated as a skin test [43], is not specific. Occasionally, circulating anticoagulants may be demonstrated [44,45]. Factor II may be absent and return with steroid therapy [46].

Inherited deficiencies of the major complement components occur with SLE [47], usually as autosomal recessive traits [48]. These include C1 [49], C2 [50] and C4 [51], as well as C5–C9. The most common is homozygous C2 deficiency in which SLE occurs in one-third of patients. Clinically, the lupus-like syndrome in C2 deficiency shows a low incidence of renal disease, low incidence and low titres of anti-DNA antibodies, infrequent occurrence of immunoglobulin and complement deposits in the skin, and frequent anti-Ro antibodies [46]. Isolated C1q deficiency has also been reported [52], and there is an association between C1-esterase inhibitor deficiency and SLE [53]. Patients may be helped by danazol [54]. Hereditary angio-oedema and SLE were found in the mother of twin boys who had DLE and angio-oedema, and this was associated with low C1 inhibitor and C4 levels [55]. Antibodies to Australia antigen can be demonstrated in 25% of cases [56]. Serum CRP levels are usually normal or only slightly elevated. A level higher than 60 mg/L suggests the presence of superimposed infection [57]. A number of soluble cytokines or their receptors may be found in serum of patients with SLE, and may correlate with disease activity: intercellular adhesion molecule-1 (ICAM-1) [58], TNF receptor [59] and IL-10 [60]. There is differential overexpression of heat-shock proteins in patients with differing patterns of systemic involvement [61]. Urinary levels of neopterin [62], or of IL-6 [63], may also be useful to monitor disease activity.

References

1 Wallace DJ, Hahn BH, eds. *Dubois' Systemic Lupus Erythematosus*, 4th edn. Philadelphia: Lea and Febiger, 1993.
2 Whittingham S, Balazs NDH, MacKay IR. The effect of corticosteroid drugs on serum iron levels in systemic lupus erythematosus and rheumatoid arthritis. *Med J Aust* 1967; **ii**: 639–41.
3 Nitsche A, Taborda GD, Bouveta HM *et al.* Pure red cell aplasia in a patient with systemic lupus erythematosus. *J Rheumatol* 1988; **15**: 1012–3.
4 Miller MH, Urowitz MB, Gladman DD. The significance of thrombocytopenia in systemic lupus erythematosus. *Arthritis Rheum* 1983; **26**: 1181–6.
5 Dillon AM, Stein HB, English RA. Splenic atrophy in systemic lupus erythematosus. *Ann Intern Med* 1982; **96**: 40–3.
6 Hazelton RA, Lowe GDO, Forbes CD *et al.* Increased blood and plasma viscosity in systemic lupus erythematosus (SLE). *J Rheumatol* 1985; **12**: 616–7.
7 Goldman JA, Klimek GA, Ali R. Allergy in systemic lupus erythematosus. *Arthritis Rheum* 1976; **19**: 669–76.
8 Gruber BL, Kaufman LD, Marchese MJ *et al.* Anti-IgE autoantibodies in systemic lupus erythematosus. *Arthritis Rheum* 1988; **31**: 1000–6.
9 Shore RN, Faricelli JA. Borderline and reactive FTA-ABS results in lupus erythematosus. *Arch Dermatol* 1977; **113**: 37–41.
10 Kraus SJ, Daniels KC. Atypical FTA-ABS test reaction. *Arch Dermatol* 1971; **104**: 260–1.
11 Quismorio FP Jr. Hemic and lymphatic abnormalities in SLE. In: *Dubois' Systemic Lupus Erythematosus*, 4th edn. Philadelphia: Lea & Febiger, 1993: 418–30.
12 Derksen RHWM, Stephens CJM. The antiphospholipid syndrome. In: Kater L, Barte de la Faille H, eds. *Multi-systemic Auto-immune Diseases: An Integrated Approach*. Amsterdam: Elsevier, 1995.
13 Hargraves MM, Richmond H, Morton R. Presentation of two bone marrow elements: the 'tart' cell and the 'LE' cell. *Proc Staff Meetings Mayo Clin* 1948; **23**: 26–8.
14 Hughes GRV. Lupus erythematosus. In: Walker G, ed. *9th Symposium of Advanced Medicine*. London: Pitman, 1973: 67.
15 Condemi JJ, Blomgren SE, Vaughan JH. Procaineamide induced LE. *Bull Rheum Dis* 1970; **20**: 604.
16 Beck JS. Auto-antibodies to cell nuclei. *Scott Med J* 1963; **8**: 373–88.
17 Casals SP, Friou GJ, O'Teague PO. Specific nuclear reaction pattern of antibody to DNA in lupus erythematosus sera. *J Lab Clin Med* 1963; **62**: 625–31.
18 Nisengard RJ, Jablonska S, Chorzelski TP *et al.* Diagnosis of systemic lupus erythematosus. *Arch Dermatol* 1975; **111**: 1298–300.
19 Burnham TK. Antinuclear antibodies. *Arch Dermatol* 1975; **111**: 203–7.
20 Mandl MAJ, Watson JI. Nuclear immunofluorescence: a guide to treatment in SLE. *Lancet* 1969; **ii**: 848.
21 Rowell NR, Swanson Beck J. The diagnostic value of an antinuclear antibody test in clinical dermatology. *Arch Dermatol* 1967; **96**: 290–5.
22 Bernstein RM, Steigenwald JC, Tan EM. Association of antinuclear and antinucleolar antibodies in progressive systemic sclerosis. *Clin Exp Immunol* 1982; **48**: 43–51.
23 Ballou SP, Kushner I. Lupus patients who lack detectable anti-DNA: clinical features and survival. *Arthritis Rheum* 1982; **25**: 1126–9.
24 Lindstedt G, Lundberg PA, Westberg G *et al.* SLE nephritis with positive tests for antibodies against native DNA but negative tests for antinuclear antibodies. *Lancet* 1977; **ii**: 135.
25 Davis P, Percy JS, Russell AS. Correlation between levels of DNA antibodies and clinical disease activity in SLE. *Ann Rheum Dis* 1977; **36**: 157–9.
26 Swaak AJG, Groenwold J, Aarden LA *et al.* Prognostic value of anti-dsDNA in SLE. *Ann Rheum Dis* 1982; **41**: 388–95.
27 Weitzman RJ, Walker SE. Relation of titred peripheral pattern ANA to anti-DNA and disease activity in systemic lupus erythematosus. *Ann Rheum Dis* 1977; **36**: 44–9.
28 Fritzler M, Ryan P, Kinsella TD. Clinical features of systemic lupus erythematosus patients with antihistone antibodies. *J Rheumatol* 1982; **9**: 46–51.
29 Aitcheson CT, Tan EM. Autoantibodies in connective tissue disease. In: Panayi GS, ed. *Scientific Basis of Rheumatology*. Edinburgh: Churchill Livingstone, 1982: 87–113.
30 Nishikai M, Okano Y, Mukohda Y *et al.* Serial estimation of anti-RNP antibody titers in systemic lupus erythematosus, mixed connective tissue disease and rheumatoid arthritis. *J Clin Lab Immunol* 1984; **13**: 15–9.
31 Provost TT, Watson R, Simmons-O'Brien E. Anti-Ro (SSA) antibody positive Sjögren's/lupus erythematosus overlap syndrome. *Lupus* 1997; **6**: 105–11.
32 Provost TT, Watson R, Simmonds-O'Brien E. Significance of the anti-Ro (SS-A) autoantibody in evaluation of patients with cutaneous manifestations of a connective tissue disease. *J Am Acad Dermatol* 1996; **35**: 147–69.
33 Mond CB, Peterson MGE, Rothfield NF. Correlation of anti-Ro antibody with photosensitivity rash in systemic lupus erythematosus patients. *Arthritis Rheum* 1989; **32**: 202–4.
34 Ben-Chetrit E, Fox RI, Tan EM. Dissociation of immune response to the SS-A (Ro) 52 kD and 60 kD polypeptides in systemic lupus erythematosus and Sjögren's syndrome. *Arthritis Rheum* 1990; **33**: 349–55.
35 Bell DA, Maddison PJ. Serologic subsets in systemic lupus erythematosus. *Arthritis Rheum* 1980; **23**: 1268–73.
36 Rowell NR, Swanson Beck J, Anderson JR. Lupus erythematosus and erythema multiforme-like lesions. *Arch Dermatol* 1963; **88**: 176–80.
37 Perek J, Mittelman M, Eisbruch A *et al.* Systemic lupus erythematosus preceded by long-term cryoglobulinaemia. *Ann Rheum Dis* 1984; **43**: 339–40.
38 Schur PH, Sanderson J. Immunologic factors and clinical activity in systemic lupus erythematosus. *N Engl J Med* 1968; **278**: 533–8.
39 Valentijn RM, van Overhagen H, Hazevoet M *et al.* The value of complement and immune complex determinations in monitoring disease activity in patients with systemic lupus erythematosus. *Arthritis Rheum* 1985; **28**: 904–13.
40 Yeung C-K, Wong K-L, Wong W-S *et al.* β_2-Microglobulin and systemic lupus erythematosus. *J Rheumatol* 1986; **13**: 1053–8.
41 Shou-Nee S, Fang FS, Yumei W *et al.* Serum interferon in systemic lupus erythematosus. *Br J Dermatol* 1987; **117**: 155–9.
42 Hopkins P, Belmont HM, Buyon J *et al.* Increased levels of plasma anaphylatoxins in systemic lupus erythematosus predict flares of the disease and may elicit vascular injury in lupus cerebritis. *Arthritis Rheum* 1988; **31**: 632–41.
43 Ores RO, Lange K. Skin test for the diagnosis of systemic lupus erythematosus. *Am J Med Sci* 1964; **248**: 562.
44 Lee SL, Miotti AB. Disorders of hemostatic function in patients with systemic lupus erythematosus. *Semin Arthritis Rheum* 1975; **4**: 241.
45 Castro O. Circulating anticoagulants against factors IX and XI in systemic lupus erythematosus. *Ann Intern Med* 1972; **77**: 543–8.
46 Natelson EA, Cyprus GS, Heltig RA. Absent factor II in systemic lupus erythematosus. *Arthritis Rheum* 1976; **19**: 79–82.
47 Walport MJ. Complement deficiency and disease. *Br J Rheumatol* 1993; **32**: 269–73.
48 Agnello V. Complement deficiency states. *Medicine* 1978; **57**: 1–23.
49 Moncada B, Day NKB, Good RA *et al.* Lupus erythematosus-like syndrome with a familial defect of complement. *N Engl J Med* 1972; **286**: 689–93.
50 Rynes RI, Urizar RE, Pickerling RJ. Genetic deficiency of the second component of complement (C2) associated with systemic lupus erythematosus. *Am J Med* 1977; **63**: 278–88.
51 Tappeiner G, Hintner H, Scholz S *et al.* Systemic lupus erythematosus in hereditary deficiency of the fourth component of complement. *J Am Acad Dermatol* 1982; **7**: 66–79.
52 Steinsson K, McLean RH, Merrow M *et al.* Selective complete C1q deficiency associated with systemic lupus erythematosus. *J Rheumatol* 1983; **10**: 590–4.
53 Bagot M, Revuz J, Intrator L *et al.* Oedème angioneurotique acquis révélant un lupus erythemateux disseminé. *Ann Dermatol Vénéréol* 1987; **114**: 1331–3.
54 Donaldson VH, Hess EV. Effect of danazol on lupus erythematosus-like disease in hereditary angioneurotic oedema. *Lancet* 1980; **ii**: 1145.
55 Kohler PF, Percy J, Campion WM *et al.* Hereditary angioedema and 'familial' lupus erythematosus in identical twin boys. *Am J Med* 1974; **56**: 406–11.
56 Alarcón-Segoviá D, Fishbein E. Australia antigen in systemic lupus. *N Engl J Med* 1971; **284**: 448.
57 Pepys MB, Lanham JG, De Beer FC. C-reactive protein in systemic lupus erythematosus. *Clin Rheum Dis* 1982; **8**: 91–103.
58 Sfikakis PP, Charalambopoulos D, Vayiopoulos G *et al.* Increased levels of intercellular adhesion molecule-1 in the serum of patients with systemic lupus erythematosus. *Clin Exp Rheumatol* 1994; **12**: 1–9.
59 Aderna D, Wysenbeek A, Engelmann H *et al.* Correlation between serum levels of soluble tumour necrosis factor receptor and disease activity in systemic lupus erythematosus. *Arthritis Rheum* 1993; **36**: 1111–20.
60 Houssiau FA, Lefebvre C, Vandenberghe M *et al.* Serum interleukin 10 titres in systemic lupus erythematosus reflect disease activity. *Lupus* 1995; **4**: 393–5.

61 Dhillon VB, McCallum S, Norton P *et al.* Differential heat shock protein overexpression and its clinical relevance in systemic lupus erythematosus. *Ann Rheum Dis* 1993; **52**: 436–42.
62 Lim KL, Jones AC, Brown NS, Powell RJ. Urine neopterin as a parameter of disease activity in patients with systemic lupus erythematosus: comparisons with serum sIL-2r and antibodies to dsDNA, erythrocyte sedimentation rate, and plasma C3, C4, and plasma C3 degradation products. *Ann Rheum Dis* 1993; **52**: 429–35.
63 Iwano M, Dohi K, Hirata E *et al.* Urinary levels of IL-6 in patients with active lupus nephritis. *Clin Nephrol* 1993; **40**: 16–21.

Antinuclear antibody-negative SLE [1,2]. Patients originally described under this title have many similarities with patients suffering from SCLE (see p. 51.22). Because the cutaneous involvement is usually the predominant feature, many patients present initially to dermatologists. Clinically, a non-scarring malar flush, oral ulceration and photosensitivity, with papulosquamous or annular lesions on the face, trunk and arms, are prominent, but arthritis, serositis, renal disease and haematological involvement are less frequent than expected in SLE. In approximately 5–10% of patients with SLE, antinuclear factor cannot be demonstrated using standard substrates such as rat or mouse liver. This is a problem in less than 1% if Hep-2 cells are used. These patients frequently have anticytoplasmic antibodies. Over 60% of patients have anti-Ro antibodies and approximately one-third have anti-La antibody (anti-La rarely occurs without anti-Ro). Twenty-five per cent have antibodies to single-stranded DNA. There is no difference in the histology of the skin between antinuclear-negative and -positive cases. Immunoglobulins and complement are found at the dermal–epidermal junction in 70% of patients, but are rare in the non-light-exposed uninvolved skin. Topical steroid therapy may be helpful, but oral antimalarials and steroids may be required. Approximately 10% of patients eventually become antinuclear factor-positive, although the pattern of anticytoplasmic antibodies does not alter.

References

1 Ahmed R, Workman S. ANA-negative systemic lupus erythematosus. *Clin Exp Dermatol* 1983; **8**: 369–77.
2 Maddison PJ, Provost TT, Reichlin M. Serological findings in patients with ANA-negative systemic lupus erythematosus. *Medicine* 1981; **60**: 87–94.

Assessment of disease activity. A number of attempts have been made to devise definitions of disease activity, accompanied by scoring systems using combinations of clinical and laboratory parameters to allow comparative and longitudinal studies. Global measures such as European Community Lupus Activity Measure (ECLAM) [1], Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [2] and the more detailed British Isles Lupus Activity Grading (BILAG) [3] are useful in the context of clinical trials in patients with active systemic disease. However, none is specifically designed for the assessment of patients who most concern dermatologists, and do not grade skin disease in any meaningful way. The CLASI has been described for assessment of cutaneous disease, but is not yet in routine clinical use [4].

References

1 Vitali C, Bencivelli W, Isenberg DA *et al.* Disease activity in systemic lupus erythematosus: report of the consensus study group of the European workshop for rheumatology research. II. Identification of the variables indicative of disease activity and their use in the development of an activity score. *Clin Exp Rheumatol* 1992; **10**: 541–7.
2 Bombardier C, Gladman DD, Urowitz MB *et al.* Derivation of SLEDAI: a disease activity index for lupus patients. *Arthritis Rheum* 1992; **35**: 630–40.
3 Hay EM, Bacon PA, Gordon C *et al.* The BILAG index: a reliable and valid instrument for measuring clinical disease activity in systemic lupus erythematosus. *QJM* 1993; **86**: 447–58.
4 Albrecht J, Taylor L, Berlin JA *et al.* The CLASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index): an outcome instrument for cutaneous lupus erythematosus. *J Invest Dermatol* 2005; **125**: 889–94.

Association with other diseases. SLE can occur concurrently with rheumatoid arthritis [1], and may present with polymyalgia in elderly patients [2]. Systemic sclerosis and SLE may occur in the same patient [3], and the demonstration of immunoglobulins at the dermal–epidermal junction may be helpful in confirming the presence of both diseases [4]. SLE occurs with lichen sclerosus and with 'en coup de sabre' morphoea [5], and linear and plaque morphoea [6]. Sjögren's syndrome and SLE occur together [7–9] but the former is usually mild, and is unlike secondary Sjögren's syndrome occurring with rheumatoid arthritis. Patients with hyperglobulinaemic purpura may have antinuclear factor; this condition may, in certain cases, have features of SLE [10]. The finding of LE cells in young females with liver disease has already been mentioned. SLE can follow primary biliary cirrhosis [11], and may occasionally occur in association with necrotizing angiitis [12] and giant cell arteritis [13]. Patients who have LE and psoriasis often have anti-Ro antibodies [14].

Myasthenia gravis may follow SLE [15], and SLE may follow thymectomy for myasthenia gravis [16] or be associated with a thymoma [17]. Myasthenia gravis, thymoma and pemphigus may occur together in patients with SLE [18], and heterozygous C2 deficiency associated with angio-oedema, myasthenia gravis and SLE also occurs [19]. Angio-oedema resulting from C1-esterase deficiency can be associated with SLE [20], and protein S deficiency can occur in these patients [21].

SLE has been reported with Hashimoto's thyroiditis and pernicious anaemia [22]. It was associated with seminoma of the ovary in one case. Removal of the tumour led to an apparent permanent cure of the LE [23]. Lymphatic leukaemia or Hodgkin's disease has followed SLE [24], and lymphoma has been reported [25]. Amyloidosis [26] can develop in SLE, and in one case this led to adrenal insufficiency and was followed by malignant lymphoma [27]. The presentation with haemolytic anaemia [28] or thrombocytopenic purpura [29] is well documented, and overt SLE may appear after splenectomy for 'idiopathic thrombocytopenic purpura'. If this occurs, it is likely that the thrombocytopenia is an early manifestation of SLE. It may also occur in association with thrombotic thrombocytopenic purpura [30], pernicious anaemia [31], von Willebrand's disease [32], myelofibrosis [33,34], selective IgA deficiency [35], erythroleukaemia [36], red cell aplasia [37], monoclonal gammopathy and multiple myeloma [38], biclonal gammopathy [39], myelofibrosis [39], hyperviscosity syndrome [40], Whipple's disease [41] and ulcerative colitis [42]. SLE also occurs with pemphigoid [43] and cicatricial pemphigoid [44], pemphigus [45], dermatitis herpetiformis [46], linear IgA disease [47], epidermolysis bullosa dystrophica [48], porphyria cutanea

tarda [49] (although the association has not been confirmed) [50], and occasionally with porphyria variegata or acute intermittent porphyria [51–53]. The disease has been reported in patients with Sweet's syndrome [54], Klinefelter's syndrome [55], hypoparathyroidism [56], partial lipodystrophy [57], relapsing polychondritis [58], pyoderma gangrenosum [59] and Kikuchi's disease [60]. In one case it has been associated with retroperitoneal fibrosis [61], and in another with eosinophilic fasciitis and retroperitoneal fibrosis [62]. It uncommonly occurs with gout [63] and sarcoidosis [64]. An unusual syndrome of breast hypertrophy, erythema annulare centrifugum, generalized melanoderma and immunodeficiency to viral warts has been associated with SLE [65]. Twelve per cent of patients with SLE have warts, which is a higher incidence than in a control population [66]. Senear–Usher syndrome (pemphigus and LE) has been associated with internal malignancy [67], but an overall increased incidence of malignancy in SLE is debatable. Malignancy occurred in 4.7% in one series [68]. Epidermodysplasia verruciformis occurs presumably as a result of immunodeficiency or prolonged treatment with corticosteroids [69]. Among other rare associations are Kaposi's sarcoma [70] and Kawasaki disease [71].

The relationship to DLE is discussed on p. 51.2. Patients with persistent false-positive serological tests for syphilis [72] may later develop SLE.

References

1 Cohen MG, Webb J. Concurrence of rheumatoid arthritis and systemic lupus erythematosus: report of 11 cases. *Ann Rheum Dis* 1987; **46**: 853–8.
2 Hutton CW, Maddison PJ. Systemic lupus erythematosus presenting as polymyalgia rheumatica in the elderly. *Ann Rheum Dis* 1986; **45**: 641–4.
3 Rowell NR. Lupus erythematosus cells in systemic sclerosis. *Ann Rheum Dis* 1962; **21**: 70–5.
4 Chorzelski J, Jablonska S. Coexistence of lupus erythematosus and scleroderma in light of immunopathological investigations. *Acta Derm Venereol (Stockh)* 1970; **50**: 81.
5 Mackel SE, Kozin F, Ryan LM *et al.* Concurrent linear scleroderma and systemic lupus erythematosus. *J Invest Dermatol* 1979; **73**: 368–72.
6 Mitchell AJ, Rusin LJ, Diaz LA. Circumscribed scleroderma with immunologic evidence of systemic lupus erythematosus. *Arch Dermatol* 1980; **116**: 69–73.
7 Alarcón-Segoviá D, Ibanez G, Velazquez-Forero F *et al.* Sjögren's syndrome in systemic lupus erythematosus. *Ann Intern Med* 1974; **81**: 577–83.
8 Andonopoulos AP, Skopouli FN, Dimou GS *et al.* Sjögren's syndrome in systemic lupus erythematosus. *J Rheumatol* 1990; **17**: 201–4.
9 Zuffery P, Meyer OC, Bourgeois P *et al.* Primary systemic Sjögren syndrome (SS) preceding systemic lupus erythematosus: a retrospective study of 4 cases in a cohort of 55 SS patients. *Lupus* 1995; **4**: 23–7.
10 Waldenstrom J. *The Harvey Lectures Series 56*. New York: Academic Press, 1961: 211.
11 Hall S, Axelsen PH, Larson DE *et al.* Systemic lupus erythematosus developing in patients with primary biliary cirrhosis. *Ann Intern Med* 1984; **100**: 388–9.
12 Winkelmann RK, Ditto WB. Cutaneous and visceral syndromes of necrotizing or 'allergic' angiitis. *Medicine* 1964; **43**: 59–89.
13 Bunker CB, Dowd PM. Giant cell arteritis and systemic lupus erythematosus. *Br J Dermatol* 1988; **33**: 71–2.
14 Kulick KB, Mogavero H, Provost TT *et al.* Serologic studies in patients with lupus erythematosus and psoriasis. *J Am Acad Dermatol* 1983; **8**: 631–4.
15 Denney D, Rose RL. Myasthenia gravis followed by systemic lupus erythematosus. *Neurology* 1961; **11**: 710–3.
16 Alarcón-Segoviá D, Galbraith RF, Maldonado JE *et al.* Systemic lupus erythematosus following thymectomy for myasthenia gravis. *Lancet* 1963; **ii**: 662–5.
17 Steven MM, Westedt ML, Eulderink F *et al.* Systemic lupus erythematosus and invasive thymoma: report of two cases. *Ann Rheum Dis* 1984; **43**: 25–8.
18 Cooper A, Wells JV. Pemphigus foliaceus, myasthenia gravis and thymoma in a patient with serological evidence of SLE. *Aust NZ J Med* 1981; **11**: 277–80.
19 Efthimiou J, D'Cruz D, Kaplan P *et al.* Heterozygous C2 deficiency associated with angioedema, myasthenia gravis, and systemic lupus erythematosus. *Ann Rheum Dis* 1986; **45**: 428–30.
20 Bagot M, Revuz J, Intrator L *et al.* Oedème angioneurotique acquis révélant un lupus erythemateux disseminé. *Ann Dermatol Vénéréol* 1987; **114**: 1331–3.
21 Perkins W, Stables GI, Lever RS. Protein S deficiency in lupus erythematosus secondary to hereditary angio-oedema. *Br J Dermatol* 1994; **130**: 381–4.
22 Hamilton DV. Systemic lupus erythematosus in a patient with Hashimoto's thyroiditis and pernicious anaemia. *J R Soc Med* 1978; **71**: 147–9.
23 Rotman M, Dorfmann H, Sèze S *et al.* Coexistence d'un lupus erythemateux disseminé et d'un seminome de l'ovarie: guerison apparente rapide du lupus aprés ablation de la tumeur. *Nouv Presse Med* 1972; **1**: 853–7.
24 Morgenfeld MC, Magnin PH. Enfermedad de Hodgkin asociada con lupus eritematoss diseminado. *Pren Med Argent* 1970; **57**: 1899–901.
25 Green JA, Dawson AA, Walker W. Systemic lupus erythematosus and lymphoma. *Lancet* 1978; **ii**: 753–6.
26 Nomura S, Kumagai N, Kanoh T *et al.* Pulmonary amyloidosis associated with systemic lupus erythematosus. *Arthritis Rheum* 1986; **29**: 680–2.
27 Schleissner LA, Sheehan WW, Orselli RC. Lupus erythematosus in a patient with amyloidosis, adrenal insufficiency and subsequent immunoblastic sarcoma. *Arthritis Rheum* 1976; **19**: 249–54.
28 Dubois EL. Acquired hemolytic anaemia as the presenting syndrome of lupus erythematosus disseminatus. *Am J Med* 1952; **12**: 197–204.
29 Rabinowitz Y, Dameshek W. Systemic lupus erythematosus after 'idiopathic' thrombocytopenic purpura. *Ann Intern Med* 1960; **52**: 1–28.
30 Fox DA, Faix JD, Coblyn J *et al.* Thrombotic thrombocytopenic purpura and systemic lupus erythematosus. *Ann Rheum Dis* 1986; **45**: 319–22.
31 Korbet SM, Corwin HL. Pernicious anaemia associated with systemic lupus erythematosus. *J Rheumatol* 1986; **13**: 193–4.
32 Poole-Wilson PA. Acquired von Willebrand's syndrome and systemic lupus erythematosus. *Proc R Soc Med* 1972; **65**: 561–2.
33 Rosen PJ, Cramer AD, Dubois EL *et al.* Systemic lupus erythematosus (SLE) and myelofibrosis. *Clin Res* 1973; **21**: 565.
34 Kaelin WG, Spivak JL. Systemic lupus erythematosus and myelofibrosis. *Am J Med* 1986; **81**: 935–8.
35 Ammann AJ, Hong R. Selective IgA deficiency: presentation of 30 cases and a review of the literature. *Medicine* 1971; **50**: 223–36.
36 Ng HS, Ng HW, Sinniah R *et al.* A case of systemic lupus erythematosus with sideroblastic anaemia terminating in erythroleukaemia. *Ann Rheum Dis* 1981; **40**: 422–6.
37 Cassileth PA, Myers AR. Erythroid aplasia in systemic lupus erythematosus. *Am J Med* 1973; **55**: 706–10.
38 Powell FC, Greipp PR, Su WPD. Discoid lupus erythematosus and monoclonal gammopathy. *Br J Dermatol* 1983; **109**: 355–60.
39 Leach IH, Jenkins JS, Murray-Leslie CF *et al.* Heavy chain and monoclonal IgG K paraproteinaemia in systemic lupus erythematosus. *Br J Rheumatol* 1987; **26**: 460–2.
40 Jara LJ, Capin NR, Lavalle C. Hyperviscosity syndrome as the initial manifestation of systemic lupus erythematosus. *J Rheumatol* 1989; **16**: 225–30.
41 Ehrenfeld M, Urowitz MB, Platts ME. Selective C4 deficiency, systemic lupus erythematosus and Whipple's disease. *Ann Rheum Dis* 1984; **43**: 91–4.
42 Stevens HP, Ostlere LS, Rustin MHA. Systemic lupus erythematosus in association with ulcerative colitis: related auto-immune diseases. *Br J Dermatol* 1994; **130**: 385–9.
43 Stoll DM, King LE. Association of bullous pemphigoid with systemic lupus erythematosus. *Arch Dermatol* 1984; **120**: 362–6.
44 Redman RS, Thorne EG. Cicatricial pemphigoid in a patient with systemic lupus erythematosus. *Arch Dermatol* 1981; **117**: 109–10.
45 Bean SF, Lynch FW. Senear–Usher syndrome (pemphigus erythematosus). *Arch Dermatol* 1970; **101**: 642–5.
46 Thomas JR, Su WPD. Concurrence of lupus erythematosus and dermatitis herpetiformis. *Arch Dermatol* 1983; **119**: 740–5.
47 Lau M, Kaufmann-Grunzinger I, Raghunath MR. A case report of a patient with features of systemic lupus erythematosus and linear IgA disease. *Br J Dermatol* 1991; **124**: 498–502.

48 Archibald GC. Epidermolysis bullosa dystrophica and systemic lupus erythematosus. *Proc R Soc Med* 1976; **69**: 881–4.
49 Clemmensen O, Thomsen K. Porphyria cutanea tarda and systemic lupus erythematosus. *Arch Dermatol* 1982; **118**: 160–2.
50 Griso D, Macri A, Biolcati G *et al.* Does an association exist between PCT and SLE? Results of a study on autoantibodies in 158 patients affected with PCT. *Arch Dermatol Res* 1989; **281**: 291–2.
51 Allard SA, Scott JT. Systemic lupus erythematosus and acute intermittent porphyria. *Br J Rheumatol* 1989; **28**: 254–6.
52 Hetherington GW, Jetton RL, Knox JM. The association of lupus erythematosus and porphyria. *Br J Dermatol* 1970; **82**: 118–24.
53 Cram DL, Epstein JH, Tuffanelli DL. Lupus erythematosus and porphyria. *Arch Dermatol* 1973; **108**: 779–84.
54 Ramsay-Goldman R, Franz T, Solano A, Medsger TA. Hydralazine induced lupus and Sweet's syndrome: report and review of the literature. *J Rheumatol* 1990; **17**: 682–4.
55 Burch PRJ, Rowell NR. Systemic lupus erythematosus and Klinefelter's syndrome. *Lancet* 1976; **i**: 1021.
56 Hajiroussou VJ. Hypoparathyroidism associated with systemic lupus erythematosus. *Postgrad Med J* 1981; **57**: 597–8.
57 Font J, Herrero C, Bosch X *et al.* Systemic lupus erythematosus in a patient with partial lipodystrophy. *J Am Acad Dermatol* 1990; **22**: 337–40.
58 Job-Deslandre C, Delrieu F, Delbarre F *et al.* Relapsing polychondritis and systemic lupus erythematosus. *J Rheumatol* 1983; **10**: 666–8.
59 Pinto GM, Cabecas MA, Riscado M, Goncalves H. Pyoderma gangrenosum associated with systemic lupus erythematosus: response to pulse steroid therapy. *J Am Acad Dermatol* 1991; **24**: 818–21.
60 Litwin MD, Kirkham B, Henderson DRF *et al.* Histiocytic necrotising lymphadenitis in systemic lupus erythematosus. *Ann Rheum Dis* 1992; **51**: 805–7.
61 Lloyd DD, Balfe JW, Barkin M *et al.* Systemic lupus erythematosus with signs of retroperitoneal fibrosis. *J Pediatr* 1974; **85**: 226–8.
62 Garcia-Morteo O, Nitsche A, Maldonado-Cocco JA *et al.* Eosinophilic fasciitis and retroperitoneal fibrosis in a patient with systemic lupus erythematosus. *Arthritis Rheum* 1987; **30**: 1314–5.
63 Decastro P, Jorizzo JL, Solomon AR *et al.* Coexistent systemic lupus erythematosus and tophaceous gout. *J Am Acad Dermatol* 1985; **13**: 650–4.
64 Fivenson DP, Crump G, Scheele P *et al.* Systemic lupus erythematosus developing in a patient with long-standing pulmonary sarcoidosis. *J Rheumatol* 1989; **16**: 1116–9.
65 Shelley WB. An unusual auto-immune syndrome. *Acta Derm Venereol (Stockh)* 1972; **52**: 33.
66 Yell JA, Burge SM. Warts and lupus erythematosus. *Lupus* 1993; **2**: 21–3.
67 Saikia NK, MacConnell LES. Senear–Usher syndrome and internal malignancy. *Br J Dermatol* 1972; **87**: 1–5.
68 Menon S, Snaith ML, Isenberg DA. The association of malignancy with SLE: an analysis of 150 patients under long-term review. *Lupus* 1993; **2**: 177–81.
69 Tanigaki T, Kanda R, Sato K. Epidermodysplasia verruciformis in a patient with systemic lupus erythematosus. *Arch Dermatol Res* 1986; **278**: 247–8.
70 Greenfield DI, Trinh P, Fulenwider A *et al.* Kaposi's sarcoma in a patient with SLE. *J Rheumatol* 1986; **13**: 637–40.
71 Laxer RM, Cameron BJ, Silverman ED. Occurrence of Kawasaki disease and systemic lupus erythematosus in a single patient. *J Rheumatol* 1988; **15**: 515–6.
72 Catterall RD. Collagen disease and the chronic biological false positive phenomenon. *QJM* 1961; **30**: 41–55.

Kikuchi's disease and SLE. Histiocytic necrotizing lymphadenitis was first described independently by Kikuchi [1] and Fujimoto *et al.* [2] from Japan in 1972. Cases are predominantly female, but it can occur in males, and can occur at all ages. Usually, patients present with lymphadenopathy, frequently cervical, although other nodes can be involved. Fever, weight loss and night sweats are found in the more severely affected cases. There may be leukopenia and elevation of the ESR. Skin changes occur in 30% of patients [3]. They are all non-specific and include multiple, indurated, red papules on the back and arms [4], erythematous plaques resembling lymphoma, erythema and acneiform eruptions on the face (Fig. 51.45), and morbilliform, urticarial and rubella-like eruptions elsewhere. The oropharynx may be red or ulcerated.



Fig. 51.45 Erythematous facial plaques in Kikuchi's disease.

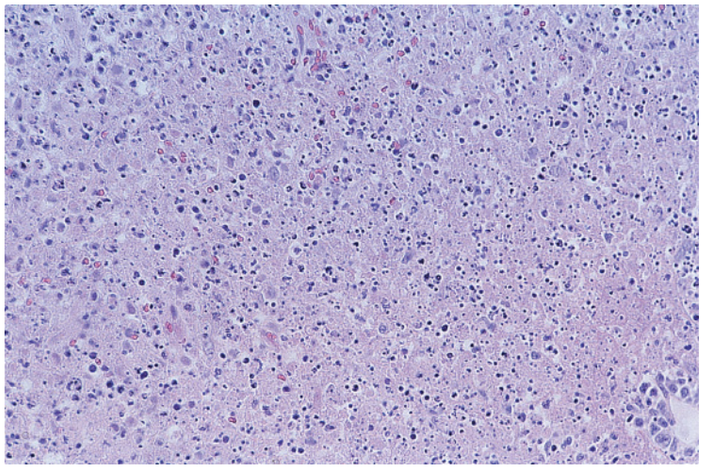


Fig. 51.46 Histiocytic necrotizing lymphadenitis (Kikuchi's disease). Lymph node. (Courtesy of Dr W. Merchant, Leeds General Infirmary, Leeds, UK.)

Histology of the skin shows oedema of the papillary dermis, with a patchy perivascular infiltrate in the dermis and subcutaneous fat. The infiltrate consists of histiocytes containing nuclear debris, and small lymphocytes. The nuclei of the histiocytes may be deformed. The lymph nodes show focal or complete loss of follicular architecture, with necrosis of cortical and paracortical areas (Fig. 51.46). The extensive infiltrate consists of small lymphocytes, immunoblasts, macrophages and so-called plasmacytoid T cells [5]. Neutrophils are rarely seen, a feature that may help to distinguish this condition from SLE. The natural history is for spontaneous healing in a few months but it can be fatal as a result of heart failure brought about by microscopic myocardial necrosis [6]. There was a 3.3% recurrence rate in one series [7]. In most cases, no treatment is required, but a course of prednisolone may speed resolution. Various triggers have been incriminated, including the human herpesvirus 6 [8], parvovirus B19 [9], Epstein–Barr virus [5], dengue virus [10] and infection by *Yersinia enterocolitica*, *Toxoplasma*, cytomegalovirus and human immunodeficiency virus (HIV) [11], and rupture of a silicone breast implant [12]. The condition is occasionally associated with SLE. It may precede SLE [13], may be the presenting feature of SLE [14] and, rarely, SLE may precede it [15]. The association was found in two of 108 patients with Kikuchi's disease studied by Dorfman [16], and two of eight patients studied by El-Ramaki *et al.* [17]. It has occurred with DLE

in a case encountered by the authors, and may be associated with other cutaneous manifestations of lupus [18]. Other associated conditions include Still's disease [19,20] and Sweet's syndrome [21]. In addition to SLE, the disorder can occur with lymphoma, tuberculous lymphadenitis, viral lymphadenitis, infectious mononucleosis and drug eruptions.

References

1 Kikuchi M. Lymphadenitis showing focal reticular cell hyperplasia with nuclear debris and phagocytes. *Acta Hem Jpn* 1972; **35**: 379–80.
2 Fujimoto Y, Kojima Y, Yamaguchi K. Cervical subacute necrotizing lymphadenitis. *Naika* 1972; **30**: 920–7.
3 Kuo T. Cutaneous manifestation of Kikuchi's histiocytic necrotizing lymphadenitis. *Am J Surg Pathol* 1990; **14**: 872–6.
4 Seno A, Torigoe R, Shimoe K *et al.* Kikuchi's disease (histiocytic necrotizing lymphadenitis) with cutaneous involvement. *J Am Acad Dermatol* 1994; **30**: 504–6.
5 Rivano MT, Falini B, Stein M *et al.* Histiocytic necrotizing lymphadenitis without granulocyte infiltration (Kikuchi lymphadenitis): morphological and immunohistochemical study of eight cases. *Histopathology* 1987; **11**: 1013–27.
6 Chan JK, Wong KC, Ng CS. A fatal case of multicentric Kikuchi's histiocytic necrotizing lymphadenitis. *Cancer* 1989; **63**: 1856–62.
7 Kuo TT. Kikuchi's disease (histiocytic necrotizing lymphadenitis): a clinicopathologic study of 79 cases with an analysis of histological subtypes, immunohistology, and DNA ploidy. *Am J Surg Pathol* 1995; **19**: 789–809.
8 Hoffmann A, Kirn E, Kuerteu A *et al.* Active human herpes virus-6 (HHV-6) infection associated with Kikuchi–Fujimoto disease and systemic lupus erythematosus (SLE). *In Vivo* 1991; **5**: 265–9.
9 Meyer O, Ribard P, Belmatoug N *et al.* Three cases of Kikuchi lymphadenitis in systemic lupus erythematosus: role of the parvovirus B19. *Ann Med Interne (Paris)* 1991; **142**: 259–64.
10 Harris VK, Danda D, Murali NS *et al.* Unusual association of Kikuchi's disease and dengue virus infection evolving into systemic lupus erythematosus. *J Indian Med Assoc* 2000; **98**: 391–3.
11 Bataille V, Harland CC, Behrens J *et al.* Kikuchi disease (histiocytic necrotizing lymphadenitis) in association with HTLV1. *Br J Dermatol* 1997; **136**: 610–2.
12 Sever CE, Leith CP, Appenzeller J, Foucar K. Kikuchi's histiocytic necrotizing lymphadenitis associated with ruptured silicone breast implant. *Arch Pathol Lab Med* 1996; **120**: 380–5.
13 Komocsi A, Tovari E, Pajor L, Czirjak L. Histiocytic necrotizing lymphadenitis preceding systemic lupus erythematosus. *J Eur Acad Dermatol Venereol* 2001; **15**: 476–80.
14 Dalkilic E, Karakoc Y, Tolunay S, Yurtkuran M. Systemic lupus erythematosus presenting as Kikuchi–Fujimoto disease. *Clin Exp Rheumatol* 2001; **19**: 226.
15 Tumiati B, Bellelli A, Portioli I *et al.* Kikuchi disease in systemic lupus erythematosus: an independent or dependent event? *Clin Rheumatol* 1991; **10**: 90–3.
16 Dorfman RF, Berry GJ. Kikuchi histiocytic necrotizing lymphadenitis: an analysis of 108 cases with emphasis on differential diagnosis. *Semin Diagn Pathol* 1988; **5**: 329–45.
17 El-Ramaki KM, Karran A, Ali MA. Kikuchi disease and its association with systemic lupus erythematosus. *Lupus* 1994; **3**: 409–11.
18 Kaur S, Thami GP, Kanawar AJ *et al.* Kikuchi's disease, skin and systemic lupus erythematosus. *Br J Dermatol* 2002; **146**: 167–8.
19 Ohta A, Matsumoto J, Ohta T *et al.* Still disease associated with necrotizing lymphadenitis (Kikuchi disease): report of 3 cases. *J Rheumatol* 1988; **15**: 981–3.
20 Lyberatos C. Two more cases of Still and Kikuchi. *J Rheumatol* 1990; **17**: 568–9.
21 Itoh H, Shimasaki S, Nakashima A *et al.* Sweet's syndrome associated with subacute necrotizing lymphadenitis. *Intern Med* 1992; **31**: 686–9.

Differential diagnosis. The conditions mentioned in the above section must be differentiated from LE. Many patients suspected of having a connective tissue disease may, even after investigation, present problems of categorization. The criteria for SLE of the ARA (1982) are shown in Table 51.9 [1]. The presence of four or more of the 11 manifestations, serially or simultaneously, is compatible with SLE (96% sensitive, 96% specific).

Other features, such as cutaneous LE lesions of any type, diffuse alopecia, involvement of the scalp or mucous membranes, preferably confirmed by histopathology, or direct immunofluorescence, may be helpful.

Several practical points are important. The ESR need not be elevated. In patients at Leeds, 15% followed up for at least 5 years have never had an ESR above 20 mm in the first hour. Several of these have had high titres of antinuclear factor, raised levels of anti-DNA antibodies and lowered serum complement. Diagnosis thus depends upon the association of features rather than on any specific abnormality. The demonstration of a high titre of antinuclear factor is important. In the acute phase, the membranous types of antinuclear factor may be present as well as a raised level of anti-DNA antibody, anti-Sm antibody and a reduction in the serum complement. In the authors' experience, the presence of antinuclear factor in high titre almost certainly excludes polyarteritis nodosa and other arteritic disorders. When a raised ESR, raised serum globulin, leukopenia and evidence of renal disease are added, the diagnosis becomes highly probable. It is important to remember that antinuclear factor is not always present in SLE, and in such cases alopecia, Raynaud's phenomenon and oral ulceration commonly occur [2]. The demonstration of immunoglobulins in the dermal–epidermal junction of uninvolved as well as involved skin may be very helpful (see p. 51.34). The combination of IgG and IgM at the dermal–epidermal junction of involved and uninvolved skin, raised DNA binding, antinuclear antibody in a titre of more than 1:64 and decreased C3 or C4 is highly suggestive of SLE [3]. In drug-induced LE, anti-DNA antibodies are absent, serum complement is normal and globulin is not found in the uninvolved skin. Acute febrile neutrophilic dermatosis (Sweet's syndrome) may mimic SLE when a 'butterfly rash' is associated with fever, myalgia, arthralgia, hepatosplenomegaly, renal disease and hyperglobulinaemia [4].

References

1 Tan EM, Cohen AS, Fries JF *et al.* The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982; **25**: 1271–7.
2 Fessel WJ. ANA-negative systemic lupus erythematosus. *Am J Med* 1970; **64**: 80–6.
3 Williams REA, O'Keefe R, MacKie RM *et al.* The contributions of direct immunofluorescence (DIF) to the diagnosis of lupus erythematosus. *Br J Dermatol* 1988; **119**: 520.
4 Frayha R, Matta M, Kurban A. Sweet's syndrome simulating systemic lupus erythematosus. *Dermatologica* 1972; **144**: 321–4.

Prognosis [1]. The course of SLE is very variable [2]. Acute fulminating cases are much less common than subacute cases, which smoulder on for many years. Mortality rates declined in both England and Wales in the 10-year period 1974–83 [3] and in the USA [4]. Although, in pre-steroid days, 52% of patients in one series [5] died within 2 years, in another series 54% of patients survived 11 years [6], compared with controls, of whom 97% survived a similar time. In 1977, an overall 5-year survival of 91% was reported [7], and 98% in another series in 1978 [8], although a 5-year survival of only 88% was reported from a rheumatological clinic in 1990 [9]. Approximately three-quarters will now survive

15 years [10]. Survival is related to organ involvement and to frequency of exacerbations [11]. Of those without renal involvement, 84% survive 15 years, compared with 57% whose kidneys are affected [10]. Spontaneous remissions, sometimes lasting 10–20 years, occurred in 35% of Dubois and Tuffanelli's [12] patients, the longest being 26 years. Serological as well as clinical remission occurred in 4% of 305 patients [13]. Exacerbations are more frequent in the first 5 years of the disease [14]. Pregnancy does not affect long-term survival. Prolonged survival is associated with an increased risk of atherosclerosis, avascular necrosis and neuropsychiatric dysfunction [15]. In elderly people the presentation is insidious and the clinical course is relatively benign. Renal disease and serological abnormalities are less frequent, and arthritis, with subcutaneous nodules, and pleuropericarditis are more prominent in elderly people [16].

The better prognosis of the more recent series is a result, not only of the administration of corticosteroids, but also of earlier diagnosis, the avoidance of stress and drugs such as sulphonamides, and the control of infections by antibiotics. The cause of death is frequently progressive renal failure, occasionally with anuria. Secondary infection, particularly bronchopneumonia, was a much more common cause of death in the pre-antibiotic era, although infection may still be more important than renal failure. The high infection rate is not caused solely by steroid [17] or antimetabolite therapy. Spontaneous peritonitis caused by Gram-positive bacteria is a complication of lupus nephritis treated with corticosteroids [18]. Unusual infections such as pneumococcal epiglottitis have been reported [19]. There is an increased risk of *Salmonella* bacteraemia [20] and rapidly fatal pneumococcal septicaemia [21]. Repeated skin infections may be a presenting feature. Cellulitis of the periorbital area caused by *Staphylococcus aureus* and group A haemolytic streptococci has been reported [22,23]. Neisserial infections may also occur [24]. Death may result from vasculitis of the CNS in patients presenting with convulsions, psychoses and paralysis. Patients with CNS lesions and psychosis have a poor prognosis. Deaths from CNS involvement become more important in the later stages of the disease [25]. Others may die from heart failure or the side effects of therapy [26].

A bimodal pattern of mortality has been described [27], but not confirmed, in black patients [28]. Patients who die early in the disease die from active LE, including renal involvement, receive large doses of steroids and have a high incidence of infection. Those who die later have relatively inactive disease, long duration of steroid therapy and a high incidence of atherosclerotic heart disease and myocardial infarction [11]. Nevertheless, it is the authors' experience that death from infection is common, even in long-standing cases. The maximum disease activity occurs early, and patients rarely develop new organ involvement after the first few years [8,14]. Late reactivation of SLE can occur [29].

Although the disease is much more common in females, the prognosis is worse in males [30–33]. Males are more likely to develop renal failure [34]. Although race and ethnic origin have been claimed not to influence prognosis [35], increased mortality has been noted in Asians [36] and black people [37], probably in part because of socioeconomic conditions. The degree of renal involvement is probably the most important factor in prognosis. Patients with nephrotic syndrome at the onset of nephritis do badly and may die within a few months, but development later in the disease does not have an adverse effect. Patients with albuminuria may survive on small doses of steroids for many years, and the overall prognosis of patients with renal involvement is not as bad as early studies suggested. Patients with cutaneous lesions of DLE and laboratory abnormalities have the same prognosis as uncomplicated cases of DLE [38]. Patients with arteritis, antiphospholipid syndrome, thrombocytopenia, haemolytic anaemia and CNS involvement have a poorer prognosis than those whose illness mainly involves the joints. There appears to be no increased risk of malignancy [39], although earlier reports suggested this might be so [40,41].

References

1 Bresnihan B. Outcome and survival in systemic lupus erythematosus. *Ann Rheum Dis* 1989; **48**: 443–5.
2 Ropes MW. *Systemic Lupus Erythematosus*. Cambridge: Harvard University Press, 1976.
3 Hochberg MC. Mortality from systemic lupus erythematosus in England and Wales, 1974–83. *Br J Rheumatol* 1987; **26**: 437–41.
4 Ginzler E, Berg A. Mortality in systemic lupus erythematosus. *J Rheumatol* 1987; **14**: 218–22.
5 Bywaters EGL, Bauer W. (Quoted by Bywaters EGL, Scott TJ. 1939.) In: Dixon A StJ, ed. *Progress in Clinical Rheumatology*. London: Churchill, 1965: 132.
6 Kellum RE, Haserick JR. Systemic lupus erythematosus. *Arch Intern Med* 1964; **113**: 200–7.
7 Lee P, Urowitz MB, Bookman AAM *et al.* Systemic lupus erythematosus. *QJM* 1977; **46**: 1–32.
8 Grigor R, Edmonds J, Lewkonia R *et al.* Systemic lupus erythematosus. *Ann Rheum Dis* 1978; **37**: 121–8.
9 Worrall JG, Snaith ML, Batchelor JR, Isenberg DA. SLE: a rheumatological view. Analysis of the clinical features, serology, and immunogenetics of 100 SLE patients during long-term follow-up. *QJM* 1990; **74**: 319–30.
10 Wallace DJ, Podell T, Weiner J *et al.* Systemic lupus erythematosus survival patterns. *JAMA* 1981; **245**: 934–8.
11 Swaak AJG, Nossent JC, Bronsveld W *et al.* Systemic lupus erythematosus. I. Outcome and survival: Dutch experience with 110 patients studied prospectively. *Ann Rheum Dis* 1989; **48**: 447–54.
12 Dubois EL, Tuffanelli DL. Clinical manifestations of systemic lupus erythematosus. *JAMA* 1964; **190**: 104–11.
13 Heller CA, Schur PH. Serological and clinical remission in systemic lupus erythematosus. *J Rheumatol* 1985; **12**: 916–8.
14 Swaak AJG, Nossent JC, Bronsvel W *et al.* Systemic lupus erythematosus. II. Observations on the occurrence of exacerbations in the disease course: Dutch experience with 110 patients studied prospectively. *Ann Rheum Dis* 1989; **48**: 455–60.
15 Gladman DD, Urowitz MB. Morbidity in systemic lupus erythematosus. *J Rheumatol* 1987; **14**: 223–6.
16 Wilson HA, Hamilton ME, Spyker DA *et al.* Age influence on the clinical and serologic expression of systemic lupus erythematosus. *Arthritis Rheum* 1981; **24**: 1230–5.
17 Staples PJ, Gerding DN, Decker JL *et al.* Incidence of infection in systemic lupus erythematosus. *Arthritis Rheum* 1974; **17**: 1–10.
18 Lipsky PE, Hardin JA, Schour L *et al.* Spontaneous peritonitis and systemic lupus erythematosus. *JAMA* 1975; **232**: 929–31.
19 Shalit M, Gross DJ, Levo V. Pneumococcal epiglottitis in systemic lupus erythematosus on high-dosage corticosteroids. *Ann Rheum Dis* 1982; **41**: 615–6.
20 Abramson S, Kramer SB, Radin A *et al.* Salmonella bacteremia in systemic lupus erythematosus. *Arthritis Rheum* 1985; **28**: 75–9.
21 Van Der Straeten C, Wei N, Rothschild J *et al.* Rapidly fatal pneumococcal septicaemia in systemic lupus erythematosus. *J Rheumatol* 1987; **14**: 1177–80.
22 Derksen RHWM, Overbeek BP, Poeschmann PH. Serious bacterial cellulitis of the periorbital area in two patients with systemic lupus erythematosus. *J Rheumatol* 1988; **15**: 840–4.

23 Rebora A, Scala D, Paneaglio E *et al.* Repeated skin infections as a manifestation of lupus erythematosus. *Arch Dermatol* 1982; **118**: 213–4.
24 Mitchell SR, Nguyen PQ, Katz P. Increased risk of Neisserial infections in systemic lupus erythematosus. *Semin Arthritis Rheum* 1990; **20**: 174–84.
25 Cheatum DE, Hurd ER, Strunk SW *et al.* Renal histology and clinical course of systemic lupus erythematosus. *Arthritis Rheum* 1973; **16**: 670–6.
26 Feng PH, Cheah PS, Lee YK. Mortality in systemic lupus erythematosus. *BMJ* 1973; **iv**: 772–4.
27 Urowitz MB, Bookman AAM, Koehler BE *et al.* The bimodal mortality pattern of systemic lupus erythematosus. *Am J Med* 1976; **60**: 221–5.
28 Harisdangkul V, Nilganuwonge S, Rockhold L. Cause of death in systemic lupus erythematosus: a pattern based on age at onset. *South Med J* 1987; **80**: 1249–53.
29 Urowitz MB, Gladman DD. Late mortality in SLE. *J Rheumatol* 1980; **7**: 412–6.
30 Rubin LA, Urowitz MB, Gladman DD. Mortality in systemic lupus erythematosus: the bimodal pattern revisited. *QJM* 1985; **216**: 87–98.
31 Fries JF, Holman HR. Systemic lupus erythematosus. *J Invest Dermatol* 1976; **67**: 554–5.
32 Kaufman LD, Gomez-Reino JJ, Keinicke MH. Male lupus: retrospective analysis of the clinical and laboratory features of 52 patients with a review of the literature. *Semin Arthritis Rheum* 1989; **18**: 189–97.
33 Folomeer M, Alekberova Z. Survival pattern of 120 males with systemic lupus erythematosus. *J Rheumatol* 1990; **17**: 856–7.
34 Zimmerman SW. Survival patterns in systemic lupus erythematosus. *JAMA* 1981; **246**: 2323.
35 Ginzler EM, Diamond HS, Weiner M *et al.* A multicentre study of outcome in systemic lupus erythematosus. *Arthritis Rheum* 1982; **25**: 601–11.
36 Kaslow RA. High rate of death caused by systemic lupus erythematosus among US residents of Asian descent. *Arthritis Rheum* 1982; **25**: 414–8.
37 Gordon MF, Stolley PD, Schinnar R. Trends in recent systemic lupus erythematosus mortality rates. *Arthritis Rheum* 1981; **24**: 762–9.
38 Beck JS, Rowell NR. Discoid lupus erythematosus. *QJM* 1966; **35**: 119–36.
39 Rosner SM, Ginzler EM, Diamond HS *et al.* A multicenter study of outcome in systemic lupus erythematosus. *Arthritis Rheum* 1982; **25**: 612–7.
40 Canoso JJ, Cohen AS. Malignancy in a series of 70 patients with systemic lupus erythematosus. *Arthritis Rheum* 1974; **17**: 383–90.
41 Lewis RB, Castor CW, Kuisley RE *et al.* Frequency of neoplasia in systemic lupus erythematosus and rheumatoid arthritis. *Arthritis Rheum* 1976; **19**: 1256–60.

Genetic counselling. The clinical genetics of lupus has been reviewed [1]. Approximately 5% of first-degree relatives of patients may have or may develop lupus. The risk is doubled if there are two affected first-degree relatives, and this risk is even greater if further family members are affected. The risk for female relatives is greater than for males and may also be increased for those with hyperglobulinaemia or antinuclear antibodies. Mothers with anti-Ro and anti-La antibodies may have children with neonatal lupus and heart block. When a child has neonatal lupus or CHB, the risk of a subsequent child having heart block is approximately 25%.

Reference

1 Lewkonia SM. The clinical genetics of lupus. *Lupus* 1992; **1**: 55–62.

Treatment [1]. The aim is to try to maintain optimal function with the minimum of therapy. SLE is an episodic disease, and treatment must be tailored to the patient's requirements and morale must be maintained. In acute cases, and during severe exacerbations, bed rest is required. Undue exposure to the sun should be avoided and patients should be advised to wear broad-brimmed hats, to cover the 'V' of the neck and the arms, and to use a sunscreen. Mental stress, physical overexertion and secondary infection should be avoided.

Hypertension must be treated aggressively and diuretics may be required for the nephrotic syndrome or cardiac failure, and anticonvulsants for epilepsy. Chlorpromazine is a good sedative for psychosis. Symptomatic therapy for joint pain using NSAIDs is valuable. Ischaemic necrosis of bone may be best treated early by core decompression [2].

Corticosteroids are required in acute cases, and should be given in adequate regimens. Prednisolone in doses up to 60 mg/day is the steroid of choice initially. It is rare for higher dosage to be needed. Once the condition appears to be under control, the dosage may be reduced gradually, until a maintenance dosage of approximately 5–15 mg/day is reached. A single dose daily, given in the morning [3], produces fewer side effects and does not impair the therapeutic response.

Not all patients require steroids, especially if there is no internal organ involvement [1]. It is important to assess the patient's progress by their general well-being and relief of symptoms, rather than by strict attention to laboratory abnormalities [4]. The ESR and DNA antibodies are variable and a poor guide to the adequacy of therapy; the titre of antinuclear antibodies often persists unchanged despite clinical remission. Anti-DNA antibody and serum complement levels may be helpful in predicting exacerbations [5]. Low C3 often indicates severe renal disease. There is some evidence that a return of serological abnormalities to normal is followed by a prolonged remission [6], but exceptions indicate that serological data alone cannot be used as a basis of therapy.

Some fulminating cases have been treated with massive doses of steroids but the advantages of such therapy rarely outweigh the risks, and complications such as steroid-induced psychosis can occur even in patients with CNS disease [7]. Prolonged high dosage of corticosteroids (e.g. prednisolone 60 mg/day for 6 months) is said to improve renal lesions more than small suppressive doses [8], but more aggressive immunosuppressive regimens are now preferred. Steroid myopathy can occur with high doses and is easily missed.

In mild cases, the administration of chloroquine or hydroxychloroquine may allow the dosage of steroids to be reduced, but the reduction may not be clinically meaningful [9]. Antimalarials are less useful than in DLE, but may have a place in patients with photosensitivity. Their use does not preclude pregnancy, as healthy live babies have been delivered by women on antimalarial therapy throughout pregnancy [10].

Immunosuppressive drugs have been used for patients not responding to corticosteroids, or to act as steroid-sparing agents [11]. The role of azathioprine is accepted, but at least some studies show that it adds nothing to high-dose prednisolone treatment in mild or moderate renal disease [12]. Another controlled trial, comparing azathioprine plus prednisolone with prednisolone alone, did not show any significant difference in the number of deaths, renal or extrarenal manifestations, serum complement levels, DNA antibodies, LE cells, antinuclear antibody titres, or Coombs' antibodies, or any evidence of a steroid-sparing effect [13]. Sudden withdrawal may be followed by relapse [14]. Cyclophosphamide is useful in SLE [15,16], although not all support routine use. Nevertheless, pulsed therapy with cyclophosphamide may be useful for renal disease and is as effective as pulsed methylprednisolone [17].

Chlorambucil has been used [18], but methotrexate is now a more widely accepted drug in SLE. Methotrexate 7.5 mg/week has improved steroid-resistant patients [19] and patients without renal or CNS involvement [20], and 10–20 mg/week is useful for mucocutaneous lesions [21].

The long-term risk of malignancy must be considered whenever immunosuppressive drugs are used. Cyclophosphamide has been associated with bladder cancer [22], acute non-lymphocytic leukaemia and solid tumours. Mesna may reduce urotoxic side effects, but 50% of patients develop rashes which may be confused with an exacerbation of SLE [23]. Reticulum cell sarcoma [24] and non-Hodgkin's lymphoma [25] are hazards of azathioprine therapy.

Ciclosporin has been used in resistant cases in a dosage of 3–5 mg/kg [26]. Pulse therapy with methylprednisolone 1 g given intravenously in 500 ml normal saline over 4 h on 3 successive days to in-patients may be helpful in individuals who are not controlled by oral prednisolone and immunosuppressives [27]. Given monthly it may prevent deterioration in renal function in patients with nephritis [28]. Mycophenolate mofetil has been used for non-renal SLE [29], and alternatives to cyclophosphamide as a modifier of B cell function have been found to be increasingly useful. Rituximab, an antibody targeting the CD20 marker antigen of B cell precursors, has been valuable for those in whom conventional therapy has failed [30].

Plasmapheresis of 2 L/day for 3–4 days each week over a period of 2–3 weeks may be helpful in a small number of patients with a high level of immune complexes, whose condition is deteriorating despite other therapy, but controlled trials have not been convincing [31]. Any benefit lasts only approximately 2–3 weeks. Plasmapheresis may be useful in managing life-threatening complications such as fulminating vasculitis or CNS disease [32]. Intravenous gammaglobulin 1 g/kg/day for 3 days improved four out of five patients. The effect lasts 4–6 weeks [33]. Provisional studies of extracorporeal photochemotherapy have shown improvement in a few patients, and treatment was not associated with any side effects [34]. Anticoagulants may be required for patients with lupus anticoagulant or anticardiolipin antibodies who have thrombotic episodes. Danazol 400–600 mg/day may help patients with premenstrual exacerbations [35], and sometimes has a marked effect on thrombocytopenia [36]. Oral levamisole, in a dosage of 150 mg three times daily has been found helpful by some [37], but not by others [38]. Antilymphocyte and antithymocyte antisera may help patients with nephritis not responding to either corticosteroids or azathioprine [39].

A new and surprising therapeutic approach is that although UV light can exacerbate SLE, it has been found in a controlled trial that exposure to UVA-1 (340–400 mm) at a dosage of 60 kJ/m^2 three times weekly reduced disease activity, reduced the need for medication and decreased antibody levels [40]. A low-fat, high marine oil diet (eicosapentaenoic acid: Maxepa 20 g/day) modified disease activity in 27 patients in a placebo-controlled trial over 3 months [41].

Some patients with cutaneous disease as their main form of disease expression will require specific treatment as for DLE. In these patients, dapsone may be helpful for urticarial lesions [42], bullous eruptions [43] and for thrombocytopenia [44].

References

1 Vasoo S, Hughes GR. Theory, targets and therapy in systemic lupus erythematosus. *Lupus* 2005; **14**: 181–8.

2 Hungerford DS, Zizic TM. The treatment of ischemic necrosis of bone in systemic lupus erythematosus. *Medicine* 1980; **59**: 143–8.

3 Ackerman GL, Nolan CM. Adrenocortical responsiveness after alternate-day corticosteroid therapy. *N Engl J Med* 1968; **278**: 405–9.

4 Rowell NR. Laboratory abnormalities in the diagnosis and management of lupus erythematosus. *Br J Dermatol* 1971; **84**: 210–6.

5 Swaak AJG, Groenwold J, Bronsveld W. Predictive value of complement profiles and anti-dsDNA in systemic lupus erythematosus. *Ann Rheum Dis* 1986; **45**: 359–66.

6 Lightfoot RW Jr, Hughes GRV. Significance of persisting serologic abnormalities in SLE. *Arthritis Rheum* 1976; **19**: 837–43.

7 Hirohata S, Iwamoto S, Mayamoto T *et al.* A patient with SLE presenting with both CNS lupus and steroid-induced psychosis. *J Rheumatol* 1988; **15**: 706–10.

8 Pollak VE, Pirani CL, Schwartz FD. The natural history of the renal manifestations of systemic lupus erythematosus. *J Lab Clin Med* 1964; **63**: 537–50.

9 Rothfield N. Efficacy of antimalarials in systemic lupus erythematosus. *Am J Med* 1988; **85**: 53–6.

10 Parke L. Antimalarial drugs, systemic lupus erythematosus and pregnancy. *J Rheumatol* 1988; **15**: 607–10.

11 Sabbour MS, Osman LM. Comparison of chlorambucil, azathioprine or cyclophosphamide combined with corticosteroids in the treatment of lupus nephritis. *Br J Dermatol* 1979; **100**: 113–25.

12 Donadio JV, Holley KE, Wagoner RD *et al.* Further observations on the treatment of lupus nephritis with prednisone and combined prednisone and azathioprine. *Arthritis Rheum* 1974; **17**: 573–81.

13 Hahn BH, Kantor OS, Osterland CK. Azathioprine plus prednisone compared with prednisone alone in the treatment of systemic lupus erythematosus. *Ann Intern Med* 1975; **83**: 597–605.

14 Sharon E, Kaplan D, Diamond HS. Exacerbation of systemic lupus erythematosus after withdrawal of azathioprine therapy. *N Engl J Med* 1973; **288**: 122–4.

15 Ioannou Y, Isenberg DA. Current concepts for the management of systemic lupus erythematosus in adults: a therapeutic challenge. *Postgrad Med J* 2002; **78**: 599–606.

16 Karim MY, Pisoni CN, Khamashta MA. Update on immunotherapy for systemic lupus erythematosus—what's hot and what's not! *Rheumatology (Oxford)* 2009; **48**: 332–41.

17 Sesso R, Monteiro M, Sato E *et al.* A controlled trial of pulse cyclophosphamide versus pulse methylprednisolone in severe lupus nephritis. *Lupus* 1994; **3**: 107–12.

18 Snaith ML, Holt JM, Oliver DO *et al.* Treatment of patients with systemic lupus erythematosus, including nephritis, with chlorambucil. *BMJ* 1973; **ii**: 197–201.

19 Wilke WS, Krall PL, Scheetz RJ *et al.* Methotrexate for systemic lupus erythematosus: a retrospective analysis of 17 unselected cases. *Clin Exp Rheumatol* 1991; **9**: 581–7.

20 Gansauge S, Breitbart A, Rinaldi N *et al.* Methotrexate in patients with moderate systemic lupus erythematosus (exclusion of renal and central nervous system disease). *Ann Rheum Dis* 1997; **56**: 382–5.

21 Bottomley WW, Goodfield MJD. Methotrexate for the treatment of severe mucocutaneous lupus erythematosus. *Br J Dermatol* 1995; **133**: 311–4.

22 Chow SK, Looi LM, Loh CS, Yeap SS. Cyclophosphamide-induced transitional cell carcinoma of bladder in lupus nephritis. *Int Med J* 2002; **32**: 114–6.

23 Zonzito E, Aberer W, Tappeiner G. Drug reactions from Mesna. *Arch Dermatol* 1992; **128**: 80–3.

24 Hehir ME, Sewell JR, Hughes GR. Reticulum cell sarcoma in azathioprine-treated systemic lupus erythematosus. *Ann Rheum Dis* 1979; **38**: 94–5.

25 Pitt PI, Sultan AH, Malone M *et al.* Association between azathioprine therapy and lymphoma in rheumatoid disease. *J R Soc Med* 1987; **80**: 428–9.

26 Manger K, Kalden JR, Manger B. Cyclosporin A in the treatment of systemic lupus erythematosus: results of an open clinical study. *Br J Rheumatol* 1996; **35**: 669–75.

27 Isenberg DA, Morrow WJW, Snaith ML. Methyl prednisolone pulse therapy in the treatment of systemic lupus erythematosus. *Ann Rheum Dis* 1982; **41**: 347–51.

28 Liebling MR, McLaughlin K, Boonsue S *et al.* Monthly pulses of methyl prednisolone in SLE nephritis. *J Rheumatol* 1982; **9**: 543–8.

29 Mok CC. Mycophenolate mofetil for non-renal manifestations of systemic lupus erythematosus: a systematic review. *Scand J Rheumatol* 2007; **36**: 329–37.
30 Ramos-Casals M, Brito-Zerón P, Muñoz S *et al.* A systematic review of the off-label use of biological therapies in systemic autoimmune diseases. *Medicine (Baltimore)* 2008; **87**: 345–64.
31 Wei N, Huston DP, Lawley TJ *et al.* Randomized trial of plasma exchange in mild systemic lupus erythematosus. *Lancet* 1983; **i**: 17–21.
32 Wallace DJ. Plasmapheresis in lupus. *Lupus* 1993; **2**: 141–3.
33 Winder A, Molad Y, Ostfeld I *et al.* Treatment of systemic lupus erythematosus by prolonged administration of high-dose intravenous immunoglobulin: a report of two cases. *J Rheumatol* 1993; **20**: 495–8.
34 Knobler RM, Graninger W, Graninger W *et al.* Extracorporeal phototherapy for the treatment of systemic lupus erythematosus: a pilot study. *Arthritis Rheum* 1992; **35**: 319–24.
35 Morley KD, Parke A, Hughes GRV. Systemic lupus erythematosus. *BMJ* 1982; **284**: 1431–2.
36 West SG, Johnson SC. Danazol for the treatment of refractory autoimmune thrombocytopenia in systemic lupus erythematosus. *Ann Intern Med* 1988; **108**: 703–6.
37 Rovensky J, Cebecauer L, Zitnan D *et al.* Levamisole treatment of systemic lupus erythematosus. *Arthritis Rheum* 1982; **25**: 470–1.
38 Hadidi T, Decker JL, El-Nagdy L *et al.* Ineffectiveness of levamisole in systemic lupus erythematosus. *Arthritis Rheum* 1981; **24**: 60–3.
39 Pirofsky B, Bardana EJ, Bayracki C *et al.* Antilymphocyte antisera in immunological mediated renal disease. *JAMA* 1969; **210**: 1059–64.
40 McGrath H Jr, Martinez-Osuna P, Lee FA. Ultraviolet-A1 (340–400 nm) irradiation therapy in systemic lupus erythematosus. *Lupus* 1996; **5**: 269–74.
41 Walton AJE, Snaith ML, Locniskar M *et al.* Dietary fish oil and the severity of symptoms in patients with systemic lupus erythematosus. *Ann Rheum Dis* 1991; **50**: 463–6.
42 Ruzicka T, Goerz A. Dapsone in the treatment of lupus erythematosus. *Br J Dermatol* 1981; **104**: 53–6.
43 Hall RP, Lawley TJ, Smith HR *et al.* Bullous eruption of systemic lupus erythematosus. *Ann Intern Med* 1982; **97**: 165–70.
44 Moss C, Hamilton PJ. Thrombocytopenia in systemic lupus erythematosus responsive to dapsone. *BMJ* 1988; **297**: 266.

The lupus anticoagulant, anticardiolipin antibodies and the antiphospholipid antibody syndrome [1]

The lupus anticoagulant was first described in SLE [2], but it also occurs in drug-induced SLE, other connective tissue diseases, polymyalgia rheumatica/giant cell arteritis (where 40–50% of patients may have antibodies [3]) and carcinoma and lymphoma [4]. It may be induced by infection, including that caused by Epstein–Barr virus [5] and varicella [6]. It also occurs as the causative abnormality of the primary antiphospholipid (Hughes') syndrome [7], although a small proportion of those classified as having the primary syndrome will progress to lupus or a lupus-like syndrome [8].

The lupus anticoagulant is only one of several antiphospholipid antibodies, which include the anticardiolipin antibody demonstrated by ELISA. IgG anticardiolipin antibody has been found in 23% of patients with SLE [9], and is associated with similar clinical features to those seen with the lupus anticoagulant [10]. The presence and titre seem to depend on disease activity and decrease with treatment, particularly when of IgM type. In a study of healthy blood donors, anticardiolipin antibodies and the lupus anticoagulant were found in 4–6% of 499 donors, mainly young females [11].

Table 51.15 Clinical features associated with the lupus anticoagulant.

Libman-Sacks endocarditis [15]
Chorea [16]
Labile hypertension
Epilepsy
Myelitis
Myocardial infarction
Valvular heart disease
Haemolytic anaemia
Retinopathy [17]
Addison's disease [18]
Avascular necrosis of bone [19]

The features associated with the lupus anticoagulant are caused by an acquired immunoglobulin (IgG or IgM), identified by prolonged activated partial thromboplastin and kaolin clotting times, which cannot be corrected by normal plasma. There may also be IgA antiphospholipid antibodies [12]. There are now a number of methods for detecting the abnormalities, and these have been reviewed [13]. The antibodies are directed against a range of phospholipids, including cardiolipin. The route by which thrombosis is induced remains unclear, but some antiphospholipid antibodies interact with a complex of phospholipid and β_2-glycoprotein-I to inhibit factor XII activation, platelet activation and prothrombinase activity [14].

Clinical features. The clinical features of the syndrome associated with the presence of the lupus anticoagulant are protean, and many are shown in Table 51.15. Rarely, patients develop vascular occlusions in multiple organs [20]. This catastrophic variety may be fatal. There is also a syndrome in which a severe reduction in clotting occurs because of a different set of antiphospholipid antibodies—the haemorrhagic lupus anticoagulant syndrome [21].

Cutaneous lesions [22] include thrombophlebitis, purpura and ecchymoses, livedo reticularis, leg ulcers, cutaneous necrosis, gangrene and subungual splinter haemorrhages. Histologically, non-inflammatory thrombosis of small dermal blood vessels can be demonstrated, but necrotizing vasculitis is not a feature [23]. Thromboses in the placenta lead to fetal death, and may recur in subsequent pregnancies. Thrombocytopenia also occurs. All women with SLE who have recurrent abortions and thrombotic episodes, or who are biological false-positive reactors, should be screened for the lupus anticoagulant, as treatment with prednisone 40–80 mg/day and aspirin 75 mg/day may result in successful pregnancy. One patient with repeated fetal loss was successfully treated with intravenous human gammaglobulin [24]. Full anticoagulation (international normalized ratio (INR) greater than 3), with or without aspirin, appears to be the most effective therapy in the non-pregnant patient [25]. The presence of the antibodies without clinical features is not an indication for either steroid therapy or anticoagulation.

References

1 Wilson WA, Gharavi AE, Piette JC. International classification criteria for antiphospholipid syndrome: synopsis of a post-conference workshop held at the Ninth International (Tours) aPL Symposium. *Lupus* 2001; **10**: 457–60.

2 Boey ML, Colaco CB, Gharavi AE *et al.* Thrombosis in systemic lupus erythematosus. *BMJ* 1983; **287**: 1021–3.
3 Espinoza LR, Jara LJ, Silveira LH *et al.* Anticardiolipin antibodies in polymyalgia rheumatica–giant cell arteritis: association with severe vascular complications. *Am J Med* 1991; **90**: 474–8.
4 Shaw BE, Perry D, Hoffbrand AV. Progressive arterial thrombosis in a patient with non-Hodgkin's lymphoma, a lupus anticoagulant, factor V Leiden mutation and paraprotein, following chemotherapy. *Leuk Lymphoma* 2001; **42**: 221–3.
5 Shiomou K, Galanakis E, Tzoufi M *et al.* Transient lupus anticoagulant and prolonged activated partial thromboplastin time secondary to Epstein–Barr virus infection. *Scand J Infect Dis* 2002; **34**: 67–9.
6 Kurogol Z, Vardar F, Ozkinay F *et al.* Lupus anticoagulant and protein S deficiency in otherwise healthy children with acute varicella infection. *Acta Paediatr* 2000; **89**: 1186–9.
7 Ames PRJ, Khamashta MA, Hughes GRV. Clinical and therapeutic aspects of the antiphospholipid syndrome. *Lupus* 1995; **4** (Suppl. 1): S23–5.
8 Mujic F, Cuadrado MJ, Lloyd M *et al.* Primary antiphospholipid syndrome evolving into systemic lupus erythematosus. *J Rheumatol* 1995; **22**: 1589–92.
9 McHugh NJ, Maymo J, Skinner RP *et al.* Anticardiolipin antibodies, livedo reticularis, and major cerebrovascular and renal disease in systemic lupus erythematosus. *Ann Rheum Dis* 1988; **47**: 110–5.
10 Laskin CA, Clark CA, Spitzer KA. Antiphospholipid syndrome in systemic lupus erythematosus: is the whole greater than the sum of the parts? *Rheum Dis Clin North Am* 2005; **31**: 255–72.
11 Shi W, Krilis SA, Chong BH *et al.* Prevalence of lupus anticoagulant and anticardiolipin antibodies in a healthy population. *Aust NZ J Med* 1990; **20**: 231–6.
12 Bertolaccini ML, Atsumi T, Escudero-Contreras A *et al.* The value of IgA antiphospholipid testing for diagnosis of antiphospholipid (Hughes) syndrome in systemic lupus erythematosus. *J Rheumatol* 2001; **28**: 2637–43.
13 Bertolaccini ML, Hughes GR. Antiphospholipid antibody testing: which are the most useful for diagnosis? *Rheum Dis Clin North Am* 2006; **32**: 455–63.
14 Pierangeli SS, Chen PP, Gonzalez EB. Antiphospholipid antibodies and the antiphospholipid syndrome: an update on treatment and pathogenic mechanisms. *Curr Opin Hematol* 2006; **13**: 366–75.
15 Ford PM, Ford SE, Lillicrap DP. Association of lupus anticoagulant with severe valvular heart disease in systemic lupus erythematosus. *J Rheumatol* 1988; **15**: 597–600.
16 Hatron P-Y, Bouchez B, Wattel A *et al.* Chorea, systemic lupus erythematosus, circulating lupus anticoagulant. *J Rheumatol* 1986; **13**: 991–3.
17 Acheson JF, Gregson RMC, Merry P, Schulenburg WE. Vaso-occlusive retinopathy in the primary anti-phospholipid antibody syndrome. *Eye* 1991; **5**: 48–55.
18 Hughes GRV. The antiphospholipid syndrome: 10 years on. *Lancet* 1993; **342**: 341–4.
19 Mok MY, Farewell VT, Isenberg DA *et al.* Risk factors for avascular necrosis of bone in patients with systemic lupus erythematosus: is there a role for antiphospholipid antibodies? *Ann Rheum Dis* 2000; **59**: 462–7.
20 Asherson RA. The catastrophic antiphospholipid syndrome. *J Rheumatol* 1992; **19**: 508–12.
21 Schmugge M, Tolle S, Marbet GA *et al.* Gingival bleeding, epistaxis and haematoma three days after gastroenteritis: the haemorrhagic lupus anticoagulant syndrome. *Eur J Pediatr* 2001; **160**: 43–6.
22 Asherson RA, Frances C, Iaccurino L *et al.* The antiphospholipid syndrome: diagnosis, skin manifestations and current therapy. *Clin Exp Rheumatol* 2006; **24**: 846–51.
23 Alegre VA, Winkelmann RK. Histopathologic and immunofluorescence study of skin lesions associated with circulating lupus anticoagulant. *J Am Acad Dermatol* 1988; **19**: 117–24.
24 Carreras LO, Perez GN, Vega HR *et al.* Lupus anticoagulant and recurrent fetal loss: successful treatment with gammaglobulin. *Lancet* 1988; **ii**: 393–4.
25 Ruiz-Irastorza G, Khamashta MA, Hunt BJ *et al.* Bleeding and recurrent thrombosis in definite antiphospholipid syndrome: analysis of a series of 66 patients treated with oral anticoagulation to a target international normalized ratio of 3:5. *Arch Intern Med* 2002; **27**: 1164–9.

Scleroderma [1]

Sclerosis of the skin occurs in a variety of conditions, such as dermatomyositis and LE, and invariably occurs as part of the cutaneous manifestations of systemic sclerosis, which is described elsewhere. However, the term 'scleroderma' should strictly be confined to sclerosis of the skin, either localized or generalized, occurring in patients as the only or prominent feature. In such circumstances it is better to use the term 'morphoea'. There has been much discussion and confusion about the relationship of morphoea to systemic sclerosis (see below), but the two conditions, despite certain similarities, are best considered as distinct entities.

Reference

1 Jablonska S. The concept of scleroderma and its classification. In: Jablonska S, ed. *Scleroderma and Pseudoscleroderma*. Warsaw: Polish Medical Publishers, 1975: 3–10.

Localized morphoea

Synonyms
- Localized scleroderma
- Circumscribed scleroderma

Definition. A disorder of unknown cause in which there is localized sclerosis of the skin. The condition has traditionally been subdivided clinically into the following types [1]:

1 Circumscribed plaques
2 Morphoea profundus/subcutaneous (deep)
3 Bullous morphoea
4 Linear morphoea
5 Frontoparietal lesions (en coup de sabre), with or without hemiatrophy of the face.

It is apparent, however, that there is sometimes overlap between these types, this occurring in up to 15% of cases in children [2]. Recently, a new classification for childhood localized scleroderma has been proposed, to include circumscribed morphoea (superficial and deep), linear scleroderma (trunk/limbs and head), generalized morphoea, pansclerotic morphoea and mixed morphoea [3].

Although some conditions, such as atrophoderma of Pasini and Pierini, eosinophilic fasciitis and lichen sclerosus, are sometimes included in the classification of morphoea, this is not widely accepted [2].

References

1 Peterson LS, Nelson AM, Su WP. Classification of morphoea (localized scleroderma). *Mayo Clin Proc* 1995; **70**: 1068–76.
2 Laxer RM, Zulian F. Localized scleroderma. *Curr Opin Rheumatol* 2006; **18**: 606–13.
3 Zulian F, Martini G. Preliminary classification criteria for juvenile systemic sclerosis. In: Zulian F, Ruperto N, eds. *Proceedings of the II Workshop on Nomenclature and Diagnostic Criteria for Juvenile Scleroderma Syndromes*; 3–6 June 2004; Padua. Padua: Associazione II Volo, 2005: 5–16.

Aetiology. The cause of morphoea is unknown. A number of studies, however, have shown *in vitro* abnormalities in fibroblasts from patients with morphoea. These include fibroblast promotion of migration of mononuclear leukocytes across endothelial cell monolayers [1], increased platelet-derived growth factor and receptor expression [2], and increased transforming growth factor-β (TGF-β) receptor expression [3]. It is postulated that this may

lead to increased connective tissue growth factor (CTGF) gene expression and ultimately fibrosis [4,5]; possibly being mediated via activation of Smad and ERX1/2 [6] or integrin alphavbeta5 pathways [7]. That morphoea is an immunologically-mediated disease also gains support from studies that have found increased levels of circulating cytokines in patients with morphoea. These include IL-2 receptor [8,9], IL-6 receptor [10], IL-13 and TNF [11], soluble CD4 and CD8 [12], CD23 [13], CD30 [14], TNF-α [15], a B-cell activating factor belonging to the tumour necrosis factor family (BAFF) [16], soluble vascular cell adhesion molecule-1 (VCAM-1) and E-selectin [17], antiendothelial cell antibodies [18], and antibodies to fibrillin 1 [19] and superoxide dismutase [20]. That they may be involved in disease activity is supported by some studies, which have found increased levels of, for instance, soluble IL-2 receptor in active but not inactive disease [8,9], although such findings are by no means universal. Additional support for an autoimmune aetiology is the occurrence of scleroderma-like lesions in chronic graft-versus-host disease, and an association with idiopathic thrombocytopenic purpura [21]. A comprehensive review of chemokines and chemokine receptors in scleroderma has been published [22].

A number of studies have reported assays which may correlate with disease activity including levels of matrix metalloproteinase-13 [23], antiagalactosyl IgG antibodies [24] and manganese superoxide dismutase [25].

Experimental exchange of Thiersch grafts between normal and affected sites resulted in rapid transformation of the normal graft to morphoea and vice versa [26]. Trauma may be a triggering factor [27,28] and may precede the onset by many months. Immobilization has also been reported as a cause [29]. Morphoea has also occurred after bacille Calmette–Guérin (BCG) vaccination [30], following varicella [31], injections of vitamin K [32] and B12 [33], after antitetanus vaccination [34], after DTP and MMR vaccinations [35] and after herpes zoster [36]. There are several reports of morphoea occurring at the site of, and extending outside the field of, previous radiotherapy [37–41], and after fluoroscopy [42]. Surgical trauma has been reported as a stimulus for the development of lesions after arteriovenous fistula formation [43], rhinoplasty [44] and laparotomy [45], and recently mechanical compression from clothing has been suggested to trigger lesions [46]. A single case of linear morphoea occurring after linear lichen aureus has been reported [47]. Hormonal factors may influence the disease; morphoea may develop during, or be exacerbated by, pregnancy, but the influence of the menopause is less clear.

Infection with borrelial organisms has been implicated in the aetiology of morphoea, some central European studies suggesting a relationship between morphoea and acrodermatitis chronica atrophicans, a disease induced by infection with *Borrelia burgdorferi* [48–50]. These studies found raised levels of antibodies against this organism in patients with morphoea compared with controls, and described the presence of viable organisms in biopsies from morphoeic lesions. In addition, using the polymerase chain reaction, *Borrelia* DNA has been found in skin biopsies from patients with morphoea [51]. However, other studies [52–56] have shown no evidence of *Borrelia* antibodies or DNA in morphoea of patients from Scandinavia, Germany, Spain or America. A recent review [57] has suggested that the reason for these contradictory findings is that either *Borrelia* infection is not the cause of morphoea or that a subset of morphoea is caused by a special species of *Borrelia* present in some parts of Europe and Asia but not in the USA and other parts of Europe.

The genetic influence on morphoea is unclear. A familial incidence has been noticed [58], and localized and systemic scleroderma has been noted in monozygotic twins [59]. Some cases of the frontal type appear to have a genetic basis [60], but there are no significant HLA associations [61]. There is an increase in the incidence of organ-specific autoantibodies in patients and relatives [62]. Morphoea has been associated with phenylketonuria, and improvement has occurred with a low-phenylalanine diet, but excretion of phenylalanine and *o*-hydroxyphenylacetic acid in nine children with morphoea was normal [63].

Morphoea has been reported after therapy with a number of drugs. Morphoea-like plaques occurred in a patient on penicillamine therapy and remitted within a year of stopping treatment [64]. Cutaneous lesions have also been reported after therapy with bromocriptine [65], hydroxytryptophan and carbidopa [66,67], valproic acid [68], pentazocine [69,70], docetaxel [71] and the related drug paclitaxel [72], bleomycin [73,74] and after melphalan limb perfusion [75]. These localized lesions are in contrast with the systemic sclerosis-like reactions reported later in this chapter.

Although the clinical picture of morphoea is usually distinctive, and different from systemic sclerosis, the histology and histochemistry [76–78] of the skin are similar, and X-ray diffraction, historadiographical and electron microscope investigations [63,79–81] show no differences. Electron microscopy may show changes in the underlying muscle fibres in both conditions, but only in systemic sclerosis are endothelial changes found in the muscle capillaries [82]. Skin collagen may be increased in morphoeic plaques [83], possibly because of clonal overactivity of fibroblasts [84], but is decreased in the involved skin in systemic sclerosis [85]. The two disorders rarely occur together. Nail fold capillaroscopy may reveal abnormal capillaries in such patients [86].

Finally, the similarities between scleroderma and chronic graft-versus-host disease has led to studies which have shown the presence of microchimerisms in the peripheral blood mononuclear cells of patients with systemic sclerosis [87], and the presence of chimeric cells (including dendritic cells and B lymphocytes) in localized scleroderma lesions, suggesting a possible pathogenic role [88].

References

1 Denton CP, Shi-Wen X, Sutton A *et al.* Scleroderma fibroblasts promote migration of mononuclear leucocytes across endothelial cell monolayers. *Clin Exp Immunol* 1998; **114**: 293–300.

2 Zheng XY, Zhang JZ, Tu P *et al*. Expression of platelet-derived growth factor B-chain and platelet-derived growth factor β-receptor in fibroblasts of scleroderma. *J Dermatol Sci* 1998; **18**: 90–7.

3 Kubo M, Ihn H, Yamane K *et al*. Up-regulated expression of transforming growth factor β receptors in dermal fibroblasts in skin sections from patients with localized scleroderma. *Arthritis Rheum* 2001; **44**: 731–4.

4 Igarashi A, Nashiro K, Kikuchi K *et al.* Connective tissue growth factor gene expression in tissue sections from localized scleroderma, keloid and other fibrotic skin disorders. *J Invest Dermatol* 1996; **106**: 729–33.

5 Stratton R, Shiwen X, Martini G *et al.* Iloprost suppresses connective tissue growth factor production in fibroblasts and in the skin of scleroderma patients. *J Clin Invest* 2001; **108**: 241–50.

6 Pannu J, Nakerakanti S, Smith E *et al*. Transforming growth factor-β receptor type 1-dependent fibrogenic gene program is mediated via activation of Smad 1 and ERK1/2 pathways. *J Biol Chem* 2006; **282**: 1405–13.

7 Asano Y, Ihn H, Jinnin M *et al*. Involvement of alphavbeta5 integrin in the establishment of autocrine TGF—beta signaling in dermal fibroblasts derived from localized scleroderma. *J Invest Dermatol* 2006; **126**: 1761–9.

8 Ihn H, Sato S, Fujimoto M *et al*. Clinical significance of serum levels of soluble interleukin-2 receptor in patients with localized scleroderma. *Br J Dermatol* 1996; **134**: 843–7.

9 Uziel Y, Krafchik BR, Feldman B *et al*. Serum levels of soluble interleukin-2 receptor: a marker of disease activity in localized scleroderma. *Arthritis Rheum* 1994; **37**: 898–901.

10 Nagaoka T, Sato S, Hasegawa M *et al*. Serum levels of soluble interleukin 6 receptor and soluble gp130 are elevated in patients with localized scleroderma. *J Rheumatol* 2000; **27**: 1917–21.

11 Hasegawa M, Sato S, Nagaoka T *et al*. Serum levels of tumour necrosis factor and interleukin-13 are elevated in patients with localized scleroderma. *Dermatol* 2003; **207**: 141–7.

12 Sato S, Fujimoto M, Kikuchi K *et al*. Soluble CD4 and CD8 in serum from patients with localized scleroderma. *Arch Dermatol Res* 1996; **288**: 358–62.

13 Sato S, Fujimoto M, Kikuchi K *et al*. Elevated soluble CD23 levels in the sera from patients with localized scleroderma. *Arch Dermatol Res* 1996; **288**: 74–8.

14 Ihn H, Yazawa N, Kubo M *et al*. Circulating levels of soluble CD30 are increased in patients with localized scleroderma and correlated with serological and clinical features of the disease. *J Rheumatol* 2000; **27**: 698–702.

15 Majewski S, Wojas-Pelc A, Malejczyk M *et al*. Serum levels of soluble TNF-α receptor type 1 and the severity of systemic sclerosis. *Acta Derm Venereol (Stockh)* 1999; **79**: 207–10.

16 Matsushita T, Hasegawa M, Matsushita Y *et al*. Elevated serum BAFF levels in patients with localized scleroderma in contrast to other organ-specific autoimmune diseases. *Exp Dermatol* 2006; **16**: 87–93.

17 Yamane K, Ihn H, Kubo M *et al*. Increased serum levels of soluble vascular cell adhesion molecule 1 and E-selectin in patients with localized scleroderma. *J Am Acad Dermatol* 2000; **42**: 64–9.

18 Salojin KV, Le-Tonqueze M, Saraux A *et al*. Antiendothelial cell antibodies: useful markers of systemic sclerosis. *Am J Med* 1997; **102**: 178–85.

19 Arnett FC, Tan FK, Uziel Y *et al*. Autoantibodies to the extracellular matrix microfibrillar protein, fibrillin 1, in patients with localized scleroderma. *Arthritis Rheum* 1999; **42**: 2656–9.

20 Nagai M, Hasegawa M, Takehara K *et al*. Novel autoantibody to Cu/Zn superoxide dismutase in patients with localized scleroderma. *J Invest Dermatol* 2004; **122**: 594–601.

21 Leibovici V, Zlotogorski A, Kanner A *et al*. Generalized morphoea and idiopathic thrombocytopenia. *J Am Acad Dermatol* 1988; **18**: 1194–6.

22 Yamamoto T. Chemokines and chemokine receptors in scleroderma. *Int Arch Allergol Immunol* 2006; **140**: 345–56.

23 Asano Y, Ihn H, Kubo M *et al*. Clinical significance of matrix metalloproteinase-13 levels in patients with localized scleroderma. *Clin Exp Rheumatol* 2006; **24**: 394–9.

24 Mimura Y, Ihn H, Jinnin M *et al*. Anti-agalactosyl immunoglobulin G antibodies in localized scleroderma. *Int J Dermatol* 2005; **44**: 817–20.

25 Jinnin M, Ihn H, Yazawa N *et al*. Serum levels of manganese superoxide dismutase in patients with localized scleroderma. *Exp Dermatol* 2004; **13**: 357–60.

26 Haxthausen H. Studies on the pathogenesis of morphea, vitiligo and acrodermatitis atrophicans by means of transplantation experiments. *Acta Derm Venereol (Stockh)* 1947; **27**: 352–67.

27 Komocsi A, Tovari E, Kovacs J *et al*. Physical injury as a provoking factor in three patients with scleroderma. *Clin Exp Rheumatol* 2000; **18**: 622–4.

28 Yamanaka CT, Gibbs NF. Trauma induced scleroderma. *Cutis* 1999; **63**: 29–32.

29 Varga J, Jimenez SA. Development of severe limited scleroderma in complicated Raynaud's phenomenon after limb immobilization: report of two cases and study of collagen biosynthesis. *Arthritis Rheum* 1986; **29**: 1160–5.

30 Mork NJ. Clinical and histopathologic morphoea with immunological evidence of lupus erythematosus: a case report. *Acta Derm Venereol (Stockh)* 1981; **61**: 367–8.

31 Sahl WJ. Koebner phenomenon, morphoea and viral exanthems. *Lancet* 1978; **i**: 832.

32 Alonso-Llamazares J, Ahmad I. Vitamin K1-induced localized scleroderma (morphea) with linear deposition of IgA in the basement membrane zone. *J Am Acad Dermatol* 1998; **38**: 322–4.

33 Ho J, Rothchild YH, Sengelmann R. Vitamin B12-associated localized scleroderma and its treatment. *Dermatol Surg* 2004; **30**: 1252–5.

34 Drago F, Rampini P, Lugani C *et al*. Generalized morphoea after antitetanus vaccination. *Clin Exp Dermatol* 1998; **23**: 142.

35 Torrelo A, Suarez J, Colmenero I *et al*. Deep morphoea after vaccination in two young children. *Paediatr Dermatol* 2006; **23**: 484–7.

36 Forschner A, Metzler G, Rassner G *et al*. Morphea with features of lichen sclerosus et atrophicus at the site of a herpes zoster scar: another case of an isotopic response. *Int J Dermatol* 2005; **44**: 524–5.

37 Colver GB, Rodger A, Mortimer PS *et al*. Post-irradiation morphoea. *Br J Dermatol* 1989; **120**: 831–5.

38 Schaffer JV, Carroll C, Dvoretsky I *et al*. Post-irradiation morphoea of the breast: presentation of two cases and review of the literature. *Dermatology* 2000; **200**: 67–71.

39 Ullen H, Bjorkholm E. Localized scleroderma in a woman irradiated at two sites for endometrial and breast carcinoma: a case history and a review of the literature. *Int J Gynecol Cancer* 2003; **13**: 77–82.

40 Reddy S, Pui JC, Gold LI *et al*. Postirradiation morphoea and subcutaneous polyarteritis nodosa: case report and literature review. *Semin Arthritis Rheum* 2004; **34**: 728–34.

41 McClelland M, VanLock S, Patterson JW *et al*. Radiation-induced morphoea occuring after fluoroscopy. *J Am Acad Dermatol* 2002; **47**: 962–4.

42 Ardern-Jones MR, Black MM. Widespread morphoea following radiotherapy for carcinoma of the breast. *Clin Exp Dermatol* 2003; **28**: 160–2.

43 Quan VA, Black CM, Scoble JE. Cutaneous scleroderma following bilateral arteriovenous fistula formation. *Nephrol Dial Transplant* 1997; **12**: 1719–20.

44 Ozgur F, Kayikcioglu A. Linear scleroderma after rhinoplasty. *Plast Reconstr Surg* 1998; **101**: 539–40.

45 Terao M, Murota H, Song M *et al*. Case of morphoea occuring on a scar after laparoscopy. *J Dermatol* 2006; **33**: 722–3.

46 Ehara M, Oono T, Yamasaki O *et al*. Generalized morphea-like lesions arising in mechanically-compressed areas by underclothes. *Eur J Dermatol* 2006; **16**: 307–9.

47 Bell HK, Obson CM, Jackson SP *et al*. Localized morphoea preceded by a pigmented purpuric dermatosis. *Clin Exp Dermatol* 2003; **28**: 369–71.

48 Aberer E, Neumann R, Stanek G. Is localized scleroderma a *Borrelia* infection? *Lancet* 1985; **ii**: 278.

49 Aberer E, Kollegger H, Kristoferitsch W *et al*. Neuroborreliosis in morphoea and lichen sclerosus et atrophicus. *J Am Acad Dermatol* 1988; **19**: 820–5.

50 Aberer E, Stanek G, Ertl M *et al*. Evidence for spirochetal origin of circumscribed scleroderma (morphea). *Acta Derm Venereol (Stockh)* 1987; **67**: 225–31.

51 Schempp C, Bocklage H, Lange R *et al*. Further evidence for *Borrelia burgdorferi* infection in morphoea and lichen sclerosus et atrophicus confirmed by DNA amplification. *J Invest Dermatol* 1993; **100**: 717–20.

52 Halkier-Sorensen L, Kragballe K, Hansen K. Antibodies to the *Borrelia burgdorferi* flagellum in patients with scleroderma, granuloma annulare and porphyria cutanea tarda. *Acta Derm Venereol (Stockh)* 1989; **69**: 116–9.

53 Hoesly JM, Mertz LE, Winkelmann RK. Localized scleroderma (morphea) and antibody to *Borrelia burgdorferi*. *J Am Acad Dermatol* 1987; **17**: 455–8.

54 Weinecke R, Schlupen EM, Zochling N *et al*. No evidence of *Borrelia burgdorferi*-specific DNA in lesions of localized scleroderma. *J Invest Dermatol* 1995; **104**: 23–6.

55 Alonso-Llamazares J, Persing DH, Anda P *et al*. No evidence for *Borrelia burgdorferi* infection in lesions of morphoea and lichen sclerosus in Spain: a prospective study and literature review. *Acta Derm Venereol* 1997; **77**: 299–304.

56 Dillon WI, Saed GM, Fivenson DP. *Borrelia burgdorferi* DNA is undetectable by polymerase chain reaction in skin lesions of morphea, scleroderma, or lichen sclerosus et atrophicus of patients from North America. *J Am Acad Dermatol* 1995; **33**: 617–20.

57 Weide B, Walz T, Garbe C. Is morphoea caused by *Borrelia burgdorferi*: a review. *Br J Dermatol* 2000; **142**: 636–44.

58 Wuthrich RC, Roenigk HH, Steck WD. Localized scleroderma. *Arch Dermatol* 1975; **111**: 98–100.

59 DeKeyser F, Peene I, Joos R *et al*. Occurrence of scleroderma in monozygotic twins. *J Rheumatol* 2000; **27**: 2267–9.

60 Franceschetti A, Koenig H. L'importance du facteur heredo-degeneratif dans L'hemiatrophie faciale progressive (Romberg) etude des complications oculaires dans ce syndrome. *J Genet Hum* 1952; **1**: 27–64.

61 Kuhnl P, Sibrowski W, Boehm BO *et al*. Association of HLA antigens with progressive systemic sclerosis and morphoea. *Tissue Antigens* 1989; **34**: 207–9.
62 Harrington CI, Dunsmore IR. An investigation into the incidence of autoimmune disorders in patients with localized morphoea. *Br J Dermatol* 1989; **120**: 645–8.
63 Kornreich HK, Shaw KNF, Koch R *et al*. Phenylketonuria and scleroderma. *J Pediatr* 1968; **73**: 571–5.
64 Berstein RM, Hall MA, Gostelow BE. Morphoea-like reaction to D-penicillamine therapy. *Ann Rheum Dis* 1981; **40**: 42–4.
65 Leshin B, Piette WW, Caplan RM. Morphea after bromocriptine therapy. *Int J Dermatol* 1989; **28**: 177–9.
66 Joly P, Lampert A, Thomine E *et al.* Development of pseudobullous morphoea and scleroderma-like illness during therapy with L-5-hydroxytryptophan and carbidopa. *J Am Acad Dermatol* 1991; **25**: 332–3.
67 Morgan JM, Adams SJ. Scleroderma and autoimmune thrombocytopenia associated with ingestion of L-tryptophan. *Br J Dermatol* 1993; **128**: 581–3.
68 Ferzli GT, El-Tal A, Kibbi A *et al*. Localized morphoea: a rare adverse effect of valproic acid. *Paediatr Neurol* 2003; **29**: 253–5.
69 Wanchu A, Misra R. Limited cutaneous scleroderma induced by pentazocine abuse. *J Assoc Phys Ind* 1995; **43**: 145.
70 Bellman B, Berman B. Localized indurated brown plaques on arms and right buttock: pentazocine-induced morphoea. *Arch Dermatol* 1996; **132**: 1366–9.
71 Battafarano DF, Zimmerman GC, Older SA *et al.* Docetaxel (Taxotere) associated scleroderma-like changes of the lower extremities: report of three cases. *Cancer* 1995; **76**: 110–5.
72 Kupfer I, Balguerie X, Courville P *et al.* Scleroderma-like cutaneous lesions induced by paclitaxel: a case study. *J Am Acad Dermatol* 2003; **48**: 279–81.
73 Kim KH, Yoon TJ, Oh CW *et al.* A case of bleomycin induced scleroderma. *J Korean Med Sci* 1996; **11**: 454–6.
74 Passiu G, Cauli A, Atzeni F *et al.* Bleomycin-induced scleroderma: report of a case with a chronic course rather than the typical acute/subacute self-limiting form. *Clin Rheumatol* 1999; **18**: 422–4.
75 Landau M, Brenner S, Gat A *et al.* Reticulate scleroderma after isolated limb perfusion with melphalan. *J Am Acad Dermatol* 1998; **39**: 1011–2.
76 Braun-Falco O. Über das Verhalten der interfibrillaren Grundsubstanz bei Sklerodermie. *Dermatol Wochenschr* 1957; **136**: 1085–92.
77 Szodorav L, Tuza C. On the histochemistry of scleroderma. *Hautarzt* 1960; **11**: 63–7.
78 Keech MK. The effect of collagenase on the fixed and unfixed skin lesions of morphoea: an electron-microscope study. *J Pathol Bacteriol* 1959; **77**: 351–69.
79 Macher E. Feinstrukturuntersuchungen an der Haut bei Sklerodermia diffusa und circumscriptum. *Arch Klin Exp Dermatol* 1957; **206**: 739–45.
80 Macher E, Brehler B. Röntgeninterferenz untersuchungen bei Sklerodermia diffusa und circumscriptum. *Hautarzt* 1958; **9**: 409–14.
81 Niebauer G. Zur feingeweblichen Untersuchung der Sklerodermie. *Acta Neuroreg* 1960; **21**: 271–86.
82 Michalowski R. Ultrastructural study of skeletal muscle in morphoea. *Br J Dermatol* 1970; **82**: 137–41.
83 Shuster S, Raffle EJ, Bottoms E. Quantitative changes in skin collagen in morphoea. *Br J Dermatol* 1967; **79**: 456–9.
84 Kahari VM, Sandberg M, Kalimo H *et al*. Identification of fibroblasts responsible for increased collagen production in localized scleroderma by *in situ* hybridization. *J Invest Dermatol* 1988; **90**: 664–70.
85 Black MM, Bottoms E, Shuster S. Skin collagen content and thickness in systemic sclerosis. *Br J Dermatol* 1970; **83**: 552–5.
86 Maricq HR. Capillary abnormalities, Raynaud's phenomenon and systemic sclerosis in patients with localized scleroderma. *Arch Dermatol* 1992; **128**: 630–2.
87 Lambert NC, Erickson TD, Yan Z *et al*. Quantification of maternal microchimerism by HLA-specific real-time polymerase chain reaction. Studies of healthy women and women with scleroderma. *Arthritis Rheum* 2004; **50**: 906–14.
88 McNallan KT, Aponte C, El-Azhary R *et al.* Immunophenotyping of chimeric cells in localized scleroderma. *Rheumatology* 2007; **46**: 398–402.

Pathology (Fig. 51.47). The epidermis may be normal, or flattened and atrophic with loss of the rete ridges. At first the dermis is oedematous, with swelling and degeneration of the collagen fibrils, which become homogeneous and eosinophilic. There may be a scanty perivascular lymphocytic infiltrate. Cellular infiltrates of lymphocytes, plasma cells and macrophages, either perivascular or diffuse, occurred in 84% in one series, and there is some evidence that the infiltrate may precede fibrosis [1,2]. Later, the dermis is markedly thickened, with dense collagen and relatively few recognizable fibroblasts. The elastic tissue is reduced. The dermal appendages and dermal and subcutaneous fat are progressively lost. Some sweat glands may survive, deep in the dense sclerotic mass. Small dermal blood vessels may show intimal thickening.

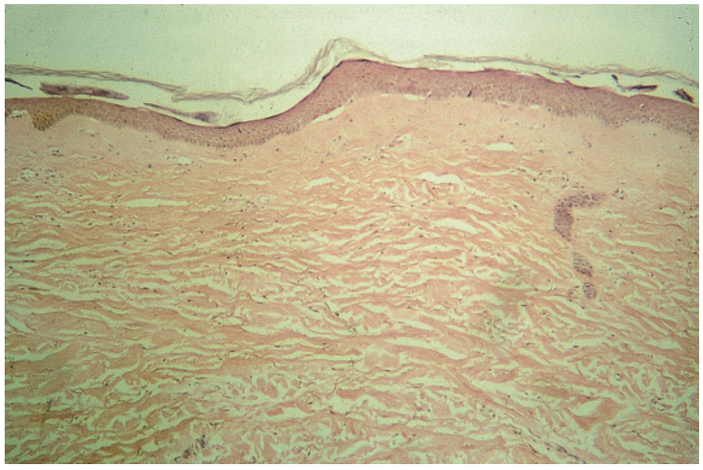


Fig. 51.47 Morphoea: slight atrophy of the epidermis with loss of dermal appendages and degeneration of dermal collagen.

Immunohistochemistry studies have shown that the main changes in morphoea consist of foci of intercollagenous staining for connective tissue antigens in the reticular layer of the dermis [3], and that there is a reduction in the size and number of dermal papillae, with increased angiogenesis in the early inflammatory stage and various numbers of enlarged vessels in inactive lesions [4]. A further study has reported an increase in dermal microvascular pericytes in the peripheral zones of active lesions, supporting the concept of a vascular pathogenesis of scleroderma [5]. IgM and C3 are found at the basement membrane and in dermal blood vessels, particularly in more extensive and deeper lesions, but there is no relation to systemic disease [6]. A study of glycosaminoglycans in normal and sclerodermatous skin has shown an increase in hyaluronic acid and altered dermatan sulphate in involved skin [7]. The histological features are similar to those seen in generalized morphoea and in the skin in systemic sclerosis.

References

1 Fleischmajer R, Perlish JS, Reeves JRT. Cellular infiltrates in scleroderma skin. *Arthritis Rheum* 1977; **20**: 975–84.
2 Winkelmann RK, Connolly SM, Doyle JA. Localized scleroderma and systemic disease. In: Kukita A, Serji M, eds. *Proceedings of the XVI International Congress of Dermatology Tokyo*. Tokyo: University of Tokyo Press, 1982: 305.
3 Rowell NR, Scott DG. Immunohistological studies with anti-connective tissue and anti-immunoglobulin antisera of the skin in lupus erythematosus and scleroderma. *Br J Dermatol* 1975; **93**: 431–41.
4 Kowalewski C, Kozlowska A, Gorska M *et al.* Alterations of basement membrane zone and cutaneous microvasculature in morphoea and extragenital lichen sclerosus. *Am J Dermatopathol* 2005; **27**: 489–96.

5 Helmbold P, Fiedler E, Fischer M *et al.* Hyperplasia of dermal microvascular pericytes in scleroderma. *J Cutan Pathol* 2004; **31**: 431–40.
6 Vincent F, Prokopetz R, Miller RAW. Plasma cell panniculitis: a unique clinical and pathologic presentation of linear scleroderma. *J Am Acad Dermatol* 1989; **21**: 357–60.
7 Passos CO, Werneck CC, Onofre GR. Comparative biochemistry of human skin: glycosaminoglycans from different body sites in normal subjects and in patients with localized scleroderma. *J Eur Acad Dermatol Venereol* 2003; **17**: 14–9.

Incidence. All ages are affected, the peak incidence occurring between 20 and 40 years of age, although 15% begin below the age of 10 years [1,2], in which age group the linear lesions predominate. The female to male ratio is around 3:1 in most studies. Most linear lesions (75%) occur before the age of 40 years, whereas 75% of localized plaques arise between the ages of 20 and 40 years [2]. In one series, localized plaques occurred in 60 patients, with linear lesions in 33 and guttate in 13 [3], but in another series [2] there were more patients with linear lesions than with plaques. A worldwide study of 750 children with juvenile localized scleroderma showed linear lesions in 65%, plaques lesions in 26%, generalized involvement in 12% and deep lesions in 2%, with 15% exhibiting a mixed subtype [4]. Six patients (0.8%) had linear lesions present at birth and were considered as having congenital scleroderma [5]. The condition is said to be rare in black people [3]. A recent epidemiological study of morphoea in the USA has found a female to male ratio of 2.5:1, an incidence of 2.7 in 10 000 and a prevalence at 80 years of age of 1 in 500 [6].

References

1 Heite HJ. Ergebnisse häufigkeitanalytischer Untersuchungen bei der Sklerodermie. *Arch Dermatol Syphilol* 1955; **200**: 426–33.
2 Christianson HB, Dorsey CS, O'Leary PA *et al.* Localized scleroderma: a clinical study of 235 cases. *Arch Dermatol* 1956; **74**: 629–39.
3 Curtis AC, Jansen TG. The prognosis of localized scleroderma. *Arch Dermatol* 1958; **78**: 749–57.
4 Zulian F, Athreya BH, Laxer R *et al.* Juvenile localized scleroderma: clinical and epidemiological features in 750 children. An international study. *Rheumatology* 2006; **45**: 614–20.
5 Zulian F, Vallongo C, De-Oliveira SKF *et al.* Congenital localized scleroderma. *J Paediatr* 2006; **149**: 248–51.
6 Peterson LS, Nelson AM, Su WPD *et al.* The epidemiology of morphea (localized scleroderma) in Olmsted County, 1960–93. *J Rheumatol* 1997; **24**: 73–80.

Clinical features

Plaque lesions. These occur as indurated areas of skin, which at first are faintly purplish or mauve in colour. After some weeks or months they lose their colour (Fig. 51.48), especially in the centre, and appear as thickened waxy areas, which are ivory in colour, with a characteristic lilac-coloured edge (Fig. 51.49). The surface is usually smooth and shiny but may be nodular [1]. The hairs are absent, and usually the area ceases to sweat. Vesicles, bullae [2] and haemorrhages may occasionally occur, and sometimes telangiectases may be seen. The plaque is attached to the deeper tissues and, if thick, may be hypoaesthetic. The lesions are round or oval, sometimes irregular, and vary in size from approximately 2 to 15 cm or more in diameter. They are usually multiple, and often bilateral, but asymmetrical. They occur on the trunk and limbs, face and genitalia. They are less commonly found in the axillae and perineum and around the nipples. Sometimes, plaques accompany linear lesions.



Fig. 51.48 Localized morphoea: plaque-like lesions on the abdomen.



Fig. 51.49 Localized morphoea on the foot: late stage but still showing lilac border.

Although the onset of lesions is usually insidious, they can occasionally occur rapidly, with erythema and oedema. Sometimes they may be preceded by pigmentation (Fig. 51.50). In subcutaneous morphoea, induration is indistinct and the lilac ring is



Fig. 51.50 Localized morphoea: pigmentation usually occurs as the lesion resolves but may occur at the onset.

absent. Deep involvement of underlying structures in morphoea of the trunk is unusual, but occurs occasionally and may be followed by deep atrophy [3]. Obscure abdominal pain and migraine were features in approximately 15% of patients in one series [4], but usually any pain is limited to the skin lesions. One study detected abnormalities of the vertebral column in 47% of those X-rayed, with spina bifida occulta occurring in 20 patients. These findings were most common in those with linear lesions, occurring in 26 of these 108 patients [4]. Other studies have not, however, reported such findings.

Recently, the term 'superficial morphoea' has been proposed for lesions with minimal induration [5]. Most cases occur in females although a single case in a male has been reported [6]. It has been suggested that atrophoderma of Pasini and Pierini may also be a primary abortive form of morphoea [7] in which induration fails to occur. Some authors argue that these two conditions are one and the same [8].

Guttate lesions. In true guttate morphoea, the lesions are similar to, but smaller and more numerous than, plaque lesions. Some cases may represent lichen sclerosus et atrophicus (white spot disease) rather than true morphoea. It has been suggested that these two diseases may have a similar pathogenesis [9] or coexist [10,11].

Bullous lesions. Peterson's classification [12], describes bullous morphoea as a distinct entity. However, blisters have been described in all types of morphoea and have been thought to result from lymphatic dilatation along with the release of major basic protein from eosinophils [13]. Others have suggested that, at least in some cases, the blisters represent the development of associated lichen sclerosus [14].

Subcutaneous morphoea/deep morphoea/morphoea profundus. Nodular [1], keloidal [15,16] or subcutaneous morphoea are variants of morphoea that exhibit differing amounts and depths of inflammatory changes and sclerosis. The term morphoea profundus was first suggested by Whittaker *et al.* [17], in 1989, to describe a solitary fibrotic plaque on the shoulder, back, neck or paraspinal area, which histologically showed fibrosis, hyalinization of collagen fibres and a deep dermal and subcutaneous inflammatory infiltrate. The overlying skin may be pigmented or hypopigmented. Osteoma cutis can develop within such lesions [18,19] and contracture of the flexor muscles of the finger has been reported in subcutaneous morphoea [20]. Most lesions of morphoea profundus are said to be non-progressive [21].

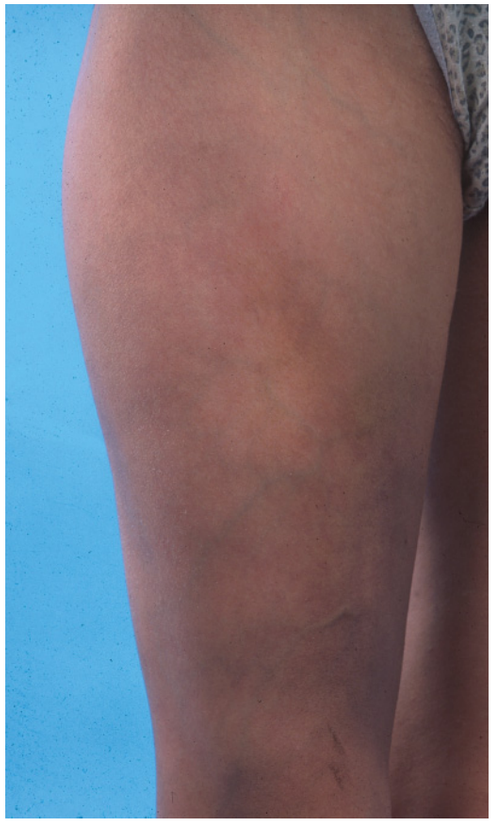


Fig. 51.51 Linear morphoea.

Linear lesions (Fig. 51.51). The essential features are similar to the plaque lesions, but the lilac ring is inconspicuous or only present at the advancing border. They are usually single and unilateral, although occasionally bilateral lesions occur. They can follow the lines of Blaschko [22–24]. The limbs are frequently affected, the legs more than the arms. They may also occur on the anterior aspect of the thorax, and sometimes the abdomen or buttocks are affected. Lesions involving one arm and one leg are usually homolateral. Rarely, half of the body (face, arm, trunk and leg) is involved [25]. Occasionally, a linear lesion on the leg is preceded by oedema of the limb. Lesions take the form of linear areas of induration, similar to those found in the plaques, but sometimes the condition may extend to involve the underlying muscles, or even bone, with resulting disturbances in growth in approximately 20% (Fig. 51.52) [26] and possibly severe flexion deformity [27,28]. The surface may show patchy hyperkeratosis. Usually, lesions occur along the length of the limb or around the trunk, but sometimes a band surrounds a limb or a finger, resembling ainhum [29,30]. The tissues

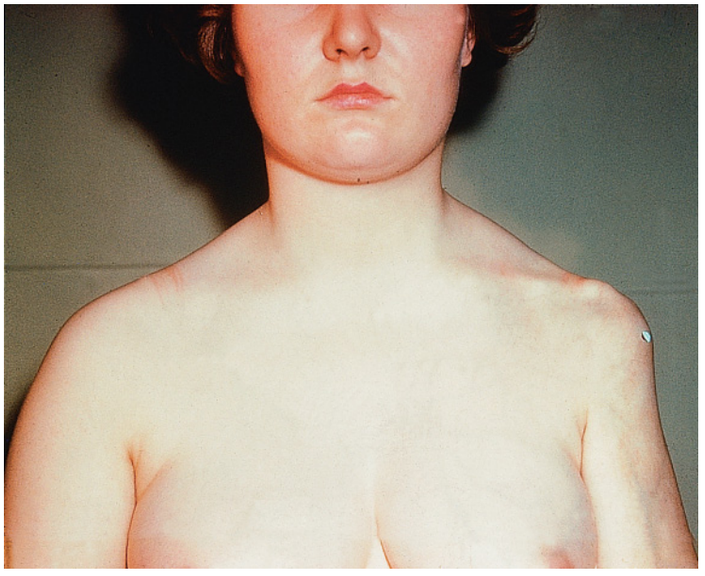


Fig. 51.52 Localized morphoea of the arm showing growth retardation.



Fig. 51.53 Frontoparietal morphoea ('en coup de sabre').

distal to such a band may be oedematous and depigmented [26]. The fibrosis may spare areas within an otherwise linear lesion, producing 'skip' lesions.

Linear scleroderma has been associated with hypertrichosis [31], melorheostosis [32–34], and ulcerated dystrophic calcinosis cutis [35]. Nodular morphoea has been reported in a linear pattern [36].

Frontoparietal lesions (Fig. 51.53) 'en coup de sabre' (from its resemblance to a sabre cut), with or without hemiatrophy. These lesions usually start with contraction and firmness of the skin over the affected area. Subsequently, an ivory irregular sclerotic plaque develops, sometimes with telangiectatic vessels coursing over it, together with hyperpigmentation at the edge. Eventually, a linear depressed groove appears on the frontoparietal region, extending into the scalp, producing a linear zone of alopecia, which may be preceded by bleaching of the hair. The groove may extend downwards into the cheek, nose and upper lip, and involve the mouth and gum. In severe cases, it extends as far as the chin and neck. The condition may affect the gingivae [37] and the jaw may also be involved, with alteration of the spacing and direction of the teeth [38]. The corresponding side of the tongue may be atrophic, although sometimes the lesion is in the midline of the tongue. Not infrequently, there is atrophy of the corresponding part of the face and cheek, with facial asymmetry, and this usually occurs within a year. The Parry–Romberg syndrome of hemifacial atrophy looks very similar, but there should be no cutaneous sclerosis at any stage [39]. Both problems may co-exist [40]. Rarely, frontoparietal lesions may be bilateral [41,42] or trilinear [43] and may follow Blaschko's lines [44]. Sometimes, there may be morphoeic plaques elsewhere on the body or evidence of linear morphoea on the extremities and trunk [45]. Facial atrophy without frontoparietal morphoea can be associated with morphoea elsewhere. Ipsilateral wasting of the upper limb occurs in less than 10% of cases [46]. Total hemiatrophy of one side of the body can occur.

Contralateral or bilateral atrophy is rare. The bones of the skull can be involved and the EEG may show evidence of dysrhythmia, maximal over the affected area. Neurological abnormalities have been reported [47–49]. A variety of ocular lesions occur [50], including enophthalmos, involvement of the lids, oculomotor muscles, iris and fundus, myopathy of the external eye muscles [51] and vasculitis [52]. Atrophy of the nasal part of the iris and loss of cilia on the upper eyelid followed exactly the line of the skin lesions in one case [53]. Heterochromia of the iris also occurs [54]. 'En coup de sabre' morphoea has presented as unilateral eyelid oedema [55]. Ossification occasionally occurs [56].

References

1 Micalizzi C, Parodi A, Rebora A. Morphoea with nodular lesions. *Br J Dermatol* 1994; **131**: 298–301.

2 Garb J, Sims CF. Scleroderma with bullous lesions: report of a case and review of the literature. *Dermatologica* 1959; **119**: 341–59.

3 Frankel H. Ein dermatologisch-neurologischer Grenzfall. *Nervenarzt* 1957; **28**: 84.

4 Christianson HB, Dorsey ES, O'Leary PA, Kierland R. Localized scleroderma: a clinical study of 235 cases. *Arch Dermatol* 1956; **74**: 629–39.

5 Jacobson L, Palazij R, Jaworsky C. Superficial morphoea. *J Am Acad Dermatol* 2003; **49**: 323–5.

6 Srinivasan SK, DiMaio D. Superficial morphoea in a man. *J Am Acad Dermatol* 2004; **51**: S156–8.

7 Kencka D, Blaszczyk M, Jablonska S. Atrophoderma Pasini–Pierini is a primary atrophic abortive morphea. *Dermatology* 1995; **190**: 203–6.

8 Jablonska S, Blaszczyk M. Is superficial morphoea synonymous with atrophoderma Pasini-Pierini? *J Am Acad Dermatol* 2003; **50**: 979–80.

9 Sawamura D, Yaguchi T, Hashimoto I *et al.* Coexistence of generalized morphea with histological changes in lichen sclerosus et atrophicus and lichen planus. *J Dermatol* 1998; **25**: 409–11.

10 Shono S, Imura M, Ota M *et al.* Lichen sclerosus et atrophicus, morphea, and coexistence of both diseases: histological studies using lectins. *Arch Dermatol* 1991; **127**: 1352–6.

11 Farrell AM, Marren PM, Wojnarowska F. Genital lichen sclerosus associated with morphoea or systemic sclerosus: clinical and HLA characteristics. *Br J Dermatol* 2000; **143**: 598–603.
12 Peterson LS, Nelson AM, Su WP. Classification of morphoea (localized scleroderma). *Mayo Clin Proc* 1995; **70**: 1068–76.
13 Daoud MS, Su WPD, Leiferman KM, Perniciaro C. Bullous morphea: clinical, pathologic, and immunopathologic evaluation of 13 cases. *J Am Acad Dermatol* 1994; **30**: 937–43.
14 Trattner A, David M, Sandbank M. Bullous morphea: a distinct entity? *Am J Dermatopathol* 1994; **16**: 414–7.
15 Perez-Wilson J, Pujol RM, Alejo M *et al.* Nodular (keloidal) scleroderma. *Int J Dermatol* 1992; **31**: 422–3.
16 Labandiera J, Leon-Mateos A, Suarez-Penaranda JM *et al.* What is nodular-keloidal scleroderma? *Dermatology* 2003; **207**: 130–2.
17 Whittaker SJ, Smith NP, Jones RR. Solitary morphoea profunda. *Br J Dermatol* 1989; **120**: 431–40.
18 Ahn SK, Won JH, Choi EH *et al.* Perforating plate-like osteoma cutis in a man with solitary morphoea profunda. *Br J Dermatol* 1996; **134**: 949–52.
19 Hulian CG, Bowers PW. Osteoma cutis in a lesion of solitary morphoea profundus. *Clin Exp Dermatol* 2003; **28**: 673–4.
20 Harris A, Burge SM, Wordsworth P *et al.* Subcutaneous morphoea with contracture of the flexor muscles of the finger. *Br J Dermatol* 1997; **136**: 476–7.
21 Azad J, Dawn G, Shaffrali FCG *et al.* Does solitary morphoea profundus progress? *Clin Exp Dermatol* 2004; **29**: 25–7.
22 Soma Y, Kawakami T, Yamasaki E *et al.* Linear scleroderma along Blaschko's lines in a patient with systematized morphoea. *Acta Derm Venereol* 2003; **83**: 362–4.
23 Mukhopadhyay A. Linear scleroderma following Blaschko's lines. *Indian J Dermatol Venereol Leprol* 2005; **71**: 421–2.
24 Hauser C, Skaria A, Harms M *et al.* Morphoea following Blaschko's lines. *Br J Dermatol* 1996; **134**: 594–5.
25 Bramley P, Forbes A. A case of progressive hemiatrophy presenting with spontaneous fractures of the lower jaw. *BMJ* 1960; **i**: 1476–8.
26 Larregue M, Ziegler JE, Lauret P *et al.* Sclerodermie en bande chez l'enfant (a propos de 27 cas). *Ann Dermatol Vénéréol* 1986; **113**: 207–24.
27 Longacre JJ, Wagner EA. The surgical management of disabling contractures due to linear scleroderma. *Plast Reconstr Surg* 1952; **9**: 367–80.
28 Weill J, Dubois M, Lewin *et al.* Sclerodermie en bandes et atrophies tissulaires multiples. *Bull Mem Soc Med Hop Paris* 1953; **69**: 490–5.
29 Tajima S, Suzuki Y, Inazumi T. A case of atypical localized scleroderma presenting with pseudoainhum: treatment with tranilast, an anti-fibrotic agent. *Acta Derm Venereol (Stockh)* 1996; **76**: 162.
30 Park BS, Hyun-Cho K, Youn JI *et al.* Pseudoainhum associated with linear scleroderma. *Arch Dermatol* 1996; **132**: 1520–1.
31 Juhn BJ, Cho YH, Lee MH. Linear scleroderma associated with hypertrichosis in the absence of melorheostosis. *Acta Derm Venereol* 2000; **80**: 62–3.
32 Alvarez MJM, Lazano MA, Espada G *et al.* Linear scleroderma and melorheostosis: case presentation and literature review. *Clin Rheumatol* 1966; **15**: 389–93.
33 Wagers LT, Young AW, Ryan SF. Linear melorheostotic scleroderma. *Br J Dermatol* 1972; **86**: 297–301.
34 Soffa DJ, Sire DJ, Dodson JH. Melorheostosis with linear sclerodermatous skin changes. *Radiology* 1975; **114**: 577–8.
35 Vereecken P, Stallenberg B, Tas S *et al.* Ulcerated dystrophic calcinosis cutis secondary to localized linear scleroderma. *Int J Clin Prac* 1998; **52**: 593–4.
36 Hsu S, Lee MWC, Carlton S *et al.* Nodular morphea in a linear pattern. *Int J Dermatol* 1999; **38**: 529–30.
37 Davis WC, Saunders TS. Scleroderma of the face involving the gingiva. *Arch Dermatol Syphilol* 1946; **54**: 133–5.
38 Looby JB, Burket LW. Scleroderma of the face with involvement of the alveolar process. *Am J Orthodontol* 1942; **28**: 493.
39 Jappe U, Holzle E, Ring J. Parry–Romberg syndrom Zussamenfassung und neue Erkenntnisse anlablich einer ungewhnlichen Kasuistik. *Hautarzt* 1996; **47**: 599–603.
40 Tollefson MM, Witman PM. En coup de sabre morphoea and Parry-Romberg syndrome: a retrospective review of 54 patients. *J Am Acad Dermatol* 2007; **56**: 257–63.
41 Dilley JJ, Perry HO. Bilateral linear scleroderma en coup de sabre. *Arch Dermatol* 1968; **97**: 688–9.
42 Rai R, Handa S, Gupta S *et al.* Bilateral en coup de sabre: a rare entity. *Pediatr Dermatol* 2000; **17**: 222–4.
43 McKenna DB, Benton EC. A tri-linear pattern of scleroderma 'en coup de sabre' following Blaschko's lines. *Clin Exp Dermatol* 1999; **24**: 467–8.
44 Soma Y, Fujimoto M. Frontoparietal scleroderma (en coup de sabre) following Blaschko's lines. *J Am Acad Dermatol* 1998; **38**: 366–8.
45 Unterberger I, Trinka E, Englhadt K *et al.* Linear scleroderma 'en coup de sabre' coexisting with plaque-morphoea: neurological manifestation and response to corticosteroids. *J Neurol Neurosurg Psych* 2003; **74**: 661–4.
46 Lakhani PK, David TJ. Progressive hemifacial atrophy with scleroderma and ipsilateral limb wasting (Parry–Romberg syndrome). *J R Soc Med* 1984; **77**: 138–9.
47 Menni S, Marzano AV, Passoni E. Neurologic abnormalities in two patients with facial hemiatrophy and sclerosis coexisting with morphoea. *Pediatr Dermatol* 1997; **14**: 113–6.
48 Appenzeller S, Montenegro MA, Dertkigil S *et al.* Neuroimaging findings in scleroderma en coup de sabre. *Neurology* 2004; **62**: 1585–9.
49 Holland KE, Steffes B, Nocton JJ *et al.* Linear scleroderma en coup de sabre with associated neurologic abnormalities. *Paediatrics* 2006; **117**: e132–6.
50 Segal P, Jablonska S, Mrzyglod S. Ocular changes in linear scleroderma. *Am J Ophthalmol* 1961; **51**: 807–13.
51 Serup J, Serup L, Sjo O. Localized scleroderma 'en coup de sabre' with external eye muscle involvement at the same time. *Clin Exp Dermatol* 1984; **9**: 196–200.
52 Holl-Wieden A, Klink T, Klink J *et al.* Linear scleroderma 'en coup de sabre' associated with cerebral and ocular vasculitis. *Scand J Rheumatol* 2006; **35**: 402–4.
53 Serup J, Alsbirk PH. Localized scleroderma 'en coup de sabre' and iridopalpebral atrophy at the same time. *Acta Derm Venereol (Stockh)* 1983; **63**: 75–7.
54 Stone RA, Scheie HG. Periorbital scleroderma associated with heterochromia iridis. *Am J Ophthalmol* 1980; **90**: 858–61.
55 Long PR, Miller OF. Linear scleroderma. *J Am Acad Dermatol* 1982; **7**: 541–4.
56 Handfield-Jones SE, Peachey RDG, Moss ALH *et al.* Ossification in linear morphoea with hemifacial atrophy: treatment by surgical excision. *Clin Exp Dermatol* 1988; **13**: 385–8.

Localized scleroderma in childhood [1–3]. Childhood onset occurs in 2–3% of all cases of scleroderma. Most present with morphoea-type lesions (particularly linear) although systemic sclerosis does occur. The clinical features are similar to adult cases but localized trauma a few months before onset of morphoeic lesions has been reported to occur in one-quarter of childhood patients. A recent large series of 750 children from 70 European centres [4] showed linear scleroderma to be the commonest subtype (65%) followed by plaque morphoea (26%), generalized morphoea (7%) and deep morphoea (2%), and 15% had a mixed subtype. Twelve per cent had a positive family history for rheumatic or autoimmune diseases and 13% reported environmental events as a possible trigger. ANA was positive in 42%, rheumatoid factor in 16%, anticardiolipin antibody in 13%, anti-double-stranded DNA in 4%, Scl-70 in 3% and anticentromere antibody in 2%.

Disabling pansclerotic morphoea of children [5]. This is a rare, severe, mutilating form of morphoea involving the dermis, fat, fascia, muscle and even bone, usually starting before the age of 14 years, although adult-onset cases have been reported [6]. It may develop from linear morphoea. Superficial and deep cutaneous sclerosis involves the trunk and extremities, scalp and face, with sparing of the fingertips and toes (Fig. 51.54). There may be a claw deformity of the hands, and patients may walk on tiptoe because of contracture of the Achilles tendons (Fig. 51.55). Arthralgia and stiffness occur at the onset, and intense pain may be a problem,



Fig. 51.54 Disabling pansclerotic morphoea of the fingers.



Fig. 51.55 Disabling pansclerotic morphoea of the legs.

presumably because of involvement of cutaneous nerves [7]. Raynaud's phenomenon is not found, but a few cases have had oesophageal, pulmonary and periodontal changes. Flexion contractures, osteoporosis and other bone changes are frequent. The electromyogram and histology of muscle may be abnormal, but creatine phosphokinase is normal. Elevation of ESR, hypergammaglobulinaemia and eosinophilia are frequent. Treatment with PUVA [8], low-dosage UVA-1 [9] and ciclosporin [10] has been reported. The response is often poor, however, and in most patients the condition is progressive [11] and occasionally fatal [5].

References

1 Vancheeswaran R, Black CM, David J *et al.* Childhood-onset scleroderma: is it different from adult-onset disease? *Arthritis Rheum* 1996; **39**: 1041–9.
2 Emery H. Paediatric scleroderma. *Semin Cutan Med Surg* 1998; **17**: 41–7.
3 Black CM. Scleroderma in childhood. *Adv Exp Med Biol* 1999; **45**: 35–48.
4 Zulian F, Athreya BH, Laxer R *et al.* Juvenile localized scleroderma: clinical and epidemiological features in 750 children. An international study. *Rheumatology* 2006; **45**: 614–20.
5 Diaz-Perez JL, Connolly SM, Winkelmann RK. Disabling pansclerotic morphoea of children. *Arch Dermatol* 1980; **116**: 169–73.
6 Maragh SH, Davis MDP, Bruce AJ *et al.* Disabling pansclerotic morphea: clinical presentation in two adults. *J Am Acad Dermatol* 2005; **53**: S115–9.
7 Rowell NR. Acral pansclerotic morphoea with intractable pain. In: Burgdorf WHC, Katz SI, eds. *Clinical Dermatology: the CMO Case Collection/World Congress of Dermatology*. Berlin: Scheltauer, 1987: 178–80.
8 Scharffetter-Kochanek K, Goldermann R, Lehmann P *et al*. PUVA therapy in disabling pansclerotic morphoea of children. *Br J Dermatol* 1995; **132**: 830–1.
9 Gruss C, Stucker M, Von Kobyletski G *et al.* Low dose UVA-1 phototherapy in disabling pansclerotic morphoea of childhood. *Br J Dermatol* 1997; **136**: 293–4.
10 Peter RU, Rizicka T, Eckert F. Low-dose cyclosporine A in the treatment of disabling morphoea. *Arch Dermatol* 1991; **127**: 1420–1.
11 Wollina U, Wollina K. Pansclerotic morphoea of childhood: follow-up over 6 years. *Paediatr Dermatol* 1999; **16**: 245–7.

Associated lesions. Arthralgia, sometimes localized to the sclerodermatous extremity, unilateral Raynaud's phenomenon, a history of migraine and intermittent recurrent colicky abdominal pain are sometimes found [1]. Abnormal radiological appearances of the spine occurred in 47% of patients in one series [1], particularly those with linear scleroderma. Spina bifida was found in 20 patients and was most common in patients with linear morphoea of the legs, lower abdomen and buttocks. Other abnormalities included sacralization of lumbar segments, the presence of six lumbar vertebrae, prolongation of transverse arches, scoliosis and kyphosis. Pain in the lumbar region, like that of a protruded lumbar intervertebral disc, was sometimes a feature. Rib abnormalities such as rudimentary or cervical ribs, torticollis, atrophic clavicle, absent pectoralis muscle, contracted pelvis, shortened ulna and deformities of the feet and toes have been reported [1], but other studies have not reported similar findings. Associated cutaneous abnormalities include warty, vascular or pigmented naevi, usually with linear morphoea on the same side, café-au-lait spots, alopecia areata, vitiligo [2], generalized ichthyosis or pigmentation, dystrophy of the nails, hirsutism and coarctation of the aorta [3]. Localized morphoea occurred in a pigmented area of Becker's melanosis [4]. A variant occurring later in life, in which morphoea confined to the face and anterior part of the scalp is associated with tissue calcification, hair loss and beaking of the nose, has been reported [5]. Sclerotic panatrophy, disseminated granuloma annulare and morphoea have occurred in the same patient [6].

Children may be intellectually precocious [1]. A recent review of 750 children with localized scleroderma from 70 European centres [7] showed that almost one-quarter had extracutaneous manifestations, including articular (47%), neurological (17%), vascular (9%), ocular (8%), gastrointestinal (6%), respiratory (3%), cardiac (1%) and renal (1%) abnormalities. Other autoimmune conditions were present in 7%.

Occasionally, morphoeic lesions may occur in association with lesions of lichen sclerosus et atrophicus. Localized patches of morphoea may occur in patients with systemic sclerosis [8] and

occasionally patients with localized patches of morphoea may later develop systemic sclerosis [1,9]. Although no systemic abnormalities were found in 27 autopsies on patients with localized morphoea [10], changes in the oesophagus, muscles and joints may occur in as many as 27% of cases [11]. The diagnosis of systemic sclerosis was confirmed at autopsy in a 71-year-old woman with two patches of localized morphoea on the front of the chest, who subsequently developed cardiac enlargement, pulmonary fibrosis and a dilated aperistaltic oesophagus [12]. Typical morphoeic patches on the skin and gastrointestinal radiological changes typical of systemic sclerosis were found in another patient [13].

Morphoea has occurred with DLE [14], mixed connective tissue disease [15] and eosinophilic fasciitis [16], and frontoparietal morphoea has been associated with SLE [17]. Morphoea has followed SCLE [18] and may also occur with dermatomyositis [19], carpal tunnel syndrome [20], nephritis [21], vitiligo [22], pemphigus [23], primary biliary cirrhosis [24] and myasthenia gravis [25]. The coexistence of morphoea, localized bullous pemphigoid and subcorneal pustulosis has been reported [26]. Elastosis perforans serpiginosa has also occurred with morphoea [27]. Localized scleroderma can follow augmentation mammoplasty [28], and linear oedema, nodularity and scarring, with hidebound skin, has been attributed to leaking of silicone into an arm [29].

There is no relationship between localized morphoea and internal malignancy [30], although systemic sclerosis has been associated with carcinoma of the lung, skin and liver [30,31]. The morphoea-like changes found in patients with carcinoid syndrome are thought to occur as a result of serotonin release by the tumour [31]. Squamous cell carcinoma has been reported in patients with long-standing pansclerotic morphoea [32] and in localized scleroderma in a patient treated with azathioprine [33].

References

1 Christianson HB, Dorsey ES, O'Leary PA *et al*. Localized scleroderma: a clinical study of 235 cases. *Arch Dermatol* 1956; **74**: 629–39.
2 Bonifati C, Impara G, Morrone A *et al*. Simultaneous occurrence of linear scleroderma and homolateral segmental vitiligo. *J Eur Acad Dermatol Venereol* 2006; **20**: 63–5.
3 Basu S, Ganguly S. Homolateral linear morphea with coarctation of aorta. *Indian Paediatr* 2003; **40**: 1108–9.
4 Rufli T. Melanosis Becker mit lokalisierter Sklerodermie. *Dermatologica* 1972; **145**: 222–9.
5 Hazen PG, Askari A. Localized scleroderma with cutaneous calcinosis. *Arch Dermatol* 1979; **115**: 871–2.
6 Holmes RC, Meara RH. Morphoea, sclerotic panatrophy and disseminated granuloma annulare. *Clin Exp Dermatol* 1983; **8**: 201–3.
7 Zulian F, Vallongo C, Woo P *et al*. Localized scleroderma in childhood is not just a skin disease. *Arthritis Rheum* 2005; **52**: 2873–81.
8 Truelove SC, Whyte HM. Acrosclerosis. *BMJ* 1951; **ii**: 873–6.
9 Curtis AC, Jansen TG. The prognosis of localized scleroderma. *Arch Dermatol* 1958; **78**: 749–57.
10 Piper WN, Helwig EB. Progressive systemic sclerosis: visceral manifestations in generalized scleroderma. *Arch Dermatol* 1955; **72**: 535–46.
11 Luderschmidt C, Konig G, Leisner B *et al*. Zirkumskripte Sklerodermie: Interne manifestationen und signikante korrelation zu HLA-DR1 und DR-5. *Hautarzt* 1985; **36**: 516–21.
12 Rodnan GP, Fennell RH. Progressive systemic sclerosis sine scleroderma. *JAMA* 1962; **180**: 665–70.
13 Donaldson EM. Morphoea (localized scleroderma) with visceral changes. *Br J Dermatol* 1962; **74**: 105.
14 Umbert P, Winkelmann RK. Concurrent localized scleroderma and discoid lupus erythematosus. *Arch Dermatol* 1978; **114**: 1473–8.
15 Golding DN. Morphoea (localized scleroderma) in a patient with mixed connective tissue disease. *Ann Rheum Dis* 1986; **45**: 523–5.
16 Piette WW, Dorsey JK, Foucar E. Clinical and serologic expression of localized scleroderma. *J Am Acad Dermatol* 1985; **13**: 342–50.
17 Mackel SE, Kozin F, Ryan LM *et al*. Concurrent linear scleroderma and systemic lupus erythematosus. *J Invest Dermatol* 1979; **73**: 368–72.
18 Rao BK, Coldiron B, Freeman RG *et al*. Subacute lupus erythematosus lesions progressing to morphoea. *J Am Acad Dermatol* 1990; **23**: 1019–22.
19 Štáva Z. Zirkumskripte Sklerodermie (klinische analyse von 50 ausgewählten fällen). *Dermatol Wochenschr* 1959; **139**: 513–23.
20 Winkelmann RK, Connolly SM, Doyle JA. Carpal tunnel syndrome in cutaneous connective tissue disease: generalized morphea, lichen sclerosus, fasciitis, discoid lupus erythematosus and lupus panniculitis. *J Am Acad Dermatol* 1982; **7**: 94–9.
21 Bourgeois-Droin C, Touraine R. Sclerodermie en plaques, perturbations immunologiques et viscerales. *Ann Med Interne* 1978; **129**: 107–12.
22 Finkelstein E, Amichai B, Metzker A. Coexistence of vitiligo and morphoea: a case report and review of the literature. *J Dermatol* 1995; **22**: 351–3.
23 Chan LS, Cooper KD. Coexistence of pemphigus vulgaris and progressive localized scleroderma. *Arch Dermatol* 1989; **125**: 1555–7.
24 Reed JR, De Luca N, McIntyre AS *et al*. Localized morphoea, xanthomatosis and primary biliary cirrhosis. *Br J Dermatol* 2000; **143**: 652–3.
25 Kim HS, Chun YS, Hann SK *et al*. A case of linear scleroderma and myasthenia gravis. *J Dermatol* 2000; **27**: 31–4.
26 Bernstein JE, Medenica M, Soltani K. Coexistence of localized bullous pemphigoid, morphoea and subcorneal pustulosis. *Arch Dermatol* 1981; **117**: 725–7.
27 Barr RJ, Siegel JM, Graham JH. Elastosis perforans serpiginosa associated with morphoea. *J Am Acad Dermatol* 1981; **3**: 19–22.
28 Spiera H. Scleroderma after silicone augmentation mammoplasty. *JAMA* 1988; **260**: 236–8.
29 Teuber SS, Ito LK, Anderson M, Gershwin ME. Silicone breast implant-associated scarring dystrophy of the arm. *Arch Dermatol* 1995; **131**: 54–6.
30 Rosenthal AK, McLaughlin JK, Gridley G *et al*. Incidence of cancer among patients with systemic sclerosis. *Cancer* 1995; **76**: 910–4.
31 Jablonska S. Scleroderma and malignancy. In: Jablonska S, ed. *Scleroderma and Pseudoscleroderma*. Warsaw: Polish Medical Publishers, 1975; 606–9.
32 Parodi F, Stolz W, Volkenandt M *et al*. Squamous cell carcinoma in a patient with long-standing pansclerotic morphoea. *Br J Dermatol* 2001; **144**: 417–9.
33 Nachbar F, Stolz W, Volkenandt M *et al*. Squamous cell carcinoma in localized scleroderma following immunosuppression with azathioprine. *Acta Derm Venereol* 1993; **73**: 217–9.

Laboratory abnormalities. ESR and serum protein assays are usually normal, but eosinophilia may occur [1]. Anti-single-stranded DNA antibodies are more frequent in generalized morphoea (75%) and linear morphoea (53.3%) than in localized morphoea (27.3%) [2]. Antihistone antibodies have been detected in 32% of patients with linear morphoea and in 25% with localized morphoea in one study [3] and in 71% of children and 65% of adults with linear morphoea in another [4]. In the latter and one further study [5], it has been suggested that they mirror disease activity. Hereditary deficiency of complement factor C2 is reported [6]. Organ-specific autoantibodies are more commonly found than in controls [7]. Thrombocytopenia responding to corticosteroid therapy has been reported in two patients [8]. Approximately 40% of patients with linear morphoea have positive antinuclear antibodies, and the presence of these antibodies (with homogeneous and nucleolar patterns), antibodies to single-stranded DNA and the presence of eosinophilia may indicate disease activity [9] and the late development of systemic complications [10]. Serum procollagen type 1 carboxy-terminal propeptide has been reported to be raised in 30% of patients with localized morphoea, correlating

with the number of lesions. Levels are lower than in generalized morphoea and may be a useful indicator of disease activity [11]. Type 3 procollagen propeptide has also been reported to be raised [12]. However, others have not found these markers as useful.

Topoisomerase 1 (Scl-70) is unusual in localized scleroderma but a recent study has found autoantibodies to topoisomerase 11α in 70% of patients with localized scleroderma and 85% of patients with generalized morphoea [13]. IgM rheumatoid factor has been suggested to be a useful marker of disease severity [14], and IgM anticardiolipin antibodies have been reported as associated with a greater number of lesions [15]. In another study, antinucleosome antibodies were found to have a higher prevalence in localized scleroderma [16]. All the serological changes associated with localized scleroderma have been recently reviewed [17].

In children, in a recent large series from 70 European centres [18], ANA was positive in 42%, rheumatoid factor in 16%, anticardiolipin antibody in 13%, anti-double-stranded DNA in 4%, Scl-70 in 3% and anticentromere antibody in 2%.

Ultrasound scanning has been reported as being helpful in diagnosing morphoea [19], in differentiating morphoea from lichen sclerosus et atrophicus [20], and in monitoring the course of localized morphoea [21]. The dermatoscope has been reported as a useful tool for assessing nail fold capillary abnormalities [22].

Prognosis. Plaque-like lesions tend to improve with time. The induration lessens and the lesions blend in with the rest of the skin, leaving a brownish stain, which may persist for a long time. The duration of activity is usually between 3 and 5 years, but some lesions last up to 25 years. It is common to find fresh lesions developing on new sites as other lesions resolve. Residual pigmentation persists for a long time in approximately one-third of patients. Linear lesions tend to persist for longer than plaque lesions, but on the whole improve with time. Calcinosis occasionally occurs in linear lesions, and sometimes requires surgical removal. Contractures may limit movement of joints and give rise to clawing of the hand. Unilateral atrophy of one or more limbs may occur. Facial hemiatrophy is usually persistent, but frontoparietal scleroderma may clear, and may be accompanied by regrowth of hair. In 63 of 88 children with morphoea, lesions resolved with minimal cosmetic disability [23]. Very rarely, patients with localized morphoea may subsequently develop classical systemic sclerosis [23,24]. It has been suggested that the presence of anti-Ku antibody may be a prognostic indicator of such progression [24].

Differential diagnosis. The diagnosis is usually not difficult, the insidious development of indurated plaques and bands in the skin, with or without hemiatrophy, being unlikely to occur in other conditions. If there is a lilac-coloured border diagnosis is easier. Reticulate lilac lesions with minimal induration can resemble cutaneous polyarteritis nodosa. Morphoeic lesions occur in sarcoidosis [25]. Lesions can start as a vascular blush, and may be mistaken for a macular vascular naevus. In the acute phase, the condition must be distinguished from scleroedema of Buschke, but in this condition the onset is much more acute, and the lesions may follow an infectious episode. Fading pigmented lesions are sometimes very difficult to diagnose, but the previous history of some induration in the area is usually helpful. Atrophic pigmented lesions resembling lesions of the atrophy of Pierini and Pasini (see Chapter 45) [26] occurred in 47% of the patients in one series [27]. Abdominal lesions may be confused with so-called lipodystrophia centrifugalis abdominalis infantilis (see Chapter 46) [28,29]. Atrophic morphoeic plaques can result from intramuscular injections of vitamin K [30] or subcutaneous corticosteroid injections [31]. Conditions producing pseudoscleroderma (see p. 51.79) may have to be considered. Melorheostosis is a rare condition in which there are painful abnormalities of the skeleton and adjacent soft tissues, usually limited to a single limb. Linear endosteal bony densities of the long bones are seen on radiography, and resemble candle wax flowing along the affected bone. In children, the usual presentation is with asymmetrical contractures of a limb, occurring in association with thickening of the overlying skin and fascia, and distal vascular problems exacerbated by attempted surgical correction of the orthopaedic problem, including angiomas and arteriovenous malformations [32]. It is suggested that the distribution of these lesions represents the sclerotome, or the areas of the body supplied by a spinal sensory nerve, and that skin and muscle involvement occur in the relevant dermatome and myotome [33]. The cutaneous lesions are almost certainly a part of the developmental abnormality, rather than coexisting linear morphoea [34].

Treatment. As the expected natural history is towards spontaneous resolution, the condition may be allowed to take its natural course, if uncomplicated. If intervention is required, localized treatment with topical or intralesional steroids may be helpful [35]. More recently, calcipotriol has been shown to inhibit the growth of morphoea fibroblasts *in vitro* [36], and has proved beneficial when used topically *in vivo*, both alone [37,38] and in combination with UVA-1 in children [39]. Topical tacrolimus has been reported as being beneficial in seven patients [40] as has 5% imiquimod cream [41].

Numerous systemic agents have been reported to be helpful in morphoea (on the basis of case reports or small open studies), including phenytoin [42], *p*-aminobenzoate [43], griseofulvin [44], etretinate [45], vitamin E [46], chloroquine and hydroxychloroquine [47]. Tranilast was reported as helpful in a boy with linear morphoea and contractures [48], and plasmapheresis was helpful (in combination with systemic corticosteroids) in three patients with localized scleroderma and antinuclear antibodies [49]. Regression of plaques of morphoea after tamoxifen therapy has been reported in one patient [50], and a child with pansclerotic morphoea showed significant improvement after 3 months' therapy with the oral endothelin receptor antagonist bosentan [51]. Topical photodynamic therapy was reported as being helpful in five patients with localized disease [52].

Systemic corticosteroids have been found to be helpful in an open trial [53], although they are probably only beneficial in the inflammatory stage of the disease [35]. d-Penicillamine has been reported as helpful in open trials [54–56] in regimens of 2–5 mg/kg/day, with or without pyridoxine 20 mg/day. However, there is a risk of renal damage [54]. Ciclosporin was found to be helpful in open studies in localized morphoea [57,58] and in a single case of linear scleroderma in a child [59]. Oral calcitriol, in regimens of 0.5–0.75 μg/day, has been reported as helpful in a small study

[60], but a recent double-blind placebo controlled trial did not confirm this [61].

In recent years, UVA irradiation, both alone at low [62–65], medium [66] and high doses [67], as bath or oral photochemotherapy [68–71], and in combination with calcipotriol [39], has been reported as helpful. Two randomized controlled trials have both confirmed that low-dose broad-band UVA (UVA1) is as effective as medium- or high-dose UVA regimens or narrow-band UVB [72,73]. The effect is thought to result from increased production of collagenase and IFN-δ, and decreased TGF-β and collagen production [74]. A single case report has suggested that low-dose UVA was helpful in softening lesions in a case of pansclerotic morphoea in an 8-year-old girl [75]. The main therapeutic advance for morphoea, however, is the greater use of methotrexate. In low dose, this agent has proved useful in both widespread morphoea [76,77] and in localized morphoea in children when used in combination with systemic corticosteroids [78–82].

Physical therapy in the form of physiotherapy may be helpful in preventing joint deformities and contractures, and in maintaining joint movement and muscle strength. It may also help to prevent sclerosis secondary to lymphoedema in the limbs of patients with linear morphoea [35]. Surgical intervention for the relief of contractures [83], the lengthening of limbs and the correction of deformities may have to be carried out in certain cases. Various plastic surgery techniques can help patients with 'en coup de sabre' morphoea [84–95] and those with ossification [96]. Ulcers associated with bullous lesions have been treated with 'tissue-engineered' skin [97]. For those patients in whom the sclerotic processes have extended into the jaw to involve the teeth, dental treatment may be required.

References

1 Giordano M, Ara M, Valentini G *et al*. Presence of eosinophilia in progressive systemic sclerosis and localized scleroderma. *Arch Dermatol Res* 1981; **271**: 411–7.

2 Ruffatti A, Peserico A, Rondinone R *et al.* Prevalence and characteristics of anti-single-stranded DNA antibodies in localized scleroderma. *Arch Dermatol* 1991; **127**: 1180–3.

3 Sato S, Ihn H, Soma Y *et al.* Antihistone antibodies in patients with localized scleroderma. *Arthritis Rheum* 1993; **36**: 1137–41.

4 El-Azhary RA, Aponte CC, Nelson AM *et al.* Antihistone antibodies in linear scleroderma variants. *Int J Dermatol* 2006; **45**: 1296–9.

5 El-Azhary RA, Aponte CC, Nelson AM *et al.* Do antihistone autoantibodies reflect disease activity in linear scleroderma? *Arch Dermatol* 2004; **140**: 759–60.

6 Hulsmans RFHJ, Asghar SS, Siddiqui AH *et al*. Hereditary deficiency of C2 in association with linear scleroderma 'en coup de sabre'. *Arch Dermatol* 1986; **122**: 76–9.

7 Harrington I, Dunsmore IR. An investigation into the incidence of auto-immune disorders in patients with localized morphoea. *Br J Dermatol* 1989; **120**: 645–8.

8 Neucks SH, Moore TL, Lichtenstein JR *et al.* Localized scleroderma and idiopathic thrombocytopenia. *J Rheumatol* 1980; **7**: 741–4.

9 Falanga V, Medsger TA, Reichlin M *et al*. Linear scleroderma: clinical spectrum, prognosis and laboratory abnormalities. *Ann Intern Med* 1986; **104**: 849–57.

10 Woo TY, Rasmussen JE. Juvenile linear scleroderma associated with serologic abnormalities. *Arch Dermatol* 1985; **121**: 1403–5.

11 Kikuchi K, Sato S, Kadono T *et al*. Serum concentration of procollagen type 1 carboxy-terminal propeptide in localized scleroderma. *Arch Dermatol* 1994; **130**: 1269–72.

12 Zachariae H, Halkier-Sorensen L, Heickendorff L. Serum aminoterminal propeptide of type III procollagen in progressive systemic sclerosis and localized scleroderma. *Acta Derm Venereol (Stockh)* 1989; **69**: 66–70.

13 Hayakawa I, Hasegawa M, Takehara K *et al.* Anti-topoisomerase 11α autoantibodies in localized scleroderma. *Arthritis Rheum* 2004; **50**: 227–32.

14 Mimura Y, Ihn H, Jinnin M *et al.* Rheumatoid factor isotypes in localized scleroderma. *Clin Exp Dermatol* 2005; **30**: 405–8.

15 Sato S, Fujimoto M, Hasegawa M *et al.* Antiphospholipid antibody in localised scleroderma. *Ann Rheum Dis* 2003; **62**: 771–4.

16 Sato S, Kodera M, Hasegawa M *et al*. Antinucleosome antibody is a major autoantibody in localized scleroderma. *Br J Dermatol* 2004; **151**: 1182–8.

17 Takehara K, Sato S. Localized scleroderma is an autoimmune disorder. *Rheumatology* 2005; **44**: 274–9.

18 Zulian F, Athreya BH, Laxer R *et al.* Juvenile localized scleroderma: clinical and epidemiological features in 750 children. An international study. *Rheumatology* 2006; **45**: 614–20.

19 Cosnes A, Anglade M-C, Revuz J *et al*. Thirteen-megahertz ultrasound probe: its role in diagnosing localized scleroderma. *Br J Dermatol* 2003; **148**: 724–9.

20 Chen HC, Kadono T, Mimura Y *et al*. High frequency ultrasound as a useful device in the preliminary differentiation of lichen sclerosus et atrophicus from morphea. *J Dermatol* 2004; **31**: 556–9.

21 Hoffman K, Gerbaulet U, El-Gammal S *et al.* 20-Mhz B-mode ultrasound in monitoring the course of localized scleroderma (morphoea). *Acta Derm Venereol* 1991; **164**: 3–16.

22 Bergman R, Sharony L, Schapira D *et al.* The handheld dermatoscope as a nailfold capillaroscopic instrument. *Arch Dermatol* 2003; **139**: 1027–30.

23 Torok E, Ablonczy E. Morphoea in children. *Clin Exp Dermatol* 1986; **11**: 607–12.

24 Birdi N, Laxer RM, Thorner P *et al*. Localized scleroderma progressing to systemic disease: case report and review of the literature. *Arthritis Rheum* 1993; **36**: 410–5.

25 Hess SP, Agudelo WL, White WL *et al*. Ichthyosiform and morpheaform sarcoidosis. *Clin Exp Rheumatol* 1990; **8**: 171–5.

26 Jablonska S, Szczepanski A. Atrophoderma Pasini–Pierini. In: Jablonska S, ed. *Scleroderma and Pseudoscleroderma*. Warsaw: Polish Medical Publishers, 1975: 521–36.

27 Serup J. Clinical appearance of skin lesions and disturbances of pigmentation in localized scleroderma. *Acta Derm Venereol (Stockh)* 1984; **64**: 485–92.

28 Imamura S, Yamada M, Ikeda T. Lipodystrophia centrifugalis abdominalis infantilis. *Arch Dermatol* 1971; **104**: 291–8.

29 Zachary CB, Wells RS. Centrifugal lipodystrophia. *Br J Dermatol* 1984; **110**: 107–10.

30 Texier L, Gendre P, Gauthier O *et al.* Hypodermites sclerodermiformes lombofessieres induites par des injections medicamenteuses intramusculaires associées a la vitamine K. *Ann Dermatol Syphiligr* 1972; **99**: 363–71.

31 Holt PJA, Marks R, Waddington E. 'Pseudomorphoea': a side effect of subcutaneous corticosteroid injection. *Br J Dermatol* 1975; **92**: 689–91.

32 Younge D, Drummond D, Herring J *et al*. Melorheostosis in children. *J Bone Joint Surg* 1979; **61**: 415–8.

33 Murray RO, McCredie J. Melorheostosis and the sclerotomes: a radiological correlation. *Skeletal Radiol* 1979; **4**: 57–71.

34 Muller SA, Henderson ED. Melorheostosis with linear scleroderma. *Arch Dermatol* 1963; **88**: 142–5.

35 Hunzelmann N, Kochanek KS, Hager C *et al.* Management of localized scleroderma. *Semin Cutan Med Surg* 1998; **17**: 34–40.

36 Bottomley WW, Jutley J, Wood EJ *et al*. The action of calcipotriol on fibroblasts from patients with active morphoea. *Acta Derm Venereol (Stockh)* 1995; **75**: 364–6.

37 Cunningham BB, Landells ID, Langman C *et al.* Topical calcipotriene for morphea/linear scleroderma. *J Am Acad Dermatol* 1998; **39**: 211–5.

38 Tay YK. Topical calcipotriol ointment in the treatment of morphea. *J Dermatolog Treat* 2002; **14**: 219–21.

39 Kreuter A, Gambichler T, Avermaete A *et al.* Combined treatment with calcipotriol ointment and low dose ultraviolet A1 phototherapy in childhood morphoea. *Paediatr Dermatol* 2001; **18**: 241–5.

40 Mancuso G, Berdondini RM. Localized scleroderma: response to occlusive treatment with tacrolimus ointment. *Br J Dermatol* 2005; **152**: 180–2.

41 Dytoc M, Ting PT, Man J *et al.* First case series on the use of imiquimod for morphoea. *Br J Dermatol* 2005; **153**: 815–20.

42 Nelder K. Treatment of localized linear scleroderma with phenytoin. *Cutis* 1978; **22**: 569–72.

43 Zarafonetis CJD. Treatment of localized form of scleroderma. *Am J Med Sci* 1962; **243**: 147–58.

44 Giordano M, Ara M, Capelli L, Tirri G. Griseofulvin in scleroderma. In: Black CM, Myers AR, eds. *Systemic Sclerosis (Scleroderma).* New York, NY: Gower Medical, 1985: 423–7.
45 Neuhofer J, Fritsch P. Treatment of localized scleroderma and lichen sclerosus with etretinate. *Acta Derm Venereol (Stockh)* 1984; **64**: 171–4.
46 Ayres S, Mihan R. Is vitamin E involved in the autoimmune mechanism? *Cutis* 1978; **21**: 321–5.
47 Nagy E, Ladanyi E. Behandlung de umschriebenen Sklerodermie im Kindesalter. *Z Hautkr* 1987; **62**: 547–9.
48 Taniguchi S, Yorifiji T, Hamada T. Treatment of linear localized scleroderma with the anti-allergic drug, Tranilast. *Clin Exp Dermatol* 1994; **19**: 391–3.
49 Wach F, Ullrich H, Schmitz G *et al*. Treatment of severe localized scleroderma by plasmapheresis: report of three cases. *Br J Dermatol* 1995; **133**: 605–9.
50 Ayoub N, Bouaziz JD, Barete S *et al.* Regression of morphoea plaques after tamoxifen therapy. *J Eur Acad Dermatol Venereol* 2004; **18**: 637–8.
51 Roldan R, Morote G, Castro M *et al.* Efficacy of bosentan in treatment of unresponsive cutaneous ulceration in disabling pansclerotic morphea in children. *J Rheumatol* 2006; **33**: 2538–40.
52 Karrer S, Abels C, Landthaler M *et al.* Topical photodynamic therapy for localized scleroderma. *Acta Derm Venereol* 2000; **80**: 26–7.
53 Joly P, Bamberger N, Crickx B *et al.* Treatment of severe forms of localized scleroderma with oral corticosteroids: follow-up study on 17 patients. *Arch Dermatol* 1994; **130**: 663–4.
54 Moynahan EJ. Morphoea (localized cutaneous scleroderma) treated with low-dosage penicillamine. *Proc R Soc Med* 1973; **66**: 1083–5.
55 Falanga V, Medsger TA. D-Penicillamine in the treatment of localized scleroderma. *Arch Dermatol* 1990; **126**: 609–12.
56 Satta MA, Guindi RT, Sugathan TN. Penicillamine in systemic sclerosis: a reappraisal. *Clin Rheumatol* 1990; **9**: 517–22.
57 Peter RU, Ruzicka T. Cyclosporin A in der Therapie entzundlicher Dermatosen. *Hautarzt* 1992; **43**: 687–94.
58 Peter RU, Ruzicka T, Eckert F. Low dose cyclosporine A in the treatment of disabling morphoea. *Arch Dermatol* 1991; **127**: 1420–1.
59 Strauss RM, Bhushan M, Goodfield MJD. Good response of linear scleroderma in a child to ciclosporin. *Br J Dermatol* 2004; **150**: 790–2.
60 Humbert PG, Dupond JL, Rochefort A *et al.* Localized scleroderma: response to 1,25-dihydroxyvitamin D_3. *Clin Exp Dermatol* 1990; **15**: 396–8.
61 Hulshof MM, Bavinck JNB, Bergman W *et al.* Double-blind, placebo controlled study of oral calcitriol for the treatment of localized and systemic scleroderma. *J Am Acad Dermatol* 2000; **43**: 1017–23.
62 Kerscher M, Dirschke T, Volkenandt M. Treatment of localized scleroderma by UVA-1 phototherapy. *Lancet* 1995; **348**: 1166.
63 Kerscher M, Volkenandt M, Gruss C *et al.* Low-dose UVA phototherapy for treatment of localized scleroderma. *J Am Acad Dermatol* 1999; **40**: 787–8.
64 El Mofty M, Zahr H, Bosseila M *et al.* Low-dose broad-band UVA in morphoea using a new method for evaluation. *Photodermatol Photoimmunol Photomed* 2000; **16**: 43–9.
65 Gruss CJ, Von Kobyletzki G, Behrens-Williams SC *et al.* Effects of low dose ultraviolet A-1 phototherapy on morphoea. *Photodermatol Photoimmunol Photomed* 2001; **45**: 697–9.
66 Camacho NR, Sanchez JE, Martin RF *et al.* Medium dose phototherapy in localized scleroderma and its effect in CD34-positive dendritic cells. *J Am Acad Dermatol* 2001; **45**: 697–9.
67 Stege H, Berneburg M, Humke S *et al.* High-dose UVA1 radiation therapy for localized scleroderma. *J Am Acad Dermatol* 1997; **36**: 938–44.
68 Kerscher M, Meurer M, Sandu C *et al.* PUVA bath photochemotherapy for localized scleroderma: evaluation of 17 consecutive patients. *Arch Dermatol* 1996; **132**: 1280–2.
69 Morison WL. Psoralen UVA therapy for linear and generalized morphoea. *J Am Acad Dermatol* 1997; **37**: 657–9.
70 Kanekura T, Fukumara S, Matsushita S *et al.* Successful treatment of scleroderma with PUVA therapy. *J Dermatol* 1996; **23**: 455–9.
71 De Rie MA, Bos JD. Photochemotherapy for systemic and localized scleroderma. *J Am Acad Dermatol* 2000; **43**: 725–6.
72 El Mofty M, Mostafa W, El-Darouty M *et al.* Different low doses of broad-band UVA in the treatment of morphea and systemic sclerosis. A clinico-pathologic study. *Photodermatol Photoimmunol Photomed* 2004; **20**: 148–56.
73 Kreuter A, Hyun J, Stucker M *et al.* A randomized controlled study of low-dose UVA1, medium-dose UVA1 and narrowband UVB phototherapy in the treatment of localized scleroderma. *J Am Acad Dermatol* 2006; **54**: 440–7.
74 El Mofty M, Mostafa W, Esmat S *et al.* Suggested mehanisms of action of UVA phototherapy in morphea: a molecular study. *Photodermatol Photoimmunol Photomed* 2004; **20**: 93–100.
75 Yildirim M, Baysal V, Aridogan BC *et al.* Pansclerotic morphea treated with UVA: a case report. *J Dermatol* 2003; **30**: 625–7.
76 Seyger MMB, Van Den Hoogen FHJ, De Boo T *et al.* Low-dose methotrexate in the treatment of widespread morphoea. *J Am Acad Dermatol* 1998; **39**: 220–5.
77 Seyger MM, Van Den Hoogen FH, Van Vlijem-Willems IM *et al.* Localized and systemic scleroderma show different histological responses to methotrexate therapy. *J Pathol* 2001; **193**: 511–6.
78 Uziel Y, Feldman BM, Krafchik BR *et al.* Methotrexate and corticosteroid therapy for pediatric localized scleroderma. *J Pediatr* 2000; **136**: 91–5.
79 Kreuter A, Gambichler T, Breukmann F *et al.* Pulsed high-dose corticosteroids combined with low-dose methotrexate in severe localized scleroderma. *Arch Dermatol* 2005; **141**: 847–52.
80 Fitch PG, Rettig P, Burnham JM *et al.* Treatment of paediatric localized scleroderma with methotrexate. *J Rheumatol* 2006; **33**: 609–14.
81 Weibel L, Sampaio MC, Visentin MT *et al.* Evaluation of methotrexate and corticosteroids for the treatment of localized scleroderma (morphoea) in children. *Br J Dermatol* 2006; **155**: 1013–20.
82 Weibel L, Harper JI, Howell KJ. Morphea (localized scleroderma). *J Pediatr* 2007; **150**: 560.
83 Longacre JJ, Wagner GA. The surgical management of disabling contractures due to linear scleroderma. *Plast Reconstr Surg* 1952; **9**: 367–80.
84 Neumann CG. The use of large buried pedicle flaps of dermis on fat: clinical and pathological evaluation in the treatment of progressive facial hemiatrophy. *Plast Reconstr Surg* 1953; **11**: 315–32.
85 Sengezer M, Deveci M, Selmanpakoglu N. Repair of 'coup de sabre': a linear form of scleroderma. *Ann Plast Surg* 1996; **37**: 428–32.
86 Eguchi T, Harii K, Sugawara Y. Repair of a large 'coup de sabre' with soft-tissue expansion and artificial bone graft. *Ann Plast Surg* 1999; **42**: 207–10.
87 Lapiere JC, Aasi S, Cook B *et al.* Successful correction of depressed scars of the forehead secondary to trauma and en coup de sabre by en bloc autologous dermal fat graft. *Dermatol Surg* 2000; **26**: 793–7.
88 Danino AM, Ichinose M, Yoshimoto S *et al.* Repair of wide coup de sabre without cutaneous excision by means of pericranial–galeal padding flap. *Plast Reconstr Surg* 1999; **104**: 2108–11.
89 Oh CK, Lee J, Jang BS *et al.* Treatment of atrophies secondary to trilinear scleroderma en coup de sabre by autologous tissue cocktail injection. *Dermatol Surg* 2003; **29**: 1073–5.
90 Nguyen XH, Hansen R, Valencia F. Severe ankle deformity secondary to pansclerotic morphea in a 9-year-old girl: correction involving arthrodesis and free flap coverage. *Pediatr Dermatol* 2002; **19**: 560–3.
91 Serel S, Uluc A, Can Z. Treatment of coup de sabre facial contour deformity with hydroxyapatite paste. *Ann Plast Surg* 2006; **57**: 241.
92 Copcu E. Treatment of coup de sabre deformity with porous polyethylene implant. *Plast Reconstr Surg* 2004; **113**: 758–9.
93 Hartwright D, Leslie IJ, Clarke S. Management of tenosynovitis in linear scleroderma. *Rheumatology* 2006; **45**: 640–1.
94 Smucker J, Heller JG, Bohleman HH *et al.* Surgical treatment of destructive calcific lesions of the cervical spine in scleroderma: case series and review of the literature. *Spine* 2006; **31**: 2002–8.
95 Worret WI, Jessberger B. Effectiveness of LPG treatment in morphea. *J Eur Acad Dermatol Venereol* 2004; **18**: 527–30.
96 Handfield-Jones SE, Peachey RDG, Moss ALH, Dawson A. Ossification in linear morphoea with hemifacial atrophy: treatment by surgical excision. *Clin Exp Dermatol* 1988; **13**: 385–8.
97 Martin LK, Kirsner RS. Ulcers caused by bullous morphea treated with tissue-engineered skin. *Int J Dermatol* 2003; **42**: 402–4.

Generalized morphoea

Synonym

- Generalized scleroderma



Fig. 51.56 Generalized morphoea showing diffuse tightness of the skin of the chest.

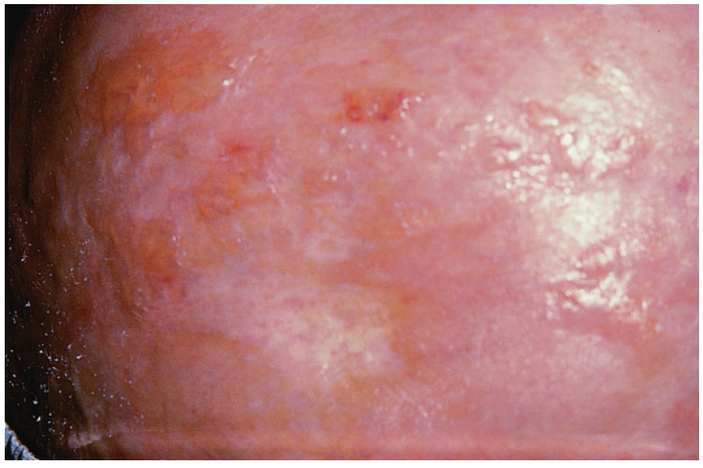


Fig. 51.57 Bullous lesions in generalized morphoea.

Definition. A rare condition in which idiopathic sclerosis of the skin occurs in a widespread manner. It usually starts on the trunk and is not associated with systemic disturbances.

Aetiology. The aetiology is unknown. The most frequent age of onset is between 30 and 40 years, and lesions start between the ages of 11 and 50 years in 80% of patients [1]. Approximately three females are affected for every male. The occurrence of generalized morphoea and localized morphoea in two sisters has been reported [2].

Pathology. This is identical to that of localized morphoea. It has been suggested that in the early stages an inflammatory infiltrate of lymphocytes, histiocytes and plasma cells is found, primarily in the subcutaneous tissue. Later, the subcutaneous tissue is replaced by hyalinized connective tissue and this is responsible for the induration of the skin. Direct immunofluorescence shows changes in approximately one-third of cases, with IgM in the basement membrane and IgM and C3 in the dermal blood vessels being the most frequent findings. Similar changes may occur less frequently in linear morphoea.

Clinical features (Fig. 51.56). The onset is usually insidious, and the patient notices the development of plaques resembling those of localized morphoea. A lilac-coloured border surrounding the indurated ivory-white shiny lesions is usually seen in the early stages. The plaques are commonly much larger than those seen in localized morphoea, being many centimetres in diameter. Usually, plaques start on the trunk and gradually increase in size, with the development of new plaques over the first year or two. The main areas involved are the upper trunk, breasts, abdomen and upper thighs. The arms may also be involved, and in some cases the hands resemble those seen in the tumid phase of systemic sclerosis, with spindling of the fingers, binding of the skin to the underlying tissues and semiflexion of the hands and fingers. The legs, face, neck and scalp may also be involved. Scarring alopecia can result from involvement of the scalp. In some cases, the whole of the body may be involved from the top of the head to the feet, although this occurred in only one out of 44 cases in one series [1]. Mechanical compression has been suggested as an aetiological factor [3]. If the chest wall is markedly involved there may be difficulty in breathing because of constriction of the thorax. The intercostal muscles may also be involved, and death may result from respiratory failure [4]. The face is expressionless, the skin being shiny, often brown, and indurated. Telangiectasia of the face is not a feature, and although mouth opening may be restricted, the radial furrowing of systemic sclerosis is not seen. Raynaud's phenomenon occurs occasionally but is not a characteristic feature. Sometimes, especially after trauma, the hands may develop whitlows, but there is no atrophy as seen in systemic sclerosis. The tissues of the trunk and limbs sometimes show a brawny non-pitting oedema and acute widespread oedema associated with hypoproteinaemia has been observed [5]. Bullae may develop in localized areas, particularly on the abdomen (Fig. 51.57). Nodular lesions may also occur [6], and multiple keloids may be the first manifestation of the disease [7]. Acral myofibromas have been reported [8]. If the condition is generalized, it may be impossible to see any area showing a lilac border. Pigmentation is common, and in some patients may be generalized. Amyloid deposition [9] and amyloidosis cutis dyschromica [10] have been reported. Keratoses and calcinosis can occur.

Contractures occur in limbs, which become thin and hard. Some patients complain of considerable soreness in the acute phase, especially of the trunk and breasts. Joint pains occur in approximately 50% of patients, particularly in the fingers, wrists, elbows and knees. Definite rheumatoid arthritis may be found. Very occasionally, severe contractures, atrophy and infection may be associated with intractable pain in the limbs, and amputation may be required. Squamous cell carcinoma may develop in lesions of over 20 years' duration [11,12].

Sometimes generalized morphoea may develop as an extension of localized morphoea or be associated with lesions of lichen sclerosus et atrophicus [13]. Subcutaneous morphoea [14] seems to be more inflammatory than generalized morphoea of the dermis, and may respond to anti-inflammatory agents. Such cases may be more likely to develop mild systemic involvement and have

eosinophilia. Generalized morphoea has been associated with polymyositis and the sick sinus syndrome [15], and necrotizing vasculitis [16], primary biliary cirrhosis [17] and fasciitis [18].

Laboratory investigations. Investigation for systemic disease is usually negative. Eosinophilia, elevated ESR and hypocomplementaemia occasionally occur. Anti-single-stranded DNA antibody occurs, but anti-double-stranded DNA antibody is rare. Serum procollagen type 1 carboxy-terminal propeptide may be a useful index of activity. Levels are higher than in localized morphoea [19]. Scl-70 antibodies are rarely found.

Differential diagnosis. The following points help to distinguish morphoea from systemic sclerosis. Raynaud's phenomenon is uncommon in generalized morphoea and is almost universal in systemic sclerosis. The distribution of the lesions also differs. In generalized morphoea, the trunk is more frequently involved, whereas the face, hands and, to a lesser extent, the feet, are most commonly involved in systemic sclerosis. Generalized morphoea usually slowly improves over the years. Scleroedema of Buschke is usually a more acute and less widespread disorder. Morphoea must also be distinguished from the various conditions described below under 'pseudoscleroderma'. Generalized morphoea may have to be distinguished from eosinophilic fasciitis (see p. 51.86).

Prognosis. Some improvement is usually seen in the course of 3–5 years, but the disease may last for many years and one patient still showed changes 33 years after diagnosis [1]. In most cases, the skin slowly softens and the pigmentation decreases. With time, the tendency to ulceration, with trauma and blistering, decreases. Although some patients may be severely disabled by the immobility associated with the sclerotic changes and contractures, others with widespread sclerosis may remain surprisingly active. Patients usually remain in good health although one patient died of bronchiolitis obliterans organizing pneumonia [20].

Treatment. The general measures outlined previously for the treatment of localized disease are just as important for patients with generalized disease.

A number of systemic agents may help generalized disease, including systemic steroids, penicillamine, antimalarials and low-dose methotrexate. In addition, individual case reports suggest a role for agents such as sulfasalazine [21], salazopyrin [22], grenz ray treatment [23] and extracorporeal photochemotherapy [24]. Initial reports suggested a role for oral calcitriol but a recent double-blind study has not confirmed this.

An increasing body of literature suggests that ciclosporin may be helpful for generalized morphoea either alone [25,26], or in combination with PUVA [27], although controlled studies are lacking. The last-mentioned case report also suggests a role for PUVA in combination with mycophenolate mofetil. Ciclosporin must be used with care, however, as side effects are common. Severe renal disease may result, although this is perhaps more likely in patients with active systemic disease [28,29]. As for localized disease, methotrexate in combination with steroids is emerging as a useful therapeutic regimen [30]. UVA phototherapy and photochemotherapy may be helpful.

References

1 Christianson HB, Dorsey ES, O'Leary PA *et al.* Localized scleroderma: a clinical study of 235 cases. *Arch Dermatol* 1956; **74**: 581–9.
2 Burge KM, Perry HO, Stickler GB. 'Familial' scleroderma. *Arch Dermatol* 1969; **99**: 681–7.
3 Ehara M, Oono T, Yamasaki O *et al.* Generalized morphoea like lesions arising in mechanically compressed areas by underclothes. *Eur J Dermatol* 2006; **16**: 307–9.
4 Russell DC, Maloney A, Muir AL. Progressive generalized scleroderma: respiratory failure from primary chest wall involvement. *Thorax* 1981; **36**: 219–20.
5 Rose RF, Goodfield MJD, Gilbey SG. Acute widespread oedema, hypoproteinaemia and generalized morphoea. *Clin Exp Dermatol* 2005; **30**: 303–4.
6 Micalizzi C, Parodi A, Rebora A. Morphoea with nodular lesions. *Br J Dermatol* 1994; **131**: 298–301.
7 Akintewe TA, Alabi GO. Scleroderma presenting with multiple keloids. *BMJ* 1985; **291**: 448–9.
8 English JC, Derdeyn AS, Smith PD *et al*. Adult acral cutaneous myofibromas in a patient with generalized morphoea. *J Am Acad Dermatol* 2002; **46**: 953–6.
9 Sumi K, Yamamoto T, Yokozeki H *et al.* Amyloid deposition associated with generalized morphea-like scleroderma. *Eur J Dermatol* 2003; **13**: 509–11.
10 Morales Callaghan AM, Vila JB, Fraile HA *et al.* Amyloidosis cutis dyschromica in a patient with generalized morphoea. *Br J Dermatol* 2004; **150**: 616–7.
11 Michalowski R. Diffuse morphoea with calcinosis cutis and squamous-cell carcinoma. *Br J Dermatol* 1967; **79**: 453–5.
12 Greco M, Kupfer BL, Delahaye JF *et al.* Multiple cutaneous squamous carcinomas arising in a patient with generalized morphea. *Eur J Dermatol* 2006; **16**: 90–1.
13 Patterson JAR, Ackerman AB. Lichen sclerosus et atrophicus is not related to morphoea: a clinical and histologic study of 24 patients in whom both conditions were reputed to be present simultaneously. *Am J Dermatopathol* 1984; **6**: 323–35.
14 Person JR, Su WPD. Subcutaneous morphoea: a clinical study of 16 cases. *Br J Dermatol* 1979; **100**: 371–80.
15 Nagai Y, Ishikawa O. A case of generalized morphea and polymyositis accompanied by sick sinus syndrome. *J Dermatol* 2001; **28**: 576–7.
16 Morita A, Tsuji T. Necrotizing vasculitis in a patient with generalized morphea. *J Am Acad Dermatol* 2001; **45**: S215–7.
17 Gonzalez-Lopez MA, Drake M, Gonzalez-vela MC *et al.* Generalized morphea and primary biliary cirrhosis coexisting in a male patient. *J Dermatol* 2006; **33**: 709–13.
18 Takamure M, Murata K, Kawahara M *et al.* Fasciitis associated with generalized morphea. *Intern Med* 2005; **44**: 679–81.
19 Kikuchi K, Sato S, Kadono T *et al*. Serum concentration of procollagen type 1 carboxy-terminal propeptide in localized scleroderma. *Arch Dermatol* 1994; **130**: 1269–72.
20 Cheung ST, Khair OA, Maheshwari MB *et al.* Fatal outcome of generalized morphea with bronchiolitis obliterans organizing pneumonia. *Clin Exp Dermatol* 2006; **31**: 722–3.
21 Taveira M, Selores M, Costa V *et al.* Generalized morphea and lichen sclerosus et atrophicus successfully treated with sulphasalazine. *J Eur Acad Dermatol Venereol* 1999; **12**: 283–4.
22 Micalizzi C, Parodi A, Rebora A. Generalized bullous morphoea: efficacy of salazopyrin. *Clin Exp Dermatol* 1996; **21**: 246–7.
23 Molin L. Reduced skin stiffness by grenz ray treatment in generalized morphea. *Adv Exp Med Biol* 1999; **45**: 317–8.
24 Cribier B, Faradji T, Le-Coz C *et al.* Extracorporeal photochemotherapy in systemic sclerosis and severe morphea. *Dermatology* 1995; **191**: 25–31.
25 Stevens HP, Ostlere LS, Black CM *et al*. Generalized morphoea secondary to porphyria cutanea tarda. *Br J Dermatol* 1993; **129**: 455–7.
26 Worle B, Hein R, Krieg T *et al.* Cyclosporin in localized and systemic scleroderma: a clinical study. *Dermatologica* 1990; **181**: 215–20.
27 Rose RF, Goodfield MJD. Combining PUVA therapy with systemic immunosuppression to treat progressive diffuse morphoea. *Clin Exp Dermatol* 2005; **30**: 226–8.
28 Morton SJ, Powell RJ. Cyclosporin and tacrolimus: their use in a routine clinical setting for scleroderma. *Rheumatology* 2000; **39**: 865–9.

29 Clements PJ, Lachenbruch PA, Sterz M *et al.* Cyclosporine in systemic sclerosis: results of a 48 week open safety study in 10 patients. *Arthritis Rheum* 1994; **37**: 301–2.
30 Kawashima H, Watanabe C, Yasuyo K *et al.* Therapy of generalized morphea: case reports and reviews of the Japanese cases. *Pediatr Int* 2006; **48**: 342–5.

Pseudoscleroderma

Sclerosis of the skin may be seen in several conditions other than morphoea or systemic sclerosis [1]. It comprises a major feature of eosinophilic fasciitis and may also be seen in dermatomyositis and SLE, and this is covered elsewhere in this chapter. Pseudoscleroderma-tous changes may also be seen in rheumatoid arthritis [2] and acrodermatitis atrophicans, a disease found in central and eastern Europe which resembles localized morphoea (see Chapter 45). Scleroderma-like changes may also be found in a number of other conditions, and these are set out below using the classification of a review article [1].

References

1 Haustein U. Scleroderma and pseudoscleroderma: uncommon presentations. *Clin Dermatol* 2005; **23**: 480–90.
2 Bergouignan M, Arne L, Guerin A, Texier L. Sclérodermie progressive, dystrophie musculaire, syndrome endocrinien. *Rev Neurol* 1950; **83**: 126–30.

Metabolic disorders

Scleroderma-like changes are sometimes seen in porphyria cutanea tarda [1,2] and in phenylketonuria [3,4], when they usually appear in the first year of life. In the latter condition, irregular indurations appear first in the muscles and subcutis of the thighs and buttocks, and later the changes extend to the trunk and proximal parts of the limbs. Contractures, especially of the legs, are characteristic. Histology shows proliferation of histiocytes and fibroblasts in the connective tissue stroma, atrophy of the skin appendages and an inflammatory infiltrate. Improvement in the skin lesions occurs with exclusion of phenylalanine from the diet. In older children, the lesions and histology resemble morphoea. Two mentally retarded siblings with phenylketonuria had morphoea and atrophoderma of Pasini and Pierini, respectively [5], suggesting that these conditions may be related. Scleroderma-like lesions have been observed in cases of muscle glycogenosis with an undetermined enzyme defect [6], when induration and atrophy occur in the skin and muscles in the first few months of life. The proximal parts of the limbs are involved early and contractures occur, particularly in the legs, giving a characteristic bent-knee gait. Mental retardation may be a feature. Sclerosis of the legs may be found in patients with the carcinoid syndrome [7,8], and sclerosis of the skin occurs in the GEMSS syndrome (*g*laucoma, lens *e*ctopia, *m*icrospherophakia, *s*tiffness of the joints and *s*hortness due to increased production of normal collagen) [9]. The skin may be oedematous and indurated in hypothyroidism, and atrophic changes in the skin in postpartum hypopituitarism may resemble scleroderma. Pseudosclerodermatous changes may also be seen in patients with long-standing diabetes mellitus in which limited joint mobility, termed cheiroarthropathy, is associated with thickening of the skin. The changes are most marked on the hands [10].

A recent report linked the onset of scleroderma-like changes to the diagnosis of cancer, this being postulated to be due to elevated expression of basic fibroblast growth factor [11].

References

1 Stevens HP, Ostlere LS, Black CM *et al.* Generalized morphoea secondary to porphyria cutanea tarda. *Br J Dermatol* 1993; **129**: 455–7.
2 Wilson PR. Porphyria cutanea tarda with cutaneous 'scleroderma' and calcification. *Australas J Dermatol* 1989; **30**: 93–6.
3 Jablonska S, Stachow A. Scleroderma-like lesions in phenylketonuria. In: Jablonska S, ed. *Scleroderma and Pseudoscleroderma*. Warsaw: Polish Medical Publishers, 1975: 489–98.
4 Nova MP, Kaufman M, Halpenin A. Scleroderma-like skin indurations in a child with phenylketonuria: a clinicopathologic correlation and review of the literature. *J Am Acad Dermatol* 1992; **26**: 329–33.
5 Lasser AE, Schultz BC, Beaff D *et al*. Phenylketonuria and scleroderma. *Arch Dermatol* 1978; **114**: 1215–7.
6 Jablonska S, Stachow A. Pseudoscleroderma concomitant with a muscular glycogenosis of unknown enzymatic defect. *Acta Derm Venereol (Stockh)* 1972; **52**: 379–85.
7 Fries JF, Lindgren JA, Bull JM. Scleroderma-like lesions and the carcinoid syndrome. *Arch Intern Med* 1973; **131**: 550–3.
8 Handley J, Walsh M, Armstrong K *et al.* Malignant carcinoid syndrome associated with cutaneous scleroderma. *Br J Dermatol* 1993; **129**: 222–3.
9 Kunz M, Paulins W, Sollberg S *et al.* Sclerosis of the skin in the GEMMS syndrome: an overproduction of normal collagen. *Arch Dermatol* 1995; **131**: 1170–4.
10 Seibold JR. Digital sclerosis in children with insulin-dependent diabetes mellitus. *Arthritis Rheum* 1982; **25**: 1357–61.
11 Kikuchi K, Hoashi T, Yazawa N *et al*. Pseudoscleroderma associated with cancer. *Clin Exp Dermatol* 2005; **31**: 381–3.

Deposition disorders

Scleroedema of Buschke is usually triggered by a febrile illness and comprises non-pitting induration of the face, neck, shoulders, arms and sometimes trunk. Scleromyxoedema also presents with thickening and tethering of the skin and is usually associated with a circulating paraprotein. The scleroderma-like lesions of primary systemic amyloidosis, with or without multiple myeloma, may be difficult to distinguish if not accompanied by nodular and papular lesions, particularly about the shoulders and neck, and by macroglossia. Primary localized cutaneous amyloidosis occurs in systemic sclerosis [1]. Pseudoscleroderma also occurs in multiple myeloma [2] and paraproteinaemia [3].

References

1 Black MM. Primary localized cutaneous amyloidosis in systemic sclerosis. *Trans St John's Hosp Dermatol Soc* 1971; **57**: 177–80.
2 Jablonska S, Stachow A. Scleroderma-like lesions in multiple myeloma. *Dermatologica* 1972; **144**: 257–69.
3 Oikarinen A, Ala-Kokko L, Palatsi R *et al*. Scleroderma and paraproteinemia. *Arch Dermatol* 1987; **123**: 226–9.

Genetic disorders

Atrophy of the acral parts occurs in Werner's syndrome and progeria; acrogeria and poikilodermatous epidermolysis bullosa [1] are other rare conditions in which scleroderma-like lesions occur. Sclerosis of the skin also occurs in the Moore–Federman syndrome (short stature, stiffness of joints, characteristic facies). The 'stiff skin syndrome' describes patients who from childhood develop stone-hard, subcutaneous indurations, which on MRI scan are seen to be derived from the fascia. The lesions are most pronounced on the buttocks, hips and knees, often leading to contractures. The children develop normally and no treatment other than physiotherapy is required [2,3].

References

1 Jablonska S, Blaszczyk M. Poikiloderma with scleroderma-like lesions. In: Jablonska S, ed. *Scleroderma and Pseudoscleroderma*. Warsaw: Polish Medical Publishers, 1975: 421–4.

2 Esterly NB, McKusick VA. Stiff skin syndrome. *Pediatrics* 1971; **47**: 360–9.

3 Jablonska S, Blaszczyk M. Scleroderma-like indurations involving fascias: an abortive form of congenital fascial dystrophy (stiff skin syndrome). *Pediatr Dermatol* 2000; **17**: 105–10.

Occupational causes

A number of chemicals have been reported to cause a scleroderma-like picture.

Vinyl chloride disease [1–4]

One to six per cent of polyvinyl chloride (PVC) workers, particularly reactor cleaners, develop coldness, stiffness, numbness, burning pain and discoloration of the fingers and hands, and to a lesser extent the feet, on exposure to cold. Other symptoms include loss of energy, loss of libido, impotence, dyspnoea and feeling light-headed, with irrational laughter and whistling. The skin of the hands, forearms, face and trunk may be thickened. The hands show mottled pink, purple or white areas. The terminal phalanges are shortened and bulbous, and the nails are curved. Telangiectases occur on the face, resembling those of systemic sclerosis, and there may be difficulty in opening the mouth, although radial furrowing and pigmentation are not features. Usually, it is possible to distinguish between classic systemic sclerosis and vinyl chloride disease [5]. Parotitis [6], hepatomegaly and splenomegaly occur. X-rays show erosion of the tufts of the terminal phalanges and thinning of the other phalanges of the fingers and toes. Erosions also occur in the metatarsals, pelvic bones, clavicles and bones of the arms and legs. Nail fold capillaroscopy shows changes similar to those seen in systemic sclerosis. Narrowing of digital arteries and hypervascularity of the digital tufts are seen on arteriography.

Histologically, there is thickening and separation of collagen fibres and fragmentation of elastic fibres in the dermis. Immunohistology reveals an immune-complex vasculitis with deposits of IgG, complement and fibrin in the media of small- and medium-sized arterioles [7]. Other immunological features include low levels of non-organ-specific autoantibodies, polyclonal hyperglobulinaemia, cryoglobulinaemia, cryofibrinogenaemia, *in vivo* complement activation and conversion, reduced T cells and moderate B-cell proliferation. Anticentromere or anti-Scl-70 antibodies cannot usually be demonstrated [8], although a patient who presented with 'pneumoconiosis' and systemic sclerosis features 10 years after exposure did have a positive ANA and Scl-70 antibodies [9]. Thrombocytopenia, abnormal platelet aggregation, abnormal liver function tests, raised serum creatine phosphokinase indicating muscle involvement, patchy defects of pulmonary ventilation and perfusion, hepatic fibrosis and oesophageal varices also occur.

The prognosis is unknown, and many men have not improved after removal from exposure. There is no effective treatment. Angiosarcoma of the liver is a serious complication. If the level of exposure to vinyl chloride monomer in PVC manufacturing plants is kept below five parts per million, further cases of vinyl chloride disease should not occur. A genetic susceptibility is shown by an increase in HLA-DR5 in all patients and of -B8 and -DR3 in those severely affected [8]. Acro-osteolysis has also been reported in a worker not exposed to vinyl chloride [10].

Scleroderma-like lesions resulting from perchlorethylene, trichlorethylene and organic solvents

A disorder, resembling vinyl chloride disease, has been reported after exposure to perchlorethylene, a solvent used in dry cleaning of clothes [11,12]. Acrocyanosis and acrosclerosis were associated with polymyopathy and hepatic damage. Some of the features, including the presence of speckled antinuclear factor and favourable response to prednisone, were suggestive of 'mixed connective tissue disease'. Exposure to trichlorethylene may be associated with scleroderma [13–16], possibly after even a single prolonged exposure. Of patients with systemic sclerosis in an eastern European series, 28% had suffered significant exposure to organic solvents [17]. Similarly, an Italian study has confirmed an aetiological role of exposure to solvents in scleroderma [18]. A man who used trichlorethylene for cleaning metal also had peripheral neuropathy, Raynaud's phenomenon, impotence, gynaecomastia, hepatomegaly, lymphadenopathy and pigmentation [16]. He was probably a case of Crow–Fukase (POEMS) syndrome. In a Japanese series, generalized morphoeic lesions, similar to those found in occupational scleroderma, were found in nine of 115 patients with systemic sclerosis. Seven had been exposed to organic solvents before the onset of Raynaud's phenomenon. Some had visceral changes of systemic sclerosis [19]. The same authors induced sclerotic skin changes in mice by the intraperitoneal injection of naphtha, *n*-hexane and hexachlorethane. A sclerodermatous syndrome consisting of cold sensitivity, restrictive lung defect, peripheral neuropathy, oesophageal dysfunction, labile hypertension and monoclonal paraproteinaemia has been reported in a man who had worked with many solvents. These included benzene, toluenes, toluidines, xylenes, xylidenes, aniline compounds, and ethanolamine and its derivatives [20]. Solvents recorded in other reports include isopropylalcohol, ethyl acetate, naphthalene, trimethylbenzene and terpene derivatives [21]. Systemic sclerosis occurred in two workers handling *meta*-phenylenediamine [22].

Scleroderma-like lesions resulting from pesticides

Sclerodermatous changes can occur in workers handling pesticides. Substances possibly incriminated include chlordane, heptochlor, malathion, parathion, DDT, sodium dinitro-orthocresolate and 7-chlorocyclohexane [2,23,24]. Raynaud's phenomenon occurs, but there is no evidence of involvement of internal organs. Hyperkeratosis of palms and soles with sclerodactyly of the fingers and toes has been reported in a weed sprayer with chloracne [25].

Scleroderma-like lesions resulting from epoxy resin

Six Japanese men exposed to the vapour of epoxy resins in the production of transformers for television sets developed scleroderma-like skin changes and erythema, with fatigue, loss of weight, myalgia and arthralgia [26]. The histological changes were those of scleroderma, but there was no definite evidence of systemic involvement. A hardener—1,1'-*bis*(3-methyl)-4-amino(cyclohexyl)methane—was thought to be the cause.

Improvement occurred when the men stopped work, and the disorder resolved completely within 5 years without any internal organ involvement developing [27]. One patient developed systemic sclerosis sine scleroderma after exposure to epoxy resin [28].

Silicosis and scleroderma

The association of silicosis and scleroderma has been reported in Italy [18], in South African coal mines [29] and in coal mines in other countries where silica is present [30–33]. Men in other occupations, such as sandblasters and quarrymen, may be affected. Because of the occupational risk, the condition occurs predominantly in men, particularly those suffering from silicosis. In East Germany, 93 of 120 male patients with systemic sclerosis had suffered long-term silica exposure, and 49 had coexisting silicosis [34]. The lung changes frequently precede the scleroderma. Visceral manifestations resembling those of systemic sclerosis occur in approximately half of cases, and antinuclear factor can be demonstrated in one-third. In these cases, the clinical and immunological changes are indistinguishable from those found in systemic sclerosis without any environmental exposure [35]. Systemic sclerosis-like syndromes may follow exposure to urea formaldehyde foam insulation [36].

References

1 Grainger RG, Walker AE, Ward AM. Vinyl chloride monomer-induced disease: clinical, radiological and immunological aspects. In: Preger L, ed. *Induced Disease: Drug, Irradiation, Occupation*. New York: Grune and Stratton, 1979: 191–214.

2 Lange CE, Juhe S, Stein G *et al.* Die sogenannte Vinylchlorid-Krankhe eine berufsbedingte Systemsklerose? *Intern Arch Arbeitsmed* 1974; **32**: 1–32.

3 Markowitz SS, McDonald CJ, Fethiere W *et al*. Occupational acro-osteolysis. *Arch Dermatol* 1972; **106**: 219–23.

4 Walker A. Occupational acro-osteolysis. *Proc R Soc Med* 1975; **68**: 343–4.

5 Ostlere LS, Harris D, Buckley C *et al*. Atypical systemic sclerosis following exposure to vinyl chloride monomer: a case report and review of the cutaneous aspects of vinyl chloride disease. *Clin Exp Dermatol* 1992; **17**: 208–10.

6 Watkinson J. Recurrent parotitis complicating a 'vinyl chloride-like' connective tissue disorder. *BMJ* 1985; **291**: 1094.

7 Ward AM, Udnoon S, Watkins J *et al*. Immunological mechanisms in the pathogenesis of vinyl chloride disease. *BMJ* 1976; **i**: 936–8.

8 Black CM, Welsh KI, Walker AE *et al.* Genetic susceptibility to scleroderma-like syndrome induced by vinyl chloride. *Lancet* 1983; **i**: 53–5.

9 Studnicka MJ, Menzinger G, Drlicek M *et al.* Pneumoconiosis and systemic sclerosis following 10 years of exposure to polyvinyl chloride dust. *Thorax* 1995; **50**: 583–5.

10 Meyerson LB, Meier CC. Cutaneous lesions in acro-osteolysis. *Arch Dermatol* 1972; **106**: 224–7.

11 Sparrow GP. A connective tissue disorder similar to vinyl chloride disease in a patient exposed to perchlorethylene. *Clin Exp Dermatol* 1977; **2**: 17–22.

12 Hinnen U, Schmid-Grendelmeier P, Muller E *et al*. Losungsmittelexposition bei Sklerodermie: disseminierte zirkumskripte Sklerodermie (Morphea) bei einem Perchlorethylen-exponierten Lackierer. *Schweiz Med Wochenschr* 1995; **125**: 2433–7.

13 Flindt-Hansen H, Isager H. Scleroderma after occupational exposure to trichlorethylene and trichlorethane. *Acta Derm Venereol (Stockh)* 1987; **67**: 263–4.

14 Lockey JE, Kelly CR, Cannon GW *et al.* Progressive systemic sclerosis associated with exposure to trichloroethylene. *J Occup Med* 1987; **29**: 493–5.

15 Reinl W. Sklerodermie durch Trichloräthylen-Einwirkung? *Zentralbl Arbeitsmed* 1957; **17**: 58–60.

16 Saihan EM, Burton JL, Heaton KW. A new syndrome with pigmentation, scleroderma, gynaecomastia, Raynaud's phenomenon and peripheral neuropathy. *Br J Dermatol* 1978; **99**: 437–40.

17 Czirjak L, Bokk A, Csontos G *et al*. Clinical findings in 61 patients with progressive systemic sclerosis. *Acta Derm Venereol (Stockh)* 1989; **69**: 533–6.

18 Bovenzi M, Barbone F, Betta A *et al*. Scleroderma and occupational exposure. *Scand J Work Environ Health* 1995; **21**: 289–92.

19 Yamakage A, Ishikawa H. Generalized morphea-like scleroderma occurring in people exposed to organic solvents. *Dermatologica* 1982; **165**: 186–93.

20 Bottomley WW, Sheehan-Dare RA, Hughes P *et al.* A sclerodermatous syndrome with unusual features following prolonged occupational exposure to organic solvents. *Br J Dermatol* 1993; **128**: 203–6.

21 Brasington RD, Thorpe Swenson AJ. Systemic sclerosis associated with cutaneous exposure to solvent: case report and review of the literature. *Arthritis Rheum* 1991; **34**: 631–3.

22 Owens GR, Medsger TA. Systemic sclerosis secondary to occupational exposure. *Am J Med* 1988; **85**: 114–6.

23 Couperus M. Discussion. *Arch Dermatol* 1973; **107**: 768.

24 Jablonska S. Scleroderma-like lesions produced by pesticides. In: Jablonska S, ed. *Scleroderma and Pseudoscleroderma*. Warsaw: Polish Medical Publishers, 1975: 603.

25 Poskitt LB, Duffill MB, Rademaker M. Chloracne, palmoplantar keratoderma and localized scleroderma in a weed sprayer. *Clin Exp Dermatol* 1994; **19**: 264–7.

26 Yamakage A, Ishikawa H, Saito Y *et al*. Occupational scleroderma-like disorder occurring in men engaged in the polymerization of epoxy resins. *Dermatologica* 1980; **161**: 33–44.

27 Ishikawa O, Warita S, Tamura A *et al*. Occupational scleroderma: a 17-year follow-up study. *Br J Dermatol* 1995; **133**: 786–9.

28 Inachi S, Mizutani H, Ando Y *et al*. Progressive systemic sclerosis sine scleroderma which developed after exposure to epoxy resin polymerization. *J Dermatol* 1996; **23**: 344–6.

29 Erasmus LD. Scleroderma in gold miners in the Witwatersrand, with particular reference to pulmonary manifestations. *S Afr J Lab Clin Med* 1957; **3**: 209–31.

30 Jablonska S. Scleroderma-like lesions of occupational origin. In: Jablonska S, ed. *Scleroderma and Pseudoscleroderma*. Warsaw: Polish Medical Publishers, 1975: 601–5.

31 Rodnan GP. A review of recent observations and current theories on the aetiology and pathogenesis of progressive systemic sclerosis (diffuse scleroderma). *J Chron Dis* 1963; **16**: 929–49.

32 Ebihara I, Kawami M. Mineral dust exposure and systemic diseases. *J Environ Pathol Toxicol Oncol* 2000; **19**: 109–27.

33 Ziegler V, Pampel W, Zschunke E *et al.* Kristalliner Quarz- (eine) Ursache der progressiven Sklerodermie? *Dermatol Monatsschr* 1982; **168**: 398–401.

34 Haustein U-F, Ziegler V, Herrman K *et al*. Silica-induced scleroderma. *J Am Acad Dermatol* 1990; **22**: 444–8.

35 Rustin MHA, Bull HA, Ziegler V *et al.* Silica-associated systemic sclerosis is clinically, serologically and immunologically indistinguishable from idiopathic systemic sclerosis. *Br J Dermatol* 1990; **123**: 725–34.

36 Rush PJ, Chaiton A. Scleroderma, renal failure and death associated with exposure to urea formaldehyde foam insulation. *J Rheumatol* 1986; **13**: 475–6.

Exogenous/iatrogenic scleroderma

Scleroderma-like changes resulting from bleomycin [1,2]

Cutaneous fibrosis with acrocyanosis, acrosclerosis, pigmentation, hair loss, flexion contractures and ulceration occurs in patients treated with the antitumour agent bleomycin. Pulmonary fibrosis is a prominent feature. Remission occurs some months after withdrawal of the drug. Cisplatin can cause similar changes.

Scleroderma resulting from other drugs

Carbidopa [3], pentazocine [4], cocaine [5] and appetite suppressants [6] have all been implicated in the development of sclerodermatous disease.

Scleroderma induced by silicone or paraffin implants (human adjuvant disease) [7]

Skin sclerosis, sometimes resembling morphoea, occurs at the site of injection of silicone for cosmetic breast surgery. It may act by the release of silica. Sometimes, more widespread connective tissue disease resembling systemic sclerosis [8], mixed connective tissue disease, SLE, rheumatoid arthritis, primary biliary cirrhosis, Sjögren's syndrome [9] or eosinophilic fasciitis [10] occurs. Paraffin injections may be a more important factor than silica in causing systemic sclerosis-like disease [11]. A causal link between silicone breast implants and autoimmune diseases seems to have been discounted [12].

References

1 Cohen IS, Mosher MB, O'Keefe EJ *et al*. Cutaneous toxicity of bleomycin therapy. *Arch Dermatol* 1973; **107**: 553–5.
2 Finch WR, Rodnan GP, Buckingham RB, Prince RK, Winkerstein A. Bleomycin-induced scleroderma. *J Rheumatol* 1980; **7**: 651–9.
3 Sternberg EM, Van Woert MH, Young SN *et al*. Development of scleroderma-like illness during therapy with L-5-hydroxytryptophan and carbidopa. *N Engl J Med* 1980; **303**: 782–7.
4 Palestine RF, Millns JL, Spigel GT *et al*. Skin manifestations of pentazocine abuse. *J Am Acad Dermatol* 1980; **2**: 47–55.
5 Trozac DJ, Gould WM. Cocaine abuse and connective tissue disease. *J Am Acad Dermatol* 1984; **10**: 525.
6 Tomlinson IM, Jayson MI. Systemic sclerosis after therapy with appetite suppressants. *J Rheumatol* 1984; **11**: 254–5.
7 Varga J, Jimenez SA. Augmentation mammoplasty and scleroderma: is there an association? *Arch Dermatol* 1990; **126**: 1220–1.
8 Varga J, Schumacher HR, Jimenez SA. Systemic sclerosis after augmentation mammoplasty with silicone implants. *Ann Intern Med* 1989; **111**: 377–83.
9 Okano Y, Nishikai M, Sato A. Scleroderma, primary biliary cirrhosis and Sjögren's syndrome after cosmetic breast augmentation with silicone injection. *Ann Rheum Dis* 1984; **43**: 520–2.
10 Spiera H. Scleroderma after silicone augmentation mammoplasty. *JAMA* 1988; **260**: 236–8.
11 Kumagai Y, Shiokawa Y, Medsger TA *et al*. Clinical spectrum of connective tissue disease after cosmetic surgery. *Arthritis Rheum* 1984; **27**: 1–12.
12 Cooper C, Dennison E. Do silicone breast implants cause connective tissue disease? *BMJ* 1998; **316**: 403–4.

'Toxic oil' epidemic syndrome [1,2]

In 1981, in certain areas of Spain, the ingestion of rapeseed oil denatured with aniline caused a multisystem disease affecting 18000 people. The most prominent pathological feature was a widespread non-necrotizing intimal vasculitis in practically every organ [3]. The early phase, lasting 2–3 months, consisted of atypical pneumonia, gastrointestinal and neurological symptoms and a pruritic rash. The rash involved the limbs, abdomen and trunk, and resembled a viral exanthem lasting approximately 5–20 days. Occasionally, palpable purpura or erythema multiforme occurred. Eosinophilia was always present, antinuclear antibodies were frequently found, and elevation of IgE and abnormal liver function tests could be demonstrated in one-third of cases. Histology showed dilatation of blood vessels, and an inflammatory exudate including eosinophils in the dermis. Three to four months after the onset, 10% of patients developed a transitory eruption consisting of multiple yellowish or brownish papules of all areas except palms and soles. Five to six months after the onset, patients, mainly women, developed a neuromyopathy, and either localized or generalized morphoea or a disorder resembling systemic sclerosis, with dysphagia, oesophageal changes and occasionally renal involvement. Sicca syndrome and pulmonary hypertension were prominent features in some cases. Histology of the skin showed dermal infiltration and sclerosis with interfibrillar mucin deposits, but immunology was negative.

Most patients recovered to some extent, although 50% had persistent symptoms when reviewed in 1984 [4]. The cause is unknown. An immune reaction to an unknown antigen seems likely. HLA typing showed an increased incidence of HLA-DR3 and -DR4 in females with chronic disease [5].

References

1 Iglesias JL, De Moragas JM. The cutaneous lesions of the Spanish toxic oil syndrome. *J Am Acad Dermatol* 1983; **9**: 159–60.
2 Toxic Epidemic Syndrome Study Group. Toxicepidermic syndrome, Spain, 1981; *Lancet* 1982; **ii**: 697–702.
3 Martinez-Tello FJ, Navas-Palacios JJ, Ricoy JR *et al*. Pathology of a new toxic syndrome caused by ingestion of adulterated oil in Spain. *Virchows Arch (Pathol Anat)* 1982; **397**: 261–85.
4 Gilsanz V, Alvarez JL, Serrano S *et al*. Evolution of the alimentary toxic oil syndrome due to ingestion of denatured rapeseed oil. *Arch Intern Med* 1984; **44**: 254–6.
5 Vicario JL, Serrano-Rios M, Son Andres F *et al*. HLA-DR3, DR4 increase in chronic stage of Spanish oil disease. *Lancet* 1982; **i**: 276.

Nephrogenic systemic fibrosis (NSF)

Synonym
- Nephrogenic fibrosing dermopathy (NFD)

Nephrogenic systemic fibrosis is a relatively recently described scleroderma-like fibrosing disorder first reported in 2000 [1]. By 2003, over 100 US cases had been reported to the NFD registry established at Yale University. The lesions of NFD are skin coloured to erythematous papules that coalesce into erythematous/brawny plaques with a peau d'orange appearance. Nodules have been described. The involved skin becomes thickened and 'woody', resembling the skin lesions seen in eosinophilic fasciitis. Joint contractures may develop rapidly, with patients becoming wheelchair-bound within days to weeks. The lesions are typically symmetrical and develop on the limbs (often between the ankles and mid-thighs and between the wrists and mid-upper arms) and trunk. Plantar flexion of the feet may make walking impossible. Patients often experience pain and pruritis, but arthritis, fever and myalgia are uncommon [2]. Some patients, however, exhibit systemic features, with involvement of the striated muscles, pleura, pericardium and myocardium. The disease has been reported in both adults and children [3].

No single test is pathognomonic but a deep skin biopsy of involved skin will show fibrosis extending into the subcutaneous fat and sometimes fascia.

All reported patients have had renal disease and initially it was thought that the condition might be triggered by surgery, coexistent hepatic or pulmonary disease, a coexistent hypercoagulable state or following erythropoietin therapy in these patients.

Recently, however, it has become clear that the triggering factor is the use of gadolinium-based contrast agents in patients with renal disease, transmetallation of gadolinium chelates possibly leading to the precipitation of free gadolinium in the dermis or other organs [4]. Surgery and erythropoietin may be also be con-

tributory factors [5]. Alternative imaging should be considered in these patients.

Treatment is unsatisfactory, although some success has been reported with intravenous immunoglobulin, topical and systemic steroids, calcipotriol ointment, d-penicillamine, ciclosporin, cyclophosphamide, thalidomide, interferon-α, UVA-1, extracorporeal photophoresis and photodynamic therapy [3].

References

1 Cowper SE, Robin HS, Steinberg SM *et al*. Scleromyxoedema-like cutaneous diseases in renal dialysis patients. *Lancet* 2000; **356**: 1000–1.

2 Cowper SE. Nephrogenic fibrosing dermopathy: the first 6 years. *Curr Opin Rheum* 2003; **15**: 785–90.

3 Lim YL, Lee HY, Low SCS *et al*. Possible role of gadolinium in nephrogenic systemic fibrosis: report of two cases and review of the literature. *Clin Exp Dermatol* 2007; **32**: 353–8.

4 Grobner T. Gadolinium—a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? *Nephrol Dial Transplant* 2006; **21**: 1104–8.

5 Pryor JG, Poggioli G, Galaria N *et al*. Nephrogenic systemic fibrosis: a clinicopathologic study of six cases. *J Am Acad Dermatol* 2007; **57**: 105–11.

Graft-versus-host disease [1–3]

Definition. Graft-versus-host disease (GVHD) occurs when immunocompetent T cells from a donor recognize and react against 'foreign' tissue antigens in an immunocompromised host. Originally reported following bone marrow transplantation (regularly used in the management of leukaemias, lymphoma, immunodeficiency and inborn errors of metabolism), GVHD is now recognized to occur following transfusion of non-irradiated blood, after maternofetal transfer of lymphoid cells, and following peripheral blood stem cell transfer [4]. Post-transfusion-related GVHD is an uncommon but potentially fatal complication of transfusing blood between immunologically related individuals. It appears that transfused white blood cells are not recognized as foreign, and react against host tissue. The reaction seems to depend on heterozygosity of class I antigens. The two recognized forms of the disease are acute and chronic.

Incidence. Even using prophylactic therapy to prevent its occurrence, GVHD occurs in approximately 50% of patients receiving successful marrow allografts for various disorders, including immunodeficiency diseases, aplastic anaemia, acute leukaemia and radiation exposure, despite careful histocompatibility matching [3]. The frequency is the same in those receiving peripheral blood stem cell grafts [5]. It is clear that the typical acute form of the syndrome can also occur after syngeneic (identical twin) or autologous bone marrow grafting, in which genetically identical material is transplanted, and may occur in approximately 10% of such cases [7].

Aetiology [3]. Billingham described the original criteria for the development of a graft-versus-host reaction in 1966:

1 Genetically determined histocompatibility differences between donor and recipient

2 Immunocompetent cells in the grafted tissue able to recognize foreign histocompatibility antigens in the host and to react against them

3 Inability of the host to recognize and react against the grafted tissue.

It is clear from animal experiments [7], as well as the occurrence of typical GVHD in human syngeneic transplants, that criterion **1** is no longer an essential prerequisite for the development of the acute form of the syndrome. GVHD in this situation occurs because of MHC class II differences. It usually only occurs after the withdrawal of immunosuppression [8].

A similar syndrome occurs in recipients of IL-2 treatment and lymphocytes activated by this stimulating lymphokine given as treatment for widespread malignancy. Cells activated by this technique are non-specifically cytotoxic, capable of self-reactivity and may have the features of NK cells. In animal models, and in humans, HLA-DR-bearing Langerhans' cells are reduced in the acute form of the disease, and T cells directed against these cells are found. In addition, IFN production by activated T cells induces HLA-DR expression on keratinocytes, making them targets for a similar reaction [9,10]. The risk of developing GVHD may be related to cytokine gene polymorphisms [11]. T-cell depletion reduces GVHD in mouse models [12] but the effect on human GVHD is no different from conventional prophylactic regimens [13].

A possible hypothesis is suggested by Ferrara [14]; immunologically competent donor T lymphocytes are not destroyed in the host because they are not recognized as foreign. Activated T cells release IL-2, IFN and probably other lymphokines. IL-2 activates cytotoxic cells (probably NK cells), and HLA-DR-bearing epidermal cells and Langerhans' cells may be specifically attacked, giving rise to acute GVHD. The same, or similar, cells recognize any persisting malignant cells in the host, and it is suggested that graft-versus-leukaemia reactions explain the lowered incidence of recurrence of the original malignancy in patients with GVHD. However, there are some criticisms of the theory of T-cell-mediated cutaneous pathogenesis, mainly that early graft-versus-host reactions do not show T-cell infiltration of the skin [15]. There are also stimulatory antibodies to PDGF and its receptor [16], as well as high levels of B cell activating factors [12], suggesting a role for B cells in the pathogenesis. In addition, successful treatment of GVHD is accompanied by the induction of apoptosis in T cells and some epidermal cells. This suggests that a failure of programmed cell death may be a feature of pathogenesis [17]. Nevertheless, the use of T-cell-depleted marrow for grafting reduces the incidence of GVHD and prevents HLA-DR expression on keratinocytes, but unfortunately the failure rate of the transplant is markedly increased.

Pathology [18]. For acute GVHD, the cutaneous histological changes have been graded for severity.

Grade I Basal cell vacuolation with or without mononuclear cell infiltration

Grade II Solitary epidermal cell necrosis, surrounded by mononuclear cells

Grade III Regional epidermal cell necrosis with bullae

Grade IV Toxic epidermal necrolysis.

Less severe histological grades may be impossible to differentiate from drug-induced reactions. At an immunocytochemical level, the earliest (preclinical) changes are an increase in dermal

macrophages expressing α_1-antichymotrypsin. In grade I disease, there is keratinocyte HLA-DR and ICAM-1 expression, and in the later stages, CD25 T cells, L1 antigen-positive keratinocytes, and VCAM-1 macrophages are increased [19].

In chronic GVHD, histological changes are lichenoid, or resemble scleroderma. IgM may occur at the dermal–epidermal junction, with granular deposits of IgM, IgA and C3 in the walls of dermal vessels. There is associated microvascular disease mediated by cytotoxic T cells [20].



Fig. 51.58 Localized eroded sclerotic graft-versus-host disease.

Clinical features [1,2]. Acute GVHD usually occurs within 60 days of a bone marrow transplant, and most often after 7–12 days, when it is termed hyperacute. Mild fever is followed by a faint red maculopapular rash on the hands, feet, face and forehead. This spreads to the trunk and limbs, becoming deeper in colour. Desquamation or even toxic epidermal necrolysis follows. Bullous and ulcerated forms are described, and a follicular pattern may indicate more severe disease [3]. Hepatitis (indicated by raised bilirubin and alkaline phosphatase) and bloody diarrhoea resulting from enteritis are other features and, in severe cases, death occurs by the 21st day. In the original cases, it was rare to have liver and gut involvement without cutaneous pathology, and skin biopsy was the simplest reliable test for diagnosis. However, the introduction of T-cell depletion as a prophylactic measure has changed the pattern of disease so that skin disease may be mild, while liver and bowel disease may be severe. Clinical stagings for each organ system, and grading for the overall clinical picture, have been proposed [2].

Chronic GVHD may be localized (Fig. 51.58) or generalized, and principally involves the skin and the liver. The former occurs in 10% of patients as hyperpigmented nodular areas, which may be guttate, and eventually soften and atrophy. The early phase of generalized GVHD generally appears up to the 100th post-transplant day and usually, but not always, follows acute GVHD. Initially, a slowly progressive erythematous rash on the face, palms and soles becomes lichenoid, with changes resembling lichen planus in many sites. Lichenoid changes may be limited to the nails [4]. Later, scleroderma-like changes occur, which are sometimes widespread and disabling. The condition resembles systemic sclerosis, with tightening of the skin of the face, hands and

References

1 Harper JI. Graft-versus-host reaction: aetiological and clinical aspects in connective tissue diseases. *Semin Dermatol* 1985; **4**: 144–51.
2 Parkman R. Graft-versus-host disease. *Ann Rev Med* 1991; **42**: 189–97.
3 Perez-Simon JA, Sanchez-Abarca I, Diez-Campelo M *et al*. Chronic graft-versus-host disease: pathogenesis and clinical management. *Drugs* 2006; **66**: 1041–57.
4 Schaffer JV. The changing face of graft-versus-host disease. *Semin Cutan Med Surg* 2006; **25**: 190–200.
5 Flowers ME, Parker PM, Johnston LJ *et al*. Comparison of chronic graft versus host disease after transplantation of peripheral blood stem cells versus bone marrow in allogeneic recipients: long-term follow-up of a randomized trial. *Blood* 2000; **15**: 415–9.
6 Hood AF, Vogelsang CB, Black LP *et al*. Acute graft-versus-host disease. *Arch Dermatol* 1987; **123**: 745–50.
7 Clazier A, Tutschka PI, Farmer ER. Graft-versus-host disease in cyclosporine A-treated rats after syngeneic and autologous bone marrow reconstitution. *J Exp Med* 1983; **158**: 1–8.
8 Hess AD, Horwitz L, Beschorner WE, Santos GW. Development of graft vs host disease-like syndrome in cyclosporine treated rats after syngeneic bone marrow transplantation. I. Development of cytotoxic T lymphocytes with apparent polyclonal anti-Ia specificity, including autoreactivity. *J Exp Med* 1985; **161**: 718–30.
9 Ferrara J, Guillen FJ, Sleckman B *et al*. Cutaneous acute graft-versus-host disease to minor histocompatibility antigens in a murine model: histologic analysis and correlation to clinical disease. *J Invest Dermatol* 1986; **86**: 371–5.
10 Paller AS, Nelson A, Steffen L *et al*. T-lymphocyte subsets in the lesional skin of allogeneic and autologous bone marrow transplant patients. *Arch Dermatol* 1988; **124**: 1795–801.
11 Dickinson AM, Cavet J, Cullup H *et al*. GvHD risk assessment in haemopoietic stem cell transplantation: role of cytokine gene polymorphisms and an *in vitro* human skin explant model. *Hum Immunol* 2001; **62**: 1266–76.
12 Chao NJ. Are there effective new strategies for the treatment of acute and chronic GvHD? *Best Pract Res Clin Haematol* 2008; **21**: 93–8.
13 Wagner JE, Thompson JS, Carter SL, Kernan NA. Effect of graft-versus-host disease prophylaxis on 3-year disease-free survival in recipients of unrelated donor bone marrow (T-cell depletion trial): a multi-centre, randomised phase II-III trial. *Lancet* 2005; **366**: 733–41.
14 Ferrara JLM. Syngeneic graft-vs-host disease. *Arch Dermatol* 1987; **123**: 741–2.
15 Sloane JP, Dilley SA. Pathogenesis of graft-versus-host disease. *Histopathology* 1988; **12**: 105–10.
16 Svegliati S, Olivieri A, Campelli N *et al*. Stimulatory autoantibodies to PDGF in patients with extensive chronic graft-versus-host disease. *Blood* 2007; **110**: 237–41.
17 Bladon J, Taylor PC. Extracorporeal photophoresis in cutaneous T cell lymphoma and graft versus host disease induces both immediate and progressive apoptotic processes. *Br J Dermatol* 2002; **146**: 59–68.
18 Pintar T, Zorc-Pleskovic R, Alessiani M *et al*. Prognostic value of skin histology in GVHD after intestinal transplantation. *Eur J Pediatr Surg* 2007; **17**: 412–5.
19 Norton J, Sloane JP. A prospective study of cellular and immunological changes in skin of allogeneic bone marrow recipients: relationship to clinical and histological features of acute graft versus host disease. *Am J Clin Pathol* 1994; **101**: 597–602.
20 Biedermann BC, Sahner S, Gregor M *et al*. Endothelial injury mediated by cytotoxic T lymphocytes and loss of microvessels in chronic graft versus host disease. *Lancet* 2002; **359**: 2078–83.

feet. Autoantibody changes similar to those found in systemic sclerosis may occur [5]. Disease may be localized to the extremities and associated with a polyneuropathy [6]. There may also be eczematoid changes [7].

Oesophageal changes and subcutaneous calcification may occur. Morphoea-like changes have been reported [8]. Eruptive violaceous vascular tumours on the legs may occur [9]. Reticulate patchy hyperpigmentation and, less commonly, hypopigmentation, poikiloderma, vitiligo (which may be total [10]), erythema, atrophy, alopecia, multiple follicular papules, deep ulcerations of the buttocks and legs, and dystrophic nail changes are other features [11]. Panniculitis may occur [12]. Gastrointestinal symptoms, a Sjögren-like syndrome [13], polymyositis [14], abnormal liver function tests, primary biliary cirrhosis [15] and other organ changes occur [14].

That there may be some interaction between viral infections and minor histocompatibility differences in the pathogenesis of chronic GVHD is suggested by the development of scleroderma-like skin changes in areas affected by measles in a patient 8 months after bone marrow transplantation [16]. Similarly, pathogen-free transplanted animals do not develop GVHD until given bacteria or endotoxin, and patients nursed in laminar flow isolation remain disease-free until they are removed from this environment [17].

References

1 Goltz RW. The graft-vs-host reaction. *Arch Dermatol* 1988; **124**: 1849–50.
2 Perez-Simon JA, Sanchez-Abarca I, Diez-Campelo M *et al*. Chronic graft-versus-host disease: pathogenesis and clinical management. *Drugs* 2006; **66**: 1041–57.
3 Lycka BAS, Kaye VN. Acute follicular graft-vs-host disease. *Arch Dermatol* 1988; **124**: 1442–4.
4 Palencia SI, Rodriguez-Peralto JL, Castano E *et al*. Lichenoid nail changes as sole external manifestation of graft vs. host disease. *Int J Dermatol* 2002; **41**: 44–5.
5 Bell SA, Faust H, Mittermuller J *et al.* Specificity of antinuclear antibodies in scleroderma-like chronic graft versus host disease: clinical correlation and histocompatibility locus antigen association. *Br J Dermatol* 1996; **134**: 848–54.
6 Aractingi S, Socie G, Devergie A *et al*. Localized scleroderma-like lesions on the legs in bone marrow transplant recipients: association with polyneuropathy in the same distribution. *Br J Dermatol* 1993; **129**: 201–3.
7 Creamer D, Martyn-Simmons CL, Osborne G *et al*. Eczematoid graft-vs-host disease: a novel form of chronic cutaneous graft-vs-host disease and its response to psoralen UV-A therapy. *Arch Dermatol* 2007; **143**: 1157–62.
8 Graham-Brown RAC, Sarkany I. Scleroderma-like changes due to chronic graft-versus-host disease. *Clin Exp Dermatol* 1983; **8**: 531–8.
9 Gamis S, Billick RC, Strolovitz H. Eruptive vascular tumours associated with chronic graft-versus-host disease. *J Am Acad Dermatol* 1984; **10**: 918–21.
10 Nagler A, Goldenhersh MA, Levi-Schaffo F, Bystryn JC. Total leukoderma: a rare manifestation of chronic graft versus host disease. *Br J Dermatol* 1996; **134**: 780–3.
11 Esterly NB. Nail dystrophy in dyskeratosis congenita and chronic graft-vs-host disease. *Arch Dermatol* 1986; **122**: 506–7.
12 Naschitz JE, Boss JH. Fasciitis and fasciitis-panniculitis in chronic graft-versus-host disease. *Ann Intern Med* 1995; **122**: 155–6.
13 Gratwhol AA, Moutsopoulos HM, Chused TM *et al.* Sjögren-type syndrome after allogeneic bone-marrow transplantation. *Ann Intern Med* 1977; **87**: 703–6.
14 Anderson BA, Young PV, Kean WF *et al.* Polymyositis in chronic graft vs host disease. *Arch Neurol* 1982; **39**: 188–90.
15 Epstein O, Thomas HC, Sherlock S. Primary biliary cirrhosis is a dry gland syndrome with features of chronic graft-versus-host disease. *Lancet* 1980; **i**: 1166–8.
16 Fenvk JR Jr, Warkentin PI, Coltz RW *et al.* Sclerodermatous graft-versus-host disease limited to an area of measles exanthem. *Lancet* 1978; **i**: 472–3.
17 Parkman R. Clonal analysis of murine graft-versus-host disease. I. Phenotypic and functional analysis of T lymphocyte clones. *J Immunol* 1986; **136**: 3543–8.

Treatment [1]. Prophylactic use of ciclosporin, methotrexate and prednisolone and, in particular, combinations of these agents, has reduced the incidence of acute GVHD. None of these regimens has produced a definite reduction in the incidence of chronic GVHD, and recent studies indicate no benefit in 24-month rather than 6-month ciclosporin therapy in this situation [2]. T-cell depletion by using anti-T-cell receptor antibodies is successful in reducing the frequency of acute GVHD when used with post-transplant ciclosporin [3]. Combination therapy appears to be better at preventing GVHD than monotherapy, but overall survival is unchanged in younger patients because of higher leukaemic relapse. Older patients survive longer on combination therapy (methotrexate with ciclosporin or T-cell depletion) [4]. Granulocyte colony-stimulating factor, used to enhance engraftment, may reduce the incidence of GVHD [5].

Once the disease is established, treatment with high-dose corticosteroids or ciclosporin is of value symptomatically, and antilymphocyte globulin may be of additional benefit [6], particularly if combined with tacrolimus [7]. Treatment with prednisone and azathioprine for at least 9–12 months helps generalized chronic GVHD in one-third of patients [8], but complications are common, and survival may be reduced by the addition of azathioprine. Thalidomide, used in both low dosage (100 mg/day) and high dosage (400 mg/day), has been of value, but may result in severe cutaneous ulceration [9,10]. PUVA therapy [11], UVB [12], UVA-1 [13] and extracorporeal photophoresis may be of benefit, even in severe disease [14]. Biological therapies [15], including etanercept [16] and particularly rituximab [17], may be helpful for steroid-resistant disease.

Prognosis. Forty to fifty per cent of patients with chronic GVHD are dead within 10 years of developing the disease. Mortality is caused both by the disease itself, and by severe superinfection, related, at least in part, to the immunosuppressive effects of treatment. Recurrence of the original disease is also a problem. Patients who develop chronic GVHD after the acute form, those with the lichenoid type of eruption, and those with significant liver disease have a worse prognosis, with 80% mortality at 10 years [18].

References

1 Bacigalupo A. Management of acute graft-versus-host disease. *Brit J Haematol* 2007; **137**: 87–98.
2 Kansu E, Gooley T, Flowers ME *et al.* Administration of cyclosporine for 24 months compared with 6 months for prevention of graft versus host disease: a prospective randomized clinical trial. *Blood* 2001; **98**: 3868–70.
3 Drobyski WR, Ash RC, Casper JT *et al.* Effect of T cell depletion as graft versus host disease prophylaxis on engraftment, relapse and disease free survival in unrelated marrow transplantation for chronic myelogenous leukaemia. *Blood* 1994; **83**: 1980–7.
4 Aschan J, Ringden O. Prognostic factors for long-term survival in leukaemic marrow recipients with special emphasis on age and prophylaxis for graft versus host disease. *Clin Transplant* 1994; **8**: 258–70.
5 Dey BR, Shaffer J, Yee AJ *et al*. Comparison of outcomes after transplantation of peripheral blood stem cells versus bone marrow following an identical nonmyeloablative conditioning regimen. *Bone Marrow Transplant* 2007; **40**: 19–27.
6 Sullivan KM, Witherspoon RP, Storb R *et al.* Prednisolone and antilymphocyte globulin versus prednisolone and placebo for treatment of chronic graft-versus-host disease: prognostic influence of prolonged thrombocytopaenia after allograft marrow transplantation. *Blood* 1988; **72**: 546–54.

7 Mollee P, Morton AJ, Irving I, Durrant S. Combination therapy with tacrolimus and anti-thymocyte globulin for the treatment of steroid-resistant acute graft versus host disease developing during cyclosporine prophylaxis. *Br J Haematol* 2001; **113**: 217–23.
8 Deeg HJ, Storb R, Thomas FD. Bone marrow transplantations: a review of delayed complications. *Br J Haematol* 1984; **57**: 185–208.
9 Koe S, Leisenring W, Flowers ME *et al.* Thalidomide for treatment of patients with chronic graft versus host disease. *Blood* 2000; **96**: 3995–6.
10 Schlossberg H, Klumpp T, Sabol P *et al.* Severe cutaneous ulceration following treatment with thalidomide for GVHD. *Bone Marrow Transplant* 2001; **27**: 229–30.
11 Hymes SR, Morison WL, Farmer ER *et al.* Methoxsalen and ultraviolet A radiation in treatment of chronic cutaneous graft-versus-host reaction. *J Am Acad Dermatol* 1985; **12**: 30–7.
12 Dooren-Greebe RJ, Schattenberg A, Koopman RJ. Chronic cutaneous graft versus host disease: successful treatment with UVB. *Br J Dermatol* 1991; **125**: 498–9.
13 Stander H, Schiller M, Schwarz T. UVA-1 therapy for sclerodermic graft-versus-host disease of the skin. *J Am Acad Dermatol* 2002; **46**: 799–800.
14 Setterblad N, Garban F, Weigl R *et al.* Extracorporeal photophoresis increases sensitivity of monocytes from patients with graft-versus-host disease to HLA-DR-mediated cell death. *Transfusion* 2008; **48**: 169–77.
15 Rivkina AM, Stump LS. Infliximab in graft versus host disease. *Am J Health Syst Pharm* 2002; **59**: 1271–5.
16 Perez-Simon JA, Sanchez-Abarca I, Diez-Campelo M *et al.* Chronic graft-versus-host disease: pathogenesis and clinical management. *Drugs* 2006; **66**: 1041–57.
17 Cutler C, Miklos D, Kim HT *et al.* Rituximab for steroid-refractory chronic graft-versus-host disease. *Blood* 2006; **108**: 756–62.
18 Wingard JR, Iantadosi S, Vogelsang CB *et al.* Predictors of death from chronic graft-versus-host disease after bone marrow transplantation. *Blood* 1989; **74**: 1428–35.

Eosinophilic fasciitis [1,2]

Synonym
- Shulman's syndrome

This scleroderma-like syndrome appears to be a distinct entity, although some have suggested that it is an early variant of systemic sclerosis [3] or linear scleroderma [4], or that it may occur in conjunction with other connective tissue disease [5]. It occurs in children and adults, more commonly in males than females. In children, persistent sclerosis may occur [6]. The clinical features are the acute onset of pain, swelling and tenderness of the distal part of the limbs, which become indurated. There is limitation of movement of the feet and hands. Occasionally, the face or abdomen can be affected, and there may be superficial blistering and haemorrhage. A relationship to strenuous exertion or trauma has been suggested. Twenty-nine per cent of 52 patients showed lesions of localized morphoea at some stage [7]. Raynaud's phenomenon is rare, there is limited evidence of involvement of internal organs such as occurs in systemic sclerosis, and no history of a previous infection to suggest scleroedema. Blood eosinophilia up to 30% is a striking feature, occurring in approximately 70% of cases [7]; it is associated with elevation of the ESR and hyperglobulinaemia, but these are not present in all cases. Rarely, aplastic anaemia and thrombocytopenia occur [8].

Histologically, there is dermal sclerosis, with inflammation and fibrosis of the fat and deep fascia. The fascia is thickened and infiltrated with lymphocytes, plasma cells, histiocytes and eosinophils. IgG and C3 deposits can be demonstrated in the deep fascia. The inflammatory infiltrate consists of macrophages and predominantly $CD8^+$ T cells with eosinophils [9]. MHC class 1 antigens are over expressed [8]. Cytokine production is enhanced with a mixed Th1/Th2 profile [10]. Antinuclear antibodies cannot be demonstrated and serum complement levels are normal.

Table 51.16 Factors associated with onset of eosinophilic fasciiis.

Neoplasia [18]
Atorvastatin [19]
Autoimmune thyroiditis [20]
Eosinophilic colitis [21]
Hypercalcaemia [22]
Amegakaryocytic thrombocytopenic purpura [23]

An eosinophilic fasciitis-like syndrome occurs after recent ingestion of L-tryptophan [11]. In addition to the usual features of fasciitis, there is muscle weakness and elevated muscle enzyme levels. This may be demonstrated by nuclear magnetic resonance imaging [12]. Enhanced type I procollagen gene expression in the skin has been demonstrated [13]. Myalgia, eosinophilia, dyspnoea, oedema, arthralgia, neuropathy and rashes occur in the eosinophilia–myalgia syndrome [14] which can also be precipitated by tryptophan. Cutaneous manifestations include localized and generalized morphoeic lesions and urticarial and papular lesions [14].

Clinical improvement and disappearance of eosinophilia follow corticosteroid therapy, but spontaneous remission has been reported. Methotrexate may be useful [15]. Phototherapy [16], ciclosporin [17] and other cytotoxic agents may rarely be necessary.

Other factors associated with disease onset are shown in Table 51.16.

References

1 Shulman LE. Diffuse fasciitis with hypergammaglobulinemia and eosinophilia. *J Rheumatol* 1974; **1** (Suppl. 1): 46.
2 Antic M, Lautenschlager S, Itin PH. Eosinophilic fasciitis 30 years after—what do we really know? Report of 11 patients and review of the literature. *Dermatology* 2006; **213**: 93–101.
3 Britt WJ, Duray PH, Dahl MN *et al.* Diffuse fasciitis with eosinophilia: a steroid responsive variant of scleroderma. *J Pediatr* 1980; **97**: 432–4.
4 Williams HJ, Zifer FA, Banta CA. Childhood eosinophilic fasciitis: progression to linear scleroderma. *J Rheumatol* 1986; **13**: 961–2.
5 Mensing H, Schmidt K-U. Diffuse fasciitis with eosinophilia associated with morphoea and lichen sclerosus et atrophicus. *Acta Derm Venereol (Stockh)* 1985; **65**: 80–3.
6 Farrington ML, Haas JE, Nazar-Stewart V, Mellins ED. Eosinophilic fasciitis in children frequently progresses to scleroderma-like cutaneous fibrosis. *J Rheumatol* 1993; **20**: 128–32.
7 Lakhampal S, Ginsberg WW, Michet CJ *et al.* Eosinophilic fasciitis: clinical spectrum and therapeutic response in 52 cases. *Semin Arthritis Rheum* 1988; **17**: 221–31.
8 Shulman LE, Hoffman R, Dainiak N *et al.* Antibody-mediated aplastic anaemia and thrombocytopenic purpura in diffuse eosinophilic fasciitis. *Clin Res* 1979; **27**: 514A.
9 Toquet C, Hamidou MA, Renaudin K *et al.* In situ immunophenotype of the inflammatory infiltrate in eosinophilic fasciitis. *J Rheumatol* 2003; **30**: 1811–5.
10 Viallard JF, Taupin JL, Ranchin V *et al.* Analysis of leukemia inhibitory factor, type 1 and type 2 cytokine production in patients with eosinophilic fasciitis. *J Rheumatol* 2001; **28**: 75–80.
11 Varga J, Peltonen J, Uitto J *et al.* Development of diffuse fasciitis with eosinophilia during L-tryptophan treatment: demonstration of elevated Type 1 collagen expression in affected tissues: a clinico-pathological study of four patients. *Ann Intern Med* 1990; **112**: 344–51.

12 Kaufman LD. The eosinophilia–myalgia syndrome: current concepts and future directions. *Clin Exp Rheumatol* 1992; **10**: 87–91.
13 Douglas AS, Eagles JM, Mowat NAC. Eosinophilia myalgia syndrome associated with tryptophan. *BMJ* 1990; **301**: 387.
14 Oursler JR, Farmer ER, Roubenoff R *et al.* Cutaneous manifestations of the eosinophilia–myalgia syndrome. *Br J Dermatol* 1992; **127**: 138–46.
15 Pouplin S, Daragon A, Le Loët X. Treatment of eosinophilic fasciitis with methotrexate. *J Rheumatol* 1998; **25**: 606–7.
16 Horacek E, Sator PG, Gschnait F. 'Venous Furrowing': a clue to the diagnosis of eosinophilic fasciitis. A case of eosinophilic fasciitis ultimately treated with oral PUVA therapy. *Dermatology* 2007; **215**: 89–90.
17 Bukiej A, Dropiski J, Dyduch G, Szczeklik A. Eosinophilic fasciitis successfully treated with cyclosporine. *Clin Rheumatol* 2005; **24**: 634–6.
18 Philpott H, Hissaria P, Warren L *et al*. Eosinophilic fasciitis as a paraneoplastic phenomenon associated with metastatic colorectal carcinoma. *Australas J Dermatol* 2008; **49**: 27–9.
19 DeGiovanni C, Chard M, Woollons A. Eosinophilic fasciitis secondary to treatment with atorvastatin. *Clin Exp Dermatol* 2006; **31**: 131–2.
20 Hur JW, Lee HS, Uhm WS *et al*. Eosinophilic fasciitis associated with autoimmune thyroiditis. *Korean J Intern Med* 2005; **20**: 180–2.
21 Suresh E, Doherty V, Schofield O *et al*. Eosinophilic fasciitis and eosinophilic colitis: a rare association. *Rheumatology (Oxford)* 2005; **44**: 411–3.
22 Rutter MM, Prahalad S, Passo M, Backeljauw PF. Idiopathic hypercalcemia and eosinophilic fasciitis: a novel association. *J Pediatr Endocrinol Metab* 2004; **17**: 1251–4.
23 Chaudhary UB, Eberwine SF, Hege KM. Acquired amegakaryocytic thrombocytopenic purpura and eosinophilic fasciitis: a long relapsing and remitting course. *Am J Hematol* 2004; **75**: 146–50.

Connective tissue panniculitis (see Chapter 46)

This term has been used [1] for focal nodular or atrophic linear or plaque-like lesions on the face, upper trunk or extremities, which histologically show lymphocytic panniculitis with caseation necrosis. The lesions may respond to chloroquine.

Reference

1 Winkelmann R, Padilha-Goncalves A. Connective tissue panniculitis. *Arch Dermatol* 1980; **116**: 291–4.

Relapsing eosinophilic perimyositis [1]

This rare disorder is in the spectrum of eosinophilic myositis, and is characterized by inflammation within the perimysium (and often epimysium) without necrosis, as opposed to polymyositis and eosinophilic myositis in which necrosis and inflammation occur in the endomysium.

Clinically, patients may present with episodic swelling of the muscles, fatigue and fever. Skin lesions include blotchy erythema over the swollen muscles and erythematous papular lesions of the palms. There is peripheral blood eosinophilia and hyperglobulinaemia, but the muscle enzyme levels are normal or only slightly elevated. Histologically, there are perimysial eosinophilic infiltrates.

The aetiology is unknown. The prognosis is good, although the patient should be followed up in case of the development of lymphoproliferative disease. Most patients respond to moderate doses of steroids or indometacin.

Reference

1 Trueb RM, Becker-Wegerich P, Hafner J *et al.* Relapsing eosinophilic perimyositis. *Br J Dermatol* 1995; **133**: 109–14.

Systemic sclerosis [1,2]

Synonyms
- Progressive systemic sclerosis
- Systemic scleroderma
- Acrosclerosis

Definition. Systemic sclerosis is a multisystem disorder characterized by vascular abnormalities, connective tissue sclerosis and atrophy, and autoantibodies (see p. 51.91 for diagnostic criteria) [2].

The name progressive systemic sclerosis was coined by Goetz in 1945; however, the term 'progressive' is now omitted by most authors because of the variable course of the disease [2–5].

Incidence. Systemic sclerosis is a rare disorder, with an incidence between 2.3 and 10 per million population [6–8]. The prevalence rates in a British study were 13 per million males and 48 per million females, although these figures may represent the minimum [9]; there may be considerable regional variations, possibly as a result of environmental factors [10]. Estimates of prevalence from South Carolina are much higher (67–265 in 100 000) [11]. The ratio of females to males is between 3 and 6 : 1 depending on the source [8,9,12]. The peak onset is in the fourth decade in females and usually later in males; however, overall, 85% of patients present between the ages of 20 and 60 years [8]. In men, the condition has a number of occupational associations, especially miners and stonemasons, and it has been suggested that pneumoconiosis and silicosis are predisposing factors [13]. It occurs in all races, but appears to be less frequent in Asians [14]. There is evidence that African American women with systemic sclerosis are more likely to develop diffuse disease at a younger age and have decreased survival compared with Caucasians [15].

References

1 Varga J. Systemic sclerosis: an update. *Bull NYU Hosp Jt Dis* 2008; **66**: 198–202.
2 Rowell NR. Systemic sclerosis. *J R Coll Phys Lond* 1985; **19**: 23–30.
3 Jayson MIV. Systemic sclerosis: a microvascular disorder? *J R Soc Med* 1983; **76**: 635–42.
4 Krieg T, Meurer M. Systemic scleroderma. *J Am Acad Dermatol* 1988; **18**: 457–81.
5 LeRoy EC. Scleroderma (systemic sclerosis). In: Kelley WN, Harris ED, Ruddy S *et al.*, eds. *Textbook of Rheumatology*. London: Saunders, 1981: 1221–8.
6 Eason RJ, Tan PL, Cow PJ. Progressive systemic sclerosis in Auckland: a 10-year review with emphasis on prognostic features. *Aust NZ J Med* 1981; **11**: 657–62.
7 Kurland LT, Hauser WA, Ferguson RH *et al.* Epidemiologic features of diffuse connective tissue disorders in Rochester, Minn., 1951 through 1967, with special reference to systemic lupus erythematosus. *Mayo Clin Proc* 1969; **44**: 649–63.
8 Medsger TA, Masi AT. Epidemiology of systemic sclerosis (scleroderma). *Ann Intern Med* 1971; **74**: 714–21.
9 Silman A, Jannini S, Symmons D *et al.* An epidemiological study of scleroderma in the West Midlands. *Br J Rheumatol* 1988; **27**: 286–90.
10 Silman AJ, Howard Y, Hicklin AJ, Black C. Geographical clustering of scleroderma in south and west London. *Br J Rheumatol* 1990; **29**: 92–6.
11 Maricq HR, Weinrich MC, Keil JE *et al.* Prevalence of scleroderma spectrum disorders in the general population of South Carolina. *Arthritis Rheum* 1989; **32**: 998–1006.
12 Medsger TA. Epidemiology of progressive systemic sclerosis. In: Black CM, Myers AR, eds. *Systemic Sclerosis (Scleroderma)*. New York: Gower, 1985: 53–60.

13 Rodnan GP, Benedek TC, Medsger TA *et al.* The association of progressive systemic sclerosis (scleroderma) with coal miners pneumoconiosis and other forms of silicosis. *Ann Intern Med* 1967; **66**: 323–34.
14 Tay CH, Khoo OT. Progressive systemic sclerosis (scleroderma). *Aust Ann Med* 1970; **2**: 145–50.
15 Laing TJ, Gillespie BW, Toth MB *et al.* Racial differences in scleroderma among women in Michigan. *Arthritis Rheum* 1997; **40**: 734–52.

Aetiology [1]. The aetiology of systemic sclerosis is unknown. The presence of vascular symptoms in virtually all patients, and the fact that these may predate the development of classic fibrotic change, and the presence of markers of vascular damage (e.g. elevated circulating von Willebrand factor antigen and endothelial adhesion molecules [2,3]), suggest the endothelial cell is either an initial target or the primary dysfunctional cell in this disease. Vascular abnormalities are not limited to the clinically abnormal skin [4]. Damage to the endothelial cell may initiate the fibrotic process, either through ischaemia/reperfusion or via growth factors released from platelets and inflammatory cells. However, the pathological changes in the internal organs do not always seem to be directly related to changes in the small blood vessels of the same area.

There is now clear evidence of endothelial injury and death [5], in addition to myofibroblast dysfunction, and the primary pathology in vascular endothelium appears to be a fibromucinous change [6]. Serum from patients with the disease is cytotoxic to endothelial cells, either directly [7] or by antibody-dependent cellular cytotoxicity [8] and, although patients' serum has no effect on unstimulated release of prostacyclin [9], stimulated release may be impaired [10]. The influence of sera from affected patients on angiogenesis varies with the phase and type of disease, being stimulatory in early limited disease, but inhibitory in chronic diffuse disease [11]. Damage to endothelium is followed by vascular occlusion resulting from thrombus formation, and tissue ischaemia follows. Abnormalities in various blood components contribute to this tissue anoxia: red cell deformability is reduced [12], platelet aggregation to collagen may be specifically enhanced [13] and *in vivo* markers of platelet activation are increased [14]. Levels of fibrinogen, von Willebrand factor antigen (possibly indicating the degree of vascular damage) [15] and other plasma proteins are also raised, contributing to increased plasma viscosity, further reducing microvascular blood flow. Anticardiolipin antibodies may be present and responsible for increased endothelial cell damage and risk of thrombosis [16].

The associated fibrosis in systemic sclerosis is caused by the increased production of collagen in the subcutaneous tissue. Scleroderma fibroblasts synthesize more collagen than those from normal controls [17,18], and collagenase activity is normal [19]. The deposited collagen is similar in composition to that deposited in other fibrotic disorders, with a normal ratio of type I to type III collagen [19]. The cause of this excessive production is unknown; both intrinsic overactivity and excessive stimulation of fibroblasts may occur. Fibroblast function is modified by endothelial cell products released in a cell culture system [20]. Small collagen fibres are increased, and the response of systemic sclerosis fibroblasts to most mitogens is normal, or reduced, indicating overstimulation [21]. Raised levels of growth factors, both platelet-derived [22] and non-platelet-derived [23], support this suggestion. In addition, glycosaminoglycan synthesis is increased in fibroblasts from patients with the disease, and is stimulated by a mononuclear cell product (possibly IL-1) [24], although other mononuclear cell products can inhibit collagen overproduction [25]. Other connective tissue proteins, including tenascin, are increased [26]. However, there is evidence for an expanded clone of overactive fibroblasts in systemic sclerosis [27], possibly derived from fibroblasts from the deeper dermis [28,29]. There is also an excessive response of fibroblasts to connective-tissue growth factor (CTGF) [30], TGF-β [31], to platelet growth factors [32] and to serum from patients with the disease [33]. TGF-β may have a role both in fibroblast stimulation and in endothelial inhibition [21]. There is a failure of the inhibitory feedback of the aminopropeptide of type I collagen on the fibroblasts [34]. Soluble cytokine receptors [35] and levels of adhesion molecules [36] are often raised in the serum of patients, reflecting disease activity. Circulating anticollagen antibodies to collagen types I and IV occur in patients with systemic sclerosis [37], but these appear to be inversely related to the severity of the disease. They occur in approximately half of British patients and in at least one relative in over 80% of their families. It has been suggested that serotonin hypersensitivity may be a factor in both the vascular and fibrous changes of the disease [38]. Abnormal metabolism of, and responses to, serotonin and tryptophan may contribute to both fibrosis and vascular abnormalities [39]. Raised numbers of mast cells in affected skin may similarly contribute.

References

1 Black CM. The aetiopathogenesis of systemic sclerosis: thick skin—thin hypotheses. *J R Coll Physicians Lond* 1995; **29**: 119–30.
2 Greaves M, Malia RC, Milford Ward A *et al.* Elevated von Willebrand factor antigen in systemic sclerosis: relationship to visceral disease. *Br J Rheumatol* 1988; **27**: 281–5.
3 Kahaleh MB, Osborn I, LeRoy EC. Increased factor VIII/von Willebrand factor antigen and von Willebrand factor activity in scleroderma and in Raynaud's phenomenon. *Ann Intern Med* 1981; **94**: 482–4.
4 Fremont AJ, Hoyland J, Fielding P *et al.* Studies of the microvascular endothelium in uninvolved skin of patients with systemic sclerosis: direct evidence for a generalized microangiopathy. *Br J Dermatol* 1992; **126**: 561–8.
5 Nunzi E, Neboro A. Are endothelial cells stimulated by autoantibody in progressive systemic sclerosis? *Acta Derm Venereol (Stockh)* 1983; **63**: 458–9.
6 Winkelmann RK. Pathogenesis and staging of scleroderma. *Acta Derm Venereol (Stockh)* 1976; **56**: 83–92.
7 Kahaleh MB, Sherer GK, LeRoy EC. Endothelial injury in scleroderma. *J Exp Med* 1979; **149**: 1326–35.
8 Penning CA, Cunningham J, French MAH *et al.* Antibody dependent cellular cytotoxicity of human vascular endothelium in systemic sclerosis. *Clin Exp Immunol* 1984; **57**: 548–56.
9 Holt CM, Moult J, Lindsey N *et al.* Prostacyclin production by human umbilical vein endothelium in response to serum from patients with systemic sclerosis. *Br J Rheumatol* 1989; **28**: 216–20.
10 Rustin MHA, Bull HA, Machin SJ *et al.* Serum from patients with Raynaud's phenomenon inhibits prostacyclin production. *J Invest Dermatol* 1987; **89**: 555–9.
11 Majewski S, Skopinska-Rozewska E, Jablonska S *et al.* Modulatory effect of sera from scleroderma patients on lymphocyte-induced angiogenesis. *Arthritis Rheum* 1985; **28**: 1133–9.
12 Kovacs IB, Sowemimo-Coker SD, Kirby JDT *et al.* Altered behaviour of erythrocytes in scleroderma. *Clin Sci* 1975; **65**: 515–22.
13 Goodfield MJD, Orchard MA, Rowell NR. Increased platelet sensitivity to collagen induced aggregation in whole blood in patients with systemic sclerosis. *Clin Exp Rheumatol* 1988; **6**: 285–8.

14 Kahaleh MB, Scharstein KK, LeRoy EC. Enhanced platelet adhesion to collagen in scleroderma: effect of scleroderma plasma and scleroderma platelets. *J Rheumatol* 1985; **12**: 468–71.
15 Goodfield MJD, Orchard M, Rowell NR. Whole blood platelet aggregation and coagulation factors in patients with systemic sclerosis. *Br J Haematol* 1993; **84**: 675–80.
16 Malia RC, Greaves M, Rowlands LM *et al.* Anticardiolipin antibodies in systemic sclerosis: immunological and clinical associations. *Clin Exp Immunol* 1988; **73**: 456–60.
17 Buckingham RB, Prince RK, Rodnan GP *et al.* Increased collagen accumulation in dermal fibroblast cultures from patients with progressive systemic sclerosis (scleroderma). *J Lab Clin Med* 1978; **92**: 5–21.
18 LeRoy EC. Increased collagen synthesis by scleroderma skin fibroblasts *in vitro*. *J Clin Invest* 1974; **54**: 880–9.
19 Uitto J, Bauer EA, Eisen EZ. Scleroderma: increased biosynthesis of triple helical type I and type III procollagen with unaltered expression of collagenase by skin fibroblasts in culture. *J Clin Invest* 1979; **64**: 921–30.
20 Denton CP, Xu SW, Welsh KI *et al.* Scleroderma fibroblast phenotype is modulated by endothelial cell co-culture. *J Rheumatol* 1996; **23**: 633–8.
21 LeRoy EC, Mercurio S, Sherer CK. Replication and phenotypic expression of control and scleroderma fibroblasts: responses to growth factors. *Proc Natl Acad Sci USA* 1982; **79**: 1288–90.
22 Pandolfi A, Florita M, Altomare C *et al.* Increased plasma levels of platelet-derived growth factor activity with progressive systemic sclerosis. *Proc Soc Exp Biol Med* 1989; **19**: 1–4.
23 Potter SR, Bienenstock J, Goldstein S *et al.* Fibroblast growth factors in scleroderma. *J Rheumatol* 1989; **12**: 1129–35.
24 Whiteside TL, Inoshita T, Roumm AD *et al.* T-lymphocytes in progressive systemic sclerosis. In: Black CM, Myers AR, eds. *Systemic Sclerosis (Scleroderma)*. New York: Gower, 1985: 326–37.
25 Jimenez SA, McArthur WM, Bashey RI *et al.* Selective inhibition of excessive scleroderma fibroblast collagen production by lymphokines from normal human mononuclear cells. *Arthritis Rheum* 1985; **28**: 502–10.
26 Lacour JP, Vitetta A, Chiquet-Ehrismann R *et al.* Increased expression of tenascin in the dermis in scleroderma. *Br J Dermatol* 1992; **127**: 328–34.
27 Maxwell DB, Grotendorst CA, Grotendorst CR *et al.* Fibroblast heterogeneity in scleroderma: C1q studies. *J Rheumatol* 1987; **14**: 756–9.
28 Harper RA, Grove G. Human skin fibroblasts derived from papillary and reticular dermis: differences in growth potential *in vitro*. *Science* 1979; **204**: 525–7.
29 Krieg T, Langer I, Gerstmeier H *et al.* Type III collagen aminopropeptide levels in serum of patients with progressive systemic scleroderma. *J Invest Dermatol* 1986; **87**: 788–91.
30 Fonseca C, Lindahl GE, Ponticos M *et al.* A polymorphism in the CTGF promoter region associated with systemic sclerosis. *N Engl J Med* 2007; **357**: 1210–20.
31 Falanga V, Tiegs SL, Alstadt SP *et al.* Transforming growth factor-β: selective increase in glycosaminoglycan synthesis by cultures of fibroblasts from patients with progressive systemic sclerosis. *J Invest Dermatol* 1987; **89**: 100–4.
32 Falanga V, Hebdo PA, Eaglestein WH. Effect of platelet homogenate on *in vitro* glycosaminoglycan production by dermal fibroblasts from systemic sclerosis patients and normal controls. *Br J Dermatol* 1985; **113**: 237–43.
33 Potter SR, Bienenstock SR, Lee P *et al.* Clinical associations of fibroblast growth promotion factor in scleroderma. *J Rheumatol* 1984; **11**: 43–7.
34 Perlish JS, Lemlich C, Fleischmajer R. Identification of collagen fibrils in scleroderma skin. *J Invest Dermatol* 1988; **90**: 48–54.
35 Steen VD, Engel EE, Charley MR, Medsger TA. Soluble serum interleukin-2 receptors in patients with systemic sclerosis. *J Rheumatol* 1996; **23**: 646–9.
36 Denton CP, Bickerstaff MCM, Shiwen X *et al.* Serial circulating adhesion molecule levels reflect disease severity in systemic sclerosis. *Br J Rheumatol* 1995; **34**: 1048–54.
37 Mackel AM, DeLustro F, Harper FE *et al.* Antibodies to collagen in scleroderma. *Arthritis Rheum* 1982; **25**: 522–31.
38 Winkelmann RK, Goldyne MF, Linscheid RLL. Hypersensitivity of scleroderma cutaneous vascular smooth muscle to 5-hydroxytryptamine. *Br J Dermatol* 1976; **95**: 51–6.
39 Stachow A, Jablonska S, Skiendzielewska A. 5-Hydroxytryptamine and tryptamine pathways in scleroderma. *Br J Dermatol* 1977; **97**: 147–54.

Autoimmunity. The presence of antinuclear antibodies in over 80% of patients and specific autoantibodies—anti-isotopomerase (22%) and anticentromere (up to 30%)—suggests an autoimmune response. However, it is not clear if this is a primary abnormality or results from cellular damage. A role for immune factors in endothelial injury is also suggested by the presence of antiendothelial cell antibodies in 30% of patients [1,2], the ability of endothelial cells to act as a modulator of immune responses [3] and the finding of an IgM vasculopathy in acute-onset systemic sclerosis. Furthermore, circulating immune complexes occur in over 50% of cases [4], but their significance is unknown.

There is evidence of abnormal cellular immunity in patients with systemic sclerosis, with leukocyte migration inhibition to a variety of autologous, homologous and heterologous antigens [5]. However, the development of delayed cutaneous hypersensitivity is normal [6]. Patients have a deficiency of circulating T lymphocytes [7] and impaired lymphocyte transformation in response to phytohaemagglutinin (PHA) [8]. Both these features are related to the severity of the disease and the degree of visceral involvement, and also to an increased incidence of HLA-B8 [9]. The haplotype B8/DR3 is associated with decreased cellular immunity [10]. Helper cells [11], T cells possibly activated by raised levels of IL-2 [12] and NK cells are increased [13], whereas suppressor T cells are decreased [14]. These T-cell changes are more marked in the later stages of generalized disease. Patients with extensive disease have reduced antibody-dependent cytotoxicity, PHA-induced T-cell cytotoxicity [15] and NK-cell cytotoxicity to Chang liver cells [16], although others have found enhanced NK activity [17]. Some patients with systemic sclerosis develop a delayed cutaneous reaction to autologous leukocytes [18]. Scleroderma-like changes have been reported after allogeneic bone marrow transplantation, suggesting a graft-versus-host response (see p. 51.83).

References

1 Baguley E, Brown KA, Haskard D *et al.* Antiendothelial cell antibodies in connective tissue diseases. *Br J Rheumatol* 1989; **26**: 95–101.
2 Hashemi S, Smith CD, Izaguirre CA. Antiendothelial cell antibodies: detection and characterization using a cellular enzyme-linked immunosorbent assay. *J Lab Clin Med* 1987; **109**: 434–40.
3 Pober JS, Collins T, Cimbrone MA *et al.* Inducible expression of class II major histocompatibility complex antigens and the immunogenicity of vascular endothelium. *Transplantation* 1986; **41**: 141–6.
4 Hughes P, Cunningham J, Day M *et al.* Immune complexes in systemic sclerosis. *J Clin Lab Immunol* 1983; **10**: 133–8.
5 Hughes P, Holt S, Rowell NR. Leukocyte migration inhibition in progressive systemic sclerosis. *Br J Dermatol* 1974; **91**: 1–6.
6 Lupoli S, Amlot P, Black C. Normal immune responses in systemic sclerosis. *J Rheumatol* 1990; **17**: 323–7.
7 Hughes P, Holt S, Rowell NR *et al.* Thymus-dependent (T) lymphocyte deficiency in progressive systemic sclerosis. *Br J Dermatol* 1976; **95**: 469–73.
8 Hughes P, Holt S, Rowell NR *et al.* The relationship of defective cell-mediated immunity to visceral disease in systemic sclerosis. *Clin Exp Immunol* 1977; **28**: 233–40.
9 Hughes P, Gelsthorpe K, Doughty RW *et al.* The association of HLA-B8 with visceral disease in systemic sclerosis. *Clin Exp Immunol* 1978; **31**: 351–6.
10 Kallenberg CGM, Van der Voort-Beelen JM, D'Aman J *et al.* Increased frequency of B8/DR3 in scleroderma and association of the haplotype with impaired cellular immune response. *Clin Exp Immunol* 1981; **43**: 478–85.
11 Krakauer RS, Sundeen J, Sauder DN *et al.* Abnormalities of immunoregulation in progressive systemic sclerosis. *Arch Dermatol* 1981; **117**: 80–2.

12 Kahaleh MB, LeRoy EC. Interleukin-2 in scleroderma: correlation of serum level with extent of skin involvement and disease duration. *Ann Intern Med* 1989; **110**: 446–50.
13 Jablonska S. *Scleroderma and Pseudoscleroderma*. Warsaw: Polish Medical Publishers, 1975.
14 Whiteside TL, Kumagai Y, Roumm AD *et al.* Suppressor cell function and T-lymphocyte subpopulations in peripheral blood of patients with progressive systemic sclerosis. *Arthritis Rheum* 1983; **26**: 841–7.
15 Wright JK, Hughes P, Rowell NR *et al.* Antibody-dependent and phytohaemagglutinin-induced lymphocyte cytotoxicity in systemic sclerosis. *Clin Exp Immunol* 1979; **36**: 175–82.
16 Wright JK, Hughes P, Rowell NR. Spontaneous lymphocyte-mediated (NK cell) cytotoxicity in systemic sclerosis: a comparison with antibody-dependent lymphocyte (K-cell) cytotoxicity. *Ann Rheum Dis* 1982; **41**: 409–13.
17 Cifone MG, Giacomelli R, Famularo G *et al.* Natural killer activity and antibody-dependent cellular cytotoxicity in progressive systemic sclerosis. *Clin Exp Immunol* 1990; **80**: 360–5.
18 Tuffanelli DL. Cutaneous hypersensitivity to leukocytes in scleroderma. *J Invest Dermatol* 1964; **42**: 179–84.

Genetic factors. Despite the rarity of familial cases of systemic sclerosis [1–4], abnormalities of the serum immunoglobulins [5] and the high incidence of antinuclear factor in first-degree relatives of patients with systemic sclerosis [6], together with an increased incidence of HLA-B8 in the more severe cases [7], suggest that genetic factors play a part in the aetiology. Clinical and immunological subsets may be genetically determined, but to date there appears to be no clear relationship between HLA, autoantibodies and clinical manifestations [8]. Chromosomal abnormalities have been described in patients with the disease [9,10] and in their relatives, and a serum factor may be responsible for this abnormality. HLA-DR typing shows an increase in DR2, DR3 and DR5 [11]. There is an association between the B8-DR3-DR52-DQB2 haplotype and the development of pulmonary fibrosis [12]. Patients with mild disease have raised DR2 and DR5 and anticentromere antibodies. No relationship between HLA type and Scl-70 antibodies has yet been demonstrated. In identical twins discordant for the disease, autoantibodies [13], T-cell abnormalities and abnormal fibroblast response to mononuclear cell stimulation were found only in the affected twin [14].

An intriguing hypothesis suggests that transfer of fetal cells to the mother or vice versa during pregnancy may result in microchimerism, which has been demonstrated in higher frequency in systemic sclerosis [15]; this may then stimulate a unique immune response.

The age distribution of the disease suggests that the susceptible genotype is probably characterized by a single inherited dominant allele on the X chromosome, explaining the female predominance, together with autosomal factors. Initiation would depend on the occurrence of specific random events believed to be somatic mutations in lymphoid stem cells [16], producing 'forbidden' clones of lymphocytes. These synthesize cellular autoantibodies that are pathogenic, damaging endothelial cells. After a variable latent period, damage to tissue occurs. Antinuclear factors are the result of the disease. Normal defence mechanisms (more efficient in females) may be inhibited by precipitating factors such as silica or other environmental hazards. The pattern of organ involvement may be related to particular forbidden clones that are active, or to local tissue differences.

References

1 Dubois FL, Chandor S, Friou GJ *et al.* Progressive systemic sclerosis (PSS) and localized scleroderma (morphoea) with positive LE cell test. *Medicine* 1971; **50**: 199–222.
2 Gregor RE. Familial progressive systemic scleroderma. *Arch Dermatol* 1975; **111**: 81–5.
3 Rendall JR, McKenzie AW. Familial scleroderma. *Br J Dermatol* 1974; **91**: 517–22.
4 Sasaki S, Yoshino H. Systemic scleroderma in mother and daughter. *Arch Dermatol* 1977; **113**: 378–9.
5 Corcos JM, Robbins WC, Rogoff B *et al.* Some serum protein abnormalities in patients with progressive systemic sclerosis and their relatives. *Arthritis Rheum* 1961; **4**: 107.
6 Pereira S, Black C, Welsh K *et al.* Autoantibodies and immunogenetics in 30 patients with systemic sclerosis and their families. *J Rheumatol* 1987; **14**: 760–5.
7 Hughes P, Gelsthorpe K, Doughty RW *et al.* The association of HLA-B8 with visceral disease in systemic sclerosis. *Clin Exp Immunol* 1978; **31**: 351–6.
8 Black CM, Briggs D, Welsh K. The immunogenetic background of scleroderma: an overview. *Clin Exp Dermatol* 1992; **17**: 73–8.
9 Emerit I. Chromosomal breakage in systemic sclerosis and related disorders. *Dermatologica* 1982; **153**: 145–56.
10 Sherer CK, Jackson BB, LeRoy EC. Chromosome-breakage and sister chromatid exchange frequencies in scleroderma. *Arthritis Rheum* 1981; **24**: 1409–13.
11 Black CM, Welsh KI, Maddison PJ *et al.* HLA antigens, autoantibodies and clinical subsets in scleroderma. *Br J Rheumatol* 1984; **23**: 267–75.
12 Briggs DC, Vaughan R, Welsh KI *et al.* Immunogenetic prediction of pulmonary fibrosis in systemic sclerosis. *Lancet* 1992; **338**: 661–2.
13 McHugh NJ, Harvey GR, Whyte J, Dorsey JK. Segregation of auto-antibodies with disease in monozygotic twin pairs discordant for systemic sclerosis: three further cases. *Arthritis Rheum* 1995; **38**: 1845–50.
14 Dustoor MM, McInerney MM, Mazanec DJ *et al.* Abnormal lymphocyte function in scleroderma: a study on identical twins. *Clin Immunol Immunopathol* 1987; **44**: 20–30.
15 Johnson KL, Nelson JL, Furst DE *et al.* Fetal cell microchimerism in tissue from multiple sites in women with systemic sclerosis. *Arthritis Rheum* 2001; **44**: 1848–54.
16 Rowell NR. Systemic sclerosis. *J R Coll Phys Lond* 1985; **19**: 23–30.

Other factors. There is no evidence of a chemical cause, although cocaine has been suggested as a trigger in some cases [1]. The role of silicone gel prostheses used for breast augmentation has been much discussed, but there is now agreement that there is no relationship between this procedure and the development of systemic sclerosis [2,3] (see Chapter 70). Physical trauma appears to precipitate the disease in genetically predisposed individuals [4], who may have the allele HLA-DR52 [5]. Virus-like particles have been observed by electron microscopy in striated muscle [6], and acid-fast bacilli, closely allied to mycobacteria, have been found in skin biopsies [7] in systemic sclerosis, but their significance is not known. Glucose-tolerance curves may suggest latent diabetes [8]. A prolongation of sensory chronaxia has been found in both normal and abnormal skin [9], and it has been suggested that the condition is a primary abnormality of the central autonomic nervous system. Reciprocal skin grafting has shown that if sclerodermatous skin is placed in a normal bed, it remains sclerodermatous, and if clinically normal skin is placed in a sclerodermatous area it becomes sclerodermatous [10]. Thus, in systemic sclerosis, the skin involvement is generalized or irreversible, in contrast with morphoea, in which the disorder is localized and reversible.

References

1 Kilaru P, Kim W, Sequerina W. Cocaine and scleroderma: is there an association? *J Rheumatol* 1991; **18**: 1753–5.

2 Englert H, Morris D, March L. Scleroderma and silicone gel breast prostheses: the Sydney study revisited. *Aust NZ J Med* 1996; **26**: 349–55.
3 Hochberg MC, Perlmutter DL, Medsger TA *et al.* Lack of association between augmentation mammoplasty and systemic sclerosis (scleroderma). *Arthritis Rheum* 1996; **39**: 1125–31.
4 Lee P. Systemic sclerosis following physical trauma. *J Rheumatol* 1996; **23**: 1689–90.
5 Rahman MAA, Jayson MIV, Black CM. Five patients who developed systemic sclerosis shortly after episodes of physical trauma. *J Rheumatol* 1996; **23**: 1816–7.
6 Kudejko J. Virus-like particles observed in the striated muscles in patients with acroscleroderma. *Dermatologica* 1966; **133**: 495–502.
7 Cantwell AR Jr, Craggs E, Wilson JW *et al.* Acid-fast bacteria as a possible cause of scleroderma. *Dermatologica* 1968; **136**: 141–50.
8 Fleischmajer R, Faludi C. A study of carbohydrate metabolism in scleroderma. *J Invest Dermatol* 1969; **52**: 326–7.
9 Jablonska S. *Scleroderma and Pseudoscleroderma*. Warsaw: Polish Medical Publishers, 1975.
10 Fries JF, Hoopes JE, Shulman LE. Reciprocal skin grafts in systemic sclerosis (scleroderma). *Arthritis Rheum* 1971; **14**: 571–8.

Diagnosis. The criteria for diagnosis have been established by the Subcommittee for Scleroderma Criteria of the ARA [1] and are generally accepted. Patients should have either:

1 Scleroderma proximal to the digits, affecting limbs, face, neck or trunk—this is the single major criterion; or
2 At least two minor criteria, consisting of:
(a) sclerodactyly
(b) digital pitted scarring
(c) bilateral basal pulmonary fibrosis.

These criteria have 97% sensitivity and 98% specificity, and difficulty arises principally in males who have a sclerodermatous condition brought about by occupational exposure to, for example, silica or vinyl chloride. These patients often fulfil two minor criteria, and indeed share many characteristics, both clinical and immunological, with true systemic sclerosis [2].

Classification of systemic sclerosis. There have been many attempts to classify the disease [3–6]. Most recently, a simplified classification has been proposed [7]. In this system, patients are classified as having diffuse cutaneous systemic sclerosis (dSSc), or limited cutaneous systemic sclerosis (lSSc). The distinction is made principally on the basis of the extent of cutaneous involvement, but also includes certain other clinical and immunological features (Table 51.17). This system appears satisfactory because systemic involvement, which determines the prognosis of the disease, is less frequent in patients with limited cutaneous disease.

Table 51.17 Classification of systemic sclerosis.

Diffuse cutaneous systemic sclerosis
Short interval (<1 year) between the onset of Raynaud's phenomenon and the development of skin changes
Truncal and peripheral skin involvement
Tendon friction rubs
Pulmonary fibrosis, renal failure, gastrointestinal disease, myocardial involvement
Capillary drop-out visible in nail folds
Scl-70 antibody-positive
Anticentromere antibody-negative
Limited cutaneous systemic sclerosis
Long history of Raynaud's phenomenon
Limited skin involvement (peripheral only)
Calcification, telangiectasia, late onset of pulmonary hypertension
Capillary dilatation visible in nail folds
Anticentromere antibody-positive

References

1 Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for the classification of systemic sclerosis. *Arthritis Rheum* 1980; **23**: 581–90.
2 Rustin MHA, Bull HA, Ziegler V *et al.* Silica exposure and silica associated systemic sclerosis. *Br J Dermatol* 1989; **121** (Suppl. 34): 29.
3 Arbeitsgruppe Sklerodermie der Arbeitsgemeinschaft Dermatologische Forschung (ADF). Klinik der progressiven systemischen Sklerodermie (PSS). *Hautarzt* 1986; **37**: 320–4.
4 Barnett AJ. *Scleroderma. Progressive Systemic Sclerosis*. Springfield: Thomas, 1974.
5 Rodnan CP, Jablonska S, Medsger TA. Classification and nomenclature of progressive systemic sclerosis (scleroderma). *Clin Rheum Dis* 1976; **5**: 5–13.
6 Winkelmann RK. Pathogenesis and staging of scleroderma. *Acta Derm Venereol (Stockh)* 1976; **56**: 83–92.
7 LeRoy EC, Black C, Fleischmajer R *et al.* Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol* 1988; **15**: 202–5.

Pathology [1]. It is important to realize that this widespread disease does not involve all organs in any patient; in certain cases it may be limited to one or two organs. Even when changes are present in an organ, the distribution of these changes is by no means uniform. Although a striking abnormality in systemic sclerosis is the sclerotic change in tissues such as the heart, lungs, submucosa and muscularis of the gastrointestinal tract, widespread vascular lesions may be a prominent feature of certain cases. The digital arteries may be severely involved, and changes of endarteritis may be seen in the lungs, heart, gastrointestinal tract, muscle and kidney. Infiltrations of inflammatory cells, particularly lymphocytes, may occur in the joints, mucosa and submucosa of the gastrointestinal tract, and in striated muscle.

In the skin, the dermis shows hyalinization of the collagen, often with associated abnormalities of elastic tissue and reticulin. The changes may be slight and difficult to detect unless the histological technique is excellent. In particular, standard fixatives must be used if hyalinization of the collagen is to be assessed. In severely involved skin, the epidermis and its appendages are usually atrophic, with loss of the rete ridges. Sometimes, there is hyperkeratosis, and the dermis shows variable degrees of homogenization of the collagen, and occasionally a light dermal lymphocytic infiltrate. In the tumid or 'inflammatory' phase in the fingers, the dermis may show a striking infiltrate, with lymphocytes predominating. Cellular infiltrates of lymphocytes, plasma cells, fibroblastic-type cells and macrophages, either perivascular or diffuse, occurred in 49% of patients of one series [2], but there was no correlation with serum serological abnormalities. Electron microscopy has shown that both T and B lymphocytes are present in the infiltrates [3], although most are activated helper T cells. Hyalinization and intimal thickening of the blood vessels may occur, but fibrinoid change is uncommon. Evidence from electron microscopy [4] and the normal distribution of cutaneous enzymes, acid mucopolysaccharides and other ground substances, together with the absence of any abnormal gammaglobulin, fibrinogen or albumin, using fluorescent antibody techniques, suggests that the

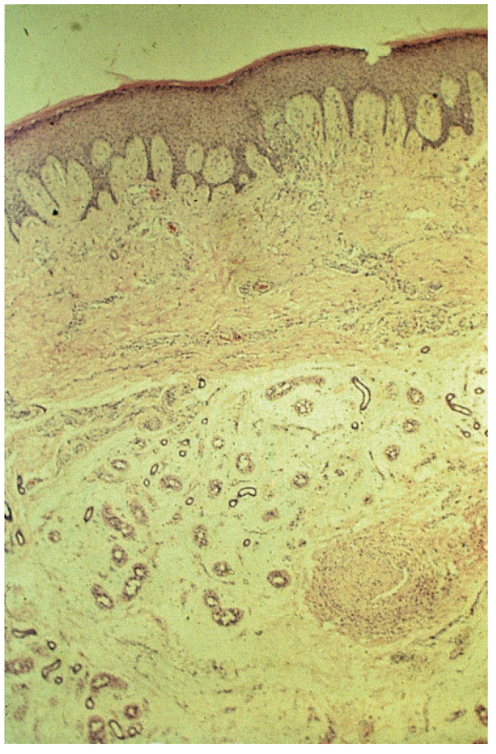


Fig. 51.59 Systemic sclerosis: section of finger showing thickened dermis with hyalinization of the collagen and almost complete occlusion of a digital vessel.



Fig. 51.60 Pearly white plaques in the oesophagus in systemic sclerosis, giving a cobblestone appearance.

alterations in dermal collagen are the result of a simple increase in the number of fibrils. Quantitatively increased fibrillogenesis, with an increased proportion of thin fibrils of type III collagen [5] in the dermis, has led some authors [6] to conclude that qualitative and quantitative disturbances in mesenchymal ground substances may play an important part in the increased formation of qualitatively normal collagen fibrils in scleroderma [7]. Further evidence that the ground substance is the tissue mainly involved has been provided by the finding of a normal concentration of water and hydroxyproline in the dermis [8]. Some authors believe that the main alterations in the skin in systemic sclerosis take place in the subcutaneous tissue and not in the dermis [9]. It is suggested that the replacement of subcutaneous tissue by connective tissue is the cause of the induration of the skin.

Histology, histochemistry, immunopathology and electron microscopy of depigmented areas of skin show changes similar to those found in vitiligo [10]. The digital vessels frequently show intimal and medial thickening, which may be so gross as to almost occlude the vessel (Fig. 51.59); this accounts in certain cases for gangrene of the fingers. Occasionally, fresh thromboses may be seen. Similar but less marked changes are found in the digital arteries of the toes, and the vessels of the leg may also show intimal thickening, which results in ischaemia and gangrene. The intimal thickening is very similar to that seen in the peripheral vascular obstruction that occurs in rheumatoid arthritis. Thromboses of major arteries can also occur [11], and reduction of local tissue fibrinolytic activity can be demonstrated in the involved vessels. Giant cell granulomatous necrosis of the intima of vessels and fat in nodular lesions of the skin has been described [12].

Immunoglobulins and complement may be demonstrated by fluorescent antibody techniques at the dermal–epidermal junction in telangiectases, but not in the indurated skin without telangiectasia [13]. Biopsies should not be taken from telangiectatic areas. The main immunohistological changes in the skin in systemic sclerosis consist of foci of intercollagenous staining for connective tissue antigens in the reticular layer of the dermis [14]. The absence of immunoglobulin and complement from the dermal–epidermal junction may be useful in distinguishing systemic sclerosis from SLE, in which the major changes are at the dermal–epidermal junction. Patients who have both systemic sclerosis and SLE have deposits of immunoglobulin and complement at the dermal–epidermal junction in involved and uninvolved skin as well as changes in the dermal collagen. Patients with scleroderma as part of 'mixed connective tissue disease' have positive immunofluorescence at the dermal–epidermal junction [15].

The gastrointestinal tract is frequently involved. The oesophagus may show areas of epithelium looking like pearly white plaques, giving a cobblestone appearance (Fig. 51.60). Microscopically, subepithelial fibrosis is the most common finding, but fibrosis may also occur in areas of muscular atrophy. The smaller arteries may show endarteritis, and some cellular infiltration also occurs. In the duodenum, jejunum, ileum and colon there is a patchy disappearance of muscle, especially of the circular layer, with replacement by fibrous tissue. The subserosal and submucosal tissues may also be thickened and fibrosed. Vessels in these areas may show sclerosis and intimal fibrosis.

Pathological changes in the lungs may be seen, even in the absence of symptoms or radiological signs of pulmonary involvement and even in the presence of normal pulmonary function.

Progressive diffuse alveolar fibrosis occurs with obliteration of capillaries and alveolar spaces, but is preceded by an inflammatory alveolitis [16,17]. In other cases, hyaline degeneration and fibrosis of alveolar walls result in the disappearance of the alveolar parenchyma and of the capillaries. Rupture of the thinned alveolar walls gives rise to cysts that are lined by cuboidal or columnar epithelium, which may be ciliated. Electron microscopy [18] may show thickening of the alveolar–capillary basement membrane. Arterial lesions in the lungs take the form of concentric thickening of the intima by loose myxomatous tissue and, later, sclerosis. In certain cases, the vessels may be almost completely occluded. Neoplastic change is a rare complication of the pulmonary abnormalities in systemic sclerosis. Various types of neoplasm have been reported [19,20], including malignant pulmonary adenomatosis, alveolar cell carcinoma, adenocarcinoma, oat cell carcinoma and squamous cell carcinoma.

The heart may show no change macroscopically, although showing widespread histological changes. The major coronary arteries are usually patent. Pericarditis, sometimes with effusion, is not uncommon, and sometimes the myocardium shows considerable streaky or focal fibrosis. Occasionally, the mitral or tricuspid valve is involved [21], and Libman–Sacks type of non-bacterial endocarditis has been reported [22]. Histologically, the myocardium may show focal or diffuse fibrosis, associated with degeneration or atrophy of some of the muscle fibres. Occasionally, smaller arteries and arterioles show thickening of the walls. Sometimes, an aneurysm of the myocardial wall develops, and the aorta may show adventitial fibrosis with a focal necrotizing panaortitis and valvulitis.

Involvement of the kidneys used to be the most common cause of serious morbidity and mortality, but this is now uncommon, probably because of the early and improved control of hypertension. In one of the first pathological studies, renal lesions were found in 74% of patients at autopsy [23], and in 90% in another series [24]. It has been suggested [25] that a triad of intimal proliferation of the small intralobular arteries and arterioles, fibrinoid necrosis of the walls of the afferent arterioles and sometimes the glomerular loops, together with cortical infarction characterizes renal lesions in systemic sclerosis. Vascular luminal occlusion may occur, particularly in patients with renal crisis [26]. These changes are not always found, and there are probably no absolutely specific features. Other changes include a mucoid appearance of the intimal thickening of the proximal part of the intralobular arteries. Hypercellularity of the glomeruli and fibrinoid necrosis of the basement membrane of the glomerular tufts may be found. The tubules may be atrophic and surrounded by increased connective tissue, or be dilated and full of hyaline eosinophilic material. A hyaline droplet nephrosis may occur. In the more chronic cases, glomerular hyalinization and interstitial fibrosis predominate. Immunohistological techniques show thickening of the glomerular capillary basement membrane and alteration in the reticular tissue of arterioles associated with deposits of fibrin and very occasionally with the presence of IgG and C3 [27].

The liver is usually normal in systemic sclerosis, although mild fibrosis of the portal tracts and around the bile ducts can occur. The gall bladder may be fibrosed. The spleen may show fibrinoid necrosis of arterioles and endarteritis obliterans, and endarteritis is also found in the adrenals, mammary glands, pancreas, uterus and ovaries.

Histological changes in the muscles are similar to, if not identical with, those of dermatomyositis. Muscle fibres show varying degrees of degeneration, such as loss of cross-striations, hyalinization of bundles, vacuolation and splitting, with interstitial and focal infiltration of lymphocytes. Later, sclerosis develops and the vessel walls may be thickened. There may also be some thickening of the endomysium and perimysium. The thyroid [28] and parathyroid [29] glands may be involved in the fibrotic process, and the thymus may show cortical atrophy [30].

Widening of, and vascular changes in the periodontal membrane of the teeth occur.

The CNS is rarely involved, but occasionally there may be thickening of the walls of vessels in the white matter, and meningeal lymphocytic or granulomatous infiltrates. Peripheral neurological involvement is characterized by increased collagen deposition in the epi- and perineuria, and intimal thickening of the vasa nervorum [31].

References

1 D'Angelo WA, Fries JF, Masi AT *et al.* Pathologic observations in systemic sclerosis (scleroderma). *Am J Med* 1969; **46**: 428–40.

2 Fleischmajer R, Perlish JS, Reeves JRT. Cellular infiltrates in scleroderma skin. *Arthritis Rheum* 1977; **20**: 975–84.

3 Fleischmajer R, Perlish JS, West WP. Ultrastructure of cutaneous cellular infiltrates in scleroderma. *Arch Dermatol* 1977; **113**: 1661–6.

4 Fisher ER, Rodman GP. Pathologic observations concerning the cutaneous lesion of progressive systemic sclerosis. *Arthritis Rheum* 1960; **3**: 536–45.

5 Perlish JS, Lemlich G, Fleischmajer R. Identification of collagen fibrils in scleroderma skin. *J Invest Dermatol* 1988; **90**: 48–54.

6 Rupec M, Braun-Falco O. Elektronenmikroskopische Untersuchungen über das Verhalten der kollagenfibrillen der Haut bei Sklerodermie. *Arch Klin Exp Dermatol* 1964; **218**: 543–60.

7 Braun-Falco O, Rupec M. Collagen fibrils of the scleroderma in ultra-thin skin sections. *Nature* 1964; **202**: 708–9.

8 Fleischmajer R. The collagen in scleroderma. *Arch Dermatol* 1964; **89**: 437–41.

9 Fleischmajer R, Damiano V, Nedwich A. Alteration of subcutaneous tissue in systemic scleroderma. *Arch Dermatol* 1972; **105**: 59–66.

10 Sanchez JL, Vazquez M, Sanchez NP. Vitiligo-like macules in systemic scleroderma. *Arch Dermatol* 1983; **119**: 129–33.

11 Furey NL, Schmid FR, Kwaan HC *et al.* Arterial thrombosis in scleroderma. *Br J Dermatol* 1975; **93**: 683–93.

12 Sannicandro F. Nodulare, granulomatose Riesenzellen-Arteriitis der Haut, vergesellschaftet mit Akroskleroderma. *Dermatologica* 1963; **127**: 467–75.

13 Jablonska S, Chorzelski T, Maciejowska E. The scope and limitations of the immunofluorescence method in the diagnosis of lupus erythematosus. *Br J Dermatol* 1970; **83**: 242–7.

14 Rowell NR, Scott DG. Immunohistological studies, with anti-connective tissue and anti-immunoglobulin antisera of the skin in lupus erythematosus and scleroderma. *Br J Dermatol* 1975; **93**: 431–41.

15 Winkelmann RK, Carapeto FJ, Jordon RE. Direct immunofluorescence in the diagnosis of scleroderma syndromes. *Br J Dermatol* 1977; **96**: 231–8.

16 Rossi GA, Bitterman PB, Rennard SI *et al.* Evidence for chronic inflammation as a component of the interstitial lung disease associated with progressive systemic sclerosis. *Ann Rev Respir Dis* 1985; **131**: 612–7.

17 Silver RM, Metcalf DF, Stanley JH *et al.* Interstitial lung disease in scleroderma. *Arthritis Rheum* 1984; **27**: 1254–62.

18 Wilson RJ, Rodman GP, Robin ED. An early pulmonary physiologic abnormality in progressive systemic sclerosis (diffuse scleroderma). *Am J Med* 1964; **36**: 361–9.

19 Haggani MT, Holti G. Systemic sclerosis with pulmonary fibrosis and oat cell carcinoma. *Acta Derm Venereol (Stockh)* 1973; **53**: 369–74.

20 Tomkin CH. Systemic sclerosis associated with carcinoma of the lung. *Br J Dermatol* 1969; **81**: 213–6.
21 Oram S, Stokes W. The heart in scleroderma. *Br Heart J* 1961; **23**: 243–59.
22 von Spuhler O, Morandi L. Sklerodermie und ihre Beziehungen zu Libman–Sacks-Syndrome, Dermatomyositis und rheumatischen Infektionskreis. *Helv Med Acta* 1949; **16**: 147–63.
23 Piper WN, Helwig EB. Progressive systemic sclerosis. *Arch Dermatol* 1955; **72**: 535–46.
24 Cannon PJ, Hassar M, Case DB *et al.* The relationship of hypertension and renal failure in scleroderma to structural and functional abnormalities of the renal cortical circulation. *Medicine* 1974; **53**: 1–46.
25 Levine RJ, Boshell BR. Renal involvement in progressive systemic sclerosis (scleroderma). *Ann Intern Med* 1960; **52**: 517–29.
26 Trostle DC, Bedetti CD, Steen VD *et al.* Renal vascular histology and morphometry in systemic sclerosis. *Arthritis Rheum* 1988; **31**: 393–400.
27 Scott DG, Rowell NR. Immunohistological studies of the kidney in systemic lupus erythematosus and systemic sclerosis using antisera to IgG, C3, fibrin, and human renal glomeruli. *Ann Rheum Dis* 1974; **33**: 473–81.
28 Serup J, Hagdrup H. Thyroid hormones in generalized scleroderma. *Acta Derm Venereol (Stockh)* 1986; **66**: 35–8.
29 Sentochnik DE, Hoffman GS. Hypoparathyroidism due to progressive systemic sclerosis. *J Rheumatol* 1988; **15**: 711–3.
30 Carter J, Ewen SWB, Gray E *et al.* The thymus in systemic sclerosis. *J Pathol* 1973; **110**: 97–100.
31 Di Trapani C, Tulli A, Lacarva A. Peripheral neuropathy in the course of progressive systemic sclerosis. *Acta Neuropathol* 1986; **72**: 103–10.

Natural history. In the majority of patients, the onset is with Raynaud's phenomenon, although this may have been present for many years, and the cutaneous changes occur after an interval. This is much shorter in males—in whom it is usually under a year—than in females, in whom it is usually approximately 5 years, but may be as long as 30 years [1]. Occasionally, Raynaud's phenomenon and cutaneous sclerosis are noticed at the same time, and sometimes Raynaud's phenomenon may follow the onset of cutaneous or other manifestations, or be absent. The risk of anyone with Raynaud's phenomenon developing systemic sclerosis is relatively small, although it seems to be greater in males than in females [2]. Sclerodactyly may be found in approximately 10% of patients with Raynaud's disease, but systemic sclerosis occurs in approximately 4% of patients with this combination [3]. The differentiation between severe Raynaud's disease and early systemic sclerosis is difficult, but may be aided by nail fold capillaroscopy and the presence or absence of autoantibody [2]. The main cause of mortality used to be renal disease, but recent studies show a preponderance of cardiovascular problems, with coronary and cerebrovascular events [4]. In addition to the microvascular changes described, it is now apparent that large vessel changes similar to atherosclerosis are also increased in systemic sclerosis [5].

References

1 Rowell NR. The prognosis of systemic sclerosis. *Br J Dermatol* 1976; **95**: 57–60.
2 Veale D, Belch JJF. Management of Raynaud's phenomenon. *Rheumatol Rev* 1993; **2**: 133–45.
3 Farmer RG, Gifford RW, Hines EA. Raynaud's disease with sclerodactylia. *Circulation* 1961; **23**: 13–5.
4 Bryan C, Knight C, Black CM, Silman AJ. Prediction of 5-year survival following presentation with scleroderma: development of a simple model using three disease factors at first visit. *Arthritis Rheum* 1999; **42**: 2660–5.
5 Ho M, Veale D, Eastmond C *et al*. Macrovascular disease and systemic sclerosis. *Ann Rheum Dis* 2000; **59**: 39–43.



Fig. 51.61 Systemic sclerosis: typical beaked nose, telangiectasia and radial furrowing round the mouth.

Clinical features. The earliest feature is usually, but not invariably, Raynaud's phenomenon. Other early presenting symptoms and signs include swelling of the hands in approximately 15% of patients, swelling of joints, ulceration of the fingers, whitlows and even gangrene. Occasionally, the diagnosis may be made in a patient presenting with leg ulcers or calcinosis cutis. With the increased availability of laser treatments, some patients' first presentation is for treatment of telangiectasia. Less common early symptoms include gastro-oesophageal reflux and dysphagia; constipation, diarrhoea and abdominal pain are usually late features.

Cutaneous changes. The hands and face are the most frequently involved, but the changes may extend proximally to involve the forearms and upper arms, usually but not always in a continuous fashion. The fingers may be oedematous and swollen, and the skin feels tight and has a shiny appearance. With increasing severity, the skin becomes immovable or hidebound. The clinical impression of thickness and toughness of the skin is enhanced because of binding down of the skin to deeper structures. The collagen content is decreased but the density is normal [1]. Sometimes, the chest becomes tight, shiny and pigmented. The facial appearance in a well-developed case is characteristic. The forehead is smooth and shiny, the skin is bound down and hard, the lines of expression are smoothed out and the nose becomes small and pinched (Fig. 51.61). The mouth opening is constricted and radial furrows appear, giving a pursed appearance (Fig. 51.62). The lower eyelids cannot be depressed by the fingers to show the conjunctivae, because of atrophy of the tissues. Very rarely, periorbital oedema

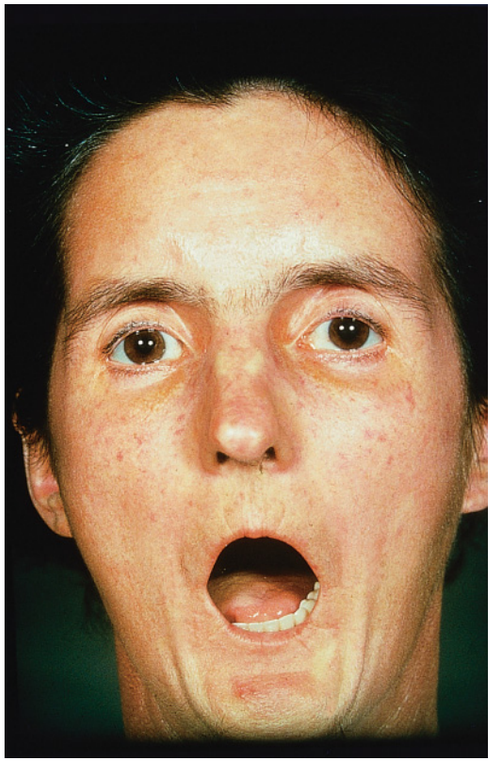


Fig. 51.62 Systemic sclerosis: restricted mouth opening.



Fig. 51.63 Systemic sclerosis: mandibular atrophy. (Courtesy of Dr J. Cotterill, Leeds, UK.)

can occur [2]. Small mat-like telangiectases are frequently found on the face. Sometimes, the changes on the face are minimal and detected only by an astute observer after the diagnosis has been suspected because of other changes. Mandibular atrophy can occur (Fig. 51.63). Chondrodermatitis nodularis helicis was found in three of 21 patients with limited cutaneous disease [3].

Just as the face may be involved to a greater or lesser extent, the hands may also show great variability in their appearance (Fig. 51.64). Sometimes, in the early stages, only a little atrophy can be seen. Occasionally, the fingers and hands are swollen and rather tumid, and there is difficulty obtaining full extension. The terminal phalanges may be bulbous. Later, however, the changes are easily recognized. Atrophy occurs first in the pulps of the fingers, and small painful ulcers are formed, which heal leaving depressed scars (Fig. 51.65). Pitted scars occur in over one-third of patients, not only on the tips of the fingers but also in a linear distribution on the ulnar border of the thumb and radial borders of the index and middle fingers, as well as the dorsa of the fingers over the joints [4]. Later, sclerosis of the overlying skin of the fingers develops, giving the fingers a smooth shiny tapered appearance, with the nails curving over the atrophic phalanges. Later still, the nails become very small and the whole of the distal part of the finger atrophies. The nail folds may show ragged cuticles. Pterygium inversum unguis-like changes are sometimes found [5]. Slow-healing whitlows and paronychia are common, and ulcers may also occur over the knuckles. Later, the atrophy and sclerosis extends to involve the whole hand, which is held in semi-flexion, full extension of the fingers and metacarpal joints being impossible. Gangrene of the fingers is not uncommon, and may occur surprisingly early in the disease. It does not necessarily indicate a poor prognosis. Digital arteriography confirms narrowing of the digital arteries [6].



Fig. 51.64 The hands in systemic sclerosis: oedematous phase.

Telangiectases are often found on the palms and on the rest of the hands. Calcium deposits occur in the skin of the fingers and hands, and may break down to discharge chalky material. Calcinosis may also be found around the elbow, where the olecranon bursa may be involved. Erythema may be seen on the thenar and hypothenar eminences. Hyperkeratotic plaques over the phalan-



Fig. 51.65 Systemic sclerosis: healed ulceration of the fingertips.



Fig. 51.66 Systemic sclerosis: 'cobblestone' appearance on the dorsum of the hand.

ges may indicate amyloid material deposited in the dermal papillae [7]. Multiple small papules of lymphangiectasia may occur in 'hidebound' skin because of obstruction of lymphatic channels by the sclerosing process (Fig. 51.66) [8]. Ivory-coloured subcutaneous nodules 3–20 mm in diameter occur rarely on the trunk and limbs. Histology shows fibromatous changes [9] or fibrinoid necrosis [10].

Similar, although less severe changes occur on the feet, and not infrequently the tips of the toes become black with incipient gangrene. The feet become encased in tight, firm skin with mottled patches of pigmentation and atrophy. These changes may extend up the legs and be present on the thighs.

In a series of patients at Leeds, changes on the hands occurred in 95% of cases, on the face in 90%, beneath the clavicles in 30% and on the feet in 15%. The changes on the face, hands and feet tend to be progressive, but changes on the trunk have been seen to regress over the years. Dilated nail fold capillaries visible without a lens occur in approximately 10% of patients and, occasionally, heliotrope cyanosis around the eye suggests a diagnosis of dermatomyositis. There is some evidence that the degree of nail fold capillary dilatation correlates with the severity of organ involvement [11], but this has not been confirmed [12]. Nail fold capillary abnormalities have been correlated with Raynaud's phenomenon, digital pitted scars and low finger temperature [13]. Using wide-field microscopy, the capillaries are enlarged and distorted. There is loss of capillaries with disruption of the capillary bed in approximately 90% of patients. These features may indicate those patients with Raynaud's phenomenon who will go on to develop systemic sclerosis [14,15], but do not distinguish between different connective tissue diseases [16]. Transient nodules resembling erythema nodosum occasionally occur; the histology of these shows panniculitis and endarteritis.



Fig. 51.67 Systemic sclerosis: pigmentation of the abdomen.

Telangiectases varying from 2 to 20 mm in diameter, blanching on pressure and refilling from several different foci, occur in 75% of patients. They are found mainly on the face, lips, mouth, upper trunk and hands, but may extend as far as the upper thighs. These mat-like telangiectases are not absolutely diagnostic of systemic sclerosis. Pigmentation occurs in approximately 50% of the patients, most frequently on the face, and to a lesser extent on the legs, thighs, lower abdomen (Fig. 51.67), axillary folds and dorsa of the hands. Occasionally, the pigmentation is so gross as to lead to a suspicion of Addison's disease [17], and sometimes gives a mottled appearance. Dense warty pigmentation in the axillae can resemble acanthosis nigricans [18]. Leg ulcers occur in 40% of patients and are difficult to heal. Livedo reticularis [19] and small white areas of atrophie blanche develop around the ankles, even without ulceration. These features can occur in patients without hypertension. A case has been reported of large soft cystic lesions over the interphalangeal joints of both hands. Aspiration revealed mucoid material, and the histology suggested focal mucinosis [20]. Rarely, papular and nodular mucinosis may occur and may be a presenting feature [21]. Lesions resembling acrokeratoelastoidosis have been described [22].

References

1 Black MM, Bottoms E, Shuster S. Skin collagen content and thickness in systemic sclerosis. *Br J Dermatol* 1970; **83**: 552–5.

2 Dorwart BB. Periorbital edema in progressive systemic sclerosis. *Ann Intern Med* 1974; **80**: 273.

3 Bottomley WW, Goodfield MJD. Chondrodermatitis nodularis helicis occurring with systemic sclerosis: an under-reported association? *Clin Exp Dermatol* 1994; **19**: 219–20.
4 Maeda M, Matubara K, Hirano H *et al.* Pitting scars in progressive systemic sclerosis. *Dermatology* 1993; **187**: 104–8.
5 Patterson JW. Pterygium inversum unguis-like changes in scleroderma. *Arch Dermatol* 1977; **113**: 1429–30.
6 Dabich L, Bookstein JJ, Zweiffer A *et al.* Digital arteries in patients with scleroderma. *Arch Intern Med* 1972; **130**: 708–14.
7 Black MM. Primary localized cutaneous amyloidosis in systemic sclerosis. *Trans St John's Hosp Dermatol Soc* 1971; **57**: 177–80.
8 Tuffanelli DL. Lymphangiectasis due to scleroderma. *Arch Dermatol* 1975; **111**: 1216.
9 Bettley FR, Seville RH. Nodular scleroderma. *Proceedings of the 10th International Congress on Dermatology*. London: BMA, 1952: 479–81.
10 Kennedy C, Leigh IM. Systemic sclerosis with subcutaneous nodules. *Br J Dermatol* 1979; **101**: 93–6.
11 Maricq HR, Spencer-Creen G, LeRoy EC. Skin capillary abnormalities as indicators of organ involvement in scleroderma, Raynaud's syndrome and dermatomyositis. *Am J Med* 1976; **61**: 862–70.
12 Statham BN, Rowell NR. Quantification of the nail fold capillary abnormalities in systemic sclerosis and Raynaud's syndrome. *Acta Derm Venereol (Stockh)* 1986; **66**: 139–43.
13 Ohtsuka T, Ishikawa H. Statistical definition of nail fold capillary pattern in patients with systemic sclerosis. *Dermatology* 1994; **188**: 286–9.
14 Lee P, Sarkozi J, Bookman AA *et al.* Digital blood flow and nail fold capillary microscopy in Raynaud's phenomenon. *J Rheumatol* 1986; **13**: 564–9.
15 Maricq HR, LeRoy EC, D'Angelo WA *et al.* Diagnostic potential of *in vivo* capillary microscopy in scleroderma and related disorders. *Arthritis Rheum* 1980; **23**: 183–90.
16 Houtman PM, Kallenberg CGM, Fidler V *et al.* Diagnostic significance of nailfold capillary patterns in patients with Raynaud's phenomenon. *J Rheumatol* 1986; **3**: 556–63.
17 Talbott JH, Gall EA, Consolazio WV *et al.* Dermatomyositis with scleroderma, calcinosis and renal endarteritis associated with focal cortical necrosis. *Arch Intern Med* 1939; **63**: 476–96.
18 Clinicopathological Conference. A case of scleroderma with pseudoacanthosis nigricans. *BMJ* 1966; **ii**: 1642–5.
19 Thomas JR, Winkelmann RH. Vascular ulcers in scleroderma. *Arch Dermatol* 1983; **119**: 803–7.
20 Marzano AV, Berti E, Gasparini G *et al.* Unique digital skin lesions associated with systemic sclerosis. *Br J Dermatol* 1997; **136**: 598–600.
21 Van Zander J, Shaw JC. Papular and nodular mucinosis as a presenting sign of progressive systemic sclerosis. *J Am Acad Dermatol* 2002; **46**: 304–6.
22 Tajima S, Tanaka N, Ishibashi A, Suzuki K. A variant of acrokeratoelastoidosis in systemic scleroderma: report of 7 cases. *J Am Acad Dermatol* 2002; **46**: 767–70.

Systemic sclerosis without skin involvement [1–4]. Although skin lesions and Raynaud's phenomenon usually precede systemic changes, there is no doubt that occasionally the situation is reversed. In these cases, diagnosis may be difficult until the disease has progressed further to give characteristic changes in other organs.

References

1 Crown S. Visceral scleroderma without skin involvement. *BMJ* 1961; **ii**: 1541–3.
2 Herington JL Jr. Scleroderma as a cause of small bowel obstruction: successful treatment by intestinal resection. *AMA Arch Surg* 1959; **78**: 17–25.
3 McBrien DT, Mummer HEL. Steatorrhoea in progressive systemic sclerosis (scleroderma). *BMJ* 1962; **2**: 1653–4.
4 Rodnan GP, Fennell RH. Progressive systemic sclerosis sine scleroderma. *JAMA* 1962; **180**: 665–70.

Calcinosis. Weber [1] described calcinosis in scleroderma long before Thibierge and Weissenbach [2], whose names are usually associated with the syndrome. Calcification in systemic sclerosis occurs most commonly (25%) in the fingers, especially on the palmar aspects of the terminal phalanges. It is less common than absorption of the phalanges, but sometimes occurs in the absence of any radiological bone change. Digital calcification is approximately 10 times as common in females as in males. Calcification also occurs in the soft tissues around the iliac crests, alongside the spine between the vertebrae, around the knees, on the dorsa of the feet and around the elbows. Occasionally, ulceration of superficial nodules occurs, with discharge of chalky material. Deposits tend to be of considerable size and less diffuse than the calcification seen in the muscles of healed dermatomyositis. Calcification may occur in the internal organs. A suggestion that warfarin may inhibit and reverse calcification requires confirmation [3].

References

1 Weber H. Case presentation. *Korrephl Schweizer Aerzte* 1878; **8**: 623.
2 Thibierge G, Weissenbach R. Concretions calcaires sous-cutanées et sclerodermie. *Ann Dermatol Syphilol* 1911; **2**: 129.
3 Moore SE, Jump AA, Smiley JD. Effect of warfarin sodium therapy on excretion of 4-carboxy-l-glutamic acid in scleroderma, dermatomyositis, and myositis ossificans progressiva. *Arthritis Rheum* 1986; **29**: 344–51.

Bone changes. Absorption of the terminal phalanges is a feature of both systemic sclerosis and Raynaud's phenomenon, but systemic sclerosis is the only condition in which phalangeal absorption is associated with calcinosis (Fig. 51.68) [1]. Approximately 70% of patients show absorption, which may be minimal and only involve one terminal phalanx, or be gross and involve several phalanges, including the middle or even proximal phalanges. An erosive arthropathy, with 'pestle and mortar' deformity of the distal interphalangeal joints, resembles that seen in psoriatic arthropathy [2]. It must also be distinguished from gouty arthritis [3]. Pain in the temporomandibular area and a grinding sensation on chewing may be associated with bone resorption of the angle of the mandible [4] and zygomatic arches [5]. Other bone changes in systemic sclerosis include an increased intraosseous deposition



Fig. 51.68 Systemic sclerosis: terminal absorption of the phalanges and calcinosis.

of calcium [6,7] and osteopoikilosis, a rare condition in which multiple small islands of dense bone occur at the epiphyses and metaphyses [8–10]. Osteolysis also occurs in the distal end of the radius and ulna, humerus [11], acromioclavicular joint, ribs and cervical spine [12]. Avascular necrosis of the head of the femur, presumably resulting from vasculitis, has been described [13,14].

References

1 Yune HY, Vix VA, Klatte EC. Early fingertip changes in scleroderma. *JAMA* 1971; **215**: 1113–6.
2 Wild W, Beetham WP. Erosive arthropathy in systemic scleroderma. *JAMA* 1975; **232**: 511–2.
3 Durback MA, Schumacher HR Jr. Acute gouty arthritis in four patients with systemic sclerosis. *J Rheumatol* 1988; **15**: 1503–5.
4 Seifert MH, Steigerwald JC, Cliff MM. Bone resorption of the mandible in progressive systemic sclerosis. *Arthritis Rheum* 1975; **18**: 507–12.
5 Ryatt KS, Hopper FE, Cotterill JA. Mandibular resorption in systemic sclerosis. *Br J Dermatol* 1982; **107**: 711–4.
6 Edeiken L. Scleroderma with sclerodactylia. *Am J Roentgenol* 1929; **22**: 42–4.
7 Podkaminsky NA. Acrosclerosis hyperplastica intraossea. *Am J Roentgenol* 1937; **38**: 889–92.
8 von Bernuthe F. Über Sklerodermie, Osteopoikilie und Kalkgicht im Kindesalter. *Z Kinderheilk* 1932; **54**: 103–16.
9 Tuffanelli DL, Winkelmann RK. Systemic scleroderma. *Arch Dermatol* 1961; **84**: 359–71.
10 Weissman C. Scleroderma associated with osteopoikilosis. *Arch Intern Med* 1958; **101**: 108–13.
11 Khonstanteen I, Wright B, Russell ML. Localized bone resorption in systemic sclerosis. *J Rheumatol* 1988; **15**: 1435–7.
12 Haverbush TJ, Wilde AH, Hawk WA *et al.* Osteolysis of the ribs and cervical spine in progressive systemic sclerosis (scleroderma). *J Bone Joint Surg Am* 1974; **56**: 637–40.
13 Taccari E, Spadaro A, Riccieri V *et al.* Avascular necrosis of the femoral head in long-term follow-up of systemic sclerosis: report of two cases. *Clin Rheumatol* 1989; **8**: 386–92.
14 Wilde AH, Mankin HJ, Rodnan CP. Avascular necrosis of the femoral head in scleroderma. *Arthritis Rheum* 1970; **13**: 445–7.

Pulmonary involvement. Lung involvment predominantly represents diffuse pulmonary fibrosis associated with diffuse disease or pulmonary hypertension, which is more associated with limited disease or CREST syndrome [1]. Symptoms may only develop some time after the lung disease, so they are a poor predictor of lung involvement. Dyspnoea on exertion is usually the first symptom, and this may progress until the patient is distressed even at rest. Cough, usually without sputum, is also a common symptom, and may be troublesome at night, suggesting aspiration; haemoptysis is rare. Cyanosis and occasionally finger clubbing may occur in patients with severe involvement, and these signs may indicate cor pulmonale. Recurrent episodes of pneumothorax, pleurisy, pulmonary effusion and pneumonia are less common features. Considerable loss of weight may also be a prominent feature at this stage. The earliest change consists of diffuse reticular shadowing extending from the cardiac borders to the peripheral and basal parts of the lungs, usually in the lower lung fields. Sometimes, nodular changes are seen, and occasionally the apices are involved (Fig. 51.69). Cystic changes are frequent. The cysts are usually small, but if extensive the appearances are those of 'honeycomb lung'. Pneumothorax may occur [2]. Pulmonary calcification has rarely been reported [3,4], as has telangiectasia [5].

Pulmonary function is frequently abnormal when radiology shows no abnormality [6]. A sensitive test of pulmonary function

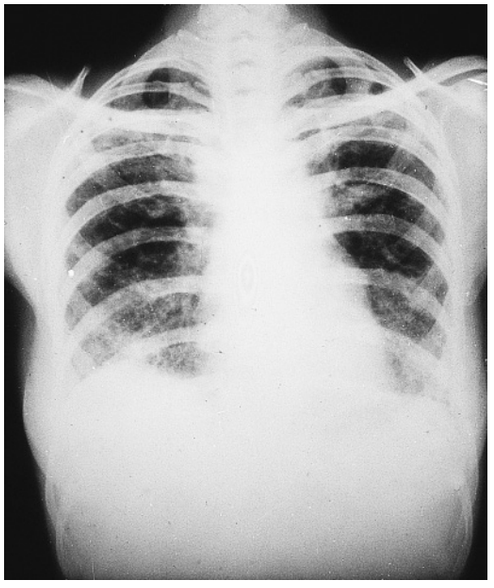


Fig. 51.69 Pulmonary involvement in systemic sclerosis: nodules are prominent, particularly in the upper zones, and there is some reticulation in the lower zones.

is the estimation of diffusing capacity (transfer factor); this test is impaired in 75% of patients. The DL_{co} may give an indication of survival; if it is less than 40% there is a 10% 5-year survival, compared with 75% if it is greater than 40%. Pulmonary involvement is more frequent in more severe and rapidly progressing disease, especially in males [7], but occurs in the CREST syndrome [8], and may precede cutaneous changes [9]. The presence of antihistone and antitopoisomerase (Scl-70) are associated with pulmonary fibrosis [10]. Small airway disease may precede measurable impairment of gas diffusion [11]. In severely affected cases, the vital capacity and maximum breathing capacity are both abnormal. Serial observations of pulmonary function may be helpful [12]. Pulmonary hypertension, sometimes severe, can occur, and does not necessarily correlate with tests of pulmonary function [1]. It is not yet possible to say whether impairment of pulmonary diffusion is caused by vascular changes or thickening of the alveolar wall and interstitial tissue. Pulmonary hypertension tends to be progressive and fatal, although new therapeutic options are available. Lung radiography may be normal in the face of symptoms and abnormal lung function, so the investigation of choice for pulmonary fibrosis is high-resolution CT scan, which is non-invasive. One series showed that high-resolution CT was 24% more accurate than radiography in demonstrating minimal evidence of fibrosing alveolitis [13]. The role of bronchoalveolar lavage is still debatable, but in expert centres it may provide additional information.

References

1 Antoniou KM, Wells AU. Scleroderma lung disease: evolving understanding in light of newer studies. *Curr Opin Rheumatol* 2008; **20:** 686–91.
2 Lang B, Ortleib H, Meske S *et al.* Progressive systemic sclerosis presenting with spontaneous pneumothorax. *J Rheumatol* 1989; **16**: 254–6.
3 Puddu V. Un caso di sclerodermia con calcificazioni operato di paratiroidectomia. *Policlinico* 1934; **41**: 1801–7.

4 Ravault PP, Moulin G, Moinex R. Apropos of a case of multiple pulmonary calcifications during scleroderma. *Lyon Med* 1960; **92**: 425–34.
5 Newman ED, Harrington TM, Amoroso A. Haemoptysis secondary to respiratory tract telangiectasia in CREST syndrome. *J Rheumatol* 1988; **15**: 1874–5.
6 Steen VD, Graham G, Conte C *et al.* Isolated diffusing capacity reduction in systemic sclerosis. *Arthritis Rheum* 1992; **35**: 765–70.
7 König G, Luderschmidt C, Hammer C *et al.* Lung involvement in scleroderma. *Chest* 1984; **85**: 318–24.
8 Steen VD, Owens CR, Fino CJ *et al.* Pulmonary involvement in systemic sclerosis (scleroderma). *Arthritis Rheum* 1985; **28**: 759–67.
9 Lomeo RM, Cornella RJ, Schabel SI *et al.* Progressive systemic sclerosis sine scleroderma presenting as pulmonary interstitial fibrosis. *Am J Med* 1989; **87**: 525–7.
10 Sato S, Ihn H, Kikuchi K *et al.* Antihistone antibodies in systemic sclerosis. *Arthritis Rheum* 1994; **37**: 391–4.
11 Guttadauria M, Ellman H, Emmanuel IG *et al.* Pulmonary function in scleroderma. *Arthritis Rheum* 1977; **20**: 1071–9.
12 Schneider PD, Wise RA, Hochberg MC *et al.* Serial pulmonary function in systemic sclerosis. *Am J Med* 1982; **73**: 385–94.
13 Strickland B, Strickland NH. The value of high definition, narrow section computed tomography in fibrosing alveolitis. *Clin Radiol* 1988; **39**: 589–94.

Involvement of the gastrointestinal tract [1]. Macroglossia may occur. The oesophagus is involved in approximately 75% of all patients and is the most frequent part of the gastrointestinal tract to be affected. Oesophageal manometry and radionuclide transit are better than radiography for showing motor abnormalities [2,3], although the changes are non-specific [4]. Although dysphagia is usually regarded as being the predominant symptom, this is not correct, as symptoms of oesophageal reflux are twice as common. The typical radiological appearance is that of an atonic dilated oesophagus, which contains air in the resting state (Fig. 51.70).

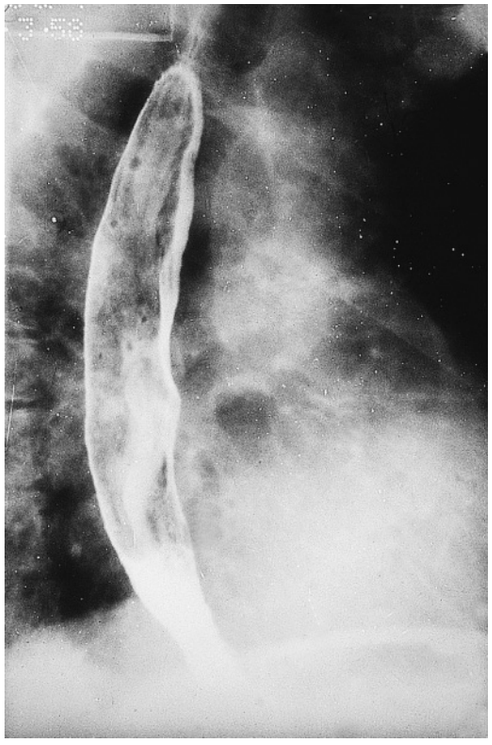


Fig. 51.70 The typical atonic, dilated, air-containing oesophagus in systemic sclerosis.

Oesophageal dilatation and abnormal peristalsis do not necessarily occur together. Stricture of the lower end of the oesophagus occurs in just over 10% of patients, is not necessarily related to gastro-oesophageal reflux or hernia, and can occur without any symptoms of dysphagia. Dysphagia is much more commonly the result of loss of propulsive activity in the oesophagus, and may occasionally be related to candidal overgrowth [5]. Hiatus hernia occurs in approximately 25% of patients. It is important to remember that approximately four out of every 10 patients with radiological changes have no symptoms. Carcinoma of the oesophagus has been reported [6,7]. Occasionally, dysphagia may be localized to the neck because of thickening of the pharyngo-oesophageal muscles [8].

Oesophageal aperistalsis has been reported in SLE and Raynaud's syndrome [9,10], but whenever aperistalsis is found systemic sclerosis must be suspected. Diffuse spasm may be detected by oesophageal manometry in approximately 5% of patients with systemic sclerosis [11].

The stomach shows dilatation and lack of peristalsis in approximately 6% of cases. Involvement of the stomach may be more common in Asians [12]. Carcinoma of the stomach has been reported [13]. Bleeding can occur from telangiectasia in all parts of the gastrointestinal tract, especially the stomach [14]. Systemic sclerosis is one cause of gastric antral vascular ectasia—the so-called 'watermelon stomach', because of the striped appearance on endoscopy. Gastric bleeding may occur at any time and may precede other signs of systemic sclerosis [15].

The duodenum shows changes of dilatation and lack of peristalsis in approximately one-third of patients. This does not appear to be a result of excess collagen deposition [16]. The changes are most pronounced in the second and third parts. Duodenal ulceration has been reported, but is probably not significant in comparison with its incidence in the normal population.

Intestinal involvement is infrequently noted in patients who have no relevant symptoms, but colicky abdominal pain and abdominal distension, with a pattern of distended loops visible through the abdominal wall, together with diarrhoea or, alternatively, constipation, may lead to a clinical diagnosis of obstruction, and death may follow from paralytic ileus. Volvulus of the small intestine may occur [17]. There may be bleeding from telangiectases. Radiological changes consist of dilated loops of bowel, with impairment of peristalsis and segments of normal or narrowed intestine. Strictures are rare. Jejunal sacculation has been reported [18,19]. Radiological changes occurred in approximately 10% of patients in the Leeds series, but others [20] found changes in 57%. Intestinal motility studies may be useful in determining changes in the small bowel [21]. If the abdomen is opened, distended loops of bowel may be seen showing a blue-grey serosal surface with numerous dilated lacteals. Small intestine involvement, determined by jejunal biopsy, small bowel radiology and tests for bacterial overgrowth and malabsorption, occurs in 55% of patients [18].

Steatorrhoea, malabsorption of glucose, calcium, vitamin B_{12} and folic acid may occasionally occur. It is important to remember that malabsorption of one or more of these substances may occur in the presence of normal fat absorption. Osteomalacia or skin changes have not been seen as the result of malabsorption.

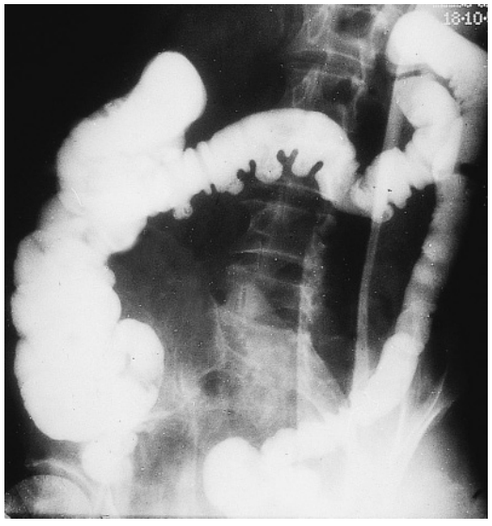


Fig. 51.71 Wide-mouthed diverticula of the colon in systemic sclerosis.

Excessive enteric loss of protein is sometimes a feature [22]. There is evidence [18] that bacterial overgrowth in the intestinal lumen as a result of stagnation because of abnormal peristalsis is a major cause of malabsorption in systemic sclerosis, and this may be corrected by therapy with tetracycline. Intestinal permeability is normal [23]. Pancreatic function is abnormal in 15% of cases [24], and death may occur from pancreatic necrosis [25].

Pneumatosis cystoides intestinalis may complicate small intestine involvement [26]. Patients present with recurrent acute or subacute intestinal obstruction [27] and rupture of cysts can cause pneumoperitoneum [28]. Treatment with respiration of high concentrations of oxygen has been successful [29].

The colon is frequently involved. In the Leeds series it occurred in 43% of cases. The patients may complain of constipation or diarrhoea. The most striking radiological change is the presence of wide-mouthed diverticula, best demonstrated on post-evacuation roentgenograms (Fig. 51.71). They usually occur on the inferior surface of the transverse colon and in the descending colon, which may be dilated and atonic; occasionally, the appearance may resemble that of ulcerative colitis [30]. Perforation of colonic diverticula may result in death from peritonitis [31]. Volvulus has been reported [32]. Colonic telangiectasia with consequent iron-deficiency anaemia may occur [33]. The mucosa of the colon has been described as being pale, dry and rather rigid on sigmoidoscopy [34], but this must be very uncommon. Anorectal pressure measurements show abnormal motility in 74% of patients [35]; symptoms are very much less common. Rectal prolapse and faecal incontinence may result. Primary exudative ascites has been reported [36].

References

1 Marie I. Gastrointestinal involvement in systemic sclerosis. *Presse Med* 2006; **35**: 1952–65.

2 Davidson A, Russell C, Littlejohn CO. Assessment of oesophageal abnormalities in progressive systemic sclerosis using radionuclide transit. *J Rheumatol* 1985; **12**: 472–7.

3 Weihrauch TR, Korting CW. Manometric assessment of oesophageal involvement in progressive systemic sclerosis, morphoea and Raynaud's disease. *Br J Dermatol* 1982; **107**: 325–32.

4 Schneider HA, Yonker RA, Longley S *et al.* Scleroderma oesophagus: a non-specific entity. *Ann Intern Med* 1984; **100**: 848–50.

5 Geirsson AJ, Akesson A, Gustafson T *et al.* Cineradiography identifies oesophageal candidiasis in progressive systemic sclerosis. *Clin Exp Rheumatol* 1989; **7**: 43–6.

6 Kilton L, Gottlieb JA. Scleroderma and carcinoma of the oesophagus. *Lancet* 1971; **ii**: 707.

7 Segel MC, Campbell WL, Medsger TAJR *et al.* Systemic sclerosis (scleroderma) and esophageal adenocarcinoma: is increased patient screening necessary? *Gastroenterology* 1985; **89**: 485–8.

8 Rajapakse CNA, Bancewicz J, Jones CJP *et al.* Pharyngo-oesophageal dysphagia in systemic sclerosis. *Ann Rheum Dis* 1981; **40**: 612–4.

9 Ramirez-Mata M, Reyes P, Alarcón-Segovia D *et al.* Oesophageal motility in systemic lupus erythematosus. *Am J Dig Dis* 1974; **19**: 132–6.

10 Stevens MB, Hookman P, Siegel CI *et al.* Aperistalsis disorders and Raynaud's phenomenon. *N Engl J Med* 1964; **270**: 1218–22.

11 Garrett JM, Winkelmann RH, Schlegel JF *et al.* Oesophageal deterioration in scleroderma. *Mayo Clin Proc* 1971; **46**: 92–6.

12 Tay CH, Khoo OT. Progressive systemic sclerosis (scleroderma). *Aust Ann Med* 1970; **2**: 145–50.

13 Rogé J, Delavierre P, Durand H *et al.* Sclérodermie et cancer d'estomac. *Semin Hôp Paris* 1971; **47**: 1211–3.

14 Rosekrans PCM, de Rooy DJ, Bosman FT *et al.* Gastrointestinal telangiectasia as a cause of severe blood loss in systemic sclerosis. *Endoscopy* 1980; **12**: 200–4.

15 Carbone LD, McKown KM, St Hilaire RJ *et al.* Scleroderma and the watermelon stomach. *Ann Rheum Dis* 1996; **55**: 560–1.

16 Hendel L, Ammitzbooll T, Dirksen K *et al.* Collagen components in the duodenal and rectal mucosa in progressive systemic sclerosis and other disease. *Acta Derm Venereol (Stockh)* 1986; **66**: 220–4.

17 Hendy MS, Torrance HB, Warnes TW. Small-bowel volvulus in association with progressive systemic sclerosis. *BMJ* 1979; **i**: 1051–2.

18 Cobden I, Axon ATR, Choneim AT *et al.* Small intestinal bacterial overgrowth in systemic sclerosis. *Clin Exp Dermatol* 1980; **5**: 37–42.

19 Queloz IM, Woloshin JH. Sacculation of the small intestine in scleroderma. *Radiology* 1972; **105**: 513–5.

20 Bluestone R, MacMahon M, Dawson JM. Systemic sclerosis and small bowel involvement. *Gut* 1969; **10**: 185–93.

21 Treacy WL, Bunting WL, Gambill EE *et al.* Scleroderma presenting as obstruction of the small bowel. *Proc Staff Meetings Mayo Clin* 1962; **37**: 607–16.

22 Greenberger NJ, Dobbins WO, Ruppert RD *et al.* Intestinal atony in progressive systemic sclerosis (scleroderma). *Am J Med* 1968; **45**: 301–8.

23 Cobden I, Rothwell J, Axon ATR *et al.* Small intestinal structure and passive permeability in systemic sclerosis. *Gut* 1980; **21**: 293–8.

24 Cobden I, Axon ATR, Rowell NR. Pancreatic exocrine function in systemic sclerosis. *Br J Dermatol* 1981; **105**: 189–93.

25 Abraham AA, Joos A. Pancreatic necrosis in progressive systemic sclerosis. *Ann Rheum Dis* 1980; **39**: 396–8.

26 Quiroz ES, Flannery MT, Martinez EJ, Warner EA. Pneumatosis cystoides intestinalis in progressive systemic sclerosis. *Am J Med Sci* 1995; **310**: 252–5.

27 Williamson DM, Bell LC. Pneumatosis cystoides intestinalis in systemic sclerosis. *Br J Dermatol* 1976; **94**: 85–8.

28 Meihoff WE, Hirschfield JS, Kem F. Small intestinal scleroderma with malabsorption and pneumatosis cystoides intestinalis. *JAMA* 1968; **204**: 854–8.

29 Watson RDS. Successful treatment of pneumatosis coli with oxygen. *BMJ* 1976; **i**: 199.

30 Wallace HJ. Ulcerative colitis, systemic sclerosis and necrobiosis. *Br J Dermatol* 1974; **91** (Suppl. 10): 45–6.

31 Robinson JC, Teitelbaum SL. Stercoral ulceration and perforation of the sclerodermatous colon: report of two cases and review of the literature. *Dis Col Rectum* 1974; **17**: 622–32.

32 Budd DC, Nirdlinger EL, Sturtz DL *et al.* Transverse colon volvulus associated with scleroderma. *Am J Surg* 1977; **113**: 370–2.

33 Baron M, Srolovitz H. Colonic telangiectasias in a patient with progressive systemic sclerosis. *Arthritis Rheum* 1986; **29**: 282–5.

34 Cullinan ER. Discussion on scleroderma. *Proc R Soc Med* 1953; **46**: 507–11.

35 Hamel-Roy J, Devroede C, Arhan P *et al.* Comparative oesophageal and anorectal motility in scleroderma. *Gastroenterology* 1985; **88**: 1–7.
36 Todd DJ, McMillan C. Primary exudative ascites in systemic sclerosis. *Int J Dermatol* 1992; **31**: 451–2.

Hepatic involvement. The liver is usually normal in systemic sclerosis, although cirrhosis and portal hypertension are occasionally found. It is by no means substantiated that such fibrosis is caused by systemic sclerosis. Bleeding from oesophageal varices may occur [1]. Systemic sclerosis has been reported in 17% of patients with primary biliary cirrhosis [2,3]. Ascites can occur without liver disease [4].

References

1 Calvert RJ, Barling B, Sopher M *et al.* Systemic scleroderma with portal hypertension. *BMJ* 1958; **i**: 22–5.
2 Clarke AK, Galbraith RM, Hamilton EBD *et al.* Rheumatic disorders in primary biliary cirrhosis. *Ann Rheum Dis* 1978; **37**: 42–7.
3 Reynolds TB, Denison EK, Frankl HD *et al.* Primary biliary cirrhosis with scleroderma, Raynaud's phenomenon and telangiectasia. *Am J Med* 1971; **50**: 302–12.
4 Quagliata F, Sebes J, Pinstein ML *et al.* Long bone erosions and ascites in progressive systemic sclerosis (scleroderma). *J Rheumatol* 1982; **9**: 641–4.

Cardiac involvement [1,2]**.** The resting ECG is abnormal in approximately 50% of cases, and cold-induced changes also occur [3]; however, the changes may be the result of other causes. Abnormalities of rhythm occur and these include paroxysmal atrial tachycardia, atrial fibrillation and flutter. Partial or complete heart block is not uncommon. In addition to abnormalities of rhythm, ECG may show bifid P waves and T-wave changes, indicating atrial or ventricular myocardial involvement. The conduction system seems to be relatively spared in systemic sclerosis and the high incidence of conduction disturbances may be the consequence of damage to the working myocardium [4]. Dyspnoea may be present but pain in the chest is not a prominent feature. Pericardial involvement occurs and is usually asymptomatic [5]. Mitral valve prolapse occurs more frequently in a number of connective tissue diseases, including systemic sclerosis, than in normal controls [6]. Other valvular abnormalities are rare [7]. Coronary reserve is reduced [8]. General enlargement of the heart, left-ventricular hypertrophy or a triangular outline are the most frequent radiological abnormalities. Radionuclide scanning [9], echocardiography [10], and 24-h ECG monitoring [11] are useful in the detection of abnormalities of the myocardium. More recently, studies using novel imaging technology including CT and magnetic resonance imaging (MRI) have demonstrated evidence of cardiac fibrosis [12].

References

1 Buckley BH. Progressive systemic sclerosis: cardiac involvement. *Clin Rheum Dis* 1979; **5**: 131–49.
2 Oram S, Stokes W. The heart in scleroderma. *Br Heart J* 1961; **23**: 243–59.
3 Gustafsson R, Kazzam E, Mannting F *et al.* Cold-induced reversible myocardial ischaemia in systemic sclerosis. *Lancet* 1989; **i**: 475–9.
4 Ridolfi RL, Bulkley BH, Hutchins CM. The cardiac conduction system in progressive systemic sclerosis. *Am J Med* 1976; **61**: 361–6.
5 Byers RJ, Marshall DAS, Freemont AJ. Pericardial involvement in systemic sclerosis. *Ann Rheum Dis* 1997; **56**: 393–4.
6 Comens SM, Alpert MA, Sharp GC *et al.* Frequency of mitral valve prolapse in systemic lupus erythematosus, progressive systemic sclerosis and mixed connective tissue disease. *Am J Cardiol* 1989; **63**: 369–70.
7 Yunus MB, Radford CM, Masi AT *et al.* Aortic regurgitation in scleroderma. *J Rheumatol* 1984; **11**: 384–6.
8 Kahan A, Nitenberg A, Foult JM *et al.* Decreased coronary reserve in primary scleroderma myocardial disease. *Arthritis Rheum* 1985; **28**: 637–46.
9 Ellis WW, Baer AN, Robertson RM *et al.* Left ventricular dysfunction induced by cold exposure in patients with systemic sclerosis. *Am J Med* 1986; **80**: 385–92.
10 Ferri C, Bernini L, Bongiorni MC *et al.* Non-invasive evaluation of cardiac dysrhythmias, and their relationship with multisystemic symptoms, in progressive systemic sclerosis patients. *Arthritis Rheum* 1985; **28**: 1259–66.
11 Geirsson AJ, Blom-Bulow B, Pahlm O *et al.* Cardiac involvement in systemic sclerosis. *Semin Arthritis Rheum* 1989; **19**: 110–6.
12 Hachulla AL, Launay D, Gaxotte V *et al*. Cardiac magnetic resonance imaging in systemic sclerosis: a cross-sectional observational study of 52 patients. *Ann Rheum Dis* 2009; **68**: 1878–84.

Renal involvement. Pathological changes in the kidney used to lead frequently to serious clinical problems, but the management of hypertension, and in particular the introduction of modern drugs such as inhibitors of angiotensin-converting enzyme (ACE), have revolutionized this aspect of the disease. Slight proteinuria is considered to be the most common clinical feature, often early in the disease. Proteinuria occurred in 36%, hypertension in 24%, azotaemia in 19% and malignant hypertension in 7% of one series [1]. One or more markers were found in 45% of patients. Approximately 40% of patients show disturbances of creatinine clearance. Nephrotic syndrome is increasingly rare [2]. Approximately 8% of patients with renal involvement develop malignant hypertension [3]. This may develop rapidly in the course of a few weeks, with headaches, nausea, vomiting and deterioration of vision in a patient whose renal function has previously been normal. Prior to 1971, survival beyond 1 year was unusual, the usual survival being 1–3 months. The prognosis, even with renal crisis, has improved dramatically since the introduction of ACE inhibitors (see p. 51.108). Although renal involvement has an adverse effect on survival in systemic sclerosis, patients with mild impairment of renal function may live for years.

References

1 Cannon PJ, Hassar M, Case DB *et al.* The relationship of hypertension and renal failure in scleroderma (progressive systemic sclerosis) to structural and functional abnormalities in the renal cortical circulation. *Medicine* 1974; **53**: 1–46.
2 Palma A, Sanchez-Palencia A, Armas JR *et al.* Progressive systemic sclerosis and nephrotic syndrome. *Arch Intern Med* 1981; **141**: 520–1.
3 Steen VD, Medsger TA Jr. Long-term outcomes of scleroderma renal crisis. *Ann Intern Med* 2000; **133**: 600–3.

Muscle involvement [1,2]. Muscle weakness may occur, and differentiation from dermatomyositis may be difficult, especially if there is a heliotrope appearance and oedema of the eyelids, and dilatation of the nail fold capillaries. In one series [3], the two diseases could not be distinguished in 36 of 727 patients. Muscles of the forearms and hands are affected as well as the proximal muscles. Creatine phosphokinase elevation and excessive creatinuria correlate well with muscle weakness. Electromyography is abnormal in 50% of patients early in the disease and in 93% in late stages [4], and histological changes are present in approximately 40%. MRI and spectroscopy can be useful non-invasive monitors of disease activity [5]. There does not appear to be any evidence that systemic sclerosis occurs as a cutaneous marker of internal

malignancy, although carcinoma of the lung may develop in patients with pulmonary involvement [6].

Tendon involvement. Leathery, palpable and audible friction rubs occur over the limbs and tendons [7] in approximately 25% of cases. Rupture of the extensor tendons of the hand has been reported [8]. The tendon was infiltrated with amyloid.

References

1 Clements PJ, Furst DE, Campions DS *et al.* Muscle disease in progressive systemic sclerosis. *Arthritis Rheum* 1978; **21**: 62–71.
2 Medsger TA, Rodnan GP, Moossy J *et al.* Skeletal muscle involvement in progressive systemic sclerosis (scleroderma). *Arthritis Rheum* 1968; **11**: 554–68.
3 Tuffanelli DL, Winkelmann RK. Scleroderma and its relationship to the 'collagenoses': dermatomyositis, lupus erythematosus, rheumatoid arthritis and Sjögren's syndrome. *Am J Med Sci* 1962; **243**: 133–46.
4 Hausmanowa-Petrusewicz L, Jablonska S, Blaszczyk M *et al.* Electro-myographic findings in various forms of progressive systemic sclerosis. *Arthritis Rheum* 1982; **25**: 61–5.
5 King LE, Olsen NJ, Vital TL, Park JH. Quantitative evaluation of muscle weakness in scleroderma patients using magnetic resonance imaging and spectroscopy. *Arch Dermatol* 1993; **129**: 246–7.
6 Roumm AD, Medsger TA. Cancer and systemic sclerosis. *Arthritis Rheum* 1985; **28**: 1336–40.
7 Shulman LE, Kurban AK, Harvey AM. Tendon friction rubs in progressive systemic sclerosis (scleroderma). *Trans Assoc Am Physicians* 1961; **74**: 378–88.
8 Horwitz HM, DiBeneditto JD, Allegra SR *et al.* Scleroderma, amyloidosis and extensor tendon rupture. *Arthritis Rheum* 1982; **25**: 1141–3.

Joint involvement [1–3]. Arthritic pain is not uncommon in the early stages of systemic sclerosis, and sometimes rheumatoid arthritis is the initial diagnosis made. Radiological changes indistinguishable from rheumatoid arthritis occur, especially in the hands, but there are no specific changes ascribable to systemic sclerosis. They include periarticular osteoporosis, joint-space narrowing, erosions and, rarely, avascular necrosis [4], erosions of long bones [5], bone ankylosis [6] and erosive osteoarthritis.

References

1 Baron M, Lee P, Kaystone EC. The articular manifestations of progressive systemic sclerosis (scleroderma). *Ann Rheum Dis* 1982; **41**: 147–52.
2 Blocka KLN, Bassett LW, Furst DE *et al.* The arthropathy of advanced progressive systemic sclerosis. *Arthritis Rheum* 1981; **24**: 874–84.
3 Misra R, Darton K, Jeurkea RF *et al.* Arthritis in scleroderma. *Br J Rheumatol* 1995; **34**: 831–7.
4 Wilde AH, Mankin JH, Rodnan CP. Avascular necrosis of the femoral head in scleroderma. *Arthritis Rheum* 1970; **13**: 445–7.
5 Quagliata F, Sebes J, Pinstein ML *et al.* Long bone erosions and ascites in progressive systemic sclerosis (scleroderma). *J Rheumatol* 1982; **9**: 641–4.
6 Huyck CJ, Hoffman GS. Bony ankylosis of the hips in progressive systemic sclerosis. *Arthritis Rheum* 1982; **25**: 1497–500.

Dental changes (see Chapter 69) [1]. Widening of the periodontal membrane because of fibrosis, with thickening of the vessel walls, occurs in approximately 30% of cases (Fig. 51.72). Usually the whole root is involved. Anterior as well as posterior teeth are affected, and the lamina dura may or may not be abnormal. Thickening of the periodontal membrane is not related to the duration of Raynaud's phenomenon, calcinosis, involvement of internal organs, antinuclear factor or prognosis. Thickening of the periodontal membrane is not diagnostic of systemic sclerosis and is also found in periapical infection. Widening of the periodontal membrane in only one tooth is usually a result of such infection.



Fig. 51.72 Widening of the periodontal membrane in systemic sclerosis.

Osteolysis of the mandibular angle and coronoid process occurs with equal frequency [2], and these osteolytic areas may fracture [3]. A patient who had multiple external and internal root resorptions for which all the teeth were removed was successfully treated with osseointegrated implants [4].

References

1 Rowell NR, Hopper FE. The periodontal membrane in systemic sclerosis. *Br J Dermatol* 1977; **96**: 15–20.
2 White SC, Frey NW, Blaschke DD *et al.* Oral radiographic changes in patients with progressive systemic sclerosis (scleroderma). *J Am Dent Assoc* 1977; **94**: 1178–82.
3 Weber DD, Blunt MH, Caldwell JB *et al.* Fracture of mandibular rami complicated by scleroderma: report of case. *J Oral Surg* 1970; **28**: 860–3.
4 Jensen J, Sindet-Pedersen S. Osseointegrated implants for prosthetic reconstruction in a patient with scleroderma: report of a case. *J Oral Maxillofac Surg* 1990; **48**: 739–41.

Central nervous system [1,2]. The nervous system is involved in fewer than 10% of cases [3], although asymptomatic involvement may be more common [4], and others have found involvement in 40% of patients, which can be associated with ulceration of the skin [5]. Neuropathy has been reported [6,7]: autonomic neuropathy may not be uncommon [8,9]; trigeminal neuropathy presents with numbness and pain in the face [10], and occurs in 4% of patients [11]. Of 22 cases with chronic trigeminal sensory neuropathy, nine had systemic sclerosis [12]. It is unilateral at first but later becomes bilateral. Other cranial nerves may be involved [13]. Carpal tunnel syndrome and meralgia paraesthetica may occur. Local anaesthetics may have an abnormally prolonged action [1]. Subacute combined degeneration is the result of vitamin B_{12} deficiency caused by malabsorption secondary to involvement of the small intestine by systemic sclerosis [14]. Spinal cord compression may occur because of soft-tissue calcification [15]. The EEG is not specific. Sensory chronaxia is prolonged in both abnormal and normal skin. Such prolongation in normal skin does not occur in any other condition apart from tabes dorsalis [16]. Impotence has been reported as an initial manifestation of the disease [17,18].

References

1 Berth-Jones J, Coates PAA, Graham-Brown RAC *et al.* Neurological complications of systemic sclerosis: a report of three cases and review of the literature. *Clin Exp Dermatol* 1990; **15**: 91–4.
2 Gordon RM, Silverstein A. Neurologic manifestations in progressive systemic sclerosis. *Arch Neurol* 1970; **22**: 126–34.
3 Lee P, Bruni J, Sukenik S. Neurological manifestations in systemic sclerosis (scleroderma). *J Rheumatol* 1984; **11**: 480–3.
4 Dierckx RA, Aichner F, Gerstenbrand F *et al.* Progressive systemic sclerosis and nervous system involvement. *Eur Neurol* 1987; **26**: 134–40.
5 Averbuch-Heller L, Steiner I, Abramsky O. Neurological manifestations of progressive systemic sclerosis. *Arch Neurol* 1992; **49**: 1292–5.
6 Hagberg B, Leonhardt T, Skogh M. Familial occurrence of collagen diseases. *Acta Med Scand* 1961; **169**: 727–34.
7 Rodnan CP. The natural history of progressive systemic sclerosis (diffuse scleroderma). *Bull Rheum Dis* 1963; **13**: 301–4.
8 Klimiuk PS, Taylor L, Baker RD *et al.* Autonomic neuropathy in systemic sclerosis. *Ann Rheum Dis* 1988; **47**: 542–5.
9 Sonnex C, Paice E, White AC. Autonomic neuropathy in systemic sclerosis: a case report and evaluation of six patients. *Ann Rheum Dis* 1986; **45**: 957–60.
10 Ashworth B, Tait CBW. Trigeminal neuropathy in connective tissue disease. *Neurology* 1971; **21**: 609–14.
11 Farrell DA, Medsger TA Jr. Trigeminal neuropathy in progressive systemic sclerosis. *Am J Med* 1982; **73**: 57–62.
12 Lecky BRF, Hughes RAC, Murray NMF. Trigeminal sensory neuropathy. *Brain* 1987; **110**: 1463–85.
13 Teasdall RD, Frayha RA, Shulman LE. Cranial nerve involvement in systemic sclerosis (scleroderma). *Medicine* 1980; **59**: 149–59.
14 Bjerregaard B, Hojgaard K. Neurological symptoms in scleroderma. *Arch Dermatol* 1976; **112**: 1030–1.
15 Petrocelli AR, Bassett LW, Mirra J *et al.* Scleroderma: dystrophic calcification with spinal cord compression. *J Rheumatol* 1988; **15**: 1733–5.
16 Jablonska S. Measurement of sensory chronaxie as a diagnostic procedure in scleroderma. *Br J Dermatol* 1975; **92**: 223–7.
17 Lally EV, Jimenez SA. Impotence in progressive systemic sclerosis. *Ann Intern Med* 1981; **95**: 150–3.
18 Sukenik S, Horowitz J, Busilka D *et al.* Impotence in systemic sclerosis. *Ann Intern Med* 1987; **106**: 910–1.

Eye changes. Tightness of the lids, diminished tear secretion, keratoconjunctivitis sicca and shallow fornices are specific ophthalmic changes [1]. Sjögren's syndrome occurs in 15% of cases. Retinopathy, with haemorrhages, exudates and cytoid bodies may occur with a relatively low blood pressure, and has been attributed to direct vascular involvement by systemic sclerosis [2]. Fluorescein angiography shows vascular abnormalities in the choroid in 50% and in the retina in 10% of patients [3]. Central retinal vein occlusion has been reported [4].

References

1 Horan EC. Ophthalmic manifestations of progressive systemic sclerosis. *Br J Ophthalmol* 1969; **53**: 388–92.
2 Ashton N, Coomes EN, Carner A *et al.* Retinopathy due to progressive systemic sclerosis. *J Pathol Bacteriol* 1968; **96**: 259–68.
3 Grennan DM, Forrester I. Involvement of the eye in SLE and scleroderma. *Ann Rheum Dis* 1977; **36**: 152–6.
4 Saari KM, Rudenberg HA, Laitinen O. Bilateral central retinal vein occlusion in a patient with scleroderma. *Ophthalmologica* 1981; **182**: 7–12.

Laboratory investigations. Anaemia may be found in patients with renal failure, gastrointestinal bleeding or malabsorption. The ESR is raised in approximately half of patients, as is the serum globulin level. Elevation of gammaglobulin occurs more frequently than elevation of α_2-globulin. Other acute-phase reactants are usually normal, although there are defects in the acute-phase response to some stimuli [1]. False-positive serology occurs in approximately 5%. Cold agglutinins may be found in 25% of cases. The Coombs' test is usually negative, although Coombs'-positive haemolytic anaemia and pancytopenia have been reported [2]. Circulating anticoagulant has been demonstrated in one case [3], but was not found in 24 patients at Leeds [4]. Anticardiolipin antibodies are found in 25% of cases overall, and occur more frequently in those severely affected [5]. Cryoglobulins are only rarely detected. Cryofibrinogenaemia has been held responsible for ulceration and gangrene of the fingers in some cases. Rheumatoid factor is present in approximately 30% of patients. Serum complement levels are usually normal. LE cells may be demonstrated in 8% of patients. Sometimes, SLE may occur in association with systemic sclerosis [6,7], but the presence of LE cells in systemic sclerosis does not necessarily imply coexistent SLE. Antinuclear antibodies have been demonstrated in 78% of patients using rat liver [8], and in 97% using Hep-2 cells [9] as substrate. Using Hep-2 cells, both speckled and homogeneous types occur, and nucleolar patterns—speckled, homogeneous and clumpy—are demonstrated more frequently than in other diseases. Centromere staining, resulting from an antibody that reacts with the kinetocore of metaphase chromosomes, occurs in 40–70% of milder (or CREST) cases [9,10] who have longer duration of disease and little renal involvement (Fig. 51.73). Anticentromere antibodies may be present in patients with Raynaud's phenomenon before the clinical features of systemic sclerosis appear. They seem to be indicative of a favourable prognosis [11]. They also occur in 6% of patients with SLE (including drug-induced lupus) [12], 6% of patients with mixed connective tissue disease, 17% of patients with primary biliary cirrhosis and systemic sclerosis [13], 11% of patients with primary biliary cirrhosis alone and 5% of patients with morphoea [14]. A diffuse 'frosted glass' staining of nuclei of Hep-2 cells is caused by Scl-70 antibody, a precipitating antibody to topoisomerase I, which is unique to systemic sclerosis and occurs in approximately 20% of patients, particularly those with lung involvement (Fig. 51.74) [10,15]. Higher frequencies are described, even in patients with acrosclerosis alone [16]. Scl-70 and anticentromere antibody occur together in 5% of cases [17], but

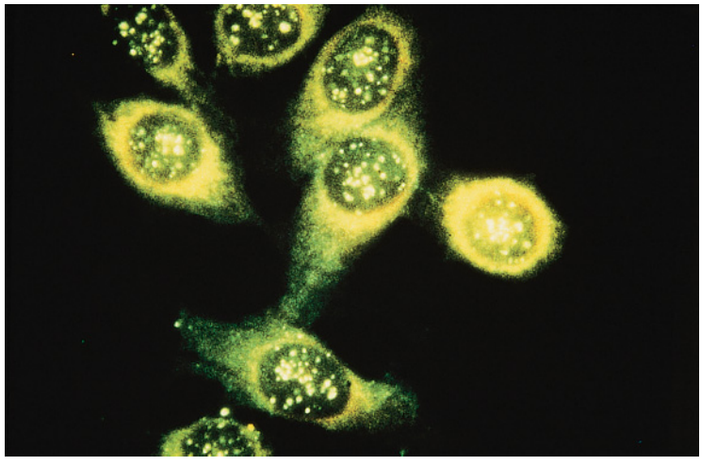


Fig. 51.73 Anticentromere antibody demonstrated on Hep-2 cells.

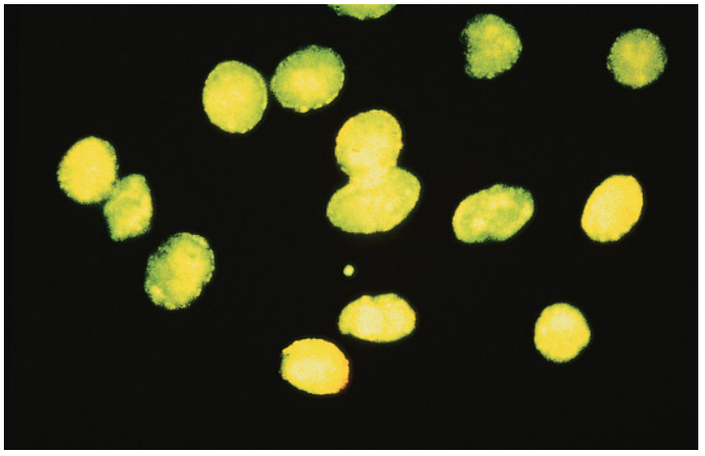


Fig. 51.74 Scl-70 antibody demonstrated on Hep-2 cells.

when occurring alone may define separate subsets of the disease. There is no relationship between Scl-70 and disease survival [18]. Scl-86 is a related antigen [19]. Other antibodies occur, presumably indicating immunological subsets, and include antibody to centriole [20,21], anti-Jo-1 [22] and anti-Ro/SS-A [23]. More intensive investigation of autoantibodies may reveal additional subsets of the disease [24]. Several patterns of nucleolar staining have been described [25]. A homogeneous pattern was associated with polymyositis/scleroderma overlap, a clumpy pattern with diffuse cutaneous systemic sclerosis and a speckled pattern with localized cutaneous systemic sclerosis. Anti-DNA antibodies are not found [26]. Anti-IgE antibodies occur [27]. Other precipitating antibodies to saline extracts of human tissue [8] may be found in 15% of patients. Anti-smooth-muscle and antiendothelial antibodies have been reported [28,29]. Antineutrophil cytoplasmic antibodies occur in 9% [30] and antihistone antibodies in 42% [31]. The latter was more frequent in patients with cardiac and renal involvement. Serum type III procollagen peptide concentrations are raised and reflect disease activity [32,33]. Urinary excretion of 5-hydroxyindole-acetic acid is normal, as is thyroid function.

References

1 Whicher JT, Bell AM, Martin MFR *et al.* Prostaglandins cause an increase in serum acute-phase proteins in man, which is diminished in systemic sclerosis. *Clin Sci* 1984; **66**: 165–71.
2 Carcassonne Y, Gastaut JA. Pancytopenia and scleroderma. *BMJ* 1976; **i**: 1446.
3 Albert J, Ekoe JM, Cunningham M *et al.* Circulating anticoagulant in CREST syndrome. *Br J Rheumatol* 1984; **23**: 20–3.
4 Rowell NR, Tate GM. Failure to demonstrate the lupus anticoagulant in systemic sclerosis. *Br J Dermatol* 1988; **119**: 549.
5 Malia RG, Greaves M, Rowlands LM *et al.* Anticardiolipin antibodies in systemic sclerosis: immunological and clinical associations. *Clin Exp Immunol* 1988; **73**: 456–60.
6 Dubois EL, Chandor S, Friou CJ *et al.* Progressive systemic sclerosis (PSS) and localized scleroderma (morphea) with positive LE cell test. *Medicine* 1971; **50**: 199–222.
7 Rowell NR. Lupus erythematosus cells in systemic sclerosis. *Ann Rheum Dis* 1962; **21**: 70–5.
8 Beck JS, Anderson JR, Gray KG *et al.* Antinuclear and precipitating autoantibodies in progressive systemic sclerosis. *Lancet* 1963; **ii**: 1188–90.
9 Bernstein RM, Steigerwald JC, Tan EM. Association of antinuclear and antinucleolar antibodies in progressive systemic sclerosis. *Clin Exp Immunol* 1982; **48**: 43–51.
10 Catoggio LJ, Bernstein RM, Black CM. Serological markers in progressive systemic sclerosis: clinical correlations. *Ann Rheum Dis* 1983; **42**: 23–7.
11 Miller MH, Littlejohn CO, Davidson A *et al.* The clinical significance of the anticentromere antibody. *Br J Rheumatol* 1987; **26**: 17–21.
12 Wade JP, Sack B, Schur PH. Anticentromere antibodies: clinical correlates. *J Rheumatol* 1988; **15**: 1759–63.
13 Bernstein RM, Callender ME, Neuberger JM *et al.* Anticentromere antibody in primary biliary cirrhosis. *Ann Rheum Dis* 1982; **41**: 612–4.
14 Powell FC, Winklemann RH, Venencie-Lemarchano F *et al.* The anticentromere antibody: disease specificity and clinical significance. *Proc Mayo Clin* 1984; **59**: 700–6.
15 Shero JH, Bordwell B, Rothfield NF *et al.* Antibodies to topoisomerase 1 in sera from patients with scleroderma. *J Rheumatol* 1987; **14**: 138–40.
16 Jarzabek-Chorzelska M, Blaszczyk M, Jablonska S *et al.* Scl 70 antibody: a specific marker of systemic sclerosis. *Br J Dermatol* 1986; **115**: 393–401.
17 Jarzabek-Chorzelska M, Blaszczyk M, Kolacinska-Strasz Z *et al.* Are AcA and Scl 70 antibodies mutually exclusive? *Br J Dermatol* 1990; **122**: 201–8.
18 Steen VD, Powell DL, Medsger JR. Clinical correlations and prognosis based on serum autoantibodies in patients with systemic sclerosis. *Arthritis Rheum* 1988; **31**: 196–203.
19 Van Venrooij WJ, Stapel SO, Houben H *et al.* Scl-86, a marker antigen for diffuse scleroderma. *J Clin Invest* 1985; **75**: 1053–60.
20 Tuffanelli DL, McKeon F, Kleinsmith DM *et al.* Anticentromere and anticentriole antibodies in the scleroderma spectrum. *Arch Dermatol* 1983; **119**: 560–6.
21 Sato S, Fujimoto M, Ihn H *et al.* Antibodies to centromere and centriole in scleroderma spectrum disorders. *Dermatology* 1994; **189**: 23–6.
22 Bernstein RM, Morgan SH, Chapman J *et al.* Anti-Jo-1 antibody: a marker for myositis with interstitial lung disease. *BMJ* 1984; **289**: 151–2.
23 Bell S, Krieg T, Meurer M. Antibodies to Ro/SSA detected by ELISA: correlation with clinical features in systemic scleroderma. *Br J Dermatol* 1989; **121**: 35–41.
24 Reimer C, Steen VD, Penning CA *et al.* Correlates between autoantibodies to nucleolar antigens and clinical features in patients with systemic sclerosis (scleroderma). *Arthritis Rheum* 1988; **31**: 525–32.
25 Blaszcyzk M, Jarzabek-Cawzelka M, Jablonska S *et al.* Autoantibodies to nucleolar antigens in systemic scleroderma: clinical correlations. *Br J Dermatol* 1990; **123**: 421–30.
26 Hughes GRV. Significance of anti-DNA antibodies in systemic lupus erythematosus. *Lancet* 1971; **ii**: 861–3.
27 Kaufman LD, Gruber BL, Marchese MJ *et al.* Anti-IgE autoantibodies in systemic sclerosis (scleroderma). *Ann Rheum Dis* 1989; **48**: 201–5.
28 Kitridou RC, Fleischmajer R, Lagosky P. Antismooth muscle antibody in scleroderma. *Clin Res* 1974; **22**: 703A.
29 Rosenbaum J, Pottinger BE, Woo P. Measurement and characterisation of circulating anti-endothelial cell IgG in connective tissue diseases. *Clin Exp Immunol* 1988; **72**: 450–6.
30 Akimoto S, Ishikawa O, Tamura T *et al.* Antineutrophil cytoplasmic autoantibodies in patients with systemic sclerosis. *Br J Dermatol* 1996: **134**: 407–10.
31 Parodi A, Drosera M, Barbieri L, Rebora A. Antihistone antibodies in systemic sclerosis. *Dermatology* 1995; **191**: 16–8.
32 Black CM, McWhirter A, Harrison NK *et al.* Serum type III procollagen peptide concentrations in systemic sclerosis and Raynaud's phenomenon: relationship to disease activity and duration. *Br J Rheumatol* 1989; **28**: 98–103.
33 Krieg T, Langer I, Gerstmeier H. Type III collagen aminopropeptide levels in serum of patients with progressive systemic scleroderma. *J Invest Dermatol* 1986; **87**: 788–91.

Variations. Patients with calcinosis, Raynaud's phenomenon, sclerodactyly and telangiectasia may form a separate entity known as CRST syndrome [1], or CREST syndrome if oesophageal (esophageal) involvement is included. This is unlikely to be a separate syndrome, distinct from systemic sclerosis [2]. The variability of expression and course of the authors' series of patients with systemic sclerosis suggests that this type of case is only a subgroup of systemic sclerosis. This has been confirmed by other workers [3,4]. However, the delineation of this group of patients emphasizes that the diagnosis of systemic sclerosis does not

always imply such a poor prognosis as has hitherto been considered.

The suggestion that 'systemic scleroderma' should be divided into two groups—diffuse scleroderma and acrosclerosis—remains to be confirmed [5]. The former, a relatively small group, can be distinguished from acrosclerosis in that the sex distribution is equal, the age of onset is later, Raynaud's phenomenon is absent, cutaneous sclerosis is the usual presenting feature, the sclerosis of the skin is usually generalized rather than acral, and the course is more rapid and fulminating, with death in a few years. However, both types show similar visceral involvement and laboratory abnormalities, and some patients with acrosclerosis have a short course, and Raynaud's phenomenon is not invariable. Occasionally, acute diffuse scleroderma may be much more benign than expected [6]. These two groups are probably clinical variants of systemic sclerosis. A more recent attempt at subdivision of the disease into diffuse and localized forms has met with more agreement (see p. 51.91) [7].

References

1 Winterbauer RH. Multiple telangiectasia, Raynaud's phenomenon, sclerodactyly, and subcutaneous calcinosis. *Bull Johns Hopkins Hosp* 1964; **114**: 361–83.
2 Rowell NR. The prognosis of systemic sclerosis. *Br J Dermatol* 1976; **95**: 57–60.
3 Mintz C, Fraga A, Orozco JH. The CRST syndrome: a non-entity. *J Rheumatol* 1974; **1** (Suppl. 1): 95.
4 Salerni R, Rodnan CP, Leon DF *et al.* Pulmonary hypertension in the CREST syndrome variant of progressive systemic sclerosis (scleroderma). *Ann Intern Med* 1977; **86**: 394–9.
5 Tuffanelli DL, Winkelmann RK. Diffuse systemic scleroderma. *Ann Intern Med* 1962; **57**: 198–203.
6 Nynzi E, Rebora A, Cormane RH. Acute diffuse scleroderma. *Acta Derm Venereol (Stockh)* 1981; **61**: 173–6.
7 LeRoy EC, Black C, Fleischmajer R *et al.* Scleroderma (systemic sclerosis): classification subsets and pathogenesis. *J Rheumatol* 1988; **15**: 202–5.

Systemic sclerosis in childhood. Systemic sclerosis occurs in childhood, and the clinical features resemble those seen in adult cases. Raynaud's phenomenon is less frequent and renal disease is rare [1]. The course of systemic sclerosis in childhood is said to be slower, and the disability and visceral involvement less severe than in adults [2], but fatal cases have been reported [3]. The problem has been reviewed in depth [4].

References

1 Larrègue M, Cannel C, Bazex J *et al.* Scléroderme systémique de l'enfant. *Ann Dermatol Vénéréol* 1983; **110**: 317–26.
2 Jaffe MO, Winkelmann RK. Generalized scleroderma in children. *Arch Dermatol* 1961; **83**: 402–13.
3 Kass H, Hanson V, Patrick J. Scleroderma in childhood. *J Pediatr* 1966; **68**: 243–56.
4 Singsen BH. Scleroderma in childhood. *Pediatr Clin North Am* 1986; **33**: 1119–39.

Involvement of the genital tract [1]. Vaginal dryness, ulcerations and dyspareunia are significantly more frequent in patients with systemic sclerosis when compared with controls. Frequency of sexual intercourse and sexual satisfaction is decreased, and the menopause may be early.

Reference

1 Bhadauria S, Moser DK, Clements PJ *et al.* Genital tract abnormalities and female sex function impairment in systemic sclerosis. *Am J Obstet Gynecol* 1995; **172**: 580–7.

Pregnancy [1]. Systemic sclerosis usually remains unchanged during pregnancy, but postpartum renal failure and peripheral gangrene have been described [2]. Severe renal, pulmonary or cardiac disease in the mother may be an indication for termination of the pregnancy [3], and such complications may occur late in pregnancy. ACE inhibitors may be of value for hypertension in pregnancy, although there are potential risks to the fetus [4]. There is conflicting evidence regarding the incidence of abortion and stillbirth [5,6]. Fertility may be impaired.

In some cases, pregnancy seems to precipitate the disease.

References

1 Black CM. Systemic sclerosis and pregnancy. *Baillière's Clin Rheumatol* 1990; **4**: 105–24.
2 Smith CA, Pinals RS. Progressive systemic sclerosis and postpartum renal failure complicated by peripheral gangrene. *J Rheumatol* 1982; **9**: 455–8.
3 Maymon R, Fejgin M. Scleroderma in pregnancy. *Obstet Gynecol Surv* 1989; **44**: 530–4.
4 Baethge BA, Wolf RE. Successful pregnancy with scleroderma, renal disease and pulmonary hypertension in a patient using angiotensin converting enzyme inhibitors. *Ann Rheum Dis* 1989; **48**: 776–8.
5 McHugh NJ, Reilly PA, McHugh LA. Pregnancy outcome and autoantibodies in connective tissue disease. *J Rheumatol* 1989; **16**: 42–6.
6 Steen VD. Pregnancy in women with systemic sclerosis. *Obstet Gynecol* 1999; **94**: 15–20.

Associations. Sometimes, systemic sclerosis occurs in association with other conditions, particularly those considered to have some autoimmune features. Usually, it is possible to differentiate between the diseases, but occasionally there is clinical and immunological overlap. The relationship to SLE and dermatomyositis has already been mentioned. Immunohistology of involved and uninvolved skin is of value. Sjögren's syndrome, the most common features of which are dryness and atrophy of the conjunctiva, cornea and buccal mucosa, together with arthritis, occurs with systemic sclerosis in approximately 17–20% of patients [1,2], and resembles the primary form of Sjögren's syndrome [3]. Extensive investigation reveals at least one abnormal test of the sicca syndrome in all cases [4]. Salivary flow is normal, but deficient in IgA [5]. Antibodies to Ro and La are useful markers of the presence of Sjögren's syndrome in systemic sclerosis [6], occurring in 60% of cases [7]. Other muscle disorders that have been reported in association with systemic sclerosis include polymyositis [8], myasthenia gravis [9] and muscular dystrophy [10]. Pathological features of systemic sclerosis are sometimes found in patients with polyarteritis nodosa [11–13], but there is not the same clinical or immunological overlap as seen with SLE. Temporal arteritis has been reported [14,15], and the condition has also occurred with malignant atrophic papulosis (Degos' syndrome) [16], thrombophlebitis and cryofibrinogenaemia. The association with Hashimoto's thyroiditis is rare. Unsuspected hypothyroidism may occur [17]. Systemic sclerosis is one of the disorders that are sometimes associated with congenital agammaglobulinaemia and IgA deficiency [18]. It may occur with autoimmune haemolytic anaemia [19], autoimmune neutropenia [20], thrombocytopenic purpura [21], microangiopathic haemolytic anaemia [22], urticaria pigmentosa [23], pemphigus vulgaris [24], monoclonal gammopathy [25], primary biliary cirrhosis [26,27], nodular hyperplasia of the liver [28], coeliac disease [29], pseudoxanthoma elasticum [30], elastosis

perforans serpiginosa [31], lymphoma [32] and multiple sclerosis [33]. Reversible myasthenia gravis may occur on treatment with penicillamine [34].

References

1 Cipoletti JF, Buckingham RB, Barnes EL *et al.* Sjögren's syndrome in progressive systemic sclerosis. *Ann Intern Med* 1977; **87**: 535–41.
2 Andonopoulos AP, Drosos AA, Skopouli FN *et al.* Sjögren's syndrome in rheumatoid arthritis and progressive systemic sclerosis: a comparative study. *Clin Exp Rheumatol* 1989; **7**: 203–5.
3 Drosos AA, Andonopoulos AP, Costopoulos JS *et al.* Sjögren's syndrome in progressive systemic sclerosis. *J Rheumatol* 1988; **15**: 965–8.
4 Alarcón-Segovia D, Ibánéz G, Hernández-Ortiz J *et al.* Sjögren's syndrome in progressive systemic sclerosis (scleroderma). *Am J Med* 1974; **57**: 78–85.
5 Matthews RW, Bhoola KD, Rasker JJ *et al.* Salivary secretion and connective tissue disease in man. *Ann Rheum Dis* 1985; **44**: 20–6.
6 Osial TA, Whiteside TL, Buckingham RB *et al.* Clinical and serologic study of Sjögren's syndrome in patients with progressive systemic sclerosis. *Arthritis Rheum* 1983; **26**: 500–8.
7 Bell S, Krieg T, Meurer M. Antibodies to Ro/SSA detected by ELISA: correlation with clinical findings in systemic sclerosis. *Br J Dermatol* 1989; **121**: 35–41.
8 Pock GF. Acute polymyositis scleroderma. *Rev Assoc Med Argent* 1959; **73**: 266–70.
9 Weber FP, Bode OB. Sclerodermia and myasthenia gravis. *Proc R Soc Med* 1931–32; **25**: 966.
10 Bergouignan M, Guerin A, Texier L. Sclerodermie progressive, dystrophie musculaire, syndrome endocrinien. *Rev Neurol* 1950; **83**: 126.
11 Calvert RI, Owen TK. True scleroderma kidney. *Lancet* 1956; **ii**: 19–22.
12 Platt R, Davson J. A clinical and pathological study of renal disease. *QJM* 1950; **19**: 33–56.
13 Swarm RL, Cermuth FC. Renal lesions in scleroderma. *Am J Pathol* 1953; **29**: 577–8.
14 Perez-Jiminez F, Lopez-Rubio F, Canadillas F *et al.* Giant cell arteritis associated with progressive systemic sclerosis. *Arthritis Rheum* 1982; **25**: 717–8.
15 Wyble M, Schirnek RA. The simultaneous occurrence of two collagen diseases in the same patient. *Trans Am Acad Ophthalmol Otolaryngol* 1962; **66**: 632–41.
16 Durie BCM, Stroud JD, Kahn JA. Progressive systemic sclerosis with malignant atrophic papulosis. *Arch Dermatol* 1969; **100**: 575–81.
17 Gordon MB, Klein I, Dekker A *et al.* Thyroid disease in progressive systemic sclerosis: increased frequency of glandular fibrosis and hypothyroidism. *Ann Intern Med* 1981; **95**: 431–5.
18 Jay S, Helm S, Wray BB. Progressive systemic scleroderma with IgA deficiency in a child. *Am J Dis Child* 1981; **135**: 965–6.
19 Sumithran E. Progressive systemic sclerosis and autoimmune haemolytic anaemia. *Postgrad Med J* 1976; **52**: 173–6.
20 Waugh D, Ibels L. Malignant scleroderma associated with autoimmune neutropenia. *BMJ* 1980; **280**: 1577–8.
21 Ivey KJ, Hwang YF, Sheets RF. Scleroderma associated with thrombocytopenia and Coombs-positive haemolytic anaemia. *Am J Med* 1971; **51**: 815–7.
22 Sayer WR, Sayer DC, Heptinstall RH. Scleroderma and microangiopathic haemolytic anaemia. *Ann Intern Med* 1973; **78**: 895–7.
23 Basler RSW, Harrell ER. Urticaria pigmentosa associated with scleroderma. *Arch Dermatol* 1974; **109**: 393–4.
24 Woscoff A, Remondino C, Jaimovich L *et al.* Progressive systemic sclerosis and pemphigus vulgaris. *J Am Acad Dermatol* 1989; **21**: 142–4.
25 Nishikai M, Funatsu Y, Homma M. Monoclonal gammopathy, penicillamine-induced polymyositis and systemic sclerosis. *Arch Dermatol* 1974; **110**: 253–5.
26 Murray-Lyon IM, Thompson RPH, Ansell ID *et al.* Scleroderma and primary biliary cirhosis. *BMJ* 1970; **iii**: 258–9.
27 Reynolds TB, Denison EK, Frankl HD *et al.* Primary biliary cirrhosis with scleroderma, Raynaud's phenomenon and telangiectasia. *Am J Med* 1971; **50**: 302–12.
28 Russell ML, Kahn JH. Nodular regenerative hyperplasia of the liver associated with progressive systemic sclerosis. *J Rheumatol* 1983; **10**: 748–52.
29 Cooper BT, Holmes GKT, Cooke WT. Coeliac disease and immunological disorders. *BMJ* 1978; **i**: 537–9.
30 Wilkinson JD. Pseudoxanthoma elasticum and acrosclerosis. *Proc R Soc Med* 1977; **70**: 567–70.
31 May NC, Lester RS. Elastosis perforans serpiginosa associated with systemic sclerosis. *J Am Acad Dermatol* 1982; **6**: 945.
32 Vignon-Pennamen MD, Janvier M, Wallach D. Sclerodermie systemique et lymphome malin ganglionnaire. *Ann Dermatol Vénéréol* 1983; **110**: 779–80.
33 Trostle DC, Helfrich D, Medsger TA. Systemic sclerosis (scleroderma) and multiple sclerosis. *Arthritis Rheum* 1986; **29**: 124–7.
34 Torres CF, Griggs RC, Baum J *et al.* Penicillamine-induced myasthenia gravis in progressive systemic sclerosis. *Arthritis Rheum* 1980; **23**: 505–8.

Differential diagnosis. Well-developed cases of systemic sclerosis presenting with Raynaud's phenomenon and typical cutaneous changes on the face and hands are easy to recognize. Generalized morphoea may sometimes cause confusion. However, Raynaud's phenomenon is less common in the latter, and the distribution of the skin changes is different in so far as generalized morphoea involves the trunk, as well as the limbs. Systemic involvement is unusual, although not unknown, and the course is usually towards improvement over the years.

Localized morphoea should present little difficulty, although occasionally morphoeic patches may be seen in systemic sclerosis, and systemic lesions may occasionally be found in morphoea [1–3]. Sometimes, patients with localized morphoea may later develop systemic sclerosis. Morphoeic lesions were seen in 6.7% of Japanese patients with systemic sclerosis [4]. Patients with atrophoderma of Pasini and Pierini may progress to systemic sclerosis [5]. Acrosclerotic skin changes occasionally occur in SLE and dermatomyositis. Cold blue hands with inability to extend the fingers has been reported in bisalbuminaemia [6]. The pigmentation of systemic sclerosis may be confused with Addison's disease [7,8]. Cutaneous changes resembling systemic sclerosis have been reported in an unusual type of porphyria with features of erythropoietic protoporphyria and hepatic cutaneous porphyria [9]. A case of primary amyloidosis presenting as scleroderma has been described [10]. There is no Raynaud's phenomenon in familial sclerodactyly [11].

The stiff-skin syndrome [12], or congenital fascial dystrophy [13], is a rare condition presenting in childhood, in which stone-hard indurations of the fascia and dermal collagen occur. There is no systemic involvement, and the resulting disability is permanent. Patients with scleromyxoedema—a variant of lichen myxoedematosus—may resemble systemic sclerosis but there is no Raynaud's phenomenon or systemic involvement apart from the characteristic slow paraprotein in the serum. The POEMS (*p*olyneuropathy, *o*rganomegaly, *e*ndocrinopathy, *M* protein, *s*kin changes) or Crow–Fukase syndrome also shows a monoclonal paraprotein among a large number of potential features, including diffuse hyperpigmentation, scleroderma, hypertrichosis and lymphadenopathy, as well as the features indicated by its acronym. Of these patients, 50% have multiple myeloma [14]. Differentiation from systemic sclerosis relies on the presence of neuropathy and gammopathy [15,16].

Raynaud's phenomenon, firmness of the skin of the fingers, radiological absorption of the terminal phalanges and thickening of the walls of dermal arteries occur in workers engaged in the polymerization of vinyl chloride (see p. 51.80). The cutaneous changes of systemic sclerosis may resemble acrogeria (see Chapter 45), but the latter dates from birth. The condition may have to be distinguished from leprosy if a peripheral neuropathy is present

[17]. Up to 40% of insulin-dependent juvenile diabetics have contractures at the proximal interphalangeal joints, with thickening of the skin of the fingers (diabetic cheiroarthropathy) [18,19].

References

1 Donaldson EM. Morphoea (localized scleroderma) with visceral changes. *Br J Dermatol* 1962; **74**: 105.
2 Leinwand I, Duryee AW, Richter MN. Scleroderma. *Ann Intern Med* 1954; **41**: 1003–41.
3 Rodnan GP, Fennell RH. Progressive systemic sclerosis sine scleroderma. *JAMA* 1962; **180**: 665–70.
4 Soma Y, Tamaki T, Kikuchi K *et al*. Coexistence of morphoea and systemic sclerosis. *Dermatology* 1993; **186**: 103–5.
5 Bisaccia EP, Scarborourgh DA, Lowney ED. Atrophoderma of Pasini and Pierini and systemic scleroderma. *Arch Dermatol* 1982; **118**: 1–2.
6 Byrne JPH. Bisalbuminaemia. *Br J Dermatol* 1977; **95** (Suppl. 14): 54–5.
7 Banks BM. Is there a common denominator in scleroderma, dermatomyositis, disseminated lupus erythematosus, the Libman–Sacks syndrome and polyarteritis nodosa? *N Engl J Med* 1941; **255**: 433–4.
8 Talbott JH, Gall EA, Consolazio WV *et al.* Dermatomyositis with scleroderma, calcinosis and renal endarteritis associated with focal cortical necrosis. *Arch Intern Med* 1939; **63**: 476–96.
9 Simon N, Berko GY, Schneider I. Hepato erythropoietic porphyria presenting as scleroderma and acrosclerosis in a sibling pair. *Br J Dermatol* 1977; **96**: 663–8.
10 Leach WB, Vassar PS, Culling CFA. Primary systemic amyloidosis presenting as scleroderma. *Can Med Assoc J* 1960; **83**: 263–5.
11 Dijk EV. Familial sclerodactyly. *Dermatologica* 1971; **143**: 253.
12 Esterly NS, McKusick VA. Stiff skin syndrome. *Pediatrics* 1971; **47**: 360–9.
13 Jablonska S, Groniowski J, Krieg T *et al.* Congenital fascial dystrophy: a non-inflammatory disease of fascia: the stiff skin syndrome. *Pediatr Dermatol* 1984; **2**: 87–97.
14 Nakanishi T, Sobue I, Toyokura Y *et al.* The Crow–Fukase syndrome: a study of 102 cases in Japan. *Neurology* 1984; **34**: 712–20.
15 Burton JL. Peripheral neuropathy associated with dysproteinaemia, skin changes, and endocrinopathy. *BMJ* 1986; **292**: 1415.
16 Viard JP, Lesavre P, Boitard C *et al.* POEMS syndrome presenting as systemic sclerosis. *Am J Med* 1988; **84**: 524–8.
17 Lapido GOA. Progressive systemic sclerosis (scleroderma). *Dermatologica* 1976; **153**: 196–201.
18 Garza-Elizondo MA, Diaz-Jonanen E, Franco-Casique JJ *et al.* Joint contractures and scleroderma-like skin changes in the hands of insulin-dependent juvenile diabetics. *J Rheumatol* 1983; **10**: 797–800.
19 Seibold JR. Digital sclerosis in children with insulin-dependent diabetes mellitus. *Arthritis Rheum* 1982; **25**: 1357–61.

Prognosis [1–3]. The prognosis for this disorder is variable. Some patients die within a year or two and others live for many years, even those whose course may initially have been rapid with gangrene of the extremities. Males have a poorer prognosis than females [2,3], although in a recent series [4] the reverse was true. Overall, there is a fourfold increase in mortality in patients with systemic sclerosis. Patients with extensive skin and visceral involvement have a poorer prognosis [5], as do approximately 20% with rapidly progressive disease [6]. Pulmonary involvement is permanent; patients with 60% or greater reduction in pulmonary diffusing capacity have a 5-year survival of less than 10% [7]. Renal involvement is also an adverse factor, although some patients live for years. Patients with telangiectases and calcinosis have the same prognosis as other patients. Those with changes confined to the hands have a good prognosis [8]. Five-year survival varies between series from 34 to 80%, the difference probably depending on the proportion of females. Cumulative survival rate in one series [9] was 80% at 2 years, 50% at 8.5 years and 30% at 12 years. There is no relation to the presence or type of antinuclear factor. Patients with depression of T cells and decreased cell-mediated immunity [10], and with histocompatibility type HLA-B8, appear to have extensive disease and a poor prognosis [11]. The usual causes of death are from intercurrent infection, respiratory failure, cardiac failure, renal failure sometimes with malignant hypertension, and perforation of the gastrointestinal tract. Occasionally, patients with pulmonary involvement develop carcinoma of the lung [12], but the association of isolated cases of carcinoma of the thyroid, ovary, cervix, brain, oesophagus, stomach, breast [13], lymphoma and leukaemia with systemic sclerosis may be fortuitous [14]. Occasionally, the two diseases occur simultaneously, and a rare improvement of systemic sclerosis with treatment of the malignancy has been observed [15]. Localized radiotherapy for solid malignant tumours in patients with systemic sclerosis has been noted to exaggerate the cutaneous and internal fibrotic reaction in the irradiated areas [16].

References

1 Bennett R, Bluestone R, Holt PJL *et al.* Survival in scleroderma. *Ann Rheum Dis* 1971; **30**: 581–8.
2 Medsger TA, Masi AT, Rodnan GP *et al.* Survival with systemic sclerosis (scleroderma). *Ann Intern Med* 1971; **75**: 369–76.
3 Rowell NR. The prognosis of systemic sclerosis. *Br J Dermatol* 1976; **95**: 57–60.
4 Bryan C, Howard Y, Brennan P *et al.* Survival following the onset of scleroderma: results from a retrospective inception cohort study of the UK patient population. *Br J Rheumatol* 1996; **35**: 1122–6.
5 Barnett AJ, Miller MH, Littlejohn GO. A survival study of patients with scleroderma diagnosed over 30 years (1953–83): the value of a simple cutaneous classification in the early stages of the disease. *J Rheumatol* 1988; **15**: 276–83.
6 Lally EV, Jimenez SA, Kaplan SR. Progressive systemic sclerosis: mode of presentation, rapidly progressive disease course, and mortality based on an analysis of 91 patients. *Semin Arthritis Rheum* 1988; **18**: 1–13.
7 Peters-Golden M, Wise RA, Hochberg M *et al.* Carbon monoxide diffusing capacity as a predictor of outcome in systemic sclerosis. *Am J Med* 1984; **77**: 1027–34.
8 Barnett AJ, Coventry DA. Scleroderma. 1. Clinical features, course of illness and response to treatment in 61 cases. *Med J Aust* 1969; **1**: 992–1001.
9 Altman RD, Medsger TA, Bloch DA *et al.* Predictors of survival in systemic sclerosis (scleroderma). *Arthritis Rheum* 1991; **34**: 403–13.
10 Hughes P, Holt S, Rowell NR *et al.* The relationship of defective cell-mediated immunity to visceral disease in systemic sclerosis. *Clin Exp Immunol* 1977; **28**: 233–40.
11 Hughes P, Gelsthorpe K, Doughty RW *et al.* The association of HLA-B8 with visceral disease in systemic sclerosis. *Clin Exp Immunol* 1978; **31**: 351–6.
12 Haqquani MT, Holti G. Systemic sclerosis with pulmonary fibrosis and oat cell carcinoma. *Acta Derm Venereol (Stockh)* 1973; **53**: 369–74.
13 Kissinger A, Lemon HM, Foley JF. Carcinoma of the breast and scleroderma. *Nebraska Med J* 1973; **58**: 186–8.
14 Talbott JH, Barrocas M. Progressive systemic sclerosis (PSS) and malignancy, pulmonary and non-pulmonary. *Medicine* 1979; **58**: 182–207.
15 Duncan SC, Winkelmann RK. Cancer and scleroderma. *Arch Dermatol* 1979; **115**: 950–5.
16 Varga J, Haustein UF, Creech RH *et al.* Exaggerated radiation-induced fibrosis in patients with systemic sclerosis. *JAMA* 1991; **265**: 3292–5.

Treatment. Symptomatic management of the patient is very important. There is no specific treatment, and no therapy is known to alter the course of the disease. Corticosteroids in low dosage may give a feeling of increased well-being and reduction of articular symptoms, and in these cases maintenance on a low dosage of prednisolone, such as 5 mg once or twice daily, is justified. Larger dosage will be required for patients with associated LE. There is

no evidence that corticosteroids retard the progress of the disease in any way, nor is there any real evidence that corticosteroids induce the onset of renal failure. Dexamethasone pulse therapy has been claimed to improve some patients [1]. It is important to advise the patient to keep as warm as possible, particularly in the winter months, and suitable work may have to be found to allow this. A light job in a warm atmosphere is ideal, and it is important to avoid even minor trauma of the hands. Electrically heated gloves are helpful [2], except in patients with incipient gangrene. Smoking should be discouraged [3]. There is no specific therapy for the skin, but applications of 0.025–0.05% tretinoin (Retin-A) have decreased perioral and facial tightening and creases [4]. Areas affected by calcium deposits may break down and heal with difficulty. Occasionally, deposits may have to be excised [5]. These techniques may be superseded by treatment with the carbon dioxide laser [6]. Treatment of digital calcinosis was successful in approximately two-thirds of cases. The average healing time was 6 weeks. Reconstructive surgery for sclerodactyly has sometimes given satisfactory results [7].

Vasodilators, such as oral reserpine [8], guanethidine [9], and particularly nifedipine 10–20 mg four times daily [10,11] and diltiazem [12], may improve the blood flow in the fingers. Ketanserin 20 mg twice daily to 40 mg three times daily may [13] or may not [14] be useful. Nifedipine may worsen oesophageal symptoms [15]. Prazosin 1 mg orally three times daily reduces the frequency and severity of vasospasm [16]. Simply warming the hands in hot water for 5–10 min produces considerable improvement in peripheral blood flow [17], and regular use of such a technique reduces the number and severity of attacks of Raynaud's phenomenon [18]. Intra-arterial reserpine is ineffective, and may have serious side effects [19]. Prostacyclin [20,21] and the synthetic prostacyclin analogue iloprost [22] are potent vasodilators and inhibitors of platelet aggregation, and have been found to be effective in decreasing the frequency, duration and severity of Raynaud's phenomenon, warming the hands, relieving pain and healing ischaemic ulcers. Earlier reports of the effect of prostaglandin E_1 have not been confirmed [23]. Infusion of prostacyclin via a central venous catheter over 72 h at a rate of 2.5–10 ng/kg/min produces improvement for approximately 8 weeks. Side effects include hypertension, headache, facial flushing, abdominal colic, nausea, vomiting and diarrhoea, and pain at the angle of the jaw at the beginning of mastication, disappearing within minutes. Similar results have been obtained by 5-h intravenous infusions given weekly for 3 weeks through a peripheral vein [24], a procedure that can be carried out on outpatients. Iloprost is useful in cases of incipient gangrene and digital ulcers [25]. Transdermal applications of these agents may be beneficial [26].

The use of intravenous low-molecular-weight dextran (Rheomacrodex) has been advocated [27], but controlled trials [28] have shown no consistent benefit, although in occasional patients there is healing of ulcerated fingertips. Renal failure and oliguria have followed this treatment [29]. Intravenous pentoxifylline may be of benefit in acute ischaemic lesions [30]. Cervical or lumbar sympathectomy may produce some improvement in the cutaneous circulation for a year or two, but there is no lasting benefit.

Penicillamine in regimens of from 500 to 1500 mg/day (mean 750 mg) given over approximately 2 years may decrease skin thickness, reduce the rate of further visceral involvement and improve the prognosis of patients if given early in their disease [31,32], particularly those with pulmonary involvement [33]. Other authors have found no benefit or no improvement in vascular or systemic complications, even if there is limited skin improvement [34]. In particular, progression of oesophageal disease continues [35]. Penicillamine therapy is associated with troublesome side effects [36]. In one study [37], the skin of 32% of patients improved, but deterioration occurred in the same percentage. In patients known to be sensitive to penicillin, the risk of an immediate allergic reaction is low [38]. Colchicine (1 mg/day or higher for 6 days per week) has also been advocated [39], but found to be ineffective [33]. Isotretinoin in a dosage of 1 mg/kg may help cutaneous sclerosis [40], as may factor XIII given intravenously [41]. Plasmapheresis [42] and plasma exchange [43], combined with prednisone and cyclophosphamide, have been used for patients with severe systemic sclerosis [42], with some clinical improvement and reduction of endothelial cell cytotoxicity. Extracorporeal photochemotherapy is encouraging but expensive. It has been shown to be more effective than penicillamine in decreasing clinical skin involvement and also safer in patients with disease of less than 4 years' duration [44]. Patients were treated for two consecutive days every 4 weeks for 6 months. It may be insufficient to control severe progressive disease with systemic involvement [45], and its use is controversial [46]. Azathioprine in a dosage of 150 mg/day has been subjectively helpful in approximately one-third of cases. Chlorambucil by mouth does not halt the progression of systemic sclerosis [47,48]. Intravenous 5-fluorouracil, given intermittently for 6 months, improved cutaneous and systemic features in an uncontrolled trial [49].

Ciclosporin may be of benefit [50,51]. It may improve skin induration but not visceral manifestations; adverse reactions, particularly nephrototoxicity, are frequent [52]. IFN-γ influences fibroblast behaviour *in vitro* [53]. It has reduced the skin score and improved blood gas analyses without any adverse effects over 12 months' therapy, but other systemic involvement was unchanged [54]. Others have noticed no alteration in skin score or improvement in visceral involvement [55]. IFN-α2a has also failed to improve visceral involvement [56]. Antithymocyte globulin is ineffective [57].

Symptomatic treatment for cardiac, renal and gastrointestinal symptoms may be required. Antihypertensive drugs, including minoxidil, reduce the blood pressure in malignant hypertension [58,59], and captopril, an oral ACE inhibitor, is a considerable advance in its treatment [60,61], as in most cases there is elevation of plasma renin activity. It controls blood pressure in most, if not all patients and relieves encephalopathy. It can improve renal function and, if given early, prevents renal failure and death. Improvement in renal function over 2 years has been reported [62], but is not uniform [63]. There is little evidence for a more general improvement in the disease resulting from these agents [64]. Benefit must be weighed against side effects. Haemodialysis and renal transplantation have helped patients with renal failure, with surprising improvement in the renal function and cutaneous manifestations [65]. Recovery of renal function can occur after months of dialysis. In one case, renal biopsy 14 months after transplant showed no evidence of the original disease [66]. Cimetidine

or ranitidine are worth trying for the symptoms of oesophageal reflux. Gastrostomy may be required for short-term feeding difficulties if dysphagia is severe [67]. Stricture of the oesophagus may benefit from surgical intervention [68]. Although the diffusion defect in the lungs cannot be altered, patients benefit from breathing exercises, and chest infections must be treated energetically with antibiotics. Pulmonary hypertension is a serious complication that may be treated with endothelin inhibitors such as bosentan [69] or sitaxsentan [70].

Immunosuppressive agents such as cyclophosphamide have been reported as useful in the treatment of systemic aspects of disease including lung fibrosis in a number of small, open studies, and, more recently, in two randomized controlled clinical trials [71–74]. So far there are only two randomized controlled trials to evaluate such immunosuppressive drugs which have enrolled mainly patients with established or long-standing disease; therefore, the potential for these drugs early in the course of disease remains unclear.

Many other preparations, including relaxin, sulfasalazine, 3-hydroxy-2-phenylcinchoninic acid (HPC), antihistamines, dihydrotachysterol and nicotinic acid, potassium *p*-aminobenzoate [75,76], intravenous disodium edetate, topical dimethylsulfoxide [77], the combination of phenformin and ethylestrenol [78], and antiplatelet therapy [79] have not proved of benefit. Hyperbaric oxygen may occasionally produce some improvement [80]. Calcitriol 1.75 µg/day may be helpful [81]. Dietary essential fatty acids such as γ-linolenic acid do not improve the vascular or other features [82].

Migraine sometimes occurs with systemic sclerosis [83], and methysergide or drugs containing ergot should not be given to such patients.

References

1 Pai BS, Srinivas CR, Sabitha L *et al.* Efficacy of dexamethasone pulse therapy in progressive systemic sclerosis. *Int J Dermatol* 1995, **34**: 726–8.
2 Kempson GE, Coggon D, Acheson ED. Electrically heated gloves for intermittent digital ischaemia. *BMJ* 1983; **286**: 268.
3 Goodfield MJD, Hume A, Rowell NR. The acute effects of cigarette smoking on peripheral blood flow in patients with and without Raynaud's phenomenon. *Br J Rheumatol* 1990; **29**: 89–91.
4 Kremer JM. Treatment of systemic sclerosis with topical tretinoin: report of two cases. *Arthritis Rheum* 1996; **39**: 1070.
5 Schlenker JD, Clark DD, Weckesser EC. Calcinosis circumscripta of the hand in scleroderma. *J Bone Joint Surg Am* 1973; **55**: 1051–6.
6 Bottomley WW, Goodfield MJD, Sheehan-Dare RA. Digital calcification in systemic sclerosis: effective treatment with good tissue preservation using the carbon dioxide laser. *Br J Dermatol* 1996; **135**: 302–4.
7 Lipscomb PR, Simons GW, Winkelmann RK. Surgery for sclerodactylia of the hand. *J Bone Joint Surg Am* 1969; **51**: 1112–7.
8 Coffman JD, Cohen AS. Total and capillary fingertip blood flow in Raynaud's phenomenon. *N Engl J Med* 1971; **285**: 259–63.
9 LeRoy EC, Downey JA, Cannon PJ. Skin capillary blood flow in scleroderma. *J Clin Invest* 1971; **50**: 930–9.
10 Kahan A, Amor B, Menkes CJ *et al.* Nifedipine in digital ulceration in scleroderma. *Arthritis Rheum* 1983; **26**: 809.
11 Winston EL, Pariser KM, Miller KB *et al.* Nifedipine as a therapeutic modality for Raynaud's phenomenon. *Arthritis Rheum* 1983; **26**: 1177–80.
12 Kahan A, Amor B, Menkes CJ. A randomized double blind trial of diltiazem in the treatment of Raynaud's phenomenon. *Ann Rheum Dis* 1985; **44**: 30–3.
13 Roald OK, Seem E. Treatment of Raynaud's phenomenon with ketanserin in patients with connective tissue disorders. *BMJ* 1984; **289**: 577–9.
14 Ortonne JP, Torzoli C, Dujardin P *et al.* Ketanserin in the treatment of systemic sclerosis: a double blind trial. *Br J Dermatol* 1989; **120**: 261–6.
15 Kahan A, Bour B, Couturier D *et al.* Nifedipine and oesophageal dysfunction in progressive systemic sclerosis. *Arthritis Rheum* 1985; **28**: 490–5.
16 Surwitt RS, Gilgor RS, Allen LM *et al.* A double-blind study of prazosin in the treatment of Raynaud's phenomenon in scleroderma. *Arch Dermatol* 1984; **120**: 329–31.
17 Goodfield MJD, Hume A, Rowell NR. The effect of simple warming procedures on finger blood flow in systemic sclerosis. *Br J Dermatol* 1988; **118**: 661–8.
18 Goodfield MJD, Rowell NR. Simple hand warming as treatment for Raynaud's phenomenon in systemic sclerosis. *Br J Dermatol* 1988; **119**: 643–6.
19 Surwitt RS, Gilgor RS, Duric M *et al.* Intra-arterial reserpine for Raynaud's syndrome. *Arch Dermatol* 1983; **119**: 733–5.
20 Dowd PM, Martin MFR, Cooke ED *et al.* Treatment of Raynaud's phenomenon by intravenous infusion of prostacyclin (PG_2 1). *Br J Dermatol* 1982; **106**: 81–9.
21 Martin MFR, Dowd PM, Ring EFJ *et al.* Prostaglandin E_1 infusions for vascular insufficiency in progressive systemic sclerosis. *Ann Rheum Dis* 1981; **40**: 350–4.
22 Rademaker M, Cooke ED, Almond NE *et al.* Comparison of intravenous infusions of iloprost and oral nifedipine in treatment of Raynaud's phenomenon in patients with systemic sclerosis: a double blind randomized study. *BMJ* 1989; **298**: 561–4.
23 Mohrland JS, Porter JM, Smith EA *et al.* A multiclinic, placebo-controlled, double-blind study of prostaglandin E_1 in Raynaud's syndrome. *Ann Rheum Dis* 1985; **44**: 754–60.
24 Belch JJF, Drury JK, Capell H *et al.* Intermittent epoprostenol (prostacyclin) infusion in patients with Raynaud's syndrome. *Lancet* 1983; **i**: 313–5.
25 Zachariae H, Halkier-Sorensen L, Bjerring P *et al.* Treatment of ischaemic digital ulcers and prevention of gangrene with intravenous iloprost in systemic sclerosis. *Acta Derm Venereol (Stockh)* 1996; **76**: 236–8.
26 Belch JJF, Madhok R, Shaw B *et al.* Double-blind trial of CL115,347, a transdermally absorbed prostaglandin E_2 analogue, in treatment of Raynaud's phenomenon. *Lancet* 1985; **i**: 1180–3.
27 Holti G. The effect of intermittent low molecular dextran infusions upon the digital circulation in systemic sclerosis. *Br J Dermatol* 1965; **77**: 560–8.
28 Dodman B, Rowell NR. Low molecular weight dextran in systemic sclerosis and Raynaud's phenomenon. *Acta Derm Venereol (Stockh)* 1982; **62**: 440–2.
29 Feest TG. Low molecular weight dextran. *BMJ* 1976; **ii**: 1300.
30 Goodfield MJD, Rowell NR. Treatment of peripheral gangrene due to systemic sclerosis with intravenous pentoxifylline. *Clin Exp Dermatol* 1989; **14**: 161–2.
31 Jimenez SA, Sigal H. A 15-year prospective study of treatment of rapidly progressive systemic sclerosis (PSS) with D-penicillamine (D-PEN). *J Rheumatol* 1991; **18**: 1496–503.
32 Clements PJ, Hurwitz EL, Wong WK *et al.* Skin thickness score as a predictor and correlate of outcome in systemic sclerosis: high-dose versus low-dose penicillamine trial. *Arthritis Rheum* 2000; **43**: 2445–54.
33 Medsger TA Jr. D-Penicillamine treatment of lung involvement in patients with systemic sclerosis (scleroderma). *Arthritis Rheum* 1987; **30**: 832–4.
34 Jayson MIV, Lovell C, Black CM *et al.* Penicillamine therapy in systemic sclerosis. *Proc R Soc Med* 1977; **70** (Suppl. 3): 82–8.
35 Hendel L, Stentoft P, Aggestrup S. The progress of oesophageal involvement in progressive systemic sclerosis during D-penicillamine treatment. *Scand J Rheumatol* 1989; **18**: 149–55.
36 Steen VD, Blair S, Medsger TA Jr. The toxicity of D-penicillamine in systemic sclerosis. *Ann Intern Med* 1986; **104**: 699–705.
37 Rook AH, Freundlich B, Jegasothy BV *et al.* Treatment of systemic sclerosis with extracorporeal photochemotherapy. *Arch Dermatol* 1992; **128**: 337–46.
38 Bell CL, Graziano FM. The safety of administration of penicillamine to penicillin-sensitive individuals. *Arthritis Rheum* 1983; **26**: 801–3.
39 Alarcón-Segovia D, Ibáñez G, Kershenobich D *et al.* Treatment of scleroderma. *Lancet* 1974; **i**: 1054–5.
40 Maurice PDL, Bunker CB, Dowd PM. Isotretinoin in the treatment of systemic sclerosis. *Br J Dermatol* 1989; **121**: 367–74.
41 Guilleven L, Euler-Ziegler L, Chouvet B *et al.* Treatment with factor XIII and long-term follow-up of 86 patients with progressive systemic sclerosis. *Presse Med* 1985; **14**: 2327–30.
42 Dau PC, Kahaleh MB, Sagebiel RW. Plasmapheresis and immuno-suppressive drug therapy in scleroderma. *Arthritis Rheum* 1981; **24**: 1128–36.

43 Mascaro G, Cadario G, Bordin G *et al.* Plasma exchange in the treatment of non-advanced stages of progressive systemic sclerosis. *J Clin Apheresis* 1987; **3**: 219–25.
44 di Spaltro FX, Cottrill C, Cahill C *et al.* Photochemotherapy for progressive systemic sclerosis. *Int J Dermatol* 1993; **32**: 417–21.
45 Zachariae H, Bjerring P, Heitckendorff L *et al.* Photophoresis and systemic sclerosis. *Arch Dermatol* 1992; **128**: 1651–3.
46 Cribier B, Faradji T, Le Coz C *et al.* Extracorporeal photochemotherapy in systemic sclerosis and severe morphoea. *Dermatology* 1995; **191**: 25–31.
47 Furst DE, Clements PJ, Hillis S *et al.* Immunosuppression with chlorambucil versus placebo for scleroderma. *Arthritis Rheum* 1989; **32**: 584–93.
48 Steigerwald JC. Chlorambucil therapy in progressive systemic sclerosis. *J Rheumatol* 1974; **1** (Suppl. 1): 74.
49 Casas JA, Subauste CP, Alarcon GS. A new promising treatment in systemic sclerosis: 5-fluorouracil. *Ann Rheum Dis* 1987; **46**: 763–7.
50 Vayssaiart M, Baudot N, Boitard C *et al.* Cyclosporine for severe systemic sclerosis associated with the anti-Scl-70 autoantibody. *J Am Acad Dermatol* 1990; **22**: 695–6.
51 Zachariae H, Halkier-Sorensen L, Heickendorff L *et al.* Cyclosporin A treatment of systemic sclerosis. *Br J Dermatol* 1990; **122**: 677–81.
52 Clements PJ, Lachenbruch PA, Sterz M *et al.* Cyclosporin in systemic sclerosis: results of a 48-week open safety study in 10 patients. *Arthritis Rheum* 1993; **36**: 75–83.
53 Rosenbloom J, Feldman G, Freundlich B *et al.* Inhibition of excessive scleroderma fibroblast collagen production by recombinant γ-interferon. *Arthritis Rheum* 1986; **29**: 851–6.
54 Hein R, Behr J, Hundegen M *et al.* Treatment of systemic sclerosis with γ-interferon. *Br J Dermatol* 1992; **126**: 496–501.
55 Hunzelmann N, Anders S, Fierbeck G *et al.* Systemic sclerosis: multicentre trial of 1 year treatment with recombinant interferon-γ. *Arch Dermatol* 1997; **133**: 609–13.
56 Stevens W, Vancheeswaran R, Black CM *et al.* Alpha interferon-2a (Roferon-A) in the treatment of diffuse cutaneous systemic sclerosis: a pilot study. *Br J Rheumatol* 1992; **31**: 683–9.
57 Matteson EL, Shbeeb MI, McCarthy TG *et al.* Pilot study of antithymocyte globulin in systemic sclerosis. *Arthritis Rheum* 1996; **39**: 1132–7.
58 Mitnick PD, Feig PU. Control of hypertension and reversal of renal failure in scleroderma. *N Engl J Med* 1978; **299**: 871–2.
59 Wasner C, Cooke CR, Fries JF. Successful medical treatment of scleroderma renal crisis. *N Engl J Med* 1978; **299**: 873–5.
60 Lopez-Ovejero JA, Saal SD, D'Angelo WA *et al.* Reversal of vascular and renal crises of scleroderma by oral angiotensin-converting-enzyme blockade. *N Engl J Med* 1979; **300**: 1417–9.
61 Whitman HH III, Case JB, Laragh JH *et al.* Variable response to oral angiotensin-converting enzyme blockade in hypertensive scleroderma patients. *Arthritis Rheum* 1982; **25**: 241–8.
62 Sorenson LB, Paunicka K, Harris M. Reversal of scleroderma renal crisis for more than 2 years in a patient treated with captopril. *Arthritis Rheum* 1983; **26**: 797–800.
63 Brown EA, MacGregor GA, Maini RN. Failure of captopril to reverse the renal crisis of scleroderma. *Ann Rheum Dis* 1983; **42**: 52–3.
64 Beckett VL, Donadio JV Jr, Brennan LA Jr *et al.* Use of captopril as early therapy for renal scleroderma: a prospective study. *Mayo Clin Proc* 1985; **60**: 763–71.
65 Simon NM, Graham MB, Kyser FA *et al.* Resolution of renal failure with malignant hypertension in scleroderma. *Am J Med* 1979; **67**: 533–9.
66 Keane WF, Danielson B, Raij L. Successful renal transplantation in progressive systemic sclerosis. *Ann Intern Med* 1976; **85**: 199–202.
67 Stainforth J, Goodfield MDJ. Severe oropharyngeal deglutition abnormalities in a patient with systemic sclerosis, managed with a gastrostomy. *Br J Dermatol* 1994; **130**: 682–3.
68 Mansour KA, Malone CE. Surgery for scleroderma of the oesophagus: a 12-year experience. *Ann Thorac Surg* 1988; **46**: 513–4.
69 Rubin LJ, Badesch DB, Barst RJ *et al.* Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002; **346**: 896–903.
70 O'Callaghan DS, Gaine SP. Sitaxsentan: an endothelin-A receptor antagonist for the treatment of pulmonary arterial hypertension. *Int J Clin Pract* 2006; **60**: 475–81.
71 Griffiths B, Miles S, Moss H *et al.* Systemic sclerosis and interstitial lung disease: a pilot study using pulse intravenous methylprednisolone and cyclophosphamide to assess the effect on high resolution computed tomography scan and lung function. *J Rheumatol* 2002; **29**: 2371–8.
72 White B, Moore WC, Wigley FM *et al.* Cyclophosphamide is associated with pulmonary function and survival benefit in patients with scleroderma and alveolitis. *Ann Intern Med* 2000; **132**: 947–54.
73 Hoyles RK, Ellis RW, Wellsbury J *et al.* A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. *Arthritis Rheum* 2006; **54**: 3962–70.
74 Tashkin DP, Elashoff R, Clements PJ *et al.* Scleroderma Lung Study Research Group. Cyclophosphamide versus placebo in scleroderma lung disease. *N Engl J Med* 2006; **354**: 2655–66.
75 Silber W, Gitlin N. Progressive systemic sclerosis (diffuse scleroderma): a follow-up report of treatment with potaba. *South Afr Med J* 1973; **47**: 1001–2.
76 Zarafonetis CJD, Dabich L, Skovronski JJ *et al.* Retrospective studies in scleroderma: skin response to potassium para-aminobenzoate therapy. *Clin Exp Rheumatol* 1988; **6**: 261–8.
77 Binnick SA, Shore SS, Corman A *et al.* Failure of dimethyl sulfoxide in the treatment of scleroderma. *Arch Dermatol* 1977; **113**: 1398–402.
78 Paolino JS, Kaplan D, Lazarus R *et al.* Phenformin and ethyloestrenol in scleroderma. *Lancet* 1972; **i**: 1023.
79 Beckett VL, Conn DL, Fuster V *et al.* Trial of platelet inhibiting drug in scleroderma. *Arthritis Rheum* 1984; **27**: 1137–43.
80 Barr P-O, Enfors W, Eriksson G. Hyperbaric oxygen therapy in dermatology. *Br J Dermatol* 1972; **86**: 631–5.
81 Humbert P, Aubin F, Delaporte E. Oral calcitriol as a new therapeutic agent in localized and systemic scleroderma. *Arch Dermatol* 1995; **131**: 850–1.
82 Stainforth JM, Layton AM, Goodfield MJD. Clinical aspects of the use of gamma linolenic acid in systemic sclerosis. *Acta Derm Venereol (Stockh)* 1996; **76**: 144–6.
83 Goldberg NC, Duncan SC, Winkelmann RK. Migraine and systemic scleroderma. *Arch Dermatol* 1978; **114**: 550–1.

Mixed connective tissue disease [1]

Overlap syndromes occur in the connective tissue diseases, and have recently been reviewed [1]. A number of attempts at defining diagnostic criteria, along the lines of those used for SLE, have been made [2]. Some associations are more frequent than others; for example, systemic sclerosis combined with dermatomyositis is more frequent than systemic sclerosis combined with SLE [3]. Some of these patients may have 'mixed connective tissue disease', an entity associated with a specific antibody to U_1-RNP, an ENA first described by Sharp and colleagues in 1972 [4]. These patients, predominantly female, show features of SLE, systemic sclerosis, dermatomyositis and polymyositis. Raynaud's phenomenon, arthritis and arthralgia, sausage-shaped fingers and swelling of the dorsa of the hands, abnormal oesophageal motility, impaired pulmonary diffusing capacity and myositis are frequent. More than half have the abnormal nail fold capillaries seen in systemic sclerosis. Angiography shows obstruction of small blood vessels in almost 90% of cases, and peripheral gangrene may occur (Fig. 51.75) [5]. The incidence of clinical renal disease is approximately 5%, but renal histology is abnormal in 20% [6]. Aseptic meningitis, trigeminal neuropathy, transverse myelitis and psychosis are prominent neurological features. Neuropsychiatric manifestations were noted in 15% of one series. Other, less frequent features have been reviewed [7], and include orogenital ulceration, pneumatosis intestinalis, protein-losing enteropathy, panniculitis and autonomic neuropathy. Enlarged



Fig. 51.75 Gangrene of the hands in mixed connective tissue disease.

nodes of Kikuchi's disease were the presenting feature in one case [8].

The response to treatment with corticosteroids is good, and other successful treatment options, including hydroxychloroquine and methotrexate, have been reviewed [9]. The characteristic antibody may be suppressed by treatment, and disappears in patients in remission [10].

Mixed connective tissue disease may be more severe in children, in whom cardiac and renal disease and arthritis are common, and thrombocytopenia may be marked, although the overall prognosis may be quite good [11]. Thrombocytopenia is also occasionally found in adult cases, and may occur with thrombotic thrombocytopenic purpura [12]. The role of silicone breast implants in the pathogenesis of the overlap syndromes is controversial, and there is probably no relationship [13]. Livedoid vasculitis [14], ankylosing spondylitis [15] and antineutrophil cytoplasmic antibody (ANCA)-related glomerulonephritis [16] are reported to occur with mixed connective tissue disease.

References

1 Venables PJ. Mixed connective tissue disease. *Lupus* 2006; **15**: 132–7.

2 Alarcón-Segoviá D, Cardiel MH. Comparison between three diagnostic criteria for mixed connective tissue disease: study of 593 patients. *J Rheumatol* 1989; **16**: 328–56.

3 Minkin W, Rabhan N. Mixed connective tissue disease. *Arch Dermatol* 1976; **112**: 1535–8.

4 Sharp GC, Irvin WS, Tan EM *et al.* Mixed connective tissue disease. *Am J Med* 1972; **52**: 148–59.

5 Kondo H. Vascular disease in mixed connective tissue disease (MCTD). *Intern Med* 2001; **40**: 1176.

6 Bennett RM, Spargo BH. Immune complex nephropathy in mixed connective tissue disease. *Am J Med* 1977; **63**: 534–41.

7 Pope JE. Other manifestations of mixed connective tissue disease. *Rheum Dis Clin North Am* 2005; **31**: 519–33.

8 Gourley I, Bell AL, Biggart D. Kikuchi's disease as a presenting feature of mixed connective tissue disease. *Clin Rheumatol* 1995; **14**: 104–7.

9 Kim P, Grossman JM. Treatment of mixed connective tissue disease. *Rheum Dis Clin North Am* 2005; **31**: 549–65.

10 Pettersson I, Wang G, Smith EI *et al.* The use of immunoblotting and immunoprecipitation of small nuclear ribonucleoproteins in the analysis of sera of patients with mixed connective tissue disease and systemic lupus erythematosus. *Arthritis Rheum* 1986; **29**: 986–96.

11 Mier RJ, Shishov M, Higginns GC *et al*. Paediatric onset mixed connective tissue disease. *Rheum Dis Clin North Am* 2005; **31**: 483–96.

12 Poullin P, Lefevre P, Durand JM. Mixed connective tissue disease with haemolytic anemia and severe thrombocytopenia due to thrombotic thrombocytopenic purpura. *Am J Hematol* 1999; **61**: 275.

13 McLaughlin JK, Lipworth L, Murphy DK, Walker PS. The safety of silicone gel-filled breast implants: a review of the epidemiologic evidence. *Ann Plast Surg* 2007; **59**: 569–80.

14 Oh YB, Jun JB, Kim CK *et al.* Mixed connective tissue disease associated with skin defects of livedoid vasculitis. *Clin Rheumatol* 2000; **19**: 381–4.

15 Lee JK, Jung SS, Kim TH *et al.* Coexistence of ankylosing spondylitis and mixed connective tissue disease in a single patient. *Clin Exp Rheumatol* 1999; **17**: 263.

16 Makita N, Katori H, Takemoto F *et al.* A case of mixed connective tissue disease (MCTD) complicated with MPO-ANCA-related necrotizing glomerulonephritis. *Clin Nephrol* 2000; **54**: 164–8.

Immunology. All patients have the speckled type of antinuclear antibody together with a high titre of antibody to ENA, which is sensitive to digestion with ribonuclease (RNase), unlike the ENA antibodies often found in patients with SLE. Different molecular forms of U_1-RNP may be associated with different clinical variants [1]. Ro and La antibodies are also frequently found, usually in association with sicca symptoms [2]. Precipitating antibodies designated PM-1 [3] and Ku [4] occur in polymyositis/systemic sclerosis overlap, and SL-Ki in patients with SLE, scleroderma and the sicca syndrome [5]. Immune complexes occur in 90% of patients, and T cells are decreased. Complement levels are normal. Sometimes, anti-DNA antibody occurs in low titre, but this usually disappears with steroid therapy. Antiendothelial antibodies occur in approximately 50% of cases, and are associated with abnormal pulmonary, neurological and cardiac function, particularly pulmonary hypertension [6]. They are also related significantly to spontaneous abortion in female patients [7]. HLA-DR4 is found more commonly in patients with arthritis than in normal controls, and is associated with a young age of onset of the condition [8]. There are also reports of familial cases [9]. Differences in HLA antigens between patients with mixed connective tissue disease and SLE indicate that they are genetically separate disorders [10].

Immunohistology of uninvolved skin, where there is basement membrane staining with IgG or M, may be helpful in distinguishing MCTD from uncomplicated systemic sclerosis where staining is absent [11].

Direct immunofluorescence study of apparently normal skin reveals particulate ('speckled') epidermal nuclear staining, and this correlates with high titres of anti-RNP. Occasionally, epidermal nucleolar staining occurs. Patients with these features [12] show a high incidence of persistent, diffuse, non-scarring and focal alopecia, hyper- and hypopigmentation with follicular retention of pigment, swollen hands with sclerodactyly, and lesions of DLE.

Although the presence of anti-RNP is usually associated with a good prognosis, death occurs in approximately 4% from pulmonary hypertension, brought about by vascular changes similar to those seen in primary pulmonary hypertension [13], nephritis, myocarditis or widespread vasculitis. Approximately one-third develop into a characteristic connective tissue disease, usually SLE or SSc [14]. A few patients with HLA-DR4 developed rheumatoid arthritis. In patients whose disease differentiated into systemic

sclerosis, there was an association with HLA-DR5 [15]. The relatively good prognosis has been confirmed recently [16].

With time, more variants of the overlap syndromes are being described, both with and without U_1-RNP antibody. Hence, some authors now regard mixed connective tissue disease as one among many 'undifferentiated connective tissue diseases' or 'overlap syndromes'. Doubts about the concept of mixed connective tissue disease have been expressed, particularly in children [17]; nevertheless, it is important to recognize this group of patients because of the good prognosis and the response to steroid therapy. There may be an increased risk of malignancy, with cancer developing in 10% of cases [18].

References

1 Greidinger EL, Casciola-Rosen L, Morris SM *et al.* Autoantibody recognition of distinctly modified forms of the U1–70-kD antigen is associated with different clinical disease manifestations. *Arthritis Rheum* 2000; **43**: 881–8.

2 Setty YN, Pittman CB, Mahale AS *et al.* Sicca symptoms and anti-SSA/Ro antibodies are common in mixed connective tissue disease. *J Rheumatol* 2002; **29**: 487–9.

3 Wolf JF, Adelstein E, Sharp GC. Antinuclear antibody with distinct specificity for polymyositis. *J Clin Invest* 1977; **59**: 176–8.

4 Mimori T, Akizuki M, Yamagata H *et al.* Characterization of a high molecular weight acidic nuclear protein recognized by autoantibodies in sera from patients with polymyositis–scleroderma overlap. *J Clin Invest* 1981; **68**: 611–20.

5 Parodi A, Nigro A, Rebora A. Anti-SL-Ki antibody in a patient with fatal connective tissue overlap disease. *Br J Dermatol* 1989; **121**: 243–6.

6 Vegh J, Szodoray P, Kappelmayer J *et al.* Clinical and immunoserological characteristics of mixed connective tissue disease associated with pulmonary hypertension. *Scand J Immunol* 2006; **64**: 69–76.

7 Bodolay E, Bojan F, Szegedi G *et al.* Cytotoxic endothelial cell antibodies in mixed connective tissue disease. *Immunol Lett* 1989; **20**: 163–8.

8 Black CM, Maddison PJ, Welsh KI *et al.* HLA and immunoglobulin allotypes in mixed connective tissue disease. *Arthritis Rheum* 1988; **31**: 131–4.

9 Shiiki H, Miyagawa S, Dohi K *et al.* Anti-nuclear RNP antibodies in two sisters. *Br J Dermatol* 1985; **113**: 617–22.

10 Ruuska P, Hameenkorpi R, Forsberg S *et al.* Differences in HLA antigens between patients with mixed connective disease and systemic lupus erythematosus. *Ann Rheum Dis* 1992; **51**: 52–5.

11 Winkelmann RK, Carapeto FJ, Jordon RE. Direct immunofluorescence in the diagnosis of scleroderma syndromes. *Br J Dermatol* 1977; **96**: 231–8.

12 Gilliam JN, Prystowsky SD. Mixed connective tissue disease syndrome. *Arch Dermatol* 1977; **113**: 583–7.

13 Bull TM, Fagan KA, Badesch DB. Pulmonary vascular manifestations of mixed connective tissue disease. *Rheum Dis Clin North Am* 2005; **31**: 451–64.

14 Bodoly E, Csiki Z, Ben T *et al.* Five year follow up of 665 Hungarian patients with undifferentiated connective tissue disease (UCTD). *Clin Exp Rheumatol* 2003; **21**: 313–20.

15 Gendi NS, Welsh KI, Van-Venrooij WJ *et al.* HLA type as a predictor of mixed connective tissue disease differentiation: 10 year clinical and immunogenetic follow-up of 46 patients. *Arthritis Rheum* 1995; **38**: 259–66.

16 Lundberg IE. The prognosis of mixed connective tissue disease. *Rheum Clin North Am* 2005; **31**: 535–47.

17 Mier R, Ansell B, Hall MA *et al.* Long-term follow-up of children with mixed connective tissue disease. *Lupus* 1996; **5**: 221–6.

18 Black KA, Zilko PJ, Dawkins RL *et al.* Cancer in connective tissue disease. *Arthritis Rheum* 1982; **25**: 1130–3.

Cold, flexed fingers (Fig. 51.76)

Several female patients have been seen with cold, flexed fingers, but no evidence of systemic abnormality, despite extensive investigations including pulmonary function tests. The presenting feature of inability to extend the fingers fully starts in the second to fourth decades. There may be difficulty in flexion of the fingers and in making a fist. All have thin, cold fingers, but there is no evidence of acrosclerosis, and Raynaud's phenomenon is not invariable. The condition remains unchanged for years and is not influenced by vasodilators or systemic corticosteroids.



Fig. 51.76 Cold flexed fingers: note the inability to extend the fingers fully.

Some patients may be early cases of systemic sclerosis. One patient has developed rheumatoid arthritis, with deformities of the hands.

The condition was first described in the first edition of this textbook in 1968 [1]. It appears to be similar to what has been termed 'bowed fingers' [2]. Some patients with bowed fingers had features of systemic sclerosis or mixed connective tissue disease.

References

1 Rowell NR. Cold flexed fingers. In: Rook A, Wilkinson DS, Ebling FJG, eds. *Textbook of Dermatology*. Oxford: Blackwell Scientific Publications, 1968: 564.

2 Palmer DG, Hale GM, Grennan DM. Bowed fingers: a helpful sign in the diagnosis of systemic sclerosis. *J Rheumatol* 1981; **8**: 266–72.

Lichen sclerosus [1,2]

Synonyms

- Lichen sclerosus et atrophicus
- Guttate morphoea
- Guttate scleroderma
- White-spot disease

Definition. An uncommon disease of unknown aetiology in which characteristic, easily recognized, small, white, sclerotic areas occur at any site on the skin. This frequently involves the perineal skin in the female, and the penis and foreskin in the male. It may occur in genital and non-genital skin separately or together. Hallopeau [3] first described the condition in 1887, and Darier [4] reported the histological changes in 1892. They considered the disorder to be a type of lichen planus; others thought that the condition was

Table 51.18 Associations of lichen sclerosus.

Morphoea
Vitiligo
Alopecia areata (in males)
Pernicious anaemia (in females)
Limited cutaneous systemic sclerosis
Systemic lupus erythematosus
Lichen planus

related to localized scleroderma. Most people now regard lichen sclerosus as a separate entity, because of the distinct clinical signs and pathological changes. The term 'white-spot disease' is sometimes applied to the skin lesions on the trunk and limbs, although some authors refer to these lesions as 'guttate scleroderma'. It may be closely related to morphoea, as the two conditions can occur together and, rarely, morphoea can produce similar genital lesions [5] (Table 51.18).

Incidence [6]. The condition is an uncommon one. Females predominate and patients with lichen sclerosus make up nearly 2% of general gynaecologists' practice [7]. In Wallace's [8] series of 359 patients, females outnumbered males by 10:1. Approximately 20% of patients with lichen sclerosus of the vulva had lesions on the trunk [9]. Certainly, involvement of the vulva, perineum and perianal skin in females is more common than balanitis xerotica obliterans, which is the corresponding lesion in the adult male. The condition occurs particularly around and after the menopause, but also occurs in girls between the ages of approximately 1 and 13 years. The disease is not uncommon in boys with phimosis [9], and the incidence is probably underestimated. The mean age of onset in one series of cases [10] was 50 for females and 43 for males. The condition has been seen in mother and daughter, mother and son, brother and sister, and sisters and brothers, but not in father and son. It has occurred in monozygotic female twins [11] and in non-identical female twins [12].

References

1 Tasker GL, Wojnarowska F. Lichen sclerosus. *Clin Exp Dermatol* 2003; **28**: 128–33.
2 Howard R, Tsuchiya A. Adult skin disease in the pediatric patient. *Dermatol Clin* 1998; **16**: 593–608.
3 Hallopeau H. Lichen plan, atrophique. *Ann Dermatol Syphiligr* 1887; **8**: 790–4.
4 Darier J. Lichen sclerosus. *Ann Dermatol Syphiligr* 1892; **3**: 833.
5 Bizzozero E. Scleroderma guttata, lichen sclerosus, kraurosis penis. *Arch Dermatol Syphilol* 1943; **183**: 493.
6 Pugliese JM, Morey AF, Peterson AC. Lichen sclerosus: review of the literature and current recommendations for management. *J Urol* 2007; **178**: 2268–76.
7 Goldstein AT, Marinoff SC, Christopher K, Srodon M. Prevalence of vulvar lichen sclerosus in a general gynecology practice. *J Reprod Med* 2005; **50**: 477–80.
8 Wallace HJ, Whimster I. Vulval atrophy and leukoplakia. *Br J Dermatol* 1951; **63**: 241–57.
9 Kiss A, Kiraly L, Kutasy B, Merksz M. High incidence of balanitis xerotica obliterans in boys with phimosis: prospective 10-year study. *Pediatr Dermatol* 2005; **22**: 305–8.
10 Simpkin S, Oakley A. Clinical review of 202 patients with vulval lichen sclerosus: a possible association with psoriasis. *Australas J Dermatol* 2007; **48**: 28–31.
11 Meyrick Thomas RH, Kennedy CTC. The development of lichen sclerosus et atrophicus in monozygotic twin girls. *Br J Dermatol* 1986; **114**: 377–9.
12 Cox NH, Mitchell JNS, Morley WN. Lichen sclerosus et atrophicus in non-identical female twins. *Br J Dermatol* 1986; **115**: 743–6.

Aetiology [1]. The aetiology is unknown, lesions usually appearing spontaneously without any precipitating factor. The predominance of females, the frequent onset around the menopause and the spontaneous improvement in girls after puberty suggest a hormonal factor, but no convincing causative factors have been identified.

The increased prevalence of organ-specific antibodies and of associated autoimmune diseases in both female patients and relatives suggest an autoimmune cause, but there is no difference in the natural history of those with or without antibodies [2]. The incidence of other autoimmune diseases in patients is highest when the onset is between the ages of 41 and 60 years, but is not related to the site or duration of lesions. Once the diagnosis of lichen sclerosus has been established, patients do not seem to be at continued excessive risk of developing autoimmune diseases [3]. Approximately 50% of female patients will have a personal or family history of autoimmune disease [4]. Male patients also have an increased prevalence of autoimmune disorders and autoantibodies [5]. Associations with HLA types have been inconsistent; HLA-A29 and -B44 were found to occur more frequently, both separately and together [6], but this was not confirmed [4]. The class II antigens DQ7, 8 or 9 were found to be present in 78% of patients [4], and in a large study HLA-DRB112 and its associated haplotype increased susceptibility to vulval disease, whereas DRB10301 conferred protection [7]. In men, HLA-DR11, -DR12 and -DQ7 were found to be positively associated with the development of the disease, and the association with autoimmune disease is less marked than in women [8].

A history of preceding vaginitis and, in the male, the limitation of genital involvement to the uncircumcised or very recently circumcised, who often give a history of chronic balanitis, suggests that infection may play a provocative or localizing part [9]. There may be geographical differences that explain the potential role of *Borrelia*, with evidence of infection found in Germany and Japan but not in the USA [10]. Vulval lesions are not related to parity. Trauma may act as a precipitating factor, and lichen sclerosus has been reported in a vaccination site [11], in the area of radiotherapy following mastectomy [12], after severe sunburn [13], in an old burn scar [14], as a result of welding sparks [15] and at the site of a strawberry naevus [16].

References

1 Tasker GL, Wojnarowska F. Lichen sclerosus. *Clin Exp Dermatol* 2003; **28**: 128–33.
2 Meyrick Thomas RH, Ridley CM, McGibbon DH *et al.* Lichen sclerosus et atrophicus and autoimmunity: a study of 350 women. *Br J Dermatol* 1988; **118**: 41–6.
3 Meyrick Thomas RH, Holmes RC, Rowland Payne CME *et al.* The incidence of development of autoimmune disease in women after the diagnosis of lichen sclerosus et atrophicus. *Br J Dermatol* 1982; **107** (Suppl. 22): 29.
4 Marren P, Yell J, Charnock FM *et al.* The association between lichen sclerosus and antigens of the HLA system. *Br J Dermatol* 1995; **132**: 197–203.
5 Meyrick Thomas RH, Ridley CM, Black MM. The association of lichen sclerosus et atrophicus and autoimmune-related disease in males. *Br J Dermatol* 1983; **109**: 661–4.
6 Purcell KG, Spencer LV, Simpson PM *et al.* HLA antigens in lichen sclerosus et atrophicus. *Arch Dermatol* 1990; **126**: 1043–5.

7 Gao XH, Barnardo MC, Winsey S *et al*. Agudelo JD. Zhai N. Powell JJ. Fuggle SV. Wojnarowska F. The association between HLA DR, DQ antigens, and vulval lichen sclerosus in the UK: HLA DRB112 and its associated DRB112/DQB10301/04/09/010 haplotype confers susceptibility to vulval lichen sclerosus, and HLA DRB10301/04 and its associated DRB10301/04/DQB10201/02/03 haplotype protects from vulval lichen sclerosus. *J Invest Dermatol* 2005; **125**: 895–9.
8 Azurdia RM, Luzzi GA, Byren I *et al*. Lichen sclerosus in adult men: a study of HLA associations and susceptibility to autoimmune disease. *Br J Dermatol* 1999; **140**: 79–83.
9 Mallon E, Hawkins D, Dinneen M *et al*. Circumcision and genital dermatoses. *Arch Dermatol* 2000; **136**: 350–4.
10 Fujiwara H, Fujiwara K, Hashimoto K *et al*. Detection of *Borrelia burgdorferi* DNA (*B. garinii* or *B. afzelii*) in morphoea and lichen sclerosus et atrophicus tissues of German and Japanese but not US patients. *Arch Dermatol* 1989; **120**: 207–9.
11 Anderton RL, Abele DC. Lichen sclerosus et atrophicus in a vaccination site. *Arch Dermatol* 1976; **112**: 1787.
12 Yates VM, King CM, Dave VK. Lichen sclerosus et atrophicus following radiation therapy. *Arch Dermatol* 1985; **121**: 1044–7.
13 Milligan A, Graham-Brown RAC, Burns DA. Lichen sclerosus et atrophicus following sunburn. *Clin Exp Dermatol* 1988; **13**: 36–7.
14 Meffert JJ, Grimwood RE. Lichen sclerosus et atrophicus appearing in an old burn scar. *J Am Acad Dermatol* 1994; **31**: 671–3.
15 Tegner E, Vrana I. Lichen sclerosus et atrophicus appearing in old scars of burns from welding sparks. *Acta Derm Venereol* 2001; **81**: 211.
16 Ostlere LS, Tildsley G, Holden CA. Lichen sclerosus over a strawberry naevus: a new example of the Koebner phenomenon? *Clin Exp Dermatol* 1996; **21**: 394–5.

Pathology. The striking histological change in lichen sclerosus is a band of hyalinization of the dermal collagen below the epidermis. The hyalinized tissue appears structureless and oedematous, and contains sparse cells, but may show dilated capillaries. The epidermis shows variable thickening, hyperkeratosis and follicular plugging. Later, the epidermis becomes thinned. A band of lymphocytic infiltration may also be seen below the hyalinized area; in older lesions this may be more scanty and focal. The subepidermal elastic tissue tends to be depressed and separated from the epidermis by oedema. The infiltrate contains immunoregulatory lymphocytes [1] which may be self-recruiting [2]. T-cell-mediated inflammation and activation [3] is associated with basement membrane damage and laminin and collagen 4 and 7 over-expression [4]. There is also blood vessel proliferation [5], and over-deposition of dermal connective tissue, including hyaluronate [6], fibrillin, collagens I and III and elastin [7], with abnormal distributions of tenascin, fibronectin and fibrinogen [8]. Androgen receptors are reduced [9].

In vulval lesions, secondary infection and superficial erosion are common, and may mask the primary changes. In lesions with sclerotic change, the epidermis shows marked thickening, irregularity and hyperkeratosis. The dermal oedema tends to regress and sclerosis and dense chronic inflammation occupy the subepidermal zone. These changes are seen in over half of all biopsies of vulval lichen sclerosus, and in two-thirds when there is itching [10].

The condition must be distinguished from lichenification, in which the dermal papillae are prolonged and oedematous, with corresponding lengthening of the rete pegs. There is usually dermal oedema and epidermal spongiosis and parakeratosis. In primary atrophy of the vulva, the epidermis is thinned, the lower border is flattened and keratinization is normal or reduced. There is also a reduction in the elastic tissue, particularly in the superficial zone, but the collagen is unaltered. Immediately beneath the epidermis there is a band of chronic inflammatory cells. In dysplastic leukoplakia, there is some degree of hyperplasia of the epidermis, with considerable irregularity in the outline of the deeper border, together with some hyperkeratosis. An inflammatory infiltrate occurs near the deeper border of the epidermis. The collagen of the superficial part of the dermis shows hyaline changes and the elastic tissue is lost.

Electron microscopy has revealed striking changes in dermal collagen fibres and increased amounts of elastin [11]. Immunoglobulins (IgG, IgM, IgA), complement and fibrin may be demonstrated in the damaged skin. IgG autoantibodies to the basement membrane zone were found and may be relevant to pathogenesis [12].

References

1 Tchorzewski H, Rotsztejn H, Banasik M *et al*. The involvement of immunoregulatory T cells in the pathogenesis of lichen sclerosus. *Med Sci Monit* 2005; **11**: CR39–43.
2 Wenzel J, Wiechert A, Merkel C *et al*. IP10/CXCL10–CXCR3 interaction: a potential self-recruiting mechanism for cytotoxic lymphocytes in lichen sclerosus et atrophicus. *Acta Derm Venereol* 2007; **87**: 112–7.
3 Hunger RE, Bronnimann M, Kappeler A *et al*. Detection of perforin and granzyme B mRNA expressing cells in lichen sclerosus. *Exp Dermatol* 2007; **16**: 416–20.
4 Cooper SM, Prenter A, Allen J *et al*. The basement membrane zone and dermal extracellular matrix in erosive lichen planus of the vulva: an immunohistochemical study demonstrating altered expression of hemidesmosome components and anchoring fibrils. *Clin Exp Dermatol* 2005; **30**: 277–81.
5 Kowalewski C, Kozlowska A, Gorska M *et al*. Alterations of basement membrane zone and cutaneous microvasculature in morphea and extragenital lichen sclerosus. *Am J Dermatopathol* 2005; **27**: 489–96.
6 Kaya G, Augsburger E, Stamenkovic I *et al*. Decrease in epidermal CD44 expression as a potential mechanism for abnormal hyaluronate accumulation in superficial dermis in lichen sclerosus et atrophicus. *J Invest Dermatol* 2000; **115**: 1054–8.
7 Farrell AM, Dean D, Millard PR *et al*. Alterations in fibrillin as well as collagens I and III and elastin occur in vulval lichen sclerosus. *J Eur Acad Dermatol Venereol* 2001; **15**: 212–7.
8 Farrell AM, Dean D, Charnock FM *et al*. Alterations in distribution of tenascin, fibronectin and fibrinogen in vulval lichen sclerosus. *Dermatology* 2000; **201**: 223–9.
9 Carlson JA, Murphy M. Androgen receptors and lichen sclerosus. *J Am Acad Dermatol* 2000; **43**: 559–60.
10 Wallace HJ. Lichen sclerosus et atrophicus. *Trans St John's Hosp Dermatol Soc* 1971; **57**: 9–30.
11 Mann PR, Cowan MA. Ultrastructural changes in four cases of lichen sclerosus et atrophicus. *Br J Dermatol* 1973; **89**: 223–31.
12 Howard A, Dean D, Cooper S *et al*. Circulating basement membrane zone antibodies are found in lichen sclerosus of the vulva. *Australas J Dermatol* 2004; **45**: 12–5.

Clinical features [1]

Non-genital lesions. The lesions on the skin are symptomless and occur on the trunk, particularly on the upper part and around the umbilicus, around the neck, in the axillae, on the flexor surfaces of the wrists (Fig. 51.77), around the eye and, very rarely, on the scalp, palms and soles [2]. They have also been described confined to the skin around the areolae [3]. Lesions can occur at sites of pressure (e.g. underneath bra straps or belts). The lesions are small, ivory or porcelain-white, shiny, round macules or papules,



Fig. 51.77 Lichen sclerosus of the front of the wrist.



Fig. 51.78 Lichen sclerosus of the vulva and adjacent skin. (Courtesy of Professor J.L. Burton, Bristol, UK.)

a few millimetres in diameter, but occasionally, they are semi-translucent and resemble mother-of-pearl. They may be very extensive, involving most of the trunk. Lesions may follow Blaschko's lines [4] even in the face [5]. They are slightly raised, or level with the surface of the skin, and typically their surface shows prominent dilated pilosebaceous or sweat duct orifices, which often contain yellow or brown horny plugs. If the plugging is marked, the surface may be rather warty. Lichenification may occur as a result of rubbing. Occasionally, bullae, which may be very extensive [6], telangiectases and purpura may occur, and resolve leaving milia [7]. In the later stages, atrophy occurs, and the surface of the lesions becomes wrinkled, and may actually be depressed. Usually, lesions are aggregated into plaques, which resemble morphoea, but the individual lesions of lichen sclerosus can nearly always still be identified. Scarring alopecia may occur, and nail disease is reported [8]. Involvement of the tendon sheath of the superior oblique muscle of the eye can give rise to diplopia [9].

References

1 Pugliese JM. Morey AF. Peterson AC. Lichen sclerosus: review of the literature and current recommendations for management. *J Urol* 2007; **178**: 2268–76.

2 Petrozzi JW, Wood MG, Tisa V. Palmar–plantar lichen sclerosus et atrophicus. *Arch Dermatol* 1979; **115**: 884.

3 Starzycki Z. Lichen sclerosus et atrophicus confined to the areolae. *Br J Dermatol* 1993; **129**: 748–9.

4 Choi SW, Yang JE, Park HJ *et al.* A case of extragenital lichen sclerosus following Blaschko's lines. *J Am Acad Dermatol* 2000; **43**: 903–4.

5 Kim YJ, Lee ES. Case of sequentially occurring lesions of facial lichen sclerosus following the lines of Blaschko. *J Dermatol* 2007; **34**: 201–4.

6 Di Silverio A, Serri F. Generalized bullous and haemorrhagic lichen sclerosus et atrophicus. *Br J Dermatol* 1975; **93**: 215–7.

7 Leppard B, Sneddon IB. Milia occurring in lichen sclerosus et atrophicus. *Arch Dermatol Syphil* 1975; **49**: 57–9.

8 Dalziel K, Reynolds AJ, Holt PJA. Lichen sclerosus et atrophicus with ocular and maxillary complications. *Br J Dermatol* 1987; **116**: 735.

9 Ramrakha-Jones VS, Paul M, McHenry B *et al.* Nail dystrophy due to lichen sclerosus? *Clin Exp Dermatol* 2001; **26**: 507–9.

Anogenital lesions in women (see Chapter 71) [1]. The condition most commonly starts between 45 and 60 years of age but is not uncommon in childhood. Lesions occur on the vulva and around the anus, and may extend to the skin of the inner side of the thighs. The ivory-coloured atrophic papules with follicular hyperkeratosis and plugging can often be identified on the vulva but, owing to friction and moisture, the lesions frequently break down to form a red raw surface, resembling macerated intertrigo (Fig. 51.78). Vesicles and bullae, sometimes haemorrhagic, may occur. In other sites, the tops of the papules become smooth and the area becomes flat and glistening. Small telangiectases and purpuric lesions sometimes occur, probably as a result of injury to the atrophic skin. Irritation may be marked, although sometimes—particularly in children—the condition is symptomless (Fig. 51.79). Patients often complain of soreness rather than pruritus, and dyspareunia may be considerable. Atrophy is a feature, and there may be gross shrinkage of the vulva, especially of the clitoris and labia minora. Labial fusion, clitoral burial and labial resorption can all occur. The vaginal introitus may become as small as 1 cm in diameter. Despite this, pregnancy and delivery are uninfluenced [2].

Mouth lesions. Occasionally, lesions are found in the mouth. They consist of bluish-white plaques, usually on the inner surface of the cheek or on the palate. There may be superficial ulceration. Sometimes, a reticulate appearance occurs and is difficult to distinguish clinically from the lesions of lichen planus [3]. The tongue can be involved. The presence of lesions of lichen sclerosus elsewhere is helpful, as biopsies from the mouth are sometimes difficult to interpret.



Fig. 51.79 Lichen sclerosus of the vulva in a young girl.



Fig. 51.80 Squamous carcinoma in an area of lichen sclerosus of the vulva.

Malignancy in lichen sclerosus. Premalignant and frankly malignant changes can occur in patients with lichen sclerosus, with squamous carcinoma occurring in 5% [4]. It usually arises in a sclerotic area, especially on the anterior part of the vulva (Fig. 51.80). The role of the human papilloma virus in this, as in other genital malignancies, has been discussed, and HPV of the strains associated with carcinogenesis has been found in pre-pubertal females with lichen sclerosus [5].

In a review of 83 cases of squamous cell carcinoma of the vulva [6], two patients with lichen sclerosus were found. Paget's disease may rarely occur in cases of lichen sclerosus of the vulva.

Lichen sclerosus in the male (balanitis xerotica obliterans) (Fig. 51.81) (see Chapter 71). Acquired phimosis or recurrent balanitis are the presenting features [7], together with itching and soreness, and erection may be painful. The prepuce becomes sclerotic and cannot be retracted. Ulceration of the foreskin can occur. The glans and undersurface of the prepuce are shining and bluish white, and there can be considerable telangiectasia. There may be back pressure affecting the urinary tract, demonstrated by urography, as a result of meatal closure. This may require surgical correction [8]. Urethral disease may occur, and lichen sclerosus was found in 14% of 925 patients with urethral stenosis [9]. The shaft of the penis is only occasionally involved. The condition is most common between the ages of 15 and 50 years. It can be overlooked in boys unless the prepuce is examined histologically in cases of circumcision for acquired phimosis. It was found in 40% of sections from boys, with the maximum frequency in those aged 9–11 [10]. In one series, the condition only occurred in patients not circumcised early in life [11]. Carcinoma may develop, and the condition may be associated with morphoea and vitiligo.



Fig. 51.81 Lichen sclerosus of the penis.

Very rarely, classical macular and papular lesions of lichen sclerosus occur on the glans and shaft of the penis and on the scrotum. The skin remains quite soft compared with the usual sclerotic skin of balanitis xerotica obliterans. Occasionally, classical lesions occur on the trunk.

References

1 Pugliese JM, Morey AF, Peterson AC. Lichen sclerosus: review of the literature and current recommendations for management. *J Urol* 2007; **178**: 2268–76.
2 Ridley CM. Lichen sclerosus et atrophicus. *Arch Dermatol* 1987; **23**: 457–60.

3 Marren P, Millard P, Chia Y *et al*. Mucosal lichen sclerosus/lichen planus overlap syndromes. *Br J Dermatol* 1994; **131**: 118–23.
4 Tasker GL. Wojnarowska F. Lichen sclerosus. *Clin Exp Dermatol* 2003; **28**: 128–33.
5 Powell J, Strauss S, Gray J, Wojnarowska F. Genital carriage of human papilloma virus (HPV) DNA in prepubertal girls with and without vulval disease. *Pediatr Dermatol* 2003; **20**: 191–4.
6 Janovski NA, Ames S. Lichen sclerosus et atrophicus of the vulva. *Obstet Gynecol* 1963; **22**: 697–708.
7 Meyrick Thomas RH, Ridley CM, Black MM. Clinical features and therapy of lichen sclerosus et atrophicus affecting males. *Clin Exp Dermatol* 1987; **12**: 126–8.
8 Larregue M, Valayer P, Cavaroc Y *et al*. Lichen sclerosus and meatal stenosis in a child. *Ann Dermatol Vénéréol* 1989; **116**: 813–4.
9 Barbagli G, Palminteri E, Balo S *et al*. Lichen sclerosus of the male genitalia and urethral stricture diseases. *Urol Int* 2004; **73**: 1–5.
10 Kiss A, Kiraly L, Kutasy B, Merksz M. High incidence of balanitis xerotica obliterans in boys with phimosis: prospective 10-year study. *Pediatr Dermatol* 2005; **22**: 305–8.
11 Ledwig PA, Weigand DA. Late circumcision and lichen sclerosus et atrophicus of the penis. *J Am Acad Dermatol* 1989; **20**: 211–4.

Lichen sclerosus in female children [1]. The disorder is much less common in children than in adults. Published series show from 2% [2] to 15% [3] of cases begin before the age of 13 years. The earliest reported age of onset was at 6 months [4]. In Wallace's series [5], 28 of 50 started between the ages of 3 and 6 years. In this group, HLA associations are seen more frequently, although these may vary [6].

General health remains normal, and often the condition is symptomless. A vaginal discharge may precede the vulval lesions in approximately 20%, and pruritus vulvae occurs in approximately half of cases. Other presentations include pain on defecation and dysuria, resulting in constipation, nocturia and nocturnal enuresis as well as rectorrhagia [6]. Lesions have followed trauma (e.g. in operation scars and in scratch marks). The individual lesions are identical to those seen in the adult [1]. The vulva and anal region may be encircled in a figure-of-eight pattern, and shrinking of the labia and stenosis of the introitus may be marked. Follicular plugging and delling are usually absent from areas of the vulva with few or no hair follicles. Vesicles and excoriations occur. The condition may be misdiagnosed as sexual abuse [7], causing much anxiety [8], but there are suggestions that sexual abuse may precipitate the condition as a Koebner phenomenon [9]. Abnormal hirsutism may be seen on the inner side of the labia majora, disappearing with resolution of the lichen sclerosus [5]. In approximately 5% of cases, the lesions are solely outside the anogenital region, and in just over 10% lesions are found both in the anogenital region and elsewhere.

The prognosis through childhood has been studied [1]; symptoms improve, but abnormal signs persist in 75% and long-term follow-up is advised. Extragenital lesions usually clear before the menarche [5].

References

1 Poindexter G, Morrell DS. Anogenital pruritus: lichen sclerosus in children. *Pediatr Ann* 2007; **36**: 785–91.
2 Montgomery H, Hill WR. Lichen sclerosus et atrophicus. *Arch Dermatol Syphilol* 1940; **42**: 755–79.
3 Chernosky ME, Derbes VJ, Burks JW. Lichen sclerosus et atrophicus in children. *Arch Dermatol* 1957; **75**: 647–52.
4 Ridley CM. Lichen sclerosus et atrophicus. *Arch Dermatol* 1987; **123**: 457–60.
5 Wallace HJ. Lichen sclerosus et atrophicus. *Trans St John's Hosp Dermatol Soc* 1951; **57**: 9–30.
6 Powell J, Wojnarowska F, Winsey S *et al*. Lichen sclerosus premenarche: autoimmunity and immunogenetics. *Br J Dermatol* 2000; **142**: 481–4.
7 Handfield-Jones SE, Hinde FRJ, Kennedy CTC. Lichen sclerosus et atrophicus in children misdiagnosed as sexual abuse. *BMJ* 1988; **294**: 404–15.
8 Berth-Jones J, Graham-Brown RAC, Burns DA. Lichen sclerosus et atrophicus: a review of 15 cases in young girls. *Clin Exp Dermatol* 1991; **16**: 14–7.
9 Warrington SA, de San Lazaro C. Lichen sclerosus et atrophicus and sexual abuse. *Arch Dis Child* 1996; **75**: 512–6.

Laboratory investigations. Approximately three-quarters of female patients have one or more organ-specific autoantibodies [1,2], usually to thyroid microsomes, thyroglobulin, gastric parietal cells or intrinsic factor. The prevalence in males is approximately half that in females, and the antibodies are mainly to smooth muscle and gastric parietal cells [3].

References

1 Harrington CI, Dunsmore IR. An investigation into the incidence of autoimmune disorders in patients with lichen sclerosus and atrophicus. *Br J Dermatol* 1981; **104**: 563–6.
2 Meyrick Thomas RH, Holmes RC, Rowland Payne CME *et al*. The incidence of development of autoimmune diseases in women after the diagnosis of lichen sclerosus et atrophicus. *Br J Dermatol* 1982; **107** (Suppl. 22): 2.
3 Meyrick Thomas RH, Ridley CM, Black MM. The association of lichen sclerosus et atrophicus and autoimmune-related disease in males. *Br J Dermatol* 1983; **109**: 661–4.

Differential diagnosis. Lichen sclerosus of the trunk must be distinguished from plaques of morphoea, but this is rarely difficult in the presence of characteristic papules with follicular plugging. Lichen planus is distinguished by its raised, itchy, violaceous papules. The atrophic form of lichen planus may simulate lichen sclerosus quite closely [1]. Lesions of lichen sclerosus may sometimes occur in association with patches of morphoea and, in some patients, typical plaque morphoea may resolve to leave the white sclerotic features of lichen sclerosus. In patients with vulval lesions, a search should be made for lesions elsewhere on the trunk, but even if none is present, the margins of the affected area of the vulva or the perianal area usually show a few typical papules, sometimes forming a well-defined edge. The differential diagnosis of the genital lesions is discussed in Chapter 71. Vulval cicatricial pemphigoid may mimic lichen sclerosus [2]. The annular atrophic plaque type of DLE on the face may resemble lesions of lichen sclerosus [3].

References

1 Connelly MG, Winkelmann RK. Coexistence of lichen sclerosus, morphoea, and lichen planus. *J Am Acad Dermatol* 1985; **12**: 844–51.
2 Marren P, Walkden V, Mallon E, Wojnarowska F. Vulval cicatricial pemphigoid may mimic lichen sclerosus. *Br J Dermatol* 1996; **134**: 522–4.
3 Chorzelski TP, Jablonska S, Blaszczyk M *et al*. Annular atrophic plaques of the face. *Arch Dermatol* 1976; **112**: 1143–5.

Prognosis [1,2]. Lichen sclerosus is a chronic condition, but signs and symptoms may wax and wane. It is usually permanent but, occasionally, spontaneous resolution occurs. This is particularly likely in girls around the menarche. Resolution of cases

appearing after puberty is uncommon, and is probably restricted to extragenital lesions arising before the age of 30 years.

References

1 Powell J, Wojnarowska F. Childhood vulvar lichen sclerosus. The course after puberty. *J Reprod Med* 2002; **47**: 706–9.

2 Simpkin S, Oakley A. Clinical review of 202 patients with vulval lichen sclerosus: a possible association with psoriasis. *Australas J Dermatol* 2007; **48**: 28–31.

Treatment. The British Association of Dermatologists provide guidelines covering the management of lichen sclerosus [1]. There is no confirmed effective treatment for extragenital lesions. Calcipotriol may be helpful [2], and phototherapy, including narrowband UVB [3] and low-dose UVA-1 [4], has been reported to be of benefit. Mycophenolate mofetil was dramatically effective in one severe case seen by the authors.

For genital lesions, there is increasing evidence that the use of potent topical steroid preparations gives both symptomatic relief and prevents scarring, and may induce complete resolution of the problem, both histologically and immunohistologically [5]. Whether this is of long-term benefit remains to be seen [6]. Oestrogen- [7] or testosterone- [8] containing creams have given symptomatic benefit, but testosterone is less effective than topical steroid [9]. No report suggests histological resolution with their use. Topical tacrolimus [10] and pimecrolimus [11] may have a role, but there are anxieties about reactivation of wart virus infection [12]. Potassium *p*-aminobenzoate, 12 g/day in divided doses, is claimed to have helped symptoms and haemorrhagic bullae, and softened the skin in some cases [13]. Etretinate may have helped both adult [14] and juvenile cases [15] and ciclosporin may be of benefit [16]. Sulfasalazine has helped a solitary case [17]. Creams containing local anaesthetic preparations should not be prescribed because of the risk of sensitization. Superficial radiation or painting with thorium X are no longer used, and are potentially dangerous.

Vulvectomy is contraindicated for uncomplicated vulval lichen sclerosus, as recurrence occurs in approximately 80% of patients. Dysplastic change should at first be treated conservatively and observed regularly. Applications of liquid nitrogen may be useful, but treatment with a nitrous oxide cryoprobe has been found to be more satisfactory [18]. The carbon dioxide laser is also effective for genital lesions in both males and females [19]. Photodynamic therapy has been used to treat vulval disease [20]. Radical surgery is obviously required if a carcinoma develops. Surgery may also be required for severe narrowing of the introitus.

Topical corticosteroids, sometimes for short periods under a condom, or intralesional injections of triamcinolone may soften the sclerotic lesions of balanitis xerotica obliterans and reduce the phimosis. Circumcision may be helpful or even curative if the condition involves only the foreskin [21]. Meatal instillation of corticosteroid may help meatal narrowing. Attention to local hygiene and treatment of balanitis may be required.

References

1 Neill SM, Tatnall FM, Cox NH. British Association of Dermatologists. Guidelines for the management of lichen sclerosus. *Br J Dermatol* 2002; **147**: 640–9.

2 Kreuter A, Gambichler T, Sauermann K *et al*. Extragenital lichen sclerosus successfully treated with topical calcipotriol: evaluation by *in vivo* confocal laser scanning microscopy. *Br J Dermatol* 2002; **146**: 332–3.

3 Colbert RL, Chiang MP, Carlin CS, Fleming M. Progressive extragenital lichen sclerosus successfully treated with narrowband UV-B phototherapy. *Arch Dermatol* 2007; **143**: 19–20.

4 Beattie PE, Dawe RS, Ferguson J, Ibbotson SH. UVA1 phototherapy for genital lichen sclerosus. *Clin Exp Dermatol* 2006; **31**: 343–7.

5 Dalziel KL, Millard PR, Wojnarowska F. The treatment of vulval lichen sclerosus with a very potent topical steroid (clobetasol propionate 0.05%). *Br J Dermatol* 1991; **124**: 461–4.

6 Renaud-Vilmer C, Cavelier-Balloy B, Porcher R, Dubertret L. Vulvar lichen sclerosus: effect of long-term topical application of a potent steroid on the course of the disease. *Arch Dermatol* 2004; **140**: 709–12.

7 Lascano EF, Montes LF, Mazzini MA. Lichen sclerosus et atrophicus in childhood. *Obstet Gynecol* 1964; **24**: 872–7.

8 Pasieczny TAH. The treatment of balanitis xerotica obliterans with testosterone propionate ointment. *Acta Derm Venereol (Stockh)* 1977; **57**: 275–7.

9 Capobianco G, Dessole S, Cossu A *et al*. Receptor modifications in vulvar dystrophies before and after treatment with topical hormones: comparison between the dextran-charcoal technique and immunohistochemical evaluation. *Eur J Gynaecol Oncol* 2006; **27**: 411–3.

10 Hengge UR, Krause W, Hofmann H *et al*. Multicentre, phase II trial on the safety and efficacy of topical tacrolimus ointment for the treatment of lichen sclerosus. *Br J Dermatol* 2006; **155**: 1021–8.

11 Nissi R, Eriksen H, Risteli J, Niemimaa M. Pimecrolimus cream 1% in the treatment of lichen sclerosus. *Gynecol Obstet Invest* 2007; **63**: 151–4.

12 Powell J, Strauss S, Gray J, Wojnarowska F. Genital carriage of human papilloma virus (HPV) DNA in prepubertal girls with and without vulval disease. *Pediatr Dermatol* 2003; **20**: 191–4.

13 Penneys NS. Treatment of lichen sclerosus with potassium paraaminobenzoate. *J Am Acad Dermatol* 1984; **10**: 1039.

14 Mork SJ, Jensen P, Hoel PS. Lichen sclerosus et atrophicus treated with etretinate (Tigason). *Acta Derm Venereol (Stockh)* 1986; **66**: 363–5.

15 Neuhofer J, Fritsch P. Treatment of localized scleroderma and lichen sclerosus with etretinate. *Acta Derm Venereol (Stockh)* 1984; **64**: 171–4.

16 Bulbul B, Turan H, Tunali S *et al*. Open-label trial of ciclosporine for vulvar lichen sclerosus. *J Am Acad Dermatol* 2007; **57**: 276–8.

17 Taveira M, Selores M, Costa V *et al*. Generalized morphea and lichen sclerosus et atrophicus successfully treated with sulphasalazine. *J Eur Acad Dermatol Venereol* 1999; **12**: 283–4.

18 August PJ, Milward TM. Cryosurgery in the treatment of lichen sclerosus et atrophicus of the vulva. *Br J Dermatol* 1980; **103**: 667–70.

19 Kartamaa M, Reitamo S. Treatment of lichen sclerosus with carbon dioxide laser vaporization. *Br J Dermatol* 1997; **136**: 356–9.

20 Romero A, Hernandez-Nunez A, Cordoba-Guijarro S *et al*. Treatment of recalcitrant erosive vulvar lichen sclerosus with photodynamic therapy. *J Am Acad Dermatol* 2007; **57** (Suppl. 2): S46–7.

21 Meyrick Thomas RH, Ridley CM, Black MM. Clinical features and therapy of lichen sclerosus et atrophicus affecting males. *Clin Exp Dermatol* 1987; **12**: 126–8.

Scleroedema

Synonyms

- Scleroedema adultorum
- Scleroedema of Buschke

Although the name of Buschke [1] is usually associated with this condition, it was originally described by Piffard in 1876. The older term, 'scleroedema adultorum', is incorrect, as the condition can occur in childhood: 29% of cases start before the age of 10 years, and a further 22% between the ages of 10 and 20 years [2].

Definition. A rare disorder of unknown cause in which areas of induration appear in the skin, frequently after an infection but also in diabetes, and spontaneously clear in months or years. There is an excess of acid mucopolysaccharides in the dermis.

Aetiology. The aetiology is unknown. Suggestions that have been considered include obstruction to lymphatic channels by inflammation, streptococcal hypersensitivity and neurohumoral disorders. Sera from patients with paraproteinaemia stimulate collagen production in dermal fibroblast cultures [3]. Some persistent cases are associated with moderate to severe diabetes mellitus [4], and both skin and diabetes are resistant to treatment. This persistent type, with no preceding infection and a strong association with diabetes, has been called scleroedema diutinum [5].

Histology. The epidermis is normal. The dermis may be three times its normal thickness. There is swelling and splitting of the dermal collagen bundles by an increase in ground substance. Clear unstained spaces, or fenestrations, occur between the bundles in severe cases. This process extends into the subcutaneous tissues, the fat of which is replaced by coarse collagen fibres. The ground substance stains metachromatically with cresyl violet or toluidine blue. Metachromasia in scleroedema is caused by the presence of hyaluronic acid [6], and is poorly seen in formalin-fixed sections as the hyaluronic acid is removed by the fixative, and in tissues treated by hyaluronidase. There is an excess of acid mucopolysaccharides, but neutral polysaccharides are normal. Mast cells may be increased [7]. Electron microscopy [8] shows an excess of interfibrillary material, and this is associated with clumping of the collagen fibrils. The voluntary muscle and heart may be affected. Deposition of IgG, IgM and C3 at the dermal–epidermal junction has been reported.

References

1 Buschke A. Vorstellung eines Falles von Skleroderm vor der Berliner Gesellschaft fur Dermatologie. *Arch Dermatol Syphilol* 1900; **53**: 83–4.
2 von Graevenitz N. Ueber einen Fall on Skleredema adultorum Buschke. *Monatschr Kinderheilk* 1928; **39**: 257.
3 Ohta A, Uitto J, Oikarinen AI *et al*. Paraproteinemia in patients with scleroedema. *J Am Acad Dermatol* 1987; **16**: 96–107.
4 Meguerditchian C, Jacquet P, Beliard S *et al*. Scleredema adultorum of Buschke: an under-recognised skin complication of diabetes. *Diabetes Metab* 2006; **32**: 481–4.
5 Binkley GW. Scleredema adultorum of Buschke. *Arch Dermatol* 1969; **99**: 124–5.
6 Braun-Falco O. Neueres zur Histopathologie des Scleredema adultorum (Buschke). *Dermatol Wochenschr* 1952; **125**: 409–14.
7 Fleischmajer R, Lara JV. Scleredema. *Arch Dermatol* 1965; **92**: 643–52.
8 Teller H, Vester G. Elektronenmikroskopische Untersuchungsergebnisse an der Interzellularsubstanz des Coriums beim Skleroedema adultorum (Buschke). *Z Haut Geschlkrankh* 1957; **23**: 142.

Clinical features. The condition is uncommon [1]. Occasional familial cases have been reported [2]. Females are more frequently affected than males in patients without diabetes, but scleroedema associated with diabetes occurs predominantly in males [3].

Although the condition may apparently start spontaneously, there is a history of an infectious episode, from a few days to 6 weeks prior to onset, in 65–90% [4] of cases. It is usually influenza, tonsillitis, pharyngitis, measles, mumps, scarlet fever, impetigo or cellulitis; prior streptococcal infections appear to be particularly common. Sometimes, there is a history of trauma. Prodromal symptoms of slight fever, malaise, muscle and joint pains occasionally occur between the infectious episode and the onset of induration. The latter is usually symmetrical and often starts on the back and sides of the neck or on the face. This loses its expression, and the patient notices difficulty in wrinkling the forehead and in smiling. There may be difficulty in opening the mouth. The tongue and pharynx may be involved, with difficulty in swallowing. Later, the shoulders, arms, hands and upper trunk become involved, but less frequently the abdomen and legs may be affected. The condition can be limited to the thighs [5]. The induration is non-pitting and hard, and there is no sharp demarcation between normal and abnormal skin. Wrinkling occurs when the skin is compressed between the thumb and index finger, indicating that the epidermis is spared. Brownish pigmentation can be widespread in the indurated areas [6]. The onset is more insidious in diabetics, and the skin induration may be preceded by erythema or pustules [7]. Sometimes, there is stiffness and restriction of movement of joints. Pleural and pericardial effusions sometimes occur, and the skeletal and cardiac muscles can be affected. Occasionally, there are ocular manifestations. The parotid glands may be involved [8].

References

1 Parmar RC, Bavdekar SB, Bansal S *et al*. Scleredema adultorum. *J Postgrad Med* 2000; **46**: 91–3.
2 Venencie PY, Powell FC, Su WP, Perry HO. Scleroedema: a review of 33 cases. *J Am Acad Dermatol* 1984; **11**: 128–34.
3 Meguerditchian C, Jacquet P, Beliard S *et al*. Scleredema adultorum of Buschke: an under-recognised skin complication of diabetes. *Diabetes Metab* 2006; **32**: 481–4.
4 Ince A, Moore TL. Scleredema adultorum of Buschke: a case report and review of the literature. *Semin Arthritis Rheum* 2006; **35**: 355–9.
5 Farrell AM, Branfoot AC, Moso J *et al*. Scleredema diabeticorum of Buschke confined to the thighs. *Br J Dermatol* 1996; **134**: 1113–5.
6 McFadden N, Ree K, Soyland E *et al*. Scleredema adultorum associated with a monoclonal gammopathy and generalized hyperpigmentation. *Arch Dermatol* 1987; **123**: 629–32.
7 Parker SC, Fenton DA, Black MM. Scleredema. *Clin Exp Dermatol* 1989; **14**: 385–6.
8 Madison LL. Scleredema. *Am J Med* 1950; **9**: 707–13.

Laboratory investigations. The ESR may be moderately elevated, and the serum proteins usually show mild, non-specific abnormalities. IgG [1], usually IgG-kappa, and IgA paraproteinaemia [2,3], have been reported. Hyperlipoproteinaemia has been reported [4], and the antistreptolysin-O titre may be raised, especially in children.

Prognosis. The condition may completely disappear in the course of some months to a few years, but a few may persist for many years. One case [5] still had changes 38 years after the onset. A fatal case occurred following the development of IgA myeloma [4].

Differential diagnosis. The condition is usually easy to diagnose in view of the rapidity of the onset, especially if there has been a

Table 51.19 Conditions associated with scleroedema.

Malignant insulinoma [6]
Paraproteinaemia and multiple myeloma [7]
Waldenström's macroglobulinaemia [8]
Rheumatoid arthritis and Sjögren's syndrome [9]
Primary hyperparathyroidism [10]
Anaphylactoid purpura [11]

history of preceding infection. Localized and generalized morphoea are usually of much slower onset, and the ivory sclerotic areas, with a well-defined and, frequently, lilac-coloured border, are characteristic. Systemic sclerosis is usually preceded by Raynaud's phenomenon. Dermatomyositis may present more difficulty, as cutaneous oedema is a feature of both conditions. However, the presence of heliotrope cyanosis, particularly around the eyes, dilatation of nail fold capillaries and muscle weakness should distinguish the condition. Pseudoscleroderma (induration of the legs as a result of chronic oedema) and localized myxoedema should rarely cause confusion. Trichinosis may have to be considered. In the newborn, sclerema and subcutaneous fat necrosis differ in their mode of onset and course. For associated conditions see Table 51.19.

Treatment. No effective remedy is known, although multiple therapies have been tried, including systemic and intralesional corticosteroids. In a case associated with multiple myeloma, the skin softened with intravenous pulses of cyclophosphamide and oral prednisolone [12]. Improvement with ciclosporin [13] and electron beam therapy [14] have been reported, and PUVA using psoralen cream [15], UVA1 [16], extracorporeal photophoresis [17] and low-dose methotrexate are more recent suggestions [18].

References

1 Kovary PM, Vakilzadeh F, Macher E *et al.* Monoclonal gammopathy in scleredema. *Arch Dermatol* 1981; **117**: 536–9.
2 Hodak E, Tamir R, David M *et al.* Scleredema adultorum associated with IgG-kappa multiple myeloma: a case report and review of the literature. *Clin Exp Dermatol* 1988; **13**: 271–4.
3 Pajarre S. Scleredema adultorum Buschke. *Acta Derm Venereol (Stockh)* 1975; **55**: 158–9.
4 Sansom JE, Sheehan AL, Kennedy CTC *et al.* A fatal case of scleredema of Buschke. *Br J Dermatol* 1994; **130**: 669–70.
5 Fleischmajer R, Lara JV. Scleredema. *Arch Dermatol* 1965; **92**: 643–52.
6 Matsunaga J, Hara M, Tagami H. Scleredema of Buschke associated with malignant insulinoma. *Br J Dermatol* 1992; **126**: 527–8.
7 Korting GW, Gilfrich HJ, Meyer zum Buschenfelde KH. Scleredema adultorum associated with multiple myeloma. *Arch Dermatol Forsch* 1974; **248**: 379.
8 Ratip S, Akin H, Ozdemirli M *et al.* Scleredema of Buschke associated with Waldenstrom's macroglobulinaemia. *Br J Dermatol* 2000; **143**: 450–2.
9 Miyagawa S, Dohi K, Tsuruta S *et al.* Scleredema of Buschke associated with rheumatoid arthritis and Sjögren's syndrome. *Br J Dermatol* 1989; **121**: 517–20.
10 Berk MA, Lorincz AL. Scleredema adultorum of Buschke and primary hyperparathyroidism. *Int J Dermatol* 1988; **27**: 647–9.
11 Okuyama R, Tagami H. Scleredema adultorum associated with anaphylactoid purpura. *Acta Derm Venereol (Stockh)* 1997; **77**: 159–61.
12 Salisbury JA, Shallcross H, Leigh IM. Scleredema of Buschke associated with multiple myeloma. *Clin Exp Dermatol* 1988; **13**: 269–70.
13 Mattheon-Vakali G, Ioannides D, Thomas T *et al.* Cyclosporine in scleredema. *J Am Acad Dermatol* 1996; **35**: 990–1.
14 Angeli-Besson C, Koeppel MC, Jacquet P *et al.* Electron-beam therapy in scleredema adultorum with associated monoclonal hypergammaglobulinaemia. *Br J Dermatol* 1994; **130**: 394–7.
15 Grundmann-Kollman M, Ochsendorf F, Zollner TM *et al.* Cream PUVA therapy for scleredema adultorum. *Br J Dermatol* 2000; **142**: 1058–9.
16 Tuchinda C, Kerr HA, Taylor CR *et al.* UVA1 phototherapy for cutaneous diseases: and experience of 92 cases in the United States. *Photodermatol Photoimmunol Photomed* 2006; **22**: 247–53.
17 Stables GI, Taylor GC, Highet AS. Scleredema associated with paraproteinaemia treated by extracorporeal photopheresis. *Br J Dermatol* 2000; **142**: 781–3.
18 Seyger MM, van den Hoogen FH, de Mare S *et al.* A patient with severe scleroedema diabeticorum, partially responding to low-dose methotrexate. *Dermatology* 1999; **198**: 177–9.

Dermatomyositis [1]

Definition. A multisystem disorder mainly affecting skin, muscle and blood vessels in which characteristic erythematous and oedematous changes in the skin are usually associated with muscle weakness and inflammation. Calcinosis is frequent, especially in childhood, and is usually associated with a more favourable prognosis for life, but functional disability may be severe. In adults, the disease is commonly associated with an underlying carcinoma or lymphoma. A wide range of systemic involvement may occur.

Incidence. Dermatomyositis is rarer than SLE, polyarteritis nodosa or systemic sclerosis. It occurs at least twice as frequently in females as in males. The incidence in children under 16 years was estimated as 1.9 per million, with the median age at onset of 6.8 years, and occurring much more frequently in girls (ratio 5:1) [2]. It may occur in infancy [3]. In adult cases, onset is predominantly between the ages of 40 and 60 years. The mean age of onset is later in men than in women [4]. Dermatomyositis affects all races and there is no obvious geographical variation, although it appears to be approximately 10 times more common in the Bantu than in the white population of the Transvaal [5].

Aetiology. The cause is not known, but there is increasing evidence of early blood vessel damage, probably humorally mediated [6]. There may be significant titres of antiendothelial cell antibodies, particularly in those patients with pulmonary involvement [7]. However, a range of factors may be relevant (Table 51.20).

Genetic factors. Familial disease is unusual [8,9], but has been found in identical twins and in first cousins. A genetic factor is suggested by the increased incidence of HLA-B8 in childhood dermatomyositis in white people but not in black people [10], and -DR3 [11] and -B14 in adult patients [12]. Other HLA haplotypes

Table 51.20 Factors important in the aetiology of dermatomyositis.

Genetics
Infections
Autoimmunity
Malignancy
Others: drugs, trauma

Table 51.21 Infections associated with dermatomyositis.

Toxoplasmosis (raised IgM antibodies) [18]
Staphylococcal osteomyelitis and arthritis [19]
Streptococcal infection (antigenic homology) [20]
Parvovirus B19 [21]
Coxsackie B virus [22]

may be associated with pulmonary disease [13]. There are associations with other type I and type II major histocompatability antigens: DRB1*0301 is a risk factor for juvenile disease, but there are also protective alleles within the DQA 1 domain [14].

Dermatomyositis has been reported in a patient with recessively inherited absence of the second component of complement (C2) [15], and antinuclear antibodies occur in a significant percentage of first-degree relatives of patients with dermatomyositis and polymyositis [16].

Infection [17]. The disorder is not consistently caused by any one infection, vaccination, immunization or drugs, but occasional cases seem to follow such events [22,23]. The infections commonly associated with the onset of dermatomyositis are indicated in Table 51.21. For *Toxoplasma* and the staphylococcal infections, treatment of the infection may produce remission of the dermatomyositis. In childhood disease, the occurrence of symptoms of respiratory or gastrointestinal infection often precedes onset of the disease [17].

Immunological abnormalities. In childhood disease, dermatomyositis appears to be a true autoimmune disorder, whereas with increasing age there is a very significant relationship with malignancy, possibly as a result of an immunological response to the neoplasm. Granular deposits of IgG, IgM and C3, alone or in combination, have been described in the walls of skeletal muscle blood vessels, especially in childhood dermatomyositis [24], and cutaneous hypersensitivity to intradermal injections of tumour extracts, but not normal tissue, has been described [25]. In some patients, myopathy seems to have been mediated by an IgGκ paraprotein with antimuscle specificity [26]. It is not clear whether paraneoplastic dermatomyositis is the same entity as the condition occurring without an associated cancer.

Autoantibodies [27]. Several precipitating autoantibodies have been demonstrated, including PM-1, Jo-1, PL-12 and, in Japanese patients, KU. There are also antibodies directed against specific myositis-related antigens, for example p155 and p155/140. Jo-1 and PL-12 antibodies are directed against tRNA synthetase enzymes and are associated with interstitial pulmonary fibrosis, and the antibody may be detected before the appearance of the lung disease [28]. It has been suggested that Jo-1 production may be linked to HLA-DR3. Patients with Jo-1 antibodies tend to have an onset of symptoms between February and July; this is not the case for the other serological subgroups of the disease [29]. In those with malignancy, there may be complement-fixing antibodies to their own tumour [30], and circulating immune complexes have been demonstrated in 70% of patients [31].

Cell-mediated immunity. There is evidence that polymyositis may be caused by lymphocyte-mediated hypersensitivity. Large numbers of T lymphocytes can be demonstrated in the infiltrates in the muscle, and there is a marked decrease of suppressor/cytotoxic cells in the blood [32]. Lymphocytes from patients with dermatomyositis and polymyositis have shown an increased response to muscle antigen in lymphocyte-stimulation tests, and the index of response showed some correlation with clinical activity. Lymphocytes from patients with dermatomyositis were cytotoxic to muscle cultures, and this cytotoxic action could be prevented by antilymphocyte serum [33].

Cytokines. Soluble CD30 levels are increased, indicating activation of T lymphocytes [34], and soluble TNF receptors are found [35]. An increased frequency of the more inflammatory polymorphisms of the TNF-α gene is found [36]. Soluble IL-2 receptor is elevated in juvenile disease [37], and expression of interferon-inducible genes in blood reflects disease activity [38].

Relationship to malignancy. Several possible mechanisms to account for the relationship with malignancy can be envisaged, but these are mainly speculative at present. Tumours are known to differ antigenically from the tissues from which they are derived, and many myositis-related antigens are expressed by tumours, possibly triggering an autoimmune response directed against muscle [39].

The primary tumour most commonly occurs in the lung, breast, female genital tract, stomach, rectum, kidney or testis. The association with a range of tumours has been reviewed [39]. In the Chinese, nasopharyngeal carcinoma accounted for 75% of malignant disease [40]. Dermatomyositis precedes the neoplasm in 40%, both conditions may occur together (26%) or the neoplasm may occur first (34%) [41]. The incidence of carcinoma in association with dermatomyositis varies from 15 to 34%. Using strict criteria, 26% of adult patients with dermatomyositis were found to have a malignancy [42]. This figure may be higher in the elderly. Patients with dermatomyositis are more likely to have a malignancy than those with polymyositis, and usually do not fare so well. Neoplasia is not associated with childhood cases. Usually, dermatomyositis worsens in parallel with the progress of the neoplasm, but it may improve when the latter is treated. Neoplasia may be missed because of failure to reinvestigate relapse of previously stable dermatomyositis [43].

Other aetiological agents. Preceding heavy muscular exertion and stress have been suggested as triggering factors [6]. Polymyositis and dermatomyositis can occur with penicillamine therapy, and may be fatal as a result of cardiac involvement [44]. A possible relationship to tamoxifen therapy for carcinoma of the breast has been reported [45]. One patient developed dermatomyositis after taking oral progesterone for dysmenorrhoea.

References

1 Lindsley CB. Juvenile dermatomyositis update. *Curr Rheumatol Rep* 2006; **8**: 174–7.

2 Symmons DPM, Sills JA, Davis SM. The incidence of juvenile dermatomyositis: results from a nationwide study. *Br J Rheumatol* 1995; **34**: 732–6.

3 Carlisle JW, Good RA. Dermatomyositis in childhood: report of studies on several cases and review of the literature. *Lancet* 1959; **79**: 266–73.
4 Degos R, Civatte J, Belaich S *et al.* The prognosis of adult dermatomyositis. *Trans St John's Hosp Dermatol Soc Lond* 1971; **57**: 98–104.
5 Findlay GH, Whiting DA, Sinson IW. Dermatomyositis in the Transvaal and its occurrence in the Bantu. *S Afr Med J* 1969; **43**: 694–7.
6 Lyon MG, Bloch DA, Hollak B *et al.* Predisposing factors in polymyositis–dermatomyositis: results of a nationwide survey. *J Rheumatol* 1989; **16**: 1218–24.
7 Cervera R, Ramirez G, Fernandez-Sola J *et al.* Antibodies to endothelial cells in dermatomyositis: association with interstitial lung disease. *BMJ* 1991; **302**: 880–1.
8 Lambie JA, Duff IF. Familial occurrence of dermatomyositis. *Ann Intern Med* 1963; **59**: 839–47.
9 Tsao CY, Mendell JR, Kissel JT. Dermatomyositis in two siblings and a brief review of familial dermatomyositis. *J Child Neurol* 2002; **17**: 540–2.
10 Friedman JM, Pachman LM, Maryjowski ML *et al.* Immunogenetic studies of juvenile dermatomyositis. *Tissue Antigens* 1983; **21**: 45–9.
11 Song MS, Farber D, Bitton A *et al*. Dermatomyositis associated with celiac disease: response to a gluten-free diet. *Can J Gastroenterol* 2006; **20**: 433–5.
12 Machulla HK, Stein J, Gautsch A *et al*. HLA-A, B, Cw, DRB1, DRB3/4/5, DQB1 in German patients suffering from rapidly progressive periodontitis (RPP) and adult periodontitis (AP). *J Clin Periodontol* 2002; **29**: 573–9.
13 Horiki T, Ichikawa Y, Moriuchi J *et al.* HLA class II haplotypes associated with pulmonary interstitial lesions of polymyositis/dermatomyositis in Japanese patients. *Tissue Antigens* 2002; **59**: 25–30.
14 Mierau R, Dick T, Bartz-Bazzanella P *et al*. Strong association of dermatomyositis-specific Mi-2 autoantibodies with a tryptophan at position 9 of the HLA-DR beta chain. *Arthritis Rheum* 1996; **39**: 868–76.
15 Leddy JP, Griggs RC, Klemperer MR *et al.* Hereditary complement (C2) deficiency with dermatomyositis. *Am J Med* 1975; **58**: 83–91.
16 Valentini G, Improta RDG, Resse M *et al.* Antinuclear antibodies in first-degree relatives of patients with polymyositis–dermatomyositis: analysis of the relationship with HLA haplotypes. *Br J Rheumatol* 1991; **30**: 429–32.
17 Pachman LM, Hayford JR, Hochberg MC *et al*. New-onset juvenile dermatomyositis: comparisons with a healthy cohort and children with juvenile rheumatoid arthritis. *Arthritis Rheum* 1997; **40**: 1526–33.
18 Harland CC, Marsden JR, Vernon SA, Allen BR. Dermatomyositis responding to treatment of associated toxoplasmosis. *Br J Dermatol* 1991; **125**: 76–8.
19 Lane S, Doherty M, Powell RJ. Dermatomyositis following chronic staphylococcal joint sepsis. *Ann Rheum Dis* 1990; **49**: 405–6.
20 Martini A, Ravelli A, Albani S *et al.* Recurrent juvenile dermatomyositis and cutaneous necrotizing arteritis with molecular mimicry between streptococcal type 5 m protein and human skeletal myosin. *J Pediatr* 1992; **121**: 739–42.
21 Crowson AN, Magro CM, Dawood MR. A causal role for parvovirus B19 infection in adult dermatomyositis and other autoimmune syndromes. *J Cutan Pathol* 2000; **27**: 505–15.
22 Christensen ML, Pachman LM, Schneiderman R *et al.* Prevalence of Coxsackie B virus antibodies in patients with juvenile dermatomyositis. *Arthritis Rheum* 1986; **11**: 1365–70.
23 Griggs RC, Karpati G. The pathogenesis of dermatomyositis. *Arch Neurol* 1991; **48**: 21–8.
24 Whitaker JN, Engel WK. Vascular deposits of immunoglobulin and complement in idiopathic inflammatory myopathy. *N Engl J Med* 1972; **286**: 333–8.
25 Curtis AC, Heckaman JH, Wheeler AH. Study of the autoimmune reaction in dermatomyositis. *JAMA* 1961; **178**: 571–3.
26 Kiprov DD, Miller RG. Polymyositis associated with monoclonal gammopathy. *Lancet* 1984; **ii**: 1183–6.
27 Benveniste O, Dubourg O, Herson S. [New classifications and pathophysiology of the inflammatory myopathies]. *Rev Med Interne* 2007; **28**: 603–12.
28 Yoshida S, Akizuki M, Mimori T *et al.* The precipitating antibody to an acidic nuclear protein antigen, the Jo-1, in connective tissue diseases. *Arthritis Rheum* 1983; **26**: 604–11.
29 Leff RL, Burgess SH, Miller FW *et al.* Distinct seasonal patterns in the onset of adult idiopathic inflammatory myopathy in patients with anti-Jo-1 and antisignal recognition particle autoantibodies. *Arthritis Rheum* 1991; **34**: 1391–6.
30 Alexander S, Forman L. Dermatomyositis and carcinoma. *Br J Dermatol* 1968; **80**: 86–9.
31 Behan WMH, Barkas T, Behan PO. Detection of immune complexes in polymyositis. *Acta Neurol Scand* 1982; **65**: 320–4.
32 Behan WMH, Micklem HS, Durward WF. Abnormalities of lymphocyte subsets in polymyositis. *BMJ* 1983; **287**: 181–2.
33 Cambridge G, Stern CM. The uptake of tritium-labelled carnitine by monolayer cultures of human fetal muscle and its potential as a label in cytotoxicity studies. *Clin Exp Immunol* 1981; **43**: 211–9.
34 Yazawa N, Ihn H, Yamane K *et al.* Elevated circulating soluble CD30 levels in patients with polymyositis/dermatomyositis. *Br J Dermatol* 2001; **145**: 676–8.
35 Shimizu T, Tomita Y, Son K *et al.* Elevation of serum soluble tumour necrosis factor receptors in patients with polymyositis and dermatomyositis. *Clin Rheumatol* 2000; **19**: 352–9.
36 Pachman LM, Fedczyna TO, Lechman TS *et al.* Juvenile dermatomyositis: the association of the TNF-α-308A allele and disease chronicity. *Curr Rheumatol Rep* 2001; **3**: 379–86.
37 Kobayashi I, Ono S, Kawamura N *et al.* Elevated serum levels of soluble interleukin-2 receptor in juvenile dermatomyositis. *Pediatr Int* 200l; **43**: 109–11.
38 Walsh RJ, Kong SW, Yao Y *et al*. Type I interferon-inducible gene expression in blood is present and reflects disease activity in dermatomyositis and polymyositis. *Arthritis Rheum* 2007; **56**: 3784–92.
39 Stockton D, Doherty VR, Brewster DH. Risk of cancer in patients with dermatomyositis or polymyositis, and follow-up implications: a Scottish population-based cohort study. *Br J Cancer* 2001; **6**: 41–5.
40 Wong KQ. Dermatomyositis: a clinical investigation of 23 cases in Hong Kong. *Br J Dermatol* 1969; **81**: 544–7.
41 Callen JP. The value of malignancy evaluation in patients with dermatomyositis. *J Am Acad Dermatol* 1982; **6**: 253–9.
42 Callen JP, Hyla JF, Bole GG *et al.* The relationship of dermatomyositis and polymyositis to internal malignancy. *Arch Dermatol* 1980; **116**: 295–8.
43 Cox NH, Lawrence CM, Langtry JAA *et al.* Dermatomyositis: disease associations and an evaluation of screening investigations for malignancy. *Arch Dermatol* 1990; **126**: 61–5.
44 Doyle DR, McCurley TL, Sergent JS. Fatal polymyositis in D-penicillamine-treated rheumatoid arthritis. *Ann Intern Med* 1983; **98**: 327–30.
45 Harris AL, Smith IE, Snaith M. Tamoxifen-induced tumour regression associated with dermatomyositis. *BMJ* 1982; **284**: 1674–5.

Pathology [1]. Dermatomyositis mainly involves the skin and muscles, although other organs, particularly the lungs, may be affected. The histological appearance of the skin depends on the stage of the disease. In acute dermatomyositis, the changes resemble those of subacute LE, although the dermal oedema may be more extensive and involve all layers of the dermis. There is usually some lymphocytic infiltrate, either perivascular or in clumps. The majority of the cells are CD4 T cells and HLA-DR-expressing macrophages. Plasmacytoid dendritic cells are present [2], but B-lymphocytes are absent [3]. The infiltrate may also include histiocytes, plasma cells and, occasionally, eosinophils. Mucin deposits commonly occur in the dermis, and mucin in an otherwise non-specific skin biopsy, although not diagnostic, is suggestive of dermatomyositis [1]. Hyperkeratosis, acanthosis and mild papillomatosis are features seen in Gottron's papules [4]. In the later stages, the collagen of the dermis may show thickening, homogenization and sclerosis, with thickening of the walls of cutaneous blood vessels. The epidermis becomes atrophic, with flattening of the rete ridges, and the basal layer may show an increase in pigment. At this stage, the appearance can be similar to that of scleroderma [5]. On direct immunofluorescence, IgM, IgG and C3 may be found at the dermal–epidermal junction in 50% of cases. Those with IgM may also have cytoid bodies [6]. The subcutaneous fat may show mucoid degeneration and lymphocytic infiltration, or sclerosis and calcification, sometimes with membranocystic changes [7].

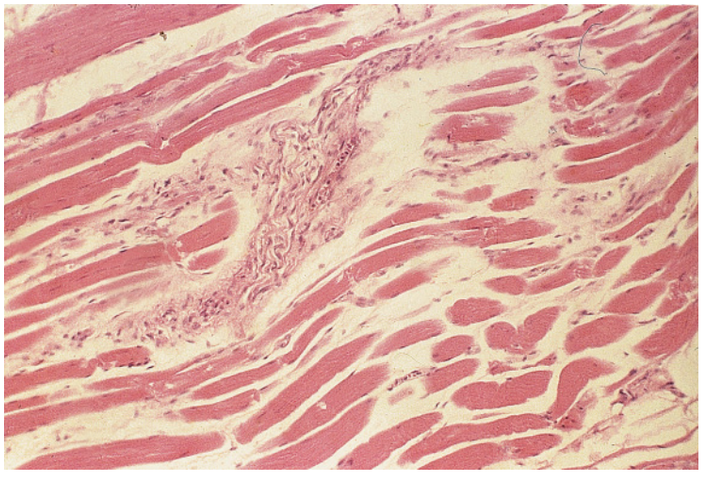


Fig. 51.82 Dermatomyositis: variable degeneration of the muscle bundles with oedema and inflammatory cells.



Fig. 51.83 Dermatomyositis: note the erythema and oedema of the eyelids.

The most frequently involved muscles are those of the limb girdles, the proximal parts of the limbs, the pharynx and the tongue. The muscle involvement [8] is not uniform, and histological examination of biopsy material may be negative. Biopsies should be taken from a muscle that is clinically weak, or that has been identified as abnormal on MRI scanning. The affected muscles may be pale, soft and flabby, or firm and fibrotic, depending on the stage of the disease. In patients with fibrosis, there may be calcification in the muscles and soft tissues. Histologically, in the early stages, the muscle fibres show loss of transverse striation, hyalinization of the sarcoplasm and an increase in sarcolemmal nuclei (Fig. 51.82). Later, the fibres fragment and show granular and vacuolar degeneration, and basophilic staining with histiocytic phagocytosis. There is variable cellular infiltration, mainly of lymphocytes, but also occasional plasma cells and macrophages. The blood vessels in the muscles may show eosinophilic intimal thickening, resembling the changes seen in malignant hypertension. Later still, the affected muscle fibres become atrophied and sclerosed, as in the muscles of patients with systemic sclerosis. No significant morphological differences have been found in the muscles in any of the diagnostic subgroups of polymyositis and dermatomyositis, and no consistent relationship between pathological changes in serial biopsies and clinical improvement in individual patients [9].

Intimal proliferation and thrombosis of arteries and arterioles of the skin, fat and alimentary tract [10] are sometimes seen, and the last accounts for the gastrointestinal ulceration and haemorrhage that occasionally occur. Changes resembling those seen in systemic sclerosis occur in the lungs or in the kidneys. The heart muscle may show changes similar to, but milder than, those in the voluntary muscles. Vasculitis of the cerebral and meningeal vessels has been reported, and in one case resulted in subarachnoid haemorrhage [11].

References

1 Janis JF, Winkelmann RK. Histopathology of the skin in dermatomyositis. *Arch Dermatol* 1968; **97**: 640–50.

2 Greenberg SA, Pinkus GS, Amato AA, Pinkus JL. Myeloid dendritic cells in inclusion-body myositis and polymyositis. *Muscle Nerve* 2007; **35**: 17–23.

3 Hausmann G, Herrero C, Cinta Cid M *et al.* Immunopathologic study of skin lesions in dermatomyositis. *J Am Acad Dermatol* 1991; **25**: 225–30.

4 Mendese G, Mahalingam M. Histopathology of Gottron's papules–utility in diagnosing dermatomyositis. *J Cutan Pathol* 2007; **34**: 793–6.

5 Dowling GB. Scleroderma and dermatomyositis. *Br J Dermatol* 1955; **67**: 275–90.

6 Vaughan-Jones SA, Bhogal BS, Black MM. Direct immunofluorescence findings in dermatomyositis. *Br J Dermatol* 1995; **133** (Suppl. 45): 55.

7 Ishikawa O, Tamura A, Ryuzaki K. Membranocystic changes in the panniculitis of dermatomyositis. *Br J Dermatol* 1996; **134**: 773–6.

8 Walton J. The inflammatory myopathies. *J R Soc Med* 1983; **76**: 998–1010.

9 Schwarz HA, Slavin G, Ward P *et al.* Muscle biopsy in polymyositis and dermatomyositis. *Ann Rheum Dis* 1980; **39**: 500–7.

10 Boylan RC, Sokoloff L. Vascular lesions in dermatomyositis. *Arthritis Rheum* 1960; **3**: 379–86.

11 Gotoff SP, Smith RD, Sugar O. Dermatomyositis with cerebral vasculitis in a patient with agammaglobulinaemia. *Am J Dis Child* 1972; **123**: 53–6.

Clinical features. The clinical picture is variable. Some patients with typical features of muscle involvement show little or no evidence of skin involvement, and the condition is then known as polymyositis [1]. Sometimes, the rash occurs alone [2], a condition that has been called amyopathic dermatomyositis, and this may imply a good prognosis, although the outlook is not uniformly good. Severe calcinosis may occur even in this variety [3]. The rash may precede muscle weakness in around 50% of patients [4].

The rash in well-developed cases is diagnostic. A purplish-red or heliotrope erythema occurs on the face, especially involving the eyelids, the upper cheeks, forehead and temples (Fig. 51.83). Oedema of the eyelids and periorbital tissues is not uncommon [5]. The distribution may resemble that of seborrhoeic dermatitis [6]. Oedema of the hands and arms, and sometimes of much of the body, may also be found, and this is usually associated with erythema of the backs of the forearms, the upper back and, sometimes, elsewhere. This more generalized erythema may resemble the widespread eruption of systemic lupus. In other cases, the rash is more poikilodermatous.

Small erythematous or violaceous, flat papules (Gottron's papules [7]) and small plaques occur over the knuckles, on the dorsa of the finger joints and around the nail folds (Fig. 51.84). They also occur on the dorsa of the toes, on the front of the knees



Fig. 51.84 Violaceous lesions on the dorsa of the finger joints in childhood dermatomyositis.



Fig. 51.86 Hyperpigmented nail fold lesions in an Afro-Caribbean patient with dermatomyositis.



Fig. 51.85 The hands in dermatomyositis: note the linear erythema on the dorsa of the fingers.



Fig. 51.87 Dermatomyositis: dilated nail fold capillaries and hypertrophic ragged cuticle.

and on the backs of the elbows. Frequently, the rash of dermatomyositis on the dorsa of the hands occurs as linear streaking over the extensor tendon sheaths (Fig. 51.85). These may be hyperpigmented as the only cutaneous sign in Afro-Caribbeans (Fig. 51.86) [8]. As well as diffuse redness and shininess of the nail folds, the capillary loops of the nail folds may be dilated, irregular and tortuous, and easily visible with or without a lens, or by capillaroscopy. The capillary changes are more marked in patients with Raynaud's phenomenon, arthritis and pulmonary involvement, but are not related to active myositis or malignancy (Fig. 51.87) [9]. Thickening, roughness, hyperkeratosis and irregularity of the cuticles, with minimal or no redness or inflammation [10], is frequent. Ragged cuticles are also found in other connective tissue diseases such as systemic sclerosis and LE.

In the Chinese, hyperkeratotic follicular erythematous papules occur on the face, back of the neck, trunk, dorsa of the hands and feet, and palms and soles. On the dorsa of the hands and feet, the lesions occur in a linear fashion [11]. A variety of other cutaneous changes have been demonstrated (Table 51.22).

Panniculitis. In some patients, red, firm, tender areas of panniculitis develop (Fig. 51.88), and these may ulcerate or break down to form sinuses [18]. Some areas of panniculitis have their origin in vasculitis, and are often followed by severe calcification. They often occur on the buttocks and upper thighs.

Table 51.22 Less common physical signs associated with dermatomyositis [12–17].

Spreading erythema and fleeting or persistent oedema of the face and neck or of the limbs
Urticarial lesions, dermographism
Bullous lesions
Photosensitivity
Erythema nodosum, erythema multiforme
Follicular keratosis
Hypertrichosis, scalp erythema with hair loss
Hyperhidrosis
Psoriasiform eruptions and pitting of the fingernails
Gingival telangiectasia (childhood disease)
Linear, violaceous, itchy and oedematous streaks on the trunk (flagellate erythema)
Exfoliative dermatitis
Hyperpigmentation
Livedo reticularis, with ulceration



Fig. 51.88 Panniculitis with calcinosis in the thigh in dermatomyositis.

Mechanics' hands. Patients with antisynthetase antibodies may develop 'mechanics' hands'—hyperkeratosis, fissuring and linear hyperpigmentation of radial and palmar surfaces of the fingers. Histology shows hyperkeratosis, acanthosis, a mononuclear dermal infiltrate and liquefaction necrosis of the basal layer [19].

Muscle symptoms. Usually, the patient first notices aching and weakness of the muscles, which may be painful and tender, and later show some atrophy. Typical histories include difficulty in going up stairs or rising from a chair, or difficulty in raising the arms high enough to comb the hair. Usually, there is a feeling of malaise, and fever may occur. Raynaud's phenomenon occurs in approximately 10% of adults, but is very rare in children. Recurrent bursitis of shoulders and hips may precede myositis, and joint effusions occur [20].

In addition to the weakness of the limb muscles, which is mainly proximal, there may be difficulty with speech and swallowing (because of involvement of the muscles of the tongue, the pharynx and the upper third or distal part of the oesophagus [21]), diverticular out-pouching of the oesophagus [22], impaired muscular activity of the small intestine, pneumatosis intestinalis [23], sometimes with pneumoperitoneum [24], wide-mouthed diverticula of the colon, weakness of the ocular muscles and respiratory difficulty from involvement of the intercostal muscles and diaphragm which may lead to death because of respiratory infection or heart failure.

Other clinical features. Other clinical features include: interstitial pneumonitis [25], with non-productive cough, dyspnoea and hypoxaemia and radiological infiltrates or pulmonary fibrosis, may be the presenting manifestations or may occur in the course of the disease. Pulmonary hypertension, with cor pulmonale and fibrosing alveolitis, has been reported. Interstitial lung disease may be more frequent than suspected. Myocarditis, myocardial fibrosis, disorders of conduction and cardiac failure occur in approximately one-third of cases [26]. Renal lesions are uncommon [27]. Retinitis produces fluffy exudates around the papilla and along the veins; permanent visual loss occurs rarely [28]. A case of myoglobinuric acute renal failure has been reported [29].

A mild inflammatory arthritis may occur, but erosive arthritis is rare although a rheumatoid picture can occur. Patients with arthritis frequently have pulmonary involvement [30]. Trigeminal neuropathy has been reported [31].

Calcification. Calcification [32] occurs in the muscles or in areas of panniculitis in more than half of childhood cases, and approximately 15% of adults. The muscles mainly involved are those of the shoulder and pelvic girdles, and to a lesser extent those of the trunk and the limbs, especially around the elbows and hands. In adults, the distribution is less markedly around the pelvic and shoulder girdles than in childhood. Calcinosis increases over the course of months or years and, if extensive, can cause severe functional disability. Extrusion of calcium through the skin is associated with ulceration and cellulitis. Calcinosis is a good sign for survival, but functional recovery is less likely, although even severe calcinosis can resolve spontaneously. Sometimes, patients present with widespread calcification and apparently have not had a preceding myositic illness. In these cases, it is presumed—but not proved—that calcinosis is the result of old dermatomyositis. Sometimes, calcinosis developing in childhood decreases in adolescence; rarely, hypercalcaemia may occur [33].

References

1 Bohan A, Peter JB, Bowman RL *et al*. A computer-assisted analysis of 153 patients with polymyositis and dermatomyositis. *Medicine* 1977; **56**: 255–86.

2 Gerami P, Schope JM, McDonald L *et al*. A systematic review of adult-onset clinically amyopathic dermatomyositis (dermatomyositis sine myositis): a missing link within the spectrum of the idiopathic inflammatory myopathies. *J Am Acad Dermatol* 2006; **54**: 597–613.

3 Olhoffer IH, Carroll C, Watsky K. Dermatomyositis sine myositis presenting with calcinosis universalis. *Br J Dermatol* 1999; **141**: 365–6.

4 Rockerbie NR, Woo TY, Callen JP *et al*. Cutaneous changes of dermatomyositis precede muscle weakness. *J Am Acad Dermatol* 1989; **20**: 629–32.

5 Sevigny GM, Mathes BM. Periorbital oedema as the presenting sign of juvenile dermatomyositis. *Pediatr Dermatol* 1999; **16**: 43–5.

6 Katayama I, Sawada Y, Nishioka K *et al*. The seborrhoeic pattern of dermatomyositis. *Br J Dermatol* 1999; **140**: 978–9.

7 Gottron H. Hautveranuderungen bei dermatomyositis. In: Lomholt S, ed. *VIII Congres International de Dermatologie et de Syphilologie*. Copenhagen: Compts Rendus de Seances, 1930: 826.
8 Bottomley W, Goodfield MJD. A case of dermatomyositis presenting as localized hyperpigmentation of the hands and face. *Br J Dermatol* 1995; **132**: 670–1.
9 Ganczarczyk ML, Lee P, Armstrong SK. Nail fold capillary microscopy in polymyositis and dermatomyositis. *Arthritis Rheum* 1988; **31**: 116–9.
10 Samitz MH. Cuticular changes in dermatomyositis. *Arch Dermatol* 1974; **110**: 866–7.
11 Wong KO. Dermatomyositis: a clinical investigation of 23 cases in Hong Kong. *Br J Dermatol* 1969; **81**: 544–7.
12 Findley GH, Price GA, Van Rinsburg CRJ. Dermatomyositis with vesicular bullous lesions. *S Afr Med J* 1951; **25**: 60.
13 Rowland Payne CME, Meyrick Thomas RH. Dermatomyositis with urticated lesions. *J R Soc Med* 1984; **77**: 137–8.
14 Garcin R, Lapresle J, Gruner J *et al.* Les polymyosites. *Rev Neurol* 1955; **92**: 465.
15 Reich NE, Reinhart JB. Dermatomyositis associated with hypertrichosis. *Arch Dermatol Syphilol* 1948; **57**: 725–32.
16 Ghali FE, Stein LD, Fine JD *et al.* Gingival telangiectases: an underappreciated physical sign of juvenile dermatomyositis. *Arch Dermatol* 1999; **135**: 1370–4.
17 Jara M, Amerigo JA, Duce S, Borbugo J. Dermatomyositis and flagellate erythema. *Clin Exp Dermatol* 1996; **21**: 440–1.
18 Fusade T, Belanyi P, Joly P *et al.* Subcutaneous changes in dermatomyositis. *Br J Dermatol* 1993; **128**: 451–3.
19 Mitra D, Lovell CL, Macleod TIF *et al.* Clinical and histological features of 'mechanics hands' in a patient with antibodies to Jo-1: a case report. *Clin Exp Dermatol* 1994; **19**: 146–8.
20 Dorph C, Englund P, Nennesmo I, Lundberg IE. Signs of inflammation in both symptomatic and asymptomatic muscles from patients with polymyositis and dermatomyositis. *Ann Rheum Dis* 2006; **65**: 1565–71.
21 De Merieux P, Verity MA, Clements PJ *et al.* Oesophageal abnormalities and dysphagia in polymyositis and dermatomyositis. *Arthritis Rheum* 1983; **26**: 961–8.
22 O'Hara JM, Szemes G, Lowman RM. The oesophageal lesions in dermatomyositis. *Radiology* 1967; **89**: 27–31.
23 Mueller CF, Morehead R, Alter AJ *et al.* Pneumatosis intestinalis in collagen disorders. *Am J Roentgenol* 1972; **115**: 300–5.
24 Oliveros MA, Herbst JJ, Lester PD *et al.* Pneumatosis intestinalis in childhood dermatomyositis. *Pediatrics* 1973; **52**: 711–2.
25 Takizawa H, Shiga J, Moroi Y *et al.* Interstitial lung disease in dermatomyositis: clinicopathological study. *J Rheumatol* 1987; **14**: 102–7.
26 Haupt HM, Hutchins GM. The heart and cardiac conduction system in polymyositis–dermatomyositis. *Am J Cardiol* 1982; **50**: 998–1006.
27 Yen TH, Lai PC, Chen CC *et al.* Renal involvement in patients with polymyositis and dermatomyositis. *Int J Clin Pract* 2005; **59**: 188–93.
28 Kessler E, Weinberger I, Rosenfeld JB. Myoglobinuric acute renal failure in a case of dermatomyositis. *Israel J Med Sci* 1972; **8**: 978–83.
29 Yeo LMW, Swaby DSA, Sitnayake RD, Murray PI. Irreversible visual loss in dermatomyositis. *Br J Rheumatol* 1995; **34**: 1179–81.
30 Schumacher HR, Schimmer B, Gordon GV *et al.* Articular manifestations of polymyositis and dermatomyositis. *Am J Med* 1979; **67**: 287–92.
31 Ashworth B, Tait GBW. Trigeminal neuropathy in connective tissue disease. *Neurology* 1971; **21**: 609–14.
32 Muller SA, Winkelmann RK, Brunsting LA. Calcinosis in dermatomyositis. *Arch Dermatol* 1959; **79**: 669–73.
33 Ostrov BE, Goldsmith DP, Eichenfield AH, Athreya BH. Hypercalcaemia during the resolution of calcinosis universalis in juvenile dermatomyositis. *J Rheumatol* 1991; **18**: 1730–4.

Dermatomyositis in childhood. This has been well described and reviewed [1]. It is possible that microchimerism may be an aetiological factor [2]. The condition resembles that seen in adults, but malignancy is rarely associated with it and it is usually much more severe than in adults. The prognosis is variable. Calcification occurs more frequently than in adults and contractures develop in under 5%. Widespread vasculitis affecting small arteries, capillaries and veins of the skin, muscle, subcutaneous tissue and gastrointestinal tract is a prominent feature of the so-called Banker type [3]. It may take many years for the disease to burn out but, occasionally, a child recovers without any residual disability and late recurrences are rare. Psychological difficulties occur more frequently than might be expected [4]. A rare feature is hypertrichosis (Fig. 51.89) [5]. Juvenile dermatomyositis can be associated with partial lipodystrophy [6].



Fig. 51.89 Hypertrichosis in an area of erythema on the knee in childhood dermatomyositis.

References

1 Ramanan AV, Feldman BM. Clinical features and outcomes of juvenile dermatomyositis and other childhood onset myositis syndromes. *Rheum Dis Clin North Am* 2002; **28**: 833–57.
2 Artlett CM, Miller FW, Rider LG. Persistent maternally derived peripheral microchimerism is associated with the juvenile idiopathic inflammatory myopathies. *Rheumatology (Oxford)* 2001; **40**: 1279–84.
3 Banker BQ, Victor M. Dermatomyositis (systemic angiopathy) of childhood. *Medicine* 1966; **45**: 261–89.
4 Pachman LM, Cooke N. Juvenile dermatomyositis: a clinical and immunologic study. *J Pediatr* 1980; **96**: 226–34.
5 Piantanida NA, Person DA, Piantanida EW. Infrapatellar hypertrichosis: an unusual cutaneous manifestation of juvenile dermatomyositis. *Pediatr Dermatol* 2002; **19**: 132–5.
6 Kavanagh GM, Colaco B, Kennedy CTC. Juvenile dermatomyositis associated with partial lipoatrophy. *J Am Acad Dermatol* 1993; **28**: 348–51.

Sclerodermatomyositis in childhood. This is an overlap syndrome in which cutaneous changes of systemic sclerosis and dermatomyositis are associated with myositis and the homogeneous nucleolar pattern of antinuclear antibody (anti-PM/Scl antibody). Serum muscle enzymes are normal or only slightly raised. The features of dermatomyositis are usually transient and respond to

Table 51.23 Association of dermatomyositis with other disorders.

Thymoma [1]
Hyperthyroidism [2]
Drugs:
penicillamine [3]
hydroxyurea [4]
Aplastic anaemia [5]
Haemolytic anaemia [6]
Agammaglobulinaemia [7]
Cystinuria [8]
Hashimoto's disease and ovarian carcinoma [9]
Generalized amyloidosis [10]
Multiple myeloma [11]
Lichen myxoedematosus [12]
Dermatitis herpetiformis [13]
Coeliac disease [14]
Bullous pemphigoid [15]
Porphyria cutanea tarda [16]
Fibrosing alveolitis [17]
Cutaneous vasculitis [18]
Sjögren's syndrome [19]
Hughes' syndrome [20]
Periorbital fasciitis [21]
Lipoatrophy [22] and lipodystrophy with phaeochromocytoma [23]

non-steroidal anti-inflammatory drugs or corticosteroids, and aggressive treatment is not usually required. The systemic sclerosis features such as Raynaud's phenomenon, calcinosis and arthritis tend to grumble on over years, but visceral involvement is not marked. One case with 'mechanics' hands'—hyperkeratosis and fissuring on the tips and sides of the fingers resembling a labourer's dirty hands—has been reported [1].

Reference

1 Garcia-Patos V, Bartralot R, Ordi J *et al.* Childhood sclerodermatomyositis: report of a case with the anti-PM/Scl antibody and mechanic's hands. *Br J Dermatol* 1996; **135**: 613–6.

Dermatomyositis in pregnancy [1]. Dermatomyositis can start in pregnancy. The overall fetal loss is over 50%, and half of pregnancies end prematurely. Pregnancy exacerbates the disease in approximately 50% and is associated with remission in 20%. Fertility is decreased in dermatomyositis [2]. Pregnancy should be planned at a time of remission and the patient monitored at least every month. If possible, treatment should be confined to oral steroids.

References

1 Harris A, Webley M, Usherwood M *et al.* Dermatomyositis presenting in pregnancy. *Br J Dermatol* 1995; **133**: 783–5.
2 Kitridou RC. Pregnancy in mixed connective tissue disease, poly/dermatomyositis and scleroderma. *Clin Exp Rheumatol* 1988; **6**: 173–8.

Association with other disorders. Many other diseases have been reported in conjunction with dermatomyositis (see Table 51.23).

References

1 Rundle LG, Sparks FP. Thymoma and dermatomyositis. *Arch Pathol* 1963; **75**: 276–83.
2 Shergy WJ, Caldwell DS. Polymyositis after propylthiouracil treatment for hyperthyroidism. *Ann Rheum Dis* 1988; **47**: 340–3.
3 Doyle DR, McCurley TL, Sergent JS. Fatal polymyositis in D-penicillamine-treated rheumatoid arthritis. *Ann Intern Med* 1983; **98**: 327–30.
4 Senet P, Aractingi S, Porneuf M *et al.* Hydroxyurea-induced dermatomyositis-like eruption. *Br J Dermatol* 1995; **133**: 455–9.
5 Duncan PR, Harvey PW, Seville RH. Dermatomyositis presenting as aplastic anaemia. *Br J Dermatol* 1959; **71**: 344–6.
6 Hardman CM, Garioch JJ, Leonard JN *et al.* Autoimmune haemolytic anaemia associated with dermatomyositis. *Clin Exp Dermatol* 1996; **21**: 437–9.
7 Gotoff SP, Smith RD, Sugar O. Dermatomyositis with cerebral vasculitis in a patient with agammaglobulinemia. *Am J Dis Child* 1972; **123**: 53–6.
8 Fawcett NP, Nyhan WL. Cystinuria and dermatomyositis. *Clin Pediatr* 1970; **9**: 727–32.
9 Chamberlain MJ, Whittaker SRF. Hashimoto's disease, dermatomyositis and ovarian carcinoma. *Lancet* 1963; **i**: 1398–9.
10 Gelderman AH, Levine RA, Arndt KA. Dermatomyositis complicated by generalized amyloidosis. *N Engl J Med* 1962; **267**: 858–61.
11 Zilko PJ, Dawkins RL. Amyloidosis associated with dermatomyositis and features of multiple myeloma. *Am J Med* 1975; **59**: 488–52.
12 Johnson BL, Horowitz IR, Charles CR *et al.* Dermatomyositis and lichen myxedematosus. *Dermatologica* 1973; **147**: 109–22.
13 White SW, Tesar JT. Dermatomyositis and dermatitis herpetiformis. *Arch Dermatol* 1982; **118**: 599–601.
14 Iannone F, Lapadula G. Dermatomyositis and coeliac disease association: a further case. *Clin Exp Rheumatol* 2001; **19**: 757–8.
15 Glover M, Leigh IM. Dermatomyositis pemphigoides: a case with coexistent dermatomyositis and bullous pemphigoid. *J Am Acad Dermatol* 1992; **27**: 849–52.
16 Belaich S, Crickx B, Picard C *et al.* Porphyrie cutanée tardive associée à une dermatomyosite cutanée pure. *Ann Dermatol Vénéréol* 1989; **116**: 826–7.
17 Holmes R, Black M, Farebrother MJB *et al.* Malignancy associated dermatomyositis with fibrosing alveolitis. *Clin Exp Dermatol* 1980; **5**: 415–20.
18 Feldman D, Hochberg MC, Zizic TM *et al.* Cutaneous vasculitis in adult polymyositis–dermatomyositis. *J Rheumatol* 1983; **10**: 85–9.
19 Ringel SP, Forstot JZ, Tan EM *et al.* Sjögren's syndrome and polymyositis or dermatomyositis. *Arch Neurol* 1982; **39**: 157–63.
20 Sherer Y, Livneh A, Levy Y *et al.* Dermatomyositis and polymyositis associated with the antiphospholipid syndrome: a novel overlap syndrome. *Lupus* 2000; **9**: 42–6.
21 Carruthers A, Carruthers J, Wright P. Necrotizing fasciitis with polymyositis. *BMJ* 1975; **iii**: 355–6.
22 Commens C, O'Neill P, Walker G. Dermatomyositis associated with multifocal lipoatrophy. *J Am Acad Dermatol* 1990; **22**: 966–9.
23 Huang JL. Juvenile dermatomyositis associated with partial lipodystrophy. *Br J Clin Pract* 1996; **50**: 112–3.

Differential diagnosis. The diagnosis depends upon the association of a typical rash with muscle weakness, and is confirmed by muscle biopsy, electromyography and certain laboratory investigations. The serum creatine phosphokinase (CPK), glutamic oxalacetic transaminase (SGOT) or aldolase are frequently, but not invariably raised [1,2], and in certain cases may reflect the activity of the disease and be helpful in regulating the dosage of steroids [3]. However, some patients continue to show considerable disease activity in the presence of normal serum enzymes, so serial estimations of the 24-h urinary creatine are helpful, if available [4]. Skin and muscle biopsy are helpful, but histological changes may be absent or minimal. Radiology of the muscles in the later stages may show calcinosis, a feature that may differentiate the condition from other connective tissue diseases [5]. In dermatomyositis, the calcium deposits are widely scattered throughout the muscles and soft tissues, whereas in systemic sclerosis the calcium deposits are found mainly in the hands and around the elbows and knees.

Table 51.24 Investigation of associated malignancy in dermatomyositis.

Clinical examination (including the breasts, pelvis and rectum),
Blood count and biochemistry
Radiography of the chest
Abdominal ultrasound
Examination of the stools for occult blood
Tumour specific markers including PSA, CEA etc.

Moreover, in the latter, the tips of the terminal phalanges often show some bone resorption. MRI scanning [6] and ultrasound give useful information for longitudinal studies and are non-invasive. In patients with little or no rash, muscular dystrophies may be closely simulated [7]; electromyography [8] is helpful in distinguishing myopathy from neuropathy. Dermatomyositis is of more rapid onset and remissions are frequent.

The ESR is moderately elevated in some, but not all patients in the active phase, and there may be some elevation of the serum globulin. It has been claimed that an elevated ESR and cutaneous necrosis are potential markers of malignancy [8]. Antinuclear factor, raised DNA binding and anti-RNP may occur, especially in overlap syndromes [9]. Antibodies to aminoacyl-tRNA synthetase are antibodies to soluble nuclear antigens and are associated with myositis [10]. The association of other antibodies with particular disease profiles has already been discussed. Antibodies to cytoplasmic antigens such as anti-SRP (signal recognition particle) occur, and antibodies to the nuclear antigen Mi-2 are strongly associated with dermatomyositis [11]. Occasionally, rheumatoid factor is found. The Wassermann reaction is negative. Anticardiolipin antibodies were found in three out of 14 patients with juvenile dermatomyositis, two of whom had vascular complications [12].

In all adult cases, a determined effort to exclude internal malignancy should be carried out [13], and although most of the neoplasms can be diagnosed by physical examination and simple investigation (Table 51.24), in a minority of patients, intensive investigation may be required.

Dermatomyositis can be confused with systemic sclerosis, and the two conditions can occur together. The muscle changes may be identical in the two disorders, but visceral changes are much more common in systemic sclerosis. From the clinical point of view, differentiation between the two diseases may be difficult, particularly in those cases showing sclerosis in the healing phase. Occasionally, patients with systemic sclerosis show heliotrope cyanosis of the eyelids, and dilatation of the nail fold capillaries. Sometimes, patients with dermatomyositis resemble patients with SLE but, in the latter, antinuclear factors and anti-DNA antibodies can usually be demonstrated. Myositis is a feature of so-called mixed connective tissue disease (see p. 51.110). Neuropathy is distinguished by the electromyographic changes and the presence of a raised CPK and urinary creatine excretion. The atrophic changes of the skin in the later stages may resemble morphoea, but the history should lead to the correct diagnosis. Polymyositis [14,15] is more common than dermatomyositis. It is usually found in adults in the third to the fifth decades. Females are three times more likely to develop the disease than males. Occasionally, sclero-edema may cause difficulty. It is important to exclude metabolic disorders in those patients with only muscle disease [16].

References

1 Bohan A, Peter JB, Bowman RL *et al*. A computer-assisted analysis of 153 patients with polymyositis and dermatomyositis. *Medicine* 1977; **56**: 255–86.
2 Carter JD, Kanik KS, Vasey FB *et al.* Dermatomyositis with normal creatine kinase and elevated aldolase levels. *J Rheumatol* 2001; **28**: 2366–7.
3 Vickers CFH. Serum transaminase estimations in the differential diagnosis of collagen diseases. *Br J Dermatol* 1961; **73**: 185–93.
4 Rowell NR, Fairris GM. Biochemical markers of myositis in dermatomyositis. *Clin Exp Dermatol* 1986; **11**: 69–72.
5 Dubois EL. Collagen disease: the overlooked diagnosis. *Med Ann DC* 1959; **28**: 681–94.
6 Park JH, Olsen NJ. Utility of magnetic resonance imaging in the evaluation of patients with inflammatory myopathies. *Curr Rheumatol Rep* 2001; **3**: 334–45.
7 Heathfield KWG, Williams JRB. Diagnosis of polymyositis. *Lancet* 1960; **i**: 1157–61.
8 Basset-Seguin N, Roujeau J-C, Gherardi R *et al.* Prognostic factors and predictive signs of malignancy in adult dermatomyositis. *Arch Dermatol* 1990; **126**: 633–7.
9 Venables PJW, Mumford PA, Maini RN. Antibodies to nuclear antigens in polymyositis. *Ann Rheum Dis* 1981; **40**: 217–23.
10 Lamedica G, Parodi A, Peris G *et al*. Polymyositis and pulmonary fibrosis associated with anti-PL-7 antibody. *J Am Acad Dermatol* 1988; **19**: 567–8.
11 Targoff IN. Humoral immunity in polymyositis/dermatomyositis. *J Invest Dermatol* 1993; **100** (Suppl.): 116S–23S.
12 Montecucco C, Ravelli A, Caporali R *et al.* Autoantibodies in juvenile dermatomyositis. *Clin Exp Rheumatol* 1990; **8**: 193–6.
13 Callen JP. The value of malignancy evaluation in patients with dermatomyositis. *J Am Acad Dermatol* 1982; **6**: 253–9.
14 Pearson CM. Patterns of polymyositis and their responses to treatment. *Ann Intern Med* 1963; **59**: 827–38.
15 Walton J, Adams RD. *Polymyositis*. Edinburgh: Livingstone, 1958.
16 Wortmann RL. Myositis or myopathy. *J Rheumatol* 1989; **16**: 1525–7.

Prognosis [1,2]. The course is variable. The prognosis is said to be better in dermatomyositis than in polymyositis; however, some have found the reverse to be true [3]. Patients without muscle involvement may have a better prognosis and may not require steroids [4]. Approximately 50% of patients seem to be responsive to therapy; the remainder appear to be relatively resistant. The overall mortality is approximately one-quarter [5], and malignancy is a significant cause of death [1]. Adverse factors include acute pulmonary infiltrations, dysphagia, cutaneous necrosis and increasing age. Fulminating cases may deteriorate rapidly despite therapy, and in the past some 20% died within the first year; other cases settle slowly and burn out in time, usually over several years. Sometimes, patients complain of vague aching in the limbs when there does not appear to be any residual activity. Some are left with minimal cutaneous change and no residual weakness. Others, particularly children, have gross disability, with contractures of the limbs and calcinosis. Of the children followed up for 5–16 years, 75% survived [6]. Removal of an underlying carcinoma in adults can lead to regression of the dermatomyositis [7].

Calcinosis is a good prognostic feature. Out of 75 adults without calcification, 26 died, usually in approximately 2 years, whereas of 12 adults with calcinosis none died [8]. Seven out of 14 children without, and only one of 17 with, calcinosis died in a mean time of approximately 16 months. Calcification can decrease without treatment. In some patients, muscle disease settles with treatment, but cutaneous disease may be persistent and resistant to therapy.

Death usually occurs from respiratory infection, cardiac failure, malnutrition, weakness or debility because of difficulty in swallowing, carcinoma, or from the side effects of steroid therapy.

References

1 Marie I, Hachulla E, Hatron PY *et al.* Polymyositis and dermatomyositis: short-term and long-term outcome, and predictive factors of prognosis. *J Rheumatol* 2001; **28**: 2230–7.
2 Medsger TA, Robinson H, Masi AT. Factors affecting survivorship in polymyositis. *Arthritis Rheum* 1971; **14**: 249–58.
3 Callen JP, Hyla JF, Bole GG *et al.* The relationship of dermatomyositis and polymyositis to internal malignancy. *Arch Dermatol* 1980; **116**: 295–8.
4 Genth E. [Inflammatory muscle diseases: dermatomyositis, polymyositis, and inclusion body myositis]. *Internist* 2005; **46**: 1218–32.
5 Airio A, Kautiainen H, Hakala M. Prognosis and mortality of polymyositis and dermatomyositis patients. *Clin Rheumatol* 2006; **25**: 234–9.
6 Henriksson KG, Sandstedt P. Polymyositis: treatment and prognosis—a study of 107 patients. *Acta Neurol Scand* 1982; **65**: 280–300.
7 Brunner MJ, Lobraico RV. Dermatomyositis as an index of malignant neoplasm. *Ann Intern Med* 1951; **34**: 1269–73.
8 Muller SA, Winkelmann RK, Brunsting LA. Calcinosis in dermatomyositis. *Arch Dermatol* 1959; **79**: 669–73.

Treatment [1]. Rest is essential in the acute phase. In adults it is important to exclude an underlying carcinoma. Treatment with corticosteroids is required in almost all cases, the dosage depending upon the degree of activity. Initial dosage of as much as 60 mg/day prednisolone may be required [1]. This dosage should be gradually reduced as the patient clinically improves and the biochemical markers improve. However, a maintenance dosage of between 5 and 15 mg/day may be required for many months, or even years, and it is important to balance the maximum therapeutic effect against the presence of side effects. If the clinical signs and serum CPK level are not improving sufficiently quickly, bolus infusions of methylprednisolone (1 g on 2–3 successive days) may be tried and are often a good alternative to a high-dose oral regimen. Alternatively, an antimetabolite should be added. Oral azathioprine (1.5–3 mg/kg/day in divided doses) as a steroid-sparing agent [2], or oral methotrexate in a small weekly dosage (7.5–15 mg) may be used to suppress disease activity [3]. Patients not responding to prednisolone and immunosuppressives may be helped by the addition of ciclosporin 5 mg/kg/day [4]. Ciclosporin is also effective in childhood in a dosage of 2.5–7.5 mg/kg [5]. A number of studies have indicated a successful role for intravenous immunoglobulin in a regimen of 1 mg/kg for 2 days each month over 4–6 months [6,7]. Cyclophosphamide 100 mg/day [8], or as pulsed intravenous therapy, is used for pulmonary interstitial fibrosis, but may also be effective for muscle and skin disease and justified in severe cases. The advent of biological agents—monoclonal antibodies directed at specific cytokines—has provided a new set of therapeutic options, and both infliximab [9] (directed against tumour necrosis factor) and more usefully rituximab [10] (directed against the CD20 molecule on B lymphocyte precursors), have been used with success.

Children with minimal myopathy may remit with indometacin without steroids [11], and antimalarials may help the rash of dermatomyositis, which may persist when muscle activity settles [12]. Topical steroid or a topical calcineurin inhibitor may be of value [13]. Less commonly, levamisole (100 mg/week) [14] or plasma exchange [15] may help patients with severe disease not responding to steroids or immunosuppressives. Improvement may occur within 48 h of plasmapheresis [16]. Extracorporeal photochemotherapy may be useful in combination with other therapies [17]. Methandienone (30 mg/day) [18], dapsone [19] and pentoxifylline [20] have all produced apparent improvement in patients unresponsive to corticosteroids. Antiplatelet agents—aspirin (650 mg/day), dipyridamole (400 mg/day) and sulfinpyrazone (400 mg/day)—helped one patient with *in vivo* platelet thrombi formation causing digital and vascular ischaemia [21].

Therapy, with either prednisolone alone or in combination with an antimetabolite, may be required for some years, and the dosage is reduced very gradually until the disease is burnt out. Any recrudescence is treated with an increase in dosage. Early treatment with low-dose steroids in children is associated with fewer relapses and lower morbidity [22]. Occasionally, weakness may arise from corticosteroid myopathy, and may be difficult to distinguish from an exacerbation of the disease. Serum enzymes are normal, but the 24-h urinary creatine excretion is raised [23]. Recovery on reduction of dosage takes up to 4 months. Weakness in dermatomyositis may occur because of hypokalaemia, the result of corticosteroid therapy. Regular electrolyte estimations are required and potassium supplements should be given.

Gastrointestinal haemorrhage may occur as a result of the disease or corticosteroid therapy. Constipation can be a feature, and octreotide may increase gastrointestinal motility. Osteoporosis is a considerable risk because of immobility and corticosteroid therapy, and prophylactic treatment should be given to both female and male patients. Treatment of calcinosis is usually ineffective, although spontaneous improvement can occur. Aluminium oxide, by producing insoluble aluminium phosphate, decreases the intestinal absorption of phosphate and has been successfully used in calcinosis in a child. Aludrox 15 mL four times daily (2.4 g/day aluminium oxide) was given by mouth [24]. Diltiazem has also been used successfully [25].

Physiotherapy plays a considerable part in preventing the development of contractures, and careful splinting may also be required. Artificial ventilation may be required in reversible transitory ventilatory failure [26], as may intravenous feeding in patients with severe oesophageal involvement. If there is definite serological evidence of recent infection with *Toxoplasma gondii*, treatment with pyrimethamine and/or sulfadiazine may be indicated [27].

References

1 Choy EH, Isenberg DA. Treatment of dermatomyositis and polymyositis. *Rheumatology* 2002; **41**: 7–13.
2 Choy EH, Hoogendijk JE, Lecky B, Winer JB. Immunosuppressant and immunomodulatory treatment for dermatomyositis and polymyositis. *Cochrane Database of Systematic Reviews* (**3**): CD003643, 2005.
3 Ramanan AV, Campbell-Webster N, Ota S *et al.* The effectiveness of treating juvenile dermatomyositis with methotrexate and aggressively tapered corticosteroids. *Arthritis Rheum* 2005; **52**: 3570–8.
4 Casato M, Bonomo L, Caccavo D *et al.* Clinical effects of cyclosporin in dermatomyositis. *Clin Exp Dermatol* 1990; **15**: 121–3.
5 Heckmat J, Saunders C, Peters AM *et al.* Cyclosporin in juvenile dermatomyositis. *Lancet* 1989; **i**: 1063–6.
6 Cherin P, Piette JC, Wechsler B *et al.* Intravenous gammaglobulin as first-line therapy in polymyositis and dermatomyositis: an open study in 11 adult patients. *J Rheumatol* 1994; **21**: 1092–7.

7 Sansome A, Dubowitz S. Intravenous immunoglobulin in juvenile dermatomyositis: 4 year review of nine cases. *Arch Dis Child* 1995; **72**: 25–8.
8 Plowman PN, Stableforth DE. Dermatomyositis with fibrosing alveolitis. *Proc R Soc Med* 1977; **70**: 738–40.
9 Dold S, Justiniano ME, Marquez J, Espinoza LR. Treatment of early and refractory dermatomyositis with infliximab: a report of two cases. *Clin Rheumatol* 2007; **26**: 1186–8.
10 Cooper MA, Willingham DL, Brown DE *et al*. Rituximab for the treatment of juvenile dermatomyositis: a report of four pediatric patients. *Arthritis Rheum* 2007; **56**: 3107–11.
11 Winkelmann RK. Dermatomyositis in childhood. *Clin Rheum Dis* 1982; **8**: 353–68.
12 Woo TY, Callen JP, Voorhees JJ *et al*. Cutaneous lesions of dermatomyositis are improved by hydroxychloroquine. *J Am Acad Dermatol* 1984; **10**: 592–600.
13 Yoshimasu T, Ohtani T, Sakamoto T *et al*. Topical FK506 (tacrolimus) therapy for facial erythematous lesions of cutaneous lupus erythematosus and dermatomyositis. *Eur J Dermatol* 2002; **12**: 50–2.
14 Rovensky J, Zitnan D, Lukac J *et al*. Effect of 'levamisole' treatment in polymyositis patients. *J Rheumatol* 1982; **9**: 158–9.
15 Dau PC. Plasmapheresis in idiopathic inflammatory myopathy. *Arch Neurol* 1981; **38**: 544–52.
16 MacPherson A, Berth-Jones J, Graham-Brown RAC. Carcinoma-associated dermatomyositis responding to plasmapheresis. *Clin Exp Dermatol* 1989; **14**: 304–5.
17 de Wilde A, DiSpaltro FX, Geller A *et al*. Extracorporeal photochemotherapy as adjunctive treatment in juvenile dermatomyositis: a case report. *Arch Dermatol* 1992; **128**: 1656–7.
18 Armstrong A, Murdoch WR. Anabolic hormone in dermatomyositis. *BMJ* 1960; **ii**: 1929–31.
19 Konohana A, Kawashima J. Successful treatment of dermatomyositis with dapsone. *Clin Exp Dermatol* 1994; **19**: 367–8.
20 Person JR. Dermatomyositis responding to pentoxifylline. *Br J Dermatol* 1996; **134**: 593–606.
21 Littlejohn GO, Deck JHN, Kelton JG *et al*. Dermatomyositis associated with platelet thrombi formation and responsive to antiplatelet therapy. *J Rheumatol* 1983; **10**: 136–9.
22 Miller G, Heckmatt JZ, Dubowitz V. Drug treatment of juvenile dermatomyositis. *Arch Dis Child* 1983; **58**: 445–50.
23 Askari A, Vignos PJ, Moskowitz RW. Steroid myopathy in connective tissue disease. *Am J Med* 1976; **61**: 485–92.
24 Nassim JR, Connolly CK. Treatment of calcinosis universalis with aluminium hydroxide. *Arch Dis Child* 1970; **45**: 118–21.
25 Palmieri GM, Sebes JI, Aelion JA *et al*. Treatment of calcinosis with diltiazem. *Arthritis Rheum* 1995; **38**: 1646–54.
26 Selva-O'Callaghan A, Sanchez-Sitjes L, Munoz-Gall X *et al*. Respiratory failure due to muscle weakness in inflammatory myopathies: maintenance therapy with home mechanical ventilation. *Rheumatology* 2000; **39**: 914–6.
27 Harland CC, Marsden JR, Vernon SA *et al*. Dermatomyositis responding to treatment of associated toxoplasmosis. *Br J Dermatol* 1991; **125**: 76–8.

Dermatological manifestations of rheumatoid disease

Although it would be unusual for patients with rheumatoid arthritis to present initially with skin problems, cutaneous disease is not uncommon, both as an intrinsic part of the condition and increasingly as a consequence of therapy (Table 51.25). Some problems, such as rheumatoid nodules and vasculitis, are well recognized, but more recently other abnormalities, such as transparent skin, linear subcutaneous bands and neutrophilic dermatoses, have been described. The array of skin problems seen in patients with rheumatoid arthritis has been well reviewed [1].

A dermatologist may also be involved in deciding between rheumatoid disease and SLE as the primary diagnosis. A skin biopsy for immunofluorescence studies may be helpful in aiding diagnosis because in the skin of the former, fluorescence of the dermal–epidermal junction is not found, even in cases with a high titre of antinuclear factor [2].

Pseudosclerodermatous changes, particularly of the hands, occur in rheumatoid arthritis, and there are common instances of overlap syndromes, where features of a number of more specific connective tissue diseases occur together [3].

Table 51.25 Cutaneous problems occurring in rheumatoid arthritis.

Rheumatoid nodules
Rheumatoid vasculitis (RV)
Felty's syndrome
Pyoderma gangrenosum (PG)
Interstitial granulomatous dermatitis with arthritis
Palisaded neutrophilic and granulomatous dermatitis
Rheumatoid neutrophilic dermatitis
Juvenile rheumatoid arthritis (JRA)
Adult-onset Still's disease

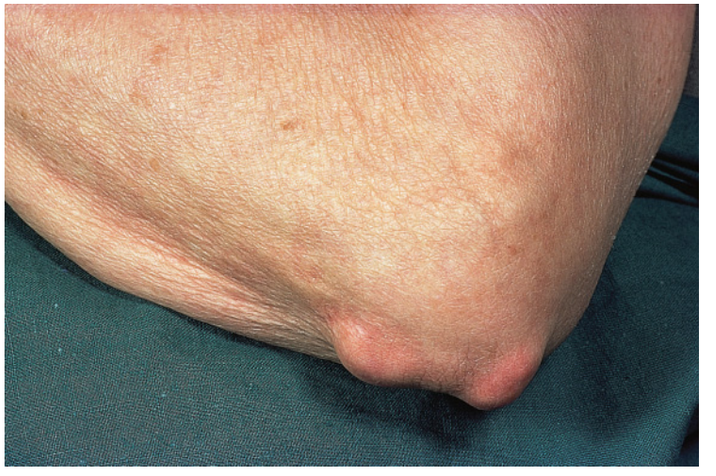


Fig. 51.90 Rheumatoid nodules on the elbow.

Rheumatoid nodules [4] (Fig. 51.90)

Palpable subcutaneous nodules occur in approximately 20% of patients with rheumatoid arthritis. The most common site is on the ulnar border of the forearm. Less commonly, they occur on the dorsa of the hands, on the knees, on the ears, over the scapulae and occasionally in other areas, especially those subject to pressure, such as the sacrum, buttocks or heels. They vary in size up to several centimetres in diameter, are firm in consistency and tend to ulcerate with trauma (Fig. 51.91), particularly on the sacrum. Secondary infection with staphylococci can result in staphylococcal septicaemia and septic arthritis. Subcutaneous nodules can erode the underlying bone [5]. Sometimes, there are numerous violaceous papules with centripetal scaling. A variant of rheumatoid disease, termed 'rheumatoid nodulosis' [6], has been described, and may precede rheumatoid disease. Multiple, small nodules occur on the hands and feet with palindromic rheumatism and little evidence of synovitis. Nodules may be found in other organ systems, particularly the lungs [4].



Fig. 51.91 Ulcerated rheumatoid nodule on the ear.

Nodules are almost invariably associated with more severe forms of the disease, and rheumatoid factor and antinuclear factors are frequently found in the serum. Occasionally, nodules may occur in mild rheumatoid arthritis and in anarthritic rheumatoid disease. Sometimes, they may precede rheumatoid arthritis by some years [4]. Rheumatoid nodules may rarely occur in the sclera (scleromalacia), which may perforate (scleromalacia perforans), leading to complete blindness. Severe nodulosis may be precipitated by therapies, including methotrexate and biological agents [7].

Histologically, rheumatoid nodules consist of fibrous tissue in which foci of fibrinoid necrosis are scattered, surrounded by a palisade of cells, mainly fibroblasts and histiocytes. A peripheral zone of lymphocytes and plasma cells occurs. Within the necrotic area are thin reticulum fibres, similar to those seen in young granulation tissue, amorphous material and some nuclear debris. Vasculitis can occur in rheumatoid nodules and papules. The histology has features in common with those of granuloma annulare (see Chapter 60).

The subcutaneous nodules of rheumatic fever [8] can be distinguished histologically from those of rheumatoid arthritis. There is much fibrinoid material, considerable oedema of the collagen, but relatively little infiltration with fibroblasts, histiocytes or lymphocytes. There is little attempt at zoning and fibrosis is minimal or absent. Large mononuclear cells, like those seen in Aschoff's nodes in the myocardium, may be found. Nodules from patients with Still's disease (juvenile rheumatoid arthritis) [8] resemble those seen in rheumatic fever. Another possible cause of nodulosis is the coexistence of erythema elevatum diutinum [9].

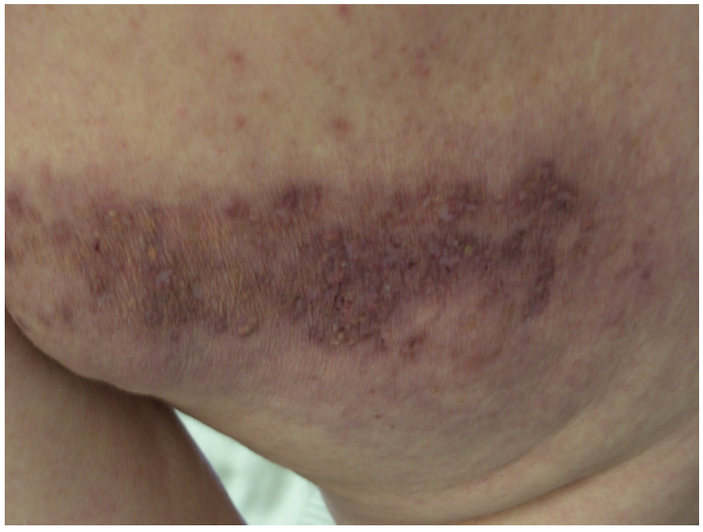


Fig. 51.92 Palisading and neutrophilic dermatosis in a patient with rheumatoid arthritis.

Linear subcutaneous bands and interstitial granulomatous dermatitis [10] (Fig. 51.92)

Elongated subcutaneous bands, 3–5 mm wide and 10 cm or more in length, have been described in patients with rheumatoid arthritis with nodules. Histologically, the bands show changes similar to the nodules, with interstitial granuloma formation, but no evidence of vasculitis. The bands, which are firm and non-tender, are adherent to the skin. They have so far been observed in the axilla, and extending from the axilla to the iliac crest. Similar histological appearances may be seen with a more papular clinical appearance.

Palisaded neutrophilic and granulomatous dermatitis

In addition, there are those who believe that another entity—palisaded neutrophilic and granulomatous dermatitis—may be part of a spectrum of cutaneous disease, with the degree of neutrophilic infiltration varying between patients. Others disagree, noting vasculitic histological change in those with more significant neutrophilic involvement [11]. Certainly, the two clinical patterns may occur together (Fig. 51.92).

Rheumatoid neutrophilic dermatosis. This may occur [12] in patients with severe arthritis as symmetrical erythematous nodules and 'urticaria-like' plaques on the dorsa of the hands and arms, extensor aspects of the joints, and the back of the neck and scalp and trunk. They are sometimes tender. Vertical symmetrical infiltrated linear cords on the median axillary line have been reported [11], as discussed above. Ulceration and vesiculation may occur. Histologically, there is a dense diffuse infiltrate of neutrophils in the dermis, papillary microabscesses and leukocytoclasia, but no vasculitis. The lunulae may be red [13]. Pyoderma gangrenosum may occur in association with neutrophilic dermatosis [14]. Dapsone, either alone or combined with colchicine, may help rheumatoid vasculitis and neutrophilic dermatosis [15].

Cutaneous changes due to steroid usage—purpura and paper-thin skin—are common.

References

1 Sayah A, English JC 3rd. Rheumatoid arthritis: a review of the cutaneous manifestations. *J Am Acad Dermatol* 2005; **53**: 191–209.
2 Muijs van de Moer WW, Cats A. Immunofluorescence of the skin in patients with rheumatoid arthritis. *Dermatologica* 1967; **134**: 351–5.
3 Pope JE. Musculoskeletal involvement in scleroderma. *Rheum Dis Clin North Am* 2003; **29**: 391–408.
4 Highton J, Hessian PA, Stamp L. The rheumatoid nodule: peripheral or central to rheumatoid arthritis? *Rheumatology* 2007; **46**: 1385–7.
5 Dorfman HD, Norman A, Smith RJ. Bone erosion in relation to subcutaneous rheumatoid nodules. *Arthritis Rheum* 1970; **13**: 69–73.
6 Ginsberg MH, Genant HK, Yu TF *et al.* Rheumatoid nodulosis: an unusual variant of rheumatoid disease. *Arthritis Rheum* 1963; **18**: 49–58.
7 Linksvan Ede A, den Broeder A, Wagenaar M *et al*. Etanercept-related extensive pulmonary nodulosis in a patient with rheumatoid arthritis. *J Rheumatol* 2007; **34**: 1590–2.
8 Bywaters EGL, Glynn LE, Zeldis A. Subcutaneous nodules of Still's disease. *Ann Rheum Dis* 1958; **17**: 278–83.
9 Balbir-Gurman A, Schapira D, Bergamn R, Nahir AM. Erythema elevatum diutinum: a rare cause of nodulosis in a patient with rheumatoid arthritis. *J Rheumatol* 2000; **27**: 2291–3.
10 Dykman CJ, Galens GJ, Good AE. Linear subcutaneous bands in rheumatoid arthritis. *Ann Intern Med* 1965; **63**: 134–40.
11 Al-Daraji WI, Coulson IH, Howat AJ. Palisaded neutrophilic and granulomatous dermatitis. *Clin Exp Dermatol* 2005; **30**: 578–9.
12 Mashek HA, Pham CT, Helm TN, Klaus M. Rheumatoid neutrophilic dermatitis. *Arch Dermatol* 1997; **133**: 757–60.
13 Jorizzo JL, Gonsalez EB, Daniels JC. Red lunulae in a patient with rheumatoid arthritis. *J Am Acad Dermatol* 1983; **8**: 711–4.
14 MacAya A, Servitje O, Jucqla A, Peyri J. Rheumatoid neutrophilic dermatitis associated with pyoderma gangrenosum. *Br J Dermatol* 2000; **142**: 1246–8.
15 Bernard P, Arnaud M, Treves R *et al.* Dapsone and rheumatoid vasculitis leg ulcerations. *J Am Acad Dermatol* 1988; **18**: 140–1.

Vascular lesions in rheumatoid arthritis [1,2]

The presence of vascular lesions in rheumatoid arthritis has been increasingly recognized in recent years. Raynaud's phenomenon is uncommon; it occurred in only 2.7% of one series [3]. However, there is now clear evidence of increased vascular pathology in RA, including the occurrence of large vessel atherosclerosis and cardiovascular disease [1,2].

The most characteristic lesions of arteritis in rheumatoid patients are small infarcts around the nails, sometimes at the apex of small cutaneous nodules. The lesions are usually transitory and may last only 2 or 3 days. Because they are usually painless, patients rarely complain about or even notice the lesions. Usually, a small brown spot persists a little longer, and sometimes scarring may occur. Occasionally, infarcts of the nail fold may result in grooving of the nail. Rarely, bullae may occur. The occurrence of digital necroses is closely correlated with the presence of rheumatoid factor and rheumatoid nodules [2]. Anticardiolipin antibodies can sometimes be demonstrated in patients with vasculitis, and are statistically significantly related to rheumatoid nodules but not to thrombotic events [4]. In addition to the infarcts around the nail folds, the pulps of the fingers may show small painful purpuric nodules (Bywaters' lesions). Histologically, these show leukocytoclastic vasculitis [5]. Palmar erythema is common.

In addition, the skin may show purpuric and necrotic arteritic lesions, which can be painful. The haemorrhagic areas appear without preceding trauma, and vary in size from small petechiae to areas of bruising and necrosis several centimetres in diameter. Sometimes, these areas develop black crusting, which may break down and ulcerate. The ulcers are well defined, with a surrounding bluish-red halo. Some of the ulcers are related to rheumatoid nodules. Healing occurs with scarring and may be slow. Arteritis occurs widely in rheumatoid disease, and involvement of the gastrointestinal tract [6] gives rise to abdominal pain, which may result from multiple ischaemic ulcers, gangrene of the bowel, intraperitoneal haemorrhage or splenic infarction.

Gangrene may result from changes in the digital vessels, and sometimes this may extend to involve a large part of the foot or hand, occasionally within a few days. Extensive pustular panniculitis, particularly on the legs, may occur as the result of breakdown of red, painful, nodular lesions. Treatment can be very difficult [7].

Leg ulcers. Leg ulcers are not uncommon in the rheumatoid population. Although vasculitis is an important cause, it was only considered to be a factor in 18% of rheumatoid patients in one recent series [8]. Venous insufficiency, complicated by immobility and postural factors, occurs in nearly half of cases, and trauma, pressure or arterial insufficiency are also major factors. Leg ulcers [9] may also be pyodermatous (Fig. 51.93). Arteritic ulcers are more common in males, particularly those with subcutaneous nodules and positive tests for rheumatoid factor. They are usually deep, punched out and slow healing. There is little discoloration of the legs and usually no sclerosis. Some of the ulcers may start as frankly purpuric or nodular lesions. Secondary infection is common, especially with *Staphylococcus aureus*. Response to treatment is slow and relapse frequent. Leg ulcers are more common in Felty's syndrome, in which arthritis is associated with splenomegaly and leukopenia.

Livedo reticularis [10] also occurs in rheumatoid arthritis, as does delayed pressure-induced vasculitis.

Peripheral sensory or motor neuropathy [11] is often associated with clinical evidence of arteritis elsewhere, and is caused by occlusion of the vasa nervorum by the arteritic process. These patients also have a high incidence of rheumatoid factor and nodule formation.



Fig. 51.93 Felty's syndrome: pyoderma gangrenosum of the perianal area.

A rash identical to that found in Still's disease (juvenile rheumatoid arthritis; see p. 51.133) occurs in adult rheumatoid arthritis, but is rare. It was found in only seven out of more than 500 patients [12].

Associations with other disorders. These have been comprehensively reviewed [13]. They include bullous pemphigoid, pemphigus vulgaris, pemphigus foliaceus, dermatitis herpetiformis, subcorneal pustular dermatosis [14], epidermolysis bullosa acquisita, yellow-nail syndrome, acquired cutis laxa [15], angioendotheliomatosis [16] and erosive pustular dermatosis of the scalp [17].

References

1 Szekanecz Z, Kerekes G, Dér H *et al.* Accelerated atherosclerosis in rheumatoid arthritis. *Ann N Y Acad Sci* 2007; **1108**: 349–58.
2 Genta MS, Genta RM, Gabay C. Systemic rheumatoid vasculitis: a review. *Semin Arthritis Rheum* 2006; **36**: 88–98.
3 Carroll GJ, Withers K, Bayliss CE. The prevalence of Raynaud's syndrome in rheumatic arthritis. *Ann Rheum Dis* 1981; **40**: 567–70.
4 Wolf P, Gretler J, Aglas F *et al.* Anticardiolipin antibodies in rheumatoid arthritis: their relation to rheumatoid nodules and cutaneous vascular manifestations. *Br J Dermatol* 1994; **131**: 48–51.
5 Craig SD, Jorizzo JL, White WL *et al.* Cutaneous signs of rheumatic disease: acral purpuric papules in a patient with clinical rheumatoid arthritis. *Arthritis Rheum* 1994; **37**: 957–9.
6 Lindsay MK, Tavadia HB, Whyte AS *et al.* Acute abdomen in rheumatic arthritis due to necrotizing arteritis. *BMJ* 1973; **ii**: 592–3.
7 Anstey A, Wilkinson JD, Wojnarowska F *et al.* Pustular panniculitis in rheumatoid arthritis. *J R Soc Med* 1991; **84**: 307–8.
8 Pun YLW, Barraclough DRE, Muirden KD. Leg ulcers in rheumatoid arthritis. *Med J Aust* 1990; **153**: 585–7.
9 Wilkinson M, Kirk J. Leg ulcers complicating rheumatoid arthritis. *Scott Med J* 1965; **10**: 175–82.
10 Champion RH. Livedo reticularis. *Br J Dermatol* 1965; **77**: 167–79.
11 Said G, Lacroix C. Primary and secondary vasculitic neuropathy. *J Neurol* 2005; **252**: 633–41.
12 Isdale IC, Bywaters EGL. The rash of rheumatoid arthritis and Still's disease. *QJM* 1956; **49**: 377–87.
13 Jorizzo JL, Daniels JC. Dermatologic conditions reported in patients with rheumatoid arthritis. *J Am Acad Dermatol* 1983; **8**: 439–57.
14 Butt A, Burge SM. Sneddon–Wilkinson disease in association with rheumatoid arthritis. *Br J Dermatol* 1995; **132**: 313–5.
15 Rongioletti F, Cutolo M, Bondavalli P, Rebora A. Acral localized acquired cutis laxa associated with rheumatoid arthritis. *J Am Acad Dermatol* 2002; **46**: 128–30.
16 Tomasini C, Soro E, Pippione M. Angioendotheliomatosis in a woman with rheumatoid arthritis. *Am J Dermatopathol* 2000; **22**: 334–8.
17 Yamamoto T, Furuse Y. Erosive pustular dermatosis of the scalp in association with rheumatoid arthritis. *Int J Dermatol* 1995; **34**: 148.

Fibroblastic rheumatism

This entity was originally described by Chaouat *et al.* [1] in 1980, and since then further cases have been described, mainly in France [2]. It occurs at all ages and affects both sexes equally. Clinically, it starts suddenly with symmetrical polyarthritis and cutaneous nodules. These are between 5 and 20 cm in diameter, and can occur before the onset of arthritis. Raynaud's phenomenon, sclerodactyly with inability to join palms, joint effusions and stiffness are frequent. The nodules occur on both surfaces of the hands, usually over the joints, and on the elbows, knees, ears and neck (Fig. 51.94). They are smooth, firm and usually skin-coloured. They resolve in 6 months to a few years. Histology shows a marked proliferation of spindle cells and dermal fibrosis. The hyperplastic cells have the phenotypic features of muscle, suggesting myofibroblastic differentiation [3]. There is a reduction of collagen and non-collagen protein synthesis by the fibroblasts from involved skin, which contrasts markedly with the increase in collagen synthesis in scleroderma.



Fig. 51.94 Nodules on the dorsa of the interphalangeal joints in fibroblastic rheumatism. (Courtesy of Dr M.H.A. Rustin, The Royal Free Hospital, London, UK.)

Systemic involvement does not usually occur—all laboratory tests are negative.

Spontaneous resolution of the nodules may be expected. Joint erosions may develop and changes tend to persist. There is little evidence indicating benefit from any treatment.

References

1 Chaouat Y, Aron-Brunetiere R, Faures B *et al.* Une nouvelle entite: le rheumatisme fibroblastique: a propos d'une observation. *Rev Rheum Mal Osteoartic* 1980; **47**: 345–51.
2 Kanzler MH, Dhillon I, Headington JT. Fibroblastic rheumatism. *Arch Dermatol* 1995; **131**: 710–2.
3 Lacour JP, Maquart FX, Bellow G *et al.* Fibroblastic rheumatism: clinical, histological, immunohistological, ultrastructural and biochemical study of a case. *Br J Dermatol* 1993; **128**: 194–202.

Still's disease

Synonym

- Juvenile rheumatoid arthritis

The characteristic rash [1] is seen in approximately 25% of patients with Still's disease. It occurs in boys (36%) more frequently than in girls (22%), the incidence decreasing with age. It consists of small, non-pruritic macules or papules up to 3 mm in diameter, with a slightly irregular margin. Larger lesions up to 5 cm show central pallor. The colour is bright salmon pink, often surrounded by a zone of pallor. The rash occurs most frequently on the limbs and trunk, but may occur on the face and neck, and lasts only a few hours, characteristically appearing at midday or in the evening with increased temperature of the patient or environment. It is more common in patients with fever, splenomegaly, lymphadenopathy and a raised ESR. It usually appears in the first 2 weeks of the disease but may precede other manifestations by up to 9 years. The rash may occur intermittently for many years and has no prognostic value [2].

Histologically, there is a scanty infiltrate, sometimes of neutrophils if the rash is marked, in the dermis. The rash fades as the disease settles; corticosteroids do not have a specific effect.

The rash can be distinguished from erythema marginatum by the smaller size of the lesions, their occurrence on the face and the fact that lesions are at their greatest size at the onset.

Subcutaneous nodules occur in Still's disease. The histology resembles that seen in the nodules of rheumatic fever rather than in those of rheumatoid arthritis [3]. Still's disease has been associated with Kikuchi's disease (see p. 51.58) [4,5].

References

1 Isdale IC, Bywaters EGL. The rash of rheumatoid arthritis and Still's disease. *QJM* 1956; **49**: 377–87.
2 Calabro JJ, Marchesano JM. Juvenile rheumatoid arthritis. *N Engl J Med* 1967; **277**: 696–9.
3 Bywaters EGL, Glynn LE, Zeldis A. Subcutaneous nodules of Still's disease. *Ann Rheum Dis* 1958; **17**: 278–85.
4 Lyberatos C. Two more cases of Still and Kikuchi. *J Rheumatol* 1990; **17**: 568–9.
5 Ohta A, Matsumoto J, Ohta T *et al.* Still's disease associated with necrotizing lymphadenitis (Kikuchi's disease): report of three cases. *J Rheumatol* 1988; **15**: 981–3.

Adult Still's disease [1]

In 1971, Bywaters [2] described 14 adults with arthritis and clinical features similar to those of juvenile rheumatoid arthritis. Features include a high spiking fever, sore throat, joint pain and arthritis, a transitory maculopapular rash, lymphadenopathy, hepatosplenomegaly and serositis. The white cell count is raised, and rheumatoid and antinuclear factors are usually absent. Both sexes are equally affected, and the onset is usually in the mid-twenties. The rash usually occurs in the evening, accompanied by fever in over 80% of patients, on the proximal limbs, trunk and face. Alopecia is another feature. Histologically, there is a perivascular dermal infiltrate of lymphocytes and histiocytes. Immunofluorescence is negative. The rash is an adverse prognostic indicator. Approximately one-third remit and another third become chronic; the remainder have an intermittent course. Aspirin and other non-steroidal anti-inflammatory drugs are the first line of treatment, but systemic steroids may be required. In the more chronic cases, intramuscular or oral gold may be helpful. Methotrexate has been of benefit in refractory cases [3].

References

1 Pouchot J, Sampalis JS, Beandet F *et al.* Adult Still's disease: manifestations, disease course, and outcome in 62 patients. *Medicine* 1991; **70**: 118–36.
2 Bywaters EGL. Still's disease in the adult. *Ann Rheum Dis* 1971; **30**: 121–33.
3 Fujii T, Akizuki M, Kameda H *et al.* Methotrexate treatment in patients with adult onset Still's disease: retrospective study of 13 Japanese cases. *Ann Rheum Dis* 1997; **56**: 144–8.

Sjögren's syndrome [1]

Synonym

- Gougerot–Houwer–Sjögren syndrome

In 1933, Sjögren [2] drew attention to the syndrome that now bears his name. The first case was described in 1888, although earlier authors, including Mikulicz, had noted several of the manifestations. The disease is caused by an immune-mediated inflammation of exocrine glands, and involves salivary, lacrimal and sweat glands. It may be primary, in which case the exocrine dysfunction occurs alone, or as secondary Sjögren's syndrome in association with a connective tissue disease. The most common features of the condition are dryness and atrophy of the conjunctiva and cornea (keratoconjunctivitis sicca), and a dry mouth (xerostomia). The diagnostic criteria, including these features and objective demonstration of exocrine dysfunction, have been reviewed, and the consensus findings are shown in Table 51.26 [3]. In addition to the commonly involved areas, other glandular structures may be affected, and there is variable internal organ involvement, but 'sicca' symptoms alone occurred in 35% of one series [4]. Malignant lymphoma is associated with the primary form of the disease [5].

Table 51.26 Revised classification criteria for Sjögren's syndrome (SS).

1 Ocular symptoms: at least one of:
  1 Dry eyes for more than 3 months
  2 Sensation of sand or gravel in the eyes
  3 Need for tear substitutes more than 3 times a day
2 Oral symptoms: at least one of:
  1 Dry mouth for more than 3 months
  2 Recurrently or persistently swollen salivary glands as an adult
  3 Need liquids to swallow dry food
3 Ocular signs—at least one of the following two tests positive:
  1 Schirmer's test, performed without anaesthesia (≤5 mm in 5 min)
  2 Rose Bengal score or other ocular dye score
4 Histopathology: in minor salivary glands, focal lymphocytic sialoadenitis (focus score ≥1).
5 Salivary gland involvement: a positive result for at least one of the following diagnostic tests:
  1 Unstimulated whole salivary flow (≤1.5 ml in 15 min)
  2 Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitary, or destructive pattern), without evidence of obstruction in the major ducts
  3 Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer
6 Autoantibodies: presence in the serum of antibodies to Ro(SSA) or La(SSB) antigens, or both

For primary SS

In patients without any potentially associated disease, primary SS may be defined as follows:

a. The presence of any four of the six items is indicative of primary SS, as long as either item 4 (Histopathology) or 6 (Serology) is positive.
b. The presence of any three of the four objective criteria items (that is, items 3, 4, 5, 6)

For secondary SS

In patients with a potentially associated disease, the presence of item 1 or item 2 plus any two from among items 3, 4, and 5 may be considered as indicative of secondary SS

Aetiology. The onset occurs most frequently in the fourth, fifth and sixth decades, and 90% of the patients with the primary form are women. A genetic predisposition is indicated by the finding of

Table 51.27 Pathological changes in Sjögren's syndrome.

Lymphocyte and plasma cell infiltration
Connective tissue proliferation
Glandular cell apoptosis, followed by atrophy of glandular structures in affected tissues (salivary glands, sebaceous glands, sweat glands etc.)
Secondary changes e.g. oedema of conjunctiva

Table 51.28 Skin manifestations in Sjögren's syndrome.

Xeroderma, pruritus and scaling
SCLE-like rashes [4], annular erythema, including Sweet's-like lesions and papular erythema [5]
Raynaud's syndrome
Hyperglobulinaemic purpura and inflammatory vasculitis, including PAN-like lesions
Vitiligo
Abnormalities of sweating
Amyloid
Alopecia—diffuse and generalized

an increased incidence of HLA-B8 and -DR3 in patients with Sjögren's syndrome, although DR4 is more closely associated with the syndrome occurring with Raynaud's phenomenon [6]. Associations with the complement allele C4AQO [7] and HLA-DRw52 [8] in Japanese patients have been reported. Antibodies to the Ro antigen occur in excess in relatives of patients with Sjögren's syndrome, especially in association with DR2 and DR3 [9]. Further evidence of an autoimmune condition is provided by the infiltration of the tissues by lymphocytes and plasma cells, and, as with the majority of autoimmune diseases, it is suggested that glandular damage, induced by a number of exogenous stimuli, leads to the expression of antigens—in this case Ro—which stimulate autoantibody production. Dendritic cells accumulate, produce interferon, which stimulates lymphocyte activation and stimulation, and glandular cell apoptosis is induced [1].

References

1 Fox RI. Sjogren's syndrome. *Lancet* 2005; **366**: 321–31.
2 Sjögren H. Zur Kenntnis der Keratoconjunctivitis sicca. *Acta Ophthalmol* 1933; **10** (Suppl. 2): 1–151.
3 Vitali C, Bombardieri S, Jonsson R *et al*. European Study Group on Classification Criteria for Sjögren's Syndrome. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 2002; **61**: 554–8.
4 Block KJ, Buchanan WW, Wohl MJ *et al*. Sjögren's syndrome. *Medicine* 1965; **44**: 187–231.
5 Voulgarelis M, Dafni UG, Isenberg DA *et al*. Malignant lymphoma in primary Sjögren's syndrome: a multicenter, retrospective, clinical study by the European Concerted Action of Sjögren's Syndrome. *Arthritis Rheum* 1999; **42**: 1765–72.
6 Mann DL, Moutsopoulos HM. HLA or alloantigens in different subsets of patients with Sjögren's syndrome and in family members. *Ann Rheum Dis* 1983; **42**: 533–6.
7 Mouichi J, Ichikawa Y, Takaya M *et al*. Association of the complement allele C4 AQO with primary Sjögren's syndrome in Japanese patients. *Arthritis Rheum* 1991; **34**: 224–7.
8 Miyagaura S, Dohi K, Shima H, Shirai T. HLA antigens in anti-Ro (SS-A) positive patients with recurrent annular erythema. *J Am Acad Dermatol* 1993; **28**: 185–8.
9 Arnett FC, Hamilton RG, Reveille JD *et al*. Genetic studies of Ro (SS-A) and La (SS-B) autoantibodies in familes with systemic lupus erythematosus and primary Sjögren's syndrome. *Arthritis Rheum* 1989; **32**: 413–9.

Pathology [1]. The salient pathological changes are shown in Table 51.27.

Reference

1 Morgan AD, Raven RW. Sjögren's syndrome: a general disease. *Br J Surg* 1952–53; **40**: 154–62.

Clinical features [1]. The clinical picture is extremely variable. The consequences of reduced exocrine gland activity may be a minor manifestation of a serious systemic illness, or the presenting, and for many years the only, features. In a prospective study of patients presenting with dry eyes, 43% were found to have keratoconjunctivitis sicca with xerostomia, and 23% had associated connective tissue disease, particularly rheumatoid arthritis [2]. Oral symptoms may precede ocular, or both may occur late in the disease. Some cases present with generalized or anogenital pruritus, or with diffuse alopecia. Reduction in the appreciation of taste and smell has been observed [3]. Infections, including pneumonia, oral candidosis and bacterial conjunctivitis, are frequent.

Skin involvement occurs in around 50% of patients, and may be more common but not recognized (Table 51.28). Annular erythema in Japanese patients may differ from others. In Japan, annular erythema has been subdivided into three types clinically: Sweet's disease-like annular erythema with an elevated border; SCLE-like marginally scaled erythema; and papular erythema [5]. Annular erythema of Asian patients, which is recurrent and non-scarring, may occur in patients with LE, Sjögren's syndrome or both diseases [6]. These lesions are not photosensitive in origin. Ro antibody-positive patients tend to develop annular polycyclic lesions of SCLE as well as neuropsychiatric and pulmonary disease, and have a guarded prognosis [7]. Vascular responsiveness may also be impaired [8] and nail fold capillary abnormalities are found [9].

Non-thrombocytopenic purpura may occur as recurrent crops of round pink lesions in dependent areas (Fig. 51.95), and is associated with hyperglobulinaemia. It may be confused with vasculitis, and fades to leave brown-pigmented stains, but crops occur over many years. Biopsy shows perivascular mononuclear infiltration, but no active vasculitis. However, inflammatory and often necrotizing vasculitis can occur, including an arteritis like that seen in rheumatoid arthritis, lesions indistinguishable from polyarteritis nodosa and nail fold infarcts, splinter haemorrhages and gangrene of the fingers [10].

Mouth. The saliva is at first thick and mucoid, but later salivary volume decreases. The tongue is red, smooth and dry, and in severe cases there may be difficulty in swallowing dry food. Parotid duct narrowing and web formation may develop [11]. Dental caries is often severe and progressive. The lips are red, dry and scaly. There are frequently cracks at the corners of the mouth. Chronic oral candidiasis is frequent. Recurrent episodes of swelling of one or both parotid glands or, less often, the submaxillary and sublingual glands, may be due to autoimmune inflammation or infection, which is common. Impaired glandular function may



Fig. 51.95 Hyperglobulinaemic purpura in Sjögren's syndrome.

Table 51.29 Other manifestations of Sjögren's syndrome.

Joint symptoms—arthralgia and arthritis
Myalgia and myositis
ENT problems: sinusitis, hearing problems including deafness
Tracheal and oesophageal reflux
Interstitial pneumonitis, pulmonary fibrosis and pulmonary hypertension
Interstitial nephritis
Gastrointestinal conditions, including primary biliary cirrhosis
Neurological abnormalities: migraine, neuropathies, cerebral vasculitis

be due to both glandular destruction and functional changes due to altered responsiveness to neurological stimulus [12].

Other mucous membranes [11]. Atrophic changes in the mucous membranes of the upper respiratory tract lead to nasal crusting and dryness, recurrent episodes of infection, hoarseness or aphonia. Pulmonary infiltration, atelectasis or fibrosis may occur. Atrophic rhinitis can occur, and the sense of smell may be reduced. Digestive symptoms are attributable to atrophy of the gastric mucous membrane with achlorhydria. Similar changes in the vulva and vagina give rise to pruritus and vaginitis, and dryness of the anal and rectal mucous membrane leads to dyschezia and pruritus.

Other manifestations (Table 51.29) [1]. In patients without associated connective tissue disease, mild articular symptoms occur in 83%, with mild synovitis. Cervical or generalized lymphadenopathy and enlargement of the liver and spleen, which is sometimes considerable, may be found. The main renal abnormalities appear to be interstitial nephritis, renal tubular acidosis, impaired renal concentrating ability and generalized aminoaciduria [13]. Impaired renal function can occur without clinical manifestations [14]. A high prevalence of fetal loss has been recorded, but there was no correlation with anticardiolipin or anti-Ro antibodies [15].

References

1 Papiris SA, Tsonis IA, Moutsopoulos HM. Sjögren's syndrome. *Semin Respir Crit Care Med* 2007; **28**: 459–71.
2 Forstot JZ, Forstot SL, Greer RO *et al.* The incidence of Sjögren's sicca complex in a population of patients with keratoconjunctivitis sicca. *Arthritis Rheum* 1982; **25**: 156–60.
3 Henkin RI, Talal N, Larson AL *et al.* Abnormalities of taste and smell in Sjögren's syndrome. *Ann Intern Med* 1972; **76**: 375–83.
4 Ruzicka T, Faes J, Bergner T *et al.* Annular erythema associated with Sjögren's syndrome: a variant of systemic lupus erythematosus. *J Am Acad Dermatol* 1991; **25**: 557–60.
5 Teramoto N, Katayama I, Arai H *et al.* Annular erythema: a possible association with primary Sjögren's syndrome. *J Am Acad Dermatol* 1989; **20**: 596–601.
6 Watanabe T, Tsuchida T, Ito Y *et al.* Annular erythema associated with lupus erythematosus/Sjögren's syndrome. *J Am Acad Dermatol* 1997; **36**: 214–8.
7 Provost TT, Talal N, Harley JB *et al.* The relationship between anti-Ro (SS-A) antibody-positive Sjögren's syndrome and anti-Ro (SS-A) antibody-positive lupus erythematosus. *Arch Dermatol* 1988; **124**: 63–71.
8 Kovacs L, Torok T, Bari F *et al.* Impaired microvascular response to cholinergic stimuli in primary Sjögren's syndrome. *Ann Rheum Dis* 2000; **59**: 48–53.
9 Tektonidou M, Kaskani E, Skopouli FN *et al.* Microvascular abnormalities in Sjögren's syndrome: nailfold capillaroscopy. *Rheumatology (Oxford)* 1999; **38**: 826–30.
10 Claeys V, Wackens G. [Sjogren syndrome: a review of the literature and a case report]. *Revue Belge de Medecine Dentaire* 2006; **61**: 161–72.
11 Doig JA, Whaley K, Dick WC *et al.* Otolaryngological aspects of Sjögren's syndrome. *BMJ* 1971; **iv**: 460–3.
12 Soto-Rojas AE, Kraus A. The oral side of Sjogren syndrome. Diagnosis and treatment. *Arch Med Res* 2002; **33**: 95–106.
13 Tu WH, Shearn MA, Lee JC *et al.* Interstitial nephritis in Sjögren's syndrome. *Ann Intern Med* 1968; **69**: 1163–70.
14 Shiozawa S, Shiozawa K, Shimizu S *et al.* Clinical studies of renal disease in Sjögren's syndrome. *Ann Rheum Dis* 1987; **46**: 768–72.
15 Valesini G, Priori R, Borsetti A *et al.* Clinical serological correlations in the evaluation of Sjögren's syndrome. *Clin Exp Rheumatol* 1989; **7**: 197–202.

Sjögren's syndrome in childhood. Primary Sjögren's syndrome is rare in childhood. Recurrent annular erythema similar to that seen in adults has been reported on the face, trunk and limbs [1]. Episodes, with or without fever and parotid swelling, occur over years and last a few months. Anti-Ro antibodies are positive but there is no evidence of SLE. Histology of the lesions shows a dermal lymphocytic infiltration but no vasculitis, and immunohistology reveals no immunoglobulins or complement at the dermal–epidermal junction or around blood vessels. The condition responds to oral steroids.

Reference

1 Miyagawa S, Iida T, Fukumoto T *et al.* Anti-Ro/SSA-associated annular erythema in childhood. *Br J Dermatol* 1995; **133**: 779–82.

Laboratory abnormalities. Hypergammaglobulinaemia and rheumatoid factor are frequently demonstrated in the serum, even in patients without arthritis, and serum viscosity is usually raised [1]. Antinuclear antibodies are present in more than 50% of patients (homogeneous factor is more frequent than speckled, and nucleolar factor is only occasionally found). Anti-DNA antibody can occasionally be demonstrated, but anti-Sm and anti-RNP antibodies are never found in the sicca syndrome alone. Anti-Ro (also called SS-A) and anti-La (SS-B) are frequently found and are an important part of the diagnostic profile of the disease. Antibodies to Ro/La were found in 53% of patients with Sjögren's syndrome [2]. Anti-Ro antibodies are particularly associated with vasculitis,

purpura, lymphadenopathy, and haematological and serological abnormalities [3]. Recurrent annular erythema is associated with anti-La antibodies in Sjögren's syndrome [4,5] but not all anti-La-positive patients have a rash, and no disease-specific epitope has been demonstrated [6]. The epitope of anti-Ro antibody is similar in the annular erythema of Sjögren's syndrome and SCLE [7]. Antibody to salivary duct epithelium can be demonstrated in approximately 50% but is also found in uncomplicated rheumatoid arthritis [8]. Thyroglobulin antibodies are present in 25% of cases [9]. Leukopenia and eosinophilia are not infrequent. Immune complexes occur in 60%, but are not related to disease activity [10].

References

1 Blaylock WM, Waller M, Normansell DE. Sjögren's syndrome: hyperviscosity and intermediate complexes. *Ann Intern Med* 1974; **80**: 27–34.
2 Pease CT, Shattles W, Charles PJ *et al.* Clinical, serological, and HLA phenotype subsets in Sjögren's syndrome. *Clin Exp Rheumatol* 1989; **7**: 185–90.
3 Alexander EL, Hirsch TJ, Arnett FC *et al.* Ro (SSA) and La (SSB) antibodies in the clinical spectrum of Sjögren's syndrome. *J Rheumatol* 1982; **9**: 239–46.
4 Teramoto N, Katayama I, Arai H *et al.* Annular erythema: a possible association with primary Sjögren's syndrome. *J Am Acad Dermatol* 1991; **20**: 596–601.
5 Ruzicka T, Faes J, Bergman T *et al.* Annular erythema associated with Sjögren's syndrome: a variant of systemic lupus erythematosus. *J Am Acad Dermatol* 1991; **25**: 557–60.
6 Yoshino Y, Hashimoto T, Mimori T *et al.* Recurrent annular erythema associated with anti-SS-B/La antibodies: analysis of the disease-specific epitope. *Br J Dermatol* 1992; **127**: 608–13.
7 McCauliffe DP, Faircloth E, Wang L *et al.* Similar Ro/SS-A autoantibody epitope and titre responses in annular erythema of Sjögren's syndrome and subacute cutaneous lupus erythematosus. *Arch Dermatol* 1996; **132**: 528–31.
8 MacSween RNM, Goudie RB, Anderson JR *et al.* Occurrence of antibody to salivary duct epithelium in Sjögren's disease, rheumatoid arthritis and other arthritides. *Ann Rheum Dis* 1967; **26**: 402–11.
9 Bloch KJ, Buchanan WW, Wohl MJ *et al.* Sjögren's syndrome. *Medicine* 1965; **44**: 187–231.
10 Fishbach M, Char D, Christensen M *et al.* Immune complexes in Sjögren's syndrome. *Arthritis Rheum* 1980; **23**: 791–5.

Associations [1]. Diseases reported in association with Sjögren's syndrome are listed in Table 51.30. Drug allergy, especially to penicillin [18], is also more common than expected.

Table 51.30 Diseases reported in association with Sjögren's syndrome.

Connective tissue disease (rheumatoid arthritis (26%), systemic sclerosis (22%)) [2]
Sweet's syndrome [3]
Lymphoproliferative disorders—B and T cell, and MALT associated [4]
Primary biliary cirrhosis, chronic hepatitis [5]
Lipodystrophy [6]
Granulomatous panniculitis [7]
Behçet's disease [8]
Coeliac disease [9]
Hypothyroidism and thyroiditis [10]
Myasthenia gravis [11]
Haemochromatosis [12]
Dermatitis herpetiformis [13]
Darier's disease [14]
Multicentric reticulohistiocytosis [15]
Sarcoidosis [16]
Waldenström's hyperglobulinaemic purpura [17]

References

1 Fox RI. Sjogren's syndrome. *Lancet* 2005; **366**: 321–31.
2 Coll J, Rives A, Grino MC *et al.* Prevalence of Sjögren's syndrome in autoimmune diseases. *Ann Rheum Dis* 1987; **46**: 286–9.
3 Levanstein MM, Fisher BK, Fisher L *et al.* Simultaneous occurrence of subacute cutaneous lupus erythematosus and Sweet syndrome: a marker of Sjögren syndrome? *Int J Dermatol* 1991; **30**: 640–3.
4 Smedby KE, Baecklund E, Askling J. Malignant lymphomas in autoimmunity and inflammation: a review of risks, risk factors, and lymphoma characteristics. *Cancer Epidemiol Biomarkers Prev* 2006; **15**: 2069–77.
5 Golding PL, Brown R, Mason AMS *et al.* 'Sicca complex' in liver disease. *BMJ* 1970; **iv**: 340–2.
6 Alarcón-Segoviá D, Ramos-Niembro F. Association of partial lipodystrophy and Sjögren's syndrome. *Ann Intern Med* 1976; **85**: 474–5.
7 Tait CP, Yu LL, Rohr J. Sjögren's syndrome and granulomatous panniculitis. *Australas J Dermatol* 2000; **41**: 187–9.
8 Ramirez-Peredo J, Cetina JA, Alarcón-Segoviá D. Sjögren's syndrome in Bechçet's disease. *Lancet* 1973; **ii**: 732.
9 Maclaurin BP, Matthews N, Kilpatrick JA. Coeliac disease associated with autoimmune thyroiditis, Sjögren's syndrome and a lymphocytotoxic serum factor. *Aust NZ J Med* 1972; **2**: 405–11.
10 Edmonds ME, Saunders A, Sturrock RD. Rheumatoid arthritis associated with hypoparathyroidism and Sjögren's syndrome. *J R Soc Med* 1979; **72**: 856–8.
11 Ito Y, Kanda N, Mitsui H *et al.* Cutaneous manifestations of Sjögren's syndrome associated with myasthenia gravis. *Br J Dermatol* 1999; **141**: 362–3.
12 Blandford RL, Dowdle JR, Stephens MR *et al.* Sicca syndrome associated with idiopathic haemochromatosis. *BMJ* 1979; **i**: 1323.
13 Fraser NG, Rennie AGR, Donald D. Dermatitis herpetiformis and Sjögren's syndrome. *Br J Dermatol* 1979; **100**: 213–5.
14 Oxholm A, da Cunha Bang F, Oxholm P. Simultaneous occurrence of Darier's disease and primary Sjögren's syndrome. *Arthritis Rheum* 1986; **29**: 1052.
15 Carey RD, Blotzer JW, Wolfe ID *et al.* Multicentric reticulohistiocytosis and Sjögren's syndrome. *J Rheumatol* 1985; **12**: 1193–5.
16 Cox NH, McCrea JD. A case of Sjögren's syndrome, sarcoidosis, previous ulcerative colitis and gastric autoantibodies. *Br J Dermatol* 1996; **134**: 1138–40.
17 Miyagaura S, Fukumoto T, Kananchi M *et al.* Hypergammaglobulinaemic purpura of Waldenstrom and Ro/SSA antibodies. *Br J Dermatol* 1996; **134**: 919–23.
18 Williams BO, St Onge RA, Young A *et al.* Penicillin allergy in rheumatoid arthritis. *Ann Rheum Dis* 1969; **28**: 607–11.

Diagnosis. So variable is the clinical picture that the diagnosis is easily overlooked, except in the more obvious cases presenting with ocular or oral symptoms.

It should also be suspected in the presence of anogenital pruritus in association with ocular and oral changes or with rheumatoid disease, and should be confirmed by specialist ophthalmological examination. Biopsy of labial salivary glands [1] or nasal mucosa [2] is useful, and the value of lip biopsy has been stressed, but a negative biopsy does not exclude the diagnosis [3]. The demonstration of anti-Ro (SS-A) and anti-La (SS-B) antibodies may be helpful in diagnosis, and anti-La may antedate clinical evidence of Sjögren's syndrome by months or even years [4]. Contrast sialography is useful [5], and sequential salivary scintigraphy [6] gives objective and sensitive estimation of salivary gland function. Once a diagnosis is made, every case requires detailed investigation to determine the extent and nature of the associated abnormalities.

Treatment. Symptomatic treatment for the dryness of the eyes is best accomplished by lubricating agents, such as 0.5% methylcellulose eye drops instilled into the eyes four or five times daily. Bromhexine 16 mg three times daily has been found to increase

the lacrimal secretion, but has no effect on salivary flow [7]. However, it does change the salivary composition towards normal [8]. Artificial saliva can be prescribed, and steam inhalations or an air humidifier may help dryness of the respiratory tract. Patients with Sjögren's syndrome associated with SLE seem to improve more than those with primary Sjögren's syndrome. Systemic corticosteroids are effective in reducing parotid swelling, but rarely increase parotid or lacrimal secretion. The immunological abnormalities in the serum are not markedly altered by corticosteroids. Chloroquine or hydroxychloroquine sulphate by mouth have been found useful by some authors [9] but not by others [10]. Ciclosporin improved subjective xerostomia and may reduce histopathological progression [11]. Nifedipine may help pulmonary Raynaud's phenomenon [12]. A patient with associated polymyositis improved with monthly intravenous pulse cyclophosphamide therapy [13]. The annular erythema in Japanese patients may be controlled by prednisolone 10–20 mg/day or by dapsone. There is no single therapy that helps hyperglobulinaemic purpura, although graduated compression hosiery may be significantly valuable. The role of biological therapies, particularly rituximab, is being evaluated [14].

References

1 Daniels TE. Labial salivary gland biopsy in Sjögren's syndrome: assessment as a diagnostic criterion in 362 suspected cases. *Arthritis Rheum* 1984; **27**: 147–56.

2 Powell RD, Larson AL, Henkin RI. Nasal mucous membrane biopsy in Sjögren's syndrome. *Ann Intern Med* 1974; **81**: 25–31.

3 Valesini G, Priori R, Borsetti A *et al.* Clinical and serological correlations in the evaluation of Sjögren's syndrome. *Clin Exp Rheumatol* 1989; **7**: 197–202.

4 Isenberg DA, Hammond L, Fisher C *et al.* Predictive value of SS-B precipitating antibodies in Sjögren's syndrome. *BMJ* 1982; **284**: 1738–40.

5 Miyachi K, Naito M, Maeno Y *et al.* Sialographic study in patients with and without antibodies to Sjögren's syndrome A (Ro). *J Rheumatol* 1983; **10**: 387–94.

6 Schall GL, Anderson LG, Wolf RO *et al.* Xerostomia in Sjögren's syndrome. *JAMA* 1971; **216**: 2109–16.

7 Frost-Larsen K, Isager H, Manthorpe R. Sjögren's syndrome treated with bromhexine: a randomized clinical study. *BMJ* 1978; **i**: 1579–81.

8 Nahir AM, Aryeh HB, Szargel R *et al.* Sialochemistry in evaluating bromhexine treatment of Sjögren's syndrome. *BMJ* 1979; **ii**: 833.

9 Fox RI, Chan E, Benton L *et al.* Treatment of primary Sjögren's syndrome with hydroxychloroquine. *Am J Med* 1988; **85**: 62–7.

10 Bloch KJ, Buchanan WW, Wohl MJ *et al.* Sjögren's syndrome. *Medicine* 1965; **44**: 187–231.

11 Drosos AA, Skopouli FN, Costopoulos JS *et al.* Cyclosporin A (CyA) in primary Sjögren's syndrome: a double-blind study. *Ann Rheum Dis* 1986; **45**: 732–5.

12 Joseph BZ, Organek HW, Grant A *et al.* Effects of nifedipine therapy on pulmonary Raynaud's in primary Sjögren's syndrome. *Clin Exp Rheum* 1988; **6**: 409–10.

13 Leroy JP, Drosos AA, Yiannopoulos DI *et al.* Intravenous pulse cyclosphosphamide therapy in myositis and Sjögren's syndrome. *Arthritis Rheum* 1990; **33**: 1579–81.

14 Bryce AH, Dispenzieri A, Kyle RA *et al.* Response to rituximab in patients with type II cryoglobulinemia. *Clin Lymphoma Myeloma* 2006; **7**: 140–4.

Rheumatic fever

Erythema marginatum is the characteristic rash of rheumatic fever, and occurs in 25% of cases [1]. It appears as evanescent, asymptomatic, pinkish superficial semicircles and rings, which disappear without scaling or pigmentation in a few days. Histologically, there is a perivascular infiltration of neutrophils in the papillary dermis, and biopsy may help in the early diagnosis of rheumatic fever when the rash precedes arthritis and carditis [2]. Erythema multiforme, petechiae and urticaria may sometimes be seen in rheumatic fever. Livedo reticularis has been reported [3]. The overall clinical picture must be distinguished from post-streptococcal reactive arthritis [4].

Subcutaneous nodules occur, particularly on the occiput, wrist and the backs of the forearms, and are smaller and more transient than those seen in rheumatoid arthritis, from which they can be distinguished histologically [5]. Generalized eruptive histiocytomas [6] and erythema elevatum diutinum [7] have also occurred with rheumatic fever.

References

1 Hill AGS. Skin manifestations in rheumatic disorders. *Trans St John's Hosp Dermatol Soc* 1964; **50**: 105–12.

2 Troyer C. Erythema marginatum in rheumatic fever: early diagnosis by skin biopsy. *J Am Acad Dermatol* 1983; **8**: 724–8.

3 Haber H. Zur Ätiologie der Livedo racemosa. *Arch Dermatol Syphilol* 1931; **163**: 1–5.

4 Jansen TL, Janssen M, de Jong AJ, Jeurissen ME. Post-streptococcal reactive arthritis: a clinical and serological description, revealing its distinction from acute rheumatic fever. *J Intern Med* 1999; **245**: 261–7.

5 Bennett GA, Zeller JW, Bauer W. Subcutaneous nodules of rheumatoid arthritis and rheumatic fever. *Arch Pathol* 1940; **30**: 70–89.

6 Matsushima Y, Ohnishi K, Ishikawa O. Generalized eruptive histiocytoma of childhood associated with rheumatic fever. *Eur J Dermatol* 1999; **9**: 548–50.

7 Wahl CE, Bouldin MB, Gibson LE. Erythema elevatum diutinum: clinical, histopathologic and immunohistochemical characteristics of six patients. *Am J Dermatopathol* 2005; **27**: 397–400.

CHAPTER 52

Non-Melanoma Skin Cancer and Other Epidermal Skin Tumours

A.G. Quinn[1] *& W. Perkins*[2]

[1]Synageva BioPharma Corporation, Waltham, Massachusetts, USA
[2]Nottingham University Hospital, Queen's Medical Centre, Nottingham, UK

Non-melanoma skin cancer and related premalignant lesions, 52.2
Epidemiology and risk factors for non-melanoma skin cancer development, 52.2
Naevoid basal cell carcinoma syndrome, 52.6
Follicular atrophoderma and basal cell carcinoma, 52.8
Rombo syndrome, 52.9
Self-healing epitheliomas, 52.9
Xeroderma pigmentosum, 52.10
Muir–Torre syndrome, 52.10
The molecular and cellular biology of non-melanoma skin cancer, 52.12
Cancer as a genetic disease, 52.12
Multistage carcinogenesis in the murine skin model, 52.12
Ultraviolet radiation mutagenesis and DNA repair, 52.13
Immunological effects of ultraviolet radiation, 52.14
Human papillomaviruses, 52.14
General principles in the management of patients with non-melanoma skin cancer, 52.15
Detection and diagnosis, 52.15
Selection of appropriate therapeutic modality for tumour treatment, 52.15
Chemoprevention and management of high-risk patients, 52.17
Basal cell carcinoma, 52.18
Basisquamous or metatypical basal cell carcinoma, 52.22
Squamous cell carcinoma, 52.24
Premalignant epithelial lesions, 52.29
Actinic keratosis, 52.30
Bowen's disease, 52.32
Arsenical keratosis, 52.34
Disseminated superficial 'actinic' porokeratosis, 52.35
Cutaneous horn, 52.36
Erythroplasia of Queyrat, 52.36
Bowenoid papulosis of the genitalia, 52.37
Intraepidermal carcinoma of the eyelid margin, 52.37
Leukokeratosis of the lips, 52.37
Post-ionizing radiation keratoses, 52.37
Tar keratoses, 52.37
Benign epidermal tumours, 52.38
Seborrhoeic keratosis, 52.38
Melanoacanthoma, 52.39
Stucco keratosis, 52.40
Dermatosis papulosa nigra, 52.40
Skin tags, 52.40
Haber's syndrome, 52.41
Clear cell acanthoma, 52.41
Keratoacanthoma, 52.42
Generalized eruptive keratoacanthoma, 52.44
Pseudoepitheliomatous hyperplasia, 52.44
Cysts, 52.45
Epidermoid cyst, 52.45
Trichilemmal cyst, 52.46
Steatocystoma multiplex, 52.47
Milium, 52.47
Premalignant fibroepithelial tumour (of Pinkus), 52.48

Introduction

The complexity of the cellular composition of the skin means that the range of tumours that can arise within it is very wide. This chapter deals chiefly with the benign and malignant tumours arising from epidermal keratinocytes. Non-melanoma skin cancers and related premalignant lesions are dealt with in a separate section in view of their clinical importance and the overlap in the epidemiology, pathogenesis and management of these tumours. Chapter 53 is devoted to appendage tumours, Chapter 54 to tumours arising from the melanocyte and Chapter 56 to soft-tissue tumours.

A *tumour* is an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of normal tissues. Although most tumours retain a resemblance to the normal tissue from which they arise, they can show an extraordinary variation in their structure and it is this variation that causes difficulties in some cases in establishing a definitive pathological diagnosis. Most of the keratinocyte-derived tumours described in this chapter are *benign*, which is the term used to describe tumours where the cells remain at their site of origin, forming a single mass of tumour cells. *Hamartomas* are difficult to distinguish from true benign tumours clinically. They are not true tumours and best considered as a localized overproduction of one or more elements of a tissue but without the progressive growth characteristics of a tumour. *Malignant* tumours are composed of cells that have acquired the ability to invade through a basement membrane and this is associated with the capacity to metastasize to other organs via the lymphatics and blood vessels. In addition, malignant tumours frequently show more rapid growth and less differentiation than benign tumours, which is reflected histologically by higher mitotic

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

rates, cellular and nuclear pleomorphism and abnormal mitoses. Differentiation between benign and malignant tumours is one of the major responsibilities of a dermatopathologist. The distinction, however, can be difficult with small tissue samples and is not absolute, which means it is vital that there is good communication between the clinician and pathologist, particularly when the pathology report suggests biological behaviour not in keeping with the clinical impression [1,2].

References

1 Leigh IM, Newton-Bishop J, Kripke ML, eds. *Skin Cancer.* Cancer Surveys no. 26. New York: Cold Spring Harbor, 1996.
2 Mackie RM. *Skin Cancer*, 2nd edn. London: Dunitz, 1996.

Non-melanoma skin cancer and related premalignant lesions

Non-melanoma skin cancer (NMSC) is the most common human cancer. The term encompasses basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) of the skin, which are both derived from epidermal keratinocytes. Although these tumours are clinically and pathologically distinctive, they share some characteristics and are frequently classified under the term NMSC for health care planning, cancer registry reporting and epidemiological purposes. In contrast to other common epithelial cancers, NMSCs rarely metastasize, which means that the case fatality rate for these cancers is low. This low mortality from NMSC has contributed to the widespread under-reporting of this cancer to disease registries in many countries which makes it challenging to quantify accurately the morbidity and health care costs associated with this disease. Nevertheless, given the high prevalence of NMSC and the frequent occurrence of multiple primary tumours in affected individuals, there is little disagreement amongst dermatologists that NMSC is an important and frequently underestimated public health problem.

Patients at risk for development of NMSC are also predisposed to the development of actinic keratoses (AK) and Bowen's disease, which are premalignant lesions that show some of the histological characteristics of SCC. The prevalence of AK and the multiplicity of lesions within individual subjects is considerably greater than that for NMSC. While there is some controversy about the premalignant potential of AK and Bowen's disease and their relationship to SCC, these lesions are, in themselves, an important clinical problem for three reasons. First, they need to be distinguished from SCC; secondly, they cause concern and anxiety in patients, particularly in those with a previous history of NMSC; and, thirdly, the scaling and inflammation associated with these lesions is an important contributor to the overall morbidity associated with photoageing.

Epidemiology and risk factors for non-melanoma skin cancer development

Epidemiological surveys have a key role in the generation of incidence and prevalence data for NMSC in populations, quantification of the clinical impression of increasing skin cancer incidence and identification of environmental and host factors important in NMSC development.

Incidence and mortality

Whilst the prevalence of NMSC is recognized as being high and represents a substantial economic burden to health providers, accurate figures for NMSC are unavailable in most geographical regions as these cancers are not reported in many national cancer registries. Giles *et al.* [1], in an Australian postal survey of 31 000 individuals, conducted in 1985, reported 652 BCCs and 160 SCCs and an increased incidence of SCCs from 166 to 250 per 100 000 over the 5-year period, and an 11% increase in the incidence of BCCs [2]. In the USA, a population-based study [3] quotes an incidence of 38 SCCs per 100 000 population, with a 3:1, male:female preponderance. Miller and Weinstock [4] have estimated that in 1994 there were 1 million new cases of NMSC in the USA. Mortality from NMSC in the USA is estimated at $0.44/10^5$ per year [5], with the main cause of death being metastases from SCC. There are a few recorded deaths from BCC, most of these being related to refusal of surgical treatment. The annual cost of treating NMSC in the USA has been estimated at over $500 million [6].

The incidence of NMSC has increased dramatically over the last 30–40 years in many populations worldwide. In addition to the study by Giles in Australia showing a 50% increase in the incidence of SCC and an 11% increase in the incidence of BCCs between 1985 and 1990 [2], Miller and Weinstock have reported a threefold increase in NMSC incidence in the USA over the past two decades with a continuing rise at a rate of 8% per year [4]. Increases in NMSC incidence have also been reported in Europe. In Wales, a population-based study has shown that the crude incidence for NMSC has increased from 173.5 to 265.4 per 100 000 population per annum between 1988 and 1998 [7]. Although differences in the methodologies between reported population-based studies make it difficult to directly compare NMSC incidence in different countries, comparison of age-specific incidence rates of BCCs in two studies from Sweden and Australia indicate that the rate in northern Europe is approximately three to four times less than that seen in the Australian population [1,7,8].

Most studies indicate that BCCs account for more than 70% of the cases of NMSC in areas with both high and low ambient sun exposure. Although a ratio of 4:1, BCC:SCC has been described as a relatively consistent finding in studies of NMSC incidence in non-immunosuppressed, white-skinned individuals, closer examination of the available information shows that this ratio differs between countries with low and high ambient sun exposure, which reflects a disproportionate increase in SCC relative to BCC with increasing sun exposure. In some groups such as white Maryland fisherman with very high occupational ultraviolet radiation (UVR) exposure, the ratio of BCC:SCC is almost 1:1 [9].

References

1 Giles GG, Marks R, Foley P. The incidence of non-melanocytic skin cancer in Australia. *BMJ* 1988; **296**: 13–7.
2 Marks R, Staples M, Giles G. Trends in non-melanocytic skin cancer treated in Australia: the second national survey. *Int J Cancer* 1993; **53**: 585–90.
3 Chuang TY, Popescu NA, Su D *et al.* Squamous cell carcinoma: a population-based incidence study in Rochester, Minnesota. *Arch Dermatol* 1990; **126**: 185–8.
4 Miller DL, Weinstock MA. Non-melanoma skin cancer in the United States: incidence. *J Am Acad Dermatol* 1994; **30**: 774–8.
5 Weinstock MA, Bogars HA, Ashley M *et al*. Non-melanoma skin cancer mortality. *Arch Dermatol* 1991; **127**: 1194–7.

6 Gloster HM Jr, Brodland DG. The epidemiology of skin cancer. *Dermatol Surg* 1996; **22**: 217–26.
7 Holme SA, Malinovszky K, Roberts DL. Changing trends in non-melanoma skin cancer in South Wales, 1988–98. *Br J Dermatol* 2000; **143**: 1224–9.
8 Dahl E, Aberg M, Rausing A, Rausing EL. Basal cell carcinoma: an epidemiologic study in a defined population. *Cancer* 1992; **70**: 104–8.
9 Vitasa BC, Taylor HR, Strickland PT *et al*. Association of non-melanoma skin cancer and actinic keratosis with cumulative solar ultraviolet exposure in Maryland watermen. *Cancer* 1990; **65**: 2811–7.

Environmental risk factors

Ultraviolet radiation

Ultraviolet radiation (UVR) is by far the most important and best understood risk factor for NMSC development. An association between sun exposure and NMSC was first suggested by Thiersch and Unna at the end of the 19th century and substantiated by the work of Hyde [1] and Dubreuilh independently at the beginning of the 20th century [2]. Since then, a large body of information from epidemiological, clinical and experimental observations has been generated to substantiate the proposed causal link between the sun and NMSC development. This evidence includes: the increased frequency of NMSC in areas of high ambient sun exposure; the latitude gradient in the annual age-adjusted incidence in the USA for cutaneous SCCs, with an increasing incidence the nearer one gets to the equator because of greater levels of the UVB component of terrestrial sunlight [3]; the increased incidence of NMSC in sun-sensitive people, which is dramatically highlighted by the differences in NMSC risk between albinos and non-albinos in countries such as Tanzania with high ambient sun exposure [4]; the association between NMSC and 'benign' sun-related conditions such as photoageing and solar telangiectasia; and the marked increase in NMSC incidence with increasing age resulting from cumulative sun exposure, which reflects both the intensity and duration of this exposure [3,5]. The strength of the evidence led the International Agency for Research on Cancer to conclude in 1992 that sun exposure is carcinogenic in humans and that it has a causal role in development of NMSC [6].

The rising incidence of NMSC over the last 30 years is largely the result of increased recreational sun exposure and there are many parallels between the changing epidemiology of NMSC with that other well-known 20th century epidemic, smoking-related lung cancer. Sunbathing, like cigarette smoking, became popular in the early half of the century with the popularization of the bronzed look by Coco Chanel in the 1930s. Although the development of sunbathing as a popular leisure pursuit has lagged behind cigarette smoking, changes in attitudes about the desirability of a tan, coupled with increased leisure time, the introduction of paid holidays and the development of cheap package holidays have seen a marked increase in the level of individual sun exposure in the latter half of the 20th century. In parallel with smoking-related lung cancer, the incidence rate for NMSC has lagged behind the changes in carcinogen exposure, which means that the current clinical impression of increasing NMSC incidence is likely to be a prelude to reporting on a more substantial scale over the next 30–40 years.

The relationship between exposure to UVR and skin cancer development is complex. Epidemiological studies have had an important role in the identification of differences between BCC and SCC with respect to age and pattern of sun exposure. Migrant studies have established that high sun exposure in childhood is especially important in determining NMSC risk and that there is a sharp change in relative risk of NMSC between arrival before and after 10 years of age [7]. Although the basis for this age effect is still unclear, an important consideration is the possibility that the skin is more susceptible to the carcinogenic effects of UVR in childhood. The concept that the response of the skin with respect to cancer susceptibility may be qualitatively different in early life is supported by the observation that susceptibility to melanocytic naevus formation is also greatest during this period [8]. Although the incidence of both BCC and SCC rises with increasing ambient sun exposure, there is a proportionately greater effect of increasing sun exposure on SCC risk [9]. Other observations suggest that the relationship between sun exposure is not the same for BCC and SCC. These observations include the greater preponderance of BCCs on intermittently sun-exposed areas, the plateauing of BCC but not SCC risk after moderate solar exposure, and the finding that for occupational sun exposure SCC but not BCC risk is related to hours of exposure, whereas BCC risk but not SCC risk is increased by sun exposure occurring during holidays [6,10].

UVR comprises a broad band of energy extending from 200 nm to visible light in the lower 400 nm range (see Chapter 29). The UV part of the solar electromagnetic spectrum is subdivided into three broad regions: UVA, UVB and UVC. Although UVB is the main wave band responsible for skin cancer induction, there is increasing interest in the carcinogenic potential of UVA. Exposure to UVA has increased considerably over the last 20 years for two reasons. First, UVB blocking sunscreens have allowed sunbathers to spend longer in the sun and, secondly, the desire to achieve a tan has led to the growth in popularity of UVA sunbeds. Experimental evidence suggests that UVA is carcinogenic [11] but it has been difficult to assess the risk of NMSC development from commercial tanning equipment, as people who tend to use sunbeds also tend to have greater levels of exposure to natural sunlight. Support for a role for UVA in NMSC induction in humans comes from recent reports of both precancerous lesions and NMSC in some individuals in areas of skin exposed almost exclusively to artificial UVA sources [12,13].

References

1 Hyde JN. On the influence of light in the production of cancer of the skin. *Am J Med Sci* 1906; **131**: 1–22.
2 Dubreuilh W. Epitheliomatose d'origine solaire. *Ann Dermatol Syphilol* 1907; **45**: 387–416.
3 Fears TR, Scotto J. Estimating increases in skin cancer morbidity due to increases in ultraviolet radiation exposure. *Cancer Invest* 1983; **1**: 119–26.
4 Luande J, Henschke CI, Mohammed N. The Tanzanian human albino skin: natural history. *Cancer* 1985; **55**: 1823–8.
5 Roberts DL. Incidence of non-melanoma skin cancer in West Glamorgan, South Wales. *Br J Dermatol* 1990; **122**: 399–403.
6 International Agency for Research on Cancer (IARC). Solar and ultra-violet radiation. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 55. Lyons: IARC, 1992.
7 Armstrong BK, Kricker A. Epidemiology of sun exposure and skin cancer. *Cancer Surv* 1996; **26**: 133–53.
8 English DR, Armstrong BK. Melanocytic nevi in children. I. Anatomic sites and demographic and host factors. *Am J Epidemiol* 1994; **139**: 390–401.
9 Kricker A, Armstrong BK, English DR, Heenan PJ. A dose–response curve for sun exposure and basal cell carcinoma. *Int J Cancer* 1995; **60**: 482–8.

10 Rosso S, Zanetti R, Martinez C *et al.* The multicentre south European study 'Helios'. II. Different sun exposure patterns in the aetiology of basal cell and squamous cell carcinomas of the skin. *Br J Cancer* 1996; **73**: 1447–54.
11 de Laat JM, de Gruijl FR. The role of UVA in the aetiology of non-melanoma skin cancer. *Cancer Surv* 1996; **26**: 173–91.
12 Roest MA, Keane FM, Agnew K *et al*. Multiple squamous skin carcinomas following excess sunbed use. *J R Soc Med* 2001; **94**: 636–7.
13 Speight EL, Dahl MG, Farr PM. Actinic keratosis induced by use of sunbed. *BMJ* 1994; **308** (6925): 415.

Photochemotherapy (PUVA) and UVB phototherapy

Photochemotherapy and UVB phototherapy are widely used by dermatologists and are recognized as highly effective treatments for a variety of skin diseases. On theoretical grounds, repeated exposure of the skin to artificial UVR or PUVA would be expected to result in cumulative actinic damage and an increased risk of NMSC. Demonstration of increased skin cancer risk and the relative risk of different types of phototherapy has, however, been challenging. This is supported by mathematical modelling approaches which demonstrate that the carcinogenic potential of UVB phototherapy can only be demonstrated with confidence in large multicentre audits with lengthy follow-up [1]. A meta-analysis has estimated an excess skin cancer incidence in patients treated with UVB phototherapy of between 0.6 and 2 extra skin cancers per 100 patients treated per year [2] which in itself is insufficient evidence to definitively establish that phototherapy for psoriasis and other dermatological problems increases skin cancer risk. Given the links between sun exposure and NMSC and the methodological challenges however, it is prudent to continue to ensure monitoring and accurate record keeping of cumulative doses of UV, particularly with the newer phototherapeutic modalities such as narrow-band UVB (TL01) and high-dose UVA1 regimens while this uncertainty remains.

In marked contrast to the lack of clinical evidence of carcinogenicity of UVB phototherapy, there is strong evidence that PUVA increases the risk of developing SCC. The carcinogenic potential of PUVA in humans was first described in 1979 [3] and there is now a substantial amount of information documenting the long-term clinical effects of PUVA [4,5]. NMSC risk in PUVA-treated patients is correlated with cumulative UVA dose and, although earlier data suggested that PUVA may increase susceptibility to both BCCs and SCCs, more recent studies indicate that the increased skin cancer risk is almost exclusively a result of increased SCC risk. Although at a population level it is clear that high-dose PUVA (defined as more than 200 treatments or 2000 J/cm^2) is associated with a 14-fold (95% CI 8.3–24.1) increase in NMSC incidence rate compared to low-dose patients [5], there is evidence that the risk is not uniformly distributed in high-exposure patients, which suggests that other factors may have an important role in modifying risk. High UVB exposure in PUVA patients has been shown to be associated with a small but significant increase in SCC risk [6]. Host factors may also be important as evidenced by the observations from a clinical review of patients exposed to more than 2000 J/cm^2 which revealed that only 50% of patients had SCCs or premalignant lesions [7]. Interestingly, none of the 13% of patients in this study without PUVA lentigines had dysplastic lesions, which suggests that the absence of lentigines may be helpful in the identification of patients at low risk of PUVA malignancy.

References

1 Diffey BL, Farr PM. The challenge of follow-up in narrowband ultraviolet B phototherapy. *Br J Dermatol* 2007; **157**: 344–9.
2 Pasker-de Jong PC, Wielink G, van der Valk PG, van der Wilt GJ. Treatment with UV-B for psoriasis and non-melanoma skin cancer: a systematic review of the literature. *Arch Dermatol* 1999; **135**: 834–40.
3 Stern RS, Thibodeau LA, Kleinerman RA *et al.* Risk of cutaneous carcinoma in patients treated with oral methoxsalen photochemotherapy for psoriasis. *N Engl J Med* 1979; **300**: 809–13.
4 Henseler T, Christophers E, Honigsmann H, Wolff K. Skin tumors in the European PUVA Study. Eight-year follow-up of 1643 patients treated with PUVA for psoriasis. *J Am Acad Dermatol* 1987; **16**: 108–16.
5 Stern RS, Lunder EJ. Risk of squamous cell carcinoma and methoxsalen (psoralen) and UV-A radiation (PUVA): a meta-analysis. *Arch Dermatol* 1998; **134**: 1582–5.
6 Lim JL, Stern RS. High levels of ultraviolet B exposure increase the risk of non-melanoma skin cancer in psoralen and ultraviolet A-treated patients. *J Invest Dermatol* 2005; **124**: 505–13.
7 Lever LR, Farr PM. Skin cancers or premalignant lesions occur in half of high-dose PUVA patients. *Br J Dermatol* 1994; **131**: 215–9.

Chemical carcinogens

The importance of exogenous carcinogens in human skin carcinogenesis was first suggested by Sir Percival Potts, based on observations of an increased incidence of scrotal cancers in chimney sweeps [1]. This hypothesis was supported by observations made by Volkmann in 1874 of a high incidence of NMSC in workers exposed to tar and mineral oil. These observations, and the occurrence of NMSC in other occupational groups exposed to aromatic hydrocarbons at work, served as a stimulus for the large body of experimental studies with chemical carcinogens in animals, which have provided considerable insight into the biology of cancer. The epidemiology of skin cancers resulting from the occupational environment has been extensively reviewed [2]. Many aspects of occupational skin cancers parallel observations made in animal chemical carcinogenesis models. The prevalence of industrial skin cancer is determined by the potency of the carcinogens and by the thoroughness of the measures used to protect workers from them. The likelihood of an individual developing tumours is influenced by the duration of the exposure. An inverse relationship has been established between the age at first exposure and the length of the latent period following exposure to cutting oils and some other industrial carcinogens [3]. The long latent period between exposure and NMSC development and the observation that cancers can develop without a requirement for ongoing exposure means it is likely that many cases of occupational-induced skin cancers are not recognized. Therefore, and by implication, the published figures are likely to reflect a lowest approximation of the true incidence.

Arsenic is another important chemical carcinogen implicated in NMSC development. The association between arsenic administration and the subsequent development of both cutaneous and systemic malignancies was first recognized by Sir Jonathan Hutchinson in 1887. Unlike aromatic hydrocarbons where exposure was frequently occupationally related, arsenic exposure in the first half of the 20th century was more often caused by the ingestion of medical arsenic in the form of potassium arsenite (Fowler's solution) used to treat asthma and psoriasis [4]. Medicinal arsenic

exposure remains a problem in some regions where local medicines may still contain arsenic in asthma remedies (Asiatic pills), Chinese herbal medicines and traditional Indian medicines [5]. Most arsenic exposure today, however, results from its high levels in well water from either natural sources or as a result of contamination from mining waste [6]. In some provinces in China the burning of high arsenic coal in unventilated indoor stoves has recently been identified as an important cause of endemic arsenic exposure [7].

References

1 Potter M. *Percival Potts' Contribution to Cancer Research*. National Cancer Institute. Monograph 10. Washington DC: Washington Government, 1974: 1–19.
2 Hueper WC. *Chemically Induced Skin Cancers in Man*. Monograph 10. Washington DC: National Cancer Institute, 1963: 377–91.
3 Waterhouse JAH. Cutting oils and cancer. *Ann Occup Hyg* 1971; **14**: 161–70.
4 Neubauer O. Arsenical cancer: a review. *Br J Cancer* 1947; **1**: 192–251.
5 Prasad HR, Malhotra AK, Hanna N *et al*. Arsenicosis from homeopathic medicines: a growing concern. *Clin Exp Dermatol* 2006; **31**: 497–8.
6 Tseng WP, Chu HM, How SW *et al*. Prevalence of skin cancer in an endemic area of chronic arsenicism in Taiwan. *J Natl Cancer Inst* 1968; **40**: 453–63.
7 Zhang A, Feng H, Yang G *et al*. Unventilated indoor coal-fired stoves in Guizhou province, China: cellular and genetic damage in villagers exposed to arsenic in food and air. *Environ Health Perspect* 2007; **115**: 653–8.

X-rays and thermal radiation

Physical agents other than solar radiation are less frequent causes of NMSC but are an important aetiological factor in some subject groups. The carcinogenic effects of X-rays on the skin were first recognized by Frieben in 1902. NMSCs resulting from X-rays still occur in some at-risk occupational groups such as dentists, radiographers, physicians and engineers. Other at-risk groups include patients treated with Grenz rays for other dermatological conditions such as scalp ringworm, and patients who have received radiotherapy for the treatment of ankylosing spondylitis [1], lymphomas and other malignancies. Exposure to X-rays in childhood appears to be an important risk factor for BCC development [2]. The long latent period between exposure to ionizing radiation and NMSC development means that cases of radiation-induced NMSC may be overlooked if a careful history is not taken, particularly if they occur on sun-exposed sites. Recent studies have highlighted the increased risk of NMSC in childhood cancer survivors with a 6.3 times increase in risk and a high frequency of multiple cancers in affected individuals. The high frequency of tumours (>90%) in irradiated fields supports the importance of ionizing radiation as a risk factor in this group [3]. Patients who develop large numbers of BCCs within an irradiated field should be examined for signs of the naevoid basal cell carcinoma syndrome (Gorlin's syndrome) as some patients with this syndrome show a marked increase in susceptibility to ionizing radiation-induced BCCs [4,5].

Chronic exposure to thermal radiation is also recognized as a risk factor for NMSC development. Most of the evidence comes from studies of different cultural groups where an increased incidence of NMSC has been linked to common practices within these groups. Examples include Kangri cancer in the people of the Kashmir, resulting from repeated contact of abdominal skin with an earthenware brazier containing burning charcoal [6]. Additional clinical signs implicating thermal radiation include erythema ab igne and/or thermal keratoses, which frequently co-localize with thermal-induced cutaneous SCCs [7,8].

References

1 Meara RH. Epitheliomata after radiotherapy of the spine. *Br J Dermatol* 1968; **80**: 620.
2 Shore RE, Albert RE, Reed M *et al*. Skin cancer incidence among children irradiated for ringworm of the scalp. *Radiat Res* 1984; **100**: 192–204.
3 Perkins JL, Liu Y, Mitby PA *et al*. Nonmelanoma skin cancer in survivors of childhood and adolescent cancer: a report from the childhood cancer survivor study. *J Clin Oncol* 2005; **23**: 3733–41.
4 Evans DG, Farndon PA, Burnell LD *et al*. The incidence of Gorlin syndrome in 173 consecutive cases of medulloblastoma. *Br J Cancer* 1991; **64**: 959–61.
5 Zvulunov A, Strother D, Zirbel G *et al*. Nevoid basal cell carcinoma syndrome: report of a case with associated Hodgkin's disease. *J Pediatr Hematol Oncol* 1995; **17**: 66–70.
6 Aziz SA, Hussain KS, Ahmad KN *et al.* Profile of Kangari cancer: a prospective study. *Burns* 1998; **24**: 763–6.
7 Rudolph CM, Soyer HP, Wolf P, Kerl H. Squamous epithelial carcinoma in erythema ab igne. *Hautarzt* 2000; **51**: 260.
8 Akasaka T, Kon S. Two cases of squamous cell carcinoma arising from erythema ab igne. *Nippon Hifuka Gakkai Zasshi* 1989; **99**: 735–74.

Human papillomavirus

The association between human papillomavirus (HPV) and squamous cell neoplasia is best established for cervical and anogenital cancers, which have served as a useful paradigm for unravelling the complex relationship between HPV and cancer development. HPV infection of mucosal keratinocytes is common and the prevalence is increased in women at high risk of cervical cancer. Epidemiological HPV typing studies had a key role in defining two distinct groups of genital HPV types that show marked differences in their strength of association with cancer development. 'High-risk' types (HPV16, 18, 31, 33 and 35) were found to be strongly associated with cancer development while 'low-risk' types (HPV6, 11, 42, 43 and 44) were not [1]. HPV typing studies to date have not generated convincing evidence that implicates high-risk genital HPV types with the development of most cutaneous squamous cell neoplasms. HPV16 and other high-risk genital HPV types have, however, been linked to the clinically distinctive cutaneous squamous cell neoplasms, periungual SCC and palmoplantar Bowen's disease. It is likely in these tumours that the oncogenic effects are mediated by mechanisms similar to those operating in mucosal keratinocytes [2]. The observed association between the skin lesions and aggressive vulval and/or cervical carcinomas in some patients highlights the importance of ensuring that patients with these neoplasms are screened for genital malignancies [3].

Observational studies of patients with the rare inherited condition epidermodysplasia verruciformis (EV) highlighted an association between cutaneous viral warts and NMSC many years before the epidemiological studies linking HPV infection to cervical cancer [4]. Patients with EV develop extensive cutaneous plane and common warts at an early age and in later life frequently develop SCCs on sun-exposed areas. Although the genetic basis for EV is still unclear, HPV typing suggests that there may be an aetiological link between HPV and skin cancer development as over 90% of the EV-associated skin cancers contain HPV types 5 and 8. A high burden of persistent viral warts, keratotic skin lesions and skin cancers in organ-transplant recipients which

resembles the phenotype of patients with EV has led to speculation that HPV may also contribute to the increased risk of NMSC development in these patients [5]. This hypothesis is supported by the frequent detection of β-papillomaviruses, formerly called epidermodysplasia verruciformis (EV)-associated human papillomavirus types, in actinic keratoses and other keratotic skin lesions of organ-transplant recipients [6].

HPV DNA has been reported to be present in more than 80% of NMSC from immunosuppressed patients with a lower frequency (less than 40%) in NMSC from immunocompetent individuals [6]. HPV DNA can be detected in SCCs, BCCs and premalignant lesions in both immunocompetent and immunosuppressed patients and the most common HPV types are the β type. In a follow-up study using the same molecular strategy, HPV DNA was detected in 87% of normal skin samples from renal transplant recipients and 35% of samples from immune competent subjects. Although the prevalence and spectrum of HPV types in normal skin was not found to be impacted by sun exposure, multivariate analysis demonstrated that there was an association between the presence of β-HPV types in normal skin and skin cancer status (odds ratio of 6.41; 95% confidence interval 1.79–22.9) [7].

References

1 zur Hausen HH. Papillomaviruses and cancer: from basic studies to clinical application. *Nat Rev Cancer* 2002; **2**: 342–50.

2 McGrae JD Jr, Greer CE, Manos MM. Multiple Bowen's disease of the fingers associated with human papilloma virus type 16. *Int J Dermatol* 1993; **32**: 104–7.

3 Hara H, Honda A, Suzuki H *et al*. Detection of human papillomavirus type 58 in polydactylous Bowen's disease on the fingers and toes of a woman—concurrent occurrence of invasive vulval and cervical carcinomas. *Dermatology* 2004; **209**: 218–22.

4 Majewski S, Jablonska S. Epidermodysplasia verruciformis as a model of human papillomavirus-induced genetic cancer of the skin. *Arch Dermatol* 1995; **131**: 1312–8.

5 Bouwes Bavinck JN, Euvrard S, Naldi L *et al*. Keratotic skin lesions and other risk factors are associated with skin cancer in organ-transplant recipients: a case-control study in The Netherlands, United Kingdom, Germany, France, and Italy. *J Invest Dermatol* 2007; **127**: 1647–56.

6 Harwood CA, Surentheran T, McGregor JM *et al*. Human papillomavirus infection and non-melanoma skin cancer in immunosuppressed and immunocompetent individuals. *J Med Virol* 2000; **61**: 289–97.

7 Harwood CA, Surentheran T, Sasieni P *et al*. Increased risk of skin cancer associated with the presence of epidermodysplasia verruciformis human papillomavirus types in normal skin. *Br J Dermatol* 2004; **150**: 949–57.

Host susceptibility factors

Familial cancer syndromes

Interindividual differences in the susceptibility to NMSC development have been recognized for many years and epidemiological studies have identified a number of phenotypic features, such as hair and skin colour, freckling tendency and ability to tan, which show a consistent correlation with NMSC risk. Genes that determine inherited susceptibility to NMSC development can be divided broadly into two main types. The first type are genes associated with rare, highly penetrant cancer predisposition syndromes and includes conditions such as the naevoid basal cell carcinoma syndrome (NBCCS), Gorlin's syndrome (MIM 109400), Bazex's syndrome (MIM 301845) and xeroderma pigmentosum. The second type are multiple low-penetrant genetic loci that may contribute to susceptibility in the general population. Evidence for the importance of these latter genes has come from quantitative trait loci mapping of other cancers in murine models. Although mapping of similar loci in humans is difficult, association studies provide some evidence to support a role for high-frequency, low-penetrant traits such as DNA damage repair capacity and xenobiotic metabolism in BCC susceptibility.

Naevoid basal cell carcinoma syndrome [1,2]

Synonyms

- Basal cell naevus syndrome
- Gorlin's syndrome

Definition. An autosomal dominant familial cancer syndrome in which affected individuals are predisposed to the development of multiple BCCs at an early age and a variable combination of other phenotypic abnormalities including a highly characteristic facies (with large forehead), bifid or otherwise misshapen ribs, vertebral and other skeletal anomalies, pits of the skin of the palms and soles, dysgenesis of the corpus callosum, calcification of the falx cerebri (at an earlier age than is seen in non-affected individuals) and macrocephaly.

Aetiology and incidence. Population-based studies suggest that the prevalence of this disorder in the UK is approximately 1 in 56 000 of the population [3]. The high rate of new mutations and the variable expressivity of the condition, however, makes full ascertainment difficult, particularly in mildly affected individuals where there is no family history of the condition. Although NBCCS differs from other autosomal dominant cancer syndromes in that many of the associated features are developmental abnormalities, the presence of multiple BCCs at an early age is consistent with the 'two hit model' for inherited cancers first proposed by Knudson. The NBCCS gene was mapped to chromosome 9q22.3–3.1 and, like other tumour suppressor genes, shows frequent deletion in both sporadic and familial BCCs [4]. The NBCCS gene was identified in 1996 with the identification of mutations in the *PATCHED* (*PTCH1*) gene in the germ line of NBCCS patients and in sporadic BCC tumour samples [5]. *PTCH1* is the human homologue of PTC, which was first identified as a key regulator of the evolutionarily conserved Hedgehog (Hh) signalling pathway in elegant genetic studies of embryonic segmentation and imaginal disc specification in *Drosophila*. This finding was the first reported example of a link between genes important in development and cancer, and provided a completely new insight into the molecular pathways important in the development of this common skin cancer. The importance of Hedgehog signalling during normal development explains many of the other phenotypic abnormalities seen in patients with NBCCS and these features are consistent with findings from studies of heterozygote *PTCH1* knock-out mice [6]. The *PTCH1* mutation rate in NBCCS in published studies appears to range between 40% and 80%. A variety of mutations have been described in these studies including nonsense mutations, in-frame deletion, frame shifts due to deletions and insertions and splice-site mutations [7]. In addition to point mutations a small number of patients have been described with larger

deletions detected by comparative genomic hybridization methodologies. These patients tend to present with additional clinical features which may be caused by codeletion of other genes in addition to *PTCH1* [8,9].

Clinical features [10]. The skin manifestations of the syndrome are varied and include BCCs, skin tags, palmoplantar pits, milia, epidermoid cysts and lesions that clinically resemble dermal naevi. Skin lesions including BCCs may be present at birth or develop in infancy but more frequently develop between puberty and 35 years of age. The number and type of skin lesions is very variable both within and between families and there is a marked difference between white people and African Americans in the number of BCCs [11]. It is not uncommon to find affected individuals with several hundred lesions. With the exception of the pits that are localized only on the palms and soles, skin lesions can occur in any region. The eyelids, nose, cheeks and forehead are the usual sites, but the neck, trunk and axillae are quite frequently involved. The scalp and limbs are usually spared.

The individual lesions are smooth surfaced, rounded, elevated papules, flesh-coloured or pigmented, varying in size from 1 to 15 mm in diameter. The lesions tend to increase in size and number up to late adolescence. There may be fine telangiectasia and milium-like bodies just below the surface. Tumours of the axillae, neck and eyelids tend to be pedunculated. Most lesions appear to behave in a relatively benign fashion with barely discernible growth and/or evidence of clinical progression. As is the case for patients with sporadic BCCs, some patients with NBCCS develop more aggressive tumours, which can be more difficult to treat and may cause significant morbidity or, rarely, death resulting from extensive invasion and/or recurrence following treatment. The proportion of NBCCS patients who develop very aggressive tumours and the risk factors for this have not been established. Aggressive tumours appear to occur more frequently on the eyelids or nose, and can cause gross destruction. In one study, four of five cases with aggressive BCCs in a series of 36 NBCCS patients received radiotherapy as the initial therapy, which suggests that radiotherapy may be a contributing factor to tumour aggressiveness in some NBCCS patients [12]. A variety of other skin manifestations have also been described, including multiple epidermoid cysts, milia and palmoplantar pits. The pits are a useful diagnostic feature that occur in about 65% of adults with NBCCS but are relatively rare in children. They are characterized by small, more or less circular pits, which may have an erythematous base and are usually 1–2 mm deep. In a recent study, re-examination of the skin phenotype in the context of data implicating Hh signalling in hair follicle biology led to the identification of discrete patches of unusually long, pigmented hair on the skin of three patients with NBCCS from two unrelated families with confirmed heterozygous mutations in the *PTCH* gene [13].

Other diagnostically useful phenotypic abnormalities in NBCCS patients include jaw cysts, a highly characteristic facies (broad nasal root, hypertelorism, frontal bossing), bifid or otherwise misshapen ribs, vertebral and other skeletal anomalies, dysgenesis of the corpus callosum, calcification of the falx cerebri (at an earlier age than is seen in non-NBCCS individuals) and macrocephaly [2]. The dental cysts are usually multiple, occurring in one or both jaws, and are odontogenic keratocysts [14]. Skeletal abnormalities include spina bifida occulta, bifid or splayed ribs, scoliosis or kyphosis, and occur with one-third of the frequency of the cysts or the basal cell naevi [15]. Less common associated anomalies include syndactyly, shortened metacarpals, cleft lip and palate, bicornuate uterus, hypogonadism in males, lymphatic cysts of the mesentery, ocular abnormalities including dystopia canthorum, cataracts and congenital blindness, and a variety of neurological disorders [16–21]. In addition to BCCs, the syndrome is associated with an increased susceptibility to other neoplasms including rhabdomyosarcoma, ovarian and cardiac fibromas and, in particular, medulloblastoma. Approximately 3% of NBCCS patients develop medulloblastomas, and approximately 3% of patients with medulloblastomas have NBCCS [22]. Atypical clinical features such as brachydactyly, pulmonary valve stenosis and mental retardation should prompt consideration of a contiguous gene deletion syndrome.

Pathology [23]. The histopathological appearance of BCCs from patients with NBCCS are indistinguishable from those seen in sporadic forms. The tumours induce a fibrous stroma as occurs with trichoepithelioma or nodular BCC, and the lesions may become papular or pedunculated. Deeper penetration, ulceration and invasion can occur, with lymphocytic infiltration. There may be pigmentation in and around the masses. The presence of calcification and the general architecture can resemble trichoepithelioma. Palmoplantar pits show focal absence of the stratum corneum with vacuolization of the spinous layer. At an ultrastructural level, pits show evidence of premature desquamation with a reduction in desmosomes and tonofibrils resulting from delay in maturation of the epidermal basal cells [24,25]. BCCs have developed in palmar pits [25–27].

Diagnosis. In many cases, the skin lesions resemble melanocytic naevi, von Recklinghausen's neurofibromatosis or skin tags rather than BCC, and their true nature may be suspected only because of associated features or family history. The correlation between the clinical and pathological features of the range of skin lesions seen in NBCCS patients is still poorly understood, which makes it difficult to draw firm conclusions about the natural history of the different skin lesions in these patients.

Treatment. The large number of lesions in patients with NBCCS means that primary excision of all lesions is not always practicable. Radiotherapy is contraindicated as many patients show an accelerated rate of development of new BCCs within an irradiated field, and where recurrences do occur they frequently are more aggressive and difficult to manage than the initial primary tumour. Surveillance of NBCCS patients who have developed BCCs can be useful for the early detection and treatment of new lesions. Although no controlled trials have established that reduced sun exposure can reduce the rate of BCC development in NBCCS patients, the reduced prevalence of BCCs in African Americans with this syndrome suggests that advice on reducing sun exposure is important [11].

Treatment of individual lesions should be guided by anatomical location, tumour size, clinical appearance and histology, with

primary excision the treatment of choice for BCCs on the central face near critical structures. For superficial BCC on the trunk, approaches such as curettage and cautery or cryotherapy are useful. While the recurrence rate is potentially greater with these therapies, they are an effective, convenient alternative for small or superficial BCCs distant from critical sites in patients with large numbers of lesions. Where the presence of large numbers of superficial lesions limits the acceptability of conventional therapies, then photodynamic therapy with a systemic or topical photosensitizer and an appropriate laser or non-laser light source can be a useful and effective treatment option. Other non-surgical approaches that can be useful in the management of superficial lesions at non-critical sites include topical 5-fluorouracil and imiquimod formulations. These approaches have been shown to induce histological clearing of some BCCs and can reduce but not replace the need for more conventional therapies in patients with large numbers of lesions [28,29]. The value of systemic chemoprevention strategies in the management of patients with NBCCS is still unclear. A few studies suggest that systemic retinoids (isotretinoin (>4 mg/kg) and etretinate (0.7–1 mg/kg)) may reduce the rate of development of new BCCs [30,31]. The clinical benefits, however, appear small relative to those seen in patients with multiple cutaneous SCCs.

References

1 Gorlin RJ, Vickers RA, Kelln E *et al*. The multiple basal-cell naevi syndrome: analysis of a syndrome consisting of multiple naevoid basal-cell carcinoma, jaw cysts, skeletal anomalies, medulloblastoma, and hyporesponsiveness to parathormone. *Cancer* 1965; **18**: 89–104.

2 Gorlin RJ. The naevoid basal cell carcinoma syndrome. *Medicine* 1987; **66**: 98–113.

3 Evans DG, Ladusans EJ, Rimmer S *et al*. Complications of the naevoid basal cell carcinoma syndrome: results of a population-based study. *J Med Genet* 1993; **30**: 460–4.

4 Quinn AG. Molecular genetics of human non-melanoma skin cancer. *Cancer Surv* 1996; **26**: 89–114.

5 Johnson RL, Rothman AL, Xie J *et al*. Human homolog of patched, a candidate gene for the basal cell naevus syndrome. *Science* 1996; **272**: 1668–71.

6 Bale AE, Gailani MR, Leffell DJ. The Gorlin syndrome gene: a tumor suppressor active in basal cell carcinogenesis and embryonic development. *Proc Assoc Am Physicians* 1995; **107**: 253–7.

7 Soufir N, Gerard B, Portela M *et al*. PTCH mutations and deletions in patients with typical nevoid basal cell carcinoma syndrome and in patients with a suspected genetic predisposition to basal cell carcinoma: a French study. *Br J Cancer* 2006; **95**: 548–53.

8 Nowakowska B, Kutkowska-Kazmierczak A, Stankiewicz P *et al*. A girl with deletion 9q22.1-q22.32 including the PTCH and ROR2 genes identified by genome-wide array-CGH. *Am J Med Genet A* 2007; **143**: 1885–9.

9 Olivieri C, Maraschio P, Caselli D *et al*. Interstitial deletion of chromosome 9, int del(9)(9q22.31-q31.2), including the genes causing multiple basal cell nevus syndrome and Robinow/brachydactyly 1 syndrome. *Eur J Pediatr* 2003; **162**: 100–3.

10 Howell JB. Naevoid basal cell carcinoma syndrome: profile of genetic and environmental features in oncogenesis. *J Am Acad Dermatol* 1984; **11**: 98–104.

11 Kimonis VE, Goldstein AM, Pastakia B *et al*. Clinical manifestations in 105 persons with nevoid basal cell carcinoma syndrome. *Am J Med Genet* 1997; **69**: 299–308.

12 Southwick GJ, Schwartz RA. The basal cell naevus syndrome: disasters occurring among a series of 36 patients. *Cancer* 1979; **44**: 2294–305.

13 Wilson LC, Ajayi-Obe E, Bernhard B *et al*. Patched mutations and hairy skin patches: a new sign in Gorlin syndrome. *Am J Med Genet A* 2006; **140**: 2625–30.

14 Binkley GW, Johnson HH. Epithelioma adenoides cysticum: basal cell naevi, agenesis of the corpus callosum and dental cysts. *Arch Dermatol* 1951; **63**: 73–84.

15 Anderson DE, Taylor WB, Falls MF *et al*. The naevoid basal cell carcinoma syndrome. *Am J Hum Genet* 1967; **19**: 12–22.

16 Berlin NI, van Scott EJ, Clendenning WE *et al*. Basal cell naevus syndrome: combined clinical staff conference at the National Institute of Health. *Ann Intern Med* 1966; **64**: 403–21.

17 Clendenning WE, Block JB, Radde IC. Basal cell naevus syndrome. *Arch Dermatol* 1964; **90**: 38–53.

18 Gorlin RJ, Goltz RW. Multiple naevoid basal-cell epithelioma, jaw cysts and bifid rib: a syndrome. *N Engl J Med* 1960; **262**: 908–12.

19 Gorlin RJ, Yunis JJ, Tuna N. Multiple naevoid basal cell carcinoma, odontogenic keratocysts and skeletal anomalies: a syndrome. *Acta Derm Venereol (Stockh)* 1963; **43**: 39–55.

20 Howell JB, Caro MR. The basal-cell naevus: its relationship to multiple cutaneous cancers and associated anomalies of development. *AMA Arch Dermatol* 1959; **79**: 67–80.

21 Van Dijk E, Sanderink JFH. Basal cell naevus syndrome. *Dermatologica* 1967; **134**: 101–6.

22 Evans DG, Farndon PA, Burnell LD *et al*. The incidence of Gorlin syndrome in 173 consecutive cases of medulloblastoma. *Br J Cancer* 1991; **64**: 959–61.

23 Zackheim HS, Howell JB, Loud AV. Naevoid basal cell carcinoma syndrome: some histologic observations on the cutaneous lesions. *Arch Dermatol* 1966; **93**: 317–23.

24 Howell JB, Mehregan AH. Pursuit of the pits in the naevoid basal cell carcinoma syndrome. *Arch Dermatol* 1970; **102**: 586–97.

25 Holubar K, Matras H, Smalik AV. Multiple palmar basal cell epitheliomas in basal cell naevus syndrome. *Arch Dermatol* 1970; **10**: 679–82.

26 Howell JB, Freeman RG. Structure and significance of the pits and their tumours in the naevoid basal cell carcinoma syndrome. *J Am Acad Dermatol* 1980; **2**: 224–38.

27 Mason JK, Helwig EB, Graham JH. Pathology of the naevoid basal cell carcinoma syndrome. *Arch Pathol* 1965; **79**: 401–8.

28 Goette DK. Topical chemotherapy with 5-fluorouracil: a review. *J Am Acad Dermatol* 1981; **4**: 633–49.

29 Micali G, De Pasquale R, Caltabiano R *et al*. Topical imiquimod treatment of superficial and nodular basal cell carcinomas in patients affected by basal cell naevus syndrome: a preliminary report. *J Dermatolog Treat* 2002; **13**: 123–7.

30 Goldberg LH, Rubin HA. Management of basal cell carcinoma: which option is best? *Postgrad Med* 1989; **85**: 57–8, 61–3.

31 Cristofolini M, Zumiani G, Scappini P, Piscioli F. Aromatic retinoid in the chemoprevention of the progression of naevoid basal-cell carcinoma syndrome. *J Dermatol Surg Oncol* 1984; **10**: 778–81.

Follicular atrophoderma and basal cell carcinoma

Synonym

- Bazex–Dupré–Christol syndrome

This syndrome is a rare genodermatosis that also predisposes affected individuals to multiple BCCs [1,2]. Additional clinical features that allow distinction from NBCCS include follicular atrophoderma, hypotrichosis and hypohidrosis. Follicular atrophoderma is present at birth or in early childhood, and shows as 'ice-pick marks', enlarged follicular ostia on the dorsa of hands, elbows, feet and face. The follicular changes are not caused by injury or inflammation but there may be facial eczema soon after birth. There may be anhidrosis of the face and head, and hypotrichosis. The BCCs appear on the face in the second or third decade and resemble cellular naevi [3].The absence of male–male transmission is suggestive of X-linked inheritance, and this has been confirmed by linkage analysis, which has mapped the gene to Xq24–q27 [4]. The association between BCCs and clinical abnormalities of the hair follicle is of interest as BCCs have the same cytokeratin profile as a subpopulation of follicular keratinocytes

[5]. The importance of the Hedgehog signalling pathway in BCC development in patients from affected families with this disorder is not yet known.

References

1 Plosila M, Kiistala R, Niemi K-M. The Bazex syndrome: follicular atrophoderma with multiple basal cell carcinomas, hypotrichosis and hypohidrosis. *Clin Exp Dermatol* 1981; **6**: 31–41.

2 Bazex A, Dupré A, Christol B. Atrophodermie folliculaire prolifération basocellulaires et hypotrichose. *Ann Dermatol Syphiligr* 1966; **93**: 241–54.

3 Viksnin SP, Berlin A. Follicular atrophoderma and basal cell carcinomas. *Arch Dermatol* 1977; **113**: 948–51.

4 Vabres P, Lacombe D, Rabinowitz LG *et al.* The gene for Bazex–Dupré–Christol syndrome maps to chromosome Xq. *J Invest Dermatol* 1995; **105**: 87–91.

5 Markey AC, Lane EB, Macdonald DM, Leigh IM. Keratin expression in basal cell carcinomas. *Br J Dermatol* 1992; **126**: 154–60.

Rombo syndrome

Rombo syndrome is a very rare, autosomal dominant syndrome first described in 1981 (MIM 180730). Affected individuals develop vermiculate atrophoderma, milia, hypotrichosis, trichoepitheliomas and peripheral vasodilatation in addition to BCCs [1,2]. Although there are some similarities with Bazex's syndrome (follicular atrophoderma and milia), there are a number of distinctive features including cyanotic discoloration of the hands and lips in childhood, and telangiectasia. The genetic locus for Rombo syndrome has not yet been mapped.

References

1 Michaelsson G, Olsson E, Westermark P. The Rombo syndrome: a familial disorder with vermiculate atrophoderma, milia, hypotrichosis, trichoepitheliomas, basal cell carcinomas and peripheral vasodilation with cyanosis. *Acta Derm Venereol* 1981; **61**: 497–503.

2 van Steensel MA, Jaspers NG, Steijlen PM. A case of Rombo syndrome. *Br J Dermatol* 2001; **144**: 1215–81.

Self-healing epitheliomas

Synonym

- Multiple self-healing epithelioma of Ferguson-Smith (MSHE)

This condition is an autosomal dominant condition first described by Ferguson-Smith in the 1930s, characterized by the intermittent development of spontaneously regressing skin tumours histologically identical to well-differentiated SCCs.

Incidence and aetiology. The incidence is unknown but the condition is very rare. Two large Scottish kindreds are well described in the literature [1–3], and accurate genetic pedigree analysis has suggested that the condition may have arisen in these two families from a single mutation around 1790. Recent haplotype analysis for polymorphic markers segregating with MSHE in non-Scottish and Scottish families has shown differences which suggest that MSHE may not be caused by a founder mutation and that the syndrome may be more common than originally thought [4]. The gene has been mapped to chromosome 9q22 in a region of less than 4 cm between the markers D9S197 and D9S1809 but has not yet been identified [5]. Other sporadic cases have been reported. The lesions develop most frequently on light-exposed skin and it is postulated that UVR is an important co-factor in the development of these tumours.

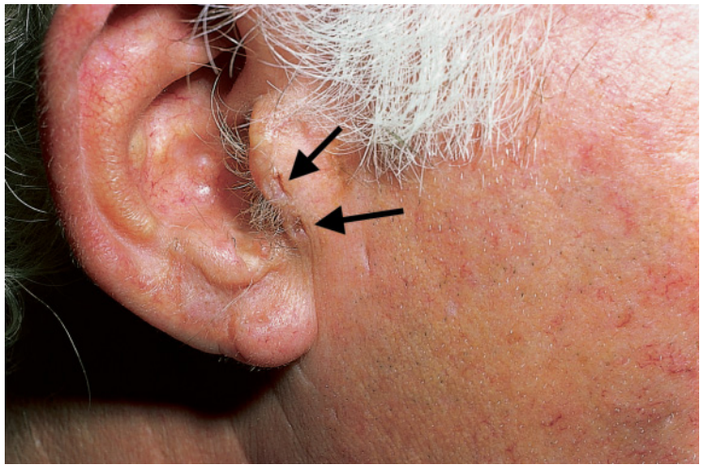


Fig. 52.1 Scarring seen in patient with multiple self-healing squamous epitheliomas of Ferguson-Smith.

Clinical features [6]. The first lesions usually appear in the second decade of life, and each patient tends to have a fairly specific pattern of development, duration and evolution. Knowledge of the 'normal' pattern for the patient is of great value in the management of individual lesions.

The lesions develop predominantly on exposed skin and may cluster around the nose or ears. In the majority of reported cases, one or more lesions have been present in the scalp, a site rarely affected by keratoacanthoma. A small, raised, red nodule is the first sign of a new lesion. This may grow over 2–4 weeks to a diameter of 2–3 cm and may become crusted or ulcerated. The lesion then may remain unchanged for 1–2 months, and then gradually shrink, leaving behind a very characteristic and unsightly, crenellated scar (Fig. 52.1). Lesions develop singly or in crops. In one case they were strikingly confined to half of the body [7].

Pathology. The lesions have features that are indistinguishable from invasive SCCs, but are quite distinct in most cases from multiple keratoacanthoma with which they should not be confused. The epidermis may be ulcerated, and demonstrates marked cellular atypia and loss of polarity. Invasive tongues of epithelial cells will be seen at the base of the lesion and isolated invasive clumps of cells may be seen detached from the main tumour mass, which is still adherent to the epidermis. There is no marked 'shouldering' of the lesion by normal keratinocytes as is seen in keratoacanthoma, and the leukocyte abscesses characteristic of the older keratoacanthoma are absent.

Management. Although spontaneous involution does occur, the resultant scar is unsightly and the end results of shaving or curetting the lesions at an early stage in their development are more acceptable. Cryotherapy of a lesion in the early stages produces an excellent result.

References

1 Charteris AA. Self-healing epithelioma of the skin. *Am J Roentgenol* 1951; **65**: 459–64.
2 Currie AR, Smith JF. Multiple primary spontaneous-healing squamous-cell carcinomata of the skin. *J Pathol Bacteriol* 1952; **64**: 827–39.
3 Ferguson-Smith MA, Wallace D, James Z *et al.* Multiple self-healing epitheliomata. *Birth Defects* 1971; **7**: 157–63.
4 D'Alessandro M, Coats SE, Morley SM *et al*. Multiple self-healing squamous epithelioma in different ethnic groups: more than a founder mutation disorder? *J Invest Dermatol* 2007; **127**: 2336–44.
5 Bose S, Morgan LJ, Booth DR *et al*. The elusive multiple self-healing squamous epithelioma (MSSE) gene: further mapping, analysis of candidates, and loss of heterozygosity. *Oncogene* 2006; **25**: 806–12.
6 Witten VH, Zak FG. Multiple, primary, self-healing prickle-cell epithelioma of the skin. *Cancer* 1952; **5**: 539–50.
7 Rook A, Moffatt JL. Multiple self-healing epithelioma of Ferguson-Smith type: report of a case of unilateral distribution. *Arch Dermatol* 1956; **74**: 525–32.

Xeroderma pigmentosum

This is a rare autosomal recessive disorder characterized by extreme sun sensitivity, associated with a marked increase in skin cancer susceptibility. Affected individuals develop multiple precancerous lesions and skin cancers at an early age (see Chapter 15). From a historical perspective, this condition is important as it is one of the key pieces of evidence that highlighted the carcinogenic potential of UVR and was the first model in humans that supported the somatic mutation theory of the initiation of cancer. Recent evidence from studies of other genetic sun-sensitive syndromes in humans has challenged the original assumption that the increased cancer susceptibility in xeroderma pigmentosum (XP) patients is exclusively the result of persistent DNA lesions caused by defective DNA repair following exposure to UVR. The new data have come from elegant studies of patients with trichothiodystrophy (TTD) who show photosensitivity and defective nucleotide excision repair that resembles that seen in XP patients [1]. In contrast to XP patients where there is a more than 2000-fold increase in skin cancer incidence, TTD does not appear to be associated with skin cancer. The basis for these differences in cancer susceptibility between XP and TTD, however, remains an enigma [2].

References

1 Stary A, Sarasin A. The genetic basis of xeroderma pigmentosum and trichothiodystrophy syndromes. *Cancer Surv* 1996; **26**: 155–71.
2 Cleaver JE. Cancer in xeroderma pigmentosum and related disorders of DNA repair. *Nat Rev Cancer* 2005; **5**: 564–73.

Muir–Torre syndrome

Synonym

- Hereditary non-polyposis colorectal cancer

This autosomal dominant syndrome, originally described in 1967, is characterized by the presence of one or more sebaceous neoplasms in association with internal malignancies, most frequently carcinoma of the colon [1]. The clinical and pathological features overlap with hereditary non-polyposis colorectal cancer (HNPCC) syndromes. Mutations reported to cause Muir–Torre syndrome include the mismatch repair genes *MLH1* and *MSH2*, *MYH* and *MSH6* [2,3]. Tumours in patients with Muir–Torre syndrome are characterized by alterations in the length of DNA sequences called microsatellites. This microsatellite instability has been identified in sebaceous neoplasms from patients with Muir–Torre syndrome [4]. A number of other skin tumours, including SCC, BCC, keratoacanthoma and AK, have also been described in patients with this syndrome but the significance of these findings has been difficult to establish as the high frequency of undiagnosed NMSC in the population makes it hard to differentiate a real increase from an increase resulting from ascertainment bias. The identification of microsatellite instability in skin tumours other than sebaceous neoplasms indicates that the NMSC noted in previous clinical studies of Muir–Torre kindreds are also likely to reflect a true increased susceptibility and not simply a result of ascertainment bias [5,6]. Recent work suggests that immunosuppression may aggravate the Muir–Torre syndrome phenotype and it is interesting that switching from tacrolimus to a sirolimus-based regimen resulted in arrest of the disease [7,8].

References

1 Jones B, Oh C, Mangold E *et al*. Muir–Torre syndrome: diagnostic and screening guidelines. *Australas J Dermatol* 2006; **47**: 266–9.
2 Ponti G, Losi L, Pedroni M *et al*. Value of MLH1 and MSH2 mutations in the appearance of Muir-Torre syndrome phenotype in HNPCC patients presenting sebaceous gland tumors or keratoacanthomas. *J Invest Dermatol* 2006; **126**: 2302–7.
3 Arnold A, Payne S, Fisher S *et al*. An individual with Muir–Torre syndrome found to have a pathogenic MSH6 gene mutation. *Fam Cancer* 2007; **6**: 317–21.
4 Honchel R, Halling KC, Schaid DJ *et al*. Microsatellite instability in Muir–Torre syndrome. *Cancer Res* 1994; **54**: 1159–63.
5 Quinn AG, Healy E, Rehman I *et al*. Microsatellite instability in human non-melanoma and melanoma skin cancer. *J Invest Dermatol* 1995; **104**: 309–12.
6 Swale VJ, Quinn AG, Wheeler JM *et al.* Microsatellite instability in benign skin lesions in hereditary non-polyposis colorectal cancer syndrome. *J Invest Dermatol* 1999; **113**: 901–5.
7 Harwood CA, Swale VJ, Bataille VA *et al*. An association between sebaceous carcinoma and microsatellite instability in immunosuppressed organ transplant recipients. *J Invest Dermatol* 2001; **116**: 246–53.
8 Levi Z, Hazazi R, Kedar-Barnes I *et al*. Switching from tacrolimus to sirolimus halts the appearance of new sebaceous neoplasms in Muir-Torre syndrome. *Am J Transplant* 2007; **7**: 476–9.

Other cancer susceptibility modifying genes

In addition to the rare, highly penetrant skin cancer predisposition syndromes described above, there is increasing evidence that other genetic loci can contribute to sporadic NMSC risk. The importance of these so-called modifying genes has been highlighted in studies using mouse cancer models in which genes have been identified that markedly reduce the rate of cancer development in mice carrying germ-line mutations in known tumour-suppressor genes [1,2]. It is likely that similar, as yet unidentified genes in humans account for the marked variations in the susceptibility to BCC development seen both within and between families with NBCCS. At present, identification of these high-frequency low-penetrant genes in humans involves educated guesswork based on consideration of factors that might contribute to NMSC development. Epidemiological studies have already identified a number of complex phenotypic traits such as skin colour, ethnicity and freckling tendency, which are associated with an increased

risk of NMSC development [3]. In addition to the well-recognized importance of differences in skin pigmentation, variations in UVR, DNA repair capacity and xenobiotic metabolism have been implicated as important modifiers of sporadic NMSC risk [4]. The published information on DNA repair enzyme polymorphisms and NMSC susceptibility is difficult to interpret at present. This is because of contradictory findings which may be due to methodological differences and/or complex gene–environment interactions in different ethnic groups exposed to a range of exposure to environmental carcinogens [5,6].

References

1 Eads CA, Nickel AE, Laird PW. Complete genetic suppression of polyp formation and reduction of CpG-island hypermethylation in Apc (Min/) Dnmt1-hypomorphic mice. *Cancer Res* 2002; **62**: 1296–9.
2 MacPhee M, Chepenik KP, Liddell RA *et al.* The secretory phospholipase A2 gene is a candidate for the Mom1 locus, a major modifier of ApcMin-induced intestinal neoplasia. *Cell* 1995; **81**: 957–66.
3 Armstrong BK, Kricker A. Epidemiology of sun exposure and skin cancer. *Cancer Surv* 1996; **26**: 133–53.
4 Lear JT, Smith AG, Strange RC, Fryer AA. Detoxifying enzyme genotypes and susceptibility to cutaneous malignancy. *Br J Dermatol* 2000; **142**: 8–15.
5 Kang SY, Lee KG, Lee W *et al*. Polymorphisms in the DNA repair gene XRCC1 associated with basal cell carcinoma and squamous cell carcinoma of the skin in a Korean population. *Cancer Sci* 2007; **98**: 716–20.
6 McCarty KM, Ryan L, Houseman EA *et al*. A case-control study of GST polymorphisms and arsenic related skin lesions. *Environ Health* 2007; **6**: 5.

Chronic injury and scarring

It has been recognized for many years that NMSC can arise at sites of chronic inflammation and/or scarring. Although there is a substantial literature on this subject, it is difficult to assess the risk as there are no prospective studies of patients with conditions recognized as being associated with NMSC development. Conditions linked to NMSC development include burns [1,2], discoid lupus erythematosus [3], necrobiosis lipoidica [4,5], lupus vulgaris and skin fistulae resulting from discharging sinuses. A particularly strong clinical association has been identified between patients with recessive dystrophic Epidemolysis bullosa (EB) and SCC development [6,7]. The basis for the association between deficiency in type VII collagen resulting from germ-line gene mutations and SCC risk in dystrophic EB patients is not known. In contrast to other forms of EB, fibroblast collagenase is increased in dystrophic EB and this has recently been shown to be associated with marked elevation of urinary excretion of basic fibroblast growth factor [8]. Further studies of SCC development in patients with dystrophic EBV may provide new insight into the long-recognized association between wounding and SCC development.

References

1 Edwards MJ, Hirsch RM, Broadwater JR *et al*. Squamous cell carcinoma arising in previously burned or irradiated skin. *Arch Surg* 1989; **124**: 115–7.
2 Ikegawa S, Saida T, Takizawa Y *et al.* Vimentin-positive squamous cell carcinoma arising in a burn scar: a highly malignant neoplasm composed of acantholytic round keratinocytes. *Arch Dermatol* 1989; **125**: 1672–6.
3 Sulica VI, Kao GF. Squamous-cell carcinoma of the scalp arising in lesions of discoid lupus erythematosus. *Am J Dermatopathol* 1988; **10**: 137–41.
4 Imtiaz KE, Khaleeli AA. Squamous cell carcinoma developing in necrobiosis lipoidica. *Diabet Med* 2001; **18**: 325–8.
5 Beljaards RC, Groen J, Starink TM. Bilateral squamous cell carcinomas arising in long-standing necrobiosis lipoidica. *Dermatologica* 1990; **180**: 96–8.
6 Newman C, Wagner RF Jr, Tyring SK, Spigel GT. Squamous cell carcinoma secondary to recessive dystrophic epidermolysis bullosa: a report of 4 patients with 17 primary cutaneous malignancies. *J Dermatol Surg Oncol* 1992; **18**: 301–5.
7 Bosch RJ, Gallardo MA, Ruiz DP *et al.* Squamous cell carcinoma secondary to recessive dystrophic epidermolysis bullosa: report of eight tumours in four patients. *J Eur Acad Dermatol Venereol* 1999; **13**: 198–204.
8 Arbiser JL, Fine JD, Murrell D *et al.* Basic fibroblast growth factor: a missing link between collagen VII, increased collagenase, and squamous cell carcinoma in recessive dystrophic epidermolysis bullosa. *Mol Med* 1998; **4**: 191–5.

Immunosuppression

Immunosuppressed patients show a marked increase in susceptibility to NMSC development, with an earlier age of onset and a higher incidence of multiple primary tumours relative to immunocompetent patients. This marked increase in NMSC incidence in these patients is powerful evidence of the importance of the immune system in limiting NMSC development in humans. The cumulative incidence for NMSC uncorrected for age has been shown to vary between 27 and 40% after 20–25 years of immunosuppression in different populations within Europe [1,2]. In Australia, the cumulative incidence appears to be significantly higher after only 10 years of immunosuppression, highlighting the importance of UVR as a co-factor for cancer development in these patients [3]. The risk of NMSC development in renal transplant recipients, which is the best-studied group of immunosuppressed patients, is very variable between different centres as a result of differences between populations including the age distribution of the transplanted patients, the duration of transplantation and the ambient sun exposure of the country. In the UK, a 50-fold increase in the risk of developing SCCs and a fivefold increase in BCC risk has been described in renal allograft recipients [1]. Even greater increases in risk have been described in another European study with a 250-fold increase in SCC incidence and a 10-fold increase in the incidence of BCCs [4]. Epidemiological studies have established that in immunosuppressed patients there is a close association between the development of NMSC and premalignant lesions and the presence of viral warts [5]. The viral warts and skin cancers both preferentially co-localize to areas of sun-exposed skin, although there are some interesting differences between immunocompetent and immunosuppressed patients in SCC distribution with a greater proportion on the hands and forearms in immunosuppressed patients [6].

References

1 McGregor JM, Proby CM. Skin cancer in transplant recipients. *Lancet* 1995; **346**: 964–5.
2 Hartevelt MM, Bavinck JN, Kootte AM *et al*. Incidence of skin cancer after renal transplantation in the Netherlands. *Transplantation* 1990; **49**: 506–9.
3 Hardie IR, Strong RW, Hartley LC *et al*. Skin cancer in Caucasian renal allograft recipients living in a subtropical climate. *Surgery* 1980; **87**: 177–83.
4 Bouwes Bavinck JN. Epidemiological aspects of immunosuppression: role of exposure to sunlight and human papillomavirus on the development of skin cancer. *Hum Exp Toxicol* 1995; **14**: 98.
5 Bouwes Bavinck JN, Feltkarmp M, Struijk L, ter Scheggett J. Human papillomavirus infection and skin cancer risk in organ transplant recipients. *J Invest Dermatol Symp Proc* 2001; **6**: 207–11.
6 Taylor AE, Shuster S. Skin cancer after renal transplantation: the causal role of azathioprine. *Acta Derm Venereol* 1992; **72**: 115–9.

The molecular and cellular biology of non-melanoma skin cancer

NMSC is unique among human cancers in that the main aetiological factors have been identified and the accessibility of the skin has facilitated analysis of the clinical, pathological and molecular characteristics of these tumours. Advances in molecular and cell biology over the last 10 years have seen an enormous growth in the amount of descriptive data cataloguing changes at the DNA, RNA and protein level in NMSC [1]. While this information in itself has provided an insight into the basis for some of the clinicopathological differences between BCCs, SCCs and related premalignant lesions, a fuller understanding of the biology of NMSC will be critically dependent on approaches that integrate emerging molecular data with the clinical and epidemiological aspects of this important disease. This section outlines current concepts and summarizes some of the more important advances in the biology of NMSC, which have important clinical implications. Topics discussed include cancer genetics, multistage carcinogenesis, UV carcinogenesis and the role of HPV infection in NMSC development.

Cancer as a genetic disease

Cancers are, with few exceptions, clonal; they are derived from a single somatic cell and have accumulated a series of changes that lead to complex and persistent changes in gene expression and cell behaviour. Although it has long been thought that these phenotypic changes require the stepwise accumulation of growth-advantageous heritable changes, direct evidence of the importance of genetic alterations in tumorigenesis has only come within the last decade [2]. Genes important in cancer development can be broadly divided into three categories:

1. Proto-oncogenes that encode for proteins that regulate cellular proliferation and differentiation. These genes are inappropriately activated in cancer cells by point mutations, gene amplification or chromosome translocation.
2. Tumour suppressor genes that maintain a normal phenotype by limiting growth, invasiveness and other features of malignant cells. Mutations are recessive at the cellular level, which means that the effects of alterations in these genes are only seen when both copies are inactivated.
3. Mutator genes encode for proteins that play a critical part in maintaining genomic integrity. The importance of this class of genes in determining cancer susceptibility was first recognized in studies of patients with rare autosomal cancer susceptibility syndromes such as XP, Bloom's syndrome and ataxia telangiectasia where there are abnormalities in the recognition, response and/or repair of DNA damage [3]. Further evidence of the importance of 'mutator' genes has come with the demonstration of instability of dinucleotide repeats in a number of common cancers that are caused by either germ-line or somatic mutations in enzymes important in mismatch repair [4]. More recently, a number of groups have shown that genetic factors also influence genetic stability at a chromosome level and there is increasing evidence that the destabilizing of the genome by mutations in genes that normally maintain chromosomal stability plays an important part in the development of some cancers [5].

Molecular genetic analysis of human NMSC has to date focused on four main areas: the role of genes identified in other human cancers; the mapping of chromosome copy number changes; the mapping and positional cloning of familial NMSC susceptibility genes; and comparisons of genetic changes in SCCs with AK and Bowen's disease [1]. As has been the case for other epithelial cancers such as breast and colon cancer, most of the genes implicated to date in NMSC development are tumour-suppressor genes. DNA sequencing has identified mutations in the *p16* and *p53* tumour-suppressor genes. Comparison of the mutational spectra of these genes in NMSC and internal malignancies has confirmed the importance of UVR-induced mutagenesis in NMSC development [6]. Although the *p53* gene has been linked to genetic instability in other cancers, the mutation frequency in BCC and SCC appears broadly similar, which raises interesting questions about the functional effects of *p53* mutations in keratinocytes. Loss of heterozygosity (LOH) studies have revealed that BCCs and SCCs show marked differences in the pattern and extent of chromosome loss. BCCs differ from SCCs and other epithelial neoplasms in that chromosome losses are largely confined to the long arm of chromosome 9 where the *PATCHED1* tumour-suppressor gene that plays a key role in BCC development maps. Allelotype analysis of cutaneous SCCs has demonstrated more widespread allelic losses with frequent loss of 9p, 13q, 17p, 17q and 3p [1]. Similar findings have recently been described in BCCs and SCCs using single nucleotide polymorphism (SNP) microarray analysis [7,8]. The methods used in these studies have revealed that some LOH events in BCCs and SCCs reflect uniparental disomy (loss of one allele and gain of the remaining allele) and that non-random allelic gains occur in SCCs on 3q and 8q. Although the high frequency of copy number changes and imbalances on these chromosome arms suggests that these regions may contain one or more genes important in the development of cutaneous SCCs, with the exception of *p16* and the protein tyrosine phosphatase receptor type D (PTPRD) locus on 9p and *p53* on 17p chromosome, the identities of the candidate tumour-suppressor genes on these chromosome arms are unknown.

Multistage carcinogenesis in the murine skin model

Mouse skin has, for more than 50 years, played a critical role in the development of the concept of multistage carcinogenesis that has underpinned studies of the biology and molecular genetics of the carcinogenic process. While there are important differences between murine and human skin in the response to both chemical carcinogens and UVR, many of the basic concepts identified using this system have been shown to be generally applicable to many human cancers including NMSC. Observational studies of skin tumour induction by chemical carcinogens led to the concept of 'initiation', 'promotion' and 'progression', which represent different stages of the carcinogenic process [9]. 'Initiation' is characterized by the acquisition of an irreversible change in a cell that in the presence of appropriate growth selection pressures ('promotion') can clonally expand to form a benign tumour (papilloma). The probability of papilloma formation within a given mouse strain is dependent on the nature of the carcinogen, the dose applied and the time course over which the mouse is observed. In

the murine two-stage skin carcinogenesis model, 'initiation' is accompanied by mutations in the H-*ras* proto-oncogene and the position and type of mutation within this gene is carcinogen-specific. Dimethylbenzanthracene (DMBA)-induced skin tumours predominately have a mutation at the middle adenosine of Ha-*ras* codon 61 (CAA → CTA)s, whereas methylnitrosurea (MNU)-induced tumours have a G → A transition at codon 12 [10]. This concept of a 'signature' mutation in critical target genes identified in the murine model has underpinned the studies of mutation spectra in the *p53* tumour-suppressor gene and other genes in UVR-induced human NMSC.

The latency period for tumour formation following the application of an initiator is significantly reduced by the application of 'promoters' such as 12-*O*-tetradecanoyl-phorbol-13-acetate (TPA) and other phorbol esters. In contrast to an 'initiator', a 'promoter' generally has to be applied repeatedly and the frequent visible consequences of promoter application, such as hyperkeratosis and scaling of the skin, subside if the application is discontinued. The observation of latency has parallels with the recent observations in humans that clones of *p53* mutant keratinocyte exist within the normal sun-exposed epidermis many years before clinical lesions become detectable [11].

Initiation and promotion, for example using DMBA and TPA, result in the development of multiple papillomas, which rarely progress to invasive carcinoma. The rate of progression of papilloma to carcinoma can be increased by application of the initiator to a papilloma after it has developed or by repeated application of the initiator to 'normal' skin before promotion. Progression is distinct from promotion in that it is considered to reflect accumulation of additional genetic changes and is generally regarded as irreversible. Support for this concept comes from studies of mouse skin tumours, which have established that the transition from benign papilloma to carcinoma is accompanied by an increase in the number of genetic abnormalities in the tumours. This requirement to accumulate additional genetic changes to facilitate tumour progression can occur without further application of an initiator in tumour cells that show 'genetic instability' as this increases the probability of additional genetic changes, which allow histological progression, invasion and metastasis.

Differences between mouse strains and between species in both their susceptibility to cancer induction and the types of tumours induced by identical regimens highlight the importance of other genetic factors in determining cancer susceptibility. The well-defined mouse model system has allowed mapping of these 'modifier' genes and it has now been established that these genes frequently exert their effect by acting in combination and that the same allele can exert opposite effects in different strains of mice [12]. These observations highlight the difficulties in interpreting results from cancer gene association studies in humans.

Ultraviolet radiation mutagenesis and DNA repair

The overwhelming evidence from clinical and epidemiological studies implicating UVR as the most important skin carcinogen makes it easy for us to answer the question, 'Does the sun cause skin cancer?' Answering the question, 'How does the sun cause skin cancer?' is much more challenging and from the information available at present it is still unclear which one or combination of the multitude of effects that UVR has on the skin is critical for all of its carcinogenic properties.

The UV part of the solar electromagnetic spectrum is subdivided into three broad regions:

- UVC (200–280 nm)
- UVB (280–315 nm)
- UVA (315–400 nm).

UVC is widely used in *in vitro* studies of the effects of UVR but is not relevant to human skin cancer as it is efficiently attenuated by the Earth's atmosphere. Although it accounts for less than 10% of the spectral energy of sunlight, UVB is the main waveband responsible for sunburn and skin cancer induction. UVA differs from UVB in a number of ways. It is the main (more than 90%) component of terrestrial sunlight but is less biologically active than UVB. Both UVB and UVA are complete carcinogens in that they are both capable of inducing benign papillomas and SCCs in murine skin.

The effects of UVR on the skin are complex and it is likely that a number of these effects contribute to its initiating and promoting properties. Exposure to both UVB and UVA cause genetic changes in many biological systems [13]. Dose for dose, UVB is a much more efficient mutagen than UVA and the types of mutations induced by these different wavebands are distinct. The action spectra for DNA damage and skin cancer induction are very similar for UVB and closely coincide with the absorption spectra of DNA, which suggests that direct DNA damage by UVB is an important contributor to its carcinogenic effect. Cyclobutane or pyrimidine dimers and the 6–4 photoproduct are the predominant photolesions induced by UVB and these are the preferential sites for UVB-induced mutagenesis [14]. For UVA, the spectra for DNA damage diverges from that of DNA absorption and it has been inferred that DNA damage by wavelengths above 347 nm is not caused by direct absorption by DNA but is more probably a consequence of indirect effects caused by the generation of reactive oxygen species [15]. The types of DNA damage associated with exposure to UVA are DNA strand breaks and DNA protein cross-links.

The mutagenic effects of UVR on keratinocytes within the skin are dependent on the amount and wavelength of the exposure, cellular antioxidant defences [16], the effectiveness of DNA repair mechanisms and the characteristics of the target keratinocyte. Studies in *Escherichia coli* have demonstrated that UVB induces a characteristic spectrum of mutations that is sufficiently distinctive to serve as a molecular 'signature' or 'fingerprint' of DNA damage [17]. This 'fingerprint' is characterized by the presence of C → T transitions at dipyrimidine sites, either singly (C → T) or as a tandem double bases substitution (CC → TT). The identification of mutations that show this molecular fingerprint in human NMSC [6] and in mouse skin tumours induced by UV provides important evidence at the molecular level of the importance of UVB as a mutagen in skin carcinogenesis [18]. Considerably less is known about the characteristics of mutations induced by UVA. As the DNA damage with UVA is predominately indirect, it is more difficult to extrapolate findings from *in vitro* studies using bacteria or mammalian cells. *In vivo* studies using a transgenic mouse model have shown a predominance of GC → AT transitions at

non-pyrimidine dimer sites, which is consistent with the proposed involvement of oxidative DNA damage [19].

Mutations induced by UVR are a result of persistence of unrepaired photoproducts at the time of DNA replication. During DNA replication, the DNA polymerase complex misreads the photoproduct on the template strand and this leads to the insertion of a default adenine residue at this position. At subsequent cell divisions, this adenine pairs with thymine and the net result is the conversion of a cytosine base to a thymine base on the originally damaged strand. A number of studies have shown that there appears to be a close relationship between photoproduct formation and carcinogenesis in that enzymatic repair of photoproducts by endogenously activated photolysase [20] or by topical application of T_4 endonuclease in liposomes [21] reduces the incidence of tumour formation. Although these studies are consistent with the original XP paradigm, which directly links unrepaired DNA lesions, mutations and cancer, recent observations from studies of patients with TTD indicate that the marked increase in susceptibility to UV carcinogenesis seen in XP patients is a result of other effects and not simply a reflection of an increased mutation rate [22]. Detailed comparisons between XP and TTD cells have revealed a number of differences in the repair efficiency and mutational spectrum, but it is still unclear which of these underpin the differences in cancer susceptibility between these syndromes [23,24].

Immunological effects of ultraviolet radiation

The importance of the immune system in human skin carcinogenesis is dramatically illustrated by the marked increases in NMSC incidence in immunosuppressed patients. UVR, in addition to its mutagenic and other direct effects on keratinocytes, has been shown in murine models to exert an immunosuppressive effect that interferes with the ability of the immune system to eliminate UV-induced skin tumours. These observations and the importance of immunosuppressants as a risk factor for NMSC development in humans has led to speculation that UV-induced immunological injury may be an important contributor to the carcinogenic effects of UVR. In mice, skin tumours induced by UVR differ from chemical carcinogen-induced skin tumours in that they are highly immunogenic and are rejected when transplanted into genetically identical recipient mice. The importance of UV-induced immunosuppression in UV carcinogenesis was first recognized in the 1970s when Kripke [25] made the seminal observation that irradiation of recipient mice abolished the ability to reject the transplanted tumours. This work and subsequent studies established that immunosuppression could be transferred to unirradiated animals by adoptive transfer of splenic lymphocytes and that UVR exerted similar effects on the normal immunological reactions to sensitizing chemicals such as dinitrochlorobenzene in contact hypersensitivity reactions. Further investigation of the immunological effects of UVR using skin contact hypersensitivity has revealed that there are marked differences between mice strains in their susceptibility to UVR-induced immunosuppression. Genetic studies have demonstrated that the UV-susceptibility phenotype is dominantly inherited and two genetic loci have been identified that are thought to mediate this effect [26]. Recent studies using genetically modified mice suggest that deficiencies in IL-10 decrease and in IL-12 increase susceptibility to UV-induced immune suppression and accelerate UV-induced skin carcinogenesis [27,28].

The significance of UVR-induced immunosuppression in humans is still unclear. There are some similarities with the findings in mice in that UV irradiation decreases the ability to mount a delayed-type hypersensitivity response when the immunization occurs on exposed skin and there appears to be interindividual differences in the susceptibility to this effect [29–31]. One study suggests that the UV-susceptibility phenotype is more common in patients with NMSC and that 50% of such patients develop hapten-specific tolerance using this test system [32]. While these observations raise the possibility that exposure to UVR may interfere with the ability of the immune system to eliminate UV-induced skin tumours in humans, the clinical importance of this effect is unclear. The observation that pharmacological inhibition of the immune system has a profound clinical effect on NMSC development suggests that the impact of UVR-induced immunosuppression on NMSC development may not be as great as that seen in murine models. However, further work is required to better understand the impact and clinical significance of other, more subtle aspects of the effects of UVR on cutaneous immunity and the implications of these effects in determining NMSC susceptibility in humans.

Human papillomaviruses

The subdivision of HPV types, based on clinical biology and epidemiological studies of anogenital cancers, played a critical part in the dissection of the molecular mechanisms of HPV carcinogenesis. This allowed identification of the characteristics specifically associated with the carcinogenic properties of the high-risk HPV types [33]. Cell biology and molecular studies have shown a good correlation between high- and low-risk HPVs and their ability to transform primary human keratinocytes [34]. The major transforming proteins of the high-risk genital HPVs are the E6 and E7 proteins, which target and inactivate tumour-suppressor genes including *p53* and the retinoblastoma gene.

Clinical and epidemiological studies have also provided compelling evidence of a link between cutaneous viral warts and NMSC and recent molecular studies have allowed analysis of HPV types. Although the increased prevalence of HPV infection in NMSC from high-risk organ transplant recipients is less compelling compared to the information from studies of other HPV-associated cancers, there are some other pieces of evidence that point to a possible direct role for HPV in NMSC development. Genetic analysis of squamous cell neoplasms from immunocompetent and immunosuppressed patients has revealed that there are significant differences between these two patient groups, with significantly less chromosome loss in SCCs from immunosuppressed patients [35]. Further support for a causal role for HPV in NMSC development has come from recent molecular studies that have shown that the E6 protein from some cutaneous HPVs blocks the epidermal apoptotic response to UVR by targeting the pro-apoptotic Bak protein for proteolytic degradation [36]. This finding and the demonstration of an inverse correlation between Bak protein levels and HPV positivity in cutaneous SCCs suggests that cutaneous HPV may promote SCC development by blocking the normal epidermal apoptotic response to UVR [37].

References

1 Quinn AG. Molecular genetics of human non-melanoma skin cancer. *Cancer Surv* 1996; **26**: 89–114.
2 Vogelstein B, Kinzler KW. Cancer genes and the pathways they control. *Nat Med* 2004; **10**: 789–99.
3 Hoeijmakers JH. Genome maintenance mechanisms for preventing cancer. *Nature* 2001; **411**: 366–74.
4 Jiricny J, Nystrom-Lahti M. Mismatch repair defects in cancer. *Curr Opin Genet Dev* 2000; **10**: 157–61.
5 Lengauer C, Kinzler KW, Vogelstein B. Genetic instabilities in human cancers. *Nature* 1998; **396**: 643–9.
6 Brash DE, Rudolph JA, Simon JA *et al.* A role for sunlight in skin cancer: UV-induced *p53* mutations in squamous cell carcinoma. *Proc Natl Acad Sci USA* 1991; **88**: 10124–8.
7 Teh MT, Blaydon D, Chaplin T *et al*. Genomewide single nucleotide polymorphism microarray mapping in basal cell carcinomas unveils uniparental disomy as a key somatic event. *Cancer Res* 2005; **65**: 8597–603.
8 Purdie KJ, Lambert SR, Teh MT *et al*. Allelic imbalances and microdeletions affecting the PTPRD gene in cutaneous squamous cell carcinomas detected using single nucleotide polymorphism microarray analysis. *Genes Chromosomes Cancer* 2007; **46**: 661–9.
9 Yuspa SH, Dlugosz AA, Denning MF, Glick AB. Multistage carcinogenesis in the skin. *J Invest Dermatol Symp Proc* 1996; **1**: 147–50.
10 Burns PA, Bremner R, Balmain A. Genetic changes during mouse skin tumorigenesis. *Environ Health Perspect* 1991; **93**: 41–4.
11 Jonason AS, Kunala S, Price GJ *et al.* Frequent clones of *p53*-mutated keratinocytes in normal human skin. *Proc Natl Acad Sci USA* 1996; **93**: 14025–9.
12 Nagase H, Mao JH, Balmain A. A subset of skin tumor modifier loci determines survival time of tumor-bearing mice. *Proc Natl Acad Sci USA* 1999; **96**: 15032–7.
13 Peak MJ, Peak JG. Solar-ultraviolet-induced damage to DNA. *Photodermatol* 1989; **6**: 1–15.
14 Ziegler A, Jonason AS, Leffell DJ *et al.* Sunburn and *p53* in the onset of skin cancer. *Nature* 1994; **372**: 773–6.
15 Peak MJ, Peak JG. DNA-to-protein crosslinks and backbone breaks caused by far- and near-ultraviolet, and visible light radiations in mammalian cells. *Basic Life Sci* 1986; **38**: 193–202.
16 Applegate LA, Frenk E. Oxidative defense in cultured human skin fibroblasts and keratinocytes from sun-exposed and non-exposed skin. *Photodermatol Photoimmunol Photomed* 1995; **11**: 95–101.
17 Mitchell DL, Jen J, Cleaver JE. Sequence specificity of cyclobutane pyrimidine dimers in DNA treated with solar (ultraviolet B) radiation. *Nucl Acids Res* 1992; **20**: 225–9.
18 Ananthaswamy HN, Fourtanier A, Evans RL *et al. p53* Mutations in hairless SKH-hr1 mouse skin tumors induced by a solar simulator. *Photochem Photobiol* 1998; **67**: 227–32.
19 Gorelick NJ. Overview of mutation assays in transgenic mice for routine testing. *Environ Mol Mutagen* 1995; **25**: 218–30.
20 Ley RD, Applegate LA, Freeman SE. Photorepair of ultraviolet radiation-induced pyrimidine dimers in corneal DNA. *Mutat Res* 1988; **194**: 49–55.
21 Yarosh D, Klein J, Kibitel J *et al.* Enzyme therapy of xeroderma pigmentosum: safety and efficacy testing of T4N5 liposome lotion containing a prokaryotic DNA repair enzyme. *Photodermatol Photoimmunol Photomed* 1996; **12**: 122–30.
22 Stary A, Sarasin A. The genetic basis of xeroderma pigmentosum and trichothiodystrophy syndromes. *Cancer Surv* 1996; **26**: 155–71.
23 Eveno E, Bourre F, Quilliet X *et al.* Different removal of ultraviolet photoproducts in genetically related xeroderma pigmentosum and trichothiodystrophy diseases. *Cancer Res* 1995; **55**: 4325–32.
24 Madzak C, Armier J, Stary A *et al*. UV-induced mutations in a shuttle vector replicated in repair deficient trichothiodystrophy cells differ with those in genetically-related cancer prone xeroderma pigmentosum. *Carcinogenesis* 1993; **14**: 1255–60.
25 Kripke ML. Ultraviolet radiation and immunology: something new under the sun. Presidential address. *Cancer Res* 1994; **54**: 6102–5.
26 Streilein JW. Immunogenetics of sunlight-induced skin cancer. *Photochem Photobiol* 1996; **63**: 422–4.
27 Loser K, Apelt J, Voskort M *et al*. IL-10 controls ultraviolet-induced carcinogenesis in mice. *J Immunol* 2007; **179**: 365–71.
28 Meeran SM, Mantena SK, Meleth S *et al*. Interleukin-12-deficient mice are at greater risk of UV radiation-induced skin tumors and malignant transformation of papillomas to carcinomas. *Mol Cancer Ther* 2006; **5**: 825–32.
29 Yoshikawa T, Rae V, Bruins-Slot W *et al.* Susceptibility to effects of UVB radiation on induction of contact hypersensitivity as a risk factor for skin cancer in humans. *J Invest Dermatol* 1990; **9**: 530–6.
30 Cooper KD, Oberhelman L, Hamilton TA *et al.* UV exposure reduces immunization rates and promotes tolerance to epicutaneous antigens in humans: relationship to dose, CD1a-DR epidermal macrophage induction, and Langerhans' cell depletion. *Proc Natl Acad Sci USA* 1992; **89**: 8497–501.
31 Tie C, Golomb C, Taylor JR, Streilein JW. Suppressive and enhancing effects of ultraviolet B radiation on expression of contact hypersensitivity in man. *J Invest Dermatol* 1995; **104**: 18–22.
32 Streilein JW, Taylor JR, Vincek V *et al.* Relationship between ultraviolet radiation-induced immunosuppression and carcinogenesis. *J Invest Dermatol* 1994; **103** (Suppl. 5): 107S–11S.
33 Zur-Hausen H. Papillomaviruses and cancer: from basic studies to clinical application. *Nat Rev Cancer* 2002; **2**: 342–50.
34 Kaur P, McDougall JK. Characterization of primary human keratinocytes transformed by human papillomavirus type 18. *J Virol* 1988; **62**: 1917–24.
35 Rehman I, Quinn AG, Takata M *et al*. Low frequency of allelic loss in skin tumours from immunosuppressed individuals. *Br J Cancer* 1997; **76**: 757–9.
36 Jackson S, Harwood C, Thomas M *et al.* Role of Bak in UV-induced apoptosis in skin cancer and abrogation by HPV E6 proteins. *Genes Dev* 2000; **14**: 3065–73.
37 Storey A. Papillomaviruses: death-defying acts in skin cancer. *Trends Mol Med* 2002; **8**: 417.

General principles in the management of patients with non-melanoma skin cancer

Many aspects of the management of patients with BCC and SCC are common to both tumour types and these general principles are discussed in this section. Tumour-specific issues are discussed in the treatment section for the relevant tumour. Management of patients with NMSC requires early detection and accurate diagnosis, selection of the appropriate treatment modality based on the clinical and/or pathological findings, consideration of patient-specific risk factors and institution of preventative measures if appropriate.

Detection and diagnosis

Early detection of NMSC is critically dependent on a good awareness of risk factors and the characteristics of tumour development in at-risk groups. Although most patients with NMSC initially present with a lesion requiring a therapeutic intervention, the high prevalence of benign skin disease and the increasing use of medical screening examinations means that there are opportunities for identifying at-risk individuals sooner than they might present with an obvious clinical lesion. Superficial BCCs on the back, Bowen's disease on the leg and AK are not uncommonly either not noticed or dismissed as a normal consequence of ageing. Although early detection of such lesions may have little impact on the clinical prognosis of the identified tumour, the ability to identify at-risk individuals means that advice on preventative measures such as sun awareness and protection can be initiated much earlier than otherwise would have been the case.

Selection of appropriate therapeutic modality for tumour treatment

The aims of any treatment directed against an NMSC are the removal or destruction of the primary tumour mass and, in the

case of SCC, the prevention of metastasis. A broad range of therapeutic options are available to achieve these aims and while surgical excision is frequently the treatment of choice, there are patient-related factors which may influence treatment choices. These factors include the patient's general health, concomitant medication such as anticoagulants and antiplatelet agents, home circumstance and responsibilities due to employment or carer duties and previous experience of treatment for NMSC. Treatment selection is dependent on a good understanding of the clinical and/or pathological aspects of NMSC that affect prognosis and clinical experience of the pros and cons of the various therapeutic modalities.

The different modalities we may consider include: curettage and cautery, cryosurgery, radiotherapy, photodynamic therapy, topical imiquimod, laser surgery, conventional surgical excision and Mohs micrographic surgery (described in detail in Chapters 77 and 78).

Treatments can be broadly divided into destructive or excisional, the latter providing histologic evaluation of the diagnosis, adequacy of removal and information on the risk associated with that tumour. Destructive treatments may be based on a firm clinical diagnosis of basal cell carcinoma but diagnostic doubt should lead to histological confirmation of the diagnosis before treatment. In general, destructive treatments should be used for lower-risk tumours with the exception of radiotherapy, which will be dealt with in more detail later.

Cryosurgery. The application of liquid nitrogen to skin lesions aiming to cause destruction of the tissue and a margin of surrounding tissue requires the achievement of lesional temperatures of –50 to –60°C. This can be achieved by a number of techniques including single or double freeze–thaw cycles [1,2]. This modality has been recommended for the treatment of AK, Bowen's disease, superficial BCC, small nodular BCC and small well-differentiated SCC. While freezing with liquid nitrogen is a quick and relatively tolerable procedure that does not require local anaesthesia, it can be associated with significant morbidity, particularly when tumours selected for treatment require prolonged freeze times to ensure adequate treatment. Although hypopigmentation is a frequent consequence of cryosurgery for skin tumours, wounds tend to heal without significant tissue contraction and this can give rise to excellent cosmetic results for some patients [3,4]. This form of treatment is considered in more detail in Chapter 78.

Curettage and cautery. This modality can be used for the same spectrum of lesions as cryotherapy. Curettage with traditional Volkman spoon reusable curettes is critically dependent on the friable nature of the tumours, which leads to a selective removal of abnormal tissue. This differential effect on tumour tissue is an effective way of delineating the extent of some tumours and can be useful before standard or Mohs excision of some BCCs to define more accurately lateral tumour spread within the epidermis [5]. With the advent of disposable loop curettes, which have a much sharper edge, the technique has been modified to include a more gentle initial curettage to delineate the tumour followed by greater pressure after this point. When used therapeutically it is important that the stroma and surrounding dermis are charred with diathermy or cautery to a depth of 1 mm following initial curettage and that this is repeated on two further occasions with curetting of the charred tumour base. As the procedure does not divide the upper dermis connective tissue network, healing is usually predictable and occurs in most cases with mild scarring. However, hypopigmentation or hypertrophic scar formation may occur, the latter particularly when the upper trunk is treated.

Radiotherapy. Most NMSCs are sensitive to ionizing radiation. Radiotherapy offers the potential to treat large tumours and a surrounding area of normal skin with minimal tissue damage. The effectiveness and cosmetic end result of this therapy is critically dependent on the treatment regimen administered. This operator dependence, which makes comparison of published studies difficult, is also an important contributor to the misconceptions that some physicians have about the value of this approach. Radiotherapy can be an effective cosmetically acceptable treatment for NMSC including BCC, SCC and premalignant lesions such as Bowen's disease. Although it is often stated that radiotherapy is best suited for elderly patients, the inconvenience and practical difficulties of frequent outpatient appointments required for a full fractionated course need to be taken into account when it is considered as an alternative to conventional surgical approaches. In addition to a primary therapy, radiotherapy is also an important adjuvant following excisional surgery for the treatment of residual microscopic disease and as a prophylaxis against systemic metastases. Situations where radiotherapy is best avoided include NMSC on the lower limbs, ear and eyelid, recurrent tumours, lesions previously treated with radiotherapy, tumours with poorly defined clinical margins and patients with multiple NMSCs and severe actinic damage. The technical details of radiotherapy are discussed elsewhere.

Photodynamic therapy. The development of topically active photosensitizing agents 5-aminolevulinate (licensed as Levulan in the United States) and its methyl ester (licensed as Metvix in Europe) has led to studies on the role of photodynamic therapy (PDT) for the treatment of NMSC. These are pro-drugs which are naturally metabolized via the haem biosynthetic pathway to protoporphyrin IX, a powerful photosensitizer. It would appear that there is a relatively selective metabolism in tumour cells allowing the therapy to target premalignant and malignant skin lesions. This therapy appears particularly effective for AK of the face and scalp. Multicentre, randomized, controlled trials have shown greater than 80% clearance of superficial AKs on the face and scalp and similar figures for the treatment of Bowen's disease and superficial basal cell carcinoma. Recurrence rates of up to 20% at 5 years make this at least as effective as other destructive treatments but it may well have advantages over other therapies with respect to tolerability and cosmesis [6–8]. There are now several guidelines on the use of PDT including advice from the National Institute for Health and Clinical Excellence [6, 9–11]. So far, PDT for nodular basal cell carcinoma has been less successful than for superficial BCC but may have a place in selected patients [12]. Interestingly, PDT may have potential to delay the onset of skin tumours in at-risk groups as studies in a mouse model of BCC demonstrated an effect in terms of delayed onset of tumours [13].

Laser therapy. This therapy is rarely used to treat NMSC. Little evidence of its efficacy exists and there are no comparisons with other treatment modalities. One study utilizing the carbon dioxide ultrapulse laser in multiple, low-risk BCCs in the context of the naevoid basal cell naevus syndrome showed some efficacy [14].

Topical immune response modifiers. These are a new class of recently introduced topical therapies which stimulate innate and cell mediated immune responses by activating Toll signalling pathways and inducing cytokine production. Efficacy has been demonstrated in placebo-controlled, randomized clinical trials for imiquimod and it has been approved by regulatory authorities for the treatment of superficial BCCs and AKs in addition to its initial approval for the treatment of genital warts. Clearance of lesions is accompanied by a localized inflammation of variable severity in most subjects. Severe reactions occur in approximately 20% of subjects and may require either temporary treatment interruption or in rare cases discontinuation. Efficacy has also been observed in off-label studies of patients with Bowen's disease [15].

Conventional surgical excision. This is regarded by many as the treatment of choice for primary NMSC. Excision with primary closure, local rotational or advancement flaps or full-thickness graft to repair the defect, when carried out by a trained operator, usually produces a good cosmetic result and provides the pathologist with a specimen that allows confirmation of the completeness of excision and identification of histological factors associated with increased risk of local or systemic recurrence. Although under treatment because of lateral or deep tumour extension may be identified in conventionally processed surgical specimens, there is potential to miss cases of incomplete excision as only a small proportion of the tumour edge is examined using conventional histopathological techniques [16].

Mohs micrographic surgery. This technique combines excision with complete histological examination of the resection margins of skin tumours and has been shown to be very effective in removing NMSC [17,18] and preserves uninvolved tissues. It is only effective in tumours which extend in continuity and is particularly useful in high-risk or recurrent tumours or where tissue conservation is of importance such as the nasal tip and eyelids. Current guidance in the UK suggests that it is the treatment of choice for the highest risk BCCs and SCCs and may be particularly useful where there is evidence of perineural involvement of SCC [19,20]. The Mohs technique is described in detail in Chapter 77.

Selection of the optimal treatment modality

The selection of the most appropriate therapy for a patient is determined by three key factors: tumour size; tumour location; and the likely tumour characteristics based on clinical and, where available, pathological assessment. Low-risk NMSC and related premalignant lesions including AK, Bowen's disease and superficial BCC can usually be adequately dealt with using curettage and cautery, cryotherapy, PDT or topical imiquimod. Although the recurrence rate for these types of lesions with these modalities when used appropriately is slightly higher than that achieved with surgical excision, this needs to be balanced against the fact that these less invasive procedures are relatively simple to carry out, often associated with less short-term morbidity and more predictably give a good cosmetic result compared to excision. Excellent cure rates for curettage and cautery and/or cryotherapy have also been reported for small (less than 1 cm) nodular BCCs and well-differentiated slow-growing SCCs on sun-exposed skin [21,22]. For intermediate-risk NMSC (tumours less than 2 cm, well-defined clinical margins), the location of the tumour is an important determinant of treatment choice. A specific advantage of surgical excision over other destructive therapies is the provision of tissue for histological examination, which provides confirmation of the diagnosis, information on the adequacy of excision and may allow recognition of histological features associated with a high risk of local recurrence and risk of metastasis. For BCC, these features include location on the central face and a morphoeic histological pattern. For SCC, depth of invasion greater than 4 mm or extension into subcutaneous fat, poor differentiation and perineural involvement have all been associated with increased risk of local recurrence and metastatic disease [20]. For high-risk NMSC, the treatment of choice is Mohs surgery.

For the management of most NMSCs a treatment plan can be defined based on a clear understanding of the pros and cons of the different treatment modalities and a careful consideration of the tumour characteristics. In some cases, such as high-risk patients with multiple NMSCs, high-risk tumours, recurrent tumours or incompletely excised NMSC, optimal selection of therapy may be best achieved in the context of a multidisciplinary tumour clinic with input from dermatologists, plastic surgeons, oncologists and radiotherapists.

Chemoprevention and management of high-risk patients

The surgical treatment of high-risk NMSC differs from that of high-risk patients with many other common cancers such as colon, breast and bladder cancer in that it is not possible to completely remove the target organ. While excision or destruction of lesions is well suited for the management of small numbers of NMSCs or related premalignant lesions, these approaches become increasingly impractical and distressing for high-risk NMSC patients with multiple lesions. Examples of patient groups where this problem arises include patients with NBCCS, immunosuppressed organ transplant recipients, high-dose PUVA patients and patients with severe actinic damage. From our current understanding of the epidemiology and biology of NMSC, the number of high-risk patients is likely to increase considerably over the next 25 years as a result of the changing age structure of the population and increased recreational sun exposure. The management of patients with multiple NMSCs is a considerable therapeutic challenge, which is not helped by the limited number of treatment options available and the lack of controlled clinical studies.

Topical 5-fluorouracil is a valuable therapy for the treatment of Bowen's disease and for patients with multiple AK. For reasons that are still not understood, 5-fluorouracil acts on both clinically detectable lesions and subclinical lesions, which means that application to a contiguous area of skin may target a greater number of lesions than would be achieved using destructive therapies of visible clinical lesions. Although there is some evidence to suggest

that 5-fluorouracil may reduce the rate of development of new AK, there is no conclusive evidence at present favouring a role for 5-fluorouracil in the prevention of NMSC [23,24].

A number of systemic approaches have been investigated as chemopreventive agents for high-risk skin cancer patients (reviewed in [25,26]). Oral retinoids are used to treat patients with multiple SCCs where the rate of new SCC development makes management by surgical intervention difficult. Although oral retinoids show clinical efficacy and are the only agent proved to be chemopreventative, there are many unanswered questions on their mode of action and long-term effects as there are very few controlled trials on their use. Etretinate has been shown to be superior to placebo in the treatment of high-risk patients with AK, some of whom also had at least one NMSC [27].

References

1 Graham G. Statistical data on malignant tumours in cryosurgery: 1982. *J Dermatol Surg Oncol* 1983; **9**: 238–9.
2 Zacharian SA. Cryosurgery of cutaneous carcinomas. An 18 year study of 3022 patients with 4228 carcinomas. *J Am Acad Dermatol* 1983; **9**: 947–56.
3 Kokoszka A, Scheinfeld N. Evidence based review of the use of cryosurgery in the treatment of basal cell carcinoma. *Dermatol Surg* 2003; **29**: 566–71.
4 Jamarilo-Ayerbe F. Cryosurgery in difficult to treat basal cell carcinoma. *Int J Dermatol* 2000; **39**: 223–9.
5 Johnson TM, Tromovitch TA, Swanson NA. Combined curettage and excision: a treatment method for primary basal cell carcinoma. *J Am Acad Dermatol* 1991; **24**: 613–7.
6 Morton CA, McKenna KE, Rhodes LE. Guidelines for topical photodynamic therapy: update. *Br J Dermatol* 2008; **159**: 1245–66.
7 Kalka K, Merk H, Mukhtar H. Photodynamic therapy in dermatology. *J Am Acad Dermatol* 2000; **42**: 389–413.
8 Morton CA. The emerging role of 5-ALA-PDT in dermatology: is PDT superior to standard treatments? *J Dermatolog Treat* 2002; **13** (Suppl. 1): S25–9.
9 Haller JC, Cairnduff F, Slack G *et al*. Routine double treatments of superficial basal cell carcinomas using aminolaevulinic acid-based photodynamic therapy. *Br J Dermatol* 2000; **143**: 1270–5.
10 Braathen LR, Szeimies R-M, Basset-Sequin N *et al*. Guidelines on the use of photodynamic therapy for nonmelanoma skin cancer: an international consensus. *J Am Acad Dermatol* 2007; **56**: 125–43.
11 National Institute for Health and Clinical Excellence. *Photodynamic Therapy for Non-melanoma Skin Tumours (Including Premalignant and Primary Non-metastatic Skin Lesions)*, 2006. www.nice.org.uk/nicemedia/pdf/ip/IPG155publicinfo.pdf
12 Rhodes LE, de Rei MA, Leifsdottir R *et al*. Five year follow-up of a randomized, prospective trial of topical methyl aminolevulinate photodynamic therapy vs surgery for nodular basal cell carcinoma. *Arch Dermatol* 2007; **143**: 1131–6.
13 Caty V, Liu Y, Viau G, Bissonnette R. Multiple large surface photodynamic therapy sessions with topical methyl aminolaevulinate in PTCH heterozygous mice. *Br J Dermatol* 2006; **154**: 740–2.
14 Nouri K, Chang A, Trent JT, Jimenez GP. Ultrapulse CO_2 used for the successful treatment of basal cell carcinomas found in patients with basal cell naevus syndrome. *Dermatol Surg* 2002; **28**: 287–90.
15 Mackenzie-Wood A, Kossard S, de Launey J *et al*. Imiquimod 5% cream in the treatment of Bowen's disease. *J Am Acad Dermatol* 2001; **44**: 462–70.
16 Abide JM, Nahai F, Bennett RG. The meaning of surgical margins. *Plast Reconstr Surg* 1984; **73**: 492–7.
17 Lawrence CM. Mohs micrographic surgery for basal cell carcinoma. *Clin Exp Dermatol* 1999; **24**: 130–3.
18 Shriner DL, McCoy DK, Goldberg DJ, Wagner RF Jr. Mohs micrographic surgery. *J Am Acad Dermatol* 1998; **39**: 79–97.
19 Telfer NR, Colver GB, Morton CA. Guidelines for the management of basal cell carcinoma. *Br J Dermatol* 2008; **159**: 35–48.
20 Motley RJ, Preston PW, Lawrence CM. *Multiprofessional Guidelines for the Management of the Patient with Primary Cutaneous Squamous Cell Carcinoma*. www.bad.org.uk.
21 Tromovitch TA. Skin cancer: treatment by curettage and electrodesiccation. *Calif Med* 1965; **103**: 107–8.
22 Freeman RG, Knox JM, Heaton CL. The treatment of skin cancer: a statistical study of 1341 skin tumours comparing results obtained with irradiation, surgery and curettage followed by electrodesiccation. *Cancer* 1964; **17**: 535–8.
23 Simmonds WL. Management of actinic keratoses with topical 5-fluorouracil. *Cutis* 1976; **18**: 298–300.
24 Carter VH, Smith KW, Noojin RO. Xeroderma pigmentosum: treatment with topically applied fluorouracil. *Arch Dermatol* 1968; **98**: 526–7.
25 Wright TI, Spencer JM, Flowers FP. Chemoprevention of nonmelanoma skin cancer. *J Am Acad Dermatol* 2006; **54**: 933–46.
26 Bath-Hextall FJ, Leonardi-Bee J, Somchand N *et al*. *Interventions for Preventing Non-melanoma Skin Cancers in High-risk Groups*. www.cochrane.org/reviews.
27 Moriarty M, Dunn J, Darragh A *et al*. Etretinate in treatment of actinic keratoses: a double-blind crossover study. *Lancet* 1982; **1**: 364–5.

Basal cell carcinoma [1–3]

Synonyms
- Basalioma
- Rodent ulcer

Definition. A malignant tumour that rarely metastasizes, composed of cells similar to those in the basal area of the epidermis and its appendages. The histology of the tumour and the surrounding stroma is characteristic.

Incidence and aetiology. BCC is the most common malignant tumour of the skin and the most common cancer in some countries, including the USA and Australia. Although the prevalence of this tumour increases within a population as exposure to sunlight increases, the distribution of the lesions does not correlate well with the area of maximum exposure to UVR in that BCCs are common on the eyelids, at the inner canthus and behind the ear, but uncommon on the back of the hand and forearm. The palm, sole and vermilion of the lips are rarely, if ever, involved. The basis for the different susceptibility of skin at different sites to BCC development is not known.

BCC is more common in males than females. A population-based incidence study in Minnesota gives annual incidence figures for males and females of 175 and 124 per 100 000, respectively [4], and an Australian survey gives an incidence in that country of 849 and 605 per 100 000 for males and females, respectively, in 1990 [5], while figures from Hawaii show an incidence of 576 per 100 000 for males and 298 in 100 000 for females [6].

A Canadian case–control study has identified outdoor occupations (particularly farming), freckling, and Scottish or Irish descent as particular risk factors [7]. The Australian case–control study by Kricker *et al*. [8,9] of 226 patients with BCC suggests that the tumour is more common in those born in Australia than in immigrants, that southern European ancestry is protective, and that poor tanners are more at risk than those who tan easily. The presence of large numbers of naevi, freckles and solar elastosis all add to the BCC risk, while a past history of acne is protective [8,9]. A large European study of 1549 southern European patients with BCC reports that those with fair or red hair, those who tan poorly and those who have a history of childhood sunburn are at greater risk, and that acute episodes of intense burning sun exposure are a greater risk factor than cumulative lifetime sun exposure [10,11].

Some clues on the potential importance of exposure to hazardous air pollutants, arsenic, ionizing radiations and burns have come from a recent European multicentre study which showed that the frequency of BCCs was highest in miners and quarrymen, railway engine drivers and firemen [12].

BCC is extremely uncommon in dark-skinned races, and less common in Chinese, Japanese and other oriental populations than in white populations [13,14]. Although it may occur at any age from childhood, more than three-quarters of patients are over 40 years old. It occurs earlier and multiple tumours are more common in those with a fair freckled complexion. On the lower leg, the incidence in women is three times as great as in men [13]. BCC appears to arise more frequently and at a younger age in patients who are immunosuppressed. These lesions are frequently aggressive [15]. It is occasionally seen adjacent to leg ulcers [16].

BCC may arise in skin damaged by sunlight and ionizing radiation. It may occur in burn scars [17] or vaccination scars [18,19]. Arsenic salts are also a proven cause [20]. BCC has been reported in identical twins [21]. The increased risk of BCC development in naevus sebaceus and other adnexal hamartomas is well recognized [22–24].

The identification of mutations in the *PTCH1* gene has provided important insights into the pathogenesis of this common skin cancer and points to a key role for the Hedgehog (Hh) signalling pathway in its pathogenesis (see above and [25,26]).

Histogenesis. Theories about the nature and origin of the cells of BCC have been put forward at intervals over the last 80 years or more. The histological variability does not accord with a derivation from any individual epithelial structure, and is now generally considered to stem from the pluripotentiality of immature cells of the epidermis. It is thus capable of maturing towards any of the epithelial structures, and its behaviour is governed, as is the normal immature cell, by the connective tissue in its proximity. Thus, the stroma dependence, the range of histological patterns and the way these merge with the more organized hamartomas are explained. It has been rightly emphasized that the stroma is an essential part of the neoplastic process and it must also be removed in treatment.

Clinical features [27]. The early tumours are commonly small, translucent or pearly, raised and rounded areas covered by thin epidermis through which a few dilated, superficial vessels show (Fig. 52.2). Tiny flecks of pigment may be seen with a hand lens. Other modes of presentation are a small, pearly, erythematous, lichenoid papule or plaque, as a keratotic and slightly indurated area, or as a small and superficial ulcer resembling an excoriation by a fingernail. It may occasionally be pedunculated and telangiectatic, resembling a pyogenic granuloma.

The more advanced tumours have as wide a variety of forms as the early lesions and tend to maintain the same pattern of growth throughout their course. One common type grows slowly as a well-marginated expanding nodule or thickened plaque. The thinned epidermis closely covers the tumour and may periodically scale or erode and crust. In this variety, ulceration occurs relatively late, and may re-epithelialize and break down several times before becoming permanent. The surface contour usually



Fig. 52.2 Typical early basal cell carcinoma on the nose.

becomes more irregular as the lesion grows. The degree of vascularity varies. There may be surface telangiectasia over a flesh-coloured mass or the tumour may be pink or red in colour. Pigment, when present, is usually unevenly distributed through the tumour. Some or all of the component nodules may have cystic centres, which add to the translucent appearance; the cystic parts may be more deeply pigmented than the peripheral parts.

Less commonly, the tumour spreads only superficially. It is bounded by a slightly raised thread-like margin, which is irregular in outline and may be deficient at part of the circumference. The epidermis covering the central zone is usually atrophic and may be scaly. This, combined with an increased vascularity, gives a resemblance to Paget's disease of the nipple. There may be a series of thickened papular islands of growth within the margin, and these may be crusted or eroded. Superficial tumours are often pigmented.

The atypical rodent ulcer has an indurated edge and base, but no thread-like margin. The edge is usually raised above the normal level but in some areas, particularly in the nasolabial furrows, it may be flush with the surface. The floor of the ulcer is depressed below the skin surface, fleshy in appearance and not very vascular. However, there is more or less inflammation around the tumour. Such an ulcerated lesion may have begun as a nodule, but more frequently it is crusted or eroded from an early stage of its evolution. If left, the tumour and its following ulcer may spread deeply and cause great destruction, especially around the eye, nose or ear (Fig. 52.3). There may be wide extension in the periorbital tissues; the bones of the face, the skull and even the meninges may be invaded, and advanced cases amply justify the title 'ulcus terebrans' (penetrating ulcer).

The morphoeic or sclerodermiform BCC is uncommon, and is so named because dense fibrosis of the stroma produces a thickened plaque rather than a tumour. The exact margin of the lesion is impossible to define, but palpation reveals a firm skin texture that extends irregularly beyond the visible changes (Fig. 52.4) [28].



Fig. 52.3 Extensive, ignored basal cell carcinoma on the back of the neck in an elderly man presenting to a British hospital in 1988.



Fig. 52.4 Recurrent basal cell carcinoma that has arisen on the basis of pre-existing morphoeic basal cell carcinoma which was incompletely excised.

The surface is smooth and may be slightly raised above, or sometimes slightly depressed below, the normal level. The colour is yellowish and has been compared with old ivory. Ulceration is uncommon and only very superficial when it does occur. Many patients, and doctors, may take little notice of this type of BCC until its slow extension produces a sizeable lesion.

The majority of BCCs arise on the head and neck, with a particular predilection for the upper central part of the face. The morphoeic type occurs almost exclusively on the face. The superficial type, however, is found mainly on the trunk. The palms and soles are rarely affected. BCCs may be multiple.

Post-irradiation tumours of the scalp [29] and those that occur in sun-damaged skin of the face may be multiple and show various stages of development. A few cases of genuine BCCs have been reported to arise from the epidermis over histiocytomas, but the not uncommon basaloid buds seen in sections of histiocytoma are of doubtful significance.

The typical BCC runs a slow progressive course of peripheral extension, which produces the thread-like margin, the nodule with a central depression or the expanding rodent ulcer. Some tumours grow at so slow a rate that they are, for all practical purposes, benign. This is true for many of the superficial lesions and some of the nodular cystic lesions also. There may be spontaneous fluctuation in size, and areas of scarring can be found within many superficial tumours. A patient who has had one BCC treated should always be followed up, not only for local recurrence but also to detect fresh tumours arising elsewhere. There is no recognized premalignant stage of BCC equivalent to solar keratoses or Bowen's disease for SCC.

Rapid growth is so uncommon as to throw doubt on the accuracy of the patient's history. Invasive rodent ulcers, if neglected, may cause death. This is preceded by prolonged mutilation of the face or scalp [30], with destruction of the nose or eye and exposure of the paranasal sinuses or the skull, dura or brain. A few giant exophytic tumours have occurred on the back [31].

In rare cases, the tumour may disseminate [32–37]. When the ulceration involves the airway, fragments of tumour cells and stroma may be inhaled and become implanted in the lungs [35]. Authentic cases of bloodstream metastasis are on record in which, for example, deposits in the viscera or spinal column have caused the presenting symptoms of the terminal illness. Other cases have spread via lymphatics to the regional lymph nodes before disseminating.

Pathology [38–40]. The tumour cells resemble those of the basal layer of the epidermis and the matrix cells of the appendages, in the relatively small amount of cytoplasm they possess and in their ability to interact with the dermis adjacent to them. Their nuclei are compact, rather darkly staining and closely set. Their cytoplasm stains poorly and the cell margins are rather indistinct. Adjacent cells are connected by bridges. The sparsity of keratin fibrils gives these connections a different appearance from the 'prickles' of the Malpighian layer, but the presence of desmosomes and tonofibrils has been shown by electron microscopy. The interaction with the dermis, which is one of the principal functions of the normal epidermal basal cell, produces the characteristic marginal palisade of tumour cells and the well-organized stroma that surrounds it. The dependence of the tumour on its stroma has been shown by transplantation experiments [41]. The cells within the palisade usually show little evidence of organization or differentiation. Mitotic figures may be frequent, and it is speculated that the combination of large numbers of mitoses and a slow growth rate result from a high rate of apoptosis. Data on cell kinetics indicate that a considerable proportion of cells in the tumour die fairly rapidly [42]. Bizarre and atypical cells occur commonly in arsenic-induced tumours [20]. In some tumours, the cells may become acantholytic and amyloid may be identified [38].

In early lesions, the tumour buds can be seen arising from the epidermis. In very small lesions, multiple buds have been seen. These very soon become confluent, and the three-dimensional examination of superficial BCC shows a coherent margin of tumour with a reticular pattern of growth along the interpapillary ridges and larger, more discrete masses centrally [39]. As the tumour progresses, the masses extend into the dermis, and may

separate from each other and from their point of origin. Growth in one area may be accompanied by involution of the tumour in nearby areas leaving an atrophic epidermis. A common site of origin in humans and in the experimental tumours of the rat is the junction between a pilosebaceous duct and the epidermis. From here the tumour may extend along the epidermis and down the duct. It is difficult to prove a purely adnexal origin for BCC, but some lesions behave as though this were so. In all considerations about the origin of the tumour, one must remember that the tumour can either sever its connection with epithelial structures or establish a secondary connection to structures to which it has grown close.

The variability of the natural history of BCCs is reflected in its pattern of growth. Most tumours are composed of rounded expansile islands. These throw out small buds that grow in the same way to produce multilobular masses with thin strands or septa of fibrous tissue penetrating them [39,40]. In some regions, a limited capacity to grow around and enclose adjacent connective tissue may be associated with a reticular or cystic pattern of growth. The capacity to invade in thin strands is often accompanied by an excessive and almost exclusive fibroblastic response, in contrast with the lymphocytic response around the expansile masses. Invasive strands may spread for long distances along nerve sheaths. BCC is truly invasive in only a small proportion of cases. In these, the tumours show no tendency to grow as rounded masses, have no palisade or organized stroma, and penetrate the dermis and deeper structures, destroying them as they go. Such tumours are almost always ulcerated, usually from an early stage. In the less invasive tumour, ulceration occurs when the epidermis is replaced by the tumour. An eroded, vegetating type of growth is rather uncommon.

Most BCCs provoke a round-cell inflammatory reaction of some degree. It increases in extent with ulceration and is often conspicuous in the papillary body, with superficial patterns of growth. Mast cells are often present in numbers among the fibroblasts of the stroma, and Langerhans' cells have been demonstrated within and near the tumour. This infiltrate has recently been correlated with the aggressive nature of the tumour [43].

The diversity of histological patterns of BCC is caused in part by features that have no direct bearing on the clinical course of the tumour. Not infrequently, melanocytes proliferate within the tumour. The melanin they produce causes the tumour to be pigmented, and numerous melanophages collect in the stroma, and sometimes in cystic cavities. Mucin is commonly found in the stroma, particularly at the margin of the tumour, and may be encysted within it. Cystic cavities also form when the centrally placed cells undergo necrosis. There is no evidence that such cavities represent glandular differentiation. Evidence of true sebaceous or sweat gland differentiation has been seen, but is very rare. Within some tumours there are strands of fusiform cells with more abundant eosinophilic cytoplasm, which may form whorls or keratinizing cysts, and which probably represent rudimentary differentiation towards hair roots. Citrulline can be demonstrated as a histochemical confirmation in such cases but does not help in the sometimes difficult separation from trichoepithelioma. Histochemical and electron microscopy investigations show little evidence of differentiation of the tumour cells. However, *in vitro* culture of tumour cells from nodular tumours produces evidence of keratinization after 30 days, suggesting that the cells possess the biochemical mechanisms for keratinization but that some factor, possibly dermal in origin, inhibits them.

Diagnosis. The common nodular type of tumour has a distinctive appearance when it is more than a few millimetres in diameter. In the initial stages it may be hard to separate from a melanocytic naevus (especially when pigmented), molluscum contagiosum or senile sebaceous hyperplasia without the aid of a biopsy. Naevi can be distinguished if hairs grow from the surface, and in molluscum contagiosum and sebaceous hyperplasia there is a central keratin-filled pit. Scaling or crusting on the surface can cause confusion with warts, keratoacanthoma, SCC or molluscum contagiosum. In all cases, the debris should be removed, and this is easily done in BCC. The friable, relatively avascular tissue beneath is characteristic, and if fragments are removed and smeared on a slide the diagnosis can be confirmed by cytology. Darkly pigmented, ulcerated tumours are occasionally confused with malignant melanoma. The margin of BCC is usually rolled, telangiectatic and multinodular, and there is no pigmented halo. The colour tends to be more definitely brown, in contrast with the dusky greyish brown of malignant melanoma.

Perhaps the most difficult problems (although least crucial from the patient's viewpoint) are found with superficial BCCs. Casual inspection may suggest that these are patches of eczema, psoriasis or Bowen's disease. When the scale is removed and the edge stretched, the thread-like margin will reveal the true diagnosis [44]. Careful inspection will almost always rule out eczema or psoriasis, which the patient's history will have also made unlikely. There are some cases, however, where distinction from Bowen's disease can be made only after biopsy. The consistency of a morphoeic BCC may resemble morphoea; the outline is usually less sharp and the evolution more gradual and relentless. A recently described elastotic nodule on the anterior crus of the antihelix of the ear in sun-damaged skin may resemble a nodular BCC on cursory examination.

Clinical diagnostic accuracy in the diagnosis of BCC, widely regarded by most dermatologists as being the easiest tumour to recognize, is surprisingly poor. One study reported a diagnostic accuracy rate of 70% for academic dermatologists, 65% for dermatologists in private practice and 64% for residents [45].

Treatment. As stated previously there are many factors that influence the treatment of BCC, these include: tumour characteristics; patient characteristics; experience of the clinician; and local facilities. In the case of BCC the factors that influence prognosis are shown in Table 52.1 and should be considered when choosing treatment options.

The aim of any therapy selected for BCC is to ensure complete removal or destruction of the primary tumour to prevent local recurrence and the need for further therapeutic intervention whilst exposing the patient to the least risk of complications and producing an acceptable cosmetic result. The wide range in natural history and biology of the different subtypes of BCC and the large number of treatment modalities available for the removal and destruction of skin tumours means it is difficult to draw up rigid

Table 52.1 Factors influencing prognosis in basal cell carcinoma.

Tumour characteristics	Risk
Tumour size	Increasing size increases risk, especially over 20 mm
Site of tumour	Risk increased with central face, periocular, nasal, ears and lips
Definition of margin	Lesions that are clinically poorly defined are of higher risk
Immunosuppressed patient	Possible higher risk
Recurrent disease	Increased risk
Histological subtype	Morphoeic/infiltrative, micronodular, basosquamous all increase risk
Aggressive histological features	Perineural or vascular invasion increased risk

guidelines for the management of this common cancer. Successful management of BCC requires a clear understanding of the clinicopathological factors that affect prognosis and a good theoretical and practical knowledge of the strengths and limitations of the many different treatments available. From published series on outcomes it is clear that successful treatment can be achieved by any one of the large range of therapies, subject to appropriate matching of the treatment to the tumour characteristics [46,47]. In most cases, treatment selection is usually based on a clinical assessment which considers a number of factors that are known to influence tumour prognosis. These factors include tumour size, location, clinical subtype and defined margin. In addition to the tumour characteristics, other factors such as the patient's age, adequacy and success of previous treatments and coexisting medical conditions that influence tumour biology or treatment tolerability need to be considered. For reasons that are still unclear, BCCs recurring following radiotherapy are particularly difficult to eradicate by conventional surgical excision and this needs to be taken into account when selecting the most appropriate therapy [48].

Destructive therapies used appropriately, mainly for low-risk tumours, can offer an effective alternative to surgical excision for small primary tumours at non-critical sites. A number of studies have shown that curettage and cautery of low-risk BCCs can give cure rates of up to 97% [49]. Similar high cure rates have also been reported for cryotherapy for low-risk BCCs [50,51]. Tumour size has an important effect on prognosis for BCCs and there is good evidence that the recurrence rate following curettage and cautery or cryotherapy increases significantly with increasing size [52,53]. In addition to risk of recurrence, it is also important to bear in mind that the morbidity associated with cryotherapy also increases with increasing size.

Conventional surgical excision with predetermined margins based on the clinical characteristics of the tumour is regarded by many as the most appropriate therapy for most nodular BCCs and provides a specimen for histological examination and assessment of the lateral and deep margins yielding <2% recurrence rate at 5 years post surgery [54,55]. Studies of Mohs surgical specimens have provided useful information about the probability of achieving complete excision in tumours with predetermined margins in different sized BCCs. For BCCs less than 2 cm in diameter with well-defined clinical margins, a 3-mm margin will clear the tumour in 85% of cases and a 4–5-mm margin in 95% of cases [56–58]. Although it has been estimated that careful inspection of the common nodular and plaque forms of the tumour with a loupe allows the margin to be determined to within 0.5 mm of the histologically proven border, inaccuracies in the clinical assessment of tumour margins are an important cause of incomplete excision of nodular BCCs. Small ulcerated nodular BCCs, which present as non-healing erosions, not infrequently extend several millimetres beyond the clinically defined margin. For these tumours and others where the margin is less clearly defined, curettage prior to excision is a useful technique for more accurately defining the true borders of the BCC [59,60]. Even in experienced hands there is a risk that nodular BCCs with apparently well-defined clinical margins may have infiltrated more extensively, leading to incomplete excision with residual tumour. In some cases, strands of cells extend along nerves for a considerable distance beyond the obvious clinical edge of the tumour [61,62]. The outlook is poor when cartilage, bone or the orbit have been invaded.

Studies of incompletely excised BCCs have demonstrated that not all incompletely excised tumours will recur but that between 21 and 41% will do so over a 2 to 5 year period [63–67]. Based on information generated over the years on residual tumour in re-excision specimens and recurrence rates of incompletely excised tumours, it may be reasonable in cases where there is incomplete excision of the lateral margin only, not to re-excise if the BCC is a primary tumour on a non-critical site with a non-aggressive histology. For all other cases and in those where the surgical defect has been repaired using a skin graft or local flaps, immediate re-excision with frozen section control or using Mohs micrographic surgery is the treatment of choice [47].

The management of morphoeic BCC, large BCCs (more than 2 cm in diameter), some smaller nodular BCCs with poorly defined clinical margins and recurrent BCCs needs to take into account the increased likelihood of subclinical extension. In the absence of either frozen section control or Mohs surgery, these tumours will require large predetermined margins; even a 5-mm margin will only give complete excision of 82% of morphoeic BCCs [56]. Management of recurrent BCCs is a difficult problem as cure rates are consistently poorer than those achieved for primary tumour. Mohs surgery is an important treatment option for the treatment of high-risk BCCs as it offers consistent high cure rates for even the most difficult BCCs. For primary BCCs and recurrent BCCs, treated with Mohs surgery, 5-year cure rates of 98.6% and 96% respectively have been reported [68]. The proportion of BCCs treated using Mohs surgery varies considerably between different countries as it is a relatively specialized technique and is more resource-intensive than simple surgical excision. Tumour characteristics that warrant consideration of Mohs surgery include BCCs at high-risk sites (nasolabial fold, periocular and nose), BCCs greater than 2 cm in diameter, morphoeic, infiltrative or micronodular BCCs and recurrent BCCs [46,47].

Basisquamous or metatypical basal cell carcinoma [69,70]

This term is used for tumours that on pathological study appear to have features of both BCC and SCC. The biological significance

is that this pathological pattern is associated with a significantly higher incidence of metastatic spread [71]. The pattern in these lesions is of small aggregates of cells lacking classic palisading and embedded in dense and profuse fibrous stroma. The cells are larger with a larger paler nucleus than in the classic BCC and have a more eosinophilic cytoplasm.

References

1 Miller SJ. Biology of basal cell carcinoma. I. *J Am Acad Dermatol* 1991; **24**: 1–13.
2 Miller SJ. Biology of basal cell carcinoma. II. *J Am Acad Dermatol* 1991; **24**: 161–75.
3 Pollack SV, Goslen JB, Sherertz EF *et al*. The biology of basal cell carcinoma: a review. *J Am Acad Dermatol* 1982; **7**: 569–77.
4 Chuang TY, Popescu A, Su WPD *et al*. Basal cell carcinoma: a population-based incidence study. *J Am Acad Dermatol* 1990; **22**: 413–7.
5 Marks R, Staples M, Giles GG. Trends in non-melanocytic skin cancer treated in Australia: the second national survey. *Int J Cancer* 1993; **53**: 585–90.
6 Reizner GT, Chuang TY, Elpern DJ *et al*. Basal cell carcinoma in Kauai, Hawaii: the highest documented incidence in the United States. *J Am Acad Dermatol* 1993; **29**: 184–9.
7 Hogan DJ, To T, Gran L *et al*. Risk factors for basal carcinoma. *Int J Dermatol* 1989; **28**: 591–4.
8 Kricker A, Armstrong BK, English DR, Heenan PJ. A dose–response curve for sun exposure and basal cell carcinoma. *Int J Cancer* 1995; **60**: 482–8.
9 Kricker A, Armstrong BK, English DR, Heenan PJ. Does intermittent sun exposure cause basal cell carcinoma? A case–control study in Western Australia. *Int J Cancer* 1995; **60**: 489–94.
10 Rosso S, Zanetti R, Martinez C *et al*. The multicentre south European study '*Helios*' II. Different sun exposure pattern in the aetiology of basal cell and squamous cell carcinomas of the skin. *Br J Cancer* 1996; **73**: 1447–54.
11 Zanetti R, Rosso S, Martinez C *et al*. The multicentre European Helios study I. Skin characteristics and sunburns in basal and squamous cell carcinomas of the skin. *Br J Cancer* 1996; **73**: 1440–6.
12 Suarez B, Lopez-Abente G, Martinez C *et al*. Occupation and skin cancer: the results of the HELIOS-I multicenter case-control study. *BMC Public Health* 2007; **7**: 180.
13 Miki Y. Basal cell epithelioma among Japanese. *Australas J Dermatol* 1968; **9**: 304–13.
14 Shanmugaranam K, Labrooy EB. *Skin Cancer in Singapore*. Monograph 10. Washington DC: National Cancer Institute, 1963: 127–40.
15 Weimar VW, Ceilley RI, Goeken JA. Aggressive biologic behavior of basal- and squamous-cell cancers in patients with chronic lymphocytic leukemia or chronic lymphocytic lymphoma. *J Dermatol Surg Oncol* 1979; **5**: 609–14.
16 Gaugman LJ, Bergeron JR, Mullins JF. Giant basal cell epithelioma developing in acute burn site. *Arch Dermatol* 1969; **99**: 594–5.
17 Burns DA, Calnan CD. Basal cell epithelioma in a chronic leg ulcer. *Clin Exp Dermatol* 1978; **3**: 443–5.
18 Hendricks WM. Basal cell carcinoma arising in chickenpox scar. *Arch Dermatol* 1980; **116**: 1304–5.
19 Rich JD, Shesol BF, Horne DW III. Basal cell carcinoma arising in a smallpox vaccination site. *J Clin Pathol* 1980; **33**: 134–5.
20 Yeh S, How SW, Lin CS. Arsenical cancer of skin: histologic study with special reference to Bowen's disease. *Cancer* 1968; **21**: 312–39.
21 Oettle AG. Rodent ulcers in identical twins. *AMA Arch Dermatol* 1956; **74**: 167–72.
22 Fergin PE, Chu AD, MacDonald DM. Basal cell carcinoma complicating naevus sebaceus. *Clin Exp Dermatol* 1981; **6**: 111–5.
23 Golberg HS. Basal cell epitheliomas developing in a localized linear epidermal naevus. *Cutis* 1980; **25**: 295–7, 299.
24 Lillis PJ, Ceilley RI. Multiple tumors arising in naevus sebaceus. *Cutis* 1979; **23**: 310–4.
25 Bale AE, Yu KP. The hedgehog pathway and basal cell carcinomas. *Hum Mol Genet* 2001; **10**: 757–62.
26 Epstein E Jr. Genetic determinants of basal cell carcinoma risk. *Med Oncol* 2001; **36**: 555–8.
27 Afzelius L-E, Ehnhage A, Nordgren H. Basal cell carcinoma in the head and neck. *Acta Pathol Microbiol Scand* 1980; **88A**: 5–9.
28 Litzow TJ, Perry HO, Soderstrom CW. Morpheaform basal cell carcinoma. *Am J Surg* 1968; **116**: 499–505.
29 Ridley CM, Spittle MF. Epitheliomas of the scalp after irradiation. *Lancet* 1974; **i**: 509 (Letter).
30 Gormley LJDE, Hirsch P. Aggressive basal cell carcinoma of the scalp. *Arch Dermatol* 1978; **114**: 782–3.
31 Curry MC, Montgomery H, Winkelmann RK. Giant basal cell carcinoma. *Arch Dermatol* 1977; **113**: 316–9.
32 Blewitt RW. Why does basal cell carcinoma metastasize so rarely? *Int J Dermatol* 1980; **19**: 144–6.
33 Von Domarus H, Stevens PJ. Metastatic basal cell carcinoma: report of five cases and review of 170 cases in the literature. *J Am Acad Dermatol* 1984; **10**: 1043–60.
34 Farmer ER, Helwig EB. Metastatic basal cell carcinoma: a clinico-pathologic study of 17 cases. *Cancer* 1980; **46**: 748–57.
35 Larson DL, Gillespie JJ, Parsons RW. Metastatic basal cell carcinoma of the lung. *South Med J* 1980; **73**: 647–9.
36 Snow SN, Sahl W, Lo JS *et al*. Metastatic basal cell carcinoma. *Cancer* 1994; **73**: 328–35.
37 Stell JS, Moyer DG, Dehne E. Basal cell epithelioma metastatic to bone. *Arch Dermatol* 1966; **93**: 338–40.
38 Weedon D, Shand E. Amyloid in basal cell carcinomas. *Br J Dermatol* 1979; **101**: 141–6.
39 Madsen A. Studies on basal-cell epithelioma of the skin: the architecture, manner of growth, and histogenesis of the tumours—whole tumours examined in serial sections cut parallel to the skin surface. *Acta Pathol Microbiol Scand Suppl* 1965; **117**: 3–63.
40 Sanderson KV. The architecture of basal-cell carcinoma. *Br J Dermatol* 1961; **73**: 455–74.
41 Van Scott EJ, Reinertson RP. The modulating influence of stromal environment on epithelial cells studied in human autotransplants. *J Invest Dermatol* 1961; **36**: 109–17.
42 Weinstein GD, Frost P. Cell proliferation in human basal cell carcinoma. *Cancer Res* 1970; **30**: 724–8.
43 Sherertz EF, Pollack SV, Jegasothy BV. Correlation of basal cell epithelioma aggressiveness with local inhibition of host lymphocyte response. *Clin Res* 1982; **30**: 266 (Abstract).
44 Epstein E. How accurate is visual assessment of basal carcinoma margins? *Br J Dermatol* 1973; **89**: 37–43.
45 Presser SE, Taylor JR. Clinical diagnostic accuracy of basal cell carcinoma. *J Am Acad Dermatol* 1987; **16**: 988–90.
46 Fleming ID, Amonette R, Monaghan T, Fleming MD. Principles of management of basal and squamous cell carcinoma of the skin. *Cancer* 1995; **75** (Suppl. 2): 699–704.
47 Telfer NR, Colver GB, Morton CA. Guidelines for the management of basal cell carcinoma. *Br J Dermatol* 2008; **159**: 35–48.
48 Smith SP, Grande DJ. Basal cell carcinoma recurring after radiotherapy: a unique, difficult treatment subclass of recurrent basal cell carcinoma. *J Dermatol Surg Oncol* 1991; **17**: 26–30.
49 Spiller WF, Spiller RF. Treatment of basal cell epithelioma by curettage and electrodesiccation. *J Am Acad Dermatol* 1984; **11**: 808–14.
50 Holt PJ. Cryotherapy for skin cancer: results over a 5-year period using liquid nitrogen spray cryosurgery. *Br J Dermatol* 1988; **119**: 231–40.
51 Kuflik EG, Gage AA. The five-year cure rate achieved by cryosurgery for skin cancer. *J Am Acad Dermatol* 1991; **24**: 1002.
52 Silverman MK, Kopf AW, Grin CM *et al*. Recurrence rates of treated basal cell carcinomas. II. Curettage-electrodesiccation. *J Dermatol Surg Oncol* 1991; **17**: 720–6.
53 Zacarian SA. Cryosurgery of cutaneous carcinomas: an 18-year study of 3022 patients with 4228 carcinomas. *J Am Acad Dermatol* 1983; **9**: 947–56.
54 Walker P, Hill D. Surgical treatment of basal cell carcinomas using standard post operative histological assessment. *Australas J Dermatol* 2006; **47**: 1–12.
55 Marchac D, Papadopoulos O, Duport G. Curative and aesthetic results of surgical treatment of 138 basal cell carcinomas. *J Dermatol Surg Oncol* 1982; **8**: 379–87.
56 Breuninger H, Dietz K. Prediction of subclinical tumor infiltration in basal cell carcinoma. *J Dermatol Surg Oncol* 1991; **17**: 574–8.
57 Wolf DJ, Zitelli JA. Surgical margins for basal cell carcinoma. *Arch Dermatol* 1987; **123**: 340–4.

58 Kimyai-Asadi A, Goldberg LH, Peterson SR *et al*. Efficacy of narrow-margin excision of well-demarcated primary facial basal cell carcinomas. *J Am Acad Dermatol* 2005; **53**: 464–8.
59 Johnson TM, Tromovitch TA, Swanson NA. Combined curettage and excision: a treatment method for primary basal cell carcinoma. *J Am Acad Dermatol* 1991; **24**: 613–7.
60 Chiller K, Passaro D, McCalmont T, Vin-Christian K. Efficacy of curettage before excision in clearing surgical margins in non-melanoma skin cancer. *Arch Dermatol* 2000; **136**: 1327–32.
61 Farley RL, Manolidis S, Ratner D. Aggressive basal cell carcinoma with invasion of the parotid gland, facial nerve and temporal bone. *Dermatol Surg* 2006; **32**: 307–15.
62 Williams LS, Mancuso AA, Mendenhall WM. Perineural spread of cutaneous squamous and basal cell carcinoma. CT and MR detection and its impact on patient management and prognosis. *Int J Radiat Oncol Biol Phys* 2001; **49**: 1061–9.
63 Sussman LA, Liggins DF. Incompletely excised basal cell carcinoma: a management dilemma? *Aust NZ J Surg* 1996; **66**: 276–8.
64 Richmond JD, Davie RM. The significance of incomplete excision in patients with basal cell carcinoma. *Br J Plast Surg* 1987; **40**: 63–7.
65 Park AJ, Strick M, Watson JD. Basal cell carcinomas: do they need to be followed up? *J R Coll Surg Edinb* 1994; **39**: 109–11.
66 De Silva SP, Dellon AL. Recurrence rate of positive margin basal cell carcinoma: results of a five-year prospective study. *J Surg Oncol* 1985; **28**: 72–4.
67 Wilson AW, Howsam G, Santhanam V *et al*. Surgical management of incompletely excised basal cell carcinomas of the head and neck. *Br J Oral Maxillofac Surg* 2004; **42**: 311–4.
68 Leibovitch I, Huilgol SC, Selva D *et al*. Basal cell carcinoma treated with Mohs surgery in Australia II. Outcome at 5 year follow up. *J Am Acad Dermatol* 2005; **53**: 452–7.
69 Bianchini R, Wolter M. Fatal outcome in a metatypical, giant, 'horrifying' basal cell carcinoma. *J Dermatol Surg Oncol* 1987; **13**: 556–7.
70 Farmer ER, Helwig EB. Metastatic basal cell carcinoma: a clinicopathologic study of 17 cases. *Cancer* 1980; **46**: 748–57.
71 Smith JM, Irons GB. Metastatic basal cell carcinoma: review of the literature and report of three cases. *Ann Plast Surg* 1983; **11**: 551–3.

Squamous cell carcinoma

Definition. A malignant tumour arising from the keratinocytes of the epidermis.

Incidence and aetiology. The epidemiology and risk factors important for cutaneous squamous cell carcinoma (SCC) development have been described in detail in the previous sections on NMSC. SCC of the skin is a heterogeneous disease both aetiologically and clinically, with different risk factors implicated in its development in different populations. The epidemiology of the disease has changed over the last 50 years, with a decrease in the importance of occupational exposure to chemical carcinogens and an increase in the proportion of cases caused by recreational sun exposure. In addition, new diseases, such as HIV infection, and therapeutic advances, such as the introduction of effective immunosuppressive therapies to prevent rejection of transplanted organs and PUVA therapy, have resulted in the emergence of new populations that are highly susceptible to cutaneous SCC development [1,2].

Cutaneous SCC is predominately a disease of white populations and is especially prevalent in this group in areas of high ambient sun exposure [3,4]. Although the incidence is low in non-white populations, SCC is still the most common skin cancer in these populations but shows differences in the anatomical location of the tumours, recognized aetiological factors and prognosis [5]. Factors implicated in the pathogenesis of cutaneous malignancy in Africans and African Americans include trauma, albinism, burn scars, ionizing radiation, chronic inflammation and chronic discoid lupus erythematosus [5,6]. There is a high incidence of SCC in albinos in Tanzania but no evidence of an increased incidence in vitiliginous skin of black people [6,7]. Additional aetiological factors implicated in development of cutaneous SCC in some populations include chronic exposure to thermal radiation and scarring. Radiant heat from coal and peat fires may cause SCC in women who habitually sit with their legs close to the fire [8,9]. The preceding lesion is called erythema ab igne (Fig. 52.5). SCC is also an occasional complication of long-standing chronic granulomas such as venereal granulomas, syphilis, lupus vulgaris and leprosy and lupus erythematosus, chronic ulcers, osteomyelitis sinuses, old burn scars and hidradenitis suppurativa. It may complicate scarring dermatoses such as poikiloderma congenitale, dystrophic epidermolysis bullosa [10] and porokeratosis of Mibelli [11].

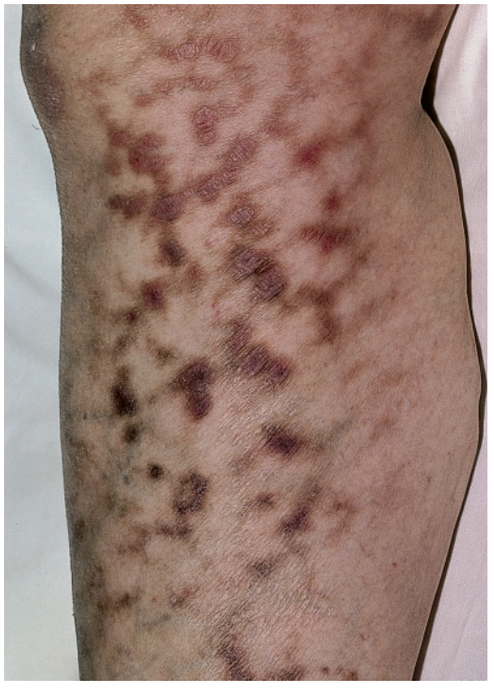


Fig. 52.5 Area of erythema ab igne on the lower leg of an elderly female.

Clinical features (Figs 52.6 & 52.7). SCC does not often arise from healthy-looking skin. Commonly, there are signs of photodamage: solar elastosis of the dermis, hyperkeratosis, irregular pigmentation and telangiectasia, or leukokeratosis and fissuring of the lip. The first clinical evidence of malignancy is induration. The area may be plaque-like, verrucous, tumid or ulcerated, but in all cases the lesion feels firm when pressed between the finger and thumb. The limits of the induration are not sharp and usually extend beyond the visible margin of the lesion. The resistance to pressure is much greater than that given by an inflammatory lesion or benign epithelial hyperplasia.



Fig. 52.6 Multiple invasive squamous cell carcinomas in a patient with a history of exposure to arsenic.



Fig. 52.7 Raised erythematous invasive squamous cell carcinoma in an elderly patient on a light-exposed site.

The tissue around the tumour is inflamed and the edge is an opaque yellowish red colour. The better-differentiated tumours are usually papillomatous and are capped by a keratotic crust in the earlier stages. This may be shed later to reveal an ulcer or eroded tumour with an indurated margin and a purulent, exuding surface that bleeds rather easily. The outline may be rounded, but is often irregular, and in premalignant lesions the induration and elevation is often asymmetrical at first. On mobile structures such as the lip or genitalia the presenting sign may be a fissure or small erosion or ulcer which fails to heal and bleeds recurrently.

The most common sites for SCC are those most exposed to the sun. They occur on the backs of the hands and forearms, the upper part of the face and, especially in males, on the lower lip and pinna.

The histological susceptibility of the scrotum in chimney sweeps, mule spinners and capstan-lathe operators was a result of the retention of the carcinogen on the skin surface. The relatively high incidence of lesions on the lower leg in the natives of tropical countries is related to the frequency of ulcers and scars. The nailbed is an uncommon site, which may be overlooked until the lesion is large enough to produce radiographical changes in the distal phalanx [12].

The evolution of SCC is usually faster than that of BCC, but is conspicuously slower than that of keratoacanthoma, which may attain the same size in as many weeks as SCC does in months or even years. Tumours arising in keratoses on the dorsum of the hand are particularly indolent and late in metastasizing. Early ulceration, and the absence of tumid outgrowth, are usually a result of an anaplastic lesion [13], and are more commonly seen on the lip and genital area than elsewhere. Regional nodes may become enlarged, either as a result of infection of the ulcer or from metastases. In the latter case, they feel harder, are more irregular and become fixed to the adjacent tissues. Spread by the bloodstream is uncommon [14].

Pathology [15–17]. SCC is a tumour that may arise in any epithelium, and its behaviour in the skin is essentially similar to its behaviour in the respiratory tract and elsewhere. Because of the accessibility of the skin, the precancerous changes that lead to the tumour are more easily observed and followed.

Potentially precancerous conditions include actinic keratoses, Bowen's disease and leukoplakia. Invasive SCC begins when atypical keratinocytes breach the dermal basement membrane and invade the dermis (Fig. 52.8). The distinction is thus architectural rather than cytological, and is based on the presence of descending strands of morphologically malignant keratinocytes, which can no longer be regarded as distorted interpapillary ridges. The distinction may be further complicated by the phenomenon of pseudoepitheliomatous hyperplasia [15], which may occur at an ulcer margin or over certain inflammatory or neoplastic states in the dermis (see below).

The cells of SCC vary from large, well-differentiated, polygonal cells with vesicular nuclei, prominent nucleoli and an abundant cytoplasm containing numerous tonofibrils and well-developed intercellular bridges, through to completely anaplastic cells with basophilic cytoplasm, which provide no cytological evidence of their origin. Some tumours have large bizarre cells, in others the cells may have a clear, almost vacuolated cytoplasm and in yet others the cells may be spindle-shaped. Well-differentiated tumours show areas of maturation that form parakeratotic horny pearls and individually keratinized cells, and also dyskeratosis, with lacunae and lumina that contain shed rounded, degenerating

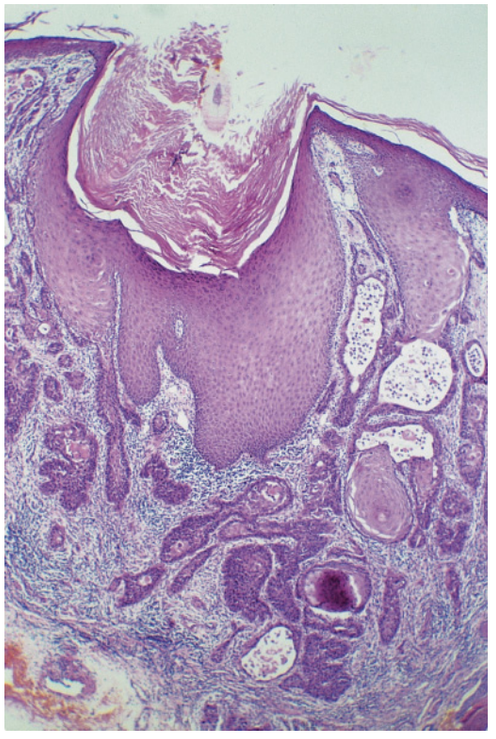


Fig. 52.8 Pathological features of well-differentiated, early invasive squamous cell carcinoma, showing differentiated keratinocytes invading the underlying dermis.

cells. The latter appearance is pseudoglandular, and is termed adenoid or acantholytic SCC [16,17].

Most tumours invade as coherent strands and columns, and reproduce the same pattern in their metastases. Many are composed of cells uniform in type and showing only moderate mitotic activity. They stimulate an inflammatory reaction in the dermis. The capillary pattern is abnormal and the number of vessels considerably increased [18]. Increasing anaplasia is associated with hyperchromatic nuclei, decreasing eosinophilia and tonofibril formation in the cytoplasm, and lessened intercellular adhesions. The cell outlines may be rounded or spindle-shaped. Mitotic figures become more frequent, and abnormal mitoses can be found. Even in extensively ulcerated tumours, the connection with the epidermis is usually maintained, and the origin can be traced to atypical epidermal cells, which may enable a distinction to be made from an anaplastic amelanotic melanoma. Its origin from an area of abnormal epidermis distinguishes it from keratoacanthoma. In rare instances, SCC may appear to arise in a keratinous cyst. Many reported instances of this occurrence, however, can now be considered as proliferating trichilemmal cysts.

Local extension of SCC may occur around nerves, sometimes for considerable distances, and may require extensive surgery [19]. Biological differences in the aggressiveness of SCCs arising in different locations and/or resulting from different aetiological factors are well recognized [20]. It is unusual for SCC originating in an AK on the hand or arm to show evidence of anaplasia or to metastasize until well advanced. In a Scandinavian series [21], fewer than 8% of tumours of the upper limb metastasized. Lesions of the vermilion of the lip, and to a lesser extent of the ear, metastasize much earlier even when they are relatively well differentiated. Those elsewhere on the face appear to be less aggressive. SCC of the external genitalia is also inclined to early invasion and metastasis. Spread is almost always by the lymphatic route.

Various ways of predicting the likelihood of metastasis from the histological features have been suggested. One that has been widely used is Broders' classification based on the proportion of differentiated to atypical tumour cells. From the practical point of view, this method needs to be supplemented by the depth of invasion. For tumours of the hand, for instance, metastasis is unlikely when the penetration does not extend deeper than the sweat coils [16]. At the two extremes of differentiation this criterion does not apply. A well-differentiated lesion such as 'epithelioma cuniculatum' may invade the soft tissues of the foot extensively without metastasis [22,23], while a completely undifferentiated tumour, of the lip for instance, may disseminate at an early stage.

Epithelioma cuniculatum [24] **and verrucous carcinoma** [25]. There are several uncommon tumours that are so well differentiated that the diagnosis may be in doubt if the unrelenting course is not taken into account. One such has been reported as the 'epithelioma cuniculatum' [22]. There is a soft bulbous mass with a squashy consistency on the distal part of the sole of the foot. Multiple sinuses open on the surface and, when pressed, greasy, rancid and foul-smelling material can be expressed. It is possible that the appearance of a vegetating pyoderma may at times be caused by the same process. In such cases, the distinction from pseudoepitheliomatous hyperplasia may be very difficult. A few examples of 'giant condyloma acuminatum' have eventually become low-grade SCC [26,27].

In both the oral cavity and on the genital mucosa [28], a strikingly verrucous lesion may develop [25,29]. These lesions, because of the site involved, may become massive, moist, cauliflower-like and often malodorous because of secondary infection. The clinically apparent relentless growth contrasts with the pathologically less aggressive appearance characterized by a lack of mitotic figures and a well-demarcated lower margin with no strands of cells becoming detached from the main bulk of the lesion.

At the other extreme, anaplastic SCC rarely may arise from skin not showing a premalignant lesion and in a form very difficult to recognize. The lesion is a red papule or nodule, relatively fast growing and looking inflammatory rather than neoplastic. It tends to ulcerate early. It may resemble a keratoacanthoma, but the central keratin core is usually absent. Induration is present, but may be less marked than in well-differentiated tumours. It can infiltrate deeply and metastasize quite early. It has been designated 'squamous cell carcinoma *de novo*' [30].

Squamous cell carcinoma following immunosuppression after organ transplantation. Recipients of organ transplants receiving immunosuppressive therapy have a much higher than expected incidence of SCC [1,31,32]. The development of carcinomas is directly related to time from transplantation, and appears to be independent of the immunosuppressive regimen used. The normal ratio of BCC:SCC is reversed, and SCC is more common. The lesions are most numerous on sun-exposed sites and are frequently multiple. They may clinically be deceptively banal, and resemble

either keratoacanthoma or actinic keratosis. All such lesions should be regarded with suspicion in transplant patients, and biopsied to establish their true nature. Female transplant recipients also have a much higher than expected incidence of genital premalignancy.

Careful, regular supervision of transplant patients by a dermatologist is required, and advice on sun avoidance should be part of the post-transplant care regimen.

Diagnosis. The indurated, well-differentiated SCC arising in skin damaged by sunlight presents no problems in diagnosis. The distinction from keratoacanthoma is usually easy, as the rate of growth and domed appearance of keratoacanthomas are characteristic. On occasions, however, a tumour develops like a typical keratoacanthoma, but proves by its progress to be an SCC [33]. In such cases, the histology of the early stage may not be conclusive one way or the other. The most important clinical distinction is between a poorly differentiated carcinoma arising *de novo* from normal skin, and an inflammatory ulcer or granuloma on the one hand, or an amelanotic melanoma or BCC on the other. The characteristic induration and opaque colour are the most important signs but any doubt is usually clarified by biopsy. Warty lesions such as viral warts or seborrhoeic keratoses are not indurated and are frequently multiple.

Treatment. The aims of any therapy selected for the treatment of cutaneous SCCs are to ensure complete removal and destruction of the primary tumour and to prevent metastasis. From published series on treatment outcomes it is clear that these aims can be achieved by any one of a range of therapies subject to appropriate matching of the therapy to the tumour characteristics [34]. There are a number of factors which influence the metastatic risk of cutaneous SCC, including clinical features such as size, site, rate of growth, aetiology and presence of immunosuppression. Histologic features influencing risk of metastases include tumour thickness, depth of invasion and degree of differentiation may or may not be available at the time of treatment planning but if available will aid in treatment decision making. Unfortunately, many of these factors are not routinely reported in the publications of outcomes of treatment in case series and there are few randomized trials comparing treatments to guide our decisions. Whilst published case series have provided insights into factors that impact metastases risk, the information is uncontrolled and does not take into account the impact of important factors such as differences between SCCs seen in office practice compared to secondary or tertiary care settings [20,34–42]. Treatment selection in clinical practice is based on an assessment of the clinical and, if available, pathologic tumour characteristics mentioned above that have been shown to be important in determining the level of therapy required and in identifying tumours with a poor prognosis. Identification of aggressive cutaneous SCCs is important as the overall 5-year rates of recurrence and metastasis for these tumours is 20–25% which is approximately three times greater than that for primary skin SCC (8%) [35].

Although there are considerable international differences in clinical practices, it is possible to make some generalizations. Destructive therapies used appropriately by experienced clinicians with careful tumour selection can offer an effective alternative to surgical excision for small (less than 1 cm in diameter), slow-growing, well-differentiated SCCs on sun-exposed sites [34,43]. For similar well-defined, low-risk tumours less than 2 cm in diameter, surgical excision with at least a 4-mm clinical margin is an appropriate starting point with anticipated complete excision rates of 95% [44]. Higher-risk tumours which are more than 2 cm, moderately or poorly differentiated, extending into the subcutis or on high-risk sites including the scalp, ears, nose, lip or eyelid require wider margins of more than 6 mm and may well benefit from histological examination of the margins with techniques such as Mohs surgery [44]. Tumour size has an important effect on the probability of both local recurrence and metastatic risk, with a doubling of local recurrence risk and a threefold increase in metastatic risk for SCCs greater than 2 cm in diameter. In addition to tumour size, other criteria used in the selection of appropriate therapy include the location of the tumour, the likely aetiological factor and histopathological characteristics [34,37,38]. UVR-associated SCCs on the ear, lip, scalp, eyelids and nose have a worse prognosis than UVR-associated SCCs at other sites. The basis for this difference has not been established but it is possible that some of the increased risk for cutaneous tumours may result from technical considerations at the time of surgery. SCCs on non-sun-exposed sites where aetiological factors other than UVR exposure are important are also associated with a worse prognosis. It has long been recognized that SCCs at sites of scarring, ulcers, chronic sinuses or previous thermal or ionizing radiation injury have a worse prognosis. SCCs arising in areas of Bowen's disease are also thought to have greater malignant potential. Although deaths resulting from metastatic cutaneous SCCs are more common in immunosuppressed patients, it is not clear if this increase is brought about by differences in the biology of SCCs in these patients or a reflection of the marked increase in the prevalence of SCCs in this group, which in itself could lead to more deaths from metastatic disease [45,46]. A further histopathological characteristic associated with a worse prognosis is the presence of perineural involvement [36,47,48]. SCCs extending into the subcutaneous fat or greater than 4 mm in depth are almost eight times (45.7% metastatic rate) more likely to recur than SCCs confined to the upper dermis (6.7% metastatic rate). Poorly differentiated tumours have a doubling in the incidence of local recurrence and a threefold increase in metastatic rate [34,49,50]. The worse prognosis and difficulties in managing recurrent SCCs highlight the importance of adequate initial treatment based on accurate clinical assessment and appropriate selection of therapy.

Radiotherapy is rarely the treatment of choice but may be indicated for some very large or rapidly enlarging tumours or in patients where aggressive surgical management may not be tolerated. It may also be better for certain sites where functional and cosmetic outcomes for surgery are less than ideal such as the lips, lower eyelid and occasionally the ear. Radiotherapy may also have a role as an adjuvant therapy in some high-risk SCCs where there are concerns about residual microscopic disease, for example in perineural involvement [51]. Mohs micrographic surgery offers advantages over conventional surgical excision and is widely regarded as the treatment of choice for high-risk SCCs as it reduces the risk of local recurrence and metastatic disease.

For patients with aggressive cutaneous SCCs, there are currently no recommended adjuvant chemotherapy regimes after definitive surgical or radiation treatment. A recent trial evaluating the effectiveness of adjuvant 13-*cis*-retinoic acid (13cRA) plus interferon alfa (IFN-α) failed to demonstrate benefit in the prevention of tumour recurrence or second primary tumour development [52].

The final results of any of the methods depend on the experience of the person using it rather than the technique itself. In experienced hands, all the techniques give 5-year cure rates of approximately 90% in a wide variety of SCCs at different sites. Patients with high-risk SCC and those who have evidence clinically of nodal disease are best managed with the help of a multidisciplinary team, which may comprise dermatologists, dermatopathologists, radiation oncologists, plastic surgeons, skin cancer specialist nurse and radiologist. In situations where treatment can at best be palliative, the involvement of the palliative care team may also be required [43].

Prevention. Patients presenting with SCCs or related premalignant lesions on sun-exposed skin should be advised about the importance of reducing exposure to solar radiation. In high-risk patients, regular follow-up and targeted treatment of small, low-risk tumours with cryotherapy and other destructive therapies may help reduce the frequency of tumours requiring surgical excision. Although intermittent 5-fluorouracil use may improve skin texture and reduce the rate of development of AK, there is no published evidence at present that this is associated with a decrease in the rate of development of invasive SCCs. In patients such as organ transplant recipients and patients with xeroderma pigmentosum, where the rate of new SCC development makes surgical management difficult, then it may be necessary to consider treatment with systemic retinoids to reduce the rate of development of new lesions and help target surgical excision to retinoid-unresponsive tumours. Etretinate and isotretinoin have both been shown to reduce the rate of development of new lesions in XP patients [53,54]. More recently, acitretin has been shown to reduce the rate of development of new SCCs [55,56]. In contrast to cytotoxic drugs, retinoids do not appear to eliminate neoplastic clones from the epidermis and discontinuation of therapy is associated with the rapid growth of numerous dysplastic lesions that were growth inhibited but not eliminated by retinoid therapy.

References

1 Nguyen P, Vin-Christian K, Ming ME, Berger T. Aggressive squamous cell carcinomas in persons infected with the human immunodeficiency virus. *Arch Dermatol* 2002; **138**: 758–63.
2 Ramsay HM, Fryer AA, Hawley CM *et al*. Non-melanoma skin cancer risk in the Queensland renal transplant population. *Br J Dermatol* 2002; **147**: 950–6.
3 Marks R, Staples M, Giles GG. Trends in non-melanocytic skin cancer treated in Australia: the second national survey. *Int J Cancer* 1993; **53**: 585–90.
4 Chuang TY, Popescu NA, Su WDP *et al*. Squamous cell carcinoma: a population based incidence study in Rochester Minnesota. *Arch Dermatol* 1990; **126**: 185–8.
5 Halder RM, Bridgeman-Shah S. Skin cancer in African Americans. *Cancer* 1995; **75** (Suppl. 2): 667–73.
6 Oettle AG. *Skin Cancer in Africa*. Monograph 10. Washington DC: National Cancer Institute, 1963: 197–214.
7 Okoro AN. Albinism in Nigeria. *Br J Dermatol* 1975; **92**: 485–92.
8 Cross F. On a turf (peat) fire cancer: malignant change superimposed on erythema ab igne. *Proc R Soc Med* 1967; **60**: 1307–8.
9 Peterkin GAG. Malignant change in erythema ab igne. *BMJ* 1955; **ii**: 1599–602.
10 Weschler HL, Krugh FJ, Domonkos A *et al*. Polydysplastic epidermolysis bullosa and development of epidermal neoplasms. *Arch Dermatol* 1970; **102**: 374–80.
11 Oberste-Lehn H, Moll B. Porokeratosis Mibelli und Stachelzellcarcinom. *Hautarzt* 1968; **19**: 399–403.
12 Hay DM, Cole FM. Postgranulomatous epidermoid carcinoma of the vulva. *Am J Obstet Gynecol* 1970; **108**: 479–84.
13 Johnson RE, Ackerman LV. Epidermoid carcinoma of the hand. *Cancer* 1950; **3**: 657–66.
14 Johnson WC, Helwig EB. Adenoid squamous cell carcinoma (adenoacanthoma): a clinicopathologic study of 155 patients. *Cancer* 1966; **19**: 1639–50.
15 Lund HZ. Tumors of the skin. In: *Atlas of Tumor Pathology*, Section 1, Fasc. 2. Washington DC: Armed Forces Institute of Pathology, 1957: 235.
16 Stout AP. Gross pathology of cutaneous cancer. *Arch Dermatol Syphilol* 1946; **53**: 597–8.
17 Willis RA, ed. *Pathology of Tumours*, 3rd edn. London: Butterworths, 1960.
18 Urbach F. *Anatomy and Pathophysiology of Skin Tumor Capillaries*. Monograph 10. Washington DC: National Cancer Institute, 1963: 539–59.
19 Dandy DJ, Munro DD. Squamous cell carcinoma of skin involving the median nerve. *Br J Dermatol* 1973; **89**: 527–31.
20 Kwa RE, Campana K, Moy RL. Biology of cutaneous squamous cell carcinoma. *J Am Acad Dermatol* 1992; **26**: 1–26.
21 Swanbeck G, Hillström L. Analysis of etiological factors of squamous cell skin cancer or different locations. III. The arm and the hand. *Acta Derm Venereol (Stockh)* 1970; **50**: 350–4.
22 Aird I, Johnson HD, Lennox B *et al*. Epithelioma cuniculatum: a variety of squamous carcinoma peculiar to the foot. *Br J Surg* 1954; **42**: 245–50.
23 Driban NE, Lacognata JJ. Subungal squamous cell carcinoma. *Dermatologica* 1975; **150**: 186–90.
24 Headington JT. Verrucous carcinoma. *Cutis* 1978; **21**: 207–11.
25 Ackermann LV. Verrucous carcinoma of the oral cavity. *Surgery* 1948; **23**: 670–9.
26 Davies SW. Giant condyloma acuminata: incidence among cases diagnosed as carcinoma of the penis. *J Clin Pathol* 1965; **18**: 142–9.
27 South LM, O'Sullivan JP, Gazet JC. Giant condylomata of Buschke and Loewenstein. *Clin Oncol* 1977; **3**: 107–15.
28 Foye G, Marshall MR, Minkowitz S. Verrucous carcinoma of the vulva. *Obstet Gynaecol* 1969; **34**: 384–90.
29 Kao G, Graham JH, Helwig EB. Carcinoma cuniculatum. *Cancer* 1982; **49**: 2395–403.
30 Graham JH, Helwig EB. *Cutaneous Precancerous Conditions in Man*. Monograph 10. Washington DC: National Cancer Institute, 1963: 323–3.
31 McGregor JM, Proby CM. Skin cancer in transplant recipients. *Lancet* 1995; **346**: 964–5.
32 Hartevelt MM, Bavinck JN, Kootte AM *et al*. Incidence of skin cancer after renal transplantation in the Netherlands. *Transplantation* 1990; **49**: 506–9.
33 Boyle J, MacKie RM, Briggs JD *et al*. Cancer warts and sunshine in renal transplant patients. *Lancet* 1984; **i**: 702–5.
34 Rowe DE, Carroll RJ, Day CL Jr. Prognostic factors for local recurrence, metastasis, and survival rates in squamous cell carcinoma of the skin, ear, and lip: implications for treatment modality selection. *J Am Acad Dermatol* 1992; **26**: 976–90.
35 Clayman GL, Lee JJ, Holsinger FC *et al*. Mortality risk from squamous cell skin cancer. *J Clin Oncol* 2005; **23**: 759–65.
36 Moore BA, Weber RS, Prieto V *et al*. Lymph node metastases from cutaneous squamous cell carcinoma of the head and neck. *Laryngoscope* 2005; **115**: 1561–7.
37 Veness MJ, Palme CE, Morgan GJ. High-risk cutaneous squamous cell carcinoma of the head and neck. Results from 266 treated patients with metastatic lymph node disease. *Cancer* 2006; **106**: 2389–96.
38 Mullen JT, Feng L, Xing Y *et al*. Invasive squamous cell carcinoma of the skin: defining a high-risk group. *Ann Surg Oncol* 2006; **13**: 902–9.
39 Dzubow LM, Rigel DS, Robins P. Risk factors for local recurrence of primary cutaneous squamous cell carcinomas. *Arch Dermatol* 1982; **118**: 900–2.
40 Epstein E. Malignant sun-induced squamous cell carcinoma of the skin. *J Dermatol Surg Oncol* 1983; **9**: 505–6.

41 Eroglu A, Berberoglu U, Berberoglu S. Risk factors related to locoregional recurrence in squamous cell carcinoma of the skin. *J Surg Oncol* 1996; **61**: 124–30.
42 Friedman NR. Prognostic factors for local recurrence, metastases and survival rates in squamous cell carcinoma of the skin, ear and lip. *J Am Acad Dermatol* 1993; **28**: 281–2.
43 Motley RJ, Preston PW, Lawrence CM. *Multiprofessional Guidelines for the Management of the Patient with Primary Cutaneous Squamous Cell Carcinoma*. www.bad.org.uk
44 Brodland DG, Zitelli JA. Surgical margins for excision of primary cutaneous squamous cell carcinoma. *J Am Acad Dermatol* 1992; **27**: 241–8.
45 Veness MJ, Quinn DI, Ong CS *et al*. Aggressive cutaneous malignancies following cardiothoracic transplantation: the Australian experience. *Cancer* 1999; **85**: 1758–64.
46 Barksdale SK, O'Connor N, Barnhill R. Prognostic factors for cutaneous squamous cell and basal cell carcinoma. Determinants of risk of recurrence, metastasis and development of subsequent skin cancers. *Surg Oncol Clin N Am* 1997; **6**: 625–38.
47 Mendenhall WM, Parsons JT, Mendenhall NP *et al*. Carcinoma of the skin of the head and neck with perineural invasion. *Head Neck* 1989; **11**: 301–8.
48 Cottel WI. Perineural invasion by squamous cell carcinoma. *J Dermatol Surg Oncol* 1982; **8**: 589–600.
49 Friedman HI, Cooper PH, Wanebo HJ. Prognostic and therapeutic use of microstaging in cutaneous squamous cell carcinoma of the trunk and extremities. *Cancer* 1985: **56**: 1099–105.
50 Breuninger H, Black B, Rassner G. Microstaging of squamous cell carcinomas. *Am J Clin Pathol* 1990: **94**: 624–7.
51 Han A, Ratner D. What is the role of adjuvant radiotherapy in the treatment of cutaneous squamous cell carcinoma with perineural invasion? *Cancer* 2007; **109**: 1053–9.
52 Brewster AM, Lee JJ, Clayman GL *et al*. Randomized trial of adjuvant 13-cis-retinoic acid and interferon alfa for patients with aggressive skin squamous cell carcinoma. *J Clin Oncol* 2007; **25**: 1974–8.
53 Kraemer KH, DiGiovanna JJ, Moshell AN *et al*. Prevention of skin cancer in xeroderma pigmentosum with the use of oral isotretinoin. *N Engl J Med* 1988; **318**: 1633–7.
54 Schnitzler L. [Retinoids and the prevention of cutaneous epitheliomas: 1977–87]. *Ann Dermatol Vénéréol* 1987; **114**: 1537–43.
55 George R, Weightman W, Russ GR *et al*. Acitretin for chemoprevention of non-melanoma skin cancers in renal transplant recipients. *Australas J Dermatol* 2002; **43**: 269–73.
56 Kovach BT, Sams HH, Stasko T. Systemic strategies for chemoprevention of skin cancers in transplant recipients. *Clin Transplant* 2005; **19**: 726–34.

Premalignant epithelial lesions

Premalignant epithelial lesions are conditions that can be recognized clinically or histopathologically and are associated with an increased risk of cancer development. Although premalignant lesions frequently share many of the histopathological changes seen in invasive cancers, the ability to order lesions on the basis of severity does not in itself imply that the lesions identified represent consecutive changes in a neoplastic process [1]. The histopathological changes seen in premalignant lesions include nuclear pleomorphism, increased mitotic rate, abnormal mitotic figures and abnormal differentiation. In the skin, a number of premalignant epithelial lesions have been identified and there is convincing clinical and epidemiological evidence of an association between many of these lesions and an increased risk of NMSC. Some lesions, such as AK and leukoplakia of mucosal surfaces, may show relatively little evidence of cellular atypia, whereas others, including Bowen's disease and erythroplasia of Queyrat, can show marked dysplasia of the epidermis that is histologically indistinguishable from the changes seen in well-differentiated SCC. Premalignant lesions are distinguished from their invasive counterparts by the absence of histological invasion with the microscopical features of intraepidermal carcinoma confined above the dermal–epidermal junction. In addition to the epidermal changes, a common feature of many premalignant lesions is the presence of a chronic inflammatory cell infiltrate in the papillary dermis immediately beneath the abnormal epidermis [2]. The importance of premalignant lesions as indicators of increased NMSC risk is well illustrated by AK, Bowen's disease, tar keratoses, ionizing radiation keratoses and arsenical keratoses, which are frequently found in patients with NMSC or at high risk of developing this type of cancer. With the exception of arsenical keratoses, which are the result of systemic carcinogen exposure, all of the other premalignant lesions localize to areas of skin exposed to the carcinogen and these areas are the same as those at risk of NMSC development. Premalignant lesions frequently occur before the development of invasive cancers and can be useful in identifying individuals at high risk of NMSC development.

Conventional models of multistage carcinogenesis, such as the human colon cancer model and murine skin cancer models, are based on tumour systems that show an orderly progression through well-defined clinicopathological changes. In these models, cancer development is indirect, progressing through discrete clinicopathological changes and this is supported by molecular studies, which have shown that 'early' lesions have less genetic abnormalities than do 'late' lesions. Other tumours develop in the absence of any recognizable precursor lesions, that is they arise directly. Clinical observation suggests that most human cancers, including cutaneous SCCs, may not progress through intermediate stages and that progression of AK and Bowen's disease to invasive SCC may be the exception rather than the rule [1]. A full consideration of the natural history of most premalignant lesions, including AK and Bowen's disease, is difficult as therapeutic removal or destruction provides evidence of what the lesion looks like but destroys any chance of consideration of future behaviour. Notwithstanding these limitations, a number of longitudinal studies indicate that AKs frequently undergo spontaneous regression and have a low potential for developing into invasive SCCs [3,4]. Support for the hypothesis that most AKs are unlikely to progress into invasive SCCs comes from molecular studies. These studies have shown that AKs frequently show more extensive chromosome losses than do SCCs, in contrast to findings in the colon cancer model where indirect cancer development as part of a linear progression process is the norm [5,6]. These findings do not undermine the importance of regular skin examination of high-risk skin cancer patients and the treatment of lesions based on clinical need but they do not support the concept that aggressive treatment of some types of premalignant lesions such as AK will prevent cancer development in these patients.

References

1 Foulds L. *Neoplastic Development*, Vol. 1. New York: Academic Press, 1969.
2 Pinkus H, Jallad M, Mehregan AH. The inflammatory infiltrate of precancerous skin lesions. *J Invest Dermatol* 1963; **41**: 247–8.
3 Frost C, Williams G, Green A. High incidence and regression rates of solar keratoses in a Queensland community. *J Invest Dermatol* 2000; **115**: 273–7.
4 Marks R, Foley P, Goodman G *et al*. Spontaneous remission of solar keratoses: the case for conservative management. *Br J Dermatol* 1986; **115**: 649–55.

5 Rehman I, Quinn AG, Healy E, Rees JL. High frequency of loss of heterozygosity in actinic keratoses, a usually benign disease. *Lancet* 1994; **344**: 788–9.
6 Kushida Y, Miki H, Ohmori M. Loss of heterozygosity in actinic keratosis, squamous cell carcinoma and sun-exposed normal-appearing skin in Japanese: difference between Japanese and Caucasians. *Cancer Lett* 1999; **140**: 169–75.

Actinic keratosis [1–3]

Synonyms
- Solar keratosis
- Keratosis senilis

Definition. Hyperkeratotic lesions occurring on chronically light-exposed adult skin, which are focal areas of abnormal proliferation and differentiation that carry a low risk of progression to invasive SCC.

Aetiology and incidence. The great majority of actinic keratoses (AKs) occur on sun-exposed sites in fair-skinned people who have had excessive exposure to solar UVR [4]. Lesions with similar clinical and histological features may be induced by ionizing radiation or radiant heat and in workers exposed to pitch and other products of coal distillation.

The prevalence of these lesions is high in many countries and is influenced by the amount of ambient UV, the proportion of susceptible individuals in the population, the age structure of the population and the time spent in outdoor occupations and recreations. In the UK, a recent study has reported an overall prevalence of 15.4% in men and 5.9% in women over the age of 40 years and 34% and 18% in men and women, respectively, aged 70 years and over [5]. In areas with high ambient UVR levels such as Australia, a prevalence rate of 43% with 18% (of a population of 197) having more than 10 AKs is recorded [3]. Longitudinal studies in patients with AK have established, firstly, that there is a high probability of developing new lesions and, secondly, that many lesions undergo spontaneous resolution [6]. Although the rate of progression of an individual AK to invasive SCC has been estimated to be low (less than 0.1%), the presence of AK is an important biomarker of excessive UV exposure and increased NMSC risk [7].

Clinical features [8–10]. These lesions occur usually in middle-aged or elderly subjects on habitually sun-exposed areas such as the face, scalp and dorsa of the hands. The sides of the neck are involved in both sexes, but the ears predominantly in men. The vermilion of the lower lip but not often of the upper lip may also show keratosis, with a much higher incidence in men than women. Lesions are usually multiple and comprised of either macules or papules with a rough scaly surface resulting from disorganized keratinization and a variable degree of inflammation. Lesions vary in size from less than 1 mm to over 2 cm and are usually asymptomatic. In many individuals, the number of lesions can be better appreciated by skin palpation, which is a sensitive way of detecting the characteristic roughness associated with smaller lesions. Many of these small lesions may pass unnoticed by most patients, and the diagnostic changes often only appear later as a dry, rough, adherent and often yellow- or brown-coloured scale (Fig. 52.9).



Fig. 52.9 Multiple actinic keratoses on the dorsum of the hand of an outdoor worker.



Fig. 52.10 Pathological features of actinic keratoses showing alternating parakeratosis and hyperkeratosis.

The adherent scale can only be picked off with difficulty, revealing a hyperaemic base with punctate bleeding points. In some cases, scaling may be prominent and in time may become thick and horny. The edge of the keratosis is usually sharply demarcated and the reddening is usually closely confined to the area immediately below the area of abnormal scaling. The flat, atrophic or lichenoid variety is most commonly seen on the face.

Many patients give a history of relapsing and/or remitting lesions, which can often disappear either spontaneously or after sun avoidance and use of sunscreens.

Pathology. The boundary between unaffected and affected epidermis is a sharp line that slopes upwards and inwards, and there is a similar margin where the appendage ducts perforate the epidermis as funnel-shaped columns of orthokeratosis. The epidermal cells have a paler cytoplasm and mature through an absent or diminished granular layer to form a parakeratotic scale of varying thickness. There is usually some acanthosis, and the more dysplastic lesions show epidermal hypertrophy with hyperkeratosis and parakeratosis (Fig. 52.10). The interpapillary ridges may

be reduced in number and broader than normal. The affected zone tends to grow under the normal epidermis and around the ductal epithelium, and may separate from it by a cleft. The basement membrane is intact but basaloid cells may form multiple buds at the junction; the combination of clefting, budding and papillomatosis produces a Darier-like change. Within the epidermis there may be a simple dysplasia or a range of abnormalities up to a picture indistinguishable from Bowen's disease. These are the Bowenoid AK.

The papillary vessels are irregularly increased and there is a lymphoid infiltrate beneath the lesion. There is a variable degeneration of dermal collagen and deposition of material staining like elastin in the upper half of the dermis, except for a narrow band at the basement membrane; this change is more or less uniform, unlike the discontinuous keratosis.

The flat type of AK, most common on the face, may resemble discoid lupus erythematosus. The distinction is made by the altered epidermal cells, deficient granular layer and parakeratosis, the band-like rather than perivascular inflammatory reaction, and the absence of immunoglobulin in the basement membrane region. Occasionally, the appearance may appear pseudoepitheliomatous [8] or similar to lichen planus [9].

The occurrence of funnel-shaped columns of normal epidermis, derived from appendage ducts that appear to be trying to cover the diseased epidermis like an umbrella, suggests an effort at biological compensation [10]. It must be remembered, however, that in keratoses and Bowen's disease, sleeves of dysplastic cells growing down appendage ducts may survive damage by freezing or cytotoxic applications. The presence of an inflammatory response appears to be a warning sign of early malignant transformation [11].

Diagnosis. The diagnosis is usually based on clinical findings which take into account the morphology of individual lesions and the clinical setting. For lesions less than 3 mm, clinical discrimination from an early SCC may be difficult. This diagnostic uncertainty, particularly for small lesions, is one of the reasons why it is difficult to establish accurate rates of progression for AK to SCC. Clinical pointers favouring the diagnosis of an early invasive SCC include the presence of tenderness, induration or a raised shoulder that extends beyond the area of disorganized scaling. Other diagnoses that need to considered, particularly in patients with large confluent areas of erythema and scaling, include discoid lupus erythematosus. The brown colour of lichenoid AK, particularly when these lesions have only minimal scaling, can sometimes cause these to be mistaken for focal areas of lichen planus. When an AK is pigmented, it may resemble a superficial seborrhoeic keratosis, but can usually be distinguished from such lesions by the lack of organization of the hyperkeratosis. Bowen's disease on exposed areas usually has a more irregular contour and a more erythematous base.

Treatment. Management of patients with AK needs to begin with a thorough explanation of the nature, natural history and risks associated with the presence of these lesions. As AKs are a highly sensitive marker of levels of UV exposure capable of inducing premalignant and therefore malignant skin lesions, patients should be educated in the signs and symptoms of skin malignancy and given information in written and pictorial format to assist them in recognizing skin cancers when they occur. Having explained the above and discussed the treatment options, asymptomatic patients may decide that no treatment is required. Other patients may wish to simply use emollients. However, treatment decisions will be influenced by the symptoms the patient experiences, the confidence of the clinical diagnosis and patient anxiety about the potential for skin malignancy. Although AKs are frequently asymptomatic, the skin roughness may cause considerable distress and can be complicated by bleeding and pain because of low-grade skin trauma leading to detachment of the overlying scale. The presence of very large numbers of lesions can make it difficult for the patient or carers to see invasive malignancies at an early stage. The similarities between AK and SCC mean that there is always a small risk, particularly for small lesions less than 3 mm in diameter, that the lesion may not be an AK. Effective management of this risk requires a careful clinical assessment, a therapy plan and clear communication with the patient.

Once a decision that treatment aimed at clearing the AK has been made there are a number of options available [12]. Cryotherapy is effective for patients with a small number of lesions, and apart from hypopigmentation, generally gives excellent cosmetic results. This treatment does require a visit to a clinic and only deals with lesions within the treated area [13,14]. Other destructive therapies, such as curettage and cautery, can be useful for larger lesions and have the advantage of providing a specimen for histological assessment. However, a deep shave biopsy would provide better material for histological examination for evidence of invasion. Alternatively, small hyperkeratotic lesions treated by curettage and cautery with two or more cycles would have adequately treated a small, low-risk, well-differentiated SCC. Where there is significant diagnostic uncertainty, lesions are best excised for pathological examination of the base to be certain that the lesion is not an early invasive SCC.

In many patients, the number of lesions or the rate of development of new lesions makes management more difficult using approaches such as cryotherapy. For patients with extensive clinical lesions, a number of approaches are available that allow treatment of large areas of AK in severely photodamaged skin. Many of these treatments offer the added advantage that they also target early lesions, which means that a more sustained clinical effect may be achieved. These treatments can be subdivided into two broad groups based on their ease of use. The first group includes topical 5-fluorouracil, diclofenac in hyaluron gel and imiquimod which are effective therapies for AK [15–18]. Although 5-fluorouracil is an effective therapy, the marked local inflammation that commonly develops after 2–4 weeks of treatment may make it unacceptable to patients. Once-weekly application for 9 weeks with 5-fluorouracil has been shown, in a small study, to reduce the treatment-induced inflammation while maintaining efficacy [19]. A recent study has surprisingly reported greater efficacy and fewer side effects in patients treated with 0.5% fluorouracil cream compared with 5% fluorouracil cream [20]. The relative effectiveness and tolerability of 5-fluorouracil and diclofenac in hyaluron gel have not as yet been formally addressed in a clinical trial. A number of other approaches, including retinoids, are currently

being investigated as topical therapies for AK [21]. The second group of therapies involves procedures that are normally carried out in the office or clinic setting and includes PDT, dermabrasion and chemical peels. PDT with topical 6-aminolaevulinic acid has been shown to be an effective, well-tolerated therapy for patients with widespread photodamage and AK [22]. A recent comparison of PDT with cryotherapy has established that PDT is as effective as cryotherapy and superior to the latter in patient satisfaction and cosmetic result [23–25]. Dermabrasion and chemical peels have been widely used in some countries for the treatment of AK and severe photodamage. There is some evidence that this approach may provide more long-term, effective prophylaxis against AK [26].

The demonstration that regular sunscreen use reduces the rate of development of new AK indicates that continuing UVR exposure plays an important role in promoting the development of clinical lesions and highlights the importance of ensuring that patients with AK are provided with practical advice on sun-avoidance strategies [27].

References

1 Marks R. Non-melanoma skin cancer and solar keratoses in Australia. *Eur J Epidemiol* 1985; **1**: 319–22.
2 Marks R, Ponsford MW, Selwood TS *et al.* Non-melanotic skin cancer and solar keratoses in Victoria. *Med J Aust* 1983; **2**: 619–22.
3 Frost CA, Green AC, Williams GM. The prevalence and determinants of solar keratoses at subtropical latitude. *Br J Dermatol* 1998; **139**: 1033–9.
4 Freeman RG. Carcinogenic effect of solar radiation and prevention measures. *Cancer* 1968; **21**: 1114–20.
5 Memon AA, Tomenson JA, Bothwell J, Friedmann PS. Prevalence of solar damage and actinic keratosis in a Merseyside population. *Br J Dermatol* 2000; **142**: 1154–9.
6 Marks R, Foley P, Goodman G *et al*. Spontaneous remission of solar keratoses: the case for conservative management. *Br J Dermatol* 1986; **115**: 649–55.
7 Salasche SJ. Epidemiology of actinic keratoses and squamous cell carcinoma. *J Am Acad Dermatol* 2000; **42**: 4–7.
8 Pinkus H. Keratosis senilis: a biologic concept of its pathogenesis and diagnosis based on the study of normal epidermis and 1730 seborrhoeic and senile keratoses. *Am J Clin Pathol* 1958; **29**: 193–207.
9 Shapiro L, Ackermann AB. Solitary lichen planus like actinic keratoses. *Dermatologica* 1966; **132**: 386–92.
10 Civatte J, Schnitzler L, Belaïch S. Hyperplasie pseudo-épithéliomateuse du dos des mains. *Ann Dermatol Syphiligr* 1973; **100**: 29–48.
11 Berhane T, Halliday GM, Cooke B, Barnetson RS. Inflammation is associated with progression of actinic keratoses to squamous cell carcinoma in humans. *Br J Dermatol* 2002; **146**: 810–5.
12 de Berker D, McGregor JM, Hughes BR, on behalf of the British Association of Dermatologists Therapy Guidelines and Audit Subcommittee. Guidelines for the management of actinic keratoses. *Br J Dermatol* 2007; **156**: 222–30.
13 Szeimies RM, Karrer S, Radakovic-Fijan S *et al*. Photodynamic therapy using topical methyl 5-aminolevulinate compared with cryotherapy for actinic keratosis: a prospective, randomized study. *J Am Acad Dermatol* 2002; **47**: 258–62.
14 Freeman M, Vinciullo C, Francis D *et al*. A comparison of photodynamic therapy using topical methyl aminolevulinate (Metvix) with single cycle cryotherapy in patients with actinic keratosis: a prospective, randomized study. *Dermatolog Treat* 2003; **14**: 99–106.
15 Goette DK. Topical chemotherapy with 5-fluorouracil: a review. *J Am Acad Dermatol* 1981; **4**: 633–49.
16 Rivers JK, Arlette J, Shear N *et al.* Topical treatment of actinic keratoses with 3.0% diclofenac in 2.5% hyaluronan gel. *Br J Dermatol* 2002; **146**: 94–100.
17 Wolf JE, Taylor JR, Tschen E, Kang S. Topical 3% diclofenac in 22.5% hyaluronan gel in the treatment of actinic keratoses. *Int J Dermatol* 2001; **40**: 709–13.
18 Hadley G, Derry S, Moore RA. Imiquimod for actinic keratosis: systematic review and meta analysis. *J Dermatol* 2006; **126**: 1251–5.
19 Pearlman DL. Weekly pulse dosing: effective and comfortable 5-fluouracil treatment of multiple facial actinic keratoses. *J Am Acad Dermatol* 1991; **25**: 665–7.
20 Loven K, Stein L, Furst K, Levy S. Evaluation of the efficacy and tolerability of 0.5% fluouracil cream and 5% fluouracil cream applied to each side of the face in patients with actinic keratoses. *Clin Ther* 2002; **24**: 990–1000.
21 Kang S, Goldfarb MT, Weiss JB *et al.* Assessment of adapalene gel for the treatment of actinic keratoses and lentigines: a randomized trial. *J Am Acad Dermatol* 2003; **49**: 83–90.
22 Dijkstra AT, Majoie IM, van Dongen JW *et al*. Photodynamic therapy with violet light and topical 6-aminolaevulinic acid in the treatment of actinic keratosis, Bowen's disease and basal cell carcinoma. *J Eur Acad Dermatol Venereol* 2001; **15**: 550–4.
23 Szeimies RM, Karrer S, Radakovic-Fijan S *et al.* Photodynamic therapy using topical methyl 5-aminolevulinate compared with cryotherapy for actinic keratosis: a prospective, randomized study. *J Am Acad Dermatol* 2002; **47**: 258–62.
24 Morton CA, Campbell S, Gupta G *et al*. Intraindividual, right-left comparison of topical methyl aminolaevulinate-photodynamic therapy and cryotherapy in subjects with actinic keratoses: a multicentre, randomized controlled study. *Br J Dermatol* 2006; **155**: 1029–36.
25 Kaufmann R, Spelman L, Weightman W *et al*. Multicentre intra-individual randomized trial of topical methyl aminolaevulinate-photodynamic therapy vs. cryotherapy for multiple actinic keratoses on the extremities. *Br J Dermatol* 2008; **158**: 994–9.
26 Coleman WP III, Yarborough JM, Mandy SH. Dermabrasion for prophylaxis and treatment of actinic keratoses. *Dermatol Surg* 1996; **22**: 17–21.
27 Thompson SC, Jolley D, Marks R. Reduction of solar keratoses by regular sunscreen use. *N Engl J Med* 1993; **329**: 1147–51.

Bowen's disease [1,2]

Definition. A form of intraepidermal SCC characterized by a persistent, non-elevated, red, scaly or crusted plaque with a small potential for invasive malignancy. Progressive growth is usual but spontaneous partial regression occurs occasionally.

Aetiology and incidence. Most cases of typical Bowen's disease in white populations are found on the lower legs of elderly women. The distribution in the context of differences between men and women in coverage of the lower leg by clothing and molecular epidemiological evidence of UVR-specific *p*53 mutations in typical Bowen's disease suggests that exposure to solar radiation is an important cause of these lesions [3]. Bowen's disease is uncommon in individuals with pigmented skin and, in these individuals, aetiological factors other than UVR exposure may be important [4].

In the past, arsenic exposure was also important [5]. Although fewer than 5% of a large series of patients with Bowen's disease gave a history of ingestion of arsenic containing medications, arsenic was found in a significantly higher proportion of the skin of patients than in that of the controls [6]. The possible sources of arsenic vary in different localities. Agricultural workers may be exposed to arsenic salts used as a fungicide, weedkiller, sheep dip or pesticide, and they frequently take inadequate precautions against accidental ingestion or inhalation. It may be a hazard in smelting and other industrial processes. In some countries, notably parts of Argentina, Bangladesh and Taiwan, the water supply has been contaminated [7].

Clinical features [8,9]. Although the lesions may occur anywhere on the skin surface or on mucosal surfaces, they are most frequently found on the lower legs of elderly women. The initial

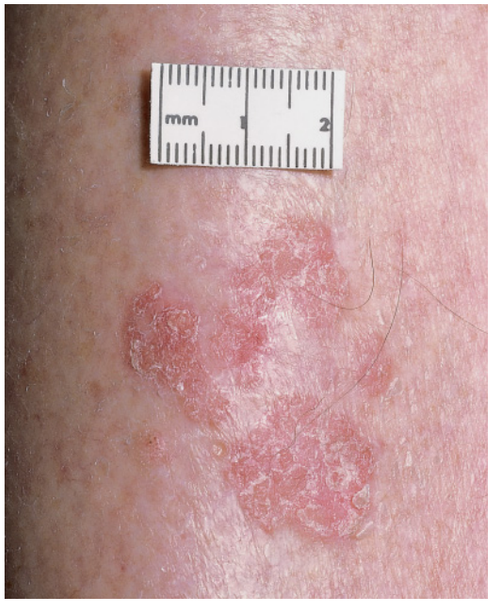


Fig. 52.11 Area of Bowen's disease on lower leg.



Fig. 52.12 Bowen's disease on the lower leg of a patient with a history of arsenic contact.

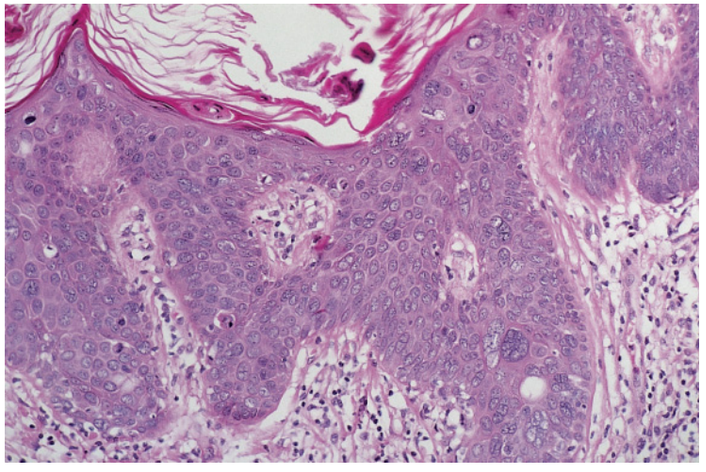


Fig. 52.13 Typical pathological features of Bowen's disease showing loss of polarity of the epidermis and the presence of atypical mitoses and giant cells.

change is a small, red and slightly scaly area, which is symptomless and gradually enlarges in a somewhat irregular fashion. The white or yellowish scale is detached without much difficulty to give a moist, reddened and at times granular surface, but without producing bleeding (Fig. 52.11). The margin is well-demarcated and the lesion slightly raised; the surface is usually flat, but may become hyperkeratotic or crusted. Ulceration is usually a sign of development of invasive carcinoma, and may be delayed for many years after the appearance of the intraepidermal change. Persistent superficial ulceration may, however, be the early clinical evidence of Bowen's disease of palmar skin without invasion. There may be several lesions, either widely spread or sometimes close together and becoming confluent with extension.

When there is good evidence of chronic arsenicalism (Fig. 52.12), either from the history or because of associated changes such as pigmentation or punctate palmoplantar keratoses, the possible evolution of a visceral malignancy, especially of the lung, should be borne in mind. Although studies in the 1950s suggested that there was a significant link between the presence of Bowen's disease on the skin and internal malignancy [10–14], more recent studies using carefully selected control populations have failed to confirm these results [15–19].

Pathology [20]. The normal epidermis is replaced by abnormal keratinocytes, which show disordered differentiation and loss of epithelial polarity. There is variable acanthosis, with increase in the length and thickness of the interpapillary ridges but retention of a distinct dermal–epidermal junction. The atypical cells have hyperchromatic nuclei, often larger than normal, giving an irregular appearance to the epidermis. Giant forms and multinucleate cells are seen and mitotic figures can be frequent (Fig. 52.13). There is a conspicuous disturbance of epidermal organization, and cells keratinize prematurely and lose their intercellular connections. The surface is formed by a thickened, loose, parakeratotic scale. The papillary body shows an inflammatory infiltrate that is often quite dense. In some cases, the proliferating cells may be surrounded by relatively normal epidermal cells to give a 'Borst–Jadassohn' appearance. The epidermis above the ducts of appendages may be normal, as in AK, but the cells of the lesion of Bowen's disease often grow down around the ducts like a collar. The condition can become invasive, and when it does it is always squamous cell in type. Arsenical Bowen's disease is said to be characterized by the presence of numerous vacuolated atypical cells. Electron microscope features have been described [21–24].

Diagnosis. The condition must be distinguished from lichen simplex, psoriasis and other papulosquamous dermatoses. If the diagnosis is uncertain on the first examination, the lack of improvement when steroids are applied is suggestive of Bowen's disease. The superficial ('pagetoid') type of BCC can produce a very similar appearance, but can usually be differentiated by the finely

elevated, 'thread-like' margin. Bowen's disease and superficial BCC can be seen in the same patient. Differentiation from the flat type of solar keratosis may be impossible.

Treatment [24]. There is a wide range of therapeutic options available for the treatment of Bowen's disease including: cryotherapy; curettage and cautery; PDT; laser destruction; excision; 5-fluorouracil cream; imiquimod cream; and radiotherapy. The preferred treatment option is based on a number of factors including size of lesion, site, previous treatment, experience of the various treatments and the number of lesions. Destructive therapies such as curettage and cautery, or cryotherapy are widely used in clinical practice. Comparison of the relative effectiveness of different therapies and regimens is difficult as published studies do not fully control for factors such as site and size and there are inconsistencies between treatment regimens used at different centres. Cryotherapy is an effective therapy with a recurrence rate when used optimally of less than 10% at 12 months. Regimens used include single freeze–thaw cycles, single freeze–thaw cycles repeated on more than one visit and multiple freeze–thaw cycles repeated at a single visit [25–27]. Prolonged single freeze cycles for larger lesions is painful and may be better performed under local anaesthesia. Slow healing can be a problem, particularly for lesions on the lower leg. Curettage and cautery is widely used in practice but poorly studied. Reported recurrence rates are higher than those described with cryotherapy but these findings are difficult to interpret as treatment regimens and equipment are poorly described. Surgical excision is a useful approach, particularly for small lesions in poor healing sites, perineal lesions and digital lesions.

Local cytotoxic agents such as 5-fluorouracil can be applied to good effect. Treatment regimens vary and include once daily application of a 5% cream for 4–8 weeks or more prolonged treatment using a once-weekly application. There is some evidence that occlusion may increase efficacy. Recurrences are common, and may come from extensions of the carcinoma *in situ* around appendage ducts that were unaffected by treatment. Current studies suggest that PDT, using a topical photosensitizer such as aminolaevulinic acid and a laser or non-laser light source may also be an effective method of treatment [24,27–29]. Imiquimod has been used in uncontrolled trials for the treatment of Bowen's disease and in one randomized controlled trial [30] which demonstrated good efficacy but with a suboptimal dosing schedule. Further work is required.

References

1 Bowen JT. Precancerous dermatosis. *J Cutan Dis* 1912; **30**: 241–55.
2 Bowen JT. Precancerous dermatosis: the further course of two cases previously reported. *Arch Dermatol* 1920; **1**: 23–4.
3 Campbell C, Quinn AG, Ro YS *et al*. *p53* mutations are common and early events that precede tumor invasion in squamous cell neoplasia of the skin. *J Invest Dermatol* 1993; **100**: 746.
4 Sau P, McMarlin SL, Sperling LC, Katz R. Bowen's disease of the nail bed and periungual area: a clinicopathologic analysis of seven cases. *Arch Dermatol* 1994; **130**: 204–9.
5 Graham JH, Helwig EB. Bowen's disease and its relationship to systemic cancer. *Arch Dermatol* 1959; **80**: 133–59.
6 Graham JH, Mazzanti GR, Helwig EB. Chemistry of Bowen's disease: relationship to arsenic. *J Invest Dermatol* 1961; **37**: 317–32.
7 Tseng WP, Chu HM, How SW *et al*. Prevalence of skin cancer in an endemic area of chronic arsenicism in Taiwan. *J Natl Cancer Inst* 1968; **40**: 453–63.
8 Callen JP, Headington J. Bowen's and non-Bowen's squamous intraepidermal neoplasia of the skin. *Arch Dermatol* 1980; **116**: 422–6.
9 Sanderson KV. Multicentric pigmented Bowen's disease. *Proc R Soc Med* 1974; **67**: 23–4.
10 Andersen SLC, Nielsen A, Reymann F. Relationship between Bowen's disease and internal malignant tumours. *Arch Dermatol* 1973; **108**: 367–70.
11 Epstein E. Association of Bowen's disease with visceral cancer. *Arch Dermatol* 1960; **82**: 349–51.
12 Kao GF. Carcinoma arising in Bowen's disease. *Arch Dermatol* 1986; **122**: 1124–6.
13 Kao GF, Graham JH. Premalignant and malignant cutaneous disorders of the head and neck. In: English GM, *Otolaryngology*, Vol 5. New York: Harper & Row, 1986.
14 Peterka ES, Lynch FW, Goltz RW. An association between Bowen's disease and internal cancer. *Arch Dermatol* 1961; **84**: 623–9.
15 Arbesmann H, Ranshoff DF. Is Bowen's disease a predictor for the development of internal malignancy? A methodological critique of the literature. *JAMA* 1987; **257**: 516–8.
16 Chuang TY, Reizner GT. Bowen's disease and internal malignancy. *J Am Acad Dermatol* 1988; **19**: 47–51.
17 Lycka BAS. Bowen's disease and internal malignancy: a meta-analysis. *Int J Dermatol* 1989; **28**: 531–3.
18 Moller R, Nielsen A, Reymann F *et al*. Squamous cell carcinoma of the skin and internal malignant neoplasms. *Arch Dermatol* 1979; **115**: 304–5.
19 Reymann F, Ravnborg L, Schon G *et al*. Bowen's disease and internal malignant disease. *Arch Dermatol* 1988; **124**: 677–9.
20 Brownstein MH, Rabinowitz AD. The precursors of squamous cell carcinoma. *Int J Dermatol* 1979; **18**: 1–16.
21 Ehlers G. Klinische und histologische Untersuchungen zur frage arzneimittelbedingter Arsen-Tumoren. *Z Haut Geschlechts-Krankheiten* 1968; **43**: 763–74.
22 Seiji M, Mizuno F. Electron microscopic study of Bowen's disease. *Arch Dermatol* 1969; **99**: 3–16.
23 Yeh S, Chen HC, How SW *et al*. Fine structure of Bowen's disease in chronic arsenicalism. *J Natl Cancer Inst* 1975; **53**: 31–3.
24 Cox NH, Eedy DJ, Morton CA. Guidelines for management of Bowen's disease. British Association of Dermatologists. *Br J Dermatol* 2007; **156**: 11–21.
25 Holt PJ. Cryotherapy for skin cancer: results over a 5-year period using liquid nitrogen spray cryosurgery. *Br J Dermatol* 1988; **119**: 231–40.
26 Cox NH, Dyson P. Wound healing on the lower leg after radiotherapy or cryotherapy of Bowen's disease and other malignant skin lesions. *Br J Dermatol* 1995; **133**: 60–5.
27 Morton CA, Whitehurst C, Moseley H *et al*. Comparison of photodynamic therapy with cryotherapy in the treatment of Bowen's disease. *Br J Dermatol* 1996; **135**: 766–71.
28 Morton CA, Whitehurst C, McColl JH *et al*. Photodynamic therapy for large or multiple patches of Bowen disease and basal cell carcinoma. *Arch Dermatol* 2001; **137**: 319–24.
29 Morton CA, Horn M, Leman J *et al*. Comparison of topical methyl aminolevulinate photodynamic therapy with cryotherapy or fluorouracil for treatment of squamous cell carcinoma in situ: results of a multicenter randomized trial. *Arch Dermatol* 2006; **142**: 729–35.
30 Patel GK, Goodwin R, Chawla M *et al*. Imiquimod 5% cream monotherapy for cutaneous squamous cell carcinoma in situ (Bowen's disease): a randomised, double-blind, placebo-controlled trial. *J Am Acad Dermatol* 2006; **54**: 1025–32.

Arsenical keratosis

Definition. A corn-like, punctate keratosis caused by arsenic, characteristically affecting the palms and soles, which may progress to SCC.

Incidence. A considerable proportion of any population exposed to chronic arsenic intoxication develops keratoses, the frequency increasing with the degree of intoxication and its duration [1]. There is great individual variation in tolerance, and it is not

possible, on present data, to construct a precise dose–response curve. The problem is greatest in parts of Bangladesh, West Bengal and Taiwan resulting from well water contamination [2].

Clinical features. The keratoses usually begin on the palms or soles as small areas of hyperkeratosis resembling corns. These enlarge, thicken and increase in number. The fingers, backs of the hands and more proximal parts of the extremities may be involved. Induration, inflammation and ulceration occur when the lesion becomes malignant. There may be areas of Bowen's disease in other sites and multiple BCCs, mainly of the trunk, may occur in association.

Pathology. A range of changes may be seen from a benign-looking hyperplasia or dysplasia, through mild or moderate atypia, to frank Bowen's disease [3–5]. There is no microscopic feature that allows a positive diagnosis of arsenic as the cause. In most lesions there is no elastotic degeneration of the upper dermis.

Diagnosis. The palmar lesions have to be differentiated from the various types of punctate keratosis, such as disseminated punctate keratoderma (see Chapter 19), which usually appears in early life, and Darier's disease and lichen planus, which usually have characteristic lesions elsewhere. Plantar warts differ in being papillomatous.

Treatment. The multiplicity of the keratoses makes treatment difficult. Where it is necessary, the use of a keratolytic ointment and trimming down of the surface is helpful. Two recent case reports suggest that oral acetretin may be beneficial [6]. All affected patients should be examined periodically for evidence of malignant change and for signs of visceral malignancy.

References

1 Montgomery H, Waisman M. Epithelioma attributable to arsenic. *J Invest Dermatol* 1941; **4**: 365–83.

2 Rahman MM, Chowdury UK, Mukherjee SC *et al.* Chronic arsenic toxicity in Bangladesh and West Bengal: a review and commentary. *J Toxicol Clin Toxicol* 2001; **39**: 683–700.

3 Hundeiker M, Petres J. Morphogenese und formenreichtum der arseninduzierten Präkanzerosen. *Arch Klin Exp Dermatol* 1968; **231**: 355–65.

4 Yeh S, How SW, Lin CS. Arsenical cancer of skin: histologic study with special reference to Bowen's disease. *Cancer* 1968; **21**: 312–39.

5 Centeno JA, Mullick FG, Martinez L *et al.* Pathology related to chronic arsenic exposure. *Environ Health Perspect* 2002; **110** (Suppl. 5): 883–6.

6 Yerebakan O, Ermis O, Yilmaz E, Basaran E. Treatment of arsenical keratoses and Bowen's disease with acetretin. *Int J Dermatol* 2002; **41**: 84–7.

Disseminated superficial 'actinic' porokeratosis

This disorder was first recognized in Texas [1,2], and is common in Australia [3]. It appears on sun-exposed areas of white-skinned individuals, becomes more prominent in summer and may improve in winter. New lesions have been provoked by exposure to a UV sun lamp [4]. The tendency to develop these lesions is inherited as an autosomal dominant [4]. The preponderance of females in reported cases has been attributed to their greater tendency to seek help for skin problems. The average age at which Texan patients first notice it is about 40 years, and its frequency in members of affected families increases with age. There are UK patients with multiple lesions who have never lived abroad, and the true role of the sun in the aetiology of the condition has been questioned, as has its degree of premalignant potential [5,6]. Genetic studies have mapped a gene, *DSAP1*, for this condition to chromosome 12q23.2–24.1 and a Chinese family with disseminated superficial 'actinic' porokeratosis (DSAP) has recently been reported with a second affected locus, *DSAP2*, on chromosome 15q25.1–26.1 [7].

Clinical features [2]. The lesion begins as a 1–3 mm conical papule, brownish red or brown in colour, and usually around a follicle containing a keratotic plug. It expands and a sharp, slightly raised, keratotic ring, a fraction of a millimetre thick, develops and spreads out to a diameter of 10 mm or more. The skin within the ring is somewhat atrophic and mildly reddened or hyperpigmented, but a hypopigmented ring may be seen just inside the ridge. The ridge itself is sometimes darkly pigmented. The central thickening usually disappears, but it may persist with an attached scale, follicular plug or central dell. Sweating is absent within the lesions. Sun exposure may cause them to itch. In sunny areas, lesions may be present in very large numbers and may change from a circular to a polycyclic outline. In less sunny climates, such as the UK, patients have fewer lesions, which tend to remain circular (Fig. 52.14). In a few cases, the centre of the area has become considerably inflamed and covered by thick hyperkeratosis, or has even ulcerated and crusted. The disorder affects areas exposed to sunlight, appearing mainly on the distal extremities and arising more frequently on the lower legs in women than men. The malar regions and the cheeks may be affected. It has not been seen on areas habitually covered by clothes, or on the palms or soles.



Fig. 52.14 Disseminated superficial actinic porokeratosis on the lower legs.

Pathology [8]. There is no microscopic feature that separates this disorder from porokeratosis of Mibelli (see Chapter 19), and both have been explained as the result of localized clones of abnormal epidermal cells [8], an idea supported by the successful autotransplantation of the disseminated superficial variety [4].

The distinctive pathological feature of porokeratosis is the cornoid lamella at the margin. This is a narrow column of altered or parakeratotic keratin, seated in a slight depression in the epidermis and directed obliquely inwards in some cases. It may involve the ostia of follicles and sweat ducts. The granular layer of the indented epidermis is usually missing and there may be dyskeratotic cells. The epidermis enclosed by the ridge is usually thinned, the interpapillary ridges and dermal papillae may be flattened, and the basal cells may show liquefaction degeneration. In addition to solar elastosis, decrease in collagen and telangiectasia, the upper dermis may have a non-specific inflammatory infiltrate with vascular proliferation, oedema and fibrosis. Malignant change has not been recorded.

Diagnosis. Porokeratosis is distinguished from other dermatoses by its sharp margin and history of outward expansion. The rim of DSAP is very much smaller than in Mibelli's porokeratosis and never contains a cleft. The onset of Mibelli's porokeratosis is often in childhood, and the lesions are usually solitary or few in number and do not necessarily affect exposed parts. Where the central keratosis and inflammation are prominent, the disseminated superficial variety may be mistaken for solar keratosis if the marginal ridge is not noticed.

Treatment. Lesions respond satisfactorily to cryotherapy with liquid nitrogen, but new lesions tend to develop [2,3].

References

1 Chernosky ME, Anderson DE. Disseminated superficial actinic porokeratosis: genetic aspects. *Arch Dermatol* 1969; **99**: 408–12.
2 Chernosky ME, Freeman RG. Disseminated superficial actinic porokeratosis (DSAP). *Arch Dermatol* 1967; **96**: 611–24.
3 Donald GF, Hunter GA. Disseminated superficial actinic porokeratosis: a report of eight cases. *Aust J Dermatol* 1968; **9**: 335–44.
4 Chernosky ME, Anderson DE. Disseminated superficial actinic porokeratosis. *Arch Dermatol* 1969; **99**: 401–7.
5 Goerttler EA, Jung EG. Porokeratosis Mibelli and skin carcinoma: a critical review. *Humangenetik* 1975; **26**: 291–6.
6 Shumack SP, Commens CA. Disseminated superficial actinic porokeratosis: a clinical study. *J Am Acad Dermatol* 1989; **20**: 1015–8.
7 Xia K, Deng H, Xia HJ *et al.* A novel locus for disseminated superficial actinic porokeratosis maps to chromosome 15q25.1–26.1. *Br J Dermatol* 2002; **147**: 650–4.
8 Reed RJ, Leone P. Porokeratosis: a mutant clonal keratosis of the epidermis. *Arch Dermatol* 1970; **101**: 340–3.

Cutaneous horn [1]

This is a clinical diagnosis. Horny plugs or outgrowths may be caused by various epidermal changes, such as epidermal naevus, virus wart, molluscum contagiosum, keratoacanthoma, seborrhoeic keratosis, or marsupialized trichilemmal or epidermoid cyst (Fig. 52.15). In most of these cases, the primary diagnosis is suggested by the appearance and clinical course and, in most, the horn has a friable quality.

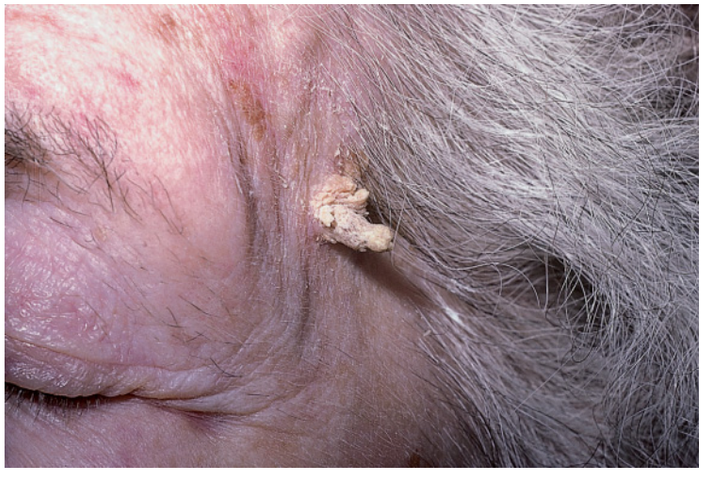


Fig. 52.15 Typical cutaneous horn. Underlying this lesion, a carcinoma *in situ* was identified after biopsy.

Clinical features. Clinical examination shows a hard, yellowish brown horn, often curved and having circumferential ridges, which is surrounded either by normal-looking epidermis or by an acanthotic collarette. Recurrent injury may cause the base to be inflamed; a combination of inflammation and induration beneath the horn is suggestive of malignant transformation. The lesions are most common on the exposed areas—particularly the upper part of the face and the ears. They are commonly single, but may be multiple; it is usual to find some more typical solar keratosis or other evidence of solar damage. Nodular AKs, which are largely confined to the dorsum of the hand and forearm and in which the histology may show an almost pseudoepitheliomatous picture, occupy a position midway between cutaneous horns and the more usual flat AKs.

Pathology. The gradual continuing development from relatively normal-looking skin to a hard keratotic protrusion resembling an animal horn in miniature is the result of dysplastic epidermal changes similar to those in a solar keratosis. Histologically, there is usually no atypicality or loss of polarity of the epidermal cells, but the granular layer is deficient or absent. In long-established lesions there may be budding from the basal layer, indicating early development of an SCC.

Reference

1 Bondeson J. Everard Home, John Hunter and cutaneous horns: a historical review. *Am J Dermatopathol* 2001; **23**: 362–9.

Erythroplasia of Queyrat [1–3]

This condition is described with the genital disorders (see Chapter 71). The histological appearance and natural history suggest that the lesion is Bowen's disease of the mucosa of the penis. However, its prevalence only in the uncircumcised indicates a different and locally acting cause.

References

1 Queyrat L. Erythroplasie du gland. *Bull Fr Soc Dermatol Syph* 1911; **22**: 378–82.
2 Goette DK. Erythroplasia of Queyrat. *Arch Dermatol* 1974; **110**: 271–3.

3 Porter WM, Hawkins D, Dineen M, Bunker CB. Penile intraepithelial neoplasis: clinical spectrum and treatment of 35 cases. *Br J Dermatol* 2002; **147**: 1159–65.

Bowenoid papulosis of the genitalia [1]

This entity is fully discussed in Chapter 71. Bowenoid papulosis (BP) is characterized clinically by lesions with a benign appearance which show histological features suggestive of squamous cell neoplasia. Most of the lesions either regress spontaneously over time or undergo resolution after local treatment. BP is now generally viewed as a localized form of *in situ* SCC which develops as a consequence of infection by high-risk human papillomavirus, especially HPV 16 and HPV 18 (reviewed in [2]). In the older literature, cases which would today be classified as BP have been reported as Bowen's disease [3–5]. Treatment of BP traditionally has included locally destructive therapies such as excisional surgery, electrocoagulation, cryotherapy and 5-fluorouracil. A number of groups have recently reported successful clearance of Bowenoid papulosis using imiquimod cream 5% [6,7].

References

1 Wade TR, Kopf AW, Ackerman AB. Bowenoid papulosis of the genitalia. *Arch Dermatol* 1979; **115**: 306–8.
2 Liu H, Urabe K, Moroi Y *et al*. Expression of p16 and hTERT protein is associated with the presence of high-risk human papillomavirus in Bowenoid papulosis. *J Cutan Pathol* 2006; **33**: 551–8.
3 Emmerson RW. Multicentric pigmented Bowen's disease of the perineum. *Proc R Soc Med* 1975; **68**: 345–6.
4 Lloyd KM. Multicentric pigmented Bowen's disease of the groin. *Arch Dermatol* 1970; **101**: 48–51.
5 Berger BW, Hori Y. Multicentric Bowen's disease of the genitalia. *Arch Dermatol* 1978; **114**: 1698–9.
6 Goorney BP, Polori R. A case of Bowenoid papulosis of the penis successfully treated with topical imiquimod cream 5%. *Int J STD AIDS* 2004; **15**: 833–5.
7 Richter ON, Petrow W, Wardelmann E *et al*. Bowenoid papulosis of the vulva—immunotherapeutical approach with topical imiquimod. *Arch Gynecol Obstet* 2003; **268**: 333–6.

Intraepidermal carcinoma of the eyelid margin

This condition (see Chapter 67), which may resemble a banal warty lesion in its early stages, represented about 6% of all eyelid malignancies in one series [1]. Occupational exposure to oils and grease may be important. The dysplastic changes seen on biopsy may not be sufficiently severe to warn of the dangers of inadequate treatment. One clue is the way the intraepidermal carcinoma invades the deepest ciliary adnexae, causing loss of eyelashes and nodularity of the margin on clinical examination. SCC may supervene and complete excision is essential.

Reference

1 McCallum DI, Kinmont PDC, Williams DW *et al*. Intra-epidermal carcinoma of the eyelid margin. *Br J Dermatol* 1975; **93**: 239–52.

Leukokeratosis of the lips

Synonym

- Actinic cheilitis [1]

Actinic cheilitis is a pathologic condition which affects predominately the lower lip and is caused by chronic and excessive exposure of the lips to solar radiation. This disorder is described in more detail in Chapter 69. Patients are frequently male outdoor workers who usually give a history of recurrent sunburn of the lips. The lower lip often shows persistent dry scaling, a tendency to fissure and atrophic changes beneath and around the keratosis. The use of lipstick by women may be protective [2], especially in preventing dehydration. Actinic cheilitis is relatively common in renal transplant recipients [3]. A number of studies suggest that progression to SCC may be more common than previously recognized. In one series, 11 of 65 cases progressed to SCC [4]. Careful follow-up is important as it is also recognized that SCC of the lip metastasize four times as frequently as cutaneous ones [5].

Treatment. A number of treatments have been described including surgical excision, cryotherapy, carbon dioxide laser ablation, electrosurgery and the topical use of 5-fluorouracil. Successful treatment has also been described with newer modalities including PDT [6].

References

1 Kaugars GE, Pillion T, Svirsky JA *et al*. Actinic cheilitis: a review of 152 cases. *Oral Med Oral Surg Oral Pathol* 1999; **88**: 181–6.
2 Wynder EL, Bross IJ. Aetiological factors in mouth cancer. *BMJ* 1957; **i**: 1137–43.
3 King GN, Healy CM, Glover MT *et al*. Increased prevalence of dysplastic and malignant lip lesions in renal-transplant recipients. *N Engl J Med* 1995; **332**: 1052–7.
4 Markopoulos A, Banidou-Farmaki E, Kayavis I. Actinic cheilitis: clinical and pathologic characteristics in 65 cases. *Oral Dis* 2004; **10**: 212–6.
5 Stender IM, Wulf HC. Photodynamic therapy with 5-aminolevulinic acid in the treatment of actinic cheilitis. *Br J Dermatol* 1996; **135**: 454–6.
6 Berking C, Herzinger T, Flaig MJ *et al*. The efficacy of photodynamic therapy in actinic cheilitis of the lower lip: a prospective study of 15 patients. *Dermatol Surg* 2007; **33**: 825–30.

Post-ionizing radiation keratoses

These may occur in an area of scarring following radiotherapy or excessive fluoroscopy where there is obvious dermal damage. They may also be seen in radiologists, surgeons, dentists and others who have exposed their skin to frequent small doses of X-rays and where the dermis is less grossly changed, although such cases are now rare. The epidermal changes are similar to solar keratosis. Histologically, the dermis shows a much more extensive replacement of collagen by scar and elastotic material, obliterative changes in the vessels and, at times, the presence of abnormally large and irregular fibroblasts (Fig. 52.16).

Tar keratoses [1–4]

These are now very rare entities. In the past, they were seen in workers with tar and pitch. There were small keratotic plaques, not unlike plane warts, or flat seborrhoeic keratoses on the face and hands, which have the microscopic features of benign acanthomas. These usually disappeared when the exposure ceased. There were also lesions resembling solar keratoses, which persisted and a few became malignant. Other lesions with the appearance of keratoacanthomas were seen. Their course was usually more prolonged and, particularly on the scrotum, a relatively high proportion became malignant.

References

1 Fisher REW. *Proceedings of the 13th International Congress on Occupational Health*. 1961: 250.

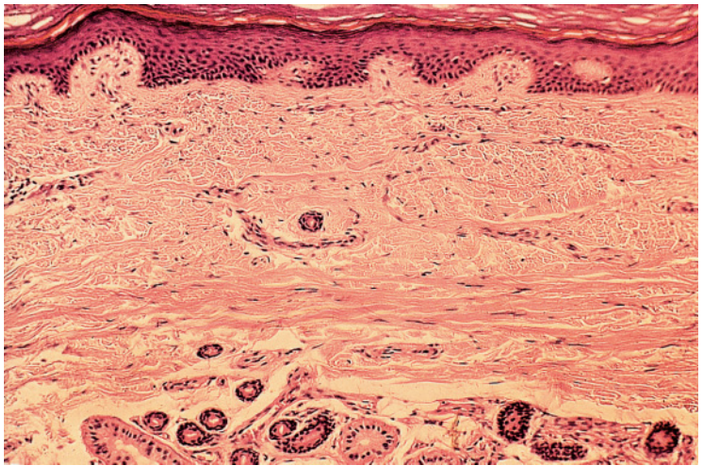


Fig. 52.16 Pathological appearance of radiodermatitis showing a scarred dermis with loss of skin appendages.



Fig. 52.17 Seborrhoeic keratosis showing dull, non-reflective, hyperkeratotic surface. This contrasts with melanocytic lesions.

2 Fisher REW. *Trans Assoc Ind Med Off* 1965; **15**: 122.
3 Colomb D, Descos L, Gauthier D. Kérato-acanthomes multiples et maladie du brai de houille. *Rev Lyonnaise Med* 1966; **15**: 449–62.
4 Letzel S, Drexler H. Occupationally related tumors in tar refinery workers. *J Am Acad Dermatol* 1998; **39**: 712–20.

Benign epidermal tumours

Seborrhoeic keratosis

Synonyms
- Seborrhoeic wart
- Senile wart
- Basal cell papilloma

Definition. A benign tumour, frequently pigmented, more common in the elderly and composed of epidermal keratinocytes.

Aetiology and incidence. Seborrhoeic keratoses (SKs) are common skin lesions that occur with increasing age; usually appear in the fifth decade in a temperate climate but may develop earlier in tropical regions. There is little tendency to spontaneous disappearance and new lesions may continue to appear for many years. Males and females are equally affected.

Although extremely common, the epidemiology is not well characterized in most populations. In studies from Australia these lesions were identified in 30% of subjects under the age of 30 years increasing to 100% of subjects older than 50 years [1]. The overall prevalence in a UK population was slightly lower with lesions identified in approximately 75% of subjects over the age of 70 years [2]. The total number and size of SKs has also been shown to increase with age. Most lesions are found on the trunk with a smaller number on the limbs, head and neck; in the Australian population no correlation was found with traditional markers of skin sensitivity to ultraviolet radiation. The rapid development of large numbers of SKs can occur in patients with an inflammatory dermatosis [3] or in association with underlying malignancies where it is known as the sign of Leser–Trélat [4]. The neoplasms most commonly associated with this skin manifestation include stomach and colon cancer and in some patients it may be associated with the development of acanthosis nigricans. It has been recognized for some time that although SK and epidermal naevi have different natural histories they share some clinical and histological characteristics, including acanthosis, papillomatosis, and variable degrees of hyperkeratosis and hyperpigmentation. These similarities and the identification of mutations in the fibroblast growth factor 3 receptor in epidermal naevi [5] triggered analysis of SKs for *FGFR3* mutations. Mutations were identified in 39% of SKs and the genetic changes identified were identical to those found in patients with a rare dwarfing chondrodysplasia and thanatophoric dysplasia, which are both also associated with acanthosis nigricans [6]. More recently, additional molecular insights into SK aetiology have emerged with the identification of activating *PIK3CA* mutations in 16% of SKs examined [7].

Clinical features. Seborrhoeic keratoses occur on any body site. They are usually asymptomatic but may be itchy. They are most frequent on the face and the upper trunk. The first evidence is slight hyperpigmentation. On the hand and face, seborrhoeic keratoses may remain superficial for a long period, and can be mistaken for melanocytic lesions. It may be difficult to distinguish superficial seborrhoeic keratoses from lentigo maligna and pigmented AK. More florid examples may be pedunculated or acanthotic, smooth-surfaced, domed and heavily pigmented, but in contrast to melanocytic naevi do not reflect light and usually have plugged follicular orifices on the surface, giving an almost cerebriform appearance. Most seborrhoeic keratoses have fewer hairs than the skin they arise from. The most common appearance is that of a very superficial verrucous plaque which appears to be stuck on the epidermis, varying from dirty yellow to black in colour and having loosely adherent, greasy keratin on the surface (Fig. 52.17). The shape is round or oval and multiple lesions may



Fig. 52.18 Histology of classic seborrhoeic keratosis showing hyperkeratotic surface and numerous horn cysts.

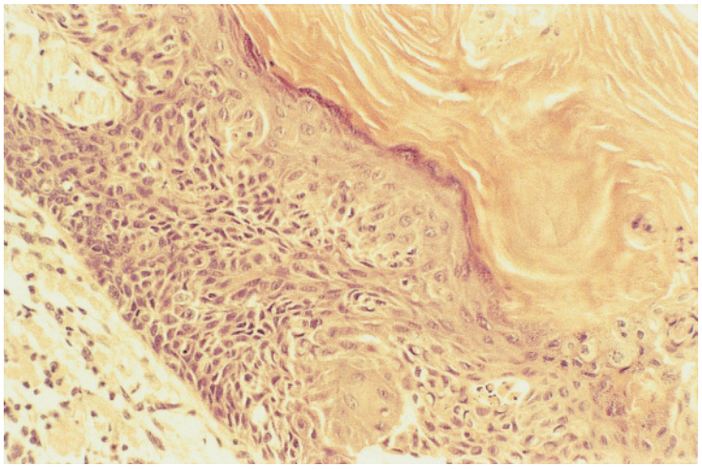


Fig. 52.19 Histology of irritated seborrhoeic keratosis. The squamous eddies are clearly seen in this illustration.

be aligned in the direction of the skin folds. The size varies from 1 mm to several centimetres. The smallest lesions occur around follicular orifices, particularly on the trunk. On the eyelids and major flexures, SKs may be pedunculated and less keratotic. Irritation or infection causes swelling, sometimes bleeding, oozing and crusting, and a deepening of the colour because of inflammation.

Pathology [8]. The essential change is an accumulation of normal keratinocytes between the basal layer and the keratinizing surface of the epidermis. Melanocytes may proliferate among these immature keratinocytes and transfer melanin to them. The dermal papillae may be elongated. Focal keratinization may occur within the mass of immature cells to produce horn cysts, which enlarge, may coalesce and can be carried to the surface by the tide of epidermal cells. If the formation and discharge of horn cysts is excessive, a verrucous surface will be formed. Marked papillomatosis will also cause an irregular 'church steeple' outer border which retains keratin. If, in contrast, the main mass of the lesion is composed of immature cells, the surface will be smooth and rounded, and the melanocyte population and degree of pigmentation will vary, so that the lesions may be deeply pigmented. The parenchymal cells are rather small and polygonal, possessing tonofibrils and intercellular bridges, and they are arranged in an orderly fashion.

The most common pathological type is the solid variant, in which a mass of immature keratinocytes is seen mainly above the level of the surrounding epidermis (Fig. 52.18). Occasional cystic areas containing fragments of stratum corneum are seen at these sites. A rarer variant is the hyperkeratotic variety, which may be clinically mistaken for an AK. The reticular form is a third variant, composed of strands of keratinocytes; this type is frequently seen as a flat lesion on the face.

If an SK becomes irritated, or develops a pattern of apparently inverted growth, frequently in association with a hair follicle opening, the pathological differential diagnosis may include an early invasive SCC. An irritated SK shows focal areas of whorls of keratinocytes in so-called squamous eddies, but mitotic figures are rare, and the base of the lesion shows a clear separation from dermal tissue, with no single-cell invasion (Fig. 52.19).

Diagnosis. The superficial type of SK has to be distinguished from simple and malignant lentigo (see Chapter 54) and from AK, especially on the face. The patterned fine fissures on the surface may be helpful. The pigmented domed variety may closely resemble a melanocytic naevus, but the surface is less lustrous and the follicular orifices are plugged. An inflamed keratosis may be confused with a malignant melanoma. If the lesion is treated with a topical antibiotic and occluded for 3–5 days the diagnosis may become obvious, but if clinical doubt persists an excision biopsy and pathological examination is indicated. Pigmented BCCs may also have to be considered in the differential diagnosis. They are usually rather irregular with a rolled edge, a thin shiny epidermis with telangiectases and a depressed or ulcerated centre.

Treatment. Removal with a small sharp curette leaves a flat surface that becomes covered by normal epidermis in a week. Cautery or diathermy should be used as little as possible to avoid scarring. Satisfactory results can be obtained by freezing briefly, a technique especially suitable for large superficial lesions, or by carefully painting the surface with pure trichloracetic acid and repeating if the full thickness is not removed on the first occasion. Seborrhoeic keratoses tend to recur, and it is often wise to encourage patients to accept them rather than to keep returning for further treatment.

Melanoacanthoma

This term has been used for a very rare lesion, originally described by Bloch as 'non-naevoid melanoepithelioma, type 1', and has been considered to be a benign neoplasm composed of epidermal keratinocytes and large dendritic melanocytes [9]. The current general view is that this is not a discrete entity. Some deeply pigmented acanthotic seborrhoeic keratoses contain, dispersed among the parenchymal cells, numerous dendritic melanocytes, which

are demonstrable by the dopa technique [10]. Normally, they transfer melanin to the surrounding immature keratinocytes. However, if irritation or inflammation caused the parenchymal cells to become more mature, the transfer of melanin would be impeded and pigment might be retained in the melanocytes, producing a microscopic appearance similar to that described as melanoacanthoma.

Stucco keratosis [11,12]

This title has been given to small, rough, whitish, keratotic plaques that are easily lifted off the skin with a fingernail and come away without causing bleeding. They are situated principally on the extremities, especially the ankle region, and occur in middle-aged or elderly persons. They have the same stuck-on appearance of SKs and a similar microscopic architecture. Basaloid cells and horn cysts are not seen and the histology is more that of a regular spiky papillomatosis, with loose lamellated hyperkeratosis capping the epidermis. If treatment is called for, curettage or cryotherapy are effective.

References

1 Yeatman JM, Kilkenny M, Marks R. The prevalence of seborrhoeic keratoses in an Australian population: does exposure to sunlight play a part in their frequency? *Br J Dermatol* 1997; **137**: 411–4.
2 Memon AA, Tomenson JA, Bothwell J *et al*. Prevalence of solar damage and actinic keratosis in a Merseyside population. *Br J Dermatol* 2000; **142**: 1154–9.
3 Williams MG. Acanthomata appearing after eczema. *Br J Dermatol* 1956; **68**: 268–71.
4 Dantzig PI. Sign of Leser-Trélat. *Arch Dermatol* 1973; **108**: 700–1.
5 Hafner C, van Oers JM, Vogt T *et al*. Mosaicism of activating FGFR3 mutations in human skin causes epidermal nevi. *J Clin Invest* 2006; **116**: 2201–7.
6 Logie A, Dunois-Larde C, Rosty C *et al*. Activating mutations of the tyrosine kinase receptor FGFR3 are associated with benign skin tumors in mice and humans. *Hum Mol Genet* 2005; **14**: 1153–60.
7 Hafner C, Lopez-Knowles E, Luis NM *et al*. Oncogenic PIK3CA mutations occur in epidermal nevi and seborrheic keratoses with a characteristic mutation pattern. *Proc Natl Acad Sci USA* 2007; **104**: 13450–4.
8 Sanderson KV. The structure of seborrhoeic keratoses. *Br J Dermatol* 1968; **80**: 588–93.
9 Mishima Y, Pinkus H. Benign mixed tumor of melanocytes and malpighian cells. *AMA Arch Dermatol* 1960; **81**: 539–50.
10 Molokhia MM, Portnoy B. A study of dendritic cells in seborrhoeic warts. *Br J Dermatol* 1971; **85**: 254–8.
11 Willoughby C, Soter NA. Stucco keratosis. *Arch Dermatol* 1972; **105**: 859–61.
12 Kocsard E, Carter JJ. The papillomatous keratoses: the nature and differential diagnosis of stucco keratosis. *Australas J Dermatol* 1971; **12**: 80–8.

Dermatosis papulosa nigra

Definition. A pigmented papular eruption of the face and neck caused by a naevoid developmental defect of the pilosebaceous follicles, with histology resembling seborrhoeic keratoses. The condition is most common in black races.

Aetiology [1]. This lesion is probably genetically determined. The incidence in black people rises from about 5% in the first decade to over 40% by the third, and is rather higher in females than males.

Clinical features [1–3]. The individual lesions are black or dark brown, flattened or cupuliform papules 1–5 mm in diameter. They are rare under the age of 7 years, after which they increase steadily in frequency, number and size. They are most numerous in the malar regions and on the forehead. They are rare on the lower parts of the face and the chin, but in a few individuals may be found on the neck, chest and back [2].

Pathology [1,4]. The lesions, which are naevoid developmental defects of the pilosebaceous follicles, show irregular acanthosis and hyperkeratosis, and somewhat resemble seborrhoeic keratoses.

Treatment. Treatment is seldom requested. Removal with the diathermy or cautery is effective.

References

1 Hairston MA Jr, Reed RJ, Derbes VJ. Dermatosis papulosa nigra. *Arch Dermatol* 1964; **89**: 655–8.
2 Castellani A. Observations on some diseases of Central America. *J Trop Med Hyg* 1925; **28**: 1–14.
3 Michael JC, Searle ER. Dermatosis papulosa nigra. *Arch Dermatol Syphilol* 1929; **20**: 629–40.
4 Diasio FA. Dermatosis papulosa nigra (Castellani) of unusual distribution (acanthosis papulosa nigra). *Arch Dermatol Syphilol* 1933; **27**: 751–5.

Skin tags

Synonyms
- Soft warts
- Achrochordon

Definition. A common, benign lesion composed of loose fibrous tissue and occurring mainly on the neck and major flexures as a small, soft, pedunculated protrusion.

Incidence and aetiology. These lesions are very common, particularly in women at the menopause or later. They are frequently found together with seborrhoeic keratoses.

Clinical features. The lesions are pedunculated and may have a long stalk. They vary in size and are about 2 mm in diameter on average. They are round, soft and inelastic. The colour may be unchanged, but they are frequently hyperpigmented. The most common site is on the sides of the neck, where they may be mixed with typical small, sessile, seborrhoeic keratoses. When more profuse, they can extend on to the face or down to the back and chest. Similar lesions may be found in and around the axillae and groins.

Pathology. The protruding mass is connected to the skin by a narrow pedicle. The bulk of the lesion is loose fibrous tissue, similar to that of the papillary dermis. The epidermis is thin, and the basal cell layer is flat and often hyperpigmented. Melanocytic proliferation and naevus cells are not usually seen and the majority of such lesions probably come within the seborrhoeic keratosis spectrum. However, there is an overlap with melanocytic naevi and neurofibromas. Some skin tags may be the last remnants of a pre-existing melanocytic naevus.

Diagnosis. The lesions are unmistakable. They are smaller than the average pedunculated melanocytic naevus or the lesions of neurofibromatosis.

Treatment. Both cautery and cryotherapy with liquid nitrogen are effective.

Haber's syndrome

Definition. A familial condition characterized by a persistent rosacea-like eruption, associated in some cases with keratotic plaques on the trunk and limbs.

Incidence. A family in which five members were affected was originally described [1]. Another case, with 15 affected relatives, has been described from Japan [2]. The rosacea-like eruption appears in childhood, and the keratotic lesions somewhat later. The mode of inheritance seems to be a simple autosomal dominant.

Clinical features. The cheeks, nose, forehead and chin are permanently flushed. The skin surface shows a combination of erythema and telangiectasia, prominent follicles, comedones, small papules, some of which are scaly, and tiny atrophic pitted areas. There is little fluctuation in the erythema, although sunlight may aggravate it. The warty lesions occur mainly on the trunk and thighs and are static, scaly or keratotic, flat and non-indurated plaques.

Pathology. The facial eruption shows perivascular inflammation leading to fibrosis, acanthosis and parakeratosis of the epidermis, distortion of pilosebaceous complexes with dilated follicular orifices, and proliferation of immature glands and basal cell strands. The warty lesions are produced by papillomatosis, acanthosis in the interpapillary ridges and dyskeratosis with areas of pale-staining cells giving a parakeratotic stratum corneum. Mitotic figures are present, but there is no evidence of malignancy.

Treatment. The facial eruption was controlled in the young patient in the first family and in the Japanese patients by steroid creams locally. The warty lesions respond to radiotherapy. Simple destructive measures are also effective.

References

1 Sanderson KV, Wilson HTH. Haber's syndrome: familial rosacea-like eruption with intraepidermal epithelioma. *Br J Dermatol* 1965; **77**: 1–8.

2 Seiji M, Otaki N. Haber's syndrome: familial rosacea-like dermatosis with keratotic plaques and pitted scars. *Arch Dermatol* 1971; **103**: 452–5.

Clear cell acanthoma [1–3]

Synonyms
- Degos' acanthoma
- Acanthome a 'cellules claires'

Definition. A scaly plaque or nodule that has a characteristic accumulation of clear glycogen-containing cells in the epidermis.

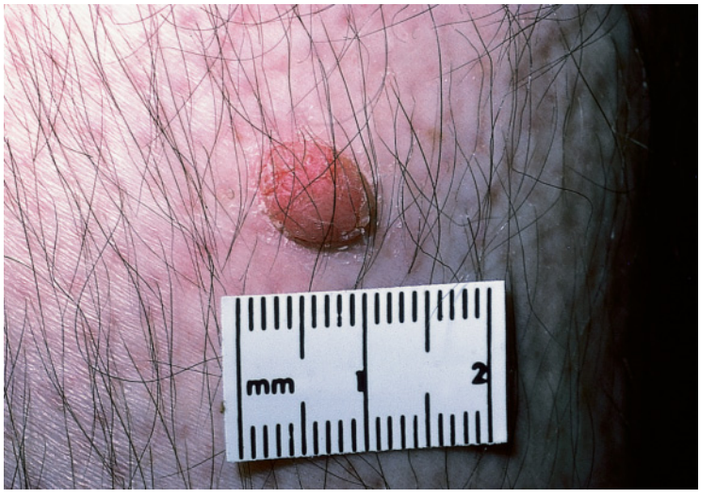


Fig. 52.20 Clear cell acanthoma.

Incidence and aetiology. Clear cell acanthoma is a relatively uncommon condition of adults. The sexes are equally affected [3]. The cause is unknown [4].

Clinical features (Fig. 52.20) [1,3,5]. The lesion is usually solitary. It is a slightly elevated to dome-shaped plaque or nodule with an abrupt margin and a wafer-like scale adherent at the periphery, which leaves a moist or bleeding surface when removed. The colour varies from pink to brown, but is most characteristically red with vascular puncta and it blanches on diascopy. It varies from 3 to 20 mm in diameter, and occurs most commonly on the lower limbs. The duration may be of many years, and there are usually no symptoms. The diagnosis can be suspected on the clinical evidence. The lesion may be mistaken for a histiocytoma, seborrhoeic keratosis or pyogenic granuloma.

Pathology [1,6,7]. The epidermis is thickened and papillomatous with sharply demarcated areas of light-coloured cells, which contrast with the normal basal cells below and Malpighian cells around them (Fig. 52.21). The cytoplasm of the clear cells contains an abundance of glycogen, which on electron microscopy is seen to displace tonofibrils [7,8]. The cells do not have the enzymes characteristic of eccrine sweat glands. There is intercellular oedema and an infiltrate often containing many polymorphonuclear leukocytes. The papillary body is oedematous and the superficial capillaries and veins are increased in number. There may be syringomatous sweat gland elements and evidence of sebaceous differentiation beneath the lesion [9].

Treatment. Excision is often needed to confirm the diagnosis [1].

References

1 Degos R, Civatte J. Clear-cell acanthoma: experience of 8 years. *Br J Dermatol* 1970; **83**: 248–54.

2 Wells GC, Wilson Jones E. Degos acanthoma (acanthoma à cellules claires): a report of five cases with particular reference to the histochemistry. *Br J Dermatol* 1967; **79**: 249–58.

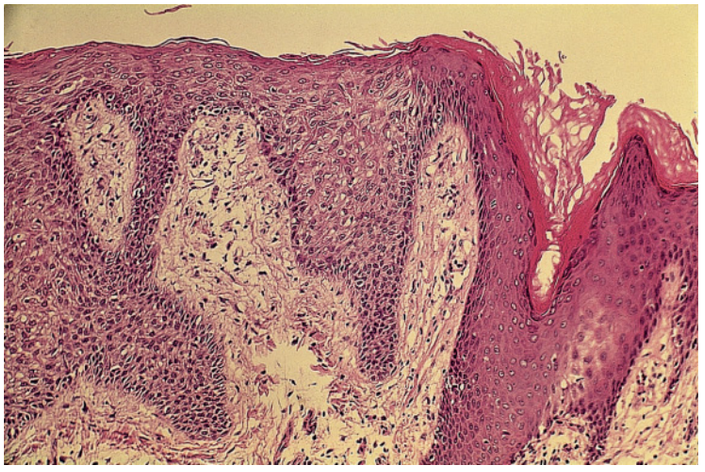


Fig. 52.21 Pathology of clear cell acanthoma of Degos, showing sharp margin between normal skin to the right and epidermis involved with the clear cells to the left.

3 Zak FG, Girerd RJ. Das blasszellige Akanthom (Degos). *Hautarzt* 1968; **19**: 559–61.
4 Duperrat B, Mascaro JM. L'acanthome a cellules unique: rapport de deux cas. *Ann Dermatol Syphiligr* 1965; **92**: 5–6.
5 Fine RM, Chernosky ME. Clinical recognition of clear-cell acanthomas (Degos'). *Arch Dermatol* 1969; **100**: 559–63.
6 Brownstein MH, Fernando S, Shapiro L. Clear cell acanthoma: clinicopathologic analysis of 37 new cases. *Am J Clin Pathol* 1973; **59**: 306–11.
7 Funan H, Sisson JK. The ultrastructure of the pale cell acanthoma. *J Invest Dermatol* 1969; **52**: 185–8.
8 Hollman KH, Civatte J. Etude au microscope électronique de l'acanthome à cellules claires. *Ann Dermatol Syphiligr* 1968; **95**: 139–46.
9 Cramer HJ. Klarzellenakanthom (Degos) mit Syringomatösen und naevus-sebaceus-artigen Anteilen. *Dermatologica* 1971; **143**: 265–70.

Keratoacanthoma

Synonym
- Molluscum sebaceum

Definition. A rapidly evolving tumour of the skin, composed of keratinizing squamous cells originating in pilosebaceous follicles and resolving spontaneously if untreated.

Incidence. Keratoacanthoma is relatively common, and in white races tends to occur with about one-third of the frequency of SCC, whatever the environmental UV levels [1]. It is uncommon in dark-skinned races and in the Japanese [2]. Males are affected about three times more often than females. The adjusted age distribution shows that it is most frequent in middle-life and does not increase in incidence in old age, unlike BCC and SCC.

Aetiology. The epidemiological data suggest that the incidence of keratocanthoma is related to sun exposure, and the localization of the tumours mainly on the head and upper limb supports this. Contact with tar and mineral oil has also been shown to cause an increased incidence [3,4] and very similar lesions have been produced in animals by painting with carcinogenic hydrocarbons. In some cases, the lesion follows injury to the skin, which suggests that infection may play a part in its origin, a view supported by the occurrence of multiple keratoacanthomas in skin grafts of patients with the tumour in the recipient site [5], the donor site [6] or both [7]. Proof of a viral cause is lacking. Cases are reported of keratoacanthoma associated with carcinoma of the larynx [8], multiple internal malignancy [9], leukaemia [10], deficient cell-mediated immunity [11] and in transplant recipients [12]. Most recently, the solid tumour multikinase inhibitor Sorafenib has been reported to lead to the development of keratoacanthomas, which resolved or stopped developing when therapy was stopped; this may give us a new insight into the aetiology of the condition [13,14].

Clinical features [1,15,16]. The first evidence of keratoacanthoma is a firm, rounded, flesh-coloured or reddish papule, which may resemble molluscum contagiosum or, if keratotic, a virus wart. The patient rarely seeks advice at this stage. There is then a rapid growth phase and in a few weeks it may become 10–20 mm across. There is no infiltration at the base. The epidermis over the nodule is smooth and shiny; the lesion is skin-coloured to red with telangiectases just beneath the surface. The centre contains a horny plug or is covered by a crust which conceals a keratin-filled crater (Fig. 52.22). As the lesion matures, the accumulating keratin expands the outermost part making the edge overhang the base somewhat, but the radial symmetry is usually well preserved. The keratin may project like a horn or it may soften and break down. Spontaneous resolution is achieved by the epidermal covering receding towards the base and the horny core being shed. The base is revealed as irregular and puckered and the edge may remain as soft but thickened epidermis, either as a continuous rim or a series of tags. The process of spontaneous healing usually takes about 3 months.

A small proportion of keratoacanthomas grow to much larger dimensions—5 cm or more in diameter being not exceptional on the forearm. One lesion on the chest was more than 15 cm in diameter [17]. In some cases, the maximum size may be reached in a month or two; others may enlarge over many months. After growth ceases, involution may not occur for some months or may occur at part of the periphery while growth continues elsewhere. There may be recurrences after curettage or excision, more frequently in lesions on the lips and fingers and when treatment is carried out in the early stages [18]. Recurrence may happen after spontaneous resolution [19].

The most frequently affected area is the central part of the face, that is the nose, cheeks, eyelids and lips. The dorsum of the hand, wrist and forearm are commonly affected; the thigh, chest, shoulder and scalp less so; and the anogenital area uncommonly except in those exposed to occupational hazards. Lesions have occurred subungually [20,21], in the vermilion of the lips [18] and on the buccal mucosa.

In most cases, the tumour presents as a solitary lesion. Multiple or recurrent tumours are more likely to be present in several circumstances. Recurrent lesions occur in patients who have been exposed to pitch or tar [3] and in rare cases as a familial disorder, although there are reasons to keep this Ferguson-Smith type as a separate entity. There are a few cases of eruptive keratoacanthoma recorded. Multiple lesions have occurred with defective cell-



(a) (b)

Fig. 52.22 Typical keratoacanthomas, on the face, showing raised margin and central keratin-filled crater.

mediated immunity and also as part of Torre's syndrome, with multiple internal malignancies [9] and with sebaceous adenomas (see Chapter 53).

Pathology. The distinctive features are best seen when the fixed specimen is being cut before processing or in sections under low magnification. The tumour has a symmetrical, more-or-less globular form and is situated in the dermis, usually extending down no deeper than the sweat glands, although deep penetration has occasionally been recorded. The epidermis around the tumour is normal or slightly acanthotic, but becomes thinned as it rises over the tumour. A narrow spur of connective tissue separates the epidermis from the proliferating squamous cells, except where the two connect at the mouth of the keratin-filled crypt. Serial sections of an early lesion have shown connection of the masses of squamous cells with the upper part of a hyperplastic follicle [22].

The histological features vary with the stage of evolution. The early lesion is composed of a mass of rapidly multiplying squamous cells. These are large and rather pale with vesicular nuclei, prominent nucleoli and frequent mitoses. Hyperchromatic cells, atypical mitotic figures, individual cell keratinization and other evidence of loss of polarity may be found. The marginal cells invade the surrounding dermis aggressively, while those more centrally placed keratinize to form a branched core of keratin that communicates with the surface. The stroma is vascular and infiltrated with round cells and histiocytes.

Resolution occurs through maturation of the hyperplastic masses. The accumulating keratin dilates the central pore, the epidermal lips recede from the centre and the lesion opens like a flower bud. When the horn is finally shed, the irregular epithelium beneath it replicates the scalloped outline of the active mass. The cells take on the morphology of epidermis, and a scar is formed, which is depressed and may have papillomatous tags at the margin, the remnants of the epidermal lip. Older lesions frequently show clusters of leukocyte microabscesses at the base. Thus, the pathological features vary with the stage of evolution of the keratoacanthoma and, if an adequate specimen is not submitted, it may be impossible for the reporting pathologist to confidently rule out early invasive SCC. Keratoacanthomas may also rarely progress to SCC. In one case [23], it may have been precipitated by treatment with oral methotrexate for a recurrence. The conjunction of two independent lesions in sun-damaged skin may account for the finding of a BCC in the scar of keratoacanthoma in this and other cases.

Experimentally produced lesions differ in their form, depending on whether the hair follicles are in anagen or telogen when the proliferation begins [24,25]. Virus-like particles have been seen under electron microscopy [26].

Diagnosis. The most important differential diagnosis is to distinguish keratoacanthoma from SCC. In most cases, the more rapid evolution to a relatively large size, the regular crateriform shape and keratotic plug, the undamaged surrounding skin and the younger age of onset make a distinction relatively easy for the clinician. Spontaneous healing adds support to the diagnosis of keratoacanthoma. The problem is made more difficult in sunny areas where actinic damage and SCC are more common, and the most important single point is the history of rapid growth. The differential diagnosis includes cutaneous horn and hypertrophic AK, viral wart, molluscum contagiosum, pseudoepitheliomatous hyperplasia and granulomas of various types. Secondary deposits from non-cutaneous malignancies can also occasionally mimic keratoacanthoma.

Treatment. The end result of leaving the tumour to regress is usually a rather unsightly scar. Curettage and coagulation of the base, or excision and suture, produce a much more acceptable result. Excision is desirable if the diagnosis is in doubt, because curetted specimens yield poor sections. Radiotherapy shortens the course and improves the scar, and can be used in patients who

refuse surgery. A total of 2000 cGy in two closely spaced doses of adequate penetration can be given.

The application of 5-fluorouracil ointment twice daily may reduce the time taken for natural resolution and diminish scarring [27]. If there is real doubt about the diagnosis, surgical removal or radiotherapy should be carried out as for SCC, and the patient followed up.

Generalized eruptive keratoacanthoma [9,28]

A small number of cases of widely disseminated lesions, some of them typical keratoacanthomas, have been reported. Both sexes have been affected. The primary lesions are flesh-coloured to red, dome-shaped follicular papules, 1–3 mm in size and affecting particularly the face (where they may be confluent), the trunk and the roots of the limbs. Itching is a prominent symptom, and ectropion and narrowing of the mouth may be produced by the keratotic facial change. Scattered among the papules are larger, more typical keratoacanthomas, which resolve spontaneously. The palms and soles are spared, but the oral and laryngeal epithelium can be involved.

Pathology. Histological examination shows the papules to consist of a dilated and plugged follicle duct with acanthotic follicular epidermis around it; the mucosal lesions are irregular acanthosis; and the nodules are keratoacanthomas, but with no inflammatory changes.

Management. The nodular lesions heal in a few months. The papules are not influenced by cytotoxic drugs, but one case responded to topical retinol [25].

References

1 Rook A, Champion RH. *Keratoacanthoma*. Monograph 10. Washington DC: National Cancer Institute, 1963: 257–73.
2 Miyaji T. *Skin Cancers in Japan: a Nationwide 5-Year Survey, 1956–60*. Monograph 10. Washington DC: National Cancer Institute, 1963: 55–70.
3 Colomb D, Descos L, Gauthier D. Kératoacanthomes multiples et maladie du brac de houille. *Rev Lyonaise Med* 1966; **15**: 449–62.
4 Ghadially FN, Barton BW, Kerridge DF. The etiology of keratoacanthoma. *Cancer* 1963; **16**: 603–11.
5 Pillsbury DM, Beerman H. Multiple keratoacanthoma. *Am J Med Sci* 1958; **236**: 614–24.
6 Wulsin JH. Keratoacanthoma: a benign cutaneous tumor arising in a skin graft. *Am Surg* 1958; **24**: 689–92.
7 Dibden FA, Fowler M. The multiple growth of molluscum sebaceum in donor and recipient sites of skin graft. *Aust NZ J Surg* 1955; **25**: 157–9.
8 Chapman RS, Finn OA. Carcinoma of the larynx in two patients with keratoacanthoma. *Br J Dermatol* 1974; **90**: 685–8.
9 Poleksic S. Keratoacanthoma and multiple carcinomas. *Br J Dermatol* 1974; **91**: 461–3.
10 Weber G, Stetter H, Pliess G. Assozilertes Vorkommen von eruptiven Keratoacanthomen, Tubercarcinom und Paramyeloblasten-leukamie. *Arch Klin Exp Dermatol* 1970; **238**: 107–19.
11 Claudy A, Thivolet J. Multiple keratoacanthomas: association with deficient cell mediated immunity. *Br J Dermatol* 1975; **93**: 593–5.
12 Bordea C, Wojnarowska F, Millard PR *et al*. Skin cancers in renal-transplant recipients occur more frequently than previously recognized in a temperate climate. *Transplantation* 2004; **77**: 574–9.
13 Smith KJ, Haley H, Hamza S, Skelton HG. Eruptive keratoacanthoma-type squamous cell carcinomas in patients taking sorafenib for the treatment of solid tumors. *Dermatol Surg* 2009, in press.
14 Kong HH, Cowen EW, Azad NS, Dahut W *et al*. Keratoacanthomas associated with sorafenib therapy. *J Am Acad Dermatol* 2007; **56**: 171–2.
15 Kingman J, Callen JP. Keratoacanthoma: a clinical study. *Arch Dermatol* 1984; **120**: 736–40.
16 Calnan CD, Haber H. Molluscum sebaceum. *J Pathol Bacteriol* 1955; **69**: 61–6.
17 Duany NP. Squamous cell pseudoepithelioma (keratoacanthoma): a new clinical variety, gigantic, multiple, and localized. *AMA Arch Dermatol* 1958; **78**: 703–9.
18 Stevanovic DV. Keratoacanthoma: mucous membranes as the site of its localization. *Dermatologica* 1960; **121**: 278–84.
19 Beare JM. Recurrent molluscum sebaceum. *Lancet* 1955; **i**: 182–3.
20 Lamp JC, Graham JH, Urbach F *et al*. Keratoacanthoma of the subungual region. *J Bone Joint Surg Am* 1964; **46**: 1721–31.
21 Shapiro L, Baraf CS. Subungal epidermoid carcinoma and keratoacanthoma. *Cancer* 1970; **25**: 141–52.
22 Kalkoff KW, Macher E. On the histogenesis of keratoacanthoma. *Hautarzt* 1961; **12**: 8–15.
23 Burge KM, Winkelmann RK. Keratoacanthoma: association with basal and squamous cell carcinoma. *Arch Dermatol* 1969; **100**: 306–11.
24 Ghadially FN. The role of the hair follicle in the origin and evolution of some cutaneous neoplasms of man and experimental animals. *Cancer* 1961; **14**: 801–16.
25 Whiteley HJ. The effect of the hair growth cycle on experimental skin carcinogenesis in the rabbit. *Br J Cancer* 1957; **11**: 196–205.
26 Zelickson AS. Virus-like particles demonstrated in keratoacanthomas by electron microscopy. *Acta Derm Venereol (Stockh)* 1962; **42**: 23–6.
27 Grupper C. Treatment of keratoacanthomas by local applications of 5-fluorouracil (5-FU) ointment. *Dermatologica* 1970; **140** (Suppl. 1): 127–32.
28 Winkelmann RK, Brown J. Generalized eruptive keratoacanthoma: report of cases. *Arch Dermatol* 1968; **97**: 615–23.

Pseudoepitheliomatous hyperplasia [1]

Aetiology. Epidermal hyperplasia is an early and essential feature in the healing of any breach of the skin surface. Ordinarily, this is coordinated with the repair of the dermis, and epidermal downgrowths eventually dissipate [2]. When the dermis is diseased, however, a persistent and much more extensive hyperplasia may occur. This is seen, for instance, at the margin of chronic leg ulcers, over chronic cutaneous granulomas such as lupus vulgaris, tuberculosis verrucosa cutis, insect-bite granulomas and halogen granulomas and, in a rather unusual form, over a small proportion of histiocytomas. It is also a component of some cases of lupus erythematosus and of lichen planus of the hypertrophic type. It may occur in association with tumours, particularly granular cell myoblastoma and malignant melanoma.

Clinical features. The appearance will vary with the primary disorder. Granulomas may be covered by a thickened, warty or heaped-up epidermis, perhaps best seen in chromomycosis. In chronic ulcers, the margin is heaped-up, often giving the appearance of being rolled, and has an irregular surface. The edge is not usually indurated to the extent that occurs in SCC. It is characteristic that the hyperplasia will subside as the ulcer is treated and heals. It is wise to remember that an ulcer whose margin has been affected by pseudoepitheliomatous hyperplasia in the past may eventually be the cause of metastasizing SCC.

Pathology. The nature of the primary disorder modifies the picture greatly. In simple ulcers and inflammatory lesions—by far the most common causes—there is disturbance of the upper part of the dermis, often with young fibroblasts and a rather myxoma-

tous connective tissue stroma replacing the normal dermal collagen. Columns of prickle cells grow down into the dermis in an irregular fashion. In some areas, there is maturation of the central parts of the columns to produce horny pearls. The general appearance is that of invasive proliferation of the epithelium. The individual cells, however, do not show the atypical features suggestive of malignancy. The columns may be penetrated by inflammatory cells, a feature that is not seen in malignant proliferations. In most instances, a weighing of dermal against epidermal changes suggests that the former are the cause and not the consequence of the latter.

Diagnosis. A good-sized biopsy from a representative area of the lesion is essential.

References

1 Winer LH. Pseudoepitheliomatous hyperplasia. *Arch Dermatol Syphilol* 1940; **42**: 856–67.

2 Gillman T. The possible importance of dermal-epidermal interactions in the pathogenesis of human and experimental wound healing and skin cancers. In: Rook A, Champion RH, eds. *Progress in the Biological Sciences in Relation to Dermatology*. Cambridge: Cambridge University Press, 1964: 113.

Cysts

Nomenclature. The term *sebaceous cyst* should be used only to describe steatocystoma multiplex, which contains oily sebum. Histological examination of all other cysts reveals the lining wall to be keratinous in nature. Keratinous cysts can be divided into two types, those with a lining identical in its stratification with epidermis and pilosebaceous duct, and those with a lining resembling the external root sheath of the follicle. The latter variety is less common, and is often familial, multiple and largely confined to the scalp [1]. This type is the trichilemmal cyst [2].

The cysts found in Gardner's syndrome are epidermoid in type [3] and are characterized by their appearance in childhood. There is no genetic overlap between trichilemmal cysts, cysts of Gardner's syndrome or steatocystoma multiplex, although all have an autosomal dominant mode of inheritance.

Histogenesis. Steatocystoma multiplex is most likely to be a genetically determined failure of canalization between the sebaceous lobules and the follicular pore. The common epidermoid cyst is the result of squamous metaplasia in a damaged sebaceous gland. Milia may result from either keratinization within the sebaceous anagen ('collars') of vellus hair follicles or cystic dilatation of an interrupted sweat duct. Trichilemmal cysts may be caused by survival of fragmented segments of the hair root during catagen.

The following cysts are described in this section or elsewhere in the book:

1 Keratinous cysts, both epidermoid and trichilemmal
2 Dermoid (see Chapters 69 and 71)
3 Milium
4 Steatocystoma multiplex
5 Eccrine hidrocystoma (see Chapter 53)
6 Apocrine hidrocystoma (see Chapter 53)
7 Bartholin's cyst (see Chapter 71)
8 Myxoid cyst of the skin (see Chapter 62)
9 Branchial cyst (see Chapter 18).

Epidermoid cyst

Synonym
- Epithelial cyst (sebaceous cyst is a misnomer)

Definition. A cyst containing keratin and its breakdown products, surrounded by an epidermoid wall.

Incidence and aetiology. Epidermoid cysts are common, most frequently affecting young and middle-aged adults. They are rare in childhood. Many are the result of inflammation around a pilosebaceous follicle, and are frequently seen following the more severe lesions of acne vulgaris. Some may result from deep implantation of a fragment of epidermis by a blunt penetrating injury. Those that occur as a part of Gardner's syndrome and of the NBCCS are probably caused by a developmental defect.

Clinical features. An epidermoid cyst is situated in the dermis and raises the epidermis to produce a firm, elastic, dome-shaped protuberance that is mobile over the deeper structures. It is tethered to the epidermis, and there may be a central keratin-filled punctum. The spherical form can be felt where the skin is sufficiently lax. Cysts near the surface, as in the ear lobe or scrotum, are yellowish or white. The size varies from a few millimetres to more than 5 cm in diameter. The common sites are the face, neck, shoulders and chest, which are areas favoured by acne vulgaris. Lesions may be solitary but are commonly multiple. They enlarge slowly and may become inflamed and tender. Suppuration may occur. Cysts that follow acne and have been subject to recurrent inflammation may be difficult to remove completely. Calcification of the contents of epidermoid cysts cannot usually be detected clinically; when it occurs in multiple cysts of the upper part of the trunk it can give a confusing picture on chest X-ray.

Traumatic inclusion cysts usually occur on the palmar or plantar surfaces, buttock or knee. A history of penetrating injury is not always obtained.

Pathology. An epidermoid cyst is unilocular and spherical, unless flattened by firm tissue beneath it. There may be an obvious connection with the surface by a keratin-filled duct, but this is probably less common than surgical texts would suggest. The cyst is situated within the dermis. The lining wall reproduces the layers of the epidermis, although attenuated in large cysts. The keratin is lamellated and birefringent. Cholesterol clefts may be seen. The basal layer may be flattened and surrounded by fibrosis, or may show papillary indentations similar to the epidermis. Some cysts have a chronic inflammatory or foreign-body type of reaction around them, at times producing (or caused by) partial disruption of the wall. Occasionally, a hair shaft may be found coiled within the cyst. These cysts probably result from inflammatory destruction of the sebaceous matrix cells and connective tissue investment of the gland and subsequent re-epithelialization of the abscess cavity, or from squamous metaplasia following impaction of a hair shaft within the sebaceous gland.



Fig. 52.23 Calcified cyst just below the eyelid margin.



Fig. 52.24 Inclusion cyst following trauma to the thumb.

Diagnosis. The uncomplicated cyst can usually be diagnosed with confidence. Other benign and rounded dermal tumours may be mistaken for epidermoid cysts, and inflammatory granulomas such as cutaneous leishmaniasis may mimic an inflamed cyst (Figs 52.23 & 52.24).

Treatment. A cyst that has not recently been inflamed can be dissected out. An inflamed cyst is better incised, drained and phenolized.

Trichilemmal cyst

Synonym
- Pilar cyst



Fig. 52.25 Clinical illustration of typical pilar cyst on the scalp.

Definition. A cyst containing keratin and its breakdown products, usually situated on the scalp, with a wall resembling external hair root sheath [4].

Incidence and aetiology. This is a fairly common condition, and accounts for about 5–10% of keratinous cysts seen by surgical pathology services. Women are affected more frequently than men. It is seen mainly in middle age [5] and is inherited as an autosomal dominant disorder [1,6].

Clinical features. The lesion occurs mainly on the scalp, and is a smooth, mobile, firm and rounded nodule (Fig. 52.25). Larger lesions may be lobular and multiple cysts are commonly found. Tenderness occurs with inflammation, and the surface may break down with infection. The cyst wall may fuse with the epidermis to form a crypt (marsupialized cyst), which can occasionally terminate by discharging its contents and healing spontaneously [6]. In contrast, the contents may protrude above the surface to form a soft cutaneous horn.

Pathology. Trichilemmal cysts differ from epidermoid cysts in the way the lining cells mature. They do not flatten and form a granular layer, and keratinization seems to occur mainly in the region of the cell membrane. The cells appear to disintegrate at the inner margin of the lining. The contents are not brightly birefringent lamellae, but may calcify (Fig. 52.26).

The wall of a trichilemmal cyst may become ruptured and the contents invaded by granulation tissue. The reaction is much less acute than in ruptured epidermoid cysts and produces proliferation rather than destruction of the wall. The proliferation may be progressive and simulate, clinically and histologically, a well-differentiated SCC [7]. Cases of proven malignant degeneration in scalp cysts are very rare.

Treatment. Uncomplicated cysts shell out of the dermis with remarkable ease. Proliferating cysts need to be excised with a margin because they will recur if tissue is left behind.

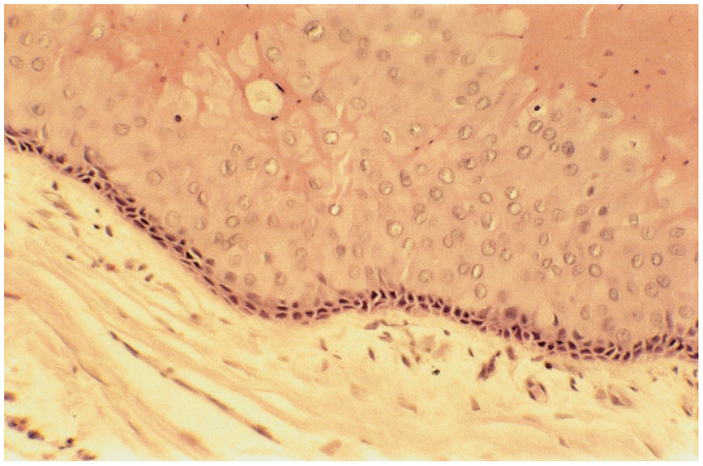


Fig. 52.26 Pilar cyst showing typical pathological features (see text).



Fig. 52.27 Clinical illustration of steatocystoma multiplex on the chest.

Steatocystoma multiplex

Synonyms
- Sebocystomatosis
- Hereditary epidermal polycystic disease

Definition. Multiple cysts in the dermis having sebaceous gland lobules in their wall and containing sebum.

Incidence and aetiology. It is a very uncommon condition, which usually begins in adolescence or early adult life [8]. It is inherited as an autosomal dominant condition in many cases [9,10]. The sexes are affected equally [11].

Clinical features. Multiple, smooth, compressible nodules are present within the dermis, varying in diameter from a few millimetres to 20 mm or more (Fig. 52.27). They usually first appear or become larger at puberty. The trunk and proximal part of the limbs are most commonly involved, particularly the presternal area. No punctum is usually apparent over the cyst, but there may be widespread comedones [12]. The more superficial lesions may have a yellowish colour. If pricked, an oily fluid can be expressed. Some lesions become inflamed, suppurate and heal with scarring.

Pathology. The cyst is situated in the mid-dermis. The wall is thin and composed of keratinizing epithelium. In some sections, lobules of sebaceous glands can be seen to form part of the wall or to empty by ducts into the cyst. The contents are oily, and are composed of the unsplit esters of sebum [13]. They may contain hairs. Hair roots and, occasionally, sweat glands may be found connected with the cyst, and the whole complex is joined to the epidermis by a short strand of undifferentiated cells [14].

Treatment. The number of cysts makes excision impractical in most cases. There is no reason, apart from cosmetic, for treating them.

Milium

Definition. A small subepidermal keratin cyst.

Incidence and aetiology. Milia are quite common at all ages from infancy onwards. Many arise in undeveloped sebaceous glands. This may occur in young women as an eruptive phenomenon, and is sometimes a sequel to sunbathing. Others may arise in the proximal part of divided sweat ducts. The cause of the duct damage is usually avulsion accompanying an acute subepidermal bulla, particularly in second-degree burns, epidermolysis bullosa, porphyria cutanea tarda and bullous lichen planus. They may also follow dermabrasion and occur in areas of chronic topical corticosteroid-induced atrophy. Destruction of skin appendages by radiotherapy may result in a ring of milium-like lesions at the margin of an area treated with tumour doses. These, unlike other forms, can be expressed easily.

Clinical features. The lesions are firm, white or yellowish, rarely more than 1 or 2 mm in diameter and appear to be immediately beneath the epidermis. They are usually noticed only on the face, and occur in the areas of vellus hair follicles, on the cheeks and eyelids particularly. Those that follow blisters are scattered more or less at random in the affected area (Fig. 52.28).

Pathology. The lesion is so easily treated that specimens for histological examination are uncommon. However, the milia that follow blistering can often be traced to eccrine sweat ducts in serial sections. Those at the margin of an irradiated area are usually situated in the distorted remnant of the pilosebaceous duct. The much more common milia of the face are found within the undifferentiated sebaceous collar that encircles many vellus hair follicles. The white milium body is composed of lamellated keratin.

Diagnosis. Milia are recognized as groups of small uniform spherical white papules with a smooth non-umbilicated top. They are usually whiter and more translucent than syringomas, which appear clinically to be more deeply situated in the skin. Milia tend



Fig. 52.28 Multiple milia on the upper cheek area.

to occur in isolation and are not associated with papules, comedones and cysts such as may be seen in closed comedones associated with acne and chloracne. Trichoepithelioma may rarely cause confusion, but tend to be larger, more multi-lobulated structures even on clinical examination.

Treatment. Incision of the epidermis over the milium with a cutting edge needle or sharp-pointed scalpel and squeezing out the contents is usually effective. Recurrence is uncommon. Spontaneous disappearance occurs in many milia in infants.

References

1 Leppard BJ, Sanderson KV, Wells RS. Hereditary trichilemmal cysts: hereditary pilar cysts. *Clin Exp Dermatol* 1977; **2**: 23–32.
2 Pinkus H. 'Sebaceous cysts' are trichilemmal cysts. *Arch Dermatol* 1969; **99**: 544–55.
3 Leppard BJ, Bussey HJR. Gardner's syndrome with epidermoid cysts showing features of pilomatrixomas. *Clin Exp Dermatol* 1976; **1**: 75–82.
4 McGauran MH, Binnington B. Keratinous cysts of the skin: identification and differentiation of pilar cysts from epidermal cysts. *Arch Dermatol* 1966; **94**: 499–508.
5 Holmes EJ. Tumors of lower hair sheath: common histogenesis of certain so-called 'sebaceous cysts', acanthomas and 'sebaceous carcinomas'. *Cancer* 1968; **21**: 234–48.
6 Leppard BJ, Sanderson KV. The natural history of trichilemmal cysts. *Br J Dermatol* 1976; **94**: 379–90.
7 Wilson Jones E. Proliferating epidermoid cysts. *Arch Dermatol* 1966; **94**: 11–9.
8 Mount LB. Steatocystome multiplex. *Arch Dermatol Syphilol* 1937; **36**: 31–9.
9 Noojin RO, Reynolds JP. Familial steatocystome multiplex: twelve cases in three generations. *Arch Dermatol Syphilol* 1948; **57**: 1013–8.
10 Sachs W. Steatocystome multiplex congenitale: ten cases in three generations. *Arch Dermatol Syphilol* 1938; **38**: 877–80.
11 Amerlinck F. Sébocystomatose héréditaire. *Arch Belges Dermatol Syphiligr* 1949; **5**: 187–91.
12 Schiff BL, Kern AB, Ronchese F. Steatocystoma multiplex. *Arch Dermatol* 1958; **77**: 516–8.
13 Nicolaides N, Wells GC. On the biogenesis of the free fatty acids in human skin surface fat. *J Invest Dermatol* 1957; **29**: 423.
14 Kligman AM, Kirschbaum JD. Steatocystoma multiplex: a dermoid tumor. *J Invest Dermatol* 1964; **42**: 383–7.

Premalignant fibroepithelial tumour (of Pinkus)

Definition. A premalignant tumour composed of cells resembling those of BCC arranged in a thin honeycomb around a prominent, overgrown papillary stroma.

Incidence. Relatively uncommon. Several examples have arisen in areas treated by radiotherapy for ankylosing spondylitis [1,2]. The author has seen one case on the chest of a patient with multiple postarsenical BCC.

Clinical features. The tumour is sessile with a domed surface and is firm and flesh-coloured. Most of the recorded lesions have been found on the abdomen or loins. There may be seborrhoeic keratoses or BCCs, or both, elsewhere [3]. Increase in size, when it occurs, is slow. The tumour is most likely to be diagnosed as a fibroma.

Pathology. The outline is domed and the surface is formed of normal epidermis. The bulk of the tumour is composed of considerably enlarged dermal papillae, more cellular and fibrotic than normal, which are surrounded by strands of small dark cells that extend down from the underside of the epidermis. Small buds of cells may arise from the strands and enlarge to form BCC, replacing part or all of the tumour [4].

Treatment. The lesions should be surgically excised.

References

1 Colomb D, Vittori F, Perraud R. Les épithéliomas baso-cellulaires et les tumeurs fibro-épithéliales de Pinkus multiples de la région lumbosacrée: discussion de role déclenchant d'un traitement radio-therapique antérieur—a propos de 4 observations. *Semin Hop Paris* 1975; **51**: 2655–64.
2 Sarkany I, Fountain RB, Evans CD *et al*. Multiple basal-cell epitheliomata following radiotherapy of the spine. *Br J Dermatol* 1968; **80**: 90–6.
3 Jaeger H, Delacrétaz J. Tumeurs fibro-épithéliales prémalignes de Pinkus: relation de deux nouveaux cas. *Dermatologica* 1956; **112**: 364–70.
4 Degos R, Hewitt J. Tumeurs fibro-épithéliales prémalignes de Pinkus et épithélioma basocellulaire: a propos de deux cas nouveaux. *Ann Dermatol Syphiligr* 1995; **82**: 124–39.

CHAPTER 53
Tumours of the Skin Appendages

E. Calonje
St John's Institute of Dermatology, St Thomas' Hospital, London, UK

Hair-follicle tumours, 53.2
Inverted follicular keratosis, 53.2
Dilated pore, 53.3
Tumour of the follicular infundibulum, 53.3
Pilar sheath acanthoma, 53.3
Trichoadenoma, 53.3
Comedo naevus, 53.4
External root-sheath tumours, 53.4
Trichilemmal cyst, 53.4
Proliferating trichilemmal tumour, 53.4
Trichilemmoma, 53.5
Trichilemmal carcinoma, 53.6
Hamartomas and hair germ tumours and cysts, 53.6
Hair-follicle naevus, 53.6
Eruptive vellus cyst, 53.7
Trichofolliculoma, 53.7
Trichoepithelioma, 53.8
Desmoplastic trichoepithelioma, 53.9
Solitary giant trichoepithelioma, 53.10
Trichoblastoma, 53.10
Cutaneous lymphadenoma, 53.11
Basaloid follicular hamartoma, 53.11
Hair matrix tumours, 53.12
Pilomatricoma, 53.12
Pilomatricarcinoma, 53.14
Lesions of hair-follicle mesenchyme, 53.14
Trichodiscoma, 53.14
Perifollicular fibroma, 53.14
Fibrofolliculoma, 53.14
Sebaceous gland tumours, 53.15
Sebaceous adenomas and sebaceomas, 53.15
Superficial epithelioma with sebaceous differentiation, 53.17
Sebaceous carcinoma, 53.17
Apocrine gland tumours, 53.18
Apocrine hidrocystoma, 53.18
Syringocystadenoma papilliferum, 53.19
Hidradenoma papilliferum, 53.20
Apocrine tubular adenoma, 53.21
Apocrine carcinoma, 53.21
Eccrine gland tumours, 53.22
Eccrine hidrocystoma, 53.22
Hidroacanthoma simplex, 53.22
Eccrine poroma, 53.23
Eccrine dermal duct tumour, 53.24
Eccrine syringofibroadenoma, 53.24
Syringoma, 53.25
Papillary eccrine adenoma, 53.26
Eccrine or apocrine/follicular tumours, 53.27
Hidradenoma, 53.27
Cylindroma, 53.28
Spiradenoma, 53.29
Mixed tumour of the skin, 53.30
Sweat gland carcinomas, including ductal apocrine/follicular carcinomas, 53.32
Eccrine gland carcinomas, 53.32
Malignant eccrine poroma, 53.32
Aggressive digital papillary adenocarcinoma, 53.33
Eccrine or apocrine/follicular carcinomas, 53.33
Malignant cylindroma, 53.33
Malignant hidradenoma, 53.34
Malignant spiradenoma, 53.34
Microcystic adnexal carcinoma, 53.35
Eccrine epithelioma, 53.36
Mucinous carcinoma, 53.36
Adenoid cystic carcinoma, 53.37
Miscellaneous tumours, 53.37
Tumours of anogenital mammary-like glands, 53.37
Paget's disease of the nipple, 53.38
Extramammary Paget's disease, 53.40
Lymphoepithelioma-like carcinoma, 53.41
Merkel cell carcinoma, 53.42

Introduction

The anatomical relationships of the epidermis and dermis are fully discussed in Chapter 3. The skin appendages are of particular interest in this respect, in that they clearly show a morphological and, in some instances, functional interrelationship. The appendageal tumours discussed in this chapter either differentiate towards or arise from the pilosebaceous apparatus (including the apocrine gland) and eccrine sweat gland [1–9].

The pilosebaceous apparatus can be divided into the hair follicle, the adjacent sebaceous gland and in some body sites the apocrine glands. Small strips of smooth muscle, the arrector pili muscle, are also found in association with these structures.

The pilosebaceous apparatus is concentrated in the head and neck area, with the pilar element predominant on the scalp and the sebaceous element on the face, chest and upper back. Thus, tumours arising from these structures are found predominantly at these anatomical sites.

The eccrine sweat glands are, in contrast, found on all body sites and comprise a double-layered, deeply situated secretory structure and a more superficial excretory duct winding through the dermis and spiralling through the epidermis to reach the surface of the skin.

The excretory (ductal) portions of the eccrine and apocrine glands are identical and cannot be differentiated on morphological grounds unless the apocrine duct can be identified entering the hair follicle. To complicate matters further, the apocrine duct rarely opens directly into the epidermis, and there are no histochemical or immunohistochemical stains that allow distinction

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

between eccrine and apocrine tumours. From this, it can be inferred that adnexal tumours showing ductal differentiation may be either eccrine or apocrine, and distinction is not possible unless there is concomitant follicular differentiation. It has therefore been proposed that the classification of adnexal tumours should follow a more logical approach that takes this into consideration [6]. It has become apparent that tumours traditionally considered to be of eccrine differentiation, such as cylindroma, spiradenoma and mixed tumour (so-called chondroid syringoma) may show either line of differentiation and this is probably most often apocrine. Even a classical eccrine tumour such as poroma has been described occasionally as differentiating towards the apocrine duct [7].

A wide range of cells make up the secretory and excretory components of the appendage ducts, the hair follicles and the sebaceous glands. As each cell type capable of dividing can give rise to a tumour as a result of inappropriate transfer of genetic material and cell division, it follows that an equal number of tumours are theoretically possible. The great majority of these appendage-derived tumours are relatively benign, with behaviour and prognosis similar to that seen in basal cell carcinoma. Thus, although local recurrence is well recorded, metastases are rare, with the exception of the malignant eccrine and apocrine gland-derived tumours and ocular sebaceous carcinoma. It is important to take into account that malignant adnexal tumours with metastasis are over-reported in the literature and that this has led to overestimation of their true malignant potential.

Appendage tumours are relatively rare, and their clinical appearance is commonly non-specific. The great majority are not diagnosed as such until after excision and pathological study. Classification systems for these lesions tend to be controversial, but in general the system groups lesions according to their morphological similarity to normal appendage structures.

References

1 Brownstein MH. The genodermatology of adnexal tumors. *J Cutan Pathol* 1984; **11**: 457–65.
2 Hashimoto K, Lever WF. *Appendage Tumors of the Skin*. Springfield: Thomas, 1968.
3 Various authors. *J Cutan Pathol* 1984; **11** [whole issue].
4 Kligman AM, Pinkus H. The histogenesis of nevoid tumors of the skin. *Arch Dermatol* 1960; **81**: 922–30.
5 Lever WF. Pathogenesis of benign tumors of cutaneous appendages and of basal cell epithelioma. *Arch Dermatol Syphilol* 1948; **57**: 679–724.
6 McCalmont TH. A call for logic in the classification of adnexal neoplasms. *Am J Dermatopathol* 1996; **18**: 104–9.
7 Mehregan AH. The origin of the adnexal tumors of the skin: a viewpoint. *J Cutan Pathol* 1985; **12**: 459–67.
8 Pinkus H. Premalignant fibroepithelial tumors of the skin. *Arch Dermatol Syphilol* 1953; **67**: 598–615.
9 Wick MR, ed. *Pathology of Unusual Malignant Cutaneous Tumours*. New York: Dekker, 1985.

Hair-follicle tumours

A large number of tumours are theoretically capable of arising from the hair follicle and matrix, depending on the exact type of cell and its situation within the dermis. A representative selection of these tumours will be described here. For a comprehensive list, the reader is referred to specialized publications [1,2]. Studies on the role of the sonic hedgehog gene and related proteins in basal cell carcinoma (see Chapter 52) have been extended to hair-follicle tumours [3]. The patched gene is located on chromosome 9q22.3, and loss of heterozygosity has been identified in sporadic trichoepitheliomas [4]. Overexpression of Gli-1, which is integral to this pathway, has been observed in trichoepitheliomas in mice [5].

β-Catenin plays a key role in signal transduction and subsequent tissue modelling, and mutations in the β-catenin gene have been recorded in pilomatricomas [6,7].

References

1 Ackermann AB. *Neoplasms with Follicular Differentiation*. New York: Lea & Febiger, 1993.
2 Headington JT. Tumours of the hair follicle: a review. *Am J Clin Pathol* 1976; **85**: 480–514.
3 Callahan CA, Oro AE. Regulating hair follicle progenitors through sonic hedgehog signalling. *Curr Opinion Genet Dev* 2001; **11**: 541–6.
4 Matt D, Xin H, Vortmeyer AO *et al*. Sporadic trichoepithelioma demonstrates deletions at 9q22.3. *Arch Dermatol* 2000; **136**: 657–60.
5 Nilsson M, Unden AB, Krause D *et al*. Induction of basal cell carcinomas and trichoepitheliomas in mice overexpressing Gli 1. *Proc Natl Acad Sci USA* 2000; **97**: 3438–43.
6 Kajino Y, Yamaguchi A, Hashimoto N *et al*. Beta catenin gene mutation in human hair follicle related tumours. *Path Int* 2001; **51**: 543–8.
7 Park SW, Suh KS, Wang HY *et al*. Beta catenin expression in the transitional cell zone of pilomatricoma. *Br J Dermatol* 2001; **145**: 624–9.

Inverted follicular keratosis [1–3]

Definition. A localized area of hyperkeratosis found in association with the pilosebaceous orifice. A number of these lesions arise as a result of infection of the infundibulum of the hair follicle by human papillomavirus (HPV). It is likely that a majority of these lesions may be regarded as the most superficial tumour of the follicular infundibulum (see below), arising as the result of irritation.

Clinical features. In common with many of the lesions described in this chapter, this lesion presents as a solitary papule on the head and neck area. It may reach a considerable size, and be inflamed and pruritic.

Pathology. The pathological features show an endophytic lesion connected to the infundibulum of the hair follicle. Irritated keratinocytes form whorls of cells, so-called 'squamous eddies', and keratin cysts. All of these features may give rise to problems with the differential diagnosis of squamous cell carcinoma, especially on small biopsies. This can be relatively easily distinguished on low-power examination, as there is no individual cell invasion into the dermis. At higher power, mitotic figures may be seen, but they are not abnormal mitoses. The appearances are identical to an irritated seborrhoeic keratosis, but the latter is exophytic.

Management. Local surgical excision is generally needed, for both diagnostic and therapeutic purposes. Occasionally, the lesions recur [3].

References

1 Azzopardi JG, Laurini R. Inverted follicular keratosis. *J Clin Pathol* 1975; **28**: 465–71.

2 Mehregan AH. Inverted follicular keratosis. *Arch Dermatol* 1964; **89**: 229–35.
3 Schweitzer JG, Yanoff M. Inverted follicular keratosis: a report of two recurrent cases. *J Ophthalmol* 1987; **94**: 1465–8.

Dilated pore [1,2]

Synonyms
- Wiener's pore
- Infundibuloma

Definition. An area of expanded follicular infundibulum with a dilated poral opening extending down to subcutaneous fat [2].

Clinical features. The pore is a comedo-like lesion found mainly on the head and neck area of the elderly.

Pathology. There is a wide, crater-like cavity, from which acanthotic areas of follicular epithelium radiate. The follicle is lined by outer root-sheath epithelium, and there is little evidence of a sebaceous gland or a well-formed emerging hair. Rare lesions may be associated with trichoblastoma [3] and exceptionally with either basal cell carcinoma [4] or squamous cell carcinoma [5].

References

1 Wiener L. The dilated pore, a trichoepithelioma. *J Invest Dermatol* 1954; **23**: 181–8.
2 Steffen C. Wiener's dilated pore: the infundibuloma. *Am J Dermatopathol* 2001; **23**: 246–53.
3 Misago N, Sada A, Narisawa Y. Thichoblastoma within a dilated pore. *J Am Acad Dermatol* 2006; **54**: 357–8.
4 Weigand DA, MacFarlane DF. Regarding trichoid basal cell carcinoma found in a dilated pore on the nose. *Dermatol Surg* 2000; **26**: 1084.
5 Zhao L, Xu J, Fang F *et al*. Squamous cell carcinoma found in a dilated pore. *J Eur Acad Dermatol Venereol* 2007; **21**: 277–8.

Tumour of the follicular infundibulum [1]

Definition. This lesion may be considered the hair-follicle equivalent of the eccrine dermal duct tumour (p. 53.24).

Clinical features. These lesions are usually found on facial skin and may be relatively large, irregular nodules. They are usually biopsied or excised to obtain a diagnosis, as the clinical appearance is not specific. It has been suggested that they can be divided into four main groups: solitary lesions; those in association with Cowden's disease; multiple eruptive tumours [2]; and follicular infundibulum-like changes in the epidermis [1].

Pathology [3–5]. The pathology is that of a large, horizontally orientated plate of small, dark cells situated in the superficial dermis, usually with multiple connections to the overlying epidermis. The cellular detail is focally similar to that seen in the trichilemmoma, with large numbers of small polygonal cells with clear cytoplasm contained within a palisaded border. Basaloid cells are often seen. The resemblance to basal cell carcinoma is striking, but the stromal element is lacking. Occasionally, sebaceous differentiation may be seen [6]. These lesions with sebaceous differentiation have been termed superficial epithelioma with sebaceous differentiation [7] and acanthomatous superficial sebaceous hamartoma [8].

References

1 Cribier B, Grosshans E. Tumours of the follicular infundibulum: a clinicopathological study. *J Am Acad Dermatol* 1995; **33**: 979–84.
2 Cheng AC, Chang YL, Wu YY *et al*. Multiple tumors of the follicular infundibulum. *Dermatol Surg* 2004; **30**: 1246–8.
3 Mehregan AH. Tumor of follicular infundibulum. *Dermatologica* 1971; **142**: 177–83.
4 Mehregan AH, Buttler JD. A tumor of follicular infundibulum. *Arch Dermatol* 1961; **83**: 924–7.
5 Mehregan AH. Infundibular tumours of the skin. *J Cutan Pathol* 1984; **11**: 387–9.
6 Mahalingam M, Bhawan J, Finn R *et al*. Tumor of the follicular infundibulum with sebaceous differentiation. *J Cutan Pathol* 2001; **28**: 314–7.
7 Rothko K, Farmer ER, Zeligman I. Superficial epithelioma with sebaceous differentiation. *Arch Dermatol* 1980; **116**: 329–31.
8 Leboeuf NR, Mahalingam M. Acanthomatous superficial sebaceous hamartoma? A study of six cases with clarification of the nomenclature. *J Cutan Pathol* 2007; **34**: 865–70.

Pilar sheath acanthoma [1]

Clinical features. These lesions are very rare and are most commonly seen on the upper lip area of the elderly [2,3].

Pathology. The pathology is that of an expanded area of the outer root-sheath epithelium within an irregularly branched cystic cavity, with large lobules of epithelial cells radiating outwards from this cavity area.

References

1 Mehregan AH, Brownstein MH. Pilar sheath acanthoma. *Arch Dermatol* 1978; **114**: 1495–7.
2 Bhawan J. Pilar sheath acanthoma. A new benign follicular tumor. *J Cutan Pathol* 1979; **6**: 438–40.
3 Vakilzadeh F. Haarscheidenakanthom. *Hautarzt* 1987; **38**: 40–2.

Trichoadenoma [1–5]

Definition. A rare benign tumour, with multiple cystic structures closely resembling the infundibular portion of the hair follicle. The keratin profile expression supports the theory that this tumour differentiates towards the follicular infundibulum and the follicular bulge region [6].

Clinical features. This lesion presents as a non-specific nodule, usually on the face, although there are some reports of lesions on the buttocks. An exceptional congenital case has been reported [7] and lesions may occur within a naevus sebaceus [8] or coexist with an intradermal naevus [9].

Pathology. The lesions are in the upper dermis, and on light-microscope scanning power give the impression of a cluster of cysts. On higher power, these cyst-like structures have an appearance similar to the infundibular portion of the hair follicle but turned through 90°; no recognizable hair shafts are seen.

References

1 Rahbari H, Mehregan AM, Pinkus H. Trichoadenoma of Nikolowski. *J Cutan Pathol* 1977; **4**: 90–8.

2 Nikolowski W. Trichoadenom. *Arch Klin Exp Dermatol* 1958; **207**: 34–45.
3 Nikolowski W. Trichoadenom. *Z Hautkrankh* 1977; **53**: 87–90.
4 Undeutsch W, Rassner G. Das Trichoadenom (Nikolowski). *Hautarzt* 1984; **35**: 650–2.
5 Rahbari H, Mehregan A, Pinkus H. Trichoadenoma of Nikolowski. *J Cutan Pathol* 1977; **4**: 90–8.
6 Kurokawa I, Mizutani H, Nishijima S *et al*. Trichoadenoma: cytokeratin expression suggesting differentiation towards the follicular infundibulum and follicular bulge regions. *Br J Dermatol* 2005; **153**: 1084–6.
7 Lee WS, Oh ST, Lee JY *et al*. Congenital trichoadenoma with an unusual clinical manifestation. *J Am Acad Dermatol* 2007; **57**: 905–6.
8 Miller CJ, Ioffreda MD, Billingsley EM. Sebaceous carcinoma, basal cell carcinoma, trichoadenoma, trichoblastoma, and syringocystadenoma papilliferum arising within a nevus sebaceous. *Dermatol Surg* 2004; **30**: 1546–9.
9 González-Vela MC, Val-Bernal JF, García-Alberdi E *et al*. Trichoadenoma associated with an intradermal melanocytic nevus: a combined malformation. *Am J Dermatopathol* 2007; **29**: 92–5.

Comedo naevus [1–3]

Definition. A rare abnormality of the follicular infundibulum presenting as a group of comedo-like lesions.

Clinical features. These lesions are rare and are seen mainly on the head and neck area. Cases may also occur at other sites including the palm and wrist [4]. The palm is not an area that contains hair follicles and the unusual presentation of nevus comedonicus in this location has led to the suggestion that these lesions may really represent variants of sweat duct naevus [5]. They may be present at birth or develop throughout adult life. They appear as a cluster of comedones or as a single giant lesion [3].

Pathology. A rudimentary pilosebaceous follicle is present, with a large overlying keratin-filled crater. The surface of the keratinous material oxidizes to give the comedone-like appearance. Rarely, lesions develop trichilemmal cysts [6].

References

1 Nabai H, Mehregan AH. Naevus comedonicus. *Acta Derm Venereol* 1973; **53**: 71–4.
2 Cestari TF, Rubim M, Valentini BC. Naevus comedonicus. *Paediatr Dermatol* 1991; **8**: 300–5.
3 Fletcher CL, Acland KM, Powles AV. Unusual giant comedo naevus. *Clin Exp Dermatol* 1999; **24**: 186–8.
4 Harper KE, Spielvogel RL. Nevus comedonicus of the palm and wrist. Case report with review of five previously unreported cases. *J Am Acad Dermatol* 1985; **12**: 185–8.
5 Marsden RA, Fleming K, Dawber RP. Comedo naevus of the palm—a sweat duct naevus? *Br J Dermatol* 1979; **101**: 717–22.
6 Leppard BJ. Trichilemmal cysts arising in an intensive comedo naevus. *Br J Dermatol* 1977; **96**: 545–8.

External root-sheath tumours

Trichilemmal cyst

Definition. A cyst apparently arising from the external root sheath, containing keratin and breakdown products [1,2].

Clinical features. These lesions are mainly seen on the scalp and are relatively common. They may be familial, inherited by autosomal-dominant transmission [3]. Females are affected more often than males. They present clinically as firm nodules, which may become infected or inflamed after minor trauma. They are commonly multiple. Unusual locations include the extremities and even the pulp of a finger [4]. A case of Merkel cell carcinoma arising from a trichilemmal cyst has been reported [5]. A further case of multiple trichilemmal cysts following Blaschko's lines and associated with filiform hyperkeratosis and referred to as trichilemmal cyst naevus has also been published [6].

Pathology. These cysts are well circumscribed in the dermis and lined by two or three layers of small, dark keratinocytes. There is then an abrupt transition, towards the centre of the lesion, to large, pale cells with features of root-sheath cells. A granular cell layer is absent. The centre of the cyst contains keratin debris. Some lesions are hybrid and show focal changes of an epidermoid cyst, with formation of a granular cell layer [7]. Occasional lesions have a verrucous lining and in one of these lesions, human papillomavirus has been identified [8].

Management. These are commonly excised to obtain a diagnosis. Lesions that are shelled out may recur [9].

References

1 McGauran MH, Binnington B. Keratinous cysts of the skin: identification and differentiation of pilar cysts from epidermal cysts. *Arch Dermatol* 1966; **94**: 499–508.
2 Pinkus H. Sebaceous cysts are trichilemmal cysts. *Arch Dermatol* 1969; **99**: 544–5.
3 Leppard BJ, Sanderson KV, Wells RS. Hereditary trichilemmal cysts. *Clin Exp Dermatol* 1977; **2**: 23–32.
4 Ikegami T, Kameyama M, Orikasa H *et al*. Trichilemmal cyst in the pulp of the index finger: a case report. *Hand Surg* 2003; **8**: 253–5.
5 Ivan D, Bengana C, Lazar AJ *et al*. Merkel cell tumor in a trichilemmal cyst: collision or association? *Am J Dermatopathol* 2007; **29**: 180–3.
6 Tantcheva-Poor I, Reinhold K, Krieg T *et al*. Trichilemmal cyst nevus: a new complex organoid epidermal nevus. *J Am Acad Dermatol* 2007; **57**: 572–7.
7 Takeda H, Miura A, Katagata Y *et al*. Hybrid cyst: case reports and review of 15 cases in Japan. *J Eur Acad Dermatol Venereol* 2003; **17**: 83–6.
8 Misago N, Narisawa Y. Verrucous trichilemmal cyst containing human papillomavirus. *Clin Exp Dermatol* 2005; **30**: 38–9.
9 Leppard BJ, Sanderson KV. The natural history of trichilemmal cysts. *Br J Dermatol* 1976; **94**: 379–90.

Proliferating trichilemmal tumour

Synonym
- Proliferating trichilemmal cyst

Clinical features. The tumour presents as a rapidly growing, large nodule, commonly on the head (scalp and less commonly the face) and neck area followed by the trunk of the elderly with predilection for females [1,2]. Some lesions are very large and may be more than 10 cm in diameter. The history of rapid expansion frequently gives rise to concern about malignancy. Malignant change has been rarely reported in these lesions (see below). Occasionally, tumours may develop within a pre-existing naevus sebaceus [3]. Multiple lesions are exceptional [4].

Pathology. These lesions may arise from pre-existing trichilemmal cysts, and remnants of a classic trichilemmal cyst may be present [1,2]. The architecture is lobular and expansile, without an infiltrative growth pattern. Tumour lobules are cystic and composed of pale squamous cells with mild atypia. However, tumour cells in the periphery of the lobules may display more prominent cytological atypia and mitotic activity. This is particularly true in early lesions that are actively growing. The surrounding stroma may be fibrotic with inflammation consisting of lymphocytes and plasma cells and a foreign body granulomatous reaction may be seen in areas where cystic structures have ruptured. Cholesterol clefts and areas of calcification may also be seen. Rarely sebaceous, apocrine and matrical differentiation may be present [5,6]. Exceptionally a malignant spindle cell component has been described [7,8]. If there is frank invasion into adjacent structures in association with tumour necrosis, cytological atypia and increased mitotic activity, the diagnosis of a malignant proliferating trichilemmal tumour should be made [9–11]. Such tumours are often characterized clinically by rapid growth and large size [11]. Metastases may occur, leading to death. The diagnosis is often very difficult in small samples of tissue, and ideally the whole tumour should be submitted for histological examination to avoid confusion with a squamous cell carcinoma. The increased expression of p53 by tumour cells similar to that seen in ordinary squamous cell carcinoma but much lower than that seen in trichilemmal cysts suggests that all these lesions may represent low-grade malignancies [12].

Management. Local recurrence takes place and complete excision is therefore necessary.

References

1 Wilson-Jones E. Proliferating epidermoid cysts. *Arch Dermatol* 1966; **94**: 11–9.
2 Sau P, Graham JH, Helwig EB. Proliferating epithelial cysts: an analysis of 96 cases. *J Cutan Pathol* 1995; **22**: 394–406.
3 Rahbari H, Pinkus H. Developmet of proliferating trichilemmal cyst in organoid nevus. Presentation of two cases. *J Am Acad Dermatol* 1986; **14**: 123–6.
4 Hendricks DL, Liang MD, Borochovitz D *et al*. A case of multiple pilar tumors and pilar cysts involving the scalp and back. *Plasr Reconstr Surg* 1991; **87**: 763–7.
5 Sakamoto F, Ito M, Nakamura A *et al*. Proliferating trichilemmal cyst with apocrine-acrosyringeal and sebaceous differentiation. *J Cutan Pathol* 1991; **18**: 137–41.
6 Noto G, Pravatà G, Aricó M. 'Shadow' cell in proliferating trichilemmal tumors. *Am J Dermatopathol* 1990; **12**: 319–20.
7 Mori O, Hachisuka H, Sasai Y. Proliferating trichilemmal cyst with spindle cell carcinoma. *Am J Dermatopathol* 1990; **12**: 479–84.
8 Plumb SJ, Stone MS. Proliferating trichilemmal tumor with a malignant spindle cell component. *J Cutan Pathol* 2002; **29**: 506–9.
9 Weis J, Heine M, Grimmel M *et al*. Malignant proliferating trichilemmal cyst. *J Am Acad Dermatol* 1995; **32**: 870–3.
10 Sethi S, Singh UR. Proliferating trichilemmal cyst: report of 2 cases—one benign, the other malignant. *J Dermatol* 2002; **29**: 214–20.
11 Folpe AL, Reisenauer AK, Mentzel T *et al*. Proliferating trichilemmal tumors: clinicopathologic evaluation is a guide to biologic behavior. *J Cutan Pathol* 2003; **30**: 492–8.
12 Fernández-Figueras MT, Casalots A, Puig L *et al*. Proliferating trichilemmal tumour: p53 immunoreactivity in association with p27Kip1 over-expression indicates low-grade carcinoma profile. *Histopathology* 2001; **38**: 454–7.

Trichilemmoma [1–3]

Definition. This lesion is classically considered to be a proliferation of the external root sheath of the hair follicle [4,5]. However, immunohistochemical studies with different molecular weight keratins normally expressed by different components of the hair follicle have not only confirmed the latter but suggest that the lesion also displays infundibular keratinization [6].

Clinical features. Clinically, these lesions are small, non-specific papules on facial skin; they present in young and middle-aged adults. Their importance lies in the fact that patients with Cowden's syndrome or multiple hamartoma and neoplasia syndrome [7–14]—which is associated with a very high incidence of breast, thyroid and gastrointestinal carcinomas—have large numbers of trichilemmomas. The diagnosis of multiple trichilemmomas should therefore stimulate a search for other evidence of Cowden's syndrome. This includes a characteristic 'cobblestone' appearance of the oral epithelium, multiple skin tags, squamous papillomas and sclerotic fibromas (storiform collagenomas). Mutations of the *PTEN* tumour suppressor gene on chromosome 10q23 are found in Cowden's syndrome [15,16]. The number of mutations identified is large and continues to increase [16]. It seems that the benign lesions in Cowden's syndrome occur without loss of the second *PTEN* allele while the malignant tumours require inactivation of both alleles and additional somatic mutations [17].

Pathology. These lesions are well-circumscribed, lobular tumours extending down from the epidermis and often connected to a hair follicle. Tumour cells display prominent clear cytoplasm secondary to the deposition of glycogen. The presence of glycogen can be confirmed with a positive periodic acid–Schiff (PAS) stain, which becomes negative after treatment with diastase. There is an irregular enclosing PAS-positive, diastase-resistant membrane. In a number of cases, there is prominent hyperplasia of the surface epithelium, with hypergranulosis, clumping of keratohyalin granules and hyperkeratosis. This suggests induction of some lesions by HPV. A viral aetiology has been confirmed by demonstration of HPV DNA by polymerase chain reaction in some [18] but not all cases of the tumour [19]. Trichilemmomas are often found within a naevus sebaceus.

A variant of trichilemmoma, described as desmoplastic trichilemmoma, has been reported [20]. The periphery of this lesion has histological features identical to those of ordinary trichilemmoma, but towards the centre there are strands of squamous cells embedded in a desmoplastic stroma. This stroma appears to contain type I collagen and tenascin but not laminin or type IV collagen [21]. This results in an infiltrative appearance that may be confused with a squamous cell carcinoma, particularly in small biopsy samples.

References

1 Brownstein MH, Shapiro L. Trichilemmoma. *Arch Dermatol* 1973; **107**: 866–9.
2 Headington JT, French AJ. Primary neoplasms of the hair follicle. *Arch Dermatol* 1962; **86**: 430–41.
3 Ingrish FM, Reed RJ. Trichilemmoma. *Dermatol Int* 1968; **7**: 182–90.
4 Brownstein MH, Shapiro EE. Trichilemmal horn: cutaneous horn overlying trichilemmoma. *Clin Exp Dermatol* 1979; **4**: 59–63.

5 Mehregan AH, Medenica M, Whitney D. A clear cell pilar sheath tumor of scalp: case report. *J Cutan Pathol* 1988; **15**: 380–4.
6 Kurokawa I, Nishijima S, Kusomoto K *et al*. Trichilemmomas: an immunohistochemical study of cytokeratins. *Br J Dermatol* 2003; **149**: 99–104.
7 Allen BS, Fitch MH, Smith JG Jr. Multiple hamartoma syndrome. *J Am Acad Dermatol* 1980; **2**: 303–8.
8 Brownstein MH, Mehregan AH, Bikowski B *et al.* The dermatopathology of Cowden's syndrome. *Br J Dermatol* 1979; **100**: 667–73.
9 Brownstein MH, Wolf M, Bikowski JB. Cowden's disease: a cutaneous marker of breast cancer. *Cancer* 1978; **41**: 2393–8.
10 Grattan CEH, Hamburger J. Cowden's disease in two sisters, one showing partial expression. *Clin Exp Dermatol* 1987; **12**: 360–3.
11 Starink TM, Hausman R. The cutaneous pathology of extrafacial lesions in Cowden's disease. *J Cutan Pathol* 1984; **11**: 338–44.
12 Taylor AJ, Dodds WJ, Stewart ET *et al.* Alimentary tract lesions in Cowden's disease. *Br J Radiol* 1989; **62**: 890–2.
13 Thyresson HN, Doyle JA. Cowden's disease (multiple hamartoma syndrome) (review). *Mayo Clin Proc* 1981; **56**: 179–84.
14 Weary PE, Gorlin RJ, Gentry WC Jr *et al.* Multiple hamartoma syndrome (Cowden's disease). *Arch Dermatol* 1972; **106**: 682–90.
15 Liew D, Marsh DJ, Li J *et al.* Germline mutations of the PTEN gene in Cowden's disease. *Nat Genet* 1997; **16**: 64–7.
16 Bussaglia E, Pujol RM, Gil MJ *et al.* PTEN mutations in eight Spanish families and one Brazilian family with Cowden syndrome. *J Invest Dermatol* 2002; **118**: 639–44.
17 Reifenberger J, Rauch L, Beckmann MW *et al*. Cowden's disease: clinical and molecular genetic findings in a patient with a novel PTEN germline mutations. *Br J Dermatol* 2003; **148**: 1040–6.
18 Rohwedder A, Keminer O, Hendricks C *et al*. Detection of HPV DNA in trichilemmomas by polymerase chain reaction. *J Med Virol* 1997; **51**: 119–25.
19 Leonardi CL, Zhu WY, Kinsey WH *et al*. Trichilemmomas are not associated with human papillomavirus DNA. *J Cutan Pathol* 1991; **18**: 193–7.
20 Hunt SJ, Kilzer B, Santa Cruz DJ. Desmoplastic trichilemmoma: histologic variant resembling invasive carcinoma. *J Cutan Pathol* 1990; **17**: 45–52.
21 Massi D, Franchi A. Desmoplastic trichilemmoma: a case report with immunohistochemical characterization of the extra cellular matrix components. *Acta Derm Venereol* 1997; **77**: 347–9.

Trichilemmal carcinoma [1–4]

Definition. A very rare tumour with metastatic capacity, usually arising in sun-exposed skin of the elderly.

Clinical features. This lesion presents as a solitary, expanding, often ulcerating lesion on the face. Clinically it may be misdiagnosed as a basal cell carcinoma. Exceptionally, multiple tumours have been described [5]. Trichilemmal carcinoma may arise from a trichoblastoma and in the context of a naevus sebaceus [6]. It has also been described in the setting of solid organ transplantation [7,8].

Pathology. These lesions invade downwards from the epidermis or outer root-sheath areas in a multilobular and infiltrative fashion. They may have a surrounding PAS-positive membrane, and there is central trichilemmal keratinization. There is a high mitotic rate, with abnormal mitoses present. The diagnosis of trichilemmal carcinoma should only be made in the presence of clear evidence of trichilemmal differentiation. The presence of clear-cell change is not enough to make this diagnosis. Most malignant cutaneous tumours with clear-cell change are squamous cell carcinomas and often show at least focal evidence of keratinization. An exceptional case of trichilemmal carcinoma with neuroendocrine differentiation has been reported [9]. Immunohistochemical studies in a single case of trichiolemmal carcinoma, suggest that the tumour shows differentiation towards the follicular infundibulum rather than towards the outer root sheath as ordinary trichilemmomas usually do [10]. However, the latter also show infundibular follicular differentiation and it is possible that malignant counterparts lose the expression of markers of outer-sheath differentiation.

Management. Surgical excision with clear margins is the treatment of choice.

References

1 Ten Seldam REJ. Tricholemmocarcinoma. *Aust J Dermatol* 1977; **18**: 62–72.
2 Wong TY, Suster S. Tricholemmal carcinoma. *Am J Dermatopathol* 1994; **16**: 463–73.
3 Headington JT. Trichilemmal carcinoma. *J Cutan Pathol* 1992; **16**: 31–9.
4 Reis JP, Tellechea O, Unha MF *et al*. Trichilemmal carcinoma: a study of seven cases. *J Cutan Pathol* 1993; **20**: 44–9.
5 Chan KO, Lim IJ, Baladas HG, Tan WT. Multiple tumour presentation of trichilemmal carcinoma. *Br J Plast Surg* 1999; **52**: 665–7.
6 Misago N, Narisawa Y. Tricholemmal carcinoma in continuity with trichoblastoma within nevus sebaceous. *Am J Dermatopathol* 2002; **24**: 149–55.
7 Kanitakis J, Euvard S, Sebbag L *et al*. Trichilemmal carcinoma of the skin mimicking a keloid in a heart transplant patient. *J Heart Lung Transplant* 2007; **26**: 649–51.
8 Garrett AB, Scott KA. Trichilemmal carcinoma: a case report of a rare skin cancer occurring in a renal transplant patient. *Transplantation* 2003; **76**: 1131.
9 Pozo L, Díaz-Cano SJ. Trichilemmal carcinoma with neuroendocrine differentiation. *Clin Exp Dermatol* 2008; **33**: 128–31.
10 Kurokawa I, Senba Y, Nishimara K *et al*. Cytokeratin expression in trichilemmal carcinoma suggests differentiation towards follicular infundibulum. *In Vivo* 2006; **20**: 583–5.

Hamartomas and hair germ tumours and cysts

Hair-follicle naevus [1,2]

Clinical features. These naevi are very rare and are recognized as plaque-like lesions with small tufts of hairs. They present in children and may be congenital. The so-called 'faun tail naevus' is a hair-follicle naevus on the sacral skin. Rare cases occur following Blaschko's lines [3]. A rare association with frontonasal dysplasia has been reported [4]. It is not clear whether some hair follicle naevi are variants of accessory tragi [5].

Pathology. The pathology of this entity consists of a group of normal vellus hair follicles clustered together.

References

1 Choi EH, Ahn SK, Lee SH, Bang D. Hair follicle naevus. *Int J Dermatol* 1992; **31**: 578–81.
2 Labandeira J, Peteiro C, Toribio J. Hair follicle naevus: case report and review. *Am J Dermatopathol* 1996; **18**: 90–3.
3 Germain M, Smith KJ. Hair follicle nevus in a distribution following Blaschko's lines. *J Am Acad Dermatol* 2002; **46**: S125–7.
4 Kuwahara H, Lao LM, Kiyohara T *et al*. Hair follicle nevus occurring in frontonasal dysplasia: an electron microscopic observation. *J Dermatol* 2001; **28**: 324–8.
5 Ban M, Kamiya H, Yamada T *et al*. Hair follicle nevi and accessory tragic: variable quantity of adipose tissue in connective tissue framework. *Pediatr Dermatol* 1997; **14**: 433–6.

Eruptive vellus cyst

Definition. Occlusion and cystic dilatation of vellus hair follicles.

Clinical features. These present as small red or brown papules on the chest, commonly in the second decade of life [1]. They are usually multiple, and family clusters have been reported with some lesions showing features of eruptive vellus hair cysts, other lesions showing features of steatocystoma and some displaying hybrid features [2,3]. Lesions may rarely be unilateral [4] or even generalized [5] and have been reported in chronic renal failure [6]. They are commoner than expected in patients who also have pachonychia congenita [7,8].

Pathology. Cysts are located in the mid-dermis, and are lined by squamous epithelium. They contain vellus hair and keratin debris. Biopsies from some lesions show features indistinguishable from steatocystoma, with absence of vellus hairs. This finding shows that there is an overlap with steatocystoma multiplex [9,10].

Management. If treatment is requested, the lesions may clear after application of topical retinoids [11]. Curettage and laser therapy may also be effective, but it is easy to cause scarring. Pulsed carbon dioxide laser is useful for facial lesions but this treatment may induce hypertrophic scarring if used for truncal lesions. Success has been reported at the latter site with erbium:YAG laser [12]. However, when this treatment is used on facial lesions, although initial results are good, there is tendency for local recurrence. This is due to the fact that the depth of ablation of facial lesions is superficial to avoid scarring and atrophy [13].

References

1 Esterly NB, Fretzin DF, Pinkus H. Eruptive vellus hair cysts. *Arch Dermatol* 1977; **113**: 500–3.
2 Mayron R, Grimwood RE. Familial occurrence of eruptive vellus cysts. *Paediatr Dermatol* 1992; **9**: 98–102.
3 Patrizi A, Neri I, Guerrini V *et al*. Persistent milia, steatocystoma multiplex and eruptive vellus hair cysts: variable expression of multiple pilosebaceous cysts within an affected family. *Dermatology* 1998; **196**: 392–6.
4 Lew BL, Lee MH, Haw CR. Unilateral eruptive vellus hair cysts occurring on the face. *J Eur Acad Dermatol Venereol* 2006; **20**: 1314–6.
5 Kwon KS, Lee HT, Jang HS *et al*. A case of generalized eruptive vellus hair cysts. *J Dermatol* 1997; **24**: 556–7.
6 Mieno H, Fujimoto N, Tajima S. Eruptive vellus hair cyst in patients with chronic renal failure. *Dermatology* 2004; **208**: 67–9.
7 Takeshita T, Takeshita H, Irie K. Eruptive vellus hair cyst and epidermoid cyst in a patient with pachonychia congenita. *J Dermatol* 2000; **27**: 655–7.
8 Lee HT, Chang SH, Yoon TY. Eruptive vellus hair cysts in a patient with pachonychia congenita. *J Dermatol* 1999; **26**: 402–4.
9 Patrizi A, Neri I, Guerrini V *et al*. Persistent milia, steatocystoma multiplex and eruptive vellus hair cysts: variable expression of multiple pilosebaceous cysts within an affected family. *Dermatology* 1998; **196**: 392–6.
10 Kiene P, Hauschild A, Christopher E. Eruptive vellus hair cysts and steatocystoma multiplex variants of one entity? *Dermatology* 1996; **134**: 365–7.
11 Urbina-González F, Aguilar-Martínez A, Cristóbal-Gil MC, Sánchez de Paz F. The treatment of eruptive vellus hair cysts with isotretinoin. *Br J Dermatol* 1987; **116**: 465–6.
12 Kageyama N, Tope WD. Treatment of multiple eruptive hair cysts with erbium:YAG laser. *Dermatol Surg* 1999; **25**: 819–22.



Fig. 53.1 Typical example of a trichofolliculoma, with a small tuft of hairs in the centre.

13 Coras B, Hohenleutner U, Landthaler M *et al*. Early recurrence of eruptive vellus cysts after Er:YAG laser therapy: case report and review of the literature. *Dermatol Surg* 2005; **31**: 1741–4.

Trichofolliculoma [1]

Definition. This lesion is a hamartoma of the pilosebaceous follicle, which results in several hairs being formed within the follicular opening and all protruding onto the epidermal surface from the one pilosebaceous orifice [2–6].

Clinical features. Most cases occur in young adults with predilection for the head and neck, particularly the face. Occasionally, tumours present in the vulva [7]. Clinically, lesions can be recognized as small, raised nodules with two or three hairs protruding together in a small tuft (Fig. 53.1).

Pathology. The pathological appearance is that of a dilated and abnormally large pilosebaceous canal containing numerous, poorly formed hairs, with several pilosebaceous-like structures opening into the canal (Fig. 53.2). The components of the lesion undergo evolutionary changes similar to those of the normal hair follicle [8]. Malignant change has been suggested in a single case with perineural invasion [9]. The so-called folliculosebaceous cystic hamartoma is considered by some authors to be a variant of trichofolliculoma in a late stage of development [10]. This view, however, is not agreed upon by other authors [11].

Management. Simple surgical excision is the treatment of choice.

References

1 Gray HR, Helwig EB. Trichofolliculoma. *Arch Dermatol* 1962; **86**: 619–25.
2 Hyman AB, Clayman SJ. Hair follicle nevus. *Arch Dermatol* 1957; **75**: 678–84.
3 Kligman AM, Pinkus H. The histogenesis of nevoid tumors of the skin. *Arch Dermatol* 1960; **81**: 922–30.
4 Pinkus H, Sutton RL Jr. Trichofolliculoma. *Arch Dermatol* 1965; **91**: 46–9.
5 Plewig G. Sebaceous trichofolliculoma. *J Cutan Pathol* 1980; **7**: 394–403.
6 Sanderson KV. Hair follicle naevus. *Trans St John's Hosp Dermatol Soc* 1961; **47**: 154–6.

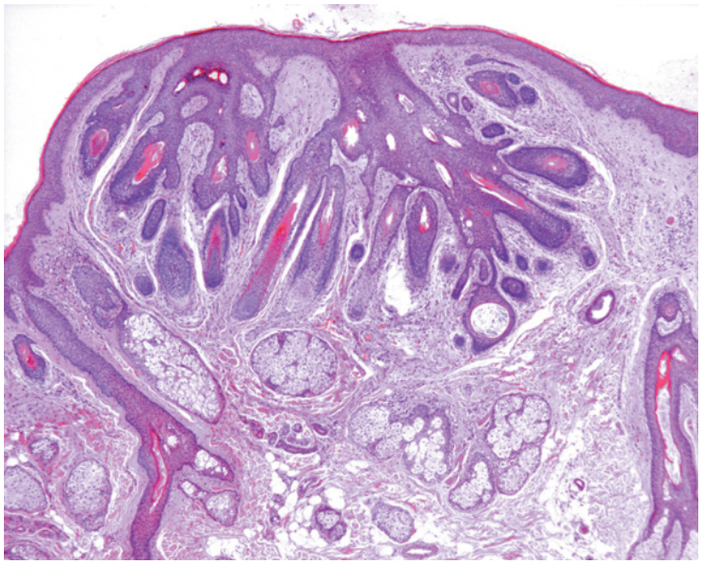


Fig. 53.2 Trichofolliculoma. A large, central follicular structure from which immature follicular structures radiate.

7 Peterdy GA, Huettner PC, Rajaram V *et al*. Trichofolliculoma of the vulva associated with vulvar intraepithelial neoplasia: report of three cases and review of the literature. *Int J Gynecol Pathol* 2002; **21**: 224–30.

8 Schulz T, Hartschuh W. The trichofolliculoma undergoes changes corresponding to the regressing normal hair follicle in its cycle. *J Cutan Pathol* 1998; **25**: 341–53.

9 Stern JB, Stout DA. Trichofolliculoma showing perineural invasion: trichofolliculocarcinoma? *Arch Dermatol* 1979; **115**: 1003–4.

10 Schulz T, Hartschuh W. Folliculo-sebaceous cystic hamartoma is a trichofolliculoma at its very late stage. *J Cutan Pathol* 1998; **25**: 354–64.

11 Tanimura S, Arita K, Iwao F *et al*. Two cases of folliculosebaceous cystic hamartoma. *Clin Exp Dermatol* 2006; **31**: 68–70.

Trichoepithelioma [1]

Synonyms
- Epithelioma adenoides cysticum
- Brooke's tumour

Definition. A hamartoma of the hair germ composed of immature islands of basaloid cells with focal, primitive follicular differentiation and induction of a cellular stroma. Trichoepithelioma is regarded nowadays as part of the spectrum of trichoblastoma and it is increasingly described under the same heading in some textbooks.

Clinical features. The presentation of a solitary lesion is that of a smooth nodule, usually on the face, which clinically resembles a non-ulcerated basal cell carcinoma. Most affected patients are young adults. Multiple lesions, which are inherited by autosomal-dominant transmission, are seen as multiple, small, pearly lesions, mainly on centrofacial skin (Fig. 53.3). Malignant transformation of trichoepithelioma is extremely rare [2].

Pathology [3–5]. The pathology is identical for solitary or multiple lesions and consists of lobules of small, dark basaloid cells,



Fig. 53.3 Multiple trichoepitheliomas on the central face.

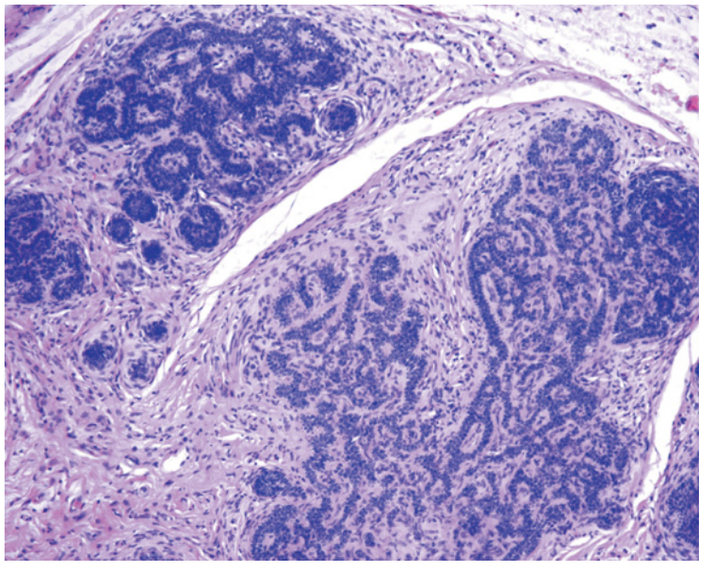


Fig. 53.4 Trichoepithelioma. A lobular basaloid tumour with induction of stroma and immature follicular differentiation.

often with a degree of peripheral palisading surrounding a central area of eosinophilic amorphous material (Fig. 53.4). Occasionally, hair shaft-like structures can be seen in these central areas. A fibrous cellular stroma is seen around the cellular lobules. There is frequently a strong resemblance to basal cell carcinoma, and at times differentiating between the two can be very difficult. However, the stroma in trichoepithelioma is distinctive in that it contains clefts, with an absence of retraction artefact between tumour cells and the surrounding stroma.

The gene for multiple trichoepitheliomas has been mapped to a locus on chromosome 9p21 [6]. The commoner sporadic cases of trichoepithelioma have, in a proportion of cases, deletions at chromosome 9q22.3, the site of the human homologue of the *Drosophila* patched gene [7]. Familial basal cell carcinomas and some cases of sporadic basal cell carcinomas also show this deletion. It has been proposed that in multiple trichoepitheliomas tumours develop

from undifferentiated germinative cells of the pilosebaceous–apocrine unit [8].This explains why in some cases tumours have features of spiradenoma and/or cylindroma, particularly in the Brooke–Spiegler syndrome. The Brooke–Spiegler syndrome inherited by autosomal dominant transmission consists of multiple trichoepitheliomas, cylindromas and spiradenomas and the gene for this syndrome has been mapped to chromosome 16q12–13 [9]. Mutations in the gene *CYLD*, a tumour suppressor gene, are responsible for the manifestations of the disease [9].

In multiple lesions, which are present in epithelioma adenoides cysticum [10–14], larger lesions may be yellow, pink, or sometimes bluish from pigmentation, and there may be dilated blood vessels over the surface. Individual tumours reach a limiting size, but the numbers may increase over the years.

Treatment. Any suspicion of malignant change calls for adequate excision and histological examination. The only other reason for treatment is cosmetic. Partial destruction is usually followed by regrowth. Many treatment modalities may be used including surgical excision, curettage, cryotherapy and dermabrasion. High energy pulsed carbon dioxide laser has also been advocated as a useful treatment [15,16].

References

1 Lever WF. Pathogenesis of benign tumors of cutaneous appendages and of basal cell epithelioma. *Arch Dermatol Syphilol* 1948; **57**: 679–724.
2 Lee KH, Kim JE, Cho BK *et al*. Malignant transformation of multiple familial trichoepithelioma: case report and literature review. *Acta Derm Venereol* 2008; **88**: 43–6.
3 Kopf AW. The distribution of alkaline phosphatase in normal and pathologic human skin. *Arch Dermatol* 1957; **75**: 1–37.
4 Müller-Hess S, Delacrétaz J. Trichoepitheliom mit Strukturen eines apokrinen Adenoms. *Dermatologica* 1973; **146**: 170–6.
5 Bettencourt MS, Prieto VG, Shea R. Trichoepithelioma: a 19-year clinicopathologic re-evaluation. *J Cutan Pathol* 1999; **26**: 398–404.
6 Harada H, Hashimoto KY, Ko MSH. The gene for multiple trichoepitheliomas maps to chromosome 9p21. *J Invest Dermatol* 1996; **107**: 41–3.
7 Matt D, Xin H, Vortmeyer AO *et al*. Sporadic trichoepithelioma demonstrates deletions at 9q22.3. *Arch Dermatol* 2000; **136**: 657–60.
8 Clarke J, Ioffreda M, Helm KE. Multiple familial trichoepitheliomas: a folliculosebaceous-apocrine genodermatosis. *Am J Dermatopathol* 2002; **24**: 402–5.
9 Hu G, Onder M, Gill M *et al*. A novel missense mutation in CYLD in a family with Brooke-Spiegler syndrome. *J Invest Dermatol* 2003; **121**: 732–4.
10 Gray HR, Helwig EB. Epithelioma adenoides cysticum and solitary trichoepithelioma. *Arch Dermatol* 1963; **87**: 102–14.
11 Anderson DE, Howell JB. Epithelioma adenoides cysticum: genetic update. *Br J Dermatol* 1976; **95**: 225–32.
12 Gaul LE. Heredity of multiple benign cystic epithelioma. *Arch Dermatol Syphilol* 1953; **68**: 517–24.
13 Pariser RJ. Multiple hereditary trichoepitheliomas and basal cell carcinomas. *J Cutan Pathol* 1986; **13**: 111–7.
14 Ziprkowski L, Schewach-Millet M. Multiple trichoepithelioma in a mother and two children. *Dermatologica* 1966; **132**: 248–56.
15 Rosenbach A, Alster TS. Multiple trichoepitheliomas successfully treated with a high energy, pulsed carbon dioxide laser. *Dermatol Surg* 1997; **23**: 708–10.
16 Retamar RA, Stengel F, Saadi ME *et al*. Brooke-Spiegler syndrome—report of four families: treatment with CO_2 laser. *Int J Dermatol* 2007; **46**: 583–6.

Desmoplastic trichoepithelioma [1–3]

Synonym
- Sclerosing epithelial hamartoma

These two terms were introduced almost simultaneously. The US group of Brownstein and Shapiro used the term 'desmoplastic trichoepithelioma' [2], while MacDonald, Wilson Jones and Marks in the UK suggested the term 'sclerosing epithelial hamartoma' [3].

Definition. A slowly expanding plaque of tissue containing hair follicle-like structures.

Clinical features. Lesions are found mainly on the face of young patients and have a depressed centre and a raised, rolled edge in many cases, causing clinical confusion with basal cell carcinoma. To date, more females than males have been reported with the condition. Exceptionally, lesions may be familial [4] and a congenital case has been described [5].

Pathology. Tumours are symmetrical on scanning magnification. The three features that characterize this lesion are large numbers of small, keratin-filled cysts, strands and ribbons of small, dark, epithelioid cells, and a dense fibrous stroma surrounding the first two structures. Perineural invasion is not a feature.

The striking palisading of the basal cell carcinoma is absent. There is, however, a considerable similarity to the sclerosing (morphoeic) variant of basal cell carcinoma, although the number of cysts is very much greater in the desmoplastic trichoepithelioma. Distinction from microcystic adnexal carcinoma may be impossible in a small and superficial biopsy. The latter, however, shows a diffuse infiltrative pattern, with prominent perineural invasion. Merkel cells are present in desmoplastic trichoepithelioma and absent in microcystic adnexal carcinoma and in most cases of morphoeic basal cell carcinoma [6]. Immunostaining with cytokeratin 20, to identify Merkel cells, is therefore useful in the differential diagnosis of these neoplasms.

An electron microscopic and immunohistochemical study with different types of keratins has suggested that this tumour derives from basal cells in the outer root sheath of the hair follicle which can differentiate into various components of the folliculosebaceous and apocrine unit [7].

Occasional desmoplastic trichoepitheliomas are combined with a benign melanocytic naevus [8].

Treatment. Local excision is effective in the majority of cases.

References

1 Dupré A, Bonafé JL, Lassere J. Hamartome épithélial sclérosant: forme clinique du trichoépithéliome. *Ann Dermatol Vénéréol* 1980; **107**: 649–54.
2 Brownstein MH, Shapiro L. Desmoplastic trichoepithelioma. *Cancer* 1977; **40**: 2979–86.
3 MacDonald DM, Wilson Jones E, Marks R. Sclerosing epithelial hamartoma. *Clin Exp Dermatol* 1977; **2**: 153–60.
4 Wang SH, Tsai RY, Chi CC. Familial desmoplastic trichoepithelioma. *Int J Dermatol* 2006; **45**: 756–8.
5 Carter JJ, Kaur MR, Hargitai B *et al*. Congenital desmoplastic trichoepithelioma. *Clin Exp Dermatol* 2007; **32**: 522–4.
6 Abesamis-Cubillan E, El-Shabrawi-Caelen L, LeBoit P. Merkel cells and sclerosing epithelial neoplasms. *Am J Dermatopathol* 2000; **22**: 311–5.
7 Yamamoto O, Hamada T, Doi Y *et al*. Immunohistochemical and ultrastructural observations of desmoplastic trichoepithelioma with a special reference to a morphological comparison with normal apocrine acrosyringium. *J Cutan Pathol* 2002; **29**: 15–26.

8 Niimi Y, Kawana S. Desmoplastic trichoepithelioma: the association with compound nevus and ossification. *Eur J Dermatol* 2002; **12**: 90–2.

Solitary giant trichoepithelioma [1,2]

Synonym
- Giant trichoblastoma

This is a rare variant of trichoblastoma with a dramatic clinical presentation that may cause concern about a rapidly growing malignancy. It has also been described under the name 'trichoblastic fibroma'. Trichoepithelioma and giant trichoepithelioma represent the more mature end of the spectrum of trichoblastoma. These tumours are described separately because they represent distinctive clinicopathological entities. However, it should be remembered that histological overlap is often seen.

Clinical features [3–5]. The clinical presentation is of a very large, polypoid lesion presenting on the lower trunk, frequently in the perianal area, with a history of recent rapid growth. The lesions may cause considerable discomfort because of their size. They affect both sexes equally.

Pathology. The pathology shows the features of the smaller, classical trichoepithelioma but the lesions are much larger, deeper and often located in the subcutaneous fat. An oedematous myxoid stroma is frequently seen and focally, various stages of follicular differentiation are identified. Mitotic figures are frequent, but abnormal mitoses are not seen.

Management. Excision is required, both to confirm the diagnosis and because of discomfort as local recurrence is exceptional [6]. Malignant change into basal cell carcinoma has been reported in a giant trichoepithelioma in a patient with multiple trichoepitheliomas [7].

References

1 Tatnall FM, Wilson-Jones E. Giant solitary trichoepitheliomas located in the perianal area: a report of three cases. *Br J Dermatol* 1986; **115**: 91–9.
2 Zeligma I. Solitary trichoepithelioma. *Arch Dermatol* 1960; **82**: 35–40.
3 Czernobilsky B. Giant solitary trichoepithelioma. *Arch Dermatol* 1972; **105**: 587–8.
4 Filho GB, Toppa NH, Miranda D *et al*. Giant solitary tricho-epithelioma. *Arch Dermatol* 1984; **120**: 797–8.
5 Jemec B, Lovgreen Nielsen P, Jemec GB *et al*. Giant solitary trichoepithelioma. *Dermatol Online J* 1999; **5**: 1.
6 Beck S, Cotton DW. Recurrent giant solitary giant trichoepithelioma located in the perianal area: a case report. *Br J Dermatol* 1988; **118**: 563–6.
7 Martínez CA, Priolli DG, Piovesan H *et al*. Nonsolitary giant perianal trichoepithelioma with malignant transformation into basal cell carcinoma: report of a case and review of the literature. *Dis Colon Rectum* 2004; **47**: 773–7.

Trichoblastoma [1–4]

Synonyms
- Trichogenic fibroma
- Trichoblastic fibroma

Definition. Tumours of the hair germ composed of follicular germinative cells.

Clinical features. These are deeply or superficially situated dermal and/or subcutaneous nodules [5], found—as is common with follicular tumours—on the head and neck. Often lesions are found within naevus sebaceus [6] and trichoblastoma is regarded as the most common neoplasm occurring in this hamartoma [7]. Tumours may be induced by low-dose X-ray depilatory treatment such as was used in the past to treat ringworm [8].

Pathology. Nests of basophilic basaloid cells with a lobular architecture and prominent induction of stroma are seen in the dermis and/or subcutaneous tissue. Focal evidence of follicular differentiation is seen, but this usually consists of less mature structures than those seen in trichoepithelioma. Characteristically, condensation of cellular stroma is seen around aggregates of basaloid cells but true follicular papillae are not formed as the stroma does not invaginate into the epithelial component. Mitotic figures vary and may be frequent. Usually, the tumour is not connected to the epidermis. According to the degree of follicular differentiation and the amount of stroma induced, lesions have been subclassified into different categories, including trichogenic and trichoblastic fibromas. However, all tumours in this category are best classified as variants of trichoblastoma. Some tumours display sebaceous and even ductal (apocrine) differentiation confirming the theory that they differentiate towards the folliculosebaceous and apocrine germ [9,10]. Melanin deposition is often seen, may be prominent and is not uncommonly associated with the presence of melanocytes [11] within the tumour as seen in normal hair follicles. In some cases, rows of tumours cells are arranged parallel to each other in a pattern that has been described as rippled trichoblastoma [12]. Occasional neoplasms consist mainly of clear cells, a change that indicates trichilemmal differentiation [13]. Histological overlap with trichoepithelioma is often seen and there is a tendency to regard all these tumours as part of the same spectrum. Distinction between nodular trichoblastoma and follicular basal cell carcinoma may be very difficult, particularly in small biopsies. Distinction is usually based on the presence of a deep infiltrative pattern in the latter [14]. The presence of Merkel cells in trichoblastoma identified by immunohistochemical markers (cytokeratin 20, chromogranin) is useful in the differentiation from basal cell carcinoma which lacks these cells [15]. Based on clinicopathological features and the presence of Merkel cells in the neoplasm it has been proposed that fibroepithelioma of Pinkus is a variant of trichoblastoma rather than a variant of basal cell carcinoma [16]. A further aid in the differential diagnosis between basal cell carcinoma and trichoblastoma is the immunohistochemical expression of androgen receptor. The latter is usually positive in basal cell carcinoma and negative in benign follicular neoplasms [17].

Management. Behaviour is usually benign but malignant transformation of the epithelial or even the mesenchymal component (trichoblastic carcinoma/sarcoma) may occasionally occur [18,19]. Complete excision is often desirable as exclusion of a basal cell carcinoma may be difficult in small biopsies.

References

1 Slater D. Trichoblastic fibroma. *Histopathology* 1987; **11**: 327–31.
2 Wong TY, Reed JA, Suster S. Benign trichogenic tumours: a report of two cases supporting a simplified nomenclature. *Histopathology* 1993; **22**: 575–80.
3 Blake Gilks C, Clement CB, Wood WS. Trichoblastic fibroma. *Am J Dermatopathol* 1989; **11**: 397–402.
4 Altman DA, Mikhail GR, Johnson TM *et al*. Trichoblastic fibroma. *Arch Dermatol* 1995; **131**: 198–201.
5 Kaddu S, Schaeppi H, Kerl H *et al*. Subcutaneous trichoblastoma. *J Cutan Pathol* 1999; **26**: 490–6.
6 Cribier B, Scrivener Y, Grosshans E. Tumors arising in nevus sebaceous: A study of 596 cases. *J Am Acad Dermatol* 2000; **42**: 263–8.
7 Jaqueti G, Requena L, Sánchez-Yus E. Trichoblastoma is the most common neoplasm developed in nevus sebaceous of Jadassohn: a clinicopathologuic study of a series of 155 cases. *Am J Dermatopathol* 2000; **22**: 108–18.
8 Fazaa B, Cribier B, Zaraa I *et al*. Low-dose X-ray depilatory treatment induces trichoblastic tumors of the scalp. *Dermatology* 2007; **215**: 301–7.
9 Chang SN, Chung YL, Kim SC *et al*. Trichoblastoma with sebaceous and sweat gland differentiation. *Br J Dermatol* 2001; **144**: 1090–2.
10 Yu DK, Joo YH, Cho KH. Trichoblastoma with apocrine and sebaceous differentiation. *Am J Dermatopathol* 2005; **27**: 6–8.
11 Kanitakis J, Brutzkus A, Butnaru AC *et al*. Melanotrichoblastoma: immunohistochemical study of a variant of pigmented trichoblastoma. *Am J Dermatopathol* 2002; **24**: 498–501.
12 Yamamoto O, Hisaoka M, Yasuda H *et al*. A rippled-pattern trichoblastoma: an immunohistochemical study. *J Cutan Pathol* 2000; **27**: 460–5.
13 Kazakov DV, Mentzel T, Erlandson RA *et al*. Clear cell trichoblastoma: a clinicopathological and ultrastructural study of two cases. *Am J Dermatopathol* 2006; **28**: 197–201.
14 Cowen EW, Helm KF, Billingsley EM. An unusually aggressive trichoblastoma. *J Am Acad Dermatol* 2000; **42**: 374–7.
15 Collina G, Eusebi V, Capella C *et al*. Merkel cell differentiation in trichoblastoma. *Virchows Arch* 1998; **433**: 291–6.
16 Bowen AR, LeBoit PE. Fibroepithelioma of Pinkus is a fenestrated trichoblastoma. *Am J Dermatopathol* 2005; **27**: 149–54.
17 Izikson L, Bhan A, Zembowicz A. Androgen receptor expression helps to differentiate basal cell carcinoma from benign trichoblastic tumors. *Am J Dermatopathol* 2005; **27**: 91–5.
18 Regauer S, Beham-Schmid C, Okcu M *et al*. Trichoblastic carcinoma ('malignant trichoblastoma') with lymphatic and hematogenous metastases. *Mod Pathol* 2000; **13**: 673–8.
19 Rosso R, Lucioni M, Savio T *et al*. Trichoblastic sarcoma: a high-grade stromal tumor arising in a trichoblastoma. *Am J Dermatopathol* 2007; **29**: 79–83.

Cutaneous lymphadenoma [1–7]

Synonym
- Adamantinoid trichoblastoma

Definition. This entity was first described in 1991 [1], and to date there are around 35 reported cases in the literature. Follicular, sebaceous and ductal differentiation has been demonstrated and therefore this tumour is regarded as a variant of trichoblastoma, a neoplasm differentiating towards the folliculosebaceous and apocrine germ [4,8].

Clinical features. The lesions are seen mainly on the head and neck area, and present as non-specific papules or nodules. Both sexes are affected equally. The preoperative clinical diagnosis is frequently either basal cell carcinoma or intradermal naevus.

Pathology. The tumour consists of nests and lobules of basaloid cells in the reticular dermis, with no connection to the epidermis.

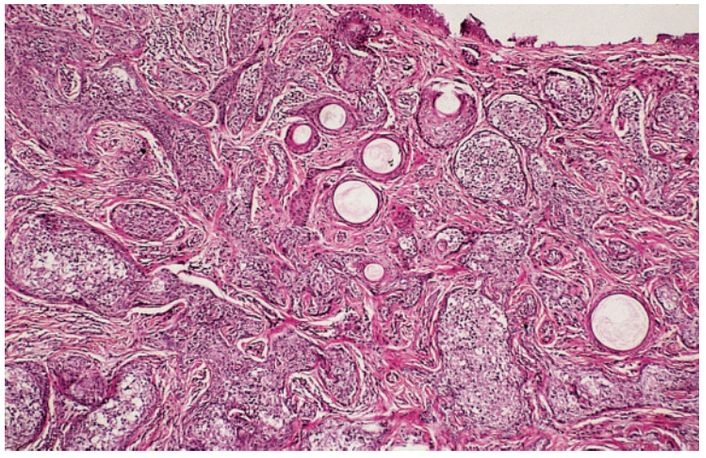


Fig. 53.5 Lymphadenoma. Nests and lobules of epithelial cells with prominent infiltration by lymphocytes.

These aggregates of cells are embedded in a fibrous stroma. Tumour cells are bland and display focal peripheral palisading. A striking feature is the presence of prominent infiltration of tumour lobules and nests by T lymphocytes and histiocytes (Fig. 53.5). These inflammatory cells are mainly located in the centre of the tumour lobules. No cellular atypia is seen, and mitotic figures are rare. Focal areas of keratinization are seen in some cases.

Treatment. Local excision is recommended. The behaviour is entirely benign.

References

1 Santa Cruz DJ, Barr RJ, Headington JT. Cutaneous lymphadenoma. *Am J Surg Pathol* 1991; **15**: 101–10.
2 Botella R, MacKie R. Cutaneous lymphadenoma: a case report and review of the literature. *Br J Dermatol* 1993; **128**: 339–41.
3 Civatte J, Moulonguet-Michau I, Marinho E *et al*. Tumeur epithelio-lymphohistiocytaire: à propos de 3 cas. *Ann Dermatol Vénéréol* 1990; **117**: 441–4.
4 Díaz-Cascajo C, Borghi S, Rey López A *et al*. Cutaneous lymphadenoma: a peculiar variant of nodular trichoblastoma. *Am J Dermatopathol* 1996; **18**: 186–92.
5 Requena L, Sánchez Yus E. Cutaneous lymphadenoma with ductal differentiation. *J Cutan Pathol* 1992; **19**: 429–33.
6 Pardal de Oliviera F, Sánchez A. Cutaneous lymphadenoma. *Histopathology* 1994; **25**: 384–7.
7 Murphy M, Brierley T, Pennoyer J *et al*. Lymphotropic adamantinoids trichoblastoma. *Pediatr Dermatol* 2007; **24**: 157–61.
8 McNiff JM, Eisen RN, Glusac EJ. Immunohistochemical comparison of cutaneous lymphadenoma, trichoblastoma, and basal cell carcinoma: support for classification of lymphadenoma as a variant of trichoblastoma. *J Cutan Pathol* 1999; **26**: 119–24.

Basaloid follicular hamartoma [1–4]

Definition. A hamartoma consisting of a proliferation of basaloid cells, with frequent involvement of hair follicles.

Clinical features. These lesions are usually small multiple papules that may become confluent to form a plaque. Involvement of the face is common but lesions may also present on the trunk. Presentation may be generalized or localized and the latter may be linear [4,5]. They may be present in isolation or inherited as an

autosomal-dominant trait [6,7]. Association with autoimmune diseases and alopecia has been described particularly in the generalized variant [8]. The autoimmune diseases include lupus erythematosus [9] and myasthenia gravis [5]. Other rare associations include cystic fibrosis [10], milia and hypohidrosis [11]. In exceptional cases, basal cell carcinomas may develop within the lesions [12].

Pathology. A multifocal proliferation of cords, strands and nests of basaloid cells is seen, with frequent connections to the epidermis. Basaloid cells focally replace neighbouring hair follicles. In addition, immature follicular bulbs may also be seen.

References

1 Mehregan AH, Baker S. Basaloid follicular hamartoma: three cases with localized and systematized unilateral lesions. *J Cutan Pathol* 1985; **12**: 55–65.
2 Brownstein MH. Basaloid follicular hamartoma: solitary and multiple types. *J Am Acad Dermatol* 1992; **22**: 237–40.
3 Walsh N, Ackerman AB. Basaloid follicular hamartoma. *J Am Acad Dermatol* 1993; **29**: 125–7.
4 Lee MW, Choi JH, Moon KC *et al*. Linear basaloid follicular hamartoma on the Blaschko's lines of the face. *Clin Exp Dermatol* 2005; **30**: 30–4.
5 El-Dorouti MA, Marzouk SA, Abdel-Halim MR *et al*. Basaloid follicular hamartoma. *Int J Dermatol* 2005; **44**: 361–5.
6 Wheeler CE, Carroll MA, Groben PA *et al*. Autosomal dominantly inherited generalized basaloid follicular hamartoma syndrome: report of a new disease in a North Carolina family. *J Am Acad Dermatol* 2000; **43**: 189–206.
7 Lee PL, Lourduraj LT, Palko MJ 3rd *et al*. Hereditary basaloid follicular hamartoma syndrome. *Cutis* 2006; **78**: 42–6.
8 Smith KJ, Skelton H. Basaloid follicular hamartoma associated with autoimmune disease: a possible role for retinoids in therapy. *J Am Acad Dermatol* 2003; **49**: 1067–70.
9 Morton S, Stevens A, Powell RJ. Basaloid follicular hamartoma, total body hair loss and SLE. *Lupus* 1998; **7**: 207–9.
10 Mascaró JM Jr, Ferrando J, Bombi JA *et al*. Congenital generalized follicular hamartoma associated with alopecia and cystic fibrosis in three siblings. *Arch Dermatol* 1995; **131**: 454–8.
11 Katayama I, Hirayama M, Eishi K. Basaloid follicular hamartoma with eruptive milia and hypohidrosis: is there is a pathogenic relationship? *Eur J Dermatol* 2003; **13**: 505–8.
12 Yoshida Y, Urabe K, Mashino T *et al*. Basal cell carcinomas in association with basaloid follicular hamartoma. *Dermatology* 2003; **207**: 57–60.

Hair matrix tumours

Pilomatricoma [1–4]

Synonyms
- Benign calcifying epithelioma of Malherbe
- Trichomatricoma
- Pilomatrixoma

Definition. A benign tumour considered to be a hamartoma of the hair matrix composed of cells resembling those of the hair matrix and cortex and inner root sheath. The cells usually undergo 'mummification'.

Incidence. This lesion makes up around 20% of all hair follicle-related tumours in most series and is therefore the commonest hair-follicle tumour. It may occur at any age from infancy and is frequently seen in children [5]. The majority of patients are under 20 years of age, and females are affected more often than males. A number of familial cases are recorded [6]. Association with myotonic dystrophy [6], Turner's syndrome [7] and Rubinstein–Taybi syndrome have been described [8]. *MYH*-associated polyposis is an autosomal recessive variant of familial adenomatous polyposis with susceptibility to colorectal carcinoma and association in some affected individuals with multiple pilomatricomas [9].



Fig. 53.6 Pilomatricoma. Small, red, firm papule.

Clinical features [10–16]. The lesion is usually a solitary, deep, dermal or subcutaneous tumour 3–30 mm in diameter situated on the head, neck or upper extremities (Fig. 53.6). Very large tumours occur occasionally [17]. The skin over the tumour is normal and the lesion has a firm to stone-hard consistency and a lobular shape on palpation. In adult life, there may be quite a short history [4] and there is usually no evidence of a preceding cyst. It may be subject to periodic inflammation and can present as a granulomatous swelling. Rarely, ulcerated lesions may show transepithelial elimination [18]. An unusual case associated with hypercalcaemia and high levels of parathyroid hormone has been described [19]. Malignant change is very rare (see below).

Pathology [20–27]. The tumour is situated in the dermis, and is composed of well-circumscribed, rounded islands giving a lobulated contour. The outer cells are small, and their rounded nuclei crowded together make this region deeply basophilic. Normal mitotic figures can usually be seen and are often numerous. The cytoplasm is scanty and the cell margins indistinct, but intercellular connections can be seen. Towards the centre of the mass, the cytoplasm becomes more abundant and eosinophilic. The nuclear outline persists, but the chromatin is sparse and clumped in dark granules; when all basophilic material disappears, a mummified 'ghost cell' remains (Fig. 53.7). The ultrastructural and histochemical characteristics of these cells mark them as hair-matrix cells maturing towards cortex or root sheath [3,26,27]. The central areas

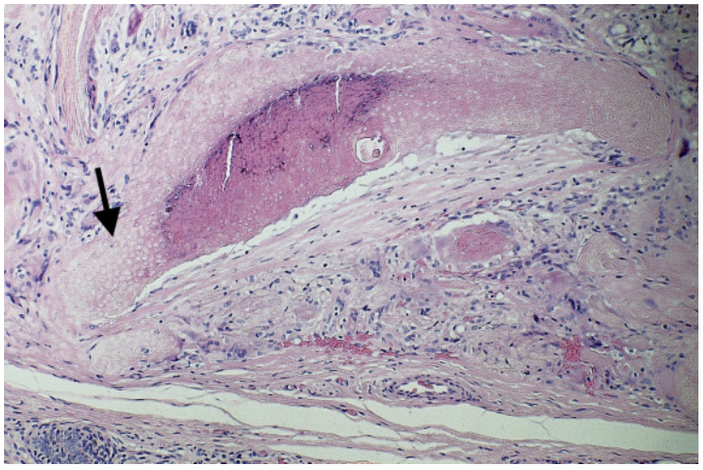


Fig. 53.7 Pilomatricoma. Lobules of basaloid cells intermixed with pale pink areas containing ghost cells.

often calcify, and calcium can be demonstrated in the basophilic areas of the tumour. In older lesions, the basophilic cells may be greatly reduced or disappear entirely. Melanin may be present, and dendritic melanocytes have been found between the tumour cells. The stroma that encapsulates the masses usually contains inflammatory and foreign-body giant cells, and occasionally ossifies. A rare variant of superficial pilomatricoma presenting clinically as a cutaneous horn and with an intraepidermal location has been reported [28]. A bullous appearance may occur consequent on lymphangiectasia [29], and anetoderma can occur in the dermis surrounding the tumour [30]. Occasional hybrid cysts may show areas of pilomatrical differentiation identical to pilomatricoma [31].

Studies have shown that 75% of pilomatricomas possess activating mutations of the β-catenin gene [32–34]. The sites of β-catenin expression within pilomatricomas suggest that this may affect cell–cell adhesion [35].

Diagnosis. The diagnosis can be suspected if a subcutaneous nodule feels hard and lobular. The presence of calcium salts may be apparent on radiographs, but these can also be deposited in other cysts and tumours of the skin. The microscopic picture is, however, diagnostic.

Malignant change is recorded in several cases, and appears to arise chiefly in large pilomatricomas that have been present for many years (see below).

Management. Local excision is required for benign lesions, as there is a tendency for local recurrence. Wider excision will be needed if malignancy is suspected.

References

1 Forbis R Jr, Helwig EB. Pilomatrixoma (calcifying epithelioma). *Arch Dermatol* 1961; **83**: 606–18.

2 Hashimoto K, Lever WF. Histogenesis of skin appendage tumors. *Arch Dermatol* 1969; **100**: 356–69.

3 McGavran MH. Ultrastructure of pilomatrixoma (calcifying epithelioma). *Cancer* 1965; **18**: 1445–56.

4 Swerlick RA, Cooper PH, Mackel SE. Rapid enlargement of pilomatricoma. *J Am Acad Dermatol* 1982; **7**: 54–6.

5 Schlechter MD, Hartsough NA, Guttman FM. Multiple pilomatricomas. *Paediatr Dermatol* 1984; **2**: 23–5.

6 Chiaramonti A, Gilgor RS. Pilomatricomas associated with myotonic dystrophy. *Arch Dermatol* 1978; **114**: 1363–5.

7 Noguchi H, Kayashima K, Nishiyama S *et al*. Two cases of pilomatrixoma in Turner's syndrome. *Dermatology* 1999; **199**: 338–40.

8 Cambiaghi S, Ermacora E, Brusasco A *et al*. Multiple pilomatricomas in Rubinstein–Taybi syndrome: a case report. *Pediatr Dermatol* 1994; **11**: 21–5.

9 Baglioni S, Melean G, Gensini F *et al*. A kindred with *MYH*-associated polyposis and pilomatricomas. *Am J Med Genet* A 2005; **134**: 212–4.

10 Lopansri S, Mihm MC Jr. Pilomatrix carcinoma or calcifying epitheliocarcinoma of Malherbe. *Cancer* 1980; **45**: 2368–73.

11 Cazers JS, Okun MR, Pearson SH. Pigmented calcifying epithelioma. *Arch Dermatol* 1974; **110**: 773–4.

12 Geiser JD. L'épithélioma calcifié de Malherbe. *Ann Dermatol Syphilol* 1959; **86**: 383–403.

13 Hadlich J, Linse R. Zur klinischen Diagnostik des Epithelioma calcificans Malherbe. *Dermatol Monatsschr* 1979; **165**: 432–9.

14 Moehlenbeck F. Pilomatrixoma (calcifying epithelioma). *Arch Dermatol* 1973; **108**: 532–4.

15 Peterson WC Jr, Hult AM. Calcifying epithelioma of Malherbe. *Arch Dermatol* 1964; **90**: 404–10.

16 Julian CG, Bowers PW. A clinical review of 209 pilomatricomas. *J Am Acad Dermatol* 1998; **39**: 191–5.

17 Lozzi GP, Soyer HP, Fruehauf J *et al*. Giant pilomatricoma. *Am J Dermatopathol* 2007; **29**: 286–9.

18 Honda Y, Ohi T, Koga M *et al*. Perforating pilomatricoma. *J Dermatol* 2002; **29**: 100–3.

19 Kambe Y, Nakano H, Kaneko T *et al*. Giant pilomatricoma associated with hypercalcaemia and elevated levels of parathyroid hormone-related protein. *Br J Dermatol* 2006; **155**: 208–10.

20 Hashimoto K, Nelson RG, Lever WF. Calcifying epithelioma of Malherbe: histochemical and electron microscopic studies. *J Invest Dermatol* 1966; **46**: 391–408.

21 Kaddu S, Soyer HP, Hodl S *et al*. Morphological stages of pilomatricoma. *Am J Dermatopathol* 1996; **18**: 333–8.

22 Lever WF, Griesemer RD. Calcifying epithelioma of Malherbe. *Arch Dermatol Syphilol* 1949; **59**: 506–18.

23 Solanki P, Ramzy I, Durr N *et al*. Pilomatrixoma. *Arch Pathol* 1987; **111**: 294–7.

24 Turhan B, Krainer L. Bemerkungen über die sogenannten verkalkenden Epitheliome der Haut und ihre Genese. *Dermatologica* 1942; **85**: 73–90.

25 Uchiyama N, Shindo Y, Saida T. Perforating pilomatricomas. *J Cutan Pathol* 1986; **13**: 312–8.

26 Wiedersberg H. Das Epithelioma calcificans Malherbe. *Dermatol Monatsschr* 1971; **157**: 867–83.

27 Lever WF, Hashimoto K. Die Histogenese einiger Hautanhangs-Tumoren im Lichte histochemischer und elektronenmikroskopischer Befunde. *Hautarzt* 1966; **17**: 161–73.

28 de la Torre JP, Saiz A, García-Arpa M *et al*. Pilomatrical horn: a new superficial variant of pilomatricoma. *Am J Dermatopathol* 2006; **28**: 426–8.

29 Yigun J, Jianfang S. Pilomatricoma with a bullous appearance. *J Cutan Pathol* 2004; **31**: 558–60.

30 Fernández-Flores A, Gonzalez-Montero JM. Anetodermic variant of pilomatricoma. *Int J Dermatol* 2005; **44**: 876–7.

31 May SA, Quirey R, Cockerell CJ. Follicular hybrid cysts with infundibular, isthmic-catagen, and pilomatrical differentiation: a report of 2 patients. *Ann Diagn Pathol* 2006; **10**: 110–3.

32 Gat U, DasGupta R, Degenstein L *et al*. De novo hair follicle morphogenesis and hair tumours in mice expressing a truncated beta catenin in skin. *Cell* 1998; **95**: 605–14.

33 Chan EF, Gat U, McNiff JM *et al*. A common skin tumour is caused by activating mutations in beta catenin. *Nat Genet* 1999; **21**: 410–3.

34 Durand M, Moles JP. Beta catenin mutations in a common skin cancer: pilomatricoma. *Bull Cancer* 1999; **86**: 725–6.

35 Park SW, Suh KS, Wang HY *et al*. Beta catenin expression in the transitional zone of pilomatricoma. *Br J Dermatol* 2001; **145**: 624–9.

Pilomatricarcinoma [1–4]

Definition. The malignant counterpart of the pilomatricoma, possessing metastatic potential.

Clinical features. A rapidly expanding firm nodule. Approximately 70 cases are reported in the literature, and the average age of the patients is 70 years. Males are more often affected than females. Most tumours develop on the head and neck followed much less frequently by the trunk [5].

Pathology. Many pilomatricarcinomas appear to arise on long-standing benign pilomatricomas. Definition of malignancy is usually very difficult on histological grounds. Malignant tumours usually have a very large predominant basaloid component, an infiltrative growth pattern and extensive necrosis. In addition, there are numerous abnormal mitotic figures, and both lymphatic and vascular invasion may be seen. There may be metastases to distant organs such as the lungs, bone and lymph nodes [6–9]. At least two cases have proved fatal.

As in pilomatricoma, mutations in β-catenin have been demonstrated in pilomatricarcinomas suggesting the activation of a common cellular pathway in both types of neoplasms despite the difference in clinical behaviour [10,11].

Management. Wide local excision is usually curative, but follow-up is required because of the possibility of metastatic spread.

References

1 Green DE, Sanusi ID, Fowler MR. Pilomatrix carcinoma. *J Am Acad Dermatol* 1987; **17**: 264–70.
2 Weedon D, Bell J, Mayze J. Matrical carcinoma of the skin. *J Cutan Pathol* 1980; **7**: 39–42.
3 Wood MG, Parhizzar B, Beerman H. Malignant pilomatricoma. *Arch Dermatol* 1984; **120**: 770–3.
4 Van Der Walt JD, Rohlova B. Carcinomatous transformation in a pilomatrixoma. *Am J Dermatopathol* 1984; **6**: 63–4.
5 Hardisson D, Linares MD, Cuevas-Santos J *et al*. Pilomatrix carcinoma: a clinicopathologic study of six cases and review of the literature. *Am J Dermatopathol* 2001; **23**: 394–401.
6 Gould E, Kurzon R, Kowalczyk P *et al*. Pilomatrix carcinoma with pulmonary metastases. *Cancer* 1984; **54**: 370–2.
7 Mir R, Cortes E, Papantoniou PA *et al*. Metastatic trichomatricial carcinoma. *Arch Pathol* 1986; **110**: 660–3.
8 Hardisson D, Linares D, Cuevas Santos J *et al*. Pilomatrix carcinoma. *Am J Dermatopathol* 2001; **23**: 394–401.
9 Sassmannhausen J, Chaffins M. Pilomatrix carcinoma. *J Am Acad Dermatol* 2001; **44**: 358–61.
10 Lazar AJ, Calonje E, Grayson W *et al*. Pilomatrix carcinoma contain mutations in CTNNB1, the gene encoding beta-catenin. *J Cutan Pathol* 2005; **32**: 148–57.
11 Hassanein AM, Glanz SM. Beta-catenin expression in benign and malignant pilomatrix neoplasms. *Br J Dermatol* 2004; **150**: 511–6.

Lesions of hair-follicle mesenchyme

Trichodiscoma [1]

Definition. This lesion is a hamartomatous proliferation of the mesodermal component of the *Haarscheibe* described by Pinkus [1]. The *Haarscheibe* is considered to be a slowly reacting mechanoreceptor associated with the hair follicle.

Clinical features. The clinical appearance of the trichodiscoma is that of multiple, discrete, flat-topped papules 2–3 mm in diameter. They occur mainly in the central area of the face. Familial cases are recorded [2,3]. Multiple trichodiscomas, trichofolliculomas and acrochordon-like lesions have been described as part of the Birt–Hogg–Dubé syndrome [4]. This syndrome is an autosomal dominant genodermatosis also associated with lung cysts, spontaneous pneumothorax and renal neoplasms (chromophobe renal carcinoma and oncocytoma) [5]. The causative gene, *FLCN*, has been mapped to chromosome 17p12q11. Interestingly, the acrochordon-like lesions display the histological features of either trichodiscomas or trichofolliculomas [6].

Pathology. A discrete but non-encapsulated area of myxoid, poorly cellular stroma with focal collagen deposition is seen in the dermis, associated with a proliferation of blood vessels, some of which are thick-walled. The proliferating cells are CD34 positive [7]. A variant with a cellular spindle-cell component has been described [8]. Pilosebaceous units are often seen on both sides of the myxoid stroma. Trichodiscomas and trichofolliculomas usually show histological overlap.

References

1 Pinkus H, Cosket R, Burgess GH. Trichodiscoma. *J Invest Dermatol* 1974; **63**: 212–8.
2 Balus L, Crovato F, Breathnach AS. Familial multiple trichodiscomas. *J Am Acad Dermatol* 1986; **15**: 603–7.
3 Camarasa JG, Calderon P, Moreno A. Familial multiple trichodiscomas. *Acta Derm Venereol* 1988; **68**: 163–5.
4 Schmidt L, Warren M, Nickerson M *et al*. Birt–Hogg–Dubé syndrome, a genodermatosis associated with spontaneous pneumothorax and kidney neoplasia, maps to chromosome 17p11.2. *Am J Hum Genet* 2002; **69**: 876–82.
5 Leter EM, Koopmans AK, Gille JJ *et al*. Birt–Hogg–Dubé síndrome: clinical and genetic studies of 20 families. *J Invest Dermatol* 2008; **128**: 45–9.
6 De la Torre C, Ocampo C, Doval IG *et al*. Acrochordons are not a component of the Birt–Hogg–Dubé syndrome: does this syndrome exist? Case reports and review of the literature. *Am J Dermatopathol* 1999; **21**: 369–74.
7 Chartier M, Reed ML, Mandavilli S *et al*. CD34-reactive trichodiscoma. *J Cutan Pathol* 2004; **31**: 398–400.
8 Kutzner H, Requena L, Rütten A *et al*. Spindle cell predominant trichodiscoma: a fibrofolliculoma/trichodiscoma variant considered formerly to be a neurofollicular hamartoma: a clinicopathological and immunohistochemical analysis of 17 cases. *Am J Dermatopathol* 2006; **28**: 1–8.

Perifollicular fibroma [1,2]

The clinical appearance of these lesions has not been well described. The pathology is that of a striking fibrous proliferation around a relatively normal pilosebaceous apparatus.

References

1 Freeman RG, Chernosky ME. Perifollicular fibroma. *Arch Dermatol* 1969; **100**: 66–9.
2 Zackheim HS, Pinkus H. Perifollicular fibromas. *Arch Dermatol* 1960; **82**: 913–7.

Fibrofolliculoma

Definition. Rare lesions of perifollicular connective tissue [1].

Clinical features. These lesions usually first appear in middle age and tend to affect the upper part of the body. Multiple lesions are seen in the Birt–Hogg–Dubé syndrome, which is an autosomal-dominant condition mapped to chromosome 17p11.2 [2–5]. In this syndrome, fibrofolliculomas are seen in association with trichodiscomas, acrochordon-like lesions, renal tumours most commonly chromophobe carcinoma and spontaneous pneumothorax [6,7]. Colonic neoplasms do not seem to be increased in this syndrome, as previously suggested [6].

Pathology. Histology shows multiple, small, poorly formed pilosebaceous follicles set in a very striking fibrous stroma. There is also an obvious proliferation of the outer root sheath similar to that seen in the perifollicular fibroma.

References

1 Scully K, Bargman H, Assaad D. Solitary fibrofolliculoma. *J Am Acad Dermatol* 1984; **11**: 361–3.
2 Birt AR, Hogg GR, Dubé J. Hereditary multiple fibrofolliculomas with trichodiscomas and acrochordons. *Arch Dermatol* 1977; **113**: 1674–7.
3 Weintraub R, Pinkus H. Multiple fibrofolliculomas (Birt–Hogg–Dubé) associated with a large connective tissue nevus. *J Cutan Pathol* 1977; **4**: 289–99.
4 Fujita WH, Barr RJ, Headley JL. Multiple fibrofolliculomas with trichodiscomas and acrochordons. *Arch Dermatol* 1981; **117**: 32–5.
5 Schmidt L, Warren MB, Nickerson ML *et al.* Birt–Hogg–Dubé syndrome, a genodermatosis associated with spontaneous pneumothorax and kidney neoplasia, maps to chromosome 17p11.2. *Am J Hum Genet* 2001; **69**: 876–82.
6 Zbar B, Alvord WG, Glenn G *et al.* Risk of renal and colonic neoplasms and spontaneous pneumothorax in the Birt–Hogg–Dubé syndrome. *Cancer Epidemiol Biomarkers Prev* 2002; **11**: 393–400.
7 Toro JR, Glenn G, Duray P *et al.* Birt–Hogg–Dubé syndrome: a novel marker of kidney neoplasia. *Arch Dermatol* 1999; **135**: 1195–202.

Sebaceous gland tumours [1]

The following tumours or tumour-like conditions of sebaceous glands are considered elsewhere in the book:

1 Naevus sebaceus (Chapter 18);
2 Senile sebaceous hyperplasia (Chapter 42);
3 'Sebaceous' cyst (Chapter 42);
4 Steatocystoma multiplex (Chapter 52).

The two main conditions discussed in this section are sebaceous adenomas and sebaceomas, and sebaceous carcinoma. The old term 'sebaceous epithelioma' is no longer used, as it causes confusion with the exceptionally rare basal cell carcinoma with sebaceous differentiation.

Sebaceous adenomas and sebaceomas [1–5]

Definition. Benign tumours composed of incompletely differentiated sebaceous cells of varying degrees of maturity. Sebaceous adenoma and sebaceoma are described together, as they do not have distinctive clinical features and, although histological separation is possible in most cases, there is also some degree of overlap.

Incidence and aetiology. These are fairly rare tumours [4]. The solitary type may occur in either sex, and most cases have occurred in the elderly. They may be associated with a cutaneous horn [6]. There is no evidence that actinic radiation or other recognized carcinogens are to blame.

Patients with multiple benign sebaceous tumours (other than sebaceous hyperplasia) should be suspected of having the Muir–Torre syndrome, associated with multiple visceral malignancies [7–18]. It is important to note, however, that a single sebaceous neoplasm and more uncommonly a sebaceous carcinoma particularly in an extraocular location may represent a marker of the syndrome [19]. It has also been demonstrated that a single sebaceous tumour outside the head and trunk is a strong indicator of the syndrome [20]. Muir–Torre syndrome is a rare subset of the hereditary non-polyposis colorectal carcinoma, representing 1–2% of cases of the latter [21,22]. It is characterized by cutaneous sebaceous tumours, gastrointestinal malignancies, especially colonic and, more rarely, renal, uterine and breast neoplasms [5]. The internal malignancies tend to be fairly low grade, and often patients develop them earlier in life than the equivalent neoplasm in the general population. Sebaceous neoplasms tend to develop later in life. Patients with Muir–Torre syndrome may also develop sebaceous keratoacanthomas [20], thus diagnosis of one of these tumours should raise the possibility of the syndrome. Microsatellite instability has been reported in the Muir–Torre syndrome [23,24], which results in the loss of a number of mismatch repair proteins particularly MLH1 and MSH2 and less commonly MSH6. Loss of expression of these proteins is a marker of patients who carry the syndrome and are therefore at risk of systemic malignancy [25,26]. The loss of expression of MLH1, MSH2 and MSH6 may be demonstrated by immunohistochemical methods [25]. In Muir–Torre syndrome, MSH2 is lost 10 times more frequently than MLH1 [21].

Clinical features. Tumours are usually rounded, raised and either sessile or somewhat pedunculated (Fig. 53.8). They are normally less than 10 mm in diameter, but older lesions may form plaques or ulcerate. Occasional tumours are more deeply located and appear cystic. The colour is fleshy or of a waxy, yellowish hue,

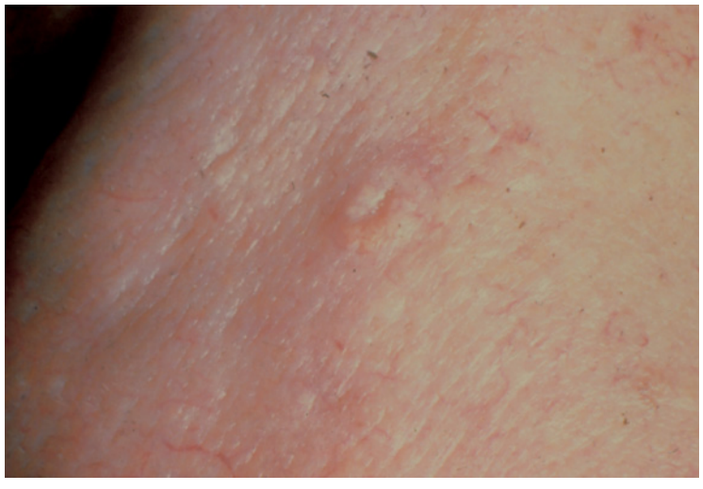


Fig. 53.8 Sebaceous adenoma. Small, yellowish papule.

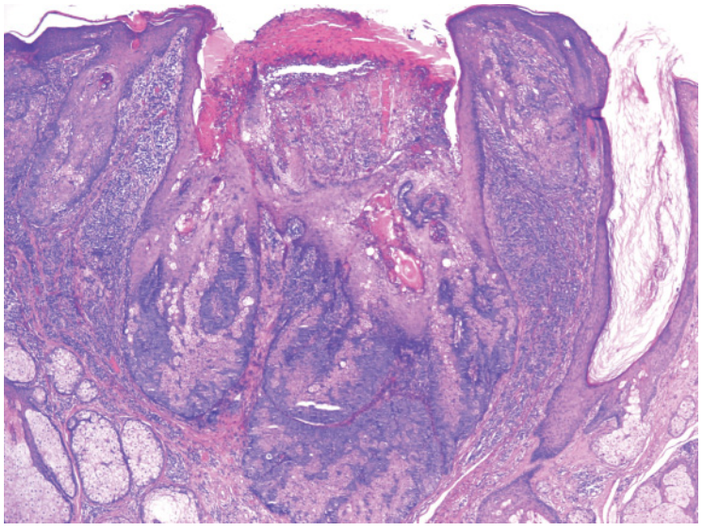


Fig. 53.9 Sebaceous adenoma. Lobular lesion with prominent maturation in the centre and immature cells in the periphery.

and the surface may be papilliferous. The common situation is the face or scalp, and it may occur on the eyelid. It usually grows slowly, but a sudden increase in growth rate can occur.

Diagnosis. A yellow-tinged facial nodule may be suggestive, but clinical differentiation from other epithelial tumours, especially basal cell carcinoma, may be impossible. The microscopic diagnosis is more certain when fat can be demonstrated, but sebaceous differentiation can usually be distinguished in ordinary sections.

Pathology [3,6,15,27]. The tumours are multilobular and usually connected to the epidermis. The lobules are well-defined, composed of variable numbers of small, basophilic, sebaceous matrix cells peripherally and larger cells—mature sebaceous cells—containing cytoplasmic fat globules. The proportion of immature, transitional and mature sebaceous cells may vary widely from one area to another. In sebaceous adenoma, mature sebaceous cells predominate in the centre of the lobules (Fig. 53.9), whilst in sebaceoma, immature basaloid sebaceous cells predominate, occupying large areas of the lobules. In both tumours, there may also be cystic spaces lined by a thin layer of eosinophilic material similar to the intraglandular sebaceous ducts. The outline of the tumour is less regular than normal sebaceous glands, and may be irregular. However, some sebaceous adenomas closely mimic the normal sebaceous gland, except for an increase in the number of immature sebaceous cells. Mitotic figures are frequent in the immature sebaceous cells, and this feature should not be regarded as evidence of malignancy. Larger and deeper tumours with cystic degeneration usually represent sebaceomas, but adenomas may also be seen. Some of these tumours have atypical histological features [28]. The cystic space contains abundant holocrine (sebaceous) material. It has been suggested that these cystic sebaceous tumours are a marker for the mismatch, repair-deficient subtype of Muir–Torre syndrome, which has a high risk of internal malignancies [28]. However, a more recent study although demonstrating that sebaceous keratoacanthomas are often associated with the syndrome failed to show the same correlation with cystic sebaceous neoplasms [20]. Glandular apocrine differentiation may occur rarely in some sebaceous neoplasms [29].

Treatment. The best treatment is surgical excision. Patients with tumours showing loss of expression of mismatch proteins should be screened for internal malignancy, particularly of the colon.

References

1 Prioleau PG, Santa Cruz DJ. Sebaceous gland neoplasms. *J Cutan Pathol* 1984; **11**: 396–414.
2 Lever WF. Sebaceous adenoma: review of the literature and report of a case. *Arch Dermatol Syphilol* 1948; **57**: 102–11.
3 Troy JL, Ackerman AB. Sebaceoma: a distinctive benign neoplasm of adnexal epithelium differentiating toward sebaceous cells. *Am J Dermatopathol* 1984; **6**: 7–13.
4 Dineen AM, Mehregan DR. Sebaceous epithelioma: a review of 21 cases. *J Am Acad Dermatol* 1996; **34**: 47–50.
5 Lazar AJF, Lyle S, Calonje E. Sebaceous neoplasia and Torre–Muir syndrome. *Curr Diagn Pathol* 2007; **13**: 301–19.
6 Thornton CM, Hunt SJ. Sebaceous adenoma with a cutaneous horn. *J Cutan Pathol* 1995; **22**: 185–7.
7 Muir EG, Yates-Bell AJ, Barlow KA. Multiple primary carcinomata of the colon, duodenum and larynx associated with keratoacanthoma of the face. *Br J Surg* 1967; **54**: 191–5.
8 Bakker PM, Tjon A, Joe SS. Multiple sebaceous gland tumours, with multiple tumours of internal organs: a new syndrome? *Dermatologica* 1971; **142**: 50–7.
9 Banse-Kupin L, Morales A, Barlow M. Torre's syndrome. *J Am Acad Dermatol* 1984; **10**: 803–17.
10 Burgdorf WHC, Pitha J, Fahmy A. Muir–Torre syndrome: histologic spectrum of sebaceous proliferation. *Am J Dermatopathol* 1986; **8**: 202–8.
11 Fathizadeh A, Medenica MM, Soltani K *et al*. Aggressive keratoacanthoma and internal malignant neoplasm. *Arch Dermatol* 1982; **118**: 112–4.
12 Finan MC, Connolly SM. Sebaceous gland tumors and systemic disease: a clinicopathologic analysis. *Medicine* 1984; **63**: 232–42.
13 Graham R, McKee P, McGibbon D *et al.* Torre–Muir syndrome: an association with isolated sebaceous carcinoma. *Cancer* 1985; **55**: 2868–73.
14 Lynch HT, Fusaro RM, Roberts L *et al.* Muir–Torre syndrome in several members of a family with a variant of the cancer family syndrome. *Br J Dermatol* 1985; **113**: 295–301.
15 Rulon DB, Helwig EB. Multiple sebaceous neoplasms of the skin: an association with multiple visceral carcinomas, especially of the colon. *Am J Clin Pathol* 1973; **60**: 745–52.
16 Schwartz RA, Torre DP. The Muir–Torré syndrome: a 25-year retrospect. *J Am Acad Dermatol* 1995; **33**: 90–104.
17 Torré D. Multiple sebaceous tumors. *Arch Dermatol* 1968; **98**: 549–51.
18 Worret WJ, Burgdorf WHC, Fahmi A *et al*. Torre–Muir syndrome. *Hautarzt* 1981; **32**: 519–24.
19 Donati P. Solitary sebaceoma in Muire–Torre syndrome. *Int J Dermatol* 1996; **35**: 601–2.
20 Singh RS, Grayson W, Redston M *et al*. Site and tumor type predicts DNA mismatch repair status in cutaneous sebaceous neoplasia. *Am J Surg Pathol* 2008; **32**: 936–42.
21 Mangold E, Pagenstecher C, Leister M *et al*. A genotype-phenotype correlation in HNPCC: strong predominance of msh2 mutations in 41 patients with Muir-Torre syndrome. *J Med Genet* 2004; **41**: 567–72.
22 Barana D, van der Klift H, Wijnen J *et al*. Spectrum of genetic alterations in Muir-Torre syndrome is the same as in HNPCC. *Am J Med Genet* 2004; **125**: 318–9.
23 Honchel R, Halling KC, Schaid DJ *et al.* Microsatellite instability in the Muir–Torre syndrome. *Cancer Res* 1994; **54**: 1159–63.
24 Southey MC, Young MA, Whitty J *et al.* Molecular pathologic analysis enhances diagnosis and management of the Muir–Torre syndrome and gives an insight into its underlying molecular pathogenesis. *Am J Surg Pathol* 2001; **25**: 936–41.
25 Mathiak M, Rutten A, Mangold E *et al.* Loss of DNA mismatch repair proteins from patients with Muir–Torre syndrome: establishment of immunohistochemical analysis as a screening test. *Am J Surg Pathol* 2002; **26**: 338–43.

26 Machin P, Catasus L, Pons C *et al*. Microsatellite instability and immunostaining for MSH-2 and MLH-1 in cutaneous and internal tumors from patients with the Muir–Torre syndrome. *J Cutan Pathol* 2002; **29**: 415–20.
27 Misago N, Mihara I, Ansai S *et al*. Sebaceoma and related neoplasms with sebaceous differentiation: a clinicopathologic study of 30 cases. *Am J Dermatopathol* 2002; **24**: 294–304.
28 Rutten A, Burgdorf W, Hugel H *et al.* Cystic sebaceous tumors as marker lesions for the Muir–Torre syndrome: a histopathologic and molecular genetic study. *Am J Dermatopathol* 1999; **21**: 405–13.
29 Kazakov DV, Calonje E, Rütten A *et al*. Cutaneous sebaceous neoplasms with a focal glandular pattern (seboapocrine lesions): a clinicopathological study of three cases. *Am J Dermatopathol* 2007; **29**: 359–64.

Superficial epithelioma with sebaceous differentiation [1–4]

This is a rare tumour that has no distinctive clinical features and presents as a solitary papule on the face or trunk of adults. Occasionally, lesions are multiple. Histological features consist of a multifocal, plate-like proliferation of basaloid cells with focal sebaceous differentiation and connections to the epidermis.

References

1 Rothko K, Farmer ER, Zeligman I. Superficial epithelioma with sebaceous differentiation. *Arch Dermatol* 1980; **116**: 329–31.
2 Kato N, Ueno H. Superficial epithelioma with sebaceous differentiation. *J Dermatol* 1992; **19**: 190–4.
3 Vaughan TK, Sau P. Superficial epithelioma with sebaceous differentiation. *J Am Acad Dermatol* 1990; **23**: 760–2.
4 Friedman KJ, Boudreau S, Farmer ER. Superficial epithelioma with sebaceous differentiation. *J Cutan Pathol* 1987; **14**: 193–7.

Sebaceous carcinoma [1–3]

Definition. A malignant tumour composed of cells showing differentiation toward sebaceous epithelium.

Incidence. The variable incidence reported for this tumour reflects the differing diagnostic criteria of different workers. It is, however, rare, comprising less than 1% of all skin malignancies. The tumour has been reported following radiodermatitis [4], and in a patient with multiple arsenical skin cancers. Lesions may rarely occur in naevus sebaceus [5]. It is likely that a number of sebaceomas with high mitotic activity have been reported in the past as sebaceous carcinomas.

Clinical features [6–14]. Most lesions occur in middle-aged and particularly old individuals. Exceptional cases have been reported in children [15]. The tumour is solitary, firm, sometimes translucent and covered with normal or slightly verrucose epidermis. The colour may be yellow or orange. The face and scalp [16] are the commonest sites, especially the eyelid (Fig. 53.10). The evolution may be very slow, and a size of 5 cm or more may be reached after many years without metastasis. Some tumours grow rapidly and invade early, but metastasis is uncommon [17,18]. In the absence of the yellow colour there is no feature to indicate the diagnosis clinically. Sebaceous carcinomas may occur in immunosuppressed organ-transplant patients, and these tumours are associated with microsatellite instability [19]. Sebaceous carcinoma may be associated with the Muir–Torre syndrome [20]. The latter association is mainly seen with extraocular carcinomas and those tumours occurring outside the head and neck area [21].



Fig. 53.10 Sebaceous carcinoma. Ulcerated, yellowish lesion of the eyelid.

Pathology. The same problem of terminology exists with sebaceous carcinoma as with the adenomas. Basal cell carcinoma with sebaceous differentiation is not included in the description of sebaceous carcinoma. It is uncommon for the lesion to be aggressively invasive on the skin, although it frequently is when situated on the eyelid [6–10]. There are, however, individual case reports of aggressive lesions with occasional metastatic spread [22,23].

The essential feature is cytological evidence of sebaceous differentiation. The proportion of cells showing fat globules and the degree of cytoplasmic vacuolation are variable. The undifferentiated cells are of moderate size, with round, centrally placed nuclei and rather basophilic cytoplasm, and they tend to group themselves in masses of a multilobular configuration. The differentiating cells tend to be more central. There are, in addition, cytological features of malignancy and evidence of an infiltrative growth pattern. Mitotic figures including atypical forms are frequent. Pagetoid infiltration of the epidermis is frequent, particularly in tumours arising around the eye [6].

Treatment. Complete surgical excision is required [12,24]. Reports of excellent results with Mohs surgery suggest that this may be the treatment of choice [25].

References

1 Nelson BR, Hamlet KR, Gillard M *et al*. Sebaceous carcinoma. *J Am Acad Dermatol* 1995; **33**: 1–15.
2 Prioleau PG, Santa Cruz DJ. Sebaceous gland neoplasia. *J Cutan Pathol* 1984; **11**: 396–414.
3 Wick MR, Goellner JR, Wolfe JT III *et al.* Adnexal carcinomas of the skin, 2: extraocular sebaceous carcinomas. *Cancer* 1985; **56**: 1163–72.
4 Hood IC, Oizilbash AH, Salama SS *et al*. Sebaceous carcinoma of the face following irradiation. *Am J Dermatopathol* 1986; **8**: 505–8.
5 Kazakov DV, Calonje E, Zelger B *et al*. Sebaceous carcinoma arising in nevus sebaceous of Jadassohn: a clinicopathological study of five cases. *Am J Dermatopathol* 2007; **29**: 242–8.
6 Dixons RS, Mikhail GR, Slater HC. Sebaceous carcinoma of the eyelid. *J Am Acad Dermatol* 1980; **3**: 241–3.
7 Doxanas MT, Green WR. Sebaceous gland carcinoma: a review of 40 cases. *Arch Ophthalmol* 1984; **102**: 245–9.

8 Rulon DB, Helwig EB. Cutaneous sebaceous neoplasms. *Cancer* 1974; **33**: 83–102.
9 Urban FH, Winkelmann RK. Sebaceous malignancy. *Arch Dermatol* 1961; **84**: 63–72.
10 Russell WG, Hough AG, Rogers LW. Sebaceous carcinoma of Meibomian gland origin. *Am J Clin Pathol* 1980; **73**: 504–11.
11 Graham R, McKee P, McGibbon D. Torre–Muir syndrome: an association with isolated sebaceous carcinoma. *Cancer* 1985; **55**: 2868–73.
12 Hernández-Pérez E, Baños E. Sebaceous carcinoma: report of two cases with metastasis. *Dermatologica* 1978; **156**: 184–8.
13 Justi RA. Sebaceous carcinoma. *Arch Dermatol* 1958; **77**: 195–200.
14 Rao NA, Hidayat AA, McLeon IW. Sebaceous carcinomas of the ocular adnexa: a clinicopathologic study of 104 cases, with five-year follow-up data. *Hum Pathol* 1982; **13**: 113–22.
15 Omura NE, Collison DW, Perry AE *et al*. Sebaceous carcinoma in children. *J Am Acad Dermatol* 2002; **47**: 950–3.
16 Mellette JR, Amonette RA, Gardner JH *et al*. Carcinoma of sebaceous glands on the head and neck. *J Dermatol Surg Oncol* 1981; **7**: 404–7.
17 King DT, Hirose FM, Gurevitch AW. Sebaceous carcinoma of the skin with visceral metastases. *Arch Dermatol* 1979; **115**: 862–3.
18 Leonard DD, Deaton WR Jr. Multiple sebaceous gland tumors and visceral carcinomas. *Arch Dermatol* 1974; **110**: 917–20.
19 Harwood CA, Swale VJ, Bataille VA *et al*. An association between sebaceous carcinoma and microsatellite instability in immunosuppressed organ transplant recipients. *J Invest Dermatol* 2001; **116**: 246–53.
20 Schwartz RA, Torre DP. The Muir–Torre syndrome: a 25-year retrospect. *J Am Acad Dermatol* 1995; **33**: 90–104.
21 Singh RS, Grayson W, Redston M *et al*. Site and tumor type predicts DNA mismatch repair status in cutaneous sebaceous neoplasia. *Am J Surg Pathol* 2008; **32**: 936–42.
22 Moreno C, Jacyk WK, Judd MJ *et al*. Highly aggressive extraocular sebaceous carcinoma. *Am J Dermatopathol* 2001; **23**: 450–5.
23 Duman DG, Ceyhan BB, Celikel T *et al*. Extraorbital sebaceous carcinoma with rapidly developing visceral metastases. *Dermatol Surg* 2003; **29**: 987–9.
24 Dowd MB, Kumar RJ, Sharma R *et al*. Diagnosis and management of sebaceous carcinoma: an Australian experience. *ANZ J Surg* 2008; **78**: 158–63.
25 Spencer JM, Nossa R, Tse DT *et al*. Sebaceous carcinoma of the eyelid treated by Mohs micrographic surgery. *J Am Acad Dermatol* 2001; **44**: 1004–9.

Apocrine gland tumours [1]

Apocrine hidrocystoma [2]

Synonym
- Apocrine cystadenoma

Definition. A lesion produced by cystic dilatation of apocrine secretory glands. Although the terms apocrine hidrocystoma and cystadenoma have been used as synonyms, and the clinical features of both lesions are identical, there are a number of histological findings that set them apart (see below).

Incidence. The lesion is not uncommon, but is most often seen in ophthalmological or surgical clinics. It occurs in adult life, in no particular age group. Males and females are equally affected.

Clinical features [3–6]. The lesions are solitary or occasionally multiple, well-defined, dome-shaped, translucent nodules [7]. The surface is smooth and the colour varies from a skin colour to greyish or blue-black; pigmentation may affect only part of the cyst. The commonest site is around the eye, particularly lateral to the outer canthus (Fig. 53.11). It has also been reported on the penis [1], fingers [8] and multiple lesions bilaterally in both axillae [9]. There are no symptoms. The cyst increases slowly in size, and may become 10 mm or more in diameter. Multiple lesions may be seen in Schöpf–Schulz–Passarge syndrome (a form of ectodermal dysplasia syndrome characterized by hypotrichosis, hypodontia, nail dystrophy, palmoplantar keratoderma and periocular apocrine hidrocystomas) [10].



Fig. 53.11 Apocrine hidrocystoma. Cystic, translucent papule on the right inner canthus.

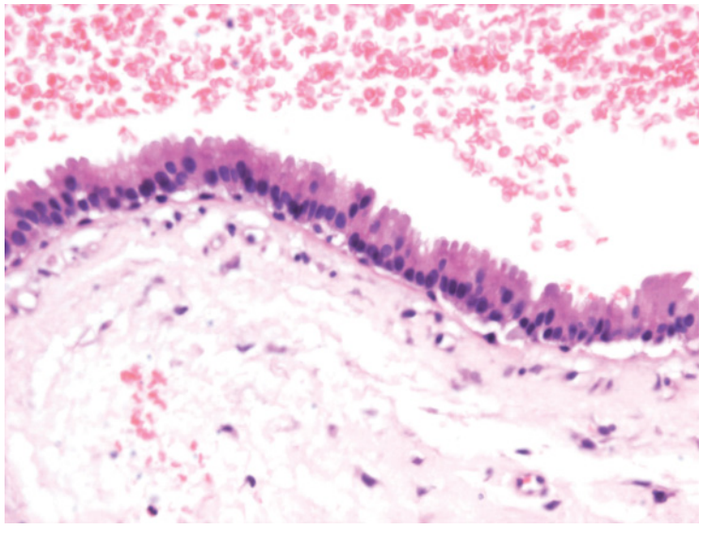


Fig. 53.12 Apocrine hidrocystoma. Cystic cavity lined by cuboidal cells with pink cytoplasm and decapitation secretion.

Pathology [11–13]. Large cystic cavities are found in the dermis if the lesion has been carefully dissected out. Commonly, the cyst is punctured and has collapsed before fixation. The cavities are lined by cuboidal or high-columnar apocrine secretory cells with decapitation secretion and a peripheral layer of myoepithelial cells (Fig. 53.12). Papillary projections or solid buds of secretory cells may break the smooth contour of the cyst lining. The secretory cells may contain pigment [5,6], which is neither melanin nor haemosiderin. The secretions in the cysts may be coagulated and

stained using the PAS technique. There is a well-organized fibrous stroma. Electron microscopy confirms the apocrine nature of the secretory epithelium [14]. Lesions designated as apocrine cystadenoma are regarded as proliferative lesions with true papillary projections (containing a fibrous core) and often display focal cytological atypia and mitotic activity. Based on these atypical features in cystadenoma, complete excision is suggested for tumours classified as such [15].

Diagnosis. Basal cell carcinoma is usually of a firmer consistency, less regular in its surface contour, and has surface telangiectases. The cystic nature of the lesion, which can often be shown by transillumination, separates it from blue naevi and malignant melanoma when pigment is present.

Treatment. The tumour is cured by surgical removal, which is commonly also needed for diagnosis. Other treatment modalities are the same as those used for eccrine hidrocystomas (see p. 53.22). Multiple lesions have been treated successfully with trichloroacetic acid [16].

References

1 Warkel RL. Selected apocrine neoplasms. *J Cutan Pathol* 1984; **11**: 437–49.
2 Hashimoto K, Lever WF. *Appendage Tumors of the Skin*. Springfield: Thomas, 1968: 52–4.
3 Benisch B, Peison B. Apocrine hidrocystoma of the shoulder. *Arch Dermatol* 1977; **113**: 71–2.
4 Hassan MO, Khan MA, Kruse TV. Apocrine cystadenoma. *Arch Dermatol* 1979; **115**: 194–200.
5 Smith JD, Chernosky ME. Apocrine hidrocystoma (cystadenoma). *Arch Dermatol* 1974; **109**: 700–2.
6 Mehregan AH. Apocrine cystadenoma. *Arch Dermatol* 1964; **90**: 274–9.
7 Schaumburg-Lever G, Lever WF. Secretion from human apocrine glands. *J Invest Dermatol* 1975; **64**: 38–41.
8 De Fontaine S, Van Geertruyden J, Vandeweyer E. Apocrine hidrocystoma of the finger. *J Hand Surg (Br)* 1998; **25**: 182–4.
9 Obaidat NA, Ghazarian DM. Bilateral multiple axillary apocrine hidrocystomas associated with benign apocrine hyperplasia. *J Cutan Pathol* 2006; **59**: 779.
10 Hampton PJ, Angus B, Carmichael AJ. A case of Schöpf–Schulz–Passarge syndrome. *Clin Exp Dermatol* 2005; **30**: 528–30.
11 Cramer HJ. Das schwarze Hidrocystom (Monfort). *Dermatol Monatsschr* 1980; **166**: 114–8.
12 Malhotra R, Bhawan J. The nature of the pigment in pigmented apocrine hidrocystoma. *J Cutan Pathol* 1985; **12**: 106–9.
13 Gross BG. The fine structure of apocrine hidrocystoma. *Arch Dermatol* 1965; **92**: 706–12.
14 Kruse TV, Khan MA, Hassan MO. Multiple apocrine cystadenomas. *Br J Dermatol* 1979; **100**: 675–81.
15 Sugiyama A, Sugiura M, Piris A *et al*. Apocrine cystadenoma and apocrine hidrocystoma: examination of 21 cases with emphasis on nomenclature according to proliferative features. *J Cutan Pathol* 2007; **34**: 912–7.
16 Dailey RA, Saulny SM, Tower RN. Treatment of multiple apocrine hidrocystomas with trichloroacetic acid. *Ophthal Plast Reconstr Surg* 2005; **21**: 148–50.

Syringocystadenoma papilliferum [1,2]

Definition. An exuberant proliferating lesion, commonly seen on the scalp in association with an organoid naevus, and showing differentiation in an apocrine pattern [3].

Clinical features [4]. These lesions may be present at birth or in childhood [5], but the majority are seen on the face and scalp of young adults. There is frequently a history of papillomatous expansion of a small pre-existing lesion at or around puberty and lesions often occur in a pre-existing organoid naevus. The lesion is composed of multiple warty papules, some of which are translucent and pigmented (Fig. 53.13). Tumours may be seen in other locations including the vulva [6], external ear [7], lower leg [8], scrotum [9] and breast [10].



Fig. 53.13 Syringocystadenoma papilliferum. Papular lesion with superficial erosion.

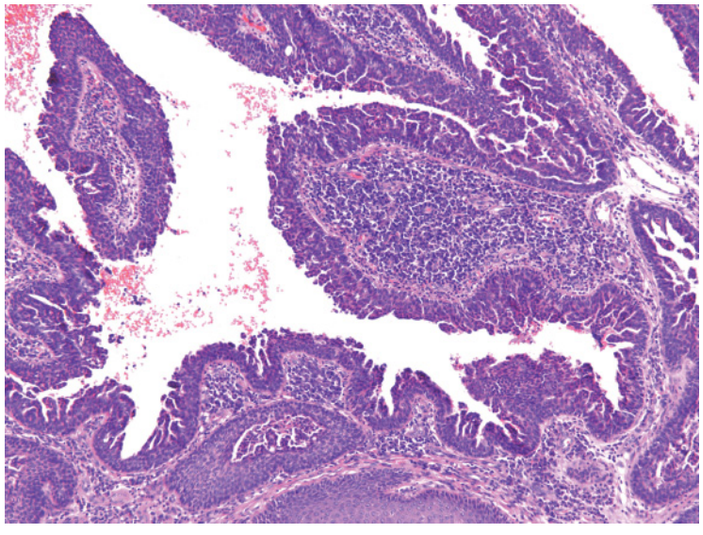


Fig. 53.14 Syringocystadenoma papilliferum. Papillary projections with a fibrovascular stroma.

Pathology [11–14]. The epidermal surface shows papillomatous expansion, and from these areas cystic invaginations are seen. The cystic structures are lined by papillae that have a lining of a double layer of columnar epithelium, which shows an apocrine pattern of secretion (Fig. 53.14) [15,16]. The underlying stroma is rich in plasma cells [17]. Sebaceous differentiation may occasionally be seen [18]. Occasionally, basal cell carcinoma, a squamous cell carcinoma (including verrucous carcinoma) [19] or a ductal carcinoma [20] develops on a pre-existing syringocystadenoma

papilliferum. *In-situ* carcinoma [21] and invasive apocrine carcinoma are exceptional. Molecular biological studies have identified loss of heterozygosity at chromosome 9q22, the locus of the patched gene [22]. Superficial lesions on apocrine tubular adenoma (see below) may overlap histologically with those of syringocystadenoma papilliferum [23].

Management. Surgical excision is recommended, both to confirm the diagnosis and for cosmetic reasons.

References

1 Hashimoto K, Lever WF. *Appendage Tumors of the Skin*. Springfield: Thomas, 1968: 47.
2 Pinkus H. Life history of naevus syringadenomatosus papilliferus. *Arch Dermatol Syphilol* 1954; **69**: 305–22.
3 Krinitz K. Naevus syringocystadenomatosus papilliferus in lineärer Anordnung. *Hautarzt* 1966; **17**: 260–5.
4 Lever WF. Pathogenesis of benign tumors of cutaneous appendages and of basal cell epithelioma. *Arch Dermatol Syphilol* 1948; **57**: 679–724.
5 Townsend TC, Bowen AR, Nobuhara KK. Syringocystadenoma papilliferum: an unusual cutaneous lesion in a pediatric patient. *J Pediatr* 2004; **145**: 131–3.
6 Al-Brahim N, Daya D, Alowami S. A 64-year-old woman with vulvar papule. Vulvar syringocystadenoma papilliferum. *Arch Pathol Lab Med* 2005; **129**: e126–7.
7 Kamakura T, Horii A, Mishiro Y *et al*. Magnetic resonance imaging of syringocystadenoma papilliferum of the external auditory canal. *Auris Nasus Larynx* 2006; **33**: 53–6.
8 Yoshii N, Kanekura T, Setoyama M *et al*. Syringocystadenoma papilliferum: report of the first case on the lower leg. *J Dermatol* 2004; **31**: 939–42.
9 Goshima J, Hara H, Okada T *et al*. Syringocystadenoma papilliferum arising on the scrotum. *Eur J Dermatol* 2003; **13**: 271.
10 Singh UR. Syringocystadenoma papilliferum mimicking breast carcinoma. *Am J Dermatopathol* 2000; **22**: 91.
11 Fusaro RM, Goltz RW. Histochemically demonstrable carbohydrates of appendageal tumors of the skin, 2: benign apocrine gland tumors. *J Invest Dermatol* 1962; **38**: 137–42.
12 Hashimoto K. Syringocystadenoma papilliferum: an electron microscopic study. *Arch Dermatol Forsch* 1972; **245**: 353–69.
13 Helwig EB, Hackney VC. Syringadenoma papilliferum. *Arch Dermatol* 1955; **71**: 361–72.
14 Landry M, Winkelmann RK. An unusual tubular apocrine adenoma. *Arch Dermatol* 1972; **105**: 869–79.
15 Mazoujian G, Margolis R. Immunohistochemical study of gross cystic disease fluid protein (GCDFP-15) in 65 benign sweat gland tumors of the skin. *Am J Dermatopathol* 1988; **10**: 28–35.
16 Niizuma K. Syringocystadenoma papilliferum: light and electron microscopic studies. *Acta Derm Venereol (Stockh)* 1976; **56**: 327–36.
17 Numata M, Hosoe S, Itoh N *et al*. Syringadenocarcinoma papilliferum. *J Cutan Pathol* 1985; **12**: 3–7.
18 Vazmitel M, Michal M, Mukensnabl P *et al*. Syringocystadenoma papilliferum with sebaceous differentiation in an intradermal tubular apocrine component. *Am J Dermatopathol* 2008; **30**: 51–3.
19 Montinniolo NL, Schmidt JD, Morgan MB. Verrucous carcinoma arising within syringocystadenoma papilliferum. *Ann Clin Lab Sci* 2002; **32**: 434–7.
20 Hügel H, Requena L. Ductal carcinoma arising from a syrincystadenoma papilliferum in a nevus sebaceous of Jadassohn. *Am J Dermatopathol* 2003; **25**: 490–3.
21 Arai Y, Kusakabe H, Kiyokane K. A case of syringocystadenocarcinoma papilliferum in situ occurring partially in syringocystadenoma papilliferum. *J Dermatol* 2003; **30**: 146–50.
22 Boni R, Xin H, Hohl D *et al*. Syringocystadenoma papilliferum: a study of potential tumor suppressor genes. *Am J Dermatopathol* 2001; **23**: 87–9.
23 Kazakov DV, Bisceglia M, Calonje E *et al*. Tubular adenoma and syringocystadenoma papilliferum: a reappraisal of their relationship. An interobserver study of a series, by a panel of dermatopathologists. *Am J Dermatopathol* 2007; **29**: 256–63.

Hidradenoma papilliferum

Definition. A skin tumour of the anogenital area of adult females, composed of frond-like papillae lined by apocrine epithelium.

Incidence. This is an uncommon tumour, which occurs predominantly in women. In one large series, the subjects were exclusively white, and 75% were between the ages of 25 and 40 years. It occurs four times as commonly on the vulva as in the perianal area [1].

Clinical features [2–4]. The patients usually seek advice for a lump in the vulval or perianal area, which may be symptomless or, less frequently, may be tender or liable to bleed. The tumour is rounded, freely mobile, often elevated and may feel firm, soft or even cystic. It may range in size from 1 to 40 mm. The commonest site is the labium majus, but it may occur elsewhere on the vulva or perianal area and, exceptionally, in other sites such as the eyelid [4,5], nose [6], arm [7] and chest [8]. Coexistence with a naevus comedonicus has been described [9].

Occasionally, the epithelial surface will ulcerate and the tumour becomes everted to form a reddish-brown papillary mass, which may be suspected of being malignant [1]. Malignant transformation, however, has not been reported.

Pathology. The tumour is well-circumscribed and located just below the skin surface. It is usually spherical in shape and enclosed by compressed connective tissue stroma. Lesions are composed partly of slender fronds of connective tissue lined by one or two layers of epithelial cells, and partly of glandular structures (Fig. 53.15). The epithelial cells have histochemical characteristics in keeping with an apocrine origin [10,11]. Sebaceous differentiation is seen occasionally [5]. Mitotic figures vary and may be frequent. In the absence of other features indicative of malignancy, the mitotic count does not imply malignant behaviour [12]. Rare cases overlap with syringocystadenoma papilliferum [13].

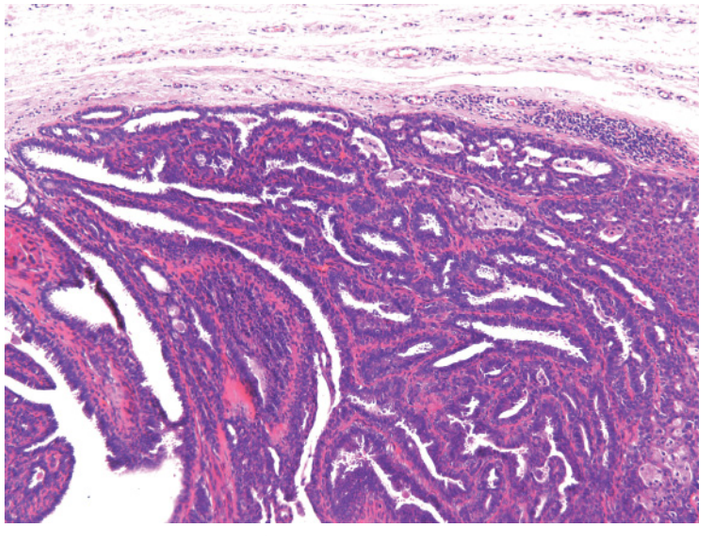


Fig. 53.15 Hidradenoma papilliferum. Well-circumscribed tumour with glands and papillary projections displaying apocrine differentiation.

Diagnosis. The tumour is usually mistaken for a cyst, polyp, angioma or haemorrhoid. A prolonged history and a firm, spherical form make the last three diagnoses unlikely.

Treatment. Simple excision is curative.

References

1 Shenoy YMV. Malignant perianal papillary hidradenoma. *Arch Dermatol* 1961; **83**: 965–7.
2 Meeker HJ, Neubecker RD, Helwig EG. Hidradenoma papilliferum. *Am J Clin Pathol* 1962; **37**: 182–95.
3 Virgili A, Marzola A, Corazza M. Vulvar hidradenoma papilliferum. A review of 10.5 years' experience. *J Reprod Med* 2000; **45**: 616–8.
4 Santa Cruz DJ, Prioleau PG, Smith ME. Hidradenoma papilliferum of the eyelid. *Arch Dermatol* 1981; **117**: 55–6.
5 Minami S, Sadanobu N, Ito T *et al*. Non-anogenital (ectopic) hidradenoma papilliferum with sebaceous differentiation: a case report and review of reported cases. *J Dermatol* 2006; **33**: 256–9.
6 Smith FB, Shemen LJ, Guerreri C *et al*. Hidradenoma papilliferum of nasal skin. *Arch Pathol Lab Med* 2003; **127**: E86–8.
7 Vang R, Cohen PR. Ectopic hidradenoma papilliferum: a case report and review of the literature. *J Am Acad Dermatol* 1999; **41**: 115–8.
8 Tanaka M, Shimizu S. Hidradenoma papilliferum occurring on the chest of a man. *J Am Acad Dermatol* 2003; **48**: S20–1.
9 Lee HJ, Chun EY, Kim YC *et al*. Nevus comedonicus with hidradenoma papilliferum and syringocystadenoma papilliferum in the female genital area. *Int J Dermatol* 2002; **41**: 933–6.
10 Hashimoto K. Hidradenoma papilliferum: an electron microscopic study. *Acta Derm Venereol (Stockh)* 1973; **53**: 22–30.
11 Tappeiner J, Wolff K. Hidradenoma papilliferum. Eine enzym-histochemische und elektronenmikroskopische Studie. *Hautarzt* 1969; **19**: 101–9.
12 Sington J, Chandrapala R, Manek S *et al*. Mitotic count is not predictive of clinical behavior in hidradenoma papilliferum of the vulva: a clinicopathologic study of 19 cases. *Am J Dermatopathol* 2006; **28**: 322–6.
13 Nishie W, Sawamura D, Mayuzumi M *et al*. Hidradenoma papilliferum with mixed histological features of syrincystadenoma papilliferum and anogenital mammary-like glands. *J Cutan Pathol* 2004; **31**: 561–4.

For erosive adenomatosis of the nipple, see Chapter 70.

Apocrine tubular adenoma [1–3]

Definition. A rare tumour usually arising on the scalp.

Clinical features. These are usually large, slowly expanding lesions on the scalp. The lesion often arises in association with a naevus sebaceus.

Pathology. Clusters of tubular structures are seen in the dermis, with a lining of cells showing decapitation secretion. There is no surrounding inflammatory response. Cytological atypia and an infiltrative margin are absent. As with many adnexal tumours, often one finds histological overlap between tubular apocrine adenoma and papillary eccrine adenoma [3,4]. Overlapping features with syringocystadenoma papilliferum are also seen, especially in superficial tumours [5].

References

1 Warkel RL, Helwig EB. Apocrine gland adenoma and adenocarcinoma of the axilla. *Arch Dermatol* 1978; **114**: 198–203.
2 Toribio J, Zulaica A, Peteiro C. Tubular apocrine adenoma. *J Cutan Pathol* 1987; **14**: 114–7.
3 Fox SB, Cotton D. Tubular apocrine adenoma and papillary eccrine adenoma: entities or unity? *Am J Dermatopathol* 1992; **14**: 149–54.
4 Ishiko A, Shimizu H, Inamoto N *et al*. Is tubular apocrine adenoma a distinct clinical entity? *Am J Dermatopathol* 1993; **15**: 482–7.
5 Kazakov DV, Bisceglia M, Calonje E *et al*. Tubular adenoma and syringcystadenoma papilliferum: a reappraisal of their relationship. An interobserver study of a series, by a panel of dermatopathologists. *Am J Dermatopathol* 2007; **29**: 256–63.

Apocrine carcinoma [1–3]

Definition. A malignant adnexal carcinoma showing clear evidence of apocrine differentiation—large cells with abundant pink cytoplasm and decapitation secretion.

Clinical features. This is a rare entity. Lesions have been reported mainly from the head and neck area, including the eyelid and external ear, anogenital skin and also the axilla [4]. It is not possible on morphological grounds or with the help of immunohistochemistry to separate a cutaneous axillary apocrine carcinoma from an apocrine breast carcinoma spreading or invading the skin by direct extension. It is therefore always important to rule out a primary breast tumour. Some tumours arise within a naevus sebaceus [5,6]. The tumour presents as a nodule, usually measuring more than 1 cm in diameter. Rare cases may be bilateral [7]. There is a slight predilection for females, and patients are middle-aged or elderly. Metastatic spread to regional lymph nodes and internal organs occurs in between 20 to 30% of the cases [6,8].

Pathology. Three histological patterns may be seen: tubular, tubulopapillary and solid (Fig. 53.16). The degree of differentiation varies, and the diagnosis is often difficult in poorly differentiated tumours. Mitotic figures, local invasion and nuclear pleomorphism all suggest a malignant lesion. The most specific pathological feature is the presence of decapitation secretion [1].

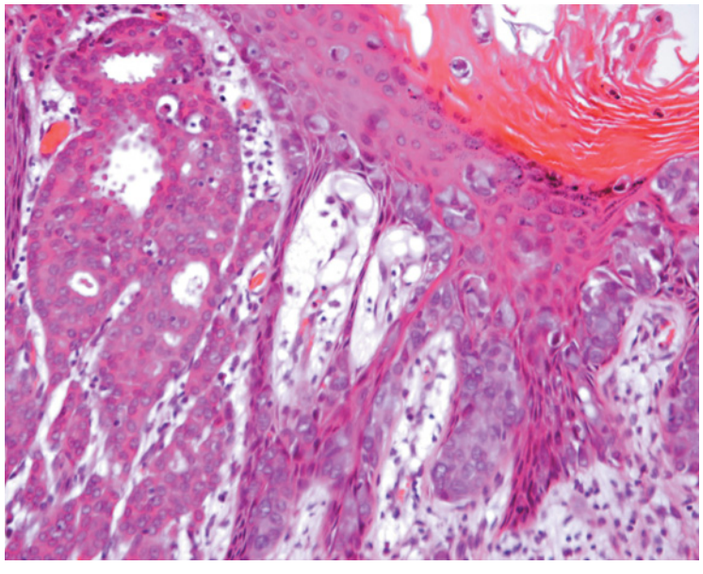


Fig. 53.16 Apocrine carcinoma. Prominent glands with decapitation secretion. Note the epidermotropism.

Some cases are associated with prominent pagetoid spread, particularly those presenting on genital skin [9]. Tumour cells are positive for gross cystic disease fluid protein-15 (GCDFP-15) [10], and they show positivity for oestrogen, progesterone and androgen receptors in up to a third of cases [6].

Treatment. It has been found that grading tumours according to the modified Bloom–Richardson method of grading breast carcinoma is very useful in establishing prognosis [6]. Patients with grade 3 tumours have a poor prognosis [6]. Wide excision and close follow-up are required. Based on the similarities between breast and apocrine carcinoma it may be of benefit to treat patients with high risk tumours and positivity for steroid receptors with medications such as tamoxifen [6].

References

1 Cooper PH. Carcinomas of the sweat glands. *Pathol Annu* 1987; **22**: 83–124.
2 Katagiri Y, Ansai S. Two cases of cutaneous apocrine ductal carcinoma of the axilla: case report and review of the literature. *Dermatology* 1999; **199**: 332–7.
3 Chamberlain RS, Huber K, White JC, Travaglino-Parda R. Apocrine gland carcinoma of the axilla: review of the literature and recommendations for treatment. *Am J Clin Oncol* 1999; **22**: 98–101.
4 Shintaku M, Tsuta K, Yoshida H *et al*. Apocrine adenocarcinoma of the eyelid with aggressive biological behavior: report of a case. *Pathol Int* 2002; **52**: 169–73.
5 Jacyk WK, Requena L, Sánchez Yus E *et al*. Tubular apocrine carcinoma arising in a nevus sebaceous of Jadassohn. *Am J Dermatopathol* 1998; **20**: 389–92.
6 Robson A, Lazar AJF, Ben Nagi J *et al*. Primary cutaneous apocrine carcinoma. A clinico-pathologic analysis of 24 cases. *Am J Surg Pathol* 2008; **32**: 682–90.
7 Nishikawa Y, Tokusashi Y, Saito Y *et al*. Apocrine adenocarcinoma associated with hamartomatous apocrine gland hyperplasia of both axillae. *Am J Pathol* 1994; **18**: 832–6.
8 Paties C, Taccagni L, Papotti M *et al*. Apocrine carcinoma of the skin. *Cancer* 1993; **71**: 375–81.
9 Castelli E, Wollina U, Anzarone A *et al*. Extramammary Paget disease of the axilla associated with comedo-like apocrine carcinoma of the skin. *Am J Dermatopathol* 2002; **24**: 351–7.
10 Ansai S, Koseki S, Hozumi Y *et al*. An immunohistochemical study of lysozyme CD-15 and gross cystic disease fluid protein 15 in various skin tumours. *Am J Dermatopathol* 1995; **17**: 249–55.

Eccrine gland tumours [1]

Eccrine gland-derived lesions make up a large and relatively common group of appendage tumours. Hidroacanthoma simplex, dermal duct tumour and eccrine poromas form a fairly homogeneous family derived from eccrine duct and pore. However, there are clear examples of apocrine poroma. Eccrine syringofibradenoma probably also belongs in this subsection. Eccrine hidradenoma, although closely related, has features suggesting both secretory and ductal differentiation, which makes the term 'acrospiroma' misleading, thus is perhaps best kept in a separate category.

Malignant tumours of sweat glands are relatively rare, but important to recognize. Their morphology and behaviour are variable.

Reference

1 Weedon D. Eccrine tumours: a selective review. *J Cutan Pathol* 1984; **11**: 421–36.

Eccrine hidrocystoma [1–7]

Definition. A tumour produced by mature, deformed eccrine sweat units, whose secretions dilate the ducts. Lesions are usually situated on the face and are often multiple.

Incidence and aetiology. This is a rare tumour that occurs mainly in middle-aged women. It was formerly reported as being more common in those who had to work exposed to heat, such as cooks. A report indicating that the lesion is usually solitary and situated close to the eyelid underlines the problem of differentiating eccrine from apocrine hidrocystomas [1].

Clinical features [1]. The lesions are largely confined to the cheeks and eyelids. They are cystic, often blue in colour and there is frequently a history of enlargement when the skin is exposed to heat and flattening of the lesion when the skin is exposed to cold. Administration of atropine also induces disappearance of the cyst [5]. The lesions may be multiple and pigmented [6]. Exceptionally, multiple eccrine hidrocystomas have been reported in Graves' disease with resolution after treatment of the condition [8].

Pathology [2–4]. The general features are those of a dermal cystic lesion uni- or multilocular lined by two layers of cells. The inner layer of cells is columnar and the outer layer consists of elongated myoepithelial cells. In cases with prominent dilatation, the epithelium appears flattened. Distinction from apocrine hidrocystoma is based on the presence of decapitation secretion in the cells of the inner layer.

Treatment. Treatment may consist of topical atropine or scopolamine but this is usually discontinued due to side effects [9]. Electrodesiccation, carbon dioxide laser and pulse dye laser have been used with good results [7,10]. Excision produces satisfactory results.

References

1 Smith JD, Chernosky ME. Hidrocystomas. *Arch Dermatol* 1973; **108**: 676–9.
2 Cordero AA, Montes LF. Eccrine hidrocystoma. *J Cutan Pathol* 1976; **3**: 292–3.
3 Ebner J, Erlach E. Ekkrine Hidrozystome. *Dermatol Monatsschr* 1975; **161**: 739–44.
4 Herzberg JJ. Ekkrines Syringocystadenom. *Arch Klin Exp Dermatol* 1962; **214**: 600–21.
5 Sperling LC, Sakas EL. Eccrine hidrocystomas. *J Am Acad Dermatol* 1982; **7**: 763–70.
6 Bourke JF, Colloby P, Graham Brown RC. Multiple pigmented eccrine hydrocystomas. *J Am Acad Dermatol* 1996; **35**: 480–1.
7 Sarabi K, Khachemoune A. Hidrocystoma—a brief review. *MedGenMed* 2006; **8**: 57.
8 Kim YD, Lee EJ, Song MH *et al*. Multiple hidrocystomas associated with Graves' disease. *Int J Dermatol* 2002; **41**: 231–6.
9 Armstrong DK, Walsh MY, Corbett JR. Multiple facial eccrine hidrocystomas: effective topical therapy with atropine. *Br J Dermatol* 1998; **139**: 558–9.
10 Tanzi E, Alster T. Pulsed dye laser treatment of multiple eccrine hydrocystomas: a novel approach. *Dermatol Surg* 2001; **27**: 898–900.

Hidroacanthoma simplex [1–4]

Definition. An intraepidermal tumour derived from the eccrine duct epithelium, which could be considered an intradermal eccrine poroma.

Clinical features. Hidroacanthoma simplex is a verrucous plaque or ring with a hyperkeratotic usually brown surface. It often mimics a flat seborrhoeic keratosis. Ulceration or elevation of the lesion suggests a dermal component. From the few reports available, it appears that the limbs are more likely to be involved than the head or trunk.

Pathology. Nests of clearly discrete, small, rounded cells are seen within the normal epidermal cells. They are smaller and more cuboidal than surrounding keratinocytes and are rich in glycogen and the glycolytic enzymes. These lesions may be confused with intraepidermal or clonal seborrhoeic keratoses, demonstrating what has in the past been called the 'Borst–Jadassohn phenomenon' [5]. The individual cells in these lesions are larger and less rich in glycogen. However, for the diagnosis to be made, ductal differentiation should be demonstrated.

Management. Excision is recommended both to confirm the diagnosis and for management. Malignant change has been reported in hidroacanthoma simplex including pigmented and clear cell variants [6–10]. If malignant change occurs, wider excision and follow-up is advisable.

References

1 Smith JLS, Coburn JG. Hidroacanthoma simplex. *Br J Dermatol* 1956; **68**: 400–18.
2 Pernicario C, Muller SA, Zelickson BD, Snow JL. Hidroacanthoma simplex. *J Cutan Pathol* 1994; **21**: 274–9.
3 Rahbari H. Hidroacanthoma simplex. *Br J Dermatol* 1983; **109**: 219–25.
4 Anzai S, Arakawa S, Fujiwara S *et al*. Hidroacanthoma simplex: a case report and analysis of 70 Japanese cases. *Dermatology* 2005; **210**: 363–5.
5 Warner T, Goell W, Cripps D. Hidroacanthoma simplex: an ultrastructural study. *J Cutan Pathol* 1982; **9**: 189–95.
6 Ansai S, Koseki S, Hozumi Y *et al*. Malignant transformation of hidradenoma simplex. *Dermatology* 1994; **188**: 57–61.
7 Bardach H. Hidroacanthoma simplex with in situ porocarcinoma. *J Cutan Pathol* 1978; **5**: 236–48.
8 Piqué E, Olivares M, Espinel ML *et al*. Malignant hidroacanthoma simplex. *Dermatology* 1995; **190**: 72–6.
9 Lee JY, Lin MH. Pigmented malignant hidroacanthoma simplex mimicking irritated seborrhoeic keratosis. *J Cutan Pathol* 2006; **33**: 705–8.
10 Rütten A, Requena L, Requena C. Clear-cell porocarcinoma in situ: a cytologic variant of porocarcinoma in situ. *Am J Dermatopathol* 2002; **24**: 67–71.

Eccrine poroma [1,2]

Definition. A tumour arising from the eccrine duct epithelium in the epidermis (acrosyringium). Traditionally, all poromas have been regarded as eccrine. However, a number of lesions may show apocrine differentiation.

Clinical features [1–11]. This lesion is one of the easiest of the appendage tumours to recognize in the clinic. The great majority of these lesions are found on the palms and soles (Fig. 53.17), in contrast to other skin-appendage tumours which tend to be concentrated around the head and neck area. The anatomical distribution is, however, wide. There is no sex predilection. Most patients are adults, tumours rarely presenting in children [12]. They are moist, exophytic lesions, pink or red in colour, and may reach 1–2 cm in diameter. Occasional lesions are pigmented and look similar to pigmented basal cell carcinoma under dermatoscopy [13,14]. Exceptional examples of poroma have been reported in a naevus sebaceus [15], with rapid growth during pregnancy [16], after electron beam therapy for mycosis fungoides [10], after radiotherapy [10] and at the site of a burn [17]. Multiple poromas have been reported in a case of hidrotic ectodermal dysplasia [18].



Fig. 53.17 Poroma. Note the red, shiny surface, which often leads to misdiagnosis of a pyogenic granuloma.

Pathology [19–21]. These lesions are relatively easy to diagnose, with a clear margin between adjacent, normal epidermal keratinocytes and a population of smaller cuboidal cells, usually with darker nuclei protruding down into the underlying dermis (Fig. 53.18). The cells are strongly PAS-positive and are similar to those seen in the dermal duct tumour [22]. Reports, however, have stressed the fact that some poromas may show either sebaceous or apocrine differentiation [23–25]—highlighting the fact that adnexal tumours with ductal differentiation may be either eccrine or apocrine, as the ducts of both structures are identical.

Malignant change has been recorded on many occasions (see under porocarcinoma).

Management. Benign eccrine poromas are treated by surgical excision.

References

1 Hashimoto K, Lever WF. Histogenesis of skin appendage tumors. *Arch Dermatol* 1969; **100**: 356–69.
2 Hyman AB, Brownstein MH. Eccrine poroma: an analysis of 45 new cases. *Dermatologica* 1969; **138**: 29–38.
3 Goldner R. Eccrine poromatosis. *Arch Dermatol* 1970; **101**: 606–8.
4 Knox JM, Spiller WF. Eccrine poroma. *Arch Dermatol* 1958; **77**: 726–9.

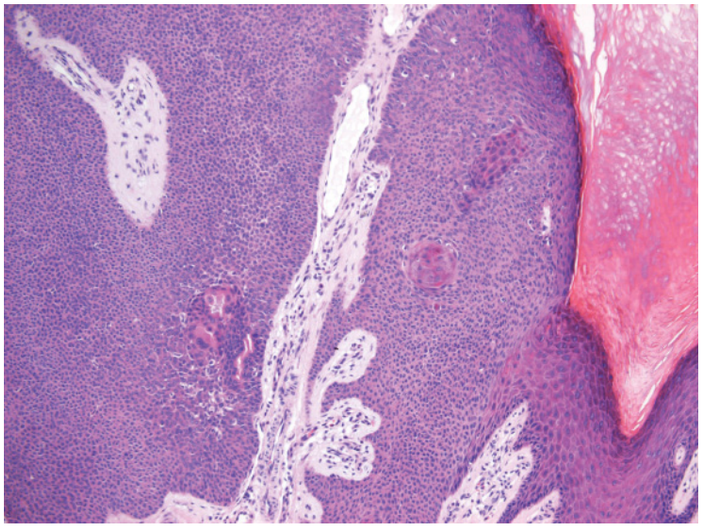


Fig. 53.18 Poroma. Note the clear demarcation between the tumour and the neighbouring epidermis.

5 Krinitz K. Ein Beitrag zur Klinik und Histologie des ekkrinen Poroms. *Hautarzt* 1967; **18**: 504–8.
6 Pinkus H, Rogin JR, Goldman P. Eccrine poroma. *Arch Dermatol* 1956; **74**: 511–21.
7 Freeman RG, Knox JM, Spiller WF. Eccrine poroma. *Am J Clin Pathol* 1961; **36**: 444–50.
8 Ogino A. Linear eccrine poroma. *Arch Dermatol* 1976; **112**: 841–4.
9 Okun MR, Anse UHB. Eccrine poroma. *Arch Dermatol* 1963; **88**: 561–6.
10 Penneys NS, Ackerman AB, Indgin SN *et al*. Eccrine poroma: two unusual variants. *Br J Dermatol* 1970; **82**: 613–5.
11 Chen CC, Chang YT, Liu HN. Clinical and histological characteristics of poroid neoplasms: a study of 25 cases in Taiwan. *Int J Dermatol* 2006; **45**: 722–7.
12 Orlandi C, Arcangeli F, Patrizi A *et al*. Eccrine poroma in child. *Pediatr Dermatol* 2005; **22**: 279–80.
13 Ohata U, Hara H, Suzuki H. Pigmented eccrine poroma occurring in the scalp: Derivation of melanocytes in the tumor. *Am J Dermatopathol* 2006; **28**: 138–41.
14 Kuo HW, Ohara K. Pigmented eccrine poroma: a report of two cases and study with dermatoscopy. *Dermatol Surg* 2033; **29**: 1076–9.
15 Jaqueti G, Requena L, Sànchez Yus E. Trichoblastoma is the most common neoplasm developed in nevus sebaceous of Jadassohn: a clinicopathologic study of a series of 155 cases. *Am J Dermatopathol* 2000; **22**: 108–18.
16 Ban M, Kitajima Y. A case of rapidly-growing eccrine poroma during pregnancy. *J Dermatol* 1997; **24**: 554–5.
17 Wakamatsu J, Yamamoto T, Minemura T *et al*. The occurrence of eccrine poroma on a burn site. *J Eur Acad Dermatol Venereol* 2007; **21**: 1128–9.
18 Wilkinson RD, Schopflocher P, Rozenfled M. Hidrotic ectodermal dysplasia with diffuse eccrine poromatosis. *Arch Dermatol* 1977; **113**: 472–6.
19 Mishima Y. Epitheliomatous differentiation of the intraepidermal eccrine sweat duct. *J Invest Dermatol* 1969; **52**: 233–46.
20 Rahbari H. Syringoacanthoma: acanthotic lesion of the acro-syringium. *Arch Dermatol* 1984; **120**: 751–6.
21 Hashimoto K, Lever WF. Eccrine poroma: histochemical and electron microscopic studies. *J Invest Dermatol* 1964; **43**: 237–47.
22 Hu CH, Marques AS, Winkelmann RK. Dermal duct tumor. *Arch Dermatol* 1978; **114**: 1659–64.
23 Moore TO, Orman HL, Orman SK *et al*. Poromas of the head and neck. *J Am Acad Dermatol* 2001; **44**: 48–52.
24 Lee NH, Lee SH, Ahn SK. Apocrine poroma with sebaceous differentiation. *Am J Dermatopathol* 2000; **22**: 261–3.
25 Kazakov DV, Kutzner H, Spagnolo DV *et al*. Sebaceous differentiation in poroid neoplasms: repoprt of 11 cases, including a case of metasplatic carcinoma associated with apocrine poroma (sarcomatoid apocrine porocarcinoma). *Am J Dermatopathol* 2008; **30**: 21–6.

Eccrine dermal duct tumour [1,2]

Definition. A benign proliferation of the eccrine dermal duct situated in the papillary dermis.

Clinical features. The clinical picture is that of a dermal nodule, occasionally with verrucous change overlying it.

Pathology. The pathology is similar to that of the hidroacanthoma simplex, but the nests of tumour cells making up the lesion are located in the dermis. The cells are small, cuboidal, regular and stain strongly with PAS. Ductal structures are often seen. An intraepidermal component may be seen in some cases, confirming that this lesion is part of the spectrum of eccrine poroma. In some cases, there is prominent clear-cell change [3].

Poroid hidradenoma is regarded as a variant of poroma with overlapping features of hidradenoma (dermal solid and cystic nests) and poroma (poroid cells and ductal differentiation) [4]. This lesion more likely represents part of the spectrum of dermal duct tumour.

Management. Excision is required for diagnostic and therapeutic purposes.

References

1 Winkelmann RK, McLeod WA. The dermal duct tumour. *Arch Dermatol* 1966; **94**: 50–5.
2 Aloi FG, Pippione M. Dermal duct tumor. *Appl Pathol* 1986; **4**: 175–8.
3 Rütten A, Hantschke M, Angulo J *et al*. Clear-cell dermal duct tumour: another distinctive, previously underrecognized cutaneous adnexal neoplasm. *Histopathology* 2007; **51**: 805–13.
4 Requena L, Sánchez M. Poroid hidradenoma: a light microscopy and immunohistochemical study. *Cutis* 1992; **50**: 43–6.

Eccrine syringofibroadenoma [1]

Clinical features. This is a rare entity, and may present as a solitary, often warty nodule on the arms or legs, especially on distal sites. The lesion may be reactive, representing hyperplasia as a result of diverse stimuli, or may be neoplastic usually presenting as a single lesion. Unusual presentations include plaques and multiple lesions [2], occasionally with a linear distribution, may be seen [3]. Coexistence with a squamous cell carcinoma and porocarcinoma has rarely been described [4,5] and lesions may rarely present within naevus sebaceus [6]. Syringofibroadenomatous hyperplasia of sweat ducts is seen in the background of other tumours, a healing ulcer, stasis, a reparative process after bullous diseases, in skin affected by leprosy, in peristomal skin, in burn scars and in association with ectodermal dysplasia [7–13]. In small biopsies, this type of hyperplasia may be confused with a syringofibroadenoma.

Pathology. A network of epithelial cells extends down from the epidermis, forming a mesh-like structure in the underlying epidermis. These cords are composed of smaller cells than in the overlying epidermis, and may contain ductal structures. This mesh is surrounded by a fibrovascular stroma. Unlike basal cell

carcinoma, there is no palisading [14,15]. Clear cells may occasionally predominate [16].

Management. Simple excision is the treatment of choice.

References

1 Mascaró J. Considérations sur les tumeurs fibroepithélials. *Ann Derm Syph* 1963; **90**: 146–53.
2 Van Leeuwen RL, Lavrijsen AP, Starink TM. Eccrine syringofibroadenoma: the simultaneous occurrence of two histopathological variants (conventional and clear cell type) in one patient. *Br J Dermatol* 1999; **141**: 947–9.
3 Starink TM. Eccrine syringofibroadenoma multiple lesions representing a new cutaneous marker of the Schopf syndrome, and solitary nonhereditary tumors. *J Am Acad Dermatol* 1997; **36**: 569–76.
4 Bjarke T, Ternesten-Bratel A, Hedblad M *et al*. Carcinoma and eccrine syringofibroadenoma: a report of five cases. *J Cutan Pathol* 2003; **30**: 382–92.
5 Schadt CR, Boyd AS. Eccrine syringofibroadenoma with co-existent squamous cell carcinoma. *J Cutan Pathol* 2007; **34**: 71–4.
6 Noguchi M, Akiyama M, Kawakami M *et al*. Eccrine syringofibroadenoma arising in a sebaceous naevus. *Br J Dermatol* 2000; **142**: 1050–1.
7 Rongioletti F, Gambini C, Parodi A *et al*. Mossy leg with eccrine syringofibroadenomatous hyperplasia resembling multiple eccrine syringofibroadenoma. *Clin Exp Dermatol* 1996; **21**: 454–6.
8 Gambini C, Rongioletti F, Semino MT *et al*. Solitary eccrine syringofibroadenoma (or eccrine syringofibroadenomatous hyperplasia?) and diabetic polyneuropathy. *Dermatology* 1996; **193**: 68–9.
9 Nomura K, Kogawa T, Hashimoto I *et al*. Eccrine syringofibroadenomatous hyperplasia in a patient with bullous pemphigoid: a case report and review of the literature. *Dermatologica* 1991; **182**: 59–62.
10 Tey HL, Chong WS, Wong SN. Leprosy-associated eccrine syringofibroadenoma of Mascaro. *Clin Exp Dermatol* 2007; **32**: 533–5.
11 Clarke LE, Ioffreda M, Abt AB. Eccrine syringofibroadenoma arising in peristomal skin: a report of two cases. *Int J Surg Pathol* 2003; **11**: 61–3.
12 Ichikawa E, Fujisawa Y, Tateishi Y *et al*. Eccrine syringofibradenoma in a patient with a burn scar ulcer. *Br J Dermatol* 2000; **143**: 591–4.
13 Utani A, Hatton Y. A reactive acrosyringeal proliferation in a patient with ectodermal dysplasia: eccrine syringofibradenoma-like lesion. *J Dermatol* 1999; **26**: 36–43.
14 Mehregan AN, Marufi N, Medenica M. Eccrine syringofibroadenoma. *J Am Acad Dermatol* 1985; **13**: 433–6.
15 Ohnishi T, Suzuki T, Watanabe S. Eccrine syringofibradenoma. *Br J Dermatol* 1995; **134**: 449–54.
16 Hu S, Bakshandeh H, Kerdel FA *et al*. Eccrine syringofibroadenoma of clear cell variant: an immunohistochemical study. *Am J Dermatopathol* 2005; **27**: 228–31.

Syringoma [1–3]

Synonyms
- Hidradenomes eruptifs
- Syringocystadenoma
- Syringocystoma

Definition. A benign skin tumour that is usually multiple. The histology is characteristic.

Incidence. It is a relatively uncommon lesion, occurring more commonly in females. It is most likely to appear at adolescence, and further lesions may develop during adult life. It does not appear to be hereditary.

Clinical features [4–11]. The individual small dermal papules [12] are skin-coloured, yellowish or mauve, but sometimes appear translucent and cystic. The surface may be rounded or flat-topped and the outline sometimes angular. Rarely, injury to the surface will allow a drop of clear, watery fluid to escape. They vary in size from 1 to 5 mm, but most are less than 3 mm. Some cases resemble milia and in these cases, the histology reveals a number of cystically dilated structures [13]. In most cases, there are multiple tumours, and they tend to have a bilateral symmetry in distribution. The front of the chest, face and neck are the chief areas affected. A few lesions are usually found on the eyelids when the cheeks are involved (Fig. 53.19). Eruptive syringomas have predilection for the neck, chest, abdomen, pubic area and more rarely on the buttocks [14,15]. They are more frequent in women and tend to occur in teenagers and young adults. Syringomas are seen more often than expected in patients with Down's syndrome [16,17] and may erupt dramatically (Fig. 53.20) [18]. Lesions may rarely occur on the vulva and are associated with pruritus [19,20]. Familial cases rarely occur [21]. A case of multiple syringomas probably sun-induced and in an acral location has been described [22]. Multiple syringomas have also been reported during radiotherapy for breast cancer [23]. The lesions regressed after cessation of radiotherapy.



Fig. 53.19 Multiple syringomas on the upper cheek area.

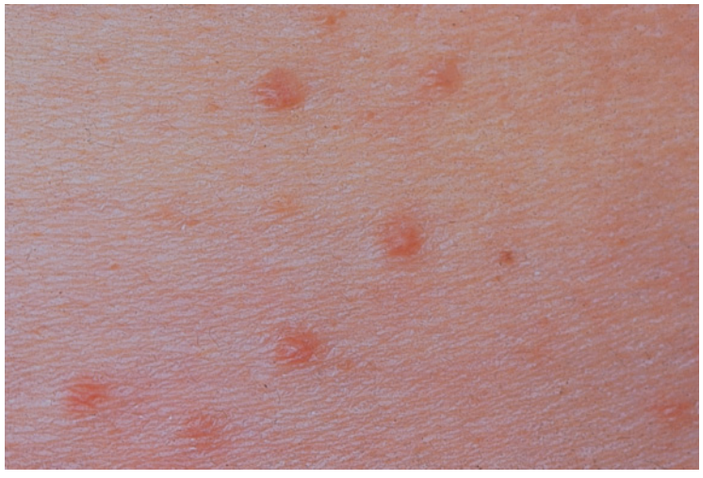


Fig. 53.20 Eruptive syringomas. Multiple, tiny, brownish or red lesions are often seen on trunk and limbs.

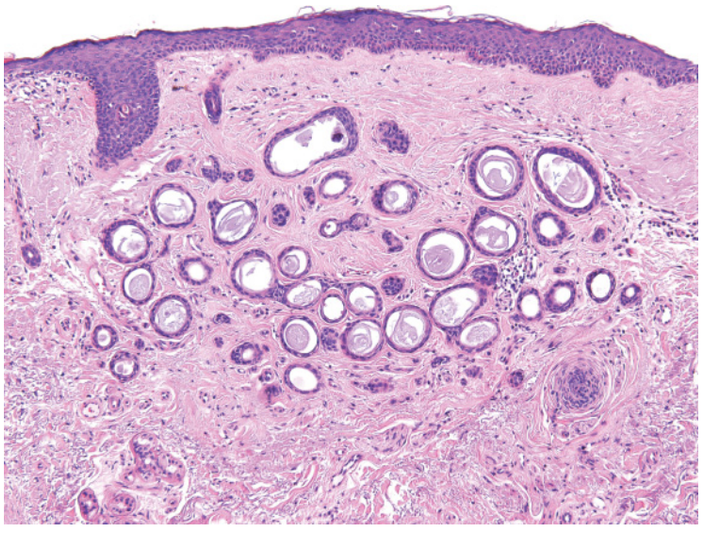


Fig. 53.21 Syringoma. Typical ductal structures with a tadpole appearance.

Pathology [24–26]. The lesion has a characteristic architectural pattern on light-microscope scanning power. Collections of convoluted and cystic ducts are seen in the upper half of the dermis. Most are lined by a double layer of cells similar to, but flatter than, those that line normal eccrine ducts. The lumina contain amorphous debris. A characteristic feature is the tail-like strand of cells projecting from one side of the duct into the stroma, giving a resemblance to a tadpole or comma (Fig. 53.21). The ducts may be enclosed in a fibrous stroma similar to the hair-follicle hamartomas, but in most cases it is narrower and less cellular. When the stroma is dense, it may be difficult to differentiate from the morphoeic basal cell carcinoma, in which, however, well-developed duct structures are not associated with cellular strands and there is a clear infiltrative margin with frequent perineurial invasion.

Diagnosis. Syringoma is most likely to be confused with trichoepithelioma on the face. The syringomas tend to be smaller, rather less superficial, more flat-topped and disposed more evenly over the cheeks and eyelids, rather than favouring the nasolabial creases. There is no family history. Lesions on the lids may be mistaken for xanthelasma, but lack the orange colour. Those erupting on the trunk may be mistaken for disseminated granuloma annulare.

Treatment. The main reason for treatment is cosmetic. Careful destruction with diathermy can produce good cosmetic results.

References

1 Hashimoto K, Lever WF. Histogenesis of skin appendage tumors. *Arch Dermatol* 1969; **100**: 356–69.
2 Lever WF. Pathogenesis of benign tumors of cutaneous appendages and of basal cell epithelioma. *Arch Dermatol Syphilol* 1948; **57**: 679–724.
3 Winkelmann RK, Muller SA. Sweat gland tumors. *Arch Dermatol* 1964; **89**: 827–31.
4 Dupre A, Bonafe JL, Christol B. Syringoma as a causative factor for cicatricial alopecia [letter]. *Arch Dermatol* 1981; **117**: 315.
5 Feibelman CE, Maize JC. Clear-cell syringoma. *Am J Dermatopathol* 1984; **6**: 139–50.
6 Friedman SJ, Butler DF. Syringoma presenting as milia. *J Am Acad Dermatol* 1987; **16**: 310–4.
7 Pujol R, Moreno A, Gonzàlez MJ *et al*. Syringoma du cuir chevelu. *Ann Dermatol Vénéréol* 1986; **113**: 693–5.
8 Shelley WB, Wood MG. Occult syringomas of scalp associated with progressive hair loss. *Arch Dermatol* 1980; **116**: 843–4.
9 Spitz DF, Stadecker MJ, Grande DJ. Subclinical syringoma coexisting with basal cell carcinoma. *J Dermatol Surg Oncol* 1987; **13**: 793–5.
10 Thomas J, Majmudar B, Gorelkin L. Syringoma localized to the vulva. *Arch Dermatol* 1979; **115**: 95–6.
11 Yung CW, Soltani K, Bernstein JE *et al*. Unilateral linear nevoidal syringoma. *J Am Acad Dermatol* 1981; **4**: 412–6.
12 Hashimoto K, Dibella RJ, Borsuk GM *et al*. Eruptive hidradenoma and syringoma. *Arch Dermatol* 1967; **96**: 500–19.
13 Wang KH, Chu JS, Lin YH *et al*. Milium-like syringoma: a case study on histogenesis. *J Cutan Pathol* 2004; **31**: 336–40.
14 Soler-Carrillo J, Estrach T, Mascaró JM. Eruptive syringoma: 27 new cases and review of the literature. *J Eur Acad Dermatol Venereol* 2001; **15**: 242–6.
15 Powell CL, Smith EP, Graham BS. Eruptive syringomas: an unusual presentation on the buttocks. *Cutis* 2005; **76**: 267–9.
16 Urban CD, Cannon JR, Cole RD. Eruptive syringomas in Down's syndrome. *Arch Dermatol* 1985; **117**: 374–9.
17 Daneshpazhooh M, Nazemi TM, Bidgeloo L *et al*. Mucocutaneous findings in 100 children with Down syndrome. *Pediatr Dermatol* 2007; **24**: 317–20.
18 Soler Carillo J, Estrach T, Mascaro JM. Eruptive syringoma: 27 new cases and a review of the literature. *J Eur Derm Venereol* 2001; **15**: 242–6.
19 Garman M, Metry D. Vulval syringomas in a 9-year-old child with review of the literature. *Pediatr Dermatol* 2006; **23**: 369–72.
20 Tay YK, Tham SN, Teo R. Localized vulvar syringomas—an unusual cause of pruritus vulvae. *Dermatology* 1996; **192**: 62–3.
21 Draznin M. Hereditary syringomas: a case report. *Dermatol Online J* 2004; **10**: 19.
22 Martin-García RF, Muñoz CM. Acral syringoma presenting as a photosensitive papular eruption. *Cutis* 2006; **77**: 33–6.
23 Yoshii N, Kanekura T, Churei H *et al*. Syringoma-like eccrine sweat duct proliferation induced by radiation. *J Dermatol* 2006; **33**: 36–9.
24 Asai Y, Ishii M, Hamada T. Acral syringoma: electron microscopic studies on its origin. *Acta Derm Venereol (Stockh)* 1982; **62**: 64–8.
25 Hashimoto K, Gross BG, Lever WF. Syringoma: histochemical and electron microscopic studies. *J Invest Dermatol* 1966; **46**: 150–66.
26 Headington JT, Koski J, Murphy PJ. Clear cell glycogenosis in multiple syringomas. *Arch Dermatol* 1972; **106**: 353–6.

Papillary eccrine adenoma

Definition. This rare lesion was first described in 1977 [1]. A solitary nodule, usually on the limbs of darker-skinned individuals it is controversial whether papillary eccrine adenoma represents the same entity as tubular apocrine adenoma [2]. The issue has not been settled but it seems that most tumours are probably apocrine and this is confirmed by examples that display follicular and sebaceous differentiation [3]. True eccrine lesions are unusual and are those arising in areas where no apocrine glands are present normally, such as the limbs [4].

Clinical features. It presents in a non-diagnostic manner as a slowly growing nodule on the limbs [5].

Pathology. The lesion is in the papillary dermis and consists of ductal structures with papillary projections. These ductal structures may display either eccrine or apocrine differentiation (decapitation secretion). Dilated ducts form a complex honeycomb-like structure.

References

1 Rulon DB, Helwig EB. Papillary eccrine adenoma. *Arch Dermatol* 1977; **113**: 596–8.
2 Tellechea O, Reis JP, Marques C *et al*. Tubular apocrine adenoma with eccrine and apocrine immunophenotypes or papillary tubular adenoma? *Am J Dermatopathol* 1995; **17**: 499–505.
3 Kazakov DV, Mukensnabl P, Michal M. Tubular adenoma of the skin with follicular and sebaceous differentiation: A report of two cases. *Am J Dermatopathol* 2006; **28**: 142–6.
4 Mizuoka H, Senzaki H, Shikata N *et al*. Papillary eccrine adenoma: immunohistochemical study and literature review. *J Cutan Pathol* 1998; **25**: 59–64.
5 Sexton M, Maize JC. Papillary eccrine adenoma: a light microscopic and immunohistochemical study. *J Am Acad Dermatol* 1988; **18**: 1114–20.

Eccrine or apocrine/follicular tumours

In recent years, it has become apparent that a number of adnexal tumours that were regarded as exclusively showing eccrine ductal differentiation often display ductal apocrine differentiation. Because of the close relationship between the apocrine and the pilosebaceous unit, these tumours may also show evidence of focal follicular and even sebaceous differentiation [1,2]. The list of tumours with potential to display apocrine ductal differentiation continues to expand and even includes rare examples of poromas showing apocrine differentiation (see p. 53.23).

References

1 McCalmont TH. A call for logic in the classification of adnexal neoplasms. *Am J Dermatopathol* 1996; **18**: 104–9.
2 Wong TY, Suster S, Cheek RF, Mihm MC Jr. Benign cutaneous adnexal tumours with combined folliculosebaceous, apocrine, and eccrine differentiation: study of eight cases. *Am J Dermatopathol* 1996; **18**: 124–36.

Hidradenoma [1]

Synonyms
- Nodulocystic hidradenoma
- Clear-cell hidradenoma
- Acrospiroma

Definition. A relatively rare tumour of sweat gland origin. Although traditionally regarded as displaying eccrine differentiation, it is now accepted that tumours can show either eccrine or apocrine differentiation [2].

Clinical features [3]. This is an uncommon tumour, found mainly in adults, and is excised more commonly in women than in men. Lesions in children are very rare [4]. The tumours are firm dermal nodules, 5–30 mm in size, and may be attached to the overlying epidermis, which can be either thickened or ulcerated (Fig. 53.22). Growth is slow and there may be a history of serous discharge. The lesions are usually solitary and are most likely to be found on the scalp, face, anterior trunk and proximal limbs.

Pathology [5–8]. The tumour may connect with the epidermis. It forms lobulated, circumscribed masses and is composed of two cell types—polygonal cells, whose glycogen content may give the cytoplasm a clear appearance; and elongated, darker and smaller cells, which may occur at the periphery. Often, tumours do not contain cells with clear cytoplasm, and the name 'clear-cell hidradenoma' is therefore misleading. Cuboidal or columnar cells are seen lining duct-like spaces and clefts. In cases with a connection to the epidermis, the superficial component displays poromatous features. Focal squamous differentiation may be seen [9] and occasional mucinous cells are also present. The latter is often seen in lesions with apocrine differentiation.

Malignant transformation is very rare, and the diagnosis relies on identification of the pre-existing benign component [10–13].



Fig. 53.22 Hidradenoma. Red–brown irregular papule.

Diagnosis. When the tumour is attached to the epidermis, the diagnosis may be suspected on clinical grounds, especially if there is a history of discharge. Ulcerated lesions may resemble basal cell carcinoma. Dermal nodules are non-diagnostic by clinical inspection.

Treatment. Surgical excision will cure benign lesions. Local recurrences are rare [14]. Malignant eccrine hidradenoma may metastasize.

References

1 Hashimoto K, Di Bella RJ, Lever WF. Clear cell hidradenoma: histologic, histochemical, and electron microscopic study. *Arch Dermatol* 1967; **96**: 18–38.
2 Gianotti F, Alessi E. Clear cell hidradenoma associated with the folliculo-sebaceous-apocrine unit. Histologic study of five cases. *Am J Dermatopathol* 1997; **19**: 351–7.
3 Winkelmann RK, Wolff K. Solid-cystic hidradenoma of the skin. *Arch Dermatol* 1968; **97**: 651–61.
4 Faulhaber D, Wörle B, Trautner B *et al*. Clear cell hidradenoma in a young girl. *J Am Acad Dermatol* 2000; **42**: 693–5.
5 Ozawa T, Fujiwara M, Nose K *et al*. Clear cell hidradenoma of the forearm in a young boy. *Pediatr Dermatol* 2005; **22**: 450–2.
6 Hernàndez-Perez E, Cestoni-Parducci R. Nodular hidradenoma and hidradenocarcinoma. *J Am Acad Dermatol* 1985; **12**: 15–20.
7 Lever WF, Castleman B. Clear cell myoepithelioma of the skin. *Am J Pathol* 1952; **28**: 691–9.
8 O'Hara JM, Bensch K, Ioannides G *et al*. Eccrine sweat gland adenoma, clear cell type. *Cancer* 1966; **19**: 1438–50.
9 Stanley RJ, Sánchez NP, Massa MC *et al*. Epidermoid hidradenoma. *J Cutan Pathol* 1982; **9**: 293–302.
10 Hernández Pérez E, Cestoni Parducci R. Nodular hidradenoma and hidradenocarcinoma. *J Am Acad Dermatol* 1985; **12**: 15–20.

11 Yildrim S, Akoz T, Apaydin I *et al*. Malignant clear cell hidradenoma with giant metastasis to the axilla. *Ann Plast Surg* 2000; **45**: 102.
12 Vaideeswar P, Madhiwale CV, Deshpande JR. Malignant hidradenoma: a rare sweat gland tumour. *J Postgrad Med* 1999; **45**: 56–7.
13 Lim SC, Lee MJ, Lee MS *et al*. Giant hidradenocarcinoma: a report of malignant transformation from nodular hidradenoma. *Pathol Int* 1998; **48**: 818–23.
14 Will R, Coldiron B. Recurrent clear cell hidradenoma of the foot. *Dermatol Surg* 2000; **26**: 685–6.

Cylindroma [1–5]

Synonyms
- Turban tumour
- Spiegler's tumour

Definition. A skin tumour of uncertain origin with a characteristic histology (see below) that usually manifests as nodules or tumours of the scalp.

Incidence. This is an uncommon tumour, affecting females more frequently than males. It is frequently familial and an autosomal-dominant gene determines its inheritance [6,7]. It has been reported to follow radiotherapy epilation of the scalp. The onset is usually in early adult life, but may be in childhood or adolescence.

Clinical features [8,9]. The tumours are frequently multiple, smooth, firm, pink to red in colour and often somewhat pedunculated (Fig. 53.23). The lesions may be familial and a suppressor gene (cylindromatosis gene, *CYLD*) has been identified on chromosome 16q12–13, loss of which is associated with cylindroma development [10–12]. Somatic mutations have also been identified in sporadic cases. The loss of this gene causes activation of NF-B which is a transcription factor with antiapoptotic activity [13]. Based on genetic studies and the identification of mutations in the same gene in the Brooke–Spiegler syndrome, multiple familial trichoepitheliomas and familial cylindromatosis it is suggested that the three diseases have the same genetic basis and are phenotypic expressions of the same disease [14,15]. The rate of growth of cylindroma is slow and often seems to cease when a certain size has been reached. Some tumours become 5 cm or more in diameter, but most are smaller. Pain is an occasional symptom. The commonest site is the scalp and adjacent skin. Tumours on the scalp may be almost hairless when pedunculated, but the smaller lesions form dermal nodules with little loss of overlying hair. Multiple tumours have attracted much attention in the literature, but solitary lesions are not uncommonly seen by surgical pathology services. A proportion of lesions occur on the face and neck away from the scalp margin; in fewer than 10% of cases, they are situated on the trunk and limbs. Rare lesions may occur in the breast sporadically or in association with Brooke–Spiegler syndrome [16]. When the lesions are multiple, new tumours arise over the years. In some patients, there may be an admixture with trichoepithelioma, either in separate tumours or sometimes in the same tumour. This is a clear confirmation of what can be inferred from the syndromes associated with cylindromas and follicular neoplasms which is that cylindromas are more likely to be related to the apocrine gland than to the eccrine gland.



Fig. 53.23 Cylindroma. Two large tumours on the head of an elderly woman.

Pathology [17–23]. The tumours have a rounded outline and are composed of closely set mosaic-like masses ('jigsaw-puzzle' appearance) and columns of cells that are invested by a hyaline basal membrane of variable thickness. Thin bands of stroma (Fig. 53.24) separate tumour lobules from one another. The cells are of two types—one large, with a moderate amount of cytoplasm and a vesicular nucleus; and the other small, with little cytoplasm and

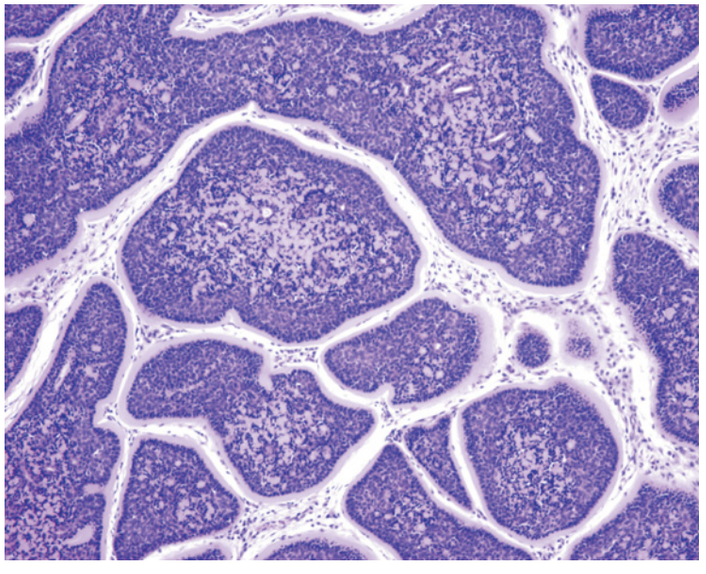


Fig. 53.24 Cylindroma. Classical jigsaw-puzzle architecture, with tumour lobules displaying a thick basal membrane.

a compact nucleus. The small cells tend to be peripheral; they also surround duct-like spaces or masses of hyaline material within the tumour lobule. There are strong immunohistochemical similarities between cylindromas and spiradenomas, and they may coexist in the same individual [24,25]. Malignant transformation is very rare and a sarcomatous component may exceptionally be seen [26–28].

Diagnosis. The multiple type on the scalp is most likely to be confused with tricholemmal cyst, which is, however, usually smoother, firmer and more mobile. Small tumours are difficult to diagnose, and must be distinguished from trichoepithelioma, steatocystoma, or basal cell carcinoma if solitary. Large, pedunculated and lobular tumours are almost unmistakable.

Treatment. Surgery is the treatment of choice. Extensive involvement of the scalp may require wide excision and replacement of the whole area by a graft. Topical salicylic acid has been used with some success in patients with multiple cylindromas [29].

References

1 Crain RC, Helwig EB. Dermal cylindroma (dermal eccrine cylindroma). *Am J Clin Pathol* 1961; **35**: 504–15.
2 Guggenheim W, Schnyder UW. Zur Nosologie der Spiegler-Brookeschen Tumoren. *Dermatologica* 1961; **122**: 274–8.
3 Hashimoto K, Lever WF. Histogenesis of skin appendage tumors. *Arch Dermatol* 1969; **100**: 356–69.
4 Holubar K, Wolff K. Zur Histogenese des Cylindromas. Eine enzymhistochemische Studie. *Arch Klin Exp Dermatol* 1967; **229**: 205–16.
5 Lever WF. Pathogenesis of benign tumors of cutaneous appendages and of basal cell epithelioma. *Arch Dermatol Syphilol* 1948; **57**: 679–724.
6 Kleine-Natrop HE. Gleichzeitige Generalisation gutartiger Basaliome der beiden Typen Spiegler und Brooke. *Arch Klin Exp Dermatol* 1959; **209**: 45–55.
7 Knoth W. Epitheliomatose Phakomatose Brooke–Spiegler (Epithelioma adenoides cysticum und Zylindrome). *Dermatol Monatschr* 1978; **164**: 63–4.
8 Guillot B, Buffiere I, Barneon G *et al.* Tricho-epitheliomas multiples, cylindromes, grain de milium. *Ann Dermatol Vénéréol* 1987; **114**: 175–82.
9 Tellechea O, Reis JP, Ilheu O, Baptista AP. Dermal cylindroma. *Am J Dermatopathol* 1995; **17**: 260–5.
10 Biggs PJ, Chapman P, Lakhani SR *et al.* The cylindromatosis gene on chromosome 16q may be the only tumour suppressor gene involved in the development of cylindromas. *Oncogene* 1996; **12**: 1375–7.
11 Takahashi M, Rapley E, Biggs PJ *et al.* Linkage and LOH studies in 19 cylindromatosis families show no evidence of genetic heterogeneity and refine the CYLD locus on chromosome 16q12-q13. *Hum Genet* 2000; **106**: 58–65.
12 Gerretson AL, Beemer FA, Deenstra W *et al.* Familial cutaneous cylindromas. *J Am Acad Dermatol* 1995; **33**: 199–206.
13 Brummelkamp TR, Nijman SM, Dirac AM *et al.* Loss of the cylindromatous tumour suppressor inhibits apoptosis by activating NF-kappaB. *Nature* 2003; **424**: 797–801.
14 Massoumi R, Paus R. Cylindromatosis and the CYLD gene: new lessons on the molecular principles of epithelial growth control. *BioEssays* 2007; **29**: 1203–14.
15 Bowen S, Gill M, Lee DA *et al.* Mutations in the CYLD gene in Brooke-Spiegler syndrome, familial cylindromatosis, and multiple familial trichoepithelioma: lack of genotype-phenotype correlation. *J Invest Dermatol* 2005; **124**: 919–20.
16 Nonaka D, Rosai J, Spagnolo D *et al.* Cylindroma of the breast of skin adnexal type: a study of 4 cases. *Am J Surg Pathol* 2004; **28**: 1070–5.
17 Ferrándiz C, Campo E, Baumann E. Dermal cylindromas (turban tumours) and eccrine spiradenomas in a patient. *J Cutan Pathol* 1985; **12**: 72–9.
18 Goette DK, McConnell MA, Fowler VR. Cylindroma and eccrine spiradenoma coexistent in the same lesion. *Arch Dermatol* 1982; **118**: 273–4.
19 Gottschalk HR, Graham JH, Aston EEIV. Dermal eccrine cylindroma, epithelioma adenoides cysticum, and eccrine spiradenoma. *Arch Dermatol* 1974; **110**: 473–4.
20 Lauseker H. Beitrag zu den Naevo-epitheliomen. *Arch Dermatol Syphilol* 1952; **194**: 639–62.
21 Gebhart W, Kokoschka WM, Wick J. The cylindroma: a model for human epithelial basement membrane [abstract]. *J Invest Dermatol* 1975; **64**: 286.
22 Mazoujian G, Margolis R. Immunohistochemistry of gross cystic disease fluid protein (GCDFP-15) in 65 benign sweat gland tumors of the skin. *Am J Dermatopathol* 1988; **10**: 28–35.
23 Munger BL, Graham JH, Helwig EB. Ultrastructure and histochemical characteristics of dermal eccrine cylindroma (turban tumor). *J Invest Dermatol* 1962; **39**: 577–94.
24 Meybehm M, Fischer HP. Spiradenoma and dermal cylindroma. *Am J Dermatopathol* 1997; **19**: 154–61.
25 Lee MW, Kelly JW. Dermal cylindroma and eccrine spiradenoma. *Australas J Dermatol* 1996; **37**: 48–9.
26 De Francesco V, Frattasio A, Pillon B *et al.* Carcinosarcoma arising in a patient with multiple cylindromas. *Am J Dermatopathol* 2005; **27**: 21–6.
27 Carlsten JR, Lewis MD, Saddler K *et al.* Spiradenocylindrocarcinoma: a malignant hybrid tumor. *J Cutan Pathol* 2005; **32**: 166–71.
28 Durani BK, Kurzen H, Jaeckel A *et al.* Malignant transformation of multiple dermal cylindromas. *Br J Dermatol* 2001; **145**: 653–6.
29 Oosterkamp HM, Neering H, Nijman SM *et al.* An evaluation of the efficacy of topical application of salicylic acid for the treatment of familial cylindromatosis. *Br J Dermatol* 2006; **155**: 182–5.

Spiradenoma [1,2]

Synonym
- Eccrine spiradenoma

Definition. A benign tumour of sweat gland origin, which is usually solitary and is distinguished by its histology (see below).

Incidence. It is relatively uncommon, appears mainly in young adults, equally in both sexes and is rarely familial (see under cylindroma).

Clinical features [3,4]. The lesion is usually solitary and painful and consists of a firm, rounded, bluish, dermal nodule 3–50 mm in diameter [3]. The usual site is on the front of the trunk and proximal limbs. Rare sites include the vulva, breast and the external ear. Congenital tumours are exceptional, and in one case lesions followed Blaschko's lines on the face [5]. Multiple neoplasms in a linear or zosteriform distribution may also be seen [6,7] and tumours may rarely be seen in a naevus sebaceus [8]. Lesions with features of spiradenoma may be part of the Brooke–Spiegler syndrome [9]. Spiradenoma often overlaps with cylindroma and this gives support to the theory that they are part of the same spectrum (see under cylindroma) [10]. Furthermore, the coexistence of spiradenoma with follicular tumours confirms an apocrine line of differentiation at least in a percentage of these tumours.

Pathology [11,12]. The tumour is lobular, with two cell types in the islands (Fig. 53.25). Larger, paler cells may be grouped around lumina, and smaller, darker cells form the periphery. Small, tubular structures or cystic spaces may occur, and large, thin-walled, dilated vascular channels are also present [13,14]. The lobules are surrounded by condensed connective tissue, which may encroach on the islands as hyaline droplets. Degenerative changes in old tumours are often prominent. Haemorrhage and

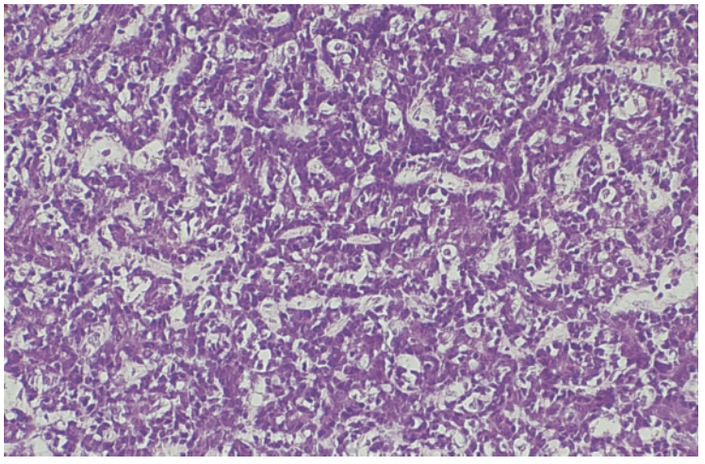


Fig. 53.25 Eccrine spiradenoma. Ductal structures and intermixed pale and dark cells.

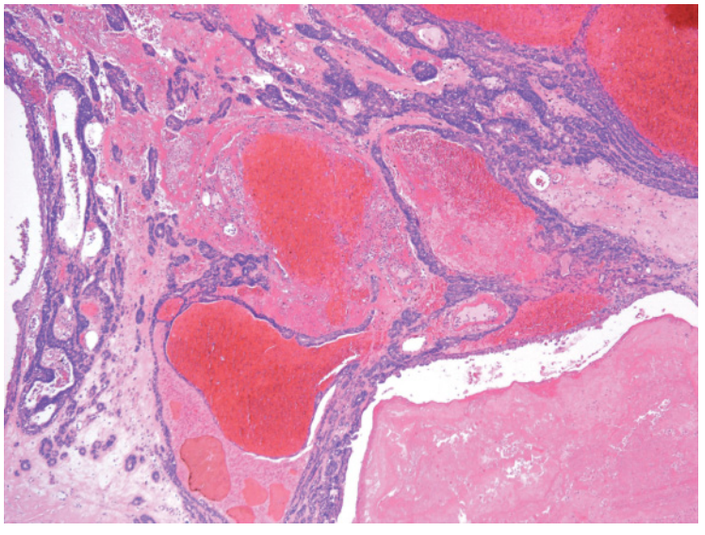


Fig. 53.26 Eccrine spiradenoma. Extensive haemorrhage with or without ischaemic necrosis may result in rapid clinical growth. Only small areas of residual spiradenoma remain.

ischaemic necrosis as a result of degeneration often obscure the histological features, and only focal areas display the typical features of a spiradenoma (Fig. 53.26). Old tumours with degenerative changes tend to be very large. Malignant transformation may occur and usually presents in long-standing tumours [15–20]; lesions may have features of cylindroma and spiradenoma [10]. The diagnosis of a malignant spiradenoma is often only made after a residual benign component is identified. Rare tumours have a sarcomatous component [21]. Malignant tumours may metastasize but it is difficult to be certain of how aggressive these neoplasms are because of their rarity and the bias to report mainly cases with aggressive behaviour.

Diagnosis. Clinical differentiation from other dermal tumours and cysts may be made if the tumour is firm, dark blue and domed.

Treatment. Surgical excision should be complete, as there may be recurrence.

References

1 Castro C, Winkelmann RK. Spiradenoma: histochemical and electron microscopic study. *Arch Dermatol* 1974; **109**: 40–8.
2 Hashimoto K, Kanzaki T. Appendage tumors of the skin: histogenesis and ultrastructure. *J Cutan Pathol* 1984; **11**: 365–81.
3 Kersting DW, Helwig EB. Eccrine spiradenoma. *Arch Dermatol* 1956; **73**: 199–227.
4 Lever WF. Myoepithelial sweat gland tumor: myoepithelioma. *Arch Dermatol Syphilol* 1948; **57**: 332–47.
5 Ekmekci TR, Koslu A, Sakiz D. Congenital blaschkoid eccrine spiradenoma on the face. *Eur J Dermatol* 2005; **15**: 73–4.
6 Yoshida A, Sato T, Sugawara Y *et al*. Two cases of multiple eccrine spiradenoma with linear or localized formation. *J Dermatol* 2004; **31**: 564–8.
7 Gupta S, Jain VK, Singh U *et al*. Multiple eccrine spiradenomas in zosteriform distribution in a child. *Pediatr Dermatol* 2000; **17**: 384–6.
8 Shapiro M, Johnson B Jr, Witmer W *et al*. Spiradenoma arising in a nevus sebaceous of Jadassohn: case report and literature review. *Am J Dermatopathol* 1999; **21**: 462–7.
9 Kim C, Kovich OI, Dosik J. Brooke-Spigler syndrome. *Dermatol Online* 2007; **13**: 10.
10 Michal M, Lamovec J, Mukensnabl P *et al*. Spiradenocylindromas of the skin: tumors with morphological features of spiradenoma and cylindroma in the same lesion: report of 12 cases. *Pathol Int* 1999; **49**: 419–25.
11 Hashimoto K, Lever WF. Histogenesis of skin appendage tumors. *Arch Dermatol* 1969; **100**: 356–69.
12 Hashimoto K, Gross BG, Nelson RG *et al*. Eccrine spiradenoma: histochemical and electron microscopic studies. *J Invest Dermatol* 1966; **46**: 347–65.
13 Munger BL, Berghorn BM, Helwig EB. A light and electron-microscopic study of a case of multiple eccrine spiradenoma. *J Invest Dermatol* 1962; **38**: 289–97.
14 van den Oord JJ, de Woolf-Peeters C. Perivascular spaces in eccrine spiradenoma. *Am J Dermatopathol* 1995; **17**: 266–70.
15 Cooper PH, Frierson HF Jr, Morrison C. Malignant transformation of eccrine spiradenoma. *Arch Dermatol* 1985; **121**: 1445–8.
16 Dabska M. Malignant transformation of eccrine spiradenoma. *Polish Med J* 1972; **11**: 388–96.
17 Evans HL, Su WPD, Smith JL *et al*. Carcinoma arising in eccrine spiradenoma. *Cancer* 1979; **43**: 1881–4.
18 Caladari C, Mehregan AH, Lee KC. Malignant transformation of eccrine tumors. *J Cutan Pathol* 1987; **14**: 15–22.
19 Mambo NC. Eccrine spiradenoma: clinical and pathologic study of 49 tumors. *J Cutan Pathol* 1983; **10**: 312–20.
20 Granter SR, Seeger K, Calonje E *et al*. Malignant eccrine spiradenoma (spiradenocarcinoma): a clinicopathologic study of 12 cases. *Am J Dermatopathol* 2000; **22**: 97–103.
21 McCluggage WG, Fon LJ, O'Rourke D *et al*. Malignant eccrine spiradenoma with carcinomatous and sarcomatous elements. *J Clin Pathol* 1997; **50**: 871–3.

Mixed tumour of the skin [1]

Synonym
- Chondroid syringoma

Definition. Although traditionally regarded as a tumour showing eccrine derivation, it has been demonstrated that a majority of lesions are folliculosebaceous-apocrine and only rare tumours are truly eccrine [2].

Clinical features [1,3–5]. This tumour is usually found on the head and neck, followed by the trunk and the extremities, as a solitary nodule. The lesions are frequently large and nodular,

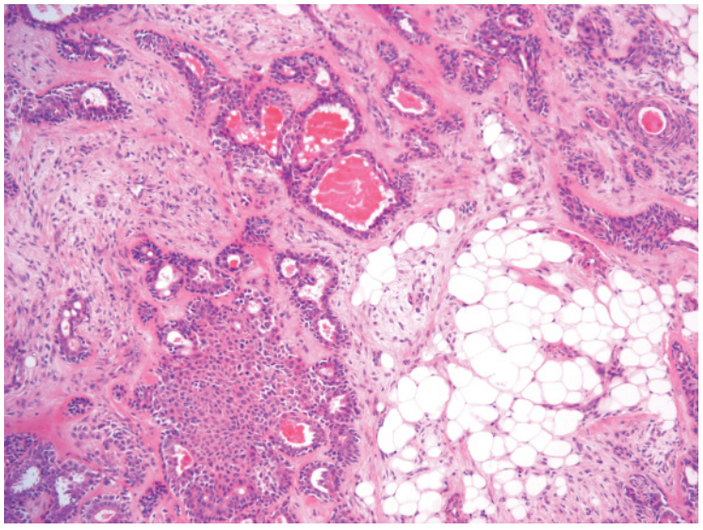


Fig. 53.27 Apocrine mixed tumour. Notice the apocrine glands with a surrounding myxoid/hyalinized stroma with fatty metaplasia.

sometimes with a diameter of 5–10 cm, and occur most commonly in middle-aged males. Lesions in children are rare [6]. Local recurrence is rarely seen.

Pathology [7–13]. This is usually a large, multilobulated tumour located in the dermis and/or subcutaneous tissue. Tumour lobules are separated by fibrous septa. A myxoid, hyalinized or chondroid stroma is variably seen in all tumours. The epithelial component consists of nests and strands of cells with pink cytoplasm and vesicular nuclei with a single, inconspicuous nucleolus. Cytological atypia is absent, and mitotic figures are sometimes seen. Tubular structures and ductal differentiation are frequently seen. Epithelial cells may show various types of metaplasia and differentiation including squamous and mucinous metaplasia and clear cell change and columnar and oxyphilic change [2]. Larger tumour cells with a plasmacytoid appearance are a frequent finding and suggest myoepithelial differentiation. Myoepithelial cells may also be spindle-shaped or display hyaline or clear cell change and collagenous spherulosis [2]. Ductal structures usually have a peripheral layer of flattened myoepithelial cells. Immunohistochemical studies reveal positivity for keratin and focal positivity for S100 and smooth muscle actin, confirming myoepithelial differentiation. Areas clearly indicative of apocrine (Fig. 53.27) and follicular differentiation are often identified [9,10,14,15]. Tumours with follicular differentiation often show numerous keratocysts indicating infundibular differentiation. Staining with cytokeratin 20 may be helpful to identify Merkel cells which, when present, confirms follicular differentiation [16]. The stroma stains positively with Alcian blue, indicating the presence of chondroitin sulphate and hyaluronic acid. Focal calcification, mature fat and bone formation may also be seen [2,17]. From this description, it is clear that all the different cellular elements in mixed tumours including the epithelial, myoepithelial and stromal components may show a wide spectrum of differentiation and metaplastic changes that may make histological interpretation difficult and a potential source of pitfalls [2]. Tumours composed exclusively of myoepithelial cells are regarded as myoepitheliomas [18]. In some cases of mixed tumours, focal architectural and cytological atypia may be seen but this does not seem to imply a more aggressive behaviour [19].

Malignant chondroid syringomas have been reported [20–27], including rare cases with metastasis [28,29].

Management. Local excision is recommended. If there is any suspicion of malignancy, wide excision and follow-up are required.

References

1 Hirsch P, Helwig EB. Chondroid syringoma. *Arch Dermatol* 1961; **84**: 835–47.

2 Kazakov DV, Belousova IE, Bisceglia M *et al*. Apocrine mixed tumor of the skin ('mixed tumor of the folliculosebaceous-apocrine complex'). Spectrum of differentiation and metaplastic changes in the epithelial, nyoepithelial, and stromal components based on a histopathologic study of 244 cases. *J Am Acad Dermatol* 2007; **57**: 467–83.

3 Kresbach H. Ein Beitrag zum sogenannten Mischtumor der Haut. *Arch Klin Exp Dermatol* 1964; **221**: 59–74.

4 Tsoitis G, Brisou B, Destombes P. Mummified cutaneous mixed tumor. *Arch Dermatol* 1975; **111**: 194–6.

5 Welkes S, Goos M. Das chondroide Syringom. *Hautarzt* 1982; **33**: 15–7.

6 Turhan-Haktanir N, Sahin O, Bukulmez A *et al*. Chondroid syringoma in a child. *Pediatr Dermatol* 2007; **24**: 505–7.

7 Headington JT. Mixed tumors of the skin: eccrine and apocrine types. *Arch Dermatol* 1961; **84**: 989–96.

8 Gartmann H, Pullmann H. Chondroides Syringom. *Z Hautkrankh* 1979; **54**: 908–13.

9 Gartmann H, Pullmann H. Apokriner und ekkriner Mischtumor der Kopfhaut. *Z Hautkrankh* 1979; **54**: 952–8.

10 Haensch R. Apokriner Mischtumor. *Z Hautkrankh* 1983; **58**: 575–9.

11 Kanitakis J, Zambruno G, Viac J *et al*. Expression of neural-tissue markers (S-100 protein and Leu-7 antigen) by sweat gland tumors of the skin. *J Am Acad Dermatol* 1987; **17**: 187–91.

12 Mazoujian G, Margolis R. Immunohistochemistry of gross cystic disease fluid protein (GCDFP-15) in 65 benign sweat gland tumors of the skin. *Am J Dermatopathol* 1988; **10**: 28–35.

13 Hernández FJ. Mixed tumors of the skin of the salivary gland type: a light and electron microscopic study. *J Invest Dermatol* 1976; **66**: 49–52.

14 Requena L, Sánchez Yus E, Santa Cruz DJ. Apocrine type of cutaneous mixed tumor with follicular and sebaceous differentiation. *Am J Dermatopathol* 1992; **14**: 186–94.

15 Yamamoto O, Yasuda H. An immunohistochemical study of the apocrine type of cutaneous mixed tumors, with special reference to their follicular and sebaceous differentiation. *J Cutan Pathol* 1999; **26**: 232–41.

16 Salama ME, Azam M, Ma CK *et al*. Chodroid syringoma. Cytokeratin 20 immunolocalization of Merkel cells and reappraisal of apocrine folliculo-sebaceous differentiation. *Arch Pathol Lab Med* 2004; **128**: 986–90.

17 Miracco C, De Santi MM, Lalinga AV *et al*. Lipomatous mixed tumor of the skin: a histological, immunohistochemical and ultrastructural study. *Br J Dermatol* 2002; **146**: 899–903.

18 Mentzel T, Requena L, Kaddu S *et al*. Cutaneous myoepithelial neoplasms: clinicopathologic and immunohistochemical study of 20 cases suggesting a continuous spectrum ranging from benign mixed tumor of the skin to cutaneous myoepithelioma and myoepithelial carcinoma. *J Cutan Pathol* 2003; **30**: 293–302.

19 Kazakov DV, Bisceglia M, Spagnolo DV *et al*. Apocrine mixed tumors of the skin with architectural and/or cytologic atypia: a retrospective clinicopathologic study of 18 cases. *Am J Surg Pathol* 2007; **31**: 1094–102.

20 Botha JBC, Kahn LB. Aggressive chondroid syringoma. *Arch Dermatol* 1978; **114**: 954–5.

21 Devine P, Sarno RC, Ucci AA. Malignant cutaneous mixed tumor. *Arch Dermatol* 1984; **120**: 576–7.

22 Harrist TJ, Aretz TH, Mihm MC Jr *et al*. Malignant chondroid syringoma. *Arch Dermatol* 1981; **117**: 719–24.

23 Hilton JMN, Blackwell JB. Metastasizing chondroid syringoma. *J Pathol* 1973; **109**: 167–70.
24 Ishimura E, Iwamoto H, Kobashi Y *et al*. Malignant chondroid syringoma. *Cancer* 1983; **52**: 1966–73.
25 Matz LR, McCully DJ, Stokes BAR. Metastasizing chondroid syringoma: case report. *Pathology* 1969; **1**: 77–81.
26 Metzler G, Schaumburg-Lever G, Hornstein O *et al*. Malignant chondroid syringoma. *Am J Dermatopathol* 1996; **18**: 83–9.
27 Redono C, Rocamora A, Villoria F *et al*. Malignant mixed tumor of the skin: malignant chondroid syringoma. *Cancer* 1982; **49**: 1690–6.
28 Shvili D, Rothem A. Fulminant metastasizing chondroid syringoma of the skin. *Am J Dermatopathol* 1986; **8**: 321–5.
29 Kiely JL, Dunne B, McCabe M *et al*. Malignant chondroid syringoma presenting as multiple pulmonary nodules. *Thorax* 1997; **52**: 395–6.

Sweat gland carcinomas, including ductal apocrine/follicular carcinomas

These lesions can be divided into two broad groups. The first group represents the situation in which malignant change develops in a pre-existing, apparently benign lesion, such as hidradenoma, mixed tumour, spiradenoma, cylindroma and eccrine poroma. The latter is the most commonly recorded example of such malignant progression [1,2]. In most adnexal tumours, with the exception of malignant eccrine poroma, the diagnosis usually requires identification of a benign component. Even when there is unmistakable cytological evidence of malignancy, the biological behaviour of malignant tumours of skin appendages is generally relatively benign, with local recurrence being much more common than cutaneous metastases.

The second group of carcinomas consists of lesions that develop as carcinomas *ab initio*. The primary eccrine carcinomas include microcystic adnexal carcinoma, eccrine epithelioma (regarded by many as part of the spectrum of microcystic adnexal carcinoma), aggressive digital papillary adenocarcinoma, mucinous carcinoma and adenoid cystic carcinoma. Lymphoepithelioma-like carcinoma of the skin is also included in this group.

A review of 60 sweat gland carcinomas reported 41 porocarcinomas, three syringomatous carcinomas, eight ductal carcinomas, five adenoid cystic carcinomas and three mucinous carcinomas [1]. The rarity of sweat gland carcinomas makes it difficult to say whether or not this distribution is the norm, but porocarcinoma does appear to be a relatively common lesion.

References

1 Urso C, Bondi R, Paglierani M *et al*. Carcinomas of sweat glands: report of 60 cases. *Arch Pathol Lab Med* 2001; **125**: 498–505.
2 Robson A, Greene J, Ansari N *et al*. Eccrine porocarcinoma: a clinicopathologic study of 69 cases. *Am J Surg Pathol* 2001; **25**: 710–20.

Eccrine gland carcinomas

Malignant eccrine poroma [1,2]

Synonym
- Porocarcinoma

Definition. A malignant tumour with metastatic potential arising from intraepidermal eccrine duct epithelium. In up to 18% of cases, tumours arise from a pre-existing benign eccrine poroma [3].

Clinical features [4–7]. These are relatively common malignancies (0.01–0.005% of all cutaneous tumours), arising most often on the lower limbs (44% of cases) in older patients, with an average age at presentation of 73 years. Females are more commonly affected than males. The lesion presents as an endoexophytic tumour, which is often ulcerated. Tumours may attain a very large size and are frequently long standing. Local recurrence is seen in 17% of cases. Regional lymph-node metastases and systemic metastases occur in 19% and 11% of patients, respectively [3]. A small number of patients present with multiple lesions, and it is not clear whether this represents epidermotropic metastasis or true multifocality [1,3,8]. An exceptional case has been reported arising in a scar [9], and a further metastatic lesion was associated with exposure to poison gas [10]. A neoplasm developed from a poroma in a child [11].

Pathology [3,12–14]. Tumours show multiple connections to the epidermis, and a pre-existing benign eccrine poroma may be present. *In-situ* lesions are seen occasionally [3,15]. The tumour infiltrates the dermis and the subcutaneous tissue in nests and lobules composed of relatively small cells that do not have a basaloid appearance. Peripheral palisading is absent. Ductal differentiation is necessary for the diagnosis to be made. This may be demonstrated by the use of immunohistochemical stains for carcinoembryonic antigen (CEA) and epithelial membrane antigen (EMA). A PAS stain may also be used, but this only highlights the ducts in very well-differentiated tumours forming ducts with a cuticle. Comedo necrosis is often present. Clear-cell change and squamous differentiation may be seen, and the latter may be prominent in some cases making it difficult to decide whether the tumour represents a squamous cell carcinoma with ductal differentiation or a porocarcinoma with squamous differentiation [16]. Sarcomatoid change may be seen in rare cases [17].

Poor prognostic factors are a large number of mitotic figures, lymphovascular invasion, tumour depth greater than 7 mm and an infiltrating rather than a pushing border [3].

Treatment. Wide excision and follow-up are required. Two series, including a total of 93 cases, suggest that these lesions may have less metastatic capacity than thought previously [3,18]. In a smaller series of 12 cases, half displayed metastases to regional lymph nodes [19]. Mohs micrographic surgery is useful in those cases with a prominent infiltrative growth pattern [20].

References

1 Pinkus H, Mehregan AH. Epidermotropic eccrine carcinoma. *Arch Dermatol* 1963; **88**: 597–606.
2 Mishima Y, Morioka S. Oncogenic differentiation of the intraepidermal eccrine sweat duct: eccrine poroma, poroepithelioma and porocarcinoma. *Dermatologica* 1969; **138**: 238–50.
3 Robson A, Greene J, Ansari N *et al*. Eccrine porocarcinoma: a clinicopathologic study of 69 cases. *Am J Surg Pathol* 2001; **25**: 710–20.

4 Miura Y. Epidermotropic eccrine carcinoma. *Jpn J Dermatol (Series B)* 1968; **78**: 226–30.
5 Bottles K, Sagebiel RW, McNutt NS *et al*. Malignant eccrine poroma. *Cancer* 1984; **53**: 1579–83.
6 Gschnait F, Horn F, Lindlbauer R *et al*. Eccrine porocarcinoma. *J Cutan Pathol* 1980; **7**: 349–53.
7 Ishikawa K. Malignant hidroacanthoma simplex. *Arch Dermatol* 1971; **104**: 529–32.
8 Landa NG, Winkelmann RK. Epidermotropic eccrine porocarcinoma. *J Am Acad Dermatol* 1991; **24**: 27–31.
9 Nemoto I, Akiyama N, Aoyagi S *et al*. Eccrine porocarcinoma and eccrine porosa arising in a scar. *Br J Dermatol* 2004; **150**: 1232–3.
10 Helmke B, Stara H, Bachter D *et al*. Metastasising porocarcinoma following exposure to poison gas. *Lancet* 2002; **359**: 1685.
11 Valverde K, Senger C, Ngan BY *et al*. Eccrine porocarcinoma in a child that evolved rapidly from an eccrine porosa. *Med Pediatr Oncol* 2001; **23**: 402–6.
12 Krinitz K. Malignes intraepidermales ekkrines Porom. *Z Hautkrankh* 1972; **47**: 9–17.
13 Mohri S, Chika K, Saito I *et al.* A case of porocarcinoma. *J Dermatol* 1980; **7**: 431–4.
14 Shaw M, McKee PH, Lowe D, Black MM. Malignant eccrine poroma: a study of 27 cases. *Br J Dermatol* 1982; **107**: 675–80.
15 Rutten A, Requena L, Requena C. Clear cell porocarcinoma in situ. *Am J Dermatopathol* 2002; **24**: 67–71.
16 Perna C, Cuevas J, Jiménez-Hefferman JA *et al.* Eccrine porocarcinoma (malignant eccrine poroma). *Am J Surg Pathol* 2002; **26**: 272–3.
17 Mahomed F, Blok J, Grayson W. The squamous variant of eccrine porocarcinoma: a clinicopathological study of 21 cases. *J Clin Pathol* 2008; **61**: 361–5.
18 Goh SG, Dayrit JF, Calonje E. Sarcomatoid eccrine porocarcinoma: report of two cases and a review of the literature. *J Cutan Pathol* 2007; **34**: 55–60.
19 Shiohara J, Koga H, Uhara H *et al*. Eccrine porocarcinoma: clinical and pathological study of 12 cases. *J Dermatol* 2007; **34**: 516–22.
20 Wittenberg GP, Robertson DB, Solomon AR *et al*. Eccrine porocarcinoma treated with Mohs micrographic surgery: a report of five cases. *Dermatol Surg* 1999; **25**: 911–3.

Aggressive digital papillary adenocarcinoma

Definition. A rare tumour found on the hands and feet, with a high risk both of local recurrence and metastasis. Prior publications have described both a benign, aggressive digital papillary adenoma and a carcinoma [1,2], but the lack of pathologically diagnostic or prognostic differentiating features suggests that all lesions in this category should be treated as carcinomas.

Clinical features. Both sexes are affected and although most patients are young adults, the age range is wide and an exceptional case in a teenager has been reported [3]. The lesion presents as a non-diagnostic, asymptomatic nodule on the fingers, toes, palms or soles. Delayed diagnosis is frequent [1,2,4,5]. Lesions may masquerade as either a fibrokeratoma [6] or paronychia [7].

Pathology [1,2,5]. The lesions are obviously cystic on low-power microscopic examination, and have papillary projections into the cystic cavities. Ductal and tubuloalveolar structures are also present. There may be focal necrosis and both nuclear hyperchromatism and a high mitotic count. In some cases, a tubular architecture tends to predominate and papillary projections may not be so prominent. Histological features do not allow accurate prediction of behaviour, as tumours with low-grade histology may metastasize [2].

Tumours may invade surrounding soft tissues and blood vessels and can destroy bone.

Treatment. Wide local excision including amputation of the affected digit and follow-up are recommended in view of the high recurrence rate, both locally and via metastatic spread [1,2,8,9]. It has been suggested that sentinel lymph-node biopsy is appropriate for these lesions [10].

References

1 Kao GF, Helwig EB, Graham JH. Aggressive digital papillary adenoma and adenocarcinoma: a clinicopathological study of 57 cases. *J Cutan Pathol* 1987; **14**: 129–46.
2 Duke WH, Sherod TT, Lupton GP. Aggressive digital papillary adenocarcinoma (aggressive digital papillary adenoma and adenocarcinoma revisited). *Am J Surg Pathol* 2000; **24**: 775–84.
3 Bazil MK, Henshaw RM, Werner A *et al*. Aggressive digital papillary adenocarcinoma in a 15-year-old girl. *J Pediatr Hematol Oncol* 2006; **28**: 529–30.
4 Ceballos PI, Penneys NS, Acosta R. Aggressive digital papillary adenocarcinoma. *J Am Acad Dermatol* 1990; **19**: 899–900.
5 Jih DM, Elenitsas R, Vottorio CC *et al*. Aggressive digital papillary adenocarcinoma: a case report and review of the literature. *Am J Dermatopathol* 2001; **23**: 154–7.
6 Chi CC, Kuo TT, Wang SH. Aggressive digital papillary adenocarcinoma: a silent malignancy masquerading as acquired digital fibrokeratoma. *Am J Clin Dermatol* 2007; **8**: 243–5.
7 Gorva AD, Mohil R, Srinivasan MS. Aggressive digital papillary adenocarcinoma presenting as paronychia of the finger. *J Hand Surg (Br)* 2005; **30**: 534.
8 Bakotic B, Antonescu CR. Aggressive digital papillary adenocarcinoma of the foot. *J Foot Ankle Surg* 2000; **39**: 402–5.
9 Altman CE, Hamill RL, Elston DM. Metastatic aggressive digital papillary adenocarcinoma. *Cutis* 2003; **72**: 145–7.
10 Malafa M, McKesey P, Stone S *et al*. Sentinel node biopsy for staging of digital papillary adenocarcinoma. *Dermatol Surg* 2000; **26**: 580–3.

Eccrine or apocrine/follicular carcinomas

Malignant cylindroma [1–7]

Definition. A rare tumour, which develops from a pre-existing benign dermal cylindroma.

Clinical features. These unusual tumours develop as expanding nodules, usually on the scalp or very rarely in the external ear [8]. They may be suspected by expansion of a previously static dermal cylindroma or turban tumour. They have been reported in familial cases of cylindromas [1,2].

Pathology. These lesions have the characteristic architecture of a dermal cylindroma, with deeply basophilic small cells surrounded by an eosinophilic basement membrane [3–6]. In addition, however, there is marked nuclear atypia, irregularity of cell size and an infiltrative growth pattern. Mitotic figures, both normal and abnormal, are present. Exceptionally, a sarcomatous component may be seen [9].

Treatment. Wide local excision and follow-up are required.

References

1 Pizinger K, Michal M. Malignant cylindroma in Brooke–Spiegler syndrome. *Dermatology* 2000; **201**: 255–7.

2 Galadari E, Mehregan AH, Lee KC. Malignant transformation of eccrine tumors. *J Cutan Pathol* 1987; **14**: 15–22.
3 Greither A, Rehrmann A. Spiegler-Karzinome mit assoziierten Symptomen. *Dermatologica* 1980; **160**: 361–70.
4 Korting GW, Hoede N, Gebhardt R. Kurzer Bericht über einen malignen entarteten Spiegler-Tumor. *Dermatol Monatsschr* 1970; **156**: 141–7.
5 Lyon JB, Rouillard LM. Malignant degeneration of turban tumour of scalp. *Trans St John's Hosp Dermatol Soc* 1961; **46**: 74–7.
6 Urbach F, Graham JH, Goldstein J *et al*. Dermal eccrine cylindroma. *Arch Dermatol* 1963; **88**: 880–94.
7 Iyer PV, Leong AS. Malignant dermal cylindromas: do they exist? A morphological and immunohistochemical study and review of the literature. *Pathology* 1989; **21**: 269–74.
8 Mashkevich G, Undavia S, Iacob C *et al*. Malignant cylindroma of the external auditory canal. *Otol Neurotol* 2006; **27**: 21–6.
9 De Francesco V, Frattasio A, Pillon B *et al*. Carcinosarcoma arising in a patient with multiple cylindromas. *Am J Dermatopathol* 2005; **27**: 21–6.

Malignant hidradenoma

Synonyms
- Hidradenocarcinoma
- Malignant acrospiroma

Definition. A malignant tumour traditionally regarded as displaying eccrine differentiation and arising from a pre-existing hidradenoma.

Clinical features. These lesions are most often recorded as red, ulcerated nodules on the face, hands or feet. They are commonest in older adults, but cases have been recorded in children [1–4]. They may be very aggressive and pulmonary metastases have occurred.

Pathology. Large clusters of glycogen-rich clear cells are present in some cases, but others may resemble basal cell carcinoma [5–9]. Focal necrosis may be present, and the range of mitoses is highly variable. Squamous differentiation may be prominent [10]. Tumour cells are usually positive for EMA, CEA, S-100, gross-cystic disease fluid protein-15, the keratin cocktail AE1/AE3 and cytokeratin 5/6 [11]. Tumours may be eccrine or apocrine. Amplification of the Her-2/neu gene has been demonstrated in a single case with lymph node metastases [12]; based on this finding the patient was treated with trastuzumab.

Treatment. Wide local excision is recommended. Mohs surgery has been used successfully for lesions on the foot [13]. Follow-up is essential, as the lesions may recur locally and/or metastasize [14]. Sentinel lymph node biopsy has been used exceptionally to demonstrate early metastatic disease [15].

References

1 Headington JT, Niederhuber JE, Beals TF. Malignant clear cell acrospiroma. *Cancer* 1978; **41**: 641–7.
2 Johnson BL Jr, Helwig EB. Eccrine acrospiroma. *Cancer* 1969; **23**: 641–57.
3 Keasbey LE, Hadley GC. Clear-cell hidradenoma: report of three cases with widespread metastases. *Cancer* 1954; **7**: 934–52.
4 Kersting DW. Clear cell hidradenoma and hidradenocarcinoma. *Arch Dermatol* 1963; **87**: 323–33.
5 Mambo NC. The significance of atypical nuclear changes in benign eccrine acrospiromas: a clinical and pathological study of 18 cases. *J Cutan Pathol* 1984; **11**: 35–44.
6 Mehregan AH, Hashimoto K, Rahbari H. Eccrine adenocarcinoma: a clinicopathologic study of 35 cases. *Arch Dermatol* 1983; **119**: 104–14.
7 Santler R, Everhartinger C. Malignes Klarzellen-Myoepitheliom. *Dermatologica* 1965; **130**: 340–7.
8 Schroeder WA Jr, Hosler MW. Malignant clear cell hidradenoma of the lip. *Mil Med* 1989; **154**: 508–11.
9 Vaideeeswar P, Madiwhale CV, Deshpande JR. Malignant hidradenoma: a rare sweat gland tumour. *J Postgrad Med* 1999; **456**: 56–7.
10 Will R, Coldiron B. Recurrent clear cell hidradenoma of the foot. *Dermatol Surg* 2000; **26**: 685–6.
11 Ko CJ, Cochran AJ, Eng W *et al*. Hidradenocarcinoma: a histological and immunohistochemical study. *J Cutan Pathol* 2006; **33**: 726–30.
12 Nash JW, Barrett TL, Kies M *et al*. Metastatic hidradenocarcinoma with demonstration of Her-2/neu gene amplification by fluorescence in-situ hybridization: potential treatment implications. *J Cutan Pathol* 2007; **34**: 49–54.
13 Park HJ, Kim YC, Cinn YW. Nodular hidradenocarcinoma with prominent squamous differentiation: case report and immunohistochemical study. *J Cutan Pathol* 2000; **27**: 423–7.
14 Jouary T, Kaiafa A, Lipinski P *et al*. Metastatic hidradenocarcinoma: efficacy of capecitabine. *Arch Dermatol* 2006; **142**: 1366–7.
15 Bogner PN, Fullen DR, Lowe L *et al*. Lymphatic mapping and sentinel lymph node biopsy in the detection of early metastasis from sweat gland carcinoma. *Cancer* 2003; **97**: 2285–9.

Malignant spiradenoma

Synonym
- Spiradenocarcinoma

Definition. A rare tumour, which usually arises in a pre-existing spiradenoma.

Clinical features. Sudden expansion of a pre-existing nodule is the most likely presentation [1]. A study of 12 cases reports the commonest site as the trunk, with limbs, head and neck less frequently involved [2]. The sex distribution appears equal, and presentation is usually in the seventh decade.

Pathology [2–4]. These lesions usually show evidence of origin from a pre-existing benign spiradenoma. Necrosis, a high mitotic count, loss of the dual cell population and an infiltrative growth pattern are features that raise the possibility of malignant transformation.

Treatment. Excision and follow-up are required. Up to 20% of these tumours have been reported to metastasize [2–5].

References

1 Biernat W, Wozniak I. Spiradenocarcinoma: a clinicopathological study of 3 cases. *Am J Dermatopathol* 1994; **16**: 377–82.
2 Granter SR, Seeger K, Calonje E, Busam K, McKee PH. Malignant eccrine spiradenoma: a study of 12 cases. *Am J Dermatopathol* 2000; **22**: 97–103.
3 Mirza I, Kloss R, Sieber SC. Malignant eccrine spiradenoma. *Arch Path Laboratory Med* 2002; **126**: 591–4.
4 Ishikawa M, Nakanishi Y, Yamazaki N, Yamamoto A. Malignant eccrine spiradenoma: a case report and review of the literature. *Dermatol Surg* 2001; **27**: 67–70.
5 Fernández-Acenero MJ, Manzerbeita F, Mestre de Juan MJ, Requena L. Malignant spiradenoma. *J Am Acad Dermatol* 2001; **44** (Suppl. 2): 395–8.

Microcystic adnexal carcinoma

Synonyms
- Sclerosing/syringomatous sweat duct carcinoma
- Malignant syringoma

Clinical features. This tumour is relatively rare, has an equal sex incidence and a predilection for the central area of the face, often as an inconspicuous, elevated or depressed sclerotic plaque or nodule in the upper lip area [1–4]. The trunk is also rarely involved. The age range is very wide, but young and middle-aged patients are more frequently affected. If the lesion is not promptly treated, or if local recurrence occurs, the lesions may present with pain or a burning sensation because of perineural spread. Cases have been reported both in patients with generalized immunosuppression and in sites of previous radiotherapy [5–7]. It has also rarely been reported arising within a naevus sebaceus [8]. Multiple tumours are exceptional [9]. The rate of local recurrence is very high (up to 40%). Bone involvement is rarely seen [10].

Pathology [11,12]. The salient histological features are the presence of cords of cytologically banal epithelial cells with focal, variable ductal differentiation set in a very sclerotic desmoplastic stroma [2–4]. Horn cysts are seen in many cases and pilar and sebaceous differentiation may also occur (Fig. 53.28) [11–14]. Superficial areas show a resemblance to syringoma, desmoplastic trichoepithelioma and, in some cases, to infiltrative basal cell carcinoma. The diagnosis can therefore be impossible if only a small, superficial biopsy is evaluated, as clues to the correct diagnosis reside in an infiltrative growth pattern and prominent perineural invasion. Immunohistochemistry is of limited value as an aid in the histological diagnosis of microcystic adnexal carcinoma. Although it has been claimed that BerEP4 is consistently negative in microcystic adnexal carcinoma [15] and this may allow distinction from infiltrative basal cell carcinoma, which is consistently positive for this marker, this finding is contradicted by a more recent study in which 38% of microcystic adnexal carcinomas were positive for this marker [15]. Although desmoplastic trichoepithelioma and microcystic adnexal carcinoma may both show positivity for CK15 and BerEP4, it has been shown that CK15 tends to be negative in infiltrative basal cell carcinoma and this may be a useful marker in the histological differential diagnosis of both tumours [16]. Cytogenetic analysis of a case of microcystic adnexal carcinoma has shown a deletion on chromosome 6q (23–25) [17].

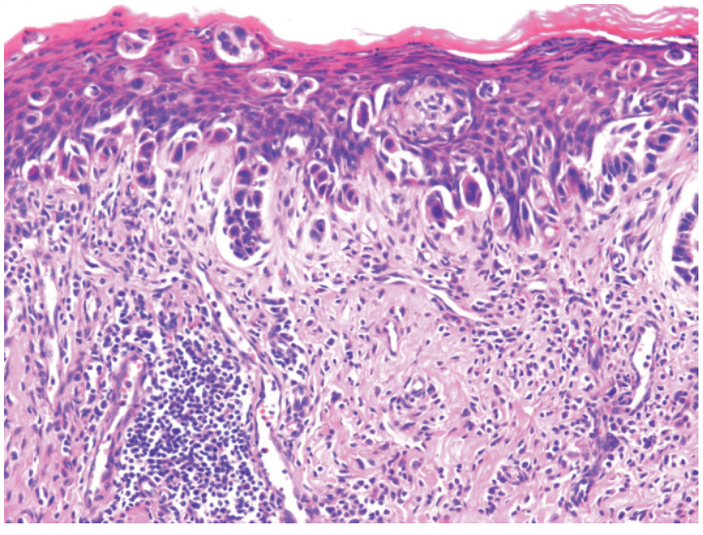


Fig. 53.28 Microcystic adnexal carcinoma. Strands and small nests of bland epithelial cells with an infiltrative growth pattern.

Management. The importance of this tumour is that perineural permeation is common, and for this reason microscopically controlled surgical excision is recommended. Mohs surgery has been recommended as the surgical approach of choice [18].

Metastatic spread is very rare [19,20], but extensive local recurrence can be a major problem. Tumours may rarely extend into the brain as a result of perineural invasion.

References

1 Cooper PH. Sclerosing carcinomas of sweat ducts (microcystic adnexal carcinoma). *Arch Dermatol* 1986; **122**: 261–4.
2 Chiller K, Passaro D, Scheuller M *et al.* Microcystic adnexal carcinoma: forty-eight cases, their treatment, and their outcome. *Arch Dermatol* 2000; **136**: 1355–9.
3 Snow S, Madjar MDD, Hardy S *et al.* Microcystic adnexal carcinoma: a report of 13 cases. *Dermatol Surg* 2001; **27**: 401–8.
4 Ohtsuka H, Nagamatsu S. Microcystic adnexal carcinoma: review of 51 Japanese patients. *Dermatology* 2002; **204**: 190–3.
5 Lei JY, Wang J, Jaffe E *et al.* Microcystic adnexal carcinoma associated with primary immunodeficiency. *Am J Dermatopathol* 2000; **22**: 524–9.
6 Carroll P, Goldstein GD, Brown CW. Metastatic microcystic adnexal carcinoma in an immunocompromised patient. *Dermatol Surg* 2000; **26**: 531–4.
7 Antley CA, Carney M, Smoller BR. Microcystic adnexal carcinoma arising in the site of previous radiation therapy. *J Cutan Pathol* 1999; **26**: 48–50.
8 Lountzis N, Junkins-Hopkins J, Uberti-Benz M *et al.* Microcystic adnexal carcinoma arising within a nevus sebaceus. *Cutis* 2007; **80**: 352–6.
9 Page RN, Hanggi MC, King R *et al.* Multiple microcystic adnexal carcinomas. *Cutis* 2007; **79**: 299–303.
10 Nagatsuka H, Riveras RS, Gunduz M *et al.* Microcystic adnexal carcinoma with mandibular bone marrow involvement: a case report with immunohistochemistry. *Am J Dermatopathol* 2006; **28**: 518–22.
11 Goldstein D, Barr R, Santa Cruz D. Microcystic adnexal carcinoma: a distinct clinicopathologic entity. *Cancer* 1982; **50**: 566–72.
12 Nickoloff BJ, Fleischmann HE, Carmel J *et al.* Microcystic adnexal carcinoma: immunohistologic observations suggesting dual (pilar and eccrine) differentiation. *Arch Dermatol* 1986; **122**: 290–4.
13 Callahan EF, Vidimos AT, Bergfeld WF. Microcystic adnexal carcinoma of the scalp with extensive pilar differentiation. *Dermatol Surg* 2002; **28**: 536–9.
14 Friedman PM, Friedman RH, Jiang SB *et al.* Microcystic adnexal carcinoma: collaborative series review and update. *J Am Acad Dermatol* 1999; **41**: 225–31.
15 Krahl D, Sellheyer K. Monoclonal antibody Ber-EP4 reliably discriminates between microcystic adnexal carcinoma and basal cell carcinoma. *J Cutan Pathol* 2007; **34**: 782–7.
16 Hoang MP, Dresser KA, Kapur P *et al.* Microcystic adnexal carcinoma: an immunohistochemical reappraisal. *Mod Pathol* 2008; **21**: 175–85.
17 Wohlfahrt C, Ternesten A, Sahlin P *et al.* Cytogenetic and fluorescence in-situ hybridization analysis of a microcystic adnexal carcinoma with del (6) (q23 q25). *Cancer Genet Cytogenet* 1997; **98**: 106–12.
18 Khachemoune A, Olbricht SM, Johnson DS. Microcystic adnexal carcinoma: report of four cases treated with Mohs' micrographic surgical technique. *Int J Dermatol* 2005; **44**: 507–12.
19 Gabillot-Carré M, Weill F, Mamelle G *et al.* Microcystic adnexal carcinoma: report of seven cases including one with lung metastasis. *Dermatology* 2006; **212**: 221–8.

20 Ohta M, Hiramoto M, Ohtsuka H. Metastatic microcystic adnexal carcinoma: an autopsy case. *Dermatol Surg* 2004; **30**: 957–60.

Eccrine epithelioma [1–4]

Synonyms
- Basal cell carcinoma with eccrine differentiation
- Syringoid eccrine carcinoma

Freeman and Winkelmann, who considered it to be a basal cell tumour with eccrine differentiation [1,2], first described this rare tumour in 1969. However, the tumour does not represent a basal cell carcinoma with eccrine differentiation [3]. Some authors have proposed that it is part of the spectrum of microcystic adnexal carcinoma. At least 12 cases are currently reported in the world literature. The lesion has some resemblance to both benign syringoma and to dermal cylindroma.

Clinical features. Two-thirds of the cases so far reported have occurred on the scalp as large, non-specific, sometimes ulcerated nodules. They may be painful, due to their position in the deep dermis.

Pathology. The tumour consists of cords and clusters of small, dark-staining, cuboidal basophilic cells set in a very dense stroma. The cells are cytologically abnormal, with a high nuclear/cytoplasmic ratio, and mitotic figures are seen. These features occur in the lower part of the dermis, extending into the subcutaneous fat. The islets of cells have a surrounding PAS-positive membrane.

Management. Wide local excision is required. Follow-up is essential, as repeated local recurrences are common. In one case, metastasis to a local lymph node was recorded.

References

1 Freeman RC, Winkelmann RK. Basal cell tumor with eccrine differentiation. *Arch Dermatol* 1969; **100**: 234–42.
2 Sánchez NP, Winkelmann RK. Basal cell tumor with eccrine differentiation (eccrine epithelioma). *J Am Acad Dermatol* 1982; **6**: 514–8.
3 Urso C, Bondi R. Eccrine epithelioma: an enigma or a chimera? *Am J Dermatopathol* 1992; **14**: 179–80.
4 McKee PH, Fletcher CD, Rasbridge SA. The enigmatic eccrine epitheliomas (eccrine syringomatous carcinoma). *Am J Dermatopathol* 1990; **12**: 552–61.

Mucinous carcinoma

Definition. A rare, adnexal apocrine mucin-producing carcinoma arising on the head and neck area in more than 90% of the cases. This tumour is very similar to mucinous carcinoma of the breast [1].

Clinical features. The most frequently described clinical presentation is that of a grey nodule on the face of an elderly male, often in the periorbital area [2–6]. Occasional tumours present in younger patients [7]. Rarely tumours are bilateral [8]. An important clinical differential diagnosis is a cutaneous secondary deposit from a more common site for mucinous carcinoma such as the stomach and breast [9]. The distinction between a primary skin tumour and a metastasis is often very difficult and has to rely on some histological features (see below), clinicopathological correlation and additional studies to rule out an internal primary. In the case of a suspected metastatic mucinous breast carcinoma, staining for oestrogen and progesterone receptors is not useful, as primary cutaneous mucinous carcinomas are often positive for these markers [10].

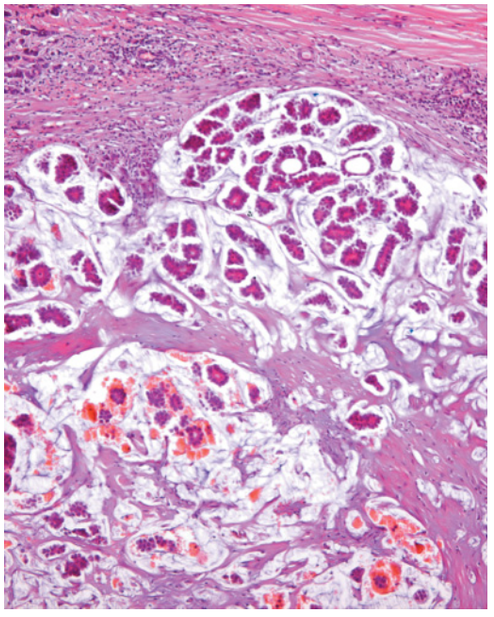


Fig. 53.29 Mucinous carcinoma. Nests of tumour cells surrounded by pools of mucin.

Pathology. These lesions are relatively deeply situated and consist of clusters of cells with pink cytoplasm and some degree of cytological atypia. The central cells are paler and surrounded by darker-staining cells arranged in a palisaded fashion. Broad, fibrous septa run between these cytologically malignant cells, and both cells and septa are separated by lakes of mucin (Fig. 53.29) [11,12]. The mucin stains with diastase-resistant PAS, and acid Alcian blue (pH 2.5). Distinction from metastatic breast of gastrointestinal mucinous carcinoma is difficult. In many cases of primary cutaneous mucinous carcinoma there is evidence of an *in situ* component in neighbouring glands and this confirms a tumour as primary arising in the skin [1,13]. Tumours presenting in the trunk often originate in the breast and those with dirty necrosis usually represent a metastasis from a gastrointestinal primary [1].

Management. Wide local excision, possibly with Mohs micrographic surgery, is recommended [14,15]. Extensive metastatic spread and invasion of bone is very rare [16,17]. Local recurrence is often seen and the risk of metastatic spread to regional lymph nodes increases after a recurrence.

References

1 Kazakov DV, Suster S, LeBoit P *et al*. Mucinous carcinoma of the skin, primary and secondary: a clinicopathologic study of 63 cases with emphasis on the

morphologic spectrum of primary cutaneous forms: homologies with mucinous lesions in the breast. *Am J Surg Pathol* 2005; **29**: 764–82.
2 Baandrup U, Sogaard H. Mucinous (adenocystic) carcinoma of the skin. *Dermatologica* 1982; **164**: 338–42.
3 Balin AK, Fine RM, Golitz LE. Mucinous carcinoma. *J Dermatol Surg Oncol* 1988; **14**: 521–4.
4 Headington JT. Primary mucinous carcinoma of the skin. *Cancer* 1977; **39**: 1055–63.
5 Breier F, Clabian M, Pokieser W *et al.* Primary mucinous carcinoma of scalp. *Dermatology* 2000; **200**: 250–3.
6 Snow SN, Reizner GT. Mucinous eccrine carcinoma of the eyelid. *Cancer* 1992; **15**: 2099–104.
7 Bindra M, Keegan DJ, Guenther T *et al*. Primary cutaneous mucinous carcinoma of the eyelid in a young male. *Orbit* 2005; **24**: 211–4.
8 Bertagnoli R, Cook DL, Goldman GD. Bilateral primary mucinous carcinoma of the eyelid treated with Mohs surgery. *Dermatol Surg* 1999; **25**: 566–8.
9 Nahass GT, Otrakji CJ, Gould E. Mucinous breast carcinoma: single cutaneous metastasis. *J Dermatol Surg Oncol* 1993; **19**: 878–80.
10 Hanby AM, McKee P, Jeffery M *et al.* Primary mucinous carcinomas of the skin express TFF1, TFF3, estrogen receptor and progesterone receptors. *Am J Surg Pathol* 1998; **22**: 1125–31.
11 Mendoza S, Helwig EB. Mucinous (adenocystic) carcinoma of the skin. *Arch Dermatol* 1971; **103**: 68–78.
12 Santa Cruz DJ, Meyers JH, Gnepp DR *et al.* Primary mucinous carcinoma of the skin. *Br J Dermatol* 1978; **98**: 645–53.
13 Qureshi HS, Salama ME, Chitale D *et al*. Primary cutaneous mucinous carcinoma: presence of myoepithelial cells as a clue to the cutaneous origin. *Am J Dermatopathol* 2004; **26**: 353–8.
14 Cecchi R, Rapicano V. Primary cutaneous mucinous carcinoma: report of two cases treated with Moh's micrographic surgery. *Australas J Dermatol* 2006; **47**: 192–4.
15 Marra DE, Schanbacher CF, Torres A. Mohs micrographic surgery of primary cutaneous mucinous carcinoma using immunohistochemistry for margin control. *Dermatol Surg* 2004; **30**: 799–802.
16 Yeung KY, Stinson JC. Mucinous (adenocystic) carcinoma of sweat glands with widespread metastases: case report with ultrastructural study. *Cancer* 1977; **39**: 2556–62.
17 Tanaka A, Hatoko M, Kuwahara M *et al.* Recurrent mucinous carcinoma of the skin invading to the frontal skull base. *Br J Dermatol* 2000; **143**: 458–9.

Adenoid cystic carcinoma [1–3]

Synonym
- Primary cutaneous adenocystic carcinoma

This is a particularly rare variant of adnexal carcinoma, which has only been recognized as an entity since 1975. Adenoid cystic carcinomas arise relatively frequently from salivary glands, and direct spread or even metastasis from this site should be ruled out before the diagnosis of primary cutaneous adenoid cystic carcinoma is made [4]. Around 50 cases are presently recorded in the literature.

Clinical features [1,2]. These lesions are non-specific, sometimes painful, nodules on the head and neck area. The pain is attributed to perineural spread. Rarely, tumours develop elsewhere in the skin including the scrotum [3].

Pathology [5–8]. The pathology is that of large masses of cells with mild or no cytological atypia, arranged in a distinct adenoid or cribriform pattern. The cystic spaces are occupied by mucin, which stains with Alcian blue (pH 2.5). The lesion occupies the middle to deep dermis and may extend to the subcutaneous tissue. A more solid variant may be seen occasionally. Many of these tumours show at least focal evidence of myoepithelial differentiation.

Management. The management of these lesions is by wide local excision and Mohs surgery is a good treatment option [9]. Local recurrence is common and metastasis to the lung and regional lymph nodes has rarely been reported [6,10–13]. Metastatic spread to the lungs has also been reported, rarely many years after removal of the primary cutaneous tumour [14]. Erosion of bone at the primary site has also been recorded.

References

1 Boggio R. Adenoid cystic carcinoma of the scalp. *Arch Dermatol* 1975; **111**: 793–4.
2 Headington JT, Tesars R, Niederhuber JE *et al.* Primary adenoid cystic carcinoma of the skin. *Arch Dermatol* 1978; **114**: 421–4.
3 Koh BK, Choi JM, Yi JY *et al.* Recurrent primary cutaneous adenoid cystic carcinoma of the scrotum. *Int J Dermatol* 2001; **40**: 724–5.
4 Pérez DE, Magrin J, de Almeida OP *et al*. Multiple cutaneous metastases from a parotid adenoid cystic carcinoma. *Pathol Oncol Res* 2007; **13**: 167–9.
5 Cooper PH, Adelson GL, Holthaus WH. Primary cutaneous adenoid cystic carcinoma. *Arch Dermatol* 1984; **120**: 774–7.
6 Seab JA, Graham JH. Primary cutaneous adenoid cystic carcinoma. *J Am Acad Dermatol* 1987; **17**: 113–8.
7 Thomas RM, Lowe DG, Munro DD *et al.* Primary adenoid cystic carcinoma of the skin. *Clin Exp Dermatol* 1987; **12**: 378–80.
8 Wick MR, Swanson PE. Primary adenoid cystic carcinoma of the skin. *Am J Dermatopathol* 1986; **8**: 2–13.
9 Krunic AL, Kim S, Medenica M *et al*. Recurrent adenoid cystic carcinoma of the scalp treated with Mohs micrographic surgery. *Dermatol Surg* 2003; **29**: 647–9.
10 Chu SS, Chang YL, Lou PJ. Primary cutaneous adenoid cystic carcinoma with regional lymph node metastasis. *J Laryngol Otol* 2001; **115**: 673–5.
11 Weekly M, Lydiatt DD, Lydiatt WM *et al*. Primary cutaneous adenoid cystic carcinoma metastatic to cervical lymph nodes. *Head Neck* 2000; **22**: 84–6.
12 Chang SE, Ahn SJ, Choi JH *et al*. Primary adenoid cystic carcinoma of skin with lung metastasis. *J Am Acad Dermatol* 1999; **40**: 640–2.
13 Doganay L, Bilgi S, Aygit C *et al*. Primary cutaneous adenoid cystic carcinomas with lung and lymph node metastases. *J Eur Acad Dermatol Venereol* 2004; **18**: 383–5.
14 Pappo O, Gez E, Craciun I *et al*. Growth rate analysis of lung metastases appearing 18 years after resection of cutaneous adenoid cystic carcinoma: case report and review of the literature. *Arch Pathol Lab Med* 1992; **116**: 76–9.

Miscellaneous tumours

Tumours of anogenital mammary-like glands

For many years it was assumed that a number of female genital tumours with features identical to those arising in the breast were derived from ectopic mammary gland tissue along the milk lines. Van der Putte, however, has proposed that this theory is not accurate as primordia of mammary glands do not extend beyond the axillary–pectoralis area [1]. His proposal is that there is a group of distinctive, mammary-like genital glands that share features with true mammary glands and eccrine and apocrine glands and from which most genital glandular neoplasms arise [1,2]. The latter include hidrocystoma, hidradenoma papilliferum, extramammary Paget's disease and tumours identical to those arising in breast tissue including fibroadenoma, cystosarcoma phylloides and adenocarcinoma [3–7].

References

1 van der Putte SC. Mammary-like glands of the vulva and their disorders. *Int J Gynecol Pathol* 1994; **13**: 150–60.

2 van der Putte SC, van Gorp LH. Adenocarcinoma of the mammary-like glands of the vulva: a concept unifying sweat gland carcinoma of the vulva, carcinoma of supranummerary mammary glands and extramammary Paget's disease. *J Cutan Pathol* 1994; **21**: 157–63.

3 Castro CY, Deavers M. Ductal carcinoma in-situ arising in mammary-like glands of the vulva. *Int J Gynecol Pathol* 2001; **20**: 277–83.

4 Sington JD, Manek S, Hollowood K. Fibroadenoma of the mammary-like glands of the vulva. *Histopathology* 2002; **41**: 563–5.

5 Ohira S, Itoh K, Osada K *et al*. Vulval Paget's disease with underlying adenocarcinoma simulating breast carcinoma: case report and review of the literature. *Int J Gynecol Cancer* 2004; **14**: 1012–7.

6 Abbott JJ, Ahmed J. Adenocarcinoma of the mammary-like glands of the vulva: Report of a case and review of the literature. *Am J Dermatopathol* 2006; **28**: 127–33.

7 Giger OT, Lacoste E, Honegger C *et al*. Expression of the breast differentiation antigen NY-BR1 in a phyllodes tumor of the vulva. *Virchows Arch* 2007; **450**: 471–4.

Paget's disease of the nipple [1]

Definition. A progressive, marginated, scaling or crusting of the nipple and areola due to invasion of the epidermis by malignant cells, which are currently thought to originate in the intraduct carcinoma of the breast that frequently accompanies the condition.

There is a strong, current view that Paget's disease arises from apocrine duct-derived epithelial cells.

Incidence and aetiology [2]. Paget's disease of the nipple is an uncommon occurrence, considering the frequency of breast cancer [3,4]. In one series, it occurred in fewer than 3% of breast cancers. It occurs chiefly in women, although rare cases have been recorded in men [5] and is exceptionally bilateral [6]. It is rare before the fourth decade and is most frequent in the fifth and sixth. Published cases suggest that the disease is more common in Anglo-Saxon countries. The current view is that the majority of cases of Paget's disease arise from either invasive or *in-situ* ductal carcinoma in the deeper breast tissue. In a minority of cases no underlying *in-situ* or invasive carcinoma is found [7]. Although the incidence of breast cancer is increasing, the incidence of Paget's disease has decreased by 45% in the USA in the last decades [8]. Equally, the incidence of Paget's disease associated with underlying invasive cancer of ductal carcinoma *in situ* has also decreased [8].

Clinical features [9,10]. The early changes may be minimal, with a small, crusted and intermittently moist area on the nipple giving a brownish stain on clothing, or producing itching, pricking or burning sensations. Less often, there is a serous or blood-stained discharge from the nipple, or a lump may be noticed in the breast (Fig. 53.30). The surface changes persist and gradually spread to produce an eczematous appearance. The nipple, areola and, at a later stage, skin of the breast are erythematous and moist or crusted (Fig. 53.31). The change is sharply marginated and may spare a segment of the areola. The edge is slightly raised and irregular in outline. If the crusts are removed, a red, glazed, moist or vegetating surface is revealed. Itching may be a prominent symptom and excoriations may be found in the established lesion. Some areas may be ulcerated. The nipple itself may be retracted, and a subjacent mass or a lump deeper in the breast may be felt. The regional glands should be examined; they are rarely enlarged when a mass cannot be felt, but are enlarged in more than half the cases with a detectable tumour. The rate of spread of the skin changes is slow, and patients often wait a year or more before seeking advice. The change may occasionally involve not only the skin of the breast but also spread on to the chest wall. Poor prognosis is associated with invasive disease and the presence of a palpable mass [11]. An exceptional case has been recorded in which the patient presented with ipsilateral eruptive seborrhoeic keratoses of the nipple and areola (Leser-Trelat sign) [12].



Fig. 53.30 Paget's disease of the nipple. Distant clinical view, showing unilateral lesion.



Fig. 53.31 Paget's disease of the nipple. Close-up view, showing erythema and well-marked lateral edge of the lesion.

Pathology [13–15]. The epidermis is thickened, with papillomatosis, enlargement of the interpapillary ridges and hyperkeratosis or parakeratosis on the surface (Fig. 53.32). Within the epidermis, characteristic Paget's cells are dispersed between the prickle cells. They vary in number, and when profuse the Malpighian layers

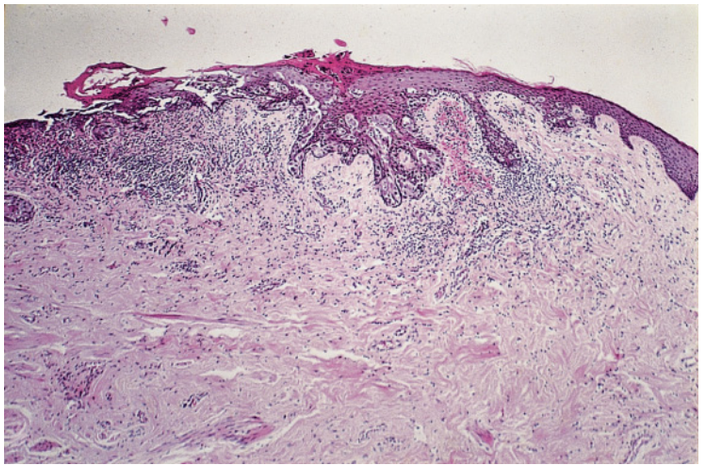


Fig. 53.32 Pathology of Paget's disease of the nipple, showing epidermal ulceration, colonization of the epidermis by large pale Paget's cells and an underlying brisk lymphocytic infiltrate.

may be disrupted and the surface covered by a crust. There is a chronic inflammatory reaction in the upper dermis. In the later stages, the epidermis may be atrophic or eroded. On scanning microscopy, the differential diagnosis may include superficial spreading malignant melanoma.

The Paget's cells have a clear, abundant cytoplasm and do not establish intercellular bridges with the adjacent normal keratinocytes. Both the cells and their nuclei are rounded; the nuclei are vesicular or hyperchromatic with a high nuclear/cytoplasmic ratio. The cytoplasm is PAS-positive and diastase-resistant [16], which indicates the presence of neutral polysaccharides and supports the glandular origin of the cells [17]. Staining with antibodies to CEA is also positive [18,19]. The cells are distributed singly among the prickle cells, or in clusters in a pattern similar to that seen in superficial spreading melanoma. The Paget's cells may also be seen in appendage ducts, so that it can be impossible to determine if these cells are migrating from these ducts to the epidermis, or invading downwards into the ducts from the epidermis.

An underlying breast carcinoma, if present, is not always seen on biopsy, as it may be deeply set. Careful examination of the amputated breast may show an intraduct carcinoma, sometimes of quite small dimensions, usually situated most distally, but sometimes in the terminal ducts, and often appearing to spread between the two layers of epithelial cells of the duct. The cells may accumulate within and distend the ducts and spread in both directions. A number of ducts are usually involved. At a later stage, the carcinoma becomes invasive and behaves like classic breast carcinoma.

Diagnosis. The principal differential diagnosis is eczema of the nipple. This is frequently bilateral and runs a more fluctuating course, improving in response to local treatment and spreading rapidly when irritated. Eczema lacks the sharp, raised and rounded margin and the superficial induration of Paget's disease. In doubtful cases, biopsy will be required. Bowen's disease and superficial basal cell carcinoma may also produce a similar clinical picture. They are both very uncommon on the nipple and can be differentiated histologically. Psoriasis and erosive adenomatosis of the nipple may also need to be considered in the clinical differential diagnosis, and again a biopsy to obtain pathology will clarify the situation. The chief pathological challenge is to distinguish Paget's disease from malignant melanoma, the latter exceptionally presenting in the nipple [20,21]. Paget's disease cells will be CEA-positive, EMA-positive and Cam 5.2-positive, while those of melanoma will be positive for Melan A mart melanoma antigens [18,19]. Positivity to antibody to S100 protein is not useful, as although it is positive in the great majority of melanomas, this is also the case in a proportion of cases of Paget's disease. The absence of melanophages and the presence of neutral mucopolysaccharides in the cells are also helpful.

Treatment [22]. All patients should have a mammogram or ultrasound to establish whether or not there is deeper pathology in the underlying breast, as this will help determine the extent of surgery required. Surgery should be carried out as for carcinoma of the breast. In patients with no evidence of an underlying breast carcinoma, conservation may be a realistic option [23,24]. A recent study has confirmed this, recommending breast conserving therapy with or without radiotherapy according to the presence or absence of an invasive component as the treatment of choice. Sentinel lymph node biopsy is performed in cases with an invasive component [7]. Surgery should always include the whole of the nipple–areolar complex [7].

References

1 Lloyd J, Flanagan AM. Mammary and extramammary Paget's disease. *J Clin Pathol* 2000; **53**: 742–9.
2 Ordoñez NG, Awalt H, MacKay B. Mammary and extramammary Paget's disease. *Cancer* 1987; **59**: 1173–83.
3 Paget J. A disease of the mammary areola preceding cancer of the mammary gland. *St Bartholomew's Hosp Rep* 1874; **10**: 87–91.
4 Kollmorgen DR, Varanasi JS, Edge SB *et al*. Paget's disease of the breast: a 33 year experience. *J Am Coll Surg* 1998; **187**: 171–7.
5 Desai DC, Brennan EJ, Carp NZ. Paget's disease of the male breast. *Am J Surg* 1996; **62**: 1068–72.
6 Ucar AE, Korukluoglu B, Ergul E *et al*. Bilateral paget disease of the male nipple: First report. *Breast* 2008; **17**: 317–8.
7 Caliskan M, Gatti G, Sosnovskikh I *et al*. Paget's disease of the breast: the experience of the European Institute of Oncology and review of the literature. *Breast Cancer Res Treat* 2008; **112**: 513–21.
8 Chen CY, Sun LM, Anderson BO. Paget disease of the breast: changing patterns of incidence, clinical presentation, and treatment in the U.S. *Cancer* 2006; **107**: 1448–58.
9 Yim JH, Wick MR, Philpott GW *et al*. Underlying pathology in mammary Paget's disease. *Ann Surg Oncol* 1997; **4**: 287–92.
10 Kay S. Paget's disease of the nipple. *Surg Gynecol Obstet* 1966; **123**: 1010–4.
11 Dalberg K, Hellborg H, Wärnberg F. Paget's disease of the nipple in a population based cohort. *Breast Cancer Res Treat* 2008; **111**: 313–9.
12 Shamsadini S, Wadji MB, Shamsadini A. Surrounding ipsilateral eruptive seborrhoeic keratosis as a warning sign of intraductal breast carcinoma and Paget's disease (Leser Trelat sign). *Dermatol Online* 2006; **12**: 27.
13 Ashikari H, Park K, Huvós AG. Paget's disease of the breast. *Cancer* 1970; **26**: 680–5.
14 Culberson JD, Horn RC Jr. Paget's disease of the nipple: review of twenty-five cases with special reference to melanin pigmentation of 'Paget cells'. *Arch Surg* 1956; **72**: 224–31.
15 Orr JW, Parish DJ. The nature of the nipple changes in Paget's disease. *J Pathol Bacteriol* 1962; **84**: 201–8.

16 Cawley LP. Extramammary Paget's disease: report of a case. *Am J Clin Pathol* 1957; **27**: 559–66.
17 Nicolau SG, Balus L. Considérations pathogéniques sur la maladie de Paget, à l'occasion de l'étude d'un cas à localisation extra-mammaire. *Dermatologica* 1959; **119**: 93–105.
18 Kariniemi AL, Forsman L, Wahlstrohm T *et al.* Expression of differentiation antigens in mammary and extramammary Paget's disease. *Br J Dermatol* 1984; **110**: 203–10.
19 Reed W, Oppedal BR, Eeg Larsen T. Immunohistology is valuable in distinguishing between Paget's disease, Bowen's disease and superficial spreading melanoma. *Histopathology* 1990; **16**: 583–8.
20 Lin CH, Lee HS, Yu JC. Melanoma of the nipple mimicking Paget's disease. *Dermatol Online J* 2007; **13**: 18.
21 Kinoshita S, Yoshimoto K, Kyoda S *et al.* Malignant melanoma originating on the female nipple: a case report. *Breast Cancer* 2007; **14**: 105–8.
22 Paone JF, Baker RR. Pathogenesis and treatment of Paget's disease of the breast. *Cancer* 1981; **48**: 825–9.
23 Lagios MD, Westdahl PR, Rose MR. Paget's disease of the nipple: Alternative management in cases without or with minimal extent of underlying breast carcinoma. *Cancer* 1984; **54**: 545–51.
24 Fourquet A, Campana F, Vielh P *et al.* Paget's disease of the nipple without detectable breast tumour: conservative management with radiation therapy. *Int J Radiat Oncol Biol Phys* 1987; **13**: 1463–5.

Extramammary Paget's disease [1]

Definition. A marginated plaque resembling Paget's disease clinically and histologically, but occurring in sites rich in apocrine glands, such as the vulva, anogenital region and axilla.

There is currently controversy as to how often this condition arises on the background of an underlying carcinoma, and how often it arises primarily in the epidermis or apocrine ductal tissue of the affected area. This has given rise to the concept of primary and secondary extramammary Paget's disease [2].

Incidence and aetiology. This is a rare disease. It occurs more frequently in women and starts usually in the fifth decade or after. The current view is that in about 75% of cases, extramammary Paget's disease arises as a primary intraepidermal neoplasm, possibly from apocrine gland ductal cells or from keratinocyte stem cells. It has also been suggested that the disease may originate from Toker's cells [3]. In the remaining 25% of cases, an underlying primary adenocarcinoma is found. These cases are referred to as secondary Paget's disease.

Clinical features. The lesion has many features in common with Paget's disease of the nipple. The margin is sharp, rounded and slightly raised, and encloses an area that is pink or red. The surface may be scaly, and small, greyish crusts may cover erosions. Itching is a prominent feature and there may be excoriations or lichenification. Variable hyperpigmentation may be present, adding to the pathological confusion between extramammary Paget's disease and superficial spreading melanoma. In a proportion of cases, there may be leukoplakia.

The appearance varies somewhat according to the site. The commonest area involved is the vulva [4–6] (Fig. 53.33), followed by the perianal area, which is more frequently affected in men than women, the scrotum, penis and axilla [7,8]. The first symptom, especially in vulval lesions, is itching and burning, which may be persistent and spread. Quite often it is regarded as a dermatitis,

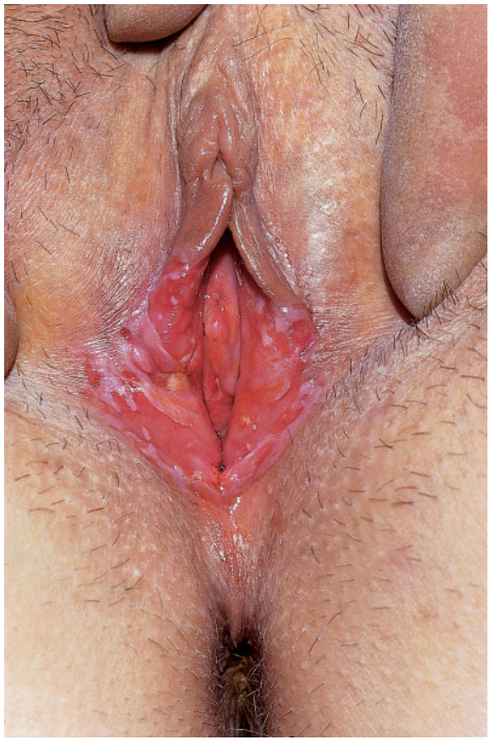


Fig. 53.33 Extramammary Paget's disease of the vulva showing inflamed eczematous presentation.

and may be irritated by topical therapy. The mucosal surfaces of the labia are frequently a rather more vivid red than the skin when both areas are involved, and the change may spread to the thighs, mons pubis and into the vaginal introitus. There may occasionally be a papillomatous surface. Perianal lesions may extend up into the anal canal. Lesions on the scrotum spread to the thigh or onto the shaft of the penis. Very occasionally, extramammary Paget's disease may be present on the eyelids or ears. Characteristic clinical features include the relentless progression, despite all local applications, and the sharp margin. Eventually, one area may become thickened and ulcerated as evidence of invasion downwards. Lymph node or distant metastases can occur.

Although most of the cases in which a primary carcinoma is found result from an underlying sweat gland adenocarcinoma, it is necessary to examine the patient for evidence of an adenocarcinoma elsewhere, particularly of the cervix and rectum.

Pathology. The changes in the epidermis are essentially similar to Paget's disease. The cells stain positively for acid as well as neutral mucopolysaccharides. They may contain melanin granules. Immunohistochemistry shows cells positive for CEA and Cam 5.2 and other low-molecular-weight keratins such as CK7 and CK8/18 [9]. GCDFP-15 is a marker of apocrine epithelium [10] and is frequently strongly expressed in primary vulval or perianal Paget's disease with no detectable underlying malignancy. Cytokeratin 20 is usually negative in primary cases and tends to be positive in lesions associated with an internal gastrointestinal tumour. Apomucin expression may be of help in establishing the origin of cases of extramammary Paget's disease [11]. Cases of

intraepidermal vulval and penile and scrotal extramammary Paget's disease usually have a phenotype that is MUC1 positive, MUC2 negative and MUC5AC positive. In contrast, mammary Paget's disease is usually negative for the latter marker and perianal lesions associated with underlying rectal adenocarcinoma are positive for MUC2 and only variably positive for MUC1 and MUC5AC. Vulval lesions with underlying apocrine carcinoma tend to be negative for MUC5AC.

Comparative genomic hybridization studies in cases of extramammary Paget's disease have shown that the most common change is amplification at chromosomes Xcent-q21 and 19 and losses at chromosome 10q24-qter [12].

Diagnosis. The differential diagnosis from eczema, intertrigo and pruritus vulvae is made by the steady spread, lack of response to topical anti-inflammatory agents and the sharp and extending margin. Bowen's disease is usually more raised and verrucous, and superficial basal cell carcinoma has a thread-like margin. It may be difficult to differentiate leukoplakia or Bowen's disease of the mucosal surfaces, and biopsy may be required. As with mammary Paget's disease, superficial spreading melanoma is an important pathological differential diagnosis.

Prognosis and treatment. Local recurrence is common, even in cases with a wider excision [13]. Poor prognosis is associated with depth of invasion and with elevated serum levels of CEA [14]. Adequate tissue sampling and other investigations are essential to establish whether or not there is an associated underlying malignancy requiring surgical excision. If an underlying malignancy is present, it should be excised together with all clinically abnormal epithelium. If no underlying malignancy is detected on careful examination, the entire affected area of epithelium should be excised. Mohs surgery with careful control of excision margins may be useful, as a common cause of recurrence is inadequate excision of the lesion [15–17].

Promising results are reported with photodynamic therapy, but larger series and longer periods of follow-up are required [18,19]. In cases with limited disease, the use of topical imiquimod has been advocated with good results [20]. However, reports are mainly anecdotal. Radiotherapy has been advocated either as an adjunct to surgical therapy [21] or as an alternative therapy for elderly patients in whom surgery may be difficult [22].

References

1 Crocker HR. Paget's disease affecting the scrotum and penis. *Trans Pathol Soc London* 1888–1889; **40**: 187–91.

2 Lloyd J, Flanagan AM. Mammary and extramammary Paget's disease. *J Clin Pathol* 2000; **53**: 742–9.

3 Willman JH, Golitz LE, Fitzpatrick JE. Vulva clear cells of Toker: precursors of extramammary Paget's disease. *Am J Dermatopathol* 2005; **27**: 185–8.

4 Curtin JP, Rubin SC, Jones WB. Paget's disease of the vulva. *Gynaecol Oncol* 1990; **39**: 374–7.

5 Goldblum JR, Hart WR. Vulvar Paget's disease. *Am J Surg Pathol* 1997; **21**: 1178–87.

6 Fanning J, Lambert HC, Hale TM *et al*. Paget's disease of the vulva: prevalence of associated vulvar adenocarcinoma invasive Paget's disease, and recurrence after surgical excision. *Am J Obstet Gynaecol* 1999; **180**: 24–7.

7 Powell FC, Bjornsson J, Doyle JA *et al*. Genital Paget's disease and urinary tract malignancy. *J Am Acad Dermatol* 1985; **13**: 84–90.

8 Allen SJR, Mclaren K, Aldridge RD. Paget's disease of the scrotum: a case exhibiting positive prostate specific antigen staining and associated prostatic carcinoma. *Br J Dermatol* 1998; **138**: 689–91.

9 Liegl B, Liegl S, Gogg-Kamerer M *et al*. Mammary and extramammary Paget's disease: an immunohistochemical study of 83 cases. *Histopathology* 2007; **50**: 439–47.

10 Kohler S, Smoller BR. Gross cystic disease fluid protein-15 reactivity in extramammary Paget's disease with and without internal malignancy. *Am J Dermatopathol* 1996; **11**: 79–92.

11 Kuan SF, Montag AG, Hart J *et al*. Differential expression of mucin genes in mammary and extramammary Paget's disease. *Am J Surg Pathol* 2001; **25**: 1469–77.

12 Lee MW, Jee KJ, Gong GY *et al*. Comparative genomic hybridization in extramammary Paget's disease. *Br J Dermatol* 2005; **153**: 290–4.

13 Black D, Tornos C, Soslow RA *et al*. The outcomes of patients with positive margins after excision for intraepithelial Paget's disease of the vulva. *Gynecol Oncol* 2007; **104**: 547–50.

14 Hatta N, Yamada M, Hirano T *et al*. Extramammary Paget's disease: treatment, prognostic factors and outcome in 76 patients. *Br J Dermatol* 2008; **158**: 313–8.

15 Lloyd J, Evans DJ, Flanagan A. Extension of extramammary Paget's disease of the vulva to the cervix. *J Clin Pathol* 1999; **52**: 538–40.

16 Stacy D, Burrell MO, Franklin EW. Extramammary Paget's disease of the vulva and anus: use of intraoperative frozen sections. *Am J Obstet Gynaecol* 1986; **155**: 519–22.

17 Thomas CJ, Wood GC, Marks VJ. Mohs micrographic surgery in the treatment of rare aggressive cutaneous tumours: the Geisinger experience. *Dermatol Surg* 2007; **33**: 333–9.

18 Shieh S, Dee AS, Cheney RT *et al*. Photodynamic therapy for the treatment of extramammary Paget's disease. *Br J Dermatol* 2002; **146**: 1000–5.

19 Raspagliesi F, Fontanelli R, Rossi G *et al*. Photodynamic therapy using a methyl ester of 5 aminolevulinic acid in recurrent Paget's disease of the vulva: a pilot study. *Gynecol Oncol* 2006; **103**: 581–6.

20 Berman B, Spencer J, Villa A *et al*. Successful treatment of extramammary Paget's disease of the scrotum with Imiquimod 5% cream. *Clin Exp Dermatol* 2003; **28**: 36–8.

21 Guerrieri M, Back MF. Extramammary Paget's disease: role of radiation therapy. *Australas Radiol* 2002; **46**: 204–8.

22 Yanagi T, Kato N, Yamane N *et al*. Radiotherapy for extramammary Paget's disease: histopathological findings after radiotherapy. *Clin Exp Dermatol* 2007; **32**: 506–8.

Lymphoepithelioma-like carcinoma

Lymphoepitheliomas are well-recognized tumours of the nasopharynx, and an entity with similar histological features has also been observed in the skin [1]. However, the latter is not associated with Epstein–Barr virus (EBV) infection and its behaviour appears to be less aggressive than that of upper respiratory tract lesions [2,3]. Association with other viruses including HPV and simian virus 40 has not been found either [4].

Clinical features. The clinical appearance is of non-specific nodules on the head and neck area of older patients. Occasional cases present on the eyelid [5] and the trunk and vulva [6] are also rarely involved.

Pathology. The pathological features are those of a very dense infiltrate of inflammatory mononuclear cells, including lymphocytes and histiocytes, with small strands and nests of atypical epithelial cells. Inflammatory cells extensively infiltrate nests and strands of tumour cells, and the epithelial nature of these cells is often not immediately apparent unless more or less intact nests of epithelial cells are found. Confusion with a lymphoma is therefore a possibility, and often immunostaining for keratin and lymphoid

cells is necessary to distinguish the two populations of cells. Cytological atypia is usually present, and mitotic figures are common. Focal evidence of adnexal differentiation and even neuroendocrine differentiation may be seen [7–12]. Some tumours appear to be arising from a squamous cell carcinoma. A sarcomatoid component may be seen [13]. It has therefore been suggested that this is not a distinctive entity but a morphological pattern in various cutaneous carcinomas [14].

Treatment. Surgery followed by radiotherapy is recommended. Some cases have been treated by Mohs surgery [15]. However, the lesions are aggressive, and both local recurrence and distant metastases, with one tumour-associated death, have been recorded [8,10,16].

References

1 Swanson SA, Cooper PH, Mills SE *et al*. Lymphoepithelioma-like carcinoma of the skin. *Mod Pathol* 1988; **1**: 359–65.

2 Ferlicot S, Plantier F, Rethers L *et al*. Lymphoepithelioma-like carcinoma of the skin: a report of 3 Epstein–Barr virus (EBV)-negative additional cases—immunohistochemical study of the stroma reaction. *J Cutan Pathol* 2000; **27**: 306–11.

3 Iezzoni JC, Gaffey MJ, Weiss LM. The role of Epstein–Barr virus in lymphoepithelioma-like carcinomas. *Am J Clin Pathol* 1995; **103**: 308–15.

4 Kazakov DV, Nemcova J, Mykiskova I *et al*. Absence of Epstein-Barr virus, human papillomavirus, and simian virus 40 in patients of central European origin with lymphoepithelioma-like carcinoma of the skin. *Am J Dermatopathol* 2007; **29**: 365–9.

5 Ho W, Taylor A, Kemp E *et al*. Lymphoepithelioma-like carcinoma of the eyelid: a report of two cases. *Br J Ophthalmol* 2005; **89**: 1222–3.

6 Axelsen SM, Stamp IM. Lymphoepithelioma-like carcinoma of the vulvar region. *Histopathology* 1995; **27**: 281–3.

7 Ortiz Fruitos FJ, Zarco C, Gil R *et al*. Lymphoepithelioma-like carcinoma of the skin. *Clin Exp Dermatol* 1993; **18**: 83–6.

8 Takayasu S, Yoshiyama M, Kutata S *et al*. Lymphoepithelioma-like carcinoma of the skin. *J Dermatol* 1996; **23**: 472–6.

9 Walker AN, Kent D, Mitchel AR. Lymphoepithelioma-like carcinoma of the skin. *J Am Acad Dermatol* 1990; **22**: 691–3.

10 Wick MR, Swanson PE, LeBoit PE *et al*. Lymphoepithelioma-like carcinoma of the skin with adnexal differentiation. *J Cutan Pathol* 1991; **18**: 93–102.

11 Otsuki T, Watanabe D, Yako K *et al*. Lymphoepithelioma-like carcinoma of the skin with potential for sweat gland differentiation. *J Dermatol* 2005; **32**: 393–6.

12 Ríos-Martín JJ, Solorzano-Amoreti A, Gonzalez-Cámpora R *et al*. Neuroendocrine carcinoma of the skin with a lymphoepithelioma-like histological pattern. *Br J Dermatol* 2000; **143**: 460–2.

13 Clarke LE, Ioffreda MD. Lymphoepithelioma-like carcinoma of the skin with spindle cell differentiation. *J Cutan Pathol* 2005; **32**: 419–23.

14 Lind AC, Breer WA, Wick MR. Lymphoepithelioma-like carcinoma of the skin with apparent origin in the epidermis—a pattern or an entity? A case report. *Cancer* 1999; **15**: 884–90.

15 Glaich AS, Behroozan DS, Cohen JL *et al*. Lymphoepithelioma-like carcinoma of the skin: a report of two cases treated with complete microscopic margin control and review of the literature. *Dermatol Surg* 2006; **32**: 316–9.

16 Hall G, Duncan A, Azurdia R *et al*. Lymphoepithelioma-like carcinoma of the skin: a case with lymph node metastasis at presentation. *Am J Dermatopathol* 2007; **29**: 365–9.

Merkel cell carcinoma [1]

Synonyms
- Trabecular cell carcinoma of skin
- Primary neuroendocrine carcinoma of the skin

Definition. An aggressive and frequently lethal tumour thought to arise from the cutaneous Merkel cell, a neuroendocrine cell [2].

Incidence and aetiology. The first definitive report of Merkel cell tumour dates from 1978 [2], although there are reports in 1972 of 'trabecular cell carcinoma of skin' [1], which is synonymous. De Wolf-Peeters *et al.* [3] were the first to suggest the use of the term 'Merkel-cell tumour'. More than 2000 cases have been recorded to date. This is a rare tumour of the elderly presenting mainly in Caucasians (0.23 annual age adjusted incidence per 100 000) [4], with a high concentration of primary tumours on sun-exposed sites. There are also a high number of cases in association with immunosuppression [5], including not only transplant patients but also those with HIV infection [6]. Incidence in patients with chronic lymphocytic leukaemia is much higher than in the general population [5]. The general incidence seems to be rising [7]. Tumours very rarely occur in patients with dark skin. An unexpectedly high proportion of Merkel cell tumours arise in association with either squamous cell or basal cell carcinomas, or in patients who have a past history of such lesions [8]. These facts suggest that excessive ultraviolet exposure may play an aetiological role in the development of Merkel cell tumours. Recently, it has been suggested that a novel type of polyomavirus (named Merkel cell polyomavirus) may play a role in the aetiology of the neoplasm as clonal integration of the virus was demonstrated in eight out of 10 cases of Merkel cell carcinoma tested [9].

Clinical features [10]. The lesions appear to have few distinctive features, and are described as raised, reddish-blue nodules, which may develop on any body site, although the head and neck area is over-represented in terms of surface area. Tumours are asymptomatic in the majority of cases and grow rapidly with most lesions measuring between 0.5 and 2 cm. Spontaneous regression of Merkel cell carcinoma has occasionally been reported [11,12]. Partial regression has been reported as a result of withdrawal of azathioprine in an immunosuppressed patient [13], although rapid growth of a tumour was described after treatment with rituximab [14].

Pathology [15,16]. The cells making up the tumour may be either a solid mass or a more diffuse collection of cells, initially situated in the mid-dermis. They are intensely basophilic, with abundant mitotic figures and also many apoptotic cells (Fig. 53.34). Lymphatic and vascular invasion is frequently present. On light microscopy, they may resemble small lymphocytes or a poorly differentiated metastatic deposit, particularly of small cell carcinoma of lung or of naevoid melanoma. The cells are argyrophilic, with sparse cytoplasm, dispersed chromatin and inconspicuous nucleoli. There may be a dense lymphoid infiltrate [17]. Exceptional cases are restricted to the epidermis (*in situ*) [18].

Electron microscopy [19] may be used for positive identification of the multiple, round, secretory granules that pack the cytoplasm of these cells. However, cytomorphology of tumour cells and immunohistochemistry is enough to establish a diagnosis.

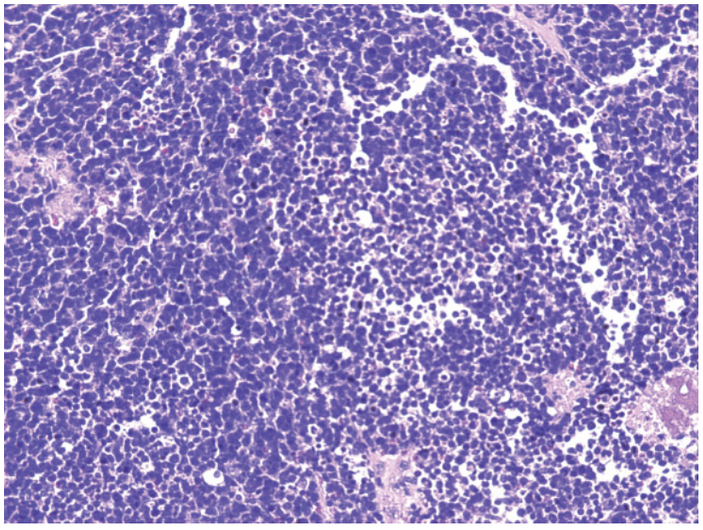


Fig. 53.34 Merkel cell carcinoma. Hyperchromatic medium-sized cells with scanty cytoplasm, prominent apoptosis and high mitotic activity.

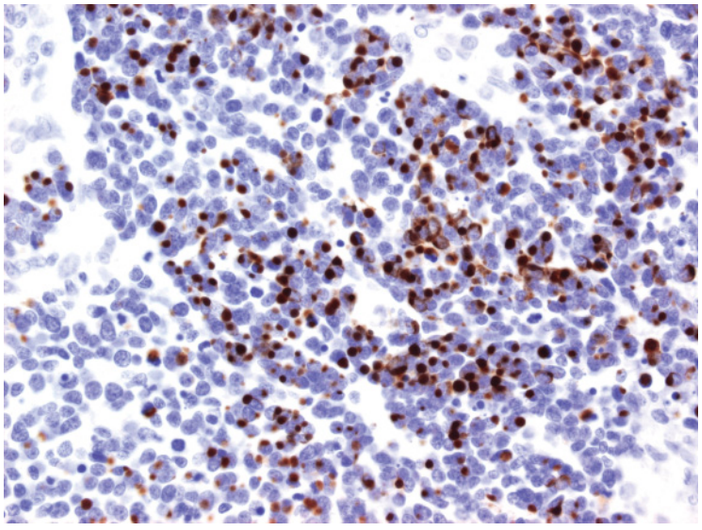


Fig. 53.35 Merkel cell carcinoma. Characteristic dot-like perinuclear positivity of cytokeratin 20.

Immunohistochemistry is useful in confirming the diagnosis. Merkel cells show a characteristic 'dot' positivity with antibodies to low-molecular-weight keratins such as cam 5.2 and CK20 (Fig. 53.35). CK20 is particularly useful in the differential diagnosis from metastatic neuroendocrine carcinomas arising in other organs. The latter except for neuroendocrine carcinoma of salivary glands tend to be negative for this marker [20]. They are also positive for neurone-specific enolase, CD56 and variably positive for chromogranin and synaptophysin. The latter is much more sensitive than chromogranin. A small subset of cases has been identified in which tumour cells are negative for cytokeratin 20 but positive for cytokeratin 7 [21]. These tumours are otherwise typical Merkel cell carcinomas.

Histological features associated with poor outcome include tumour size (≥5 mm), extension into the subcutaneous tissue, diffuse growth pattern and a heavy mononuclear inflammatory cell infiltrate [22]. A further study, however, has found that absence of lymphocytic infiltration adversely influences disease-free survival. In the same study a further important adverse variable was the presence of positivity of more than 50% of tumour cells for Ki-67 [23]. Expression of p63 by tumour cells has also been found to be an independent factor indicating poor prognosis [24]. Tumour thickness does not seem to influence prognosis [25].

Treatment. Surgical excision is required [26], but metastases occur early and 30–50% of patients may die from metastases. Arterial limb perfusion has been used for lesions on limbs and may be beneficial [27]. Merkel cell tumours are considered to be radiosensitive, and trials of postoperative radiotherapy suggest a survival advantage [28]. Sentinel lymph node biopsy is a useful procedure not only to demonstrate spread in patients that have been understaged by clinical and radiological (CT scan) examination but is also important in predicting prognosis and improving survival in patients with positive results who undergo lymph node dissection [29]. The detection of micrometastasis in sentinel lymph nodes is increased by the use of immunohistochemistry for cytokeratin 20 [30]. The preferred treatment at present is surgical excision with sentinel lymph node biopsy followed by lymph node dissection if the latter is positive. Postoperative radiotherapy is also given and this approach improves locoregional control and also improves disease-free survival [31,32]. Treatment of involved regional lymph nodes, with or without lymphadenectomy, has also been found to increase survival [33]. Chemotherapy is not routinely recommended as there is lack of evidence that it increases survival, there is important morbidity and mortality associated with this modality of treatment and resistance to chemotherapy quickly develops in many patients [34].

References

1 Toker C. Trabecular cell carcinoma of the skin. *Arch Dermatol* 1972; **105**: 107–10.

2 Tang C, Toker C. Trabecular cell carcinoma of the skin: an ultrastructural study. *Cancer* 1978; **42**: 2311–21.

3 De Wolf-Peeters C, Marien K, Mebis J *et al.* A cutaneous APUDoma or Merkel cell tumor? A morphologically recognizable tumor with a biological and histological malignant aspect in contrast with its clinical behavior. *Cancer* 1980; **46**: 1810–6.

4 Miller RW, Rabkin CS. Merkel cell carcinoma and melanoma: etiological similarities and differences. *Cancer Epidemiol Biomarkers Prev* 1999; **8**: 153–8.

5 Heath M, Jaimes N, Lemos B *et al*. Clinical characteristics of Merkel cell carcinoma at diagnosis in 195 patients: the AEIOU features. *J Am Acad Dermatol* 2008; **58**: 375–81.

6 Manganoni MA, Farisoglio C, Tucci G *et al*. Merkel cell carcinoma and HIV infection: a case report and review of the literature. *AIDS Patient Care STDS* 2007; **21**: 447–51.

7 Lemos B, Nghiem P. Merkel cell carcinoma: more deaths but still no pathway to blame. *J Invest Dermatol* 2007; **127**: 2100–3.

8 Dancey AL, Rayatt SS, Soon C *et al*. Merkel cell carcinoma: a report of 34 cases and literature review. *J Plast Reconstr Aesthet Surg* 2006; **59**: 1294–9.

9 Feng H, Shuda M, Chang Y *et al*. Clonal integration of a polyomavirus in human Merkel cell carcinoma. *Science* 2008; **319**: 1096–100.

10 Akhtar S, Oza KK, Wright J. Merkel cell carcinoma: report of 10 cases and review of the literature. *J Am Acad Dermatol* 2000; **43**: 755–67.

11 Kubo H, Matsushita S, Fukushige T *et al*. Spontaneous regression of recurrent and metastatic Merkel cell carcinoma. *J Dermatol* 2007; **34**: 773–7.

12 Vesely MJ, Murray DJ, Neligan PC *et al*. Complete spontaneous regression of Merkel cell carcinoma. *J Plast Reconstr Aesthet Surg* 2008; **61**: 165–71.

13 Muirhead R, Ritchie DM. Partial regression of Merkel cell carcinoma in response to withdrawal of azathioprine in an immunosuppression-induced case of metastatic Merkel cell carcinoma. *Clin Oncol (R Coll Radiol)* 2007; **19**: 96.
14 Wirges ML, Saporito F, Smith J. Rapid growth of Merkel cell carcinoma after treatment with rituximab. *J Drugs Dermatol* 2006; **5**: 180–1.
15 Skelton HG, Smith KJ, Hitchcock CL *et al.* Merkel cell carcinoma: analysis of clinical, histologic and immunohistochemical features of 132 cases with relation to survival. *J Am Acad Dernatol* 1997; **175**: 734–9.
16 Smith PD, Patterson JW. Merkel cell carcinoma (neuroendocrine carcinoma of the skin). *Am J Clin Pathol* 2001; **115** (Suppl.): S68–78.
17 Kasami M, Murmatsu K, Kawahata K *et al*. Large-cell neuroendocrine carcinoma of the skin, with lymphoid stroma. *Am J Dermatopathol* 2007; **29**: 578–80.
18 Ferringer T, Rogers HC, Metcalf JS. Merkel cell carcinoma in situ. *J Cutan Pathol* 2005; **32**: 162–5.
19 Haneke E. Electron microscopy of Merkel cell carcinoma from formalin fixed tissue. *J Am Acad Dermatol* 1985; **12**: 487–92.
20 Chan JK, Suster S, Wenig BM *et al*. Cytokeratin 20 immunoreactivity distinguishes Merkel cell (primary cutaneous neuroendocrine) carcinomas and salivary gland small carcinomas from small cell carcinomas of various sites. *Am J Surg Pathol* 1997; **21**: 226–34.
21 Calder KB, Coplowitz S, Schlauder S *et al*. A case series and immunophenotypic analysis of CK20-/CK7 + primary neuroendocrine carcinoma of the skin. *J Cutan Pathol* 2007; **34**: 918–23.
22 Mott RT, Smoller BR, Morgan MB. Merkel cell carcinoma: a clinicopathologic study with prognostic implications. *J Cutan Pathol* 2004; **31**: 217–23.
23 Llombart B, Monteagudo C, López-Guerrero JA *et al*. Clinicopathological and immunohistochemical analysis of 20 cases of Merkel cell carcinoma in search of prognostic markers. *Histopathology* 2005; **46**: 622–34.
24 Asioli S, Righi A, Volante M *et al*. p63 expression as a new prognostic marker in Merkel cell carcinoma. *Cancer* 2007; **110**: 640–7.
25 Goldberg SR, Neifield JP, Frable WJ. Prognostic value of tumor thickness in patients with Merkel cell carcinoma. *J Surg Oncol* 2007; **95**: 618–22.
26 Wong KC, Zuletta F, Clark SJ *et al*. Clinical management and treatment outcomes of Merkel cell carcinoma. *Aust NZ J Surg* 1998; **68**: 354–8.
27 Dawson R, Williams OM, Mansel RE. Isolated hyperthermic limb perfusion chemotherapy in Merkel cell tumour. *J R Coll Surg Edinb* 1996; **41**: 255–6.
28 Kokoska ER, Kokoska MS, Collins BT *et al*. Early aggressive treatment for Merkel cell carcinoma improves outcome. *Am J Surg* 1997; **174**: 688–93.
29 Gupta SG, Wang LC, Peñas PF *et al*. Sentinel lymph node biopsy for evaluation and treatment of patients with Merkel cell carcinoma: The Dana-Faber experience and meta-analysis of the literature. *Arch Dermatol* 2006; **142**: 685–90.
30 Su LD, Lowe L, Bradford CR *et al*. Immunostaining for cytokeratin 20 improves detection of micrometastatic Merkel cell carcinoma in sentinel lymph nodes. *J Am Acad Dermatol* 2002; **46**: 661–6.
31 Mojica P, Smith D, Ellenhom JD. Adjuvant radiation therapy is associated with improved survival in Merkel cell carcinoma of the skin. *J Clin Oncol* 2007; **25**: 1043–7.
32 Eng TY, Boersma MG, Fuller CD *et al*. A comprehensive review of the treatment of Merkel cell carcinoma. *Am J Clin Oncol* 2007; **30**: 624–36.
33 Jabbour J, Cumming R, Scolyer RA *et al*. Merkel cell carcinoma: assessing the effect of wide local excision, lymph node dissection, and radiotherapy on recurrence and survival in early-stage disease—results from a review of 82 consecutive cases diagnosed between 1992 and 2004. *Ann Surg Oncol* 2007; **14**: 1943–52.
34 Garneski KM, Nghiem P. Merkel cell carcinoma adjuvant therapy: current data support radiation but not chemotherapy. *J Am Acad Dermatol* 2007; **57**: 166–9.

CHAPTER 54
Lentigos, Melanocytic Naevi and Melanoma

J.A. Newton Bishop
Leeds Institute of Molecular Medicine, St James's University Hospital, Leeds, UK

The freckle or ephelis, 54.1
Lentigines, 54.2
Simple lentigo, 54.3
Solar or actinic lentigo, 54.4
Photochemotherapy (PUVA) lentigo, 54.4
Ink-spot lentigo, 54.5
Mucosal melanotic lesions, 54.6
Pigmented melanotic macules (mucosal melanosis/genital lentiginosis), 54.6
Labial melanotic macules, 54.7
Dermal melanocytic lesions, 54.7
Mongolian spot, 54.7
Naevus of Ota, 54.8
Naevus of Ito, 54.9
Melanocytic naevi, 54.9
Congenital melanocytic naevi, 54.10
Speckled and lentiginous naevus, 54.14
Acquired melanocytic naevi, 54.15
Naevi in unusual sites, 54.17
Halo naevus, 54.19
Meyerson's naevus, 54.20
Cockade naevus, 54.20
Spitz naevus, 54.21
Blue naevus and cellular blue naevus, 54.25
Malignant blue naevus, 54.27
Clinically atypical naevi, 54.27
Malignant melanoma of the skin (melanoma): background, 54.32
Incidence and mortality, 54.32
Aetiology, 54.32
Phenotypic risk factors for melanoma, 54.33
Familial melanoma, 54.33
Identification of 'at risk' patients, 54.34
Prevention, 54.34
Clinicopathological variants and growth phases of primary melanoma, 54.35
Clinical diagnostic aids, 54.37
Melanoma: specific histogenetic types, sites and variants, 54.37
Superficial spreading melanoma, 54.37
Nodular melanoma, 54.40
Lentigo maligna melanoma, 54.40
Acral lentiginous melanoma (palmoplantar malignant melanoma), 54.44
Subungual melanoma, 54.44
Mucosal melanoma, 54.46
Secondary melanoma from an occult primary site, 54.47
Multiple primary malignant melanomas, 54.47
Rare histological subtypes of melanoma, 54.48
Childhood melanomas, 54.48
Melanoma: prognosis and management, 54.49
The estimation of prognosis for patients with melanoma, 54.49
Management of cutaneous malignant melanoma after excision of the primary, 54.50
Melanoma, pregnancy and female sex hormones, 54.56

Introduction

Factors responsible for variation in skin pigmentation are discussed in Chapter 58. Melanin pigment is synthesized and distributed to adjacent cells by cutaneous melanocytes, which are found in normal skin in the basal layer of the epidermis. Melanocytes lie in continuity with adjacent keratinocytes into which they transfer melanosomes. Melanocytes and keratinocytes are therefore biologically interdependent and cells of both lineages may be involved in many of the entities discussed below. Melanin synthesis and distribution is accelerated by exposure to UV radiation. Cutaneous pathology attributable to the melanocyte may arise as a result of overproduction of melanin by a normal quota of melanocytes as in the simple freckle, by proliferation of benign melanocytes as in a melanocytic naevus, or as a result of malignant transformation of the melanocyte as in malignant melanoma (henceforth referred to as melanoma).

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

The freckle or ephelis

Definition. A pale-brown, macular lesion, usually less than 3 mm in diameter with a poorly defined lateral margin, which appears and darkens on light-exposed skin sites during periods of UV exposure.

Clinical features. At any age, simple freckles are commoner in individuals who are red- or fair-haired and fair-skinned (Fig. 54.1). They fade during the winter months.

The clinical distinction between a freckle and a lentigo is that the lentigo persists in the absence of UV stimulation, and histologically a lentigo has a linear increase of melanocytes at the dermal–epidermal junction, but the two entities coexist in the same individuals and the risk factors for both are generally the same.

Pathology. The simple freckle shows no anatomical abnormality on biopsy [1,2]. It arises as a result of temporary overproduction of melanin by a normal quota of melanocytes due to stimulation

by UV radiation. It has been claimed that the melanocortin 1 receptor gene (MCR1) is the major freckle gene, and that *MC1R* gene variants are required for the development of freckles [3], but it is still unclear what mechanism underlies this. Elder and Murphy have even speculated that the signal for increased transfer of pigment from the melanocyte might come from the keratinocyte [4].

Diagnosis. This is usually obvious with the presence of regular macular brown lesions on light-exposed skin. The freckles and café-au-lait spots of neurofibromatosis (Chapter 15) are distinguished as they are commonly on the trunk and axilla, and other features of neurofibromatosis may be present.

Management. No treatment is needed for these benign lesions, and their biological significance lies in the fact that they have been identified in case–control studies as an independent risk factor for skin cancer and in particular for melanoma: in a meta-analysis a high density of freckles was associated with a relative risk of melanoma of 2.10 (95% CI 1.80–2.45) [5].



Fig. 54.1 Freckles in a child with red hair: freckles are indicative of fair skin vulnerable to sunburn.

Lentigines (Table 54.1)

These are also macular hyperpigmented skin lesions, but they persist throughout the year, and on microscopy have an increase in the number of melanocytes at the dermal–epidermal junction compared to that expected for the body site in question. The proliferation of melanocytes occurs usually in response to sun exposure in fair-skinned people (common lentigines). Rarely, syndromal lentigines occur when melanocyte proliferation is determined by inherited genetic anomalies.

Common lentigines are usually seen in fair-skinned people, and represent proliferative responses of melanocytes to the sun. They are commonly subclassified, but excessive exposure to natural or artificial UV radiation is the major aetiological factor for all of the following: simple lentigines, actinic (or solar) lentigines, psoralen UVA (PUVA) lentigines and the ink-spot lentigo. To some extent, the distinction between these subtypes is artificial as they represent a continuum or variations on a theme. Their features are described below, and compared in Table 54.1.

Rare forms of lentiginoses are also seen as characteristic features of a number of rare but potentially serious hereditary multisystem syndromes associated with an increased risk of tumours (Fig. 54.2; Chapter 15).

Very rarely, segmental lentiginoses may be seen; these emerge during childhood and are presumed to represent mosaicism of an unidentified gene [6]. Usually there are no other congenital anom-

Table 54.1 Comparison of freckles, lentigines and related disorders.

Lesion	Distribution	Melanocyte number	Significance
Freckle	Sun-exposed skin	Not increased	Risk factor for skin cancer and sunburn
Simple lentigo	Sun-exposed skin	Increased	Risk factor for skin cancer and sunburn
Solar lentigo	Sun-exposed skin	Increased and accompanied by pathological evidence of solar damage	Risk factor for skin cancer and sunburn
PUVA lentigo	Anywhere	Increased	Risk factor for skin cancer
Ink-spot lentigo	Anywhere but commonly shoulders	Increased and accompanied by pigment in the epidermis and dermis	Probably a risk factor for skin cancer and sunburn but no data are available
Hereditary lentiginoses	Generalized and not preferentially sun-exposed skin. Mucosal surfaces also often involved	Increased	Marker of risk of hamartomas and cancer
Genital melanosis	Genital skin	Debated: no (or extremely subtle) increase in number	None: if *in situ* melanoma excluded by biopsy
Labial melanotic macule	Lower lip generally	Debated: no (or extremely subtle) increase in number	Sun protection required



Fig. 54.2 Multiple lentigos in a patient with hereditary lentiginosis and cardiac anomalies.



Fig. 54.3 A systematized lentiginosis in which a superficial spreading melanoma developed on the knee.

alies and the differential diagnosis includes neurofibromatosis type 1. Melanoma may occur in patients with segmental or generalized lentiginosis (Figs 54.3 & 54.4).

Simple lentigo

Definition. A brown macule, arising as a result of an increased number of melanocytes at the dermoepidermal junction, without evidence of proliferation of these melanocytes downwards into the dermis.

Aetiology and incidence. Multiple, benign lentigines occurring as an isolated phenomenon are very common, particularly in those with red hair and fair skin with melanocytes which produce a high phaeomelanin/eumelanin ratio.

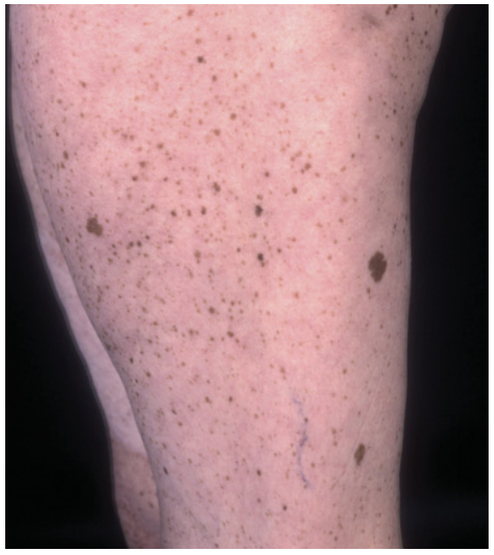


Fig. 54.4 Generalized lentiginosis in a patient who developed cutaneous melanoma in her 50s.

Clinical features. A lentigo is a macular area of brown or brown-black pigmentation, usually circular or oval, although several individual lentigines may coalesce. There may be slight scaling of the surface, but the skin markings are unaltered. The pigmentation is usually light brown and fairly uniform. Lentigines usually start to appear in childhood and increase in number in the second and third decades. Rarely, they may erupt in large numbers [7], sometimes after inflammation, or related to use of immunosuppressive agents [8,9]. The majority of lentigines remain static in adult life. Most commonly, lentigos occur on sun exposed skin as they are part of the spectrum of lesions (ephiledes, simple lentigos, solar lentigos) which occur in fair-skinned people exposed to excessive amounts of sun exposure for their phenotype.

Whilst a lentigo, by definition, is characterized by an increased number of melanocytes, there is a clinical and even a pathological overlap with lesions in which there is an increased number of melanocytes but in which there is also a proliferation of keratinocytes; these are often referred to as 'flat seborrhoeic keratoses' or, on the back of the hands, as 'liver spots'. In practice, this overlap is of little clinical importance; all are markers of fair skin, excessive sun exposure and some risk of skin cancer. All are to be distinguished from lentigo maligna, which is usually relatively easy.

There are a number of hereditary disorders, however, in which multiple lentigines are markers of syndromes characterized by hyperplasias, hamartomas and neoplasia [10], and in these people the lentigos develop much earlier in life and are not restricted in site to sun-exposed skin. In some of these, the causal genetic mutations specifically affect tissues sharing a common origin in the neural crest [11,12] such as melanocytes and cardiac tissues. The familial lentigines include Peutz–Jeghers syndrome [13], the LEOPARD syndrome (*l*entigines, *e*lectrocardiogram anomalies, *o*cular anomalies, *p*ulmonary stenosis, *a*bnormal genitalia, *r*etardation of growth and *d*eafness), in which mutations in the *PTEN* gene have been described [14], the Carney complex and

the closely related NAME and LAMB syndromes. The genetic origin of these syndromes appears to involve diverse pathways which are supposed to converge in embryogenesis and the development of systems including the neural crest [10]. Rarely, lentiginoses may develop in childhood in the absence of multisystem disease [15].

Even more rarely, multiple lentigines may be seen in patients with an evident increased susceptibility to melanoma (Fig. 54.4). A single case report of a patient with lentiginoses and gastrointestinal stromal tumours in the presence of a hereditary *c-kit* mutation suggests that this may represent a further, extremely rare, new subtype [16].

Pathology. There is a linear increase in the number of melanocytes along the dermal–epidermal junction. There is more melanin than normal in the adjacent epidermis and stratum corneum, and melanophages are abundant in the papillary body. The papillae and interpapillary ridges may be elongated—hence the overlap with pigmented seborrhoeic keratoses.

Diagnosis. Lentigines are distinguished from freckles by their darker colour, comparative sparseness and scattered distribution, and by the fact that they do not darken or increase in number on sun exposure, and do not disappear during the winter months. It is often impossible to distinguish lentigines from flat junctional or compound naevi on clinical grounds.

Treatment. As common lentigines are usually multiple, and have no pre-malignant potential, the patient should be reassured. They are however a marker of fair skin, as are freckles. For treatment, see Solar or actinic lentigo, below. Patients with lentiginoses presenting in childhood or early adult life, on non-sun-exposed sites, should be examined for multisystem disease. Extremely rare patients who present with systematized or generalized lentiginoses may be at increased risk of melanoma, and so should be educated about avoidance of sunburn and about self-examination.

Solar or actinic lentigo

Definition. A macular area of brown pigmentation appearing after either acute or chronic sun exposure.

Clinical features. In younger patients, solar lentigines are most commonly seen on sun-exposed sites, such as the face in both sexes and the shoulders in males. They are macular, tan coloured and may be very large, with a striking irregular border. There is frequently a history of acute sunburn, followed by the sudden appearance of large numbers of these irregular macular lesions [17,18]. In the UK, they are rare before the age of 12 years but in sunnier countries they may appear at a very young age.

Solar lentigines are also seen on older fair-skinned patients who have had excessive sun exposure [19]. The backs of the hands and the face are common sites. Once again the lesions are large and macular, have an irregular edge and are usually a uniform shade of brown. They are situated in an area of obviously sun-damaged epidermis and as above there is a clinical and pathological overlap with flat seborrhoeic keratoses.

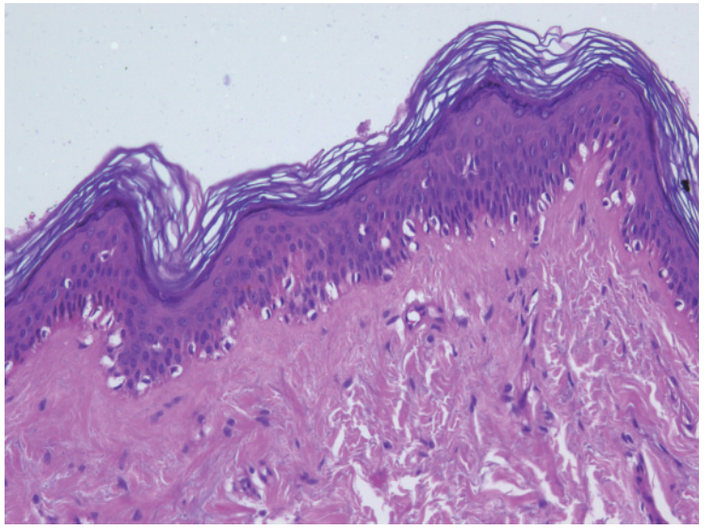


Fig. 54.5 An increased number of melanocytes is seen in this solar lentigo. The dermis also shows elastosis as evidence of sun damage. (Courtesy of Dr S. Edward, Leeds Teaching Hospitals Trust, Leeds, UK.)

Pathology. The pathological features of a solar lentigo are a continuum of those seen in the smaller simple lentigines. There is a linear increase of melanocytes at the dermal–epidermal junction, but no cytological atypia of these melanocytes, and no budding down of these cells into the underlying dermis. There is frequently associated actinic damage to the adjacent dermal collagen (Fig. 54.5).

Treatment. Because of the large size and unsightly appearance of some actinic lentigines, patients frequently request treatment. Prevention of further UV-induced damage should be encouraged by sun avoidance and the use of a high sun-protection factor, broad-spectrum sunscreen. With these measures, there is often some spontaneous resolution of existing lesions. A consensus supported the use of cryotherapy as first line therapy, where cosmesis is required [20]. There is, however, an extensive literature on the cosmetic treatment of lentigines using a variety of additional treatments including intense pulsed light [21,22], laser therapy and topical agents such as retinoids [23]. A review suggested that superficial pigmented lesions of this type respond well to the high-energy QS red and infrared lasers [24].

The majority of solar lentigos progress little over time. A small proportion, however, do slowly progress to become lentigo malignas over many years (Fig. 54.6). A well-defined, large solar lentigo on the face of a younger patient should therefore probably be treated although there are no data to support this advice.

Photochemotherapy (PUVA) lentigo

Lentigines are a well-recognized complication of long-term use of PUVA therapy [25]. They were reported in 20% of a small series of 198 patients given a mean cumulative dose of UVA of 169.5 J/cm^2 [26], and PUVA lentigines of any degree (slight, moderate or extensive) were noted on the buttocks of 53% of 1380 psoriatic patients an average of 5.7 years after starting PUVA [27]. They are



Fig. 54.6 This lentigo maligna developed from a tiny lentigo over a period of 30 years.

relatively large, macular, pigmented lesions, which develop on the skin of patients receiving photochemotherapy. The number of melanocytes in the relevant body site is increased, and ultrastructural examination reveals morphological abnormalities of the melanosomes [28]. Follow-up of PUVA-treated patients in the USA has indicated that PUVA lentigines are a marker of patients at increased risk of non-melanoma skin cancer [29]. The association of risk of melanoma with PUVA treatment generally is less clear, as although an increased risk was seen in a series from the USA [30] this was not seen in a series from Scandinavia [31].

Ink-spot lentigo

Definition. A small (less than 5 mm in diameter), densely black, irregular macule, usually on sun-exposed skin (such as the upper back in a very fair-skinned person who has had a good deal of sun exposure), which resembles an ink spot (Fig. 54.7) [32].

Clinical features. These lesions commonly cause concern because they are so black and irregular in shape. The clinical diagnosis is obvious, however, when the dermoscope is used (Fig. 54.8).

Pathology. The pathology of the lesion is that of a lentigo, with a linear increase in melanocytes in the basal layer of the epidermis, and an associated increase in melanin pigmentation both in the basal cells of the epidermis and also lying free in the underlying epidermis. The melanocytes are normal, and there is no evidence of cellular atypia.

Management. These lesions do not require treatment.



Fig. 54.7 An ink-spot lentigo.



Fig. 54.8 The dermoscopic appearance of an ink-spot lentigo. (Courtesy of Dr S. Puig, Hospital Clinic Barcelona, IDIBAPS.)

References

1 Breathnach AS. Melanocyte distribution in forearm epidermis of freckled human subjects. *J Invest Dermatol* 1957; **29**: 253–61.

2 Breathnach AS, Wyllie LM. Electron microscopy of melanocytes and melanosomes in freckled human epidermis. *J Invest Dermatol* 1964; **42**: 389–94.

3 Bastiaens M, ter Huurne J, Gruis N *et al*. The melanocortin-1-receptor gene is the major freckle gene. *Hum Mol Genet* 2001; **10**: 1701–8.

4 Elder DE, Murphy GF. *Melanocytic Tumors of the Skin*. Washington, DC: American Registry of Pathology, in press.

5 Gandini S, Sera F, Cattaruzza MS *et al*. Meta-analysis of risk factors for cutaneous melanoma: III. Family history, actinic damage and phenotypic factors. *Eur J Cancer* 2005; **41**: 2040–59.

6 Toelle SP, Boltshauser E, Wirth MG, Itin P. Association of lentiginous mosaicism and congenital cataract in a girl. *Eur J Dermatol* 2006; **16**: 360–2.

7 Na JI, Park KC, Youn SW. Familial eruptive lentiginosis. *J Am Acad Dermatol* 2006; **55**: S38–40.

8 Hickey JR, Robson A, Barker JN, Smith CH. Does topical tacrolimus induce lentigines in children with atopic dermatitis? A report of three cases. *Br J Dermatol* 2005; **152**: 152–4.

9 Tosti A, Piraccini BM, Misciali C, Vincenzi C. Lentiginous eruption due to topical immunotherapy. *Arch Dermatol* 2003; **139**: 544–5.

10 Bauer AJ, Stratakis CA. The lentiginoses: cutaneous markers of systemic disease and a window to new aspects of tumourigenesis. *J Med Genet* 2005; **42**: 801–10.

11 Abdelmalek NF, Gerber TL, Menter A. Cardiocutaneous syndromes and associations. *J Am Acad Dermatol* 2002; **46**: 161–83, quiz 183.

12 Ho JC, Chan YC, Giam YC *et al*. Flexural pigmentation with multiple lentigines: a new primary pigmentary disorder? *Br J Dermatol* 2006; **154**: 382–4.
13 Stratakis CA. Genetics of Peutz–Jeghers syndrome, Carney complex and other familial lentiginoses. *Hormone Res* 2000; **54**: 334–43.
14 Digilio MC, Conti E, Sarkozy A *et al*. Grouping of multiple-lentigines/LEOPARD and Noonan syndromes on the *PTEN11* gene. *Am J Hum Genet* 2002; **71**: 389–94.
15 Chong WS, Klanwarin W, Giam YC. Generalized lentiginosis in two children lacking systemic associations: case report and review of the literature. *Pediatr Dermatol* 2004; **21**: 139–45.
16 Shibusawa Y, Tamura A, Mochiki E *et al*. c-kit Mutation in generalized lentigines associated with gastrointestinal stromal tumor. *Dermatology* 2004; **208**: 217–20.
17 Derancourt C, Bourdon-Lanoy E, Grob JJ *et al*. Multiple large solar lentigos on the upper back as clinical markers of past severe sunburn: a case–control study. *Dermatology* 2007; **214**: 25–31.
18 McLean DL, Gallagher RP. Sunburn freckles, cafe-au-lait macules, and other pigmented lesions of schoolchildren: The Vancouver Mole Study. *J Am Acad Dermatol* 1995; **32**: 565–70.
19 Monestier S, Gaudy C, Gouvernet J *et al*. Multiple senile lentigos of the face, a skin ageing pattern resulting from a life excess of intermittent sun exposure in dark-skinned caucasians: a case–control study. *Br J Dermatol* 2006; **154**: 438–44.
20 Ortonne JP, Pandya AG, Lui H, Hexsel D. Treatment of solar lentigines. *J Am Acad Dermatol* 2006; **54**: S262–71.
21 Kawana S, Ochiai H, Tachihara R. Objective evaluation of the effect of intense pulsed light on rosacea and solar lentigines by spectrophotometric analysis of skin color. *Dermatol Surg* 2007; **33**: 449–54.
22 Yamashita T, Negishi K, Hariya T *et al*. Intense pulsed light therapy for superficial pigmented lesions evaluated by reflectance-mode confocal microscopy and optical coherence tomography. *J Invest Dermatol* 2006; **126**: 2281–6.
23 Ortonne JP. Retinoid therapy of pigmentary disorders. *Dermatol Ther* 2006; **19**: 280–8.
24 Tanzi EL, Lupton JR, Alster TS. Lasers in dermatology: four decades of progress. *J Am Acad Dermatol* 2003; **49**: 1–31, quiz 31–4.
25 Basarab T, Millard TP, McGregor JM, Barker JN. Atypical pigmented lesions following extensive PUVA therapy. *Clin Exp Dermatol* 2000; **25**: 135–7.
26 Abdullah AN, Keczkes K. Cutaneous and ocular side-effects of PUVA photochemotherapy—a 10-year follow-up study. *Clin Exp Dermatol* 1989; **14**: 421–4.
27 Rhodes AR, Stern RS, Melski JW. The PUVA lentigo: an analysis of predisposing factors. *J Invest Dermatol* 1983; **81**: 459–63.
28 Nakagawa H, Rhodes AR, Momtaz TK, Fitzpatrick TB. Morphologic alterations of epidermal melanocytes and melanosomes in PUVA lentigines: a comparative ultrastructural investigation of lentigines induced by PUVA and sunlight. *J Invest Dermatol* 1984; **82**: 101–7.
29 Stern RS. Risks of cancer associated with long-term exposure to PUVA in humans: current status—1991. *Blood Cells* 1992; **18**: 91–7, discussion 98–9.
30 Stern RS. The risk of melanoma in association with long-term exposure to PUVA. *J Am Acad Dermatol* 2001; **44**: 755–61.
31 Lindelof B, Sigurgeirsson B, Tegner E *et al*. PUVA and cancer risk: the Swedish follow-up study. *Br J Dermatol* 1999; **141**: 108–12.
32 Bolognia JL. Reticulated black solar lentigo ('ink spot' lentigo). *Arch Dermatol* 1992; **128**: 934–40.

Mucosal melanotic lesions

Pigmented melanotic macules (mucosal melanosis/genital lentiginosis)

Some macular pigmentation of the mucosa in the mouth or on the genitalia is normal; the pigmentation may be increased at sites of trauma and is generally subtle. In the mouth, smoking is thought to induce melanosis and post-inflammatory pigmentation occurs. Lentines may also occur in familial lentiginoses discussed above.

More discrete, more deeply pigmented macules are also common on the vulva and sometimes on the glans penis, when they are usually referred to as genital melanotic macules, or mucosal melanosis. These macules result from local excessive pigment production with normal numbers of melanocytes [1]. There is confusion around aetiology and nomenclature so that some authors refer to melanoses, others to lentiginoses, but the entities probably overlap.



Fig. 54.9 Genital melanosis; a benign condition of unknown aetiology which none-the-less can cause considerable clinical concern.

Rarely, these melanotic macules may expand to several centimetres in size, they may be patchy in distribution and may develop irregular deep pigmentation, which resembles melanoma and causes concern. Melanoma must be excluded by biopsy as melanoma in the genital area may begin with a protracted *in situ* phase, but normally the histological appearance of such lesions is banal, although it has been suggested that the majority have a subtle increase in melanocyte number [2]. The aetiology of genital melanosis is unclear; the presence of pruritus has led to suggestions of a precursor inflammation but none has been clearly identified [1].

The presence of pigmented patches in the genital skin of women affected by lichen sclerosus et atrophicus has been reported [3]. Biopsy of these lesions has shown the lesions to be atypical melanocytic naevi. There is no obvious explanation for the development of these naevi in lichen sclerosus et atrophicus, but it is important to be aware of this association, as clinically the lesions may suggest melanoma.

Clinical features. These lesions are relatively large macular areas of uniform brown, black or grey pigmentation (Fig. 54.9). They may have slowly expanded to reach a large diameter over several years. The differential diagnosis in the mouth is that of oral melanoma which is a rare tumour, representing 0.5% of oral cancers [4]. Oral melanomas may be subtle in appearance (see Fig. 54.64 below) and are described as a smooth swelling which might be evenly hyperpigmented or irregularly pigmented.

Pathology. The pathology of mucosal melanosis is usually much less dramatic than their clinical appearance. There is a clear increase of melanin pigment in the basal layer keratinocytes with some overspill into the dermis, resulting in pigment-laden macro-

phages. The melanocyte count is relatively normal with only a slight linear increase and no junctional activity.

Treatment. No treatment is required if an incisional biopsy of appropriate area(s) has confidently excluded a significant lentiginosis or melanoma. The often dramatically intense pigmentation, however, usually leads to persistent concern and it is therefore reasonable to keep under review, although the issue is actually only one of excluding *in situ* melanoma; mucosal melanosis without the proliferation of atypical melanocytes is held not to be pre-malignant. A change in appearance would merit another biopsy, as the differential diagnosis is *in situ* melanoma.

If there is a significantly increased number of melanocytes, particularly if there is confluent proliferation resembling lentigo maligna, then treatment is required. The treatment options are limited in these circumstances. In the presence of clear *in situ* change, then surgery would be the normal treatment choice. The mutilating effect of this surgery, however, is such that a therapeutic trial of topical imiquimod might be justified with biopsy after treatment [5], although patients may find it difficult to tolerate in this site.

Labial melanotic macules [6,7]

Definition. Flat areas of benign, non-progressive melanin pigmentation on the lips, which may be best viewed as a type of freckle or a lesion akin to a simple lentigo [8].

Clinical features. Labial melanotic macules usually affect the lower lip in the central third. More females than males seek treatment for these lesions. The site suggests that excessive exposure to natural UV radiation may be an aetiological factor. The natural history is of the relatively rapid appearance of a brown to black macule on the lower lip in a young adult. The macules rarely become larger than 0.5 cm in diameter, and are usually single lesions (Fig. 54.10). The differential diagnosis includes an amalgam tattoo.

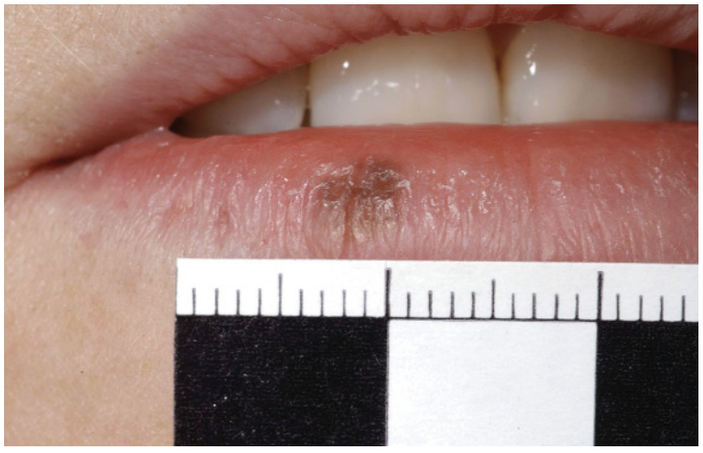


Fig. 54.10 A labial melanotic macule. This is a benign lesion seen in fair-skinned people, which is thought to be related to sun damage.

Pathology. The pathology is that of linear increase in melanin pigment in the basal cells. There may be a very modest increase in the number of melanocytes [8]. Malignant transformation has not been reported in these lesions.

Treatment. Reassurance is all that is needed on medical grounds. If removal is requested for cosmetic reasons, cryotherapy, use of the infrared coagulator or laser therapy [9] may all be effective.

References

1 Lenane P, Keane CO, Connell BO *et al*. Genital melanotic macules: clinical, histologic, immunohistochemical, and ultrastructural features. *J Am Acad Dermatol* 2000; **42**: 640–4.
2 Barnhill RL, Albert LS, Shama SK *et al*. Genital lentiginosis: a clinical and histopathologic study. *J Am Acad Dermatol* 1990; **22**: 453–60.
3 Carlson JA, Mu XC, Slominski A *et al*. Melanocytic proliferations associated with lichen sclerosus. *Arch Dermatol* 2002; **138**: 77–87.
4 Meleti M, Rene Leemans C, Mooi WJ *et al*. Oral malignant melanoma: a review of the literature. *Oral Oncol* 2007; **43**: 116–21.
5 Rajpar SF, Marsden JR. Imiquimod in the treatment of lentigo maligna. *Br J Dermatol* 2006; **155**: 653–6.
6 Gupta G, Williams RE, Mackie RM. The labial melanotic macule: a review of 79 cases. *Br J Dermatol* 1997; **136**: 772–5.
7 Weathers DR, Corio RL, Crawford BE *et al*. The labial melanotic macule. *Oral Surg Oral Med Oral Pathol* 1976; **42**: 196–205.
8 Maize JC. Mucosal melanosis. *Dermatol Clin* 1988; **6**: 283–93.
9 Gupta G, MacKay IR, MacKie RM. Q-switched ruby laser in the treatment of labial melanotic macules. *Lasers Surg Med* 1999; **25**: 219–22.

Dermal melanocytic lesions [1]

Common acquired melanocytic naevi described later in this chapter are believed, on the basis of biopsies from multiple lesions in patients at varying ages, to develop from epidermal melanocytes that completed their migration from the neural crest to the dermal–epidermal junction in fetal life, proliferated and then senesced (i.e. ceased proliferation). By contrast, the dermal lesions described here differ in that they are believed to arise from dermal melanocytes that have become arrested in the dermis during fetal life and tissue modelling and have not reached their normal site in the basal layer of the epidermis. Many mammals have a population of dermal melanocytes normally but these are not commonly observed in human dermis, with the possible exception of the Mongolian spot.

Mongolian spot

Definition. Macular blue-grey pigmentation present at birth on the sacral area in normal infants.

Incidence. The incidence of Mongolian spot varies with skin colour. They are rare in white-skinned European infants (the highest prevalence in Europe being in the Mediterranean region). By comparison, the majority of babies born to families from the Far East have a Mongolian spot. The incidence in other populations lies between these extremes. It has been found in some 26% of Turkish babies [2] and 71% of Iranian babies [3]. The relationship with skin colour raises the possibility that such lesions are



Fig. 54.11 A Mongolian spot which was evident on the limbs as well as in the lumbosacral area.

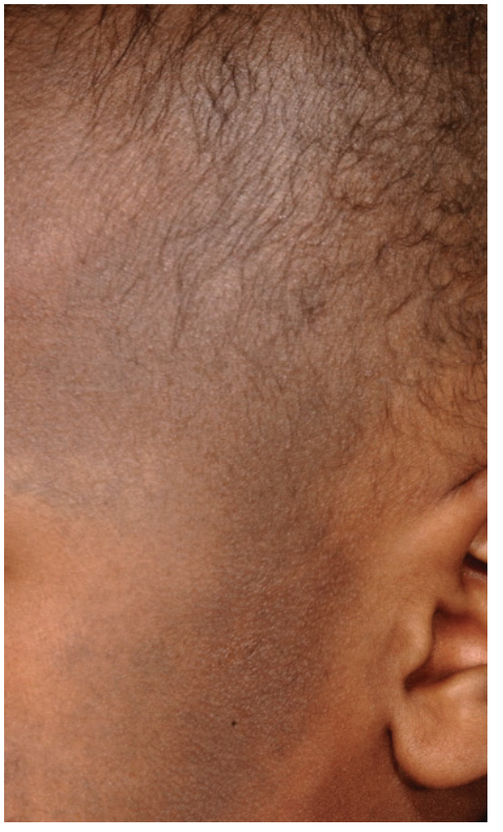


Fig. 54.12 A naevus of Ota visible in a young child.

merely more obvious in the skin where the patient has melanocytes producing a good deal of pigment.

Clinical features. The pigmentation is macular, diffuse and more or less uniform, slate blue to grey and usually relatively faint. The patches are usually rounded or oval in shape, up to 10 cm or so in diameter, and usually single but occasionally multiple. The lumbosacral region is the common site, and the buttocks, flanks or even shoulders and lower legs (Fig. 54.11) may be affected in extensive lesions. The pigmentation develops in fetal life, increases in depth for a period after birth and then diminishes. It usually disappears during the first decade, but has occasionally persisted into adult life.

Pathology. Melanocytes are dispersed in a ribbon-like pattern between the collagen fibres and around the neurovascular bundles of the dermis. They run parallel to the skin surface and contain very fine granules of melanin. There is no disturbance of the pattern of collagen and elastic fibres. Melanophages are not found. The last two characteristics enable it to be differentiated from blue naevus.

Management. No treatment is needed.

Naevus of Ota

Synonym
- Naevus fuscocaeruleus ophthalmomaxillaris

Definition. An extensive, blue, patch-like area of dermal melanocytic pigmentation of the sclera and the skin adjacent to the eye due to the presence of dermal melanocytes. The melanocytes may also extend into the uveal tract, dura and nasopharynx.

Incidence. This disorder is most common in Asian people (but still seen in less than 1%) [4] but is very rare in other groups. Unlike the Mongolian spot, it is not usually visible at birth, but becomes progressively darker in childhood (Fig. 54.12) and persists in adult life. There are published cases in which these lesions are acquired in adult life (Fig. 54.13) [5].

Clinical features. The pigmentation is often speckled and is composed of deeper bluish and more superficial brownish elements, which do not always coincide. The two colours are perhaps best seen in the eye, where the affected sclera is blue and the conjunctiva brown. The brown pigmentation is patchy and may be patterned in a reticular or geographical way; the blue pigmentation is more diffuse. The areas involved are the eyelids, the bulbar and palpebral conjunctiva and the sclera, and the cheeks, forehead, scalp, alae nasi and ears. The mucosa of the palate and cheeks may also be affected. The distribution is usually restricted to the first and second divisions of the trigeminal nerve, but rarely patches may occur on the trunk.

The pigmented spots usually appear in childhood and increase in number and extent to become confluent in some areas. There is one report of the onset following trauma, and in another the ocular



Fig. 54.13 This patient acquired a naevus of Ota in adult life and then developed a meningeal melanoma in relation to this blue naevus.

pigmentation became much more pronounced after an attack of conjunctivitis. The distribution is usually, but not always, unilateral.

Benign intracerebral proliferations, known as melanocytomas, are described as complications of these lesions [6]. In very rare instances malignant melanoma has developed in naevus of Ota, and this may also occur within the meninges, as in the patient seen in Fig. 54.13, or in the choroid [7,8]. Survival after excision of meningeal melanoma in these circumstances may have a surprisingly good prognosis [9].

Pathology. The features are the same as those of Mongolian spot. A variety is described called Naevus fusco-caeruleus zygomaticus [10] in which speckled naevi are seen on the upper cheek, and microscopy shows bipolar pigment-bearing cells in the upper dermis only, in contrast to the naevus of Ota in which pigment-bearing cells are seen throughout the dermis.

Treatment. Laser therapy may be of value [11], although post-treatment hypopigmentation may result [12], and cosmetic camouflage may also be useful.

Naevus of Ito

This type of dermal melanocytosis involves the acromioclavicular region and the upper chest and, like the naevus of Ota, is largely confined to the Japanese (Fig. 54.14).



Fig. 54.14 Naevus of Ito, showing typical distribution over the shoulder area.

References

1 Zembowicz A, Mihm MC. Dermal dendritic melanocytic proliferations: an update. *Histopathology* 2004; **45**: 433–51.

2 Egemen A, Ikizoglu T, Ergor S *et al*. Frequency and characteristics of Mongolian spots among Turkish children in Aegean region. *Turkish J Pediatr* 2006; **48**: 232–6.

3 Moosavi Z, Hosseini T. One-year survey of cutaneous lesions in 1000 consecutive Iranian newborns. *Pediatr Dermatol* 2006; **23**: 61–3.

4 Chan HH, Kono T. Nevus of Ota: clinical aspects and management. *Skinmed* 2003; **2**: 89–96, quiz 97–8.

5 Stanford DG, Georgouras KE. Dermal melanocytosis: a clinical spectrum. *Australas J Dermatol* 1996; **37**: 19–25.

6 Rahimi-Movaghar V, Karimi M. Meningeal melanocytoma of the brain and oculodermal melanocytosis (nevus of Ota): case report and literature review. *Surg Neurol* 2003; **59**: 200–10.

7 Baroody M, Holds JB. Extensive locoregional malignant melanoma transformation in a patient with oculodermal melanocytosis. *Plast Reconstr Surg* 2004; **113**: 317–22.

8 Sharan S, Grigg JR, Billson FA. Bilateral naevus of Ota with choroidal melanoma and diffuse retinal pigmentation in a dark skinned person. *Br J Ophthalmol* 2005; **89**: 1529.

9 Theunissen P, Spincemaille G, Pannebakker M, Lambers J. Meningeal melanoma associated with nevus of Ota: case report and review. *Clinical Neuropathol* 1993; **12**: 125–9.

10 Sun CC, Lu YC, Lee EF, Nakagawa H. Naevus fusco-caeruleus zygomaticus. *Br J Dermatol* 1987; **117**: 545–53.

11 Lu Z, Fang L, Jiao S *et al*. Treatment of 522 patients with Nevus of Ota with Q-switched Alexandrite laser. *Chin Med J* 2003; **116**: 226–30.

12 Kono T, Nozaki M, Chan HH, Mikashima Y. A retrospective study looking at the long-term complications of Q-switched ruby laser in the treatment of nevus of Ota. *Lasers Surg Med* 2001; **29**: 156–9.

Melanocytic naevi

Epidemiology. Melanocytic naevi are normal, benign proliferations of melanocytes. Although the risk of a naevus evolving into a melanoma is extremely small, melanocytic naevi are both risk factors for melanoma and precursors of melanoma.

The prevalence of pigmented lesions present at birth varies considerably between published series; this is principally because of the ethnic mix of the patients examined, as congenital melanocytic naevi may be more common in black or Asian children [1], but they are generally considered to be present in between 1 and 2% of newborns [2]. Most congenital naevi are deeply pigmented at birth but it may be difficult to differentiate congenital naevi from café-au-lait spots clinically. There is very limited sequential information about the eruption of acquired naevi in the period immediately after birth, but it is thought that naevi clinically and

Table 54.2 Terms commonly used in the description of melanocytic naevi.

Melanocyte	A pigment-producing cell characterized by its ability to synthesize melanosomes. Contains the enzyme 3,4-dihydroxyphenylalanine (DOPA)
Theque	A group of melanocytes (generally four or more) in contact with the basal layer of the epidermis but budding downwards into the dermis
Freckle	An area of increased melanin pigmentation The only histological abnormality is an excess of melanin pigment; the lesion would therefore appear to be the result of functionally overactive melanocyte/keratinocyte units These lesions are stimulated by UV irradiation
Lentigo	An area of increased melanin pigmentation, which shows histologically a linear replacement of keratinocytes in the basal layer of the epidermis by melanocytes This replacement does not reach the level of theque formation; if this were the case, the term junctional naevus would be appropriate
Junctional activity	The presence at the dermal–epidermal junction of theques of melanocytes
Junctional naevus	A pigmented melanocytic naevus in which the main histological feature is that of junctional activity A few naevus cells are usually observed scattered in the underlying dermis
Compound naevus	A pigmented melanocytic naevus in which the histological features include both junctional activity and the presence of naevus cells in the dermis Such naevi usually contain melanin
Intradermal naevus	A melanocytic naevus in which there is little or no abnormality of melanocytes in the epidermis The main feature is the presence of packets of naevus cells in the dermis Melanin pigmentation is often absent and such naevi may be clinically non-pigmented The deepest dermal cells tend to neural or fibroblastic differentiation

histologically similar to the congenital type may erupt within the first year of life. In adults, it has been reported that around 2% of individuals have congenital naevus-like lesions [3]. In the only sequential study reported to date of acquired naevi in the same cohort of children [4], 0.5% of 1012 babies examined at birth had melanocytic naevi compared with 35% at the age of 1 year.

Terminology commonly used in describing melanocytic naevi is included in Table 54.2.

References

1 Castilla E, Da Graca Dutra M, Orioli-Parreiras I. Epidemiology of congenital pigmented naevi: risk factors. *Br J Dermatol* 1981; **104**: 421–7.

2 Osburn K, Schosser RH, Everett MA. Congenital pigmented and vascular lesions in newborn infants. *J Am Acad Dermatol* 1987; **16**: 788–92.

3 Kopf AW, Levine LJ, Rigel DS *et al*. Prevalence of congenital-nevus-like nevi, nevi spili, and café au lait spots. *Arch Dermatol* 1985; **121**: 766–9.

4 Goss B, Forman D, Ansell P *et al*. The prevalence and characteristics of congenital pigmented lesions in newborn babies in Oxford. *Paed Perinatal Epidemiol* 1990; **4**: 448–57.

Congenital melanocytic naevi

Congenital melanocytic naevi have been arbitrarily divided into three size ranges in order to develop consistent approaches to prognosis and management. Of those melanomas that have evolved from or within congenital naevi, the majority have occurred in large naevi; because of this, great distinction has been drawn between congenital naevi less than 10 cm in diameter and larger ones. Most authors use the American National Institutes of Health (NIH) consensus definition to categorize these naevi according to size. In this document, small congenital naevi are defined as under 1.5 cm in diameter, large as having a diameter between 1.5 and 20 cm and giant naevi as having a diameter of 20 cm or more [1] (Table 54.3). The great majority of congenital

Table 54.3 Overview of congenital melanocytic naevi.

Naevus type	Subtype	Characteristic pathology	Significance	Treatment
Congenital melanocytic naevus, evident at birth	Small (<1.5 cm) May appear in the first 2 years of life	Deeper naevus cells exhibiting a tendency to extend deeply in relation to skin appendages	Very small risk of melanoma	None, other than self-examination Consider excision in sites where review is difficult such as the scalp
	Large (1.5 to 20 cm)	Deeper naevus cells exhibiting a tendency to extend deeply in relation to skin appendages	Increased risk of melanoma	Excise if technically feasible with good cosmetic result
	Giant (>20 cm)	Deeper naevus cells exhibiting a tendency to extend deeply in relation to skin appendages May be associated with benign but atypical proliferations such as hamartomas	Increased risk of melanoma especially if over the trunk and associated with many satellite naevi Lifetime risk is poorly quantified but is likely to be less than 14%	Removal of risk not possible because such lesions cannot be fully excised Surgical decisions should be based upon the cosmetic likelihood of success and should be deferred to assess spontaneous improvement in the first few years of life
Naevi thought to be variants of congenital naevi but which appear in childhood	Speckled naevus	Banal naevi arising in a macular lentigo with subtle increase in melanocyte number	Uncommon cases of melanoma described arising in such naevi	Education about self-examination
	Agminate Spitz naevus	Spitzoid proliferations arising in a macular area of pigmentation	Similar to a speckled naevus but with spitzoid elements	Review at intervals and excise changing elements within

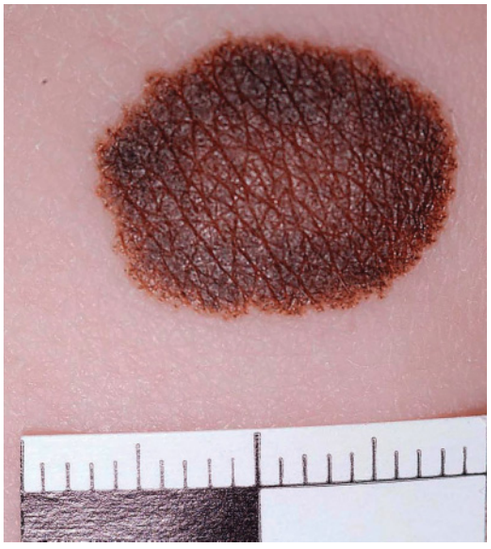


Fig. 54.15 A small congenital melanocytic naevus in a child.



Fig. 54.16 A large congenital melanocytic naevus with junctional and compound elements.

naevi are small, although the published studies in the literature, particularly in relation to the malignant potential of congenital naevi, mainly relate to the giant, or garment, type. The giant type is rare; Castilla *et al*. described a study of 500 000 infants in South America in which one naevus at least 10 cm in diameter was identified per 20 445 subjects [2].

Clinical features. Congenital naevi are usually obvious and deeply pigmented at birth, although occasional naevi may be initially obscured by vernix and a proportion appear in the months after birth (Figs 54.15 & 54.16). The majority are macular at birth.

As the child grows the naevus usually grows in proportion. At some sites, such as the scalp, there is commonly a considerable increase in terminal hair (which is often darker than normal hair and more wiry), soon after birth, which causes alarm. In other sites, an increase in terminal hair tends to occur more subtly over time and may be accompanied by the development of rugosity. A significant proportion of naevi become paler in the first 1 to 2 years of life, and at sites such as the scalp may fade to cosmetic insignificance [3] (Fig. 54.17). There is, therefore, much to be said for deferring treatment decisions until after this period if surgery is being considered for cosmetic reasons, as, in a good proportion, the cosmetic appearance of the naevus will have considerably improved and this may influence decisions regarding the need for surgery.

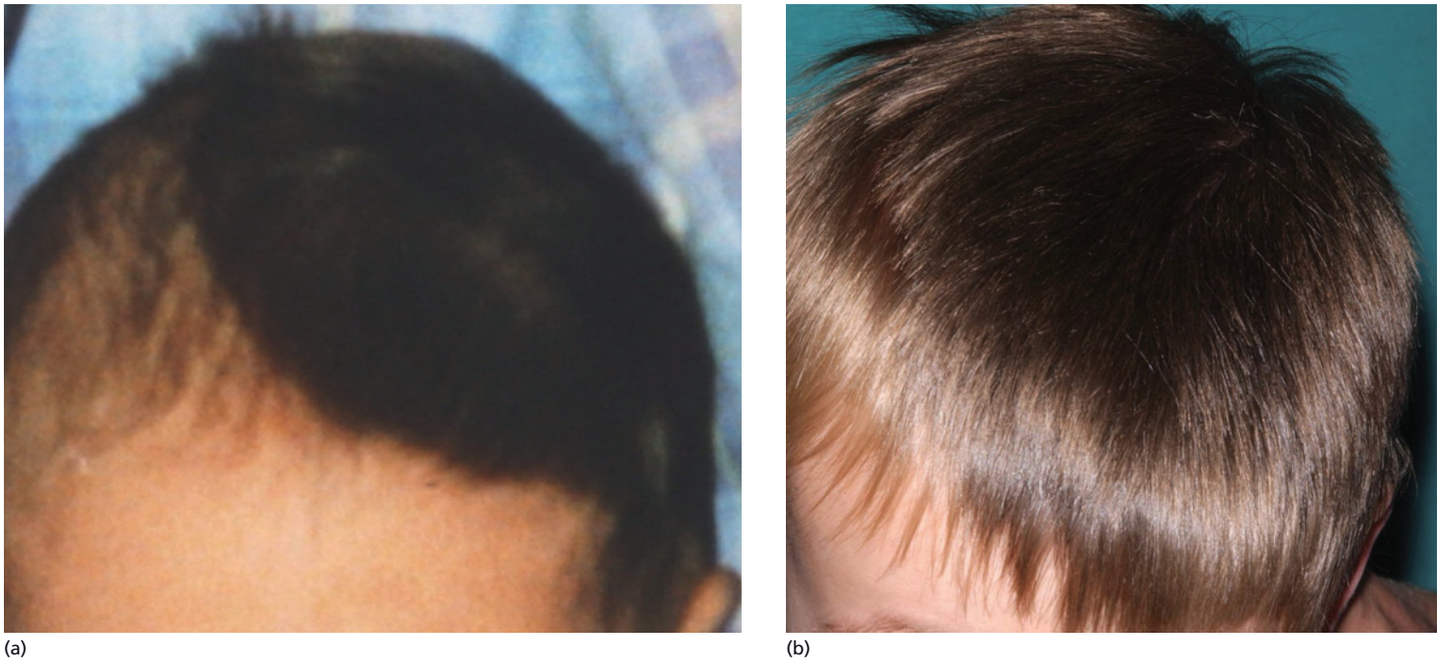
The giant, garment or bathing-trunk naevus is very rare but is a considerable cosmetic problem for children and their families. The common site is the lower back and thigh area and a very large proportion of the infant's surface area may be involved (Fig. 54.18). There may also be large numbers of smaller congenital naevi present elsewhere on the infant's skin; increased numbers of these will develop over time. Such so-called satellite naevi (Fig. 54.19) were reported in 74% of one series [4]. In the same series, 31% of the patients also had naevi on mucous membranes.

As the infant grows, the surface of the naevus may become rugose or warty and nodules can develop within a large naevus (Fig. 54.20). The hairy component, which occurs in 95% of lesions, tends to become more prominent in late childhood, but at this stage the naevus itself ceases to thicken and may become paler. The hair growth pattern may have a 'vortex' distribution, often centred on the midline in giant naevi of the back. Some lesions involve both the opposed surfaces of the upper and lower eyelid so that when the eyes are shut the naevus takes its normal rounded shape. This shows that the site of the naevus was determined during the period when the lids were fused, that is between the second and sixth month of fetal life.

Neurocutaneous melanosis may produce raised intracranial pressure, hydrocephalus or space-occupying spinal lesions; this is a very rare complication. In a series of 80 Mexican patients with giant naevi only one case of hydrocephalus was reported [4]. There may be associated abnormalities such as meningeal involvement, spina bifida or meningocoele when the naevus is over the vertebral column, or club-foot and hypertrophy or atrophy of the deeper structures of a limb. Absence of subcutaneous fat is the most common associated anomaly and may be symptomatic in sites such as over the sacrum.

Congenital melanocytic naevi are said to occur in the epidermal naevus syndrome [5]. There is also a less well-substantiated association with neurofibromatosis [6].

Pathology. The majority of congenital naevi are dermal or compound melanocytic naevi with naevus cells typically extending more deeply into the dermis (within appendages and even into striated muscle and fat) than those of acquired naevi [7]. It was suggested, on the basis of histological studies, that congenital



(a) (b)

Fig. 54.17 (a) A large congenital melanocytic naevus of the scalp, which faded dramatically (b) until there was nothing visible on the skin in the first few years of life.



Fig. 54.18 Giant or garment congenital naevus on the lower back area of a child.

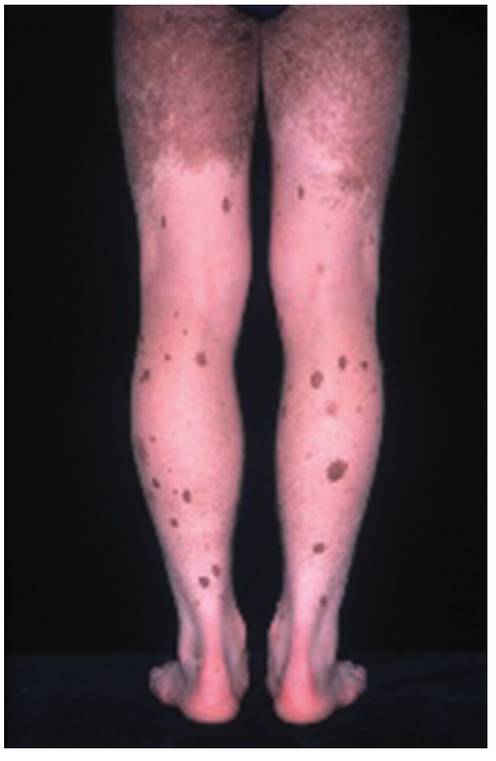


Fig. 54.19 Multiple satellite naevi in an adult with a giant congenital melanocytic naevus. These naevi usually emerge in children with giant congenital naevi, in the first 2 years of life.

naevi evolve within the first few months of life from junctional to deep lesions and it was thought that this transition offered the possibility of early treatment having an effect on long-term distribution of naevus cells, giving potential for early treatment by dermabrasion [8–10]. The current view, however, is that variation in depth of melanocytes reflects variation between individuals rather than being time-dependent.

There are a variety of proliferative neoplasms that may develop in congenital melanocytic naevi, which cause great consternation

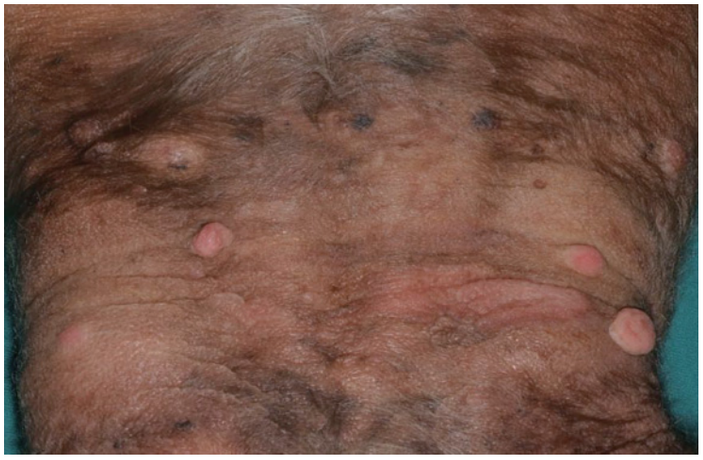


Fig. 54.20 Hypertrichosis and benign hamartomatous proliferations in a toddler with a particularly troublesome giant congenital melanocytic naevus.

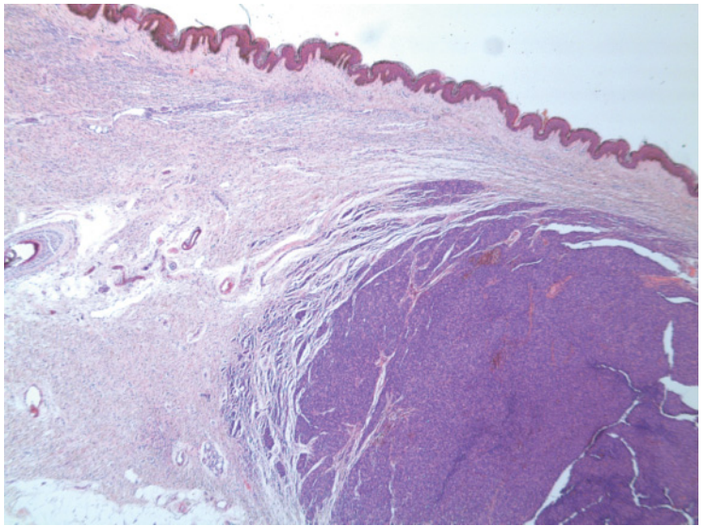


Fig. 54.21 The histological appearance of a benign proliferative nodule which arose in a giant congenital pigmented naevus in a child aged 12 years. (Courtesy of Dr S. Edward, Leeds Teaching Hospitals Trust, Leeds, UK.)

and confusion (Fig. 54.21). Certainly, malignant melanoma may arise [11]. In addition, a rapidly growing, ulcerative tumour called nodular proliferative neurocristic hamartoma has been described at birth [12]. This fetal hamartoma consists of diverse tissues of neuroectodermal and ectomesenchymal origin. The greatest diagnostic difficulty occurs when simulants of melanoma occur, characterized by the proliferation of epithelioid melanocytes.

Genetic counselling. Congenital naevi are essentially considered to be developmental abnormalities of the skin, with a very low risk of recurrence in subsequent pregnancies, which is particularly important when reassuring parents who have a child with a giant melanocytic naevus [13]. However, there are extremely rare instances of families in which more than one case has occurred, raising the possibility that, at least in these families, there may be an inherited tendency to develop giant congenital naevi. Such risks, however, are very low.

Prognosis and complications. Superficial spreading melanoma is the most significant complication of congenital naevi but the level of that risk remains the most controversial, mainly because most of the reported series come from large referral centres and may therefore suffer from ascertainment bias.

There seems to be no doubt that there is an increased risk of melanoma in patients with very large naevi. In the series reported by Swerdlow *et al*. [14], two melanomas, both fatal, occurred in 265 patients with melanoma covering at least 5% of their body area. The melanomas occurred at the ages of 18 and 20 years. In a second series of 80 patients, three melanomas occurred [4], including two in children under the age of 3 years. In giant naevi there therefore appears to be a definite risk, with the age of onset of the melanoma being very much earlier than in the general population. In contrast to the normal development pattern of melanomas, those occurring within congenital naevi may arise from below the dermoepidermal junction, which may delay diagnosis [15]. There have been several attempts to estimate lifetime risk, giving values between 4.6 and 14% [16]. Krengel *et al.* performed a useful review of a total of 6571 patients with congenital melanocytic naevi, followed up for a mean of 3.4–23.7 years, and 46 patients (0.7%) developed 49 melanomas [17]. The mean age at diagnosis of melanoma was 15.5 years (median 7 years). Primary melanomas arose inside the naevi in 33 of 49 cases (67%). In seven cases (14%), metastatic melanoma with unknown primary was encountered; in four cases (8%) the melanoma developed at an extracutaneous site. The risk of developing melanoma and the rate of fatal courses were highest by far in congenital melanocytic naevi 40 cm or greater in diameter.

There are numerous case reports of melanoma arising in smaller congenital naevi [18] but such naevi are relatively common and it is very difficult from studies reported so far to compare, for example, the relative risk of melanoma arising from a small congenital naevus with that of a melanoma arising in an acquired naevus. It seems likely, as congenital naevi tend to be bigger, that the risk might be greater at least in proportion to the melanocyte mass. Various estimates of risk have been made. Rhodes and coworkers have estimated a lifetime risk of between 2.6 and 4.9% [18,19] in naevi less than 4.5 cm in diameter. However, Swerdlow *et al*. [14] failed to demonstrate any increased risk for naevi smaller than those covering 5% of the body surface. It seems unlikely that the true risk from a small congenital naevus will ever be established accurately because of the impossibility of gathering a sufficiently large cohort of patients whose congenital naevi are left *in situ*.

Rarely, intracerebral primary melanoma may complicate leptomeningeal melanocytosis [20].

Treatment. An MRI scan should be considered in babies with naevi over the cranium or spine to exclude significant leptomeningeal melanocytosis. However, although MRI anomalies are common, occurring in around 30% [21], symptomatic neurocutaneous melanosis is rare, so the value of scanning seems

questionable in the absence of neurological signs. Regular neurological examination, however, is clearly important.

The aims of treatment are to improve the cosmetic effect of naevi and to reduce the risk of malignant transformation. To date, there is no proof that any treatment regimen fulfils the second aim for giant naevi in which there is no possibility of complete excision of the naevus, because of the surface area of skin involved and the depth of the naevus within the skin and subcutis. There is perhaps a stronger argument for prophylactic excision of large naevi where complete excision of the naevus is technically possible with reasonable cosmetic result. The most common treatment is surgical, using a variety of plastic surgical techniques such as multistep surgery, the use of tissue expanders and grafting. Tissue expansion is usually used for the head and neck, but in other sites excision and grafting are more usual, with consequently poorer cosmetic results. The cosmetic results of surgery for giant naevi on the trunk are generally poor and there have been attempts to improve results, mainly by treatment within the first few weeks of life by dermabrasion or curettage [22]. The rationale for this is that there may be a natural plane of cleavage within the upper dermis very early in life which may be exploited by the curette to reduce the risk of subsequent scarring [23]. It is difficult from the literature to assess the long-term cosmetic results of the approach of curettage but those from dermabrasion seem disappointing. A review of 215 patients treated in Germany reported hypertrophic scars in 15% (particularly on the lower back) but there was good, permanent reduction in pigmentation in 34% (which was more likely when treatment was carried out early) [24]. A smaller series of 12 neonates treated by dermabrasion reported good results in 10, although six went on to have surgery later [25]. The long-term cosmetic results of surgery may therefore be disappointing, although children in one study reported a preference for a surgical scar rather than the naevus [26]. Other ablative techniques have been tried such as cryotherapy and, more recently, the Q-switched ruby laser. This laser emits light at 694 nm, which is relatively selectively taken up by melanin, but its value remains unclear.

Overall, the choice about intervention in children born with large or giant naevi is made on the basis of balancing a risk of melanoma (which is poorly quantified), and the cosmetic deficit of the naevus, against the risks of surgery. The psychological impact of giant congenital naevi is great and the risk of melanoma established, so that there is a need to establish better approaches for removal. Currently available methods leave much to be desired and it is eminently possible to operate on children to little overall benefit indeed, even do harm. The decision as to whether to proceed to surgery or not may be very difficult for families.

Parents of children with congenital naevi left *in situ* should be advised to keep the naevus under review and to seek advice if it changes in shape, size or colour. As such naevi do change through life in an entirely benign way, education about the nature of changes which would cause concern is essential. Photographs of the child's naevus and images of melanomas are useful for the family to take home. It would seem reasonable to prophylactically excise small naevi that are difficult to keep under review, such as those in the scalp or in the middle of the back, particularly if they have any atypical features such as intense or irregular pigmentation which persists beyond infancy.



Fig. 54.22 Speckled and lentiginous naevus. Note the variation in colour of this lesion.

Speckled and lentiginous naevus

This term is recommended in preference to the term naevus spilus. Such naevi may be viewed as a type of congenital melanocytic lesion which is lentiginous in early childhood and which might develop palpable components at puberty in a 'speckled' distribution.

Clinical features. Speckled and lentiginous naevus is a relatively uncommon entity. It is comprised of a flat, macular component, subtly darker shade than the surrounding skin, resembling a café-au-lait spot. Within this pale background there are lentigo-like lesions and also elevated darker-brown naevi (Fig. 54.22). It may also coexist with other types of melanocytic naevus such as a blue [27] or Spitz naevus, indeed there is a clinical overlap with the agminate Spitz naevus described below (see also Table 54.3).

Pathology. Pathological examination shows, as the clinical appearance suggests, a background macular lesion with a very subtle increase in melanocytes, and lentigos with superimposed individual compound naevi.

Management. There have been reports of malignant change in these lesions [27,28]. There are no data however on which to estimate the risk of such a change and it is likely that the risk is very low. Patients should generally, therefore, be counselled as to self examination as is done for patients with congenital melanocytic naevi. There are very rare patients in which the naevus develops atypical melanocytic proliferations at puberty and in these patients excision should be considered if technically feasible.

References

1 Anon. Consensus conference: Precursors to malignant melanoma. *JAMA* 1984; **251**: 1864–6.

2 Castilla E, Dutra M, Orioli-Parreiras I. Epidemiology of congenital pigmented nevi. Incidence rates and relative frequencies. *Br J Dermatol* 1981; **104**: 307–15.
3 Strauss RM, Newton Bishop JA. Spontaneous involution of congenital melanocytic nevi of the scalp. *J Am Acad Dermatol* 2008; **58**: 508–11.
4 Ruiz-Maldonado R, Tamayo L, Laterza AM, Duran C. Giant pigmented nevi: clinical, histopathologic, and therapeutic considerations. *J Pediatr* 1992; **120**: 906–11.
5 Carney J, Gordon H, Carpenter P *et al*. The complex of myxomas, spotty pigmentation and endocrine overactivity. *Medicine* 1985; **64**: 270–83.
6 Marghoob AA, Orlow SJ, Kopf AW. Continuing medical education—syndromes associated with melanocytic nevi. *J Am Acad Dermatol* 1993; **29**: 373–88.
7 Rhodes AR, Silverman RA, Harrist TJ, Melski JW. A histologic comparison of congenital and acquired nevomelanocytic nevi. *Arch Dermatol* 1985; **121**: 1266–73.
8 Walton R, Jacobs A, Cox A. Pigmented lesions in newborn infants. *Br J Dermatol* 1976; **95**: 389–96.
9 Johnson H. Permanent removal of pigmentation from giant hairy nevi by dermabrasion in early age. *Br J PLast Surg* 1977; **30**: 321.
10 Mark F, Mihm M, Litelpo M *et al*. Congenital melanocytic naevi of the small and garment type. *Hum Pathol* 1973; **4**: 396–418.
11 Borges AF, Lineberger AS. Malignant melanoma without metastasis in a giant nevus. *Ann Plast Surg* 1984; **12**: 454–60.
12 Mancianti M-L, Clark WH, Hayes FA, Herlyn M. Malignant melanoma simulants arising in congenital melanocytic nevi do not show experimental evidence for a malignant phenotype. *Am J Pathol* 1990; **136**: 817–29.
13 Goodman RM, Caren J, Ziprkowski M *et al*. Genetic considerations in giant pigmented hairy naevus. *Br J Dermatol* 1971; **85**: 150–7.
14 Swerdlow AJ, English JSC, Qiao Z. The risk of melanoma in patients with congenital nevi: A cohort study. *J Am Acad Dermatol* 1995; **32**: 595–9.
15 Reed R, Martin P. Variants of melanoma. *Semin Cutan Med Surg* 1997; **16**: 137–58.
16 Illig L, Weidner F, Hundeiker M *et al*. Congenital nevi ≤10 cm as precursors to melanoma. 52 cases, a review, and a new conception. *Arch Dermatol* 1985; **121**: 1274–81.
17 Krengel S, Hauschild A, Schafer T. Melanoma risk in congenital melanocytic naevi: a systematic review. *Br J Dermatol* 2006; **155**: 1–8.
18 Rhodes A, Melski J. Small congenital nevocellular nevi and the risk of cutaneous melanoma. *J Pediatrics* 1982; **100**: 219–24.
19 Rhodes A, Sober A, Day C *et al*. The malignant potential of small congenital naevi. *J Am Acad Dermatol* 1982; **6**: 230–41.
20 Slaughter J, Hardman J, Kemple L *et al*. Neurocutaneous melanosis and leptomeningeal melanocytosis in children. *Arch Dermatol* 1969; **88**: 298–304.
21 Foster RD, Williams ML, Barkovich AJ *et al*. Giant congenital melanocytic nevi: the significance of neurocutaneous melanosis in neurologically asymptomatic children. *Plast Reconstr Surg* 2001; **107**: 933–41.
22 Miller C, Becker DJ. Removing pigmentation by dermabrading nevi in infancy. *Plast Reconstr Surg* 1979; **32**: 124–6.
23 De Raeve LE, De Coninck AL, Dierickx PR, Roseeuw DI. Neonatal curettage of giant congenital melanocytic nevi. *Arch Dermatol* 1996; **132**: 20–2.
24 Rompel R, Moser M, Petres J. Dermabrasion of congenital nevocellular nevi: experience in 215 patients. *Dermatology* 1997; **194**: 261–7.
25 Bohn J, Svensson H, Aberg M. Dermabrasion of large congenital melanocytic naevi in neonates. *Scand J Plast Reconstr Surg Hand Surg* 2000; **34**: 321–6.
26 Koot H, de Waard-van der Spek F, Peer C *et al*. Psychological sequelae in 29 children with giant congenital naevi. *Clin Dermatol* 2000; **25**: 598–3.
27 Cox NH, Malcolm A, Long ED. Cases of superficial spreading melanoma and of blue naevus within naevus spilus, with ultrastructural assessment of giant pigment granules. *Dermatology* 1997; **194**: 213–6.
28 Piana S, Gelli MC, Grenzi L *et al*. Multifocal melanoma arising on nevus spilus. *Int J Dermatol* 2006; **45**: 1380–1.

Acquired melanocytic naevi

Synonyms
- Cellular naevus
- Naevocytic naevus
- Mole

Definition. A benign cluster of melanocytic naevus cells arising as a result of proliferation of melanocytes at the dermal–epidermal junction. These may all remain in contact with the basal layer of the epidermis, giving rise to the junctional naevus. In other naevi, some of the naevus cells may migrate into the dermis over time, giving rise to the compound naevus. The end stage of this process is when there are no naevus cells attached to the epidermis and all are lying free in the dermis. This pattern is that of the mature intradermal naevus. A melanocytic naevus is therefore a benign tumour of melanocytes, in which the melanocytes (naevus cells) proliferate for some time but then cease proliferation and differentiate (or senesce) and come to resemble cells of neural or fibroblast lineage. Different types are summarized in Table 54.4.

Aetiology and incidence. Melanocytic naevi are almost universal. They develop through childhood and twin studies provide good evidence that naevus number is predominantly genetically determined [1] with a smaller effect of sun exposure [2]. There are a number of studies from Europe and Australia, which suggest that naevus number is higher in children exposed to more sun, particularly intermittent sun exposure as on sunny holidays [3–6].

Naevi continue to erupt in adult life so that the mean number bigger than 2 mm in diameter in 754 healthy women between the ages of 18 and 46 in the UK was 57 [7]. After this age naevi then involute so that the elderly usually have very few. In a UK study, 30% of 20 to 34 year olds had 50 or more moles compared with 4% of patients between 65 and 75 years old [8]. This natural history of naevi means, therefore, that new naevi developing in later life should be viewed with more suspicion than naevi of similar appearance in younger individuals.

The number of melanocytic naevi is the strongest phenotypic risk factor for melanoma [9] and the genes that control naevus number are therefore candidate melanoma susceptibility genes.

There is some, as yet unexplained, variation in naevus number. Patients with atopic dermatitis may have significantly lower naevus counts than age-matched controls [10] and individuals with Turner's syndrome have larger than average numbers of naevi, although there is no evidence that they have an increased risk of melanoma [11]. Children who have been treated for leukaemia [12] and recipients of renal transplants [13] also have increased numbers of naevi, which is postulated to be a consequence of immune suppression. There is some evidence that survivors of childhood cancer do appear to be at increased risk of melanoma [14] although, as melanoma was not increased as a second malignancy after haematological malignancies, other than possibly after Hodgkin lymphoma [15], it is not clear whether that increased risk is treatment related or genetic.

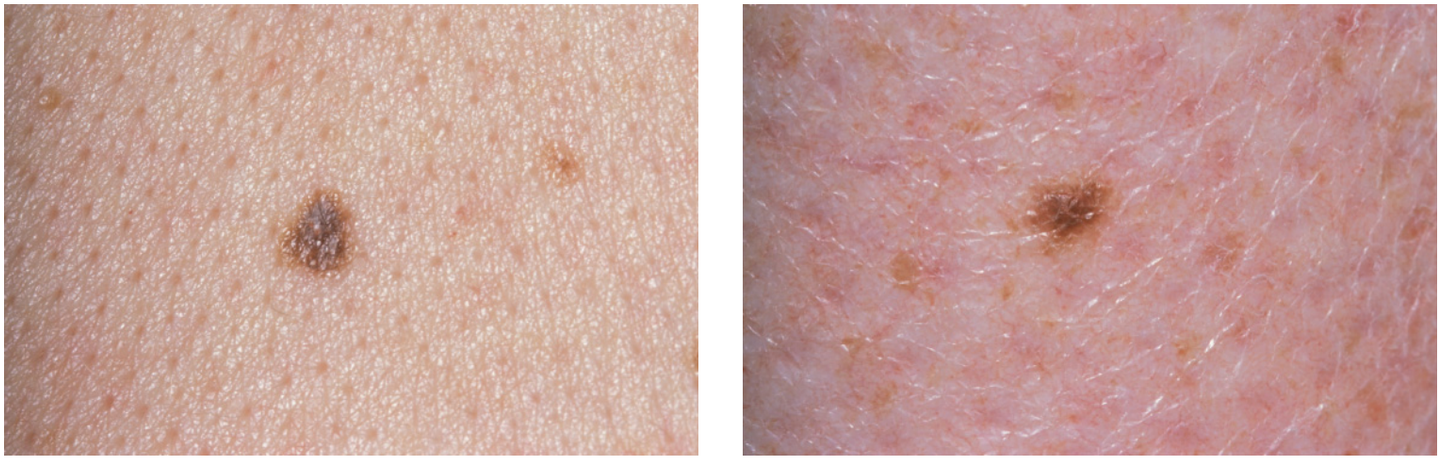
Clinical features. The new naevus is a junctional naevus and is a macular brown lesion, which may show pigment lying along the normal skin markings. It may have a slightly irregular lateral margin because of this, and may have a large diameter of up to 10 mm. The pigmentation tends to be uniform and regular (Fig. 54.23). In some body sites, such as the limbs, junctional naevi may

Table 54.4 Overview of acquired melanocytic naevi.

Naevus type	Subtype	Pathological characteristics	Significance	Treatment
Common acquired melanocytic naevus	Junctional	Benign proliferations of melanocytes in the epidermis	Normal finding but increased numbers of naevi are a risk factor for melanoma	None
	Compound	Benign proliferations of melanocytes in the epidermis, showing evidence of migration of cells into the dermis and 'maturation' of those cells within the deeper dermis	Normal finding but increased numbers of naevi are a risk factor for melanoma	None
	Dermal	Benign tumours of melanocytes in which there is no longer epidermal proliferation; the naevus cells have migrated into the dermis and matured there	Normal finding but increased numbers of naevi are a risk factor for melanoma	None
	Balloon cell naevus	Compound naevus with balloon cells (the melanocyte cytoplasm is foamy)	None	None
	Naevi of unusual sites such as the nail bed, palms and soles and genitalia	More likely to have more atypical junctional proliferation of melanocytes. However, the criteria used for the diagnosis of melanoma in these sites remain the same	None usually	Excise if there are atypical clinical features as for any naevus elsewhere
	Halo naevus	Dense lymphocytic infiltrate in the early phase and subsequent removal of naevus cells	None	None in the absence of atypical features clinically
	Meyerson's naevus	Benign naevus with overlying spongiosis of the epidermis	None	The eczematous component should be treated and the naevus re-examined
	Naevus en cockarde	None	None: unusual rosette-like variant of no significance	None
Spitz naevus	Classical type	See text	Differentiation from melanoma is the key	Excision except for very bland lesions in young children
	Pigmented spindle cell naevus of Reed	See text	Differentiation from melanoma is the key	Excision to exclude melanoma
	Atypical spitzoid tumour of unknown malignant potential (STUMP)	See text	Should be managed as for melanoma	Treat as for melanoma
Blue naevus	Common	Spindle or dendritic melanocytes within the dermis, containing pigment even deeply in the dermis (which naevus cells in acquired naevi do not do)	None save differentiation from a melanoma	None
	Cellular blue naevus	As for the common blue naevus except that the dermal naevus cells are more numerous and extend deeply even up to the fat	None save differentiation from a melanoma	
	Combined blue and acquired naevus	Histological features of both blue and acquired naevi	None	None
	Deep penetrating naevus	Larger than most naevi with extension of naevus cells deep into the dermis with a wedge shape (base abutting onto the epidermis)	None save distinction from melanoma	Excision to exclude melanoma is usual because the appearance of the naevus may be unusual
Atypical or dysplastic naevus	Junctional or compound	Characteristic architectural and cytological atypical (see text)	Precursors, and marker, of risk for melanoma although the vast majority behave in an entirely benign way	Excise only to exclude melanoma

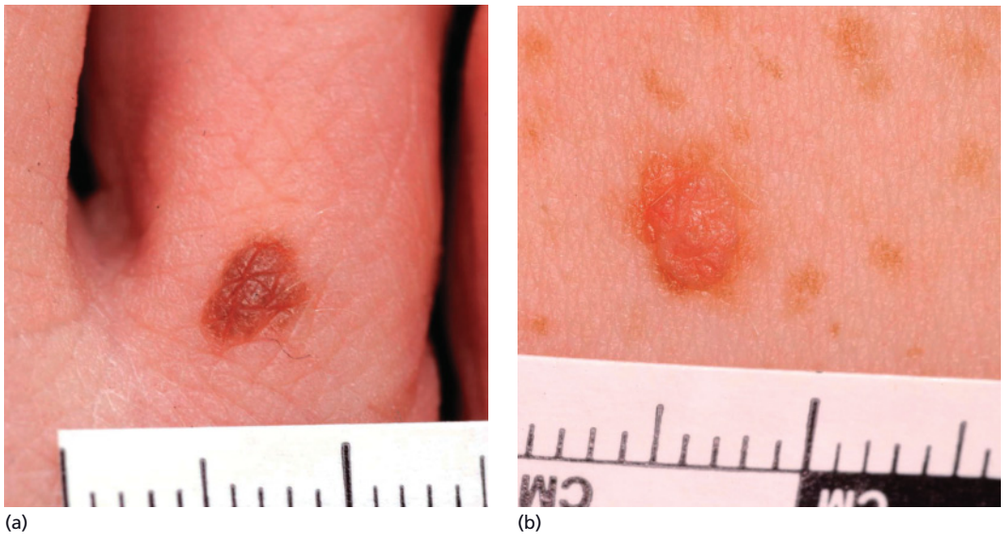
remain unchanged through much of adult life, but the majority do 'mature' with age, becoming first a 'compound naevus' and then an 'intradermal naevus'.

The compound naevus usually slowly becomes raised above the epidermal surface and may be round or oval (Fig. 54.24). The colour varies with the natural pigmentation of the patient and may be very dark, but the majority become paler with age. There is usually little if any pigment on the flat surrounding epidermis. It is important to recognize that slow elevation and the transformation of a macular melanocytic naevus to a palpable symmetrical,



(a) (b)

Fig. 54.23 Two junctional naevi: macular brown lesions which are composed of a proliferation of melanocytes at the dermoepidermal junction.



(a) (b)

Fig. 54.24 Two compound melanocytic naevi in which junctional melanocytes persist but senescence of melanocytes has also occurred and those cells lie within the dermis.

evenly pigmented symmetrical papule over time, is not a sign of malignant change but a normal maturation pattern of these naevi.

Intradermal naevi are frequently raised, dome-shaped, non-pigmented nodules, most commonly seen on the face (Figs 54.25 & 54.26). There are often some overlying telangiectatic vessels (leading to diagnostic confusion with basal cell carcinomas) and outgrowth of one or two coarse terminal hairs is common. A proportion in some body sites, such as the flexures, may become skin tags with time.

Inflammation within intradermal naevi may occur, as a result of bacterial infection in hair follicles or granulomatous inflammation. These changes often cause alarm for patients and their family doctors, but the symptoms associated develop 'overnight' and it is useful to reassure those concerned that acute changes like this are rarely indicative of malignant change. Fragments of hair shaft can often be demonstrated histologically. The inflammation may recur and leave a fibrous nodule, or one that goes on to calcification or even ossification.

The balloon cell naevus is a subtype of compound melanocytic naevus, which has a predominant population of cells with a high volume of foamy cytoplasm [16]. These are called balloon cell naevi because of their pathological appearance. The pathological picture is striking, but there is no known biological significance. There is also a malignant counterpart of balloon cell melanoma, but the balloon cell naevus is not a precursor to balloon cell melanoma.

Naevi in unusual sites

Naevi on the palms and soles may cause concern because they are relatively infrequent and because public education has in the past suggested that they are easily confused with acral lentiginous melanoma. It is also recognized that histologically naevi in these sites show more architectural and mild cytological atypia [17]. In fact, naevi in these sites are not so rare and as they behave as do junctional naevi in other sites, they can be distinguished from melanoma. The incidence of pigmented naevi on the palms, soles



(a) (b)

Fig. 54.25 Two mature dermal naevi, one of which has prominent vessels which can cause confusion with basal cell carcinomas. In these naevi, junctional proliferation of melanocytes has ceased and all the melanocytes are senesced and lie in the dermis.

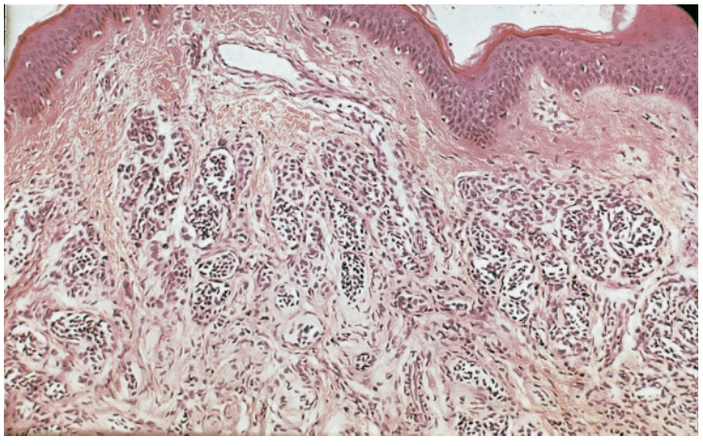


Fig. 54.26 Histology of intradermal naevus. Note the normal overlying epidermis and the maturation of dermal naevus cells, with neural appearance at lower levels.

and genitalia has been studied in a large series of normal young men [18], and more than 10% of the sample were found to have one or more. They should therefore be managed as junctional naevi elsewhere.

Conjunctival naevi are similar in their behaviour and histology to cellular naevi of the skin; and the same clinical changes would evoke the same concern.

Naevi of the nail matrix or bed may present as a longitudinal brown stripe on the underside of the nail plate (Chapter 65). There may be difficulty in distinguishing such lesions from early subungual melanoma. Benign naevi and melanoma both originate in the nail matrix and therefore typically produce a linear band of pigmentation along the length of the nail. However, as applies to melanoma at other sites, subungual melanoma has a disorganized irregular appearance, so that the pigmented band of a melanoma appears later in life than those due to naevi, tends to widen progressively and shows variable colour. Due to rapid growth, the proximal diameter is wider than the distal so the pigmented band appears funnel-shaped (see Fig. 54.63 below). Dermoscopy can be used to improve the clinical diagnosis of such lesions, demonstrating irregular pigmentation [19,20].

Pathology. The pattern of evolution of pigmented naevi has been deduced by pathological examination of a large number of lesions removed at different ages. Elder and Murphy describe how normal melanocytes are rarely seen in contact with each other, being normally surrounded by keratinocytes even in lentigos, but in naevi proliferative groups of contiguous cells are seen [21]. In childhood, over 90% of naevi are *junctional* and show melanocyte proliferation at the dermoepidermal junction to form small clusters of cells that indent both the overlying epidermis and the underlying papillae. The cells have abundant cytoplasm containing melanin granules. The majority of naevi on the palms and soles, and also on the vulva, appear to be junctional naevi.

The next stage occurs when some of these melanocytes migrate into the dermis, where they form nests and columns of cells. In the *compound* naevus both junctional proliferation and dermal cells are present. The dermal cells accumulate in the papillary body and extend more deeply around appendages and neurovascular bundles. The more superficial cells (type A) remain recognizable as naevus cells, continuing to form melanin, which is taken up by melanophages in the stroma. The deeper cells (type B) are smaller and usually contain no melanin. The more superficial cells may throw the epidermis into a series of folds by expanding dermal papillae (so that the naevus is clinically warty in appearance). The deeper cells are arranged as a band (type B) or as arborizing columns in the deeper dermis, when the cells become spindle shaped (type C) and more closely resemble cells of neural or fibroblast lineage. Thus, as cells migrate into the dermis they are at first similar to junctional naevus cells, but over time lose the characteristics of melanocytes.

When the junctional melanocytes stop proliferating, and the overlying epidermis returns to normal, the naevus becomes *intradermal*. Many intradermal naevi have neuroid cells in their deeper parts, and some are composed of little else. These neural areas in

the deeper areas of intradermal naevi are sometimes referred to as Masson's naevic corpuscles, after Pierre Masson who first evolved the theory of evolution of melanocytic naevi [22]. The stroma around the dermal naevus cells is loose and fibrillar, the nests of cells are often enclosed by flattened cells that resemble endothelium and may give an erroneous impression of naevus cells in vessels. Multinucleated naevus cells are commonly seen, but mitotic figures are rare and occur only in the type A cells. The end stage of a melanocytic naevus is a flesh-coloured, pedunculated skin tag in which very few naevus cells are observed. Pigment is sparse and fat cells may be present. The evolution of neural like cells with age has led some to suggest that melanocytic naevi are hamartomas, but they are more likely to be proliferative lesions [23] and that as the cells cease proliferation and senesce, they have a more 'neural' phenotype. Understanding why melanocytes proliferate and then senesce is crucial to understanding tumourigenesis [24].

Diagnosis. In older adults, there may be difficulty in clinical differentiation between seborrhoeic keratoses (Chapter 52) and larger papillomatous compound naevi. The seborrhoeic keratosis usually has a 'stuck-on' appearance with its bulk above the normal skin contour, and the colour is usually more grey-brown than the typical melanocytic naevus. In addition, the surface is usually dull and pitted, with a tendency to crumble, and does not reflect light in the same way as naevi.

The most important clinical differential diagnosis is from early malignant melanoma. A history of very rapid growth, over days rather than weeks, and tenderness suggests the development of an underlying infection/granuloma rather than malignant change. Features suggestive of an early malignant melanoma either developing *ab initio* or in a pre-existing naevus are progressive change in size (surface area), shape and colour. Typically, melanomas develop irregularity of outline and the presence in the lesion of several shades of brown, red, blue or black. Melanomas do sometimes itch or produce at least a changed sensation, but itch poorly differentiates between melanoma and benign naevi.

The techniques of dermoscopy and of computerized diagnosis are discussed in the section on malignant melanoma (p. 54.38). Several groups have produced useful atlases of the clinical dermatoscopic appearances of melanocytic naevi and the differences between these naevi and malignant melanoma. Dermoscopy is an essential technique used to distinguish benign from malignant, and must be learnt by all dermatologists.

Management. The management of naevi is essentially that of differentiating benign maturing naevi from those that are behaving atypically, and which therefore might either be melanomas or naevi having the potential to develop into melanomas (such as severely atypical or dysplastic naevi). The keys to the diagnosis are the history of the lesion, and its appearance to the naked eye and the dermoscopic appearance. Thus a pigmented lesion, which arises in childhood and grows progressively in size in the following months is likely to be benign, but a similar story in a 50 year old should be viewed as suspicious. Normal junctional naevi may show minor variations in shape and colour but are essentially symmetrical and the variation in colour is usually limited to shades of brown. Severely atypical naevi and melanomas tend to be asymmetrical and the colours tend to be mixtures of browns, grey/blues, reds and blacks (see Figs 54.42–54.45 below). Dermoscopy is essential in order to examine the pigment pattern for irregularity, as described below.

If a melanocytic naevus is excised for whatever reason, it should always be sent for pathological examination. Partial removal must be avoided, both because this may lead to sampling error and the wrong diagnosis, and in order to avoid failure to completely remove the deeper dermal cells. When this occurs, residual naevus cells may proliferate soon after excision and give rise to a pathological picture very like an early melanoma. This picture has been termed 'pseudomelanoma' or, more appropriately, a traumatically activated naevus. This can give rise to needless anxiety and is avoidable. Elder and Murphy suggest that the observation of pigment beyond the original scar suggests recurrent melanoma rather than the benign simulant [21].

Halo naevus

Synonym
- Sutton's naevus

Definition. A melanocytic naevus surrounded by a depigmented halo of otherwise normal skin.

Incidence and epidemiology. Halo naevi are relatively common, particularly in older children and young teenagers. They are frequently multiple. They are thought to result from immunologically mediated host responses to a naevus: there is some laboratory evidence for local and circulating immunological T-cell activation in affected patients [25].

Clinical features. These lesions have a characteristic appearance and progression. A halo of depigmentation appears around a pre-existing melanocytic naevus, and on white skin this will usually be seen during the summer months when the rest of the epidermis has acquired a tan, showing the non-tanned halo in sharp contrast to the normal skin (Fig. 54.27). The back is the commonest site and several naevi may develop haloes simultaneously, while other adjacent naevi remain unchanged. Over the next few months, the central naevus will gradually disappear leaving a macular area of non-pigmented skin. This depigmented area may persist for years and may never, or only gradually, return to a normal colour. On biopsy, all traces of the original naevus will be found to have disappeared.

Pathology. These lesions are variants of compound melanocytic naevi, and at the time of appearance of the halo they show a very striking lymphocytic infiltrate admixed with the intradermal naevus cells. The use of DOPA stains will reveal a loss of epidermal melanocytes in the halo area.

Management. Reassurance rather than excision is recommended in young people, particularly if the lesions are multiple. The patient should be warned that the depigmented areas will burn in

sunlight because of the reduced numbers of melanocytes and should be advised to use a sunscreen.

In older patients, the differential diagnosis may include an early superficial spreading melanoma with surrounding depigmentation. In this case the surrounding area of depigmentation is usually irregular, and the central pigmented area may also be irregular in both shape and pigmentation. The central area has dermoscopic appearances suggestive of melanoma [26] whereas the dermoscopic appearance of a halo naevus is bland. If there is any clinical doubt, excision biopsy and pathological confirmation must be obtained.

Meyerson's naevus [27]

This name is used to describe a melanocytic naevus that has developed an associated inflammatory reaction, which looks like eczema. Meyerson's naevus is a similar lesion to the halo naevus and they may coexist although in Meyerson's naevus the central naevus does not usually subsequently disappear [28], although it may do so [29].



Fig. 54.27 Clinical appearance of a halo naevus.

Clinical features. These lesions present as melanocytic naevi with associated epidermal scaling and a halo of inflammation. The original report was of multiple naevi developing this associated inflammatory reaction simultaneously. The naevus may be pruritic, and there may be overlying scaling and the appearance is of a naevus with superimposed discoid eczema.

Pathology. The pathology is usually that of a banal, usually compound, naevus with associated spongiotic dermatitis in the overlying dermis.

Treatment. These are benign naevi and it is reasonable in the first instance to treat for 1–2 weeks with a moderately potent topical steroid before re-examination. Normally, the secondary eczematous reaction will settle and examination with dermoscopy can be carried out to ensure that the underlying naevus is benign (Fig. 54.28).

Cockade naevus

Synonyms
- Kokardennaevus
- Naevus en cocarde

This rare variant of the pigmented naevus was first described by Mehregan and King in 1972 [30]. The lesion is named because of its resemblance to a rosette. All cases so far reported are in young patients with multiple, target-like naevi showing concentric circles of increased melanin pigmentation. The central lesion in all cases would appear to be a junctional naevus (Fig. 54.29).



(a)



(b)

Fig. 54.28 (a) Meyerson's naevus in which an eczematous response to the naevus occurred, which cleared with 2 weeks' treatment with topical steroids (b). This allowed dermoscopic examination of the naevus, which then looked banal.

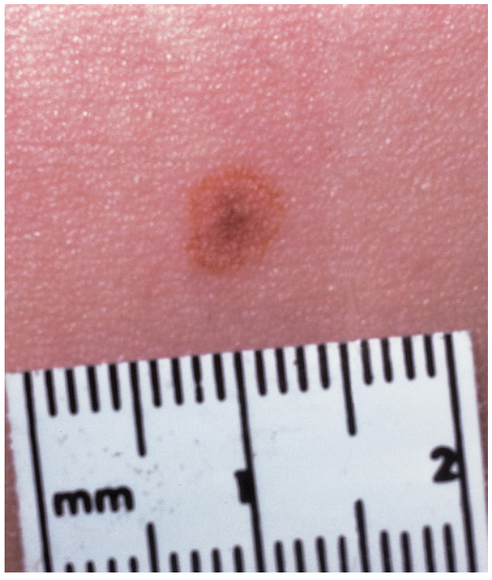


Fig. 54.29 Cockade naevus (naevus en cocarde). Note the darker outline to this lesion.

References

1 Zhu G, Duffy DL, Eldridge A *et al*. A major quantitative-trait locus for mole density is linked to the familial melanoma gene CDKN2A: a maximum-likelihood combined linkage and association analysis in twins and their sibs. *Am J Hum Genet* 1999; **65**: 483–92.
2 Wachsmuth RC, Turner F, Barrett JH *et al*. The effect of sun exposure in determining nevus density in UK adolescent twins. *J Invest Dermatol* 2005; **124**: 56–62.
3 Gefeller O, Tarantino J, Lederer P *et al*. The relation between patterns of vacation sun exposure and the development of acquired melanocytic nevi in German children 6–7 years of age. *Am J Epidemiol* 2007; **165**: 1162–9.
4 Green A, Siskind V, Hansen ME *et al*. Melanocytic nevi in schoolchildren in Queensland. *J Am Acad Dermatol* 1989; **20**: 1054–60.
5 Kelly JW, Rivers JK, MacLennan R *et al*. Sunlight: a major factor associated with the development of melanocytic nevi in Australian schoolchildren. *J Am Acad Dermatol* 1994; **30**: 40–8.
6 Rodvall Y, Wahlgren CF, Ullen H, Wiklund K. Common melanocytic nevi in 7-year-old schoolchildren residing at different latitudes in Sweden. *Cancer Epidemiol Biomarkers Prev* 2007; **16**: 122–7.
7 dos Santos Silva I, Higgins C, Abramsky T *et al*. Overseas sun exposure, nevus counts, and premature skin aging in young English women: a population-based survey. *J Invest Dermatol* 2009; **129**: 50–9.
8 Bataille V, Grulich A, Sasieni P *et al*. The association between naevi and melanoma in populations with different levels of sun exposure: a joint case-control study of melanoma in the UK and Australia. *Br J Cancer* 1998; **77**: 505–10.
9 Gandini S, Sera F, Cattaruzza MS *et al*. Meta-analysis of risk factors for cutaneous melanoma: I. Common and atypical naevi. *Eur J Cancer* 2005; **41**: 28–44.
10 Broberg A, Augustsson A. Atopic dermatitis and melanocytic naevi. *Br J Dermatol* 2000; **142**: 306–9.
11 Zvulunov A, Wyatt DT, Laud PW, Esterly NB. Influence of genetic and environmental factors on melanocytic naevi: a lesson from Turner's syndrome. *Br J Dermatol* 1998; **138**: 993–7.
12 Hughes B, Bailey CC. Excess benign melanocytic naevi. *BMJ* 1989; **299**: 854–5.
13 Szepietowski J, Wasik F, Szepietowski T. Excess benign melanocytic naevi in renal transplant recipients. *Dermatology* 1997; **194**: 17–9.
14 Inskip PD, Curtis RE. New malignancies following childhood cancer in the United States, 1973–2002. *Int J Cancer* 2007; **121**: 2233–40.
15 Maule M, Scelo G, Pastore G *et al*. Risk of second malignant neoplasms after childhood leukemia and lymphoma: an international study. *J Natl Cancer Inst* 2007; **99**: 790–800.
16 Schrader WA, Helwig EB. Balloon cell nevi. *Cancer* 1967; **20**: 1502–14.
17 Evans MJ, Gray ES, Blessing K. Histopathological features of acral melanocytic nevi in children: study of 21 cases. *Pediatr Dev Pathol* 1998; **1**: 388–92.
18 Cullen SI. Incidence of nevi. Report of survey of the palms, soles, and genitalia of 10,000 young men. *Arch Dermatol* 1962; **86**: 40–3.
19 Braun RP, Baran R, Le Gal FA *et al*. Diagnosis and management of nail pigmentations. *J Am Acad Dermatol* 2007; **56**: 835–47.
20 Thomas L, Dalle S. Dermoscopy provides useful information for the management of melanonychia striata. *Dermatol Ther* 2007; **20**: 3–10.
21 Elder DE, Murphy GF. *Melanocytic Tumors of the Skin*. Washington, DC: American Registry of Pathology, in press.
22 Masson P. My conception of cellular nevi. *Cancer* 1951; **4**: 9–38.
23 Krengel S. Nevogenesis—new thoughts regarding a classical problem. *Am J Dermatopathol* 2005; **27**: 456–65.
24 Gray-Schopfer VC, Cheong SC, Chong H *et al*. Cellular senescence in naevi and immortalisation in melanoma: a role for p16? *Br J Cancer* 2006; **95**: 496–505.
25 Baranda L, Torres-Alvarez B, Moncada B *et al*. Presence of activated lymphocytes in the peripheral blood of patients with halo nevi. *J Am Acad Dermatol* 1999; **41**: 567–72.
26 Kolm I, Di Stefani A, Hofmann-Wellenhof R *et al*. Dermoscopy patterns of halo nevi. *Arch Dermatol* 2006; **142**: 1627–32.
27 Meyerson LB. A peculiar papulosquamous eruption involving pigmented nevi. *Arch Dermatol* 1971; **103**: 510–2.
28 Brandt O, Christophers E, Folster-Holst R. Halo dermatitis followed by the development of vitiligo associated with Sutton's nevi. *J Am Acad Dermatol* 2005; **52**: S101–4.
29 Ramon R, Silvestre JF, Betlloch I *et al*. Progression of Meyerson's naevus to Sutton's naevus. *Dermatology* 2000; **200**: 337–8.
30 Mehregan AH, King JR. Multiple target-like pigmented nevi. *Arch Dermatol* 1972; **105**: 129–30.

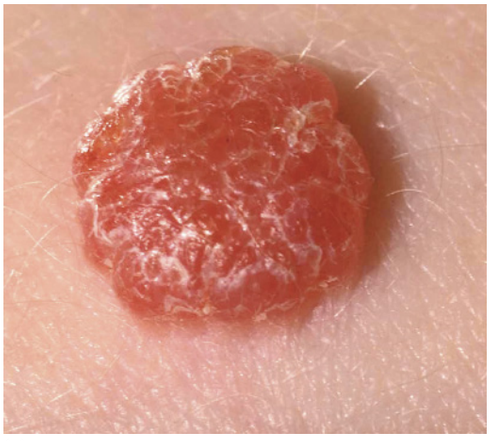
Spitz naevus

Synonyms
- Spindle and epithelioid cell naevus
- Spitz tumour
- Juvenile melanoma

Definition. An uncommon type of melanocytic lesion, seen most commonly in children but also in adults, which has distinctive pathological features first described by Sophie Spitz as an unusual type of melanoma [1], but subsequently called benign. The entity has been controversial ever since. Whilst a characteristic clinical and histological appearance of a benign lesion usually called a Spitz naevus is recognized, there are three types of lesion that are often difficult to distinguish from each other: Spitz naevus, spitzoid melanoma and an entity that has become increasingly diagnosed an 'atypical spitzoid tumour of unknown malignant potential', reflecting the difficulties of pathological interpretation of spitzoid lesions. Much controversy still surrounds the pathology of spitzoid lesions, as reviewed [2,3], and it is clear that we have much yet to learn.

Incidence. Spitz naevi are most common under the age of 14 years; indeed 50% are thought to occur under this age, around 25% between the ages of 14 and 30 and 25% over the age of 30 years [4].

Clinical features. The classic Spitz naevus usually appears in early childhood as a firm, rounded or dome shaped, red or reddish-brown symmetrical nodule. The red colour is due to increased



(a)



(b)

Fig. 54.30 Two classical Spitz naevi in children. The differential diagnosis is often that of a haemangioma.

vascularity and the naevus can usually be bleached by firm pressure or diascopy to show the residual degree of true melanin pigmentation (Figs 54.30 & 54.31).

The lesions usually grow rapidly over a period of 3–6 months and may reach diameters of 1–2 cm. The surface can remain smooth, with a thin, fragile, overlying epidermis. This may cause bleeding and crusting after minor injury, causing diagnostic confusion with haemangiomas or pyogenic granulomas. The commonest sites for Spitz naevi are the face, particularly the cheeks, and the legs (in young adults), but other areas may be affected. After rapid initial growth they may remain static for years. Spitz naevi may be more pigmented in some patients, particularly adults.

The spindle cell naevus of Reed is a more deeply pigmented variant, which was first described in 1975 [5]. The majority of patients reported with such lesions are young females, and they are most commonly seen on the thighs. They are densely pigmented, irregularly shaped dark-brown or black nodules and are usually isolated (Fig. 54.32a).

Spitz naevi may have a characteristic dermoscopic appearance, the most common being a 'starburst' pattern (Fig. 54.32b) [4]. Some have a more globular pattern however, and others a multicomponent pattern.

A striking and unusual variant is that of *multiple Spitz naevi*. In these very rare cases multiple Spitz naevi erupt over a period of time [6]. The aetiology is unknown although authors have suggested that they may develop in relation to triggers [7] such as sunburn. An important differential diagnosis in these cases is epidermotropic metastatic melanoma.

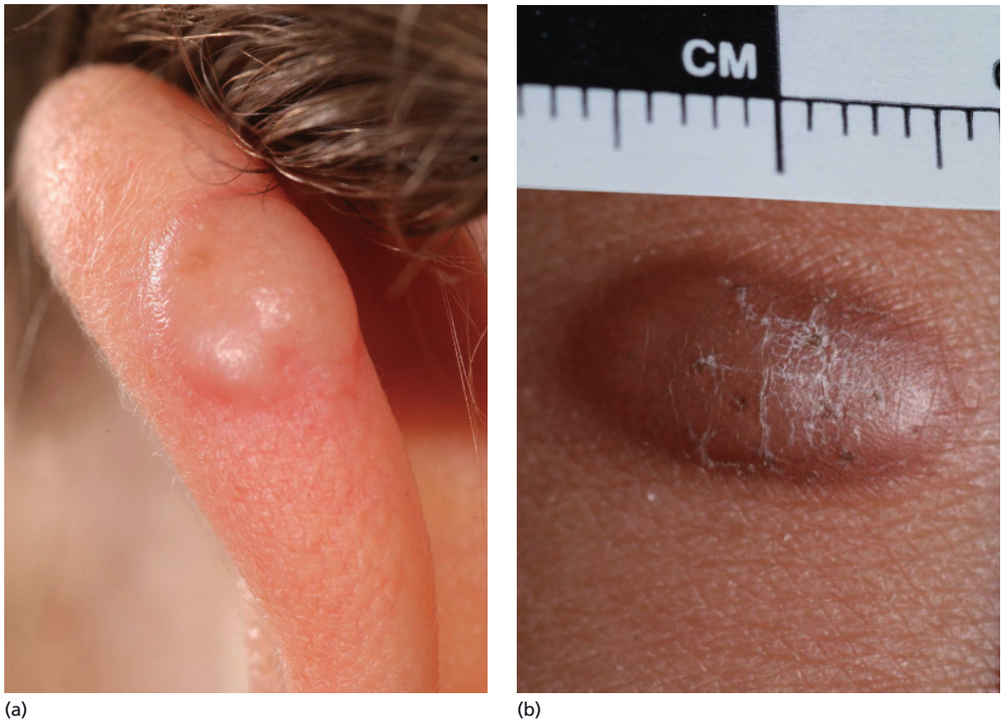
Agminate Spitz naevi are lesions seen in childhood where a group of Spitz naevi develop on skin which looks normal other than for the presence of a macular pigmentary background. The individual Spitz naevi develop rapidly and thereafter remain relatively static. In some ways these lesions resemble speckled naevi and it is likely that all are subtypes of congenital pigmented naevus.

A rare subtype of the Spitz naevus is a *desmoplastic naevus* (desmoplastic Spitz naevus), seen most commonly in adults [8]. These are usually firm and may show little or no clinically visible melanocytic pigmentation, to appear as pink or red, firm, raised nodules. The lesions may be woody hard, and the clinical differential may include a keloid, although there is no history of injury (Fig. 54.33).

Some authors have developed the concept of a metastasizing Spitz as being different to melanoma. It seems unlikely, however, that there is a fundamental difference between a spitzoid lesion, which spreads to a regional node, and melanoma, although it is possible that spitzoid melanoma may have a better prognosis. This remains an area of unresolved controversy, which requires long-term investigation.

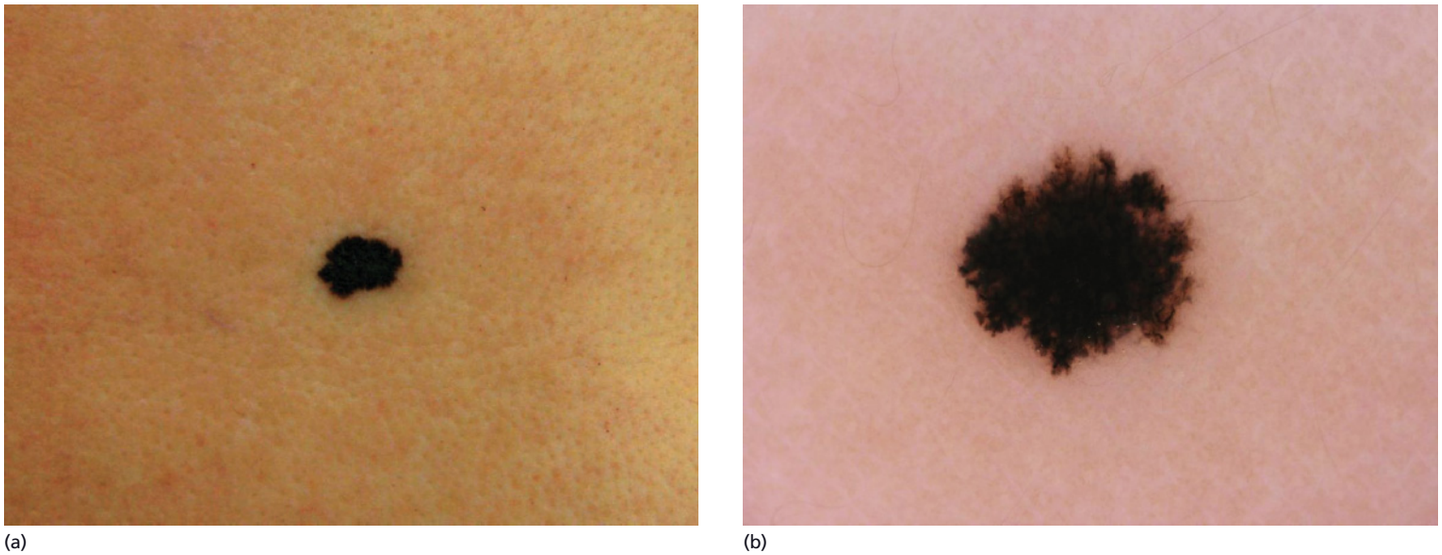
Pathology. The 'classic' Spitz naevus typically is a symmetrical and well-defined compound naevus. There is a degree of epidermal acanthosis overlying the naevus cells, in the absence of any upward epidermal invasion by naevus cells. The melanocytes at the dermal–epidermal junction are often separated from the underlying dermis by a cleft, and may be associated with amorphous pink globules. These globules are thought to be degenerating keratinocytes and are called *Kamino bodies*. They are frequently seen in Spitz naevi, but their presence is neither totally sensitive nor specific for Spitz naevi, as they may also be present in early melanoma.

The Spitz naevus cells may be either spindle-shaped, and stream into the dermis in interlacing bundles, or epithelioid, and arranged in clusters with giant and multinucleated naevus cells among them. Mitotic figures may occur but abnormal mitoses are not seen. Mitotic figures are rarer in the deeper naevus cells, and their presence should alert the observer to the possibility that the lesion is, in fact, a spitzoid melanoma. The deepest naevus cells show some degree of maturation and are usually smaller than those seen at the dermal–epidermal junction. The dermal vessels are usually dilated, and the stroma may be oedematous and infiltrated with lymphocytes. Melanin is rarely abundant, and may often be absent.



(a) (b)

Fig. 54.31 Two Spitz naevi showing less typical appearances: both were excised.



(a) (b)

Fig. 54.32 (a) The naked-eye appearance of a typical pigmented spindle cell naevus of Reed in a child and (b) the corresponding dermoscopic appearance. (Courtesy of Dr S. Puig, Hospital Clinic Barcelona, IDIBAPS.)

In the variety known as a pigmented spindle cell naevus of Reed, there is well-demarcated junctional melanocytic activity with large quantities of melanin pigment. Spindle-shaped melanocytes proliferate downwards towards the dermis, but there is no upward movement of naevus cells through the epidermis, and usually very little, if any, intradermal component. Some naevus cells may be seen in the papillary dermis, but these naevi do not involve the reticular dermis. A sparse lymphocytic infiltrate is seen at the base of the naevus cells, but the lesion is relatively small and circumscribed. As with 'classical' Spitz naevi, symmetry is an important feature.

The problem is that many lesions with clinical and histological characteristics of Spitz naevi have some atypical features, which cause concern (Fig. 54.34), so that the most important and difficult pathological differential diagnosis is the separation of true benign Spitz naevi from spitzoid malignant melanoma. Two useful studies have tried to identify pathological factors that may help in this situation. Crotty and colleagues [9] have identified symmetry of

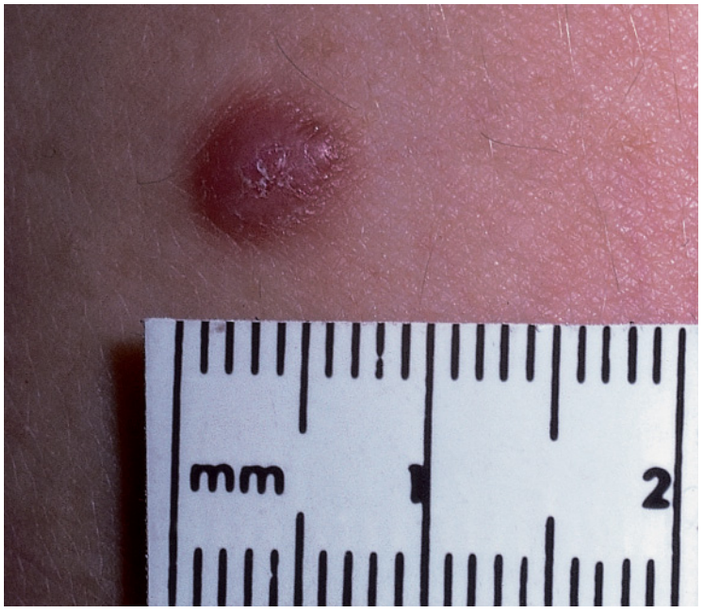


Fig. 54.33 Desmoplastic Spitz naevus.

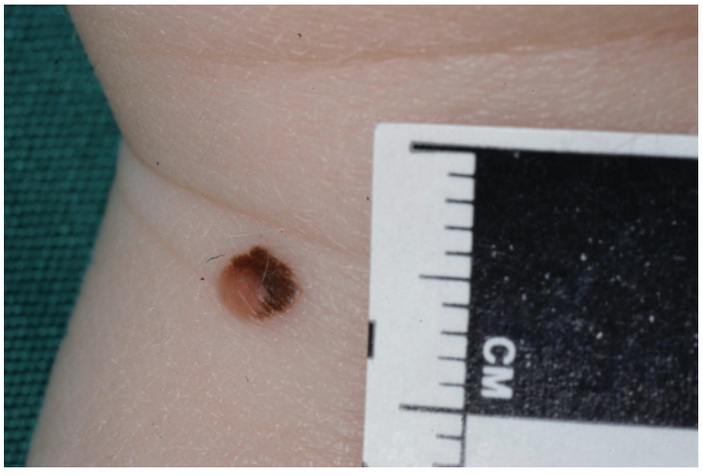


Fig. 54.34 This child developed a pigmented lesion on the wrist at the age of 1 year. At 2 and a half years the lesion was asymmetrical and showed variation in colour. Although clinically likely to be a benign Spitz nevus, prompt excision was necessary.

the lesion from side to side, the presence of Kamino bodies and the uniformity of cell nests or sheets in the dermis as features of benign Spitz naevi. In contrast, they identify abnormal mitoses, mitotic counts of over 2/mm^2 and deep mitoses as suggestive of spitzoid melanoma. Spatz *et al*. [10] have identified age over 10 years, diameter over 10 mm, ulceration, invasion to subcutaneous fat and mitotic activity of over 6/mm^2 as suggestive of spitzoid melanoma rather than Spitz naevi. Whilst these approaches are helpful, even between expert pathologists interobserver variation for spitzoid lesions is significant [11], and metastases have been reported from lesions categorized as 'low risk' [10]. Any atypical features should therefore be regarded with suspicion.

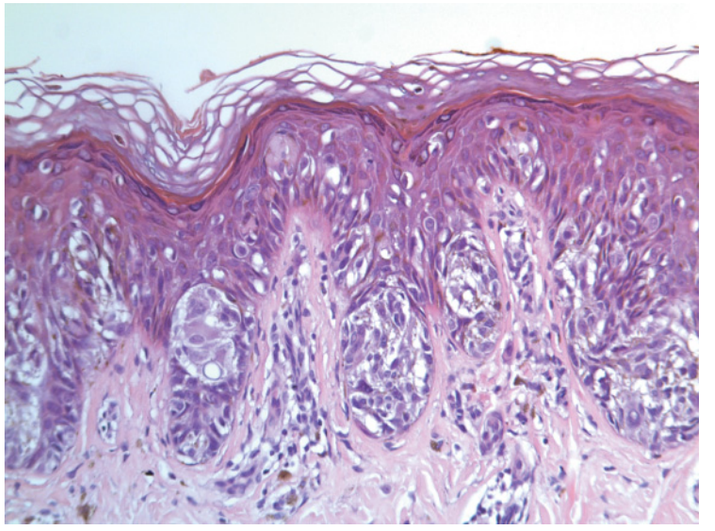


Fig. 54.35 The histological appearance of a classical Spitz naevus, with epitheliod cells and Kamino bodies. (Courtesy of Dr S. Edward, Leeds Teaching Hospitals Trust, Leeds, UK.)

In clinical practice, therefore, it is increasingly common for pathologists to report atypical Spitz naevi as 'atypical spitzoid tumours of unknown malignant potential', or STUMPs [3]. In this case, the norm is to manage the patient as if they had had a melanoma, but to reassure the patient that the lesion may, in fact, be benign although it is preferable to take a cautious view. Given the pathological difficulties around diagnosis, this seems a sensible approach to management.

Molecular biology may ultimately allow better characterization of spitzoid tumours. Comparative genomic hybridization (CGH) has been used, for example, to show differences between Spitz naevi and melanoma [12].

The pathology of the desmoplastic Spitz was well described by Barr *et al.* in 1980 [13] and it has a very striking and characteristic pathological appearance. The lesions are predominantly intradermal, and a relatively small number of naevus cells will be found embedded in thick collagen fibres. The naevus cells are usually distributed singly through the stroma rather than in clumps, and may be very large and bizarre, with copious cytoplasm, which may contain inclusions. The nuclei look unusual but not frankly malignant, and mitotic figures are rare (Fig. 54.35).

Diagnosis. Most Spitz naevi in children are red rather than brown, and may be confused clinically with vascular tumours, pyogenic granuloma, histiocytoma, juvenile xanthogranuloma or granulomas. Pigmented Spitz naevi may resemble compound melanocytic naevi or spindle cell naevi of Reed, but often cause diagnostic confusion with superficial spreading melanomas. Dermoscopy may improve the accuracy of the clinical diagnosis, especially if the lesion has the typical starburst appearance (Fig. 54.32b).

In young children, a lesion typical of a Spitz naevus, being symmetrical and red-brown in appearance, is very unlikely to be a melanoma and would normally not be excised, although review in clinic at 2 to 3 months is essential to ensure that the lesion is not developing any atypical features. In older individuals, or in

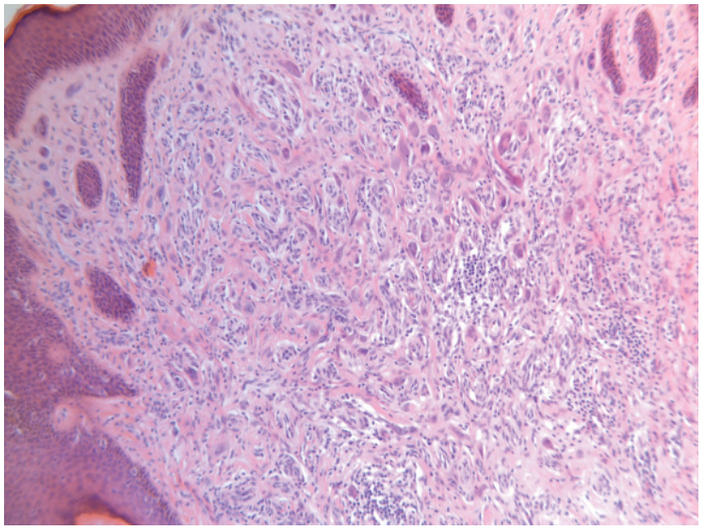


Fig. 54.36 The histological appearance of an atypical spitzoid tumour, showing relative lack of symmetry. (Courtesy of Dr S. Edward, Leeds Teaching Hospitals Trust, Leeds, UK.)

all patients (regardless of age) in which the lesion is asymmetrical or irregular in colour, excision should be carried out to exclude a 'spitzoid' melanoma (atypical spitzoid lesion) (Fig. 54.36). It is said that Spitz naevi are more common in adults on the thigh but rare on the trunk and therefore spitzoid lesions on the trunk of adults [14] would be viewed with particular suspicion. Complete excisions must be carried out, never incisional or punch biopsy. Because of the clinical and histological overlap between Spitz naevi and melanoma, some authors suggest that all spitzoid lesions should be excised [2] and Elder and Murphy suggest that a consensus is emerging towards excision of all [15]. In summary then, it seems reasonable not to remove very typical Spitz naevi in young children unable to tolerate local anaesthetic, but a 3-month review would be sensible. All other clinically spitzoid lesions should be removed in their entirety.

Treatment. Local excision with a narrow margin of 1–2 mm of normal skin is usually required to confirm the clinical diagnosis. Local recurrence has been recorded in both isolated and agminate lesions [16]. In the presence of atypical features (either clinically or histologically), or where the diagnosis of a STUMP is made, the margin of excision should be as for melanoma: 1 cm for tumours of less than 2 mm in thickness; 2 cm or more where the thickness is 2 mm or greater.

There are small reported series of sentinel node biopsies in patients with atypical spitzoid tumours that demonstrate positivity in a proportion [17], supporting the view that such lesions may be melanomas in terms of how they behave. The use of sentinel node biopsy in such patients is subject to the same limitations as for melanoma. In particular there is a no survival benefit.

References

1 Spitz S. Melanomas of childhood. *Am J Pathol* 1947; **24**: 591–609.

2 Barnhill RL. The spitzoid lesion: rethinking Spitz tumors, atypical variants, 'spitzoid melanoma' and risk assessment. *Mod Pathol* 2006; **19** (Suppl. 2): S21–33.

3 Mooi WJ, Krausz T. Spitz nevus versus spitzoid melanoma: diagnostic difficulties, conceptual controversies. *Adv Anat Pathol* 2006; **13**: 147–56.

4 Ferrara G, Argenziano G, Soyer HP *et al*. The spectrum of Spitz nevi: a clinicopathologic study of 83 cases. *Arch Dermatol* 2005; **141**: 1381–7.

5 Reed RJ, Ichinose H, Clark WH Jr, Mihm MC Jr. Common and uncommon melanocytic nevi and borderline melanomas. *Semin Oncol* 1975; **2**: 119–47.

6 Morgan CJ, Nyak N, Cooper A *et al*. Multiple Spitz naevi: a report of both variants with clinical and histopathological correlation. *Clin Exp Dermatol* 2006; **31**: 368–71.

7 Smith SA, Day CL Jr, Vander Ploeg DE. Eruptive widespread Spitz nevi. *J Am Acad Dermatol* 1986; **15**: 1155–9.

8 Cesinaro AM, Foroni M, Sighinolfi P *et al*. Spitz nevus is relatively frequent in adults: a clinico-pathologic study of 247 cases related to patient's age. *Am J Dermatopathol* 2005; **27**: 469–75.

9 Crotty KA, Scolyer RA, Li L *et al*. Spitz naevus versus spitzoid melanoma: when and how can they be distinguished? *Pathology* 2002; **34**: 6–12.

10 Spatz A, Calonje E, Handfield-Jones S, Barnhill RL. Spitz tumors in children: a grading system for risk stratification. *Arch Dermatol* 1999; **135**: 282–5.

11 Barnhill RL, Flotte TJ, Fleischli M, Perez-Atayde A. Cutaneous melanoma and atypical Spitz tumors in childhood. *Cancer* 1995; **76**: 1833–45.

12 Bastian BC, Wesselmann U, Pinkel D, Leboit PE. Molecular cytogenetic analysis of Spitz nevi shows clear differences to melanoma. *J Invest Dermatol* 1999; **113**: 1065–9.

13 Barr RJ, Morales RV, Graham JH. Desmoplastic nevus: a distinct histologic variant of mixed spindle cell and epithelioid cell nevus. *Cancer* 1980; **46**: 557–64.

14 Schmoeckel C, Wildi G, Schafer T. Spitz nevus versus malignant melanoma: Spitz nevi predominate on the thighs in patients younger than 40 years of age, melanomas on the trunk in patients 40 years of age or older. *J Am Acad Dermatol* 2007; **56**: 753–8.

15 Elder DE, Murphy GF. *Melanocytic Tumors of the Skin*. Washington, DC: American Registry of Pathology, in press.

16 Gambini C, Rongioletti F. Recurrent Spitz nevus. Case report and review of the literature. *Am J Dermatopathol* 1994; **16**: 409–13.

17 Urso C, Borgognoni L, Saieva C *et al*. Sentinel lymph node biopsy in patients with 'atypical Spitz tumors.' A report on 12 cases. *Hum Pathol* 2006; **37**: 816–23.

Blue naevus and cellular blue naevus

Definition. A blue or blue-black melanocytic naevus comprised of aberrant collections of pigment-producing but benign melanocytes, in the dermis rather than at the dermoepidermal junction (as in common acquired naevi).

Incidence and aetiology. Blue naevi are relatively common. Their aetiology and pathogenesis is unclear. Some authors view these as equivalents of dermal melanocytic proliferations seen in animals [1]. Uncommon lesions have mixed 'blue' and 'acquired' characteristics (combined naevus, below) and this might suggest that others are variants of common acquired melanocytic naevi. Multiple epithelioid blue naevi may be associated with the Carney complex (Chapter 62).

Clinical features. There is an area of diffuse blue pigmentation, usually slightly raised and smooth surfaced. Blue naevi may be found on any site but patients with facial naevi most often request excision for cosmetic reasons. The cellular blue naevus is seen most often on the extremities, particularly the dorsa of the hands and feet (Fig. 54.37), the buttocks and the face. The onset may be before birth, but lesions frequently first appear around puberty. The blue naevus is usually very symmetrical, and has an



Fig. 54.37 A cellular blue naevus.

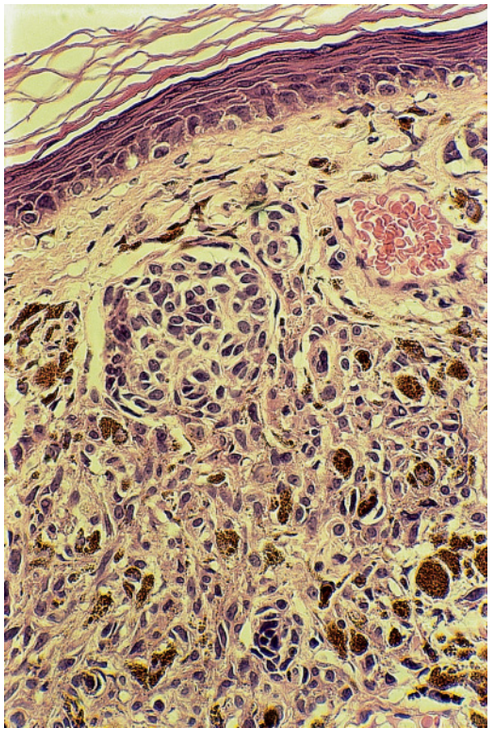


Fig. 54.38 Histology of a blue naevus. Note the normal overlying epidermis with spindle cells and dense pigmentation in underlying dermis.

amorphous, structureless pigment pattern on dermoscopy which may be blue, white or darker in colour [2].

The combined naevus is a rare variant in which there are elements of a blue naevus and a common acquired melanocytic naevus. They may cause concern clinically because of their unusual appearance and are therefore commonly removed.

The deep penetrating naevus is a further rare variant said to be more common on the head and neck [3]. Clinically, it may be a deep blue or black colour with a diffuse, irregular lateral margin. The clinical differential diagnosis is therefore frequently melanoma. The blue appearance is attributed to the 'Tyndall effect', which states that red light penetrating the skin is diffused by the dermis allowing blue light to be reflected by deep pigment.

Progressive growth in blue naevi is rare and would cause concern, although malignant transformation is very rare indeed (below). There is a view that the term malignant blue naevus is confusing and that lesions dubbed 'malignant blue naevi' are just melanomas which resemble blue naevi, or that these are very rare instances of malignant transformation in a blue naevus [4].

Pathology. In the common or classic variety, bipolar and dendritic melanocytes lie singly or in masses in the dermis (Fig. 54.38). The melanocytes tend to be profuse in the lower dermis and are often concentrated around appendages or in the perivascular and perineural areas. Deeper tissues may be involved. The melanocytes are relatively inconspicuous, containing fine granules of melanin dispersed through their cytoplasm. There are varying numbers of melanophages in which the melanin granules are coarse and more closely clumped.

The cellular blue naevus is composed of the same elements as the common blue naevus, but in addition possesses islands of larger cells arranged in a neuroid ('pigmented neurofibroma') or sarcomatoid fashion. The appearance may raise suspicions of malignant melanoma, but the lack of mitotic activity, vascularity or inflammatory reaction, the regularity of the cells and the absence of junctional proliferation in continuity with the cellular masses enable the distinction to be made [5,6].

The compound blue naevus is a more recently described entity [7], with additional dendritic cells in the overlying epidermis. This lesion may clinically be very similar to early malignant melanoma.

The deep penetrating naevus may be considered as a distinct entity [3] or as a variant which frequently has features of both a compound and a blue naevus or Spitz naevus, making it a variant of the so-called combined naevus but with minimal junctional activity. They are larger than most naevi, with extension of naevus cells deep into the dermis in a wedge shape, the base abutting onto the epidermis. The diagnostic feature is the presence of clusters of widely separated but deep naevus cells throughout the dermis. Frequently these clusters are around the skin appendages. The cytology is of a spindle cell population and mitotic figures are rare [8].

Malignant blue naevus is discussed below.

Diagnosis. The blue naevus is characterized by its colour and symmetrical shape and must be differentiated from other dermal melanoses. It is a relatively static, non-progressive lesion.

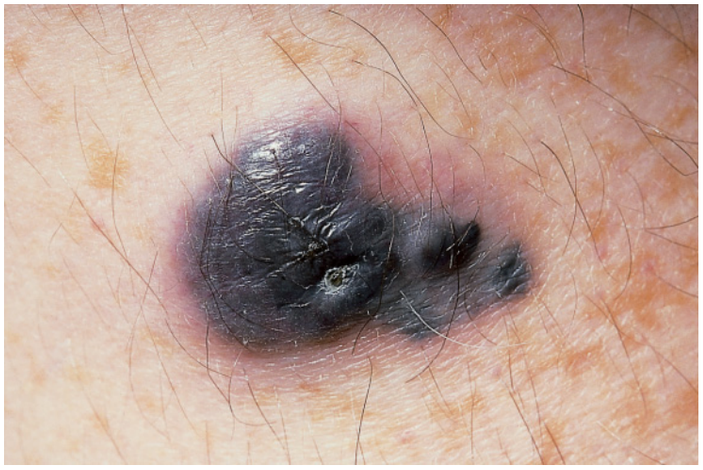


Fig. 54.39 Malignant blue naevus which has arisen in a previous cellular blue naevus. This lesion subsequently metastasized to lymph nodes.

Treatment. None is needed save for distinction from melanoma.

Malignant blue naevus

Definition. A very rare malignancy often confused with melanoma although it is argued that the difference is semantic [4]; in some cases it is not possible to differentiate between classic malignant melanoma and malignant change within a blue naevus.

Pathology. Malignant cells of melanocytic origin are seen in the deeper dermis with no overlying abnormality of epidermal melanocytes. Pathologically there is a sheet-like growth pattern. Necrosis and atypical mitotic figures are diagnostic features which will distinguish these lesions from benign classic or cellular blue naevi [9]. Mitotic figures are rare [10], but the presence of any at all should suggest the diagnosis of melanoma rather than a blue naevus.

Clinical features. Malignant blue naevus usually arises in a cellular blue naevus, and the scalp is the commonest site (Fig. 54.39). Expansion of a previously identified blue naevus should suggest the diagnosis. Metastases do occur [9].

Treatment. Wide surgical excision is required as for other types of melanoma.

References

1 Levene A. On the natural history and comparative pathology of the blue naevus. *Ann Roy Coll Surg* 1980; **62**: 327–34.
2 Ferrara G, Soyer HP, Malvehy J *et al*. The many faces of blue nevus: A clinicopathologic study. *J Cutan Pathol* 2007; **34**: 543–51.
3 Flauta VS, Lingamfelter DC, Dang LM, Lankachandra KM. Deep penetrating nevus: a case report and brief literature review. *Diag Pathol* 2006; **1**: 31.
4 Mones JM, Ackerman AB. 'Atypical' blue nevus, 'malignant' blue nevus, and 'metastasizing' blue nevus: a critique in historical perspective of three concepts flawed fatally. *Am J Dermatopathol* 2004; **26**: 407–30.

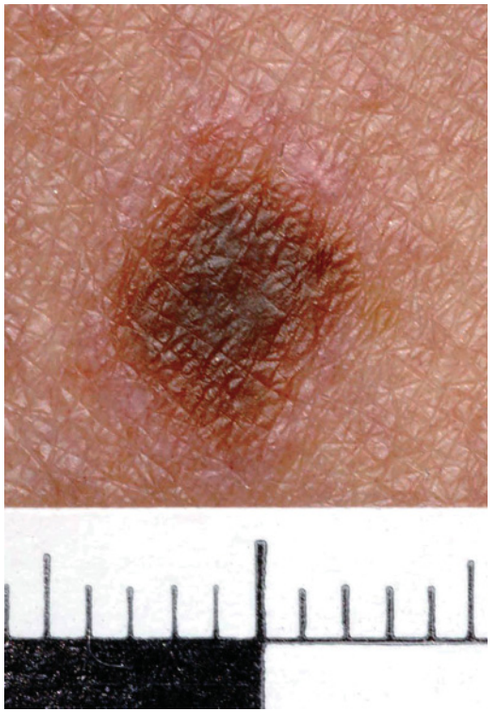


Fig. 54.40 An 'atypical' or dysplastic naevus. Such naevi are clinically defined. They are 5 mm or more in diameter, with a diffuse, or irregular edge and variable pigmentation.

5 Leopold JG, Richards DB. Cellular blue naevi. *J Pathol Bacteriol* 1967; **94**: 247–55.
6 Merkow LP, Burt RC, Hayeslip DW *et al*. A cellular and malignant blue nevus: a light and electron microscopic study. *Cancer* 1969; **24**: 888–96.
7 Ferrara G, Argenziano G, Zgavec B *et al*. 'Compound blue nevus': a reappraisal of 'superficial blue nevus with prominent intraepidermal dendritic melanocytes' with emphasis on dermoscopic and histopathologic features. *J Am Acad Dermatol* 2002; **46**: 85–9.
8 Elder DE, Murphy GF. *Melanocytic Tumors of the Skin*. Washington, DC: American Registry of Pathology, in press.
9 Granter SR, McKee PH, Calonje E *et al*. Melanoma associated with blue nevus and melanoma mimicking cellular blue nevus: a clinicopathologic study of 10 cases on the spectrum of so-called 'malignant blue nevus'. *Am J Surg Pathol* 2001; **25**: 316–23.
10 Pich A, Chiusa L, Margaria E, Aloi F. Proliferative activity in the malignant cellular blue nevus. *Hum Pathol* 1993; **24**: 1323–9.

Clinically atypical naevi

Synonym
- Dysplastic naevus

Definition/pathogenesis. A melanocytic naevus, which is 5 mm or larger in diameter, with an irregular or diffuse edge and variable or mottled pigmentation (Fig. 54.40). Although there are histological correlates, the diagnosis is a clinical one.

Natural history. The natural history of acquired benign naevi is of proliferation of melanocytes until the naevus reaches up to

5 mm in diameter, and the proliferation at the dermoepidermal junction then ceases. The naevus cells migrate down into the dermis but subsequent cellular senescence occurs, resulting in the development of a compound and then a dermal cellular naevus. In an atypical naevus, the melanocyte proliferation continues so that the naevus continues to grow in size beyond the 'usual' size, and the junctional proliferative component may show some features reminiscent of an early melanoma, resulting in some irregularity of shape and colour clinically. Although in the majority of such naevi the melanocytes eventually cease proliferation, resulting in 'maturation' of the naevus as a compound and then a dermal naevus, a proportion of such naevi continue to grow and may evolve into radial growth phase melanoma. Thus, although the majority of atypical naevi behave in a benign manner, they are viewed as lesions exhibiting a more proliferative phenotype than common acquired naevi, and are therefore both markers of risk of melanoma and precursor lesions for melanoma.

Incidence and epidemiology. The term 'dysplastic naevus' was first used by Elder [1] as a pathological description of a sporadically occurring melanocytic naevus, which was clinically larger and more irregular, and showed a constellation of pathological features that also distinguished it from common or banal naevi. Earlier, Clark *et al*. [2] and Frichot *et al*. [3] had separately, but almost simultaneously, described families in which multiple primary melanomas were much more common than expected and who also had large numbers of unusual naevi—the BK mole syndrome or FAMMM syndrome (*f*amilial *a*typical *m*ultiple *m*ole *m*elanoma syndrome) [4]. The naevi seen in these syndromes have come to be recognized as 'atypical naevi'. Technically, atypical is a clinical description and dysplasia is determined histologically; although a clinically atypical naevus may not exhibit histological dysplasia, and vice versa, the terms have often been used interchangeably.

Atypical (or dysplastic) naevi are common in white-skinned peoples. In studies reported from Sweden, 18% of the population were reported to have at least one clinically diagnosed atypical naevus [5], as had 37% of young men in an Italian study [6]. In other populations the prevalence is lower, so that in a German study 5% of adults were reported to have at least one [7]. The prevalence is therefore variable and some of this variation is explained by differences in skin type, age of people studied and probably differences in clinical definitions or interobserver variability. There is no doubt, however, that they are common, although most individuals who do have some atypical naevi only have small numbers—one or two generally.

Atypical naevi are undoubtedly precursors of melanoma, although progression to melanoma is uncommon. They are also markers of risk of melanoma; in a meta-analysis the melanoma relative risk associated with the number of atypical naevi was 6.36 (95% CI 3.80–10.33) for five versus none [8]. Twin studies have provided evidence that benign naevi in general are genetically determined [9] and it is supposed that atypical naevi are also genetically determined at least in part, although with evidence that sunburn is also important [10].



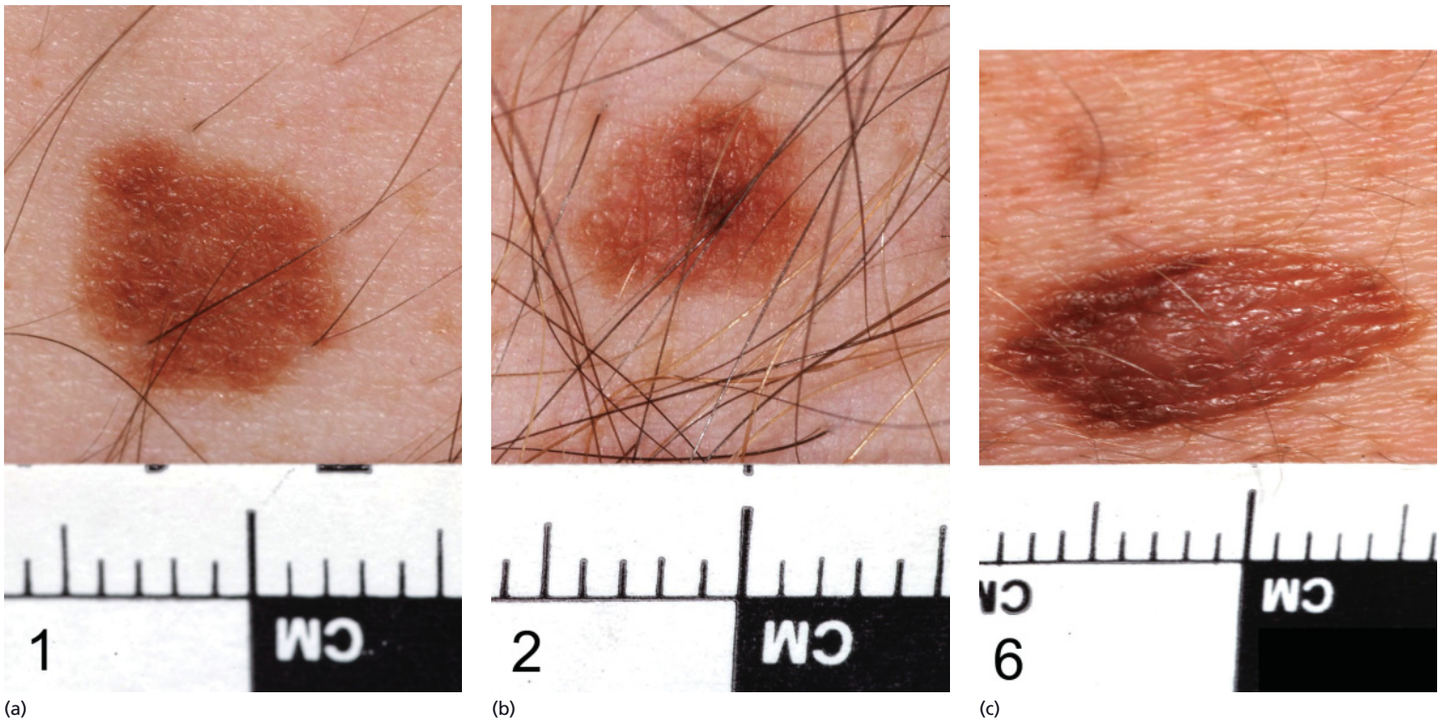
Fig. 54.41 The atypical mole syndrome is characterized by the presence of an increased number of naevi and clinically atypical naevi. This is the strongest phenotypic risk factor for melanoma.

Although small numbers of atypical naevi are common in most fair-skinned populations, as documented above, and although they are both a precursor and an associate of melanoma, the majority of people with some atypical naevi have neither a personal nor a family history of melanoma. However, many such individuals will also have increased numbers of small benign naevi (Fig. 54.41) and are recognized to be at increased risk of melanoma. The atypical mole syndrome is my preferred term to describe patients with this phenotype, but others use the 'dysplastic naevus syndrome' or the FAMMM syndrome phenotype. Their relative risk of melanoma is something around 6 to 10 times that of people with very few naevi [8,11]. The identification of this 'at risk' group, which accounts for around 2% of the UK population [12], is therefore important in terms of prevention and for education around early detection.

Clinical features. The original description of dysplastic naevi indicated that these were lesions larger than 5 mm with an irregular edge, irregular pigmentation and a degree of inflammation. Although there is a recognizable histological pattern associated with such naevi, the correlation between clinical and pathological features is poor. This, in some respects, is not a problem. The diagnosis of an atypical naevus is a clinical one. The importance of this diagnosis is only in terms of educating the patient about risk and what to look for when self-examining.

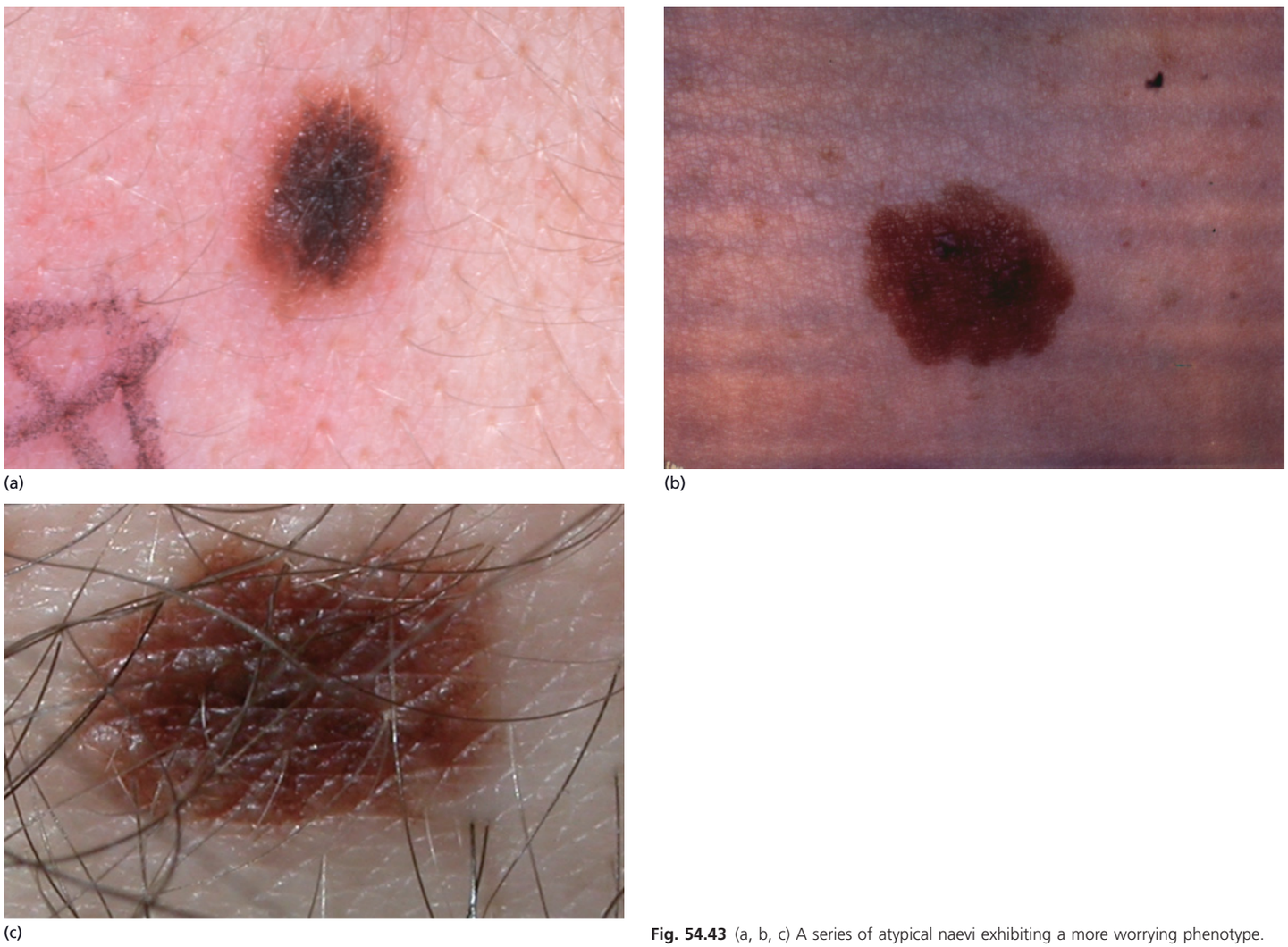
The clinical imperative is to distinguish the atypical naevus from *in situ* or early radial growth phase melanoma. In practice, the clinical features of atypical naevi are in continuum with those of *in situ* melanoma, and the clinician must have a sufficiently low threshold for excision to avoid missing the latter whilst avoiding the excision of excessive numbers of benign naevi (Figs 54.42–45).

Pathology. The great majority of atypical naevi are variants of acquired compound melanocytic naevi, although features described in atypical lesions may be seen in junctional naevi, in some congenital naevi and, occasionally, in Spitz naevi and variants.



(a) (b) (c)

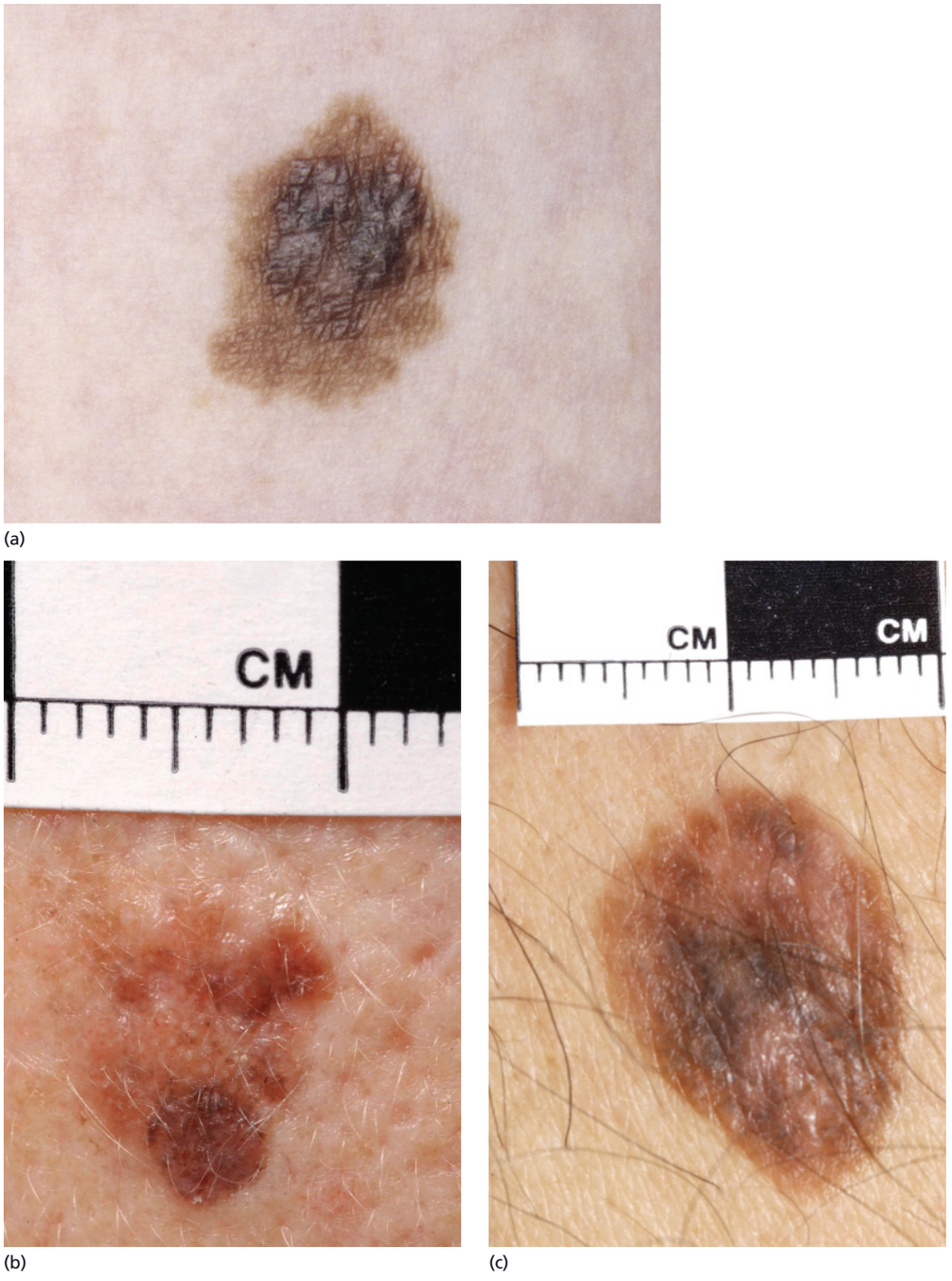
Fig. 54.42 (a, b, c) A series of bland but atypical naevi which appear to be behaving in an entirely benign fashion, showing evidence of little proliferation or stromal reaction. (c) A compound atypical naevus.



(a) (b)

(c)

Fig. 54.43 (a, b, c) A series of atypical naevi exhibiting a more worrying phenotype.



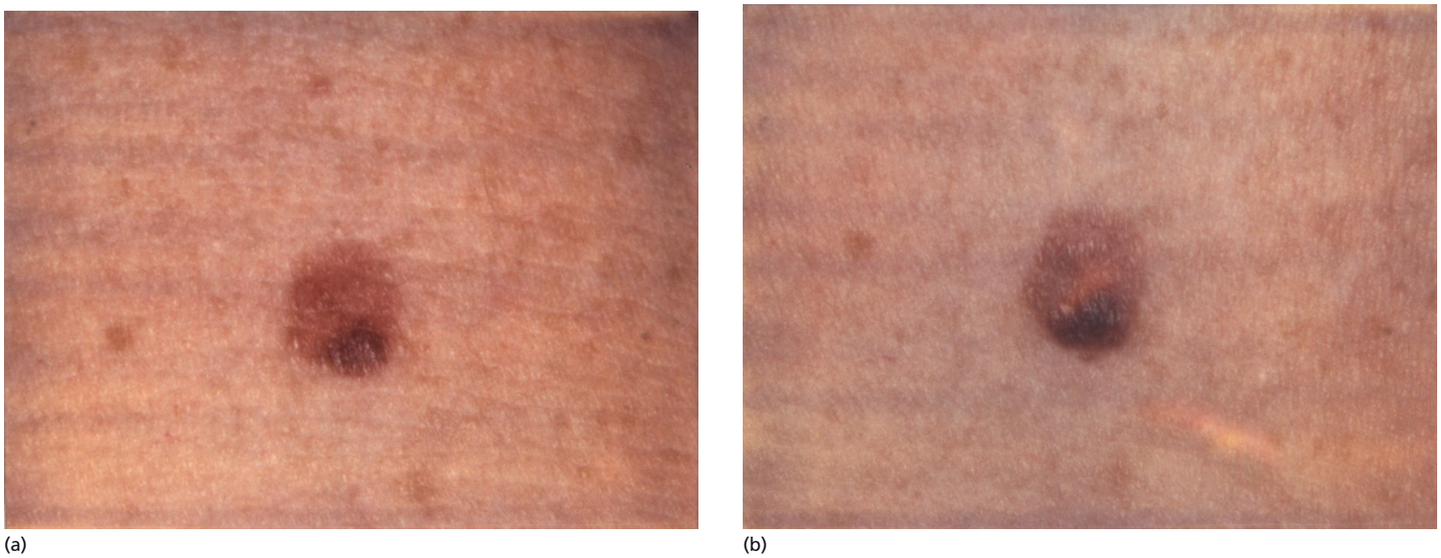
(a)

(b)

(c)

Fig. 54.44 (a, b, c) A series of *in situ* melanomas to illustrate the continuum of clinical change that is the progression from atypical naevi to melanoma.

The specific pathological features described in atypical naevi can be divided into architectural features, cytological features and features indicative of a host response to the naevus cells. The architectural features are lentiginous melanocytic hyperplasia, fusion of individual nests of naevomelanocytes and associated elongation of epidermal rete ridges (Fig. 54.46). The cytological abnormalities are the increase in the nuclear to cytoplasmic ratio of individual melanocytes, an increase in nuclear staining and occasional normal mitotic figures in melanocytes. Elder and Murphy describe random, slight to moderate atypia, occasional macronuclei, scattered epithelioid naevus cells and scattered cells with dusky pigment [13]. Most groups would not make the diagnosis on architectural features alone but consider melanocyte cytological atypia an essential feature for the diagnosis. It is preferable to report the presence of architectural and cytological atypia specifically. The three pathological features indicating a host response



(a) (b)

Fig. 54.45 (a, b) A change in the appearance of an atypical naevus over a 4-month period signifying evolution of an early superficial spreading melanoma in a *CDKN2A* mutation carrier.

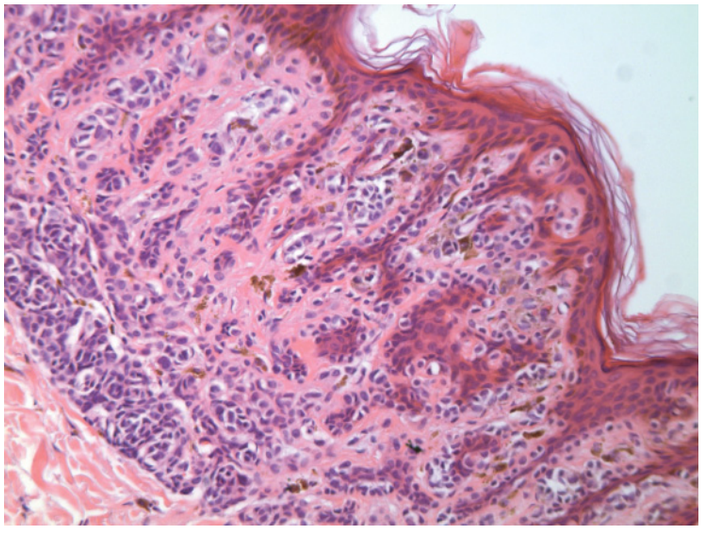


Fig. 54.46 Architectural atypia in a mildy atypical (dysplastic) compound naevus. (Courtesy of Dr S. Edward, Leeds Teaching Hospitals Trust, Leeds, UK.)

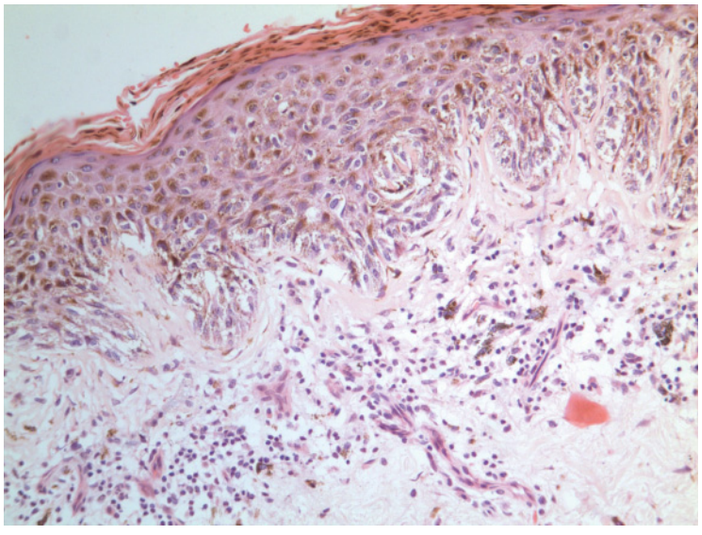


Fig. 54.47 A severely atypical (dysplastic) naevus with an inflammatory stromal reaction. (Courtesy of Dr S. Edward, Leeds Teaching Hospitals Trust, Leeds, UK.)

are the presence of a lymphocytic infiltrate, a degree of fibroplasia of the collagen of the papillary dermis and a relative increase in the vascularity of the underlying dermis (Fig. 54.47). The presence of these changes in an atypical naevus that has evolved into a melanoma may cause confusion with the possible presence of regression.

Treatment. Atypical naevi are in the majority of cases benign, stable lesions, which are bland in appearance, clinically and using dermoscopy. They can be left in place although the patient must be educated about monitoring the appearance of such naevi over time. Photographs of early melanomas are essential for this purpose, as leaflets or on line [14]. A picture of the naevus given to the patient may also be helpful.

Where the naevus is sufficiently atypical (and particularly when a single naevus is present) then it should be removed in its entirety with a 2-mm clinical margin and subjected to pathological examination, to exclude *in situ* melanoma. Such naevi should NEVER be punch biopsied or an incisional biopsy taken, as sampling error may cause an early melanoma to be missed.

Two per cent of the UK population [12] have the atypical mole syndrome in which there are multiple naevi, many of which may be clinically atypical, although this is variable. The majority have no family history of melanoma. In these patients the phenotype is

a marker of risk and that risk cannot be removed by removal of the naevi. Such patients must be counselled about avoidance of sunburn for themselves and their children. They should be taught how to self examine with the aid of images [14] and a short period of follow-up is sensible, to ensure that the naevi are stable and that the patient is confident about self examination. Advice for follow-up of those with a family history of melanoma is discussed below.

References

1 Elder DE. The dysplastic nevus. *Pathology* 1985; **17**: 291–7.
2 Clark WH Jr, Reimer RR, Greene M *et al*. Origin of familial malignant melanomas from heritable melanocytic lesions. 'The B-K mole syndrome'. *Arch Dermatol* 1978; **114**: 732–8.
3 Frichot BC 3rd, Lynch HT, Guirgis HA *et al*. New cutaneous phenotype in familial malignant melanoma. *Lancet* 1977; **1**: 864–5.
4 Bergman W, Palan A, Went LN. Clinical and genetic studies in six Dutch kindreds with the dysplastic naevus syndrome. *Ann Hum Genetics* 1986; **50**: 249–58.
5 Augustsson A, Stierner U, Suurkula M, Rosdahl I. Prevalence of common and dysplastic naevi in a Swedish population. *Br J Dermatol* 1991; **124**: 152–6.
6 Ballone E, Passamonti M, Lappa G *et al*. Pigmentary traits, nevi and skin phototypes in a youth population of Central Italy. *Eur J Epidemiol* 1999; **15**: 189–95.
7 Schafer T, Merkl J, Klemm E *et al*. The epidemiology of nevi and signs of skin aging in the adult general population: Results of the KORA-survey 2000. *J Invest Dermatol* 2006; **126**: 1490–6.
8 Gandini S, Sera F, Cattaruzza MS *et al*. Meta-analysis of risk factors for cutaneous melanoma: I. Common and atypical naevi. *Eur J Cancer* 2005; **41**: 28–44.
9 Zhu G, Duffy DL, Eldridge A *et al*. A major quantitative-trait locus for mole density is linked to the familial melanoma gene CDKN2A: a maximum-likelihood combined linkage and association analysis in twins and their sibs. *Am J Hum Genet* 1999; **65**: 483–92.
10 Carli P, Biggeri A, Nardini P *et al*. Epidemiology of atypical melanocytic naevi: an analytical study in a Mediterranean population. *Eur J Cancer Prev* 1997; **6**: 506–11.
11 Bataille V, Newton Bishop JA, Sasieni P *et al*. Risk of cutaneous melanoma in relation to the numbers, types and sites of naevi: a case–control study. *Br J Cancer* 1996; **73**: 1605–11.
12 Newton JA, Bataille V, Griffiths K *et al*. How common is the atypical mole syndrome phenotype in apparently sporadic melanoma? *J Am Acad Dermatol* 1993; **29**: 989–96.
13 Elder DE, Murphy GF. *Melanocytic Tumors of the Skin*. Washington, DC: American Registry of Pathology, in press.
14 Melanoma Genetics Consortium. www.genomel.org.

Malignant melanoma of the skin (melanoma): background

Definition. A malignant tumour arising from the epidermal melanocyte.

Incidence and mortality [1]

There has been a steady rise in the incidence of melanoma of the skin in many areas of Australia, New Zealand, North America and Europe since the 1950s. The most recent incidence figures are available on line from the Globocan 2002 project at the Cancer Mondial Statistical Information website through the International Agency for Research on Cancer [2]. The highest incidence is seen in Australia and New Zealand. There has been a levelling off in incidence in many areas of Western Europe in recent years, but in Eastern and Southern Europe levels are still increasing [3]. In the UK, there is some evidence for a levelling off in some areas [4,5] but not in all [6]. In the USA, the SEER programme reported that the incidence of melanoma continued to rise at least till 1995, with a trebling of melanoma incidence in males aged 45–64 years over the 30-year period 1969–99, from 13.5 to 40.0 per 100 000 population per annum, and a fivefold increase in older males aged over 65 years, from 18.8 to 91.9 per 100 000 population per annum. Incidence rates for females aged 45–64 years and for those aged over 65 years have also risen but less steeply than for males, while the incidence of melanoma in younger adults of both sexes aged under 45 years has only risen slightly over a 40-year period [7]. In Australia, age-standardized incidence is continuing to increase despite long-standing prevention campaigns. However, a study has provided evidence for stabilization of incidence rates in those younger than 35 years and the proportionate increase for both *in situ* and invasive lesions appears to be lower for the most recent period compared with previous periods, providing hope of a reversal in years to come [8].

Despite the increase in incidence in the north of the UK recently, mortality seems to be levelling off [6]. In Australia, melanoma mortality seems to have peaked in the 1980s [9]; statistically significant decreases in mortality rates for both men and women younger than 55 years have occurred in recent years, for 55–79 year olds, rates are now stable for both men and women whereas previously the rates were increasing. For both men and women 80 years or older, rates have continued an increase of 3–4% per year [10]. Similarly, in the USA, mortality appears to be stabilizing in women, but still rising slightly in men [7].

Overall then, melanoma is most common in white-skinned peoples living at lower latitudes such as Australia, and the incidence continues to increase in many countries but has levelled off in others. The mortality seems to have levelled off or have reduced in most areas, however, suggesting that early diagnosis may have been effective in reducing mortality. Some authors have contested this, suggesting that increased numbers of melanocytic lesions may be being removed which would not necessarily have progressed to invasive melanoma [11]. Certainly, in many areas of the world the absolute numbers of thick tumours appear to be relatively constant over time [12] suggesting persistent difficulties in early diagnosis. Thicker tumours occur particularly in older patients [6,12], and, in many series, males had a higher proportion of thicker tumours than did females [7,12]. Furthermore, in Europe generally, mortality has continued to increase in older men [13]. In terms of prevention, therefore, an important target group for early detection are older patients, particularly males.

Aetiology

Melanoma is predominantly a cancer of white-skinned peoples, which gave the first clue that sun exposure is causal. The variation in incidence amongst such populations with latitude of residence (as described above) is further evidence, the highest incidence being in Australasia where susceptible, fair-skinned peoples live in sunny climes. The aetiological factors for melanoma are therefore both genetic (related to cutaneous responses to the sun such as skin type) and environmental.

The precise type of sun exposure that is causal has been controversial but the data are now strong that the dominant cause is

intermittent sun exposure. Holidays in the sun, associated with sunburn, have been identified in numerous case–control studies, and results have been subjected to meta-analysis [14]. Chronic sun exposure does not seem to be causal, at least in many areas of the world; there was even some evidence for a protective role for occupational sun exposure in the same meta-analysis [14]. In Australasia, however, solar keratoses appear to be risk factors for melanoma and it has been suggested that there are two routes to melanoma [15,16]: one associated with short sharp exposures to excessive sun exposure and sunburn and another related to chronic sun exposure which might be responsible for a greater proportion of cases in hot countries. These hypotheses are still being explored.

There is some evidence that sunbed usage is also causal for melanoma: in a meta-analysis based on 19 informative studies [17], use of sunbeds ever was positively associated with melanoma (summary relative risk 1.15; 95% CI 1.00–1.31), although there was no consistent evidence of a dose–response relationship. First exposure to sunbeds before 35 years of age significantly increased the risk of melanoma, based on seven informative studies (summary relative risk 1.75; 95% CI 1.35–2.26). It is difficult to separate the effects of sunbed use from those of sunbathing, however, and sunbed usage is likely to explain a relatively small proportion of melanoma cases.

Whether the continued increase in incidence is an artefact of the removal of increased numbers of lesions which might have progressed or not, the relationship between melanoma and intermittent sun exposure and increased mobility of fair-skinned peoples to hot countries is a cause for concern.

Phenotypic risk factors for melanoma

The strongest phenotypic risk factor for melanoma is the presence of increased numbers of melanocytic naevi. In a meta-analysis of 46 studies, 101–120 common naevi compared with less than 15 was associated with a significantly increased risk of melanoma (pooled relative risk (RR) = 6.89; 95% CI 4.63–10.25) as was the number of atypical naevi (RR = 6.36; 95% CI 3.80–10.33, for 5 versus 0) [18]. Twin studies have provided strong evidence that naevus number is predominantly genetically determined [19], with a smaller effect of environmental factors, particularly sun exposure [20]. It is theorized, therefore, that the genes that determine naevus number are also common melanoma susceptibility genes. The first evidence for inherited genes that are both naevus and melanoma susceptibility genes was published in 2009 [21].

Weaker phenotypic risk factors relate to the presence of skin that burns easily in the sun such as: skin type (I vs. IV: RR = 2.09, 95% CI 1.67–2.58), high density of freckles (RR = 2.10, 95% CI 1.80–2.45), skin colour (fair vs. dark: RR = 2.06, 95% CI 1.68–2.52), eye colour (blue vs. dark: RR = 1.47, 95% CI 1.28–1.69) and hair colour (red vs. dark: RR = 3.64, 95% CI 2.56–5.37) [22]. These phenotypes are also genetically determined; a key gene, *MC1R,* codes for the melanocortin receptor receptor, which, at least in part, determines the presence of both red hair [23] and freckles [24]. The gene mediates these effects by modulation of the ratio between the pheomelanin and eumelanin produced by the melanocyte.

Skin changes indicative of sun damage are also shown to be risk factors at meta-analysis [22], such as pre-malignant and skin cancer lesions (RR = 4.28, 95% CI 2.80–6.55) and actinic damage indicators (RR = 2.02, 95% CI 1.24–3.29).

Familial melanoma

Any family history increases the risk of melanoma. A study from the Swedish Cancer Registry estimated the standardized incidence ratio for melanoma to be 2.40 (95% CI 2.10–2.72) for offspring if one parent had a melanoma, 2.98 (95% CI 2.54–3.47) for an affected sibling and 8.92 (95% CI 4.25–15.31) if a parent and a sibling were both affected. The highest ratio was for offspring when a parent had multiple melanomas [25].

A strong family history is rare, but families with multiple cases are reported from around the world. In these families, inheritance of melanoma is consistent with inheritance of an autosomal dominant gene with incomplete penetrance (Fig. 54.48). Inheritance of mutations in the *CDKN2A* gene on chromosome 9 [26] (which codes for the cell cycle inhibitor protein, p16) explains a proportion of these families, but not all. The importance of p16 in the pathogenesis of melanoma was emphasized by the identification of germline mutations of *CDK4* as the second highest penetrance melanoma susceptibility gene [27,28], as mutations in this gene, found at chromosome 12q13, occur at the p16 binding site. Families with mutations in *CDK4* are excessively rare. Many of the reported *CDKN2A* mutations have been shown to be founder mutations, such as Gly101Trp [29], which is common in mainland Europe (France and Italy), the so-called Leiden mutation, which is an exon 2 19-bp deletion [30], and Met53Ile [31], which may be of Scottish origin. 113insArg is a Swedish founder mutation [32] and a common founder for Val126Arp has been shown by haplotype studies in North American families [33]. To date, only one mutation seems to appear repeatedly at a hotspot, a 24-bp duplication at the N-terminus [31]. An on-line database of locus specific variants, named eMelanoBase, is maintained by the Leiden Medical Center group of GenoMEL [34]. The proportion of families with identifiable mutations is higher with larger numbers of affected family members, early age of onset and if there are cases with multiple primaries, and if family members have pancreatic cancer [33], although there is variation by continent so that the association with pancreatic cancer, for example, is much less clear in Australia than it is in many parts of Europe and the USA. The majority of families appear to be predisposed to melanoma alone, if risk is assessed by pedigree examination. The gene penetrance has been estimated by GenoMEL, the Melanoma Genetics Consortium [35]. Overall, *CDKN2A* mutation penetrance was estimated to be 0.30 (95% CI 0.12–0.62), meaning that on average 30% of mutation carriers develop a melanoma by the age of 50 years and 0.67 (95% CI 0.31–0.96) by age 80 years, in 80 families pooled from the US, Australia and Europe. Not surprisingly, penetrance was higher in families living in Australia where sun exposure is more intense. A lower penetrance was reported in a population based study [36].

A significant proportion of families do not have identifiable *CDKN2A* or *CDK4* mutations and there are, therefore, other high-risk genes yet to be identified. Two possible sites are at 1p36 [37] and 1p22 [38].

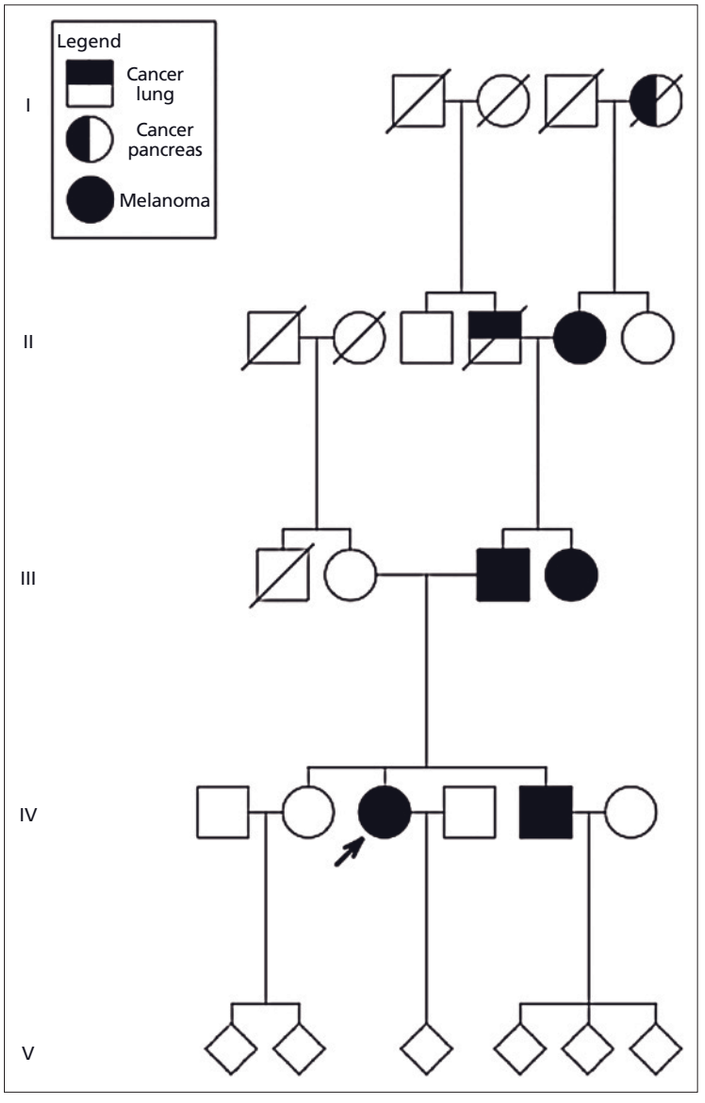


Fig. 54.48 A family tree from a family with a hereditary mutation in the *CDKN2A* gene, which is a high-risk gene for melanoma. The black circles represent melanoma cases in women, the squares, cases in men. There was a single case of pancreatic cancer.

Families with multiple cases of melanoma should be referred to specialist units for screening, education about early detection and prevention and counselling about risk. Although testing for mutations in the *CDKN2A* gene does take place in some countries, the value of the test is currently unclear and GenoMEL has taken the view that it is as yet premature [39]. GenoMEL is working to establish the information necessary to inform this counselling process in the future. The increased risk of pancreatic cancer in some countries but not in others remains confusing and may be due to variation between mutations or environmental factors. As pancreatic cancer is associated with smoking and alcohol-induced pancreatitis [40,41], it is important to advise members of melanoma families to avoid smoking and moderate alcohol intake. Screening for pancreatic cancer remains a difficult issue but there are trials currently taking place to establish the role of radiographic screening.

Identification of 'at risk' patients

The strongest risk of melanoma to an individual is that associated with familial melanoma where there are multiple cases. Within such families, all first-degree relatives are considered at risk regardless of naevus phenotype, although the presence of increased numbers of naevi increases the likelihood that the family member is a *CDKN2A* mutation carrier [42].

Patients with the atypical mole syndrome are at increased risk irrespective of family history and those with red hair and freckles are also at increased risk, although at a lower level. Algorithms have been, or are being, developed in order to estimate risk [43,44].

Prevention

The continued increase in incidence of melanoma in most white-skinned populations, and the very strong evidence that intermittent sun exposure is causal, suggests that sun exposure on holidays in sunny places is the most important behaviour to be addressed. As air fares are currently much lower than they were, there is a concern that this will prove even more difficult to modify in the next few years. It might be that directing the advice to those at increased risk will be more effective, stressing freckles, naevi and family history as risk factors for the cancer. For such people, protection using avoidance and clothing is optimal but less popular than the use of sunscreens. The wavelength of light that is causal for melanoma is still not known and therefore sunscreens should be broad-spectrum types, providing protection across both UVB and UVA ranges. Advice should be to use sunscreens that are water proof, and are applied regularly and in sufficient quantities.

Sun exposure for vitamin D synthesis is critical to human health. 1,25-dihydroxyvitamin D_3 is synthesized in the skin as a result of exposure to sunlight and is present in a few foods and dietary supplements. It has become apparent that suboptimal vitamin D levels are widespread [45], and increasing epidemiological evidence has emerged for a role for vitamin D deficiency in a number of cancers [46,47]. Most European peoples rely upon cutaneous synthesis as a result of sun exposure and the UV action spectrum for vitamin D synthesis and non-melanoma skin cancer carcinogenesis is the same [48], so that the balance between benefit and risk is close. There are, therefore, concerns that we should not give blanket advice to all to reduce their sun exposure. It seems sensible to direct advice to those at particular risk and to give the following advice:

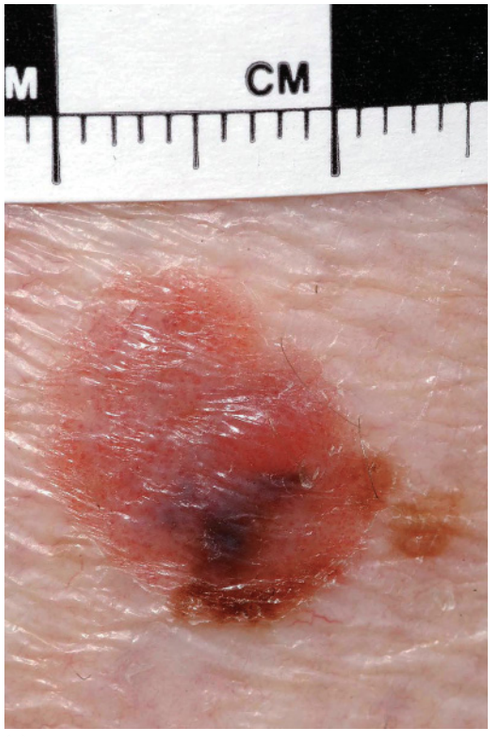
- That people who burn in the sun, who have freckles, red hair or a larger number of melanocytic naevi, and those with a family history of skin cancer should be careful in the sun
- That these people should in particular avoid any sunburn
- That those who burn readily in the sun should probably avoid direct exposure to the sun and compensate for this avoidance by taking vitamin D supplements sufficient to maintain normal levels of vitamin D in the serum
- That dark-skinned peoples who have a low risk of skin cancer should avoid sunburn but, to avoid vitamin D depletion, which would be detrimental to their health overall, should not practise too much sun avoidance.

References

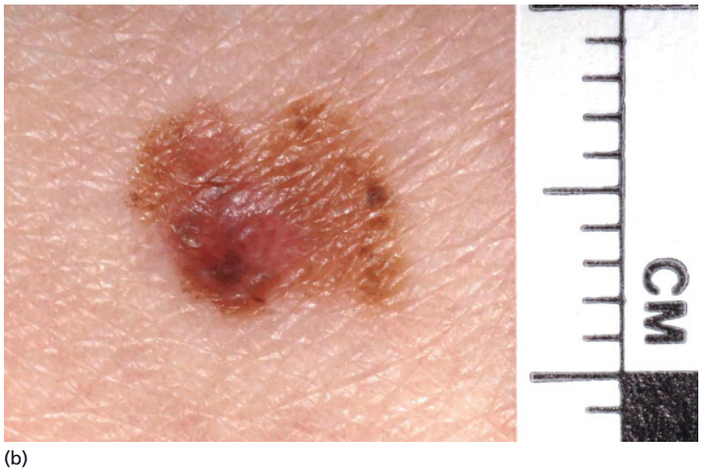
1 Parkin D, Whelan S, Ferlay J *et al*. *Cancer Incidence in Five Continents*. IARC Scientific Publications No 143, Lyon, International Agency for Research on Cancer II, 1997.
2 International Agency for Research on Cancer. CANCERMondial. http://www-dep.iarc.fr/.
3 de Vries E, Bray FI, Coebergh JW, Parkin DM. Changing epidemiology of malignant cutaneous melanoma in Europe 1953–1997: rising trends in incidence and mortality but recent stabilizations in western Europe and decreases in Scandinavia. *Int J Cancer* 2003; **107**: 119–26.
4 MacKie RM, Bray CA, Hole DJ *et al*. Incidence of and survival from malignant melanoma in Scotland: an epidemiological study. *Lancet* 2002; **360**: 587–91.
5 Newnham A, Moller H. Trends in the incidence of cutaneous malignant melanomas in the south east of England, 1960–1998. *J Public Health Med* 2002; **24**: 268–75.
6 Downing A, Newton-Bishop JA, Forman D. Recent trends in cutaneous malignant melanoma in the Yorkshire region of England; incidence, mortality and survival in relation to stage of disease, 1993–2003. *Br J Cancer* 2006; **95**: 91–5.
7 Jemal A, Devesa SS, Fears TR, Hartge P. Cancer surveillance series: changing patterns of cutaneous malignant melanoma mortality rates among whites in the United States. *J Natl Cancer Inst* 2000; **92**: 811–8.
8 Coory M, Baade P, Aitken J *et al*. Trends for in situ and invasive melanoma in Queensland, Australia, 1982–2002. *Cancer Causes Control* 2006; **17**: 21–7.
9 Giles GG, Armstrong BK, Burton RC *et al*. Has mortality from melanoma stopped rising in Australia? Analysis of trends between 1931 and 1994. *BMJ* 1996; **312**: 1121–5.
10 Baade P, Coory M. Trends in melanoma mortality in Australia: 1950–2002 and their implications for melanoma control. *Aust N Z J Public Health* 2005; **29**: 383–6.
11 Florez A, Cruces M. Melanoma epidemic: true or false? *Int J Dermatol* 2004; **43**: 405–7.
12 Murray CS, Stockton DL, Doherty VR. Thick melanoma: the challenge persists. *Br J Dermatol* 2005; **152**: 104–9.
13 de Vries E, Hontermans S, Jansses-Heijnen MLG *et al*. Up-to-date survival estimates and historical trends of cutaneous malignant melanoma in the south-east of the Netherlands. *Ann Oncol* 2007; **18**: 1110–6.
14 Gandini S, Sera F, Cattaruzza MS *et al*. Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. *Eur J Cancer* 2005; **41**: 45–60.
15 Bataille V, Sasieni P, Grulich A *et al*. Solar keratoses: a risk factor for melanoma but negative association with melanocytic naevi. *Int J Cancer* 1998; **78**: 8–12.
16 Whiteman DC, Watt P, Purdie DM *et al*. Melanocytic nevi, solar keratoses, and divergent pathways to cutaneous melanoma. *J Natl Cancer Inst* 2003; **95**: 806–12.
17 Green A, Autier P, Boniol M *et al*. The association of use of sunbeds with cutaneous malignant melanoma and other skin cancers: a systematic review. *Int J Cancer* 2007; **120**: 1116–22.
18 Gandini S, Sera F, Cattaruzza MS *et al*. Meta-analysis of risk factors for cutaneous melanoma: I. Common and atypical naevi. *Eur J Cancer* 2005; **41**: 28–44.
19 Easton D, Cox G, Macdonald A, Ponder B. Genetic susceptibility to naevi—a twin study. *Br J Cancer* 1991; **64**: 1164–7.
20 Wachsmuth RC, Turner F, Barrett JH *et al*. The effect of sun exposure in determining nevus density in UK adolescent twins. *J Invest Dermatol* 2005; **124**: 56–62.
21 Falchi M, Bataille V, Hayward NK *et al*. Genome-wide association study identifies variants at 9p21 and 22q13 associated with development of cutaneous nevi. *Nat Genet* 2009.
22 Gandini S, Sera F, Cattaruzza MS *et al*. Meta-analysis of risk factors for cutaneous melanoma: III. Family history, actinic damage and phenotypic factors. *Eur J Cancer* 2005; **41**: 2040–59.
23 Rees JL. Genetics of hair and skin color. *Annu Rev Genet* 2003; **37**: 67–90.
24 Bastiaens M, ter Huurne J, Gruis N *et al*. The melanocortin-1-receptor gene is the major freckle gene. *Hum Mol Genet* 2001; **10**: 1701–8.
25 Hemminki K, Zhang H, Czene K. Familial and attributable risks in cutaneous melanoma: effects of proband and age. *J Invest Dermatol* 2003; **120**: 217–23.
26 Kamb A. Role of a cell cycle regulator in hereditary and sporadic cancer. *Cold Spring Harb Symp* 1994; **59**: 39–47.
27 Soufir N, Avril M, Chompret A *et al*. Prevalence of p16 and CDK4 germline mutations in 48 melanoma-prone families in France. *Hum Molec Genet* 1998; **7**: 209–16.
28 Zuo L, Weger J, Yang Q *et al*. Germline mutations in the $p16^{INK4a}$ binding domain of CDK4 in familial melanoma. *Nature Genetics* 1996; **12**: 97–9.
29 Ciotti P, Struewing JP, Mantelli M. A single genetic origin for the G101W *CD2KN2A* mutation in 20 melanoma-prone families. *Am J Hum Genet* 2000; **67**: 311–9.
30 Gruis N, Sandkuijl L, Van der Velden P *et al*. *CDKN2* explains part of the clinical phenotype in Dutch familial multiple-mole melanoma (FAMMM) syndrome families. *Melanoma Res* 1995; **5**: 169–77.
31 Pollock PM, Spurr N, Bishop T *et al*. Haplotype analysis of two recurrent *CDKN2A* mutations in 10 melanoma families: evidence for common founders and independent mutations. *Hum Mutat* 1998; **11**: 424–31.
32 Borg A, Johannsson U, Johannsson O *et al*. Novel germline p16 mutation in familial malignant melanoma in southern Sweden. *Cancer Res* 1996; **56**: 2497–500.
33 Goldstein AM, Chan M, Harland M *et al*. Features associated with germline *CDKN2A* mutations: a GenoMEL study of melanoma-prone families from three continents. *J Med Genet* 2007; **44**: 99–106.
34 Melanoma Genetics Consortium. www.genomel.org
35 Bishop DT, Demenais F, Goldstein AM *et al*. Geographical variation in the penetrance of *CDKN2A* mutations for melanoma. *J Natl Cancer Inst* 2002; **94**: 894–903.
36 Begg CB, Orlow I, Hummer AJ *et al*. Lifetime risk of melanoma in CDKN2A mutation carriers in a population-based sample. *J Natl Cancer Inst* 2005; **97**: 1507–15.
37 Bale SJ, Dracopoli NC, Tucker MA *et al*. Mapping the gene for hereditary cutaneous malignant melanoma-dysplastic nevus to chromosome 1p. *N Engl J Med* 1989; **320**: 1367–72.
38 Gillanders E, Hank Juo SH, Holland EA *et al*. Localization of a novel melanoma susceptibility locus to 1p22. *Am J Hum Genet* 2003; **73**: 301–13.
39 Kefford R, Bishop JN, Tucker M *et al*. Genetic testing for melanoma. *Lancet Oncol* 2002; **3**: 653–4.
40 Otsuki M, Tashiro M. 4. Chronic pancreatitis and pancreatic cancer, lifestyle-related diseases. *Internal Med (Tokyo, Japan)* 2007; **46**: 109–13.
41 Welsch T, Kleeff J, Seitz HK *et al*. Update on pancreatic cancer and alcohol-associated risk. *J Gastroenterol Hepatol* 2006; **21** (Suppl. 3): S69–75.
42 Newton Bishop JA, Bataille V, Pinney E, Bishop DT. Family studies in melanoma: identification of the atypical mole syndrome (AMS) phenotype. *Melanoma Res* 1994; **4**: 199–206.
43 MacKie RM, Freudenberger T, Aitchison TC. Personal risk-factor chart for cutaneous melanoma. *Lancet* 1989; **2**: 487–90.
44 Whiteman DC, Green AC. A risk prediction tool for melanoma? *Cancer Epidemiol Biomarkers Prev* 2005; **14**: 761–3.
45 Holick MF. High prevalence of vitamin D inadequacy and implications for health. *Mayo Clin Proc* 2006; **81**: 353–73.
46 Chen TC, Holick MF. Vitamin D and prostate cancer prevention and treatment. *Trends Endocrinol Metab* 2003; **14**: 423–30.
47 Holick MF. Vitamin D: Its role in cancer prevention and treatment. *Prog Biophys Mol Biol* 2006; **92**: 49–59.
48 Wolpowitz D, Gilchrest BA. The vitamin D questions: how much do you need and how should you get it? *J Am Acad Dermatol* 2006; **54**: 301–17.

Clinicopathological variants and growth phases of primary melanoma

In 1969, Clark *et al*. suggested that, using a combination of clinical and pathological features, malignant melanoma could be divided into three main subsets [1]; the superficial spreading melanoma, the nodular melanoma and the lentigo maligna melanoma. In 1975, Reed *et al*. added a fourth group, the acral lentiginous or palmoplantar malignant melanoma [2]. There is some controversy as to whether or not these subsets are completely discrete entities, and it has been established that the clinicopathological variant is not an independent determinant of prognosis [3]. However, the four subtypes have distinct clinical features and possibly some biological distinctions, which are useful in clinical practice and each will be discussed in more detail later. The growth phases of melanoma also have clinical importance and are discussed here.



(a)



(b)

Fig. 54.49 (a, b) Two superficial spreading melanomas showing typical variation in colour and shape.

In situ disease

Melanomas arise from melanocytes within the epidermis generally. In the majority of cases, the proliferation of melanocytes is limited to the epidermis for some time, before the cells acquire the capacity for survival and growth in the dermis. This phase is known as '*in situ*' disease, which may last for a period of years.

The commonest type of melanoma, the superficial spreading melanoma (SSM), for example, may evolve from an atypical naevus, through a borderline *in situ* lesion, to an SSM (Figs 54.49–54.51). In some subtypes of melanoma, such as lentigo maligna melanoma, acral lentiginous melanoma and genital melanoma, the *in situ* phase is particularly protracted. The *in situ* component in these rarer subtypes may, furthermore, be widespread and ill-defined and this is often known as the 'field effect'. Although ill-defined *in situ* disease typifies the subtypes of melanoma listed above, it may rarely occur on other sites, such as chronically sun-exposed skin of the arm or leg, in the skin around an SSM.



Fig. 54.50 A superficial spreading melanoma which has developed into a vertical growth phase tumour. Variable colours are seen with prominent vasculature and variable pigment. Even without a dermoscope large pigment dots can be seen.

So-called nodular melanomas are the only type in which the malignant melanoma cells appear to have the capacity for invasive growth into the dermis and beyond from the beginning, without an *in situ* phase, and these tumours therefore develop much more rapidly and are much more difficult to diagnose at an early, curable stage.

Radial growth phase melanoma

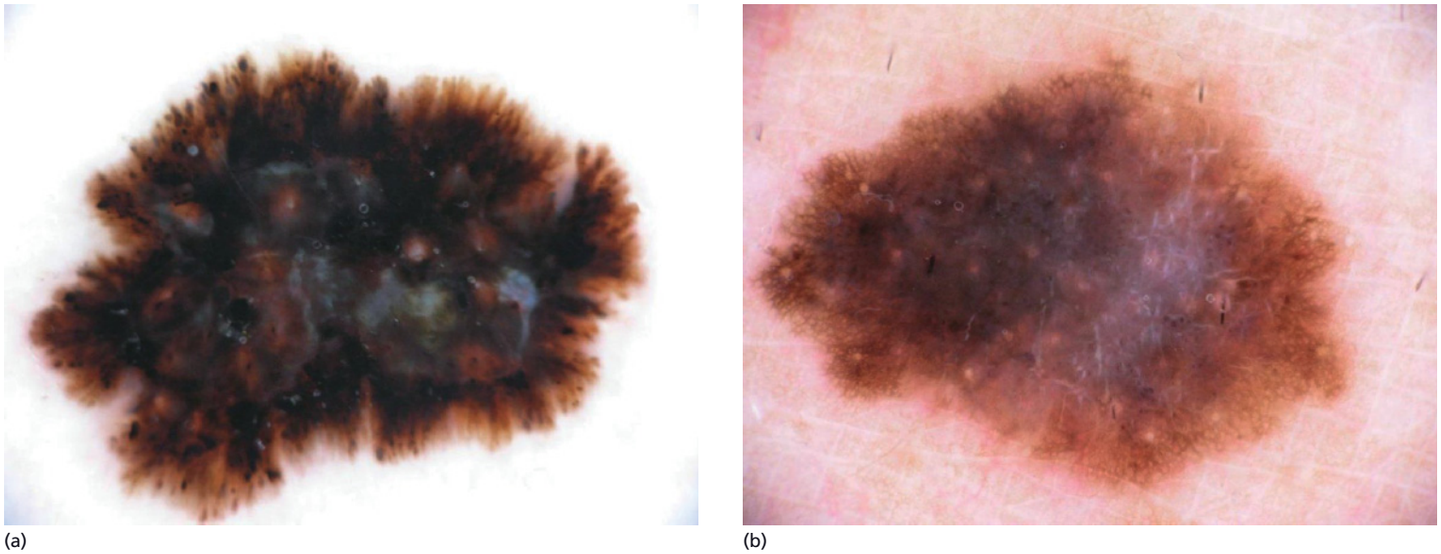
The concept of evolution from *in situ* disease to invasive disease which is still unlikely to metastasize, called the 'radial growth phase', was developed by Clark and Elder [4]. Radial growth phase melanoma is strictly defined histologically. There is epidermal melanocyte proliferation and there may be some dermal cells provided that they are single or in small clusters, falling short of a dermal tumour nodule. A tumour nodule in the dermis is one which exceeds the diameter of any nest of cells along the dermo-epidermal junction [5]. The concept of radial growth phase melanoma as a lesion that should not recur means that these authors estimate a 100% expectation of survival for patients from whom such a lesion is removed.

Vertical growth phase melanoma

Melanoma in vertical growth phase is a tumour in which growth of malignant cells occurs within the dermis. These tumours have acquired the capacity for growth and, to a variable degree, the capacity for invasion of vessels and growth in other tissues. Variation in the characteristics of vertical growth phase melanoma histologically and immunohistochemically mirrors biological differences between tumours having prognostic significance, considered below.

References

1 Clark WH Jr, From L, Bernardino EA, Mihm MC. The histogenesis and biologic behavior of primary human malignant melanomas of the skin. *Cancer Res* 1969; **29**: 705–27.



(a) (b)

Fig. 54.51 The dermoscopic appearance of superficial spreading melanoma showing (a) an abnormal pigment network, radial streaming and large/variably sized pigment globules and (b) a melanoma with an irregular structure and pigment network and a blue/white veil.

2 Reed RJ, Ichinose H, Clark WH Jr, Mihm MC Jr. Common and uncommon melanocytic nevi and borderline melanomas. *Semin Oncol* 1975; **2**: 119–47.
3 Cox NH, Aitchison TC, Sirel JM, MacKie RM. Comparison between lentigo maligna melanoma and other histogenetic types of malignant melanoma of the head and neck. Scottish Melanoma Group. *Br J Cancer* 1996; **73**: 940–4.
4 Clark WH Jr, Elder DE, Guerry DT *et al*. Model predicting survival in stage I melanoma based on tumor progression. *J Natl Cancer Inst* 1989; **81**: 1893–904.
5 Elder DE, Murphy GF. *Melanocytic Tumors of the Skin*. Washington, DC: American Registry of Pathology, in press.

Clinical diagnostic aids

The clinical diagnosis of melanoma is based upon recognition of a progressively changing melanocytic lesion, which is growing and becoming irregular in shape and colour.

There are two diagnostic systems, which are intended to aid recognition by non-experts and the general public. Both apply mainly to the superficial spreading variant of malignant melanoma, which is the commonest subtype and generally has a relatively slow growth rate, at least in its early radial growth phase. These are the American ABCD categories and the Glasgow seven-point check-list. The American ABCD mnemonic is A = asymmetry, B = irregular border, C = irregular colour and D = diameter over 1 cm. The Glasgow seven-point check-list is divided into three major and four minor features. These are:

Major features:
1 Change in size
2 Change in shape
3 Change in colour

Minor features:
4 Diameter more than 5 mm
5 Inflammation
6 Oozing or bleeding
7 Mild itch or altered sensation.

It is suggested that any lesion with one major feature in an adult be considered for removal, and that the presence of additional minor features should add to clinical suspicion. For experts and possibly even for non-experts, however, assessment of lesions appears to be made using a 'global' assessment and it may be that widespread availability of images of melanomas may be the most effective means to promote recognition [1]. Images on the Internet may be particularly helpful here.

A number of computer-based systems are in clinical trial to aid in the diagnostic process, but these remain of unclear value.

Reference

1 Bishop JN, Bataille V, Gavin A *et al*. The prevention, diagnosis, referral and management of melanoma of the skin: concise guidelines. *Clin Med* 2007; **7**: 283–90.

Melanoma: specific histogenetic types, sites and variants

Superficial spreading melanoma

This is by far the most frequent type of melanoma. The commonest sites are the female leg and the male back, but any body site may be involved. An evolving, superficial spreading melanoma has the appearance of a flat, pigmented lesion, which becomes increasingly irregular in shape and colour over time. Shades of brown, black, red and grey or white may be present (Figs 54.49–54.51). The red colour usually indicates a degree of inflammation/vascular neogenesis and the resultant 'juicy' appearance should cause concern. White–grey areas may be indicative of a degree of regression. The lesion may still be very small, only 4–5 mm in diameter, but there may be a history of growth or change, and of subtle altered sensation, often described as a new awareness of the lesion or a tickling sensation. At this stage, the lesion will almost certainly be in the early radial growth phase, but as growth continues the lesion will become palpable, indicating that the lesion is progressing to the vertical growth phase. If the melanoma is developing in a pre-existing naevus, which occurs in approximately 50% of lesions, the irregular appearance of the growing melanoma may contrast strikingly with the more regularly pigmented and outlined residual naevus component.

Differential diagnosis. Benign naevi are usually smaller than melanoma, have a regular oval or circular outline, and are a uniform shade of brown. Seborrhoeic keratoses are dull, non-reflective lesions, which have a hyperkeratotic surface and a tendency to crumble. The main differential diagnosis in practice is between an early melanoma and a benign but atypical melanocytic naevus. A history of growth or change strongly suggests early melanoma, as does a size of 6 mm or greater, but the clinical features may be very similar in atypical naevi and early melanomas, and an excision biopsy may be needed.

Dermoscopy is an essential diagnostic aid for early melanoma. The most widely used dermoscope allows a 10-fold magnification. Fluid placed on the lesion (oil, water or even antiseptic gel) eliminates surface reflection and renders the cornified layer translucent, thus allowing a better visualization of pigmented structures within the epidermis, the dermoepidermal junction and the superficial dermis. The size and shape of vessels of the superficial vascular plexus can also be inspected. The technique of dermoscopy requires training; there are tutorials on the Internet [1–3] but it is desirable to attend a course. Benign naevi typically have an even pigment pattern on dermoscopy, which might be reticulate or globular. Melanomas typically have a disordered pigment pattern with variation in size of the pigment network, variably sized dots and often blue-grey or blue-white areas (Fig. 54.51).

There are also currently a number of computerized image analysis systems in development to aid preoperative diagnosis of malignant melanoma. These include the Mole Max system™ and spectrophotometric intracutaneous analysis using the Siascope. The absolute value of these machines in increasing both sensitivity and specificity of preoperative diagnosis of melanomas, thus reducing the number of unnecessary removals of benign naevi in routine practice, is not yet established.

Biopsy. All patients with suspected malignant melanoma should have an excision biopsy of the lesion carried out with a margin of 1–2 mm of clinically normal skin. This will enable the pathologist both to confirm the diagnosis and also to measure the thickness of the melanoma, which is an essential guide to further management. In rare situations when an excisional biopsy is not practical, such as a large possible melanoma on the face, an incisional biopsy from the area of the lesion which appears to be most invasive is acceptable, provided any necessary definitive surgery follows promptly. This procedure should probably be carried out by specialists.

Incisional or punch biopsies should not be performed in suspected melanoma because of sampling error, because an inaccurate tumour thickness may be obtained due to biopsy trauma, and also because the overall shape and symmetry of the whole lesion is important to the diagnosis of melanocytic lesions. There is a theoretical risk of displacing melanoma cells deeper into the dermis, although there is no evidence for this.

The surgeon should measure accurately the clinical excision margins, as biopsy samples shrink by 20–30% during fixation in formalin and the pathologist may report a narrower margin than was excised. It is the clinical rather than the pathologically measured excision margins that should be used in decisions concerning further surgery.

Pathology. The specimen should be examined by the pathologist in total. Features required in the biopsy report are the diagnosis, the tumour thickness, histogenetic type, growth phase, presence (and probably width) of ulceration, presence of regression, presence of tumour infiltrating lymphocytes (and whether they are brisk or non-brisk) [4], an estimate of the number of mitoses in the tumour, and whether there is evidence of vascular invasion. The presence of regression, if observed, may influence decisions on the width of definitive excision. Clark levels add little prognostic information for thicker primary melanomas, but should also be included, particularly for melanomas less than 1 mm in thickness, as Clark level 4 lesions in this thickness range appear to have a worse prognosis than level 3 lesions. In about 40% of cases [5] there will be pathological evidence of a pre-existing, benign melanocytic naevus on which the melanoma has developed. In these cases the pathologist may feel it necessary to give two tumour thicknesses, one measuring the entire thickness of the lesion and one measuring only to the deepest obvious tumour cell, ignoring any deeper apparent naevus cells. The presence of desmoplasia or neurotropism should be recorded.

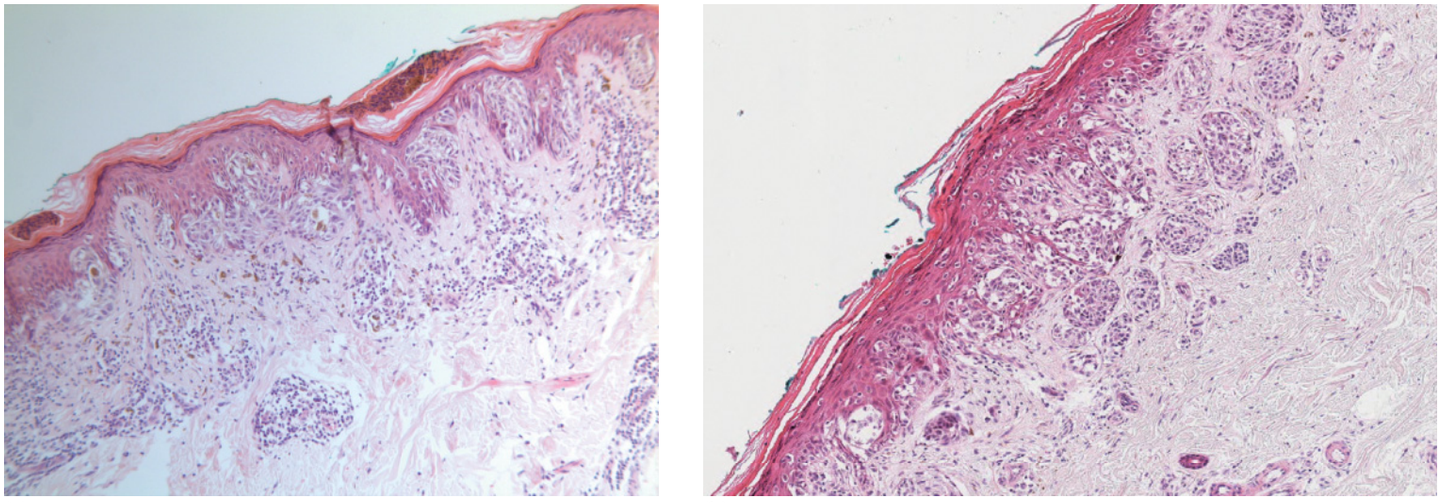
The margin of excision should be recorded—both the minimum lateral margin and the deep margin in mm.

The essential pathological features of superficial spreading melanoma are the presence of a focus of malignant melanoma cells invading the dermis with areas of *in situ* malignant change in the adjacent epidermis. This consists of the presence of cytologically atypical melanocytes in the suprabasal layers of the epidermis, both singly and in clumps (Fig. 54.52). On H&E sections, the pattern may be very similar to that seen in extramammary Paget's disease, and the term pagetoid melanoma may therefore also be used to describe this lesion.

The verrucous variant. These are melanomas simulating benign warts that are easy to miss. They are characterized by gross hyperkeratosis and also epidermal hyperplasia. The significance of this lesion is the fact that it is not usually recognized clinically because of the hyperkeratosis, and it may be confused with both benign and malignant lesions derived from the keratinocyte, such as a seborrhoeic keratosis or a squamous cell carcinoma.

Pathological differential diagnosis. There are two quite distinct problems in pathological differential diagnosis of primary malignant melanoma. The first is distinguishing it from benign melanocytic naevus, the second is distinguishing non-melanocytic but malignant tumours, either primary or secondary. These are more often a problem when a clinically indeterminate, large nodule is excised.

The differentiation between benign and malignant melanocytic lesions rests on both the pattern of involvement and the cytological features of individual cells. The association of cytologically atypical melanocytic cells in the upper layers of the epidermis with apparent proliferation at the dermoepidermal junction and invasion of the underlying dermis by atypical melanocytic cells is a malignant pattern. The cells in the deeper areas of the dermis



(a) (b)

Fig. 54.52 (a) The histological appearance of an *in situ* melanoma with atypical melanocytes within the epidermis. There are dermal inflammatory cells but no tumour cells. (b) A superficial spreading melanoma showing more proliferation of tumour cells in the epidermis (known as pagetoid spread). Dermal nests of tumour cells indicate that the tumour is in vertical growth phase.

will show no maturation such as is seen in a benign naevus with dermal involvement. The cytological characteristics of malignancy are a high nuclear to cytoplasmic ratio, intense nuclear staining, size variation between adjacent cells and the presence of abnormal mitotic figures.

Two of the more difficult pathological differential diagnoses of melanoma are the halo naevus and the Spitz naevus. It is unusual for a melanoma to elicit as intense a lymphocytic response as in the halo naevus, but a careful search should be made through the lymphocytic infiltrate in a putative halo naevus for cytologically malignant cells, particularly if the clinical information suggests an unusual history, such as presence in an elderly individual.

The differentiation between malignant melanoma and Spitz naevus can be extremely difficult, as discussed above. Features suggesting that the lesion is a melanoma and not a Spitz naevus are asymmetry with a poorly defined lateral margin, the presence of abnormal (or deep) mitoses in the melanocytic cells, lack of any maturation or differentiation in the deeper naevus cells, nuclear pleomorphism, and an epithelioid cell pattern with striking lack of adhesion of one cell to the other. These features are not absolute, and there are times when it may be necessary to state that a firm diagnosis cannot be made on pathological grounds when the term STUMP is used, as discussed above. In such cases the lesion should be managed as if it was a melanoma.

A range of antibodies are currently in routine diagnostic use. They will confirm the melanocytic nature of the lesion, but cannot differentiate between benign and malignant melanocytic lesions. S100, gp100/HMB-45, typrosinase, MART-1/Melan-A and HMW_MAA are melanocyte differentiation markers. S100 is less specific than the other three, but highly sensitive and therefore is usually used in combination with at least one of the others [6].

Definitive surgical treatment to the primary site. Once the diagnosis of primary malignant melanoma is established, and the thickness of the melanoma has been measured, the definitive excision can be planned. The extent of this excision will relate to the tumour thickness. At present, if the diagnosis is of a level 1 or *in situ* melanoma, a margin of only 2–5 mm of surrounding normal skin is considered adequate [7]. This may have been included in the diagnostic biopsy and therefore no further surgery may be necessary. There are no data, however, to support this margin, and the rare occurrence of a 'field effect' of atypical melanocytes around primary melanoma means that the patient and his doctor often elect to remove up to 1 cm of normal skin, especially if a second operation is required.

Invasive melanomas up to 2 mm thick may be safely treated with a minimal excision margin of 1 cm based upon the WHO trial [8]. Patients with thicker tumours are more likely to develop lymph node recurrence if a 1-cm margin is used [9], and therefore the recommended excision margin is 2 to 3 cm [7] where anatomically possible. Margins of this size are most difficult to achieve on the face.

In some centres, sentinel node biopsy (see p. 54.51) is offered to patients as a staging tool. Sentinel node biopsy can only be carried out at the time of wide local excision of the primary and therefore patients should be counselled about this option prior to definitive excision.

References

1 DS Medica. *Dermoscopy*. http://www.dermoscopy.org

2 New Zealand Dermatological Society. *Dermoscopy*. http://dermnetnz.org/procedures/dermoscopy.html

3 Interactive Medical Media. Dermatology lectures on line. *Dermoscopy*. http://www.dermlectures.com

4 Elder DE, Murphy GF. *Melanocytic Tumors of the Skin*. Washington, DC: American Registry of Pathology, in press.

5 Purdue MP, From L, Armstrong BK *et al*. Etiologic and other factors predicting nevus-associated cutaneous malignant melanoma. *Cancer Epidemiol Biomarkers Prev* 2005; **14**: 2015–22.

6 de Wit NJ, van Muijen GN, Ruiter DJ. Immunohistochemistry in melanocytic proliferative lesions. *Histopathology* 2004; **44**: 517–41.



(a) (b)

Fig. 54.53 Two nodular melanomas. (a) A melanoma that has already developed *in transit* metastases. (b) A nodular component of a melanoma that has evolved over time from an atypical naevus, which can be seen in the image.

7 Newton Bishop JA, Corrie PG, Evans J *et al*. UK guidelines for the management of cutaneous melanoma. *Br J Plast Surg* 2002; **55**: 46–54.
8 Veronesi U, Cascinelli N. Narrow excision (1-cm margin). A safe procedure for thin cutaneous melanoma. *Arch Surg* 1991; **126**: 438–41.
9 Thomas JM, Newton-Bishop J, A'Hern R *et al*. Excision margins in high-risk malignant melanoma. *N Engl J Med* 2004; **350**: 757–66.

Nodular melanoma

This variety presents most commonly in the fifth or sixth decade and occurs more frequently in males than in females. The trunk is a common site. These lesions grow rapidly and are therefore more likely to present as thicker tumours and they tend, therefore, to have a poor prognosis. Thicker tumours are more common in the elderly and diagnostic delay may be associated with living alone and lack of knowledge [1].

Nodular melanomas develop as an elevated, dome-shaped polypoid or even pedunculated structure (Fig. 54.53). Melanin pigment may be sparse in these lesions and a raised, red central area, with only a peripheral brown ring of melanin, is a common clinical pattern; in others the more typically variable pigmentation may be seen. Ulceration and bleeding from the lesion occur frequently. This variety of malignant melanoma is misdiagnosed prior to surgery more frequently than either a superficial spreading melanoma or a lentigo maligna melanoma, as they may be symmetrical and have a relative lack of melanin pigment. Thus they are not readily identified using the ABCD rule, for example.

Lesions to consider in the differential diagnosis are angioma or pigmented basal cell carcinoma. Histiocytoma or sclerosing angioma may also cause clinical confusion. Dermoscopy is very helpful in distinguishing melanoma from these benign lesions.

Pathology. The nodular melanoma has the pathological features of a focus of invasive melanoma cells in the dermis with direct contact with the immediately overlying epidermis, but no morphological abnormality apparent in the adjacent epidermis on either side of the invasive nodule (Fig. 54.54). This is, therefore, a primary melanoma with no recognizable adjacent *in situ* or radial growth phase. There is a tendency to use the term nodular melanoma inappropriately for any primary melanoma that has a visible nodule. This is incorrect usage, as superficial spreading, acral and lentigo maligna melanomas can all develop elevated nodular areas in the course of later growth.

Management. The management of nodular melanoma is the same as for superficial spreading melanoma, described above.

Reference

1 Baumert J, Plewig G, Volkenandt M, Schmid-Wendtner MH. Factors associated with a high tumour thickness in patients with melanoma. *Br J Dermatol* 2007; **156**: 938–44.

Lentigo maligna melanoma

In this histogenetic variant the preceding horizontal or *in situ* growth phase is known as a lentigo maligna (Hutchinson's melanotic freckle; melanosis circumscripta precancerosa of Dubreuilh). By comparison with the radial growth phase of the superficial spreading melanoma, lentigo maligna represents a much more prolonged period of lateral extension. Most occur on the face, commonly on the upper cheek, temple or forehead: the facial skin most exposed to the sun through life. A small proportion of lentigo malignas are observed on extrafacial exposed sites such as the arm, hand or leg.

Occasionally, periocular lentigo maligna extends into the conjunctiva. Sometimes the *in situ* component may even arise in the conjunctiva as a condition known as 'primary acquired melanosis'

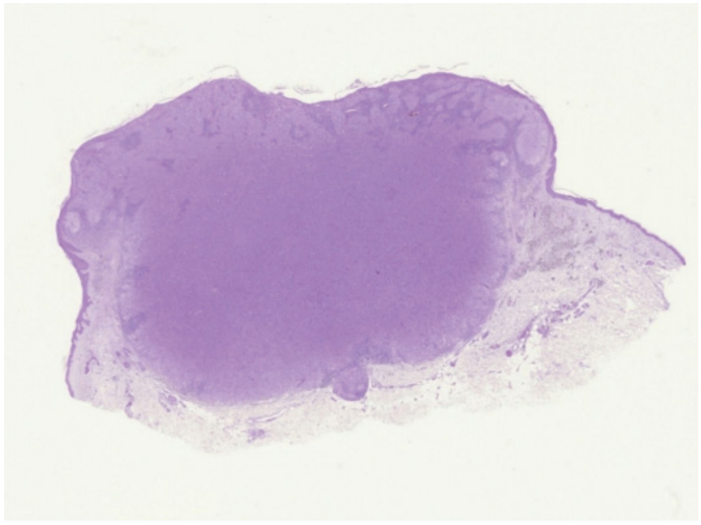


Fig. 54.54 A low power image of nodular melanoma pathology. (Courtesy of Dr S. Edward, Leeds Teaching Hospitals Trust, Leeds, UK.)



Fig. 54.55 Primary acquired melanosis of the eye, which can be likened to a continuum between an atypical naevus and *in situ* melanoma.

(PAM) [1]. PAM typically presents as irregular pigmentation at the limbus of the eye (Fig. 54.55). The pigmentation may progress very slowly over many years and then, generally, ophthalmic surgeons tend merely to observe, but a proportion do go on to invasive melanoma and melanoma may develop within the conjunctiva and in the adjacent skin. The histology of PAM has been subdivided into PAM with and without atypia, but PAM which progressed into melanoma is said to be architecturally more irregular and the melanocytes are more likely to be epithelioid in nature [1]. PAM bears some clinical and histological similarities to atypical naevi and indeed has been reported in patients with the atypical mole syndrome [2]. PAM may therefore be considered to be a continuum in the conjunctiva equivalent to the atypical naevus/*in situ* melanoma spectrum.

The *in situ* component of lentigo maligna may be extremely slow growing and probably evolves from solar lentigos (although the vast majority of solar lentigos clearly do not progress). Progression from a solar lentigo to a lentigo maligna is usually characterized by darkening, enlargement and the development of a more defined edge (Fig. 54.56). A difficulty of management is that atypical melanocytes often extend out from the edge of the lentigo for considerable distances, even involving 'skip' lesions. This is often known as the 'field effect'. Treatment may therefore initially appear to be successful, yet there may commonly be recurrence at the edge after treatment.

A proportion of lentigo malignas will evolve into invasive melanoma, developing as discrete colour change or nodules within the lentigo (Fig. 54.56). Rarely, the melanoma may be desmoplastic in type, in which case the lesion may present as a central, firm thickening, within a macular pigmented area, which may be quite subtle. These melanomas are very easy to misdiagnose; it is particularly important to write the differential diagnosis of desmoplastic melanoma on the histopathology form if there is any suspicion at all of this diagnosis, so that the pathologist will carry out an S100 stain.

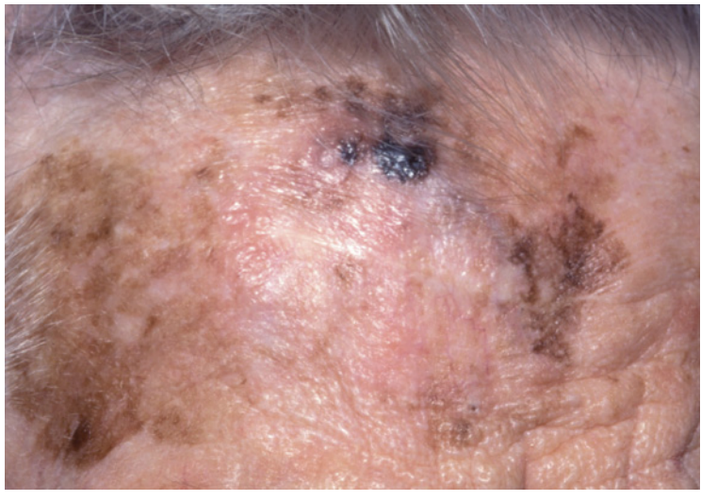


Fig. 54.56 A very extensive lentigo maligna melanoma in which a nodular element developed at the hair line.

Patients tend to be older than those presenting with the other types of melanoma. Many of the identified risk factors suggest that the aetiology of this variety of melanoma has a greater similarity to squamous cell carcinoma than to the other melanoma variants. Affected patients have evident solar damage both clinically and pathologically.

Initially the lentigo maligna is a flat, brown or black, irregularly shaped lesion. These lesions will grow very slowly, over months or years, and there may be central regression while the peripheral margin continues to extend. In time, a raised central nodule will develop, indicating transition to the vertical growth phase.

In clinic, referral of macular pigmented facial lesions is common and the differential diagnosis of very early lentigo maligna includes solar lentigo, and pigmented actinic keratoses and the

flatter variant of seborrhoeic keratoses. Both of the latter tend to have more surface scaling, lack a visible melanin pigment network and have a dull, non-reflective surface. Size, depth of colour and irregularity of pigment are pointers to the diagnosis of lentigo maligna.

Pathology. This variant of melanoma is the most distinct histologically. It has a long pre-invasive or radial growth phase, during which there is striking lentiginous replacement of the basal keratinocytes by atypical melanocytes but no downward invasion into the underlying dermis, which will show actinic damage of the dermal collagen. During this phase, the names *lentigo maligna* or Hutchinson's melanotic freckle are appropriate. There is also often extensive colonization of the hair-follicle epithelium by atypical melanocytes. After a variable period of time, invasion into the underlying dermis will take place. The site of such early invasion in its earliest stages may be marked by a lymphocytic infiltrate. Once obvious dermal invasion is present, the name *lentigo maligna melanoma* is appropriate (Fig. 54.57).

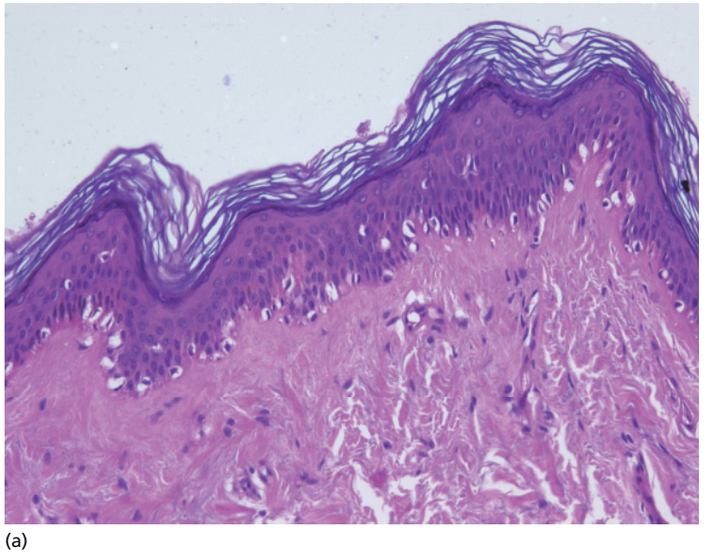
Desmoplastic, neurotropic and myxoid variants. The very rare desmoplastic variant of malignant melanoma may be seen in association with chronically sun-damaged skin and overlying lentigo maligna in the epidermis. The clinical appearance may be very subtle and has few easily recognizable features. In desmoplastic melanoma arising from lentigo maligna then, the lesion may present as a subtle area of thickening associated with macular pigmentation. In other sites it may resemble a pink scar-like nodule (Fig. 54.58) and there may be an inflammatory component.

As the name suggests, this lesion represents a combination of malignant melanocytes in association with extremely dense desmoplastic change of the dermis. The stromal change in the dermis is usually much more obvious than the malignant melanocytes, which may be few in number. If an S100 stain is not carried out it may be extremely difficult to recognize the lesion as a melanoma, as the spindly dermal cells extend singly between the more obvious stromal cells.

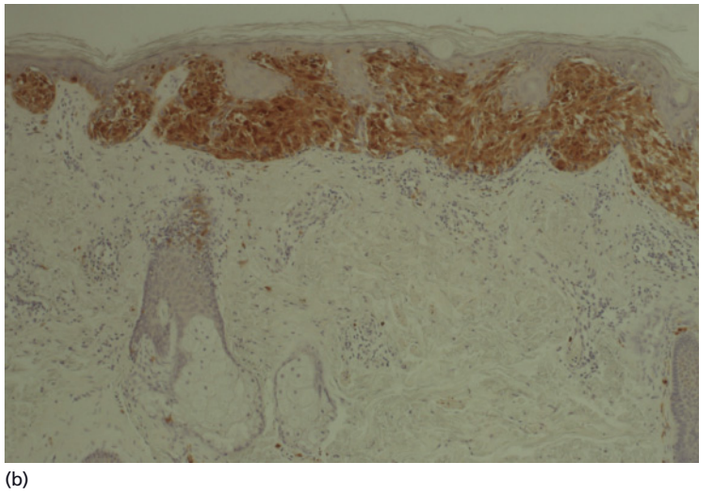
The clinical importance of this variant is that it can be difficult to be absolutely certain that excision is complete, and local recurrence is a common problem.

In a review of published studies of desmoplastic melanoma [3], a total of 856 patients with this diagnosis were evaluated in the 17 included studies. There were 539 males (63.0%) and 317 females (37.0%). The mean age of patients varied from 55.6 to 71.3 years across the included studies, while the age range was from 4 to 99 years. The lesions were most commonly located on the head and neck (53.2%), followed by the extremities (20.6%) and the trunk (26.2%). Desmoplastic melanoma is associated with a high local recurrence rate, a lower nodal recurrence rate but systemic metastatic rates not dissimilar from melanoma as a whole [3]. Overall survival in 16 published studies ranged from 67.1 to 100%. Disease free survival in 14 studies at the end of follow-up ranged from 52 to 100%.

A pathological variant sometimes coexisting with the desmoplastic pattern is the neurotropic melanoma. In this variant, the pattern of metastatic spread is along the cutaneous nerve trunks.



(a)



(b)

Fig. 54.57 The range of pathologies described as lentigo maligna. (a) Very early lentiginous proliferation. (b) Confluent proliferation at atypical melanocytes in a lentigo maligna melanoma; the slide has been stained with S100. (Courtesy of Dr S. Edward, Leeds Teaching Hospitals Trust, Leeds, UK.)

This is seen particularly in lesions on the head and neck area, and may cause severe, relentless pain. In a review of desmoplastic melanoma, the percentage of desmoplastic melanomas with neurotropism ranged from 16.7 to 77.8% among included studies [3]. As with the desmoplastic variant, completeness of excision can be difficult to determine. Myxoid melanoma is a rare variant in which there is a striking myxoid stroma in the dermis surrounding malignant spindle cells. The morphology has some features in common with desmoplastic melanoma.

Treatment of lentigo maligna. The diagnosis of lentigo maligna is made clinically and confirmed histologically. It is one of the very few instances where incisional biopsy of a melanocytic lesion is justifiable, where a suspicious but large macular lesion is present in a cosmetically sensitive area such as the face. The site for incisional biopsy is chosen based upon clinical examination and

dermoscopy, choosing the most irregular or darkest area of pigmentation and/or any palpable or thickened areas. More than one site may be necessary. The concern is both to make the diagnosis of lentigo maligna and to determine the presence of invasion; however, exclusion of the presence of any invasive disease requires examination of the whole lesion.

If the diagnosis of lentigo maligna is confirmed, then the treatment is usually surgical excision. However, there are few clinical trial data to inform that choice. Standard excision with 5-mm margins proves to be insufficient in 50% of cases. The recurrence rate with standard excision ranges from 8 to 20%. Mohs' micrographic surgery and staged excision may offer better margin control and lower recurrence rates (0–5%) [4,5]. Estimates of recurrence rates following non-surgical therapies such as cryosurgery, radiotherapy, electrodesiccation and curettage, laser surgery, and topical medications range from 20 to 100% at 5 years [4]. The most pressing argument for surgical excision is the consequent ability to review the whole specimen for invasive disease, which occurs in 5 to 16% of lentigo malignas excised [6,7].

Topical imiquimod is an encouraging new therapeutic option but the data so far are few, and randomized clinical trials are needed. It may cause significant inflammation or ulceration at the site (Fig. 54.59) or, when treating the face, on the lip (Fig. 54.60). A review summarized 11 case reports and four open-label studies, with a total of 67 patients. There was significant variability in treatment schedules and regimens. Eight patients failed to respond, with lentigo maligna melanoma developing in two of these. In certain cases there were discrepancies between clinical and histological response with some patients clearing clinically but not histologically, and vice versa. Follow-up periods were short, exceeding 12 months in only five cases [8]. Some centres are using surgery as the primary treatment with imiquimod as an adjuvant but this needs to be formally evaluated. The development of lentigo maligna melanoma within lentigo maligna incompletely eradicated by imiquimod is a concern.

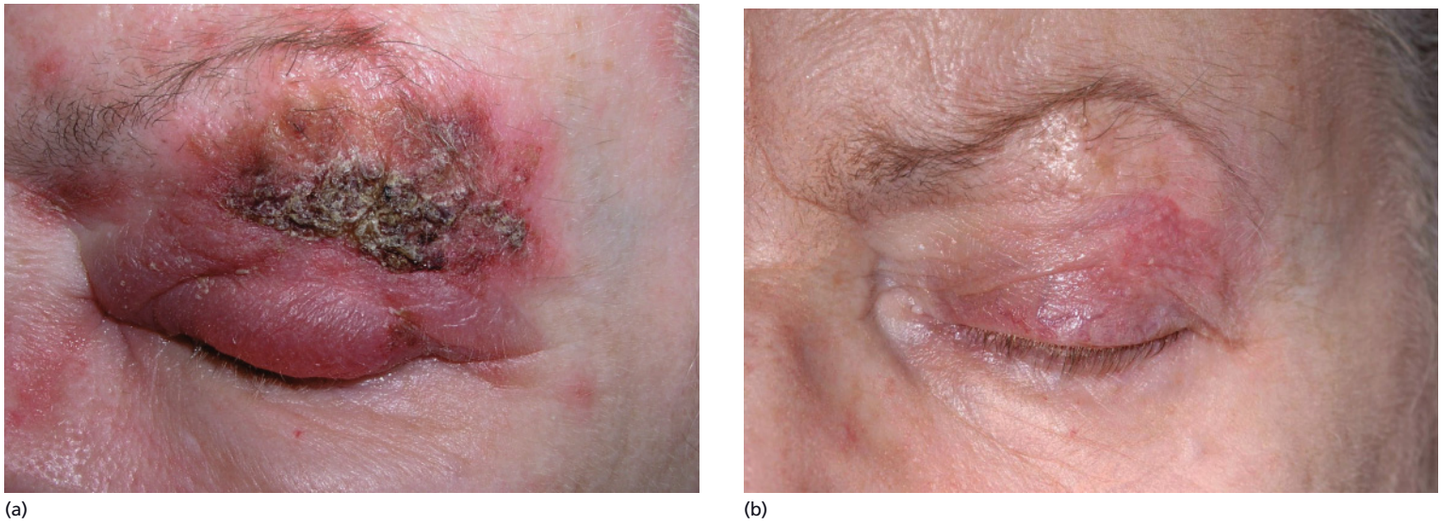


Fig. 54.58 An ill-defined, ulcerated lesion which proved to be a desmoplastic melanoma. Desmoplastic melanoma can be very difficult to diagnose clinically, being commonly sparsely pigmented but indurated to the touch.

Treatment of lentigo maligna melanoma. The treatment of the melanoma is as for other sites in that the margin of excision for tumours thinner than 2 mm is 1 cm minimum and for thicker tumours should be 2 to 3 cm. It is recognized, however, that on the face these margins may not be attainable without unacceptable cosmetic deficit. The surgery is also subject to the same constraints as described above for lentigo maligna, in that there is a high local recurrence rate of the *in situ* component.

References

1 Sugiura M, Colby KA, Mihm MC Jr, Zembowicz A. Low-risk and high-risk histologic features in conjunctival primary acquired melanosis with atypia: Clinicopathologic analysis of 29 cases. *Am J Surg Pathol* 2007; **31**: 185–92.



(a) (b)

Fig. 54.59 This lady had persistent local recurrence of lentigo maligna on the eyelid. (a) She was treated with imiquimod and developed a profound inflammatory response. (b) The inflammation settled promptly and the response to treatment was clinically complete.



Fig. 54.60 Ulceration of the lip occurs quite commonly when imiquimod is used to treat lentigo maligna on the face. This may represent an immunological reaction to quiescent herpes.

2 Bataille V, Boyle J, Hungerford JL, Newton JA. Three cases of primary acquired melanosis of the conjunctiva as a manifestation of the atypical mole syndrome. *Br J Dermatol* 1993; **128**: 86–90.

3 Lens MB, Newton-Bishop JA, Boon AP. Desmoplastic malignant melanoma: a systematic review. *Br J Dermatol* 2005; **152**: 673–8.

4 McKenna JK, Florell SR, Goldman GD, Bowen GM. Lentigo maligna/lentigo maligna melanoma: current state of diagnosis and treatment. *Dermatol Surg* 2006; **32**: 493–504.

5 Temple CL, Arlette JP. Mohs micrographic surgery in the treatment of lentigo maligna and melanoma. *J Surg Oncol* 2006; **94**: 287–92.

6 Agarwal-Antal N, Bowen GM, Gerwels JW. Histologic evaluation of lentigo maligna with permanent sections: implications regarding current guidelines. *J Am Acad Dermatol* 2002; **47**: 743–8.

7 Bub JL, Berg D, Slee A, Odland PB. Management of lentigo maligna and lentigo maligna melanoma with staged excision: a 5-year follow-up. *Arch Dermatol* 2004; **140**: 552–8.

8 Rajpar SF, Marsden JR. Imiquimod in the treatment of lentigo maligna. *Br J Dermatol* 2006; **155**: 653–6.

Acral lentiginous melanoma (palmoplantar malignant melanoma)

This type of melanoma comprises around 10% of all melanomas on white skin but over 50% of all melanomas on darker-skinned peoples. It is the commonest type of melanoma, for example, in Japan. The recorded incidence in different ethnic groups is around 1 to 2 per million per annum [1]. The lesions are found mainly on the sole of the foot but also on the palm of the hand, and are characterized, as their name would suggest, by a large, macular, lentiginous pigmented area around an invasive, raised tumour. Approximately 50% of all melanomas on the foot are of this type (Fig. 54.61).

This precursor *in situ* component is in many ways similar to lentigo maligna in that its growth rate may be very slow, it may be very extensive, and it shows a tendency to recur because of failure to excise sufficient normal skin laterally (Fig. 54.62).

The clinical differential diagnosis may include a plantar wart, which is a common cause of delayed diagnosis, and black heel (talon noir) (Chapter 28), due to haemorrhage into the superficial layers of the epidermis. Any tender, growing nodule, or an 'ulcer' that won't heal, on the sole of the foot, should give rise to concern that the lesion is a melanoma and biopsy should be considered. The risks of missing the diagnosis are higher in circumstances where delayed healing of an ulcer is expected, such as in a diabetic ulcer.

Pathology. The essential pathological features are the presence of an extensive area of lentiginous change in the epidermis around the focus of invasive primary melanoma. In early disease, the lentiginous component may be large, but the invasive focus is small and difficult to find, requiring cutting of many sections. The basal keratinocytes are replaced by cytologically malignant melanocytes, and there is often an associated inflammatory flare of lymphoid cells in the underlying dermis. An important feature is the presence of skip areas, with foci of relatively normal epidermis in areas of gross lentiginous change, as in lentigo maligna. This feature makes it particularly important to examine the excision specimen thoroughly to determine whether or not the lesion has been completely excised.

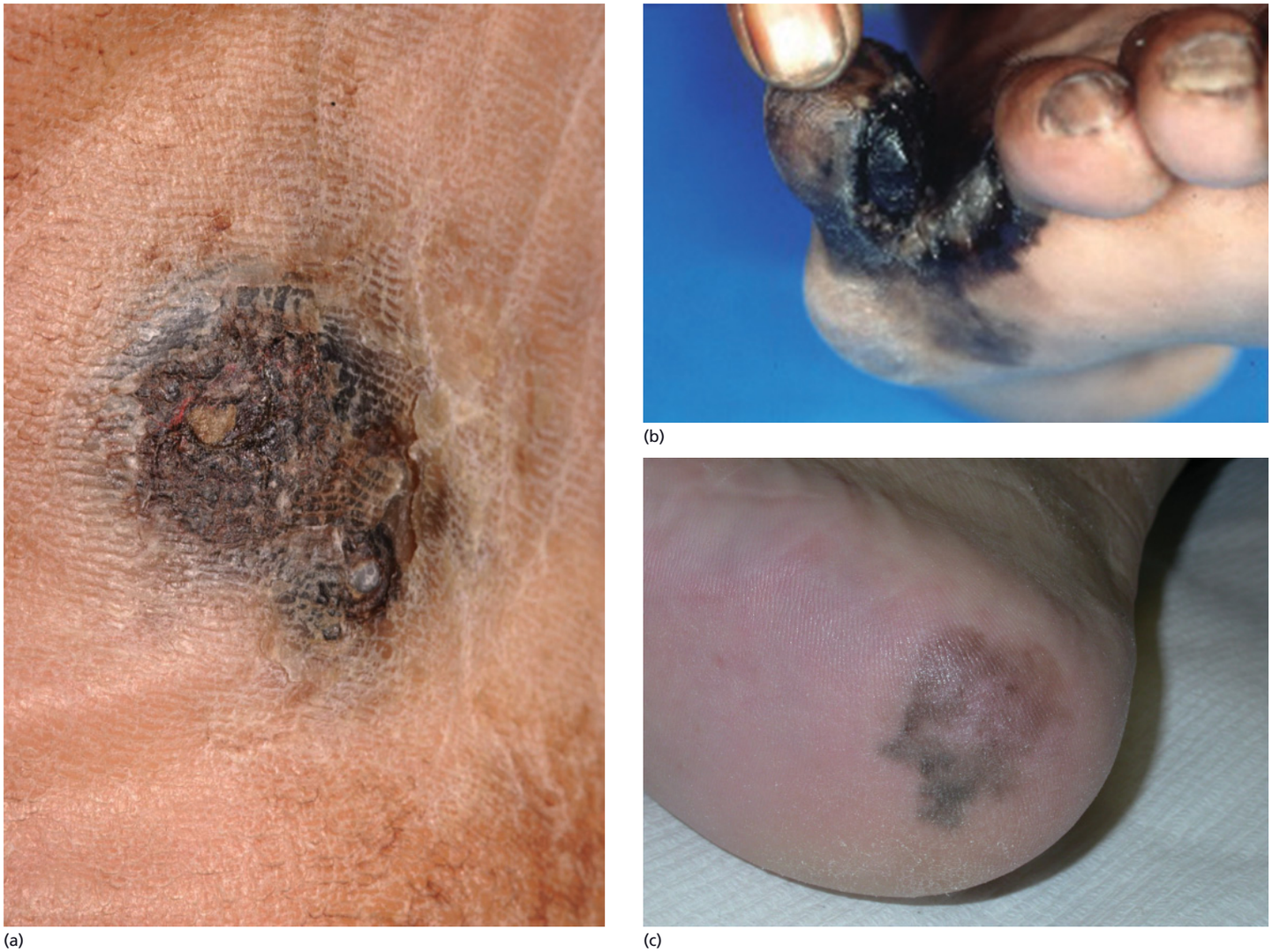
Treatment. As for lentigo maligna, the management of acral lentiginous melanoma is one of the few occasions where incisional biopsy may be acceptable in order to plan treatment. The area chosen is that showing the most pigmentary irregularity or the most palpable nodular area.

The margins of excision are as for melanomas in other sites, 1 cm for tumours thinner than 2 mm and 2 to 3 cm for thicker tumours. As for other melanomas characterized by extensive *in situ* disease, however, there is also a need to resect adjacent precursor lentiginous hyperplasia so that the clinical margin should be measured from the most distal area of macular pigmentation. It can be easier to see this margin if emollient is applied to the sole before examination. If the patient has elected to proceed to sentinel node biopsy, this would be carried out at the time of definitive surgery. The margins used in practice are subject to the functional implications of the surgery. Acral lentiginous melanoma is commonly on the weight-bearing sole and the implications of the surgery must be discussed with the patient and in practice a compromise may be reached between margin and function.

Subungual melanoma

Subungual melanomas are rare. Like acral lentiginous (palmoplantar) melanomas they occur in people of all skin types and their aetiology is unknown. They are most common on the thumb or the great toe. It has been suggested that this indicates that trauma may play a role in their aetiology, but this localization may simply reflect the relative surface area (and therefore the number of melanocytes) of the nail matrix from which all subungual melanomas are thought to arise.

Because they arise from the nail matrix, subungual melanomas usually produce an abnormal nail and a variable degree of pigmentation of the nail itself. The classical presentation is of a new, linear, pigmented band along the length of the nail, which starts to widen progressively, especially at the base, so that the pigmented band tends to be funnel shaped. Over time, proliferation of the melanoma cells within the nail matrix then additionally



(a) (b) (c)

Fig. 54.61 (a, b, c) Three acral lentiginous melanomas arising on the sole of the foot in a black, asian and white-skinned person, respectively. This is the only form of melanoma to have a similar prevalence in all ethnic groups.

interferes with nail formation and a progressively dystrophic nail results (Fig. 54.63). Eventually, pigment may spread to the surrounding normal skin as 'Hutchinson's sign'.

A sizeable proportion of subungual melanomas, however, are either amelanotic or produce little pigment so that the 'classical' linear pigmented band is actually uncommon. In these tumours, therefore, the lesions present as a progressively abnormal nail, such as a fissured nail or destruction of the nail beginning proximally.

Subungual melanoma is commonly diagnosed at a late stage in development because of earlier confusion with a benign melanocytic lesion, a traumatic haemorrhage under the nail, pyogenic granuloma, persistent paronychia, a fungal infection or even a subungual wart. A high degree of suspicion is required if subungual melanoma is not to be missed. Dermoscopy may help; a band of brown to black pigment comprised of thin irregular bands which are not parallel may be seen in melanoma [2] and origin from the nail matrix may be confirmed. Subungual pigmentation due to causes other than melanoma, which must be considered as differential diagnoses, is usually distal rather than arising from the nail matrix.

Diagnosis. The diagnosis of early lesions usually requires biopsy of the nail matrix. The proximal nail plate may be reflected and the matrix biopsied. Pigment bands less than 3 mm in diameter may be biopsied using a punch biopsy, which may produce minimal damage if the lesion proves to be benign. Wider bands require elliptical biopsy, which is likely to damage the nail permanently [2]. Confirmed melanomas, or clinically obvious more advanced subungual melanomas, should be managed by expert multidisciplinary teams, as they are sufficiently rare and surgically difficult to merit pooling of experience.



Fig. 54.62 Two skin grafts used to treat multifocal acral lentiginous melanoma. Residual *in situ* or lentiginous disease is seen between the two grafts. The whole of the area was subsequently excised. Subtle precursor lentiginous disease is common.

Treatment. The treatment of subungual melanoma is surgical. The affected digit is usually the thumb or great toe and preservation of function is therefore highly desirable. Early lesions may therefore be managed, if possible, using excision and grafting. *In situ* disease, however, is very common in the skin around the nail and therefore it is rare to achieve adequate clearance without at least partial amputation. For more advanced disease partial amputation is the norm, through either the distal interphalangeal or proximal interphalangeal joints. The choice of surgical option should be made in discussion with the patient depending on the functional implications for the patient and the thickness of the tumour. Transplantation of a toe to the thumb stump may be possible to restore function. If the patient has elected to proceed to sentinel node biopsy this must be done at the time of definitive surgery.

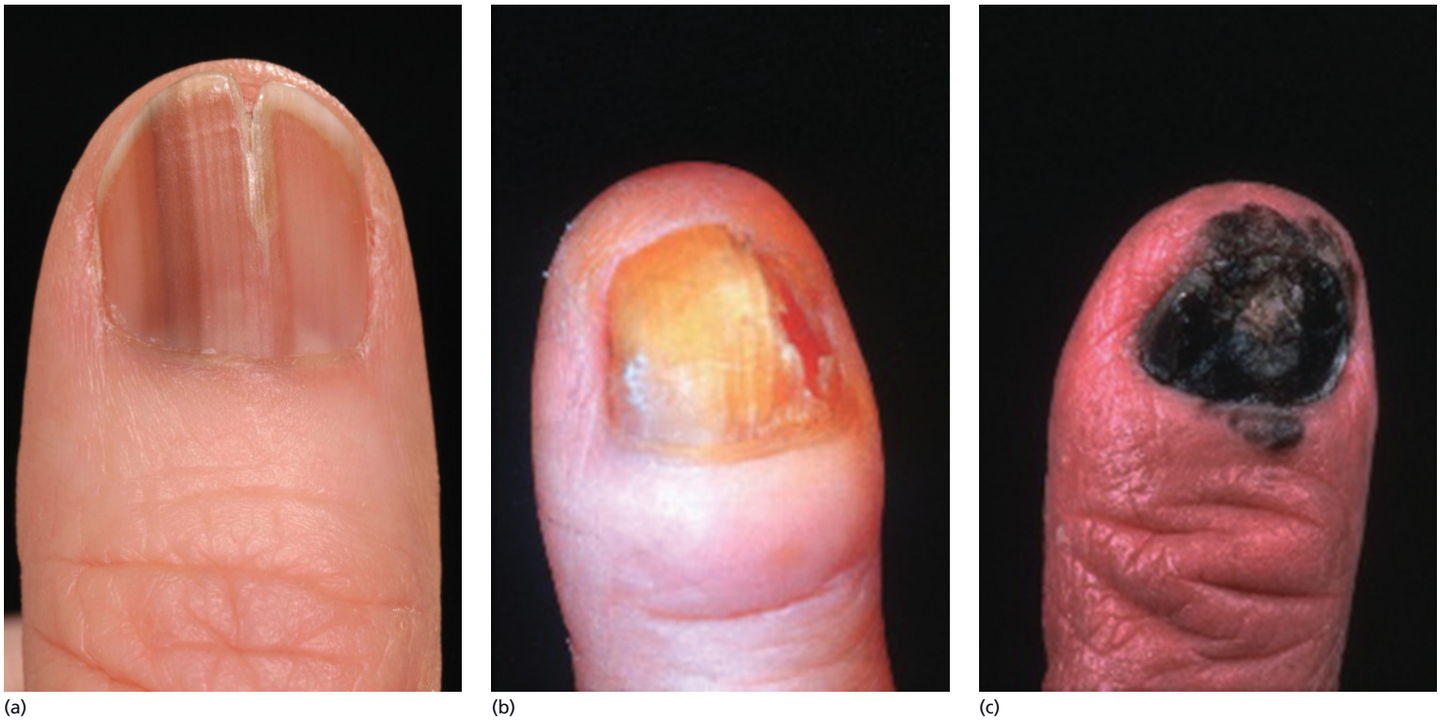
References

1 Stevens NG, Liff JM, Weiss NS. Plantar melanoma: is the incidence of melanoma of the sole of the foot really higher in blacks than whites? *Int J Cancer* 1990; **45**: 691–3.

2 Braun RP, Baran R, Le Gal FA *et al*. Diagnosis and management of nail pigmentations. *J Am Acad Dermatol* 2007; **56**: 835–47.

Mucosal melanoma

Mucosal melanomas are rare, but can be seen in the oral cavity, on the genital mucosa and in the perianal area. The most common presenting feature of mucosal melanoma is the presence of extensive, irregular macular pigmentation. This may be extensive but



(a) (b) (c)

Fig. 54.63 Subungual melanoma. (a) A linear, new, pigmented band and nail dystophy. (b) An amelanotic melanoma lifting up a dystrophic nail. (c) Typical pigmentation arising proximally, irregular in shape and colour.



Fig. 54.64 A melanoma arising on the buccal mucosa. In this site the appearance may be subtle.

spotty and may extend laterally for years before becoming elevated. Such lesions should be biopsied without delay, although clinically they may look deceptively benign (Fig. 54.64).

Genital melanomas are also discussed on p. 54.6. They are rare variants of melanoma, which unfortunately usually still present late as a mass or with vaginal bleeding. The average age at presentation is in the seventh decade, significantly older than for cutaneous melanomas. On biopsy the majority of the tumours are in vertical growth phase and unfortunately many are thick and have a poor prognosis (Fig. 54.65).



Fig. 54.65 Vulvar melanoma. This lesion is obviously deeply invasive and has a poor prognosis.

Pathology. Primary melanomas arising on the mucosal surface of the oral cavity, the vulvovaginal and the rectal areas have some features in common with acral lentiginous melanomas, and the term palmoplantar mucosal melanoma is sometimes used to describe the entire group. Extensive lentiginous change is frequently visible, both clinically and pathologically, and the focus of invasion may be very difficult to find in early tumours, even in the presence of obvious metastases.

Treatment. Wide local excision of the melanoma is necessary. The extensive surrounding *in situ* disease makes this difficult in practice in many patients, partly because of the anatomical constraints and partly because it is very difficult clinically to distinguish involved tissue from normal. It may be necessary to do multiple biopsies prior to surgery to determine the extent of disease, and radical excision is unfortunately often necessary. Where the margins of excision are by necessity suboptimal, topical imiquimod may be used to try and remove *in situ* disease, although the treatment may be difficult to tolerate and there are insufficient data to support its use.

Secondary melanoma from an occult primary site

About 8% of melanomas present as metastatic disease from an unknown primary. The commonest site of the metastasis is regional lymph nodes but very rarely the patient may present with stage IV disease. In the majority of such patients, there is evidence of a regressed primary, presenting typically as an area of depigmentation, or a history of a lesion, which spontaneously cleared. Rare primary sites should, however, be inspected, such as the mucosae (including the anus). In a proportion, however, no origin for the metastasis can be found. As naevus cells may be seen not uncommonly in the subcapsular area of lymph glands it seems possible that melanoma may arise *de novo* in a lymph gland.

Where no origin for the melanoma can be found, the disease should be treated as usual; lymph node metastases should be treated by block dissection after imaging has been carried out.

Multiple primary malignant melanomas

At present around 5% of patients who have already had one melanoma diagnosed will develop a second and possibly a third or further primary melanoma. This is more common in patients with the atypical mole syndrome. These primaries are not infrequently in the same anatomical area, such as on one leg of a woman. This often causes concern that the second and later tumours might represent metastatic disease. It is important that the pathologist consider this as a possibility.

For patients who have had a thin melanoma diagnosed, the risk of a second primary melanoma is greater than the risk of the first melanoma metastasizing. Complete skin examination is therefore important in follow up of melanoma patients.

Treatment. Each primary should be treated by wide local excision. An important part of the management, however, is to take a family history, as the development of multiple primaries is indicative of genetic predisposition to melanoma. Patients who have a family history of melanoma comprise a proportion of those who

develop multiple primary melanomas, and a small number will have mutations in the *CDKN2A* gene. In the presence of a family history of melanoma or pancreatic cancer, referral to a specialist familial melanoma clinic or clinical geneticist is appropriate.

It is supposed that the majority of those who do not have a family history have lower risk susceptibility genes and have had extensive sun exposure, although a proportion will carry high-risk genes. Patients should be advised to moderate their sun exposure and taught how to self examine. Whilst all melanoma patients should also be advised to protect the skin of their families without becoming vitamin D deficient, this is particularly appropriate in the presence of multiple primaries and a family history.

Rare histological subtypes of melanoma

Naevoid melanoma (minimal deviation melanoma, small cell melanoma). A further pathological variant is the so-called naevoid, minimal deviation or small cell melanoma. These lesions lack epidermal involvement, are fairly well defined at their lateral margins, and the small naevoid cells in the dermis, which make up the bulk of the tumour, show partial differentiation. However, careful examination will reveal the presence of abnormal mitoses in naevomelanocytes. These lesions may be confused with compound naevi.

Animal-type melanoma. This is a rare pathological variant of melanoma, which, as the name suggests, has some morphological similarities to melanoma found in grey horses. Blue-black nodules are the clinical presenting feature, and the pathology shows heavy dermal melanin pigmentation with sheets of atypical spindle cells, which may be difficult to visualize without bleaching because of the quantity of pigment present. The epidermis is usually, but not always, involved, and mitotic figures may be difficult to find. Metastases to both regional nodes and to distant organs may occur.

Melanoma of the soft parts (clear cell sarcoma). This is a further rare pathological variant of malignant melanoma. The tumours usually arise on the tendons and aponeuroses. The ankle appears to be a relatively common site, and the tumours generally appear in young people. There appears to be no epidermal component, which gives rise to diagnostic confusion with various types of sarcoma, but the malignant cells contain premelanosomes and melanosomes. Plump, pale spindle cells with clear cytoplasm are seen in the tendons (Fig. 54.66). They may be deceptively bland on microscopy as mitotic figures are difficult to find, but both local recurrence and distant metastases are relatively common.

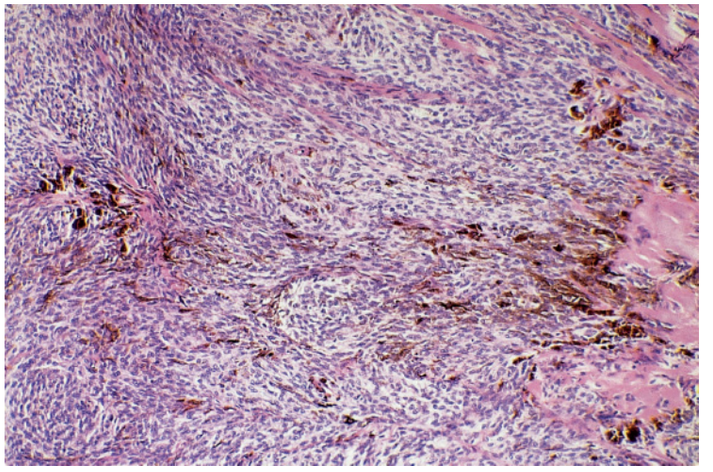


Fig. 54.66 Pathology of melanoma of the soft parts. Note the eosinophilic cytoplasm and also the pigmentation.

Childhood melanomas

Incidence. Metastasizing melanoma is fortunately extremely rare in children. The true incidence of cutaneous melanoma is unknown, not least because of the difficulties of histological diagnosis of melanoma in children and, in particular, its differentiation from the Spitz naevus, but pre-pubertal melanoma is thought to be rare [1].

After puberty the incidence of melanoma starts to rise slowly [2]; melanoma is unusual amongst solid tumours in that the incidence is proportionately greater in young adults. In Europe the age-standardized incidence rates for girls range from 0.2 new cases per million in Bulgaria to 3.8 in Norway [3]. Incidence is higher (as it is in adults) in Queensland, where the age-standardized incidence is 0.1/100 000 per annum in 0 to 4 year olds and 3/100 000 per annum in 10 to 14 year olds [4,5].

This section refers to melanoma in children both before and after puberty.

Aetiology. Childhood melanoma may occur in the normal host but there are three known predispositions: congenital naevi (see above), the atypical mole syndrome (AMS) (see above), familial melanoma and other cancer family syndromes such as retinoblastoma and xeroderma pigmentosum (XP) [6–8]. Melanoma accounts for 7% of second malignancies in familial retinoblastoma [8]. Many of these have developed within the field of irradiation. The role of chemotherapy in the induction of melanoma as a second malignancy is unclear. Xeroderma pigmentosum occurs as a rare autosomal recessive condition. There are a variety of subtypes with very different degrees of severity. In the severe types there is extreme photosensitivity, with freckling of the skin and the occurrence of multiple skin cancers, including melanoma. Most melanomas appear to occur in the teens [9]. In the mildest types the phenotype is similar but much less marked and there are patients described who appear to overlap clinically with Cockayne's syndrome or who do not yet fit into any well-defined entity [10].

There are several small series of childhood melanomas in the literature [1,4,11,12] and the relative importance of these predisposing conditions varies, as would be expected in such inevitably selected series. In a series of 15 cases in children under the age of 12 years from the MD Anderson Cancer Centre [2], four occurred in children with either giant congenital naevi or meningeal melanocytosis. In a review article, Williams and Pennella concluded that only 3% of reported childhood tumours occurred in giant congenital naevi [13] but 19% of the reported cases had been thought to have developed in small congenital

naevi. In a series from New South Wales, none of 52 cases were associated with giant congenital naevi or xeroderma pigmentosum [4].

Although the single most common predisposition to childhood melanoma appears to be congenital naevi, the majority of childhood cases occur in patients with no obvious increased susceptibility. A case–control study from Australia of adolescent melanoma identified the same risk factors for melanoma as are seen in the adult population: family history (23/201 cases compared with 6/205 controls), red hair and an abnormal naevus phenotype; 2/147 had germline *CDKN2A* mutations [14].

Rarely, transplacental transmission of melanoma has been recorded [9,15].

References

1 Schmid-Wendtner MH, Berking C, Baumert J *et al*. Cutaneous melanoma in childhood and adolescence: an analysis of 36 patients. *J Am Acad Dermatol* 2002; **46**: 874–9.
2 Boddie A, Smith J, McBride C. Malignant melanoma in children and young adults. *Southern Med J* 1978; **71**: 1074–8.
3 Conti EM, Cercato MC, Gatta G *et al*. Childhood melanoma in Europe since 1978: a population-based survival study. *Eur J Cancer* 2001; **37**: 780–4.
4 Milton GW, Shaw HM, Thompson JF, McCarthy WH. Cutaneous melanoma in childhood: incidence and prognosis. *Australas J Dermatol* 1997; **38** (Suppl. 1): S44–8.
5 Parkin D, Whelan S, Ferlay J *et al*. *Cancer Incidence in Five Continents*. IARC Scientific Publications No 143, Lyon, International Agency for Research on Cancer II, 1997.
6 Stern JB, Peck GL, Haupt HM *et al*. Malignant melanoma in xeroderma pigmentosum: Search for a precursor lesion. *J Am Acad Dermatol* 1993; **28**: 591–4.
7 Van Der Spek PJ, Smit EME, Beverloo HB *et al*. Chromosomal localization of three repair genes: the xeroderma pigmentosum group c gene and two human homologs of yeast *RAD23*. *Genomics* 1994; **23**: 651–8.
8 Traboulsi EI, Zimmerman LE, Manz HJ. Cutaneous malignant melanoma in survivors of heritable retinoblastoma. *Arch Ophthalmology* 1988; **106**: 1059–61.
9 Roth ME, Grant-Kels JM, Kuhn MK *et al*. Melanoma in children. *J Am Acad Dermatol* 1990; **22**: 265–74.
10 Itoh T, Fujiwara Y, Ono T, Yamaizumi M. UV syndrome, a new general category of photosensitive disorder with defective DNA repair, is distinct from xeroderma pigmentosum variant and rodent complementation group 1. *Am J Hum Genet* 1995; **56**: 1267–76.
11 Ceballos P, Ruiz-Maldonado R, Mihm M. Melanoma in children. *New Eng J Med* 1995; **332**: 656–62.
12 Rao B, Hayes F, Pratt C *et al*. Malignant melanoma in children: its management and prognosis. *J Pediatric Surg* 1990; **25**: 198–203.
13 Williams M, Pennella R. Melanoma, melanocytic nevi and other risk factors in children. *J Pediatrics* 1994; **124**: 833–45.
14 Youl P, Aitken J, Hayward N *et al*. Melanoma in adolescents: a case–control study of risk factors in Queensland, Australia. *Int J Cancer* 2002; **98**: 92–8.
15 Scov-Jensen T, Hastrup J, Lambrethsen E. Malignant melanoma in children. *Cancer* 1966; **19**: 620–6.

Melanoma: prognosis and management

The estimation of prognosis for patients with melanoma

A large number of pathological features have been suggested as offering prognostic information. Tumour thickness was established by Alexander Breslow as the most valuable prognostic guide [1]. Blocks are cut from the apparently thickest area of the primary melanoma by the pathologist and the slides cut from this block are examined using an ocular micrometer to measure the distance between the overlying epidermal granular layer and the deepest invasive area of the primary lesion (Fig. 54.67). This figure in millimetres is the Breslow or tumour-thickness measurement and should be included in all pathology reports of primary melanoma. The thickness is indicative of the likelihood of vertical growth phase, tumour volume and correlates with biological markers of tumour progression.

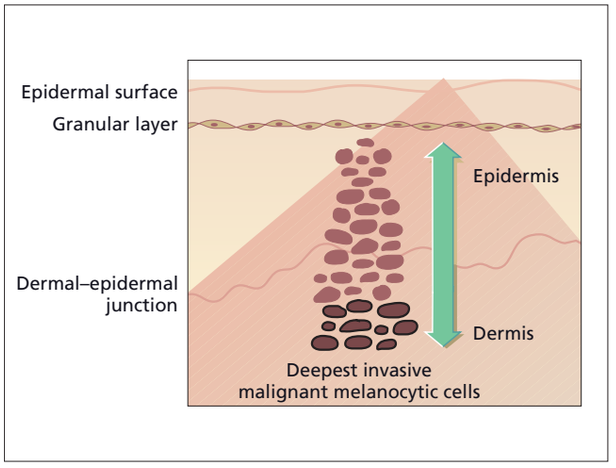


Fig. 54.67 Malignant melanoma thickness measurement (Breslow). The pathologist measures in millimetres the distance between the granular layer in the epidermis and the deepest invasive melanoma cell.

Subsequently, additional histological measures predictive of survival have been established, which have been used to develop the AJCC staging system [2] (Table 54.5). In this system the key roles of thickness and ulceration of the primary in determining outcome are recognized as are the number of lymph nodes involved in metastatic disease.

With respect to primary disease, the AJCC system benefits from very large data sets and it has been validated in population-based data sets (although with a somewhat better survival in the population based SEER data set [3]). The AJCC system is still being improved and a further revision will follow soon. Attempts, however, have been made in the interim to improve the estimates by other groups, particularly the Melanoma Programme at the University of Pennsylvania. Patient sex, mitotic rate, growth phase [4] and tumour site are important determinants of survival, which are not as yet taken into account by the AJCC system; a number of algorithms have been developed that take these additional factors into consideration.

Factors associated with a higher risk of recurrence in those diagnosed with thin primaries have been identified using prognostic trees [5]. In this system the acknowledged effects of sex, site and tumour growth phase are taken into account, so that, for example, females with level II, thin, non-ulcerated tumours had 100% 10-year survival rates compared with males with level III and IV tumours and a 'mitogenic' histological subtype who had an 83.4% 10-year survival. Ultimately, additional information may come from immunohistochemistry (using dermal Ki67 expression, for example [6]), and it seems entirely preferable that this will be incorporated into web-based risk algorithm tools.

Table 54.5 The AJCC staging system [2].

Stage	Primary tumour (pT)	Lymph node (N)	Distant metastases (M)
0	*In situ* tumours	No nodes	None
IA	<1.0 mm no ulceration	No nodes	None
IB	<1.0 mm with ulceration	No nodes	None
	1.01–2.0 mm no ulceration	No nodes	None
IIA	1.01–2.0 mm with ulceration	No nodes	None
	2.01–4.0 mm no ulceration	No nodes	None
IIB	2.01–4.0 mm with ulceration	No nodes	None
	>4.0 mm no ulceration	No nodes	None
IIC	>4.0 mm with ulceration	No nodes	None
IIIA	Any Breslow no ulceration	Micrometastases in nodes	None
IIIB	Any Breslow with ulceration	Micrometastases in nodes	None
	Any Breslow no ulceration	Up to 3 palpable nodes	None
	Any Breslow ± ulceration	No nodes but *in transit* Metastases or satellite lesions	None
IIIC	Any Breslow with ulceration	Up to 3 palpable nodes	None
	Any Breslow ± ulceration	4 or more palpable nodes Or matted nodes Or *in transit* metastases with nodes	None
IVM1			Skin, subcutaneous or distant lymph nodes
IVM2			Lung
IVM3			All other sites or any site with raised LDH

Prognostic tables published by Elder and Murphy [7] are useful aids to management of patients in the clinic, although caution must be exercised as these are not population specific and must be judged as estimates only.

The most recent TNM staging system for melanoma published by the AJCC is outlined in Table 54.5, based upon validation in 17 000 subjects. The staging system reflects the dominant effects of Breslow thickness and the presence of ulceration on outcome for primary disease but for the first time allows risk stratification by the results of sentinel node biopsy (SLNB), a positive SLNB being Stage IIIa. The staging system also reflects the poorer prognosis associated with multiple nodes, matted nodes or *in transit* disease in Stage III melanoma, and the observation that outcome for Stage IV patients is poorer with visceral metastases rather than soft tissue disease, and poorer still when lactic dehydrogenase (LDH) levels are raised. This staging system was validated in 41 417 patients in the SEER registry [3], although the survival was generally higher so that the authors suggest that population-specific figures would be preferable (although very difficult to achieve). The 10-year survival rates of the SEER registry patients are compared with the AJCC figures in Table 54.6.

References

1 Breslow A. Prognostic factors in the treatment of cutaneous melanoma. *J Cutan Pathol* 1979; **6**: 208–12.

2 Balch CM, Buzaid AC, Soong SJ *et al*. Final version of the American Joint Committee on Cancer staging system for cutaneous melanoma. *J Clin Oncol* 2001; **19**: 3635–48.

3 Gimotty PA, Botbyl J, Soong SJ, Guerry D. A population-based validation of the American Joint Committee on Cancer melanoma staging system. *J Clin Oncol* 2005; **23**: 8065–75.

4 Gimotty PA, Elder DE, Fraker DL *et al*. Identification of high-risk patients among those diagnosed with thin cutaneous melanomas. *J Clin Oncol* 2007; **25**: 1129–34.

5 Gimotty PA, Guerry D, Ming ME *et al*. Thin primary cutaneous malignant melanoma: a prognostic tree for 10-year metastasis is more accurate than American Joint Committee on Cancer staging. *J Clin Oncol* 2004; **22**: 3668–76.

6 Gimotty PA, Van Belle P, Elder DE *et al*. Biologic and prognostic significance of dermal Ki67 expression, mitoses, and tumorigenicity in thin invasive cutaneous melanoma. *J Clin Oncol* 2005; **23**: 8048–56.

7 Elder D, Murphy G. Malignant tumors (melanomas and related lesions). *Atlas of Tumor Pathology: Melanocytic Tumors of the Skin* 2 (third series). Armed Forces Institute of Pathology, 1991: 103–205.

Management of cutaneous malignant melanoma after excision of the primary

UK guidelines are available for the management of all stages of melanoma [1] and similar guidelines have been published by other national groups [2,3].

Staging

The only form of staging normally offered to the majority of patients presenting with primary melanoma is sentinel node biopsy. Some centres perform base-line chest X-ray and blood tests, including LDH, although there are no data supporting their use [4]. The likely yield of true positives on chest X-ray here is likely to be around 0%.

Staging imaging is necessary at relapse. The most typical first relapse is detected as enlarged regional lymph nodes and it would be usual to perform a CT scan prior to surgery, on the basis that the patient might choose to decline surgery if they had metastatic disease elsewhere. In practice, however, it is a very rare event to find true positive scans, and if waiting for a scan would delay surgery this may be carried out after surgery. A post-surgery scan may also be needed for trials of adjuvant therapies. For melanomas on the arm metastatic to the axilla or supraclavicular nodes,

Table 54.6 Prognosis of melanoma according to disease stage. Adapted from [2] and [3].

Substage	Characteristics of the primary such as depth and ulceration, presence of nodal or distant metastases, see Table 54.5	AJCC 10-year survival (% ± S.E.) [2]	SEER 10 year survival (% ± S.E) [3]
IA	≤1 mm	87.9 ± 1.0	97.4 ± 0.35
IB	≤1 mm with ulceration	83.1 ± 1.5	90.2 ± 1.8
	1.01–2.0 mm, no ulceration	79.2 ± 1.1	84.1 ± 1.4
IIA	1.01–2.0 mm, with ulceration	64.4 ± 2.2	65.2 ± 7.7
	2.01–4.0 mm, no ulceration	63.8 ± 1.7	67.3 ± 2.6
IIB	2.01–4.0 mm, with ulceration	50.8 ± 1.7	62.1 ± 5.9
	> 4 mm, no ulceration	53.9 ± 3.3	56.3 ± 4.4
IIC	> 4 mm, with ulceration	32.3 ± 2.1	47.5 ± 7.1
IIIA	1 micrometastases in node	62.0 ± 4.4	
	2–3 nodes	56.9 ± 6.8	
IIIB	Micrometastases and ulcerated primary	37.8 ± 4.8	
	1 palpable node	35.9 ± 7.2	49.7 ± 7.6
	2–3 nodes	47.7 ± 5.8	43.6 ± 10.6
	Satellites, no nodes	39.2 ± 5.8	59.2 ± 7.1
IIIC	1 node and ulcerated primary	24.4 ± 5.3	36.6 ± 15.7
	2–3 nodes and ulcerated primary	15.0 ± 3.9	32.9 ± 16.3
	≥4 nodes	18.4 ± 2.5	22.4 ± 6.7
IV	Overall		14.1 ± 3.2
	Skin and SC	15.7 ± 2.9	
	Lung	2.5 ± 1.5	
	Other visceral	6.0 ± 0.9	

then a scan with contrast of the chest and abdomen is the norm. For melanomas on the head and neck or upper trunk, a scan with contrast of the thorax and abdomen is usual. For melanomas on the lower leg and lower trunk including the genitalia, a scan with contrast should be performed of the thorax, abdomen and pelvis. A chest X-ray and bloods, including liver function tests and LDH, are also justified, but only as a baseline. Although LDH is commonly measured it is a poor biomarker of relapse (see below).

Patients who present with clinical signs and symptoms of Stage IV disease would normally have a CT scan with contrast of the abdomen, thorax and pelvis. As melanoma commonly metastasizes to the brain, a CT scan of the brain is also appropriate. A chest X-ray and bloods, including LDH, as a baseline are also helpful.

There is no widely used biomarker with which to monitor high-risk melanoma patients. Circulating levels of protein S100beta, melanoma-inhibitory activity (MIA), LDH, alkaline phosphatase (AP), and tyrosinase/MART-1 reverse transcription-polymerase chain reaction (RT-PCR) are biomarkers that have been evaluated. In one study of 286 patients, protein S100beta and MIA demonstrated a higher sensitivity, specificity, and diagnostic accuracy in the diagnosis of newly occurring metastasis compared with the tumour markers AP, LDH and RT-PCR diagnostics [5]. The superior value of measuring S100 compared with LDH has been reported by other groups [6,7]. When there is an effective treatment for Stage IV disease, the clinical value of markers such as S100 will be higher and it is likely that their use will increase.

Sentinel node biopsy (SLNB)

SLNB grew out of a recognition that elective lymph node dissection (ELND) does not offer a survival advantage to melanoma patients and it is worth briefly considering this history. Three randomized controlled trials that evaluated the effectiveness of ELND on survival in melanoma patients were identified with sufficient data for a meta-analysis [8–10], the Intergroup Melanoma Trial and two WHO Melanoma Trials (No.1 and No.14). The total number of participants was 1533; 768 were assigned to have ELND and 765 to delayed lymphadenectomy or no treatment. A total of 416 deaths within 5 years of the primary tumour excision were recorded in the three trials. Death occurred in 197 patients who underwent ELND compared to 219 from control groups. The pooled odds ratio was 0.86 (95% CI 0.68–1.09), showing no evidence of any therapeutic effect [11]. Whilst these trials and the subsequent meta-analysis showed no significant effect, they did not exclude a small effect and because lymphatic draining in individuals may vary, Morton developed sentinel node biopsy as a means of ensuring that the node biopsied was the one most likely to be the first draining lymph node [12]. The technique was widely adopted although the first randomized clinical trial to evaluate it was only published in 2006 [13]. In SLNB, lymphoscintigraphy is used to identify the lymphatic drainage pattern from the site of the primary melanoma, by injecting radiolabelled colloid and/or blue dye at the site of the primary melanoma. The tracer/dye are concentrated in the so-called sentinel node and are detected using a hand-held gamma probe (neoprobe) and examination by naked eye for the blue stained node. Sometimes there is more than one sentinel node and sometimes these sentinel nodes are in different

lymph node basins. The node is removed, sectioned and subjected to detailed, time-consuming examination by specialist pathologists using immunohistochemistry (S100 and HMB-45). Protocols have been developed to ensure consistency between groups and the identification of small deposits in only one part of a node [14]. The Dewar classification was developed by Cook in the UK [15], to describe the anatomic metastatic deposits in the sentinel node; they were found to be subcapsular in 26.0% of patients. None of the patients with only subcapsular disease had any non-sentinel nodes involved on completion of lymphadenectomy. In the patients whose sentinel node metastases had a different microanatomic location (such as parenchymal or mixed subcapsular or parenchymal), the rate of non-sentinel node involvement was 22.2% overall. Thus it would appear that if melanoma patients have subcapsular deposits of melanoma only, they are less likely to have involvement of other glands. This finding, therefore, has prognostic importance but needs to be established in prospective trials.

The surgical technique must be learnt and false-negative results are more common in trainees, so that many centres require a training experience of around 30 cases. The pathological examination of the nodes is also a skilled procedure; naevus cells may be seen, for example, in the subcapsular area of the node and must be distinguished from melanoma cells. The technique is expensive of resources and expert time.

The likelihood of a positive SLNB result is correlated with Breslow thickness so that in a review of 4218 published cases only two were positive for patients with thickness less than 0.75 mm [16]. Patients with melanoma of Breslow thickness more than 1.0 mm and less than 1.5 mm have a low but definite risk of having micrometastases (around 8%). Use of SLNB to stage patients for trials of adjuvant therapies would appear reasonable but the patient should be aware that the risk of positivity is low. In patients with melanoma of Breslow thickness from 1.5 to 4.0 mm the risk of positive SLNBs is significantly higher at 23%. The value of SLNB in patients with tumours of Breslow thickness 4 mm or thicker is questionable (if the intent is therapeutic as well as being a staging tool) because the risk of haematogenous spread is so high. More recently, some authors have suggested that additional prognostic information does come from SLNB in these patients [17].

The first randomized clinical trial of SLNB in 1269 patients with an intermediate-thickness primary melanoma has been reported [13], and the prognostic value of SLNB was confirmed. The 5-year survival rate was 72.3 ± 4.6% among patients with tumour-positive sentinel nodes and 90.2 ± 1.3% among those with tumour-negative sentinel nodes (hazard ratio for death 2.48; 95% CI 1.54–3.98; $P < 0.001$). There was no overall survival benefit however of SLNB; the mean (±SE) estimated 5-year disease-free survival rate for the population was 78.3 ± 1.6% in the biopsy group and 73.1 ± 2.1% in the observation group (hazard ratio for death 0.74; 95% CI 0.59–0.93; $P = 0.009$). Five-year melanoma-specific survival rates were similar in the two groups (87.1 ± 1.3% and 86.6 ± 1.6%, respectively). The authors suggested that within patients with nodal metastases, there might be some benefit in that the 5-year survival rate was higher among those who underwent immediate lymphadenectomy than among those in whom lymphadenectomy was delayed (72.3 ± 4.6% vs. 52.4 ± 5.9%; hazard ratio for death 0.51; 95% CI 0.32–0.81; $P = 0.004$). This conclusion requires that an assumption is made that all patients with a positive SLNB will progress (which may not be true). The conclusion from the study may also be that SLNB could have a survival benefit for a small proportion of melanoma patients overall, but the study is as yet insufficiently powered to show this effect.

Lymphoscintigraphy for SLNB of the head and neck is technically more difficult than in other sites [18], as is the surgery [19], and is not therefore offered in all SLNB centres.

Thus, at present, SLNB is of proven staging value but of no established therapeutic value. Its use in identifying patients for adjuvant therapies means that it will continue to be used, but its role must be evaluated in the long term.

References

1 Newton Bishop JA, Corrie PG, Evans J *et al*. UK guidelines for the management of cutaneous melanoma. *Br J Plast Surg* 2002; **55**: 46–54.

2 Sober AJ, Chuang TY, Duvic M *et al*. Guidelines of care for primary cutaneous melanoma. *J Am Acad Dermatol* 2001; **45**: 579–86.

3 Kroon BB, Bergman W, Coebergh JW, Ruiter DJ. Consensus on the management of malignant melanoma of the skin in The Netherlands. Dutch Melanoma Working Party. *Melanoma Res* 1999; **9**: 207–12.

4 Wang TS, Johnson TM, Cascade PN *et al*. Evaluation of staging chest radiographs and serum lactate dehydrogenase for localized melanoma. *J Am Acad Dermatol* 2004; **51**: 399–405.

5 Garbe C, Leiter U, Ellwanger U *et al*. Diagnostic value and prognostic significance of protein S-100beta, melanoma-inhibitory activity, and tyrosinase/MART-1 reverse transcription-polymerase chain reaction in the follow-up of high-risk melanoma patients. *Cancer* 2003; **97**: 1737–45.

6 Krahn G, Kaskel P, Sander S *et al*. S100 beta is a more reliable tumor marker in peripheral blood for patients with newly occurred melanoma metastases compared with MIA, albumin and lactate-dehydrogenase. *Anticancer Res* 2001; **21**: 1311–6.

7 Mohammed MQ, Abraha HD, Sherwood RA *et al*. Serum S100beta protein as a marker of disease activity in patients with malignant melanoma. *Med Oncol (Northwood, London, England)* 2001; **18**: 109–20.

8 Balch CM, Soong SJ, Bartolucci AA *et al*. Efficacy of an elective regional lymph node dissection of 1 to 4 mm thick melanomas for patients 60 years of age and younger. *Ann Surg* 1996; **224**: 255–63; discussion 263–6.

9 Cascinelli N, Morabito A, Santinami M *et al*. Immediate or delayed dissection of regional nodes in patients with melanoma of the trunk: a randomised trial. WHO Melanoma Programme. *Lancet* 1998; **351**: 793–6.

10 Veronesi U. Delayed node dissection in stage one malignant melanoma: justification and advantages. *Cancer Invest* 1987; **5**: 47–53.

11 Lens MB, Dawes M, Goodacre T, Newton-Bishop JA. Elective lymph node dissection in patients with melanoma: systematic review and meta-analysis of randomized controlled trials. *Arch Surg* 2002; **137**: 458–61.

12 Morton DL, Wen DR, Wong JH *et al*. Technical details of intraoperative lymphatic mapping for early stage melanoma. *Arch Surg* 1992; **127**: 392–9.

13 Morton DL, Thompson JF, Cochran AJ *et al*. Sentinel-node biopsy or nodal observation in melanoma. *N Engl J Med* 2006; **355**: 1307–17.

14 Cook MG, Green MA, Anderson B *et al*. The development of optimal pathological assessment of sentinel lymph nodes for melanoma. *J Pathol* 2003; **200**: 314–9.

15 Dewar DJ, Newell B, Green MA *et al*. The microanatomic location of metastatic melanoma in sentinel lymph nodes predicts nonsentinel lymph node involvement. *J Clin Oncol* 2004; **22**: 3345–9.

16 Lens MB, Dawes M, Newton-Bishop JA, Goodacre T. Tumour thickness as a predictor of occult lymph node metastases in patients with stage I and II melanoma undergoing sentinel lymph node biopsy. *Br J Surg* 2002; **89**: 1223–7.

17 Cherpelis BS, Haddad F, Messina J *et al*. Sentinel lymph node micrometastasis and other histologic factors that predict outcome in patients with thicker melanomas. *J Am Acad Dermatol* 2001; **44**: 762–6.

18 Mar MV, Miller SA, Kim EE, Macapinlac HA. Evaluation and localization of lymphatic drainage and sentinel lymph nodes in patients with head and neck melanomas by hybrid SPECT/CT lymphoscintigraphic imaging. *J Nucl Med Technol* 2007; **35**: 10–6; quiz 17–20.

19 Doting EH, de Vries M, Plukker JT *et al*. Does sentinel lymph node biopsy in cutaneous head and neck melanoma alter disease outcome? *J Surg Oncol* 2006; **93**: 564–70.

Follow-up after surgery for Stage I or II melanoma

Patients who have had surgery for primary melanoma with no evidence of spread beyond the primary site have traditionally undergone a period of hospital-based follow-up at varying intervals for a varying number of years. The three main purposes of this follow-up are to detect any local recurrence around the scar of the excised melanoma, to palpate the local draining nodes for any clinically detectable evidence of nodal spread and to examine the rest of the skin surface for a second primary melanoma. Regular ultrasound examination of draining nodes is carried out in some centres and there is some evidence that this leads to earlier detection of metastatic disease, although this must be operator dependent [1].

Accepted intervals and duration of follow-up are 3-monthly intervals for 3–5 years. As, however, there is no evidence that this routine follow-up examination advances the time of diagnosing metastatic spread, and the majority of recurrences are detected between such visits, these intervals can be interpreted according to the needs of individual patients and the geographical situation. Some patients benefit emotionally from follow-up in hospital, and some find it traumatic. All patients should be taught how to look for local recurrence, how to palpate the relevant area for enlarged nodes, and be made aware of the clinical features that would suggest a second primary melanoma. They should have information about an appropriate contact in case they detect possible recurrence between regular appointments. The opportunity should also be taken to educate the family about the risk of melanoma and the avoidance of behaviours thought to be causal.

Patients with only an *in situ* melanoma do not require to be placed on a follow-up regime but can be discharged after appropriate surgery and education about self examination and sun protection.

Reference

1 Saiag P, Bernard M, Beauchet A *et al*. Ultrasonography using simple diagnostic criteria vs palpation for the detection of regional lymph node metastases of melanoma. *Arch Dermatol* 2005; **141**: 183–9.

Management of melanoma metastatic to lymph glands

Patients with a positive SLNB would normally proceed to completion lymphadenectomy, although a randomized clinical trial is currently taking place to address its value after SLNB. Axillary surgery would normally be performed to levels I, II and III. For inguinal nodes, a superficial groin dissection would normally be carried out. An additional deep ilioinguinal dissection may also be performed if a pelvic node was seen on lymphoscintigraphy which was not retrieved at SLNB, if there were multiple positive sentinel nodes superficially in the groin (often four or more is suggested), if Cloquet's node (the first of the deep pelvic nodes, lying just below the inguinal ligament) was shown to be involved with melanoma [1], or if lymphatics were seen bypassing nodes superficially and entering the pelvis directly. There are no data to support these clinical practice guidelines.

Patients who present with palpable lymph glands in the drainage area of their primary melanoma should be examined, and, in the majority of such patients, the nodes feel sufficiently firm and large (usually greater than 1 cm in diameter) for a clinical diagnosis of presumptive metastatic melanoma to be made. Patients do commonly present concerned about palpable lesions which prove to be benign such as pea sized normal lymph glands, glands which have enlarged as a result of an insult such as a recent immunization or viral illness, and lipomas.

Where there is doubt about the diagnosis, fine needle aspiration cytology should be used to aspirate a sample under vacuum for pathological examination. A slide preparation can be made in clinic and cytological examination carried out immediately in order to expedite management. An additional cytospin preparation can be examined if insufficient sample is obtained. A negative result should not be taken to exclude metastatic disease if either there was insufficient sample, or in the presence of very suggestive clinical evidence.

The examination of lymph glands is easier in some anatomical locations (inguinal and neck) than in others. The axilla may be particularly difficult, especially in larger men. In these circumstances ultrasonic examination plus fine needle aspiration cytology may be helpful.

If the diagnosis of metastatic disease is clear either clinically or cytologically, then lymphadenectomy is carried out. Again for axillary nodes, levels I, II and III should be removed. A superficial ilioinguinal dissection is usual, extended to a deep dissection if there is evidence of a pelvic node clinically or on CT scan, involvement of Cloquet's node, extensive superficial nodal involvement or a node distal to the inguinal ligament is involved [1].

Melanoma metastatic to the neck should be operated on by surgeons specialized in head and neck surgery. A functional neck dissection is usually carried out for melanoma.

Reference

1 Badgwell B, Xing Y, Gershenwald JE *et al*. Pelvic lymph node dissection is beneficial in subsets of patients with node-positive melanoma. *Ann Surg Oncol* 2007; **14**: 2867–75.

Biological therapies for melanoma

Melanoma is an immunogenic tumour; immune-mediated regression is common in primary tumours and immune-mediated vitiligo in Stage IV disease correlates with a higher chance of response to chemotherapy. Biological therapies have therefore been trialled extensively and the most widely used as an adjuvant is interferon. There have been numerous trials and much controversy but the conclusion now seems to be that interferon-alpha (IFN-α) appears to increase disease-free survival in some patients [1] but is associated with no significant overall survival benefit. Except for TNM stage, there are currently no well-recognized factors that predict outcome. There are some data however from Gogas *et al*., which might suggest that host variation in immune response predicts outcome [2]. In a study of 200 melanoma patients treated with high-dose IFN-α 2b, the median relapse-free survival was 28.0 months, and the median overall survival was 58.7 months. Autoantibodies and clinical manifestations of autoimmunity were detected in 52 patients (26%). The median relapse-free survival

was only 16.0 months among patients without autoimmunity (108 of 148 had a relapse) and more than 45 months (median not reached) in patients with autoimmunity (seven of 52 had a relapse). The median survival was 37.6 months in patients without autoimmunity (80 of 148 died) and was not reached in patients with autoimmunity (two of 52 died). The significance of this remains to be evaluated.

Of the newer biological therapies, the anti-CTLA-4 antibodies, ipilimumab and ticilumumab, intended to enhance immune response, and the antiangiogenic agent bevacizumab, are currently being investigated in clinical trials.

A series of different vaccines have been trialled, from single agents such as ganglioside vaccines to multivalent vaccines. Despite early enthusiasm however, unfortunately, as yet no adjuvant value has been established for these treatments. There is also some evidence of poorer [3] survival in patients receiving vaccine.

Interleukin 2 showed encouraging responses in conjunction with chemotherapy in Phase II clinical trials but not in Phase III trials [4]. A Cochrane review failed to show any evidence that the addition of biological therapies to chemotherapeutic regimes for melanoma increased survival [5].

Interest remains therefore in biological therapies for melanoma, but there are no established roles for these agents as yet. It is fair to say that, despite early optimism, biological therapies have proved disappointing.

Management of patients with Stage IV disease

The AJCC TNM staging revision has clearly indicated that patients with metastatic spread to certain tissues, including the lungs and soft tissue, have a better outlook than those patients with spread to the liver or central nervous system. Lung and soft tissue lesions tend to be more responsive to chemotherapy, but even for these patients such responses are rarely complete and tend to be of short duration.

Where patients have small volume disease, such as a single deposit in the liver or lung, then excision of this lesion should be considered. In these circumstances a PET scan might be used to ensure the absence of disease elsewhere.

No chemotherapeutic agent gives a high proportion of complete responses in melanoma. The current chemotherapeutic agent of choice is dacarbazine (DTIC). In large randomized trials, response rates with dacarbazine ranged from 6 to 15%. Almost all responses were partial, with a median response duration of only 7–8 months [6]. With modern antiemetics, DTIC is relatively non-toxic and can be given as an out-patient, usually at 3-week intervals. Patients should be assessed for response after four to six courses. There is no evidence that combination therapy of DTIC with other chemotherapeutic agents [2] or with biologicals [5] increases the response rate or the duration of response achieved by DTIC alone.

Temozolomide has demonstrated efficacy equal to that of dacarbazine in a randomized Phase III trial. However, unlike dacarbazine, temozolomide is a convenient oral treatment that penetrates the blood–brain barrier and that has shown activity against brain metastases. Although surgery is the preferred treatment modality for patients with solitary brain metastases from melanoma, temozolomide is the preferred chemotherapy for patients with brain metastases who require systemic treatment [6].

Management of recurrent disease in a limb

Recurrent disease is common in patients after resection of melanoma on a limb, particularly the leg. When recurrence occurs within 2 cm of the primary, convention is that this is called a 'local recurrence', but in fact the majority are *in transit* metastases.

More distant deposits in the skin or subcutaneous tissues are called '*in transit*' metastases. Occasionally, these may be present at diagnosis. Usually these are proximal, along the line of lymphatics, but rarely they may actually be distal to the primary tumour site. They are usually well under 1 cm in diameter at removal but larger deposits may occur. They may be pigmented or non-pigmented (Fig. 54.68). *In transit* disease is usually accompanied by regional lymph node metastases at some time or other, either simultaneously or years later. Sometimes, multiple *in transit* metastases may develop over years without spread elsewhere.

Treatment

The treatment of such lesions is essentially surgical. Tiny lesions may be removed by punch excision and if large numbers are present, these may be left to heal by secondary intention. Larger ones will require more extensive surgery, even skin grafting. The CO_2 laser may be a very useful means of removing large numbers of small lesions.

If it appears that the disease within the limb is becoming difficult to control surgically then isolated limb perfusion [7] should be considered. Isolated limb perfusion with the administration of cytotoxic drugs (primarily melphalan) has been successfully used to treat melanomas of the extremity since it was first introduced in 1958. The vessels are dissected at open surgery and cannulated. Blood transfusions, systemic drug leak, infection and damage to the blood vessels and nerves, even rare limb loss, are all potential hazards associated with this technique.

Isolated limb perfusion is used to palliate disease [8], although there is some weak evidence for an effect on survival; in a meta-analysis of four trials of 1038 patients, the analysis confirmed the reported increase in survival in two of the trials, but neither had sufficient power to detect significant benefit for perfusion [9]. There is a significant morbidity associated with the treatment and a 1% limb loss rate in most studies [10]. In order to increase the efficacy of treatment, tumour necrosis factor (TNF) may be added [11]. Perfusion with melphalan results in complete response rates of 54% (meta-analysis). The addition of TNF can improve these complete response rates (59–85%) and although no data from randomized controlled trials are available, it is said to be of value in large, bulky lesions or in patients with recurrent disease after previous isolated limb perfusion [12]. The addition of TNF adds to the toxicity. The treatment may be repeated if there is an initial good response but relapse occurs later [13]. Other cytotoxics used in isolated limb perfusion in some centres include dacarbazine and fotemustine [14].

As a result of the morbidity, an alternative, simpler technique termed isolated limb infusion (ILI), was developed by the Sydney Melanoma Unit [15]. ILI is a less invasive procedure involving the



(a) (b)

Fig. 54.68 *In transit* metastases in a limb are reasonably frequent. Some recur over long periods of time without distant relapse.

use of angiographically placed catheters inserted percutaneously through the femoral vessels, which does not require use of a heart–lung machine. It has been suggested (although based on single institution experiences) that there are fewer resultant morbidities but no compromise in patient outcomes. The overall reported response rate [16] in the treated limb of 135 patients was 85% (complete response [CR] rate 41%, partial response rate 44%). Median response duration response was 16 months (24 months for patients with CR). Median patient survival was 34 months. In those with a CR, the median survival was 42 months.

There is no value for isolated limb infusion as an adjuvant therapy [17].

The treatment of melanoma metastatic to the brain

Melanoma commonly metastasizes to the brain in Stage IV disease, presenting usually as headaches and/or fits. It can occasionally present as motor or sensory symptoms. In a series of 133 patients, 82 patients had involvement of only the cerebrum at the initial diagnosis, whereas in seven patients only the cerebellum and the brainstem were involved. Seizures (n = 29) were the single most often reported symptom. The overall median survival time was 24 weeks. Women had a significantly longer survival with 36 weeks (3–196) compared to 17 weeks (1–159) for men [18]. Although these survival figures are poor, there is a view that aggressive treatment does palliate symptoms and prolong survival [19]. The diagnosis is confirmed by CT scan, and the immediate treatment is with oral dexamethasone to control the secondary oedema.

A single (or few) brain metastasis might be amenable to surgery or stereotactic radiotherapy, and it is unclear which is most effective. Surgical resection is preferred when a pathologic diagnosis is needed, for tumours larger than 3.5 cm or when immediate tumour mass decompression is required. Stereotactic radiosurgery (SRS) is the use of highly collimated beams of radiation to deliver high-dose radiotherapy to defined areas with rapid fall off into surrounding tissues; it should be applied for single tumours less than 3.5 cm in surgically inaccessible areas and for patients who are not surgical candidates. Small tumours (i.e. <3.5 cm) that cause minimal oedema and are surgically accessible may be treated with either surgery or SRS [19]. Both surgery and SRS are normally followed by whole-brain radiotherapy, although it is not clear how much benefit this gives, and neurocognitive late effects are a side effect. There is a view that the whole-brain radiotherapy increases local control but has no effect on survival [20] and in some centres it is therefore avoided.

For unresectable lesions or multiple lesions the options are radiotherapy or chemotherapy, neither of which are very effective. Radiotherapy is usually given as whole-brain radiotherapy, but SRS may be used. In a series of 244 patients given SRS for the management of 754 metastatic tumours, the median survival was 5.3 months (mean 10 months; range, 0.2–114.3 months) [21]. Sustained local control was achieved in 86.2% of tumours. Multiple lesions and failure to provide systemic immunotherapy were predictors for the occurrence of new brain metastases, which developed in 41.7% of the patients. Symptomatic radiation changes occurred in 6.6% of the patients. Overall, 71.4% of the patients improved or remained clinically stable. Whole-brain radiotherapy is usually delivered as a short course over 1 to 2 weeks.

Temozolomide is an oral alternative to dacarbazine for the treatment of metastatic melanoma; it penetrates the blood–brain barrier and is therefore preferred treatment for brain metastases [6], although it is not yet approved in many countries. The response rates are, however, low.

References

1 Eggermont AM. Current status of interferon-alpha in the treatment of melanoma. *Cancer Chemother Biol Response Modif* 2005; **22**: 729–37.
2 Gogas H, Ioannovich J, Dafni U *et al*. Prognostic significance of autoimmunity during treatment of melanoma with interferon. *N Engl J Med* 2006; **354**: 709–18.
3 Eggermont AM. Immunotherapy: Vaccine trials in melanoma—time for reflection. *Nat Rev Clin Oncol* 2009; **6**: 256–8.
4 Buzaid AC. Biochemotherapy for advanced melanoma. *Crit Rev Oncol Hematol* 2002; **44**: 103–8.
5 Sasse AD, Sasse EC, Clark LG *et al*. Chemoimmunotherapy versus chemotherapy for metastatic malignant melanoma. *Cochrane Database Syst Rev*: CD005413, 2007.
6 Quirbt I, Verma S, Petrella T *et al*. Temozolomide for the treatment of metastatic melanoma. *Curr Oncol* 2007; **14**: 27–33.
7 McDermott P, Lawson DS, Walczak R Jr *et al*. An isolated limb infusion technique: a guide for the perfusionist. *J Extra-corp Technol* 2005; **37**: 396–9.
8 Rossi CR, Foletto M, Pilati P *et al*. Isolated limb perfusion in locally advanced cutaneous melanoma. *Semin Oncol* 2002; **29**: 400–9.
9 Lens MB, Dawes M. Isolated limb perfusion with melphalan in the treatment of malignant melanoma of the extremities: a systematic review of randomised controlled trials. *Lancet Oncol* 2003; **4**: 359–64.
10 Knorr C, Meyer T, Janssen T *et al*. Hyperthermic isolated limb perfusion (HILP) in malignant melanoma. Experience with 101 patients. *Eur J Surg Oncol* 2006; **32**: 224–7.
11 Lejeune FJ, Eggermont AM. Hyperthermic isolated limb perfusion with tumor necrosis factor is a useful therapy for advanced melanoma of the limbs. *J Clin Oncol* 2007; **25**: 1449–50; author reply 1450–1.
12 Grunhagen DJ, de Wilt JH, van Geel AN, Eggermont AM. Isolated limb perfusion for melanoma patients—a review of its indications and the role of tumour necrosis factor-alpha. *Eur J Surg Oncol* 2006; **32**: 371–80.
13 Noorda EM, Vrouenraets BC, Nieweg OE *et al*. Repeat isolated limb perfusion with TNFalpha and melphalan for recurrent limb melanoma after failure of previous perfusion. *Eur J Surg Oncol* 2006; **32**: 318–24.
14 Bonenkamp JJ, Thompson JF, de Wilt JH *et al*. Isolated limb infusion with fotemustine after dacarbazine chemosensitisation for inoperable loco-regional melanoma recurrence. *Eur J Surg Oncol* 2004; **30**: 1107–12.
15 Thompson JF, Kam PC, Waugh RC, Harman CR. Isolated limb infusion with cytotoxic agents: a simple alternative to isolated limb perfusion. *Semin Surg Oncol* 1998; **14**: 238–47.
16 Lindner P, Doubrovsky A, Kam PC, Thompson JF. Prognostic factors after isolated limb infusion with cytotoxic agents for melanoma. *Ann Surg Oncol* 2002; **9**: 127–36.
17 Koops HS, Vaglini M, Suciu S *et al*. Prophylactic isolated limb perfusion for localized, high-risk limb melanoma: results of a multicenter randomized phase III trial. European Organization for Research and Treatment of Cancer Malignant Melanoma Cooperative Group Protocol 18832, the World Health Organization Melanoma Program Trial 15, and the North American Perfusion Group Southwest Oncology Group-8593. *J Clin Oncol* 1998; **16**: 2906–12.
18 Hofmann MA, Coll SH, Kuchler I *et al*. Prognostic factors and impact of treatment in melanoma brain metastases: better prognosis for women? *Dermatology* 2007; **215**: 10–6.
19 Peacock KH, Lesser GJ. Current therapeutic approaches in patients with brain metastases. *Curr Treat Options Oncol* 2006; **7**: 479–89.
20 Bafaloukos D, Gogas H. The treatment of brain metastases in melanoma patients. *Cancer Treat Rev* 2004; **30**: 515–20.
21 Mathieu D, Kondziolka D, Cooper PB *et al*. Gamma knife radiosurgery in the management of malignant melanoma brain metastases. *Neurosurgery* 2007; **60**: 471–81; discussion 481–2.

Radiotherapy

Malignant melanoma is traditionally regarded as a radioresistant tumour but it does have a role, particularly in palliation, and there is a view that it is underused [1]. The view that melanoma is radioresistant originated from radiobiological experiments, but a modern view is that melanomas have a wide range of sensitivities and that some are radiosensitive [1]. It is usually held that melanoma responds better to hypofractionation (larger, more infrequent doses) but this remains contested.

Radiotherapy has little part to play in the management of primary tumours, although it has been recorded in the past that the lentigo maligna melanoma variant is relatively radiosensitive, and radiotherapy has been used (low-energy electron or X-ray beams with limited penetration). It may be particularly useful where extensive disease occurs in difficult sites such as at the eyelid margin. However, data are inadequate to compare treatment modalities for lentigo maligna.

Radiotherapy may have palliative value for locoregional disease, which is not amenable to surgery. Radiotherapy can also be of considerable value in the palliation of metastatic disease in relieving pain from bony metastases.

There has been a persistent interest in postoperative adjuvant radiotherapy for Stage III melanoma, particularly where there is extracapsular spread and therefore an increased risk of local recurrence. The data on efficacy are interesting but are not based upon sufficiently large randomized clinical trials [2]. Stevens and McKay, however, have compared nodal basin relapse rates after surgery alone with those after radiotherapy and local recurrence did seem to be much lower when adjuvant radiotherapy is used [1], although the morbidity in terms of lymphoedema, for example, is increased. Randomized clinical trials are needed, and one trial began in 2002 in Australia and New Zealand.

References

1 Stevens G, McKay MJ. Dispelling the myths surrounding radiotherapy for treatment of cutaneous melanoma. *Lancet Oncol* 2006; **7**: 575–83.
2 O'Brien CJ, Petersen-Schaefer K, Stevens GN *et al*. Adjuvant radiotherapy following neck dissection and parotidectomy for metastatic malignant melanoma. *Head Neck* 1997; **19**: 589–94.

Melanoma, pregnancy and female sex hormones

Concern about the effect of pregnancy on outcome from melanoma began in 1951, when Pack and Scharnagel reviewed 32 cases of melanoma diagnosed during pregnancy reporting extremely poor prognosis due to the rapid development of metastases [1]. A number of studies subsequently, however, have not shown any adverse effect on outcome [2]. A large study based on a Swedish cancer registry of 185 women diagnosed with melanoma during pregnancy and 5348 women of the same childbearing age diagnosed with melanoma while not pregnant, showed no evidence of an adverse effect of pregnancy on survival, before or after diagnosis [3]. Clinicians often advise patients with thicker primaries to defer pregnancy after diagnosis, but this is social rather than medical, based upon waiting until the period during which metastasis is most likely has passed.

Placental and fetal metastasis of melanoma is a rare but well described phenomenon. In a review of published cases the risk of

fetal disease in the presence of placental metastases was estimated to be 22% [4], so that examination of the placenta at delivery in patients with poor prognosis disease is sensible.

There is no evidence that the contraceptive pill has any effect on causation of melanoma [5] and none that hormone replacement therapy should be avoided [6].

References

1 Pack GT, Scharnagel IM. The prognosis for malignant melanoma in the pregnant woman. *Cancer* 1951; **4**: 324–34.

2 O'Meara AT, Cress R, Xing G *et al*. Malignant melanoma in pregnancy. A population-based evaluation. *Cancer* 2005; **103**: 1217–26.

3 Lens MB, Rosdahl I, Ahlbom A *et al*. Effect of pregnancy on survival in women with cutaneous malignant melanoma. *J Clin Oncol* 2004; **22**: 4369–75.

4 Alexander A, Samlowski WE, Grossman D *et al*. Metastatic melanoma in pregnancy: risk of transplacental metastases in the infant. *J Clin Oncol* 2003; **21**: 2179–86.

5 Karagas MR, Stukel TA, Dykes J *et al*. A pooled analysis of 10 case-control studies of melanoma and oral contraceptive use. *Br J Cancer* 2002; **86**: 1085–92.

6 Durvasula R, Ahmed SM, Vashisht A, Studd JW. Hormone replacement therapy and malignant melanoma: to prescribe or not to prescribe? *Climacteric* 2002; **5**: 197–200.

CHAPTER 55
Histiocytoses

A.C. Chu
Hammersmith Hospital, London, UK

Ontogeny of the histiocyte, 55.1
Function of the histiocyte, 55.4
Classification of the histiocytoses, 55.5
Class I histiocytosis: Langerhans' cell histiocytosis, 55.6
Class IIa histiocytosis: histiocytoses involving cells of the dermal dendrocyte lineage, 55.14
Dermatofibroma, 55.15
Juvenile xanthogranuloma, 55.15
Benign cephalic histiocytosis, 55.17
Erdheim–Chester disease, 55.18
Fat-storing hamartoma of dermal dendrocytes, 55.19
Generalized eruptive histiocytoma, 55.19
Papular xanthoma, 55.19
Progressive nodular histiocytosis, 55.20
Xanthoma disseminatum, 55.20
Diffuse plane xanthomatosis, 55.22
Class IIb histiocytosis: histiocytoses involving cells other than Langerhans' cells and dermal dendrocytes, 55.23
Reticulohistiocytoma, 55.23
Multicentric reticulohistiocytosis, 55.23
Familial haemophagocytic lymphohistiocytosis, 55.25
Familial sea-blue histiocytosis, 55.26
Hereditary progressive mucinous histiocytosis, 55.27
Malakoplakia, 55.27
Necrobiotic xanthogranuloma, 55.27
Sinus histiocytosis with massive lymphadenopathy, 55.29
Virus-associated haemophagocytic syndrome, 55.30
Class III histiocytosis: malignant histiocytoses, 55.31
Monocytic leukaemia, 55.31
Malignant histiocytosis, 55.32
True histiocytic lymphoma, 55.33

The histiocytoses are a heterogeneous group of diseases that are characterized by the accumulation of reactive or neoplastic histiocytes in various tissues. Many of the signs and symptoms of the histiocytoses may be the result of the functional activity of histiocytoses, and which may also be important in the pathogenesis of these diseases (Fig. 55.1).

Ontogeny of the histiocyte

Synonym
- Tissue macrophage

Histiocytes are derived from circulating monocytes and thus share a common bone marrow progenitor cell, the *neutrophil/macrophage colony-forming unit* (NM-CFU; Fig. 55.2). Promonocytes are actively dividing cells and their replication is controlled by a series of stimulatory glycoprotein hormones, colony-stimulating factor (CSF) and inhibitory prostaglandins. Colony-stimulating factor has a molecular mass of 20–50 kDa. Its main source is cells of the monocyte/macrophage lineage [1] but activated T cells [2], keratinocytes [3] and neoplastic monocytes and macrophages [4] are also capable of secreting CSF. Cell division is limited by a negative feedback mechanism involving the E prostaglandins, which are released by macrophages after stimulation by CSF.

Other factors have been shown to influence the maturation of monocyte precursors, including 1,25-dihydroxyvitamin D_3 [5], retinoic acid [6], interferon-γ (IFN-γ) [7] and phorbol esters [8]. The promonocyte matures into a monocyte, which is released into the circulation where it represents a replacement pool for tissue macrophages or histiocytes. The half-life of a circulating monocyte is about 71 h [9], after which the cells migrate into various tissues where they differentiate into histiocytes without further division. Most histiocytes do not actively divide, although in some tissues, such as the lung, they are capable of replication [10].

The Langerhans' cell is a histiocytic cell that represents a resident immigrant population in the epidermis. It is an archetypal member of a subpopulation of histiocytic cells, the dendritic cells, which play key roles in various aspects of immunity. As with all histiocytic cells, Langerhans' cells are of bone marrow origin [11] and are ultimately derived from the haemopoietic stem cell. Haemopoietic stem cells can differentiate into myeloid or lymphoid-committed precursors and Langerhans' cells can differentiate through both lineages [12]. The intermediate stages of Langerhans' cell development are unknown, but a possible intermediate cell in the bone marrow has been identified, which, in common with the Langerhans' cell, expresses the CD1 complex [13]. In the blood of healthy individuals, CD1a cells are found in very low numbers, but in cord blood [14] and blood from burns patients [15] high levels of CD1a cells are observed. It is speculated that these represent immature Langerhans' cells.

The factors that control the migration and development of Langerhans' cells in the skin are not fully understood. Langerhans' cell precursors express the cutaneous leukocyte antigen (CLA), a glycosylated form of p-selectin which acts as a homing molecule for the skin and express CCR6, the receptor for the chemokine CCL20 which is produced by epidermal keratinocytes [16]. Granulocyte/macrophage CSF (GM-CSF), interleukin (IL)-3 and tumour necrosis factor-α (TNF-α) all induce CD34 cells to

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

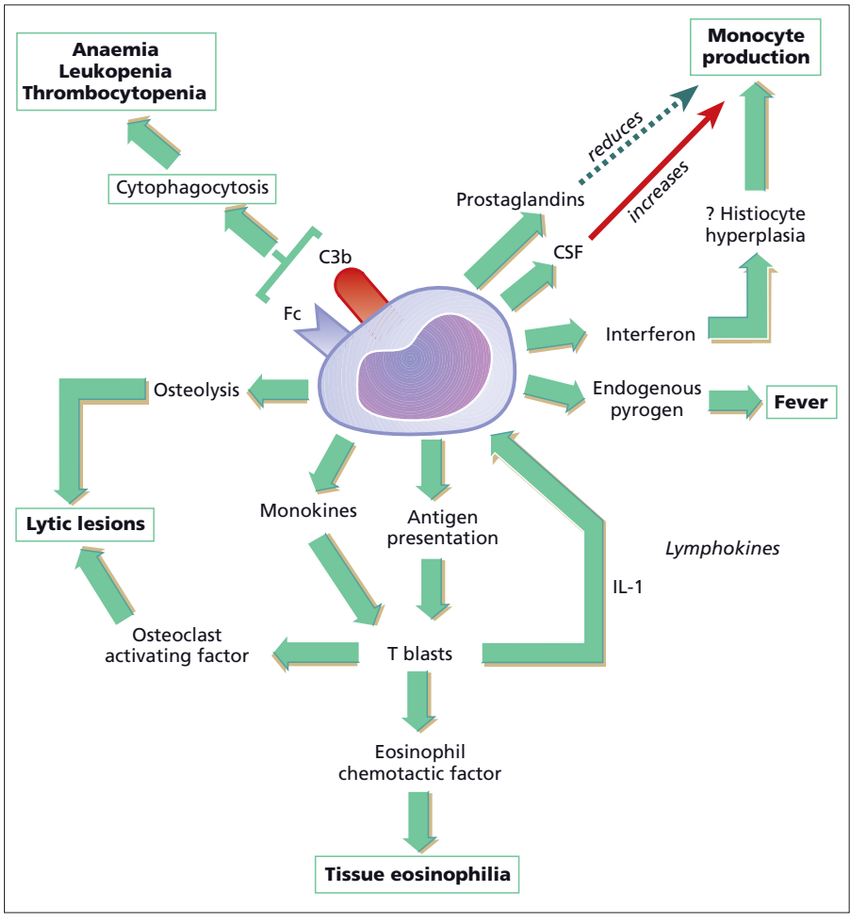


Fig. 55.1 Alteration in histiocyte function causing symptoms of the histiocytoses. CSF, colony-stimulating factor; C3b, complement 3b; Fc, heavy chain fragment of immunoglobulin; IL-1, interleukin-1; T blasts, thymus-derived lymphoblasts.

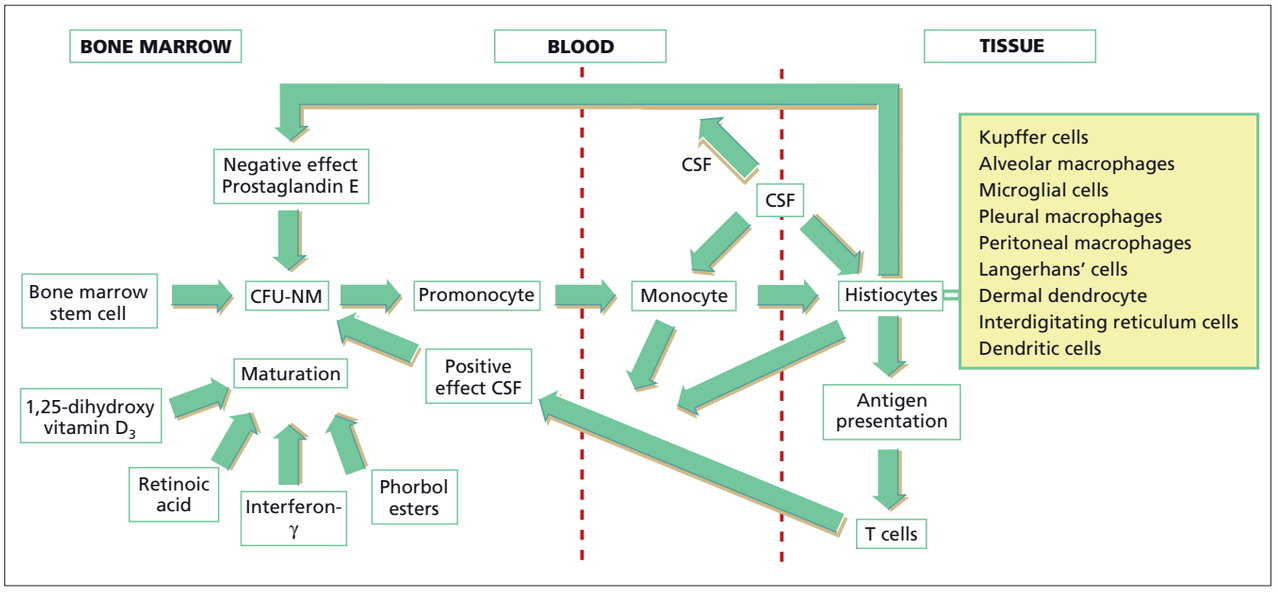


Fig. 55.2 Ontogeny of histiocytes showing factors that can influence the division and maturation of the cells. CFU-NM, neutrophil/macrophage colony-forming unit; CSF, colony-stimulating factor.

Table 55.1 Surface markers of Langerhans' cell (LC), activated LC and LC histiocytosis (LCH) cells.

Marker	LC	Activated LC	LCH cells
Surface ATPase	+	+	+
MHC II	+	+	+
MHC I	±	±	±
FcIgG receptor	+	+	+
FcIgE receptor	+	+	?
C3bi receptor	+	+	+
CD1a and CD1c	+	+	+
CD4	±	+	+
CD45	+	+	+
CD14	+	+	?
CDw29	+	+	?
IL-2 receptor	–	+	+
Langerin (CD207)	+	+	+
E-cadherin	+	–	–
Fascin	–	+	+
B7 (CD80, 86)	–	+ (cultured)	+
CD11b and CD11c	+	+	+
S100	+	+	+
Placental alkaline phosphatase	–	+ (transient)	+
Peanut agglutinin	–	–	+
IFN-γ receptor	–	–	+
Neurone-specific enolase	+	+	+
Birbeck granule	+	±	+

ATPase, adenosine triphosphatase; IFN, interferon; IL, interleukin; MHC, major histocompatibility complex.

develop the phenotypic features of Langerhans' cells. Caux *et al.* [17] generated CD1a cells from CD34 bone marrow cells using GM-CSF and TNF-α. The cells demonstrated potent antigen-presenting function. However, further research has shown that the whole field of Langerhans' cells ontogeny is more complex. Studies have now shown that GM-CSF will induce expression of CD1a, CD1b and CD1c by blood monocytes [18]. *In vitro*, human monocytes can differentiate into dendritic cells with some characteristics of Langerhans' cells on culture with GM-CSF, IL4 and TGF-β [19]. $CD34^+$ bone marrow cells can be induced to differentiate into Langerhans' cells with GM-CSF and TNF-α [20], IL3 and TNF-α [21], or FMS-like tyrosine kinase-3 (FLT3) ligand and transforming growth factor-β (TGF-β) [22]. A possible immediate precursor of epidermal Langerhans' cell in the epidermis is the *indeterminate cell* [23], which bears a Langerhans' cell surface phenotype but lacks the characteristic Birbeck granule (see Chapter 3 and section on the phenotype of Langerhans' cells below).

Within the epidermis, Langerhans' cells are immature, able to process antigen but do not express the co-stimulatory molecules CD80 and CD86 unless activated and are poor antigen-presenting cells. Maturation and migration out of the epidermis can be stimulated by a wide variety of signals including TNF-α and IL1β, CD40 ligand, microbial products and ultraviolet radiation. Langerhans' cells down-regulate CD1a, express CD80 and CD86, lose CCR6 expression and express CCR7 which directs migration to the lymphatics and regional lymph nodes. The fate of Langerhans' cells after their development in the skin is speculative. Some authors maintain that Langerhans' cells migrate from the skin in the efferent lymphatics as *veiled cells* and eventually develop into *interdigitating reticulum cells* in the paracortical zone of the regional lymph nodes. If Langerhans' cells are cultured *in vitro*, they lose their characteristic phenotype and adopt an interdigitating reticulum cell phenotype [24]; this phenomenon has been proposed as evidence for their extraepidermal differentiation. However, the *in vitro* culture conditions are unphysiological, and it is more probable that Langerhans' cell, veil cell and interdigitating cell are related but differentiate separately from an early common progenitor cell series.

Dermal dendrocytes, first described by Headington in 1986 [25], are highly dendritic interstitial cells of the papillary and reticular dermis. They are positive for adenosine triphosphatase (ATPase), α-napthylbutyrate esterase, β-glucuronidase and acid phosphatase, indicating they are of monocyte/macrophage lineage. They are also phagocytic *in vivo*, showing melanin and haemosiderin phagocytosis. Dermal dendrocytes are of bone marrow origin and are thought to have a possible role in phagocytosis, antigen presentation or in homeostasis of macromolecules of the dermis [26]. Elegant computer-assisted three-dimensional reconstruction of dermal dendrocytes in adult human skin has shown that in those associated with superficial blood vessels, the dendrites are thin, membrane-bound flaps that enshroud the vessel wall. In subepidermal dermal dendrocytes, the flap-like dendrites are parallel to the dermal–epidermal junction. Twenty to 40% of perivascular and some subepidermal dermal dendrocytes are closely associated with mast cells, their membrane flaps enshrouding 50–90% of the surface of the mast cell [27].

Phenotype of Langerhans' cells

For many years after the original description of Langerhans' cells [28], this epidermal clear cell was considered to be an effete melanocyte. Significant interest was generated by the finding that Langerhans' cells express a number of surface molecules, which suggested immunological importance. These molecules include major histocompatibility complex (MHC) class II molecules (which are constitutively expressed by Langerhans' cells), FcIgG receptors and C3b receptor. Langerhans' cells also express the chemokine receptors CCR5 and CCR6. A full list of the phenotypic markers of Langerhans' cells is given in Table 55.1.

A major advance was the finding that epidermal Langerhans' cells expressed the CD1 complex [29], previously considered to be restricted to cortical thymocytes. CD1 is a group of non-polymorphic membrane glycoproteins that non-covalently bind to β_2-microglobulin. Five genes have been identified and cloned [30]. Four molecules have been described: CD1a, CD1b, CD1c and CD1d [31]. CD1a and CD1c are expressed by Langerhans' cells and may play a role in presenting lipid antigen to T cells [32]. Langerhans' cells have since been shown to express other molecules, identified by antibodies to CD4 and CD25, which were initially thought to be specific for lymphocytes.

The unique phenotypic feature of Langerhans' cells is the trilaminate cytoplasmic organelle, the *Birbeck granule* [33]. This organelle is only observed in Langerhans' cells, Langerhans' cell histiocytosis (LCH) cells (which are abnormal Langerhans' cells) and some hairy cell leukaemia cells. The granules are rod-shaped

structures with a central lamella. They are of uniform width (33 nm) and of variable length (200–360 nm). The granules often have terminal vesicular dilations, giving rise to the characteristic 'tennis racket' appearance. The Birbeck granule was initially thought to originate from the Golgi apparatus, but studies now suggest that it arises from the cytoplasmic membrane by receptor-specific endocytosis [34]. Lag is an antigen expressed on Birbeck granules and anti-Lag antibodies can be used to identify Langerhans' cells [35].

The phenotype of the Langerhans' cell changes with activation or with culture *in vitro*. Activation involves up-regulation of human leukocyte antigen (HLA)-DR and expression of CD4 and the co-stimulatory molecules CD80 and CD86 [36]. At the same time, Birbeck granules become sparser and CD1a is down-regulated (see Table 55.1).

Phenotype of the dermal dendrocyte

In addition to showing the enzyme histochemical features of the monocyte/macrophage lineage, a characteristic feature of dermal dendrocytes is expression of factor XIIIa. The cells are always negative for CD1a, which differentiates them from Langerhans' cells, and express HLA-DR, HLA-DQ, CD36, CD68, CD34, CD11a and CD11b but neither CD15, CD54 nor CD2. Thus, they show the immunophenotype of monocyte/macrophages and antigen-presenting cells, with no features of granulocytes or T cells [37]. Following stimulation with IFN-γ, the expression of HLA-DR increases and dermal dendrocytes express CD54. In atopic dermatitis and psoriasis, cells positive for factor XIIIa, HLA-DR and CD54 are observed in the upper dermis and foci of factor XIIIa-positive cells are seen in the epidermis [37].

Dermal dendrocytes have been shown to express S100A6 [38] and type XVI collagen [39]. CD14 peripheral blood monocytes stimulated with GM-CSF and IL-4 express factor XIIIa [40] and collagen XVI [39]. It is postulated that type XVI collagen forms an intermolecular cross-link through its non-collagenous domain, contributing to the integrity of factor XIIIa.

Dermal dendrocytes also express the von Willebrand factor receptor GPIbα. Expression of this factor *in vitro* is up-regulated by mast cell degranulation [41]. Expression of GPIbα on dermal dendrocytes suggests that these cells may have a role in skin remodelling and repair.

The fate of dermal dendrocytes is unknown. The factors that influence maturation of these cells include mast cell products, although *in vitro* studies using TNF-α have failed to demonstrate up-regulation of GPIbα on factor XIIIa-positive cells [42]. When skin is maintained in organ culture, dermal dendrocytes lose their dendritic morphology and become more rounded. This change is accentuated by mast cell degranulation, regardless of stimulus. These non-dendritic cells express variable amounts of factor XIIIa, CD34 and CD68.

Function of the histiocyte

Histiocytes can be broadly divided into two functionally separate cell populations: the 'professional' phagocyte; and the antigen-presenting cell.

Phagocytes include the majority of resident tissue macrophages and immature macrophages. Immature macrophages are cells that have migrated, as monocytes, from the blood but remain responsive to chemotactic stimuli and are attracted to sites of inflammation where they become inflammatory macrophages. Phagocytes take up foreign or altered material and digest it using a number of lysosomal enzymes, they also recognize material to be taken up by a variety of different cell-surface receptors. Important in this are the carbohydrate and lectin receptors, which are involved in the phagocytosis of bacteria and possibly tumour cells. The cells also express the specific complement component receptors CR1 and CR3, which bind to C3b and C3bi respectively, and FcIgG receptors, which bind to the Fc fragment of IgG. These receptors are important in the phagocytosis of material that has bound IgG and complement, which act as opsonins and augment phagocytosis.

Phagocytosis is important in the removal of particulate matter and destruction of bacteria and parasites. The phagocytosed particles are internalized and destroyed in phagolysosomes. Partially degraded antigen may subsequently become associated with MHC class II antigens and be re-expressed on the surface of a macrophage, where it can be presented to T-helper cells.

Phagocytes also possess some antigen-presenting capacity, although this is limited—cells express class II MHC molecules and can process and re-express antigen on their surface in association with these specific molecules, but only elicit responses in specific responder T-cell populations. In general, phagocytes present antigen to sensitized T cells but not to naïve or 'memory' T cells.

Antigen-presenting cells are histiocytic cells, or in some instances other cell types, that have specialized functional activity in presenting antigen to T cells. These cells are represented in humans by the blood dendritic cell, epidermal Langerhans' cell, interdigitating reticulum cell of the lymph node paracortex and veil cell of the efferent lymph. These cells have no phagocytic activity and, unlike professional phagocytes, are unable to adhere to surfaces. They are able to internalize antigen by endocytosis, process it by lysosomal digestion and re-express the antigen on their surface in association with MHC class II molecules. In addition, these cells are potent antigen-presenting cells and are able to present antigen not only to sensitized T cells but also to memory and naïve T cells, and are also able to present self antigen to allogeneic T cells to elicit an allogeneic or mixed-cell reaction [43].

Langerhans' cells are central to the regulation of contact allergic dermatitis, responsible for cutaneous immune surveillance and the target for skin graft rejection [44]. Epidermal Langerhans' cells are immature but, following stimulation, they migrate from epidermis to lymphatics and thus to the regional lymph nodes, and during this process undergo maturation. The signals that initiate and regulate the directed movement of Langerhans' cells from skin to regional lymph nodes include chemokines and cytokines. In cutaneous sensitization, TNF-α, GM-CSF, IL-1β and IL-18 are required, while IL-4 and IL-10 antagonize this process [45,46]. Maturation of Langerhans' cells is accompanied by specific phenotypic changes, with up-regulation of HLA-DR, down-regulation of CD1a, and expression of CD4 and CD25. There is a switch in chemokine receptor expression from CCR5 and CCR6 to CCR7 and CXCR4, which enables Langerhans' cells to exit the epidermis and follow a gradient of chemokines (CCL19, CCL21 and CXCL12) to the paracortical zone of the lymph nodes [47]. Langerhans' cells

also express other activation markers, including CD83 and CD40 and the T-cell co-stimulatory molecules CD80 and CD86 [48].

References

1 Golde DW, Finley TN, Cline MJ. Production of colony stimulating factor by human macrophages. *Lancet* 1972; **ii**: 1397–9.
2 Cline M, Golde DW. Production of colony-stimulating activity by human lymphocytes. *Nature* 1974; **248**: 703–4.
3 Mann A, Breuhahn K, Schirmacher P *et al.* Keratinocyte derived granulocyte-macrophage colony stimulating factor accelerates wound healing: stimulation of keratinocyte proliferation, granulation tissue formation and vascularisation. *J Invest Dermatol* 2001; **117**: 1382–90.
4 Golde DW, Rothman B, Cline MJ. Production of colony stimulating factor by malignant leukocytes. *Blood* 1974; **43**: 749–56.
5 Amento EP, Bhalla AK, Kurnick JT. 1-Alpha, 25-dihydroxyvitamin D3 induces maturation of the human monocyte cell line U937 and, in association with a factor from human T lymphocytes, augments production of the monokine, mononuclear cell factor. *J Clin Invest* 1984; **73**: 731–9.
6 Abita JP, Gauville C, Balitrand N. Binding of ^{125}I-insulin to the human histio-cytic lymphoma cell line U-937: effect of differentiation with retinoic acid. *Leuk Res* 1984; **2**: 213–21.
7 Griffin JD, Sabbath KD, Hermann F *et al.* Differential expression of HLA-DR antigen in subsets of human CFU-GM. *Blood* 1985; **66**: 788–95.
8 Nilsson K, Andersson LC, Gahmberg CG *et al.* Differentiation *in vitro* of human leukaemia and lymphoma cell lines. In: Serrou B, Rosenfeld C, eds. *International Symposium on New Trends in Human Immunology and Cancer Immunotherapy.* Paris: Doin, 1980: 271–92.
9 Van Furth R. Development of mononuclear phagocytes. In: Forster O, Landy M, eds. *Heterogeneity of Mononuclear Phagocytes*. London: Academic Press, 1981: 323–69.
10 Evans MJ, Sherman MP, Campbell LA *et al.* Proliferation of pulmonary alveolar macrophages during postnatal development of rabbit lungs. *Am Rev Respir Dis* 1987; **136**: 384–7.
11 Katz SI, Tamaki K, Sachs DH. Epidermal Langerhans cells are derived from cells originating in bone marrow. *Nature* 1979; **282**: 324–6.
12 Takeuchi S, Furue M. Dendritic cells—Ontogeny. *Allergol Internat* 2007; **56**: 215–23.
13 de Fraissinette A, Dezutter-Dambuyant C, Schmitt D *et al.* Cultured bone marrow myelomonocyte CD1 positive cells: are they Langerhans cell progenitors? *Coll Inserm* 1988; **172**: 41–53.
14 Griffiths-Chu S, Patterson J, Berger C *et al.* Characterization of immature T cell subpopulations in neonatal blood. *Blood* 1984; **64**: 296–300.
15 Gothelf Y, Hanau D, Sharon N *et al.* Precursors of Langerhans cells of the skin can be identified in the peripheral blood of burns patients. *J Invest Dermatol* 1986; **87**: 141.
16 Bartz H, Rothoeft T, Anhenn O *et al.* Large scale isolation of immature dendritic cells with features of Langerhans' cells by sorting CD34+ cord blood stem cells cultured in the presence of TGF-beta1 for cutaneous leukocyte antigen (CLA). *J Immunol Methods* 2003; **275**: 137–48.
17 Caux C, Dezutter-Dambuyant C, Schmitt D *et al.* GM-CSF and TNFα cooperate in the generation of dendritic Langerhans cells. *Nature* 1992; **360**: 258–61.
18 Kasinrerk W, Baumruker T, Majdic O *et al.* CD1 molecule expression on human monocytes induced by granulocyte-macrophage colony stimulating factor. *J Immunol* 1993; **150**: 579–84.
19 Sallusto F, Lanzavecchia A. Efficient presentation of soluble antigen by cultured human dendritic cells is maintained by granulocyte/macrophage colony-stimulating factor plus interleukin 4 and down regulated by tumour necrosis factor alpha. *J Exp Med* 1994; **179**: 1109–18.
20 Caux C, Vanbervliet B, Massacrier C *et al.* CD34+ hematopoietic progenitors from human cord blood differentiate along two independent dendritic cell pathways in response to GM-CSF + TNF alpha. *J Exp Med* 1996; **184**: 695–706.
21 Caux C, Vanbervliet B, Massacrier C *et al.* Interleukin 3 cooperates with tumour necrosis factor alpha for the development of human dendritic/Langerhans cells from cord blood CD34+ hematopoietic progenitor cells. *Blood* 1996; **87**: 2376–85.
22 Strobl H, Riedl E, Scheinecker C *et al.* TGF-beta 1 promotes in vitro development of dendritic cells from CD34+ hematopoietic progenitors. *J Immunol* 1996; **157**: 1499–507.
23 Chu A, Eisinger M, Lee JS *et al.* Immunoelectronmicroscopic identification of Langerhans cells using a new antigenic marker. *J Invest Dermatol* 1982; **28**: 177–80.
24 Romani N, Lenz A, Glossel H *et al.* Cultured human Langerhans cells resemble lymphoid dendritic cells in phenotype and function. *J Invest Dermatol* 1989; **93**: 600–9.
25 Headington JT. The dermal dendrocyte. *Adv Dermatol* 1986; **1**: 159–71.
26 Hoyo E, Kanitakis J, Schmitt D. The dermal dendrocyte. *Pathol Biol (Paris)* 1993; **41**: 613–8.
27 Sueki H, Telegan B, Murphy GF. Computer-assisted three-dimensional reconstruction of human dermal dendrocytes. *J Invest Dermatol* 1995; **105**: 704–8.
28 Langerhans P. Uber die Nerven der menschlichen Haut. *Virchows Arch (Pathol Anat Physiol)* 1868; **44**: 325–31.
29 Fithian E, Kung P, Goldstein G *et al.* Reactivity of Langerhans cells with hybridoma antibody. *Proc Natl Acad Sci USA* 1981; **78**: 2541–4.
30 Martin LH, Calabri F, Milstein C. Isolation of CD1 genes: a family of major histiocompatibility complex-related differentiation antigens. *Proc Natl Acad Sci USA* 1980; **83**: 9154–8.
31 Chu AC, Jaffe R. The normal Langerhans cell and the LCH cell. *Br J Cancer* 1994; **70**: S4–S10.
32 Zajonc DM, Crispin MD, Bowden TA *et al.* Molecular mechanism of lipopeptide presentation by CD1a. *Immunity* 2005; **22**: 209–19.
33 Birbeck MS, Breathnach AS, Everall JD. An electronmicroscopic study of basal melanocytes and high level clear cells (Langerhans cells) in vitiligo. *J Invest Dermatol* 1961; **37**: 51–64.
34 Hanau D, Gothelf Y, Fabre M *et al.* Internalisation of T6 (CD1) antigen in a subset of human cord blood mononuclear cells expressing T6 surface antigen. *J Invest Dermatol* 1986; **87**: 143.
35 Kashihara M, Ueda M, Huriguchi Y *et al.* A monoclonal antibody specifically reactive to human Langerhans cells. *J Invest Dermatol* 1986; **87**: 602–8.
36 Symington FW, Brady W, Linsley PS. Expression and function of B7 on human epidermal Langerhans cells. *J Immunol* 1993; **150**: 1286–95.
37 Cerio R, Griffiths CEM, Cooper KD *et al*. Characterization of factor XIIIa positive dermal dendritic cells in normal and inflamed skin. *Br J Dermatol* 1989; **121**: 421–31.
38 Fullen DR, Reed JA, Finnerty B, McNutt NS. S100A6 expression in fibrohistiocytic lesions. *J Cutan Pathol* 2001; **28**: 229–34.
39 Akagi A, Tajima S, Ishibashi A *et al.* Type XVI collagen is expressed in a factor XIIIa monocyte derived dermal dendrocytes and constitutes a potential substrate for factor XIIIa. *J Invest Dermatol* 2002; **118**: 267–74.
40 Young DA, Lowe LD, Clark SC. Comparison of the effects of IL-3, granulocyte-macrophage colony-stimulating factor, and macrophage colony-stimulating factor in supporting monocyte differentiation in culture. *J Immunol* 1990; **145**: 607–15.
41 Monteiro MR, Shapiro SS, Takafuta T *et al.* Von Willebrand factor receptor GPIbα is expressed by human factor XIIIa-positive dermal dendrocytes and is upregulated by mast cell degranulation. *J Invest Dermatol* 1999; **113**: 272–6.
42 Monteiro MR, Murphy EE, Galaria NA *et al.* Cytological alterations in dermal dendrocytes *in vitro*: evidence for transformation to a non-dendritic phenotype. *Br J Dermatol* 2000; **143**: 84–90.
43 Austyn JM. Lymphoid dendritic cells. *Immunology* 1987; **62**: 161–70.
44 Wolff K, Stingl G. The Langerhans cell. *J Invest Dermatol* 1983; **80**: 17s–21s.
45 Cumberbatch M, Dearman RJ, Griffiths CEM, Kimber I. Langerhans cell migration. *Clin Exp Dermatol* 2000; **25**: 413–8.
46 Kimber I, Cumberbatch M, Dearman RJ *et al*. Cytokines and chemokines in the initiation and regulation of epidermal Langerhans cell migration. *Br J Dermatol* 2000; **142**: 401–12.
47 Sallusto F, Schaerli P, Loetscher P *et al.* A rapid and co-ordinated switch in chemokine receptor expression during dendritic cell maturation. *Eur J Immunol* 1998; **28**: 2760–9.
48 Bjorck P, Flores Romo L, Liu YJ. Human interdigitating dendritic cells directly stimulate CD40 activating naïve B cells. *Eur J Immunol* 1997; **27**: 1266–74.

Classification of the histiocytoses

Understanding of the histiocytoses has been severely hampered by the lack of a universally accepted classification of these diseases and the widespread use of eponyms to describe them. For these

reasons, the Histiocyte Society published their classification of the histiocytoses for use as a standard in both diagnosis and management [1]. This classification has been generally accepted and is now widely used. In this chapter the original classification has been modified in the light of new insights into reactive histiocytoses of dermal dendrocyte phenotype. The histiocytoses are separated into four classes according to our current understanding of the biology of these diseases.

Class I: Langerhans' cell histiocytosis (LCH)

Class I histiocytoses are a diverse group of clinical diseases that are all reactive histiocytoses in which the predominant histiocyte is of Langerhans' cell phenotype. Patients with LCH can be further subdivided on the basis of the clinical organ involvement present. Bone disease and lung disease in adults appear to be significantly different in their biology from other single-system involvement and it is valid to separate them. The significance of organ involvement is discussed further in the section on LCH.

Class IIa: histiocytoses involving cells of the dermal dendrocyte lineage

Class IIa histiocytoses are reactive diseases in which cells with the phenotype of the dermal dendrocyte (positive for CD68 and factor XIIIa) accumulate in the skin and other tissues causing tissue damage. The typical histological change is a xanthogranulomatous reaction, although the histological changes reflect the cell type present. Juvenile xanthogranuloma is typical of this group of diseases, and some of the conditions described may not be specific disease entities but clinical variants of a single disease. These diseases are reactive with no clinical evidence of malignancy.

Class IIb: histiocytoses involving cells other than Langerhans' cells and dermal dendrocytes

Class IIb histiocytoses are reactive diseases in which histiocytes other than those bearing the Langerhans' cell or dermal dendrocyte phenotype accumulate in various tissues and may cause tissue damage. Within this heterogeneous group of diseases are included a number of rare and often poorly understood disorders. The major features of all these histiocytoses are that they are reactive, with no clinical or laboratory evidence of malignancy, and that Langerhans' cells and related cells are not involved.

Class III: malignant histiocytic disorders

Class III histiocytoses include all the malignant histiocytic diseases. These include monocytic leukaemias, malignant histiocytosis, which may be of the mononuclear phagocyte, dendritic cell or Langerhans' cell type, and the true histiocytic lymphoma, which once again may be of the mononuclear phagocyte, dendritic or Langerhans' cell type.

Reference

1 Chu A, D'Angio G, Favara B *et al*. Histiocytosis syndromes in children. *Lancet* 1987; **i**: 208–9.

Class I histiocytosis: Langerhans' cell histiocytosis

Synonyms

- Histiocytosis X
- Eosinophilic granuloma
- Letterer–Siwe disease
- Hand–Schüller–Christian syndrome
- Hashimoto–Pritzker syndrome
- Self-healing histiocytosis
- Pure cutaneous histiocytosis
- Langerhans' cell granulomatosis
- Type II histiocytosis
- Non-lipid reticuloendotheliosis

Definition. LCH is a reactive condition in which a clonal population of cells with the phenotype of the Langerhans' cell accumulate in various tissues and cause damage. Tissue damage appears to be due, in part, to cytokine production.

Aetiology. The aetiology of LCH is unknown but over the last century several possibilities have been considered, including tuberculosis [1] and a lipid abnormality [2,3]. The discovery of Birbeck granules in the cytoplasm of lesional cells using electron microscopy [4] led to the suggestion that these cytoplasmic bodies could be viral inclusion bodies and that LCH could be a virally mediated disease [5]. However, a large retrospective study on the fulminant form of LCH showed a random geographical distribution and little month-to-month variation in the incidence of the disease, which argued against it being due to a conventional virus [6]. A study of 56 LCH tissue samples using *in situ* hybridization and polymerase chain reaction (PCR) analysis failed to show any consistent evidence of adenovirus, cytomegalovirus, herpesvirus, parvovirus, human T-cell virus or human immunodeficiency virus infection [7].

The possibility of an immunological aetiology for LCH has been suggested by the occurrence of a number of immunological abnormalities in this disease. The fact that the lesional cell bears the phenotype of the Langerhans' cell, which is a key cell in the immune system, also suggests that the immune system is in some way involved in its pathogenesis. However, none of the immunological abnormalities have been a consistent feature, and most authors now consider them to be epiphenomena.

Serum immunoglobulins may be increased or decreased. The most common finding is that of reduced IgA and IgG levels, with normal IgE and IgM levels. In some reported cases, IgE and IgM levels were elevated [8].

In some patients, particularly those with aggressive disease, cutaneous anergy has been found on cutaneous testing, and *in vitro* studies have shown reduced T-cell responses to mitogens, recall antigens and alloantigens [9]. A reasonably consistent feature in three reported series of LCH [10–12] is a reduction of the CD8 T-cell subpopulation in the blood, with an associated normal or reduced total T-cell number. In one report [12], this reduction in the number of CD8 cells was associated with reduced suppressor T-cell activity *in vitro*.

Considering that Langerhans' cells are members of the monocyte/macrophage series of cells, very few abnormalities of this group of cells have been reported. Reduced monocyte-mediated, antibody-dependent cytotoxicity occurred in six patients with LCH, all of whom were in clinical remission [13]. This certainly warrants further study. LCH cells are unable to provide accessory cell function in a mitogen-driven T-cell response, and are inhibitory to T-cell proliferative responses [14]. Only one study has investigated the functional activity of LCH cells in depth [15]. In this report, LCH cells were shown to be functionally deficient in presenting alloantigen to T cells. It is possible that the defect in functional activity may be linked with the apparent arrest of these cells in an early stage of activation, leaving the cells immature so that they do not have the functional capacity of a normal Langerhans' cell.

Historically, LCH has been considered a malignant disease, and care of children with the disease has been in the hands of paediatric oncologists. The main reason for this is the clinical course and high mortality associated with the more fulminant forms of LCH. Flow cytometric studies have in general failed to identify aneuploidy in LCH [16,17]. In one report of an adult case with clinically and histologically confirmed LCH involving the skin, flow cytometry revealed an aneuploid peak [18]. Many features of this case were unusual and it is possible that the patient had the rare form of malignant histiocytosis of Langerhans' cell type.

Studies have demonstrated that lesional CD1a cells in LCH are clonal. Clonality studies in LCH have been difficult to perform because of the lack of cell-specific markers. Unlike the T-cell receptor in T cells and immunoglobulins in B cells, histiocytic cells have no markers that can be employed in such studies. The study of genes carried on the X chromosome have now allowed such studies in female patients with this disease. Of the gene loci examined, the human androgen receptor (*HUMARA*) is the most informative as there is a high degree of heterogeneity for this locus in the population. The underlying theory behind the assay is that the two alleles for *HUMARA* are acquired from maternal and paternal genes, each of which is a different size because of the presence of tandem repeats. Only one allele is activated, the other being inactivated by methylation, and the use of methylation-sensitive restriction enzymes in PCR allows the inactivated allele to be expanded and identified. In a normal population of cells, activation of the alleles is random so that 50% are derived from maternal and 50% from paternal genes, giving two bands on gel electrophoresis. In a clonal population of cells, all cells are derived from a single cell and therefore all these cells will have an inactivated allele, which is either maternal or paternal, giving a single band on gel electrophoresis. In a study of four female patients with LCH, purified lesional CD1a cells were shown to be clonal using this assay system [19]. Studies by Willman *et al.* [20] have confirmed these studies and shown that lesional cells are clonal regardless of the extent or severity of the disease. In isolated pulmonary LCH in adults, a study using X chromosome inactivation at the *HUMARA* locus has shown that 29% were clonal and 71% non-clonal. Discrete lung nodules from the same patient showed different allele inactivation [21]. Pulmonary LCH in adults is often an isolated disease that may remain restricted to the lungs and thus behaves in a different way biologically compared to other forms of LCH. It is possible that primary lung disease is a separate entity and only when it progresses to involve other organs does it become a clonal disease.

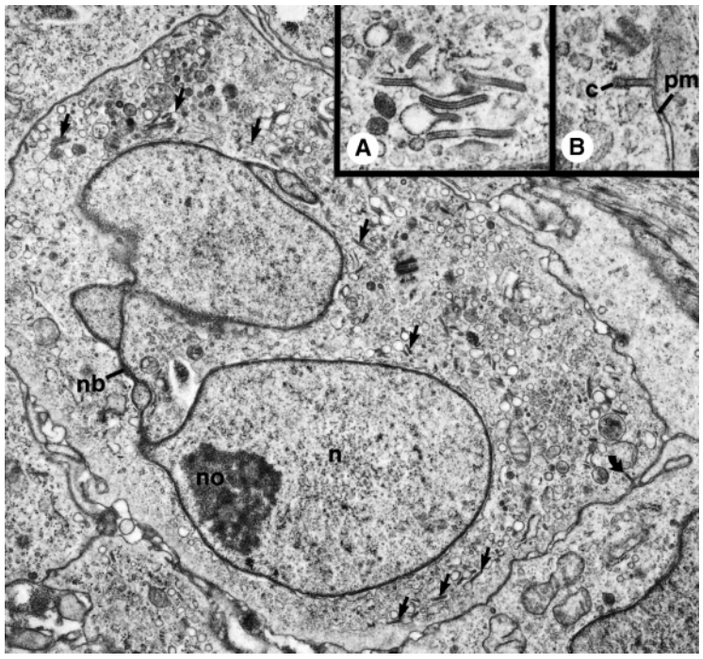


Fig. 55.3 Electron micrograph of a Langerhans' cell histiocytosis (LCH) cell in the epidermis of a patient with multisystem LCH. The cell shows a lobulated nucleus (n) with a prominent nucleolus (no) and attenuated nuclear bridge (nb). Numerous Birbeck granules (straight arrows) are evident in the cytoplasm. One granule (curved arrow) is seen projecting from the plasma membrane (× 13 000). (A) Birbeck granule in the cytoplasm. Some show characteristic vesiculation of the end, forming typical tennis-racket bodies. (B) Birbeck granules appear to be budding from the plasma membrane (pm) (× 39 000). (Courtesy of Professor R.A.J. Eady, St John's Dermatology Centre, London, UK.)

What clonality in LCH means is difficult to interpret. It certainly identifies the LCH cell as the primary cell in this disease but this does not mean that LCH is a malignancy. Many reactive diseases, for example lymphomatoid papulosis, have been shown to be clonal. Although of major interest, such studies have thus not altered our management of patients with this disease, nor have they identified the disease as malignant.

Pathology. The histological picture of LCH depends on the age of the lesion biopsied and the organ involved. The pathology of LCH was reviewed by the Histiocyte Society in 1987 [22], who recommended three levels of diagnostic confidence. A presumptive diagnosis is made when the histological appearance of the biopsy is consistent with the diagnosis of LCH. Diagnostic confidence increases if marker studies are performed and lesional cells are found to be positive for S100 protein, peanut agglutinin or α-D-mannosidase. If lesional cells are found to express the CD1 complex or to exhibit Birbeck granules on electron microscopy (Fig. 55.3), this constitutes a definitive diagnosis.

The characteristic histological appearance of LCH in the skin is of an upper dermal and junctional accumulation of large histiocytic cells with homogeneous pink cytoplasm. These cells have

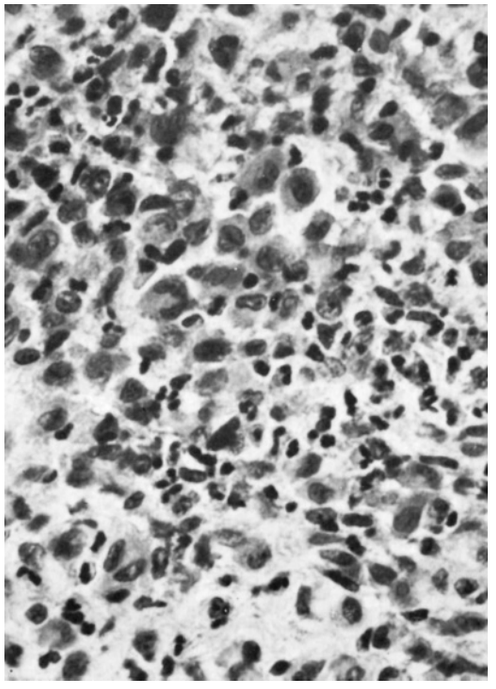


Fig. 55.4 Langerhans' cell histiocytosis cells in the dermis intermingled with polymorphs and eosinophils (H&E × 250). (Courtesy of Professor E. Wilson Jones, St John's Dermatology Centre, London, UK.)

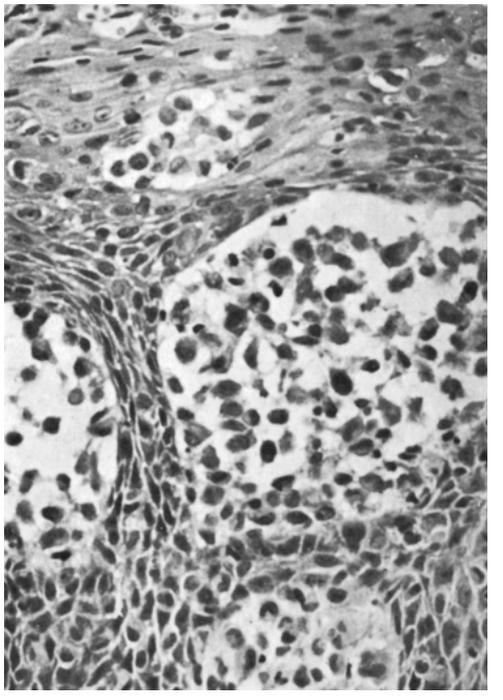


Fig. 55.5 Langerhans' cell histiocytosis (LCH). Details of a papillary tip containing LCH cells, with a small intraepidermal abscess overlying it (H&E × 250). (Courtesy of Professor E. Wilson Jones, St John's Dermatology Centre, London, UK.)

lobulated, bean-shaped or boat-shaped nuclei (Fig. 55.4). There is a variable lymphocytic infiltrate, deep to the aggregates of LCH cells. In some patients with LCH, large numbers of γ/δ T cells have been identified in the lymphocytic infiltrate [23]. Eosinophils are present in variable numbers, being rare in the more fulminant forms of LCH but present in high numbers in the less aggressive spectrum of LCH. Within the epidermis, LCH cells are often observed either singly or forming Pautrier-like microabscesses (Fig. 55.5).

With time, the histological picture changes, with fewer LCH cells present and the emergence of a more xanthomatous pattern, which is eventually followed by fibrosis. Several studies have shown no correlation between histology and extent of disease, morbidity or mortality [24–27].

In one clinical variant of LCH, described by Hashimoto and Pritzker [28], in which the disease is restricted to the skin and regresses spontaneously over a period of several months, the pathology in the skin is sufficiently different to warrant separate description. In this variant, the infiltrate is deep within the dermis, with sparing of papillary dermis and epidermis. Lesional cells are large histiocytic cells with copious glassy eosinophilic cytoplasm. Multinucleate giant cells are often observed. Up to 25% of these histiocytes contain Birbeck granules.

Immunocytochemistry. Immunohistochemical studies have demonstrated that LCH cells show many of the characteristics of the epidermal Langerhans' cell, particularly in its activated state (see Table 55.1) [29–31]. The labelling pattern with certain markers (C3b and C3bi receptors, CDW14, Ki-M1 and Ki-M6) has been shown to be variable. This does not correlate with the clinical course of the disease but probably reflects different phenotypic 'ages' of the Langerhans' cell [30].

Table 55.2 Diagnostic markers for Langerhans' cell histiocytosis (LCH) cell.

Marker	Tissue needed
S100	Paraffin-embedded
Peanut agglutinin	Paraffin-embedded
Placental alkaline phosphatase	Paraffin-embedded
α-D-Mannosidase	Fresh
CD1a	Fresh-frozen (paraffin-embedded with 010 monoclonal antibody)
Birbeck granules	Electron microscopy prepared

Three markers have now been shown to be expressed by LCH cells but not by normal epidermal Langerhans' cells. These are peanut agglutinin, an epitope shared with IFN-γ [32,33] and placental alkaline phosphatase [34]. Placental alkaline phosphatase is negative in normal Langerhans' cells and is not observed in reactive dermatoses where Langerhans' cells are present in the dermal infiltrate. However, *in vitro* studies have shown that placental alkaline phosphatase expression is an early and transient activation marker of Langerhans' cells [35]. These observations are of particular interest, as they show that LCH cells are not merely reactive Langerhans' cells but are arrested at a particular stage of their ontogeny.

Immunohistochemistry is important in confirming the diagnosis of LCH. For retrospective studies where only formalin-fixed and paraffin-embedded tissue is available (Table 55.2), three

markers are of value: S100 protein, peanut agglutinin and placental alkaline phosphatase. S100 protein staining is a consistent feature of LCH cells but is also present in normal Langerhans' cells and a variety of other skin cells and structures, including nerve tissue, melanocytes and naevus cells. In a study by Rowden *et al.* [36], the histiocytic cells and giant cells in juvenile xanthogranuloma, necrobiotic xanthogranuloma, papular xanthoma, eruptive histiocytoma and reticulohistiocytosis were all negative for S100 protein, but all LCH specimens were positive.

Peanut agglutinin shows characteristic labelling of LCH cells, with paranuclear and cell-surface deposition of reaction products. Peanut agglutinin labels other cell types in the same way, including interdigitating reticulum cells [37], but normal Langerhans' cells and other histiocytic cells show diffuse cytoplasmic labelling with this marker [32].

Placental alkaline phosphatase is normally found in placental tissue and in the female reproductive tract. It is also expressed in malignancies of the ovary and testis. In normal skin, placental alkaline phosphatase is negative and cells expressing this enzyme are absent in reactive disorders. It is perhaps the most informative marker that can be used in archival LCH material, where only the LCH cells express this enzyme [34].

Fascin is a 55-kDa actin bundling protein that is highly selective for dendritic cells of lymphoid tissue and blood. It is involved in the formation of dendritic processes in maturing epidermal Langerhans' cells and can be used to differentiate LCH from other histiocytoses. In a study of 34 samples of LCH from skin, bone, lymph node, thyroid, orbit and extradural cranial tissue, all samples stained positive for fascin, CD1a and S100. Normal epidermal Langerhans' cells were consistently negative for fascin [38].

To establish a definitive diagnosis by the criteria of the Histiocyte Society, the involved tissue must be examined for CD1a staining or for the presence of Birbeck granules (which requires fixation and processing for electron microscopy). Staining with monoclonal anti-CD1a antibodies may be carried out in paraffin-embedded tissue [39].

Incidence. The incidence of LCH is unknown because of the heterogeneity of clinical expression of the disease. In many patients, the disease is undiagnosed, with mild skin involvement being attributed to seborrhoeic dermatitis and isolated bone disease remaining undetected. Also, the diverse clinical presentation of the disease means that patients may be under the care of orthopaedic surgeons, ear, nose and throat surgeons, paediatricians, paediatric oncologists or dermatologists. In the UK, 15–20 cases are reported to the UK Children's Cancer Study Group Register each year. These represent only the more severe paediatric cases, and the real incidence in the general population is more likely to be at least four to six per million, with 50–70 new cases presenting annually.

Clinical features. LCH can affect many different organs and may cause fever, malaise and, in children, failure to thrive.

Of 58 patients with LCH seen at the Hospital for Sick Children, London, over a 7-year period, 14 had single-system disease (13 bone and one skin) and 44 had multisystem disease, of whom 50% had vital organ dysfunction [40]. At the Children's Hospital in Philadelphia, 64 patients were seen over a 14-year period of whom 33 had single-organ involvement in bone (27 patients) or skin (six patients), 22 had multifocal single-organ disease affecting bone (17 patients) or soft non-osseous tissue (five patients), and nine patients had disseminated disease with dysfunction of liver or lungs [41].



Fig. 55.6 Langerhans' cell histiocytosis of the scalp and ear of a child showing the characteristic seborrhoeic dermatitis-like eruption.

In a large series of 124 patients [42], bone, lymph node and skin lesions were the most frequently seen, but 50% of patients showed liver disease and 23% lung disease with frequent haematological changes.

Skin. The most characteristic presentation is with scalp involvement. The scalp is erythematous with greasy scales, looking very like seborrhoeic dermatitis (Fig. 55.6). On the trunk, the lesions are discrete, yellow-brown, scaly papules, often showing areas of purpura (Figs 55.7 & 55.8). Lesions may become nodular and crusted or eroded. Ulceration of the flexures, groin or perianal or vulval region is a common presentation in adult patients (Fig. 55.9).

In the Hashimoto–Pritzker variant of LCH, the eruption starts in the neonatal period with nodular lesions that resemble healing chickenpox. The eruption may involve any skin surface, including palms and soles, and is self-limiting over a few weeks. In a report of four cases of Hashimoto–Pritzker LCH, follow-up showed recurrence of disease in two children, with cutaneous relapse in one at 3 months of age and bony relapse requiring systemic therapy at 6 months in the other child. Follow-up of such children is therefore necessary [43].



Fig. 55.7 Langerhans' cell histiocytosis in a child. Scaly maculopapular eruption on the back with mild purpura.



Fig. 55.9 Langerhans' cell histiocytosis in an adult showing a characteristic erosive lesion in the groin.



Fig. 55.8 Langerhans' cell histiocytosis in an infant showing typical eruption on the abdomen and groins mimicking seborrhoeic dermatitis and napkin eruption.

In patients with peripheral lymph node involvement, chronic draining sinuses may develop over involved sites (Fig. 55.10).

Juvenile xanthogranuloma has been associated with LCH. In a report of three children with multisystem LCH, juvenile xanthogranulomas appeared 3–6 years after the initial presentation with LCH [44]. It is possible that the juvenile xanthogranulomas developed as a reaction to the inflammatory reaction in LCH.



Fig. 55.10 Langerhans' cell histiocytosis in an adult with multisystem involvement. Scarring is present at sites of previous fistulae from underlying involved lymph nodes. Active skin lesions are scattered over the chest. These are scaly, erythematous, maculopapular lesions. Marked striae are the result of high-dose steroids used in therapy.



Fig. 55.11 Langerhans' cell histiocytosis: involvement of nails in an adult patient showing nail-fold destruction. (Courtesy of Dr D.A.R. de Berker, Bristol Royal Infirmary, Bristol, UK.)



Fig. 55.12 Radiograph of the jaw of an adult with oral involvement in Langerhans' cell histiocytosis. The alveolar bone shows marked reabsorption and the teeth have become detached and appear to be floating.

Nails. Nail involvement in LCH is rare. Changes include paronychia, nail fold destruction, onycholysis and subungual expansion with nail plate loss (Fig. 55.11) [45].

Ears. Disease of the ears is common [46], with involvement of external and middle ear and mastoid. This may present with persistent aural discharge due to skin involvement or polypoid involvement of the external auditory canal. If the middle ear or mastoid is involved, deafness is common.

Oral. The commonest presentation in the mouth is with periodontal involvement, affecting particularly the lower molar areas [47]. There may be destruction of the alveolar ridge with infiltration of the gums with LCH cells resulting in the teeth floating free from their sockets (Fig. 55.12). Premature eruption of the teeth may be a presenting sign [48]. Mandible involvement is frequently observed in adults, with a palpable tender mass over the affected area. This is usually associated with oral involvement.

Bone marrow. Involvement may be occult or there may be pancytopenia. When bone marrow involvement is severe, splenomegaly is generally present. In bone marrow aspirates, LCH cells are often sparse and staining for CD1a is essential for assessment [49].

Lungs. Primary pulmonary LCH is rare and is usually seen in young or middle-aged adults. In adult patients, smoking is invariably associated with lung involvement, and in any adult smoker with LCH the lung should be examined for possible involvement. Computed tomography is usually more informative in such patients as it identifies lung disease at an earlier stage than chest X-ray. Abnormalities consist of nodular opacities representing aggregates of LCH cells which progressively show cystic central change, and cystic changes. Diagnosis is established by lung biopsy or bronchial lavage, as LCH of the lungs may be impossible to differentiate from other chronic interstitial lung diseases on clinical and radiographic findings.

Pulmonary signs and symptoms are non-specific and are rarely observed until there is frank dysfunction, with dyspnoea, tachypnoea and subcostal recession. Pain and sudden dyspnoea may indicate a pneumothorax due to rupture of a peripheral bulla. Pneumothoraces are common [50], but up to 23% may be asymptomatic.

Patients with multisystem LCH and lung involvement often have progressive lung disease and progressive dysfunction which may result in respiratory failure. Isolated pulmonary LCH may respond to cessation of smoking with regression of the nodular lesions. It is important in assessing patients with lung LCH to perform sequential lung function tests and to start treatment as soon as any fall in lung function is noted. Studies have demonstrated that lung function and gas exchange parameters correlate to cystic change but not to nodular lesions, which suggests that treatment should be directed to early nodular lesions before cystic changes lead to irreversible reduction in lung function [51].

Gastrointestinal tract. Liver involvement is very common as part of multisystem LCH, producing hepatomegaly or ascites. Cholestatic jaundice may be a late feature due to fibrotic obstruction of the biliary tree. Diarrhoea may be the result of infiltration of the lamina propria by LCH cells or may be caused by abnormal bile acid metabolism or infection within the gastrointestinal tract. Digestive tract involvement in LCH is very rare but in children even mild involvement of the gastrointestinal tract, which produces no overt symptoms of diarrhoea, may still cause failure to thrive due to mild malabsorption [52].

Central nervous system. Diabetes insipidus may be the presenting feature of LCH. Other focal lesions may occur, commonly affecting the cerebellum, temporal lobe and occipital lobe. Intracerebral disease is more frequently seen with bone involvement

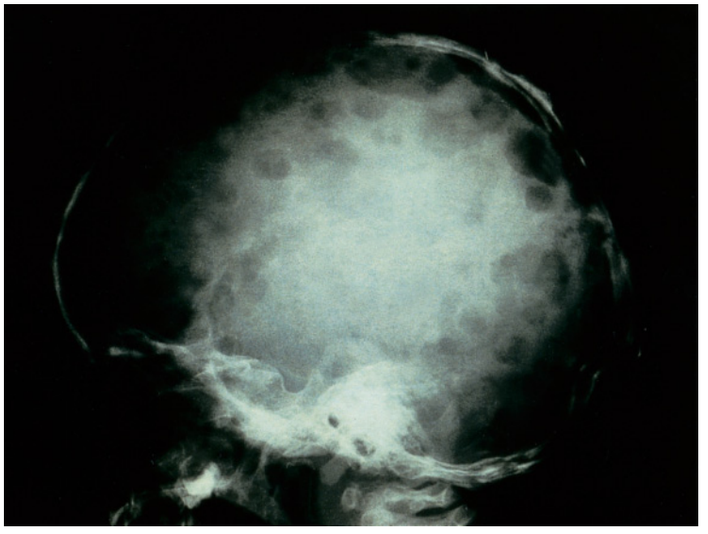


Fig. 55.13 Multiple osteolytic lesions in the skull of an infant with Langerhans' cell histiocytosis.

of the skull. A cerebellar syndrome with ataxia, dysarthria and choreoathetoid movements may be a late sequel of LCH. This is caused by progressive cerebellar atrophy. Biopsies of the cerebellum have so far failed to show infiltration with LCH cells only gliosis [53].

Bone. Solitary bone involvement with LCH is common but occasionally goes undiagnosed. The commonest sites are the bones of the calvarium, but femur, scapula, rib, mandible and vertebra are often affected [54]. Lesions may be asymptomatic or may present with swelling over the affected bone, pain or pathological fracture. Radiography is better than radionucleotide studies in detecting bone involvement in LCH [55]. Lesions appear as osteolytic areas that are sharply demarcated and may have a scalloped border (Fig. 55.13) [56]. When vertebrae are affected, the structural bone is lost and the vertebra may collapse. Spinal cord compression resulting from vertebral collapse has been reported with LCH [24]. Healing of bone lesions is usually seen as peripheral sclerosis of the lytic lesion. Radiographic changes may still be evident for long periods after the disease has been adequately treated or has undergone spontaneous remission.

Endocrine system. Diabetes insipidus is the commonest endocrine problem, the incidence in children with multisystem disease ranging from 22 to 50% [57–59]. Diabetes insipidus may result from pituitary involvement or hypothalamic involvement. Magnetic resonance imaging may show thickening of the pituitary stalk with recent-onset disease. Patients with multisystem disease and those with craniofacial bone involvement carry a significantly increased risk of developing diabetes insipidus [60]. Anterior pituitary dysfunction is always accompanied by diabetes insipidus and may develop slowly after the initial diagnosis of diabetes insipidus is made [61]. In the author's experience, men with LCH-related diabetes insipidus often develop hypoandrogenism and require testosterone replacement.

Short stature in children with LCH has been associated with growth hormone deficiency, which may be secondary to hypothalamic involvement [62]. Some of these children respond to treatment with growth hormone [58,62]. Hypogonadism with delayed puberty and thyroid involvement have also been reported [63,64].

Prognosis. Three important, independent, prognostic indices in LCH are the age of the patient, the extent of the disease and the presence of vital organ failure.

Children under the age of 2 years with multisystem disease have a much poorer prognosis than older children. In a study by Komp *et al.* [65], the mortality in children under the age of 2 years with disseminated LCH was 37% compared with 16% in the group aged over 2 years.

Lahey [66] found a positive relationship between increased mortality rate and widespread organ involvement, but Greenberger *et al.* [67] found that organ failure was a better prognostic indicator than organ involvement. Organ failure relates to lung, liver and bone marrow in children and lung and liver in adults. Studies have also suggested that survival in children is better if they respond to treatment in the first 6 weeks of therapy [68]. Both Lahey and Greenberger *et al.* [66,67] looked at prognosis in relation to mortality, but since LCH is a reactive rather than a malignant disease, prognosis should consider morbidity as well as mortality. The long-term sequelae of LCH can be related to both disease and treatment. Morbidity caused by the disease itself may be minor (e.g. skin lesions) or there may be major consequences if organs such as the liver, lungs and brain are damaged. Treatment with cytotoxic reagents may result in sterility and may cause leukaemias and other secondary malignancies. In a long-term follow-up of children with LCH over a 16-year period, only 33% of children with multisystem disease were alive and healthy without sequelae; 15% had diabetes insipidus, 10% had CNS complications and 11% had late-stage pulmonary disease [69].

Diagnosis. Pathological diagnosis is most important as many diseases can clinically mimic LCH, and S100 staining or even CD1a staining is insufficient to establish a diagnosis of LCH if the histological picture is not consistent. The differential diagnosis in cutaneous LCH includes seborrhoeic dermatitis, juvenile xanthogranuloma, xanthoma disseminatum and benign cephalic histiocytosis. In disseminated LCH there may be diagnostic problems with familial haemophagocytic lymphohistiocytosis, sinus histiocytosis with massive lymphadenopathy (SHML) and virus-associated haemophagocytic syndrome. Histological examination of tissue biopsy with specific marker studies is usually sufficient to differentiate LCH from these other conditions.

Investigation. LCH may present in various organs and it is important to investigate the patient for other sites of disease so that treatment can be properly planned. Patients may present with skin, bone, lymph node, pituitary, lung or liver disease as primary site but need to be fully investigated before a diagnosis of single-system disease can be made. Table 55.3 details investigations that should be conducted on all suspected cases and indication for more specialized investigations in some patients.

Table 55.3 Investigating the patient with LCH.

Investigations on all patients
Full blood count and ESR
Electrolytes, urea, liver function tests and CRP
Skeletal survey
Chest X-ray
Tests indicated in some patients
MRI of brain: lytic skull lesions, diabetes insipidus, symptoms suggestive of CNS involvement
Water deprivation test: polyuria, polydipsia
High resolution CT chest: adult smoker, respiratory symptoms
Lung function tests: lung involvement
Abdominal ultrasound, liver biopsy: abnormal liver function tests

In some patients with LCH, ESR and CRP are raised and these prove to be valuable markers of disease activity and response to treatment in these patients. A recent study has advocated the use of whole-body MRI to assess bony and extraosseous LCH, showing that it is superior to conventional X-rays and bone scintigraphy [70].

Treatment. Treatment depends on the extent and severity of disease. Patients with single-system bone or skin disease have a good prognosis and often require no or only limited treatment. In one study, McLelland *et al.* [40] showed that in 14 patients with single-system disease, eight required no treatment. In isolated bone disease, curettage to establish the diagnosis may be curative. In weight-bearing bones that are symptomatic, intralesional steroid injections are effective [9]. If vital structures are compromised, such as the optic nerve or spinal cord, low-dose radiotherapy (700–1000 cGy) can be given.

In single-system skin disease, topical treatment with 20% nitrogen mustard is effective [71]. Psoralen and UVA (PUVA) therapy may be useful for those patients who do not tolerate topical nitrogen mustard or fail to respond adequately. Reports have shown a good response of isolated skin disease to thalidomide [72], but poor responses in patients with multisystem disease [73].

Single-system bone disease may respond to simple curettage or intralesional steroid injections. Radiotherapy has been used in the past but is now generally restricted to use in single vertebral lesion or if there is a risk of pathological fracture in the greater trochanter [74].

In multisystem LCH where there is evidence of organ dysfunction, systemic chemotherapy is indicated. Treatment in children should initially be with prednisolone 2 mg/kg for a short course of about 2 months, with the dose adjusted to disease response [40]. Adults tend not to respond to systemic steroids and often suffer severe side effects from their use. In disease that is either unresponsive, aggressive or in adults, a number of chemotherapeutic agents have been tried, mainly the vinca alkaloids, especially vinblastine, but also methotrexate and 6-mercaptopurine in combination with prednisolone. Response rates of about 50–70% can be achieved using these agents. Evidence suggests that the epipodophyllotoxin etoposide as a single drug is better than other drugs tested [75], and ciclosporin and IFN-α have also been beneficial [76]. 2-Chlorodeoxyadenosine, a purine analogue with antiproliferative effects on histiocytes and lymphocytes, has been used in recurrent or high-risk LCH. Treatment is with 5–7 mg/m^2 daily for 5 days every 21–28 days. In a study of six children with LCH, five patients remained in clinical remission with a follow-up of 15 months [77]. 2-Chlorodeoxyadenosine also seems to be of particular value for patients with lung involvement but should ideally be used when patients have nodular involvement rather than late-stage cystic change [78].

References

1 Hand A. Polyuria and tuberculosis. *Arch Pediatr* 1893; **10**: 673–8.
2 Rowland RS. Xanthomatosis and the reticulo-endothelial system. *Arch Intern Med* 1928; **42**: 611–8.
3 Thannhauser SJ. Serum lipids and their value in diagnosis. *N Engl J Med* 1947; **237**: 515–46.
4 Basset F, Turiaf J. Identification par la microscopie electronique de particles de nature probablement virale dans les lesions granulomateuses d'une histiocytose X pulmonaire. *C R Acad Sci Hebd Seances Acad Sci D* 1965; **261**: 3701–3.
5 Nezelof C, Basset F, Rousseau MF. Histiocytosis X. Histiogenetic arguments for a Langerhans cell origin. *Biomedicine* 1973; **18**: 365–71.
6 Glass AG, Miller RW. US mortality from Letterer–Siwe disease, 1960–1964. *Pediatrics* 1968; **42**: 364–7.
7 McClain K, Weiss R. Viruses and Langerhans cell histiocytosis: is there a link? *Br J Cancer* 1994; **70**: S34–6.
8 Leikin S, Puruganan G, Frankel A *et al.* Immunologic parameters in histiocytosis X. *Cancer* 1973; **32**: 796–802.
9 Nesbit ME Jr, O'Leary M, Dehner LP *et al.* The immune system and the histiocytosis syndromes. *Am J Pediatr Hematol Oncol* 1981; **3**: 141–9.
10 Broadbent V, Pritchard J, Davies EG *et al.* Spontaneous remission of multisystem histiocytosis X. *Lancet* 1986; **i**: 253–4.
11 Davies EG, Levinsky RJ, Butler M *et al.* Thymic hormone therapy for histiocytosis X. *N Engl J Med* 1983; **309**: 493–4.
12 Shannon BT, Newton WA, Jacobs D. Lack of suppressor cell activity in children with active histiocytosis X. *Med Pediatr Oncol* 1986; **14**: 111–4.
13 Kragballe K, Zachariae H, Herlin T *et al.* Histiocytosis X: an immune deficiency disease? Studies on antibody-dependent monocyte mediated cytotoxicity. *Br J Dermatol* 1981; **105**: 13–8.
14 Meacham R, Morris J, Chu AC. Morphological and immunological characteristics of histiocytosis X (HX) cells. *J Invest Dermatol* 1985; **84**: 440.
15 Yu RC, Morris JF, Pritchard J *et al.* Defective alloantigen presenting capacity of Langerhans cell histiocytosis cells. *Arch Dis Child* 1992; **67**: 1370–2.
16 McLelland J, Newton J, Malone M *et al.* Flow cytometric study of Langerhans cell histiocytosis. *Br J Dermatol* 1989; **120**: 485–91.
17 Rabkin MS, Wittmer CT, Kjeldsberg CR *et al.* Flow cytometric DNA content of histiocytosis X (Langerhans cell histiocytosis). *Am J Pathol* 1988; **131**: 283–9.
18 Goldberg NS, Bauer K, Rosen ST *et al.* Histiocytosis X: flow cytometric DNA-content and immunohistochemical and ultrastructural analysis. *Arch Dermatol* 1986; **122**: 446–50.
19 Yu RC, Chu C, Buluwela L *et al.* Clonal proliferation of Langerhans cells in Langerhans cell histiocytosis. *Lancet* 1994; **343**: 767–8.
20 Willman CL, Busque L, Griffith BD *et al.* Langerhans cell histiocytosis (histiocytosis X): a clonal proliferative disease. *N Engl J Med* 1994; **331**: 154–60.
21 Yousem SA, Colby TV, Chen YY. Pulmonary Langerhans cell histiocytosis: molecular analysis of clonality. *Am J Surg Pathol* 2001; **25**: 630–6.
22 Chu AC, D'Angio DJ, Favara B *et al.* Histiocytosis syndromes in children. *Lancet* 1987; **i**: 208–9.
23 Aliabac M, Chu AC. T-lymphocytes bearing the gamma delta T-cell receptor in cutaneous lesions of Langerhans cell histiocytosis. *Med Pediatr Oncol* 1993; **21**: 347–9.
24 Esterly NB, Maures HS, Gonzales-Crussi F. Histiocytosis X, a seven year experience at a Children's Hospital. *J Am Acad Dermatol* 1985; **13**: 481–96.
25 Nezelof C, Frileux-Herbet F, Cronier-Sachot J. Disseminated histiocytosis X: analysis of prognostic factors based on a retrospective study of 50 cases. *Cancer* 1979; **44**: 1824–38.
26 Risdall RJ, Dehner LP, Duray P *et al.* Histiocytosis X (Langerhans cell histiocytosis). Prognostic role of histopathology. *Arch Pathol* 1983; **107**: 59–63.

27 Simmons PS, Wold LE, Ivebach LR *et al.* Prognostic factors and management of histiocytosis X. *J Pediatr* 1981; **98**: 1023.

28 Hashimoto K, Pritzker MS. Electron microscopic study of reticulohistiocytoma: an unusual case of congenital, self-healing reticulohistiocytosis. *Arch Dermatol* 1973; **107**: 263–70.

29 Azumi N, Sheibani K, Swartz WG *et al.* Antigenic phenotype of Langerhans cell histiocytosis: an immunohistochemical study demonstrating the value of LN-2, LN-3 and vimentin. *Hum Pathol* 1988; **19**: 1376–82.

30 Groh V, Gadner H, Radaskiewicz T *et al.* The phenotypic spectrum of histiocytosis X cells. *J Invest Dermatol* 1988; **90**: 441–7.

31 Santamaria M, Lamas L, Ree HJ *et al.* Expression of sialyated Leu M1 antigen in histiocytosis X. *Am J Clin Pathol* 1988; **89**: 211–6.

32 McLelland J, Chu AC. Comparison of peanut agglutinin and S100 stain in the paraffin tissue diagnosis of Langerhans cell histiocytosis. *Br J Dermatol* 1988; **119**: 513–21.

33 Neumann C, Schamburg-Lever G, Dopfer R *et al.* Interferon gamma is a marker for histiocytosis X cells in the skin. *J Invest Dermatol* 1988; **91**: 280–2.

34 Hage C, Bullman CL, Favara BE *et al.* Langerhans cell histiocytosis (histiocytosis X). Immunophenotype and growth fraction. *Hum Pathol* 1993; **24**: 840–5.

35 Murray S, Hage C, Isaacson P *et al.* Expression of placental alkaline phosphatase in Langerhans cells and Langerhans cell histiocytosis (abstract). *J Invest Dermatol* 1993; **100**: 482.

36 Rowden G, Connelly EM, Winkelmann R. Cutaneous histiocytosis X. The presence of S100 protein and its use in diagnosis. *Arch Dermatol* 1983; **119**: 553–9.

37 Ree HJ, Kadin ME. Peanut agglutinin: a useful marker for histiocytosis X and interdigitating reticulum cells. *Cancer* 1986; **57**: 282–7.

38 Pincus GS, Lones MA, Matsumura F. Langerhans cell histiocytosis: immunohistochemical expression of fascin, a dendritic cell marker. *Am J Clin Pathol* 2002; **118**: 335–43.

39 Emile JE, Wechsler J, Brousse N *et al.* Langerhans cell histiocytoses. Definitive diagnosis with the use of monoclonal antibody 010 on routinely paraffin embedded samples. *Am J Surg Pathol* 1995; **19**: 636–41.

40 McLelland J, Broadbent V, Yeoman E *et al.* Langerhans cell histiocytosis: a conservative approach to treatment. *Arch Dis Child* 1990; **65**: 301–3.

41 Raney RB Jr, D'Angio GJ. Langerhans cell histiocytosis (histiocytosis X): experience at the Children's Hospital Philadelphia, 1970–1984. *Med Pediatr Oncol* 1989; **17**: 20–8.

42 Rivera-Luna R, Martinez-Guerra G, Altamirano-Awarez E *et al.* Langerhans cell histiocytosis: clinical experience with 124 patients. *Pediatr Dermatol* 1988; **5**: 145–50.

43 Longaker MA, Frieden IJ, Le Boit PT *et al.* Congenital self-limiting Langerhans cell histiocytosis: the need for long term follow up. *J Am Acad Dermatol* 1994; **31**: 910–6.

44 Hoeger PH, Diaz C, Malone M *et al.* Juvenile xanthogranuloma as a sequel to Langerhans cell histiocytosis: a report of three cases. *Clin Exp Dermatol* 2001; **26**: 391–4.

45 de Berker D, Lever LR, Windebank K. Nail features in Langerhans cell histiocytosis. *Br J Dermatol* 1994; **130**: 523–7.

46 Cunningham MJ, Curtin HD, Jaffe R *et al.* Otological manifestations of Langerhans cell histiocytosis. *Arch Otolaryngal Head Neck Surg* 1989; **115**: 807–13.

47 Artzi Z, Grosky M, Raviv M. Periodontal manifestations of adult onset histiocytosis. *J Periodontol* 1989; **60**: 57–66.

48 McDonald JS, Miller RL, Bernstein ML *et al.* Histiocytosis X, a clinical presentation. *J Oral Pathol* 1980; **9**: 342–9.

49 Minkov M, Potschger U, Grois N *et al.* Bone marrow assessment in Langerhans cell histiocytosis. *Pediatr Blood Cancer* 2007; **49**: 694–8.

50 Hoffman L, Cohn JE, Gaensler EA. Respiratory abnormalities in eosinophilic granuloma of the lung: long term study of 5 cases. *N Engl J Med* 1962; **267**: 577–89.

51 Canuet M, Kessler R, Jeung MY *et al.* Correlation between high-resolution computed tomography findings and lung function in pulmonary Langerhans cell histiocytosis. *Respiration* 2007; **74**: 640–6.

52 Hait E, Liang M, Degar B *et al.* Gastrointestinal tract involvement in Langerhans cell histiocytosis : case report and literature review. *Pediatrics* 2006; **118**: 1593–9.

53 Grois N, Prayer D, Prosch H *et al.* Neuropathology of CNS disease in Langerhans cell histiocytosis. *Brain* 2005; **128**: 829–38.

54 McGavran MH, Spady HA. Eosinophilic granuloma of bone. A study of 28 cases. *J Bone Joint Surg* 1960; **42**: 979–92.

55 Crone-Munzebrock W, Brassow F. Comparison of radiographic and bone scan findings in histiocytosis X. *Skeletal Radiol* 1983; **9**: 170–3.

56 Ochsner SF. Eosinophilic granuloma of bone: experience with 20 cases. *Am J Roentgenol Radium Ther Nucl Med* 1966; **97**: 719–26.

57 Braunstein GD, Kohler PO. Endocrine manifestations of histiocytosis. *Am J Pediatr Hematol Oncol* 1981; **3**: 67–75.

58 Greenberger JS, Cassady JR, Jaffe N *et al.* Radiation therapy in patients with histiocytosis: management of diabetes insipidus and bone lesions. *Int J Radiat Oncol Biol Phys* 1979; **5**: 1749–55.

59 Sims DG. Histiocytosis X: follow up of 43 cases. *Arch Dis Child* 1977; **52**: 433–40.

60 Grosi N, Potschger U, Prosch H *et al*. Risk factors for diabetes insipidus in Langerhans cell histiocytosis. *Pediatr Blood Cancer* 2006; **46**: 228–33.

61 Makras P, Alexandraki KI, Chrousos GP *et al*. Endocrine manifestations in Langerhans cell histiocytosis. *Trends Endocrinol Metab* 2007; **18**: 252–7.

62 Zinkham WH. Multifocal eosinophilic granulomas: natural history, etiology and management. *Am J Med* 1976; **60**: 457–63.

63 Braunstein GD, Raiti S, Hansen JW *et al.* Response of growth retarded patients with Hand–Schuller–Christian disease to growth hormone therapy. *N Engl J Med* 1975; **292**: 332–3.

64 Yagci B, Kandemir N, Yazici N *et al.* Thyroid involvement in Langerhans cell histiocytosis: a report of two cases and review of the literature. *Eur J Pediatr* 2007; **166**: 901–4.

65 Komp DM, Herson J, Starling KA *et al.* A staging system for histiocytosis X. A Southwest Oncology Group study. *Cancer* 1981; **47**: 798–800.

66 Lahey ME. Prognosis in reticuloendotheliosis in children. *J Pediatr* 1962; **60**: 664–71.

67 Greenberger JS, Crocker AC, Vawter G *et al.* Results of treatment of 127 patients with systemic histiocytosis (Letterer–Siwe syndrome, Schuller–Christian syndrome and multifocal eosinophilic granuloma). *Medicine (Baltimore)* 1981; **60**: 311–38.

68 Campos MK, Viana MB, de Oliveira BM *et al.* Langerhans cell histiocytosis: a 16 year experience. *J Pediatr* 2007; **83**: 79–86.

69 Bernstrand C, Sandstedt B, Ahstrom L *et al*. Long-term follow-up of Langerhans cell histiocytosis: 39 years' experience at a single centre. *Acta Paediatr* 2005; **94**: 1073–84.

70 Goo HW, Yang DH, Ra YS *et al*. Whole body MRI of Langerhans cell histiocytosis: comparison with radiography and bone scintigraphy. *Pediatr Radiol* 2006; **36**: 1019–31.

71 Wong E, Holden CA, Broadbent V *et al.* Histiocytosis X presenting as intertrigo and responding to topical nitrogen mustard. *Clin Exp Dermatol* 1986; **11**: 183–7.

72 Meunier L, Marck Y, Ribeyre C *et al.* Adult cutaneous Langerhans cell histiocytosis: remission with thalidomide treatment (letter). *Br J Dermatol* 1995; **132**: 168.

73 McClain KL, Kosinetz CA. A phase II trial using thalidomide for Langerhans cell histiocytosis. *Pediatr Blood Cancer* 2007; **48**: 44–9.

74 Allen CE, McClain KL. Langerhans cell histiocytosis: A review of past, current and future therapies. *Drugs Today* 2007; **43**: 627–43.

75 Broadbent V, Pritchard J, Yeoman E. Etoposide (VP16) in the treatment of multisystem Langerhans cell histiocytosis. *Med Pediatr Oncol* 1989; **17**: 97–100.

76 McLelland J, Pritchard J, Chu AC. Current controversies. *Hematol Oncol Clin North Am* 1987; **1**: 147–62.

77 Rodriguez-Galindo C, Kelly P, Jeng M *et al.* Treatment of children with Langerhans cell histiocytosis with 2-chlorodeoxyadenosine. *Am J Hematol* 2002; **69**: 179–84.

78 Aerni MR, Aubry CM, Myers JL *et al*. Complete remission of nodular pulmonary Langerhans cell histiocytosis lesions induced by 2-chlorodeoxyadenosine in a non-smoker. *Respir Med* 2008; **102**: 316–9.

Class IIa histiocytosis: histiocytoses involving cells of the dermal dendrocyte lineage

Class IIa histiocytoses are non-malignant diseases in which mononuclear phagocytic cells with the dermal dendrocyte phenotype

accumulate in various tissues where they may or may not cause symptoms.

In many of these diseases the histological features are of a xanthogranulomatous reaction in the skin. This pattern is seen in juvenile xanthogranuloma, benign cephalic histiocytosis, generalized eruptive histiocytosis, xanthoma disseminatum and necrobiotic xanthogranuloma. In some, such as progressive nodular histiocytosis, the cells have a more spindle-shaped appearance in a storiform pattern, particularly as the lesions progress.

Histopathological studies have suggested that benign cephalic histiocytosis represents a clinical variant of a xanthogranulomatous reaction rather than being a distinct entity in its own right. In one study [1], biopsies from benign cephalic histiocytosis, generalized eruptive histiocytosis, papular xanthoma and juvenile xanthogranuloma were examined in an observer blinded fashion. In all specimens examined, three distinct patterns of histiocyte proliferation were observed—papillary dermal, lichenoid and diffuse. Benign cephalic histiocytosis, generalized eruptive histiocytosis and early non-xanthomatous juvenile xanthogranuloma could not be specifically differentiated on histopathological grounds. This study certainly suggests that benign cephalic histiocytosis may be a localized form of generalized eruptive histiocytosis or an aborted phase of juvenile xanthogranuloma. In a further study, sequential biopsies were taken from a patient with solitary giant xanthogranuloma and from a patient with benign cephalic histiocytosis. In both cases, early stages of the disease showed infiltration with histiocytes positive for Ki-M1p, HAM56 and factor XIIIa. This was followed by a polymorphic infiltrate of mononuclear and multinuclear histiocytes, which were CD68 positive. This study suggests that both entities are variants of a xanthogranulomatous reaction [2]. In one case report, a 2-year-old girl with clinical, histopathological and ultrastructural benign cephalic histiocytosis developed a varicella-zoster infection with evolution of her skin disease both clinically and histologically to juvenile xanthogranuloma [3]. In a further report of a child with generalized eruptive histiocytosis, where the diagnosis was made on clinical, histological and ultrastructural grounds, the disease progressed with the growth of yellowish confluent papules and the development of diabetes insipidus. At this stage the diagnosis was changed to xanthoma disseminatum [4].

The dermal dendrocytes involved in these diseases show a spectrum of maturation of the cells. In juvenile xanthogranuloma and benign cephalic histiocytosis, the cells are morphologically the most immature and the disease has the shortest life span. Generalized eruptive histiocytosis and xanthoma disseminatum show increasing maturation of the cells and at the other end of the spectrum, progressive nodular histiocytosis shows mature spindle shaped cells with no tendency to spontaneous remission of the disease [5].

References

1 Gianotti R, Allessi E, Caputo R. Benign cephalic histiocytosis: a distinctive entity or a part of a widespread spectrum of histiocytic proliferative disorders of children? A histopathological study. *Am J Dermatopathol* 1993; **15**: 315–9.

2 Zelger BG, Zelger B, Steiner H *et al.* Solitary giant xanthogranuloma and benign cephalic histiocytosis: variants of juvenile xanthogranuloma. *Br J Dermatol* 1995; **133**: 598–600.

3 Rodriguez-Jurado R, Duran-McKinster R, Ruis-Maldonado R. Benign cephalic histiocytosis progressing into juvenile xanthogranuloma: a non-Langerhans cell histiocytosis transforming under the influence of a virus. *Am J Dermatopathol* 2000; **22**: 70–4.

4 Repiso T, Roca-Miralles M, Kanitakis J. Generalised eruptive histiocytosis evolving into xanthoma disseminatum in a 4 year old boy. *Br J Dermatol* 1995; **132**: 978–82.

5 Chu AC. The confusing state of the histiocytoses. *Br J Dermatol* 2000; **143**: 475–6.

Dermatofibroma

This benign, nodular, dermal lesion is discussed in Chapter 56.

Juvenile xanthogranuloma

Synonyms

- Naevoxanthoendothelioma
- Xanthoma multiplex
- Juvenile xanthoma
- Multiple eruptive xanthoma in infancy
- Congenital xanthoma tuberosum
- Xanthoma naeviforme
- Juvenile giant-cell granuloma

Definition. Juvenile xanthogranulomas are benign tumours of histiocytic cells that occur predominantly in infancy and early childhood and spontaneously regress.

Aetiology. The aetiology of juvenile xanthogranuloma is unknown. The tumours represent accumulations of differentiated histiocytes. These cells express the phenotype of the dermal dendrocyte, although it has been suggested that the cell of origin could be the plasmacytoid monocyte [1]. The appearance of giant cells and foamy lipid-laden histiocytes occurs late, and they are almost certainly secondary events, possibly in response to cytokine production by the lesional histiocyte. Serum lipid levels are normal. Conflicting reports have suggested that juvenile xanthogranuloma can be associated with cytomegalovirus infection. A study by Vasconcelos *et al.* [2] has demonstrated early and late cytomegalovirus antigens in some histiocytes in a case of oral juvenile xanthogranuloma.

Pathology. An established lesion shows a mixed cellular dermal infiltrate with histiocytes, lymphocytes, eosinophils and occasional neutrophils and plasma cells. This extends from the epidermis into the subcutaneous fat but epidermal involvement is rare. A typical feature is the presence of giant cells with a wreath-like arrangement of nuclei (Touton giant cells).

In very early lesions, only spindle-shaped fibrohistiocytic cells are seen. In older lesions, foamy lipid-laden histiocytes appear, and resolution is marked by gradual replacement by fibrous tissue. A spindle cell variant of juvenile xanthogranuloma has been described [3]. In deep juvenile xanthogranuloma the lesions tend to be more cellular with fewer Touton giant cells [4].

Immunocytochemical examination in most cases shows that lesional cells are positive for lysozyme, α_1-antichymotrypsin, CD68, Ki-MIP [5], fascin, factor XIIIa and may express HLA-DR and CD4, but are negative for S100 protein [6]. However, Tahan *et al.* [7] found a small population of S100 dendritic cells in juvenile

xanthogranuloma, which they felt were important in pathogenesis, and Kraus *et al.* [1] have shown reactivity to polyclonal S100 in six of eight specimens they examined. Cells are always CD1a negative.

At the ultrastructural level, the lesional histiocytes do not exhibit Birbeck granules but do show complex interdigitation of the cytoplasmic membrane [8].

Incidence. Half of the cases of juvenile xanthogranuloma have been reported in infants less than 6 months of age. Lesions may occur in children over 3 years of age and cases have been reported in adults [9]. There is no sex association and no familial tendency. Juvenile xanthogranuloma is 10 times more frequent in white than in black people.

Clinical features. The characteristic clinical features of juvenile xanthogranuloma are its onset in infancy, sudden appearance of lesions and spontaneous regression. Most patients develop single lesions, but in others several lesions may develop and occasionally hundreds of lesions may be present. In one case report, a generalized lichenoid variant of xanthogranuloma was described. The eruption consisted of small, flat, shiny papules, which resolved spontaneously [10]. The lesions most commonly occur on the upper part of the body, particularly affecting the face, neck, scalp and upper trunk (Fig. 55.14). Lesions may occur in the oral mucosa with or without skin involvement [11]. They generally start as reddish-yellow papules, which may enlarge up to 1 cm in diameter and evolve into yellow–brown plaques and macules. The lesions are firm and rubbery and can develop surface telangiectasia. Larger lesions, up to 2–3 cm in size, have been reported [12] and ulceration and satellite lesions have been described [13]. Deep dermal lesions may occur which may infiltrate skeletal muscle. Such lesions may exhibit a more aggressive biological behaviour [4]. Resolution occurs spontaneously over a period of months or years, leaving small atrophic scars. There are no subjective symptoms.

Visceral involvement may occur in lung, liver, spleen, testes [14], pericardium, gastrointestinal tract, kidney [15,16], deeper soft tissues [17] and central nervous system. Eye involvement occurs in up to 10% of cases [18] and may lead to secondary glaucoma or may be mistaken for a malignant tumour, such as melanoma or neuroblastoma. The iris is most commonly affected, producing haemorrhage into the anterior chamber, which may result in secondary glaucoma. Infiltration of the orbit, iris, ciliary body and episclera may occur, with unilateral glaucoma, recurrent hyphaema, uveitis, heterochromia, iritis or severe and sudden proptosis [19]. Eye lesions may precede the appearance of skin lesions. Central nervous system involvement is rare but several reports have been published. Lesions may present as isolated or multiple tumours of the brain involving the cortex and cerebellum [20,21], and extensive involvement of cranial nerves has been reported [22]. Central nervous system involvement may occur with or without cutaneous involvement.

Juvenile xanthogranuloma has been associated with neurofibromatosis [23], Niemann–Pick disease [24], myelogenous leukaemia [25], lymphocytic leukaemia [26], urticaria pigmentosa [27] and LCH [28].



Fig. 55.14 Juvenile xanthogranuloma in an infant with typical lesions on the back.

Prognosis. Juvenile xanthogranuloma is a self-healing tumour and lesions generally resolve in 1–5 years. Disseminated neonatal juvenile xanthogranuloma may be more aggressive and fatalities in this group have been reported [29]. In addition, a recent case report describes juvenile xanthogranuloma diffusely involved the brain in an 11-year-old boy. Initial partial response was achieved with 2-cholorodeoxyadenosine but the patient then failed to respond to further chemotherapy, with dissemination of the disease to the peritoneum and bone marrow. Biopsy at this stage showed pleomorphic histiocytes with tetraploidy suggesting malignant transformation. Despite continued chemotherapy the patient died [30].

Diagnosis. Juvenile xanthogranuloma can be differentiated from xanthomas by the distribution of the lesions and the absence of lipid abnormalities. Papular urticaria can be distinguished by the symptomatic nature of the lesions and histology. The major difficulty in clinical diagnosis is with the nodular forms of LCH. Histology and immunocytochemistry will easily differentiate the two disorders.

Treatment. No treatment is necessary for the cutaneous lesions as they are self-healing. Where treatment is indicated in ocular, upper airways and central nervous system lesions, surgery or radiotherapy gives good results [31,32]. In patients with multiple cutaneous juvenile xanthogranulomas, carbon dioxide laser has been successfully used [33]. In patients with symptomatic visceral involvement, systemic steroids [16] with or without chemotherapy with vinca alkaloids have been used successfully [34]. Patients

with aggressive disease with vital organ involvement, that is lungs, liver and bone marrow, are generally treated with multiagent chemotherapy, including cytarabine, methotrexate, vincristine and prednisolone [29].

References

1 Kraus MD, Haley JC, Ruiz R *et al.* 'Juvenile' xanthogranuloma: an immunophenotypic study with a reappraisal of histiogenesis. *Am J Dermatopathol* 2001; **23**: 104–11.
2 Vasconcelos FO, Oliveira LA, Naves MD *et al.* Juvenile xanthogranuloma: case report with immunohistochemical identification of early and late cytomegalovirus antigens. *J Oral Sci* 2001; **43**: 21–5.
3 DeStafeno JJ, Carlson JA, Meyer DR. Solitary spindle-cell xanthogranuloma of the eyelid. *Ophthalmology* 2002; **109**: 258–61.
4 Barroca H, Farinha NJ, Lobo A *et al.* Deep-seated congenital juvenile xanthogranuloma: report of a case with emphasis on cytologic features. *Acta Cytol* 2007; **51**: 473–6.
5 Janssen D, Harms D. Juvenile xanthogranuloma in childhood and adolescence: a clinicopathologic study of 129 patients from the kiel pediatric tumor registry. *Am J Surg Pathol* 2005; **29**: 21–8.
6 Sonda T, Hashimoto H, Enjoji M. Juvenile xanthogranuloma. Clinicopathologic analysis and immunohistochemical study of 57 patients. *Cancer* 1985; **56**: 2280–6.
7 Tahan SR, Pastel-Levy C, Bhan AK *et al.* Juvenile xanthogranuloma. Clinical and pathological characterisation. *Arch Pathol Lab Med* 1989; **113**: 1057–61.
8 Seifert HW. Membrane activity in juvenile xanthogranuloma. *J Cutan Pathol* 1981; **8**: 24–33.
9 Rodriguez J, Ackerman AB. Xanthogranuloma in adults. *Arch Dermatol* 1976; **112**: 43–4.
10 Holde G, Bonsmann G. Generalised lichenoid juvenile xanthogranuloma. *Br J Dermatol* 1992; **120**: 66–70.
11 Flaitz C, Allen C, Neville B *et al.* Juvenile xanthogranuloma of the oral cavity in children: a clinicopathological study. *Oral Surg Oral Med Oral Pathol* 2002; **94**: 345–52.
12 Fishman SJ, Brodie S, Popkin G. Juvenile xanthogranuloma. *Cutis* 1973; **11**: 499–501.
13 Gartmann H, Tritsch H. Small and large nodular nevoxanthoendothelioma: report of 13 cases. *Arch Klin Exp Dermatol Syphilol* 1963; **215**: 409–27.
14 Townell NH, Gledhill A, Robinson T *et al.* Juvenile xanthogranuloma of the testis. *J Urol* 1985; **133**: 1054–5.
15 Gilbert TJ, Parker BR. Juvenile xanthogranuloma of the kidney. *Pediatr Radiol* 1988; **18**: 169–71.
16 Unuvar E, Devecioglu O, Akay A *et al.* Successful therapy of systemic xanthogranuloma in a child. *J Pediatr Hematol Oncol* 2007; **29**: 425–7.
17 Webster SB, Reister HC, Harman LE. Juvenile xanthogranuloma with extracutaneous lesions. *Arch Dermatol* 1966; **93**: 71–6.
18 Roper SR, Spraker MK. Cutaneous histiocytosis syndromes. *Pediatr Dermatol* 1985; **3**: 19–30.
19 Labelette P, Guilbert F, Jourdel D *et al.* Bilateral multifocal uveal juvenile xanthogranuloma in a young boy with systemic disease. *Graefes Arch Clin Exp Ophthalmol* 2002; **240**: 506–9.
20 Bostrom J, Janssen G, Messing-Junger M *et al.* Multiple intracranial juvenile xanthogranulomas. Case report. *J Neurosurg* 2000; **93**: 335–41.
21 Cauro F, Houtteville JP, Mesnil JL *et al.* Cerebellar, pulmonary and cutaneous localizations of juvenile xanthogranuloma. *Ann Dermatol Vénéréol* 2002; **129**: 307–10.
22 Ernemann U, Skalej M, Hermisson M *et al.* Primary cerebral non-Langerhans cell histiocytosis: MRI and differential diagnosis. *Neuroradiology* 2002; **44**: 759–63.
23 Jensen NE. Nevoxanthoendothelioma and neurofibromatosis. *Br J Dermatol* 1971; **85**: 326–31.
24 Sibulkin D, Olichney JJ. Juvenile xanthogranuloma in a patient with Nieman–Pick disease. *Arch Dermatol* 1973; **108**: 829–34.
25 Cooper PH, Frierson HF, Kayne AL *et al.* Association of juvenile xanthogranuloma with juvenile myeloid leukaemia. *Arch Dermatol* 1984; **120**: 371–5.
26 Sarthou-Bruere S, Milpied-Homsi B, Mahe B *et al.* Eruptive xanthogranulomatosis in a trisomy 21 patient with acute lymphoblastic leukemia. *Ann Dermatol Vénéréol* 2000; **127**: 80–2.
27 DeVillez RL, Limmer BL. Juvenile xanthogranuloma and urticaria pigmentosa. *Arch Dermatol* 1975; **111**: 365–6.
28 Hoeger PH, Diaz C, Malone M *et al.* Juvenile xanthogranuloma as a sequel to Langerhans cell histiocytosis: a report of three cases. *Clin Exp Dermatol* 2001; **26**: 391–4.
29 Nakatani T, Morimoto A, Kato R *et al.* Successful treatment of congenital systemic juvenile xanthogranuloma with Langerhans cell histiocytosis-based chemotherapy. *J Pediatr Hematol Oncol* 2004; **26**: 371–4.
30 Orsey A, Paessler M, Lange BJ *et al.* Central nervous system juvenile xanthogranuloma with malignant transformation. *Pediatr Blood Cancer* 2008; **50**: 927–30.
31 MacLeod PM. Juvenile xanthogranuloma of the iris managed with superficial radiotherapy. *Clin Radiol* 1986; **37**: 295–6.
32 Somorai M, Goldstein NA, Alexis R *et al.* Managing isolated subglottic juvenile xanthogranuloma without tracheostomy: case report and review of the literature. *Pediatr Pulmonol* 2007; **42**: 181–5.
33 Klemke CD, Held B, Dippel E *et al.* Multiple juvenile xanthogranulomas successfully treated with CO_2 laser. *J Dtsch Dermatol Ges* 2007; **5**: 30–2.
34 Freyer DR, Kennedy R, Bostrom BC *et al.* Juvenile xanthogranuloma: forms of systemic disease and their clinical implications. *J Pediatr* 1996; **129**: 227–37.

Benign cephalic histiocytosis

Synonym
- Papular histiocytosis of the head

This is a rare, self-limiting histiocytosis that typically starts in early childhood [1]. As stated before, many now feel that benign cephalic histiocytosis represents a clinical variant of juvenile xanthogranuloma [2] but the clinical features of the disease are distinct enough to maintain a separate nomenclature. Erythematous papules, nodules and macules develop on the cheeks and spread to the forehead, earlobes and neck. The lesions, which are asymptomatic, gradually become reddish-brown and may spread onto the trunk, upper limbs and rarely the buttocks. Mucous membrane involvement has not been described.

No sex predisposition has been reported. In a review of the literature, the average age of onset was 15 months (range 2 to 66 months). The disease is self-limiting, and in 39 cases the mean age at resolution was 50 months in 10 patients where this detail was recorded [3]. In one case report, a 5-year-old girl developed diabetes insipidus 1 year after presenting with typical benign cephalic histiocytosis. Imaging demonstrated infiltration of the pituitary stalk [4]. Histologically, the epidermis is thinned over a well-circumscribed histiocytic infiltrate in the superficial and mid-dermis. Histiocytic cells have oval to reniform nuclei and occasionally may be pleomorphic. In older lesions, a few giant cells may be present. The cells are S100 and CD1a negative [5] but stain positively for OKM1, Leu-3 and factor XIIIa [3]. Electron microscopy shows that 5–30% of the infiltrating cells have cytoplasm rich in comma-shaped bodies and coated vesicles [3]. Dense bodies may be present and worm-like bodies have been described [6]. Since the condition is self-limiting, no therapy is indicated.

References

1 Pena Penabad C, Unamuno P, Garcia Silva J *et al.* Benign cephalic histiocytosis: case report and literature review. *Pediatr Dermatol* 1994; **11**: 164–7.
2 Sidwell RU, Francis N, Slater DN *et al.* Is disseminated juvenile xanthogranulomatosis benign cephalic histiocytosis? *Pediatr Dermatol* 2005; **22**: 40–3.
3 Jih DM, Salcedo SL, Jaworsky C. Benign cephalic histiocytosis: a case report and review. *J Am Acad Dermatol* 2002; **47**: 908–13.

4 Weston WL, Travers SH, Mierau GW *et al.* Benign cephalic histiocytosis with diabetes insipidus. *Pediatr Dermatol* 2000; **17**: 296–8.
5 de Luna ML, Glikin I, Golberg J *et al.* Benign cephalic histiocytosis: report of four cases. *Pediatr Dermatol* 1989; **6**: 198–201.
6 Eisenberg EL, Bronson DM, Barsky S. Benign cephalic histiocytosis. A case report and ultrastructural study. *J Am Acad Dermatol* 1985; **12**: 328–31.

Erdheim–Chester disease

Synonym
- Uber lipoidgranulomatose

This is a rare lipoid granulomatosis characterized by infiltration of viscera, bones, retroperitoneum and skin. It was first described by William Chester while working in the laboratory of Jakob Erdheim in 1930 [1] and the eponym was first used by Jaffe in 1972 [2].

Veyssier-Belot *et al.* [3] reviewed the literature on Erdheim–Chester disease in a comprehensive study of 59 patients. The age range was 7–84 years with a mean of 53 ± 14 years, and there was a male to female ratio of 33 : 26. The most common presentation is with chronic mild bone pain, particularly of the lower limbs. Radiography shows symmetrical sclerosis, typically affecting the long bones, with involvement of the diaphyseal and metaphyseal regions; 86% of reported cases have involvement of the long bones [4], with the distal femur, proximal tibia and fibula being most commonly affected [5]. Up to 30% of patients show lytic lesions of flat bones, which can cause problems in differentiating this disease from LCH.

Half of patients have extraosseous involvement of the retroperitoneal space, lungs, heart, kidneys, liver, pituitary, central nervous system, orbit and skin. Approximately 30% of patients have exophthalmos (Fig. 55.15), diabetes insipidus or retroperitoneal involvement. Retroperitoneal disease is often asymptomatic and may develop over many years. It may present with dysuria, abdominal pain, obstructive renal damage or renal artery stenosis [6]. Adrenal infiltration may occur and in a study of 22 patients with Erdheim–Chester disease, 31.8% showed CT evidence of adrenal involvement and one patient developed clinical adrenal insufficiency [7].



Fig. 55.15 Erdheim–Chester disease: a 47-year-old man presented with diplopia and unsteady gait. Clinically he had exophthalmos and MRI of brain showed retro-orbital masses and lesions in the mid-brain and temporal lobes. CT scan of the abdomen showed thickening of perirenal fascia and hydronephrosis demonstrating extensive disease in the retroperitoneal space.

Skin involvement is seen in about 20% of patients, usually presenting with xanthoma-like lesions, usually on the eyelids but occasionally on the trunk and submammary area. Two patients have been reported with cutaneous masses. Lung disease is seen in 35% of patients, with accumulation of histiocytes and fibrosis in a perilymphatic and subpleural pattern. It is generally asymptomatic and found on chest X-ray with diffuse interstitial fibrosis or infiltration. Advanced pulmonary involvement is associated with extensive fibrosis, which may result in cardiopulmonary failure. Prognosis tends to be poor despite treatment [8].

Cardiovascular involvement with Erdheim–Chester disease is relatively common. In a review of 72 patients with cardiovascular involvement, 55.6% had periaortic fibrosis, 44.4% had pericardial involvement and 30.6% had myocardial involvement. Six patients had a right atrial tumour and six had symptomatic valvular heart disease; 26.4% developed heart failure and 11 patients died of cardiovascular complications [9].

Central nervous system involvement is seen in 15% of patients, presenting with ataxia, paraparesis, hemiparesis or change in mental state. Imaging has shown thickening of the dura, with infiltration extending into the cerebellum. More rarely, intracerebral masses have been described. In a review of 66 patients with Erdheim–Chester disease and neurological involvement, cerebellar and pyramidal syndromes were the most common clinical manifestation, affecting 41% and 45% respectively. Seizures, headache, neuropsychiatric and cognitive problems, sensory disturbances and cranial nerve paralysis have been reported. Neurological involvement resulted in severe functional handicap in almost all of the reported patients and resulted in death in six of them. Three patterns of involvement have been demonstrated by imaging: infiltrative in 44% with widespread nodules or masses, meningeal in 37% with thickening of the dura or meningioma-like tumours, and composite in 19% with elements of both [10]. A case of slowly progressive cerebellar syndrome, similar to that seen in LCH, has been reported in a 50-year-old patient with Erdheim–Chester disease associated with unilateral exophthalmos, secondary hypogonadism and skin lesions [11].

Histological examination shows a xanthogranulomatous infiltration by lipid-laden histiocytes within a mesh and surrounded by fibrosis. Touton giant cells and eosinophils may be prominent. Cells are positive for CD68 and factor XIIIa [6] but negative for CD1a and S100 [12]. In one study of a 35-year-old woman with Erdheim–Chester disease, clonality studies based on the *HUMARA* assay in paraffin-embedded tissue showed only random distribution of allele activation and thus no evidence of clonality [13]. In a further male patient, balanced chromosomal translocation t(12; 15; 20)(q11; q24; p13.3) was identified amongst other chromosomal abnormalities, suggesting that Erdheim–Chester disease could be a clonal neoplastic disorder [14]. Further studies are needed to confirm this.

A variety of treatments have been used in Erdheim–Chester disease, including IFN-α [15,16], corticosteroids, radiotherapy, vinblastine, vincristine, cyclophosphamide [3] and 2-chlorodeoxyadenosine [17], with variable responses. There is no clear consensus as to the best therapeutic regimen. Overall mortality is 57%, with death resulting from pulmonary, cardiac or renal failure [3].

References

1 Chester W. Uber Lipoidgranulomatose. *Virchows Arch Pathol Anat* 1930; **279**: 561–602.
2 Jaffe HL. Gaucher's disease and certain other inborn metabolic disorders: lipid (cholesterol) granulomatosis. In: Jaffe HL, ed. *Metabolic, Degenerative and Inflammatory Diseases of Bones and Joints.* Philadelphia: Lea & Febiger, 1972: 535.
3 Veyssier-Belot C, Cacoub P, Caparros-Lafebvre D *et al.* Erdheim–Chester disease: clinical and radiological characteristics of 59 cases. *Medicine (Baltimore)* 1996; **75**: 157–69.
4 Tan APA, Tan LKA, Choo IHF. Erdheim–Chester disease involving breast and muscles: imaging findings. *Am J Rheumatol* 1995; **164**: 1115–7.
5 Egan AJM, Bordman LA, Tazelaar HD *et al.* Erdheim–Chester disease: clinical, radiological and histopathological findings in five patients with interstitial lung disease. *Am J Surg Pathol* 1999; **23**: 17–26.
6 Leluc O, Andre M, Marchano S *et al.* Retroperitoneal complications of Erdheim–Chester disease. *J Radiol* 2001; **82**: 580–2.
7 Haroche J, Amoura Z, Touraine P *et al.* Bilateral adrenal infiltration with Erdheim-Chester disease. Report of seven cases and literature review. *J Clin Endocrinol Metab* 2007; **92**: 2007–12.
8 Shamburek RD, Brewer HB, Gochuico BR. Erdheim–Chester disease: a rare multisystem histiocytic disorder associated with interstitial lung disease. *Am J Med Sci* 2001; **321**: 65–75.
9 Haroche J, Amoura Z, Dion E *et al.* Cardiovascular involvement, an overlooked feature of Erdheim Chester disease. *Medicine* 2004; **83**: 371–92.
10 Lachenal F, Cotton F, Desmurs-Clavel H *et al.* Neurological manifestations and neuroradiological presentation of Erdheim-Chester disease: report of 6 cases and systematic review of the literature. *J Neurol* 2006; **253**: 1267–77.
11 Grothe C, Urbach H, Bos M *et al.* Cerebellar syndrome, exophthalmos and secondary hypogonadism in Erdheim–Chester disease. *Nervenarzt* 2001; **72**: 449–52.
12 Rush WL, Andriko JA, Galateau-Salle F *et al.* Pulmonary pathology of Erdheim–Chester disease. *Mod Pathol* 2000; **13**: 747–54.
13 Al-Quran S, Reith J, Bradley J *et al.* Erdheim–Chester disease: case report, PCR-based analysis of clonality and review of literature. *Mod Pathol* 2002; **15**: 666–72.
14 Vencio EF, Jenkins RB, Schiller JL *et al.* Clonal cytogenetic abnormalities in Erdheim-Chester disease. *Am J Surg Pathol* 2007; **31**: 319–21.
15 Esmael B, Ahmadi A, Tang R *et al.* Interferon therapy for orbital infiltration secondary to Erdheim–Chester disease. *Am J Ophthalmol* 2001; **132**: 945–7.
16 Braiteh F, Boxrud C, Esmaeli B *et al.* Successful treatment of Erdheim-Chester disease, a non-Langerhans-cell histiocytosis, with interferon-alpha. *Blood* 2005; **106**: 2992–4.
17 Myra C, Sloper L, Tighe PJ *et al.* Treatment of Erdheim-Chester disease with cladribine: a rational approach. *Br J Opthalmol* 2004; **88**: 844–7.

Fat-storing hamartoma of dermal dendrocytes

A single case report has described this entity [1]. The patient was a 30-year-old man who had a very large, circumscribed, red-brown plaque in the lumbosacral area. The plaque was composed of firm papules and nodules and was asymptomatic. The lesion had been present since birth and had slowly grown since that time.

Histology showed a slightly acanthotic epidermis and a Grenz zone, below which was a dense infiltrate of foamy histiocytes, which extended deep into the dermis. Occasional Touton giant cells were present. Lesional cells stained for factor XIIIa and vimentin and 40% of the cells labelled with Mac-387, a monoclonal antibody directed against monocyte-derived macrophages. S100 and CD1a staining were negative. Electron microscopy showed large histiocytic cells with convoluted nuclei filled with lipid droplets.

Reference

1 Bork K, Gabbert H, Knop JK. Fat-storing hamartoma of dermal dendrocytes. Clinical, histologic and ultrastructural study. *Arch Dermatol* 1990; **126**: 794–6.

Generalized eruptive histiocytoma

This is a rare cutaneous histiocytosis that mainly affects adults [1], although children with the disease have been reported [2,3]. Clinically, the disease presents as multiple, symmetrical papules that occur on the face, trunk and proximal extremities. The papules are skin coloured, brownish or blue–red and tend to come up in crops, although they are not grouped. The number of lesions is variable but may reach hundreds. Mucosal lesions are rare. The lesions are asymptomatic and resolve spontaneously to leave a macular area of hyperpigmentation.

Histology shows a proliferation of monomorphic histiocytic cells in the upper and mid dermis. No giant cells or foam cells are present. Scattered lymphocytes may be present. Ultrastructural studies have shown that the histiocytic cells lack Birbeck granules but do have cytoplasmic laminated bodies [4]. These bodies are often clustered in the cytoplasm of the cells and each measure about 1.5 μm. They are not restricted to generalized histiocytoma but have been reported in congenital self-healing histiocytosis [5].

In one case report of a 4-year-old boy with generalized eruptive histiocytoma, diagnosed using clinical, histological and ultrastructural studies, the patient subsequently developed a new eruption of yellowish confluent papules with associated diabetes insipidus. Histology of the lesions and ultrastructure confirmed the diagnosis of xanthoma disseminatum. The authors suggest that generalized eruptive histiocytoma and xanthoma disseminatum are variants of a continuous spectrum of histiocytoses [3].

The disease is generally self-limiting and often does not require treatment. PUVA has been shown to be an effective treatment in one patient with widespread disease [6].

References

1 Muller SA, Wolff K, Winkelmann RK. Generalised eruptive histiocytoma: enzyme histochemistry and electronmicroscopy. *Arch Dermatol* 1967; **96**: 11–7.
2 Winkelmann RK, Kossard S, Fraga S. Eruptive histiocytoma of childhood. *Arch Dermatol* 1980; **116**: 565–7.
3 Repiso T, Roc A, Miralles M *et al.* Generalised eruptive histiocytosis evolving into xanthoma disseminatum in a four year old boy. *Br J Dermatol* 1995; **132**: 978–82.
4 Caputo R, Alessi E, Allera F. Generalised eruptive histiocytoma: a clinical, histologic and ultrastructural study. *Arch Dermatol* 1981; **117**: 216–21.
5 Caputo R, Gianotti F. Cytoplasmic markers and ultrastructural features in histiocytic proliferations of the skin. *G Ital Dermatol Venereol* 1980; **115**: 107–20.
6 Lan M, Metze D, Luger TA *et al.* Successful treatment of generalised eruptive histiocytoma with PUVA. *J Dtsch Dermatol Ges* 2007; **5**: 131–4.

Papular xanthoma

This is a rare histiocytic disorder that was first described in adults [1] and subsequently reported in children [2]. Whether it represents a separate clinicopathological entity or a variant of other xanthogranulomatous conditions is open to debate. Clinically it

can resemble juvenile xanthogranuloma but has not been associated with systemic involvement or café-au-lait spots, and may resemble xanthoma disseminatum but papules do not coalesce and there is no predilection for flexures.

Clinically, papular xanthoma is characterized by 2–15 mm yellow or reddish-yellow papules affecting both skin and mucous membranes. The back and head are most commonly affected. There are marked clinical differences between papular xanthoma occurring in adults and children. Mucous membranes are affected in adults but this has not been reported in children. In adults progressive disease has been reported [3] but in children spontaneous resolution is the norm, with involution starting after weeks or months and being complete in 1–5 years, often leaving anetoderma-like scarring [4].

Histologically, there is an upper- and mid-dermal infiltrate of foamy histiocytes and giant cells. Few inflammatory cells are present. Histiocytic cells are positive for CD68 and factor XIIIa and negative for S100 and CD1a [2,4]. More recent studies, however, have shown that the foamy cells in this disease are factor XIIIa negative [5,6]. In such a rare condition, further studies are needed to confirm the dermal dendrocyte origin of lesional cells. Electron microscopy shows similar changes to those seen in mature juvenile xanthogranuloma, with myeloid bodies filling the cytoplasm of the histiocytes with associated lysosomal inclusions, laminate bodies and lipid droplets.

No treatment is needed in children while none has been shown to be effective in adults.

References

1 Winkelmann RK. Adult histiocytic skin diseases. *G Ital Dermatol Venereol* 1980; **15**: 67–76.
2 Caputo R, Gianni E, Imondi D *et al*. Papular xanthoma in children. *J Am Acad Dermatol* 1992; **22**: 1052–6.
3 Beurey J, Lamaze B, Welere M. Xanthoma disseminatum (syndrome de Montgomery). *Ann Dermatol Vénéréol* 1979; **106**: 353–9.
4 Fonseca E, Contreras F, Cuevas J. Papular xanthoma in children: report and immunohistochemical study. *Pediatr Dermatol* 1993; **2**: 139–41.
5 Chen CG, Chen CL, Liu HN. Primary papular xanthoma of children: a clinicopathologic and ultrastructural study. *Am J Dermatopathol* 1997; **19**: 596–601.
6 Breier F, Zelger B, Reiter H *et al*. Papular xanthoma: a clinicopathological study of 10 cases. *J Cutan Pathol* 2002; **29**: 200–6.

Progressive nodular histiocytosis

Synonyms
- Progressive nodular histiocytoma
- Spindle cell xanthogranuloma

This is a rare histiocytosis first described by Taunton *et al.* [1] in 1978. The eruption consists of two different types of lesions, superficial papules and deep nodules, both of which may number into hundreds [2,3]. Papules are 2–10 mm and yellow–orange (Fig. 55.16). Nodules are 1–5 cm in diameter and may be skin coloured or reddish-orange. Distribution is random with no predilection for the flexures. Lesions may occur in the oral cavity, larynx and conjunctival mucosa.

Over the years new lesions may develop and although patients remain in good general health, the eruption may be very disfiguring causing a marked reduction in quality of life.



Fig. 55.16 Progressive nodular histiocytosis in a 48-year-old man with nodular lesions in the posterior axillary fold. (Courtesy of Professor J.M. Naeyaert, University Hospital, Gent, Belgium.)

Histologically, this is a dermal disease with neither epidermal involvement nor epidermotropism. Early lesions show an accumulation of xanthomatized and scalloped histiocytes with some infiltrating lymphocytes. In older lesions the histiocytes are spindle shaped and arranged in a storiform pattern. Occasional giant cells may be present. Cells are positive for CD68 and factor XIIIa and negative for S100 and CD1a [4].

Progressive nodular histiocytosis is not generally associated with systemic involvement or other disorders. In one case report, a 57-year-old man had suffered from progressive nodular histiocytosis for 26 years and during that time had developed chronic myeloid leukaemia, hepatosplenomegaly, hypothyroidism, hyperuricaemia and hypocholesterolaemia, although the relationship between progressive nodular histiocytosis and the systemic disorders remains unclear [5].

Progressive nodular histiocytosis is a benign disease and no treatment has yet been shown to be effective in reducing the size of skin lesions or in inducing remission.

References

1 Taunton OD, Yeshurun D, Jarratt M. Progressive nodular histiocytoma. *Arch Dermatol* 1978; **114**: 1505–8.
2 Gibbs NF, O'Grady TC. Progressive nodular histiocytomas. *J Am Acad Dermatol* 1996; **35**: 323–5.
3 Laftl M, Seybold H, Simon M *et al*. Progressive nodular histiocytosis—rare variant of cutaneous non-Langerhans cell histiocytosis. *J Dtsch Dermatol Ges* 2006; **4**: 236–8.
4 Zelger BWH, Standacher CH, Orchard G *et al*. Solitary and generalised variants of spindle cell xanthogranuloma (progressive nodular histiocytosis). *Histopathology* 1995; **27**: 11–9.
5 Gonzales Ruiz A, Bernal Ruiz AI, Artagoneses Fraile H *et al*. Progressive nodular histiocytosis accompanied by systemic disorders. *Br J Dermatol* 2000; **143**: 628–31.

Xanthoma disseminatum

Synonyms
- Disseminated xanthosiderohistiocytosis
- Montgomery's disease



Fig. 55.17 Xanthoma disseminatum. (Courtesy of Dr R. Cerio, Royal London Hospital, London, UK.)



Fig. 55.18 Xanthoma disseminatum with verrucous lesions over the back of a 10-year-old boy.

This is a rare non-familial disease, characterized by proliferation of histiocytic cells in which lipid deposition is a secondary event. The disease predominantly affects male children and young adults, with involvement of the skin, mucous membranes of eyes and upper respiratory tract, the meninges and rarely other organs including liver, spleen and bone marrow [1–4].

The clinical lesions of xanthoma disseminatum are erythematous, yellow-brown papules and nodules, which are symmetrically distributed on the trunk, face and proximal extremities (Fig. 55.17). The lesions become confluent, especially in flexures, to form xanthomatous plaques, which may become verrucous (Fig. 55.18). In 30% of patients, the mucous membranes are affected, with particular involvement of the lips, pharynx, larynx, conjunctivae and bronchus. Involvement of the upper respiratory tract is not uncommon and may lead to stridor and respiratory distress requiring tracheostomy. Upper respiratory tract involvement has been fatal in one reported case of a 61-year-old woman with involvement of large and medium-sized bronchi who died of acute respiratory failure [5]. Lower respiratory tract involvement is very rare but in one 8-year-old boy, resulted in bronchiectasis [6].

Meningeal involvement is common, with infiltration at the base of the brain leading to diabetes insipidus in up to 40% of cases. Other manifestations of meningeal involvement are seizures and growth retardation. Intracranial involvement presenting as a discrete mass simulating glioma has been reported [7] and progressive intracranial disease may be fatal [8]. Progressive bone disease has been reported in xanthoma disseminatum [9,10], but this is a rare complication of the disease. Lytic bone lesions have been reported in a patient with xanthoma disseminatum, but are very rare [11,12]. Hepatic involvement is rare but a 12-year-old boy has been reported with liver dysfunction secondary to liver involvement by xanthoma disseminatum presenting as sclerosing cholangitis [13].

A clinical variant of this disease was described by Halprin and Lorincz [14] under the name xanthosiderohistiocytosis. In this variant, there is diffuse infiltration of the skin, subcutaneous tissue and muscle, giving rise to sclerodermatous changes in the skin and muscle wasting. The foamy histiocytes that are involved contain significant amounts of iron, which gives the skin a greenish-brown colour.

Histologically, xanthoma disseminatum is a dermal disease, characterized by early infiltration of the dermis with spindle-shaped mononuclear cells, foamy histiocytes, giant cells, lymphocytes, polymorphs and eosinophils. Lesional cells in xanthoma disseminatum have irregular scalloped borders with extensive cytoplasm and ovoid vesicular nuclei. Cells label strongly with factor XIIIa and KP1 [15]. Iron and lipid can be detected in the histiocytes. In older lesions, more foamy histiocytes are evident and Touton giant cells may be observed. At the ultrastructural level, histiocytic cells contain myeloid bodies and membrane-bound fat droplets.

Xanthoma disseminatum is a self-limiting disease but may persist for years. Lesions are only mildly radiosensitive. Skin lesions of xanthoma disseminatum are disfiguring and patients often request treatment. The carbon dioxide laser has been used with good results [16] and azathioprine and cyclophosphamide have been effective in some patients with cutaneous disease [17]. Conjunctival involvement can be treated with surgery. Systemic involvement with lung, liver or CNS involvement requires active

treatment. Surgery has been used in CNS disease but recurrences may occur [8]. Liver involvement in one patient responded to systemic steroids and azathioprine [13]. Response to various modalities including radiotherapy, alkylating agents and antimetabolites has been variable [18].

References

1 Komatsuda A, Chubach A, Miura AB. Virus associated haemophagocytic syndrome due to measles accompanied by acute respiratory failure. *J Intern Med* 1995; **34**: 203–6.
2 Atlman J, Winklemann RK. Xanthoma disseminatum. *Arch Dermatol* 1962; **86**: 582–9.
3 Calverly DC, Wismer J, Rosonthal D *et al.* Xanthoma disseminatum in an infant with skeletal and marrow involvement. *J Pediatr Hematol Oncol* 1995; **17**: 61–5.
4 Fleishmajer R. Xanthoma disseminatum. In: Fleishmajer R, ed. *Dyslipoides.* Springfield, IL: Thomas, 1960: 176–83.
5 Davies CW, Marran P, Juniper MC *et al.* Xanthoma disseminatum with respiratory tract involvement and fatal outcome. *Thorax* 2000; **55**: 170–2.
6 Ozcelik U, Dogru D, Akcoren Z *et al.* Xanthoma disseminatum: a child with respiratory system involvement and bronchiectasis. *Pediatr Pulmonol* 2005; **39**: 84–7.
7 Chepuri NB, Challa VR. Xanthoma disseminatum: a rare intracranial mass. *Am J Neuroradiol* 2003; **24**: 105–8.
8 Zak IT, Altinok D, Neilsen SSF *et al.* Xanthoma disseminatum of the central nervous system and cranium. *Am J Neuroradiol* 2006; **27**: 919–21.
9 Blobstein SH, Caldwell D, Carter M. Bone lesions in xanthoma disseminatum. *Arch Dermatol* 1985; **121**: 1313–7.
10 Szekeres E, Tibia A, Korom I. Xanthoma disseminatum: a rare condition with non-X, non-lipid cutaneous histiocytopathy. *J Dermatol Surg Oncol* 1988; **14**: 1021–4.
11 Calverly DCV, Wismer J, Rosenthal D *et al.* Xanthoma disseminatum in an infant with skeletal and marrow involvement. *J Pediatr Hematol Oncol* 1995; **17**: 61–5.
12 Khandpur S, Manchanda Y, Sharma VK *et al.* Rare association of xanthoma disseminatum with skeletal involvement. *Australas J Dermatol* 2003; **44**: 190–3.
13 Buyukavci M, Selimoglu A, Yildrim U *et al.* Xanthoma disseminatum with hepatic involvement in a child. *Pediatr Dermatol* 2005; **22**: 550–3.
14 Halprin KM, Lorincz AL. Disseminated xanthosiderohistiocytosis (xanthoma disseminatum). Report of a case and discussion of possible relationship to other disorders showing histiocytic proliferation. *Arch Dermatol* 1960; **82**: 171–4.
15 Zelger B, Cerio R, Orchard G *et al.* Histologic and immunohistochemical study comparing xanthoma disseminatum and histiocytosis X. *Arch Dermatol* 1992; **128**: 1207–12.
16 Carpo BG, Grevelink SV, Brady S *et al.* Treatment of cutaneous lesions of xanthoma disseminatum with CO_2 laser. *Dermatol Surg* 1999; **25**: 751–4.
17 Seaton ED, Pillai GJ, Chu AC. Treatment of xanthoma disseminatum with cyclophosphamide. *Br J Dermatol* 2004; **150**: 346–9.
18 Alexander AS, Turner R, Uniate L *et al.* Xanthoma disseminatum: a case report and literature review. *Br J Radiol* 2005; **78**: 153–7.

Diffuse plane xanthomatosis

Synonyms
- Atypical xanthoma disseminatum
- Diffuse normolipaemic plane xanthomatosis

This is a rare, non-lipaemic disease in which xanthomatous lesions develop in the skin in association with paraproteinaemia. The disease generally occurs in adults but rare paediatric cases have been reported [1]. Patients present with large, flat, plaque-like, xanthomatous skin lesions involving the eyelids, neck, upper trunk, buttocks and flexures [2,3]. Serum lipids are usually normal. About 50% of patients have a myeloproliferative disorder with multiple myeloma, granulocytic or lymphocytic leukaemia [4]. One patient with tumour stage cutaneous T-cell lymphoma developed diffuse plane xanthomatosis coincident with the appearance of new lymphoma lesions [5]. The majority of patients have a circulating paraprotein and have some abnormalities of serum complement [6,7].

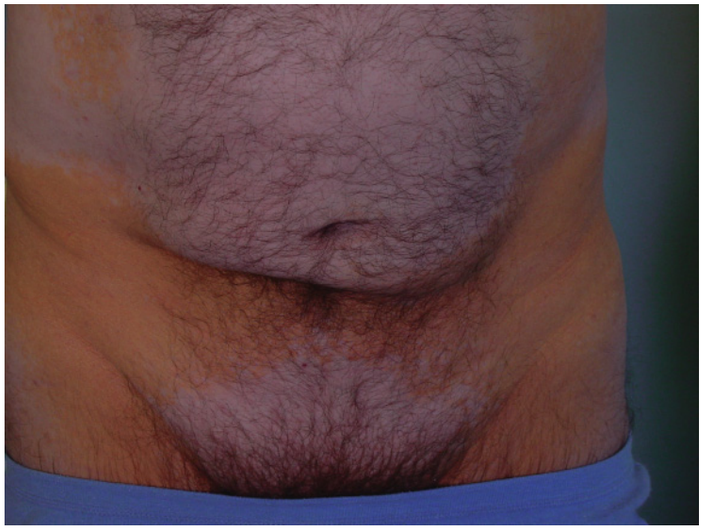


Fig. 55.19 Diffuse plane xanthomatosis in a 73-year-old man of 7 years' duration with associated IgGκ paraprotein.

The histological features include both xanthomatous and inflammatory elements. Accumulations of foamy macrophages infiltrate the dermis, with a distinct perivascular accentuation, and are associated to a variable degree with a mixed inflammatory cell reaction. There are no reported immunohistochemical studies in the world literature but a recent patient we have seen with characteristic skin changes (Fig. 55.19) and an IgGκ paraprotein, showed that the foamy macrophages were CD1a negative but strongly positive for CD68 and factor XIIIa.

The condition arises as a result of perivascular deposition of lipoprotein–immunoglobulin complexes. Antilipoprotein antibodies are formed in association with paraproteinaemia [7]. Although serum lipid levels are usually normal, they may be raised, possibly due to reduced clearance of lipoprotein–antibody complexes. Treatment of this condition is that of the underlying myeloproliferative disease or paraprotein. Theoretically, plasma exchange should be of value but its use has not yet been reported.

References

1 Hofmann M, Zappel K, Trefzer U *et al.* Diffuse normolipemic plane xanthoma in a 9 year old boy. *Pediatr Dermatol* 2005; **22**: 127–9.
2 Altman J, Winklemann RK. Diffuse normolipemic plane xanthoma. *Arch Dermatol* 1962; **85**: 115–22.
3 Lynch P, Winklemann RK. Generalized plane xanthoma and systemic disease. *Arch Dermatol* 1966; **93**: 639–46.
4 Macfarlane AW, Verbov JL. Necrobiotic xanthogranuloma with paraproteinaemia. *Br J Dermatol* 1985; **113**: 339–43.
5 Garcia-Arpa M, Rodriguez-Vazquez M, Vera E *et al.* Normolipaemic plane xanthomas and mycosis fungoides. *Actas Dermosifiliogr* 2005; **96**: 307–10.
6 Jordon RE, McDuffie FC, Good RA *et al.* Diffuse normolipemic plane xanthomatosis. An abnormal complement component profile. *Clin Exp Immunol* 1974; **18**: 407–15.
7 Russell Jones R, Baughan ASJ, Cream JJ *et al.* Complement abnormalities in plane xanthomata with paraproteinaemia. *Br J Dermatol* 1979; **101**: 711–6.

Class IIb histiocytosis: histiocytoses involving cells other than Langerhans' cells and dermal dendrocytes

Reticulohistiocytoma

Synonyms
- Solitary epithelioid histiocytoma
- Solitary histiocytoma

This is an uncommon tumour which is generally solitary and asymptomatic. Lesions less than 1 cm in diameter, presenting as papules or dome-shaped nodules, tend to occur in young adults but may appear from early childhood to old age. Lesions may occur anywhere on the body including the genitalia. Oral mucosal lesions have been reported [1].

Histology shows nodules of epithelioid histiocytes with abundant, glassy cytoplasm extending from the papillary dermis to the mid-dermis associated with lymphoid cells and occasionally neutrophils. Cells may have a lacuna space-like clearing at the periphery and scalloped cytoplasm. Cells are CD68 and CD163 positive and generally CD1a and S100 negative. In a study of five cases of solitary reticulohistiocytoma, factor XIIIa was found to be positive [2] but in a larger study of 44 cases, factor XIIIa was generally negative; however in five cases, histiocytic cells close to the dermoepidermal junction were found to be variably positive for factor XIIIa [1].

Treatment is surgical excision. Follow-up in 12 patients, with a median follow-up of 13 years, showed no recurrence following primary excision.

References

1 Miettinen M, Fetsch JF. Reticulohistiocytoma (solitary epithelioid histiocytoma): A clinicopathological and immunohistochemical study of 44 cases. *Am J Surg Pathol* 2006; **30**: 512–58.

2 Zelger B, Cerio R, Soyer HP *et al.* Reticulohistiocytoma and multicentric reticulohistiocytosis. *Am J Surg Pathol* 1994; **16**: 577–84.

Multicentric reticulohistiocytosis

Synonyms
- Reticulohistiocytic granuloma
- Lipoid dermatoarthritis
- Giant-cell histiocytoma
- Reticulohistiocytoma cutis
- Multicentric giant-cell reticulohistiocytosis

Definition. This is a rare histiocytic proliferative disease in which joints, skin and mucous membranes are affected [1]. The arthropathy usually precedes nodular skin involvement and mucosal infiltration. Other organs may be involved and 20% of patients have an associated internal malignancy. This must be differentiated from solitary or multiple reticulohistiocytomas that are restricted to skin with neither associated arthropathy nor internal malignancy.

Aetiology. Pathogenesis is unknown. The cells involved are phagocytic histiocytes, and the disease is considered to be a reactive histiocytosis. No infective agent has been implicated but there is evidence of exposure to tuberculosis in some patients. In one study, 33% of patients had evidence of exposure to tuberculosis and 5% of patients had active tuberculosis on clinical examination [2]. There is no recorded genetic link. Those cases with internal malignancy have no clinical or pathological differences from those without associated malignancy.

Pathology. The characteristic pathological picture in the skin and mucous membranes is of infiltration by mononucleated and multinucleated giant cells with voluminous ground-glass cytoplasm. In early lesions, the predominant infiltrating cells are histiocytes, lymphocytes and eosinophils, with few giant cells, but the giant cell infiltrate quickly follows. The giant cells are large (100 μm) with 1–20 nuclei. The cells are periodic acid–Schiff (PAS) positive, contain diastase resistant material and variable amounts of lipid and free or esterified cholesterol. In older lesions, fibrosis usually signals regression of the lesions, with a reduction in the inflammatory cell infiltrate.

Ultrastructural studies have shown inclusions of type IV collagen inclusions in multicentric reticulohistiocytosis. These inclusions were both intracytoplasmic and extracytoplasmic. Such inclusions are usually found in lymphohistiocytic neoplasms, suggesting that multicentric reticulohistiocytosis is a proliferative rather than an inflammatory disorder [3].

Immunocytochemical studies show a histiocytic phenotype of the cells, which are positive for acid phosphatase, ATPase, lysozyme and α_1-antitrypsin [4]. The cells are also positive for vimentin, CD45 and CD68, but negative for CD1, S100 and CD34 and factor XIIIa [5]. Cells contain TNF-α, IL-1β and IL-12 [6]. Ultrastructural studies have shown that the cells contain dense bodies, coated vesicles, fat droplets in limiting membranes and myeloid bodies [7].

Clinical features. The disease typically affects women, with a female to male ratio of 3 : 1 [8]. It is a disease of middle age, and rarely affects children [9] or adolescents. Some 60% of patients present with polyarthritis, which typically affects the hands. The interphalangeal joints are affected symmetrically and are erythematous with an accompanying deforming polyarthritis, which ultimately results in shortening of the fingers and mutilation (Fig. 55.20). Other joints may be involved, including the knees, shoulders, wrists, hips, ankles, feet, elbows, spine and temporomandibular joints. Radiography of the affected joints shows destruction of the articular surfaces, with bone resorption and eventually secondary osteoarthritis [10]. Two case reports have highlighted the presence of osteolytic bone damage in this disease, in one patient affecting the bones of the upper limb [11] and in the second the skull, mimicking Langerhans' cell histiocytosis [12]. The authors suggest that the osteolytic lesions are due to the action of pro-inflammatory cytokines, TNF-α and IL-1, in inducing osteoclastic activity [12].

The classical skin lesions are firm brown or yellow papules and plaques, which predominantly affect extensor surfaces, particularly on the hands and forearms. The face (Fig. 55.21), scalp, hands and ears are often affected but involvement of the lower trunk and legs is rare. Coral bead-like lesions may occur around the nail



Fig. 55.20 Multicentric reticulohistiocytosis showing the characteristic skin changes, with multiple firm papular lesions on the sides of the fingers and obvious destructive arthropathy. (Courtesy of Professor N. Saxe, Groote Schuur Hospital, Cape Town, South Africa.)

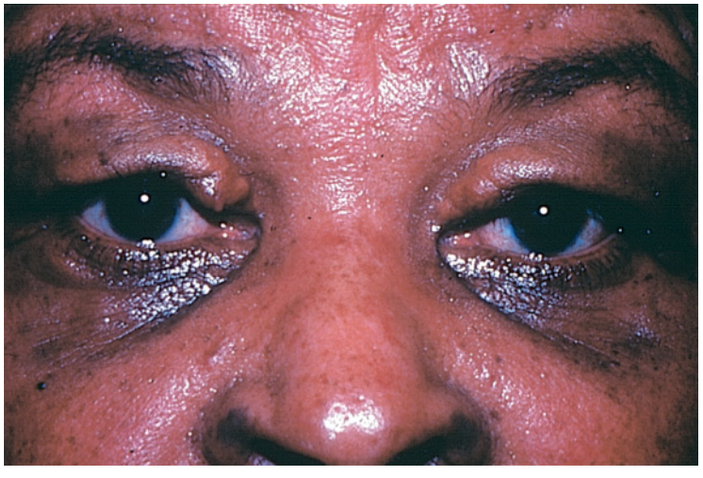


Fig. 55.21 Multicentric reticulohistiocytoma with characteristic lesions around the eyes. (Courtesy of Professor N. Saxe, Groote Schuur Hospital, Cape Town, South Africa.)

folds, which may result in nail dystrophy. Skin lesions are of variable size and rarely ulcerate. Large nodular lesions in proximity to affected joints and cystic swellings of tendon sheaths may occur. About 25% of patients complain of pruritus associated with skin lesions. Diffuse cutaneous reticulohistiocytosis without arthropathy [9] and isolated reticulohistiocytomas [13] have been described. The cutaneous lesions have the same histology as lesions in multicentric reticulohistiocytosis but are not associated with joint problems or neoplasms.

More than 50% of patients have mucosal involvement affecting the mouth, gingiva, pharynx, larynx and sclera. Characteristically, the lips and tongue are involved [14], and 30% of patients have abnormalities of serum lipids. Laboratory findings are normal with a negative rheumatoid factor. Even in the most active stages of the disease, the erythrocyte sedimentation rate is only marginally elevated.

Constitutional symptoms of pyrexia and weight loss may occur. Involvement of bone marrow, skeletal muscle, lymph nodes, heart, pericardium, lungs, pleura, bones, liver, duodenal mesentery and kidney have been reported. Deaths have occurred with cardiac involvement [15]. Multicentric reticulohistiocytosis has been reported in association with Sjögren's syndrome [16] and thyroid involvement [17].

Around 20% of patients have been found to have an associated internal malignancy. The commonest tumours are gastric, ovarian [18], breast and uterine carcinomas [19], myeloma [20], melanoma [21] and lymphomas. Rare case reports have described Ki-1 lymphoma occurring in association with multicentric reticulohistiocytosis [22]. Myelodysplastic syndrome has been reported in one patient with multicentric reticulohistiocytosis, although this patient had been treated with cytotoxic drugs for many years and the myelodysplasia may have been drug related [23]. The diagnosis of multicentric reticulohistiocytosis precedes that of the neoplasm in most cases, and the disease may relapse with recurrence of the neoplasm [24].

Prognosis. The prognosis is good if there is no systemic malignancy, the disease becoming quiescent in 7–8 years. Fatal cardiac involvement may occur with widespread systemic involvement [15]. It does, however, leave considerable morbidity, with a crippling arthropathy and scarred skin.

Diagnosis. Multicentric reticulohistiocytosis has been clinically mistaken for dermatomyositis in a patient with a macular eruption in a photodistribution [25], lupus erythematosus [26] and lepromatous leprosy [27]. Biopsy of skin nodules helps to differentiate multicentric reticulohistiocytosis from eruptive xanthomas and juvenile xanthogranulomas. The disease can usually be clinically differentiated from other disorders involving cutaneous nodules and arthritis (e.g. rheumatoid arthritis, sarcoidosis, gout and xanthomatosis).

Treatment. No treatment is of consistent value in this disease. Systemic steroids may be successful for brief periods but their long-term value is uncertain. Combination of systemic steroids with azathioprine has been used with success [28]. One case report of a patient with joint and skin involvement showed persistent improvement in all sites with the bisphosphonate, alendronate [29]. Non-steroidal anti-inflammatory agents have no effect on the arthropathy. Immunosuppressive drugs give variable results. Cyclophosphamide is reported to give high success rates [30], and ciclosporin has been reported to give good results [31]. Some case reports suggest that TNF-α antagonists may have a role in the treatment of this disease [32,33].

References

1 Luz FB, Gaspar NK, Gaspar AP *et al*. Multicentric reticulohistiocytosis: a proliferation of macrophages with tropism for skin and joints, part II. *Skinmed* 2007; **6**: 227–33.

2 Campbell DA, Edwards NL. Multicentric reticulohistiocytosis: systemic macrophage disorder. *Baillieres Clin Rheumatol* 1991; **5**: 301–19.

3 Fortier-Beaulieu M, Thomine E, Boullie MC *et al*. New electron microscopic findings in a case of multicentric reticulohistiocytosis. Long spacing collagen inclusions. *Am J Dermatopathol* 1993; **15**: 587–9.

4 Heathcote JG, Guenther LC, Wallace AC. Multicentric reticulohistiocytosis: a report of a case and review of the pathology. *Pathology* 1985; **17**: 601–8.
5 Luz FB, Gaspar AP, Ramos-e-Silva M *et al.* Immunohistochemical profile of multicentric reticulohistiocytosis. *Skinmed* 2005; **4**: 71–7.
6 Gorman JD, Danning C, Schmacher HR. Multicentric reticulohistiocytosis: case report with immunohistochemical analysis and literature review. *Arthritis Rheum* 2000; **43**: 930–8.
7 Flam M, Ryan SC, Mah-Poy GL *et al.* Multicentric reticulohistiocytosis: report of a case with atypical features and electron microscopy study of skin lesions. *Am J Med* 1972; **52**: 841–8.
8 Barrow MV, Holubar K. Multicentric reticulosis: a review of thirty-three patients. *Medicine (Baltimore)* 1969; **48**: 287–305.
9 Raphael SA, Cowery SL, Faeber EN *et al.* Multicentric reticulohistiocytosis in a child. *J Pediatr* 1989; **114**: 266–9.
10 Toporcer MB, Kantor GR, Benedetto AV. Multiple cutaneous reticulohistiocytosis. *J Am Acad Dermatol* 1991; **25**: 948–51.
11 Chen CH, Chen CH, Chen HA *et al.* Multicentric reticulohistiocytosis presenting with destructive polyarthritis, laryngopharyngeal dysfunction, and a huge reticulohistiocytoma. *J Clin Rheumatol* 2006; **12**: 252–4.
12 Ho SG, Yu RC. A case of multicentric reticulohistiocytosis with multiple lytic skull lesions. *Clin Exp Dermatol* 2005; **30**: 515–8.
13 Anaguchi S, Sinomiya S, Kinebuchi S *et al.* Solitary reticulohistiocytic granuloma: a report of three cases and a review of the literature. *Nippon Hifuka Gakkai Zasshi* 1991; **101**: 735–42.
14 Katz RW, Anderson KF. Multicentric reticulohistiocytosis. *Oral Surg Oral Med Oral Pathol* 1988; **65**: 721–5.
15 Yee KC, Bowker CM, Tam CY *et al.* Cardiac and systemic complications in multicentric reticulohistiocytosis. *Clin Exp Dermatol* 1993; **18**: 558–68.
16 Carey RN, Blotzer JW, Wolfe ID *et al.* Multicentric reticulohistiocytosis and Sjogren's syndrome. *J Rheumatol* 1985; **12**: 1193–5.
17 Finelli LG, Tenner LK, Ratz JL *et al.* A case of multicentric reticulohistiocytosis with thyroid involvement. *J Am Acad Dermatol* 1986; **15**: 1097–100.
18 Kishikawa T, Miyashita T, Fujiwara E *et al.* Multicentric reticulohistiocytosis associated with ovarian cancer. *Mod Rheumatol* 2007; **17**: 422–5.
19 Malik MK, Regan L, Robinson-Bostom L *et al.* Proliferating multicentric reticulohistiocytosis associated with papillary serous carcinoma of the endometrium. *J Am Acad Dermatol* 2005; **53**: 1075–9.
20 Fenniche S, Haoulet S, Hauman H *et al.* Multicentric histiocytosis revealing multiple myeloma. *Eur J Dermatol* 1996; **6**: 450–7.
21 Snow JC, Muller SA. Malignancy associated histiocytosis: a clinical, histiological and immunophenotypic study. *Br J Dermatol* 1995; **133**: 71–6.
22 Kuramoto Y, Lizawa O, Matsunaga J *et al.* Development of Ki-1 lymphoma in a child suffering from multicentric reticulohistiocytosis. *Acta Derm Venereol (Stockh)* 1991; **71**: 448–9.
23 Bauer A, Garbe C, Detmar M *et al.* Multicentric reticulohistiocytosis and myelodysplastic syndrome. *Hautarzt* 1994; **45**: 91–6.
24 Nunnink JC, Krusinski PA, Yates JW. Multicentric reticulohistiocytosis and cancer: a case report and review of the literature. *Med Pediatr Oncol* 1985; **13**: 273–9.
25 Muñoz-Santos C, Sàbat M, Sáez A *et al.* Multicentric reticulohistiocytosis-mimicking dermatomyositis. Case report and review of the literature. *Dermatology* 2007; **214**: 268–71.
26 Badlissi F, Setty Y, Folzenlogen D. A case of multicentric reticulohistiocytosis initially misdiagnosed as lupus. *J Clin Rheumatol* 2002; **8**: 232–3.
27 Agarwal US, Mathur DK, Jain R *et al.* Multicentric reticulohistiocytosis misdiagnosed as lepromatous leprosy. *Indian J Lepr* 2003; **75**: 259–62.
28 Fedler R, Grantzmann Y, Schwarze EW *et al.* Multicentric reticulohistiocytosis. Therapy with azathiopine and prednisolone. *Hautarzt* 1995; **46**: 118–20.
29 Goto H, Inaba M, Imanishi Y *et al.* Successful treatment of multicentric reticulohistiocytosis with alendronate: evidence for direct effect of bisphosphonate on histiocytes. *Arthritis Rheum* 2003; **48**: 3538–41.
30 Ginsberg WW, O'Duffy JD, Morris JL *et al.* Multicentric reticulohistiocytosis: response to alkylating agents in six patients. *Ann Intern Med* 1989; **111**: 384–8.
31 Saito K, Fujii K, Awazu Y *et al.* A case of systemic lupus erythematosus complicated with multicentric reticulohistiocytosis (MRH): successful treatment of MRH and lupus nephritis with cyclosporin A. *Lupus* 2001; **10**: 129–32.
32 Lovelace K, Loyd A, Adelson D *et al.* Etanercept and the treatment of multicentric reticulohistiocytosis. *Arch Dermatol* 2005; **141**: 1167–8.
33 Sellam J, Deslandre CJ, Dubreuil F *et al.* Refractory multicentric reticulohistiocytosis treated by infliximab: two cases. *Clin Exp Rheumatol* 2005; **23**: 97–9.

Familial haemophagocytic lymphohistiocytosis

Synonyms
- Familial haemophagocytic reticulosis
- Generalized lymphohistiocytic infiltration
- Familial erythrophagocytic lymphohistiocytosis
- Familial histiocytic reticulosis
- Familial lymphohistiocytosis
- Farquhar's disease

This is a rare reactive histiocytosis in which there is widespread infiltration of multiple organs by lymphocytes and mature histiocytes showing prominent cytophagocytosis. It is rapidly fatal in most patients. The incidence is 1.2 per million children [1], with a slight preponderance in boys. Three-quarters of cases are familial, and it is generally considered to be an autosomal recessive disease [2].

The genes responsible in some cases have been identified and studies have identified subsets of familial haemophagocytic lymphohistiocytosis (FHL) depending on the genetic defect. In one patient a constitutional inversion in chromosome 9 (p23;q31) was observed in cells from bone marrow, lymphocytes and fibroblasts [3]. This locus accounts for approximately 10% of cases (FHL-1) [4]. FHL-2 represents 20–30% of all cases and is characterized by mutation in genes coding for perforin, a lytic granule constituent (*PRF-1*; MIMI 70280). The mutation in the perforin gene occurs at position 374, resulting in a premature stop codon. A study of 34 families and linkage studies of a subset of consanguineous families indicates that perforin mutations account for 20–40% of cases of FHL [4]. FHL-3 represents 20–25% of all cases and is characterized by mutations in *MUNC13–14* genes [4]. Other mutations include nonsense and missense mutations and deletions of amino acids [5].

Fever is usually the first sign of the disease, with symptoms of an upper respiratory or gastrointestinal tract infection in 30%. Pallor, anorexia, vomiting and irritability are often noted. Hepatosplenomegaly is usually present at presentation and is progressive. Moderate lymphadenopathy is common. Around 50% of patients develop a transient, non-specific, maculopapular rash, which is often seen at times of high fever, but no persistent skin infiltration is seen. About 20% of patients have neurological symptoms, due to meningeal involvement, usually with convulsions but also with other signs of meningeal irritation.

Laboratory tests show anaemia, thrombocytopenia and raised liver enzymes and hyperbilirubin. Hyperlipidaemia (with elevation of triglycerides and very low-density lipoproteins) and hypofibrinogenaemia are common.

Immunological testing shows abnormalities of both the humoral and cellular limbs of the immune system. Natural antibody titres are low, antibody titres after previous immunization are low and there is an impaired response to primary immunization. All T-cell responses to mitogens, antigens and alloantigens are reduced. There is also a T-cell-suppressor factor, probably related to triglycerides, in the plasma of the patients [6]. Cytotoxic T-cell and

natural killer cell activity is markedly reduced or absent in affected patients.

A number of studies have now demonstrated hypercytokinaemia in this disease, with elevated amounts of circulating IFN-γ, TNF-γ and IL-6 during active disease [7]. Serum levels of IL-6 have been shown to be of no prognostic importance [8]. Soluble CD8 has also been shown to be elevated, suggesting a role for cytotoxic T cells in the pathogenesis of this disease.

Histologically, the involved tissue shows a diffuse infiltrate with lymphocytes and mature histiocytes. The histiocytes exhibit active phagocytosis, especially of erythrocytes but also of leukocytes and occasionally platelets. The histiocytes stain positively for acid phosphatase, non-specific esterase, lysozyme and α_1-antichymotrypsin. A striking histological finding is lymphocyte depletion of lymph nodes, spleen and thymus.

Prognosis is poor, with median survival of 2–3 months [9] from diagnosis and 96% dying within 12 months. Central nervous system disease and persistently low natural killer cell activity are associated with poorer prognosis [10]. Long-term survivors have been reported after chemotherapy, but maintenance therapy is always required.

Initial treatment regimens used splenectomy, exchange transfusion [11] and chemotherapy [12], including vinblastine and intrathecal methotrexate. Henter *et al.* [13] reported a more successful regimen using etoposide and teniposide with prednisolone and intrathecal methotrexate until remission is achieved, followed by maintenance therapy with teniposide or etoposide. A recent study advocated the use of antithymocyte globulin in early stages of the disease showing low toxicity and good responses [14].

Bone marrow transplantation and haemopoietic stem cell transplantation [15] are now regarded as being the most effective treatments for this disease. Results are much better when HLA-identical siblings are used as donors. Studies have now shown that even partial engraftment is compatible with long-term remission [10,16].

References

1 Henter J-I. Familial haemophagocytic lymphohistiocytosis. A clinical, metabolic and immunological study of lymphohistiocytic inflammatory disorder. *Kongl Carolinska Medico Chirurgiska Institutet (Stockh)* 1990.

2 Genik A, Signer E, Muller H. Genetic analysis of familial erythrophagocytic lymphohistiocytosis. *Eur J Pediatr* 1984; **142**: 248–52.

3 Hasle H, Brandt C, Kerndrup G *et al.* Haemophagocytic lymphohistiocytosis associated with constitutional inversion of chromosome 9. *Br J Haematol* 1996; **93**: 808–9.

4 Ishii E, Ueda I, Shirakawa R *et al.* Genetic subtypes of familial hemophagocytic lymphohistiocytosis: correlations with clinical features and cytotoxic T lymphocyte/natural killer cell functions. *Blood* 2005; **105**: 3442–8.

5 Janka G, Schneider M, Gurgey A *et al.* Spectrum of perforin gene mutations in familial haemophagocytic lymphohistiocytosis. *Am J Hum Genet* 2001; **68**: 590–7.

6 Ladisch S, Poplack DG, Holiman B *et al.* Immunodeficiency in familial erythrophagocytic lymphohistiocytosis. *Lancet* 1978; **i**: 581–3.

7 Henter J-I, Elinder G, Soder O *et al.* Hypercytokinaemia in familial haemophagocytic lymphohistiocytosis. *Blood* 1991; **78**: 2918–22.

8 Imashuku S, Hibi S, Gujiwara F *et al.* Hyperinterleukinaemia (IL)6 in haemophagocytic lymphohistiocytosis. *Br J Haematol* 1996; **93**: 803–7.

9 Janka G. Familial haemophagocytic lymphohistiocytosis. *Eur J Pediatr* 1983; **140**: 221–30.

10 Imashuku S, Hyakuna N, Funabiki T *et al.* Central nervous system as a high risk prognostic indicator in young patients with familial haemophagocytic lymphohistiocytosis. *Cancer* 2002; **94**: 3023–31.

11 Ladisch S, Ho W, Matheson D *et al.* Immunologic and clinical effects of repeated blood exchange in familial erythrophagocytic lymphohistiocytosis. *Blood* 1982; **60**: 814–21.

12 Lillyman JS. The treatment of familial erythrophagocytic lymphohistiocytosis. *Cancer* 1980; **46**: 468–70.

13 Henter J-I, Elinder G, Finkel Y *et al.* Successful induction with chemotherapy including teniposide in familial erythrophagocytic lymphohistiocytosis. *Lancet* 1986; **ii**: 1402.

14 Mahlaoui N, Ouachee-Chardin M, de Saint Basile G *et al.* Immunotherapy of familial hemophagocytis lymphohistiocytosis with antithymocyte globulins: a single centre retrospective report of 38 patients. *Pediatrics* 2007; **120**: 622–8.

15 Ouachee-Chardin M, Elie C, de saint Basile G *et al.* Hematopoietic stem cell transplantation in hemophagocytic lymphohistiocytosis: a single centre report of 48 patients. *Pediatrics* 2006; **117**: 743–50.

16 Landman-Parker J, LeDeist F, Blaise A *et al.* Partial engraftment of donor bone marrow cells associated with long term remission of haemophagocytic lymphohistiocytosis. *Br J Haematol* 1993; **81**: 37–41.

Familial sea-blue histiocytosis

This is a rare inherited abnormality of lipid metabolism [1] in which characteristic histiocytic cells are found in the bone marrow and other tissues. The histiocytes are identified by the May–Gruenwald stain, which colours the cytoplasmic granules a deep azure blue, hence the name 'sea-blue histiocytosis'.

Familial sea-blue histiocytosis in an autosomal recessive trait [2]. It usually presents in young adulthood with hepatosplenomegaly and thrombocytopenia, although the age at presentation ranges from 1 to 83 years. The skin, lungs, gastrointestinal tract, eye and nervous system may be involved. In the skin, patchy and irregular brownish-grey pigmentation of the face, upper chest and shoulders has been reported. In one case [3], skin involvement, with eyelid swelling and facial nodules, was confirmed histologically. In the eye, white stippled deposits may be observed at the margins of the fovea or macula, with discoloration of the macular region. Neurological symptoms occur early, with ataxia, epilepsy and dementia.

Sea-blue histiocytosis is not malignant, but it may disseminate and lead to death from liver or lung involvement. The biological abnormality is poorly understood, but the condition probably represents a storage disease in which glycolipid, phospholipid or both accumulate in histiocytic cells in various organs. Sea-blue histiocytes have also been described in chronic myelogenous leukaemia [4,5], adult Niemann–Pick disease [6], following the prolonged use of intravenous fat emulsions in children [7] and in partial sphingomyelinase deficiency [8].

References

1 Wewalka F. Zur Frage der 'blauen pigment Makrophagen in sternal Punktat. *Wien Klin Wochenschr* 1950; **62**: 788–91.

2 Sawitsky A, Rodner F, Chodsky S. The sea blue histiocyte syndrome, a review: genetic and biochemical studies. *Semin Hematol* 1972; **9**: 285–97.

3 Zina AM, Bundino S, Pippione M. Sea blue histiocyte syndrome with cutaneous involvement. Case report with ultrastructural findings. *Dermatologica* 1987; **174**: 39–44.

4 Dosik H, Rosner F, Sawitsky A. Acquired lipidoses: Gaucher-like cells and blue cells in chronic myeloid leukaemia. *Semin Hematol* 1972; **9**: 309–16.

5 Hogan SF, Osborne BM, Butler JJ. Unexpected splenic nodules in leukaemic patients. *Hum Pathol* 1989; **20**: 62–8.

6 Dewhurst N, Besley GTN, Finlayson NDC *et al.* Sea blue histiocytosis in a patient with chronic non-neuropathic Niemann–Pick disease. *J Clin Pathol* 1979; **32**: 1121–7.
7 Goulet O, Girot R, Maier-Redelsperger M *et al.* Hematologic disorders following prolonged use of intravenous fat emulsions in children. *J Parenter Enteral Nutr* 1986; **10**: 284–8.
8 Konagaya M, Konishi T, Konagaya Y *et al.* Partial sphingomyelinase deficiency with sea blue histiocytosis and neurovisceral dysfunction. *Jpn J Med* 1989; **28**: 85–8.

Hereditary progressive mucinous histiocytosis

This is a rare autosomal dominant genodermatosis, which was first described in 1988. All case reports to date have been in women, thus suggesting a link to hormones [1]. Skin lesions appear in the first decade of life and gradually increase throughout life. Lesions consist of skin-coloured to red-brown papules that characteristically affect the nose, hands, forearms and thighs. Two sets of case reports have described mothers and daughters who have both presented with the disease [2,3]. Histologically, the epidermis is normal but within the dermis there are small collections of epithelioid histiocytes with telangiectatic vessels in the upper dermis in early lesions. As tumours develop, the infiltrate changes to nodular mid-dermal aggregates of tightly packed, spindle-shaped cells. In both early and established lesions, there is moderate to extensive mucin production by the epithelioid histiocytes and spindle-shaped cells. On electron microscopy, the spindle-shaped cells are shown to be dendritic histiocytes with abundant lysosomal storage organelles, myelin bodies and zebra bodies.

Immunohistochemically, these cells stain with CD68 and MS1 [3]. The condition is progressive, with gradual increase in numbers of tumours throughout life. These patients show no evidence of spontaneous resolution. No systemic involvement has been described and no treatment seems to have any impact on the disease [4,5].

References

1 Antoni-Bach N, Pfister R, Grosshans E *et al.* Hereditary progressive mucinous histiocytosis. *Ann Dermatol Venereol* 2000; **127**: 400–4.
2 Bork K. Hereditary progressive mucinous histiocytosis. Immunohistochemical and ultrastructural studies in an additional family. *Arch Dermatol* 1994; **130**: 1300–4.
3 Schroder K, Hettmannsperger U, Schmid M *et al.* Hereditary progressive mucinous histiocytosis. *J Am Acad Dermatol* 1996; **35**: 298–303.
4 Wong D, Killingsworth M, Crosland G *et al.* Hereditary progressive mucinous histiocytosis. *Br J Dermatol* 1999; **141**: 1101–5.
5 Young A, Olivere J, Yoo S *et al.* Two sporadic cases of adult onset progressive mucinous histiocytosis. *J Cutan Pathol* 2006; **32**: 166–70.

Malakoplakia

Malakoplakia is an immunodeficiency disease in which macrophages fail to phagocytose and digest bacteria adequately. The term 'malakoplakia', which means soft plaque, was adopted as a descriptive term [1].

Malakoplakia can affect many organs but most commonly affects the urinary and gastrointestinal tracts [2,3]. Cutaneous lesions are rare, non-specific and variable. Draining abscesses, sinuses, ulcers, fluctuant masses, isolated tender nodules and grouped papules have been reported. Mucous membranes may be affected, including the tongue [4] and cervix [5]. The disease generally runs a benign self-limiting course, but fatal cases have been reported [6].

Histologically, sheets of large histiocytic cells with abundant cytoplasm are present in the skin, affecting any level from epidermis to subcutaneous fat. The cells have fine eosinophilic granules in their cytoplasm and are referred to as Hansemann cells. They also contain one or more round basophilic inclusion bodies (Michaelis–Gutmann bodies). Michaelis–Gutmann bodies are 5–15 μm and stain positively with PAS, von Kossa stain (for calcium) and Perls ferrocyanide reaction (for ferric iron). They are considered pathognomonic for this disease and are thought to represent abnormal degradation of bacteria, with calcium and iron deposited on the remaining glycolipid.

The commonest bacterium found in this disease is *Escherichia coli* [7,8], although *Staphylococcus aureus* has also been cultured [9]. Mycobacteria have been identified in two cases of cutaneous malakoplakia using polyclonal anti-*Mycobacteria bovis* antibodies [10]. In some patients, the disease is related to drug-induced immunosuppression [11]. In one patient [6], intracellular cyclic guanosine monophosphate (cGMP) levels were found to be low, and *in vivo* and *in vitro* treatment of the cells with bethanechol chloride, a cholinergic agonist, increased cGMP and restored their bactericidal activity.

References

1 Michaelis L, Gutmann C. Uber Einschlusse in Blastentumoren. *Z Klin Med* 1902; **47**: 208–15.
2 Long JP Jr, Althausen AF. Malakoplakia: a 25 year experience with a review of the literature. *J Urol* 1989; **141**: 1328–31.
3 Yousef GM, Naghibi B. Malakoplakia outside the urinary tract. *Arch Pathol Lab Med* 2007; **131**: 297–300.
4 Love RB, Bernard PA, Carpenter BF. Malakoplakia of the tongue. *J Otolaryngol* 1985; **14**: 179–82.
5 Falcon-Escobedo R, Mora Tiscareno A, Pubeblitz-Peredo S *et al.* Malakoplakia of the uterine cervix: histologic, cytologic and ultrastructural study of a case. *Acta Cytol* 1986; **30**: 281–4.
6 Dervan PA, Teeling M, Dempsey J *et al.* Lymphadenopathy due to fatal histiocytic proliferative disorder containing Michaelis Gutmann bodies. *Cancer* 1986; **57**: 1337–40.
7 Abdou NI, Pombejara C, Sagawa A *et al.* Malakoplakia: evidence for monocyte lysosomal abnormality correctable by cholinergic agonist *in vitro* and *in vivo*. *N Engl J Med* 1977; **297**: 1413–9.
8 Nieland ML, Borochovitz D, Silverman AR *et al.* Cutaneous malakoplakia. *Am J Dermatopathol* 1981; **3**: 287–94.
9 Sencer O, Sencer H, Uluoglu O *et al.* Malakoplakia of the skin. *Arch Pathol* 1979; **103**: 446–50.
10 Mehregan DR, Mehregan AM, Mehregan DA. Cutaneous malakoplakia: a report of two cases with use of anti-BCG for detection of micro-organisms. *J Am Acad Dermatol* 2000; **43**: 351–4.
11 Sian CS, McCabe RE, Lattes CG. Malakoplakia of the skin and subcutaneous tissue in a renal transplant recipient. *Arch Dermatol* 1981; **117**: 654–5.

Necrobiotic xanthogranuloma

The syndrome of necrobiosis with xanthomatous granulomas and an associated paraprotein has been recognized since 1966 [1–3], but it was not until 1980 that it was recognized as a distinct dermatosis [4].

The characteristic clinical lesions are periorbital nodular and ulcerative lesions, which have the reddish-yellow colour of xanthomas (Fig. 55.22). On the trunk and limbs, subcutaneous nodules and xanthomatous plaques are present with atrophy and



Fig. 55.22 Early lesions of necrobiotic xanthogranuloma with characteristic distribution in the periorbital area. (Courtesy of Dr A. Layton, Leeds General Infirmary, Leeds, UK.)



Fig. 55.23 Established lesions of necrobiotic xanthogranuloma on the abdomen showing xanthomatous plaques and atrophy. (Courtesy of Dr P. Holt, University Hospital, Cardiff, UK.)

ulceration (Fig. 55.23). The eyes are often affected with conjunctivitis, keratitis, uveitis, iritis and proptosis. Blindness has been reported in two affected patients [4]. Only one case report of a patient with typical cutaneous lesions and cerebral involvement presenting as tonic–clonic seizures has been published [5]. Systemic symptoms have been reported, including nausea, vomiting, fatigue, epistaxis, back pain and Raynaud's phenomenon. Atypical forms of necrobiotic xanthogranuloma have been reported, including solitary tumours of the skin [6].

The majority of cases have an associated paraprotein, usually an IgG κ or λ monoclonal protein. In a series of 22 patients, 16 had IgG monoclonal protein, three had multiple myeloma, three had cryoglobulinaemia and one had normal serum protein electrophoresis [7].

Decreased levels of C1 inhibitor have been reported in some patients with necrobiotic xanthogranuloma, occasionally associated with angio-oedema. Immune complex formation resulting from autoantibodies against the paraproteins have been implicated in the depletion of C1 inactivator [8].

Histologically, confluent granulomatous masses are present as either sheets or nodules, replacing much of the dermis and extending into the subcutaneous tissue [9]. Hyaline areas of necrobiosis separate individual nodules. Numerous giant cells are present, with Touton cells and bizarre angulated giant cells. Cholesterol clefts, lymphoid nodules (some of which develop germinal centres) and perivascular aggregates of plasma cells are frequent features. Less common, but characteristic when present, are palisading cholesterol cleft granulomas and xanthogranulomatous panniculitis. Granulomatous invasion of blood vessels with thrombosis has been described.

The pathogenesis of necrobiotic xanthogranuloma is unknown. Bullock *et al*. [10] suggested that the abnormal paraprotein becomes complexed with lipid and deposited in the skin, where it produces a foreign-body granulomatous reaction.

Treatment is generally directed to the associated paraproteinaemia. Alkylating agents such as melphalan, with or without prednisolone, have resulted in temporary clearing of the skin [11]. In one patient where cytotoxic drugs had failed, plasmapheresis reduced the level of the circulating monoclonal IgG and resulted in clearing of the skin [12]. Successful treatment with chlorambucil 2 mg/day for 7 months has been reported in a 51-year-old man with necrobiotic xanthogranuloma and associated paraproteinaemia [13]. Radiotherapy was successful in one case involving the eye [14]. Cutaneous disease has been successfully treated with carbon dioxide laser with no evidence of relapse after 12 months [15].

References

1 Frank SB. Xanthomatous granuloma. *Arch Dermatol* 1977; **113**: 1450–8.
2 Muller SA, Winkelmann RK. Atypical forms of necrobiosis lipoidica diabeticorum: a report of 3 cases. *Arch Pathol* 1966; **81**: 352–61.
3 Risdall RJ, Venhegan RI, Robb-Smith AH *et al.* Atypical multicentric reticulohistiocytosis with paraproteinaemia. *Arch Dermatol* 1977; **113**: 1576–82.
4 Kossard S, Winkelmann RK. Necrobiotic xanthogranuloma with paraproteinaemia. *J Am Acad Dermatol* 1980; **3**: 257–70.
5 Shah KC, Poonnoose SI, George R *et al.* Necrobiotic xanthogranuloma with cutaneous and cerebral manifestations. *J Neurosurg* 2004; **100**: 1111–4.
6 Stork J, Kodetova D, Vosmik F *et al.* Necrobiotic xanthogranuloma presenting as a solitary tumour. *Am J Dermatopathol* 2000; **22**: 453–6.
7 Finan MC, Winklemann RK. Necrobiotic xanthogranuloma with paraproteinaemia. A review of 22 cases. *Medicine (Baltimore)* 1986; **65**: 376–88.
8 Finan MC, Winkelmann RK. Histopathology of necrobiotic xanthogranuloma with paraproteinaemia. *J Cutan Pathol* 1987; **14**: 92–9.
9 Hafner O, Witte T, Schmidt RE *et al.* Nekrobiotisches xanthogranulom bei IgG-kappa plasmazytom und Quincke odem. *Hautarzt* 1994; **45**: 339–43.
10 Bullock JD, Bartley GB, Cambell RJ *et al.* Necrobiotic xanthogranuloma with paraproteinaemia. Case report and a pathogenetic theory. *Ophthalmology* 1986; **93**: 1233–6.
11 Macfarlane AW, Verbov JL. Necrobiotic xanthogranuloma with paraproteinaemia. *Br J Dermatol* 1985; **113**: 339–43.
12 Finelli LG, Ratz JL. Plasmapheresis, a treatment modality for necrobiotic xanthogranuloma. *J Am Acad Dermatol* 1987; **17**: 351–4.
13 Machado S, Alves R, Lima M *et al.* Cutaneous necrobiotic xanthogranuloma (NXG): successfully treated with low dose chlorambucil. *Eur J Dermatol* 2001; **11**: 458–62.
14 Char DH, LeBoit PE, Ljung BM *et al.* Radiation therapy for ocular necrobiotic xanthogranuloma. *Arch Ophthalmol* 1987; **105**: 174–5.

15 Vieira V, Del Pozo J, Martinez W *et al*. Necrobiotic xanthogranuloma associated with lymphoplasmacytic lymphoma. Palliative treatment with carbon dioxide laser. *Eur J Dermatol* 2005; **15**: 182–5.

Sinus histiocytosis with massive lymphadenopathy

Synonym
- Rosai–Dorfman disease

Sinus histiocytosis with massive lymphadenopathy (SHML) is a rare histiocytic proliferative disorder that is defined by its histopathological features [1,2]. A registry of this disease contains information on 423 patients [3].

SHML is currently considered to be a reactive rather than a malignant histiocytosis [4]. An infectious cause has been suggested by the occurrence of fever and pharyngitis, which often precede the onset of SHML. However, the search for a possible infectious agent has been inconclusive. Some patients show evidence of Epstein–Barr virus infection while others have demonstrable infection with *Klebsiella rhinoscleroma* and *Brucella*, but these are not consistent findings. A study failed to show evidence of human herpesvirus 6 and 8 in skin lesions [5].

The onset of SHML is usually in young adults, with a range from birth to 74 years. The sex incidence is equal. Clinical presentation is usually with painless lymph node enlargement, which may reach massive proportions. About 90% of patients present with cervical adenopathy, the rest presenting with axillary, inguinal or mediastinal node enlargement. Fever, weight loss, malaise and night sweats have been reported, usually at presentation.

Extranodal involvement is common, with 43% of patients having at least one extranodal site of involvement. Skin is the most common extranodal site and may be involved without nodal disease. Pure cutaneous SHML may remain localized to the skin with no systemic involvement even with long-term follow-up [6]. Skin lesions are usually yellow, but may be violaceous or purple. Macular erythema, papules, nodules or infiltrated plaques have been reported (Fig. 55.24). Scaling is often present and telangiectasia may be observed. Skin lesions may occur at any site [7]. Of patients with skin SHML, 50% have evidence of one or more additional extranodal sites, particularly involving the nasal cavity, with polyps and paranasal sinuses.

Other organs involved in SHML include bone with lytic bone lesions [8], salivary gland, central nervous system, genitourinary system, lower respiratory tract, liver, gastrointestinal tract, heart and thyroid gland. Isolated central nervous system involvement in SHML is well recognized. In a report of 11 cases, seven were male and four female, with an age range of 22–64 years. Presentation was with headaches, seizures, numbness or paraplegia. Eight cases involved the cranial area and three the spinal cord. Most lesions were dura based and only one case involved the brain parenchyma [9]. Treatment of these patients was surgical, with one patient dying of surgical complications and nine showing no evidence of disease progression after a mean of 15 months follow-up.

Laboratory investigations usually show a mild normochromic normocytic anaemia or hypochromic microcytic anaemia with elevation of erythrocyte sedimentation rate. Serum proteins are often abnormal, with a low serum albumin and polyclonal gammopathy. Serum lipids are normal.



Fig. 55.24 A 41-year-old Asian woman with cutaneous SHML presenting as a pruritic papular and plaque lesion on the upper thigh.

Histology of involved nodes reveals the pathognomonic features of SHML. The sinuses are expanded by large pale histiocytes. The histiocytes have abundant pale-pink cytoplasm and indistinct margins or may have glassy eosinophilic cytoplasm and well-defined cytoplasmic membrane. Nuclei are round or oval, usually with a single small nucleolus. Occasionally, multinucleate cells or cells showing nuclear atypia are present but mitoses are rare. Lymphophagocytosis or emperipolesis (phagocytosis of leukocytes, particularly lymphocytes) is always present, and less frequently intracytoplasmic plasma cells, neutrophils and red blood cells may be seen. Between the expanded sinuses, lymphocytes and plasma cells are present and reactive germinal centres are occasionally seen. Rarely, neutrophils are observed scattered throughout the involved node. Electron microscopy shows numerous lipid vacuoles and moderate numbers of lysosomes in the cytoplasm of the histiocytes. The surface of the cells is often thrown into complex, convoluted, villous processes.

In extranodal SHML, the histological picture is strikingly similar to that seen with nodal disease, with what appears to be abnormal lymph node architecture, dilated sinuses and reactive germinal centres in the extranodal site. Extranodal SHML usually shows more fibrosis and lymphophagocytosis.

On immunophenotypic analysis, SHML cells show pan-macrophage markers (EBM11, HAM56 and Leu M3, FcIgG and C3 receptors), monocyte markers (OKM5 and Leu M1), activation antigens (Ki-1, transferrin receptor and CD25) and lysosomal enzymes (lysozyme and α_1-antichymotrypsin) [10]. Surprisingly, however, these cells also display factor XIIIa, a marker of dermal dendrocytes [11], and the S100 antigen that is usually present on dendritic cells; and of two frozen samples tested, both were positive for NA1/34, one for OKT6 but neither for Leu 6. These three monoclonal antibodies react with different epitopes on CD1a, which is characteristic for Langerhans' cells. The exact cell lineage is therefore still uncertain.

The prognosis in SHML is reasonably good. In 238 patients followed for more than a year [7], 49 were well and clear of the disease, 126 had persistent disease, three had progressive disease and 21 patients died, although four deaths were unrelated to SHML. Poor prognostic features in this disease are immunological abnormalities and multiple extranodal sites of disease.

Many treatments have been tried, including the vinca alkaloids, etoposide, ciclosporin and X-rays but no ideal treatment has been identified and the response is poor [12]. A review of the literature showed that 32 of 40 patients received no treatment and underwent spontaneous regression. Radiotherapy gave complete remission in three of nine patients. Surgical debulking was successful in eight of nine patients, resulting in complete remission. Chemotherapy was generally unsuccessful [13], but a case report showed complete resolution of disease with low-dose 2-chlorodeoxyadenosine in a child with nodal and extranodal disease [8].

References

1 Rosai J, Dorfman RF. Sinus histiocytosis with massive lymphadenopathy: a newly recognised benign clinicopathological entity. *Arch Dermatol* 1969; **87**: 63–70.

2 Rosai J, Dorfman RF. Sinus histiocytosis with massive lymphadenopathy: a pseudolymphomatous benign disorder. Analysis of 34 cases. *Cancer* 1972; **30**: 1174–88.

3 Foucar E, Rosai J, Dorfman R. Sinus histiocytosis with massive lymphadenopathy (Rosai–Dorfman disease): review of the entity. *Semin Diagn Pathol* 1990; **7**: 19–73.

4 Gaitonde S. Multifocal sinus histiocytosis with massive lymphadenopathy: an overview. *Arch Pathol Lab Med* 2007; **131**: 1117–21.

5 Ortonne N, Fillet AM, Kosuge H *et al.* Cutaneous Destombes–Rosai–Dorfman disease: absence of detection of HHV-6 and HHV-8 in skin. *J Cutan Pathol* 2002; **29**: 113–8.

6 Frater JL, Maddox JS, Obadiah JM *et al.* Cuttaneous Rosai-Dorfman disease: comprehensive review of cases reported in the medical literature since 1990 and presentation of an illustrative case. *J Cutan Med Surg* 2006; **10**: 281–90.

7 Perez A, Rodriguez M, Febrer I *et al.* Sinus histiocytosis confined to the skin. Case report and review of the literature. *Am J Dermatopathol* 1995; **17**: 384–8.

8 Tasso M, Esquembre C, Blanco E *et al.* Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease) treated with 2-chlorodeoxyadenosine. *Pediatr Blood Cancer* 2006; **47**: 612–5.

9 Andriko JA, Morrison A, Colegial CH *et al.* Rosai–Dorfman disease isolated to the central nervous system: a report of 11 cases. *Mod Pathol* 2001; **14**: 172–8.

10 Eisen RN, Buckley PJ, Rosai J. Immunophenotypic characterisation of sinus histiocytosis with massive lymphadenopathy (Rosai–Dorfman disease). *Semin Diagn Pathol* 1990; **7**: 74–82.

11 Perrin C, Michiels JF, Lacour JP *et al.* Sinus histiocytosis (Rosai–Dorfman disease) clinically limited to the skin. An immunohistochemical and ultra structural study. *J Cutan Pathol* 1993; **20**: 368–74.

12 Komp D. The treatment of sinus histiocytosis with massive lymphadenopathy (Rosai–Dorfman disease). *Semin Diagn Pathol* 1990; **7**: 83–6.

13 Pulsoni A, Anghel G, Falcucci P *et al.* Treatment of sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease): report on a case and literature review. *Am J Hematol* 2002; **69**: 67–77.

Virus-associated haemophagocytic syndrome

Synonyms

- Virus-induced histiocytosis with erythrophagocytosis
- Virus-induced histiocytic medullary reticulosis

Virus-associated haemophagocytic syndrome is a rare reactive histiocytosis in patients with an active viral infection. Patients can be divided into two groups: group 1 have no evidence of underlying disease; group 2 are receiving immunosuppressive therapy for underlying disease [1–3]. The disease results from a cytokine storm derived from an inappropriate immune reaction caused by proliferating or activated T cells or natural killer cells associated with macrophage activation or inadequate apoptosis of immunoresponsive cells.

Any age group can be affected and, although children and neonates are often affected, many adult cases have been reported. The syndrome presents suddenly with fever, constitutional symptoms, hepatosplenomegaly, lymphadenopathy, pancytopenia, coagulopathies with thrombocytopenia and hypofibrinogenaemia, raised liver enzymes and bilirubin, pulmonary involvement and skin rashes. Non-specific, generalized, macular eruptions occur fairly frequently.

The viruses implicated include adenovirus, herpesvirus [4], human herpesvirus 6 [5], Epstein–Barr virus, measles virus [6], parainfluenza virus type 2, enterovirus, cytomegalovirus [7] and influenza A (H3N2) [8]. In the bone marrow, lymph nodes and other involved tissue, there is infiltration by histiocytes showing erythrophagocytosis. These cells are banal looking histiocytes with no cytological evidence of malignancy.

The differential diagnosis includes familial haemophagocytic lymphohistiocytosis, malignant histiocytosis and LCH. In the past, many patients with virus-associated haemophagocytic syndrome have been misdiagnosed as malignant histiocytosis and given inappropriate treatment with cytotoxic drugs. It is important to differentiate between these two entities, as the administration of cytotoxic drugs in a viral disease such as virus-associated haemophagocytic syndrome can precipitate a fulminant fatal infection.

The prognosis is variable. In a series of 19 patients [9], 30% died in the acute stages of the disease. The other patients recovered completely in 1–8 weeks with no recurrence in a follow-up period of 32 months. Prognosis is related to prompt introduction of immunosuppressive therapy to control the cytokine storm; ciclosporin or systemic steroids are used in low-risk groups and etoposide-containing regimens in high-risk groups [10].

References

1 Bishop JW, Marsh WL, Keonig HM. Hemophagocytic syndrome in Kawasaki disease. *Clin Res* 1980; **28**: 111A.

2 Manoharan A, Catovsky D, Lampert IA *et al.* Histiocytic medullary reticulosis complicating chronic lymphocytic leukaemia: malignant or reactive? *Scand J Haematol* 1981; **26**: 5–13.

3 Rendall RJ, McKenna RW, Nesbit ME *et al.* Virus-associated hemophagocytic syndrome. A benign histiocytic proliferation distinct from malignant histiocytosis. *Cancer* 1979; **44**: 993–1002.

4 Rosai J, Dorfman RF. Sinus histiocytosis with massive lymphadenopathy: a newly recognised benign clinicopathological entity. *Arch Dermatol* 1969; **87**: 63–70.

5 Liu DL, Teng RJ, Ho MM *et al.* Human herpes virus 6 associated haemophagocyte syndrome in beta thalassemia: report of one case. *Acta Paediatr Sin* 1995; **36**: 373–5.

6 Komatsuda A, Chubach A, Miura AB. Virus associated haemophagocytic syndrome due to measles accompanied by acute respiratory failure. *J Intern Med* 1995; **34**: 203–6.

7 Kashiwagi Y, Kawashima H, Sato S *et al.* Virological and immunological characteristics of fatal virus-associated haemophagocytic syndrome (VAHS). *Microbiol Immunol* 2007; **51**: 53–62.

8 Ando M, Miyazaki E, Hiroshige S *et al.* Virus associated hemophagocytic syndrome accompanied by acute respiratory failure caused by influenza A (H3N2). *Intern Med* 2006; **45**: 1183–6.

9 Wilson ER, Malluh A, Stagno S *et al.* Fatal Epstein–Barr virus associated hemophagocytic syndrome. *J Pediatr* 1981; **98**: 260–2.
10 Imashuku S, Teramura T, Morimoto A *et al.* Recent developments in the management of hemophagocytic lymphohistiocytosis. *Expert Opin Pharmacother* 2001; **2**: 1437–48.

Class III histiocytosis: malignant histiocytoses

Class III histiocytoses are malignancies of the monocyte/macrophage series of cells. These diseases are separated into monocytic leukaemia, malignant histiocytosis and true histiocytic lymphoma on clinical criteria, but there is an enormous overlap and it may not always be possible to differentiate them.

In monocytic leukaemia, the malignancy primarily affects the bone marrow and blood but extramedullary involvement is common. In malignant histiocytosis, the histiocytes retain their ability to migrate through the body, which results in widespread involvement of the reticuloendothelial system. In true histiocytic lymphoma, the cells are derived from fixed tissue histiocytes and the tumours are localized, although they may disseminate.

In a study by the International Lymphoma Study Group [1], tumours of histiocytes were phenotypically assessed using a panel of markers. Four groups were identified:

1 Histiocytic sarcoma: CD68 and lysozyme positive, CD1a and CD21/35 negative, with 33% showing S100 reactivity. This tumour was predominantly extranodal and associated with a high mortality.
2 Langerhans' cell sarcoma: CD68, lysozyme, CD1a and S100 positive but CD21/35 negative. This tumour was predominantly extranodal, with a 50% mortality rate.
3 Follicular dendritic cell sarcoma: CD21/35 positive. This tumour was localized to lymph nodes and associated with a low mortality.
4 Interdigitating dendritic cell sarcoma: S100 positive, 50% CD68 positive, CD1a and CD21/35 negative.

Most of these tumours were localized to lymph nodes and associated with a low mortality. This is a useful phenotypic aid for recognizing tumours of histiocytic origin. In the Histiocyte Society classification, malignant histiocytosis and true histiocytic lymphoma can be subdivided into tumours of these four phenotypes.

Reference

1 Pileri SA, Grogan TM, Harris NL *et al.* Tumours of histiocytes and accessory dendritic cells: an immunohistochemical approach to classification from the International Lymphoma Study Group based on 61 cases. *Histopathology* 2002; **41**: 1–29.

Monocytic leukaemia

Definition. Monocytic leukaemia may be acute or chronic. The acute myelogenous leukaemias have been classified in the Franco–American–British classification according to the characteristics of the cells involved. Acute myelomonocytic leukaemia is classified as M5. Acute myeloid leukaemia (AML) M(5) can be immunophenotypically subdivided into AML-M(5a) and AML-M(5b) with AML-M(5a) expressing higher levels of CD68 and CD11b. Prognosis does not seem to differ in these two subtypes [1]. The chronic myelomonocytic/monocytic leukaemias usually transform into acute forms of the leukaemia in a matter of months.

The monocytic leukaemias typically exhibit increased extramedullary disease and organomegaly, and are associated with reduced remission rates and a poorer prognosis.

Aetiology. The aetiology of monocytic leukaemias is unknown. A characteristic karyotype has been reported in M5 leukaemias, translocation t(9;11)(p22;q23).

Pathology. Leukaemic cells in monocytic leukaemia show varying degrees of monocyte differentiation. In acute forms of the disease, the cells stain positively for peroxidase, Sudan black B and non-specific esterase. The cells also contain granules that stain for α-naphthylbutyrate esterase [2]. The cells demonstrate CD13 and CD33, with 30% of cells exhibiting HLA-DR. Monocyte-associated membrane antigen (CD14) expression is variable [3].

Ultrastructurally, the cells have irregular nuclei with nuclear blebs, numerous pinocytic vesicles and perinuclear fibrillar bodies [4].

Skin infiltration favours the lower dermis and subcutaneous fat, with prominent involvement of adnexal structures, nerves and vessels of the superficial and deep plexus. Cellular atypia may be prominent and mitotic figures are common. Differentiation from other forms of leukaemia depends on examination of the blood and bone marrow and special stains in skin sections. The best marker for monocytic leukaemia is non-specific esterase.

Clinical features. Skin lesions in monocytic leukaemia may be specific, for example leukaemia cutis, or non-specific, related to anaemia, thrombocytopenia, infection or drugs. Leukaemia cutis occurs in about 20% of patients with acute monocytic leukaemia [3,5]. Specific skin lesions are light-red, brown or violaceous macules and nodules [6]. These are firm and generally asymptomatic. Skin lesions may undergo rapid cycles of development and spontaneous regression. Skin involvement is not related to the circulating white cell count. Gum involvement occurs in 25–50% of patients.

The prognosis in acute monocytic leukaemia is not related to skin involvement, and leukaemia cutis may spontaneously regress. The prognosis depends on the age of the patient, presence of renal failure and serum β_2-microglobulin levels. Aggressive chemotherapy is associated with complete remission in 60% of patients.

Diagnosis. Diagnosis is made on clinicopathological features of the disease. Differentiation from other forms of leukaemia cutis demands examination of the blood or bone marrow and the use of special stains. M4 and M5 leukaemias are associated with elevated serum lysozyme levels [2].

Treatment. Treatment of leukaemia cutis is that of the underlying leukaemia. Leukaemia cutis in monocytic leukaemia has a tendency to spontaneous regression, but large lesions or ulcerating lesions may be treated with local radiotherapy. Acute monocytic leukaemia is sensitive to the currently used chemotherapeutic

regimes used in acute myeloid leukaemia with similar response rates to the other acute myeloid leukaemias [7].

References

1 Liu LB, Li L, Xiao J *et al*. Comparison of immunophenotype and clinical manifestations between patients with M5a and M5b of acute monocytic leukaemia. *Zhongguo Shi Yan Xue Ye Xue Za Zhi* 2006; **14**: 1079–82.
2 Baker AM, Falk RE, Greaves MR. Detection of monocyte specific antigen on human acute leukaemia cells. *Br J Haematol* 1976; **32**: 13–9.
3 Scott CS, Stark AN, Limbert J *et al*. Diagnostic and prognostic factors in acute monocytic leukaemia: an analysis of 51 cases. *Br J Haematol* 1988; **69**: 247–52.
4 Freeman AI, Journey LJ. Ultrastructural studies on monocytic leukaemias. *Br J Haematol* 1971; **20**: 225–31.
5 Baden TJ, Gammon WR. Leukaemia cutis in acute myelomonocytic leukaemia. *Arch Dermatol* 1987; **123**: 88–90.
6 Bernasconi C, Serri F. Skin manifestations of monocytic and myelomonocytic leukaemias. *G Ital Dermatol Venereol* 1980; **115**: 91–100.
7 Tallman MS, Kim HT, Paietta E *et al*. Acute monocytic leukaemia (French-American-British classifiaction M5) does not have a worse prognosis than other subtypes of acute myeloid leukemia: a report from the Eastern Cooperative Oncology Group. *J Clin Oncol* 2004; **22**: 1276–86.

Malignant histiocytosis

Synonyms

- Malignant reticulohistiocytosis
- Malignant reticulosis
- Histiocytic medullary reticulosis
- Sinusoidal haematolymphoid malignancy
- Malignant astrocytosis
- Aleukaemic reticulosis
- Histiocytic reticulosis

Definition. Malignant histiocytosis is a widespread neoplastic proliferation of histiocytic cells that typically involves liver, spleen, lymph nodes and bone marrow. The cells usually arise from sinusoidal histiocytes, although very rare cases of malignant histiocytosis of Langerhans' cell phenotype have been reported.

Aetiology. Malignant histiocytosis is a neoplastic proliferation of cells of the mononuclear phagocyte system. There is no evidence of a viral aetiology in this disease and no reported familial incidence. There have been reports of a characteristic chromosomal translocation t(5;6)(q35;p21) in malignant histiocytosis [1,2]. The major problem with these reports is that the large cell anaplastic lymphoma (Ki-1-positive lymphoma) is often grouped with malignant histiocytosis, but these are T-cell lymphomas. However, the 5q35 break-point does appear to be specific for malignant histiocytosis [3].

Incidence. Malignant histiocytosis is a rare disease with a male to female ratio of 3.5 : 1. It has been reported in all age groups, with a median age of 35 years [4]. Childhood disease is uncommon with few reported series [5]. The disease tends to occur earlier in women (second to third decades) than in men (third to fourth decades) [6]. Reports have suggested an increased incidence of this disease in parts of tropical Africa, with reports from Malawi [7] and Uganda [8].

Pathology. The histological picture in skin and lymph nodes is similar and the diagnosis can be established in either site. Characteristically, there is an infiltrate of histiocytic cells showing varying degrees of atypia that are typically non-cohesive. Cells are large (up to 50 μm in diameter) with abundant cytoplasm and distinct cytoplasmic membranes.

The histiocytic cells are heterogeneous. Some show more marked histiocytic differentiation, with pale cytoplasm, prominent vacuolation or even foamy cytoplasm, and exhibit phagocytosis of erythrocytes, leukocytes and cellular debris. Other cells are more 'primitive', with deeply eosinophilic or amorphous cytoplasm. Nuclei are usually lobulated, with finely granular or reticulated chromatin and prominent or bizarre nucleoli. Nuclear membranes tend to be thickened. Mitoses are common.

Cytochemical and immunohistochemical studies have shown that the cells in malignant histiocytosis are negative for chloracetate esterase, Sudan black B, alkaline phosphatase and β-glucuronidase [9]. Presence of non-specific esterase, acid phosphatase and lysozyme is variable, with the better differentiated cells showing these enzymes [10]. The more differentiated phagocytosing cells usually stain for factor XIIIa and the antimonocyte monoclonal antibody MOI [11]. In some cases, EMA, HLA-DR, CD25, CD30, CD68 and CD71 have been detected. In rare cases, CD1a or CD21/35 may be found. In lymph nodes, the architecture is disarranged but not effaced by the malignant cells.

In the skin, there is extensive perivascular and periappendageal infiltration of the dermis, with extension into subcutaneous fat. In advanced lesions, fat necrosis may occur. The epidermis and papillary dermis are characteristically spared but in the more tumid lesions epidermal ulceration may be present.

Clinical features. Malignant histiocytosis is usually of acute onset, with fever, sweats, wasting, generalized painful lymphoadenopathy and hepatosplenomegaly. As the disease progresses, jaundice, purpura, anaemia and leukopenia occur. In 50% of patients, extranodal extension of the disease is seen, most commonly affecting the skin, bone and gastrointestinal tract.

In the skin, single or multiple lesions may be present [12,13], ranging from skin coloured to violaceous. Large lesions may ulcerate. A widespread, papulonodular eruption similar to that in acute monocytic leukaemia may also be seen.

In bone, the lesions are focal, destructive, lytic and may become widespread with associated hypercalcaemia. Gastrointestinal involvement is usually observed late in the disease. Small and large bowel may be involved, with infiltration of the lamina propria and local intraluminal masses. This presents with obstruction or haemorrhage or both. A rare presentation with multiple lesions is with malabsorption.

In the past, this disease has been associated with a poor prognosis. However, with aggressive management (radiotherapy or radiotherapy and chemotherapy) complete remission has been reported in up to 50% of cases, with a mean duration of complete remission of over 12 months [4]. Microscopic evidence of vascular invasion carries a poor prognosis.

Diagnosis. The major differential diagnosis is with large cell anaplastic lymphomas, in which the clinical and histological features

may be similar. Other diseases that may be confused with malignant histiocytosis are familial haemophagocytic lymphohistiocytosis, virus-associated haemophagocytic syndrome, Hodgkin's disease and SHML. Diagnosis can usually be established on clinicopathological features of the disease, although special stains may be needed to exclude large cell anaplastic lymphoma.

Treatment. Malignant histiocytosis is sensitive to both radiotherapy and chemotherapy but treatment must be started early, as many patients die before therapy can be started [5]. Chemotherapy is usually with a combination regimen, which includes doxorubicin and radiotherapy. In one series, complete remission was achieved in seven of nine patients treated [4]. In a study of 27 children with malignant histiocytosis, complete remission was achieved in 22 children using a regimen of vincristine, cyclophosphamide, doxorubicin and prednisolone, with a 5-year survival of 81% [14]. In patients who relapse after conventional chemotherapy, autologous bone marrow transplantation has successfully achieved long-term remission [15]. Large skin tumours or ulcerated tumours can be treated with local radiotherapy. A review of the treatment of malignant histiocytosis has been published [16]. Conventional chemotherapy and radiotherapy are still the mainstay of treatment.

References

1 Kamesaki H, Koya M, Miwa H *et al.* Malignant histiocytosis with rearrangement of the heavy gene and evidence of monocyte-macrophage lineage. *Cancer* 1988; **62**: 1306–9.

2 Morgan R, Smith SD, Hecht BK *et al.* Lack of involvement of the c-fos and N-myc genes by chromosomal translocation t(2;5)(p23;q35) common to malignancies with features of so-called malignant histiocytosis. *Blood* 1989; **73**: 2155–64.

3 Nezelof C, Barbey S, Gogusen J *et al.* Malignant histiocytosis in childhood: a distinct CD30 positive clinicopathological entity associated with a chromosomal translocation involving 5q35. *Semin Diagn Pathol* 1992; **9**: 75–89.

4 Rilke F, Carbone A, Musumed T *et al.* Malignant histiocytosis: a clinico-pathological study of 18 consecutive cases. *Tumori* 1978; **64**: 221–7.

5 Ornvold K, Nielsen MH, Clausen N. Malignant histiocytosis in childhood: clinicopathological study of 14 cases. *Acta Pathol Microbiol Immunol Scand* 1986; **94**: 291–6.

6 Warnke RA, Kim H, Dorfman RF. Malignant histiocytosis (histiocytic medullary reticulosis). 1. Clinicopathological study of 29 cases. *Cancer* 1975; **35**: 215–30.

7 Molyneux ME, Tozer RA, Hutt MSR. Histiocytic medullary reticulosis in Africa. *Lancet* 1978; **ii**: 259.

8 Amsel S, Bijlsma F. Histiocytic medullary reticulosis. Clinical and pathological studies in Uganda. *Trop Geogr Med* 1974; **26**: 31–8.

9 Carbone A, Micheau C, Caillard J-M *et al.* A cytochemical and immunohistochemical approach to malignant histiocytosis. *Cancer* 1981; **47**: 2862–71.

10 Van Heerde P, Feltkamp CA, Hart AAM *et al.* Malignant histiocytosis and related tumours. A clinicopathological study of 42 cases using cytological, histochemical and ultrastructural parameters. *Hematol Oncol* 1984; **2**: 13–32.

11 Nemes Z, Thomazy V. Diagnostic significance of histiocyte-related markers in malignant histiocytosis and true histiocytic lymphoma. *Cancer* 1988; **62**: 1970–80.

12 Ducatman BS, Wick MR, Morgan TW *et al.* Malignant histiocytosis: a clinical, histologic and immunohistochemical study of 20 cases. *Hum Pathol* 1984; **15**: 368–77.

13 Willemze R, Ruiter DJ, Willem A *et al.* Reticulum cell sarcomas (large cell lymphomas) presenting in the skin. High frequency of true histiocytic lymphoma. *Cancer* 1982; **50**: 1367–79.

14 Brugieres L, Caillaud JM, Patte C *et al.* Malignant histiocytosis: therapeutic results in 27 children treated with single polychemotherapy regimes. *Med Pediatr Oncol* 1989; **17**: 193–6.

15 Berry J, Russel JA. Salvage of relapsed malignant histiocytosis by autologous bone marrow transplantation. *Bone Marrow Transplant* 1989; **4**: 123–4.

16 Bucsky P, Egeler RM. Malignant histiocytic disorders in children. Clinical and therapeutic approaches with a nostalgic discussion. *Hematol Oncol Clin North Am* 1998; **12**: 465–71.

True histiocytic lymphoma

Synonyms
- Reticulum cell sarcoma
- Histiosarcoma
- Monocytic sarcoma

Definition. A malignant histiocytic neoplasm that may disseminate.

Aetiology. The aetiology is unknown. The disease represents malignant proliferation of non-Langerhans' cell histiocytes or more rarely of Langerhans' cells. Differentiation from malignant histiocytosis may be difficult.

Pathology. True histiocytic lymphoma exhibits many of the features described in malignant histiocytosis, infiltrating cells being predominantly dermal and non-cohesive. Nemes and Thomazy [1] suggest that the cells in true histiocytic lymphoma are more differentiated than those in malignant histiocytosis and that the cell population is more homogeneous, showing phagocytosis and labelling for factor XIIIa. These cells stain with macrophage markers CD11c and CD68 and are negative for T- and B-cell markers [2]. A rare spindle cell variant has been described which expressed CD163, CD68, CD45, lysozyme and NSE [3].

Clinical features. This is a localized tumour of malignant histiocytes that may be nodal or extranodal. In 40% of patients, presentation is with the painless enlargement of one or more groups of superficial lymph nodes. Constitutional symptoms of malaise, anorexia, sweating and fever may be present.

Extranodal presentation may be with bone, gastrointestinal tract or skin lesions. Bone and gastrointestinal tract lesions are as described in malignant histiocytosis. Skin lesions are localized bluish-red tumours that can attain a large size. An isolated skin tumour of true histiocytic lymphoma in a 79-year-old patient has been described that reached 20 cm in diameter at presentation [4]. In one case report from Japan, an isolated dark-red skin tumour developed on the leg of a 49-year-old woman. Histology showed a monomorphous infiltrate of large cells, with erosion of the overlying epidermis. These cells were CD1a positive and on electron microscopy contained multiple Birbeck granules. This Langerhans' cell, true histiocytic lymphoma disseminated to regional lymph nodes, liver, lungs, kidneys, bone marrow and skin and the patient died 3 years after diagnosis [5]. Hepatosplenomegaly occurs in only a minority of patients with true histiocytic lymphoma, and peripheral blood involvement is rare. In one case report, a 44-year-old man with true histiocytic lymphoma was treated with autologous bone marrow transplantation and subsequently developed histiocytic leukaemia classified as M5c monocytic leukaemia [6].

Prognosis. True histiocytic lymphoma is treatable, and the prognosis is probably better than in malignant histiocytosis.

Treatment. True histiocytic lymphoma is both radiosensitive and chemosensitive. Complete remission has been achieved in localized skin disease using electron-beam therapy [4]. Reports of therapeutic responses are difficult to evaluate because of doubt over the diagnosis in older series.

References

1 Nemes Z, Thomazy V. Diagnostic significance of histiocyte-related markers in malignant histiocytosis and true histiocytic lymphoma. *Cancer* 1988; **62**: 1970–80.

2 Soriac Orradre JL, Garcia Almagro D, Martinez B *et al.* True histiocytic lymphoma (monocytic sarcoma). *Am J Dermatopathol* 1992; **14**: 511–7.

3 Alexiev BA, Sailey CJ, McClure SA *et al*. Primary histiocytic sarcoma arising in the head and neck with predominant spindle cell component. *Diagn Pathol* 2007; **26**: 2–7.

4 Forestier JY, Schmitt D, Thivolet J. Malignant and isolated cutaneous tumour of pure histiocytic origin (cutaneous histiocytosarcoma). *G Ital Dermatol Venereol* 1980; **115**: 143–5.

5 Tani M, Ishii N, Kumagai M *et al.* Malignant Langerhans cell tumour. *Br J Dermatol* 1992; **126**: 398–403.

6 Esteve J, Rozman M, Campo E *et al.* Leukaemia after true histiocytic lymphoma: another type of acute monocytic leukaemia with histiocytic differentiation (AMC-M5c). *Leukaemia* 1995; **9**: 1389–91.

CHAPTER 56
Soft-Tissue Tumours and Tumour-like Conditions

E. Calonje
St John's Institute of Dermatology, St Thomas' Hospital, London, UK

Fibrous and myofibroblastic tumours, 56.2
Fibrous papule of the face, 56.2
Storiform collagenoma, 56.3
Pleomorphic fibroma, 56.3
Acquired digital fibrokeratoma, 56.4
Nodular fasciitis, 56.4
Fibro-osseous pseudotumour of the digits, 56.5
Ischaemic fasciitis, 56.5
Superficial acral fibromyxoma, 56.6
Fibrous hamartoma of infancy, 56.6
Calcifying fibrous tumour/pseudotumour, 56.6
Calcifying aponeurotic fibroma, 56.7
Dermatomyofibroma, 56.7
Angiomyofibroblastoma, 56.7
Cellular angiofibroma, 56.8
Elastofibroma, 56.8
Infantile myofibromatosis and adult myofibroma, 56.9
Inclusion body (digital) fibromatosis, 56.9
Fibroma of tendon sheath, 56.10
Collagenous fibroma, 56.10
Nuchal fibroma, 56.11
Palmar and plantar fibromatosis (superficial fibromatoses), 56.11
Penile fibromatosis, 56.11
Lipofibromatosis, 56.12
Dermatofibrosarcoma protuberans, 56.12
Giant cell fibroblastoma, 56.14
Myxoinflammatory fibroblastic sarcoma, 56.15
Fibrohistiocytic tumours, 56.15
Giant cell tumour of tendon sheath, 56.15
Fibrous histiocytoma (dermatofibroma), 56.16
Medallion-like dermal dendrocytic hamartoma, 56.18
Hemosiderotic fibrohistiocytic lipomatous lesion, 56.19
Angiomatoid fibrous histiocytoma, 56.19
Plexiform fibrous histiocytoma, 56.20
Atypical fibroxanthoma, 56.20
Malignant fibrous histiocytoma, 56.22
Myxofibrosarcoma, 56.22
Low-grade fibromyxoid sarcoma, 56.22
Vascular tumours, 56.23
Reactive vascular lesions, 56.23
Intravascular papillary endothelial hyperplasia, 56.23
Reactive angioendotheliomatosis, 56.24
Glomeruloid haemangioma, 56.24
Benign vascular tumours, 56.25
Lobular capillary haemangioma (pyogenic granuloma), 56.25
Cirsoid aneurysm, 56.26
Epithelioid haemangioma, 56.27
Cutaneous epithelioid angiomatous nodule, 56.28
Acquired elastotic haemangioma, 56.28
Hobnail haemangioma, 56.29
Microvenular haemangioma, 56.29
Sinusoidal haemangioma, 56.30
Spindle cell haemangioma, 56.30
Symplastic haemangioma, 56.31
Vascular tumours of intermediate malignancy, 56.31
Kaposiform haemangioendothelioma, 56.31
Giant cell angioblastoma, 56.32
Retiform haemangioendothelioma, 56.32
Papillary intralymphatic angioendothelioma, 56.32
Kaposi's sarcoma, 56.33
Malignant vascular tumours, 56.37
Angiosarcoma, 56.37
Epithelioid haemangioendothelioma, 56.40
Epithelioid angiosarcoma, 56.40
Lymphatic tumours, 56.41
Progressive lymphangioma, 56.41
Atypical vascular proliferation after radiotherapy, 56.41
Tumours of perivascular cells, 56.42
Myopericytoma, 56.42
Glomus tumour, 56.43
Peripheral neuroectodermal tumours, 56.44
Neuromuscular hamartoma, 56.44
Multiple mucosal neuromas, 56.45
Amputation stump neuroma, 56.45
Morton's neuroma, 56.45
Solitary circumscribed neuroma, 56.45
Schwannoma, 56.46
Solitary neurofibroma, 56.47
Plexiform neurofibroma, 56.48
Diffuse neurofibroma, 56.49
Perineurioma, 56.49
Dermal nerve sheath myxoma, 56.49
Cellular neurothekeoma, 56.50
Granular cell tumour, 56.50
Meningothelial heterotopias, 56.51
Glial heterotopic nodules, 56.52
Epithelial sheath neuroma, 56.52
Pigmented neuroectodermal tumour of infancy, 56.52
Malignant peripheral nerve sheath tumour, 56.53
Clear cell sarcoma, 56.53
Peripheral primitive neuroectodermal tumour, 56.54
Tumours of muscle, 56.54
Congenital smooth muscle hamartoma, 56.54
Leiomyoma, 56.54
Leiomyosarcoma, 56.56
Skeletal muscle tumours, 56.56
Rhabdomyosarcomatous congenital hamartoma, 56.56
Rhabdomyoma, 56.57
Cutaneous rhabdomyosarcoma, 56.57
Tumours of fat cells, 56.57
Lipoma, angiolipoma and hibernoma, 56.57
Lipoblastoma and lipoblastomatosis, 56.57
Spindle cell and pleomorphic lipoma, 56.57
Atypical lipomatous tumour, 56.58
Liposarcoma, 56.58
Tumours of uncertain histogenesis, 56.59
Superficial angiomyxoma, 56.59
Digital myxoma, 56.59
Dermal non-neural granular cell tumour, 56.59
Perivascular epithelioid cell tumour ('PEComa'), 56.60
'Aggressive' angiomyxoma, 56.60
Epithelioid sarcoma, 56.60
Ossifying lesions in the dermis, 56.61
Osteoma cutis, 56.61
Cutaneous calculus, 56.62
Progressive osseous heteroplasia, 56.62

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

Introduction

For many clinical dermatologists, soft-tissue tumours arising in the dermis, subcutis or deeper soft tissues are a confusing group of lesions. This is probably partly explained by the facts that there

is a very long list of soft-tissue tumours, and that a large majority of these can arise in the skin or affect it secondarily. Most of these tumours have no characteristic clinical appearance, and present as non-specific, dermal, or deep-seated nodules. However, it is necessary for all clinical dermatologists to have an understanding of the range of tumours that may arise in the dermis, and also of the likely biological behaviour of individual lesions. Although cutaneous malignant soft-tissue tumours are rare, many benign lesions may be histologically confused with a malignancy. Furthermore, there is a group of soft-tissue tumours that have low-grade malignant potential (intermediate malignancy) with frequent local recurrences but little or no potential for metastatic spread (e.g. dermatofibrosarcoma protuberans). These tumours may cause important morbidity, and their recognition is therefore essential for the planning of treatment and follow-up. Recognizing a wide range of soft-tissue tumours is also important as a number of these lesions—particularly when multiple—may be markers of genetic syndromes (for example, multiple neurofibromas and plexiform neurofibroma in neurofibromatosis type I).

A broad division can be made between tumours according to the morphological lines of differentiation. The latter include fibroblastic, myofibroblastic, neural, vascular, muscular and adipocytic types. In a number of tumours, the line of differentiation is not clear, as a normal cell of origin cannot be identified (e.g. epithelioid sarcoma). In a still larger group of tumours, their origin is descriptively ascribed to fibrohistiocytic cells, but with mounting evidence that many of these lesions have fibroblast and/or myofibroblastic differentiation and almost none display true histiocytic differentiation. The list of tumours discussed in this chapter is not all-inclusive. For a full account of the very wide range of these tumours, the reader is referred to the standard major work in this field [1]. True histiocytic tumours are discussed in Chapter 55, and keloids and hypertrophic scars in Chapter 45. Metastatic malignant tumours are covered in Chapter 62.

The most useful biological triage is into totally benign lesions; lesions that may recur locally but never or almost never metastasize; and those that are truly malignant and may metastasize. The great majority of dermal or superficial soft-tissue tumours come into the first two categories, whilst truly malignant soft-tissue tumours much more frequently arise below the deep fascia. In the case of these rare malignant tumours, there is a relationship between bulk and prognosis, smaller lesions carrying a better prognosis. More superficially situated lesions tend to carry a better prognosis than those deeply situated. Mitoses (particularly abnormal mitotic figures) and necrosis both tend to be associated with malignant rather than benign lesions.

The usual clinical presentation of many of the tumours described in this chapter is of a non-specific lump or nodule. An incisional biopsy should be arranged, and it must be adequately deep so that the nature of the lesion at its deepest margin can be determined. Once the pathologist has established the nature of the tumour, appropriate definitive surgery can be planned. Prior consultation with the pathologist is strongly recommended, as samples may be needed for cytogenetics, electron microscopy or immunohistochemistry. All of these may be helpful in arriving at an accurate diagnosis.

Reference

1 Weiss SW, Goldblum JR. *Enzinger and Weiss's Soft Tissue Tumours*, 5th edn. St Louis: Mosby, 2007.

Fibrous and myofibroblastic tumours

Fibrous papule of the face [1]

Synonym
- Fibrous papule of the nose

Definition and incidence. A small facial papule with a distinctive fibrovascular component on histological examination. The condition is relatively common, and several large series have been reported [2–4].

Clinical features [2–4]. The lesions usually occur singly on the nose. Occasionally, they may occur on the forehead, cheeks, chin or neck, and there may be several lesions [5]. The lesion usually presents in middle life, and both sexes are equally affected.

The papule develops slowly as a dome-shaped, skin-coloured or slightly red or pigmented lesion, which is usually sessile. Most are asymptomatic, but about one-third bleed on minor trauma.

Pathology [2–4]. The epidermis appears normal, although there may be an increased number of clear cells overlying the lesion. In the dermis there is increased collagen with a hyalinized appearance and scattered, somewhat dilated vascular channels (Fig. 56.1). In the background there is increased cellularity with mono- and multinucleated cells with a histiocyte-like appearance. In some lesions epithelioid or clear cells may predominate [6,7]. There are prominent dilated capillaries, but relatively few elastic fibres.

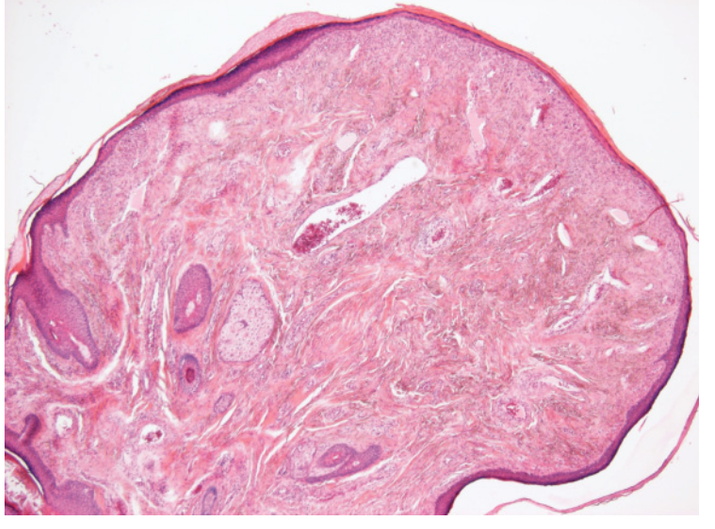


Fig. 56.1 Fibrous papule with hyalinized collagen bundles and increased dilated vascular channels.

It has been suggested that the condition may be a variant of a melanocytic naevus [2,4], but others disagree [3]. S100 protein, which is an immunohistochemical marker of neuroepithelial elements, is present neither in the stellate cells in the papillary dermis nor in the mesenchymal 'naevus' cells [8].

Treatment. The lesion is benign, but it may easily be excised or surgically pared for cosmetic reasons.

References

1 Okun M. Fibrous papules and nevocellular nevi. *J Am Acad Dermatol* 1984; **10**: 670–1.
2 Graham JH, Sanders JB, Johnson WC *et al*. Fibrous papule of the nose. *J Invest Dermatol* 1965; **45**: 194–203.
3 Meigel WN, Ackerman AB. Fibrous papule of face. *Am J Dermatopathol* 1979; **1**: 329–40.
4 Saylan T, Marks R, Wilson Jones E. Fibrous papule of the nose. *Br J Dermatol* 1971; **85**: 111–8.
5 Yamamoto T, Katayama I, Nishioka K. Fibropapule multiplex of the nose: a variant of Cowden's disease? *Dermatology* 1996; **192**: 379–81.
6 Kucher C, McNiff JM. Epithelioid fibrous papule—a new variant. *J Cutan Pathol* 2007; **34**: 571–5.
7 Lee AN, Stein SL, Cohen LM. Clear cell fibrous papule with NKI/C3 expression: clinical and histologic features in six cases. *Am J Dermatopathol* 2005; **27**: 296–300.
8 Spiegel J, Nadji M, Penneys NS. Fibrous papule: an immunohistochemical study with an antibody to S-100 protein. *J Am Acad Dermatol* 1963; **9**: 360–2.

Storiform collagenoma [1,2]

Synonym
- Sclerotic fibroma

Definition. Storiform collagenoma is a fibrous hypocellular cutaneous lesion which, when multiple, may be associated with Cowden's disease or PTEN hamartoma syndrome (multiple hamartoma and neoplasia syndrome; see Chapter 62) [3].

Clinical features. It usually presents as a small, solitary, asymptomatic papule in adults of either sex, with wide anatomical distribution.

Pathology. It typically consists of a fairly well-circumscribed dermal nodule with prominent, hypocellular, hyalinized collagen bundles in a storiform pattern (Fig. 56.2). Bland spindle-shaped cells are rare. A similar histological pattern may be seen in the late stages of lesions as diverse as pleomorphic fibroma, fibrous histiocytoma (FH) and myofibroma and it has been proposed that it does not represent a distinctive entity but a reaction pattern [4,5].

A more cellular variant containing multinucleated bizarre cells has been described as giant cell collagenoma [6]. The latter is a potential link between pleomorphic fibroma (see below) and sclerotic fibroma as it has been proposed that both entities are part of the same spectrum [7].

Treatment. Simple excision is curative.

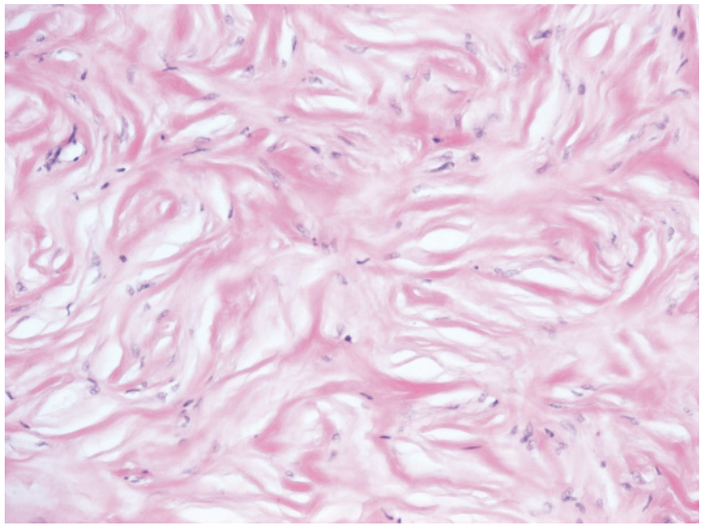


Fig. 56.2 Storiform collagenoma. Poorly cellular stroma composed of hyalinized collagen in a storiform pattern.

References

1 Rapini RP, Golitz LE. Sclerotic fibromas of the skin. *J Am Acad Dermatol* 1989; **20**: 266–71.
2 Metcalf JS, Maize JC, LeBoit PE. Circumscribed storiform collagenoma (sclerosing fibroma). *Am J Dermatopathol* 1991; **13**: 122–9.
3 Starink TM, Meijer CJLM, Brownstein MH. The cutaneous pathology of Cowden's disease: new findings. *J Cutan Pathol* 1985; **12**: 83–93.
4 Chen TM, Purohit SK, Wang AR. Pleomorphic sclerotic fibroma: a case report and literature review. *Am J Dermatopathol* 2002; **24**: 54–8.
5 High WA, Stewart D, Essary LR *et al*. Sclerotic fibroma-like change in various neoplastic and inflammatory skin lesions: is sclerotic fibroma a distinct entity? *J Cutan Pathol* 2004; **31**: 373–8.
6 Rudolph P, Schubert C, Harms D *et al*. Giant cell collagenoma: a benign dermal tumor with distinctive multinucleate cells. *Am J Surg Pathol* 1998; **22**: 57–63.
7 García Doval I, Casas L, Toribio J. Pleomorphic fibroma of the skin, a form of sclerotic fibroma: an immunohistochemical study. *Clin Exp Dermatol* 1998; **23**: 22–4.

Pleomorphic fibroma

Definition [1]. Pleomorphic fibroma is a relatively rare lesion with features very similar to those of a fibroepithelial polyp (skin tag), but characterized histologically by bizarre mono- or multinucleated stromal cells.

Clinical features. Lesions present in adults as a polyp, with no sex predilection and a wide anatomical distribution, including a subungual location [2].

Pathology. Normal or mildly acanthotic epidermis surrounds a collagenous and vascular stroma containing scattered bizarre mono- or multinucleated cells with hyperchromatic and pleomorphic nuclei. Mitotic figures are rare.

Treatment. Simple excision is curative, and there is no tendency for local recurrence.

References

1 Kamino H, Lee JY, Berke A. Pleomorphic fibroma of the skin: a benign neoplasm with cytologic atypia—a clinicopathologic study of eight cases. *Am J Surg Pathol* 1989; **13**: 107–13.

2 Hsieh YJ, Lin YC, Wu YH *et al*. Subungual pleomorphic fibroma. *J Cutan Pathol* 2003; **30**: 567–71.

Acquired digital fibrokeratoma [1]

Definition. A benign lesion, possibly a reaction to trauma, which occurs on the fingers and toes [2] (Fig. 56.3), although the palms and the soles have occasionally been involved.

Clinical features. The lesion usually occurs in adults as a solitary, dome-shaped lesion, with a collarette of slightly raised skin at its base. Occasionally, it may be elongated or pedunculated. Giant lesions may occasionally occur [3]. The surface may appear to be slightly warty.

There is a wide clinical differential diagnosis, which includes dermatofibroma, viral wart, supernumerary digit and cutaneous horn. Histologically, the lesion is extremely similar to the Koenen tumour [4], the periungual fibrous papule that arises from the nail fold in tuberous sclerosis.

Pathology. The histology shows thick collagen bundles, thin elastic fibres and increased vascularity. Occasionally, there is an obvious increase in fibroblasts, and rarely the collagen bundles may be separated by oedema [5]. The epidermis is relatively normal, but acanthosis and hyperkeratosis may occur.

Treatment. Acquired digital fibrokeratoma is cured by simple excision.

References

1 Hare PJ, Smith AJ. Acquired digital fibrokeratoma. *Br J Dermatol* 1969; **81**: 667–70.
2 Berger RS, Spielvogel RL. Dermal papule on a distal digit. *Arch Dermatol* 1988; **124**: 1559.
3 Kakurai M, Yamada T, Kiyosawa T *et al*. Giant acquired digital fibrokeratoma. *J Am Acad Dermatol* 2003; **48** (5 Suppl.): S67–8.
4 Kint A, Baran R. Histopathologic study of Koenen tumors: are they different from acquired digital fibrokeratoma? *J Am Acad Dermatol* 1988; **18**: 369–72.
5 Kint A, Baran R, de Keyser H. Acquired (digital) fibrokeratoma. *J Am Acad Dermatol* 1985; **12**: 816–21.



Fig. 56.3 Clinical appearance of an acquired digital fibrokeratoma.

Nodular fasciitis [1–4]

Synonym
- Subcutaneous pseudosarcomatous fibromatosis

Definition. A rapidly enlarging subcutaneous nodule, which is due to a benign proliferation of myofibroblasts and fibroblasts and has a superficial resemblance to a sarcoma.

Incidence and aetiology. A number of quite large series have been published in the last 10 years, suggesting that the condition is not uncommon. It is most frequent in young adults, but has been reported in patients from 5 months to 75 years. There is no predilection for either sex. It is not associated with other diseases. There is no evidence that trauma initiates the lesions.

Clinical features [1–4]. The majority of tumours appear as tender, rapidly growing masses beneath the skin. The average size is 1–3 cm in diameter. The commonest situation is the upper extremities, particularly the forearm, but the lesion can occur anywhere, including the orbit and the mouth [5]. Lesions on the head and neck often present in children. In nearly half the patients, the tumour has been noticed for only 2 weeks or less when they come for advice.

Pathology [1–4]. These lesions may look extremely worrying in view of the high mitotic rate and rapid growth (see below). The tumour is only focally circumscribed and it is composed of bundles of fairly uniform fibroblasts and myofibroblasts with pink cytoplasm, vesicular nuclei and a single, small nucleolus. Myxoid change and mucin deposition is often prominent, resulting in a typical tissue culture-like appearance (Fig. 56.4). In the background, there are numerous small, delicate blood vessels, extravasated red blood cells and scattered mononuclear inflammatory cells. Multinucleated giant cells may be seen, and they resemble osteoclasts. Mitoses are usually numerous, but there are no abnormal forms. Hyalinized collagen bundles are often present and may display a keloidal appearance. At the periphery, compact bundles of fibroblasts and capillaries probe the fascial planes and may infiltrate fat or skeletal muscle. It is not surprising that this histological picture is relatively often confused with that of a malignant tumour. Variants of nodular fasciitis include those with metaplastic bone (ossifying fasciitis); a variant that involves the periosteum (periosteal fasciitis); a variant that involves the scalp and tends to occur in children (cranial fasciitis); and a variant within the lumen of a blood vessel (intravascular fasciitis) [6]. A rare variant of intradermal nodular fasciitis has also been described [6,7]. Intra-articular location may also be seen [8]. Tumour cells are variably positive for smooth muscle actin and calponin [9] and usually negative for smooth-muscle markers including desmin and h-caldesmon [10]. The histological diagnosis may be very difficult, especially in small biopsies. Confusion with a sarcoma

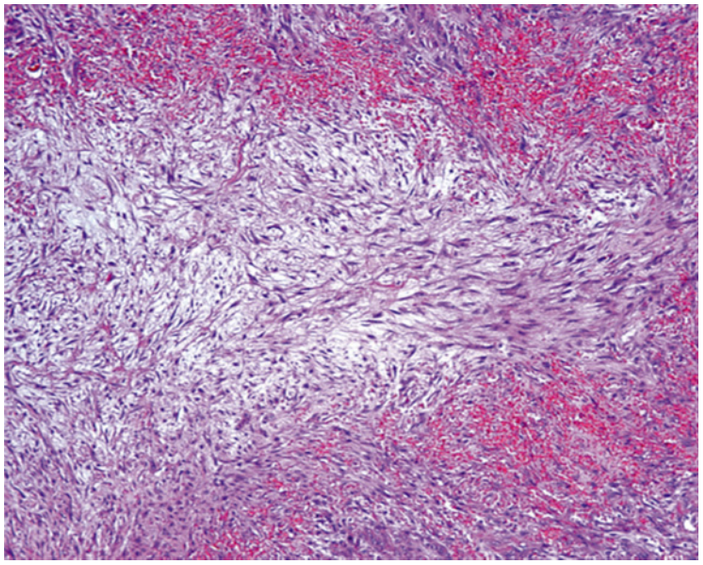


Fig. 56.4 Typical tissue culture-like appearance of nodular fasciitis with prominent myxoid background.

or with fibromatosis are major pitfalls, with obvious detrimental consequences.

Immunohistochemistry may be useful in the distinction between fibromatosis and nodular fasciitis. The former tend to display nuclear beta-catenin positivity, while the latter are usually negative or display cytoplasmic positivity only [11]. However, some fibromatoses, especially those superficially located, are negative for this marker and the diagnosis should be based on careful clinicopathological correlation.

Treatment. Resolution usually follows incomplete surgical removal. Simple excision is therefore an adequate treatment. Local recurrence is exceptional.

References

1 Bernstein KE, Lattes R. Nodular (pseudosarcomatous) fasciitis, a nonrecurrent lesion: clinicopathologic study of 134 cases. *Cancer* 1982; **49**: 1668–78.
2 Konwaler BE, Keasbey L, Kaplan L. Subcutaneous pseudosarcomatous fibromatosis (fasciitis). *J Clin Pathol* 1955; **25**: 241–52.
3 Shimizu S, Hashimoto H, Enjoji M. Nodular fasciitis: an analysis of 250 patients. *Pathology* 1984; **16**: 161–6.
4 Hutter RVP, Stewart FW, Foote FW. Fasciitis: a report of 70 cases with follow-up proving the benignity of the lesion. *Cancer* 1962; **15**: 992–1003.
5 Dayan D, Nasrallah V, Vered M. Clinicopathologic correlations of myofibroblastic tumors of the oral cavity: 1. Nodular fasciitis. *J Oral Pathol Med* 2005; **34**: 426–35.
6 Price S, Kahn L, Saxe N. Dermal and intravascular fasciitis. *Am J Dermatopathol* 1993; **15**: 539–43.
7 Nishi SP, Brey NV, Sanchez RL. Dermal nodular fasciitis: three case reports of the head and neck and literature review. *J Cutan Pathol* 2006; **33**: 378–82.
8 Hornick JL, Fletcher CD. Intrarticular nodular fasciitis—a rare lesion: clinicopathologic analysis of a series. *Am J Surg Pathol* 2006; **30**: 237–41.
9 Pérez-Montiel MD, Plaza JA, Domínguez-Malagón H *et al*. Differential expression of smooth muscle myosin, smooth muscle actin, h-caldesmon, and calponin in the diagnosis of myofibroblastic and smooth muscle lesions of skin and soft tissue. *Am J Dermatopathol* 2006; **28**: 105–11.
10 Ceballos KM, Nielsen GP, Selig MK *et al*. Is anti-h-caldesmon useful for distinguishing smooth muscle and myofibroblastic tumors? An immunohistochemical study. *Am J Clin Pathol* 2000; **114**: 746–53.
11 Bhattacharya B, Dilworth HP, Iocabuzio-Donahue C *et al*. Nuclear beta-catenin expression distinguishes deep fibromatosis from other benign and malignant fibroblastic and myofibroblastic lesions. *Am J Surg Pathol* 2005; **29**: 653–9.

Fibro-osseous pseudotumour of the digits [1,2]

Definition. This is a reactive myofibroblastic proliferation with bone formation, which occurs exclusively on the digits.

Clinical features. It presents predominantly in young adults, with a predilection for females. The fingers are more commonly affected than the toes. The lesion grows rapidly and it is not attached to bone.

Pathology. The tumour is ill-defined and similar to nodular fasciitis, except for the fact that there is formation of osteoid and mature bone. Oedematous stroma, vascular proliferation and bundles of spindle-shaped myofibroblast-like cells are seen intermixed with osteoid and mature bone. Mitotic figures are found and their number depends on the age of the lesion.

Treatment. Local recurrence is rare, and excision is the treatment of choice.

References

1 Dupree WB, Enzinger FM. Fibro-osseous pseudotumor of the digits. *Cancer* 1986; **58**: 2103–9.
2 de Silva MV, Reid R. Myositis ossificans and fibroosseous pseudotumor of digits: a clinicopathological review of 64 cases with emphasis on diagnostic pitfalls. *Int J Surg Pathol* 2003; **11**: 187–95.

Ischaemic fasciitis [1–4]

Synonym
- Atypical decubitus fibroplasia

Definition. Ischaemic fasciitis is a reactive fibroblastic/myofibroblastic proliferation that simulates malignancy and occurs as a result of alterations in local circulation and sustained pressure.

Clinical features. Most patients are elderly and immobilized, and there is a slight predilection for females. The lesion presents as an asymptomatic subcutaneous mass, predominantly over bony prominences that may extend to deeper soft tissues and to the overlying dermis.

Pathology. The lesion is poorly circumscribed and contains areas of fibrosis, vascular proliferation, necrosis and focal myxoid change. Thrombosed blood vessels with recanalization and areas of fibrinoid necrosis, focal haemorrhage and mononuclear inflammatory cells are additional features. In the background, there are variable numbers of spindle-shaped myofibroblasts/fibroblasts with vesicular or hyperchromatic nuclei and a prominent nucleolus. Mitotic figures may be seen, but are not prominent.

Treatment. Excision of the lesion is an adequate treatment.

References

1 Montgomery EA, Meis JM, Mitchell MS *et al*. Atypical decubital fibroplasia: a distinctive fibroblastic pseudotumor occurring in debilitated patients. *Am J Surg Pathol* 1992; **16**: 708–15.
2 Baldassano MF, Rosenberg AE, Flotte TJ. Atypical decubital fibroplasia: a series of three cases. *J Cutan Pathol* 1998; **25**: 149–52.
3 Perosio PM, Weiss SW. Ischemic fasciitis: a juxta-skeletal fibroblastic proliferation with a predilection for elderly patients. *Mod Pathol* 1993; **6**: 69–72.
4 Scanlon R, Kelehan P, Flannelly G *et al*. Ischemic fasciitis: an unsual vulvovaginal spindle cell lesion. *Int J Gynecol Pathol* 2004; **23**: 65–7.

Superficial acral fibromyxoma [1,2]

Definition. Superficial acral fibromyxoma is a distinctive, recently delineated, benign, dermal and/or subcutaneous, fibroblastic tumour with a strong predilection for hands and feet.

Incidence and aetiology. Lesions are relatively rare and are regarded as neoplastic.

Clinical features. Most cases present as a long-standing, solitary mass measuring between 1 and 2 cm, on the hands and feet (particularly the digits, often in a subungual location), of middle-aged adults and with some predilection for males.

Pathology. Tumours are circumscribed and consist of bland stellate and spindle-shaped cells in a variably prominent myxoid and collagenous stroma and with small blood vessels in the background. Some lesions are more cellular and have been described in the literature under the rubric of cellular fibroma of the digits [3]. In myxoid areas, mast cells are often seen. Scattered multinucleated cells may be seen in some cases. Mitotic figures are very rare. Tumour cells are diffusely positive for CD34 and may be focally positive for EMA and CD99.

In the past, it is likely that these tumours were classified as neurofibromas because of the cytomorphology of tumour cells and the myxoid background, with fairly frequent mast cells. However, neurofibroma is rare in acral sites and tumour cells are positive for S100 and only focally positive for CD34.

Prognosis and treatment. These lesions are entirely benign and local recurrence is very rare. Simple local excision is the treatment of choice.

References

1 Fetsch JF, Laskin WB, Mietinnen M. Superficial acral fibromyxoma: a clinicopathologic and immunohistochemical analysis of 37 cases of a distinctive soft tissue tumour with a predilection for the fingers and toes. *Hum Pathol* 2001; **32**: 704–14.
2 André J, Theunis A, Richert B *et al*. Superficial acral fibromyxoma: clinical and pathological features. *Am J Dermatopathol* 2004; **26**: 472–4.
3 McNiff JM, Subtil A, Cowper SE *et al*. Cellular digital fibromas: distinctive CD34-positive lesions that may mimic dermatofibrosarcoma protuberans. *J Cutan Pathol* 2005; **32**: 413–8.

Fibrous hamartoma of infancy [1–5]

Definition. This is a benign, fibroblastic/myofibroblastic, deep dermal and subcutaneous tumour presenting in children and characterized by three distinctive pathological components, as described below.

Incidence and aetiology. This is a rare tumour, often considered to be a hamartoma, but probably neoplastic in nature.

Clinical features. Most cases present in children aged under 2 years, as an asymptomatic, solitary, skin-coloured plaque/nodule only a few centimetres in diameter. Rarely, pigmentary changes and or hypertrichosis may be seen [6]. A quarter of the cases present at birth. Males are more affected than females. The tumour grows rapidly and has a predilection for the axillae, arm and shoulder girdle [1–3]. A familial association has not been reported.

Pathology. The tumour is composed of three components:
1 Bundles of interlacing, elongated, bland, wavy spindle-shaped cells in a variable collagenous background
2 Nests of more immature round cells with focal myxoid change
3 Mature adipose tissue.
A focal resemblance to a neurofibroma may be seen when the first component predominates, but tumour cells are actin-positive and S100-negative [7].

In the dermis overlying the tumour, eccrine glands may show secondary changes including hyperplasia, papillary projections and squamous syringometaplasia [8].

Treatment. Simple excision is the treatment of choice [5]; recurrences are exceptional.

References

1 Enzinger FM. Fibrous hamartoma of infancy. *Cancer* 1965; **18**: 241–8.
2 Mitchell ML, di Sant'Agnese PA, Gerber JE. Fibrous hamartoma of infancy. *Hum Pathol* 1982; **13**: 586–8.
3 Paller AS, Gonzalez-Crussi F, Sherman JO. Fibrous hamartoma of infancy: eight additional cases and a review of the literature. *Arch Dermatol* 1989; **125**: 88–91.
4 Sotelo-Avila C, Bale PM. Subdermal fibrous hamartoma of infancy: pathology of 40 cases and differential diagnosis. *Pediatr Pathol* 1994; **14**: 39–52.
5 Carretto E, Dall'Igna P, Alaggio R *et al*. Fibrous hamartoma of infancy: an Italian multi-institutional experience. *J Am Acad Dermatol* 2006; **54**: 800–3.
6 Yon TY, Kim JW. Fibrous hamartoma of infancy manifesting as multiple nodules with hypertrichosis. *J Dermatol* 2006; **33**: 427–9.
7 Groisman G, Lichtig C. Fibrous hamartoma of infancy: an immunohistochemical and ultrastructural study. *Hum Pathol* 1991; **22**: 914–8.
8 Grynspan D, Meir K, Senger C *et al*. Cutaneous changes in fibrous hamartoma of infancy. *J Cutan Pathol* 2007; **34**: 39–43.

Calcifying fibrous tumour/pseudotumour [1–3]

Definition. This is a rare, benign, hypocellular tumour characterized by dense collagen bundles, areas of calcification and a patchy mononuclear cell infiltrate. This lesion has no relation with inflammatory myofibroblastic tumour as was originally suggested [3].

Clinical features. Most lesions occur in children, and less commonly in young adults, as a fairly large, subcutaneous or deeper asymptomatic mass with a wide anatomical distribution. Cases may also occur in internal organs [3].

Pathology. The tumour typically consists of haphazardly arranged collagen bundles with scattered bland fibroblasts, focal small calcifications and focal aggregates of lymphocytes and plasma cells. Tumour cells are positive for CD34 and may be focally positive for smooth-muscle actin and more rarely for desmin [3].

Treatment. Local recurrence is rare, and the treatment of choice is simple excision.

References

1 Rosenthal NS, Abdul-Karim FW. Childhood fibrous tumor with psammoma bodies. *Arch Pathol Lab Med* 1988; **112**: 565–8.
2 Fetsch JF, Montgomery EA, Meis JM. Calcifying fibrous pseudotumour. *Am J Surg Pathol* 1993; **17**: 502–8.
3 Nascimento AF, Ruiz R, Hornick JL *et al*. Calcifying fibrous 'pseudotumor': clinicopathologic study of 15 cases and analysis of its relationship to inflammatory myofibroblastic tumor. *Int J Surg Pathol* 2002; **10**: 189–96.

Calcifying aponeurotic fibroma [1,2]

Definition. This is a rare, fibroblastic tumour characterized by a nodular proliferation of bland spindle-shaped cells surrounding nodules at different stages of calcification. Cartilage and, less commonly, bone formation may be seen.

Clinical features [1]. Most cases present in children, with a predilection for the hands and, less commonly, the feet. Occurrence at other sites is rare but tumours may present in places as diverse as the knee, the back and the thigh [2]. Tumours are small, slowly growing and usually asymptomatic. Multiple lesions are exceptional [3].

Pathology. The growth pattern is multinodular. Tumour cells are elongated, with scanty pink cytoplasm, vesicular nuclei and very rare mitotic figures. Tumour nodules frequently contain areas of calcification, which are surrounded by tumour cells in a pattern reminiscent of palisading.

Treatment. Local recurrence is observed in up to 50% of the cases, but malignant transformation is exceptional [4] and conservative treatment is therefore indicated.

References

1 Allen PW, Enzinger FM. Juvenile aponeurotic fibroma. *Cancer* 1970; **26**: 857–67.
2 Fetsch JF, Miettinen M. Calcifying aponeurotic fibroma: a clinicopathologic study of 22 cases arising in uncommon sites. *Hum Pathol* 1998; **29**: 1504–10.
3 Hassel B. Calcifying aponeurotic fibroma. A case of multiple primary tumours. Case report. *Scand J Plast Reconstr Surg Hand Surg* 1992; **26**: 115–6.
4 Lafferty KA, Nelson EL, Demuth RJ *et al*. Juvenile aponeurotic fibroma with disseminated fibrosarcoma. *J Hand Surg (Am)* 1986; **11**: 737–40.

Dermatomyofibroma

Synonym
- Dermal plaque-like fibromatosis

Definition [1–4]. A benign, dermal and superficial subcutaneous myofibroblastic proliferation microscopically mimicking a fibromatosis. The tumour, however, has no potential for local recurrence and lacks an infiltrative growth pattern.

Clinical features. It presents as a solitary, asymptomatic, skin-coloured or hypopigmented plaque measuring less than 4 cm in diameter. Multiple lesions are rarely seen and an exceptional case has presented with a linear pattern [5]. Most lesions occur on the trunk, and there is a predilection for young adults, particularly females. Children are only exceptionally affected [6].

Pathology. Low-power examination reveals a plaque-like proliferation of fascicles of myofibroblast-like cells with an almost parallel orientation to the epidermis. Tumour cells are bland, and mitotic figures are very rare. The tumour does not destroy adnexal structures, but may extend focally into the subcutaneous tissue. Rare cases with haemorrhage may mimic plaque-stage Kaposi's sarcoma [7]. The latter, however, is always positive for human herpes virus 8 (HHV8). Tumour cells are variably positive for smooth-muscle actin and calponin.

Treatment. Simple excision is curative.

References

1 Hugol H. Die plaqueformige dermale Fibromatose. *Hautarzt* 1991; **42**: 223–6.
2 Kamino H, Reddy VB, Gero M *et al*. Dermatomyofibroma: a benign cutaneous plaque-like proliferation of fibroblasts and myofibroblasts in young adults. *J Cutan Pathol* 1992; **19**: 85–91.
3 Mentzel T, Calonje E, Fletcher CDM. Dermatomyofibroma-additional observations of a distinctive cutaneous myofibroblastic tumour with emphasis on differential diagnosis. *Br J Dermatol* 1993; **129**: 69–73.
4 Colome MI, Sanchez RL. Dermatomyofibroma: report of two cases. *J Cutan Pathol* 1994; **21**: 371–6.
5 Trotter MJ, McGregor GI, O'Connell JX. Linear dermatomyofibroma. *Clin Exp Dermatol* 1996; **21**: 307–9.
6 Mortimore RJ, Whitehead KJ. Dermatomyofibroma: a report of two cases, one occurring in a child. *Australas J Dermatol* 2001; **42**: 22–5.
7 Mentzel T, Kutzner H. Haemorrhagic dermatomyofibroma (plaque-like dermal fibromatosis): clinicopathological and immunohistochemical analysis of three cases resembling plaque-stage Kaposi's sarcoma. *Histopathology* 2003; **29**: 426–9.

Angiomyofibroblastoma [1–4]

Definition. Angiomyofibroblastoma is a distinctive, benign neoplasia that occurs almost always in the pelvis and perineum, particularly affecting the vulva. There is some overlap with another tumour that presents in the pelvis and perineum (cellular angiofibroma, see below) and also with aggressive angiomyxoma [5].

Clinical features. Tumours are rare and present mainly in the vulva of young to middle-aged females and rarely elderly women. Cases in males are exceptional and usually affect the scrotum. Lesions are subcutaneous, asymptomatic and measure less than 5 cm in diameter.

Pathology. Lesions are well-circumscribed and consist of a mixture of round and spindle-shaped bland cells in a myxoid or oedematous stroma with numerous small, dilated blood vessels. There is a tendency for tumour cells to surround the vascular

channels. Mitotic activity is not usually present. In a number of cases there are collections of mature adipocytes [4].

Cytological atypia secondary to degeneration is sometimes seen. Tumour cells are positive for desmin and for oestrogen and progesterone receptors. They are only focally positive for smooth-muscle actin and muscle-specific actin. Some tumours are variably positive for CD34.

Prognosis and treatment. Tumours are benign with no tendency for local recurrence. The treatment is simple excision. Only one malignant tumour has been reported [6].

References

1 Fletcher CD, Tsang WY, Fisher C *et al*. Angiomyofibroblastoma of the vulva. A benign neoplasm distinct from aggressive angiomyxoma. *Am J Surg Pathol* 1992; **16**: 373–82.
2 Hisaoka M, Kouho H, Aoki T *et al*. Angiomyofibroblastoma of the vulva: a clinicopathologic analysis of 7 cases. *Pathol Int* 1995; **45**: 487–92.
3 Nielsen GP, Rosenberg AE, Young RH *et al*. Angiomyofibroblastoma of the vulva and vagina. *Mod Pathol* 1996; **9**: 284–91.
4 Laskin WB, Fetsch JF, Tavasoli FA. Angiomyofibroblastoma of the female genital tract analysis of 17 cases including a lipomatous variant. *Hum Pathol* 1997; **28**: 1046–55.
5 Granter SR, Nucci MR, Fletcher CD. Aggressive angiomyxoma: reappraisal of its relationship to angiomyofibroblastoma in a series of 16 cases. *Histopathology* 1997; **30**: 3–10.
6 Nielsen GP, Young RH, Dickersin GR *et al*. Angiomyofibroblastoma of the vulva with sarcomatous transformation ('angiomyofibrosarcoma'). *Am J Surg Pathol* 1997; **21**: 1104–8.

Cellular angiofibroma [1–4]

Synonym
- Male angiomyofibroblastoma-like tumour

Definition. Cellular angiofibroma is a distinctive, benign neoplasm that occurs almost exclusively in the vulva and less commonly in the scrotum and inguinal soft tissues of men. Some cases overlap histologically with angiomyofibroblastoma and a relationship with spindle cell lipoma has been suggested [2].

Clinical features. Tumours are relatively rare, affecting mainly females and presenting as a small, well-circumscribed, asymptomatic, subcutaneous nodule. In males tumours tend to be larger and may be related to a hydrocele or a hernia [2].

Pathology. Tumours are sharply circumscribed but not encapsulated and are characterized by short, usually bland, spindle-shaped cells with scanty, ill-defined pale pink cytoplasm. These cells are arranged in bundles and the degree of cellularity varies. In the background there are thin collagen bundles and numerous small to medium-sized blood vessels. Mitotic figures are rare and cytological atypia may be occasionally seen in some cases. Scattered mononuclear inflammatory cells, mainly lymphocytes, and degenerative changes are often identified. The latter consist of haemorrhage, thrombosis, hyalinization and haemosiderin deposition. In myxoid areas, mast cells are present and many tumours contain variable numbers of mature adipocytes. The most consistent immunohistochemical finding is the presence of diffuse positivity for CD34 in many cases. Muscular markers including actin and desmin tend to be negative but positivity has been reported in male tumours. In a few cases, there is focal positivity for oestrogen and progesterone receptors.

Prognosis and behaviour. Lesions are benign and there is no tendency for local recurrence. Simple excision is the treatment of choice.

References

1 Nucci MR, Granter SR, Fletcher CD. Cellular angiofibroma: a benign neoplasm distinct from angiomyofibroblastoma and spindle cell lipoma. *Am J Surg Pathol* 1997; **21**: 636–644
2 Laskin WB, Fetsch JF, Mostofi FK. Angiomyofibroblastoma-like tumor of the male genital tract: analysis of 11 cases with comparison to female angiomyofibroblastoma and spindle cell lipoma. *Am J Surg Pathol* 1998; **22**: 6–16.
3 Lane JE, Walker AN, Mullis EN Jr *et al*. Cellular angiofibroma of the vulva. *Gynecol Oncol* 2001; **81**: 326–9.
4 Curry JL, Olejnik JL, Wojcik EM. Cellular angiofibroma of the vulva with DNA ploidy analysis. *Int J Gynecol Pathol* 2001; **20**: 200–3.

Elastofibroma [1–3]

Definition. Elastofibroma is a reactive, probably degenerative, process of the elastic fibres of deep soft tissues that occurs almost exclusively around the shoulder. Although the lesion is regarded as degenerative, the finding of chromosomal alterations (see below), and of clonality in some cases, has led to the suggestion that it represents a neoplastic process [4].

Clinical features. It presents as an asymptomatic, slowly growing mass on the posterior upper trunk of middle-aged individuals. Lesions in other locations, including internal organs, are exceptional. Multiple lesions are usually bilateral and may be symmetrical [5].

Pathology. The mass is poorly circumscribed, and the appearances are characteristic. Abundant hypocellular hyalinized collagen containing numerous large, thick eosinophilic elastic fibres is the most distinctive feature. Sometimes the fibres are beaded and fragmented. Staining for elastic tissue nicely highlights the changes. Comparative genomic hybridization in a series of elastofibromas has found chromosomal alterations in a percentage of cases. The most common alteration consists of gains at chromosome Xq12-q22 [6].

Treatment. Simple excision is all that is necessary, as the tumours do not have a tendency to recur.

References

1 Jarvi OH, Saxen AE, Hopsu HV *et al*. Elastofibroma: a degenerative pseudotumor. *Cancer* 1969; **23**: 42–63.
2 Nagamine N, Nohara Y, Ito E. Elastofibroma in Okinawa: a clinicopathologic study of 170 cases. *Cancer* 1982; **50**: 1794–805.
3 Fukuda Y, Miyake H, Masuda Y *et al*. Histogenesis of unique elastinophilic fibers of elastofibroma: ultrastructural and immunohistochemical studies. *Hum Pathol* 1987; **18**: 424–9.
4 Hisaoka M, Hashimoto H. Elastofibroma: clonal fibrous proliferation with predominant CD34-positive cells. *Virchows Arch* 2006; **448**: 195–9.

5 Shimizu S, Yasui C, Tateno M *et al*. Multiple elastofibromas. *J Am Acad Dermatol* 2004; **50**: 126–9.
6 Nishio JN, Iwasaki H, Ohjimi Y *et al*. Gain of Xq detected by comparative genomic hybridization in elastofibroma. *Int J Mol Med* 2002; **10**: 277–80.

Infantile myofibromatosis and adult myofibroma [1–6]

Synonyms
- Congenital generalized fibromatosis
- Infantile haemangiopericytoma

Definition. This tumour is composed of cells showing differentiation towards perivascular contractile cells, and has been described in the past as infantile haemangiopericytoma [7]. Infantile myofibromatosis and adult myofibroma/myofibromatosis are best regarded as part of the spectrum of lesions recently described as myopericytomas (see section on tumours of perivascular cells, p. 56.42) [8,9].

Clinical features [1–3]. Most cases of infantile myofibromatosis present before the age of 2 years, with slight male predominance. Congenital tumours occur in up to a third of the cases. Multiple lesions are present in 25% of patients. The preferred sites are the head and neck, followed by the trunk. Familial cases are rare. Involvement of other organs, including the gastrointestinal tract, lungs and bone, is seen in some cases. Multicentric involvement may be associated with mortality. Multiple lesions in the skin and soft tissues behave in a benign fashion and may regress spontaneously. Solitary myofibroma tends to occur in adults, with the same anatomical distribution as that of cutaneous and soft-tissue lesions presenting in infantile myofibromatosis [5,6]; multiple superficial tumours are rarely seen in adults. Intraoral lesions tend to be more common in young adults [10,11]. Exceptionally, associated thrombocytopenia has been reported [12].

Pathology [1,2,5–8]. Tumours have a distinctive biphasic growth pattern:

1 Areas composed of bundles of mature, spindle-shaped myofibroblasts with pink cytoplasm and vesicular nuclei
2 Areas composed of immature round cells, with scanty cytoplasm arranged around small blood vessels, often displaying a haemangiopericytoma-like pattern ('staghorn-like').

Protrusion of tumour cells into vascular lumina is frequent, often mimicking vascular invasion. Old lesions often undergo hyalinization of the more mature areas. Mitotic figures and necrosis are relatively common. Tumour cells, particularly in the mature areas, are focally positive for actin.

Treatment. Lesions tend to regress spontaneously, but it is important to remember that patients with visceral tumours may die from the disease. Solitary lesions are treated by simple excision and do not tend to recur locally.

References

1 Chung EB, Enzinger FM. Infantile myofibromatosis. *Cancer* 1981; **48**: 1807–18.
2 Goldberg NS, Bauer BS, Kraus H *et al*. Infantile myofibromatosis: a review of clinicopathology with perspectives on new treatment choices. *Pediatr Dermatol* 1988; **5**: 37–46.
3 Coffin CM, Neilson KA, Ingels S *et al*. Congenital generalized myofibromatosis: a disseminated angiocentric myofibromatosis. *Pediatr Pathol Lab Med* 1995; **15**: 571–87.
4 Roggli VL, Kim HS, Hawkins E. Congenital generalized fibromatosis with visceral involvement: a case report. *Cancer* 1980; **45**: 954–60.
5 Beham A, Badve S, Suster S *et al*. Solitary myofibroma in adults: clinicopathological analysis of a series. *Histopathology* 1993; **22**: 335–41.
6 Daimaru Y, Hashimoto H, Enjoji M. Myofibromatosis in adults (adult counterpart of infantile myofibromatosis). *Am J Surg Pathol* 1989; **13**: 859–65.
7 Mentzel T, Calonje E, Nascimento AG *et al*. Infantile hemangiopericytoma versus infantile myofibromatosis: study of a series suggesting a continuous spectrum of infantile myofibroblastic lesions. *Am J Surg Pathol* 1994; **18**: 922–30.
8 Granter SR, Badizadegan K, Fletcher CDM. Myofibromatosis in adults, glomangiopericytoma and myopericytoma: a spectrum of tumors showing perivascular myoid differentiation. *Am J Surg Pathol* 1998; **22**: 513–25.
9 Mentzel T, Dei Tos AP, Sapi Z *et al*. Myopericytoma of skin and soft tissues: clinicopathologic and immunohistochemical study of 54 cases. *Am J Surg Pathol* 2006; **30**: 104–13.
10 Vered M, Allon J, Buchner A *et al*. Clinico-pathologic correlations of myofibroblastic tumors of the oral cavity. II. Myofibroma and myofibromatosis of the oral soft tissues. *J Oral Pathol Med* 2007; **36**: 304–14.
11 Foss RD, Ellis GL. Myofibromas and myofibromatosis of the oral region: A clinicopathologic analysis of 79 cases. *Oral Surg Oral Med* 2000; **89**: 57–65.
12 Leon-Villapalos J, Wolfe K, Calonje E *et al*. Involuting solitary cutaneous infantile myofibroma and thrombocytopaenia: a previously unreported clinical association. *J Plast Reconstr Aesthet Surg* 2007; **60**: 1260–2.

Inclusion body (digital) fibromatosis [1–3]

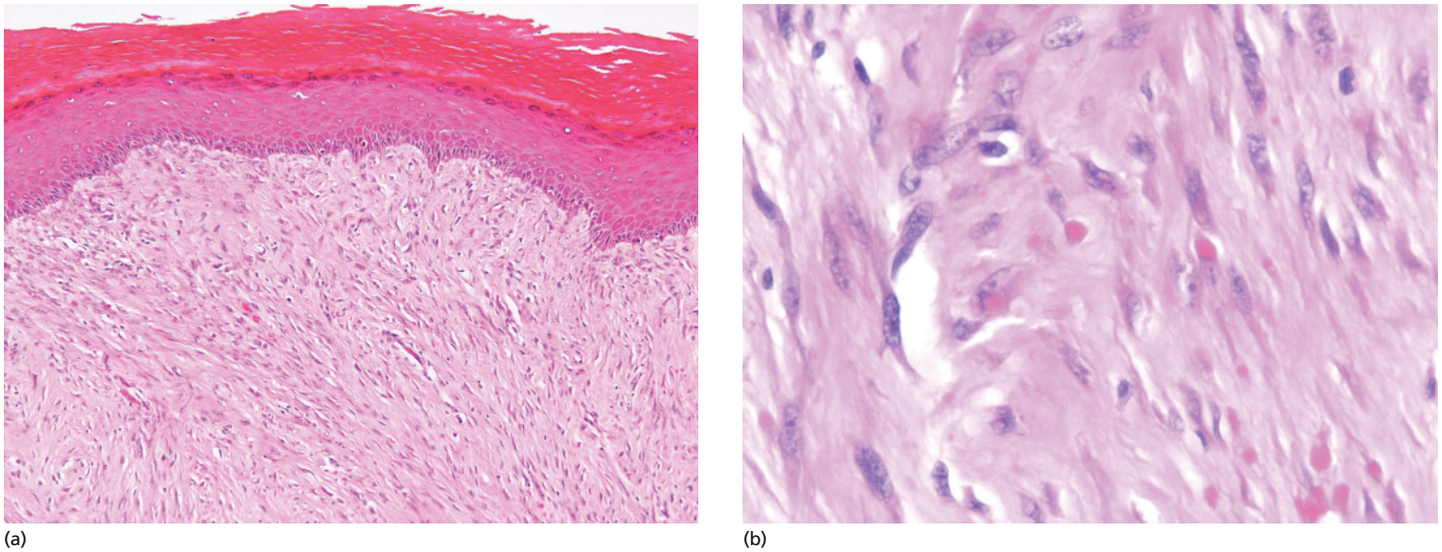
Synonym
- Infantile digital fibromatosis

Definition. Inclusion body fibromatosis is a fibro/myofibroblastic proliferation that almost only occurs on the fingers and toes. It is characterized by bright, round, intracytoplasmic, eosinophilic inclusions.

Clinical features. Most lesions present either at birth or during the first year of life as small, multiple nodules with predilection for the third, fourth and fifth digits. Involvement of the first digits (thumb and hallux) does not occur. New lesions often develop over a long period of time. Only rare cases have been described at other sites or in adults [4,5]. Spontaneous regression is sometimes seen [6]. Aggressive behaviour has not been described.

Pathology. Monomorphic bundles of bland, myofibroblast-like cells are seen in the dermis (Fig. 56.5a) and often the subcutis. Tumour cells have vesicular nuclei, an inconspicuous nucleolus and pink cytoplasm. Some mitotic figures may be seen. A distinctive feature is the presence of variable numbers of small, round, eosinophilic, intracytoplasmic inclusions in tumour cells (Fig. 56.5b). These are periodic acid–Schiff (PAS)-negative, but stain red with Masson's trichrome. They also stain for actin.

Treatment. Simple excision may be required for lesions that interfere with function, but simple observation of histologically confirmed lesions may be all that is necessary.



(a) (b)

Fig. 56.5 (a) Bundles of bland myofibroblast-like cells in the dermis in a case of inclusion body fibromatosis. (b) Numerous typical eosinophilic intracytoplasmic eosinophilic inclusions.

References

1 Reye R. Recurring digital fibrous tumors of childhood. *Arch Pathol* 1965; **80**: 228–36.
2 Beckett JH, Jacobs AH. Recurring digital fibrous tumors of childhood: a review. *Pediatrics* 1977; **59**: 401–6.
3 Choi KC, Hashimoto K, Setoyama M *et al.* Infantile digital fibromatosis: immunohistochemical and immunoelectron microscopic studies. *J Cutan Pathol* 1990; **17**: 225–32.
4 Purdy LJ, Colby TV. Infantile digital fibromatosis occurring outside the digit. *Am J Surg Pathol* 1984; **8**: 787–90.
5 Viale G, Doglioni C, Iuzzolino P *et al.* Infantile digital fibromatosis-like tumor (inclusion body fibromatosis) of adulthood: report of two cases with ultrastructural and immunocytochemical findings. *Histopathology* 1988; **12**: 415–24.
6 Kawaguchi M, Mitsuhashi Y, Hozumi Y *et al*. A case of infantile digital fibromatosis with spontaneous regression. *J Dermatol* 1998; **25**: 523–6.

Fibroma of tendon sheath [1,2]

Definition. This is a distinctive, well-circumscribed fibroblastic tumour, presenting almost exclusively on the distal extremities.

Clinical features [1,2]. It is a small, slowly growing, asymptomatic tumour, presenting in young to middle-aged adults and with a marked predilection for the distal upper limb, particularly the hand and fingers. Rare lesions may present with carpal tunnel syndrome [3]. Lesions on the foot are much less common.

Pathology [1,2]. The neoplasm is multilobular and well-circumscribed and consists of cellular or poorly cellular areas on a background of variably hyalinized stroma. Stromal clefting is usually prominent. Tumour cells are spindle-shaped, with scanty cytoplasm and vesicular nuclei. Cytological atypia tends to be absent, and the mitotic count is low. A t(2;11)(q31-32;q12) has been demonstrated in a case of fibroma of tendon sheath [4].

Treatment. About 25% of cases recur locally, but the growth is not destructive. Simple excision is therefore the treatment of choice.

References

1 Chung EB, Enzinger FM. Fibroma of tendon sheath. *Cancer* 1979; **19**: 45–54.
2 Pulitzer DR, Martin PC, Reed RJ. Fibroma of tendon sheath: a clinicopathologic study of 32 cases. *Am J Surg Pathol* 1989; **13**: 472–9.
3 Tiong WH, Ismael TS, Regan PJ. Fibroma of tendon sheath: a rare cause of carpal tunnel syndrome. *J Hand Surg (Br)* 2006; **31**: 579–80.
4 Dal Cin P, Sciot R, De Smet L *et al*. Translocation 2;11 in a fibroma of tendon sheath. *Histopathology* 1998; **32**: 433–5.

Collagenous fibroma [1,2]

Synonym
- Desmoplastic fibroblastoma

Definition. Collagenous fibroma represents a distinctive, subcutaneous, fibroblastic tumour consisting of a prominent collagenous stroma.

Clinical features. It is relatively common and presents in adults as an asymptomatic nodule less than 4 cm in diameter, at any body site.

Pathology. This is a well-circumscribed tumour composed of bland elongated or stellate cells, with a background collagenous stroma and focal myxoid change. Mitotic figures are very rare. A translocation t(2;11)(q31;q12) has been found in two cases of collagenous fibroma suggesting that this is a non-random association in this type of tumour [3].

Treatment. Simple excision is the treatment of choice, as there is no tendency for local recurrence.

References

1 Evans HL. Desmoplastic fibroblastoma: a report of seven cases. *Am J Surg Pathol* 1995; **19**: 1077–81.

2 Mietinnen M, Fetsch JF. Collagenous fibroma (desmoplastic fibroblastoma): a clinicopathological analysis of 63 cases of a distinctive soft tissue lesion with stellate-shaped fibroblasts. *Hum Pathol* 1998; **29**: 676–82.
3 Bernal K, Nelson M, Neff JR *et al*. Translocation (2;11)(q31;q12) is recurrent in collagenous fibroma (desmoplastic fibroblastoma). *Cancer Genet Cytogenet* 2004; **149**: 161–3.

Nuchal fibroma [1,2]

Definition. Nuchal fibroma is a dermal or subcutaneous tumour consisting of hypocellular dense collagen.

Clinical features. Tumours are rare and occur in adult males. Patients often have diabetes. The great majority of cases present on the nape of the neck. Coexistence with scleroedema is possible, probably reflecting the association with diabetes, and lesions identical to nuchal fibroma are now recognized to occur in Gardner's syndrome (Chapter 62) and are known as Gardner-associated fibromas [3,4]. The latter may be multiple, present in various locations and may recur. These lesions may be the first clue as to the existence of Gardner's syndrome.

Pathology. Dense aggregates of collagen with very few cells and entrapment of adipose tissue.

Treatment. Simple excision is the treatment of choice but local recurrence is possible.

References

1 Balachandran K, Allen RW, McCormac LB. Nuchal fibroma: a clinicopathological analysis of nine cases. *Am J Surg Pathol* 1995; **19**: 313–7.
2 Michal M, Fetsch JF, Hes O *et al*. Nuchal-type fibroma: a clinicopathologic study of 52 cases. *Cancer* 1999; **85**: 156–63.
3 Wehrli BM, Weiss SW, Yandow S *et al*. Gardner-associated fibromas (GAF) in young patients: a distinct fibrous lesion that identifies unsuspected Gardner syndrome and risk for fibromatosis. *Am J Surg Pathol* 2001; **25**: 645–61.
4 Non-nuchal-type fibroma associated with Gardner's syndrome. A hitherto-unreported mesenchymal tumor different from fibromatosis and nuchal-type fibroma. *Pathol Res Pract* 2000; **196**: 857–60.

Palmar and plantar fibromatosis (superficial fibromatoses) [1,2]

Synonym Plantar fibromatosis
- Ledderhose's disease

Synonyms Palmar fibromatosis
- Dupuytren's disease
- Dupuytren's contracture

Definition. Palmar and plantar fibromatoses are superficial neoplastic proliferations of fibroblasts and myofibroblasts that have a tendency for local recurrence, but do not metastasize.

Incidence and aetiology. Palmar fibromatosis is more common than plantar fibromatosis. Both lesions are more common in men, but the sex difference is more marked in palmar lesions. Both conditions affect middle-aged to elderly patients and are more uncommon in younger individuals. However, children may rarely be affected, particularly by plantar fibromatosis [3]. Affected patients are mainly of Northern European origin; non-whites are rarely affected. Coexistence between the two variants of fibromatoses and desmoid tumours, penile fibromatosis (Peyronie's disease) and knuckle pads may be seen. Genetic predisposition, as well as trauma, is thought to play an important role in the pathogenesis of these conditions. Associations with diabetes, alcoholic liver disease and epilepsy have also been described.

Clinical features. Palmar fibromatosis presents as indurated nodules or as an ill-defined area of thickening, bilateral in about 50% of cases, that may result in contracture. Plantar fibromatosis usually consists of a single nodule. Functional limitation is common.

Pathology. Early lesions are fairly cellular and consist of bundles of bland fibroblasts with some collagen deposition. The latter increases considerably in older lesions. Interestingly, although superficial fibromatoses are very similar histologically to deep fibromatosis (abdominal, extra-abdominal and mesenteric fibromatosis), the behaviour of superficial fibromatosis is not usually aggressive. This may be due to the fact that deep fibromatosis often display mutations of the *APC* gene or somatic mutations of the gene encoding beta-catenin, while these mutations are absent in superficial fibromatosis. Intriguingly however, although deep fibromatoses often display nuclear expression of beta-catenin, this is also seen in a smaller percentage of superficial fibromatoses without gene mutations [4].

Treatment. Complete excision is desirable, as there is otherwise a risk of local recurrence.

References

1 Allen PW. The fibromatoses: a clinicopathologic classification based on 140 cases. *Am J Surg Pathol* 1977; **1**: 255–70.
2 Mikkelsen OA. Dupuytren's disease: initial symptoms, age of onset and spontaneous course. *Hand* 1977; **9**: 11–5.
3 Fetsch JF, Laskin WB, Miettinen M. Palmar-plantar fibromatosis in children and pre-adolescents: a clinicopathologic study of 56 cases with newly recognized demographics and extended follow-up information. *Am J Surg Pathol* 2005; **29**: 1095–105.
4 Montgomery E, Lee JH, Abraham SC *et al*. Superficial fibromatoses are genetically distinct from deep fibromatosis. *Mod Pathol* 2001; **14**: 695–701.

Penile fibromatosis [1–3]

Synonym
- Peyronie's disease

Definition. Although usually regarded as a variant of superficial fibromatosis, it is more likely that this disease represents a reactive fibrotic disorder of unknown aetiology.

Clinical features. It presents as a solitary nodule or multiple nodules close to the corpus cavernosum on the dorsal surface of the shaft. Most patients are middle-aged, and in most the lesion is small. Pain and curvature of the penis on erection are frequent complaints. The presence of diabetes mellitus increases the severity of the disease [4].

Pathology. In early lesions, there is a patchy chronic mononuclear inflammatory cell infiltrate and focal vasculitic changes. These changes lead to dense bands of hyalinized collagen in late stages.

References

1 Smith BH. Peyronie's disease. *Am J Clin Pathol* 1966; **85**: 670–8.
2 McRoberts JW. Peyronie's disease. *Surg Gynecol Obstet* 1969; **129**: 1291–4.
3 Billig R, Baker R, Immergut Maxted W. Peyronie's disease. *Urology* 1975; **6**: 409–18.
4 Kendirci M, Trost L, Sikka SC *et al*. Diabetes mellitus is associated with severe Peyronie's disease. *BJU Int* 2007; **99**: 383–6.

Lipofibromatosis [1]

Definition. Lipofibromatosis is a locally aggressive childhood tumour composed of variable amounts of mature adipose and fibroblastic elements.

Clinical features. Tumours present in infants and children, with the majority of cases presenting in the first decade of life. Some tumours are congenital. There is a male predominance. The classical presentation is of a slowly growing, ill-defined mass. There is a predilection for the hands and feet, but other sites in the limbs, and less commonly on the trunk, may be affected. The rate of local recurrence is high.

Pathology. Tumours are infiltrative and consist of lobules of mature adipose tissue intermixed with bundles of fibroblast-like cells with no cytological atypia and low mitotic activity. By immunohistochemistry, tumour cells are focally positive for S100 protein, CD34, bcl-2, actin, EMA and CD99. The lesion closely resembles a fibrous hamartoma of infancy but has more prominent adipose tissue and lacks the third cellular component seen in the latter, which consists of round, primitive-looking cells in a myxoid background.

Prognosis and treatment. In view of the local aggressive nature of this tumour, complete excision is desirable.

Reference

1 Fetsch JF, Miettinen M, Laskin WB *et al*. A clinicopathologic study of 45 soft tissue tumors with an admixture of adipose tissue and fibroblastic elements, and a proposal for classification as lipofibromatosis. *Am J Surg Pathol* 2000; **24**: 1491–500.

Dermatofibrosarcoma protuberans [1–3]

Definition. Dermatofibrosarcoma protuberans (DFSP) is a locally invasive tumour arising in the dermis and showing fibroblastic differentiation.

Incidence and aetiology [1–3]. DFSP is uncommon, more common in black than in white patients, and slightly more common in females than males [4]. Most patients present in the third and fourth decades of life. The incidence in the USA has been estimated as 4.2 cases per million [4]. Some cases develop at the site of previous trauma, reports have included a burn scar [5] and the site of vaccination. Exceptional cases have been associated with previous radiotherapy to the area [6].



Fig. 56.6 Recurrent abdominal dermatofibrosarcoma protuberans.

Clinical features. The tumour is more often situated on the trunk (up to half of the cases), particularly in the flexural regions, than on the extremities or the head [1,2]. Involvement of the limbs is usually proximal. Presentation on hands and feet, particularly on the digits, is vanishingly rare. It may begin in early adult life with one or more small, firm, painless, flesh-coloured or red dermal nodules (Fig. 56.6). There are rare examples of DFSP occurring in infancy [7–9], and congenital cases have been described [9,10].

The tumour starts as a plaque, which may occasionally be atrophic [8,11]. Progression is usually very slow, and may occur over many years; a significant proportion of tumours only become protuberant after a long period of time [12]. Eventually, nodules develop, coalesce and extend, becoming redder or bluish as they enlarge to form irregular, protuberant swellings. At this stage, the base of the lesion is a hard, indurated plaque of irregular outline. In the later stages, a proportion of lesions become painful and there may be rapid growth, ulceration and discharge.

Local recurrence of ordinary DFSP is reported to vary from 15% to up to 60% [3,13,14], and that of the fibrosarcomatous variant is as high as 75% [15–18]. Metastases to lymph nodes and internal organs tend to be extremely rare in pure DFSP [15,19,20] but occur in up to 20% of cases with fibrosarcomatous transformation [16–18].

Pathology [1–3,13]. The tumour is usually a solitary, multinodular mass. The dermis and subcutaneous tissue are replaced by bundles of uniform, spindle-shaped cells with little cytoplasm and elongated hyperchromatic, but not pleomorphic, nuclei. Usually there is little mitotic activity. Deeper involvement may be seen in some cases. Laterally, the tumour cells infiltrate widely between collagen bundles of the deeper dermis and blend into the normal dermis, forming quite definite bands, which interweave or radiate like spokes of a wheel; this is described as a 'storiform' pattern (Fig. 56.7). The interstitial tissue contains collagen fibres, except in the most cellular parts of the tumour. The subcutaneous tissue is

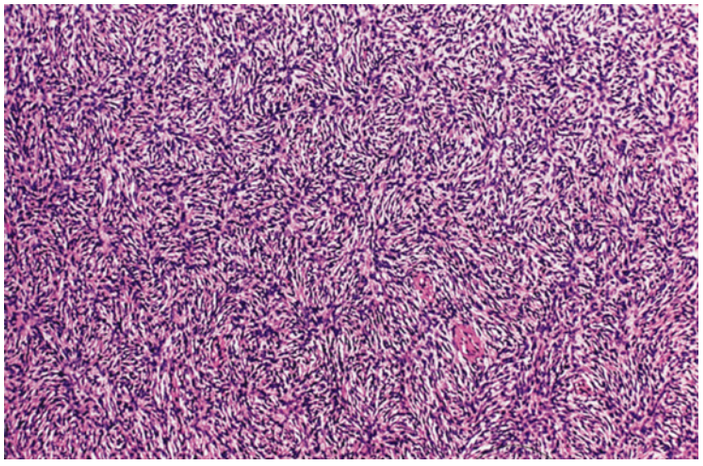


Fig. 56.7 Pathological appearance of dermatofibrosarcoma protuberans, showing the storiform or 'cartwheel' distribution of the fairly uniform, spindle-shaped tumour cells.

extensively infiltrated and replaced in a typical lace-like pattern. Myxoid change may be focal or, rarely, prominent; in the latter setting, the histological diagnosis is difficult [21,22]. Some tumours are colonized by scattered, deeply pigmented melanocytes, a variant known as pigmented DFSP (Bednar tumour) [23,24]. A further variant consists of myoid nodules and is thought to represent myofibroblastic differentiation [25]. Rare cases show focal granular cell change.

Fibrosarcomatous DFSP [16–18,26] is an important variant of this tumour, which is recognized by the focal presence of areas with long, sweeping fascicles of tumour cells intersecting at acute angles in a typical 'herring-bone' pattern, almost identical to that seen in fibrosarcoma. In these areas, mitoses are increased and there is more nuclear hyperchromatism. P53 expression is increased in fibrosarcomatous areas [26]. Identification of the presence of this pattern, and its quantity, is very important, as it is related to metastatic potential. Fibrosarcomatous areas are more common in recurrent tumours.

Very rare variants of DFSP may show areas of high-grade sarcoma either in the primary tumour or in a recurrence [27].

DFSP may show areas of giant cell fibroblastoma (see below) and either tumour may recur, displaying features of the other tumour [28].

The majority of the lesions are positive on staining with the antibody CD34, although this is not specific for DFSP [13]. Other markers are usually negative but in some cases focal positivity for epithelial membrane antigen may be seen. Fibrosarcomatous areas often show decreased staining with CD34 [18].

Cytogenetic studies are helpful, as ring chromosomes indicative of a 17;22 translocation are invariably found [28]. However, it is important to highlight that some cases demonstrate a variant ring chromosome with cryptic rearrangements of chromosomes 17 and 22 [29]. This chromosomal translocation involves the collagen type I alpha 1 (*COL1A1*) gene on chromosome 17 and the platelet-derived growth factor B (*PDGFB*) gene on chromosome 22. The abnormal fusion transcripts resulting from this translocation leads to autocrine stimulation of PDGFB and platelet-derived growth factor receptor beta (PDGFRB) and cell proliferation. The fusion transcript is found in almost all examples of the tumour by polymerase chain reaction (PCR) and fluorescence *in situ* hybridization (FISH) [30]. The same cytogenetic abnormality is found in giant cell fibroblastoma, confirming that both tumours are part of the same spectrum (see below).

Diagnosis. In the early stages, it may be impossible to distinguish this tumour from a histiocytoma or a keloid. Some lesions may also be confused with morphoea profunda. The slow progression, deep red or bluish-red colour, and the characteristic irregular contour and extended plaque-like base, are strongly suggestive of DFSP.

Treatment. The tumour should be excised completely, with a generous margin of healthy tissue [31]. The best chance of achieving a complete cure with no recurrence is early detection of small tumours. Local recurrence invariably follows inadequate removal; the clearance necessary to cure the tumour is often underestimated [32]. A margin of between 2 and 4 cm has been recommended [14,33]. Mohs micrographic surgery has been reported as effective in reducing the rate of local recurrence [34,35]. If this type of treatment is used it should be performed using formalin-fixed paraffin-embedded sections rather than frozen sections, and evaluation should be by an experienced pathologist. Although Mohs surgery clearly reduces the rate of local recurrences, the latter still occur and sometimes this happens more than 5 years after surgery [36]. Postsurgical radiotherapy has been advocated to reduce the rate of local recurrence [37] but this type of treatment has not been assessed in large series of patients. In recent years, it has been demonstrated that imatinib mesylate, a potent inhibitor of a number of protein kinases including the platelet-derived growth factor receptor, results in good clinical response in patients with large unresectable or metastatic tumours [38–42].

References

1 Taylor HB, Helwig EB. Dermatofibrosarcoma protuberans: a study of 115 cases. *Cancer* 1962; **15**: 717–25.

2 Burkhardt BR, Soule EH, Winkelmann RK *et al.* Dermatofibrosarcoma protuberans: study of 56 cases. *Am J Surg* 1966; **111**: 638–44.

3 Gloster HM. Dermatofibrosarcoma protuberans. *J Am Acad Dermatol* 1996; **35**: 355–74.

4 Criscione VD, Weinstock MA. Descriptive epidemiology of dermatofibrosarcoma protuberans in the United States, 1973 to 2002. *J Am Acad Dermatol* 2007; **56**: 968–73.

5 Tanaka A, Hatoko M, Tada H *et al.* Dermatofibrosarcoma protuberans arising from a burn scar of the axilla. *Ann Plast Surg* 2004; **52**: 423–5.

6 Huber GF, Matthews TW, Dort JC. Radiation-induced soft tissue sarcomas of the head and neck. *J Otolaryngol* 2007; **36**: 93–7.

7 McKee PH, Fletcher CDM. Dermatofibrosarcoma presenting in infancy and childhood. *J Cutan Pathol* 1991; **18**: 241–6.

8 Martin L, Combemale P, Dupin MJ *et al.* The atrophic variant of dermatofibrosarcoma protuberans in childhood: a report of six cases. *Br J Dermatol* 1998; **139**: 719–25.

9 Checketts SR, Hamilton TK, Baughman RD. Congenital and childhood dermatofibrosarcoma protuberans: a case report and review of the literature. *J Am Acad Dermatol* 2000; **42**: 907–13.

10 Maire G, Fraitag S, Galmiche L *et al.* A clinical, histologic, and molecular analysis of 9 cases of congenital dermatofibrosarcoma protuberans. *Arch Dermatol* 2007; **143**: 203–10.

11 Zelger BW, Ofner D, Zelger BG. Atrophic variants of dermatofibroma and dermatofibrosarcoma protuberans. *Histopathology* 1995; **26**: 519–27.

12 Martin L, Piette F, Blanc P *et al*. Clinical variants of the preprotuberant stage of dermatofibrosarcoma protuberans. *Br J Dermatol* 2005; **153**: 932–6.
13 Fletcher CDM, Evans BJ, Macartney JC *et al.* Dermatofibrosarcoma protuberans: a clinicopathological and immunohistochemical study with a review of the literature. *Histopathology* 1985; **9**: 921–38.
14 Rutgers EJ, Kroon BB, Albus-Lutter CE *et al*. Dermatofibrosarcoma protuberans: treatment and prognosis. *Eur J Surg Oncol* 1992; **18**: 241–8.
15 McPeak CJ, Cruz T, Nicastri AD. Dermatofibrosarcoma protuberans: an analysis of 86 cases—five with metastasis. *Ann Surg* 1967; **166**: 803–16.
16 Ding J, Hashimoto H, Enjoji M. Dermatofibrosarcoma protuberans with fibrosarcomatous areas: a clinicopathologic study of nine cases and a comparison with allied tumors. *Cancer* 1989; **64**: 721–9.
17 Conelly JH, Evans HL. Dermatofibrosarcoma protuberans: a clinicopathologic review with emphasis on fibrosarcomatous areas. *Am J Surg Pathol* 1992; **16**: 921–5.
18 Mentzel T, Beham A, Katenkamp D *et al*. Fibrosarcomatous ('high grade') dermatofibrosarcoma protuberans. Clinicopathologic study and immunohistochemical study of a series of 41 cases with emphasis on prognostic significance. *Am J Surg Pathol* 1998; **22**: 576–87.
19 Fisher ER, Helstrom HR. Dermatofibrosarcoma with metastases simulating Hodgkin's disease and reticulum cell sarcoma. *Cancer* 1966; **19**: 1165–71.
20 Brenner W, Schaefler K, Chhabra H *et al*. Dermatofibrosarcoma protuberans metastatic to a regional lymph node: report of a case and review. *Cancer* 1975; **36**: 1897–902.
21 Reimann JD, Fletcher CD. Myxoid dermatofibrosarcomas protuberans: a rare variant analyzed in a series of 23 cases. *Am J Surg Pathol* 2007; **31**: 1371–7.
22 Mentzel T, Sharer L, Kazakov DV *et al*. Myxoid dermatofibrosarcoma protuberans: clinicopathologic, immunohistochemical, and molecular analysis of eight cases. *Am J Dermatopathol* 2007; **29**: 443–8.
23 Bednar B. Storiform neurofibromas of the skin, pigmented and nonpigmented. *Cancer* 1957; **10**: 368–75.
24 Fletcher CDM, Theaker JM, Flanagan A *et al.* Pigmented dermatofibrosarcoma protuberans (Bednar tumour): melanocytic colonization or neuroectodermal differentiation? A clinicopathological and immunohistological study. *Histopathology* 1988; **13**: 631–43.
25 Calonje E, Fletcher CDM. Myoid differentiation in dermatofibrosarcoma protuberans and its fibrosarcomatous variant: clinicopathologic analysis of 5 cases. *J Cutan Pathol* 1996; **23**: 30–6.
26 Abbott JJ, Oliveira AM, Nascimento AG. The prognostic significance of fibrosarcomatous transformation in dermatofibrosarcoma protuberans. *Am J Surg Pathol* 2006; **30**: 436–43.
27 Szollosi Z, Nemes Z. Transformed dermatofibrosarcoma protuberans: a clinicopathological study of eight cases. *J Clin Pathol* 2005; **58**: 751–6.
28 Rubin B, Fletcher J, Fletcher CD. The histologic, genetic and histological relationship between dermatofibrosarcoma protuberans and giant cell fibroblastoma: an unexpected story. *Adv Anat Pathol* 1997; **4**: 336–41.
29 Bigby SM, Oei P, Lambie NK *et al*. Dermatofibrosarcoma protuberans: report of a case with a variant ring chromosome and metastases following pregnancy. *J Cutan Pathol* 2006; **33**: 383–8.
30 Patel KU, Szabo SS, Hernandez VS *et al*. Dermatofibrosarcoma protuberans COL1A1-PDGFB fusion is identified in virtually all dermatofibrosarcoma protuberans cases when investigated by newly developed multiplex reverse transcription polymerase chain reaction and fluorescence in situ hybridization assays. *Hum Pathol* 2008; **39**: 184–93.
31 Fiore M, Miceli R, Mussi C *et al*. Dermatofibrosarcoma protuberans treated at a single institution: a surgical disease with a high cure rate. *J Clin Oncol* 2005; **23**: 7669–75.
32 Smola MG, Soyer HP, Scharnagl E. Surgical treatment of dermatofibrosarcoma protuberans: a retrospective study of 20 cases with review of literature. *Eur J Surg Oncol* 1991; **17**: 447–53.
33 Roses DF, Valensi Q, LaTrenta G *et al*. Surgical treatment of dermatofibrosarcoma protuberans. *Surg Gynecol Obstet* 1986; **162**: 449–52.
34 Robinson JK. Dermatofibrosarcoma protuberans resected by Mohs' surgery (chemosurgery): a 5-year prospective study. *J Am Acad Dermatol* 1985; **12**: 1093–8.
35 Thomas CJ, Wood GC, Marks VJ. Mohs micrographic surgery in the treatment of rare aggressive cutaneous tumors: the Geisinger experience. *Dermatol Surg* 2007; **33**: 333–9.
36 Snow SN, Gordon EM, Larson PO *et al*. Dermatofibrosarcoma protuberans: a report on 29 cases treated by Mohs micrographic surgery with long-term follow-up and review of the literature. *Cancer* 2004; **101**: 28–38.
37 Dagan R, Morris CG, Zlotecki RA *et al*. Radiotherapy in the treatment of dermatofibrosarcoma protuberans. *Am J Clin Oncol* 2005; **28**: 537–9.
38 McArthur GA. Molecular targeting of dermatofibrosarcoma protuberans: a new approach to a surgical disease. *J Natl Compr Canc Netw* 2007; **5**: 557–62.
39 Sjöblom T, Shimizu A, O'Brien KP *et al*. Growth inhibition of dermatofibrosarcoma protuberans tumors by the platelet-derived growth factor receptor antagonist ST1571 through induction of apoptosis. *Cancer Res* 2001; **61**: 5778–83.
40 Kondapalli L, Soltani K, Lacouture ME. The promise of molecular targeted therapies: protein kinases inhibitors in the treatment of cutaneous malignancies. *J Am Acad Dermatol* 2005; **53**: 291–302.
41 Price VE, Fletcher JA, Zielenska M *et al*. Imatinib mesylate: an attractive alternative in young children with large, surgically challenging dermatofibrosarcoma protuberans. *Pediatr Blood Cancer* 2005; **44**: 511–5.
42 Sirvent N, Maire G, Pedeutour F. Genetics of dermatofibrosarcoma protuberans family of tumors: from ring chromosomes to tyrosinase inhibitor treatment. *Genes Chromosomes Cancer* 2003; **37**: 1–19.

Giant cell fibroblastoma [1–4]

Definition. This is a locally recurrent, fibroblastic tumour, closely related to DFSP. It is characterized by spindle-shaped, oval or stellate, mono- or multinucleated cells in a fibromyxoid stroma with irregular pseudovascular spaces lined by tumour cells.

Clinical features [1–4]. The large majority of cases present as a subcutaneous, ill-defined mass in the first few years of life. It is rare in young adults and more exceptional in older adults. The trunk is much more commonly involved than the proximal limbs. Tumours measure a few centimetres in diameter, have a predilection for males and tend to be asymptomatic.

Pathology. Solid fibromyxoid areas with variable collagen deposition contain stellate and spindle-shaped mono- and multinucleated tumour cells with hyperchromatic nuclei. Dilated, irregularly branching pseudovascular spaces are commonly seen scattered throughout the lesion. These spaces are lined by tumour cells, which often appear multinucleated (Fig. 56.8). Mitotic figures are exceptional. Aggregates of perivascular lymphocytes in an onion-ring pattern and focal haemorrhage are often seen [4]. Focal areas identical to DFSP may be seen and can occupy a substantial part of the tumour. Excised lesions can recur as a pure giant cell fibroblastoma, as a tumour with focal DFSP, or as pure DFSP [4–7]. Tumour cells are focally positive for CD34 and only very focally positive for actin. Ring chromosomes with sequences of chromosomes 17 and 22, identical to those found in DFSP, have been described in this tumour, confirming their close histogenetic relationship [8,9].

Treatment. Recurrence may be seen in about half of the cases, but metastasis has not been reported.

References

1 Dymock RB, Allen PW, Stirling JW, Gilbert EF, Thornbery JM. Giant cell fibroblastoma: a distinctive, recurrent tumour of childhood. *Am J Surg Pathol* 1987; **11**: 263–71.
2 Shmookler BM, Enzinger FM. Giant cell fibroblastoma: a juvenile form of dermatofibrosarcoma protuberans. *Cancer* 1989; **64**: 2154–61.
3 Chou P, Gonzalez-Crussi G, Mangkornikanok M. Giant cell fibroblastoma. *Cancer* 1989; **63**: 756–62.

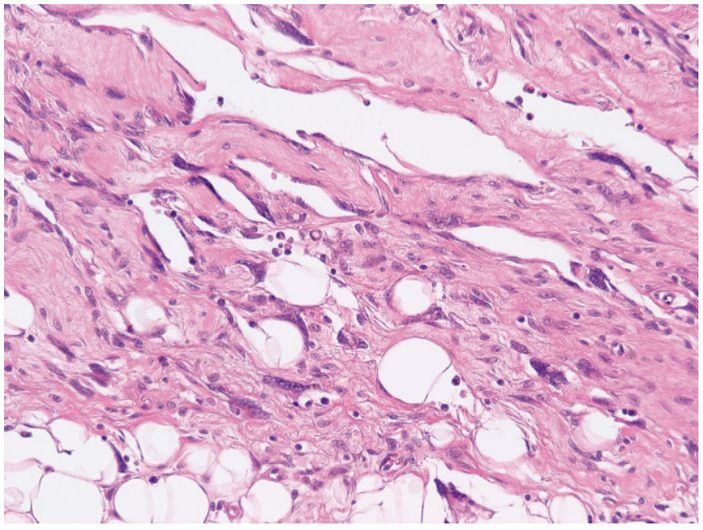


Fig. 56.8 Typical pseudovascular spaces focally lined by multinucleated cells in a case of giant cell fibroblastoma.

4 Jha P, Moosavi C, Fanburg-Smith JC. Giant cell fibroblastoma: un update and addition of 86 cases from the Armed Forces Institute of Pathology, in honor of Dr. Franz M. Enzinger. *Ann Diagn Pathol* 2007; **11**: 81–8.

5 Alguacil-García A. Giant cell fibroblastoma recurring as dermatofibrosarcoma protuberans. *Am J Surg Pathol* 1991; **21**: 184–7.

6 Harvell JD, Kilpatrick SE, White WL. Histogenetic relations between giant cell fibroblastoma and dermatofibrosarcoma protuberans. *Am J Dermatopathol* 1998; **20**: 339–45.

7 Beham A, Fletcher CD. Dermatofibrosarcoma protuberans with areas resembling giant cell fibroblastoma: report of two cases. *Histopathology* 1990; **17**: 165–7.

8 Dal Cin P, Sciot R, de Wever I *et al*. Cytogenetic and immunohistochemical evidence that giant cell fibroblastoma is related to dermatofibrosarcoma protuberans. *Genes Chrom Cancer* 1996; **15**: 73–5.

9 Terrier-Lacombe MJ, Guillou L, Maire G *et al*. Dermatofibrosarcoma protuberans, giant cell fibroblastoma and hybrid lesions in children: clinicopathologic comparative analysis of 28 cases with molecular data—a study of the French Federation of Cancer Centers Sarcoma Group. *Am J Surg Pathol* 2003; **27**: 27–9.

Myxoinflammatory fibroblastic sarcoma [1–3]

Synonyms

- Inflammatory myxohyaline tumour of the distal extremities with virocyte or Reed–Sternberg-like cells
- Acral myxoinflammatory fibroblastic sarcoma

Definition. Myxoinflammatory fibroblastic sarcoma is a distinctive, neoplastic process with marked predilection for acral sites, and with histological features closely mimicking an inflammatory process due to the presence of prominent inflammation and virocyte-like inclusions in the nuclei of tumour cells. The latter features were initially thought to indicate an infectious aetiology. However, no firm evidence of this has yet emerged.

Clinical features. Most patients are middle-aged adults with an equal sex incidence. Characteristically, tumours are long-standing, asymptomatic and slowly growing, usually measuring no more than 4 cm. The great majority occur on acral sites, particularly the hands and wrists, followed by the feet. However, lesions may rarely present elsewhere on the limbs (arm, forearm and thigh) [4] and exceptionally elsewhere in the body, including the neck [5]. Most cases are clinically diagnosed as a ganglion cyst or as a giant cell tumour of tendon sheath.

Pathology. Lesions are lobulated and poorly circumscribed and involve the subcutaneous fat and often extend to the dermis and deeper tissues, sparing bone. Low-power examination is misleading and the initial impression is that of an inflammatory process. Lobules of hyalinized and myxoid tissue containing variable numbers of inflammatory cells are seen. The latter include lymphocytes, histiocytes, neutrophils and less commonly eosinophils and plasma cells. Closer examination reveals variable numbers of neoplastic cells that vary from round to spindle-shaped. Some of these cells may be multinucleated. Round cells mimic ganglion cells with nucleoli resembling viral inclusions. Less commonly, vacuolated tumour cells resembling lipoblasts are seen. Mitotic activity is very low. Immunohistochemistry shows that tumour cells are variably positive for CD34 and CD68 and are rarely positive for smooth-muscle actin and exceptionally for keratin. Very few cases have been subjected to cytogenetic studies [6,7]. In two cases published, one showed a complex karyotype with a reciprocal translocation t(1;10)(p22;q24) and loss of chromosomes 3 and 13 [6] and the other a translocation t(2;6)(q31;p21.3) [7]. These findings support the theory that these lesions are neoplastic.

Prognosis and treatment. The rate of local recurrence is high, varying from 11 to 67% in different series [1,2]. Distal metastases are exceptional and are mainly to regional lymph nodes. The treatment of choice is wide local excision and this often implies amputation.

References

1 Montgomery EA, Devaney KO, Giordano TJ *et al*. Inflammatory myxohyaline tumor of distal extremities with virocyte or Reed-Sternberg-like cells: a distinctive lesion with features simulating inflammatory conditions, Hodgkin's disease, and various sarcomas. *Mod Pathol* 1998; **11**: 384–91.

2 Meis-Kindblom JM, Kindblom LG. Acral myxoinflammatory fibroblastic sarcoma: a low-grade tumor of the hands and feet. *Am J Surg Pathol* 1998; **22**: 911–24.

3 Sakaki M, Hirokawa M, Wakatsuki S *et al*. Acral myxoinflammatory fibroblastic sarcoma: a report of five cases and review of the literature. *Virchows Arch* 2003; **442**: 25–30.

4 Jurcić V, Zidar A, Montiel MD *et al*. Myxoinflammatory fibroblastic sarcoma: a tumor not restricted to acral sites. *Ann Diagn Pathol* 2002; **6**: 272–80.

5 McFarlane R, Meyers AD, Golitz L. Myxoinflammatory fibroblastic sarcoma of the neck. *J Cutan Pathol* 2005; **32**: 375–8.

6 Lambert I, Debiec-Rychter M, Guelinckx P *et al*. Acral myxoinflammatory fibroblastic sarcoma with unique clonal chromosomal changes. *Virchows Arch* 2001; **438**: 509–12.

7 Ida CM, Rolig KA, Hulshizer RL *et al*. Myxoinflammatory fibroblastic sarcoma showing t(2;6)(q31;p21.3) as a sole cytogenetic abnormality. *Cancer Genet Cytogenet* 2007; **177**: 139–42.

Fibrohistiocytic tumours

Giant cell tumour of tendon sheath [1–3]

Definition. This is a benign tumour that in its localized variant occurs mainly on the hands, and consists of a nodular proliferation

of histiocyte-like cells with scattered multinucleated giant cells and variable numbers of mononuclear inflammatory cells. The diffuse variant of this tumour that involves joints is not discussed further in this chapter.

Clinical features. Tumours present mainly on the hands with predilection for the fingers. They are typically between 1 and 3 cm in diameter and asymptomatic, although they may interfere with function. There is a predilection for young females. Multiple tumours are very rare [4].

Pathology. It is a multinodular lesion composed of sheets of histiocyte-like cells with bland vesicular nuclei, intermixed with multinucleated giant cells, foamy cells, siderophages and scattered mononuclear inflammatory cells. Hyalinization, haemosiderin deposition and cholesterol clefts are often seen. No histological features predict lesions that recur locally [3].

Treatment. Excision is the treatment of choice; the rate of local recurrence is around 30%.

References

1 Myers BW, Masi AT, Feigenbaum SL. Pigmented villonodular synovitis and tenosynovitis: a clinical epidemiologic study of 166 cases and literature review. *Medicine* 1980; **59**: 223–38.

2 Ushjima M, Hashimoto H, Tsuneyoshi M *et al.* Giant cell tumor of the tendon sheath (nodular tenosynovitis): a study of 207 cases to compare the large joint group with the common digit group. *Cancer* 1986; **57**: 875–84.

3 Mohaghan H, Salter DM, Al-Nafussi A. Giant cell tumour of tendon sheath (localised nodular tenosynovitis): clinicopathological features of 71 cases. *J Clin Pathol* 2001; **54**: 404–7.

4 Park JW. Multiple separated giant cell tumors of the tendon sheath in a thumb. *J Am Acad Dermatol* 2006; **54**: 540–2.

Fibrous histiocytoma (dermatofibroma) [1–4]

Synonyms
- Histiocytoma cutis
- Subepidermal nodular fibrosis
- Sclerosing angioma

Definition. Fibrous histiocytoma (FH) is a benign dermal and often superficial subcutaneous proliferation of oval cells resembling histiocytes, and spindle-shaped cells resembling fibroblasts and myofibroblasts. Their line of differentiation remains uncertain, but these lesions are descriptively classified as fibrohistiocytic tumours because of the microscopic appearance of the tumour cells. The aetiology of FH is unknown, but recent cytogenetic studies demonstrating clonality favour these lesions being neoplastic [5,6]. The neoplastic nature of FH is also suggested by their clinical persistence and by the frequency of local recurrence of some variants (cellular, aneurysmal and atypical; see below) as well as the exceptional anecdotal metastases of some tumours (cellular and atypical types). The previous theory that they are a dermal response to injury, such as an insect bite, has been challenged [7].

Clinical features. FH is commonest on the limbs and appears as a firm papule, which is frequently yellow-brown in colour and slightly scaly (Fig. 56.9). If the overlying epidermis is squeezed, the 'dimple sign' will be seen, indicating tethering of the overlying epidermis to the underlying lesion. Giant lesions (>5 cm in diameter) are occasionally seen [8] and large tumours are more often encountered in some of the variants (see below). Multiple lesions may develop and eruptive variants have been described. The latter may be familial [9], or may be associated with immunosuppression (HIV) [10], with systemic disease, including autoimmune diseases such as lupus erythematosus and neoplasia, particularly haematological malignancies [11–15], and even with highly active antiretroviral therapy (HAART) [16].



Fig. 56.9 Clinical appearance of a fibrous histiocytoma or dermatofibroma.

A number of clinicopathological variants of FH have been described, which should be recognized by clinicians and pathologists in order to avoid a misdiagnosis of malignancy. These variants include: cellular FH [17,18], aneurysmal FH [19,20], atypical FH (pseudosarcomatous FH, dermatofibroma with monster cells) [21,22] and epithelioid FH [23,24]. A further variant, described as 'atrophic' [25], may mimic a scar and does not usually pose a problem in differential diagnosis. Rare cases may be ulcerated, erosive or lichenoid [26].

Cellular FH represents less than 5% of all FHs [17]. Like ordinary FH, it has a predilection for the limbs of young adults, but it tends to occur more commonly in males. However, the distribution of age and site is wide; cellular FH is not infrequent in children, and on sites such as the head, neck, fingers and toes. The size of these lesions is also larger than that of ordinary FH. Most cellular FHs are less than 2 cm in diameter, but lesions measuring more than 5 cm may occur. Recognition of this variant is important, because it has a local recurrence rate of 25%, and metastases have been reported anecdotally in a small number of cases [18,27].

Aneurysmal FH has the same age and sex distribution as ordinary FH [19,20]. Tumours are usually rapidly growing and may attain a very large size. They clinically mimic a vascular tumour.

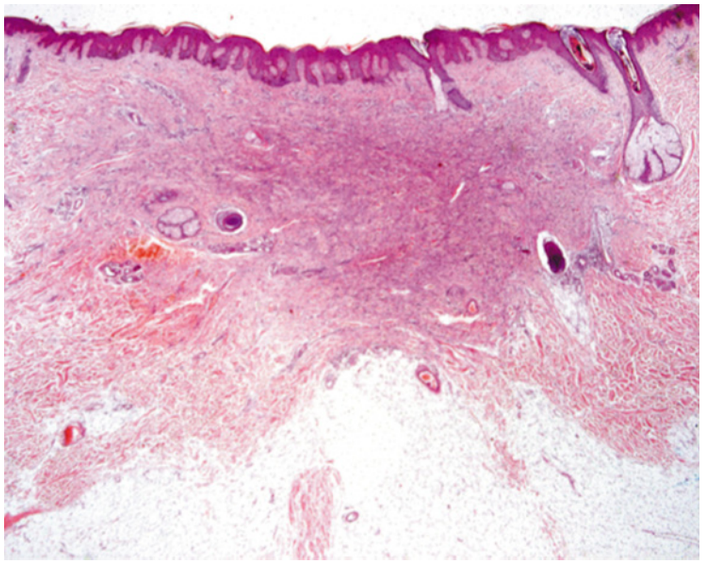


Fig. 56.10 Histological appearance of dermatofibroma, showing epidermal hyperplasia overlying the dermal sclerotic component.

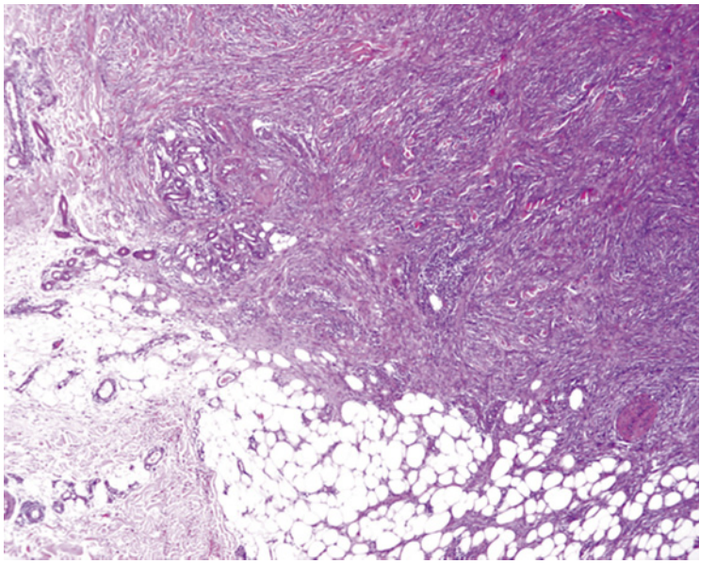


Fig. 56.11 Cellular fibrous histiocytoma. Note the increased cellularity, fascicular appearance and focal extension into the subcutis.

Exceptional tumours are multiple [28]. The rate of local recurrence is 19% [19].

Atypical FH presents mainly in young adults, with a predilection for the lower limbs [21,22]. It is commoner in males than in females. The clinical presentation is that of a papule, nodule or plaque, usually less than 1.5 cm in diameter. The rate of local recurrence is around 14%, and exceptional metastases have been reported [22].

Epithelioid FH [23,24] presents on the limbs of young patients, with a predilection for females. The typical clinical appearance is that of a polypoid, often vascular, lesion resembling a non-ulcerated pyogenic granuloma.

Pathology. The overlying epidermis frequently shows a degree of epidermal hyperplasia [29] (Fig. 56.10). The latter displays different patterns including changes mimicking a squamous papilloma, a seborrhoeic keratosis and lichen simplex chronicus. Occasionally, the epidermal proliferation is associated with immature follicular structures, which are often confused with a basal cell carcinoma. In the dermis, there is a localized proliferation of histiocyte-like cells and fibroblast-like cells, associated with variable numbers of mononuclear inflammatory cells. Foamy macrophages, siderophages and multinucleated giant cells are also variably present. A focal storiform pattern is often seen. The tumour blends with the surrounding dermis. Collagen bundles at the periphery of the lesion are surrounded by scattered tumour cells and appear somewhat hyalinized. As variable expression of factor XIIIa antigen is often seen, it has been suggested that this tumour shows differentiation towards dermal dendrocytes [30]. Focal myofibroblastic differentiation is often suggested, particularly in the cellular variant. Older lesions show focal proliferation of small blood vessels in association with haemosiderin deposition and fibrosis, hence the older name of 'sclerosing haemangioma'.

Cellular FH [17] also shows epidermal hyperplasia, but the lesions are more cellular, less polymorphic and consist of bundles of spindle-shaped cells with pink cytoplasm and a focal storiform pattern (Fig. 56.11). The mitotic rate varies, and necrosis may be found in up to 12% of cases. Extension into the subcutaneous tissue is more prominent than that seen in ordinary FH. However, the pattern of infiltration is mainly along the septae, and only focally into the subcutaneous lobule in a lace-like pattern. The cellularity and growth pattern often make distinction from DFSP difficult, particularly in small biopsies. DFSP is, however, more monomorphic, tends to infiltrate the subcutaneous tissue diffusely and is generally uniformly positive for CD34 [30]. Cellular FH may be focally positive for CD34, but this is predominantly seen at the periphery of the tumour. Staining for FXIIIa is positive in FH and negative in DFSP. Furthermore, cellular FH is often focally positive for smooth muscle actin, whereas this marker is negative in DFSP.

Aneurysmal FH [19,20] shows extensive haemorrhage, with prominent cavernous-like pseudovascular spaces (Fig. 56.12) which are not lined by endothelial cells. The mitotic rate varies, but may be prominent. The background is that of an ordinary FH.

Atypical FH [21,22] shows variable numbers of mono- or multinucleated, pleomorphic, spindle-shaped or histiocyte-like cells on a background of an ordinary FH. These cells may be very prominent, making the histological diagnosis difficult. Mitotic figures, including atypical forms, may be seen. These lesions used to be classified as 'atypical fibroxanthoma occurring in non-sun-exposed skin of young patients'.

Epithelioid FH [23,24] contains a predominant population of cells with abundant pink cytoplasm and vesicular nuclei, and there is often myxoid change and a prominent vascular component. Distinction from a Spitz naevus may be difficult, but in epithelioid

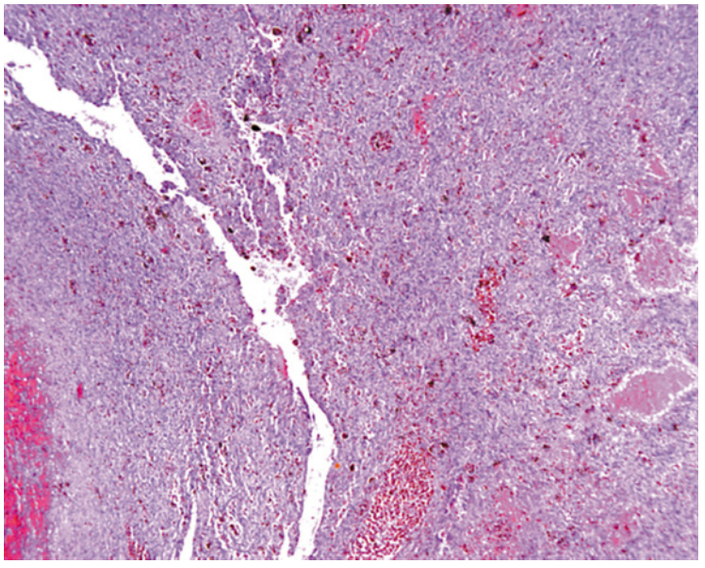


Fig. 56.12 Aneurysmal fibrous histiocytoma. Prominent haemorrhage and cavernous-like spaces obscure the typical background of a fibrous histiocytoma.

FH there is no junctional component, tumour cells are not nested and they are negative for S100.

Many histological variants of FH have been described; recognizing these variants is important to avoid misdiagnosis. They include lesions with palisading, granular cell change [31], abundant lipid (ankle-type) [32], clear cell change [33], balloon cell change [34] and keloidal change [35]. The presence of lipid within lesions of FH is not usually associated with systemic lipid abnormalities [36].

Treatment. Most FHs are no more than a cosmetic nuisance, and no treatment is necessary. However, cellular, atypical and aneurysmal variants should be completely removed, because of the risk of local recurrence and the occurrence of occasional distant metastases in the first two variants.

References

1 Niemi KM. The benign fibrohistiocytic tumours of the skin. *Acta Dermatol Venereol (Stockh)* 1970; **50** (Suppl. 63): 7–42.
2 Vilanova JR, Flint A. The morphologic variants of histiocytomas. *J Cutan Pathol* 1974; **1**: 155–64.
3 Gonzáles S, Duarte I. Benign fibrous histiocytoma of the skin: a morphologic study of 290 cases. *Pathol Res Pract* 1982; **174**: 379–91.
4 Calonje E, Fletcher CDM. Cutaneous fibrohistiocytic tumors: an update. *Adv Anat Pathol* 1994; **1**: 2–15.
5 Vanni R, Marras S, Faa G *et al*. Cellular fibrous histiocytoma of the skin: evidence of a clonal process with different karyotype from dermatofibrosarcoma. *Genes Chromosomes Cancer* 1997; **18**: 314–7.
6 Calonje E. Dermatofibroma (fibrous histiocytoma): an inflammatory or neoplastic disorder? *Histopathology* 2001; **39**: 213.
7 Evans J, Clarke T, Mattacks CA *et al*. Dermatofibromas and arthropod bites: is there any evidence to link the two? *Lancet* 1989; **ii**: 36–7.
8 Requena L, Farina MC, Fuente C *et al*. Giant dermatofibroma. *J Am Acad Dermatol* 1994; **30**: 714–8.
9 Yazici AC, Baz K, Ikizoglu G *et al*. Familial eruptive dermatofibromas in atopic dermatitis. *J Eur Acad Dermatol Venereol* 2006; **20**: 90–2.
10 Kanitakis J, Carbonnel E, Delmonte S *et al*. Multiple eruptive dermatofibromas in a patient with HIV infection: case report and literature review. *J Cutan Pathol* 2000; **27**: 54–6.
11 Niiyama S, Katsuoka K, Happle R *et al*. Multiple eruptive dermatofibromas: a review of the literature. *Acta Derm Venereol* 2002; **82**: 241–4.
12 Yamamoto T, Sumi K, Yokozeki H *et al*. Multiple cutaneous fibrous histiocytomas in association with systemic lupus erythematosus. *J Dermatol* 2005; **32**: 645–9.
13 Lee HW, Lee DK, Oh SH *et al*. Multiple eruptive dermatofibromas in a patient with primary pulmonary hypertension. *Br J Dermatol* 2005; **153**: 845–7.
14 Alexandrescu DT, Wiernik PH. Multiple eruptive dermatofibromas occurring in a patient with chronic myelogenous leukaemia. *Arch Dermatol* 2005; **141**: 397–8.
15 Chang SE, Choi JH, Sung KJ *et al*. Multiple eruptive dermatofibromas occurring in a patient with acute myeloid leukaemia. *Br J Dermatol* 2000; **142**: 1062–3.
16 Bachmeyer C, Cordier F, Blum L *et al*. Multiple eruptive dermatofibromas after highly active antiretroviral therapy. *Br J Dermatol* 2000; **143**: 1336–7.
17 Calonje E, Mentzel T, Fletcher CDM. Cellular benign fibrous histiocytoma: clinicopathologic analysis of 74 cases of a distinctive variant of cutaneous fibrous histiocytoma with frequent recurrence. *Am J Surg Pathol* 1994; **18**: 668–76.
18 Colome-Grimmer MI, Evans HL. Metastasizing cellular dermatofibroma: a report of two cases. *Am J Surg Pathol* 1996; **20**: 1361–7.
19 Santa Cruz DJ, Kyriakos M. Aneurysmal ('angiomatoid') fibrous histiocytoma of the skin. *Cancer* 1981; **47**: 2053–61.
20 Calonje E, Fletcher CDM. Aneurysmal benign cutaneous fibrous histiocytoma: clinicopathologic analysis of a tumor frequently misdiagnosed as a vascular lesion. *Histopathology* 1995; **26**: 323–31.
21 Leyva WH, Santa Cruz DJ. Atypical cutaneous fibrous histiocytoma. *Am J Dermatopathol* 1986; **8**: 467–71.
22 Kaddu S, McMenamin M, Fletcher CD. Atypical fibrous histiocytoma of the skin: clinicopathologic analysis of 59 cases with evidence of infrequent metastasis. *Am J Surg Pathol* 2002; **26**: 35–46.
23 Wilson Jones E, Cerio R, Smith NP. Epithelioid cell histiocytoma: a new entity. *Br J Dermatol* 1989; **120**: 185–95.
24 Glusac EJ, Barr RJ, Everett MA *et al*. Epithelioid cell histiocytoma: a report of 10 cases including a new cellular variant. *Am J Surg Pathol* 1994; **18**: 583–90.
25 Hendi A, Jukic DM, Kress DW *et al*. Atrophic dermatofibroma: a case report and review of the literature. *Dermatol Surg* 2002; **28**: 1085–7.
26 Sánchez Yus E, Soria L, de Eusebio E *et al*. Lichenoid, erosive and ulcerated dermatofibromas. Three additional clinico-pathologic variants. *J Cutan Pathol* 2000; **27**: 112–7.
27 Gu M, Sohn K, Kim D *et al*. Metastasizing dermatofibroma in lung. *Ann Diagn Pathol* 2007; **11**: 64–7.
28 Ichikawa N, Kobayashi M, Kimoto M *et al*. A case of multiple aneurysmal fibrous histiocytomas. *Br J Dermatol* 2005; **153**: 664–5.
29 Schoenfeld RJ. Epidermal proliferations overlying histiocytomas. *Arch Dermatol* 1964; **90**: 266–70.
30 Abenoza P, Lillemoe T. CD 34 and factor 13a in the differential diagnosis of dermatofibroma and dermatofibrosarcoma protuberans. *Am J Dermatopathol* 1993; **15**: 429–34.
31 Soyer HP, Metze D, Kerl H. Granular cell dermatofibroma. *Am J Dermatopathol* 1997; **19**: 168–73.
32 Iwata J, Fletcher CDM. Lipidized fibrous histiocytoma: clinicopathologic analysis of 22 cases. *Am J Dermatopathol* 2000; **22**: 126–34.
33 Zelger BW, Steiner H, Kutzner H. Clear cell dermatofibroma: case report of an unusual fibrohistiocytic lesion. *Am J Surg Pathol* 1996; **20**: 483–91.
34 Tran TA, Hayner-Buchan A, Jones DM *et al*. Cutaneous balloon cell dermatofibroma (fibrous histiocytoma). *Am J Dermatopathol* 2007; **29**: 197–200.
35 Kuo TT, Hu S, Chan HL. Keloidal dermatofibroma: report of 10 cases of a new variant. *Am J Surg Pathol* 1998; **22**: 564–8.
36 Wagamon K, Somach SC, Bass J *et al*. Lipidized dermatofibromas and their relationship to serum lipids. *J Am Acad Dermatol* 2006; **54**: 494–8.

Medallion-like dermal dendrocytic hamartoma [1,2]

Definition. This is a very rare lesion that appears to derive from dermal dendrocytes and is usually congenital.

Clinical features. The handful of cases described have occurred in females with predilection for the trunk. Lesions are round or oval and have an atrophic appearance and a yellow–red colour.

Pathology. The epidermis appears atrophic and in the dermis there is a fairly monotonous proliferation of spindle-shaped bland cells. These cells are positive for CD34, factor XIIIa and fascin. The appearance may resemble DFSP, which may occasionally be congenital, and distinction between the two conditions is very important. However, medallion-like dermal dendrocytic hamartoma does not replace the subcutaneous tissue in a lace-like pattern and the proliferating cells are positive not only for CD34 but also for FXIIIa, a marker that is usually negative in dermatofibrosarcoma protuberans.

Treatment. Simple excision is the treatment of choice.

References

1 Rodríguez-Jurado R, Palacio C, Durán-McKinster C *et al*. Medallion-like dermal dendrocyte hamartoma: a new clinically and histopathologically distinct lesion. *J Am Acad Dermatol* 2004; **51**: 359–63.

2 Shah KN, Anderson E, Junkins-Hopkins J *et al*. Medallion-like dermal dendrocyte hamartoma. *Pediatr Dermatol* 2007; **24**: 632–6.

Hemosiderotic fibrohistiocytic lipomatous lesion [1,2]

Synonym

- Haemosiderotic fibrolipomatous tumour

Definition. This is a distinctive, benign, rare lesion that occurs almost exclusively on the foot, particularly the ankle, and that was initially thought to represent a reactive process [1]. A relationship with impaired circulation, particularly stasis, has been suggested [3]. However, other authors suggest that it is more likely to be neoplastic and related to a lesion described as pleomorphic angiectatic hyalinizing tumour [4]. The latter is regarded as a tumour of intermediate malignancy that occurs in most cases in deeper soft tissues and will not be described further in this chapter.

Clinical features. Lesions present as a slowly growing, fairly well-defined subcutaneous tumour, which tends to be asymptomatic and has some predilection for middle-aged to elderly females. Size is variable and may be several centimetres in diameter.

Pathology. The tumour is fairly circumscribed and it is composed of lobules of mature adipose tissue with scattered areas containing variable numbers of spindle-shaped cells which may be slightly hyperchromatic and often contain abundant intracytoplasmic haemosiderin. Histiocyte-like cells may also be seen. These cells are bland and only rarely slightly atypical. In the background there may be a few mononuclear inflammatory cells, mainly lymphocytes. Mitotic figures are exceptional. Spindle cells are positive for calponin and CD34 and may be positive for CD68 but negative for other markers, including desmin and h-caldesmon.

Prognosis and management. Tumours are benign and local recurrences occur rarely. The treatment of choice is simple excision.

References

1 Marshall-Taylor C, Farnburg-Smith JC. Hemosiderotic fibrohistiocytic lipomatous lesion: ten cases of a previously undescribed fatty lesion of the foot/ankle. *Mod Pathol* 2000; **13**: 1192–9.

2 Browne TJ, Fletcher CD. Haemosiderotic fibrolipomatous tumour (so-called haemosiderotic fibrohistiocytic lipomatous tumour): analysis of 13 new cases in support of a distinct entity. *Histopathology* 2006; **48**: 453–61.

3 Kazakov DV, Sima R, Michal M. Hemosiderotic fibrohistiocytic lipomatous lesion: clinical correlation with venous stasis. *Virchows Arch* 2005; **447**: 103–6.

4 Folpe AL, Weiss SW. Pleomorphic hyalinizing angiectatic tumor: analysis of 41 cases supporting evolution from a distinctive precursor lesion. *Am J Surg Pathol* 2004; **28**: 1417–25.

Angiomatoid fibrous histiocytoma [1–5]

Synonym

- Previously known as angiomatoid malignant fibrous histiocytoma

Definition. Angiomatoid FH was initially described as a variant of malignant FH [1]. It has recently been reclassified as a neoplasm with low-grade malignant behaviour, unrelated to malignant FH. Although it is considered to be 'fibrohistiocytic' due to the cytological resemblance of tumour cells to histiocytes, focal positivity of these cells to desmin raises the possibility of muscular differentiation. However, the lesion is now regarded as of uncertain histiogenesis.

Clinical features. It presents in children and young adults, with no sex predilection, as an asymptomatic blue or skin-coloured, subcutaneous or deeper mass. Primary dermal tumours are exceptional. Most cases occur on the limbs and patients may present with systemic symptoms including fever, anaemia and weight loss. Generalized lymphadenopathy may also be seen.

Pathology [1–4]. Low-power examination reveals haemorrhagic, pseudovascular, cavernous-like, cystic spaces filled with red blood cells. Mononuclear inflammatory cells are prominent and germinal centres are present in some cases. Tumour cells are arranged in sheets and consist of short spindle-shaped and round cells with pink cytoplasm and vesicular nuclei. Cytological atypia is sometimes present, and the mitotic count tends to be low. Tumour cells are focally positive in some cases to desmin [3,4], muscle-specific actin, calponin, CD99 and CD68, but not for smooth muscle actin.

Initial cytogenetic studies demonstrated a translocation between chromosomes 16p11 involving the *FUS* (*TLS*) gene and chromosome 12q13 involving the *ATF1* gene. The resultant protein (FUS/ATF1) is similar to the protein present in clear cell sarcoma (EWS/ATF1) involving t(12;22)(q13;q12) [6]. However, other cases show a different fusion gene, *EWSR1-CREB1*, which seems to be, in fact, the most common fusion gene in these tumours [7].

Prognosis and management. Most cases are cured after adequate excision, but local recurrence is observed in about 15% of patients

and, exceptionally, metastasis to neighbouring soft tissues or regional lymph nodes may occur. Complete excision and follow-up are therefore indicated. Local recurrence is more likely with deep tumours, those with an infiltrative growth pattern and those that are incompletely removed [2].

References

1 Enzinger FM. Angiomatoid malignant fibrous histiocytoma: a distinct fibrohistiocytic tumor of children and young adults simulating a vascular neoplasm. *Cancer* 1979; **44**: 2147–57.
2 Costa MJ, Weiss SW. Angiomatoid malignant fibrous histiocytoma: a follow-up study of 108 cases with evaluation of possible predictors of outcome. *Am J Surg Pathol* 1990; **14**: 1126–32.
3 Fletcher CD. Angiomatoid 'malignant fibrous histiocytoma': an immunohistochemical study indicative of myoid differentiation. *Hum Pathol* 1991; **22**: 563–8.
4 Fanburgh-Smith JC, Miettinen M. Angiomatoid 'malignant' fibrous histiocytoma: a clinicopathologic study of 158 cases and further exploration of the myoid phenotype. *Hum Pathol* 1999; **30**: 1336–43.
5 Billings SD, Folpe AL. Cutaneous and subcutaneous fibrohistiocytic tumors of intermediate malignancy: an update. *Am J Dermatopathol* 2004; **26**: 141–55.
6 Waters BL, Panagopoulos I, Allen EF. Genetic characterization of angiomatoid fibrous histiocytoma identifies fusion of the FUS and ATF-1 genes induced by a chromosomal translocation involving bands 12q13 and 16p11. *Cancer Genet Cytogenet* 2000; **121**: 109–16.
7 Antonescu CR, Dal Cin P, Nafa K *et al*. EWSR1-CREB1 is the predominant gene fusion in angiomatoid fibrous histiocytoma. *Genes Chromosomes Cancer* 2007; **46**: 1051–60.

Plexiform fibrous histiocytoma [1–4]

Synonym
- Plexiform fibrohistiocytic tumour

Definition. Plexiform FH is a distinctive, predominantly subcutaneous tumour with two distinctive components:
1 A fibro/myofibroblastic fascicular component
2 A nodular histiocytic-like component, which also includes giant cells.
Despite its new name, it does not represent a plexiform variant of an ordinary FH (dermatofibroma).

Clinical features [1–4]. It mainly occurs in children and young adults, most commonly in females, and has a predilection for the upper limbs. An exceptional case has been congenital [5]. The tumour is solitary, measures no more than a few centimetres in diameter and is asymptomatic.

Pathology [1–4]. Low-power examination reveals a predominantly subcutaneous tumour, with focal involvement of the dermis and a distinctive plexiform growth pattern. Purely dermal lesions are occasionally seen [6]. Two components are usually identified and consist of fascicles of bland spindle-shaped fibro/myofibroblast-like cells and nodules of histiocyte-like cells with scattered giant cells, focal haemorrhage and haemosiderin deposition. In some tumours, one of the components may predominate. The spindle-shaped cells stain focally for smooth muscle actin, and the cells in the nodules are focally positive for CD68.

Prognosis and treatment. Local recurrences are observed in up to 30% of cases. Metastases to regional lymph nodes or to the lungs have been reported [1,3,7]. Complete surgical excision and follow-up are therefore indicated. The histological features do not predict cases with more aggressive behaviour.

References

1 Enzinger FM, Zhang R. Plexiform fibrohistiocytic tumor presenting in children and young adults: an analysis of 65 cases. *Am J Surg Pathol* 1988; **12**: 816–26.
2 Hollowood K, Holley MP, Fletcher CD. Plexiform fibrohistiocytic tumour: clinicopathological, immunohistochemical and ultrastructural analysis in favour of a myofibroblastic lesion. *Histopathology* 1991; **19**: 503–13.
3 Remstein ED, Arndt CA, Nascimento AG. Plexiform fibrohistiocytic tumor. Clinicopathologic analysis of 22 cases. *Am J Surg Pathol* 1999; **23**: 662–70.
4 Taher A, Pushpanathan C. Plexiform fibrohistiocytic tumor: a brief review. *Arch Pathol Lab Med* 2007; **131**: 1135–8.
5 Leclerc S, Hamel-Teillac D, Oner P *et al*. Plexiform fibrohistiocytic tumor: three unusual cases occurring in infancy. *J Cutan Pathol* 2005; **32**: 572–6.
6 Zelger B, Weinlich G, Steiner H *et al*. Dermal and subcutaneous variants of plexiform fibrohistiocytic tumor. *Am J Surg Pathol* 1997; **21**: 235–41.
7 Salomao D, Nascimento A. Plexiform fibrohistiocytic tumor with systemic metastases: a case report. *Am J Surg Pathol* 1997; **21**: 469–76.

Atypical fibroxanthoma [1–4]

Definition. Atypical fibroxanthoma (AFX), by definition, arises in sun-damaged skin of elderly people. Ultraviolet radiation-induced *p53* mutations have been observed in these lesions, confirming the association with sun-damaged skin [5]. Tumours described in younger patients in non-sun-damaged skin represent examples of atypical FH.

Clinical features. The lesions occur most frequently on the ears, bald scalp and cheeks of elderly males (Fig. 56.13). Females are



Fig. 56.13 Typical clinical appearance of an atypical fibroxanthoma with a polypoid architecture.

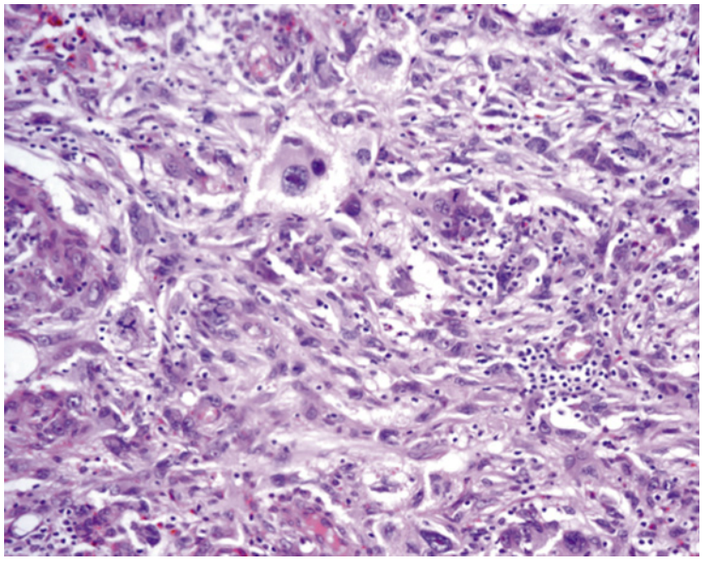


Fig. 56.14 Prominent cellular pleomorphism in a case of atypical fibroxanthoma.

much less frequently affected. The lesions are often ulcerated and have a red, fleshy appearance; they rarely exceed 30 mm in diameter, and are usually of less than 6 months' duration. Exceptional cases occur in association with xeroderma pigmentosum [6] or as a result of immunosuppression in cardiac transplant [7]. Multiple lesions have been reported [8]. Local recurrence may be seen in about 10% of cases and metastases to lymph nodes and internal organs are occasionally reported [9,10]. However, since the advent of immunohistochemistry, reports of metastatic tumours have been very rare. This suggests that many lesions reported in the past as metastatic AFX, which were diagnosed by examination of haematoxylin and eosin stained slides alone, probably represented other tumours, such as spindle cell melanomas or sarcomatoid squamous cell carcinoma.

Pathology. The tumours are exophytic, fairly well circumscribed and surrounded by an epidermal collarette. The remarkable and paradoxical feature of AFX is its histological resemblance to a highly malignant soft tissue sarcoma (Fig. 56.14) [11–13]. It arises in the dermis and may extend into the fat, but the edge is pushing rather than infiltrative. It is composed of large, spindle-shaped and histiocyte-like pleomorphic cells, many of which appear multinucleated. The cells are arranged in a haphazard fashion and mitotic figures, including atypical forms, are frequent. The histiocytic cells may contain lipid or haemosiderin [14,15]. A series of a less pleomorphic spindle cell variant, which may cause considerable problems in differential diagnosis, has been described [16]. Rare cases display prominent sclerosis [17] which may indicate regression. In some tumours there is focal or prominent clear or granular cell change [18–20]. The diagnosis of AFX is a diagnosis of exclusion. An immunohistochemical panel to rule out melanoma (S100), sarcomatoid squamous cell carcinoma (pan-keratin, mainly MNF 116 and AE1/AE3, as the low molecular weight keratin Cam 5.2 is usually negative in sarcomatoid squamous cell carcinoma of the skin) and even leiomyosarcoma (desmin, h-caldesmon) should be performed in all cases. The basic panel should be enough to accurately diagnose most cases of AFX. Other markers have been described that are often positive in AFX, and tend to be negative in other tumours that enter the differential diagnosis. These include CD99, CD10 and pro-collagen 1 [21–23].

Treatment. The benign behaviour of the tumour enables it to be treated by limited local removal. Although rare cases are treated by Mohs micrographic surgery [24], tumours are usually relatively well-circumscribed and the former treatment is rarely needed to achieve good clearance. Radiotherapy is not recommended.

References

1 Bourne RG. Paradoxical fibrosarcoma of skin: a review of 13 cases. *Med J Aust* 1963; **50**: 504–10.
2 Fretzin DF, Helwig EB. Atypical fibroxanthoma of the skin: a clinicopathological study of 140 cases. *Cancer* 1973; **31**: 1541–52.
3 Kempson RL, McGavran MH. Atypical fibroxanthomas of the skin. *Cancer* 1964; **17**: 1463–71.
4 Mirza B, Weedon D. Atypical fibroxanthoma: a clinicopathological study of 89 cases. *Australas J Dermatol* 2005; **46**: 235–8.
5 dei Tos AP, Maestro R, Doglione C *et al.* UV-induced p53 mutations in atypical fibroxanthoma. *Am J Pathol* 1994; **145**: 11–7.
6 Berk DR, Lind AC, Tapia B *et al*. Atypical fibroxanthoma in a child with xeroderma pigmentosum. *Pediatr Dermatol* 2007; **24**: 450–2.
7 Kovach BT, Sams HH, Stasko T. Multiple atypical fibroxanthomas in a cardiac transplant patient. *Dermatol Surg* 2005; **31**: 467–70.
8 Jensen KJ, Peterson SR. Multiple recurrent atypical fibroxanthomas/superficial malignant fibrous histiocytomas of the forehead excised with Mohs micrographic surgery. *Dermatol Surg* 2006; **32**: 588–91.
9 Cooper JZ, Newman SR, Scott GA *et al*. Metastasizing atypical fibroxanthoma (cutaneous malignant histiocytoma): report of five cases. *Dermatol Surg* 2005; **31**: 221–5.
10 Lum DJ, King AR. Peritoneal metastases from an atypical fibroxanthoma. *Am J Surg Pathol* 2006; **30**: 1041–6.
11 Dahl I. Atypical fibroxanthoma of the skin: a clinico-pathological study of 57 cases. *Acta Pathol Microbiol Scand* 1976; **84**: 183–97.
12 Kroe OJ, Pitcock JA. Atypical fibroxanthoma of the skin. *Am J Clin Pathol* 1969; **51**: 487–92.
13 Kuwano H, Hashimoto H, Enjoji M. Atypical fibroxanthoma distinguishable from spindle cell carcinoma in sarcoma-like skin lesions. *Cancer* 1985; **55**: 172–80.
14 Leong ASY, Milios J. Atypical fibroxanthoma of the skin: a clinicopathological and immunohistochemical study and a discussion of its histogenesis. *Histopathology* 1987; **11**: 463–75.
15 Reed RJ. Atypical fibroxanthomas and spindle cell carcinomas of the skin. *Bull Tulane Univ Med Fac* 1967; **26**: 75–89.
16 Calonje E, Wadden C, Wilson Jones E *et al*. Spindle cell nonpleomorphic atypical fibroxanthoma. *Histopathology* 1993; **22**: 247–54.
17 Bruecks AK, Medlicott SA, Trotter MJ. Atypical fibroxanthoma with prominent sclerosis. *J Cutan Pathol* 2003; **30**: 336–9.
18 Rudisaile SN, Hurt MA, Santa Cruz DJ. Granular cell atypical fibroxanthoma. *J Cutan Pathol* 2005; **32**: 314–7.
19 Rios-Martín JJ, Delgado MD, Moreno-Ramírez D *et al*. Granular cell atypical fibroxanthoma: report of two cases. *Am J Dermatopathol* 2007; **29**: 84–7.
20 Lázaro-Santander R, Andrés-Gozalbo C, Rodríguez-Pereira C *et al*. Clear cell atypical fibroxanthoma. *Histopathology* 1999; **35**: 484–5.
21 Hultgren TL, DiMaio DJ. Immunohistochemical staining of CD10 in atypical fibroxanthomas. *J Cutan Pathol* 2007; **34**: 415–9.
22 Hartel PH, Jackson J, Ducatman BS *et al*. CD99 immunoreactivity in atypical fibroxanthoma and pleomorphic malignant fibrous histiocytoma: a useful diagnostic marker. *J Cutan Pathol* 2006; **33** (Suppl. 2): 24–8.
23 Jensen K, Wilkinson B, Wines N *et al*. Procollagen 1 expression in atypical fibroxanthoma and other tumors. *J Cutan Pathol* 2004; **31**: 57–61.

24 Seavolt M, McCall M. Atypical fibroxanthoma: review of the literature and summary of 13 patients treated with Mohs micrographic surgery. *Dermatol Surg* 2006; **32**: 435–41.

Malignant fibrous histiocytoma [1–4]

Definition. 'Malignant FH' is an umbrella term encompassing a heterogeneous group of neoplasms that initially included five different clinicopathologic subtypes: pleomorphic, myxoid, giant cell, inflammatory and angiomatoid. There is little relation between the different subtypes; the angiomatoid variant has recently been reclassified in the group of fibrohistiocytic tumours and the name changed to 'angiomatoid FH'. The concept of pleomorphic malignant FH has been challenged as not representing a distinct group of neoplasms but a heterogeneous category, including pleomorphic poorly differentiated sarcomas. If cases classified as such are extensively studied with ancillary studies including immunohistochemistry, electron microscopy and more recently cytogenetics [5,6], a large percentage may be reclassified as pleomorphic variants of other soft-tissue tumours, including liposarcoma, rhabdomyosarcoma and leiomyosarcoma. The myxoid variant of malignant FH is now known as 'myxofibrosarcoma', and it is likely to show fibroblastic differentiation; this tumour often involves the skin because of its frequent origin in the subcutis, and it will therefore be discussed in more detail below. Angiomatoid FH has been described under fibrohistiocytic tumours. The inflammatory and giant cell variants of malignant FH hardly ever involve the skin and will not be discussed further.

References

1 Fletcher CDM, McKee PH. Sarcomas: a clinicopathological guide with particular reference to cutaneous manifestation, 1. *Clin Exp Dermatol* 1984; **9**: 451–65.
2 Lawson CW, Fisher C, Gatter KC. An immunohistochemical study of differentiation in malignant fibrous histiocytoma. *Histopathology* 1987; **11**: 375–83.
3 Weiss SW, Enzinger FM. Malignant fibrous histiocytoma: an analysis of 200 cases. *Cancer* 1978; **41**: 2250–66.
4 Enzinger FM. Malignant fibrous histiocytoma 20 years after Stout. *Am J Surg Pathol* 1986; **10**: 43–53.
5 Fletcher CD. Pleomorphic malignant fibrous histiocytoma: fact or fiction? A critical reappraisal based on 159 tumors diagnosed as pleomorphic sarcoma. *Am J Surg Pathol* 1992; **16**: 213–28.
6 Nakayama R, Nemoto T, Takahashi H *et al*. Gene expression analysis of soft tissue sarcomas: characterization and reclassification of malignant fibrous histiocytoma. *Mod Pathol* 2007; **20**: 749–59.

Myxofibrosarcoma [1–4]

Synonym
- Myxoid malignant fibrous histiocytoma

Definition. Myxofibrosarcoma is a neoplasm of the subcutis and deeper soft tissues with variable cellularity, myxoid change and cells with pleomorphic nuclei. The cellular end of the spectrum is identical to a pleomorphic malignant FH, and the diagnosis is made based on the presence of myxoid areas with less cellularity and a lobular pattern. The myxoid change should be seen in 10% or more of the tumour before a lesion is classified as myxofibrosarcoma.

Clinical features. This tumour mainly presents in middle-aged to old adults, with a slight predilection for females and for involvement of the extremities, particularly the lower limbs and followed by the trunk [4]. Typically, an asymptomatic mass, measuring several centimetres in diameter, is found in the subcutis or deeper soft tissues. This is one of the sarcomas that more often involves the dermis as a result of extension from the subcutis or deeper soft tissues, rather than having a dermal origin.

Pathology [4]. These tumours have a lobular growth pattern. They are classified according to the degree of cellularity and pleomorphism into low, medium and high grade. Low-grade tumours are paucicellular and consist of round or elongated bland and pleomorphic cells in a prominent myxoid stroma. The atypical cells have irregular hyperchromatic nuclei, and mitotic figures are relatively frequent. In the background, a fairly prominent number of thin-walled vascular channels with a typical curvilinear pattern are seen. Vacuolated, Alcian blue-positive cells, focally mimicking lipoblasts, are relatively frequent. In some tumours, hypocellular areas blend with more cellular areas containing cells with increased pleomorphism; such tumours are classified as intermediate-grade. Tumours with high cellularity (high-grade) are indistinguishable from the so-called pleomorphic malignant FH and may have necrosis. Grading of lesions is important, because the rate of local recurrence and metastasis varies (see below). Some tumours, particularly high-grade lesions, may have epithelioid morphology [5]. Tumour cells are positive for vimentin and only rarely display very focal positivity for actin.

Prognosis and treatment [4]. Excision with clear margins is essential. High-grade lesions have a higher tendency for local recurrence and for metastatic spread to regional lymph nodes. The overall 5-year survival is around 60%. Tumours with epithelioid morphology appear to have a more aggressive behaviour [5].

References

1 Angervall L, Kindblom LG, Merck C. Myxofibrosarcoma: a study of 30 cases. *Acta Pathol Microbiol Scand* 1977; **85**: 127–40.
2 Weiss SW, Enzinger FM. Myxoid variant of malignant fibrous histiocytoma. *Cancer* 1977; **39**: 1672–85.
3 Merck C, Angervall L, Kindblom LG *et al*. Myxofibrosarcoma, a malignant soft tissue tumor of fibroblastic-histiocytic origin: a clinicopathologic and prognostic study of 110 cases using multivariate analysis. *Acta Pathol Microbiol Immunol Scand* 1983; **91**: 3–40.
4 Mentzel T, Calonje E, Wadden C *et al*. Myxofibrosarcoma: clinicopathologic analysis of 75 cases with emphasis on the low-grade variant. *Am J Surg Pathol* 1996; **20**: 391–405.
5 Nascimento AF, Bertoni F, Fletcher CD. Epithelioid variant of myxofibrosarcoma: expanding the clinicomorphologic spectrum of myxofibrosarcoma in a series of 17 cases. *Am J Surg Pathol* 2007; **31**: 99–105.

Low-grade fibromyxoid sarcoma [1–3]

Synonym
- Hyalinizing spindle cell tumour with giant rosettes

Definition. This distinctive neoplasm is regarded as a low-grade variant of fibrosarcoma and it is characterized by deceptive, bland

spindle-shaped cells in a stroma with curvilinear blood vessels and either collagenous or myxoid background.

Clinical features. The tumour usually presents as a slowly growing lesion in young to middle-aged adults, with an equal sex incidence; it has a predilection for the proximal extremities, followed by the trunk. Tumours tend to be long-standing and asymptomatic and present as a mass, measuring several centimetres in diameter, and located in the subcutis or deeper soft tissues. Subcutaneous lesions are often clinically diagnosed as a lipoma.

Pathology [1–3]. The tumour consists of a proliferation of wavy, bland, spindle-shaped cells arranged in short fascicles and surrounded by a collagenous or myxoid stroma. Cellularity varies and tumour cells are usually bland with very rare mitotic figures. Frequent, elongated, thin-walled blood vessels are seen throughout the tumour. Only a small number of cases display some degree of cytological atypia. As a result of the deceiving histological appearances, the tumour is often diagnosed as benign. In a proportion of cases there are focal areas with hyalinized collagen surrounded by epithelioid tumour cells forming rosettes. This variant of the tumour was originally described as hyalinizing spindle cell tumour with giant rosettes [4]. The presence of rosettes does not influence the behaviour of the neoplasm. Immunohistochemistry is of limited value as tumour cells are negative for most markers. They may be, however, positive for epithelial membrane antigen (EMA) and this may lead to a misdiagnosis of perineurioma.

Tumours show a distinctive translocation, t(7;16)(q33;p11), leading to fusion of the *FUS* and *CREB3L2* genes [5]. This finding is very useful for confirmation of the diagnosis by fluorescent in situ hybridization (FISH).

Prognosis and treatment. Excision with clear margins is essential. In the largest series of cases reported so far it has been shown that local recurrence occurs in 9% of cases, metastases in 9% and mortality in 2% [6]. It seems that areas with higher grade morphology do not confer a more aggressive behaviour. However, this needs to be confirmed in further studies. Metastatic spread may occur many years after the original diagnosis and therefore long-term follow-up is indicated.

References

1 Evans HL. Low-grade fibromyxoid sarcoma: A report of 12 cases. *Am J Surg Pathol* 1993; **17**: 595–600.

2 Goodlad JR, Mentzel T, Fletcher CD. Low-grade fibromyxoid sarcoma: clinicopathological analysis of eleven new cases in support of a distinct entity. *Histopathology* 1995; **26**: 229–37.

3 Zamecnik M, Michal M. Low-grade fibromyxoid sarcoma: a report of 8 cases with histologic, immunohistochemical, and ultrastructural study. *Ann Diagn Pathol* 2000; **4**: 207–17.

4 Lane KL, Shannon RJ, Weiss SW. Hyalinizing spindle cell tumor with giant rosettes: a distinctive tumor closely resembling low-grade fibromyxoid sarcoma. *Am J Surg Pathol* 1997; **21**: 1481–8.

5 Folpe AL, Lane KL, Paull G *et al*. Low-grade fibromyxoid sarcoma and hyalinizing spindle cell tumor with giant rosettes: a clinicopathologic study of 73 cases supporting their identity and assessing the impact of high-grade areas. *Am J Surg Pathol* 2000; **24**: 1353–60.

6 Panagopoulos I, Storlazzi CT, Fletcher CD *et al*. The chimeric FUS/CREB3l2 gene is specific for low-grade fibromyxoid sarcoma. *Genes Chromosomes Cancer* 2004; **40**: 218–28.

Vascular tumours

Reviews of vascular tumours may be found in [1,2]. The vascular ectasias, verrucous haemangioma, tufted angioma, cavernous and capillary haemangiomas and congenital haemangiomas are described in Chapter 18.

References

1 Calonje E, Fletcher CDM. Tumors of blood vessels/lymphatics. In: Fletcher CDM, ed. *Diagnostic Histopathology of Tumors*, 3rd edition. London: Churchill Livingstone, 2007: 45–86.

2 Weiss SW, Goldblum JR. *Enzinger and Weiss's Soft Tissue Tumours*, 5th edn. St Louis: Mosby, 2007: 837–1036.

Reactive vascular lesions

Intravascular papillary endothelial hyperplasia [1–4]

Synonyms

- Masson's pseudoangiosarcoma
- Masson's vegetant intravascular haemangioendothelioma

Definition. Intravascular papillary endothelial hyperplasia is regarded as a form of organizing thrombus in which endothelial cells line hyalinized papillae.

Incidence and aetiology. This is a relatively common lesion, which usually presents as a primary phenomenon within a thrombosed blood vessel, usually a vein [2–4]. The secondary variant is commonly seen as an incidental finding within other vascular tumours, or in lesions such as haemorrhoids. Exceptionally, the same phenomenon is seen within a haematoma [4]. The primary form presents in young adults, with a slight predilection for females.

Clinical features. The primary form presents as a slowly growing solitary asymptomatic or slightly painful bluish nodule less than 20 mm in diameter. The site of predilection is the head and neck, followed by the hand (particularly the fingers). Multiple lesions are exceptional [5].

Pathology. The pathology is that of a widely dilated vascular channel in the dermis or subcutis, containing an organizing thrombus and prominent papillary projections with a hyalinized collagenous core. The papillae are lined by a single layer of usually bland endothelial cells with few mitotic figures. The presence of hyalinized collagen lined by endothelial cells produces an appearance similar to the 'dissection of collagen bundles' described in angiosarcoma. Distinction from angiosarcoma, however, is easy, as the latter is only exceptionally purely intravascular; it also displays cytological atypia, multilayering and mitotic figures. In secondary forms of Masson's tumour, the changes are seen within one or several vascular channels of a vascular tumour, usually a cavernous haemangioma or a vascular malformation.

Diagnosis. The clinical diagnosis suggested is usually that of a vascular tumour.

Treatment. Simple excision is usually curative and there is no tendency for local recurrence.

References

1 Masson P. Hémangioendothéliome végétant intra-vasculaire. *Bull Soc Anat* 1923; **93**: 517–23.
2 Kuo T, Sayers CP, Rosai J. Masson's 'vegetant intravascular hemangioendothelioma', a lesion often mistaken for angiosarcoma: study of seventeen cases located in the skin and soft tissues. *Cancer* 1976; **38**: 1227–36.
3 Hashimoto H, Daimaru Y, Enjoji M. Intravascular papillary endothelial hyperplasia: a clinicopathologic study of 91 cases. *Am J Dermatopathol* 1983; **5**: 539–45.
4 Pins MR, Rosenthal DI, Springfield DS *et al*. Florid extravascular papillary endothelial hyperplasia (Masson's pseudoangiosarcoma) presenting as a soft tissue sarcoma. *Arch Pathol Lab Med* 1993; **117**: 259–63.
5 Reed CN, Cooper PH, Swerlick RA. Intravascular papillary endothelial hyperplasia: multiple lesions simulating Kaposi's sarcoma. *J Am Acad Dermatol* 1984; **10**: 110–3.

Reactive angioendotheliomatosis [1–3]

Definition. A reactive vascular proliferation, which is usually multifocal and which is associated with a number of systemic diseases. In the past, it was divided into a reactive and a malignant form. With the advent of immunohistochemistry, it became apparent that the malignant form is a variant of aggressive intravascular lymphoma (see Chapter 57).

Incidence and aetiology. This condition is rare and involves adults, with a wide age range and no sex predilection. Most cases present with cutaneous involvement only and are idiopathic. It has been described in association with systemic diseases, including bacterial endocarditis, peripheral vascular atherosclerotic disease, cryoglobulinaemia [2], liver and renal disease, antiphospholipid syndrome [4], amyloidosis [5] and sarcoidosis [6]. It is not clear how systemic diseases induce this vascular proliferation.

Clinical features. Most patients present with multiple erythematous and/or haemorrhagic macules, papules and plaques on the trunk and limbs. Patients with fewer, more localized, lesions may also be seen. In the latter cases, the association with systemic disease is not usually present. In patients with antiphospholipid syndrome or cryoglobulinaemia, ulcerated lesions may be present.

Pathology [7]. The dermis and, in some cases, the subcutis show a multifocal proliferation of clusters of capillaries lined by plump endothelial cells with little or no cytological atypia. A layer of pericytes surrounds each capillary. In some areas, dilated capillaries appear to contain smaller vascular channels within their lumina. Patients with cryoglobulinaemia show thrombosis of capillaries by hyaline eosinophilic globules.

Treatment. There is no treatment available, but the condition is usually self-limited and resolves spontaneously within a few weeks.

References

1 Wick MR, Rocamora A. Reactive and malignant 'angioendotheliomatosis': a discriminant clinicopathologic study. *J Cutan Pathol* 1988; **15**: 260–71.
2 Le Boit PE, Solomon AR, Santa Cruz DJ *et al*. Angiomatosis with luminal cryoprotein deposition. *J Am Acad Dermatol* 1992; **27**: 969–73.
3 Krell JM, Sanchez RL, Solomon AR. Diffuse dermal angiomatosis: a variant of reactive cutaneous angioendotheliomatosis. *J Cutan Pathol* 1994; **21**: 363–70.
4 Creamer D, Black MM, Calonje E. Reactive angioendotheliomatosis in association with the antiphospholipid syndrome. *J Am Acad Dermatol* 2000; **42**: 903–6.
5 Ortonne N, Vignon-Pennamen MD, Majdalani G *et al*. Reactive angioendotheliomatosis secondary to dermal amyloid angiopathy. *Am J Dermatopathol* 2001; **23**: 315–9.
6 Shyong EQ, Gorevic P, Lebwohl M *et al*. Reactive angioendotheliomatosis and sarcoidosis. *Int J Dermatol* 2002; **41**: 894–7.
7 McMenamin ME, Fletcher CD. Reactive angioendotheliomatosis: a study of 15 cases demonstrating a wide clinicopathologic spectrum. *Am J Surg Pathol* 2002; **26**: 685–97.

Glomeruloid haemangioma [1,2]

Definition. This is a distinctive multifocal vascular proliferation that occurs in association with POEMS syndrome (*p*olyneuropathy, *o*rganomegaly, *e*ndocrinopathy, *M* protein and *s*kin changes; Chapter 62) or with multicentric Castleman's disease. This condition is best considered as a form of reactive angioendotheliomatosis in the setting of POEMS syndrome.

Incidence and aetiology. This is a rare disease that presents almost exclusively in the context of POEMS syndrome and multicentric Castleman's disease. It presents in adults, with no sex predilection. Exceptional cases with no clinical features of POEMS syndrome have been reported [3,4].

Clinical features. Patients present with multiple vascular papules on the trunk and limbs. Only a minority of these vascular lesions have the histological appearance of glomeruloid haemangioma; most have the histological appearance of cherry angiomas, or overlap with other vascular lesions, including cirsoid aneurysm (p. 56.26).

Pathology. The histological appearances in a typical case are striking, consisting of a multifocal dermal proliferation of clusters of closely packed dilated capillaries with a striking similarity to renal glomeruli. A layer of pericytes surrounds each capillary. Vacuolated cells are focally present and, in some cases, there are eosinophilic hyaline globules within the lumina of capillaries. These globules represent deposits of protein.

Treatment. The lesions do not tend to regress spontaneously. Individual lesions can be removed surgically, but because of their numbers this is not generally a practical option.

References

1 Chan JKC, Fletcher CDM, Hicklin GA *et al*. Glomeruloid hemangioma: a distinctive cutaneous lesion of multicentric Castleman's disease associated with POEMS syndrome. *Am J Surg Pathol* 1990; **14**: 1036–46.
2 Rongioletti F, Gambini C, Lerza R. Glomeruloid hemangioma: a cutaneous marker of POEMS syndrome. *Am J Dermatopathol* 1994; **16**: 175–8.
3 Piña-Oviedo S, López-Patiño S, Ortiz-Hidalgo C. Glomeruloid hemangioma localized to the skin of the trunk with no clinical features of POEMS syndrome. *Int J Dermatol* 2006; **45**: 1449–50.

4 Vélez D, Delgado-Jiménez Y, Fraga J. Solitary glomeruloid hemangioma without POEMS syndrome. *J Cutan Pathol* 2005; **32**: 449–52.

Benign vascular tumours

Lobular capillary haemangioma (pyogenic granuloma) [1,2]

Synonym
- Granuloma telangiectaticum

Definition. A vascular nodule that develops rapidly, often at the site of a recent injury, and which is composed of a lobular proliferation of capillaries in a loose stroma.

Incidence and aetiology. This is a common lesion affecting both sexes with a predilection for males [3] except for lesions that occur in the oral cavity which are more common in females [4]. It may occur at any age with a peak in the second decade of life [3], and is seen quite often in children and young adults but is unusual in the elderly [5]. In a minority of cases, a minor injury, usually of a penetrating kind, has occurred a few weeks before the nodule appears. Lesions may also occur at the sites of burns [6]. In other cases, no injury can be recollected, but this is likely on the basis of the patient's occupation or the body site affected. The balance of evidence indicates a reactive lesion.

Granuloma gravidarum is a variant of pyogenic granuloma that presents in the oral cavity during pregnancy.

Clinical features. The tumour is vascular, bright red to brownish-red or blue-black in colour. It is partially compressible, but cannot be completely blanched and does not show pulsation. The surface of early, bright-red lesions is usually thin, intact epidermis. Older and darker lesions are frequently eroded and crusted, and may bleed very easily. Occasionally, the surface is raspberry-like or even verrucous. The size is commonly between 5 and 10 mm, but may reach 50 mm. The outline is rounded. The base is often pedunculated and surrounded by a collar of acanthotic epidermis; the lesion may be sessile. The common sites are the hands, especially the fingers (Fig. 56.15), the feet, lips, head and upper trunk, and the mucosal surfaces of the mouth and perianal area. The initial evolution is rapid, but growth ceases after a few weeks. Spontaneous disappearance is rare. Lesions are not painful; patients mainly complain of the appearance or of recurrent bleeding. Rarely, pyogenic granulomas may occur within a port wine stain [7]. There are reported cases of multiple pyogenic granulomas developing after exfoliative dermatitis [8] and, in a periungual location, after HAART [9]. Lesions mimicking pyogenic granuloma may occur during therapy with gefitinib [10], systemic 5-fluorouracil [11] and capecitabine [12]. Eruptive forms of this tumour have rarely been reported [13]. In this setting, distinction from bacillary angiomatosis is crucial, as the latter often presents with multiple lesions that can be clinically and histologically difficult to distinguish from pyogenic granuloma. Multiple lesions closely resembling pyogenic granulomas have been reported after systemic [14] and topical [15] treatment with retinoids.



Fig. 56.15 Clinical appearance of a pyogenic granuloma on a typical site at the tip of the finger.

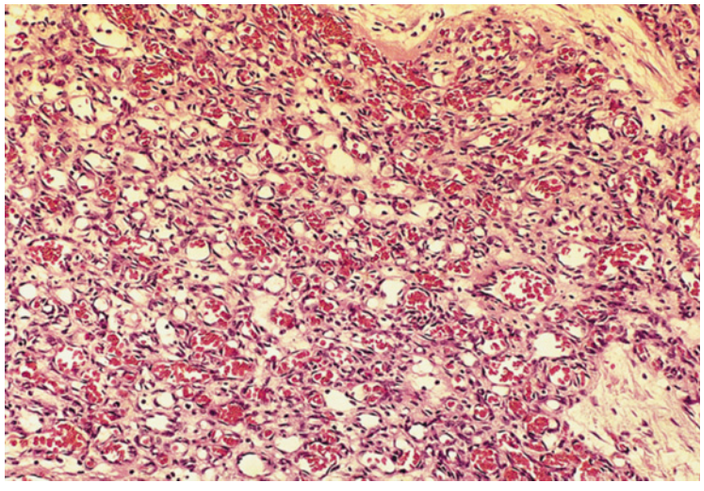


Fig. 56.16 Typical lobules of capillaries in a myxoid background, in a case of pyogenic granuloma.

Subcutaneous [16,17] and intravascular [18] variants are rarely seen and do not have distinctive clinical features. Interestingly, two cases of subcutaneous lesions have been described in patients with antiphospholipid antibodies [19].

Pathology. There is a lobular proliferation of small blood vessels, which erupt through a breach in the epidermis to produce a globular pedunculated tumour. The epidermis forms a collarette at the base of the lesion and covers part, or all, of the tumour in a thin layer. The proliferating vessels are set in a myxoid stroma, lacking in collagen in the earlier stages and relatively rich in mucin. The endothelial cells are plump, as in new granulation tissue, lining the vessels in a single layer. They are surrounded by a mixed cell population of fibroblasts, mast cells, lymphocytes, plasma cells and, where the surface is eroded, polymorphonuclear leukocytes (Fig. 56.16). Mitotic figures may be prominent. Older lesions tend

to organize and partly fibrose and may show focal bone formation. Late lesions can display focal degenerative atypia, raising the possibility of malignancy. In rare instances, particularly in children, and sometimes following treatment, satellite lesions which have a similar pathology to the primary lesion may develop around a pyogenic granuloma. These respond to simple destructive measures, thus ruling out malignancy [20]. In exceptional cases extramedullary haemopoiesis may be seen [21]. Bacillary angiomatosis shows an almost identical histology to that of pyogenic granuloma [22]. However, in bacillary angiomatosis, pale epithelioid endothelial cells are prominent, neutrophils and nuclear dust are seen throughout the lesion and violaceous amorphous aggregates of bacilli which are positive with either Giemsa or Warthin–Starry stains are easily identified. The causative organism may also be identified by PCR.

Diagnosis. In most cases, the history and clinical appearance leave little doubt about the diagnosis, and microscopic confirmation is straightforward. In 38% of one case series, the clinical diagnosis of pyogenic granuloma proved to be wrong [23]. The errors included keratoacanthoma and other epithelial neoplasms, inflamed seborrhoeic keratoses, melanocytic naevi, 'juvenile' and malignant melanoma, virus warts, molluscum contagiosum, angioma, glomus tumour, eccrine poroma, Kaposi's sarcoma and metastatic carcinoma.

Treatment. The pedunculated lesions are easy to treat by curettage with cauterization or diathermy coagulation of the base. A considerable proportion of pyogenic granulomas recur after such treatment, because the proliferating vessels in the base extend in a conical manner into the deeper dermis. In some areas—for instance in the nail fold or on the palmar aspect of a finger—it may be reasonable to carry out curettage and hope for the best. Wherever possible, it is desirable to excise a narrow, but deep, ellipse of skin beneath the lesion and close the wound with sutures. A small number of lesions have been treated with topical imiquimod 5% cream both in children and adults with complete resolution [24,25]. Other treatment modalities that have been used include Nd:YAG laser [26], cryosurgery [27], intralesional steroids, flash lamp pulsed dye laser and even injection of absolute ethanol [28].

References

1 Lee FD. A comparative study of Kaposi's sarcoma and granuloma pyogenicum in Uganda. *J Clin Pathol* 1968; **21**: 119–28.
2 McGeoch AH. Pyogenic granuloma. *Aust J Dermatol* 1961; **6**: 33–40.
3 Harris MN, Desai R, Chuang TY *et al*. Lobular capillary hemangioma: An epidemiologic report, with emphasis on cutaneous lesions. *J Am Acad Dermatol* 2000; **42**: 1012–6.
4 Jafarzadeh H, Sanatkhani M, Mohtasham N. Oral pyogenic granuloma: a review. *J Oral Sci* 2006; **48**: 167–75.
5 Knoth W, Ehlers G. On the problem of the existence of telangiectatic pyogenic granuloma with special reference to its relations to hemangioma and hemangioendothelioma. *Arch Klin Exp Dermatol* 1962; **214**: 394–414.
6 Bozkurt M, Kulahci Y, Zor F *et al*. Multiple giant disseminated pyogenic granuloma in a burn lesion. *J Burn Care Res* 2006; **27**: 247–9.
7 Sheehan DJ, Lesher JL Jr. Pyogenic granuloma arising within a port-wine stain. *Cutis* 2004; **73**: 175–80.
8 Torres JE, Sánchez JL. Disseminated pyogenic granuloma developing after an exfoliative dermatitis. *J Am Acad Dermatol* 1995; **32**: 280–2.
9 Williams LH, Fleckman P. Painless periungual pyogenic granulomata associated with reverse transcriptase inhibitor therapy in a patient with human immunodeficiency virus infection. *Br J Dermatol* 2007; **156**: 163–4.
10 High WA. Gefitinib: a cause of pyogenic granulomalike lesions of the nail. *Arch Dermatol* 2006; **142**: 939.
11 Curr N, Saunders H, Murugasu A *et al*. Multiple periungual pyogenic granulomas following systemic 5-fluorouracil. *Australas J Dermatol* 2006; **47**: 130–3.
12 Piquet V, Borradori L. Pyogenic granuloma-like lesions during capecitabine therapy. *Br J Dermatol* 2002; **147**: 1270–2.
13 Nappi O, Wick MR. Disseminated lobular capillary hemangioma (pyogenic granuloma): a clinicopathologic study of two cases. *Am J Dermatopathol* 1986; **8**: 379–85.
14 Exner JH, Dahod S, Pochi PE. Pyogenic granuloma-like acne lesions during isotretinoin therapy. *Arch Dermatol* 1983; **119**: 808–11.
15 MacKenzie-Wood AR, Wood G. Pyogenic granuloma-like lesions in a patient using topical tretinoin. *Australas J Dermatol* 1998; **39**: 248–50.
16 Cooper PH, Mills SE. Subcutaneous granuloma pyogenicum: lobular capillary hemangioma. *Arch Dermatol* 1982; **118**: 30–3.
17 Fortna RR, Junkins-Hopkins JM. A case of lobular capillary hemangioma (pyogenic granuloma). Localized to the subcutaneous tissue, and a review of the literature. *Am J Dermatopathol* 2007; **29**: 408–11.
18 Cooper PH, McAllister HA, Helwig EB. Intravenous pyogenic granuloma: a study of 18 cases. *Am J Surg Pathol* 1979; **3**: 221–8.
19 Kuroda K, Mizoguchi M. Subcutaneous granuloma pyogenicum in patients with antiphospholipid antibodies. *Dermatology* 2004; **208**: 331–4.
20 Warner J, Wilson Jones E. Pyogenic granuloma recurring with multiple satellites: a report of 11 cases. *Br J Dermatol* 1968; **80**: 218–27.
21 Vega Harring SM, Niyaz M, Okada S *et al*. Extramedullary hematopoiesis in a pyogenic granuloma: a case report and review. *J Cutan Pathol* 2004; **31**: 555–7.
22 LeBoit PE, Berger TG, Egbert BM *et al*. Bacillary angiomatosis: the histopathology and differential diagnosis of a pseudoneoplastic infection in patients with human immunodeficiency virus disease. *Am J Surg Pathol* 1989; **13**: 909–20.
23 Rowe L. Granuloma pyogenicum. *AMA Arch Dermatol* 1958; **78**: 341–7.
24 Fallah H, Fischer G, Zagarella S. Pyogenic granuloma in children: treatment with topical imiquimod. *Australas J Dermatol* 2007; **48**: 217–20.
25 Goldenberg G, Krowchuk DP, Jorizzo JL. Successful treatment of a therapy-resistant pyogenic granuloma with topical imiquimod 5% cream. *J Dermatol Treat* 2006; **17**: 121–3.
26 Bourguignon R, Paquet P, Pierard-Franchimont C *et al*. Treatment of pyogenic granulomas with Nd- YAG laser. *J Dermatol Treat* 2006; **17**: 247–9.
27 Mirshams M, Daneshpazhooh M, Mirshekari A *et al*. Cryotherapy in the treatment of pyogenic granuloma. *J Eur Acad Dermatol Venereol* 2006; **20**: 788–90.
28 Ichimiya M, Yohikawa Y, Hamamoto Y *et al*. Successful treatment of pyogenic granuloma with injection of absolute ethanol. *J Dermatol* 2004; **31**: 342–4.

Cirsoid aneurysm [1–4]

Synonyms
- Cutaneous arteriovenous haemangioma
- Acral arteriovenous tumour

Definition. Cirsoid aneurysm is a small vascular proliferation characterized by small to medium-sized channels with features of arteries and veins. As opposed to deeper tumours showing similar features, shunting is absent.

Clinical features. Most lesions present on the head and neck region of young adults, with no sex predilection, as a small, blue/red, asymptomatic papule.

Pathology. The dermis contains a mixture of scattered blood vessels with thick walls and features of veins and arteries (Fig. 56.17).

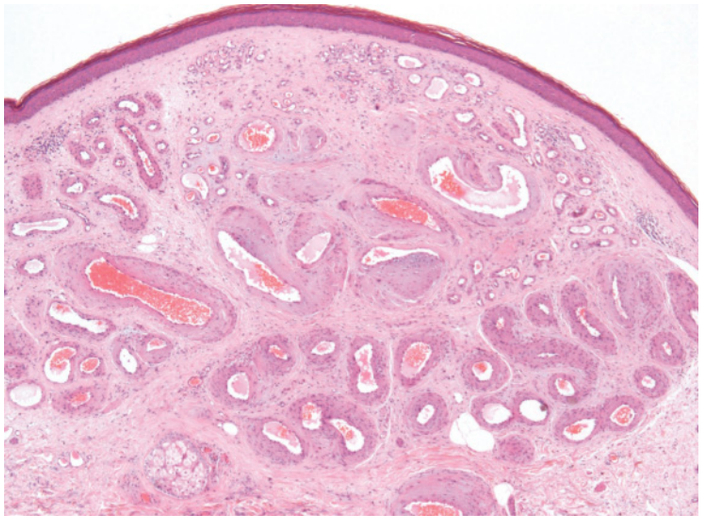


Fig. 56.17 A dermal collection of thick and thin walled blood vessels in a typical case of cirsoid aneurysm.

Treatment. As there is no associated shunting or deep component, simple excision is the treatment of choice.

References

1 Girard C, Graham JH, Johnson WC. Arteriovenous hemangioma (arteriovenous shunt): a clinicopathological and histochemical study. *J Cutan Pathol* 1974; **1**: 73–87.

2 Connelly MG, Winkelmann RK. Acral arteriovenous tumor: a clinicopathologic review. *Am J Surg Pathol* 1985; **9**: 15–21.

3 Koutlas IG, Jessurun J. Arteriovenous hemangioma: a clinicopathological and immunohistochemical study. *J Cutan Pathol* 1994; **21**: 343–9.

4 Gurbuz Y, Muezzinoglu B, Apaydin R *et al*. Acral arteriovenous tumor (cirsoid aneurysm): clinical and histopathological analysis of 6 cases. *Adv Clin Path* 2002; **6**: 25–9.

Epithelioid haemangioma [1,2]

Synonyms

- Angiolymphoid hyperplasia with eosinophilia
- Pseudopyogenic granuloma
- Histiocytoid haemangioma

Definition. A benign, locally proliferating lesion composed of vascular channels lined by endothelial cells with abundant pink cytoplasm and vesicular nuclei. There has, on occasion, been a difficulty with nomenclature such that the term Kimura's disease has been applied but this condition is now viewed as distinct from angiolymphoid hyperplasia with eosinophils. In Kimura's disease, the lesions occur in younger patients, are deeper-seated, are associated with lymphadenopathy, have no initial overlying skin lesions and do not contain epithelioid endothelial cells [3,4]. Furthermore, peripheral blood eosinophilia is much more common in Kimura's disease. Exceptionally, angiolymphoid hyperplasia with eosinophilia may co-exist with Kimura's disease [5].

Incidence and aetiology. These lesions have now been reported from many parts of the world. The cause is unknown, but most studies suggest a reactive process [6].



Fig. 56.18 Epithelioid haemangioma, or angiolymphoid hyperplasia with eosinophilia. (Courtesy of Dr R.H. Champion, Addenbrooke's Hospital, Cambridge, UK.)

Clinical features [7–11] (Fig. 56.18)**.** Affected individuals are commonly young adults who present with a cluster of small, translucent nodules on the head and neck, particularly around the ear or the hairline. The lesions may also involve the oral mucosa [12]. Less frequently, lesions can involve the trunk and extremities. Involvement of deeper soft tissues and internal organs, including bone, can be seen. Both sexes are equally affected. Individual nodules rarely exceed 2–3 cm in diameter, but occasionally deeper extension and larger subcutaneous lesions occur. Spontaneous regression is seen in the majority of cases after a variable period of time. Peripheral blood eosinophilia may be present but only in less than 10% of patients.

Pathology [2,13]. A poorly circumscribed lobular lesion is seen. It is composed of clusters of proliferating capillaries and, often, thicker blood vessels lined by plump, epithelioid endothelial cells (Fig 56.19) with little cytological atypia and rare mitotic figures. Around the blood vessels there is a cellular inflammatory infiltrate composed mainly of lymphocytes and large numbers of eosinophils. However, only less than half of cases contain a prominent infiltrate. Older lesions show sclerosis of the stroma and the endothelial cells become more prominent. A frequent finding, particularly in larger lesions, is the involvement of larger blood vessels. Rare cases are entirely intravascular [14,15]. The endothelial cells stain for vascular markers including CD34, von Willebrand factor and CD31. In cutaneous cases, endothelial cells are negative for pan-keratin.

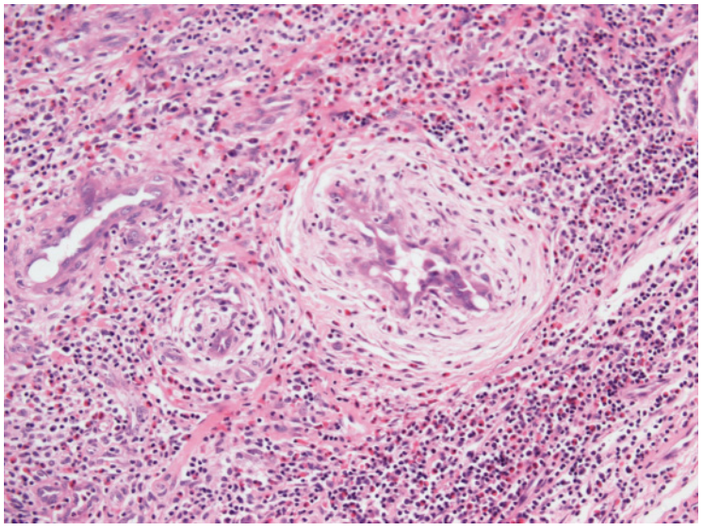


Fig. 56.19 Vascular channels lined by epithelioid endothelial cells with abundant pink cytoplasm in a case of epithelioid haemangioma.

Treatment. The natural history of the lesion is such that if a confident diagnosis is made on a small lesion, it is reasonable to observe the lesion for 3–6 months and await spontaneous regression. Both surgery and radiotherapy are effective, but local recurrences are common. Treatment with Nd-YAG laser has been effective [16] and there is an anecdotal report of response to imiquimod cream [17].

References

1 Olsen TG, Helwig EB. Angiolymphoid hyperplasia with eosinophilia. *J Am Acad Dermatol* 1985; **12**: 781–96.
2 Wells GC, Whimster IW. Subcutaneous angiolymphoid hyperplasia with eosinophilia. *Br J Dermatol* 1969; **81**: 1–15.
3 Chan JKC, Hui PK, Ng CS *et al.* Epithelioid haemangioma (angiolymphoid hyperplasia with eosinophilia) and Kimura's disease in Chinese. *Histopathology* 1989; **15**: 557–74.
4 Fetsch JF, Weiss SW. Observations concerning the pathogenesis of epithelioid haemangioma/angiolymphoid hyperplasia. *Mod Pathol* 1991; **4**: 449–55.
5 Chong WS, Thomas A, Goh CL. Kimura's disease and angiolymphoid hyperplasia with eosinophilia: two entities in the same patient: case report and review of the literature. *Int J Dermatol* 2006; **45**: 139–45.
6 Kuo TT, Shih LY, Chan HL. Kimura's disease: involvement of regional lymph nodes and distinction from angiolymphoid hyperplasia with eosinophilia. *Am J Surg Pathol* 1988; **12**: 843–54.
7 Baler GR. Angiolymphoid hyperplasia with eosinophilia: a report of two cases. *J Dermatol Surg Oncol* 1981; **7**: 229–34.
8 Grimwood R, Swinehart JM, Aeling JL. Angiolymphoid hyperplasia with eosinophilia. *Arch Dermatol* 1979; **115**: 205–7.
9 Reed RJ, Terazekis N. Subcutaneous angioblastic lymphoid hyperplasia with eosinophilia (Kimura's disease). *Cancer* 1972; **29**: 489–97.
10 Vazquez-Botet M, Sanchez JL. Angiolymphoid hyperplasia with eosinophilia: report of a case and a review of the literature. *J Dermatol Surg Oncol* 1978; **4**: 931–6.
11 Wilson Jones E. Inflammatory angiomatous nodules with abnormal blood vessels occurring about the ears and scalp (pseudo or atypical pyogenic granuloma). *Br J Dermatol* 1969; **81**: 804–16.
12 Bartralot R, Garcia Patos V, Hueto J *et al.* Angiolymphoid hyperplasia with eosinophils affecting the oral mucosa. *Br J Dermatol* 1996; **134**: 744–8.
13 Kung ITM, Gibson JB, Bannatyne PM. Kimura's disease: a clinicopathological study of 21 cases and its distinction from angiolymphoid hyperplasia with eosinophilia. *Pathology* 1984; **16**: 39–44.
14 Rosai J, Ackerman LR. Intravenous atypical vascular proliferation: a cutaneous lesion simulating a malignant blood vessel tumor. *Arch Dermatol* 1974; **109**: 714–7.
15 Koubaa W, Verdier M, Perez M *et al.* Intra-arterial angiolymphoid hyperplasia with eosinophilia. *J Cutan Pathol* 2008; **35**: 495–8.
16 Kadurina MI, Dimitrov BG, Bojinova ST *et al.* Angiolymphoid hyperplasia with eosinophilia: successful treatment with Nd:YAG laser. *J Cosmet Laser Ther* 2007; **9**: 107–11.
17 Gencoglan G, Karaca S, Ertekin B. Angiolymphoid hyperplasia with eosinophilia successfully treated with imiquimod. A case report. *Dermatology* 2007; **215**: 233–5.

Cutaneous epithelioid angiomatous nodule

Definition. This is a recently described tumour within the spectrum of vascular lesions characterized by epithelioid endothelial cells [1–3]. It is regarded by some as part of the spectrum of epithelioid haemangioma.

Clinical features. It is rare, with only a handful of cases reported. Lesions consist of a papule or nodule presenting in an adult, with a predilection for the trunk and limbs and, less commonly, involving the face. Multiple lesions are rare and there is no tendency for local recurrence.

Pathology. The majority of lesions are superficial, well-circumscribed and surrounded by an epithelial collarette. Occasional, deeper tumours may be observed. It is composed of sheets of epithelioid endothelial cells with abundant pink cytoplasm, vesicular nuclei and a single, small nucleolus. Cytological atypia is mild or absent and mitotic figures are variable. There is little tendency for formation of vascular channels but individual endothelial cells often contain intracytoplasmic vacuoles. In the background, scattered mononuclear inflammatory cells and eosinophils may be seen.

References

1 Brenn T, Fletcher CDM. Cutaneous epithelioid angiomatous nodule: a distinct lesion in the morphologic spectrum of epithelioid vascular tumors. *Am J Dermatopathol* 2004; **26**: 14–21.
2 Fernández-Flores A, Montero MG, Renedo G. Cutaneous epithelioid angiomatous nodule of the external ear. *Am J Dermatopathol* 2005; **27**: 175–6.
3 Kantrow S, Martin JD, Vnencak-Jones CL, Boyd AS. Cutaneous epithelioid angiomatous nodule: report of a case and absence of microsatellite instability. *J Cutan Pathol* 2007; **34**: 515–6.

Acquired elastotic haemangioma [1]

Definition. This is a distinctive vascular lesion that develops in sun-exposed skin in association with solar elastosis.

Incidence and aetiology. Acquired elastotic haemangioma is rare and seems to be aetiologically related to chronic sun-exposure.

Clinical features. Lesions present mainly on the forearms or neck of middle-aged to elderly patients, with a predilection for females. The clinical presentation consists of a small, red or blue, circumscribed and asymptomatic plaque.

Pathology. Lesions are well circumscribed and consist of a superficial, band-like proliferation of capillaries in the background of solar elastosis. Each capillary is surrounded by a layer of pericytes.

Treatment. Simple excision is the treatment of choice and there is no tendency to local recurrence.

Reference

1 Requena L, Kutzner H, Mentzel T. Acquired elastotic hemangioma: a clinicopathologic variant of hemangioma. *J Am Acad Dermatol* 2002; **47**: 371–6.

Hobnail haemangioma [1–4]

Synonym

- Targetoid haemosiderotic haemangioma

Definition. This is a benign vascular dermal proliferation characterized by small channels lined by endothelial cells with little cytoplasm and a prominent dark nucleus (hobnail cells). Formation of small papillae is also often seen. The original name proposed for this condition was based on a distinctive targetoid clinical appearance produced by bleeding and haemosiderin deposition. However, only a minority of lesions present with this typical appearance and, therefore, the alternative name of hobnail haemangioma has been proposed.

Incidence and aetiology. It is relatively uncommon and occurs mainly in young to middle-aged adults with a slight predilection for males. Trauma may play a part in its pathogenesis [4]. Occasionally, lesions vary according to the timing within the menstrual cycle [5].

Clinical features. This entity presents as a rapidly developing, asymptomatic, solitary red or brown lesion, which in some cases has a central, raised, violaceous papule and is surrounded by a paler brown halo (targetoid appearance) [1]. Any body site may be affected, but it has predilection for the lower limbs and trunk. The oral mucosa may also be affected [3].

Pathology. Pathological examination shows dilated vascular channels in the papillary and high reticular dermis, with a single layer of endothelial cells lining intraluminal papillary projections. These cells have a hobnail ('matchstick') appearance. They may occasionally be more numerous and appear to fill the lumen of the vessel. The vascular channels tend to disappear in the mid and lower reticular dermis, and the endothelial cells become less prominent and lose the hobnail appearance. Haemosiderin deposition is prominent and can be highlighted with a Perl's stain. The endothelial cells stain for the lymphatic marker podoplanin (D2-40), suggesting that these lesions represent lymphangiomas rather than haemangiomas [6]. The pathological appearance may resemble Kaposi's sarcoma, but this differential diagnosis can usually be resolved by clinicopathological correlation, as hobnail haemangioma is a solitary entity whereas Kaposi's sarcoma is usually composed of multiple lesions. Histological distinction can be made if attention is paid to the symmetry of the lesion, the presence of hobnail endothelial cells with papillary projections and the absence of inflammation in hobnail haemangioma. Furthermore, hobnail haemangioma is not associated with HHV8 while all cases of Kaposi's sarcoma are associated with this virus.

Diagnosis. It is usually suspected clinically if lesions have a targetoid appearance. The diagnosis is otherwise made histologically.

Treatment. Simple surgical excision is the treatment of choice; there is no tendency for recurrence.

References

1 Santa Cruz DJ, Aronberg J. Targetoid hemosiderotic hemangioma. *J Am Acad Dermatol* 1988; **19**: 550–8.

2 Torrelo A. Hobnail hemangioma. *Dermatology* 1995; **191**: 154–6.

3 Guillou L, Calonje E, Speight P *et al*. Hobnail hemangioma: a pseudomalignant vascular lesion with a reappraisal of targetoid hemosiderotic hemangioma. *Am J Surg Pathol* 1999; **23**: 97–105.

4 Mentzel T, Partanen TA, Kutzner H. Hobnail hemangioma ('targetoid hemosiderotic hemangioma'): clinicopathologic and immunohistochemical analysis of 62 cases. *J Cutan Pathol* 1999; **26**: 279–86.

5 Ortiz-Rey JA, González-Ruiz A, San Miguel P *et al*. Hobnail hemangioma associated with the menstrual cycle. *J Eur Acad Dermatol Venereol* 2005; **19**: 367–9.

6 Franke FE, Steger K, Marks A *et al*. Hobnail hemangiomas (targetoid hemosiderotic hemangiomas) are true lymphangiomas. *J Cutan Pathol* 2004; **31**: 362–7.

Microvenular haemangioma [1–3]

Definition. This is a benign dermal vascular lesion characterized by proliferation of small vascular channels with features suggestive of venules.

Incidence and aetiology. It is relatively rare and presents mainly in young adults, with no sex predilection. Presentation in children is very rare [4]. Although the histological appearances suggest venular differentiation, this has not been proven.

Clinical features. It presents as a solitary, red–brown or bluish papule, nodule or plaque with predilection for the limbs. Most lesions are less than 10 mm in diameter.

Pathology. There is a superficial and deep dermal proliferation of angulated, thin-walled, vascular channels, all of which are surrounded by a single layer of pericytes. These channels are lined by flat, bland, endothelial cells and are surrounded by somewhat hyalinized collagen. A frequent finding is the infiltration of arrector pili muscles by vascular channels. Inflammation is not usually a feature. These lesions are negative for HHV8.

Treatment. Simple surgical excision is the treatment of choice; there is no tendency for local recurrence.

References

1 Hunt SJ, Santa Cruz DJ, Barr RJ. Microvenular hemangioma. *J Cutan Pathol* 1991; **18**: 235–40.

2 Aloi F, Tomasini C, Pippione M. Microvenular hemangioma. *Am J Dermatopathol* 1993; **15**: 534–8.

3 Fukunaga M, Ushigome S. Microvenular hemangioma. *Pathol Int* 1998; **48**: 237–9.

4 Sànz-Trelles A, Ojeda-Martos A, Jiménez-Fernandéz A *et al*. Microvenular haemangioma: a new case in a child. *Histopathology* 1998; **32**: 89–90.

Sinusoidal haemangioma [1]

Definition. This is a benign dermal and/or subcutaneous variant of cavernous haemangioma composed of thin-walled, dilated vascular spaces in a typical sieve-like distribution.

Incidence and aetiology. Lesions are rare and present in adults, with a slight predilection for females.

Clinical features. Sinusoidal haemangioma presents as a solitary, blue, asymptomatic nodule, particularly on the trunk or upper limbs. The dermis and subcutaneous tissue overlying the breast is not uncommonly involved and may suggest a diagnosis of angiosarcoma (differentiating features are discussed below; see also p. 56.37).

Pathology. The lesion is usually well circumscribed, but several lobules of subcutaneous tissue may be focally affected by the tumour. A striking feature is the presence of back-to-back, dilated and congested thin-walled vascular channels. These channels are interconnected, and transverse sectioning is, in part, responsible for the distinctive sinusoidal appearance. Pseudopapillary projections are focally present and thrombosis with dystrophic calcification may also be seen. Focal cytological atypia secondary to degenerative changes may be seen. Distinction from angiosarcoma, particularly in tumours presenting in the breast, is based on the fact that the latter occurs in the breast parenchyma and only invades the dermis and subcutis secondarily. Tumour cells in angiosarcoma also display cytological atypia, multilayering and mitotic figures.

Treatment. Simple surgical excision is the treatment of choice, and there is no tendency for local recurrence.

Reference

1 Calonje E, Fletcher CDM. Sinusoidal hemangioma. *Am J Surg Pathol* 1991; **15**: 1130–5.

Spindle cell haemangioma [1–5]

Synonym
- Spindle cell haemangioendothelioma

Definition. This is a benign vascular tumour. Although initially described as a low-grade malignant lesion with a high tendency for local recurrence and minimal potential for metastasis, further studies demonstrated that it is a benign multifocal process, often associated with a vascular malformation [3–5]. Confirmation of its benign nature has led to change of the name 'haemangioendothelioma' for 'haemangioma', as the former implies low-grade (intermediate-grade) malignant potential [6].

Incidence and aetiology. Spindle cell haemangioma is relatively rare. Males and females are affected equally, and the age range is wide. Often, lesions present in childhood or early adulthood and tend to be long-standing. The process appears to be reactive or may be a form of malformation, and it is often associated with lymphoedema, Maffucci's syndrome (multiple enchondromas) [7], early-onset varicose veins or Klippel–Trenaunay syndrome.

Clinical features. The majority of cases present in the distal limbs, particularly the hands and feet, as multiple cutaneous or subcutaneous, red or bluish nodules. Deeper tumours are rare. Presentation at other sites including the neck and oral cavity is very rare [8,9]. Lesions continue to appear over many years, indicating multifocality rather than true recurrences. Most nodules are less than a few centimetres in diameter; they may occasionally be painful.

Pathology. Low-power magnification reveals single or multiple, fairly well-circumscribed, haemorrhagic nodules. Origin from a pre-existing blood vessel is often seen, and individual lesions may be entirely intravascular. Dilated, thin-walled, congested, cavernous-like vascular spaces are intermixed with more cellular areas composed of bland, short, spindle-shaped cells, with formation of slit-like spaces. Scattered, more epithelioid cells, with pink cytoplasm and prominent vacuolation, are also seen. The spindle-shaped cells are a mixture of endothelial cells, pericytes and fibroblasts. Focal degenerative cytological atypia may be present. Immunohistochemistry reveals staining for CD31 and CD34 and focal staining for smooth muscle actin.

Diagnosis. The clinical appearances usually suggest a vascular process, but the final diagnosis usually requires histological confirmation.

Treatment. Single lesions are easily treated with simple excision. Treatment is more difficult in the presence of multiple lesions, as new lesions are more likely to appear over time.

References

1 Weiss SW, Enzinger FM. Spindle cell hemangioendothelioma: a low grade angiosarcoma resembling a cavernous hemangioma and Kaposi's sarcoma. *Am J Surg Pathol* 1986; **10**: 521–30.
2 Scott GA, Rosai J. Spindle cell hemangioendothelioma: report of seven additional cases of a recently described vascular neoplasm. *Am J Dermatopathol* 1988; **10**: 281–8.
3 Fletcher CDM, Beham A, Schmid C. Spindle cell haemangioendothelioma: a clinicopathological and immunohistochemical study indicative of a nonneoplastic lesion. *Histopathology* 1991; **18**: 291–301.
4 Ding J, Hashimoto H, Imayama S *et al*. Spindle cell hemangioendothelioma, probably a benign vascular lesion not a low-grade angiosarcoma: a clinicopathological, ultrastructural and immunohistochemical study. *Virchows Arch (A)* 1992; **420**: 77–85.
5 Imayama S, Murakamai Y, Hashimoto H *et al*. Spindle cell hemangioendothelioma exhibits the ultrastructural features of reactive vascular proliferation rather than of angiosarcoma. *Am J Clin Pathol* 1992; **97**: 279–87.
6 Perkins P, Weiss SW. Spindle cell hemangioendothelioma: an analysis of 78 cases with reassessment of its pathogenesis and biologic behavior. *Am J Surg Pathol* 1996; **20**: 1196–204.
7 Fanburg JC, Meis Kindblom JM, Rosenberg AE. Multiple enchondromas associated with spindle cell hemangioendotheliomas: an overlooked variant of Maffucci's syndrome. *Am J Surg Pathol* 1995; **19**: 1029–38.
8 Sheehan M, Roumpf SO, Summerlin DJ *et al*. Spindle cell hemangioma: report of a case presenting in the oral cavity. *J Cutan Pathol* 2007; **34**: 797–800.

9 Tosios KI, Gouveris I, Sklavounou A *et al*. Spindle cell hemangioma (hemangioendothelioma) of the head and neck: report of an unusual (or underdiagnosed) tumor. *Oral Surg Oral Med* 2008; **105**: 216–21.

Symplastic haemangioma

Definition. This is not a distinctive variant of haemangioma but represents extensive degenerative changes in a pre-existing haemangioma, closely mimicking malignancy [1–3]. Only a handful of cases have been reported. From personal experience with a small number of cases, the pre-existing vascular lesion is often either not identifiable or it represents a cirsoid aneurysm.

Clinical features. These are not distinctive. However, the patient is usually an adult, and the description is usually of a long-standing lesion that has rapidly increased in size.

Pathology. These tumours are often polypoid and well-circumscribed and do not tend to be ulcerated. The typical histological picture consists of dilated and congested, thin to thick-walled vascular spaces surrounded by a variable cellular stroma with frequent myxoid change and haemorrhage. Stromal cells and smooth muscle cells within the vessel walls show variable cytological atypia, consisting of nuclear enlargement and hyperchromatism. The endothelial cells lining the vascular spaces may be plump but do not display cytological atypia, multilayering or mitotic activity, allowing distinction from an angiosarcoma. Often cells have a bizarre appearance and multinucleated cells are common. Mitotic figures may be found but tend to be rare. Very occasional, atypical mitotic figures may also be seen.

References

1 Tsang WYW, Chan JKC, Fletcher CDM *et al*. Symplastic hemangioma: a distinctive vascular neoplasm featuring bizarre stromal cells. *Int J Surg Pathol* 1994; **1**: 202.
2 Kutzner H, Winzer M, Mentzel T. [Symplastic hemangioma]. *Hautarzt* 2000; **51**: 327–31.
3 Goh N, Dayrit J, Calonje E. Symplastic hemangioma. Report of two cases. *J Cutan Pathol* 2006; **33**: 735–40.

Vascular tumours of intermediate malignancy

Kaposiform haemangioendothelioma [1–5]

Synonym
- Kaposi-like infantile haemangioendothelioma

Definition. Kaposiform haemangioendothelioma is a locally aggressive, vascular neoplasm, which occurs mainly in the abdominal cavity [1] but can affect primarily the skin or deeper soft tissues.

Incidence and aetiology. This tumour is rare and presents mainly in young children under the age of 2 years, with no sex predilection. Some lesions are congenital [6]. Rare cases occur in older children and adults. In 20% of cases, there is an association with lymphangiomatosis [3]. It appears clear that this lesion is truly neoplastic. Although it is not malignant, it causes morbidity and mortality due to its location and the frequent occurrence of consumption coagulopathy (Kasabach–Merritt syndrome).

Clinical features. The most common presentation by far is that of a large, retroperitoneal, infiltrative mass. Involvement of neighbouring organs and the very common association with Kasabach–Merritt syndrome may lead to death. This complication is less common in more superficial tumours, particularly those located in the dermis and subcutaneous tissue [5,7,8]. Multifocal lesions are exceptional [9].

Pathology. The growth pattern is lobular and infiltrative. Multiple nodules with haemorrhage and surrounding fibrosis are seen. Tumour lobules are composed of bland, spindle-shaped cells with poorly defined, pink cytoplasm. Cleft-like spaces are often seen between spindle-shaped cells, and the resemblance to Kaposi's sarcoma can be striking. However, numerous capillaries, often associated with microthrombi, are also present in tumour lobules. Epithelioid endothelial cells with focal vacuolation are also present. These features, along with the striking lobular architecture of the tumour and negative staining for HHV8, allow distinction from Kaposi's sarcoma. Podoplanin (D2-40), a marker of lymphatic endothelium, is positive in the spindle cells and lymphatic channels around tumour lobules [10]. This finding not only suggests a lymphatic line of differentiation for this tumour, but it is also useful in making the histological diagnosis and in differential diagnosis from other tumours such as tufted angioma in which the tumour lobules are negative for D2-40 [11]. However, it has been suggested that Kaposiform hemangioendothelioma and tufted angioma are part of the same spectrum [12].

Treatment. Complete excision is desirable as local recurrence is frequent, but this may be difficult to achieve when involvement is extensive. Spontaneous regression does not occur. Treatment of Kasabach–Merritt syndrome is difficult and good response has been reported with vincristine [13]. Anecdotal cases responding to interferon-α have been described [14].

References

1 Tsang WY, Chan JK. Kaposi-like infantile hemangioendothelioma: a distinctive vascular neoplasm of the retroperitoneum. *Am J Surg Pathol* 1991; **15**: 982–9.
2 Niedt GW, Alba Greco M, Wieczorek R *et al*. Hemangioma with Kaposi's sarcoma-like features: report of two cases. *Pediatr Pathol* 1989; **9**: 567–75.
3 Zukerberg LR, Nickoloff BJ, Weiss SW. Kaposiform hemangioendothelioma of infancy and childhood: an aggressive neoplasm associated with Kasabach–Merritt syndrome and lymphangiomatosis. *Am J Surg Pathol* 1993; **17**: 321–8.
4 Fukunaga M, Ushigome S, Ishikawa E. Kaposiform haemangioendothelioma associated with Kasabach–Merritt syndrome. *Histopathology* 1996; **28**: 281–4.
5 Vin-Christian K, McCalmont TH, Frieden IJ. Kaposiform hemangioendothelioma: an aggressive, locally invasive vascular tumor that can mimic hemangioma of infancy. *Arch Dermatol* 1997; **133**: 1573–8.
6 Gianotti R, Gelmetti C, Alessi E. Congenital cutaneous multifocal kaposiform hemangioendothelioma. *Am J Dermatopathol* 1999; **21**: 557–61.
7 Mentzel T, Mazzoleni G, Dei Tos AP *et al*. Kaposiform hemangioendothelioma in adults: clinicopathologic and immunohistochemical analysis of three cases. *Am J Clin Pathol* 1997; **108**: 450–5.

8 Mac-Moune Lai F, To KF, Choi PC *et al*. Kaposiform hemangioendothelioma: five patients with cutaneous lesions and long follow-up. *Mod Pathol* 2001; **14**: 1087–92.
9 Deraedt K, Vander Poorten V, Van Geet C *et al*. Multifocal kaposiform haemangioendothelioma. *Virchows Arch* 2006; **448**: 843–6.
10 Debelenko LV, Perez-Atayde AR, Mulliken JB *et al*. D2-40 immunohistochemical analysis of pediatric vascular tumors reveals positivity in kaposiform hemangioendothelioma. *Mod Pathol* 2005; **18**: 1454–60.
11 Arai E, Kuramochi A, Tsuchida T *et al*. Usefulness of D2-40 immunohistochemistry for differentiation between kaposiform hemangioendothelioma and tufted angioma. *J Cutan Pathol* 2006; **33**: 492–7.
12 Chu CY, Hsiao CH, Chiu HC. Transformation between Kaposiform hemangioendothelioma and tufted angioma. *Dermatology* 2003; **206**: 334–7.
13 Haisley-Royster C, Enjolras O, Frieden IJ *et al*. Kasabach-Merritt phenomenon: a retrospective study of treatment with vincristine. *J Pediatr Hematol Oncol* 2002; **24**: 459–62.
14 Harper L, Michel JL, Emjolras O *et al*. Successful management of a retroperitoneal kaposiform hemangioendothelioma with Kasabach-Merritt phenomenon using alpha-interferon. *Eur J Pediatr Surg* 2006; **16**: 369–372.

Giant cell angioblastoma [1,2]

Definition. This is a very rare entity of which only a handful of cases have been reported. It is not clear whether it represents a true vascular tumour and, until it is more clearly delineated and defined, it has not been included in the latest WHO classification of vascular tumours.

Clinical features. Tumours are congenital and have been described on the hand, the palate and the scalp. The tumour is diffusely infiltrative and slowly growing. Two of the reported cases showed no progression after incomplete excision.

Pathology. The tumour is composed of infiltrative vascular channels lined by a single layer of bland endothelial cells and intermixed with solid nodules composed of spindle-shaped cells, histiocyte-like cells and osteoclasts. A plexiform growth pattern is often seen.

Treatment. Two cases have been successfully treated with interferon-α-2b [3].

References

1 Gonzalez-Crussi F, Choud P, Crawford SE. Congenital infiltrating giant cell angioblastoma, a new entity? *Am J Surg Pathol* 1991; **15**: 175–83.
2 Vargas SO, Perez-Atayde AR, Gonzalez-Crussi F *et al*. Giant cell angioblastoma: three additional occurrences of a distinct pathologic entity. *Am J Surg Pathol* 2001; **25**: 185–96.
3 Marler JJ, Rubin JB, Trede NS *et al*. Successful antiangiogenic therapy of giant cell angioblastoma with interferon alfa 2b: report of two cases. *Pediatrics* 2002; **109**: E37.

Retiform haemangioendothelioma [1–3]

Synonym
- Hobnail haemangioendothelioma

Definition. Retiform haemangioendothelioma is a rare variant of low-grade angiosarcoma with a tendency for local aggressive behaviour. It is characterized by arborizing vascular channels lined by endothelial cells with hobnail morphology.

Clinical features [1–4]. Retiform haemangioendothelioma presents mainly in young adults, with no sex predilection, as a slowly growing, asymptomatic, dermal and subcutaneous plaque or nodule. Rarely lesions present as a bruise [5]. Exceptional cases present with multiple lesions [6]. Rarely there is an association with lymphoedema or radiotherapy. Local recurrence occurs in up to 60% of cases. So far, there has only been one report of a tumour metastasizing to a regional lymph node, and a further lesion has spread locally to soft tissues [7]. No tumour-related deaths have been reported.

Pathology. Scanning magnification is distinctive and reveals arborizing, thin-walled, narrow, vascular channels with a striking resemblance to the rete testis. The growth pattern is infiltrative, and the vascular spaces are lined by bland hobnail endothelial cells with prominent nuclei and scanty cytoplasm. Intravascular papillae with collagenous cores, similar to those seen in papillary endolymphatic angioendothelioma, are sometimes seen. The surrounding stroma often appears hyalinized; a prominent mononuclear inflammatory cell infiltrate is common. The endothelial cells stain for vascular markers. There is no relationship to HHV8.

Treatment. Wide local excision is the treatment of choice.

References

1 Calonje E, Fletcher CD, Wilson Jones E *et al*. Retiform hemangioendothelioma: a distinctive form of low-grade angiosarcoma delineated in a series of 15 cases. *Am J Surg Pathol* 1994; **18**: 115–25.
2 Dufau JP, Pierre C, De SaintMaur PP *et al*. Hemangioendothelioma retiforme. *Ann Pathol* 1997; **17**: 47–51.
3 Fukunaga M, Endo Y, Masui F *et al*. Retiform haemangioendothelioma. *Virchows Arch* 1996; **428**: 301–4.
4 Tan D, Kraybill W, Cheney RT *et al*. Retiform hemangioendothelioma: a case report and review of the literature. *J Cutan Pathol* 2005; **23**: 634–7.
5 Ioannidou D, Panayiotides J, Krasagakis K *et al*. Retiform hemangioendothelioma presenting as bruise-like plaque in an adult woman. *Int J Dermatol* 2006; **45**: 53–5.
6 Duke D, Dvorak AM, Harrist TJ *et al*. Multiple retiform hemangioendotheliomas: a low grade angiosarcoma. *Am J Dermatopathol* 1996; **18**: 606–10.
7 Mentzel T, Stengel B, Katenkamp D. Retiform hemangioendothelioma: clinicopathologic case report and discussion of the group of low grade malignancy vascular tumors. *Pathologe* 1997; **18**: 390–4.

Papillary intralymphatic angioendothelioma [1]

Synonyms
- Endovascular lymphatic angioendothelioma
- Dabska's tumour

Definition. Defining this entity is difficult because, since its original description in 1969, few further convincing cases have been described [1–4]. Furthermore, the original series included some examples of what is now known as retiform haemangioendothelioma. Recently, the tumour has been better characterized under the preferred name of 'papillary endolymphatic angioendothelioma' [5]. It belongs to the family of tumours with hobnail endothelial cells, and it is characterized by dilated, cavernous-like lymphatic spaces with frequent papillary projections.

Clinical features. It presents mainly in infants and children, with 25% of the cases occurring in adults. There is no sex predilection. Presentation is as a slowly growing, asymptomatic plaque or nodule with a predilection for the limbs. In the original series of six cases, a tendency for local recurrence and metastasis to regional lymph nodes was reported [1], but in a recent series of 12 cases, none of the eight cases with follow-up recurred locally or metastasized [5]. It therefore seems likely that the behaviour of this tumour is benign. Further studies are needed to confirm whether it deserves to be kept in the group of tumours of intermediate behaviour.

Pathology. This tumour is composed of dilated, thin-walled channels simulating a cavernous lymphangioma. These channels are lined by bland hobnail endothelial cells with very rare mitotic figures. A striking feature is the formation of intraluminal papillary tufts with hyaline cores. Aggregates of mononuclear inflammatory cells may be seen around the vascular channels.

Treatment. Until the issue regarding the biological behaviour of this tumour is resolved, complete excision is recommended.

References

1 Dabska M. Malignant endovascular angioendothelioma of childhood. *Cancer* 1969; **24**: 503–9.
2 Manivel JC, Wick MR, Swanson PE *et al.* Endovascular papillary angioendothelioma of childhood. *Hum Pathol* 1986; **17**: 1240–4.
3 Morgan J, Robinson NJ, Rosen LB *et al.* Malignant endovascular papillary angioendothelioma. *Am J Dermatopathol* 1989; **11**: 64–8.
4 Patterson K, Chandra RS. Malignant endovascular papillary angioendothelioma. *Arch Pathol Lab Med* 1985; **109**: 671–3.
5 Fanburgh-Smith JC, Michal M *et al.* Papillary intralymphatic angioendothelioma (PILA): a report of twelve cases of a distinctive vascular tumor with phenotypic features of lymphatic vessels. *Am J Surg Pathol* 1999; **23**: 1004–10.

Kaposi's sarcoma [1–3]

Synonyms
- Kaposi's disease
- Granuloma multiplex haemorrhagicum
- Idiopathic multiple pigmented sarcoma

Definition. A multifocal, endothelial proliferation predominantly involving the skin and other organs and associated with formation of vascular channels and proliferation of spindle-shaped cells. It is not clear whether Kaposi's sarcoma is a reactive vascular proliferation or a neoplastic process (see below).

Aetiology and pathogenesis. In the mid 1990's, Chang *et al.* described a new human gammaherpesvirus associated with Kaposi's sarcoma [4]. This virus is closely associated to Epstein–Barr virus, was named human herpesvirus type 8 (HHV8), and it is associated with all clinical variants of Kaposi's sarcoma (HIV/AIDS-related Kaposi's sarcoma, the African endemic type, Kaposi's sarcoma induced by iatrogenic immunosuppresion and Mediterranean endemic Kaposi's sarcoma) [5,6]. The virus can be found in the blood of patients before lesions of Kaposi's sarcoma develop [7]. This gives further support to the belief that this virus, along with genetic, immunological and environmental factors, is closely involved in the pathogenesis of Kaposi's sarcoma [8].

The multifocal development, symmetry of lesions, slow evolution of the classic form of the disease, regression when immunosuppression is reduced or stopped, and histology both of inflammation and of cells lacking cytological atypia, has led many to suggest that Kaposi's sarcoma is a reactive condition and not a neoplastic process. A few reports demonstrating the presence of clonality tend to support the hypothesis that this disorder is neoplastic [9]. Recent studies have suggested that the disease, in fact, starts as a reactive angioproliferative and inflammatory process, but progresses to become a monoclonal neoplastic process [10,11]. This is probably the result of close complex interactions between inflammatory cytokines, angiogenic factors, HHV8 and, in HIV-positive patients, the HIV virus itself [12]. In the latter setting it has been demonstrated that the HIV-1 trans-activating protein Tat-1 promotes the development of lesions by increasing the activity of different cytokines and angiogenic factors [13].

For many years, the line of differentiation of the proliferating cell in Kaposi's sarcoma remained difficult to elucidate. The suspicion has always been that the main proliferating cells are endothelial cells with lymphatic differentiation. This has recently been substantiated by the development of lymphatic endothelium-specific antibodies, including Lyve-1, podoplanin (D2-40) and Prox-1, which are positive in the proliferating cells in Kaposi's sarcoma [14,15].

At present, there are four recognized clinical subsets of Kaposi's sarcoma. These are:

1 Classic
2 Endemic
3 Iatrogenic
4 Human immunodeficiency virus (HIV)-related (Chapter 35).

Classic Kaposi's sarcoma [16–18] is as described originally by Kaposi. It is found mainly in elderly males, particularly from Southern Europe (mainly Italian and Greek) or Jews of Eastern European origin. The lesions begin slowly and insidiously around the ankle and slowly spread up the leg (Fig. 56.20). Lymphoedema



Fig. 56.20 Classic Kaposi's sarcoma arising on the feet of a male patient of Mediterranean origin.

can occur as a complication. Lesions in other locations, including the oral mucosa, are very rare. Involvement of internal organs is not usually seen. The disease is very rarely responsible for the death of the patient. An association with haemopoietic malignancies may be seen.

Endemic Kaposi's sarcoma [19,20] is found in equatorial Africa, mainly in the Democratic Republic of Congo, Uganda [21,22] and Rwanda. In adults, males predominate, but this form is also seen in children. Crops of cutaneous, vascular lesions develop, and may be associated with gross oedema. Visceral lesions may also occur; the prognosis is poor if there is extracutaneous involvement.

Iatrogenic Kaposi's sarcoma [16,23,24]. This is seen in transplant patients and after cytotoxic chemotherapy for lymphomas. Drug-induced immunosuppression to prevent rejection of transplanted organs markedly increases the risk of developing lymphomas and other tumours, including Kaposi's sarcoma. In transplant patients, Kaposi's sarcoma is 150 times more common than expected and affected patients may be younger than those with other types of Kaposi's sarcoma (excepting those with HIV infection). In a large, retrospective study over 23 years, Kaposi's sarcoma developed in 3.9% of cases of kidney transplant patients [23]. Both systemic and cutaneous involvement may occur, and the progress of the disease may be aggressive, causing the death of the patient. If it is possible to remove the immunosuppression, the lesions will regress.

Kaposi's sarcoma associated with HIV infection [25–28]. This variant was first recognized in 1979 [29,30] when an epidemic of Kaposi's sarcoma was identified in the homosexual community in New York. Since that time, it became firmly associated with the later stages of HIV infection. It is much commoner in homosexual and bisexual men than in others at risk, such as drug abusers or haemophiliacs. Kaposi's sarcoma usually develops in the later stages of the disease and it may be a presenting feature of HIV infection. With the advent of highly active antiretroviral therapy (HAART) the incidence of Kaposi's sarcoma in HIV/AIDS has decreased dramatically in the Western world [31]. As a result of HAART it is rare to see patients presenting with widespread lesions of Kaposi's sarcoma and the latter may regress as a result of this therapy, making the clinical and histological diagnosis even more difficult. This is not true, however, in third world countries, particularly in Africa [32,33] where the availability of HAART is still very limited. In patients on HAART and according to the degree of restoration of the immune system, lesions may regress; also, if they develop during treatment they are usually limited in number and extent. It is more common now to see patients with early lesions consisting of only one or two flat, macular lesions (Fig. 56.21) than with extensive nodular or plaque lesions. However, in patients with prominent immunosuppression, as still seen in many sub-Saharan African countries, the lesions may occur anywhere on the body, develop with explosive rapidity and become large nodules. The face and mucous membranes, such as the soft palate, are relatively frequently involved (Fig. 56.22). Involvement of lymph nodes, lungs and gastrointestinal tract is common.



Fig. 56.21 Patch-stage Kaposi's sarcoma in an HIV-positive patient.

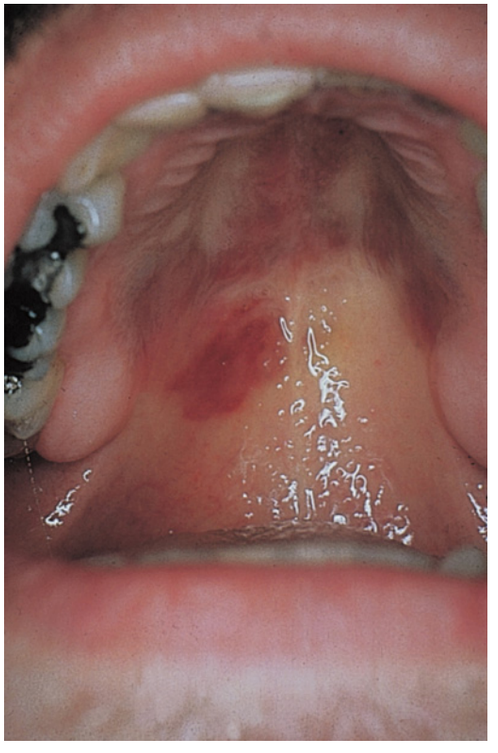


Fig. 56.22 Early lesion of Kaposi's sarcoma in an HIV-positive patient.

Clinical features [2,34–36]. Kaposi's sarcoma tends to occur in males. The lesions have a dark-blue or purplish colour. Initially, they may be almost macular and when they become tumid, pressure may produce partial blanching to reveal a brown tinge. The process usually begins on the extremities, most commonly on the feet and occasionally on the hands, ears or nose. Individual tumours enlarge to a diameter of 10–30 mm and stop growing. The process is multifocal, and adjacent areas may fuse to form a plaque or tumour. Oedema of the limb may follow, or at times precede, the appearance of the tumour. There are few subjective symptoms;

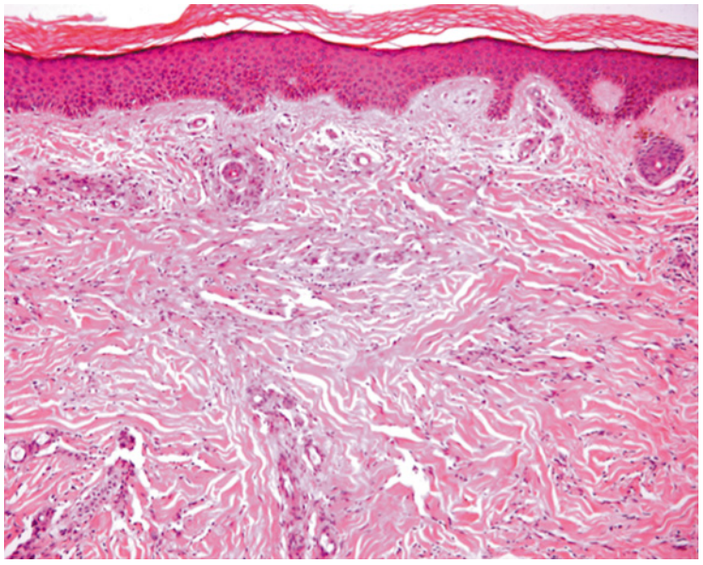


Fig. 56.23 Patch-stage Kaposi's sarcoma. Note the dermal proliferation of small, thin-walled, irregular lymphatic-like channels around pre-existing, normal blood vessels and adnexal structures.

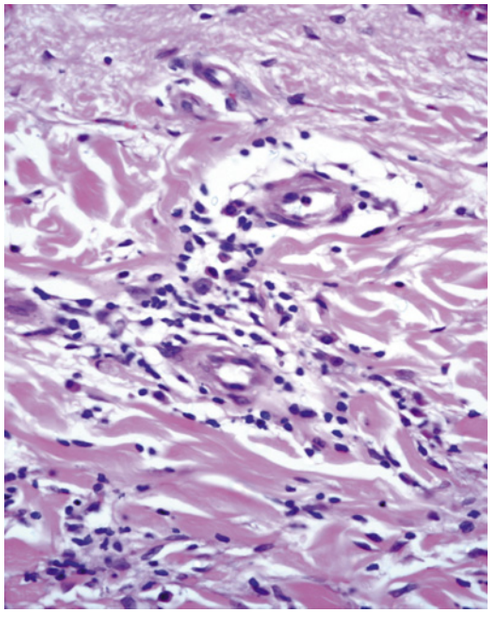


Fig. 56.24 Patch-stage Kaposi's sarcoma. Small, irregular vascular channels lined by bland endothelial cells. Note the promontory sign, in which a normal pre-existing capillary seems to be floating in a newly formed channel.

pain may be felt in nodules on pressure areas. The lesions may involute to leave pigmented scars, or may become eroded, ulcerated or fungating. New lesions may appear along the course of superficial veins, and in time most patients have more or less symmetrical lesions. The rate of spread is remarkably variable. It tends to be slow in Europeans and more rapid in Africans, where oedema is often the first sign. Lymph nodes, mucosal surfaces and internal organs, particularly the small intestine, may all be involved as the disease progresses. Kaposi's sarcoma may at times start in other organs and run its course without skin manifestation. Visceral involvement is the common pattern in African children, with lymph nodes as the main tissue involved.

Patients presenting with Kaposi's sarcoma associated with severe immunosuppression have subtle lesions, which may well be missed by the unwary [2]. They may have only one or two lesions scattered over the body, and these may resemble slight areas of trauma or a simple bruise. The lesions are therefore quite dissimilar from the classic, florid lesions developing on the lower limbs of the older patients from central Europe.

Pathology [37–39]. The cutaneous lesions of Kaposi's sarcoma can generally be divided into patch, plaque and nodular stages. These stages often overlap clinically and histologically. In the patch stage of the disease, there is a proliferation of jagged, irregular, lymphatic-like vascular channels lined by a single layer of bland endothelial cells; these channels particularly surround pre-existing blood vessels and adnexal structures (Fig. 56.23). Normal, pre-existing capillaries and even adnexal structures seem to be floating within the newly formed channels, the so-called 'promontory sign' (Fig. 56.24). From the early stages a patchy, variably prominent, mononuclear inflammatory cell infiltrate containing plasma cells is seen. This is associated with extravasation of red blood cells and haemosiderin deposition. In some cases, numerous, irregular, widely dilated, lymphatic-like channels impart a prominent lymphangiomatous appearance (lymphangiomatous Kaposi's sarcoma) [40].

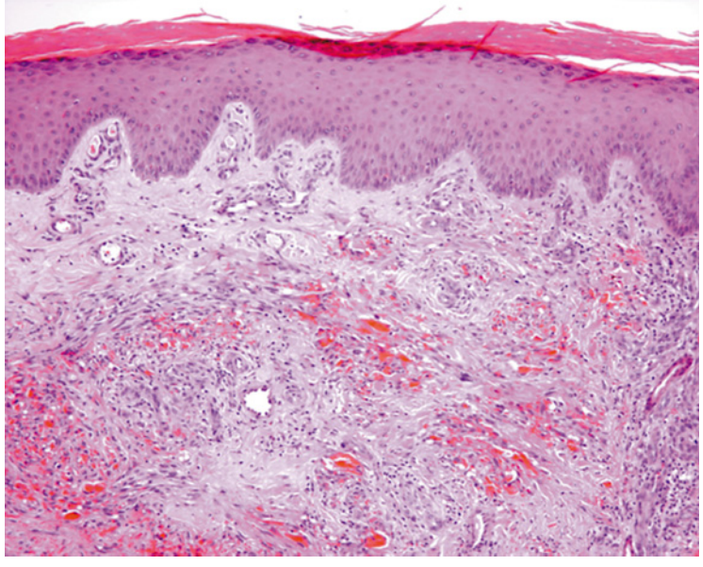


Fig. 56.25 Plaque-stage Kaposi's sarcoma. More diffuse proliferation of vascular channels with prominent haemorrhage.

The plaque stage is an exaggeration of the patch stage (Fig. 56.25). The vascular channels increase in number, and a network of bland spindle-shaped cells with pink cytoplasm develops. Dilated vascular channels in a back-to-back pattern may also be seen. Intra- or extracellular, hyaline, PAS-positive, eosinophilic globules are common, and probably represent degenerate red blood cells [41]. Involvement of the whole dermis and superficial subcutis is frequent.

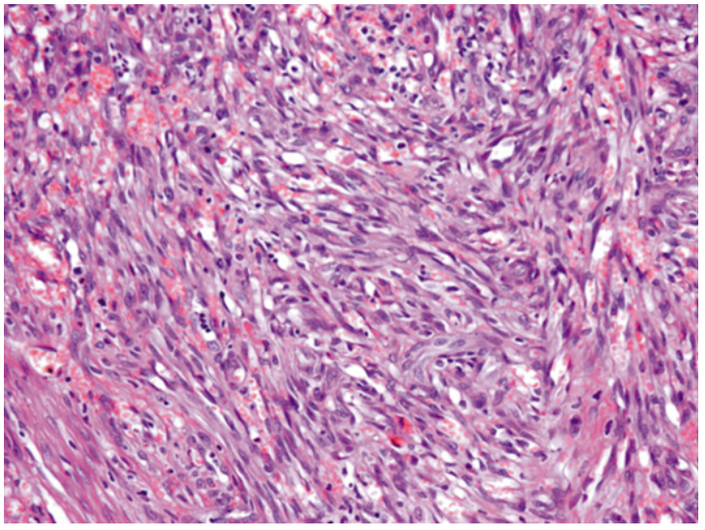


Fig. 56.26 Nodular Kaposi's sarcoma. Note the typical, sieve-like appearance, with blood cells between the cleft-like spaces.

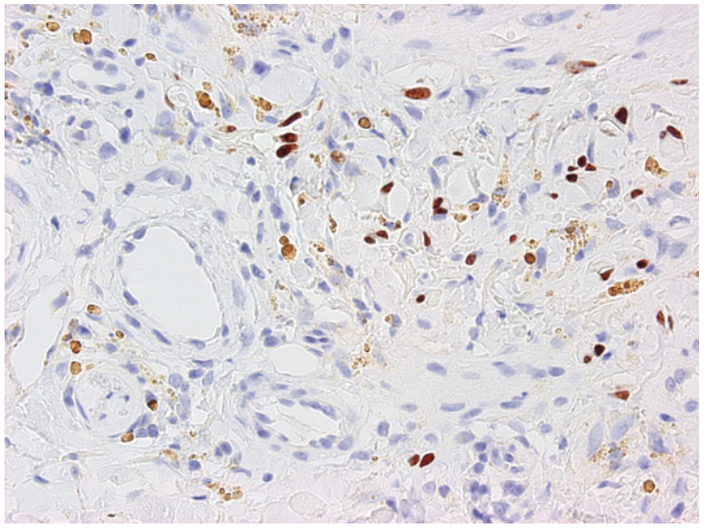


Fig. 56.27 Immunohistochemistry for the LNA of HHV8 in a case of Kaposi's sarcoma highlighting the presence of nuclear staining in the proliferating endothelial cells.

In the nodular stage, there are fairly well-circumscribed nodules of generally bland, spindle-shaped cells forming frequent cleft-like spaces that impart a typical sieve-like appearance (Fig. 56.26). Extravasated red blood cells are plentiful, as are hyaline globules. Mitotic figures are common. The periphery of the nodules may display a more angiomatous appearance.

Rarely, lesions of Kaposi's sarcoma may be partially or totally in an intravascular location, particularly within a vein [42].

Very rare examples of Kaposi's sarcoma display a high degree of cytological atypia and behave in an aggressive fashion.

The histology of lesions of Kaposi's sarcoma that have regressed after chemotherapy or with angiogenesis inhibitors, including Col-3 or HAART, may be very difficult to interpret [43]. Regression may be partial or complete. In completely regressed lesions there is absence of irregular lymphatic-like channels and spindle-shaped cells, increase in the number of capillaries in the superficial dermis and a superficial, perivascular lymphohistiocytic inflammatory cell infiltrate with variable numbers of siderophages. Partially regressed lesions show prominent decrease in the number of lymphatic-like vascular channels and spindle-shaped cells and focal inflammation with siderophages. The residual spindle-shaped cells tend to be arranged around superficial and mid-dermal capillaries. These changes are correlated with prominent decrease in the expression of LAN-1.

A useful aid in the histological diagnosis of Kaposi's sarcoma is a monoclonal antibody against the latent nuclear antigen 1 (LNA-1) of HHV8, which stains tumour cells in all cases of the disease [44]. Positive cases demonstrate granular nuclear staining (Fig. 56.27). *In situ* hybridization was the only technique initially used to demonstrate the virus, but this is a more expensive and time consuming technique and it is not widely available.

The pathological differential diagnosis includes many benign vascular tumours or reactive proliferations, including spindle cell haemangioma, tufted angioma, microvenular haemangioma, hobnail haemangioma, progressive lymphangioma and, on the lower legs, a 'venous' dermatitis (acroangiodermatitis). Angiosarcoma is also often considered in the differential diagnosis, but in the latter there is clear evidence of cytological atypia, mitotic activity and multilayering.

Differential diagnosis. The early lesion is most likely to be confused with a wide variety of benign vascular proliferations. It must also be distinguished from fibrous histiocytoma or from other types of soft-tissue tumours. Its evolution from a macular lesion and its characteristic colour, slow development and multifocal distribution make the diagnosis likely in most instances. Cases in which the tumour is preceded by oedema may cause difficulty, as angiosarcoma may arise in chronic lymphoedema. In prolonged venous hypertension of the lower legs, or in association with underlying vascular malformations, nodules with a close resemblance to Kaposi's sarcoma may develop (acroangiodermatitis, pseudo-Kaposi's sarcoma); they differ, however, in lack of progression, and a spindle-cell proliferation is not seen in the histological sections.

Treatment. Where a small area is involved, excision or radiotherapy can be used. Superficial radiotherapy is rapid and effective, and is the treatment of choice for the majority of patients with nodular disease of the extremities. For more extensive disease a number of treatment options have been used including antiviral, cytotoxic and immunomodulator drugs. In HIV/AIDS regression of lesions may be seen with HAART [45]. Liposomal doxorubicin may also be a useful treatment and interleukin-12, either alone or in combination with the latter, may also induce remission in AIDS patients with Kaposi's sarcoma who are on HAART [46]. Pegylated liposomal doxorubicin has been used with success on its own, as second line treatment of AIDS-related Kaposi's sarcoma and in advanced, classic Kaposi's sarcoma [47,48].

References

1 Cox FH, Helwig EG. Kaposi's sarcoma: a review. *Cancer* 1959; **12**: 289–98.
2 Gottlieb G, Ackermann AB, eds. *Kaposi's Sarcoma: a Text Atlas*. Philadelphia: Lea & Febiger 1989.
3 Schwartz R. Kaposi's sarcoma: advances and perspectives. *J Am Acad Dermatol* 1996; **34**: 804–14.
4 Beral V, Peterman TA, Berkelman R *et al*. Kaposi's sarcoma among persons with AIDS: a sexually transmitted infection. *Lancet* 1990; **i**: 123–8.
5 Moore PS, Chang Y. Detection of herpes virus-like sequences in Kaposi's sarcoma in patients with and without HIV infection. *N Engl J Med* 1995; **332**: 1181–5.
6 Nickoloff BJ, Foreman KE. Charting a new course through the chaos of KS (Kaposi's sarcoma). *Am J Pathol* 1996; **148**: 1323–9.
7 Gao SJ, Kingsley L, Hoover SR *et al*. Seroconversion to antibodies against Kaposi's sarcoma-associated herpes virus-related nuclear antigens before the development of Kaposi's sarcoma. *N Engl J Med* 1996; **335**: 233–41.
8 Ensoli B, Sgadari C, Barillari G *et al*. Biology of Kaposi's sarcoma. *Eur J Cancer* 2001; **37**: 1251–69.
9 Rabkin CS, Janz S, Lash A *et al*. Monoclonal origin of multicentric Kaposi's sarcoma lesions. *N Engl J Med* 1997; **336**: 988–93.
10 Judde JG, Lacoste V, Brière J *et al*. Monoclonality or oligoclonality of human herpesvirus-8 terminal repeat sequences in Kaposi's sarcoma and other diseases. *J Nat Cancer Inst* 2000; **92**: 677.
11 Duprez R, Lacoste V, Brière J *et al*. Evidence for a multiclonal origin of multicentric advanced lesions of Kaposi sarcoma. *J Natl Cancer Inst* 2007; **99**: 1086.
12 Gessain A, Duprez R. Spindle cells and their role in Kaposi's sarcoma. *Int J Biochem Cell Biol* 2005; **37**: 2457.
13 Aoki Y, Tosato G. Interactions between HIV-1 Tat and KSHV. *Curr Top Microbiol Immunol* 2007; **312**: 309.
14 Carroll PA, Brazeau E, Lagunoff M. Kaposi's sarcoma-associated herpesvirus infection of blood endothelial cells induces lymphatic differentiation. *Virology* 2004; **328**: 7.
15 Xu H, Edwards JR, Espinosa O *et al*. Expression of a lymphatic endothelial cell marker in benign and malignant vascular tumors. *Hum Pathol* 2004; **35**: 857.
16 Bluefarb SM, ed. *Kaposi's Sarcoma: Multiple Idiopathic Haemorrhagic Sarcoma*. Springfield: Thomas, 1957.
17 Losspalluti M, Mastrolonardo M, Lonosole F *et al*. Classical Kaposi's sarcoma: a survey of 163 cases observed in Bari, Italy. *Dermatology* 1995; **191**: 104–8.
18 Tedeschi CG. Some considerations concerning the nature of the so-called sarcoma of Kaposi. *AMA Arch Pathol* 1958; **66**: 656–84.
19 Oettle AG. Geographical and racial differences in the frequency of Kaposi's sarcoma as evidence of environmental or genetic causes. *Acta UICC Cancer* 1962; **18**: 330–63.
20 Olowasanmi JO, Williams AO, Alli AF. Superficial cancer in Nigeria. *Br J Cancer* 1969; **23**: 714–28.
21 Taylor JF, Templeton AC, Vogel CL *et al*. Kaposi's sarcoma in Uganda: a clinicopathological study. *Int J Cancer* 1971; **8**: 122–35.
22 Templeton AC, Viegas OAC. Racial variations in tumour incidence in Uganda. *Trop Geogr Med* 1970; **22**: 431–8.
23 Serraino D, Angeletti C, Carrieri MP *et al*. Kaposi's sarcoma in transplant and HIV infected patients: an epidemiologic study in Italy and France. *Transplantation* 2005; **80**: 1699.
24 Moosa MR. Kaposi's sarcoma in kidney transplant recipients: a 23-year experience. *QJM* 2005; **98**: 205.
25 Lemlich G, Schwam L, Lebwohl M. Kaposi's sarcoma and acquired immunodeficiency syndrome. *J Am Acad Dermatol* 1987; **16**: 319–25.
26 Jessop S. HIV-associated Kaposi's sarcoma. *Dermatol Clin* 2006; **24**: 509.
27 Lemlich G, Schwam L, Lebwohl M. Kaposi's sarcoma and acquired immunodeficiency syndrome: postmortem findings in twenty-four cases. *J Am Acad Dermatol* 1987; **16**: 319–25.
28 Friedmann-Kien AE, Laubenstein LJ, Rubinstein P *et al*. Disseminated Kaposi's sarcoma in homosexual men. *Ann Intern Med* 1982; **96**: 693–700.
29 Gottlieb GJ, Ragaz A, Vogel JV *et al*. A preliminary communication on extensively disseminated Kaposi's sarcoma in young homosexual men. *Am J Dermatopathol* 1981; **3**: 111–4.
30 Groopman JE. Causation of AIDS revealed. *Nature* 1984; **308**: 769.
31 Biggar RJ. AIDS-related cancers in the era of highly active antiretroviral therapy. *Oncology (Williston Park)* 2001; **15**: 439–48.
32 Onunu AN, Okoduwa C, Eze EU *et al*. Kaposi's sarcoma in Nigeria. *Int J Dermatol* 2007; **46**: 204.
33 Mwanda OW, Fu P, Collea R, Whalen C *et al*. Kaposi's sarcoma in patients with and without human immunodeficiency virus infection, in a tertiary referral centre in Kenya. *Ann Trop Med Parasitol* 2005; **99**: 81.
34 Viera J, Frank E, Spira TJ *et al*. Acquired immune deficiency in Haitians: opportunistic infections in previously healthy Haitian immigrants. *N Engl J Med* 1983; **308**: 125–9.
35 Templeton AC. Kaposi's sarcoma. *Pathol Ann* 1981; **16**: 315–36.
36 Tappero JW, Connant MA, Wolfe SF *et al*. Kaposi's sarcoma: epidemiology, pathogenesis, histology, clinical spectrum, staging criteria and therapy. *J Am Acad Dermatol* 1993; **28**: 371–95.
37 Dorfman RF. Kaposi's sarcoma revisited. *Hum Pathol* 1984; **15**: 1013–7.
38 Murray JF, Lothe F. The histopathology of Kaposi's sarcoma. *Acta Unio Int Contra Cancrum* 1962; **18**: 413–28.
39 Chor PJ, Santa Cruz DJ. Kaposi's sarcoma: a clinicopathologic review and differential diagnosis. *J Cutan Pathol* 1992; **19**: 6–20.
40 Gange RW, Wilson Jones E. Lymphangioma-like Kaposi's sarcoma: a report of three cases. *Br J Dermatol* 1979; **100**: 327–34.
41 Kao GF, Johnson FB, Sulica VI. The nature of hyaline (eosinophilic) globules and vascular slits of Kaposi's sarcoma. *Am J Dermatopathol* 1990; **12**: 256–67.
42 Luzar B, Antony F, Ramdial PK *et al*. Intravascular Kaposi's sarcoma – A hitherto unrecognized phenomenon. *J Cutan Pathol* 2007; **34**: 861–4.
43 Pantanowitz L, Dezube BJ, Pinkus GS *et al*. Histological characterization of regression in acquired immunodeficiency syndrome-related Kaposi's sarcoma. *J Cutan Pathol* 2004; **31**: 26.
44 Cheuk W, Wong KO, Wong CS *et al*. Immunostaining for human herpesvirus 8 latent nuclear antigen-1 helps distinguish Kaposi's sarcoma from its mimics. *Am J Clin Pathol* 2004; **121**: 335.
45 Leder HA, Galor A, Peters GB *et al*. Resolution of conjunctival Kaposi sarcoma after institution of highly active antiretorviral therapy alone. *Br J Ophthalmol* 2008; **92**: 151.
46 Yarchoan R, Pluda JM, Wyvill KM *et al*. Treatment of AIDS-related Kaposi's sarcoma with interleukin-12: rationale and preliminary evidence of clinical activity. *Crit Rev Immunol* 2007; **27**: 401–14.
47 Udhrain A, Skubitz KM, Northflet DW. Pegylated liposomal doxorubicin in the treatment of AIDS-related Kaposi's sarcoma. *Int J Nanomedicine* 2007; **2**: 345–52.
48 Di Lorenzo G, Di Trolio R, Montesarchio V *et al*. Pegylated liposomal doxorubicin as second-like therapy in the treatment of patients with advanced classic Kaposi sarcoma. A retrospective study. *Cancer* 2008; **112**: 1147–52.

Malignant vascular tumours

Angiosarcoma [1–4]

Synonyms
- Malignant haemangioendothelioma
- Haemangiosarcoma
- Lymphangiosarcoma

Definition. A malignant vascular tumour, arising from both vascular and lymphatic endothelium. Except for the pure epithelioid variant of angiosarcoma (see below), cutaneous angiosarcoma almost exclusively occurs in three settings: idiopathic angiosarcoma of the face, scalp and neck [2–4], angiosarcoma associated with chronic lymphoedema (Stewart–Treves syndrome) [5–9] and post-irradiation angiosarcoma [10–12]. In this chapter, the terms 'angiosarcoma' and 'lymphangiosarcoma' are used interchangeably.

Incidence. This is a rare tumour in any form. Angiosarcoma of the scalp and face of the elderly is very rare, affects mainly males and it is almost invariably fatal.

Stewart–Treves syndrome occurs in 0.5% of patients who survive mastectomy for more than 5 years. The mean age at appearance of the angiosarcoma is 62 years, and the mean interval between mastectomy and the appearance of the tumour is 10.5 years [9]. Two cases have been reported in men following mastectomy [13]. Not all patients have received radiotherapy in association with the mastectomy, and not all have had axillary nodes removed.

Lymphoedema is not invariably present, or it may be late in appearing and antedate the tumour by only a short time. The incidence and cause of postmastectomy lymphoedema have been reviewed [14]. In the majority of cases, the clinical course and autopsy findings have shown that the treatment of the breast carcinoma was successful and that patients have had less frequent involvement of the axillary nodes than usual [9]. A small number of cases have arisen in lymphoedema of the lower limb, or in the upper limb without breast cancer and mastectomy [15]. Most of these patients were women.

Multiple primary malignancies have occurred in 8% of cases of Stewart–Treves syndrome [6] and a systemically acting carcinogen has been suggested [8,9]. There is no evidence to support this.

Post-irradiation angiosarcoma is rare and most cases arise in the skin after radiotherapy for breast or, less commonly, internal cancer [10–12].

Angiosarcoma occurring in other settings is very rare. Presentation in children is extremely rare [16]. Angiosarcoma may also exceptionally occur in benign vascular tumours including vascular malformations [17], in a large blood vessel [18], in association with a plexiform neurofibroma in neurofibromatosis [19], in a schwannoma [20], in a malignant peripheral nerve sheath tumour [21,22], in xeroderma pigmentosum [23], in a gouty tophus [24], in association with vinyl chloride exposure [25], in association with immunosuppression in organ transplantation [26] and as the mesenchymal component in a metaplastic carcinoma [27]. An exceptional case of an angiosarcoma producing granulocyte colony-stimulating factor and inducing a leukaemoid reaction has been described [28].



Fig. 56.28 Typical haemorrhagic appearance of an angiosarcoma.

Clinical features [3,4,29,30]. In all types of angiosarcoma, the first sign may be an area of bruising, often thought by the patient to be traumatic (Fig. 56.28). Dusky blue or red nodules develop and grow rapidly, and fresh, discrete nodules appear nearby. In some cases, haemorrhagic blisters are a prominent feature. As the tumours grow, the oedema may increase and older lesions may ulcerate. Multifocality is a very frequent finding; this makes surgical excision very difficult, particularly in those cases occurring on the face and scalp. Dissemination occurs early, with the first visceral deposits usually being in the lung and pleural cavity.

Most studies reporting outcome have confined their attention to idiopathic angiosarcoma of the face, neck and scalp, in which the reported 5-year survival is low, at between 12% and 33% [3,31]. Angiosarcomas arising in the setting of chronic lymphoedema and after radiotherapy appear to be equally aggressive. Combined series of idiopathic angiosarcoma of the face and scalp, other cutaneous angiosarcomas and angiosarcomas occurring in internal organs report 5-year survival rates varying between 24 and 34% [1,32–34]. Features found to affect prognosis vary between different studies. Tumour size and completeness of excision appear to be more reliable factors to predict outcome [28]. It has been suggested that a high mitotic count correlates with poor prognosis and that a heavy mononuclear inflammatory cell infiltrate correlates with good prognosis [3,5,28]. A recent study of cutaneous sporadic angiosarcomas, excluding those associated with radiotherapy or with chronic lymphoedema, has found by univariate analysis that factors associated with higher mortality include older age, lesions on trunk and limbs compared to those on the head and neck, necrosis and an epithelioid cell morphology [35]. Tumours with necrosis and epithelioid morphology were classified as high risk and confirmed by multivariate analysis to be associated with higher mortality. The depth of invasion correlated with higher risk of local recurrence. The caveat with this study is that it combines traditional head and neck angiosarcomas with those showing a more pure epithelioid cell morphology that usually occur elsewhere and are usually classified under a different category.

Pathology [4,36–38]. In the well-differentiated tumour, vascular channels infiltrate the normal structures in a disorganized fashion, as if trying to line every available tissue space with a layer of endothelial cells. The collagen is characteristically lined by tumour cells in a pattern that has been described as ‘dissection of collagen’ (Fig. 56.29). Tumour cells may be plumper than normal, double-layered in places and form solid, intravascular buds. The pattern of growth is more suggestive of lymphatic vessels than blood vessels, but both are probably involved. Haemorrhage is often prominent. Less well-differentiated tumours show more atypical, pleomorphic, endothelial cells, often with a spindle-cell morphology, which may be heaped into several layers or become syncytial.

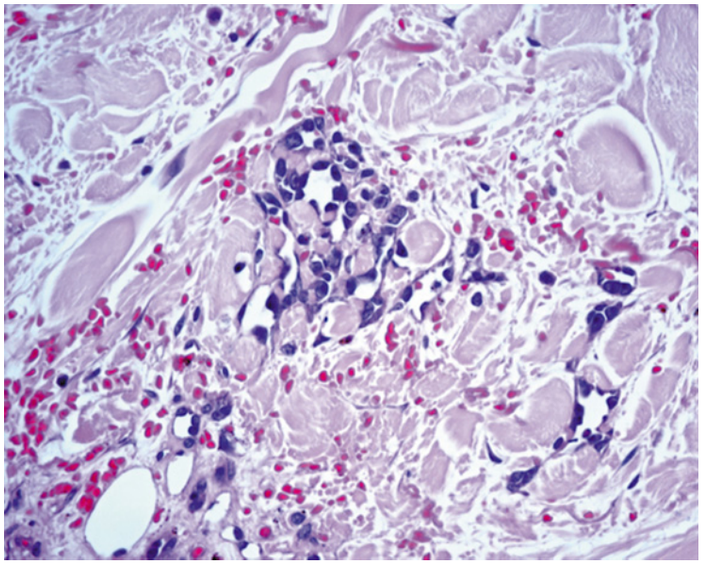


Fig. 56.29 Well-differentiated angiosarcoma, with thin-walled irregular vascular channels lined by atypical endothelial cells. Note the dissection of collagen pattern.

Advancing malignancy may be associated with loss of vascular pattern and proliferation of cell masses. Rare cases are composed of granular cells [39]. In exceptional cases, tumours may be extensively infiltrated by lymphocytes or macrophages. In these cases, distinction from a lymphoma may be difficult [40,41].

Immunohistochemical studies have indicated that antibodies to CD31 are the most reliable markers for routine use, compared with antibodies against von Willebrand factor and CD34 [7]. However, a panel of antibodies including the three markers is recommended in difficult cases as positivity to the various markers varies. Recently, an antibody against the carboxy terminal of the Fli-1 protein, a nuclear transcription factor member of the ETS family of DNA-binding transcription factors, has been shown to be a fairly specific marker of endothelial cells [42].

Cytogenetics studies of soft tissue and cutaneous angiosarcoma are limited to a few case reports. Most analyzed cases have shown complex cytogenetic aberrations [43,44].

Treatment [3]. All angiosarcomas, regardless of the setting in which they occur, have a bad prognosis. In the less malignant types, wide excision and grafting has controlled some cases. The response to radiotherapy is disappointing and is usually only palliative. In the early stages of angiosarcoma of a limb, radical amputation may offer a hope of cure. In idiopathic angiosarcoma of the head and neck, a very small percentage of patients with smaller lesions (usually less than between 5 and 10 cm in diameter at presentation) can be successfully treated with radical wide-field radiotherapy and surgery [1,32–34]. The best chance of survival in these patients resides in wide surgical excision followed by radiotherapy [45].

References

1 Mark RJ, Poen JC, Tran LM *et al.* Angiosarcoma: a review of 67 patients and review of the literature. *Cancer* 1996; **77**: 2400–6.

2 Bardwill JM, Mocega EE, Butler JJ *et al.* Angiosarcomas of the head and neck region. *Am J Surg* 1968; **11**: 548–53.

3 Holden CA, Spittle MF, Wilson Jones E. Angiosarcoma of the face and scalp: prognosis and treatment. *Cancer* 1987; **48**: 1907–21.

4 Maddox JC, Evans HL. Angiosarcoma of skin and soft tissue: a study of 44 cases. *Cancer* 1981; **48**: 1907–21.

5 Chen KTK, Gilbert EF. Angiosarcoma complicating generalized lymphangiectasia. *Arch Pathol Lab Med* 1979; **103**: 86–8.

6 Eby CS, Brennan MF, Fine G. Lymphangiosarcoma: lethal complication of chronic lymphedema—report of two cases and review of the literature. *Arch Surg* 1967; **94**: 223–30.

7 MacKenzie DH. Lymphangiosarcoma arising in chronic congenital and idiopathic lymphoedema. *J Clin Pathol* 1971; **24**: 524–9.

8 Stewart FW, Treves N. Lymphangiosarcoma in postmastectomy lymphedema: a report of six cases in elephantiasis chirurgica. *Cancer* 1948; **1**: 64–81.

9 Herrman JB. Lymphangiosarcoma of the chronically edematous extremity. *Surg Gynecol Obstet* 1965; **121**: 1107–15.

10 Goette DK, Detlefs RL. Postirradiation angiosarcoma. *J Am Acad Dermatol* 1985; **12**: 922–6.

11 Fineberg S, Rosen PP. Cutaneous angiosarcoma and atypical vascular lesions of the skin of the breast after radiation therapy for breast carcinoma. *Am J Clin Pathol* 1994; **102**: 757–63.

12 Karlsson P, Holmberg E, Johansson KA *et al.* Soft tissue sarcoma after treatment for breast cancer. *Radiother Oncol* 1996; **38**: 25–31.

13 Oettle AG, van Blerk PJP. Postmastectomy lymphostatic endothelioma of Stewart and Treves in a male. *Br J Surg* 1963; **50**: 736–43.

14 Treves N. An evaluation of the etiological factors of lymphedema following radical mastectomy: an analysis of 1007 cases. *Cancer* 1957; **10**: 444–59.

15 Scott RB, Nydick I, Conway H. Lymphangiosarcoma arising in lymphedema. *Am J Med* 1960; **28**: 1008–12.

16 Lezana-del Valle P, Gerald WL, Tsai J *et al*. Malignant vascular tumors in young patients. *Cancer* 1998; **83**: 1634–9.

17 Rossi S, Fletcher CD. Angiosarcoma arising in hemangioma/vascular malformation: report of four cases and review of the literature. *Am J Surg Pathol* 2002; **26**: 1319–29.

18 Abratt RP, Williams M, Raff M *et al*. Angiosarcoma of the superior vena cava. *Cancer* 1983; **52**: 740–3.

19 Chadhuri B, Ronan SG, Manahgod JR. Angiosarcoma arising in a plexiform neurofibroma. *Cancer* 1980; **46**: 605–10.

20 Trassard M, Le Doussal V, Bui BN *et al*. Angiosarcoma arising in a solitary schwannoma (neurilemoma) of the sciatic nerve. *Am J Surg Pathol* 1996; **20**: 1412–7.

21 Mentzel T, Katencamp D. Intraneural angiosarcoma and angiosarcoma arising in benign and malignant peripheral nerve sheath tumours: clinicopathological and immunohistochemical analysis of four cases. *Histopathology* 1999; **35**: 114–20.

22 Morphopoulos GD, Banerjee SS, Ali HH *et al*. Malignant peripheral nerve sheath tumour with vascular differentiation: a report of four cases. *Histopathology* 1996; **28**: 401–10.

23 Marcon I, Collini P, Casanova M *et al*. Cutaneous angiosarcoma in a patient with xeroderma pigmentosum. *Pediatr Hematol Oncol* 2004; **21**: 23–6.

24 Folpe AL, Johnston CA, Weiss SW. Cutaneous angiosarcoma arising in a gouty tophus: report of a unique case and a review of foreign material-associated angiosarcoma. *Am J Dermatopathol* 2000; **22**: 418–21.

25 Ghandur-Mnaymneh L, Gonzales MS. Angiosarcoma of the penis with hepatic angiomas in a patient with low vinyl chloride exposure. *Cancer* 1981; **47**: 1318.

26 Ahmed I, Hamacher KL. Angiosarcoma in a chronically immunosuppresed renal transplant recipient: report of a case and review of the literature. *Am J Dermatopathol* 2002; **24**: 330–5.

27 Kantrow SM, Boyd AS. Primary cutaneous metaplastic carcinoma: report of a case involving angiosarcoma. *Am J Dermatopathol* 2007; **29**: 270–3.

28 Nake N, Ohsawa M, Tomita Y *et al.* Prognostic factors in angiosarcoma: a multivariate analysis of 55 cases. *J Surg Oncol* 1996; **61**: 170–6.

29 Wilson Jones E. Malignant vascular tumours. *Clin Exp Dermatol* 1976; **1**: 287–312.

30 Orchard GE, Zelger B, Wilson Jones E, Russell Jones R. An immunohistochemical assessment of 19 cases of angiosarcoma. *Histopathology* 1996; **28**: 235–40.

31 Hori Y. Malignant hemangioendothelioma of the skin. *J Dermatol Surg Oncol* 1981; **7**: 130–6.

32 Morgan MB, Swann M, Somach S *et al*. Cutaneous angiosarcoma: a case series with prognostic correlations. *J Am Acad Dermatol* 2004; **50**: 867–74.
33 Abraham JA, Hamicek FJ, Kaufman AM *et al*. Treatment and outcome of 82 patients with angiosarcoma. *Ann Surg Oncol* 2007; **14**: 1953–67.
34 Mendenhall WM, Mendenhall CM, Werning JW *et al*. Cutaneous angiosarcoma. *Am J Clin Oncol* 2006; **29**: 524–8.
35 Deyrup AT, McKenney JK, Tighiouart M *et al*. Sporadic cutaneous angiosarcomas: a proposal for risk stratification based on 69 cases. *Am J Surg Pathol* 2008; **32**: 72–7.
36 Wilson Jones E. Malignant angioendothelioma of the skin. *Br J Dermatol* 1964; **76**: 21–39.
37 Girard C, Johnson WC, Graham JH. Cutaneous angiosarcoma. *Cancer* 1970; **26**: 868–83.
38 Lydiatt WM, Shaha AR, Sha JP. Angiosarcoma of the head and neck. *Am J Surg* 1994; **168**: 451–4.
39 Hitchcock MG, Hurt MA, Santa Cruz DJ. Cutaneous granular cell angiosarcoma. *J Cutan Pathol* 1994; **21**: 256–62.
40 Brightman LA, Demierre MF, Byers HR. Macrophage-rich epithelioid angiosarcoma mimicking malignant melanoma. *J Cutan Pathol* 2006; **33**: 38–42.
41 Requena L, Santonja C, Stutz N *et al*. Pseudolymphomatous cutaneous angiosarcoma: a rare variant of cutaneous angiosarcoma readily mistaken for cutaneous lymphoma. *Am J Dermatopathol* 2007; **29**: 342–50.
42 Folpe AL, Chand EM, Goldblum JR *et al*. Expression of Fli-1, a nuclear transcription factor distinguishes vascular neoplasms from potential mimics. *Am J Surg Pathol* 2001; **25**: 1061–6.
43 Schuborg C, Mertens F, Rydholm A *et al*. Cytogenetic analysis of four angiosarcomas from deep and superficial soft tissue. *Cancer Genet Cytogenet* 1998; **100**: 52–6.
44 Kindblom LG, Stenman G, Angervall L. Morphological and cytogenetic studies of angiosarcoma in Stewart-Treves syndrome. *Virchows Arch A Pathol Anat Histopathol* 1991; **419**: 439–45.
45 Pawlik TM, Paulino AF, McGinn C *et al*. Cutaneous angiosarcoma of the scalp: a multidisciplinary approach. *Cancer* 2003; **98**: 1716–26.

Epithelioid haemangioendothelioma [1–3]

Definition. Epithelioid haemangioendothelioma is a distinctive tumour characterized by epithelioid endothelial cells arranged in strands or as individual units, in a myxoid or hyalinized stroma. It was initially described as a low-grade malignant tumour, but it has recently been proposed that it should be classified as a fully malignant neoplasm, in view of the associated morbidity and mortality [3]. However, small, primary cutaneous lesions appear to have an indolent behaviour.

Clinical features [1–3]. This tumour may occur in many internal organs, and it is more commonly seen in deeper soft tissues. Involvement of the skin may occur primarily or as a result of direct extension from a deep-seated primary. Less than 10% of cases occur primarily in the skin. Tumours present in middle-aged adults, with an equal sex incidence. Cutaneous tumours are usually small, but deeper lesions are often several centimetres in diameter. Pain is a frequent complaint, probably due to angiocentricity. Involvement of other organs, including the lung, liver and bone, may be seen in some cases, and it is not clear whether this represents multicentricity or metastatic spread.

Pathology [1–3]. The neoplasm is infiltrative and is composed of strands, cords and nests of endothelial cells in a hyaline or myxoid stroma. Dermal lesions often consist of a fairly well-defined nodule. The tumour cells have epithelioid morphology and consist of pink cytoplasm, vesicular nuclei and inconspicuous nucleoli. Angiocentricity is commonly seen. Formation of vascular channels is not readily apparent but a common finding is the presence of intracytoplasmic vacuoles with or without red blood cells. A small number of cases display cytological atypia, which may be prominent, and a high mitotic count. There is no clear correlation between cytological grade and behaviour. Occasional tumours overlap with epithelioid angiosarcoma. Staining for endothelial cell markers, especially factor VIII-related antigen and CD31, is usually positive, and 20% of cases are focally positive for keratin [3,4].

Prognosis and treatment. Purely cutaneous tumours appear to have a benign behaviour, but there is some tendency for local recurrence. Deeper tumours have a recurrence rate of up to 15% and a mortality rate of 20%. Complete excision with clear margins is therefore necessary.

References

1 Weiss SW, Enzinger FM. Epithelioid hemangioendothelioma: a vascular tumor often mistaken for a carcinoma. *Cancer* 1982; **50**: 970–81.
2 Weiss SW, Ishak KG, Dail DH *et al*. Epithelioid hemangioendothelioma and related lesions. *Semin Diagn Pathol* 1986; **3**: 259–87.
3 Mentzel T, Beham A, Calonje E *et al*. Epithelioid hemangioendothelioma of skin and soft tissues: clinicopathologic and immunohistochemical study of 30 cases. *Am J Surg Pathol* 1997; **21**: 363–74.
4 Grey MH, Rosenberg AE, Dickersin GR *et al*. Cytokeratin expression in epithelioid vascular neoplasms. *Hum Pathol* 1990; **21**: 212–7.

Epithelioid angiosarcoma [1–3]

Definition. A distinctive variant of angiosarcoma composed almost exclusively of endothelial cells with an epithelioid morphology, often mimicking a carcinoma. This tumour represents the malignant end of the spectrum of tumours with epithelioid cell morphology.

Incidence. This is a rare tumour that mainly occurs in deep soft tissue, but that may present primarily in the skin or other organs.

Clinical features [1–3]. Cutaneous tumours present in young to middle-aged adults, mainly in males, with a predilection for the extremities. The typical presentation is that of solitary, or more rarely multiple, asymptomatic papules or nodules which are often haemorrhagic. It is not clear whether multiple lesions represent multifocality or metastatic disease. Occasional cases have been reported in association with a foreign body [4], radiotherapy [1] or an arteriovenous fistula [5]. Epithelioid angiosarcoma arising in another organ may present with cutaneous metastases [6].

Pathology [1–3]. Sheets of atypical epithelioid cells with abundant pink cytoplasm, vesicular nuclei and a single eosinophilic nucleolus occupy the dermis and/or subcutis. Haemorrhage and haemosiderin deposition is often seen. Formation of vascular channels is not readily apparent, and the main feature is the presence of intracytoplasmic vacuoles with or without red blood cells in variable numbers of tumour cells. Mitotic figures are common. Tumour cells are variably positive for vascular markers including

CD31, CD34, Fli-1 and von Willebrand factor. In 50% of cases, there is positivity for cytokeratin. Focal positivity for epithelial membrane antigen is also seen in some cases. Ordinary angiosarcomas such as those occurring on the head of elderly patients, those associated with radiotherapy and those associated with chronic lymphoedema may display focal areas with epithelioid endothelial cells. This is no reason to classify these tumours as epithelioid angiosarcomas.

Prognosis and treatment. Although it was initially suggested that cutaneous epithelioid angiosarcoma has a relatively good prognosis, this was based on only very few cases with limited follow-up [2]. Overall, the behaviour of these tumours appears to be aggressive, and complete excision and close follow-up are therefore indicated.

References

1 Fletcher CDM, Beham A, Bekir S *et al.* Epithelioid angiosarcoma of deep soft tissue: a distinctive tumor readily mistaken for an epithelial neoplasm. *Am J Surg Pathol* 1991; **15**: 915–24.
2 Marrogi AJ, Hunt SJ, Santa Cruz DJ. Cutaneous epithelioid angiosarcoma. *Am J Dermatopathol* 1990; **12**: 350–6.
3 Prescott RJ, Banerjee SS, Eyden BP *et al.* Cutaneous epithelioid angiosarcoma: a clinicopathological study of four cases. *Histopathology* 1994; **25**: 421–9.
4 Jennings TA, Peterson L, Axiotis CA *et al.* Angiosarcoma associated with foreign body material. *Cancer* 1988; **62**: 2436–44.
5 Byers RJ, McMahon RFT, Freemont AJ *et al.* Epithelioid angiosarcoma arising in an arteriovenous fistula. *Histopathology* 1992; **21**: 87–9.
6 Val-Bernal JF, Figols J, Arce FP *et al.* Cardiac epithelioid angiosarcoma presenting as cutaneous metastases. *J Cutan Pathol* 2001; **28**: 265–70.

Lymphatic tumours

Cavernous lymphangioma, cystic hygroma and lymphangioma circumscriptum are described in Chapter 48.

Progressive lymphangioma

Synonym
- Benign lymphangioendothelioma

Definition This is a benign dermal tumour composed of irregular, lymphatic channels dissecting between collagen bundles.

Clinical features [1–4]. Most cases present in middle-aged adults, but the age range is wide and children may be affected. The tumour presents as a slowly enlarging red macule, usually several centimetres in diameter with predilection for the limbs. Males are slightly more affected than females. Multiple lesions are exceptional [3].

Pathology [1–4]. Low-power examination reveals an ill-defined, often pan-dermal, proliferation of irregular, thin-walled lymphatic channels dissecting between collagen bundles. These channels tend to be orientated parallel to the epidermis and are lined by a single layer of bland endothelial cells. Involvement of the subcutaneous tissue is rare. Distinction from the lymphangiomatous variant of Kaposi's sarcoma is often very difficult, but in the former there are aggregates of inflammatory cells including plasma cells, and the cells lining the vascular channels are usually positive for HHV8. Distinction from a well-differentiated angiosarcoma is based on the absence of cytological atypia and mitotic figures.

Treatment. Excision is all that is required; there is no tendency for local recurrence.

References

1 Jones EW, Winkelmann RK, Zachary CB *et al.* Benign lymphangioendothelioma. *J Am Acad Dermatol* 1990; **23**: 229–35.
2 Mehregan DR, Mehregan AH, Mehregan DA. Benign lymphangioendothelioma: report of 2 cases. *J Cutan Pathol* 1992; **19**: 502–5.
3 Watanabe M, Kishiyama K, Ohkawara A. Acquired progressive lymphangioma. *J Am Acad Dermatol* 1983; **8**: 663–7.
4 Guillou L, Flecher CDM. Benign lymphangioendothelioma (acquired progressive lymphangioma), a lesion not to be confused with well-differentiated angiosarcoma and patch stage Kaposi's sarcoma: clinicopathologic analysis of a series. *Am J Surg Pathol* 2000; **24**: 1047–57.

Atypical vascular proliferation after radiotherapy [1–7]

Definition. Atypical vascular proliferation after radiotherapy (AVPR) defines a group of vascular lesions that occur months or years after radiotherapy—mainly, but not exclusively, after breast cancer. Lesions may also present after radiotherapy for ovarian and endometrial carcinoma.

Incidence and aetiology. These lesions are rare and there is a clear aetiological link with radiotherapy [1–7]. The demonstration of staining of the endothelial cells for lymphatic markers suggests a lymphatic line of differentiation. Although it has been suggested that AVPR represents part of a spectrum of lesions with post-radiation angiosarcomas [4], this view has recently been challenged in a study that stated that all lesions in this group are benign [7]. The problem with the latter study is that follow-up was limited.

Clinical features. AVPR presents a few years or months after radiotherapy for breast cancer (by comparison, post-irradiation angiosarcomas usually but not always tend to present many years after radiotherapy) [1–3]. The clinical lesions are not distinctive and vary from macules to papules. Occasional cases may mimic lymphangioma circumscriptum. As mentioned before, it is controversial whether these lesions are uniformly benign or whether they overlap with radiation-induced angiosarcoma.

Pathology. Irregular lymphatic-like vascular channels, lined by a single layer of endothelial cells, are seen in the dermis and may be multifocal. The endothelial cells are flat or have a hobnail appearance, and papillary projections can also be found. Careful examination of multiple sections is recommended to make sure that there are no mitotic figures or cytological atypia, as distinction from a well-differentiated angiosarcoma can be very difficult.

Treatment. Complete conservative excision of these lesions with close follow-up is recommended.

References

1 Fineberg S, Rosen PP. Cutaneous angiosarcoma and atypical vascular lesion of the skin and breast after radiation therapy for breast carcinoma. *Am J Clin Pathol* 1994; **102**: 757–63.
2 Díaz-Cascajo C, Borghi S, Weyers W *et al*. Benign lymphangiomatous papules of the skin after radiotherapy: a report of five new cases and review of the literature. *Histopathology* 1999; **35**: 319–27.
3 Requena L, Kutzner H, Mentzel T *et al*. Benign vascular proliferations in irradiated skin. *Am J Surg Pathol* 2002; **26**: 328–37.
4 Brenn T, Fletcher CD. Radiation-induced cutaneous atypical vascular lesions and angiosarcoma: clinicopathologic analysis of 42 cases. *Am J Surg Pathol* 2005; **29**: 983–96.
5 Brenn T, Fletcher CD. Post-radiation vascular proliferation: an increasing problem. *Histopathology* 2006; **48**: 106.
6 Mattoch IW, Robbins JB, Kempson RL *et al*. Post-radiotherapy vascular proliferations in mammary skin: a clinicopathologic study of 11 cases. *J Am Acad Dermatol* 2007; **57**: 126–33.
7 Gengler C, Coindre JM, Leroux A *et al*. Vascular proliferations of the skin after radiation therapy for breast cancer: clinicopathologic analysis of a series in favour of a benign process: a study from the French Sarcoma Group. *Cancer* 2007; **109**: 1584–98.

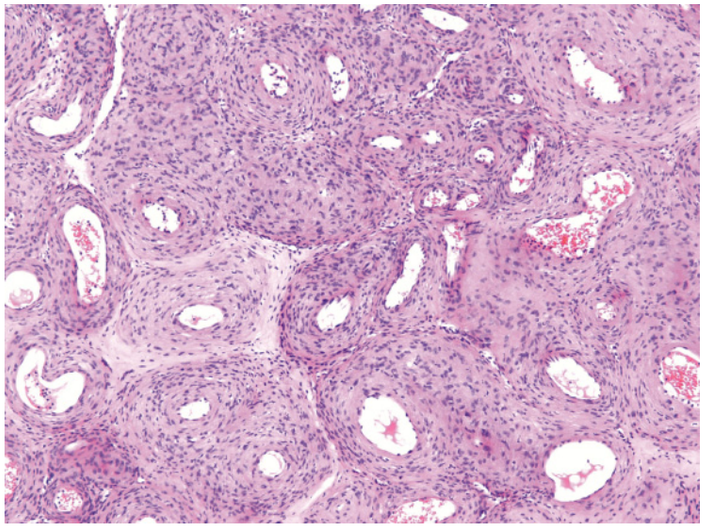


Fig. 56.30 Numerous vascular channels surrounded by layers of pericytes in an onion ring distribution in a case of myopericytoma.

Tumours of perivascular cells

Myopericytoma

Definition. For many years, tumours thought to differentiate towards pericytes (perivascular myoid cells) were divided into two main categories: infantile hemangiopericytoma and adult hemangiopericytoma. Both variants, however, appear to have very little in common except for the histological presence of a pericytomatous pattern characterized by elongated, branching thin-walled vascular spaces with a stag-horn pattern. With the combination of immunohistochemistry and electron microscopy, most tumours previously classified as adult hemangiopericytoma on light microscopy represent other tumours, including synovial sarcoma, mesenchymal chondrosarcoma and solitary fibrous tumour [1]. In very few cases the line of differentiation remains obscure, and these represent the 'true' adult hemangiopericytomas. They are more likely to arise from an undifferentiated mesenchymal cell than from a pericyte. 'True' adult hemangiopericytomas do not usually occur in the skin and will not be discussed further here.

The concept of myopericytoma was introduced to describe a group of lesions characterized by short, oval to spindle-shaped myofibroblasts and a characteristic concentric perivascular growth [2]. Tumours tend to be mainly deep dermal and subcutaneous and include lesions classified in the past as glomangiopericytoma, myopericytoma, myofibroma and myofibromatosis in adults. Infantile hemangiopericytoma and infantile myofibromatosis represent identical conditions and the former term has been abandoned.

Infantile myofibroma/myofibromatosis has already been described in the section on myofibroblastic tumours (p. 56.9).

Clinical features. Myopericytoma is relatively rare and presents mainly in middle-aged adults with a predilection for the limbs, especially the distal lower limb. Lesions are small (no more than 2 cm in diameter), long-standing, usually asymptomatic and may be solitary or, rarely, multiple [2–4]. Exceptionally they are painful. In the setting of multiple myopericytomas, these often develop simultaneously with a predilection for a single anatomic site. Very rarely, malignant examples of myopericytoma have been reported [5].

Pathology. The histological spectrum of myopericytoma is wide and varies from lesions that are very similar to myofibromatosis (p. 56.9), to tumours that closely resemble glomus tumours and even to angioleiomyoma. Lesions are well circumscribed and composed of a mixture of solid cellular areas intermixed with variable numbers of vascular channels. The later are often elongated and display prominent branching resulting in a stag-horn appearance (hemangiopericytoma-like). The cells in the solid areas are bland, round or short and spindle-shaped with eosinophilic or amphophilic cytoplasm and vesicular nuclei. Mitotic figures are exceptional. A common feature is the presence of concentric layers of tumour cells around vascular channels resulting in a typical onion ring appearance (Fig. 56.30). Myxoid change may be focally prominent. Occasional findings include hyalinization, cystic degeneration and bone formation. Nodules of tumour cells may protrude into the lumina of vascular channels. Rare examples are entirely intravascular [6]. In some cases, tumour cells closely resemble glomus cells and are characterized by round punched-out central nuclei and pale eosinophilic cytoplasm. These cases are referred to as glomangiopericytomas. Tumour cells are positive for smooth-muscle actin and in most cases negative for desmin.

References

1 Fletcher CDM. Haemangiopericytoma: a dying breed? Reappraisal of an entity and its variants. *Curr Diagn Pathol* 1994; **1**: 19–25.
2 Granter SR, Badizadegan K, Fletcher CD. Myofibromatosis in adults, glomangiopericytoma, and myopericytoma: a spectrum of tumors showing perivascular myoid differentiation. *Am J Surg Pathol* 1998; **22**: 513–25.
3 Dray MS, McCarthy SW, Palmer AA *et al*. Myopericytoma: a unifying term for a spectrum of tumors that show overlapping features with myofibroma. A review of 14 cases. *J Clin Pathol* 2006; **59**: 67–73.

4 Mentzel T, Dei Tos AP, Sapi Z *et al*. Myopericytoma of skin and soft tissues: clinicopathologic and immunohistochemical study of 54 cases. *Am J Surg Pathol* 2006; **30**: 104–13.
5 McMenamin ME, Fletcher CDM. Malignant myopericytoma: expanding the spectrum of tumors with myopericytic differentiation. *Histopathology* 2002; **41**: 450–60.
6 McMenamin ME, Calonje E. Intravascular myopericytoma. *J Cutan Pathol* 2002; **29**: 557–61.

Glomus tumour [1–3]

Synonyms
- Glomangioma
- Glomangiomyoma

Definition. A tumour of the myoarterial glomus, composed of vascular channels surrounded by proliferating glomus cells. The tumours have variable quantities of glomus cells, blood vessels and smooth muscle. According to this finding, they are classified as either solid glomus tumour, glomangioma or glomangiomyoma.

Incidence and aetiology. Glomus tumours are comparatively uncommon. Some are present at birth; they rarely appear during infancy, but from the age of 7 years onwards the incidence increases gradually. There may be a history of trauma preceding the tumour. Multiple tumours are 10 times more frequent in children than in adults [3,4]. The occurrence of familial cases with autosomal dominant inheritance [1,5,6], and the association of multiple tumours with malformation of the same limb, suggests involvement of genetic factors. This theory has been confirmed by the identification of the *glomulin* gene for multiple inherited glomangiomas (also known as glomuvenous malformations [7]) at chromosome 1p21-22 [8–10].

Clinical features. A solitary glomus tumour is a pink or purple nodule varying in size from 1 to 20 mm; it is conspicuously painful (Fig. 56.31). Pain may be provoked by direct pressure or a change in skin temperature, or may be spontaneous. There is an equal sex incidence; adults present mainly during the third or fourth decades of life. The commonest site is the hands, particularly the fingers, followed by other sites on the extremities including the head, neck and penis [11]. Tumours beneath the nail are particularly painful, and patients present for treatment while the lesions are still very small. The affected nail has a bluish-red flush. An association between subungual glomus tumour and neurofibromatosis type 1 has been reported [12]. Glomus tumours may also involve internal organs.

Multiple glomus tumours are larger and usually dark blue in colour, and are situated deep in the dermis. They are less restricted to the extremities, may be widely scattered and are not usually painful [13–16]. In some cases, grouped multiple tumours may be painful, and pain, intermittent discoloration and sweating of a limb may precede the development of a palpable tumour.

Pathology. The tumour is lobulated, well-circumscribed and situated in the dermis. The proportion of glomus cells to vascular spaces varies. The smaller, painful lesions tend to be mainly cellular. The larger, multiple and often painless lesions are angiomatous, with only a band of cells around the dilated vascular channels. The glomus cell is cuboidal, with a well-marked cell membrane and a round central nucleus. The cells align themselves in rows around the single layer of endothelial cells of the vascular spaces and in a somewhat less orderly fashion further out. Numerous, non-myelinated nerve fibres course through the cellular masses. More than 50% of tumours can be classified as glomangiomas, and a minority (less than 15%) are classified as glomangiomyomas (Fig. 56.32). Electron microscopy [17–19] suggests that glomus cells are transversely cut smooth muscle cells and that there are many mast cells around the tumour, but that nerve fibres are not associated with the glomus cells. Tumour cells are universally positive for smooth muscle actin and are usually negative for desmin. Positivity for CD34 may be seen [20]. An oncocytic variant has been described [21], and also variants developing within a cutaneous nerve [22] and within a vein [23]. Malignant glomus tumour (glomangiosarcoma) is exceedingly rare. Even tumours that are histologically malignant rarely metastasize, but they have a potential for local recurrence [24,25].



Fig. 56.31 Clinical appearance of a glomus tumour.

Diagnosis. The solitary tumour is to be distinguished from other painful tumours such as leiomyoma and eccrine spiradenoma. Distinction is usually only possible on histological examination. The multiple glomangioma may be indistinguishable clinically from a cavernous haemangioma, and is possibly identical to 'blue rubber bleb' naevus [5].

Treatment. Surgical excision is usually curative. Local recurrence is very rare and occurs mainly after incomplete excision. Most

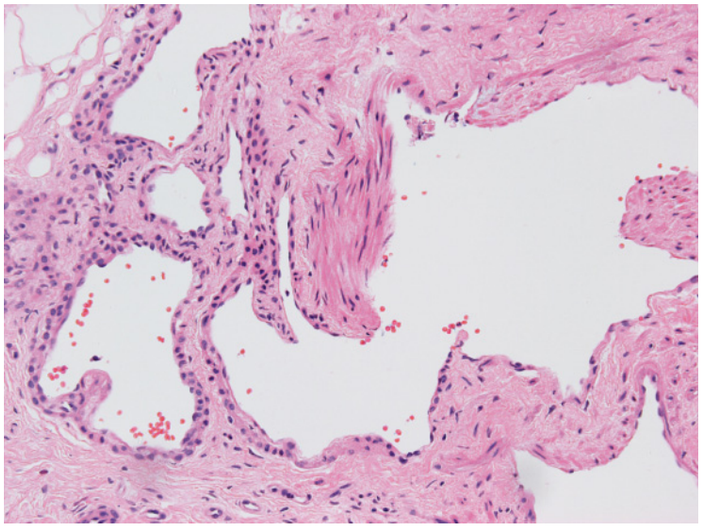


Fig. 56.32 A typical case of glomangiomyoma displaying vascular channels, smooth muscle and thin layers of glomus cells.

recurrences are seen in deeper lesions with an infiltrative growth pattern. These lesions have been described as infiltrating glomus tumours [24].

References

1 Carroll RE, Berman AT. Glomus tumors of the hand: review of the literature and report on twenty-eight cases. *J Bone Joint Surg* 1972; **54A**: 691–703.
2 Anagnostou GD, Papademetriou DG, Toumazani MN. Subcutaneous glomus tumors. *Surg Gynecol Obstet* 1973; **136**: 945–50.
3 Kohout E, Stout AP. The glomus tumor in children. *Cancer* 1961; **14**: 555–66.
4 Sluiter JT, Postma C. Multiple glomus tumours of the skin. *Acta Derm Venereol (Stockh)* 1959; **39**: 98–107.
5 De Sablet M, Mascaro JM. Tumeurs glomiques multiples et blue rubber bleb naevus. *Ann Dermatol Syphiligr* 1967; **94**: 35–46.
6 Touraine A, Renault P. Tumeurs glomiques multiples du tronc et des membres. *Bull Soc Franc Dermatol Syphiligr* 1936; **43**: 736–40.
7 Henning JS, Kovich OI, Schaffer JV. Glomuvenous malformations. *Dermatol Online J* 2007; **13**: 17.
8 Boon LM, Brouillard P, Irrthum A *et al*. A gene for inherited cutaneous venous anomalies ('glomangiomas') localizes to chromosome 1p21-22. *Am J Hum Genet* 1999; **65**: 125–33.
9 Calvert JT, Burns S, Riney TJ *et al*. Additional glomangioma family link to chromosome 1p: no evidence for genetic heterogeneity. *Hum Hered* 2001; **51**: 180.
10 Brouillard P, Boon LM, Mulliken JB *et al*. Mutations in a novel factor, glomulin, are responsible for glomuvenous malformations ('glomangiomas'). *Am J Hum Genet* 2002; **70**: 866–74.
11 Schiefer TK, Parker WL, Anakwenze OA *et al*. Extradigital glomus tumors: a 20-year experience. *Mayo Clin Proc* 2006; **81**: 1337–44.
12 Sawada S, Honda M, Kamide R *et al*. Three cases of subungual glomus tumors with von Recklinghausen neurofibromatosis. *J Am Acad Dermatol* 1995; **32**: 277–8.
13 Chevrant-Breton J, Dunn JE, Laudren A. Multiple glomus tumors associated with multiple neoplasias. *Dermatologica* 1984; **168**: 290–2.
14 Goodman TF, Abele DC. Multiple glomus tumours. *Arch Dermatol* 1971; **103**: 11–23.
15 Gorlin RJ, Fusaro RM, Benton JW. Multiple glomus tumour of the pseudocavernous hemangioma type. *Arch Dermatol* 1960; **8**: 776–8.
16 Rycroft RJG, Menter MA, Sharvill DE *et al*. Hereditary multiple glomus tumours. *Trans St John's Hosp Dermatol Soc Lond* 1975; **61**: 70–81.
17 Tarnowski WM, Hashimoto K. Multiple glomus tumors: an ultrastructural study. *J Invest Dermatol* 1969; **52**: 474–8.
18 Tsuneyoshi M, Enjoji M. Glomus tumour. *Cancer* 1982; **50**: 1601–7.
19 Venkatachalam MA, Greally JG. Fine structure of glomus tumor: similarity of glomus cells to smooth muscle. *Cancer* 1969; **23**: 1176–84.
20 Mentzel T, Hugel H, Kutzner H. CD34-positive glomus tumor: clinicopathologic and immunohistochemical analysis of six cases with myxoid stromal changes. *J Cutan Pathol* 2002; **29**: 421–5.
21 Slater DN, Cotton DWK, Azzopardi JG. Oncocytic glomus tumour: a new variant? *Histopathology* 1987; **11**: 523–31.
22 Calonje E, Fletcher CDM. Cutaneous intraneural glomus tumour. *Am J Dermatopathol* 1995; **17**: 395–8.
23 Beham A, Fletcher CDM. Intravascular glomus tumour: a previously undescribed phenomenon. *Virchows Arch (A) Pathol Anat Histol* 1991; **418**: 175–7.
24 Gould EW, Manivel JC, Albores-Saavedra J *et al*. Locally infiltrative glomus tumors and glomangiosarcoma: a clinical, ultrastructural and immunohistochemical study. *Cancer* 1990; **65**: 310–8.
25 Folpe AL, Fanburgh-Smith JC, Miettinen M *et al*. Atypical glomus tumors: analysis of 52 cases, with a proposal for the reclassification of glomus tumors. *Am J Surg Pathol* 2001; **25**: 1–12.

Peripheral neuroectodermal tumours

Reviews of neural tumours may be found in [1–4].

References

1 Argenyi ZB. Cutaneous neural heterotopias and related tumours relevant for the dermatopathologist. *Semin Diagn Pathol* 1996; **13**: 60–71.
2 Weiss SW, Goldblum JR. *Enziger and Weiss's Soft Tissue Tumors*, 5th edn. St Louis: Mosby, 2007: 1111–264.
3 Reed RJ. Cutaneous manifestation of neural crest disorders. *Int J Dermatol* 1977; **16**: 807–26.
4 Requena L, Sangueza OP. Benign neoplasms with neural differentiation. *Am J Dermatopathol* 1995; **17**: 75–96.

Neuromuscular hamartoma [1,2]

Synonym
- Triton tumour

Definition. These lesions appear to be combined hamartomas of both muscular and neural tissue.

Clinical features. The clinical appearance is of a subcutaneous mass.

Pathology. Multinodular masses of skeletal muscle are mixed with both myelinated and unmyelinated nerve fibres. Malignant triton tumours, composed of a mixture of schwannoma-like material and rhabdomyosarcoma, are very much commoner than the benign variety of triton tumour.

Management. Surgical excision is required.

References

1 Louhimo I, Rapola J. Intraneural muscular hamartoma: report of two cases in small children. *J Pediatr Surg* 1972; **7**: 696–9.
2 Markel SF, Enzinger FM. Neuromuscular hamartoma: a benign 'triton tumor' composed of mature neural and striated muscle elements. *Cancer* 1982; **49**: 140–4.

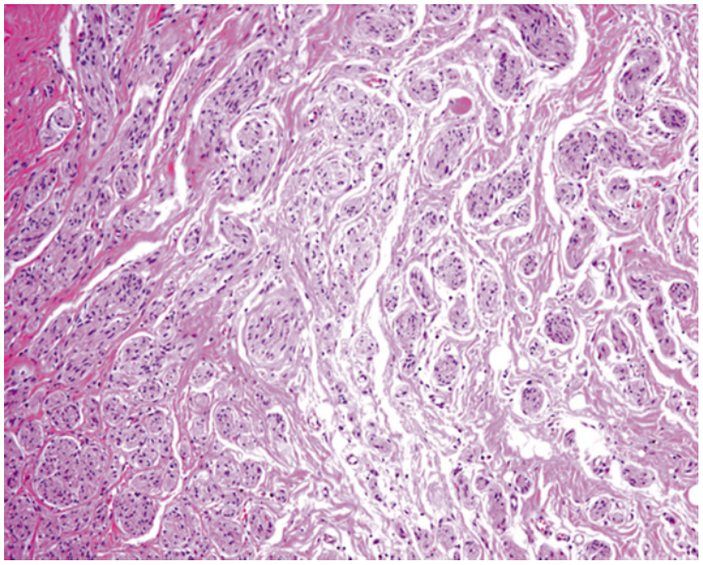


Fig. 56.33 Histological appearance of an amputation neuroma. Small nerves proliferate in the dermis in a background of fibrosis.

Multiple mucosal neuromas [1]

Synonym
- Sipple's syndrome

In Sipple's syndrome, multiple neuromas of the oral mucosa may be associated with phaeochromocytoma, parafollicular thyroid cysts secreting calcitonin, medullary thyroid carcinoma and opaque nerve fibres on the cornea (Chapters 15 and 62).

Reference

1 Gorlin RJ, Sedano HO, Vickers RA *et al.* Multiple mucosal neuromas, pheochromocytoma and medullary carcinoma of the thyroid: a syndrome. *Cancer* 1968; **22**: 293–9.

Amputation stump neuroma [1]

Synonym
- Traumatic neuroma

Definition. This is a benign response of nerve tissue to injury.

Clinical features. A small, tender nodule is found in a scar site.

Pathology. Foci of proliferating nerve tissue surrounded by scar tissue are typically seen (Fig. 56.33). Accessory digits may show a very similar pattern of tissue involvement.

Management. Surgical excision is usually required. The problem can be prevented by apposing ends of nerves at sites of injury.

Reference

1 Cieslak AK, Stout AP. Traumatic and amputation neuromas. *Arch Surg* 1946; **53**: 646–51.

Morton's neuroma [1,2]

Synonym
- Morton's metatarsalgia

Definition. This is the result of damage to the plantar digital nerve, followed by fibrosis. The condition has been associated with the use of high-heeled footwear.

Clinical features. It is most common in women, who complain of severe pain, usually between the third and fourth metatarsals, especially when walking.

Pathology. On pathological examination, there is very prominent perineurial, endoneurial and epineurial fibrosis. Perivascular fibrosis and intimal thickening are also seen.

Management. Excision is the recommended therapy and is curative.

References

1 Lassmann G, Lassmann H, Stockinger L. Morton's metatarsalgia: light and electron microscopic observations and their relation to entrapment neuropathies. *Virchows Arch (A)* 1976; **370**: 307–21.
2 Meachim G, Abberton MJ. Histological findings in Morton's metatarsalgia. *J Pathol* 1971; **103**: 209–17.

Solitary circumscribed neuroma

Synonym
- Palisaded encapsulated neuroma

Definition. This is a distinctive variant of cutaneous neuroma composed of variable proportions of the normal components of nerve tissue.

Clinical features [1–3]. It is fairly common and presents mainly on the face of adults as a small, asymptomatic papule, which may resemble a naevus. There is an equal sex incidence.

Pathology [1–3]. Examination reveals a well-circumscribed, partially encapsulated dermal nodule (Fig. 56.34), often associated with a nerve in the deep dermis. It is composed of uniform cells with pink cytoplasm in a collagenous background and with artefactual clefting between bundles. The capsule displays epithelial membrane antigen-positive perineurial cells. Most of the cells within the nodule are S100-positive, and special stains may demonstrate axons.

Treatment. Simple excision is curative.

References

1 Reed RJ, Fine RM, Meltzer HD. Palisaded, encapsulated neuromas of the skin. *Arch Dermatol* 1972; **106**: 865–70.
2 Fletcher CDM. Solitary circumscribed neuroma of the skin (so-called palisaded, encapsulated neuroma): a clinicopathologic and immunohistochemical study. *Am J Surg Pathol* 1989; **13**: 574–80.

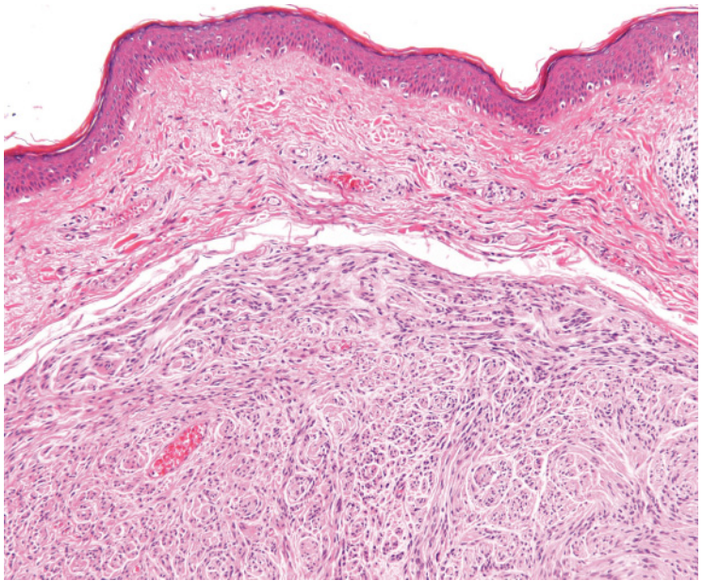


Fig. 56.34 Sharply demarcated dermal nodule in a case of solitary circumscribed neuroma.

3 Dover JS, From L, Lewis A. Palisaded encapsulated neuromas: a clinicopathologic study. *Arch Dermatol* 1989; **125**: 386–9.

Schwannoma

Synonym
- Neurilemmoma

Definition. A tumour of nerve sheaths composed of Schwann cells.

Incidence. The tumour is relatively rare in the skin and relatively uncommon in other sites including soft tissues. It arises most frequently from the acoustic nerve. Bilateral acoustic schwannomas are characteristic of neurofibromatosis type 2. A further manifestation of the latter is the occurrence of multiple cutaneous plexiform schwannomas [1]. There is no association with neurofibromatosis type 1. In the peripheral nervous system, it is usually found in association with one of the main nerves of the limbs, usually on the flexor aspect near the elbow, wrist or knee, the hands or the head and neck [2]. It may be seen on the tongue. Other sites include the wall of the gastrointestinal tract and the posterior mediastinum. It may occur at any age, but is most common in the fourth and fifth decades. Females are affected more often than males [3].

Clinical features [4]. They are rounded or ovoid, circumscribed nodules varying in size up to 5 cm, usually firm (but sometimes soft and cystic) in consistency, and sometimes painful. The colour is pink-grey or yellowish. Small lesions may be intradermal, but larger ones are subcutaneous. They usually grow slowly. Malignant transformation of a schwannoma is exceedingly rare and may contain areas of epithelioid angiosarcoma [5–7].

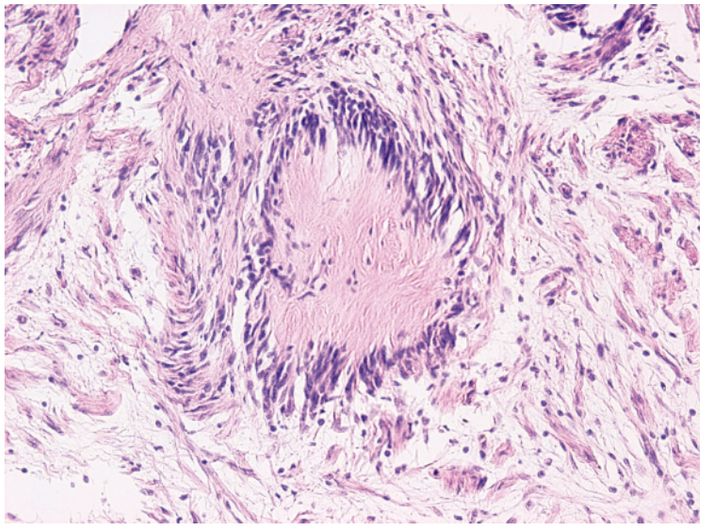


Fig. 56.35 Typical Verocay body in a case of schwannoma.

Pathology [2,8]. The tumour is rounded, circumscribed and encapsulated. It is situated in the course of a nerve, usually in the subcutaneous fat. The cells are spindle shaped with poorly defined cytoplasm and elongated, wavy, basophilic nuclei. Variable amounts of collagen are seen in the background. Cells are arranged in bands, which stream and interweave. The nuclei display palisading and are arranged in parallel rows with intervening eosinophilic cytoplasm in a typical appearance known as Verocay bodies (Fig. 56.35). Cellular areas known as Antoni A areas are intermixed with areas showing prominent myxoid change known as Antoni B areas [9]. The latter areas are likely to be the result of degeneration. In some tumours, there is mucous secretion, producing a vacuolated stroma. Scattered mononuclear inflammatory cells are often seen. In some cases, the nerve of origin may be found associated with the capsule. Electron microscopy shows that tumour cells have typical features of Schwann cells [10]. S100 protein staining is strong and uniform [11]. For many years it was thought that schwannomas lack axons and this was regarded as a useful way in distinguishing these tumours from neurofibromas which contain variable numbers of axons. The presence of the latter is demonstrated by immunostaining for neurofilaments. This view, however, has been challenged recently as both hereditary and sporadic schwannomas may contain axons, suggesting that both entities may in fact be more closely related than previously thought [12]. This explains the rare occurrence of hybrid lesions combining features of neurofibroma and schwannoma [13].

There are several variants of schwannoma, which may be confused histologically with other benign or malignant tumours.

Ancient schwannoma [14] often occurs in a deep location and is characterized by prominent degenerative changes, which often result in cytological atypia. Ectatic blood vessels, haemorrhage, haemosiderin deposition and focal inflammation consisting of lymphocytes are often seen. There is loss of Antoni A areas, which makes histological diagnosis difficult.

Cellular schwannoma [15] also tends to have a predilection for deep soft tissues. It is characterized by high cellularity, with almost complete absence of Antoni B areas. This, coupled with the presence of mitotic figures, often leads to a misdiagnosis of malignancy [16]. A multinodular plexiform variant may occur in children and some examples are congenital.

Plexiform schwannoma [17,18] tends to occur in younger patients, may be painful and has a predilection for the dermis. Multiple cellular nodules composed of bland Schwann cells are seen in the dermis. Distinction from plexiform neurofibroma is important, as these tumours are not usually associated with neurofibromatosis type 1. Multiple cutaneous plexiform schwannomas, however, are associated with neurofibromatosis type 2 [1,19].

Melanotic schwannoma [20] only exceptionally occurs in the skin; it has a predilection for spinal nerve roots. Tumour cells are epithelioid and melanin pigment is prominent. The importance of this variant is that they are capable of malignant behaviour and may be a marker of Carney complex (Chapter 62).

Pacinian schwannoma is a rare variant composed of structures closely resembling the Pacinian corpuscles.

Neuroblastoma-like schwannoma is very rare and characterized histologically by areas composed of round, blue, small Schwann cells which may form perivascular rosettes or rosettes with collagenous cores [21]. The tumour in other areas has the typical appearance of a schwannoma and the immunohistochemical profile is typical of the latter.

Epithelioid schwannoma is an infrequent type of schwannoma composed predominantly of cells with epithelioid morphology [22]. However, although these tumours are positive for S-100 protein, they lack palisading, are composed of uniform tumour cells and contain a population of CD34-positive cells. It has therefore been proposed that these lesions do not represent classical examples of schwannomas [23].

Glandular schwannoma [24,25] represents in most cases an ordinary schwannoma with entrapment of normal sweat glands.

Diagnosis. Of the various nodular dermal and hypodermal tumours, schwannoma is most likely to be mistaken for a glomus tumour when painful, and for a lipoma, epidermoid cyst, synovial ganglion, juxta-articular node or neurofibroma when asymptomatic. The diagnosis can be suspected when it is in the course of a nerve; otherwise, histological examination is necessary.

Treatment. Simple excision is curative.

References

1 Miyakawa T, Kamada N, Kobayashi T *et al*. Neurofibromatosis type 2 in an infant with multiple plexiform schwannomas as first symptom. *J Dermatol* 2007; **34**: 60–4.

2 Stout AP. The peripheral manifestations of the specific nerve sheath tumour (neurilemmoma). *Am J Cancer* 1935; **24**: 751–96.

3 Das Gupta TK, Brasfield RD, Strong EW *et al.* Benign solitary schwannomas (neurilemmomas). *Cancer* 1969; **24**: 355–66.

4 Mercantini ES, Mopper C. Neurilemmoma of the tongue. *AMA Arch Dermatol* 1959; **79**: 542–4.

5 Woodruff JM, Selig AM, Crowley K *et al*. Schwannoma (neurilemmoma) with malignant transformation: a rare, distinctive peripheral nerve tumor. *Am J Surg Pathol* 1994; **18**: 882–95.

6 Trassard M, Le Doussal V, Bui BN *et al*. Angiosarcoma arising in a solitary schwannoma (neurilemoma) of the sciatic nerve. *Am J Surg Pathol* 1996; **20**: 1412–7.

7 McMenamin ME, Fletcher CD. Expanding the spectrum of malignant change in schwannomas: epithelioid malignant change, epithelioid malignant peripheral nerve sheath tumor, and epithelioid angiosarcoma: a study of 17 cases. *Am J Surg Pathol* 2001; **25**: 13–25.

8 Geschikler CF. Tumours of the peripheral nerves. *Am J Cancer* 1935; **25**: 377–89.

9 Sian CS, Ryan SF. The ultrastructure of neurilemmoma with emphasis on Antoni B tissue. *Hum Pathol* 1981; **12**: 145–52.

10 Waggener JD. Ultrastructure of benign peripheral nerve sheath tumors. *Cancer* 1966; **19**: 699–709.

11 Weiss SW, Langloss JM, Enzinger F. The role of the S100 protein in the diagnosis of soft tissue tumours with particular reference to benign and malignant Schwann cell tumours. *Lab Invest* 1983; **49**: 299–304.

12 Nascimento AF, Fletcher CD. The controversial nosology of benign nerve sheath tumors: neurofilament protein demonstrates intratumoral axons in many sporadic schwannomas. *Am J Surg Pathol* 2007; **31**: 1363–70.

13 Feany MB, Anthony DC, Fletcher CD. Nerve sheath tumours with hybrid features of neurofibroma and schwannoma: a conceptual challenge. *Histopathology* 1998; **32**: 405–10.

14 Dahl I. Ancient neurilemmoma (schwannoma). *Acta Pathol Microbiol Scand A* 1977; **85**: 812–8.

15 White WM, Shiu MH, Rosenblum MK *et al*. Cellular schwannoma: a clinicopathologic study of 57 patients and 58 tumors. *Cancer* 1990; **66**: 1266–75.

16 Woodruff JM, Scheithauer BW, Kurtkaya-Yapicier O *et al*. Congenital and childhood plexiform (multinodular) cellular schwannoma: a troublesome mimic of malignant peripheral nerve sheath tumor. *Am J Surg Pathol* 2003; **27**: 1321–9.

17 Fletcher CDM, Davies SE. Benign plexiform (multinodular) schwannoma: a rare tumour unassociated with neurofibromatosis. *Histopathology* 1986; **10**: 971–80.

18 Kao GF, Laskin WB, Olson TG. Solitary cutaneous plexiform neurilemmoma (schwannoma): a clinicopathologic, immunohistochemical and ultrastructural study of 11 cases. *Mod Pathol* 1989; **2**: 20–6.

19 Lim HS, Jung J, Chung KY. Neurofibromatosis type 2 with multiple plexiform schwannomas. *Int J Dermatol* 2004; **43**: 336–40.

20 Carney JA. Psammomatous melanotic schwannoma: a distinctive heritable tumor with special associations including cardiac myxoma and the Cushing syndrome. *Am J Surg Pathol* 1990; **14**: 206–22.

21 Goldblum JR, Beals TF, Weiss SW. Neuroblastoma-like neurilemmoma. *Am J Surg Pathol* 1994; **18**: 266–73.

22 Smith K, Mezebish D, Williams JP *et al*. Cutaneous epithelioid schwannomas: a rare variant of a benign peripheral nerve sheath tumor. *J Cutan Pathol* 1998; **25**: 50–5.

23 Laskin WB, Fetsch JF, Lasota J *et al*. Benign epithelioid peripheral nerve sheath tumors of the soft tissues: clinicopathologic spectrum of 33 cases. *Am J Surg Pathol* 2005; **29**: 39–51.

24 Brooks JJ, Draffen RM. Benign glandular schwannoma. *Arch Pathol Lab Med* 1992; **116**: 192–5.

25 Deng A, Petrali J, Jaffe D *et al*. Benign cutaneous pseudoglandular schwannoma: a case report. *Am J Dermatopathol* 2005; **27**: 432–5.

Solitary neurofibroma [1–4]

Definition. An isolated lesion probably arising from the endoneurium and composed of a mixture of Schwann cells, fibroblasts and perineurial fibroblasts. It is not related to neurofibromatosis type 1. Although it appears to be hamartomatous in nature, the demonstration of clonality suggests a neoplastic origin [5].



Fig. 56.36 Multiple soft papules, typical of neurofibroma in a patient with neurofibromatosis type 1.



Fig. 56.37 Clinical appearance of a plexiform neurofibroma.

Clinical features. Both sexes and any body site may be affected. It usually appears during the third decade as a slow-growing, small, polypoid lesion. Multiple neurofibromas are rare outside the setting of neurofibromatosis type 1 (Fig. 56.36).

Simple excision is curative. Malignant change is said not to occur outside the setting of neurofibromatosis type 1.

Pathology. These lesions differ from neurilemmomas in that they do not have a capsule, they are only focally positive for S100 protein, and they do not usually have well-defined Antoni A and Antoni B areas. Instead, they are composed of bland, spindle-shaped cells with wavy nuclei in a myxoid or collagenous stroma. Mast cells are usually prominent. Degenerative changes are sometimes seen but mitotic activity is absent. Less than 50% of the cells in these lesions are S100-positive. There is also focal positivity for CD34 and epithelial membrane antigen (EMA).

Several histological variants of neurofibroma have been described, including epithelioid neurofibroma, granular cell neurofibroma, pigmented neurofibroma [6] and a variant with dendritic cells and pseudorosettes [3,7].

Cytogenetic analysis in a single case of solitary neurofibroma has found a reciprocal translocation t(4;9)(q31;p22) [8].

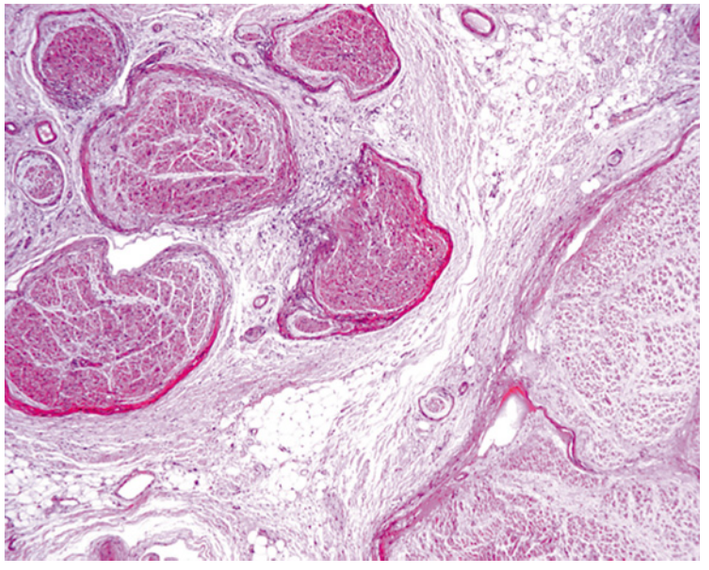


Fig. 56.38 Irregular, poorly formed nerves in a plexiform neurofibroma.

References

1 Geschikler CF. Tumours of the peripheral nerves. *Am J Cancer* 1935; **25**: 377–89.

2 Reed RJ. Cutaneous manifestations of neural crest disorders (neurocristopathies). *Int J Dermatol* 1977; **16**: 807–26.

3 Megahed M. Histopathological variants of neurofibroma: a study of 114 lesions. *Am J Dermatopathol* 1994; **16**: 486–95.

4 Erlandson RA. Peripheral nerve sheath tumors. *Ultrastruct Pathol* 1985; **9**: 113–22.

5 Colman DS, Williams CA, Wallace MR. Benign neurofibromas in type 1 neurofibromatosis (NF1) show somatic deletions of the NF1 gene. *Nature Genet* 1995; **11**: 90–2.

6 Fetsch JF, Michal M, Mietinnen M. Pigmented (melanotic) neurofibroma: a clinicopathologic and immunohistochemical analysis of 19 lesions from 17 patients. *Am J Surg Pathol* 2000; **24**: 331–43.

7 Michal M, Fanburg-Smith JC, Mentzel T *et al*. Dendritic cell neurofibroma with pseudorosettes: a report of 18 cases of a distinct and hitherto unrecognized neurofibroma variant. *Am J Surg Pathol* 2001; **25**: 587–94.

8 Sawyer JR, Parr LG, Gokden N *et al*. A reciprocal t(4;9)(q31;p22) in a solitary neurofibroma. *Cancer Genet Cytogenet* 2005; **156**: 172–4.

Plexiform neurofibroma

This tumour is considered to be pathognomonic of neurofibromatosis type I (see Chapter 15). However, it has been contested whether the presence of a single plexiform neurofibroma in the absence of other signs of neurofibroma can be regarded as pathognomonic of neurofibromatosis type I [1,2]. It presents in children and young adults of either sex, with predilection for the lower limbs and the head and neck. Tumours are large and located in the dermis, subcutis and even deeper soft tissues. The overlying skin is folded and hyperpigmented and the lesion is described as having an appearance like a 'bag of worms' (Fig. 56.37). This reflects the typical histological appearance of nerve trunks of different sizes randomly distributed throughout the involved tissues (Fig. 56.38). Careful histological examination of these lesions is

necessary because the presence of any mitotic activity usually indicates malignant transformation.

Surgical removal of these lesions is usually very difficult because of the extensive involvement. When planning the surgical removal of these tumours, surgeons should remember that there is a tendency for haemorrhage within the tumour that may lead to morbidity or mortality.

References

1 Lin V, Daniel S, Forte V. Is a plexiform neurofibroma pathognomonic of neurofibromatosis type I? *Laryngoscope* 2004; **114**: 1410–4.

2 Fisher DA, Chu P, McCalmont T. Solitary plexiform neurofibroma is not pathognomonic of von Recklinghausen's neurofibromatosis: report of a case. *Int J Dermatol* 1997; **36**: 439–42.

Diffuse neurofibroma

This lesion presents as a diffuse, poorly-defined induration or plaque-like lesion of the skin and subcutaneous tissue in children or young adults, with a predilection for the trunk and head and neck area. Only a minority of cases are associated with neurofibromatosis type 1. The histological features are identical to those of a solitary neurofibroma except for the fact that there is diffuse replacement of involved tissue by the tumour. Local recurrence is frequent unless the lesion is widely excised.

Perineurioma [1–4]

Synonym

- Storiform perineural fibroma

Definition. Perineurioma is a tumour originally described in soft tissues. It is relatively common in the skin and it is composed of cells showing differentiation towards perineural fibroblasts.

Clinical features. The lesion has predilection for the lower limbs of young females. Tumours are small and asymptomatic. A distinctive, sclerosing variant has been described, affecting most commonly, but not always, the hands [4,5].

Pathology. Tumours are well-circumscribed and composed of bipolar and slender bland, thin, spindle-shaped cells with scanty cytoplasm and wavy nuclei. They are often arranged in concentric whorls (Fig. 56.39) or in a storiform pattern. Cellularity varies and is low in the sclerosing variant where hyalinized collagen predominates. The architecture may be plexiform in some cases [6]. Tumour cells are distinctively positive for EMA. They are also positive for a tight junction associated protein, claudin-1 [7]. Focal positivity for factor XIIIa and CD34 may also be seen.

Treatment. Lesions are entirely benign, and simple excision is the treatment of choice.

References

1 Robson AM, Calonje E. Cutaneous perineurioma: a poorly recognized tumour often misdiagnosed as epithelioid histiocytoma. *Histopathology* 2000; **37**: 332–9.

2 Smith K, Skelton H. Cutaneous fibrous perineuroma. *J Cutan Pathol* 1998; **25**: 333–7.

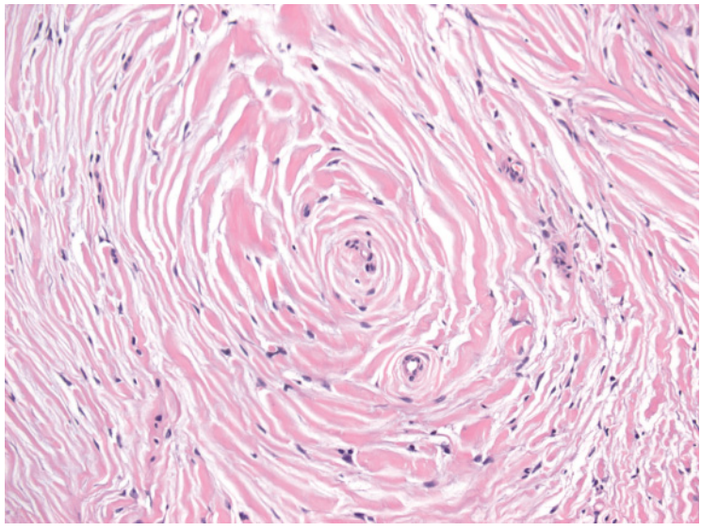


Fig. 56.39 Typical whirling appearance and some degree of sclerosis in a case of perineurioma.

3 Fetsch JF, Miettinen M. Sclerosing perineurioma: a clinicopathological study of 15 cases of a distinctive soft tissue lesion with a predilection for the fingers and palms of young adults. *Am J Surg Pathol* 1997; **21**: 1433–42.

4 Rankine AJ, Filion PR, Platten MA *et al*. Perineurioma: a clinicopathologic study of eight cases. *Pathology* 2004; **36**: 309–15.

5 Skelton HG, Williams J, Smith KJ. The clinical and histologic spectrum of cutaneous fibrous perineuriomas. *Am J Dermatopathol* 2001; **23**: 190–6.

6 Zelger B, Weinlich G, Zelger B. Perineuroma. A frequently unrecognized entity with emphasis on a plexiform variant. *Adv Clin Pathol* 2000; **4**: 25–33.

7 Folpe AL, Billings SD, McKenney JK *et al*. Expression of claudin-1, a recently described tight junction-associated protein, distinguishes soft tissue perineurioma from potential mimics. *Am J Surg Pathol* 2002; **26**: 1620–6.

Dermal nerve sheath myxoma [1–3]

Synonym

- Neurothekeoma

Definition. This is a myxoid tumour that is thought to display nerve sheath differentiation.

Clinical features [1,2,4]. It presents most commonly on the upper limbs (particularly the fingers and hands) and lower limbs (mainly the knees, shins or feet) of young adults, with a predilection for males. The trunk and head and neck are rarely affected. Lesions are long-standing, small, usually less than 1 cm, skin-coloured and asymptomatic.

Pathology [1–3]. The dermis shows a well-defined tumour composed of lobules that vary in size and shape and are separated by fibrocollagenous stroma. Each lobule is composed of slender stellate or spindle-shaped Schwann cells with bland nuclei and indistinct cytoplasm margins in the background of prominent myxoid change. Mitotic figures are very rare. Tumour cells are uniformly positive for S100. They are also positive for glial fibrillary acid protein and CD57 [4]. EMA-positive cells are seen in the periphery of tumour lobules. These tumours have no relationship with the so-called cellular neurothekeoma [5].

Treatment. Simple excision is curative. There is high tendency for local recurrence [4].

References

1 Gallager RL, Helwig EB. Neurothekeoma: a benign tumor of neural crest origin. *Am J Clin Pathol* 1980; **74**: 759–64.
2 Pulitzer DR, Reed RJ. Nerve-sheath myxoma (perineurial myxoma). *Am J Dermatopathol* 1985; **7**: 409–21.
3 Fletcher CDM, Chen JKC, McKee PH. Dermal nerve sheath myxoma: a study of three cases. *Histopathology* 1986; **10**: 135–45.
4 Fetsch JF, Laskin WB, Mietinen M. Nerve sheath myxoma: a clinicopathologic and immunohistochemical analysis of 57 morphologically distinctive, S-100 protein and GFAP positive myxoid peripheral nerve sheath tumors with a predilection for the extremities and a high local recurrence rate. *Am J Surg Pathol* 2005; **29**: 1615–24.
5 Rosati LA, Fratamico CM, Eusebi V. Cellular neurothekeoma. *Appl Pathol* 1986; **4**: 186–91.

Cellular neurothekeoma [1–4]

Definition. Despite its name, this tumour is not related to dermal nerve sheath myxoma, and its line of differentiation has not been established. It should not be confused with ordinary nerve sheath myxomas showing focal cellular areas [1–3].

Clinical features. The tumour presents as a small, asymptomatic papule in children and young adults, more common in females than males and with a predilection for the upper limbs and face and neck [4,5]. Multiple lesions are exceptional [6].

Pathology. In the dermis and frequently extending into the subcutis [5], there is an ill-defined tumour composed of nests and fascicles of epithelioid or spindle-shaped cells (Fig. 56.40) with vesicular nuclei and a single small eosinophilic nucleolus. Lesions presenting in the face may extend into the underlying skeletal muscle. Mitotic figures are relatively common and scattered multinucleated cells (osteoclast-like) may be seen. Tumour cells resemble melanocytes, and this often leads to the lesion being confused with a melanoma. However, there is no junctional activity, and cells are invariably negative for S100. Some tumours have larger size, more cytological atypia and increased mitotic count, and these tumours have been classified as atypical cellular neurothekeoma [4,5]. However, this does not seem to be related to a more aggressive behaviour. Tumour cells are often positive for smooth muscle actin (in about 57% of cases), NKI-C3, neuron-specific enolase and PGP 9.5 [5].

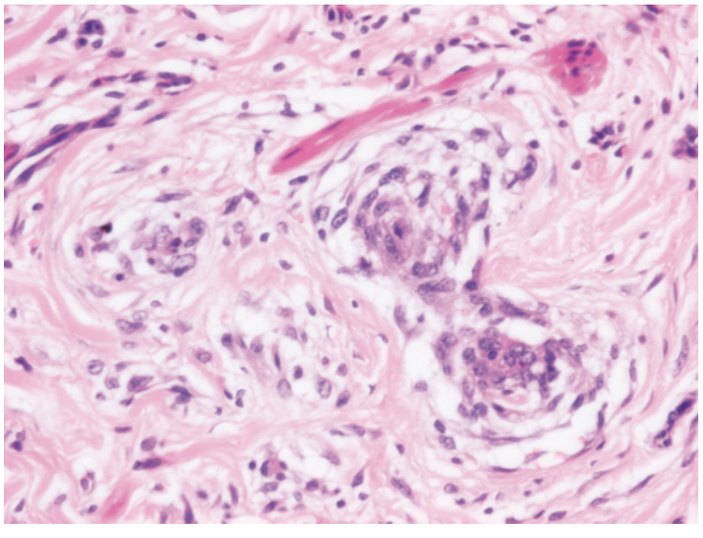


Fig. 56.40 Cellular neurothekeoma. Nests of epithelioid cells in the background of a hyalinized stroma. In cases with cytological atypia and mitotic activity, confusion with a melanoma is more likely.

Treatment. Simple excision is curative, and there is very little tendency for local recurrence [5].

References

1 Barnhill RL, Mihm MC. Cellular neurothekeoma: a distinctive variant of neurothekeoma mimicking nevomelanocytic tumors. *Am J Surg Pathol* 1990; **14**: 113–20.
2 Calonje E, Wilson-Jones E, Smith NP *et al*. Cellular 'neurothekeoma': an epithelioid variant of pilar leiomyoma? Morphological and immunohistochemical analysis of a series. *Histopathology* 1992; **20**: 397–404.
3 Barnhill RL, Dickersin GR, Nickeleit V *et al*. Studies on the cellular origin of neurothekeoma: clinical, light microscopic, immunohistochemical and ultrastructural observations. *J Am Acad Dermatol* 1991; **25**: 80–8.
4 Busam KJ, Mentzel T, Colpaert C *et al*. Atypical or worrisome features in cellular neurothekeoma: a study of 10 cases. *Am J Surg Pathol* 1998; **22**: 1067–72.
5 Hornick JL, Fletcher CD. Cellular neurothekeoma: detailed characterization in a series of 133 cases. *Am J Surg Pathol* 2007; **31**: 329–40.
6 Mahalingam M, Alter JN, Bhawan J. Multiple cellular neurothekeomas—a case report and review on the role of immunohistochemistry as a histologic adjunct. *J Cutan Pathol* 2006; **33**: 51–6.

Granular cell tumour [1–4]

Synonyms
- Abrikossoff's tumour
- Granular cell myoblastoma

Definition. A tumour composed of cells with characteristic granular cytoplasm. The histogenesis of the classic granular cell tumour seems to be neuroectodermal. However, it is worth remembering that many tumours of different histogenesis may show granular cell change, due to the cytoplasmic accumulation of secondary lysosomes.

Incidence. This is a rare tumour, occurring in the tongue as well as in the skin, and also in a variety of deeper locations including internal organs. Females are slightly more affected than males, and it is common in the third to fifth decade of life. It can occur in childhood [5,6].

Clinical features. The tumour is usually solitary, situated in the skin, the gingiva [7], or beneath the epithelium of the tongue. It is firm and rounded but with rather indefinite margins, sessile or pedunculated, and between 5 and 20 mm in diameter, although larger tumours may be seen. The colour may vary from flesh colour to pink or greyish-brown. It is most common in the tongue, where the epithelium over it may be thickened. On the skin surface, the epithelium covering the tumour is usually normal,

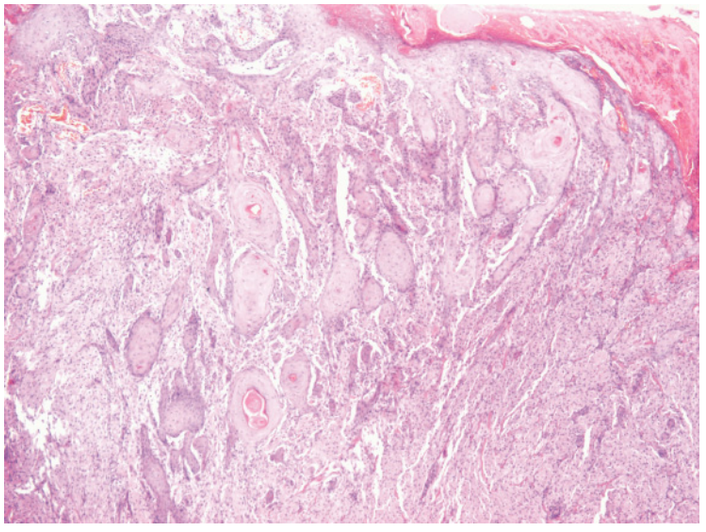


Fig. 56.41 Prominent pseudoepitheliomatous hyperplasia mimicking a squamous cell carcinoma in a case of granular cell tumour.

although it may thicken or at times ulcerate. There is no particular site of predilection. Multiple tumours may occur [8], and several have been reported in children, one of whom also had axillary freckling [5]. The tumour grows slowly.

A malignant type of granular cell tumour that metastasizes has been reported [9,10]. Among the internal sites reported are muscle, lip, jaws, parotid gland, pharynx, larynx, trachea, bronchus, lung, chest wall, breast, lacrimal sac, orbit, heart, oesophagus, common bile duct, urinary bladder, spermatic cord, male urethra, perineum, anal region, vulva and ovary [6,11].

Pathology [12,13]. Large polyhedral cells arranged in sheets, which infiltrate the dermal connective tissue and subcutaneous fat, form the tumour. The cytoplasm is pale and contains brightly acidophilic granules. The nuclei are relatively small and round, and tend to be vesicular. Clear cell change may occasionally be prominent [14]. The epithelium over the area may show pseudoepitheliomatous hyperplasia and in small biopsies this may be confused with a squamous cell carcinoma (Fig. 56.41). Perineural extension is often seen. Occasionally, tumour cells involve the epidermis and distinction from melanoma may be difficult [15]. However, although S-100 positivity is seen in both tumours, other melanocytic markers, including HMB45 and melan-A, are negative in granular cell tumour. The original suggestion that the cells are myoblasts probably arose from examination of tumours of the tongue in which infiltration between the striated muscle bundles gave the impression of origin from the muscle. The general belief now is that the cells are of neural or nerve sheath origin [16–21].

Diagnosis. Histological examination is usually necessary to separate this tumour from other tumours of the deeper dermis.

Treatment. Local recurrence, mainly due to incomplete excision, is uncommon, and simple excision is therefore the treatment of choice.

References

1 Garancis JC, Komorowski RA, Kuzma FJ. Granular cell myoblastoma. *Cancer* 1970; **25**: 542–50.
2 Pugh JI, Rigg BM, Murley RS. Granular cell myoblastoma of the breast. *Br J Surg* 1967; **54**: 590–4.
3 Stefansson K, Wollmann RL. S-100 protein in granular cell tumors (granular cell myoblastoma). *Cancer* 1982; **49**: 1834–7.
4 White SW, Gallager RL, Rodman OG. Multiple granular cell tumors. *J Dermatol Surg Oncol* 1980; **6**: 57–62.
5 Apted JH. Multiple granular cell myoblastoma (Schwannoma) in a child. *Br J Dermatol* 1968; **80**: 257–60.
6 Cave VG, Koff AW, Vegas FK. Multiple myoblastomas in children. *Arch Dermatol* 1955; **71**: 579–86.
7 Anderson PJ, Kirkland P, Schafer K *et al.* Congenital gingival granular cell tumour. *J R Soc Med* 1996; **89**: 53–4.
8 Hazan C, Fangman W. Multiple cutaneous granular-cell tumors. *Dermatol Online J* 2007; **13**: 4
9 Gamboa LG. Malignant granular cell myoblastoma. *AMA Arch Pathol* 1995; **60**: 663–8.
10 Svejd J, Horn V. A disseminated granular cell pseudotumour, so-called metastasising granular cell myoblastoma. *J Pathol Bacteriol* 1958; **76**: 343–8.
11 Seo IS, Azarelli B, Warner TF *et al.* Multiple visceral and cutaneous granular cell tumors: ultrastructural and immunocytochemical evidence of Schwann cell origin. *Cancer* 1984; **53**: 2104–10.
12 Lack EE, Worsham GF, Calliham MD *et al.* Granular cell tumor: a clinicopathologic study of 100 patients. *J Surg Oncol* 1980; **13**: 301–9.
13 Bangle R Jr. A morphological and histochemical study of the granular cell myoblastoma. *Cancer* 1952; **5**: 950–65.
14 Zedek DC, Murphy BA, Shea CR *et al.* Cutaneous clear-cell granular cell tumors: the histologic description of an unusual variant. *J Cutan Pathol* 2007; **34**: 397–404.
15 Ray S, Jukic DM. Cutaneous granular cell tumor with epidermal involvement: a potential mimic of melanocytic neoplasia. *J Cutan Pathol* 2007; **34**: 188–94.
16 Bedetti CD, Martinez AJ, Beckford NS *et al.* Granular cell tumours arising in myelinated peripheral nerves: light and electron microscopy and immunoperoxidase study. *Virchows Arch (Pathol Anat)* 1983; **402**: 175–84.
17 Chimelli L, Symon L, Scaravilli F. Granular cell tumor of the fifth cranial nerve: further evidence for Schwann cell origin. *J Neuropathol Exp Neurol* 1984; **43**: 634–40.
18 Dhillon AP, Rode J. Immunohistochemical studies of S100 protein and other neural characteristics expressed by granular cell tumour. *Diagn Histopathol* 1983; **6**: 23–8.
19 Fust JA, Custer RP. On the neurogenesis of so-called granular cell myoblastoma. *Am J Clin Pathol* 1949; **19**: 522–35.
20 Miettinen M, Lehtonen E, Lehtola H *et al.* Histogenesis of granular cell tumour: an immunological and ultrastructural study. *J Pathol* 1984; **142**: 221–31.
21 Nakazato Y, Ishizeki J, Takahashi K *et al.* Immunohistochemical localization of S-100 protein in granular cell myoblastoma. *Cancer* 1982; **49**: 1624–9.

Meningothelial heterotopias [1–8]

Synonym
- Cutaneous meningioma

Lesions with meningothelial elements presenting in the skin and soft tissue were divided into three groups by Lopez *et al*. [4]. The first two groups of lesions represent meningothelial heterotopias or hamartomas. The main difference between both groups is that affected patients are children in the first group and adults in the second group. The third group consists of intracranial meningiomas that extend secondarily into the skin or soft tissues. This group will not be discussed in more detail here.

A small number of cases of meningothelial heterotopias have been associated with von Recklinghausen's disease [1]. The tumour occurs over the scalp or in the paraspinous region of the trunk of

children and young adults. Occasionally it appears to be familial [6]. The lesions resemble 'soft naevi'. On the scalp, the area may be bald. The skin is adherent to the mass, which is dermal or subcutaneous, and there may be a central depression with epidermal atrophy or ulceration. A connection with the cranial cavity is not usually demonstrated. The size ranges from 2 to 10 cm.

Pathology [6–8]. Low-power examination often reveals a lesion with a striking resemblance to a lymphangioma. Irregular dilated spaces are seen dissecting between collagen bundles. The spaces are partially lined by plump epithelioid cells, which are also seen in clusters in the surrounding stroma. Focal formation of psammoma bodies may be present. The dermal collagen and blood vessels also appear to be increased. Some lesions contain more solid areas. The presence of meningothelial cells can be demonstrated by positive staining for EMA.

References

1 Argenyi ZB, Thieberg MD, Hayes CM, Whitaker DC. Primary cutaneous meningioma associated with von Recklinghausen's disease. *J Cutan Pathol* 1994; **21**: 549–56.
2 Argenyi ZB. Cutaneous neural heterotopias and related tumours relevant for the dermatopathologist. *Semin Diagn Pathol* 1996; **13**: 60–71.
3 Bain GO, Shnitka TK. Cutaneous meningioma (psammoma). *AMA Arch Dermatol* 1956; **74**: 590–4.
4 Lopez DA, Silvers DN, Helwig EB. Cutaneous meningiomas: a clinico-pathologic study. *Cancer* 1974; **34**: 728–44.
5 Miyamoto T, Mihara M, Hagari Y *et al*. Primary cutaneous meningioma of the scalp: report of 2 siblings. *J Dermatol* 1995; **22**: 611–9.
6 Suster S, Rosai J. Hamartoma of the scalp with ectopic meningothelial elements: a distinctive soft tissue lesion that may simulate angiosarcoma. *Am J Surg Pathol* 1990; **14**: 1–11.
7 Bale PM, Hughes L, De Silva M. Sequestrated meningoceles of the scalp: extracranial meningeal hamartoma. *Hum Pathol* 1990; **21**: 1156–63.
8 Theaker JM, Fletcher CDM, Tudway AJ. Cutaneous heterotopic meningeal nodules. *Histopathology* 1990; **16**: 475–9.

Glial heterotopic nodules [1,2]

Synonym
- Nasal glioma

Definition. This represents the presence of heterotopic mature glial tissue in the dermis or subcutis, predominantly on the central face. It may be considered to be a developmental defect in the closure of the neural tube. However, rare cases occur away from the midline, suggesting a different unexplained mechanism for its occurrence [3].

Clinical features. Most lesions present in infants or children as a subcutaneous mass on the bridge of the nose. Presentation in adults is exceptional. Communication with the cranial cavity is present in up to 20% of cases.

Pathology. Nodules of astrocytes in a neurofibrillar background are characteristic. Less commonly, oligodendrocytes are seen; neuronal elements are exceptional.

Treatment. Excision is curative, but it is very important to make sure that an underlying communication with the cranial cavity is ruled out, as failure to do so may result in complications such as meningitis or cerebrospinal fluid leakage.

References

1 Fletcher CDM, Carpenter G, McKee PH. Nasal glioma: a rarity. *Am J Dermatopathol* 1986; **8**: 341–6.
2 Theaker JM, Fletcher CDM. Heterotopic glial nodules: a light microscopic and immunohistochemical study. *Histopathology* 1991; **18**: 255–60.
3 McDermott MB, Glasner SD, Nielsen PL, Dehner LP. Soft tissue gliomatosis: morphologic unity and histogenetic diversity. *Am J Surg Pathol* 1996; **20**: 148–55.

Epithelial sheath neuroma [1]

Definition. This is a novel, rare and intriguing dermal lesion that combines a neural and an epithelial component. Although some features suggest that this may be a hamartoma, the fact that it has only been described in adults makes this possibility unlikely.

Clinical features. In view of the fact that so few cases have been described, very little can be said about the clinical features. The clinical presentation is not distinctive and lesions appear to have a predilection for the back.

Pathology. Histologically there are scattered, prominent nerves in the superficial dermis, encased by mature, non-dysplastic squamous epithelium with focal keratinization and dyskeratotic cells. Immunohistochemistry displays the normal staining of nerves and epidermis respectively.

Prognosis and treatment. Lesions appear to be benign and no recurrences have been reported so far.

Reference

1 Requena L, Grosshans E, Kutzner H *et al*. Epithelial sheath neuroma: a new entity. *Am J Surg Pathol* 2000; **24**: 190–6.

Pigmented neuroectodermal tumour of infancy [1,2]

Synonyms
- Melanotic progonoma
- Retinal anlage tumour

For many years, there has been a debate as to whether this tumour is of neural or melanocytic origin [3–5]. Recent evidence seems to indicate that this tumour recapitulates the early stages of development of the retinal epithelium [6].

Clinical features. This tumour occurs most frequently in the anterior part of the maxilla, usually in infants less than 6 months old, and often presents as a pigmented oral mass [7]. It has been reported also in the anterior fontanelle, the shoulder, epididymis, femur and mediastinum. There is a slight predilection for males. It may cause a high urinary excretion of vanillylmandelic acid [3]. This tumour has been mistaken in the past for malignant melanoma, and could also be confused with a cellular blue naevus.

The clinical appearance is that of a rapidly expanding nodule in the jaw, which may affect dentition. Although classified as benign, the lesions may cause considerable local destruction, and around 5% of cases may metastasize and prove fatal [8].

Pathology [9,10]. A mass of irregular alveolar spaces surrounded by fibrous stroma is seen. Two types of cells are easily recognized: small round blue cells with scanty cytoplasm in a fibrillary matrix, and large epithelioid cells with pink cytoplasm and vesicular nuclei. These cells often contain melanin. Both types of tumour cells stain for synaptophysin and neurone-specific enolase, and are negative for S100. The large cells are positive for cytokeratin and HMB45.

Treatment. Complete surgical excision is the treatment of choice.

References

1 Koudstaal J, Oldhoff J, Panders AK *et al.* Melanotic neuroectodermal tumor of infancy. *Cancer* 1968; **22**: 151–61.
2 Krused-Lösler B, Gaertner C, Bürger H *et al.* Melanotic neuroectodermal tumor of infancy: systematic review of the literature and presentation of a case. *Oral Surg Oral Pathol* 2006; **102**: 204–16.
3 Borello ED, Gorlin RJ. Melanotic neuroectodermal tumour of infancy: a neoplasm of neural crest origin. *Cancer* 1966; **19**: 196–203.
4 Cutler LS, Chaudhury AP, Topiazian R. Melanotic neuroectodermal tumour of infancy: an ultrastructural literature review and reevaluation. *Cancer* 1981; **48**: 257–68.
5 Johnson RE, Scheithauer BW, Dahlin DC. Melanotic neuroectodermal tumour of infancy. *Cancer* 1983; **52**: 661–6.
6 Pettinato G, Manivel JC, d'Amore ESG *et al.* Melanotic neuroectodermal tumor of infancy: a reexamination of a histogenetic problem based on immunohistochemical, flow cytometric and ultrastructural study of 10 cases. *Am J Surg Pathol* 1991; **15**: 233–45.
7 Takeda Y, Kuroda M, Suzuki A. Melanocytes in odontoameloblastoma: a case report. *Acta Pathol Jpn* 1989; **39**: 465–8.
8 Dehner LP, Sibley RK, Sauk JJ *et al.* Malignant melanotic neuroectodermal tumor of infancy: a clinical, pathologic, ultrastructural and tissue culture study. *Cancer* 1979; **43**: 1389–410.
9 Johnson RE, Scheithauer BW, Dahlin DC. Melanotic neuroectodermal tumor of infancy: a review of seven cases. *Cancer* 1983; **52**: 661–6.
10 Stirling RW, Powell G, Fletcher CDM. Pigmented neuroectodermal tumour of infancy: an immunohistochemical study. *Histopathology* 1988; **12**: 425–35.

Malignant peripheral nerve sheath tumour [1,2]

Synonyms
- Neurofibrosarcoma
- Malignant schwannoma

Definition. A malignant tumour arising from the nerve sheath.

Aetiology. Cutaneous tumours usually arise from a plexiform neurofibroma in patients with neurofibromatosis type 1 [3]. Rare cutaneous lesions may arise within ordinary neurofibromas or *de novo* [4]. Deep-seated lesions arise *de novo* or in association with neurofibromatosis type 1. Patients with this disease develop malignancy in 30–50% of cases.

Incidence. It is an uncommon tumour. It occurs in young adults, or even children, when it complicates multiple neurofibromatosis. Sporadic cases occur in older individuals.

Clinical features [5]. The diagnosis should be suspected when a previously static tumour in a patient with neurofibromatosis begins to enlarge or becomes painful. The pain may become radicular as the lesion progresses but the tumours are not always associated with nerve trunks. The commoner sites are the flexor aspects of the limbs. A minority of cases occur as a complication of radiotherapy.

Pathology. The basic pattern is that of fascicles of tumour cells, often with a herringbone pattern and resembling a fibrosarcoma. Tumour cells tend to concentrate around blood vessels and myxoid change is common. The degree of pleomorphism and the number of mitotic figures varies. Immunohistochemical markers are not usually of help in the diagnosis as S-100 is only focally positive and often entirely negative.

Treatment. Wide local excision or amputation is necessary because of the aggressive behaviour of the tumour, and even then the prognosis is not good. Systemic metastases, particularly to the lungs, are common. The prognosis is worse in cases occurring after previous radiotherapy.

References

1 D'Agostino AN, Soule EH, Miller RH. Sarcomas of the peripheral nerves and somatic soft tissues associated with multiple neurofibromatosis (von Recklinghausen's disease). *Cancer* 1963; **16**: 1015–27.
2 George E, Swanson PE, Wick MR. Malignant peripheral nerve sheath tumours of the skin. *Am J Dermatopathol* 1989; **11**: 213–21.
3 Demitsu T, Murata S, Kiyosawa T *et al.* Malignant Schwannoma arising in patients with von Recklinghausen's disease. *J Dermatol* 1995; **22**: 747–54.
4 Allison KH, Patel RM, Goldblum JR *et al*. Superficial malignant peripheral nerve sheath tumor: a rare and challenging diagnosis. *Am J Clin Pathol* 2005; **124**: 685–92.
5 Giodillo PP, Helson L, Hajdu SI *et al.* Malignant schwannoma: clinical characteristics and response to therapy. *Cancer* 1981; **47**: 2503–9.

Clear cell sarcoma [1–5]

Definition. Clear cell sarcoma is a distinctive, malignant soft-tissue tumour that displays melanocytic differentiation.

Clinical features. Most cases occur on the lower limbs, with a predilection for the foot. The upper limb is affected in about 25% of cases. There is a predilection for females. Tumours tend to grow around tendons, are usually less than 3 cm in diameter and are often painful. Primary dermal tumours are exceptional.

Pathology. The lesion has a lobular growth pattern. Tumour cells are fairly homogeneous and contain clear or pale pink cytoplasm and a prominent eosinophilic nucleolus. Mitotic figures are not prominent, but multinucleated giant cells with a wreath-like arrangement of the nuclei are often identified. Loose, thin bands of collagen surround tumour cells. Secondary involvement of the dermis is relatively common. Necrosis is sometimes seen. Melanin is sometimes identified, and S100, HMB45 and melan A are usually positive. Electron-microscopic examination of tumour cells reveals the presence of melanosomes.

Cytogenetic analysis often reveals a translocation t(12; 22)(q13;q12); this translocation is not found in melanoma, which often has mutations in the *BRAF* gene (a feature not seen in clear cell sarcoma) [6,7]. The clear cell sarcoma translocation results in an *EWSR1—ATF1* fusion gene [8].

Prognosis and treatment [1–4]. About 50% of patients develop metastatic disease, often many years after the initial diagnosis. Prognosis is associated with mitotic index, size of the tumour and presence of necrosis [9,10]. The 5- and 10-year survival rates are 52% and 25% respectively [9]. Wide excision is the treatment of choice. Chemotherapy does not seem to be effective in the treatment of disseminated disease.

References

1 Enzinger FM. Clear cell sarcoma of tendons and aponeuroses: an analysis of 21 cases. *Cancer* 1965; **18**: 1163–76.
2 Eckardt JJ, Pritchard DJ, Soule EH. Clear cell sarcoma: a clinicopathologic study of 27 cases. *Cancer* 1983; **52**: 1482–8.
3 Lucas DR, Nascimento AG, Sim FH. Clear cell sarcoma of soft tissues: Mayo Clinic experience with 35 cases. *Am J Surg Pathol* 1992; **16**: 1197–204.
4 Montgomery EA, Meis JM, Ramos AG *et al.* Clear cell sarcoma of tendons and aponeurosis: a clinicopathologic study of 58 cases with analysis of prognostic factors. *Int J Surg Pathol* 1993; **1**: 59–62.
5 Meis-Kindblom JM. Clear cell sarcoma of tendon and aponeuroses: a historical perspective and tribute to the man behind the entity. *Adv Anat Pathol* 2006; **13**: 286–92.
6 Reeves BR, Fletcher CD, Gusterson BA. Translocation t(12;22)(q13;q13) is a non-random rearrangement in clear cell sarcoma. *Cancer Genet Cytogenet* 1992; **64**: 101–3.
7 Panagopoulos I, Mertens F, Isaksson M *et al*. Absence of mutations of the BRAF gene in malignant melanoma of soft parts (clear cell sarcoma of tendons and aponeuroses). *Cancer Genet Cytogenet* 2005; **156**: 74–6.
8 Panagopoulos I, Mertens F, Dëbiec-Rychter M *et al*. Molecular genetic characterization of the EWS/ATF1 fusion gene in clear cell sarcoma of tendons and aponeuroses. *Int J Cancer* 2002; **99**: 560–7.
9 Clark MA, Johnson MB, Thway K *et al*. Clear cell sarcoma (melanoma of soft parts): The Royal Marsden Hospital experience. *Eur J Surg Oncol* 2008; **34**: 800–4.
10 Coindre JM, Hostein I, Terrier P *et al*. Diagnosis of clear cell sarcoma by real-time reverse transcriptase-polymerase chain reaction analysis of paraffin embedded tissues: clinicopathological and molecular analysis of 44 patients from the French sarcoma group. *Cancer* 2005; **107**: 1055–64.

Peripheral primitive neuroectodermal tumour [1,2]

Synonyms
- Peripheral neuroepithelioma
- Extraosseous Ewing's sarcoma

Primary cutaneous or subcutaneous peripheral primitive neuroectodermal tumour is extremely rare, and only a handful of cases have been reported in the literature. The tumour presents in children and has no distinctive clinical features, although it is often confused with a vascular tumour. It has been suggested that superficial tumours have a better prognosis than those presenting in deeper soft tissues, but the number of cases reported and their follow-up is too limited for this to be certain. The histological diagnosis includes tumours composed of small, blue, round cells, for which immunohistochemistry plays an important role in diagnosis. Tumour cells are diffusely positive for CD99. This tumour usually presents a reciprocal chromosome translocation t(11;22)(q24;q12) that is an important aid in diagnosis.

References

1 Banerjee SS, Agbamu DA, Eyden BP *et al*. Clinicopathological characteristics of peripheral neuroectodermal tumour of skin and subcutaneous tissue. *Histopathology* 1997; **31**: 355–66.
2 Hasegawa S, Davidson JM, Rutten A *et al*. Primary cutaneous Ewing's sarcoma: immunophenotypic and molecular cytogenetic evaluation of five cases. *Am J Surg Pathol* 1998; **22**: 310–8.

Tumours of muscle

Congenital smooth muscle hamartoma

This lesion is described in Chapter 18.

Leiomyoma [1–3]

Definition. A benign tumour of smooth muscle derived from the arrector pili muscle, from the media of blood vessels, or from smooth muscle of the scrotum, labia majora or nipples (genital leiomyoma) [4,5].

Incidence. The tumour occurs in three main types, all of which are relatively uncommon.

Pilar leiomyoma (leiomyoma cutis) originates in the pilomotor muscle and is the most frequent. It can occur at any age from birth onwards, but appears usually in early adult life. It has been reported in identical twins, in siblings and in several generations of a family [6–8]. The cases with a familial background have all had multiple tumours. The sexes are affected equally.

Genital leiomyoma (dartoic myoma) arises in the smooth muscle of the genitalia and areola of the nipple [9,10]. It can occur at any age. The cutaneous variety is about six times more frequent than the genital type [11].

Angioleiomyoma arises from the muscular coat of veins, and is seen mainly in middle age or later as a solitary nodule on a limb. It is rather more prevalent than glomus tumour in published series [6,12,13]. Females are more commonly affected than males.

Clinical features [6,14]. Pilar leiomyoma generally presents as a collection of pink, red or dusky brown, firm dermal nodules of varying size but usually less than 15 mm diameter (Fig. 56.42). The nodules are often subject to episodes of pain and may be tender. The pain can be provoked by touching or chilling the skin, or by emotional disturbance, and is often worse in winter. Some lesions contract and become paler when painful [12,15]. The condition usually begins with the appearance of one small nodule, which gradually increases in size, and further similar lesions appear nearby or at some other area. Adjacent tumours may coalesce to form a plaque. The areas most commonly affected are the extremities, with the proximal and extensor aspects somewhat favoured. The trunk is involved more often than the head and neck. Multiple lesions may be regional and unilateral, or more than one region



Fig. 56.42 Clinical appearance of multiple leiomyomas.

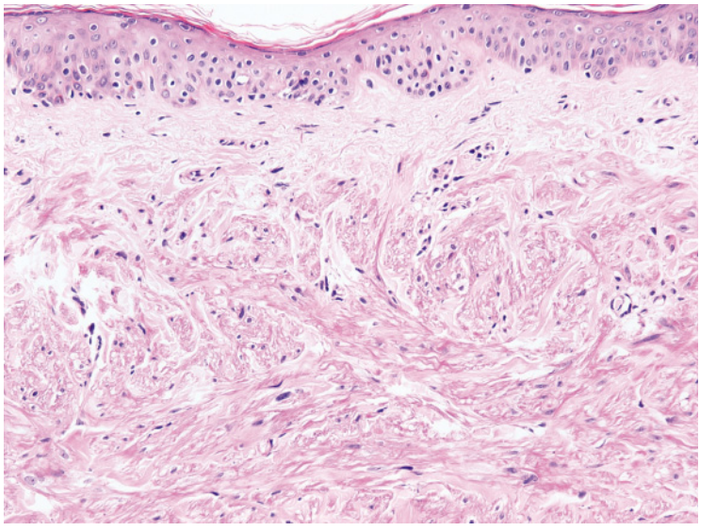


Fig. 56.43 Pathology of leiomyoma, showing spindle-shaped cells with eosinophilic cytoplasm arranged in bundles closely resembling the arrector pili muscle.

can be affected. Solitary lesions may occur, apart from the dartoic type. The gene that predisposes to multiple pilar leiomyomas has been mapped to chromosome 1q 42.3-q43 [16]. It also predisposes to uterine leiomyomas (multiple cutaneous and uterine leiomyomatosis, MCUL) and to renal cancer [17]. This is as a result of mutations in the gene encoding the enzyme fumarate hydratase [18]. In patients with associated renal cancer the syndrome is known as hereditary leiomyomatosis and renal cancer.

Genital leiomyoma is a solitary dermal nodule occurring most commonly in the scrotum, but also appearing on the penis, labia majora and nipple area. Scrotal tumours are often large. Pain is less frequent than with leiomyoma cutis. Contraction in response to stimulation by touch or cold can occur.

Angioleiomyoma is usually a solitary, flesh-coloured, rounded, subcutaneous or deep dermal tumour up to 40 mm in diameter. It is more frequent on the lower limb than the upper and may appear on the trunk or face. About half the reported cases have been painful [6,12]. Lesions are long-standing and present between the fourth and sixth decades of life. Pain may be triggered by changes in temperature, pregnancy or menses.

Pathology [12,14,19,20]. The smooth muscle cells proliferate to produce interweaving bundles of spindle-shaped cells, which are strongly eosinophilic (Fig. 56.43). The nuclei are long and thin, and the general appearance of the mass in ordinary sections may suggest a hypertrophic fibrous reaction. The smooth muscle cells can be distinguished from collagen by their different reaction with trichrome stains, and by the presence of myofibrils, which stain with phosphotungstic acid haematoxylin, and by their blunt-ended nuclei. Tumour cells are positive for actin and desmin.

The tumour of pilomotor origin (leiomyoma cutis, multiple cutaneous leiomyomas) is usually composed of numerous dermal nodules with vague margins where the cells penetrate the surrounding collagen bundles, and an upper border that approaches the papillary body. Associated epidermal hyperplasia is common. Focal nuclear atypia likely to be degenerative in origin and very low mitotic activity (up to one per 10 high-power fields) may be seen without this being indicative of malignant degeneration [21]. Genital leiomyomas are nodular tumours with a similar appearance. Scrotal tumours are less circumscribed and more cellular than those developing in the vulva. The angiomyomas are related to veins in the subcutaneous tissue, and are rounded and well circumscribed [22]. Vessels of variable thickness are intermixed with bundles of mature smooth muscle. Focal degenerative cytological atypia may be seen, but mitotic figures are absent. Calcification, hyalinization and thrombosis of vessels are often seen.

Diagnosis. The multiple type should cause little difficulty, and even without pain it is fairly distinctive. The solitary painful lesion may be mistaken for a glomus tumour or an eccrine spiradenoma, and a history of contraction is helpful. In practice the diagnosis can be elusive.

Treatment. Surgical excision cures the solitary tumour. The severity of the pain may make the patient demand treatment, and extensive lesions require plastic surgery. Excision of an area containing multiple tumours is often followed by their appearance in the neighbourhood of the treated area. Medical treatments that may relieve pain include calcium-channel blockers and gabapentin.

References

1 Eldor A, Even-Paz Z, Polliak A. Erythrocytosis associated with multiple cutaneous leiomyomata: report of a case with demonstration of erythropoietic activity in the tumour. *Scand J Haematol* 1976; **16**: 245.

2 Merrill RG, Downs JR. Oral leiomyomas: report of two cases. *Oral Surg* 1967; **23**: 438–40.

3 Venencie PY, Puissant A, Boffa GA *et al.* Multiple cutaneous leiomyomata and erythrocytosis. *Br J Dermatol* 1982; **107**: 483–6.

4 Nascimento AG, Karas M, Rosen PP *et al.* Leiomyoma of the nipple. *Am J Surg Pathol* 1979; **3**: 151–6.

5 Prabhakar BR, Davessar K, Chitkara NL *et al.* Leiomyoma of the areolar region of the breast. *Int J Cancer* 1969; **6**: 260–1.

6 Hachisuga T, Hashimoto H, Enjoji M. Angioleiomyoma: a clinical reappraisal of 562 cases. *Cancer* 1984; **54**: 126–30.

7 Kloepfer HW, Krafchuk J, Derbes V *et al.* Hereditary multiple leiomyoma of the skin. *Am J Hum Genet* 1958; **10**: 48–52.

8 Verma KC, Chawdhry SD, Rathi KS. Cutaneous leiomyomata in two brothers. *Br J Dermatol* 1973; **90**: 351–3.
9 Matsubara J, Miura K. Leiomyoma of the scrotum: a case report and review of the literature. *Jpn J Cancer Clin* 1971; **17**: 151–4.
10 Newman PL, Fletcher CDM. Smooth muscle tumours of the external genitalia: clinicopathological analysis of a series. *Histopathology* 1991; **18**: 523–9.
11 Fisher WC, Helwig EB. Leiomyomas of the skin. *Arch Dermatol* 1963; **88**: 510–20.
12 Duhig JT, Ayer JP. Vascular leiomyoma: a study of sixty-one cases. *AMA Arch Pathol* 1959; **68**: 424–30.
13 MacDonald DM, Sanderson KV. Angioleiomyoma of the skin. *Br J Dermatol* 1974; **91**: 161–8.
14 Bardach H, Ebner H. Das Angioleiomyom der Haut. *Hautarzt* 1975; **26**: 638–44.
15 Engelke H, Christophers E. Leiomyomatosis cutis et uteri. *Acta Derm Venereol (Stockh)* 1979; **59** (Suppl. 85): 51.
16 Alam NA, Bevan S, Churchman M *et al*. Localization of a gene (MCUL1) for multiple cutaneous leiomyomata and uterine fibroids to chromosome 1q,42.3–q43. *Am J Hum Genet* 2001; **68**: 1264–9.
17 Alam NA, Barclay E, Rowan AJ, Tyrer JP *et al*. Clinical features of multiple cutaneous and uterine leiomyomatosis: an underdiagnosed tumor syndrome. *Arch Dermatol* 2005; **141**: 199–206.
18 Alam NA, Olpin S, Leigh IM. Fumarate hydratase mutations and predisposition to cutaneous leiomyomas, uterine leiomyomas and renal cancer. *Br J Dermatol* 2005; **153**: 11–7.
19 Mann PR. Leiomyoma cutis: an electron microscopy study. *Br J Dermatol* 1970; **82**: 463–9.
20 Seifert HW. Ultrastructural investigation on cutaneous angioleiomyoma. *Arch Dermatol Res* 1981; **271**: 91–9.
21 Raj S, Calonje E, Kraus M *et al*. Cutaneous pilar leiomyoma: clinicopathologic analysis of 53 lesions in 45 patients. *Am J Dermatopathol* 1997; **19**: 2–9.
22 Magner D, Hill D. Encapsulated angiomyoma of the skin and subcutaneous tissue. *Am J Clin Pathol* 1961; **35**: 137–41.

Leiomyosarcoma [1–4]

Definition. A malignant tumour displaying smooth muscle differentiation. Tumours are divided into those occurring in the subcutaneous tissue and those arising in the dermis. Pure dermal lesions have a very different behaviour from those arising in the subcutis and it is therefore important to separate them (see below).

Incidence. This is a rare tumour. Dermal leiomyosarcoma presents predominantly on the lower limbs of young adults, with a predilection for males. Subcutaneous leiomyosarcoma affects middle-aged to elderly patients with slight predilection for males.

Clinical features [5,6]. The tumour may be situated in the dermis, when it is reddish in colour and may bleed on trauma. It is usually larger than a leiomyoma and dermal lesions may be painful. The majority of tumours have, however, arisen in the subcutaneous or deeper tissues as nodular tumours, ulcerated plaques [7] or diffuse swellings [8]. It may invade underlying muscle fascia. It is most common on the thigh, followed by the head and neck, arm and trunk, and may arise from the penis [9] or vulva. It is unlikely to be diagnosed clinically. An exceptional tumour has been reported arising in a naevus sebaceous [10]. Dermal leiomyosarcomas have a 40% recurrence rate, but they almost never metastasize [11]. Subcutaneous tumours metastasize in up to 50% of cases and they are associated with a mortality of about 30%.

Pathology [3,11–15]. The lesion is distinguished from other dermal malignant tumours composed of spindle-shaped cells by the presence of fascicles of eosinophilic spindle-shaped cells with vesicular cigar-shaped nuclei. The degree of differentiation varies and necrosis tends to be present in deeper tumours, but not in those arising primarily in the dermis. Most tumours are actin- and desmin-positive, but staining for the latter may be lost in poorly differentiated variants. Dermal variants tend to be consistently positive for both markers. Rare cases have a desmoplastic stroma making histological diagnosis difficult [16,17]. About 30% of leiomyosarcomas are immunohistochemically positive for keratin, but this is less commonly seen in cutaneous examples.

Treatment. Wide surgical excision is necessary, as local recurrence follows inadequate excision.

References

1 Headington JT, Beals TF, Niederhuber JE. Primary leiomyosarcoma of skin. *J Cutan Pathol* 1977; **4**: 308–17.
2 Wang P, Hornstein OP, Schricker KTH. Kutanes Leiomyosarkom und osteomedullaeres Plasmozytom mit Nachweis von IgA kappa-Paraprotein in Serum und Hauttummor. *Hautarzt* 1976; **27**: 441–8.
3 Oliver GF, Reiman HM, Gonchoroff NT *et al*. Cutaneous and subcutaneous leiomyosarcoma: a clinicopathological review of 14 cases with reference to antidesmin staining and nuclear DNA patterns studied by flow cytometry. *Br J Dermatol* 1991; **124**: 252–7.
4 Bellezza G, Sidoni A, Cavaliere A *et al*. Primary cutaneous leiomyosarcoma: a clinicopathological and immunohistochemical study of 7 cases. *Int J Surg Pathol* 2004; **12**: 39–44.
5 Haim S, Gellei B. Leiomyosarcoma of the skin: report of two cases. *Dermatologica* 1970; **140**: 30–5.
6 Orellana-Díaz O, Hernández-Pérez E. Leiomyoma cutis and leiomyosarcoma: a 10-year study and a short review. *J Dermatol Surg Oncol* 1983; **9**: 283–7.
7 Karroum KE, Zappi EG, Cockerell CJ. Sclerotic primary cutaneous leiomyosarcoma. *Am J Dermatopathol* 1995; **17**: 292–6.
8 Phelan JT, Sherer W, Mesa P. Malignant smooth-muscle tumors (leiomyosarcomas) of soft tissue origin. *N Engl J Med* 1962; **266**: 1027–30.
9 Greenwood N, Fox H, Edwards EC. Leiomyosarcoma of the penis. *Cancer* 1972; **29**: 481–3.
10 Premalata CS, Kumar RV, Malathi M *et al*. Cutaneous leiomyosarcoma, trichoblastoma, and syringocystadenoma papilliferum arising from nevus sebaceous. *Int J Dermatol* 2007; **46**: 306–8.
11 Kaddu S, Beham A, Cerroni L *et al*. Cutaneous leiomyosarcoma. *Am J Surg Pathol* 1997; **21**: 979–87.
12 Akers WA, Prazak G. Leiomyosarcoma metastatic to scalp from primary in retroperitoneal area: report of a case. *Arch Dermatol* 1960; **81**: 953–7.
13 Cháves E, Sa HH, Gadelha N *et al*. Leiomyosarcoma in the skin. *Acta Dermatol Vénéréol* 1972; **52**: 288.
14 Dahl I, Angervall L. Cutaneous and subcutaneous leiomyosarcoma: a clinicopathologic study of 47 patients. *Pathol Eur* 1974; **9**: 307–15.
15 Fields JP, Helwig EB. Leiomyosarcoma of the skin and subcutaneous tissue. *Cancer* 1981; **47**: 156–69.
16 Choy C, Cooper A, Kossard S. Primary cutaneous diffuse leiomyosarcoma with desmoplasia. *Australas J Dermatol* 2006; **47**: 291–5.
17 Berzal-Cantalejo F, Sabater-Marco V, Pérez-Vallés A *et al*. Desmoplastic cutaneous leiomyosarcoma: case report and review of the literature. *J Cutan Pathol* 2006; **33** (Suppl. 2): 29–31.

Skeletal muscle tumours

Rhabdomyosarcomatous congenital hamartoma

This lesion is described in Chapter 18.

Rhabdomyoma

Rhabdomyomas are divided into adult, fetal and genital types. They mainly occur in soft tissues, vulva or vagina, upper respiratory tract and internal organs. Presentation in the skin is almost never seen, and they will not be discussed further in this chapter.

Cutaneous rhabdomyosarcoma

Malignant tumours with skeletal-muscle differentiation are classified into two large groups, namely embryonal and alveolar types. Although rhabdomyosarcomas represent up to 8% of tumours in children, primary involvement of the skin by this tumour is very rare [1]. Much more common is involvement of the skin by direct extension from deeper soft tissues. Only 16 cases of primary cutaneous rhabdomyosarcoma have been reported in the literature so far, and only five of these have occurred in adults [2,3]. The most common subtype occurring in the skin is the alveolar variant. The majority of cases have presented on the face. The prognosis is difficult to estimate because of the rarity of these cases and the limited follow-up available.

References

1 Brecher AR, Reyes-Mugica M, Kamino H *et al*. Congenital primary cutaneous rhabdomyosarcoma in a neonate. *Pediatr Dermatol* 2003; **20**: 335–8.
2 Schmidt D, Fletcher CD, Harms D. Rhabdomyosarcoma with primary presentation in skin. *Pathol Res Pract* 1993; **189**: 422–7.
3 Setterfield J, Sciot R, Debiec-Rychter M *et al*. Primary cutaneous epidermotropic alveolar rhabdomyosarcoma with t(2;13) in an elderly woman: case report and review of the literature. *Am J Surg Pathol* 2002; **26**: 938–44.

Tumours of fat cells

Lipoma, angiolipoma and hibernoma

These lesions are described in Chapter 46.

Lipoblastoma and lipoblastomatosis

Definition. Lipoblastoma is a tumour that occurs almost exclusively in infants and children. It is characterized by a proliferation of immature fat cells in a myxoid stroma (that may mimic myxoid liposarcoma) and intermixed with mature adipocytes [1]. Lipoblastoma is a well-circumscribed, subcutaneous tumour; lipoblastomatosis refers to a deeper lesion or those that have an infiltrative growth pattern.

Clinical features [1–3]. Most cases present during the first few years of life, with a predilection for males. The majority of tumours occur on the limbs as an asymptomatic mass no more than a few centimetres in diameter. Lipoblastoma is much more common than lipoblastomatosis.

Pathology [1–3]. Tumours have a characteristic lobular appearance. Each tumour lobule is separated by fibrous septae and consists of a mixture of small, univacuolated, signet-ring cells, spindle-shaped or stellate cells and scattered mature adipocytes. In the background, there are prominent myxoid changes and numerous small vessels in a typical 'crow's-feet' distribution, mimicking a myxoid liposarcoma. Distinction from the latter may be very difficult, especially in small biopsies. The clinical information is therefore crucial, as myxoid liposarcoma is vanishingly rare in children and almost never occurs before the age of 10 years [4]. Furthermore, lipoblastoma tends to be less cellular than myxoid liposarcoma and has a lobular architecture. Over time, maturation occurs, and in some cases most of the tumour is composed of mature fat cells.

Cytogenetic studies in lipoblastoma have shown rearrangements on chromosome 8q [5,6].

Treatment. The tumour is benign, and simple excision is the treatment of choice. Deeper lesions have some tendency for local recurrence.

References

1 Chung EB, Enzinger FM. Benign lipoblastomatosis. *Cancer* 1973; **32**: 482–92.
2 Mentzel T, Calonje E, Fletcher CDM. Lipoblastoma and lipoblastomatosis: a clinicopathological study of 14 cases. *Histopathology* 1993; **23**: 527–33.
3 Collins MH, Chatten J. Lipoblastoma/lipoblastomatosis: a clinicopathologic study of 25 tumors. *Am J Surg Pathol* 1997; **21**: 1131–7.
4 Shmookler BM, Enzinger FM. Liposarcoma occurring in children: an analysis of 17 cases and review of the literature. *Cancer* 1983; **52**: 567–74.
5 Fletcher JA, Kozakewich HP, Schoenberg ML *et al*. Cytogenetic findings in pediatric adipose tumors: consistent rearrangement of chromosome 8 in lipoblastoma. *Genes Chromosomes Cancer* 1993; **6**: 24–9.
6 Hicks J, Dilley A, Patel D *et al*. Lipoblastoma and lipoblastomatosis in infancy and childhood: histopathologic, ultrastructural, and cytogenetic features. *Ultrastruct Pathol* 2001; **25**: 321–33.

Spindle cell and pleomorphic lipoma [1–5]

Definition. Spindle cell lipoma is composed of mature adipocytes and variable numbers of short, bland, spindle-shaped cells with indistinct cytoplasm. Pleomorphic lipoma is composed of mature adipocytes, cells with hyperchromatic nuclei and frequent multinucleation, and collagen bundles. Both types of tumour may overlap, and they are therefore considered to be part of the same spectrum.

Clinical features [1,2,4,5]. Spindle cell lipoma usually presents as a small subcutaneous nodule on the upper back or nape of the neck of middle-aged to old patients, with marked predilection for males. Occasional, purely dermal examples may be seen [6]. Multiple lesions, and familial cases, occur rarely [3]. Pleomorphic lipoma has a similar clinical presentation.

Pathology [1,2,4]. Spindle cell lipoma presents as a well-circumscribed tumour composed of mature adipocytes intermixed with short, spindle-shaped cells with wavy nuclei. Hyalinized collagen bundles and focal myxoid change are prominent. Pseudovascular spaces are prominent in some cases. The spindle-shaped cells stain for CD34 and the adipocytes are positive for S100. Pleomorphic lipoma is also well-circumscribed and composed of mature adipocytes intermixed with uninucleated or multinucleated cells with hyperchromatic nuclei. The nuclei in the multinucleated cells are often arranged in a circle (floret cell). The histological diagnosis may be quite difficult in cases with few or no mature fat cells [7]. Rare variants contain real prominent vascular spaces [8].

Cytogenetic studies of both tumours have shown variable abnormalities, most commonly in chromosome 16q and rarely in chromosomes 13q and 6p [9,10].

Treatment. There is little tendency for local recurrence, and simple excision is therefore the treatment of choice.

References

1 Enzinger FM, Harvey DA. Spindle cell lipoma. *Cancer* 1975; **36**: 1852–9.
2 Fletcher CDM, Martin-Bates E. Spindle cell lipoma: a clinicopathological study with some original observations. *Histopathology* 1987; **11**: 803–17.
3 Fanburgh-Smith JC, Devaney KO, Miettinen M, Weiss SW. Multiple spindle cell lipomas: a report of 7 familial and 11 nonfamilial cases. *Am J Surg Pathol* 1998; **22**: 40–8.
4 Schmookler BM, Enzinger FM. Pleomorphic lipoma: a benign tumor simulating liposarcoma: a clinicopathologic analysis of 48 cases. *Cancer* 1981; **47**: 126–33.
5 Griffin TD, Goldstein J, Johnson WC. Pleomorphic lipoma: case report and discussion of 'atypical' lipomatous tumors. *J Cutan Pathol* 1992; **19**: 330–3.
6 Mentzel T. Cutaneous lipomatous neoplasms. *Semin Diagn Pathol* 2001; **18**: 250–7.
7 Billings SD, Folpe AL. Diagnostically challenging spindle cell lipomas: a report of 34 'low-fat' and 'fat-free' variants. *Am J Dermatopathol* 2007; **29**: 437–42.
8 Zamecnik M, Michal M. Angiomatous spindle cell lipoma: report of three cases with immunohistochemical and ultrastructural study and reappraisal of former 'pseudoangiomatous' variant. *Pathol Int* 2007; **57**: 26–31.
9 Fletcher CD, Akerman M, Dal Cin P *et al.* Correlation between clinicopathologic features and karyotype in lipomatous tumors. *Am J Pathol* 1996; **148**: 623–30.
10 Rubin BP, Fletcher CD. The cytogenetics of lipomatous tumours. *Histopathology* 1997; **30**: 507–11.

Atypical lipomatous tumour [1–4]

Synonym
- Well-differentiated liposarcoma

Definition. This is a lesion composed of lobules of mature adipose cells, with scattered larger cells with variation in nuclear size and hyperchromatism. The term 'atypical lipomatous tumour' is usually used for neoplasms occurring in the subcutis or within skeletal muscle. Similar tumours occurring in the abdominal cavity are regarded as well-differentiated liposarcomas, in view of the fact that they have a potential to cause death as a result of extensive growth. Only subcutaneous lesions will be discussed here.

Clinical features [1–3]. Subcutaneous atypical lipomatous tumours occur in middle-aged to old adults with predilection for the lower limbs. Tumours may be large, are asymptomatic and have the same clinical appearance as a lipoma.

Pathology. Typically, lobules of mature adipose tissue, with or without fibrous tissue and myxoid change, are seen. Focal variation in the size and shape of adipocytes is seen and this is associated with nuclear enlargement and hyperchromatism. Vacuolated cells may also be found. Atypical cells are often present in the fibrous tissue. Some tumours are classified as cellular based on the presence of non-lipogenic areas of increased cellularity with low-mitotic activity [5]. Dedifferentiated tumours are lesions that develop a high-grade sarcomatous component that is associated with poor prognosis [6]. This change does not usually develop in tumours that are superficially located.

Cytogenetic studies of these neoplasms have found chromosomal abnormalities in most cases. About a third of cases show supernumerary ring chromosomes affecting chromosome 12q.13–15 [4]. This results in amplification of *MDM2* and *CDK4* genes [7]. Expression of these genes can be detected by FISH, real-time PCR or immunohistochemistry, making it a useful diagnostic aid. Of these methods, FISH and real-time PCR, but particularly the former, are more sensitive than immunohistochemistry for detection of these amplifications [8].

Prognosis and treatment. There is a tendency for local recurrence, but metastases are not seen unless the tumour undergoes dedifferentiation which does not tend to happen in superficially located tumours, particularly those in the subcutaneous tissue [6]. Complete surgical excision is indicated.

References

1 Azumi N, Curtis J, Kempson RL, Hendrickson MR. Atypical and malignant neoplasms showing lipomatous differentiation: a study of 111 cases. *Am J Surg Pathol* 1987; **11**: 161–83.
2 Evans HL, Soule EH, Winkelmann RK. Atypical lipoma, atypical intramuscular lipoma, and well-differentiated retroperitoneal liposarcoma: a reappraisal of 30 cases formerly classified as well-differentiated liposarcoma. *Cancer* 1979; **43**: 574–84.
3 Evans HL. Liposarcoma and atypical lipomatous tumors: a study of 66 cases followed for a minimum of 10 years. *Surg Pathol* 1988; **1**: 41–54.
4 Rosai J, Akerman M, Dal Cin P *et al.* Combined morphologic and karyotypic study of 59 atypical lipomatous tumors: evaluation of their relationship and differential diagnosis with other adipose tissue tumors (a report of the CHAMP Study Group). *Am J Surg Pathol* 1996; **20**: 1182–9.
5 Evans HL. Atypical lipomatous tumour, its variants, and its combined forms: a study of 61 cases, with a minimum follow-up of 10 years. *Am J Surg Pathol* 2007; **31**: 1–14.
6 Weiss SW, Rao VK. Well-differentiated liposarcoma (atypical lipoma) of deep soft tissue of the extremities, retroperitoneum, and miscellaneous sites: a follow-up study of 92 cases with analysis of the incidence of dedifferentiation. *Am J Surg Pathol* 1992; **16**: 1051–8.
7 Binh MB, Sastre-Garau X, Gillou L *et al*. MDM2 and CDK4 immunostainings are useful adjuncts in diagnosing well-differentiated and dedifferentiated liposarcoma subtypes: a comparative analysis of 559 soft tissue neoplasms with genetic data. *Am J Surg Pathol* 2005; **29**: 1340–7.
8 Sirvent N, Coindre JM, Maire G *et al*. Detection of MDM2-CDK4 amplification by fluorescence in situ hybridization in 200 paraffin-embedded tumor samples: utility in diagnosing adipocytic lesions and comparison with immunohistochemistry and real-time PCR. *Am J Surg Pathol* 2007; **31**: 1476–89.

Liposarcoma [1]

Myxoid and round cell liposarcoma and pleomorphic liposarcoma are vanishingly rare in the skin. Only a few cases of primary cutaneous liposarcoma have been described. Follow-up is limited, but the behaviour seems to be better than that of their deeper counterparts, probably reflecting early detection and treatment and the easy accessibility to the skin. Liposarcoma will not be discussed further in this chapter.

Reference

1 Dei Tos AP, Mentzel T, Fletcher CD. Primary liposarcoma of the skin: a rare neoplasm with unusual high grade features. *Am J Dermatopathol* 1998; **20**: 332–8.

Tumours of uncertain histogenesis

Superficial angiomyxoma [1,2]

Definition. Superficial angiomyxoma is a dermal or subcutaneous tumour composed of a mixture of small blood vessels and sparse spindle-shaped cells in a prominent myxoid stroma.

Clinical features [1,2]. Most cases occur in adults as an asymptomatic solitary papule or nodule with equal sex incidence. Lesions are usually less than 3 cm and have a wide anatomical distribution with a predilection for the trunk, head and neck and genital skin. In patients with multiple lesions, the possibility of Carney complex should be considered (see Chapter 62) [3].

Pathology. Tumours are multilobulated, with copious myxoid stroma, numerous delicate small blood vessels and spindle-shaped or stellated bland cells, probably representing fibroblasts. Aggregates of inflammatory cells, mainly neutrophils, are frequent. In up to 30% of cases epithelial structures, probably representing hyperplastic trapped adnexal structures (particularly hair follicles), are identified.

Treatment. Local recurrence is seen in up to 30% of cases [3], but the behaviour is benign and therefore excision is the treatment of choice.

References

1 Allen PW, Dymock RB, MacCormac WB. Superficial angiomyxoma with or without epithelial components: report of 30 tumors in 28 patients. *Am J Surg Pathol* 1988; **12**: 519–30.

2 Calonje E, Guerin D, McCormick D *et al*. Superficial angiomyxoma: clinicopathologic analysis of a series of distinctive but poorly recognized cutaneous tumors with a tendency for recurrence. *Am J Surg Pathol* 1999; **23**: 910–7.

3 Carney JA, Headington JT, Wu SP. Cutaneous myxomas: a major component of the complex of myxomas, spotty pigmentation and endocrine overactivity. *Arch Dermatol* 1986; **122**: 790–8.

Digital myxoma [1]

Synonym
- Cutaneous myxoid cyst

Digital myxoma is relatively rare and presents mainly on the fingers as a small, solitary painful nodule. Females are much more commonly affected than males and there is a tendency for local recurrence. Lesions are poorly circumscribed and consist of abundant myxoid stroma with only scattered, bland, spindle-shaped cells.

Reference

1 Johnson WC, Graham JH, Helwig EB. Cutaneous myxoid cyst: a clinicopathologic and histochemical study. *JAMA* 1965; **191**: 15–20.

Dermal non-neural granular cell tumour

Synonyms
- Primitive polypoid granular cell tumour
- Primitive non-neural granular cell tumour

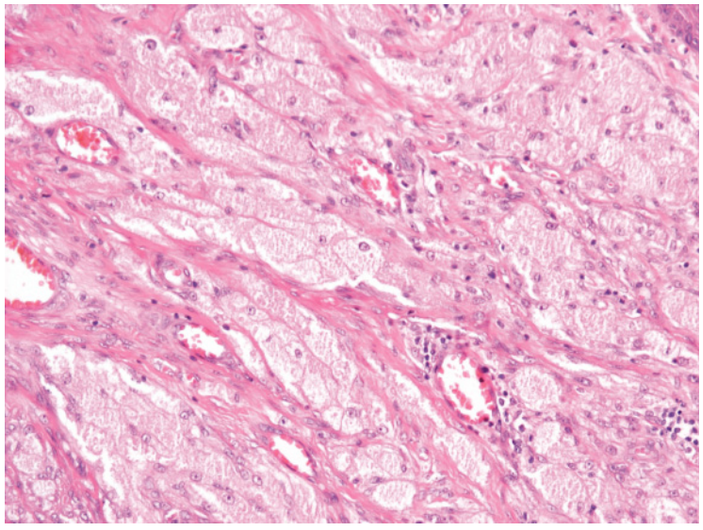


Fig. 56.44 Large cells with prominent granular cell change in a case of dermal non-neural granular cell tumour.

Definition. This is a distinctive dermal tumour with no specific line of differentiation, initially described as primitive polypoid granular cell tumour in 1991 [1]. Tumours are not related to neural granular cell tumours, which are uniformly S-100 positive. They occur both in the dermis and in subcutaneous tissue.

Clinical features. This tumour usually presents as an exophytic, small, cutaneous lesion with a wide anatomical distribution, wide age range and no sex predilection. Not all tumours are polypoid. Clinical behaviour is usually benign with only rare local recurrences [2–4]. However, a single case of metastasis to a regional lymph node has been reported [3].

Pathology. Histologically, lesions show rounded or spindle-shaped cells with prominent granular cell change (Fig. 56.44). Polypoid tumours have an epithelial collarette. Nuclear pleomorphism varies but does not tend to be prominent. Mitotic figures may be prominent. Multinucleated cells are sometimes seen. There is diffuse positivity for NKI-C3, which is a non-specific marker for lysosomes, and focal positivity for CD68 and NSE. Tumour cells do not stain for keratin, EMA, actin, desmin, H-caldesmon or S-100 [3,4].

Treatment. Complete conservative excision is the treatment of choice.

References

1 LeBoit PE, Barr RJ, Burall S *et al*. Primitive polypoid granular cell tumor and other cutaneous granular cell neoplasms of apparent non-neural origin. *Am J Surg Pathol* 1991; **15**: 48–58.

2 Lacroix-Triki M, Rochaix P, Marques B *et al*. Granular cell tumors of the skin of nonneural origin: report of 8 cases. *Ann Pathol* 1999; **19**: 94–8.

3 Lazar AJ, Fletcher CD. Primitive nonneural granular cell tumors of the skin: clinicopathologic analysis of 13 cases. *Am J Surg Pathol* 2005; **29**: 927–34.

4 Chaudhry IH, Calonje E. Dermal non-neural granular cell tumour (so-called polypoid granular cell tumour): a distinctive entity further delineated in a clinicopathological study of 11 cases. *Histopathology* 2005; **47**: 179–85.

Perivascular epithelioid cell tumour ('PEComa')

Definition. Perivascular epithelioid cell tumour is part of a spectrum of neoplasms that includes clear cell 'sugar' tumour of the lung, angiomyolipoma, lymphangioleiomyomatosis and clear cell myomelanocytic tumour of the falciform ligament [1–3]. Occurrence in the skin and soft tissue is rare but it is likely that the lesion is under-recognized. Although tumour cells are usually positive for melanocytic markers such as HMB45 and melan-A, the cell of origin has not been identified.

Clinical features. Cutaneous lesions are rare [4] and mainly occur in the lower extremities with a strong predilection for females.

Pathology [3,4]. Histology is distinctive and consists of bland epithelioid cells, typically arranged radially around thin-walled vascular channels. A smaller population of spindle cells is often seen. Tumour cells have pale pink cytoplasm and vesicular nuclei. Malignant examples may be seen but have not been reported in the skin. The immunophenotype is distinctive, as the tumour cells stain for melanocytic markers including HMB45, MITF-1, Melan-A and tyrosinase and for muscular markers including SMA and calponin. They are usually negative for S-100 and keratin.

Treatment. Simple excision is the treatment of choice.

References

1 Folpe AL, Goodman ZD, Ishak KG *et al*. Clear cell myomelanocytic tumor of the falciform ligament/ligamentum teres: a novel member of the perivascular epithelioid clear cell family of tumors with predilection for children and young adults. *Am J Surg Pathol* 2000; **24**: 1239–46.

2 Folpe AL, McKenney JK, Li Z *et al*. Clear cell myomelanocytic tumor of the thigh: report of a unique case. *Am J Surg Pathol* 2002; **26**: 809–12.

3 Hornick JL, Fletcher CD. PEComa: what do we know so far? *Histopathology* 2006; **48**: 75–82.

4 Mentzel T, Reisshauer S, Rütten A *et al*. Cutaneous clear cell myomelanocytic tumour: a new member of the growing family of perivascular epithelioid cell tumours (PEComas). Clinicopathological and immunohistochemical analysis of seven cases. *Histopathology* 2005; **46**: 498–504.

'Aggressive' angiomyxoma [1,2]

Definition. 'Aggressive' angiomyxoma is a distinctive tumour occurring in the genital region and pelvis, predominantly of females. It is characterized by bland, spindle-shaped cells in the background of a prominent myxoid stroma and frequent, thick-walled blood vessels.

Clinical features. This tumour occurs almost exclusively in females of reproductive age, but rare lesions have been described in males [3]. Cases in children are exceptional and may involve the spermatic cord [4]. Tumours are slowly growing and by the time of presentation they are large and ill-defined, often measuring 10 cm or more. The most commonly affected sites are the vulva and perineum. Extension into deeper soft tissues is often found.

Pathology. The lesion is infiltrative and is composed of spindle or stellate-shaped, bland cells with scanty cytoplasm, surrounded by prominent myxoid stroma. Small to medium-sized, thick-walled blood vessels are seen throughout the tumour. Mitotic figures are very rare. Rare cases contain multinucleated giant cells [5]. Interestingly, tumour cells are positive for actin and desmin. Tumour cells are often positive for oestrogen and/or progesterone receptors [6].

Cytogenetics in one case demonstrated a translocation t(8;12)(p12;p15) involving a rearrangement of *HMGIC* (a DNA architectural factor gene) [7], and analysis in a further case found a translocation t(5;8)(p15;q22) [8].

Prognosis and treatment. Local recurrence is observed in up to a third of cases, and complete surgical excision is usually difficult because of the infiltration of surrounding tissue. However, recurrences are not usually destructive, and radical surgical procedures are therefore not indicated.

References

1 Steeper TA, Rosai J. Aggressive angiomyxoma of the female pelvis and peritoneum: report of nine cases of a distinctive type of gynecologic soft tissue neoplasm. *Am J Surg Pathol* 1983; **7**: 463–75.

2 Fetsch JF, Laskin WB, Lefkowitz M *et al*. Aggressive angiomyxoma: a clinicopathologic study of 29 female patients. *Cancer* 1996; **78**: 79–90.

3 Tsang WY, Chang JK, Lee KC *et al*. Aggressive angiomyxoma: a report of four cases occurring in men. *Am J Surg Pathol* 1992; **16**: 1059–65.

4 Carlinfante G, De Marco L, Mori M *et al*. Aggressive angiomyxoma of the spermatic cord. Two unusual cases occurring in childhood. *Pathol Res Pract* 2001; **197**: 139–44.

5 Zamecnik M, Skalova A, Michal M *et al*. Aggressive angiomyxoma with multinucleated giant cells: a lesion mimicking liposarcoma. *Am J Dermatopathol* 2000; **22**: 368–71.

6 McCluggage WG, Patterson A, Maxwell P. Aggressive angiomyxoma of pelvic parts exhibits oestrogen and progesterone receptor positivity. *J Clin Pathol* 2000; **53**: 603–5.

7 Nucci MR, Weremowicz S, Neskey DM *et al*. Chromosomal translocation t(8;12) induces aberrant HMGIC expression in aggressive angiomyxoma of the vulva. *Gene Chromosome Canc* 2001; **32**: 172–6.

8 Tsuji T, Yoshinaga M, Inomoto Y *et al*. Aggressive angiomyxoma of the vulva with a sole t(5;8)(p15;q22). *Int J Gynecol Pathol* 2007; **26**: 494–6.

Epithelioid sarcoma [1–3]

Definition. A distinctive, malignant soft-tissue tumour composed of cells with epithelial differentiation. It is not clear whether this tumour represents a primary soft-tissue carcinoma or a sarcoma with epithelial differentiation.

Incidence. It is an uncommon tumour, affecting males more often than females and tending to begin in early adult life.

Clinical features [4,5]. The presenting sign can be a dermal nodule that grows outwards and may ulcerate early, a nodule or lobular subcutaneous tumour that is painless and grows slowly, or a tumour attached to deeper structures that is rather poorly defined and causes pain, paraesthesiae or muscular wasting when growing along a large trunk nerve. As a result of prominent perineurial and perivascular extension of tumour cells, multiple nodules in a sporotrichoid distribution may be seen. The distal extremities are the usual situation for the tumour, particularly the flexor aspect of the finger and the palm. It may grow at a deceptively slow rate.

A distinctive variant of epithelioid sarcoma previously described as 'extrarenal rhabdoid tumour' has been reported in older patients who present with a large mass on the proximal limbs, genitalia, buttocks, trunk or head and neck [6,7]. This variant is known as 'proximal-type epithelioid sarcoma'.

Pathology [8,9]. The tumour is composed of firm nodules, 5–50 mm or larger in diameter surrounded by fibrous tissue and fat. It is often closely associated with fascia, periosteum, tendon or nerve sheaths. The cut surface is greyish-white and flecked or mottled with yellow or brown, reflecting the presence of areas of necrosis. Microscopically, there are masses of large, round, polygonal or spindle cells with acidophilic cytoplasm. Spindle cells are often present and may predominate. The larger nodules have necrotic centres and show so-called 'geographical necrosis', which may be mistaken on scanning power microscopy for a granuloma. Mitotic figures are common, and binucleate cells occur. Variable cytological atypia is always present and may be prominent. Intercellular hyalinized collagen increases the acidophilia, while calcification, with osteoid or bone formation, may take place in the necrotic areas. The tumour spreads along dense fibrous structures and may ulcerate in areas with little subcutaneous fat. Local recurrence after excision is common, and metastasis, principally to lymph nodes, lung and pleura, may occur. Tumour cells show clear histological, ultrastructural and immunohistochemical evidence of epithelial differentiation.

The proximal type of epithelioid sarcoma shows a similar multinodular growth pattern but tumour cells are larger and with a more rhabdoid appearance consisting of abundant cytoplasm and large nuclei with or without a prominent eosinophilic nucleolus. Immunohistochemically, tumour cells in both variants of epithelioid sarcoma have the same profile. They are positive for vimentin, keratin and EMA, and 50% of cases are positive for CD34 [10].

No distinctive and consistent cytogenetic abnormality has been identified in this tumour. However, lesions often display chromosomal gains and the most frequent of these is on chromosome 22q [11,12].

Diagnosis. Superficial lesions can easily be mistaken for an ulcerating squamous cell carcinoma, deeper ones are usually regarded as inflammatory in nature. Histological diagnoses have varied, with granulomatous inflammation and synovial sarcoma being the commonest benign and malignant diagnoses, respectively.

Prognosis and treatment. Complete removal by surgical excision is essential if local recurrence and eventual metastasis are to be avoided, and the earlier this is done the less likely is the process to spread along fascial planes. Surgical excision followed by radiotherapy is often recommended. Involvement of regional lymph nodes is associated with distant metastasis and death [13]. Local recurrence and metastasis may occur years after the original diagnosis. The survival rate has been estimated at between 65% and 70% [8,13]. Features associated with poorer prognosis include male sex, older age at diagnosis, proximal location, rhabdoid phenotype, tumour size, mitotic rate, necrosis, vascular invasion, local recurrence and lymph node metastasis [3,8,9,13].

References

1 Enzinger F. Epithelioid sarcoma: a sarcoma simulating granuloma or carcinoma. *Cancer* 1970; **26**: 1029–41.
2 Fletcher CDM, McKee PH. Sarcomas: a clinicopathological guide with particular reference to cutaneous manifestation, 1. *Clin Exp Dermatol* 1984; **9**: 451–65.
3 Fisher C. Epithelioid sarcoma of Enzinger. *Adv Anat Pathol* 2006; **13**: 114–21.
4 Santiago H, Feinerman LK, Lattes R. Epithelioid sarcoma: a clinical and pathologic study of 9 cases. *Hum Pathol* 1972; **3**: 1706–10.
5 Evans HL, Baer SC. Epithelioid sarcoma: a clinicopathologic and prognostic study of 26 cases. *Semin Diagn Pathol* 1993; **10**: 286–91.
6 Guillou L, Wadden C, Coindre JM *et al*. Proximal-type epithelioid sarcoma, a distinctive aggressive neoplasm showing rhabdoid features: clinicopathologic, immunohistochemical, and ultrastructural study of a series. *Am J Surg Pathol* 1997; **21**: 130–46.
7 Hasegawa T, Matsuno Y, Shimoda T *et al*. Proximal-type epithelioid sarcoma: a clinicopathologic study of 20 cases. *Mod Pathol* 2001; **14**: 655–63.
8 Halling AC, Wollan PC, Pritchard DJ *et al*. Epithelioid sarcoma: a clinicopathologic review of 55 cases. *Mayo Clin Proc* 1996; **71**: 636–42.
9 Prat J, Woodruff JM, Marcove RC. Epithelioid sarcoma: an analysis of 22 cases indicating the prognostic significance of vascular invasion and regional lymph node metastases. *Cancer* 1978; **41**: 1472–87.
10 Arber DA, Kandalaft PL, Mehta P *et al*. Vimentin-negative epithelioid sarcoma: the value of an immunohistochemical panel that includes CD34. *Am J Surg Pathol* 1993; **17**: 302–7.
11 Lualdi E, Modena P, Debiec-Rychter M *et al*. Molecular cytogenetic characterization of proximal-type epithelioid sarcoma. *Genes Chromosomes Cancer* 2004; **41**: 283–90.
12 Lee MW, Jee KJ, Han SS *et al*. Comparative genomic hybridization in epithelioid sarcoma. *Br J Dermatol* 2004; **151**: 1054–9.
13 Chase DR, Enzinger FM. Epithelioid sarcoma: diagnosis, prognostic indicators and treatment. *Am J Surg Pathol* 1985; **9**: 241–63.

Ossifying lesions in the dermis [1]

A wide range of subcutaneous lesions may occasionally show partial ossification. The most common are pilomatricomas and melanocytic naevi. Other soft-tissue lesions, such as soft-tissue chondromas and fibromyxoid tumours, may show metaplastic bone formation.

Reference

1 Fletcher CDM. Calcifying and ossifying soft tissue lesions presenting in the skin. *J Cutan Pathol* 1996; **23**: 297.

Osteoma cutis [1]

Definition. A true bony new growth arising within the skin from bone-forming tissue and showing no tendency to invade.

Incidence and aetiology. Osteoma cutis is a rare tumour. Most osseous nodules in the skin are not true neoplasms, but result from metaplastic ossification, which usually occurs in a focus of calcification; the initiating lesion is frequently an inflammatory granuloma or scar. The majority of these lesions are best classified as dystrophic ossification rather than as osteomas. Dystrophic ossification has been reported in scleroderma, in old acne cysts and at sites of puncture of the skin or of haematomas. They may be found in melanocytic naevus, pilomatricoma, histiocytoma and chondroid syringoma, and may be secondary to basal cell carcinoma [2,3]. Another cause is Albright's hereditary osteodystrophy, in which cutaneous ossification has recently been recognized with

increasing frequency [4–6]. Rarely, multiple miliary osteomas of the skin can occur after acne [7,8], sometimes with neurotic excoriations or after dermabrasion [9]. There remain a minority of reported cases that appear to be primary osteomas, the majority of which are multiple and on the face or scalp [9–11].

There is no point in trying to estimate the age and sex incidence for a group as heterogeneous as individuals with dystrophic calcification of the skin. It seems likely that primary osteomas will become even more rare if hereditary osteodystrophy and other causes are sought.

Clinical features. Metaplastic osteomas are frequently small and clinically undetectable in the primary lesion. They are usually situated deep in the dermis or subcutaneous tissue. They may be seen when radiographs of the area are taken, but are most commonly first noticed by the histology technician as a hard body that damages the knife edge. The distinguishing feature, if the tumour is found clinically, is the stone-hard texture on palpation, similar to pilomatricoma. A case of osteoma cutis associated with diaphyseal aclasis has been reported [12].

Pathology [3]. Whether metaplastic or primary, the microscopic picture is of a small circumscribed nodule of osseous tissue with trabeculae enclosing fat and, occasionally, marrow cells.

Treatment. If required, simple excision is curative.

References

1 Reichenberger M, Löhnert J. Osteosis cutis multiplex. *Hautarzt* 1971; **22**: 73–7.
2 Duperrat B. Cutaneous osteomas: study based on 24 personal cases. *Ann Dermatol Syphiligr* 1961; **88**: 11–31.
3 Roth SL, Stowell RE, Helwig EB. Cutaneous ossification: report of 120 cases and review of the literature. *Arch Pathol* 1963; **76**: 44–54.
4 Brook CGD, Valman HB. Osteoma cutis and Albright's hereditary osteodystrophy. *Br J Dermatol* 1971; **85**: 471–5.
5 Eyre WG, Reed WB. Albright's hereditary osteodystrophy with cutaneous bone formation. *Arch Dermatol* 1971; **104**: 636–42.
6 Peterson WC, Mandel SL. Primary osteomas of skin. *Arch Dermatol* 1963; **87**: 626–32.
7 Basler RSW, Taylor WB, Peacor DR. Postacne osteoma cutis: X-ray diffraction analysis. *Arch Dermatol* 1974; **110**: 113–4.
8 Delaney TJ, Gold SC, Leppard B. Disseminated perforating granuloma annulare. *Br J Dermatol* 1974; **89**: 523–6.
9 Rossman RE, Freeman RG. Osteoma cutis, a stage of preosseous calcification. *Arch Dermatol* 1964; **89**: 68–73.
10 Helm F, De La Pava S, Klein E. Multiple miliary osteomas of the skin. *Arch Dermatol* 1967; **96**: 681–2.
11 Zabel R. Osteosis cutis multiplex faciei. *Dermatol Monatsschr* 1970; **156**: 798–801.
12 Donaldson EM, Summerly R. Primary osteoma cutis and diaphyseal aclasis. *Arch Dermatol* 1962; **85**: 261–5.

Cutaneous calculus [1,2]

Synonym
- Subepidermal calcified nodule

This small tumour, which is relatively common, has a characteristic yellowish white colour and is situated in the subepidermal tissue. It is seen most commonly on the face in children; it varies in size up to 10 mm or so, but may occasionally be larger and plaque-like, and it has a hard consistency. The epidermis over it may be verrucose. Episodes of inflammation and shedding of a portion of the lesion may occur. Microscopic examination shows calcareous bodies in the superficial part of the dermis. A histiocytic or foreign-body reaction often surrounds some of the calcified bodies. The exact histogenesis is uncertain. Calcification of naevus cells has been suggested. The lesion can be removed easily by curettage.

References

1 Hunter GA, Donald GF. Cutaneous calculus: a report of three cases. *Aust J Dermatol* 1963; **7**: 23–5.
2 Woods B, Kellaway TD. Cutaneous calculi: subepidermal calcified nodules. *Br J Dermatol* 1963; **75**: 1–11.

Progressive osseous heteroplasia

This is discussed in Chapter 45.

CHAPTER 57
Cutaneous Lymphomas and Lymphocytic Infiltrates

S.J. Whittaker
St John's Institute of Dermatology, Guy's and St Thomas' Hospital, London, UK

Primary cutaneous T-cell lymphomas, 57.3
Mycosis fungoides, 57.3
Follicular mucinosis, 57.14
Pagetoid reticulosis, 57.15
Granulomatous slack-skin disease, 57.15
Sézary syndrome, 57.17
Treatment of mycosis fungoides and Sézary syndrome, 57.22
Primary cutaneous CD30$^+$ lymphoproliferative disorders, 57.29
Lymphomatoid papulosis, 57.29
Primary cutaneous (anaplastic) CD30$^+$ large cell lymphoma, 57.31
Subcutaneous panniculitis-like T-cell lymphoma (SPTL), 57.33
Primary cutaneous peripheral T-cell lymphoma (unspecified), 57.34
Primary cutaneous aggressive epidermotropic CD8$^+$ T-cell lymphoma (provisional), 57.35
Primary cutaneous γδ T-cell lymphomas (provisional entity), 57.36
Primary cutaneous CD4$^+$ small/medium sized pleomorphic T-cell lymphoma, 57.36
Adult T-cell leukaemia–lymphoma (HTLV-1-associated), 57.37
CD4$^+$/CD56$^+$ haematodermic neoplasm (blastic NK-cell lymphoma), 57.39
Extranodal NK/T-cell lymphoma (nasal type), 57.40
Primary cutaneous B-cell lymphomas, 57.41
Marginal zone lymphoma, 57.43
Follicle centre cell lymphoma, 57.45
Diffuse large B-cell lymphoma, 57.47
Secondary cutaneous B-cell lymphomas, 57.50
Intravascular large B-cell lymphoma, 57.50
Lymphomatoid granulomatosis, 57.51
Secondary cutaneous T-cell lymphomas, 57.51
Angioimmunoblastic T-cell lymphoma, 57.51
Post-transplant lymphoproliferative disorder (PTLD), 57.52
Pseudolymphomas, 57.53
Pityriasis lichenoides, 57.54
Parapsoriasis, 57.57
Actinic reticuloid, 57.58
Lymphocytoma cutis, 57.59
Jessner's lymphocytic infiltrate, 57.60
Leukaemia cutis, 57.61
Cutaneous Hodgkin's disease, 57.63
Lennert's lymphoma, 57.64

Introduction

Over the past 20 years, advances in understanding the biology of lymphoid cells have greatly improved our knowledge of primary cutaneous lymphomas. Various node-based classifications of lymphomas, including the Kiel classification first introduced in 1980 and updated in 1988 [1], were of relatively little value for primary cutaneous lymphoma as they were based purely on detailed pathological assessment of nodes with no clinical correlation. In contrast, the current World Health Organization/European Organization of Research and Treatment of Cancer (WHO–EORTC) classification is based on clinical, pathological, immunopathological, molecular and cytogenetic findings [2], and implicitly recognizes that the site of origin of extranodal lymphomas rather than just tumour morphology determines clinical behaviour, which in turn has a critical influence on prognosis and therapeutic approach.

In 1975, it was demonstrated that the great majority of lymphoid infiltrates associated with the skin were of T-cell type and Edelson introduced the term cutaneous T-cell lymphoma (CTCL) [3]. In Europe, the work of the Dutch Cutaneous Lymphoma Working Party (DCLWP) and the Graz group delineated different subsets of primary cutaneous T- and B-cell lymphomas, which led directly to the EORTC proposal for classification of primary cutaneous lymphomas and the recent WHO–EORTC classification (Table 57.1) [2,4]. This consensus is now reflected in the 2008 WHO classification of haematologic malignancies as all the primary cutaneous lymphoma variants have been recognized as distinct entities [5].

Mycosis fungoides (MF) is the most common primary CTCL subset, but other subsets with clearly identifiable clinicopathological features and varying prognoses have also been described. A critical observation has been the realization that lymphomas with a similar pathology arising in different organs have different prognoses and a distinct molecular pathogenesis; nodal CD30$^+$ anaplastic large cell lymphomas are usually ALK$^+$ and can be associated with a poor prognosis, especially for ALK$^-$ variants, whereas primary cutaneous CD30$^+$ anaplastic large cell lymphomas are invariably ALK$^-$ and generally associated with a good prognosis [2]. Primary cutaneous B-cell lymphomas represent [2] about one-third of all primary cutaneous lymphomas, and primary cutaneous follicle centre lymphomas are now recognized as pathogentically distinct from nodal follicular lymphomas. The majority of these primary cutaneous B-cell lymphomas have an excellent prognosis [2].

The concept of a subset of circulating lymphocytes with a special avidity or affinity for the skin has been supported by the identification of T cells expressing the cutaneous lymphocyte antigen

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

Table 57.1 WHO–EORTC classification of primary cutaneous lymphomas (frequency and prognosis based on Dutch and Austrian clinical data).

WHO–EORTC classification	No.	Frequency (%)	Disease-specific 5-year survival (%)
Primary cutaneous T-cell lymphoma			
Indolent clinical behaviour			
Mycosis fungoides	800	44	88
Folliculotropic MF	86	4	80
Pagetoid reticulosis	14	<1	100
Granulomatous slack skin	4	<1	100
Primary cutaneous anaplastic large cell lymphoma	146	8	96
Lymphomatoid papulosis	236	12	100
Subcutaneous panniculitis-like T-cell lymphoma	18	1	82
Primary cutaneous $CD4^+$ small/medium pleomorphic T-cell lymphoma	39	2	75
Aggressive clinical behaviour			
Sézary syndrome	52	3	24
Primary cutaneous NK/T-cell lymphoma, nasal type	7	<1	NR
Primary cutaneous aggressive $CD8^+$ T-cell lymphoma	14	<1	18
Primary cutaneous γδ T-cell lymphoma	13	<1	NR
Primary cutaneous peripheral T-cell lymphoma, unspecified	47	2	16
Cutaneous B-cell lymphoma			
Indolent clinical behaviour			
Primary cutaneous marginal zone B-cell lymphoma	127	7	99
Primary cutaneous follicle centre lymphoma	207	11	95
Intermediate clinical behaviour			
Primary cutaneous diffuse large B-cell lymphoma, leg type	85	4	55
Primary cutaneous diffuse large B-cell lymphoma, other	4	<1	50
Primary cutaneous intravascular large B-cell lymphoma	6	<1	65

NR – not reached.

(CLA; HECA 452), which binds to its ligand, E-selectin, on dermal endothelial cells [6]. These subsets of skin trafficking T cells comprise the skin-associated lymphoid tissue (SALT), and contribute to the skin immune system (SIS), in a similar manner to other mucosal sites such as the gut mucosa-associated lymphoid tissue (MALT). The expression of the chemokine receptors CCR4 and CCR10 by tumour cells may also contribute to epidermotropism in cutaneous T-cell lymphoma (CTCL) while the expression of the lymph node chemokine receptor CCR7 may contribute to tumour dissemination in Sézary syndrome (SS) [7].

The identification of T-cell clones in skin using T-cell receptor (TCR) gene analysis has established both the neoplastic nature and lineage of a wide variety of cutaneous lymphoproliferative entities, and both TCR and immunoglobulin gene analysis are now part of the standard diagnostic assessment of cutaneous lymphoid infiltrates [8]. The presence of a lymphoid clone is not synonymous with malignancy and its significance in benign cutaneous lymphoid infiltrates is at present unknown. It is unclear whether these techniques will also provide prognostic information but they complement existing staging approaches, particularly for analysis of lymph node and peripheral blood in MF and SS.

It has been apparent for some time that the original American Joint Committee on Cancer (AJCC) staging system for MF/SS was not ideal, with markedly variable outcomes for patients with stage IIB and slightly better outcomes for stage III than stage IIB. Also there has been a lack of consensus regarding the measurement of tumour burden in peripheral blood. This has led to new staging proposals for MF/SS and non-MF/SS primary cutaneous lymphomas, which now require prospective validation [9,10].

The underlying molecular pathogenesis of CTCL is unknown but various abnormalities have been identified, including inactivation of genes controlling the cell cycle and apoptosis [11]. These abnormalities appear to be associated with disease progression and may contribute to treatment resistance. In addition, molecular cytogenetic techniques have detected a consistent pattern of chromosomal abnormalities, indicating the location of putative genes that may have a fundamental role in the pathogenesis of CTCL [11].

Several novel therapies have been licensed for CTCL, including a retinoid, bexarotene, that binds to the retinoid X receptor (RXR), a diphtheria interleukin-2 (IL-2) fusion toxin, denileukin diftitox (Onzar; Ontak), and a histone deacetylase inhibitor, suberoylanilide hydroxamic acid (SAHA/vorinostat) [12–15]. A number of other novel therapies have been proven to have efficacy in CTCL and offer promising alternatives to existing therapies [16]. These studies have also facilitated the current development of more robust response criteria for MF and SS.

References

1 Stansfield AG, Diebold J, Kapanci Y *et al*. Updated Kiel classification for lymphomas. *Lancet* 1988; **1**: 292–3.
2 Willemze R, Jaffe E, Burg G *et al*. WHO-EORTC classification for cutaneous lymphomas. *Blood* 2005; **105**: 3768–85.
3 Edelson RL. Cutaneous T-cell lymphoma: the Sézary syndrome, mycosis fungoides and other variants. *J Am Acad Dermatol* 1980; **2**: 89–106.

4 Willemze R, Kerl H, Sterry W *et al*. EORTC classification for primary cutaneous lymphomas: a proposal from the Cutaneous Lymphoma Study Group of the European Organization for Research on Treatment of Cancer. *Blood* 1997; **90**: 354–71.
5 Jaffe E, Ralfkiaer E. Mycosis fungoides and Sézary syndrome. In: *World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues*. IARC, 2008.
6 Picker LJ, Michie SA, Rott LS, Butcher EC. A unique type of skin-associated lymphocytes in humans: preferential expression of the HECA452 epitope by benign and malignant T cells at cutaneous sites. *Am J Pathol* 1990; **136**: 1053–68.
7 Pals S, Gorter D, Spaargaren M. Lymphoma dissemination: the other face of lymphocyte homing. *Blood* 2007; **110**: 3102–11.
8 Whittaker S. T-cell receptor gene analysis in cutaneous T-cell lymphomas. *Clin Exp Dermatol* 1996; **21**: 81–7.
9 Olsen E, Vonderheid E, Pimpinelli N *et al*. Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organisation of Research and Treatment of Cancer (EORTC). *Blood* 2007; **110**: 1713–22.
10 Kim Y, Willemze R, Pimpinelli N *et al*. TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphoma (ISCL) and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer (EORTC). *Blood* 2007; **110**: 479–84.
11 Whittaker S. Biological insights into the pathogenesis of cutaneous T-cell lymphomas (CTCL). *Semin Oncol* 2006; **33**: S3–6.
12 Duvic M, Martin A, Kim Y *et al*. Phase 2 and 3 clinical trial of oral bexarotene (Targretin capsules) for the treatment of refractory or persistent early stage cutaneous T-cell lymphoma. *Arch Dermatol* 2001; **137**: 581–93.
13 Duvic M, Hymes K, Heald P *et al*. Bexarotene is effective and safe for treatment of refractory advanced-stage cutaneous T-cell lymphoma: multinational phase II–III trial results. *J Clin Oncol* 2001; **19**: 2456–71.
14 Olsen E, Duvic M, Frankel A *et al*. Pivotal phase III trial of two dose levels of Denileukin Diftitox for the treatment of cutaneous T-cell lymphoma. *J Clin Oncol* 2001; **19**: 376–88.
15 Olsen E, Kim Y, Kuzel T *et al*. Phase IIB multicenter trial of vorinostat in patients with persistent, progressive or treatment refractory cutaneous T-cell lymphoma. *J Clin Oncol* 2007; **25**: 1–9.
16 Whittaker S, Foss F. Efficacy and tolerability of currently available therapies for the mycosis fungoides and Sezary syndrome variants of cutaneous T-cell lymphoma variants. *Cancer Treat Rev* 2007; **33**: 146–60.

Primary cutaneous T-cell lymphomas

Mycosis fungoides

Definition. The most common variant of primary CTCL, generally associated with an indolent clinical course and characterized by well-defined clinicopathological features.

Aetiology. The aetiology of MF is not yet established. The HTLV-1 retrovirus was first isolated from a patient with CTCL and subsequently it was appreciated that this patient had adult T-cell leukaemia–lymphoma (ATLL). Because of clinical and pathological similarities to cutaneous involvement in ATLL, there has been an intensive search for HTLV-1 and related viruses in MF. However, although an association with HTLV-1 has been suggested, subsequent extensive investigations have failed to identify conclusively any of the currently recognized HTLV-associated viruses in MF [1–5]. For over 20 years, one of the theories associated with the development of MF has been that this is a disease of antigen persistence associated with chronic lymphocyte stimulation and eventual transformation of benign lymphocytes to a low-grade malignant T-cell lymphoma [6]. This is a plausible and attractive theory, but as yet the antigen or antigens responsible for this transformation have not been identified.

A number of case–control studies have investigated the possibility of environmental agents precipitating or aggravating early CTCL. One study from the east coast of North America [7] recorded a significantly higher incidence of allergies and of fungal and viral infections in patients who developed CTCL compared with healthy controls, and also reported that a higher proportion of CTCL patients had worked in the petrochemical, textile, machine and metal industries. Other case–control studies have suggested possible links with occupational exposure to glass, pottery and ceramics [8], as well as workers exposed to solar radiation [9]. Other studies have not confirmed these observations but did record a significantly higher incidence of atopic disease in MF patients [10] and there have been subsequent reports of CTCL developing in patients with severe atopic dermatitis [11]. An association with atopic disease has not been confirmed in another case–control study [12]. A more recent study from North America has also failed to confirm any clear occupational or environmental exposure [13] but other studies have observed a higher than expected prevalence of other malignancies, including non-lymphoma cutaneous malignancies in patients with MF [14]. Further reports have also suggested that there is a possible increased incidence of non-melanoma skin cancer, melanoma and also lung cancer in MF but whether or not this is related to prior therapy remains to be clarified [15–17].

The incidence of MF (0.64/100 000 for CTCL) is increasing but the explanation for this is unclear. The rise could represent a combination of improved diagnosis and previous coding problems as well as a genuine increasing disease incidence, as seen for non-Hodgkin's lymphoma [18].

Clinical features. Mycosis fungoides is characterized by typical cutaneous stages of disease, consisting of patches and plaques involving less than 10% of the body surface area (stage T1/IA), more than 10% of the body surface area (stage T2/IB), tumours (stage T3/IIB) and erythrodermic disease (stage T3/III). Patients may progress from having limited patches and plaques to extensive plaques or tumours and even erythroderma [19]. However, many patients do not show any evidence of progression. Stage IA MF is characterized by subtle, fine scaly and often slightly atrophic erythematous patches on the trunk, usually involving the limb girdle areas, breast and particularly the buttocks (Fig. 57.1). There may be mild pruritus but patients are often asymptomatic. At this stage, the clinical differential diagnosis includes pityriasis rosea, fungal infection, mild dermatitis or even a rather atypical form of psoriasis. Plaques are more obvious, persistent, polymorphic, erythematous lesions with a similar distribution but, with the development of stage T2/IB, there is usually involvement of the head, neck and limbs as well as the trunk (Figs 57.2 & 57.3). Individual plaques may become very large, and there may be some degree of regression, giving rise to unusual arcuate and horseshoe-shaped lesions that can show considerable variation in colour, degree of scaling and border definition. Striking psoriasiform scaling can sometimes be a feature. There is some evidence that the overall



Fig. 57.1 Early mycosis fungoides showing plaques in the buttock area.



Fig. 57.2 More advanced mycosis fungoides showing typical polycyclic plaques.

thickness of plaques in stage T2/IB may have prognostic significance [20]. Once again, patients may complain of pruritus or be asymptomatic. Rarely, individual plaques may become eroded or ulcerated and painful, which is often associated with secondary bacterial infection and such patients may have a very poor quality of life and high morbidity despite having an early stage of disease. Tumours can show considerable variation in size (Fig. 57.4), and if there are only a few small tumours it may be difficult to categorize as truly stage T3/IIB disease. Many patients with early stages (T1/IA–T2/IB) of disease do not progress but rarely patients may gradually develop an erythroderma (stage T3/III), which is usually associated with severe pruritus. A *tumeur d'emblée* form of MF, in which patients rapidly develop large nodules and tumours without the prior presence of patches and plaques, has been described in the past [21], but it is now appreciated that many of these patients have other CTCL variants, which should be excluded on the basis of a critical assessment of the histological and immunophenotypical features. Patients may also rarely present with erythrodermic stages of disease and the differential diagnosis for these patients includes inflammatory dermatoses and Sézary syndrome.

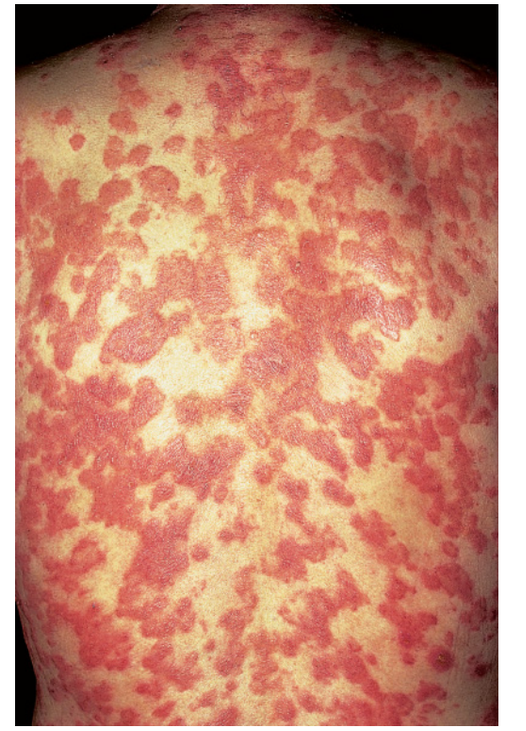


Fig. 57.3 Further stage of mycosis fungoides showing plaques involving more than 10% of the body surface.



Fig. 57.4 Nodular mycosis fungoides showing striking nodules on the back of the neck. Similar lesions were present on all four limbs.

The development of peripheral lymphadenopathy in MF alters the staging regardless of the cutaneous stage of disease [22]. Although the great majority of patients with early stage disease do not develop overt clinical involvement of lymph nodes or other organs (see prognosis), a small proportion do eventually show generalized, systemic spread and may exhibit typical 'B' symptoms with fever and weight loss. Histological involvement of central lymph nodes and other organs is a very poor prognostic sign. Any systemic organ can be involved but apart from liver, spleen and bone marrow, other sites commonly involved include the pulmonary, skeletal, nasopharyngeal and central nervous systems (CNS).

There are a large number of clinical variants of MF. Some plaques have a rather verrucous [23] or hyperkeratotic appearance, and bullae may rarely develop in the course of progression of individual plaques [24]. Rare ichthyosiform variants have been described [25]. An important subset of patients have MF that appears to be associated with pilosebaceous follicles, giving rise to a follicular clinical pattern often with alopecia (pilotropic or folliculotropic MF; see below) and there is evidence that these patients may be resistant to treatment and have a poorer prognosis independent of their stage of disease [26]. Rarely, younger patients present with a purpuric eruption not unlike the pigmented purpuric dermatosis associated with capillaritis but with histological features of MF [27]. Non-white younger adult patients may also present with a hypopigmented variant of MF [28,29], characterized by striking hypopigmented scaly patches often involving the trunk and especially the pelvic girdle area rather than the limbs. Histologically, these lesions tend to show marked epidermotropism, in contrast to the subtle clinical features. In poikilodermatous MF, patients develop clinical lesions characterized by either widespread or isolated poikiloderma, which may or may not be associated with typical patches and plaques of MF. The trunk is usually involved and the breasts and pelvic girdle area may also be affected (Fig. 57.5). The poikiloderma is typically characterized by atrophy, pigmentation and telangiectasia and must be distinguished from poikiloderma resulting from other disorders by appropriate histology. Rarely, patients may have extensive poikiloderma as a feature of erythrodermic disease. These clinical variants do not have any prognostic significance with the exception of folliculotropic/pilotropic MF [26].



Fig. 57.5 Poikilodermatous mycosis fungoides showing involvement of both breasts.

Clinical differential diagnosis. In the early stages of MF, the clinical differential diagnosis may include such diverse conditions as allergic contact dermatitis, atopic dermatitis, psoriasis and fungal infection. Any patient with persistent polymorphic plaques, particularly involving the pelvic girdle area, should have a skin biopsy and histological confirmation of the disease. Multiple biopsies may be required to confirm a clinical suspicion of MF in early stages of disease and criteria for the early diagnosis of MF have been published by the International Society for Cutaneous Lymphoma (ISCL) [30].

References

1 Pancake B, Zucker-Franklin D, Coutavas E. The cutaneous T-cell lymphoma, mycosis fungoides, is a human T cell lymphotropic virus-associated disease. *J Clin Invest* 1995; **95**: 547.

2 Whittaker S, Luzatto L. HTLV-1 and mycosis fungoides. *Science* 1993; **259**: 1470–1.

3 Lisby G, Reitz MR, Vejlsgaard GL. No detection of HTLV-1 DNA in punch biopsies from patients with cutaneous T-cell lymphoma by the polymerase chain reaction. *J Invest Dermatol* 1992; **98**: 417–20.

4 Boni R, Daneschfar A, Burg G *et al*. No detection of HTLV-1 proviral DNA in lesional skin biopsies from Swiss and German patients with cutaneous T-cell lymphoma. *Br J Dermatol* 1996; **134**: 282.

5 Li G, Vowels B, Benoit B *et al*. Failure to detect human T-lymphotropic virus type 1 (HTLV-1) proviral DNA in cell lines and tissues from patients with cutaneous T-cell lymphoma. *J Invest Dermatol* 1996; **107**: 308–13.

6 Tan RSH, Butterworth CM, McLaughlin H *et al.* Mycosis fungoides: a disease of antigen persistence. *Br J Dermatol* 1974; **91**: 607–16.

7 Cohen SR, Stenn KS, Bravermann IS *et al*. Mycosis fungoides: clinicopathological relationships, survival and therapy in 59 patients with observations on occupation as a new prognostic factor. *Cancer* 1980; **46**: 2654–6.

8 Morales M, Varela R, Olsen J *et al*. Occupational risk factors for mycosis fungoides: a European multicentre case-control study. *J Occup Environ Med* 2004; **46**: 205–11.

9 Morales M, Varela R, Olsen J *et al*. Occupational sun exposure and mycosis fungoides: a European mulitcentre case-control study. *J Occup Environ Med* 2006; **48**: 390–3.

10 Tuyp E, Burgoyne A, Mackie RM. A case–control study of possible causative factors in mycosis fungoides. *Arch Dermatol* 1987; **123**: 196–200.

11 Fletcher C, Orchard G, Hubbard V *et al*. CD30$^+$ cutaneous lymphoma in association with atopic eczema. *Arch Dermatol* 2004; **140**: 449–54.

12 Morales M, Olsen J, Johansen P *et al*. Viral infection, atopy and mycosis fungoides: a European multicentre case-control study. *Eur J Cancer* 2003; **39**: 511–6.

13 Whitmore AS, Holly EA, Lee IM *et al.* Mycosis fungoides in relation to environmental exposure and immune response. *J Natl Cancer Inst* 1989; **81**: 1560–7.

14 Huang K, Weinstock M, Clarke C *et al*. Second lymphomas and other malignant neoplasms in patients with mycosis fungoides and Sezary syndrome. *Arch Dermatol* 2007; **143**: 45–50.

15 Scarisbrick J, Child F, Evans A *et al*. Secondary malignant neoplasms in 71 patients with Sézary syndrome. *Arch Dermatol* 1999; **135**: 1381–5.

16 Vakeva L, Pukkala E, Ranki A. Increased risk of secondary cancers in patients with primary cutaneous T-cell lymphoma. *J Invest Dermatol* 2000; **115**: 62–5.

17 Evans A, Scarisbrick J, Child F *et al*. Cutaneous malignant melanoma in association with mycosis fungoides. *J Am Acad Dermatol* 2004; **50**: 701–5.

18 Criscione V, Weinstock M. Incidence of cutaneous T-cell lymphoma in the United States, 1973–2002. *Arch Dermatol* 2007; **143**: 854–9.

19 Willemze R, Jaffe E, Burg G *et al*. WHO-EORTC classification for cutaneous lymphomas. *Blood* 2005; **105**: 3768–85.

20 Kashani-Sabet M, McMillan A, Zackheim H. A modified staging classification for cutaneous T-cell lymphoma. *J Am Acad Dermatol* 2001; **45**: 700–6.

Table 57.2 TNM classification of mycosis fungoides (MF).

Cutaneous involvement (T)	
T_0	Lesions clinically and/or histologically suspicious but not diagnostic
T_1	Plaques involving less than 10% of skin
T_2	Plaques involving more than 10% of skin
T_3	Tumours present
T_4	Erythroderma
Lymph nodes (N)	
N_0	Clinically and pathologically normal
N_1	Palpable; pathologically not involved
N_2	Clinically non-palpable; pathologically MF
N_3	Clinically enlarged; pathologically MF
Viscera (M)	
M_0	No visceral spread
M_1	Visceral spread present
Peripheral blood (B)	
B_0	No atypical circulating cells
B_1	Atypical circulating cells present

Table 57.3 A staging system for mycosis fungoides related to TNM classification.

Stage	T	N	M
IA	T_1	N_0	M_0
IB	T_2	N_0	M_0
IIA	T_{1-2}	N_1	M_0
IIB	T_3	N_{0-1}	M_0
III	T_4	N_{0-1}	M_0
IVA	T_{1-4}	N_{2-3}	M_0
IVB	T_{1-4}	N_{0-3}	M_1

21 Willemze R, Beljaards RC, Meijer CJLM. Classification of primary cutaneous T cell lymphomas. *Histopathology* 1994; **24**: 405–15.
22 Sausville E, Worsham G, Matthews M *et al*. Histologic assessment of lymph nodes in mycosis fungoides/Sézary syndrome (cutaneous T-cell lymphoma): clinical correlation and prognostic import of a new classification system. *Hum Pathol* 1985; **16**: 1098–109.
23 Price NM, Fuks ZY, Hoffman TE. Hyperkeratotic and verrucous features of mycosis fungoides. *Arch Dermatol* 1977; **113**: 57–60.
24 Roenigk HH, Castrovina AJ. Mycosis fungoides bullosa. *Arch Dermatol* 1971; **104**: 402–6.
25 Eisman S, O'Toole E, Jones A, Whittaker S. Granulomatous mycosis funogides presenting as an acquired icthyosis. *Clin Exp Dermatol* 2003; **28**: 174–6.
26 Van Doorn R, Scheffer E, Willemze R. Follicular mycosis fungoides, a distinct disease entity with or without associated follicular mucinosis. *Arch Dermatol* 2002; **138**: 191–8.
27 Magro C, Schaefer J, Crowson A *et al*. Pigmented purpuric dermatosis. Classification by phenotypic and molecular profiles. *Am J Clin Pathol* 2007; **128**: 218–29.
28 Smith NP, Samman PD. Mycosis fungoides presenting with areas of cutaneous hypopigmentation. *Clin Exp Dermatol* 1978; **3**: 213–6.
29 Lambroza E, Cohen SR, Phelps R *et al*. Hypopigmented variant of mycosis fungoides: demography, histopathology and treatment of seven cases. *J Am Acad Dermatol* 1995; **32**: 987–93.
30 Pimipinelli N, Olsen E, Santucci M *et al*. Defining early mycosis fungoides. *J Am Acad Dermatol* 2005; **53**: 1053–63.

Staging. There are two staging systems in current use that have prognostic significance [1–3]. The Tumour, Nodes, Metastases classification and the staging system suggested by the North American MF Cooperative Group are given in Tables 57.2 and 57.3. All patients should have a defined stage so that appropriate advice can be given regarding prognosis and treatment.

All patients with MF should have a full clinical examination and adequate diagnostic biopsies for histology and immunophenotypic and preferably molecular studies as, even for stage IA disease, studies suggest that patients with a detectable T-cell clone have a shorter duration of response and a higher rate of treatment failure [4]. Occasionally, multiple skin biopsies and the opinion of experienced dermatopathologists are required to make a diagnosis. Peripheral blood samples should be taken for routine haematology, biochemistry, serum lactate dehydrogenase (LDH), Sézary cells, lymphocyte subsets, CD4 : CD8 ratio, HTLV-1 serology and, ideally, TCR gene analysis of peripheral blood mononuclear cells. These tests are necessary to distinguish patients with ATLL and those patients with peripheral blood T-cell clones identical to skin who may have a poor prognosis. Any palpable and bulky peripheral nodes should be biopsied but the practice of 'blind' lymph node biopsy of non-palpable nodes is not essential, although histological evidence of lymphoma can very rarely be detected in the absence of palpable lymphadenopathy. Chest X-ray should be performed in those with advanced stages of disease. Staging CT scans of the chest, abdomen and pelvis are indicated in all those patients with stage IIA, IIB, III and IV MF, but not in those with stage IA or IB MF [5]. Peripheral nodes with a diameter greater than 1.5 cm are considered to be abnormal in patients with cutaneous lymphomas whereas for central nodes a diameter greater than 1.0 cm is considered to be the limit. The value of PET-CT in MF has yet to be established but this may increase the detection rate of systemic disease with PET activity correlating with histologic lymph node grade [6]. Bone marrow aspirate and trephine biopsies may be indicated in patients with stage IIB, III and IV MF and those patients with peripheral blood involvement, as indicated by the presence of Sézary cell counts representing more than 5% of the total leukocyte count, although the overall positive yield will be low [7,8]. The ISCL and EORTC have published a revised staging system for MF/SS which is currently being validated in prospective studies [9]. This staging system attempts to distinguish patients with early stage IA/IB who only have patches and to stratify more accurately lymph node disease incorporating molecular analysis for T-cell clones as well as assessing the degree of peripheral blood involvement more specifically (Table 57.4). Prospective validation of this staging system will also clarify the prognostic relevance of features such as folliculotropism and large cell transformation.

References

1 Green S, Byar D, Lamberg S. Prognostic variables in mycosis fungoides. *Cancer* 1981; **47**: 2671–7.
2 Lamberg S, Green S, Byar D *et al*. Clinical staging for cutaneous T-cell lymphomas. *Ann Intern Med* 1984; **100**: 187–92.
3 Bunn P, Lamberg S. Report of the committeee on staging and classification of cutaneous T-cell lymphomas. *Cancer Treat Rep* 1979; **63**: 725–8.
4 Delfau-Larue M, Dalac S, Lepage E *et al*. Prognostic significance of a polymerase chain reaction-detectable dominant T-lymphocyte clone in cutaneous lesions of patients with mycosis fungoides. *Blood* 1998; **92**: 3376–80.

Table 57.4 Proposed revised staging classification for mycosis fungoides/Sézary syndrome.

TNMB stages	
Skin	
T_1	Limited patches, papules and plaques covering <10% of the skin surface; may further stratify into T_{1a} (patch only) vs T_{1b} (plaque ± patch)
T_2	Patches, papules and plaques covering ≥10% of the skin surface; may further stratify into T_{2a} (patch only) vs T_{2b} (plaque ± patch)
T_3	One or more tumours (≥1 cm diameter)
T_4	Confluence of erythema covering ≥80% body surface area
Node	
N_0	No clinically abnormal peripheral lymph nodes; biopsy not required
N_1	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 1 or NCI $LN_{0–2}$
N_{1a}	Clone negative
N_{1b}	Clone positive
N_2	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 2 or NCI LN_3
N_{2a}	Clone negative
N_{2b}	Clone positive
N_3	Clinically abnormal peripheral lymph nodes; histopathology Dutch grades 3–4 or NCI LN_4; clone positive or negative
N_X	Clinically abnormal peripheral lymph nodes; no histologic conformation
Visceral	
M_0	No visceral organ involvement
M_1	Visceral involvement (must have pathology confirmation and organ involved should be specified)
Blood	
B_0	Albescence of significant blood involvement; ≤5% of peripheral blood lymphocytes are atypical (Sézary cells)
B_{0a}	Clone negative
B_{0b}	Clone positive
B_1	Low blood tumour burden; >5% of peripheral blood lymphocytes are atypical (Sézary cells) but does not meet the criteria of B_2
B_{1a}	Clone negative
B_{1b}	Clone positive
B_2	High blood tumour burden; ≥1000/μL Sézary cells with positive clones

Prognosis (Table 57.5). Multivariate analysis has established that age at onset (over 60 years), skin stage and the presence of nodal (IVA) or visceral (IVB) disease are independent prognostic factors in MF [1–6]. Studies have confirmed that a patient's life expectancy is not adversely affected in stage IA disease [6]. Patients with stage IB–IIA disease at diagnosis have a 72–86%/49% overall 5-year survival, while patients with stage IIB disease have a 40–65% 5-year survival [6–8]. The 5-year survival of patients with erythrodermic stage III disease is 41–57%, for those with stage IVA 27–40% and for stage IVB disease 0–27% [6–8]. The presence of a peripheral blood T-cell clone may indicate which patients with early stage disease are likely to develop disease progression but this requires confirmation in large studies [9]. The development of lymph node disease has a significant impact on prognosis [10]. Sézary syndrome patients by definition are staged as T4 N1–3 M0 B1 and have a poor prognosis, with an overall median survival of 32 months from diagnosis [11]. Recent studies of erythrodermic CTCL have shown that the presence of peripheral nodal disease is the most important prognostic factor in a multivariate analysis, although the peripheral blood tumour burden is also very close to significance [12]. In addition, prognostic data on a large series of patients have suggested that patients with thick plaques may have a worse prognosis than those with thin or patch stage disease and this has formed the basis for a suggested modification of the staging system, although the reproducibility of this histological assessment has not been confirmed [13].

A high incidence of second malignancies in MF patients, notably non-melanoma skin cancer and pulmonary small cell lung cancer (including small incidence of melanoma), and also of malignancies in relatives of patients, mainly lymphomas and leukaemias, have been reported [14–16]. Other types of lymphoma–leukaemia and Hodgkin's lymphoma have also been described in association with MF and Sézary syndrome [17–20].

References

1 Fuks ZY, Bagshaw MA, Farber EM. Prognostic signs and the management of mycosis fungoides. *Cancer* 1973; **32**: 1385–95.

2 Hamminga L, Hermans J, Noordijk EM *et al.* Cutaneous T-cell lymphoma: clinicopathological relationship, therapy and survival in 92 patients. *Br J Dermatol* 1982; **107**: 145–56.

3 Sausville E, Eddy J, Makuch R *et al.* Histopathologic staging at initial diagnosis of mycosis fungoides and the Sézary syndrome: definition of three distinctive prognostic groups. *Ann Intern Med* 1988; **109**: 372–82.

4 Weinstock MA, Horne JW. Population-based estimate of survival and determinants of prognosis in patients with mycosis fungoides. *Cancer* 1988; **62**: 1658–61.

5 Marti L, Estrach T, Reverter J, Mascaro J. Prognostic clinicopathologic factors in cutaneous T-cell lymphoma. *Arch Dermatol* 1991; **127**: 1511–6.

6 Kim Y, Liu H, Mraz-Gernhard S *et al.* Long term outcome of 525 patients with mycosis fungoides and Sezary syndrome. *Arch Dermatol* 2003; **139**: 857–66.

7 Doorn R, Van Haselan C, Voorst Vader P *et al.* Mycosis fungoides: disease evolution and prognosis of 309 Dutch patients. *Arch Dermatol* 2000; **136**: 504–10.

8 Zackheim H, Amin S, Kashani-Sabet M, McMillan A. Prognosis in cutaneous T-cell lymphoma by skin stage: long term survival in 489 patients. *J Am Acad Dermatol* 1999; **40**: 418–25.

9 Fraser-Andrews E, Woolford A, Russell Jones R *et al.* Detection of a peripheral blood clone is an independent prognostic marker in mycosis fungoides. *J Invest Dermatol* 2000; **114**: 117–21.

10 Sausville E, Worsham G, Matthews M *et al.* Histologic assessment of lymph nodes in mycosis fungoides/Sézary syndrome (cutaneous T-cell lymphoma): prognostic significance. *Hum Pathol* 1985; **16**: 1209–15.

11 Bunn PA, Huberman MS, Whang-Peng J *et al.* Prospective staging evaluation of patients with cutaneous T-cell lymphomas: demonstration of a high frequency of extracutaneous dissemination. *Ann Intern Med* 1980; **93**: 223–30.

12 Tsai E, Taur A, Espinosa L *et al.* Staging accuracy in mycosis fungoides and Sezary syndrome using positron emission tomography and computed tomography. *Arch Dermatol* 2006; **142**: 577–84.

13 Epstein EH Jr, Levin DL, Schein P *et al.* Mycosis fungoides: survival, prognostic features, response to therapy, and autopsy findings. *Medicine* 1972; **51**: 61–72.

14 Sibaud V, Beylot-Barry M, Thiebaut R *et al.* Bone marrow histopathologic and molecular staging in epidermotropic T-cell lymphomas. *Am J Clin Pathol* 2003; **119**: 444–53.

15 Olsen E, Vonderheid E, Pimpinelli N *et al.* Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organisation of Research and Treatment of Cancer (EORTC). *Blood* 2007; **110**: 1713–22.

Table 57.5 Published prognostic data in mycosis fungoides.

	IA (%)	IB (%)	IIA (%)	IIB (%)	III (%)	IVA (%)	IVB (%)	Overall (%)	Reference	No.	Median follow up (years)
OS at 5 years	99	86	49	65		40	0	80	Doorn *et al*. [7]	309	5.2
	100	84		52	57				Zackheim *et al*. [8]	489	4.7
	97	72		40	41	27	27	68	Kim *et al*. [6]	525	5.5
OS at 10 years	84	61	49	27		20	0	57	Doorn *et al*. [7]	309	5.2
	100	67		39	41				Zackheim *et al*. [8]	489	4.7
	88	55		26	24			53	Kim *et al*. [6]	525	5.5
DSS at 5 years	100	96 (81)	68	80		40	0	89	Doorn *et al*. [7]	309	5.2
	100	95	84	56	65	30	30	81	Kim *et al*. [6]	525	5.5
DSS at 10 years	97	83 (36)	68	42		20	0	75	Doorn *et al*. [7]	309	5.2
DSS at 15 years	98	85	71	32	49	14	14	74	Kim *et al*. [6]	525	5.5
Median survival	NR	12.1 years		3.3 years	4.0 years	1.2	0.7		Kim *et al*. [6]	556	9.8
Disease progression (5 years)	4	21	65	32		70	100		Doorn *et al*. [7]	309	5.2
	10	22		56	48				Kim *et al*. [6]	525	5.5
Disease progression (10 years)	10	39	65	60		70	100		Doorn *et al*. [7]	309	5.2
	13	32		72	57				Kim *et al*. [6]	525	5.5
Disease progression (20 years)	16	40		81	78				Kim *et al*. [6]	525	5.5

DSS, disease-specific survival; NR, not reached; OS, overall survival.

Comments:

1. All actuarial survival curves calculated according to method of Kaplan–Meier and based on stage at diagnosis.
2. In the study by Doorn *et al*. [7] (and in a subsequent publication: van Doorn *et al*. *Arch Dermatol* 2002; **138**: 191–8), the presence of follicular mucinosis was an independent poor prognostic feature, possibly related to depth of infiltrate in patients with stage IB disease (DSS of 81% and 36% and OS of 75% and 21% at 5 and 10 years respectively). A lack of a complete response to initial therapy was also associated with a poor outcome ($P < 0.001$) in a multivariate analysis as well as increasing clinical stage and the presence of extracutaneous disease. A different staging system was used in this study (based on Hamminga *et al*. [2]) but for the purposes of this table the staging has been altered to be consistent. Only three patients had stage IVB disease and only 18 patients each had stage IIA and IVA disease. Therefore the results for these stages must be interpreted cautiously.
3. In the study by Zackheim *et al*. [8], black patients had a relatively more advanced stage of disease than white patients. The TNM classification was used in this study. Lymph node stage had an unfavourable impact on survival but this trend did not reach significance for each individual T stage because of a lack of sufficient power (an estimated 1700 subjects required) and IIA/IVA patients were not designated separately. Similar considerations apply to peripheral blood involvement. Similar outcomes for patients with stage IIB (T_3) and III (T_4) disease is consistent with other studies but this might reflect a lack of lymph node staging data included in this study.
4. The study by Kim *et al*. [6] included data on 525 patients and showed that the majority presented with early stage disease and that independent multivariate prognostic factors were age, skin stage and presence of extracutaneous disease at presentation. With the exception of stage IA, the relative risk for death is greater in MF than in a control population; 2.2 for stage IB/IIA; 3.9 for stage IIB/III; 12.8 for stage IV disease.

clinical correlation and prognostic import of a new classification system. *Hum Pathol* 1985; **16**: 1098–109.
11 Toro JR, Stoll HL, Stomper PC *et al*. Prognostic factors and evaluation of mycosis fungoides and Sézary syndrome. *J Am Acad Dermatol* 1997; **37**: 58–67.
12 Scarisbrick J, Whittaker S, Evans A *et al*. Prognostic significance of tumour burden in the blood of patients with erythrodermic primary cutaneous T-cell lymphoma. *Blood* 2001; **97**: 624–30.
13 Kashani-Sabet M, McMillan A, Zackheim H. A modified staging classification for cutaneous T-cell lymphoma. *J Am Acad Dermatol* 2001; **45**: 700–6.
14 Greene MH, Pinto HA, Kant JA *et al*. Lymphomas and leukemias in the relatives of patients with mycosis fungoides. *Cancer* 1982; **49**: 737–41.
15 Epstein EH Jr, Levin DL, Craft JD Jr *et al*. Mycosis fungoides: survival, prognostic features, response to therapy, and autopsy findings. *Medicine* 1972; **51**: 61–72.
16 Evans A, Scarisbrick J, Child F *et al*. Cutaneous malignant melanoma in association with mycosis fungoides. *J Am Acad Dermatol* 2004; **50**: 701–5.
17 Harland C, Whittaker S, Ng Y *et al*. Coexistent cutaneous T-cell lymphoma and B-cell chronic lymphocytic leukaemia. *Br J Dermatol* 1992; **127**: 519–23.
18 Brousset P, Lamant L, Viraben R *et al*. Hodgkin's disease following mycosis fungoides: phenotypic and molecular evidence for different tumour cell clones. *J Clin Pathol* 1996; **49**: 504–7.
19 Scarisbrick J, Child F, Spittle M *et al*. Systemic Hodgkin's lymphoma in a patient with Sézary syndrome. *Br J Dermatol* 2000; **142**: 771–5.
20 Hallerman C, Kaune M, Tiemann M *et al*. High frequency of primary cutaneous lymphomas associated with lymphoproliferative disorders of different lineage. *Ann Haematol* 2007; **86**: 509–15.

Pathology [1–3]. The features of MF vary according to the clinical stage. The earliest pathological features of MF are the presence of a moderate, predominantly lymphocytic infiltrate in the papillary dermis. Many of the small lymphoid cells may be hyperchromatic and show a tendency to 'line up' just below the dermal–epidermal junction. Even at this early stage, the affinity of these T lymphocytes for the epidermis and papillary dermis is apparent, as there is rarely significant involvement in the underlying reticular dermis.

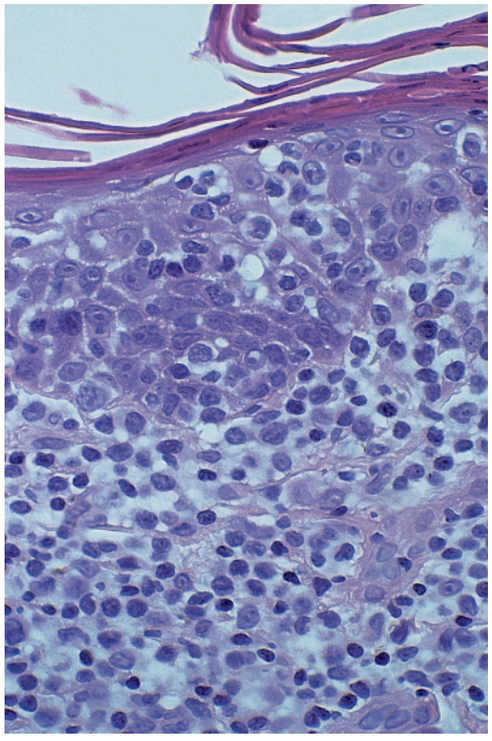


Fig. 57.6 Histology of mycosis fungoides showing striking epidermotropism with the presence in the epidermis of cytologically atypical small dark cells proven on marker studies to be $CD4^+$ helper T lymphocytes.

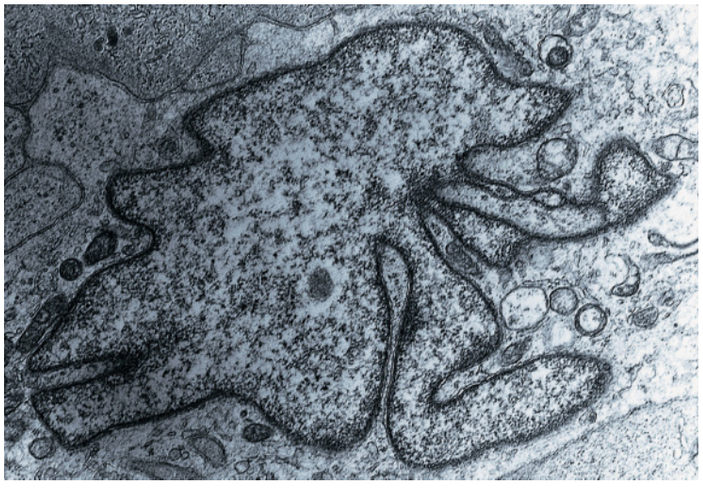
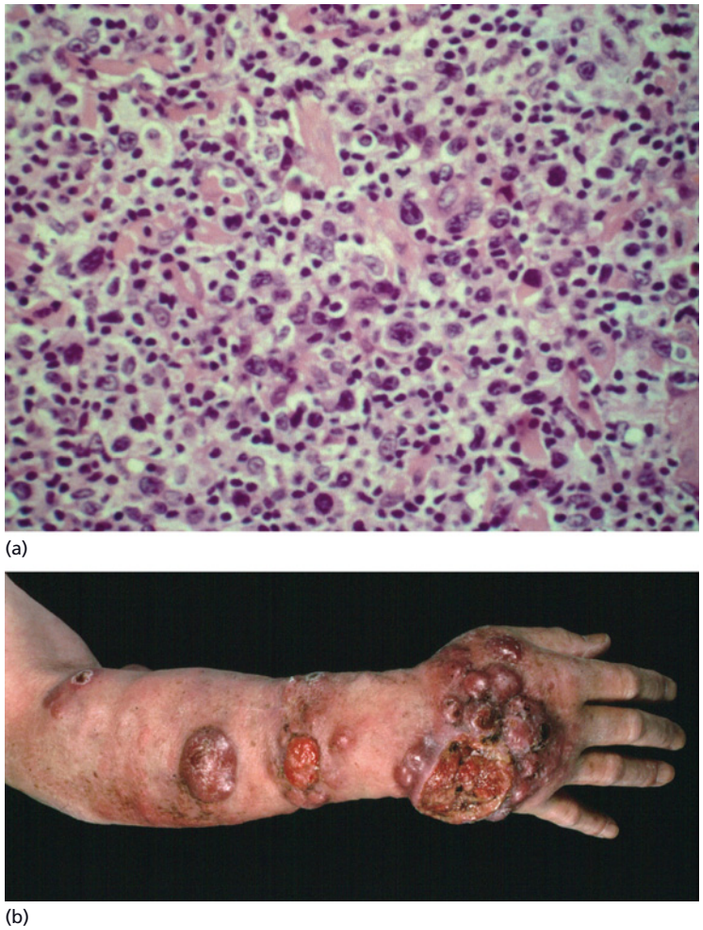


Fig. 57.7 Electron micrograph of T cell infiltrating the epidermis in mycosis fungoides, showing the striking cellular contours of the typical cell of Lutzner with a typical high nuclear contour index.



(a)

(b)

Fig. 57.8 High-power view (a) of large cell transformation in mycosis fungoides (b).

As the disease progresses with the development of thicker plaques, prominent epidermotropism (Fig. 57.6) is seen. This describes the selective colonization of the epidermis by these atypical T cells and is characterized by single-cell colonization, often along the basal layer, or by clusters of atypical lymphocytes in the epidermis—so-called Pautrier microabscesses. The lymphocytes in the epidermis are often strikingly cerebriform (Fig. 57.7), with a very irregular nuclear outline and heavy nuclear staining as well as a characteristic halo appearance to the cells. If these cells are examined either under high power or with thin sections, the cerebriform and irregular nature of the nuclei can be better appreciated in three dimensions. In early MF, the T-cell lymphocytic infiltrate may be associated with a number of other cell types including small numbers of plasma cells or eosinophils, but as the infiltrate becomes more intense and more epidermotropic, the infiltrate becomes monotonous and monomorphic. Granulomatous features may be rarely present and a prominent histiocytic infiltrate can be seen, so called interstitial MF [4].

In more advanced stages of disease (IIB–III), the striking epidermotropic quality of the lymphocytic infiltrate may be lost, with scattered larger tumour cells showing marked cellular atypia. Large cell transformation may also occur and is a poor prognostic feature on univariate analysis, although this does not appear to be independent of age and stage of disease on multivariate analysis [5]. An earlier study showed no difference in survival for stage IIB patients showing histological features of large cell transformation compared to those without, but there was a significant difference in survival from diagnosis [6]. Large cell transformation (Fig. 57.8) is defined as the presence of more than 25–50% of large cells

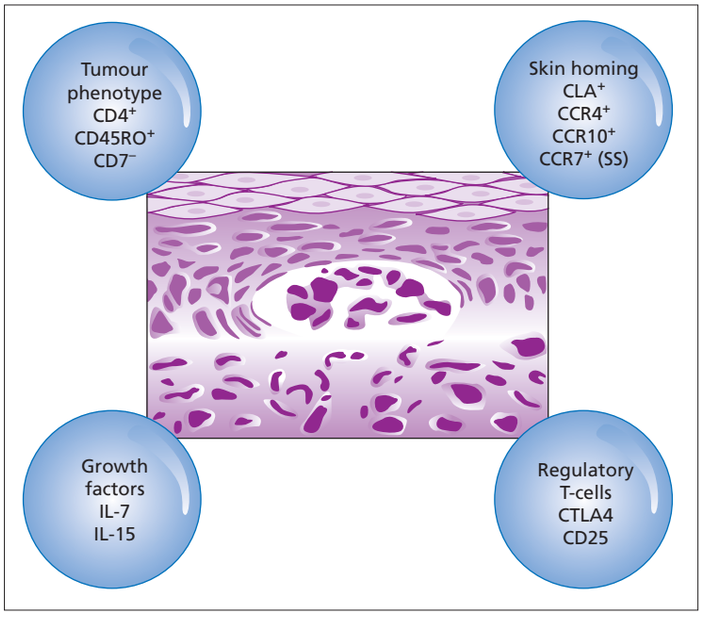


Fig. 57.9 Immunopathology of mycosis fungoides/Sézary syndrome.

(either CD30 positive or negative) within the dermal infiltrate or the development of microscopic dermal nodules consisting of larger cells with pleomorphic and occasionally anaplastic morphology [5]. It is important to distinguish large histiocytic cells from large tumour cells with an anaplastic morphology and occasionally the presence of reactive germinal centres in MF can also cause histological confusion.

The differentiation between large cell transformation in MF and the association with a primary cutaneous CD30$^+$ lymphoproliferative disorder such as lymphomatoid papulosis or anaplastic large cell lymphoma, which have a good prognosis, is crucial and based on a careful clinical assessment of the patient. The development of large tumours in patients with typical patches or plaques of MF would suggest large cell transformation of MF if the histological criteria were fulfilled. In contrast, the presence of very large numbers (more than 75%) of CD30$^+$ large cells in only one or a few isolated tumours developing in patients with no concurrent or previous clinical evidence of MF, as indicated by patches and plaques, suggests that the patient has a primary cutaneous CD30$^+$ lymphoproliferative disorder.

Immunopathology (Fig. 57.9). The tumour cells in MF are CD3$^+$, CD4$^+$, CD45RO$^+$ and usually CD7$^-$ T cells. This is the phenotype of a mature helper T cell of memory subtype [7]. The tumour cells are CLA$^+$, CCR4$^+$, CCR10$^+$ consistent with a skin homing T cell [8,9]. In rare cases, the tumour cells are CD8$^+$ rather than CD4$^+$ but this does not appear to have any prognostic significance [10]. Interestingly, CD8$^+$ cases of MF are more common in childhood and in hypopigmented variants [11]. CD8$^+$ MF must be distinguished from an epidermotropic cytotoxic variant of CTCL with a poor prognosis (see below). Occasionally, there is a very prominent infiltrate of reactive tumour infiltrating CD8$^+$ T cells expressing cytotoxic proteins, which may indicate a good prognosis [12–14]. The dermal infiltrate often consists of a prominent population of CD1a$^+$ dendritic cells and CD68$^+$ histiocytic cells. In advanced disease, tumour cells may express an aberrant phenotype with either loss of T-cell surface antigens 'null-cell phenotype' or expression of the CD30 antigen either by scattered larger tumour cells or by prominent dermal nodules consisting of large pleomorphic or anaplastic tumour cells [5,7]. The latter feature may be associated with large cell transformation but CD30 expression per se does not appear to have any prognostic significance [5]. The tumour cells usually express the αβ T-cell receptor and only rarely express cytotoxic proteins with disease progression [14].

A subset of CD4$^+$ CD25$^+$ T-cells has been defined with suppressive function. These regulatory T cells (T-regs) are cytotoxic T-lymphocyte antigen 4+ (CTLA4+) and express the transcription factor FoxP3. Studies in MF/SS have analysed the expression of FoxP3, as well as T-reg function, and have established that a proportion of the intraepidermal and dermal T cells in early stages of MF are FoxP3$^+$ T-cells but this decreases significantly with more advanced disease [15,16]. This suggests that in MF the presence of T-regs may be a good prognostic factor and that T-regs may actually suppress the expansion of tumour cells. Whether tumour cells also function as T-regs remains to be established; CTLA4 is expressed by a proportion of Sézary cells, and Sézary cells which have immunosuppressive T-reg function have only been described in a minority of SS patients [17–19].

Pathological differential diagnosis. In early MF, the main differential diagnosis includes a dermatitis reaction. The epidermotropic quality of the T-cell infiltrate in MF may be helpful, as may the cytology of the individual T cells, as in MF these intraepidermal lymphocytes tend to be larger than surrounding keratinocytes and have intensely stained nuclei with a very irregular outline. Spongiosis, if present in association with epidermotropic T cells or Pautrier microabscesses, is minimal, whereas this tends to be more striking in dermatitis reactions. A useful clue may be the characteristic basal layer colonization and the larger size of the intraepidermal T cells compared to the dermal mononuclear cells [20].

The pathological diagnosis of early MF can still, however, be extremely subjective and is best made in full collaboration with the clinician and only after careful correlation with the clinical features. It is often wise to take several biopsies from separate lesions, and if necessary to arrange for repeat biopsies to be carried out as the clinical picture evolves over a period of months or even years. An algorithm for establishing an early clinical and histological diagnosis of MF has been proposed by the ISCL (Table 57.6) [21].

Immunophenotypic studies are usually of minimal value in differentiating early MF from other cutaneous lymphocytic infiltrates, as the majority of these cells will also be CD3$^+$, CD4$^+$ although a predominance of larger CD4$^+$ cells within the epidermis compared to the mixed population of smaller cells within the dermis can sometimes be helpful [7,20].

The differential diagnosis of early MF from conditions such as arthropod bites and lymphomatous drug eruptions can also be difficult, and good clinicopathological correlation is essential. In

Table 57.6 ISCL diagnostic criteria for early mycosis fungoides (4 points).

Criteria	Major (2 points)	Minor (1 point)
Clinical Persistent and/or progressive patches and plaques plus 1. Non-sun exposed location 2. Size/shape variation 3. Poikiloderma	Any 2	Any 1
Histopathological Superficial lymphoid infiltrate plus 1. Epidermotropism 2. Atypia	Both	Either
Molecular/biological Clonal TCR rearrangement		Present
Immunopathological 1. CD2, 3, 5 <50% 2. CD7 <10% 3. Epidermal discordance		Any 1

general, reactions to arthropod bites tend to show a higher proportion of eosinophils, and the disposition of the infiltrate in lymphomatous drug reactions will be perivascular rather than epidermotropic. In a proportion of cases, however, the diagnosis is suspected on clinical grounds but cannot confidently be made with certainty on histological examination. In these cases, sequential biopsies at 3–6-month intervals may be needed.

Pathology of extracutaneous disease. The usual pattern of extracutaneous spread is from the skin to the draining peripheral lymph nodes and thereafter to other organs such as the liver and spleen, but pulmonary, skeletal and CNS involvement have been documented.

An NCI classification system was proposed in 1985 (Table 57.4) [22]. In this system, lymph node architecture is preserved in LN1–3 in which dermatopathic changes may predominate. LN1 is characterized by single infrequent atypical cells, LN2 shows small clusters of atypical lymphocytes and LN3 shows larger aggregates of atypical cells in paracortical areas. LN4 is characterized by partial or complete effacement by atypical cells [22].

A further histological assessment of peripheral nodes is utilized and based on the study by Scheffer *et al*. [23]. Those biopsies with no abnormalities are recorded as LN0 while those with dermatopathic changes are designated LN1 (dermatopathic lymphadenopathy), which is characterized by enlargement of the paracortical area of the lymph node because of the presence of large numbers of macrophages and pale dendritic (interdigitating reticulum) cells (grade 1 = LN1–2). The macrophages contain aggregates both of melanin and lipid material, giving rise to the older term 'lipomelanic reticulosis'. Histological evidence of possible involvement (grade 2 = LN3) is characterized by the additional presence of small clusters of larger atypical mononuclear cells within the expanded paracortical areas (Fig. 57.10). In contrast, partial (grade 3 = LN4) or complete effacement (grade 4 = LN4) of the lymph node architecture is consistent with definite lymphomatous involvement (Fig. 57.10).

A comparison of these systems has shown that both have a poor prognosis for partial or totally effaced nodes with non-effaced nodes showing no difference in survival [24]. In the WHO classification system, a modification of these classifications has been proposed whereby LN1 and LN2 have been grouped together as grade I (no histological involvement), with LN3 as grade II and LN4 as grade III, both representing definite histological involvement, although this system has not yet been validated [25]. However, there is a subtle difference in this system because in the WHO proposal grade I can be characterized by scattered but not clusters of atypical cerebriform cells, whereas nodes showing clusters of atypical cerebriform cells are graded as II (LN3).

The ISCL EORTC revised staging classification suggests grouping lymph node biopsies N1– with no definite histologic involvement (grade 1/LN1–2), N2– possible involvement (grade 2/LN3) and N3– definite involvement (grade 3–4/LN4) with each group reflecting the results of TCR gene analysis as clone present or absent, but this has not yet been validated prospectively [26].

References

1 Nickoloff B. Light microscopic assessment of 100 patients with patch/plaque stage mycosis fungoides. *Am J Dermatopathol* 1988; **10**: 469–77.
2 Shapiro PE, Pinto FJ. The histologic spectrum of mycosis fungoides/Sézary syndrome. *Am J Surg Pathol* 1994; **18**: 645–67.
3 Smoller B, Bishop K, Glusac E, Warnke R. Reassessment of histologic parameters in the diagnosis of mycosis fungoides. *Am J Surg Pathol* 1995; **19**: 1423.
4 Scarabello A, Leinweber B, Ardigo M *et al*. Cutaneous lymphomas with prominent granulomatous reaction. *Am J Surg Pathol* 2002; **26**: 1259–68.
5 Vergier B, Muret A, Beylot-Barry M *et al*. Transformation of mycosis fungoides: clinicopathological and prognostic features. *Blood* 2000; **95**: 2212–8.
6 Cerroni l, Rieger E, Hodl S, Kerl H. Clinicopathologic and immunologic features associated with transformation of mycosis fungoides to large-cell lymphoma. *Am J Surg Pathol* 1992; **16**: 543–52.
7 Ralfkiaer E. Immunohistological markers for the diagnosis of cutaneous lymphomas. *Semin Diagn Pathol* 1991; **8**: 62–72.
8 Kallinch T, Muche M, Qin S *et al*. Chemokine receptor expression in neoplastic and reactive T cells in the skin at different stages of of mycosis fungoides. *J Invest Dermatol* 2003; **121**: 1045–52.
9 Capriotti E, Vonderheid E, Thoburn C *et al*. Chemokine receptor expression by leukemic T-cells of cutaneous T-cell lymphoma: clinical and histopathological correlations. *J Invest Dermatol* 2007; **127**: 2882–92.
10 Dummer R, Kamarashev J, Kempf W *et al*. Junctional CD8 cutaneous lymphomas with non-aggressive clinical behaviour. *Arch Dermatol* 2002; **138**: 199–203.
11 Wain M, Orchard G, Whittaker S *et al*. Outcome in 34 patients with juvenile-onset mycosis fungoides. *Cancer* 2003; **98**: 2282–90.
12 Hoppe R, Medeiros L, Warnke R *et al*. CD8-positive tumour infiltrating lymphocytes influence the long-term survival of patients with mycosis fungoides. *J Am Acad Dermatol* 1995; **32**: 448–53.
13 Vermeer M, Van Doorn R, Dukers D *et al*. CD8 T cells in cutaneous T-cell lymphoma: expression of cytotoxic proteins, Fas ligand and killing inhibitory receptors and their relationship with clinical behaviour. *J Clin Oncol* 2001; **19**: 4322–9.
14 Vermeer M, Geelen F, Kummer J *et al*. Expression of cytotoxic proteins by neoplastic T cells in mycosis fungoides increases with progression from plaque to tumor stage disease. *Am J Pathol* 1999; **154**: 1203–10.
15 Klemke C, Fritzsching B, Franz B *et al*. Paucity of FOXP3$^+$ cells in skin and peripheral blood distinguishes Sezary syndrome from other cutaneous T-cell lymphomas. *Leukemia* 2006; **20**: 1123–9.
16 Gjerdrum L, Woetmann A, Odum N *et al*. FOXP3$^+$ regulatory T cells in cutaneous T-cell lymphomas: association with disease stage and survival. *Leukemia* 2007; **21**: 2512–8.

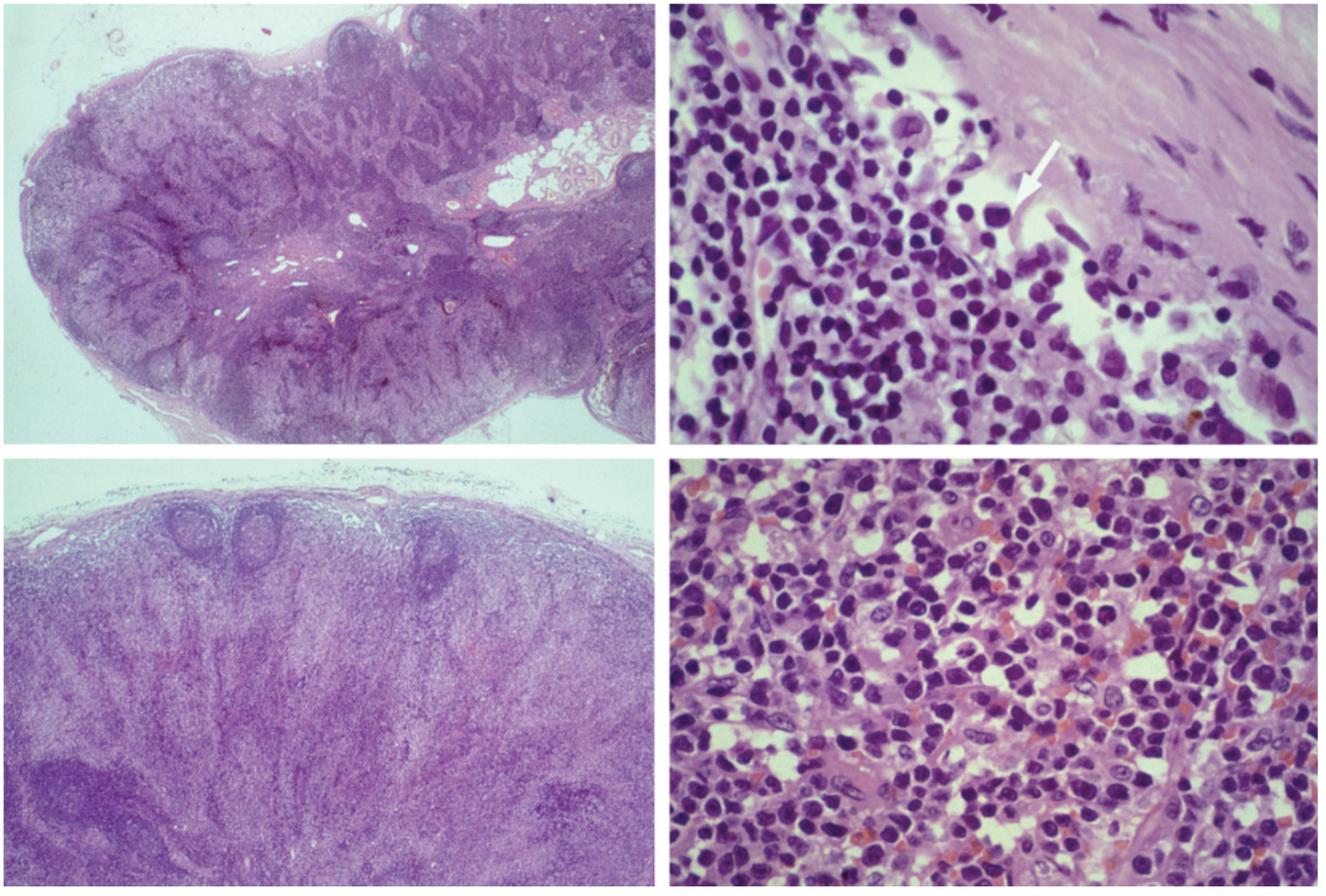


Fig. 57.10 Composite photomicrograph showing features of dermatopathic lymphadenopathy. LN1 is characterized by dermatopathic changes with melanin deposition and occasional atypical lymphocytes. LN2 with paracortical expansion of T-cell areas. LN4 showing a high-power view of lymph node effacement by small and medium sized atypical convoluted cells.

17 Wong H, Wilson A, Gibson H *et al*. Increased expression of CTLA-4 in malignant T cells from patients with mycosis fungoides—cutaneous T-cell lymphoma. *J Invest Dermatol* 2006; **126**: 212–9.

18 Berger C, Tigelaar R, Cohen J *et al*. Cutaneous T-cell lymphoma: malignant proliferation of T-regulatory cells. *Blood* 2005; **105**: 1640–7.

19 Tiemessen M, Mitchell T, Hendry L *et al*. Lack of suppressive $CD4^+$ $CD25^+$ $FOXP3^+$ T cells in advanced stages of primary cutaneous T-cell lymphoma. *J Invest Dermatol* 2006; **126**: 2217–23.

20 Bagot M, Wechsler J, Lescs M *et al*. Intra-epidermal localization of the clone in cutaneous T-cell lymphoma. *J Am Acad Dermatol* 1992; **27**: 235–7.

21 Pimipinelli N, Olsen E, Santucci M *et al*. Defining early mycosis fungoides. *J Am Acad Dermatol* 2005; **53**: 1053–63.

22 Sausville E, Worsham G, Matthews M *et al*. Histologic assessment of lymph nodes in mycosis fungoides/Sézary syndrome (cutaneous T-cell lymphoma). *Hum Pathol* 1985; **16**: 1098–109.

23 Scheffer E, Meijer C, Van Vloten W. Dermatopathic lymphadenopathy and lymph node involvement in mycosis fungoides. *Cancer* 1980; **45**: 137–48.

24 Vonderheid E, Diamond L, Van Vloten W *et al*. Lymph node classification systems in cutaneous T-cell lymphoma. *Cancer* 1994; **73**: 207–18.

25 Jaffe E, Ralfkiaer E. Mycosis fungoides and Sézary syndrome. In: *World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues*. IARC, 2001: 216–20.

26 Olsen E, Vonderheid E, Pimpinelli N *et al*. Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organisation of Research and Treatment of Cancer (EORTC). *Blood* 2007; **110**: 1713–22.

T-cell receptor gene analysis. TCR gene analysis consists of analysis of DNA from tissue samples for the detection of clonal rearrangements of the TCR genes as a marker of a monoclonal T-cell population. A similar approach can be used to identify a B-cell clone using analysis of immunoglobulin genes. A clonal lymphoid population is usually synonymous with a neoplastic proliferation but this does not signify malignancy. In contrast, the malignant potential of a lymphoid clone is related to the underlying molecular abnormalities. Analysis of TCR genes in MF is now a standard approach that has diagnostic, prognostic and therapeutic implications. Originally, Southern blot analysis of the β TCR gene was employed but this approach is time-consuming, requires large amounts of high-quality DNA and is relatively insensitive [1,2]. Consequently, most studies are now based on more sensitive PCR techniques and several different methods are employed including denaturing gradient gel electrophoresis (DGGE), temperature gra-

dient gel electrophoresis (TGGE), single-strand conformational gel electrophoresis (SSCP) and gene scan methods for analysis of the γ TCR gene [3–8]. Although MF tumour cells usually express an αβ TCR, the γ TCR gene is rearranged in lymphocytes expressing both a γδ and an αβ TCR and this gene is much easier to analyse comprehensively than the β TCR gene. These different electrophoretic approaches have not been compared adequately but most results are broadly consistent and the standardization of this technique has been partly achieved by the use of Biomed 2 primers for the γ and βTCR genes [9].

T-cell clones can be detected in a proportion (approximately 70% overall) of patients with early stage disease and are almost invariable in patients with later stages of disease [5,6]. The lack of T-cell clones in all patients with early stages of disease almost certainly reflects a lack of sensitivity of the technique, although studies have shown that those early stage patients without a T-cell clone achieve a higher complete remission rate with skin-directed therapy than those with a T-cell clone [10]. This suggests that the proportion of non-tumour cells in the infiltrate, possibly reflecting the host immune response, may also be critical. Identical T-cell clones can be detected in peripheral blood of a proportion of patients with all stages of disease and this may have independent prognostic significance [7,11]. In contrast, non-identical peripheral blood T-cell clones can also be detected and may not be pathological, emphasizing that results from all samples must be carefully compared [12]. In patients with both MF and lymphomatoid papulosis or $CD30^+$ large cell anaplastic lymphoma, identical T-cell clones can be found, suggesting a common pathogenesis [1,2,13]. T-cell clones identical to those in the skin can also be detected in dermatopathic lymph nodes (LN1–LN2) and this might provide independent prognostic information, although larger studies are required to prove this conclusively [14–16]. Assessment of enlarged lymph nodes with fine needle aspirate in CTCL has shown that T-cell clones cannot be detected with the same frequency compared to TCR gene analysis of excised nodes, suggesting sampling error [17]. Because of the sensitivity of these PCR-based techniques, T-cell clones have rarely been detected in non-neoplastic inflammatory disorders and therefore it is critical that the presence or absence of a clonal TCR gene rearrangement must always be interpreted in conjunction with the clinical and pathological features. Recent PCR-based studies have also detected clonal T-cell proliferations in some cases of pityriasis lichenoides acuta, small and large plaque parapsoriasis and pityriasis lichenoides chronica [18–23]. The clinical significance of these findings is unclear at present. Although these results would appear to support clinical impressions that large plaque parapsoriasis probably represents early stage MF, small plaque parapsoriasis has been thought to be a separate inflammatory condition that is not related to MF. The findings in pityriasis lichenoides acuta support previous suggestions that this represents part of a spectrum with lymphomatoid papulosis and, intriguingly, lesions resembling pityriasis lichenoides chronica can be associated with MF [23].

References

1 Whittaker S, Smith N, Russell Jones R, Luzatto L. Analysis of β, γ and δ T-cell receptor genes in mycosis fungoides and Sézary syndrome. *Cancer* 1991; **68**: 1572–82.

2 Zelickson B, Peters M, Muller S *et al*. T-cell receptor gene rearrangement analysis: cutaneous T-cell lymphoma, peripheral T-cell lymphoma and premalignant and benign cutaneous lymphoproliferative disorders. *J Am Acad Dermatol* 1991; **25**: 787–96.

3 Whittaker S. T-cell receptor gene analysis in cutaneous T-cell lymphomas. *Clin Exp Dermatol* 1996; **21**: 81–7.

4 Wood G, Tung R, Haeffner A *et al*. Detection of clonal T-cell receptor γ gene rearrangements in early mycosis fungoides/Sézary syndrome by polymerase chain reaction and denaturing gradient gel electrophoresis (PCR/DGGE). *J Invest Dermatol* 1994; **103**: 34–41.

5 Theodorou I, Delfau-Larue M, Bigorgne C *et al*. Cutaneous T-cell infiltrates: analysis of T-cell receptor γ gene rearrangement by polymerase chain reaction and denaturing gradient gel elctrophoresis. *Blood* 1995; **86**: 305–10.

6 Bottaro M, Berti E, Biondi A *et al*. Heteroduplex analysis of T-cell receptor γ gene rearrangements for diagnosis and monitoring of cutaneous T-cell lymphomas. *Blood* 1994; **83**: 3271–8.

7 Fraser Andrews E, Woolford A, Russell Jones R *et al*. Detection of a peripheral blood T-cell clone is an independent prognostic marker in mycosis fungoides. *J Invest Dermatol* 2000; **114**: 117–21.

8 Klemke C, Dippel E, Dembinski A *et al*. Clonal T cell receptor γ-chain gene rearrangement by PCR-based genescan analysis in the skin and blood of patients with parapsoriasis and early stage mycosis fungoides. *J Pathol* 2002; **197**: 348–54.

9 Sandberg Y, Heule F, Lam K *et al*. Molecular immunoglobulin/T-cell receptor clonality analysis in cutaneous lymphoproliferations. Experience with the Biomed-2 standardized polymerase chain reaction protocol. *Haematologica* 2003; **88**: 659–70.

10 Delfau-Larue M, Dalac S, Lepage E *et al*. Prognostic significance of a polymerase chain reaction-detectable dominant T-lymphocyte clone in cutaneous lesions of patients with mycosis fungoides. *Blood* 1998; **92**: 3376–80.

11 Muche M, Lukowsky A, Asadullah K *et al*. Demonstration of frequent occurrence of clonal T cells in the peripheral blood of patients with primary cutaneous T-cell lymphoma. *Blood* 1997; **4**: 1636–42.

12 Delfau-Larue M, Laroche L, Wechsler J *et al*. Diagnostic value of dominant T-cell clones in the peripheral blood in 363 patients presenting consecutively with a clinical suspicion of cutaneous lymphoma. *Blood* 2000; **96**: 2987–92.

13 Whittaker S, Smith N, Russell Jones R, Luzzatto L. Analysis of β, γ and δ TCR genes in lymphomatoid papulosis: cellular basis of two distinct histologic subsets. *J Invest Dermatol* 1991; **96**: 786–91.

14 Assaf C, Hummel M, Steinhoff M *et al*. Early TCR-β and TCR-γ PCR detection of T-cell clonality indicates mimimal tumour disease in lymph nodes of cutaneous T-cell lymphoma: diagnostic and prognostic implications. *Blood* 2005; **105**: 503–10.

15 Juarez T, Isenhath S, Polissar N *et al*. Analysis of T-cell receptor gene rearrangement for predicting clinical outcome in patients with cutaneous T-cell lymphoma. *Arch Dermatol* 2005; **141**: 1107–13.

16 Fraser-Andrews E, Mitchell T, Ferreira S *et al*. Molecular staging of lymph nodes from 60 patients with mycosis fungoides and Sezary syndrome: correlation with histopathology and outcome suggests prognostic relevance in mycosis fungoides. *Br J Dermatol* 2006; **155**: 756–62.

17 Galindo L, Garcia F, Hanau C *et al*. Fine needle aspiration biopsy in the evaluation of lymphadenopathy associated with cutaneous T-cell lymphoma (mycosis fungoides/Sézary syndrome). *Am J Clin Pathol* 2000; **113**: 865–71.

18 Dereure O, Levi E, Kadin M. T-cell clonality in pityriasis lichenoides et varioliformis acuta. *Arch Dermatol* 2000; **136**: 1483–6.

19 Haeffner A, Smoller B, Zepter K, Wood G. Differentiation and clonality of lesional lymphocytes in small plaque parapsoriasis. *Arch Dermatol* 1995; **131**: 321–4.

20 Simon M, Flaig M, Kind P *et al*. Large plaque parapsoriasis: clinical and genotypic correlations. *J Cutan Pathol* 2000; **27**: 57–60.

21 Shieh S, Mikkola D, Wood G. Differentiation and clonality of lesional lymphocytes in pityriasis lichenoides chronica. *Arch Dermatol* 2001; **137**: 305–8.

22 Weinberg J, Kristal L, Chooback L *et al*. The clonal nature of pityriasis lichenoides. *Arch Dermatol* 2002; **138**: 1063–7.

23 Magro C, Crowson A, Morrison C, Jingwei L. Pityriasis lichenoides chronica: stratification by molecular and phenotypic profile. *Human Pathol* 2007; **38**: 479–90.



Fig. 57.11 Clinical appearance of follicular mucinosis showing boggy mucin-secreting plaques on the trunk.

Follicular mucinosis [1–4]

Synonym
- Alopecia mucinosa

Definition. Boggy cutaneous plaques showing follicular prominence and histological evidence of mucinous degeneration of hair follicles that is often associated with an atypical pilotropic T-cell infiltrate and clinical features of MF (pilotropic or folliculotropic MF).

Clinical features. There appear to be two distinct forms of follicular mucinosis, one associated with MF and an entirely separate, benign, inflammatory form of follicular mucinosis, which is not associated with the development of MF. The clinical features of these two types of follicular mucinosis are identical; follicular papules and plaques often associated with severe pruritus and with a predilection for the face and scalp but the trunk and limbs can be affected and the classic patches and plaques of MF may also be present. A younger age group is affected by inflammatory forms but there are no satisfactory criteria for distinguishing this from MF-associated follicular mucinosis, suggesting that both may represent forms of MF. Prominent giant comedones are often a feature with acneiform lesions (Fig. 57.11), and significant alopecia may be present, rarely with mucinorrhoea [5].

Pathology. There is degeneration of involved hair follicles, associated in MF with a prominent pilotropic atypical T-cell infiltrate. In MF there may also be associated interfollicular epidermotropism. Although these histological features distinguish follicular mucinosis from pilotropic MF, both conditions may simply represent points on a spectrum [5]. Mucin stains such as alcian blue show the presence of large quantities of mucin (Fig. 57.12). In MF, a pilotropic or folliculotropic infiltrate may also occur without mucinosis. In contrast, the inflammatory form of follicular mucinosis does not show a prominent atypical pilotropic T-cell infiltrate, although repeated biopsies may be required to fully exclude MF. It may be impossible to distinguish these two forms with confidence and there is an emerging consensus that most, if not all, patients with follicular mucinosis have a form of CTCL (pilotropic mycosis fungoides) [6]. However, histologic features of follicular mucinosis, without atypia, can also occur as an incidental histological feature in the context of a variety of inflammatory dermatoses [7].

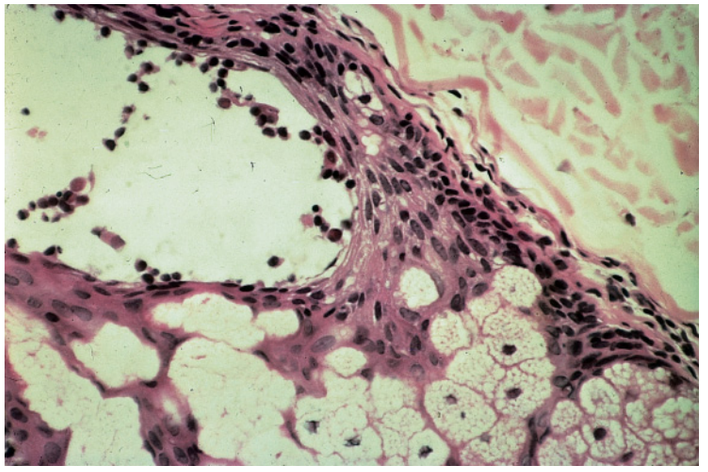


Fig. 57.12 Histology of lesion illustrated in Fig. 57.11 showing degeneration of the hair follicle.

Immunophenotype. The tumour cells in both follicular mucinosis and folliculotropic/pilotropic MF are usually $CD3^+$, $CD4^+$ and $CD8^-$. Prominent $CD30^{+/-}$ blast cells may be associated with a poor prognosis [5,6]. T-cell receptor clonal gene rearrangements can be detected in both MF-associated follicular mucinosis and so-called benign forms of inflammatory follicular mucinosis, consistent with suggestions that both may represent MF variants [6,8].

Pathogenesis. It is accepted that follicular mucinosis represents a follicular (pilotropic) variant of MF with mucinous degeneration of the hair follicle, although the reason for mucin deposition is not currently known. This is supported by the presence of this clinical and histological pattern in patients with typical features of MF. The poor prognosis of folliculotropic variants may relate to the poorer efficacy of skin-directed therapies because of the depth of the associated T-cell infiltrate or a currently unknown pathogenetic difference.

Treatment. There is emerging evidence that follicular variants of MF have a worse prognosis, with disease-specific survival rates of 81% at 5 years and 36% at 10 years [5,9]. Mycosis fungoides associated with follicular mucinosis is treated with skin-directed therapy

as for early stages of MF, but patients may also require systemic treatment with IFN-α or retinoids (bexarotene). Radiotherapy is ideal for isolated plaques of folliculotropic MF. Total skin electron beam therapy may be appropriate for resistant cases. Dapsone can be effective for inflammatory forms of follicular mucinosis. However, if the hair follicles have been destroyed, scarring alopecia will be present and the hair loss permanent.

References

1 Binnick AN, Wax FD, Clendenning WE. Alopecia mucinosa of the face associated with mycosis fungoides. *Arch Dermatol* 1978; **114**: 791–8.
2 Coskey RJ, Mehregan AH. Alopecia mucinosa: a follow-up study. *Arch Dermatol* 1970; **102**: 193–4.
3 Emmerson RW. Follicular mucinosis: a study of 47 patients. *Br J Dermatol* 1969; **81**: 395–413.
4 Pinkus H. Alopecia mucinosa. *Arch Dermatol* 1957; **76**: 419–26.
5 Van Doorn R, Scheffer E, Willemze R. Follicular mycosis fungoides, a distinct disease entity with or without associated follicular mucinosis. *Arch Dermatol* 2002; **138**: 191–8.
6 Cerroni L, Fink-Puches R, Back B, Kerl H. Follicular mucinosis. *Arch Dermatol* 2002; **138**: 182–9.
7 Hempstead R, Ackerman B. Follicular mucinosis: a reaction pattern in follicular epithelium. *Am J Dermatopathol* 1985; **7**: 245–57.
8 Meehan S, Jensen K, Kim Y *et al*. Use of polymerase chain reaction heteroduplex analysis in the evaluation of follicular mucinosis. *J Cutan Pathol* 1999; **26**: 458.
9 Gerami P, Rosen S, Kuzel T *et al*. Follicolotropic mycosis fungoides. An aggressive variant of cutaneous T-cell lymphoma. *Arch Dermatol* 2008; **144**: 738–46.

Pagetoid reticulosis

Synonym
- Woringer–Kolopp disease

Definition. A localized, solitary variant of CTCL, which histologically shows intense epidermotropism.

Clinical features. This entity was first described in 1939 [1] and is rare but appears to affect younger adults [2]. It is characterized by an isolated, persistent, scaly plaque, commonly involving an acral site (Fig. 57.13). The lesion may be asymptomatic and slowly expands, but no further plaques develop on other body sites. A more generalized variant with multiple plaques at other sites has also been described (Ketron–Goodman), but it is likely that this represents an epidermotropic variant of MF or the more recently described $CD8^+$ epidermotropic CTCL variant [3] (see below).



Fig. 57.13 Pagetoid reticulosis. Striking solitary scaling lesion on the side of the foot of a young male.

Pathology. Biopsies show very striking colonization of an acanthotic epidermis [4,5] by atypical, large, pale, mononuclear cells, which usually either fail to express lymphoid markers or express an aberrant T-cell phenotype. Originally there was controversy over whether these cells were derived from histiocytes, Langerhans' cells or Merkel cells. However, the detection of an aberrant T-cell phenotype ($CD4^-$ and $CD8^-$) in some cases and clonal TCR gene rearrangements has clearly established that this entity represents a CTCL variant [6–8].

Pathogenesis. This entity may either represent a localized epidermotropic variant of either MF [9] or the more recently described $CD8^+$ epidermotropic CTCL [3]. However, the underlying pathogenesis will not be understood fully until the fundamental biology of MF has been clarified.

Treatment. The natural history of this lesion is of very slow local extension with an excellent prognosis. Successful remission and probable cure has been reported with both surgical excision and low-dose superficial radiotherapy.

References

1 Woringer F, Kolopp P. Lesion erythematosquameuse polycyclique de l'avant bras evoluant depuis 6 ans chez un garcon de 13 ans: histologiquement infiltrat intraepidermique d'apparence tumorale. *Ann Dermatol Vénéréol* 1939; **10**: 945–58.
2 Mandojana RM, Helwig EB. Localized epidermotropic reticulosis (Woringer–Kolopp disease). *J Am Acad Dermatol* 1983; **8**: 813–29.
3 Berti E, Tomasini D, Vermeer M *et al*. Primary cutaneous CD8-positive epidermotropic cytotoxic T-cell lymphomas: a distinct clinicopathological entity with an aggressive clinical behaviour. *Am J Pathol* 1999; **155**: 483–92.
4 Haneke E, Tulusan AH, Weidner F. Histological features of 'pagetoid reticulosis' (Woringer–Kolopp) in premycosis fungoides. *Arch Dermatol Res* 1977; **258**: 265–73.
5 Degreef H, Holvoet C, van Vloten WA *et al*. Woringer–Kolopp disease: an epidermotropic variant of mycosis fungoides. *Cancer* 1976; **38**: 2154–65.
6 Deneau D, Wood G, Beckstead J *et al*. Worringer–Kollopp disease (pagetoid reticulosis): four cases with histopathologic, ultrastructural and immunohistologic observations. *Arch Dermatol* 1984; **120**: 1045–51.
7 MacKie RM, Turbitt ML. A case of pagetoid reticulosis bearing the T cytotoxic suppressor surface marker on the lymphoid infiltrate: further evidence that pagetoid reticulosis is not a variant of mycosis fungoides. *Br J Dermatol* 1984; **110**: 89–94.
8 Wood G, Weiss L, Hu C *et al*. T-cell antigen deficiences and clonal rearrangements of T-cell receptor genes in pagetoid reticulosis (Woringer–Kolopp disease). *N Engl J Med* 1988; **318**: 164–7.
9 Burns MK, Chan LS, Cooper KD. Woringer–Kolopp disease or unilesional mycosis fungoides? *Arch Dermatol* 1995; **131**: 325–9.

Granulomatous slack-skin disease

Definition. A rare disease characterized clinically by the slow development of pendulous folds of lax erythematous skin and histologically by dermal granulomas and elastolysis.

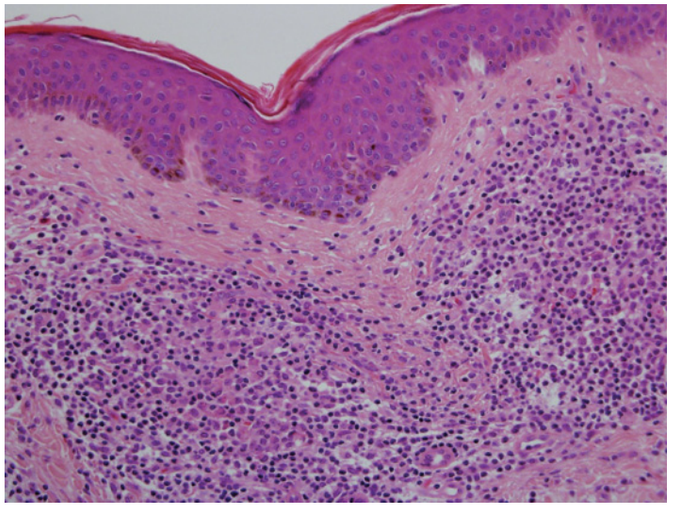


Fig. 57.14 Granulomatous slack skin showing prominent, lax folds of markedly indurated axillary skin with superficial scaling and wrinkling.

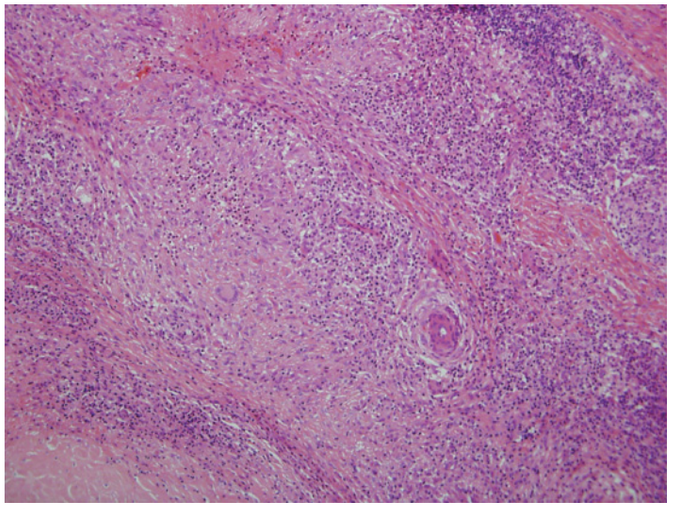
Clinical features. The lesions develop slowly, usually in middle-aged adults, and then progress over several years [1]. They are typically flexural in distribution and consist of thickened, pendulous folds (Fig. 57.14). This condition appears to be caused by cutaneous elastolysis associated with an underlying lymphoma. Several patients have died of Hodgkin's disease or non-Hodgkin's lymphoma [2–4] and the otherwise unaltered epidermis may show epidermotropism, similar to that seen in MF. The condition must be distinguished from other forms of cutis laxa.

Pathology. Histology reveals a dense granulomatous dermal infiltrate (Fig. 57.15) with destruction of dermal elastic tissue (elastolysis) [5–7]. The destruction appears to be mediated by histiocytic giant cells [8]. Similar granulomas may occasionally be found in the spleen and lymph nodes [4]. The lymphocytic infiltrate in the dermis shows some cytologic atypia and has an aberrant T-cell phenotype suggestive of lymphoma. TCR gene analysis has also confirmed that T-cell clones are present, suggesting a CTCL variant in most cases [9], but whether this condition represents a granulomatous variant of MF or a different type of CTCL is currently unclear [10], especially as a novel balanced translocation has recently been detected in granulomatous slack skin [11].

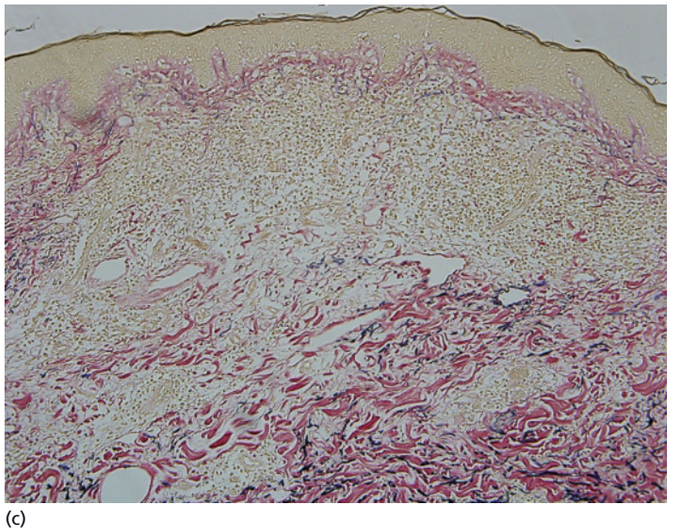
Treatment. No definitive therapy has yet been identified but radiotherapy, retinoids and surgery have been reported to be effective [12–14].



(a)



(b)



(c)

Fig. 57.15 (a) Histology showing a prominent infiltrate of histiocytic cells and lymphoid cells showing mild cytologic atypia. (b) Giant cells are present and marked loss of elastic tissue (elastolysis) shown with an elastic van Gieson stain (EVG) in the upper dermis (c).

References

1 Schot JDL. Granulomatous slack skin. *Br J Dermatol* 1989; **120**: 807.

2 Degregorio R, Fenske NA, Glass LF. Granulomatous slack skin: a possible precursor of Hodgkin's disease. *J Am Acad Dermatol* 1995; **33**: 1044–7.

3 Noto G, Pravata G, Arico M. Granulomatous slack skin: report of a case associated with Hodgkin's disease and review of the literature. *Br J Dermatol* 1994; **131**: 275–9.

4 Le T, Pierard G. Granulomatous slack skin syndrome and Hodgkin's disease. *Ital Gen Rev Dermatol* 1986; **23**: 48–9.

5 Balus L, Bassetti F, Gentili G. Granulomatous slack skin. *Arch Dermatol* 1985; **121**: 250–2.
6 Convit J, Kerdel F, Goihman M *et al*. Progressive atrophying chronic granulomatous dermohypodermatitis. *Arch Dermatol* 1973; **107**: 371–4.
7 White CR, Holbrook KA, Atkin E *et al*. Granulomatous slack skin. *Arch Dermatol* 1984; **120**: 1085.
8 Helm KF, Cerio R, Winkelmann RK. Granulomatous slack skin: a clinico-pathological and immunohistochemical study of three cases. *Br J Dermatol* 1992; **126**: 142–7.
9 Le Boit PE, Beckstead K, Atkin E *et al*. Granulomatous slack skin: clonal rearrangement of the T-cell receptor β gene is evidence for the lymphoproliferative nature of the cutaneous elastolytic disorder. *J Invest Dermatol* 1987; **89**: 183–6.
10 Kempf W, Ostheeren-Michaelis S, Paulli M *et al*. Granulomatous mycosis fungoides and granulomatous slack skin. *Arch Dermatol* 2008; **144**: 1069–617.
11 Ikonomou I, Aamot V, Heim S *et al*. Granulomatous slack skin with a translocation t(3;9)(q12;24). *Am J Surg Pathol* 2007; **31**: 803–6.
12 Wollina U, Greafe T, Fuller J. Granulomatous slack skin or granulomatous mycosis fungoides: a case report. Complete response to percutaneous radiation and interferon alpha. *J Cancer Res Clin Oncol* 2002; **128**: 50–4.
13 Balus L, Manente L, Remotti D. Granulomatous slack skin: report of a case and review of the literature. *Am J Dermatopathol* 1996; **18**: 199–206.
14 Benton E, Morris S, Robson A, Whittaker S. An unusual case of granulomatous slack skin with necrobiosis. *Am J Dermatopathol* 2008; **30**: 462–5.

Sézary syndrome [1–4]

Definition. The presence of a clinical triad consisting of erythroderma, peripheral lymphadenopathy and atypical mononuclear cells (Sézary cells) comprising 5% or more of peripheral blood lymphocytes on a buffy coat smear (B1), or more than 20% of total lymphocyte count or a total Sézary count of more than 1000×10^9/L (B2). The presence of a peripheral blood T-cell clone as indicated either by a CD4:CD8 ratio greater than 10, aberrant expression of pan T-cell antigens, cytogenetics or TCR gene analysis is now also required to confirm that the patient has a malignant disease, Sézary T-cell lymphoma–leukaemia [5].

Clinical features. The majority of patients are elderly males and may develop the syndrome either *ab initio* or as progression from classical MF. Many patients describe a prolonged history of 'dermatitis'. Patients present with a generalized exfoliative erythroderma, and may have systemic problems because of shunting of blood through grossly dilated cutaneous vasculature, and resulting high-output cardiac failure. There may be associated ectropion, scalp alopecia, palmoplantar hyperkeratoses and fissuring and the nails often show gross subungual hyperkeratoses (Fig. 57.16). Peripheral lymphadenopathy is often present. The distinction from erythrodermic MF (T4 N0–3 M0/stage III–IVA) is based on the degree of peripheral blood involvement (more than 5% Sézary cells per 100 lymphocytes (T4 N0–3 M0B1/stage III–IVA) as suggested in the original National Cancer Institute (NCI) staging system) [6]. However, there has been a debate about the diagnostic and prognostic relevance of the proportion of peripheral blood Sézary cells as low numbers of Sézary cells can be detected in the peripheral blood of healthy individuals and patients with inflammatory dermatoses. In 1988, the NCI published a revised staging system, with over 20% Sézary cell count (per 100 lymphocytes) as the B1 rating [7], based on previous studies showing that this figure had prognostic significance in Sézary syndrome [8,9]. However, this has been shown to include some patients with benign disorders and may actually represent a larger tumour burden (B2). An absolute Sézary cell count of over $1000/mm^3$ has recently been proposed as a criterion for the diagnosis of Sézary syndrome, which most closely represents the B2 rating for peripheral blood involvement, but this figure may exclude those patients with a lower tumour burden (more than 5% per 100 lymphocytes; B1), who nevertheless have a neoplastic form of SS [5,10]. The recent ISCL EORTC proposal for a revision of the staging system provides a well-defined staging of peripheral blood in SS and should clarify these issues [11]. A recent study suggests that the presence of lymph node disease in Sézary syndrome is an independent prognostic factor while the degree of peripheral blood involvement also has some prognostic significance [12]. The prognosis for patients with SS is poor, with a median survival of 35 months from diagnosis. Most die of opportunistic infection. However, with improved earlier diagnosis the prognosis may now be better.



Fig. 57.16 Sézary syndrome showing erythroderma with palmoplantar hyperkeratoses and prominent nail dystrophy.

Immunopathology. Skin biopsies can show large numbers of atypical mononuclear cells in the dermis with epidermotropism, but it has been shown that non-diagnostic and lymphomatoid

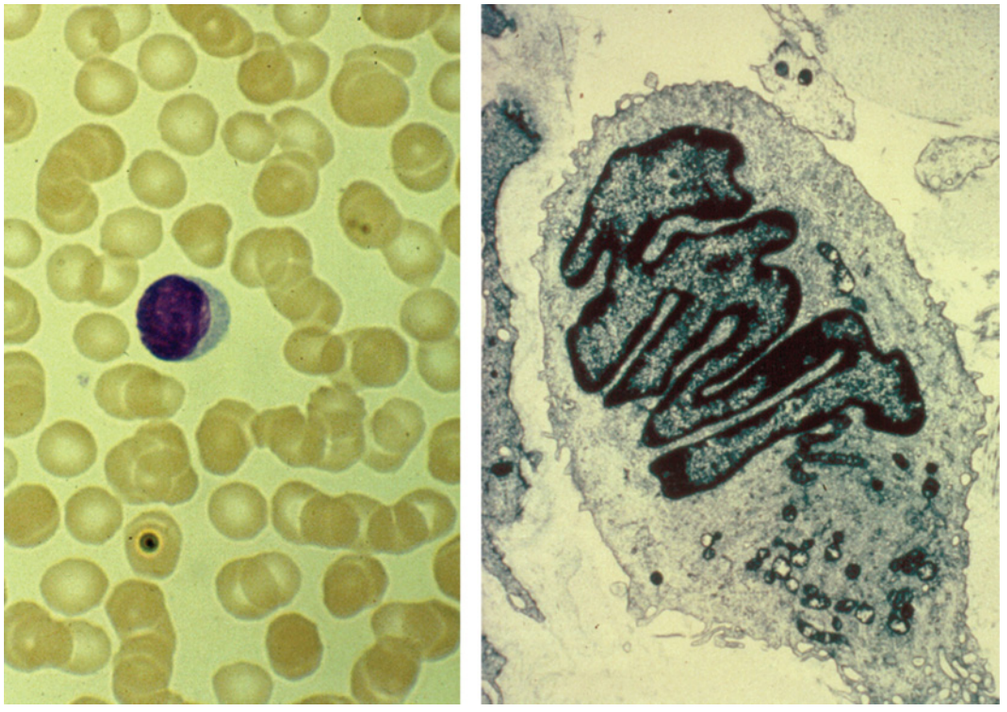


Fig. 57.17 High-power view of Sézary cells in peripheral blood showing large cell with very large nucleus and minimal cytoplasm and ultrastructural features of a typical cerebriform nucleus.

histology is frequently seen in proven cases of SS [13]. The presence of atypical (Sézary-like) peripheral blood cerebriform mononuclear cells has also been reported in a variety of inflammatory conditions including actinic reticuloid, erythroderma associated with dermatitis and psoriasis, and severe drug reactions, but in general the percentage of atypical cells in such conditions is lower than in SS (Fig. 57.17) [14,15]. In addition, T cells with the morphological and ultrastructural features of Sézary cells can be identified in the peripheral blood of normal healthy individuals [16,17]. However, it is important to realize that the total lymphocyte count does not have to be raised for the diagnosis to be made, and the presence of a normal total white cell count without careful morphological examination of the 'tail' of a blood smear or of a buffy coat preparation may mask this diagnosis. Consequently, it can be difficult to conclusively distinguish cases of T-cell leukaemia–lymphoma from inflammatory dermatoses. Large Sézary cell variants (over 16 μm diameter) are easier to recognize but small Sézary cell variants (12–14 μm) are more common and are more difficult to distinguish from activated lymphocytes [4]. Sézary cells are usually $CD3^+$, $CD4^+$, $CD7^-$, $CD26^-$ T cells but $CD26^+$, $CD7^+$ and $CD8^+$ variants have been reported and CD26 loss can occur in control populations albeit at low levels [18–23]. Absolute CD4 counts and CD4:CD8 ratios are elevated. A CD4:CD8 ratio greater than 10 distinguishes most cases of T-cell leukaemia–lymphoma from inflammatory dermatosis associated with Sézary cells but is not pathognomonic as it usually represents a large peripheral blood tumour burden. A consensus has now been agreed that diagnostic criteria should include the clinical triad of features plus the presence of a peripheral blood T-cell clone detected either by expression of aberrant pan T-cell antigens, cytogenetics or TCR gene analysis [5]. Those patients without evidence of a T-cell clone may have a benign inflammatory dermatosis with an excellent prognosis [24]. Sézary syndrome should also be distinguished from other T-cell malignancies such as T-prolymphocytic leukaemia, which can present with cutaneous involvement including rarely erythroderma, although this diagnosis is usually apparent on the basis of clinicopathological and immunophenotypic features [25].

References

1 Sézary A, Bouvrain Y. Erythrodermie avec presence de cellules monstreuses dans derme et sang circulant. *Bull Soc Fr Dermatol Syphilol* 1938; **45**: 254–60.

2 Main R, Goodall H, Swanson W. Sézary's syndrome. *Br J Dermatol* 1959; **71**: 254–60.

3 Lutzner M, Jordan H. The ultrastructure of an abnormal cell in Sézary's syndrome. *Blood* 1968; **31**: 719–26.

4 Lutzner M, Emerit I, Durepaire R *et al*. Cytogenetic, cytophotometric and ultrastructural study of large cerebriform cells of the Sézary syndrome and description of the small-cell variant. *J Natl Cancer Inst* 1973; **50**: 1145–62.

5 Vonderheid E, Bernengo M, Burg G *et al*. Update on erythrodermic cutaneous T-cell lymphoma: report of the International Society for Cutaneous Lymphomas. *J Am Acad Dermatol* 2002; **46**: 95–106.

6 Lamberg SI, Bunn PA Jr. Cutaneous T-cell lymphomas: summary of the Mycosis Fungoides Cooperative Group—National Cancer Institute Workshop. *Arch Dermatol* 1979; **115**: 1103–5.

7 Sausville E, Eddy J, Makuch R *et al*. Histopathologic staging at initial diagnosis of mycosis fungoides and the Sézary syndrome: definition of three distinctive prognostic groups. *Ann Intern Med* 1988; **109**: 372–82.

8 Schechter G, Sausville E, Fischmann A *et al*. Evaluation of circulating malignant cells provides prognostic information in cutaneous T-cell lymphoma. *Blood* 1987; **69**: 841–9.

9 Vonderheid E, Sobel E, Nowell P *et al*. Diagnostic and prognostic significance of Sézary cells in peripheral blood smears from patients with cutaneous T cell lymphoma. *Blood* 1985; **66**: 358–66.

10 Russell Jones R, Whittaker S. T-cell receptor gene analysis in the diagnosis of Sézary syndrome. *J Am Acad Dermatol* 1999; **41**: 254–7.

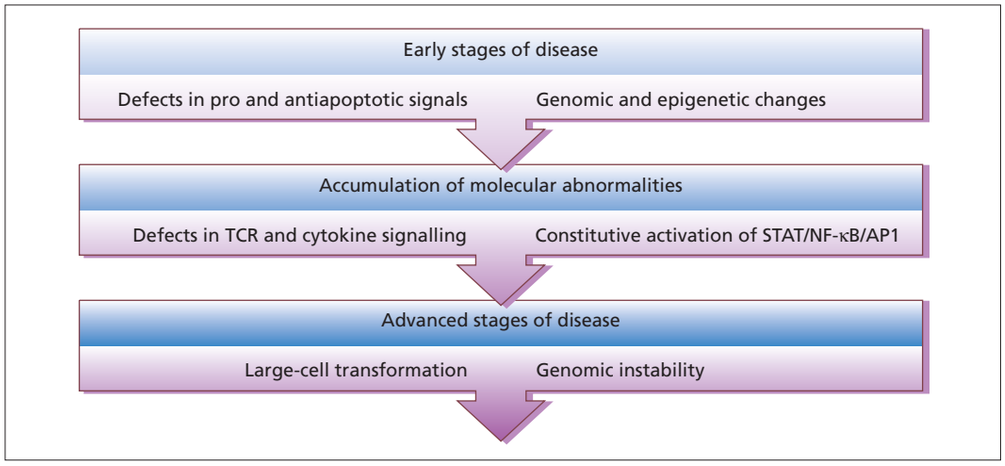


Fig. 57.18 Molecular pathogenesis of mycosis fungoides/Sézary syndrome.

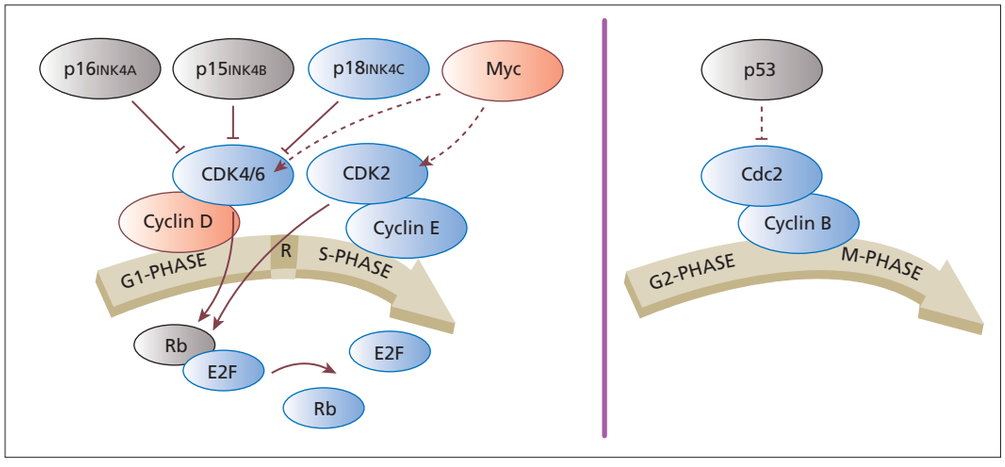


Fig. 57.19 Abnormalities of genes controlling cell-cycle checkpoints in mycosis fungoides/Sézary syndrome (grey, loss of function; red, gain of function).

11 Olsen E, Vonderheid E, Pimpinelli N *et al.* Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organisation of Research and Treatment of Cancer (EORTC). *Blood* 2007; **110**: 1713–22.

12 Scarisbrick J, Whittaker S, Evans A *et al*. Prognostic significance of tumour burden in the blood of patients with erythrodermic primary cutaneous T-cell lymphoma. *Blood* 2001; **97**: 624–30.

13 Trotter M, Whittaker S, Orchard G, Smith N. Cutaneous histopathology of Sézary syndrome: a study of 41 cases with a proven circulating T-cell clone. *J Cutan Pathol* 1997; **24**: 286–91.

14 Chu A, Robinson D, Hawk J *et al*. Immunologic differentiation of the Sézary syndrome due to cutaneous T-cell lymphoma and chronic actinic dermatitis. *J Invest Dermatol* 1986; **86**: 134–7.

15 D'Incan M, Souteyrand P, Bignon Y *et al*. Hydantoin-induced cutaneous pseudolymphoma with clinical, pathologic and immunologic aspects of Sézary syndrome. *Arch Dermatol* 1992; **128**: 1371–4.

16 Meijer C, Van Leeuwen A, Van der Loo E *et al*. Cerebriform (Sézary-like) mononuclear cells in healthy individuals: a morphologically distinct population of T-cells. *Arch B Cell Pathol* 1977; **25**: 95–104.

17 Matutes E, Robinson D, O'Brien M *et al*. Candiate counterparts of Sézary cells and adult T-cell lymphoma–leukaemia cells in normal peripheral blood: an ultrastructural study with immunogold method and monoclonal antibodies. *Leuk Res* 1983; **7**: 787–801.

18 Lutzner M, Edelson R, Schein P *et al*. Cutaneous T-cell lymphomas: the Sézary syndrome, mycosis fungoides, and related disorders. *Ann Intern Med* 1975; **83**: 534–52.

19 Miller RA, Coleman CN, Fawcett HD *et al*. Sézary syndrome: a model for migration of T lymphocytes to skin. *N Engl J Med* 1980; **303**: 89–92.

20 Willemze R, Van Vloten W, Hermans J *et al*. Diagnostic criteria in Sézary's syndrome: a multiparameter study of peripheral blood lymphocytes in 32 patients with erythroderma. *J Invest Dermatol* 1983; **81**: 392–7.

21 Bernengo M, Novelli M, Quaglino P *et al*. Prognostic factors in Sézary syndrome: a multivariate analysis of clinical, haematological, and immunological features. *Ann Oncol* 1998; **9**: 857–63.

22 Bernengo M, Novelli M, Quaglino P *et al*. The relevance of the CD4 $CD26^-$ subset in the identication of circulating Sézary cells. *Br J Dermatol* 2001; **144**: 25–135.

23 Kelemen K, Guitart J, Kuzel T *et al*. The usefulness of CD26 in flow cytometric analysis of peripheral blood in Sezary syndrome. *Am J Clin Pathol* 2008; **129**: 146–56.

24 Fraser-Andrews E, Russell-Jones R, Woolford A *et al*. Diagnostic and prognostic importance of T-cell receptor gene analysis in patients with Sézary syndrome. *Cancer* 2001; **92**: 1745–52.

25 Matutes E, Brito-Babapulle V, Swansbury J *et al*. Clinical and laboratory features of 78 cases of T-prolymphocytic leukaemia. *Blood* 1991; **78**: 3269–74.

Molecular features (MF/SS) (Fig. 57.18). The underlying molecular pathogenesis of MF and SS has not yet been fully characterized. No disease-specific translocations have yet been identified [1], but studies have shown consistent abnormalities of cell cycle (Fig. 57.19), DNA repair and apoptotic pathways which contributes to both genomic instability and a failure of activation-induced cell

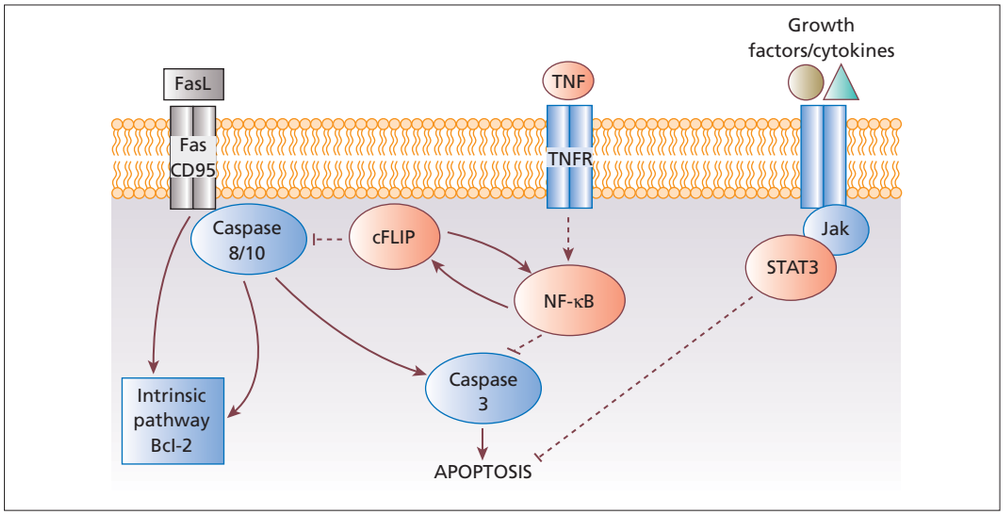


Fig. 57.20 Abnormalities of T-cell activation induced cell death in mycosis fungoides/Sézary syndrome causing defective T-cell homeostasis (grey, loss of function; red, gain of function).

death, which is primarily responsible for T-cell homeostasis (Fig. 57.20).

Extensive studies have shown complex but consistent and recurrent numerical and structural chromosomal abnormalities in all stages of disease [1–9]. In SS an abnormal karyotype is a poor prognostic factor [10]. These studies, using conventional cytogenetics, allelotyping, metaphase and array comparative genomic hybridization (CGH) techniques, have shown similar patterns of chromosomal losses (1p, 13, 19, 17p and 10q) and gains (4, 8q and 17q), and patterns of loss of heterozygosity (9p, 10q and 17p) in both MF and SS suggesting a shared pathogenesis. Minimal regions of deletion have been detected on 10q, suggesting a number of potential candidate genes [11,12]. High resolution array CGH studies have confirmed these 10q findings in SS and suggest a high frequency (40–75% of cases) of candidate gene abnormalities, including gains of *cMYC* and *STAT3/5* and loss of cMYC antagonists including *MXI1* and *MNT* and *p53* [13]. Gains of *Her 2/neu* gene copy number at 17q have also been detected using fluorescent *in situ* hybridization (FISH) in a small series of SS patients [14]. High resolution array CGH studies in early stages of MF have also shown recurrent losses (7p, 7q, 9q, 12q, 16q and 19) with gains (8q and 21q) and specific deletions of tumour suppressor genes *BCL7a*, *SMAC/DIABLO* and *RHOF* [15].

Although as yet no disease-specific balanced translocation has been defined, a balanced t(12;18)(q21;21.2) translocation was recently described in a patient with SS and led to the identification of a *NAV3* gene deletion on chromosome 12q21-22 using interphase FISH in a majority of MF and SS patients [16]. However, subsequent studies have not detected specific *NAV3* deletions in a separate series of MF and SS patients; 12q losses were detected in a few cases but in only two cases did the 12q deletions include *NAV3* [17].

Specific chromosomal abnormalities have been detected in early stages of disease, suggesting that chromosomal instability occurs early [18]. Microsatellite instability (MSI) has also been detected in some studies, and has been attributed to hypermethylation of the mismatch repair enzyme gene promoter, *MLH1* [19]. Undoubtedly MSI also contributes to genomic instability in MF/SS. Telomerase activity is increased in MF/SS [20], which is essential to prevent tumour cell senescence but also will potentially contribute to genomic instability.

Specific gene abnormalities in MF/SS include overexpression and mutation of *p53* in advanced stages of disease [21–24]. In one study, UVB-type *p53* mutations were found [23]. Additional 17p copy number losses also contribute to loss of p53 function in MF/SS [6]. *p53* abnormalities are not found in early stages of disease, suggesting that inactivation of *p53* is related to disease progression, similar to findings in other nodal and extranodal lymphomas. At present, it is unclear if *p53* abnormalities are associated with treatment resistance and a poor prognosis, as seen in other non-Hodgkin's lymphomas, but loss of p53 would contribute to both apoptotic defects and genomic instability. Inactivation of both *p14*, *p15* and *p16* genes has also been detected in MF [25–27]. This is a consequence of 9p deletions involving the *CDKN2A* locus and epigenetic abnormalities due to hypermethylation of gene promoter sequences rather than mutation (Fig. 57.19). It is still unclear whether this is restricted to late-stage disease and transformation. Other genes shown to be inactivated through epigenetic mechanisms involving promoter hypermethylation include tumour suppressor genes, *BCL7a*, *PTPRG* and *p73* [28]. Deletions of *BCL7a* have also been demonstrated in early stages of MF [15]. The tumour suppressor gene on 10q, *PTEN*, has been shown to be homozygously deleted in a proportion of patients, suggesting that the pro-apoptotic AKT signalling pathway is dysregulated [11]. Recent studies have identified infrequent mutations of the *Fas* gene on 10q in early stages of MF and loss of *Fas* expression in advanced disease, providing a further mechanism by which tumour cells may escape apoptosis [29,30]. Fas-mediated apoptosis may also be inhibited in tumour cells by over-expression of *cFLIP* which inhibits the extrinsic apoptotic pathway [31] (Fig. 57.20). Dysregulation of the intrinsic apoptotic pathway has also been detected in MF/SS [32]. Gains of oncogenes, including *RAF1* and *CTSB*, have been detected in a small series of MF/SS cases [33]. In addition, gains of *JUNB* on chromosome 19p have been detected in a large series of MF/SS patients and this appears to be due to chromosomal amplification in some cases with over-

expression in tumour cells identified in tumour samples as well [34]. JunB is a member of the AP1 transcription factor family involved in controlling cell proliferation and differentiation. JunB is also essential for expression of a Th2 cytokine profile and so over-expression in MF/SS may explain the characteristic Th2 cytokine expression by MF/SS [35].

Gene expression studies in MF have shown abnormalities of TNF signalling pathways and gene expression signatures which reportedly distinguish inflammatory dermatoses from MF [36]. A further array cDNA study of MF has identified three signature profiles using consensus clustering which distinguishes those patients with: (i) early stage disease (IA–IIA) who respond to therapy; (ii) an intermediate group (stage IB–III) who show a degree of resistance to therapy; and (iii) a poor prognostic group (predominantly stage IIB) [37]. Both these findings have yet to be validated and may explain more about the host immune response than the actual tumour gene expression profile.

In SS, cDNA array studies have identified a gene signature that is reported to be associated with poor prognosis and a diagnostic gene signature that can be used to distinguish it from inflammatory dermatoses has also been described [38,39]. A further study using a different array platform showed expression of a tyrosine kinase receptor, *EphA4* and a transcription factor, *Twist* [40]. The functional relevance and validation of these findings requires further study. Several studies have now confirmed over-expression of T-plastin in SS. This is an actin bundling protein and the T-plastin isoform is normally only expressed in epithelial tissues and could prove to be an important biomarker [38,41].

Fundamental questions remaining include the cause(s) of the genomic instability which defines MF/SS even at early stages as well as a need to define the specific genomic abnormalities that distinguish SS from MF. However, it is apparent that critical abnormalities of apoptosis are prevalent in both MF and SS and almost certainly this affects T-cell homeostasis. Such defects are probably essential acquired abnormalities allowing tumour cells in MF/SS to adopt a malignant phenotype. Defective activation-induced cell death in MF/SS is further exemplified by other key findings (Fig. 57.21); constitutive expression of STAT3 protein which is integral to cytokine mediated T-cell activation and inhibition of IL-2 mediated expression of STAT5 have been clearly defined in advanced stages of disease such as SS [42–44]. In addition, constitutive expression of NFkB has also been shown in both MF and SS [45,46]. The consequent dysregulation of multiple signalling pathways controlled by STAT and NFkB will contribute to prevention of tumour cell apoptosis in MF/SS and these pathways may also be potential therapeutic targets.

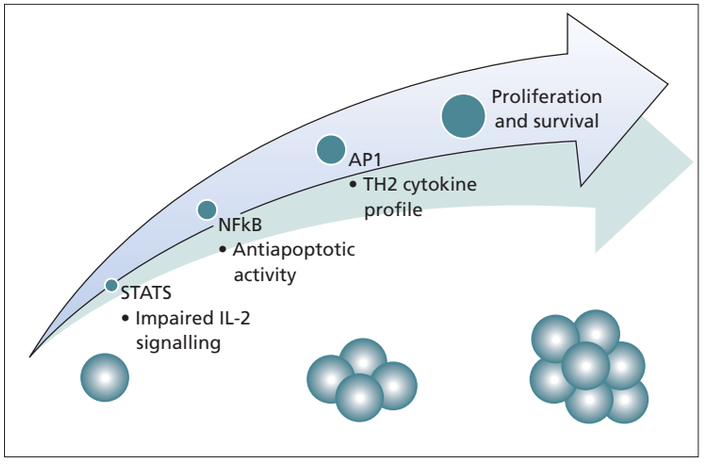


Fig. 57.21 Dysregulated T-cell signalling pathways in mycosis fungoides/Sézary syndrome.

References

1 Thangavelu M, Finn W, Yelavarthi K *et al*. Recurring structural chromosomal abnormalities in peripheral blood lymphocytes of patients with mycosis fungoides/Sézary syndrome. *Blood* 1997; **89**: 3371.

2 Karenko L, Kahkonen M, Hyytinen E *et al*. Notable losses at specific regions of chromosome 10q and 13q in the Sézary syndrome detected by comparative genomic hybridization. *J Invest Dermatol* 1999; **112**: 392.

3 Mao X, Lillington D, Scarisbrick J *et al*. Molecular cytogenetic analysis of cutaneous T-cell lymphomas: identification of common genetic alterations in Sézary syndrome and mycosis fungoides. *Br J Dermatol* 2002; **147**: 464–75.

4 Karenko L, Sarna S, Kahkonen M, Ranki A. Chromosomal abnormalities in relation to clinical disease in patients with cutaneous T-cell lymphoma: a 5 year follow-up study. *Br J Dermatol* 2003; **148**: 55–64.

5 Scarisbrick JJ, Woolford AJ, Russell-Jones R, Whittaker SJ. Allelotyping in mycosis fungoides and Sézary syndrome: common regions of allelic loss identified on 9p, 10q, and 17p. *J Invest Dermatol* 2001; **117**: 663–70.

6 Mao X, Lillington D, Czepulkowski B *et al*. Molecular cytogenetic characterization of Sézary syndrome. *Genes Chromosomes Cancer* 2003; **36**: 250–60.

7 Batista D, Vonderheid E, Hawkins A *et al*. Multicolor fluoresecence in situ hybridization (SKY) in mycosis fungoides and Sezary syndrome: search for recurrent chromosome abnormalities. *Genes Chrom Cancer* 2006; **45**: 383–91.

8 Padilla-Nash H, Wu K, Just H *et al*. Spectral karyotyping demonstrates genetically unstable skin homing T lymphocytes in cutaneous T-cell lymphoma. *Exp Dermatol* 2006; **16**: 98–103.

9 Prochazkova M, Chevret E, Mainhaguiet G *et al*. Common chromosomal abnormalities in mycosis fungoides transformation. *Genes Chrom Cancer* 2007; **46**: 828–38.

10 Whang-Peng J, Bunn P, Knutsen T *et al*. Clinical implications of cytogenetic studies in cutaneous T-cell lymphoma (CTCL). *Cancer* 1982; **50**: 1539–53.

11 Scarisbrick J, Woolford A, Russell-Jones R *et al*. Loss of heterozygosity on 10q and microsatellite instability in advanced stages of primary cutaneous T-cell lymphoma and possible association with homozygous deletion of *PTEN*. *Blood* 2000; **95**: 2937–42.

12 Wain M, Mitchell T, Russell Jones R, Whittaker S. Fine mapping of chromosome 10q deletions in mycosis fungoides and Sezary syndrome: identification of two discrete regions of deletion at 10q23.33-24.1 and 10q24.33-25.1. *Genes Chrom Cancer* 2005; **42**: 184–92.

13 Vermeer M, van Doorn R, Dijkman R *et al*. Novel and highly recurrent chromosomal alterations in Sezary syndrome. *Cancer Res* 2008; **68**: 2689–98.

14 Utikal J, Poenitz N, Gratchev A *et al*. Additional Her 2/*neu* gene copies in patients with Sezary Syndrome. *Leuk Res* 2006; **30**: 755–60.

15 Carbone A, Bernardini L, Valenzano F *et al*. Array-based comparative genomic hybridization in early-stage mycosis fungoides: recurrent deletion of tumour suppressor genes *BCL7A*, *SMAC/DIABLO* and *RHOF*. *Genes Chrom Cancer* 2008; **47**: 1067–75.

16 Karenko L, Hahtola S, Paivinen S *et al*. Primary cutaneous T-cell lymphomas show a deletion or translocation affecting *NAV3*, the human *UNC-53* homologue. *Cancer Res* 2005; **65**: 8101–10.

17 Marty M, Prochazkova M, Lahranne E *et al*. Primary cutaneous T-cell lymphomas do not show specific *NAV3* gene deletion or translocation. *J Invest Dermatol* 2008; **128**: 2458–66.

18 Barab G, Matteucci C, Girolomoni G *et al*. Comparative genomic hybridization identifies 17q11.2-q12 duplication as an early event in cutaneous T-cell lymphomas. *Cancer Gen Cytogen* 2008; **184**: 48–51.

19 Scarisbrick J, Mitchell T, Calonje E *et al*. Microsatellite instability is associated with hypermethylation of the hMLH1 gene and reduced expression in mycosis fungoides. *J Invest Dermatol* 2003; **121**: 894–901.

20 Wu K, Lund M, Bang K, Thestrup-Pedersen K. Telomerase activity and telomere length in lymphocytes from patients with cutaneous T-cell lymphoma. *Cancer* 1999; **86**: 1056–63.
21 Lauritzen A, Vejlsgaard G, Hou-Jensen K *et al*. P53 protein expression in cutaneous T-cell lymphomas. *Br J Dermatol* 1995; **133**: 32–6.
22 MacGregor J, Dublin E, Levison D *et al*. P53 immunoreactivity is uncommon in primary cutaneous lymphoma. *Br J Dermatol* 1995; **132**: 353.
23 MacGregor J, Crook T, Fraser-Andrews E *et al*. Spectrum of *p53* gene mutations suggests a possible role for ultraviolet radiation in the pathogenesis of advanced cutaneous lymphomas. *J Invest Dermatol* 1999; **112**: 317–21.
24 Marrogi A, Khan M, Vonderheid E *et al*. *P53* tumour suppressor gene mutations in transformed cutaneous T-cell lymphoma: a study of 12 cases. *J Cutan Pathol* 1999; **26**: 369–78.
25 Peris K, Stanta G, Fargnoli C *et al*. Reduced expression of CDKN2a/p16 in mycosis fungoides. *Arch Dermatol Res* 1999; **291**: 207–11.
26 Navas I, Oritz-Romero P, Villuendas R *et al*. *P16* gene alterations are frequent in lesions of mycosis fungoides. *Am J Pathol* 2000; **156**: 1565–72.
27 Scarisbrick JJ, Woolford AJ, Calonje E *et al*. Frequent abnormalities of the *p15* and *p16* genes in mycosis fungoides and Sézary syndrome. *J Invest Dermatol* 2002; **118**: 493–9.
28 van Doorn R, Zoutman W, Dijkman R *et al*. Epigenetic profiling of cutaneous T-cell lymphoma: promoter hypermethylation of multiple tumour suppressor genes including *BCL7a, PTPRG* and *p73*. *J Clin Oncol* 2005; **23**: 3886–96.
29 Dereure O, Levi E, Vonderhied E, Kadin M. Infrequent Fas mutations but no BAX or p53 mutations in early mycosis fungoides: a possible mechanism for the accumulation of malignant T lymphocytes in the skin. *J Invest Dermatol* 2002; **118**: 949–56.
30 Zoi-Toli O, Vermmer M, De Vries E *et al*. Expression of Fas and Fas-ligand in primary cutaneous T-cell lymphoma (CTCL): association between lack of Fas expression and aggressive types of CTCL. *Br J Dermatol* 2000; **143**: 313–9.
31 Contassot E, Kerl K, Roques S *et al*. Resistance to FasL and tumour necrosis factor-related apoptosis-inducing ligand-mediated apoptosis in Sezary syndrome T-cells associated with impaired death receptor and FLICE-inhibitory protein expression. *Blood* 2006; **111**: 4780–7.
32 Zhang C-L, Kamarashev J, Qin J-Z *et al*. Expression of apoptosis regulators in cutaneous T-cell lymphoma (CTCL) cells. *J Pathol* 2003; **200**: 249–54.
33 Mao X, Orchard G, Lillington D *et al*. Amplification and overexpression of *JUNB* is associated with primary cutaneous T-cell lymphomas. *Blood* 2003; **101**: 1513–9.
34 Mao X, Orchard G, Mitchell T *et al.* A genomic and expression study of AP-1 in primary cutaneous T-cell lymphoma: evidence for dysregulated expression of JUNB and JUND in MF and SS. *J Cutan Pathol* 2008; **35**: 899–910.
35 Hahtola S, Tuomela S, Elo L *et al*. Th1 response and cytotoxicity genes are down-regulated in cutaneous T-cell lymphoma. *Clin Cancer Res* 2006; **12**: 4812–21.
36 Tracey L, Villuendas R, Dotor A *et al*. Mycosis fungoides shows concurrent deregulation of multiple genes involved in the TNF signaling pathway: an expression profile study. *Blood* 2003; **102**: 1042–50.
37 Shin J, Monti S, Aires D *et al*. Lesional gene expression profiling in cutaneous T cell lymphoma reveals natural clusters associated with disease outcome. *Blood* 2007; **110**: 3015–27.
38 Kari L, Loboda A, Nebozhyn M *et al*. Classification and prediction of survival in patients with the leukemic phase of cutaneous T cell lymphoma. *J Exp Med* 2003; **197**: 1477–88.
39 Nebozhyn M, Loboda A, Kari L *et al*. Quantitative PCR on 5 genes reliably identifies CTCL patients with 5% to 99% circulating tumour cells with 90% accuracy. *Blood* 2006; **107**: 3189–96.
40 van Doorn R, Dijkman R, Vermeer M *et al*. Aberrant expression of the tyrosine kinase receptor EphA4 and the transcription factor Twist in Sezary syndrome identified by gene expression analysis. *Cancer Res* 2004; **64**: 5578–86.
41 Su M, Dorocicz I, Dragowska W *et al*. Aberrant expression of T-plastin in Sezary cells. *Cancer Res* 2003; **63**: 7122–7.
42 Zhang Q, Nowak I, Vonderheid E *et al*. Activation of Jak/STAT proteins involved in signal transduction pathway mediated by receptor for interleukin 2 in malignant T lymphocytes derived from cutaneous anaplastic large T-cell lymphoma and Sezary syndrome. *PNAS* 1996; **93**: 9148–53.
43 Qin J-Z, Kamarashev J, Zhang C-L *et al*. Constitutive and interleukin-7 and interleukin-15 stimulated DNA binding of STAT and novel factors in cutaneous T cell lymphoma cells. *J Invest Dermatol* 2001; **117**: 583–9.
44 Mitchell T, Whittaker S, John S. Dysregulated expression of COOH-terminally truncated Stat5 and loss of IL2-inducible Stat5-dependent gene expression in Sezary syndrome. *Cancer Res* 2003; **63**: 9048–54.
45 Izban K, Ergin M, Qin J-Z *et al*. Constitutive expression of NF-kB is a characteristic feature of mycosis fungoides: implications for apoptosis resistance and pathogenesis. *Hum Pathol* 2000; **31**: 1482–90.
46 Sors A, Jean-Loius F, Pellet C *et al*. Down-regulating constitutive activation of the NFkB canonical pathway overcomes the resistance of cutaneous T-cell lymphoma to apoptosis. *Blood* 2006; **107**: 2354–63.

Treatment of mycosis fungoides and Sézary syndrome

Current therapy of MF and Sézary syndrome includes:

1 Topical steroids
2 Topical chemotherapy—mechlorethamine (nitrogen mustard) and carmustine (BCNU)
3 Phototherapy—both UVB and psoralen with UVA (PUVA) and UVA-1
4 Radiotherapy, including total skin electron beam therapy (TSEB)
5 Immunotherapy (IFN-α, IFN-γ and IL-12)
6 Retinoids
7 Combination therapies
8 Systemic single and multiagent chemotherapy
9 Photopheresis
10 Toxin therapies
11 Monoclonal antibodies
12 Histone deacetylase inhibitors
13 Other novel therapies.

The choice of initial treatment for the MF patient will depend on the stage of the disease as well as the general condition and age of the patient (performance status). At present, there are very few published studies that could form the basis for evidence-based therapy, mainly because of the rarity of the condition and also because of the variation between individual patients in disease pattern and progress. A large proportion of patients with MF are frail, elderly and likely to succumb either to other general medical problems or to the side effects of overenthusiastic therapy. In addition, the patient's quality of life should always be considered when selecting a treatment regimen. One of the few randomized trials of treatment of MF reported on 103 patients who received either TSEB (3000 cGy total skin electron beam) together with cyclophosphamide, daunorubicin, etoposide and vincristine (a rigorous 'treat to cure' regimen) or sequential topical therapy consisting of nitrogen mustard, superficial radiotherapy and TSEB, progressing to PUVA if required (a 'gentle palliative' regimen). After a median follow-up time of 75 months, there was no difference in disease-free or overall survival between the 52 patients who received TSEB plus chemotherapy and the 51 who received sequential palliative topical therapy [1]. This study established a consensus that therapy in MF should be based on stage of disease and aimed at disease palliation rather than an aggressive intent to cure. Therefore the current consensus is that patients with early

Table 57.7 Treatment algorithm for cutaneous T-cell lymphoma.

Stage Prognostic group	1st line	2nd line	3rd line
Stage IA-IIA Good prognosis	SDT	SDT + α-interferon/ bexarotene	TSEB Trials
Stage III Intermediate prognosis	PUVA ECP/bexarotene/ α-interferon	TSEB Single-agent chemotherapy Antibody therapies	Trials RISCT
Stage IIB/IV* Poor prognosis	Radiotherapy (TSEB) Chemotherapy (single/multiagent)	Trials Toxin therapy RISCT	Palliation

SDT, skin directed therapy; RISCT, reduced intensity stem cell transplant; TSEB, total skin electron beam therapy; ECP, extracorporeal photopheresis.

* Maintenance therapy with SDT ± α interferon/bexarotene for residual skin disease (patches/plaques).

stage disease should receive skin directed therapies. Systemic therapies are reserved for those with either early stage disease resistant to skin directed therapy or advanced disease (Table 57.7) [2]. The precise role of a wide variety of novel therapeutic approaches remains to be established but these studies have helped to develop an emerging consensus about the optimal methods for assessment of disease response assessment [3–4].

References

1 Kaye FJ, Bunn PA Jr, Steinberg SM *et al*. A randomized trial comparing combination electron-beam radiation and chemotherapy with topical therapy in the initial treatment of mycosis fungoides. *N Engl J Med* 1989; **321**: 1784–90.

2 Trautinger F, Knobler R, Willemze R *et al*. EORTC consensus recommendations for the treatment of mycosis fungoides/Sezary syndrome. *Eur J Cancer* 2006; **42**: 1014–30.

3 Schmid M, Bird P, Dummer R *et al*. Tumour burden index as a prognostic tool for cutaneous T-cell lymphoma. *Arch Dermatol* 1999; **135**: 1204–8.

4 Stevens S, Ke M, Parry E *et al*. Quantifying skin disease burden in mycosis fungoides-type cutaneous T-cell lymphomas. *Arch Dermatol* 2002; **138**: 42–8.

Skin directed therapy

Topical steroids

For patients with limited early stage MF, life expectancy may not be adversely affected and it is acceptable to simply use emollients with or without moderate-potency topical steroids. Potent topical corticosteroids can produce a clinical response, although this is usually short-lived [1].

Reference

1 Zackheim H, Kashani-Sabet M, Amin S. Topical corticosteroids for mycosis fungoides. *Arch Dermatol* 1998; **134**: 949–54.

Topical chemotherapy—nitrogen mustard (mechlorethamine) and carmustine (BCNU)

Topical mechlorethamine (nitrogen mustard) 0.01% or 0.02%, either as an aqueous solution (normal saline) or ointment base (emulsifying ointment), is effective for superficial disease with response rates of 51–80% for IA, 26–68% for IB and 61% for IIA disease [1–5]. The aqueous solution is relatively unstable, and the ointment base—more commonly than the aqueous solution—can cause irritancy or an allergic dermatitis in sensitized individuals (35–58%), but efficacy is similar. This product must not be used in pregnancy and there are rare reports of non-melanoma skin cancer in patients treated with topical mechlorethamine. There is no consensus as to whether mechlorethamine should be applied to individual lesions or to the whole skin, daily or twice weekly, or about the duration of topical therapy after a clinical remission has been produced; responses can be sustained for prolonged periods.

Topical BCNU is an alternative topical chemotherapeutic agent in MF, with similar efficacy to mechlorethamine as indicated by response rates of 86% in stage IA, 47% in stage IB and 55% in stage IIA patients [6]. Alternate day or daily treatment with 10 mg BCNU in 60 mL dilute alcohol (95%) or 20–40% BCNU ointment can be used. Hypersensitivity reactions occur less often (5–10%) than with mechlorethamine. All patients treated topically with carmustine should have regular monitoring of their full blood counts and treatment is normally given for only 2–4 weeks to avoid myelosuppression; maintenance therapy is contraindicated.

References

1 Van Scott EJ, Kalmanson JD. Complete remissions of mycosis fungoides lymphoma induced by topical nitrogen mustard (HN2): control of delayed hypersensitivity to HN2 by desensitization and by induction of specific immunologic tolerance. *Cancer* 1973; **32**: 18–30.

2 Hoppe R, Abel E, Deneau D, Price N. Mycosis fungoides: management with topical nitrogen mustard. *J Clin Oncol* 1987; **5**: 1796–803.

3 Ramsay DL, Halperin PS, Zeleniuch-Jacquotte A. Topical mechlorethamine therapy for early stage mycosis fungoides. *J Am Acad Dermatol* 1988; **19**: 684–91.

4 Vonderheid E, Tan E, Kantor AF *et al*. Long-term efficacy, curative potential and carcinogenicity of mechlorethamine chemotherapy in cutaneous T-cell lymphoma. *J Am Acad Dermatol* 1989; **20**: 416–28.

5 Kim Y, Martinez G, Varghese A *et al*. Topical nitrogen mustard in the management of mycosis fungoides: update of the Stanford experience. *Arch Dermatol* 2003; **139**: 165–73.

6 Zackheim HS, Epstein EH Jr, Crain WR. Topical carmustine (BCNU) for cutaneous T cell lymphoma: a 15 year experience in 143 patients. *J Am Acad Dermatol* 1990; **22**: 802–10.

Topical retinoids

Recently, a novel retinoid, 1% Targretin (bexarotene) gel, has been approved by the Food and Drug Administration (FDA) for topical therapy in stage I MF in patients who are resistant to, or intolerant of, other topical therapies [1]. In open uncontrolled studies, response rates of 63% with 21% complete response rates have been reported in 67 patients with early stage (IA–IIA) disease. Median time to and duration of response were 20 and 99 weeks, respectively.

Other topical therapies

There has only been one randomized placebo-controlled trial of topical therapy in MF. Topical peldesine cream (BCX-34, an inhibitor of the purine nucleoside phosphorylase enzyme) showed no benefit, compared to vehicle, with complete responses of 28% and 24%, respectively, emphasizing the difficulties in interpretation of uncontrolled studies of topical therapy in early stages of MF [2].

References

1 Breneman D, Duvic M, Kuzel T *et al.* Phase I and II trial of bexarotene gel for skin-directed treatment of patients with cutaneous T-cell lymphoma. *Arch Dermatol* 2002; **138**: 325–32.

2 Duvic M, Olsen E, Omura G *et al.* A phase III, randomized, double-blind, placebo-controlled study of peldesine (BCX-34) cream as topical therapy for cutaneous T-cell lymphoma. *J Am Acad Dermatol* 2001; **44**: 940–7.

Phototherapy and photochemotherapy

The clinical benefit of PUVA (photochemotherapy) was noted over 25 years ago and complete response rates of 79–88% in stage IA and 52–59% in stage IB disease have been reported [1–5]. Flexural sites ('sanctuary sites') often fail to respond completely and the duration of response varies. There is no significant response in tumour (IIB) stage disease. One study has shown that 56% of stage IA and 39% of stage IB complete PUVA responders had no recurrence of disease after 44 months follow-up without maintenance therapy [6]. A recent retrospective study on long-term outcome for MF patients treated with PUVA reported that 50% of patients with a higher cumulative UVA dose achieved a longer duration of response but these patients also received maintenance therapy while those who relapsed early did not [7]. Furthermore, there was no difference in clinical outcome in terms of disease progression or survival in the two groups. Maintenance therapy is rarely effective at preventing relapse and therefore should be avoided if possible so as to limit the total cumulative dose, as patients will often require repeated courses over many years.

PUVA is an ideal therapy for patients with stage IB–IIA disease who are intolerant of, or fail to respond to, topical therapies such as mechlorethamine, although both therapies can be complementary for some patients. Treatment regimens have varied in reported studies of PUVA in CTCL with two to four times weekly and different protocols for incremental dosage, but usually two to three times weekly treatment is acceptable until disease clearance or best partial response. Many patients will inevitably have a high total cumulative UVA dosage and the risks of non-melanoma and melanoma skin cancer are consequently increased for these patients. Efforts should be made to restrict the total PUVA dosage to less than 200 treatment sessions or a total cumulative dose of 1200 J/cm^2. In some circumstances patients may receive a greater total dosage if clinically justified and with the consent of the patient. PUVA remains one of the most effective therapies for patients with early stage disease but there are surprisingly no data to establish if PUVA can improve overall survival or reduce rates of disease progression in stage IB. PUVA therapy is rarely tolerated in erythrodermic (stage III) disease but occasional patients will respond repeatedly.

Broad- and narrow-band UVB and high-dose UVA-1 phototherapy have also been used in MF with success [8–10]. There have been no adequate comparative studies of different phototherapy regimens in CTCL but narrow-band UVB therapy may be an effective option in patients with patches as opposed to plaques.

References

1 Vella Briffa D, Warin AP. Photochemotherapy in mycosis fungoides: a study of 73 patients. *Lancet* 1980; **ii**: 49–53.

2 Molin L, Thomsen K, Volden G *et al.* Photochemotherapy (PUVA) in the pre-tumour stage of mycosis fungoides. *Acta Derm Venereol (Stockh)* 1980; **61**: 47–51.

3 Gilchrest BA, Parrish JA, Tannenbaum L *et al.* Oral methoxsalen photochemotherapy of mycosis fungoides. *Cancer* 1976; **38**: 683–9.

4 Abel EA, Sendagorta E, Hoppe RT *et al.* PUVA treatment of erythrodermic and plaque-type mycosis fungoides. *Arch Dermatol* 1987; **123**: 897–901.

5 Honigsmann Brenner W, Rauschmeier W, Konrad K, Wolff K. Photochemotherapy for cutaneous T cell lymphoma. *J Am Acad Dermatol* 1984; **10**: 238–45.

6 Hermann J, Roenigk H, Hurria A *et al.* Treatment of mycosis fungoides with photochemotherapy (PUVA): long-term follow-up. *J Am Acad Dermatol* 1995; **33**: 234–42.

7 Querfeld C, Rosen S, Kuzel T *et al.* Long term follow-up of patients with early stage cutaneous T-cell lymphoma who achieved complete remission with psoralen plus UV-A monotherapy. *Arch Dermatol* 2005; **141**: 305–11.

8 Ramsey D, Lish K, Yalowitz C, Soter N. Ultraviolet-B phototherapy for early stage cutaneous T-cell lymphoma. *Arch Dermatol* 1992; **128**: 931–3.

9 Clark C, Dawe R, Evans A *et al.* Narrow-band TL-01 phototherapy for patch stage mycosis fungoides. *Arch Dermatol* 2000; **136**: 748–52.

10 Zane C, Leali C, Airo P *et al.* 'High dose' UVA-1 therapy of widespread plaque-type, nodular and erythrodermic mycosis fungoides. *J Am Acad Dermatol* 2001; **44**: 629–33.

Radiotherapy and electron beam therapy

MF and other CTCL variants are very radiosensitive malignancies and individual thick plaques, or tumours can be treated successfully with low-dose superficial radiotherapy (orthovoltage or electrons) often administered in several fractions (e.g. two or three fractions of 400 cGy at 80–120 kV). Large tumours may require a different energy source. Radiotherapy is often used with other therapeutic modalities such as PUVA, and closely adjacent and overlapping fields can often be retreated because of the low doses used [1].

Whole body TSEB therapy has been evaluated extensively in CTCL [2,3]. Different field arrangements have been used in an attempt to treat the whole skin uniformly to a depth of 1 cm with various total dosage administered and additional radiotherapy to shielded areas. A meta-analysis of open uncontrolled and mostly retrospective studies of TSEB as monotherapy in 952 patients with CTCL has established that responses are stage dependent, with complete responses of 96% in stage IA, IB and IIA disease but disease relapse rates are very high, indicating that this approach is not curative even in early stage disease [4]. In stage IIB disease, complete responses are less common (36%), but erythrodermic (stage III) disease shows complete responses of 60%. Greater skin surface dose (32–36 Gy) and higher energy (4–6 MeV electrons) are associated with a higher rate of complete response and 5-year relapse-free survivals of 10–23% were noted [4]. A retrospective study of erythrodermic disease has also shown 60% complete responses with 26% progression-free at 5 years [5]. In this study, the overall median survival was 3.4 years with a median dose of 32 Gy given as five weekly fractions over 6–9 weeks. Patients with stage III disease did best compared to those with significant nodal or haematological (IVA–B) disease. The duration of response was also longer for those who received more than 20 Gy using 4–9 MeV [5].

Comparative studies of TSEB versus topical mechlorethamine in early stage MF show similar response rates and duration of response, suggesting that TSEB therapy should be reserved for those who fail first- and second-line therapies [6,7]. Adverse effects of TSEB include temporary alopecia, telangiectasia and skin malignancies, and the treatment is only available in a limited number

of centres [8]. Although TSEB is usually only given once in a lifetime, several reports have documented patients who have received two or three courses, although the total dosage tolerated and duration of response have been lower with subsequent courses [9,10]. EORTC consensus guidelines have been produced for TSEB [11].

References

1 Cotter G, Baglan R, Wasserman T, Mill W. Palliative radiation treatment of cutaneous mycosis fungoides: a dose–response. *Int J Radiat Oncol Biol Phys* 1983; **9**: 1477–80.
2 Hoppe RT, Cox RS, Fuks ZY *et al.* Electron-beam therapy for mycosis fungoides: the Stanford University experience. *Cancer Treat Rep* 1979; **63**: 691–700.
3 Spittle MF. Electron beam therapy in England. *Cancer Treat Rep* 1979; **63**: 639–41.
4 Jones G, Hoppe R, Glatstein E. Electron beam treatment for cutaneous T-cell lymphoma. *Haematol Oncol Clin North Am* 1995; **9**: 1057–76.
5 Jones G, Rosenthal D, Wilson L. Total skin electron beam radiation for patients with erythrodermic cutaneous T-cell lymphoma (mycosis fungoides and the Sézary syndrome). *Cancer* 1999; **85**: 1985–95.
6 Hamminga B, Noordijk EM, van Vloten WA. Treatment of mycosis fungoides: total-skin electron-beam irradiation versus topical mechlorethamine therapy. *Arch Dermatol* 1982; **118**: 150–3.
7 Chinn D, Chow S, Kim Y, Hoppe R. Total skin electron beam therapy with or without adjuvant topical nitrogen mustard or nitrogen mustard alone as initial treatment of T2 and T3 mycosis fungoides. *Int J Rad Onc Biol Phys* 1999; **43**: 951–8.
8 Price NM. Radiation dermatitis following electron beam therapy: an evaluation of patients 10 years after total skin irradiation for mycosis fungoides. *Arch Dermatol* 1978; **114**: 63–6.
9 Becker M, Hoppe R, Knox S. Multiple courses of high dose total skin electron beam therapy in the management of mycosis fungoides. *Int J Radiat Oncol Biol Phys* 1995; **30**: 1445–9.
10 Wilson L, Quiros P, Kolenik S *et al.* Additional courses of total skin electron beam therapy in the treatment of patients with recurrent cutaneous T-cell lymphoma. *J Am Acad Dermatol* 1996; **35**: 69–73.
11 Jones G, Kacinski B, Wilson L *et al.* Total skin electron beam radiation in the management of mycosis fungoides: consensus of the European Organisation for Research and Treatment of Cancer (EORTC) Cutaneous Lymphoma Project Group. *J Am Acad Dermatol* 2002; **47**: 364–70.

Systemic therapy

Immunotherapy

Different forms of immunotherapy have been evaluated in CTCL, with the intention of enhancing antitumour host immune responses by promoting the generation of cytotoxic T cells and Th1 cytokine responses. Studies of IFN-α have shown overall response rates of 45–74%, with complete responses of 10–27% [1–3]. Various regimens have been employed (from 3 MU three times weekly to 36 MU/day) and it appears that response rates are higher for larger-dosage regimens (overall responses of 78% compared to 37% for the lower-dosage regimen) [2]. Overall response rates are also higher in early (IB–IIA 88%) compared to late (III–IV 63%) stages of disease [2].

Other small pilot studies have shown that both IL-12 and IFN-γ can produce clinical responses in CTCL but their therapeutic value remains to be established [4,5]. Ciclosporin has been used in CTCL, particularly in erythrodermic variants, to relieve severe pruritus but there is some evidence that treatment may actually cause rapid disease progression and its use in CTCL is not recommended [6].

References

1 Bunn P, Ihde D, Foon K. The role of recombinant interferon-α2a in the therapy of cutaneous T-cell lymphomas. *Cancer* 1986; **57**: 1689–95.
2 Olsen E, Rosen S, Vollmer R *et al.* Interferon-α2a in the treatment of cutaneous T-cell lymphoma. *J Am Acad Dermatol* 1989; **20**: 395–407.
3 Papa G, Tura S, Mandelli F *et al.* Is interferon-α in cutaneous T-cell lymphoma a treatment of choice? *Br J Haematol* 1991; **79**: 48–51.
4 Rook A, Wood G, Yoo E *et al.* Interleukin-12 therapy of cutaneous T-cell lymphoma induces lesion regression and cytotoxic T-cell responses. *Blood* 1999; **94**: 902–8.
5 Kaplan E, Rosen S, Norris D *et al.* Phase II study of recombinant interferon-γ for treatment of cutaneous T-cell lymphoma. *J Natl Cancer Inst* 1990; **82**: 208–12.
6 Cooper D, Braverman I, Sarris A *et al.* Cyclosporine treatment of refractory T-cell lymphomas. *Cancer* 1993; **71**: 2335–41.

Retinoids

Oral retinoid therapy has been used both as a single agent and in combination with interferons and PUVA in the management of MF (see below). A non-randomized, small study comparing acitretin and isotretinoin in MF and SS has shown no obvious differences, with complete responses of 21% in both groups [1].

Phase II and III studies of a novel synthetic retinoid in CTCL prompted licensing of this retinoid for MF/SS [2,3]. Bexarotene (Targretin) is the only retinoid that selectively binds and activates the RXR receptor. Bexarotene has been shown to promote apoptosis and inhibit cell proliferation. It is relatively selective and therefore should have little effect on the RAR receptor involved in cell differentiation. In phase II and III studies of 152 patients with CTCL, response rates from 20% to 67% have been reported [2,3]. The most effective tolerated oral dosage is 300 mg/m^2/day, although responses improve with higher dosage. Side effects are transient and generally mild but most patients while on therapy require treatment for hyperlipidaemia and central (hypothalamic) hypothyroidism according to an algorithm [4,5]. At a dosage of 300 mg/m^2/day in early stage disease (IA, IB, IIA), overall response rates of 54% have been noted [2], while advanced MF patients (stage IIB–IVB) have shown overall response rates of 45% with a notable reduction in pruritus in stage III disease [3].

References

1 Molin L, Thomsen K, Volden G *et al.* Oral retinoids in mycosis fungoides and Sézary syndrome: a comparison of isotretinoin and etretinate. *Acta Derm Venereol (Stockh)* 1987; **67**: 232–6.
2 Duvic M, Martin A, Kim Y *et al.* Phase 2 and 3 clinical trial of oral bexarotene (Targretin capsules) for the treatment of refractory or persistent early stage cutaneous T-cell lymphoma. *Arch Dermatol* 2001; **137**: 581–93.
3 Duvic M, Hymes K, Heald P *et al.* Bexarotene is effective and safe for treatment of refractory advanced-stage cutaneous T-cell lymphoma: multinational phase II–III trial results. *J Clin Oncol* 2001; **19**: 2456–71.
4 Gniadecki R, Assaf C, Bagot M *et al.* The optimal use of Bexarotene in cutaneous T-cell lymphoma. *Br J Dermatol* 2007; **157**: 433–40.
5 Assaf C, Bagot M, Dummer R *et al.* Minimizing adverse side-effects of oral bexarotene in cutaneous T-cell lymphoma: an expert opinion. *Br J Dermatol* 2006; **155**: 261–6.

Combination therapy

Combined IFN-α and retinoids produces similar response rates to IFN alone and is not recommended [1]. Studies comparing PUVA and IFN-α with IFN-α and acitretin in early stage disease have shown complete response rates of 70% and 38%, respectively, but there are no data on duration of response [2]. Uncontrolled studies

of combined PUVA and IFN-α (maximum tolerated dosage 12 MU/m^2 three times weekly) in MF and SS have shown overall response rates of 100%, with 62% complete response rates [3]. This combination may also be useful in patients with resistant early stage disease, such as those with thick plaques and folliculotropic disease. Open studies comparing PUVA with combined PUVA and acitretin have shown a similar complete response rate (73 and 72%, respectively), although the cumulative dose to best response was lower in patients receiving the combination therapy [4]. Current randomized controlled studies are comparing: (i) PUVA versus PUVA and IFN-α in early stage MF; (ii) the role of maintenance IFN-α after induction of a complete response with PUVA and IFN; and (iii) PUVA alone compared to PUVA combined with bexarotene. At present there are few data on the impact on disease-free and overall survival.

References

1 Dreno B, Claudy A, Meynadier J *et al*. The treatment of 45 patients with cutaneous T-cell lymphoma with low doses of interferon-α2a and etretinate. *Br J Dermatol* 1991; **125**: 456–9.

2 Stadler R, Otte H, Luger T *et al*. Prospective randomized multicentre clinical trial on the use of interferon-α2a plus acitretin versus interferon-α2a plus PUVA in patients with cutaneous T-cell lymphoma stages I and II. *Blood* 1998; **10**: 3578–81.

3 Kuzel T, Roenigk H, Samuelson E *et al*. Effectiveness of interferon-α2a combined with phototherapy for mycosis fungoides and the Sézary syndrome. *J Clin Oncol* 1995; **13**: 257–63.

4 Thomson K, Hammar H, Holin L *et al*. Retinoids plus PUVA (RePUVA) and PUVA in mycosis fungoides, plaque stage: a report from the Scandinavian mycosis fungoides group. *Acta Derm Venereol (Stockh)* 1989; **69**: 536–8.

Systemic chemotherapy

MF and SS are relatively chemoresistant and responses are usually short lived [1]. This may partly reflect the low proliferative rate of tumour cells and a high prevalence of inactivating *p53* mutations, which produce a relative resistance to tumour cell apoptosis. A systematic review of published data on different regimens has shown complete response rates of 33% in 526 patients treated with single-agent chemotherapy with a median duration of 3–22 months [2]. Combination chemotherapy regimes (including cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP)) in 331 patients produced complete response rates of 38%, with a median duration of 5–41 months [2]. CTCL patients are prone to infection and septicaemia is a common preterminal event.

Chemotherapy should not be used in patients with early stage IA, IB or IIA disease. However, treatment of stage IIB and IVA disease remains problematic. Individual tumours and effaced peripheral lymph nodes will respond to superficial radiotherapy and additional chemotherapy should be considered in patients with a good performance status (WHO 0–2). However, responses are likely to be short-lived and patients should be entered into ongoing clinical trials. Single-agent chemotherapy that has been shown to produce a clinical response in stage IIB–IVB disease, and especially erythrodermic patients, includes oral chlorambucil (four to six cycles of 0.15–0.2 mg/kg/day for 2 weeks every 28 days), methotrexate and etoposide, and the intravenous use of the purine analogues 2-deoxycoformycin, 2-chlorodeoxyadenosine and fludarabine [2]. Open studies of 2-deoxycoformycin in MF and SS have reported response rates of 35–71%, with complete response rates of 10–33% [3,4]. Methotrexate has been reported to produce a complete response rate of 41% in 29 patients with erythrodermic (stage III/T4) disease, with a median survival of 8.4 years with single weekly doses of 5–125 mg. However, this study was uncontrolled and it is unclear if the patients included represented an usually good prognostic group [5]. In contrast, liposomal doxorubicin [6,7] and gemcitabine [8,9] have shown excellent responses in stage IIB and IVA non-erythrodermic MF with overall responses of 88% (44% complete remission (CR)) and 70–85% (10–22% CR), respectively, but once again the duration of response is often short-lived with a median duration of response of 10 months for CR patients treated with gemcitabine [9]. In a further study, liposomal doxorubicin showed similar responses (56% overall response rate (ORR) with 20% CR) in both transformed MF and erythrodermic SS patients [10].

Recent pilot studies assessing the use of TSEB and/or total body irradiation (TBI) combined with high-dose conditioning chemotherapy prior to autologous stem cell transplantation in patients with stage IIB–IVA disease have shown good clinical responses [11,12] but high relapse rates and there are no data available at present to indicate if this approach affects disease-free or overall survival. Allogeneic stem cell or bone marrow transplantation has only been used in a few patients with encouraging results [13–15], but the associated mortality suggests that this approach is difficult to justify. However, reduced intensity allogeneic stem cell transplantation has shown promising results in small studies [16] with clear evidence of a graft-versus-lymphoma effect indicating that this may potentially have a durable effect for selected CTCL patients [17].

References

1 Kaye FJ, Bunn PA Jr, Steinberg SM *et al*. A randomized trial comparing combination electron-beam radiation and chemotherapy with topical therapy in the initial treatment of mycosis fungoides. *N Engl J Med* 1989; **321**: 1784–90.

2 Bunn P, Hoffman S, Norris D, Golitz L, Aeling J. Systemic therapy of cutaneous T-cell lymphomas (mycosis fungoides and the Sézary syndrome). *Ann Intern Med* 1994; **121**: 592–602.

3 Kurzrock R, Pilat S, Duvic M. Pentostatin therapy of T-cell lymphomas with cutaneous manifestations. *J Clin Oncol* 1999; **17**: 3117–21.

4 Deardon C, Matutes E, Catovsky D. Pentostatin treatment of cutaneous T-cell lymphoma. *Oncology* 2000; **14**: 37–40.

5 Zackheim H, Kashani Sabet M, Hwang ST. Low dose methotrexate to treat erythrodermic cutaneous T cell lymphoma. *J Am Acad Dermatol* 1996; **34**: 626–31.

6 Wollina U, Graefe T, Kaatz M. Pegylated doxorubicin for primary cutaneous T-cell lymphoma: a report on 10 patients with follow-up. *J Cancer Res Clin Oncol* 2001; **127**: 128–34.

7 Wollina U, Dummer R, Brockmayer N *et al*. Multicentre study of pegylated liposomal doxorubicin in patients with cutaneous T-cell lymphoma. *Cancer* 2003; **98**: 993–1001.

8 Zinzani P, Baliva G, Magagnoli M *et al*. Gemcitabine treatment in pretreated cutaneous T-cell lymphoma: experience in 44 patients. *J Clin Oncol* 2000; **18**: 2603–6.

9 Marchi E, Alinari L, Tani M *et al*. Gemcitabine as frontline treatment for cutaneous T-cell lymphoma. *Cancer* 2005; **104**: 2437–41.

10 Quereux G, Marques S, Nguyen J-M *et al*. Prospective multicenter study of pegylated liposomal doxorubicin treatment in patients with advanced or refractory mycosis fungoides or Sezary syndrome. *Arch Dermatol* 2008; **144**: 727–33.

11 Olavarria E, Child F, Woolford A *et al*. T-cell depletion and autologous stem cell transplantation in the management of tumour stage mycosis fungoides with peripheral blood involvement. *Br J Haematol* 2001; **114**: 624–31.

12 Bigler R, Crilley P, Micaily B *et al.* Autologous bone marrow transplantation for advanced stage mycosis fungoides. *Bone Marrow Tranplant* 1991; **7**: 133–7.
13 Burt R, Guitart J, Traynor A *et al.* Allogeneic haematopoietic stem cell transplantation for advanced mycosis fungoides: evidence of a graft-versus-tumour effect. *Bone Marrow Transplant* 2000; **25**: 111–3.
14 Molina A, Nademanee A, Arber D, Forman S. Remission of refractory Sézary syndrome after bone marrow transplantation from a matched unrelated donor. *Biol Blood Marrow Transplant* 1999; **5**: 400–4.
15 Guitart J, Wickless S, Oyama Y *et al.* Long term remission after allogeneic hematopoietic stem cell transplantation for refractory cutaneous T-cell lymphoma. *Arch Dermatol* 2002; **138**: 1359–65.
16 Molina A, Zain J, Arber D *et al.* Durable clinical, cytogenetic and molecular remissions after allogeneic hematopoietic cell transplantation for refractory Sezary syndrome and mycosis fungoides. *J Clin Oncol* 2005; **23**: 6163–71.
17 Duarte R, Schmitz N, Servitje O, Sureda A. Haematopoietic stem cell transplantation for patients with primary cutaneous T-cell lymphoma. *Bone Marrow Transplant* 2008; **41**: 597–604.

Photopheresis

Extracorporeal photopheresis (ECP) involves administration of oral psoralen, followed by *ex vivo* collection of an enriched buffy coat preparation using a cell separator. These leukocytes are then passed through thin polythene tubing with exposure to UVA and the cells thereafter returned to the patient. This regimen is repeated on 2 successive days and the 2-day cycle repeated monthly or fortnightly in an accelerated regimen. A specially designed photopheresis apparatus is required for this technique. The underlying theory is that a proportion of the UVA-exposed leukocytes, including some tumour lymphocytes, undergo apoptosis and that dendritic cells are activated during the *ex vivo* circulation with induction of a host antitumour immune response after the treated cells are returned to the patient. Different models of autoimmune disease support this suggestion [1,2] and recent evidence has also shown activation of dendritic cells during an expanded period of *ex vivo* incubation overnight (transimmunization) [3].

ECP is licensed by the FDA for the treatment of CTCL but there are no randomized studies to clarify whether ECP has an impact on overall survival. The original open study of ECP in 29 patients with erythrodermic CTCL reported a response rate of 73% but response rates in patients with earlier stages of MF were much lower (38%) [4]. Subsequently, a median survival of 62 months was reported in the original cohort of 29 erythrodermic patients, which compares favourably with historical controls (30 months) [5]. A study of 33 patients with SS treated with ECP reported a median survival of 39 months, which was similar to historical controls from the same institution [6]. Other studies have shown more prolonged median survival data [7]. An accelerated regimen consisting of nine collections rather than six for each cycle and an increase to treatment every 2 weeks has shown overall response rates of 50%, with 18% complete responses in erythrodermic disease [8]. A systematic review of response rates in erythrodermic disease (stage III–IVA) with ECP has shown overall responses of 35–71%, with complete responses of 14–26% [9]. Other studies are more difficult to interpret because they have either involved small numbers, patients with earlier stages of disease and in most studies many of the patients have been on other concurrent therapies [10,11]. Preliminary pilot studies suggest that the combination of IFN-α and ECP is more effective than ECP alone but this has yet to be confirmed in randomized studies [12,13]. There are isolated case reports of combined ECP and IFN-α and/or bexarotene that have induced complete clinical and molecular responses [14–16].

Randomized, controlled trials of ECP are required to establish an effect on disease-free and overall survival. There have been claims that the CD8 count is critical in predicting whether patients will respond to ECP [5], although others have provided evidence that the total baseline Sézary count is the only predictor of response [17].

References

1 Perez M, Edelson R, Laroche L, Berger C. Inhibition of anti-skin allograft immunity by infusion with syngeneic photoinactivated effector lymphocytes. *J Invest Dermatol* 1989; **92**: 669–76.
2 Berger C, Perez M, Laroche L, Edelson R. Inhibition of autoimmune disease in a murine model of systemic lupus erythematosus induced by exposure to syngeneic photoinactivated lymphocytes. *J Invest Dermatol* 1990; **94**: 52–7.
3 Berger C, Xu A, Hanlon D *et al.* Induction of tumour loaded dendritic cells. *Int J Cancer* 2001; **91**: 438–47.
4 Edelson R, Berger C, Gasparro F *et al.* Treatment of cutaneous T cell lymphoma by extracorporeal photochemotherapy. *N Engl J Med* 1987; **316**: 297–303.
5 Heald P, Rook A, Perez M *et al.* Treatment of erythrodermic cutaneous T cell lymphoma with extracorporeal photochemotherapy. *J Am Acad Dermatol* 1992; **27**: 427–33.
6 Fraser-Andrews E, Seed P, Whittaker S, Russell-Jones R. Extracorporeal photophoresis in Sézary syndrome: no significant effect in the survival of 44 patients with a peripheral blood T-cell clone. *Arch Dermatol* 1998; **134**: 1001–5.
7 Zic J, Stricklin G, Greer J *et al.* Long-term follow-up of patients with cutaneous T-cell lymphoma treated with extracorporeal photochemotherapy. *J Am Acad Dermatol* 1996; **35**: 935–45.
8 Duvic M, Hester J, Lemak N. Photophoresis therapy for cutaneous T-cell lymphoma. *J Am Acad Dermatol* 1996; **35**: 573–9.
9 Russell-Jones R. Extracorporeal photophoresis in cutaneous T-cell lymphoma: inconsistent data underline the need for randomized studies. *Br J Dermatol* 2000; **142**: 16–21.
10 Gottlieb S, Wolfe J, Fox F *et al.* Treatment of cutaneous T-cell lymphoma with extracorporeal photophoresis monotherapy and in combination with recombinant interferon-α: a 10-year experience at a single institution. *J Am Acad Dermatol* 1996; **35**: 946–57.
11 Vonderheid E, Bigler R, Greenberg A, Neukum S, Micaily B. Extracorporeal photophoresis and recombinant interferon-α2b in Sézary syndrome. *Am J Clin Oncol* 1994; **17**: 255–63.
12 Wollina U, Looks A, Meyer J *et al.* Treatment of stage II cutaneous T-cell lymphoma with interferon-α2a and extracorporeal photochemotherapy: a prospective controlled trial. *J Am Acad Dermatol* 2001; **44**: 253–60.
13 Dippel E, Schrag H, Goerdt S, Orfanos C. Extracorporeal photophoresis and interferon-α in advanced cutaneous T-cell lymphoma. *Lancet* 1997; **350**: 32–3.
14 Haley H, Davis D, Sams M. Durable loss of a malignant T-cell clone in a stage IV cutaneous T-cell lymphoma patient treated with high-dose interferon and photophoresis. *J Am Acad Dermatol* 1999; **41**: 880–3.
15 Yoo E, Cassin M, Lessin S, Rook A. Complete molecular remission during biologic response modifier therapy for Sézary syndrome is associated with enhanced helper T type I cytokine production and natural killer cell activity. *J Am Acad Dermatol* 2001; **45**: 208–16.
16 Suchin K, Cucchiara A, Gottlieb S *et al*. Treatment of cutaneous T-cell lymphoma with combined immunomodulatory therapy. *Arch Dermatol* 2002; **138**: 1054–60.
17 Evans A, Wood B, Scarisbrick J *et al.* Extracorporeal photophoresis in Sézary syndrome: haematologic parameters as predictors of response. *Blood* 2001; **98**: 1298–301.

Toxin therapies

Denileukin diftitox, a DAB_{389}–IL-2 fusion toxin (Ontak USA/Onzar Europe), received provisional FDA approval for the treatment of

resistant or recurrent CTCL after completion of open-label, phase I/II studies. Onzar is a recombinant fusion protein consisting of peptide sequences for the enzymatically active domain (389) of diphtheria toxin and the membrane translocation domain of IL-2 that is capable of inhibiting protein synthesis in tumour cells expressing high levels of the IL-2 receptor, resulting in cell death. Phase III studies of 71 heavily pre-treated patients with stage IB–IVA, and more than 20% $CD25^+$ T cells, showed an overall response rate of 30%, including 10% with complete responses [1]. Patients were assessed with a rigorous skin scoring system and documented responses were defined as lasting at least 6 weeks. The median duration of response was 6.9 months (range 2.7–46.1 months). The optimally tolerated intravenous regimen is 18 µg/kg/day for 5 days, repeated every 21 days for four to eight cycles. Adverse effects include fever, chills, myalgia, nausea and vomiting, and a mild increase in transaminase levels. Acute hypersensitivity reactions occurred in 60%, invariably within 24 h and during the initial infusion but this can be prevented with steroid pre-treatment [2]. A vascular leak syndrome characterized by hypotension, hypoalbuminaemia and oedema was defined retrospectively within the first 14 days of a given dose in 25% of patients. Myelosuppression is rare. Five per cent of adverse effects are severe or life-threatening. The clinical relevance of antibody responses to denileukin diftitox is unclear. The duration of clinical response has not yet been established and current studies are comparing different regimens of Onzar and are also assessing the use of this therapy in $CD25^-$ tumours. This therapy is not likely to be appropriate for early stage disease but may be useful in advanced disease.

References

1 Olsen E, Duvic M, Frankel A *et al.* Pivotal phase III trial of two dose levels of denileukin diftitox for the treatment of cutaneous T-cell lymphoma. *J Clin Oncol* 2001; **19**: 376–88.

2 Foss F, Bacha P, Osann K *et al*. Biological correlates of acute hypersensitivity events with DAB(389)IL-2 (denileukin diftitox, ONTAK) in cutaneous T-cell lymphoma: decreased frequency and severity with steroid premedication. *Clin Lymphoma* 2001; **1**: 298–302.

Monoclonal antibody therapy

The first antibody approach was a humanized chimeric anti-CD4 monoclonal antibody used to treat eight patients with CTCL, of whom seven showed a clinical response but this was of short duration [1]. A radiolabelled anti-CD5 antibody has also been used in MF with some objective results [2] and CAMPATH (anti-CD52/alemtuzumab) has also been studied in patients (stage III) with overall responses in 55–85% and a median response duration/time to treatment failure of 12 months [3,4]. Studies of a fully humanized anti-CD4 antibody (Zanolimumab) in bexarotene-refractory MF/SS have shown overall responses of 56% and median response duration of 81 weeks [5].

References

1 Knox S, Hoppe R, Maloney D *et al.* Treatment of cutaneous T-cell lymphoma with chimeric anti-CD4 monoclonal antibody. *Blood* 1996; **87**: 893–9.

2 Foss F, Raubitscheck A, Mulshine J *et al.* Phase I study of the pharmacokinetics of a radioimmunoconjugate, 90Y–T101, in patients with CD5-expressing leukaemia and lymphoma. *Clin Cancer Res* 1998; **4**: 2691–700.

3 Lundin J, Hagberg H, Repp R *et al*. Phase 2 study of alemtuzumab (anti-CD52 monoclonal antibody) in patients with advanced mycosis fungoides/Sezary syndrome. *Blood* 2003; **101**: 4267–72.

4 Bernengo M, Quaglino P, Comessantti A *et al*. Low-dose intermittent alemtuzumab in the treatment of Sezary syndrome: clinical and immunologic findings in 14 patients. *Haematologica* 2007; **92**: 784–94

5 Kim Y, Duvic M, Obitz E *et al*. Clinical efficacy of zanolimimab (HuMax-CD4): two phase 2 studies in refractory cutaneous T-cell lymphoma. *Blood* 2007: **109**: 4655–62.

Histone deacetylase inhibitors

A novel class of drugs has been assessed in both MF and SS in a series of open label studies. These histone deacetylase (HDAC) inhibitors affect gene expression by inhibiting deacetylation of histone proteins which causes the chromatin structure to adopt an open configuration therefore allowing binding of transcription factors to promoter regions and gene transcription. While the effect of these drugs on histone proteins within chromatin is best understood there are almost certainly widespread effects on non-histone proteins as well, which may be therapeutically important. There are four classes of HDAC inhibitors and several including SAHA and depsipeptide have been studied in both MF and SS [1–3]. Phase I/II studies of SAHA (vorinostat) have shown overall response rates of 30% with a median time to progression of 5 months [1,2]. This has prompted the US Food and Drug Administration to license vorinostat for second line-therapy of MF/SS. Side-effects include lethargy, thrombocytopenia. gastrointestinal symptoms and prolongation of the QT interval. Whether HDAC inhibitors are best used as maintenance therapy or in combination for advanced disease remains unclear but constitutive expression of STAT3 may indicate resistance to histone deacetylase inhibition in MF/SS [4].

References

1 Duvic M, Talpur R, Ni X *et al*. Phase 2 trial of oral vorinostat (suberoylanilide hydroxamic acid, SAHA) for refractory cutaneous T-cell lymphoma (CTCL). *Blood* 2007; **109**: 31–9.

2 Olsen E, Kim Y, Kuzel T *et al*. Phase IIB multicenter trial of vorinostat in patients with persistent, progressive or treatment refractory cutaneous T-cell lymphoma. *J Clin Oncol* 2007; **25**: 1–9.

3 Piekarz R, Fryer A, Wright J *et al*. Cardiac studies in patients treated with depsipeptide, FK228, in a phase II trial for T-cell lymphoma. *Clin Cancer Res* 2006; **12**: 3762–73.

4 Fantin V, Lobock A, Poweletz L *et al*. Constitutive activation of signal transducers of activation and transcription predicts vorinostat resistance in cutaneous T-cell lymphoma. *Cancer Res* 2008; **68**: 3785–94.

Other novel therapies

Several novel therapies currently being assessed in open phase II studies show promise of significant efficacy in both MF and SS [1] including the proteasome inhibitor, bortezomib (Velcade) [2] but whether additional studies will confirm this promise is currently unclear.

References

1 Whittaker S and Foss F. Efficacy and tolerability of currently available therapies for the mycosis fungoides and Sezary syndrome variants of cutaneous T-cell lymphoma variants. *Cancer Treat Rev* 2007; **33**: 146–60.

2 Zinzani P, Musuraca G, Tani M *et al*. Phase II trial of proteasome inhibitor bortezomib in patients with relapsed or refractory cutaneous T-cell lymphoma. *J Clin Oncol* 2007; **25**: 4293–7.

Primary cutaneous CD30+ lymphoproliferative disorders

Primary cutaneous CD30+ lymphoproliferative disorders consist of a spectrum of conditions; lymphomatoid papulosis and CD30+ anaplastic large cell lymphomas which are defined on the basis of clinical and pathologic features. Where a distinction cannot be made, patients are designated as 'borderline cases'. This group represents approximately 30% of all primary cutaneous lymphomas.

In the skin, CD30+ lymphoproliferative disorders are invariably of T-cell origin although nodal CD30+ lymphomas can be derived from B, T or null cells. By definition, primary cutaneous CD30+ disorders do not have any systemic or nodal involvement [1–3]. CD30 positivity was originally identified on Reed–Sternberg cells in Hodgkin's disease, but is expressed on a proportion of activated T and B lymphocytes. In general, cutaneous lymphomas that are CD30+ *ab initio* are associated with a good prognosis, in contrast to CD30+ lymphomas in other anatomical sites such as the lymph nodes where CD30 positivity is more commonly associated with a poor prognosis and is invariably associated with a disease-specific t(2;5)(p23;q35) translocation not found in primary cutaneous CD30+ lymphoproliferative disorders [4]. In MF, the situation in which tumour cells acquire CD30 expression, during the course of disease, is also generally associated with a poor prognosis [5].

Molecular studies show the presence of the Epstein–Barr genome in a proportion of CD30+ infiltrates in Hodgkin's disease, but this has not been found in patients with lymphomatoid papulosis [6]. CD30 is a cell-surface receptor for tumour necrosis factor-α like cytokines [7], and it has been demonstrated that CD30 expression can be up-regulated by EBV. The pathogenesis of primary cutaneous CD30+ lymphoproliferative disorders remains unknown but studies have suggested that there may be restriction of the normal T-cell repertoire in peripheral blood [8] and abnormalities of Notch signalling [9].

References

1 Leboit PE. Lymphomatoid papulosis and CD30+ lymphoma. *Am J Dermatopathol* 1996; **18**: 221–35.

2 Kadin ME. Primary Ki positive anaplastic large cell lymphoma. *Ann Oncol* 1994; **5** (Suppl. 1): 25–30.

3 Bekkenk MW, Geelen FAMJ, van Voorst Vader PC *et al.* Primary and secondary cutaneous CD30 positive lymphoproliferative disorders: a report from the Dutch Cutaneous Lymphoma Group. *Blood* 2000; **95**: 3653–61.

4 DeCoteau J, Butmarc J, Kinney M, Kadin M. The t(2;5) chromosomal translocation is not a common feature of primary cutaneous CD30+ lymphoproliferative disorders: comparison with anaplastic large cell lymphoma of nodal origin. *Blood* 1996; **87**: 3437–41.

5 Willemze R, Beljaards RC. The spectrum of primary cutaneous CD30+ lymphoproliferative disorders: a proposed classification, and guidelines for management and treatment. *J Am Acad Dermatol* 1993; **28**: 973–80.

6 Kadin ME, Vonderheid EC, Weiss LM. Absence of Epstein–Barr viral RNA in lymphomatoid papulosis. *J Pathol* 1993; **170**: 145–8.

7 Smith CA, Gruss HJ, Davis T. CD30 antigen a marker for Hodgkin's lymphoma is a receptor whose ligand defines an emerging family of cytokines with homology to TNF. *Cell* 1993; **73**: 1349–60.

8 Humme D, Lukowsky A, Steinhoff M *et al*. Dominance of nonmalignant T-cell clones and distortion of the TCR repertoire in the peripheral blood of patients with cutaneous CD30+ lymphoproliferative disorders. *J Invest Dermatol* 2009; **129**: 89–98.



Fig. 57.22 Lymphomatoid papulosis. Note multiple scars on the upper chest area of this patient, with a small number of fresh papular lesions.

9 Kamstrup M, Ralfikiaer E, Skovgaard G, Gniadecki R. Potential involvement of Notch signalling in the pathogenesis of primary cutaneous CD30-positive lymphoproliferative disorders. *Br J Dermatol* 2008; **158**: 747–53.

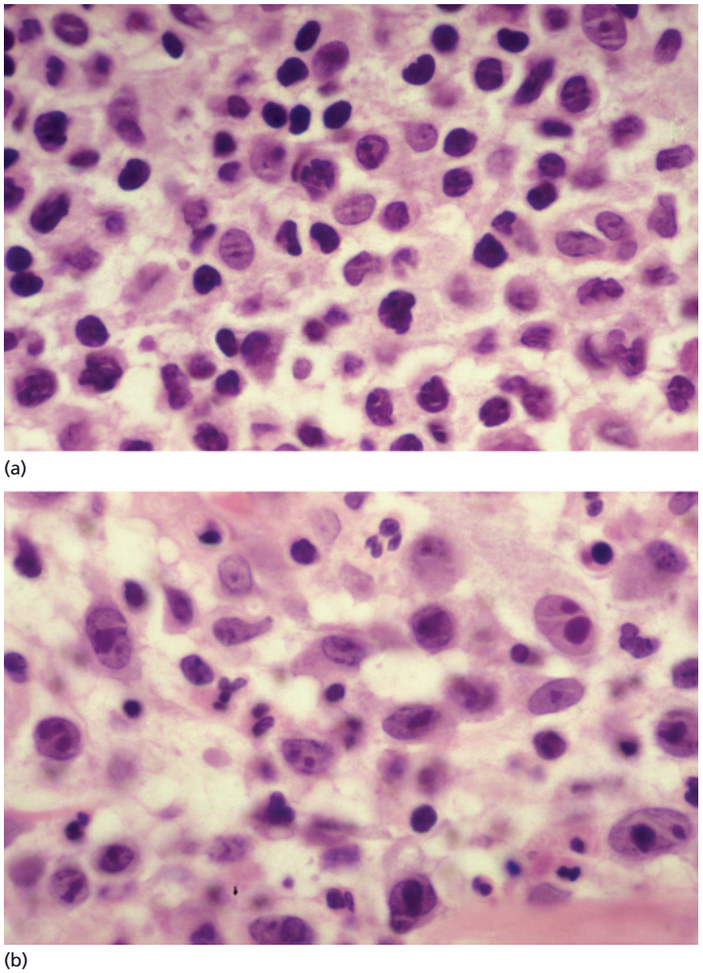
Lymphomatoid papulosis

Definition. This term was first used in 1968 by Macaulay to describe a 'self-healing rhythmical paradoxical papular eruption, histologically malignant but clinically benign' [1–6]. It is a chronic recurrent self-healing papulonecrotic or papulonodular eruption with histological features of a CD30+ cutaneous lymphoma.

Clinical features. Affected patients have recurrent crops of papular or papulonecrotic or nodular lesions predominantly affecting the trunk, although any body site can be involved and regional localized patterns may occur (Fig. 57.22) [7]. These lesions grow rapidly over a few days and develop ulcerated necrotic centres. Healing occurs slowly over 3–12 weeks, with fine atrophic circular or varioliform scars, but the cycle recurs every few months, with no obvious initiating factor. The lesions generally occur first in adult life and may recur in crops for up to 40 years. Over time, every individual skin lesion will resolve and there may eventually be a persistent remission. A small number of cases have been reported in children [8,9].

The original description of lymphomatoid papulosis suggested a benign and non-progressive chronic pattern of the disease, but there are well-documented rare cases both of patients with lymphomatoid papulosis developing primary cutaneous or nodal CD30+ large cell anaplastic T-cell lymphoma or more commonly MF, and of patients with pre-existing MF developing lesions indistinguishable from those of lymphomatoid papulosis [10,11]. A follicular variant of the condition has also been described [12]. A proportion of patients have developed Hodgkin's disease, or develop lymphomatoid papulosis-like lesions with a preceding history of Hodgkin's disease [13–15].

Pathology. The histological features are a relative lack of epidermotropism and Pautrier abscesses, but the presence in the dermis



(a)

(b)

Fig. 57.23 Composite high-power view of atypical cerebriform cells in type B lymphomatoid papulosis (a) and large 'Reed–Sternberg-like' ($CD30^+$) cells in type A histology (b).

of a mixed infiltrate composed of atypical lymphocytes with large nuclei and frequent abnormal mitoses, eosinophils, neutrophils, extravasated red cells and large histiocytic cells [16]. Some of these cells may show gross cytological atypia (Fig. 57.23). The epidermis may be ulcerated and the infiltrate may extend deeply into the reticular dermis. True vasculitis is rarely seen.

Lymphomatoid papulosis can be divided on histological grounds into types A, B and C subgroups [17]. In the A subgroup there appears to be a predominance of scattered large, strikingly atypical $CD30^+$ cells similar to those seen in Hodgkin's disease [18]. In the B subgroup, smaller atypical T lymphocytes with convoluted nuclei similar to those seen in MF predominate and are $CD3^+$ and $CD4^+$ but $CD30^-$. Rare cases of lymphomatoid papulosis are $CD8^+$ [19]. Group C lesions have large clusters of $CD30^+$ cells and an overall pattern suggestive of an anaplastic $CD30^+$ large cell lymphoma. Many cases, however, have all types of lesions coexisting simultaneously or a mixed pattern of A and B. Some patients with clinical lesions resembling pityriasis lichenoides et variol's acuta (PLEVA) show a lymphomatoid histology and this probably represents a form of lymphomatoid papulosis (type B) [20,21]. Recent studies have shown that *MUM1*, a transcription factor expressed in myeloma and lymphomas with plasmacytoid differentiation as well as activated T-cells and Hodgkin's lymphoma, is expressed by the $CD30^+$ cells in a majority of cases of lymphomatoid papulosis but only rarely in primary cutaneous $CD30^+$ ALCL [22]. Furthermore *TRAF1*, expressed by activated T-cells and in Hodgkin's lymphoma, is also differentially expressed in PC$CD30^+$ lymphoproliferative disorders, with expression restricted mostly to lymphomatoid papulosis as opposed to PCALCL [23]. The functional significance of differential *MUM1* and *TRAF1* expression in lymphomatoid papulosis remains to be confirmed.

Clonal TCR gene rearrangements can be identified and are identical in different lesions from the same patient, but some biopsies may not show a clonal pattern either because of an inability to detect a small clonal T-cell population as a result of a lack of sensitivity, or because of a non-T-cell lineage in type A lesions [4,24]. Identical T-cell clones can be detected in skin biopsies from patients with both MF and lymphomatoid papulosis [24]. Studies using laser captured $CD30^+$ cells and sequencing of TCR genes have shown contradictory findings with one study suggesting that the large $CD30^+$ cells show clonal TCR gene rearrangements while other studies have shown that these large $CD30^+$ are polyclonal and that the monoclonal population resides in the smaller population of $CD30^-$ cells [25,26]. The t(2;5) characteristic of nodal $CD30^+$ lymphomas is not detected in lymphomatoid papulosis [27].

Treatment. There is no current treatment that alters the natural history of the disease but some therapies appear to accelerate healing and may reduce or prevent the frequency and severity of new crops of lesions for a short time. There is no evidence that intensive combination chemotherapy alters beneficially the course of lymphomatoid papulosis, and indeed there are individual case reports suggesting that high-dose intensive chemotherapy may cause transition to a more aggressive $CD30^+$ lymphoproliferative disorder. Topical or intralesional steroids and topical nitrogen mustard applied to developing lesions may accelerate clearance, but have little effect on well-developed lesions. Narrow-band UVB therapy and PUVA both appear to benefit individual patients for short periods of time. Low-dose oral methotrexate appears to be the most useful systemic therapy, and there are reports of a beneficial effect with oral dapsone [28,29].

Long-term follow-up is necessary in all cases because of the risk of progression to a more aggressive lymphoma such as a primary cutaneous $CD30^+$ anaplastic lymphoma, MF or Hodgkin's disease in less than 5% of cases. The prognosis in patients with both MF and lymphomatoid papulosis appears to be excellent [10]. There appear to be no currently available clinical or pathological prognostic markers to indicate whether such progression is likely.

An excellent recent review of 118 patients with lymphomatoid papulosis followed for many years suggests that approximately 4% will develop extracutaneous disease within 10 years [30].

References

1 Leboit P. Lymphomatoid papulosis and cutaneous $CD30^+$ lymphoma. *Am J Dermatopathol* 1996; **18**: 221–35.

2 Thomsen K, Wantzin GL. Lymphomatoid papulosis: a follow-up study of 30 patients. *J Am Acad Dermatol* 1987; **17**: 632–6.

3 Weinman VF, Ackerman AB. Lymphomatoid papulosis: a critical review and new findings. *Am J Dermatopathol* 1981; **3**: 129–63.
4 Weiss LM, Wood GS, Trela M *et al*. Clonal T cell populations in lymphomatoid papulosis: evidence of a lymphoproliferative origin for a clinically benign disease. *N Engl J Med* 1986; **315**: 475–9.
5 Macaulay WL. Lymphomatoid papulosis. *Arch Dermatol* 1986; **97**: 23–30.
6 Macaulay WL. Lymphomatoid papulosis update: a historical perspective. *Arch Dermatol* 1989; **125**: 1387–9.
7 Scarisbrick J, Evans A, Woolford A *et al*. Regional lymphomatoid papulosis: a report of four cases. *Br J Dermatol* 1999; **141**: 1125–8.
8 Ashworth J, Paterson WD, MacKie RM. Lymphomatoid papulosis in two children. *Paediatr Dermatol* 1987; **4**: 238–41.
9 Zirbel GM, Gellis SE, Kadin ME, Esterly NB. Lymphomatoid papulosis in children. *J Am Acad Dermatol* 1995; **33**: 741–8.
10 Basarab T, Fraser-Andrews EA, Orchard G *et al*. Lymphomatoid papulosis in association with mycosis fungoides: a study of 15 cases. *Br J Dermatol* 1998; **139**: 630–8.
11 Kadin M. Lymphomatoid papulosis and associated lymphomas: how are they related? *Arch Dermatol* 1993; **129**: 351–2.
12 Pierard GE, Ackerman AB, Lapiere CM. Follicular lymphomatoid papulosis. *Am J Dermatopathol* 1980; **2**: 173–80.
13 Lederman JS, Sober AJ, Harrist TJ *et al*. Lymphomatoid papulosis following Hodgkin's disease. *J Am Acad Dermatol* 1987; **16**: 331–5.
14 Zackheim HS, Leboit P, Gordon BI, Glassberg A. Lymphomatoid papulosis followed by Hodgkin's lymphoma. *Arch Dermatol* 1993; **129**: 86–8.
15 Demierre MF, Goldberg LJ, Kadin ME *et al*. Is it lymphoma or lymphomatoid papulosis? *J Am Acad Dermatol* 1997; **36**: 765–72.
16 Kadin ME. Characteristic immunologic profile of large atypical cells in lymphomatoid papulosis. *Arch Dermatol* 1986; **122**: 1388–90.
17 Willemze R, Meijer CJLM, van Vloten WA, Scheffer E. The clinical and histological spectrum of lymphomatoid papulosis. *Br J Dermatol* 1982; **107**: 131–44.
18 Shabrawi-Caelen L, Kerl H, Cerroni L. Lymphomatoid papulosis. Reaapraisal of clinicopathologic presentation and classification into subtypes A, B and C. *Arch Dermatol* 2004; **140**; 441–7.
19 Magro C, Crowson A, Morrison C *et al*. CD8+ lymphomatoid papulosis and its differential diagnosis. *Am J Clin Pathol* 2006; **125**: 490–501.
20 Verallo VM, Haserick JR. Mucha–Habermann disease simulating lymphoma cutis: report of two cases. *Arch Dermatol* 1966; **94**: 295–9.
21 Black MM, Wilson-Jones E. 'Lymphomatoid' pityriasis lichenoides: a variant with histological features simulating a lymphoma—a clinical and histopathological study of 15 cases with details of long-term follow-up. *Br J Dermatol* 1972; **86**: 329–47.
22 Kempf W, Kutzner H, Cozzio A *et al*. MUM1 expression in cutaneous CD30+ lymphoproliferative disorders: a valuable tool for the distinction between lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma. *Br J Dermatol* 2008; **158**: 1280–7.
23 Assaf C, Hirsch B, Wagner F *et al*. Differential expression of TRAF1 aids in the distinction of cutaneous CD30-positive lymphoproliferations. *J Invest Dermatol* 2007; **127**: 1898–904.
24 Whittaker S, Smith N, Jones RR, Luzzatto L. Analysis of β, γ, and δ T-cell receptor genes in lymphomatoid papulosis: cellular basis of two distinct histologic subsets. *J Invest Dermatol* 1991; **96**: 786–91.
25 Steinhof M, Hummel M, Anagnostopoulos I *et al*. Single cell analysis of CD30+ cells in lymphomatoid papulosis demonstrates a common clonal T-cell origin. *Blood* 2002; **100**: 578–84.
26 Gellrich S, Wernicke M, Wilks A *et al*. The cell infiltrate in lymphomatoid papulosis comprises a mixture of polyclonal large atypical cells (CD30-positive) and smaller monoclonal T cells (CD30-negative). *J Invest Dermatol* 2004; **12**: 859–61.
27 DeCoteau J, Butmarc J, Kinney M, Kadin M. The t(2;5) chromosomal translocation is not a common feature of primary cutaneous CD30+ lymphoproliferative disorders: comparison with anaplastic large cell lymphoma of nodal origin. *Blood* 1996; **87**: 3437–41.
28 Vonderheid EC, Sajjadian A, Kadin M. Methotrexate is effective therapy for lymphomatoid papulosis and other primary cutaneous CD30-positive lymphoproliferative disorders. *J Am Acad Dermatol* 1996; **34**: 470–81.
29 Wantzin GL, Thomsen K. Methotrexate in lymphomatoid papulosis. *Br J Dermatol* 1984; **111**: 93–5.
30 Bekkenk MW, Geelen FAMJ, van Voorst Vader PC *et al*. Primary and secondary cutaneous CD30-positive lymphoproliferative disorders. *Blood* 2000; **95**: 3653–61.

Primary cutaneous (anaplastic) CD30+ large cell lymphoma

Definition. A primary cutaneous CD30+ anaplastic (or rarely pleomorphic or blastic) large cell lymphoma in which the CD30+ tumour cells comprise the majority of the infiltrate. Clinical features of mycosis fungoides are absent.

Clinical features. These lymphomas are usually seen in adults and present as large solitary or multiple and often ulcerated nodules, most often on the trunk (Fig. 57.24) [1]. There are no patches or plaques of MF elsewhere, and some individual lesions may regress spontaneously. Some individuals develop disease localized to a limb. Progression to extracutaneous sites is rare but has been recorded in approximately 10% [1,2] and recent evidence suggests that patients with extensive regional disease may be at risk of disease progression [3,4]. Careful staging consisting of bone marrow and CT scans are required to exclude systemic CD30+ anaplastic large T-cell proliferation in which there is secondary cutaneous involvement. Disease-related 5-year survival rates of 90% have been reported but as low as 50% for generalized tumours [1,3–5].

Flynn *et al.* described patients with large ulcerative nodules, often on the thighs and buttocks, which show variable rates of spontaneous resolution and were labelled as 'regressing atypical histiocytosis' [6]. These 'borderline cases' are now considered to be closely related to both lymphomatoid papulosis and primary cutaneous CD30+ large cell lymphoma with the detection of a T-cell phenotype and clonal rearrangements of the TCR gene confirming a T-cell origin [2,7,8].

A rare variant has been described in which there are palpable and pathologically involved regional lymph nodes at presenta-



Fig. 57.24 CD30+ cutaneous lymphoma showing typical ulcerated lesion on shoulder.

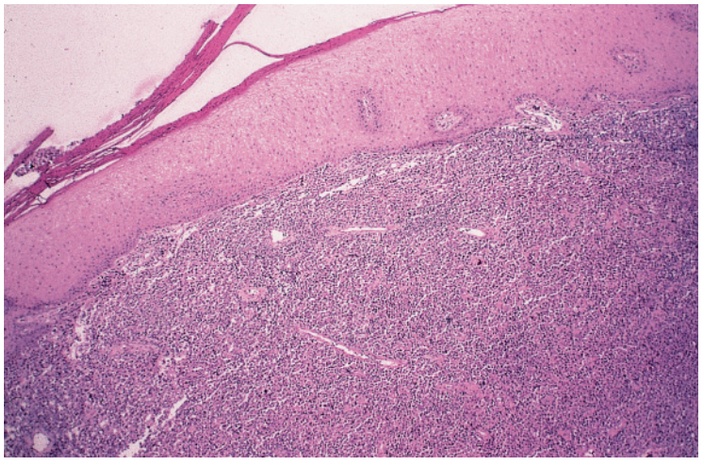


Fig. 57.25 Low-power view of CD30$^+$ infiltrate showing lack of epidermotropism but dense infiltrate in the underlying dermis.

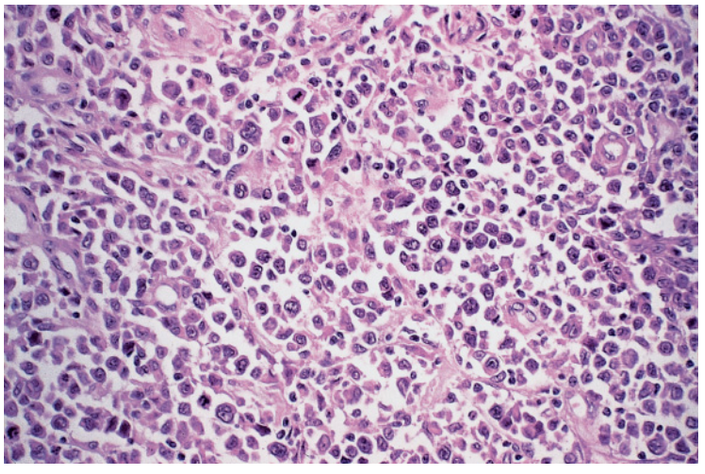


Fig. 57.26 CD30$^+$ lymphocytic infiltrate showing striking large atypical cells.

tion, but no evidence of lymphoma beyond the regional nodal basin [1]. The limited evidence to date on treatment and prognosis suggests that this lymphoma is similar, if not identical, to primary cutaneous CD30$^+$ anaplastic large cell lymphomas.

Pathology. Biopsy shows a dense lymphocytic infiltrate consisting of sheets of large atypical cells with an anaplastic morphology and mitoses, but usually there is no epidermotropism as seen in MF (Figs 57.25 & 57.26). The tumour cells variably express T-cell antigens and the vast majority will be CD30$^+$. Some tumour cells show a pleomorphic or blast-like morphology [1,2,9,10]. Pseudoepitheliomatous hyperplasia may occur. Clonal TCR gene rearrangements are detected in almost all cases consistent with a T-cell origin [11].

Immunophenotype. The tumour cells are generally CD4$^+$ and by definition CD30$^+$ with expression of cytotoxic proteins [9,10]. There is variable loss of other T-cell antigens such as CD2, CD5 and CD3. Some cases are CD8$^+$. Tumour cells are EMA and CD15. ALK is not expressed, in contrast to those systemic CD30$^+$ lymphomas with secondary cutaneous involvement, but CD56 may be rarely expressed. The t(2;5) is absent [12]. While the morphology and phenotype are similar in lymphomatoid papulosis [13], the key distinguishing feature is the presence of cohesive nodules and sheets of anaplastic cells in PCALCL. Recent studies also suggest that in PCALCL the tumour cells generally do not express *MUM1* and *TRAF1* in contrast to lymphomatoid papulosis [14,15].

Pathogenesis. Primary cutaneous CD30$^+$ ALCL express CCR3 and Th2 cytokines [16] as well as CCR4 as in MF/SS. There is no evidence for the t(2;5) chromosomal translocation seen in a high proportion of nodal CD30$^+$ anaplastic lymphomas (NPM-ALK) [12], but molecular studies in PCCD30$^+$ALCL have shown allelic loss at 9p21-22, although the frequency of p16 loss/inactivation has yet to be determined [17]. Array CGH studies have also shown chromosomal imbalances with gains of chromosomes 1p and 5 and amplification of several different oncogenes as well as *JUNB*, a member of the AP1 transcription family [18]. Recent studies have also shown over-expression of AP1 proteins in Pc CD30$^+$ ALCL which might explain the characteristic Th2 cytokine profile [19].

Treatment. Both excision and localized radiotherapy are acceptable methods of treating isolated lesions [20]. The recurrence rate on the treated site is very low, but over time new lesions may develop elsewhere on the skin. Spontaneous clearance of even quite large lesions is recorded, and therefore a short period of observation after the diagnosis is made is also acceptable. Systemic chemotherapy, including CHOP, may be effective but cutaneous recurrence is likely, and chemotherapy is therefore not the treatment of choice for disease confined to the skin. Low-dose methotrexate may also be effective. Rare variants with regional nodal disease have been successfully treated with radiotherapy and do not always require systemic chemotherapy.

References

1 Bekkenk MW, Geelen FAMJ, van Voorst Vader PC *et al.* Primary and secondary cutaneous CD30-positive lymphoproliferative disorders. *Blood* 2000; **95**: 3653–61.

2 Beljaards RC, Kaudewitz P, Berti E *et al.* Primary cutaneous CD30-positive large cell lymphoma: definition of a new type of cutaneous lymphoma with a favourable prognosis. *Cancer* 1993; **71**: 2097–3002.

3 Liu H, Hoppe R, Kohler S *et al*. CD30$^+$ cutaneous lymphoproliferative disorders: The Stanford experience in lymphomatoid papulosis and primary cutaneous anaplastic large cell lymphoma. *J Am Acad Dermatol* 2003; **49**: 1049–58.

4 Shehan J, Kalaaji A, Markovic S, Ahmed I. Management of multifocal primary cutaneous CD30$^+$ anaplastic large cell lymphoma. *J Am Acad Dermatol* 2004; **51**: 103–10.

5 Yu J, Blitzblau R, Decker R *et al*. Analysis of primary CD30$^+$ cutaneous lymphoproliferative disease and survival from the surveillance, epidemiology and end results database. *J Clin Oncol* 2008; **26**: 1438–88.

6 Flynn KJ, Dehner LP, Gajl-Peczalka K *et al.* Regressing atypical histiocytosis. *Cancer* 1982; **49**: 959–70.

7 Bernier M, Bagot M, Broyer M *et al.* Distinctive clinicopathological features associated with regressive primary CD30-positive cutaneous lymphomas: analysis of six cases. *J Cutan Pathol* 1997; **24**: 157–63.

8 Headington JT, Roth MS, Ginsburg D *et al.* T-cell receptor gene rearrangement in regressing atypical histiocytosis. *Arch Dermatol* 1987; **123**: 1183–7.

9 Beljaards RC, Meier CJ, Scheffer E *et al.* Prognostic significance of CD30 expression in primary cutaneous large cell lymphomas of T cell origin. *Am J Pathol* 1989; **44**: 119–24.
10 Krishnan J, Tomaszewski MM, Kao GF. Primary cutaneous anaplastic large cell lymphoma: report of 27 cases. *J Cutan Pathol* 1993; **20**: 193–6.
11 Greisser J, Palmedo G, Sander C *et al*. Detection of clonal rearrangement of T-cell receptor genes in the diagnosis of primary cutaneous CD30+ lymphoproliferative disorders. *J Cutan Pathol* 2006; **33**: 711–5.
12 DeCoteau J, Butmarc J, Kinney M, Kadin M. The t(2;5) chromosomal translocation is not a common feature of primary cutaneous CD30+ lymphoproliferative disorders: comparison with anaplastic large cell lymphoma of nodal origin. *Blood* 1996; **87**: 3437–41.
13 Tomaszewski MM, Lupton G, Krishnan J, May DI. A comparison of clinical morphological and immunohistochemical features of lymphomatoid papulosis and primary cutaneous CD30-positive anaplastic large cell lymphoma. *J Cutan Pathol* 1995; **22**: 310–5.
14 Kempf W, Kutzner H, Cozzio A *et al*. MUM1 expression in cutaneous CD30+ lymphoproliferative disorders: a valuable tool for the distinction between lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma. *Br J Dermatol* 2008; **158**: 1280–7.
15 Assaf C, Hirsch B, Wagner F *et al*. Differential expression of TRAF1 aids in the distinction of cutaneous CD30-positive lymphoproliferations. *J Invest Dermatol* 2007; **127**: 1898–904.
16 Kleinhans M, Tun-kyi A, Gilliet M *et al*. Functional expression of the eotaxin receptor CCR3 in CD30+ cutaneous T-cell lymphoma. *Blood* 2003; **101**: 1487–93.
17 Boni R, Xin H, Kamarashev J *et al*. Allelic deletion at 9p21-22 in primary cutaneous CD30+ large cell lymphoma. *J Invest Dermatol* 2000; **115**; 1104–7.
18 Mao X, Orchard G, Lillington D *et al*. Genetic alterations in primary cutaneous CD30+ anaplastic large cell lymphoma. *Genes Chrom Cancer* 2003; **37**: 176–85.
19 Mao X, Orchard G, Russell-Jones R, Whittaker S. Abnormal activator 1 protein expression in primary cutaneous CD30 positive large cell lymphomas. *Br J Dermatol* 2007; **157**: 914–21.
20 Yu J, McNiff J, Lund M, Wilson L. Treatment of primary cutaneous CD30+ anaplastic large cell lymphoma with radiation therapy. *Int J Radiat Oncol Biol Phys* 2008; **70**: 1542–5.

Subcutaneous panniculitis-like T-cell lymphoma (SPTL)

Definition. This is a rare cytotoxic T-cell lymphoma, representing less than 1% of all non-Hodgkin's lymphomas, which usually affects younger adults with an equal sex incidence [1,2]. Two subsets have been defined consisting of those cases derived from an αβ T cell which have an indolent course and those derived from a γδ T cell [3]. The term SPTL is now restricted to those lymphomas derived from an αβ T cell [1].

Clinical features. Patients present with indolent, slowly expanding, subcutaneous nodules usually involving the limbs, which may initially be misdiagnosed as panniculitis (Fig. 57.27) [4–6]. Occasionally, patients present with more diffuse erythematous induration mimicking a cellulitis. Ulceration is rare. Lymphadenopathy is usually absent at presentation. There is often a prolonged indolent phase before the diagnosis is established [7]. Cases must be carefully distinguished from lupus panniculitis as both conditions share similar clinical and pathological features [8,9]. Systemic symptoms may occur, particularly in those patients who develop a haemophagocytic syndrome consisting of fever, pancytopenia and hepatosplenomegaly although this is more common in those with a γδ T-cell lymphoma [10,11]. The prognosis is reasonable with a 5-year survival of 80%, and dissemination to extracutaneous sites is rare in contrast to primary cutaneous γδ T-cell lymphomas which has a poor prognosis [1].



Fig. 57.27 Subcutaneous panniculitis-like T-cell lymphoma: indurated and eroded deep plaque on the thigh.

Pathology. There is a diffuse infiltrate restricted to and extending throughout the subcutis without epidermotropism [1,3,5,11]. In contrast, primary cutaneous γδ T-cell lymphomas may show prominent involvement of the subcutis which is indistinguishable but there is invariably associated dermal and/or epidermal involvement [1]. The degree of cellular atypia can be minimal but medium-sized and occasionally large pleomorphic cells are usually present (Fig. 57.28). Rimming of the tumour cells around fat cells is a characteristic feature, although not restricted to SPTL [12]. A prominent reactive inflammatory infiltrate is common and the tumour cells may show vascular invasion with angiocentricity. Necrosis and erythrolymphophagocytosis may be present. Indolent cases were previously diagnosed as benign cytophagic histiocytosis (Weber–Christian disease) [13,14].

Immunophenotype. Tumour cells have a mature T-cell phenotype and are usually $\beta F1^+$ $CD3^+$ $CD8^+$ $CD4^-$ [1,3,9]. CD30 and CD56 are generally negative. They express cytotoxic molecules including granzyme B, perforin and TIA-I [15]. Clonal rearrangements of the TCR genes are present [3,16].

Pathogenesis. There is no evidence for an association with EBV, and the underlying molecular pathogenesis remains to be established but recent studies have characterized a specific pattern of chromosomal abnormalities using CGH, LOH and FISH techniques, which have shown losses of 10q, 17p and 19 similar to MF/SS, with additional 5q and 13q gains, which appear to be distinct from findings in MF/SS [17].

Treatment. Patients with αβ subcutaneous panniculitis–like T-cell lymphoma can be treated successfully with systemic steroids and there are reports of responses to ciclosporin [1,18]. Superficial radiotherapy can be used for individual lesions. Denileukin

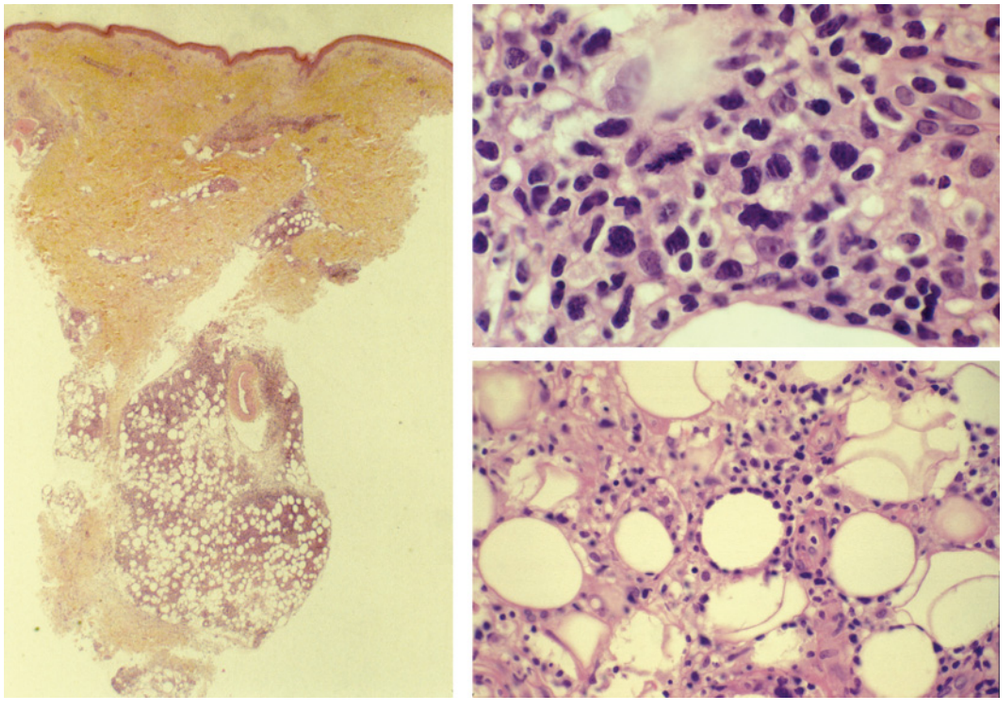


Fig. 57.28 Low-power view of subcutaneous infiltrate with high-power view showing rimming of fat cells by atypical mononuclear cells and medium/large pleomorphic tumour cells seen in subcutaneous panniculitis-like T-cell lymphoma.

diftitox has been used successfully in SPTL [19]. Combination chemotherapy can be associated with successful clinical responses and resolution of haemophagocytic syndrome, although this is usually restricted to those with extracutaneous disease [1]. High-dose therapy and autologous/allogeneic stem cell transplantation has been successful in patients with refractory disease [20,21].

References

1 Willemze R, Jansen P, Cerroni L *et al*. Subcutaneous panniculitis-like T-cell lymphoma: definition, classification and prognostic factors: an EORTC cutaneous lymphoma group study of 83 cases. *Blood* 2008; **111**; 838–45.

2 Shabrawi-Caelen L, Cerrono L, Kerl H. The clinicopathologic spectrum of cytotoxic lymphomas of the skin. *Semin Cutan Med Surg* 2000; **19**: 118–23.

3 Salhany K, Macon W, Choi J *et al*. Subcutaneous panniculitis-like T-cell lymphoma: clinicopathologic, immunophenotypic and genotypic analysis of α/β and γ/δ subtypes. *Am J Surg Pathol* 1998; **22**: 881–93.

4 Aronson IK, West DP, Variakojis D. Panniculitis associated with cutaneous T-cell lymphoma and cytophagic histiocytosis. *Br J Dermatol* 1985; **112**: 87–96.

5 Mehregan D, Su WDP, Kurtin P. Subcutaneous T-cell lymphoma. *J Cutan Pathol* 1994; **21**: 110–7.

6 Monterrosso V, Bujan W, Jaramillo O, Medeiros J. Subcutaneous tissue involvement by T-cell lymphoma. *Arch Dermatol* 1996; **132**: 1345–50.

7 Perniciaro C, Zalla MJ, White JW. Subcutaneous T-cell lymphoma. *Arch Dermatol* 1993; **129**: 1171–6.

8 Gonzalez E, Selvi E, Lorenzini S *et al*. Subcutaneous panniculitis-like T-cell lymphoma misdiagnosed as lupus erythematosus panniculitis. *Clin Rheumatol* 2007; **26**: 244–6.

9 Massone C, Kodama K, Salmhofer W *et al*. Lupus erythematosus panniculitis (lupus profundus): clinical, histopathological and molecular analysis of nine cases. *J Cutan Pathol* 2005; **32**: 396–404.

10 Romero LS, Goltz RW, Bagi C *et al*. Subcutaneous T-cell lymphoma with associated haemophagocytic syndrome and terminal leukemic transformation. *J Am Acad Dermatol* 1996; **34**: 904–10.

11 Gonzalez C, Medeiros L, Brazieln R, Jaffe E. T-cell lymphoma involving subcutaneous tissue: a clinicopathologic entity commonly associated with haemophagocytic syndrome. *Am J Surg Pathol* 1991; **15**: 17–27.

12 Lozzi G, Massone C, Citarella L *et al*. Rimming of adipocytes by neoplastic lymphocytes: a histopathologic feature not restricted to subcutaneous T-cell lymphoma. *Am J Dermatopathol* 2006; **28**: 9–12.

13 Winkelmann R, Bowie E. Haemophagic diathesis associated with benign histiocytic, cytophagic panniculitis and systemic histiocytosis. *Arch Dermatol* 1980; **140**: 1460–3.

14 Perniciaro C, Winkelmann R, Herhardt D. Fatal systemic cytophagic histiocytic panniculitis: a histopathologic and immunohistochemical study of multiple organ sites. *J Am Acad Dermatol* 1994; **31**: 901–5.

15 Kumar S, Krenacs L, Medeiros J *et al*. Subcutaneous panniculitic T-cell lymphoma is a tumour of cytotoxic T-lymphocytes. *Hum Pathol* 1998; **29**: 397–403.

16 Hoque S, Child F, Whittaker S *et al*. Subcutaneous panniculitis-like T-cell lymphoma: a clinicopathological, immunophenotypic and molecular analysis of six patients. *Br J Dermatol* 2003; **148**: 516–25.

17 Hahtola S, Burghart E, Jeskanen L *et al*. Clinicopathological characterisation and genomic aberrations in subcutaneous panniculitis-like T-cell lymphoma. *J Invest Dermatol* 2008; **128**: 2304–9.

18 Rojnuckarin P, Nakoprn T, Assanasen T *et al*. Cyclosporin in subcutaneous panniculitis-like T-cell lymphoma. *Leuk Lymphoma* 2007; **48**: 560–3.

19 Hathaway T, Subtil A, Kuo P, Foss F. Efficacy of denileukin diftitox in subcutaneous panniculitis-like T-cell lymphoma. *Clin Lymphoma Myeloma* 2007; **7**: 541–5.

20 Alaibac M, Berti E, Pigozzi B *et al*. High-dose chemotherapy with autologous blood stem cell transplantation for aggressive subcutaneous panniculitis-like T-cell lymphoma. *J Am Acad Dermatol* 2005; **52**: S121–3.

21 Ichii M, Hatanaka K, Imakita M *et al*. Successful treatment of refractory subcutaneous panniculitis-like T-cell lymphoma with allogeneic peripheral blood stem cell transplantation from HLA-mismatched sibling donor. *Leuk Lymphoma* 2006; **47**: 2250–2.

Primary cutaneous peripheral T-cell lymphoma (unspecified)

Definition. These lymphomas represent a heterogeneous group of T-cell malignancies which are not defined by any of the recognized clinicopathologic subsets. In all cases mycosis funogides

must be carefully excluded especially on the basis of the clinical features. Several subtypes (listed below) are currently considered as provisional entities based on characteristic clinical, pathologic and immunophenotypic features [1]. For patients who do not fulfil the characteristic features of these provisional entities, the designation of peripheral T-cell lymphoma (not otherwise specified (NOS)) should be used and the prognosis is generally poor with a high probability of systemic involvement. Full staging investigations are required for all patients to exclude a systemic nodal/extranodal peripheral T-cell lymphoma.

Primary cutaneous aggressive epidermotropic CD8$^+$ T-cell lymphoma (provisional)

Definition. A primary cutaneous CD8$^+$ T-cell lymphoma that expresses cytotoxic proteins and shows a prominent epidermotropic infiltrate [1,2]. Although there are currently few reports of this entity, the distinctive pathological and immunophenotypic features and poor prognosis suggest that it represents a distinct subtype of CTCL [1–3].

Clinical features. These patients rapidly develop generalized papules, plaques, nodules and/or tumours (Fig. 57.29a) which may show ulceration and necrosis [1,2]. Mucosal involvement may occur. The characteristic clinical features and distribution of MF, namely polymorphic patches and plaques and involvement of the limb girdle areas, are absent. Primary cutaneous CD30$^+$ lymphoproliferative disorders with a CD8$^+$ phenotype should also be distinguished. The prognosis is very poor, with a 5-year survival of 18% [1].

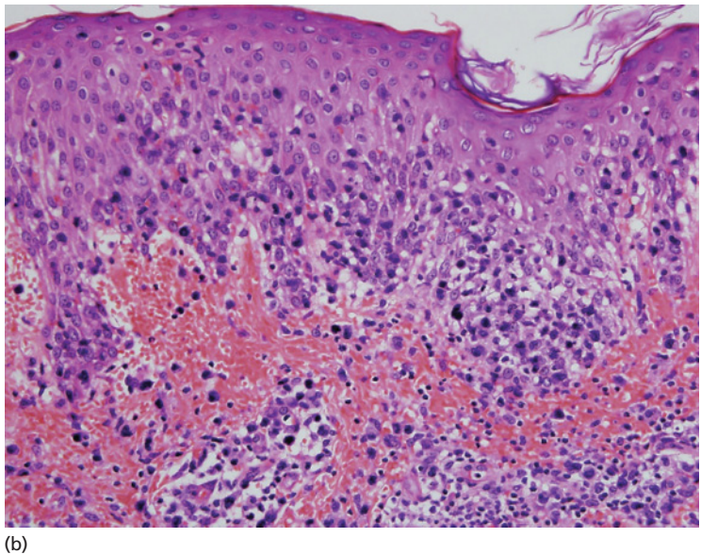
Pathology. These lymphomas show a prominent epidermotropic band-like infiltrate (pagetoid) with nodular infiltrates of large or small- to medium-sized pleomorphic or blastic T cells often accompanied by haemorrhage in the upper dermis (Fig. 57.29b). Angiocentricity and invasion can be a feature. These cutaneous lymphomas must be distinguished from MF and primary cutaneous γδ T-cell lymphomas [1,4]. An indolent CD8$^+$ cutaneous lymphoma characterized by solitary nodular lesions, often around the ear, has been suggested to be a distinct entity but appears to be very rare [5], and its relationship to epidermotropic CD8$^+$ T-cell lymphoma is unclear.

Immunophenotype. The tumour cells are CD8$^+$ and usually βF1$^+$ CD45RA$^+$ and CD3$^+$ [1–3]. The tumour cells also express cytotoxic proteins such as T-cell intracellular antigen-I (TIA-I), granzyme B and perforin. CD4, CD45RO, CD56 and CD30 are negative. Epstein–Barr virus (EBV) is not detected, in contrast to nasal-type natural killer (NK)/T-cell lymphomas [1,4].

Pathogenesis. This CTCL subset may previously have represented disseminated pagetoid reticuloses (Ketron–Goodman). Clonal TCR gene rearrangements are detected but the pathogenesis has not been established. Although the number of cases reported is small, these cases can be distinguished from peripheral T-cell lymphomas derived from γδ T-cells (βF1 negative) which show clonal rearrangements of the γ TCR gene with the β TCR gene in a germline configuration [1,6].



(a)



(b)

Fig. 57.29 (a) Primary cutaneous aggressive epidermotropic CD8$^+$ cutaneous T-cell lymphoma showing necrotic haemorraghic plaques and (b) an epidermotropic infiltrate of large pleomorphic lymphoid cells and marked papillary dermal haemorrhage.

Treatment. These patients have a very poor prognosis and dissemination to visceral sites such as CNS, testis and lung is more common than to nodal sites. Responses to radiotherapy and chemotherapy are limited and the treatment of choice may be a reduced intensity allograft procedure.

References

1 Willemze R, Jaffe E, Burg G *et al*. WHO-EORTC classification for cutaneous lymphomas. *Blood* 2005; **105**: 3768–85.
2 Berti E, Tomasini D, Vermeer M *et al*. Primary cutaneous CD8-positive epidermotropic cytotoxic T-cell lymphomas: a distinct clinicopathological entity with an aggressive clinical behaviour. *Am J Pathol* 1999; **155**: 483–92.
3 Agnarsson B, Vonderhied E, Kadin M. Cutaneous T-cell lymphoma with suppressor/cytotoxic (CD8) phenotype: identification of rapidly progressive and chronic subtypes. *J Am Acad Dermatol* 1990; **22**: 569–77.
4 Santucci M, Pimpinelli N, Massi D *et al*. Cytotoxic/natural killer cell cutaneous lymphomas. *Cancer* 2003; **97**: 610–27.
5 Petrella T, Maubec E, Cornillet-Lefebvre P *et al*. Indolent CD8-positive lymphoid proliferation of the ear: a distinct primary cutaneous T-cell lymphoma? *Am J Surg Pathol* 2007; **31**: 1887–92.
6 Munn SE, McGregor JM, Jones A *et al*. Clinical and pathological heterogeneity in cutaneous γδ T-cell lymphoma: a report of three cases and a review of the literature. *Br J Dermatol* 1996; **135**: 976–81.

Primary cutaneous γδ T-cell lymphomas (provisional entity)

Definition. A T-cell lymphoma consisting of γδ T-cells with a cytotoxic phenotype which may present primarily with skin involvement. A subgroup of patients with subcutaneous panniculitis-like T-cell lymphoma derived from γδ T-cells are included in this category [1–3].

Clinical features. The characteristic presentation is the sudden appearance of multiple cutaneous plaques, nodules or tumours which may be ulcerated and with no preceding polymorphic plaques or patches of typical MF. The clinical presentation may be similar to primary cutaneous $CD8^+$ aggressive epidermotropic lymphomas but some patients present with only subcutaneous involvement. Mucosal involvement and extranodal involvement is common. Some cases of disseminated pagetoid reticulosis (Ketron–Goodman) may have represented cutaneous γδ T-cell lymphomas [4]. A haemophagocytic syndrome may complicate some cases. The prognosis is very poor [1–3].

Pathology. Prominent nodular or diffuse infiltrates are characteristic with medium to large pleomorphic or blast like T cells. Epidermotropism may occur but the infiltrate is often extensive with dermal and subcutaneous patterns. Angiocentricity and rimming of fat cells may occur [1].

Immunophenotype. The tumour cells are usually $CD2^+$ $CD3^+$ $CD5^-CD7^{+/-}$ and $CD56^+$ but are $CD4^-CD8^-$ and $\beta F1^-$. EBV is negative and clonal TCR gene rearrangements are usually present.

Pathogenesis. This variant must be distinguished from transformed MF, ATLL, primary cutaneous aggressive epidermotropic cytotoxic $CD8^+$ CTCL and blastic NK-cell or extranodal NK/T-cell lymphomas (nasal type).

Treatment. Superficial radiotherapy and multiagent chemotherapy are usually required but the overall prognosis is very poor and reduced intensity allografts may be appropriate.

References

1 Willemze R, Beljaards RC, Meier CJLM. Classification of primary cutaneous T-cell lymphomas. *Histopathology* 1994; **24**: 405–15.
2 Willemze R, Jaffe E, Burg G *et al*. WHO-EORTC classification for cutaneous lymphomas. *Blood* 2005; **105**: 3768–85.
3 Toro J, Liewehr D, Pabby N *et al*. Gamma-delta T-cell phenotype is associated with significantly decreased survival in cutaneous T-cell lymphoma. *Blood* 2003; **101**: 3407–12.
4 Berti E, Cerri A, Cavicchini S *et al*. Primary cutaneous gamma/delta lymphoma presenting as disseminated pagetoid reticulosis. *J Invest Dermatol* 1991; **96**: 718–23.

Primary cutaneous $CD4^+$ small/medium sized pleomorphic T-cell lymphoma

Definition. This subtype of CTCL must be distinguished clinically from MF and is characterized by small to medium sized pleomorphic tumour cells which are $CD4^+$ [1].

Clinical features. Patients present with solitary or a few small plaques, nodules or tumours, often on the upper trunk or head and neck, without typical patches or plaques of MF. Patients are HTLV-1 negative. The estimated 5-year survival is 62–80%, but this is only based on small series [1–4]. Systemic involvement is very unusual.

Pathology. There are dense nodular or diffuse infiltrates of small to medium-sized pleomorphic T cells within the dermis, often extending into the subcutis [1–3]. Occasional larger pleomorphic cells may be present but are a minority. Epidermotropism may be present.

Immunophenotype. The tumour cells are usually $CD4^+$ and $CD3^+$ but loss of some T-cell antigens is common [1–3]. CD30 and CD8 are negative and cytotoxic proteins are not expressed. Clonal TCR gene rearrangements are present [5].

Pathogenesis. Currently, little is known about the underlying aetiology and pathogenesis of this rare group of primary cutaneous lymphomas. Cases must be distinguished from MF and pseudo T-cell lymphomas and also peripheral T-cell lymphoma (NOS) in order to avoid inappropriately aggressive therapy.

Treatment. In view of the excellent prognosis, superficial radiotherapy is appropriate for solitary lesions. Single-agent chemotherapy and IFN-α have been reported to be effective [3,4].

References

1 Willemze R, Jaffe E, Burg G *et al*. WHO-EORTC classification for cutaneous lymphomas. *Blood* 2005; **105**: 3768–85.
2 Friedmann D, Wechsler J, Delfau MH *et al*. Primary cutaneous pleomorphic small T-cell lymphoma. *Arch Dermatol* 1995; **131**: 1009–15.
3 Sterry W, Siebel A, Mielke V. HTLV-1 negative pleomorphic T-cell lymphoma of the skin. *Br J Dermatol* 1992; **126**: 456–62.
4 Garcia-Nerrera A, Colmo L, Camos M *et al*. Primary cutaneous small/medium $CD4^+$ T-cell lymphomas: a heterogenous group of tumours with different clinicopathologic features and outcome. *J Clin Oncol* 2008; **26**: 3364–71.
5 Grogg K, Jung S, Erickson L *et al*. Primary cutaneous CD4-positive small/medium-sized pleomorphic T-cell lymphoma: a clonal T-cell lymphoproliferative disorder with indolent behaviour. *Mod Pathol* 2008; **21**: 708–15.



Fig. 57.30 Three clinical presentations of cutaneous adult T-cell leukaemia–lymphoma: (a) a pruritic papular eruption confined to the auricle, (b) an extensive nodular eruption on the forearm, and (c) superficial patches and plaques involving the limb girdle area similar to mycosis fungoides.

Adult T-cell leukaemia–lymphoma (HTLV-1-associated)

Definition. Adult T-cell leukaemia–lymphoma (ATLL) is a peripheral T-cell leukaemia–lymphoma caused by the human retrovirus HTLV-1. HTLV-1 infection is prevalent in certain parts of the world, including Japan, central Africa, the Caribbean and south-eastern states of the USA, and consequently ATLL is endemic in these regions. Sporadic cases are found throughout the world. The disease has a long latency and the incidence of ATLL among HTLV-1 carriers has been estimated to be 2.5% [1]. The virus can be transmitted in breast milk and in blood products. There is a slight male predominance and the median age of onset is 55 years [1].

Clinical features. Patients with ATLL often have extensive lymph node and peripheral blood involvement but the skin is the most common extranodal site of disease (50% of patients) and primary cutaneous disease can occur [2,3]. Other extranodal sites of disease include bone, lung, liver, gastrointestinal tract and CNS. Cutaneous involvement is characterized by widespread or solitary papules, nodules, tumours or erythroderma, often associated with intense pruritus (Fig. 57.30) [4,5]. Patients may present with patches and plaques that are clinically indistinguishable from MF [6]. Several clinical variants have been defined [7]: an acute variant is characterized by a leukaemic phase with generalized lymphadenopathy and hepatosplenomegaly often associated with cutaneous involvement and hypercalcaemia with lytic bone lesions. Opportunistic infections are common because of a relative T-cell immunodeficiency. A lymphomatous variant is similar but with the absence of peripheral blood involvement. A chronic variant is typically characterized by cutaneous disease and a peripheral blood lymphocytosis without hypercalcaemia. The smouldering variant is also characterized by prominent cutaneous disease without overt peripheral blood involvement. Pulmonary lesions may occur. Progression from the chronic and smouldering variants to acute disease occurs in at least 25% of cases but often only after a long duration [6]. HTLV-1 serology is invariably positive [7]. Patients with cutaneous ATLL have shown marked photosensitivity mimicking actinic reticuloid [8,9].

Pathology. In the skin, a prominent epidermotropic infiltrate consisting of medium to large cells with a pleomorphic nuclear morphology is usually found, particularly in the acute and lymphomatous variants (Fig. 57.31) [3–7]. Blast-like cells may be present. Pautrier-like microabscesses and a cerebriform nuclear morphology can be seen, simulating MF. However, the degree of cellular atypia may also be mild, causing diagnostic difficulties. Eosinophilia is often present. Granulomatous features have been rarely described [6]. In the peripheral blood, the tumour cells have polylobulated nuclei ('flower cells'). Lymph nodes usually show a leukaemic pattern of infiltration, with preservation and dilatation of lymph node sinuses containing tumour cells. Rarely, Hodgkin-like features are present within an expanded lymph

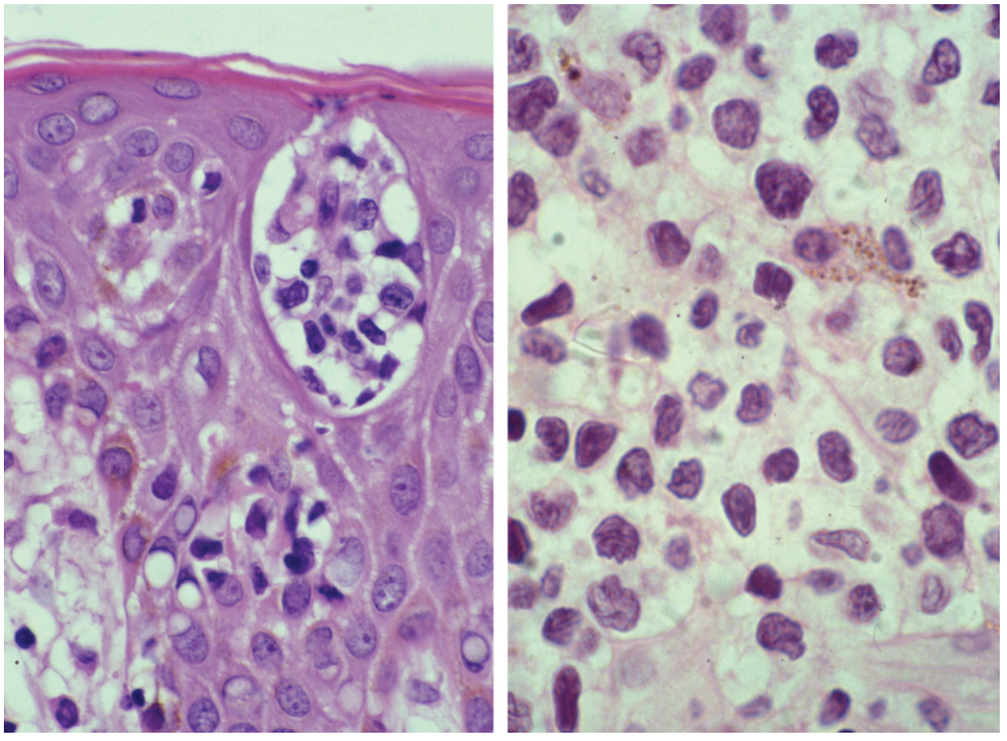


Fig. 57.31 Adult T-cell leukaemia–lymphoma: prominent atypical cells forming a Pautrier microabscess and large pleomorphic cells within the dermis.

node paracortex containing a diffuse infiltrate of small, mildly atypical lymphocytes and scattered $CD30^+$, $CD15^+$ Reed–Sternberg-like EBV-positive cells resulting from expansion of EBV-positive cells as a consequence of a relative T-cell immunodeficiency [10].

Immunophenotype. Tumour cells are $CD2^+$, $CD3^+$, $CD5^+$ and $CD7^-$. Most cells are $CD4^+$, although $CD8^+$ and $CD4^-$, $CD8^-$ variants also occur [11]. CD25 expression is almost universal. Large blast-like cells can be $CD30^+$ but are ALK^-. Cytotoxic proteins are not expressed. Analysis of TCR genes shows clonal TCR gene rearrangements.

Pathogenesis. HTLV-1 is the underlying cause of ATLL. The virus is randomly integrated into the host genome following expression of viral reverse transcriptase, and the viral tax protein is a potent transactivation factor that induces expression of numerous host genes with additional molecular abnormalities producing a malignant phenotype [12]. The HTLV-1 proviral DNA is clonally integrated, confirming a pathogenetic role for the virus in individual cases [11]. Tumour burden can be assessed by monitoring viral RNA expression levels [13].

Treatment. Cutaneous disease can respond to skin-directed therapy but patients with the acute and lymphomatous variants have a poor prognosis (less than 10% 5-year survival) and require combination chemotherapy. In contrast, patients with the chronic (30% 5-year survival) and smouldering (65% 5-year survival) variants can have a prolonged course, although disease transformation eventually occurs for most patients [7]. Combination azathioprine and IFN therapy is a standard of care for those with chronic and smouldering variants of ATLL [14,15], and trials of antibody therapies have suggested promise for daclizumab (anti-CD25) [16]. Younger patients may be candidates for stem cell transplantation and reduced intensity allograft procedures have been shown to induce a graft-versus-lymphoma effect [17].

References

1 Yamaguchi K. Human T-lymphotropic virus type 1 in Japan. *Lancet* 1994; **343**: 213–6.

2 Bunn P, Schechter G, Jaffe E *et al*. Clinical course of retrovirus-associated adult T-cell lymphoma in the United States. *N Engl J Med* 1983; **309**: 257–64.

3 Yamaguchi T, Ohshima K, Karube K *et al*. Clinicopathological features of cutaneous lesions of adult T-cell leukaemia/lymphoma. *Br J Dermatol* 2005; **152**: 76–81.

4 Lessin SR, Vowels BR, Rook AH. Retroviruses and cutaneous lymphoma. *Dermatol Clin* 1994; **12**: 243–53.

5 Dicaudo DJ, Perniciaro C, Worrell JT *et al*. Clinical and histologic spectrum of human T-cell lymphotropic virus type 1-associated lymphoma involving the skin. *J Am Acad Dermatol* 1996; **34**: 69–76.

6 Whittaker S, Ng Y, Rustin M *et al*. HTLV-1 associated cutaneous disease: a clinicopathological and molecular study of patients from the UK. *Br J Dermatol* 1993; **128**: 483–92.

7 Shimoyama M. Diagnostic criteria and classification of clinical subtypes of adult T-cell leukaemia–lymphoma: a report from the Lymphoma Study Group (1984–87). *Br J Haematol* 1991; **79**: 428–37.

8 Ohshima K, Suzumiya J, Kato A *et al*. Clonal HTLV-1 infected $CD4^+$ T-lymphocytes and non-clonal non-HTLV-1-infected giant cells in incipient ATLL with Hodgkin-like histologic features. *Int J Cancer* 1997; **72**: 592–8.

9 Adachi Y, Horio T. Chronic actinic dermatitis in a patient with adult T-cell leukemia. *Photodermatol Photoimmunol Photomed* 2008: **24**: 147–9.

10 Agar N, Morris S, Russell Jones R *et al*. Case report of four patients with erythrodermic cutaneous T-cell lymphoma and severe photosensitivity mimicking chronic actinic dermatitis. *Br J Dermatol* 2009; **160**: 698–703.

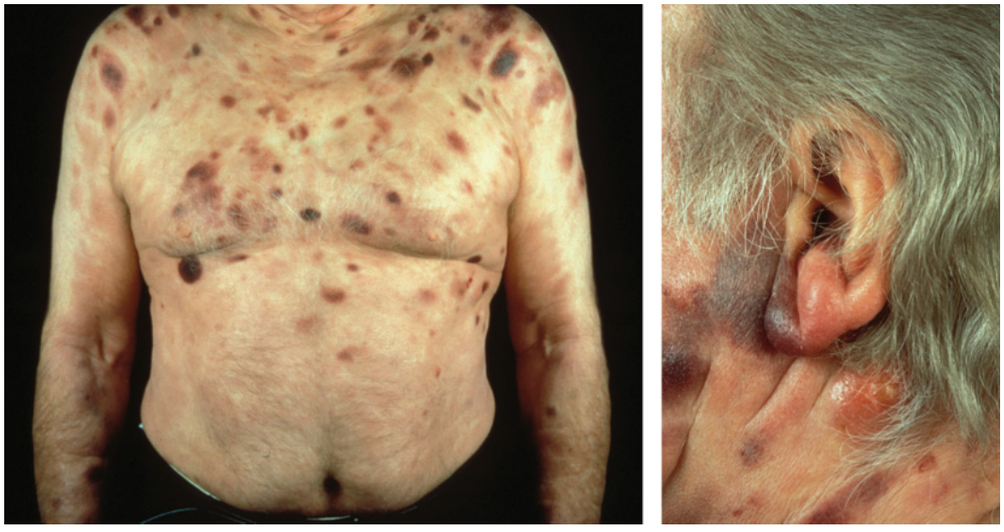


Fig. 57.32 Typical clinical presentations of blastic lymphoma in the skin with large mauvish and pigmented dermal plaques involving the head/neck and trunk.

11 Ohshima K, Suzumiya J, Sato K *et al*. Nodal T-cell lymphoma in an HTLV-1 endemic area: proviral HTLV-1 DNA, histological classification and clinical evaluation. *Br J Haematol* 1998; **101**: 444–50.
12 Taylor G. Molecular aspects of HTLV-1 infection and adult T-cell leukaemia/lymphoma. *J Clin Pathol* 2007; **60**: 1392–6.
13 Amano M, Kurokawa M, Ogata K, Itoh H *et al*. New entity, definition and diagnostic criteria of cutaneous adult T-cell leukaemia/lymphoma: human T-lymphotropic virus type 1 proviral DNA load can distinguish between cutaneous and smouldering types. *J Dermatol* 2008; **35**: 270–5.
14 Ishitsuka K, Tamura K. Treatment of adult T-cell leukemia/lymphoma: past, present and future. *Eur J Haematol* 2008; **80**: 185–96.
15 Bazarbachi A, Lepelletier Y, Nasr R *et al*. New therapeutic approaches for adult T-cell leukaemia. *Lancet Oncol* 2004; **5**: 664–72.
16 Waldmann T. Daclizumab (anti-Tac, zenapax) in the treatment of leukemia/lymphoma. *Oncogene* 2007; **28**: 3699–703.
17 Shiratori S, Yasumoto A, Tanaka J *et al*. A retrospective anyalsis of allogeneic hematopoietic stem cell transplantation for adult T cell leukemia/lymphoma (ATL): clinical impact of graft-versus-leukemia/lymphoma effect. *Biol Blood Marrow Transplant* 2008; **14**: 817–23.

CD4$^+$/CD56$^+$ haematodermic neoplasm (blastic NK-cell lymphoma)

Definition. This is a rare haematologic neoplasm, which is now thought to be derived from plasmacytoid dendritic cells and shows a predilection for extranodal sites, particularly the skin, and a tendency to leukaemic dissemination [1]. Previously, this tumour was erroneously thought to be derived from NK-cells because of CD56 expression. There is no racial predisposition. Elderly male patients are mostly affected and the prognosis is poor.

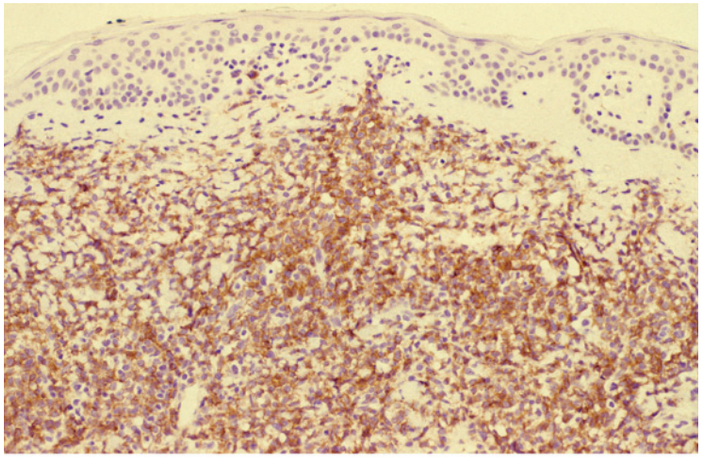
Clinical features. Patients usually present with multiple and rarely solitary, large, dusky mauve dermal tumours, which can become ulcerated (Fig. 57.32). There is no specific site predilection but the upper trunk is often affected. Primary cutaneous disease is common but lymphadenopathy and peripheral blood/bone marrow involvement is likely during the course of disease [2–5]. This neoplasm must be differentiated from myelomonocytic leukaemia and is closely related to 'aleukaemia' leukaemia cutis.

Pathology. A dense monomorphic infiltrate of medium-sized tumour cells with a fine chromatin resembling lymphoblasts is seen throughout the dermis with a well-defined grenz zone (Fig. 57.33) [4,5]. Occasionally, tumour cells show a rosette pattern. Necrosis and angiocentricity are usually absent.

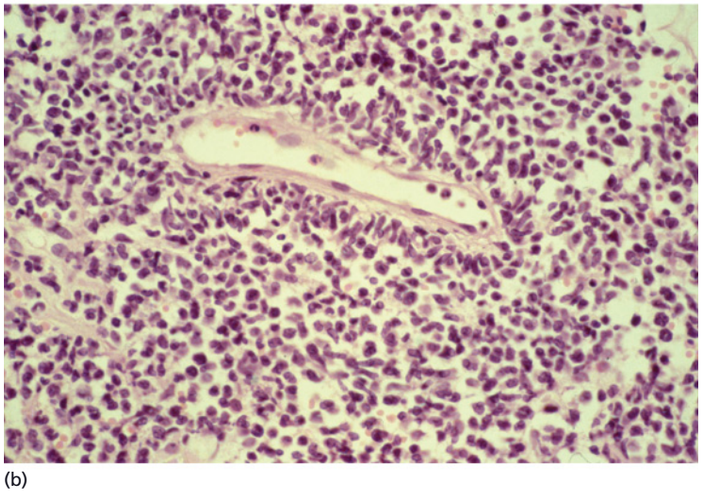
Immunophenotype. Tumour cells are CD56$^+$ with variable expression of CD4, CD45RA and CD43 but do not express surface CD3. CD2, CD7 and cytoplasmic CD3ε are usually negative [3–5]. Cytotoxic proteins may be rarely expressed. Rare cases are CD34$^+$CD68$^+$ and TdT$^+$. Because of a morphological resemblance to myeloblastic and precursor T-lymphoblastic leukaemia which also express CD56, it is important to confirm that the tumour cells are negative for surface CD3, CD33 and myeloperoxidase/lysozyme. TCR gene analysis reveals a germline pattern for all TCR genes consistent with a non-lymphoid origin [4–6]. The tumours are CD123$^+$ TCL1a$^+$, confirming a derivation from rare peripheral blood plasmacytoid dendritic cells [7,8].

Pathogenesis. EBV has not been detected in tumour cells and no disease-specific cytogenetic abnormality has been detected [5,6]. Comparative genomic hybridization techniques and gene expression studies have shown a distinct pattern of chromosomal abnormalities and over-expression of the oncogene, *FLT3*, and loss of expression of the *Rb1* gene [9–12]. These studies have also shown that CD4$^+$ CD56$^+$ haematodermic neoplasms and cutaneous infiltrates of myeloid leukaemia have different chromosomal and gene expression profiles.

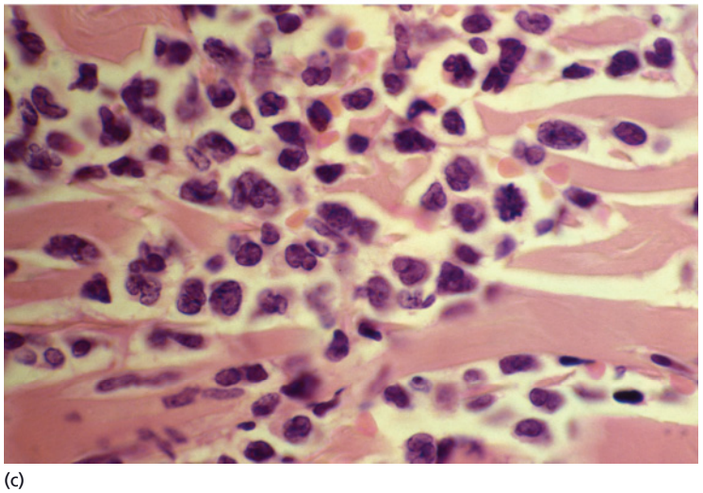
Treatment. Combination chemotherapy and radiotherapy can produce a partial remission, which is invariably short-lived, and the prognosis is very poor with a median survival of 14 months reported. Survival may be better in patients less than 40 years old and high TdT expression. Myeloid leukaemia protocols may be appropriate [12].



(a)



(b)



(c)

Fig. 57.33 Extranodal NK/T-cell lymphoma in the skin: (a) CD56 positivity; (b) rosetting of blood vessels; (c) large atypical mononuclear cells.

References

1 Harris N, Jaffe E, Diebold J *et al.* The World Health Organization classification of neoplastic disease of the haematopoietic and lymphoid tissues: report of the clinical advisory committee. *Histopathology* 2000; **36**: 69–87.

2 Petrella T, Dalac S, Maynadie M *et al.* CD4$^+$ CD56$^+$ cutaneous neoplasms: a distinct haematological entity? *Am J Surg Pathol* 1999; **23**: 137–46.

3 Shabrawi-Caelen L, Cerrono L, Kerl H. The clinicopathologic spectrum of cytotoxic lymphomas of the skin. *Semin Cutan Med Surg* 2000; **19**: 118–23.

4 Nakamura S, Suchi T, Koshikawa T *et al.* Clinicopathologic study of CD56 (NCAM)–positive angiocentric lymphoma occuring in sites other than the upper and lower respiratory tract. *Am J Surg Pathol* 1995; **19**: 284–96.

5 Chan J, Sin V, Wong K *et al.* Non-nasal lymphoma expressing the natural killer cell marker CD56: a clinicopathologic study of 49 cases of an uncommon aggressive neoplasm. *Blood* 1997; **89**: 4501–13.

6 Child F, Mitchell T, Whittaker S *et al.* Blastic natural killer cell and extranodal natural killer cell-like T-cell lymphoma presenting in the skin: report of six cases in the UK. *Br J Dermatol* 2003; **148**: 507–15.

7 Petrella T, Comeau M, Maynadie M *et al.* 'Agranular CD4$^+$ CD56$^+$ haematodermic neoplasm' (blastic NK-cell lymphoma) originates from a population of CD56$^+$ precursor cells related to plasmacytoid monocytes. *Am J Surg Pathol* 2002; **26**: 852–62.

8 Petrella T, Meijer C, Dalac S *et al*. TCL1 and CLA expression in agranular CD4/CD56 hematodermic neoplasms (Blastic NK-cell lymphomas) and leukaemia cutis. *Am J Clin Pathol* 2004; **122**: 307–13.

9 Hallerman C, Middel P, Griesenger F *et al*. CD4$^+$ CD56$^+$ blastic tumour of the skin: cytogenetic observations and further evidence of an origin from plasmacytoid dendritic cells. *Eur J Dermatol* 2004; **14**: 317–22.

10 Mao X, Onadim Z, Price E *et al*. Genomic alterations in blastic natural killer/extranodal natural killer like T-cell lymphoma with cutaneous involvement. *J Invest Dermatol* 2003; **121**: 618–27.

11 Dijkman R, Van Doorn R, Szuhai K *et al*. Gene expression profiling and array based CGH classify CD4$^+$ CD56$^+$ haematodermic neoplasm and cutaneous myelomonocytic leukaemia as distinct disease entities. *Blood* 2007; **109**: 1720–7.

12 Bekkenk M, Jansen P, Meijer C, Willemze R. CD56$^+$ hematological neoplasms presenting in the skin: a retrospective analysis of 23 new cases and 130 cases from the literature. *Ann Oncol* 2004; **15**: 1097–108.

Extranodal NK/T-cell lymphoma (nasal type)

Definition. This rare type of extranodal EBV-positive angiocentric lymphoma preferentially involves the nasal cavity and nasopharynx but also shows a predilection for the skin and used to be referred to as polymorphic reticuloses or angiocentric immunoproliferative lesion [1–4]. The disease is more prevalent in Asia and Central and South America. Most cases are derived from NK cells but rare cases have a cytotoxic T-cell phenotype.

Clinical features. Involvement of the nasal cavity, nasopharynx, paranasal sinuses, orbit and oropharynx is associated with tissue destruction ('lethal midline granuloma'). Secondary involvement of other extranodal sites including the skin and gastrointestinal tract occurs but primary cutaneous disease is rare. Cutaneous plaques, nodules and tumours may ulcerate and become necrotic. Purpura, bullous lesions, cellulitis and diffuse maculopapular rashes have been described [5–9]. A haemophagocytic syndrome can develop rarely and systemic symptoms are common. Bone marrow and peripheral blood involvement is rare but such cases can be indistinguishable from aggressive NK-cell leukaemia.

Pathology. There is a diffuse infiltrate in the dermis and often the subcutis with prominent angiocentricity and angiodestruction [1–4,6]. Extensive necrosis is common. Tumour cells can show a variable morphology with small/medium and large pleomorphic/anaplastic cells. An associated heavy mixed inflammatory infiltrate is common and pseudoepitheliomatous hyperplasia may be found, which can lead to diagnostic confusion.

Immunophenotype. Tumour cells are CD56$^+$, CD2$^+$, surface CD3$^-$ and cytoplasmic CD3ε$^+$. Most cases express cytotoxic proteins, namely granzyme B, perforin and TIA-I [1–4,6]. Rare cases are CD30$^+$ and this may confer a more favourable prognosis [6]. TCR genes are in a germline configuration consistent with an NK-cell origin. However, rare cases of extranodal NK/T-cell lymphomas have a CD56$^-$, CD3ε$^+$ cytotoxic phenotype and show a clonal TCR gene rearrangement consistent with derivation from a cytotoxic T cell [4,7,10,11].

Pathogenesis. EBV is present in almost all cases of extranodal NK/T-cell lymphoma, whether CD56$^+$ or CD56$^-$ [3]. EBV is present in a clonal episomal form, suggesting that the virus has a critical pathogenetic role. No disease-specific cytogenetic abnormality has been identified but deletions of 6q and isochromosome 6q are common and genomic abnormalities are distinct to those found in NK-cell leukaemias [12,13].

Reports have implicated EBV-infected cytotoxic T cells in the pathogenesis of both the photosensitive disorder hydroa vacciniforme and hypersensitivity to mosquito bites in patients from Asia and South America [14]. Furthermore, there is now substantial evidence that such patients are at risk of developing extranodal NK/T-cell lymphomas with a fatal outcome [15–18]. This suggests that in genetically susceptible individuals an EBV-driven NK/T-cell lymphoproliferative inflammatory disorder has the potential to transform into an aggressive EBV-associated NK/T-cell lymphoproliferative disorder [14].

Treatment. The prognosis is poor despite aggressive chemotherapy, particularly for those patients with disease outside the nasal cavity [4]. The multidrug resistance phenotype is often expressed in cutaneous cases and the median survival for patients presenting with cutaneous disease is 12–15 months although the prognosis may be better for those patients with only cutaneous involvement (27 months) [6–9].

References

1 Kern W, Spier C, Hanneman E *et al.* Neural cell adhesion molecule-positive peripheral T-cell lymphoma: a rare variant with a propensity for unusual sites of involvement. *Blood* 1992; **79**: 2432–7.

2 Wong K, Chan J, Ng C *et al.* CD56 (NCAM)–positive hematolymphoid malignancies: an aggressive neoplasm featuring frequent cutaneous/mucosal involvement, cytoplasmic azurophilic granules and angiocentricity. *Hum Pathol* 1992; **23**: 798–804.

3 Kanavaros P, Lescs M, Briere J *et al.* Nasal T-cell lymphoma: a clinicopathologic entity associated with peculiar phenotype and with Epstein–Barr virus. *Blood* 1993; **81**: 2688–95.

4 Chan J, Sin V, Wong K *et al.* Non-nasal lymphoma expressing the natural killer cell marker CD56: a clinicopathologic study of 49 cases of an uncommon aggressive neoplasm. *Blood* 1997; **89**: 4501–13.

5 Shabrawi-Caelen L, Cerrono L, Kerl H. The clinicopathologic spectrum of cytotoxic lymphomas of the skin. *Semin Cutan Med Surg* 2000; **19**: 118–23.

6 Gernhard S, Natkunam Y, Hoppe R *et al.* Natural killer/natural killer-like T-cell lymphoma, CD56$^+$, presenting in the skin: an increasingly recognized entity with an aggressive course. *J Clin Oncol* 2001; **19**: 2179–88.

7 Nakamura S, Suchi T, Koshikawa T *et al.* Clinicopathologic study of CD56 (NCAM)–positive angiocentric lymphoma occuring in sites other than the upper and lower respiratory tract. *Am J Surg Pathol* 1995; **19**: 284–96.

8 Wong K, Chan J, Ng C. CD56 (NCAM)–positive malignant lymphoma. *Leuk Lymphoma* 1994; **14**: 29–36

9 Jia H, Sun T. Extranodal NK/T-cell lymphoma mimicking cellulitis. *Leuk Lymphoma* 2004; **45**: 1467–70.

10 Massone C, Chott A, Metze D *et al.* Subcutaneous, blastic natural killer (NK), NK/T-cell and other cytotoxic lymphomas of the skin: a morphologic, immunophenotypic and molecular study of 50 patients. *Am J Surg Pathol* 2004; **28**: 719–35.

11 Child F, Mitchell T, Whittaker S *et al.* Blastic natural killer cell and extranodal natural killer cell-like T-cell lymphoma presenting in the skin: report of six cases from the UK. *Br J Dermatol* 2003; **148**: 507–15.

12 Siu L, Wong K, Chan J, Kwong Y. Comparative genomic hybridization analysis of natural killer cell lymphoma–leukaemia: recognition of consistent patterns of genetic alterations. *Am J Pathol* 1999; **155**: 1419–25.

13 Nakashima Y, Tagawa H, Suzuki R *et al.* Genome-wide array-based comparative genomic hybridization of natural killer cell lymphoma/leukemia: different genomic patterns of aggressive NK-cell leukemia and extranodal NK/T-cell lymphoma, nasal type. *Genes Chrom Cancer* 2005: **44**: 247–55.

14 Iwatsuki K, Satoh M, Yamamoto T *et al.* Pathogenic link between hydroa vacciniforme and Epstein-Barr virus-associated hematologic disorders. *Arch Dermatol* 2006; **142**: 587–95.

15 Chen H, Hsiao C, Chiu H. Hydroa vacciniforme-like primary cutaneous CD8-positive lymphoma. *Br J Dermatol* 2002; **147**: 587–91.

16 Iwatsuki K, Ohtsuka M, Akiba H, Kaneko F. Atypical hydroa vacciniforme in childhood: from a smoldering stage to Epsein-Barr virus-associated lymphoid malignancy. *J Am Acad Dermatol* 1999; **40**: 283–4.

17 Barrionuevo C, Anderson V, Zevallos-Giamietri E *et al.* Hydroa-like cutaneous T-cell lymphoma: a clinicopathologic and molecular genetic study of 16 pediatric cases from Peru. *Appl Immunohistochem Mol Morphol* 2002; **10**: 7–14.

18 Tomita N, Kanamori H, Fujimaki K *et al.* Epstein-Barr virus-associated extranodal NK/T-cell lymphoma following mosquito bites in an elderly patient without prior hypersensitivity. *Leuk Lymphoma* 2004; **45**: 2153–5.

Primary cutaneous B-cell lymphomas

Primary cutaneous B-cell lymphomas constitute approximately one-quarter of all primary cutaneous lymphomas [1]. Increasing recognition of this group of primary cutaneous lymphomas led to controversy following the first publication of the EORTC classification of primary cutaneous lymphomas which included a subgroup of diffuse large B-cell lymphomas situated almost exclusively on the leg [2]. In addition, the description of a low-grade primary cutaneous lymphoma derived from follicle centre cells, which was distinct from both nodal follicular lymphoma and primary cutaneous diffuse large B-cell lymphoma, also caused controversy although this entity was recognized in the early WHO classification [3]. However, there is now a consensus classification of cutaneous B-cell lymphomas, illustrated by the recent WHO–EORTC classification which defines three specific subtypes of primary cutaneous B-cell lymphoma: marginal zone (MZL), follicle centre cell (FCL) and diffuse large B-cell (LBCL) lymphomas [4]. Full staging investigations are essential for patients with a cutaneous B-cell lymphoma to exclude secondary cutaneous involvement with a nodal lymphoma. Most primary cutaneous B-cell lymphomas are indolent with an excellent long-term prognosis, with the exception of PCLBCL [4,5]. An ISCL–EORTC TNM classification has been proposed for staging primary cutaneous lymphomas other than MF and SS (Table 57.8) [6]. This staging classification has shown prognostic relevance for PCLBCL as multifocal disease appears to be a poor prognostic feature but the value of staging the skin tumour burden in PCMZL and PCFCL has not yet been shown to have an impact on prognosis [7,8]. Recent ISCL–EORTC

Table 57.8 Proposed staging classification of non-mycosis fungoides/Sézary syndrome primary cutaneous lymphomas.

T	
T_1	Solitary skin involvement
T_{1a}	a solitary lesion <5 cm diameter
T_{1b}	a solitary lesion >5 cm diameter
T_2	Regional skin involvement; multiple lesions limited to 1 body region or 2 contiguous body regions
T_{2a}	all-disease-encompassing in a <15-cm diameter circular area
T_{2b}	all-disease-encompassing in a >15- and <30-cm diameter circular area
T_{2c}	all-disease-encompassing in a >30-cm diameter circular area
T_3	Generalized skin involvement
T_{3a}	multiple lesions involving 2 non-contiguous body regions
T_{3b}	multiple lesions involving ≥3 body regions
N	
N_0	No clinical or pathological lymph node involvement
N_1	Involvement of 1 peripheral lymph node region that drains an area of current or prior skin involvement
N_2	Involvement of 2 or more peripheral lymph node regions or involvement of any lymph node region that does not drain an area of current or prior skin involvement
N_3	Involvement of central lymph nodes
M	
M_0	No evidence of extracutaneous non-lymph node disease
M_1	Extracutaneous non-lymph node disease present

Table 57.9 Summary of cytogenetic findings in primary cutaneous B-cell lymphomas.

Cytogenetic abnormality	PCMZL	PCFCL	PCLBCL
t(14;18) IgH : MALT1	22% (21/95)	0% (0/6)	0% (0/14)
t(14;18) IgH : BCL2	11% (9/80)	17% (24/143)	7% (4/54)
t(11;18) AP12 : MALT1	4% (4/96)	0% (0/1)	0% (0/6)
t(1;14) BCL10 : IgH	0% (0/63)	ND	ND
t(8;14) MYC : IgH	0% (0/9)	0% (0/6)	36% (5/14)
t(3;14) BCL6 : IgH	0% (0/9)	6% (2/33)	14% (2/14)
Trisomy 3	17% (11/63)	ND	ND
Trisomy 18	6% (4/63)	ND	ND
BCL2/MALT1 amplification	0% (0/11)	8% (2/25)	60% (12/20)
BCL10 mutation	3% (1/33)	50% (2/4)	ND
BCL6 mutation	0% (0/9)	37% (7/19)	47% (15/32)
cMYC amplification	0% (0/9)	0% (0/6)	17% (3/18)
cREL amplification	ND	25% (3/12)	63% (12/19)
9p21.3 (p16/p14ARF) deletion	ND	0% (0/19)	62% (43/64)

PCMZL, primary cutaneous marginal zone lymphoma; PCFCL, primary cutaneous follicle centre cell lymphoma; PCLBCL, primary cutaneous diffuse large B-cell lymphoma; ND, not determined.

consensus recommendations for the management of primary cutaneous B-cell lymphomas have been published and conservative management is appropriate for PCMZL and PCFCL, although more aggressive therapy may be required for PCLBCL [9]. Distinction between cutaneous B-cell pseudolymphomas and marginal zone lymphomas can be particularly difficult. Systemic B-cell non-Hodgkin's lymphomas such as small cell lymphocytic lymphoma and mantle cell lymphomas are only found within skin as secondary cutaneous involvement associated with underlying nodal disease [10–11], although very rarely mantle cell lymphomas can be restricted to skin [12].

The pathogenetic relationship between these primary cutaneous B-cell lymphomas and their nodal counterparts remains unclear (Table 57.9). Specific translocations characteristic of marginal mucosa associated lymphoid tissue (MALT) lymphomas of nodal and extranodal origin have been detected in a minority of primary cutaneous marginal zone lymphomas. Genomic abnormalities detected in nodal diffuse large B-cell lymphomas have been identified in a primary cutaneous large B-cell lymphoma, suggesting a similar pathogenesis [4]. However, primary cutaneous follicle centre cell lymphomas appear to be distinct pathogenetically from nodal follicular lymphomas [4].

In 1982, Burgdorf *et al*. suggested that Lyme disease was caused by the tick *Ixodes ricinus*, and subsequently the spirochete *Borrelia burgdorferi* was recognized as being the vehicle responsible for carrying infection from the tick to human [13]. Prior to the publication by Burgdorf *et al.*, it had been recognized that patients with acrodermatitis chronica atrophicans, now known to be part of the cutaneous spectrum of Lyme disease, could develop low-grade cutaneous B-cell lymphomas [14–16]. These patients developed multiple plaques and nodules superimposed on lesions of acrodermatitis chronica atrophicans. In a small number of reported cases, the lesions of acrodermatitis chronica atrophicans cleared with antibiotic therapy, but the B-cell lymphoma nodules often persisted [17]. Nevertheless, this suggested the possibility that *Borrelia* might have a role in the pathogenesis of PCMZL [18]. For those patients without clinical evidence of acrodermatitis the causal relationship has been more controversial, with some studies detecting positive *Borrelia* serology and the presence of *Borrelia* in tumour DNA using PCR [19,20] and others consistently reporting negative results [21–23]. Nevertheless this suggests that chronic antigenic stimulation in skin, such as the presence of *Borrelia burgdorferi* infection, may rarely encourage emergence of a neoplastic B-cell clone from a previously benign reactive proliferation of B lymphocytes.

References

1 Kerl H. The morphologic spectrum of B cell lymphomas. *Arch Dermatol* 1996; **132**: 1376–7.

2 Willemze R, Kerl H, Sterry W *et al*. EORTC classification for primary cutaneous lymphomas: a proposal from the Cutaneous Lymphoma Study Group of the European Organization for Research on Treatment of Cancer. *Blood* 1997; **90**: 354–71.

3 Harris N, Jaffe E, Diebold J *et al*. The World Health Organization classification of neoplastic disease of the haematopoietic and lymphoid tissues: report of the clinical advisory committee. *Histopathology* 2000; **36**: 69–87.

4 Willemze R, Jaffe E, Burg G *et al*. WHO-EORTC classification for cutaneous lymphomas. *Blood* 2005; **105**: 3768–85.

5 Pandolfino T, Siegel R, Kuzel T *et al*. Primary cutaneous B-cell lymphoma: review and current concepts. *J Clin Oncol* 2000; **18**: 2152–68.

6 Kim Y, Willemze R, Pimpinelli N *et al*. TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphoma (ISCL) and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer (EORTC). *Blood* 2007; **110**: 479–84.

7 Senff N and Willemze R. The applicability and prognostic value of the new TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sezary syndrome: results on a large cohort of primary cutaneous

B-cell lymphomas and comparison with the system used by the Dutch Cutaneous Lymphoma Group. *Br J Dermatol* 2007; **157**: 1205–11.
8 Golling P, Cozzio A, Dummer R *et al*. Primary cutaneous B-cell lymphomas—clinicopathological, prognostic and therapeutic characterisation of 54 cases according to the new WHO-EORTC classification and the ISCL/EORTC TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sezary syndrome. *Leukaemia Lymphoma* 2008; **49**: 1094–103.
9 Senff N, Noordijk E, Kim Y *et al*. European Organization for Research and Treatment of Cancer and International Society for Cutaneous Lymphoma consensus recommendations for the management of cutaneous B-cell lymphomas. *Blood* 2008; **112**: 1600–9.
10 Bertero M, Novelli M, Fierro MT, Bernengo MG. Mantle zone lymphoma: an immunohistologic study of skin lesions. *J Am Acad Dermatol* 1994; **30**: 23–30.
11 Burg G, Kempf W, Haeffner A *et al*. Cutaneous lymphomas. *Curr Probl Dermatol* 1997; **9**: 137–204.
12 Sen F, Medeiros L, Lu D *et al*. Mantle cell lymphoma. *Skin Am J Surg Pathol* 2002; **26**: 1312–8.
13 Steere AC. Lyme disease. *N Engl J Med* 1989; **321**: 386–96.
14 Braun-Falco O, Guggenberger K, Burg G. Immunozytom unter dem Bild einer Acrodermatitis chronica atrophicans. *Hautarzt* 1978; **29**: 644–7.
15 Geiger HG, Hagedorn M, Petres J. Retikulumzellsarcom bei acrodermatitis chronica atrophicans Herxheimer. *Z Hautkr* 1974; **49**: 359–65.
16 Orfanos CE, Steigleder GK. Die tumorbilende kutane Form des morbus Waldenstrom. *Deutsch Med Wochenschr* 1967; **33**: 1449–77.
17 Garbe C, Stein H, Dienemann D, Orfanos CE. *Borrelia burgdorferi*-associated cutaneous B-cell lymphoma: clinical and immunohistologic characterization of four cases. *J Am Acad Dermatol* 1991; **24**: 584–90.
18 Weber K, Schierz G, Wilkse B. Das Lymphozytom: eine Borreliose? *Z Hautkr* 1985; **60**: 1585–98.
19 Cerroni L, Zochling N, Putz B *et al*. Infection by *Borrelia burgdorferi* and cutaneous B-cell lymphoma. *J Cutan Pathol* 1997; **24**: 457–61.
20 Goodlad J, Davidson M, Hollowood K *et al*. Primary cutaneous B-cell lymphoma and *Borrelia burgdorferi* infection in patients from the highlands of Scotland. *Am J Surg Pathol* 2000; **245**: 1279–85.
21 LeBoit P, McNutt N, Reed J *et al*. Primary cutaneous immunocytoma: a B-cell lymphoma that can easily be mistaken for cutaneous lymphoid hyperplasia. *Am J Surg Pathol* 1994; **18**: 969–78.
22 Dillon W, Saed G, Fivenson D. *Borrelia burgdorferi* DNA is undetectable by polymerase chain reaction in skin lesions of morphoea, scleroderma or lichen sclerosis et atrophicus of patients from North America. *J Am Acad Dermatol* 1995; **33**: 617–20.
23 Wood G, Kamath N, Guitart J *et al*. Absence of *Borrelia burgdorferi* DNA in cutaneous B-cell lymphomas from the United States. *J Cutan Pathol* 2001; **28**: 502–7.

Marginal zone lymphoma

Definition. An indolent cutaneous B-cell lymphoma derived from post-germinal centre cells and characterized by a proliferation of small lymphocytes, marginal zone B-cells (small centrocyte-like), lymphoplasmacytoid cells and plasma cells with monotypic cytoplasmic immunoglobulin [1–3]. Primary cutaneous marginal zone lymphoma (PCMZL) is considered part of the spectrum of extranodal marginal zone B-cell lymphomas which often involve mucosal sites (MALT lymphomas).

This category also includes primary cutaneous immunocytoma [4] and rare primary cutaneous plasmacytoma without overt evidence of underlying myeloma or localized bony or other extramedullary involvement [5,6]. Extraosseous lesions in multiple myeloma are common, and the skin is infiltrated in approximately 10% of cases [7] but primary involvement of the skin without evidence of bone involvement is extremely rare.

Clinical features. These lymphomas present as asymptomatic solitary or multiple dermal papules, plaques or nodules on any body site, although the trunk is most often involved (Fig. 57.34) [1–4]. Spontaneous resolution can occur. Full staging investigations are indicated and a benign monoclonal paraproteinaemia may be present. In cases of plasmacytoma skeletal surveys are required to exclude underlying myeloma. There is a slight male predominance. Anetoderma associated with individual lesions has been described [8]. The estimated 5-year survival is 98–100% [3,4,9].



Fig. 57.34 Marginal zone primary cutaneous B-cell lymphoma: typical urticated dermal erythematous papules and plaques predominantly situated on the trunk.

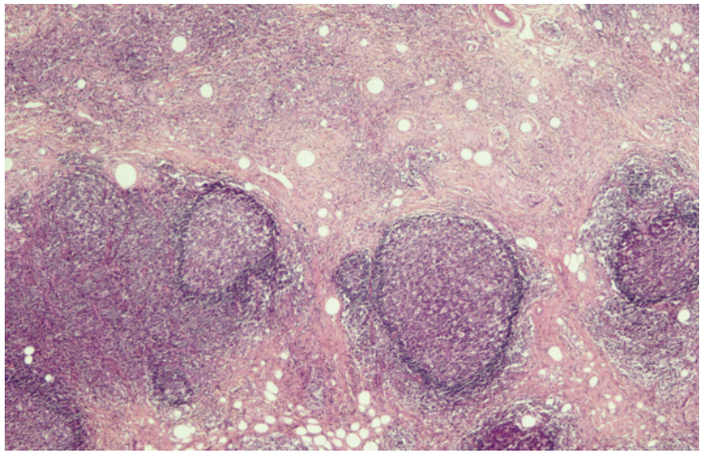


Fig. 57.35 Marginal zone primary cutaneous B-cell lymphoma: reactive germinal centres with a non-epidermotropic monomorphic infiltrate of lymphoplasmacytoid cells and mature plasma cells.

Pathology. Histology is characterized by nodular or diffuse dermal infiltrates of small- to medium-sized lymphocytes, marginal B-cells (centrocyte-like), lymphoplasmacytoid cells and plasma cells, often with a reactive T-cell infiltrate [1–4]. There is no epidermotropism. Reactive follicular structures are often present and tumour cells present within expanded marginal zones and interfollicular areas may colonize these follicular structures (Fig. 57.35). This pattern has to be distinguished immunophenotypically from rare follicular patterns of PCFCL [10,11]. Occasional scattered centrocytes, centroblasts and immunoblasts may be

present. Tumour cells, characterized by monotypic κ or λ positive larger paler lymphoplasmacytoid cells, are concentrated at the periphery of the cellular aggregates or residual follicular structures. PAS-positive intranuclear or intracytoplasmic inclusions may be present [1–3]. Cases with a monomorphic infiltrate of plasma cells (immunocytoma-like) are included [4]. Rare cases of cutaneous plasmacytoma have to be distinguished from benign reactive plasma cell infiltrates (plasmacytosis) by identifying monotypic light chain expression.

Immunophenotype. Tumour cells express CD20, CD79a and Bcl-2, but are Bcl-6, CD5 and CD10 negative [3,12]. PCMZL of the skin should be distinguished from cutaneous infiltrates chronic B-lymphocytic leukaemia, which are $CD5^+$. Plasma cells are $CD138^+$ and $CD79a^+$ (but $CD19^-$ and $CD20^-$) and the infiltrate usually shows either κ or λ light chain restriction (although this can often be difficult to detect in cutaneous sections because of non-specific staining of collagen). Reactive follicles are $Bcl\text{-}6^+$ and $CD10^+$ positive but $Bcl\text{-}2^-$.

Clonal immunoglobulin gene rearrangements are detected in most cases [13]. False-negative results may occur because of somatic hypermutation, which interferes with primer annealing in the analysis of immunoglobulin genes as for follicle centre cell lymphomas although this is less common with the current standardized Biomed primers [14]. The demonstration of light chain restriction and/or a clonal immunoglobulin gene rearrangement represents a critical technique for distinguishing these low-grade cutaneous lymphomas from reactive cutaneous B-cell infiltrates (pseudolymphomas).

Pathogenesis. PCMZL is considered to be part of the spectrum of extranodal marginal zone B-cell lymphomas which were first described in the stomach, the so-called MALT lymphoma, and have since been described in the thyroid, salivary gland, orbit and lung as well as the skin.

As would be expected, PCMZL shows a plasma cell signature in a subset of cases [15]. No disease-specific cytogenetic abnormalities have been identified in PCMZL, although CGH techniques have shown amplification of the *BCL2* locus on chromosome 18 [16]. Fas mutations have rarely been described [17]. Studies (Table 57.9) have also clearly demonstrated that approximately 50% of PCMZL have identical translocations to those found in other extranodal MALT lymphomas, including the t(14;18) involving the *IgH* gene locus and the *MALT-1* gene, which is mostly found in monocytoid variants [18–20]. Trisomy 3 and 18 have also been detected in up to 40% of cases [20,21]. The t(11;18) which produces a fusion protein involving the *AP12* gene and the *MALT-1* gene has also been detected in PCMZL [21,22], although other studies have failed to detect this translocation [17,20,23]. Other translocations found in extranodal marginal zone B-cell lymphomas, such as the t(1;14) involving the *Bcl-10* gene on 1q, have not yet been identified in PCMZL [17,20,21,23]. The t(14;18) involving *Bcl2* has also not been consistently detected in PCMZL [20,24] except in isolated reports [18,25].

Development of immunocytomas has been reported in patients with acrodermatitis chronica atrophicans and has led to speculation about the role of *Borrelia burgdorferi* producing chronic antigen stimulation, leading to neoplastic transformation. The detection of *Borrelia* DNA in some cutaneous lesions of PCMZL, using polymerase chain reaction (PCR), has provided support for this role, but the frequency of positivity varies considerably in different geographical regions, with positive results in central Europe and Scotland [26,27] but no evidence of an association in the USA [28,29]. To date, most cases of PCMZL associated with *Borrelia* have been κ-chain positive.

Treatment. Radiotherapy (low dose) is appropriate and some patients may be managed simply by observation in view of the excellent long-term prognosis [30–32]. Surgical excision may be used for isolated small lesions. The role of IFN-α has not been established but it may be effective either systemically or intralesionally [32]. In cases associated with *Borrelia burgdorferi* relevant antibiotic therapy is appropriate [33]. In patients with multifocal disease chlorambucil may be appropriate [31,32]. Cutaneous recurrences are common and can be treated in a similar manner.

References

1 Sander C, Kaudewitz P, Schirren C *et al*. Immunocytoma and marginal zone B-cell lymphoma (MALT lymphoma), presenting in skin: different entities or a spectrum of disease? *J Cutan Pathol* 1996; **23**: 59.

2 Cerroni L, Signoretti S, Hofler G *et al.* Primary cutaneous marginal zone B-cell lymphoma: a recently described entity of low-grade malignant cutaneous B-cell lymphoma. *Am J Surg Pathol* 1997; **21**: 1307–15.

3 Willemze R, Jaffe E, Burg G *et al*. WHO-EORTC classification for cutaneous lymphomas. *Blood* 2005; **105**: 3768–85.

4 Rijlaarsdam JU, Van Der Putte SCJ, Berti E *et al.* Cutaneous immunocytomas: a clinicopathologic study of 26 cases. *Histopathology* 1993; **23**: 117–25.

5 Johnson WH Jr, Taylor BG. Solitary extramedullary plasmacytoma of the skin: a review of the world literature and the report of an additional case. *Cancer* 1970; **26**: 65–8.

6 Wong KF, Chan JKC, Li LPK *et al.* Primary cutaneous plasmacytoma: report of two cases and review of the literature. *Am J Dermatopathol* 1994; **16**: 392–7.

7 Bluefarb SM. Cutaneous manifestations of multiple myeloma. *Arch Dermatol* 1955; **72**: 506–22.

8 Child F, Woolons A, Price M *et al*. Multiple cutaneous immunocytoma with secondary anetoderma: a report of two cases. *Br J Dermatol* 2000; **143**: 165–70.

9 Senff N, Hoefnagel J, Jansen P *et al*. Reclassification of 300 primary cutaneous B-cell lymphomas according to the new WHO-EORTC classification for cutaneous lymphomas: comparison with previous classifications and identification of prognostic markers. *J Clin Oncol* 2007; **25**: 1581–7.

10 de Laval Harris N, Longtime J, Ferry J, Duncan L. Cutaneous B-cell lymphomas of follicular and marginal zone types. *Am J Surg Pathol* 2001; **25**: 732–41.

11 Pimpinelli N, Santucci M, Moria M *et al.* Primary cutaneous B-cell lymphoma: a clinically homogeneous entity? *J Am Acad Dermatol* 1997; **37**: 1012–6.

12 Gronbaek K, Moller P, Nedergaard T *et al.* Primary cutaneous B-cell lymphoma: a clinical, histological, phenotypic and genotypic study of 21 cases. *Br J Dermatol* 2000; **142**: 913–23.

13 Child F, Woolford A, Calonje E *et al*. Molecular analysis of the immunoglobulin heavy chain gene in the diagnosis of primary cutaneous B-cell lymphoma. *J Invest Dermatol* 2001; **117**: 984–9.

14 Sandberg Y, Heule F, Lam K *et al*. Molecular immunoglobulin/T-cell receptor clonality in cutaneous lymphoproliferations. Experience with the BIOMED-2 standardised polymerase chain reaction protocol. *Haematologica* 2003; **88**: 659–70.

15 Storz M, van de Rijn M, Kim Y *et al*. Gene expression profiles of cutaneous B-cell lymphoma. *J Invest Dermatol* 2003; **120**: 865–70.

16 Mao X, Lillington D, Child F *et al*. Comparative genomic hybridization analysis of primary cutaneous B-cell lymphoma: identification of common genetic alterations in disease pathogenesis. *Genes Chromosomes Cancer* 2002; **35**: 144–55.

17 Gronbaek K, Ralfkiaer E, Kalla J *et al*. Infrequent somatic FAS mutations but no evidence of Bcl10 mutations or t(11;18) in primary cutaneous MALT-type lymphoma. *J Pathol* 2003 **201**: 134–40.
18 Palmedo G, Hautschke M, Rutten A *et al*. Primary cutaneous marginal zone B-cell lymphoma may exhibit both the t(14;18)(q32;21)IGH/BCL2 and the t(14;18)(q32;21) IGH/MALT1 translocation: an indicator for clonal transformation towards higher grade B-cell lymphoma. *Am J Dermatopathol* 2007; **29**: 231–6.
19 Streubel B, Lamprecht A, Dierlamm J *et al*. T(14;18)(q32;q21) involving IGH and MALT-1 is a frequent chromosomal aberration in MALT lymphoma. *Blood* 2003; **101**: 2335–9.
20 Schreuder M, Hoefnagel J, Jansen P *et al*. FISH analysis of MALT lymphoma-specific translocations and aneuploidy in primary cutaneous marginal zone lymphoma. *J Pathol* 2005; **205**: 302–10.
21 Streubel B, Simonitsch-Klupp I, Mullauer L *et al*. Variable frequency of MALT lymphoma-associated genetic aberrations in MALT lymphomas of different sites. *Leukemia* 2004; **18**: 1722–6.
22 Remstein E, James C, Kurtin P. Incidence and subtype specificity of AP12 MALT-1 fusion translocations in extranodal, nodal and splenic marginal zone lymphomas. *Am J Pathol* 2000; **156**: 1183–8.
23 Li C, Inagaki H, Kuo T *et al*. Primary cutaneous marginal zone B-cell lymphoma: a molecular and clinicopathologic study of 24 asian cases. *Am J Surg Pathol* 2003; **27**: 1061–9.
24 Child F, Russell Jones R, Woolford A *et al*. Absence of the t(14;18) translocation in primary cutaneous B-cell lymphomas. *Br J Dermatol* 2001; **144**: 735–44.
25 Servitje O, Gallardo F, Estrach T *et al*. Primary cutaneous marginal zone B-cell lymphoma: a clinical, histopathological, immunophenotypic and molecular genetic study of 22 cases. *Br J Dermatol* 2002; **147**: 1147–58.
26 Cerroni L, Zochling N, Putz B *et al*. Infection by *Borrelia burgdorferi* and cutaneous B-cell lymphoma. *J Cutan Pathol* 1997; **24**: 457–61.
27 Goodlad J, Davidson M, Hollowood K *et al*. Primary cutaneous B-cell lymphoma and *Borrelia burgdorferi* infection in patients from the highlands of Scotland. *Am J Surg Pathol* 2000; **245**: 1279–85.
28 Wood G, Kamath N, Guitart J *et al*. Absence of *Borrelia burgdorferi* DNA in cutaneous B-cell lymphomas from the United States. *J Cutan Pathol* 2001; **28**: 502–7.
29 Dillon W, Saed G, Fivenson D. *Borrelia burgdorferi* DNA is undetectable by polymerase chain reaction in skin lesions of morphoea, scleroderma or lichen sclerosis et atrophicus of patients from North America. *J Am Acad Dermatol* 1995; **33**: 617–20.
30 Santucci M, Pimpinelli N, Arganini L. Primary cutaneous B-cell lymphoma: a unique type of low grade lymphoma—clinicopathologic and immunologic study of 83 cases. *Cancer* 1991; **67**: 2311–26.
31 Hoefnagel J, Vermeer M, Jansen P *et al*. Primary cutaneous marginal zone B-cell lymphoma. *Arch Dermatol* 2005; **141**: 1139–45.
32 Senff N, Noordijk E, Kim Y *et al*. European Organization for Research and Treatment of Cancer and International Society for Cutaneous Lymphoma consensus recommendations for the management of cutaneous B-cell lymphomas. *Blood* 2008; **112**: 1600–9.
33 Kutting B, Bonsmann G, Metz D *et al*. *Borrelia burgdorferi*-associated primary cutaneous B-cell lymphoma: complete clearing of skin lesions after antibiotic pulse therapy or intralesional injection of interferon-α2a. *J Am Acad Dermatol* 1997; **36**: 31–4.

Follicle centre cell lymphoma

Synonym
- Crosti's lymphoma

Definition. An indolent primary cutaneous B-cell lymphoma derived from follicle centre cells (PCFCL) and consisting of a mixture of centrocytes (small/large cleaved cells) and centroblasts (larger non-cleaved cells).

Clinical features. Patients present with clinically non-specific solitary or grouped papules, nodules or tumours, most commonly on the head and neck or trunk [1–3], although any body site may be involved (Figs 57.36–57.38). A gradual increase in size of pre-existing lesions and the appearance of new nodules over a period of years is likely without treatment [1–3]. Rarely, multifocal lesions may occur. Staging investigations including CT scans of the chest, abdomen and pelvis, and bone marrow aspirate and trephine



Fig. 57.36 Primary cutaneous follicle centre cell lymphoma. Extensive erythematous plaque and nodular lesions on the lower back.



Fig. 57.37 Typical clinical presentation of primary cutaneous follicle centre cell lymphoma on the scalp.



Fig. 57.38 Primary cutaneous follicle centre cell lymphoma. Cutaneous presentation of a systemic follicular t(14;18) lymphoma on the trunk with subtle dermal papules and plaques.

biopsies are negative at the time of diagnosis. The estimated 5-year survival of PCFCL is 94–97% [3,4].

Pathology. The histology of PCFCL is variable but the infiltrate shows no epidermotropism and there is a clear grenz zone in the papillary dermis. In the reticular dermis and subcutaneous fat, there is a 'bottom-heavy' nodular or diffuse infiltrate composed of a mixture of centrocytes (small/large cleaved cells), centroblasts (large non-cleaved cells with prominent nucleoli) and a prominent infiltrate of reactive T cells with the remnants of poorly formed germinal centres [1–3]. Some tumour cells show a 'strap-like' or 'fibroblast-like' morphology. The growth pattern may be follicular, follicular and diffuse, or diffuse. Individual patients may show different histological patterns in biopsies from the same group of lesions. PCFCL has to be distinguished from marginal zone lymphomas with follicular colonization of reactive germinal centres. Prominent larger tumours tend to show a more diffuse infiltrate of larger centrocytes, centroblasts and occasional immunoblasts with fewer reactive T cells and no evidence of follicular structures. Such lymphomas should be distinguished from PCLBCL although the presence of a monotonous infiltrate of centroblasts and immunoblasts should be classified as a PCLBCL [3]. A subset of PCFCL shows neoplastic follicular structures with an expansile growth pattern, a thin poorly formed mantle zone and an absence of tingible body (starry sky) macrophages similar to nodal follicular lymphoma although the phenotypic and molecular features are distinct [5].

Immunophenotype. The tumour cells express B-cell associated markers such as CD19, CD20, CD22 and CD79a but are $CD5^-$ [3,6]. CD10 and monotypic cytoplasmic and/or surface immunoglobulin are variably expressed by the neoplastic cells [7]. Follicular structures can be more clearly defined by identifying networks of $CD21^+$ and $CD23^+$ follicular dendritic cells. The tumour cells are mostly Bcl-2 negative, in contrast to systemic nodal follicular lymphoma and diffuse large B-cell lymphoma (DLBCL) in which a significant proportion of the tumour cells are $CD10^+$ and Bcl-2 positive [8]. In those cases with a follicular growth pattern CD10 may be expressed and Bcl-2 may be weakly positive. In contrast, Bcl-6 is usually expressed by PCFCL tumour cells indicative of somatic mutation, as also seen in nodal follicular lymphoma and DLBCL [4]. *MUM-1* and *FOXP1* are usually negative but may be rarely expressed [9,10]. Clonal immunoglobulin gene rearrangements are present in most cases. However false-negative cases are common, caused by somatic hypermutation affecting the primer binding for PCR immunoglobulin gene analysis [11]. Extensive somatic mutation of variable region genes has been identified, which is also consistent with an origin from germinal centre cells [12,13].

Pathogenesis. The relationship between PCFCL and nodal systemic follicular and diffuse large B-cell lymphomas remains unclear. While there are morphological similarities, PCFCL follows an indolent clinical course and the immunophenotypic features (CD10 expression is mostly confined to PCFCL with an exclusively follicular growth pattern and Bcl-2 is usually negative or rarely only weakly positive) are distinct. Microdissection of tumour cells has also confirmed the germinal centre cell origin of PCFCL $Bcl\text{-}2^-$ tumour cells, with no evidence of the t(14;18) translocation, also suggesting a different pathogenesis to nodal follicular lymphoma [13]. Gene expression studies have detected a germinal centre B-cell signature in PCFCL [14] distinct from the activated B-cell signature detected in primary cutaneous DLBCL [15]. While the t(14;18), characteristic of nodal systemic follicular lymphoma and a significant proportion of DLBCLs, has not been consistently detected in most studies of PCFCL [8,16–18], other studies especially from the USA have detected the t(14;18) in a proportion of $CD10^+$ and Bcl-2 positive PCFCL with a follicular growth pattern [19,20], suggesting that there might be some unexplained geographical or histological subset distinction although there are no obvious prognostic differences. A study using a FISH based technique has detected the t(14;18) translocation involving *Bcl-2* in 41% of 27 cases in which a PCR based technique had failed to identify any *Bcl-2* rearrangement [21]. However, this study restricted the cases of PCFCL to those with a follicular growth pattern only.

CGH studies have also identified patterns of chromosomal gains and losses associated with specific oncogene abnormalities in PCFCL including *c-REL* amplification but a consistent pattern has not yet emerged [22,23]. FISH studies (Table 57.9) have not identified chromosomal breakpoints involving the IgH, *myc* or *bcl-6* loci [24] although one study did show a t(3;14) in two of 27 cases involving *Bcl6* and IgH in PCFCL (21). Inactivation of both the cyclin-dependent kinase inhibitors, namely the *p15* and *p16* genes, by promoter hypermethylation has been detected in a proportion of cases but the clinical significance is unclear [25]. A recent study has identified aberrant somatic hypermutation affecting certain oncogenes in PCFCL including *BCL6*, *PAX5*, *MYC* and *RhoH/TTF* similar to findings in nodal and primary cutaneous LBCL [26].

At present, a detailed characterization of the molecular abnormalities in PCFCL is required to clarify the pathogenetic relationship between PCFCL and systemic nodal follicular and diffuse large B-cell lymphomas.

Treatment. Superficial radiotherapy is the treatment of choice for solitary, recurrent and multifocal cutaneous disease, except in rare cases with very extensive cutaneous disease or systemic involvement when single-agent treatment with chlorambucil or combination chemotherapy may be indicated [27–31]. Solitary lesions may be excised, although subsequent radiotherapy is probably advisable to reduce the risk of local recurrence [28]. Recurrences occur in approximately 30% of cases, are usually confined to the skin and do not signify a worse prognosis [30]. Therefore treatment options remain similar.

References

1 Willemze R, Meijer CJLM, Scheffer E. Diffuse large cell lymphomas of follicular centre origin presenting in the skin. *Am J Pathol* 1987; **126**: 325–33.
2 Garcia C, Weiss L, Warnke R, Wood G. Cutaneous follicular lymphoma. *Am J Surg Pathol* 1986; **10**: 454–63.
3 Willemze R, Meijer CJLM, Sentis HJ *et al.* Primary cutaneous large cell lymphomas of follicular center cell origin. *J Am Acad Dermatol* 1987; **16**: 518–26.
4 Willemze R, Jaffe E, Burg G *et al*. WHO-EORTC classification for cutaneous lymphomas. *Blood* 2005; **105**: 3768–85.
5 Cerroni L, Arzberger E, Putz B *et al.* Primary cutaneous follicle center cell lymphoma with follicular growth pattern. *Blood* 2000; **95**: 3922–8.
6 Franco R, Fernadez-Vazquez A, Rodriguez-Peralto J *et al.* Cutaneous follicular B-cell lymphoma. *Am J Surg Pathol* 2001; **25**: 875–83.
7 Gronboek Moller P, Nedergaard T *et al.* Primary cutaneous B-cell lymphoma: a clinical, histological, phenotypic and genotypic study of 21 cases. *Br J Dermatol* 2000; **142**: 913–23.
8 Cerroni L, Volkenandt M, Rieger E *et al.* Bcl-2 protein expression and correlation with the interchromosomal 14;18 translocation in cutaneous lymphomas and pseudolymphomas. *J Invest Dermatol* 1994; **102**: 231–5.
9 Kodama K, Massone C, Chott A *et al*. Primary cutaneous large B-cell lymphomas: clinicopathologic features, classification, and prognostic factors in a large series of patients. *Blood* 2005; **106**: 2491–7.
10 Senff N, Hoefnagel J, Jansen P *et al*. Reclassification of 300 primary cutaneous B-cell lymphomas according to the new WHO-EORTC classification for cutaneous lymphomas: comparison with previous classifications and identification of prognostic markers. *J Clin Oncol* 2007; **25**: 1581–7.
11 Child F, Woolford A, Calonje E *et al*. Molecular analysis of the immunoglobulin heavy chain gene in the diagnosis of primary cutaneous B-cell lymphoma. *J Invest Dermatol* 2001; **117**: 984–9.
12 Aarts W, Willemze R, Bende R *et al.* VH gene analysis of primary cutaneous B-cell lymphomas: evidence for ongoing somatic hypermutation and isotype switching. *Blood* 1998; **92**: 3857–64.
13 Gellrich S, Rutz S, Golembowski S *et al.* Primary cutaneous follicle center cell lymphomas and large B-cell lymphomas of the leg descend from germinal center cells: a single cell polymerase chain reaction analysis. *J Invest Dermatol* 2001; **117**: 1512–20.
14 Storz M, van de Rijn M, Kim Y *et al*. Gene expression profiles of cutaneous B-cell lymphoma. *J Invest Dermatol* 2003; **120**: 865–70.
15 Hoefnagel J, Dijkman R, Basso K *et al*. Distinct types of primary cutaneous large B-cell lymphoma identified by gene expression profiling. *Blood* 2005; **105**: 3671–8.
16 Child F, Russell Jones R, Woolford A, Whittaker S. Absence of the t(14;18) chromosomal translocation in primary cutaneous B-cell lymphoma. *Br J Dermatol* 2001; **144**: 735–44.
17 Goodlad J, Krajewski A, Batstone P *et al.* Primary cutaneous follicular lymphoma; a clinicopathologic and molecular study of 16 cases in support of a distinct entity. *Am J Surg Pathol* 2002; **26**: 733–41.
18 Mirza I, Macpherson N, Paproski R *et al.* Primary cutaneous follicular lymphoma: an assessment of clinical, histopathologic, immunophenotypic, and molecular features. *J Clin Oncol* 2002; **20**: 647–55.
19 Bergman R, Kurtin P, Gibson L *et al.* Clinicopathologic, immunophenotypic and molecular characterization of primary cutaneous B-cell lymphoma. *Arch Dermatol* 2001; **137**: 432–9.
20 Yang B, Tubbs R, Finn W *et al*. Clinicopathologic reassessment of primary cutaneous B-cell lymphomas with immunophenotypic and molecular genetic characterization. *Am J Surg Pathol* 2000; **24**: 694–702.
21 Streubel B, Scheucher B, Valencak J *et al*. Molecular cytogenetic evidence of t(14;18)(IGH;BCL2) in a substantial proportion of primary cutaneous follicle center lymphomas. *Am J Surg Pathol* 2006; **30**: 529–36.
22 Mao X, Lillington D, Child F *et al*. Comparative genomic hybridization analysis of primary cutaneous B-cell lymphoma: identification of common genetic alterations in disease pathogenesis. *Genes Chrom Cancer* 2002; **35**: 144–55.
23 Dijkman R, Tensen C, Jordanova E *et al*. Array based comparative hybridization analysis reveals recurrent chromosomal alterations and prognostic parameters in primary cutaneous large B-cell lymphomas. *J Clin Oncol* 2006; **24**: 296–305.
24 Hallerman C, Kaune K, Gesk S *et al*. Molecular cytogenetic analysis of chromosomal breakpoints in the IGH, MYC, BCL6 and MALT1 gene loci in primary cutaneous B-cell lymphomas. *J Invest Dermatol* 2004; **123**: 213–9.
25 Child F, Scarisbrick J, Calonje E *et al*. Inactivation of tumour suppressor genes *p15* (INK4b) and *p16* (INK4a) in primary cutaneous B cell lymphoma. *J Invest Dermatol* 2002; **118**: 941–8.
26 Dijkman R, Tensen C, Buettner M *et al*. Primary cutaneous follicle center lymphoma and primary cutaneous large B-cell lymphoma, leg type, are both targeted by aberrant somatic hypermutation but demonstrate differential expression of AID. *Blood* 2006; **107**: 4926–9.
27 Rijlaarsdam J, Toonstra J, Meijer C *et al*. Treatment of primary cutaneous B-cell lymphomas of follicle centre cell origin: a clinical follow-up study of 55 patients treated with radiotherapy or chemotherapy. *J Clin Oncol* 1996; **14**: 549–55.
28 Santucci M, Pimpinelli N, Arganini L. Primary cutaneous B-cell lymphoma: a unique type of low grade lymphoma—clinicopathologic and immunologic study of 83 cases. *Cancer* 1991; **67**: 2311–26.
29 Bekkenk M, Vermeer M, Geerts M *et al*. Treatment of multifocal primary cutaneous B-cell lymphoma: a clinical follow-up study of 29 patients. *J Clin Oncol* 1999; **17**: 2471–8.
30 Senff N, Hoefnagel J, Nelis K *et al*. Results of radiotherapy in 153 primary cutaneous B-cell lymphomas classified according to the WHO-EORTC classification. *Arch Dermatol* 2007; **143**: 1520–6.
31 Senff N, Noordijk E, Kim Y *et al*. European Organization for Research and Treatment of Cancer and International Society for Cutaneous Lymphoma consensus recommendations for the management of cutaneous B-cell lymphomas. *Blood* 2008; **112**: 1600–9.

Diffuse large B-cell lymphoma

Definition. Primary cutaneous diffuse large B-cell lymphoma (PCLBCL) is a rare primary cutaneous lymphoma characterized by a diffuse proliferation of large B cells consisting of centroblasts and immunoblasts occurring most commonly on the leg [1]. PCLBCL is closely related to systemic nodal diffuse large B-cell lymphomas, which is the most common form of non-Hodgkin's lymphoma.

Clinical features. PCLBCL affects an elderly population with a female predominance. These lymphomas tend to develop on the lower limbs, predominantly as large dermal nodules or tumours, which are either solitary or multifocal and rapidly enlarging (Fig. 57.39) [1]. PCLBCL can also rarely occur at other cutaneous sites (PCLBCL/other) [2]. Full staging investigations are critical to exclude systemic involvement. The prognosis of PCLBCL is poor, with a 5-year survival of 41–58% [1–4].

Pathology. There is a diffuse non-epidermotropic infiltrate of large cells with morphological similarity to centroblasts and immunoblasts which may extend to involve the subcutis (Fig. 57.40). The infiltrate is monotonous with relatively few associated inflammatory cells or reactive T-cells present. Germinal centres



Fig. 57.39 Clinical presentation of primary cutaneous large B-cell lymphoma on the legs.

are not apparent and mitoses are prominent. Morphological variants recognized in cutaneous disease include cleaved and round cell types but the reproducibility of this distinction is poor [3]. Initially it was reported that the presence of round cell morphology was an adverse prognostic feature. However, this may be explained by subsequent recognition that the cleaved cell type, showing a predominance of large centrocytes and multilobated cells, with few exceptions represents diffuse PCFCL (Crosti's lymphoma) [2].

Immunophenotype. The tumour cells are $CD19^+$, $CD20^+$, $CD22^+$ and $CD79a^+$ with monotypic expression of surface and/or cytoplasmic immunoglobulin in some cases [2,5]. Tumour cells are usually strongly Bcl-2 positive [5,6] and Bcl-6 is also expressed by most cases with evidence of *Bcl-6* gene mutations [5,7]. CD10 expression is only rarely detected in PCLBCL [5]. *MUM-1* and *FOX-P1* are invariably expressed by tumour cells in PCLBCL in contrast to PCFCL [8].

Pathogenesis. Although PCLBCL by definition arises *de novo* in the skin, some tumours might result from high-grade transformation of a low-grade primary cutaneous B-cell lymphoma such as PCFCL [9]. At present, it is unclear whether PCLBCL has the same pathogenesis as primary nodal DLBCL. When PCLBCL presents at sites other than the leg, it is important to distinguish this from diffuse forms of PCFCL, because PCFCL has an excellent prognosis [9].

Clonal rearrangements of immunoglobulin genes are present in most cases with false-negative results resulting from somatic hypermutation [10]. No disease-specific cytogenetic abnormalities have been identified. The t(14;18) translocation has not been identified in Bcl-2 positive cutaneous cases [11–14], except in rare cases from one series [15], The t(14;18) is a common feature of nodal DLBCL reflecting a likely transformation from nodal follicular lymphoma and is found in nodal DLBCL with secondary cutaneous involvement [12]. Unlike PCFCL and PCMZL, 6q losses and 2p, 12 and 18q gains are characteristic findings in PCLBCL and chromosomal amplification of the *bcl2* gene may account for bcl-2 overexpression in PCLBCL [15–17]. In addition, inactivation of *p15* and *p16* genes by promotor hypermethylation and deletion of the 9p21.3 locus containing the *p14/16* genes has been detected [17,18] and CGH studies have identified specific oncogene abnormalities including *c-REL* and *MALT1* gene amplification [16,17]. Recent studies suggest that *p16* loss may have prognostic significance [19]. Studies (Table 57.9) have also shown rare translocations involving *myc* and IgH in PCLBCL in contrast to PCFCL [14,15]. *BCL6* rearrangements have not been detected in PCLBCL [15] but mutations of the *BCL6* gene have been detected [7] and this provides an alternative explanation for over-expression of Bcl-6.

Recent studies in nodal DLBCL using microarray technology have confirmed that these tumours are heterogeneous in origin with the detection of three distinct gene expression profiles which also have prognostic significance: one characteristic of germinal centre cells; one with an expression profile consistent with activated peripheral blood B cells; and one with an indeterminate profile [20,21]. Studies have shown that PCLBCL has an origin from activated B-cells compared to PCFCL which show a germinal centre B-cell gene expression profile [22].

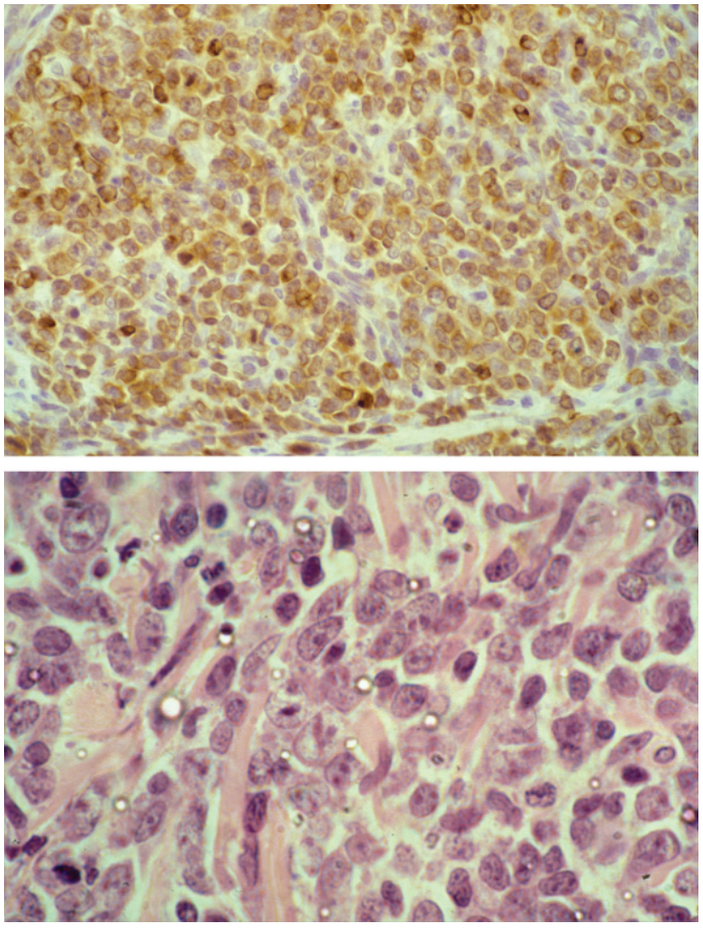


Fig. 57.40 Primary cutaneous large B-cell lymphoma showing a diffuse pattern of large mononuclear cells and strong Bcl-2 positivity.

Prognosis. The prognosis for PCLBCL is poor, with a 41–58% 5-year survival, but this is generally better than for nodal DLBCL [1–4]. Although studies initially suggested that *Bcl-2* expression was site-related (lower limbs and multifocal lesions are more frequently Bcl-2 positive) and associated with a worse prognosis [3], the prognostic significance of *Bcl-2* expression has since been disputed [23]. Recent studies have shown that multifocal disease and location on the leg, are associated with a worse prognosis in multivariate analysis [2,4,8].

Treatment. In elderly patients with solitary tumours, radiotherapy may be appropriate but multiagent chemotherapy is usually required, especially for multifocal disease [24,25,26]. The role of rituximab (a chimeric mouse/human anti-CD20 antibody which induces antibody-dependent cytotoxicity) as a single agent in cutaneous disease has yet to be determined [27,28], but CHOP chemotherapy (R-CHOP) is now the standard of care in nodal DLBCL and an appropriate consideration for patients with PCLBCL. Intralesional rituximab may prove to be effective for selected patients in whom radiotherapy or R-CHOP is not possible [29].

References

1 Vermeer MH, Geelen FAMJ, van Haselen CW *et al.* Primary cutaneous large B-cell lymphomas of the legs. *Arch Dermatol* 1996; **132**: 1304–8.

2 Willemze R, Jaffe E, Burg G *et al.* WHO-EORTC classification for cutaneous lymphomas. *Blood* 2005; **105**: 3768–85.

3 Grange F, Bekkenk M, Wechsler J *et al.* Prognostic factors in primary cutaneous large B-cell lymphomas: a European multicenter study. *J Clin Oncol* 2001; **19**: 3602–10.

4 Grange F, Beylot-Barry M, Courville P *et al.* Primary cutaneous diffuse large B-cell lymphoma, leg type. *Arch Dermatol* 2007; **143**: 1144–50.

5 Yang B, Tubbs R, Finn W *et al.* Clinicopathologic reassessment of primary cutaneous B-cell lymphomas with immunophenotypic and molecular genetic characterization. *Am J Surg Pathol* 2000; **24**: 694–702.

6 Geelen F, Vermeer M, Meijer C *et al.* Bcl-2 protein expression in primary cutaneous large B-cell lymphoma is site related. *J Clin Oncol* 1998; **16**: 2080–5.

7 Paulli M, Viglio A, Vivenza D *et al.* Primary cutaneous large B-cell lymphoma of the leg: histogenetic analysis of a controversial clinicopathologic entity. *Hum Pathol* 2002; **33**: 937–43.

8 Kodama K, Massone C, Chott A *et al.* Primary cutaneous large B-cell lymphomas: clinicopathologic features, classification, and prognostic factors in a large series of patients. *Blood* 2005; **106**: 2491–7.

9 Willemze R, Meijer CJLM, Sentis HJ *et al.* Primary cutaneous large cell lymphomas of follicular center cell origin. *J Am Acad Dermatol* 1997; **16**: 518–26.

10 Child F, Woolford A, Calonje E *et al.* Molecular analysis of the immunoglobulin heavy chain gene in the diagnosis of primary cutaneous B-cell lymphoma. *J Invest Dermatol* 2001; **117**: 984–9.

11 Child F, Russell Jones R, Woolford A, Whittaker S. Absence of the t(14;18) chromosomal translocation in primary cutaneous B-cell lymphoma. *Br J Dermatol* 2001; **144**: 735–44.

12 Kim B, Surti U, Pandya A, Swerdlow S. Primary and secondary cutaneous diffuse large B-cell lymphomas. *Am J Surg Pathol* 2003; **27**: 356–64.

13 Hallerman C, Kaune K, Siebert R *et al.* Chromosomal aberration patterns differ in subtypes of primary cutaneous B-cell lymphomas. *J Invest Dermatol* 2004; **122**: 1495–502.

14 Hallerman C, Kaune K, Gesk S *et al.* Molecular cytogenetic analysis of chromosomal breakpoints in the IGH, MYC, BCL6 and MALT1 gene loci in primary cutaneous B-cell lymphomas. *J Invest Dermatol* 2004; **123**: 213–9.

15 Wiesner T, Streubel B, Huber D, Kerl H, Chott A, Cerroni L. Genetic aberrations in primary cutaneous large B-cell lymphoma. *Am J Surg Pathol* 2005; **29**: 666–73.

16 Mao X, Lillington D, Child F *et al.* Comparative genomic hybridization analysis of primary cutaneous B-cell lymphoma: identification of common genetic alterations in disease pathogenesis. *Genes Chromosomes Cancer* 2002; **35**: 144–55.

17 Dijkman R, Tensen C, Jordanova E *et al.* Array based comparative genomic hybridisation analysis reveals recurrent chromosomal alterations and prognostic parameters in primary cutaneous large B-cell lymphoma. *J Clin Oncol* 2006; **24**: 296–305.

18 Child F, Scarisbrick J, Calonje E *et al.* Inactivation of tumour suppressor genes *p15* and *p16* in primary cutaneous B-cell lymphoma. *J Invest Dermatol* 2002; **118**: 941–8.

19 Senff NJ, Zoutman WH, Vermeer MH *et al.* Fine-mapping chromosomal loss at 9p21: correlation with prognosis in primary cutaneous diffuse large B-cell lymphoma, leg type. *J Invest Dermatol* 2009; **129**: 1149–55.

20 Rosenwald A, Wright G, Chan W *et al.* The use of molecular profiling to predict survival after chemotherapy for diffuse large B-cell lymphoma. *N Engl J Med* 2002; **346**: 1937–47.

21 Alizadeh A, Eisen M, Davis R *et al.* Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. *Nature* 2000; **403**: 503–11.

22 Hoefnagel J, Dijkman R, Basso K *et al.* Distinct types of primary cutaneous large B-cell lymphoma identified by gene expression profiling. *Blood* 2005; **105**: 3671–8.

23 Fernadez-Vazquez A, Rodriguez-Peralto J, Martinez M *et al.* Primary cutaneous large B-cell lymphoma: the relation between morphology, clinical presentation, immunohistochemical markers and survival. *Am J Surg Pathol* 2001; **25**: 307–15.

24 Brice P, Cazals D, Mounier N *et al.* Primary cutaneous large-cell lymphoma: analysis of 49 patients included in the LNH87 prospective trial of polychemotherapy for high-grade lymphomas. *Leukaemia* 1998; **12**: 213–9.



Fig. 57.41 Clinical illustration of histology illustrated in Fig. 57.42. Note marbled appearance of inner thigh which was woody hard on palpation. B-cell lymphoma showing lack of epidermotropism and clear grenz zone in the papillary dermis. (Courtesy of R.S. Lever, Western Infirmary, Glasgow, UK.)

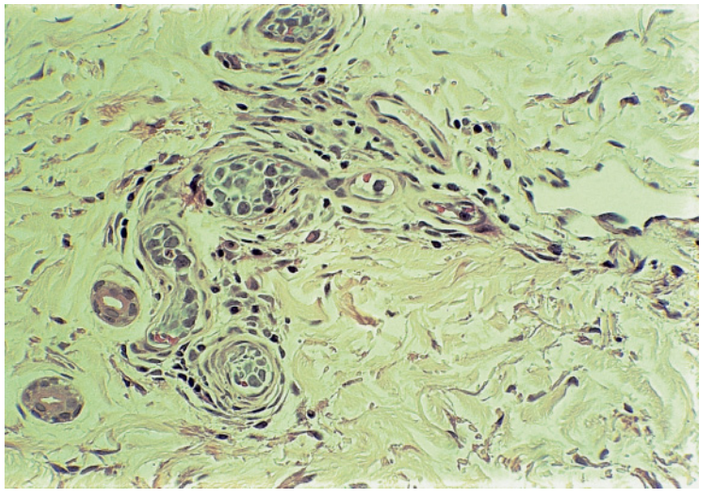


Fig. 57.42 Histology of angiocentric B-cell lymphoma showing B cells within small vascular channels in the dermis. These are stained with membrane markers for B cells, not with membrane markers for endothelial cells.

25 Bekkenk M, Vermeer M, Geerts M *et al.* Treatment of multifocal primary cutaneous B-cell lymphoma: a clinical follow-up study of 29 patients. *J Clin Oncol* 1999; **17**: 2471–8.

26 Senff N, Noordijk E, Kim Y *et al*. European Organization for Research and Treatment of Cancer and International Society for Cutaneous Lymphoma consensus recommendations for the management of cutaneous B-cell lymphomas. *Blood* 2008; **112**: 1600–9.

27 Sabroe R, Child F, Woolford A *et al*. Rituximab in cutaneous B-cell lymphoma: a report of two cases. *Br J Dermatol* 2000; **143**: 157–61.

28 Heinzerling L, Urbanek M, Funk J *et al.* Reduction of tumour burden and stabilization of disease by systemic therapy with anti-CD20 antibody (rituximab) in patients with primary cutaneous B-cell lymphoma. *Cancer* 2000; **89**: 1835–44.

29 Heinzerling L, Dummer R, Kempf W *et al*. Intralesional therapy with anti-CD20 monoclonal antibody rituximab in primary cutaneous B-cell lymphoma. *Arch Dermatol* 2000; **136**: 374–8.

Secondary cutaneous B-cell lymphomas

Intravascular large B-cell lymphoma [1–11]

Synonyms
- Malignant angioendotheliomatosis
- Angiotrophic lymphoma

Definition. A rare extranodal B-cell lymphoma characterized by accumulation of large B cells within small blood vessels. This tumour usually involves multiple extranodal sites including the CNS, lung and skin, and symptoms and/or signs at these sites may be the presenting feature.

Clinical features. Patients present with diffuse, tender, hard, infiltrated plaques, commonly on the thigh (Fig. 57.41); the clinical appearance may suggest a sclerotic connective tissue disorder or panniculitis. A variety of clinical features may occur as a consequence of occlusion of small vessels including telangiectatic skin lesions. Colonization of benign haemangiomas by tumour cells has been reported. The prognosis is poor, although rare cases with disease confined to the skin may have a better outlook with a 3-year survival of 56% versus 22% if spread beyond the skin.

Pathology. The tumour cells are large and show striking atypia with an occasional anaplastic morphology. These cells are situated entirely within dilated vessel lumina in the dermis and subcutis (Fig. 57.42). Occlusion of vessels by tumour cells and fibrin thrombi may be present.

Immunophenotype. The tumour cells are positive for B-cell-associated antigens consistent with origin from a peripheral post-germinal centre B cell. Clonal immunoglobulin gene rearrangements are present. Rare cases are derived from T cells and show a clonal TCR gene rearrangement. Rarely, factor VIII, an endothelial cell-related antigen, may be positive but this is thought to be caused by absorption of antigen by tumour cells rather than indicating an endothelial cell origin.

Treatment. There are some reports of partial response to combination chemotherapy, but the disease has a poor prognosis and is usually fatal.

References

1 Berger TG, Dawson NA. Angioendotheliomatosis. *J Am Acad Dermatol* 1988; **18**: 407–12.

2 Dominguez FE, Rosen LB, Kramer HC. Malignant angioendotheliomatosis proliferans. *Am J Dermatopathol* 1986; **8**: 419–25.

3 Perniciaro C, Winkelmann RK, Daoud MS, Su WPD. Malignant angioendotheliomatosis is an angiotropic intravascular lymphoma. *Am J Dermatol* 1995; **17**: 242–8.

4 Petroff N, Koger OW, Fleming MG *et al.* Malignant angioendotheliomatosis: an angiotropic lymphoma. *J Am Acad Dermatol* 1989; **21**: 727–33.

5 Wick MR, Rocamora A. Reactive and malignant 'angioendotheliomatosis': a discriminant clinicopathological study. *J Cutan Pathol* 1988; **15**: 260–1.

6 Willemze R, Kruyswijk MRJ, De Bruin CD *et al.* Angiotropic (intravascular) large cell lymphoma of the skin previously classified as malignant angioendotheliomatosis. *Br J Dermatol* 1987; **116**: 393–9.

7 Braverman IM, Lerner AB. Diffuse malignant proliferation of vascular endothelium. *Arch Dermatol* 1961; **84**: 72–80.

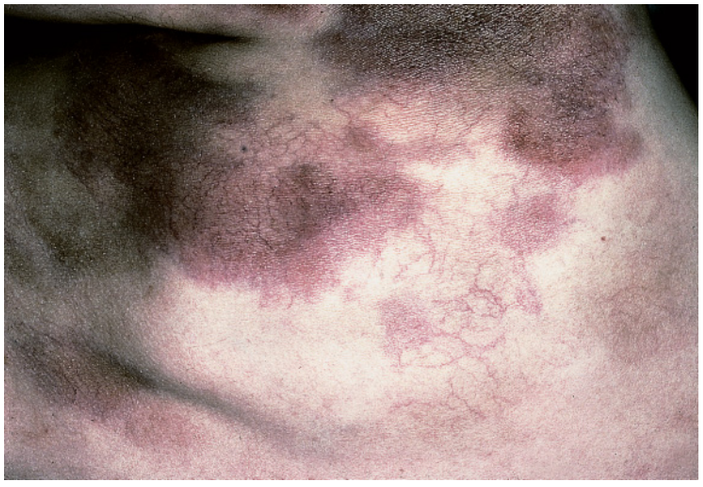


Fig. 57.43 Clinical features of lymphomatoid granulomatosis showing extensive purpuric, bruise-like lesions on the trunk.

8 Eros N, Karolyi Z, Kovacs A *et al.* Intravascular B-cell lymphoma. *J Am Acad Dermatol* 2002; **47**: S260–2.

9 Ferreri A, Campo E, Seymour J *et al*. Intravascular lymphoma: clinical presentation, natural history and prognostic factors in a series of 38 cases with special emphasis on the 'cutaneous variant'. *Br J Haematol* 2004; **127**: 173–83.

10 Rubin M, Cossman J, Freter C, Azumi N. Intravascular large cell lymphoma coexisting within hemangiomas of the skin. *Am J Surg Pathol* 1997; **21**: 860–4.

11 Kobayashi T, Munakata S, Sugiura H *et al*. Angiotropic lymphoma: proliferation of B-cells in the capillaries of cutaneous angiomas. *Br J Dermatol* 2000; **143**: 162–4.

Lymphomatoid granulomatosis

Definition. An angiocentric and angiodestructive extranodal EBV-positive B-cell lymphoma, which invariably involves the lungs and may involve the skin and CNS [1–3].

Clinical features. Patients most frequently present with pulmonary symptoms associated with systemic malaise, arthralgias, weight loss and fever. The skin (50% of cases), CNS and kidneys are also often directly involved. The cutaneous lesions described are diverse but include subcutaneous nodules and plaques, more superficial plaques and a diffuse erythematous maculopapular eruption (Fig. 57.43) with epidermal atrophy and purpura [4–10]. Necrosis and ulceration may also occur [4]. Some patients have a fluctuating course with spontaneous remissions but eventually progressive disease develops.

Pathology. The striking feature is the angiocentricity of the infiltrate and gross vessel destruction sometimes accompanied by fibrinoid necrosis (angiodestruction) [7]. The infiltrate is polymorphous and contains both lymphocytes and histiocytes with pleomorphic or large (immunoblast-like) tumour cells and often a prominent reactive T-cell infiltrate. Multinucleated cells may be present although well-formed granulomas are rare. The presence of large transformed cells is associated with a worse prognosis.

Immunophenotype. The tumour cells are EBV$^+$, express CD20 and are variably CD79a$^+$. CD30 may be expressed but the cells are CD15$^-$. The reactive T cells are CD3$^+$ and CD4$^+$. Clonal immunoglobulin gene rearrangements can be detected in most cases and Southern blot analysis usually confirms the presence of clonal episomal EBV [8].

Pathogenesis. Lymphomatoid granulomatosis is an EBV-driven lymphoproliferative disorder that can be associated with immunodeficiency states including post-transplantation and long-term therapies such as methotrexate for rheumatoid arthritis [9,10]. This lymphoma should be distinguished from extranodal NK/T-cell lymphoma (nasal type), which is also EBV$^+$ and characterized by an angiodestructive histology [8].

Treatment. Although some patients have spontaneous remissions, the development of high-grade disease is associated with a median survival of less than 2 years. Short-lived remissions with high-dose chemotherapy have been described. There are reports of responses to cyclophosphamide and IFN-α, particularly for patients with low-grade disease [11].

References

1 Liebow AA, Carrington CRB, Friedman PJ. Lymphomatoid granulomatosis. *Hum Pathol* 1972; **3**: 457–558.

2 Katzenstein A-LA, Carrington CB, Liebow AA. Lymphomatoid granulomatosis: a clinicopathologic study of 152 cases. *Cancer* 1979; **43**: 360–73.

3 Lee SC, Roth LM, Brashear RE. Lymphomatoid granulomatosis. *Cancer* 1976; **38**: 846–53.

4 Minars N, Kay S, Escobar MR. Lymphomatoid granulomatosis: a new clinicopathologic entity. *Arch Dermatol* 1975; **111**: 493–6.

5 Macdonald DM, Sarkany I. Lymphomatoid granulomatosis. *Clin Exp Dermatol* 1976; **1**: 163–73.

6 Jambrosic J, From L, Assaad DA *et al.* Lymphomatoid granulomatosis. *J Am Acad Dermatol* 1987; **17**: 621–31.

7 Madison Mcniff J, Cooper D, Howe G *et al.* Lymphomatoid granulomatosis of the skin and lung. *Arch Dermatol* 1996; **132**: 1464–70.

8 Harris N, Jaffe E, Diebold J *et al.* The World Health Organization classification of neoplastic disease of the haematopoietic and lymphoid tissues: report of the clinical advisory committee. *Histopathology* 2000; **36**: 69–87.

9 Kwon E, Katz K, Draft K *et al*. Posttransplantation lymphoproliferative disease with features of lymphomatoid granulomatosis in a lung transplant patient. *J Am Acad Dermatol* 2006; **54**: 657–63.

10 Beaty M, Toro J, Sorbara L *et al.* Cutaneous lymphomatoid granulomatosis: correlation of clinical and biologic features. *Am J Surg Pathol* 2001; **25**: 111–20.

11 Fauci AS, Haynes B, Costa J *et al.* Lymphomatoid granulomatosis; prospective clinical trial and therapeutic experience over 10 years. *N Engl J Med* 1982; **306**: 68–74.

Secondary cutaneous T-cell lymphomas

Angioimmunoblastic T-cell lymphoma

Synonym
- Angioimmunoblastic lymphadenopathy (AILD)

Definition. AILD is a nodal T-cell lymphoma derived from follicular helper T-cells and associated with a complex dysregulation of B-cells [1]. Extranodal involvement of sites, including skin, is well recognized [2].

Clinical features. Patients may present with systemic and/or peripheral lymphadenopathy often accompanied by 'B' symptoms [2]. Splenomegaly occurs in over 50% of cases and many patients will have advanced disease and bone marrow involvement at diagnosis [2]. Autoimmune phenomena are common, including neurological abnormalities, arthritis, hypergammaglobulinaemia, haemolytic anaemia and thrombocytopenic purpura [2]. Cutaneous extranodal involvement is common (45% of cases) and rarely can be a presenting feature [2]. Skin changes are highly variable and can be subtle, including maculopapular and papulonodular eruptions. Erythroderma, haemorrhagic and urticarial eruptions have been described as well as dermal plaques [3]. Occasionally, cutaneous involvement in AILD can mimic drug eruptions and infections [4,5].

Pathology. The nodal pathologic features in AILD are characterized by hyperplastic follicles and a prominent arborizing vascular proliferation with expanded follicular dendritic cells. There is an associated polymorphous infiltrate with clusters of large clear cells [1]. The infiltrate consists of $CD10^+$ T-cells and an expansion of EBV infected B-cells (EBER positive). Cutaneous involvement is characterized by variable features; a non-specific perivascular lymphocytic infiltrate with minimal atypia and capillary hyperplasia can be found in some biopsies or more prominent dermal perivascular infiltrates showing cytologically atypical pleomorphic cells and occasionally more obvious dense infiltrates of atypical lymphocytes are present [6]. Granulomatous infiltrates and vasculitis have been reported [6]. There is no epidermotropism. The atypical cells express T-cell antigens and are also $CD10^+$ [3].

Pathogenesis. Clonal rearrangements of TCR genes are detected in a majority of cases but additional monoclonal or oligoclonal IgH rearrangements are often found consistent with the characteristic EBV^+ B-cell proliferation seen in lymph nodes from AILD patients [1]. The recent finding of *CXCL13* expression by tumour cells in AILD has confirmed a derivation from follicular helper T cells [1]. Specific patterns of chromosomal abnormalities, including deletions of chromosome 7, have been reported but no disease-specific translocations [1].

Treatment. The disease can be indolent but transformation is associated with a poor prognosis. Immunomodulatory therapies have been used successfully including ciclosporin, steroids, thalidomide and angiogenesis inhibitors such as bevacizumab [1].

References

1 Dunleavy K, Wilson W, Jaffe E. Angioimmunoblastic T-cell lymphoma: pathobiological insights and clinical implications. *Curr Opin Haematol* 2007; **14**: 348–53.

2 Lachenal F, Berger F, Ghesquieres H *et al*. Angioimmunoblastic T-cell lymphoma. Clinical and laboratory features at diagnosis in 77 patients. *Medicine* 2007; **86**: 282–92.

3 Huang C, Chuang S. Angioimmunoblastic T-cell lymphoma with cutaneous involvement. *Arch Pathol Lab Med* 2004; **128**: 122–4.

4 Yoon G, Chang S, Kim H *et al*. Cutaneous relapse of angioimmunoblastic lymphadenopathy-type peripheral T-cell lymphoma mimicking an exanthematous drug eruption. *Int J Dermatol* 2003; **42**: 816–8.

5 Jayaraman A, Cassarino D, Advani R *et al*. Cutaneous involvement by angioimmunoblastic T-cell lymphoma: a unique histologic presentation mimicking an infectious etiology. *J Cutan Pathol* 2006; **33** (Suppl): 6–11.

6 Martel P, Laroche L, Courville P *et al*. Cutaneous involvement in patients with angioimmunoblastic lymphadenopathy with dysproteinemia: a clinical, immunohistological and molecular analysis. *Arch Dermatol* 2000; **136**: 881–6.

Post-transplant lymphoproliferative disorder (PTLD)

Definition. Lymphomas occurring in solid organ transplant recipients on immunosuppressive therapy. The incidence varies according to the organ transplanted (heart–lung : renal transplant rates of 10–1% respectively) and although extranodal lymphomas are overrepresented in PTLD, primary cutaneous involvement is very rare. Less than 20 cases have been reported of primary cutaneous B-cell PTLD and primary cutaneous T-cell PTLD is even less frequent [1–2].

Clinical features. The clinical features described are diverse; solitary or multiple plaques, nodules or tumours, with or without ulceration, have been described affecting any site. Systemic involvement and in particular involvement of the transplanted organ must be excluded in patients with primary cutaneous PTLD. Spontaneous resolution has been reported. For primary cutaneous T-cell PTLD, erythroderma is the most common clinical presentation but all types of CTCL have been described [3].

Pathology. Diffuse dermal infiltrates extending to the subcutis and consisting of large pleomorphic lymphocytes or centroblasts. Plasmacytoid differentiation and plasmablasts may be a feature. Necrosis may be present. For PC B-cell PTLD the tumour cells express B-cell antigens while PC T-cell PTLD may be $CD30^+$ but histological features mimicking all types of CTCL have been described [2,3].

Pathogenesis. B-cell PTLD is associated with EBV infection and progression from an early reactive phase can be identified. Three distinct types of PTLD are recognized: (i) plasmacytic hyperplasia is a polyclonal proliferation associated with multiple copies of EBV and occurring early after transplantation; (ii) polymorphic lymphoproliferative disorder usually occurring several years after transplantation is a monoclonal EBV proliferation with a single copy of EBV but without secondary genomic abnormalities; and (iii) malignant lymphoma is a monoclonal EBV infection with a single copy of EBV and associated secondary genomic abnormalities and widespread disease. Rare cases of PC B-cell PTLD have been associated with HHV-8 infection [4]. No viral association has been described for systemic or cutaneous T-cell PTLD although rare EBV^+ T-cell lymphomas have been reported. Primary cutaneous presentations can also occur in non-organ transplant recipients such as HIV^+ patients or those with other forms of profound immunodeficiency. Similarly EBV^+ lymphoproliferative disorders can develop in patients who have undergone high-dose chemotherapy for primary lymphomas although cutaneous involvement has not been reported as yet in this context.

Treatment. While surgery and radiotherapy can be used, reduction in immunosuppression is often effective [5]. Both chemotherapy and rituximab have been reported to be effective. While the prognosis for B-cell PTLD is generally good [6], both primary cutaneous and systemic T-cell PTLD have a very poor prognosis.

References

1 Blokx W, Andriessen M, Hamersvelt H, van Krieken J. Initial spontaneous regression of posttransplantation Epstein Barr virus-related B-cell lymphoproliferative disorder of the skin in a renal transplant recipient. *Am J Dermatopathol* 2002; **24**: 414–22.

2 Lok C, Viseux V, Denoeux J, Bagot M. Post-transplant cutaneous T-cell lymphomas. *Crit Rev Oncol/Haematol* 2005; **56**: 137–45.

3 Ravat F, Spittle M, Russell Jones R. Primary cutaneous T-cell lymphoma occuring after organ transplantation. *J Am Acad Dermatol* 2006; **54**: 668–75.

4 Verma S, Nuovo J, Porcu P *et al*. Epstein-Barr virus and human herpesvirus 8-associated primary cutaneous plasmablastic lymphoma in the setting of renal transplantation. *J Cutan Pathol* 2005; **32**: 35–9.

5 Mohsin N, Budruddin M, Kamble P *et al*. Complete regression of cutaneous B-cell lymphoma in a renal transplant patient after conversion from cyclosporin to sirolimus. *Transplant Proc* 2007; **39**: 1267–71.

6 McGregor J, Carmen C, Lu Q *et al*. Post-transplant cutaneous lymphoma. *J Am Acad Dermatol* 1993; **29**: 549–54.

Pseudolymphomas

Definition. Benign but persistent lymphoid proliferations in the dermis, which may be difficult to distinguish from a low-grade malignant lymphoma and possibly may rarely transform to a lymphoma in some cases [1–3]. The term cutaneous lymphoid hyperplasia has been suggested and both terms are more commonly used to describe a pathological rather than a clinical appearance. Confusion between pseudolymphoma and lymphoma can easily arise if a biopsy is submitted to the pathologist without an adequate history of recent events such as drug ingestion or scabies infestation.

Aetiology. T-cell pseudolymphomas may arise as a form of adverse drug reaction. The range of drugs causing T-cell pseudolymphomas is wide but includes anticonvulsants, angiotensin-converting enzyme inhibitors, β-blockers, cytotoxics, antirheumatics, antibiotics, antidepressants and many others [4–8]. Persistent contact dermatitis may produce a T-cell pseudolymphoma [9]. Persistent nodular scabies and arthropod bites may also cause a T-cell pseudolymphomatous histology [10], possibly caused by retained foreign material stimulating a persistent antigenic reaction [11,12]. There are three reports in the literature of putative CTCL arising in association with silicone breast implants, which may be examples of this phenomenon [13]. Actinic reticuloid (see below) may resemble a cutaneous T-cell lymphoma histologically. Jessner's lymphocytic infiltrate (see below) can also be classified as a T-cell pseudolymphoma, although there is a view that it is a variant of cutaneous lupus erythematosus.

B-cell pseudolymphomas may arise in the course of Lyme disease with *Borrelia burgdorferi* infection [14], in tattoos as a reaction to certain pigments [15,16], after vaccination and trauma [17], acupuncture [18] and within scars after herpes zoster infection [19]. The classic entity of lymphocytoma cutis histologically resembles a B-cell pseudolymphoma, and is at present of unknown aetiology.



Fig. 57.44 Clinical appearance of a persistent photosensitive drug eruption induced by co-trimoxazole (Septrin).

It is generally wise to be guarded in the diagnosis and prognosis of pseudolymphoma, as in a number of cases clear progression from apparent pseudolymphoma to malignant lymphoma has been recorded. This appears to confirm the concept that chronic, initially benign, reactive inflammatory conditions may very rarely progress to frank lymphoma or that indeed these conditions may be low grade lymphomas initially which then transform and adopt a more obvious malignant cellular cytology/morphology.

Clinical features. Both T- and B-cell pseudolymphomas may present as multiple cutaneous nodules (Fig. 57.44) as in persistent nodular scabies or lymphocytoma cutis. T-cell pseudolymphomas may also present as persistent erythema sometimes developing into an exfoliative erythroderma [20]. This is characteristic of T-cell pseudolymphomas caused by drug reactions or contact dermatitis. B-cell pseudolymphomas may also be associated with palpable lymphadenopathy, adding to diagnostic confusion.

Pathology [21–26]. If the distinction between lymphoma and pseudolymphoma is to be made, it is vital to give the pathologist a good clinical history as the pathological, phenotypic and molecular differentiation is not absolute. The salient feature of a pseudolymphoma is the presence of T- or B-cell lymphoid proliferations. A few mitotic figures may be present, but the degree of cytologic atypia is minimal. T-cell pseudolymphomas may be band-like or nodular in distribution, whereas B-cell pseudolymphomas are

usually nodular. Germinal centre formation may or may not be present in B-cell pseudolymphomas but typically reactive germinal centres have tingible body macrophages. Rarely, the lymphoid cells may be very bizarre and resemble mitogen-stimulated lymphocytes seen *in vitro* during the lymphocyte-transformation test [27]. In general, T-cell pseudolymphomas do not show significant epidermotropism such as Pautrier's microabscesses.

Immunophenotypic studies show a normal T-cell phenotype and a mixed κ/λ expression. When germinal centres are present, Bcl-2 is not expressed in B-cell pseudolymphomas [28]. TCR and immunoglobulin gene analysis usually show evidence of a polyclonal proliferation, but rarely a monoclonal pattern has been detected, suggesting a neoplastic proliferation, but the significance of this finding is unclear at present [29–33].

Management. If the diagnosis of pseudolymphoma is considered likely, the presumed cause should be removed if possible. This is probably easiest in the case of an adverse drug reaction, but it may take weeks or even months for the cutaneous reaction to subside. In the cases of persistent nodular scabies or other pseudolymphomas that cause symptomatic itch, application of topical steroids will accelerate clearance.

References

1 Ploysangam T, Breneman DL, Mutasim DF. Cutaneous pseudolymphomas. *J Am Acad Dermatol* 1998; **38**: 877–905.
2 Halevy S, Sandbank M. Transformation of lymphocytoma cutis into malignant lymphoma. *Acta Derm Venereol (Stockh)* 1987; **67**: 172–5.
3 Nakayama H, Mihara M, Shimao S. Malignant transformation of lymphadenosis benigna cutis. *J Dermatol* 1987; **14**: 266–9.
4 Furness PN, Goodfield MJ, Maclennan KA *et al.* Severe cutaneous reactions to captopril and enalapril. *J Clin Pathol* 1986; **39**: 902–7.
5 Henderson CA, Shamy HK. Atenolol induced pseudolymphoma. *Clin Exp Dermatol* 1990; **115**: 119–20.
6 Kaurdan SH, Scheffer E, Vermeer BJ. Drug-induced pseudolymphomatous reactions. *Br J Dermatol* 1988; **188**: 545–52.
7 Souteyrand P, Duncan M. Drug-induced mycosis fungoides-like lesions. *Curr Prob Dermatol* 1990; **19**: 176–82.
8 Nathan DL, Belsito DV. Carbamazepine induced pseudolymphoma with CD30 positive cells. *J Am Acad Dermatol* 1998; **38**: 806–9.
9 Ecker RI, Winkelmann RD. Lymphomatoid contact dermatitis. *Contact Dermatitis* 1981; **7**: 84–93.
10 Walton S, Bottomley WW, Wyatt EH, Bury HPR. Pseudo T-cell lymphoma due to scabies in a patient with Hodgkin's disease. *Br J Dermatol* 1991; **124**: 277–8.
11 Burg G, Dummer R, Kadin M. From inflammation to neoplasia. *Arch Dermatol* 2001; **137**: 949–52.
12 Hermes B, Haas N, Grabbe J, Cznarnetzki B. Foreign body granuloma and IgE-pseudolymphoma after multiple bee stings. *Br J Dermatol* 1994; **130**: 780–4.
13 Duvic M, Moore D, Menter A, Vonderheid EC. Cutaneous T-cell lymphoma in association with silicone breast implants. *J Am Acad Dermatol* 1995; **32**: 939–42.
14 Garbe C, Stein H, Dienemann D, Orfanos C. *Borrelia burdorferi*-associated cutaneous B-cell lymphoma. *J Am Acad Dermatol* 1991; **24**: 584–90.
15 Blumental G, Okun MR, Ponitch A. Pseudolymphomatous reactions to tattoos. *J Am Acad Dermatol* 1982; **6**: 485–8.
16 Rijlaarsdam J, Bruynzeel D, Vos W *et al.* Immunohistochemical studies of lymphadenosis benigna cutis occurring in a tattoo. *Am J Dermatopathol* 1998; **10**: 518–23.
17 Lanzafame S, Micali G. Cutaneous lymphoid hyperplasia (pseudolymphoma) secondary to vaccination. *Pathologica* 1993; **85**: 555–6.
18 Kim K, Lee M, Choi J *et al.* CD30-positive T-cell rich pseudolymphoma induced by gold acupuncture. *Br J Dermatol* 2002; **146**: 882–4.
19 Roo E, Villegas C, Lopez-Bran E *et al.* Postzoster cutaneous pseudolymphoma. *Arch Dermatol* 1994; **130**: 661–3.
20 Rijlaarsdam JU, Scheffer E, Meier CJLM, Willemze R. Cutaneous pseudo T-cell lymphomas. *Cancer* 1992; **69**: 717–24.
21 Kawada A, Mori S, Hayashi T. Lymphadenosis benigna cutis: pseudomalignant form and its imprint smear cytology. *Dermatologica* 1970; **141**: 339–47.
22 Geerts ML, Kaiserling E. A morphologic study of lymphadenosis benigna cutis. *Dermatologica* 1985; **170**: 121–7.
23 Shelley WB, Wood MG, Wilson JF *et al.* Premalignant lymphoid hyperplasia. *Arch Dermatol* 1981; **117**: 500–3.
24 Evans HL, Winkelmann RK, Banks PM. Differential diagnosis of malignant and benign cutaneous infiltrates. *Cancer* 1979; **44**: 699–717.
25 Burg G, Braun-Falco O, Schmoeckel C. Differentiation between pseudolymphomas and malignant B-cell lymphomas of the skin. In: Goos M, Christophers E, eds. *Lymphoproliferative Diseases of the Skin*. Berlin: Springer-Verlag, 1982: 101–34.
26 van der Putte SCJ, Toonstra J, Felten PC, van Vloten WA. Solitary nonepidermotropic T-cell pseudolymphoma of the skin. *J Am Acad Dermatol* 1986; **14**: 444–53.
27 Bernstein H, Shupack J, Ackerman AB. Cutaneous pseudolymphoma resulting from antigen injections. *Arch Dermatol* 1974; **110**: 756–7.
28 Chimenti S, Cerroni L, Zenahlik P *et al.* The role of MT2 and anti bcl-2 protein antibodies in the differentiation of benign from malignant cutaneous infiltrates of B lymphocytes with germinal centre formation. *J Cutan Pathol* 1996; **23**: 319–22.
29 Wood G, Ngan B, Tung R *et al.* Clonal arrangements of immunoglobulin genes and progression to B-cell lymphoma in cutaneous lymphoid hyperplasia. *Am J Pathol* 1989; **35**: 969–78.
30 Bignon YJ, Souteyrand P. Genotyping of cutaneous T-cell lymphomas and pseudolymphomas. *Curr Probl Dermatol* 1990; **19**: 114–23.
31 Zelickson BD, Peters MS, Muller SA *et al.* T-cell receptor gene rearrangement analysis. *J Am Acad Dermatol* 1991; **25**: 787–96.
32 Weinberg J, Rook A, Lessin S. Molecular diagnosis of lymphocytic infiltrates of the skin. *Arch Dermatol* 1993; **129**: 1491–500.
33 Wood GS. Analysis of clonality in cutaneous T-cell lymphoma and associated diseases. *Ann NY Acad Sci* 2001; **941**: 26–30.

Pityriasis lichenoides [1–8]

Synonym
- Mucha–Habermann disease

Definition. This disorder or group of disorders is difficult to classify. Clinically, pityriasis lichenoides is divided into two main conditions: pityriasis lichenoides chronica (PLC) and pityriasis lichenoides et varioliformis acuta (PLEVA; Mucha–Habermann disease). A third, much rarer and aggressive form, febrile ulceronecrotic Mucha–Habermann disease (FUMHD) also occurs [2,5–7]. Despite their names, the distinction between PLC and PLEVA is based on clinical morphology and histology (see below) rather than the course of the disease [6], as both conditions last for an average of about 18 months with an episodic course.

PLC is the most common type, occurring largely in children and young adults, with a male predominance [9], although a recent large study suggested that PLEVA is the most common pattern in younger children (57% compared with 37% PLC and 6% mixed pattern) [8]. In contrast, in adults there is an approximately equal sex incidence [6,9]. All types are rare in infancy and old age, but PLEVA has been reported at birth [10]. Some patients may have simultaneous lesions of both PLC and PLEVA types, or may have transitional lesions; FUMHD usually occurs in isolation but can evolve from PLC or PLEVA [7]. There is a strong male predominance in FUMHD (about 75%), and most cases occur in the second or third decade of life [6].

References

1 Patel DG, Kihiczak G, Schwartz RA *et al*. Pityriasis lichenoides. *Cutis* 2000; **65**: 17–23.
2 Tsuji T, Kasamatsu M, Yokota M *et al*. Mucha–Habermann disease and its febrile ulceronecrotic variant. *Cutis* 1996; **58**: 123–31.
3 Romani J, Puig L, Fernandez-Figueras MT, de Moragas JM. Pityriasis lichenoides in children: clinicopathologic review of 22 patients. *Pediatr Dermatol* 1998; **15**: 1–6.
4 Gelmetti C, Rigioni C, Alessi E *et al*. Pityriasis lichenoides in children: a long-term follow-up of 89 cases. *J Am Acad Dermatol* 1990; **23**: 473–8.
5 Degos R, Duperrat B, Daniel F. Le parapsoriasis ulcero-necrotique hyperthermique. *Ann Dermatol Syphiligr* 1966; **93**: 481–96.
6 Bowers S, Warshaw EM. Pityriasis lichenoides and its subtypes. *J Am Acad Dermatol* 2006; **55**: 557–72.
7 Khachemoune A, Blyumin ML. Pityriasis lichenoides. Pathophysiology, classification, and treatment. *Am J Clin Dermatol* 2007; **8**: 29–36.
8 Ersoy-Evans S, Greco F, Mancini AJ *et al*. Pityriasis lichenoides in childhood. A retrospective review of 124 patients. *J Am Acad Dermatol* 2007; **56**: 205–10.
9 Wahie S, Hiscutt E, Natarajan S, Taylor A. Pityriasis lichenoides: the differences between children and adults. *Br J Dermatol* 2007; **157**: 941–5.
10 Longley J, Demar L, Feinstein RP *et al*. Clinical and histological features of pityriasis lichenoides et varioliformis acuta in children. *Arch Dermatol* 1987; **123**: 1335–9.

Clinical features [1–10]. The skin eruption is usually the first manifestation of the disease, and generally the only manifestation in PLC, but constitutional symptoms such as fever, headache, malaise and arthralgia may precede and/or accompany the onset of PLEVA.

PLEVA. The eruption develops in crops, and consequently appears polymorphic. The initial lesion is an oedematous pink papule that undergoes central vesiculation and haemorrhagic necrosis, which may be intense. In the vesicular forms [4], the vesicles may be small or so large that the eruption appears frankly bullous. The rate of progression of individual lesions varies greatly, as does the frequency and extent. New lesions may cause irritation or a burning sensation as they appear, but often they are asymptomatic. The trunk, thighs and upper arms, especially the flexor aspects, are chiefly affected, but the eruption may be generalized. Lesions of the palms and soles are less common, and the face and scalp are often spared; erythematous or necrotic lesions of mucous membranes may be present. Lesions heal with scarring, which may be varioliform. PLEVA in pregnancy carries a potential risk of premature labour if there are mucosal lesions in the region of the cervical os [7].

FUMHD. In the acute ulceronecrotic form there is high fever and large necrotic lesions; new crops may continue to develop over many months. About 50–75% of cases occur in adults, with a fulminating course that may even be fatal [2,8–10]. General malaise, weakness, myalgia, neuropsychiatric symptoms and lymphadenopathy occur, with non-specific serological markers of inflammation such as raised ESR and C-reactive protein; there may be serological evidence of associated viral infection.

PLC. The characteristic lesion is a small, firm lichenoid papule 3–10 mm in diameter, and reddish brown in colour. An adherent 'mica-like' scale can be detached by gentle scraping to reveal a shining brown surface—a distinctive diagnostic feature. Over the course of 3 or 4 weeks the papule flattens and the scale separates spontaneously to leave a pigmented macule which gradually fades. Post-inflammatory hypopigmentation may occur, and is occasionally persistent, but scarring is unusual in PLC. The body site distribution is the same as for PLEVA but an isolated acral form may occur [11,12]; segmental forms have been reported.

The course of pityriasis lichenoides varies. If the onset is acute, new crops may cease to develop after a few weeks, and many cases are clear within 6 months. However, acute recurrences may occur over a period of years, or chronicity may supervene. In some cases, all lesions are of the chronic scaling type from the onset, and new crops of similar lesions may develop from time to time over the years. Uncommonly, acute attacks occur after chronic lesions have been present for months or years. In general, the immediate prognosis is said to be better when the onset is acute and the lesions in successive crops are also of the acute type, but one large study of 124 children showed only a small difference in clearance times between PLEVA (mean 18 months) and PLC (mean 20 months) [13]. A smaller study comparing adults and children found that the disease tended to run a longer course in children, with greater extent of lesions, more pigmentation, and poor response to conventional treatments [14].

Differential diagnosis. The acute vesicular form must be distinguished from varicella; acute necrotic lesions may suggest other necrotic skin infections, vasculitis or pyoderma gangrenosum. Lymphomatoid papulosis is a particularly difficult differential diagnosis in patients with necrotic lesions in view of its histological similarity, discussed above, although lymphomatoid papulosis is usually characterized by less vesicular and more necrotic papulonodular lesions than those of PLEVA.

PLC must be differentiated from guttate psoriasis and lichen planus. The acral form of PLC in particular may mimic psoriasis, and secondary syphilis needs to be excluded especially if the palms and soles are involved or if there are mucosal lesions. The single, detachable 'mica-like' scale on the red-brown papule is a characteristic sign of PLC. Gianotti–Crosti syndrome is less likely to be confused with pityriasis lichenoides, but insect bites and drug eruptions should be included in the differential diagnosis.

References

1 Patel DG, Kihiczak G, Schwartz RA, Janniger CK, Lambert WC. Pityriasis lichenoides. *Cutis* 2000; **65**: 17–23.
2 Tsuji T, Kasamatsu M, Yokota M *et al*. A. Mucha–Habermann disease and its febrile ulceronecrotic variant. *Cutis* 1996; **58**: 123–31.
3 Romani J, Puig L, Fernandez-Figueras MT, de Moragas JM. Pityriasis lichenoides in children: clinicopathologic review of 22 patients. *Pediatr Dermatol* 1998; **15**: 1–6.
4 Gelmetti C, Rigioni C, Alessi E *et al*. Pityriasis lichenoides in children: a long-term follow-up of 89 cases. *J Am Acad Dermatol* 1990; **23**: 473–8.
5 Bowers S, Warshaw EM. Pityriasis lichenoides and its subtypes. *J Am Acad Dermatol* 2006; **55**: 557–72.
6 Khachemoune A, Blyumin ML. Pityriasis lichenoides. Pathophysiology, classification, and treatment. *Am J Clin Dermatol* 2007; **8**: 29–36.
7 Brazzini B, Ghersetich I, Urso C *et al*. Pityriasis lichenoides et varioliformis acuta during pregnancy. *J Eur Acad Dermatol Venereol* 2001; **15**: 458–60.
8 Degos R, Duperrat B, Daniel F. Le parapsoriasis ulcero-necrotique hyperthermique. *Ann Dermatol Syphiligr* 1966; **93**: 481–96.
9 Puddu P, Cianchini G, Colonna L *et al*. Febrile ulceronecrotic Mucha–Habermann's disease with fatal outcome. *Int J Dermatol* 1997; **36**: 691–4.

10 De Cuyper C, Hindryckx P, Deroo N. Febrile ulceronecrotic pityriasis lichenoides et varioliformis acuta. *Dermatology* 1994; **189** (Suppl. 2): 50–3.
11 Kossard S. Acral pityriasis lichenoides. *Australas J Dermatol* 2002; **43**: 68–71.
12 Chung HG, Kim SC. Pityriasis lichenoides chronica with acral distribution mimicking palmoplantar syphilid. *Acta Derm Venereol* 1999; **79**: 239.
13 Ersoy-Evans S, Greco F, Mancini AJ *et al*. Pityriasis lichenoides in childhood. A retrospective review of 124 patients. *J Am Acad Dermatol* 2007; **56**: 205–10.
14 Wahie S, Hiscutt E, Natarajan S, Taylor A. Pityriasis lichenoides: the differences between children and adults. *Br J Dermatol* 2007; **157**: 941–5.

Aetiology and pathogenesis. Pityriasis lichenoides has been reported mainly from Europe and America, but there is no specific geographical variation in incidence. The aetiology is unknown. Nosologically, pityriasis lichenoides has been considered to be a variant of parapsoriasis and to show overlap with lymphomatoid papulosis [1,2]. Evidence of T-cell clonality has also been detected in most cases of PLEVA and some cases of isolated PLC without MF [4–6], and in FUMHD [7]. PLEVA has also been reported with an associated lymphoma [8]. PLC-like lesions have also been described in patients with typical features of mycosis fungoides and identical T-cell clones have been identified in both types of cutaneous lesions from the same patients which may explain the overlap with 'parapsoriasis' [9]. Therefore these findings suggest that at least some cases represent a cytotoxic $CD8^+$ T-cell lymphoproliferative disease which may coexist with other primary cutaneous T-cell lymphomas.

Histological features of an underlying vasculitis in PLEVA suggest an immune complex-mediated pathogenesis. In support of this hypothesis there are many documented cases of infective or drug triggers (see below). Seasonal peaks of onset in autumn and winter [10], and rare familial outbreaks [11], suggest the possibility of an infectious trigger. Numerous potential infectious triggers have been summarized in reviews [1,2], and include toxoplasmosis [12,13], cytomegalovirus [14], parvovirus B19 [15], adenovirus, EBV [16], varicella-zoster virus, HIV [17], measles vaccine, streptococci [18], staphylococci and *Mycoplasma* infections. In many such reports, there is evidence of seroconversion at the time of onset or of resolution of pityriasis lichenoides when the infective trigger was treated thus supporting a casual relationship. Parvovirus B19 genomic DNA was identified in lesional skin in 30% of patients with PLEVA [19]. A therapeutic response of PLC to tonsillectomy in the setting of chronic tonsillitis has been reported [20], as well as responses to antibiotics such as erythromycin [21,22] or tetracycline [23]. Resolution has also followed pegylated interferon and ribavirin in a patient with hepatitis C infection. Other reported triggers include medications, such as chemotherapeutic agents, oral contraceptives, astemizole, and possibly herbs. Therefore the combination of several well-documented infective triggers (mainly viral) and the nature of the cellular infiltrate suggest that pityriasis lichenoides may be caused by an antiviral immune response leading to aberrant skin recruitment of CLA^+ $CCR4^+$ $CD8^+$ T-cells [24].

These findings collectively suggest that pityriasis lichenoides is a diverse group of entities which share a similar morphologic pattern due to a variety of underlying aetiologies including a reactive immune complex mediated hypersensitivity vasculitis to different triggers, an immune response to a T-cell dyscrasia or a primary cutaneous T-cell lymphoma.

Pathology [1,2]. The histology varies with the stage, intensity and extent of the reaction; changes are more severe in PLEVA than in PLC. In early lesions, an infiltrate of predominantly small lymphocytes surrounds and involves the walls of dilated dermal capillaries, which show endothelial proliferation. In PLEVA, the infiltrate may be deep, dense and wedge-shaped rather than predominantly perivascular. The epidermis is oedematous, with an interface dermatitis comprised mainly of $CD8^+$ lymphocytes; some necrotic keratinocytes are generally present, especially in PLEVA. Intraepidermal and perivascular extravasation of erythrocytes is typical. Later, over the centre of the lesion, a parakeratotic scale forms, containing lymphocytic pseudo-Munro abscesses and prominent exocytosis of lymphocytes and a little cytologic atypia can be present. If the reaction is still more intense, as occurs in FUMHD, frank necrosis occurs and the lesion may be difficult to distinguish from other forms of acute necrosis of the skin on histology. In FUMHD there may be marked fibrinoid necrosis of deep vessels with luminal thrombi, partial necrosis of follicles and complete necrosis of eccrine glands.

Immunofluorescent studies variably demonstrate IgM, C3 and fibrin in vessel walls of fresh lesions [2]. Macrophages are increased in number and Langerhans' cells decreased. HLA-DR is expressed by the lymphocytic infiltrate and the overlying epidermis.

There is a histological resemblance to many other conditions, including common inflammatory conditions such as psoriasis and resolving eczema. The most important is the distinction from parapsoriasis and particularly (as they may also be clinically similar) differentiation between PLEVA and lymphomatoid papulosis. The most useful distinction from lymphomatoid papulosis is that the latter shows a more pronounced collection of papulonodular lesions with a predominant population of large atypical $CD30^+$ cells (usually $CD4^+$ but occasionally $CD8^+$) whereas atypical $CD30^+$ cells in pityriasis lichenoides are usually few and invariably $CD8^+$ [9]. *CLA* and *TIA-1* are expressed in both conditions and indicate a proliferation of cytotoxic T-cells [25].

References

1 Benmaman O, Sanchez JL. Comparative clinicopathological study on pityriasis lichenoides chronica and small plaque parapsoriasis. *Am J Dermatopathol* 1988; **10**: 189–96.
2 Bowers S, Warshaw EM. Pityriasis lichenoides and its subtypes. *J Am Acad Dermatol* 2006; **55**: 557–72.
3 Khachemoune A, Blyumin ML. Pityriasis lichenoides. Pathophysiology, classification, and treatment. *Am J Clin Dermatol* 2007; **8**: 29–36.
4 Shieh S, Mikkola DL, Wood GS. Differentiation and clonality of lesional lymphocytes in pityriasis lichenoides chronica. *Arch Dermatol* 2001; **137**: 305–8.
5 Dereure O, Levi E, Kadin ME. T-cell clonality in pityriasis lichenoides et varioliformis acuta: a heteroduplex analysis of 20 cases. *Arch Dermatol* 2000; **136**: 1483–6.
6 Weinberg JM, Kristal L, Chooback L *et al*. The clonal nature of pityriasis lichenoides. *Arch Dermatol* 2002; **138**: 1063–7.
7 Helmbold P, Gaisbauer G, Fielder E *et al*. Self-limited variant of febrile ulceronecrotic Mucha–Habermann disease with polyclonal T-cell receptor rearrangement. *J Am Acad Dermatol* 2006; **54**: 1113–4.
8 Kempf W, Kutzner H, Kettelhack N *et al*. Paraneoplastic pityriasis lichenoides in cutaneous lymphoma: case report and review of the literature on paraneoplastic reactions of the skin in lymphoma and leukaemia. *Br J Dermatol* 2005; **152**: 1327–31.
9 Magro C, Crowson A, Morrison C *et al*. Pityriasis lichenoides chronica: stratification by molecular and phenotypic profile. *Hum Pathol* 2007; **38**: 479–90.

10 Ersoy-Evans S, Greco F, Mancini AJ *et al*. Pityriasis lichenoides in childhood. A retrospective review of 124 patients. *J Am Acad Dermatol* 2007; **56**: 205–10.
11 Dupont C. Pityriasis lichenoides in a family. *Br J Dermatol* 1995; **133**: 388–9.
12 Rongioletti F, Delmonte S, Rebora A. Pityriasis lichenoides and acquired toxoplasmosis. *Int J Dermatol* 1999; **38**: 372–4.
13 Nassef NE, Hammam MA. The relation between toxoplasmosis and pityriasis lichenoides chronica. *J Egypt Soc Parasitol* 1997; **27**: 93–9.
14 Tsai KS, Hsieh HJ, Chow KC *et al*. Detection of cytomegalovirus infection in a patient with febrile ulceronecrotic Mucha–Habermann's disease. *Int J Dermatol* 2001; **40**: 694–8.
15 Labarthe MP, Salomon D, Saurat JH. Ulcers of the tongue, pityriasis lichenoides and primary parvovirus B19 infection. *Ann Dermatol Venereol* 1996; **123**: 735–8.
16 Edwards BL, Bonagura VR, Valacer DJ *et al*. Mucha–Habermann's disease and arthritis: possible association with reactivated Epstein–Barr virus infection. *J Rheumatol* 1989; **16**: 387–9.
17 Smith KJ, Nelson A, Skelton H *et al*. Pityriasis lichenoides et varioliformis acuta in HIV-1+ patients: a marker of early stage disease. *Int J Dermatol* 1997; **36**: 104–9.
18 English JC, Collins M, Bryant-Bruce C. Pityriasis lichenoides et varioliformis acuta and group A β-hemolytic streptococcal infection. *Int J Dermatol* 1995; **34**: 642–4.
19 Tomasini D, Tomasini CF, Cerri A *et al*. Pityriasis lichenoides: a cytotoxic T-cell-mediated skin disorder. Evidence of human parvovirus B19 DNA in nine cases. *J Cutan Pathol* 2004; **31**: 531–8.
20 Takahashi K, Atsumi M. Pityriasis lichenoides chronica resolving after tonsillectomy. *Br J Dermatol* 1993; **129**: 353–4.
21 Tsuji T, Kasamatsu M, Yokota M *et al*. Mucha–Habermann disease and its febrile ulceronecrotic variant. *Cutis* 1996; **58**: 123–31.
22 Romani J, Puig L, Fernandez-Figueras MT, de Moragas JM. Pityriasis lichenoides in children: clinicopathologic review of 22 patients. *Pediatr Dermatol* 1998; **15**: 1–6.
23 Piamphongsant T. Tetracycline for the treatment of pityriasis lichenoides. *Br J Dermatol* 1974; **911**: 319–22.
24 Wenzel J, Gütgemann I, Distelmaier U *et al*. The role of cytotoxic skin-homing CD8$^+$ lymphocytes in cutaneous cytotoxic T-cell lymphoma and pityriasis lichenoides. *J Am Acad Dermatol* 2005; **53**: 422–7.
25 Jang KA, Choi JC, Choi JH. Expression of cutaneous lymphocyte-associated antigen and TIA-1 by lymphocytes in pityriasis lichenoides et varioliformis acuta and lymphomatoid papulosis: immunohistochemical study. *J Cutan Pathol* 2001; **28**: 453–9.

Treatment [1–5]. Treatment options include antibiotics such as tetracyclines or erythromycin (preferred in young children because of dental pigmentation side effects of tetracycline) [1], and phototherapy of different types, including natural sunlight, UVB [2], narrow-band UVB, UVA1 and PUVA [3]. Results of phototherapy for pityriasis lichenoides are summarized in [4]. Topical corticosteroids may improve symptoms and healing of lesions but are not felt to alter the course of the disease [1]. A report of topical tacrolimus suggested success in a refractory case of PLC [5]. In more aggressive disease of PLEVA or FUMHD pattern, and less commonly in PLC, various immunosuppressive agents and intravenous immunoglobulin have been used.

References

1 Piamphongsant T. Tetracycline for the treatment of pityriasis lichenoides. *Br J Dermatol* 1974; **911**: 319–22.
2 Le Vine MJ. Phototherapy for pityriasis lichenoides. *Arch Dermatol* 1983; **119**: 378–80.
3 Powell FC, Muller SA. Psoralens and ultraviolet A therapy of pityriasis lichenoides. *J Am Acad Dermatol* 1984; **10**: 59–64.
4 Bowers S, Warshaw EM. Pityriasis lichenoides and its subtypes. *J Am Acad Dermatol* 2006; **55**: 557–72.
5 Mallipeddi R, Evans AV. Refractory pityriasis lichenoides chronica successfully treated with topical tacrolimus. *Clin Exp Dermatol* 2003; **28**: 456–8.

Parapsoriasis

This term has caused confusion since its introduction in 1902 because of a lack of a universally agreed definition of the clinical entities to be included. For this reason, many dermatologists prefer not to use the term at all, and to substitute one of the many synonyms for clinical conditions that might be included in one of the parapsoriasis groups. There is unresolved controversy as to whether two of the parapsoriasis variants are either precursors to cutaneous lymphoma in the form of MF (so-called premycotic eruptions) or established, but early, MF from the outset. There is a broad division of parapsoriasis into small and large plaque variants, each with a number of synonyms. The evidence that the majority of cases of small-plaque parapsoriasis are a chronic, benign condition is reasonable. In contrast, large series of patients with large-plaque parapsoriasis have recorded the development of definite MF in 11% of cases but whether these cases were MF from the outset remains unclear at present [1]. Unfortunately, TCR gene rearrangement studies have been in conclusive, although the proportion of cases with evidence of monoclonality is lower in small-plaque parapsoriasis. Long-term follow-up of these cases is now required.

Small-plaque parapsoriasis [1,2]

Synonyms
- Chronic superficial scaly dermatitis
- Persistent superficial dermatitis
- Digitate dermatosis
- Xanthoerythroderma perstans

Definition. A chronic asymptomatic condition, characterized by the presence of persistent, small, scaly plaques, mainly on the trunk.

Clinical features. The lesions usually appear insidiously and asymptomatically on the trunk and, to a lesser extent, on the limbs of young adults. Individual lesions are monomorphic round or oval erythematous patches, 2.5–5 cm in diameter, with slight scaling (Fig. 57.45). Some have a slightly yellow, waxy tinge. The lesions persist for years or even decades, and may be more obvious in the winter months. There is sparing of the pelvic girdle area and the striking polymorphic appearance of individual patches in MF is lacking.

Pathology. This is non-specific. There are small focal areas of hyperkeratosis and parakeratosis, and in the underlying dermis there are small aggregates of morphologically normal CD4$^+$ T cells, mainly around the vasculature. There is no epidermotropism, and no Pautrier's microabscesses.

Immunophenotypic studies reveal a normal mature T-cell phenotype. One report has identified a 'dominant T-cell clone' in two out of five cases of small-plaque parapsoriasis, using PCR analysis [3]. The significance of this observation in terms of relationship to MF and disease progression is not yet clear. There is also a report of a higher frequency of clonal T cells in the peripheral blood of patients with small-plaque parapsoriasis [4] with no evidence of clonality in the skin, although the significance of this finding is



Fig. 57.45 Typical chronic superficial scaly dermatitis showing linear plaques on the trunk that change little over time.

now questionable because non-pathological T-cell clones can occasionally be found in the peripheral blood of normal, healthy volunteers.

Treatment. Often little treatment is needed. Emollients may help control the scaling, and a course of UVB phototherapy may result in temporary clearance of the lesions, but recurrence is invariable [5].

References

1 Ackerman AB, Schiff TA. If small plaque parapsoriasis is a cutaneous T-cell lymphoma, even an abortive one, it must be mycosis fungoides. *Arch Dermatol* 1996; **132**: 562–6.

2 Burg G, Dummer R. Small plaque parapsoriasis is an abortive cutaneous T-cell lymphoma, and is not mycosis fungoides. *Arch Dermatol* 1995; **131**: 336–8.

3 Haeffner AC, Smoller BR, Zepter K, Wood GS. Differentiation and clonality of lesional lymphocytes in small plaque parapsoriasis. *Arch Dermatol* 1995; **131**: 321–8.

4 Muche JM, Lukowsky A, Heim J *et al*. Demonstration of frequent occurrence of clonal T cells in the blood but not the skin of patients with small plaque parapsoriasis. *Blood* 1999; **94**: 1409–17.

5 Hofer A, Cerroni L, Kerl H, Wolf P. Narrow-band UVB therapy for small plaques parapsoriasis and early stage mycosis fungoides. *Arch Dermatol* 1999; **135**: 1377–80.

Large-plaque parapsoriasis

Synonyms

- Parakeratosis variegata
- Retiform parapsoriasis
- Atrophic parapsoriasis
- Poikilodermatous parapsoriasis

Definition. A chronic condition characterized by the presence of fixed, large, atrophic, erythematous plaques, usually on the trunk and occasionally on the limbs.

Clinical features. Patients present with persistent, large, yellow–orange atrophic patches and thin plaques on the trunk and limbs. Involvement of covered skin on the breast and buttock areas should suggest MF and in these cases patches and plaques may show striking polymorphism and poikiloderma with slow progression [1].

Pathology [2,3]. There is frequently epidermal atrophy, and a lichenoid or interface reaction may also be seen at the dermal–epidermal junction. There is a band-like lymphocytic infiltrate in the papillary dermis, and there may also be free red cells present. The histology is not diagnostic for MF and most biopsies only show a mild dermatitis.

Immunophenotypic studies reveal a normal T-cell phenotype. TCR gene rearrangement studies have shown a clonal T-cell population in the skin in six of 12 patients, but progression to overt CTCL was only noted in one of the 12 patients [4].

Treatment. Topical emollients, UVB and PUVA are all helpful in offering symptomatic relief. Topical steroids should be used with caution because of the atrophic nature of the condition.

References

1 Lambert WC, Everett MA. The nosology of parapsoriasis. *J Am Acad Dermatol* 1981; **5**: 373–95.

2 Kempf W, Dummer R, Burg G. Approach to lymphoproliferative conditions of the skin. *Am J Clin Pathol* 1999; **111** (Suppl. 1): S84–S93.

3 Liu V, McKee PH. Cutaneous lymphoproliferative disorders. *Adv Anat Pathol* 2002; **9**: 79–100.

4 Simon M, Flaig MJ, Kind P *et al*. Large plaque parapsoriasis: clinical and genotypic considerations. *J Cutan Pathol* 2000; **27**: 57–60.

Actinic reticuloid [1,2]

Definition. This condition was first described by Ive *et al*. in 1969 [3]. The original description was of a group of elderly, exclusively male patients who developed a severe and very disabling photosensitivity involving reaction to light throughout the UVB, UVA and visible part of the spectrum. A number of these patients had a past history of contact dermatitis and a milder form of photosensitivity ('persistent light reactors'), but the true relationship between contact dermatitis, particularly to plants of the Compositae family [4], persistent light reactors (chronic actinic dermatitis) and actinic reticuloid is not yet established. The photosensitivity is very severe.

Clinical features. The clinical features are the symptoms of severe and persistent photosensitivity with erythema, oedema and striking 'leonine' thickening of the light-exposed skin of the face, neck and hands which can mimic closely the features of erythrodermic MF/SS (Fig. 57.46) [5].

Patients with atopic dermatitis may be more likely to develop actinic reticuloid, and this should be considered in those with chronic atopic dermatitis who develop photosensitivity [6].

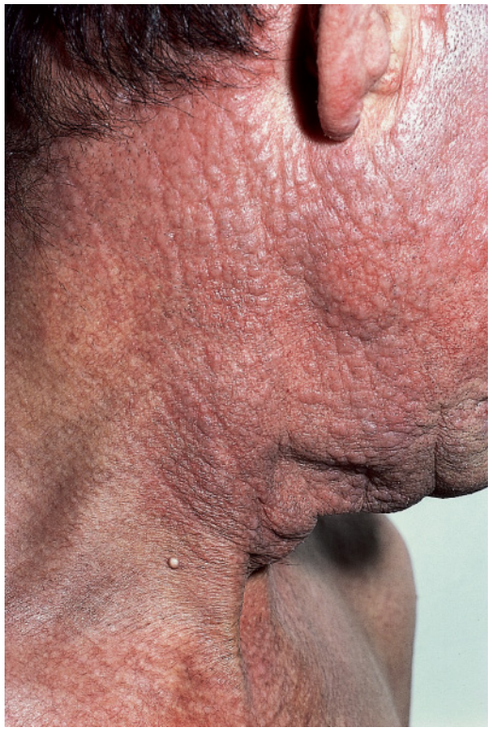


Fig. 57.46 Actinic reticuloid showing marked infiltration of light-exposed skin of the face, with a striking change in skin texture at the collar area and normal skin on the area usually covered by clothing.

Pathology. The histological picture is that of an intense, superficial and deep lymphocytic infiltrate extending from the papillary dermis deep into the reticular dermis. Signs of actinic damage to collagen are present and some of the lymphocytic cells are large and atypical mimicking a cutaneous lymphoma, hence the term 'reticuloid'. The majority of the lymphoid infiltrate consists of $CD8^+$ T cells.

TCR gene analysis does not show a clonal T-cell population [7], but the development of a T-cell clone has been reported in a single patient with mild photosensitivity who developed MF [8]. A recent case series of patients with MF/SS and a report of a patient with cutaneous ATLL suggests that patients with cutaneous lymphomas can show marked photosensitivity with clinical features mimicking chronic actinic dermatitis/actinic reticuloid, emphasizing the importance of considering carefully a diagnosis of a cutaneous T-cell lymphoma in patients with actinic reticuloid [9,10].

Treatment. Treatment is based on light avoidance and the use of both the titanium dioxide-containing physical barrier creams and the newer, more effective chemical UVA and UVB blockers. Low-dose systemic steroid therapy, ciclosporin, hydroxyurea [11] and azathioprine [12] may be effective in some patients.

The prognosis for recovery is poor and the majority of patients tend to have severe photosensitivity for the remainder of their lives.

References

1 Dawe RS, Crombie IK, Ferguson J. The natural history of chronic actinic dermatitis. *Arch Dermatol* 2000; **136**: 1215–20.
2 Zak Prelich M, Schwartz RA. Actinic reticuloid. *Int J Dermatol* 1999; **38**: 335–42.
3 Ive FA, Magnus IA, Warin RP *et al*. 'Actinic reticuloid': a chronic dermatosis associated with severe photosensitivity and the histological resemblance to lymphoma. *Br J Dermatol* 1969; **81**: 469–85.
4 Johnson SC, Cripps DJ, Norbach DH. Actinic reticuloid: a clinical, pathologic, and action spectrum study. *Arch Dermatol* 1979; **115**: 1078–83.
5 Dawe RS, Green CM, MacLeod TM, Ferguson J. Daisy, dandelion and thistle contact allergy in the photosensitivity dermatitis and actinic reticuloid spectrum. *Contact Dermatitis* 1996; **35**: 109–10.
6 Russell S, Dawe RS, Collins P *et al*. The photosensitivity and actinic reticuloid syndrome occurring in seven young atopic dermatitis patients. *Br J Dermatol* 1998; **138**: 496–501.
7 Bakels V, Oostveen JW, Pressman AH *et al*. Differentiation between actinic reticuloid and cutaneous lymphoma by T-cell receptor gamma gene rearrangement and immunophenotyping. *J Clin Pathol* 1998; **51**: 154–8.
8 De Silva BD, McLaren K, Kavanagh GM. Photosensitive dermatitis or actinic reticuloid? *Br J Dermatol* 2000; **142**: 1221–7.
9 Agar N, Morris S, Russell Jones R *et al*. Case report of four patients with erythrodermic cutaneous T-cell lymphoma and severe photosensitivity mimicking chronic actinic dermatitis. *Br J Dermatol* 2009; **160**: 698–703.
10 Adachi Y, Horio T. Chromic actinic dermatitis in a patient with adult T-cell leukemia. *Photodermatol Photoimmunol Photomed* 2008; **24**: 147–9.
11 Gramvussakis S, George SA. Chronic actinic dermatitis: beneficial effect from hydroxyurea. *Br J Dermatol* 2000; **143**: 1340.
12 Kingston TP, Lowe NJ, Sofen HL *et al*. Actinic reticuloid in a black man: successful therapy with azathioprine. *J Am Acad Dermatol* 1987; **16**: 1079–83.

Lymphocytoma cutis

Synonyms
- Spiegler–Fendt sarcoid
- Lymphadenosis benigna cutis of Bafverstedt

Definition. Lymphocytoma cutis is a benign, cutaneous B-cell lymphoproliferative condition. It presents as papules, nodules or plaques usually on the head and neck and pursues a chronic course [1–3].

Aetiology. This is at present unknown.

Clinical features. More cases are reported in females than males. Most patients show solitary or grouped, asymptomatic, erythematous or violaceous papules, nodules or plaques, on the head, especially the ear lobes, and rarely the trunk or limbs (Fig. 57.47). Occasionally, they may have a translucent appearance. They are asymptomatic and not tender, painful or itchy. Lesions are often multiple and may be in all stages of development. They enlarge slowly and may reach a diameter of 3–5 cm. Associated sunlight sensitivity has been reported in some patients. Bafverstedt [4] has described an unusual form of lymphocytoma that presented as a solitary tumour of scrotal skin. Disseminated or miliary lymphocytoma cutis is also rare [5], and occurs in older patients on any body site.

Pathology [6,7]. The epidermis is usually unaffected and is often separated by a relatively acellular grenz zone from the dermis, which is replaced by a nodular dense infiltrate extending through the full thickness of the dermis but without cellular atypia. In



Fig. 57.47 Clinical presentation of a patient with lymphocytoma cutis.

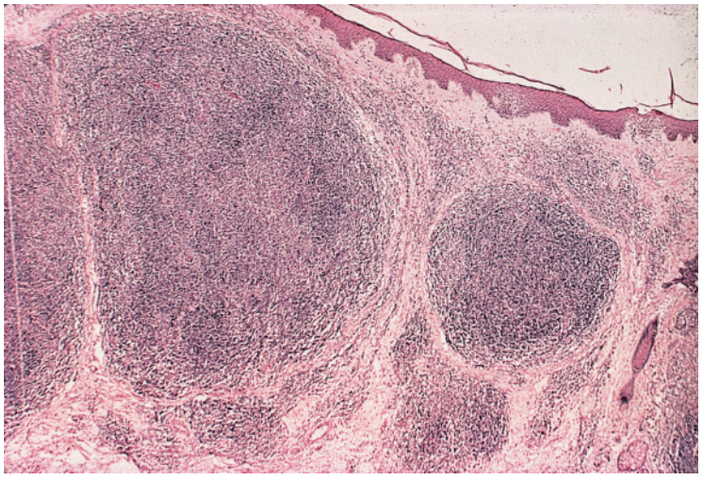


Fig. 57.48 Histology of Spiegler–Fendt sarcoid showing striking lymphoid follicles.

classic cases, lymphocytes and histiocytes form a follicular arrangement resembling the appearance of a lymph node (Fig. 57.48). Mitotic figures may be visible in the cells of the follicles and occasional eosinophils may also be present. Appendages and blood vessels are spared. In some instances, there is no tendency for lymphoid follicle formation, although the histological appearance with normal lymphocytes and histiocytes is otherwise similar. The histological differential diagnosis includes primary cutaneous lymphoma, particularly of marginal zone origin.

Immunopathology. The majority of lymphocytes in the dermis are B cells. Germinal centres are frequently seen in lymphocytoma cutis, and appropriate markers will confirm the morphological similarity of these structures to the germinal centres of lymph nodes. A cuff of reactive T cells may be seen around the periphery of the main B-cell aggregate.

Differential diagnosis. Histological examination should distinguish lymphocytoma cutis from granulomatous disorders including sarcoidosis, granuloma faciale and rosacea. Distinction from primary cutaneous B-cell marginal zone lymphoma (MZL) is difficult, although the presence of atypical lymphoid cells would suggest a primary cutaneous MZL. Insect bite reactions may also be impossible to distinguish with any confidence from lymphocytoma cutis.

Jessner's benign lymphocytic infiltration, tumid discoid lupus erythematosus (LE) and polymorphic light eruption can also cause difficulties. However, in Jessner's lymphocytic infiltrate, which characteristically waxes and wanes in severity, the dermal lymphocytic infiltrate is dominated by T cells. The presence of basal cell liquefaction degeneration and positive direct immunofluorescence helps distinguish LE.

Treatment. There is no treatment of proven value for lymphocytoma cutis. Penicillin and radiotherapy have been advocated in the past without adequate clinical trials. Intralesional steroids have also been advocated. Miliary lesions may partially respond to topical steroids. Hydroxychloroquine has also been effective.

Prognosis. Lymphocytoma cutis is a benign disorder in both localized and disseminated forms, although often running a very protracted course. Long-term follow-up of these patients suggests that a small proportion progress to or begin as a primary cutaneous B-cell lymphoma (MZL) and therefore the prognosis must be guarded [8–11].

References

1 Lange Wantzin G, Hou Jensen K, Nielsen M *et al.* Cutaneous lymphocytomas: clinical and histological aspects. *Acta Derm Venereol* 1982; **62**: 119–24.
2 Van Hale HM, Winkelmann RK. Nodular lymphoid disease of the head and neck. *J Am Acad Dermatol* 1985; **12**: 455–61.
3 Clark WH, Mihm MC, Reed RJ *et al.* The lymphoytic infiltrates of the skin. *Hum Pathol* 1974; **5**: 25–43.
4 Bafverstedt B. Unusual forms of lymphadenosis benigna cutis (LABC). *Acta Derm Venereol (Stockh)* 1962; **42**: 3–10.
5 Bafverstedt B. Lymphadenosis benigna cutis (LABC): its nature, course and prognosis. *Acta Derm Venereol (Stockh)* 1960; **40**: 10–8.
6 Mach KW, Wilgram GF. Charactersitic histopathology of cutaneous lymphoplasia. *Arch Dermatol* 1966; **94**: 26–32.
7 Kawada A, Mori S, Hayashi T. Lymphadenosis benigna cutis: pseudomalignant form and its imprint smear technology. *Dermatologica* 1970; **141**: 339–47.
8 Shelley WB, Wood MG, Wilson JF. Premalignant lymphoid hyperplasia. *Arch Dermatol* 1981; **117**: 500–3.
9 Halevy S, Sandbank M. Transformation of lymphocytoma cutis into malignant lymphoma. *Acta Derm Venereol* 1987; **67**: 172–5.
10 Evans HL, Winkelman RK, Banks PM. Differential diagnosis of malignant and benign cutaneous infiltrates. *Cancer* 1970; **44**: 699–717.
11 Burg G, Braun-Falco O, Schmoeckel C. Differentiation between pseudolymphomas and malignant B-cell lymphomas of the skin. In: Goos M, Christophers E, eds. *Lymphoproliferative Diseases of the Skin.* Berlin: Springer Verlag, 1982: 10–4.

Jessner's lymphocytic infiltrate [1]

Definition. A chronic benign T-cell lymphoproliferative disorder, usually of exposed skin.



Fig. 57.49 Clinical appearance of a young woman with Jessner's lymphocytic infiltrate.

Clinical features. Females are more often affected than males [2]. Both children [3,4] and familial cases [5,6] have been recorded. Benign lymphocytic infiltration of Jessner is characterized by the presence of red tumid nodules, usually on facial skin (Fig. 57.49). The lesions may involute spontaneously, but more commonly are persistent, and new lesions develop over time. There is variation in seasonal activity of the lesions, with winter exacerbations. The individual lesions are smooth raised non-scaling erythematous nodules or plaques and are commonly asymptomatic, although some patients complain of burning or pruritus.

Pathology [7–11]. Biopsies reveal a lymphocytic infiltrate predominantly in the lower dermis and concentrated tightly around blood vessels (Fig. 57.50). The epidermis and papillary dermis are relatively normal, and within the lymphocytic infiltrate there is no evidence of cellular atypia, germinal centre or follicle formation. The great majority of these cells are $CD4^+$ T cells.

Differential diagnosis. The clinical differential diagnosis includes a fixed drug eruption and cutaneous discoid LE. The lesions are usually more numerous than would be associated with a fixed drug eruption, although the histology is very similar. The individual lesions of Jessner's lymphocytic infiltrate are smooth and non-scarring, in contrast to the scaling atrophic scarring associated with chronic discoid LE. In addition, Jessner's lymphocytic infiltrate does not demonstrate a lupus band as seen at the dermal–epidermal junction in chronic discoid LE. However, there is a view that Jessner's lymphocytic infiltrate is a variant of LE.

Treatment. This is unsatisfactory, and lesions tend both to persist and to increase in numbers. There are individual case reports of successful therapy with topical steroids, systemic steroids, PUVA, radiotherapy, dapsone, hydroxychloroquine and gold [12].

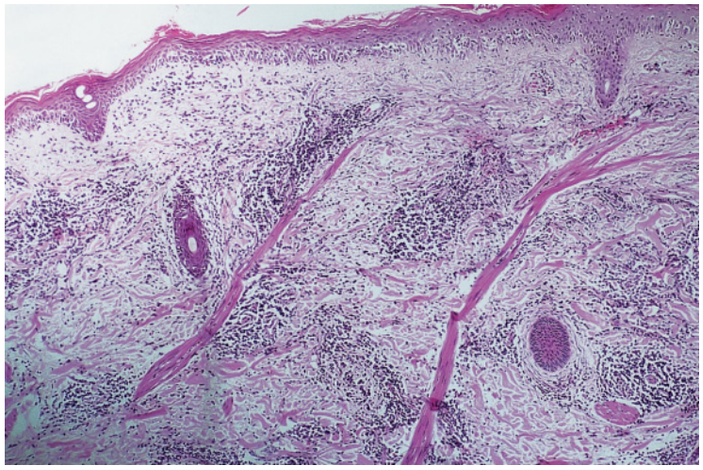


Fig. 57.50 Pathological pattern of Jessner's lymphocytic infiltrate. Note perivascular distribution and absence of epidermotropism.

References

1 Jessner M, Kanof NB. Lymphocytic infiltration of the skin. *Arch Dermatol* 1953; **68**: 447–9.
2 Toonstra J, Wildschut A, Boer J *et al.* Jessner's lymphocytic infiltrate of the skin: a clinical study of 100 patients. *Arch Dermatol* 1989; **125**: 1525–30.
3 Mullen RH, Jacobs AH. Jessner's lymphocytic infiltrate in two girls. *Arch Dermatol* 1988; **124**: 1091–3.
4 Higgins CR, Wakeel RAP, Cerio R. Childhood Jessner's lymphocytic infiltrate of the skin. *Br J Dermatol* 1994; **131**: 99–101.
5 Toonstra J, Van der Putte SCJ, Baart de la Faille H, van Vloten W. Familial Jessner's lymphocytic infiltrate of the skin occurring in a father and daughter. *Clin Exp Dermatol* 1993; **18**: 142–5.
6 O'Toole EA, Powell F, Barnes L. Jessner's lymphocytic infiltrate and probable discoid lupus erythematosus occurring separately in two sisters. *Clin Exp Dermatol* 1999; **24**: 90–3.
7 Willemze R, Dijkstra A, Meijer CJ. Lymphocytic infiltration of the skin (Jessner): a T-cell lymphoproliferative disease. *Br J Dermatol* 1984; **110**: 523–9.
8 Calnan CD. Lymphocytic infiltration of the skin (Jessner): cutaneous Hodgkin's disease. *Br J Dermatol* 1957; **69**: 169–73.
9 Rijlaarsdam JU, Nieboer C, de Vries E *et al.* Characterization of the dermal infiltrates in Jessner's lymphocytic infiltrate of the skin. *J Cutan Pathol* 1990; **17**: 2–8.
10 Hellier FF. Lymphocytoma of the face. *Br J Dermatol* 1939; **51**: 260–5.
11 Postma C, Sluiter JTF. The relationship between Bafverstedt's benign lymphadenosis of the skin and Jessner's lymphocytic infiltration of the skin. *Acta Derm Venereol (Stockh)* 1958; **38**: 180–8.
12 Farrell AM, McGregor JM, Staughton RC, Bunker CB. Jessner's lymphocytic infiltrate treated with auranofin. *Clin Exp Dermatol* 1999; **24**: 500.

Leukaemia cutis [1–3]

Diagnosis. The diagnosis of the specific type of leukaemia depends on detailed examination of the blood and bone marrow. The cutaneous infiltrate rarely indicates the type of leukaemia involved.

Specific cutaneous lesions occur most often in myelomonocytic leukaemia and T-cell malignancies such as T-cell prolymphocytic leukaemia and T-ALL [4]. Cutaneous involvement in



Fig. 57.51 Specific deposits in a child with leukaemia. Note two large nodular lesions on the back.

the other forms of leukaemia is unusual as a presenting feature, and usually appear after the diagnosis has been established. There are a few cases where the diagnosis of leukaemia has been established first by analysis of the skin lesions [5]. These lesions usually consist of small, reddish papules or nodules which may be fleeting or persistent. Clinically, they may resemble lesions of Sweet's syndrome, sarcoidosis, panniculitis, other granulomas or cutaneous lymphoma (Fig. 57.51). Ulceration, especially around the ankles, simulating gravitational ulceration, has been described in chronic lymphatic leukaemia and may represent the development of a leukaemic deposit in an area of low vascular resistance.

Although 'non-specific' lesions are said to be common, they are rarely reported by dermatologists. Generalized pruritus may be a presenting symptom and prurigo-like papules develop in some cases. Erythroderma has been recorded in association with an underlying T-cell leukaemia such as T-cell prolymphocytic leukaemia which must be distinguished from Sézary syndrome. There is usually marked exfoliation and the skin may be markedly thickened, especially over the face. The histological features in the skin may or may not be diagnostic.

Disseminated or unusually severe herpes zoster is common in association with all types of malignant disease. Specific leukaemic infiltrations into herpetic scars may occur and bullous lesions have been recorded [6]. In multiple myeloma, both generalized and local amyloidosis is common. Anhidrosis has been recorded. Patients with myelomatosis may subsequently develop variants of acute myelogenous leukaemia [7,8] and it has been suggested

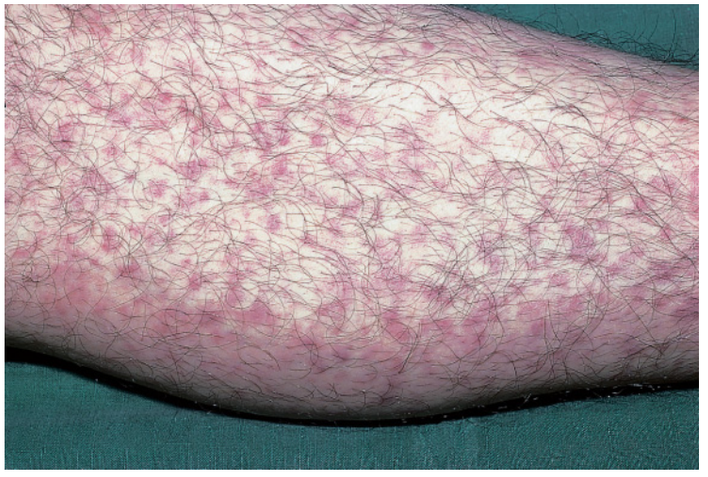


Fig. 57.52 Purpuric lesions in an adult patient with myelocytic leukaemia.

that this complication is the result of treating the underlying disease with irradiation or alkylating agents [9].

Three cases of a perniotic syndrome associated with monocytosis and neutropenia have been described as a possible association with a preleukaemic state [10]. Sweet's disease and bullous pyoderma have also been associated with leukaemia (see Chapter 52).

Thrombocytopenic purpura is a characteristic symptom of the acute leukaemias and may occur on skin or mucous membranes, often as the presenting symptom (Fig. 57.52).

Beek [9] recorded 289 cases of lymphatic leukaemia with skin lesions and, in these, tumours were present in 50%, the head being the most common site. Erythroderma was present in 25%, herpes zoster in 26%, prurigo-like papules in 21%, bullae in 10%, varicelliform eruptions and urticaria in 3%. Haemorrhagic gangrene of the skin has also been recorded. The usual age at presentation of patients with lymphatic leukaemia is 45–54 years, but those with cutaneous lesions tend to be older. Skin lesions in myelogenous leukaemia are much less frequent, with only 72 recorded cases. When the skin is involved the prognosis is poor.

A relatively specific picture is observed in a number of patients with chronic T-cell lymphatic leukaemia [6]. These patients are frequently elderly males and may present with diffuse generalized erythroderma, splenomegaly and lymphadenopathy. This may be caused by lymphokine release by the malignant T cells during their passage through the dermal vasculature, as skin biopsy of these lesions does not reveal a specific cutaneous infiltrate, or epidermotropism characteristic of MF.

Diagnosis. Diagnosis of all these conditions is based on pathological examination of material from blood, bone marrow, lymph nodes and skin [8,11–13].

Treatment. The treatment for leukaemia cutis is management of the underlying disease, with symptomatic measures for the skin lesions when required. Superficial radiotherapy may be useful, giving rapid symptomatic relief, and regression of specific cutaneous deposits.

References

1 Bonvalet D, Foldes C, Civatte J. Cutaneous manifestations in chronic lymphocytic leukaemia. *J Dermatol Surg Oncol* 1984; **10**: 278–82.
2 Buechner SA, Li CY, Su WPD. Leukaemia cutis: a histopathologic study of 42 cases. *Am J Dermatopathol* 1985; **7**: 109–19.
3 Su WPD, Buechner SA, Li CY. Clinicopathologic correlations in leukaemia cutis. *J Am Acad Dermatol* 1984; **11**: 121–8.
4 Hubler WR, Netherton EW. Cutaneous manifestations of monocytic leukaemia. *Arch Dermatol* 1947; **56**: 70–89.
5 Blaustein JC, Narany S, Palutke M *et al.* Extra-medullary (skin) presentation of acute monocytic leukaemia resembling cutaneous lymphoma. *J Cutan Pathol* 1987; **14**: 232–7.
6 Cote J, Trudel M, Gratton D. T-cell chronic lymphocytic leukaemia with bullous manifestations. *J Am Acad Dermatol* 1983; **8**: 874–8.
7 Costello MJ, Canizares O, Montague M *et al.* Cutaneous manifestations of myelogenous leukaemia. *Arch Dermatol* 1955; **71**: 605–14.
8 Eubanks SW, Patterson JW. Subacute myelomonocytic leukaemia, an unusual skin manifestation. *J Am Acad Dermatol* 1983; **9**: 581–4.
9 Beek CH. Skin manifestations associated with lymphomas and leukaemias. *Dermatologica* 1948; **96**: 350–6.
10 Marks R, Lim CC, Borrie PF. A perniotic syndrome with monocytosis and neutropenia: a possible association with a preleukaemic state. *Br J Dermatol* 1969; **81**: 327–32.
11 Arai E, Ideda S, Itoh S *et al.* Specific skin lesions as the presenting symptom of hairy cell leukaemia. *Am J Clin Pathol* 1988; **90**: 459–64.
12 Finan MC, Su WPD, Li CY. Cutaneous findings in hairy cell leukaemia. *J Am Acad Dermatol* 1984; **11**: 788–97.
13 Lawrence DM, Sun NCJ, Mena R *et al.* Cutaneous lesions in hairy cell leukaemia. *Arch Dermatol* 1983; **119**: 322–5.

Cutaneous Hodgkin's disease

The existence of a variant of Hodgkin's disease that begins in the skin is still debated, and it can be difficult if not impossible to differentiate from Hodgkin's disease beginning in the nodes, which spreads in a contiguous manner at an early stage to the skin [1–5]. Invariably, cutaneous Hodgkin's disease only occurs as direct extension from an underlying involved regional lymph node. Thus, careful clinical examination, followed if appropriate by node biopsy and CT scans, should be performed before a diagnosis of primary cutaneous Hodgkin's disease is made. In view of the cytological similarity between the cells of lymphomatoid papulosis and those of Hodgkin's disease, this differential diagnosis must be carefully considered and positively excluded.

Clinical features. One review of 1810 cases of Hodgkin's disease reports only nine (0.5%) with specific cutaneous lesions [6] but a more recent study records involvement in 16 of 465 cases (3.4%) [7]. They usually consist of small nodules, but ulcerative lesions have been recorded and rarely are the presenting symptom.

Pathology [1,2,8]. To consider the diagnosis of Hodgkin's disease either involving the skin as a secondary process, or originating in the skin, the cutaneous infiltrate should consist of nodules of atypical lymphoid and histiocytic cells, including the presence of Reed–Sternberg cells that are $CD30^+$ and lymphoid cells that are $CD15^+$ [9–11]. CD15 positivity is not seen in lymphomatoid papulosis.

Non-specific cutaneous signs associated with Hodgkin's disease [5,12] are very common and occur in 3–50% of cases. These include pigmentation, pruritus, prurigo, atrophy, alopecia, exfoliative dermatitis and herpes zoster.

Pigmentation. This is melanin pigmentation and is very common. It resembles the pigmentation of Addison's disease, being most marked in areas that normally show some darkening such as the axillae, groins and around the nipples. Less often it is more widespread, and occasionally a bizarre pigmentation occurs. The mucous membranes are usually spared.

Pruritus. This often occurs together with pigmentation. Pruritus is not infrequently the presenting feature of the disease, and may precede the presence of palpable nodes by months or years. It tends to start on the legs. It is especially severe in patients who show other general symptoms such as fever and weight loss. Both pigmentation and pruritus occur in association with enlarged mediastinal or retroperitoneal glands, the presence of which should always be suspected when itching is severe.

Prurigo. This is a development from pruritus. In addition to the widespread irritation, there are excessively itchy papules, which are scratched until the skin surface is removed and is replaced by a blood crust. The papules and crusts are usually found on the trunk. When present in association with enlarged superficial glands, this forms a very characteristic picture, often called Hodgkin's prurigo.

Ichthyosiform atrophy. An acquired ichthyosis occurring in the course of a chronic wasting disease is fairly common. Hodgkin's disease is probably the most common condition to be associated with this change. It usually starts on the legs and may remain restricted, but in severe cases progresses until it becomes universal. It resembles ichthyosis vulgaris, with thin, dry and rather firmly attached scales. It is not static and may regress for a time, only to return later. Red streaks are often visible between the scales. The patient is usually wasted and severely ill. Malabsorption from the gut may occur in some cases and contribute to this problem.

Alopecia. Hair loss is common in Hodgkin's disease. It can be caused by rubbing or scratching to relieve itching. It may also be part of the ichthyosiform atrophy or be caused by endocrine dysfunction, when specific infiltration occurs in organs such as the pituitary or adrenal. Rarely, it may be brought about by specific infiltration in the scalp.

Exfoliative dermatitis. Erythroderma and exfoliative dermatitis have been recorded as occurring in Hodgkin's disease on many occasions [4]. Most recorded cases would probably be more correctly included under ichthyosiform atrophy.

Herpes zoster. Herpes zoster is common in the course of Hodgkin's disease, but disseminated zoster is much less likely to occur in Hodgkin's disease than in chronic lymphatic leukaemia.

Miscellaneous conditions. Many other non-specific skin lesions have been described in association with Hodgkin's disease, but

they are probably incidental. Erythema nodosum is seen occasionally and is apparently caused by the disease itself; in these cases, differentiation from sarcoidosis may be difficult, but the Kveim test or node biopsy should establish the diagnosis.

References

1 Carbone PP, Kaplan HS, Musshoff K *et al.* Report of the committee on Hodgkin's disease staging classification. *Cancer Res* 1971; **31**: 1860–1.
2 Franssila KO, Kalma TV, Voutilainen A. Histologic classification of Hodgkin's disease. *Cancer* 1967; **20**: 1594–601.
3 O'Bryan-Tear CG, Burke M, Coulson IH *et al.* Hodgkin's disease presenting in the skin. *Clin Exp Dermatol* 1987; **12**: 69–71.
4 Rubins J. Cutaneous Hodgkin's disease. *Cancer* 1978; **42**: 1219–21.
5 Silverman CL, Strayer DS, Wasserman TH. Cutaneous Hodgkin's disease. *Arch Dermatol* 1982; **118**: 918–21.
6 Gordon RA, Lookingbill DP, Abt AB. Skin infiltration in Hodgkin's disease. *Arch Dermatol* 1980; **116**: 1038–40.
7 White RM, Patterson JW. Cutaneous involvement in Hodgkin's disease. *Cancer* 1985; **55**: 1136–45.
8 Jaffe ES. The elusive Reed–Sternberg cell. *N Engl J Med* 1989; **320**: 529–31.
9 Kadin ME. Histogenesis of Hodgkin's disease. *Hum Pathol* 1987; **18**: 1085–8.
10 Kaplan HS. Hodgkin's disease: unfolding concepts concerning its nature, management and prognosis. *Cancer* 1980; **45**: 2439–74.
11 Schwab V, Stein H, Gerdes J *et al.* Production of a monoclonal antibody specific for Hodgkin and Sternberg–Reed cells of Hodgkin's disease and a subset of normal lymphoid cells. *Nature* 1982; **299**: 65–7.
12 Smith JL, Butler JJ. Skin involvement in Hodgkin's disease. *Cancer* 1980; **45**: 354–61.

Lennert's lymphoma

Definition. A rare variant of systemic lymphoma with a characteristic histology, first described in 1968 as a variant of Hodgkin's disease [1].

Clinical features. Most patients have lymphadenopathy, fever, fatigue and weight loss. The skin is involved very rarely as a secondary event and this usually consists of clinically non-specific papules or nodules [2]. One patient presented with chronic cutaneous infection and pyoderma [3], and another simulating atypical granuloma annulare [4].

Pathology. The characteristic pattern is an infiltrate with a high content of epithelioid histiocytes, admixed with $CD4^+$ cells. If the skin is involved, there may be a subcutaneous infiltrate consisting of epithelioid histiocytes and T cells. Reed–Sternberg cells are rare [2,3].

References

1 Lennert K, Mestdagh J. Lymphogranulomatosen mit kinstant hohem epitheloidzellgehalt. *Virchows Arch Pathol Anat* 1968; **344**: 1–20.
2 Kiesewetter F, Haneke E, Lennert K *et al.* Cutaneous lymphoepithelioid lymphoma. *Am J Dermatopathol* 1989; **11**: 549–54.
3 Zamora A, Nunez C, Hu CH. Lennert's lymphoma presenting with clusters of cutaneous infection. *J Am Acad Dermatol* 1981; **5**: 450–4.
4 Bhushan M, Craven NM, Armstrong GR, Chalmers RJG. Lymphoepitheloid cell lymphoma (Lennert's lymphoma) presenting as atypical granuloma annulare. *Br J Dermatol* 2000; **142**: 776–80.

CHAPTER 58
Disorders of Skin Colour

A.V. Anstey
Royal Gwent Hospital, Newport, Gwent, UK

The colour of the skin, 58.1
The melanocyte, 58.2
Epidermal melanin unit, 58.2
Distribution of melanocytes, 58.2
Melanoblast migration and differentiation, 58.3
Melanosome transport, 58.4
Melanosome transfer to keratinocytes, 58.4
Melanocyte culture, 58.5
Biochemistry of melanogenesis, 58.5
Regulation of human pigmentation by ultraviolet light and by endocrine, paracrine and autocrine factors, 58.7
Biological significance of melanin, 58.8
Classification of disorders of melanin pigmentation, 58.9
Constitutive pigmentation, human pigmentation and the response to sun exposure, 58.9
Hypermelanosis, 58.10
Ephelides, 58.10
Lentiginosis, 58.11
Incontinentia pigmenti, 58.15
Fanconi's anaemia, 58.17
McCune–Albright syndrome, 58.18
Other hereditary disorders with hypermelanosis, 58.19
Hypermelanosis in endocrine disorders, 58.24
Hypermelanosis in other systemic disorders, 58.25
Hypermelanosis of drug origin, 58.29
Post-inflammatory hypermelanosis, 58.30
Tanning with UV light, 58.31
Erythema dyschromicum perstans, 58.33
Facial melanoses, 58.34
Dermal melanocytosis, 58.36
Hypermelanosis associated with other cutaneous lesions, 58.38
Treatment of hypermelanosis, 58.38
Hypomelanosis, 58.39
Genetic and naevoid disorders, 58.39
Acquired hypomelanosis, 58.50
Endogenous non-melanin pigmentation, 58.53
Exogenous pigments, 58.54
Metals, 58.54
Drugs, 58.55
Tattoos, 58.57

The colour of the skin [1–7]

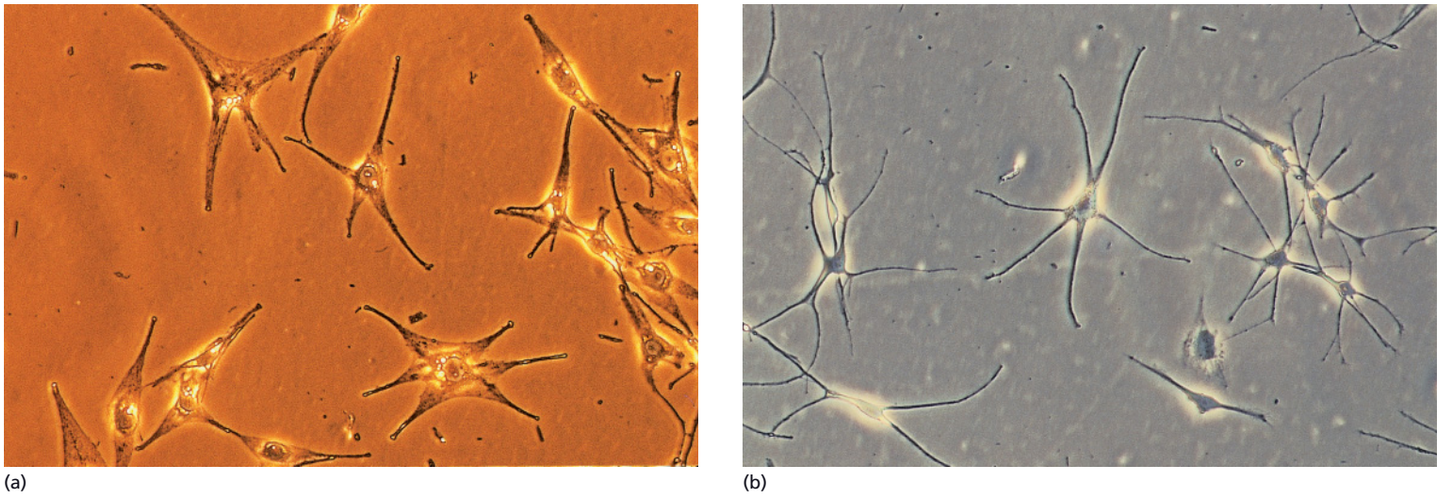
Normal skin colour is determined by a number of chromophores, the most important of which is melanin. Besides melanin, other chromophores that contribute significantly to skin colour include haemoglobin (in both the oxygenated and reduced state) and carotenoids. Racial and ethnic differences in skin colour are related to the number, size, shape, distribution and degradation of melanin-laden organelles called melanosomes. These are produced by melanocytes (Fig. 58.1) and are transferred to the surrounding epidermal keratinocytes. Two types of melanin pigmentation occur in humans [1]. The first is *constitutive* skin colour, which is the amount of melanin pigmentation that is genetically determined in the absence of sun exposure and other influences. The other is *facultative* (inducible) skin colour or 'tan', which results from sun exposure. Increased pigmentation can also be due to endocrine, paracrine and autocrine factors [1,2].

The least pigmented human subjects are almost white and have a skin colour similar to that of an albino. In contrast, the darkest pigmented human subjects are deep brown or black-brown in colour. Most peoples of the world fall between these two extremes and are moderate brown or yellow-brown in colour. The Caucasian peoples of Europe exhibit a light brown colour that can be enhanced by exposure to sunlight. The ability to tan is marked in the Mediterranean and Middle Eastern peoples. In contrast, some of those from the western parts of Northern Europe have fair skin, red hair, and a tendency to develop red-brown freckles after exposure to sunlight. The definitive method for objective measurement of skin colour uses the recording spectrophotometer adapted for reflectance readings [3]. Application of reflectance chromameters in clinical practice includes the measurement of skin colour, the measurement of ultraviolet (UV)-induced pigmentation, and the quantification of the bleaching effect of depigmenting agents [3].

In some ethnic groups, a sharply demarcated linear border is seen between more and less pigmented skin [4]. This has been studied most extensively in the Japanese and in black Americans, and is most frequently observed in darkly pigmented individuals. Six major forms (designated A–F) of natural pigmentary demarcation boundaries in the skin have been described [4]. These are summarized in Table 58.1.

A blue colour is seen in the congenital pigmentation termed 'Mongolian spot', a form of dermal pigmentation that can occur on any part of the body, although it is most commonly found in the sacral region [5,6]. These spots fade after birth, but can persist in certain sites as in the naevus of Ota (see p. 58.36). Blue naevus is an example of acquired blue pigmentation of skin. The blue coloration of the skin in both of these lesions is due to an optical effect that alters the perceived colour of brown pigment in the dermis. The melanin dispersed in the dermis absorbs incident visible light such that the diffuse reflectance in the longer (red) wavelengths is reduced, giving the pigmented sites a blue appearance.

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.



(a) (b)

Fig. 58.1 (a,b) Melanocytes in culture. (Courtesy of Professor P. Friedmann, Royal Liverpool University Hospital, Liverpool, UK.)

Table 58.1 Pigmentary demarcation lines [4].

A: Located on the anterolateral portion of the upper arm (Futcher's line)
B: Posteromedial portion of the leg
C: Hypopigmented lines band on the mid chest in the pre- or parasternal region
D: A vertical line in the posteromedial area of the spine
E: Hypopigmented macules located on the chest extending from the clavicle to the periareolar skin
F: Lines on face

Carotenoids are lipid-soluble yellow to orange-red pigments that are exogenously produced and can be obtained only from plants in the diet. Carotenoids serve a photoprotective role in green plants, but their photoprotective effect in humans is small, even when taken in excess [7]. Carotenoids are found in the epidermis as well as the subcutaneous fat. When present in excess, carotenoids impart a yellowish hue to the skin which may sometimes be prominent [7].

The evolution of pigmentary systems and their variety throughout the animal kingdom are reviewed in Chapter 2.

References

1 Abdel-Malek Z, Kadekaro AL. Human pigmentation: its regulation by ultraviolet light and by endocrine, paracrine, and autocrine factors. In Nordlund JJ, Boissy RE, Hearing VJ *et al.*, eds. *The Pigmentary System,* 2nd edn. Oxford: Blackwell Publishing, 2006: 410–20.

2 Imokawa G. Paracrine interactions of melanocytes in pigmentary disorders. In Nordlund JJ, Boissy RE, Hearing VJ *et al.*, eds. *The Pigmentary System,* 2nd edn. Oxford: Blackwell Publishing, 2006: 421–44.

3 Westerhof W. Colourimetry. In: Serup J, Jemec GBE, Grove GL, eds. *Handbook of Non-Invasive Methods and the Skin,* 2nd edn. Florida: CRC Press, Taylor & Francis, 2006: 634–47.

4 James WD, Carter JM, Rodman OG. Pigmentary demarcation lines: a population survey. *J Am Acad Dermatol* 1987; **16**: 584–90.

5 Kikuchi I. What is a Mongolian spot? *Int J Dermatol* 1982; **21**: 131–3.

6 Kim JH, Herr H. A statistical study of Mongolian spot. *Korean J Dermatol* 1986; **24**: 373–9.

7 Anstey AV. Systemic photoprotection with alpha-tocopherol (vitamin E) and beta-carotene. *Clin Exp Dermatol* 2002; **27**: 170–6.

The melanocyte [1–3]

Epidermal melanin unit

The estimated mass of all pigment cells within the body is about 1.5 g. Most of these are melanocytes within the epidermis [1]. The process of melanin production within these melanocytes is a three-stage process, which involves not only the production of melanosomes within the melanocyte, termed melanogenesis, but also the trafficking and transfer of these pigment granules via long arborizing dendrites to surrounding epidermal keratinocytes. Each epidermal melanocyte together with the epidermal cells that it serves, comprises an 'epidermal melanin unit' as first described by Fitzpatrick and Breathnach in 1963 [2,3]. Although the number of active epidermal melanin units varies considerably in the different regions of the body (Fig. 58.2), the number of keratinocytes served by each melanocyte remains constant. It is estimated that a single melanocyte supplies melanosomes to a group of about 36 viable keratinocytes. This intricate interface between melanocytes and their keratinocytes is essential for skin pigmentation. Adequate pigmentation of the skin is as dependent upon successful transport and transfer of melanosomes to keratinocytes as it is on the formation of the organelle itself.

References

1 Rosdahl I, Rorsman H. An estimate of melanocyte mass in humans. *J Invest Dermatol* 1983; **81**: 278–81.

2 Fitzpatrick TB, Breathnach AS. Das epidermale melamim-einheit System. *Dermatol Wochenschr* 1963; **147**: 481–9.

3 Hadley MacE, Quevedo WC. Vertebrate epidermal melanin unit. *Nature* 1966; **209**: 1334–5.

Distribution of melanocytes [1–3]

Melanocytes are situated in the basal epidermis (Fig. 58.3). The number of melanocytes within the skin shows little variation between different races or between the sexes. However, the capacity of melanocytes to synthesize melanin, both in the basal state (constitutive colour) and after stimulation (facultative colour) by sunlight, shows great variation. Melanocytes in those with dark

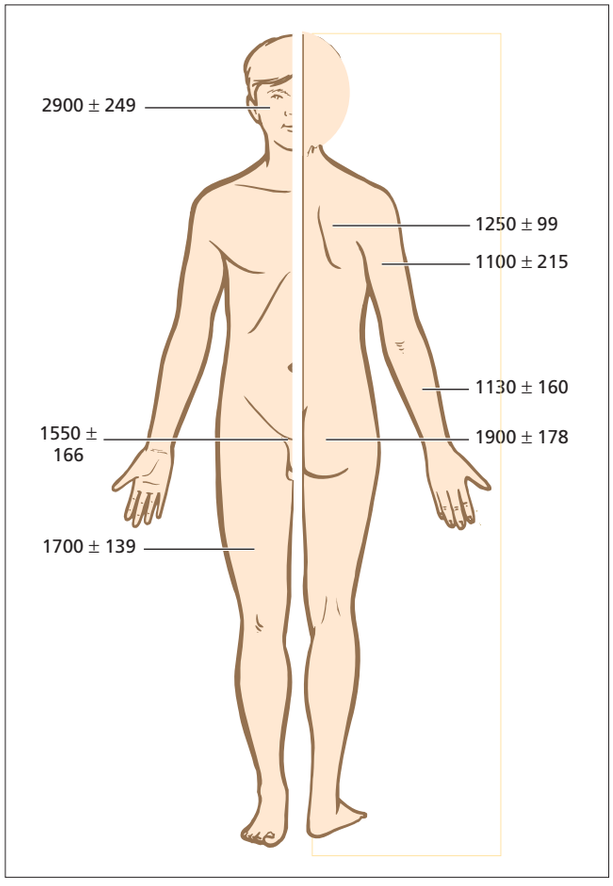


Fig. 58.2 Regional variation in the distribution of epidermal melanocytes. The figures are mean values per mm^2 ± standard error of the mean. (From Rosdahl & Rorsman [1].)

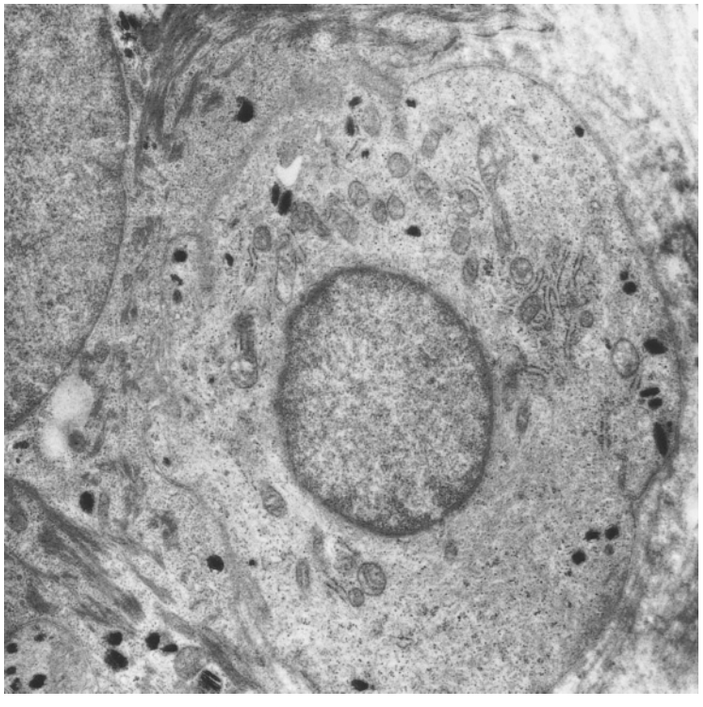


Fig. 58.3 Melanocyte in the basal layer of the epidermis, × 12 000.

skin or with the facility to tan darkly have a great capacity to synthesize melanin and to transfer it to surrounding keratinocytes. In contrast, those with fair skin and lack of tanning facility have very limited capacity. Melanocytes are found in nearly every tissue but are most numerous in the epidermis, hair follicles and the eye [1,2]. A reduction in the number of melanocytes occurs with ageing, with a decrease in melanocyte density of about 6–8% per decade [3]. The density of melanocytes is about two-fold higher in exposed than in non-exposed skin [2].

References

1 Rosdahl I, Rorsman H. An estimate of the melanocyte mass in humans. *J Invest Dermatol* 1983; **81**: 278–81.
2 Szabo G. Regional anatomy of the human integument with special reference to the distribution of hair follicles, sweat glands, and melanocytes. *Philos Trans R Soc Lond B* 1967; **252**: 447–85.
3 Gilchrest BA, Blog FB, Szabo G. Effects of aging and chronic sun exposure on melanocytes in human skin. *J Invest Dermatol* 1979; **73**: 141–3.

Melanoblast migration and differentiation

Pigment cells arise from the neural crest [1], a region of the embryonic ectoderm that originates from the margins of the neural plate at the time when it sinks in to form the tubular central nervous system. The developmental potential of neural crest cells has been studied by a variety of means including clonal analysis, cell grafting experiments and lineage-specific marker studies. Collectively, these studies indicate that most early neural crest cells are multipotent, and become fate-restricted over time [2–4]. Melanoblasts originate in the neural crest and migrate laterally, first to the dermis and then to the basal lamina of the epidermis. Immunocytochemical marker studies with the melanocyte-specific HMB-45 antibody have revealed that melanoblasts appear in the epidermis by 7 weeks' gestation, with a cell density of about 50% of that observed at birth [4]. Ultrastructural studies on early human embryos have demonstrated the presence of melanocytes containing melanosomes showing early melanization [5]. HMB-45 staining has revealed an approximately two-fold increase in melanocyte numbers between gestation weeks 10 and 14, possibly due to mitosis of cells already *in situ* rather than due to addition cell migration. Melanocytes associated with hair follicles arrive at their final location by following the downgrowth of epidermal cells in developing hair follicles [6].

Studies in mice have demonstrated that melanocyte lineage segregation starts early in neural crest development, with melanoblasts specified prior to or coincident with their emigration from the neural tube [7]. Initial segregation of melanocyte lineage involves the Wnt/β-catenin pathway [8]. The transcription factor *mi* is relatively specific for melanocytes differentiation, as was first identified in the *microthalmia (mi)* mutant. *Mi* encodes the transcription factor Mitf, which regulates several melanocyte-specific genes [9,10]. In humans, mutations in *mi* are associated with Waardenburg's syndrome type 2A, an autosomal dominant condition characterized by deafness and patchy abnormal pigmentation [11]. *Sox10* and *Pax3* are two other genes associated with Waardenburg's syndrome, probably through regulation of expression of Mitf protein [12]. *Pax3* appears to prime cells for differentiation, whereas *Wnt* signalling allows cells to proceed along this route [13].

Much of our knowledge about melanocytes development in humans has been derived from studies on mouse pigment mutants [11]. To summarize this body of work in broad terms, mouse coat colour mutants arise from three main groups: those that affect the subcellular structure of melanocytes, those that disrupt the normal synthesis of melanin and those that alter development and differentiation of normal melanocytes. Where possible in the following chapter, molecular and biochemical mechanisms for pigmentary abnormalities in humans with genetic disorders will be highlighted.

References

1 Bagnara JT, Matsumoto J, Ferris W *et al*. On the common origin of pigment cells. *Science* 1979; **203**: 410–5.
2 Le Douarin NM, Creuzet S, Couly G, Dupin E. Neural crest cell plasticity and its limits. *Development* 2004; **131**: 4637–50.
3 Weston JA. Sequential segregation and fate of developmentally restricted intermediate cell populations in the neural crest. *Curr Top Dev Biol* 1991; **25**: 133–53.
4 Holbrook KA, Vogel AM, Underwood RA, Foster CA. Melanocytes in human embryonic and fetal skin: a review and new findings. *Pig Cell Res* 1988; **1** (Suppl.): 6–17.
5 Sagebiel RW, Odland GF. In: Riley V, ed. *Pigmentation: its Genesis and Biologic Control*. New York: Appleton-Century-Crofts, 1972: 43.
6 Mishima Y, Widlan S. Embryonic development of melanocytes in human hair and epidermis. *J Invest Dermatol* 1966; **46**: 263–77.
7 Wilson YM, Richards KL, Ford-Perriss ML *et al*. Neural crest cell lineage segregation in the mouse neural tube. *Development* 2004; **131**: 6153–62.
8 Dunn JD, Brady M, Ochsebauer-Jambor C *et al*. WNT1 and WNT3a promote expansion of melanocytes through distinct modes of action. *Pigment Cell Res* 2005; **18**: 167–80.
9 Baxter LL, Pavan WJ. Pmel17 expression is Mitf-dependent and reveals cranial melanoblasts migration during murine development. *Gene Expr Patterns* 2003; **3**: 703–7.
10 Bentley NJ, Eisen T, Goding CR. Melanocyte-specific expression of the human tyrosinase promoter: activation by the microphthalmia gene product and role of the initiator. *Mol Cell Biol* 1994; **14**: 7996–8006.
11 Baxter LL, Hou L, Loftus SK, Pavan WJ. Spotlight on spotted mice: a review of white spotting mutants and associated human pigmentation disorders. *Pigment Cell Res* 2004; **17**: 215–24.
12 Potterf SB, Furumura M, Dunn KJ *et al*. Transcription factor hierarchy in Waardenburg syndrome: regulation of MITF expression by SOX10 and PAX3. *Hum Gen* 2000; **107**: 1–6.
13 Lang D, Lu MM, Huang L *et al*. Pax3 functions at a nodal point in melanocytes stem cell differentiation. *Nature* 2005; **433**: 884–7.

Melanosome transport [1–10]

Melanosome transport depends upon effective dendrite formation by melanocytes. Ultraviolet radiation and melanocyte-stimulating hormone are both known to stimulate this process [1]. Melanocyte dendrite formation requires actin polymerization, which in turn is controlled by the activity of the small guanosine triphosphate (GTP)-binding proteins Rac and Rho [2–4]. These are themselves controlled by regulatory associated proteins. Direct visualization of melanosome trafficking by video microscopy has revealed evidence to suggest that transfer of melanosomes along dendrites occurs on microtubules [5,6], a process driven by dynein (a minus end microtubule motor) and kinesin (a plus end microtubule motor) [7,8]. Dynein binds microtubules and adenosine triphosphate and produces forces which move the dynein and melanosome complex along the microtubule. Both dynein and kinesin remain bound to the melanosomes and their regulation modifies the direction of melanosome movement along the microtubules [9]. Three individual proteins work together in the final stages of melanosome trafficking. One of these, myosin Va, functions to facilitate the 'capture' of melanosomes at the actin-rich tip of the dendrite [7]. Another, Rab protein, Rab27A, associates with the membrane of melanocytes and then forms a complex with myosin Va and a third protein, melanophylin. The ability of melanophylin to bind actin, in addition to its ability to link with Rab27A and myosin Va, has led to the postulate that transfer of melanosomes from microtubules to actin filaments at the tip of melanocyte dendrites is the final part of the transport process prior to melanosome transfer [10].

References

1 Scott GA, Cassidy L. Rac1 mediates dendrite formation in response to melanocyte stimulating hormone and ultraviolet light in a murine melanoma model. *J Invest Dermatol* 1998; **111**: 243–50.
2 Busca R, Bertolotto C, Abbe P *et al*. Inhibition of Rho is required for cAMP-induced melanoma cell differentiation. *Mol Biol Cell* 1998; **9**: 1367–78.
3 Scott G, Leopardi S. The cAMP signalling pathway has opposing effects on Rac and Rho in B16F10 cells: implications for dendrite formation in melanocytic cells. *Pig Cell Res* 2003; **16**: 139–48.
4 Scott G. Rac and Rho: the story behind melanocyte dendrite formation. *Pig Cell Res* 2002; **15**: 322–30.
5 Scott G, Leopardi S, Printup S, Madden BC. Filopedia are conduits for melanosome transfer to keratinocytes. *J Cell Sci* 2002; **115**: 1441–51.
6 Wu X, Bowers B, Wei Q *et al*. Myosin V associates with melanosomes in mouse melanocytes: evidence that myosin V is an organelle motor. *J Cell Sci* 1997; **110**: 847–59.
7 Byers HR, Yaar M, Eller MS *et al*. Role of cytoplasmic dynein in melanosome transport in human melanocytes. *J Invest Dermatol* 2000; **114**: 990–7.
8 Hara M, Yaar M, Byers HR *et al*. Kinesin participates in melanosomal movement along melanocyte dendrites. *J Invest Dermatol* 2000; **114**: 438–43.
9 Gross SP, Tuma MC, Deacon SW *et al*. Interactions and regulation of molecular motors in *Xenopus* melanophores. *J Cell Biol* 2002; **156**: 855–65.
10 Strom M, Hume AN, Tarafder AK *et al*. A family of Rab27-binding proteins. Melanophilin links Rab27a and myosin Va function in melanosome transport. *J Biol Chem* 2002; **277**: 25423–30.

Melanosome transfer to keratinocytes [1–7]

The successful synthesis of a melanosome, and its transport to the tip of a dendrite, is followed by transfer of the melanosome to the keratinocyte. Both ultraviolet radiation and the hormone MSH stimulate this transfer, while niacinamide has been shown to suppress it [1]. However, the exact mechanism by which the melanosome is transferred to the keratinocyte remains unclear. One possibility is exocytosis of melanosomes from the tips of dendrites with subsequent keratinocyte uptake by endocytosis. In support of this, exocytosis-associated proteins soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) and Rab3a have both been identified on melanosomes [2–4]. Furthermore, *in vivo* high-resolution time-lapse digital images of this process have identified long, dynamic filopedia arising from the melanocyte dendrite tips packed with melanosomes [4]. The filopedia have been observed to attach and detach from the keratinocyte membrane; melanocytes have been observed travelling in both directions within the filopedia [4]. Work from several groups has revealed that lectins and their glycosolated ligands may function as receptor-ligand pairs in these melanocyte-keratinocyte interactions [5–7].

References

1 Hakozaki T, Minwalla L, Zhuang J *et al*. The effect of niacinamide on reducing cutaneous pigmentation and suppression of melanosome transfer. *Br J Dermatol* 2002; **147**: 200–31.
2 Takai Y, Sasaki T, Shirataki H, Nakanishi H. Rab3A small GTP-binding protein in Ca(2+)-dependent exocytosis. *Genes Cells* 1996; **1**: 615–32.
3 Jahn R, Sudhof TC. Membrane fusion and exocytosis. *Ann Rev Biochem* 1999; **68**: 863–911.
4 Scott G, Zhao Q. Rab3a and SNARE proteins: potential regulators of melanosome movement. *J Invest Dermatol* 2001; **116**: 296–304.
5 Cerdan D, Grillon C, Monsigny M, Redziniak G, Keida C. Human keratinocyte membrane lectins: characterization and modulation of their expression by cytokines. *Biol Cell* 1991; **73**: 35–42.
6 Condaminet B, Redziniak G, Monsigny M, Keida C. Ultraviolet rays induced expression of lectins on the surface of a squamous carcinoma keratinocyte cell line. *Exp Cell Res* 1997; **232**: 216–24.
7 Minwalla I, Zhao Y, Cornelius J *et al*. Inhibition of melanosome transfer from melanocytes to keratinocytes by lectins and neoglycoproteins in an *in vitro* model system. *Pigment Cell Res* 2001; **14**: 185–94.

Melanocyte culture [1–8]

Melanocytes fail to grow, and usually die, in culture media used for skin fibroblasts or keratinocytes. In contrast to many other cell types, melanocytes do not produce any of the growth factors that are known to stimulate them [1]. Following an intensive search, the first highly effective natural melanocyte mitogen was identified as basic fibroblast growth factor (now termed FGF2) [2]. As more mitogens for melanocytes emerged, it was apparent that a combination of synergistic growth factors was required to stimulate quiescent or moribund melanocytes in culture [1,3]. Additional stimulatory peptides include mast cell growth factor/stem cell factor (M/SCF, also known as Kit ligand and Steel factor), hepatocyte growth factor/scatter factor (HGF/SF), endothelins and, to a lesser degree, melanocyte-stimulating hormone (MSH). In the presence of FGF2, phorbol ester and cyclic adenosine monophosphate these peptides act synergistically on melanocytes in culture [1,4]. A more recent addition to the list of melanocyte mitogens is leukaemia inhibitory factor (LIF) [5]. With the exception of FGF2, most of these factors also promote melanocyte differentiation [6,7]. Endothelin 1 (ET1) can also sustain the viability of human melanocytes in the absence of other growth factors and can also stimulate the formation and elongation of dendrites [4,8].

References

1 Halaban R. The regulation of normal melanocytes proliferation. *Pigment Cell Res* 2000; **13**: 4–14.
2 Halaban R, Ghosh S, Baird A. bFGF is the putative natural growth factor for human melanocytes. *In Vitro Cell Dev Biol* 1987; **23**: 47–52.
3 Halaban R. Growth factors and tyrosine protein kinases in normal and malignant melanocytes. *Cancer Metast Rev* 1991; **10**: 129–40.
4 Böhm M, Moellmann GE, Cheng M *et al*. Identification of p90RSK as the probable CREB-Ser 133 kinase in human melanocytes. *Cell Growth Differ* 1995; **6**: 291–302.
5 Hirobe T. Role of leukaemia inhibitory factor in the regulation of differentiation of neonatal mouse epidermal melanocytes in culture. *J Cell Physiol* 2002; **192**: 315–26.
6 Halaban R, Tyrrell L, Longley J, Yarden Y, Rubin J. Pigmentation and proliferation in human melanocytes and the effects of melanocyte-stimulating hormone and ultraviolet B light. *Ann N Y Acad Sci* 1993; **680**: 290–301.
7 Odecamp K, Kos L, Arnheiter H, Pavan WJ. Endothelin signaling in the development of neural crest-derived melanocytes. *Biochem Cell Biol* 1998; **76**: 1093–9.
8 Hara M, Yaar M, Gilchrest BA. Endothelin-1 of keratinocytes origin is a mediator of melanocytes dendricity. *J Invest Dermatol* 1995; **105**: 744–8.

Table 58.2 Main types of epidermal melanin pigments. (Courtesy of Prota [2].)

Eumelanins	Brown or black nitrogenous pigments, insoluble in all solvents, which arise by oxidative polymerization of 5,6-dihydroxyindoles derived biogenetically from tyrosine
Phaeomelanins	Alkali-soluble pigments, ranging from yellow to reddish-brown; most of them contain sulphur in addition to nitrogen and arise by oxidative polymerization of cysteinyl-dopa via 1,4-benzothiazine intermediates
Trichochromes	A variety of sulphur-containing phaeomelanic pigments with a well-defined structure, characterized by a $\Delta^{2,2'}$-bi(1,4-benzothiazine) chromophore

Biochemistry of melanogenesis [1–5]

Melanins are usually classified into two main groups: the brown to black insoluble eumelanins, and the yellow to reddish-brown alkali-soluble phaeomelanins (Table 58.2). Both pigments are derived from dopaquinone, which is formed by the oxidation of the common amino acid L-tyrosine by tyrosinase.

Eumelanin formation

Dopaquinone is a highly reactive intermediate and in the absence of sulfhydryl compounds it forms cyclodopa. The redox exchange between cyclodopa and dopaquinone then gives rise to the red intermediate dopachrome and dopa. Dopachrome then rearranges to 5,6-dihydroxyindole (DHI) and to a lesser extent to 5,6-dihydroxyindole carboxylic acid (DHICA). Finally, these two compounds are oxidized and polymerized to produce eumelanins. In addition to tyrosinase, dopachrome tautomerase and Tryp1 (DHICA oxidase) are now both recognized as having a role in the regulation and promotion of eumelanogenesis [1].

Pheomelanin formation

In contrast to eumelanins, pheomelanins contain sulphur in addition to nitrogen and are formed from cysteinyldopa (Fig. 58.4). Further oxidation of the thiol adducts leads to the formation of pheomelanin via benzothiazine intermediates. Most melanin pigments in skin are mixtures or copolymers of eumelanins and pheomelanins. However, the situation is complicated by the fact that some pheomelanin-like pigments may be structural variants of eumelanins [2]. Thus, in the presence of metal ions, black insoluble eumelanin may be oxidized chemically or photochemically to a soluble form (melanin-free acid), which is light in colour [3,4].

Trichochromes

A further complication is that red human hair contains, in addition to pheomelanins, small amounts of intensely coloured pigments known as trichochromes [2,5], originally isolated from the red feathers of New Hampshire hens. Trichochromes are sulphur-containing pigments of a well-defined structure, of which six variants have so far been identified (Fig. 58.5).

References

1 Hearing VJ. Invited editorial: unraveling the melanocytes. *Am J Hum Genet* 1993; **52**: 1–7.

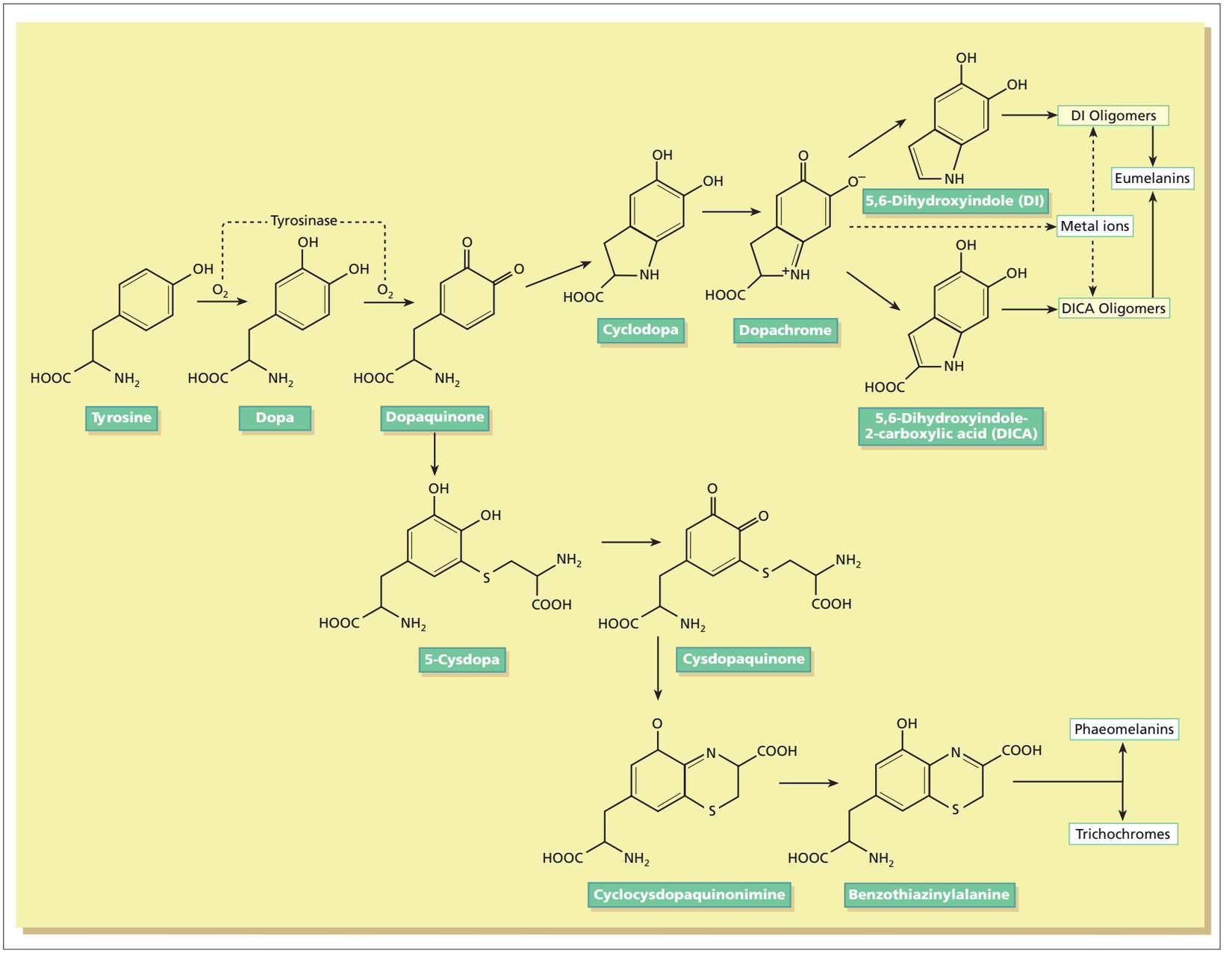


Fig. 58.4 A simplified overview of the major metabolic pathways in the synthesis of melanins and trichochromes. (From Prota [2].)

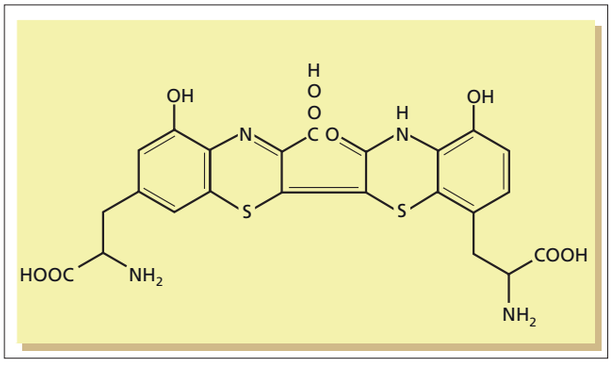


Fig. 58.5 Structure of trichochrome B, one of six trichochromes so far identified.

2 Prota G. Progress in the chemistry of melanins and related metabolites. *Med Res Rev* 1988; **8**: 525–56.
3 Albrecht L, Patil D, Wolfram LJ. Photochemical properties of pheo and eumelanins. *J Invest Dermatol* 1986; **87**: 396.
4 Chedekel MR, Bahn P, Patil D *et al*. Melanin free acid: a chemical standard for eumelanin research. *J Invest Dermatol* 1986; **87**: 397.
5 Prota G. Recent advances in the chemistry of melanogenesis in mammals. *J Invest Dermatol* 1980; **75**: 122–7.

Regulation of human pigmentation by ultraviolet light and by endocrine, paracrine and autocrine factors

Regulation of human melanocytes is complex; in addition to a direct stimulatory effect of ultraviolet radiation, there are also effects mediated by endocrine, paracrine and autocrine factors. Constitutive melanin content is determined by the rate of synthesis by melanocytes and by the rate and mode of melanosome delivery to keratinocytes. The response of cultured melanocytes to ultraviolet radiation involves growth arrest in conjunction with increased melanogenesis. A differential response is observed between melanocytes derived from individuals of skin types I or II and those from skin types V or IV, with the former showing more prolonged growth arrest, more cyclobutane pyrimidine dimers and less melanogenesis. Exposure of human skin to ultraviolet radiation induces a number of epidermal cytokines and growth factors which in turn induce proliferation of melanocytes and/or melanogenesis. Many devoted sun-worshippers know that by deliberately overdosing on sun exposure, the inflammatory sunburn that ensues is more effective at inducing tanning than a more patient, non-burning approach.

Melanocyte response to UV radiation

Sun exposure is associated with an increased number of active melanocytes in sun-protected skin in the same individual. Friedmann and Gilchrest [1] were the first to demonstrate this direct responsiveness in cultured melanocytes, by showing that irradiation with solar-simulated ultraviolet light resulted in a dose-dependent decrease in proliferation and an increase in pigmentation. More recently, research using sub-lethal doses of UVB showed inhibition of melanocyte proliferation as a result of arrest in G_2 phase of the cell cycle, and an increased tyrosinase activity and melanin content [2]. Melanocytes derived from different skin types all showed a similar pattern of response [2]. Subsequent research has confirmed that this UV-induced growth arrest of melanocytes is related to increased levels of the tumour suppressor gene product p53, with lightly pigmented melanocytes experiencing a more prolonged growth arrest, and a more sustained increase in the p53 protein, than occurs in darkly pigmented melanocytes [3]. Furthermore, lightly pigmented melanocytes show more cyclobutane pyrimidine dimers (a reliable marker for UV-induced DNA damage) after UV irradiation than occurs in heavily pigmented melanocytes [3]. In addition to increased activity of melanocyte tyrosinase, sun exposure leads to elongation and branching of melanocyte dendrites, and an increase in the number and size of melanosomes.

Melanocyte regulation by endocrine factors

The effects of oestrogens on cutaneous pigmentation have been recognized for more than 60 years [4,5]. High levels of oestrogens during pregnancy are implicated in the increased pigmentation that occurs on the face, areola, lower central abdomen and genitalia. Oestrogens have been shown to stimulate melanogenesis in cultured melanocytes by increased tyrosinase activity [6]; these include α-oestradiol, β-oestradiol and oestriol [7]. However, no specific receptors for oestrogens have yet been identified in melanocytes.

In Addison disease the diffuse brown hyperpigmentation results from the melanogenic action of melanocortins derived from the pituitary. The melanocortins are all derived from a precursor molecule, pro-opiomelanocortin. Other melanocortins released from the pituitary in increased quantities in Addison disease include β-lipotrophin, γ-melanotrophin (γ-MSH), β-melanotropin (β-MSH) and α-melanotropin (α-MSH). These peptides all have a stimulatory effect on melanocytes [8], and, in the absence of negative feedback to inhibit their secretion, the hyperpigmentation produced is insidious and progressive (Fig. 58.6). Human melanocytes express the melanocortin 1 receptor (MC1R) that binds α-MSH and ACTH with the same affinity [9]. α-MSH causes a small rise in cAMP but has no effect on basal or ultraviolet-stimulated melanogenesis in human melanocytes [10].

Melanocyte regulation by paracrine and autocrine factors

Post-inflammatory hyperpigmentation is believed to be mediated by immune inflammatory mediators including IL-1α, IL-1β, IL-6 and TNF-α [11]. Human melanocytes have also been demonstrated to respond to, and synthesise, IL-1α and IL-1β, which suggests an autocrine as well as a paracrine regulatory role [12]. Other inflammatory mediators that act on human melanocytes include ecosanoids, metabolites of arachidonic acid. Melanocytes respond to PGE_2 with increased melanogenesis and dendrite formation [13]. Scott *et al.* demonstrated an increase in dendricity of human melanocytes in response to PGE_2 and $PGF_{2\alpha}$ [14]. Basic fibroblast growth factor was the first paracrine factor for human melanocytes to be identified. It exerts its effect by binding to a tyrosine kinase receptor that is expressed on human melanocytes [15]. In contrast to IL-1α, IL-1β, IL-6 and TNF-α and the ecosanoids, basic fibroblast growth factor is not secreted by keratinocytes; direct contact between melanocytes and keratinocytes is required for its



Fig. 58.6 Diffuse hyperpigmentation with darkening of hair and mucous membranes in a woman with Nelson's syndrome following bilateral adrenalectomy.

biological effects [16]. Additionally, leukotrienes C_4 and D_4 have been shown to act as potent mitogens on cultured human neonatal melanocytes [17].

Endothelins are a further important group of peptides that act upon melanocytes in a paracrine manner [18]. Endothelin-1 (ET-1) is both mitogenic and melanogenic for human melanocytes that express ET-1 receptors [19]. ET-1 acts synergistically with α-MSH and basic fibroblast growth factor to stimulate human melanocytes proliferation [20]. Endothelin-3 (ET-3) has similar effects to ET-1; both peptides bind the endothelin receptor on melanocytes with equal affinity [21]. Furthermore, endothelins appear to have a role in protecting melanocytes: Kadekaro *et al.* demonstrated that treatment of human melanocytes with ET-1 reduced UVR-induced apoptosis and prolonged melanocyte survival [22].

References

1 Friedmann PS, Gilchrest BA. Ultraviolet radiation directly induces pigment production by cultured human melanocytes. *J Cell Physiol* 1987; **133**: 88–94.

2 Abdel-Malek Z, Swope V, Smalara D *et al*. Analysis of the UV-induced melanogenesis and growth arrest in human melanocytes. *Pig Cell Res* 1994; **7**: 326–32.

3 Barker D, Dixon K, Medrano EE *et al*. Comparison of the responses of human melanocytes with different melanin contents to ultraviolet B irradiation. *Cancer Res* 1995; **55**: 4041–6.

4 Hamilton JB, Hubert G. Photographic nature of tanning of human skin as shown by studies of male hormone therapy. *Science* 1938; **88**: 481.

5 Hamilton JB. Significance of sex hormones in tanning of the skin in women. *Proc Soc Exp Biol Med* 1941; **40**: 502–3.

6 Ransom M, Posen S, Mason RS. Human melanocytes as a target tissue for hormones: in vitro studies with 1α-25, dihydroxy-vitamin D3, α-melanocyte stimulating hormone, and β-estradiol. *J Invest Dermatol* 1988; **91**: 593–8.

7 McLeod SD, Ranson M, Mason RS. Effects of estrogens on human melanocytes in vitro. *J Steroid Biochem* 1994; **49**: 9–14.

8 Shizume K. Thirty five years of progress in the study of MSH. *Yale J Biol Med* 1985; **58**: 561–70.

9 Suzuki I, Cone R, Im S *et al*. Binding capacity and activation of the MC1 receptors by melanotropic hormones correlate directly with their mitogenic and melanogenic effects on human melanocytes. *Endocrinology* 1996; **137**: 1627–33.

10 Friedmann PS, Wren F, Buffey J, MacNeil S. α-MSH causes a small rise in cAMP but has no effect on basal or ultraviolet-stimulated melanogenesis in human melanocytes. *Br J Dermatol* 1990; **123**: 145–51.

11 Swope VB, Abdel-Malek ZA, Kassem L, Nordlund JJ. Interleukins 1-α and 6 and tumor necrosis factor-α are paracrine inhibitors of human melanocytes proliferation and melanogenesis. *J Invest Dermatol* 1991; **96**: 180–5.

12 Swope VB, Sauder DN, McKenzie RC *et al*. Synthesis of interleukin-1α and β by normal human melanocytes. *J Invest Dermatol* 1994; **102**: 749–53.

13 Tomita Y, Iwamoto M, Masuda T, Tagami H. Stimulatory effect of prostaglandin E_2 on the configuration of normal human melanocytes. *J Invest Dermatol* 1987; **89**: 299–301.

14 Scott G, Leopardi S, Printup S *et al*. Proteinase-activated receptor-2 stimulates prostaglandin production in keratinocytes: analysis of prostaglandin receptors on human melanocytes and effects of PGE_2 and $PGF_{2\alpha}$ on melanocytes dendricity. *J Invest Dermatol* 2004; **122**: 1214–24.

15 Pittelkow MR, Shipley GD. Serum-free culture of normal human melanocytes: growth kinetics and growth factor requirements. *J Cell Physiol* 1989; **140**: 565–76.

16 Gordon PR, Mansur CP, Gilchrest BA. Regulation of human melanocyte growth, dendricity, and melanization by keratinocyte derived factors. *J Invest Dermatol* 1989; **92**: 565–72.

17 Morelli JG, Yohn JJ, Lyons MM *et al*. Leukotrienes C_4 and D_4 as potent mitogens for cultured human neonatal melanocytes. *J Invest Dermatol* 1989; **93**: 719–22.

18 Rubanyi GM, Polokoff MA. Endothelins: molecular biology, biochemistry, pharmacology, physiology and pathophysiology. *Pharmacol Rev* 1994; **46**: 325–415.

19 Yada Y, Higuchi K, Imokawa G. Effects of endothelins on signal transduction and proliferation in human melanocytes. *J Biol Chem* 1991; **166**: 18352–7.

20 Swope VB, Medrano EE, Smalara D, Abdel-Malek Z. Long-term proliferation of human melanocytes is supported by the physiologic mitogens α-melanotropin, endothelin-1, and basic fibroblast growth factor. *Exp Cell Res* 1995; **217**: 453–9.

21 Tada A, Suzuki I, Im S *et al*. Endothelin-1 is a paracrine growth factor that modulates melanogenesis of human melanocytes and participates in their responses to ultraviolet radiation. *Cell Growth Differ* 1998; **9**: 575–84.

22 Kadekaro AL, Kanto H, Kavanagh R *et al*. α-Melanocortin and endothelin-1 promote the survival of human melanocytes by activating anti-apoptotic pathways and enhancing the repair of DNA photoproduct. *Cancer Res* 2005; **65**: 4292–9.

Biological significance of melanin

The major biological function of melanin is generally assumed to be protection of the lower layers of the skin against UV light. If human pigment has such adaptive significance, we might expect to find that, among the races of the world, pigment is geographically distributed in relation to solar intensity. It appears to be generally true that pigmentation is greatest in the tropics and reduced in temperate zones, reappearing to some extent in northern races subjected to prolonged snow glare [1]. However, there are exceptions, for example native Americans are not notably different in skin colour throughout the whole continent, and Tasmanians are dark even though they live in a temperate climate.

The damaging role of UV light is well illustrated by the high incidence of epidermal carcinoma in Europeans exposed to excess sun. The evolutionary usefulness of pigmentation may be twofold. On the one hand, it protects against damage by sunburn. On the other, since it efficiently absorbs UV radiation and is readily activated to a free radical by incident light, it may serve to eliminate genetically damaged cells by a phototoxic mechanism.

Not all the effects of pigmentation are advantageous. There is no doubt that pigmentation increases the heat load in hot climates, so that black people absorb 30% more heat from sunlight than do white people, although this factor may be offset by more profuse sweating [2,3]. In addition, in cold climates pale skin has the advantage that heat loss by radiation is reduced.

A further disadvantage of pigmentation is that it hinders synthesis of vitamin D, so that in areas of poor nutrition black children are more liable to rickets than white children. Thus, loss of pigmentation may facilitate vitamin D synthesis in temperate climates. It might be presumed that the retention of pigment in Arctic latitudes, while providing a protection against snow glare, is only permitted by natural selection because of the high-fat diet in these areas.

Since pigmentation appears to be not entirely advantageous to life in the tropics, other hypotheses about its biological significance have been advanced. For example, Wassermann [4,5] suggested that the major adaptation of black people to tropical Africa is in the ability to survive malaria, multiple parasites and tropical diseases under the hazards of intense solar radiation and, more often than not, poor nutrition. He suggests that diseases, not climatic conditions, are the primary selective factors, and lists evidence that black Africans, in comparison with white people, show increased reticuloendothelial activity and increased serum γ-globulin fractions. These features are inversely related to the size and activity of the adrenal cortex. Because of their primary decrease in adrenocortical function, black people show increased MSH and adrenocorticotrophic hormone (ACTH) activity, which enhances melanogenesis. Pigmentation might thus be a secondary phenomenon.

References

1 Fleure HJ. The distribution of types of skin colour. *Geogr Rev* 1945; **35**: 580–95.
2 Blum HF. The physiological effects of sunlight on man. *Physiol Rev* 1945; **25**: 483–530.
3 Blum HF. Does the melanin pigment of human skin have adaptive value? An essay in human ecology and the evolution of race. *Q Rev Biol* 1961; **36**: 50–63.
4 Wassermann HP. Melanokinetics and the biological significance of melanin. *Br J Dermatol* 1970; **82**: 530–4.
5 Wassermann HP. *Ethnic Pigmentation*. Amsterdam: Excerpta Medica, 1974.

Classification of disorders of melanin pigmentation

Disorders of melanin pigmentation can be divided on morphological grounds into two types. The first is hypermelanosis, where there is an increased amount of melanin in the skin. This excess may be confined to the epidermis, when the skin appears browner than normal, or it may be present in the dermis, producing a slaty-grey or blue appearance. The second type is hypomelanosis, where there is a lack of pigment in the skin, which therefore appears white or lighter than the normal colour. Amelanosis is the term applied when there is a total lack of melanin in the skin. Hypermelanosis and hypomelanosis can be generalized and diffuse, or may be localized and circumscribed. Sometimes, localized areas may have a segmental or dermatomal pattern. The term 'depigmentation' is used to describe a loss of pre-existing pigment from the skin. Leukoderma is a white skin that may be congenital or acquired and can be due to a variety of aetiological factors. Examination of the skin with a source of long-wave UV light, for example Wood's lamp, is often helpful in localizing abnormal variations in melanin pigmentation in the skin and as an aid to the diagnosis of various disorders [1].



Fig. 58.7 Occupational vitiligo due to tertiary-butylphenol.

Changes in pigmentation can arise in a number of ways and can be due to a variety of genetic and environmental factors. It is also pertinent to consider non-melanin pigmentation as a cause of cutaneous colour changes, as discussed at the end of this chapter.

Hypermelanosis similarly can be due to many factors, both genetic and acquired (Fig. 58.7). It can be due to an increased number of melanocytes in the skin such as occurs in the dermal melanocytoses: the naevus of Ota, the naevus of Ito and the Mongolian spot. Many of the hypermelanotic disorders are due to an increase in melanogenesis due to genetic factors. Some may be induced by UV light, hormones and chemical compounds. Finally, the degradation of melanosomes may vary in different disorders of pigmentation.

Reference

1 Gilchrest BA, Fitzpatrick TB, Anderson RR, Parrish JA. Localization of melanin pigmentation in the skin with Wood's lamp. *Br J Dermatol* 1977; **96**: 245–8.

Constitutive pigmentation, human pigmentation and the response to sun exposure

Genetic factors play the primary role in determining the degree of pigmentation that is normal for the individual. Variation in skin pigmentation is not due to differences in the number of melanocytes but is explained by differences in melanocyte structure and function; melanogenic activity, the size and number of melanosomes, the type of melanin deposited onto melanosomes, and the donation of mature melanosomes to adjacent keratinocytes all contribute to the resulting colour of the skin and are genetically

determined. Thus, constitutive skin colour, as well as how the colour changes in response to exposure to sunlight, are both genetically determined, and show relatively little variation within different racial groups. There is, however, marked variation in human skin colour between the main racial groupings ranging from white (Caucasoid), through lightly pigmented (Asian and Oriental), to black (Negroid and Australoid and some Asian races). Racial differences in melanocyte morphology and function are apparent, but there is little inter-racial variation in the density of melanocytes at a particular skin site. Ultrastructural studies have shown that melanosomes in white skin are small and tend to be in membrane-bound complexes containing three or more within the keratinocytes [1]. The ellipsoidal melanosomes of aboriginals and black people are larger, about 1 μm in length, and tend to be distributed as singlets rather than being aggregated. These larger melanosomes can be found intact in the stratum corneum. The melanosomes in the complexes in white people show degradative changes even in the basal layer of the epidermis and are presumably broken up by lysosomal enzymes [2]. Whether melanosomes are individually dispersed or aggregated in melanosomal complexes appears to depend on the size of the melanosome [1].

Melanin in the skin exerts its photoprotective effect by reducing the penetration of ultraviolet light through the epidermis and by quenching reactive oxygen radicals that contribute to the sun-induced DNA damage [3]. The superior photoprotection of the black epidermis is due not only to its increased melanin content but also to melanogenic activity, the size and number of melanosomes, the type of melanin deposited onto melanosomes, and the donation of mature melanosomes to adjacent keratinocytes. A classification of sun-reactive skin types based on sunburn and tanning history has been in widespread use since its introduction (Table 58.3) [4]. Two types of pigmentation of the skin in humans occur in response to sun exposure. The first is immediate pigment darkening, sometimes referred to as the Meirowsky phenomenon or 'IPD'. This is best observed in those with hyperpigmented skins and is most effectively induced by long-wave UV light (UVA). It is transient and, although rapidly induced, soon fades. The second is the increased pigmentation that follows the erythemal response. This is the delayed tanning reaction and can be seen 48–72 h after skin exposure to UV light.

References

1 Olson RL, Gaylon J, Everett MA. Skin color, melanin and erythema. *Arch Dermatol* 1973; **108**: 541–4.

2 Hori Y, Toda K, Pathak MA *et al*. A fine-structure study of the human epidermal melanosome complex and its acid phosphatase activity. *J Ultrastruct Res* 1968; **25**: 109–20.

3 Kaidbey KH, Poh Agin P, Sayre RM, Kligman AM. Photoprotection by melanin: a comparison of black and caucasian skin. *J Am Acad Dermatol* 1979; **1**: 249–60.

4 Fitzpatrick TB. The validity and practicality of sun-reaction skin types I through VI. *Arch Dermatol* 1988; **124**: 869–71.

Table 58.3 Classification of sun-reactive skin types.

Skin type	Sun sensitivity	Pigmentary response
I	Very sensitive, always burn easily	Little or no tan
II	Very sensitive, always burn	Minimal tan
III	Sensitive, burn moderately	Tan gradually (light brown)
IV	Moderately sensitive, burn minimally	Tan easily (brown)
V	Minimally sensitive, rarely burn	Tan darkly (dark brown)
VI	Insensitive, never burn	Deeply pigmented (black)

Hypermelanosis

Ephelides

Synonym
- Freckles

Freckling is probably determined by an autosomal dominant gene [1]. It is most frequent in individuals with red or blonde hair and blue eyes, particularly in those of Celtic (Scottish, Irish, Welsh) extraction. Red-haired individuals with fair skin (and freckles) have a significantly higher incidence of the gene encoding melanocortin receptors [2,3].

Pathology [4]. There is no increase in the number of melanocytes in the pigmented macules but their melanosomes are long and rod-shaped, like those found generally in dark-skinned people. They form melanin more rapidly after exposure to sunlight than do those in the surrounding pale skin, which are spherical and often granular, and are of the type usually found in fair- and red-haired individuals. With the light microscope, the only abnormality detectable is an increase in the quantity of melanin in the epidermis.

Clinical features (Fig. 58.8). Freckles are small macules of hyperpigmentation, usually measuring 2–4 mm in size. They first appear at about the age of 5 years as light-brown pigmented macules on

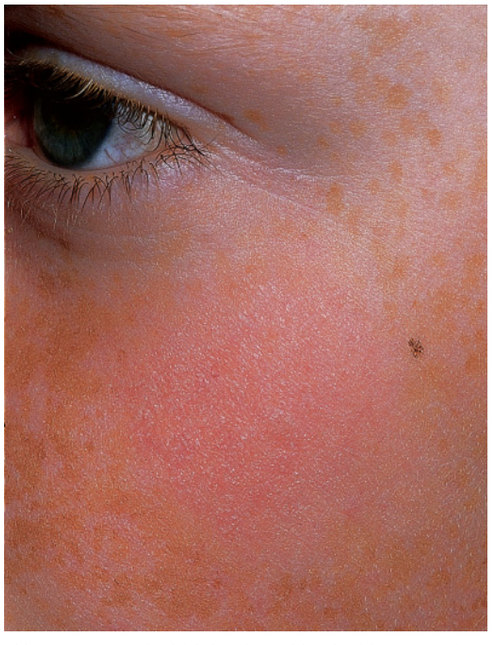


Fig. 58.8 Freckles, one area of which has been bleached by a superimposed patch of pityriasis alba.

light-exposed skin. They are most numerous on the face, upper back, and dorsal forearms and hands. They increase in number, size and depth of pigmentation during the summer months and are smaller, lighter and fewer in number in the winter. They may be cosmetically disfiguring or may enhance appearance, but are not otherwise of significance.

The incidence of melanocytic naevi is increased in freckled individuals.

Treatment. Freckles seldom require treatment and may sometimes be regarded as a desirable cutaneous feature. Application of 2–4% hydroquinone with a UVA-blocking sunscreen in the morning and retinoic acid in the evening produces significant lightening in most freckles. Alternatively, they are amenable to removal by laser [5,6]. Solar lentigines may be improved in appearance by topical treatment which includes retinoic acid [7].

Freckles in various syndromes. Freckles are a feature of a number of inherited and acquired disorders described in this chapter. These include xeroderma pigmentosum [8], neurofibromatosis, Moynahan's syndrome and progeria. The lesions in the various forms of lentiginosis (see below) must also be differentiated. Their distribution and the lack of relationship to light exposure should be noted.

References

1 Brues AM. Linkage of body build with sex, eye colour and freckling. *Am J Hum Genet* 1950; **2**: 215–39.
2 Valverde P, Healy E, Jackson I *et al*. Variants of the melanocyte-stimulating hormone-receptor gene are associated with red hair and fair skin in humans. *Nat Genet* 1995; **11**: 328–30.
3 Box NF, Wyeth JR, O'Gorman LE *et al*. Chacterization of melanocyte stimulating hormone receptor variant alleles in twins with red hair. *Hum Mol Genet* 1997; **6**: 1891–7.
4 Breathnach AS. Electron microscopy of melanocytes and melanosomes in freckled human epidermis. *J Invest Dermatol* 1964; **42**: 389–94.
5 Brazzini B, Hautmann G, Ghersitich I *et al*. Laser tissue interaction with epidermal pigmented lesions. *J Eur Acad Dermatol* 2001; **15**: 468–9.
6 Rosenbach A, Lee S-J. Treatment of medium-brown solar lentigines using an alexandrite laser designed for hair reduction. *Arch Dermatol* 2002; **138**: 547–8.
7 Fleisher AB, Schwartzel EH, Colby SI, Altman DJ. The combination of 2% 4-hydroxyanisole (Mequinol) and 0.01% tretinoin is effective in improving the appearance of solar lentigines and related hyperpigmented lesions in two double-blind multicenter clinical studies. *J Am Acad Dermatol* 2000; **42**: 459–67.
8 Ito M. Genetical studies on skin diseases: ephelides, dyschromatosis symmetrica hereditaria and xeroderma pigmentosum. *Tohoku J Exp Med* 1950; **3**: 69–72.

Lentiginosis

The histological and clinical features of lentigo, together with other lesions in which the number of melanocytes is increased, are fully described in Chapter 54. A lentigo is a benign, pigmented macule in which there is an increased number of melanocytes. The term 'lentiginosis' is applied either when lentigines are present in exceptionally large numbers, or when they occur in a distinctive distribution. The following clinical syndromes are recognized.

Generalized lentiginosis

Lentigines are commonly multiple but appear singly or in small crops at irregular intervals from infancy onwards. Their pathogenesis is unknown and in the great majority of cases no genetic factor is demonstrable.

Unilateral lentiginosis (zosteriform lentiginosis)

Lentigines may occur on one side of the body [1]. Cases have been reported with and without associated neurological abnormalities [2–4]. The lentigines can be zosteriform and occur in a dermatomal-like distribution [5–7]. These cases are usually without central nervous system abnormalities and are naevoid. Lentigines have also been reported within naevoid hypopigmentation [8]. A case of unilateral lentiginosis with contralateral naevus depigmentosus has been reported [9].

References

1 Davis DG, Shaw MW. An unusual human mosaic for skin pigmentation. *N Engl J Med* 1964; **270**: 1384–9.
2 Pickering JG. Partial unilateral lentiginosis with associated developmental abnormalities. *Guys Hosp Rep* 1973; **122**: 361–70.
3 Thompson GW, Diehl AK. Partial unilateral lentiginosis. *Arch Dermatol* 1980; **116**: 356.
4 Trattner H, Metzker A. Partial unilateral lentiginosis. *J Am Acad Dermatol* 1993; **29**: 693–5.
5 Matsudo H, Reed WB, Homme D *et al*. Zosterform lentiginous nevus. *Arch Dermatol* 1973; **107**: 902–5.
6 Port M, Courniotes J, Podwal M. Zosteriform lentiginous naevus with ipsilateral rigid left cavus foot. *Br J Dermatol* 1978; **98**: 693–8.
7 Schaffer JV, Lazova R, Bolognia JL. Partial unilateral lentiginosis with occular involvement. *J Am Acad Dermatol* 2001; **44**: 387–90.
8 Khumalo NP, Huson S, Burge S. Development of lentigines within naevoid hypopigmentation. *Br J Dermatol* 2001; **144**: 188–9.
9 Alkemade H, Juhlin L. Unilateral lentiginosis with nevus depigmentosus on the other side. *J Am Acad Dermatol* 2000; **43**: 361–3.

Inherited patterned lentiginosis in black people [1]

O'Neill reported generalized lentiginosis in 10 adult black patients, with onset in childhood; seven showed familial clustering, suggesting autosomal dominant inheritance [1]. Distribution of the lentigines included the face, lips, extremities, buttocks, palms and soles, but not mucosal surfaces.

Reference

1 O'Neill JF, James WD. Inherited patterned lentiginosis in blacks. *Arch Dermatol* 1989; **125**: 1231–5.

Eruptive lentiginosis [1,2]

Widespread occurrence of very large numbers of lentigines that develop rapidly over the course of a few months to years is typical of eruptive lentiginosis. The condition usually occurs in adolescents and young adults who show no evidence of systemic abnormalities. In 1956, Degos and Carteaud described telangiectatic papules that darkened and evolved into depressed, scaly lentigines [1]. In spite of the misleading title of their report, Eady *et al.* reported two patients in whom very large numbers of lentigines developed over 2 years; histology and electron microscopy confirmed the diagnosis of eruptive lentiginosis [2].

References

1 Degos R, Carteaud A. Lentiginose profuse kératosique. *Ann Dermatol Syphiligr* 1956; **83**: 125–9.
2 Eady RA, Gilkes JJ, Jones EW. Eruptive naevi: report of 2 cases, with enzyme histochemical, light and electron microscopical findings. *Br J Dermatol* 1977; **97**: 267–78.

Multiple lentigines syndrome (LEOPARD syndrome, MIM #151100) [1–4]

In 1969, Gorlin *et al*. postulated that multiple lentigines represented one aspect of a syndrome and proposed the acronym LEOPARD (Lentigines, Electrocardiographic abnormalities, Ocular hypertelorism, Pulmonary stenosis, Abnormalities of genitalia, Retardation of growth and Deafness of sensorineural type) [1]. It is determined by an autosomal dominant gene with high penetrance and variable expression [2]. Lentigines are present at birth or first appear early in life and increase in number until puberty. They are most numerous on the neck and upper trunk, but occur all over the body, including the scalp, genitalia, palms and soles. Cardiac abnormalities are frequent—sometimes pulmonary or subaortic stenosis but more commonly conduction defects [3]. Several patients with this syndrome have died at an early age from obstructive cardiomyopathy [4]. Growth tends to be retarded. Ocular hypertelorism and mild mandibular prognathism are the most usual of a variety of skeletal abnormalities. Inconstant features are deafness and genital abnormalities. The deafness, which may be profound, is of sensorineural type. The genital abnormalities include gonadal hypoplasia, hypospadias and delayed puberty.

References

1 Gorlin RJ, Anderson RC, Blaw M. Multiple lentigines syndrome. *Am J Dis Child* 1969; **117**: 652–62.
2 Gorlin RJ, Sedano H. Leopard syndrome. *Modern Med* 1969; **37**: 178.
3 Smith RF, Pulicicchio LV, Holmes AV. Generalized lentigo: electrocardiographic abnormalities, conduction disorders and arrhythmias in three cases. *Am J Cardiol* 1970; **25**: 501–6.
4 Polani PE, Moynahan EJ. Progressive cardiomyopathic lentiginosis. *QJM* 1972: **41**: 205–25.

Centrofacial lentiginosis (MIM 151000) [1]

This poorly defined syndrome remains an enigma more than 30 years after the last English language report of the disorder. It is characterized by a triad of clinical features: lentigines limited to the medial face, neuropsychiatric problems and dysraphic anomalies. It is apparently determined by an autosomal dominant gene. Small brown or black macules appear during the first year and increase in number up to the age of 8 or 10 years. Their distribution is restricted to a horizontal band across the centre of the face. The mucous membranes are not involved. Associated defects include coalescence of the eyebrows, a high-arched palate, absent upper median incisors, sacral hypertrichosis, spina bifida and scoliosis. Mental retardation is frequent and many affected individuals are epileptic.

Reference

1 Dociu I, Galactin-Nitelea O, Sirgitã N, Murgu V. Centrofacial lentiginosis. *Br J Dermatol* 1976; **94**: 39–43.

Peutz–Jeghers syndrome (MIM 175200)

Synonym
- Periorificial lentiginosis

Definition. Peutz–Jeghers syndrome is an autosomal dominant disorder with a high degree of penetrance. It is characterized by hamartomatous polyps in the gastrointestinal tract in association with mucocutaneous melanin pigmentation and an increased rate of soft tissue malignancy. All races are affected.

History. The first reported cases of what is now known as 'Peutz–Jeghers syndrome' were twin sisters reported by a British physician, Dr Connor, in 1895 [1]. Interestingly, one of the sisters died from intestinal obstruction at the age of 20, while the other died of breast cancer aged 59 years [2,3]. They were illustrated by the British surgeon Jonathan Hutchinson in 1896 [4]. The first description of intestinal polyposis in this condition was by the Dutch physician, Dr Johannes Peutz in 1921 [5]. In 1949, Jeghers confirmed the association of intestinal polyposis with hyperpigmentation of the skin and mucous membranes and described its familial characteristics [3]. It was the American, Dr A Bruwer, who was the first to coin the term 'Peutz–Jeghers syndrome' in the title of his paper on the disorder [6].

Genetics. Variable penetrance and clinical heterogeneity make it difficult to determine the exact frequency of Peutz–Jeghers syndrome. In about 40% of cases there is no family history and these represent new mutations. The disorder is due to inactivating germline mutations in the serine–threonine kinase gene *LKB1* (*STK11/LKB1* gene), mapping to 19q13.3 [7]. This gene is now the focus of additional research interest due to its central role as a signalling pathway for tumour suppression [8].

Clinical features. A recent review of Peutz–Jeghers syndrome confirmed the variability of the manifestations [9]. The syndrome is characterized by mucocutaneous pigmentation, multiple gastrointestinal hamartomatous polyps and by an increased risk of developing malignant tumours involving several different organs [9]. Both sexes and all races may be affected. The pigmented macules usually appear in infancy and early childhood, but may be present at birth or may develop later in life. The oral mucous membrane is consistently involved; round, oval or irregular patches of brown or almost black pigmentation 1–5 mm in diameter are irregularly distributed over the buccal mucosa, gums, hard palate and lips, especially the lower lip. The pigmented macules on the face are smaller, often under 1 mm, and darker, and are concentrated around the nose and mouth. Larger macules may be present on both aspects of the hands and feet and may be conspicuous on palms and soles. The oral pigmentation is usually permanent, but the macules on the lips and skin may become less prominent after puberty. Rarely, the nails may be pigmented, diffusely or in longitudinal bands. Mucosal and facial pigmentation without evidence of intestinal polyposis may be found in relatives. Indistinguishable pigmentary changes beginning in adult life also occur sporadically in individuals without intestinal involvement.

Symptoms attributable to the polyps usually occur between the ages of 10 and 30 years, but may occur in early childhood or be delayed until later adult life. The most common symptoms are repeated attacks of abdominal pain caused by intestinal obstruc-

tion. Rectal bleeding is common and haematemesis may occur with gastric or duodenal polyps. Many patients are anaemic.

Pathology. The pigmented macules show an increase in the amount of melanin in the basal layer of the epidermis. Polyps are found throughout the gastrointestinal tract. They are most numerous in the jejunum and ileum and less frequent in the colon, rectum, stomach and duodenum. In general, the polyps are benign hamartomas. The malignant potential of the polyps is not as great as in some other genetically determined syndromes with colonic polyps, but is not negligible. There is also increased incidence of malignancy in other organs, including the pancreas, breast, uterus and ovary.

Diagnosis. The mucosal pigmentation is the most constant feature of the syndrome. Freckling occurs in those of fair complexion, but the macules in freckling are light-influenced, are not focused on the skin around the nose and mouth and do not involve the mucous membranes. Examination of relatives may assist the diagnosis. At a stage when the polyps are already giving rise to symptoms they may not always be radiologically detectable.

Management. Cancer genetic counselling is now a key component to the successful management of patients with Peutz–Jeghers syndrome [10]. This also provides an opportunity for predictive testing of at-risk family members [10]. Age-related cancer risks for *STKL/LKB1* mutation carriers may be used to inform the cancer surveillance strategy [11]. Additionally, patients with mutations on exon 6 of *LKB1* appear to be at higher risk of developing cancer, which may justify a more vigilant protocol [11]. Guidelines for Peutz–Jeghers syndrome management recommend colonoscopic polypectomies every 1–3 years [12]. In many cases, it may be appropriate to undertake regular endoscopic examinations of the upper gastrointestinal tract and of the whole colon, together with barium follow-through studies of the small intestine every 2 years or so. In females, increased risk of breast cancer and gynaecological malignancy confirm that breast and pelvic examination should be included in the cancer surveillance programme [13]. In view of the generally benign nature of the polyps, routine radical surgery is not required. Individual polyps may require endoscopic or surgical removal. Prophylactic colectomy is recommended for cases with numerous colonic polyps, dysplastic polyps and uncontrolled bleeding [12]. Screening for at-risk individuals (first degree relatives of Peutz–Jeghers syndrome patients) should be annually from birth for history and physical examination for melanotic spots, precocious puberty and testicular tumours [9]. At-risk individuals who are asymptomatic and free from stigmata at age 8 years should be offered genetic testing for mutation analysis in the *STK11/LKB1* gene [14].

References

1 Connor JT. Aesculapian society of London. *Lancet* 1895; **2**: 1169.
2 Weber FP. Patches of deep pigmentation of oral mucus membranes not connected with Addison's disease. *QJM* 1949; **12**: 404–8.
3 Jeghers H, McKusick VA, Katz KH. Generalized intestinal polyposis and melanin spots of the oral mucosa, lips and digits. *N Engl J Med* 1949; **241**: 993–1005.
4 Hutchinson J. Pigmented spots on the lips in twin sisters. *Arch Surg* 1896; **7**: 290.
5 Peutz JLA. Very remarkable case of familial polyposis of mucous membrane of intestinal tract and nasopharynx accompanied by peculiar pigmentations of skin and mucous membrane. *Ned Maandschr Geneeskd* 1921; **10**: 134–6.
6 Bruwer A, Bargen JA, Kieland RR. Surface pigmentation and generalized intestinal polyposis (Puetz–Jeghers syndrome). *Proc Mayo Clin* 1954; **29**: 168–71.
7 Jenne DE, Reimann H, Nezu J *et al*. Peutz–Jeghers syndrome is caused by mutations in a novel serine threonine kinase. *Nat Genet* 1998; **18**: 38–43.
8 Alessi DR, Dario R, Sakamoto K, Bayascas JR. LKB1-dependent signaling pathways. *Ann Rev Biochem* 2006; **75**: 137–63.
9 Giardiello FM, Trimbath JD. Peutz–Jeghers syndrome and management recommendations. *Clin Gastroenterol Hepatol* 2006; **4**: 408–15.
10 Zbuk KM, Eng C. Hamartomatous polyposis syndromes. *Nat Clin Prac Gastroenterol Hepatol* 2007; **4**: 492–502.
11 Mehenni H, Resta N, Park JG *et al*. Cancer risks in LKB1 germline mutation carriers. *Gut* 2006; **55**: 984–90.
12 Bonner MP. Gastrointestinal polyposis syndromes. *Am J Med Genet* 2003; **122A**: 335–41.
13 Hearle N, Schumacher V, Menko FH *et al.* Frequency and spectrum of cancers in Peutz-Jeghers syndrome. *Clin Cancer Res* 2006; **12**: 3209–15.
14 McGrath DR, Spigelman AD. Preventative measures in Peutz-Jeghers syndrome. *Fam Cancer* 2001; **1**: 121–5.

Polyposis, skin pigmentation, alopecia, and fingernail changes (MIM: 175500)

Synonym
- Cronkhite–Canada syndrome

Definition. Cronkhite and Canada first described the syndrome that now bears their names in 1955 [1]. The syndrome is rare, non-inherited and is characterized by generalized gastrointestinal polyposis, cutaneous hyperpigmentation, hair loss and nail atrophy.

Aetiology. Nutritional, infectious and immunological associations have been considered, but the cause of Cronkhite–Canada syndrome remains elusive. All cases have been sporadic. The skin changes are assumed to be the result of malabsorption associated with the protein-losing enteropathy.

Clinical features. Sixty per cent of reported cases occur in men. It has a worldwide distribution, with mean age of symptom onset at 59 years (range 31–86 years). No familial cases have been reported. Hyperpigmentation is present in most patients [2–4]. It consists of light to dark brown, lentigo-like macules ranging in size up to 10 cm in diameter. These hyperpigmented macules are scattered but are most numerous on upper and lower extremities, and the face. The hands tend to show diffuse pigmentation of the palms and fingers, with macular pigmentation of the dorsae. The mucosal surfaces are usually spared, although the buccal mucosa is occasionally affected. In some patients hyperpigmentation is generalized.

Diarrhoea, abdominal pain and weight loss, beginning in adult life, are the presenting manifestations. Alopecia, patchy at first but becoming total, begins a few months later, and dystrophic changes in the nails develop at the same stage. The nail dystrophy is distinctive but not pathognomonic and could be explained by the formation of ventral nail in the absence of normal nail production by the matrix [5]. Exceptionally, the nail changes may precede gastrointestinal symptoms by months or years [6].

Management. Treatment of the malabsorption leads to reversal of hyperpigmentation in most cases. However, the overall prognosis is generally poor.

References

1 Cronkhite LW, Canada WJ. Generalized gastrointestinal polyposis. *N Engl J Med* 1955; **252**: 1011–5.
2 Daniel ES, Ludwig S, Lewin KJ. The Cronkhite–Canada syndrome. *Medicine (Baltimore)* 1982; **61**: 293–309.
3 Ortonne J-P, Bazex J, Berbis P. Les troubles pigmentaire de la maladie de Cronkhite–Canada. *Ann Dermatol Vénéréol* 1985; **112**: 951–8.
4 Nishiyama S, Mori S, Harada S. Gastrointestinale Polyposis mit universelle Alopecie, Onychodystrophie und Pigmentation der Haut. *Arch Klin Exp Dermatol* 1965; **221**: 144–61.
5 Cunliffe WJ, Anderson J. Case of Cronkhite–Canada syndrome with associated jejunal diverticulosis. *BMJ* 1967; **4**: 601–2.
6 Manousos O, Webster CV. Diffuse gastrointestinal polyposis with ectodermal changes. *Gut* 1966; **7**: 375–9.

Cutaneous lentiginosis with atrial myxomas (Type I: OMIM 160980; Type II: OMIM *160980) [1–4]

Synonyms
- Carney complex
- CNC
- Carney syndrome
- NAME syndrome
- LAMB syndrome

Definition. In 1986, Carney described the complex that is now associated with this name [1]. Carney syndrome is a complex with three associated features: (i) primary pigmented nodular adrenocortical disease, a pituitary-independent, primary adrenal form of Cushing's syndrome; (ii) lentigines and blue naevi of the skin and mucosae; and (iii) a variety of non-endocrine and endocrine tumours, including atrial myxomas.

Aetiology. This inherited disorder shows an autosomal dominant pattern of inheritance. In more than 50% of patients with Carney syndrome disease-associated mutations are present in the gene encoding the R1-α regulatory subunit of cyclic monophosphate-dependent protein kinase on chromosome 2p16 [2]. Cytogenetic studies of tumours from patients with Carney syndrome suggest that the responsible gene may not have a tumour suppression function [3].

Clinical features. NAME syndrome and LAMB syndrome are simply variations of Carney syndrome and are terms that could usefully be dropped. NAME syndrome comprises *n*aevi, *a*trial myxomas, *m*yxomas of the skin and *e*phelides [4]. LAMB syndrome comprises *l*entigines, *a*trial myxomas, *m*ucocutaneous myxomas and *b*lue naevi [5]. Cardiac myxomas are the most important internal myxomas, due to the causation of cardiac symptoms and potentially life-threatening effects [6]. Carney syndrome often affects the adrenal cortex, thyroid and pituitary glands and gonads [7]. Life-long echocardigraphic screening and surveillance in all family members of affected cases is important [8].

References

1 Carney JA, Hruska LS, Beauchamp GD, Gordon H. Dominant inheritance of the complex of myxomas, spotty pigmentation, and endocrine overactivity. *Mayo Clin Proc* 1986; **61**: 165–72.
2 Aspres N, Bleasel NR, Stapleton KM. Genetic testing of the family with a Carney-complex member leads to successful early removal of an asymptomatic atrial myxoma in the mother of the patient. *Australas J Dermatol* 2003; **44**: 121–2.
3 Chrousos GP, Stratakis CA. Carney complex and the familial lentiginosis syndromes: link to inherited neoplasias and developmental disorders, and genetic loci. *J Int Med* 1998; **243**: 573–9.
4 Atherton DJ, Pitcher DW, Wells RS, MacDonald DM. A syndrome of various cutaneous pigmented lesions, myxoid neurofibromata and atrial myxoma: the NAME syndrome. *Br J Dermatol* 1980; **103**: 421–9.
5 Rhodes AR, Silverman RA, Harrist TJ *et al*. Mucocutaneous lentigines, cardiomucocutaneous myxomas and multiple blue naevi: the LAMB syndrome. *J Am Acad Dermatol* 1984; **10**: 72–82.
6 Reed OM, Mellette JR, Fitzpatrick JE. Cutaneous lentiginosis with atrial myxomas. *J Am Acad Dermatol* 1986; **15**: 398–402.
7 Handley J, Carson D, Sloan J *et al*. Multiple lentigines, myxoid tumours and endocrine overactivity; four cases of Carney's complex. *Br J Dermatol* 1992; **126**: 367–71.
8 Zahedi RG, Wald DS, Ohri S. Carney complex. *Ann Thorac Surg* 2006; **82**: 320–2.

Arterial dissections and lentiginosis (MIM: 600459)

Arterial dissections and lentiginosis is a familial syndrome that was first described in 1995 in two sets of siblings from a series of 240 patients with arterial dissections seen at the Mayo Clinic (Rochester, MN, USA) [1]. Six additional sporadic cases were also reported.

Genetics. The gene for this disorder has yet to be identified. However, disease expression in offspring from a consanguineous marriage suggests that it is autosomal recessive.

Clinical features. The lentigines are located on the trunk and the extremities, particularly the lower legs. The arteries prone to dissection include the aorta, renal artery and extra-cranial internal carotid artery. These vessels are the same that are prone to dissection in Marfan syndrome and other connective tissue diseases.

Reference

1 Schievink WI, Michels VV, Mokri B *et al*. A familial syndrome of arterial dissections with lentiginosis. *New Eng J Med* 1995; **332**: 576–9.

Laugier–Hunziker syndrome [1–5]

This rare syndrome of unknown aetiology was first recognized and described by Laugier and Hunziker in 1970 [1]. It has no known genetic basis. It is characterized by macular pigmentation of the lips and buccal mucosa together with linear black streaks of the nails [2]. Onset is usually in adult life. There have been no systemic changes reported, and the condition is therefore regarded as having a benign prognosis. Histological examination of affected skin shows accumulation of melanin in the basal layer keratinocytes and an increased number of melanophages in the papillary dermis [3]. Ultrastructural examination revealed numerous mature melanosomes in the cytoplasm of basal layer keratinocytes and melanophages in the papillary dermis [3]. Conjunctival and genital hyperpigmentation have also been reported [4]. The differential diagnosis of striate melanonychia is considered in Chapter 65. The term 'essential mucocutaneous hyperpigmentation' has been proposed to replace the eponym for this condition [5].

References

1 Laugier P, Hunziker N. Pigmentation melaniques lenticulaire essentielle de la muquese jugale et des lèvres. *Arch Belge Derm Syph* 1970; **26**: 391–9.
2 Kemmett D, Ellis J, Spencer MJ, Hunter JA. The Laugier-Hunziker syndrome. A clinical review of six cases. *Clin Exp Dermatol* 1990; **15**: 111–4.
3 Veraldi S, Cavicchini S, Benelli C, Gasparini G. Laugier-Hunziker syndrome: a clinical, histopathologic and ultrastructural study of four cases and review of the literature. *J Am Acad Dermatol* 1991; **25**: 632–6.
4 Ayoub N, Barete S, Bouaziz JD *et al*. Additional conjunctival and penile pigmentation in Laugier-Hunziker syndrome: a report of two cases. *Int J Dermatol* 2004; **43**: 571–4.
5 Seoane Leston JM, Vazwqez Garcia J, Cazenave Jiminez AM *et al*. Laugier-Hunziker syndrome. A clinical and pathological study. Presentation of 13 cases. *Revue de Stomatologie et de Chirurgie Maxillo-Faciale* 1998; **99**: 44–8.

Penile melanosis/vulvovaginal melanosis [1–4]

Acquired, irregular, brownish or slaty-brown discoloration of the glans or shaft of the penis or of the vulva and vagina may give rise to fears of malignant potential. Histologically, there is only an increase of pigment without any increase or atypia of the melanocytes.

References

1 Barnhill RL, Albert LS, Sharma SK *et al*. Genital lentiginosis: a clinical and histopathologic study. *J Am Acad Dermatol* 1990; **22**: 453–60.
2 Revuz J, Clerici T. Penile melanosis. *J Am Acad Dermatol* 1989; **20**: 567–70.
3 Hwang L, Wilson H, Orengo I. Off-center fold: irregular, pigmented genital macules. *Arch Dermatol* 2000; **136**: 1559–64.
4 Rudolph RI. Vulvar melanosis. *J Am Acad Dermatol* 1990; **23**: 982–4.

Incontinentia pigmenti (MIM #308300)

Synonyms
- Bloch–Sulzberger syndrome
- Bloch–Siemens syndrome

Historical background. A number of cases of probable incontinentia pigmenti (IP) were presented in Europe in the early 20th century. However, it was Bloch who first used the term 'incontinentia pigmenti' for this condition [1], and Sulzberger who provided a more detailed account of Bloch's patient [2].

Definition. Incontinentia pigmenti is a rare and complex hereditary syndrome in which vesicular, verrucous and pigmented cutaneous lesions are associated with developmental defects of the eye, teeth and central nervous system [3,4].

Aetiology. Most pedigrees are small, but accumulated genetic data point to an X-linked dominant trait that is lethal for hemizygous affected males [5]. The IP gene has been mapped to Xq28 [6,7]. The 23-kb gene encodes nuclear factor B essential modulator (NEMO), and consists of 10 exons. More than 80% of cases of IP are caused by a deletion of exons 4–10 [8]. Mutations involving other alleles of the NEMO gene result in phenotypes different from IP, including anhidrotic ectodermal dysplasia with immunodeficiency [9,10].

Pathology. The bullae are situated beneath the horny layer or within a spongiotic epidermis. The dermis shows non-specific inflammatory changes with a cellular infiltrate, including numerous eosinophils. The infiltrate extends into the epidermis, and the contents of the bullae may consist predominantly of eosinophils [11] (Fig. 58.9). The lichenoid papules show hyperkeratosis, acanthosis and oedema of the basal layer, many cells of which are degenerate. Macrophages laden with melanin are present in the upper dermis. In the warty lesions, the hyperkeratosis is further increased, and within the irregularly acanthotic epidermis are hyaline bodies representing individual cell keratinization. The epidermal changes at this stage may suggest pseudoepitheliomatous hyperplasia. The pigmented patches show diminution or absence of pigment in the basal cells and large quantities of melanin in melanophages in the upper dermis. The epidermis may be normal or slightly acanthotic.

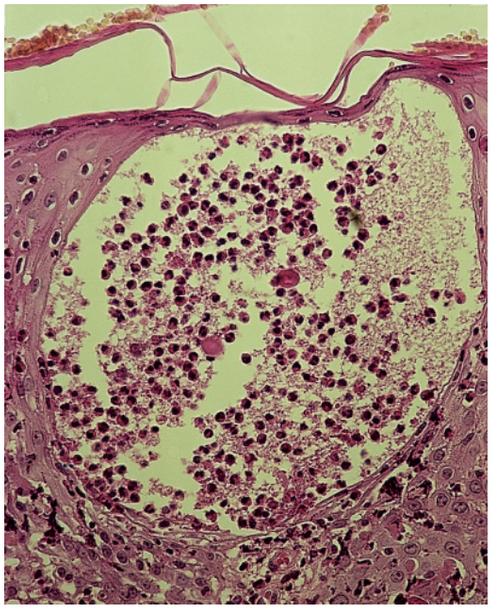
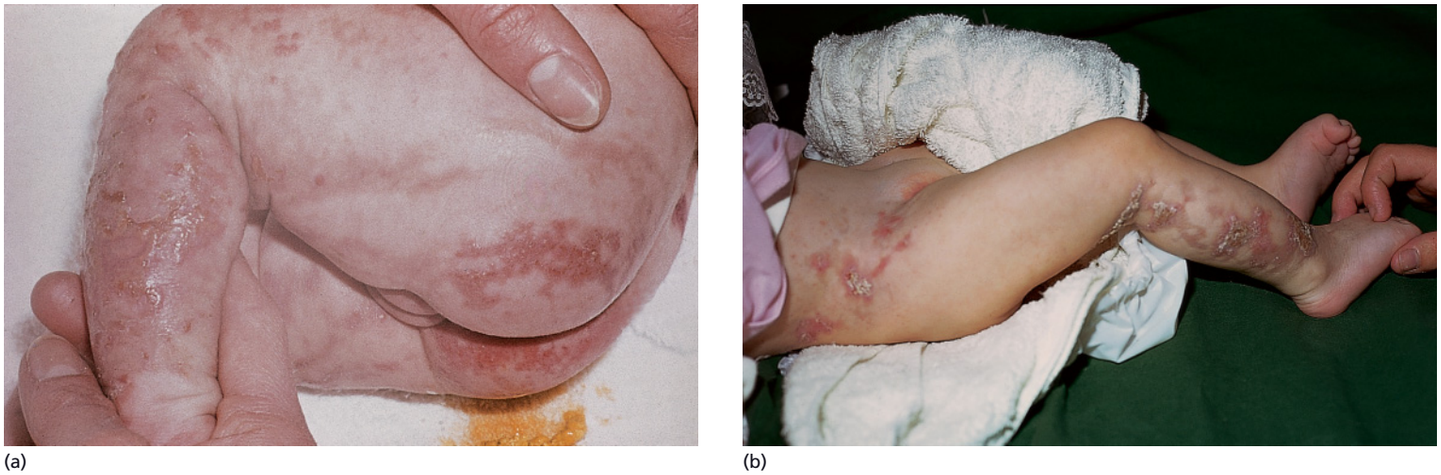


Fig. 58.9 Incontinentia pigmenti. Intraepidermal vesicle containing eosinophils. The spongiotic epidermis has been invaded by an inflammatory infiltrate that includes many eosinophils. Dyskeratotic cells are present.

Ultrastructural studies [12] show that, particularly in the early stages, there are many dyskeratotic cells in the epidermis. In addition to eosinophils, there are activated lymphocytes, basophils and mast cells, especially in the upper dermis. In all three stages, melanophages are present.

Clinical features. Two large studies have defined the clinical features of IP; Carney reviewed 653 cases from the world's literature [4], and more recently Landy and Donnai reported their experience of over 100 cases [5]. The skin changes are often present at birth, have usually developed before the end of the first week and rarely appear after the first 2 months. Four distinct clinical stages are recognized:

Stage 1: inflammatory macules, papules, vesicles and pustules
Stage 2: hyperkeratotic and verrucous lesions
Stage 3: grey-brown pigmentation
Stage 4: atrophic, hypopigmented and depigmented bands or streaks that are hairless and anhidrotic and fail to tan on sun exposure [13].



(a) (b)

Fig. 58.10 Incontinentia pigmenti: (a) linear groups of blisters in a child aged 3 weeks; (b) linear warty lesions on the lower leg of the same child aged 3 months.

The sequence of these stages is irregular, their duration variable and they may overlap. It is possible that the earlier inflammatory stages can occur *in utero* and do not progress after birth. The most striking feature of IP is the clear, tense bullae in linear array that tend to develop along lines of Blaschko on the trunk and limbs (Fig. 58.10). These lesions are usually in recurrent crops; less often they are generalized. The crops persist for a few days or for a month or two. They are accompanied or followed by smooth red nodules or plaques, often irregularly linear, on the limbs and trunk. The plaques may be extensive and may precede the bullae. They may be bluish-purple in colour and may ulcerate. Linear warty lesions may be present on the dorsa of hands and feet at birth, but more typically develop in early infancy, tending to wane by 6 months of age. The pigmentation, which may be the only abnormality, may be present from the outset or may appear as the inflammatory lesions are subsiding. Inflammatory lesions can develop in areas that are already pigmented. Activity may rarely persist into adult life [14]. The pigmentation, ranging in colour from blue-grey or slate to brown (Fig. 58.11), is characteristic of the syndrome, and the bizarre 'Chinese letter pattern' is diagnostic. The hair is usually normal, but in about 25% of cases patches of cicatricial alopecia, resembling pseudopelade, are present from birth or develop in infancy at or near the vertex. The nails are usually normal but may be small and dystrophic.

A number of extra-cutaneous features are also reported (Table 58.4).

Diagnosis. The combination of bullae with linear nodular or warty lesions in a female infant is pathognomonic. During a purely bullous phase the following differential diagnosis should be considered and excluded: infantile pemphigoid, herpes simplex infection, mastocytosis, Langerhans' cell histiocytosis, epidermolysis bullosa. Biopsy of the skin in the blistering phase is often of help in establishing the diagnosis (see Fig. 58.10) with the presence of many eosinophils in the epidermis and dermis.

Treatment. Usually no treatment is necessary other than the control of secondary infection. Systemic therapy with corticosteroids or sulfapyridine (sulphapyridine) is usually unsuccessful. Skilled dental supervision will minimize the cosmetic disability. As with other serious genetically determined disorders, family counselling should be offered. Ophthalmic examination in infancy is mandatory. Dental examination should also be carried out in the early infantile period after the age of one. If neurological features are present, the child should be seen by a neurologist.

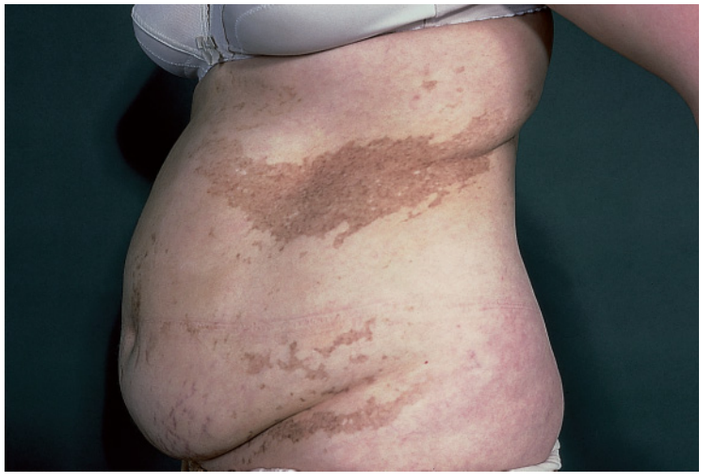


Fig. 58.11 Slate-grey pigmentation on the abdomen of a woman who had blistering lesions in childhood and who gave birth to a child with typical incontinentia pigmenti.

Prognosis. The prognosis is determined by the spectrum of clinical features [5]. Thus, those with neurological features tend to do less well than those with more minor manifestations of the syndrome. The pigmentary changes typically fade during childhood years.

References

1 Bloch B. Eigentumliche, bisher nicht beschriebene pigmentaffektion (incontinentia pigmenti). *Sch Med Wochenschr* 1926; **56**: 404–5.

Table 58.4 Extra-cutaneous features of incontinentia pigmenti.

Central nervous system	Microcephaly
	Hydrocephaly
	Mental retardation
	Motor delay
	Spastic paralysis
	Ataxia
	Seizures
Ocular [15]	Blindness
	Strabismus
	Microphthalmos
	Cataracts
	Retinal detachment
	Proliferative retinopathy
	Fibrovascular retinal membrane
	Optic atrophy
Dental	Delayed eruption of teeth
	Hypodontia
	Partial anodontia
	Cone- or peg-shaped teeth
	Absence of teeth in apparently unaffected first degree relatives
Haematological	Blood eosinophilia when acute inflammatory skin changes are present
	Neutrophil and lymphocyte dysfunction
Immunological	Altered immunological reactivity is observed in some patients [16]
Skeletal abnormalities	Skull defects
	Palatal defects

2 Sulzberger MB. Uber eine bisher nicht beschriebene congenitale pigmentanomalie (incontinentia pigmenti). *Arch Dermatol Syphilol* 1927; **154**: 19–32.
3 Berlin AL, Paller AS, Chan LS. Incontinentia pigmenti: a review and update on the molecular basis of pathophysiology. *J Am Acad Dermatol* 2002; **47**: 169–87.
4 Carney RG Jr. Incontinentia pigmenti: a world statistical analysis. *Arch Dermatol* 1976; **112**: 535–42.
5 Landy SJ, Donnai D. Incontinentia pigmenti (Bloch–Sulzberger syndrome). *J Med Genet* 1993; **30**: 53–9.
6 Hyden-Granskog C, Salonen R, Von Koskull H. Three Finnish incontinentia pigmenti (IP) families with recombinations with the IP loci at Xq28 and Xp11. *Hum Genet* 1993; **91**: 185–9.
7 Smahi A, Hyden-Granskog C, Peterlin B *et al*. The gene for the familial form of incontinentia pigmenti (IP2) maps to the distal part of Xq28. *Hum Mol Genet* 1994; **3**: 273–8.
8 Aradhya S, Woffendin H, Jakins T *et al*. A recurrent deletion in the ubiquitously expressed NEMO (IKK-gamma) gene accounts for the vast majority of incontinentia mutations. *Hum Mol Genet* 2001; **I**: 2171–9.
9 Berlin AL, Paller AS, Chan LS. Incontinentia pigmenti: a review and update on the molecular basis of pathphysiology. *J Am Acad Dermatol* 2002; **124**: 169–87.
10 Smahi A, Courtois G, Rabia SH *et al*. The NF-kappaß signaling pathway in human diseases: from incontinentia pigmenti to ectodermal dysplasias and immunodeficiency syndromes. *Hum Mol Genet* 2002; **11**: 2371–5.
11 Mihm MC Jr, Murphy GF, Kwan TH *et al*. Characterisation of the nature of the inflammatory cell infiltrate of the vesicular stage of incontinentia pigmenti. In: Fitzpatrick TB, ed. *Biology and Diseases of Dermal Pigmentation*. Tokyo: University of Tokyo Press, 1981: 163–74.
12 Schaumburg-Lever G, Lever WF. Electron microscopy of incontinentia pigmenti. *J Invest Dermatol* 1973; **61**: 151–8.
13 Moss C, Ince P. Anhidrotic and achromians lesions in incontinentia pigmenti. *Br J Dermatol* 1987; **116**: 839–49.
14 Barnes CM. Incontinentia pigmenti: a report of a case with persistent activity into adult life. *Cutis* 1978; **22**: 621–4.
15 Jain RB, Willetts GS. Fundus changes in incontinentia pigmenti (Bloch–Sulzberger syndrome): a case report. *Br J Ophthalmol* 1978; **62**: 622–6.
16 Menni S, Piccinno R, Biolchini A, Plebani A. Immunologic investigations in eight patients with incontinentia pigmenti. *Pediatr Dermatol* 1990; **7**: 275–7.

Fanconi's anaemia (OMIM 227650) [1–8]

Definition. Fanconi's syndrome is a rare, autosomal recessive condition characterized by widespread, mottled skin pigmentation, bone marrow failure and a tendency to develop malignancy. The syndrome was first described in three brothers with aplastic anaemia, skeletal malformations, genital hypoplasia, retarded growth and pigmented macules on the trunk [1]. The full syndrome occurs more frequently in boys than in girls.

Pathogenesis. Most of the Fanconi genes have been cloned yet the exact function of their gene products remains uncertain [2]. Possibilities include a role in DNA repair, cell cycle control, regulation of oxidative stress or even the maintenance of apoptosis and telomeres [3].

Clinical features. The age of onset is usually between 4 and 10 years, and either cutaneous or haematological abnormalities may be the presenting manifestation [4]. In most cases there is generalized, dusky or olive-brown pigmentation, often most intense on the lower trunk, flexures and neck. Typically, scattered over the dusky areas are depigmented macules of 'raindrop' type and macules of darker pigmentation. Rarely, only café-au-lait macules are present. The oral mucosa is not involved [5].

A constant feature is progressive hypoplastic anaemia with neutropenia and thrombocytopenia, usually presenting as an increased bleeding tendency. The haematological manifestations appear earlier in males. The pancytopenia usually causes death in 2–5 years. Treatment of anaemia with anabolic steroids improves survival. Haematological defects may also be present in otherwise normal siblings. There is an increased incidence of acute leukaemia and other neoplasms.

Diagnosis. The diagnosis of Fanconi's anaemia is usually suspected in a child with hypogonadism, pigmentary changes and aplastic anaemia. The association of pigmentation of very similar type with pancytopenia is seen only in dyskeratosis congenita. Prenatal diagnosis is now possible by demonstrating increased spontaneous and induced chromosomal breakage in cultured fetal amniocytes or chorionic villous cells [6]. Complementation groups can be determined using retroviruses expressing FANCA, FANCC or FANCG cDNA [3].

Prognosis. The prognosis is poor due to aplastic anaemia. Bone marrow or cord blood transplant can be curative [7]. Average life expectancy for Fanconi's anaemia is 20 years [8].

References

1 Fanconi G. Familiarere infantile perniziosaartage anaemie (pernizioeses Blutbild und Konstitution). *Jahrbuch Kinderheild* 1927; **117**: 257–80.
2 Strathdee CA, Gavish H, Shannon WR *et al*. Cloning of cDNAs for Fanconi's anaemia by functional complentation. *Nature* 1992; **356**: 763–7.
3 Tischkowtiz MD, Hodgson SV. Fanconi anaemia. *J Med Genet* 2003; **40**: 1–10.

4 Butturini A, Gale RP, Verlander PC *et al*. Hematologic abnormalities in Fanconi anemia: an international Fanconi Anemia Registry study. *Blood* 1994; **84**: 1650–5.
5 Auerbach AD. Fanconi anemia. *Dermatol Clin* 1995; **13**: 41–9.
6 Auerbach AD, Sagi M, Adler B. Fanconi anaemia: prenatal diagnosis in 30 fetuses at risk. *Pediatrics* 1985; **76**: 794–800.
7 Alter BP. Fanconi anaemia. Current concept. *Am J Pediatr Hematol Oncol* 1992; **14**: 170–6.
8 Joenje H, Patel KJ. The emerging genetic and molecular basis of Fanconi anaemia. *Nat Rev Genet* 2001; **2**: 446–59.

McCune–Albright syndrome (OMIM 174800, 139320) [1–8]

Albright *et al*. [1] described a syndrome, in 1937, characterized by polyostotic fibrous dysplasia, skin pigmentation and (in females) precocious puberty. In McCune–Albright syndrome, fibrous dysplasia of bone occurs in association with hyperpigmented skin lesions (café-au-lait macules), gonadotropin-independent sexual precocity, and/or endocrine and non-endocrine manifestations [2].

Aetiology. McCune–Albright syndrome results from somatic mutations during early development, resulting in a widespread mosaic of normal and mutant-bearing cells. Thus, the clinical presentation of each patient is determined by the extent and distribution of abnormal cells. These mutations encode constitutively active forms of G(s)α, the ubiquitously expressed G protein α-subunit that links hormone receptors to intracellular cAMP generation. These mutations result in the loss of amino acid residues required to deactivate the G protein, leading to prolonged activation of G(s)α and its downstream effectors. This explains why McCune–Albright syndrome patients suffer from the effects of excess stimulation of multiple peripheral endocrine glands, without having appropriately raised stimulatory hormones. The skin hyperpigmentation is one such example of this phenomenon; increase in skin pigmentation is mediated through G(s)α/cAMP. Parental origin of the mutated allele influences the clinical presentation, as G(s)α is imprinted and expressed only from the maternal allele in some tissues [3].

Simple monostotic and polyostotic fibrous dysplasia affects the sexes equally and is relatively common. Fibrous dysplasia with associated pigmentation is unusual and is more frequent in females than in males. The full McCune–Albright syndrome with precocious puberty is seen mainly in girls [2–4], although males may develop isolated testicular enlargement [5].

Pathology. In the majority of patients, the number of melanocytes is not increased either in the lesions or in normal skin, and in split-skin preparations the giant pigment granules characteristically seen in Malpighian cells and melanocytes in neurofibromatosis are rarely to be found [6].

Clinical features [7]. Cutaneous pigmentation usually develops between the ages of 4 months and 2 years, but may be present at birth. Extensive light-brown patches, often with an irregular or serrated margin, occur mainly on the trunk, buttocks and thighs, but may rarely involve the face and neck. They tend to be asymmetrical and to be most extensive on the side showing the most severe bone involvement (Fig. 58.12).



Fig. 58.12 Large pigmented macules in a child with Albright's syndrome. (Courtesy of Professor N.R. Rowell, Leeds General Infirmary, Leeds, UK.)

The bone lesions usually reveal themselves during the first decade by aching pain, pathological fractures and secondary deformities [3]. Bony overgrowth at the base of the skull may produce defective vision or proptosis. Serum calcium and phosphorus are normal but alkaline phosphatase may be elevated if the bone lesions are numerous. In females, precocious puberty, manifested by breast enlargement or by vaginal bleeding and growth of pubic hair, occurs below the age of 5 years in about 50% of cases and between 5 and 10 years in 30%. Growth in childhood is accelerated but the epiphyses unite prematurely. Other developmental abnormalities may be associated. The prognosis for life is good and the pathological fractures unite normally.

Diagnosis. There is no single clinical feature of the pigmented lesions that reliably differentiates McCune–Albright syndrome from neurofibromatosis, in which bone lesions and endocrine disturbances may also occur. The presence of many café-au-lait macules, freckles in the axillae and Lisch nodules on the iris are diagnostic for neurofibromatosis. Giant pigment granules may also rarely be found in McCune–Albright syndrome. Peptidic nucleic acid clamping is a rapid, reliable and economical method to diagnose McCune–Albright syndrome [8]. Negative results by peptidic nucleic acid clamping should be confirmed by nested polymerase chain reaction [8].

References

1 Albright F, Butler AM, Hampton AO *et al*. Syndrome characterized by osteitis fibrosa disseminata, area of pigmentation and endocrine dysfunction, with precocious puberty in females: report of five cases. *N Engl J Med* 1937; **21**: 727–46.

2 Feuillan P, Calis K, Hill S *et al*. Leterozole treatment of precocious puberty in girls with McCune-Albright syndrome: a pilot study. *J Clin Endocrinol Metabol* 2007; **92**: 2100–6.
3 Weinstein LS. G(s)alpha mutations in fibrous dysplasia and McCune-Albright syndrome. *J Bone Mineral Res* 2006; **21** (Suppl. 2): P120–4.
4 Sung SH, Yoon HD, Shon HS *et al*. A case of McCune-Albright syndrome with associated multiple endocrinopathies. *Korean J Internal Med* 2007; **22**: 45–50.
5 Rey RA, Venara M, Coutant R *et al*. Unexpected mosaicism of R201H-GNAS1 mutant-bearing cells in the testes underlie macro-orchidism without sexual precocity in McCune-Albright syndrome. *Hum Mol Genetics* 2006; **15**: 3538–43.
6 Benedict PH, Szabó G, Fitzpatrick TB, Sinesi SJ. Melanotic macules in Albright's syndrome and in neurofibromatosis. *JAMA* 1968; **205**: 618–26.
7 Gelfand IM, Eugster EA, DiMeglio LA. Presentation and clinical progression of pseudohypoparathyroidism with multi-hormone resistance and Albright hereditary osteodystrophy: a case series. *J Pediatrics* 2006; **149**: 877–80.
8 Kalfa N, Philibert P, Audran F *et al*. Searching for somatic mutations in McCune-Albright syndrome: a comparative study of the peptidic nucleic acid versus the nested PCR method based on 148 DNA samples. *Eur J Endocrinol* 2006; **155**: 839–43.

Other hereditary disorders with hypermelanosis

Increased pigmentation is an incidental or inconstant feature of many other genetically determined syndromes characterized predominantly by ectodermal dysplasia or diffuse connective-tissue defects. Such conditions are described in other chapters but are briefly mentioned below in differential diagnosis. There are also a number of unusual syndromes of which pigmentation is the most conspicuous or the only manifestation. The inter-relationships, classification and nomenclature of some of these syndromes, of which few examples have been reported, are not reliably established [1,2].

References

1 Fulk CS. Primary disorders of pigmentation. *J Am Acad Dermatol* 1984; **10**: 1–16.
2 Griffiths WAD. Reticulate pigmentary disorders: a review. *Clin Exp Dermatol* 1984; **9**: 439–50.

Familial progressive hyperpigmentation (MIM *145250) [1–4]

Familial progressive hyperpigmentation was first reported using this diagnostic term by Chernosky *et al*. in 1971 [1]. They described a black family with diffuse macular areas of hyperpigmentation that were present at birth and increased in size and number with age. Pigmented macules also involved mucosal surfaces. Four individuals in two generations were affected. More recent reports in both large and small kindreds suggest autosomal dominant inheritance [2–4]. The diagnosis is made on the basis of the extent and depth of the hyperpigmentation in the absence of an alternative explanation. Histological features include markedly increased amounts of melanin throughout the epidermis, with great density in the basal layer and no pigmentation in the dermis. There is no known effective treatment, but the prognosis is good with no adverse associations.

References

1 Chernosky ME, Anderson DE, Chang JP *et al*. Familial progressive hyperpigmentation. *Arch Dermatol* 1971; **103**: 581–91.
2 Debao L, Ting L. Familial progressive hyperpigmentation: a family study in China. *Br J Dermatol* 1991; **125**: 607.
3 Rebora A, Parodi A. Universal inherited melanodyschromatosis: a case of melanosis universalis hereditaria. *Arch Dermatol* 1989; **125**: 1442–3.
4 Betts CM, Bardazzi F, Fanti PA *et al*. Progressive hyperpigmentation: case report with a clinical, histological, and ultrastructural investigation. *Dermatology* 1994; **189**: 384–91.

Periorbital hyperpigmentation

Some darkening of the skin around the eyes is not uncommon. Familial periorbital hyperpigmentation is characterized by dark circular areas around the eyes. Peters [1] reported a kindred of 20 individuals in five generations and first speculated that this might be an autosomal dominant disorder. Additional large pedigrees have confirmed the heritable nature of this condition [2–4]. The sexes are equally affected. Increased pigmentation is first noted below the lower eyelids at the approach of puberty. There is wide variation in its ultimate extent and intensity, but it is seen more frequently in individuals with dark complexions [5]. There is no known treatment for this disorder.

References

1 Peters R. Auffallende dunkelfarbung der unteren lider als erbliche anomalie. *Zbl Prakt Augenheilk* 1918; **42**: 8–11.
2 Goodman RM, Belcher RW. Periorbital hyperpigmentation. *Arch Dermatol* 1969; **100**: 169–74.
3 Franceschetti A, Jadassohn W, Paillard R. Démonstration d'un syndrome de Sjögren associé a una hyperpigmentation familiale des paupières. *Dermatologica* 1953; **106**: 277.
4 Fulk CS. Primary disorders of hyperpigmentation. *J Am Acad Dermatol* 1984; **10**: 1–16.
5 Gellin GA. Dark circles around the eyes. *J Am Med Assoc* 1981; **245**: 1165.

Naegeli–Franceschetti–Jadassohn syndrome (MIM *161000) [1–11]

Synonym
- Naegeli's syndrome

This rare syndrome, inherited as an autosomal dominant condition, is known in one large Swiss family [3]. A very similar condition with associated onychodystrophy is described in an English family [4].

Reticulate pigmentation develops during the second or third year in a previously normal child. It may become very extensive and is not preceded by any inflammation. Often the neck and axillae are particularly affected. The fine network of hyperpigmentation differs from the irregular splashes and whirls seen in incontinentia pigmenti. Keratoderma of the palms and soles is usual. Hypohidrosis with intolerance to heat is common. The hair and nails are normal, except in the English family where the fingernails and toenails are of almond shape. The teeth may be normal or defective, with yellow discoloration of the enamel. Mental and physical development is normal. In addition to pigmentary incontinence, varying amounts of colloid–amyloid bodies have been found in the superficial dermis [5].

A number of cases have been described that show a combination of some of the features of Naegeli–Franceschetti–Jadassohn syndrome and of incontinentia pigmenti [6–8].

Reticulate hyperpigmentation may be associated with alopecia, nail changes and growth retardation [7] and there may be a history of blisters [9]. There may or may not be sweating defects [10].

Reticular pigmentation with milia has also been described as a variant of Naegeli–Franceschetti–Jadassohn syndrome [11].

References

1 Fulk CS. Primary disorders of pigmentation. *J Am Acad Dermatol* 1984; **10**: 1–16.
2 Griffiths WAD. Reticulate pigmentary disorders: a review. *Clin Exp Dermatol* 1984; **9**: 439–50.
3 Franceschetti A, Jadassohn W. A propos de l'incontinentia pigmenti: délineation de deux syndromes différents figurant sous le même terme. *Dermatologica* 1954; **108**: 1–28.
4 Sparrow GP, Samman PD, Wells RS. Hyperpigmentation and hypohidrosis (the Naegeli–Franceschetti–Jadassohn syndrome). *Clin Exp Dermatol* 1976; **1**: 127–40.
5 Frenk E, Mevorah B, Hohl D. The Nägeli–Franceschetti–Jadassohn syndrome: a hereditary ectodermal defect leading to colloid–amyloid formation in the dermis. *Dermatology* 1993; **187**: 169–73.
6 Curth HO, Warburton D. The genetics of incontinentia pigmenti. *Arch Dermatol* 1965; **92**: 229–35.
7 Jäckli W. Ein Fall von infantiler Poikilodermie combiniert mit Alopeci, Mikrodontie und frühzeitiger Cataracta complicata. *Monatsschr Kinderheilkd* 1939; **78**: 773–81.
8 Kitamura K, Hirako T. Uber zwei japanische Fälle einer eigenartigen retulären Pigmentierung. *Dermatologica* 1955; **110**: 97–107.
9 Greither A, Haensch R. Syndrome d'Albright et troubles associés. *Schweiz Med Wochenschr* 1970; **100**: 228–33.
10 Vilanova X, Aguade JP. Incontinentia pigmenti. Troubles sudoripares fonctionnels dysplasiques et pigmentaires chez les ascendants. *Ann Dermatol Syphiligr* 1959; **86**: 247–58.
11 Tzermias C, Zioga A, Hatzis I. Reticular pigmented genodermatosis with milia: a special form of Naegeli–Franceschetti–Jadassohn syndrome or a new entity? *Clin Exp Dermatol* 1995; **20**: 331–5.

Dermatopathia pigmentosa reticularis (OMIM *125595)

Definition. Dermatopathia pigmentosa reticularis was first described by Hauss and Oberste-Lehn in 1958 [1]. It is characterized by widespread reticulate pigmentation in combination with alopecia, nail changes, palmoplantar hyperkeratosis and loss of dermatoglyphics.

Aetiology. It is a rare form of autosomal dominant ectodermal dysplasia, closely related to Naegeli–Franceschetti–Jadassohn syndrome. Loss of protection against proapoptotic signals by a defect in the N-terminal part of keratin molecules may partly explain the unusual features of this syndrome.

Genetics. Both Naegeli–Franceschetti–Jadassohn syndrome and dermatopathia pigmentosa reticularis have been mapped to a common 6-cM interval on 17q11.2-q21 [2,3] which supports the idea that they are allelic disorders [4].

Clinical features. Onset is usually in early childhood or from birth. There is reticulate hyperpigmentation which is most prominent on the trunk. An isolated case from the Netherlands also presented ainhum-like constrictions of the digits [5].

References

1 Hauss H, Oberste-Lehn H. Dermatopathia pigmentosa reticularis. *Dermatol Wochenschr* 1958; **138**: 1337.
2 Whittock NV, Coleman CM, McLean WH *et al*. The gene for Naegeli-Franceschetti-Jadassohn syndrome maps to 17q21. *J Invest Dermatol* 2000; **115**: 694–8.
3 Sprecher E, Itin P, Whittock MW *et al*. Refined mapping of Naegeli-Franceschetti-Jadassohn syndrome to a 6 cM interval on chromosome 17q11.2-q21 and investigation of candidate genes. *J Invest Dermatol* 2002; **119**: 692–8.
4 Itin PH, Lautenschlager S. Genodermatoses with reticulate, patchy and mottled pigmentation of the neck—a clue to rare dermatological disorders. *Dermatology* 1998; **197**: 281–90.
5 Van Der Lugt L. Dermatopathia pigmentosa reticularis hyperkeratotica et mutilans. *Dermatologica* 1970; **140**: 294–302.

Mendes da Costa–van der Valk syndrome

Synonyms
- Dystrophia bullosa hereditaria
- Typus maculatus

Patients with this rare syndrome, determined by a sex-linked recessive gene, present at birth or in early infancy with universal alopecia associated with red-brown pigmentation on the face and extremities [1]. Affected individuals, all boys, develop non-traumatic intraepidermal bullae, irregularly scattered on trunk and limbs. Conspicuous, coarsely reticulate pigmentation develops on the face and limbs in association with macular atrophy. Some patients are physically and mentally retarded and life expectancy is short [1].

Reference

1 Hassing JH, Doeglas HMG. Dystrophia bullosa hereditaria, typus maculates (Mendes da Costa-van der Valk): a rare genodermatosis. *Br J Dermatol* 1980; **102**: 474–6.

Cantú's syndrome (MIM 114620)

This is an autosomal dominant disorder characterized by hyperkeratosis and hyperpigmentation [1]. Multiple small (1 mm diameter) macules develop on the face, forearms, hands and feet during childhood and adolescence. Some of these coalesce to produce larger lesions. The palms and soles show punctate hyperkeratoderma [1].

Reference

1 Cantú JM, Sánchez-Corona J, Fragoso R *et al*. A 'new' autosomal dominant genodermatosis characterized by hyperpigmented spots and palmoplantar hyperkeratosis. *Clin Genet* 1978; **14**: 165–8.

Dyskeratosis congenita (MIM #305000, 224230, 127550)

Synonym
- Zinsser–Engman–Cole syndrome

History. The first description of dyskeratosis congenita is credited to Zinsser [1]. The condition was further defined by Engman [2] and Cole [3].

Genetics and pathogenesis. Three different patterns of inheritance have been reported for dyskeratosis congenita: X-linked recessive (MIM 305000), autosomal recessive (MIM 224230) and autosomal dominant (MIM 127550). Of these, the X-linked recessive variant is the commonest, the autosomal dominant variant

the mildest with the best prognosis [4]. The gene for the X-linked variant, *DKC1,* was mapped to Xq28 [5,6] and then identified by Heiss *et al.* in 1998 [7]. The protein encoded by this gene, dyskerin, has been shown to be associated with human telomerase RNA [8]. This in turn led to the identification of *TERC,* which codes for telomerase component 3, as a candidate gene for autosomal dominant dyskeratosis congenita. Subsequent gene studies confirmed the presence of short telomeres and mutations in *TERC* in autosomal dominant dyskeratosis congenita [9,10].

Clinical features. Dyskeratosis congenita is a progressive, degenerative disorder characterized by reticulate hyperpigmentation with poikiloderma of the neck, chest and thighs. Cutaneous and mucosal changes occur in childhood, followed in the second and third decade by marrow failure and malignancy. Other features include nail dystrophy and leukoplakia of the oral, ocular and anal mucous membranes [11–13].

Management. Leukoplakia should be closely monitored for early signs of malignant transformation. Oral retinoids may help to cause regression of skin or mucous membrane dysplasia. Marrow aplasia requires treatment from a haematologist. About half of patients with dyskeratosis congenita die from bone marrow failure.

References

1 Zinsser F. Atrophia cutis reticularis cum pigmentatione, dystrophia et leukoplakia oris. *Ikonogr Dermatol* 1910; **5**: 219–23.
2 Engman FM. A unique case of reticular pigmentation of the skin with atrophy. *Arch Dermatol* 1926; **13**: 685–7.
3 Cole HN, Rauschkolb JE, Toomey J. Dyskeratosis congenita with pigmentation, dystrophia unguis, and leukokeratosis oris. *Arch Dermatol* 1929; **21**: 71–95.
4 Drachtman RA, Alter BP. Dyskeratosis congenita. *Dermatol Clin* 1995; **13**: 33–9.
5 Connor JM, Gathere D, Gray FC *et al*. Assignment of the gene for dyskeratosis congenita to Xq28. *Hum Genet* 1986; **72**: 348–51.
6 Arngrimsson R, Dokal I, Luzzatto L *et al*. Dyskeratosis congenita: three additional families show linkage to a locus in Xq28. *J Med Genet* 1993; **30**: 618–9.
7 Heiss NS, Knight SW, Vulliamy TJ *et al*. X-linked dyskeratosis is caused by mutations in a highly conserved gene with putative nucleolar functions. *Natr Genet* 1998; **19**: 32–8.
8 Mitchell JR, Wood E, Collins K. A telomerase component is defective in the human disease dyskeratosis congenita. *Nature* 1999; **402**: 551–5.
9 Vulliamy TJ, Knight SW, Mason PJ *et al*. Very short telomeres in the peripheral blood of patients with X-linked and autosomal recessive dyskeratosis congenita. *Blood Cells Mol Dis* 2001; **27**: 353–7.
10 Vuliamy TJ, Marrone A, Goldman F *et al*. The RNA component of telomerase is mutated in autosomal dominant dyskeratosis congenita. *Nature* 2001; **413**: 432–5.
11 Connor JM, Teague RH. Dyskeratosis congenita. Report of a large kindred. *Br J Dermatol* 1981; **105**: 321–5.
12 Davidson HR, Connor JM. Dyskeratosis congenita. *J Med Genet* 1988; **25**: 843–6.
13 Limmer RL, Zurowski SM, Swinfard RW. Abnormal nails in a patient with severe anaemia. Dyskeratosis congenita. *Arch Dermatol* 1997; **133**: 97–8.

Becker's syndrome [1–4]

This is different from Becker's naevus. Becker reported three sisters in 1939 with discrete or confluent brown macules on the neck and forearms, present from early infancy [1]. There was no atrophy or telangiectasia. In another case, somewhat similar mottled pigmentation of neck and elbows appeared at the age of 10 years [2].

Two other syndromes defy classification: diffuse pigmentation of the trunk and neck, beginning in the first year, with later development of small white macules in the pigmented areas [3]; and diffuse pigmentation with conspicuous macular depigmentation on the trunk, associated with macular and reticulate pigmentation of the neck [4].

References

1 Becker SW, Reuter MJ. A familial pigmentary anomaly. *Arch Dermatol Syphilol* 1939; **40**: 987–98.
2 Wodniansky P. Zur kemtris poikilodermatischer und poikilodermie: ahnlicher Pigmentverschebungen. *Z Haut-U Geschl Krankh* 1962; **32**: 33–44.
3 Pegum JS. Diffuse pigmentation in brothers. *Proc R Soc Med* 1955; **48**: 179–80.
4 Jost K. Hereditäre connatale, Pigmentanomalie. *Hautarzt* 1955; **6**: 458–60.

Acromelanosis [1–21]

Diffuse hyperpigmentation of the dorsal aspects of fingers and toes is not uncommon in individuals of dark complexion [1]. It has been reported in individuals of mixed race, white-skinned, black-skinned and oriental people. There may be more than one genotype. The pigmentation begins in infancy or childhood and increases in depth and extent [2,3]. There may be increased pigmentation in the flexures of the finger joints and in the larger joint flexures. A single case report of acromelanosis with hyperpigmentation of genital mucosa in a baby girl has been reported from Spain [4]. The condition must be differentiated from hyperpigmentation induced by repeated trauma. The term 'acromelanosis' has also been used to describe acquired hyperpigmentation of the hands or feet as a manifestation of a drug reaction [5].

Reticulate acropigmentation [6–21]

Reticulate acropigmentation generally has an autosomal dominant pattern of inheritance. Two main variants have been reported: reticulate acropigmentation of Kitamura and reticulate hyperpigmentation of Dohi.

Reticulate acropigmentation of Kitamura

Reticulate acropigmentation of Kitamura is characterized by a network of freckle-like areas of pigmentation which develop on the dorsa of the hands in the first two decades [6–9]. The reticulate pigmentation may subsequently involve most parts of the body (Fig. 58.13). Palmar pits and breakages of epidermal ridge pattern are found. Several individual cases and families have been reported with features of both Kitamura's disease and reticulate pigmented anomaly of the flexures (Dowling–Degos disease) [10–12]. Histologically, the pigment macules show epidermal atrophy and an increased number of melanocytes. It is unclear if bony abnormalities reported in a Saudi female with Kitamura's syndrome were coincidental or linked [13]. Differing patterns of inheritance suggest that this is not always an autosomal dominant disorder [14].

*Symmetrical dyschromatosis of the extremities (MIM *127400)* [15–21]

Synonyms

- Dyschromatosis symmetrica hereditaria
- Reticulate acropigmentation of Dohi



Fig. 58.13 Reticulate acropigmentation of Kitamura. (Courtesy of Dr W.A.D. Griffiths, St John's Institute of Dermatology, London, UK.)

Symmetrical dyschromatosis of the extremities is an autosomal dominant disorder caused by mutations in the double-stranded RNA-specific adenosine deaminase gene (*ADAR1* or *DSRAD*) [15,16]. The syndrome has been reported from Japan, where it is not uncommon, and also in European [17], Afro-Caribbean and Indian patients [18]. During infancy or early childhood, mottled pigmentation with areas of depigmentation develop on the dorsa of the hands and feet and sometimes on the arms and legs [19]. The face is spared, apart from a few scattered, small, discrete, pigmented macules. A single case of neurofibromatosis occurring in association with reticulate acropigmentation of Dohi has been reported from Singapore [20]. A comprehensive review of the literature on acropigmentation of Dohi that included cases reported in Japanese, identified 185 cases worldwide [21].

References

1 Weidman AI. Acropigmentation (acromelanosis). *Cutis* 1969; **5**: 1119–20.
2 Furuya T, Mishima Y. Progressive pigmentary disorder in Japanese child. *Arch Dermatol* 1962; **86**: 412–8.
3 Gonzalez JR, Botet MV. Acromelanosis. *J Am Acad Dermatol* 1980; **2**: 128–31.
4 Sopena Barona J, Gamo Villegas R, Guerra Tapia A, Iglesias Diez L. Acromelanosis. *Anales de Pediatria* 2003; **58**: 277–80.
5 Kanwar AJ, Jaswal R, Thami GP, Bedi GK. Acquired acromelanosis due to phenytoin. *Dermatology* 1997; **194**: 373–4.
6 Kitamura K, Akamatsu S, Hirokawa K. Eine besondere form der akropigmentation: Acropigmentatio reticularis. *Hautarzt* 1953; **4**: 152–6.
7 Kitamura K. Acropigmentatio reticularis, eine Allgemein in der Welt vorkommende Krankheit. *Hautarzt* 1976; **27**: 352–4.
8 Griffiths WAD. Reticulate acropigmentation of Kitamura. *Br J Dermatol* 1976; **95**: 437–43.
9 Woodley DT, Caro I, Wheeler CE. Reticulate acropigmentation of Kitamura. *Arch Dermatol* 1979; **115**: 760–1.
10 Crovato F, Rebora A. Reticulate pigmentary anomaly of the flexures associating reticulate acropigmentation: one single entity. *J Am Acad Dermatol* 1986; **14**: 359–61.
11 Berth-Jones J, Graham-Brown RA. A family with Dowling Degos disease showing features of Kitamura's reticulate acropigmentation. *Br J Dermatol* 1989; **120**: 463–6.
12 Cox NH, Long E. Dowling–Degos disease and Kitamura's reticulate acropigmentation: support for the concept of a single disease. *Br J Dermatol* 1991; **125**: 169–71.
13 el-Hoshy K, Hashimoto K. Bony anomalies in a patient with reticulate acropigmentation of Kitamura. *J Dermatol* 1996; **23**: 713–5.
14 Singal A, Bhattacharya SN, Baruah MC *et al*. Is the hereditary of reticulate acropigmentation of Kitamura always autosomal dominant? *J Dermatol* 1998; **25**: 57–9.
15 Liu Q, Liu W, Jiang L *et al*. Novel mutations of the RNA-specific adenosine deaminase gene (DSRAD) in Chinese families with dyschromatosis symmetrica hereditaria. *J Invest Dermatol* 2004; **122**: 896–9.
16 Suzuki N, Suzuki T, Inagaki K *et al*. Mutation analysis of the ADAR1 gene in dyschromatosis symmetrica hereditaria and genetic differentiation from both dyschromatosis universalis hereditaria and acropigmentation reticularis. *J Invest Dermatol* 2005; **124**: 1186–92.
17 Danese P, Zanca A, Bertazzoni MG. Familial reticulate acropigmentation of Dohi. *J Am Acad Dermatol* 1997; **37**: 884–6.
18 Ostlere LS, Ratnavel RC, Lawlor F *et al*. Reticulate acropigmentation of Dohi. *Clin Exp Dermatol* 1995; **20**: 477–9.
19 Sugai T, Saito T, Hamata T. Symmetric acroleukopathy in mother and daughter. *Arch Dermatol* 1965; **92**: 172–3.
20 Tan HH, Tay YK. Neurofibromatosis and reticulate acropigmentation of Dohi: a case report. *Pediatric Dermatology* 1997; **14**: 296–8.
21 Oyama M, Shimizu H, Ohata Y *et al*. Dyschromatosis symmetrica hereditaria (reticulate acropigmentation of Dohi): report of a Japanese family with the condition and a literature review of 185 cases. *Br J Dermatol* 1999; **140**: 491–6.

Universal acquired melanosis [1–2]

Pigmentation is usually present from early infancy but it may be progressive. It is often diffuse and generalized but may later become rather mottled.

References

1 Maldonado-Ruiz R, Tamayo L, Fernandez-Diez J. Universal acquired melanosis. *Arch Dermatol* 1978; **114**: 775–8.
2 Betts CM, Bardazzi F, Fanti PA *et al*. Progressive hyperpigmentation: case report with a clinical, histological and ultrastructural investigation. *Dermatology* 1994; **189**: 384–91.

Reticulate pigmented anomaly of the flexures (OMIM 179850) [1]

Synonym
- Dowling–Degos disease

Reticulate pigmentation of the flexures arises during childhood. The characteristic histological finding is filiform downgrowths in the epidermis with hyperpigmentation of the deepest areas [1–3].

References

1 Wilson Jones E, Grice K. Reticulate pigmented anomaly of the flexures. Dowling-Degos disease, a new genodermatosis. *Arch Dermatol* 1978; **114**: 1150–7.
2 Rebora A, Crovato F. The clinical spectrum of Dowling-Degos disease. *Br J Dermatol* 1984; **110**: 627–30.
3 Crovato F, Rebora A. Reticulate pigmented anomaly of the flexures associating reticulate acropigmentation: one single entity. *J Am Acad Dermatol* 1986; **14**: 359–61.

Zosteriform reticulate hyperpigmentation [1–3]

The description of this disorder is encapsulated by its name. There may be an associated change in the texture of the skin within the lesions. This condition arises in children. All four cases reported from Japan showed eosinophilia [1,2].

References
1 Iijima S, Naito Y, Naito S, Uyeno K. Reticulate hyperpigmentation distributed in a zosteriform fashion: a new clinical type of hyperpigmentation. *Br J Dermatol* 1987; **117**: 503–10.
2 Iijima S, Naito Y, Naito S, Uyeno K. Reticulate hyperpigmentation distributed in a zosteriform fashion: a new clinical type of hyperpigmentation. *Br J Dermatol* 1989; **121**: 280.
3 Rower JM, Carr RD, Lowney ED. Progressive cribriform and zosteriform hyperpigmentation. *Arch Dermatol* 1978; **114**: 98–9.

Human chimera with pigment anomalies

True human chimeras, formed from more than one zygote, with pigment anomalies are described [1].

Reference
1 Findlay GH, Moores PP. Pigment anomalies of the skin in the human chimaera. *Br J Dermatol* 1980; **103**: 489–98.

Schimke immuno-osseous dysplasia (OMIM #242900) [1]

Schimke immuno-osseous dysplasia is a rare autosomal recessive spondyloepiphyseal dysplasia characterized by short stature, unusual facies, hyperpigmented macules, proteinuria with progressive renal failure, lymphopenia with recurrent infections and cerebral ischaemia. There is no effective treatment for patients suffering from this syndrome other than supportive measures.

Reference
1 Boerkoel CF, O'Neill S, Andre JL *et al*. Manifestations and treatment of Schimke immuno-osseous dysplasia: 14 new cases and a review of the literature. *Eur J Pediatr* 2000; **159**: 1–7.

Neurofibromatosis (OMIM *162200) (see Chapter 15)

Café-au-lait marks are present in 90% of patients with neurofibromatosis, particularly in those with NF-1, and may appear early. They are round or oval patches of light-brown pigmentation. They are also found in 10% of normal subjects. The presence of one or two is not diagnostic in the absence of other signs of the disease but if six or more are present, with a diameter of 5 mm or more, the probability of neurofibromatosis is high.

Extensive melanotic macules can also occur and resemble those seen in Albright's syndrome; however, these tend to be confined to a particular site and are on either side of the midline. Axillary freckling is common in neurofibromatosis and is an aid to the diagnosis. Lisch nodules and iris hamartomas are present in most patients over the age of 6 years (Fig. 58.14). Giant pigment granules (macromelanosomes) are found in the café-au-lait macules (Fig. 58.15).

NF-1 accounts for 85% of all neurofibromatosis. The NF-1 gene has been identified on the proximal long arm of chromosome 17 [1,2]. It is inherited as an autosomal dominant trait with variable penetrance and expression, and a spontaneous mutation rate of around 50%. NF-2 has the same mode of inheritance, high spontaneous mutation rate, high penetrance and variable expression as NF-1. The NF-2 gene is located near the centre of the long arm of chromosome 22 [3].

References
1 Barker D, Wright T, Neuyen K *et al*. Gene for von Recklinghausen neurofibromatosis in the pericentromeric region of chromosome 17. *Science* 1987; **236**: 1100–2.

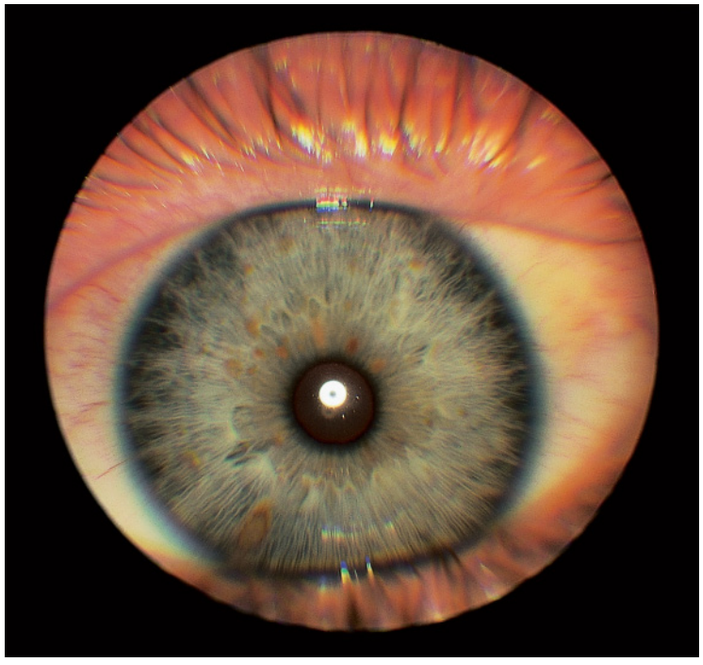


Fig. 58.14 Lisch nodules in the iris.

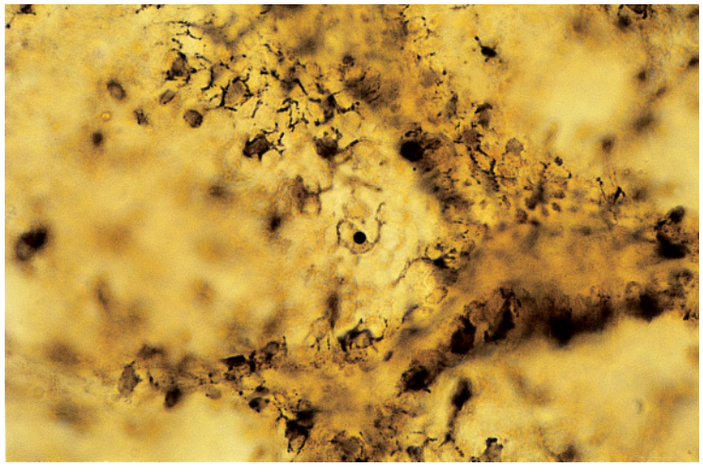


Fig. 58.15 Giant pigment granules in epidermal melanocyte in neurofibromatosis.

2 Seizinger BR, Rouleau GA, Ozelius LJ *et al*. Genetic linkage of von Recklinghausen neurofibromatosis to the nerve growth factor receptor gene. *Cell* 1987; **49**: 589–94.
3 Werteleck W, Rouleau GA, Superneau DW *et al*. Neurofibromatosis 2: clinical and DNA linkage studies of a large kindred. *N Engl J Med* 1988; **319**: 278–83.

Werner's syndrome (MIM #277700) [1–5]

Werner's syndrome is a rare, autosomal recessive disorder characterized by primary growth retardation, premature ageing, an increased prevalence of malignancy, high levels of atherosclerosis and type 2 diabetes [1]. Localized or diffuse hyperpigmentation is commonly seen [2]. Less commonly, depigmented spots with greying of the hair are present [2–3]. Most cases are caused by mutations in the gene encoding the RecQ helicase WRN [4].

Marked genomic instability explains the increased cancer risk in Werner's syndrome [5].

References

1 Davis T, Wyllie FS, Rokicki MJ *et al*. The role of cellular senescence in Werner syndrome: toward therapeutic intervention in human premature aging. *Ann N Y Acad Sci* 2007; **1100**: 455–69.
2 Hatamochi A. Dermatological features and collagen metabolism in Werner syndrome. *Gann Monogr Cancer Res* 2001; **49**: 51–9.
3 Nakayama T, Ochiai T, Takahashi Y *et al*. A novel mutation in a patient with Werner's syndrome. *Gerontology* 2002; **48**: 215–9.
4 Ramirez CL, Cadinanos J, Varela I *et al*. Human progeroid syndromes, aging and cancer: new genetic and epigenetic insights into old questions. *Cell Mol Life Sci* 2007; **64**: 155–70.
5 Crabbe L, Jauch A, Naeger CM *et al*. Telomere dysfunction as a cause of genetic instability in Werner syndrome. *Proc Natl Acad Sci USA* 2007; **104**: 2205–10.

Gaucher's disease and Niemann–Pick disease

(see Chapter 59)

Pigmentation of two types occurs in adults with Gaucher's disease: brown patches of chloasma type on the face, neck and hands; and symmetrical pigmentation of the lower legs with a sharp lower margin and an irregular upper margin. There may also be a brown, wedge-shaped thickening of the bulbar conjunctiva.

In the acute infantile form of Gaucher's disease, the skin is not pigmented, but in Niemann–Pick disease there is diffuse brown pigmentation, most marked on the face.

Xeroderma pigmentosum (see Chapter 15) [1]

Freckle-like pigmentation of the face and other exposed skin begins in infancy or early childhood. The light- or dark-brown macules are associated with telangiectases, small white atrophic spots and later with keratoses and tumours. The freckled sun-exposed skin with associated severe photosensitivity in a young child is a striking clinical phenotype not easily overlooked.

Reference

1 Kraemer KH, Lee MM, Scotto J. Xeroderma pigmentosum: cutaneous, ocular, and neurologic abnormalities in 830 published cases. *Arch Dermatol* 1987; **123**: 241–50.

Hypermelanosis in endocrine disorders

Some of the mechanisms by which endocrine glands influence melanogenesis are discussed on pp. 58.5–58.7. Here are considered clinical syndromes showing endocrine-induced pigmentary changes (see also Chapter 62).

Addison's disease [1–4]

Increased pigmentation is such a well-known feature of Addison's disease that its absence may significantly delay diagnosis and endanger life [1,2]. When present, the hyperpigmentation of Addison's disease is typically diffuse, and is most intense on areas exposed to light [3]. It is also accentuated in the flexures, at sites of pressure and friction, and in the creases of palms and soles [3]. Normally pigmented areas, such as the nipples and genital skin, darken. Pigmentation of the buccal mucous membrane is often present, and the conjunctival and vaginal mucous membranes may also be involved [3]. However, less distinctive patterns of pigmentation are not exceptional, and in any unexplained cases of hypermelanosis adrenal function should be carefully evaluated. Similarly, patients without hyperpigmentation, but with other features suggesting Addison's disease should have adrenal function assessed. Vitiligo-like lesions may also occur in Addison's disease [3].

The hypermelanosis is the result of increased secretion of melanotrophic hormones by the pituitary. Affected patients have elevated plasma levels of β-MSH-like immunoreactivity [4]. Absence of hypermelanosis in Addison's disease was explained in a single case by a high degree of melanosome degradation in secondary lysosomes [1].

References

1 Kendereski A, Mici D, Sumarac M *et al*. White Addison's disease: what is the possible cause? *J Endocrinolog Invest* 1999; **22**: 395–400.
2 Runcie CJ, Semple CG, Slater SD. Addison's disease without pigmentation. *Scott Med J* 1986; **31**: 111–2.
3 Dunlop D. Eighty-six cases of Addison's disease. *BMJ* 1963; **ii**: 887–91.
4 Deutsch S, Mescon H. Melanin pigmentation and its endocrine control. *N Engl J Med* 1957; **257**: 222–6, 268–72.

Acromegaly

Pigmentation of Addisonian pattern is present in some cases of acromegaly, and may be a striking feature.

Cushing's syndrome [1–4]

Pigmentation of Addisonian pattern has been noted in about 10% of reported patients with Cushing's syndrome. It is an indication of secretion of ACTH and β-MSH by the pituitary and suggests the presence of a pituitary tumour. After adrenalectomy, progressive hypermelanosis develops in a proportion of patients, about 10%, in spite of adequate hormone replacement therapy. Only in half of these patients is the sella turcica enlarged [1,2]. These patients with Nelson's syndrome [3] show marked hypermelanosis, with the mucous membranes also being involved (see Fig. 58.6). The hair is often darker and there are sometimes multiple lentigines and longitudinal pigmented bands in the nails. High levels of both β-MSH and ACTH are found in the plasma, with degree of clinical hyperpigmentation correlating well with the quantity of β-MSH in the plasma [4].

References

1 McKenzie AD, McIntosh HW. Hyperpigmentation and pituitary tumor as sequelae of the surgical treatment of Cushing's syndrome. *Am J Surg* 1965; **110**: 135–41.
2 Sawin CT, Abe K, Orth DN. Hyperpigmentation due solely to increased plasma β-melanotropin. *Arch Intern Med* 1970; **125**: 708–10.
3 Nelson DH, Meakin JW, Thorn GW. ACTH-producing pituitary tumors following adrenalectomy for Cushing's syndrome. *Ann Intern Med* 1960; **52**: 560–9.
4 Abe K, Nicholson WE, Liddle GW *et al*. Normal and abnormal regulation of β-MSH in man. *J Clin Invest* 1969; **48**: 1580–5.

Hyperthyroidism

Pigmentation occurs in about 10% of patients with primary thyrotoxicosis [1]. It is usually diffuse and is broadly of Addisonian pattern, although involvement of the mucous membranes is uncommon and pigmentation of nipples and genital skin is less striking. The eyelids are occasionally conspicuously pigmented (Jellinek's sign). Some patients show chloasmal rather than diffuse

pigmentation. The incidence of vitiligo is increased. Diffuse pigmentation was present at birth in the infant of a thyrotoxic mother [2].

References
1 Readett MD. Constitutional eczema and thyroid disease. *Br J Dermatol* 1964; **76**: 126–39.
2 Arakawa T. Hyperpigmentation of the skin with DOPA-uria of a newborn. *Tohoku J Exp Med* 1963; **80**: 329–37.

Pregnancy and menstruation

Increased pigmentation is almost invariable in pregnancy and is most marked in brunettes. A blotchy hypermelanosis of the face involving the cheeks, forehead and chin is frequently seen. This was called chloasma, but the term 'melasma' is now preferred (see p. 58.34). The pigmentation may involve the neck and is associated with darkening of the nipples, the linea alba to form the linea nigra, and the anogenital skin. The pigmentation usually fades after parturition, but may persist for months and years. The same pigmentation can be idiopathic and familial and is particularly seen in those who tan readily when exposed to bright sunlight [1,2]. It is noted by some women to be more apparent just prior to menstruation [3].

Oral contraceptives

Melasma (chloasma) (see p. 58.34) is frequently seen in women on oral contraceptives. No one oral contraceptive appears to be more liable than any other to cause pigmentation in predisposed subjects. The hypermelanosis is made more apparent with sun exposure. These patients also develop the same pigmentation when pregnant [4]. The pigmentation takes a long time to fade after discontinuing oral contraception and, as after pregnancy, it may never fade completely.

The mechanism is not fully elucidated and although MSH may be involved it plays a minor part. Oestrogens and progesterone are involved in the increased pigmentation but other factors are also implicated [2]. In a study of idiopathic melasma it was suggested that some of the patients had mild ovarian dysfunction [5]. Plasma concentrations of MSH are normal in patients with idiopathic melasma [5] and in those on oral contraceptives [6].

References
1 Carruthers R. Chloasma and oral contraceptives. *Med J Aust* 1966; **2**: 17–20.
2 Sanchez NP, Pathak MA, Sato S *et al*. Melasma: a clinical, light microscopic, ultrastructural and immunofluorescence study. *J Am Acad Dermatol* 1981; **4**: 698–710.
3 Snell RS, Turner R. Skin pigmentation in relation to the menstrual cycle. *J Invest Dermatol* 1966; **47**: 147–55.
4 Resnik S. Melasma induced by oral contraceptive drugs. *JAMA* 1967; **199**: 95–9.
5 Pérez M, Sánchez JL, Aguiló F. Endocrinologic profile of patients with idiopathic melasma. *J Invest Dermatol* 1981; **81**: 543–5.
6 Smith AG, Shuster S, Thody AJ, Peberdy M. Chloasma, oral contraceptives, and plasma immunoreactive β-melanocyte-stimulating hormone. *J Invest Dermatol* 1977; **68**: 169–70.

Phaeochromocytoma

Pigmentation of Addisonian pattern occurs in some cases of malignant phaeochromocytoma. Hypertension, headaches, profuse sweating, palpitation and apprehension will suggest the diagnosis, which is established by the abnormal plasma catecholamines.

Carcinoid syndrome

Hyperpigmentation of the skin has been noted in a number of patients with this syndrome.

ACTH administration [1,2]

A small proportion of patients treated with ACTH in high dosage (120 units/day) develop pigmentation of Addisonian pattern. The pigmentation, which is accompanied by a combination of Addisonian and cushingoid manifestations, fades when the dose is reduced. The incidence of melanosis appears to be rather higher in patients treated with tetracosactrin [2].

References
1 Cass LJ, Alexander L, Frederik WS *et al*. ACTH-induced Addisonian-like melanoderma in man. *Curr Ther Res* 1964; **6**: 601–7.
2 Khan SA, Smith AF. Intermittent tetracosactrin-depot therapy in dermatology. *Br J Dermatol* 1970; **82**: 389–96.

Hypermelanosis in other systemic disorders

Increased pigmentation is an inconstant feature of a wide variety of systemic disorders and may be associated with malignant disease. In most instances, the mechanism is obscure although, in some, elevated levels of β-MSH-like immunoreactivity are found. A genetic predisposition may be present in those affected. The hypermelanosis may be diffuse or localized. It may be confined to the epidermis, when the skin appears brown in colour, or it may be in the dermis, when often the skin is a slate-grey or blue colour. Pigments other than melanins may also be present.

Neoplastic disease [1–5]

In cachectic states there may be diffuse hyperpigmentation of the skin as in Addison's disease. The mechanism is uncertain. In the ectopic ACTH syndrome, which may occur in patients with oat cell carcinoma of the bronchus, pigmentation is usual. The tumour has been shown to produce a distinct MSH-like compound [1].

In adults, acquired acanthosis nigricans may rarely be associated with internal malignancy, almost invariably an adenocarcinoma. The hypermelanosis affects the axillae, nipples and umbilicus, which also show a warty papillomatosis. These skin changes may later become generalized. The mucous membranes are frequently involved.

A diffuse dermal melanosis, having a slaty-blue colour, can occur secondary to melanoma and melanogenuria [2,3]. Ultrastructural studies on this rare condition have shown in one patient [4] single-cell metastases disseminated widely through the skin; in another [5] the dermal histiocytes contained many lysosomal bodies containing electron-dense granular material, presumably melanin.

References
1 Liddle GW, Givens JR, Nicholson WE *et al*. The ectopic ACTH syndrome. *Cancer Res* 1965; **25**: 1057–61.
2 Fitzpatrick TB, Montgomery H, Lerner AB. Pathogenesis of generalised dermal pigmentation secondary to malignant melanoma and melanuria. *J Invest Dermatol* 1954; **22**: 163–72.

3 Sexton M, Snyder CR. Generalized melanosis in occult primary melanoma. *J Am Acad Dermatol* 1989; **20**: 261–6.
4 Konrad K, Wolff K. Pathogenesis of diffuse melanosis secondary to malignant melanoma. *Br J Dermatol* 1974; **91**: 635–55.
5 Adrian RM, Murphy GF, Sato S *et al*. Diffuse melanosis secondary to metastatic malignant melanoma. *J Am Acad Dermatol* 1981; **5**: 308–18.

Lymphomas [1–3]

Pigmentation is an uncommon manifestation of lymphomas, occurring in 10% of cases of Hodgkin's disease and in 1 or 2% of cases of lymphosarcoma and lymphatic leukaemia. The pigmentation is of Addisonian type, but allegedly without involvement of the mucous membranes. Malnutrition may be a factor and post-inflammatory pigmentation after scratching may modify the clinical pattern. Diffuse progressive hyperpigmentation can also be a manifestation of mycosis fungoides [1,2]. A number of different clinical patterns of early mycosis fungoides have been described, including pigmented purpura-like lesions [3]. Several of the cytostatic drugs used for the treatment of these disorders can also produce increased pigmentation of the skin.

References

1 David M, Shanon A, Hazay B, Sandbank M. Diffuse, progressive, hyperpigmentation: an unusual skin manifestation of mycosis fungoides. *J Am Acad Dermatol* 1987; **16**: 257–60.
2 Kikuchi A, Shimizu H, Nishikawa T. Mycosis fungoides with marked hyperpigmentation. *Dermatology* 1996; **192**: 360–3.
3 Barnhill RL, Braverman IM. Progression of pigmented purpura-like eruptions to mycosis fungoides: report of three cases. *J Am Acad Dermatol* 1988; **19**: 25–31.

Diseases of the nervous system [1–3]

Pigmentation, usually conforming to the Addisonian pattern, occurs in some diseases of the nervous system, particularly those involving the diencephalon and the substantia nigra. Intense pigmentation is a feature of Schilder's disease [1] but some increase in pigmentation is not uncommon in hepatolenticular degeneration [2] and in ependymomas. It is occasionally noted in chronic schizophrenia. In post-encephalitic Parkinsonism, it may be diffuse but may be melasmal. Pigmentation may sometimes develop after intense and prolonged emotional stress [3].

References

1 Derbes VJ, Fleming G, Becker SW. Generalized cutaneous pigmentation of diencephalic origin. *Arch Dermatol* 1955; **72**: 13–22.
2 Leu ML, Strickland GT, Wang CC *et al*. Skin pigmentation in Wilson's disease. *JAMA* 1970; **211**: 1542–3.
3 Meerloo JAM. Human camouflage and identification with the environment. *Psychosom Med* 1957; **19**: 89–98.

Rheumatoid arthritis and Still's disease [1,2]

Pigmentation, usually generalized, is occasionally observed in rheumatoid arthritis and is a more frequent feature of Still's disease. It may sometimes be caused by medication taken to treat the rheumatoid arthritis, such as minocycline [1] or methotrexate [2].

References

1 Langevitz P, Livneh A, Bank I, Pras M. Benefits and risks of minocycline in rheumatoid arthritis. *Drug Saf* 2000; **22**: 405–14.
2 Toussirot E, Wendling D. Methotrexate-induced hyperpigmentation in a rheumatoid arthritis patient. *Clin Exp Rheumatol* 1999; **17**: 751.



Fig. 58.16 Generalized pigmentation in a woman aged 33 years with systemic sclerosis.

Systemic sclerosis, scleroderma and morphoea [1–9]

Generalized pigmentation in systemic sclerosis and scleroderma may be intense and diffuse or of Addisonian type, but without mucous membrane involvement [1]. It may involve predominantly the face and limbs but is often far more extensive than the scleroderma (Fig. 58.16). Hyperpigmentation in systemic sclerosis is seen most commonly in patients with pigmented skin, and is less common in whites [2]. Keratinocyte endothelin-1 production has been implicated as playing a central role in the pathogenesis of cutaneous hyperpigmentation in systemic sclerosis [3], as has local expression and systemic release of a stem cell factor [4]. Levels of soluble cell surface L-selectin are elevated in systemic sclerosis with diffuse hyperpigmentation [5].

Pigmentation may also be a conspicuous feature of morphoea [6] and is occasionally the presenting symptom (Fig. 58.17). Hyperpigmentation is sometimes a feature of atrophoderma of Pasini and Pierini [7], and has also been reported in the linear atrophoderma of Moulin [8]. Prominent post-inflammatory hyperpigmentation has been reported in a case of porphyria cutanea tarda with idiopathic myelofibrosis and CREST syndrome [9]. A colorimetry device has helped to define the pigmentation changes of extensive scleroderma [10].

References

1 McFadden N, Ree K, Søyland E, Larson TE. Scleredema adultorum associated with a monoclonal gammopathy and generalised hyperpigmentation. *Arch Dermatol* 1987; **123**: 629–32.
2 Reveille JD, Fischbach M, McNearney T *et al*. Systemic sclerosis in three US ethnic groups: a comparison of clinical, sociodemographic, serologic, and immunogenetic determinants. *Semin Arthritis Rheum* 2001; **30**: 332–46.
3 Tabata H, Hara N, Otsuka S *et al*. Correlation between diffuse pigmentation and keratinocyte-derived endothelin-1 in systemic sclerosis. *Int J Dermatol* 2000; **39**: 899–902.
4 Yamamoto T, Sawada Y, Katayama I, Nishioka K. Local expression and systemic release of stem cell factor in systemic sclerosis with diffuse hyperpigmentation. *Br J Dermatol* 2001; **144**: 199–200.
5 Shimada Y, Hasegawa M, Takehara K, Sato S. Systemic sclerosis with elevated cell surface L-selectin levels. *Clin Exp Immunol* 2001; **124**: 474–9.
6 Weinberg JM, Russo M, Hirsch RJ, Don PC. Morphoea of the breast in a young girl. *Clin Exp Dermatol* 2001; **26**: 497–8.



Fig. 58.17 Morphoea. Hyperpigmentation was the presenting symptom.

7 Iranzo P, Lopez I, Palou J *et al*. Morphoea in three siblings. *J Eur Acad Dermatol Venereol* 2001; **15**: 46–7.
8 Rompel R, Mischke AL, Langner C, Happle R. Linear atrophoderma of Moulin. *Eur J Dermatol* 2000; **10**: 611–3.
9 Lee SC, Yun SJ, Lee JB *et al*. A case of porphyria cutanea tarda in association with idiopathic myelofibrosis and CREST syndrome. *Br J Dermatol* 2001; **144**: 182–5.
10 Maeda M, Kachin H, Matubara K *et al*. Pigmentation abnormalities in systemic scleroderma examined by using a colorimeter. *J Dermatological Sci* 1996; **11**: 228–33.

Dermatomyositis and lupus erythematosus [1,3]

Diffuse pigmentation may accompany or follow the cutaneous lesions of dermatomyositis [1]. Acanthosis nigricans has also been reported in association with dermatomyositis [2]. In systemic lupus erythematosus, diffuse pigmentation of light-exposed skin occurs in about 10% of cases. It may gradually darken, although the disease is controlled by treatment. Longitudinal melanonychia may occasionally be a feature of systemic lupus erythematosus [3].

References

1 Bottomley WW, Goodfield MD. A case of dermatomyositis presenting as localized hyperpigmentation of the hands and face. *Br J Dermatol* 1995; **132**: 670–1.
2 Castro MA, Kutzbach A. Acanthosis nigricans associated with long-standing dermatomyositis. *J Rheum* 1996; **23**: 1487–8.
3 Skowron F, Combemale P, Faisant M *et al*. Functional melanonychia due to involvement of the nail matrix in systemic lupus erythematosus. *J Am Acad Dermatol* 2002; **47** (2 Suppl.): S187–S188.

Multiple organ failure [1]

Patients with multiple organ failure who survive for long periods are susceptible to hyperpigmentation. Renal failure, hepatic failure and polypharmacy may all contribute to this. An unusual case of intense green colour in a patient with multiple organ failure was attributed to dyes in the liquid tube feeds [1].

Reference

1 Czop M, Herr DL. Green skin discoloration associated with multiple organ failure. *Crit Care Med* 2002; **30**: 598–61.

Renal failure [1–4]

Chronic renal disease with nitrogen retention is frequently accompanied by increased pigmentation of the skin. This hypermelanosis is diffuse and brown in colour. It is most intense on the hands and face. Hyperpigmented macules are common on the palms and soles [3]. Elevated levels of β-MSH are found in the plasma of these patients [1,2] and cause the excess production of melanin in the skin. The increased levels of β-MSH-like immunoreactivity are due to slow clearance by the kidney rather than increased production by the pituitary. Lipochromes and carotenoids deposited in the skin may also play a part. Paradoxically, hypopigmentation with acquired lightening of hair is sometimes a feature of chronic renal failure [4].

References

1 Gilkes JJH, Eady RAJ, Rees LH *et al*. Plasma immunoreactive melanotrophic hormones in patients on maintenance haemodialysis. *BMJ* 1975; **1**: 656–7.
2 Smith AG, Shuster S, Comaish JS *et al*. Plasma immunoreactive β-melanocyte-stimulating hormone and skin pigmentation in chronic renal failure. *BMJ* 1975; **1**: 658–9.
3 Pico MR, Lugo-Somolinos A, Sanchez JL, Burgos-Calderon R. Cutaneous alterations in patients with chronic renal failure. *Int J Dermatol* 1992; **31**: 860–3.
4 Hmida MB, Turki H, Hachicha J *et al*. Hypopigmentation in haemodialysis. Acquired hair and skin fairness in a uraemic patient undergoing maintenance haemodialysis: case report and review of the literature. *Dermatology* 1996; **192**: 148–52.

Anaemia [1–8]

Hyperpigmentation of the skin occurs in vitamin B_{12} deficiency and is more common in dark-skinned races [1]. A diffuse brown pigmentation is also seen occasionally in patients with folic acid deficiency [2,4]. Pigmentation of the fingertips and nails of a patient with B_{12} deficiency has been reported [5]. The pigmentation seen in association with B_{12} deficiency often has a rather dappled and mottled appearance, and particularly affects the face, hands and feet [3,5,7]. Sometimes, only the fingers are affected. Treatment with vitamin B_{12} reverses the pigmentation of the skin to normal [7,8]. Pigmentation also occurs in megaloblastic anaemia associated with pregnancy [2]. In the haemolytic anaemias, hypermelanosis and haemosiderosis may develop on the lower legs.

References

1 Baker SJ, Ignatius M, Johnson S, Vaish SK. Hyperpigmentation of skin: a sign of vitamin B_{12} deficiency. *BMJ* 1963; **i**: 1713–5.
2 Baumslag N, Metz J. Pigmentation in megaloblastic anaemia associated with pregnancy and lactation. *BMJ* 1969; **ii**: 737–9.
3 Gilliam JN, Cox AJ. Epidermal changes in vitamin B_{12} deficiency. *Arch Dermatol* 1973; **107**: 231–61.
4 Downham TF, Rehbein HM, Taylor KE. Hyperpigmentation and folate deficiency. *Arch Dermatol* 1976; **112**: 562.
5 Ridley CM. Pigmentation of fingertips and nails in vitamin B_{12} deficiency. *Br J Dermatol* 1977; **97**: 105–6.
6 Marks VJ, Briggaman RA, Wheeler CE Jr. Hyperpigmentation in megaloblastic anaemia. *J Am Acad Dermatol* 1985; **12**: 914–7.
7 Mori K, Ando I, Kukita A. Generalized hyperpigmentation of the skin due to vitamin B12 deficiency. *J Dermatol* 2001; **28**: 282–5.

8 Sabatino D, Kosuri S, Remollino A, Shotter B. Cobalamin deficiency presenting with cutaneous hyperpigmentation: a report of two siblings. *Pediatr Hematol Oncol* 1998; **15**: 447–50.

Primary biliary cirrhosis

A diffuse hypermelanosis is seen in patients with cirrhosis due to many aetiological factors, and is particularly striking in patients with primary biliary cirrhosis. The hyperpigmentation is particularly striking on sun-exposed sites. The excess melanin is dispersed widely in the epidermis [1]. No significant difference from normal controls is observed in the levels of MSH-like peptides [1].

Reference

1 Mills PR, Skerrow CJ, MacKie RM. Melanin pigmentation of the skin in primary biliary cirrhosis. *J Cutan Pathol* 1981; **8**: 404–10.

Haemochromatosis

The disease haemochromatosis was first described by Troisier, Hanot and Chauffard in 1865 [1]. The term 'haemochromatosis' was subsequently coined by von Recklinghausen in 1899 in recognition that the skin pigmentation originated from the blood [1]. Pigmentation, bronzed or greyish in colour, initially involves exposed sites but later becomes generalized [2,3]. It is present in most cases [3], but may be subtle. The diagnosis should be suspected when pigmentation of this pattern occurs in middle-aged men in association with an enlarged liver and diabetes [4]. The diagnosis is confirmed by the high level of serum iron. Hyperpigmentation is reversible with phlebotomy [5]. Haemochromatosis is a common disease whose diagnosis is often overlooked [6]. However, only 50% of homozygous patients show clinical features of the disease [7].

References

1 Pietrangelo A. Haemochromatosis. *Gut* 2003; **52** (Suppl. 2): ii23–ii30.
2 Finch SC, Finch CA. Idiopathic hemochromatosis, an iron storage disease. *Medicine (Baltimore)* 1955; **34**: 381–430.
3 Chevrant-Breton J, Simon M, Bourel M, Ferrand B. Cutaneous manifestations of idiopathic hemochromatosis. Study of 100 cases. *Arch Dermatol* 1977; **113**: 161–5.
4 Adams PC, Deugnier Y, Moirand R, Rissot P. The relationship between iron overload, clinical symptoms and age in 410 patients with genetic hemochromatosis. *Hepatology* 1997; **25**: 162–6.
5 Barton JC, McDonnell SM, Adams PC *et al*. Management of hemochromatosis. Hemochromatosis Management Working Group. *Ann Intern Med* 1998; **129**: 932–9.
6 Bomford A. Genetics of haemochromatosis. *Lancet* 2002; **360**: 1673–81.
7 Olynyk JK, Cullen DJ, Aquilia S *et al*. A population-based study of the clinical expression of the hemochromatosis gene. *Gastroenterology* 1999; **341**: 718–24.

Amyloidosis

Localized pigmentation, often symmetrical, is seen in both lichen and macular amyloidosis [1,2]. The macular type of amyloidosis may be mistaken for post-inflammatory hyperpigmentation, but the lesions usually have a distinctive 'ripple' pattern, and microscopic studies reveal the presence of amyloid. Melanophages are found in the papillary dermis. The melanin contained in these dermal cells is derived from degenerating basal keratinocytes and melanocytes [1,3]. Macular amyloidosis is seen most commonly on the upper back (interscapular areas), chest, buttocks, forearms and shins.

References

1 Black MM, Wilson Jones E. Macular amyloidosis. *Br J Dermatol* 1971; **84**: 199–209.
2 Brownstein MH, Hashimoto K. Macular amyloidosis. *Arch Dermatol* 1972; **106**: 50–7.
3 Hori Y, Koboni T. Macular amyloidosis: clinical and pathological studies. In: Fitzpatrick TB, ed. *Biology and Diseases of Dermal Pigmentation*. Tokyo: University of Tokyo Press, 1981: 299–309.

Vitamin A deficiency

Severely malnourished patients with the ocular lesions of vitamin A deficiency tend also to show cutaneous changes. In children, dry skin is the main manifestation of vitamin A deficiency and may be associated with hyperpigmentation of the face and limbs. In adults there is dryness and scaling of the skin with desquamation and generalized hyperpigmentation. Conjunctival pigmentation has been noted particularly in oriental races and may be striking, especially in the lower fornix and bulbar conjunctiva.

Pellagra

Pellagra, the classic clinical manifestation of niacin deficiency, is characterized by erythema and hyperpigmentation of sun-exposed sites. It was first described by Gaspar Casal in the Asturias region of Spain in 1735 [1]. The nutritional basis for the disorder was established by Joseph Goldberger of the United States Public Health Service in the 1910s [2]. However, it was Conrad Elvehjem of the University of Wisconsin who finally proved that pellagra was caused by a deficiency in niacin [3]. Affected skin becomes hard, dry and cracked and in extreme cases is black in colour [4]. The sites of involvement are the sun-exposed skin of the face, neck, dorsa of hands and feet, and sometimes the forearms. Mucosal sites are also affected. Treatment of pellagra consists of 300 mg of oral niacin per day.

References

1 Sebrell WH Jr. History of pellagra. *Fed Proc* 1981; **40**: 1520–2.
2 Goldberger J, Tanner WF. Amino acid deficiency is probably the primary etiologic factor in pellagra. *Public Health Rep* 1922; **37**: 462–86.
3 Elvehjem CA, Madden RJ, Strong FM, Wooley DW. Isolation and identification of anti-black tongue factor. *J Biol Chem* 1938; **123**: 137–49.
4 Karthikeyan K, Mohan TD. Pellagra and skin. *Rev Int J Dermatol* 2002; **41**: 476–81.

Malabsorption syndromes

In sprue and other malabsorption syndromes, pigmentation is of common occurrence and may sometimes be prominent [1,2]. It may be of Addisonian type but without involvement of the mucous membranes, or may occur in well-defined patches on the face and neck and occasionally on the trunk. The scaly inflammatory plaques (see Chapter 59) that may develop in these syndromes are usually followed by intense pigmentation.

References

1 Dutly F, Altwegg M. Whipple's disease and 'trephoryma whippelii'. *Clin Microbiol Rev* 2001; **14**: 561–83.
2 Panicker JN, Vijayaraghavan L, Madhusudanan S. Whipple's disease. *J Assoc Physicians India* 2001; **49**: 853–5.

Vagabond's disease

This classically occurs in those in whom lack of food is combined with lack of cleanliness, and heavy infestation with pediculi. The

pigmentation is basically of Addisonian pattern and the mucous membranes may be involved. The pathogenesis is uncertain, but the hypermelanosis is probably post-inflammatory and related to the scratching from the pediculosis infestation. Areas of hypomelanosis occur and there is a decrease in the number of melanocytes that show degenerative changes [1]. Adrenal function is in most cases normal [2].

References

1 Grosshans E, Stoebner P, Basset A. La leucomélanodermie des vagabonds. *Ann Dermatol Syphiligr* 1972; **99**: 141–59.

2 Thiers H, Colomb D, Durand B. Deux cas de mélanodermie des vagabonds. *Bull Soc Fr Dermatol Syphiligr* 1965; **72**: 82–4.

Peripheral neuropathy with dysproteinaemia, skin changes and endocrinopathy

Synonyms

- Crow–Fukase syndrome
- Shimpo's syndrome
- PEP syndrome
- POEMS syndrome

This multisystem disorder, characterized by polyneuropathy, dysglobulinaemia, anasarca, pigmentation, scleroderma, hypertrichosis, endocrinopathy, hepatosplenomegaly and lymphadenopathy, is discussed in Chapter 62.

Hypermelanosis of drug origin [1–4]

Skin pigmentation may be induced by a wide variety of drugs [1]. Several mechanisms are involved in drug-induced changes of pigmentation of the skin. These include increased melanin synthesis, increased lipofuscin synthesis, deposition of drug-related material and post-inflammatory hyperpigmentation. For example, the phenothiazines, particularly chlorpromazine, react with melanin to form drug–pigment complexes. In contrast to melanin, the chlorpromazine–melanin complexes are not metabolized by the body. On discontinuing chloropromazine and related phenthiazines, the pigmentation sometimes fades slowly, but more often is permanent. Many drugs induce hypermelanosis as a non-specific post-inflammatory change in predisposed subjects. The pigmentation following fixed drug eruptions is of this type. Other drugs induce pigmentation more directly; in the case of arsenic it is believed that it combines avidly with sulphydryl groups in the epidermal cells and promotes the action of tyrosinase. A post-inflammatory hyperpigmentation of the skin is seen following the resolution of drug-induced lichenoid reactions. Oestrogens stimulate melanin production, and drug-induced hyperpigmentation may be seen with the combined oral contraceptive. Hyperpigmentation in AIDS patients may occur as a complication of drug therapy, most notably with zidovudine which causes pigmentation of nail, skin and oral mucosa.

References

1 Dereure O. Drug-induced skin pigmentation. Epidemiology, diagnosis and treatment. *Am J Clin Dermatol* 2001; **2**: 253–62.

2 Lerner EA, Sober AJ. Chemical and pharmacologic agents that cause hyperpigmentation or hypopigmentation of the skin. *Dermatol Clin* 1988; **6**: 327–37.

3 Ferguson J, Frain-Bell W. Pigmentary disorders and systemic drug therapy. *Clin Dermatol* 1989; **7**: 44–54.

4 Ming ME, Bhawan J, Stefanato CM *et al*. Imipramine-induced hyperpigmentation: four cases and a review of the literature. *J Am Acad Dermatol* 1999; **40**: 159–66.

Chlorpromazine and related phenothiazines [1–10]

Blue-grey pigmentation of the sun-exposed areas of the skin is seen in a small percentage of patients receiving high doses of chlorpromazine for long periods [1,2]. The pigmentation is cumulative and some develop a purplish tint. Related phenothiazines may cause a similar effect, but chlorpromazine is usually implicated [3]. Some of those affected also develop cataracts, corneal opacities and pigmentation of the conjunctivae [4]. The nail beds are also affected in severe cases [2]. The mechanism is uncertain, as discussed above, but probably involves drug–melanin complexes. There is extensive deposition of melanin-like material throughout the reticuloendothelial system and involving the parenchymal cells of internal organs. The pigment found in the cells of the dermis stains as for melanin [1,2]. Electron microscopy studies [5] show increased melanin in the epidermis and perivascular macrophages in the dermis that contain electron-dense particles. Radioactively labelled chlorpromazine is found to localize in tissues containing melanin [6]. It is believed that this drug or some metabolite is bound to melanin in the tissues [8]. The level of immunoreactive β-MSH in the plasma of these patients is within the normal range [7]. A blue-grey pigmentation of the sun-exposed areas of skin has also been reported with trifluoperazine and imipramine [9,10].

References

1 Hays GB, Lyle CB, Wheeler CE. Slate-gray color in patients receiving chlorpromazine. *Arch Dermatol* 1964; **90**: 471–6.

2 Satanove A. Pigmentation due to phenothiazines in high and prolonged dosage. *JAMA* 1965; **191**: 263–8.

3 Hägermark Ö, Wennersten G, Almeyda J. Cutaneous side effects of phenothiazines. *Br J Dermatol* 1971; **84**: 605–7.

4 Greiner AC, Berry K. Skin pigmentation and corneal and lens opacities with prolonged chlorpromazine therapy. *Can Med Assoc J* 1964; **90**: 663–5.

5 Hashimoto K, Wiener W, Albert J *et al*. An electron microscopic study of chlorpromazine pigmentation. *J Invest Dermatol* 1966; **47**: 296–306.

6 Blois MS. On chlorpromazine binding *in vivo*. *J Invest Dermatol* 1965; **45**: 475–81.

7 Smith AG, Goolamali SIK, Thody AJ *et al*. Phenothiazine therapy and plasma immunoreactive β-MSH in schizophrenia and pruritic dermatoses. *Br J Dermatol* 1977; **96**: 537–9.

8 Benning TL, McCormack KM, Ingram P *et al*. Microprobe analysis of chlorpromazine pigmentation. *Arch Dermatol* 1988; **124**: 1541–4.

9 Buckley C, Thomas V, Lewin J *et al*. Stelazine-induced pigmentation. *Clin Exp Dermatol* 1994; **19**: 149–51.

10 Hashimoto K *et al*. Imipramine hyperpigmentation: a slate grey discolouration caused by long-term imipramine administration. *J Am Acad Dermatol* 1991; **25**: 357–61.

Hydantoin [1,2]

Phenytoin (diphenylhydantoin) is the prototype of the hydantoin derivatives. Some 10% of patients receiving hydantoin preparations develop pigmentation of the face and neck, resembling chloasma, which fades in a few months when the drug is stopped. It has been suggested that hydantoin exerts a direct action on the melanocytes inducing dispersion of melanin granules in the cutis, in addition to increased pigmentation of the basal epidermis.

A patient on this drug developed pigmentation of Addisonian type and other evidence of hypoadrenalism [2].

References

1 Kuske H, Krebs A. Hyperpigmentierungen vom Typus des Chloasmas nach Behandlung mit Hydantoin-Präparaten. *Dermatologica* 1964; **129**: 121–39.

2 Gottwald W, Aksoy F. Mesantoin-Begleiteffekte mit Addisonpigmentierung und cerebrale Anfalls-Rhythmik. *Hautarzt* 1965; **16**: 445–9.

Arsenic (see Chapter 75)

Prolonged ingestion of inorganic arsenic may result in diffuse pigmentation, most intense on the trunk, where macular areas of depigmentation within areas of hyperpigmentation produce the distinctive 'raindrop' appearance [1]. Many cases also show arsenical keratoses, but the severity of the two manifestations of arsenic poisoning is not necessarily proportionate and either may be present alone.

Reference

1 Meyhofer W, Knoth W. Uber die Auswirkung einer langjahrigen antipsoriatischen Arsentherapie auf mehrere Organe unter besonderer Berucksichtigung andrologischer Befunde. *Hautarzt* 1966; **17**: 309–13.

Antimalarial drugs [1–5]

About 25% of patients receiving chloroquine or hydroxychloroquine for several years develop bluish-grey pigmentation on the face and neck and sometimes the lower legs and forearms. With continued therapy, the areas darken, particularly oval patches on the shins, which increase in size. A blue-black colour may develop. Also, these patches are more pigmented in the light-exposed areas. The nail beds may be affected diffusely or in transverse bands and the hard palate may be bluish-grey. Bleaching of the colour of the hair occurs and when associated with pigmentation of the skin should suggest the diagnosis [4]. Corneal and retinal changes may develop following pigmentation of the skin due to antimalarials [3]. Chloroquine has been shown to have an affinity for dermal melanin [4]. A yellowish pigmentation of the skin is common with mepacrine [5]. Pigmentation appears to result from complexes of melanin, haemosiderin and mepacrine, in combination with sulphur [5]. Quinine and quinidine may also produce a generalized pigmentation [3,6].

References

1 Sams WM, Epstein WM. The affinity of melanin for chloroquine. *J Invest Dermatol* 1965; **45**: 482–8.

2 Shee JC, Bernard PJ. Pigmentation from amodiaquine simulating cyanosis. *Trans R Soc Trop Med Hyg* 1963; **57**: 379–81.

3 Tuffanelli D, Abraham RK, Dubois E. Pigmentation from antimalarial therapy. *Arch Dermatol* 1963; **88**: 419–26.

4 Marriott P, Borrie PF. Pigmentary changes following chloroquine. *Proc R Soc Med* 1975; **68**: 535–6.

5 Leigh IM, Kennedy CT, Ramsey JD, Henderson WJ. Mepacrine pigmentation in systemic lupus erythematosus. New data from an ultrastructural, biochemical and analytical electron microscope investigation. *Br J Dermatol* 1979; **101**: 147–53.

6 Mahler R, Sissons W, Watters K. Pigmentation induced by quinidine therapy. *Arch Dermatol* 1986; **122**: 1062–4.

Antitumour agents [1–7]

Long-term administration of busulfan (busulphan) produces a diffuse brown pigmentation, particularly in non-white people with a dark complexion. Less commonly, Addison's disease is simulated [2,3]. Light and electron microscopy studies suggest that busulfan has both a stimulatory and a toxic effect on melanocytes [4]. Both busulfan and doxorubicin cause mucous membrane pigmentation. Other cytostatic drugs that may produce hyperpigmentation include cyclophosphamide, bleomycin, fluorouracil, hydroxyurea, daunorubicin, methotrexate, mithramycin, mitomycin, thiotepa and adriamycin [6,7]. Topical cytostatic drugs that produce localized hyperpigmentation include carmustine, mechlorethamine and fluorouracil. Patients on cyclophosphamide [5], bleomycin, daunorubicin, doxorubicin and fluorouracil can develop banded or diffuse pigmentation of the nails. Hair pigmentation may be induced by methotrexate, and pigmentation of the teeth may be seen with cyclophosphamide.

References

1 Bronner AK, Hood AF. Cutaneous complications of chemotherapeutic agents. *J Am Acad Dermatol* 1983; **9**: 645–63.

2 Feingold ML, Koss LG. Effects of long-term administration of busulfan. *Arch Intern Med* 1969; **124**: 66–71.

3 Kyle RA, Schwartz RS, Oliver HL *et al*. A syndrome resembling adrenal cortical insufficiency associated with long term busulfan (myleran) therapy. *Blood* 1961; **18**: 497–510.

4 Adam BA, Ismail R, Sivanesan S. Busulfan hyperpigmentation. *J Dermatol* 1980; **7**: 405–11.

5 Shah PC, Rao KRP, Patel AR. Cyclophosphamide induced nail pigmentation. *Br J Dermatol* 1978; **98**: 675–80.

6 Kerker BJ, Hood AF. Chemotherapy-induced cutaneous reactions. *Semin Dermatol* 1989; **8**: 173–81.

7 Vassallo C, Passamonti F, Merante S *et al*. Muco-cutaneous changes during long-term therapy with hydroxyurea in chronic myeloid leukaemia. *Clin Exp Dermatol* 2001; **26**: 141–8.

Fixed eruptions [1–6]

Circumscribed areas of slate-brown pigmentation commonly follow the erythematous and bullous stages of fixed eruptions (see Chapter 75) but almost universal brown pigmentation has followed the long-continued ingestion of phenolphthalein [3]. Fixed eruptions are particularly frequent in black people. More or less symmetrical, discrete patches are usually seen but the melanosis may be diffuse or melasmal, and the mucous membranes may be involved [4,5]. The slate-brown colour in fixed drug eruption is due to pigmentary incontinence with melanophages in the upper dermis [6].

References

1 Browne SG. Fixed eruption in deeply pigmented subjects. *BMJ* 1964; **ii**: 1041–4.

2 Gelfand M. 'Melanotic' lesions in the Africans. *Cent Afr J Med* 1964; **10**: 443–7.

3 Weiss RS, Kile RL. Unusual phenolphthalein eruptions. *Arch Dermatol Syphilol* 1935; **32**: 915–21.

4 Tagami H. Pigmented macules of the tongue following fixed drug eruption. *Dermatologica* 1973; **147**: 157–60.

5 Westerhof W, Wolters EC, Brookbakker JT *et al*. Pigmented lesions of the tongue in heroin addicts: fixed drug eruption. *Br J Dermatol* 1983; **109**: 605–10.

6 Masu S, Seiji M. Pigmentary incontinence in fixed drug eruptions. *J Am Acad Dermatol* 1983; **8**: 525–32.

Post-inflammatory hypermelanosis

Hypermelanosis commonly follows acute or chronic inflammatory processes in the skin. The intensity and persistence of the hypermelanosis are greater in dark-skinned subjects. The degree

of inflammation appears to be of less significance in determining the pigmentary response than the nature of the dermatosis, for it may be frequent and severe after some conditions and slight after others. Disorders where there is disruption of the basal layer of the epidermis, such as lichen planus or lupus erythematosus, frequently develop areas of slate-brown hypermelanosis. Similarly, in fixed drug eruptions, hyperpigmentation occurs owing to damage of cells in the basal layer. There is pigmentary incontinence with melanophages in the upper dermis [1]. In the late phase of chronic graft-versus-host reaction, there is a poikilodermatous appearance with hyperpigmentation [2].

Hypermelanosis of the epidermis may also occur in inflammatory disorders, but more frequently there is hypomelanosis of the skin. This results from an increased mitotic rate of keratinocytes and diminished transfer of melanosomes from the melanocyte to these cells, which also exhibit a reduced transit time from the basal layer to being shed on the skin surface. Very frequently in inflammatory disease in the skin, hypermelanosis and hypomelanosis occur together, often with a slaty-blue colour due to the presence of melanophages in the upper dermis. There may be an associated loss of functional melanocytes in the skin [3].

The cause of the pigmentation is usually obvious, although the preceding lesions have sometimes not been noticed by the patient or have been transitory or clinically imperceptible. The pattern and distribution of the pigmentation will sometimes allow a retrospective diagnosis, as in lichen planus, herpes zoster, dermatitis herpetiformis and papular urticaria. Pigmentation is often conspicuous after lichenoid drug eruptions, and is a feature of lipomelanic reticulosis.

An unexplained, but not excessively rare, clinical syndrome has been reported in some dark-skinned white people [4]. A small, irregular patch of hypermelanosis of the interscapular skin is often intensely pruritic. It seems likely that this condition is in fact notalgia paraesthetica [5,6] (see Chapter 63).

Reticulate pigmentation following the vascular network is characteristic of erythema ab igne (see Chapter 28), which may occur at any site regularly exposed to the heat of a fire or a hot-water bottle. A reticulate pigmentation is also seen in prurigo pigmentosa, a dermatosis mostly occurring in Japan [7].

Post-inflammatory hyperpigmentation may occur following trauma to the skin. It can occur following dermabrasion and particularly in those who are racially pigmented. Unusual patterns may declare their origin, for example the tooth-mark pattern on an ill-treated child [8] or the symmetrical pigmentation of the sides of the chin in a patient who, as a nervous tic, chews the buccal mucosa [9].

In late secondary syphilis, especially in women, so-called syphilitic leukoderma is occasionally seen. Diffuse hypermelanosis of the sides and back of the neck and the shoulders is mottled with depigmented macules 1–2 cm in diameter. The Wassermann reaction is always positive. A deep-blue or slate-grey hyperpigmentation is seen in late pinta (see Chapter 30).

References

1 Masu S, Seiji M. Pigmentary incontinence in fixed drug eruptions. *J Am Acad Dermatol* 1983; **8**: 525–32.

2 Touraine R, Revuz J, Dreyfus B *et al*. Graft-versus-host reaction and lichen planus. *Br J Dermatol* 1975; **92**: 589.

3 Papa CM, Kligman AM. The behaviour of melanocytes in inflammation. *J Invest Dermatol* 1965; **45**: 465–74.

4 Gibbs RC, Frank SB. A peculiar spotty pigmentation: report of five cases. *Dermatol Int* 1969; **8**: 14–6.

5 Leibson I, Honecke H, Mas P. Puzzling posterior pigmented pruritic patches. *Cutis* 1973; **23**: 471–3.

6 Weber PJ, Poullos EG. Notalgia paresthetica. *J Am Acad Dermatol* 1988; **18**: 25–30.

7 Joyce AP, Horn TD, Anhalt GJ. Prurigo pigmentosa. Report of a case and review of the literature. *Arch Dermatol* 1989; **125**: 1551–4.

8 Palomeque FE, Hairston MA. 'Battered child' syndrome. *Arch Dermatol* 1964; **90**: 326–7.

9 Penev SG. Peribuccal pigmentation as an artefact. *Br J Dermatol* 1970; **82**: 40–1.

Tanning with UV light

Tanning is the term used to describe the pigmentary response of the skin following exposure to ultraviolet radiation. Tanning occurs in three distinct phases: immediate pigment darkening, persistent pigment darkening and delayed tanning. Immediate pigment darkening (IPD) occurs in response to low doses of UVA. It appears within minutes of UV exposure and typically fades within 10–20 min. Clinically, immediate pigment darkening manifests as grey-brown pigmentation. IPD is believed to result from oxidation and redistribution of pre-existing melanin. Higher doses of UVA induce persistent pigment darkening (PPD) which persists for 2–24 h. This pigmentation is brown and is also caused by oxidation and redistribution of pre-existing melanin. Delayed tanning involves the formation of new melanin due to increased numbers of melanocytes and increased melanocyte activity. Both UVA and UVB are able to induce delayed tanning, but UVB is more effective. Delayed tanning becomes visible about 72 h after UV exposure and persists for 1–2 weeks before gradually fading as keratinocytes are shed from the skin surface.

Tanning and DNA damage are closely associated. Repeated suberythemal doses of UV light induce tanning but have also been shown to induce DNA damage [1]. Tanning salon exposure has also been demonstrated to induce cyclobutane pyrimidine dimers and p53 protein expression in epidermal keratinocytes, changes linked with the early stages of cutaneous carcinogenesis [2]. It is widely believed by lay people that a tan provides good protection against sunburn [3]. However, tanned skin has been shown to be less effective against formation of DNA photoproducts than constitutive pigmentation [3] and has a sun protection factor of 3–5 at best. Population-based surveys reveal that tanning remains popular, particularly with the young, and that episodes of sunburn remain common [4,5]. However, newer sunbeds with a greater proportion of UVB are significantly more carcinogenic than the older lamps that emitted primarily UVA, with little UVB [6,7].

References

1 Sheehan JM, Cragg N, Chadwick CA *et al*. Repeated ultraviolet exposure affords the same protection against DNA photodamage and erythema in human skin types II and IV but is associated with faster DNA repair in skin type IV. *J Invest Dermatol* 2002; **118**: 825–9.

2 Whitmore SE, Morison WL, Potten CS, Chadwick C. Tanning salon exposure and molecular alterations. *J Am Acad Dermatol* 2001; **44**: 775–80.

3 Bykov VJ, Marcusson JA, Hemminki K. Protective effects of tanning on cutaneous DNA damage in situ. *Dermatology* 2001; **202**: 22–6.

4 Boldeman C, Branstrom R, Dal H *et al*. Tanning habits and sunburn in a Swedish population age 13–50 years. *Eur J Cancer* 2001; **37**: 2441–8.

5 Pratt K, Borland R. Predictors of sun protection among adolescents at the beach. *Aust Psychol* 1994; **29**: 135–9.
6 Diffey B. Sunbeds, beauty and melanoma. *Br J Dermatol* 2007; **157**: 215–6.
7 Oliver H, Ferguson J, Moseley H. Quantitative risk assessment of sunbeds: impact of new high power lamps. *Br J Dermatol* 2007; **157**: 350–6.

Photodynamic and phototoxic reactions [1–5]

Drugs and other chemicals with photodynamic and phototoxic activity have the potential to induce skin hyperpigmentation. Tanning follows the sunburn-like reactions to drugs such as demethylchlortetracycline and imipramine, but does not usually occur after photoallergic reactions [3].

If the photodynamic agent is applied directly to the skin, the intensity of the pigmentary response is greatly enhanced. Transient hyperpigmentation has been reported due to photodynamic therapy in acne [4] and localized scleroderma [5]. Hypermelanosis may sometimes be heavy and persistent following photodynamic and phototoxic reactions. The more or less diffuse patterns of pigmentation so induced are considered below, together with other facial melanoses. Two distinctive clinical syndromes are Berloque dermatitis and phytophotodermatitis.

References
1 Epstein JH. Photoallergy. *Arch Dermatol* 1972; **106**: 741–8.
2 Epstein JH. Phototoxicity and photoallergy: clinical syndromes. In: Fitzpatrick TB, ed. *Sunlight and Man*. Tokyo: University of Tokyo Press, 1974: 459–77.
3 Hashimoto K, Joselow SA, Tye MJ. Imipramine hyperpigmentation: a slate-gray discoloration caused by long-term imipramine administration. *J Am Acad Dermatol* 1991; **25**: 357–61.
4 Hongcharu W, Taylor CR, Chang Y *et al*. Topical ALA-photodynamic therapy for the treatment of acne vulgaris. *J Invest Dermatol* 2000; **115**: 183–92.
5 Karrer S, Abels C, Landthaler M, Szeimies RM. Topical photodynamic therapy for localized scleroderma. *Acta Derm Venereol (Stockh)* 2000; **80**: 26–7.

Phytophotodermatitis

Synonyms
- Meadow dermatitis
- Strimmer dermatitis
- Weed-wacker dermatitis

This is an inflammatory and pigmentary reaction of the skin to light, potentiated by furocoumarins in plants (Fig. 58.18). All the plants reliably recorded as inducing this reaction in humans have been shown to contain furocoumarins, including cow parsley (*Anthrisus sylvestris*) and giant hogweed (*Heracleum sphondylium*) [1,2]. The reaction occurs in those exposed to sunlight after these plants have been crushed on the skin. There is some individual variation in susceptibility but with adequate exposure most will react. If the inflammatory phase is severe, bullae are formed. Milder cases show pigmentary changes without inflammation. Serial dilutions of psoralens may, in exceptional cases, be needed to distinguish photoallergy from phototoxicity [3].

Common clinical patterns for phytophotodermatitis include a bizarre network of pigmented streaks on the legs or arms (meadow dermatitis), and much finer spots and small streaks on forearms and legs from contact with plant material during strimming (strimmer dermatitis). Squeezing limes outside when preparing cold drinks can cause blistering of the hands if carried out on sunny days. Handling celery either at harvest or when it is sold can cause phytophotodermatitis of the fingertips if it takes place in direct sunlight [4].



Fig. 58.18 Phytophotodermatitis. Linear, streaky pigmentation following an acute blistering reaction caused by giant hogweed and sunlight.

References
1 Gawkrodger DJ, Savin JA. Phytophotodermatitis due to common rue (*Ruta graveolens*). *Contact Dermatitis* 1983; **9**: 224.
2 Tunget CL, Turchen SG, Manoguerra AS *et al*. Sunlight and the plant: a toxic combination: severe phytophotodermatitis from *Cneoridium dumosum*. *Cutis* 1994; **54**: 400–2.
3 Ljunggren B. Psoralen photoallergy caused by plant contact. *Contact Dermatitis* 1977; **3**: 85–90.
4 Birmingham DJ, Key MM, Tubich GE, Perone VB. Phototoxic bullae among celery harvesters. *Arch Dermatol* 1961; **83**: 73–87.

Berloque dermatitis (Fig. 58.19) [1–4]

Berloque dermatitis results from the potentiation of UV-stimulated melanogenesis by 5-methoxypsoralen (bergapten) in perfumes containing bergamot oil. There is wide variation in susceptibility, with the reaction occurring in only a small proportion of those exposed [1]. This variation depends on the readiness with which the bergapten is absorbed, the quantity applied, and the intensity and duration of exposure to UV light. Susceptibility is increased by stripping the horny layer. Hot humid conditions favour absorption. The pigmentation occurs in susceptible subjects who have been exposed to light after the application of perfume [2,3]. The distribution of the lesions is therefore variable but their configuration is usually distinctive. Deep-brown pigmentation follows the pattern formed by the trickle of the droplets of perfume over the skin from their points of application. The pigmentation fades after weeks or months. The condition is now much less frequent, although it is a continuing cosmetic problem [4].

References
1 Marzulli FN, Maibach HT. Perfume phototoxicity. *J Soc Cosmet Chem* 1970; **21**: 695–715.
2 Harber LC, Harris H, Leider M *et al*. Berloque dermatitis. *Arch Dermatol* 1964; **90**: 572–6.
3 Burdick KH. Phototoxicity of Shalimar perfume. *Arch Dermatol* 1966; **93**: 424–5.
4 Zaynoun ST, Aftimos BA, Tenekjian KK *et al*. Berloque dermatitis: a continuing cosmetic problem. *Contact Dermatitis* 1981; **7**: 111–6.



Fig. 58.19 Berloque dermatitis.

PUVA lentigines [1–5]

These pigmented macules are a common complication of PUVA therapy occurring on treatment-exposed areas [1–3]. There is a dose effect with a tendency to greater numbers of lentigines in those who have had more therapy [3]. They vary in appearance and may be numerous in number and small in size. Occasionally, larger irregular lentigines are seen, some with a stellate configuration [3] (Fig. 58.20). PUVA lentigines are usually permanent and show little tendency to remit. A less common clinical pattern is localization of lentigines to sites previously affected by psoriasis, creating an appearance not unlike a naevus spilus [2]. The histology is that of a lentigo. The melanocytes are hypertrophic and some may be cytologically atypical [3]. Similar melanocytic macules have been reported following use of a sunbed [4]. PUVA has also been reported to cause hyperpigmentation of the nails [5].

References

1 Miller RA. Psoralens and UV-A-induced stellate hyperpigmented freckling. *Arch Dermatol* 1982; **118**: 619–20.

2 Helland S, Bang G. Nevus spilus-like hyperpigmentation in psoriatic lesions during PUVA therapy. *Acta Derm Venereol (Stockh)* 1980; **60**: 81–3.

3 Rhodes AR, Stern RS, Melski JW. The PUVA lentigo: an analysis of predisposing factors. *J Invest Dermatol* 1983; **81**: 459–63.

4 Kadunce DP, Piepkorn MW, Zone JJ. Persistent melanocytic lesions associated with cosmetic tanning bed use: 'sunbed lentigines'. *J Am Acad Dermatol* 1990; **23**: 1029–31.

5 Naik RP, Parameswara YR. 8-Methoxypsoralen-induced nail pigmentation. *Int J Dermatol* 1982; **21**: 275–6.

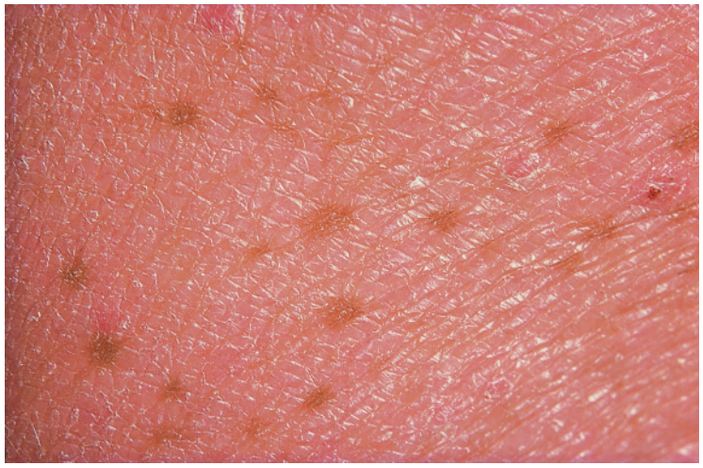


Fig. 58.20 Psoralen and UVA (PUVA)-induced freckles in a patient on long-term treatment.

Erythema dyschromicum perstans

Synonym
- Ashy dermatosis of Ramirez

This clinical syndrome of unknown origin was first reported by Ramirez of El Salvador in 1957 [1]. He initially used the term 'los cenicientos' (the ashen ones) for the ashy discoloration of the skin, but subsequently called this condition 'erythema dyschromicum perstans' [2]. It occurs in both sexes from childhood to old age, and is not uncommon in individuals of intermediate skin colour. Most published cases have been from Central America [3]. Histologically, the active border shows vacuolar degeneration of the basal cells. The epidermis contains much pigment and there is pigmentary incontinence; the dermal vessels are sleeved with an infiltrate of lymphocytes and histiocytes, and there are many melanophages [4]. Ultrastructural studies show vacuoles within the cytoplasm of basal and suprabasal keratinocytes that contain many melanosomal complexes. One study found IgM cytoid bodies on direct immunofluorescence [5].

Clinically, the condition is characterized by numerous macules of varying shades of grey with a red, slightly raised and palpably infiltrated margin. They vary in size and tend to coalesce over extensive areas of the trunk, limbs and face. Against the general greyish background are macules of hypomelanosis or hypermelanosis. The condition is persistent and slowly extends, but causes no symptoms. The pigmented macules resemble very closely the lesions of late pinta, but the negative dark-field examinations, negative serological tests for syphilis and lack of response to penicillin are important features that allow the dermatologist to exclude this treponematosis. There is no established therapy for this condition [6].

References

1 Ramirez CO. Los cenicientos, problemo clinico. In: *Memoria del Primer Congresso Centroamericano de Dermatologica.* San Salvador, 1957: 122–30.

2 Convit J, Kerdel-Vegas F, Rodriguez G. Erythema dyschromicum perstans: a hitherto undescribed skin disease. *J Invest Dermatol* 1961; **6**: 457–62.



Fig. 58.21 Melasma.

3 Ramirez CO. The ashy dermatoses (erythema dyschromicum perstans). *Cutis* 1967; **3**: 244–7.
4 Migagawa S, Komatsu M, Okuchi T *et al*. Erythema dyschromicum perstans: immunopathologic studies. *J Am Acad Dermatol* 1989; **20**: 882–6.
5 Person JR, Rogers RS. Ashy dermatosis. *Arch Dermatol* 1981; **117**: 701–4.
6 Novick NL, Phelps R. Erythema dyschromicum perstans. *Int J Dermatol* 1985; **24**: 630–3.

Facial melanoses

Hypermelanosis involving predominantly the face and the neck is relatively common and often presents a complex diagnostic problem. Several more or less well-defined clinical syndromes can be recognized, but many transitional forms defy classification. The causes of the pigmentation are often obscure.

Genetic and racial factors are important, the increased pigmentation occurring more frequently in those with dark skins, especially Oriental people. Endocrine factors play a major role in melasma and are implicated to some degree in other melanoses. External agents (light and photodynamic chemicals) are essential factors in the occupational melanoses but are also concerned in Riehl's melanosis, erythrosis and poikiloderma of Civatte. Other unknown factors are certainly implicated, and wide individual variation in susceptibility must be postulated.

Cosmetics may occasionally cause facial melanosis. Facial melanosis is, of course, also a conspicuous feature of Addisonian pigmentation.

Melasma (Figs 58.21 & 58.22)

Synonyms
- Mask of pregnancy
- Chloasma



Fig. 58.22 Melasma.

This common acquired hypermelanosis is seen mainly in women, and occurs mainly on sun-exposed skin on the face, only occasionally affecting the forearms. Many cases are attributed to pregnancy or the combined oral contraceptive pill. In the context of pregnancy melasma is regarded as a normal physiological change, along with darkening of the nipples and linea nigra. It is not uncommon at any time during the years of reproductive activity and has been attributed, without acceptable proof, to a variety of ovarian disorders. The rarity of melasma in post-menopausal women on oestrogen-containing hormone replacement therapy and the fact that men are occasionally affected suggests that oestrogen alone is not the causative agent. Despite light microscopic, ultrastructural and immunofluorescence studies, the condition remains an enigma [1]. An endocrine mechanism is postulated but the cause of melasma is unknown.

Clinical features. Hypermelanosis affects the upper lip, cheeks, forehead and chin and is more apparent following sun exposure. Affected skin is brown in colour. The pigmentary changes are usually bilateral and are frequently symmetrical. After pregnancy or after stopping oral contraceptives the condition may fade but is often persistent. Melasma-like hyperpigmentation has been reported from use of phenytoin or mephenytoin (hydantoins). Up to 10% of cases of melasma are seen in men, particularly Latin Americans and those from the Middle East or Asia.

Treatment. A variety of topical treatments are effective at lightening melasma [2–5], but these treatments should be combined with assiduous sun-protection measures if the reduced pigmentation is to be maintained.

References

1 Sanchez NP, Pathak MA, Sato S *et al*. Melasma: a clinical, light microscopic, ultrastructural and immunofluorescence study. *J Am Acad Dermatol* 1981; **4**: 698–710.
2 Pathak MA, Fitzpatrick TB, Kraus EW. Usefulness of retinoic acid in the treatment of melasma. *J Am Acad Dermatol* 1986; **15**: 894–9.
3 Grimes PE. Melasma: etiologic and therapeutic considerations. *Arch Dermatol* 1995; **131**: 1453–7.

4 Jimbow K. *N*-Acetyl-4-*S*-cysteaminylphenol as a new type of depigmenting agent for the melanoderma of patients with melasma. *Arch Dermatol* 1991; **127**: 1928–34.
5 Breathnach AS. Melanin hyperpigmentation of skin: melasma, topical treatment with azelaic acid and other therapies. *Cutis* 1996; **57**: 36–45.

Riehl's melanosis

Synonyms
- Melanodermatitis toxica
- Pigmented cosmetic dermatitis

Background. A distinctive pattern of grey-brown facial pigmentation was first described by Riehl in Vienna between 1916 and 1920 [1]. Riehl attributed this pigmentation to contact with noxious substances or to wartime living conditions. It was subsequently seen in Europe and Asia during and after the Second World War and has also occurred in Argentina [2] and in the South African Bantu [3]. The condition is more frequent in women, and tar derivatives and fragrances are suspected to be the cause [4]. An outbreak of Riehl's melanosis in Japan was attributed to contact dermatitis to cosmetic ingredients and prompted the phrase 'pigmented cosmetic dermatitis' for this condition [5].

Histopathology. In the early stages there is liquefaction degeneration of the basal layer of the epidermis and a perivascular or band-like dermal infiltrate with pigmentary incontinence. Later, the epidermis appears normal but many melanophages are present in the upper dermis [6]. Ultrastructural studies show intercellular and intracellular oedema of keratinocytes and a multilayered basal lamina, as well as many melanophages in the dermis [6].

Course, prognosis and treatment. Brownish-grey pigmentation develops quite rapidly over the greater part of the face but is more intense on the forehead and temples. Smaller pigmented macules, often perifollicular, lie beyond the indefinite margin. The pigmentation may extend to the chest, neck and scalp, and occasionally involves hands and forearms. Horny plugs fill the follicles and there may be some scaling. Where a contact cause can be identified and avoided, there follows a slow improvement over many months.

References

1 Riehl G. Über eine eigenartige Melanose. *Wien Klin Wochenschr* 1917; **30**: 780–1.
2 Peirini LE. Melanosis de Riehl. *Arch Argent Dermatol* 1952; **2**: 315.
3 Findlay GH. Some observations on melanosis of Riehl. *S Afr Med J* 1952; **26**: 373–5.
4 Serrano G, Pujol C, Cuadra J, Aliaga A. Riehl's melanosis: pigmented contact dermatitis caused by fragrances. *J Am Acad Dermatol* 1989; **21**: 1057–60.
5 Nakayama H, Harada R, Toda M. Pigmented cosmetic dermatitis. *Int J Dermatol* 1976; **15**: 673–5.
6 Nagao S, Iijima S. Light and electron microscopic study of Riehl's melanosis. *J Cutan Pathol* 1974; **1**: 165–75.

Poikiloderma of Civatte (Fig. 58.23) [1]

Background. This characteristic pattern of reticulate hyperpigmentation of the face and neck was first reported in 1923 by Civatte [1].



Fig. 58.23 Poikiloderma of Civatte on side of neck.

Clinical features. It tends to occur in women aged 30–50. Poikilodermatous changes develop on the sides of the neck with hyperpigmentation, telangiectasia and dermal atrophy. The submandibular and submental areas are spared thus implicating sunlight in the pathogenesis of this condition. Milder forms are common and few patients seek medical advice.

Treatment. Laser therapy with the tuneable dye laser may be effective but care is needed as it may also cause scarring and may even worsen the appearance [2]. Photoprotection with a high SPF sunscreen may help prevent disease progression.

References

1 Civatte A. Poikilodermie reticule pigmentaire du visage et du col. *Ann Dermatol Syphilol (Paris)* 1923; **6**: 605–20.
2 Wheeland RG, Applebaum J. Flashlamp-pumped pulsed dye laser therapy for poikiloderma of Civatte. *J Dermatol Surg Oncol* 1990; **16**: 12–6.

Pigmented peribuccal pigmentation of Brocq

Background. It was Brocq in 1923 who first reported a case of perioral hyperpigmentation in a clinical pattern that now bears his name [1].

Clinical features. This syndrome occurs predominantly in middle-aged women and has rarely been reported in men. A photodynamic substance in cosmetics is probably responsible. Diffuse brownish-red pigmentation develops symmetrically around the mouth but spares a narrow perioral ring. It may extend up the centre of the face to the forehead and in some cases there are well-defined patches of pigmentation over the angles of the jaw and the temples. The erythematous component, and hence the intensity of the pigmentation, may fluctuate over short periods. The pigmentation is usually persistent but tends gradually to fade if the cause is eliminated. A similar post-inflammatory hyperpigmentation is seen in some patients with perioral dermatitis and may be the result of topical steroid therapy [2].



(a) (b)

Fig. 58.24 Mongolian spot: (a) extensive blue coloration on the back of an oriental child; (b) involvement of the legs in the same child.

References
1 Brocq JL. L'eryththrose pigmentée péri-buccale. *Presse Med* 1923; **31**: 720–8.
2 Allen BR, Hunter JAA. Abnormal facial pigmentation associated with the prolonged use of topical corticosteroids. *Scott Med J* 1975; **20**: 277.

Erythromelanosis follicularis of the face and neck

This syndrome, of unknown origin, was originally described in Japan by Kitamura [1]. Affected individuals are usually young or middle-aged males [2,3] although it has also been reported in adult females [4]. Histologically, there is slight hyperkeratosis. The hair follicles are enlarged and contain lamellar horny masses. The sebaceous glands are also enlarged. The epidermis overlying the affected follicle is flattened and contains excess melanin. In the dermis, an inconspicuous lymphocytic infiltrate surrounds dilated vessels.

The clinical picture is distinctive. A background of reddish-brown pigmentation with telangiectasia is studded with pale follicular papules. The hairs are lost from the majority of affected follicles in the vellus region, but less conspicuously from the terminal hair of scalp or beard. The pigmentation involves the skin in front of, beneath and behind the ear, extending to the side of the neck. It spreads slowly, is persistent and is not influenced by treatment. The distribution and lack of clinical follicular keratosis or scarring readily distinguish erythromelanosis from the various forms of keratosis pilaris and from other facial melanoses.

References
1 Kitamura K, Kato H, Mishima Y *et al*. Erythromelanosis follicularis faciei. *Hautarzt* 1960; **11**: 391–3.
2 Watt TL, Kaiser JS. Erythromelanosis follicularis faciei et colli. *J Am Acad Dermatol* 1981; **5**: 533–4.
3 Anderson BL. Erythromelanosis follicularis faciei et colli. *Br J Dermatol* 1980; **102**: 323–5.
4 Warren FM, Davis LS. Erythromelanosis follicularis faciei in women. *J Am Acad Dermatol* 1995; **32**: 863–6.

Dermal melanocytosis

Synonym
- Ceruloderma

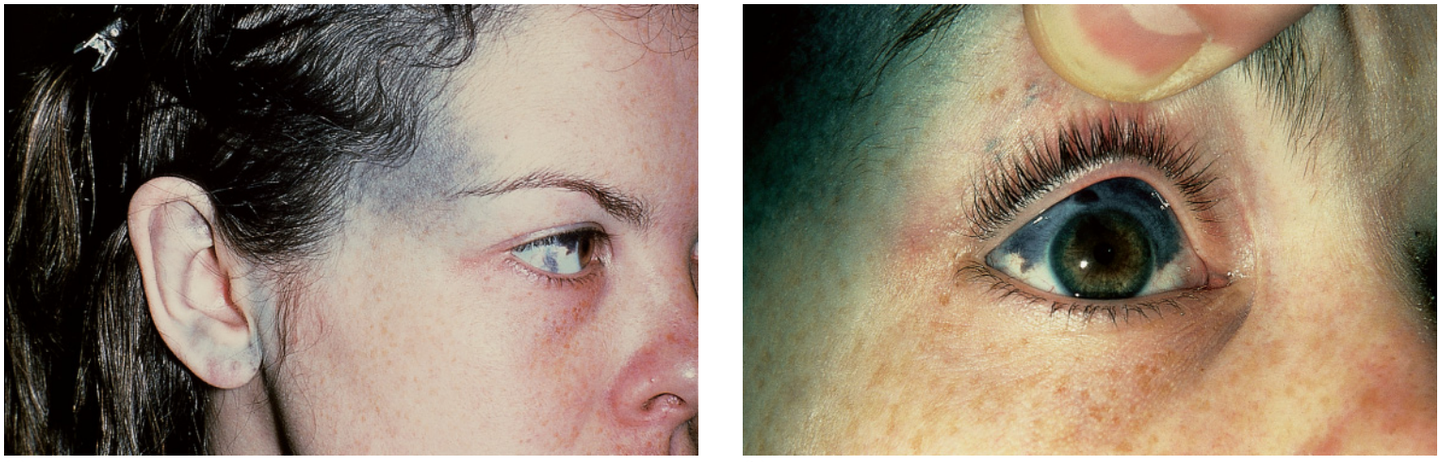
Hyperpigmentation of the skin may be due to the presence of functional fusiform and dendritic melanocytes that lie in the dermis [1]. Although dermal melanocytes are common in other mammals, they are not often seen in humans. These cells have failed to reach their proper location in the basal layer of the epidermis in their migration from the neural crest of the developing embryo. Several conditions are grouped under the term 'dermal melanocytosis'. In all of them, the affected areas have a slate-brown or blue colour (ceruloderma) due to an optical effect from the pigment lying in the dermis.

Mongolian spot (Fig. 58.24) [1–4]

Mongolian blue spots are seen in 90% of Oriental babies and less frequently in black babies. The usual site of involvement is the lumbosacral region. The spots are poorly circumscribed areas of slate-brown or blue-black pigmentation that are sometimes extensive and may be mistaken for bruises. A case of generalized dermal melanocytosis of the newborn has been described [2]. Mongolian blue spots usually fade in early childhood, although the aberrant extrasacral spots can persist [3]. Very extensive Mongolian blue spots may regress more slowly, and some areas may persist indefinitely. The dermal melanocytes in persistent Mongolian spots have an extracellular sheath [4], as also seen in the naevus of Ito. The aetiology of this birthmark is unknown.

Naevus of Ota

Synonyms
- Nevus fuscocaeruleus ophthalmomaxillaris
- Oculodermal melanocytosis



(a) (b)

Fig. 58.25 (a) Naevus of Ota in a white subject. (b) Marked blue coloration of the sclera in the same patient.

Naevus of Ota was first described by the Japanese dermatologist Ota in 1939 [5]. The hyperpigmentation affects one side of the face in the area supplied by the ophthalmic and maxillary divisions of the trigeminal nerve [6,7]. Occasionally, it is bilateral. It is usually congenital but may appear later in life. It is more prevalent in the Japanese but is observed in other races. The colour is variable, but is usually either slate-brown or blue. The sclera is involved and there may be hyperpigmentation of the cornea, iris, retina, ocular muscles and orbit [8] (Fig. 58.25). Sometimes, there is pigmentation of the hard palate. An ipsilateral sensorineural deafness occurring in a patient with naevus of Ota has been reported [9].

Naevus of Ota does not improve with time. Malignant change in the cutaneous lesions of naevus of Ota is extremely rare. However, melanomas are more common in the choroid, iris, orbit and brain of these patients [10]. A bilateral, acquired dermal melanosis of the face resembling naevus of Ota has been described [11]. Promising results with the Q-switch ruby laser have been reported in the treatment of naevus of Ota, with multiple treatments increasing the response rate [12].

Naevus of Ito (Fig. 58.26) [4,12,13]

In this condition, the increased pigmentation affects the area supplied by the posterior supraclavicular and lateral brachial cutaneous nerves. It is relatively common in the Japanese.



Fig. 58.26 Naevus of Ito.

Blue naevus

These commonly occur on or near the dorsa of hands and feet, usually early in life. Malignant transformation does not occur in the common blue naevus. However, the cellular blue naevus may rarely undergo malignant change.

References

1 Dorsey CS, Montgomery H. Blue nevus and its distinction from Mongolian spot and the nevus of Ota. *J Invest Dermatol* 1954; **22**: 225–36.

2 Bashiti HM, Blair JD, Triska RA, Keller L. Generalized dermal melanocytosis. *Arch Dermatol* 1981; **117**: 791–3.

3 Hidano A. Persistent Mongolian spot in the adult. *Arch Dermatol* 1971; **103**: 680–1.

4 Okawa Y, Yokota R, Yamauchi A. On the extracellular sheath of dermal melanocyte in nevus fuscoceruleus acromiodeltoideus (Ito) and mongolian spot. *J Invest Dermatol* 1979; **73**: 224–30.

5 Ota M, Tanino H. The naevus fusco-caeruleus opthalmomaxillaris and its relationship to pigmentary changes in the eye. *Jikeikai Med J* 1939; **63**: 1243–4.

6 Hidano A, Kajima H, Ikeda S *et al*. Natural history of nevus of Ota. *Arch Dermatol* 1967; **95**: 187–95.

7 Mishima Y, Mevorah B. Nevus Ota and nevus Ito in American Negroes. *J Invest Dermatol* 1961; **36**: 133–54.

8 Cowan TH, Balistocky M. The nevus of Ota or oculodermal melanocytosis. *Arch Ophthalmol* 1961; **65**: 483–92.

9 Reed WB, Sugarman Gi. Unilateral nevus of Ota with sensorineural deafness. *Arch Dermatol* 1974; **109**: 881–3.

10 Enriquez R, Egbert B, Bullock J. Primary malignant melanoma of the central nervous system. *Arch Pathol* 1973; **95**: 392–5.

11 Hori Y, Kawashima M, Oohara K, Kukita A. Acquired bilateral nevus of Ota-like macules. *J Am Acad Dermatol* 1984; **10**: 961–4.

12 Waatanabe S, Takahashi H. Treatment of nevus of Ota with the Q-switch ruby laser. *N Engl J Med* 1994; **331**: 1745–50.

13 Ito M. Studies on melanin XXII. Nevus fusco-ceruleus acromiodeltoideus. *Tohoku J Exp Med* 1954; **60**: 10.

Table 58.5 Hypermelanosis due to genetic and naevoid factors.

Brown colour	Grey, slate or blue colour
Ephelides (freckles)	Mongolian spot
Lentigines	Naevus of Ota
Multiple lentigines syndrome	Naevus of Ito
Peutz–Jeghers syndrome	Blue naevus
Café-au-lait and freckle-like macules in neurofibromatosis	Diffuse melanocytosis
	Incontinentia pigmenti (Bloch–Sulzberger syndrome)
Melanotic macules in Albright's syndrome	Naegeli–Franceschetti–Jadassohn syndrome
Acanthosis nigricans, juvenile type	
Xeroderma pigmentosum	
Fanconi's syndrome	
Dyskeratosis congenita	
Familial progressive hyperpigmentation	

Table 58.6 Acquired hypermelanosis.

Causative factor	Brown	Grey, slate or blue
Metabolic	Liver disease	Haemochromatosis
	Haemochromatosis, hepatolenticular degeneration, biliary cirrhosis	
	Porphyria	
	Porphyria cutanea tarda and variegata, erythropoietic (congenital) porphyria	
Endocrine	ACTH and MSH-producing pituitary and other tumours	
	Addison's disease	
	ACTH therapy	
	Pregnancy	
	Contraceptive pill and oestrogens	
	Melasma (chloasma)	
Chemical	Arsenic	Minocycline
	Busulfan, bleomycin, cyclophosphamide	Fixed drug eruptions, barbiturates, phenolphthalein
	Adriamycin	Phenothiazines
	Psoralens	Chlorpromazine
	Berloque dermatitis	
	Phytophotodermatitis	
Physical	UV light, ionizing radiation, trauma	
Nutritional	Kwashiorkor	Chronic nutritional deficiency
	Pellagra	
	Sprue	
	Vitamin B_{12} deficiency	
Post-inflammatory	Eczema	Pinta
	Lichen planus, lupus erythematosus	Erythema dyschromicum perstans
	Lichen and macular amyloidosis	
	Systemic sclerosis, morphoea	
Tumours	Malignant melanoma	Metastatic melanoma with melanogenuria
	Acanthosis nigricans with adenocarcinoma	
	Malignant tumours	

ACTH, adrenocorticotrophic hormone; MSH, melanocyte-stimulating hormone.

Disseminated dermal melanocytosis [1]

Progressive dermal melanocytosis has been described in a patient who developed profuse, bluish, bruise-like spots in childhood. The woman died in the fifth decade from melanoma.

Reference

1 Levene A. Disseminated dermal melanocytosis terminating in melanoma. *Br J Dermatol* 1979; **101**: 197–205.

Hypermelanosis associated with other cutaneous lesions

Hypermelanosis is a characteristic feature of urticaria pigmentosa but the mechanism of its production is unknown. Tyrosinase-positive cells have been found in the upper dermis in some cases. In the childhood type, the light-brown macules often exceed 2 cm in diameter and the lesions are frequently nodular. In the adult types, the smaller and more numerous macules are purplish-brown in colour and not palpably infiltrated, and often fail to urticate on friction. They are usually widely distributed over the trunk and limbs.

The differential diagnosis of hypermelanosis

The very large number of conditions associated with widespread or localized hypermelanosis cannot readily be classified. The present classification is based on the colour of the skin and on various causative factors. The hypermelanosis may be due to genetic and naevoid factors (Table 58.5) or it is acquired and due to a variety of factors (Table 58.6).

The areas of hypermelanosis may be circumscribed or may be diffuse with intensification of the normal pattern of pigmentation. Hypermelanosis confined to the face and neck is considered on pp. 58.34–58.35. In acquired, circumscribed patches of hypermelanosis, a post-inflammatory origin should be considered (see p. 58.30).

Treatment of hypermelanosis

Hypermelanosis, particularly affecting areas on the face, can be the cause of marked cosmetic disability and give rise to much mental distress. Treatment depends essentially on establishing the cause and if possible reversing the conditions that have given rise to the hypermelanosis. In the majority of cases, topical therapy has no place, although some who are perturbed about their cosmetic disability will demand treatment with a skin-bleaching preparation. Because in many cases exposure to sunlight intensifies the pigmentation, a photoprotective preparation should be prescribed and applied during sunny weather. Cosmetic camouflage may also be indicated.

A number of compounds have been used in skin-bleaching preparations and of these hydroquinone is the most safe. Preparations containing 2% hydroquinone, although not very effective,

are of help in producing cutaneous depigmentation [1]. Although higher concentrations of hydroquinone are more potent, these preparations frequently irritate the skin and may produce, if used for long periods of time, an exogenous ochronosis and pigmented colloid milium [2,3]. A formulation of hydroquinone and retinoic acid has some effect in depigmenting human skin and is of use in the treatment of hypermelanotic conditions such as melasma [4–6]. It is not very effective for post-inflammatory hyperpigmentation. Topical tretinoin has been found to be effective in the treatment of actinic lentigines ('liver spots') in photodamaged skin [7] and also improves melasma [8]. The monobenzylether of hydroquinone is responsible for many therapeutic and cosmetic disasters and the compound should be used only to bleach away the remaining pigmented areas in patients with extensive vitiligo [9]. Several other substituted phenols, such as 4-isopropylcatechol, can produce cutaneous depigmentation; however, this compound and others are irritant and may produce sensitization [10].

References

1 Fitzpatrick TB, Arndt KA, El Mofty AM *et al*. Hydroquinone and psoralens in the therapy of hypermelanosis and vitiligo. *Arch Dermatol* 1966; **93**: 589–600.
2 Findlay GH, Morrison JGL, Simson IW. Exogenous ochronosis and pigmented colloid milium from hydroquinone bleaching creams. *Br J Dermatol* 1975; **93**: 613–22.
3 Hoshaw RA, Zimmerman KG, Menter A. Ochronosis-like pigmentation from hydroquinone bleaching cream in American Blacks. *Arch Dermatol* 1985; **121**: 105–8.
4 Bleehen SS. Skin bleaching preparations. *J Soc Cosmet Chem* 1977; **28**: 407–12.
5 Engasser PG, Maibach HI. Cosmetics and dermatology: bleaching creams. *J Am Acad Dermatol* 1981; **5**: 143–7.
6 Kligman AM, Willis I. A new formula for depigmenting human skin. *Arch Dermatol* 1975; **111**: 40–8.
7 Rafal ES, Griffiths CEM, Ditre CM. Topical tretinoin (retinoic acid) treatment for liver spots associated with photodamage. *N Engl J Med* 1992; **326**: 368–74.
8 Griffiths CE, Finkel LT, Ditre CM *et al*. Topical tretinoin (retinoic acid) improves melasma: a vehicle controlled clinical trial. *Br J Dermatol* 1993; **129**: 415–21.
9 Mosher DB, Parrish JA, Fitzpatrick TB. Monobenzylether of hydroquinone. *Br J Dermatol* 1977; **97**: 669–79.
10 Bleehen SS. The treatment of hypermelanosis with 4-isopropyl-catechol. *Br J Dermatol* 1976; **94**: 687–94.

Hypomelanosis

Genetic and naevoid disorders

A number of genetically determined or naevoid conditions are characterized by localized and/or generalized hypomelanosis of the skin. These are listed in Table 58.7.

Albinism [1–9]

There are many distinct types of oculocutaneous albinism (OCA), each of which is characterized by partial or complete failure to produce melanin in the skin and the eyes. The classification is rapidly changing with the advent of advances in molecular genetics (e.g. rufous OCA is now *TRP-1* gene-related OCA or type III OCA). Melanocytes are present in normal distribution but fail to synthesize melanin adequately. These conditions are inherited as autosomal recessive disorders; one rare type with apparent autosomal dominant inheritance is now felt to be due to quasi-dominant pedigree patterns or to partial expression of OCA II in OCA I heterozygotes (Table 58.7). The gene encoding tyrosinase has been localized to chromosome 11 [2] and many different mutations are now recognized for OCA [3]. The gene for type II OCA has been mapped to chromosome 15q11.13 [4]. Tyrosinase-negative albinism is characterized by hair bulbs that, after plucking and incubation with tyrosine, fail to produce darkening. In tyrosinase-positive albinism, the hair bulbs do darken in this test and the precise metabolic defects have yet to be ascertained. The tyrosinase-positive types are the most common. Ultrastructural studies of skin and hair show that in tyrosinase-negative albinos most of the melanosomes are stage 1 and stage 2 without any melanization. Other types may show melanosomes up to stage 3 of their development.

In ocular albinism, only the eyes are clinically involved, although careful investigation of the melanocytes in the skin does show some changes. There are four different types, two X-linked, one dominant and one recessive. Carrier females of the X-linked types may show irregular retinal pigmentation. In two types there is an associated deafness, the melanocytes apparently failing to play a protective role in the ear. In most albinos this defect leads to little or no change in ear function.

Table 58.7 Hypomelanosis due to genetic and naevoid factors (MIM numbers in parentheses).

Oculocutaneous albinism (OCA)	
Tyrosinase negative (type IA, #203100)	Recessive
Yellow mutant (type IB, #606952)	Recessive
Temperature sensitive (type 1TS; included in IB #606952)	Recessive
Tyrosinase positive (type II, *203200)	Recessive
Brown	Recessive*
Minimal pigment (203280)	Recessive
Platinum	Recessive†
TRP-1 gene-related (type III) (was rufous OCA, #278400)	Recessive
Hermansky–Pudlak syndrome (203300)	Recessive
Chédiak–Higashi syndrome (#214500)	Recessive
Autosomal dominant	Dominant‡
Ocular albinism	X-linked
With deafness	X-linked, recessive, dominant
Albinoidism (*126070)	Dominant§
Cross syndrome (*257800)	Recessive
Piebaldism (#172800)	Dominant
Waardenburg syndrome (#193150, #193510)	Dominant
Phenylketonuria (*261200)	Recessive
Vitiligo	Polygenic
Tuberous sclerosis (#191100)	Dominant
Achromic naevus	
Incontinentia pigmenti achromians	

* Brown OCA is currently included as a type of OCA II.
† Platinum OCA may be an allelic variant of minimal pigment OCA.
‡ Dominant OCA probably does not exist: instances appear to be due to quasidominant pedigree patterns or to partial expression of albinism II in OCA I heterozygotes.
§ The term 'albinoidism' is applied to both pigmentary dilution (MIM *126070) and OCA II.



(a)



(b)

Fig. 58.27 (a) Tyrosinase-positive oculocutaneous albinism in a black woman aged 40 years. (b) Dark-brown freckles on light-exposed areas.

Incidence. Albinism is found in all races and the prevalence varies considerably. In the UK, the incidence is estimated at 1 in 20 000. In the USA, the incidence of albinism is estimated at 1 in 39 000 in Caucasians and 1 in 28 000 in Afro-Caribbeans. In some countries it is more common, particularly where there is a tendency towards inbreeding and especially in isolated communities. The Cuna tribe on the San Blas islands off the coast of Panama have the highest incidence of albinism in the world (63 per 10 000). In Nigeria, the incidence of albinism is much higher in the south [5]. There are no adequate studies of the incidence of the different genotypes of OCA in the different races.

Clinical features. In all races there is marked dilution of the pigmentation of the skin, hair and eyes. In tyrosinase-negative OCA the skin is pink in colour, the hair is white and the patients show a prominent red reflex. This is the most severe variant of OCA.

In tyrosinase-positive OCA, some pigment is formed and with increasing age is to be found in the iris, skin and hair, the latter often developing a flaxen-yellow colour. These patients may also tan and in black people the skin has a yellowish-brown colour that with age develops dark-brown freckles, particularly in sun-exposed areas (Fig. 58.27). Also in this type, the iris is less translucent and in black people may be brown in colour.

In both types, patients have photophobia; often they have a characteristic facial expression due to apparent squinting. Errors of refraction are common, especially in the tyrosinase-negative type (OCA IA), and almost all patients have horizontal or rotatory nystagmus, sometimes with head nodding. In the tyrosinase-positive type, visual acuity may improve as patients get older and they may have less severe nystagmus [6]. There are abnormalities of the optic pathway. Foveal hypoplasia occurs in the tyrosinase-negative type [6].

In the yellow mutant type of albinism, the newborn resembles the tyrosinase-negative type, but by the age of 1 year the hair is yellow-red in colour. Hair bulbs incubated in tyrosine plus cysteine produce an intensification of the yellow-red pheomelanin. This type of albinism is prevalent in the Amish communities in the USA [7].

The other types of albinism listed in Table 58.7 have pigment changes described by their names. Each has a rather distinctive racial predisposition.

In temperate climates, the prognosis for the albino is good, the visual defects constituting the greatest disability. In the tropics the fate of albinos is grim. At an early age [8] most of them develop in solar-exposed skin many actinic keratoses, squamous cell carcinomas and, occasionally, melanomas. Some die young from these tumours [5].

Treatment. No treatment is possible other than prescribing photoprotective preparations and limiting sun exposure, vigorous enforcement of which from early childhood can be very helpful. The regular examination of all albinos for the early detection and treatment of premalignant and malignant conditions of the skin is

advisable, especially in the tropics. Prenatal diagnosis of albinism has been reported [9].

References

1 Bolognia JL, Pawelek JM. Biology of hypopigmentation. *J Am Acad Dermatol* 1988; **19**: 217–55.
2 Barton DE, Kwon BS, Francke U. Human tyrosinase gene, mapped to chromosome 11 (q14–q21), defines second region of homology with mouse chromosome 7. *Genomics* 1988; **3**: 17–24.
3 Tomita Y. Tyrosinase gene mutations causing oculocutaneous albinisms. *J Invest Dermatol* 1993; **100**: 1865–905.
4 Ramsay M, Colman M-A, Stevens G *et al*. The tyrosinase-positive oculocutaneous albinism locus maps to chromosome 15q11.2–q12. *Am J Hum Genet* 1992; **51**: 879–84.
5 Okoro AN. Albinism in Nigeria. *Br J Dermatol* 1975; **92**: 485–92.
6 Mietz H, Green WR, Wolf SM, Abundo GP. Foveal hypoplasia in complete oculocutaneous albinism: a histopathologic study. *Retina* 1992; **12**: 254–60.
7 King RA, Witkop CJ. Hair-bulb tyrosinase activity in oculocutaneous albinism. *Nature* 1976; **263**: 69–71.
8 Lookingbill DP, Lookingbill GL, Leppard B. Actinic damage and skin cancer in albinos in northern Tanzania: findings in 164 patients enrolled in an outreach skin care program. *J Am Acad Dermatol* 1995; **32**: 653–8.
9 Eady RAJ, Gunner DB, Garner A, Rodeck CH. Prenatal diagnosis of oculocutaneous albinism by electron microscopy of fetal skin. *J Invest Dermatol* 1983; **80**: 210–2.

Albinoidism (MIM *126070)

Albinoidism is the name applied to families where there is some partial defect in melanin production in the skin but only minimal changes in the eyes. The biochemical basis of this is uncertain. Several families are described with this type of albinism [1,2]. Although there is hypopigmentation of the skin and hair, it is not as marked as in OCA. Slight tanning is reported and the hair-bulb test is positive. A diffuse punctate pattern of iris transillumination is seen. The eyes are usually normal, but there may be photophobia. In one large Swiss pedigree there was high-grade myopia [2]. The condition appears to have autosomal dominant inheritance, but in some families it is recessive.

References

1 Bergsma DR, Kaiser-Kupfer M. A new form of albinism. *Am J Ophthalmol* 1974; **77**: 837–44.
2 Busti-Rosner L. Deux cas d'albinisme universel incomplet (albinoidisme) d'un biotype particulier dans une souche valaisanne. *J Génét Hum* 1956; **5**: 197–215.

Hermansky–Pudlak syndrome (MIM #203300)

Hermansky–Pudlak syndrome is a rare type of OCA associated with a haemorrhagic diathesis [1]. About 250 cases have been reported, most of whom are from Puerto Rico or the south of the Netherlands [1]. Two different mutations in the gene for Hermansky–Pudlak syndrome have been identified. Tyrosinase-positive OCA occurs in association with a bleeding tendency and deposits of a ceroid-like pigment in the cells of the reticuloendothelial system [2]. The bleeding tendency is attributed to a storage-pool platelet defect. The platelets have decreased numbers of dense granules and reduced levels of serotonin and ADP [3]. Pulmonary fibrosis, granulomatous colitis and lupus nephritis have been associated [4]. There is no defect in circulating lymphocytes or neutrophils [5]. Two cases of Hermansky–Pudlak syndrome have been complicated by systemic lupus erythematosus [6].

References

1 Hermansky F, Pudlak P. Albinism associated with a haemorrhagic diathesis and unusual pigmented reticular cells in the bone marrow. *Blood* 1959; **14**: 162–9.
2 Shanahan F, Randolph L, King R *et al*. Hermansky–Pudlak syndrome: an immunologic assessment of 15 cases. *Am J Med* 1988; **85**: 823–8.
3 Garay SM, Gardella JE, Fazzini EP, Goldring RM. Hermansky–Pudlak syndrome. Pulmonary manifestations of a ceroid storage disease. *Am J Med* 1979; **66**: 737–47.
4 Schinella RA, Greco MA, Colbert BL *et al*. Hermansky–Pudlak syndrome with granulomatous colitis. *Ann Intern Med* 1980; **92**: 20–3.
5 Schachne JP, Glaser N, Lee S *et al*. Hermansky–Pudlak syndrome: case report and clinicopathologic review. *J Am Acad Dermatol* 1990; **22**: 926–32.
6 Mitsui H, Komine M, Watanabe T *et al*. Does Hermansky–Pudlak syndrome predispose to systemic lupus erythematosus? *Br J Dermatol* 2002; **146**: 908–11.

Chédiak–Higashi syndrome (MIM #214500)

Chédiak–Higashi syndrome is a rare, autosomal recessive disorder characterized by hypopigmentation of the skin and eye [1]. The skin is fair, the retinae are pale and the irides translucent. The hair is light blonde or silvery grey. These children are very susceptible to bacterial and viral infections, and intractable respiratory and cutaneous infections usually prove fatal before the age of 10 years. Longer survival is possible but later the lymph nodes, spleen and liver are enlarged and a malignant lymphoma develops. A similar condition is seen in Aleutian mink [2], Hereford cattle [3] and the beige mouse [4].

The hereditary defect concerns membrane-bound organelles of various cell types and is due to mutations in a gene encoding a protein known as lysosomal trafficking regulator. The melanocytes contain giant pigment granules (Fig. 58.28), which arise by autophagocytosis and fusion of large melanosomes that show degradative changes within the cells [5]. Similar defects of granules and other organelles occur in white cells and platelets. Cytoplasmic inclusions are present in a variety of cells of neuroectodermal origin. The white cells are defective in combating infection and if children with this condition survive infancy, they usually die later from a malignant lymphoma.

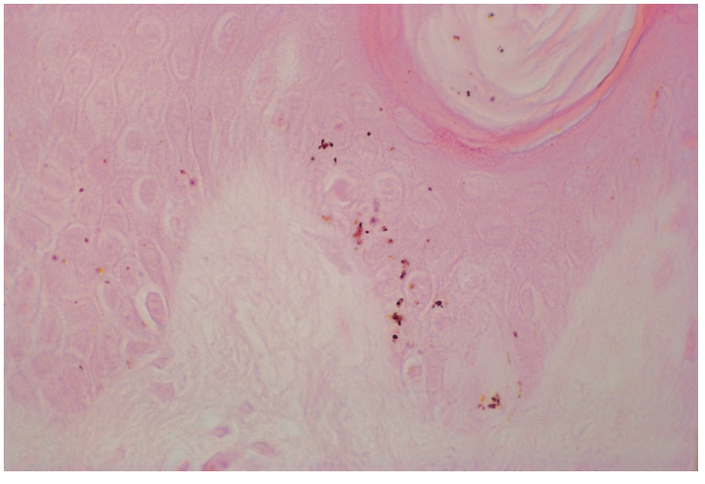


Fig. 58.28 Chédiak–Higashi syndrome. Large pigment granules in the epidermis as seen by light microscopy. Fontana stain, × 40.

References
1 Blume RS, Wolff SM. The Chediak–Higashi syndrome: studies in four patients and a review of the literature. *Medicine (Baltimore)* 1972; **51**: 247–80.
2 Windhorst DB, Zelickson AS, Good RA. A human pigmentary dilution based on a heritable subcellular structural defect. *J Invest Dermatol* 1968; **50**: 9–18.
3 Padgett GA, Reiquam CW, Gorham JR *et al*. Comparative studies of the Chediak–Higashi syndrome. *Am J Pathol* 1967; **51**: 553–71.
4 Lutzner MA, Lowrie CT, Jordan HW. Giant granules in leukocytes of the beige mouse. *J Hered* 1967; **58**: 299–300.
5 Zelickson AS, Windhorst DB, White JG, Good RA. The Chediak–Higashi syndrome: formation of giant melanosomes and the basis for hypopigmentation. *J Invest Dermatol* 1967; **49**: 575–81.

Griscelli syndromes type I (MIM #214450) and type II (MIM #607624)

Griscelli syndrome type I comprises partial albinism with neurological deficiency due to mutations in the myosin type V gene.

Griscelli syndrome type II, due to mutations in the *RAB27A* gene, combines partial albinism and immunodeficiency [1], but is distinct from Chédiak–Higashi syndrome. It is inherited as an autosomal recessive condition. In addition to pigmentary dilution, there is immune deficiency and the affected children are prone to recurrent pyogenic infection. There is hypogammaglobulinaemia and defective cell-mediated immunity with lymphohistiocytosis and haematophagocytosis.

Reference
1 Griscelli C, Durandy A, Guy-Grand D *et al*. A syndrome associating partial albinism and immunodeficiency. *Am J Med* 1978; **65**: 691–702.

Prader–Willi syndrome (MIM #176270) and Angelman syndrome (MIM #105830) [1]

Both syndromes are associated with mental retardation, abnormal behaviour and hypopigmentation. In both there are deletions of the same region of chromosome 15, with deletion on the paternal chromosome in Prader–Willi syndrome and the maternal in Angelman syndrome.

Reference
1 Kirkilionis AJ, Chudley AE, Gregory CA, Hamerton JL. Molecular and clinical overlap of Angelman and Prader–Willi syndrome phenotypes. *Am J Med Genet* 1991; **40**: 454–9.

Cross' syndrome (MIM *257800)

Synonym
- Oculocerebral syndrome with hypopigmentation

Cross' syndrome is one of the 'silvery hair' syndromes and is characterized by generalized hypopigmentation associated with ocular anomalies, mental and physical retardation, ataxia and spasticity [1]. It is probably determined by an autosomal recessive gene [2,3]. The pigmentary and ocular defects are manifest from birth. The hypopigmentation resembles albinism; blood tyrosine levels are normal and the light-coloured hair pigments poorly in tyrosine solution. The ocular defects include microphthalmos, a small opaque cornea and coarse nystagmus. Spasticity soon becomes evident, and physical and mental development is retarded [3].

References
1 Cross HE, McKusick VA, Breen W. A new oculocerebral syndrome with hypopigmentation. *J Pediatr* 1967; **70**: 398–406.
2 Lerone M, Pessagno A, Taccone A *et al*. Oculocerebral syndrome with hypopigmentation (Cross syndrome): report of a new case. *Clin Genet* 1992; **41**: 87–9.
3 Tezcan I, Demir E, Asan E *et al*. A new case of oculocerebral hypopigmentation syndrome (Cross syndrome) with additional findings. *Clin Genet* 1997; **51**: 118–21.

Piebaldism (MIM #172800) [1–11]

Piebaldism is a rare autosomal dominant condition characterized by stable areas of vitiligo-like amelanotic skin associated with a white forelock [2,3]. The incidence of piebaldism is estimated at less than 1 in 20 000. Both sexes are affected equally, and no race is spared. A similar condition of 'white spotting' is seen in mice and results from deletion or mutation of the c-*kit* proto-oncogene that codes for an embryonic growth factor called Steel factor [4]. Missense and frameshift mutations of the *kit* proto-oncogene, which encodes the cellular receptor tyrosine kinase for the mast cell/stem cell growth factor, are responsible for a range of phenotypes with piebaldism [5,6].

The plurality of defects revealed by electron microscopy suggests that a number of different gene loci are concerned. Ultrastructural studies have shown either an absence of melanocytes and melanosomes in the hypomelanotic areas or sometimes reduced numbers of abnormal large melanocytes. In the hypermelanotic islands in the areas of hypomelanosis, melanocytes are present that produce normal melanosomes but also abnormal spherical and granular melanosomes [9]. When transferred to the keratinocytes, these show abnormal degradation and fusion.

Clinical features. Patches of skin totally devoid of pigment are present at birth and usually remain unchanged throughout life. Most common is a frontal median or paramedian patch, associated with a mesh of white hair (white forelock); rarely, this may be the only lesion. Often, white patches occur on the upper chest, abdomen and limbs, bilaterally but not necessarily symmetrically (Fig. 58.29). Occasionally, they are found on the face, particularly the chin. The hands and feet, as well as the back, remain normally pigmented. Islands of normal or hypermelanotic skin occur in the white areas, or less often on normal skin.

Piebaldism can easily be distinguished from vitiligo where the lesions are acquired later in life and their configuration and distribution are quite different. In piebaldism, there is almost invariably a white forelock and the pattern of arrangement of the lesions is quite characteristic. Also the presence of islands of normal pigmented skin in the hypomelanotic areas is typical. If the interpupillary distance is increased or the patient is deaf, the diagnosis of Waardenburg's syndrome (see below) must be considered. The patterns of hypomelanosis as seen in the localized and systematized types of naevus depigmentosus differ from piebaldism. Microscopy of the skin in naevus depigmentosus reveals normal numbers of melanocytes with sometimes rather stubby dendrites [9]. A progressive variant of piebaldism has been described in association with a novel mutation in the *kit* gene [11].

Treatment. Photoprotective preparations should be prescribed to protect the amelanotic areas from burning with sun exposure.



Fig. 58.29 Piebaldism. The lesions had been present from birth.

Cosmetic camouflage or skin dyes may be helpful for some patients. Skin grafts, minigrafts and grafts of autologous cultured melanocytes have some promise [12,13]. PUVA therapy is generally disappointing, as are topical corticosteroids.

References

1 Bolognia JL, Pawelek JM. Biology of hypopigmentation. *J Am Acad Dermatol* 1988; **19**: 217–55.
2 Comings DE, Odland GF. Partial albinism. *JAMA* 1966; **195**: 519–23.
3 Mosher DB, Fitzpatrick TB. Piebaldism. *Arch Dermatol* 1988; **124**: 364–5.
4 Morrison-Graham K, Takahashi Y. Steel factor and c-kit receptor. From mutants to a growth factor system. *Bioessays* 1993; **15**: 77–83.
5 Sprite RA, Holmes SA, Ramesar R *et al*. Mutations of the *kit* (mast/stem cell growth-factor receptor) proto-oncogene accounts for a continuous range of phenotypes in piebaldism. *Am J Hum Genet* 1992; **51**: 1058–65.
6 Ward KA, Moss C, Sanders DSA. Human piebaldism: relationship between phenotype and site of *kit* gene mutation. *Br J Dermatol* 1995; **132**: 929–35.
7 Breathnach AS, Fitzpatrick TB, Wyllie LM. Electron microscopy of melanocytes in human piebaldism. *J Invest Dermatol* 1965; **45**: 28–37.
8 Hayashibe K, Mishima Y. Tyrosinase-positive melanocyte distribution and induction of pigmentation in human piebald skin. *Arch Dermatol* 1988; **124**: 381–6.
9 Jimbow K, Fitzpatrick TB, Szabo G *et al*. Congenital circumscribed hypomelanosis. *J Invest Dermatol* 1975; **64**: 50–6.
10 Cooke JV. Familial white skin spotting (piebaldness) ('partial albinism') with white forelock. *J Pediatr* 1952; **41**: 1–12.
11 Richards KA, Fukai K, Oiso N, Paller AS. A novel KIT mutation results in piebaldism with progressive depigmentation. *J Am Acad Dermatol* 2001; **44**: 288–92.
12 Falabella R. Grafting and transplantation of melanocytes for repigmenting vitiligo and other types of leukoderma. *Int J Dermatol* 1989; **28**: 363–72.
13 Njoo MD, Nieuweboer-Krobotova L, Westerhof W. Repigmentation of leucodermic defects in piebaldism by dermabrasion and thin split-thickness skin grafting in combination with minigrafting. *Br J Dermatol* 1998; **139**: 829–33.

Tietz's syndrome (MIM #103500)

Tietz reported a six-generation pedigree with the constant association of total absence of pigment in the skin and hair, normal eyes, complete deaf-mutism and hypoplasia of the eyebrows [1]. An autosomal dominant gene appeared to be implicated. There is some doubt that this syndrome is a distinct entity.

The analogy with a syndrome in cats, in which severe deafness is associated with total absence of skin pigment but normal eye colour, suggests that Tietz's syndrome probably represents a 'generalized white spot' rather than albinism.

Reference

1 Tietz W. A syndrome of deaf-mutism associated with albinism showing dominant autosomal inheritance. *Am J Hum Genet* 1963; **15**: 259–64.

Waardenburg syndrome (MIM #193150) [1–8]

Historical background. Waardenburg syndrome (WS) was first described by a Dutch ophthalmologist in 1951 [1].

Aetiology. All of the abnormalities of Waardenburg syndrome involve the neural crest. Waardenburg syndrome is therefore considered to represent a global disorder of neural crest development.

Clinical features. Waardenburg syndrome is characterized by lateral displacement of the inner canthi and the lacrimal puncta, prominent nasal root and medial eyebrows, congenital deafness and heterochromic irides [2,3]. Other pigmentary changes are a 'dappled' appearance of the skin, a white forelock, and premature greying of hair, eyebrows and cilia. A few patients show piebaldism; pigment-free patches may be large and multiple or small and inconspicuous. WS has been reported in both black and white people.

Classification. Four classical clinical variants of WS have been described. Type I is the classic form [4], while type II lacks dystopia canthorum but has a high incidence of congenital sensorineural deafness and heterochromia. Type III resembles type I but is associated with limb abnormalities in addition to dystopia canthorum. Type IV, like type III, is autosomal recessive and is characterized by associated Hirschsprung's disease and, in some cases, by more extensive hypopigmentation [5]. Recent molecular genetic findings have demonstrated at least nine distinct genetic subtypes of Waardenburg syndrome, several of which correspond to distinct clinical subtypes not included in these four classical subtypes. Thus, a new and more comprehensive classification can be anticipated soon.

Incidence and genetics. It is a relatively rare autosomal dominant condition with an estimated incidence of 1 in 20–40 000 [6]. Autosomal recessive forms of Waardenburg syndrome are rare. Variable expression and penetrance explain milder or incomplete

phenotypes. A number of different mutations of the *PAX*-3 gene on chromosome 2q35 have now been reported in different forms of type I and type III. None of the cases of type II have been linked to 2q markers but type IIA is now known to be due to mutations in the *MITF* gene. Mutations in the endothelin-3 gene [7] and in endothelin-B genes have been reported in type IV, and mutations in the *SOX10* gene [8] have also been implicated as causing WS. Types IIB and IIC are further subdivisions linked to genes mapping to chromosomes 1p and 8p, respectively.

References

1 Waardenburg PJ. A new syndrome combining developmental anomalies of the eyelids, eyebrows, and nose root with pigmentary defects of the iris and head hair with congenital deafness. *Am J Hum Genet* 1951; **3**: 195–253.
2 DiGeorge AM, Olmstead RW, Harley RD. Waardenburg's syndrome. *J Pediatr* 1960; **57**: 649–69.
3 Ortonne J-P. Piebaldism, Waardenburg's syndrome and related disorders. *Dermatol Clin* 1988; **6**: 205–16.
4 Farrer LA, Grundfast KM, Amos J *et al*. Waardenburg syndrome (WS) type I is caused by defects at multiple loci one of which is near ALPP on chromosome 2: first report of the WS consortium. *Am J Hum Genet* 1992; **50**: 902–13.
5 Shah KN. White forelock, pigmentary disorder of irides and long segment Hirschsprung disease: a possible variant of Waardenburg's syndrome. *J Pediatr* 1981; **99**: 432–5.
6 Liu XZ, Newton VE, Read AP. Waardenburg syndrome type II: phenotypic findings and diagnostic criteria. *Am J Med Genet* 1995; **55**: 95–100.
7 Edery P, Attie T, Amiel J *et al*. Mutation of the endothelin-3 gene in the Waardenburg–Hirschsprung disease (Shah–Waardenburg syndrome). *Nat Genet* 1996; **12**: 442–4.
8 Pingault V, Bondurand N, Kuhlbrodt K *et al*. SOX10 mutations in patients with Waardenburg–Hirschsprung disease. *Nat Genet* 1998; **18**: 171–3.

Albinism–deafness syndrome (MIM #300700) [1–4]

Synonyms
- Ziprkowski–Margolis syndrome
- Woolf syndrome

Albinism–deafness syndrome (ADFN) is a rare X-linked recessive syndrome that was first described (separately) by Ziprkowski [1] and Margolis [2] in 1962. Ziprkowski reported 14 members of an Egyptian–Jewish family with males showing deaf-mutism, heterochromic irides and piebald-like hypomelanosis of skin and hair [1]. The skin appears completely amelanotic at birth, but pigmented macules develop on the extremities, trunk and scalp. The hair usually remains white. Genetic linkage studies and somatic cell hybrid mapping studies localize the *ADFN* gene to Xq26.3-q27.1 [3]. However, the gene has not yet been identified. Piebaldism in association with congenital nerve deafness [4] has been reported in two brothers with no other manifestation of ADFN. It is unclear whether this is the same or a genetically distinct condition.

References

1 Ziprkowski L, Krakowski A, Adam A *et al*. Partial albinism and deaf-mutism due to a recessive sex-linked gene. *Arch Dermatol* 1962; **86**: 530–9.
2 Margolis E. A new hereditary syndrome: sex-linked deaf-mutism associated with total albinism. *Acta Genet Stat Med (Basel)* 1962; **12**: 12–9.
3 Shiloh Y, Litvak G, Ziv Y *et al*. Genetic mapping of X-linked albinism deafness syndrome (ADFN) to xq26.3-27.1. *Am J Hum Genet* 1990; **47**: 20–7.
4 Woolf CM, Dolowitz Aldous HE. Congenital deafness associated with piebaldness. *Arch Otolaryngol* 1965; **82**: 244–50.

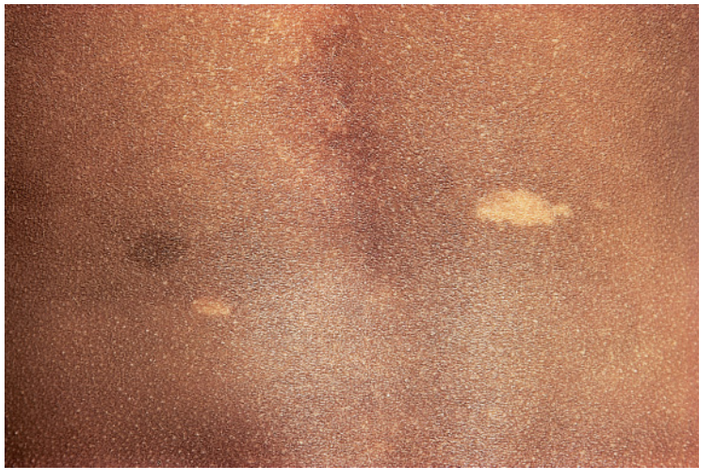


Fig. 58.30 Ash-leaf-shaped hypopigmented macules in tuberous sclerosis.

Hypomelanotic macules of tuberous sclerosis

In this neurocutaneous disorder (see Chapter 15), transmitted as an autosomal dominant trait, hypomelanotic macules are found in about 50–100% of affected babies [1–3]. It is a significant feature as it is often the earliest feature of tuberous sclerosis [1]. These macules are usually multiple, irregularly scattered and frequently have a lance–ovate shape, likened by Thomas Fitzpatrick in 1968 to the leaflet of the mountain ash [1] (Fig. 58.30). The macules are of diagnostic significance in a baby with fits, especially infantile spasms [1]. They are best identified in the fair-skinned with the aid of a Wood's lamp. Electron microscopy of the macules shows the presence of normal or reduced numbers of melanocytes that have poorly developed dendrites containing fewer and smaller melanosomes than normal [2]. The gene responsible for tuberous sclerosis has been localized to 9q34 (*TSC1*) and 16p13.3 (*TSC2*) [4,5].

References

1 Fitzpatrick TB, Szabó G, Hori Y *et al*. White leaf-shaped macules: earliest visible sign of tuberous sclerosis. *Arch Dermatol* 1968; **98**: 1–6.
2 Jimbow K, Fitzpatrick TB, Szabó G, Hori Y. Congenital circumscribed hypomelanosis. *J Invest Dermatol* 1975; **64**: 50–62.
3 Zulanov A, Esterly NB. Neurocutaneous syndromes associated with pigmentary skin lesions. *J Am Acad Dermatol* 1995; **32**: 915–35.
4 European Chromosome 16 Tuberous Sclerosis Consortium. Identification and characterization of the tuberous sclerosis gene on chromosome 16. *Cell* 1993; **75**: 1305–15.
5 Nellist M, Brook-Carter PT, Connor JM *et al*. Identification of markers flanking the tuberous sclerosis locus on chromosome 9 (TSC1). *J Med Genet* 1993; **30**: 224–7.

Naevus depigmentosus

Synonym
- Achromic naevus

Definition. This is a rare, localized area of depigmented skin, first described by Lesser in 1884 [1]. It remains stable in size and colour over time and typically has no associated findings.

Clinical features. This circumscribed area of depigmentation is congenital, but may not be apparent at birth. There are three clinical variants; the commonest is the single, circumscribed, rounded lesion. Segmental and systematized forms are very rare, and may resemble hypomelanosis of Ito. Lesions occur most commonly on the trunk. Hairs within the depigmented macules are usually depigmented. Histology may show either normal or reduced numbers of melanocytes [2]. A functional defect in melanocytes, with morphological abnormalities of melanosomes, has been identified [3].

References

1 Lesser E. In: Ziemssen HV, ed. *Hanbuchder Hautkrankheiten*, 2nd edn. Leipzig: Vogel, 1884: 183.
2 Jimbow K, Fitzpatrick TB, Szabó G, Hori Y. Congenital circumscribed hypomelanosis. *J Invest Dermatol* 1975; **64**: 50–62.
3 Lee HS, Chun YS, Hann SK. Nevus depigmentosus: clinical features and histopathologic characteristics in 67 patients. *J Am Acad Dermatol* 1999; **40**: 21–6.

Hypomelanosis of Ito (MIM *300337) [1–8]

Synonym

- Incontinentia pigmenti achromians of Ito

In 1952 the Japanese dermatologist Minor Ito described a 21-year-old woman with widespread, symmetrical, depigmented whorls and streaks that had started at the age of 5 years [1]. This neurocutaneous disorder is variable in extent and may be unilateral or bilateral. The areas of hypomelanosis occur along Blaschko's lines, a requirement for the diagnosis of this condition (Fig. 58.31). There may be associated disorders in the musculoskeletal system, teeth, eyes and central nervous system [2]. Convulsions and mental deficiency occur commonly in the reported cases [3]. The appearances resemble the late stages of incontinentia pigmenti, but this is clearly a quite separate disease without the preceding inflammatory stages and without the sex-linked inheritance of incontinentia pigmenti. There is no basal layer damage and no pigmentary incontinence. Nearly all cases are sporadic suggesting a postzygotic mutation. The mutation can only survive in a mosaic and is usually lethal when transmitted to offspring due to the lack of admixture with normal cell lines. However, one case of inheritance of hypomelanosis of Ito has been reported, consistent with X-linked dominant inheritance with lethality to male embryos [4]. The white streaks are usually present at birth and tend to progress thereafter. Eventually, they may repigment. The skin lesions have to be distinguished from the more bizarre-shaped depigmented naevi and from focal dermal hypoplasia where the skin also shows atrophic changes.



Fig. 58.31 Incontinentia pigmenti achromians of Ito.

References

1 Ito M. Studies on melanin XI: Incontinentia pigmenti achromians. A singular case of nevus depigmentosus systematicus bilateralis. *Tohoku J Exp Med* 1952; **55**: 57–9.
2 Pascual-Castroviejo I, Lopez-Rodriguez L, de la Cruz Medina M *et al*. Hypomelanosis of Ito. Neurologic complications. *Can J Neurol Sci* 1988; **15**: 124–9.
3 Glover MT, Brett EM, Atherton DJ. Hypomelanosis of Ito: spectrum of the disease. *J Pediatr* 1989; **115**: 75–80.
4 Grosshans EM, Stoebner P, Bergoend H, Stoll C. Incontinentia pigmenti achromians (Ito). Etude clinique at histopathologique. *Dermatologica* 1971; **142**: 65–78.
5 Ritter CL, Steele MW, Wenger SL, Cohen BA. Chromosome mosaicism in hypomelanosis of Ito. *Am J Med Genet* 1990; **35**: 14–7.
6 Ruiz-Maldonado R, Toussaint S, Tamayo L *et al*. Hypomelanosis of Ito: diagnostic criteria and report of 41 cases. *Pediatr Dermatol* 1992; **9**: 1–10.
7 Moss C, Larkins S, Stacey M *et al*. Epidermal mosaicism and Blaschko's lines. *J Med Genet* 1993; **30**: 752–5.
8 Koiffmann CP, de Souza DH, Diament A *et al*. Incontinentia pigmenti achromians (hypomelanosis of Ito, MIM 146150): further evidence of localization at Xp11. *Am J Med Genet* 1993; **46**: 529–33.

Vogt–Koyanagi–Harada syndrome

Historical background. In 1906 Vogt reported a patient with atraumatic, idiopathic uveitis, poliosis and alopecia, a syndrome that in time would be associated with his name [1]. In 1926, Harada reported five cases of bilateral posterior uveitis and retinal detachment [2]. In 1929, Koyanagi reported 16 patients with headache, fever, dysacousia, vitiligo, poliosis, alopecia, bilateral anterior uveitis with occasional exudative retinal detachment [3]. Various combinations of synonym have been used for this disorder, which is now generally referred to with the above three names, and abbreviated to VKHS.

Aetiology. The aetiology of VKHS has yet to be established. An abnormal response to a virus, and immunological mechanisms, have been postulated.

Pathology. Electron microscopy of depigmented skin shows an absence of melanocytes as in vitiligo [4]. Colloid–amyloid bodies are also found at the dermal–epidermal junction [5]. Inflammatory

skin lesions are characterized by a chronic, mixed inflammatory cell infiltrate [6].

Clinical features [7,8]. VKHS mainly affects dark-skinned people or white people with dark pigmentation. It is rare but widely distributed. Most cases occur in the third and fourth decades but children may be affected. It affects the skin, eyes, inner ears and meninges. Criteria for diagnosis are as follows:

- No history of ocular trauma or surgery preceding the initial onset of uveitis
- No clinical or laboratory evidence suggestive of ocular disease entities
- Bilateral ocular involvement: an early sign is diffuse choroiditis; a late sign is ocular depigmentation
- Neurological and auditory findings: meningismus, tinnitus, cerebrospinal fluid pleocytosis
- Skin and hair changes: alopecia, vitiligo, poliosis.

Typically, this condition is first diagnosed by ophthalmologists as the uveitis starts the march of symptoms and signs.

Diagnosis. The association of vitiligo with loss of pigment in brows and lashes and with the residual ocular defects should clearly differentiate this syndrome from any other.

References

1 Vogt A. Frühseitiges Ergrauen der Zilen und Bemerkungen über den sogenannten plötzlichen Eintritt dieser Veränderung. *Klin Monatsbl Augenheilkd* 1906; **44**: 228–42.
2 Harada Y. Beitrag zur klinischen Kenntnis von viechteitriger Choroiditis (Choroiditis diffusa acuta). *Nippon Gankai Zasshi* 1926; **30**: 356–78.
3 Koyanagi Y. Dysakusis, alopecia and poliosis bei schwerer uveitis nicht traumatischen ursprunges. *Klin Monatsbl Augenheilkd* 1929; **82**: 194–211.
4 Morohashi M, Hashimoto K, Goodman TF. Ultrastructural studies of vitiligo, Vogt–Koyanagi syndrome, and incontinentia pigmenti achromians. *Arch Dermatol* 1977; **113**: 755–66.
5 Okada T, Sakamoto T, Ishibashi T, Inomata H. Vitiligo in Vogt–Koyanagi–Harada disease: immunohistological analysis of inflammatory site. *Graefes Arch Clin Exp Ophthalmol* 1996; **234**: 359–63.
6 Tsuruta D, Hamada T, Teramae H *et al*. Inflammatory vitiligo in Vogt–Koyanagi–Harada disease. *J Am Acad Dermatol* 2001; **44**: 129–31.
7 Nordlund JJ, Albert D, Forget B, Lerner AB. Halo nevi and the Vogt–Koyanagi–Harada syndrome. *Arch Dermatol* 1980; **116**: 690–2.
8 Rabsmen PE, Gass DM. Vogt–Koyanagi–Harada syndrome: clinical course, therapy and long-term visual outcome. *Arch Ophthalmol* 1991; **10**: 682–7.

Alezzandrini's syndrome [1–4]

Historical background. Alezzandrini was involved in three papers describing the syndrome that now bears his name in the late 1950s and early 1960s [1–3].

Aetiology. The aetiology of this syndrome is unknown.

Clinical features. Alezzandrini's syndrome has only been reported in a small number of cases [1–4]. It is characterized by unilateral, facial vitiligo associated with unilateral retinal degeneration, white hair, poliosis and deafness. There are similarities with the Vogt–Koyanagi–Harada syndrome in which skin, eye and auditory changes are also observed.

References

1 Casala AM, Alezzandrini AA. Vitiligo y poliosis unilateral con retinitis pigmentaria y hypoacusia. *Arch Argent Dermatol* 1959; **9**: 449–56.
2 Cremona AC, Alezzandrini AA, Casala AM. Vitiligo, poliosis and unilateral macular degeneration. *Arch Oftalmol B Aires* 1961; **36**: 102–6.
3 Alezzandrini AA. Manifestations unilaterales degenerescence tapetoretinienne, de vitiligo, de poliose, de cheveux blancs et d'hypoacousie. *Ophthalmologica* 1964; **147**: 409–19.
4 Hoffmann MD, Dudley C. Suspected Alezandrini's syndrome in a diabetic patient with unilateral retinal detachment and ipsilateral vitiligo and poliosis. *J Am Acad Dermatol* 1992; **26**: 496–7.

Vitiligo [1–3]

Aetiology. Vitiligo affects all races and has a long history [4]. It is stated that it occurs in 1% of the world's population [2]. An epidemiological survey on the island of Bornholm in Denmark [5] found the prevalence to be 0.38%. It is likely that this figure applies also to other countries in north-west Europe. The incidence of vitiligo in those with racially pigmented skins is higher (and the social impact greater), although reliable figures are not available. There is a preponderance of females in most series based on outpatient attendances, but the frequency in the population is probably the same in both sexes [5]. Between 30 and 40% of patients have a positive family history [2], and a genetic factor is undoubtedly involved. Inheritance may be polygenic or may be determined by an autosomal dominant gene of variable penetrance. Vitiligo has been reported in monozygotic twins [6].

Various theories have been suggested for the aetiology of vitiligo; the same mechanism may not apply to all cases.

- *Autoimmune hypothesis*: this is based on the clinical association of vitiligo with a number of disorders also considered to be autoimmune (Table 58.8). Organ-specific autoantibodies to thyroid, gastric parietal cells and adrenal tissue are found in the serum more frequently in patients with vitiligo than in the general population [11,12]. A complement-fixing antibody to melanocytes has been found in the serum of several patients who in addition to vitiligo had alopecia areata, mucocutaneous candidiasis and multiple endocrine insufficiencies [11]. Antibodies to normal human melanocytes have been detected using a specific immunoprecipitation assay [13,14], and have a cytolytic effect [15]. T-cell profiles are abnormal in vitiligo, with a decrease in T-helper cells [16–18].

Table 58.8 Disorders associated with vitiligo.

Thyroid disease* (hyperthyroidism and hypothyroidism [7])
Pernicious anaemia*
Addison's disease* [8]
Diabetes mellitus* [9]
Hypoparathyroidism*
Myasthenia gravis*
Alopecia areata
Morphoea and lichen sclerosus
Halo naevus*
Malignant melanoma* [10]

* Autoantibodies demonstrable.

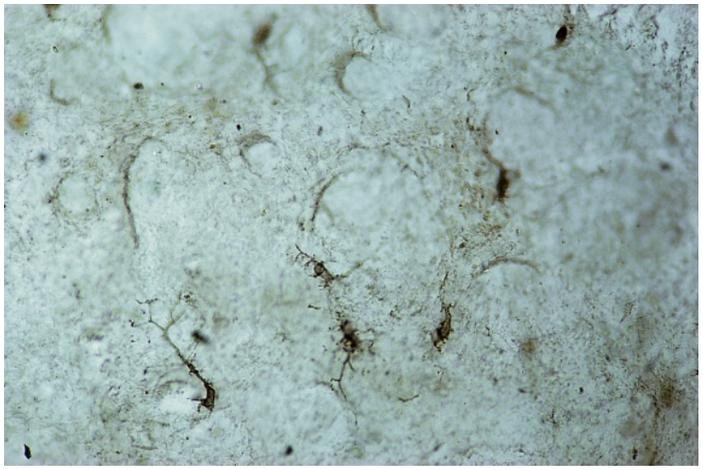


Fig. 58.32 Vitiligo. Epidermal sheet of marginal depigmented area showing marked reduction in number of melanocytes.



Fig. 58.33 Vitiligo.

- *Neurogenic hypothesis* [19]: this suggests that a compound is released at peripheral nerve endings in the skin that may inhibit melanogenesis and could have a toxic effect on melanocytes. Although vitiligo may sometimes occur in a dermatomal distribution and electron microscopy shows abnormalities of terminal portions of peripheral nerves, there is little support for this hypothesis. However, recent studies on neuropeptide and neuronal markers in vitiligo suggest that neuropeptide Y may have a role [20].
- *Self-destruct theory of Lerner* [2]: this suggests that melanocytes destroy themselves due to a defect in a natural protective mechanism that removes toxic melanin precursors. This hypothesis is based on the clinical features of vitiligo and on experimental studies of cutaneous depigmentation by chemical compounds that have a selective lethal effect on functional melanocytes [21]. These compounds can produce a leukoderma indistinguishable from idiopathic vitiligo.

It has been suggested that defective keratinocyte metabolism plays a major role, with low catalase levels in the epidermis of vitiligo [22]. A new hypothesis involving defective tetrahydrobiopterin and catecholamine biosynthesis has been put forward to explain the pathogenesis of this disorder [23].



Fig. 58.34 Isomorphic or Koebner phenomenon at site of a scratch in a patient with vitiligo.

Pathology. There is a marked absence of melanocytes and melanin in the epidermis. Histochemical studies [24] show a lack of dopa-positive melanocytes in the basal layer of the epidermis (Fig. 58.32). Recent immunohistochemical studies with a large panel of antibodies show only an occasional melanocyte in lesional skin [25]. Electron microscopy studies [9,26,27] confirm the loss of melanocytes, which appear to be replaced by Langerhans' cells. In the epidermis of areas around the margins of vitiligo are abnormalities of keratinocytes [9] as well as degenerating melanocytes. There is increased cellularity of the dermis and occasional colloid amyloid bodies are found. In inflammatory vitiligo, where there is a raised erythematous border, there is an infiltrate of lymphocytes and histiocytes. This infiltrate is also found in the marginal areas of some biopsies [27].

Clinical features [2,3]. Vitiligo can begin at any age, but in 50% of cases it develops before the age of 20 years. The condition is gradually progressive, sometimes extending rapidly over a period of several months and then remaining quiescent for many years.

Hypomelanotic macules are usually first noted on the sun-exposed areas of skin, on the face or on the dorsa of hands (Fig. 58.33). These areas are prone to sunburn. Rarely, itching in the absence of sunburn may occur. Damage to the 'normal' skin frequently results in an area of depigmentation—an isomorphic or Koebner phenomenon (Fig. 58.34).

The amelanotic macules in vitiligo are found particularly in areas that are normally hyperpigmented, for example the face, axillae, groins, areolae and genitalia. Areas subjected to repeated friction and trauma are also likely to be affected, for example the

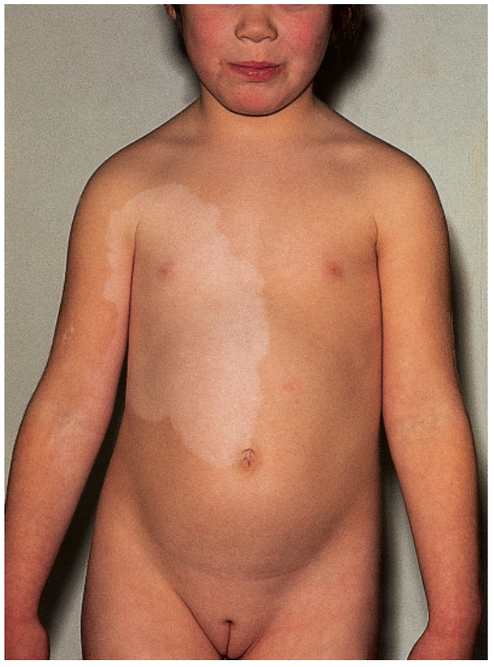


Fig. 58.35 Segmental vitiligo.

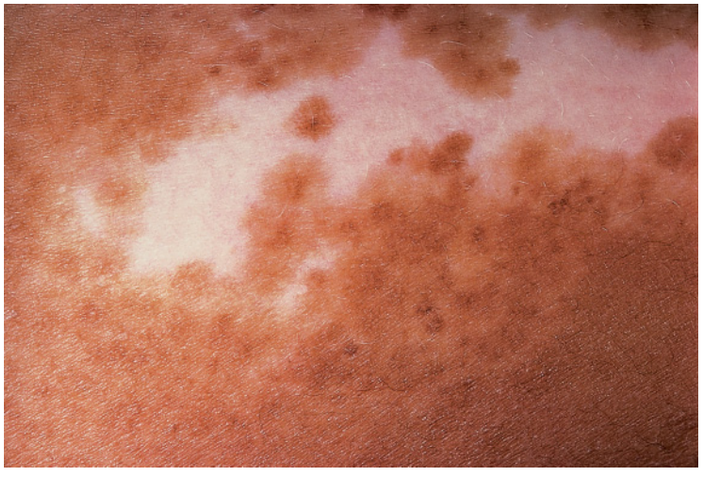


Fig. 58.36 'Trichrome' vitiligo.

dorsa of hands, feet, elbows, knees and ankles. The distribution of the lesions is usually symmetrical, although sometimes it is unilateral and may have a dermatomal arrangement (Fig. 58.35). Rarely, there is complete vitiligo, although a few pigmented areas always remain.

The pigment loss may be partial or complete, or both may occur in the same areas (trichrome vitiligo) (Fig. 58.36).

The macules have a convex outline, increase irregularly in size and fuse with neighbouring lesions to form complex patterns. The hairs in the patches frequently remain normally pigmented, but in older lesions the hairs too are often amelanotic. The margins of the lesions may become hyperpigmented. The main symptom is the cosmetic disability, although some patients present because of sunburn in the amelanotic areas. Vitiligo commonly starts in children, who are more likely to show segmental vitiligo, autoimmune diseases or to have a family history of canities [28].

Spontaneous repigmentation is noted in about 10–20% of patients, most frequently in sun-exposed areas. It is usually seen in younger patients, the repigmentation being quite trivial and mainly perifollicular.

In addition to premature greyness of the hair, uveitis also rarely occurs [29]. Careful examination of the ocular fundus may show abnormalities [30]. There have also been suggestions of an increased incidence of deafness [31].

Associated disorders. A number of conditions occur in association with vitiligo and are listed in Table 58.8. Halo naevi [2,3] occur not infrequently and often antedate the onset of vitiligo. Areas of depigmentation sometimes develop in patients with malignant melanoma [10]. Vitiligo with uveitis, central nervous system involvement and premature greying of the hair occurs in the Vogt–Koyanagi syndrome (see p. 58.45).

Diagnosis. The distribution, age of onset and hyperpigmented border will suggest the diagnosis. In piebaldism, the lesions are present at birth, are usually confined to the head and trunk, and rarely show a hyperpigmented border. Careful examination of the texture of the unpigmented skin should exclude lichen sclerosus and scleroderma. Post-inflammatory leukoderma, which is frequent in the darker races, shows an irregular mottling of hyperpigmented and hypopigmented blotches. Hypomelanosis of the affected skin is commonly seen in pityriasis alba, producing slightly scaly areas with rather ill-defined edges on children's faces. Hypopigmented slightly scaly macules are seen in pityriasis versicolor. These areas often fluoresce a golden yellow when examined under a Wood's lamp. The hypomelanotic macules in leprosy are anaesthetic.

Treatment. The treatment of vitiligo is unsatisfactory and in most cases the patient is best advised to seek effective cosmetic camouflage for the lesions on exposed skin. In sunny climates, the prescription of sunscreens is often necessary.

Treatment with systemic psoralens, 4,5′,8-trimethylpsoralen, 8-methoxypsoralen or 5-methoxypsoralen, combined with exposure to sunlight or to light sources providing high-intensity long-wave UV light, is effective in a proportion of cases [3,32,33]. The patient is instructed to take the psoralens in a dose of 0.6 mg/kg 2 h before carefully controlled, graduated exposure to sunlight, preferably around midday. Therapy is continued for at least 6 months and in some for several years. In the majority of patients, the areas retain the pigment long after psoralen therapy has been discontinued. The use of topical applications of psoralens is hazardous and may result in untoward blistering of the skin. Khellin has also been used with UVA [34].

Narrow-band UVB phototherapy has been found to be effective and safe for vitiligo [35].

In some patients, the more potent topical corticosteroid preparations, 0.1% betamethasone valerate and 0.05% clobetasol propio-

nate, are effective in producing repigmentation of areas of vitiligo, but often at the price of some atrophy [36].

In those patients with extensive vitiligo and only a few residual areas of hyperpigmentation, skin-bleaching creams, such as 20% monobenzylether of hydroquinone, are of use [37].

The use of grafting techniques, minigrafts and autologous cultured melanocytes is interesting but may be limited by the Koebner phenomenon [38–40]. Minigrafting has been carried out with success in some patients with more widespread vitiligo [41]. A systematic review of autologous transplantation methods in vitiligo has recently been performed [42].

References

1 Bologna J, Pawelek JM. Biology of hypopigmentation. *J Am Acad Dermatol* 1988; **19**: 217–55.
2 Lerner AB. On the etiology of vitiligo and gray hair. *Am J Med* 1971; **51**: 141–7.
3 Gawkrodger DJ, Ormerod AD, Shaw L *et al*. Guideline for the diagnosis and management of vitiligo. *Br J Dermatol* 2008; **159**: 1051–76.
4 Koranue RV, Sachdeva KG. Vitiligo. *Int J Dermatol* 1988; **27**: 676–81.
5 Howitz J, Brodthagen H, Schwartz M *et al*. Prevalence of vitiligo. *Arch Dermatol* 1977; **113**: 47–52.
6 Mohr J. Vitiligo in a pair of monovular twins. *Acta Genet* 1951; **2**: 252–5.
7 Cunliffe WJ, Hall R, Newell DJ *et al*. Vitiligo, thyroid disease and autoimmunity. *Br J Dermatol* 1968; **80**: 135–9.
8 Dunlop D. Eighty-six cases of Addison's disease. *BMJ* 1963; **ii**: 887–91.
9 Dawber RPR. Clinical associations of vitiligo. *Postgrad Med J* 1970; **46**: 276–7.
10 Frenk E. Dépigmentations vitiligineuses chez des patients atteints de mélanomes malins. *Dermatologica* 1969; **139**: 84–91.
11 Betterle C, Peserico A, Bersani G. Vitiligo and autoimmune polyendocrine deficiencies with autoantibodies to melanin-producing cells. *Arch Dermatol* 1979; **115**: 364.
12 Woolfson H, Finn OA, Mackie RM *et al*. Serum anti-tumour antibodies and autoantibodies in vitiligo. *Br J Dermatol* 1975; **92**: 395–400.
13 Naughton GK, Eisinger M, Bystryn J-C. Detection of antibodies to melanocytes in vitiligo by specific immunoprecipitation. *J Invest Dermatol* 1983; **81**: 540–2.
14 Naughton GK, Reggiardo D, Bystryn J-C. Correlation between vitiligo antibodies and extent of depigmentation in vitiligo. *J Am Acad Dermatol* 1986; **15**: 978–81.
15 Cui J, Arita Y, Bystryn JC. Cytolytic antibodies to melanocytes in vitiligo. *J Invest Dermatol* 1993; **100**: 812–5.
16 Ghoneum M, Grimes E, Gill G *et al*. Natural cell-mediated cytotoxicity in vitiligo. *J Am Acad Dermatol* 1987; **17**: 600–5.
17 Grimes PE, Ghoneum M, Stockton T *et al*. T-cell profiles in vitiligo. *J Am Acad Dermatol* 1986; **14**: 196–201.
18 Mozzanica N, Frigerio U, Finzi AF *et al*. T cell subpopulations in vitiligo: a chronobiologic study. *J Am Acad Dermatol* 1990; **22**: 223–30.
19 Lerner AB. Vitiligo. *J Invest Dermatol* 1959; **32**: 285–310.
20 Al-Abadie MSK, Senior HJ, Bleehen SS, Gawkrodger DJ. Neuropeptide and neuronal marker studies in vitiligo. *Br J Dermatol* 1994; **131**: 160–5.
21 Bleehen SS, Pathak MA, Hori Y, Fitzpatrick TB. Depigmentation of skin with 4-isopropylcatechol, mercaptoamines, and other compounds. *J Invest Dermatol* 1968; **50**: 103–17.
22 Schallreuter KU, Wood JM, Berger J. Low catalase levels in epidermis of patients with vitiligo. *J Invest Dermatol* 1991; **97**: 1081–5.
23 Schallreuter KU, Wood JM, Ziegler I *et al*. Defective tetrahydrobiopterin and catecholamine biosynthesis in the depigmentation disorder vitiligo. *Biochim Biophys Acta* 1994; **122**: 181–92.
24 Jarrett A, Szabo G. The pathological varieties of vitiligo and their response to treatment with meladinine. *Br J Dermatol* 1956; **68**: 313–26.
25 Le Poole IC, van den Wijngaard RMJGF, Westerhof W *et al*. Presence or absence of melanocytes in vitiligo lesions: an immunohistochemical investigation. *J Invest Dermatol* 1993; **100**: 816–22.
26 Birbeck M. An electron microscope study of basal melanocytes and high level clear cells (Langerhans cells) in vitiligo. *J Invest Dermatol* 1961; **37**: 51–64.
27 Bleehen SS. Histology of vitiligo. In: Klaus SN, ed. *Pigment Cell*, Vol. 5. Basel: Karger, 1979: 54–61.
28 Halder RM, Grimes PE, Cowan CA *et al*. Childhood vitiligo. *J Am Acad Dermatol* 1987; **16**: 948–54.
29 Nordlund JJ, Todes Taylor N, Albert DM *et al*. The presence of vitiligo and poliosis in patients with uveitis. *J Am Acad Dermatol* 1981; **4**: 528–36.
30 Cowan CL, Halder RM, Grimes PE *et al*. Ocular disturbances in vitiligo. *J Am Acad Dermatol* 1986; **15**: 17–24.
31 Tosti A, Bardazzi F, Tosti G *et al*. Audiologic abnormalities in cases of vitiligo. *J Am Acad Dermatol* 1987; **17**: 230–3.
32 Parrish JA, Fitzpatrick TB, Shea C *et al*. Photochemotherapy of vitiligo. *Arch Dermatol* 1976; **112**: 1531–4.
33 Bleehen SS. Treatment of vitiligo with oral 4,5′,8-trimethylpsoralen (tripsoralen). *Br J Dermatol* 1972; **86**: 54–60.
34 Ortel B, Tanew A, Hönigsmann H. Treatment of vitiligo with khellin and ultraviolet A. *J Am Acad Dermatol* 1988; **18**: 693–701.
35 Scherschum L, Kim JJ, Lim HW. Narrow-band ultraviolet B is a useful and well-tolerated treatment for vitiligo. *J Am Acad Dermatol* 2001; **44**: 999–1003.
36 Kandil E. Treatment of vitiligo with 0.1% betamethasone 17-valerate in isopropyl alcohol: a double-blind trial. *Br J Dermatol* 1974; **91**: 457–60.
37 Mosher DB, Parrish JA, Fitzpatrick TB. Monobenzylether of hydroquinone. *Br J Dermatol* 1977; **97**: 669–79.
38 Lerner AB, Halaban R, Klaus SN *et al*. Transplantation of human melanocytes. *J Invest Dermatol* 1987; **89**: 219–24.
39 Falabella R. Treatment of localized vitiligo by autologous minigrafting. *Arch Dermatol* 1988; **124**: 1649–55.
40 Hatchome N, Kato T, Tagami H. Therapeutic success of epidermal grafting in generalized vitiligo is limited by the Koebner phenomenon. *Int J Dermatol* 1988; **27**: 676–81.
41 Boersma BR, Westerhof W, Bos JD. Repigmentation in vitiligo vulgaris by autologous minigrafting: results in nineteen patients. *J Am Acad Dermatol* 1995; **33**: 990–5.
42 Njoo MD, Westerhof W, Bos JD *et al*. A systematic review of autologous transplantation methods in vitiligo. *Arch Dermatol* 1998; **34**: 1543–9.

Halo naevus [1,2]

Synonyms
- Sutton's naevus
- Leukoderma acquisitum centrifugum

Definition and aetiology. Leukoderma acquisitum centrifugum designates the development of a halo of hypomelanosis around a central cutaneous tumour. This tumour is usually a benign melanocytic naevus but may be a neuroid naevus, a blue naevus, a neurofibroma, or a primary or secondary malignant melanoma [1]. The phenomenon, which is not uncommon, is usually seen in children or young adults of either sex.

Halo naevi occur with increased frequency in patients with certain organ-specific autoimmune disorders, as does vitiligo (see above), with which it is often associated. An immunological association of halo naevus with cutaneous malignant melanoma exists. Antibodies against the cytoplasm of malignant melanoma cells are found in the serum of patients with halo naevi [3]. Multiple halo naevi may occur in patients with melanoma.

Pathology [1,4]. Most halo naevi are compound naevi. There is frequently a lymphocytic infiltration of the naevus and the constituent cells may show damage. Ultrastructural studies show the apposition of mononuclear cells with naevus cells that show cytotoxic changes [5]. In the depigmented halo, there is an absence of melanocytes, but Langerhans' cells are present [6]. Melanophages are often present in the dermis.

Clinical features [1,7]. Circular areas of hypomelanosis occur around pigmented naevi, particularly on the trunk, less commonly on the head and rarely on the limbs. Multiple lesions are common, the halos being about 0.5–1.0 cm wide and developing simultaneously or at intervals around several, but not all, naevi (Fig. 58.37). The condition is usually seen in young people. The naevus tends to flatten and may disappear completely. The depigmented areas often persist, but may pigment after many years. Eczema around naevi (Meyerson's naevi) is discussed in Chapter 54.

Treatment. Normally none is required. The usual diagnostic criteria must be applied if there is any possibility that the central tumour is a melanoma. It should be remembered that a halo around a benign naevus is relatively common, whereas malignant melanoma is rare, and a melanoma surrounded by a halo is extremely rare. Mutilating surgery must never be undertaken without preliminary histological examination by an experienced pathologist.

References

1 Kopf AW, Morrill SD, Silberberg I. Broad spectrum of leukoderma acquisitum centrifugum. *Arch Dermatol* 1965; **92**: 14–35.
2 Ortonne J-P. In: Ortonne J-P, Mosher DB, Fitzpatrick TB, eds. *Vitiligo and other Hypomelanoses of Hair and Skin*. New York: Plenum, 1983: 567–82.
3 Copeman PWM, Lewis MG, Phillips TM, Elliott PG. Immunological associations of the halo naevus with cutaneous malignant melanoma. *Br J Dermatol* 1973; **88**: 127–37.
4 Wayte DM, Helwig EB. Halo nevi. *Cancer* 1968; **22**: 69–90.
5 Gauthier Y, Surleve-Bazeille JE, Gauthier O. Ultrastructure of halo nevi. *J Cutan Pathol* 1975; **2**: 71–81.
6 Swanson JL, Wayte DM, Helwig EB. Ultrastructure of halo nevi. *J Invest Dermatol* 1968; **50**: 434–7.
7 Stegmaier OC, Becker SW, Medenica M. Multiple halo nevi. *Arch Dermatol* 1965; **99**: 180–9.

Acquired hypomelanosis

The disorders in which there is frequently an acquired loss of melanin pigment not due to genetic factors are shown in Table 58.9.

Chemical depigmentation

A number of chemicals can produce cutaneous depigmentation when applied to the skin [1,2]. Several substituted phenols produce an occupational leukoderma in workers coming in contact with them (see also Chapter 27). Of these, *p*-tertiary-butylphenol is the most important [2–4]. Occupational leukoderma occurs in workers in contact with the monobenzylether of hydroquinone [5]; this compound is used in the treatment of hypermelanosis and can produce confetti-like areas of depigmentation in the treated areas [6] (Fig. 58.38). The monomethylether of hydroquinone can induce a similar leukoderma [7]. Several phenolic germicidal preparations can produce depigmentation of the skin [4]. 4-Tertiary-butylcatechol is also a cause of occupational leukoderma [8], and this may follow contact sensitization [9]. The areas most likely to be affected in occupational leukoderma are the dorsa of the hands (see Fig. 58.7), but other areas are involved, not necessarily in contact with the chemicals. The depigmented areas frequently enlarge, and new ones appear even after the patient is no longer



(a)



(b)



(c)

Fig. 58.37 (a) Multiple halo naevi in a young man who also had vitiligo. (b) Unusually large halo naevus. (c) Halo phenomenon developing within a malignant melanoma that later proved fatal.

Table 58.9 Acquired hypomelanosis.

Endocrine factors
Hypopituitarism*
Addison's disease†
Thyroid disease†
Chemical factors (occupational and therapeutic)
Monobenzylether of hydroquinone†
Monomethylether of hydroquinone
p-tertiary-butylphenol†
p-tertiary amylphenol†
Chloroquine and hydroxychloroquine
Arsenic‡
Nutritional factors
Chronic protein deficiency§
Pernicious anaemia§
Post-inflammatory and infections
Eczema (pityriasis alba)‡
Psoriasis‡
Pityriasis versicolor‡
Pinta‡, syphilis‡, yaws‡
Leprosy‡
Sarcoidosis‡
Lupus erythematosus‡
Lichen planus‡
Neoplasms
Halo naevus†
Malignant melanoma†
Miscellaneous
Idiopathic guttate hypomelanosis‡
Vogt–Koyanagi–Harada syndrome†

* Diffuse loss of pigment: lack of melanocyte-stimulating hormone.
† Circumscribed areas: vitiligo-like lesions.
‡ Partial loss of pigment in circumscribed areas.
§ Loss of pigment in hair.

in contact. The areas may or may not repigment. Treatment with psoralens is usually ineffective. In the hypomelanotic and amelanotic areas, there is often an almost complete absence of melanocytes [3,4]. Experimental studies [1,10] indicate that these substituted phenols have a selective lethal effect on functional melanocytes.



Fig. 58.38 Depigmentation on the face following treatment of melasma with monobenzylether of hydroquinone. (Courtesy of St John's Dermatology Centre, London, UK.)



Fig. 58.39 Hypopigmentation in a girl with resolving psoriasis.

Post-inflammatory and infections

Hypomelanotic areas occur following the resolution of areas of eczema and psoriasis (Fig. 58.39). These are also seen in pityriasis lichenoides and cutaneous T-cell lymphoma [1].

References

1 Bleehen SS, Pathak MA, Hori Y, Fitzpatrick TB. Depigmentation of skin with 4-isopropylcatechol, mercaptoamines and other compounds. *J Invest Dermatol* 1968; **50**: 103–17.
2 Lerner EA, Sober AJ. Chemical and pharmacologic agents that cause hyperpigmentation or hypopigmentation of the skin. *Dermatol Clin* 1988; **6**: 327–37.
3 Bleehen SS. Vitiligo-like leukoderma produced by substituted phenols. In: Seijii M, ed. *Pigment Cell 1981. Phenotypic Expression in Pigment Cells*. Tokyo: University of Tokyo Press, 1981: 461–6.
4 Kahn G. Depigmentation caused by phenolic detergent germicides. *Arch Dermatol* 1970; **102**: 177–87.
5 Oliver EA, Schwartz L, Warren LH. Occupational leukoderma. *Arch Dermatol Syphilol* 1940; **42**: 993–1014.
6 Bleehen SS. Skin bleaching preparations. *J Soc Cosmet Chem* 1977; **28**: 407–12.
7 Boyle J, Kennedy CTC. Leucoderma induced by monomethyl ether of hydroquinone. *Clin Exp Dermatol* 1985; **10**: 154–8.
8 Gellin GA, Maibach H. *Dermatopharmacology and Toxicology: Chemically Induced Depigmentation. Models in Dermatology*, Vol. 2. Basel: Karger, 1985: 282–6.
9 Gawkrodger DJ, Cork MJ, Bleehen SS. Occupational vitiligo and contact sensitisation. *Contact Dermatitis* 1991; **25**: 200–1.
10 Riley PA. Mechanism of pigment-cell toxicity produced by hydroxyanisole. *J Pathol* 1970; **101**: 163–9.



Fig. 58.40 Pityriasis alba. (Courtesy of St John's Institute of Dermatology, London, UK.)

The superficial eczema known as pityriasis alba (see Chapter 23) commonly presents with white, somewhat scaly, and not so well-defined areas of skin, which are most noticeable on the cheeks of racially pigmented children (Fig. 58.40).

Hypopigmented macules occur in the superficial fungal infection pityriasis versicolor, a condition frequently mistaken for vitiligo. Hyperpigmented areas are also present. It is suggested that the fungus forms oxidation products of unsaturated fatty acids of skin surface lipids that inhibit the tyrosinase activity of melanocytes [2]. Other mechanisms are suggested, including the fungus acting as a sun barrier in a thickened stratum corneum. Light and electron microscopy studies of hypopigmented macules [3,4] and of hyperpigmented areas [5] have been unhelpful in determining the mechanisms involved and are confusing. The lack of sunburn in the pale areas may be explained by the fact that the causative yeast produces pityriacitrin, an indole compound that has a broad spectrum of ultraviolet absorption [6].

In a number of inflammatory disorders of the skin, there are areas of hypomelanosis and in these there may be a loss of functional melanocytes. This loss is seen in lupus erythematosus and lichen planus. Hypopigmentation is seen in sarcoidosis [7,8] and leprosy [9]. A leukomelanoderma occurs in syphilis.

References

1 Whitmore SE, Simmons-O'Brein E, Rotter FS. Hypopigmented mycosis fungoides. *Arch Dermatol* 1994; **130**: 476–80.

2 Nazzaro Porro M, Passi S, Balus L. The monoene fatty acids of human surface lipids and their relation to skin melanogenesis. *Br J Dermatol* 1977; **97** (Suppl. 15): 16.

3 Galadari I, El Komy M, Mousa A *et al*. Tinea versicolor: histologic and ultrastructural investigation of pigmentary changes. *Int J Dermatol* 1992; **31**: 253–6.

4 Charles CR, Sire DJ, Johnson BL *et al*. Hypopigmentation in tinea versicolor. *Int J Dermatol* 1973; **12**: 48–58.

5 Allen HB, Charles R, Johnson BL. Hyperpigmented tinea versicolor. *Arch Dermatol* 1976; **112**: 1110–2.

6 Mayser P, Schäfer U, Krämer H-J *et al*. Pityriacitrin: an ultraviolet-absorbing indole alkaloid from the yeast *Malassezia furfur*. *Arch Dermatol Res* 2002; **294**: 131–4.

7 Clayton R, Breathnach A, Martin B, Feiwel M. Hypopigmented sarcoidosis in the negro. *Br J Dermatol* 1977; **96**: 119–25.

8 Cornelius CE, Stein KM, Hanshaw WJ, Sprott DA. Hypopigmentation and sarcoidosis. *Arch Dermatol* 1973; **108**: 249–51.

9 Job CK, Nayar A, Narayanan JS. Electronmicroscopic study of hypopigmented lesions in leprosy. *Br J Dermatol* 1972; **87**: 200–12.

Idiopathic guttate hypomelanosis [1–3]

This clinical entity, also known as disseminate lenticular leukoderma [4], can be mistaken for vitiligo. It is common. The lesions in white people most frequently occur in sun-exposed areas of the limbs. Solar damage is a factor in these cases. Non-actinic lesions occur in black people and may be on the trunk in unexposed areas [1].

Clinically, the lesions are porcelain-white macules, usually 2–6 mm in size but sometimes much larger. The borders are sharply defined, often angular and irregular. The skin markings are normal. Histologically, there is a decrease in pigment granules. Histochemical and ultrastructural studies [5,6] show a reduction in the number of melanocytes, many of which lack mature melanosomes. It has been suggested that this disorder results from an age-related somatic mutation of melanocytes.

References

1 Cummings KI, Cottel WI. Idiopathic guttate hypomelanosis. *Arch Dermatol* 1966; **93**: 184–6.

2 Falabella R, Escobar C, Giraldo N *et al*. On the pathogenesis of idiopathic guttate hypomelanosis. *J Am Acad Dermatol* 1987; **16**: 35–44.

3 Whitehead WJ, Moyer DG, Vander Ploeg DE. Idiopathic guttate hypomelanosis. *Arch Dermatol* 1966; **94**: 279–81.

4 Argnelles-Casals D, Gonzalez D. La leucoderme lenticulaire disséminée. *Ann Dermatol Syphiligr* 1969; **96**: 283–6.

5 Ortonne J-P, Perrot H. Idiopathic guttate hypomelanosis. *Arch Dermatol* 1980; **116**: 664–8.

6 Wilson PD, Lavker RM, Kligman AM. On the nature of idiopathic guttate hypomelanosis. *Acta Derm Venereol (Stockh)* 1982; **62**: 301–6.

Symmetrical progressive leukopathy [1]

This has been reported from Japan and Brazil, where it is relatively common. Punctate leukoderma develops in young adults, symmetrically on the front of the shins and on the extensor aspects of the arms, and less often on the abdomen and interscapular region. It is persistent.

Reference

1 Costa OG. Leucopathie symétrique progressiva des extrémités. *Ann Dermatol Syphiligr* 1951; **78**: 452–4.

Cutanous lymphoma [1,2]

Cutaneous T-cell lymphoma may sometimes show prominent hypopigmentation. In poikilodermatous mycosis fungoides, clinical lesions are characterized by widespread poikiloderma rather than plaques or nodules. On clinical examination there is alternating increase and decrease in pigmentation associated with epidermal atrophy. In hypopigmented mycosis fungoides, the areas of hypopigmentation are more prominent than in poikilodermatous mycosis fungoides [1,2].

References

1 Smith NP, Samman PD. Mycosis fungoides presenting with areas of cutaneous hypopigmentation. *Clin Exp Dermatol* 1978; **3**: 213–6.

2 Lambroza E, Cohen SR, Phelps R *et al*. Hypopigmented variant of mycosis fungoides: demography, histopathology and treatment of seven cases. *J Am Acad Dermatol* 1995; **32**: 987–93.

Endogenous non-melanin pigmentation [1]

A variety of substances that are normal constituents of the body may, if present in excess or in an abnormal form or site, give rise to alterations in skin colour. Other substances formed only by patients with certain metabolic defects may also produce pigmentary changes. Special stains of histological specimens, or techniques such as spectroscopy, may help to identify the nature of exogenous and other non-melanin pigments.

Haemosiderosis

The deposition in the tissue of the iron-containing pigment haemosiderin is commonly the result of the local destruction of red blood cells, but also occurs in haemochromatosis. The presence of haemosiderin stimulates melanogenesis, and hypermelanosis may dominate the clinical and histological picture. Such is the case in haemochromatosis (see Chapters 59 & 62). Much more frequently, haemosiderin in the skin is derived locally from red blood cells (Chapter 49); in such conditions, the pigmentation is orange–red at first, later fading through ochre and tawny shades.

Hypostatic haemosiderosis

Haemosiderosis of the lower legs is extremely common in the presence of venous insufficiency. Recently involved areas show grouped points of reddish pigment, but recurrent extravasation of red cells combined with increasing hypermelanosis soon produce a more or less uniform deep brown or coppery colour. The pigmentation usually persists even if the venous insufficiency is relieved.

Sickle-cell anaemia and congenital haemolytic anaemia

Haemosiderosis and melanosis may give rise to conspicuous pigmentation of the lower leg in the third decade or earlier.

Schamberg's disease and related disorders [2]

(see Chapter 49)

Haemosiderosis without clinically evident hypermelanosis is seen in Schamberg's disease and other types of capillaritis. Reddish-brown plaques with cayenne-pepper points beyond their margins are present on the legs and thighs and sometimes on the arms.

Small patches of haemosiderosis, most numerous on the lower legs but progressively involving thighs and buttocks, are characteristic of drug reactions to ureides. Haemosiderosis of the trunk is a feature of some reactions to clothing.

Jaundice

Jaundice results from the staining of the skin with bilirubin, which has a great affinity for elastic tissue, hence the early involvement of the sclerae. The range of yellow shades produced by bilirubin may be modified by the presence of biliverdin, which adds a greenish hue. Bronzing is the effect of added melanin pigmentation and is often seen in jaundice of long duration. The sclerae are not involved in carotenaemia and only rarely in mepacrine pigmentation (p. 58.55).

References

1 Jeghers H. Pigmentation of the skin. *N Engl J Med* 1944; **231**: 88–100.

2 Satoh T, Yokozeki H, Nishioka K. Chronic pigmented purpura associated with odontogenic infection. *J Am Acad Dermatol* 2002; **46**: 942–4.

Bronze baby syndrome [1–3]

This striking grey-brown discoloration of the skin of neonates follows phototherapy for hyperbilirubinaemia and is often associated with evidence of liver dysfunction. The serum is also brownish. The nature and origin of the pigment are uncertain. The changes are reversible unless there is some underlying liver disease.

References

1 Ashley JR, Littler CM, Burgdorf WHC. Bronze baby syndrome: report of a case. *J Am Acad Dermatol* 1985; **12**: 325–8.

2 Kopelman A, Brown R, Odell G. The bronze baby syndrome: a complication of phototherapy. *J Pediatr* 1972; **81**: 466–72.

3 Purcell SM, Wians FH, Ackerman AB *et al*. Hyperbilirubinemia in bronze baby syndrome. *J Am Acad Dermatol* 1987; **16**: 172–7.

Riboflavinaemia [1]

Yellow skin and hair have been described in a patient with myeloma, due to riboflavin being avidly bound by a monoclonal antiflavin antibody.

Reference

1 Farhangi M, Osserman EF. Myeloma with xanthoderma due to an IgG monoclonal anti-flavin antibody. *N Engl J Med* 1976; **294**: 177–83.

Carotenaemia [1]

Carotene, a lipochrome, contributes a yellow component to the colour of normal skin. In the presence of excessive blood carotene levels, this yellow component is increased, and is most conspicuously accentuated where the horny layer is thick on the palms and soles. The sclerae are not discoloured. The most striking coloration is seen in food faddists who overindulge in oranges or carrots. Some increased yellowness is seen in conditions with hyperlipaemia, diabetes, nephritis and hypothyroidism, and where conversion of carotene to vitamin A is impaired by an inborn metabolic error [2] or by hepatic disease. However, it is now more commonly seen in young women drastically reducing their weight and eating foodstuffs with high carotene content [3,4].

Carotenaemia is seen in patients on oral supplements of β-carotene as a photoprotective agent in erythropoietic protoporphyria [5,6] and in those taking carotenoids that contain canthaxanthin.

References

1 Cohen H, Lord. Observations on carotenemia. *Ann Intern Med* 1958; **48**: 219–27.

2 Monk BE. Metabolic carotenemia. *Br J Dermatol* 1982; **106**: 485–7.

3 Bilimoria S, Keczkes K, Williamson D. Hypercarotenaemia in weight watchers. *Clin Exp Dermatol* 1979; **4**: 331–5.

4 Pops MA, Schwabe AD. Hypercarotenemia in anorexia nervosa. *JAMA* 1968; **205**: 533–4.

5 Mathews-Roth MM, Pathak MA, Fitzpatrick TB *et al*. Beta-carotene as a photoprotective agent in erythropoietic protoporphyria. *N Engl J Med* 1970; **282**: 1231–4.

6 Anstey AV. Systemic photoprotection with alpha-tocopherol (vitamin E) and beta-carotene. *Clin Exp Dermatol* 2002; **27**: 170–6.

Ochronosis (see Chapter 59)

In alkaptonuria, a deficiency in homogentisic acid oxidase causes accumulation of homogentisic acid throughout the body. Ochronosis is the term used to describe the pigmentary changes that occur in connective tissue in patients with alkaptonuria [1]. The term was coined by Virchow in 1866 for the ochre-like (pale yellow) colour of the connective tissue when viewed down a microscope. Ochronosis is present in about 75% of patients with alkaptonuria, and the majority show some pigmentation. Most frequent is darkening of the ear cartilages and of the sclerae and conjunctiva. Less often the axillary skin is pigmented and there is brown mottled pigmentation of the face, sometimes in a butterfly distribution, and of the neck and trunk. Rarely, pigmentation of the palmar and plantar skin is seen [2]. Examination of the urine establishes the diagnosis.

References

1 Lubics A, Schneider I, Sebok B, Havass Z. Extensive bluish gray skin pigmentation and severe arthropathy. Endogenous ochronosis (alkaptonuria). *Arch Dermatol* 2000; **136**: 548–52.
2 Vijaikumar M, Thappa DM, Srikanth S *et al*. Alkaptonuric ochronosis presenting as palmoplantar pigmentation. *Clin Exp Dermatol* 2000; **25**: 305–7.

Exogenous pigments

A wide variety of chemicals, either from industrial or medicinal exposure, can produce discoloration of the skin. Some of these may not only produce an alteration of pigmentation by being deposited in the dermis but may also result in an increase in the amount of melanin in the skin. Of importance are the metals silver, gold, mercury and bismuth, which are cumulatively deposited in the dermis and can produce permanent disfiguring pigmentation. A number of drugs can cause discoloration of the skin. These include the antimalarials, the phenothiazines, clofazimine and minocycline. Of less importance is the transient staining of the skin produced by picric acid, dinitrophenol and chemical dyes.

Metals

Argyria [1–8]

Silver may be deposited in the skin either from industrial exposure or as a result of medication with silver salts [2–4]. Blue macules have appeared at sites of acupuncture needles [6]. Cases have followed the use of silver salts for the irrigation of nasal, oral and urethral mucous membranes and the excessive use of an oral smoking remedy containing silver acetate [2,7]. 'Food supplements' may also contain colloidal silver [8]. The pigmentation is usually a slate-grey colour and may be clinically apparent after a few months, but usually takes many years to develop and depends on the degree of exposure. The hyperpigmentation is most apparent in sun-exposed areas of skin, especially the forehead, nose and hands (Fig. 58.41). In some patients, the entire skin has a slate blue-grey colour. The sclerae, nails and mucous membranes may become hyperpigmented. Light and electron microscopy studies

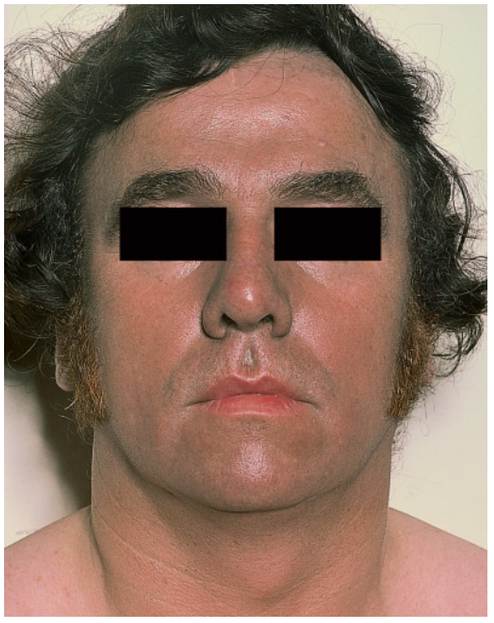


Fig. 58.41 Occupational argyria.

[1,5,6,8,9] show silver granules in the dermis that are most numerous in relation to the basal lamina of the eccrine sweat glands, and in the dermal elastic fibres. Furthermore, silver particles may be seen lying free within the cell cytoplasm of epithelial cells of the secretory segment of eccrine sweat glands and in mast cells [8,9]. Silver granules are readily visible with dark-field illumination. X-ray-dispersive microanalysis confirms that the granules contain silver [1,6]. Silver is widely deposited in the tissues as well as in the skin. The diagnosis of argyria is established by skin biopsy. The pigmentation is permanent; treatment with depigmentary preparations is not effective.

References

1 Bleehen SS, Gould DJ, Harrington CI *et al*. Occupational argyria: light and electron microscopic studies and X-ray microanalysis. *Br J Dermatol* 1981; **104**: 19–26.
2 Buckley WR, Terhaar CJ. The skin as an excretory organ in argyria. *Trans St John's Hosp Dermatol Soc Lond* 1973; **59**: 39–44.
3 Marshall JP II, Schneider RP. Systemic argyria secondary to topical silver nitrate. *Arch Dermatol* 1977; **113**: 1077–9.
4 East BW, Boddy K, Williams ED *et al*. Silver retention, total body silver and tissue silver concentrations in argyria associated with exposure to an anti-smoking remedy containing silver acetate. *Clin Exp Dermatol* 1980; **5**: 305–11.
5 Pariser RJ. Generalized argyria. *Arch Dermatol* 1978; **114**: 373–7.
6 Tanita Y, Kato T, Hanada K *et al*. Blue macules of localized argyria caused by implanted acupuncture needles. *Arch Dermatol* 1985; **121**: 1550–2.
7 Farina MC, Escalonilla P, Griilli R *et al*. Generalized argyria secondary to topical administration of silver nitrate. *Actas Dermo-Sifiliograficas* 1998; **89**: 547–52.
8 White JML, Powell AM, Brady K *et al*. Severe generalised argyria secondary to ingestion of colloidal silver protein. *Clin Exp Dermatol* 2002; **28**: 254–6.
9 Massi D, Santucci M. Human generalized argyria. A submicroscopic and X-ray spectroscopic study. *Ultrastruct Pathol* 1998; **22**: 47–53.

Chrysiasis [1–5]

Chrysiasis and chrysoderma are terms used to describe permanent pigmentation of the skin due to parenteral administration of gold salts. Excessive administration of gold leads to its deposition

in connective tissue. Chrysiasis has not been observed in any patient who has received less than 50 mg/kg of gold thiosulphate, and it has not failed to develop in any patient receiving more than 150 mg/kg. It may first develop after a few months or after a long latent period. The pigmentation is blue-grey or may show a purplish hue, and is limited to light-exposed skin and to the sclerae [3]. The oral mucous membrane is not affected. The diagnosis is confirmed histologically on microscopy with dark-field illumination and on electron microscopy with electron probe microanalysis [4]. The granules of gold are larger and more irregular than those of silver. The pigmentation is permanent [5].

References

1 Altmeyer R, Hufnagl D. Chrysiasis: Nebenwirkung einer intra-muskulären Goldtherapie. *Hautarzt* 1975; **26**: 330–3.
2 Jeffery DA, Biggs DF, Percy JS, Russell AS. Quantitation of gold in skin in chrysiasis. *J Rheumatol* 1975; **2**: 28–35.
3 Leonard PA, Moatamed F, Ward JR *et al*. Chrysiasis: the role of sun exposure in dermal hyperpigmentation secondary to gold therapy. *J Rheumatol* 1986; **13**: 58–64.
4 Smith RW, Leppard B, Barnett NL *et al*. Chrysiasis revisited: a clinical and pathological study. *Br J Dermatol* 1995; **133**: 671–8.
5 Miller ML, Harford RR, Yeager JK, Johnson F. A case of chrysiasis. *Cutis* 1997; **59**: 256–8.

Mercury [1–4]

Repeated applications of mercury-containing compounds can produce localized hyperpigmentation of the treated areas [1–3]. Systemic administration of mercury results in gingival hyperpigmentation. The pigment is observed in the upper dermis around capillaries and associated with collagen and elastic fibres. Electron microscopy shows an increase in melanin pigmentation and the metal is present as granules in dermal macrophages [1,3]. A case report of homicidal subcutaneous injection of metallic mercury resulted in widespread skin lesions, remote from the radiologically visible mercury; these appeared at 40 days and began to clear at 6 months [4].

References

1 Burge KM, Winkelmann RK. Mercury pigmentation. *Arch Dermatol* 1970; **102**: 51–61.
2 Jeghers H. Pigmentation of the skin. *N Engl J Med* 1944; **231**: 181–9.
3 Kennedy C, Molland EA, Henderson WJ, Whiteley AM. Mercury pigmentation from industrial exposure. *Br J Dermatol* 1977; **96**: 367–74.
4 Souza EM, Cintra ML, Vieira RJ *et al*. Subcutaneous injection of elemental mercury with distant skin lesions. *J Toxicol* 2000; **38**: 441–3.

Bismuthia

The administration of bismuth at regular intervals over a period of years has often been practised, yet generalized pigmentation is extremely rare. The diffuse grey pigmentation resembles that of argyria and involves also the sclera and the oral and sometimes the vaginal mucous membrane [1].

A distinctive blue-black line occurs at the gingival margin. This is due to deposition of bismuth that reacts with hydrogen sulphide formed by bacteria in the mouth [2].

References

1 Dummett CO. Oral mucosal discolorations related to pharmacotherapeutics. *J Oral Ther* 1964; **1**: 106–10.
2 Lueth HC, Sutton DC, McMullen CJ *et al*. Generalized discoloration of skin resembling argyria following prolonged oral use of bismuth. *Arch Intern Med* 1936; **57**: 1115–24.

Drugs

Mepacrine [1,2]

Pigmentation of the skin is first noticed a few days after the administration of mepacrine commences and may persist for several weeks after it ceases. The dye is deposited in the skin. A bright-yellow or greenish-yellow colour develops first and remains most prominent on the face, hands and feet, but occurs diffusely with accentuation in the skin flexures. The sclerae are sometimes affected, which may mimic jaundice [2]. The melanin-containing pigment induced by antimalarials is discussed in Chapter 75.

References

1 Schachter AJ, Taylor HM. Atabrine pigmentation. *Am J Med Sci* 1936; **192**: 645–50.
2 Leigh IM, Kennedy CT, Ramsey JD, Henderson WJ. Mepacrine pigmentation in systemic lupus erythematosus. New data from an ultrastructural, biochemical and analytical electron microscopic investigation. *Br J Dermatol* 1979; **101**: 147–53.

Clofazimine (Lamprene) [1–4]

This synthetic riminohenazine dye used in the treatment of leprosy produces an initial redness of the skin due to an accumulation of the drug. Later, with prolonged treatment, a violaceous brown colour develops that is most noticeable in lesional areas [1]. Histochemical studies indicate a ceroid-lipofuscin pigment as well as clofazimine inside macrophage phagolysosomes [2,3]. Reddish-blue pigmentation has been reported within scarred areas of lupus erythematosus in one patient [4].

References

1 Pettit JHS. B 663 (Lampren) in mycobacterial infections. *Br J Dermatol* 1969; **81**: 794–5.
2 Sakurai I, Skinsnes OK. Histochemistry of B 663 pigmentation: ceroid-like pigmentation in macrophages. *Int J Lepr* 1977; **45**: 343–54.
3 Job CK, Yoder L, Jacobson RR, Hastings RC. Skin pigmentation from clofazimine therapy in leprosy patients: a reappraisal. *J Am Acad Dermatol* 1990; **23**: 236–41.
4 Kossard S, Doherty E, Mccoll I, Ryman W. Autofluorescence of clofazimine in discoid lupus erythematosus. *J Am Acad Dermatol* 1987; **17**: 867–71.

Hydroxyurea [1]

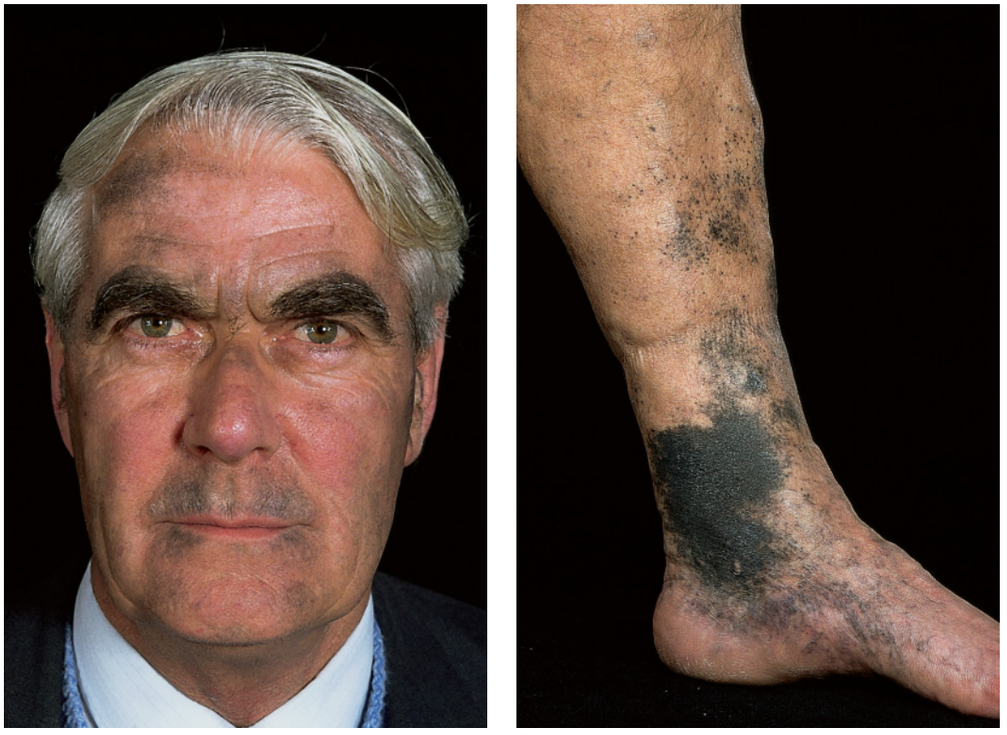
Nail pigmentation has been reported in association with use of hydroxyurea and most commonly consists of longitudinal melanonychia. Occasionally all 20 nails are affected and there is associated hyperpigmentation of the skin.

Reference

1 Aste N, Fumo G, Contu F *et al*. Nail pigmentation caused by hydroxyurea: report of nine cases. *J Am Acad Dermatol* 2002; **47**: 146–7.

Minocycline [1–8]

Long-term therapy with minocycline may result in pigmentation, but this is generally agreed to be rare. Three types of cutaneous pigmentation are seen in patients treated with minocycline [6] (Fig. 58.42):



(a) (b)

Fig. 58.42 (a) Hyperpigmentation of the skin in sun-exposed areas of the face due to long-term therapy with minocycline. (b) Blue-black pigmentation on the lower legs in the same patient.

1 A focal type with well-demarcated blue-black pigmentation at sites of previous inflammation as first described in acne scars [1]
2 A more diffuse and generalized pigmentation that is most apparent in sun-exposed areas of skin and nails [2], but may also involve the sclera [5]
3 A more persistent brown-grey change most prominent on sun-exposed sites.

The pigmentation usually occurs following prolonged courses and high doses of this drug. Histological studies show the presence of brown-black granules in the upper dermis that stain for iron [1,3]. Electron microscopy reveals electron-dense material in dermal macrophages and X-ray microanalysis confirms the presence of iron [4]. Partial resolution of the pigmentation occurs after the drug is stopped [6]. Similar blue-black pigmentation of the legs has resulted from treatment with the 4-quinolone antibiotic pefloxacin [7] and the tetracycline antibiotic methacycline [8].

References

1 Basler RSW. Minocycline-related hyperpigmentation. *Arch Dermatol* 1985; **121**: 606–8.
2 Simons JJ, Morales A. Minocycline and generalized cutaneous pigmentation. *J Am Acad Dermatol* 1980; **3**: 244–7.
3 Gordon G, Sparano BM, Iatropoulos MJ. Hyperpigmentation of the skin associated with minocycline therapy. *Arch Dermatol* 1985; **121**: 618–23.
4 Argenyi ZB, Finelli L, Bergfeld WF *et al*. Minocycline-related cutaneous hyperpigmentation as demonstrated by light microscopy, electron microscopy and X-ray energy spectroscopy. *J Cutan Pathol* 1987; **14**: 176–80.
5 Angeloni VL, Salasche SJ, Ortiz R. Nail, skin, and scleral pigmentation induced by minocin. *Cutis* 1987; **40**: 229–33.
6 Layton AM, Cunliffe WJ. Minocycline induced pigmentation in the treatment of acne: a review and personal observations. *J Dermatol Treat* 1989; **1**: 9–12.
7 Le Cleach L, Chosidow O, Peytavin G *et al*. Blue–black pigmentation of the legs associated with pefloxacin therapy. *Arch Dermatol* 1995; **131**: 856–7.
8 Moller H, Rausing A. Methacycline pigmentation: a five-year follow-up. *Acta Derm Venereol (Stockh)* 1980; **60**: 495–501.

Amiodarone [1–5]

Amiodarone is a drug used for prolonged periods in the treatment of ventricular tachycardia. It induces photosensitivity in more than 50% of patients; however, fewer than 5% develop cutaneous hyperpigmentation [1–5]. A grey-blue pigmentation of the face and other sun-exposed areas is a rare late effect of this drug, and may also involve non-exposed sites (Fig. 58.43) [1]. Yellow-brown granules are present in dermal histiocytes. Ultrastructural studies show membrane-bound dense lysosomal bodies in macrophages that probably contain degradation products of the drug bound to lipofuscin [1,2]. Dose reduction or withdrawal of amiodarone can lead to complete disappearance of the pigmentation [5].

References

1 Delage C, Legacé R, Huard J. Pseudocyanotic pigmentation of the skin induced by amiodarone. *Can Med Assoc J* 1975; **112**: 1205–8.
2 Zachary CB, Slater DN, Holt DW *et al*. The pathogenesis of amiodarone-induced pigmentation and photosensitivity. *Br J Dermatol* 1984; **110**: 451–6.
3 Ferguson J, Addo HA, Jones S *et al*. A study of cutaneous photosensitivity induced by amiodarone. *Br J Dermatol* 1985; **113**: 537–49.
4 Sivaram CA, Beckman KJ. Images in clinical medicine. Amiodarone-induced skin discoloration. *N Engl J Med* 1997; **337**: 1813.
5 Scholz S, Rompel R. Amiodarone-induced pigmentation. *Z Hautkr* 1997; **72**: 901–4.

Picric acid, dinitrophenol and other chemicals

Picric acid, self-administered by malingerers to simulate jaundice, stains the skin yellow. Dinitrophenol, formerly used in industry



Fig. 58.43 Bluish pigmentation on the nose caused by amiodarone therapy.

and as a metabolic stimulant, also produces yellow staining of the skin and of the sclerae. Trinitrotoluene, santonin and acriflavine also stain the skin yellow.

Tattoos

Accidental tattoos

Pigmented particles may be accidentally introduced as contaminants of wounds or may, at high velocity, penetrate previously intact skin.

Superficial abrasions contaminated with chemically inert particles may be followed by disfiguring tattoos. Such irregularly spattered pigmentation is quite commonly seen after road accidents and blast injuries. Some particles may eventually be extruded, but the disfigurement is often permanent. Small lesions may be excised and larger areas treated by dermabrasion, the results of which depend on the depth to which the particles have penetrated.

Collier's stripes [1]

These are a very distinctive occupational mark in coalminers. The bluish grey, linear or angular stripes develop at the sites of abrasions. The commonest sites are the forehead, bridge of the nose, wrists and elbows. Histologically, particles of coal dust up to 100 µm in diameter are seen at all levels in the dermis. They tend to be grouped around blood vessels.

Therapeutic agents

Iron salts. The use of solutions of ferric sulphate and ferric chloride in the treatment of dermatitis has been followed by a reddish-brown tattoo [2,3]. The pigmentation may disappear after a few months or may persist indefinitely [4].

Occupational contact with iron salts [5] produced red-brown punctate perifollicular pigmentation of the forearms in a man employed in pickling metal in hydrochloric acid.

Gentian violet (pararosaniline chloride). This has, exceptionally, given rise to a tattoo when applied to a wound of the face [6].

References

1 Bettley FR. Colliers' stripes: the coal miners' dermatosis. *Br J Dermatol Syphilol* 1940; **52**: 129–30.
2 Reyner CE. Pigmentation following the use of iron salts. *Arch Dermatol Syphilol* 1939; **40**: 380–1.
3 Traub EF, Tennen JS. Permanent pigmentation following application of iron salts. *JAMA* 1936; **106**: 1711–2.
4 Sutton RL. Pigmentation of the skin due to iron (copperas) applied locally. *JAMA* 1937; **108**: 112–3.
5 Hare PJ. A case of occupational iron pigmentation of the skin. *Br J Dermatol* 1951; **63**: 63–6.
6 Sutton RL. Gentian violet as a therapeutic agent. *JAMA* 1938; **110**: 1733–8.

Decorative tattoos (see also Chapter 28) [1–5]

History and prevalence. From ancient origins the practice of tattooing has developed along more or less parallel lines in most countries. Tattoos have been used to accentuate beauty, as a permanent adornment or to make a statement. Occasionally, tattoos serve to accentuate aggression or ugliness in order to make the wearer more intimidating. Tattoos with words or a name as a symbol of dedication or devotion have always been popular. Tattoos have also been used for more sinister motives. Tattoos were used as a means of identification by the Nazis in the Second World War for members of concentration and labour camps as well as for members of the SS. Formerly associated with religious ceremonies, fertility and marriage rites, tattooing in contemporary westernized civilizations thus fulfils a number of diverse functions and in so doing it survives and flourishes.

Contemporary life finds tattooing more popular than ever [1], even among the elite [2]. Tattoos are no longer the exclusive preserve of street gangs, prisoners and members of the armed forces [1,2]. Not all who submit to tattooing are emotionally unstable, immature individuals. Indeed, tattooing is viewed by many as an acceptable fashion accessory like any other, and is increasingly popular in Western societies with the young and with women, as well as the more traditional male stereotypes [1,2]. Tattooing and body piercing are now so common that health-care workers are advised to maintain a non-judgemental attitude to tattoos [1], even in the face of the unexpected [4]. The decision to have a tattoo may be taken when an individual is in no position to make such a lifelong commitment, for example when intoxicated, under peer pressure or when mentally unwell [5]. Tattoos may also be a manifestation of deliberate self-harm [6].

Another contemporary trend is the use of temporary black henna 'tattoos' [3,7]. These are not true tattoos but represent application of a black dye to produce a tattoo-like appearance that lasts for a few days. Unfortunately, a high concentration of the well-known contact sensitizer paraphenylenediamine is usually present in these 'tattoos', which results in a risk of contact allergy [3,7].

Techniques and materials. The professional tattooist uses an electric needle to introduce particles of pigment into the dermis; the amateur, often a child, pricks particles of soot or Indian ink into skin with any pointed object. The individual's choice of design may be motivated by subconscious psychological factors. The pigments commonly employed include:

- Blue-black (carbon)
- Red (cinnabar and vegetable dyes)
- Light blue (cobaltous aluminate)
- Green (chromic oxide or chromium sesquioxide)
- Yellow (cadmium sulphide)
- Brown (ochre, iron oxides).

Complications of tattoos

Unhappiness with the tattoo

Many regret having a tattoo, which may cause a significant psychological, social and financial burden [8].

Introduction of infection

Significant infection of tattoos is now unusual, and pyogenic infection, although the most frequent, is seldom serious. Erysipelas and gangrene, necessitating amputation, are mentioned in the older literature. Syphilis and tuberculosis have been inoculated by the tattoo needle, and small outbreaks have been traced to an infected operator. The tattooing of many people in rapid succession has been suspected of transmitting infective hepatitis. Also there is the risk of transmitting retrovirus infection. The transmission of leprosy is suspected [9]. Both vaccinia and warts have developed in recently inflicted tattoos.

Allergic reactions to pigment

Once the initial inflammatory changes have subsided, by far the most frequent reaction observed in tattoos is the development of allergic sensitivity to one of the pigments.

In most cases, the tattoo pigment itself, or a derived compound formed locally in the tissues, provokes the development of hypersensitivity, which is manifest clinically by the sudden onset of irritation, swelling and redness in a part of the tattoo a few weeks or many years after its infliction. In recent years, lichenoid tattoo reactions have been reported; these appear to be confined entirely to the red areas (Fig. 58.44) [10]. These resemble the reactions to cinnabar (mercuric sulphide); although this pigment has now been replaced by vegetable dyes, cases do still occur [11].

The allergic reaction can remain localized but may become generalized as a patchy eczematous eruption or an exfoliative dermatitis. In some cases, the primary sensitization is induced by some other contact with the metal, and the reaction in the tattoo accompanies or follows an attack of contact dermatitis.

Mercury [12]. The red areas of the tattoo are affected. The reaction may eventually subside spontaneously, but the risk of a generalized eruption is high. The tattoo reaction may be accompanied by erosions of the oral mucosa in contact with amalgam dental fillings [13]. Patch tests are positive to mercuric chloride and ammoniated mercury but not necessarily to cinnabar.



Fig. 58.44 Lichenoid reaction in red areas of a tattoo.

Chrome [14]. The green areas are affected. The patient is often primarily sensitized by exposure to cement. Patch tests with 0.5% potassium dichromate are positive.

Cobalt [15]. The light-blue areas are affected. In three patients, the tattoo reaction was accompanied by the simultaneous development of uveitis [16]. Patch tests are positive with 2% cobalt chloride.

Manganese [17]. A reaction in the purple areas of a tattoo was due to manganese.

Carbon [18]. A case is reported of a reaction in the black areas of a tattoo, presumably to carbon particles.

Light-induced reactions [19]. A high proportion of yellow tattoos develop redness and swelling only on exposure to sunlight, and the same phenomenon is occasionally observed in red tattoos. The mechanism is uncertain, although the yellow pigment, cadmium sulphide, has photoconducting properties.

Localization of skin disease in tattoos

Some skin disorders show a predilection for tattooed skin, in which they may appear first or be accentuated. Syphilis in the secondary or tertiary stage has often been observed in tattoos but tends to spare the red areas, apparently deterred by the mercury. Lichen planus and psoriasis may be localized in tattoos but show no colour predilection. Lupus erythematosus is more rarely seen. A sarcoidal granuloma in a tattoo may be the presenting manifestation of generalized sarcoidosis [20]. Melanoma has been reported in a tattoo [21], although the association may be fortuitous. Foreign-body granulomas of sarcoid type are extremely unusual after decorative tattoos, but have been reported in ochre tattoos [22]; ochre has a high silica content.

References

1 Millner VS, Eichold BH. Body piercing and tattooing perspectives. *Clin Nurs Res* 2001; **10**: 424–41.
2 Mayers LB, Judelson DA, Moriarty BW, Rundell KW. Prevalence of body art (body piercing and tattooing) in university undergraduates and incidence of medical complications. *Mayo Clin Proc* 2002; **77**: 29–34.
3 Onder M, Atahan CA, Oztas P, Oztas MO. Temporary henna tattoo reactions in children. *Int J Dermatol* 2001; **40**: 577–9.
4 Bowling JC, Groves R. An unexpected tattoo. *Lancet* 2002; **359**: 649.
5 Gittleson NL, Wallen GOP, Dowson-Butterworth K. The tattooed psychiatric patient. *Br J Psychiatry* 1969; **115**: 1249–53.
6 Joe EK, Li VW, Magro CM *et al*. Diagnostic clues to dermatitis artefacta. *Cutis* 1999; **63**: 209–14.
7 Brancaccio RR, Brown LH, Chang YT *et al*. Identification and quantification of para-phenylenediamine in a temporary henna tattoo. *Am J Contact Dermatitis* 2002; **13**: 15–8.
8 Varma S, Lanigan SW. Reasons for requesting laser removal of unwanted tattoos. *Br J Dermatol* 1999; **140**: 483–5.
9 Sehgal VN. Inoculation leprosy appearing after several years of tattooing. *Dermatologica* 1971; **142**: 58–61.
10 Taaffe A, Knight A, Marks R. Lichenoid tattoo hypersensitivity. *BMJ* 1978; **i**: 616–8.
11 Sowden JM, Byme JPH, Smith AH *et al*. Red tattoo reactions: X-ray microanalysis and patch test studies. *Br J Dermatol* 1991; **124**: 576–80.
12 Biro L, Klein WP. Unusual complication of mercurial (cinnabar) tattoo. *Arch Dermatol* 1967; **96**: 165–7.
13 Juhlin L, Oleman S. Allergic reactions to mercury in red tattoos and in mucosa adjacent to amalgam fillings. *Acta Derm Venereol (Stockh)* 1968; **48**: 103–5.
14 Björnberg A. Allergic reactions to chrome in green tattoo markings. *Acta Derm Venereol (Stockh)* 1959; **39**: 23–9.
15 Björnberg A. Allergic reactions to cobalt in light blue tattoo markings. *Acta Derm Venereol (Stockh)* 1961; **41**: 259–63.
16 Rorsman H, Dahlquist I, Jacobsson S *et al*. Tattoo granuloma and uveitis. *Lancet* 1969; **ii**: 27–8.
17 Scwartz RA, Mathias CA, Muller CH *et al*. Granulomatous reaction to purple tattoo pigment. *Contact Dermatitis* 1987; **16**: 198–202.
18 Tope WD, Arbiser JL, Duncan LM. Black tattoo reaction: the peacock's tale. *J Am Acad Dermatol* 1996; **35**: 477–9.
19 Björnberg A. Reactions to light in yellow tattoos from cadmium sulfide. *Arch Dermatol* 1963; **88**: 267–71.
20 Dickinson JA. Sarcoidal reactions in tattoos. *Arch Dermatol* 1969; **100**: 315–9.
21 Kirsch N. Malignant melanoma developing in a tattoo. *Arch Dermatol* 1969; **99**: 596–8.
22 Hoffman-Martinot R, Gratadour P. Divers modes de comportement des tatouages. A propos d'un cas clinique particulier du type granulome silicotique. *Presse Med* 1963; **71**: 2095–7.

Treatment of tattoos [1–9]. The removal of a tattoo may become essential on account of the development of one of the complications considered above, most commonly an allergic reaction within the tattoo. Some cases will settle with intralesional or even topical steroids, but more often excision of the offending area of tattoo, followed if necessary by grafting, is the only satisfactory treatment to secure elimination of all particles of pigment.

Far more frequently, removal of a tattoo is sought on aesthetic or cosmetic grounds, often only a few weeks after its infliction. If the area involved is small and simple or serial excision without grafting is practicable, this is undoubtedly the treatment of choice. If grafting is essential, the inevitable cosmetic imperfections of grafts are such that alternative procedures may be considered. Salabrasion using table salt is of use [6]. Some good results have been achieved with lasers, but scarring, at times quite troublesome, is likely to remain. The best results are with Q-switched red or near-infrared laser systems [7]. Infrared coagulation has also been used [8]. The keratotome [9] gives moderately good results and at least partially obliterates the design. For very extensive tattoos, dermabrasion or chemosurgery [4] have been advocated. The choice of technique should be influenced by personal predilections, and the experience of the plastic surgeon consulted. The patient should be warned that there is usually some residual pigment following superficial abrasion and there may be scarring.

References

1 Apfelberg DB, Maser MR, Lash H. Argon laser treatment of decorative tattoos. *Br J Plast Surg* 1979; **32**: 141–4.
2 Buncke HJ, Conway H. Surgery of decorative and traumatic tattoos. *Plast Reconstr Surg* 1957; **20**: 67–77.
3 Clabaugh W. Removal of tattoos by superficial dermabrasion. *Arch Dermatol* 1968; **98**: 515–21.
4 Lerner C. Removal of tattoo marks. *NY State J Med* 1948; **48**: 1937–9.
5 Scutt RWB. The chemical removal of tattoos. *Br J Plast Surg* 1972; **25**: 189–94.
6 Crittenden FM Jr. Salabrasion: removal of tattoos by superficial abrasion with table salt. *Cutis* 1971; **7**: 295–300.
7 Alster TS. Q-switched alexandrite laser treatment (755 nm) of professional and amateur tattoos. *J Am Acad Dermatol* 1995; **33**: 69–73.
8 Venning VA, Colver GB, Millard PR *et al*. Tattoo removal using infrared coagulation: a dose comparison. *Br J Dermatol* 1987; **117**: 99–105.
9 Grice KA. The removal of tattoos with a keratotome. *Br J Dermatol* 1964; **76**: 318–21.

CHAPTER 59

Metabolic and Nutritional Disorders

R.P.E. Sarkany[1], S.M. Breathnach[1], A.A.M. Morris[2], K. Weismann[3] & P.D. Flynn[4]

[1]St John's Institute of Dermatology, St Thomas' Hospital, London, UK
[2]Willink Biochemical Genetics Unit, Royal Manchester Children's Hospital, Manchester, UK
[3]The Skin Clinic, Privatehospital Hamlet, Søborg, Denmark
[4]Addenbrooke's Hospital, Cambridge, UK

The cutaneous porphyrias, 59.1
General considerations: theoretical basis, clinical features and laboratory testing in porphyria, 59.2
A theoretical basis for understanding the porphyrias, 59.2
Clinical features of the porphyrias: general considerations, 59.3
A clinician's guide to laboratory testing in porphyria, 59.8
The individual porphyrias, 59.10
Porphyrias that cause cutaneous disease but do not cause acute attacks, 59.10
Porphyrias that cause cutaneous disease and acute attacks, 59.19
Mucinoses, 59.21
Classification of the cutaneous mucinoses, 59.21
Lichen myxoedematosus, 59.21
Acral persistent papular mucinosis, 59.24
Papular mucinosis of infancy, 59.24
Self-healing papular mucinosis; juvenile and adult, 59.24
Hereditary progressive mucinous histiocytosis, 59.25
Cutaneous focal mucinosis, 59.25
Mucinous naevus, 59.25
Reticular erythematous mucinosis, 59.25
Follicular mucinosis, 59.26
Secondary mucinoses, 59.29
Lysosomal storage disorders, 59.30
Mucopolysaccharidoses, 59.30
Mucolipidoses, 59.32
Disorders of glycoprotein degradation, 59.33
Angiokeratoma corporis diffusum, 59.35
Gaucher's disease, 59.39
Niemann–Pick disease types A and B, 59.40
Farber's disease, 59.41
Lipoid proteinosis, 59.41
Amyloid and the amyloidoses of the skin, 59.42
Primary localized cutaneous amyloidosis, 59.44
Secondary localized cutaneous amyloidosis, 59.50
Systemic amyloidosis, 59.50
Primary and myeloma-associated cutaneous amyloidosis, 59.50
Secondary systemic amyloidosis, 59.56
Dialysis-related amyloidosis, 59.57
Inherited systemic amyloidosis, 59.57
Nutrition and the skin, 59.58
Malabsorption, 59.58
Mucoviscidosis, 59.59
Vitamins, 59.60
Kwashiorkor and marasmus, 59.67
Calcification and ossification of the skin, 59.68
Iron metabolism, 59.70
Sulphur metabolism, 59.72
Zinc metabolism, 59.72
Copper metabolism, 59.76
Selenium metabolism, 59.76
Skin disorders in diabetes mellitus, 59.77
Xanthomas and abnormalities of lipid metabolism and storage, 59.81
Lipid metabolism, 59.81
Dyslipidaemias: classification, 59.83
Xanthomata, 59.84
Primary dyslipidaemias, 59.86
Secondary dyslipidaemias, 59.92
Disorders of amino-acid metabolism, 59.94
Hyperphenylalaninaemia syndromes, 59.94
Tyrosinaemia, 59.97
Alkaptonuria, 59.98
Homocysteinurias, 59.99
Hartnup disease, 59.100
Gout, 59.101
Lesch–Nyhan syndrome, 59.102

The cutaneous porphyrias

R.P.E. Sarkany, pp. 59.1–59.21

Introduction

The porphyrias are a group of disorders caused by defects in the biosynthesis of haem. Their relevance to the skin arises from the phototoxic properties of the porphyrins, which accumulate in most porphyrias and cause photosensitivity.

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

The majority of the porphyrias are inherited. Many of them affect other organs as well as the skin. The recognition and management of both the genetic and internal consequences of porphyrias presenting in the skin are a key challenge for the dermatologist.

Clinical management in these disorders is made easier when the clinician understands their theoretical basis. Thus, this section is divided into two halves. The first provides a theoretical basis for understanding the porphyrias, the general principles of clinical management and a clinician's guide to laboratory testing. The second half covers individual porphyries in detail.

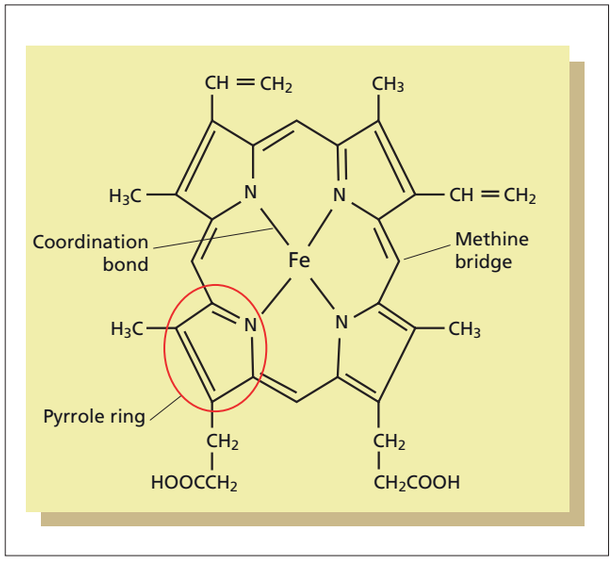


Fig. 59.1 The haem molecule and its key structural features. The alternation of single and double bonds around the tetrapyrrole ring indicates the aromaticity of the molecule, central to its chemical characteristics. The four coordination bonds between iron and nitrogen atoms are shown. The two remaining bonds between the iron and either molecular oxygen or amino acid residues lie perpendicular to the page.

General considerations: theoretical basis, clinical features and laboratory testing in porphyria

A theoretical basis for understanding the porphyrias

The phototoxicity of porphyrins

The phototoxic properties of porphyrins are responsible for the cutaneous features of the porphyrias. Porphyrins are intermediates in the biosynthesis of haem, and consideration of the chemical features of the haem and porphyrin molecules is necessary to understand the cause of porphyrin phototoxicity.

The chemistry of porphyrins and haem [1]. A pyrrole is a ring composed of four carbon atoms and one nitrogen atom. Four pyrroles linked into a ring create a tetrapyrrole, a remarkable and biologically critical molecular structure found in chlorophyll, haem and vitamin B_{12}. A porphyrin is a special type of tetrapyrrole in which four pyrrole rings are linked by methine bridges into a large ring structure.

Haem is the molecule created by the insertion of ferrous iron into the centre of the porphyrin molecule, protoporphyrin IX (Fig. 59.1). Essentially, incorporation of iron into the porphyrin molecule enables it to become biologically useful. Iron's capacity to bind to molecular oxygen, and to transfer electrons (by moving between the 2+ and 3+ oxidation states) makes it potentially useful in biological systems, but free iron precipitates in the presence of water. For iron to be useful, it has to be kept soluble by protecting its binding sites against water. In addition, subtle modification of the electronic structure of the iron atom can optimize its ability to transfer electrons and reversibly bind molecular oxygen. Binding of iron to the porphyrin molecule solubilizes iron and also optimizes its electronic structure. The porphyrin's central cavity is the right size to fit an iron atom, and its four central nitrogen atoms occupy four of the iron's coordination binding sites, leaving only two free. A key feature of the porphyrin structure is that each double bond is adjacent to a single bond, so it is 'aromatic' with 18 of its electrons being delocalized and free to move around the molecule (Fig. 59.1). This electron current results in the central nitrogen atoms tending to donate electrons to the iron atom, as well as other subtler electronic interactions involving transient changes in the porphyrin's electronic state [2]. Haem can bind to a variety of proteins, and the nature of this interaction reflects the protein's function. In proteins with electron transport functions, such as respiratory cytochromes, amino acids bind to both remaining coordination binding sites on the iron so that haem can transfer electrons through alterations in the iron's oxidation state. In proteins with oxygen-binding functions, such as haemoglobin, an amino acid binds to one of the iron's remaining coordination binding sites, leaving the sixth site free to bind to oxygen. In summary, the aromatic porphyrin structure is well suited to complexing with iron to form haem, rendering the iron useful for electron transfer (respiratory cytochromes), reversible oxygen binding (haemoglobin and myoglobin), and oxidation and reduction reactions (cytochrome P450, catalase), with fine tuning of the iron's functionality being determined by the apoprotein which binds to the haem.

Photochemistry of the porphyrins [3,4]. The complex electronic structure of the large aromatic porphyrin molecule results in its 18 delocalized electrons having unusual excitation characteristics. These electrons are excited by relatively long wavelength light. The main absorption peak is at 408 nm ('Soret band') [3], and this long wavelength of exciting light predisposes to phototoxic behaviour by the porphyrin; these photons have insufficient energy to chemically alter the porphyrin structure, so that alternative fates for the energy, particularly fluorescence and phosphorescence, become more likely [4]. Thus, following excitation by light around the 408 nm peak, electrons either return to the non-excited ground state by releasing the energy as the characteristic red fluorescence, or the porphyrin's excited singlet state transforms (by intersystem crossing) to the longer-lived excited triplet state. Transfer of energy from this excited triplet state to neighbouring molecules leads to the phototoxicity responsible for the clinical features of the cutaneous porphyrias. Thus cutaneous disease in the porphyrias can be thought of as a by-product of the unusual porphyrin structure which enables haem-proteins to fulfil their biological functions.

References

1 Wilkins PC, Wilkins RG. *Inorganic Chemistry in Biology*. Oxford: Oxford University Press, 1997.
2 Constable EC. *Coordination Chemistry of Macrocyclic Compounds*. Oxford: Oxford University Press, 1999.
3 Drabkin DL. Selected landmarks in the history of porphyrins and their biologically functional derivatives. In: Dolphin D, ed. *The Porphyrins*. New York: Academic Press, 1979: 31–71.
4 Wayne CE, Wayne RP, eds. Photophysics. In: *Photochemistry*. Oxford: Oxford University Press, 1996: 39–58.

Enzyme deficiencies and the porphyrias

The porphyrias all result from a partial deficiency of one of the enzymes required for the biosynthesis of haem, thus causing accumulation of the enzyme's substrate. The toxicity profile of the accumulated molecule determines the clinical features of the resulting porphyria. A basic understanding of the biosynthetic pathway enables the clinician to interpret laboratory results and to predict the clinical features of each porphyria on the basis of each porphyrin's properties.

The biosynthesis of haem [1,2] (Fig. 59.2). Haem is synthesized from simple biochemicals (glycine and succinyl CoA) via an eight-step pathway, each step being catalysed by an enzyme. Synthesis of the pyrrole ring (porphobilinogen (PBG)) is followed by assembly of the tetrapyrrole structure (hydroxymethylbilane). One of the pyrrole rings (the 'D' ring) is 'flipped' around to create the III isomer (the alternative I isomer forms in the absence of the cosynthase enzyme). Next, the carboxylic acid side-chains of uroporphyrinogen III are progressively decarboxylated via coproporphyrinogen III to protoporphyrinogen, which is then oxidized to protoporphyrin IX. It is likely that the progressive decarboxylation to remove six of the eight electron-withdrawing carboxylate groups increases the flux of electrons onto the molecule's central nitrogens to facilitate coordination with iron. Finally, ferrous iron is chelated into the protoporphyrin's central cavity to form haem. Around 80% of haem is synthesized in erythroid cell precursors in the bone marrow (for haemoglobin production). The decarboxylation of uroporphyrinogen to coproporphyrinogen, and thence to protoporphyrinogen, decreases water solubility, so that uroporphyrinogen is only excreted via the kidneys whereas hydrophobic protoporphyrinogen and protoporphyrin are exclusively excreted into the bile. Coproporphyrinogen is excreted by both routes. Physiological concentrations of porphyrins stay low because of the high efficiency of haem synthesis.

References

1 Elder GH. The cutaneous porphyrias. In: Hawk JLM, ed. *Photodermatology*. London: Arnold, 1999: 171–99.

2 del C, Battle AM. Tetrapyrrole biosynthesis. *Semin Dermatol* 1986; **5**: 70–87.

Clinical features of the porphyrias: general considerations

Porphyrias present with either skin disease or acute attacks or both.

The classification of the porphyrias [1,2]

In any porphyria, a partial enzyme deficiency causes the accumulation of porphyrins. The enzyme deficiency associated with each disorder is shown in Fig. 59.3. The porphyrias have previously been classified, according to the predominant site of porphyrin accumulation, into the erythropoietic group (congenital erythropoietic porphyria and erythropoietic protoporphyria) and the hepatic group (all the others). This division is not of value clinically. For the clinician, the key division is between porphyrias that cause acute attacks and those that cause skin disease. In this chapter the following classification is used for the six common porphyrias:

1 Cutaneous disease only:
Porphyria cutanea tarda (PCT)
Congenital erythropoietic porphyria (CEP)
Erythropoietic protoporphyria (EPP).
2 Cutaneous disease and acute attacks:
Hereditary coproporphyria (HC)
Variegate porphyria (VP).
3 Acute attacks only:
Acute intermittent porphyria (AIP)

References

1 Elder GH. The cutaneous porphyrias. In: Hawk JLM, ed. *Photodermatology*. London: Arnold, 1999: 171–99.

2 Dean G. Historical background. In: Dean G, ed. *The Porphyrias. A Story of Inheritance and Environment*, 2nd edn. London: Pitman Medical, 1971: 14–9.

Porphyria and the skin

The cutaneous porphyrias share many features. Consideration of these underlying similarities is necessary for a logical approach to clinical management of patients.

All the cutaneous porphyrias, except EPP, present with fragility and blistering of light-exposed skin; the term 'bullous porphyrias' is often used for this group of diseases. Not only can they appear very similar clinically, but the mechanism underlying the skin disease in all cutaneous porphyrias is a local porphyrin phototoxicity reaction. This shared pathogenetic mechanism means that the histopathological appearances in each of these conditions are also similar. As a result, these disorders can only be reliably differentiated by biochemical analysis. The other important similarity between them is that they are all caused by Soret wavelength light (408 nm), so the same strategy for photoprotection applies to them all, as detailed below.

The pathogenesis of skin disease in porphyria (Fig. 59.4) [1–3]. Photons of violet light, with a wavelength peak at 408 nm, transform the porphyrin molecule into an excited singlet state. This may revert to the unexcited ground state by emission of the characteristic red porphyrin fluorescence, but intersystem crossing can convert it to the excited triplet state, long-lived enough to interact with other molecules, particularly molecular oxygen, converting it to excited singlet oxygen in the process. The singlet oxygen stimulates production of hydroxyl radicals which damage tissue directly, and also indirectly by stimulating complement activation [4], mast cell degranulation [5] and matrix metalloproteinase activity [6]. The site of this phototoxic reaction in the skin determines the clinical characteristics of the porphyria. In EPP, lipophilic protoporphyrin tends to localize to membranes including endothelial cell membranes, and to remain within erythrocytes, and the phototoxic reaction involves upper dermal blood vessels causing pain. In PCT, the water-soluble uroporphyrin diffuses easily into surrounding tissues and the phototoxic reaction occurs in the upper dermis, causing lysis of cells in the superficial dermis with the formation of membrane-limited vacuoles which merge to produce a blister under the basal lamina, producing the characteristic clinical presentation [7]. In VP, copro- and protoporphyrin accumulate (Fig. 59.3), but patients suffer from PCT-like upper dermal blisters rather than EPP-like acute pain. This is likely to be

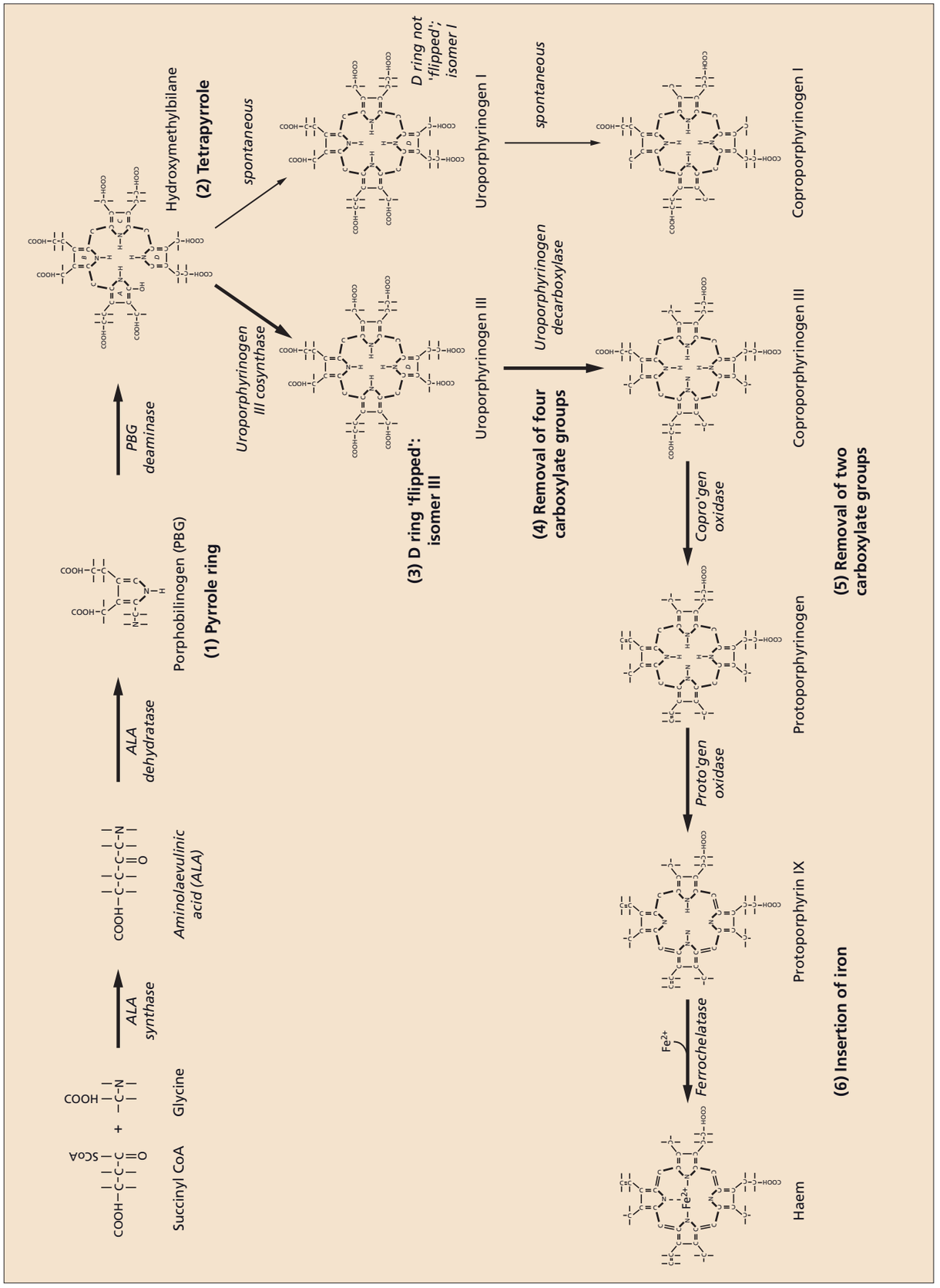


Fig. 59.2 The pathway of haem biosynthesis showing the six key structural changes.

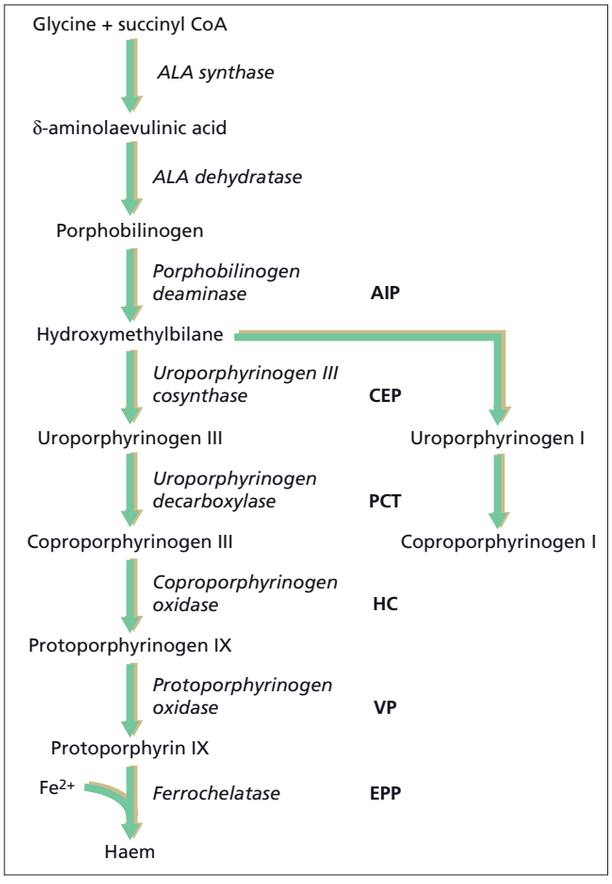


Fig. 59.3 The pathway of haem biosynthesis showing the enzyme deficiency associated with each porphyria. (The abbreviations of disease names are defined in the text relating to classification of the porphyrias.)

because, although hydrophobic porphyrins predominate in plasma in VP, hydrophilic porphyrins, particularly uroporphyrin, predominate in the skin, probably due to secondary local photoinactivation of uroporphyrinogen decarboxylase (UROD) in the skin by coproporphyrin [2]. In addition, the protoporphyrin in VP is conjugated to a peptide which may reduce its phototoxicity.

There is no simple correlation between the plasma porphyrin concentration and the severity of cutaneous disease in porphyria because of the large number of local variables which can alter the extent of the phototoxic reaction in the skin, and an increased plasma porphyrin concentration is not always associated with cutaneous disease [8].

Histopathology of the skin in porphyria [9,10]. In all the cutaneous porphyrias, homogeneous material is seen within vessel walls of the upper dermal and papillary vascular plexus. It is periodic acid–Schiff (PAS)-positive and diastase resistant, and contains a protein polysaccharide complex, lipids and tryptophan. Immunofluorescence reveals immunoglobulins (mainly IgG) in a similar vascular distribution, and IgG at the dermal–epidermal basement membrane zone, in involved skin. Electron microscopy shows reduplication of the vascular basal lamina and the presence of masses of fine fibrillar material, mainly around these blood vessels and often also at the dermal–epidermal junction. In EPP the vessel wall changes are more pronounced, whereas the basement membrane zone changes predominate in affected skin in PCT and VP. In the bullous porphyrias, bullae are subepidermal with the split occurring in the lamina lucida [11] (Fig. 59.5) leaving the dermal papilla protruding into the blister cavity, an appearance called 'festooning' [10]. The findings in bullous porphyrias are indistinguishable from those of pseudoporphyria. In EPP in the acute

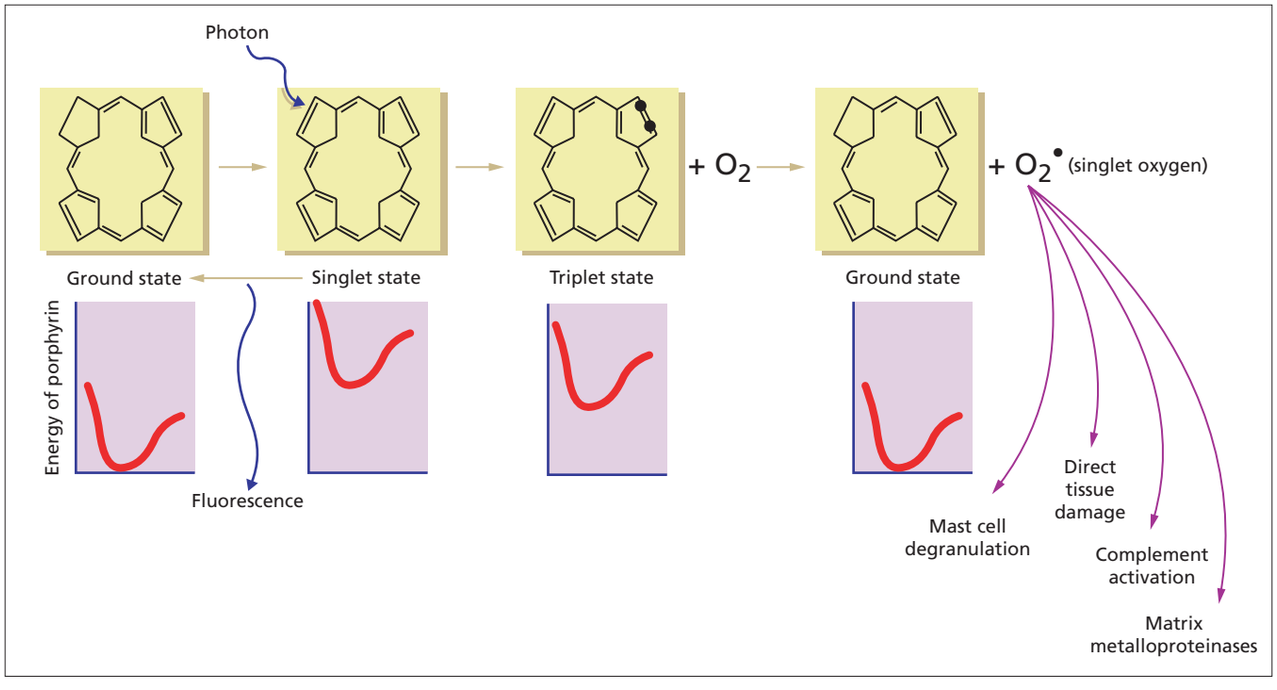
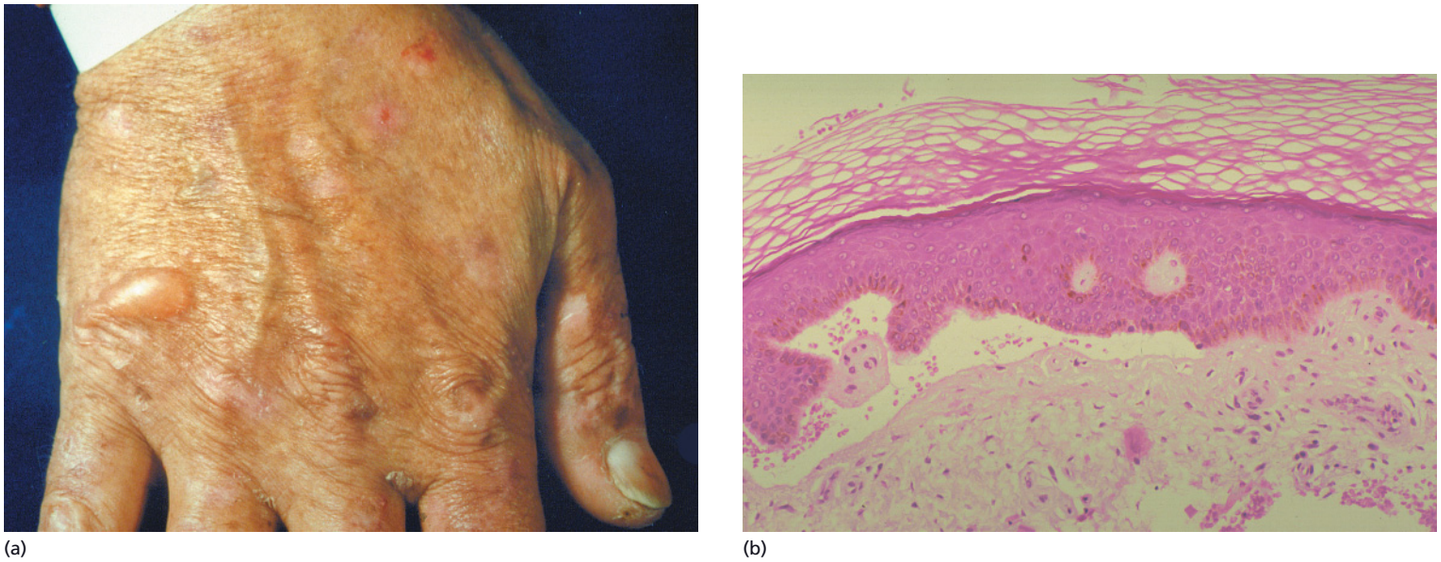


Fig. 59.4 The pathogenesis of skin disease in porphyria.



(a) (b)

Fig. 59.5 Typical subepidermal bulla in a bullous porphyria: (a) clinical appearance, (b) histological appearance.

phase there is visible endothelial damage in superficial dermal vessels [12]. Electron microscopy shows the 'amorphous' material seen in vessel walls on light microscopy in light-exposed skin to be a replicated, layered and fragmented basement membrane, with fine fibrillar material permeating the capillary connective tissue sheath and extending beyond the vessel walls, caused by the repeated episodes of damage [13,14].

General considerations in the management of skin disease in porphyria. Apart from PCT, and to some extent CEP, where effective specific treatments exist, the management of the skin in the other cutaneous porphyrias is based on preventing violet (Soret wavelength) light penetrating the epidermis. The connection between sun exposure and symptoms is obvious in EPP, but is not obvious to patients with the bullous porphyrias where fragility and blistering are not related to individual episodes of sun exposure. It can therefore be difficult to convince these patients of the importance of photoprotection. Basic measures include sun avoidance behaviour, sun-protective clothing and hats. Most sunscreens, including UV-absorbent chemical 'total sunblocks', do not protect against the visible violet Soret wavelength [15]; any sunscreen providing significant visible light protection will be opaque rather than transparent. Sunscreens containing reflectant particles, particularly large particle size titanium dioxide (pigmentary grade), zinc oxide and iron oxide, can effectively protect against violet light [16], and cosmetically acceptable sunscreens with reasonable protection up to 430 nm are available commercially, for example Dundee sunscreen (Tayside Pharmaceuticals, Dundee, UK) [15,16]. Dihydroxyacetone paint induces formation of a light-absorbing brown pigment in the stratum corneum, and has been used in some patients with EPP [17]. Some reasonably clear window films can absorb some violet light, and are useful on car or home windows, particularly in EPP and CEP [18]. This author generally uses two films which are clear and provide reasonable, though not complete, protection against Soret wavelength light (Dermagard film, Bonwyke, Hants, UK; and CLS200XSR film, Madico, USA). The Madico TA81XSR film is yellower but does provide better protection. Clearly, films applied to car windows must comply with local legislation, which varies considerably in different parts of the world.

References

1 Brun A, Sandberg S. Mechanisms of photosensitivity in porphyric patients with special emphasis on erythropoietic protoporphyria. *J Photochem Photobiol B* 1991; **10**: 285–302.

2 Day RS. Variegate porphyria. *Semin Dermatol* 1986; **5**: 138–54.

3 Takeshita K, Takajo T, Hirata H *et al.* In vivo oxygen radical generation in the skin of the protoporphyria model mouse with visible light exposure: an L-band ESR study. *J Invest Dermatol* 2004; **122**: 1463–70.

4 Lim HW, Poh-Fitzpatrick M, Gigli I. Activation of the complement system in patients with porphyrias after irradiation *in vivo*. *J Clin Invest* 1984; **74**: 1961–5.

5 Glover RA, Bailey CS, Barrett KE *et al.* Histamine release from rodent and human mast cells induced by protoporphyrin and ultraviolet light: studies of the mechanism of mast-cell activation in erythropoietic protoporphyria. *Br J Dermatol* 1990; **122**: 501–12.

6 Herrmann G, Wlaschek M, Bolsen K *et al.* Photosensitization of uroporphyrin augments the ultraviolet A-induced synthesis of matrix metalloproteinases in human dermal fibroblasts. *J Invest Dermatol* 1996; **107**: 398–403.

7 Caputo R, Berti E, Gasparini G, Monti M. The morphologic events of blister formation in porphyria cutanea tarda. *Int J Dermatol* 1983; **22**: 467–72.

8 Poh-Fitzpatrick MB, Sosin AE, Bemis J. Porphyrin levels in plasma and erythrocytes of chronic hemodialysis patients. *J Am Acad Dermatol* 1982; **7**: 100–4.

9 Epstein JH, Tuffanelli DL, Epstein WL. Cutaneous changes in the porphyrias. A microscopic study. *Arch Dermatol* 1973; **107**: 689–98.

10 Wolff K, Hönigsmann H, Rauschmeier W *et al.* Microscopic and fine structural aspects of porphyrias. *Acta Derm Venereol Suppl (Stockh)* 1982; **100**: 17–28.

11 Dabski C, Beutner EH. Studies of laminin and type IV collagen in blisters of porphyria cutanea tarda and drug-induced pseudoporphyria. *J Am Acad Dermatol* 1991; **25**: 28–32.

12 Gschnait FG, Wolff K, Konrad K. Erythropoietic protoprophyria—submicroscopic events during the acute photosensitivity flare. *Br J Dermatol* 1975; **92**: 545–57.

13 Wick G, Honigsmann H, Timpl R. Immunofluorescence demonstration of type IV collagen and a noncollagenous glycoprotein in thickened vascular basal membranes in protoporphyria. *J Invest Dermatol* 1979; **73**: 335–8.

14 Ryan EA, Madill GT. Electron microscopy of the skin in erythropoietic protoporphyria. *Br J Dermatol* 1968; **80**: 561–70.
15 Moseley H, Cameron H, MacLeod T *et al.* New sunscreens confer improved protection for photosensitive patients in the blue light region. *Br J Dermatol* 2001; **145**: 789–94.
16 Kaye ET, Levin JA, Blank IH *et al.* Efficiency of opaque photoprotective agents in the visible light range. *Arch Dermatol* 1991; **127**: 351–5.
17 Johnson JA. Durable protection against long-wavelength UV-A radiation and blue light. *Arch Dermatol* 1992; **128**: 409.
18 Huang JL, Zaider E, Roth P *et al.* Congenital erythropoietic porphyria: clinical, biochemical, and enzymatic profile of a severely affected infant. *J Am Acad Dermatol* 1996; **34**: 924–7.

Acute attacks of porphyria [1,2]

AIP, HC and VP can all cause acute attacks, and HC and VP may also cause cutaneous disease. (A rare autosomal recessive acute porphyria, aminolaevulinic acid (ALA) dehydratase porphyria, has also been reported but does not cause skin disease, and will not be discussed further.)

Definition. An acute and potentially fatal illness, frequently triggered by drugs and hormones which are metabolized by cytochrome P450. It is characterized by an acute neurotoxic reaction in many tissues.

Prevalence. The commonest acute porphyria is AIP, followed by VP. HC is rare. The prevalence of clinically overt acute porphyria in Europe is 1–2/100 000 inhabitants, but over 90% of individuals possessing AIP or VP gene defects are asymptomatic, so the enzyme deficiencies are common; PBG deaminase deficiency, which causes AIP, is present in 0.2% of all blood donors [3].

Aetiology [4]. Impaired activity of PBG deaminase is associated with acute attacks. The deficiency can be primary (as in AIP) or secondary, the latter being due to inhibition of the enzyme by accumulated coproporphyrinogen and protoporphyrinogen (as in HC and VP) [5]. In the liver, haem is mostly incorporated into cytochrome P450 proteins, whose production is induced by many of the drugs and hormones metabolized by the P450 system. When a drug or hormone induces cytochrome P450, and hence acutely increases the hepatic requirement for haem, the inability of the pathway to respond adequately because of the PBG deaminase deficiency is exposed. This acute hepatic haem deficiency in turn causes secondary accumulation of ALA and increased ALA synthase activity due to loss of end-product negative feedback. The symptoms of the acute attack result from neuronal dysfunction, the pathogenesis of which is not fully understood though postulated mechanisms include disturbed metabolism of neurotransmitters (due to reduced activity of haem-containing hepatic tryptophan dioxygenase), direct neurotoxicity of accumulated ALA (which structurally resembles the neurotransmitter γ-aminobutyric acid (GABA)) and acute haem deficiency within neurones.

Factors that may precipitate an acute attack [1]. The most common precipitants are drugs and the menstrual cycle, with recurrent attacks often occurring in the late luteal phase. Alcohol, cannabis, fasting, stress and infection may also trigger attacks. It is not possible to predict whether a specific drug will provoke an attack in an individual. Drugs should be prescribed only after reference to an up-to-date drug list. The author recommends using the lists available on the Internet from the Welsh Medicines Information Centre [6] or the European Porphyria Initiative [7]. These lists are regularly reviewed and updated by experts, and are lists of drugs, by type, that are known to be safe in acute porphyria, that is the lists are designed to answer questions such as 'which antihypertensive can be safely used in a patient with acute porphyria?'. The recommendations on such lists are not absolute and do not substitute for clinical judgement. The risk of a drug provoking an attack is obviously highest where that drug has previously caused an attack in that patient, and in any patients who have previously had symptoms suggestive of an acute attack.

Clinical presentation [1,2]. Acute attacks are five times more common in females, and most frequently occur between the ages of 10 and 40 years. They are rare before puberty. The severity of acute attacks varies from mild abdominal pain, sometimes accompanied by vomiting and constipation, through to very severe attacks with bulbar palsy and respiratory paralysis. Severe, constant abdominal pain occurs in almost all acute attacks. It can be in any quadrant or even in the back, buttocks and thighs, and may require large amounts of opiate analgesia. There may be guarding but no true peritonism. Vomiting and constipation (due to partial ileus) occur in at least half of attacks. The pulse rate and blood pressure are often moderately raised, dehydration is common and hyponatraemia (probably caused by inappropriate secretion of vasopressin) may be severe enough to cause convulsions. The pain, tachycardia, hypertension and partial ileus are all caused by an acute autonomic neuropathy. Sensory or sympathetic involvement, manifest as severe dysaesthesia or causalgia, is rarer. A motor neuropathy occurs in 5–10% of cases, usually heralded by aching pains in the limbs and sometimes by disappearance of the abdominal pain. It may cause a severe acute Guillain–Barré-type syndrome. The motor neuropathy usually occurs when porphyrinogenic drugs have been administered inadvertently during the developing acute attack. Respiratory paralysis is the commonest cause of death. Confusion, abnormal behaviour, agitation and hallucinations occur in up to 50% of attacks. Porphyria is not related to any chronic psychiatric disease, except generalized anxiety.

Biochemical diagnosis of an acute attack [8,9]. The diagnostic finding is of increased urinary PBG excretion. Although qualitative screening tests may be useful in an emergency, their low sensitivity makes it essential to also carry out a quantitative assay. Commercially available kits can provide a rapid and reasonably sensitive semi-quantitative assay, after which a specific quantitative assay should be carried out (reliable quantitative assay kits are commercially available). A normal urinary PBG concentration excludes an acute porphyric attack (except in ALA dehydratase porphyria). An increased PBG concentration does not necessarily mean that an acute attack is occurring since urinary PBG falls between attacks but does not always return to normal, particularly in AIP. The higher the PBG concentration, the more likely an acute attack, but, in the presence of an increased urinary PBG, an acute attack can only be diagnosed on clinical grounds. Urinary ALA is

also increased during an acute attack but to a lesser extent than PBG and is not as useful diagnostically (the only exception being ALA dehydratase porphyria in which only ALA is increased and urinary PBG is normal).

Long-term management of patients with acute porphyria [1,2]. The dermatologist may diagnose VP (or less commonly HC) on the basis of cutaneous disease before any acute attack has occurred. Once an acute porphyria has been diagnosed, the patient should be given a list of drugs with information about their safety in acute porphyria. Many lists exist both of 'safe' drugs and 'unsafe' drugs [6,7]. It is obviously vital for clinicians and patients to be clear about whether they are dealing with a list of 'safe' or of 'unsafe' drugs, and there are advantages to using a 'safe' list, as discussed above. It is important to recognize that a list of safe drugs is a guide, and that no drug can be guaranteed to be safe in an individual patient. Conversely, drugs which do not appear on a 'safe' list should not be withheld in patients who need them to treat a serious or life-threatening illness; in that situation expert advice should be sought from a specialist centre.

The patient should also be advised to abstain from alcohol, cannabis and from prolonged calorie-restricted diets, and to wear an emergency identification bracelet (e.g. MedicAlert) so that medical staff are aware of the diagnosis if the patient is ever found in an unconscious or confused state. Screening of relatives is essential to identify those with clinically latent disease, who are also at risk of acute attacks. The choice of test and interpretation of results can be complex and details are covered in the 'laboratory testing' section and under each individual disorder in this chapter. Such testing is ideally carried out in a specialist centre. Relatives diagnosed with an acute porphyria need the same advice as the index case. Conversely, patients with PCT, EPP and CEP can be reassured that acute attacks are not part of their disease.

Treatment of the acute attack [1,2]. The key to managing an acute attack is early diagnosis. Once the diagnosis has been made, avoidance of acute attack-inducing drugs is essential to prevent exacerbation. Supportive treatment includes analgesia, sedatives and antiemetics (in each case using drugs known to be safe in acute porphyria) and careful management of fluid balance with rehydration and correction of hyponatraemia. The specific treatments are intravenous haematin or haem arginate (Normosang, Orphan Pharmaceuticals), which have now replaced carbohydrate as the treatment of choice. These drugs suppress hepatic ALA synthase activity and so reduce ALA and PBG accumulation. Haem arginate is more effective when given earlier during an attack, increasing the importance of early diagnosis. Advice from a specialist centre should be sought when treating an acute attack.

References

1 Elder GH, Hift RJ, Meissner PN. The acute porphyrias. *Lancet* 1997; **349**: 1613–7.

2 Day RS. Variegate porphyria. *Semin Dermatol* 1986; **5**: 138–54.

3 Mustajoki P, Kauppinen R, Lannfelt L, Lilius L, Koistinen J. Frequency of low erythrocyte porphobilinogen deaminase activity in Finland. *J Intern Med* 1992; **231**: 389–95.

4 Meyer UA, Schuurmans MM, Lindberg RL. Acute porphyrias: pathogenesis of neurological manifestations. *Semin Liver Dis* 1998; **18**: 43–52.

5 Meissner P, Adams P, Kirsch R. Allosteric inhibition of human lymphoblast and purified porphobilinogen deaminase by protoporphyrinogen and coproporphyrinogen. A possible mechanism for the acute attack of variegate porphyria. *J Clin Invest* 1993; **91**: 1436–44.

6 Welsh Medicines Information Centre. http://www.wmic.wales.nhs.uk.

7 European Porphyria Initiative/ The European Porphyria NETwork. http://www.porphyria-europe.com

8 Deacon AC, Elder GH. ACP Best Practice No 165: front line tests for the investigation of suspected porphyria. *J Clin Pathol* 2001; **54**: 500–7.

9 Deacon A. The porphyrias and their investigation. *CPD Bull Clin Biochem* 1999; **1**: 122–6.

A clinician's guide to laboratory testing in porphyria [1–3]

Although clinical features may raise the possibility of a porphyria, the cutaneous presentations of several porphyrias are very similar. Precise diagnosis is essential in porphyria because of the great differences in clinical management between porphyrias which can be clinically indistinguishable. An accurate diagnosis can only be made on the basis of porphyrin analyses carried out in an experienced laboratory. The clinician's role is to suspect the diagnosis of cutaneous porphyria, and then to use laboratory testing to confirm whether this is the diagnosis, and if so to precisely identify the porphyria. For any porphyria characterized by acute attacks, testing for latent porphyria in relatives will then be necessary.

What samples to send. In an adult with suspected bullous porphyria, it is generally sufficient to analyse urine and either plasma (where fluorimetry is available) or faeces (where it is not). However, urine, plasma and faeces need to be analysed in children, because of the increased complexity of the differential diagnosis. Faecal analysis is also necessary in instances when urine and plasma results do not differentiate HC from CEP, and in renal failure, where urine may be unavailable and plasma analysis unhelpful because renal failure increases plasma porphyrins. In suspected EPP, red cells and either plasma or faeces should be analysed.

Handling of samples. Laboratory testing of body fluids measures porphyrins, since porphyrinogens are spontaneously oxidized to their respective porphyrins outside the body. PBG has a tendency to polymerize to other molecules but porphyrins are reasonably stable when protected from light and oxidants. Thus, all specimens should be kept at room temperature or at 4°C in the dark and ideally should be analysed within 48 h of collection.

For urine and faecal analysis, fresh random specimens (10–20 mL urine or 5–10 g dry weight faeces) are preferable to 24 h collections. Random specimens yield equally useful results, and 24 h collections delay samples reaching the laboratory. Very dilute urine (creatinine <4 mmol/L) is unsuitable.

Laboratory analysis of porphyrins. Old-fashioned qualitative screening methods for detecting porphyrins in specimens (often involving a Wood's light) are insensitive, and negative results from such tests are not of value. Whether testing urine, faeces, red cells or whole blood, quantitative screening using spectrophotometric or fluorimetric techniques is necessary and yields results as a total porphyrin concentration. Whole blood or red cell por-

phyrin testing measures both the total and free protoporphyrin concentrations. Plasma is analysed by fluorimetric scanning, a diagnostically powerful and simple qualitative technique. In urine and faeces, the finding of an increased porphyrin concentration will lead on to high-performance liquid chromatography (HPLC) which can be used to rapidly identify the accumulated porphyrins (Fig. 59.6). For PBG measurement in urine, qualitative tests are insensitive, and quantitative measurement, usually using a kit, is required, with semi-quantitative test kits being useful in emergencies where a result is needed quickly.

Interpretation of results [4] (Table 59.1). In cutaneous porphyrias, the accumulated porphyrin can usually be detected in plasma as an emission peak on spectrofluorimetry. Uro- and coproporphyrin are excreted into the urine and copro- and protoporphyrin into the faeces. Protoporphyrin accumulates in red cells in EPP.

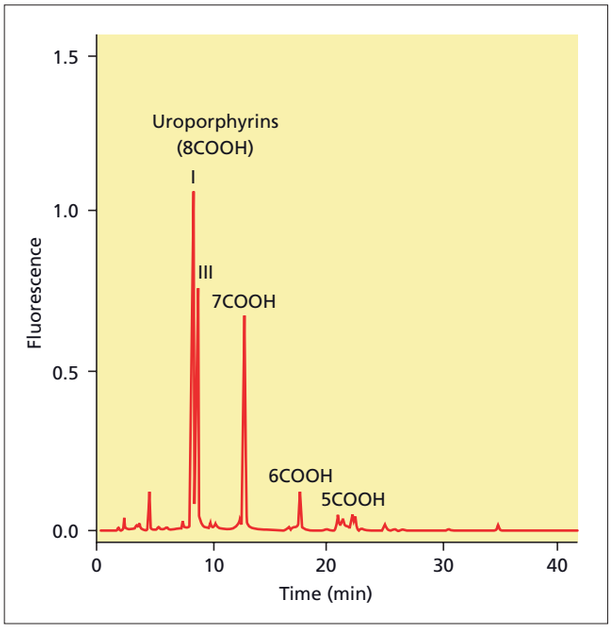


Fig. 59.6 High-performance liquid chromatography (HPLC) analysis: the more carboxylate groups it possesses, the faster a porphyrin molecule passes through the column. After passing through the column, porphyrins are detected by fluorimetry. This HPLC trace of urine shows the porphyrin profile typical of porphyria cutanea tarda (PCT). (Courtesy of Dr A. Deacon, King's College Hospital, London, UK.)

1 **Plasma spectrofluorimetry.** In plasma spectrofluorimetry, the sample is excited by 410 nm light, and fluorescent emissions detected. An emission peak at 615–620 nm indicates the presence of uro- or coproporphyrin and suggests a diagnosis of PCT, HC, CEP or HEP (urine analysis will differentiate PCT and HEP from the other two conditions). A peak at 624–626 nm indicates the presence of a porphyrin–peptide conjugate diagnostic of VP. This 624–626 nm peak is a sensitive indicator of VP and may even persist during periods of clinical remission when faecal excretion becomes normal. It is also positive in most cases of latent VP (in relatives) [5,6]. A peak around 633 nm (it can lie between 626 and 634 nm) is caused by protoporphyrin and suggests EPP, and EPP is an unlikely diagnosis in the absence of this peak. Plasma porphyrin concentrations, particularly uroporphyrin, increase in renal failure and can be as high as those found in patients with PCT.
2 **Whole blood/red cell.** An increased free protoporphyrin concentration is the diagnostic finding in EPP. The total protoporphyrin concentration includes both free and zinc-protoporphyrin. Zinc-protoporphyrin is also increased in iron deficiency, lead poisoning and certain anaemias. In a child with plasma, urine and faecal results typical of PCT, red cell UROD activity needs to be measured to exclude hepatoerythropoietic porphyria (HEP).
3 **Urinary and faecal analysis.** An increased total porphyrin concentration suggests a diagnosis of cutaneous porphyria. The total urinary porphyrin concentration is used to monitor disease activity in PCT. HPLC analysis is used to identify the porphyrins once an increased concentration has been found.
   (a) **In urine.** An increase in uroporphyrin (and other highly carboxylated porphyrins especially heptacarboxy-porphyrin) is typical of PCT though this does not exclude VP. Plasma spectrofluorimetry differentiates these two conditions and faecal analysis is required where this is unavailable. When PCT goes into remission and the total urinary porphyrin concentration returns to normal, it may still be possible to diagnose PCT from the characteristic urinary HPLC pattern. Coproporphyrinuria, in the presence of normal faecal porphyrin levels, does not indicate porphyria

Table 59.1 The major biochemical findings in the cutaneous porphyrias. (Adapted from Deacon and Elder [4].)

	Urine	Faeces	Red cell	Plasma fluorimetry
Congenital erythropoietic porphyria	Uroporphyrin I; coproporphyrin I	Coproporphyrin I	Zinc- and free protoporphyrin; uroporphyrin I; coproporphyrin I	Peak at 615–620 nm
Porphyria cutanea tarda	Uroporphyrin III; heptacarboxy-porphyrin	Isocoproporphyrin; heptacarboxy-porphyrin	Normal	Peak at 615–620 nm
Hereditary coproporphyria	Coproporphyrin III	Coproporphyrin III	Normal	Peak at 615–620 nm
Variegate porphyria	Coproporphyrin III	Protoporphyrin; coproporphyrin III; X-porphyrin	Normal	Peak at 624–627 nm
Erythropoietic protoporphyria	Normal	Protoporphyrin (not diagnostically helpful)	Free protoporphyrin	Peak at 626–634 nm

and can be caused by certain drugs, lead toxicity and hepatobiliary disease.

(b) **In urine and faeces.** Increased coproporphyrin suggests VP, but does not exclude HC. Isomer III to isomer I ratios are increased in every porphyria except CEP (where they are decreased). In CEP, excess type I isomers of uro- and coproporphyrin are present in urine and type I coproporphyrin in faeces.

(c) **In faeces.** In the presence of a plasma spectrofluorimetry peak at 615–620 nm, if urine HPLC does not show the PCT pattern, faecal analysis is required to differentiate HC (increased coproporphyrin III concentration) from CEP (increased coproporphyrin I concentration). Increased faecal isocoproporphyrin is characteristic of PCT. In renal failure, faecal analysis is vital, since urine may be unavailable and plasma porphyrins are increased in renal failure (PCT is the porphyria most commonly associated with renal failure). Increased faecal protoporphyrin is suggestive but not diagnostic of EPP, since it can also derive from bacterial degradation of haem in the gut and may indicate gastrointestinal haemorrhage when porphyrin concentrations are normal elsewhere.

Biochemical diagnosis of an acute attack of porphyria [3,4]. This is discussed above (Acute attacks of porphyria, p. 59.7). A definitive diagnosis of VP or HC can usually be made on the basis of detailed porphyrin analysis. A definitive diagnosis of AIP requires enzyme or genetic tests.

Screening of relatives. In VP and HC, porphyrin levels are normal before puberty. Over the age of 15 years, a plasma fluorimetry scan is a reasonably sensitive biochemical test for latent VP in asymptomatic relatives of patients, picking up most cases. A positive scan is diagnostic of latent VP but a negative result is uninformative [5,6]. Faecal analysis, to measure the ratio of coproporphyrin isomers, will pick up some cases of latent HC after puberty [7]. In VP and HC, a negative porphyrin screening test in a relative needs to be followed by DNA analysis before latent disease can be excluded. The lack of any common mutations in porphyria (apart from South African VP) means that the causative mutation usually has to be identified for each family.

References

1 Kappas A, Sassa S, Galbraith RA, Nordmann Y. The porphyrias. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic and Molecular Bases of Inherited Disease*, 7th edn. New York: McGraw-Hill, 1995: 2103–59.

2 Elder GH. Testing for the cutaneous porphyrias (Appendix D). In: Hawk JLM, ed. *Photodermatology*. London: Arnold, 1999: 281–91.

3 Deacon A. The porphyrias and their investigation. *CPD Bull Clin Biochem* 1999; **1**: 122–6.

4 Deacon AC, Elder GH. ACP Best Practice No 165: front line tests for the investigation of suspected porphyria. *J Clin Pathol* 2001; **54**: 500–7.

5 Long C, Smyth SJ, Woolf J *et al.* Detection of latent variegate porphyria by fluorescence emission spectroscopy of plasma. *Br J Dermatol* 1993; **129**: 9–13.

6 Da Silva V, Simonin S, Deybach JC *et al.* Variegate porphyria: diagnostic value of fluorometric scanning of plasma porphyrins. *Clin Chim Acta* 1995; **238**: 163–8.

7 Kuhnel A, Gross U, Doss MO. Hereditary coproporphyria in Germany: clinical-biochemical studies in 53 patients. *Clin Biochem* 2000; **33**: 465–73.

The individual porphyrias

Porphyrias that cause cutaneous disease but do not cause acute attacks

Congenital erythropoietic porphyria (Günther's disease)

Definition. A severe and rare childhood porphyria causing lifelong mutilating photosensitivity and haematological disease.

Aetiology. Congenital erythropoietic porphyria (CEP) is caused by an autosomal recessive inherited deficiency of the uroporphyrinogen III cosynthase enzyme. Since this enzyme is required to form the biologically useful type III porphyrin isomers, its absence results in non-enzymatic reactions producing large amounts of type I isomer porphyrins which cannot participate in haem formation, and which massively accumulate in erythroid cells and then gradually leak into the plasma. The incidence in the UK is 2 per 3 million live births and less than 100 cases have ever been reported worldwide. Rare adult onset cases of acquired CEP have been reported secondary to myelodysplasia [1].

Clinical features [2–4]. CEP has a wide spectrum of presentation, from hydrops fetalis through to severe disease starting in infancy and also mild forms presenting later in life. The first sign of CEP is often the child's mother noting brown discoloration of amniotic fluid at the onset of labour, or observing pink or brown porphyrin staining of nappies (which fluoresce red-orange under Wood's light).

The skin in CEP [2,4]. Severe photosensitivity begins in infancy, often in the neonatal period, with blisters developing in light-exposed skin on minimal light exposure. Phototherapy for neonatal jaundice may trigger lesions. Most children are so sensitive to the light that they have problems throughout the year. Exposed (and sometimes non-exposed) skin is fragile. The repeated bouts of inflammation with vesicles and bullae, often complicated by secondary infection, cause mutilating scarring, particularly of the face and hands (Fig. 59.7). This photomutilation is associated with erosion of the terminal phalanges, onycholysis and destructive changes affecting the pinnae and nose. A diffuse pseudoscleroderma-tous thickening of exposed skin often gradually develops, with microstomia and sclerodactyly-like changes [4]. Hypertrichosis is found in most patients, particularly on the upper arms, temples and malar region. Patchy hypo- and hyperpigmentation occur even in minimally exposed areas.

A milder late onset form, presenting at any age from the third decade onward, has been described; this presents in a manner similar to PCT, and occurs either as a result of mild inherited gene mutations [5] or as an acquired disease secondary to bone marrow myelodysplasia [1].

Involvement of eyes and internal organs [4]:

- Eyes. Keratoconjunctivitis, blepharitis, cataracts, corneal ulcers, scars, cicatricial ectropion and scarring alopecia of eyelashes and eyebrows may all occur. Scleromalacia, pterygium formation, optic atrophy and retinal haemorrhage are less common.



Fig. 59.7 Congenital erythropoietic porphyria (CEP): scarring of skin with resorption of terminal phalanges. (Courtesy of Dr A. du Vivier, King's College Hospital, London, UK.)

- Bones and teeth. When teeth emerge, they are almost always stained brown (and fluoresce under Wood's light). Decreased bone density, osteopenia and osteolytic lesions secondary to erosion by hyperplastic bone marrow are seen on X-ray and are associated with vertebral compression and collapse, and with pathological fractures. In the hands there is resorption of terminal phalanges with acroosteolysis and cortical bone rarefaction. Occasionally, strict avoidance of the sun may impair vitamin D metabolism.
- Haematology [2,4]. The high concentrations of porphyrins in red cells cause haemolytic anaemia, severe enough to induce marrow hyperplasia often with visible expansion of the maxillary bones in the face. Hypersplenism is common. The haemolysis can be fully compensated or may cause a severe anaemia, and is occasionally so severe that some patients become transfusion dependent. The severity of the anaemia often fluctuates strikingly over time. Very severe haemolytic anaemia may even cause hydrops fetalis. Bone marrow examination reveals normoblastic hyperplasia, and under violet illumination most normoblasts have persistent red fluorescence localized to their nuclei, with haem-containing inclusion bodies being seen in the nuclei of these fluorescent cells.

Differential diagnosis. The photosensitivity differentiates CEP from other scarring blistering disorders of childhood, including epidermolysis bullosa dystrophica. The cutaneous changes may resemble HEP (the homozygous form of familial PCT) or homozygous VP. The cutaneous disease in late-onset CEP is clinically indistinguishable from PCT or VP.

Biochemical findings [2]. The uroporphyrinogen III cosynthase enzyme deficiency results in the massive accumulation in all tissues of type I isomers of porphyrins, mainly uroporphyrin, along with coproporphyrin and smaller amounts of 7-, 6- and 5-carboxylic acid porphyrins. Red cells and urine contain large amounts of uro- and coproporphyrin (mainly type I) and faeces contains increased concentrations of coproporphyrin (mainly type I). A plasma spectrofluorimetry peak is seen at 615–620 nm. The absence of isocoproporphyrins and the normal level of 5-carboxylic porphyrin excretion in faeces distinguish CEP from HEP.

Prognosis. In the past, most patients died by the age of 40 years but improvements in supportive care (particularly use of antibiotics) have improved the prognosis, though the haematological complications may be fatal. Long-term hypertransfusion causes significant problems with iron overload as patients reach adulthood, even when iron chelation has been used. Bone marrow transplantation now holds out the promise of cure for these patients (see below).

Treatment [6]. The photosensitivity is so severe that photoprotection is crucial. Sun avoidance and use of sun protective clothing and hats are essential. Opaque sunscreens containing pigmentary grade titanium dioxide or zinc oxide, possibly with added iron oxide, may be of limited value [7,8], and amber window films on home or car windows can reduce exposure to Soret wavelength light (TA81XSR, Madico, USA) [9], though more opaque films may be necessary (which are obviously not allowed on car windows). Prompt treatment of secondary infection is important.

β-Carotene may help cutaneous disease in some patients [2].

Many therapies reduce the porphyrin concentrations by suppressing erythropoiesis. Hypertransfusion with regular blood transfusions to maintain a polycythaemia inhibits endogenous haemoglobin production and decreases porphyrin formation, and may reduce haemolysis and cutaneous symptoms in moderately affected patients. However, splenomegaly may increase transfusion requirements and the value of hypertransfusion often decreases at puberty [6]. Hypertransfusion is frequently complicated by iron overload, even when desferrioxamine has been used, and blood-borne infections can be a complication. Hydroxyurea has been used with hypertransfusion and may be useful in transfusion-dependent CEP [10]. Intravenous haematin has been tried in late-onset disease [11]. Haemolysis worsens the porphyria by causing anaemia and usually necessitates blood transfusion. Splenectomy may reduce haemolysis though the improvement may be temporary [6]. Lights during surgical procedures may cause phototoxic reactions and filters should be used over the operation lights during any unavoidable surgery, preferably a yellow filter (e.g. Madico TA81XSR).

Since 1991, allogeneic bone marrow transplantation (bone marrow or umbilical cord blood stem cells) from a human leukocyte antigen (HLA)-compatible donor has emerged as the treatment of choice in severe CEP. It provides a long-term cure [12,13] though the difficulties of finding a tissue-matched donor, and the dangers of marrow transplantation, mean that it should be reserved for the most severely affected patients [14]. Gene therapy has been successfully used *in vitro*, but no *in vivo* studies have been carried out yet [15].

Genetic counselling. Since CEP is autosomal recessive, parents will be unaware of the risk until an affected child has been born, and the risk of disease is in further offspring rather than subsequent generations. For parents of an affected child, the chance of each future offspring suffering from the disease is 25%. The diagnosis may be made before birth by measuring the uroporphyrin I concentration in amniotic fluid, which is increased as early as 16 weeks *in utero*. If the mutations in the index case have been identified, or the fetus is homozygous for the common C73R mutation, prenatal diagnosis from chorionic villous biopsy is possible [16].

References

1 Kontos AP, Ozog D, Bichakjian C, Lim HW. Congenital erythropoietic porphyria associated with myelodysplasia presenting in a 72-year-old man: report of a case and review of the literature. *Br J Dermatol* 2003; **148**: 160–4.

2 Nordmann Y, Deybach JC. Congenital erythropoietic porphyria. *Semin Dermatol* 1986; **5**: 106–14.

3 Elder GH. The cutaneous porphyrias. In: Hawk JLM, ed. *Photodermatology*. London: Arnold, 1999: 171–99.

4 Fritsch C, Bolsen K, Ruzicka T, Goerz G. Congenital erythropoietic porphyria. *J Am Acad Dermatol* 1997; **36**: 594–610.

5 Berry AA, Desnick RJ, Astrin KH *et al*. Two brothers with mild congenital erythropoietic porphyria due to a novel genotype. *Arch Dermatol* 2005; **141**: 1575–9.

6 Harada FA, Shwayder TA, Desnick RJ, Lim HW. Treatment of severe congenital erythropoietic porphyria by bone marrow transplantation. *J Am Acad Dermatol* 2001; **45**: 279–82.

7 Moseley H, Cameron H, MacLeod T *et al*. New sunscreens confer improved protection for photosensitive patients in the blue light region. *Br J Dermatol* 2001; **145**: 789–94.

8 Kaye ET, Levin JA, Blank IH, Arndt KA, Anderson RR. Efficiency of opaque photoprotective agents in the visible light range. *Arch Dermatol* 1991; **127**: 351–5.

9 Huang JL, Zaider E, Roth P *et al*. Congenital erythropoietic porphyria: clinical, biochemical, and enzymatic profile of a severely affected infant. *J Am Acad Dermatol* 1996; **34**: 924–7.

10 Guarini L, Piomelli S, Poh-Fitzpatrick MB. Hydroxyurea in congenital erythropoietic porphyria. *N Engl J Med* 1994; **330**: 1091–2.

11 Rank JM, Straka JG, Weimer MK *et al*. Hematin therapy in late onset congenital erythropoietic porphyria. *Br J Haematol* 1990; **75**: 617–8.

12 Shaw PH, Mancini AJ, McConnell JP *et al*. Treatment of congenital erythropoietic porphyria in children by allogeneic stem cell transplantation: a case report and review of the literature. *Bone Marrow Transplant* 2001; **27**: 101–5.

13 Dupuis-Girod S, Akkari V, Ged C *et al*. Successful match-unrelated donor bone marrow transplantation for congenital erythropoietic porphyria (Gunther disease). *Eur J Pediatr* 2005; **164**: 104–7.

14 Dawe SA, Peters TJ, Du Vivier A, Creamer JD. Congenital erythropoietic porphyria: dilemmas in present day management. *Clin Exp Dermatol* 2002; **27**: 680–3.

15 Geronimi F, Richard E, Lamrissi-Garcia I *et al*. Lentivirus-mediated gene transfer of uroporphyrinogen III synthase fully corrects the porphyric phenotype in human cells. *J Mol Med* 2003; **81**: 310–20.

16 Lazebnik N, Lazebnik RS. The prenatal presentation of congenital erythropoietic porphyria: report of two siblings with elevated maternal serum alpha-fetoprotein. *Prenat Diagn* 2004; **24**: 282–6.

Porphyria cutanea tarda [1,2]

Definition. Porphyria cutanea tarda (PCT) is the commonest of all the porphyrias. It is characterized by fragility and blistering of exposed skin. It is usually acquired and is often associated with liver disease. It does not cause acute attacks.

Aetiology and classification. PCT results from deficiency of UROD [3]. This causes accumulation of uroporphyrin and other highly carboxylated porphyrins. Seventy-five per cent of patients have the *type I* (*sporadic*) form in which the enzyme deficiency is acquired and restricted to hepatocytes, due to inhibition of a normal UROD enzyme [3]. Twenty-five per cent have *type II* (*familial*) disease where the enzyme deficiency is hereditary, present in all tissues and associated with a UROD gene mutation. The penetrance of this autosomal dominant inherited form is so low that a family history is present in under 7% of cases, and since at least a 75% reduction in enzyme activity is required for clinical expression, some enzyme inhibition in the liver also occurs in familial PCT. Thus, UROD mutations are increasingly thought of as a risk factor for the development of PCT, rather than as representing a completely separate familial form of the disease. *Type III* disease is rare and characterized by an hereditary enzyme deficiency localized to the liver. *Toxic porphyria*, in which halogenated aromatic hydrocarbons inhibit the enzyme, is rare and mainly affects workers making herbicides [4]. A major epidemic of toxic porphyria in the 1950s in Turkey was caused by hexachlorobenzene added as a fungicide to seed wheat [5].

In PCT, the UROD enzyme is inactivated by an inhibitor which binds to its catalytic site. The inhibitor is generated in the liver by reactive oxygen species in the presence of iron (Fig. 59.8) [6]. The

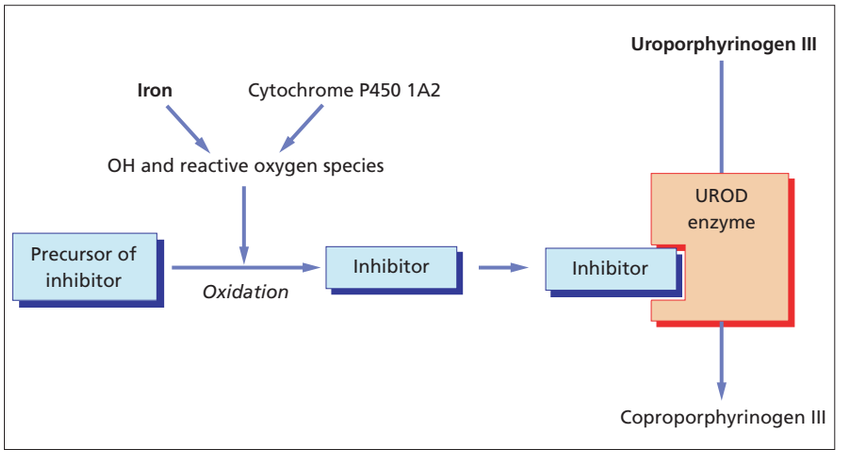


Fig. 59.8 Porphyria cutanea tarda (PCT) is caused by production of an inhibitor of uroporphyrinogen decarboxylase (UROD) in the liver, in the presence of iron. (Adapted from Elder [2].)



Fig. 59.9 Porphyria cutanea tarda (PCT): erosions, blisters, pigmentary changes and scarring.

accumulated uroporphyrin diffuses from the plasma into surrounding tissues, causing a phototoxic reaction in the upper dermis in sun-exposed skin. This leads to lysis of cells in the superficial dermis with the formation of membrane-limited vacuoles which merge to produce a blister cavity under the basal lamina [7].

Histopathology [8]. The bullae in PCT are subepidermal with a sparse inflammatory infiltrate and 'festooning' of dermal papillae into the bullae. There is deposition of PAS-positive diastase-resistant fibrillar glycoprotein material in and around upper dermal blood vessel walls, and reduplication of the basement membrane. Immunofluorescence reveals IgG, a little IgM, fibrinogen and complement at the epidermal–dermal junction. Morphoea-like lesions in PCT are histologically indistinguishable from other forms of morphoea.

Clinical features (Fig. 59.9) [9]. Sporadic PCT usually presents in middle age whilst the familial form can occur at a younger age. Almost all patients notice increased fragility on light-exposed skin, particularly the backs of the hands and forearms, with minor trauma shearing the skin away to leave sharply marginated erosions. Most patients suffer from bullae, which can be over 1 cm in diameter and may be painful. They crust and resolve over a few weeks, leaving atrophic scars, milia and often mottled hyper- or hypopigmentation. Patients rarely associate development of new lesions with sun exposure, but symptoms are generally worse in the summer. Other common features are: patches of scarring alopecia following resolution of bullae on the scalp; hypertrichosis, usually on the upper face and forehead, sometimes on the ears or arms [10] and occasionally affecting the whole body; hyperpigmentation in a melasma-like pattern on the cheeks and around the eyes, or in a diffuse pattern on light-exposed skin, or occasionally in a reticulate distribution [9,10]. Photo-induced onycholysis [11] and accelerated solar elastosis [10] may also occur. Morphoea-like plaques may develop, particularly on the head and upper trunk. They are histologically indistinguishable from true scleroderma and mainly occur in longstanding untreated disease. It has been postulated that they arise as a result of the induction of collagen synthesis by uroporphyrin I [12]. These plaques may calcify, and may require excision and grafting if they ulcerate [13].

On the scalp, the morphoea-like change may cause a slowly expanding scarring alopecia starting in the frontoparietal and occipital areas [9,10,14], and even sclerodactyly or the facial changes of systemic sclerosis have been reported. Rare presentations of PCT include cicatricial conjunctivitis [15] and hair darkening [16].

Hepatoerythropoietic porphyria [10,17]. The homozygous form of familial PCT, hepatoerythropoietic porphyria (HEP), is associated with over 90% reduction in UROD activity. It usually causes a severe disease clinically similar to CEP, with photosensitivity during infancy causing immediate pain on sun exposure, blisters on sun-exposed skin, and mutilating scarring of face and fingers. Prominent hypertrichosis, fluorescent teeth, eye involvement and shortened distal phalanges also occur. Haemolysis is milder than in CEP, and life expectancy is normal. HEP can occasionally present with a milder disease similar to PCT. Since the mutated alleles in HEP have to be associated with some residual enzyme activity to be compatible with life, the UROD gene mutations in HEP patients are different to those found in type II PCT [18].

Differential diagnosis. PCT can be clinically indistinguishable from VP, drug-induced pseudoporphyria, renal pseudoporphyria, HC, late-onset Günther's disease or mild HEP. Biochemical analysis is necessary to diagnose PCT and it is particularly important to exclude VP and HC among the differential diagnoses, since they can cause acute attacks.

Biochemical findings [2]. In PCT, the urinary porphyrin concentration is increased, consisting mainly of uroporphyrin, some heptacarboxylic acid porphyrin, and sometimes also hexa- and pentacarboxylic acid porphyrins. A plasma spectrofluorimetry peak is seen at 615–620 nm. Isocoproporphyrin accumulates in the faeces. Urine analysis alone is insufficient to diagnose PCT, since a few patients with VP have the PCT urine pattern ('dual porphyria') [19]. In patients with renal failure, faecal analysis is essential, since plasma porphyrins are increased by haemodialysis and urine collection may not be possible. The biochemical marker of disease activity and response to treatment is quantitative urinary porphyrin excretion measured in a random urine sample.

In HEP, the findings are as in PCT, but with the additional finding of a raised red cell zinc-protoporphyrin, and lower red cell UROD activity than occurs in type II PCT.

The investigation of the patient with PCT. PCT is essentially a liver disorder with secondary effects in the skin. It is crucial to investigate patients thoroughly both regarding other systemic diseases predisposing to the development of PCT, and in order to assess the severity of any liver disease.

1 Risk factors for the development of PCT [20]. The major risk factors for developing PCT are subclinical genetic haemochromatosis, hepatitis C infection, alcohol and oestrogens. They all predispose to the inhibition of the UROD enzyme in the liver. Since some inhibition of the hepatic enzyme is also required for

clinical expression of familial PCT, the same risk factors apply to sporadic and familial PCT. Since most of the risk factors have significant implications both for treatment and for the patient's general health, it is essential to investigate for risk factors in all patients diagnosed with PCT.

(i) Haemochromatosis. As expected in a disorder where hepatic iron plays a key role, almost all patients have increased stainable iron in the liver, and total body iron stores are increased in at least 60% of patients [2,20,21]. In the USA and Northern Europe, around 20% of PCT patients have true hereditary haemochromatosis [20,22] with homozygosity for the Cys282Tyr haemochromatosis mutation. Homozygosity for this mutation increases the risk of developing PCT 60-fold [20]. The clinical relevance of heterozygosity for the mutation is unclear. In Southern Europe, haemochromatosis is a less important risk factor. The iron overload found in PCT patients who do not have haemochromatosis is milder, and its cause obscure.

(ii) Hepatitis C infection. In Southern Europe, 70–90% of all PCT patients are infected with the hepatitis C virus [23,24], compared with around 60% of patients in the USA [20] and 7–36% in Northern Europe [25,26].

(iii) Alcohol. Between 30% and 90% of PCT patients consume over 40 g of alcohol daily, and 2% of all alcoholics with cirrhosis develop PCT [6].

(iv) Oestrogens. Ingested oestrogens, in the oral contraceptive pill or in hormone replacement therapy, are the sole risk factor in over a quarter of female patients [20]. Stopping the hormone may be sufficient to induce remission if the duration of therapy has been short [27]. If it is not possible to stop the hormone therapy, transdermal drug delivery is a safer alternative than the oral route [28].

There are other less common risk factors for developing PCT: haemodialysis predisposes to PCT [10], though PCT is less common in renal failure than pseudoporphyria—faecal porphyrin analysis differentiates these disorders. Human immune deficiency virus (HIV) infection predisposes to PCT [29], an association which may be due to coinfection with the hepatitis C virus [30]. Non-insulin dependent diabetes mellitus, systemic lupus erythematosus, dermatomyositis, hepatitis A and B infection, haematological malignancy, sideroblastic anaemia, thalassaemia and the drug tamoxifen have all been reported to be associated with PCT [2,9,31,32].

Most patients possess more than one risk factor for developing PCT, with hepatitis C infection and alcohol being strongly linked in men.

2 Liver disease in PCT [21]. Since PCT is primarily a liver disorder with secondary effects in the skin, liver disease is a major concern. In almost all cases, liver biopsy reveals increased stainable iron, fatty change and intracellular porphyrin crystals. Fifty per cent of patients have more severe changes (lobular necrosis or inflamed fibrotic portal tracts), and cirrhosis occurs in 15% [21]. As one would expect, the most severe liver disease tends to occur in patients who have alcoholism, hepatitis C infection and iron overload [20]. The accumulated porphyrins are carcinogenic to the liver, and so PCT confers an additional risk for developing hepatocellular carcinoma on top of the risk conferred by the hepatitis C infection present in many patients [33]. In Southern Europe around 3% of PCT patients develop hepatocellular carcinoma during the decade after presentation [34], and the incidence of hepatic malignancy is probably lower than this in countries with lower hepatitis C infection rates. Risk factors for developing hepatocellular carcinoma are thought to be a symptomatic period longer than 10 years prior to treatment, severe changes on hepatic histology at presentation, hepatitis C infection, male sex and age over 50 years at presentation [35,36]. The converse situation, where a primary hepatic tumour secretes porphyrins to cause a PCT-like skin disease, is rare [37]. Hepatic function must be assessed at presentation in all PCT patients, and patients at high risk of hepatic malignancy require regular ultrasounds and serum α-fetoprotein measurement to detect carcinoma at a treatable stage [35]. PCT should be managed as a liver disorder, and the threshold for referral to a hepatologist should be low.

Treatment

Photoprotection. Visible light sunscreens containing pigmentary grade titanium dioxide or zinc oxide, sometimes with added iron oxide [38,39], filter films for car and home windows, gloves, hats and clothes play an important role in controlling symptoms during the period of several months before specific therapies take effect.

Elimination of risk factors. Stopping oestrogen therapy [27], if it has not been used for more than 2 years, can induce remission. However, elimination of the underlying cause by abstaining from alcohol, or by treating hepatitis C with interferon-α [40], does not always induce remission. All patients should be advised to abstain from alcohol or oestrogen therapy to prevent exacerbation of the disease.

Specific treatments. Definitive treatment with venesection or low-dose antimalarials is required in almost all cases. Venesection depletes iron stores and eliminates hepatic iron overload, thus restoring normal enzyme activity. Around 500 mL of blood is removed every week or every 2 weeks, aiming to decrease transferrin saturation to 15%, haemoglobin to 11–12 g/dL and plasma ferritin to below 25 μg/L [41,42]. Blistering usually resolves within 2–3 months, skin fragility within 6–9 months [43], and porphyrin concentrations generally normalize within 13 months or so [9], at which point treatment should be stopped. Hypertrichosis [9] and sclerodermoid lesions [14] respond more slowly during the years after treatment has stopped. Excision and grafting may be needed for ulcerated sclerodermoid lesions [9]. Desferrioxamine leads to earlier remission than venesection because it rapidly chelates hepatic iron, and it may be of value in PCT with renal failure but it is expensive and requires use of a subcutaneous pump at night [44,45]. Erythropoietin mobilizes hepatic iron into haemoglobin and is the treatment of choice for PCT in renal failure where patients are too anaemic for venesection and cannot excrete chloroquine [46]. Low-dose antimalarials are a very effective treatment for PCT. They work by complexing with uroporphyrin and promoting its excretion into the bile [47]. Daily doses of chloroquine cause a potentially dangerous acute hepatitis but chloroquine at the low dose of 125 mg [48,49] or 250 mg [50,51] taken twice a

week is safe and effective. It leads to clinical remission within 6 months or so and biochemical remission after 6–15 months, at which point treatment is stopped [48–51]. Retinopathy does not seem to occur with such low doses of chloroquine [50]. Hydroxychloroquine (200 mg twice weekly) can be used but duration of remission is shorter than with chloroquine [52,53].

Low-dose chloroquine is the treatment of choice except in the following situations, in which venesection is preferable: (i) patients who do not respond to chloroquine; (ii) patients with a pathologically high serum ferritin concentration or homozygous for the Cys282Tyr mutation (if genetic analysis is available), who require iron depletion to protect internal organs; and (iii) patients with significant hepatitis C liver disease, who require iron depletion since hepatic siderosis increases their virally induced liver damage [54] and reduces the effectiveness of interferon [55]. Anyway, chloroquine is usually less effective in the patients with haemochromatosis [56]. However, chloroquine is not contraindicated in these situations, and may be needed when venesection is not possible, particularly in patients with hepatitis C liver disease where venous access is impaired by previous intravenous drug abuse.

Remission with low-dose chloroquine generally lasts 17–24 months [49,50]. With venesection, relapse generally occurs around 2.5 years after the end of treatment [9,48]. Long-term follow-up is necessary for all patients to monitor for relapse (by measuring urinary porphyrin excretion), and for the management of coexisting liver disease.

Genetic counselling [57]. Familial and sporadic PCT can be differentiated by measuring red cell UROD activity. Since additional inhibition of the hepatic enzyme is required for clinical expression of disease in familial PCT, UROD mutations can be considered as a risk factor for developing the disease rather than as a different form of PCT. In view of the identical management of sporadic and familial PCT, the lack of evidence that identifying latent PCT in relatives alters outcomes, and the very low penetrance of familial PCT, it is difficult to justify family screening in familial PCT. It is therefore of little value to measure red cell UROD activity unless one is trying to differentiate HEP from PCT.

References

1 Sarkany RPE. The management of porphyria cutanea tarda. *Clin Exp Dermatol* 2001; **26**: 225–32.

2 Elder GH. Porphyria cutanea tarda. *Semin Liver Dis* 1998; **18**: 67–75.

3 Elder GH, Urquhart AJ, De Salamanca RE *et al.* Immunoreactive uroporphyrinogen decarboxylase in the liver in porphyria cutanea tarda. *Lancet* 1985; **2**: 229–33.

4 Bleiberg J, Wallew M, Brodkin K *et al.* Industrially acquired porphyria. *Arch Dermatol* 1964; **89**: 793–7.

5 Dean G. The Turkish epidemic of porphyria. In: Dean G, ed. *The Porphyrias: a Story of Inheritance and Environment*, 2nd edn. London: Pitman Medical, 1971: 67–72.

6 Elder GH. Alcohol intake and porphyria cutanea tarda. *Clin Dermatol* 1999; **17**: 431–6.

7 Caputo R, Berti E, Gasparini G, Monti M. The morphologic events of blister formation in porphyria cutanea tarda. *Int J Dermatol* 1983; **22**: 467–72.

8 Wolff K, Hönigsmann H, Rauschmeier W *et al.* Microscopic and fine structural aspects of porphyrias. *Acta Derm Venereol Suppl (Stockh)* 1982; **100**: 17–28.

9 Grossman ME, Bickers DR, Poh-Fitzpatrick MB *et al.* Porphyria cutanea tarda: clinical features and laboratory findings in 40 patients. *Am J Med* 1979; **67**: 277–86.

10 Mascaro JM, Herrero C, Lecha M *et al.* Uroporphyrinogen-decarboxylase deficiencies: porphyria cutanea tarda and related conditions. *Semin Dermatol* 1986; **5**: 115–24.

11 Byrne JP, Boss JM, Dawber RP. Contraceptive pill-induced porphyria cutanea tarda presenting with onycholysis of the finger nails. *Postgrad Med J* 1976; **52**: 535–8.

12 Varigos G, Schiltz JR, Bickers DR. Uroporphyrin I stimulation of collagen biosynthesis in human skin fibroblasts. A unique dark effect of porphyrin. *J Clin Invest* 1982; **69**: 129–35.

13 Inglese MJ, Bergamo BM. Large, nonhealing scalp ulcer associated with scarring alopecia and sclerodermatous change in a patient with porphyria cutanea tarda. *Cutis* 2005; **76**: 329–33.

14 Doyle JA, Friedman SJ. Porphyria and scleroderma. A clinical and laboratory review of 12 patients. *Australas J Dermatol* 1983; **24**: 109–14.

15 Park AJ, Webster GF, Penne RB, Raber IM. Porphyria cutanea tarda presenting as cicatricial conjunctivitis. *Am J Ophthalmol* 2002; **134**: 619–21.

16 Shaffrali FC, McDonagh AJ, Messenger AG. Hair darkening in porphyria cutanea tarda. *Br J Dermatol* 2002; **146**: 325–9.

17 Smith SG. Hepatoerythropoietic porphyria. *Semin Dermatol* 1986; **5**: 125–37.

18 Castano Suarez E, Zamarro Sanz O, Guerra Tapia A *et al.* Hepatoerythropoietic porphyria: relationship with familial porphyria cutanea tarda. *Dermatology* 1996; **193**: 332–5.

19 Sturrock ED, Meissner PN, Maeder DL, Kirsch RE. Uroporphyrinogen decarboxylase and protoporphyrinogen oxidase in dual porphyria. *S Afr Med J* 1989; **76**: 405–8.

20 Bulaj ZJ, Phillips JD, Ajioka RS *et al.* Hemochromatosis genes and other factors contributing to the pathogenesis of porphyria cutanea tarda. *Blood* 2000; **95**: 1565–71.

21 Bruguera M. Liver involvement in porphyria. *Semin Dermatol* 1986; **5**: 178–85.

22 Roberts AG, Whatley SD, Morgan RR *et al.* Increased frequency of the haemochromatosis Cys282Tyr mutation in sporadic porphyria cutanea tarda. *Lancet* 1997; **349**: 321–3.

23 Quecedo L, Costa J, Enriquez de Salamanca R. Role of hepatitis C virus in porphyria cutanea tarda hepatopathy. *Med Clin (Barc)* 1996; **106**: 321–4.

24 Fargion S, Piperno A, Cappellini MD *et al.* Hepatitis C virus and porphyria cutanea tarda: evidence of a strong association. *Hepatology* 1992; **16**: 1322–6.

25 Linde Y, Harper P, Floderus Y, Ros AM. The prevalence of hepatitis C in patients with porphyria cutanea tarda in Stockholm, Sweden. *Acta Derm Venereol* 2005; **85**: 164–6.

26 Murphy A, Dooley S, Hillary IB, Murphy GM. HCV infection in porphyria cutanea tarda. *Lancet* 1993; **341**: 1534–5.

27 Haberman HF, Rosenberg F, Menon IA. Porphyria cutanea tarda. Comparison of cases precipitated by alcohol and estrogens. *Can Med Assoc J* 1975; **113**: 653–5.

28 Bulaj ZJ, Franklin MR, Phillips JD *et al.* Transdermal estrogen replacement therapy in postmenopausal women previously treated for porphyria cutanea tarda. *J Lab Clin Med* 2000; **136**: 482–8.

29 Blauvelt A, Ross Harris H, Hogan DJ *et al.* Porphyria cutanea tarda and human immunodeficiency virus infection. *Int J Dermatol* 1992; **31**: 474–9.

30 Castanet J, Lacour JP, Bodokh J *et al.* Porphyria cutanea tarda in association with human immunodeficiency virus infection: is it related to hepatitis C virus infection? *Arch Dermatol* 1994; **130**: 664–5.

31 Cram DL, Epstein JK, Tuffanelli DL. Lupus erythematosus and porphyria. *Arch Dermatol* 1973; **108**: 779–84.

32 Agarwal R, Peters TJ, Coombes RC, Vigushin DM. Tamoxifen-related porphyria cutanea tarda. *Med Oncol* 2002; **19**: 121–3.

33 Smith AG, Francis JE, Dinsdale D *et al.* Hepatocarcinogenicity of hexachlorobenzene in rats and the sex difference in hepatic iron status and development of porphyria. *Carcinogenesis* 1985; **6**: 631–6.

34 Gisbert JP, Garcia-Buey L, Alonso A *et al.* Hepatocellular carcinoma risk in patients with porphyria cutanea tarda. *Eur J Gastroenterol Hepatol* 2004; **16**: 689–92.

35 Siersema PD, ten Kate FJW, Mulder PGH, Wilson JHP. Hepatocellular carcinoma in porphyria cutanea tarda: frequency and factors related to its occurrence. *Liver* 1992; **12**: 56–61.

36 Salata H, Cortes JM, Enriquez de Salamanca R *et al.* Porphyria cutanea tarda and hepatocellular carcinoma. Frequency of occurrence and related factors. *J Hepatol* 1985; **1**: 477–87.

37 Tio TH, Leijnse B, Jarrett A. Acquired porphyria from a liver tumor. *Clin Sci* 1957; **16**: 517–27.
38 Moseley H, Cameron H, MacLeod T *et al.* New sunscreens confer improved protection for photosensitive patients in the blue light region. *Br J Dermatol* 2001; **145**: 789–94.
39 Kaye ET, Levin JA, Blank IH, Arndt KA, Anderson RR. Efficiency of opaque photoprotective agents in the visible light range. *Arch Dermatol* 1991; **127**: 351–5.
40 Sheikh MY, Wright RA, Burruss JB. Dramatic resolution of skin lesions associated with porphyria cutanea tarda after interferon-alpha therapy in a case of chronic hepatitis C. *Dig Dis Sci* 1998; **43**: 529–33.
41 Rocchi E, Gibertini P, Cassanelli M *et al.* Serum ferritin in the assessment of liver iron overload and iron removal therapy in porphyria cutanea tarda. *J Lab Clin Med* 1986; **107**: 36–42.
42 Ratnaike S, Blake D, Campbell D *et al.* Plasma ferritin levels as a guide to the treatment of porphyria cutanea tarda by venesection. *Australas J Dermatol* 1988; **29**: 3–7.
43 Wennersten G, Ros A-M. Chloroquine in treatment of porphyria cutanea tarda. Long-term efficacy of combined phlebotomy and high-dose chloroquine therapy. *Acta Derm Venereol Suppl (Stockh)* 1982; **100**: 119–23.
44 Pitche P, Corrin E, Wolkenstein P *et al.* Successful treatment of haemodialysis-related porphyria cutanea tarda with deferoxamine. *Ann Dermatol Venereol* 2003; **130**: 37–9.
45 Rocchi E, Gibertini P, Cassanelli M *et al.* Iron removal therapy in porphyria cutanea tarda: phlebotomy versus slow subcutaneous desferrioxamine infusion. *Br J Dermatol* 1986; **114**: 621–9.
46 Sarkell B, Patterson JW. Treatment of porphyria cutanea tarda of end-stage renal disease with erythropoietin. *J Am Acad Dermatol* 1993; **29**: 499–500.
47 Scholnick PL, Epstein J, Marver HS. The molecular basis of the action of chloroquine in porphyria cutanea tarda. *J Invest Dermatol* 1973; **61**: 226–32.
48 Malina L, Chlumsky J. A comparative study of the results of phlebotomy therapy and low-dose chloroquine treatment in porphyria cutanea tarda. *Acta Derm Venereol Suppl (Stockh)* 1981; **61**: 346–50.
49 Ashton RE, Hawk JLM, Magnus IA. Low-dose oral chloroquine in the treatment of porphyria cutanea tarda. *Br J Dermatol* 1984; **111**: 609–13.
50 Valls V, Ena J, Enriquez-de-Salamanca R. Low-dose oral chloroquine in patients with porphyria cutanea tarda and low-moderate iron overload. *J Dermatol Sci* 1994; **7**: 164–75.
51 Kordac V, Kotal JP, Kalab M. Agents affecting porphyrin formation and secretion: implications for porphyria cutanea tarda treatment. *Semin Hematol* 1989; **26**: 16–23.
52 Cainelli T, Di Padova C, Marchesi L *et al.* Hydroxychloroquine versus phlebotomy in the treatment of porphyria cutanea tarda. *Br J Dermatol* 1983; **108**: 593–600.
53 Malkinson FD, Levitt L. Hydroxychloroquine treament of porphyria cutanea tarda. *Arch Dermatol* 1980; **116**: 1147–50.
54 Farinati F, Cardin R, DeMaria N *et al.* Iron storage, lipid peroxidation and glutathione turnover in chronic HCV-positive hepatitis. *J Hepatol* 1995; **22**: 449–56.
55 Roeckel IE. Commentary: iron metabolism in hepatitis C infection. *Ann Clin Lab Sci* 2000; **30**: 163–5.
56 Stolzel U, Kostler E, Schuppan D *et al.* Hemochromatosis (HFE) gene mutations and response to chloroquine in porphyria cutanea tarda. *Arch Dermatol* 2003; **139**: 309–13.
57 Elder GH. The cutaneous porphyrias. In: Hawk JLM, ed. *Photodermatology*. London: Arnold, 1999: 171–99.

Erythropoietic protoporphyria

Definition. EPP is an hereditary porphyria characterized by painful, lifelong photosensitivity and occasionally liver disease.

Incidence and aetiology. The prevalence of EPP is around 1/100 000 [1]. EPP results from deficient activity of ferrochelatase, the final enzyme of haem biosynthesis. This causes the accumulation of protoporphyrin predominantly in cells of the erythroid series, which causes a phototoxic reaction as the porphyrin-laden cells pass through small upper dermal blood vessels and are exposed to the Soret wavelength in sunlight. The photoactivated porphyrin from red cells and plasma causes an acute injury to the endothelium mediated by singlet oxygen and the hydroxyl radical [2,3]. Many ferrochelatase gene mutations have been identified in EPP patients and none are particularly common [4]. A few adult-onset cases have been reported which are associated with haematological malignancy and may be associated with chromosomal deletions involving the ferrochelatase gene [5].

Histopathology [6,7]. In the acute phase there is visible endothelial damage in superficial dermal vessels [8]. In the chronic phase, in exposed areas of skin, the repeated episodes of damage to small vessels in the upper dermis cause deposition of PAS-positive diastase-resistant hyaline material in the walls of blood vessels of the upper dermal and papillary vascular plexuses. Immunofluorescence shows immunoglobulins (mainly IgG) in a similar distribution. On electron microscopy the hyaline material can be seen to be a greatly replicated, layered and fragmented basement membrane, with fine fibrillar material permeating the capillary connective tissue sheath and extending beyond the vessel walls [6,9].

Clinical features [1,10]. Unlike the other cutaneous porphyrias, EPP causes immediate pain on exposure to bright sunlight. It presents most commonly in the first year, quite often in babies who usually present with crying in their prams in sunny weather, or crying for no obvious reason at night in the summer. Onset later in childhood does occur but onset in adulthood is rare. In spring and summer, after anything from a few minutes to an hour or two of sun exposure, patients describe discomfort, tingling or itching in exposed skin, particularly the dorsae of the hands and the face. If exposure continues, severe burning pain follows which can last anything between an hour and several days. Children often find partial relief with cold water and wet cloths, and this feature may be diagnostically useful. Usually the only physical sign during an attack is oedema, which may be subtle (Fig. 59.10). Erythema is less common. The lack of physical signs often leads to delay in diagnosis, with some patients initially being labelled as malingerers. Many patients experience a 'priming phenomenon' in which sunlight tolerance is reduced on the day after significant sun exposure [11]. In severe attacks, purpuric lesions and crusted erosions or vesicles may occur; these take a week or two to resolve after the attack settles down, and the pain may be severe enough to require hospital admission. Rare cases of EPP with prominent purpura and histological changes resembling a leukocytoclastic vasculitis [12], acute photo-onycholysis [13] or erythematous plaques [14] have been described. Physical signs may develop during childhood, with slight thickening of skin over the metacarpophalangeal and interphalangeal joints, superficial vermicular waxy scarring on the nose, shallow linear, punctate or small circular scars on cheeks and forehead and radial scars around the lips (Fig. 59.11). The skin over the nose, cheeks and forehead can become roughened and 'pebbly' in texture. Fifteen per cent of patients have no physical signs at all [1]. Children with EPP suffer from social isolation due to difficulty joining friends to play outside, and sensitivity to psychosocial issues is important for clinicians. Although EPP is lifelong, childhood and adolescence



Fig. 59.10 Oedema during an acute painful attack in a child with erythropoietic protoporphyria (EPP).



Fig. 59.11 Typical scars on the cheeks in erythropoietic protoporphyria (EPP).

are frequently the most difficult times because it is easier for adults to organize their lives to reduce sun exposure, but it is not surprising that the disease has such a profound impact on quality of life [1]. Symptoms often improve and porphyrin levels fall during pregnancy [1,15]. Patients may develop a mild hypochromic microcytic or normocytic anaemia, which can be associated with decreased serum iron levels and increased serum iron binding capacity [10]. With the exception of patients with EPP liver failure, operating theatre lights do not cause any problems during or after surgery in EPP patients [16]. Anaesthetists can also be reassured that acute attacks do not occur in EPP. In contrast, operating theatre lights can cause a devastating and potentially fatal phototoxic reaction in patients undergoing liver transplantation for protoporphyric liver failure.

Biochemical investigation [17]. The diagnostic finding is of an increased red cell free protoporphyrin concentration. Protoporphyrin is seen as a peak at 633 nm on plasma fluorimetric scanning. Sixty per cent of EPP patients have an increased faecal protoporphyrin concentration though this is not very useful diagnostically because of its lack of specificity. Urinary porphyrins are normal except in biliary impairment, when coproporphyrinuria develops.

Treatment [1]. No therapy has ever been proven to be effective in EPP mainly because of the lack of an objective test for disease activity in EPP, and high placebo rates make useful clinical trials difficult. This author's experience is that results with the specific therapies are generally fairly disappointing, and that attention to sunlight protection is the key to management.

Photoprotection. Basic measures include sun avoidance behaviour, sun-protective clothing and hats. It is important to use correct sunscreens [18,19]. Dihydroxyacetone paint has been used in some patients with EPP [20], and window films, which absorb violet light, can be useful for car or home windows, particularly in severely affected patients; all of these are discussed in detail on p. 59.6.

The acute reaction. For the acute reaction, complete sun avoidance (even through windows) leads to earlier resolution, and fans and cold water provide some pain relief. Antihistamines and most analgesics are of little value. For severe attacks, hospital admission may be necessary, for light avoidance and analgesia (usually opiate).

Specific therapies. Oral β-carotene is the most widely used treatment, usually at a dose around 180 mg daily in adults (90 mg daily in children) taken throughout the spring and summer. It is postulated to scavenge free radicals involved in the acute phototoxic reaction. Although some patients report that it reduces symptoms, others do not, and proof of efficacy from controlled trials is lacking. Patients may need to take it for several months before any effect is observed. The most common adverse effect of β-carotene is reversible skin discoloration. A controlled trial of *N*-acetyl cysteine has shown no benefit [21]. Short courses of a few weeks of psoralen and long-wave UV radiation (PUVA) [22] and narrow-band UVB [23] used in the early spring may be valuable, particularly in milder cases, and probably increase photoprotection by inducing epidermal thickening and pigmentation. Unlike PUVA, narrow-band UVB does not overlap with the EPP action spectrum and so cannot trigger attacks of pain. Many other systemic treatments with antioxidant or free radical scavenging properties have been used in EPP in an uncontrolled way on small numbers of patients, with conflicting and generally unconvincing results.

Genetic counselling. Although rare cases of autosomal recessive inheritance have been reported [24,25], EPP is generally an autosomal dominant disorder with incomplete penetrance, the disease resulting from co-inheritance of a gene mutation on one ferrochelatase allele with a low expression variant on the other allele. This

low expression variant is present in around 10% of the Caucasian population and is associated with reduced ferrochelatase mRNA levels resulting from the presence of the polymorphic variant IVS3-48C [26]. This low expression variant is common in Japan and South-East Asia and rare in Africa, which may explain the observed variations between continents [27]. Overall, the probability of each offspring of an EPP patient suffering from the disease is under 10%, but testing for the IVS3-48C polymorphism in a patient's partner is now available and can indicate more precisely whether there is a significant probability of future offspring being affected. This is useful for patients who would not consider having children if there were a significant likelihood of them having the disease. For a disorder which is rarely life-threatening, termination of pregnancy and thus antenatal diagnosis are not relevant.

Liver disease in EPP [24]. Protoporphyrin is excreted exclusively into the bile. It precipitates to form gallstones in around 12% of patients. It is also hepatotoxic, particularly to bile canaliculi, and severe liver damage occurs in around 1% of patients. EPP liver failure is most common in the teens and twenties. Usually a patient develops jaundice, worsening photosensitivity and often upper abdominal pain over a period of weeks or months. Investigation shows severe or total cholestasis, and a dramatically high red cell protoporphyrin concentration (due to its impaired excretion), which causes the worsening photosensitivity. Liver histology reveals deposition of protoporphyrin in vacuoles within bile canaliculi and hepatocytes, which may be accompanied by cirrhosis (Fig. 59.12). Although such acute episodes may resolve spontaneously, the porphyrin-induced cholestasis may become increasingly severe and itself further increase the protoporphyrin concentration in a vicious cycle, in which case the patient will die unless a liver transplant can be performed. Under operating theatre lights during the transplant surgery, the very high protoporphyrin concentration may cause a severe phototoxic reaction with postoperative burns, massive haemolysis and a severe neuropathy. Yellow filters blocking out light below 460 nm (e.g. Madico TA81XSR) must be used over the operating theatre lights, and do not impair the surgeon's view [16]. Even if these immediate postoperative complications are avoided, protoporphyric liver disease recurs in the graft in most patients over several years, severe enough to require retransplantation in a minority [28]. Recently, two patients with severe liver disease have been treated by bone marrow transplantation (in one of them with a liver transplant). Although the marrow transplantation does cure the EPP, the dangers of the procedure mean that it is reserved for these rare, life-threatening situations [29,30].

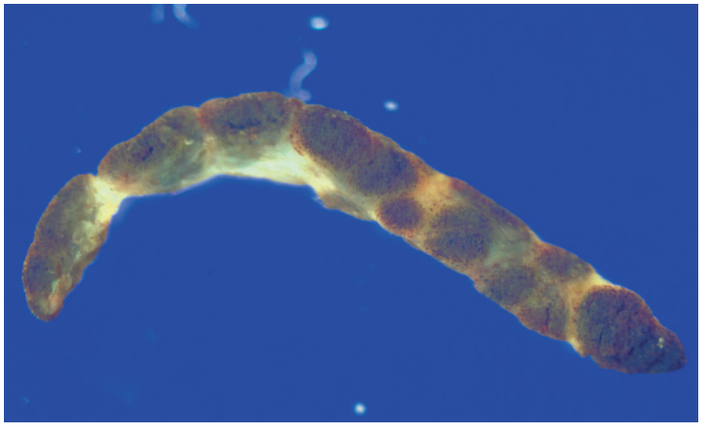


Fig. 59.12 Liver biopsy in protoporphyric liver disease, showing nodules of cirrhosis and black staining by deposits of protoporphyrin.

It is vital to recognize impending protoporphyric liver failure early enough that arrangements can be made for a liver transplant if it should become necessary. Thus, all EPP patients should have liver function tests and red cell protoporphyrin concentration checked at least once a year. The appearance of coproporphyrin in the urine has been proposed as an indicator of significant liver disease in EPP [31]. Worsening photosensitivity may be the only clinical indication of the development of severe liver disease. Although protoporphyric liver failure is rare, mild abnormalities of liver function tests are common in EPP [31]. Since the significance of these abnormalities is unclear, it is advisable to monitor closely in these patients, and to refer the patient to a hepatologist if the abnormality is persistent or deteriorating. In such patients, an ion exchange resin such as cholestyramine may protect the liver against further porphyrin toxicity. The major difficulty for the dermatologist is the lack of any means of identifying those EPP patients at risk of liver failure. Since several cases have been described in siblings, patients with a relative who has suffered protoporphyric liver failure should be treated as being at increased risk of developing it themselves. Recessive inheritance of EPP may increase the risk of severe hepatic disease, though it is not clear how significant an association this is [24].

Iron deficiency anaemia may trigger or exacerbate hepatic disease by increasing porphyrin accumulation [24], and subsequent iron replacement may make the situation temporarily worse by acutely stimulating haem biosynthesis.

References

1 Holme SA, Anstey AV, Finlay AY *et al.* Erythropoietic protoporphyria in the U.K.: clinical features and effect on quality of life. *Br J Dermatol* 2006; **155**: 574–81.

2 Brun A, Sandberg S. Mechanisms of photosensitivity in porphyric patients with special emphasis on erythropoietic protoporphyria. *J Photochem Photobiol B* 1991; **10**: 285–302.

3 Takeshita K, Takajo T, Hirata H *et al.* In vivo oxygen radical generation in the skin of the protoporphyria model mouse with visible light exposure: an L-band ESR study. *J Invest Dermatol* 2004; **122**: 1463–70.

4 Minder EI, Gouya L, Schneider-Yin X, Deybach JC. A genotype–phenotype correlation between null-allele mutations in the ferrochelatase gene and liver complication in patients with erythropoietic protoporphyria. *Cell Mol Biol (Noisy-le-grand)* 2002; **48**: 91–6.

5 Sarkany RP, Ross G, Willis F. Acquired erythropoietic protoporphyria as a result of myelodysplasia causing loss of chromosome 18. *Br J Dermatol* 2006; **155**: 464–6.

6 Ryan EA, Madill GT. Electron microscopy of the skin in erythropoietic protoporphyria. *Br J Dermatol* 1968; **80**: 561–70.

7 Epstein JH, Tuffanelli DL, Epstein WL. Cutaneous changes in the porphyrias. A microscopic study. *Arch Dermatol* 1973; **107**: 689–98.

8 Gschnait FG, Wolff K, Konrad K. Erythropoietic protoprophyria—submicroscopic events during the acute photosensitivity flare. *Br J Dermatol* 1975; **92**: 545–57.

9 Wick G, Honigsmann H, Timpl R. Immunofluorescence demonstration of type IV collagen and a noncollagenous glycoprotein in thickened vascular basal membranes in protoporphyria. *J Invest Dermatol* 1979; **73**: 335–8.

10 Deleo VA, Poh-Fitzpatrick M, Mathews-Roth M, Harber LC. Erythropoietic protoporphyria. Ten years experience. *Am J Med* 1976; **60**: 8–22.
11 Poh-Fitzpatrick MB. The 'priming phenomenon' in the acute phototoxicity of erythropoietic protoporphyria. *J Am Acad Dermatol* 1989; **21**: 311.
12 Patel GK, Weston J, Derrick EK, Hawk JL. An unusual case of purpuric erythropoietic protoporphyria. *Clin Exp Dermatol* 2000; **25**: 406–8.
13 Marsden RA, Dawber RP. Erythropoietic protoporphyria with onycholysis. *Proc R Soc Med* 1977; **70**: 572–4.
14 Murphy GM, Hawk JL, Magnus IA. Late-onset erythropoietic protoporphyria with unusual cutaneous features. *Arch Dermatol* 1985; **121**: 1309–12.
15 Poh-Fitzpatrick MB. Human protoporphyria: reduced cutaneous photosensitivity and lower erythrocyte porphyrin levels during pregnancy. *J Am Acad Dermatol* 1997; **36**: 40–3.
16 Wahlin S, Harper P, Brun A. Protection from phototoxic injury in erythropoietic protoporphyria. Presented at: *Porphyrins and Porphyrias International Conference*, Rotterdam, May 2007.
17 Deacon A. The porphyrias and their investigation. *CPD Bull Clin Biochem* 1999; **1**: 122–6.
18 Moseley H, Cameron H, MacLeod T *et al.* New sunscreens confer improved protection for photosensitive patients in the blue light region. *Br J Dermatol* 2001; **145**: 789–94.
19 Kaye ET, Levin JA, Blank IH *et al.* Efficiency of opaque photoprotective agents in the visible light range. *Arch Dermatol* 1991; **127**: 351–5.
20 Johnson JA. Durable protection against long-wavelength UV-A radiation and blue light. *Arch Dermatol* 1992; **128**: 409.
21 Norris PG, Baker CS, Roberts JE, Hawk JL. Treatment of erythropoietic protoporphyria with *N*-acetylcysteine. *Arch Dermatol* 1995; **131**: 354–5.
22 Roelandts R. Photo (chemo) therapy and general management of erythropoietic protoporphyria. *Dermatology* 1995; **190**: 330–1.
23 Collins P, Ferguson J. Narrow-band UVB (TL-01) phototherapy. An effective preventative treatment for the photodermatoses. *Br J Dermatol* 1995; **132**: 956–63.
24 Sarkany RPE, Cox TM. Autosomal recessive erythropoietic protoporphyria: a syndrome of severe photosensitivity and hepatic failure. *QJM* 1995; **88**: 541–9.
25 Whatley SD, Mason NG, Khan M *et al.* Autosomal recessive erythropoietic protoporphyria in the United Kingdom: prevalence and relationship to liver disease. *J Med Genet* 2004; **41**: e105.
26 Gouya L, Puy H, Robreau AM *et al.* The penetrance of dominant erythropoietic protoporphyria is modulated by expression of wildtype FECH. *Nat Genet* 2002; **30**: 27–8.
27 Gouya L, Martin-Schmitt C, Robreau AM *et al.* Contribution of a common single-nucleotide polymorphism to the genetic predisposition for erythropoietic protoporphyria. *Am J Hum Genet* 2006; **78**: 2–14.
28 McGuire BM, Bonkovsky HL, Carithers RL Jr *et al.* Liver transplantation for erythropoietic protoporphyria liver disease. *Liver Transpl* 2005; **11**: 1590–6.
29 Wahlin S, Aschan J, Bjornstedt M *et al.* Curative bone marrow transplantation in erythropoietic protoporphyria after reversal of severe cholestasis. *J Hepatol* 2007; **46**: 174–9.
30 Rand EB, Bunin N, Cochran W, Ruchelli E *et al.* Sequential liver and bone marrow transplantation for treatment of erythropoietic protoporphyria. *Pediatrics* 2006; **118**: e1896–9.
31 Doss MO, Frank M. Hepatobiliary implications and complications in protoporphyria, a 20-year study. *Clin Biochem* 1989; **22**: 223–9.

Porphyrias that cause cutaneous disease and acute attacks

Hereditary coproporphyria

Like VP, this porphyria presents from puberty onwards. The skin is not affected in most patients suffering from this rare acute porphyria but around 10–20% [1] of patients have cutaneous involvement with fragility and blistering in sun-exposed areas, indistinguishable from that seen in PCT or VP. The skin disease may be triggered or exacerbated by intercurrent liver disease [2]. HC is caused by an autosomal dominant inherited deficiency of coproporphyrinogen oxidase. The biochemical findings are of a 615–620 nm peak on plasma spectrofluorimetry, increased uro- and coproporphyrin concentrations in urine, and increased coproporphyrin in faeces. Predominance of the type III isomer in faeces is a sensitive indicator of HC [1]. Rare variants include a homozygous form characterized by short stature, acute attacks and skin changes with prominent hypertrichosis and pigmentation [3], and harderoporphyria which causes haemolysis in the neonate or bullae.

References

1 Kuhnel A, Gross U, Doss MO. Hereditary coproporphyria in Germany: clinical-biochemical studies in 53 patients. *Clin Biochem* 2000; **33**: 465–73.
2 Hawk JL, Magnus IA, Parkes A *et al.* Deficiency of hepatic coproporphyrinogen oxidase in hereditary coproporphyria. *J R Soc Med* 1978; **71**: 775–7.
3 Grandchamp B, Phung N, Nordmann Y. Homozygous case of hereditary coproporphyria. *Lancet* 1977; **2**: 1348–9.

Variegate porphyria

Definition. A rare inherited disease usually characterized by photo-induced skin fragility and blistering, which may cause acute attacks.

Aetiology and incidence. VP is caused by an autosomal dominant inherited deficiency of protoporphyrinogen oxidase. In addition to causing photosensitization, accumulated coproporphyrinogen and protoporphyrinogen also inhibit PBG deaminase, the probable mechanism for acute attacks in VP [1]. In South Africa, VP is common (due to a founder effect) with a prevalence in whites and Afrikaner-descended non-whites of 1/200. Elsewhere the prevalence is around 0.5–1/100 000 [2]. At least 80% of South African carriers of a pathogenic VP mutation are completely asymptomatic [3].

Pathogenesis of skin lesions in VP. It is perhaps unexpected that the accumulated copro- and protoporphyrin should cause PCT-like upper dermal blistering rather than EPP-like acute pain. This is likely to be because, although hydrophobic porphyrins predominate in plasma, hydrophilic porphyrins, especially uroporphyrin, predominate in the skin. This local accumulation is thought to result from secondary local photo-inactivation of UROD in the skin by coproporphyrin [3]. In addition, the protoporphyrin in VP is conjugated to a peptide which may reduce its phototoxicity.

Clinical features [2–4]

Skin. Of those patients with symptomatic VP, around 70% of patients have cutaneous involvement, and only around 17% of these patients will ever suffer an acute attack [5]. VP only very rarely presents before puberty, and usually the skin disease begins in adolescence or young adulthood. Patients describe skin fragility, usually fairly mild, affecting sun-exposed skin particularly on the backs of the hands [2,3]. The skin disease is generally indistinguishable from PCT, with painful tense bullae occurring in sun-exposed skin, as well as scarring, pigmentary abnormalities, sometimes pseudosclerodermatous changes of the hands and fingers, and occasionally photo-onycholysis. However, a significant number of patients do not describe worsening in the summer,

and the patients who do describe seasonal variation often have their worst problems in late summer and autumn. In addition, around half of patients with VP describe mild, transient, light-related eruptions in the early summer. The examination findings of scarring, patches of hypo- and hyperpigmentation at sites of blisters, milia and mild hypertrichosis particularly around the eyes, are indistinguishable from PCT. Intercurrent biliary obstruction exacerbates the cutaneous disease since the accumulated porphyrins are excreted into the bile. Acute photosensitivity can occur in patients with disturbed liver function. Hormonally induced hepatic dysfunction may explain the exacerbations of skin disease seen in females taking oral contraceptives and during pregnancy. VP sometimes goes into clinical and biochemical remission in old age.

Acute attacks [2,3,5,6]. As in other acute porphyrias, women are three times as frequently affected as men, and 70% of acute attacks occur between the ages of 20 and 40 years. Around 17% of patients with cutaneous VP ever suffer an acute attack; the number has declined recently due to improved use of prophylactic measures. The severity of acute attacks varies from mild abdominal pain, sometimes accompanied by vomiting and constipation, through to very severe attacks with bulbar palsy and respiratory paralysis. The presentation, diagnosis and management of acute attacks is covered in the section on acute attacks of porphyria, p. 59.7.

Homozygous VP [7]. In this disease, a mutation on both protoporphyrinogen oxidase alleles results in an enzyme activity less than 20% of normal, compared to the 50% in other VP patients. In homozygous VP, fragility, bullae and often hypertrichosis develop in exposed (and sometimes non-exposed) skin in neonates or infants and the skin disease may be severe. Delayed development, epilepsy, sensory neuropathy, nystagmus, various hand deformities and growth retardation also commonly occur. Acute attacks do not occur in these patients. The biochemical findings are the same as in VP, except for the lower enzyme activity.

Differential diagnosis. VP cutaneous disease is easily distinguished from non-photosensitive blistering disorders. It can be clinically very similar to PCT, late-onset CEP, HC and pseudoporphyria. Biochemical analysis is required to diagnose VP.

Biochemical findings. A plasma spectrofluorimetry peak around 626 nm (caused by a porphyrin–protein complex) is diagnostic of VP in the absence of a raised free red cell protoporphyrin level, and is present in virtually all symptomatic cases of VP. It may persist during periods of clinical remission when faecal excretion becomes normal and is a more sensitive test than measurement of faecal porphyrins [8]. A persistently normal faecal protoporphyrin concentration in adulthood in patients with the VP genetic defect has been proposed as a prognostic marker indicating a greater likelihood of the VP never causing any clinical problems and staying clinically latent [6]. The urine contains increased levels of coproporphyrin, and increased concentrations of copro- and protoporphyrin are found in faeces. In a few patients, the urine shows the typical PCT pattern of uroporphyrin accompanied by hepta- and sometimes hexa- and pentacarboxylic acid porphyrins, a situation known as 'dual porphyria' [9]. Thus, urinary analysis alone can result in the misdiagnosis of VP as PCT, with potentially disastrous consequences. During acute attacks, urinary PBG (and ALA) are raised. The urinary PBG usually falls to normal within weeks of the attack resolving, but may stay a little increased outside the context of an acute attack [10].

Treatment. The key to successful management of the skin disease is photoprotection with sun avoidance using clothes, hats and gloves. Opaque sunscreens, containing pigmentary grade titanium dioxide or zinc oxide sometimes with the addition of iron oxide, are protective against Soret wavelength light [11,12]. The skin disease is rarely severe enough to require filter films for car and home windows. Since the relationship between sun exposure and skin lesions is not obvious, the role of light in producing the skin lesions should be explained to the patient. β-Carotene and canthaxanthin have also been claimed to provide limited protection in some patients, and UVB phototherapy may also be of value [3]. If liver function tests indicate biliary obstruction, relief of this will reduce cutaneous symptoms. The risk of acute attacks is the key issue for safe management of patients and their families. Patients should be directed to a list of drugs to avoid [13,14], including those which can induce attacks, and also those known to induce cholestasis, and cannabis; they should also be advised to wear an emergency identification bracelet, to avoid low calorie diets, and to become teetotal. Liver transplantation has been successfully used to cure variegate porphyria (and acute intermittent porphyria) in cases where acute attacks are frequent, severe and uncontrollable by medical means [15].

Genetic counselling. It is important to identify relatives who have latent VP because of the risk of acute attacks. The plasma 624–626 nm peak is found in the majority of cases of latent VP but only from teenage onwards. A positive plasma fluorimetry result is diagnostic of latent VP but a negative result is uninformative [16,17]. The only completely reliable way to identify those carrying the VP gene defect if the plasma scan is negative is to identify the protoporphyrinogen oxidase gene mutation in the index case and then assess its presence or absence in relatives. This is labour intensive because, outside South Africa, most families have their own private mutation. Relatives found to have the gene defect are at a low risk (roughly 5–10%) of acute attacks and should take all the precautions taken by any patient diagnosed with an acute porphyria. The risk of a patient passing the mutated gene on to each offspring is 50%, and around 20% of those carrying the mutation will eventually develop symptoms of some sort.

References

1 Meissner P, Adams P, Kirsch R. Allosteric inhibition of human lymphoblast and purified porphobilinogen deaminase by protoporphyrinogen and coproporphyrinogen. A possible mechanism for the acute attack of variegate porphyria. *J Clin Invest* 1993; **91**: 1436–44.

2 Mustajoki P. Variegate porphyria. Twelve years' experience in Finland. *QJM* 1980; **49**: 191–203.

3 Day RS. Variegate porphyria. *Semin Dermatol* 1986; **5**: 138–54.

4 Timonen K, Niemi KM, Mustajoki P, Tenhunen R. Skin changes in variegate porphyria. Clinical, histopathological, and ultrastructural study. *Arch Dermatol Res* 1990; **282**: 108–14.

5 Elder GH, Hift RJ, Meissner PN. The acute porphyrias. *Lancet* 1997; **349**: 1613–7.
6 von und zu Fraunberg M, Timonen K *et al.* Clinical and biochemical characteristics and genotype-phenotype correlation in Finnish variegate porphyria patients. *Eur J Hum Genet* 2002; **10**: 649–57.
7 Hift RJ, Meissner PN, Todd G *et al.* Homozygous variegate porphyria: an evolving clinical syndrome. *Postgrad Med J* 1993; **69**: 781–6.
8 Hift RJ, Davidson BP, van der Hooft C *et al.* Plasma fluorescence scanning and fecal porphyrin analysis for the diagnosis of variegate porphyria: precise determination of sensitivity and specificity with detection of protoporphyrinogen oxidase mutations as a reference standard. *Clin Chem* 2004; **50**: 915–23.
9 Sturrock ED, Meissner PN, Maeder DL, Kirsch RE. Uroporphyrinogen decarboxylase and protoporphyrinogen oxidase in dual porphyria. *S Afr Med J* 1989; **76**: 405–8.
10 Deacon A. The porphyrias and their investigation. *CPD Bull Clin Biochem* 1999; **1**: 122–6.
11 Moseley H, Cameron H, MacLeod T *et al.* New sunscreens confer improved protection for photosensitive patients in the blue light region. *Br J Dermatol* 2001; **145**: 789–94.
12 Kaye ET, Levin JA, Blank IH *et al.* Efficiency of opaque photoprotective agents in the visible light range. *Arch Dermatol* 1991; **127**: 351–5.
13 Welsh Medicines Information Centre. http://www.wmic.wales.nhs.uk.
14 European Porphyria Initiative/The European Porphyria NETwork. http://www.porphyria-europe.com.
15 Stojeba N, Meyer C, Jeanpierre C *et al.* Recovery from a variegate porphyria by a liver transplantation. *Liver Transpl* 2004; **10**: 935–8.
16 Long C, Smyth SJ, Woolf J *et al.* Detection of latent variegate porphyria by fluorescence emission spectroscopy of plasma. *Br J Dermatol* 1993; **129**: 9–13.
17 Da Silva V, Simonin S, Deybach JC *et al.* Variegate porphyria: diagnostic value of fluorometric scanning of plasma porphyrins. *Clin Chim Acta* 1995; **238**: 163–8.

Mucinoses [1–5]

S.M. Breathnach, pp. 59.21–59.30

Mucins are jelly-like acid glycosaminoglycans (formerly known as mucopolysaccharides) of the ground substances and probably play a part in the extravascular exchange of metabolites. Mucin is normally produced in small quantities by fibroblasts. Acid glycosaminoglycans, such as hyaluronic acid and heparin, stain with toluidine blue, colloidal iron, or with Alcian blue at pH 2.5, the coloration depending on the number and nature of the acid groups [6]. Periodic acid Schiff (PAS) stains heparin, but not hyaluronic acid. In general, acid glycosaminoglycans stain much brighter in frozen fixed tissue, or in specimens preserved in 1% cetylpyridinium chloride solution [7], rather than in formalin-fixed biopsies [8].

Neutral glycosaminoglycans are glycoproteins in which the hexosamine sugar polymer is incorporated in a protein chain. Hale and Alcian blue stains are negative but PAS stain is positive. The mucins in the skin and their histochemistry have been well reviewed [9]. Histopathological examination of many cutaneous mucinoses reveals that collagen fibres are fragmented [10].

Classification of the cutaneous mucinoses [1–5]

Mucinous infiltration of the skin is found in many widely differing disorders, some affecting the skin only, others related to systemic disease [1–5,11]. The association of HIV infection with lichen myxoedematosus seems to be more than coincidental [12]. They can be classified as shown in Table 59.2.

Table 59.2 Classification of the cutaneous mucinoses.

Primary
Diffuse (degenerative-inflammatory mucinoses):
Generalized myxoedema (Chapter 62)
Pretibial myxoedema (Chapter 62)
Lichen myxoedematosus (papular mucinosis, scleromyxoedema)
Acral persistent papular mucinosis
Cutaneous papular mucinosis of infancy
Self-healing papular cutaneous mucinosis; juvenile and adult
Hereditary progressive mucinous histiocytosis
Reticular erythematous mucinosis (plaque-like mucinosis)
Scleredema (Chapter 51)
Follicular forms:
Follicular mucinosis (alopecia mucinosa)
Urticaria-like follicular mucinosis
Focal (neoplastic-hamartomatous mucinoses):
Cutaneous focal mucinosis
Mucous (myxoid) cyst
Mucinous naevus
Secondary
Papular and nodular mucinosis associated with lupus erythematosus
Collagen vascular diseases (especially dermatomyositis, lupus erythematosus)
Malignant atrophic papulosis (Degos' syndrome) [13]
Papular mucinosis in L-tryptophan-induced eosinophilia–myalgia syndrome
Papular mucinosis of the toxic oil syndrome
Mucinosis accompanying mesenchymal and neural tumours

References

1 Rongioletti F, Rebora A. The new cutaneous mucinoses: a review with an up-to-date classification of cutaneous mucinoses. *J Am Acad Dermatol* 1991; **24**: 265–70.
2 Stephens CJM, McKee PH, Black MM. The dermal mucinoses. *Adv Dermatol* 1993; **8**: 201–27.
3 Truhan AP, Roenigk HH. The cutaneous mucinoses. *J Am Acad Dermatol* 1986; **14**: 1–18.
4 Rongioletti F, Rebora A. Updated classification of papular mucinosis, lichen myxedematosus, and scleromyxedema. *J Am Acad Dermatol* 2001; **44**: 273–81.
5 Rongioletti F, Rebora A. Cutaneous mucinoses: microscopic criteria for diagnosis. *Am J Dermatopathol* 2001; **23**: 257–67.
6 Scott JE, Dorling J. Differential staining of acid glycosaminoglycans (mucopolysaccharides) by alcian blue in salt solutions. *Histochemie* 1965; **5**: 221–3.
7 Matsuoka LY, Wortsmann J, Dietrich JG. Glycosaminoglycans in histologic sections. *Arch Dermatol* 1987; **123**: 862–3.
8 Cole HG, Winkelmann RK. Acid mucopolysaccharide staining in scleredema. *J Cutan Pathol* 1990; **17**: 211–3.
9 Wells GC. Mucins in the skin and their histochemistry. *Trans Rep St John's Hosp Derm Soc Lond* 1962; **48**: 35–9.
10 Alves MF, Filgueira AL, Lorena DE, Porto LC. Type I and type III collagens in cutaneous mucinosis. *Am J Dermatopathol* 1998; **20**: 41–7.
11 Reed RJ, Clark WH, Mihm MC. The cutaneous mucinoses. *Hum Pathol* 1973; **4**: 201–5.
12 Rongioletti F, Ghigliotti G, De Marchi R, Rebora A. Cutaneous mucinoses and HIV infection. *Br J Dermatol* 1998; **139**: 1077–80.
13 Black MM. Malignant atrophic papulosis (Degos' syndrome). *Br J Dermatol* 1971; **85**: 290–2.

Lichen myxoedematosus

Synonyms

- Papular mucinosis
- Lichen fibromucinodosis
- Scleromyxoedema

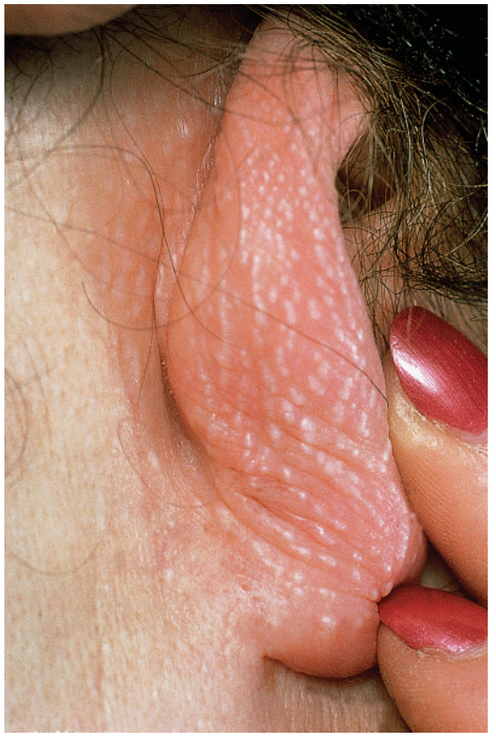


Fig. 59.13 Lichen myxoedematosus. Close-up of micropapules behind earlobe. (Courtesy of St Thomas' Hospital, London, UK.)



Fig. 59.14 Scleromyxoedema. View of forehead showing sclerodermoid appearance and linear papulation. (Courtesy of St Thomas' Hospital, London, UK.)

Lichen myxoedematosus is a cutaneous myxoedematous condition characterized by formation of numerous lichenoid papules which coalesce to form generalized plaques, causing extensive thickening and hardening of the skin [1–3] (Fig. 59.13). It is a rare disorder characterized by proliferation of fibroblasts with fibrosis and excessive deposition of acid glycosaminoglycans in the skin, and is distinct from scleroderma [4].

It has been proposed [2,3] that there are really only two main divisions of lichen myxoedematosus: (i) a generalized papular and sclerodermoid form (scleromyxoedema) with systemic, even lethal, manifestations; and (ii) a localized form, without a demonstrable paraprotein, which runs a more benign course. The localized form in turn is subdivided into five subtypes: (i) a discrete papular form involving any site [5]; (ii) acral persistent papular mucinosis involving only the extensor surface of the hands and wrists [6]; (iii) papular mucinosis of infancy, a paediatric variant of the discrete form or the acral form of persistent papular mucinosis; (iv) self-healing papular mucinosis, of juvenile and adult types; and (v) a nodular form.

A third group of atypical or intermediate forms, not meeting the criteria for either scleromyxoedema or the localized form, includes cases of (i) scleromyxoedema without monoclonal gammopathy; (ii) localized forms with monoclonal gammopathy and/or systemic symptoms; (iii) localized forms with mixed features of the subtypes; and (iv) poorly-specified cases and a localized papular form.

Scleromyxoedema is usually associated with a monoclonal gammopathy. Serum from patients with lichen myxoedematosus, even after elution of the IgG paraprotein, can stimulate synthesis of DNA and cell proliferation in cultured fibroblasts [7].

Histopathology [2,8,9]. Mucinous deposits occur in the middle and deeper layers of the dermis, where they displace collagen fibres, but do not involve the dermal papillae or accumulate around blood vessels. Histochemically, the mucinous deposits are heterogeneous mixtures of acid glycosaminoglycans, which stain positively with Alcian blue and toluidine blue. Large, stellate, elongated fibroblasts are present within the mucinous stroma [10]. Mucin deposition in the media and adventitia of vessels and in many organs including the myocardium is reported, and the skeletal muscles may be infiltrated with lymphocytes [11].

Clinical features [1,12–14]. In scleromyxoedema (the Arndt–Gottron syndrome) the pattern of lichen myxoedematosus is confluent, papular and sclerotic. Diffuse thickening of the skin underlies the papules. The facial features may be distorted by exaggeration of the facial ridges (Fig. 59.14), and flexion of the fingers may be limited. Multiple periorbital myxomas may progress to scleromyxoedema [15]. The involvement of the hands may simulate the sclerodactyly of scleroderma (Fig. 59.15), but the clinical appearance of numerous small papules of more or less uniform size, often in linear patterns on an erythematous and palpably thickened background, is very distinctive.

No endocrine abnormalities have been demonstrated, but cardiovascular abnormalities may occur in 10% of cases [8], whereas others may complain of extreme muscular weakness and lassitude due to myopathic or neurological involvement [16]. Occasionally, systemic involvement may occur in other internal organs [17].

An IgG class paraproteinaemia is almost always found on serum electrophoresis, although total serum protein values are usually normal [1,18]. Bone marrow studies may show a mild plasmacytic infiltration. Radiological survey of the skeletal system is normal. In one case, acid glycosaminoglycan levels in the serum were elevated [19].



Fig. 59.15 Scleromyxoedema. Sclerodermoid appearance of finger. Same patient as shown in Fig. 59.14. (Courtesy of St Thomas' Hospital, London, UK.)

Localized lichen myxoedematosus is characterized by small, firm, waxy papules of limited distribution [1], although a rare nodular form has larger lesions.

Diagnosis. Infiltrates appearing in and around old scars may simulate 'scar sarcoidosis'. Papules on the dorsa of the hands and ears may cause confusion with granuloma annulare. Systemic scleroderma may show many features simulating scleromyxoedema. However, in scleroderma the skin is thickened and bound-down, whereas in scleromyxoedema it is also thickened but moveable over the subcutis. Papules are absent in scleroedema and scleroderma, but common in scleromyxoedema. Nephrogenic systemic fibrosis, previously known as nephrogenic fibrosing dermopathy, a fibromucinous scleromyxoedema-like disorder associated with renal dysfunction, has been linked to administration of gadolinium-based contrast medium (see Chapter 75).

Prognosis. The prognosis of scleromyxoedema is poor despite a multiplicity of potential treatments. Death may result from nonspecific complications such as bronchopneumonia, coronary occlusion or from haematological malignancies.

Treatment. The potential for spontaneous long-term regression renders treatment of scleromyxoedema difficult to assess [20]. Localized lichen myxoedematosus of the discrete type has been treated with tacrolimus ointment [21]. Topical betamethasone and dimethylsulphoxide (DMSO) has produced regression in one case [22]. Systemic steroids alone may be ineffective [23,24]. Oral aromatic retinoids produce inconsistent but occasionally successful results [25,26]. Thalidomide has been advocated [27–29], as has interferon-α [30]. Plasmapheresis can be beneficial if combined with pulsed corticosteroid and/or immunosuppressive therapy [31,32]. Other therapies reported to be successful in isolated cases include extracorporeal photochemotherapy [33,34], intravenous immunoglobulin [35–37] and electron-beam therapy [38]. High-dose melphalan chemotherapy with autologous stem cell transplantation offers durable remission in most patients [39–41]. Aggressive surgical intervention for palliation of severe aesthetic and functional disability may be indicated [42].

References

1 Montgomery H, Underwood LJ. Lichen myxedematosus (differentiation from cutaneous myxedemas or mucoid states). *J Invest Dermatol* 1953; **20**: 213–36.
2 Rongioletti F, Rebora A. Updated classification of papular mucinosis, lichen myxedematosus, and scleromyxedema. *J Am Acad Dermatol* 2001; **44**: 273–81.
3 Rongioletti F. Lichen myxedematosus (papular mucinosis): new concepts and perspectives for an old disease. *Semin Cutan Med Surg* 2006; **25**: 100–4.
4 Jablonska S, Blaszczyk M. Scleromyxedema is a scleroderma-like disorder and not a coexistence of scleroderma with papular mucinosis. *Eur J Dermatol* 1999; **9**: 551–4.
5 Poswig A, Hinrichs R, Megahed M *et al.* Discrete papular mucinosis—a rare subtype of lichen myxoedematosus. *Clin Exp Dermatol* 2000; **25**: 289–92.
6 Rebora A, Rongioletti F. Acral persistent papular mucinosis and lichen myxoedematosus. *Dermatology* 1992; **185**: 81.
7 Harper RA, Rispler J. Lichen myxoedematosus serum stimulating human skin fibroblast proliferation. *Science* 1978; **199**: 545–7.
8 McCuiston CH, Schoch EP. Autopsy findings in lichen myxedematosus. *Arch Dermatol* 1956; **74**: 259–62.
9 Rongioletti F, Rebora A. Cutaneous mucinoses: microscopic criteria for diagnosis. *Am J Dermatopathol* 2001; **23**: 257–67.
10 Matsuoka LY, Wortsman J, Carlisle KS *et al.* The acquired cutaneous mucinoses. *Arch Intern Med* 1984; **144**: 1974–80.
11 Dirneen AM, Dicken CH. Scleromyxoedema. *J Am Acad Dermatol* 1995; **33**: 37–43.
12 Cokonis Georgakis CD, Falasca G, Georgakis A, Heymann WR. Scleromyxedema. *Clin Dermatol* 2006; **24**: 493–7.
13 Heymann WR. Scleromyxedema. *J Am Acad Dermatol* 2007; **57**: 890–1.
14 Perry HO, Montgomery H, Stickney JM. Further observations on lichen myxedematosus. *Ann Intern Med* 1960; **53**: 955–69.
15 Craig NM, Putterman AM, Roenigk RK *et al.* Multiple periorbital cutaneous myxomas progressing to scleromyxedema. *J Am Acad Dermatol* 1996; **34**: 928–30.
16 Rothe MJ, Rivas R, Gauld E *et al.* Scleromyxedema and severe myositis. *Int J Dermatol* 1989; **28**: 657–60.
17 Truhan AP, Roenigk HH. Lichen myxoedematosus: an unusual case with rapid progression and possible internal involvement. *Int J Dermatol* 1987; **26**: 91–5.
18 Ayala F, Balato N, Ceparano S *et al.* Immunochemical characterization of the abnormal paraprotein in a case of scleromyxoedema. *Clin Exp Dermatol* 1984; **9**: 351–7.
19 Rudner EJ, Mehregan A, Pinkus H. Scleromyxedema. *Arch Dermatol* 1966; **93**: 3–12.
20 Boffa MJ, Ead RD. Spontaneous improvement of scleromyxoedema. *Clin Exp Dermatol* 1995; **20**: 157–60.
21 Rongioletti F, Zaccaria E, Cozzani E, Parodi A. Treatment of localized lichen myxedematosus of discrete type with tacrolimus ointment. *J Am Acad Dermatol* 2008; **58**: 530–2.
22 Bonnetblanc JM, Bedane C. Regression of scleromyxoedema with topical betamethasone and dimethyl sulfoxide: a 30-month follow-up. *Arch Dermatol* 1991; **127**: 1733–4.
23 Kreuter A, Altmeyer P. High-dose dexamethasone in scleromyxedema: report of 2 additional cases. *J Am Acad Dermatol* 2005; **53**: 739–40.
24 Lin YC, Wang HC, Shen JL. Scleromyxedema: an experience using treatment with systemic corticosteroid and review of the published work. *J Dermatol* 2006; **33**: 207–10.
25 Milam CP, Cohen LE, Fenske NA *et al.* Scleromyxoedema: therapeutic response to isotretinoin in three patients. *J Am Acad Dermatol* 1988; **19**: 469–77.
26 Hisler BM, Savoy LB, Hashimoto K. Improvement of scleromyxoedema associated with isotretinoin therapy. *J Am Acad Dermatol* 1991; **24**: 854–7.
27 Sansbury JC, Cocuroccia B, Jorizzo JL *et al.* Treatment of recalcitrant scleromyxedema with thalidomide in 3 patients. *J Am Acad Dermatol* 2004; **51**: 126–31.
28 Amini-Adle M, Thieulent N, Dalle S *et al.* Scleromyxedema: successful treatment with thalidomide in two patients. *Dermatology* 2007; **214**: 58–60.
29 Martins A, Paiva Lopes MJ, Tavares Belo R, Rodrigues JC. Scleromyxedema—thalidomide therapy. *J Eur Acad Dermatol Venereol* 2008; **22**: 622–4.
30 Tschen JA, Chang JR. Scleromyxedema: treatment with interferon alfa. *J Am Acad Dermatol* 1999; **40**: 303–7.

31 Keong CH, Asaka Y, Fukuro S *et al.* Successful treatment of scleromyxoedema with plasmapheresis and immunosuppression. *J Am Acad Dermatol* 1990; **22**: 842–4.
32 Nieves DS, Bondi EE, Wallmark J *et al.* Scleromyxedema: successful treatment of cutaneous and neurologic symptoms. *Cutis* 2000; **65**: 89–92.
33 Berkson M, Lazarus GS, Uberti-Benz M, Rook AH. Extracorporeal photo-chemotherapy: a potentially useful treatment for scleromyxoedema. *J Am Acad Dermatol* 1991; **25**: 724.
34 D'Incan M, Franck F, Kanold J *et al.* Cutaneo-systemic papulosclerotic mucinosis (scleromyxedema): remission after extracorporeal photochemotherapy and corticoid bolus. *Ann Dermatol Vénéréol* 2001; **128**: 38–41.
35 Gholam P, Hartmann M, Enk A. Arndt-Gottron scleromyxoedema: successful therapy with intravenous immunoglobulins. *Br J Dermatol* 2007; **157**: 1058–60.
36 Körber A, Franckson T, Grabbe S, Dissemond J. Successful therapy of scleromyxoedema Arndt-Gottron with low-dose intravenous immunoglobulin. *J Eur Acad Dermatol Venereol* 2007; **21**: 553–4.
37 Blum M, Wigley FM, Hummers LK. Scleromyxedema: a case series highlighting long-term outcomes of treatment with intravenous immunoglobulin (IVIG). *Medicine (Baltimore)* 2008; **87**: 10–20.
38 Koeppel Rampino M, Garibaldi E, Ragona R, Ricardi U. Scleromyxedema: treatment of widespread cutaneous involvement by total skin electron-beam therapy. *Int J Dermatol* 2007; **46**: 864–7.
39 Lacy MQ, Hogan WJ, Gertz MA *et al.* Successful treatment of scleromyxedema with autologous peripheral blood stem cell transplantation. *Arch Dermatol* 2005; **141**: 1277–82.
40 Donato ML, Feasel AM, Weber DM *et al.* Scleromyxedema: role of high-dose melphalan with autologous stem cell transplantation. *Blood* 2006; **107**: 463–6.
41 Iranzo P, López-Lerma I, Bladé J *et al.* Scleromyxoedema treated with autologous stem cell transplantation. *J Eur Acad Dermatol Venereol* 2007; **21**: 129–30.
42 Elliott MP, Dooley P. Scleromyxedema (papular mucinosis): a surgical perspective. *Ann Plast Surg* 1998; **41**: 436–9.

Acral persistent papular mucinosis

Acral persistent papular mucinosis has been proposed as a distinct form of cutaneous mucinosis [1–4]. The characteristic findings include discrete papules or annular lesions on the extensor surfaces of the hands, wrists and forearms, mucinous deposits within the dermis, persisting for several years, and usually an absence of systemic abnormalities. However, a monoclonal IgA of kappa light chain isotype was detected in one case [5]. Familial occurrence has been reported in two sisters [6]. The accumulation of lysosomal structures in acral persistent papular mucinosis may be a distinctive feature of the disorder [7]. However, it is still debatable whether acral persistent papular mucinosis is a distinct entity [8] or whether it is a variant of the discrete papular form of lichen myxoedematosus [1]. A case resembling acral persistent papular mucinosis has been described in which transient carpal tunnel syndrome appeared, suggesting that extracutaneous involvement might occur [9]. 'Aypical' soft minuscule mucinous papules occurred localized to the axillae of a mother and her (identical) twin daughters; again, it is difficult to classify this entity [10].

References

1 Flowers SL, Cooper PH, Landes HB. Acral persistent papular mucinosis. *J Am Acad Dermatol* 1989; **21**: 293–7.
2 Rongioletti F, Rebora A. Acral persistent papular mucinosis: a new entity. *Arch Dermatol* 1986; **122**: 1237–9.
3 Barba A, Maruccia A, D'Onghia FS. Persistent acral papulous mucinosis. *Ann Dermatol Vénéréol* 1996; **123**: 256–8.
4 Harris JE, Purcell SM, Griffin TD. Acral persistent papular mucinosis. *J Am Acad Dermatol* 2004; **51**: 982–8.
5 Borradori L, Aractingi S, Blanc F *et al.* Acral persistent papular mucinosis and IgA monoclonal gammopathy: report of a case. *Dermatology* 1992; **185**: 134–6.
6 Menni S, Cavicchim S, Brezzi A *et al.* Acral persistent papular mucinosis in two sisters. *Clin Exp Dermatol* 1995; **20**: 431–3.
7 Heikki JA, Forsten Y, Hopsu-Havo VK. Ultrastructural signs of altered intracellular metabolism in acral persistent papular mucinosis. *J Cutan Pathol* 1991; **18**: 347–52.
8 Fosko SW, Perez MI, Longley BJ. Acral persistent papular mucinosis. *J Am Acad Dermatol* 1992; **27**: 1026–9.
9 Stephens CJM, Ross JS, Charles-Holmes R *et al.* An unusual case of transient papular mucinosis associated with carpal tunnel syndrome. *Br J Dermatol* 1993; **129**: 89–91.
10 Scheidegger EP, Itin P, Kempf W. Familial occurrence of axillary papular mucinosis. *Eur J Dermatol* 2005; **15**: 70–2.

Papular mucinosis of infancy [1–4]

In this rare condition, opalescent papules may be noted at birth [2] or develop a few months later [1,3]. The papules are scattered on the dorsa of the hands or around the elbows, and may have a linear distribution [2]. Focal mucinous material is deposited in the papillary dermis without overt fibroblast proliferation. It is not clear what the long-term outlook of cutaneous mucinosis of infancy is, but some cases appear to progress [3]. Thus, certain cases of cutaneous mucinosis of infancy are in fact the infantile presentation of lichen myxoedematosus [5].

References

1 Lum D. Cutaneous mucinosis of infancy. *Arch Dermatol* 1980; **116**: 198–200.
2 McGrae JD. Cutaneous mucinosis of infancy: a congenital and linear variant. *Arch Dermatol* 1983; **119**: 272–3.
3 Carapeto FJ, Charlez L, Marron J *et al.* Infantile and progressive papular mucinosis. *Pediatr Dermatol* 1987; **4**: 62.
4 Velho GC, Oliveira M, Alves R *et al.* Childhood cutaneous mucinosis. *J Eur Acad Dermatol Venereol* 1998; **10**: 164–6.
5 Podda M, Rongioletti F, Greiner D *et al.* Cutaneous mucinosis of infancy: is it a real entity or the paediatric form of lichen myxoedematosus (papular mucinosis)? *Br J Dermatol* 2001; **144**: 590–3.

Self-healing papular mucinosis; juvenile and adult

Self-healing juvenile cutaneous mucinosis [1–5] is a rare disorder characterized by an early age of onset accompanied by inflammatory phenomena and spontaneous resolution over a few months. The condition has also been reported in a child undergoing chemotherapy for nephroblastoma [6], and in two brothers [7]. Clinically, there are papules, nodules or plaques with a predilection for the head and trunk rather than the extremities. Histologically, there is dermal mucinosis and a mild increase in fibroblasts and mast cells. It is postulated that a temporary alteration of fibroblast synthetic function occurs, possibly as a result of a viral infection. Rare cases of self-healing cutaneous mucinosis have been reported in adults [8–10].

References

1 Pucevich MV, Latour DL, Bale GF *et al.* Self-healing juvenile cutaneous mucinosis. *J Am Acad Dermatol* 1984; **11**: 327–32.
2 Kim YJ, Kim YT, Kim JH. Self-healing juvenile cutaneous mucinosis. *J Am Acad Dermatol* 1994; **31**: 815–6.
3 Aydingoz IE, Candan I, Dervent B. Self-healing juvenile cutaneous mucinosis. *Dermatology* 1999; **199**: 57–9.
4 Cowen EW, Scott GA, Mercurio MG. Self-healing juvenile cutaneous mucinosis. *J Am Acad Dermatol* 2004; **50** (5 Suppl.): S97–100.
5 Nagaraj LV, Fangman W, White WL *et al.* Self-healing juvenile cutaneous mucinosis: cases highlighting subcutaneous/fascial involvement. *J Am Acad Dermatol* 2006; **55**: 1036–43.

6 Wadee S, Roode H, Schulz EJ. Self-healing juvenile cutaneous mucinosis in a patient with nephroblastoma. *Clin Exp Dermatol* 1994; **19**: 90–3.
7 Gonzalez-Ensenat MA, Vicente MA, Castella N *et al.* Self-healing infantile familial cutaneous mucinosis. *Pediatr Dermatol* 1997; **14**: 460–2.
8 Jang KA, Han MH, Choi JH *et al.* Recurrent self-healing cutaneous mucinosis in an adult. *Br J Dermatol* 2000; **143**: 650–1.
9 Sperber BR, Allee J, James WD. Self-healing papular mucinosis in an adult. *J Am Acad Dermatol* 2004; **50**: 121–3.
10 Yokoyama E, Muto M. Adult variant of self-healing papular mucinosis in a patient with rheumatoid arthritis: predominant proliferation of dermal dendritic cells expressing CD34 or factor XIIIa in association with dermal deposition of mucin. *J Dermatol* 2006; **33**: 30–5.

Hereditary progressive mucinous histiocytosis [1]

Hereditary progressive mucinous histiocytosis (MIM 142630) is a rare, probably autosomal dominant, disease in which small skin-coloured papules or nodules begin to appear anywhere in the first decade of life. In contrast to other benign histiocytic skin diseases there is no spontaneous resolution, so that a steadily increasing number of papules is noted. To date the disease has been confined to females. Histologically, the disease is associated with a progressive proliferation of histiocytes (non-X type) and dermal mucinosis but there is no evidence of any known lysosomal storage disease.

Reference

1 Bark K. Hereditary progressive mucinous histiocytosis: immunohistochemical and ultrastructural studies in an additional family. *Arch Dermatol* 1994; **130**: 1300–4.

Cutaneous focal mucinosis [1–3]

Cutaneous focal mucinosis has been accepted as a distinct entity, although recently it has been classified as a superficial angiomyxoma [4,5]. Clinically, it is characterized by a solitary, asymptomatic, flesh-coloured papule or nodule that can occur on the face, trunk or extremities. Histologically, there is localized accumulation of mucin in the dermis with an increased number of fibroblasts. The fibroblasts appear to function as mucoblasts with many large condensing vacuoles or secretory granules in their cytoplasm [2]. It is suggested that cutaneous focal mucinosis arises as a result of a dysfunction of the fibroblasts in a localized area only. If treatment is required, local excision is satisfactory, since recurrence is unusual. The condition may show some overlap with other mucinoses, for example REM syndrome and scleromyxoedema [6].

Focal cutaneous mucinosis forms part of the Birt–Hogg–Dubé syndrome, where it is associated with multiple fibrofolliculomas and a predisposition to renal cancer [7].

Oral focal mucinosis of the tongue, causing a clinically elevated mass, is an uncommon clinicopathological entity which is considered to be the oral counterpart of cutaneous focal mucinosis [8].

References

1 Johnson WC, Helwig EB. Cutaneous focal mucinosis: a clinico-pathological and histochemical study. *Arch Dermatol* 1966; **93**: 13–20.
2 Nishiura S, Mihara M, Shimao S *et al.* Cutaneous focal mucinosis. *Br J Dermatol* 1989; **121**: 511–5.
3 Nebrida ML, Tay YK. Cutaneous focal mucinosis: a case report. *Pediatr Dermatol* 2002; **19**: 33–5.
4 Allen PW, Dymock RB, MacCormac LB. Superficial angiomyxomas with and without epithelial components. *Am J Surg Pathol* 1988; **12**: 519–30.
5 Nakayama H, Hirol M, Kiyoku H *et al.* Superficial angiomyxoma of the right inguinal region: report of a case. *Jpn J Clin Oncol* 1997; **27**: 200–3.
6 Rongioletti F, Amantea A, Balus L *et al.* Cutaneous focal mucinosis associated with reticular erythematous mucinosis and scleromyxoedema. *J Am Acad Dermatol* 1991; **24**: 656–7.
7 Lindor NM, Hand J, Burch PA, Gibson LE. Birt–Hogg–Dubé syndrome: an autosomal dominant disorder with predisposition to cancers of the kidney, fibrofolliculomas, and focal cutaneous mucinosis. *Int J Dermatol* 2001; **40**: 653–6.
8 Soda G, Baiocchini A, Bosco D *et al.* Oral focal mucinosis of the tongue. *Pathol Oncol Res* 1998; **4**: 304–7.

Mucinous naevus

The association of dermal mucinosis in association with a congenital plaque-like lesion in the interscapular area was first reported in a 16-year-old female [1]. In the absence of an overt connective tissue naevus and associated systemic disease, it was felt the lesion represented a congenital cutaneous mucinosis (mucinous naevus). Analysis of further cases suggests that these lesions may be a connective tissue naevus of proteoglycan type, and the only type to contain hyaluronic acid [2].

References

1 Redondo Bellòn PR, Vázquez-Doval J, Idoate M, Quintanilla E. Mucinous nevus. *J Am Acad Dermatol* 1993; **28**: 797–8.
2 Rongioletti F, Rebora A. Mucinous nevus. *Arch Dermatol* 1996; **132**: 1522–3.

Reticular erythematous mucinosis [1]

Synonyms
- REM syndrome
- Plaque-like cutaneous mucinosis [2]

This syndrome comprises areas of reticular erythema on the trunk with a mucinous and round cell infiltrate in the dermis, and is frequently called the REM syndrome. Plaque-like cutaneous mucinosis is essentially the same disease process [3].

Aetiology. The aetiology is unknown, but there is some clinical and also experimental evidence that light is a factor in the pathogenesis of this disorder [4,5]. REM syndrome can be associated with the production of a monoclonal paraprotein, suggesting that the disease may involve disturbance of immune mechanisms [6]. Immunophenotypic studies have suggested a potential overlap between REM syndrome and Jessner's lymphocytic infiltration [7]. An hormonal influence may be operative [8]. Interleukin (IL)-1β may be involved in the abnormal hyaluronic acid metabolism in REM syndrome, as patient fibroblasts exhibit an abnormal response to stimulation by exogenous IL-1β [9]. Rare familial cases have been reported [10].

Pathology. The epidermis appears normal. In the papillary and upper reticular dermis there is a perivascular, and occasionally perifollicular, infiltrate largely composed of small mononuclear cells and populations of FXIIIa+/hyaluronan synthase 2+ dermal dendrocytes, which have been postulated to be responsible for accumulation of hyaluronan, rather than this being derived from fibroblasts [11]. There is separation of collagen bundles and fragmentation of elastic fibres. Histochemical stains show an increase in dermal mucin with a profile consistent with hyaluronic acid [4].



Fig. 59.16 Reticular erythematous mucinosis syndrome. View of anterior chest to show erythematous rash in photodistributed location.

Direct immunofluorescence is usually negative for immunoglobulins, fibrin and complement [4], although granular basement-membrane deposits of IgM, IgA and C3 have been described in isolated cases [5,12].

Clinical features. Most affected patients are female [1,3,4,13] and usually middle aged, but the condition has been reported in children [14]. Areas of pink, reticulate or sheet-like erythema are present on the central part of the chest and back, particularly over the sternum and on the upper back (Fig. 59.16). There is usually no pruritus, although sometimes the areas become itchy following sun exposure, and the erythema may be then more apparent. The areas become infiltrated and then slowly increase in size. Coexisting disorders reported in association with occasional cases of REM syndrome include hyperthyroidism, hypothyroidism, discoid lupus erythematosus, carcinoma and thrombocytopenic purpura [15]. Evolution of REM syndrome to systemic lupus erythematosus has been reported [16]. Mycosis fungoides presenting as reticular erythematous mucinosis has been documented [17].

Treatment. Topical steroids are ineffective, but fortunately antimalarials are almost invariably effective in controlling the eruption [1,4,13]. Ciclosporin appears to be of no value in treating REM syndrome [18]. UVB radiation combined with steroid impregnated tape [19], and use of the pulsed dye laser [20], have been beneficial.

References

1 Steigleder GK, Gartmann H, Linker V. REM syndrome: reticular erythematous mucinosis (round-cell erythematosis): a new entity? *Br J Dermatol* 1974; **91**: 191–9.

2 Perry HO, Kierland RR, Montgomery H. Plaque-like form of cutaneous mucinosis. *Arch Dermatol* 1960; **82**: 980–5.

3 Quimby SR, Perry HO. Plaque-like cutaneous mucinosis: its relationship to reticular erythematous mucinosis. *J Am Acad Dermatol* 1982; **6**: 856–61.

4 Bleehen SS, Slater DN, Mahood J *et al.* Reticular erythematous mucinosis: light and electron microscopy, immunofluorescence and histochemical findings. *Br J Dermatol* 1982; **106**: 9–18.

5 Dodd HJ, Sarkany I, Sadrudin A. Reticular erythematous mucinosis syndrome. *Clin Exp Dermatol* 1987; **12**: 36–9.

6 Zaki I, Shall L, Millard LG. Reticular erythematous mucinosis syndrome and a monoclonal IgG kappa paraprotein—is there an association? *Br J Dermatol* 1993; **129**: 347–56.

7 Braddock SW, Kay HD, Maemle D *et al.* Clinical and immunologic studies in reticular erythematous mucinosis and Jessner's lymphocytic infiltrate of skin. *J Am Acad Dermatol* 1993; **28**: 691–5.

8 Sidwell RU, Francis N, Bunker CB. Hormonal influence on reticular erythematous mucinosis. *Br J Dermatol* 2001; **144**: 633–4.

9 Izumi T, Tajima S, Harada R, Nishikawa T. Reticular erythematous mucinosis syndrome: glycosaminoglycan synthesis by fibroblasts and abnormal response to interleukin-1 beta. *Dermatology* 1996; **192**: 41–5.

10 Caputo R, Marzano AV, Tourlaki A, Marchini M. Reticular erythematous mucinosis occurring in a brother and sister. *Dermatology* 2006; **212**: 385–7.

11 Tominaga A, Tajima S, Ishibashi A, Kimata K. Reticular erythematous mucinosis syndrome with an infiltration of factor XIIIa and hyaluronan synthase 2 dermal dendrocytes. *Br J Dermatol* 2001; **145**: 141–5.

12 Del Pozo J, Martinez W, Almagro M *et al.* Reticular erythematous mucinosis syndrome. Report of a case with positive immunofluorescence. *Clin Exp Dermatol* 1997; **22**: 234–6.

13 Steigleder GK, Kanzow G. Muzinablagerungen in der Dermis und REM syndrom. *Hautarzt* 1980; **31**: 575–83.

14 Cohen PR, Rabinowitz AD, Ruszkowski AM *et al.* Reticular erythematous mucinosis syndrome: a review of the world literature and report of the syndrome in a pre-pubertal child. *Pediatr Dermatol* 1990; **7**: 1–10.

15 Braddock SW, Davis CS, Davis RB. Reticular erythematosus mucinosis and thrombocytopenic purpura. Report of a case and review of the world literature, including plaque-like cutaneous mucinosis. *J Am Acad Dermatol* 1988; **19**: 859–68.

16 Del Pozo J, Pena C, Almagro M *et al.* Systemic lupus erythematosus presenting with a reticular erythematous mucinosis-like condition. *Lupus* 2000; **9**: 144–6.

17 Twersky JM, Mutasim DF. Mycosis fungoides presenting as reticular erythematous mucinosis. *Int J Dermatol* 2006; **45**: 230–3.

18 Bulengo-Ramsby SM, Ellis CN, Griffiths CEM *et al.* Failure of reticular erythematous mucinosis to respond to cyclosporine. *J Am Acad Dermatol* 1992; **27**: 825–8.

19 Yamazaki S, Katayama I, Kurumaji Y *et al.* Treatment of reticular erythematous mucinosis with a large dose of ultraviolet B radiation and steroid impregnated tape. *J Dermatol* 1999; **26**: 115–8.

20 Greve B, Raulin C. Treating REM syndrome with the pulsed dye laser. *Lasers Surg Med* 2001; **29**: 248–51.

Follicular mucinosis

Synonym
- Alopecia mucinosa

Definition and nomenclature. Follicular mucinosis is an inflammatory disorder characterized clinically by infiltrated plaques with scaling and loss of hair, and histologically by the accumulation of acid glycosaminoglycans in the sebaceous gland and the outer root sheath of the hair follicles. The condition was first described by Pinkus in 1957 [1] under the name alopecia mucinosa, but alopecia is not always evident, especially when only vellus follicles are involved.

Aetiology [2–6]. The cause of follicular mucinosis is unknown, but cell-mediated immune mechanisms may play a role in its pathogenesis [7]. Follicular mucinosis may be subclassified into three groups. The first and largest group consists of patients with solitary or only a few lesions, clearing spontaneously in 2 months to 2 years. In a second group are patients in whom the lesions persist, or new lesions continue to develop over many years. In the third group (about 15% of cases [2]) the mucinosis is associated with a lymphoma [4–6]; in such cases, histological evidence of the

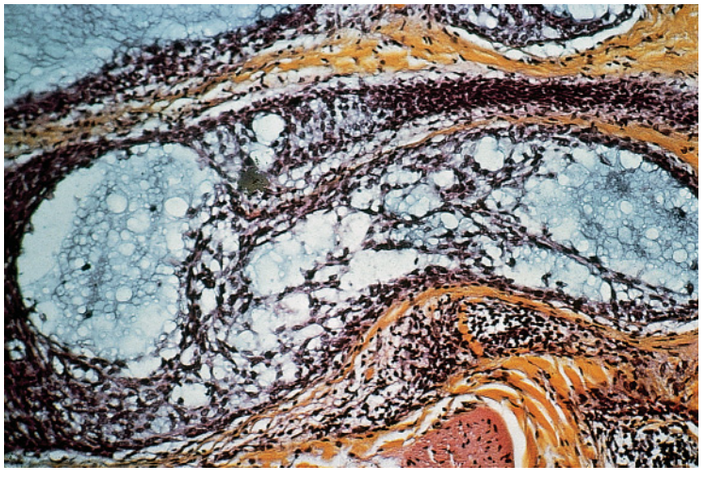


Fig. 59.17 Follicular mucinosis. Marked spongiosis and mucinous degeneration of outer root sheath of a follicle. Alcian blue, H&E, × 50. (Courtesy of St John's Institute of Dermatology, London, UK.)



Fig. 59.18 Follicular mucinosis. 'Boggy' erythematous plaque on forehead. (Courtesy of St John's Institute of Dermatology, London, UK.)

lymphoma is present from the onset, but it may be overlooked until the sections are later re-examined with hindsight.

Patients with lymphoma-associated follicular mucinosis tend to be older (age 20–70 years; average 45 years) than those with benign disease (age 2–75 years; peak between 20 and 40 years), but there is no absolute distinction in age incidence [2,8,9].

Some authorities regard follicular mucinosis as a non-specific follicular reaction [3], as similar changes have been observed in association with lupus erythematosus, angiolymphoid hyperplasia [10], Hodgkin's disease [11], cutaneous B-cell lymphoma [12], secondary extramedullary cutaneous plasmacytoma [13] and alopecia areata [14].

Pathology [2,3]. The earliest change appears to be oedema of the outer root sheath and sebaceous gland, with formation of cystic spaces in which mucin accumulates. The entire depth of the follicle may be involved, but the degree of damage to the hair matrix is variable. Later, the sebaceous glands may appear to be absent, or the whole follicle may be converted into a cystic cavity containing mucin and degenerate root-sheath cells (Fig. 59.17). Dermal inflammatory changes are variable, and may become granulomatous. Electron-microscopic studies [15] have shown changes in the keratinocytes of the follicular epithelium. Autoradiographic studies [16] have failed to show increased synthesis of glycosaminoglycans in affected follicles.

Histopathological findings may not allow clear-cut differentiation between idiopathic and lymphoma-associated follicular mucinosis [4]. In general, the presence of large numbers of eosinophils in the inflammatory infiltrate and marked mucinous changes in the follicular epithelium favour a benign form, whereas lymphocytic epidermotropism and a dense perifollicular infiltrate with atypical cells suggests an associated lymphoma. Similarly, monoclonal rearrangement of the T-cell receptor (TCR) gamma gene on polymerase chain reaction analysis does not reliably differentiate the benign and lymphoma-associated forms. In one study, TCR gene rearrangements were found in about 50% of tested cases from both idiopathic primary and lymphoma-associated groups of patients [5], whilst a study of patients with primary follicular mucinosis found no evidence of progression to cutaneous T-cell lymphoma despite the presence of a clonal TCR gene rearrangement [17]. When a lymphoma is demonstrated, this is usually of T-cell type [18–21], although B-cell lymphoma has been reported [12]. A follicular variant of mycosis fungoides is being increasingly recognized, although overt mucinous spongiosis is not necessarily present [21]. Syringolymphoid hyperplasia with alopecia and anhidrosis is a syringotropic variant of follicular mucinosis and should be viewed as a facultative precursor lesion of mycosis fungoides [22].

Clinical features [2,23]. In the acute benign form, the earliest changes are grouped, skin-coloured papules or erythematous plaques, with some scale, and with prominent follicles. Each plaque, commonly 2–5 cm in diameter but sometimes larger, changes little in appearance. Multiple lesions may be present from the onset or may develop within a period of a few weeks. The face, scalp, neck and shoulders are commonly affected. The hairs are shed from the affected follicles, so that alopecia may therefore be the presenting symptom when the scalp or eyebrow region is involved. Spontaneous recovery usually takes place within a few months, but may be delayed for a year or more.

In the chronic form, the lesions are often more numerous and more widely distributed and their morphology tends to be more variable. There may be elevated, flat or domed plaques or nodules, some of which may ulcerate. The plaques and nodules are often of soft, gelatinous consistency; sometimes mucin can be squeezed out of affected follicles (Fig. 59.18). Non-infiltrated, red, scaly plaques, patchy scaling, alopecia (Fig. 59.19) and indurated plaques may all be present. In some cases, leprosy may be simulated [24]. Presentation with an unusual acneiform eruption has been recorded [25].

Rarely, follicular papules may be generalized without obvious grouping. Irritation may be troublesome and persistent. Destruction of follicles may give rise to patches of permanent alopecia, which may be studded with horny plugs. This chronic form may



Fig. 59.19 Follicular mucinosis. Circumscribed patch of hair loss associated with erythematous plaque on forearm. (Courtesy of St John's Institute of Dermatology, UK.)

persist for many years without any evidence of associated disease. An unusual case associated with erythroderma and boggy plaques on the scalp and face, associated with alopecia and purulent paronychia and nail loss, has been described [26].

Unfortunately, no single clinical feature distinguishes lymphoma-associated cases from the chronic benign form. Extensive cystic changes have been recorded in the lymphoma-associated type [27]. Contrary to earlier opinion [2,7] lymphoma-associated follicular mucinosis has been reported where the lesions occurred on the head and neck [19,28]. The temporal relationship between lymphoma and follicular mucinosis is very variable. Gross manifestations of the lymphoma may have been present for some time before the mucinosis develops; in other cases, the first indication of the lymphoma is uncovered by histology.

Diagnosis. The loss of hair in plaques with prominent follicles but minimal inflammatory changes should suggest the diagnosis. Sometimes, mucin can be expressed from the follicle. Eczema, seborrhoeic dermatitis, lichen simplex, pityriasis rosea, traumatic alopecia and tinea capitis can all be closely simulated. Biopsy and serial sectioning of the tissue should confirm the diagnosis.

Treatment. There are no clear guidelines for treating follicular mucinosis. Some improve spontaneously, while treatment with topical and intralesional steroids has been claimed to be of benefit. Superficial radiotherapy may be beneficial in some of the lymphoma-associated cases [28], but some cases fail to respond [29]. Response to dapsone [30], isotretinoin [31] or photodynamic therapy [32] has been reported. Low-dose systemic steroids may benefit widespread pruritic follicular mucinosis, and interferon therapy, with or without acitretin, has also proved successful [33,34].

Urticaria-like follicular mucinosis

Urticaria-like follicular mucinosis appears to be a variant of follicular mucinosis, largely confined to middle-aged men, in which urticarial pruritic papules or plaques appear on the head and neck on an erythematous 'seborrhoeic' background [35]. The lesions tend to fade but recur for months to years leaving neither follicular plugging nor alopecia. Sun exposure may temporarily clear the eruption. The histopathological features are identical to follicular mucinosis but the prognosis is good, with a long, benign course.

References

1 Pinkus H. Alopecia mucinosa: inflammatory plaques with alopecia characterized by root-sheath mucinosis. *Arch Dermatol* 1957; **76**: 419–26.
2 Emmerson RW. Follicular mucinosis. A study of 47 patients. *Br J Dermatol* 1969; **81**: 395–413.
3 Hempstead RW, Ackerman AB. Follicular mucinosis: a reaction pattern in follicular epithelium. *Am J Dermatopathol* 1985; **7**: 245–57.
4 Cerroni L, Fink-Puches R, Back B, Kerl H. Follicular mucinosis. A critical reappraisal of clinicopathologic features and association with mycosis fungoides and Sézary syndrome. *Arch Dermatol* 2002; **138**: 182–9.
5 van Doorn R, Scheffer E, Willemze R. Follicular mycosis fungoides, a distinct disease entity with or without associated follicular mucinosis: a clinicopathologic and follow-up study of 51 patients. *Arch Dermatol* 2002; **138**: 191–8.
6 Cerroni L, Kerl H. Primary follicular mucinosis and association with mycosis fungoides and other cutaneous T-cell lymphomas. *J Am Acad Dermatol* 2004; **51**: 146–7.
7 Lancer HA, Bronstein BR, Nakagawa H *et al.* Follicular mucinosis: a detailed morphologic and immunopathologic study. *J Am Acad Dermatol* 1984; **10**: 760–8.
8 Plotnick H, Abrecht M. Alopecia mucinosa and lymphoma. *Arch Dermatol* 1965; **92**: 137–41.
9 Hess Schmid M, Dummer R, Kempf W *et al.* Mycosis fungoides with mucinosis follicularis in childhood. *Dermatology* 1999; **198**: 284–7.
10 Wolff HH, Kinney J, Ackermann AB. Angiolymphoid hyperplasia with follicular mucinosis. *Arch Dermatol* 1978; **114**: 229–32.
11 Stewart M, Smoller BR. Follicular mucinosis in Hodgkin's disease: a poor prognostic sign? *J Am Acad Dermatol* 1991; **24**: 784–5.
12 Benchikhi H, Wechsler J, Rethers L *et al.* Cutaneous B-cell lymphoma associated with follicular mucinosis. *J Am Acad Dermatol* 1995; **33**: 673–5.
13 Rodríguez-Lozano J, Del Pozo J, Almagro M *et al.* Localized cutaneous mucinosis as a presentation of secondary extramedullary cutaneous plasmacytoma. *Br J Dermatol* 2004; **150**: 367–9.
14 Fanti PA, Tosti A, Morelli R *et al.* Follicular mucinosis in alopecia areata. *Am J Dermatopathol* 1992; **14**: 542–5.
15 Ishibashi A, Chujo T. Ultrastructure of follicular mucinosis. *J Cutan Pathol* 1974; **1**: 126–31.
16 Langner A, Jablonska S, Darzynkiewicz Z. Studies on the origin of the mucin in mucinosis follicularis. *Acta Derm Venereol (Stockh)* 1960; **49**: 76–81.
17 Brown HA, Gibson LE, Pujol RM *et al.* Primary follicular mucinosis: long-term follow-up of patients younger than 40 years with and without clonal T-cell receptor gene rearrangement. *J Am Acad Dermatol* 2002; **47**: 856–62.
18 Wilkinson JD, Black MM, Chu A. Follicular mucinosis associated with mycosis fungoides presenting with gross cystic changes on the face. *Clin Exp Dermatol* 1982; **7**: 333–40.
19 Gibson LE, Muller SA, Leiferman KM *et al.* Follicular mucinosis: clinical and histopathologic study. *J Am Acad Dermatol* 1989; **20**: 441–6.
20 Mehregan AD, Gibson EL, Muller SA. Follicular mucinosis. A histopathologic review of 33 cases. *Mayo Clin Proc* 1991; **66**: 387–90.

21 Lacour JP, Castanet J, Perrin C *et al.* Follicular mycosis fungoides: a clinical and histologic variant of cutaneous T-cell lymphoma. *J Am Acad Dermatol* 1993; **29**: 330–4.
22 Haller A, Elzubi E, Petzelbauer P. Localized syringolymphoid hyperplasia with alopecia and anhidrosis. *J Am Acad Dermatol* 2001; **45**: 127–30.
23 Kim R, Winkelmann RK. Follicular mucinosis (alopecia mucinosa). *Arch Dermatol* 1962; **85**: 490–8.
24 Fan J, Chang HS, Ma B. Alopecia mucinosa simulating leprosy. *Arch Dermatol* 1967; **95**: 354–6.
25 Passaro EM, Silveira MT, Valente NY. Acneiform follicular mucinosis. *Clin Exp Dermatol* 2004; **29**: 396–8.
26 Fairris GM, Kirkham N, Goodwin PG *et al.* Erythrodermic follicular mucinosis. *Clin Exp Dermatol* 1987; **12**: 50–2.
27 Wilkinson JD, Ryan TJ, Dawber RPR *et al.* Follicular mucinosis (lymphoma) occurring on the head and neck. *J R Soc Med* 1979; **72**: 281–2.
28 Lacour JP, Castanet J, Lagrange JL *et al.* Follicular mycosis fungoides: a response to radiation therapy. *Br J Dermatol* 1994; **130**: 256–63.
29 Oliwiecki S, Ashworth J. Mycosis fungoides with a widespread follicular eruption, comedones and cysts. *Br J Dermatol* 1992; **127**: 54–6.
30 Kubba RK, Stewart TW. Follicular mucinosis responding to dapsone. *Br J Dermatol* 1974; **91**: 217–20.
31 Arca E, Köse O, Ta tan HB, Gür AR, Safali M. Follicular mucinosis responding to isotretinoin treatment. *J Dermatolog Treat* 2004; **15**: 391–5.
32 Fernández-Guarino M, Harto Castaño A, Carrillo R, Jaén P. Primary follicular mucinosis: excellent response to treatment with photodynamic therapy. *J Eur Acad Dermatol Venereol* 2008; **22**: 393–4.
33 Meissner K, Weyer U, Kowalzick L *et al.* Successful treatment of primary progressive follicular mucinosis with interferons. *J Am Acad Dermatol* 1991; **24**: 848–50.
34 Kontochristopoulos GJ, Exadaktylou D, Hatziolou E *et al.* Follicular mucinosis associated with early stage cutaneous T-cell lymphoma: successful treatment with interferon alpha-2b and acitretin. *J Dermatolog Treat* 2001; **12**: 117–21.
35 Govato F, Nazzari G, Nunzi E *et al.* Urticaria-like follicular mucinosis. *Dermatologica* 1985; **170**: 133–5.

Secondary mucinoses [1]

Dermal mucinosis may be associated to a greater or lesser extent with histopathological features otherwise typical of the disease in question [1]. In some, the mucinous deposition may be so striking as to suggest the diagnosis, for example Degos' disease [2]. Cutaneous mucinosis and polymyositis have been reported as presenting features of hypothyroidism [3].

Papulonodular mucinosis associated with systemic lupus erythematosus [1–6]

Papulonodular mucinosis is a distinct but rare cutaneous manifestation occurring in patients with discoid, subacute cutaneous or systemic lupus erythematosus. It presents as indolent, flesh-coloured papulonodules or plaques [7] on the neck, trunk and upper limbs due to diffuse mucinosis in the dermis. It differs from the diffuse mucinosis that may be found in lesional skin of lupus erythematosus in that it occurs in areas free of specific lupus erythematosus lesions. Clinical recognition is important because in one-third of cases it precedes both clinical and serological evidence of systemic lupus erythematosus, sometimes by several years. Cutaneous mucin deposition in papulonodular lupus erythematosus is associated with increased glycosaminoglycan production by dermal fibroblasts, which appears to be due to an unidentified serum factor [8].

References

1 Rongioletti F, Rebora A. Papular and nodular mucinosis associated with systemic lupus erythematosus. *Br J Dermatol* 1986; **115**: 631–6.
2 Lowe L, Rapini RP, Golitz LE *et al.* Papulonodular dermal mucinosis in lupus erythematosus. *J Am Acad Dermatol* 1992; **27**: 312–5.
3 Kano Y, Sagawa Y, Yagita A, Nagashima M. Nodular cutaneous lupus mucinosis: report of a case and review of previously reported cases. *Cutis* 1996; **57**: 441–4.
4 Kanda N, Tsuchida T, Watanabe T, Tamaki K. Cutaneous lupus mucinosis: a review of our cases and the possible pathogenesis. *J Cutan Pathol* 1997; **24**: 553–8.
5 Sonntag M, Lehmann P, Megahed M *et al.* Papulonodular mucinosis associated with subacute cutaneous lupus erythematosus. *Dermatology* 2003; **206**: 326–9.
6 Ortiz VG, Krishnan RS, Chen LL, Hsu S. Papulonodular mucinosis in systemic lupus erythematosus. *Dermatol Online J* 2004; **10**: 16.
7 Kobayashi T, Shimizu H, Shimizu S *et al.* Plaque-like cutaneous lupus mucinosis. *Arch Dermatol* 1993; **129**: 383–4.
8 Pandya AG, Santheimen RD, Cockerell CJ *et al.* Papulonodular mucinosis associated with systemic lupus erythematosus: possible mechanisms of increased glycosaminoglycan accumulation. *J Am Acad Dermatol* 1995; **32**: 199–205.

Collagen vascular diseases

Dermal mucinosis occurs in lupus erythematosus [1] and dermatomyositis, and has been linked in some patients to parvovirus B19 infection [2]. Marked periorbital oedema from massive mucinosis has been reported in a patient with discoid lupus erythematosus [3]. Infiltrated erythematous plaques on the back progressing to erythematous and elastic, soft, tumorous masses over 20 cm in diameter were recorded in a patient with systemic lupus erythematosus [4]. Dermatomyositis may present as plaque-like mucinosis [5,6]. Papular and nodular mucinosis has been recorded as a presenting sign of progressive systemic sclerosis [7], and development of multiple, large, soft skin lesions over the interphalangeal joints of both hands, resembling cutaneous focal mucinosis, has also been reported [8]. Lesions typical of papular mucinosis without evidence of paraproteinaemia occurred in a patient with generalized morphoea [9]. Dermal mucinosis has been associated with severe chronic cutaneous graft-versus-host disease of the sclerodermoid variety [10].

Papular mucinosis in L-tryptophan-induced eosinophilia–myalgia syndrome [11]

The L-tryptophan-induced eosinophilia–myalgia syndrome, due to ingestion of contaminants of L-tryptophan, was first recognized in 1989. The skin lesions include a diffuse morbilliform eruption, urticaria and angio-oedema, dermographism, alopecia and cutaneous induration. Papular mucinosis may coexist for a while, although the lesions slowly regress after cessation of L-tryptophan ingestion. There is associated weakness, fatigue, arthralgia and pneumonitis.

Cutaneous mucinosis in the toxic oil syndrome [12]

Toxic oil syndrome occurred in Spain in 1981 related to the ingestion of adulterated oil. During the late recovery stages, an asymptomatic papular eruption developed on the arms, thighs and legs due to dermal mucin deposition. The papular eruption gradually resolved but sometimes led to sclerodermoid changes.

References

1 Knisley RR, Kobayashi TT. Lupus mucinosis: a case report and review of cutaneous lupus. *Cutis* 2003; **72**: 366–71.
2 Magro CM, Dawood MR, Crowson AN. The cutaneous manifestations of human parvovirus B19 infection. *Hum Pathol* 2000; **31**: 488–97.

3 Williams WL, Ramos-Caro FA. Acute periorbital mucinosis in discoid lupus erythematosus. *J Am Acad Dermatol* 1999; **41**: 871–3.
4 Maruyama M, Miyauchi S, Hashimoto K. Massive cutaneous mucinosis associated with systemic lupus erythematosus. *Br J Dermatol* 1997; **137**: 450–3.
5 Kaufmann R, Greiner D, Schmidt P, Wolter M. Dermatomyositis presenting as plaque-like mucinosis. *Br J Dermatol* 1998; **138**: 889–92.
6 del Pozo J, Almagro M, Martinez W *et al.* Dermatomyositis and mucinosis. *Int J Dermatol* 2001; **40**: 120–4.
7 Van Zander J, Shaw JC. Papular and nodular mucinosis as a presenting sign of progressive systemic sclerosis. *J Am Acad Dermatol* 2002; **46**: 304–6.
8 Marzano AV, Berti E, Gasparini G *et al.* Unique digital skin lesions associated with systemic sclerosis. *Br J Dermatol* 1997; **136**: 598–600.
9 Rongioletti F, Rampini P, Parodi A, Rebora A. Papular mucinosis associated with generalized morphoea. *Br J Dermatol* 1999; **141**: 905–8.
10 Ameen M, Russell-Jones R. Macroscopic and microscopic mucinosis in chronic sclerodermoid graft-versus-host disease. *Br J Dermatol* 2000; **142**: 529–32.
11 Valicenti JMK, Fleming MG, Pearson RW *et al.* Papular mucinosis in L tryptophan-induced eosinophilia–myalgia syndrome. *J Am Acad Dermatol* 1991; **25**: 54–8.
12 Fonseca E, Contreras F. Cutaneous mucinosis in the toxic oil syndrome. *J Am Acad Dermatol* 1987; **16**: 139–40.

Lysosomal storage disorders

A.A.M. Morris, pp. 59.30–59.36

Lysosomes are a major site for the degradation of macromolecules and contain more than 50 acid hydrolases. Lysosomal storage disorders are inherited conditions in which deficiency of one or more hydrolases leads to the accumulation of various molecules in lysosomes. Typically, these are progressive multisystem diseases but the clinical features vary depending on the precise disorder and the severity of the enzyme deficiency. The presence of some residual enzyme activity reduces the severity of problems, delays their onset and may completely prevent the involvement of some organs (such as the brain in some disorders). Dermatological abnormalities are seen in lysosomal disorders affecting the degradation of glycosaminoglycans, glycoproteins and sphingolipids. Two characteristic dermatological findings are angiokeratomas (discussed later) and a combination of thickened skin and hypertrichosis. This combination, together with abnormalities of the facial skeleton, gives rise to a 'coarse' facial appearance. These facial features are seen in most mucopolysaccharidoses and glycoprotein breakdown disorders and in a few sphingolipidoses. Though it is widely used among professionals, the term 'coarse' should be avoided when talking to families, as many find it offensive. Lysosomal disorders are often associated with characteristic histological abnormalities, especially on electron microscopy. If a mucopolysaccharidosis or glycoprotein breakdown disorder is suspected, the next step is analysis of urinary glycosaminoglycans and oligosaccharides. Definitive diagnosis requires demonstration of the enzyme deficiency, usually in leukocytes.

Mucopolysaccharidoses [1,2]

The mucopolysaccharidoses (MPS) result from deficiencies of the enzymes required for the normal degradation of glycosaminoglycans (GAGs, formerly known as mucopolysaccharides). GAGs are long sugar chains composed of alternating sulphated hexuronic acid and hexosamine residues; in connective tissue, they are bound to core proteins to form proteoglycans. Dermatan sulphate, heparan sulphate and keratan sulphate are the main GAGs that accumulate in the MPS disorders; one or more GAGs are found in each disorder. Characteristic clinical features include coarse facial features, hepatosplenomegaly, bone dysplasia (known as dysostosis multiplex) and developmental regression. Some of these features, however, are absent in some disorders. Moreover, there is a considerable range of severity for each disorder; for MPS I, the spectrum is divided into Hurler syndrome (severe), Hurler–Scheie (intermediate) and Scheie syndrome (relatively mild). MPS III (Sanfilippo syndrome) can result from deficiencies of four different enzymes. The biochemical and clinical features of the different disorders are summarized in Table 59.3. The clinical features of MPS IX are not yet clear as only one case has been reported in detail [3].

Genetics. All the mucopolysaccharidoses are inherited as autosomal recessive traits except for MPS II (Hunter syndrome), which is X-linked.

Dysmorphism. MPS patients seldom show abnormalities at birth, except that some have umbilical or inguinal hernias. Patients presenting with an MPS-like phenotype at birth are likely to have mucolipidosis type II or GM_1 gangliosidosis (see below) [4]. The dysmorphism of MPS becomes more apparent with time (Fig. 59.20). Hypoplasia of the mid-facial bones leads to a flat nasal bridge. The skin is thickened, as are the lips, and the tongue is enlarged. The mouth is often slightly open due to adenoidal hypertrophy and the need for mouth breathing. Many patients have generalized hypertrichosis and some have synophrys. Corneal clouding is seen in MPS I, VI and VII. The hands appear podgy with short, broad digits. The facial dysmorphism is relatively subtle in MPS III (Sanfilippo syndrome), which presents with developmental delay. Facial abnormalities are not seen in MPS IV (Morquio disease), which presents with skeletal problems.

Dermatological features. In addition to the hypertrichosis and thickened skin mentioned above, ivory-white papules or nodules are often seen on the back of patients with severe MPS II (Hunter syndrome) [5–7]; similar pebbly skin may also occur in MPS I (Hurler and Hurler–Scheie syndromes) [8]. Individual nodules range from 1 to 10 mm in size and they may coalesce to form ridges or a reticular pattern. Typically, they are found laterally, between the angles of the scapulae and posterior axillary lines (Fig. 59.21). Papules may also be found on the upper arms and outer thighs. Typically, the papules appear at 1–4 years of age and progress for a few years; they may clear spontaneously in older patients. Mongolian blue spots are common in Hurler and Hunter syndromes and, in addition to the sacrococcygeal region, they may be found on the upper back, the anterior trunk or the limbs [9–11]. The spots fade more slowly than in the general population; in Japanese patients they persist until teenage years [11].

Other clinical features. Developmental regression is the dominant feature in MPS III. After presenting with developmental delay, patients have a period of hyperactivity, behaviour problems and sleep disturbance at 3–10 years of age; following this, they gradually deteriorate into a vegetative state. Learning difficulties are also present in Hurler syndrome and severe cases of MPS II and VII. Other neurological problems may include sei-

Table 59.3 Classification of the mucopolysaccharidoses.

Number	MIM no.	Eponym	Clinical features	Enzyme deficiency	GAGs stored and excreted
MPS IH	252800	Hurler	Dysmorphism, corneal clouding, DM, HSM, PR, heart disease, death in childhood	α-L-iduronidase	DS, HS
MPS IS	252800	Scheie	Dysmorphism, corneal clouding, DM, normal IQ and life span	α-L-iduronidase	DS, HS
MPS IH/S	252800	Hurler–Scheie	Phenotype intermediate between I H and I S	α-L-iduronidase	DS, HS
MPS II	309900	Hunter (severe)	Dysmorphism, DM, HSM, heart disease, PR, death before 15 years	Iduronate sulphatase	DS, HS
		Hunter (mild)	Normal IQ, short stature, survive to adulthood	Iduronate sulphatase	DS, HS
MPS IIIA	252900	Sanfilippo A	PR, regression, hyperactivity, mild somatic features	Heparan-N-sulphatase	HS
MPS IIIB	252920	Sanfilippo B	Similar to III A	α-*N*-acetyl-glucosaminidase	HS
MPS IIIC	252930	Sanfilippo C	Similar to III A	Acetyl-CoA glucosamine *N*-acetyl-transferase	HS
MPS IIID	252940	Sanfilippo D	Similar to III A	*N*-acetyl-glucosamine 6-sulphatase	HS
MPS IVA	253000	Morquio A	DM, odontoid hypoplasia, corneal clouding	Galactose-6-sulphatase	KS
MPS IVB	253010	Morquio B	Milder DM, slow neurodegeneration	β-galactosidase	KS
MPS VI	253200	Maroteaux–Lamy	Dysmorphism, DM, corneal clouding, normal IQ	*N*-acetyl-galactosamine 4-sulphatase	DS
MPS VII	253220	Sly	Hydrops fetalis, dysmorphism, DM, HSM, PR	β-glucoronidase	DS, HS
MPS IX	601492	Natowicz	Soft tissue masses in the one reported patient	Hyaluronidase	Hyaluronan

The terms MPS V and MPS VIII are no longer used.
IQ, intelligence quotient; DM, dysostosis multiplex; HSM, hepatosplenomegaly; PR, psychomotor retardation; DS, dermatan sulphate; HS, heparan sulphate; KS, keratan sulphate.



Fig. 59.20 Facial features of an 8-year-old boy with Hunter syndrome (MPS II).

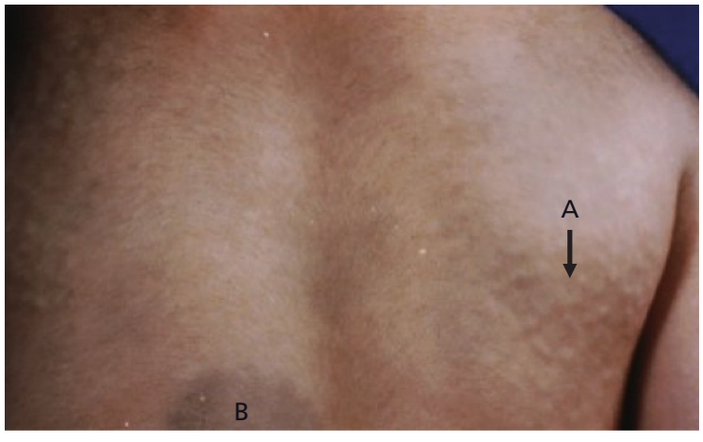


Fig. 59.21 'Pebbling' of the skin (A) and extensive Mongolian blue spot (B) on the back of a boy with Hunter syndrome (MPS II). (Reproduced from J.E. Wraith [2] with permission of author and publisher.)

zures, hydrocephalus, spinal cord compression and carpal tunnel syndrome.

Dysostosis multiplex is a particular problem in patients with MPS IV, who have very short stature and a high risk of atlanto-axial dislocation. Dysplasia of the hip and knee leads to arthritis and sometimes to dislocation. Joint problems, short stature and kyphosis are also seen in the other mucopolysaccharidoses. Ear, nose and throat infections, upper airway obstruction and deafness are common. Valvular heart disease is another frequent problem and is often the cause of death. MPS VII is rare but may present with hydrops fetalis.

Histology. The skin may show distinctive changes even in the absence of clinical skin abnormalities. A few Malpighian cells in the epidermis are distended with pale cytoplasm. Fibroblasts, Schwann cells and some smooth muscle and sweat gland cells show cytoplasmic metachromasia when stained with toluidine blue (due to the presence of GAGs) [12,13]. Fragmentation of collagen and increased tissue mucin may be seen. In Hunter syndrome, examination of the nodules shows pooling of

metachromatic material between the collagen bundles of the lower reticular dermis [14].

Ultrastructurally, in all forms of MPS, dermal fibroblasts and Schwann cells contain membrane-bound cytoplasmic vacuoles; these may appear empty or contain fibrillogranular material [12–14].

Diagnosis. If MPS is suspected, it may be worth undertaking a skeletal survey to look for dysostosis multiplex. 'Spot tests' for urine GAGs are unreliable, especially for MPS III and IV. Quantitation usually shows increased amounts of GAGs in the urine but even this can miss patients at the mild end of the spectrum. Two-dimensional electrophoresis allows the clearest discrimination between different GAGs. The diagnosis can be confirmed by enzyme assay in leukocytes, plasma or fibroblasts. The main differential diagnoses are other lysosomal disorders, such as the glycoprotein breakdown disorders, mucolipidoses and the severe forms of galactosialidosis and GM_1 gangliosidosis (see below).

Treatment. Symptomatic treatment is important and requires a multidisciplinary approach. Ear, nose and throat, orthopaedic and neurosurgery may all be needed. Medication can be useful for sleep and behaviour problems, especially in MPS III. Haematopoietic stem cell transplantation (HSCT) is an established treatment for Hurler and Maroteaux–Lamy syndromes, using bone marrow or umbilical cord blood [15]. Transplantation in infancy leads to improvement in most systems and can preserve normal developmental progress in Hurler syndrome but the skeletal problems progress [16] and ophthalmological problems persist. Moreover, HSCT is associated with a high morbidity and mortality. Enzyme replacement therapy is now available for MPS I, II and VI [17–19]. Its major limitation is the inability of the enzyme to cross the blood–brain barrier. Bone and heart valve disease are also resistant to enzyme replacement therapy, though outcomes can be improved by starting treatment early.

References

1 Neufeld EF, Muenzer J. The mucopolysaccharidoses. In: Scriver CR, Beaudet AL, Sly WS *et al.*, eds. *The Metabolic and Molecular Bases of Inherited Disease*, 8th edn. New York: McGraw-Hill, 2001: 3421–52.

2 Wraith JE. Mucopolysaccharidoses and oligosaccharidoses. In: Fernandes J, Saudubray J-M, van den Berghe G, Walter JH, eds. *Inborn Metabolic Diseases*, 4th edn. Heidelberg: Springer, 2006: 495–507.

3 Natowicz MR, Short MP, Wang Y *et al.* Clinical and biochemical manifestations of hyaluronidase deficiency. *N Engl J Med* 1996; **335**: 1029–33.

4 Wraith JE. Lysosomal disorders. *Semin Neonatol* 2002; **7**: 75–83.

5 Hunter C. A rare disease in two brothers. *Proc R Soc Med* 1917; **10**: 104–16.

6 Prystowsky SD, Maumenee IH, Freeman RG *et al.* A cutaneous marker in the Hunter syndrome: a report of four cases. *Arch Dermatol* 1977; **113**: 602–5.

7 Demitsu T, Kakurai M, Okubo Y *et al.* Skin eruption as the presenting sign of Hunter syndrome IIB. *Clin Exp Dermatol* 1999; **24**: 179–82.

8 Schiro JA, Mallory SB, Demmer L *et al.* Grouped papules in Hurler–Scheie syndrome. *J Am Acad Dermatol* 1996; **5**: 68–70.

9 Grant BP, Beard JS, de Castro F *et al.* Extensive mongolian spots in an infant with Hurler syndrome. *Arch Dermatol* 1998; **134**: 108–9.

10 Sapadin AN, Friedman IS. Extensive Mongolian spots associated with Hunter syndrome. *J Am Acad Dermatol* 1998; **39**: 1013–5.

11 Ochiai T, Suzuki Y, Kato T *et al.* Natural history of extensive Mongolian spots in mucopolysaccharidosis type II (Hunter syndrome): a survey among 52 Japanese patients. *J Eur Acad Dermatol Venereol* 2007; **21**: 1082–5.

12 Belcher RW. Ultrastructure of the skin in the genetic mucopolysaccharidoses. *Arch Pathol* 1972; **94**: 511–8.

13 Alroy J, Jones MZ, Rutledge JC *et al.* The ultrastructure of skin from a patient with mucopolysaccharidosis IIID. *Acta Neuropathol (Berl)* 1997; **93**: 210–3.

14 Freeman RG. A pathological basis for the cutaneous papules of mucopolysaccharidosis II (the Hunter syndrome). *J Cutan Pathol* 1977; **4**: 318–28.

15 Staba SL, Escolar ML, Poe M *et al.* Cord-blood transplants from unrelated donors in patients with Hurler's syndrome. *N Engl J Med* 2004; **350**: 1960–9.

16 Weisstein JS, Delgado E, Steinbach LS *et al.* Musculoskeletal manifestations of Hurler syndrome: long-term follow-up after bone marrow transplantation. *J Pediatr Orthop* 2004; **24**: 97–101.

17 Kakkis ED, Muenzer J, Tiller GE *et al.* Enzyme-replacement therapy in mucopolysaccharidosis I. *N Engl J Med* 2001; **344**: 182–8.

18 Muenzer J, Wraith JE, Beck M *et al.* A phase II/III clinical study of enzyme replacement therapy with idursulfase in mucopolysaccharidosis II (Hunter syndrome). *Genet Med* 2006; **8**: 465–73.

19 Harmatz P, Giugliani R, Schwartz I *et al.* Enzyme replacement therapy for mucopolysaccharidosis VI. *J Pediatr* 2006; **148**: 533–9.

Mucolipidoses [1]

The term 'mucolipidosis' (ML) was originally used to describe lysosomal disorders with clinical features of MPS and the sphingolipidoses. ML I is now called sialidosis; it is considered with the other disorders of glycoprotein degradation. ML IV presents in infancy with psychomotor retardation and corneal clouding; though there are no dermatological problems, electron microscopy reveals a variety of inclusions in skin, as in other tissues [2].

ML II and III refer to different severities of an autosomal recessive disorder (MIM 252600), in which multiple lysosomal enzymes fail to enter their organelle. The underlying problem is a deficiency of UDP-*N*-acetylglucosamine-1-phosphotransferase, which is needed for lysosomal enzymes to acquire a mannose-6-phosphate residue. The transport of lysosomal enzymes into the lysosome depends on the binding of this residue to a mannose-6-phosphate receptor. ML II (I cell disease) refers to the severe end of the spectrum; patients often present at birth with coarse facial features. They also have gum hypertrophy, severe neurological involvement, dysostosis multiplex and cardiomyopathy, which is frequently the cause of death. In patients with ML III, the main problem is arthritis caused by the skeletal dysplasia. Other features may include mild learning difficulties and dysmorphism. MPS excretion is normal in ML II and III but there are abnormal urinary oligosaccharides. The diagnosis is established by demonstrating raised levels of the mistargetted lysosomal enzymes in plasma. Cultured fibroblasts from patients with ML II and III contain dense cytoplasmic inclusions, which gave rise to the name, I cell disease [3]. Histology reveals vacuoles in fibroblasts and other mesenchymal cells in skin and elsewhere; ultrastructurally, the vacuoles are membrane-bound and contain electron-lucent or fibrillogranular material [4].

References

1 Kornfeld S, Sly WS. I-cell disease and pseudo-Hurler polydystrophy: disorders of lysosomal enzyme phosphorylation. In: Scriver CR, Beaudet AL, Sly WS *et al.*, eds. *The Metabolic and Molecular Bases of Inherited Disease*, 8th edn. New York: McGraw-Hill, 2001: 3469–82.

2 Bargal R, Goebel HH, Latta E, Bach G. Mucolipidosis IV: novel mutation and diverse ultrastructural spectrum in the skin. *Neuropediatrics* 2002; **33**: 199–202.

3 Leroy JG, De Mars RI. Mutant enzymatic and cytological phenotypes in cultured human fibroblasts. *Science* 1967; **157**: 804–7.

4 Tondeur M, Vamos-Hurwitz E, Mockel-Pohl S *et al.* Clinical, biochemical and ultrastructural studies in a case of chondrodystrophy presenting the I-cell phenotype in tissue culture. *J Pediatr* 1971; **79**: 366–78.

Table 59.4 Glycoprotein storage disorders, sphingolipidoses and mucolipidoses with cutaneous features

Name	Enzyme deficiency	Cutaneous features*	Other clinical features*	Abnormal urine oligosaccharides	Sample for enzymology
Fucosidosis	α-L-fucosidase	MLF (mild), AK	PR	(+)	leukocytes
α-Mannosidosis	α-Mannosidase	MLF	PR, deafness, DM, HSM, frequent infections	+	leukocytes
β-Mannosidosis	β-Mannosidase	AK	PR, deafness, frequent infections	(+)	leukocytes
Sialidosis type I	neuraminidase		(Late onset) myoclonus, CRS	(+)	cultured cells
Sialidosis type II	neuraminidase	MLF	(Early onset) PR, DM, HSM	(+)	cultured cells
Aspartylglucosaminuria	aspartylglucosaminidase	MLF, AK	PR, regression, seizures	(+)	leukocytes
GM1 gangliosidosis	β-galactosidase	MLF, AK, T	Early onset form: hydrops, HSM, DM, PR, regression, spasticity, CRS	+	leukocytes
			Late onset: Dysarthria, dystonia, DM, PR	+	leukocytes
Galactosialidosis	PPCA	MLF, T	Early onset form: hydrops, HSM, Heart disease, DM, PR, CRS	+	leukocytes
		AK, MLF (mild)	Later onset: myoclonus, ataxia, PR, CRS	+	leukocytes
Fabry	α-galactosidase A	AK, hypohydrosis	Acroparaesthesia, renal failure, heart disease, strokes		leukocytes
Schindler	α-*N*-acetylgalactosaminidase		(Early onset) PR, regression, spasticity		
Kanzaki	α-*N*-acetylgalactosaminidase	AK, MLF (mild)	(Late onset) PR		
Niemann–Pick A	sphingomyelinase	Papules, pigmentation	HSM, lymphadenopathy, PR, regression, spasticity, CRS		leukocytes
Niemann–Pick B	sphingomyelinase	Papules, pigmentation	HSM, lung disease		leukocytes
Gaucher type I	β-glucosidase	Pigmentation, T	Bone pain, DM, HSM		leukocytes
Gaucher type II	β-glucosidase	Collodion baby	HSM, squint, stridor, dysphagia, spasticity		leukocytes
Gaucher type III	β-glucosidase		HSM, abnormal eye movements, regression		leukocytes
Farber	ceramidase	Nodules	Hoarse voice, arthritis, PR, regression, CRS		leukocytes
Mucolipidosis type II	multiple	MLF	Gum hypertrophy, DM, PR, cardiomyopathy	+	plasma
Mucolipidosis type III	multiple	MLF (mild)	Arthritis, DM, PR	+	plasma
Multiple sulphatase def.	multiple	MLF ± ichthiosis	PR, regression, HSM, DM (references A & B)	+	leukocytes
ISSD	sialic acid transporter	MLF, hypopigmentation	PR, HSM, DM, hydrops/ascites (references C & D see Table footnote)	+	cultured cells

* Features that are characteristic or have been reported in a number of patients.

MLF = Mucopolysaccharidosis-like facies; AK = angiokeratomas; T = telangiectasia; PR = psychomotor retardation; DM = dysostosis multiplex; HSM = hepatosplenomegaly; CRS cherry red spot; PPCA = protective protein/cathepsin A; ISSD = infantile free sialic acid storage disease

Mucolipidosis type I is now called sialidosis.

References:

A Díaz-Font A, Santamaría R, Cozar M, Blanco M, Chamoles N, Josep Coll M, Chabás A, Vilageliu L, Grinberg D. Clinical and mutational characterization of three patients with multiple sulfatase deficiency. *Mol Genet Metab* 2005; **86:** 205–11.

B Loffeld A, Gray RG, Green SH, Roper HP, Moss C. Mild ichthyosis in a 4-year-old boy with multiple sulphatase deficiency. *Br J Dermatol* 2002; **147:** 353–5.

C Aulla P, Gahl WA. Disorders of free sialic acid storage. In: Scriver CR, Beaudet AL, Sly WS *et al.,* eds. *The Metabolic and Molecular Bases of Inherited Disease*, 8th edn. New York: McGraw-Hill, 2001: 5109–120.

D Lemyre E, Russo P, Melancon SB, Gagne R, Potier M, Lambert M. Clinical spectrum of infantile free sialic acid storage disease. *Am J Med Genet* 1999; **82:** 385–91.

Disorders of glycoprotein degradation

Most secreted and cell surface proteins are glycosylated, with oligosaccharides attached to asparagine (*N*-linked glycoproteins) or to serine or threonine (*O*-linked glycoproteins). The oligosaccharide components of glycoproteins are degraded by lysosomal hydrolases which sequentially remove the terminal monosaccharides. Deficiency of an enzyme prevents subsequent degradation steps and leads to the storage of various oligosaccharides and/or glycopeptides, depending on the precise defect [1,2]. The disorders of glycoprotein degradation are all very rare and are sometimes called glycoproteinoses or oligosaccharidoses. They resemble the mucopolysaccharidoses in several respects, including the facial appearance in many cases. Angiokeratomas are found in some disorders. Mucopolysaccharides are not present in the urine but abnormal oligosacharides may be detected by thin-layer chromatography and staining with orcinol (α-mannosidosis), resorcinol (sialidosis) or ninhydrin (aspartylglucosaminuria). In other disorders, abnormal oligosaccharides are not consistently detected (β-mannosidosis, fucosidosis). Enzyme assays are, therefore, important for diagnosis. Most of the assays can be performed on leukocytes but neuraminidase can only be measured reliably in cultured cells. Because it can be difficult to distinguish these disorders from the sphingolipidoses on clinical grounds, many laboratories offer a set of lysosomal enzyme assays on leukocytes for screening patients with relevant clinical features. The clinical and biochemical features of these disorders are summarized in Table 59.4 (along with relevant mucolipidoses and sphingolipidoses).



Fig. 59.22 Angiokeratoma corporis diffusum on the limbs of a 7-year-old girl with fucosidosis.

Genetics. All the disorders of glycoprotein degradation are inherited as autosomal recessive traits.

Fucosidosis (MIM 230000) [1]

Patients with α-L-fucosidase deficiency usually present by the age of 3 years with developmental delay, followed by neurological deterioration. Approximately 50% patients lose the ability to sit and talk by 10 years of age [3]. Most patients have a mild MPS-like facial appearance and short stature, with dysostosis multiplex that principally affects the spine. Angiokeratomas usually appear in mid- to late childhood and they are present in 85% of patients aged over 20 years [3]. The angiokeratomas usually have the same appearance and distribution as in Fabry's disease but they may be confined to the limbs (Fig. 59.22). Similar lesions may occur on the lips, gums or tongue [4]. Other clinical features include hypohydrosis [5], recurrent infections, hepatosplenomegaly and epilepsy. Bone marrow transplantation may improve the neurological outcome [6].

Ultrastructure of endothelial cells and fibroblasts reveals numerous cytoplasmic vacuoles that appear empty or contain fine granular material [5]; by contrast, concentric lamellar inclusions are seen in Fabry's disease. Lamellar inclusions are, however, seen in Schwann cells and in the myoepithelial cells of sweat glands in fucosidosis [5]. Fucose-containing oligosaccharides can be detected in the urine of some patients but not others. The diagnosis is confirmed by measuring enzyme activity in leukocytes or cultured fibroblasts.

The mannosidoses [1]

α-Mannosidase deficiency (MIM 248500) is associated with MPS-like facial features, learning difficulties, deafness, corneal clouding and cataracts, dysostosis multiplex, hepatosplenomegaly and frequent infections.

β-Mannosidase deficiency (MIM 248510) is associated with learning difficulties, deafness and frequent infections; the face is not coarse but angiokeratomas appear in some patients during late childhood or adulthood. Ultrastructural examination shows lysosomal vacuoles containing granular material in basal keratinocytes, endothelial cells, fibroblasts and eccrine sweat glands [7,8].

Abnormal urinary oligosaccharides can readily be detected in α-mannosidosis but the mannose-containing disaccharides excreted in β-mannosidosis can easily be missed, especially during infancy. Both diagnoses can be confirmed by enzyme measurement in leukocytes.

Sialidosis (MIM 256550) [1]

This disorder results from a deficiency of α-neuraminidase (also called sialidase). Mildly affected patients are said to have sialidosis type I: they present as adolescents or adults with myoclonus and visual impairment associated with a macular 'cherry red spot' on fundoscopy. Sialidosis type II refers to more severely affected patients, who present in infancy or childhood with an MPS-like phenotype, developmental delay, dysostosis multiplex and hepatosplenomegaly [9]. Histology shows vacuolation of many cell types, particularly reticuloendothelial cells and fibroblasts. Abnormal urinary oligosaccharides can be seen when stained with resorcinol. Cultured fibroblasts are needed to demonstrate the enzyme deficiency because normal activity is low in leukocytes.

Aspartylglucosaminuria (MIM 208400) [10]

This disease is caused by deficiency of aspartylglucosaminidase, which catalyses the final step in the lysosomal breakdown of glycoproteins. Patients usually present with developmental delay at 2–4 years of age. They make some developmental progress until puberty following which they regress and may develop epilepsy. Subtle facial dysmorphism is present in children; from adolescence onwards, there is coarsening of the facial features, with sagging skin, thick lips, a broad low nasal bridge and coarse hair [11]. Facial angiofibromas are common in adults, as are gingival overgrowths and oedema of the buccal mucosa [12]. Angiokeratomas are less common and may be confined to the limbs [13,14]. Ultrastructurally, dermal fibrocytes have enlarged lysosomes containing scanty fibrillogranular material. The diagnosis can be established by demonstrating aspartylglucosamine in the urine or by measuring the enzyme activity in leukocytes or cultured fibroblasts. The disorder is extremely rare in most countries but a common mutation in the Finnish population has led to a higher incidence there [13].

α-N-acetyl-galactosaminidase deficiency (MIM 104170) [15–17]

This extremely rare disorder leads to the accumulation of oligosaccharides, glycopeptides and glycosphingolipids with terminal α-*N*-acetyl-galactosamine residues. The few reported patients have presented either as infants with neurodegeneration and histologi-

Table 59.5 Lysosomal diseases associated with angiokeratomas.

Name/eponym	Enzyme deficiency	Usual age of onset	Ultrastructure of lysosomal storage in mesenchymal cells
Fabry	α-galactosidase A	>10 years (males), adulthood (females)	Dense concentric lamellar inclusions
Fucosidosis	α-L-fucosidase	Mid- to late childhood	Vacuoles with granular material
Kanzaki	α-*N*-acetylgalactosaminidase	Adulthood	Vacuoles with fibrillary material
Galactosialidosis	β-galactosidase and neuraminidase	Adulthood	Vacuoles with granular material
GM_1 gangliosidosis	β-galactosidase	Infancy	Vacuoles with fibrillogranular material
Aspartylglycosaminuria	aspartylglucosaminidase	Late childhood or adulthood	Vacuoles with fibrillogranular material
β-Mannosidosis	β-mannosidase	Late childhood or adulthood	Vacuoles with granular material

cal features of neuroaxonal dystrophy (Schindler disease) or as adults with angiokeratomas and mild learning difficulties (Kanzaki disease) [15–17]. The angiokeratomas appeared first between the knees and the umbilicus but later spread to the breasts, limbs, face, mouth and gastric mucosa. Ultrastructural examination showed clear vacuoles with scanty fibrillary contents, especially in endothelial and eccrine sweat gland cells [16]. Adult patients have slightly coarse facial features, lymphoedema in the legs and peripheral neuroaxonal degeneration [16,17].

References

1 Thomas GH. Disorders of glycoprotein degradation: α-mannosidosis, β-mannosidosis, fucosidosis and sialidosis. In: Scriver CR, Beaudet AL, Sly WS *et al.*, eds. *The Metabolic and Molecular Bases of Inherited Disease*, 8th edn. New York: McGraw-Hill, 2001: 3507–34.

2 Wraith JE. Mucopolysaccharidoses and oligosaccharidoses. In: Fernandes J, Saudubray J-M, van den Berghe G, Walter JH, eds. *Inborn Metabolic Diseases*, 4th edn. Heidelberg: Springer, 2006: 495–507.

3 Williams PJ, Gatti R, Darby JK *et al.* Fucosidosis revisited: a review of 77 patients. *Am J Med Genet* 1991; **38**: 111–31.

4 Kanitakis J, Allombert C, Doebelin B *et al.* Fucosidosis with angiokeratoma. Immunohistochemical & electronmicroscopic study of a new case and literature review. *J Cutan Pathol* 2005; **32**: 506–11.

5 Kornfeld M, Snyder RD, Wenger DA. Fucosidosis with angiokeratoma. Electron microscopic changes in the skin. *Arch Pathol Lab Med* 1977; **101**: 478–85.

6 Miano M, Lanino E, Gatti R *et al.* Four year follow-up of a case of fucosidosis treated with unrelated donor bone marrow transplantation. *Bone Marrow Transplant* 2001; **27**: 747–51.

7 Rodriguez-Serna M, Botella-Estrada R, Chabas A *et al.* Angiokeratoma corporis diffusum associated with beta-mannosidase deficiency. *Arch Dermatol* 1996; **132**: 1219–22.

8 Uchino Y, Fukushige T, Yotsumoto S *et al.* Morphological and biochemical studies of human beta-mannosidosis: identification of a novel beta-mannosidase gene mutation. *Br J Dermatol* 2003; **149**: 23–9.

9 Aylsworth AS, Thomas GH, Hood JL *et al.* A severe infantile sialidosis: clinical, biochemical and microscopic features. *J Pediatr* 1980; **96**: 662–8.

10 Aula P, Jalanko A, Peltonen L. Aspartylglucosaminuria. In: Scriver CR, Beaudet AL, Sly WS *et al.*, eds. *The Metabolic and Molecular Bases of Inherited Disease*, 8th edn. New York: McGraw-Hill, 2001: 3535–50.

11 Arvio MA, Peippo MM, Arvio PJ, Kaariainen HA. Dysmorphic facial features in aspartylglucosaminuria patients and carriers. *Clin Dysmorphol* 2004; **13**: 11–5.

12 Arvio P, Arvio M, Kero M *et al.* Overgrowth of oral mucosa and facial skin, a novel feature of aspartylglucosaminuria. *J Med Genet* 1999; **36**: 398–404.

13 Arvio M, Autio S, Louhiala P. Early clinical symptoms and incidence of aspartylglucosaminuria in Finland. *Acta Paediatr* 1993; **82**: 587–9.

14 Vargas-Diez E, Chabas A, Coll MJ *et al.* Angiokeratoma corporis diffusum in a Spanish patient with aspartylglucosaminuria. *Br J Dermatol* 2002; **147**: 760–4.

15 Deanick RJ, Schindler D. α-*N*-Acetylgalactosaminidase deficiency: Schindler disease. In: Scriver CR, Beaudet AL, Sly WS *et al.*, eds. *The Metabolic and Molecular Bases of Inherited Disease*, 8th edn. New York: McGraw-Hill, 2001: 3483–506.

16 Kanzaki T, Yokota M, Irie F *et al.* Angiokeratoma coporis diffusum with glycopeptiduria due to deficient lysosomal α-*N*-acetylgalactosaminidase activity. Clinical, morphologic and biochemical studies. *Arch Dermatol* 1993; **129**: 460–5.

17 Chabas A, Coll MJ, Aparicio M, Rodriguez DE. Mild phenotypic expression of alpha-N-acetylgalactosaminidase deficiency in two adult siblings. *J Inherit Metab Dis* 1994; **17**: 724–31.

Angiokeratoma corporis diffusum

Angiokeratoma corporis diffusum is the dermatological hallmark of several rare inherited lysosomal disorders, summarized in Table 59.5. Fabry's disease is much the commonest of these disorders. Angiokeratomas are mainly found in the milder (late-onset) forms of galactosialidosis and α-*N*-acetylgalactosaminidase deficiency and they are only an occasional finding in GM_1 gangliosidosis, aspartylglycosaminuria and β-mannosidosis. The angiokeratomas are accompanied by various problems affecting other parts of the body, depending on the underlying diagnosis. Fucosidosis, β-mannosidosis, aspartylglycosaminuria and Kanzaki disease have been described above; the other disorders primarily affect sphingolipid degradation and are described below. There have been a few reports of patients with angiokeratoma corporis diffusum in whom no specific enzyme deficiency has been identified [1–4]. In some cases, the presence of cytoplasmic vacuolation and associated clinical features suggests an unrecognized lysosomal disorder [2]; in cases without these features, a different aetiology seems more likely [3,4].

In each of the disorders, the skin lesions develop slowly as clusters of individual telangiectases or small angiomas. The colour ranges from dark red to blue-black. They are flat or slightly raised and do not blanch with pressure. The larger and older lesions may become hyperkeratotic. Bleeding can occur from the larger angiokeratomas. In patients with sparse angiokeratomas, the differential diagnoses include purpura, angioma serpiginosum and other types of angiokeratoma: solitary, circumscriptum, Fordyce type (scrotal) and Mibelli type [5]. Angiokeratomas can be removed by argon laser treatment if bleeding is a recurrent problem or for cosmetic reasons.

References

1 Holmes RC, Fenson AH, McKee P *et al.* Angiokeratoma corporis diffusum in a patient with normal enzyme activities. *J Am Acad Dermatol* 1984; **10**: 384–7.

2 McCallum DI, Macadam RF, Johnston AW. Angiokeratoma corporis diffusum with features of a mucopolysaccharidosis. *J Med Genet* 1980; **17**: 21–6.

3 Marsden J, Allen R. Widespread angiokeratomas without evidence of metabolic disease. *Arch Dermatol* 1987; **123**: 1125–7.

4 Gasparini G, Sarchi G, Cavicchini S *et al.* Angiokeratoma corporis diffusum in a patient with normal enzyme activities and Turner's syndrome. *Clin Exp Dermatol* 1992; **17**: 56–9.

5 Schiller PI, Itin PH. Angiokeratomas: an update. *Dermatology* 1996; **193**: 275–82.

Sphingolipidoses

Sphingolipids are amphiphilic molecules found in cell membranes. In all sphingolipids, the lipophilic component is ceramide. The hydrophilic portion is phosphorylcholine in sphingomyelin and usually an oligosaccharide in the glycosphingolipids. Glycosphingolipids containing neuraminic acid are called gangliosides. Sphingolipids are degraded in a stepwise fashion by lysosomal hydrolases and deficiencies of these enzymes (or their protector/activator proteins) cause the sphingolipidoses [1]. In some sphingolipidoses (e.g. Tay–Sachs disease), problems are confined to the nervous system; these are not considered further here. Other sphingolipidoses may be associated with an MPS-like facial appearance, angiokeratomas or other dermatological abnormalities. In many of these disorders, histology reveals vacuolated cells, whose ultrastructural appearance provides clues to the diagnosis. Thin layer chromatography reveals abnormal urinary oligosaccharides in a few disorders but the diagnosis is generally established by enzyme assays on leukocytes (or cultured cells). The clinical and biochemical features of the sphingolipidoses with dermatological features are included in Table 59.4.

Genetics. All the disorders are rare and show an autosomal recessive pattern of inheritance, except Fabry's disease, which is X-linked.

GM_1 gangliosidosis (MIM 230500) [1,2]

Deficiency of acid β-galactosidase leads to the accumulation of GM_1 ganglioside, other glycosphingolipids, galactose-containing oligosaccharides and keratan sulphate. GM_1 gangliosidosis is very rare and has a wide range of severity. Some patients present with hydrops fetalis or as neonates with hypotonia, hepatosplenomegaly and dysmorphism. The face is often puffy, with macroglossia, gum hypertrophy and a depressed nasal bridge; radiological investigation reveals dysostosis multiplex. These patients develop spasticity, seizures, dysphagia, loss of vision and macular cherry red spots; most die by 2 years of age. Other patients present with regression in early childhood and develop a spastic quadriplegia. The most mildly affected patients present later in childhood or as adults with dysarthria, dystonia and an abnormal gait; they may have mild learning difficulties and skeletal dysplasia, affecting the spine and hip. Widespread angiokeratomas have been reported in a few infants with GM_1 gangliosidosis [3]; the age of onset contrasts with other disorders, in which angiokeratomas seldom appear before mid-childhood. Telangiectasia and extensive Mongolian blue spots have also been reported in some infants [3,4]. Electron microscopy shows vacuolated histiocytes, fibroblasts and endothelial cells with fibrillogranular material in the vacuoles. The diagnosis is made by demonstrating β-galactosidase deficiency in leukocytes, with normal neuraminidase activity (which excludes galactosialidosis). There is no treatment for early-onset forms but substrate reduction therapy with miglustat may help late-onset patients.

Galactosialidosis (MIM 256540) [1,5]

In this extremely rare disorder, there is a combined deficiency of neuraminidase and β-galactosidase. The primary defect is in a protein (PPCA) that normally protects the two enzymes from rapid proteolysis. The protective protein is also called cathepsin A (hence PPCA) and has peptidase activity towards certain neuropeptides. The most severely affected patients present with hydrops fetalis or with MPS-like facial dysmorphism and organomegaly in the neonatal period and die within the first year from renal or cardiac failure. Many of these patients have telangiectases [6] and a few have angiokeratomas. Other patients present in early childhood with coarse facies, organomegaly, dysostosis multiplex and neurodevelopmental problems. Mildly affected patients are mostly Japanese. They present in late childhood or adulthood with myoclonus, ataxia, mental retardation and loss of vision with cherry red spots. They have no organomegaly but do have mild MPS-like facial features and spinal abnormalities. Half of these patients have angiokeratomas, similar to those seen in Fabry's disease [7]. Electron microscopy shows vacuoles, some containing granular material, in endothelial cells and fibroblasts. The diagnosis is made by finding deficiencies of β-galactosidase, neuraminidase and cathepsin A in leukocytes or cultured fibroblasts.

References

1 Vanier M-T. Disorders of sphingolipid metabolism. In: Fernandes J, Saudubray J-M, van den Berghe G, Walter JH, eds. *Inborn Metabolic Diseases*, 4th edn. Heidelberg: Springer, 2006: 479–94.

2 Suzuki Y, Oshima A, Nanba E. β-Galactosidase deficiency: GM_1 gangliosidosis and Morquio B disease. In: Scriver CR, Beaudet AL, Sly WS *et al.*, eds. *The Metabolic and Molecular Bases of Inherited Disease*, 8th edn. New York: McGraw-Hill, 2001: 3775–810.

3 Beratis NG, Varvarigou-Frimas A, Beratis S, Sklower SL. Angiokeratoma corporis diffusum in GM1 gangliosidosis, type 1. *Clin Genet* 1989; **36**: 59–64.

4 Weissbluth M, Esterly NB, Caro WA. Report of an infant with GM1 gangliosidosis type I and extensive and unusual mongolian spots. *Br J Dermatol* 1981; **104**: 195–200.

5 d'Azzo A, Andria G, Strisciuglio P, Galjaard H. Galactosialidosis. In: Scriver CR, Beaudet AL, Sly WS *et al.*, eds. *The Metabolic and Molecular Bases of Inherited Disease*, 8th edn. New York: McGraw-Hill, 2001: 3811–26.

6 Patel MS, Callahan JW, Zhang S *et al.* Early infantile galactosialidosis. *Am J Med Genet* 1999; **85**: 38–47.

7 Nobeyama Y, Honda M, Niimura M. A case of galactosialidosis. *Br J Dermatol* 2003; **149**: 405–9.

Fabry's disease (MIM 301500) [1]

A.A.M. Morris & S.M. Breathnach, pp. 59.36–59.39

Synonym

- Anderson–Fabry disease

This is a rare X-linked sphingolipidosis, with an estimated incidence of 1 in 40 000–60 000 male births [1,2]. Affected males usually present in childhood with episodes of pain in the extremities, followed by the appearance of angiokeratomas. Most adult males develop renal failure, cardiac and cerebrovascular disease. Many heterozygous females also develop symptoms, though the onset is usually later.

Aetiology. Deficiency of the lysosomal enzyme, α-galactosidase A, leads to the accumulation of glycosphingolipids with terminal galactose residues, predominantly globotriaosylceramide (galactose–galactose–glucose–ceramide) but also galabiosylceramide (galactose–galactose–ceramide) and blood group B substances [1]. These are found in the lysosomes of endothelial, perithelial and

vascular smooth muscle cells; the swollen endothelial cells encroach on the lumen of blood vessels, leading to focal increases in pressure and aneurysmal dilatation of the weakened vascular wall. Glycosphingolipids also accumulate in renal glomeruli and tubules, cardiac muscle, autonomic ganglion cells and the corneal epithelium. More than 300 mutations have been identified in the GLA gene; none are highly prevalent. Some mutations seem to be associated with mild variants (e.g. N215S with the 'cardiac' variant) [3] but others are found in both mild variants and in classical disease [3,4].

Clinical features. The first symptoms are usually episodes of severe burning pain in the palms and soles (acroparesthesiae). These occur in 70–85% of male patients, usually starting between 5 and 15 years, though it may take many years for the diagnosis to be established [4]. Acroparesthesiae occur in 50–70% of females, with a mean age of onset of 15 years [5,6]. Painful crises are often triggered by fever or exertion and may last hours or days. Pain may diminish spontaneously in older men.

Angiokeratomas are found in 65–70% of male and 35–40% of female patients [4,5,7]. In males, they often start to appear shortly before puberty (age of onset 19 ± 14 years, mean ± SD) whereas in females they usually appear later (28 ± 17 years). The initial lesion is a dark-red or black telangiectatic macule or papule up to 4 mm across, that does not blanch with pressure; there is usually mild hyperkeratosis over larger lesions. Angiokeratomas are clustered and numerous in some patients but they are sparse in most women and in many men [7]. In men, the commonest sites are around the umbilicus (Fig. 59.23) and in the bathing-trunk area, affecting the inner thighs, lower back, buttocks, penis and scrotum. Lesions may also be found on the upper arms, around the border of the lips, around the nail folds and on the palms and soles; these are usually macular angiomas with minimal hyperkeratosis [7]. In women, lesions are most frequent on the trunk and proximal limbs; genital lesions are rare. Telangiectases are present in 23% of males and 9% of females, usually on the lips, buccal mucosa, ears or conjunctivae [7,8]. The other common dermatological problem is anhidrosis or hypohidrosis (in 53% of males and 28% of females) [7,9]. This probably results from an autonomic neuropathy. It is associated with heat and exercise intolerance, and sometimes with unexplained bouts of fever. Onset is most often in the third decade. Hyperhidrosis occurs in about 10% of patients, predominantly females, often starting in adolescence [10]. Later, vasomotor disturbances may cause the hands to be blue or blanched, or there may be flushing of the extremities. Lymphoedema is much commoner than in the general population [7] and may be due to lymphatic microangiopathy [11].



Fig. 59.23 Angiokeratoma corporis diffusum around the umbilicus in a man with Fabry's disease.

Cardiac involvement occurs in almost all adult males [1,2,4]. It includes left ventricular dilatation and hypertrophy, mitral valve regurgitation, arrhythmias and ischaemic heart disease. Most adult males have proteinuria, hypertension and gradually deteriorating renal function. Without enzyme replacement therapy, end-stage renal failure is usually reached between 40 and 50 years of age, though it can occur much earlier [1,4]. Cerebrovascular disease is also common and may lead to early strokes or transient ischaemic attacks. Other patients develop severe neurological problems without any obvious thrombotic episodes, presumably due to the involvement of multiple small vessels [1]. Vertigo, dizziness and high frequency hearing loss are common.

Most male patients have the full syndrome but atypical, milder variants have been reported. Men with the 'cardiac variant' usually present after the age of 40 years with cardiomyopathy and proteinuria [2]. Cardiac and cerebrovascular disease are commoner in heterozygous women than previously thought [5]. In a survey of 248 female patients, 26% had left ventricular hypertrophy (mean age of onset 50 years) and 7% had suffered strokes (mean age 50 years) [6].

Slit-lamp examination reveals an asymptomatic corneal dystrophy in most adult male and female patients [12]. Glycosphingolipid deposits under the epithelium initially cause superficial haziness, which progresses to characteristic whorled streaks radiating to the periphery (cornea verticillata). Identical appearances have been reported after long-term chloroquine or amiodarone [13]. Other ophthalmological findings include lens opacities and tortuosity of the conjunctival and retinal vessels.

Episodes of abdominal pain and diarrhoea are common and there may be achalasia of the oesophagus. Some patients suffer arthritis in the distal interphalangeal joint of the hand.

Prognosis. Men and women with Fabry's disease have a reduced life expectancy due to renal, cerebrovascular and cardiac disease. In a cohort of male patients, the median survival was 50 years, approximately 20 years less than the normal population [4]. School attendance, sport and social activities were all affected and only 57% of patients were in employment [4]. In a cohort of heterozygous women, the median survival was 70 years, approximately 15 years less than the normal population [5].

Histopathology. Light microscopy of the angiokeratomas shows dilated vessels in the upper dermis beneath a thinned epidermis, with or without hyperkeratosis (Fig. 59.24). Vacuolated cells are present in the media and intima of small blood vessels. The accumulated glycosphingolipids are birefringent and, in frozen sections, they appear as 'Maltese crosses' in polarized light [1]. Electron microscopy shows cytoplasmic inclusion bodies in the



Fig. 59.24 Angiokeratoma corporis diffusum: H&E, × 4. Dilated blood-filled vessels in papillary dermis.

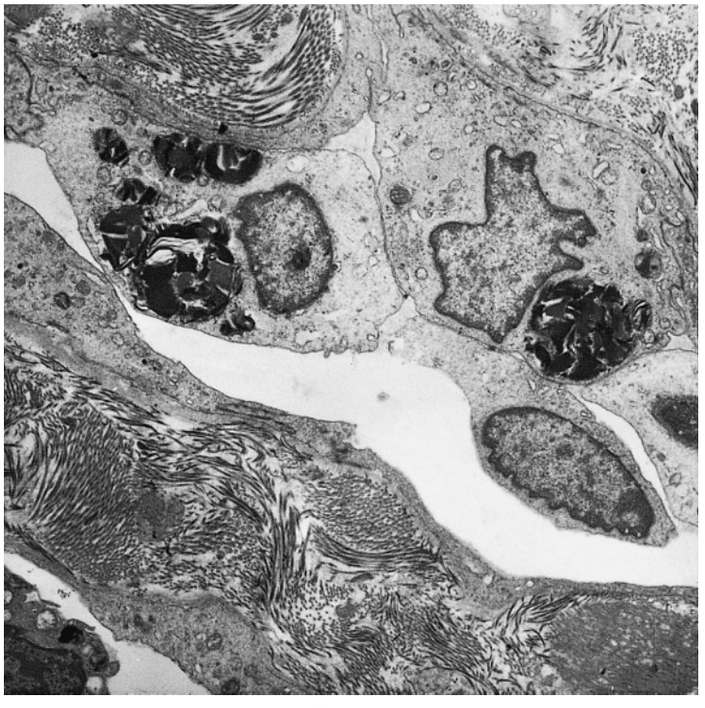


Fig. 59.25 Angiokeratoma corporis diffusum. Electron-dense cytoplasmic inclusion bodies are present within endothelial cells. (Courtesy of Dr P.H. McKee, King's College, London, UK.)

endothelial (Fig. 59.25) and perithelial cells of blood vessels, smooth muscle, perineural cells and dermal macrophages. The inclusions are electron-dense and lamellar, with a periodicity of 4–6 nm [1,14]. In contrast, other lysosomal disorders associated with angiokeratomas have electron-lucent vacuoles containing scanty fibrillary or granular material. The inclusions in Fabry's disease represent lipid deposits within lysosomes [14]. They are present in clinically unaffected skin, even in infancy [15], and in other tissues (e.g. myocardial and glomerular epithelial cells).

Diagnosis. If the angiokeratomas are sparse, it may be difficult to distinguish them from angiokeratomas without systemic disease. The diagnosis of Fabry's disease can be established by skin histology or slit-lamp examination of the cornea. In males, it should be confirmed by demonstrating α-galactosidase A deficiency in plasma or leukocytes (or cultured skin fibroblasts). This technique is unsuitable for heterozygous females, who often have normal enzyme activity. Urinary globotriacylceramide concentrations are raised in most heterozygous females [16] but the assay is not widely available. Molecular analysis is, therefore, the preferred technique for confirming the diagnosis in women, though occasionally it is difficult to distinguish pathogenic mutations from benign polymorphisms.

Treatment. The acroparesthesiae may respond to carbamazepine, gabapentin or phenytoin [17,18] or they may require opiates. Angiokeratomas can be removed by laser therapy for cosmetic or other reasons but this is seldom requested [19]. Cardiac complications should be managed conventionally. Aspirin may reduce the risk of stroke. Smoking should be avoided; statins should be prescribed if there is hyperlipidaemia and hypertension should be controlled. ACE inhibitors should be started if there is proteinuria. Patients developing renal failure warrant dialysis or transplantation; glycolipids do not reaccumulate in the graft [20].

Enzyme replacement therapy (ERT) with recombinant human α-galactosidase A has been shown to clear microvascular deposits of globotriaosylceramide from the kidneys, heart and skin [21]. It reduces neurogenic pain [22], reduces left ventricular hypertrophy [23] and prevents the development of renal impairment in patients with normal baseline renal function [24]. In the UK, ERT is now started following diagnosis in symptomatic male patients; in female patients, it is started if there is cardiac, neurological or renal disease, troublesome gastrointestinal symptoms or pain that cannot be controlled by other means.

References

1 Desnick RJ, Ioannou YA, Eng CM. α-Galactosidase deficiency: Fabry disease. In: Scriver CR, Beaudet AL, Sly WS *et al.*, eds. *The Metabolic and Molecular Bases of Inherited Disease*, 8th edn. New York: McGraw-Hill, 2001: 3733–74.

2 Nakao S, Takenaka T, Maeda M *et al.* An atypical variant of Fabry's disease in men with left ventricular hypertrophy. *N Engl J Med* 1995; **333**: 288–93.

3 Eng CM, Resnick-Silverman LA, Niehaus DJ *et al.* Nature and frequency of mutations in the alpha-galactosidase A gene that cause Fabry disease. *Am J Hum Genet* 1993; **53**: 1186–97.

4 MacDermot KD, Holmes A, Miners AH. Anderson–Fabry disease. Clinical manifestations and impact of disease in a cohort of 98 hemizygous males. *J Med Genet* 2001; **38**: 750–60.

5 MacDermot KD, Holmes A, Miners AH. Anderson–Fabry disease. Clinical manifestations and impact of disease in a cohort of 60 obligate carrier females. *J Med Genet* 2001; **38**: 769–75.

6 Deegan PB, Baehner AF, Barba Romero MA *et al.* Natural history of Fabry disease in females in the Fabry Outcome Survey. *J Med Genet* 2006; **43**: 347–52.

7 Orteu CH, Jansen T, Lidove O *et al.* Fabry disease and the skin: data from FOS, the Fabry outcome survey. *Br J Dermatol* 2007; **157**: 331–7.

8 Chesser RS, Gentry RH, Fitzpatrick JE *et al.* Perioral telangiectases: a new cutaneous finding in Fabry's disease. *Arch Dermatol* 1990; **126**: 1655–6.

9 Lao LM, Kumakiri M, Mima H *et al.* The ultrastructural characteristics of eccrine sweat glands in a Fabry disease patient with hypohidrosis. *J Dermatol Sci* 1998; **18**: 109–17.

10 Lidove O, Ramaswami U, Jaussaud R *et al.* Hyperhidrosis: a new and often early symptom in Fabry disease. International experience and data from the Fabry Outcome Survey. *Int J Clin Pract* 2006; **60**: 1053–9.

11 Amann-Vesti BR, Gitzelmann G, Widmer U *et al.* Severe lymphatic microangiopathy in Fabry disease. *Lymphat Res Biol* 2003; **1**: 185–9.

12 Sodi A, Ioannidis AS, Mehta A *et al.* Ocular manifestations of Fabry's disease: data from the Fabry Outcome Survey. *Br J Ophthalmol* 2007; **91**: 210–4.
13 Chew E, Ghosh M, McCulloch C. Amiodarone-induced cornea verticillata. *Can J Ophthalmol* 1982; **17**: 96–9.
14 Hashimoto K, Lieberman P, Lamkin N. Angiokeratoma corporis diffusum (Fabry's disease): a lysosomal disease. *Arch Dermatol* 1976; **112**: 1416–23.
15 Breathnach SM, Black MM, Wallace HJ. Anderson–Fabry disease: characteristic ultrastructure features in cutaneous blood vessels in a 1-year-old boy. *Br J Dermatol* 1980; **103**: 81–4.
16 Young E, Mills K, Morris P *et al.* Is globotriaosylceramide a useful biomarker in Fabry disease? *Acta Paediatr Suppl* 2005; **94**: 51–4.
17 Lockman LA, Hunninglake DB, Krivit W *et al.* Relief of pain of Fabry's disease by diphenylhydantoin. *Neurology* 1973; **23**: 871–5.
18 Ries M, Mengel E, Kutschke G *et al.* Use of gabapentin to reduce chronic neuropathic pain in Fabry disease. *J Inherit Metab Dis* 2003; **26**: 413–4.
19 Mohrenschlager M, Braun-Falco M, Ring J, Abeck D. Fabry disease: recognition and management of cutaneous manifestations. *Am J Clin Dermatol* 2003; **4**: 189–96.
20 Ojo A, Meier-Kriesche HU, Friedman G *et al.* Excellent outcome of renal transplantation in patients with Fabry's disease. *Transplantation* 2000; **69**: 2337–9.
21 Eng CM, Guffon N, Wilcox WR *et al.* Safety and efficacy of recombinant human α-galactosidase A replacement therapy in Fabry's disease. *N Engl J Med* 2001; **345**: 9–16.
22 Schiffmann R, Kopp JB, Austin HA 3rd *et al.* Enzyme replacement therapy in Fabry disease: a randomized controlled trial. *JAMA* 2001; **285**: 2743–9.
23 Hughes DA, Elliott PM, Shah J *et al.* Effects of enzyme replacement therapy on the cardiomyopathy of Anderson-Fabry disease: a randomized, double-blind, placebo-controlled clinical trial of agalsidase-alfa. *Heart* 2008; **94**: 15–8.
24 Germain DP, Waldek S, Banikazemi M *et al.* Sustained, long-term renal stabilization after 54 months of agalsidase beta therapy in patients with Fabry disease. *J Am Soc Nephrol* 2007; **18**: 1547–57.

Gaucher's disease (MIM 606463) [1]

A.A.M. Morris, pp. 59.39–59.42

This autosomal recessive disorder results from deficiency of acid β-glucosidase (glucocerebrosidase). Glycosphingolipids (principally glucosylceramide, also known as glucocerebroside) accumulate in macrophages in the liver, spleen and bones. Though Gaucher's disease is rare, it is the most prevalent lysosomal disorder (1:57 000 in Australia [2]).

Clinical features. Gaucher's disease is classified clinically into type 1 (non-neuronopathic), type 2 (acute neuronopathic) and type 3 (subacute neuronopathic). Type 1 is much the commonest, particularly in Ashkenazi Jews, in whom the incidence is over 1:1000, mainly due to a high prevalence of the N370S mutation. It presents in childhood or adulthood, with hepatosplenomegaly, features of hypersplenism (usually thrombocytopenia) or bone problems. Some children and adolescents suffer painful 'bone crises' due to ischaemia, typically in the femoral head or shaft. Later, loss of bone mass can lead to pathological fractures [3]. Lung infiltration is a rare but serious complication. The prognosis for type 1 Gaucher's disease depends on the severity of the mutations [4]; some patients can die by the age of 20 years without treatment, whereas some N370S homozygotes never develop symptoms.

Cutaneous features are common but not troublesome in type 1 Gaucher's disease [5]. In a series of 50 South African patients, 50% had diffuse yellow-brown pigmentation, 40% reported easy tanning, 30% had brown macules and 20% had telangiectasia [6]. Thrombocytopenia may lead to petechiae or ecchymoses.



Fig. 59.26 The hand of a 'collodion baby' with Gaucher's disease type 2.

Type 2 Gaucher's disease presents during the first 6 months of life with brainstem problems, such as squint, dysphagia and hyperextension of the neck, followed by episodes of apnoea. Other features include stridor, spasticity, epilepsy, lung disease and hepatosplenomegaly. Most type 2 patients die by the age of 2 years [7]. There is also a perinatal-lethal form that usually presents with hydrops fetalis. Some of these patients have severe ichthyosis, leading to the collodion baby phenotype (Fig. 59.26) [8]. The baby is encased in thick, tight, shiny skin that cracks and desquamates to leave erythroderma. The thickened skin causes ectropia of the eyes. The skin may return to normal if the baby survives for more than a month.

Type 3 disease is particularly common in the Norrbottnian population of northern Sweden, where it is associated with homozygosity for the L444P mutation. These patients usually present with hepatosplenomegaly in infancy, followed a few years later by an eye movement disorder, impaired hearing and other neurological problems [9]. Some type 3 patients have progressive myoclonic epilepsy and dementia with less severe organomegaly.

Pathology. Numerous characteristic histiocytes (Gaucher cells) are found in the spleen, liver, bone marrow and lymph nodes, with smaller numbers in other organs. Gaucher cells are large cells with pale-staining cytoplasm that has a delicate, striated, 'wrinkled tissue paper' appearance, best seen in thicker sections (10 μm). They differ markedly from the foam cells seen in other lipidoses. Ultrastructurally, Gaucher cells have membrane bound twisted tubular inclusions that represent aggregated glucocerebroside molecules within lysosomes [1,10].

Diagnosis. The diagnosis should be confirmed by enzyme assay in lymphocytes, leukocytes or cultured fibroblasts or by mutation analysis.

Treatment. Enzyme replacement therapy (ERT) is safe and effective for the treatment of type 1 Gaucher's disease but it is expensive and requires slow intravenous infusion at least every 2 weeks [11–13]. In the UK, all paediatric patients receive ERT, as do adults

with significant symptoms but not those who only have mild splenomegaly or mild skeletal abnormalities. Miglustat is an oral drug that decreases the accumulation of glucocerebroside by reducing the synthesis of glycosphingolipids (substrate reduction therapy) [14]. In the UK, it is used in mildly affected patients who are unable or unwilling to receive ERT. Diarrhoea and weight loss are common side effects. Splenectomy reduces abdominal distension and can relieve thrombocytopenia but it is seldom indicated in countries that can afford ERT. Other supportive measures include transfusion of blood products, bisphosphonates and analgesia.

There is no effective treatment for type 2 Gaucher's disease. ERT relieves the systemic complications in type 3 Gaucher's disease but it does not cross the blood–brain barrier; addition of miglustat or haematopoietic stem cell transplantation should be considered if there is neurological deterioration [15].

References

1 Beutler E, Grabowski GA. Gaucher's disease. In: Scriver CR, Beaudet AL, Sly WS *et al.*, eds. *The Metabolic and Molecular Bases of Inherited Disease*, 8th edn. New York: McGraw-Hill, 2001: 3635–68.
2 Meikle PJ, Hopwood JJ, Clague AE, Carey WF. Prevalence of lysosomal storage disorders. *JAMA* 1999; **281**: 249–54.
3 Wenstrup RJ, Roca-Espiau M, Weinreb NJ, Bembi B. Skeletal aspects of Gaucher disease: a review. *Br J Radiol* 2002; **75** (Suppl. 1): A2–12.
4 Charrow J, Andersson HC, Kaplan P *et al.* The Gaucher registry: demographics and disease characteristics of 1698 patients with Gaucher disease. *Arch Intern Med* 2000; **160**: 2835–43.
5 Reich C, Seife M, Kessler BJ. Gaucher's disease. A review and discussion of 20 cases. *Medicine (Baltimore)* 1951; **30**: 1–20.
6 Goldblatt J, Beighton P. Cutaneous manifestations of Gaucher disease. *Br J Dermatol* 1984; **111**: 331–4.
7 Mignot C, Doummar D, Maire I, De Villemeur TB. Type 2 Gaucher disease: 15 new cases and review of the literature. *Brain Dev* 2006; **28**: 39–48.
8 Stone DL, Carey WF, Christodoulou J *et al.* Type 2 Gaucher disease: the collodion baby phenotype revisited. *Arch Dis Child (Fetal Neonatal Edn)* 2000; **82**: F163–6.
9 Dreborg S, Erikson A, Hagberg B. Gaucher disease–Norrbottnian type. I. General clinical description. *Eur J Pediatr* 1980; **133**: 107–18.
10 Lee RE. The fine structure of the cerebroside occurring in Gaucher's disease. *Proc Natl Acad Sci USA* 1968; **61**: 484–9.
11 Weinreb NJ, Charrow J, Andersson HC *et al.* Effectiveness of enzyme replacement therapy in 1028 patients with type 1 Gaucher disease after 2–5 years of treatment: a report from the Gaucher Registry. *Am J Med* 2002; **113**: 112–9.
12 Baldellou A, Andria G, Campbell PE *et al.* Paediatric non-neuronopathic Gaucher disease: recommendations for treatment and monitoring. *Eur J Pediatr* 2004; **163**: 67–75.
13 Andersson HC, Charrow J, Kaplan P *et al.* Individualization of long-term enzyme replacement therapy for Gaucher disease. *Genet Med* 2005; **7**: 105–10.
14 Weinreb NJ, Barranger JA, Charrow J *et al.* Guidance on the use of miglustat for treating patients with type 1 Gaucher disease. *Am J Hematol* 2005; **80**: 223–9.
15 Capablo JL, Franco R, de Cabezon AS *et al.* Neurologic improvement in a type 3 Gaucher disease patient treated with imiglucerase/miglustat combination. *Epilepsia* 2007; **48**: 1406–8.

Niemann–Pick disease types A and B (MIM 257200) [1]

Aetiology. Niemann–Pick disease (NPD) types A and B are autosomal recessive sphingolipidoses, caused by sphingomyelinase deficiency. Sphingomyelin accumulates in histiocytes and leads to hepatosplenomegaly. In NPD type A, sphingomyelin also accumulates in the brain, leading to progressive neurodegeneration during early childhood. NPD type B is non-neuronopathic. Both types are very rare but type A is more common in Ashkenazi Jews. (NPD type C is an unrelated disorder characterized by defective intracellular lipid trafficking.)

Clinical features. Classical NPD type A patients present with diarrhoea, vomiting and failure to thrive in the first 2 months. By 6 months of age, there is hepatosplenomegaly, lymphadenopathy, trunkal hypotonia and spasticity in the limbs. Deafness and blindness are common and half the patients have retinal cherry red spots. Most patients die by 3 years of age. Other NPD type A patients have milder systemic features and juvenile or adult-onset neurological disease [2]. Type B patients usually present with splenomegaly or hepatosplenomegaly, sometimes not until adulthood. Interstitial lung disease, poor growth, hyperlipidaemia and thrombocytopenia are common. Nevertheless, some patients have a normal lifespan [3].

The skin may show patches of waxy induration and brownish-yellow pigmentation [4]. Papular, papulonodular or suppurative lesions may be found on the face or trunk [5,6], occasionally becoming confluent [6]. These may be commoner in patients with NPD of intermediate severity. Xanthomas and xanthogranulomas [7], café-au-lait macules and Mongolian blue spots have also been reported. Thrombocytopenia may lead to purpura or bruising.

Pathology. Niemann–Pick cells are the hallmark of NPD; some are present in virtually all tissues, including the skin [4,5]. They are large, usually mononucleate histiocytes, whose cytoplasm is filled with lipid droplets, giving rise to a foamy appearance. In cryostat sections, they stain readily with Sudan stains and contain doubly refractile material. Ultrastructurally, the cytoplasm contains concentric lamellar inclusions [5]. Similar cells are found in Wolman disease, cholesterol ester storage disease and lipoprotein lipase deficiency; Niemann–Pick cells stain poorly with PAS, in contrast to Gaucher cells. The diagnosis can be confirmed by measuring sphingomyelinase activity in leukocytes or cultured fibroblasts.

Treatment. There is no effective treatment for NPD type A. Trials of enzyme replacement therapy are planned for NPD type B.

References

1 Schuchman EH, Desnick RJ. Niemann–Pick disease types A and B. Acid sphingomyelinase deficiencies. In: Scriver CR, Beaudet AL, Sly WS *et al.*, eds. *The Metabolic and Molecular Bases of Inherited Disease*, 8th edn. New York: McGraw-Hill, 2001: 3589–610.
2 Wasserstein MP, Aron A, Brodie SE *et al.* Acid sphingomyelinase deficiency: prevalence and characterization of an intermediate phenotype of Niemann-Pick disease. *J Pediatr* 2006; **149**: 554–9.
3 Wasserstein MP, Desnick RJ, Schuchman EH *et al.* The natural history of type B Niemann-Pick disease: results from a 10-year longitudinal study. *Pediatrics* 2004; **114**: e672–e677.
4 Mardini MK, Gergan P, Akltar M *et al.* Niemann–Pick disease: report of a case with skin involvement. *Am J Dis Child* 1982; **136**: 650–1.
5 Toussaint M, Worret WI, Drosner M *et al.* Specific skin lesions in a patient with Niemann–Pick disease. *Br J Dermatol* 1994; **131**: 895–7.
6 Raddadi AA, Al Twaim AA. Type A Niemann-Pick disease. *J Eur Acad Dermatol Venereol* 2000; **14**: 301–3.
7 Crocker AC, Farber S. Niemann–Pick disease. A review of 18 patients. *Medicine (Baltimore)* 1958; **37**: 1–95.

Farber's disease (MIM 228000) [1]

Synonym
- Disseminated lipogranulomatosis

Farber's disease is an extremely rare autosomal recessive lipid-storage disease of infants, in which deficiency of lysosomal acid ceramidase leads to the accumulation of ceramide [1,2].

Clinical features. Patients usually present in early infancy with a hoarse cry, painful swollen joints and subcutaneous nodules. The most commonly affected joints are those of the hand and wrist, elbows, knees and ankles. The subcutaneous nodules may be associated with erythematous papules and are generally close to affected joints or over pressure points, such as the occiput and lower spine. Laryngeal involvement can lead to stridor as well as hoarseness. Most patients have psychomotor retardation, poor weight gain and die in early childhood from respiratory infections. A few patients present with hydrops fetalis or neonatal hepatosplenomegaly [2]. In other patients, neurodegeneration is the main feature [3]; these patients usually have cherry-red spots at the macula.

Histopathology. In the skin and subcutaneous tissue, dense areas of mixed granulomatous infiltration are found among a fibrovascular stroma. Groups of large, foamy histiocytes are found towards the centre of the granulomas. Ultrastructurally, the histiocytes have cytoplasmic vacuoles containing curvilinear inclusions (Farber bodies) [2,4]. Histochemical studies indicate that the storage material consists of ceramide and glycolipids [1,2]. The diagnosis can be confirmed by enzyme assay in leukocytes or fibroblasts.

Treatment. Symptomatic treatment includes analgesia and corticosteroids. Haematopoietic stem cell transplantation does not prevent neurological deterioration but may be appropriate for atypical patients without neurological involvement [5].

References

1 Moser HW, Linke T, Fensom AH, Levade T, Sandhoff K. Acid ceramidase deficiency: Farber lipogranulomatosis. In: Scriver CR, Beaudet AL, Sly WS *et al.*, eds. *The Metabolic and Molecular Basis of Inherited Disease*, 8th edn. New York: McGraw-Hill, 2001: 3573–88.

2 Qualman SJ, Moser HW, Valle D *et al.* Farber disease: pathologic diagnosis in sibs with phenotypic variability. *Am J Med Genet Suppl* 1987; **3**: 233–41.

3 Eviatar L, Sklower SL, Wisniewski K *et al.* Farber lipogranulomatosis: an unusual presentation in a black child. *Pediatr Neurol* 1986; **2**: 371–4.

4 Schmoeckel C, Hohlfell M. A specific ultrastructural marker for disseminated lipogranulomatosis (Farber). *Arch Dermatol Res* 1979; **266**: 187–96.

5 Vormoor J, Ehlert K, Groll AH *et al.* Successful hematopoietic stem cell transplantation in Farber disease. *J Pediatr* 2004; **144**: 132–4.

Lipoid proteinosis (MIM 247100) [1,2]

Synonyms
- Urbach–Wiethe disease
- Hyalinosis cutis et mucosae
- Lipoglycoproteinosis

Aetiology. Lipoid proteinosis is a very rare, autosomal recessive disorder, characterized by infiltration of hyaline material into the skin, oral cavity, larynx and internal organs. The exact nature of the hyaline material is still uncertain. The disorder is caused by mutations in the extracellular matrix protein 1 (ECM1) gene [3]. ECM1 binds to various proteins (perlecan, fibulins and matrix metalloproteinase-9) but its function is unknown [1]. Interestingly, antibodies to ECM1 are present in 75% of patients with lichen sclerosis [4]. Lipoid proteinosis is common in the Namaqualand region of South Africa, where cases can be traced back to a German immigrant [2].

Clinical features. Lipoid proteinosis usually presents in infancy with hoarseness, which can progress to complete aphonia. The vocal cords are thickened, with nodules here and on the epiglottis. Occasionally, stridor necessitates a tracheostomy [5]. The lips, pharynx, soft palate, uvula and tonsils develop yellow-white submucous infiltrates. The tongue is enlarged and firm with infiltrates on its under-surface. The frenulum becomes short and thick, restricting tongue movement, such that it cannot be protruded. There may be recurrent inflammation of the salivary glands [2].

The first skin lesions are often blisters in early childhood, which become eroded and crusted after minor trauma [2]. Acneiform, pock-like scars appear on the face and elsewhere, either following trauma or spontaneously. Infiltration of the skin can cause waxy papules, hyperkeratosis or warty plaques, which may become darker with time. These lesions may affect the palms or backs of the hands, the forehead or the elbows, where they can be prominent and resemble xanthomas. Characteristic 'beaded' papules are present along the margins of the eyelids but they may be subtle (moniliform blepharosis) (Fig. 59.27). There may be loss of eyelashes or patchy alopecia due to scalp involvement [6]. Some patients complain of itching or increased sensitivity to sunlight [2].



Fig. 59.27 Lipoid proteinosis. Typical 'beaded' papules present along the margins of the upper eyelids. (Courtesy of Dr R.C.D. Staughton, Chelsea and Westminster Hospital, London, UK.)

Epilepsy and psychiatric problems occur in a number of patients and may be associated with intracranial calcification (e.g. in the temporal lobes or amygdala) [7]. Visceral involvement has also been reported [8]. Problems progress until early adult life but subsequently stabilize.

Histopathology. The epidermis shows hyperkeratosis and irregular acanthosis. The dermis is thickened and the upper dermis contains large deposits of extracellular hyaline material that stains strongly with PAS. There is also thickening of the (PAS-positive) basement membranes at the dermal–epidermal junction and around blood vessels and sweat glands. Immunofluorescence labelling for type IV collagen confirms the basement membrane thickening. Staining for type I and type III collagen is decreased in the upper dermis; the deposits of hyaline material do not stain with anticollagen antibodies [6]. Ultrastructurally, there are multiple concentric rings of basement membrane around blood vessels and irregular reduplication of the lamina densa at the dermal–epidermal junction. The hyaline deposits are featureless. Lysosomes containing curved tubular inclusions have been reported in histiocytes and eccrine sweat glands [9] but this is not thought to be a primary lysosomal disorder. Histochemical diagnosis is now possible using an antibody to ECM1 [10].

Diagnosis. The combination of hoarseness from early childhood, thickening of the tongue and frenulum and cutaneous nodules suggests the diagnosis. Erythropoietic protoporphyria also causes waxy papules and depressed scars but the scars are confined to sun-exposed skin; on histology, the hyaline material is less extensive and there are fine lipid droplets. Xanthomatosis and amyloidosis are also excluded by the histological appearances. In adults, other differential diagnoses include lichen myxoedematosus and myxoedema with hoarseness.

Treatment. Microlaryngoscopy and dissection of the vocal cords can be successful. Dermabrasion [11], chemical skin peeling, blepharoplasty and carbon dioxide laser therapy [12] may be helpful. Oral dimethylsulphoxide was reported to help one patient [13] but not others [14]. Beneficial effects of etretinate [15] and of penicillamine [16] have also been reported.

References

1 Chan I, Liu L, Hamada T, Sethuraman G, McGrath JA. The molecular basis of lipoid proteinosis: mutations in extracellular matrix protein 1. *Exp Dermatol* 2007; **16**: 881–90.

2 Hougenhouck-Tulleken W, Chan I, Hamada T *et al.* Clinical and molecular characterization of lipoid proteinosis in Namaqualand, South Africa. *Br J Dermatol* 2004; **151**: 413–23.

3 Hamada T, McLean WH, Ramsay M *et al.* Lipoid proteinosis maps to 1q21 and is caused by mutations in the extracellular matrix protein 1 gene (ECM1). *Hum Mol Genet* 2002; **11**: 833–40.

4 Oyama N, Chan I, Neill SM *et al.* Autoantibodies to extracellular matrix protein 1 in lichen sclerosus. *Lancet* 2003; **362**: 118–23.

5 Konstantinov K, Kabakchiev P, Karchev T *et al.* Lipoid proteinosis. *J Am Acad Dermatol* 1992; **27**: 293–7.

6 Newton JA, Rasbridge S, Temple A *et al.* Lipoid proteinosis: new immunopathological observations. *Clin Exp Dermatol* 1991; **16**: 350–4.

7 Siebert M, Markowitsch HJ, Bartel P. Amygdala, affect and cognition: evidence from 10 patients with Urbach-Wiethe disease. *Brain* 2003; **126**: 2627–37.

8 Caplan RM. Visceral involvement in lipoid proteinosis. *Arch Dermatol* 1967; **95**: 149–55.

9 Navarro C, Fachal C, Rodriguez C *et al.* Lipoid proteinosis. A biochemical and ultrastructural investigation of two new cases. *Br J Dermatol* 1999; **141**: 326–31.

10 Chan I, South AP, McGrath JA *et al.* Rapid diagnosis of lipoid proteinosis using an anti-extracellular matrix protein 1 (ECM1) antibody. *J Dermatol Sci* 2004; **35**: 151–3.

11 Bannerot H, Aubin F, Tropet Y *et al.* Lipoid proteinosis: importance of dermabrasion. Apropos of a case. *Ann Chir Plast Esthet* 1998; **43**: 78–81.

12 Rosenthal G, Lifshitz T, Monos T *et al.* Carbon dioxide laser treatment for lipoid proteinosis (Urbach–Wiethe syndrome) involving the eyelids. *Br J Ophthalmol* 1997; **81**: 253.

13 Wong CK, Lin CS. Remarkable response of lipoid proteinosis to oral dimethyl sulphoxide. *Br J Dermatol* 1988; **119**: 541–4.

14 Ozkaya-Bayazit E, Ozarmagan G, Baykal C, Ulug T. Oral DMSO therapy in three patients with lipoidproteinosis. Results of long-term therapy. *Hautarzt* 1997; **48**: 477–81.

15 Gruber F, Manestar D, Stasic A, Grgurevic Z. Treatment of lipoid proteinosis with etretinate. *Acta Derm Venereol (Stockh)* 1996; **76**: 154–5.

16 Kaya TI, Kokturk A, Tursen U *et al.* D-penicillamine treatment for lipoid proteinosis. *J Eur Acad Dermatol Venereol* 2002; **16**: 286–8.

Amyloid and the amyloidoses of the skin

S.M. Breathnach, pp. 59.42–59.58

Amyloidosis is a generic term, originally coined by Rudolf Virchow in 1854, which denotes extracellular deposition of a proteinaceous substance composed of one of a family of biochemically unrelated proteins, depending on the underlying condition, and which is usually associated with considerable tissue dysfunction [1–7]. A classification based on the biochemical nature of amyloid fibril proteins is shown in Tables 59.6 and 59.7. Amyloidosis now tends to be classified on the basis of characterization of the fibril proteins (of which over 20 have now been identified) rather than according to clinicopathological features. Fibrils in primary and myeloma-associated systemic amyloidosis, as well as in nodular primary localized cutaneous amyloidosis, are composed of immunoglobulin protein AL, whereas in secondary systemic amyloidosis they are composed of a non-immunoglobulin protein termed protein AA. Fibrils in other forms of primary localized cutaneous amyloidosis, and in secondary localized cutaneous amyloidosis, contain material related to cytokeratin [8].

Amyloid proteins, regardless of biochemical constitution, share certain characteristic physicochemical properties, tinctorial properties (Congophilia and green birefringence under polarized light) and a fibrillar ultrastructure. Paired, 7.5–10.0 nm, rigid, linear, non-branching, aggregated, hollow fibrils of indefinite length constitute the bulk of amyloid deposits, regardless of clinicopathological type or the tissue involved, and are arranged in a loose meshwork. Amyloid fibrils have been shown by X-ray diffraction crystallography and infrared spectroscopy to have, at least in part, a beta-pleated sheet configuration; this probably accounts for their ability to bind Congo red and for the low solubility and resistance to proteolytic digestion of amyloid.

Non-fibrillar amyloid proteins

All types of amyloid contain small amounts of a protein termed amyloid P component (AP) derived from, and identical to, serum amyloid P component (SAP), present in the blood of all normal

Table 59.6 Biochemical nature of fibril proteins in systemic amyloidosis.

Clinical type of amyloidosis	Amyloid fibril protein	Precursor substance
Primary (immunocyte dyscrasia)	AL	Monoclonal immunoglobulin light chains
Myeloma-associated	AL	Monoclonal immunoglobulin light chains
Secondary (chronic active disease)	AA	Serum amyloid A protein (SAA)
Haemodialysis-associated (periarticular, bony and renal)	β2-microglobulin	
Heredofamilial		
Predominantly nephropathic		
Familial Mediterranean fever	AA	SAA
Muckle–Wells syndrome	AA	SAA
Predominantly neuropathic		
Familial amyloid polyneuropathy	Transthyretin variant or apoliprotein A1 or gelsolin	
Non-neuropathic forms (Ostertag)	Apoliprotein A1 or lysozyme variant or fibrinogen α chain	
Predominantly cardiomyopathic	Transthyretin variant	
Cardiomyopathy with persistent atrial standstill	Unknown	
Senile systemic	Transthyretin from plasma	

Table 59.7 Biochemical nature of fibril proteins in organ-limited (localized) amyloidosis.

Nodular (skin, lung, genitourinary)	AL
Primary localized cutaneous	
Nodular	AL
Macular amyloid and lichen amyloidosus	?Altered cytokeratin
Secondary localized cutaneous amyloidosis	?Altered cytokeratin
Hereditary syndromes	
Hereditary cerebral haemorrhage with amyloidosis	
Icelandic type	Cystatin C
Dutch type	β-protein
Cerebral amyloid angiopathy and cortical plaques (Alzheimer's disease, senile dementia, Down's syndrome)	Amyloid β-protein (Abeta)
Sporadic Creutzfeldt–Jakob disease, kuru	Prion protein
Focal senile amyloidosis	
Heart atria	Atrial natriuretic peptide
Joints	Unknown
Seminal vesicles	Seminal vesicle exocrine protein
Prostate	β2-microglobulin
Ocular deposits (corneal, conjunctival)	Unknown
Endocrine amyloidosis (APUD organs, APUDomas)	
Elderly non-insulin-dependent diabetics, benign insulinomas of the pancreas, normal aged pancreas	Islet amyloid polypeptide (homology with calcitonin gene-related peptide)
Medullary carcinoma of the thyroid	Precalcitonin-related

individuals [1–3]. SAP prevents proteolysis of the amyloid fibrils of Alzheimer's disease, of AA amyloidosis and of AL amyloidosis, and may contribute to persistence of amyloid *in vivo* [9]. AP is constantly associated with the microfibrillar sheath of elastic fibres throughout the body in normal adults [10]. AP binds to isolated amyloid fibrils *in vitro* in a calcium-dependent manner, which may account for the frequent observation of amyloid deposition in the vicinity of elastic fibres [11]. Amyloid deposits also contain extracellular matrix components, including glycosaminoglycans and proteoglycans, which may be involved in the pathogenesis [12].

References

1 Lachmann HJ, Hawkins PN. Systemic amyloidosis. *Curr Opin Pharmacol* 2006; **6**: 214–20.
2 Pepys MB. Amyloidosis. *Annu Rev Med* 2006; **57**: 223–41.
3 Pepys MB. Science and serendipity. *Clin Med* 2007; **7**: 562–78.
4 Sipe JD, Cohen AS. Review: history of the amyloid fibril. *J Struct Biol* 2000; **130**: 88–98.
5 Buxbaum Bellotti V, Nuvolone M, Giorgetti S *et al.* The workings of the amyloid diseases. *Ann Med* 2007; **39**: 200–7.
6 Skinner M. AL amyloidosis: the last 30 years. *Amyloid* 2000; **7**: 13–4.
7 Westermark P, Araki S, Benson MD *et al.* Nomenclature of amyloid fibril proteins. Report from the meeting of the International Nomenclature Committee on Amyloidosis, August 8–9, 1998, Part 1. *Amyloid* 1999; **6**: 63–6.
8 Chang YT, Liu HN, Wang W *et al.* A study of cytokeratin profiles in localized cutaneous amyloids. *Arch Dermatol Res* 2004; **296**: 83–8.
9 Tennent GA, Lovat LB, Pepys MB. Serum amyloid P component prevents proteolysis of the amyloid fibrils of Alzheimer disease and systemic amyloidosis. *Proc Natl Acad Sci USA* 1995; **92**: 4299–303.
10 Breathnach SM, Melrose SM, Bhogal B *et al.* Amyloid P component is located on elastic fibre microfibrils in normal human tissue. *Nature* 1981; **293**: 652–4.
11 Sepp N, Pichler E, Breathnach SM *et al.* Amyloid elastosis: analysis of the role of amyloid P component. *J Am Acad Dermatol* 1990; **22**: 27–34.
12 Husby G, Stenstad T, Magnus JH *et al.* Interaction between circulating amyloid fibril protein precursors and extracellular tissue matrix components in the pathogenesis of systemic amyloidosis. *Clin Immunol Immunopathol* 1994; **70**: 2–9.

Staining reactions [1–3]

Special stains for amyloid include the triphenyl-methane dyes methyl and cresyl violet for the demonstration of metachromasia, the PAS method, the substantive cotton dyes Congo red and Sirius red with or without fluorescence [4] or polarized light microscopy (Fig. 59.28), and fluorescence with thiazole dyes such as thioflavine T (Fig. 59.29). Immunohistochemical staining with anti-SAP has also been advocated [5].

The staining properties depend to some extent upon the duration of fixation in formalin and tend to be far brighter on frozen fixed material. Congophilia is the most specific [6]. Unfortunately, methyl violet and Congo red staining may be equivocal and inadequate for detecting small deposits of amyloid; false-positive results occur in colloid milium (which may mimic nodular amyloidosis histopathologically [7]) and in lipoid proteinosis. False-positive staining with thioflavine T is seen with stromal hyaline deposits, collagen fibres and colloid bodies in lichen planus; anti-

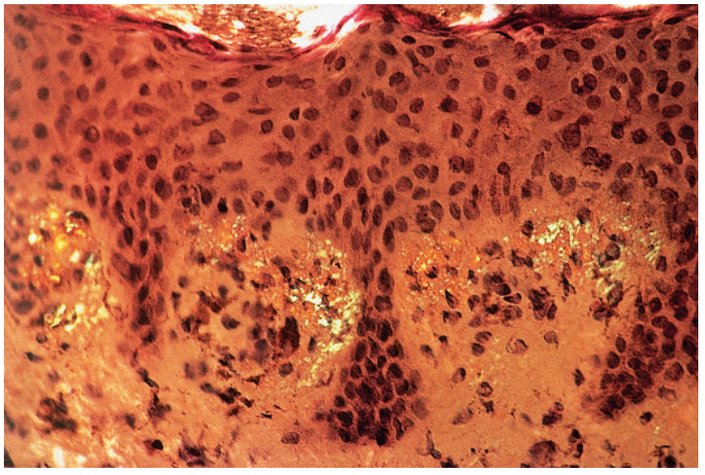


Fig. 59.28 Lichen amyloidosus. Alkaline Congo red, × 100. View under polarized light to show specific green fluorescence in amyloid deposits in papillary dermis.

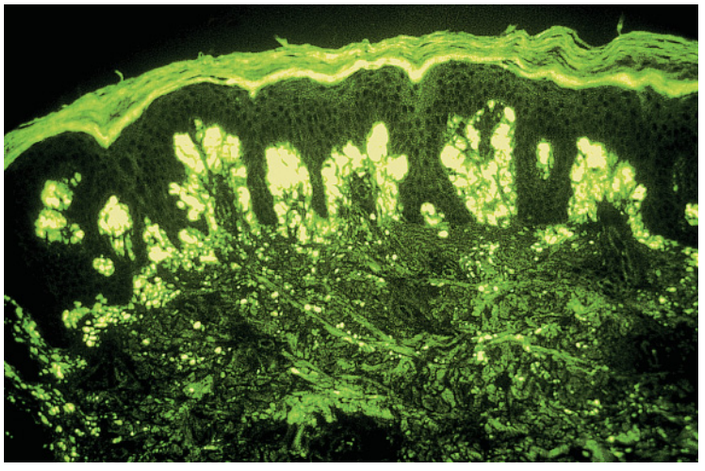


Fig. 59.29 Cutaneous amyloidosis. Thioflavine T, × 50. Viewed under fluorescence microscopy to show bright-yellow staining of amyloid deposits.

SAP also stains colloid bodies and elastotic elastic fibres. Use of a battery of stains is therefore recommended. In some cases it may be necessary to resort to electron microscopy to look for the characteristic ultrastructure of the fibrils. *In vivo* scintigraphy techniques using ^{123}I-labelled human SAP component can be used to delineate amyloid deposits in systemic amyloidosis and to monitor the effects of therapy [8].

AL type amyloid, unlike AA type amyloid, retains its affinity for Congo red and its typical polarization characteristics after exposure to potassium permanganate [9]. Immunohistochemical staining with specific antisera [10,11], or either amino acid sequencing or mass spectroscopy of material extracted from fibrillar deposits (using sections of formalin-fixed, paraffin-embedded biopsy specimens) [12], are used to differentiate between the various types of fibril protein in amyloid deposits. Immunohistochemical staining with antikeratin antibody EAB-903 using formalin-fixed tissue appears to be a useful method in the differential diagnosis of primary localized cutaneous amyloidosis [13].

References

1 Black MM. Primary localized amyloidosis of the skin: clinical variants, histochemistry and ultrastructure. In: Wegelius O, Pasternack A, eds. *Amyloidosis*. London: Academic Press, 1976: 479–513.
2 Wong CK, Breathnach SM, eds. Cutaneous amyloidosis. *Clin Dermatol* 1990; **8** (2).
3 Elghetany MT, Saleem A. Methods for staining amyloid in tissues: a review. *Stain Technol* 1988; **63**: 201–12.
4 Linke RP. Highly sensitive diagnosis of amyloid and various amyloid syndromes using Congo red fluorescence. *Virchows Arch* 2000; **436**: 439–48.
5 Breathnach SM, Bhogal B, Dyck RF *et al.* Immunohistochemical demonstration of amyloid P component in skin of normal subjects and patients with cutaneous amyloidosis. *Br J Dermatol* 1981; **105**: 115–24.
6 Cheung ST, Maheshwari MB, Tan CY. A comparative study of two Congo red stains for the detection of primary cutaneous amyloidosis. *J Am Acad Dermatol* 2006; **55**: 363–4.
7 Desai AM, Pielop JA, Smith-Zagone MJ, Hsu S. Colloid milium: a histopathologic mimicker of nodular amyloidosis. *Arch Dermatol* 2006; **142**: 784–5.
8 Hawkins PN, Richardson S, MacSweeney JE *et al.* Scintigraphic quantification and serial monitoring of human visceral amyloid deposits provide evidence for turnover and regression. *QJM* 1993; **86**: 365–74.
9 Wright JR, Calkins E, Humphrey RL. Potassium permanganate reaction in amyloidosis: a histologic method to assist in differentiating forms of this disease. *Lab Invest* 1977; **36**: 274–81.
10 Fujihara S, Balow JE, Costa JC, Glenner GG. Identification and classification of amyloid in formalin-fixed, paraffin-embedded tissue sections by the unlabelled immunoperoxidase method. *Lab Invest* 1980; **43**: 358–65.
11 Linke RP, Gartner HV, Michels H. High-sensitivity diagnosis of AA amyloidosis using Congo red and immunohistochemistry detects missed amyloid deposits. *J Histochem Cytochem* 1995; **43**: 863–9.
12 Murphy CL, Eulitz M, Hrncic R *et al.* Chemical typing of amyloid protein contained in formalin-fixed paraffin-embedded biopsy specimens. *Am J Clin Pathol* 2001; **116**: 135–42.
13 Yoneda K, Watnabe H, Yanagihara M *et al.* Immunohistochemical staining properties of amyloids with anti-keratin antibodies using formalin-fixed, paraffin-embedded sections. *J Cutan Pathol* 1989; **16**: 133–6.

Primary localized cutaneous amyloidosis

In primary localized cutaneous amyloidosis (PLCA) there is deposition of amyloid in previously apparently normal skin, with no evidence of deposits occurring in internal organs. Various subtypes of PLCA are recognized, including the more common macular and papular (lichen amyloidosus) types and the rare nodular (tumefactive) form. Both macular and papular lesions can occur in the same patient.

Aetiology. Nodular PLCA may be regarded as a form of extramedullary plasmacytoma, since the fibrils are of immunoglobulin AL type, and are thought to arise as a result of local aberrant light chain material production by clonally expanded plasma cells [1,2]. Modified β_2-microglobulin has also been reported to be a component of amyloid fibrils of primary localized cutaneous nodular amyloidosis [3].

The aetiology of other forms of PLCA remains unknown. Lichen amyloidosus is commoner among the Chinese [4]. Macular amyloidosis is rare in Europe and North America, but is much more common in Central and South America, the Middle East and Asia, suggesting the importance of genetic factors [4–9]. The occurrence of rare familial cases reinforces this view [9–16]. Familial primary localized cutaneous amyloidosis is an autosomal-dominant disorder mapped to 5p13.1-q11.2. Mutations in the OSMR gene, encoding oncostatin M-specific receptor beta (OSMRβ), have been reported [17]. OSMRβ is a component of the oncostatin M (OSM)

type II receptor and the IL-31 receptor; OSM and IL-31 signalling have been implicated in keratinocyte proliferation, differentiation, apoptosis and inflammation. Primary cutaneous amyloidosis has been described in identical twins, who also had numerous congenital abnormalities [18]. A review of the current literature has revealed no instance of systemic deposition of amyloid.

Fibrils in lichen amyloidosus and macular amyloidosis do not bind antibodies to protein AA or prealbumin [19], and although immunoglobulins, κ and λ light chains, and complement are frequently observed in deposits of macular and papular PLCA [20], they are not thought to be integral constituents of the fibrils, since they are readily eluted. The close proximity of the amyloid deposits to the lower epidermis in macular amyloidosis and in lichen amyloidosus suggests that the epidermis plays a role in its pathogenesis [21,22]. It has been proposed that focal epidermal damage and filamentous degeneration of keratinocytes is followed by apoptosis and conversion of filamentous masses (colloid bodies) into amyloid material in the papillary dermis [23,24]. There may be a contribution from the dermal–epidermal junction [25]. In support of this theory is the fact that dermal amyloid deposits in these forms of PLCA react immunohistochemically with antihuman cytokeratin antibody [26–28]. It is not clear why colloid (keratin) bodies produced in other dermatoses such as lichen planus are not transformed into amyloid. It has been proposed that in lichen amyloidosus specific immunological tolerance to the presence of colloid bodies in the papillary dermis favours their transformation into amyloid by macrophages or fibroblasts, whereas in lichen planus a brisk inflammatory response ensures their removal [29].

PLCA is associated with chronic friction, perhaps causing epidermal damage, as in the so-called friction amyloidosis seen especially in the Japanese as a result of rubbing the skin vigorously with a nylon towel or brush, bath sponge, towel, plant sticks or leaves [30–33], and in nodular prurigo and lichen simplex chronicus [34]. The association of macular amyloidosis with notalgia paraesthetica supports the role of chronic pruritus in development of macular amyloidosis [35,36]. In the dyschromic forms of primary cutaneous amyloidosis, hypersensitivity to UVB with a possible DNA-repair defect may be significant [37]. An association of maculopapular amyloidosis with chronic active Epstein–Barr viral infection was reported [38].

References

1 Grunewald K, Sepp N, Weyrar K *et al.* Gene rearrangement studies in the diagnosis of primary systemic and nodular primary localized cutaneous amyloidosis. *J Invest Dermatol* 1991; **97**: 693–6.

2 Hagari Y, Mihara M, Konohana I *et al.* Nodular localized cutaneous amyloidosis: further demonstration of monoclonality of infiltrating plasma cells in four additional Japanese patients. *Br J Dermatol* 1998; **138**: 652–4.

3 Fujimoto N, Yajima M, Ohnishi Y *et al.* Advanced glycation end product-modified beta2-microglobulin is a component of amyloid fibrils of primary localized cutaneous nodular amyloidosis. *J Invest Dermatol* 2002; **118**: 479–84.

4 Wong CK. Cutaneous amyloidoses. *Int J Dermatol* 1987; **26**: 273–7.

5 Black MM. Primary localized amyloidosis of the skin: clinical variants, histochemistry and ultrastructure. In: Wegelius O, Pasternack A, eds. *Amyloidosis*. London: Academic Press, 1976: 479–513.

6 Breathnach SM. Amyloid and amyloidosis. *J Am Acad Dermatol* 1988; **18**: 1–16.

7 Wong CK, Breathnach SM, eds. Cutaneous amyloidosis. *Clin Dermatol* 1990; **8** (2).

8 Kurban AK, Malak JA, Afifi AK *et al.* Primary localized macular cutaneous amyloidosis: histochemistry and electron microscopy. *Br J Dermatol* 1971; **85**: 52–60.

9 Shanon J, Sagher F. Interscapular cutaneous amyloidosis. *Arch Dermatol* 1970; **102**: 195–8.

10 Rajagopalan K, Tay CH. Familial lichen amyloidosis. Report of 19 cases in four generations of a Chinese family in Malaysia. *Br J Dermatol* 1972; **87**: 123–9.

11 De Pietro WP. Primary familial cutaneous amyloidosis. A study of HLA antigens in a Puerto Rican family. *Arch Dermatol* 1981; **117**: 639–43.

12 Vasily DB, Bhatia SG, Uhlin SR. Familial primary cutaneous amyloidosis: clinical, genetic and immunofluorescent studies. *Arch Dermatol* 1978; **114**: 1173–6.

13 Newton JA, Jagjivan A, Bhogal B *et al.* Familial primary cutaneous amyloidosis. *Br J Dermatol* 1985; **112**: 201–8.

14 Partington MW, Marriott PJ, Prentice RSA *et al.* Familial cutaneous amyloidosis with systemic manifestations in males. *Am J Med Genet* 1991; **10**: 65–75.

15 Gallardo F, Juan A, Condom E *et al.* Familial primary localized amyloidosis L. *Br J Dermatol* 1999; **140**: 544–6.

16 Hartshorne ST. Familial primary cutaneous amyloidosis in a South African family. *Clin Exp Dermatol* 1999; **24**: 438–42.

17 Arita K, South AP, Hans-Filho G *et al.* Oncostatin M receptor-beta mutations underlie familial primary localized cutaneous amyloidosis. *Am J Hum Genet* 2008; **82**: 73–80.

18 Le Boit PH, Greene I. Primary cutaneous amyloidosis: identically distributed lesions in identical twins. *Pediatr Dermatol* 1986; **3**: 244–6.

19 Breathnach SM, Bhogal B, de Beer FC *et al.* Primary localised cutaneous amyloidosis: dermal amyloid deposits do not bind antibodies to amyloid A protein, prealbumin or fibronectin. *Br J Dermatol* 1982; **107**: 453–9.

20 Habermann MC, Montenegro MR. Primary cutaneous amyloidosis; clinical, laboratorial and histopathological study of 25 cases: identification of gammaglobulins and C3 and in the lesions by immunofluorescence. *Dermatologica* 1980; **160**: 240–8.

21 Black MM. The role of the epidermis in the histopathogenesis of lichen amyloidosus: histochemical correlations. *Br J Dermatol* 1971; **85**: 524–30.

22 Black MM, Wilson Jones E. Macular amyloidosis. *Br J Dermatol* 1971; **84**: 199–209.

23 Kumakiri M, Hashimoto K. Histogenesis of primary localized cutaneous amyloidosis: sequential change of epidermal keratinocytes to amyloid via filamentous degeneration. *J Invest Dermatol* 1979; **73**: 150–62.

24 Chang YT, Wong CK, Chow KC *et al.* Apoptosis in primary cutaneous amyloidosis. *Br J Dermatol* 1999; **140**: 210–5.

25 Horiguchi Y, Fine JD, Leigh IM *et al.* Lamina densa malformation involved in histogenesis of primary localized cutaneous amyloidosis. *J Invest Dermatol* 1992; **99**: 12–8.

26 Kobayashi H, Hashimoto K. Amyloidogenesis in organ-limited cutaneous amyloidosis: an antigenic identity between epidermal keratin and skin amyloid. *J Invest Dermatol* 1983; **80**: 66–72.

27 Huilgol SC, Ramnarain N, Carrington P *et al.* Cytokeratins in primary cutaneous amyloidosis. *Australas J Dermatol* 1998; **39**: 81–5.

28 Chang YT, Liu HN, Wang W *et al.* A study of cytokeratin profiles in localized cutaneous amyloids. *Arch Dermatol Res* 2004; **296**: 83–8.

29 Black MM. The role of the epidermis in the histopathogenesis of lichen amyloidosus: histochemical correlations. *Br J Dermatol* 1971; **85**: 524–30.

30 Wong CK, Lin CS. Friction amyloidosis. *Int J Dermatol* 1988; **27**: 302–7.

31 Sumitra S, Yesudian D. Friction amyloidosis—a variant or an etiologic factor in amyloidosis cutis? *Int J Dermatol* 1993; **32**: 422–3.

32 Hashimoto K, Ito K, Kumakiri M *et al.* Nylon brush macular amyloidosis. *Arch Dermatol* 1987; **123**: 633–7.

33 Venkataram MN, Bhushnurmath SR, Muirhead DE *et al.* Frictional amyloidosis: a study of 10 cases. *Australas J Dermatol* 2001; **42**: 176–9.

34 Weyers W. Lichen amyloidosus—Krankheitsentität oder Kratzeffekt. *Hautarzt* 1995; **46**: 165–72.

35 Goulden V, Highet AS, Sharry HK. Notalgia paraesthetica—report of an association with macular amyloidosis. *Clin Exp Dermatol* 1994; **19**: 346–9.

36 Pena-Penabad MC, Garcia-Silva J, Armijo M. Notalgia paraesthetica and macular amyloidosis: cause-effect relationship? *Clin Exp Dermatol* 1995; **20**: 279.

37 Moriwaki S, Nishigori C, Horiguchi Y *et al.* Amyloidosis cutis dyschromica: DNA repair reduction in the cellular response to UV light. *Arch Dermatol* 1992; **128**: 966–70.

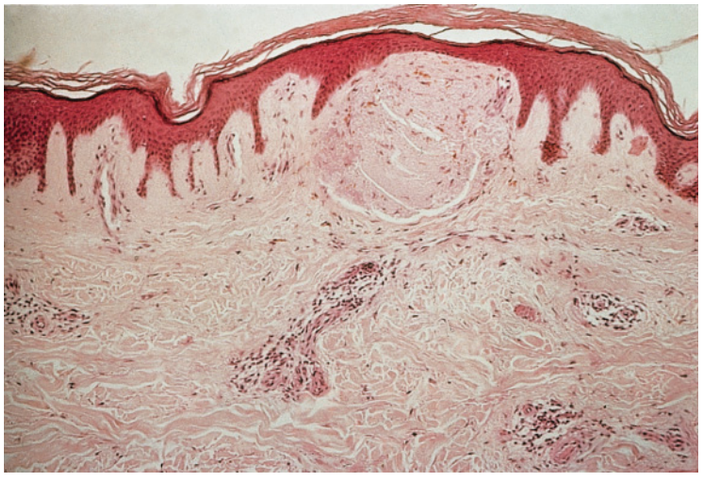


Fig. 59.30 Lichen amyloidosis. H&E, × 4. Amorphous globular hyaline amyloid deposition widening the rete ridges.

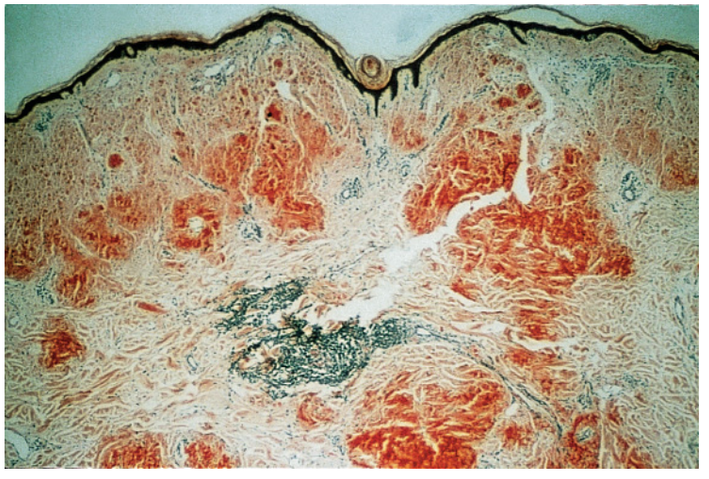


Fig. 59.31 Nodular or tumefactive cutaneous amyloidosis. Congo red, × 4. Amorphous masses of amyloid are present in the entire dermis with focal collections of plasma cells.

38 Drago F, Ranieri E, Pastorino A *et al*. Epstein–Barr virus related primary cutaneous amyloidosis and successful treatment with acyclovir and interferon-α. *Br J Dermatol* 1996; **134**: 170–4.

Pathology. In papular and macular forms of PLCA, the amyloid deposits are confined to the papillary dermis, and do not involve blood vessels or adnexal structures [1,2]. In macular amyloidosis, the deposits of amyloid are composed of small, multifaceted, amorphous globules, similar in size to the hyaline bodies found in lichen planus. They may be so sparse that more than one biopsy is necessary to confirm the diagnosis, and are easily missed without the use of special stains. The epidermis is usually of normal thickness but pigmentary incontinence with melanophages is a notable feature. In papular lichen amyloidosus, focal deposits of amyloid are often large enough to expand the dermal papillae and displace the elongated rete ridges laterally (Fig. 59.30). The overlying epidermis shows considerable irregular acanthosis and hyperkeratosis. The amyloid deposits are in close apposition to the basal layer of the epidermis and contain a few melanophages. Near the amyloid deposits, there is usually a sparse lymphohistiocytic perivascular infiltrate.

By contrast, in the nodular or tumefactive forms of PLCA the dermis, subcutis and blood vessel walls are diffusely infiltrated with amyloid as seen in primary systemic amyloidosis (Fig. 59.31). However, there is usually a perivascular infiltrate of plasma cells [3–5].

Table 59.8 Clinical classification of primary localized amyloidosis.

Papular or lichen amyloidosus
Macular amyloidosus
Maculopapular amyloidosis
Nodular or tumefactive
Familial (dyschromic)

Clinical features [1–7]. Several distinctive clinical forms of PLCA have been described (Table 59.8). Because macular amyloid and lichen amyloidosus may coexist in an affected individual (biphasic amyloidosis), they are regarded as variants of a single pathological process [6].

The papular form (lichen amyloidosus) is perhaps the best known. It usually presents as a pruritic eruption of multiple, discrete, hyperkeratotic papules, scaly and often hyperpigmented, distributed principally on the shins (Figs 59.32 & 59.33). The calves, ankles, dorsa of the feet and thighs, and the extensor aspects of the arms and abdominal or chest wall, may also be involved. A rare bullous variant of lichen amyloidosus has been documented [8]. A 'thermosensitive' form sparing skin overlying the superficial limb veins has been described [9]. Papules may coalesce to form thickened plaques, closely simulating hypertrophic lichen planus or lichen simplex chronicus. The condition usually persists for many years with localized pruritus as the prominent symptom.

The predominant sign in macular amyloidosis is clusters of small, pigmented macules, about 2 or 3 mm in diameter, which may coalesce to produce macular hyperpigmented areas. A reticulate or 'rippled' pattern of pigmentation is a characteristic diagnostic feature in many cases (Figs 59.34 & 59.35). The lesions tend to be associated with mild to moderate pruritus, but pruritus may be absent in 18% of cases. The lesions may be confined to the interscapular area (Fig. 59.34), but more commonly are extensively distributed over the back or chest [10,11]. Macular amyloidosis on the back has been reported to follow prolonged chronic friction

References

1 Brownstein MH, Helwig EB. The cutaneous amyloidoses. I. Localized forms. *Arch Dermatol* 1970; **102**: 8–19.
2 Black MM. Primary localized amyloidosis of the skin: clinical variants, histochemistry and ultrastructure. In: Wegelius O, Pasternack A, eds. *Amyloidosis*. London: Academic Press, 1976: 479–513.
3 Westermark P. Amyloidosis of the skin: a comparison between localized and systemic amyloidosis. *Acta Derm Venereol (Stockh)* 1979; **59**: 341–5.
4 Masuda C, Moturi S, Nakajima H. Histopathological and immunohistochemical study of amyloidosis cutis nodularis atrophicus: comparison with systemic amyloidosis. *Br J Dermatol* 1988; **119**: 33–43.
5 Nguyen TU, Oghalai JS, McGregor DK *et al*. Subcutaneous nodular amyloidosis: a case report and review of the literature. *Hum Pathol* 2001; **32**: 346–8.



Fig. 59.32 Lichen amyloidosus (papular form). Typical appearance of pigmented pruritic papular eruption on shin in an Asian male. (Courtesy of St John's Institute of Dermatology, UK.)



Fig. 59.33 Lichen amyloidosus (papular form). Close-up of small hyperkeratotic papules on shin. (Courtesy of St John's Institute of Dermatology, London, UK.)



Fig. 59.34 Macular amyloidosis. Confluent pigmentation in an interscapular area in an Asian male. (Courtesy of St John's Institute of Dermatology, London, UK.)



Fig. 59.35 Macular amyloidosis. Close-up to show characteristic reticular or 'rippled' pigmentation over deltoid region. (Courtesy of St John's Institute of Dermatology, London, UK.)

(see above). Lesions may also occur on the extensor aspect of extremities, and occasionally on the chest and buttocks. Hypopigmented areas may produce a 'poikilodermatous' appearance. The condition usually presents in early adult life and persists for many years; both sexes are equally affected. Macular amyloidosis can be misdiagnosed as post-inflammatory pigmentation, resolving lichen planus or neurodermatitis, or as the reticulate hyperpigmentation of the neck ('dirty neck') that has been described in association with atopic eczema [12,13]. Amyloid-like material has been demonstrated by electron microscopy, but not at light microscope level, in the atopic dirty neck [14].

Unusual variants of PLCA include: macular forms with widespread diffuse hyperpigmentation without papules but with poikiloderma-like facial involvement [15]; causing periocular hyperpigmentation [16]; simulating naevoid hyperpigmentation [17]; following Blaschko's lines [18]; resembling incontinentia pigmenti [19,20]; and a poikiloderma-like form [21–23]. Amyloidosis

cutis dyschromica is assumed to be a congenital disorder with hypersensitivity to UVB radiation, with possible DNA repair defects; hyperpigmented and hypopigmented xerotic lesions with deposits of amyloid in the papillary dermis occur in sun-exposed skin [24,25]. Primary cutaneous amyloidosis of the auricular concha, in which small papules are grouped on the concha of the ear, is also believed to be a variant of PLCA, and may coexist with lichen amyloidosus [26,27].

Associations of PLCA in a few kindreds with pachyonychia congenita [28], dyskeratosis congenita [29], familial palmar–plantar keratoderma [30] and multiple endocrine neoplasia type 2a (caused by germline mutations in the RET proto-oncogene) with multiple cutaneous neuromas and medullary thyroid carcinoma, have been described; in the latter, macular lichen amyloidosus is confined to the interscapular region [31–33]. Cases of PLCA have also been described in association with a variety of connective tissue disorders: systemic lupus erythematosus [34], systemic sclerosis [35], dermatomyositis [36], primary biliary cirrhosis and scleroderma [3,37], and Raynaud's phenomenon with livedo reticularis [38]. An association with angiolymphoid hyperplasia and Kimura's disease has been reported [39,40].

Anosacral cutaneous amyloidosis is a rare syndrome described in Japanese and Chinese males, in which pigmented macules and glossy hyperkeratotic lesions radiate out from the anus [41]. Fifty per cent of patients present below the age of 60 years, and the disease may be misdiagnosed as lichen simplex chronicus, post-inflammatory hyperpigmentation or tinea cruris.

The nodular or tumefactive form is a rare variant of PLCA (Fig. 59.36). Most reported patients have been females. Single or more commonly multiple nodules or plaques, indistinguishable from those associated with plasma cell dyscrasia-related systemic amyloidosis, may occur on the face, trunk, limbs, genitalia or palate [1,3,5,42–55]. They vary in size from a few millimetres to several centimetres. The overlying skin is often atrophic, and there may be petechial haemorrhages within the nodules. Some cases are associated with diabetes mellitus and Sjögren's syndrome [45,46].



Fig. 59.36 Nodular or tumefactive cutaneous amyloidosis. Close-up of tumour on side of nose. (Courtesy of St John's Institute of Dermatology, London, UK.)

The condition, as with localized nodular amyloidosis in other organs [56], may follow a prolonged benign course over many years [47,48]; however, some patients later develop paraproteinaemia and overt systemic amyloidosis [1,3]. In a series of 16 patients, only one progressed to systemic amyloidosis over a follow-up period ranging from 8 months to 24 years (mean 10 years), and this patient had a serum monoclonal lambda protein initially [57]. Rare familial cases of nodular cutaneous amyloidosis have been reported [58].

References

1 Brownstein MH, Helwig EB. The cutaneous amyloidoses. I. Localized forms. *Arch Dermatol* 1970; **102**: 8–19.
2 Black MM, Wilson Jones E. Macular amyloidosis. *Br J Dermatol* 1971; **84**: 199–209.
3 Black MM. Primary localized amyloidosis of the skin: clinical variants, histochemistry and ultrastructure. In: Wegelius O, Pasternack A, eds. *Amyloidosis*. London: Academic Press, 1976: 479–513.
4 Wong C-K. Lichen amyloidosus: a relatively common skin disorder in Taiwan. *Arch Dermatol* 1974; **110**: 438–40.
5 Breathnach SM. Amyloid and amyloidosis. *J Am Acad Dermatol* 1988; **18**: 1–16.
6 Brownstein MH, Hashimoto K, Greenwald G. Biphasic amyloidosis: link between macular and lichenoid forms. *Br J Dermatol* 1973; **88**: 25–9.
7 Garg A, Mahalingam M, Alavian C. Pruritic patches on the back and papules on the legs. Primary localized cutaneous amyloidosis (PLCA) (cutaneous lichen amyloidosis and macular amyloidosis). *Arch Dermatol* 2007; **143**: 255–60.
8 Kuroda K, Mizoguchi M. Lichen amyloidosus with subepidermal blister formation. *Eur J Dermatol* 2004; **14**: 262–3.
9 Parsi K, Kossard S. Thermosensitive lichen amyloidosis. *Int J Dermatol* 2004; **43**: 925–8.
10 Kurban AK, Malak JA, Afifi AK *et al.* Primary localized macular cutaneous amyloidosis: histochemistry and electron microscopy. *Br J Dermatol* 1971; **85**: 52–60.
11 Shanon J, Sagher F. Interscapular cutaneous amyloidosis. *Arch Dermatol* 1970; **102**: 195–8.
12 Colver GB, Mortimer PS, Millard PR *et al.* The 'dirty neck'—reticulate pigmentation in atopics. *Clin Exp Dermatol* 1987; **12**: 1–4.
13 Hughes BR, Cunliffe WJ. Rippled hyperpigmentation resembling macular amyloidosis—a feature of atopic eczema. *Clin Exp Dermatol* 1990; **15**: 380–1.
14 Humphreys F, Spencer J, McLaren K, Tidman M. An histological and ultrastructural study of the 'dirty neck' appearance in atopic eczema. *Clin Exp Dermatol* 1996; **21**: 17–9.
15 Wang CK, Lee JY. Macular amyloidosis with widespread diffuse pigmentation. *Br J Dermatol* 1996; **135**: 135–8.
16 Van den Berg WH, Starink TM. Macular amyloidosis presenting as periocular hyperpigmentation. *Clin Exp Dermatol* 1983; **8**: 195–7.
17 Black MM, Maibach HI. Macular amyloidosis simulating naevoid hyperpigmentation. *Br J Dermatol* 1974; **90**: 461–4.
18 Bourke JF, Berth-Jones J, Burns DA. Diffuse primary cutaneous amyloidosis. *Br J Dermatol* 1992; **127**: 641–4.
19 An HT, Han KH, Cho KH. Macular amyloidosis with an incontinentia pigmenti-like pattern. *Br J Dermatol* 2000; **142**: 371–3.
20 Wu JJ, Su YN, Hsiao CH *et al.* Macular amyloidosis presenting in an incontinentia pigmenti-like pattern with subepidermal blister formation. *J Eur Acad Dermatol Venereol* 2008; **22**: 635–7.
21 Ho MH, Chong LY. Poikiloderma-like cutaneous amyloidosis in an ethnic Chinese girl. *J Dermatol* 1998; **25**: 730–4.
22 Serna-Perez MJ, Vazquez-Doval FJ, Idoate M *et al.* Extensive macular amyloidosis associated with poikiloderma. *Int J Dermatol* 1992; **31**: 277–8.
23 Pardo Arranz L, Escalonilla García-Patos P, Román Curto C *et al.* Familial poikylodermic cutaneous amyloidosis. *Eur J Dermatol* 2008; **18**: 289–91.
24 Moriwaki S, Nishigori C, Horiguchi Y *et al.* Amyloidosis cutis dyschromica: DNA repair reduction in the cellular response to UV light. *Arch Dermatol* 1992; **128**: 966–70.
25 Ozcan A, Senol M, Aydin NE, Karaca S. Amyloidosis cutis dyschromica: a case treated with acitretin. *J Dermatol* 2005; **32**: 474–7.

26 Errol C. Lichen amyloidosis of the auricular concha: report of two cases and review of the literature. *Dermatol Online J* 2006; **12**: 1.
27 Shimauchi T, Shin JH, Tokura Y. Primary cutaneous amyloidosis of the auricular concha: case report and review of published work. *J Dermatol* 2006; **33**: 128–31.
28 Tidman MJ, Wells RS, MacDonald DM. Pachyonychia congenita with cutaneous amyloidosis and hyperpigmentation—a distinct variant. *J Am Acad Dermatol* 1987; **16**: 935–40.
29 Llistosella E, Moreno A, de Moragas JM. Dyskeratosis congenita with macular amyloid deposits. *Arch Dermatol* 1984; **120**: 1381–2.
30 Graells J, Marcoval J, Moreno A *et al.* Cutaneous amyloid deposits in familial palmo-plantar keratoderma. *J Eur Acad Dermatol Venereol* 1996; **6**: 32–4.
31 Hofstra RM, Sijmons RH, Stelwagen T *et al.* RET mutation screening in familial cutaneous lichen amyloidosis and in skin amyloidosis associated with multiple endocrine neoplasia. *J Invest Dermatol* 1996; **107**: 215–8.
32 Seri M, Celli I, Betsos N *et al.* A Cys634Gly substitution of the RET proto-oncogene in a family with recurrence of multiple endocrine neoplasia type 2A and cutaneous lichen amyloidosis. *Clin Genet* 1997; **51**: 86–90.
33 Baykal C, Buyukbabani N, Boztepe H *et al.* Multiple cutaneous neuromas and macular amyloidosis associated with medullary thyroid carcinoma. *J Am Acad Dermatol* 2007; **56** (2 Suppl.): S33–7.
34 Danielsen L, Christensen HE, Wanstrup J *et al.* Amyloidosis of the skin. In: Wegelius O, Pasternack A, eds. *Amyloidosis*. London: Academic Press, 1976: 471–7.
35 Ogiyama Y, Hayashi Y, Kou C *et al.* Cutaneous amyloidosis in patients with progressive systemic sclerosis. *Cutis* 1996; **57**: 28–32.
36 Orihara T, Yanase S, Furuya T. A case of sclerodermatomyositis with cutaneous amyloidosis. *Br J Dermatol* 1985; **112**: 213–9.
37 Fujiwara K, Kono T, Ishii M *et al.* Primary localized cutaneous amyloidosis associated with autoimmune cholangitis. *Int J Dermatol* 2000; **39**: 768–71.
38 Naldi L, Marchesi L, Locati F *et al.* Unusual manifestations of primary cutaneous amyloidosis in association with Raynaud's phenomenon and livedo reticularis. *Clin Exp Dermatol* 1992; **17**: 117–20.
39 Shankar S, Russell-Jones R. Co-existence of lichen amyloidosus and angiolymphoid hyperplasia with eosinophilia. *Clin Exp Dermatol* 2004; **29**: 363–5.
40 Teraki Y, Katsuta M, Shiohara T. Lichen amyloidosus associated with Kimura's disease: successful treatment with cyclosporine. *Dermatology* 2002; **204**: 133–5.
41 Wang WJ, Huang CY, Chang YT *et al.* Anosacral cutaneous amyloidosis: a study of 10 Chinese cases. *Br J Dermatol* 2000; **143**: 1266–9.
42 Northcutt AD, Vanover MJ. Nodular cutaneous amyloidosis involving the vulva. *Arch Dermatol* 1985; **121**: 518–21.
43 Kitajima Y, Seno J, Aoki S *et al.* Nodular primary cutaneous amyloidosis. *Arch Dermatol* 1986; **122**: 1425–30.
44 Truhan AP, Garden JM, Roenigk HH. Nodular primary localized cutaneous amyloidosis: immunohistochemical evaluation and treatment with the carbon dioxide laser. *J Am Acad Dermatol* 1986; **14**: 1058–62.
45 Cheng-Chung A, Lin CS, Wong CK. Nodular amyloidosis. *Clin Exp Dermatol* 1988; **13**: 20–3.
46 Srivastava M. Primary cutaneous nodular amyloidosis in a patient with Sjögren's syndrome. *J Drugs Dermatol* 2006; **5**: 279–80.
47 Woollons A, Black MM. Nodular localized primary cutaneous amyloidosis: a long-term follow-up study. *Br J Dermatol* 2001; **145**: 105–9.
48 Kalajian AH, Waldman M, Knable AL. Nodular primary localized cutaneous amyloidosis after trauma: a case report and discussion of the rate of progression to systemic amyloidosis. *J Am Acad Dermatol* 2007; **57** (2 Suppl.): S26–9.
49 Kakani RS, Goldstein AE, Meisher I *et al.* Nodular amyloidosis: case report and literature review. *J Cutan Med Surg* 2001; **5**: 101–4.
50 Nguyen TU, Oghalai JS, McGregor DK *et al.* Subcutaneous nodular amyloidosis: a case report and review of the literature. *Hum Pathol* 2001; **32**: 346–8.
51 Yu LL, Heenan PJ, Randell P. Nodular amyloidosis of the lip mimicking an infiltrating neoplasm. *Australas J Dermatol* 1997; **38**: 91–2.
52 Evers M, Baron E, Zaim MT, Han A. Papules and plaques on the nose. Nodular localized primary cutaneous amyloidosis. *Arch Dermatol* 2007; **143**: 535–40.
53 Love WE, Miedler JD, Smith MK *et al.* The spectrum of primary cutaneous nodular amyloidosis: two illustrative cases. *J Am Acad Dermatol* 2008; **58** (2 Suppl.): S33–5.
54 Borrowman TA, Lutz ME, Walsh JS. Cutaneous nodular amyloidosis masquerading as a foot callus. *J Am Acad Dermatol* 2003; **49**: 307–10.
55 Henley E, Houghton N, Bucknall R *et al.* Localized amyloidosis of the palate. *Clin Exp Dermatol* 2008; **33**: 100–1.
56 Biewend ML, Menke DM, Calamia KT. The spectrum of localized amyloidosis: a case series of 20 patients and review of the literature. *Amyloid* 2006; **13**: 135–42.
57 Moon AO, Calamia KT, Walsh JS. Nodular amyloidosis: review and long-term follow-up of 16 cases. *Arch Dermatol* 2003; **139**: 1157–9.
58 Hashimoto H, Itami S, Kurata S *et al.* Primary localized amyloidosis in one family. *Int J Dermatol* 1991; **30**: 632–4.

Treatment. In general, the treatment of PLCA is disappointing. Milder cases can be helped by hydrocolloid dressings [1] or by using potent topical corticosteroids with or without occlusive dressings, but usually in the short term only. Calcipotriol or phototherapy are similarly of limited use [2,3]. There have been reports of response to topical DMSO therapy in some [4–7] but not all [8] cases. Acitretin therapy has been beneficial in some but not all patients, either alone [9–11] or in combination with bath-PUVA photochemotherapy [12]; the condition relapses after therapy is stopped. A trial of long-term cyclophosphamide 50 mg daily in lichen amyloidosus found that itching was markedly decreased within 4 months [13]. Dexamethasone cyclophosphamide pulse therapy stopped itching after five sessions and lesions cleared after nine sessions with no relapse during 30 months of follow-up [14]. Ciclosporin given to treat atopic eczema coincidentally improved lichen amyloidosus [15]. Dermabrasion may have a long-term beneficial effect on papular lichen amyloidosus of the shins [16]. Pulsed dye laser therapy has been used [17].

Nodular PLCA shows a good response to excision and grafting [18], shave removal [19], curettage and cautery [20], cryotherapy, dermabrasion [21] or the carbon dioxide or pulsed dye laser [22–24], but subsequent recurrence is likely.

References

1 Hallel-Halevy D, Finkelstein E, Grunwald MH, Halevy S. Lichen amyloidosus treated by hydrocolloid dressings. *J Eur Acad Dermatol Venereol* 2004; **18**: 691–2.
2 Khoo BP, Tay YK, Goh CL. Calcipotriol ointment vs. betamethasone 17-valerate ointment in the treatment of lichen amyloidosis. *Int J Dermatol* 1999; **38**: 539–41.
3 Jin AG, Por A, Wee LK *et al.* Comparative study of phototherapy (UVB) vs. photochemotherapy (PUVA) vs. topical steroids in the treatment of primary cutaneous lichen amyloidosis. *Photodermatol Photoimmunol Photomed* 2001; **17**: 42–3.
4 Ollague W. Primary cutaneous amyloidosis. *Int J Dermatol* 1987; **26**: 135.
5 Monfrecola G, Iandoli R, Bruno G, Martellotta D. Lichen amyloidosus: a new therapeutic approach. *Acta Derm Venereol (Stockh)* 1985; **65**: 453–5.
6 Pravata G, Pinto G, Bosco M *et al.* Unusual localization of lichen amyloidosus. Topical treatment with dimethylsulfoxide. *Acta Derm Venereol (Stockh)* 1989; **69**: 259–60.
7 Ozkaya-Bayazit E, Kavak A, Gungor H *et al.* Intermittent use of topical dimethyl sulfoxide in macular and papular amyloidosis. *Int J Dermatol* 1998; **37**: 949–54.
8 Lim KB, Tan SH, Tan KT. Lack of effect of dimethyl sulphoxide (DMSO) on amyloid deposits in lichen amyloidosus. *Br J Dermatol* 1988; **119**: 409–10.
9 Reider N, Sepp N, Fritsch P. Remission of lichen amyloidosus after treatment with acitretin. *Dermatology* 1997; **194**: 309–11.
10 Hernandez-Nunez A, Dauden E, Moreno de Vega MJ *et al.* Widespread biphasic amyloidosis: response to acitretin. *Clin Exp Dermatol* 2001; **26**: 256–9.
11 Choi JY, Sippe J, Lee S. Acitretin for lichen amyloidosus. *Australas J Dermatol* 2008; **49**: 109–13.
12 Grimmer J, Weiss T, Weber L *et al.* Successful treatment of lichen amyloidosis with combined bath PUVA photochemotherapy and oral acitretin. *Clin Exp Dermatol* 2007; **32**: 39–42.

13 Pasricha JS, Seetharam KA. Low dose cyclophosphamide therapy in lichen amyloidosis. *Indian J Dermatol Venereol Leprol* 1987; **53**: 273–4.
14 Gupta R, Gupta S. Dexamethasone cyclophosphamide pulse therapy in lichen amyloidosus: a case report. *J Dermatolog Treat* 2007; **18**: 249–51.
15 Behr FD, Levine N, Bangert J. Lichen amyloidosis associated with atopic dermatitis: clinical resolution with cyclosporine. *Arch Dermatol* 2001; **137**: 553–5.
16 Wong CK, Li WM. Dermabrasion for lichen amyloidosus. *Arch Dermatol* 1982; **118**: 302–4.
17 Sawamura D, Sato-Matsumura KC, Shibaki A *et al*. A case of lichen amyloidosis treated with pulsed dye laser. *J Eur Acad Dermatol Venereol* 2005; **19**: 262–3.
18 Bozikov K, Janezic T. Excision and split thickness skin grafting in the treatment of nodular primary localized cutaneous amyloidosis. *Eur J Dermatol* 2006; **16**: 315–6.
19 Grattan CEH, Burton JL, Dahl MGC. Two cases of nodular cutaneous amyloid with positive organ-specific antibodies, treated by shave excision. *Clin Exp Dermatol* 1988; **13**: 187–9.
20 Vestey JP, Tidman MJ, McLaren KM. Primary nodular cutaneous amyloidosis—long-term follow-up and treatment. *Clin Exp Dermatol* 1994; **19**: 159–62.
21 Lien MH, Railan D, Nelson BR. The efficacy of dermabrasion in the treatment of nodular amyloidosis. *J Am Acad Dermatol* 1997; **36**: 315–6.
22 Kakani RS, Goldstein AE, Meisher I *et al*. Nodular amyloidosis: case report and literature review. *J Cutan Med Surg* 2001; **5**: 101–4.
23 Truhan AP, Garden JM, Roenigk HH. Nodular primary localized cutaneous amyloidosis: immunohistochemical evaluation and treatment with the carbon dioxide laser. *J Am Acad Dermatol* 1986; **14**: 1058–62.
24 Alster TS, Manaloto RM. Nodular amyloidosis treated with a pulsed dye laser. *Dermatol Surg* 1999; **25**: 133–5.

Secondary localized cutaneous amyloidosis [1–3]

Microscopic deposits of amyloid material have been described in association with a variety of cutaneous tumours, including intradermal melanocytic naevus [4], sweat gland tumours, pilomatrixoma, dermatofibroma, seborrhoeic wart, photosensitive annular elastolytic giant cell granuloma [5], solar keratosis, porokeratosis of Mibelli [6,7], disseminated superficial actinic porokeratosis [8], Bowen's disease [9,10], basal cell carcinoma [11,12] and trichoepithelioma [13,14]. The amount of amyloid material in tumours is usually clinically insignificant but massive deposits may occur and cause diagnostic difficulty [15]. A similar phenomenon has been noted following PUVA therapy [16,17].

References

1 Brownstein MH, Helwig EB. The cutaneous amyloidoses. I. Localized forms. *Arch Dermatol* 1970; **102**: 8–19.
2 Malak JA, Smith EW. Secondary localised cutaneous amyloidosis. *Arch Dermatol* 1962; **86**: 465–77.
3 Runne U, Orfanos CE. Amyloid production by dermal fibroblasts. Electron microscopic studies on the origin of amyloid in various dermatoses and skin tumours. *Br J Dermatol* 1977; **97**: 155–66.
4 MacDonald DM, Black MM. Secondary localized cutaneous amyloidosis in melanocytic naevi. *Br J Dermatol* 1980; **103**: 553–6.
5 Lee Y-S, Vijayasingam S, Chan HL. Photosensitive annular elastolytic giant cell granuloma with cutaneous amyloidosis. *Am J Dermatopathol* 1989; **11**: 443–50.
6 Amantea A, Giuliano MC, Balus L. Disseminated superficial porokeratosis with dermal amyloid deposits: case report and immunohistochemical study of amyloid. *Am J Dermatopathol* 1998; **20**: 86–8.
7 Demitsu T, Okada O. Disseminated superficial porokeratosis with dermal amyloid deposition. *J Dermatol* 1999; **26**: 405–6.
8 Ginarte M, León A, Toribio J. Disseminated superficial porokeratosis with amyloid deposits. *Eur J Dermatol* 2005; **15**: 298–300.
9 Speight EL, Milne DS, Lawrence CM. Secondary localized cutaneous amyloid in Bowen's disease. *Clin Exp Dermatol* 1993; **18**: 286–8.
10 Vazquez-Doval J, Mosquera O, Iglesias ME *et al*. Bowen's disease with amyloid deposit on the palmar surface of a finger. *Eur J Dermatol* 1995; **5**: 145–7.
11 Satti MB, Azzopardi JG. Amyloid deposits in basal cell carcinoma of the skin. A pathologic study of 199 cases. *J Am Acad Dermatol* 1990; **22**: 1082–7.
12 Nojiri K, Ono T, Johno M *et al*. BCC-associated amyloidosis with a peculiar pattern of deposition. *J Dermatol* 1992; **19**: 618–21.
13 Lee YS, Fong PH. Secondary localized amyloidosis in trichoepithelioma: light microscopic and ultrastructural study. *Am J Dermatopathol* 1990; **12**: 469–78.
14 Yang JE, Kim KM, Kang H *et al*. Multiple trichoepithelioma with secondary localized amyloidosis. *Br J Dermatol* 2000; **143**: 1343–4.
15 Cox NH, Nicoll JJ, Popple AW. Amyloid deposition in basal cell carcinoma: a cause of apparent lack of sensitivity to radiotherapy. *Clin Exp Dermatol* 2001; **26**: 499–500.
16 Green I, Cox AJ. Amyloid deposition after psoriasis therapy with psoralen and long-wave ultraviolet light. *Arch Dermatol* 1979; **115**: 1200–2.
17 Hashimoto K, Kumakiri M. Colloid-amyloid bodies in PUVA-treated human psoriatic patients. *J Invest Dermatol* 1979; **72**: 70–80.

Systemic amyloidosis

Systemic types of amyloidosis include those associated with plasma cell dyscrasia, either overt as in multiple myeloma, or occult as in 'primary' systemic amyloidosis, amyloidosis secondary to a variety of chronic diseases, and in the heredofamilial amyloidoses. Clinically evident involvement of the skin is frequent in 'primary' systemic and myeloma-associated systemic amyloidosis, but occurs only rarely in secondary systemic amyloidosis. Although there is a degree of overlap, primary and myeloma-associated systemic amyloidosis typically involve the tongue, heart, gastrointestinal tract, skeletal and smooth muscle, carpal ligaments, nerves and skin, whereas secondary systemic amyloidosis affects the liver, spleen, kidneys and adrenals [1]. Skin manifestations are associated with a number of systemic heredofamilial syndromes of amyloid deposition including familial Mediterranean fever [2], the Muckle–Wells syndrome [3] and heredofamilial amyloid polyneuropathy [4].

References

1 Isobe T, Osserman EF. Patterns of amyloidosis and their association with plasma cell dyscrasia, monoclonal immunoglobulins and Bence Jones proteins. *N Engl J Med* 1974; **290**: 473–7.
2 Sohar E, Gafni J, Pras M, Heller H. Familial Mediterranean fever. A survey of 470 cases and a review of the literature. *Am J Med* 1967; **43**: 227–53.
3 Lieberman A, Grossman ME, Silvers DN. Muckle–Wells syndrome: case report and review of cutaneous pathology. *J Am Acad Dermatol* 1998; **39**: 290–1.
4 Rubinow A, Cohen AS. Skin involvement in familial amyloidotic polyneuropathy. *Neurology* 1981; **31**: 1341–5.

Primary and myeloma-associated cutaneous amyloidosis

Aetiology. In primary and myeloma-associated amyloidosis, the fibrils are composed of 'protein AL' (amyloid L-chain protein) and appear to be a consequence of plasma cell dyscrasia, although bone marrow aspiration may not reveal any abnormality. Amino acid sequence analysis has demonstrated that protein AL consists of fragments of immunoglobulin polypeptide light chain, particularly the variable (amino-terminal) region, or of an intact immunoglobulin light chain, or of both [1–4], and is usually associated with a similar abnormal immunoglobulin light chain in the serum, commonly of λ class. Abnormal light chain material is almost always present in the serum or urine, even in so-called primary systemic amyloidosis, and can be demonstrated on tissue culture of bone marrow cells from affected patients. Only a proportion of

Bence Jones proteins produce amyloid fibrils on digestion [5], which may account for the fact that amyloidosis develops in only about 15% of patients with myelomatosis. Amyloidogenic immunoglobulin AL monoclonal proteins appear to be preferentially of λ type, of lower molecular weight, and of lower isoelectric point [6]. Domains may be destabilized by specific amino acid residue changes due to point mutation, rendering them susceptible to the formation of ordered, fibril-like aggregates *in vitro* [7]. The organ tropism (i.e. whether there is predominant renal, cardiac or hepatic involvement) in AL amyloidosis may reflect germ-line gene use and plasma cell burden [8]. Rare cases of AH amyloidosis associated with monoclonal gammopathy and renal amyloid deposition, in which the amyloid fibrils are composed of immunoglobulin heavy chain variable region (VH) fragments, are recorded [9].

References

1 Glenner GG, Terry W, Horada M. Amyloid fibril proteins: proof of homology with immunoglobulin light chains by sequence analyses. *Science* 1971; **172**: 1150–1.
2 Stevens FJ, Kisilevsky R. Immunoglobulin light chains, glycosaminoglycans, and amyloid. *Cell Mol Life Sci* 2000; **57**: 441–9.
3 Skinner M. AL amyloidosis: the last 30 years. *Amyloid* 2000; **7**: 13–4.
4 Sipe JD, Cohen AS. Review: history of the amyloid fibril. *J Struct Biol* 2000; **130**: 88–98.
5 Glenner GG, Ein D, Eanes ED *et al*. Creation of 'amyloid' fibrils from Bence-Jones proteins *in vitro*. *Science* 1971; **174**: 712–4.
6 Bellotti V, Merlini G, Bucciarelli E *et al*. Relevance of class, molecular weight and isoelectric point in predicting human light chain amyloidogenicity. *Br J Haematol* 1990; **74**: 65–9.
7 Helms LR, Wetzel R. Specificity of abnormal assembly in immunoglobulin light chain deposition disease and amyloidosis. *J Mol Biol* 1996; **257**: 77–86.
8 Comenzo RL, Zhang Y, Martinez C *et al*. The tropism of organ involvement in primary systemic amyloidosis. Contributions of Ig V (L) germ line gene use and clonal plasma cell burden. *Blood* 2001; **98**: 714–20.
9 Miyazaki D, Yazaki M, Gono T *et al*. AH amyloidosis associated with an immunoglobulin heavy chain variable region (VH1) fragment: a case report. *Amyloid* 2008; **15**: 125–8.

Histopathology [1–5]. In primary and myeloma-associated amyloidosis, deposits of amyloid are usually superficially placed in the papillary dermis as amorphous, faintly eosinophilic, often fissured masses, with associated thinning or obliteration of the rete ridges, accounting for the papules seen clinically. Amyloid deposits in the deep reticular dermis and subcutis give rise to the clinical appearance of nodules and tumefactions, and infiltration of blood vessel walls correlates with the clinical finding of purpura. Marked thickening of blood vessel walls due to amyloid infiltration has been described [6]. Usually, there is little in the way of any inflammatory infiltrate, unlike nodular PLCA in which infiltration of plasma cells is a significant feature [3,4]. In areas of alopecia, amyloid deposits may surround and compress pilosebaceous units with resultant atrophy and loss of hair from the shafts. Amyloid may also be deposited in arrector pili muscles, in the lamina propria of sweat glands and ducts, and around individual fat cells in the subcutis as characteristic 'amyloid rings'. Amyloid deposition in the nail fold and bed of dystrophic nails has been reported [7]. An affinity for amyloid to coat elastic fibres has been noted [8].

References

1 Brownstein MH, Helwig EB. The cutaneous amyloidoses. II. Systemic forms. *Arch Dermatol* 1970; **102**: 20–8.
2 Wong CK, Breathnach SM, eds. Cutaneous amyloidosis. *Clin Dermatol* 1990; **8** (2).
3 Westermark P. Amyloidosis of the skin: a comparison between localized and systemic amyloidosis. *Acta Derm Venereol Suppl (Stockh)* 1979; **59**: 341–5.
4 Masuda C, Moturi S, Nakajima H. Histopathological and immuno-histochemical study of amyloidosis cutis nodularis atrophicus: comparison with systemic amyloidosis. *Br J Dermatol* 1988; **119**: 33–43.
5 Lee DD, Huang CY, Wong CK. Dermatopathologic findings in 20 cases of systemic amyloidosis. *Am J Dermatopathol* 1998; **20**: 438–42.
6 Henry RB, Fisher GB, Cooper PH. Vascular amyloid in a patient with multiple myeloma. *J Am Acad Dermatol* 1986; **15**: 379–82.
7 Breathnach SM, Wilkinson JD, Black MM. Systemic amyloidosis with an underlying lymphoproliferative disorder: report of a case in which nail involvement was a presenting feature. *Clin Exp Dermatol* 1979; **4**: 495–9.
8 Winkelmann RK, Peters MS, Venencie PY. Amyloid elastosis. A new cutaneous and systemic pattern of amyloidosis. *Arch Dermatol* 1985; **121**: 498–502.

Clinical features [1–10]. The mean age of onset of primary amyloidosis is about 65 years, and there is a slight male preponderance. Presenting symptoms may be rather non-specific, and include fatigue, weight loss, paresthesiae, hoarseness, oedema, dyspnoea, and syncope secondary to orthostatic hypotension. These features may predate the histological diagnosis by up to 2 years. The classical presentation with symptoms of carpal tunnel syndrome, macroglossia, specific mucocutaneous lesions which occur in up to 40% of cases, hepatomegaly and oedema should always alert the clinician to the presence of an underlying plasma cell dyscrasia.

Amyloidosis is the commonest cause of macroglossia in adults [11], and occurs in about 10% of cases. The tongue is usually diffusely enlarged and firm (Fig. 59.37), but it may also be fissured,



Fig. 59.37 Primary systemic amyloidosis. Macroglossia. (Courtesy of St John's Institute of Dermatology, London, UK.)

Table 59.9 Cutaneous lesions in primary and myeloma-associated systemic amyloidosis.

Common	Less common
Petechiae, purpura, ecchymoses	Pigmentary changes
Waxy, translucent or purpuric papules	Scleroderma-like infiltration
Nodules	Bullous lesions
Plaques	Alopecia
Tumefactive lesions	Cord-like blood vessel thickening
	Nail dystrophy
	Cutis laxa; localized redundant skin folds and depressions



Fig. 59.38 Primary systemic amyloidosis. Prominent eyelid purpura following coughing. (Courtesy of St John's Institute of Dermatology, London, UK.)

with haemorrhagic papules, nodules, plaques or even bullae on its surface. There may be permanent tooth indentations along its lateral borders. Macroglossia may be so extensive as to cause dysphagia.

The commonest skin lesions are those related to intracutaneous haemorrhage due to infiltration of blood vessel walls by amyloid deposits (Table 59.9). Petechiae, purpura and ecchymoses may occur spontaneously or after minor trauma on normal or clinically involved skin, especially in the body folds, for example eyelids, sides of neck, axillae, umbilicus, oral and anogenital regions. Purpuric haloes may occur around long-standing Campbell de Morgan spots [12]. Eyelid purpura after pinching, and periorbital purpura after proctoscopy ('post-proctoscopic palpebral purpura'), coughing (Fig. 59.38), vomiting or the Valsalva manoeuvre, are characteristic. Pigmentary changes include jaundice due to hepatic disease, cardiac failure or severe haemorrhage, pallor due to anaemia and hyperpigmentation due to haemorrhage.



Fig. 59.39 Primary systemic amyloidosis. Purpuric plaques situated on upper eyelids. (Courtesy of St John's Institute of Dermatology, London, UK.)

Smooth, shiny, waxy papules or plaques, often with a haemorrhagic component, may also be found (Fig. 59.39). Translucent areas may resemble vesicles. Flexural areas are sites of predilection, including the eyelids, retroauricular region, neck, axillae, umbilicus, inguinal and anogenital regions. Lesions may also be found on the central face, lips, tongue and buccal mucosa. Widespread nodules may occur, coalescing to form large tumefactions. They may resemble condylomata lata on perianal and vulval skin [13,14], and when widespread may appear like xanthomas [15]. Diffuse infiltration of large areas, especially on the face, hands and feet, may simulate scleroderma [16,17], or on the face produce a myxoedema-like appearance. Alopecia may be patchy or widespread [18], and the scalp skin may be thrown into longitudinal folds resembling cutis verticis gyrata. Nail involvement due to infiltration of the nail matrix by amyloid may produce longitudinal striation (Fig. 59.40), crumbling, brittleness and partial anonychia, and may be a presenting sign [19–21]. Chronic paronychia with palmodigital erythema has also been described [22]. Signs which occur rarely include bullae of the skin or mucous membranes as a result of shearing within dermal amyloid deposits [23–27], which may result in changes resembling porphyria cutanea tarda or epidermolysis bullosa acquisita (Fig. 59.41). Extensive amyloid infiltration may lead to cord-like thickening of superficial blood vessels [28]. Extensive cutaneous ulceration has been recorded [29]. Amyloid elastosis is an unusual syndrome in which papulonodular cutaneous lesions are associated with widespread amyloid infiltration of visceral and cutaneous blood vessels, particularly in relation to elastic fibres [30,31]. Acquired cutis laxa has also been reported [32,33]. Localized elastolytic cutaneous lesions may present as soft, loose folds or indentations on the fingertips [34]. Other cases of cutis laxa may reveal fibrillar extracellular deposits, which are different from amyloid fibrils [35].

Hepatomegaly occurs in about 50%, and splenomegaly in about 10% of patients. The nephrotic syndrome or congestive cardiac failure (each of which occur in about 30% of cases), and rarely



Fig. 59.40 Primary systemic amyloidosis. Close-up of thumbnail showing longitudinal ridging and splitting. A nail biopsy in this case confirmed amyloid deposition. (Courtesy of St John's Institute of Dermatology, London, UK.)



Fig. 59.41 Primary systemic amyloidosis. Haemorrhagic bulla on side of wrist. (Courtesy of St John's Institute of Dermatology, London, UK.)

protein-losing enteropathy from amyloid involvement of the small bowel, may cause pitting oedema. Ascites may develop. Cardiac infiltration results in angina, infarction, congestive cardiac failure, orthostatic hypotension or arrhythmias [36]; it accounts for death in about 40% of cases of AL type systemic amyloidosis. Pulmonary involvement is common but usually asymptomatic. Amyloid infiltration of blood vessels may lead to claudication of the legs or jaw. Gastrointestinal tract involvement [37,38] may simulate inflammatory bowel disease with haemorrhage; malabsorption is found in 5% of cases. The carpal tunnel syndrome [39] has been reported in up to 25% of patients with 'primary' systemic amyloidosis. Neurological complications [40] include peripheral neuropathy [41], initially of the lower extremities, which tends to pursue a chronic course; there may be superimposed autonomic neuropathy leading to orthostatic hypotension, diarrhoea, loss of bladder control or impotence. Muscle weakness may be caused by neuropathy, or by amyloid infiltration of muscle or its vascular supply; infiltration between muscle fibres leading to pseudohypertrophy is reported [42]. Lymphadenopathy occurs in about 10% of patients [43]. Sjögren's syndrome or sicca syndrome due to amyloid infiltration of lacrimal and parotid glands [44] are occasional presenting features. Amyloid deposition in joints may mimic rheumatoid arthritis [45], and deposition around the shoulders may cause extensive soft-tissue enlargement (the shoulder-pad sign) [46]. Giant cell arteritis and polymalgia rheumatica are recorded [47], as are isolated factor X deficiency [48], disseminated intravascular coagulation and fibrinolysis with severe bleeding.

References

1 Brownstein MH, Helwig EB. The cutaneous amyloidoses. II. Systemic forms. *Arch Dermatol* 1970; **102**: 20–8.
2 Breathnach SM. Amyloid and amyloidosis. *J Am Acad Dermatol* 1988; **18**: 1–16.
3 Wong CK, Breathnach SM, eds. Cutaneous amyloidosis. *Clin Dermatol* 1990; **8** (2).
4 Wong Wang WJ. Systemic amyloidosis. A report of 19 cases. *Dermatology* 1994; **189**: 47–51.
5 Kyle RA, Gertz MA. Primary systemic amyloidosis: clinical and laboratory features in 474 cases. *Semin Hematol* 1995; **32**: 45–59.
6 Gertz MA, Lacy MQ, Dispenzieri A. Amyloidosis: recognition, confirmation, prognosis, therapy. *Mayo Clin Proc* 1999; **74**: 490–4.
7 Kyle RA. Clinical aspects of multiple myeloma and related disorders including amyloidosis. *Pathol Biol (Paris)* 1999; **47**: 148–57.
8 Daoud MS, Lust JA, Kyle RA *et al.* Monoclonal gammopathies and associated skin disorders. *J Am Acad Dermatol* 1999; **40**: 507–35.
9 Terrier B, Jaccard A, Harousseau JL *et al.* The clinical spectrum of IgM-related amyloidosis: a French nationwide retrospective study of 72 patients. *Medicine (Baltimore)* 2008; **87**: 99–109.
10 Mason AR, Rackoff EM, Pollack RB. Primary systemic amyloidosis associated with multiple myeloma: a case report and review of the literature. *Cutis* 2007; **80**: 193–200.
11 Murthy P, Laing MR. Macroglossia. *BMJ* 1994; **309**: 1386–7.
12 Brear SG, Rademaker M, Hasleton P *et al.* Target-like skin lesions in primary amyloidosis. *Br J Dermatol* 1985; **112**: 209–11.
13 Buezo GF, Penas PF, Firaga J *et al.* Condyloma-like lesions as the presenting sign of multiple myeloma associated amyloidosis. *Br J Dermatol* 1996; **135**: 665–6.
14 Konig A, Wennemuth G, Soyer HP *et al.* Vulvar amyloidosis mimicking giant condylomata acuminata in a patient with multiple myeloma. *Eur J Dermatol* 1999; **9**: 29–31.
15 Chapman RS, Neville EA, Lawson JW. Xanthoma-like skin lesions as a presenting feature in primary systemic amyloidosis. *Br J Clin Pract* 1973; **27**: 271–3.
16 Gerster JC, Landry M, Dudler J. Scleroderma-like changes of the hands in primary amyloidosis. *J Rheumatol* 2000; **27**: 2275–7.

17 Reyes CM, Rudinskaya A, Kloss R *et al*. Scleroderma-like illness as a presenting feature of multiple myeloma and amyloidosis. *J Clin Rheumatol* 2008; **14**: 161–5.
18 Hunt SJ, Caserio RJ, Abell E. Primary systemic amyloidosis causing diffuse alopecia by telogen arrest. *Arch Dermatol* 1991; **127**: 1067–8.
19 Breathnach SM, Wilkinson JD, Black MM. Systemic amyloidosis with an underlying lymphoproliferative disorder. Report of a case in which nail involvement was a presenting feature. *Clin Exp Dermatol* 1979; **4**: 495–9.
20 Fujita Y, Tsuji-Abe Y, Sato-Matsumura KC *et al*. Nail dystrophy and blisters as sole manifestations in myeloma-associated amyloidosis. *J Am Acad Dermatol* 2006; **54**: 712–4.
21 Prat C, Moreno A, Viñas M, Jucglà A. Nail dystrophy in primary systemic amyloidosis. *J Eur Acad Dermatol Venereol* 2008; **22**: 107–9.
22 Ahmed I, Cronk JS, Crutchfield CE 3rd *et al.* Myeloma-associated systemic amyloidosis presenting as chronic paronychia and palmodigital erythematous swelling and induration of the hands. *J Am Acad Dermatol* 2000; **42**: 339–42.
23 Hunter JAA. Primary systemic amyloidosis imitating porphyria cutanea tarda. *Proc R Soc Med* 1976; **69**: 235–6.
24 Bieber T, Ruzicka T, Linke RD. Hemorrhagic bullous amyloidosis. *Arch Dermatol* 1988; **124**: 1683–6.
25 Robert C, Aractingi S, Prost C, Verola O *et al.* Bullous amyloidosis. Report of three cases and review of the literature. *Medicine (Baltimore)* 1993; **72**: 38–44.
26 Pramatarov Wang XD, Shen H, Liu ZH. Diffuse haemorrhagic bullous amyloidosis with multiple myeloma. *Clin Exp Dermatol* 2008; **33**: 94–6.
27 Rekhtman N, Hash KS, Moresi JM. Mucocutaneous bullous amyloidosis with an unusual mixed protein composition of amyloid deposits. *Br J Dermatol* 2006; **154**: 751–4.
28 Breathnach SM, Wells GC. Amyloid vascular disease: cord-like thickening of mucocutaneous arteries, intermittent claudication and angina in a case with underlying myelomatosis. *Br J Dermatol* 1980; **102**: 591–5.
29 Alhaddab M, Srolovitz H, Rosen N. Primary systemic amyloidosis presenting as extensive cutaneous ulceration. *J Cutan Med Surg* 2006; **10**: 253–6.
30 Winkelmann RK, Peters MS, Venencie PY. Amyloid elastosis. A new cutaneous and systemic pattern of amyloidosis. *Arch Dermatol* 1985; **121**: 498–502.
31 Sepp N, Pichler E, Breathnach SM *et al.* Amyloid elastosis: analysis of the role of amyloid P component. *J Am Acad Dermatol* 1990; **22**: 27–34.
32 Newton JA, McKee PH, Black MM. Cutis laxa associated with amyloidosis. *Clin Exp Dermatol* 1986; **11**: 87–91.
33 Appiah YE, Onumah N, Wu H *et al*. Multiple myeloma-associated amyloidosis and acral localized acquired cutis laxa. *J Am Acad Dermatol* 2008; **58** (2 Suppl.): S32–3.
34 Yoneda K, Kanoh T, Nomura S *et al*. Elastolytic cutaneous lesions in myeloma-associated amyloidosis. *Arch Dermatol* 1990; **126**: 657–60.
35 Niemi KM, Anton-Lamprecht A, Virtanen I *et al.* Fibrillar protein deposits with tubular substructure in a systemic disease beginning as cutis laxa. *Arch Dermatol* 1993; **129**: 757–62.
36 Dubrey SW, Cha K, Anderson J *et al.* The clinical features of immunoglobulin light-chain (AL) amyloidosis with heart involvement. *QJM* 1998; **91**: 141–57.
37 Ebert EC, Nagar M. Gastrointestinal manifestations of amyloidosis. *Am J Gastroenterol* 2008; **103**: 776–87.
38 Petre S, Shah IA, Gilani N. Review article: gastrointestinal amyloidosis—clinical features, diagnosis and therapy. *Aliment Pharmacol Ther* 2008; **27**: 1006–16.
39 Nestle FO, Burg G. Bilateral carpal tunnel syndrome as a clue for the diagnosis of systemic amyloidosis. *Dermatology* 2001; **202**: 353–5.
40 Kelly JJ. Neurologic complications of primary systemic amyloidosis. *Rev Neurol Dis* 2006; **3**: 173–81.
41 Duston MA, Skinner M, Anderson J, Cohen AS. Peripheral neuropathy as an early marker of AL amyloidosis. *Arch Intern Med* 1989; **149**: 358–60.
42 Sibelt LA, Lokhorst HM, van de Kerkhof PC, van Dooren-Greebe RJ. A 'muscle' man without exercise: muscle pseudohypertrophy in myeloma-associated generalized amyloidosis. *J Eur Acad Dermatol Venereol* 2007; **21**: 986–8.
43 Matsuda M, Gono T, Shimojima Y *et al*. AL amyloidosis manifesting as systemic lymphadenopathy. *Amyloid* 2008; **15**: 117–24.
44 Jardinet D, Westhovens R, Peeters J. Sicca syndrome as an initial symptom of amyloidosis. *Clin Rheumatol* 1998; **17**: 546–8.
45 Katoh N, Tazawa K, Ishii W, Matsuda M, Ikeda S. Systemic AL amyloidosis mimicking rheumatoid arthritis. *Intern Med* 2008; **47**: 1133–8.
46 Liepnieks JJ, Burt C, Benson MD. Shoulder-pad sign of amyloidosis: structure of an Ig κ III protein. *Scand J Immunol* 2001; **54**: 404–8.
47 Salvarani C, Gabriel SE, Gertz MA *et al.* Primary systemic amyloidosis presenting as giant cell arteritis and polymyalgia rheumatica. *Arthritis Rheum* 1994; **37**: 1621–6.
48 Marcatti M, Mauri S, Tresoldi M *et al.* Unusual bleeding manifestations in a case of primary amyloidosis with factor X deficiency but elevations of *in vivo* markers of thrombin formation and activity. *Thromb Res* 1995; **80**: 333–7.

Diagnosis. The diagnosis should always be considered when a patient presents with the triad of carpal tunnel syndrome, macroglossia and mucocutaneous skin lesions [1,2]. Biopsy of classical mucocutaneous lesions should be the procedure of first choice. Biopsy of even clinically normal forearm skin has been reported positive in up to 50% of cases of primary and myeloma-associated disease. Fine-needle biopsies of the subcutaneous fat from clinically normal abdominal skin have a high positive yield in AL- and AA-type amyloidosis as well as in heredofamilial amyloidoses [3–5]. Rectal biopsy is positive in up to 80% of cases of AL or AA amyloidosis, jejunal biopsy in about two-thirds, but gingival biopsy in only 19%. Gastric biopsy may produce a higher yield than rectal biopsy. Ninety-six per cent of hepatic, and 90% of renal and of splenic percutaneous needle biopsies, as well as carpal tunnel tissue biopsies at the time of decompression, are positive. Bone marrow aspiration may be positive in up to 45% of cases. Electrocardiography, echocardiography, angiocardiography, technetium scanning and endomyocardial biopsy are useful in the diagnosis of amyloid heart disease [6–8]. Computed tomography, ultrasound examination, and Doppler analysis of blood flow may be useful in renal amyloidosis. Sural nerve biopsy in patients with peripheral neuropathy [9], and synovial fluid analysis in patients with arthropathy, may be helpful. Scanning with ^{123}I-labelled SAP component enables specific localization and imaging of amyloid deposits *in vivo* [10,11].

Immunoelectrophoresis of both serum and concentrated urine is essential if the clinical presentation suggests the presence of a plasma cell dyscrasia, as conventional urine heat tests and simple electrophoresis of serum and urine may not detect small amounts of paraprotein or Bence Jones protein. Protein electrophoresis of serum shows a spike pattern in just under half of patients with primary AL, and in about two-thirds of those with myeloma. Immunoelectrophoresis of serum reveals a monoclonal protein in two-thirds of patients with AL amyloidosis; only 45% have a monoclonal heavy chain, while 20% have free monoclonal light chains (Bence Jones proteinaemia). Immunoelectrophoresis of concentrated urine reveals a monoclonal light chain in about two-thirds of cases (λ to κ ratio 2 : 1). When screening of both serum and urine is performed, the frequency of patients with an identifiable monoclonal protein rises to about 86%. A combination of immunofixation on agarose gel electrophoresis and bone marrow plasma cell light chain λ to κ ratio analysis improves diagnostic sensitivity [12]. Nevertheless, in some cases with the clinical features of AL amyloidosis it is not possible to demonstrate a paraprotein, even after prolonged follow-up for as long as 24 years [13].

Skeletal survey may be useful, as 50% of patients with myeloma-associated amyloidosis have radiological abnormalities, compared with only 6% of those with primary amyloidosis. Most myeloma cases, but no primary systemic amyloidosis cases, have more than 15% plasma cells in the marrow. In general, myeloma is not present

if a patient has no lytic bone lesions, hypercalcaemia or anaemia, has only a small serum or urine monoclonal component, and has less than 25% bone marrow plasma cells.

References

1 Gertz MA, Lacy MQ, Dispenzieri A. Amyloidosis: recognition, confirmation prognosis, therapy. *Mayo Clin Proc* 1999; **74**: 490–4.
2 Kyle RA. Clinical aspects of multiple myeloma and related disorders including amyloidosis. *Pathol Biol (Paris)* 1999; **47**: 148–57.
3 Westermark P. Diagnosing amyloidosis. *Scand J Rheumatol* 1995; **24**: 327–9.
4 Guy CD, Jones CK. Abdominal fat pad aspiration biopsy for tissue confirmation of systemic amyloidosis: specificity, positive predictive value, and diagnostic pitfalls. *Diagn Cytopathol* 2001; **24**: 181–5.
5 Dhingra S, Krishnani N, Kumari N, Pandey R. Evaluation of abdominal fat pad aspiration cytology and grading for detection in systemic amyloidosis. *Acta Cytol* 2007; **51**: 860–4.
6 Bellavia D, Pellikka PA, Abraham TP *et al*. Evidence of impaired left ventricular systolic function by Doppler myocardial imaging in patients with systemic amyloidosis and no evidence of cardiac involvement by standard two-dimensional and Doppler echocardiography. *Am J Cardiol* 2008; **101**: 1039–45.
7 Vogelsberg H, Mahrholdt H, Deluigi CC *et al*. Cardiovascular magnetic resonance in clinically suspected cardiac amyloidosis: noninvasive imaging compared to endomyocardial biopsy. *J Am Coll Cardiol* 2008; **51**: 1022–30.
8 Rapezzi C, Guidalotti P, Salvi F *et al*. Usefulness of 99mTc-DPD scintigraphy in cardiac amyloidosis. *J Am Coll Cardiol* 2008; **51**: 1509–10.
9 Rajani B, Rajani V, Prayson RA. Peripheral nerve amyloidosis in sural nerve biopsies. A clinicopathologic analysis of 13 cases. *Arch Pathol Lab Med* 2000; **124**: 114–8.
10 Hawkins PN, Richardson S, MacSweeney JE *et al.* Scintigraphic quantification and serial monitoring of human visceral amyloid deposits provide evidence for turnover and regression. *QJM* 1993; **86**: 365–74.
11 Hachulla E, Maulin L, Deveaux M *et al.* Prospective and serial study of primary amyloidosis with serum amyloid P component scintigraphy: from diagnosis to prognosis. *Am J Med* 1996; **101**: 77–87.
12 Perfetti V, Garini P, Vignarelli MC *et al.* Diagnostic approach to and follow-up of difficult cases of AL amyloidosis. *Haematologica* 1995; **80**: 409–15.
13 Crow KD. Primary amyloidosis. *Br J Dermatol* 1977; **97** (Suppl. 15): 58–60.

Prognosis. Prognosis in primary systemic and myeloma-associated amyloidosis is poor, the major causes of death being cardiac and renal failure, and is linked to degree of plasma cell clonality and marrow infiltration [1]. The prognosis of AL amyloidosis has improved, with a currently reported median survival of about 40 months compared to 13 months in the early 1990s. Autologous stem cell transplantation (ASCT) achieves the highest rates of complete clonal response but is associated with substantial treatment-related mortality unless restricted to highly selected patients. Newer chemotherapy regimens which can be used more widely may achieve better safety and respectable efficacy [2]. Median survival on high-dose melphalan and autologous stem-cell transplantation was 4.6 years [3] and 4.75 years respectively [4] in other series; 21% of patients died within the first year of treatment-related complications or progressive disease, but median survival exceeded 10 years for patients achieving a complete haematological response [4]. Median survival was only 26 months in patients undergoing dialysis [5]; a good renal response after high-dose melphalan and stem cell transplantation is a favourable marker [6]. Occasional patients surviving longer than 10 years have been recorded [3,7–10]. Patients presenting with amyloid neuropathy without associated cardiac, renal or hepatic involvement may have a better prognosis (median survival 40–50 months; 5 years survival 31.6%) [11]. Survival for more than 10 years has been recorded in a patient with primary systemic amyloidosis with sensorimotor polyneuropathy only [12].

Treatment. Most patients receive a trial of chemotherapy, usually melphalan and prednisone, with or without autologous bone marrow stem-cell transplantation [2,3,13–17]. There is a risk of development of leukaemia or a dysmyelopoietic syndrome [14]. Other chemotherapeutic regimens have been used [18–20]. Cardiac [21,22] or renal transplantation can prolong survival; renal amyloidosis is not an absolute contraindication to transplantation, although amyloid may re-accumulate in the transplanted kidney.

References

1 Perfetti V, Colli Vignarelli M, Anesi E *et al.* The degrees of plasma cell clonality and marrow infiltration adversely influence the prognosis of AL amyloidosis patients. *Haematologica* 1999; **84**: 218–21.
2 Gertz Wechalekar AD, Hawkins PN, Gillmore JD. Perspectives in treatment of AL amyloidosis. *Br J Haematol* 2008; **140**: 365–77.
3 Skinner M, Sanchorawala V, Seldin DC *et al*. High-dose melphalan and autologous stem-cell transplantation in patients with AL amyloidosis: an 8-year study. *Ann Intern Med* 2004; **140**: 85–93.
4 Sanchorawala V, Skinner M, Quillen K *et al*. Long-term outcome of patients with AL amyloidosis treated with high-dose melphalan and stem-cell transplantation. *Blood* 2007; **110**: 3561–3.
5 Bollée G, Guery B, Joly D *et al*. Presentation and outcome of patients with systemic amyloidosis undergoing dialysis. *Clin J Am Soc Nephrol* 2008; **3**: 375–81.
6 Leung N, Dispenzieri A, Fervenza FC *et al*. Renal response after high-dose melphalan and stem cell transplantation is a favorable marker in patients with primary systemic amyloidosis. *Am J Kidney Dis* 2005; **46**: 270–7.
7 Kyle RA, Gertz MA, Greipp PR *et al.* Long-term survival (10 years or more) in 30 patients with primary amyloidosis. *Blood* 1999; **93**: 1062–6.
8 Crow KD. Primary amyloidosis. *Br J Dermatol* 1977; **97** (Suppl. 15): 58–60.
9 Fritz DA, Luggen ME, Hess EV. Unusual longevity in primary systemic amyloidosis: a 19-year survivor. *Am J Med* 1989; **86**: 245–8.
10 Goldsmith DJ, Sandooran D, Short CD *et al.* Twenty-one years survival with systemic AL-amyloidosis. *Am J Kidney Dis* 1996; **28**: 278–82.
11 Duston MA, Skinner M, Anderson J, Cohen AS. Peripheral neuropathy as an early marker of AL amyloidosis. *Arch Intern Med* 1989; **149**: 358–60.
12 Rinaldi R, Azzimondi G, Preda P *et al.* Primary systemic amyloidosis presenting with polyneuropathy characterized by very long survival. *Acta Neurol Scand* 1995; **91**: 511–3.
13 Palladini G, Perfetti V, Obici L *et al*. Association of melphalan and high-dose dexamethasone is effective and well tolerated in patients with AL (primary) amyloidosis who are ineligible for stem cell transplantation. *Blood* 2004; **103**: 2936–8.
14 Jaccard A, Moreau P, Leblond V *et al*. High-dose melphalan versus melphalan plus dexamethasone for AL amyloidosis. *N Engl J Med* 2007; **357**: 1083–93.
15 Sanchorawala V, Seldin DC. An overview of high-dose melphalan and stem cell transplantation in the treatment of AL amyloidosis. *Amyloid* 2007; **14**: 261–9.
16 Akay OM, Sahin G, Kabukcuoglu S *et al*. Successful treatment of nephrotic syndrome due to systemic AL amyloidosis after autologous stem cell transplantation: renal response is an important therapeutic end point. *Clin Nephrol* 2008; **69**: 294–7.
17 Gertz MA, Kyle RA. Acute leukemia and cytogenetic abnormalities complicating melphalan treatment of primary systemic amyloidosis. *Arch Intern Med* 1990; **150**: 629–33.
18 Imagawa S, Ohmine K *et al.* Successful treatment of multiple myeloma-associated amyloidosis by interferon-α, dimethyl sulfoxide, and VAD (vincristine, adriamycin, and dexamethasone). *Int J Hematol* 2000; **72**: 491–3.
19 Kastritis E, Anagnostopoulos A, Roussou M *et al*. Treatment of light chain (AL) amyloidosis with the combination of bortezomib and dexamethasone. *Haematologica* 2007; **92**: 1351–8.
20 Matsuda M, Gono T, Katoh N *et al*. Nephrotic syndrome due to primary systemic AL amyloidosis, successfully treated with VAD (vincristine, doxorubicin and dexamethasone) alone. *Intern Med* 2008; **47**: 543–9.

21 Sack FU, Kristen A, Goldschmidt H *et al*. Treatment options for severe cardiac amyloidosis: heart transplantation combined with chemotherapy and stem cell transplantation for patients with AL-amyloidosis and heart and liver transplantation for patients with ATTR-amyloidosis. *Eur J Cardiothorac Surg* 2008; **33**: 257–62.

22 Mignot A, Bridoux F, Thierry A *et al*. Successful heart transplantation following melphalan plus dexamethasone therapy in systemic AL amyloidosis. *Haematologica* 2008; **93**: e32–5.

Secondary systemic amyloidosis

In secondary systemic amyloidosis, the fibrils are composed of a non-immunoglobulin protein designated protein AA [1]. A precursor of protein AA, known as serum amyloid A protein (protein SAA), is present in the serum of normal individuals as an apolipoprotein of high-density lipoprotein, and behaves as an acute phase reactant.

Secondary amyloidosis occurs as a complication of many chronic inflammatory diseases in which the immune system is stimulated [2,3]. These include acute recurrent and chronic infections, rheumatoid arthritis [4], juvenile chronic arthritis [5], ankylosing spondylitis [6], Reiter's syndrome, Behçet's syndrome [7], Sjögren's syndrome, dermatomyositis, scleroderma, systemic lupus erythematosus [8], inflammatory bowel disease [9], Hodgkin's disease, non-Hodgkin's lymphoma [10], histiocytosis X [11], Schnitzler's syndrome [12] and some solid non-lymphoid tumours, as well as Castleman's disease [13] and Rosai–Dorfman disease [14]. Secondary systemic amyloidosis may also arise as a complication of a number of dermatoses [15], such as venous ulceration [16], generalized psoriasis and psoriatic arthritis [17,18], pustular psoriasis [19], lepromatous leprosy [20], hidradenitis suppurativa, chronically infected burns, chronic skin infection in drug addicts [21], nodular non-suppurative panniculitis [22], giant, ulcerated or metastatic basal cell carcinoma [23], acne conglobata [24], epidermolysis bullosa of dystrophic [25,26] and aquisita types, and X-linked anhidrotic ectodermal dysplasia.

Secondary systemic amyloidosis rarely produces specific skin lesions. An elbow skin nodule due to deposition of AA amyloid was reported in a patient with primary Sjögren syndrome, myopathy, severe osteoporosis, and vertebral fractures attributed to coeliac disease [27]. By contrast, secondary systemic amyloidosis commonly involves the kidneys (causing the nephrotic syndrome), spleen, alimentary tract and adrenals; the diagnosis should be confirmed by rectal or renal biopsy. Needle aspirates of abdominal wall subcutis may yield positive histological identification of amyloid [28]. Small or minute amyloid deposits are most often found around the adnexae, sometimes in small blood vessels and in the subcutis around fat cells: 'amyloid rings'.

There is no specific treatment, and many die from progressive renal failure. Treatment of the primary disease may arrest progression of the amyloidosis. Estimated survival at 10 years was 90% in patients whose median protein SAA level was under 10 mg/L, and only 40% among those whose median SAA level exceeded this in one study [29]. Median survival after diagnosis was 133 months, with renal dysfunction being the predominant disease manifestation in another recent study, which reiterated the prognostic value of the SAA level [30]. Renal disease has responded to colchicine therapy, cyclophosphamide, or high dose melphalan and autologous stem cell transplantation [4,31,32]. Etanercept therapy is reportedly of benefit in inflammatory arthritis-related AA amyloidosis [33–35]. Renal transplantation is certainly worthy of consideration.

References

1 Cunnane G. Amyloid precursors and amyloidosis in inflammatory arthritis. *Curr Opin Rheumatol* 2001; **13**: 67–73.

2 Brownstein MH, Helwig EB. Secondary systemic amyloidosis: analysis of underlying disorders. *South Med J* 1971; **64**: 491–6.

3 Gertz MA. Secondary amyloidosis (AA). *J Intern Med* 1992; **232**: 517–8.

4 Chevrel G, Jenvrin C, McGregor B *et al.* Renal type AA amyloidosis associated with rheumatoid arthritis: a cohort study showing improved survival on treatment with pulse cyclophosphamide. *Rheumatology (Oxford)* 2001; **40**: 821–5.

5 Immonen K, Savolainen A, Kautiainen H, Hakala M. Longterm outcome of amyloidosis associated with juvenile idiopathic arthritis. *J Rheumatol* 2008; **35**: 907–12.

6 Kobak S, Oksel F, Kabasakal Y, Doganavsargil E. Ankylosing spondylitis-related secondary amyloidosis responded well to etanercept: a report of three patients. *Clin Rheumatol* 2007; **26**: 2191–4.

7 Skhiri H, Mahjoub S, Harzallah O *et al*. Secondary amyloidosis, a fatal complication of Behcet's disease: three case reports. *Saudi J Kidney Dis Transpl* 2004; **15**: 57–60.

8 Aktas Yilmaz B, Düzgün N, Mete T *et al*. AA amyloidosis associated with systemic lupus erythematosus: impact on clinical course and outcome. *Rheumatol Int* 2008; **28**: 367–70.

9 Leiper K, Howse ML, Bell GM. Resolution of nephrotic syndrome caused by amyloidosis following surgery for Crohn's disease. *Hosp Med* 2000; **61**: 802–3.

10 Piskin O, Alacacioglu I, Ozkal S *et al*. A patient with diffuse large B-cell non-Hodgkin's lymphoma and AA type amyloidosis. *J Bulkan Union Oncol* 2008; **13**: 113–6.

11 Pérez-Martínez J, Marques M, Kilmurray L *et al*. Secondary amyloidosis associated with histiocytosis X. *Amyloid* 2008; **15**: 69–71.

12 Claes K, Bammens B, Delforge M *et al*. Another devastating complication of the Schnitzler syndrome: AA amyloidosis. *Br J Dermatol* 2008; **158**: 182–4.

13 Morita-Hoshi Y, Tohda S, Miura O, Nara N. An autopsy case of multicentric Castleman's disease associated with interstitial nephritis and secondary AA amyloidosis. *Int J Hematol* 2008; **87**: 69–74.

14 Rocken C, Wieker K, Grote HJ *et al.* Rosai–Dorfman disease and generalized AA amyloidosis: a case report. *Hum Pathol* 2000; **31**: 621–4.

15 Brownstein MH, Helwig EB. Systemic amyloidosis complicating dermatoses. *Arch Dermatol* 1970; **102**: 1–7.

16 Landau M, Ophir J, Gal R *et al.* Systemic amyloidosis secondary to chronic leg ulcers. *Cutis* 1992; **50**: 47–9.

17 Wittenberg GP, Ousler JR, Peters MS. Secondary amyloidosis complicating psoriasis. *J Am Acad Dermatol* 1995; **32**: 465–8.

18 Ryan JG, Dorman AM, O'Connell PG. AA amyloidosis in psoriatic arthritis. *Ir J Med Sci* 2006; **175**: 81–2.

19 MacKie RM, Burton J. Pustular psoriasis in association with renal amyloidosis. *Br J Dermatol* 1974; **90**: 567–71.

20 McAdam KPWJ, Anders RF, Smith SR *et al.* Association of amyloidosis with erythema nodosum leprosum reactions and recurrent neutrophil leucocytosis in leprosy. *Lancet* 1975; **ii**: 572–5.

21 Neugarten J, Gallo GR, Buxbaum J *et al.* Amyloidosis in subcutaneous heroin abusers ('skin popper's amyloidosis'). *Am J Med* 1986; **81**: 635–40.

22 Pallares R, Sancho S, Nogues R *et al.* Amyloidosis (AA type) associated with nodular nonsuppurative panniculitis. *Ann Intern Med* 1983; **99**: 488–9.

23 Yamamoto S, Johno O, Kayashima K *et al.* Giant basal cell carcinoma associated with systemic amyloidosis. *J Dermatol* 1996; **23**: 329–34.

24 Pérez-Villa F, Campistol JM, Montoliu J, Trilla A. Renal amyloidosis secondary to acne conglobata. *Int J Dermatol* 1989; **28**: 132–3.

25 Bourke JF, Browne G, Gaffney EF, Young M. Fatal systemic amyloidosis (AA type) in two sisters with dystrophic epidermolysis bullosa. *J Am Acad Dermatol* 1995; **33**: 370–2.

26 Gunduz K, Vatansever S, Turel A *et al.* Recessive dystrophic epidermolysis bullosa complicated with nephrotic syndrome due to secondary amyloidosis. *Int J Dermatol* 2000; **39**: 151–3.

27 Katsikas GA, Maragou M, Rontogianni D *et al*. Secondary cutaneous nodular AA amyloidosis in a patient with primary Sjögren syndrome and celiac disease. *J Clin Rheumatol* 2008; **14**: 27–9.
28 Westermark P. Occurrence of amyloid deposits in the skin in secondary systemic amyloidosis. *Acta Pathol Microbiol Scand* 1972; **80**: 718–20.
29 Gillmore JD, Lovat LB, Persey MR *et al*. Amyloid load and clinical outcome in AA amyloidosis in relation to circulating concentration of serum amyloid A protein. *Lancet* 2001; **358**: 24–9.
30 Lachmann HJ, Goodman HJ, Gilbertson JA *et al*. Natural history and outcome in systemic AA amyloidosis. *N Engl J Med* 2007; **356**: 2361–71.
31 Kagan A, Husza'r M, Frumkin A *et al*. Reversal of nephrotic syndrome due to AA amyloidosis in psoriatic patients on long-term colchicine treatment. Case report and review of the literature. *Nephron* 1999; **82**: 348–53.
32 Ogita M, Hoshino J, Sogawa Y *et al*. Multicentric Castleman disease with secondary AA renal amyloidosis, nephrotic syndrome and chronic renal failure, remission after high-dose melphalan and autologous stem cell transplantation. *Clin Nephrol* 2007; **68**: 171–6.
33 Kobak S, Oksel F, Kabasakal Y, Doganavsargil E. Ankylosing spondylitis-related secondary amyloidosis responded well to etanercept: a report of three patients. *Clin Rheumatol* 2007; **26**: 2191–4.
34 Nakamura T, Higashi S, Tomoda K *et al*. Efficacy of etanercept in patients with AA amyloidosis secondary to rheumatoid arthritis. *Clin Exp Rheumatol* 2007; **25**: 518–22.
35 Perry ME, Stirling A, Hunter JA. Effect of etanercept on serum amyloid A protein (SAA) levels in patients with AA amyloidosis complicating inflammatory arthritis. *Clin Rheumatol* 2008; **27**: 923–5.

Dialysis-related amyloidosis

In systemic amyloidosis related to haemodialysis, the major constituent protein of amyloid fibrils is β_2-microglobulin. Most of the clinical findings are related to amyloid deposition in osseo-articular tissues [1,2]. Extensive tissue deposition of β_2-microglobulin may rarely present as masses in the buttocks [3,4], or as lichenoid lesions [5,6].

References

1 Danesh F, Ho LT. Dialysis-related amyloidosis: history and clinical manifestations. *Semin Dial* 2001; **14**: 80–5.
2 Kiss E, Keusch G, Zanetti M *et al*. Dialysis-related amyloidosis revisited. *Am J Roentgenol* 2005; **185**: 1460–7.
3 Lipner HI, Minkowitz S, Neiderman G *et al*. Dialysis-related amyloidosis manifested as masses in the buttocks. *South Med J* 1995; **88**: 876–8.
4 Takayama K, Satoh T, Maruyama R, Yokozeki H. Dialysis-related amyloidosis on the buttocks. *Acta Derm Venereol* 2008; **88**: 72–3.
5 Sato KC, Kumakiu M, Koizumi H *et al*. Lichenoid lesions as a sign of β_2-microglobulin-induced amyloidosis in a long-term haemodialysis patient. *Br J Dermatol* 1993; **128**: 686–9.
6 Uenotsuchi T, Imafuku S, Nagata M *et al*. Cutaneous and lingual papules as a sign of beta 2 microglobulin-derived amyloidosis in a long-term hemodialysis patient. *Eur J Dermatol* 2003; **13**: 393–5.

Inherited systemic amyloidosis

Several distinct genetic types of amyloidosis are recognized, which may be associated with mutations in a number of plasma proteins including transthyretin (MIM *176300), apolipoprotein AI (MIM *107680), fibrinogen A α chain (MIM *134820), lysozyme (MIM *153450), gelsolin (MIM *137350) and the 55-kDa tumour necrosis factor (TNF) receptor [1–4]. The kidney, peripheral nerves and spinal ganglia, or the heart are predominantly affected. Skin manifestations are associated with a number of systemic heredofamilial syndromes of amyloid deposition, including familial Mediterranean fever [5], the Muckle–Wells syndrome [6] and heredofamilial amyloid polyneuropathy [7–10]. The most prevalent forms of the autosomal dominantly inherited hereditary sensory neuropathies are HSN I, associated with mutations in the *SPTLC1* gene, and CMT 2b, associated with mutations in the *RAB7* gene.

Familial Mediterranean fever is inherited as an autosomal recessive disorder, and is caused by mutations in the *MEFV* gene, leading to defects in the pyrin protein which normally blunts neutrophil-mediated inflammation, probably via IL-1 down-regulation [11–13]. It may involve erysipelas-like lesions on the lower legs, urticaria, Henoch–Schönlein purpura and vasculitic nodules [5]. Associated features are intermittent fevers with abdominal pain and joint effusions, and a tendency to peritonitis, pleurisy, synovitis and renal amyloidosis. Colchicine at a dose of 1 to 2 mg daily reduces the frequency of attacks and prevents development of secondary amyloidosis. There have been case reports of benefits with catecholamine blockade (prazosin), tumour necrosis factor antagonists (etanercept, thalidomide), and IL-1 receptor blockade (anakinra) [12,13].

The Muckle–Wells syndrome, which has autosomal dominant inheritance, is characterized by periodic attacks of fever, urticaria, conjunctivitis and arthropathy with limb pains, associated with progressive perceptive nerve deafness and renal amyloidosis [6,14–16]; cold urticaria [14,15] and hyperpigmented scleroderma-moid skin lesions [17] have been described. Levels of C-reactive protein, serum amyloid A, and IL-1β are elevated. Patients with Muckle–Wells syndrome have a mutation in *NALP3/CIAS1/PYPAF1*, the gene encoding cryopyrin, a component of the inflammasome that regulates the processing of IL-1β. Treatment with the recombinant human IL-1 receptor antagonist anakinra has resulted in resolution of clinical symptoms including deafness, and normalizes laboratory abnormalities [14,16].

Trophic skin changes with skin ulceration and sweating abnormalities may develop in heredofamilial amyloid polyneuropathy [7–10]. The Finnish type of heredofamilial neuropathic amyloidosis, a gelsolin-related systemic amyloidosis characterized by cranial neuropathy and corneal lattice dystrophy, may be associated with cutis laxa, blepharochalasis and lichen amyloidosus [18]. Cutis laxa is a principal clinical manifestation of hereditary gelsolin amyloidosis (AGel amyloidosis), an age-associated systemic disease with global distribution, caused by a G654A or G654T gelsolin gene mutation [19]. Heart and liver transplantation may be successful in familial amyloidotic neuropathy [20,21].

References

1 Buxbaum JN, Tagoe CE. The genetics of the amyloidoses. *Annu Rev Med* 2000; **51**: 543–69.
2 Benson MD, Liepnieks JJ, Yazaki M *et al*. A new human hereditary amyloidosis: the result of a stop-codon mutation in the apolipoprotein AII gene. *Genomics* 2001; **72**: 272–7.
3 Aksentijevich I, Galon J, Soares M *et al*. The tumor-necrosis-factor receptor-associated periodic syndrome: new mutations in TNFRSF1A, ancestral origins, genotype–phenotype studies, and evidence for further genetic heterogeneity of periodic fevers. *Am J Hum Genet* 2001; **69**: 301–14.
4 Ando Y, Ueda M. Novel methods for detecting amyloidogenic proteins in transthyretin related amyloidosis. *Front Biosc* 2008; **13**: 5548–58.
5 Sohar E, Gafni J, Pras M, Heller H. Familial Mediterranean fever. A survey of 470 cases and a review of the literature. *Am J Med* 1967; **43**: 227–53.
6 Lieberman A, Grossman ME, Silvers DN. Muckle–Wells syndrome: case report and review of cutaneous pathology. *J Am Acad Dermatol* 1998; **39**: 290–1.
7 Rubinow A, Cohen AS. Skin involvement in familial amyloidotic polyneuropathy. *Neurology* 1981; **31**: 1341–5.

8 Auer-Grumbach M. Hereditary sensory neuropathies. *Drugs Today (Barc)* 2004; **40**: 385–94.
9 Rocha N, Velho G, Horta M *et al*. Cutaneous manifestations of familial amyloidotic polyneuropathy. *J Eur Acad Dermatol Venereol* 2005; **19**: 605–7.
10 Auer-Grumbach M. Hereditary sensory neuropathy type I. *Orphanet J Rare Dis* 2008; **3**: 7.
11 Chae JJ, Wood G, Masters SL *et al*. The B30.2 domain of pyrin, the familial Mediterranean fever protein, interacts directly with caspase-1 to modulate IL-1beta production. *Proc Natl Acad Sci U S A* 2006; **103**: 9982–7.
12 Bhat A, Naguwa SM, Gershwin ME. Genetics and new treatment modalities for familial Mediterranean fever. *Ann N Y Acad Sci* 2007; **1110**: 201–8.
13 Sugiura T, Kawaguchi Y, Fujikawa S *et al*. Familial Mediterranean fever in three Japanese patients, and a comparison of the frequency of MEFV gene mutations in Japanese and Mediterranean populations. *Mod Rheumatol* 2008; **18**: 57–9.
14 Hawkins PN, Lachmann HJ, Aganna E, McDermott MF. Spectrum of clinical features in Muckle-Wells syndrome and response to anakinra. *Arthritis Rheum* 2004; **50**: 607–12.
15 Haas N, Küster W, Zuberbier T, Henz BM. Muckle-Wells syndrome: clinical and histological skin findings compatible with cold air urticaria in a large kindred. *Br J Dermatol* 2004; **151**: 99–104.
16 Yamazaki T, Masumoto J, Agematsu K *et al*. Anakinra improves sensory deafness in a Japanese patient with Muckle-Wells syndrome, possibly by inhibiting the cryopyrin inflammasome. *Arthritis Rheum* 2008; **58**: 864–8.
17 El-Darouti MA, Marzouk SA, Abdel-Halim MR. Muckle-Wells syndrome: report of six cases with hyperpigmented sclerodermoid skin lesions. *Int J Dermatol* 2006; **45**: 239–44.
18 Boysen G, Galassi G, Kamieniecka Z *et al*. Familial amyloidosis with cranial neuropathy and corneal lattice dystrophy. *J Neurol Neurosurg Psychiatry* 1979; **42**: 1020–30.
19 Kiuru-Enari S, Keski-Oja J, Haltia M. Cutis laxa in hereditary gelsolin amyloidosis. *Br J Dermatol* 2005; **152**: 250–7.
20 Yamamoto S, Wilczek HE, Nowak G *et al*. Liver transplantation for familial amyloidotic polyneuropathy (FAP): a single-center experience over 16 years. *Am J Transplant* 2007; **7**: 2597–604.
21 Pilato E, Dell'Amore A, Botta L, Arpesella G. Combined heart and liver transplantation for familial amyloidotic neuropathy. *Eur J Cardiothorac Surg* 2007; **32**: 180–2.

Nutrition and the skin

K. Weismann, pp. 59.58–59.81

Lack of essential nutrients is most commonly due to a reduced or insufficient intake of food, malabsorption (see below), vomiting or decreased passage time of food due to diarrhoea or fistulae. Some medications may interfere with utilization of nutrients. An increased metabolic requirement of nutrients occurs during periods of sudden weight gain, such as growth and convalescence. This may lead to relative deficiencies, as seen in patients receiving long-term parenteral nutrition who may become severely deficient in zinc (p. 59.73).

Often, the cutaneous changes of inadequate nutrition are varied, reflecting combined deficiencies. When there is an apparently isolated deficiency, an underlying genetic or enzymatic defect should be suspected.

Malabsorption

Malabsorption is a condition characterized by a decreased intestinal uptake of nutrients associated with an increased faecal excretion of fat (steatorrhoea). This leads to various degrees of lack of proteins, minerals, trace elements, fat-soluble vitamins, carbohydrates and water. Some causes of malabsorption are listed in Table 59.10.

Table 59.10 Various causes of malabsorption.

Chelating substances in the gut
Phytates
Insufficient digestive enzyme activity
Pancreatic diseases (pancreatitis, mucoviscidosis)
Defective micelle formation
Obstructive jaundice, liver cirrhosis
Contaminated small bowel syndrome (i.e. presence of an abnormal bacterial flora in the small bowel)
Gastric resection (lack of hydrochloric acid production)
Stagnant loop syndrome (strictures, surgical blind loops, scleroderma, diabetic enteropathy)
Colonic reflux (intestinal fistula, extensive small bowel resection)
Agammaglobulinaemia
Defective enzyme activity or carrier function in the intestinal mucosa
Disaccharidase deficiency
Coeliac disease
Acrodermatitis enteropathica (zinc deficiency)
Hartnup disease (pellagra)
Loss of absorption capacity
Intestinal resection and bypass operation
Crohn's disease
Pernicious anaemia
Interference with intestinal lymphatics
Lymphangiectasis
Tuberculous mesenteric adenitis
Hodgkin's disease
Inadequate transport mechanisms in the blood
Abetalipoproteinaemia
Miscellaneous
Polyarteritis nodosa
Lupus erythematosus
Amyloidosis
Mastocytosis
Diabetes mellitus
Zollinger–Ellison syndrome
Protein-losing enteropathy
Hyperthyroidism
Hypothyroidism
Cronkhite–Canada syndrome
Dermatogenic enteropathy

Clinical features

Non-specific cutaneous symptoms [1,2]. Non-specific symptoms may be observed in patients who have lost weight due to malabsorption or malignant disease. The skin changes reflect general illness rather than specific disease.

Itching and acquired ichthyosis. Itch is mostly caused by dry skin. Elderly patients are especially prone to developing dry skin, which becomes eczematized. Patients with cancer, chronic liver or kidney diseases, or with lymphoma, may develop an itchy atrophic ichthyosis [3]. Hypoferraemia may cause itch, which disappears after initiation of iron therapy. Serum ferritin is a sensitive indicator of the state [4]. Polycythaemia rubra vera may cause generalized itch (see Chapters 21 and 62).

Melanosis. Malnutrition due to malabsorption may cause symmetrical melanin hyperpigmentation of the skin, although melanocyte-stimulating hormone (MSH) levels are seldom increased. Other skin colour changes associated with malnutrition are those due to wasting and atrophy, and pallor due to anaemia.

Arsenic pollution of drinking water in a primitive rural area caused blackening of hands and feet [5].

Skin appendages. Brittle nails and hair loss are frequent findings in poorly nourished patients. In some cases, lack of zinc, iron and vitamins is the main cause. In the majority of patients the aetiology is probably multifactorial.

Specific cutaneous effects [1]**.** Vitamin deficiencies occur due to malabsorption. Lack of fat-soluble vitamins, in particular, may cause skin changes including follicular hyperkeratosis (lack of vitamin A), ecchymoses and haematuria (lack of vitamin K), and cheilitis, glossitis, neuritis and dermatitis (lack of vitamin B complex). Zinc deficiency-related skin changes may be seen.

Investigations. Patients presenting with skin changes suggestive of malabsorption should have a thorough medical examination and laboratory tests to determine both the causes and the consequences of malabsorption. Relevant tests include serum calcium, zinc, folate and albumin levels, faecal fat excretion and X-ray examination of the small intestine.

Treatment. The cause of malabsorption should be treated where possible, and dietary measures instituted to ensure adequate supply of all essential nutrients from a wide variety of foods [2].

References

1 Wells GC. Skin disorders in relation to malabsorption. *BMJ* 1962; **ii**: 937–43.
2 Bender AE. Nutritional requirements. *J R Soc Health* 1985; **105**: 1–4.
3 Flint GL, Flam M, Soter NA. Acquired ichthyosis: a sign of nonlymphoproliferative malignant disorders. *Arch Dermatol* 1975; **111**: 1446–7.
4 Adams SJ. Iron deficiency, serum ferritin, generalized pruritus and systemic disease: a case-controlled study. *Br J Dermatol* 1989; **121** (Suppl. 34): 15.
5 Loewenberg S. Scientists tackle water contamination in Bangladesh. *Lancet* 2007; **370**: 471–2.

Specific syndromes with malabsorption

Cronkhite–Canada syndrome [1]
See Chapter 62.

Whipple's disease
This is a rare disease of uncertain aetiology involving the gastrointestinal tract, skin, joints, heart and lymph nodes (Chapter 62). There is diffuse hyperpigmentation of the skin, and leg nodules or erythema nodosum may occur. The involvement of the heart includes inflammatory changes of the pericardium, myocardium and endocardium and may lead to valvular insufficiency [2].

Dermatitis herpetiformis (see Chapter 40)
Enteropathy is present in at least two-thirds of all patients and may respond to a gluten-free diet. Patients may be managed on a gluten-free diet alone, and it at least enables most patients to reduce their requirement for dapsone [3].

References

1 Cronkhite LW, Canada WJ. Generalized gastrointestinal polyposis. *N Engl J Med* 1955; **252**: 1011–5.
2 McAllister HA, Fenoglio JJ. Cardiac involvement in Whipple's disease. *Circulation* 1975; **52**: 152–6.
3 Garioch JJ, Lewis HM, Sargent SA *et al.* Twenty-five years experience of a gluten-free diet in the treatment of dermatitis herpetiformis. *Br J Dermatol* 1994; **131**: 541–5.

Mucoviscidosis

Synonyms
- Fibrocystic disease
- Cystic fibrosis of the pancreas (MIM #219700)

Mucoviscidosis is an inherited disorder characterized by three major components: chronic lung disease, exocrine pancreatic insufficiency and an abnormally high sodium concentration of the sweat.

Aetiology. The mode of genetic transmission is autosomal recessive. The basic metabolic defect is unknown. The mucous secretion has an increased viscosity resulting in obstruction of the small bronchial branches, the excretory ducts of the pancreas and the bile ducts of the liver. This eventually leads to respiratory disease, pancreatic insufficiency and hepatic failure. The high sodium concentration in sweat is due to a lowered reabsorption of sodium in the sweat glands [1] (Chapter 44).

Histopathology. The exocrine sweat glands and pancreas show electron-dense bodies, and there are fewer than normal secretory vacuoles in the 'dark cells' of the sweat coils [2].

Clinical features. The main presenting features are chronic pulmonary disease, exocrine pancreatic insufficiency with malabsorption, retarded growth and hepatic disease. Skin changes in the form of acrodermatitis enteropathica-like lesions due to essential fatty acid and zinc deficiency have been seen [3,4]. Several studies have indicated that atopy is more common in patients with cystic fibrosis than in the general population [5], although the prevalence of urticaria is not increased [6]. A purpuric rash may occur in patients with cystic fibrosis.

Diagnosis. The diagnosis is established by the finding of high sodium concentration in the sweat, absence of pancreatic enzymes in the duodenum, chronic respiratory disease, retarded growth and a family history of the disease.

Aquagenic wrinkling of the palms and fingers is characterized by formation of oedematous whitish plaques on the palms on exposure to water. Cystic fibrosis should be considered in patients with this type of reaction [7].

Treatment. Respiratory infection is controlled by prolonged antibiotic therapy according to bacterial cultures. Pancreatic insufficiency is treated by pancreatic enzyme preparations orally and a diet low in fat. The liver disease and the sweat abnormality are not amenable to treatment at present.

References

1 Report of the Committee for a Study for the Evaluation of Testing for Cystic Fibrosis. *J Pediatr* 1976; **88**: 711–34.
2 Munger BL, Brunsilow SW, Cooke RE. An electron microscopic study of eccrine sweat glands in patients with cystic fibrosis of the pancreas. *J Pediatr* 1961; **59**: 497–511.
3 Hansen RC, Leme R, Revsin B. Cystic fibrosis manifesting with acrodermatitis enteropathica-like eruption. *Arch Dermatol* 1983; **119**: 51–5.
4 Schmidt CP, Tunessen W. Cystic fibrosis with periorificial dermatitis. *J Am Acad Dermatol* 1991; **25**: 896–7.
5 Tacier-Eugster H, Wuthrich B, Meyer H. Atopic allergy, serum IgE and RAST specific IgE antibodies in patients with cystic fibrosis. *Helv Paediatr Acta* 1980; **35**: 31–7.
6 Laufer P. Urticaria in cystic fibrosis. *Cutis* 1985; **36**: 245–6.
7 Katz K, Yan AC, Turner ML. Aquagenic wrinkling of the palms in patients with cystic fibrosis homozygous for the F508 CFTR mutation. *Arch Dermatol* 2005; **141**: 621–4.

Vitamins [1]

Vitamins are biologically active organic compounds, which are indispensable for the normal functions of the body. They have no direct function as an energy source or as structural tissue components, but in most cases act as coenzymes in various enzyme systems.

Reference

1 Miller S. Nutritional deficiency and the skin. *J Am Acad Dermatol* 1989; **21**: 1–30.

Vitamin A

Vitamin A (retinol) is a cyclic polyene alcohol present in yellow and green vegetables, egg yolk, butter, liver and fish oils [1]. β-Carotene occurs in fruits, carrots and green vegetables, and is absorbed and converted to vitamin A in the body. The recommended daily allowance is 5000 i.u. (equivalent to 6000–12 000 i.u. β-carotene). The plasma level in normal adults is about 600 ng/mL [2]. Vitamin A is mobilized from liver stores and transported in plasma, in which it is bound to retinol-binding protein [3].

Vitamin A is essential for the reproductive system, bone formation, vision and epithelial tissues [4]. *In vitro* studies on human keratinocytes have shown that vitamin A affects their growth and differentiation [5]. In human volunteers, 150 000 i.u. daily of vitamin A produced demonstrable retardation of keratinocyte maturation [6]. Skin disorders with abnormal keratinization, such as ichthyosis, pityriasis rubra pilaris and Darier's disease, have been treated with high doses of oral vitamin A. There is a risk of intoxication by such treatment and stereoisomers of retinoic acid are now used instead [1,7].

Vitamin A deficiency

Vitamin A deficiency is seldom seen in the Western world today. It is observed mainly in diseases causing malabsorption and is often associated with deficiency of other fat-soluble vitamins.

Clinical features. Classical manifestations of vitamin A deficiency include xerophthalmia, follicular hyperkeratosis and generalized xerosis [8]. Follicular papules are seen especially on the dorsal and lateral areas of the extremities, so-called phrynoderma. Histologically, there is lamellated hyperkeratosis around the hair follicles with keratinous plugs and atrophy of the sebaceous glands [9]. Diagnosis is confirmed by the finding of a low vitamin A level in blood and a positive response to vitamin A supplementation.

Zinc deficiency may lead to vitamin A deficiency as zinc acts on the retinol-binding protein, which is the transport protein for vitamin A and which is indispensable for mobilization of the vitamin from the liver. Furthermore, zinc acts on the oxidation–reduction interconversion of vitamin A (alcohol dehydrogenase is a zinc metalloenzyme). Lack of zinc may provoke symptoms of vitamin A deficiency [10], and night blindness in alcoholics may be due to a combined lack of vitamin A and zinc [11].

Vitamin A intoxication

Aetiology. Chronic hypervitaminosis A is observed in young children if they are persistently overdosed with strong vitamin preparations. Most reported adult cases have ingested more than 100 000 i.u. daily for several months. There is probably a risk of toxic effects if more than 50 000 i.u. daily is ingested for longer periods [1].

Clinical features. There is lethargy, anorexia, weight loss and diffuse alopecia. The skin becomes pruritic, rough and dry with desquamation. The lips are dry and cracked. Follicular keratosis, patchy erythema and purpura may occur in hypervitaminosis A or due to administration of synthetic retinoids [2]. In young children, painful swellings of the limbs due to bone changes are conspicuous.

Diagnosis. Vitamin A intoxication is diagnosed by consistent clinical findings associated with an increased vitamin A level in the blood. Radiology may demonstrate bone changes in young children and in some adults.

Treatment. No treatment is needed except immediate discontinuation of the vitamin A.

Carotenoderma

β-Carotene is the natural provitamin of vitamin A (retinol). A high intake of food containing carotene, especially carrots, causes carotenaemia (increased carotene in plasma) and may induce carotenoderma due to excess carotenes in the sweat. The condition is characterized by orange discoloration of the stratum corneum, especially on palms, soles and in areas where sebaceous glands predominate. The condition is quite harmless and subsides gradually when the dietary habits are regulated. It may occur in pregnancy as a 'pica'.

Carotenaemia is also seen in patients with hyperlipidaemia (diabetes mellitus, myxoedema) and occurs in subjects unable to convert ingested β-carotene into vitamin A [12].

β-Carotene traps free radicals and has been studied together with vitamin E and selenium as a possible dietary factor that may inhibit cancers [13], although this hypothesis remains unproven [14].

Carotenoderma provides no photoprotection [15].

References

1 Keller KL, Fenske NA. Uses of vitamins A, C, and E and related compounds in dermatology: a review. *J Am Acad Dermatol* 1998; **39**: 611–25.

2 Larsen FG, Vahlquist C, Andersson E *et al.* Oral acitretin in psoriasis: drug and vitamin A concentration in plasma, skin and adipose tissue. *Acta Derm Venereol Suppl (Stockh)* 1992; **72**: 84–8.
3 Siegenthaler G, Saurat J-H. Plasma and skin carriers for natural and synthetic retinoids. *Arch Dermatol* 1987; **123**: 1690a–2a.
4 Bollag W. Vitamin A and retinoids: from nutrition to pharmacotherapy in dermatology and oncology. *Lancet* 1983; **i**: 860–3.
5 Chopra PP, Flaxman BA. The effect of vitamin A on growth and differentiation of human keratinocytes *in vivo*. *J Invest Dermatol* 1975; **64**: 19–22.
6 Pinkus H, Hunter R. Biometric analysis of the effect of oral vitamin A on human epidermis. *J Invest Dermatol* 1964; **42**: 131–6.
7 Thomas JR, Cooke JP, Winkelmann RK. High-dose vitamin A therapy for Darier's disease. *Arch Dermatol* 1982; **118**: 891–4.
8 Frazier CN, Hu CK. Cutaneous lesions associated with a deficiency in vitamin A. *Arch Intern Med* 1931; **48**: 507–9.
9 Miller S. Nutritional deficiency of the skin. *J Am Acad Dermatol* 1989; **21**: 1–30.
10 Weismann K, Christensen E, Dreyer V. Zinc supplementation in alcoholic cirrhosis: a double-blind clinical trial. *Acta Med Scand* 1979; **205**: 361–6.
11 Solomons NW, Russel RM. The interaction of vitamin A and zinc: implications for human nutrition. *Am J Clin Nutr* 1980; **33**: 2031–40.
12 Monk BE. Metabolic carotenaemia. *Br J Dermatol* 1982; **106**: 485–8.
13 Menkes MS, Comstock GW, Vuilleumier JP *et al.* Serum beta-carotene, vitamins A and E, selenium, and the risk of lung cancer. *N Engl J Med* 1986; **315**: 1250–4.
14 Rowe PM. Beta-carotene takes a collective beating. *Lancet* 1996; **347**: 249.
15 Pathak MA. Sunscreens: topical and systemic approaches for protection of human skin against harmful effects of solar radiation. *J Am Acad Dermatol* 1982; **7**: 285–312.

Vitamin D [1,2]

Vitamin D is a group of antirachitic steroid derivatives with similar biochemical activity. It is synthesized in the body as vitamin D_3 (cholecalciferol), and is present in the diet from some animal sources (as vitamin D_3) or from plant sources as vitamin D_2 (ergocalciferol). There is little vitamin D_3 in the diet although it is present in cod-liver oil, butter, eggs and liver. Vitamin D is synthesized in the skin from 7-dehydrocholesterol, which is present in abundance, by the action of 290–320-nm UV irradiation (to previtamin D) followed by a temperature-dependent conversion stage. Vitamin D_2 is synthesized from its inactive provitamin, ergosterol, in plants, also by the action of UV irradiation. With adequate exposure to sunlight, dietary vitamin D is unnecessary [1]. Cholecalciferol is hydroxylated in the liver to form 25-hydroxyvitamin D, and further hydroxylation takes place in the kidney to form the biologically active 1,25-dihydroxyvitamin D [1,2]. Vitamin D_2 follows the same hydroxylation pathway, and is equipotent to vitamin D_3. 1α-Hydroxyvitamin D_3 is a synthetic, highly potent vitamin D analogue used in the management of hypoparathyroidism, vitamin-D-resistant rickets and osteomalacia.

Circulating vitamin D is usually measured as 25-hydroxyvitamin D, low status being defined as a level below 30–60 ng/L. Low levels do not reflect the degree of exposure to solar ultraviolet light [3]. Sunbeds (tanning parlour) have been proposed as a means to increase vitamin D status. This claim is controversial since UVA does not participate in the production of vitamin D of the skin, and UVA exposure increases the risk of skin cancer and malignant melanoma [4].

Vitamin D regulates calcium and phosphorus absorption and deposition, and influences the level of serum alkaline phosphatase. The skin is of unique importance in the synthesis, storage and release of vitamin D into the circulation [2]. Lack of vitamin D in children results in tetany and rickets (rachitis), and causes osteomalacia in adults. Elderly people produce less vitamin D_3. In children, limited exposure to sunshine may play an aetiological role; the same applies to some Asian women in the UK in whom there may be a combination of dietary deficiency and little sunlight exposure. Regular use of sunscreens may also lead to reduced synthesis of vitamin D_3 [3]. It is remarkable how exposure to sunlight a few times a week can reduce the risk of osteoporosis, osteomalacia, muscle weakness and fractures [1]. The daily need for calciferol is 400–800 i.u.

Vitamin D intoxication (long-continued administration of more than 100 000 i.u. daily) causes anorexia, vomiting, headache, diarrhoea, hypercalcaemia and hypercalciuria with osteoporosis, resembling the action of parathyroid hormone. Treatment consists of withdrawal of vitamin D, a low-calcium diet and systemic corticosteroids.

Combined calcium and vitamin D supplementation has been shown to reduce the risk of osteoporosis in people aged 50 years or older. A minimum dose of 1200 mg calcium and 800 i.u. vitamin D daily is recommended [5].

References

1 Holick MF. Sunlight 'D'ilemma. Risk of skin cancer or bone disease and muscle weakness. *Lancet* 2001; **357**: 4–6.
2 Holick MF, Smith E, Pincus S. Skin as the site of vitamin D synthesis and target tissue for 1,25-dihydroxyvitamin D_3. *Arch Dermatol* 1987; **123**: 1677–83.
3 Binkley N, Novotny R, Krueger D *et al*. Low vitamin D status despite abundant sun exposure. *J Clin Endocrinol Metab* 2007; **92**: 2130–5.
4 Levine JA, Soarce M, Spencer J *et al*. The indoor UV-tanning industry: a review of skin cancer risk, health benefit claims, and regulation. *J Am Acad Dermatol* 2005; **53**: 1038–44.
5 Reginster J-Y. Calcium and vitamin D for osteoporotic fracture risk. *Lancet* 2007; **370**: 632–3.

Vitamin E [1,2]

Synonym
- α-Tocopherol

Tocopherols are present in oils of vegetables, seeds, corn, whole wheat flour, nuts and some meats; D-α-tocopherol is the most biologically active form. The main physiological activity of tocopherol is antioxidation. Whether the vitamin is essential to humans is still a matter of debate. In rats, guinea pigs and rabbits, a true vitamin effect has been demonstrated. Various dermatological diseases and conditions have been claimed to respond to vitamin E [1–3]. So far, no true benefit has been definitely documented. Fat-soluble vitamin E is located in the stratum corneum and seems to play a role in protecting this layer from damage [2]. An inhibitory effect on hyaluronidase and a protective effect on cellular membranes and on vitamin A oxidation have been suggested, but the clinical relevance is doubtful. Neurological function in children with chronic cholestasis was improved following large doses of vitamin E [4]. Large doses of vitamin E in a controlled trial have been shown to reduce the risk of myocardial infarction [5]. Vitamin E has also been used in dermatology to reduce dapsone-induced haemolysis [6] and headache [7].

References

1 Keller KL, Fenske NA. Uses of vitamins A, C, and E and related compounds in dermatology: a review. *J Am Acad Dermatol* 1998; **39**: 611–25.
2 Edwards H. Vitamin E: an important antioxidant in the skin? *Retinoids* 2001; **17**: 43.
3 Pollack SV. Wound healing: a review. IV. Systemic medications affecting wound healing. *J Dermatol Surg Oncol* 1983; **8**: 667–72.
4 Sokol RJ, Guggenheim MA, Jannacone ST *et al.* Improved neurologic function after long-term correction of vitamin E deficiency in children with chronic cholestasis. *N Engl J Med* 1985; **313**: 1580–6.
5 Stephens NG, Parsons A, Schofield PM *et al.* Randomized controlled trial of vitamin E in patients with coronary disease: Cambridge Heart Antioxidant Study (CHAOS). *Lancet* 1996; **347**: 781–6.
6 Prussick R, Ali MA, Rosenthal D, Guyatt G. The protective effect of vitamin E on the hemolysis associated with dapsone treatment in patients with dermatitis herpetiformis. *Arch Dermatol* 1992; **128**: 210–3.
7 Cox NH. Vitamin E for dapsone-induced headache. *Br J Dermatol* 2002; **156**: 174.

Vitamin B complex

The vitamins of the B complex are of great clinical significance. Isolated deficiencies of certain B vitamins are uncommon. Mostly combined deficiencies of the vitamins belonging to the group are involved, often occurring as a result of insufficient supply of protein and other essential nutrients (zinc, essential fatty acids).

The vitamin B group includes:

1 Aneurin (thiamine) (vitamin B_1)
2 Riboflavine (vitamin B_2)
3 Niacin (nicotinic acid) (B_3)
4 Pyridoxine (vitamin B_6)
5 Cyanocobalamin (vitamin B_{12})
6 Folic acid
7 Pantothenic acid
8 Biotin (vitamin H).

Aneurin

Synonyms
- Vitamin B_1
- Thiamine

Aneurin is present in yeast, cereals, liver, meat, eggs and vegetables. It functions as cocarboxylase in carbohydrate metabolism and in numerous other enzyme systems. It is involved in growth processes and in the function of the nervous system. Deficiency results in accumulation of pyruvic and lactic acids. Dietary deficiency may be a consequence of consuming polished rice as the staple food or, more commonly, of insufficient nutrition associated with chronic alcoholism. Beer drinkers have a reduced risk of developing B vitamin deficiency due to the presence of the vitamins in beer. Hypovitaminosis B_1 may be associated with pregnancy, lactation, diabetes mellitus, ulcerative colitis, coeliac disease, achlorhydria or myxoedema [1].

Clinical features [1]. The classical form of vitamin B_1 deficiency is beriberi, characterized by anorexia, weakness, constipation, symmetrical progressive polyneuritis, cardiac insufficiency with oedema and wasting of musculature. The diagnosis is based on the history and a low urinary aneurin excretion following an injection of 1.0 mg of aneurin. Excretion of less than 50 µg indicates a deficiency state.

Treatment. Aneurin 2–3 mg is given three times daily in mild cases. With severe cardiac and gastrointestinal involvement, polyneuritis and muscular paresis, 20 mg aneurin twice a day given parenterally is indicated.

Riboflavine

Synonyms
- Vitamin B_2
- Lactoflavine

Riboflavine is a D-ribitol isoalloxazine derivative that is widely distributed in plant and animal tissues. It plays a part in intracellular redox reactions. Nutritional sources are milk and the same sources as those of vitamin B_1 [1]. The human requirement is 1–2 mg daily.

Clinical features. Deficiency becomes clinically manifest after several months of deprivation due to chronic illness and malnutrition, especially in elderly women who suffer from achlorhydria, or in malnourished children with malabsorption.

Ariboflavinosis may occur in alcoholic liver cirrhosis, and an association with other deficiencies, such as pellagra, is frequent. Clinically, there is photophobia due to conjunctivitis, sometimes with corneal vascularization, angular stomatitis (perlèche) and sore lips, tongue and mouth [1]. The tongue is purplish red and smooth. A scaly seborrhoeic dermatitis-like eruption may be seen around the nose, eyes, ears and genital area (oro-oculo-genital syndrome). There is an association with zinc deficiency as the content of the two nutrients in foodstuffs is correlated [2].

Treatment. Treatment consists of 5–15 mg riboflavine two to three times daily for 2 weeks and correction of dietary errors.

Pyridoxine

Synonyms
- Vitamin B_6
- Pyridoxal

Pyridoxine is a pyridine derivative, participating as a coenzyme in transaminase and decarboxylase reactions and in the metabolism of cystein, tryptophan and essential fatty acids. It is present in many foods including yeast, eggs and various grains. The recommended daily allowance is about 2 mg.

Although much is known about experimental deficiency in many species, the manifestations in humans are not well defined. Convulsions, anaemia and acrodynia may develop in infants [3]. Dermatitis has occurred and is attributed to disturbed metabolism of unsaturated fatty acids. Pyridoxine deficiency may follow therapy with isoniazid, hydralazine and penicillamine [4].

Vitamin B_{12}

Synonyms
- Cyanocobalamin
- Cycobemine

Vitamin B_{12} is involved in nucleic acid synthesis and erythrocyte production. Deficiency may occur in vegetarians, as plants do not contain the vitamin. Most frequently it is due to lack of the 'intrinsic factor' in pernicious anaemia. Hyperpigmentation, especially in dark-skinned races, may occur. It is most pronounced in skin flexures, such as finger and palm creases, and on the knuckles. Pigmented streaks of the nails may be seen. An enlarged, red tongue is a characteristic finding [5].

Folic acid

Folic acid is a compound consisting of pteridine, *p*-aminobenzoic acid and glutamic acid. It is present in liver, meat, green leaves and milk. In the organism, folic acid is converted to folinic acid, which is the biologically active form. The conversion requires the presence of vitamin C. Folinic acid is needed for the transport of one-carbon units and plays a role in growth and erythrocyte production. The daily requirement is estimated to be about 0.4 mg.

Although no consistent or specific cutaneous changes are related to folate deficiency, greyish brown pigmentation on light-exposed parts has been described in megaloblastic anaemia [5,6]. Cheilitis, glossitis and mucosal erosions are common. Pigmentation similar to that of vitamin B_{12} deficiency has been associated with folate deficiency in pregnancy and during lactation. Spotty pigmentation of palms and soles and pigmented palmar creases have been described. Folate deficiency is estimated by serum and erythrocyte folate levels. Subclinical deficiency may be present in patients with extensive skin disease.

Deficiency causing macrocytic anaemia may result in retinal haemorrhages [7].

Synthetic folic acid may cause anaphylactic reactions [8]. The requirement for folate supplementation during methotrexate therapy is discussed in Chapters 20 and 74.

Niacin

Synonyms
- Nicotinic acid
- Vitamin B_3

Niacin is an essential component of two coenzymes, coenzyme I (nicotinamide adenine dinucleotide, NAD) and coenzyme II (NAD phosphate, NADP), which either donate or accept hydrogen in a wide range of biochemical reactions. Tryptophan, an essential amino acid, can be transformed to niacin, which is converted to the amide in the body. Niacin is involved in the biosynthesis of ceramides as well as of other stratum corneum lipids which improve the epidermal permeability layer [9].

Pellagra [10]

Cellular deficiency of niacin, resulting from an inadequate dietary supply of niacin and tryptophan, is termed pellagra. In Western Europe and North America pellagra is only rarely encountered now, mostly in subjects living on an unbalanced diet, such as chronic alcoholics, and in patients with gastrointestinal diseases or severe psychiatric disturbances. Rare causes are functioning carcinoid tumours (Chapter 43) and Hartnup disease (p. 59.100). Therapy with isoniazid (which competes biochemically with niacin owing to a close structural resemblance), 6-mercaptopurine or 5-fluorouracil may provoke pellagra.



Fig. 59.42 Pellagra with erythematous, brownish scaling on the neck (Casal's necklace).

The classical triad of clinical features is *dermatitis*, *diarrhoea* and *dementia*, not invariably appearing in this order. Redness and superficial scaling appear on areas exposed to sunlight, heat, friction or pressure. The changes resemble sunburn and subside leaving a dusky, brown-red coloration, but this occurs more slowly than typical in sunburn and exacerbation follows re-exposure to sunlight. On the face, a symmetrical 'butterfly' eruption is frequently observed and there is often a characteristic well-marginated eruption on the front of the neck ('Casal's necklace'). Asymmetrical lesions may appear at sites of sun exposure, eczema, injury or stasis [11–12] (Figs 59.42–59.45).

Gastrointestinal symptoms include pain, diarrhoea and achlorhydria in 50% of cases. In mild instances, the mental disturbance may pass unnoticed, patients perhaps being slightly depressed or apathetic. Sometimes, there may be frank disorientation, restlessness or other severe central nervous system symptoms [13]. Peripheral neuritis and myelitis are occasionally encountered.

Histology. Histological examination shows hyper- and parakeratosis, acanthosis and multiple melanin granules throughout the epidermis. Such changes are suggestive, but not diagnostic, of pellagra.

Drug eruptions, various forms of porphyria, photodermatitis, lupus erythematosus and actinic reticuloid may cause diagnostic difficulty. The so-called pellagrous vulvitis, vaginitis and scrotal dermatitis may be attributed to accompanying ariboflavinosis and other deficiencies of the vitamin B group and of zinc.

Therapy. In severe cases, intravenous niacin is required in doses of 50–100 mg once or twice a day. Otherwise, oral niacin amide in a total dose of 0.5 g/day should be given. The amide is to be preferred, as it does not precipitate flushing, itching and burning as is seen following ingestion of niacin in large doses. Improvement can be expected within a day or two.

Kava dermopathy. Kava, a psychoactive intoxicating beverage used ceremonially and socially by Pacific Islanders, may produce a pellagra-like ichthyosiform dermopathy with widespread acquired ichthyosis [14,15]. Kava is produced by infusing dried roots of *Piper methysticum* with water or coconut milk. The cause of the skin disease has not been established; interference with tryptophan or niacin as previously suggested is not likely [15]. Interference with cholesterol metabolism akin to changes associated with lipid-lowering agents is a possibility. Kava dermopathy is curable with abstinence.

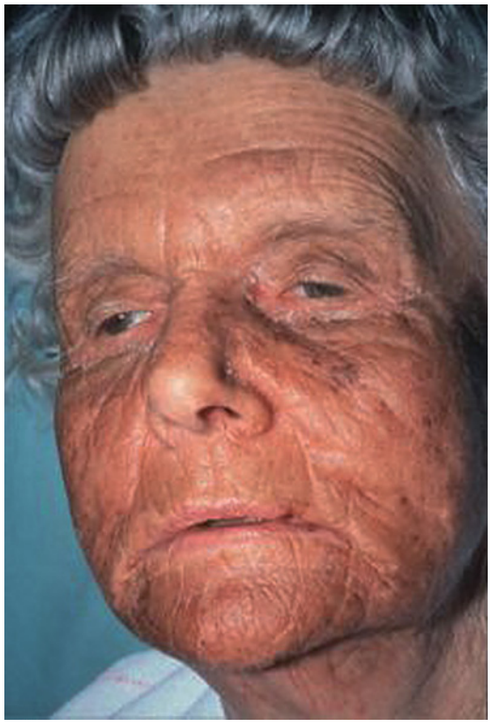


Fig. 59.43 Pellagra on the face provoked by sun exposure.

Biotin

Synonym
- Vitamin H

Biotin is a water-soluble, sulphur-containing, heterocyclic carboxylic acid involved in bacterial metabolism and possibly functioning as a coenzyme in decarboxylation and other enzymatic processes. Deficiency can be induced by feeding raw egg-white containing avidin which binds biotin and makes it poorly absorbable [16]. Short bowel syndrome in association with parenteral nutrition may cause biotin deficiency [17,18]. Symptoms include alopecia, conjunctivitis, eczema around the nose and mouth, nail dystrophy, hyperaesthesia, paraesthesia, depression and muscle pain. A multivitamin preparation supplying 60 µg of biotin daily cured an adult patient within 3 weeks [16]. Biotin seems to possess some antiseborrhoeic actions and has been used in high doses for therapy of Leiner's disease in infants (Chapter 17) [19].

Inborn errors of biotin metabolism [20]**.** The genetically determined disorders of biotin metabolism consist of two separate diseases: holocarboxylase synthetase deficiency and biotinidase deficiency. Both are transmitted as an autosomal recessive trait.

Holocarboxylase deficiency (MIM #253270) presents in the neonatal period, affected subjects having severe symptoms of organic acidaemia. The patients may have shown recurrent episodes of



(a) (b)

Fig. 59.44 Pellagra (a) in a patient with anorexia nervosa. (b) Note marked reaction in sun exposed areas on the feet.



Fig. 59.45 Pellagra on sun exposed dorsal hands.

vomiting from birth and rapid respiration as a sign of severe metabolic acidosis. There are seizures, hypo- as well as hypertonia, electroencephalogram abnormalities, and the disease progresses to death unless diagnosis and effective therapy supervene. An erythematous, scaly rash is prominent over most of the body in the patients who survive the first days of life. The skin lesions may resemble ichthyosis and seborrhoeic dermatitis. The pattern of excretion of organic acids is characteristic, especially 3-hydroxyisovaleric acid and 3-methylcrotonylglycine in urine being increased. Lactic acidaemia is striking. The molecular defect is in the enzyme holocarboxylase synthetase.

Biotinidase deficiency (multiple decarboxylase deficiency, MIM #253260) usually presents after 3 months of age. The cutaneous lesions may resemble those of acrodermatitis enteropathica, that is severe zinc deficiency, with periorificial eczematous rash on the face, nail dystrophy (onychoschizia) and skin infection. The hair is sparse, and there may be total alopecia. Neurological symptoms are prominent with myoclonic seizures, ataxia, lethargy and developmental delay [21]. There are low levels of biotin in blood and urine. The fundamental defect is in biotinidase, which normally acts on biocytin, a biotin–lysine complex, thereby separating biotin from lysine [19].

Biotin treatment. Both of the biotin-related disorders discussed above are treated with an oral dose of biotin, usually 10 mg/day but some patients need less and some have required as much as 40 mg/day.

Uncombable hair syndrome (Chapter 66) may respond to a low oral dose of biotin [22].

References

1 Miller SJ. Nutritional deficiency of the skin. *J Am Acad Dermatol* 1989; **21**: 1–30.
2 Weismann K. *Zinc Deficiency and Effects of Systemic Zinc Therapy*. Copenhagen: FADL's Forlag, 1980: 46.
3 Vilter RW, Mueller JF, Glazer HF. The effect of vitamin B_6 deficiency induced by desoxypyridoxine in human beings. *J Lab Clin Med* 1953; **42**: 335–7.
4 Capps JC, Meddler EM, Jacobs LW *et al.* Effects of orally administered *N*-acetyl-1-cysteine and *N*-acetyl-DL-penicillamine on vitamin B_6 availability and copper excretion in the rat. *Am J Clin Nutr* 1968; **21**: 715–22.
5 Noppakun N, Swasdikul D. Reversible hyperpigmentation of skin and nails with white hair due to vitamin B_{12} deficiency. *Arch Dermatol* 1986; **122**: 896–9.
6 Marks VJ, Briggaman RA, Wheeler CE. Hyperpigmentation in megaloblastic anemia. *J Am Acad Dermatol* 1985; **12**: 914–7.
7 Hughes M, Learch M. Dietary folate deficiency and bilateral retinal haemorrhages. *Lancet* 2006; **368**: 2155.
8 Stratigos JD, Katsambas A. Pellagra: a still existing disease. *Br J Dermatol* 1977; **96**: 99–106.
9 Smith J, Empson M, Wall C. Recurrent anaphylaxis to synthetic folic acid. *Lancet* 2007; **370**: 652.
10 Tanno O, Ota Y, Kitamura N, Katsube T, Inoue S. Nicotinamide increases biosynthesis of ceramides as well as other stratum corneum lipids to improve the epidermal permeability barrier. *Br J Dermatol* 2000; **143**: 524–31.
11 Findlay GH. Pellagra, kwashiorkor and sun exposure. *Br J Dermatol* 1965; **77**: 666–7.
12 Bean WR, Spies TD, Vilter RW. Asymmetric cutaneous lesions in pellagra. *Arch Dermatol Syphilol* 1944; **49**: 335–45.
13 Risum G. Pellagra et tilfælde med alvorlige symptomer central nerve systemet. *Ugeskr Læger* 1977; **113**: 935–8.
14 Ruze P. Kava-induced dermopathy: a niacin deficiency? *Lancet* 1990; **335**: 1142–5.
15 Norton SA, Ruze P. Kava dermopathy. *J Am Acad Dermatol* 1994; **31**: 89–97.
16 Roth KS. Biotin in clinical medicine—a review. *Am J Clin Nutr* 1981; **34**: 1967–74.
17 Mock DM, Delorimer AA, Liebman WM *et al.* Biotin deficiency: an unusual complication of parenteral alimentation. *N Engl J Med* 1981; **304**: 820–3.
18 McClain CI, Baker H, Onstad GR. Biotin deficiency in an adult during parenteral nutrition. *JAMA* 1982; **247**: 3116–7.
19 Nisenson A. Seborrhoeic dermatitis of infants with Leiner's disease: a biotin deficiency. *J Pediatr* 1957; **51**: 537–48.
20 Nyhan WI. Inborn errors of biotin metabolism. *Arch Dermatol* 1982; **123**: 1696–8.
21 Redondo-Maleo J, Urbon-Artero A. Facial erythema and onychoschizia. *Arch Dermatol* 2005; **141**: 1457–62.
22 Shelley WB, Shelley ED. Uncombable hair syndrome: observations on response to biotin and occurrence in siblings with ectodermal dysplasia. *J Am Acad Dermatol* 1985; **13**: 97–102.

Vitamin C [1–3]

Synonym
- Ascorbic acid

Vitamin C is a relatively strong organic acid, chemically related to the carbohydrates. Only the laevo form is biologically active. Ascorbic acid is a strong reducing agent, easily oxidized to dehydroascorbic acid, with which it constitutes a reversible redox system. Vitamin C plays a central role in collagen and ground-substance formation, metabolism of aromatic amino acids (phenylalanine, tyrosine), reduction of folic acid to folinic acid and a broad range of biochemical redox reactions, including the preservation of sulphur-containing enzymes in a reduced form. It occurs naturally in cabbage, potatoes, green vegetables and fruits. The recommended daily dose is 30–80 mg; a daily intake of 10 mg prevents scurvy.

Vitamin C deficiency

Synonyms
- Scurvy
- Scorbutus
- Hypovitaminosis C

Unlike most other animals, humans and guinea pigs are unable to synthesize ascorbic acid due to lack of the enzymatic pathways



Fig. 59.46 Scurvy. Purpuric rash on the trunk. The lower extremities were also affected.



Fig. 59.47 Scurvy, showing purpura on the hard palate.

for synthesis of L-ascorbic acid from D-glucuronic acid. In the deficiency state, collagen and ground-substance synthesis are depressed, which leads to a multiplicity of symptoms involving bones, mucous membranes and skin.

Aetiology. Lack of vitamin C is still a serious problem in many parts of the world where access to fruit and vegetables is limited and where general malnutrition prevails. By contrast, most cases in developed countries are a consequence of food faddism, ignorance or alcoholism [4,5]. Danish beer no longer contains vitamin C as an antioxidant, and can therefore no longer prevent scurvy in alcoholics [6]. Malnourished children with scurvy (Barlow's disease) [7] may still be a paediatric problem [8] and vitamin C deficiency has been observed in teenagers living on processed food devoid of fresh fruit and vegetables [9]. In patients with chronic gastrointestinal disturbances, subclinical scurvy may be present. Elderly men living alone, who rarely get fresh fruit or vegetables and who may abuse alcohol, are particularly at risk.

Scurvy may be a presenting sign of undiagnosed psychiatric illness [10], and may appear with ecchymosis, perifollicular petechiae and haemorrhagic pustules on a previously injured extremity [11].

The cause of scurvy observed in liver transplant patients is not clear [12].

Clinical features [4]. (Figs 59.46 and 59.47). The initial skin change is follicular keratosis with coiled hairs on the upper arms, back, buttocks and lower extremities. Later, perifollicular haemorrhage with blood pigment discoloration especially on the legs, swollen bleeding gums, stomatitis and epistaxis occur. Large skin haemorrhages may be seen. Anaemia is usually present, and the patient appears resentful and mentally depressed. In the infant, dental development is impaired and oral changes may be severe. Tender subperiostal haematomas may develop and dominate the picture. Chronic hypovitaminosis C with 'woody' oedema and discoloration of the legs as the presenting feature has been described. Subnormal serum levels of vitamin C are present (normal range about 17–94 μmol/L). The significance of low values without clinical symptoms is doubtful.

Treatment. The scorbutic patient should be treated with oral vitamin C 100 mg three times daily in addition to protein-rich food [4]. The response is dramatic. It is advisable to continue the therapy for several weeks to ensure repletion of the emptied body stores.

References

1 Dickman SR. The search for the specific factor in scurvy. *Perspect Biol Med* 1981; **24**: 382–6.
2 Levine M. New concepts in the biology and biochemistry of ascorbic acid. *N Engl J Med* 1986; **314**: 892–902.
3 Kutsky RJ. *Handbook of Vitamins and Hormones*. New York: Reinhold, 1973.
4 Hirschmann JV, Raugi GJ. Adult scurvy. *J Am Acad Dermatol* 1999; **41**: 895–906.
5 Leung FW, Guze PA. Adult scurvy. *Ann Emerg Med* 1981; **10**: 652–6.
6 Jørgensen J, Paulson PA, Klemp P. Skørbug. *Ugeskr Læger* 1983; **145**: 1525–7.
7 Weismann K. Infantile scurvy's true father: Vilhelm Ingerslev. *Bibl Laeger* 1996; **188**: 345–52 (Summary in English).
8 Heymann WR. Scurvy in children. *J Am Acad Dermatol* 2007; **57**: 358–9.
9 McKenna KE, Dawson JF. Scurvy occurring in a teenager. *Clin Exp Dermatol* 1993; **18**: 75–7.
10 Arron ST, Lizo W, Maurer T. Scurvy: a presenting sign of phychosis. *J Am Acad Dermatol* 2007; **57**: S8–10.
11 Walters RW. Scurvy with manifestations limited to a previously injured extremity. *J Am Acad Dermatol* 2007; **57**: S 48–9.
12 Hatuel H, Buffet M, Mateus C, Calmos Y *et al*. Scurvy in liver transplant patients. *J Am Acad Dermatol* 2006; **55**: 154–6.

Kwashiorkor and marasmus [1,2]

Kwashiorkor is a nutritional syndrome with characteristic cutaneous changes due to severe protein malnutrition with relative carbohydrate excess. In children, there is retardation of skeletal and mental development, muscular wasting, fatty infiltration of the liver and oedema. Marasmus is the result of prolonged starvation, a wasting syndrome, resulting in 40–50% reduction in body weight but with no peripheral oedema.

Kwashiorkor

Aetiology [2]. Protein–energy deficiency is one of the commonest and most widespread nutritional disorders in developing countries. The majority of kwashiorkor cases are found in countries where the diet consists of corn, rice or beans. Kwashiorkor is more common in children than in adults and is a major paediatric problem in certain parts of the world. The onset in infancy is during the weaning and postweaning period. In Europe and North America, occasional cases are seen in patients suffering from malabsorption or eating a diet that includes an inadequate amount of protein. Milder forms are probably not uncommon, particularly in the elderly.

Kwashiorkor refers to the 'deposed child' who is no longer suckled. It is a multiple deficiency syndrome. The cause is related to lack of essential amino acids, vitamins and trace elements, particularly zinc. The skin manifestations, hair changes and failure to thrive may mimic those seen in acrodermatitis enteropathica. Serum zinc is low, but this may be attributable partly to hypoalbuminaemia. Hospitalized children may show persistent hypozincaemia after clinical cure has occurred, indicating a need for zinc supplementation together with vitamins and protein-rich nutrition [3,4].

Clinical features [1,2,5]. The symptoms of kwashiorkor usually first develop between the age of 6 months and 5 years. The most important feature in the child is a failure to thrive, with inhibition of growth and mental development; oedema and muscle wasting are also found.

The skin lesions are initially erythematous and later purple or reddish brown in colour with marked exfoliation. In milder cases a lacquered 'flaky paint' ('enamel paint') or 'cracked skin' appearance is present. The hair is dry and lustreless and may become light red-brown in colour. In more severe cases it may be prematurely grey or show a 'pepper and salt' appearance, and become sparse, fine and brittle.

The skin often shows dyschromia with hypopigmentation, perhaps the result of phenylalanine deficiency, and patchy postinflammatory hyperpigmentation. In severe cases pigmentary changes are particularly striking. There is convincing evidence that the skin changes of kwashiorkor are primarily due to zinc deficiency [6]. Mucosal lesions, such as cheilosis, xerophthalmia and vulvovaginitis may be found, which are related to other deficiencies.

Mental disturbances are variable and may appear either as apathy or irritability. The child does not smile; when it does, it is a sign of recovery.

Table 59.11 Clinical features distinguishing kwashiorkor from pellagra.

Kwashiorkor	Pellagra
Children more than adults	Adults more than children
Dermatitis with systemic signs of apathy and oedema	Dermatitis precedes gastrointestinal and neuropsychiatric symptoms in most cases
Eruption generalized; pale, ill-defined; 'crackled skin'	Exposed areas; red, thickened, well-defined lesions; later, dry, branny scales
Hair light, 'pepper and salt' appearance, thin	Normal
Nails sometimes soft and thin	Normal
High mortality	Low mortality

Oedema is the result of hypoalbuminaemia (less than 2.5 g/100 mL). The α- and β-globulins are low, while an increase in gammaglobulin is usual.

Hypoglycaemia with hypothermia, coma and severe bacterial or parasitic disease are rare, often fatal, complications [7].

Mild cases of kwashiorkor appearing in the elderly show as a 'cracked skin' appearance on the front of the legs and lower abdomen. They have been reported under the title of geriatric nutritional eczema.

Prognosis. The short-term prognosis of mild cases which are given full dietary treatment is good, but mortality is high in severe and relapsing cases.

Diagnosis. Diagnostic difficulties occur in mild cases. The dietary history, 'cracked skin' and oedema, particularly when associated with pigmentary changes, should lead to the suspicion of protein deficiency. Acrodermatitis enteropathica may be mistaken for kwashiorkor. The features distinguishing kwashiorkor from pellagra are shown in Table 59.11.

Prevention and treatment. Prevention of kwashiorkor depends on increasing the supply of animal proteins, and on education and social welfare in poor areas.

In an established case, a complete and balanced diet should be given as soon as possible. Skimmed milk is the most useful treatment, presumably through its amino-acid content. Appropriate measures should be taken to correct any electrolyte disturbance.

Marasmus [1]

Aetiology. Marasmus is derived from the Greek *marasmos*, which means wasting. It is a result of severe protein and calorie deprivation for a prolonged period. Worldwide, marasmus is more frequent than kwashiorkor and is especially seen in developing countries where food is absent or scarce. Severely ill, hospitalized patients may show signs of marasmus. Low zinc levels are a predominant feature.

Clinical features. Patients have a wrinkled, loose, dry skin. There is a substantial loss of subcutaneous fat tissue, and the facial expression is described as 'monkey facies' due to loss of the buccal adipose tissue. Follicular hyperkeratosis may be prominent in

adults. The hair is thin and sparse and readily lost and the nails are fissured. Skin ulceration occurs.

Diagnosis. The combined finding of a severely reduced body weight, loss of subcutaneous fat, poor hair and nail growth and a loose, wrinkled, dry skin that appears too large is diagnostic. There is no peripheral oedema.

Prevention and treatment. This is as for kwashiorkor. Skin ulceration may respond to topical zinc paste or oral zinc supplementation in addition to a protein-rich nutritional supply.

References

1 Miller SJ. Nutritional deficiency and the skin. *J Am Acad Dermatol* 1989; **21**: 1–30.
2 McLaren DS. Skin in protein energy malnutrition. *Arch Dermatol* 1987; **123**: 1674–6.
3 Golden BE, Golden MHN. Plasma zinc, rate of weight gain, and the energy cost of tissue deposition in children recovering from severe malnutrition on a cow's milk or soya protein-based diet. *Am J Clin Nutr* 1981; **34**: 892–9.
4 Hambidge KM, Walravens PA. Zinc deficiency in infants and preadolescent children. In: Prasad AS, Oberlaeas D, eds. *Trace Elements in Human Health and Disease*, Vol. 1. New York: Academic Press, 1976: 21–32.
5 Editorial. Classification of infantile nutrition. *Lancet* 1970; **2**: 302–3.
6 McLaren. Skin in protein energy malnutrition. *Arch Dermatol* 1987; **123**: 1674–6.
7 Wharton B. Hypoglycaemia in children with kwashiorkor. *Lancet* 1970; **i**: 170–20.

Calcification and ossification of the skin [1–5]

Calcification or calcinosis cutis is the result of deposition of calcium and phosphate in organic matrices of the tissues. The process occurs in a wide range of different conditions. The mineral phase may be arranged in the manner seen in normal bone formation, *ossification*. If the deposition is not organized, the condition is termed *calcification*. The organic matrix consists largely of collagen or elastic tissue. All organic matrices of calcified or ossified tissues contain protein-bound phosphorus. In pathological ectopic calcification, the matrix is altered and contains acid proteins. In pseudoxanthoma elasticum, γ-carboxyglutamic acid, an amino acid present in calcium-binding proteins, has been found in high concentrations in the dermis. The solid phase of calcified tissue is made up of hydroxyapatite and amorphous calcium phosphate. Once formed, the focus increases in size by growth and may result in disorganized masses of pasta-like material.

Aberrant calcium deposition in the skin may be divided into three main groups:

1 Associated with localized or widespread tissue changes or damage (dystrophic calcification)
2 Unassociated with tissue damage or demonstrable metabolic disorder (idiopathic calcification)
3 Associated with an abnormal calcium and phosphorus metabolism (metastatic calcification) (Table 59.12).

Table 59.12 Various forms of calcinosis cutis.

Dystrophic calcification
Calcification usually associated with localized injury
Congenital
Fibrodysplasia ossificans
Traumatic
Subcutaneous injection with calcium-containing heparin
Radiotherapy
Foreign-body, haematoma, fat cell necrosis
Inflammatory
Acne, varicose veins, tuberculous granuloma, postoperative inflammation in scars
Degenerative infarcts (arterial, venous), venous stasis, parasitic cysts (e.g. echinococcal cysts)
Neoplastic
Benign: sebaceous cysts, lipomas, angiomas, calcifying epithelioma of Malherbe
Malignant: some liposarcomas
Calcification associated with widespread tissue injury
Dermatomyositis
Generalized scleroderma (Thibierge–Weissenbach or CREST syndrome)
Systemic lupus erythematosus
Acrodermatitis atrophicans
Pseudoxanthoma elasticum
Ehlers–Danlos syndrome
Idiopathic calcification
Calcinosis universalis; calcinosis circumscripta
Solitary nodular calcification of the skin ('cutaneous calculus')
Pinnal calcification
Tumoral calcinosis
Metastatic calcification
Hypercalcaemic
Hyperparathyroidism
Sarcoidosis
Vitamin D excess
Milk–alkali syndrome
Destructive bone disease
Metastatic carcinoma, lymphoma, multiple myeloma, leukaemia
Paget's disease
Normocalcaemic
Chronic renal failure
Pseudohypoparathyroidism

Dystrophic calcification [6]

The calcinosis is confined to the dermis or subcutaneous tissue and related to local connective tissue or fatty tissue damage, in the absence of any detectable abnormality of calcium metabolism. The calcification appears a variable time after the injury; for example, in dermatomyositis it occurs after a few years and in generalized scleroderma usually after 10 or more years. Dystrophic calcification may also occur in systemic lupus erythematosus [1,7,8].

Electrical injuries may be particularly likely to result in dystrophic calcification. An accumulation of calcium salts on dermal collagen fibres of pig skin was observed in scars following electrical injury [9]. Deposition of calcium salts in high concentration on a damaged skin surface may induce dermal calcification, as observed following electroencephalography in children [10]. In these cases, the skin was abraded prior to application of an electrode paste containing calcium chloride; lesions developed shortly after electroencephalography and disappeared in 2–6 months without therapy. An intact stratum corneum is protective.

Idiopathic calcification

Calcinosis universalis

The deposition of calcium in the dermis, subcutis and muscles is unrelated to any recognizable tissue injury or metabolic disorder.

Many cases reported in the literature under the diagnosis were probably suffering from undetected dermatomyositis, systemic lupus erythematosus or scleroderma, but there remain a number of instances in which no underlying disease is demonstrable [2].

Histopathology. Initially, calcium particles gather around fat cells. Electron microscopy of early lesions has shown apatite crystals lying in parallel to the collagen fibres [11].

Clinical features. Nodules or plaques 0.5–5.0 cm in size are symmetrically distributed over the extremities and, less commonly, the trunk. The lesions may become tender and ulcerate, discharging chalk-like creamy material consisting mainly of calcium phosphate with a small amount of calcium carbonate. After ulceration, a slowly healing sinus remains. Fingertip lesions are often painful, while in other sites there may be limitation of movement due to stiffening of the skin. The disease is eventually fatal.

X-ray examination is valuable for localizing the deeper deposits. Biochemical investigations are normal.

Treatment. Surgical removal of painful deposits may give temporary relief. In some instances, corticosteroids may be considered, although the response is variable. Cellulose phosphate combined with a low-calcium diet should be considered [12].

Calcinosis circumscripta

There may be only a few calcium deposits in the skin. Most cases of calcinosis circumscripta are found in generalized scleroderma or dermatomyositis but rarely it may occur as an idiopathic disorder [3]. Keloid formation with calcification has been described [13].

Idiopathic calcinosis of the scrotum [13,14]

Calcinosis scrotalis (Fig. 59.48) is a rare, benign disorder consisting of multiple asymtomatic firm nodules 0.2–1.0 cm in diameter. It is often misdiagnosed as scrotal cysts. Dystrophic calcification in the penis has been reported following trauma, Peyronie's disease and cytostatic therapy.

Calcifying epithelioma of Malberbe

See Chapter 53.

Tumoral calcinosis [2,15,16]

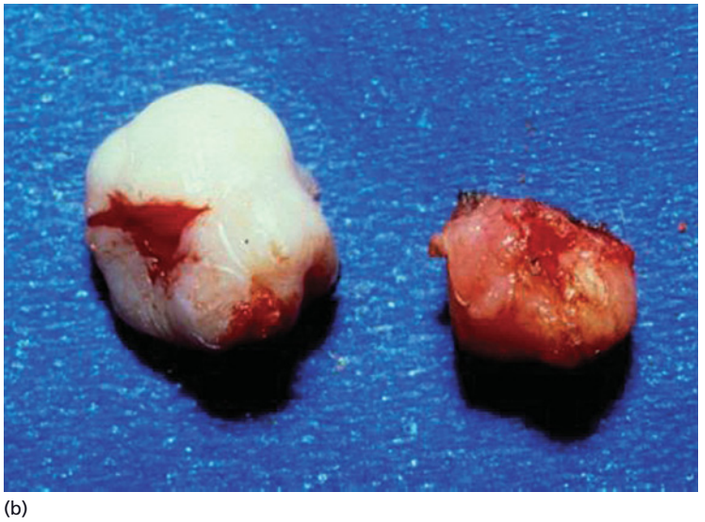
Tumoral calcinosis occurs most commonly in the native population of Africa, particularly among younger age groups. Clinically, the lesions present as swellings around the large joints (hip, elbow, ankle and scapula), but there is no actual involvement of the joint. Extrusion of calcified material, which has been likened to a suspension of procaine-penicillin, may take place. Histologically, there is initially collagen necrobiosis, which results in cyst formation and a foreign-body response. The calcification is first granular; later, dense deposits are seen [15]. The aetiology is unknown, but it is probably a form of dystrophic calcification caused by mechanical injury.

Pinnal calcification [2]

Calcified ear cartilage has been observed in several conditions such as Addison's disease, ochronosis, acromegaly, diabetes mellitus, hyperthyroidism, systemic chondromalacia (von Meyenburg's disease), familial cold hypersensitivity and frostbite.



(a)



(b)

Fig. 59.48 (a) Calcinosis scrotalis; (b) solitary nodules after removal.

Metastatic calcification [3,17]

In metastatic calcification, calcinosis occurs as a precipitation of calcium salts in normal skin, subcutaneous tissue, muscles and internal organs.

Aetiology. In all cases, there is an increase in the serum levels of calcium or phosphate. Hypercalcaemia may be due to hyperparathyroidism, vitamin D intoxication, milk–alkali syndrome or destructive bone disease with excessive osteoclastic activity. Metastatic carcinoma, multiple myeloma, leukaemia and Paget's disease

of bone may all be associated with metastatic calcification. Calciphylaxis, now termed calcific uraemic arteriolopathy (Chapters 49 and 62), is a potentially fatal syndrome, in which there is usually a raised serum calcium phosphate product. Most cases occur in the context of chronic renal insufficiency in patients undergoing long-term renal dialysis, in whom there has been development of secondary or tertiary hyperparathyroidism [18].

Clinical features. The cutaneous manifestations are similar to those of calcinosis universalis. Additional clinical features reflect the primary disease.

Treatment. Only in hypervitaminosis D and the milk–alkali syndrome can improvement be expected by regulation of dietary habits and withdrawal of vitamin D and milk intake. In cases of renal insufficiency, restriction of dietary phosphate and oral administration of an aluminium hydroxide gel may be useful.

Ossification of the skin

Synonyms
- Osteomatosis
- Osteoma cutis

Osteomatosis represents cutaneous calcification with *de novo* bone formation in the skin [19]. It has been noted in suprapubic prostatectomy scars and in otherwise normal postoperative scars [20]. It may also occur in collagen vascular disease (lupus erythematosus, scleroderma and dermatomyositis) [21]. Cutaneous ossification without any known causative factor (also known as osteomatosis cutis, primary osteoma cutis or osteosis cutis) has been reported [17].

Post-acne osteoma cutis

This is a rare complication of long-standing acne vulgaris. It has been reported to occur as pigmented osteomas during tetracycline or minocycline therapy. The osteomas that represent metaplastic bone formation are located in the mid- or reticular dermis, and consist of concentric lamellae with lacunae, Haversian canals and marrow cavities. With the use of tetracycline, more patients develop bluish, 1–2-mm, moveable papules on the face. Treatment consists of surgery or local 0.5% tretinoin cream with resultant transepidermal elimination of the lesions [22].

References

1 Rothe MJ, Grant-Kels JM, Rothfield NF. Extensive calcinosis cutis with systemic lupus erythematosus. *Arch Dermatol* 1990; **126**: 1060–3.
2 Mehregan AH. Calcinosis cutis. A review of the clinical forms and report of 75 cases. *Semin Dermatol* 1984; **3**: 53–61.
3 Walsh JS, Fairley JA. Calcifying disorders of the skin. *J Am Acad Dermatol* 1995; **33**: 693–706.
4 Lewis VJ, Holt PJ. Subcutaneous calcification following high-dose radiotherapy. *Br J Dermatol* 2004; **150**: 1049–50.
5 Eich D, Scharffetter-Kochanek K, Weilrauch J *et al*. Calcinosis cutis and subcutis: an unusual non-immunologic adverse reaction to subcutaneous infections of low-molecular-weight calcium containing heparins. *J Am Acad Dermatol* 2004; **50**: 210–4.
6 Touart DM, Sau P. Cutaneous deposition diseases. Part II. *J Am Acad Dermatol* 1998; **39**: 527–44.
7 Bhatia S, Silverberg NB, Don PC, Weinberg JM. Extensive calcinosis cutis in association with systemic lupus erythematosus. *Acta Derm Venereol* 2001; **81**: 446–7.
8 Quismorio FP, Dubois EL, Chandor SB. Soft-tissue calcification in systemic lupus erythematosus. *Arch Dermatol* 1975; **111**: 352–6.
9 Karlsmark T, Danielsen L, Thomsen HK *et al*. Tracing the use of torture: electrically induced calcification of collagen in pig skin. *Nature* 1983; **301**: 75–8.
10 Wiley HE, Eaglstein WE. Calcinosis cutis in children following electro-encephalography. *JAMA* 1979; **242**: 455–6.
11 Cornelius CE, Tenenhouse A, Weber JC. Calcinosis cutis: metabolic, sweat, histochemical, X-ray diffraction and electron microscopic study. *Arch Dermatol* 1968; **98**: 219–29.
12 Marks J. Studies with ^{47}Ca in patients with calcinosis cutis. *Br J Dermatol* 1970; **82**: 1–9.
13 Song DH, Lee KH, Kang WH. Idiopathic calcinosis of the scrotum. Histopathologic observations of fifty-one nodules. *J Am Acad Dermatol* 1988; **19**: 1095–101.
14 Ito A, Sakamoto F, Ito M. Dystrophic scrotal calcinosis originating from benign eccrine epithelial cysts. *Br J Dermatol* 2001; **144**: 146–50.
15 McKee PH, Liomba NG, Hutt MSR. Tumoral calcinosis. A pathological study of 56 cases. *Br J Dermatol* 1982; **107**: 669–74.
16 Whiting DA, Simson IW, Kallmeyer JC, Dannheimer IP. Unusual cutaneous lesions in tumoral calcinosis. *Arch Dermatol* 1970; **102**: 465–73.
17 Raimer SS, Archer ME, Jorizzo JL. Metastatic calcinosis cutis. *Cutis* 1983; **32**: 463–5.
18 Kolton B, Pedersen J. Calcinosis cutis and renal failure. *Arch Dermatol* 1974; **110**: 256–7.
19 Goldminz D, Greenberg RD. Multiple miliary osteoma cutis. *J Am Acad Dermatol* 1991; **24**: 878–81.
20 Lim MO, Mukherjee AB, Hansen JW. Dysplastic cutaneous osteomatosis: a unique case of true osteoma. *Arch Dermatol* 1981; **117**: 797–801.
21 Maclean GD, Main RA, Andersen TE *et al*. Connective tissue ossification presenting in the skin. *Arch Dermatol* 1966; **94**: 168–74.
22 Moritz DL, Elewski B. Pigmented postacne osteoma cutis in a patient treated with minocycline: report and review of the literature. *J Am Acad Dermatol* 1991; **24**: 851–3.

Iron metabolism [1]

The total iron content of an adult man is 4–5 g, 60–70% of which is blood haemoglobin iron. Small amounts of ferritin iron are present in erythrocytes, plasma and leukocytes [1]. Iron is stored in the liver, spleen and bone marrow as ferritin and haemosiderin. It is released readily from these sites according to the body's needs. Serum ferritin levels vary with the iron status of the individual and with certain diseases. The body has a limited ability to excrete iron, and homeostasis is therefore regulated mainly by adjusting iron absorption. Iron compounds need to be reduced to the ferrous form (Fe^2) to be absorbed. Ascorbic acid, which can reduce and chelate iron, enhances iron absorption.

The mechanism of iron absorption is not completely understood. Recent evidence points to an iron-transport system involving the binding of iron to the plasma membrane of mucosal cells and the interaction of transferrin in plasma with these sites.

Total iron in faeces varies between 6 and 16 mg/day depending on the amount ingested. Most of it is unabsorbed food iron.

Iron deficiency

Iron deficiency is a major risk factor for disability and disease worldwide, affecting about two billion people. Targeted iron supplementation, fortification of foods and selective plant breeding are means to improve iron nutritional status in the developing world [2].

General symptoms include fatigue, palpitations on exertion, sore tongue with atrophic filiform papillae, angular cheilitis (per-

lèche), dysphagia and koilonychia (Chapter 65). Generalized itch may occur [3], and hair loss with or without morphological changes of the hair shaft may be seen [4,5]. In infants and children, anorexia, retarded growth and decreased resistance to infections are the outstanding features. The recommended daily allowance is 10 mg in infants, 10–15 mg in children, 18 mg in young males and females, and 10 mg in both sexes above 20 years of age [6]. Pregnant women should receive supplemental iron, as the increased need for iron can barely be met by ordinary diets [7].

The diagnosis of iron deficiency is based on low serum iron levels, clinical symptoms and improvement following iron therapy. Serum ferritin is significantly correlated to bone marrow haemosiderin iron and provides a convenient method for assessing iron stores in normal subjects [8].

Iron intoxication

Daily ingestion of 50–75 mg iron is reported as safe [1,2], and even higher intakes in some individuals turn out to be harmless. Chronic iron intoxication has been reported among Bantus consuming beer that is brewed in iron utensils. The iron is in a soluble form and may supply a substantial net supply of iron. Iron-contaminated cereals do not induce siderosis because iron is present in a less available form.

Haemochromatosis (MIM +253200 and others) [1,9]

Haemochromatosis is a syndrome characterized by the triad of hyperpigmentation, diabetes mellitus and cirrhosis of the liver, associated with increased iron deposition in the internal organs. Hypogonadism is frequently present. The female/male ratio is 1:10. Onset of symptoms is gradual, usually between 40 and 60 years.

Aetiology. Haemochromatosis can be found in the following conditions: idiopathic or primary haemochromatosis; chronic iron intoxication (e.g. Bantu haemochromatosis); chronic liver disease and iron overload (alcoholic haemochromatosis); hepatic haemosiderosis in anaemic patients with an ineffective erythropoiesis; and congenital transferrin deficiency. The cause of primary haemochromatosis is basically unknown, but a defective control of iron absorption is involved. The abnormality is inherited as an autosomal recessive trait (see Chapter 62). Erythrocyte ferritin is increased 60-fold in idiopathic haemochromatosis, which allows a distinction between this disorder and alcoholic liver disease with iron overload [10]. In alcoholic haemochromatosis, alcohol consumption, particularly red wine and iron-containing beverages, play an aetiological role. Whether the acquired form is seen in patients heterozygous for the trait is not known.

Histopathology. Liver biopsy in primary haemochromatosis shows marked iron deposits in the parenchymal cells and to a lesser degree in the Kupffer cells. The hyperpigmentation of the skin is due to increased epidermal melanin and upper dermal melanophages, but iron deposits can be identified in the deeper dermis.

Clinical features. The skin shows a distinctive grey-brown pigmentation, especially on the face, flexural creases and exposed parts. This may precede other signs by many years but can appear late in the course. Sometimes, the buccal mucosa is involved as in Addison's disease but adrenal insufficiency is not present. The various skin changes were studied in 100 patients [11]. There was almost 100% frequency of hyperpigmentation, 75% had hair loss (including axillary and pubic hair), about 50% had koilonychia and 45% had ichthyosis-like, atrophic dry skin. Less frequent signs included palmar erythema, striate onychia, leukonychia and spider angiomas (findings that may be seen in cirrhosis of any cause). Hepatomegaly, diabetes, testicular atrophy, heart disease and weight loss are additional findings. Arthropathy, present in 25–50% of the patients, resembles rheumatoid arthritis, but serology is negative.

Diagnosis. The diagnosis should be suspected in a patient with diabetes mellitus, liver cirrhosis and hyperpigmentation. Liver biopsy is usually diagnostic.

Routine laboratory tests may reveal evidence of chronic hepatic disease or of diabetes mellitus. Total serum iron is increased to the range 180–300 mg/100 mL [1], serum transferrin saturation is above 80%, and the transferrin level and the total iron binding capacity (TIBC) may be reduced [9,11]. Serum and erythrocyte ferritin is high, reflecting the increased iron stores [10]. HLA-typing has revealed an increased frequency of HLA-A3 and -B14 [12] but has largely been superseded by genotyping for the commoner haemochromatosis genes (Chapter 62).

Treatment. A liver concentration above 100 µmol/g iron weight is an indication for therapy [1,7]. Organ damage may be reversed by reducing the excessive iron stores by repeated venesection for 1–2 years. Serum iron and serum transferrin and transferrin saturation remain unchanged until excess iron has been removed. Serum or erythrocyte ferritin should be monitored as a guide to the efficacy of treatment. Family members should have their serum iron estimated and, if found to have iron overload, should be treated with prophylactic venesection.

References

1 Underwood EJ. *Trace Elements in Human and Animal Nutrition*. New York: Academic Press 1977: 13–55.

2 Zimmermann M, Hurrell R. Nutritional iron deficiency. *Lancet* 2007; **370**: 511–20.

3 Adams SJ. Iron deficiency and other haematological causes of generalized pruritus. In: Bernhard JD, ed. *Itch: Mechanisms and Management of Pruritus*. New York: McGraw-Hill, 1994: 243–50.

4 Blankship ML. Dysplastic hairs in iron deficiency anaemia. *Cutis* 1971; **7**: 467.

5 Hard S. Non-anaemic iron deficiency as an aetiological factor in diffuse loss of hair of the scalp in women. *Acta Derm Venereol Suppl (Stockh)* 1963; **43**: 652–9.

6 Food and Nutrition Board. *Recommended Dietary Allowances*. Washington, DC: National Academy of Sciences, 1974.

7 Finch CA, Monsen ER. Iron nutrition and the fortification of food with iron. *JAMA* 1972; **219**: 1462–5.

8 Millman N, Pedersen NS, Visfeldt J. Serum ferritin in healthy Danes: relation to marrow haemosiderin iron stores. *Dan Med Bull* 1983; **30**: 115–20.

9 Anhalt GJ, Dubin HV. Hemochromatosis and cirrhosis. In: Callen JP, ed. *Cutaneous Aspects of Internal Disease*. London: Year Book, 1981: 525–30.

10 Weyden MB, Vander BM, Fong H *et al.* Erythrocyte ferritin content in idiopathic haemochromatosis and alcoholic liver disease with iron overload. *BMJ* 1983; **286**: 752–4.

11 Chevrant-Breton J, Simon M, Bourel M *et al.* Cutaneous manifestations of idiopathic hemochromatosis: study of 100 cases. *Arch Dermatol* 1977; **113**: 161–5.

12 Shewan WG, Mouat SA, Allan TM. HLA antigens in haemochromatosis (Letter). *BMJ* 1976; **i**: 280–2.

Sulphur metabolism [1]

Sulphur is a vital element for the normal function of the human body. It is an essential component of the amino acids methionine and cysteine and of chondroitin sulphate, which are involved in keratinization and formation of dermal collagen, respectively. Dietary thionine and cysteine are the main precursors for the synthesis of sulphur-containing components in the body. In homocystinuria there is a metabolic block in the pathway; clinical features include tissue-paper scars on the hands and sparse, fair hair due to impaired keratin formation. When the supply of sulphur-containing amino acids is inadequate, less sulphur is available to maintain nail and hair growth, but the keratin produced seems to be normal [2]. The liver plays a central role in degradation of sulphur-containing amino acids. In chronic liver disease, low urinary levels of inorganic sulphate are present [1].

In exfoliative psoriasis with increased epidermopoiesis, relative sulphur depletion is found and the urinary excretion of inorganic sulphate is decreased. Hair loss in chronic exfoliative dermatoses may be related to diversion of sulphur-containing amino acids to synthesis of skin protein instead of hair keratin formation [2]. Mucopolysaccharide synthesis in the dermis is influenced by certain hormonal factors. Thyrotrophin (thyroid-stimulating hormone, TSH) has a stimulant action on connective tissue and the pituitary somatrophic hormone (growth hormone, GH) stimulates chondroitin sulphate formation.

Trichothiodystrophy

Trichothiodystrophy is a sulphur-deficient brittle hair syndrome associated with ectodermal dysplasias [3,4]. The hair is short and brittle with a characteristic microscopy in polarized light showing alternating light and dark bands (Chapter 66). There is a 50% decrease or more in the cysteine and sulphur content of the hair. The disease is inherited as an autosomal recessive trait; there are photosensitive (MIM #601675) and non-photosensitive (MIM #234050) variants. Collodion baby syndrome may herald trichothiodystrophy [5].

References

1 Mårtensson J. *Studies on Human Sulphur Metabolism*. Linköping: Linköping University Medical Dissertations, 1981: no. 119.
2 Roe DA. Sulphur metabolism in relation to cutaneous disease. *Br J Dermatol* 1969; **81** (Suppl. 2): 49–69.
3 Itin PH, Sarasin A, Pittelkow MR. Trichothiodystrophy: update on the sulfur-deficient brittle hair syndromes. *J Am Acad Dermatol* 2001; **44**: 891–920.
4 Richetta Giustini S, Rossi A, Calvieri S. What's new in trichothiodystrophy. *J Eur Acad Dermatol Venereol* 2001; **15**: 1–4.
5 Larrégue M, Guillet G. Collodion baby syndrome with neonatal signs of trichothiodystrophy misdiagnosed as Netherton syndrome: reassessment of a previous diagnostic error. *Ann Dermatol Venereol* 2007; **134**: 245–8.

Zinc metabolism [1–3]

Zinc belongs to the group of essential trace elements that comprises zinc, iron, copper, manganese, nickel, cobalt, molybdenum, selenium, chromium, iodine, fluorine, tin, silicon, vanadium and arsenic. High concentrations of zinc are present in shellfish, legumes, nuts, whole grain and green leafy vegetables, whereas fruits usually contain insignificant levels. Wine, beer and spirits contain very low concentrations of zinc. The zinc supply depends largely on the protein content of the food, and protein undernourishment will lead to an insufficient zinc supply.

Recommended dietary allowance of zinc [4]**.** The daily oral intake of zinc should average 3 mg in infants less than 6 months, 5 mg in infants 0.5–1.0 years old, 10 mg in children 1–7 years old and 16 mg from 11 years old onwards. Pregnant and lactating women should receive 20–25 mg zinc daily.

Biological functions. More than 300 catalytically active zinc metalloproteins and more than 2000 zinc-dependent transcription factors involved in gene expression of various proteins have been recognized [5]. Zinc is indispensable to the normal function of all cells, cellular systems, tissues and organs in the human body. The essentiality is related mainly to its function as the metal moiety of important enzymes, such as alkaline phosphatase, alcohol dehydrogenase and several different dehydrogenases, and digestive enzymes. Zinc regulates DNA and RNA polymerases, thymidine kinase and ribonuclease, and plays an important role in immunological functions.

Zinc deficiency

Dietary zinc deficiency, like iron deficiency, is a worldwide risk factor, most prevalent in the developing world. It is involved in severe deficiency syndromes such as kwashiorkor, marasmus and growth retardation. It affects about 2 billion people mainly living on phytate- and fibre- rich cereals, and soy products [6].

Zinc deficiency may be caused by a specific absorptive defect, acrodermatitis enteropathica, or may be due to diseases of the gastrointestinal tract causing diarrhoea and malabsorption (conditioned, or acquired, zinc deficiency).

Acrodermatitis enteropathica (MIM #201100 and others)

Acrodermatitis enteropathica was first recognized in 1936 by the Swedish dermatologist Thore Brandt [7] and further described by Danbolt and Closs [8] (Fig. 59.49). It is a rare disease believed to be transmitted as an autosomal recessive trait. In Denmark, the prevalence is about 1/500 000 inhabitants. Adema disease in blackpied cattle of Dutch descent, an autosomal recessive disease due to reduced zinc absorption, represents an animal parallel to acrodermatitis enteropathica in man [9] (Fig. 59.50).

Aetiology. Zinc absorption in acrodermatitis enteropathica is abnormally low, in young patients about 2–3% compared to 27–65% in normal adults [10]. The cause of the specific zinc malabsorption is not known. It can be overcome by an oral zinc load. Without zinc therapy, serum zinc levels are consistently low.

Clinical features. The disease typically starts after weaning or earlier if the infant is not given breast milk. The child turns peevish, withdrawn and photophobic, and develops a vesicobullous dermatitis on hands, feet and periorificial areas. The scalp hair is lost. Diarrhoea is often present. Growth is retarded and there is a decreased resistance to infections. Wound healing is poor and skin lesions tend not to heal [3,11].



Fig. 59.49 Acrodermatitis enteropathica with typical eczematous skin lesions. The vermilion area is free, the hair growth poor and sparse.



Fig. 59.50 Adema disease. The black-pied calf shows stunted growth, a poor scaly fur and characteristic keratotic muzzle eczema.

Prognosis. Without proper management, the prognosis is poor and in the past a lethal outcome within 4–5 years was the rule.

Treatment. Halogenated 8-hydroxyquinolines (e.g. diodoquin) were formerly used successfully for therapy on an empirical basis. Experimental animal studies using rats have shown that 8-hydroxyquinolines, which were used as antibacterial agents, increase ^{65}Zn absorption significantly [3]. Zinc sulphate for acrodermatitis enteropathica was introduced in the 1970s [3,11]. An oral zinc dose of 2–3 mg/kg/day cures all clinical manifestations, apart from hair and nail growth, within a few days. Prolonged high-dose therapy up to adult age is necessary, then a continuous zinc supplementation is indicated, often with oral doses of 1–2 mg zinc/kg/day.

Endemic nutritional zinc deficiency [6]

Endemic zinc deficiency presenting with dwarfism and hypogonadism as the main symptoms has been reported from rural districts in Iran, Egypt and Turkey. The chronic zinc deficiency is attributed to the diet, which consists mainly of unleavened whole grain bread with a high fibre and phytate content. Zinc deficiency has been described in severely malnourished children in Jamaica, Egypt and various parts of Africa [12]. In the Western world anorexia nervosa has been reported with symptoms of acquired zinc deficiency, often described as 'acrodermatitis enteropathica' [13] although it is acquired deficiency.

Acquired zinc deficiency

Zinc depletion syndrome. Where there is disturbed bowel function, zinc loss is increased; if combined with decreased absorption and low dietary zinc intake, severe zinc depletion will develop within 1–3 months. Zinc depletion syndrome was originally identified in patients who received prolonged total parenteral nutrition without zinc [14,15]. Most patients had undergone extensive intestinal resections. The serum zinc level was decreased, often below 20 µg/100 mL (3 µmol/L) (normal range 70–125 µg/100 ml or 10–19 µmol/L).

Zinc deficiency in breastfed infants. Premature infants receiving mother's milk are at risk of developing zinc deficiency due to rapid growth and insufficient zinc supply via the breast milk. Premature infants have an extra need for zinc, and zinc absorption is lower than in mature infants (Fig. 59.51a). Zinc deficiency may also be seen in normal infants due to low zinc levels in their mother's milk (Fig. 59.51b) [16].

Diseases of liver and pancreas. Chronic zinc deficiency has been reported in patients suffering from malabsorption–malnutrition associated with alcoholic liver cirrhosis and alcoholic pancreatitis [17]. A defective exocrine pancreatic function causing malabsorption and increased urinary zinc excretion in liver cirrhosis add to a negative zinc balance.

Cancer chemotherapy. Cancer chemotherapy for leukaemia in children may provoke zinc deficiency [18].

Zinc deficiency and the skin [19]

Acute zinc deficiency. General symptoms include septicaemia, photophobia and mental depression. Skin changes consist of eczematous eruptions on face, hands, feet, in the anogenital regions and around the body orifices. Finger and palm skin creases show characteristic flat bullous lesions surrounded by brownish erythema (Fig. 59.52). Oozing lesions may be seen on the sacral area and heels in bedridden patients. Some lesions are necrotic and burn-like. There is angular stomatitis with perioral lesions sparing the vermilion border.



(a) (b)

Fig. 59.51 (a) Zinc deficiency in a premature breastfed infant and (b) in a normal breastfed infant.



Fig. 59.52 Acute zinc depletion syndrome with denuded finger tips and bullae on finger flexural creases.



Fig. 59.53 Chronic zinc deficiency with scaly eczema on the perianal area. Note peripheral collarette scaling.

Chronic zinc deficiency. The patient is listless and mentally depressed. Skin lesions are typically seen on areas subject to repeated pressure and trauma, such as elbows, knees, knuckles, malleolar regions of the ankles and the sacral area. The lesions are brownish and scaly, sometimes psoriasis-like (Fig. 59.53). Seborrhoeic dermatitis-like changes may be seen on the face, and acne may flare.

A non-itchy, scaly dermatitis on the trunk has been described in zinc-deficient alcoholics.

Hair and nail changes. In zinc deficiency, hair and nail growth ceases or stops. Diffuse thinning of the scalp hair progresses, eventually leading to total alopecia. Structural changes of the hair may be observed, such as broken spearhead-like endings, transverse striation of the shaft, pseudomonilethrix, longitudinal splits and



Fig. 59.54 Beau's line on thumbnail in a case of zinc depletion syndrome, appearing one month after start of zinc therapy. Note faster growth of left thumb nail, typically seen in right-handed patients.

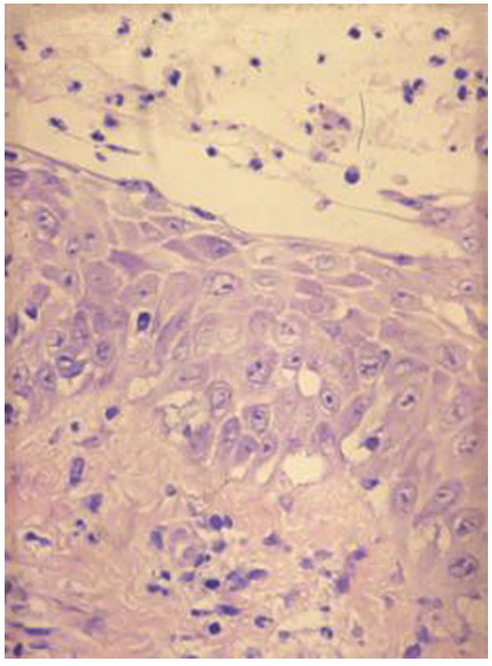


Fig. 59.55 Acute zinc deficiency with spongiotic dermatitis and degenerate basal cells.

bayonet hairs. Severe zinc deficiency causes total arrest of nail growth. Transverse depressions (Beau's lines) on the fingernails become visible about 4 weeks after zinc therapy is started and normal nail growth is re-established (Fig. 59.54) [20].

Pathology. In the acute stage, light microscopy reveals spongiosis, sometimes with suprabasal cysts and clefts (Fig. 59.55). The horny layer is often separated or lost, and necrosis of the epidermal cells may be seen. In chronic zinc deficiency, there are chronic eczema or psoriasis-like changes of the epidermis (Fig. 59.56). Electron microscopy of acute lesions shows degenerate basal cells

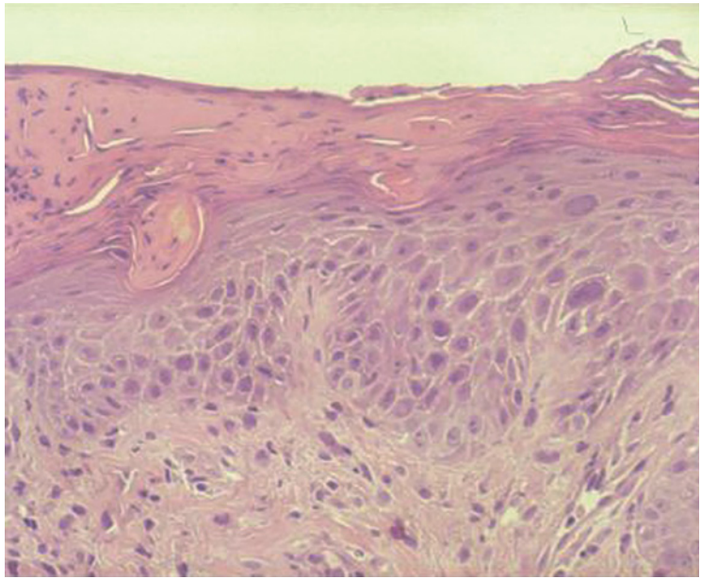


Fig. 59.56 Chronic zinc deficiency with parakeratosis, acanthosis and slight spongiosis.

with slender cytoplasmic protrusions and an intact basal lamina with multiple invaginations.

Diagnosis. Severe zinc deficiency is usually suspected from the clinical findings. The serum zinc and alkaline phosphatase levels are low and will rise during zinc therapy [19]. It is important to consider the level of plasma albumin as albumin binds 60–70% of circulating zinc. As a result, hypoalbuminaemia is associated with lowered serum zinc values, which may not necessarily reflect a state of zinc deficiency.

In suspect cases, a therapeutic trial with oral or parenteral zinc should be undertaken. If no clinical improvement occurs within a few days and the serum alkaline phosphatase remains stable as the serum zinc level goes up, the patient is not deficient in zinc.

Treatment with zinc. In adult patients, oral zinc sulphate ($Zn_2SO_4{\cdot}7H_2O$) tablets of 0.2 g (45 mg elemental zinc) are given two to three times a day (about 2 mg zinc/kg/day). Similar doses on a body weight basis are given to children. Parenterally, 0.2–0.3 mg zinc/kg/day (about 10–20 mg/day in adult patients) is sufficient and safe. For prophylactic purposes, total parenteral nutrition should supply no less than 70–80 µg zinc/kg/day. Infants and premature babies on parenteral nutrition should receive a prophylactic dose of 0.1–0.3 mg/kg/day [21].

There is no evidence of benefit from the use of zinc sulphate for patients with chronic leg ulcers [22], common cold [23] or acne vulgaris [24].

A variety of cutaneous disorders not related to zinc deficiency have been reported to respond to zinc supplementation. Zinc has no known pharmacological effect, so the significance of such observations seems dubious.

References

1 Kirchgessner M, Roth HP, Weigand E. Biochemical changes in zinc deficiency. In: Prasad AS, Oberleas D, eds. *Trace Elements in Human Health and Disease*. London: Academic Press, 1976: 189–225.

2 Underwood EJ. *Trace Elements in Human and Animal Nutrition*, 4th edn. New York: Academic Press, 1977.
3 Weismann K. *Zinc Deficiency and Effects of Systemic Zinc Therapy*. Copenhagen: FADL's Forlag, 1980: 26–8.
4 Food and Nutrition Board. *Recommended Dietary Allowances*, 8th edn. Washington, DC: National Academy of Sciences, 1980.
5 Prasad AS. Zinc and enzymes. In: Prasad AS. *Biochemistry of Zinc*. New York: Plenum Press 1993: 17–33.
6 Prasad AS. Zinc deficiency. *Br J Dermatol* 2003; **326**: 409–10.
7 Brandt T. Dermatitis in children with disturbances of general condition and absorption of food. *Acta Derm Venereol Suppl (Stockh)* 1936; **17**: 513–46.
8 Danbolt N, Closs K. Acrodermatitis enteropathica. *Acta Derm Venereol Suppl (Stockh)* 1942; **23**: 127.
9 Weismann K, Flagstad T. Hereditary zinc deficiency (Adema disease) in blackpied cattle, an animal parallel to acrodermatitis enteropathica. *Acta Derm Venereol* 1976; **56**: 151–4.
10 Weismann K, Hoe S, Knuden L *et al.* ^{65}Zinc absorption in patients suffering from acrodermatitis enteropathica and in normal adults assessed by whole-body counting techniques. *Br J Dermatol* 1979; **101**: 573–9.
11 Michaelsson G. Zinc therapy in acrodermatitis enteropathica. *Acta Derm Venereol Suppl (Stockh)* 1974; **54**: 377–81.
12 Golden PE, Golden MHN. Plasma zinc, rate of weight gain, and the energy cost of tissue deposition in children recovering from severe malnutrition on a cow's milk or soya-protein based diet. *Am J Clin Nutr* 1981; **34**: 892–9.
13 Quirk CM, Seykora J, Wingate BJ *et al*. Acrodermatitis enteropathica associated with anorexia nervosa. *JAMA* 2002; **288**: 2655–6.
14 Weismann K, Hjorth N, Fischer A. Zinc depletion syndrome during long term intravenous feeding. *Clin Exp Dermatol* 1976; **1**: 237–42.
15 Kay RG, Tasman-Jones C, Whiting R *et al*. A syndrome of acute zinc deficiency during total parenteral alimentation in man. *Ann Surg* 1976; **183**: 331–40.
16 Ottevanger V, Hansen ER, Petersen CS, Weismann K. Severe conditioned zinc deficiency in breastfed premature infants. *Eur J Pediatr Dermatol* 1994; **4**: 13–6.
17 Vallee BL, Wacker EWC, Bartholomay F *et al.* Zinc metabolism in hepatic dysfunction. I. Serum zinc concentrations in Laënnec's cirrhosis and their validation by sequential analysis. *N Engl J Med* 1986; **255**: 403–8.
18 Cutler EA, Palmer J, Kontras SB. Chemotherapy and possible zinc deficiency. *N Engl J Med* 1977; **297**: 168–72.
19 Weismann K. Zinc metabolism and the skin. In: Rook A, Savin J, eds. *Recent Advances in Dermatology*, Vol. 5. London: Churchill Livingstone, 1980: 109–29.
20 Weismann K. Lines of Beau: possible markers of zinc deficiency. *Acta Derm Venereol Suppl (Stockh)* 1971; **57**: 88–90.
21 Shils ME, Burke AW, Greene HI *et al*. Guidelines for essential trace element preparations for parenteral use. A statement by an expert panel. *J Am Acad Dermatol* 1979; **241**: 2051–4.
22 Wilkinson EAJ, Hawke CI. Does oral zinc aid the healing of chronic leg ulcers? *Arch Dermatol* 1998; **134**: 1556–60.
23 Weismann K, Jakobsen JP, Weismann JE *et al.* Zinc gluconate for common cold. *Dan Med Bull* 1990; **37**: 279–81.
24 Weismann K, Wadskov S, Søndergaard J. Oral zinc sulphate therapy for acne vulgaris. *Acta Derm Venereol* 1977; **57**: 357–60.

Copper metabolism

The normal adult body contains about 80 mg of elemental copper. Copper in plasma occurs in two forms: about 90% is firmly bound as the blue copper protein coeruloplasmin, the remainder is loosely bound to plasma proteins, primarily albumin. Copper competes with the albumin-binding sites for zinc, so fluctuations in concentration of one of these metals are reflected by a change in concentration of the other. Coeruloplasmin is an oxidase involved in iron utilization. It does not play a role in copper transport to the tissue; this is done by albumin, which is the true transport protein. Copper is part of superoxide dismutase, catalysing superoxide anion radicals into hydrogen peroxide and oxygen.

Copper-induced green hair

Green hair is usually caused by deposition of copper from exogenous sources. Usually, the patient has blond or reddish hair that has been exposed to physical or chemical damage (sun damage or bleaching) whereby high-sulphur matrix proteins (mainly cysteine) are exposed, and are therefore available to bind copper ions. A high copper concentration may occur in swimming-pool water due to copper-containing algicides, and in household tapwater due to copper piping [1,2]. Hair shampoo with an added copper-chelating agent such as dimethylcystein (penicillamine) can remove the green discoloration.

Copper deficiency

Copper deficiency has been reported to occur in infants receiving milk low in copper, and in malnourished children given high-calorie nutrition with an insufficient copper supply. The symptoms include anaemia, neutropenia and failure to thrive.

Menkes' kinky hair syndrome (MIM #309400). This is an X-linked defect in copper absorption, resulting in low copper levels in blood, liver and hair. There is progressive mental deterioration, metaphyseal lesions, degenerative aortic elastin and defective keratinization of hair (Chapter 66). There is no effective treatment [3].

Wilson's disease (hepatolenticular degeneration syndrome) (MIM #277900). This is a rare, inborn error of copper metabolism, inherited as an autosomal recessive trait [4]. It is characterized by cirrhosis of the liver and degenerative changes in the brain, particularly the basal ganglia. Deposition of copper takes place primarily in the liver, brain, kidneys and cornea (Kayser–Fleischer ring). The patients have low coeruloplasmin and plasma copper levels.

Treatment consists of cupriuretic chelating agents such as penicillamine or by competing intestinal copper absorption with oral zinc [4].

References

1 Mascaró JM, Ferrando J, Fontarneau R *et al.* Green hair. *Cutis* 1995; **56**: 37–40.
2 Munkvad S, Weismann K. Copper-induced green hair. *Ugeskr Læger* 1996; **158**: 3791–2.
3 Danks DM. Steely hair, mottled mice and copper metabolism. *N Engl J Med* 1975; **293**: 1147–8.
4 Hoogenraad TU, van der Hamer CJA, Hattum JV. Effective treatment of Wilson's disease with oral zinc sulphate: two case reports. *BMJ* 1984; **289**: 273–6.

Selenium metabolism [1]

Selenium is an essential element of the enzyme glutathione peroxidase. It plays a role against oxidative damage by endogenous peroxides. Selenium deficiency has long been known in several animal species. Selenium-deficient rats grow slowly, develop cataracts, lose their hair and show aspermogenesis. In humans, selenium deficiency has been reported in children, causing hypopigmented skin lesions and various other symptoms. Treatment consists of supplementation of selenium in low doses of

2 mg/kg/day [2]. Patients with psoriasis, atopic dermatitis, dermatitis herpetiformis and acne vulgaris have a lower glutathione peroxidase activity than normal controls [3], although the significance of this is unclear. In a study on malignant melanoma, significantly lower serum selenium levels were demonstrated as compared with controls [4]. Serum selenium levels have been shown to be of a prognostic value in the follow-up of malignant melanoma and cutaneous T-cell lymphoma [5]. There is no apparent protective effect of selenium supplementation against the development of non-melanoma skin cancer [6–8].

Selenium is incorporated as the sulphide into shampoos for the treatment of seborrhoeic dermatitis. Selenium sulphide is water-insoluble and possesses a very low toxicity. A possible protective role of selenium on cancer, cardiovascular diseases and rheumatic diseases has attracted much attention but there is no proven reason to recommend selenium supplementation.

References

1 Underwood EJ. *Trace Elements in Human and Animal Nutrition*. New York: Academic Press, 1977: 302–46.
2 Vinton NE, Dahlstrom KA, Strobel CT *et al*. Macrocytosis and pseudoalbinism: manifestations of selenium deficiency. *J Pediatr* 1987; **111**: 711–7.
3 Juhlin L, Edqvist L-E, Ekman LG *et al*. Blood glutathione–peroxidase levels in skin disease: effect of selenium and vitamin E treatment. *Acta Derm Venereol Suppl (Stockh)* 1982; **62**: 211–4.
4 Reinhold U, Biltz H, Bayer W *et al*. Serum selenium levels in patients with malignant melanoma. *Acta Derm Venereol Suppl (Stockh)* 1989; **69**: 132–6.
5 Deffuant C, Celerier P, Boiteau HL *et al*. Serum selenium in melanoma and epidermotropic cutaneous T-cell lymphoma. *Acta Derm Venereol Suppl (Stockh)* 1994; **74**: 90–2.
6 Clark LC, Combs JF Jr, Turnbull BW *et al*. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group. *JAMA* 1996; **276**: 1957–63.
7 Bialy TL, Rothe MJ, Grant-Kels JM. Dietary factors in the prevention and treatment of nonmelanoma skin cancer and melanoma. *Dermatol Surg* 2002; **28**: 1143–52.
8 Fleshner N, Zlotta AR. Prostate cancer prevention: past, present and future. *Cancer* 2007; **110**: 1889–99.

Skin disorders in diabetes mellitus

Diabetes mellitus [1,2]. Diabetes mellitus is a metabolic disorder characterized by elevated fasting and postprandial blood glucose levels and a variety of multisystem complications, mainly in the blood vessels, eye, kidney, nervous system and integument. Three main types can be distinguished. Type 1, also known as insulin-dependent diabetes mellitus or juvenile-onset diabetes, is characterized by abrupt onset of symptoms, insulinopenia, dependence on insulin injections, proneness to ketoacidosis and lack of ability to produce C peptide. Type 2, non-insulin-dependent diabetes mellitus or adult-onset diabetes, is characterized by lack of ketoacidosis except under stressful circumstances, ability to produce C peptide, a tendency to obesity and improvement following loss of weight. Type 3, secondary diabetes, is an additional type of diabetes, which occurs as a complication of pancreatic, hormonal or genetic disease or following ingestion of certain drugs or chemical compounds.

There are several reviews of skin disorders associated with diabetes mellitus [2–8].

Skin symptoms due to diabetic vascular abnormalities [3–5]

Diabetic microangiopathy. Both small and large blood vessels are affected in diabetes mellitus. In diabetic microangiopathy, there is proliferation of endothelial cells and deposits of PAS-positive material in the basement membrane of arterioles, capillaries and venules with resulting decreased luminal area [9]. Basement-membrane thickening is a characteristic finding in diabetic and prediabetic patients, but it is neither absolute nor pathognomonic for the disease [10]. The diabetic microangiopathy precedes manifest abnormalities of the disease, and it is possible that vascular changes are the primary expression of the disease. Microangiopathy is responsible for the retinopathy, nephropathy and possibly also neuropathy and dermopathy associated with diabetes.

Erysipelas-like erythema [10]. This condition is seen mostly in elderly diabetic patients with an average duration of diabetes mellitus of 5 years. Well-demarcated, red areas occur on the legs or feet, and there may be underlying destructive bone disease caused by a small vessel insufficiency. Cardiac decompensation may be involved.

Wet gangrene of the foot. This is a late manifestation of diabetic microangiopathy. Non-diabetic atherosclerotic subjects tend to develop a dry form as a result of large vessel insufficiency.

Diabetic rubeosis [11]. A peculiar rosy reddening of the face, and sometimes of the hands and feet, may be seen in long-standing diabetes. The changes have been attributed to decreased vascular tone or diabetic microangiopathy. Rubeosis may have some practical diagnostic significance, especially in fair-skinned patients.

Diabetic dermopathy (diabetic shin spots). This is the most common dermatosis associated with diabetes mellitus. Microangiopathy and neuropathy are involved [12]. Lesions are predominantly situated on the shins, forearms, thighs and over bony prominences. About half of patients show such lesions, more frequently men than women. The initial lesion is an oval, dull-red papule 0.5–1 cm in diameter. It evolves slowly, producing a superficial scale, leaving an atrophic brownish scar. The colour is due to haemosiderin in histiocytes near the vessels [13] (Fig. 59.57). Microscopically, a combination of vascular disease with PAS-positive thickening of the vessel wall and minor collagen changes is found. Although not confirmed in all studies, recent research suggests that there is a significant correlation between the presence of these lesions and other complications of diabetes, such as retinopathy, nephropathy and neuropathy [14].

Large vessel disease [4]. Atherosclerosis is the second form of vascular disease frequently associated with diabetes mellitus. The patient shows intermittent claudication with pallid and cool skin distally on the extremities. The postural test discloses delayed filling of the veins. Common clinical sequelae are myocardial infarction, cerebral thrombosis, nephrosclerosis and ischaemic gangrenous lesions of the legs and feet. Microangiopathy is usually present together with large vessel involvement.



Fig. 59.57 Diabetic dermopathy on both shins.



Fig. 59.58 Diabetic foot with neurotrophic ulceration and necrosis ('mal perforans').

Diabetic neuropathy

Elderly patients with an insidious onset of the disease are especially at risk. Commonly, there is a distal symmetrical polyneuropathy with mixed motor and sensory nerve involvement. The motor neuropathy of the foot is characterized by dorsally subluxed digits, distally displaced plantar fat pads, depressed metatarsal heads, hammer toes and pes cavus [3]. Proper foot care is essential to prevent formation of indolent perforating ulcers ('mal perforans'). A painless and slowly penetrating ulcer of the sole and of other pressure sites is suggestive of diabetic neuropathy. The ulcer is circular and punched out in shape, occurring in the middle of a callosity (Fig. 59.58). An initial subepidermal haemorrhagic bulla may give rise to discoloration of the surrounding skin [4]. Loss of temperature and pain sensation and absence of the ankle reflex (an early sign of diabetic neuropathy) indicate a neuropathic origin. Sensory abnormalities of the lower extremities include numbness, tingling, aching and burning. Burning feet and restless legs are common complaints, which intensify at night while lying down. Autonomic neuropathy may cause decreased or absent sweating of the lower extremities with compensatory sweating in other skin areas. Damage to autonomic nerves of the skin in chronic advanced cases is manifested by oedema, erythema and atrophy [3].

The complex nature of the diabetic foot requires special attention. There is a multifactorial aetiology [6,8]. Predisposing factors include abnormal plantar pressure points, foot deformities and minor trauma. Peripheral neuropathy causes ulcers, loss of ankle jerks and vibration sensation. The foot has accentuated plantar arches and hammer toes, there is interdigital maceration leading to bacterial and fungal infection. Diabetic angiopathy leads to ulceration, necrosis, gangrene and osteomyelitis [15].

Local treatment of the ulcer consists of repeated debridement, treatment of infection, dressings and pressure-relieving footwear [8,16]. Simple surgery such as split skin grafting or minor toe amputations may be necessary [16], and some patients require more complex orthopaedic procedures to correct abnormal foot shape.

Cutaneous infections in diabetes mellitus

Skin infections due to *Staphylococcus aureus* and group A *Streptococcus haemolyticus* are common in diabetic patients [17]. Before insulin and antibiotics were available, infections causing severe furuncles, carbuncles and styes were frequent among diabetic individuals. Invasive *Pseudomonas* infection of the ear can progress through cellulitis and osteitis to cranial nerve damage and meningitis with a high mortality rate, so-called malignant otitis externa (Chapter 68) [18].

Non-clostridial gas gangrene. This complication develops in the soft tissues near a gangrenous focus. It was diagnosed in 17% of diabetics who were admitted to hospital because of gangrene or ulceration [19]. The commonest pathogens are *Escherichia coli*, *Klebsiella*, *Pseudomonas* and *Bacteroides* spp. in various combinations. The outcome is generally good.

Candida albicans. *Candida albicans* infections of mouth, nail folds, genitals and intertriginous skin areas are frequent in diabetics. Candidiasis may be the presenting feature of diabetes, and is frequently seen in diabetic patients whose disease is not well controlled [3]. A high glucose level of the saliva seems to account for the oral infection [20]. Phimosis is a common complaint of diabetic men, and recurring candidal infection is usually the cause. Dermatophyte infections are not more frequent in diabetic than in non-diabetic individuals [21].

Insulin resistance and acanthosis nigricans [22–24]

Tissue resistance to insulin is a major feature underlying the development of acanthosis nigricans in many diseases (e.g. Cushing's syndrome, acromegaly, Laurence–Moon–Bardet–Biedel syndrome, Prader–Willi syndrome and congenital lipodystrophy). There are two syndromes of insulin resistance. The type A syndrome has been reported in hyperandrogenetic women with clinical signs of virilization or accelerated growth (the acronym HAIR-AN has been proposed: HA, hyperandrogenism; IR, insulin resistance; AN, acanthosis nigricans). A genetic defect at the insulin receptor or in a post-receptor pathway has been postu-



Fig. 59.59 Necrobiosis lipoidica with ulcerations on the shins.



Fig. 59.60 Scleredema diabeticorum with a 'buffalo hump' in a young woman with diabetes mellitus.

lated. The type B syndrome has been reported in older women with signs of immunological dysfunction. High plasma levels of insulin are thought to contribute to the development of acanthosis nigricans.

Various skin disorders associated with diabetes mellitus

Necrobiosis lipoidica [2–8]. Necrobiosis lipoidica is associated with diabetes mellitus (Fig. 59.59). Frequencies of diabetes between 42% and 62% have been reported in patients with necrobiosis lipoidica, whereas necrobiosis lipoidica is uncommon (0.3%) among diabetic patients [3]. See also Chapter 60.

Disseminated granuloma annulare (Chapter 60). This is rarely seen in diabetic patients; the evidence that granuloma annulare is associated with diabetes mellitus is inconclusive [8,25].

Pruritus. Pruritus was once considered a typical symptom of diabetes mellitus. The frequency of generalized pruritus in diabetic patients is unknown. Anogenital pruritus may be due to secondary infection with candidiasis or haemolytic streptococci.

Stiff joints and waxy skin. Waxy tight skin on the backs of the hands and limited joint mobility may be seen in patients with insulin-dependent diabetes [8,26].

Scleredema diabeticorum. Whether post-infectious scleredema and diabetic scleredema are identical diseases, with a more severe course in the diabetes-associated form due to altered host response, is still a matter of debate [27]. The most common sites of involvement are the neck and upper back (Fig. 59.60). The condition is mainly seen in overweight adults with non-insulin-dependent diabetes, is essentially permanent, painless and causes no morbidity. There is no specific treatment although penicillin, methotrexate, ciclosporin and PUVA have been used with various degrees of benefit.

Vitiligo (Chapter 58). Vitiligo occurs more frequently in diabetic individuals. In late-onset diabetes, a 4.5% frequency has been reported [28].

Lichen planus (Chapter 41). An increased incidence of abnormal glucose tolerance tests in patients with lichen planus, especially oral lichen planus, has been reported [29]. The overall support for a true association seems limited [6].

Haemochromatosis (Chapter 62). The main symptoms are liver disease, hyperpigmentation, joint disease, hypogonadism and, eventually, diabetes.

Eruptive xanthomas of the skin. Eruptive xanthomas may develop in diabetic patients with hyperlipidaemia. The lesions slowly resolve when the diabetes is properly managed (Fig. 59.61).

Finger pebbles. Among 60 patients with diabetes mellitus, 45 (75%) had a pebbly appearance of the knuckle and distal finger skin. Similar changes were observed in 21% of control subjects [30]. The changes may be of external origin (trauma) or internal (acanthosis nigricans).

Skin tags. Skin tags are small, soft, pedunculated lesions occurring on eyelids, neck and axillae, often associated with obesity. Among 216 patients with skin tags, 57 (26%) had diabetes of the non-insulin-dependent type, of whom only about one-quarter were classified as obese [31].



Fig. 59.61 Eruptive xanthomas in a diabetic patient with hyperlipidaemia.



(a)



(b)

Fig. 59.62 (a) Perforating collagenosis on the back of a 64-year-old woman with diabetic retinopathy. (b) Close-up view.

Local insulin reactions [6,32]. Insulin may cause immediate local reactions, starting as erythema, which turn urticarial within 30 min and subside within an hour; these are probably IgE mediated. Serious generalized immediate reactions are rare.

The most common reactions are delayed, starting about 2 weeks after onset of insulin therapy. An itchy nodule develops at the site of injection. It lasts for days and heals with hyperpigmentation and perhaps a scar. Delayed hypersensitivity is involved.

Insulin lipodystrophy. Insulin lipodystrophy is rare. Patients present with atrophic plaques at the sites of insulin injection. There is atrophy of the subcutaneous fat. The lesions seldom show complete spontaneous resolution. The mechanism is not known.

Reactive perforating collagenosis (folliculitis) (Fig. 59.62). There have been reports of perforating collagenosis in patients with diabetes with and without renal insufficiency. The cause is attributed to diabetic microangiopathy and lesions are due to minor injury such as pressure or scratching [8,33].

Diabetic bullae. Diabetic bullae are uncommon, but believed to be a distinct marker for diabetes [34,35]. The location is the lower legs and feet, occasionally hands and fingers. They range in size from less than one centimetre to several centimetres (Fig. 59.63). A typical blister arises on a non-inflamed base, and heals without scarring in 2–5 weeks. Histological examination shows intra- or subepidermal separation without acantholysis.

References

1 National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes* 1979; **28**: 1039–57.

2 Perez MI, Kohn SR. Cutaneous manifestations of diabetes mellitus. *J Am Acad Dermatol* 1994; **30**: 519–31.

3 Huntley AC. The cutaneous manifestations of diabetes. *J Am Acad Dermatol* 1982; **7**: 427–55.

4 Kalkoff KW. Diabetes and the skin. *Hexagon* 1982; **9**: 1–10.

5 Braverman IA. *Skin Signs of Systemic Disease*, 3rd edn. Philadelphia: Saunders, 1998: 457–64.

6 Ferringer T, Miller OF III. Cutaneous manifestations of diabetes mellitus. *Dermatol Clin* 2002; **20**: 483–92.



Fig. 59.63 A large diabetic bulla on the shin of a patient with diabetes mellitus.

7 Boyne M, Dobs AS, Krasner AS, Provost TT. Evaluation and treatment of endocrine disorders. In: Provost TT, Flynn JA, eds. *Cutaneous Medicine. Cutaneous Manifestations of Systemic Disease*. Hamilton, Ontario: B.C. Decker, 2001: 413–51.
8 Cox NH. Diabetes and the skin: an update for dermatologists. *Expert Rev Dermatol* 207; **2**: 305–16.
9 Ajam Z, Barton SP, Marks R. Characterization of abnormalities in the cutaneous microvasculature of diabetic subjects. *Br J Dermatol* 1982; **107** (Suppl. 22): 22–3.
10 Lithner F. Cutaneous erythema, with or without necrosis. Localized to the legs and feet—a lesion in elderly diabetics. *Acta Med Scand* 1974; **196**: 333–42.
11 Gitelson S, Wertheimer-Kaplinski N. Color of the face in diabetes mellitus: observations on a group of patients in Jerusalem. *Diabetes* 1965; **14**: 201–8.
12 Binkley GW, Giraldo B, Stoughton RB. Diabetic dermopathy—a clinical study. *Cutis* 1967; **3**: 955–8.
13 Baur FM, Levan NE. Diabetic dermangiopathy: a spectrum including pigmented pretibial patches and necrobiosis lipoidica diabeticorum. *Br J Dermatol* 1970; **83**: 528–35.
14 Shemer A, Bergman R, Linn S *et al*. Diabetic dermopathy and internal complications in diabetes mellitus. *Int J Dermatol* 1998; **37**: 113–5.
15 Lipsky BA. Diabetic foot infections. Pathophysiology, diagnosis and treatment. *Int J Dermatol* 1991; **30**: 560–2.
16 Leung PC. Diabetic foot ulcers—a comprehensive review. *Surgeon* 2007; **5**: 219–93.
17 Breen JD, Karchmer AW. *Staphylococcus aureus* infection in diabetic patients. *Infect Dis Clin N Am* 1995; **9**: 11–5.
18 Zaky DA, Bentley DW, Lowy K *et al.* Malignant external otitis: a severe form of otitis in diabetics. *Am J Med* 1976; **61**: 298–301.
19 Bessman AN, Wagner W. Nonclostridial gas gangrene. A report of 48 cases and review of the literature. *JAMA* 1975; **233**: 958–63.
20 Knight L, Fletcher J. Growth of *Candida albicans* in saliva: stimulation by glucose associated with antibiotics, corticosteroids and diabetes mellitus. *J Infect Dis* 1971; **123**: 371–7.
21 Alteras J, Saryt E. Prevalence of pathogenic fungi in the toe-webs and toenails of diabetic patients. *Mycopathologia* 1979; **67**: 157–9.
22 Barth JH, Wojnarowska F, Dawber RPR. Acanthosis nigricans, insulin resistance and cutaneous virilism. *Br J Dermatol* 1988; **118**: 613–9.
23 Rendon MI, Ponciano PD, Sontheimer RD *et al.* Acanthosis nigricans: a cutaneous marker of tissue resistance to insulin. *J Am Acad Dermatol* 1989; **21**: 461–9.
24 Schwartz RA. Acanthosis nigricans. *J Am Acad Dermatol* 1994; **31**: 1–19.
25 Andersen BL, Verdich J. Granuloma annulare and diabetes mellitus. *Clin Exp Dermatol* 1979; **4**: 31–7.
26 Rosenbloom AL, Silverstein JM, Lezotte DC *et al.* Limited joint mobility in childhood diabetes mellitus indicates increased risk of microvascular disease. *N Engl J Med* 1981; **305**: 191–4.
27 Krakowski A, Covo J, Berlin C. Diabetic scleredema. *Dermatologica* 1973; **146**: 193–8.
28 Dawber RPR. Vitiligo and diabetes mellitus (Letter). *Br J Dermatol* 1971; **84**: 600.
29 Halevy S, Feuerman EJ. Abnormal glucose tolerance associated with lichen planus. *Acta Derm Venereol Suppl (Stockh)* 1979; **59**: 167–70.
30 Huntley AC. Finger pebbles in diabetes mellitus. *J Am Acad Dermatol* 1986; **14**: 612–7.
31 Kahana M, Grossman E, Feinstein A *et al.* Skin tags: a cutaneous marker for diabetes mellitus. *Acta Derm Venereol Suppl (Stockh)* 1986; **67**: 175–7.
32 Sibbald RG, Schachter RK. Skin and diabetes mellitus. *Int J Dermatol* 1984; **23**: 567–83.
33 Cochran RJ, Tucker SB, Wilkin JK. Reactive perforating collagenosis of diabetes mellitus and renal failure. *Cutis* 1983; **31**: 55–8.
34 Bernstein JE, Medenica M, Soltani K. Bullous eruption of diabetes mellitus. *Arch Dermatol* 1979; **115**: 324–5.
35 Basarab T, Munn SE, McGrath J, Jones RR. Bullosis diabeticum. A case report and literature review. *Clin Exp Dermatol* 1995; **20**: 218–20.

Xanthomas and abnormalities of lipid metabolism and storage

P.D. Flynn, pp. 59.81–59.103

Introduction [1,2]

Disorders of lipid metabolism are heterogeneous. They include the very rare and the very common. They range from monogenic diseases with high penetrance through polygenic disorders to those that are paradigms of gene–environment interaction. Some are entirely or partially secondary to other diseases such as diabetes mellitus, hypothyroidism, renal failure or hepatic disorders. Dyslipidaemias are of relevance to all medical and surgical disciplines, and to all involved in delivering health care in the 21st century, as most are associated with an increased risk of atherosclerosis and its complications. They are of particular relevance to dermatologists because they may present with subcutaneous lipid deposits, collectively known as xanthomata. These may require treatment in their own right for the relief of the symptoms they cause; they may also allow the identification and treatment of a dyslipidaemia before the onset of premature cardiovascular disease.

This account will include a brief description of the principal lipid metabolic pathways and an overview of the classification of the dyslipidaemias, followed by a more detailed discussion of some of the individual primary lipid disorders, focusing on those most likely to be seen by dermatologists. The section will conclude with summaries of the secondary dyslipidaemias and of the overall management of dyslipidaemia.

References

1 Durrington PN. *Hyperlipidaemia: Diagnosis and Management*, 3rd edn. London: Hodder Arnold, 2007.
2 Scriver VR, Beaudet AL, Sly WS *et al*. *The Metabolic and Molecular Bases of Inherited Disease*, 8th edn. New York: McGraw Hill, 2001.

Lipid metabolism [1]

Most metabolic pathways initially appear daunting; those describing lipid metabolism are no exception. Circulating lipids (cholesterol, cholesterol esters, triglycerides and phospholipids) are insoluble and therefore have to be solubilized by combination

Table 59.13 Classification of lipoproteins (adapted from [1]).

Class	Density (g/ml)	Electrophoretic mobility	Lipids*	Apolipoproteins
Chylomicrons	0.93	Remains at origin	Triglycerides 86% Cholesterol 5%	Apo B-48, Apo C, Apo E
VLDL	0.93–1.006	Pre-β-lipoproteins	Triglycerides 55% Cholesterol 19%	Apo B-100, Apo C, Apo E
IDL	1.006–1.019	Slow pre-β-lipoproteins	Cholesterol 38% Triglycerides 23%	Apo B-100, Apo E
LDL	1.019–1.063	β-lipoproteins	Cholesterol 50% Triglycerides 6%	Apo B-100
HDL	1.063–1.210	α-lipoproteins	Cholesterol 19% Triglycerides 4%	Apo A-I, A-II, A-IV
Lipoprotein (a)	1.040–1.090	Slow pre-β-lipoproteins		Apo (a), Apo B-100

* Expressed as % of dry mass.

with proteins; the resulting particles are called lipoproteins and the proteins they contain are generally called apolipoproteins. Understanding of the production, clearance and interrelationships of lipoproteins is growing rapidly and the following account aims merely to provide an overview of current understanding and a framework into which future advances can (hopefully) be incorporated. It is worth remembering that the current classification of lipoproteins is a pragmatic one based on their densities, a physical property we can measure, rather than their biological functions, which we would like to measure; there is fortunately some correlation between the two but it is not always absolute. The classification is shown in Table 59.13.

To discuss the metabolic pathways linking these differing lipoprotein classes it is helpful to consider those involved in the absorption of dietary fats and their transport to places of storage (the exogenous lipid pathway), those involved in the transport of lipids from the liver to peripheral tissues where they are required (the endogenous pathway), and those involved in the return of excess cholesterol to the liver from peripheral tissues (reverse cholesterol transport). In reality all three are closely interrelated.

Reference

1 Havel RJ, Kane JP. Structure and metabolism of plasma lipoproteins. In: Scriver CR, Beaudet AL, Sly WS *et al.*, eds. *The Metabolic and Molecular Bases of Inherited Diseases*, 8th edn. New York: McGraw Hill, 1995: 2705–16.

The exogenous lipid pathway [1,2]

The majority of fat absorbed from the diet derives from triglycerides. These are hydrolysed by pancreatic lipase and the resulting free fatty acids and monoglycerides pass across the brush border of the small intestine into the enterocytes. Here they are reassembled into triglycerides which are packaged with apo B-48 and apo A-I, A-II and A-IV, and the relatively small amount of dietary cholesterol that is absorbed, to form nascent chylomicrons that are released and enter the lacteals. Chylomicron formation is completed by the transfer of apo C and apo E from high density lipoproteins (HDL) before release from the thoracic duct into the systemic circulation. Here chylomicron apo C-II is recognized by endothelial-bound lipoprotein lipase which acts to hydrolyse triglycerides, releasing fatty acids that can be taken up by adipose tissue for storage, or by other cells (e.g. muscle) for oxidation to provide a source of energy, or that are released into the circulation where they are largely bound by albumin. This loss of triglyceride is accompanied by a loss of apolipoproteins (A-I, A-II, A-IV and C) producing a chylomicron remnant that is itself bound by receptors expressed on hepatocytes (principally the low-density lipoprotein (LDL) receptor and the LDL receptor related protein (LRP)) and then endocytosed. The triglycerides and cholesterol thus delivered to the hepatocyte can be stored in intracellular lipid droplets, excreted in the bile or be re-packaged into nascent lipoproteins to participate in the endogenous lipid pathway.

The endogenous lipid pathway

This lipid pathway starts in the hepatocyte where triglycerides, and to a lesser extent cholesterol and cholesterol esters, are assembled with apo B-100 to produce nascent very-low-density lipoproteins (VLDL) in a manner similar to the production of chylomicrons in enterocytes. (Indeed apo B-48 and apo B-100 are produced from the same gene, the former representing simply the amino terminal 48% of the latter.) Following secretion, VLDL accept further apo C and apo E from HDL and can thus be bound, like chylomicrons, by endothelial lipoprotein lipase with subsequent hydrolysis of their triglycerides and uptake of the released fatty acids by peripheral cells. The resulting VLDL remnants comprise a population of lipoproteins heterogeneous both in density and in affinity for the hepatic LDL receptors that mediate their removal from the circulation; the smaller remnants include intermediate density lipoproteins (IDL) which remain relatively longer in the circulation and so can be further processed, probably by hepatic lipase, to produce LDL. LDL are cleared from the circulation by LDL receptors, 90% of which are hepatic.

Reverse cholesterol transport [3–5]

The process of reverse cholesterol transport begins in peripheral tissues with the transfer of cholesterol, cholesterol esters and phospholipids to two pools of HDL precursor particles—discoidal apo A-I and A-IV, produced by the liver, and nascent pre-β HDL, produced from chylomicrons. Lipid transfer to these particles depends

on the lipid transporter ATP binding cassette A-1 (ABCA1); stabilization of the newly formed HDL depends additionally on the esterification and internalization of these transferred lipids by lecithin cholesterol acyl transferase (LCAT) and phospholipid transfer protein (PLTP). The cholesterol taken up by HDL returns to the liver by two principal routes. One involves the transfer of cholesterol esters from HDL to apo B containing lipoproteins (principally VLDL) mediated by cholesterol ester transfer protein (CETP) and subsequent uptake by hepatic LDL receptors; the other is mediated by direct uptake of HDL by hepatic scavenger receptors, mainly SR-B1. Cholesterol returned to the liver by reverse cholesterol transport can be stored in hepatocytes or converted into bile acids and then excreted.

References

1 Havel RJ, Goldstein JL, Brown MS. Lipoproteins and lipid transport. In: Bondy PK, Rosenberg LE, eds. *Metabolic Control and Disease*, 8th edn. Philadelphia: Saunders, 1980: 393–494.
2 Myant NB. *The Biology of Cholesterol and Related Steroids*. London: Heinemann Medical, 1981.
3 Reichl D, Miller NE. The anatomy and physiology of reverse cholesterol transport. *Clin Sci* 1986; **70**: 221–31.
4 Barter P. High-density lipoproteins and reverse cholesterol transport. *Curr Opin Lipidol* 1993; **4**: 210–7.
5 Schmidt G, Kaminski WE, Orso E. ABC transporters in cellular lipid trafficking. *Curr Opin Lipidol* 2000; **11**: 493–501.

Lipids, lipoproteins and atherosclerosis [1–4]

There is now near universal acceptance that there is a causal relationship between circulating lipid concentrations and the development of atherosclerosis and its clinical sequelae (angina, myocardial infarctions, strokes and peripheral vascular disease). That it has taken so long to reach this point reflects both the influence of other risk factors for cardiovascular disease (and their often complicated interaction with lipid metabolism) and the complexity of the metabolism and variable atherogenicity of the different lipoproteins. It is very clear that high LDL cholesterol levels confer an increased risk of cardiovascular disease (CVD) and that this risk is decreased if LDL cholesterol levels are reduced, evidence for the latter coming most clearly from trials of the 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG CoA reductase) inhibitors, or 'statin' group of drugs. There is also evidence that some LDL are more atherogenic than others; a preponderance of small, dense LDL or increased levels of oxidized LDL are both associated with increased CVD risk. Elevated concentrations of lipoprotein(a), which differs from LDL only by the additional presence of apolipoprotein(a), are also correlated with increased risk of atherosclerosis.

Epidemiological studies have also shown a strong and consistent inverse relationship between HDL and risk of atherosclerosis, that is high HDL levels are associated with a lower risk of CVD. There are some exceptions, for example apo AI Milano, where low levels of HDL are, apparently paradoxically, linked to low levels of CVD. In fact apo AI Milano is extremely efficient both at accepting lipid species from peripheral cells and at transporting them back to the liver; at any one time there is high flux through the reverse cholesterol transport pathway but concentrations of HDL cholesterol are low. There is also growing evidence that HDL have additional antiatherogenic properties; under appropriate conditions they can be anti-inflammatory and antioxidant. Taken together, these factors may explain the conflicting results of trials that have attempted to reduce CVD risk by increasing HDL concentration; some have yielded positive results (e.g. the Helsinki Heart Study, VA-HIT and HATS) but others have not (e.g. the WHO Clofibrate trial, FIELD and ILLUMINATE). Interpretation of such trials is further compounded by the fact that the agents used also altered other lipid risk factors including LDL cholesterol and triglycerides. A number of epidemiological studies have shown an association between high fasting triglyceride concentrations and CVD risk, albeit a rather weaker one than for LDL or HDL cholesterol and one which often loses significance in multivariate analysis, especially when correcting for HDL cholesterol concentrations with which fasting triglyceride levels are often negatively correlated. High fasting triglycerides are certainly linked to acute pancreatitis, often as a consequence but sometimes as a cause, with the risk rising significantly once levels exceed 10 mmol/L.

References

1 Ross R. The pathogenesis of atherosclerosis. An update. *N Engl J Med* 1984; **314**: 488–500.
2 Libby P, Theroux P. Pathophysiology of coronary artery disease. *Circulation* 2005; **111**: 3481–8.
3 Cholesterol Treatment Triallists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005; **366**: 1267–78.
4 Studer M, Briel M, Leimenstall B *et al.* Effect of different antilipidemic agents and diets on mortality: a systematic review. *Arch Intern Med* 2005; **165**: 725–30.

Dyslipidaemias: classification

There are a number of classifications of disordered lipid and lipoprotein metabolism, none of them entirely satisfactory. Perhaps the most straightforward is the WHO classification, usually referred to as the Fredrickson classification, based on the class of lipoprotein present in excess (Table 59.14) [1]. However, this requires plasma ultracentrifugation, does not include disorders characterized by low levels of HDL cholesterol or secondary dyslipidaemias and is not a diagnostic classification.

Pragmatically, given that for most patients all that is likely to be available is a lipid profile comprising total cholesterol, triglycerides and HDL cholesterol with a calculated LDL cholesterol, it may be most convenient to group patients rather broadly as having hypercholesterolaemia, hypertriglyceridaemia, combined (or mixed) dyslipidaemia, or other dyslipidaemia; wherever possible, further characterization and diagnosis may be based on

Table 59.14 WHO classification of hyperlipoproteinaemias [1].

Type	Lipoprotein abnormality
I	Hyperchylomicronaemia
IIa	Elevated LDL
IIb	Elevated LDL and VLDL
III	Broad β-VLDL
IV	Elevated VLDL
V	Elevated chylomicrons and VLDL

Table 59.15 Working classification of dyslipidaemias.

	Lipid abnormalities	WHO type	Primary dyslipidaemias	Secondary causes
Hypercholesterolaemia	↑ TC	IIa	Familial hypercholesterolaemia	Hypothyroidism
	↑ LDL-C		Familial defective Apo B-100	Anorexia
	Normal Tgs		Polygenic hypercholesterolaemia	Cholestatic liver disease
				Nephrotic syndrome
				Acute intermittent porphyria
				Drugs: thiazide diuretics, corticosteroids
Combined dyslipidaemia	↑ TC	III	Familial dysbetalipoproteinaemia	Diabetes mellitus
	↑ LDL-C	IIb	Familial combined hyperlipidaemia	Metabolic syndrome
	↑ Tgs	IV		Lipodystrophies
	± ↓ HDL-C			Hypothyroidism
				Hepatocellular liver disease
				Nephrotic syndrome
				Chronic renal failure
				Paraproteinaemias
				Pregnancy
				Drugs: β blockers, antiretrovirals, retinoic acid derivatives
Hypertriglyceridaemia	↑↑ Tgs	I	Lipoprotein lipase deficiency	Diabetes mellitus
	↑ TC	IV, V	Apo CII deficiency	Alcohol excess
	↓ HDL-C			Chronic renal failure
				Paraproteinaemias
				Pregnancy (esp. 3rd trimester)
				Drugs: retinoic acid derivatives, oral contraceptives
Other dyslipidaemias	↓ HDL-C only		Tangier disease	
			Apo AI Milano	
	↑ HDL-C		Hyperalphalipoproteinaemia	Alcohol, anabolic steroids
	↓↓ LDL-C		Abetalipoproteinaemia	
	↓ LDL-C		Hypobetalipoproteinaemia	

additional tests. (The LDL cholesterol in a standard lipid profile is calculated from the Friedewald formula:

$$\text{LDL-C} = \text{total cholesterol} - \text{HDL cholesterol} - 0.42 \times \text{triglycerides}$$

To provide a valid estimate of the LDL cholesterol the sample should be taken from a fasting subject and the triglyceride level should be below 4.5 mmol/L.) Such a working classification is shown in Table 59.15; it might at first sight seem confusing that total cholesterol is raised in conditions characterized by predominant hypertriglyceridaemia but this reflects the much increased contribution of triglyceride-rich lipoprotein cholesterol to the total cholesterol in these disorders.

Reference

1 Fredrickson DS, Levy RI, Lees RS. Fat transport in lipoproteins—an integrated approach to mechanisms and disorders. *N Engl J Med* 1967; **276**: 34–42, 94–103, 148–56, 215–25, 273–81.

Xanthomata

The term xanthoma derives from the Greek 'xanthos' meaning yellow and is used to describe a variety of subcutaneous lipid deposits, even those that do not appear particularly yellow. All xanthomata contain macrophages loaded with cholesterol and cholesterol esters ('foam cells') [1]; any distinctive features of the different types of xanthoma are discussed below.

Tendon xanthomata

These occur most commonly attached to the extensor tendons over the knuckles and in the Achilles tendon, though other tendons can sometimes be affected. In these sites they can usually be moved from side to side. Occasionally, they can involve the periosteum at the site of insertion of the patellar tendon where they cannot be moved. As the accumulation of cholesterol is deep within the tendons the overlying skin does not appear yellow. The xanthomata contain collagen in addition to foamy macrophages and so feel quite hard. They are most frequently seen in familial hypercholesterolaemia [2,3], but are also a feature of the secondary hypercholesterolaemia seen in prolonged cholestasis and the rare lipid disorders cerebrotendinous xanthomatosis [4] and sitosterolaemia [5]. In all cases other than sitosterolaemia they are indicative of raised levels of LDL cholesterol, though they do not completely resolve with LDL-lowering treatment. However, in the occasional patients where the tendon xanthomata are painful this symptom does improve with LDL cholesterol reduction.

Xanthelasmata (Fig. 59.64)

Xanthelasmata are the xanthomata that develop around the eyes, and were among the earliest recognized historically. They most



Fig. 59.64 Extensive xanthelasmas palpebrarum. (Courtesy of Addenbrooke's Hospital, Cambridge, UK.)



Fig. 59.65 Tuberous xanthomas. (Courtesy of Addenbrooke's Hospital, Cambridge, UK.)

commonly affect the upper eyelids and the area around the medical canthus. They are relatively soft to the touch and range from pale yellow to yellow-orange in colour. They are seen in familial hypercholesterolaemia, type III hyperlipoproteinaemia and in chronic cholestasis (especially primary biliary cirrhosis) [6], but are also often seen in people with circulating lipid levels considered normal in Western populations. Given their rather prominent site they are often noticed by patients, to whom they may be a source of considerable cosmetic distress. They can be removed surgically, or by cauterization or by application of silver nitrate but often recur, particularly if LDL cholesterol levels are high. In these circumstances subsequent treatment to lower LDL cholesterol, for example with a 'statin', seems sensible even if not yet confirmed by clinical trial. Such treatment is often associated with regression of xanthelasmata in hypercholesterolaemic patients without the need for other intervention.

Tuberous xanthomata (Fig. 59.65)
Although starting as small xanthomata, usually over the extensor aspects of the elbows and knees, these can develop into quite



Fig. 59.66 Xanthomatosis and yellow palmar creases. (Courtesy of Addenbrooke's Hospital, Cambridge, UK.)

exuberant exophytic lesions several centimetres in diameter and height. They can develop over other pressure areas such as the heels and plantar surfaces of the feet, and very occasionally can occur in the bone marrow. They can be itchy and are susceptible to trauma given their position. They usually indicate the presence of type III hyperlipoproteinaemia [7]. They respond well to effective treatment of the combined dyslipidaemia characteristic of this disorder.

Palmar xanthomata (Fig. 59.66)
Linear palmar xanthomata consisting of an orange-yellow lipid deposition running along the palmar creases, and occasionally the flexor creases of the wrists, are pathognomonic of type III hyperlipoproteinaemia [7]. Like tuberous xanthomata they respond well to treatment of the dyslipidaemia. They were formerly known as xanthoma striata palmaris.

Eruptive xanthomata (Fig. 59.67)
These small xanthomata consist of small yellow papules 2–5 mm in diameter, arising out of a slightly wider red base and usually appear in large numbers over extensor surfaces, particularly of the buttocks, back, legs and arms. In extreme cases they can be itchy and have an even more widespread distribution, potentially leading to diagnostic confusion. Their foamy macrophages contain triglycerides as well as cholesterol [8]. They only occur with severe hypertriglyceridaemia of any cause (serum triglycerides at least greater than 20 mmol/L), and are therefore almost always accompanied by lipaemia retinalis, a creamy yellow discoloration of the retinal blood vessels, and a lipaemic appearance of blood or serum samples. Eruptive xanthomata resolve well within a couple of weeks of treatment of the hypertriglyceridaemia.

Planar xanthomata (Fig. 59.68)
These xanthomata are wide based and rather flat and can cover the areas usually affected by xanthelasmata, but are usually



Fig. 59.67 Eruptive xanthomas. (Courtesy of Addenbrooke's Hospital, Cambridge, UK.)

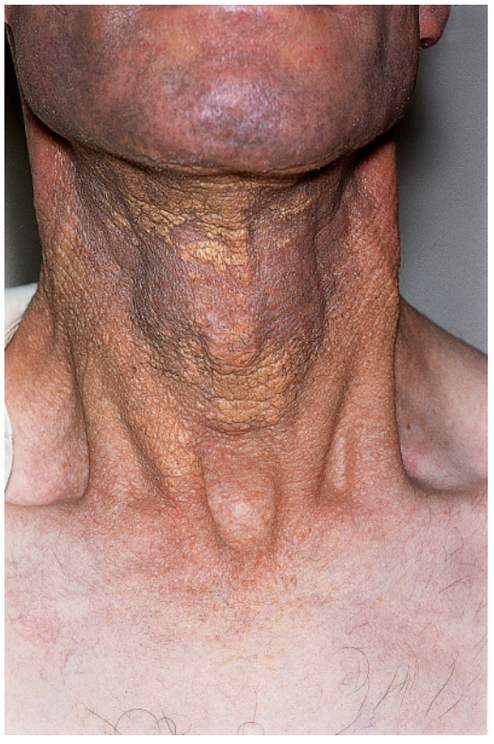


Fig. 59.68 Plane xanthomatosis. (Courtesy of Addenbrooke's Hospital, Cambridge, UK.)

broader and more widespread. They most frequently occur with paraproteinaemias (multiple myeloma or monoclonal gammopathy of uncertain significance (MGUS)) [9,10], when they often develop in areas subject to pressure from clothing or jewellery. Serum lipid levels are infrequently raised, indeed they may be below average, and the precise aetiology is unclear though complexes between immunoglobulins and lipoproteins are often found. When hyperlipidaemia is present a type III hyperlipoproteinaemic pattern is quite common. Occasionally planar xanthomata can be seen in lymphoma and systemic lupus erythematosus; they are also a feature of homozygous familial hypercholesterolaemia. Rarely, patients with paraproteinaemia develop necrobiotic xanthogranuloma with widespread, severe xanthelasmata that can cause complete closure of the eyelids accompanied by subcutaneous xanthogranulomata of the face and body [11].

Corneal arcus

Corneal arcus is not strictly a xanthoma, but does represent the deposition of cholesterol esters in the peripheral cornea. It is commoner in young people with familial hypercholesterolaemia (it is present in 50% of heterozygotes by the age of 30), but can occur with other causes of longstanding hypercholesterolaemia and in subjects with normal circulating lipid levels. In its early stages it is not a complete ring, but comprises superior and inferior crescents that may only be evident with eyelid retraction. With increasing age its specificity for familial hypercholesterolaemia falls even further. Corneal arcus does not regress with lipid-modulating drug treatment, but neither does it ever impair vision.

References

1 Takahashi W, Naito M. Lipid storage disease: part I. Ultrastructure of xanthoma cells in various xanthomatous diseases. *Acta Pathol Jpn* 1983; **33**: 959–77.

2 Burns FS. A contribution to the study of the aetiology of xanthoma. *Arch Derm Syph* 1920; **2**: 415–29.

3 Thannhauser SJ, Magendanta H. The different clinical groups of xanthomatous diseases: a clinical physiological study of 22 cases. *Ann Intern Med* 1938; **11**: 1662–746.

4 Björkhem I, Boberg KM, Leitersdorf E. Inborn errors in bile acid biosynthesis and storage of sterols other than cholesterol. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic and Molecular Bases of Inherited Disease*, 8th edn. New York: McGraw-Hill, 2001: 2961–88.

5 Bhattacharyya AK, Conner WE. Beta-sitosterolaemia and xanthomatosis. *J Clin Invest* 1974; **53**: 1033–43.

6 Ahrens EH, Kunkel HG. The relationship between serum lipids and skin xanthomata in eighteen patients with primary biliary cirrhosis. *J Clin Invest* 1949; **28**: 1565–74.

7 Polano MK. Xanthomatosis and hyperlipoproteinaemia. *Dermatologica* 1974; **149**: 1–9.

8 Parker F, Bagdade JD, Odland GF, Bierman EL. Evidence for the chylomicron origin of lipids accumulating in diabetic eruptive xanthomas. A correlative lipid biochemical, histological and electron microscopic study. *J Clin Invest* 1970; **49**: 2172–87.

9 Groszek E, Abrams JJ, Grundy SM. Normolipidaemic planar xanthomatosis associated with benign monoclonal gammopathy. *Metabolism* 1981; **30**: 927–35.

10 Lynch PJ, Winkelmann RK. Generalised plane xanthoma and systemic disease. *Arch Dermatol* 1960; **93**: 639–46.

11 Jeziorska M, Hassan A, Mackness MI et al. Clinical, biochemical and immunohistochemical features of necrobiotic xanthogranulomatosis. *J Clin Pathol* 2003; **56**: 64–8.

Primary dyslipidaemias

Hypercholesterolaemia

Familial hypercholesterolaemia

Clinical features. Familial hypercholesterolaemia (FH) is an autosomal co-dominant condition characterized by:

- High total and LDL cholesterol, slightly low HDL cholesterol and normal triglyceride concentrations

Table 59.16 Lipid concentrations in familial hypercholesterolaemia [6].

	Total Cholesterol (mM)	LDL-Cholesterol (mM)	HDL-Cholesterol (mM)	Triglycerides (mM)
Normal	4.52 ± 0.72	2.84 ± 0.64	1.37 ± 0.33	0.68 ± 0.28
Heterozygotes	7.73 ± 1.63	6.23 ± 1.55	1.11 ± 0.31	0.93 ± 0.58
Homozygotes	17.5 ± 4.39	16.1 ± 4.13	0.88 ± 0.26	1.14 ± 0.58

- Frequent tendon xanthomata (especially of the Achilles tendons)
- Premature onset of cardiovascular disease.

The familial clustering of these three features has been recognized since at least the late 19th century and was the subject of detailed studies in the 1930s [1,2]. In the 1950s, the development of ultracentrifugation for quantifying lipoproteins revealed that the biochemical hallmark of FH is an accumulation of LDL [3], and in 1973 Goldstein and Brown discovered the LDL receptor and showed that its defective functioning was the underlying cause of the condition [4]. Homozygotes number about 1 per million in Caucasian populations and can have total cholesterol levels of 15 mmol/L or higher, may be born with tendon xanthomas and can suffer from the clinical effects of coronary heart disease as early as their teens. They can also develop a supravalvular aortic stenosis. Heterozygotes occur at a frequency of about 1 in 500 in most Caucasian populations, though with notably higher frequency in certain groups, for example Afrikaners and the Lebanese, where there are marked founder gene effects. They have less marked elevations in their cholesterol than homozygotes (Table 59.16), but of untreated males 50% will have suffered a myocardial infarction (MI) and 24% will have died by age 50 years. Heterozygous females have a slightly delayed onset of CVD compared with males but 58% will have had an MI and 15% have died by the age of 60 if not treated [5]. FH thus accounts for a significant proportion of premature cardiovascular disease and of premature sudden cardiac death. There is a striking preponderance in FH of coronary arterial disease, as opposed to cerebrovascular or peripheral vascular disease.

The presence of tendon xanthomata is the principal cutaneous manifestation of FH [1], and may often be helpful in establishing the diagnosis. They are usually present in childhood in homozygotes and become more prevalent with age in untreated heterozygotes. They occur most frequently in extensor tendons, especially the Achilles tendons and those over the knuckles. They feel rather hard as they contain fibrous tissue as well as cholesterol, and they can become inflamed. They are not invariably present, especially if treatments to reduce the LDL cholesterol are begun at a sufficiently early age. They can also occur in two other disorders of sterol metabolism, cerebrotendinous xanthomatosis [6] and sitosterolaemia [7], both of which are extremely rare. Subcutaneous planar and tuberous xanthomata may occasionally be seen in FH homozygotes, but not heterozygotes. Corneal arcus is seen in many but not all cases and lacks both sensitivity and specificity for establishing the diagnosis though it does feature in some sets of criteria. Specifically, its presence and severity does not correlate with the risk of CVD in FH. Xanthelasmata are not commonly seen in FH; where they do occur they can respond to treatment that reduces LDL cholesterol concentrations. They can also be removed surgically but can recur more markedly thereafter; the efficacy of LDL reduction in this setting awaits confirmation but is quite common clinical practice.

Genetics and diagnosis. The majority of patients with FH have mutations in their LDL receptor associated with a variable degree of loss of function. As a result there is both defective clearance of VLDL from the circulation with consequent increased conversion to LDL and impaired clearance of LDL resulting in the significant elevation of LDL cholesterol concentration which accounts for the raised plasma total cholesterol. Over 1000 disease-associated mutations have so far been described in the LDL receptor gene (which is one of the largest human genes) [8]. They have been classified on the basis of the effect they have on the synthesis, expression and processing of the LDL receptor [9]:

Type 1 prevent receptor synthesis
Type 2 impair transport of the receptor from the endoplasmic reticulum to the Golgi
Type 3 affect receptor binding of circulating LDL
Type 4 prevent clathrin-mediated receptor clustering and internalization
Type 5 interfere with receptor recycling from the endosome.

Type 1 mutations tend to result in a complete absence of LDL receptor activity ('receptor negative') while the other classes of mutations usually cause markedly reduced but not completely absent activity ('receptor defective').

In a small proportion of patients with FH (around 2%) the mutation affects not the LDL receptor but the receptor binding domain in the LDL apo B-100 (familial defective apo B-100) [10]. This is almost always due to a mutation in codon 3500 (R3500Q) resulting in a substitution of arginine for glutamine; rarely it is due to a different mutation in codon 3500 (R3500W, in which tryptophan replaces arginine) or in codon 3531. Such patients are phenotypically indistinguishable from those with LDL receptor mutations though there is some evidence that their cardiovascular risk is not as dramatically raised. Recently, a new genetic locus has been found to account for some of the previously mutation-negative cases of FH; the gene codes for proprotein convertase subtilisin kexin 9 (PCSK9) [11], a serine protease whose activity appears to decrease LDL receptor expression and LDL clearance and thus increases LDL cholesterol concentration. It has emerged that statins upregulate PCSK9, so it represents an interesting target for agents to augment the LDL-lowering effect of these drugs. Finally, a small group of patients, all from Sardinia, have a phenotype similar to homozygous FH but inherited in a recessive pattern—autosomal recessive hypercholesterolaemia (ARH) [12].

Given the genetic heterogeneity underlying FH, diagnosis has largely rested on clinical and biochemical criteria. In the United Kingdom, the criteria used by the Simon Broome Register of patients with FH have been widely adopted (Table 59.17). Other sets of diagnostic criteria have also been developed, for example the Dutch Lipid Clinic Network Criteria [13] and the Make Early Diagnosis to Prevent Early Disease on Medical Pedigree (MEDPED) system [14]. Increasingly, advances in molecular biological

Table 59.17 Simon Broome Register criteria for diagnosing familial hypercholesterolaemia. (From Scientific Steering Committee of the Simon Broome Register Group. Risk of fatal coronary heart disease in familial hypercholesterolaemia. *BMJ* 1991; **303**: 893–6.)

Definite FH
- total cholesterol above 6.7 mM or LDL cholesterol above 4.0 mM in children under 16 or total cholesterol above 7.5 mM or LDL cholesterol above 4.9 mM in adults

plus
- tendon xanthomata in patient or 1st or 2nd degree relative

or
- FH mutation detected

Possible FH
- total cholesterol above 6.7 mM or LDL cholesterol above 4.0 mM in children under 16 or total cholesterol above 7.5 mM or LDL cholesterol above 4.9 mM in adults

plus
- family history of MI <50 in 2nd degree relative or <60 in 1st degree relative

or
- family history of total cholesterol >7.5 mM in 1st or 2nd degree relative.

techniques are proving helpful in diagnosing FH; this is particularly true where a disease-causing mutation has been identified in one family member.

Treatment. The hypercholesterolaemia of FH will only respond marginally to lifestyle measures such as reducing saturated fat intake. However, encouraging patients with measures that reduce cardiovascular risk, such as avoiding smoking and exercising regularly, clearly make sense, and may help account for the reduced risk of cancer, particularly lung and colon cancer, seen in the Simon Broome Register [15]. In recent years, statins have become the mainstay of treatment and they are likely to have played a large part in the reduction of cardiovascular mortality seen in recent years in FH. In comparison with the general population, statins usually have to be started at a much earlier age in patients with FH, and to achieve the desired reduction in LDL cholesterol (recently the National Institute for Health and Clinical Excellence (NICE) in the UK has advised a greater than 50% reduction) [16], higher doses of the more potent statins may well have to be used. Referral to a specialist lipid clinic is advised to allow counselling of young patients starting lifelong therapy, especially young women where the specific issue of the potential teratogenicity of the statins and family planning needs to be fully explored. Such clinics will have experience of other therapies that can prove helpful, including the bile acid sequestrants and LDL apheresis. Ezetimibe is a relatively new agent that works to reduce intestinal cholesterol absorption mediated by the recently described transporter Niemann Pick C-1 Like Protein 1 (NPC1L1); it is well tolerated and can augment the LDL reduction achieved by statins by a further 20% [17], but evidence that it is clinically effective in reducing CVD risk is still awaited. Tendon xanthomata and xanthelasmata may respond to the reduction in LDL cholesterol; corneal arcus does not. FH homozygotes must be referred for specialist assessment and treatment; their cholesterol does not respond well to statins or other drug therapies that work by up-regulating LDL receptor expression. These patients often require LDL apheresis and occasionally liver transplantation as well as coronary revascularization and aortic valve surgery [18].

References

1 Thannhauser SJ, Magendanta H. The different clincal groups of xanthomatous diseases: a clinical physiological study of 22 cases. *Ann Intern Med* 1938; **11**: 1662–746.
2 Müller C. Angina pectoris in hereditary xanthomatosis. *Arch Intern Med* 1939; **64**: 675–700.
3 Gofman JW, De Lalla O, Glazier F *et al*. The serum lipoprotein transport system in health, metabolic diseases, atherosclerosis and coronary artery disease. *Plasma* 1954; **2**: 413–84.
4 Goldstein JL, Brown MS. Familial hypercholesterolaemia: identification of a defect in the regulation of 3-hydroxy-3-methylglutaryl coenzyme A reductase activity associated with overproduction of cholesterol. *Proc Natn Acad Sci USA* 1973; **70**: 2804–8.
5 Slack J. Risks of ischaemic heart disease in familial hyperlipoproteinaemia states. *Lancet* 1969; **ii**: 1380–2.
6 Björkhem I, Boberg KM, Leitersdorf E. Inborn errors in bile acid biosynthesis and storage of sterols other than cholesterol. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic and Molecular Bases of Inherited Disease,* 8th edn. New York: McGraw-Hill, 2001: 2961–88.
7 Bhattacharyya AK, Conner WE. Beta-sitosterolaemia and xanthomatosis. *J Clin Invest* 1974; **53**: 1033–43.
8 Villeger L, Abifadel M, Allard D *et al.* The UMD-LDLR data-base: additions to the software and 490 new entries to the data-base. *Hum Mutat* 2002; **20**: 81–7.
9 Hobbs HH, Brown MS, Goldstein JL. Molecular genetics of the LDL receptor gene in familial hypercholesterolaemia. *Hum Mutat* 1992; **1**: 445–66.
10 Myant NB. Familial defective apolipoprotein B-100: a review, including some comparisons with familial hypercholesterolaemia. *Atherosclerosis* 1993; **104**: 1–19.
11 Timms KM, Wagner S, Samuels ME *et al*. A mutation in PCSK9 causing autosomal dominant hypercholesterolaemia in a Utah pedigree. *Hum Genet* 2004; **114**: 349–53.
12 Soutar AK, Nauomova RP, Traub LM. Genetics, clinical phenotype, and molecular cell biology of autosomal recessive hypercholesterolaemia. *Arterioscler Thromb Vasc Biol* 2003; **23**: 1963–70.
13 World Health Organization. *Familial Hypercholesterolaemia*. Report of a Second WHO Consultation. WHO publication no. WHO/HGN/FH/CONS/99.2, 1999.
14 Williams RR, Hunt SC, Schumacher MC *et al*. Diagnosing heterozygous familial hypercholesterolaemia using new practical criteria validated by molecular genetics. *Am J Cardiol* 1993; **72**: 171–6.
15 Neil HAW, Hawkins MM, Durrington PN *et al*. Non-coronary heart disease mortality and risk of fatal cancer in patients with treated heterozygous familial hypercholesterolaemia: a prospective study. *Atherosclerosis* 2005; **179**: 293–7.
16 NICE guideline CG71. Identification and management of familial hypercholesterolaemia. August 2008.
17 Davidson MH, McGarry T, Bettis R *et al*. Ezetimibe coadministered with Simvastatin in patients with primary hypercholesterolaemia. *J Am Coll Cardiol* 2002; **40**: 2125–34.
18 Naoumova RP, Thompson GR, Soutar AK. Current management of severe homozygous hypercholesterolaemias. *Curr Opin Lipidol* 2004; **15**: 413–22.

Combined dyslipidaemia

Type III hyperlipoproteinaemia

Clinical features. Type III hyperlipoproteinaemia merits discussion for several reasons. It may have been the first recognized disorder of lipoprotein metabolism; Addison and Gull reported a patient with its typical cutaneous hallmarks in 1851. It has a plethora of aliases (including broad-beta disease, dysbetalipoproteinaemia and remnant removal disease) reflecting the gradual

emergence of our understanding of the biochemical basis of the condition. It is an excellent example of a disease resulting from a gene–environment interaction.

There are several skin manifestations of type III hyperlipoproteinaemia. The most characteristic are linear yellow-orange lipid deposits within the palmar creases and sometimes the flexor creases of the fingers and wrists. They are called striate palmar xanthomata (Fig. 59.66). Tuberous xanthomata are also common over the tuberosities of the elbows and knees (Fig. 59.65). They start as yellowish papules that gradually coalesce to form larger, sometimes exuberant, exophytic lesions. Where a central tuberous xanthoma is surrounded by several smaller lesions they are sometimes called tuberoeruptive xanthomata. They can also occur over the heel; being subcutaneous and yellow in colour they are not difficult to distinguish from Achilles tendon xanthomata. Patients with type III hyperlipoproteinaemia with particularly high triglyceride concentrations may also develop lipaemia retinalis and eruptive xanthomata over their buttocks (Fig. 59.67). Striate palmar and tuberous xanthomata can occasionally be seen in the paraproteinaemias and systemic lupus erythmatosus.

Estimates of the frequency of type III hyperlipoproteinaemia vary, reflecting the lack of clear diagnostic criteria, but range between about 1 and 10 in 10 000. There is evidence of an increased risk of both coronary artery and peripheral arterial disease, especially in those with all the clinical and biochemical features of the disorder in whom up to 50% have premature CVD [1]. Gout also appears common in this group of patients [2]. Type III hyperlipoproteinaemia has been associated with lipoprotein glomerulopathy, manifesting as proteinuria or the nephrotic syndrome [3]. Renal biopsy shows glomerular foam cells; the condition usually resolves with successful treatment of the abnormal lipid profile.

Biochemistry and genetics. Patients with type III hyperlipoproteinaemia have a characteristic lipoprotein electrophoretic pattern; indeed this remains the gold standard diagnostic test. There is an increase in small VLDL and IDL and a decrease in LDL. VLDL isolated from type III patients is uncharacteristically enriched with cholesterol esters and gives rise to a broad-β migrating band, rather than the usual pre-β band [4,5]. This results from an accumulation of VLDL remnants and chylomicron remnants and produces a marked increase in plasma total cholesterol and triglycerides. The underlying defect is an abnormal apoE [6], the apolipoprotein in remnant lipoproteins that mediates their binding to the LDL receptor and the LRP. There are three common isoforms of apo E: apo E2, E3 and E4, each differing by one amino acid (Table 59.18).

Apo E2 homozygosity represents by far the commonest abnormality associated with type III hyperlipoproteinaemia; its cysteine at residue 112 is within the receptor binding domain of the protein and its cysteine at residue 158 affects salt bridges within the protein and thereby the conformation of the receptor binding domain. Very occasionally, other apo E mutations are associated with type III hyperlipoproteinaemia, many of which severely reduce apo E mediated receptor binding and can cause the disorder in heterozygotes [7].

However, less than 10% of subjects homozygous for apo E2 develop type III hyperlipoproteinaemia, and most of the rest have lower than average lipid levels. It is clear that a second factor is required for the development of type III hyperlipoproteinaemia, either environmental or genetic. Increased production of chylomicrons or VLDL can be one such factor and may result from excessive caloric intake, increased alcohol consumption, obesity, type 2 diabetes mellitus, the metabolic syndrome or from an interplay of multiple genetic influences on lipoprotein metabolism (as presumed to underlie familial combined hyperlipidaemia (FCH)). Equally, increasing age, hypothyroidism or post-menopausal oestrogen deficiency can further impair apo E mediated receptor catabolism of lipoproteins and result in the development of the disorder.

Table 59.18 The amino acid differences between the isoforms of apo E.

	E2	E3	E4
Residue 112	Cysteine	Cysteine	Arginine
Residue 158	Cysteine	Arginine	Arginine

Treatment. Identification and treatment of any contributing lifestyle factors or diseases is clearly central to the management of patients with type III hyperlipoproteinaemia. Patients should be screened for obesity, diabetes and hypothyroidism and treated accordingly. Dietary advice should be given and exercise, which increases the activity of lipoprotein lipase and thereby reduces chylomicron and VLDL remnant production, encouraged. Such measures are often successful in improving the lipid profile on their own; in their absence drug therapy is usually less effective. Normally both statins [8] and fibrates [9] work well, both in improving the lipid profile and also in causing regression of the palmar and tuberous xanthomata. Occasionally combined statin and fibrate therapy may be required.

References

1 Morganroth J, Levy RI, Fredrickson DS: The biochemical, clinical and genetic features of type III hyperlipoproteinaemia. *Ann Intern Med* 1975; **82**: 158–74.

2 Brewer HB, Zech LA, Gregg RE *et al*. Type III hyperlipoproteinaemia. Diagnosis, molecular defects, pathology and treatment. *Ann Intern Med* 1983; **98**: 623–40.

3 Yang AH, Ng YY, Tarng DC *et al*. Association of apolipoprotein E polymorphism with lipoprotein glomerulopathy. *Nephron* 1998; **78**: 266–70.

4 Gofman IW, Rubin L, McGinley JP, Jones HB. Hyperlipoproteinaemia. *Am J Med* 1954; **17**: 514–20.

5 Gofman IW, Rubin L, Lees RS. Fat transport in lipoproteins. An integrated approach to mechanisms and disorders. *N Engl J Med* 1967; **276**: 32–44, 94–103, 148–56, 215–26, 273–81.

6 Utermann G. Apolipoprotein E polymorphisms in health and disease. *Am Heart J* 1987; **113**: 433–40.

7 Mahley RW, Rall SC. Type III hyperlipoproteinaemia (dysbetalipoproteinaemia): the role of apolipoprotein E in normal and abnormal lipoprotein metabolism. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic and Molecular Bases of Inherited Disease*, 8th edn. New York: McGraw-Hill, 2001: 2835–62.

8 Vega GL, East C, Grundy SM. Lovastatin therapy in familial dysbetalipoproteinaemia: effects on kinetics of apolipoprotein B. *Atherosclerosis* 1988; **70**: 131–43.

9 Kuo PT, Wilson AC, Kostis JB *et al*. Treatment of type III hyperlipoproteinaemia with gemfibrozil to retard progression of coronary artery disease. *Am Heart J* 1988; **116**: 85–90.

Hypertriglyceridaemias

Type I hyperlipoproteinaemia

Clinical, biochemical and genetic features. In type I hyperlipoproteinaemia there is an accumulation of chylomicrons alone. It results from a deficiency of lipoprotein lipase (LPL), and as such shows an autosomal recessive pattern of inheritance (though there is accumulating evidence that some heterozygotes for LPL deficiency may show a milder degree of hypertriglyceridaemia). The condition is extremely rare with a frequency of perhaps 1 per million in most populations, but with higher frequency in some populations such as French Canadians due to founder gene effects. An increasing number of mutations in the LPL gene have been described. Some cases result from apo CII deficiency, an essential factor for LPL activation; this discovery followed from the observation that the hyperchylomicronaemia was alleviated in some patients following plasma infusions [1].

Familial LPL deficiency causes extremely elevated levels of serum triglycerides, often greater than 20 mM. Total cholesterol levels are often substantially elevated as well, reflecting the extreme concentrations of chylomicrons which do contain some cholesterol and cholesterol esters as well as their predominant triglycerides. Blood, serum or plasma from such patients will appear milky and a creamy layer will separate on top of the sample if centrifuged or allowed to stand for some hours. Hyperchylomicronaemia will be present from childhood onwards in homozygous LPL deficiency. It remains unclear why LPL deficiency can cause an isolated accumulation of chylomicrons, given the role of the enzyme in VLDL catabolism. However, with increasing age there is a progressive shift towards a type V hyperlipoproteinaemic pattern (see below).

The principal concern in type I hyperlipoproteinaemia is the increased risk of acute pancreatitis with its attendant morbidity and mortality [2]. Whilst hypertriglyceridaemia may be a consequence of acute pancreatitis there is clear evidence it may also be a cause, perhaps accounting for up to 10% of cases. The risk increases with increasing fasting triglyceride levels, with a threshold around 10 mmol/L, rising markedly beyond 20 mmol/L, although other factors must play a part as some patients seem remarkably immune from attacks despite grossly elevated triglyceride concentrations. The mortality is further increased because the serum amylase, so often used as a sole diagnostic test for acute pancreatitis, may well not be elevated [3]. (It is possible that the very elevated triglyceride levels interfere with the amylase assay; dilution of the serum sample can sometimes reveal the raised amylase concentration.) As a result, many such patients have undergone laparotomy to establish the cause of their severe abdominal pain and the examination findings of generalized tenderness and guarding, with the consequent physical stress further exacerbating their hypertriglyceridaemia.

The characteristic skin finding in patients with type I hyperlipoproteinaemia is eruptive xanthomata (Fig. 59.67), yellowish papules several millimetres in diameter occurring over extensor surfaces, particularly the buttocks and the backs of the legs [4]. The rash may be itchy. It usually indicates triglyceride levels in excess of 20 mmol/L, and is seen with all causes of such severe hypertriglyceridaemia. It responds to lowering of the triglycerides, though it tends to last a few days longer than the lipid abnormality. Clearance of chylomicrons from the circulation by cells of the reticuloendothelial system can result in hepatomegaly and splenomegaly, with splenic infarcts in some cases. Lipaemia retinalis, with creamy yellow discoloration of the retinal arterioles and veins, can be seen on fundoscopy and in very severe hypertriglyceridaemia can appear almost fluorescent [5].

Treatment. The principal treatment of severe hypertriglyceridaemia involves strict restriction of all dietary fats (not just saturated fats) to reduce chylomicron production as much as possible [6]. Attention must be paid to any other factors that may increase the production of, or decrease the clearance of, the triglyceride rich lipoproteins (TRLs); good control of diabetes, weight reduction where appropriate, alcohol restriction and a review of all other medications are particularly important. Intake of refined carbohydrates should also be limited. Fibrates usually have little effect in genetic LPL deficiency. Nicotinic acid derivatives can be helpful. Bile acid sequestrants are contraindicated as they may increase the triglyceride level. Infusions of fresh frozen plasma are beneficial in those with apo CII deficiency who present with acute pancreatitis. Antioxidant therapy has proved very effective in reducing the frequency of attacks of acute pancreatitis in a number of patients with severe hypertriglyceridaemia [7]. All patients with severe hypertriglyceridaemia should have access to specialist lipid clinics.

References

1 Brunzell JD, Deeb SS. Familial lipoprotein lipase deficiency, apo CII deficiency and hepatic lipase deficiency. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic and Molecular Bases of Inherited Disease*, 8th edn. New York: McGraw-Hill, 2001: 2789–816.

2 Durrington PN, Twentyman OP, Braganza JM, Miller JP. Hypertriglyceridaemia and abnormalities of triglyceride metabolism persisting after pancreatitis. *Int J Pancreatol* 1996; **1**: 195–203.

3 Fallat RW, Vestor JW, Glueck CJ. Suppression of amylase activity by hypertriglyceridaemia. *JAMA* 1973; **225**: 1331–4.

4 Parker F, Bagdade JD, Odland GF, Bierman EL. Evidence for the chylomicron origin of lipids accumulating in diabetic eruptive xanthomas. A correlative lipid biochemical, histological and electron microscopic study. *J Clin Invest* 1970; **49**: 2172–87.

5 Holt LE, Aylward FX, Timbres HG. Idiopathic familial lipaemia. *Johns Hopkins Hosp Bull* 1939; **64**: 279–314.

6 Durrington PN. Hypertriglyceridaemia. In: *Hyperlipidaemia: Diagnosis and Management*, 3rd edn. London: Hodder Arnold, 2007: 169–202.

7 Heaney AP, Sharer N, Rameh B *et al*. Prevention of recurrent pancreatitis in patients with familial lipoprotein lipase deficiency with high dose antioxidant therapy. *J Clin Endocrinol Metab* 1999; **84**: 1203–5.

Type V hyperlipoproteinaemia

Clinical and biochemical features. Type V differs from type I hyperlipoproteinaemia in that there is an accumulation of VLDL as well as chylomicrons. It is also far commoner, perhaps affecting 1 in every 5–10 000, and although it can result from LPL deficiency this only accounts for a very small proportion of cases. Patient samples will demonstrate some milkiness with the separation of a creamy layer after standing or centrifugation (made up of chylomicrons) but the serum or plasma will be opaque, representing the presence of VLDL. Patients with type V hyperlipoproteinae-

mia may have relatives with hypertriglyceridaemia as well, though many of these will have a type IV lipoprotein pattern (see below). This has led to the hypothesis that most type V patients have a reasonably marked defect in the catabolism of TRLs combined with some additional factor that either further decreases catabolism or additionally increases the production of TRLs. Such factors include obesity, poor diabetic control, alcohol consumption, pregnancy, drugs (oral contraceptives, highly-active antiretroviral therapy, β-blockers and thiazide diuretics being the main offenders), hypothyroidism, lipodystrophy and renal failure.

Lipid levels in type V hyperlipoproteinaemia may be as markedly elevated as in type I. Acute pancreatitis, eruptive xanthomata, hepatosplenomegaly, lipaemia retinalis and all the other clinical features of type I hyperlipoproteinaemia may be present. Additionally, hyperuricaemia, glucose intolerance and hepatic steatosis are often seen.

Treatment. The treatment of type V hyperlipoproteinaemia is exactly as for type I, though fibrates are generally far more effective.

Type IV hyperlipoproteinaemia

Clinical and biochemical features. In type IV hyperlipoproteinaemia VLDL accumulate but without any increase in chylomicrons. The degree of hypertriglyceridaemia is usually much less marked than in type I or type V hyperlipoproteinaemia, with many patients having fasting triglycerides less than 6 mmol/L and most less than 10 mmol/L. Patients with type IV hyperlipoproteinaemia are heterogeneous, the common abnormality being an increased production of VLDL by the liver [1], often accompanied by a partial defect in their catabolism [2]. As with other forms of hypertriglyceridaemia, LDL tend to be smaller and denser, a pattern of abnormalities associated with increased cardiovascular risk. Apart from those rare type IV patients with marked hypertriglyceridaemia, the clinical features of type I and type V hyperlipoproteinaemia are not present.

Treatment. Lifestyle modification along the lines of that advocated for severe hypertriglyceridaemia (see above) is appropriate for type IV hyperlipoproteinaemia. However, dietary fat restriction does not have to be so marked, and can be mainly restricted to saturated fats. Indeed intake of omega-3 unsaturated fatty acids may be beneficial. The need for drug therapy will largely be guided by estimations of the 10-year CVD risk; many type IV patients will require such treatment and the first line will often be the statins because of their proven efficacy in reducing that risk, even though they do not usually much affect hypertriglyceridaemia.

References

1 Brunzell JD, Albers JJ, Chait AI *et al*. Plasma lipoproteins in familial combined hyperlipidaemia and monogenic familial hypertriglyceridaemia. *J Lipid Res* 1983; **24**: 147–55.

2 Krauss RH, Levy RI, Fredrickson RS. Selective measurement of two lipase activities in postheparin plasma from normal subjects and patients with hyperlipoproteinaemia. *J Clin Invest* 1974; **54**: 1107–24.

Other primary dyslipidaemias [1,2]

Cerebrotendinous xanthomatosis

This autosomal recessive condition is a rare cause of tendon xanthomata and xanthelasmata. It results from a defect in sterol 27-hydroxylase with consequent increased production of cholestanol and 7-hydroxycholesterol which accumulate in plasma and throughout the body. Accumulation in the central nervous system causes myelin destruction leading to mental retardation, seizures, spasticity and ataxia; peripheral neuropathy results from similar pathology in the peripheral nervous system. Presentation occurs during childhood or early adult life. Early-onset cataracts, diarrhoea and premature osteoporosis are additional features. Patients are at risk of cardiovascular disease, although plasma cholesterol levels are normal. Treatment with chenodeoxycholate reduces plasma cholestanol concentrations and improves the neurological manifestations of the disease.

Sitosterolaemia

This is another rare, autosomal recessive cause of tendon and tuberous xanthomata. It results from mutations in the genes *ABCG5* or *ABCG8* which encode the proteins sterolin-1 and sterolin-2 in enterocytes and hepatocytes. Sterolin-1 and sterolin-2 act together to form a lipid transporter that is thought to facilitate immediate excretion of any plant sterols absorbed across the small intestinal brush border. Defective function thereby allows much increased absorption of plant sterols into the body, principally β-sitosterol but also sitostanol, campesterol and stigmasterol. Patients suffer from impaired growth, anaemia, thrombocytopenia and arthritis and are at risk of premature CVD. Diagnosis is made by measuring serum plant sterol concentrations. It has recently been shown that ezetimibe reduces plant sterol levels effectively in this condition, suggesting a role for the Niemann–Pick C1-like protein in plant sterol transport in the intestine.

Tangier disease

In Tangier disease cholesterol esters accumulate in foam cells throughout the reticuloendothelial system. Clinically, this manifests most consistently as enlarged, yellow-orange tonsils, but similar deposits can also be seen in the rectal mucosa and generalized lymphadenopathy and hepatosplenomegaly can be found. Thrombocytopenia is a frequent finding, resulting usually from a combination of hypersplenism and foam cell infiltration of the bone marrow. Peripheral neuropathy and corneal opacities have also been described; the latter only evident on slit-lamp examination. The biochemical hallmark of Tangier disease is a low level of HDL-cholesterol with near complete absence of apo AI. Total cholesterol levels are also lower than average, partly because of the low HDL cholesterol but LDL cholesterol is also usually reduced. The disease results from mutations in the gene coding for ABCA1; this discovery led to the elucidation of the role of this lipid transporter in cellular cholesterol efflux, the first step in reverse cholesterol transport. It has been shown that the majority of HDL cholesterol arises from expression of ABCA1 in the liver, and that if liver ABCA1 is defective the newly secreted discoidal apo AI/AIV particles cannot be stabilized by incorporating cholesterol, are rapidly cleared by the kidney and cannot participate in peripheral cellular cholesterol efflux. (It is striking how much of our under-

standing of human lipoprotein metabolism has come from studies of rare dyslipidaemias.) Although there are reports of premature CVD in Tangier disease, this does not seem as common as might be expected from the low levels of HDL cholesterol.

References

1 Björkhem I, Boberg KM, Leitersdorf E. Inborn errors in bile acid biosynthesis and storage of sterols other than cholesterol. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic and Molecular Bases of Inherited Disease,* 8th edn. New York: McGraw-Hill, 2001: 2961–88.

2 Assmann G, von Eckardstein A, Brewer HB. Familial analphalipoproteinaemia: Tangier Disease. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic and Molecular Bases of Inherited Disease,* 8th edn. New York: McGraw-Hill, 2001: 2937–60.

Secondary dyslipidaemias [1]

Dyslipidaemias are frequently secondary to, or exacerbated by, a range of other diseases or medications. The following account is far from exhaustive but will concentrate on those that may produce xanthomata or follow from the use of drugs used by dermatologists.

Perhaps the commonest cause of secondary dyslipidaemia at present is diabetes mellitus. Type 1 diabetics frequently have quite high HDL cholesterol levels, but they also have a number of abnormalities of their LDL and VLDL and they are at high CVD risk. Type 2 diabetics have insulin resistance; their typical lipid profile includes relatively normal total and LDL cholesterol levels, but often somewhat increased triglyceride and reduced HDL cholesterol concentrations. These quantitative abnormalities are usually accompanied by qualitative changes in the LDL with a preponderance of highly atherogenic small dense LDL. As a result, type 2 diabetics are also at high risk of developing premature CVD. It is now recommended that statins should be considered for all diabetics over the age of 40 years, and in younger diabetic patients with other CVD risk factors including microalbuminuria. In some patients the development of type 2 diabetes, or worsening of its glycaemic control, can cause marked hypertriglyceridaemia (with a type IV or V hyperlipoproteinaemia) with all its clinical features including eruptive xanthomata, lipaemia retinalis and acute pancreatitis. This is most likely to occur on the background of some mild defect of triglyceride-rich lipoprotein clearance, and may be further exacerbated by the concomitant presence of obesity and excess alcohol intake. Diabetes can also precipitate the development of type III hyperlipoproteinaemia in those with the appropriate genetic background (usually homozygosity for apo E2); such patients may present to a dermatologist with the typical xanthomata of this condition. It follows that in any patient presenting with eruptive, tuberous or planar xanthomata a fasting glucose and/or HbA1c should be requested along with the lipid profile and other appropriate tests.

Patients with insulin resistance, but without type 2 diabetes mellitus, have a similar combined dyslipidaemia. In some a marked hypertriglyceridaemia can develop, sufficient to cause eruptive xanthomata. This is seen quite commonly in the lipodystrophies, a group of disorders with either partial or generalized loss of subcutaneous fat. They can be inherited (e.g. Dunnigan–Köbberling syndrome) or acquired. The latter is now most commonly seen in patients with human immunodeficiency virus/acquired immunedeficiency syndrome (HIV/AIDS) who are having treatment with protease inhibitors, especially saquinavir and ritonavir. Management of lipodystrophy-associated dyslipidaemia is likely to require specialist input; the principles are lifestyle change, especially strict dietary fat restriction in hypertriglyceridaemia, optimization of the drug regimen in HIV, and judicious, monitored use of lipid-modulating drug therapy, given the potential for significant interactions between statins, fibrates and the antiretroviral agents.

It has already been noted that xanthelasmata can be a feature of chronic cholestasis. This can occur, for example, in primary biliary cirrhosis and the presence of xanthelasmata should prompt a request for blood tests including a bilirubin and an alkaline phosphatase at least. Long-standing cholestasis is associated with hypercholesterolaemia due to the accumulation of an abnormal lipoprotein, lipoprotein X. It remains unclear whether this dyslipidaemia increases CVD risk, but it can cause a wide range of xanthomata as well as xanthelasmata. Both the dyslipidaemia and the xanthomata improve with relief of biliary obstruction; where this is not possible bile acid sequestrants can be helpful (and may also relieve the pruritus associated with cholestasis). Where necessary statins can be used, but cautiously to avoid accumulation and toxicity. Hepatocellular liver disease leads to specific lipoprotein abnormalities, principally abnormal HDL secondary to progressive deficiency of lecithin-cholesterol acyl transferase with mild hypertriglyceridaemia, but these are not usually severe enough to cause xanthomata.

Nephrotic syndrome is complicated by hypercholesterolaemia or a combined dyslipidaemia that can prove difficult to treat. Hypertriglyceridaemia is not usually marked though occasionally a type IV hyperlipoproteinaemia may occur. Xanthomata are not a frequent feature and the dyslipidaemia resolves if the nephrotic syndrome responds to therapy. Chronic renal failure leads to hypertriglyceridaemia, often exacerbated by haemodialysis or peritoneal dialysis, and this can sometimes lead to eruptive xanthomata especially if other risk factors are present. Lipoprotein(a) levels are elevated and may contribute to the increased CVD risk in this population but do not produce any dermatological signs.

The characteristic xanthomata associated with the paraproteinaemias (planar xanthomata and necrobiotic xanthogranuloma) have been discussed earlier. Their presence does not necessarily reflect a measurable dyslipidaemia, though a hyperlipoproteinaemia similar to type III may be present. The pathophysiology underlying paraproteinaemia-associated xanthomata and dyslipidaemia remains unclear although lipoprotein–immunoglobulin complexes are a common finding, usually involving VLDL. These abnormalities have occasionally also been reported in lymphoma and systemic lupus erythematosus. Very rarely, immunoglobulins directed against the LDL receptor can produce a hypercholesterolaemia with total and LDL cholesterol levels similar to those seen in FH homozygotes but without any tendon xanthomata. This has been referred to as 'pseudo familial hypercholesterolaemia'.

Many drugs can produce dyslipidaemia, alcohol perhaps being the commonest example and a frequent contributor to marked hypertriglyceridaemia. Of the prescription drugs used by dermatologists it is worth considering corticosteroids, ciclosporin and retinoic acid derivatives. Systemic corticosteroids increase total, LDL and HDL cholesterol levels. Unless they precipitate diabetes

mellitus in a susceptible individual, they do not cause hypertriglyceridaemia. Ciclosporin increases LDL cholesterol levels, sometimes quite significantly. It also inhibits cytochrome P450 3A4, the isoform responsible for the metabolism of fluvastatin, simvastatin and atorvastatin, so patients taking these statins should be advised of the possible interaction and the risk of myalgia. In some patients (e.g. those with hepatic or renal impairment, or taking other drugs that affect CYP450 3A4), it may be appropriate to reduce the statin dose or to change to an alternative (pravastatin or rosuvastatin are less dependent on CYP450 3A4). Retinoic acid derivatives often induce hypertriglyceridaemia; this is usually mild and does not necessarily require anything other than dietary modification. Occasionally, however, marked hypertriglyceridaemia with a type IV or V hyperlipoproteinaemic pattern can be provoked—usually in a susceptible individual who may well have evidence of dyslipidaemia prior to treatment. It is therefore sensible to include a full lipid profile on any pre-treatment blood tests and to repeat this several weeks after starting any retinoids.

Reference

1 Durrington PN. Secondary hyperlipidaemia. In: Durrington PN, *Hyperlipidaemia: Diagnosis and Management*, 3rd edn. London: Hodder Arnold, 2007: 310–59.

Treatment [1]. Treatment of dyslipidaemia requires the identification and treatment of any secondary cause, dietary modification and drug therapy in appropriate cases. The mainstay of dietary therapy is a reduction in the total intake of fat, especially saturated fat. Associated dietary interventions that are worthwhile include increasing the intake of monounsaturated and omega-3 unsaturated fatty acids and of antioxidant vitamins (found in fresh fruit and vegetables); these may not alter the standard lipid profile but some do cause qualitative differences in various lipoproteins and they are of benefit in reducing cardiovascular risk. The only exception to this is in cases of severe hypertriglyceridaemia where all fat intake must be severely restricted (to 20–25 g per day) to reduce intestinal chylomicron production. Given that one of the principal aims of treating dyslipidaemia is to reduce CVD risk, dietary therapy should be accompanied by discussion of exercise, smoking cessation and weight optimization.

Statins are the most effective and best tolerated of the drugs available that reduce cholesterol levels. They act by inhibiting 3-hydroxy, 3-methyl-glutaryl CoA reductase, the rate-limiting step in intracellular cholesterol biosynthesis, with a consequent up-regulation of hepatic LDL receptor expression and increased clearance of LDL from the circulation. Throughout the various statin trials there has been a highly consistent relationship between the absolute reduction achieved in the LDL cholesterol level and the relative reduction in cardiovascular risk; other means of lowering LDL cholesterol levels (e.g. bile acid sequestrants and ileal resection) produce a strikingly similar relationship though based on a much smaller body of evidence. The role of statins in treating FH has already been discussed; they should also be offered to all patients with clinical cardiovascular disease, to all diabetics aged over 40 years (and to diabetics under age 40 years with other CVD risk factors including microalbuminuria), to patients with other diseases that predispose to CVD (e.g. renal failure, metabolic syndrome, rheumatoid arthritis, etc.), or to anyone whose 10-year CVD risk exceeds 20% after lifestyle modification. Some patients do develop muscle problems with statin therapy; it is wise to inform patients of this possibility when starting or changing statins, with the advice that if they develop widespread muscle ache or pain they should stop the drug and seek medical review. Risk factors for developing myalgia include high statin dose, hepatic or renal impairment and co-administration of drugs that inhibit cytochrome enzymes. Females of child-bearing age should be counselled about the potential teratogenicity of the statins; current advice is that they should stop the statins 1 month before starting to try to conceive and that if they do become pregnant while taking a statin they should be seen urgently in a specialist lipid clinic. Liver enzymes should be monitored periodically after introducing statins.

Bile acid sequestrants lower total and LDL cholesterol but rather less effectively than statins. Nonetheless they have been shown to reduce CVD risk. They have the advantage that they are not absorbed from the intestine, where they work by binding the bile acids resulting from hepatic cholesterol catabolism and preventing their reabsorption in the terminal ileum. They therefore do not cause myalgia or abnormal liver function tests and are safe during pregnancy and breastfeeding. However, they have the disadvantage of being unpleasant to take and do cause gastrointestinal side effects. Ezetimibe is the latest agent that reduces total and LDL cholesterol. It works by blocking the newly described intestinal lipid transporter Niemann–Pick C1 like protein. It is well tolerated. Evidence that it reduces CVD risk is still awaited, so it remains a second- or third-line agent for those unable to tolerate statins or bile acid sequestrants or who fail to achieve satisfactory lipid profiles with them. It is the drug of choice for sitosterolaemia.

Fibrates are also well tolerated. They are now known to exert their multiple effects as agonists of peroxisome proliferators-activated receptor α (PPAR-α). Their main lipid effect is to reduce triglyceride levels by decreasing VLDL, and they also reduce β-VLDL in type III hyperlipoproteinaemia. They can increase HDL cholesterol. Trial evidence of their overall clinical effect is mixed; some trials have certainly shown reduced CVD risk with fibrates but others have not and there are as yet no clear data that they reduce overall mortality. Their main clinical role is in the treatment of severe hypertriglyceridaemia and of type III hyperlipoproteinaemia. They can also improve the lipid profile of those type 2 diabetic patients whose CVD risk remains high and largely driven by high triglycerides and low HDL cholesterol despite optimal statin therapy. Such combination therapy seems to run a lower risk of myalgia, myositis and rhabdomyolysis than once thought, but should be instituted in a clinic with experience of its monitoring. Clinical trials of statin–fibrate co-administration are under way. Fibrates can increase the serum creatinine and potentiate oral anticoagulants so renal function and INR need to be checked after initiation.

For some time, high-dose nicotinic acid has been known to have very favourable effects on the lipid profile. It lowers total and LDL cholesterol and triglycerides, increases HDL cholesterol more than any of the other drugs so far discussed and is the only drug that significantly reduces lipoprotein(a) levels. The mechanisms by which it achieves these changes are largely unknown. However, its clinical use has been much limited by its side effects: severe

flushing especially at higher doses, hyperglycaemia (a particular issue for the diabetics whose lipid profile might best be helped by it), and worsening of peptic ulcer disease. A couple of trials have found a reduction in CVD or atherosclerosis progression, either in combination with diet or statins. A new preparation of nicotinic acid (Niaspan®) does seem to have a reduced tendency to cause flushing or hyperglycaemia; this is also shortly to be combined with a prostaglandin D2 receptor-1 antagonist, which promises further improvements in tolerability. At present, use of nicotinic acid derivatives remains largely confined to specialist lipid clinics.

Reference

1 Durrington PN. Lipid-modifying therapy. In: Durrington PN, *Hyperlipidaemia: Diagnosis and Management*, 3rd edn. London: Hodder Arnold, 2007: 258–91.

Conclusion

Dyslipidaemias may present to dermatologists because they may cause subcutaneous and other lipid deposits collectively known as xanthomata. Not all such xanthomata are associated with abnormal circulating lipids, but where they are the underlying dyslipidaemia is likely to be severe and to require therapy that can reduce the risks of acute pancreatitis (in severe hypertriglyceridaemia) and of premature cardiovascular disease. Appropriate recognition of xanthomata and identification and management of any underlying dyslipidaemia can therefore be as effective a life saver as DC cardioversion during an acute MI in the Emergency Department—and more timely!

Disorders of amino-acid metabolism

There is a very wide array of disorders of the metabolism of the amino acids. This section will concentrate on those with significant cutaneous components in their presentation.

Hyperphenylalaninaemia syndromes

These syndromes result from defective hydroxylation of phenylalanine to tyrosine, with the consequent accumulation of phenylalanine in plasma, since this is the principal pathway for the breakdown of phenylalanine. This reaction is catalysed by phenylalanine hydroxylase (PAH) and requires the presence of the cofactor tetrahydrobiopterin (BH_4), which is itself converted to 4α-hydroxytetrahydropterin (also called 4α-carbinolamine) in the process. BH_4 is restored by the sequential action of 4α-carbinolamine dehydratase and dihydropterin reductase (DHPR). Synthesis of BH_4 from guanosine triphosphate (GTP) is catalysed by GTP-cyclohydrolase and 6-pyruvoyl tetrahydopterin synthase (6-PTS). The commonest clinical hyperphenylalaninaemia syndrome is phenylketonuria.

Phenylketonuria (MIM *261600)

Synonyms

- Hyperphenylalaninaemia type I
- Folling's disease
- Phenylpyruvic oligophrenia

Phenylketonuria (PKU) is a rare inherited disease defined by plasma phenylalanine levels exceeding 1000 µmol/L (normal range less than 120 µmol/L). (Patients with phenylalanine levels above the normal range but less than the defining concentration are described as having non-PKU hyperphenylalaninaemia.) PKU can be caused by primary deficiency of PAH, reduced BH_4 recycling secondary to DHPR deficiency (PKU2, MIM *261630), or impaired BH_4 synthesis secondary to GTP-cyclohydrolase or 6-PTS deficiency (MIM *261640). PAH deficiency is the commonest of these and causes 'classical' PKU; impaired BH_4 metabolism can cause plasma phenylalanine levels in excess of 1000 µmol/L, thus satisfying the biochemical diagnostic criterion for PKU, but the clinical course and treatment show some significant deviations from 'classical' PKU.

Aetiology [1,2]. Inheritance of PKU is autosomal recessive with an overall incidence of one in 8–12 000 live births. One in 50 individuals carry one of the mutant alleles. The genotype is markedly heterogeneous, PAH deficiency itself being caused by over 400 mutations at the PAH locus on chromosome 12q22–q24.1 [1]. The *DHPR* gene has been localized to chromosome 4 band 15.1p16.1 [1,3]. BH_4 deficiency is linked to three other loci: one on chromosome 4 and the others unmapped to date [3,4]. In PAH deficiency, hyperphenylalaninaemia requires exposure to phenylalanine, but in deficiencies of BH_4 recycling or synthesis PKU arises in the presence of the mutation alone. The usual gene dose effects are seen in heterozygotes.

In PKU, the accumulation of phenylalanine is accompanied by high levels of other derivatives of phenylalanine (such as phenylethylamine and phenylpyruvate, formed by decarboxylation and transamination, respectively) but there is ample evidence that it is the hyperphenylalaninaemia that is directly pathogenic. Tyrosine deficiency will reduce the availability of its metabolites, including acetoacetate and fumarate which contribute to the pool of two-carbon metabolites and glucose, so could contribute to impaired brain development. The oxidation rate in the brain is probably diminished but, although degenerative changes have been described in the cortex and basal ganglia and in the liver, they are inconstant [5–7]. In fact, there is little evidence of tyrosine deficiency in PKU, and tyrosine supplementation makes no impact on cognitive function. However, the reduction of melanin formation in the hair may be due to the inhibition of tyrosine–tyrosinase reaction by phenylalanine, and the hair will darken if large amounts of tyrosine are ingested. Disorders of BH_4 synthesis and recycling have additional pathological effects secondary to impaired tryptophan and tyrosine hydroxylation, as well as those secondary to hyperphenylalaninaemia.

Clinical features [1,5–7]. The clinical phenotype of PKU should now be a thing of the past because the damaging features of the disease can be reduced or prevented with early diagnosis and treatment. Affected infants are of average height and weight at birth, but thereafter show variable developmental delay. Unless diagnosis is made early, they present with psychomotor delay in early childhood leading on to mental retardation and often the need for long-term institutional care. Brain phenylalanine levels may better predict intellectual impairment than plasma concentra-

tions. About 50% have epilepsy, and extrapyramidal manifestations, such as athetosis and exaggerated tendon reflexes, may be found. The electroencephalogram is abnormal in 80% of patients and correlates with the metabolic phenotype. Magnetic resonance imaging has demonstrated changes consistent with disturbance in the water content of the white matter. It is not clear whether these are of clinical significance [8].

Recent studies have suggested that other clinical features previously associated with PKU may not be linked. However, patients almost invariably have fair skin and hair (due to impaired melanin synthesis). The fair and sensitive skin readily develops eczema. This may be of the atopic variety. Although clinical light sensitivity has been reported, the ability to tan and the erythemal response to UV radiation are normal [9]. The incidence of pyogenic infections is increased. Scleroderma-like lesions with involvement of the muscles have been described [10]. Eye abnormalities associated with hypopigmentation may occur [1,11]. Impaired physical growth affects the head circumference and height (abnormal long bone metaphyseal endplates) in the untreated condition [7,11].

There is clear evidence that in mothers with PKU, phenylalanine crosses the placental barrier (along a concentration gradient) causing impaired growth, congenital malformations, microcephaly, epilepsy or mental deficiency in the fetus [6]. Treatment is therefore recommended before conception and during pregnancy.

Diagnosis. Newborn screening is the established way to determine hyperphenylalaninaemia (HPA); plasma phenylalanine determination is far more sensitive than urine testing for phenylpyruvate and it is recommended that screening is performed on blood samples during the first week of life [12]. The most widely used method is based on the Guthrie test [13]. The test is performed on a dried capillary blood sample collected on filter paper and analysed by microbiological inhibition assay (Guthrie) or by chromatography, fluorimetry or tandem mass spectrometry. The latter test has few false negatives. Where hyperphenylalaninaemia is detected it is appropriate also to establish whether this is secondary to PAH deficiency or to abnormal BH_4 metabolism as the latter will require specific therapy to limit disease expression.

Prenatal diagnosis. Indications for this are uncertain, as treatment is experimental. Families at risk can have prenatal diagnosis by a combination of DNA analysis, enzyme activity, or amniocyte or chorion villus sample metabolite levels [1,3,12]. There are advantages to gene testing by DNA analysis, if alleles have been identified in an affected family member.

Treatment [5–19]. The aim of treatment is to normalize phenylalanine levels as soon and for as long as possible, and particularly during pregnancy. It is vital that the diagnosis is made early so that a low phenylalanine diet can be instituted immediately to avoid cerebral damage produced by high blood phenylalanine levels. Blood phenylalanine levels are routinely measured to monitor treatment. The diet is selectively restricted in phenylalanine to about 250–550 mg/day to keep the plasma phenylalanine level below the toxic range [20], and may need supplementation with tyrosine/tryptophan. The aim is to keep the plasma phenylalanine as low as possible and certainly less than 480 µmol/L. Phenylalanine is monitored twice weekly in the neonate, weekly in infants, 2–3 weekly in toddlers and ideally monthly thereafter even during adult life. This can now be achieved using dried blood spot samples. Particularly careful dietary treatment is necessary before conception and during pregnancy to reduce the risk of congenital heart disease [21–23] and abnormal brain development. Twice-weekly sampling blood tests are ideal to maintain levels of 100–250 µmol/L. There is evidence that reduction in maternal phenylalanine levels during pregnancy results in neonates with a higher birth weight [24].

The diet is based on a synthetic substitute for most of the dietary protein and should be continued throughout adult life as it has now been established that neurological sequelae can develop in the untreated affected adult [1,21,22,24,25]. Unfortunately, the response to dietary treatment is variable despite early and careful control. The amount of phenylalanine supplied in the diet should be low enough to prevent its accumulation in the blood, but high enough to allow protein synthesis and growth. Foods are given on an exchange basis using tables to indicate food with 1 g protein (equivalent 50 mg phenylalanine). Close collaboration with a metabolic dietician is an integral part of a successful treatment regimen and food diaries can also be helpful.

References

1 Scriver CR, Kaufman S. The hyperphenylalaninemias. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic and Molecular Bases of Inherited Disease*, 8th edn. New York: McGraw-Hill, 2001: 1677–725.

2 Scriver CR, Eisensmith RC, Woo SLC, Kaufman S. The hyperphenylalaninemias of man and mouse. *Annu Rev Genet* 1994; **28**: 141–65.

3 Guttler F, Guldberg P. Mutations in the phenylalanine hydroxylase gene. Genetic determinants for the phenotypic variability of hyperphenylalaninemia. *Acta Paediatr Suppl* 1994; **407**: 49–56.

4 Lidsky AS, Law ML, Morse HG *et al.* Regional mapping of the phenylalanine hydroxylase gene and the phenylketonuria locus in the human genome. *Proc Natl Acad Sci USA* 1985; **82**: 6221–5.

5 Smith I. Phenylketonuria due to phenylalanine hydroxylase deficiency, an unfolding story. Report of MRC Working Party on PKU. *BMJ* 1993; **306**: 115–9.

6 Tourian A, Sidbury JB. Phenylketonuria and hyperphenylalaninemia. In: Stanbury JB, Wyngaarden JB, Friedrickson DS, eds. *The Metabolic Basis of Inherited Disease*, 5th edn. New York: McGraw-Hill, 1983: 270–86.

7 Pitt DB, Danks DM. The natural history of untreated phenylketonuria. *J Paediatr Child Health* 1991; **27**: 189–90.

8 Cleary MA, Walter JH, Wraith JE *et al.* Magnetic resonance imaging of the brain in phenylketonuria. *Lancet* 1994; **344**: 87–90.

9 Hassell CW, Brunsting LA. Phenylpyruvic oligophrenia: an evaluation of the light-sensitive and pigmentary characteristics of seventeen patients. *Arch Dermatol* 1959; **79**: 458–65.

10 Jablonska S, Stachow A, Suffczynska M. Skin and muscle indurations in phenylketonuria. *Arch Dermatol* 1967; **95**: 443–50.

11 Walter JH. Late effects of phenylketonuria. *Arch Dis Child* 1995; **73**: 485–6.

12 MRC Working Party on Phenylketonuria. Present status of different mass screening procedures for phenylketonuria. *BMJ* 1968; **3**: 7–13.

13 Guthrie R, Susi A. A simple phenylalanine method for detecting phenylketonuria in large populations of newborn infants. *Pediatrics* 1963; **32**: 338–43.

14 Blaskovics ME, Schaeffler GE, Hack S. Phenylalaninaemia: differential diagnosis. *Arch Dis Child* 1974; **49**: 835–43.

15 Smith I. Treatment of phenylalanine hydroxylase deficiency. *Acta Paediatr* (Suppl.) 1994; **407**: 60–5.

16 Beasley MG, Costello PM, Smith I. Outcome of treatment in young adults with phenylketonuria detected by routine neonatal screening between 1964 and 1971. *QJM* 1994; **87**: 155–60.

17 Giovannini M, Biasucci G, Agostoni C *et al.* Lipid status and fatty acid metabolism in phenylketonuria. *J Inherit Metab Dis* 1995; **18**: 265–72.
18 Eisensmith RC, Woo SL. Gene therapy for phenylketonuria. *Acta Paediatr Suppl* 1994; **407**: 124–9.
19 Sutherland BS, Umbarger B, Berry HK. The treatment of phenylketonuria: a decade of results. *Am J Dis Child* 1966; **111**: 505–23.
20 Smith I. Recommendations on dietary management of phenylalanine. Report of MRC Working Party on phenylketonuria. *Arch Dis Child* 1993; **68**: 426–7.
21 Brenton DP, Hasler ME. Maternal phenylketonuria. In: Fernandes J, Saudubray JM, Tada K, eds. *Inborn Metabolic Diseases, Diagnosis and Management*. Berlin: Springer-Verlag, 1990: 175.
22 Dobblelaere D, Michaud L, Debrabander A *et al.* Evaluation of nutritional status and pathophysiology of growth retardation in patients with phenylketonuria. *J Inherit Metab Dis* 2003; **26**: 1–11.
23 Platt LD, Koch R, Azen C *et al.* Maternal phenylketonuria collaborative study, obstetric aspects and outcome: the first six years. *Am Obstet Gynecol* 1992; **166**: 1150–60.
24 Lenke R, Levy HL. Maternal phenylketonuria and hyperphenylalaninaemia. *New Engl J Med* 1980; **303**: 1202–8.
25 Burgard P, Link R, Schweitzer-Krantz S. Phenylketonuria: evidence-based clinical practice. Summary of the roundtable discussion. *Eur J Pediatr* 2000; **159** (Suppl. 2): S163–8.

Non-PKU hyperphenylalaninaemia (types II and III)

Where phenylalanine levels are raised but do not exceed 1000 µmol/L the patient is described as having non-PKU hyperphenylalaninaemia [1]. The clinical spectrum of this condition ranges from the apparently normal infant to those indistinguishable from classical PKU. There is a general correlation between PAH activity and blood levels of phenylalanine [2]. Accurate classification usually requires testing with phenylalanine loading and measurement of metabolites [3,4]. Treatment needs to be modified according to the severity of the enzyme deficiency, but essentially is as for PKU.

References

1 Scriver CR, Kaufman S. The hyperphenylalaninaemias. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic and Molecular Bases of Inherited Disease*, 8th edn. New York: McGraw-Hill, 2001: 1667–725.
2 Kang ES, Kaufman S, Gerald PS. Clinical and biochemical observations of patients with atypical phenylketonuria. *Pediatrics* 1970; **45**: 83–92.
3 Güttler F. Hyperphenylalaninaemia: diagnosis and classification of the various types of phenylalanine hydroxylase deficiency in childhood. *Acta Paediatr Suppl* 1980; **280**: 1–80.
4 Williamson M, Dobson JC, Koch R. Collaborative study of children treated for phenylketonuria: study design. *Pediatrics* 1977; **60**: 815–21.

Hyperphenylalaninaemia (types IV and V)

Hyperphenylalaninaemia types IV and V are due to deficiencies of tetrahydrobiopterin (BH_4) recycling or synthesis [1]. Together they account for 1–2% of all hyperphenylalaninaemias; failure of BH_4 recycling results from deficiency of dihydopteridine reductase (DHPR) and failure of synthesis from deficiency of either GTP cyclohydrase or 6-pyruvoyl tetrahydropterin synthase (6-PTS), the latter being about 20 times as common as the former.

Patients lacking DHPR have hyperphenylalaninaemia and other metabolic abnormalities reflecting the wide range of effects of DHPR [2]. They have defects of folate metabolism and are deficient in those neurotransmitters whose synthesis is dependent on tyrosine and tryptophan hydroxylation. They therefore have low urinary and cerebrospinal fluid levels of vanillyl mandelic acid (derived from norepinephrine), homovanillic acid (from dopamine) and 5-hydroxyindoleacetic acid (from 5-hydroxytryptamine). Treatment should aim to reduce plasma phenylalanine and to correct deficiencies of monoamines and folate metabolism. Thus the standard PKU diet should be instituted, together with supplementation of L-dopa (10–12 mg/kg/day) and 5-hydroxytryptophan (8–10 mg/kg/day) administered with a peripheral dopa decarboxylase inhibitor (e.g. carbidopa) to prevent nausea. Folinic acid (12.5 mg/day) is the recommended method of restoring normal folate balance. Early diagnosis is essential as in the absence of specific treatment there will be rapid neurological deterioration despite a low phenylalanine diet, and the earlier specific treatment starts the better the outcome. As the clinical picture is initially indistinguishable from PKU, biochemical diagnosis is required; urine screening for monoamine derivatives may help increase the suspicion of DHPR deficiency but direct assay of DHPR activity is now available and is the only reliable way to confirm or refute the diagnosis [3].

Patients with GTP cyclohydrolase deficiency have defective BH_4 synthesis [1]. They present with a progressive neurological disease with extrapyramidal features, mental retardation, seizures and occasional hyperthermia. Biochemically they have low levels of neopterin and biopterin as expected from a defect early in the biopterin synthetic pathway. Diagnosis can be confirmed by assaying GTP cyclohydrolase activity. Treatment with BH_4 as soon as possible is recommended, though the disorder is sufficiently rare that secure outcome data are not yet available. A commoner cause of reduced BH_4 synthesis is 6-PTS deficiency [4], which accounts for the commonest form of hyperphenylalaninaemia not resulting from PAH deficiency. These patients have high neopterin but low biopterin levels (and thus a high neopterin : biopterin ratio), and reduced synthesis of monoamine neurotransmitters (as in DHPR deficiency). They also present with the clinical features of PKU, with an additional progressive extrapyramidal syndrome. They typically have a low birth weight. Diagnosis rests on detection of hyperphenylalaninaemia, measurement of pterins, and correction of phenylalanine levels with test doses of BH_4. Treatment requires administration of BH_4, which is effective at reducing phenylalanine levels, but also administration of L-dopa and 5-hydroxytryptophan supplements (with a dopa decarboxylase inhibitor exactly as for DHPR deficiency) as BH_4 does not readily cross the blood–brain barrier.

Prenatal diagnosis. DHPR deficiency can now be detected prenatally by direct measurement of enzyme activity in amniocytes and by genetic screening in families with known mutations. GTP cyclohydrolase deficiency is more difficult to diagnose before birth as the enzyme is not expressed in amniocytes; but 6-PTS deficiency can be looked for by measurement of pterins in amniotic fluid and DNA analysis in families with previously defined mutations.

References

1 Blau N, Thony B, Cotton RGH, Hyland K. Disorders of tetrabiopterin and related biogenic amines. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic and Molecular Bases of Inherited Disease,* 8th edn. New York: McGraw-Hill, 2001: 1735–47.
2 Kaufman S, Holtzman NA, Milstien S *et al.* Phenylketonuria due to a deficiency of dihydrobiopterine reductase. *N Engl J Med* 1975; **293**: 785–90.

3 Dhondt JL. Strategy for the screening of tetrahydrobiopterin deficiency among hyperphenylalaninaemic patients: 15 years experience. *J Inherit Metab Dis* 1991; **14**: 117–27.
4 Naylor EW, Ennis D, Davidson AGF, Wong LT. Guanosine triphosphate cyclohydrolase I deficiency. Early diagnosis by routine urine pteridine screening. *Pediatrics* 1987; **79**: 374–8.

Tyrosinaemia

There are a number of inherited conditions that cause hypertyrosinaemia. These include inborn errors of metabolism (e.g. oculocutaneous and hepatorenal tyrosinaemia) and secondary causes (e.g. severe hepatocellular dysfunction and transient tyrosinaemia of the newborn). Tyrosine comes either from dietary intake or from hydroxylation of phenylalanine, and is the starting point of the synthetic pathways for catecholamines, thyroid hormone and melanin. Catabolism occurs mainly in hepatocytes and results in the formation of the gluconeogenic fumaric acid and the ketogenic acetoacetic acid. The inborn errors that lead to hypertyrosinaemia result from deficiency of one of the enzymes involved in this catabolic pathway.

Tyrosinaemia I (hepatorenal) (MIM *276700) [1–3]

This is a rare but well-documented, autosomal recessive disorder due to a deficiency in fumarylacetoacetic hydroxylase (FAH) which catalyses the last step in tyrosine catabolism. This enzyme has been located to chromosome 15. It can present as an acute or chronic form, and principally affects the liver, kidney and peripheral nerves.

The acute form presents in the first few weeks of life with failure to thrive, vomiting, jaundice, ascites and often gastrointestinal bleeding, and is often precipitated by infection or metabolic stress. An unusual odour said to resemble boiled cabbage may be detectable. Hepatomegaly may be present. Some acute crises proceed to liver failure and encephalopathy, while others resolve though may then recur. During acute attacks plasma tyrosine and methionine levels are high, as are transaminases (sometimes to a marked degree in severe attacks) and often α-fetoprotein.

The chronic form is characterized by chronic liver and renal disease (Fanconi-like syndrome) with death within the first decade. Some patients may develop porphyria-like neurological crises with painful paraesthesiae, autonomic dysfunction (with tachycardia and hypertension) and occasionally a progressive paralysis. These crises are due to the accumulation of succinylacetone, the most powerful known inhibitor of delta aminolaevulinic acid (δ-ALA) dehydratase [3]. Plasma tyrosine and methionine are elevated diagnostically and there is a global increase in urine amino acids, with particular increase in δ-ALA [3].

Secondary deficiency of hepatic 4-hydroxyphenylpyruvic acid dioxygenase (pHPPD) occurs in FAH deficiency, accounts for the increased tyrosine levels and was indeed originally thought to be the primary cause of hepatorenal tyrosinaemia. Some patients develop hypermethioninaemia, due to a secondary inhibition of methionine adenosyltransferase.

Cirrhosis is probably invariable in patients with hepatorenal tyrosinaemia and there is a very high incidence of hepatocellular carcinoma, though it is now thought that some of the initial estimates of this particular complication may have been overestimated [2]. Nonetheless, regular screening is recommended, despite some of the recognized pitfalls of liver ultrasound or CT in distinguishing benign and malignant nodules.

Diagnosis. Prenatal diagnosis is either by direct determination of the FAH enzyme activity or detection of succinylacetone directly or from its inhibitory activity in amniocytes or chorionic villus samples [2,4]. Neonatal screening is aimed at detecting increased levels of tyrosine, methionine or succinylacetone from blood spots on filter paper; more recently these have also been used for screening δ-ALA dehydratase. Several different mutations have been reported, and where the mutation is known, molecular analysis should be carried out.

Treatment. This is with a low tyrosine and phenylalanine diet which can reduce plasma tyrosine levels and does improve renal function, though with less certain benefit for liver disease. Treatment with NTBC (2-(nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione), which inhibits pHPPD, has been tried in a number of patients with hepatorenal tyrosinaemia with some benefit [5–7]. However liver transplantation, which cures the underlying metabolic defect, has revolutionized the prognosis for this condition and remains the treatment of choice [5–7].

References

1 Goldsmith LA, Laberge C. Tyrosinemia and related disorder. In: Scriver CR, Beaudet AL, Sly WS *et al.*, eds. *The Metabolic Basis of Inherited Disease*, 6th edn. New York: McGraw-Hill, 1989: 547–62.
2 Mitchell GA, Lambert M, Tanguay RM. Hypertyrosinemia. In: Scriver CR, Beaudet AL, Sly WS *et al.*, eds. *The Metabolic and Molecular Basis of Disease*, 7th edn. New York: McGraw-Hill, 1995: 1077–106.
3 Berger R. Biochemical aspects of type I hereditary tyrosinaemia. In: Bickel H, Wachtel H, eds. *Inherited Diseases of Amino Acid Metabolism*. New York: Thieme Verlag, 1985: 192.
4 Goulden KJ, Moss MA, Cole DE *et al.* Pitfalls in the initial diagnosis of the tyrosinaemia: three case reports and a review of the literature. *Clin Biochem* 1987; **20**: 207–12.
5 Kvittingen EA. Tyrosinaemia—treatment and outcome. *J Inherit Metab Dis* 1995; **18**: 375–9.
6 Mitchell GA, Grompe M, Lambert M, Tanguay RM. Hypertyrosinosinemia. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic and Molecular Bases of Inherited Disease*, 8th edn. New York: McGraw-Hill, 2001: 1777–805.
7 Gissen P, Preece MA, Willshaw HA, McKiernan PJ. Ophthalmic follow-up of patients with tyrosinaemia type 1 on NTBC. *J Inherit Metab Dis* 2003; **26**: 13–6.

Tyrosinaemia II (MIM *276710)

Synonym
- Richner–Hanhart oculocutaneous syndrome

This is a very rare disorder, inherited as an autosomal recessive trait, due to a deficiency of cytoplasmic tyrosine aminotransferase (TAT), which catalyses the first and rate-limiting step in tyrosine catabolism [1,2]. Males and females are equally affected. The skin, eyes and nervous system are the only organs affected.

The skin manifestations of oculocutaneous tyrosinaemia do not usually appear until after the first year of life. They consist of painful hyperkeratotic plaques on the soles and palms with a particular predilection for the fingertips and thenar and hypothenar eminences [3]. They do not itch but can be sufficiently painful that they prevent walking. Hyperhidrosis of the affected area may

also occur, as may leukokeratosis of the tongue [4]. Skin biopsy reveals hyperkeratosis, acanthosis and parakeratosis with homogeneous refractile eosinophilic inclusions in the stratum corneum and upper Malpighian layer; none of these are pathognomonic [1]. On electron microscopy lipid-like granules, myelin-like fragments, keratinocytes with increased tonofibrils and tightly packed microtubular and tonofibrillar masses have all been described. There is minimal, if any, evidence of inflammation and tyrosine crystals are not seen, unlike the conjunctival biopsies of these patients [5].

By contrast with the skin manifestations, eye symptoms are usually present in the first year, though they can develop later. They consist of episodes of pain, photophobia, redness and lacrimation. On examination, central corneal dendritic erosions are seen with prominent neovascularization also occurring quite frequently. There can be progression to corneal opacities with consequent reduced visual acuity [6,7]. A variable degree of mental retardation is present in less than 50% of patients with oculocutaneous tyrosinaemia [3].

Biochemically, this disease produces a highly characteristic pattern with plasma tyrosine as the only elevated plasma amino acid and the only amino acid excreted in the urine. Metabolites of tyrosine are also detectable in urine [1].

Diagnosis. This is made by detection of increased blood tyrosine levels, normal phenylalanine and increased urinary metabolites of 4-hydroxyphenylacetic acid, *N*-acetyltyrosine and 4-tyramine.

Treatment. Most patients respond to dietary restriction of tyrosine and phenylalanine [1,8] with the aim of reducing blood levels to less than 600 µmol/L. Skin and eye symptoms and signs usually respond fairly rapidly, though can recur if the diet is discontinued. Oral retinoids have proved beneficial but steroids make skin symptoms worse.

References

1 Mitchell GA, Marcus G, Lambert M, Tanguay RM. Hypertyrosinemia. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic and Molecular Bases of Inherited Disease*, 8th edn. New York: McGraw-Hill, 2001: 1777–805.

2 Goldsmith LA, Thorpe J, Roe CR. Hepatic enzymes of tyrosine metabolism in tyrosinemia II. *J Invest Dermatol* 1979; **73**: 530–2.

3 Hanhart E. Neue Sonderformen von Keratosis palmoplantaris. *Dermatologica* 1947; **94**: 286–308.

4 Larrègue M, de Giacomoni P, Bressieux JM, Odievre M. Syndrome de Richner-Hanhart ou tyrosinose oculo-cutanée. A propos d'un cas. *Ann Dermatol Vénéréol* 1979; **106**: 53–62.

5 Bohnert A, Anton-Lamprecht I. Richner-Hanhart's syndrome: ultrastructural abnormalities of epidermal keratinization indicating a causal relationship to high intracellular tyrosine levels. *J Invest Dermatol* 1982; **79**: 68.

6 Bienfang DC, Kuwabara T, Pueschel SM. The Richner–Hanhart syndrome: report of a case with associated tyrosinemia. *Arch Ophthalmol* 1976; **94**: 1133–7.

7 Bardelli AM, Borgogni P, Farnetani MA *et al.* Familial tyrosinaemia with eye and skin lesions. *Ophthalmologica* 1977; **175**: 5–9.

8 Hill A, Nordin PM, Zaleski WA. Dietary treatment of tyrosinosis. *J Am Diet Assoc* 1970; **56**: 308–12.

Alkaptonuria (MIM #203500) [1,2]

This is a rare metabolic disorder first described by Garrod in 1902 [1], which results from a single gene defect. It is characterized by a discrete biochemical lesion, with deposition of oxidized homogentisic acid pigment throughout the body, particularly in fibrous and cartilaginous tissues. Dark urine (homogentisic aciduria), distinctive cutaneous pigmentation (ochronosis) and arthritis are characteristic. Generally, it is considered a benign degenerative disorder with normal life expectancy [2].

Aetiology [1–3]. Alkaptonuria is characterized by a constitutional deficiency of homogentisic oxidase (homogentisic 1,2-dioxygenase activity), an enzyme usually found in liver and kidney. This leads to an accumulation of homogentisic acid, an intermediate metabolite of phenylalanine and tyrosine catabolism.

Ochronosis [4,5] describes the deposition of a melanin-like brownish-black pigment, derived from the oxidized product of homogentisic acid (benzoquinone acetic acid), in connective tissues and cartilage. The enzyme homogentisic acid oxidase contains an essential sulphhydryl group, which is inhibited by certain chemicals. These include various drugs such as phenol, resorcin, mepacrine and perhaps other antimalarials that may cause acquired ochronosis. An exogenous ochronosis can also occur from hydroquinone-containing skin-bleaching creams [4].

Genetics. Alkaptonuria is an autosomal recessive condition. The gene locus (*AKU*) has been assigned to chromosome 3q by consanguinity and by comparative mapping. The gene has been cloned to 3q21–q23 with demonstration that the human 1890 gene harbours missense mutations and co-segregates with the disease [3]. The incidence is one in 200 000 but in areas of consanguinity it is higher [6].

Histopathology. There is deposition of black pigment in the cartilage, fibrous tissue, tendons and atheromatous areas. The intervertebral discs, larynx, tracheal rings and articular cartilages are jet-black as if 'dipped in Indian ink'. Differentiation of the ochronotic pigment from melanin is difficult, and stains do not consistently differentiate between the two pigments.

Clinical features [2,7]. Cardinal features are due to homogentisic acid in urine, and pigmentation of cartilage, connective tissue and joints. The patient with the hereditary type is symptom-free until adult life. The only manifestations in childhood are discoloration of the urine and 'spotting or staining' of the napkins or clothing due to alkaline pH. The clinical sequence of events is alkaptonuria, then ochronosis and lastly ochronotic arthropathy (fifth decade). The cutaneous manifestations appear in the fourth decade. One of the earliest signs is thickening of the ear cartilage, associated with blue-black or grey-blue discoloration. The pinna feels noticeably thickened and inflexible, and in later stages there may be gross calcification. Cerumen is often brown or jet black. Scleral pigmentation is noted as early as the third decade; it appears as brown or grey deposits midway between the corneal margin and the medial canthus. The skin of the eyelids and forehead is also pigmented and the tarsal plates often appear blue on transillumination. All the tendons are similarly discoloured; the dark discoloration over the extensor tendons on the knuckles is best seen when the patient makes a fist. Widespread, dusky cutaneous pigmentation may be noted, but this feature is particularly marked over the cheeks, forehead, axillae and genital regions. The buccal mucosa and

larynx are also affected and the nails are sometimes distinctly coloured brown. Ochronotic changes affecting the ear drum and ossicles may produce deafness; prostatic concretions and black renal calculi, as well as calcific aortic disease, have been recorded. The urine is of normal colour but darkens on exposure to air or within seconds of adding an alkaline solution. Patients sometimes observe that both their sweat and urine discolour clothing.

Ochronotic arthropathy follows a fairly consistent clinical pattern. There is low back pain with stiffness early in the fourth decade; during the next 10 years the knees become involved and, later, the shoulders and hips. The friable articular cartilages lead to prolapsed intervertebral discs or a ruptured nucleus pulposus with accompanying acute pain. Spondylosis spreads to the thoracic spine; patients then assume a stooping posture and can lose up to 15 cm in height. Limitation of expansion of the chest provokes dyspnoea. The spinal X-ray appearances are diagnostic, consisting of narrowing of the lumbar disc spaces with intense calcification of the narrowed discs.

Marked atherosclerosis is common in the older age groups as well as valvulitis and calcification of aortic and mitral valves. In spite of their marked disability, many patients reach old age.

Diagnosis. The diagnosis is by demonstration on gas–liquid chromatography of homogentisic acid in the urine (by its reducing ability), or with specific enzyme tests [8].

Differential diagnosis. An incorrect diagnosis of glycosuria or diabetes can be made if the urine is tested with Fehling's solution (but this is rarely used now). The pigmentation of acquired ochronosis from exogenous foreign chemicals or drugs is identical to the genetic disorder, but is unaccompanied by homogentisic acid in the urine or by arthropathy.

The overall clinical picture and the localization of pigment thus distinguish the genetic disease from other pigmentation disorders such as Addison's disease, haemochromatosis, argyria, chronic photosensitivity pigmentation, cutaneous porphyria and pellagra. The ferric chloride urine test gives variable results; other phenolic compounds give similar colour reactions and thus, when the test is positive, the urine should be examined by chromatography.

Treatment [2]. Since the major damage induced by the metabolic defect is pigmentation and joint changes, treatment is directed towards reducing connective tissue damage by ascorbic acid (acting as an antioxidant), and by analgesics and physiotherapy for the arthropathy. A low protein diet limiting the amount of phenylalanine and tyrosine is not practicable as a long-term measure, although it could be used intermittently. Use of vitamins (B_{12}, C) may be helpful (for example ascorbic acid in reducing homogentisic acid oxidation).

References

1 Garrod AE. The incidence of alkaptonuria: a study in clinical individuality. *Lancet* 1908; **ii**: 73–9.

2 La Du BN. Alkaptonuria. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic and Molecular Bases of Inherited Disease*, 8th edn. New York: McGraw-Hill, 2001: 2109–23.

3 Fernandez-Canon JM, Granadino B, Beltron-Valero de Bernabe D *et al*. The molecular basis of alkaptonuria. *Nat Genet* 1996; **14**: 19–24.

4 Findlay GH, Morrison JGL, Simson IW. Exogenous onchronosis and pigmented colloid milium from hydroquinone bleaching creams. *Br J Dermatol* 1975; **93**: 613–22.

5 Woolley PB. Exogenous onchronosis. *BMJ* 1952; **2**: 760–1.

6 Lee PJ, Brenton DP. Inborn errors of amino acid and organic acid metabolism. In: Warrell DA, Cox TM, Firth JD, Benz EJ, eds. *Oxford Textbook of Medicine*, 4th edn. Oxford: Oxford University Press, 2003: 9–31.

7 O'Brien WM, La Du BN, Bunim JJ. Biochemical, pathologic and clinical aspects of alkaptonuria, ochronosis and ochronotic arthropathy. Review of world literature. *Am J Med* 1963; **34**: 813–38.

8 Seegmiller JE, Zannoni VG, Laster L, Brent N. An enzymatic spectrophotometric method for the determination of homogentisic acid in plasma and urine. *J Biol Chem* 1961; **236**: 774–7.

Homocysteinurias [1–5]

Synonym

- Homocystinurias

Homocysteinurias are a group of rare, inborn errors of amino-acid metabolism first reported in 1962 [4]. They also encompass hypermethioninaemia and cystathioninuria. The defects arise when there is abnormality in transfer of the sulphur from methionine to homocysteine in the biochemical pathway responsible for the disposal of methionine and the formation of cysteine, resulting in the accumulation of homocysteine, methionine and other sulphurated metabolites in a wide range of tissues and in the urine.

Aetiology. Initially homocysteinuria was thought to be due solely to deficiency of cystathionine-β synthase (CBS; MIM *236200), but it is now apparent that homocysteine accumulation may also result from inherited defects in the 5-methyltetrahydrofolate–homocysteine methyltransferase reaction (MIM # 236250) [1,3,6]. These can be distinguished because there is an increase in urine methionine in the CBS deficiency whereas it is low in hyperhomocystinaemia secondary to defects of the folate pathway. Secondary forms of homocysteinuria can occur in vegetarians with vitamin B_{12} deficiency, or with treatment with isonicotinic acid. The accumulated homocysteine is believed to interfere with collagen cross-linking accounting for the wide range of clinical features.

Clinical features. CBS deficiency is inherited as an autosomal recessive trait, with a world prevalence of 1 : 344 000 though with wide variation between different countries [1]. Four major systems are affected: the eye, skeletal system, central nervous system and the vascular system. The newborn infant appears clinically normal, but lens dislocation, mental deficiency, growth disorder and cutaneous signs may develop slowly over the next few years. The skin features of homocysteinuria include fine, brittle hair and thin skin. Livedo reticularis of the legs and tissue-paper scars on the hands may be present. In some cases, hair examination shows no fluorescence with acridine orange, indicating abnormality of disulphide bonds. The cysteine content is normal. Abnormal glucose tolerance and increased growth hormone levels are often present.

Osteoporosis of the spine is common and predisposes to scoliosis. Lengthening and thinning of the long bones may lead to a variety of skeletal abnormalities and their presence together with the arachnodactyly that also occurs may lead to a Marfanoid

appearance. Other features include hepatomegaly (secondary to fatty change) and myopathy. Many patients with CBS deficiency exhibit some degree of mental impairment; developmental delay may be the presenting feature of the disease and about 20% also suffer seizures. Psychiatric abnormalities occur in about 50% of patients, including episodic depression (10%), chronic behavioural disorders (17%) [7], chronic obsessive–compulsive disorders (5%) and personality disorders (19%). Some children develop spontaneous venous and arterial thrombosis, probably secondary to increased platelet adhesiveness, and venous thromboembolic disease is a frequent cause of mortality [6,8]. There has been much interest in recent years in establishing whether milder forms of hyperhomocystinaemia, seen quite frequently in folate deficiency, may be associated with increased risk of cardiovascular disease [9,10]. Although the initial epidemiology seemed convincing, trials of folic acid supplementation have not generally reduced the clinical endpoints of atherosclerosis such as myocardial infarcts and strokes.

Differential diagnosis. Marfan's syndrome, an hereditary mesodermal dysplasia, exhibits visceral manifestations without mental deficiency. The hair is normal and homocysteine is absent from the urine.

Diagnosis. This is by detection of urinary homocysteine by a positive urinary cyanide–nitroprusside reaction. Recently, plasma homocysteine measurement (with increases of 50–200 µmol/L), confirmed by changes after methionine loading, is regarded as a more accurate assessment. Heterozygotes can be detected by assaying for the enzyme in the liver, phytohaemagglutinin-stimulated lymphocytes and in cultured fibroblasts. In addition, the presence of abnormal sulphur-containing metabolites can be detected in the urine after an oral load of L-methionine. CBS deficiency can be diagnosed by hypermethioninaemia or by detection of increased homocysteine in urine or blood. Methods for detecting heterozygotes rest on enzyme assays, metabolite measurements or a combination using liver tissue, cultured fibroblasts or phytohaemagglutinin-stimulated lymphocytes. Newer techniques include tandem mass spectrometry [11].

Treatment [1,12]. There are two aims of treatment: (i) control/elimination of the biochemical abnormality; and (ii) treatment of complications. Patients are usually divided into pyridoxine-responsive or non-responsive individuals, detected after the newborn period. For the newborn, diets restricting methionine and supplemented with cysteine have been used with encouraging results when started early in life. Large doses of vitamin B_6 (pyridoxine) in the form of pyridoxine hydrochloride 150–300 mg/day produce complete reversal of the biochemical abnormality in some cases. Some may become folate deficient; administration of vitamin B_{12} and folic acid improves clinical symptoms. For the non-pyridoxine responsive patients, a low protein diet with methionine-free amino acid supplements and exchanges, and minerals and vitamins may be helpful. In non-responsive patients diagnosed after birth (non-responsive after a trial of 500–1000 mg/day for several weeks), the use of betaine as a methyl donor agent to lower homocysteine levels can prove effective in lowering plasma homocysteine levels in combination with a low-methionine diet. Aspirin can help reduce the thrombotic risk and other cardiovascular risk factors, such as hypertension, diabetes and dyslipidaemia should be sought and treated appropriately.

Prognosis. Prognosis is more favourable than might be thought, with recent surveys showing that fewer than 5% of affected individuals die by the age of 20 years [1–3].

References

1 Mudd H, Levy HL, Kraus JP. Disorders of transsulfuration. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic and Molecular Bases of Inherited Disease*, 8th edn. New York: McGraw-Hill, 2001: 2007–56.

2 Brenton DP, Cusworth DC, Dent CE, Jones EE. Homocystinuria. Clinical and dietary studies. *QJM* 1966; **35**: 325–46.

3 Carson NAJ, Cusworth DC, Dent CE *et al.* Homocystinuria. *Arch Dis Child* 1963; **38**: 425–36.

4 Field CMB *et al. Abstracts of the Xth International Congress of Paediatrics*. Lisbon, 1962: 274.

5 Fourth International Conference on Homocysteine Metabolism (Abstracts). *J Inherit Metab Dis* 2003; **26**: 1–129.

6 McDonald L, Bray C, Field C *et al*. Homocystinuria, thrombosis, and the blood platelets. *Lancet* 1964; **1**: 745–6.

7 Abbott MH, Folstein SE, Abbey H, Pyeritz RE. Psychiatric manifestations of homocystinuria due to cystathione-synthase deficiency. *Am J Med Genet* 1987; **26**: 959–69.

8 McKusick VA. *Heritable Disorders of Connective Tissue*, 4th edn. St Louis: Mosby, 1972: 224.

9 Scott J, Weir D. Homocyst(e)ine and cardiovascular disease (Editorial). *QJM* 1996; **89**: 571–7.

10 Wilcken DEL, Wilcken B. The natural history of vascular disease in homocystinuria and the effects of treatment. *J Inherit Metab Dis* 1997; **20**: 295–300.

11 Chace DH, Hillman SL, Millington DS *et al*. Rapid diagnosis of homocystinuria and other hypermethioninemias from newborns' blood spots by tandem mass spectrometry. *Clin Chem* 1996; **42**: 349–55.

12 Barber GW, Spaeth GL. Pyridoxine therapy in homocystinuria (Letter). *Lancet* 1967; **1**: 337.

Hartnup disease (MIM *2345000) [1–3]

This is a very rare hereditary recessive disorder of neutral amino acid transport, which is characterized by a pellagrous eruption, a temporary and intermittent cerebellar ataxia, and a characteristic renal aminoaciduria with excessive indicanuria [1].

Aetiology [1,4]. Hartnup disease is believed to be caused by a genetic defect in the specific system for transport of neutral amino acids in the kidney and across the brush border epithelium of the intestine, leading to hyperaminoaciduria and urinary excretion of indolic compounds formed by bacterial action on the unabsorbed tryptophan [5–7]. It is likely that Hartnup disorder is a monogenic defect which interacts with polygenic and environmental factors giving a wide clinical spectrum [8]. The failure of absorption of tryptophan results in a deficiency in the synthesis of nicotinamide causing a pellagra-like syndrome.

Clinical features. The onset is usually in childhood between 3 and 9 years, but the first signs are occasionally encountered as early as 10 days after birth. The cutaneous signs precede the neurological manifestations. The rash is dry, scaly and well marginated, affecting the light-exposed areas, notably the forehead, cheeks, periorbital regions, the uncovered areas of the arms and the dorsal

surface of the hands. After exposure to sunlight, the skin reddens and blistering may occur. With recovery there is often desquamation and depigmentation.

Cerebellar ataxia is the most commonly encountered neurological feature. It usually develops later than the skin lesions. Other signs of cerebellar origin include nystagmus and diplopia, and occasionally tremor of the hands and tongue. Early reports suggested mental retardation, but this has not been the case with most patients. Minor cognitive defects have been reported. Less commonly, there are associated psychiatric disturbances such as depression, delusions and hallucinations. Exacerbations are most frequently seen in the spring or early summer [2], cutaneous manifestations being accompanied by transient ataxia. Rarely, the attacks are provoked by febrile illness. Other somatic abnormalities include oedema and hypoproteinaemia with fatty change in the liver [2], fever, diarrhoea and atrophic glossitis.

Intravenous tryptophan is metabolized normally and the serum amino acid profile is normal. The urine contains increased amounts of amino acids of the monoamine monocarboxylic groups [5], and it is the pattern of the amino acid excretion that confirms the diagnosis.

Differential diagnosis. The eruption in mild cases closely simulates infantile atopic eczema, seborrhoeic eczema or pityriasis alba; in Hartnup disease the covered areas are usually spared. Florid cases closely mimic nutritional pellagra. The congenital poikilodermas, particularly the light-sensitive hereditary disorders such as Cockayne's syndrome, may present diagnostic difficulties.

Treatment [2,3]. The rationale for the treatment is to replace the defect by giving nicotinamide (50–300 mg/day) orally. Treatment usually results in amelioration of the rash and may improve ataxia and psychotic behaviour. A high-protein diet may be a useful adjunct. Intravenous nutrition may be necessary in severely affected patients.

Prognosis. Symptoms become milder with increasing age.

References

1 Baron DN, Dent CE, Harris H *et al.* Hereditary pellagra-like skin rash with temporary cerebellar ataxia. Constant renal amino-aciduria, and other bizarre biochemical features. *Lancet* 1956; **2**: 421–8.

2 Halvorsen K, Halvorsen S. Hartnup disease. *Pediatrics* 1963; **31**: 29–38.

3 Levy HL. Hartnup disorder. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic and Molecular Bases of Inherited Disease*, 8th edn. New York: McGraw-Hill, 2001: 4957–81.

4 Scriver CR, Mahon B, Levy HL *et al.* The Hartnup phenotype: Mendelian transport disorder, multifactorial disease. *Am J Hum Genet* 1987; **40**: 401–12.

5 Milne MD. Disorders of amino acid transport. *BMJ* 1964; **1**: 327–36.

6 Milne MD, Crawford MA, Girdo CB *et al.* The metabolic disorder in Hartnup disease. *QJM* 1960; **29**: 407–21.

7 Scriver CR. Hartnup disease: a genetic modification of intestinal and renal transport of certain neutral alpha amino acids. *N Engl J Med* 1965; **273**: 530–2.

8 Matthews DM. Experimental approach in chemical pathology. *BMJ* 1971; **3**: 659–64.

Gout

This heterogeneous group of abnormalities of purine metabolism is characterized by hyperuricaemia, and recurrent attacks of acute arthritis in some cases, with the deposition of monosodium urates in the articular cartilage and urate deposits in the skin (tophi) (Fig. 59.69). Arthritis may be progressive and nephropathy is common. Nephrolithiasis due to uric acid may precede arthritis.



Fig. 59.69 Gouty tophi. (Courtesy of Dr R.H. Champion, West Suffolk Hospital, Bury St Edmunds, UK.)

Aetiology [1–4]. Uric acid is the degradative product of purine metabolism in humans. Increased circulating levels of uric acid arise because of overproduction or underexcretion of uric acid. Primary gout has long been recognized as a heterogeneous disorder; in up to 40% of patients the family history suggests a genetic component [4]. Population studies suggest that the disorder is multifactorial and attributable to a combination of genetic and non-genetic factors [1]. There are two very rare specific enzyme deficiencies associated with gout, which have X-linked inheritance. These are partial deficiency of hypoxanthine–guanine phosphoribosyl transferase (HGPRT; HPRT-related gout, MIM #300323) and increased activity of phosphoribosyl-pyrophosphate (PRPP) synthetase [5]. Most patients with primary gout appear to have reduced excretion of uric acid [6,7] but the molecular mechanisms underlying this remain poorly understood. Fewer than 10% of patients with primary gout have an increase in the rate of purine biosynthesis [8].

Secondary gout may result from decreased excretion of uric acid. The most important cause of this is diuretic therapy but it may also occur in a number of disease states, especially renal tubular disease. Increased uric acid production is commonly secondary to increased turnover of nucleic acids in conditions such as polycythaemia rubra vera, lymphoma, myeloma and leukaemia especially when patients are receiving active chemotherapy. A number of other disorders may be associated with hyperuricaemia and gout. 82% of patients with pure or combined hypertriglyceridaemia have increased uric acid levels, and conversely 74% of patients with gout have raised lipoproteins (TG, VLDL [5,9] and Lp(a) [10]); the link between the two is likely to be insulin resistance. There has been a suggestion that hyperuricaemia may be a risk factor for cardiovascular disease [9,11]. Hypertension, obesity, diabetes mellitus and ethanol consumption in susceptible persons may also be associated with gout [12].

Histopathology. Sodium urate crystals may be found in joint fluid. The crystals can be identified by microscopic examination and by their ability to polarize light strongly. In the dermis and medulla of the kidney, the urate crystals provoke a giant cell reaction [12,13].

Clinical features [1,3,4,7]. Hyperuricaemia develops at around puberty in males but usually later in females, often after the menopause. Patients normally remain asymptomatic until the fourth to sixth decades when the first attack of acute gouty arthritis occurs. Recurrent, self-limiting attacks usually follow after a period of about 6 months to 2 years. Initially single joints, classically the great toe, are involved, but later the condition may become polyarticular and then usually involves the joints of the lower extremities. Later in the disease, a chronic tophus state develops with deposits in cartilage, synovial membranes, tendons and soft tissues. The classical locations for tophi are the helix and antihelix of the ear, and the index fingers (Fig. 59.69). Criteria for clinical diagnosis of acute gout have been reported [3,14].

Acute uric acid nephropathy results from precipitation of uric acid crystals in the collecting ducts of the kidney and is most commonly seen in patients with leukaemia undergoing aggressive chemotherapy. Renal stones develop in up to one-quarter of patients [12] and renal colic may be a presenting manifestation of gout. Chronic urate nephropathy is common [6,15] and contributes significantly to the morbidity and mortality of gout [15].

Differential diagnosis. Pseudogout [2,16] (calcium pyrophosphate deposition disease) shows close similarities to gout (particularly the acute attacks), and is characterized by familial incidence and later chronic arthropathy, pseudotophi and precipitation by surgical operations and diuretic therapy. The serum uric acid level is normal, calcium pyrophosphate is found in synovial fluid and X-rays show articular calcification [2]. Multicentric reticulohistiocytosis is frequently accompanied by papules and nodules on the ears and fingers with an associated arthropathy. Rheumatoid arthritis with necrobiotic nodules is usually sufficiently characteristic to avoid confusion with gout. Psoriatic arthropathy may cause diagnostic difficulties.

Treatment [1,3,15,17,18]. All patients with gout or a raised uric acid level should be investigated for its cause. Acute attacks are treated by rest of the affected joint and with regular anti-inflammatory treatment, such as indomethacin. Where non-steroidal anti-inflammatory drugs are contraindicated, corticosteroids can sometimes be helpful. Colchicine (0.5 mg 6-hourly until symptoms subside, or a maximum oral dose of 6 mg has been reached) may also be useful in acute episodes. Side effects of diarrhoea, renal and hepatic damage need to be carefully monitored during treatment with colchicine. It is a matter of clinical judgement whether to treat asymptomatic hyperuricaemia.

Antiuricaemic therapy using allopurinol, a xanthine oxidase inhibitor, is effective after the acute event and in prophylaxis. Allopurinol should be avoided in an acute attack, and its introduction sometimes precipitates an acute attack. If this happens, reintroduction of allopurinol after a suitable interval should be covered by concomitant administration of colchicine or non-steroidal anti-inflammatory drugs for the first couple of weeks. Drugs such as probenecid and sulfinpyrazone may be used to increase uric acid excretion, but are usually less effective prophylaxis. Treatment must be tailored to the needs of individual patients [8,19].

References

1 Becker MA. Hyperuricemia and gout. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic and Molecular Bases of Inherited Disease*, 8th edn. New York: McGraw-Hill, 2001: 2513–55.
2 Howell DS. Diseases due to the deposition of calcium pyrophosphate and hydroxyapatite. In: Kelley WN *et al*., eds. *Textbook of Rheumatology*, 2nd edn. Philadelphia: Saunders, 1985.
3 Watts RWE. Disorders of purine and pyrimidine metabolism. In: Warrell DA, Cox TM, Firth JD, Benz EJ, eds. *Oxford Textbook of Medicine*, 4th edn. Oxford: Oxford University Press, 2003: 49–60.
4 Grahame R, Scott JT. Clinical survey of 354 patients with gout. *Ann Rheum Dis* 1970; **29**: 461–8.
5 Stout JT, Caskey CG. Hypoxanthine. The Lesch–Nyhan syndrome and gouty arthritis. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic Basis of Inherited Disease*, 6th edn. New York: McGraw-Hill, 1989: 1007–28.
6 Snaith ML, Scott JT. Uric acid clearance in patients with gout and normal subjects. *Ann Rheum Dis* 1971; **30**: 285–9.
7 Barlow KA, Beilin LJ. Renal disease in primary gout. *QJM* 1968; **37**: 79–96.
8 Kelley KN. Approach to the patient with hyperuricemia. In: Kelley WN *et al*., eds. *Textbook of Rheumatology*, 2nd edn. Philadelphia: Saunders, 1985.
9 Laskarzewski PM, Khoury P, Morrison JA *et al*. Familial hyper- and hypouricaemias in random and hyperlipidaemic recall cohorts: The Princeton School District Family Study. *Metabolism* 1983; **32**: 230–43.
10 Takahashi S, Yamamoto T, Moriwaki Y *et al*. Increased concentrations of serum Lp(a) lipoprotein in patients with primary gout. *Ann Rheum Dis* 1995; **54**: 90–3.
11 Waring WS, Webb DJ, Maxwell SRJ. Uric acid as risk factors for cardiovascular disease. *QJM* 2000; **93**: 707–13.
12 Landis RC, Haskard DO. Pathogenesis of crystal-induced inflamation. *Curr Rheumatol Rep* 2001; **3**: 36–41.
13 Gutman AB, Yu TF. Uric acid nephrolithiasis. *Am J Med* 1968; **45**: 756–79.
14 Hochberg MC. Gout. In: Silman AJ, Hochberg MC, eds. *Epidemiology of the Rheumatic Diseases*, 2nd edn. Oxford: Oxford University Press, 2001: 230–42.
15 Talbott JH, Terplan KL. The kidney in gout. *Medicine* 1960; **39**: 405–67.
16 McCarty DJ, Kohn NN, Faires JS. The significance of calcium phosphate crystals in the synovial fluid of arthritic patients: the 'pseudogout' syndrome. Clinical aspects. *Ann Intern Med* 1962; **56**: 711–37.
17 Emerson BT. The management of gout. *N Engl J Med* 1996; **334**: 445–51.
18 Fam AG. Difficult gout and new approaches for control of hyperuricaemia in the allopurinol-allergic patient. *Curr Rheumatol Rep* 2001; **3**: 29–35.
19 Yu T. Milestones in the treatment of gout. *Am J Med* 1974; **56**: 676–85.

Lesch–Nyhan syndrome (MIM #300322) [1–6]

Lesch–Nyhan syndrome results from a complete lack of the purine salvage enzyme hypoxanthine-guanine phosphoribosyltransferase (HGPRT). HGPRT is coded for by a single gene on the X chromosome (Xq26-q27), and is expressed in all tissues, and at high level in the basal ganglia. This enzyme catalyses the salvage of hypoxanthine and guanine to inosine monophosphate (IMP) and guanosine monophosphate (GMP). The principal clinical features are choreoathetosis, spasticity, mental retardation and self-mutilation, particularly biting of the lower lip in childhood. There may also be a macrocytic/megaloblastic anaemia. Patients are normal at birth, but by 6 months developmental abnormalities are apparent with choreiform movements usually being the first to appear. The origin of the neurological abnormality in humans is still unknown; HGPRT-deficient mice do not show any of the neurological features of Lesch–Nyhan syndrome. It is, however,

thought that it is the accumulation of purine metabolites rather than deficiency of purine nucleotides that is pathogenic with secondary effects on neurotransmitter function. Changes in terminal arborization of dopaminergic neurones have been found, probably occurring secondary to reduced concentrations of dopamine homovanillic acid, dopa and tyrosine decarboxylase in dopaminergic neurones in the putamen. Blood uric acid levels are high and, although there are no reports of gouty arthritis, renal function is impaired by deposit of urates. However, patients with partial deficiency of HGPRT may develop gouty arthritis and/or uric acid calculi though without any of the neurological and behavioural features of the full-blown syndrome.

Prenatal diagnosis. HGPRT analysis can be carried out on amniocyte or chorionic villus samples in the ninth week of pregnancy. Affected male heterozygotes can be identified by HGPRT assay on red cell lysates. Carrier females can be identified by HGPRT and $HGPRT^{-}$ mosaicism in hair roots; mosaicism can also be identified in cultured fibroblasts [7].

Treatment. Allopurinol, in appropriate dosage, can reduce plasma urate and urinary uric acid to reduce occurrence of gouty arthritis, urate nephropathy and renal calculi. There is no effective treatment of the neurological features. However, padded wheelchairs and physical restraints may reduce spinal injury and self-mutilation. Dental extraction may also assist in preventing the latter [5,7].

References

1 Hoefnagel D, Andrew ED, Mireault NG, Berndt WO. Hereditary choreoathetosis, self-mutilation and hyperuricemia in young males. *N Engl J Med* 1965; **273**: 130–5.

2 Lesch M, Nyhan WL. A familial disorder of uric acid metabolism and central nervous system function. *Am J Med* 1964; **36**: 561–70.

3 Kelley WN, Greene ML, Rosenbloom FM, Helderson JF. Hypoxanthineguanine phosphoribosyltransferase deficiency in gout. *Ann Intern Med* 1969; **70**: 155–206.

4 Nyhan WL, Oliver WJ, Lesch M. A familial disorder of uric acid metabolism and central nervous system function. II. *J Pediatr* 1965; **67**: 257–63.

5 Jinnah HA, Friedmann T. Lesch–Nyhan disease and its variants. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic and Molecular Bases of Inherited Disease*, 8th edn. New York: McGraw-Hill, 2001: 2537–70.

6 Reed WB, Fish CH. Hyperuricemia with self-mutilation and choreoathetosis. Lesch–Nyhan syndrome. *Arch Dermatol* 1966; **94**: 194–5.

7 Watts RWE. Disorders of purine and pyrimidine metabolism. In: Warrell DA, Cox TM, Firth JD, Benz EJ, eds. *Oxford Textbook of Medicine*, 4th edn. Oxford: Oxford University Press, 2003: 49–60.

CHAPTER 60
Necrobiotic Disorders

D.A. Burns
Leicester Royal Infirmary, Leicester, UK

Granuloma annulare, 60.1 | Necrobiosis lipoidica, 60.12 | Granuloma multiforme, 60.17

Granuloma annulare

Introduction. Granuloma annulare was first described by Colcott Fox in 1895 [1], and established as a specific entity by Radcliffe Crocker in 1902 [2]. It is a disease in which, in typical cases, the skin and/or subcutis is involved in a process characterized by foci of alteration of collagen (necrobiosis) surrounded by histiocytes and lymphocytes. Clinical variants include localized, generalized, perforating and subcutaneous patterns [3,4].

References

1 Fox TC. Ringed eruption of the fingers. *Br J Dermatol* 1895; **7:** 91–2.
2 Radcliffe Crocker H. Granuloma annulare. *Br J Dermatol* 1902; **14:** 1–9.
3 Muhlbauer JE. Granuloma annulare. *J Am Acad Dermatol* 1980; **3:** 217–30.
4 Smith MD, Downie JB, DiCostanzo D. Granuloma annulare. *Int J Dermatol* 1997; **36:** 326–33.

Aetiology [1–3]. Although the aetiology and pathogenesis of granuloma annulare are unclear, it appears likely that it represents a reaction pattern to a variety of triggering factors. Reported triggering factors have included insect bites [4], scabies [5], a cat bite [6], waxing-induced pseudofolliculitis [7], tuberculin tests [8], BCG vaccination [9,10], hepatitis B vaccination [11,12] and chronic hepatitis B virus infection, with resolution soon after treatment with interferon-α [13], a possible relationship to antitetanus and diphtheria toxoid vaccination [14,15], and various forms of trauma such as occupational pressure on the fingers in a milkman [16] and saphenectomy [17]. In the past, its occurrence with tuberculosis was noted in a number of reports, and cases may still be encountered in which there appears to be an association between these two disorders [18,19]. Other infectious agents that have been implicated in the causation of lesions of granuloma annulare include human papilloma virus [20], varicella/zoster virus [21–29] (although persistence of viral DNA does not appear to be related to granuloma formation [26,30]), Epstein–Barr virus (EBV) [31,32] (although EBV could not be demonstrated in lesions occurring in HIV-positive patients [33]), parvovirus B19 [34], hepatitis C virus [35] and during pegylated interferon-α treatment for hepatitis C virus infection [36], and human immunodeficiency virus [33,37–46]. Although there has been evidence implicating *Borrelia burgdorferi* in some cases [47,48], it was absent in others [49]. Examination of several biopsy specimens using polymerase chain reaction amplification did not reveal any evidence of *Bartonella* infection [50]. Granuloma annulare at the site of an infection such as herpes zoster has been termed an 'isotopic' response.

Seasonally recurrent granuloma annulare has been described [51,52], and sun exposure may have acted as a precipitating factor in one of these cases [52]. Sun exposure is thought to have provoked or contributed to localization of lesions in a number of cases [53–56]. Disseminated granuloma annulare has occurred in a patient undergoing PUVA therapy [57]. Whether actinic granuloma is a distinct entity, or represents granuloma annulare on sun-exposed skin, has been the subject of debate [58–66].

A report of granuloma annulare occurring in the red areas of tattoos [67] prompted description of a similar case and the suggestion that both were examples of a perforating collagenosis [68].

There is a report of disseminated granuloma annulare occurring in the same sites as lesions of erythema multiforme minor [69].

Some cases of granuloma annulare-like lesions attributed to drugs may have been examples of drug-induced interstitial granulomatous reactions [70].

It has been suggested that an immunoglobulin-mediated vasculitis is the cause of the necrobiotic granulomas [2,71], but evidence from immunofluorescence studies is conflicting—some authors have demonstrated immunoreactants in vessel walls [71], whereas others have not [72,73]. An alternative view is that the pathogenetic mechanism is a delayed-type hypersensitivity response [2,73–77].

An increased prevalence of HLA-Bw35, compared with controls and those with localized lesions, has been demonstrated in individuals with generalized granuloma annulare [78].

The relationship between diabetes mellitus and granuloma annulare is discussed below, as are apparent associations with several other disorders.

References

1 Muhlbauer JE. Granuloma annulare. *J Am Acad Dermatol* 1980; **3:** 217–30.
2 Dahl MV. Speculations on the pathogenesis of granuloma annulare. *Australas J Dermatol* 1985; **26:** 49–57.

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

3 Smith MD, Downie JB, DiCostanzo D. Granuloma annulare. *Int J Dermatol* 1997; **36:** 326–33.
4 Moyer DG. Papular granuloma annulare. *Arch Dermatol* 1964; **89:** 41–5.
5 Wilsmann TD, Wenzel J, Gerdsen R *et al*. Granuloma annulare induced by scabies. *Acta Derm Venereol* 2003; **83:** 318.
6 Trujillo-Santos AJ, Aguiar-Garcia F, González-Hermoso C. Subcutaneous nodules after a cat bite. *Arch Intern Med* 2001; **161:** 2043–4.
7 Young HS, Coulson IH. Granuloma annulare following waxing-induced folliculitis. *Clin Exp Dermatol* 2000; **25:** 274–6.
8 Beer WE, Wilson Jones E. Granuloma annulare following tuberculin Heaf tests. *Trans St. John's Hosp Dermatol Soc* 1966; **52:** 68–70.
9 Houcke-Bruge C, Delaporte E, Catteau B *et al*. Granuloma annulaire après vaccination par le BCG. *Ann Dermatol Vénéréol* 2001; **128:** 541–4.
10 Kakurai M, Kiyosawa T, Ohtsuki M, Nakagawa H. Multiple lesions of granuloma annulare following BCG vaccination: case report and review of the literature. *Int J Dermatol* 2001; **40:** 579–81.
11 Wolf F, Grezard P, Berard F *et al*. Generalized granuloma annulare and hepatitis B vaccination. *Eur J Dermatol* 1998; **8:** 435–6.
12 Criado PR, de Oliveira RR, Vasconcellos C *et al*. Two case reports of cutaneous adverse reactions following hepatitis B vaccine: lichen planus and granuloma annulare. *J Eur Acad Dermatol Venereol* 2004; **18:** 603–6.
13 Ma HJ, Zhu WY, Yue XZ. Generalized granuloma annulare associated with chronic hepatitis B virus infection. *J Eur Acad Dermatol Venereol* 2006; **20:** 186–9.
14 Baykal C, Ozkaya-Bayazit E, Kaymaz R. Granuloma annulare possibly triggered by antitetanus vaccination. *J Eur Acad Dermatol Venereol* 2002; **16:** 516–8.
15 Baskan EB, Tunali S, Kacar SD *et al*. A case of granuloma annulare in a child following tetanus and diphtheria toxoid vaccination. *J Eur Acad Dermatol Venereol* 2005; **19:** 639–40.
16 Beer WE, Wayte DM, Morgan GW. Knobbly granuloma annulare (GA) of the fingers of a milkman—a possible relationship to his work. *Clin Exp Dermatol* 1992; **17:** 63–4.
17 Borgia F, Cannavò SP, Guaneri F *et al*. Isomorphic response after saphenectomy in a patient with granuloma annulare. *J Am Acad Dermatol* 2004; **50** (Suppl. 2): S31–3.
18 Winkelmann RK. The granuloma annulare phenotype and tuberculosis. *J Am Acad Dermatol* 2002; **46:** 948–52.
19 Herron MD, Florell SR. Disseminated granuloma annulare accompanying *Mycobacterium tuberculosis* lymphadenitis. *Int J Dermatol* 2004; **43:** 961–3.
20 Ward WH. Warts and granuloma annulare. *BMJ* 1956; **2:** 1484.
21 Guill MA, Goette DK. Granuloma annulare at sites of healing herpes zoster. *Arch Dermatol* 1978; **114:** 1383.
22 Kleber R, Landthaler M, Burg G. Post-zoster granuloma annulare. *Hautarzt* 1989; **40:** 110–1.
23 Zanolli MD, Powell BL, McCalmont T *et al*. Granuloma annulare and disseminated herpes zoster. *Int J Dermatol* 1992; **31:** 55–7.
24 Hayakawa K, Mizukawa Y, Shiohara T, Nagashima M. Granuloma annulare arising after herpes zoster. *Int J Dermatol* 1992; **31:** 745–6.
25 Krahl D, Hartschuh W, Tilgen W. Granuloma annulare perforans in herpes zoster scars. *J Am Acad Dermatol* 1993; **29:** 859–62.
26 Requena L, Kutzner H, Escalonilla P *et al*. Cutaneous reactions at sites of herpes zoster scars: an expanded spectrum. *Br J Dermatol* 1998; **138:** 161–8.
27 Bygum A. Granuloma annulare after herpes zoster: isotopic response. *Ugeskr Laeger* 1998; **20:** 4429–30.
28 Ohata C, Shirabe H, Takagi K, Kawatsu T. Granuloma annulare in herpes zoster scars. *J Dermatol* 2000; **27:** 166–9.
29 Chang SE, Bae GY, Moon KC *et al*. Subcutaneous granuloma annulare following herpes zoster. *Int J Dermatol* 2004; **43:** 298–9.
30 Serfling U, Penneys NS, Zhu WY *et al*. Varicella-zoster virus DNA in granulomatous skin lesions following herpes zoster: a study by the polymerase chain reaction. *J Cutan Pathol* 1993; **20:** 28–33.
31 Spencer SA, Fenske NA, Espinoza CG *et al*. Granuloma annulare-like eruption due to chronic Epstein–Barr virus infection. *Arch Dermatol* 1988; **124:** 250–5.
32 Person JR. Generalized granuloma annulare, mononucleosis and positive rheumatoid factor. *Int J Dermatol* 1995; **34:** 40–1.
33 Toro JR, Chu P, Ben Yen T-S, LeBoit PE. Granuloma annulare and human immunodeficiency virus infection. *Arch Dermatol* 1999; **135:** 1341–6.
34 Magro CM, Dawood MR, Crowson AN. The cutaneous manifestations of human parvovirus B19 infection. *Hum Pathol* 2000; **31:** 488–97.
35 Granel B, Serratrice J, Rey J *et al*. Chronic hepatitis C virus infection associated with a generalized granuloma annulare. *J Am Acad Dermatol* 2000; **43:** 918–9.
36 Kluger N, Moguelet P, Chaslin-Ferbus D *et al*. Generalized interstitial granuloma annulare induced by pegylated interferon-alpha. *Dermatology* 2006; **213:** 248–9.
37 Huerter CJ, Bass J, Bergfeld WF, Tubbs RR. Perforating granuloma annulare in a patient with acquired immunodeficiency syndrome. *Arch Dermatol* 1987; **123:** 1217–20.
38 Bakos L, Hampe S, da Rocha JL *et al*. Generalized granuloma annulare in a patient with acquired immunodeficiency syndrome. *J Am Acad Dermatol* 1987; **17:** 844–5.
39 Jones SK, Harman RRM. Atypical granuloma annulare in patients with the acquired immunodeficiency syndrome. *J Am Acad Dermatol* 1989; **20:** 299–300.
40 Cohen PR, Grossman ME, Silvers DN, DeLeo VA. Generalized granuloma annulare located on sun-exposed areas in a human immunodeficiency virus–seropositive man with ultraviolet B photosensitivity. *Arch Dermatol* 1990; **126:** 830–1.
41 McGregor JM, McGibbon DH. Disseminated granuloma annulare as a presentation of acquired immunodeficiency syndrome (AIDS). *Clin Exp Dermatol* 1992; **17:** 60–2.
42 Muñoz-Pérez MA, García-Bravo B, Rodriguez-Pichardo A, Camacho F. Coexistence of allergic contact dermatitis and granuloma annulare in an HIV-I-infected patient: a casual association? *Am J Contact Dermatitis* 1999; **10:** 100–1.
43 Cohen PR. Granuloma annulare. A mucocutaneous condition in human immunodeficiency virus-infected patients. *Arch Dermatol* 1999; **135:** 1404–7.
44 O'Moore EJ, Nandawni R, Uthayakumar S *et al*. HIV-associated granuloma annulare (HAGA): a report of six cases. *Br J Dermatol* 2000; **142:** 1054–6.
45 Morris SD, Cerio R, Paige DG. An unusual presentation of diffuse granuloma annulare in an HIV-positive patient—immunohistochemical evidence of predominant CD8 lymphocytes. *Clin Exp Dermatol* 2002; **27:** 205–8.
46 Calista D, Landi G. Disseminated granuloma annulare in acquired immunodeficiency syndrome: case report and review of the literature. *Cutis* 1995; **55:** 158–60.
47 Strle F, Preac-Mursic V, Ruzic E *et al*. Isolation of *Borrelia burgdorferi* from a skin lesion in a patient with granuloma annulare. *Infection* 1991; **19:** 351–2.
48 Aberer E, Schmidt BL, Breier F *et al*. Amplification of DNA of *Borrelia burgdorferi* in urine samples of patients with granuloma annulare and lichen sclerosus et atrophicus. *Arch Dermatol* 1999; **135:** 210–2.
49 Halkier-Sorensen L, Kragballe K, Hansen K. Antibodies to the *Borrelia burgdorferi* flagellum in patients with scleroderma, granuloma annulare and porphyria cutanea tarda. *Acta Derm Venereol* 1989; **69:** 116–9.
50 Smoller BR, Madhusudhan KT, Scott MA, Horn TD. Granuloma annulare: another manifestation of *Bartonella* infection? *Am J Dermatopathol* 2001; **23:** 510–3.
51 McLelland J, Young S, Marks JM, Lawrence CM. Seasonally recurrent granuloma annulare of the elbows. *Clin Exp Dermatol* 1991; **16:** 129–30.
52 Uenotsuchi T, Imayama S, Furue M. Seasonally recurrent granuloma annulare on sun-exposed areas. *Br J Dermatol* 1999; **141:** 367.
53 Leppard B, Black MM. Disseminated granuloma annulare. A variant in which the lesions involve the sun-exposed areas. *Trans St John's Hosp Dermatol Soc* 1972; **58:** 186–90.
54 Duncan WC, Smith JD, Knox JM. Generalized perforating granuloma annulare. *Arch Dermatol* 1973; **108:** 570–2.
55 Izumi AK. Generalized perforating granuloma annulare. *Arch Dermatol* 1973; **108:** 708–9.
56 Derancourt C, Sensor M, Atallah L *et al*. Granuloma annulaire des zones photoexposées chez deux malades ayant en une greff hépatique. *Ann Dermatol Vénéréol* 2000; **127:** 723–7.
57 Dorval J-C, Leroy J-P, Masse R. Granulomes annulaires disséminés après PUVA thérapie. *Ann Dermatol Vénéréol* 1979; **106**: 79–80.
58 Al-Hoqail IA, Al-Ghamdi AM, Martinka M, Crawford RI. Actinic granuloma is a unique and distinct entity. A comparative study with granuloma annulare. *Am J Dermatopathol* 2002; **24:** 209–12.
59 Ackerman AB. Vasculitis: the true and near-true. *Am J Dermatopathol* 2002; **24:** 521–2.
60 Al-Hoqail IA, Martinka M, Crawford RI. Vasculitis: the true and near-true: authors' reply. *Am J Dermatopathol* 2002; **24:** 522–3.
61 Hanke CW, Bailin PL, Roenigk HH Jr. Annular elastolytic giant cell granuloma. A clinicopathologic study of five cases and a review of similar entities. *J Am Acad Dermatol* 1979; **1:** 413–21.

62 Ragaz A, Ackerman AB. Is actinic granuloma a specific condition? *Am J Dermatopathol* 1979; **1:** 43–50.
63 Wilson Jones E. Actinic granuloma. *Am J Dermatopathol* 1980; **2:** 89–90.
64 Weedon D. Actinic granuloma: the controversy continues. *Am J Dermatopathol* 1980; **2:** 90–1.
65 Revenga F, Rovira I, Pimentel J, Alejo M. Annular elastolytic giant cell granuloma—actinic granuloma. *Clin Exp Dermatol* 1996; **21:** 51–3.
66 O'Brien JP, Regan W. Actinically degenerate elastic tissue is the likely antigenic basis of actinic granuloma of the skin and of temporal arteritis. *J Am Acad Dermatol* 1999; **40:** 214–22.
67 Gradwell E, Evans S. Perforating granuloma annulare complicating tattoos. *Br J Dermatol* 1998; **138:** 360–1.
68 Bedlow AJ, Wong E, Cook MG, Marsden RA. Perforating collagenosis due to red dye in a tattoo. *Br J Dermatol* 1998; **139:** 926–7.
69 Abraham Z, Feuerman Ej, Schafer I, Feinmesser M. Disseminated granuloma annulare following erythema multiforme minor. *Australas J Dermatol* 2000; **41:** 238–41.
70 Lim AC, Hart K, Murrell D. A granuloma annulare-like eruption associated with the use of amlodipine. *Australas J Dermatol* 2002; **43:** 24–7.
71 Dahl MV, Ullman S, Goltz RW. Vasculitis in granuloma annulare: histopathology and direct immunofluorescence. *Arch Dermatol* 1977; **113:** 463–7.
72 Umbert P, Winkelmann RK. Granuloma annulare: direct immunofluorescence study. *Br J Dermatol* 1976; **95:** 487–92.
73 Bergman R, Pam Z, Lichtig C *et al*. Localized granuloma annulare. Histopathological and direct immunofluorescence study of early lesions, and the adjacent normal-looking skin of actively spreading lesions. *Am J Dermatopathol* 1993; **15:** 544–8.
74 Cherney KJ, Lindroos WE, Goltz RW *et al*. Leukocyte function in granuloma annulare. *Br J Dermatol* 1979; **101:** 23–31.
75 Buechner SA, Winkelmann RK, Banks PM. Identification of T-cell sub-populations in granuloma annulare. *Arch Dermatol* 1983; **119:** 125–8.
76 Modlin RL, Vaccaro SA, Gottlieb B *et al*. Granuloma annulare. Identification of cells in the cutaneous infiltrate by immunoperoxidase techniques. *Arch Pathol Lab Med* 1984; **108:** 379–82.
77 Fayyazi A, Schweyer S, Eichmeyer B *et al*. Expression of IFN gamma, coexpression of TNF alpha and matrix metalloproteinases and apoptosis of T lymphocytes and macrophages in granuloma annulare. *Arch Dermatol Res* 2000; **292:** 384–90.
78 Friedman-Birnbaum R, Haim S, Gideone O, Barzilai A. Histocompatibility antigens in granuloma annulare. Comparative study of the generalized and localized types. *Br J Dermatol* 1978; **98:** 425–8.

Histopathology [1–5] (Figs 60.1 & 60.2). The most characteristic histological lesion in granuloma annulare is the necrobiotic granuloma, but there are three histological patterns that may occur: necrobiotic palisading granulomas, an interstitial form, and granulomas of sarcoidal or tuberculoid type [1]. Umbert and Winkelmann [3] found that the commonest histological pattern was the interstitial type, as did Friedmann-Birnbaum *et al*. [4]. The latter authors compared the histopathological features of localized and generalized granuloma annulare, and noted that the interstitial pattern was more frequent in localized than in generalized disease; the prevalence of the palisading granuloma pattern was almost equal in both clinical types. Dabski and Winkelmann [5] also found that the interstitial pattern was common in both these types of granuloma annulare, and in many cases it occurred alone, without palisading granulomas. However, they noted a prominent palisading pattern more frequently in localized disease than in the generalized variety. Observer variation and the existence of more than one pattern in the same section may have contributed to differences in the findings in these series.

Necrobiotic granulomas are characterized by foci of necrobiosis surrounded by histiocytes and lymphocytes, with the histiocytes

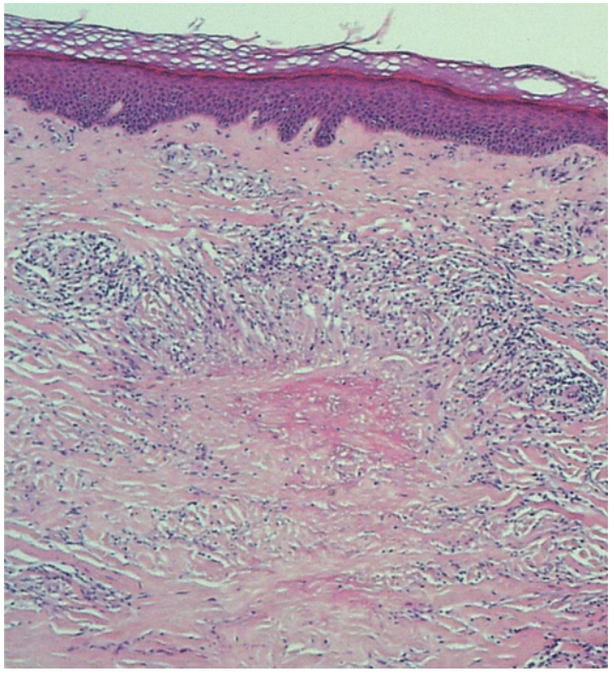


Fig. 60.1 Granuloma annulare. Nodule in upper dermis. H&E stain. (Courtesy of Dr M. Bamford, Dept. of Pathology, Leicester Royal Infirmary, Leicester, UK.)

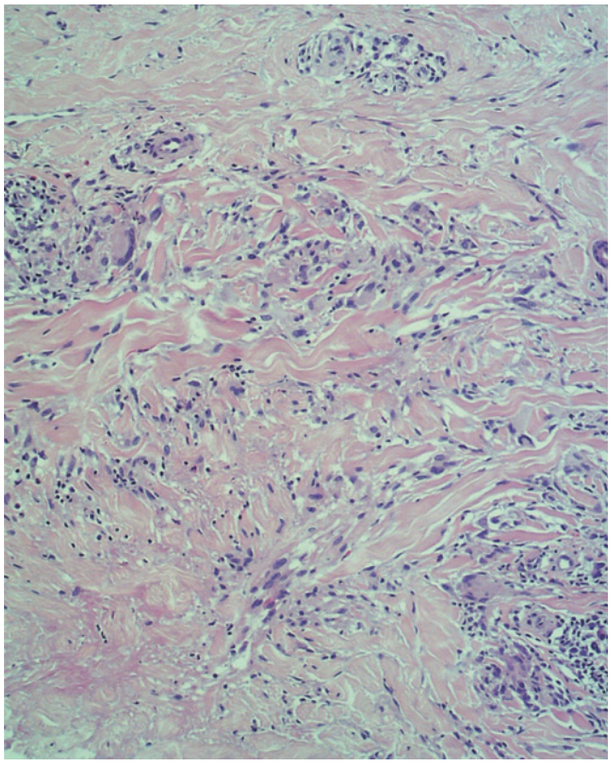


Fig. 60.2 Granuloma annulare. Nodule—well circumscribed with good palisade of histiocytes and central necrobiosis. H&E stain. (Courtesy of Dr M. Bamford, Dept. of Pathology, Leicester Royal Infirmary, Leicester, UK.)

commonly forming a palisaded pattern. There are varying numbers of multinucleate giant cells in this peripheral zone. T cells in the lymphocytic infiltrate are of the helper/inducer phenotype (CD4+) [6–8], but in two cases associated with HIV infection a predominantly T-suppressor (CD8+) infiltrate was demonstrated [9,10]. Analysis of the T-cell repertoire and cytokine pattern has shown a T-cell response characterized by a combination of a few skin-specific clones together with many non-specific T cells, and abundant production of interleukin-2 [8]. The high local production of interleukin-2 could be responsible for the non-specific attraction of T cells to the granulomas.

Mucin is present within the foci of necrobiosis, and it can be seen more readily by staining with Alcian blue or colloidal iron. Small deposits of lipid material may also be present in these areas. Some form of collagen alteration, most commonly fragmentation of collagen bundles, was observed in 79% of cases of localized and 53% of cases of generalized granuloma annulare by Dabski and Winkelmann [5]. There is a marked reduction in, or absence of, elastic fibres [11,12]. Metalloproteinases are probably involved in the damage to collagen and elastic fibres [13,14]. The granulomas are situated in the superficial and mid-dermis and, in contrast with necrobiosis lipoidica, areas between them are relatively normal.

In the interstitial pattern there are no formed areas of necrobiosis, histiocytes and lymphocytes are present around blood vessels and between collagen bundles, and collagen fibres are separated by mucin.

The sarcoidal or tuberculoid pattern is uncommon, and may cause problems in diagnosis. The presence of mucin and eosinophils can help to distinguish granuloma annulare from sarcoidosis. Blau syndrome is rare but causes histological differential diagnostic difficulties as it comprises an interstitial infiltrate as well as a sarcoidal pattern.

There is a perivascular infiltrate of lymphocytes and histiocytes. Eosinophils are variably present [15]. In one study [16], the presence of eosinophils was strongly associated with a palisaded architectural pattern and the presence of necrobiosis. Plasma cells are rare. A vasculitis has been described in or near foci of necrobiosis [17].

Histiocytes express the marker PG-M1 [18]. They may show an increased mitotic rate, and recognition of this is important, in particular in differentiating granuloma annulare from epithelioid sarcoma [19–22].

Epidermal changes are inconspicuous except in perforating granuloma annulare. In this variant there is a superficial area of necrobiosis surrounded by palisading histiocytes, situated beneath a perforation in the epidermis [1,2,23]. The necrobiotic material is extruded via the perforation. At the margins of the perforation there are varying degrees of epidermal hyperplasia.

The lesions of subcutaneous granuloma annulare often contain large areas of necrobiosis, and they are similar to rheumatoid nodules both clinically and histologically. Patterson [24] found that Alcian blue staining of mucin in lesions of granuloma annulare was the most helpful distinguishing feature.

Other disorders with similar histological features include mycosis fungoides variants [25–28], interstitial granulomatous dermatitis (interstitial granulomatous dermatitis with arthritis; interstitial granulomatous dermatitis with plaques; palisaded neutrophilic granulomatous dermatitis) [29–35], and the interstitial granulomatous drug reaction [36,37].

References

1 Weedon D. *Skin Pathology*, 2nd edn. London: Churchill Livingstone, 2002: 200–2.

2 Elder D, Elenitsas R, Jaworsky C, Johson B Jr, eds. *Lever's Histopathology of the Skin* 8th edn. Philadelphia: Lippincott-Raven, 1999: 328–30.

3 Umbert P, Winkelmann RK. Histologic, ultrastructural and histochemical studies of granuloma annulare. *Arch Dermatol* 1977; **113:** 1681–6.

4 Friedman-Birnbaum R, Weltfriend S, Munichor M, Lichtig C. A comparative histopathologic study of generalized and localized granuloma annulare. *Am J Dermatopathol* 1989; **11:** 144–8.

5 Dabski K, Winkelmann RK. Generalized granuloma annulare: histopathology and immunopathology. Systematic review of 100 cases and comparison with localized granuloma annulare. *J Am Acad Dermatol* 1989; **20:** 28–39.

6 Buechner SA, Winkelmann RK, Banks PM. Identification of T-cell subpopulations in granuloma annulare. *Arch Dermatol* 1983; **119:** 125–8.

7 Kallioinen M, Sandberg M, Kinnunen T, Oikarinen A. Collagen synthesis in granuloma annulare. *J Invest Dermatol* 1992; **98:** 463–8.

8 Mempel M, Musette P, Flageul B *et al*. T-cell receptor repertoire and cytokine pattern in granuloma annulare: defining a particular type of cutaneous granulomatous inflammation. *J Invest Dermatol* 2002; **118:** 957–66.

9 Huerter CJ, Bass J, Bergfeld WF, Tubbs RR. Perforating granuloma annulare in a patient with acquired immunodeficiency syndrome. Immunohistologic evaluation of the cellular infiltrate. *Arch Dermatol* 1987; **123:** 1217–20.

10 Morris SD, Cerio R, Paige DG. An unusual presentation of diffuse granuloma annulare in an HIV-positive patient—immunohistochemical evidence of predominant CD8 lymphocytes. *Clin Exp Dermatol* 2002; **27:** 205–8.

11 Friedman-Birnbaum R, Weltfriend S, Kerner H, Lichtig C. Elastic tissue changes in generalized granuloma annulare. *Am J Dermatopathol* 1989; **11:** 429–33.

12 Hanna WM, Moreno-Merlo F, Andrighetti L. Granuloma annulare: an elastic tissue disease? Case report and literature review. *Ultrastruct Pathol* 1999; **23:** 33–8.

13 Vaalamo M, Kariniemi A-L, Shapiro SD, Saarialho-Kere U. Enhanced expression of human metalloelastase (MMP-12) in cutaneous granulomas and macrophage migration. *J Invest Dermatol* 1999; **112:** 499–505.

14 Fayyazi A, Schweyer S, Eichmeyer B *et al*. Expression of IFNγ, coexpression of TNFα and matrix metalloproteinases and apoptosis of T lymphocytes and macrophages in granuloma annulare. *Arch Dermatol Res* 2000; **292:** 384–90.

15 Silverman RA, Rabinowitz AD. Eosinophils in the cellular infiltrate of granuloma annulare. *J Cutan Pathol* 1985; **12:** 13–17.

16 Romero LS, Kantor GR. Eosinophils are not a clue to the pathogenesis of granuloma annulare. *Am J Dermatopathol* 1998; **20:** 29–34.

17 Dahl MV, Ullman S, Goltz RW. Vasculitis in granuloma annulare: histopathology and direct immunofluorescence. *Arch Dermatol* 1977; **113:** 463–7.

18 Groisman GM, Schafer I, Amar M, Sabo E. Expression of the histiocytic marker PG-M1 in granuloma annulare and rheumatoid nodules of the skin. *J Cutan Pathol* 2002; **29:** 590–5.

19 Heenan PJ, Quirk CJ, Papadimitriou JM. Epithelioid sarcoma. A diagnostic problem. *Am J Dermatopathol* 1986; **8:** 95–104.

20 Trotter MJ, Crawford RI, O'Connell JX, Tron VA. Mitotic granuloma annulare: a clinicopathologic study of 20 cases. *J Cutan Pathol* 1996; **23:** 537–45.

21 Lopez-Rios F, Rodriguez-Peralto JL, Castano E, Gil R. Epithelioid sarcoma masquerading as perforating granuloma annulare. *Histopathology* 1997; **31:** 102–3.

22 Shmookler BM, Gunther SF. Superficial epithelioid sarcoma: a clinical and histologic simulant of benign cutaneous disease. *J Am Acad Dermatol* 1986; **14:** 893–8.

23 Peñas PF, Jones-Caballero M, Frage J *et al*. Perforating granuloma annulare. *Int J Dermatol* 1997; **36:** 340–8.

24 Patterson JW. Rheumatoid nodule and subcutaneous granuloma annulare. A comparative histologic study. *Am J Dermatopathol* 1988; **10:** 1–8.

25 Chen K-R, Tanaka M, Miyakawa S. Granulomatous mycosis fungoides with small intestinal involvement and a fatal outcome. *Br J Dermatol* 1998; **138:** 522–5.

26 Fischer M, Wohlrab J, Audring TH *et al*. Granulomatous mycosis fungoides. Report of two cases and review of the literature. *J Eur Acad Dermatol Venereol* 2000; **14:** 196–202.
27 Su LD, Kim YH, LeBoit PE *et al*. Interstitial mycosis fungoides, a variant of mycosis fungoides resembling granuloma annulare and inflammatory morphoea. *J Cutan Pathol* 2002; **29:** 135–41.
28 Eisman S, O'Toole EA, Jones A, Whittaker SJ. Granulomatous mycosis fungoides presenting as an acquired ichthyosis. *Clin Exp Dermatol* 2003; **28:** 174–6.
29 Chu P, Connolly MK, LeBoit PE. The histopathologic spectrum of palisaded neutrophilic and granulomatous dermatitis in patients with collagen vascular disease. *Arch Dermatol* 1994; **130:** 1278–83.
30 Long D, Thiboutot DM, Majeski JT *et al*. Interstitial granulomatous dermatitis with arthritis. *J Am Acad Dermatol* 1996; **34:** 957–61.
31 Ackerman AB, Chongchitnant N, Sanchez J *et al*. Interstitial granulomatous dermatitis with arthritis. In: Ackerman AB, ed. *Histologic Diagnosis of Inflammatory Skin Diseases. An Algorithmic Method Based on Pattern Analysis*. Baltimore: Williams & Wilkins, 1997: 459–62.
32 Aloi P, Tomasini C, Pippione M. Interstitial granulomatous dermatitis with plaques. *Am J Dermatopathol* 1999; **21:** 320–3.
33 Verneuil L, Dompmartin A, Comoz F *et al*. Interstitial granulomatous dermatitis with cutaneous cords and arthritis: a disorder associated with autoantibodies. *J Am Acad Dermatol* 2001; **45:** 286–91.
34 Sangueza OP, Caudell MD, Mengesha YM *et al*. Palisaded neutrophilic granulomatous dermatitis in rheumatoid arthritis. *J Am Acad Dermatol* 2002; **47:** 251–7.
35 Kroesen S, Itin PH, Hasler P. Arthritis and interstitial granulomatous dermatitis (Ackerman syndrome) with pulmonary silicosis. *Semin Arthritis Rheum* 2003; **32:** 334–40.
36 Magro CM, Crowson AN, Schapiro BL. The interstitial granulomatous drug reaction: a distinctive clinical and pathological entity. *J Cutan Pathol* 1998; **25:** 72–8.
37 Perrin C, Lacour J-P, Castanet J, Michiels J-F. Interstitial granulomatous drug reaction with a histological pattern of interstitial granulomatous dermatitis. *Am J Dermatopathol* 2001; **23:** 295–8.

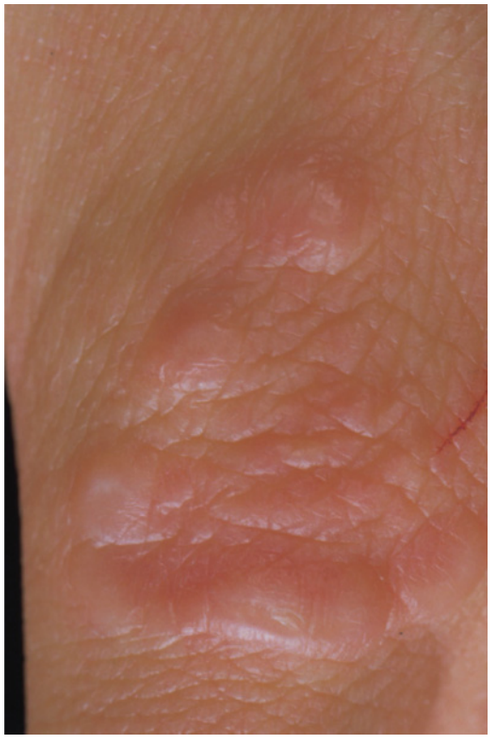


Fig. 60.3 Typical papules of granuloma annulare.

Clinical features [1,2]. Granuloma annulare can occur at almost any age—in one series the youngest patient was 1 year old and the oldest 76 [3]—but the majority of affected individuals are under 30 years of age [3]. It is twice as common in women as in men. There are a few reports of familial cases [3–9]. Clinical variants include localized, generalized, perforating and subcutaneous.

Localized granuloma annulare is the commonest form, and typically presents as a ring of small, smooth, flesh-coloured or erythematous papules (Fig. 60.3). Stretching the skin enables the papules to be seen more readily. The surface of the skin over the papules is intact and there is usually no scaling. Annular lesions tend to enlarge centrifugally. They may be solitary or multiple, and may occur anywhere on the skin, although the dorsa of the hands (Figs 60.4 & 60.5) and feet (Fig. 60.6), and the fingers (Fig. 60.7) are the commonest sites. Lesions are usually symptomless, although some may be tender to touch, and acute-onset, painful acral lesions have been described [10]. Some, often acral, lesions enlarge as nodules rather than having an annular morphology.

The other patterns of granuloma annulare may occur alone or in association with the annular lesions. In the generalized or disseminated pattern, there are numerous skin-coloured or erythematous papules, which may have an annular configuration or consist of myriad, symmetrically distributed, often coalescing lesions, on the trunk and limbs [11–14] (Fig. 60.8). The area enclosed by annular papules is often violaceous in colour. Pruritus may be a prominent complaint in generalized lesions [13]. Although generalized granuloma annulare may occur in children, the mean age



Fig. 60.4 Granuloma annulare on the dorsum of the hand—a typical site.



Fig. 60.5 Granuloma annulare on the dorsum of the hand. Altered pigmentation and atrophy in the centre of the lesions.



Fig. 60.7 Granuloma annulare on the side of a finger.



Fig. 60.6 Granuloma annulare on the dorsum of a child's foot. Often mistaken for tinea—but there is no scale and tinea in this site would be unlikely in a child.



Fig. 60.8 These annular lesions were part of an extensive eruption on the limbs in a patient with generalized granuloma annulare.

at onset is later than in the localized variety, and in the series of Dabski and Winkelmann [13] it was 51.7 years. The exact incidence of the generalized pattern is unknown, but 8.9% of all patients with granuloma annulare seen at the Mayo Clinic had a generalized or disseminated pattern [13]. As in the localized form, twice as many females are affected as males. Although in immunocompetent individuals localized disease is more common than generalized granuloma annulare, in HIV-infected patients the generalized pattern predominates [14–18]. The sparing of vaccination sites in a case of generalized granuloma annulare is an interesting phenomenon [19].

Perforating granuloma annulare was named by Owens and Freeman in 1971 [20]. In this uncommon variety, some of the papules develop yellowish centres and discharge a little clear, viscous fluid. This dries to form a crust, which eventually separates, and may leave a hypo- or hyperpigmented scar. Lesions may be localized or generalized [21–24]. A high incidence of perforating granuloma annulare has been reported in the Hawaiian Islands [22,23]. Perforating lesions have been present in some of the reported HIV-positive individuals with granuloma annulare. Generalized perforating granuloma annulare has been described in an infant [25].

Subcutaneous granuloma annulare is also uncommon. It occurs predominantly in children, and has been given a variety of names, including benign rheumatoid nodules [26], pseudorheumatoid nodules [27,28], deep granuloma annulare [29,30], subcutaneous palisading granuloma [31], isolated subcutaneous granuloma and subcutaneous necrobiotic granuloma [32]. Lesions are nodular and occur predominantly on the scalp and legs, particularly in the pretibial region [4,32–34], but unusual locations include periorbital subperiosteal [35], palm [36,37] and penis [38]. A congenital case has been recorded [39]. Magnetic resonance imaging features are diagnostically helpful [40–42].

Other reported variants of granuloma annulare include a papular umbilicated form on the dorsa of the hands in children [43], a case of 'follicular pustulous' granuloma annulare, in which palisading necrobiotic granulomas occurred in a perifollicular distribution [44], pustular generalized perforating granuloma annulare, in which a dense infiltrate of neutrophils was present in areas of necrobiosis [45], linear granuloma annulare [46,47], and 'patch' granuloma annulare, in which erythematous patches occur on the trunk and limbs [48]. It has been suggested that cases with 'linear' lesions may be examples of interstitial granulomatous dermatitis, and those with 'patch' lesions may represent examples of the interstitial granulomatous form of drug reaction [49].

Uncommon sites for lesions of granuloma annulare are the ears (Fig. 60.9), where the perforating variety is particularly unusual [50], penis [51–56], palms [57] and periocular regions [58–63]. Mucous membranes are spared, although there is a report of involvement of the oral mucosa in a patient with HIV infection [64].

A destructive form has been described [65,66].

The postal questionnaire survey carried out by Wells and Smith [3] revealed that in about 50% of patients the lesions resolved within 2 years. However, about 40% of those whose lesions cleared had a recurrence, in the majority of cases at the same sites as the original lesions. In this study, there did not appear to be any difference in prognosis between individuals with single lesions and those with multiple lesions, and although there is an impression that spontaneous resolution is less likely to occur with generalized granuloma annulare there does not appear to be any documented confirmation of this.



Fig. 60.9 Granuloma annulare on the ear.

There are reports of anetoderma secondary to generalized lesions [67], and mid-dermal elastolysis occurring with granuloma annulare [68] and subsequent to lesions resembling granuloma annulare [69]. In another case, loss of elastic fibres was presumed to be responsible for development of open comedones on the rim of granuloma annulare lesions occurring on light-exposed areas [70].

Levin *et al*. [71] have discussed the matter of resolution of lesions following biopsy, and have noted the paucity of information relating to this phenomenon in the literature. There appears to be anecdotal evidence of its occurrence, but little documentation. However, it is of interest, in this context, that scarification is one form of physical treatment that has been advocated in the past [72–74].

References

1 Muhlbauer JE. Granuloma annulare. *J Am Acad Dermatol* 1980; **3:** 217–30.
2 Smith MD, Downie JB, DiCostanzo D. Granuloma annulare. *Int J Dermatol* 1997; **36:** 326–33.
3 Wells RS, Smith MA. The natural history of granuloma annulare. *Br J Dermatol* 1963; **75:** 199–205.
4 Rubin M, Lynch FW. Subcutaneous granuloma annulare. Comment on familial granuloma annulare. *Arch Dermatol* 1966; **93:** 416–20.
5 Arner S, Aspergren N. Familial granuloma annulare. *Acta Derm Venereol (Stockh)* 1968; **48**: 253–4.

6 Goolamali SK, Stevenson CJ. Granuloma annulare in identical twins. *Br J Dermatol* 1972; **86**: 636–7.
7 Friedman SJ, Winkelmann RK. Familial granuloma annulare. Report of two cases and review of the literature. *J Am Acad Dermatol* 1987; **16:** 600–5.
8 Abrusci V, Weiss E, Planus G. Familial generalized perforating granuloma annulare. *Int J Dermatol* 1988; **27:** 126–7.
9 Suite M, Jankey N. Familial granuloma annulare. *Int J Dermatol* 1992; **31:** 818.
10 Brey NV, Malone J, Callen JP. Acute-onset, painful acral granuloma annulare. *Arch Dermatol* 2006; **142:** 49–54.
11 Stankler L, Leslie G. Generalized granuloma annulare: a report of a case and review of the literature. *Arch Dermatol* 1967; **95:** 509–13.
12 Dicken CH, Carrington SG, Winkelmann RK. Generalized granuloma annulare. *Arch Dermatol* 1969; **99:** 556–63.
13 Dabski K, Winkelmann RK. Generalized granuloma annulare: clinical and laboratory findings in 100 patients. *J Am Acad Dermatol* 1989; **20:** 39–47.
14 Bakos L, Hampe S, daRocha JL *et al*. Generalized granuloma annulare in a patient with acquired immunodeficiency syndrome. *J Am Acad Dermatol* 1987; **17:** 844–5.
15 Toro JR, Chu P, Ben Yen T-S, LeBoit PE. Granuloma annulare and human immunodeficiency virus infection. *Arch Dermatol* 1999; **135:** 1341–6.
16 Cohen PR. Granuloma annulare. A mucocutaneous condition in human immunodeficiency virus-infected patients. *Arch Dermatol* 1999; **135:** 1404–7.
17 O'Moore EJ, Nandawni R, Uthayakumar S *et al*. HIV-associated granuloma annulare (HAGA): a report of six cases. *Br J Dermatol* 2000; **142:** 1054–6.
18 Morris SD, Cerio R, Paige DG. An unusual presentation of diffuse granuloma annulare in an HIV-positive patient—immunohistochemical evidence of predominant CD8 lymphocytes. *Clin Exp Dermatol* 2002; **27:** 205–8.
19 Huilgol SC, Liddell K, Black MM. Generalized granuloma annulare sparing vaccination sites. *Clin Exp Dermatol* 1995; **20:** 51–3.
20 Owens DW, Freeman RG. Perforating granuloma annulare. *Arch Dermatol* 1971; **103:** 64–7.
21 Delaney TJ, Gold SC, Leppard B. Disseminated perforating granuloma annulare. *Br J Dermatol* 1973; **89:** 523–6.
22 Izumi AK. Generalized perforating granuloma annulare. *Arch Dermatol* 1973; **108:** 708–9.
23 Samlaska CP, Sandberg GD, Maggio KL, Sakas EL. Generalized perforating granuloma annulare. *J Am Acad Dermatol* 1992; **27:** 319–22.
24 Peñas PF, Jones-Caballero M, Fraga J *et al*. Perforating granuloma annulare. *Int J Dermatol* 1997; **36:** 340–8.
25 Choi JC, Bae JY, Cho S *et al*. Generalized perforating granuloma annulare in an infant. *Pediatr Dermatol* 2003; **20:** 131–3.
26 Simons FER, Schaller JG. Benign rheumatoid nodules. *Pediatrics* 1975; **56:** 29–33.
27 Burrington JD. 'Pseudorheumatoid' nodules in children: report of 10 cases. *Pediatrics* 1970; **45:** 473–8.
28 Barzilai A, Huszar M, Shpiro D *et al*. Pseudorheumatoid nodules in adults: a juxta-articular form of nodular granuloma annulare. *Am J Dermatopathol* 2005; **27:** 1–5.
29 McDermott MB, Lind AC, Marley EF, Dehner LP. Deep granuloma annulare (pseudorheumatoid nodule) in children: clinicopathologic study of 35 cases. *Pediatr Dev Pathol* 1998; **1:** 300–8.
30 Salomon RJ, Gardepe SF, Woodley DT. Deep granuloma annulare in adults. *Int J Dermatol* 1986; **25:** 109–12.
31 Minifee PK, Buchino JJ. Subcutaneous palisading granulomas (benign rheumatoid nodules) in children. *J Pediatr Surg* 1986; **21:** 1078–80.
32 Hutchinson ACS, Hurray DH, Smith MT, Shannon AB. Subcutaneous granuloma annulare of the scalp: a case report and case review. *Cutis* 2005; **76:** 377–82.
33 Felner EI, Steinberg JB, Weinberg AG. Subcutaneous granuloma annulare: a review of 47 cases. *Pediatrics* 1997; **100:** 965–7.
34 Grogg KL, Nascimento AG. Subcutaneous granuloma annulare in childhood: clinicopathologic features in 34 cases. *Pediatrics* 2001; **107:** E42 p.580 (Abstr.).
35 Dutton JJ, Escaravage GK Jr. Periocular subperiosteal deep granuloma annulare in a child. *Ophthalmol Plast Reconstr Surg* 2006; **22:** 141–3.
36 Takeyama J, Sanada T, Watanabe M *et al*. Subcutaneous granuloma annulare in a child's palm: a case report. *J Hand Surg Am* 2006; **31:** 103–6.
37 Mur EC, Fernández CM, Hermosa JMH. Bilateral and subcutaneous palmar nodules in a 2-year-old child suggesting deep granuloma annulare. *J Eur Acad Dermatol Venereol* 2005; **19:** 100–3.
38 Sidwell RU, Green JSA, Agnew K *et al*. Subcutaneous granuloma annulare of the penis in 2 adolescents. *J Pediatr Surg* 2005; **40:** 1329–31.
39 De Aloe G, Risulo M, Sbano P *et al*. Congenital subcutaneous granuloma annulare. *Pediatr Dermatol* 2005; **22:** 234–6.
40 Kransdorf MJ, Murphey MD, Temple HT. Subcutaneous granuloma annulare: radiologic appearance. *Skeletal Radiol* 1998; **27:** 266–70.
41 Chung S, Frush DP, Prose NS *et al*. Subcutaneous granuloma annulare: MR imaging features in six children and literature review. *Radiology* 1999; **210:** 845–9.
42 Shehan JM, El-Azhary RA. Magnetic resonance imaging features of subcutaneous granuloma annulare. *Pediatr Dermatol* 2005; **22:** 377–8.
43 Lucky AW, Prose NS, Bove K *et al*. Papular umbilicated granuloma annulare. A report of four pediatric cases. *Arch Dermatol* 1992; **128:** 1375–8.
44 Vargas-Díez E, Feal-Cortizas C, Fraga J *et al*. Follicular pustulous granuloma annulare. *Br J Dermatol* 1998; **138:** 1075–8.
45 Gamo Villegas R, Sopena Barona J, Guerra Tapia A *et al*. Pustular generalized perforating granuloma annulare. *Br J Dermatol* 2003; **149:** 866–8.
46 McDow RA, Fields JP. Linear granuloma annulare of the finger. *Cutis* 1987; **39:** 43–4.
47 Harpster EF, Mauro T, Barr RJ. Linear granuloma annulare. *J Am Acad Dermatol* 1989; **21:** 1138–41.
48 Mutasim DF, Bridges AG. Patch granuloma annulare: clinicopathologic study of 6 patients. *J Am Acad Dermatol* 2000; **42:** 417–21.
49 Weedon D. *Skin Pathology*, 2nd edn. London: Churchill Livingstone, 2002: 200.
50 Farrar CW, Bell HK, Dobson CM, Sharpe GR. Perforating granuloma annulare presenting on the ears. *Br J Dermatol* 2002; **147:** 1026–8.
51 Trap R, Wiebe B. Granuloma annulare localized to the shaft of the penis. *Scand J Urol Nephrol* 1993; **27:** 549–51.
52 Narouz N, Allan PS, Wade AH. Penile granuloma annulare. *Sex Transm Infect* 1999; **75:** 186–7.
53 Kossard S, Collins AG, Wegman A, Hughes MR. Necrobiotic granulomas localized to the penis: a possible variant of subcutaneous granuloma annulare. *J Cutan Pathol* 1990; **17:** 101–4.
54 Hillman RJ, Waldron S, Walker MM, Harris JR. Granuloma annulare of the penis. *Genitourin Med* 1992; **68:** 47–9.
55 Laird SM. Granuloma annulare of the penis. *Genitourin Med* 1992; **68:** 277.
56 Lucas F, Viraebn R. Granulome palissadique du pénis: une variante de granulome annulaire profond. *Ann Dermatol Vénéréol* 2002; **129:** 1046–8.
57 Hsu S, Lehner AC, Chang JR. Granuloma annulare localized to the palms. *J Am Acad Dermatol* 1999; **41:** 287–8.
58 Mc Farland JP, Kauh YC, Luscombe HA. Periorbital granuloma annulare. *Arch Dermatol* 1982; **118:** 190–1.
59 Bucji ER, Daicker B, Huber P, Bucker SA. Granuloma annulare des Augenlides. *Klin Montabl Augenheikd* 1995; **207:** 91–4.
60 Moegelin A, Thalmann U, Haas N. Subcutaneous granuloma annulare of the eyelid. A case report. *Int J Oral Maxillofac Surg* 1995; **24:** 236–8.
61 Sandwich JT, David LS. Granuloma annulare of the eyelid: a case report and review of the literature. *Pediatr Dermatol* 1999; **16:** 373–6.
62 Cronquist SD, Stashower ME, Benson PM. Deep dermal granuloma annulare presenting as an eyelid tumor in a child, with review of pediatric eyelid lesions. *Pediatr Dermatol* 1999; **16:** 377–80.
63 Ramaesh K, Bhagat S, Wharton SB, Singh J. Orbital nodular granuloma annulare in a juvenile diabetic. *Eye* 2002; **16:** 670–3.
64 Toro JR, Chu P, Ben Yen T-S, LeBoit PE. Granuloma annulare and human immunodeficiency virus infection. *Arch Dermatol* 1999; **135:** 1341–6.
65 Dabski K, Winkelmann RK. Destructive granuloma annulare of the skin and underlying tissues—report of two cases. *Clin Exp Dermatol* 1991; **16:** 218–21.
66 Bancroft LW, Perniciaro C, Berquist TH. Granuloma annulare: radiographic demonstration of progressive mutilating arthropathy with vanishing bones. *Skeletal Radiol* 1998; **27:** 211–4.
67 Ozkan S, Fetil E, Izler F *et al*. Anetoderma secondary to generalized granuloma annulare. *J Am Acad Dermatol* 2000; **42:** 335–8.
68 Adams BB, Mutasim DF. Colocalization of granuloma annulare and mid-dermal elastolysis. *J Am Acad Dermatol* 2003; **48:** S25–7.
69 Yen A, Tschen J, Raimer SS. Mid-dermal elastolysis in an adolescent subsequent to lesions resembling granuloma annulare. *J Am Acad Dermatol* 1997; **37:** 870–2.
70 Sudy E, Urbina F, Espinosa X. Open comedones overlying granuloma annulare in a photoexposed area. *Photodermatol Photoimmunol Photomed* 2006; **22**: 273–4.

71 Levin NA, Patterson JW, Yao LL, Wilson BB. Resolution of patch-type granuloma annulare lesions after biopsy. *J Am Acad Dermatol* 2002; **46:** 426–9.
72 Shakhnes IE. Lechenic kol'tsevidnoi granulemy methodom skarifikatsii. *Vestn Dermatol Venerol* 1977; **4:** 78–9.
73 Robinson HM Sr. Treatment for granuloma annulare. *Arch Dermatol* 1953; **67:** 320.
74 Wilkin JK, DuComb D, Castrow FF. Scarification treatment of granuloma annulare. *Arch Dermatol* 1982; **118:** 68–9.

Differential diagnosis. When the typical annular arrangement of papules is present, the diagnosis is usually straightforward. However, granuloma annulare may be mistaken for tinea, although the latter is more inflammatory, and the annular margin is scaly. Other annular lesions and granulomatous conditions may cause diagnostic confusion, including annular lichen planus, erythema annulare centrifugum, erythema multiforme, erythema migrans of Lyme disease, tuberculides [1] and tertiary syphilis [2]. The morphology and distribution of lesions may simulate mycosis fungoides [3].

With regard to subcutaneous granuloma annulare, the differential diagnosis of subcutaneous nodules of the scalp and legs in children is extensive, and includes trauma, infection and tumours, and a diagnostic biopsy will usually be necessary. In adults, nodular lesions have to be distinguished from sarcoidosis and rheumatoid nodules.

The differential diagnosis of perforating granuloma annulare includes molluscum contagiosum [4], transepithelial elimination disorders such as perforating collagenosis and acquired perforating dermatosis, sarcoidosis and papulonecrotic tuberculide [5,6]. As mentioned above, epithelioid sarcoma may masquerade as perforating granuloma annulare.

Mycobacterium marinum infection has histologically simulated interstitial granuloma annulare [7], and other histological differential diagnoses include granulomatous mycosis fungoides [8], interstitial granulomatous dermatitis and interstitial granulomatous drug reaction, as mentioned above.

References

1 Tsai J, Chen GS, Lan LH, Lan CCE. Cutaneous tuberculid clinically resembling generalized granuloma annulare. *Clin Exp Dermatol* 2007; **32**: 450–1.
2 Jones Wu S, Nguyen EQ, Nielsen TA, Pellegrini EA. Nodular tertiary syphilis mimicking granuloma annulare. *J Am Acad Dermatol* 2000; **42:** 378–80.
3 Wu H, Barusevicius A, Lessin SR. Granuloma annulare with a mycosis fungoides-like distribution and palisaded granuloma of CD68-positive histiocytes. *J Am Acad Dermatol* 2004; **51:** 39–44.
4 Kapembwa MS, Goolamali SK, Price A, Boyle S. Granuloma annulare masquerading as molluscum contagiosum-like eruption in an HIV-positive African woman. *J Am Acad Dermatol* 2003; **49** (Suppl. 2)**:** S184–6.
5 Samlaska CP, Sandberg GD, Maggio KL, Sakas EL. Generalized perforating granuloma annulare. *J Am Acad Dermatol* 1992; **27:** 319–22.
6 Peñas PF, Jones-Caballero M, Fraga J *et al*. Perforating granuloma annulare. *Int J Dermatol* 1997; **36:** 340–8.
7 Barr KL, Lowe L, Su LD. *Mycobacterium marinum* infection simulating interstitial granuloma annulare: a report of two cases. *Am J Dermatopathol* 2003; **25:** 148–51.
8 Jouary T, Beylot-Barry M, Vergier B *et al*. Mycosis fungoides mimicking granuloma annulare. *Br J Dermatol* 2002; **146:** 1102–4.

Associations. There has been much discussion of whether there is an association between granuloma annulare and diabetes mellitus [1–13]. A number of studies have not demonstrated any relationship, whereas others suggest an association [1–12]. In the latter, some have favoured an association with generalized granuloma annulare [4–6] and others an association with localized disease [3,7], and possibly localized nodular granuloma annulare [8]. It is of interest to note that in three reports [3,7,8] the majority of diabetics were insulin-dependent (type 1). One study, employing a case–control design, did not show any association between granuloma annulare and type 2 diabetes [9]. The patient population studied did not include anyone with type 1 diabetes. In order to clarify the situation, further, large-scale studies are required, in which the pattern of granuloma annulare and type of diabetes are recorded.

Thomas *et al*. [14] reported a man with granuloma annulare of the skin, and intra-abdominal lesions, insulin-dependent diabetes and polyendocrine disease, in whom there appeared to be a relationship between diabetic control and the granuloma annulare. Granuloma annulare has been described in a child with Mauriac's syndrome (juvenile diabetes, stunted growth and hepatomegaly) [15].

There are a number of reports of the coexistence of both localized and generalized granuloma annulare and autoimmune thyroiditis in women [16–22], and results of a case–control study indicated an association between localized granuloma annulare and autoimmune thyroiditis [22]. In one case with generalized granuloma annulare the skin lesions improved in concert with disappearance of antithyroid antibodies and restoration of the euthyroid state [17]. Generalized granuloma annulare has also been reported in a patient with a toxic adenoma of the thyroid (Plummer's disease) [23].

Recent reports suggest the possibility of an association between uveitis and granuloma annulare [24,25].

Li *et al*. [26] have summarized and analyzed reports addressing a possible relationship between granuloma annulare and malignant neoplasms. In the cases reviewed, skin lesions that had histological features of granuloma annulare, but were often atypical clinically (for example, painful lesions on the palms and soles), occurred in patients with a neoplasm (in 56% of cases this was a lymphoma). They concluded that there was no definite relationship between granuloma annulare and malignant neoplasms.

There are isolated reports of the occurrence of temporal arteritis in a patient with generalized granuloma annulare [27], and of the coexistence of granuloma annulare and morphoea [28].

There are a number of reports of the occurrence of granuloma annulare and necrobiosis lipoidica in the same patient [29–32], and of the association of granuloma annulare and sarcoidosis [33–36].

References

1 Muhlbauer JE. Granuloma annulare. *J Am Acad Dermatol* 1980; **3:** 217–30.
2 Smith MD, Downie JB, DiCostanzo D. Granuloma annulare. *Int J Dermatol* 1997; **36:** 326–33.
3 Veraldi S, Bencini PL, Drudi E, Caputo R. Laboratory abnormalities in granuloma annulare: a case–control study. *Br J Dermatol* 1997; **136:** 652–3.
4 Romaine R, Rudner EJ, Altman J. Papular granuloma annulare and diabetes mellitus. Report of cases. *Arch Dermatol* 1968; **98:** 152–4.
5 Haim S, Friedman-Birnbaum R, Shafrir A. Generalized granuloma annulare: relationship to diabetes mellitus as revealed in 8 cases. *Br J Dermatol* 1970; **83:** 302–5.

6 Haim S, Friedman-Birnbaum R, Haim N *et al*. Carbohydrate intolerance in patients with granuloma annulare. Study of fifty-two cases. *Br J Dermatol* 1973; **88:** 447–51.
7 Muhlemann MF, Williams DRR. Localized granuloma annulare is associated with insulin-dependent diabetes mellitus. *Br J Dermatol* 1984; **111:** 325–9.
8 Choudry K, Charles-Holmes R. Are patients with localized nodular granuloma annulare more likely to have diabetes mellitus? *Clin Exp Dermatol* 2000; **25:** 451–3.
9 Nebesio CL, Lewis C, Chuang T-Y. Lack of an association between granuloma annulare and type 2 diabetes mellitus. *Br J Dermatol* 2002; **146:** 122–4.
10 Gannon TF, Lynch PJ. Absence of carbohydrate intolerance in granuloma annulare. *J Am Acad Dermatol* 1994; **30:** 662–3.
11 Studer EM, Calza A-M, Saurat J-H. Precipitating factors and associated diseases in 84 patients with granuloma annulare: a retrospective study. *Dermatology* 1996; **193:** 364–8.
12 Kakourou T, Psychou F, Voutetakis A *et al*. Low serum insulin values in children with multiple lesions of granuloma annulare: a prospective study. *J Eur Acad Dermatol Venereol* 2005; **19:** 30–4.
13 Cox NH. Diabetes and the skin: an update for dermatologists. *Expert Rev Dermatol* 2007; **2**: 305–16.
14 Thomas DJB, Rademaker M, Munro DD *et al*. Visceral and skin granuloma annulare, diabetes, and polyendocrine disease. *BMJ* 1986; **293:** 977–8.
15 Goldin D, Rook A, Gairdner D. Granuloma annulare in Mauriac's syndrome. *Br J Dermatol* 1975; **93** (Suppl. 11): 31.
16 Gross PR, Shelley WB. The association of generalized granuloma annulare with antithyroid antibodies. *Acta Derm Venereol (Stockh)* 1971; **51:** 59–62.
17 Willemsen MJ, de Coninck AL, Jonckheer MH, Roseeuw DI. Autoimmune thyroiditis and generalized granuloma annulare: remission of the skin lesions after thyroxine therapy. *Dermatologica* 1987; **175:** 239–43.
18 Dabski K, Winkelmann RK. Generalized granuloma annulare: clinical and laboratory findings in 100 patients. *J Am Acad Dermatol* 1989; **20:** 39–47.
19 Magro CM, Crowson AN, Regauer S. Granuloma annulare and necrobiosis lipoidica tissue reactions as a manifestation of systemic disease. *Hum Pathol* 1996; **27:** 50–6.
20 Vázquez-López F, González-López MA, Raya-Aguado C, Pérez-Oliva N. Localized granuloma annulare and autoimmune thyroiditis: a new case report. *J Am Acad Dermatol* 2000; **43:** 943–5.
21 Kappeler D, Troendle A, Mueller B. Localized granuloma annulare associated with autoimmune thyroid disease in a patient with a positive family history for autoimmune polyglandular syndrome type II. *Eur J Endocrinol* 2001; **145:** 101–2.
22 Vásquez-López F, Pereiro M Jr, Manjón Haces JA *et al*. Localized granuloma annulare and autoimmune thyroiditis in adult women: a case–control study. *J Am Acad Dermatol* 2003; **48:** 517–20.
23 Tursen U, Pata C, Kaya TI *et al*. Generalized granuloma annulare associated with Plummer's disease. *J Eur Acad Dermatol Venereol* 2002; **16:** 419–20.
24 Oz O, Tursen U, Yildirim O *et al*. Uveitis associated with granuloma annulare. *Eur J Ophthalmol* 2003; **13:** 93–5.
25 van Kooij B, Canninga van Dijk M, de Boer J *et al*. Is granuloma annulare related to intermediate uveitis with retinal vasculitis? *Br J Ophthalmol* 2003; **87:** 763–6.
26 Li A, Hogan DJ, Sanusi DI, Smoller BR. Granuloma annulare and malignant neoplasms. *Am J Dermatopathol* 2003; **25:** 113–6.
27 Fukai K, Ishii M, Kobayashi H *et al*. Generalized granuloma annulare in a patient with temporal arteritis—are these conditions associated? *Clin Exp Dermatol* 1990; **15:** 70–2.
28 Ben-Amitai D, Hodak E, Lapidoth M, David M. Coexisting morphoea and granuloma annulare—are the conditions related? *Clin Exp Dermatol* 1999; **24:** 86–9.
29 Feldman FF. Granuloma annulare and necrobiosis lipoidica in the same patient. *Arch Dermatol* 1968: **98:** 677–8.
30 Schwartz ME. Necrobiosis lipoidica and granuloma annulare. Simultaneous occurrence in a patient. *Arch Dermatol* 1982; **118:** 192–3.
31 Burton JL. Granuloma annulare, rheumatoid nodules and necrobiosis lipoidica. *Br J Dermatol* 1977; **77** (Suppl. 15): 52–4.
32 Berkson MH, Bondi EE, Margolis DJ. Ulcerated necrobiosis lipoidica diabeticorum in a patient with a history of generalized granuloma annulare. *Cutis* 1994; **53:** 85–6.
33 Umbert P, Winkelmann RK. Granuloma annulare and sarcoidosis. *Br J Dermatol* 1977; **97:** 481–6.
34 Harrison P, Shuster S. Granuloma annulare and sarcoidosis. *Br J Dermatol* 1979; **100:** 231.
35 Kato H, Yoshihiko F, Kitajima Y *et al*. A case of granuloma annulare and sarcoidosis. *J Dermatol* 1985; **12:** 63–9.
36 Ehrich EW, McGuire JL, Kim YH. Association of granuloma annulare with sarcoidosis. *Arch Dermatol* 1992; **128:** 855–6.

Treatment. The tendency of granuloma annulare to remit spontaneously complicates accurate assessment of the efficacy of any treatment, but in some patients explanation that this is the natural course of the disease is all that is required, and certainly in children it is preferable to await spontaneous resolution rather than subjecting them to the discomfort of some of the treatment methods. Potent topical steroids, with or without occlusion, are used by many dermatologists, but often with little benefit. Intralesional steroids, given by either needle injection or jet injector [1], appear to be more effective in the management of localized lesions. Cryosurgery also appears to be an effective treatment for localized disease. In a study of 31 patients, in which nitrous oxide and liquid nitrogen were employed, resolution was achieved in all, following a single freeze–thaw cycle in the majority [2]. The cosmetic result obtained by cryosurgery with nitrous oxide was independent of the size of the lesion, whereas in individuals treated with liquid nitrogen a better cosmetic result was obtained with smaller lesions. Because of this, the authors of the report proposed that use of nitrous oxide as refrigerant was preferable to liquid nitrogen.

Localized granuloma annulare has also been treated with local injections of low-dose recombinant interferon gamma [3]. Complete resolution of lesions occurred in the three treated patients, with no recurrence during 12 months of follow-up. More recently, photodynamic therapy was used successfully for localized disease [4], as was the pulsed dye laser [5].

Although some reports have indicated a beneficial effect of oral potassium iodide in the treatment of disseminated granuloma annulare [6,7], a double-blind, placebo-controlled, crossover study showed that it had no advantage over placebo [8]. PUVA therapy appears to be an effective treatment for generalized granuloma annulare, and good results have been reported using both oral and topical psoralens [9–17]. In many cases, however, maintenance therapy is required to sustain the benefit. Narrowband UVB [18] and UVA-1 phototherapy [19,20] have also been reported as effective in the treatment of generalized granuloma annulare. Etretinate [21–23] and isotretinoin [24–29] have both been of benefit in disseminated disease. Isotretinoin has also improved localized [30] and perforating granuloma annulare [31]. There are a few reports of the use of ciclosporin in generalized granuloma annulare [32–35], with good results in most cases. Other treatments which have been used with apparent benefit in isolated cases or small numbers of patients with disseminated granuloma annulare include low-dose chlorambucil [36–40], dapsone [41], antimalarials [42–44], niacinamide [45], pentoxifylline [46], tranilast [47], fumaric acid esters [48–50], clofazimine [51], topical vitamin E [52], a combination of vitamin E and a 5-lipoxygenase inhibitor [53], and defibrotide [54].

Recent reports suggest that topical imiquimod [55,56], tacrolimus [57,58] and pimecrolimus [59] may be helpful, and rapid reso-

lution of recalcitrant disseminated lesions on treatment with infliximab [60] and efalizumab [61] has been reported. Shupack and Siu [62] noted clearing of disseminated lesions in a patient treated with etanercept, but in a series of four patients reported by Kreuter *et al*. [63] there was either no change or deterioration during therapy with this agent.

Most of the treatments mentioned above have been employed in patients with perforating lesions, with varying degrees of success [64].

Lesions of subcutaneous granuloma annulare should be left to resolve spontaneously once the diagnosis has been confirmed [65].

References

1 Sparrow G, Abell E. Granuloma annulare and necrobiosis lipoidica treated by jet injector. *Br J Dermatol* 1975; **93:** 85–9.

2 Blume-Peytavi U, Zouboulis Ch C, Jacobi H *et al*. Successful outcome of cryosurgery in patients with granuloma annulare. *Br J Dermatol* 1994; **130:** 494–7.

3 Weiss JM, Muchenberger S, Schöpf E, Simon JC. Treatment of granuloma annulare by local injections with low-dose recombinant human interferon gamma. *J Am Acad Dermatol* 1998; **39:** 117–9.

4 Kim YJ, Kang HY, Lee ES, Kim YC. Successful treatment of granuloma annulare with topical 5-aminolaevulinic acid photodynamic therapy. *J Dermatol* 2006; **33:** 642–3.

5 Sniezek PJ, De Bloom JR 2nd, Arpey CJ. Treatment of granuloma annulare with the 585 nm pulsed dye laser. *Dermatol Surg* 2005; **31:** 1370–3.

6 Giessel M, Graves K, Kalivas J. Treatment of disseminated granuloma annulare with potassium iodide. *Arch Dermatol* 1979; **115:** 639–40.

7 Caserio RJ, Eaglstein WH, Allen CM. Treatment of granuloma annulare with potassium iodide. *J Am Acad Dermatol* 1984; **10:** 294–5.

8 Smith JB, Hansen CD, Zone JJ. Potassium iodide in the treatment of disseminated granuloma annulare. *J Am Acad Dermatol* 1994; **30:** 791–2.

9 Hindson TC, Spiro JG, Cochrane H. PUVA therapy of diffuse granuloma annulare. *Clin Exp Dermatol* 1988; **13:** 26–7.

10 Kerker BJ, Huang CP, Morison WL. Photochemotherapy of generalized granuloma annulare. *Arch Dermatol* 1990; **126:** 359–61.

11 Langrock A, Weyers W, Schill WB. Balneophotochemotherapie bei disseminiertem Granuloma anulare. *Hautarzt* 1998; **49:** 303–6.

12 Setterfield J, Huilgol SC, Black MM. Generalized granuloma annulare successfully treated with PUVA. *Clin Exp Dermatol* 1999; **24:** 458–60.

13 Szegedi A, Bégány A, Hunyadi J. Successful treatment of generalized granuloma annulare with polythene sheet bath PUVA. *Acta Derm Venereol (Stockh)* 1999; **79:** 84–5.

14 Salomon N, Walchner M, Messer G *et al*. Bade-PUVA-Therapie bei Granuloma anulare. *Hautarzt* 1999; **50:** 275–9.

15 Schmutz JL. PUVA therapy of granuloma annulare. *Clin Exp Dermatol* 2000; **25:** 451–3.

16 Grundmann-Kollmann M, Ochsendorf FR, Zollner TM *et al*. Cream psoralen plus ultraviolet A therapy for granuloma annulare. *Br J Dermatol* 2001; **144:** 996–9.

17 Batchelor R, Clark S. Clearance of generalized papular umbilicated granuloma annulare in a child with bath PUVA therapy. *Pediatr Dermatol* 2006; **23:** 72–4.

18 Inui S, Nishida Y, Itami S, Katayama I. Disseminated granuloma annulare responsive to narrowband ultraviolet B therapy. *J Am Acad Dermatol* 2005; **53:** 533–4.

19 Muchenberger S, Schöpf E, Simon JC. Phototherapy with UV-A-1 for generalized granuloma annulare. *Arch Dermatol* 1997; **133:** 1605.

20 Schnopp C, Tsaneva S, Mempel M *et al*. UVA1 phototherapy for disseminated granuloma annulare. *Photodermatol Photoimmunol Photomed* 2005; **21:** 68–71.

21 Botella-Estrada R, Guillen C, Sanmartin O, Aliaga A. Disseminated granuloma annulare: resolution with etretinate therapy. *Arch Dermatol* 1992; **26:** 777–8.

22 Harth W, Richard G. Retinoide in der Therapie des Granuloma anulare disseminatum. *Hautarzt* 1993; **44:** 693–8.

23 Asano Y, Saito A, Idezuki T, Igarashi A. Generalized granuloma annulare treated with short-term administration of etretinate. *J Am Acad Dermatol* 2006; **54:** S245–7.

24 Schleicher SM, Milstein HJ. Resolution of disseminated granuloma annulare following isotretinoin therapy. *Cutis* 1985; **36:** 147–8.

25 Schleicher SM, Milstein HJ, Lim SJM, Stanton CD. Resolution of disseminated granuloma annulare with isotretinoin. *Int J Dermatol* 1992; **31:** 371–2.

26 Tang WY, Chong LY, Lo KK. Resolution of generalized granuloma annulare with isotretinoin therapy. *Int J Dermatol* 1996; **35:** 455–6.

27 Adams DC, Hogan DJ. Improvement of chronic generalized granuloma annulare with isotretinoin. *Arch Dermatol* 2002; **138:** 1518–9.

28 Looney M, Smith KM. Isotretinoin in the treatment of granuloma annulare. *Ann Pharmacother* 2004; **38:** 494–7.

29 Pasmatzi E, Georgiou S, Monastirli A, Tsambaos D. Temporary remission of disseminated granuloma annulare under oral isotretinoin therapy. *Int J Dermatol* 2005; **44:** 169–71.

30 Young HS, Coulson IH. Granuloma annulare following waxing induced folliculitis. *Clin Exp Dermatol* 2000; **25:** 274–6.

31 Ratnavel RC, Norris PG. Perforating granuloma annulare: response to treatment with isotretinoin. *J Am Acad Dermatol* 1995; **32:** 126–7.

32 Filotico R, Vena GA, Coviello C, Angelini G. Cyclosporine in the treatment of generalized granuloma annulare. *J Am Acad Dermatol* 1994; **30:** 487–8.

33 Ho VC. Cyclosporine in the treatment of generalized granuloma annulare. *J Am Acad Dermatol* 1995; **32:** 298.

34 Fiallo P. Cyclosporin for the treatment of granuloma annulare. *Br J Dermatol* 1998; **138:** 369–70.

35 Spadino S, Altomare A, Cainelli C *et al*. Disseminated granuloma annulare: efficacy of cyclosporine therapy. *Int J Immunopathol Pharmacol* 2006; **19:** 433–8.

36 Kossard S, Winkelmann RK. Response of generalized granuloma annulare to alkylating agents. *Arch Dermatol* 1978; **114:** 216–20.

37 Kossard S, Winkelmann RK. Low-dose chlorambucil in the treatment of generalized granuloma annulare. *Dermatologica* 1979; **158:** 443–50.

38 Rudolph RI. Disseminated granuloma annulare treated with low-dose chlorambucil. *Arch Dermatol* 1979; **115:** 1212–3.

39 Dabski K, Winkelmann RK. Generalized granuloma annulare: clinical and laboratory findings in 100 patients. *J Am Acad Dermatol* 1989; **20:** 39–47.

40 Winkelmann RK, Stevens JC. Successful treatment response of granuloma annulare and carpal tunnel syndrome to chlorambucil. *Mayo Clin Proc* 1994; **69:** 1163–5.

41 Saied N, Schwartz RA, Estes SA. Treatment of generalized granuloma annulare with dapsone. *Arch Dermatol* 1980; **116:** 1345–6.

42 Mandel EH. Disseminated granuloma annulare. Report of a case treated with chloroquine phosphate (Aralen). *Arch Dermatol* 1959; **79:** 352–3.

43 Stritzler C. Generalized granuloma annulare (apparently responding well to chloroquine therapy). *Arch Dermatol* 1961; **83:** 1033–4.

44 Carlin MC, Ratz JL. A case of generalized granuloma annulare responding to hydroxychloroquine. *Cleve Clin J Med* 1987; **54:** 229–32.

45 Ma A, Medenica M. Response of generalized granuloma annulare to high-dose niacinamide. *Arch Dermatol* 1983; **119:** 836–9.

46 Rubel DM, Wood G, Rosen R, Jopp-McKay A. Generalized granuloma annulare successfully treated with pentoxifylline. *Australas J Dermatol* 1993; **34:** 103–8.

47 Yamada H, Ide A, Sugiura M *et al*. Treatment of granuloma annulare with tranilast. *J Dermatol* 1995; **22:** 354–6.

48 Schulze DA, Petzoldt D. Granuloma anulare disseminatum—erfolgreiche Therapie mit Fumarsäureester. *Hautarzt* 2001; **52:** 228–30.

49 Eberlein-König B, Mempel M, Stahlecker J *et al*. Disseminated granuloma annulare—treatment with fumaric acid esters. *Dermatology* 2005; **210:** 223–6.

50 Breuer K, Gutzmer R, Völker B *et al*. Therapy of noninfectious granulomatous skin diseases with fumaric acid esters. *Br J Dermatol* 2005; **152:** 1290–5.

51 Mensing H. Clofazimine—therapeutische Alternative bei Necrobiosis lipoidica und Granuloma anulare. *Hautarzt* 1989; **40:** 99–103.

52 Burg G. Disseminated granuloma annulare: therapy with vitamin E topically. *Dermatology* 1992; **184:** 308–9.

53 Smith KJ, Norwood C, Skelton H. Treatment of disseminated granuloma annulare with a 5-lipoxygenase inhibitor and vitamin E. *Br J Dermatol* 2002; **146:** 667–70.

54 Rubegni P, Sbano P, Fimiani M. A case of disseminated granuloma annulare treated with defibrotide: complete clinical remission and progressive hair darkening. *Br J Dermatol* 2003; **149:** 437–9.

55 Kuwahara RT, Skinner RB Jr. Granuloma annulare resolved with topical application of imiquimod. *Pediatr Dermatol* 2002; **19:** 368–9.

56 Badavanis G, Monastirli A, Pasmatzi E, Tsambaos D. Successful treatment of granuloma annulare with imiquimod cream 5%: a report of four cases. *Acta Derm Venereol (Stockh)* 2005; **85:** 547–8.
57 Jain S, Stephens CJM. Successful treatment of disseminated granuloma annulare with topical tacrolimus. *Br J Dermatol* 2004; **150:** 1042–3.
58 Harth W, Linse R. Topical tacrolimus in granuloma annulare and necrobiosis lipoidica. *Br J Dermatol* 2004; **150:** 792–4.
59 Rigopoulos D, Prantsidis A, Christofidou E *et al*. Pimecrolimus 1% cream in the treatment of disseminated granuloma annulare. *Br J Dermatol* 2005; **152:** 1364–5.
60 Hertl MS, Haendle I, Schuler G, Hertl M. Rapid improvement of recalcitrant disseminated granuloma annulare upon treatment with the tumour necrosis factor-alpha inhibitor, infliximab. *Br J Dermatol* 2005; **152:** 552–5.
61 Goffe BS. Disseminated granuloma annulare resolved with the T-cell modulator efalizumab. *Arch Dermatol* 2004; **140:** 1287–8.
62 Shupack J, Siu K. Resolving granuloma annulare with etanercept. *Arch Dermatol* 2006; **142**: 394–5.
63 Kreuter A, Altmeyer P, Gambichler T. Failure of etanercept therapy in granuloma annulare. *Arch Dermatol* 2006; **142:** 1236–7.
64 Peñas PF, Jones-Caballero M, Fraga J *et al*. Perforating granuloma annulare. *Int J Dermatol* 1997; **36:** 340–8.
65 Felner EI, Steinberg JB, Weinberg AG. Subcutaneous granuloma annulare: a review of 47 cases. *Pediatrics* 1997; **100:** 965–7.

Necrobiosis lipoidica

Introduction. Necrobiosis lipoidica was first described by Oppenheim, in 1930 [1], and subsequently named *necrobiosis lipoidica diabeticorum* by Urbach, in 1932 [2]. Because it is not peculiar to diabetes, it is now usually called necrobiosis lipoidica. It is similar in histological appearance to granuloma annulare, but has a distinctive clinical appearance characterized by sharply demarcated plaques of atrophic yellowish skin, which may ulcerate.

Aetiology [3]. This condition was originally regarded as a complication of diabetes mellitus, but it was soon realized that some patients with necrobiosis lipoidica did not have overt diabetes. The precise relationship of the diabetic state to necrobiosis lipoidica is still not clear, although they are undoubtedly associated as discussed below.

Some authors have considered vascular changes to be important in the pathogenesis of necrobiosis lipoidica, but in Muller and Winkelmann's histopathological study vascular involvement was very mild in about a third of the cases [4]. An altered plasma protein profile [5], elevated factor VIII-related antigen [6] and fibronectin [7] may contribute to the vascular changes.

The possible role of an antibody-mediated vasculitis as an initiating event in necrobiosis lipoidica has provoked debate, as results of immunofluorescence studies differ. Laukkanen *et al*. [8] did not demonstrate immunoreactants in lesional skin, but others have shown immunoreactants, principally IgM, C3 and fibrin, in vessel walls in the involved skin, and IgM, C3 and fibrinogen at the dermoepidermal junction [9,10]. Dahl [11] has discussed immunofluorescence findings in necrobiosis lipoidica.

Whatever the mechanism, there is evidence of impaired microcirculation in non-diabetic individuals with necrobiosis lipoidica compared with controls, as measured by laser-Doppler flowmetry [12].

Although vascular factors may play a role, the precise pathogenesis of necrobiosis lipoidica remains unknown.

References

1 Oppenheim M. Eigentümliche disseminierte Degeneration des Bindegewebes der Haut bei einem Diabetiker. *Zentralbl Haut Geschlechtskr* 1930; **32:** 179.
2 Urbach E. Beiträge zu einer physiologischen und pathologischen Chemie der Haut; eine neue diabetische Stoffwechseldermatose: Nekrobiosis lipoidica diabeticorum. *Arch Dermatol Syph* 1932; **166:** 273–85.
3 Lowitt MH, Dover JS. Necrobiosis lipoidica. *J Am Acad Dermatol* 1991; **25:** 735–48.
4 Muller SA, Winkelmann RK. Necrobiosis lipoidica diabeticorum. Histopathologic study of 98 cases. *Arch Dermatol* 1966; **94:** 1–10.
5 Majewski BBJ, Barter S, Rhodes EL. Serum α_2 globulin levels in granuloma annulare and necrobiosis lipoidica. *Br J Dermatol* 1981; **105**: 557–62.
6 Majewski BBJ, Koh MS, Barter S, Rhodes EL. Increased factor VIII-related antigen in necrobiosis lipoidica and widespread granuloma annulare without associated diabetes. *Br J Dermatol* 1982; **107**: 641–5.
7 Koh MS, Majewski BBJ, Barter S, Rhodes EL. Increased plasma fibronectin in diabetes mellitus, necrobiosis lipoidica and widespread granuloma annulare. *Clin Exp Dermatol* 1984; **9:** 293–7.
8 Laukkanen A, Fräki JE, Väätäinen N *et al*. Necrobiosis lipoidica: clinical and immunofluorescent study. *Dermatologica* 1986; **172:** 89–92.
9 Ullman S, Dahl MV. Necrobiosis lipoidica. An immunofluorescence study. *Arch Dermatol* 1977; **113:** 1671–3.
10 Quimby SR, Muller SA, Schroeter AL. The cutaneous immunopathology of necrobiosis lipoidica diabeticorum. *Arch Dermatol* 1988; **124:** 1364–71.
11 Dahl MV. Immunofluorescence, necrobiosis lipoidica, and blood vessels. *Arch Dermatol* 1988; **124:** 1417–9.
12 Boateng B, Hiller D, Albrecht HP, Hornstein OP. Kutane Mikrozirkulation bei prätibialer Nekrobiosis lipoidica. Vergleichende Laser-Doppler Fluxmetrie und Sauerstoffpartialdruckmessungen bei Patienten und Hautgesunden. *Hautarzt* 1993; **44:** 581–6.

Histopathology [1–3] (Fig. 60.10). The histological appearances are similar to those of granuloma annulare, but some features differ. The epidermis is normal or atrophic, and absent if there is ulceration. The dermal changes involve its full thickness, and often extend into the subcutaneous fat. Early lesions show a perivascular and interstitial mixed inflammatory cell infiltrate. Areas of necrobiosis are usually more extensive and less well-defined than in granuloma annulare. There is degeneration of collagen and elastin within lesions [4]. Histiocytes border the areas of necrobiosis. There are variable numbers of Langhans' or foreign-body giant cells. A perivascular inflammatory infiltrate includes occasional eosinophils and, in contrast with granuloma annulare, plasma cells. Lymphoid nodules, containing germinal centres, may be present in the deep dermis or subcutaneous fat [5]. Lipid can be demonstrated in the necrobiotic areas, and cholesterol clefts may be present [6]. Mucin may be present in the dermis, but it is not as prominent as in granuloma annulare.

Small, superficial blood vessels are increased in number and telangiectatic. Deeper dermal blood vessels often show thickening of their walls and proliferation of endothelial cells. The walls are often infiltrated with periodic acid–Schiff-positive, diastase-negative material. Histologically, comedo-like plugs at the periphery of lesions represent elimination of necrotic material through hair follicles [7,8]. Anaesthesia in the lesions appears to be related to a decreased number of nerves within them [9]. In old, atrophic lesions there is considerable fibrosis in the dermis and subcutis.

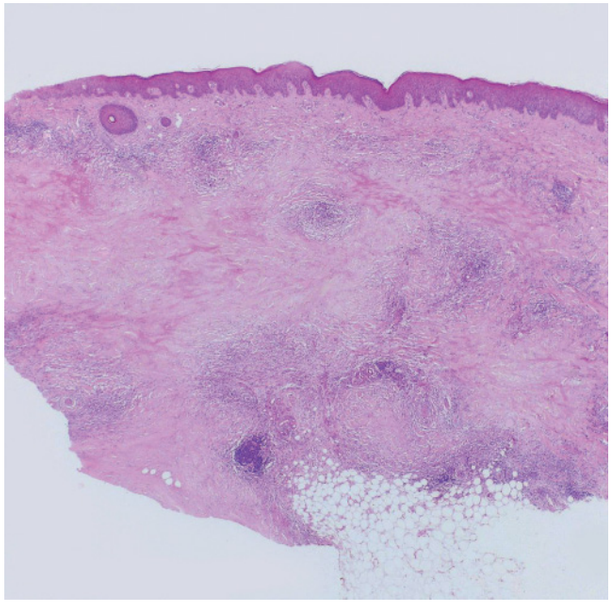


Fig. 60.10 Necrobiosis lipoidica. Extensive necrobiosis in the dermis. H&E stain. (Courtesy of Dr M. Bamford, Dept. of Pathology, Leicester Royal Infirmary, Leicester, UK.)

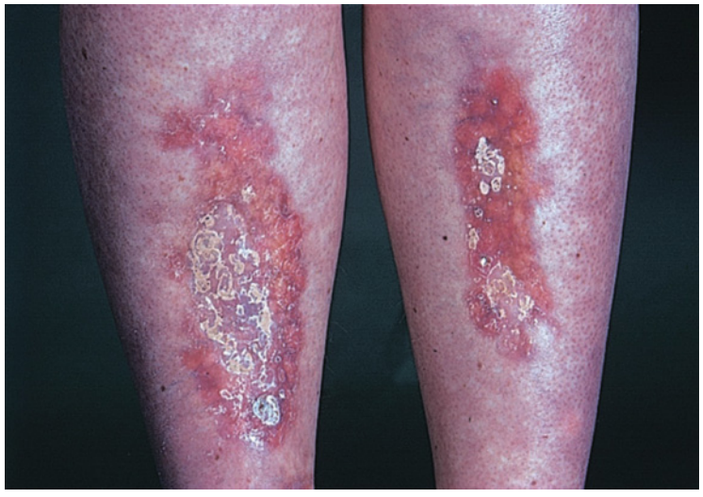


Fig. 60.11 Necrobiosis lipoidica. Lesions on both shins.

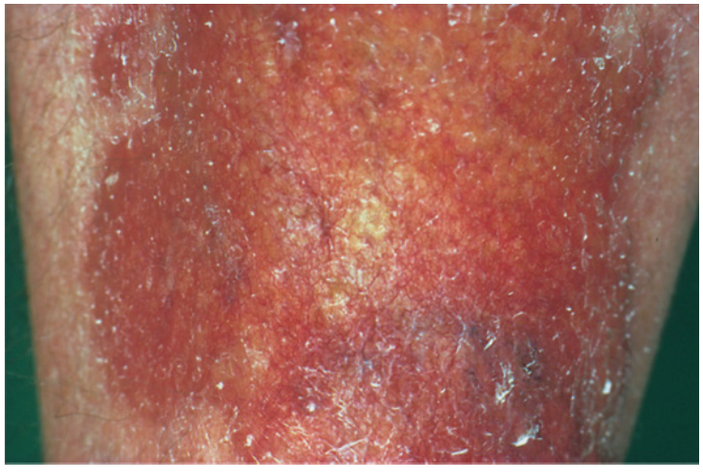


Fig. 60.12 Area of necrobiosis showing yellowish colour, atrophy and prominent vessels.

References

1 Weedon D. *Skin Pathology*, 2nd edn. London: Churchill Livingstone, 2002: 202–4.
2 Elder D, Elenitsas R, Jaworsky C, Johnson B Jr, eds. *Lever's Histopathology of the Skin*, 8th edn. Philadelphia: Lippincott-Raven, 1999: 330–3.
3 Muller SA, Winkelmann RK. Necrobiosis lipoidica diabeticorum. Histopathologic study of 98 cases. *Arch Dermatol* 1966; **94:** 1–10.
4 Oikarinen A, Mörtenhumer M, Kallionen M, Savolainen ER. Necrobiosis lipoidica: ultrastructural and biochemical demonstration of a collagen defect. *J Invest Dermatol* 1987; **88:** 227–32.
5 Alegre VA, Winkelmann RK. A new histopathologic feature of necrobiosis lipoidica diabeticorum: lymphoid nodules. *J Cutan Pathol* 1988; **15:** 75–7.
6 De la Torre C, Losada A, Cruces MJ. Necrobiosis lipoidica: a case with prominent cholesterol clefting and transepithelial elimination. *Am J Dermatopathol* 1999; **21:** 575–7.
7 Parra CA. Transepithelial elimination in necrobiosis lipoidica. *Br J Dermatol* 1977; **96:** 83–6.
8 Pestoni C, Ferreirós MMP, de la Torre C, Toribio J. Two girls with necrobiosis lipoidica and type 1 diabetes mellitus with transfollicular elimination in one girl. *Pediatr Dermatol* 2003; **20:** 211–4.
9 Boulton AJM, Cutfield RG, Abouganem D *et al*. Necrobiosis lipoidica diabeticorum: a clinicopathologic study. *J Am Acad Dermatol* 1988; **18:** 530–7.

Clinical features [1–3]. Necrobiosis lipoidica may occur at any age, but usually develops in young adults and in early middle-age. In insulin-dependent diabetics the age of onset is earlier than in non-insulin-dependent and non-diabetic individuals [4]. It is rare in childhood [5,6]. The female:male ratio is 3:1. Familial occurrence is rare [7,8].

Typical lesions occur on the pretibial skin, and begin as a firm, dull-red papule or plaque which enlarges radially to become a yellowish, atrophic plaque with an erythematous edge (Figs 60.11 & 60.12). The surface is often glazed in appearance, and telangiectatic vessels may be prominent (Fig. 60.13). Lesions are usually symptomless. Hypoaesthesia or anaesthesia, and hypohidrosis, are features of the affected skin [2,9,10]. Comedo-like plugs may occur at the periphery of lesions [11]. In most cases, lesions are bilateral, and they are similar in appearance whether occurring in diabetic or non-diabetic individuals [1]. They tend to be persistent, and some may ulcerate [12] (Fig. 60.14). In one study [4], ulceration correlated with sensory impairment. Squamous cell carcinoma may develop in long-standing lesions [13–20].

Lesions can also occur on other parts of the body, including the trunk [21] and penis [22,23], and rarely may be diffuse [24]. They may also occur at sites of trauma [25–28]. The number of lesions, and their rate of progress, are very variable. Slow extension over many years is usual, but long periods of quiescence, or resolution with variable atrophy and scarring (Fig. 60.15), may occur.

Wilson Jones [29] described an 'atypical annular form' of necrobiosis lipoidica affecting the upper face and scalp margins. The majority of affected individuals were female, and some developed lesions of necrobiosis lipoidica elsewhere. Since then, other authors have described similar annular lesions occurring predominantly on the exposed skin of the head, neck and arms, and these have been named Miescher's granuloma [30] and actinic granuloma [31]. Hanke *et al.* [32] proposed the term 'annular elastolytic giant

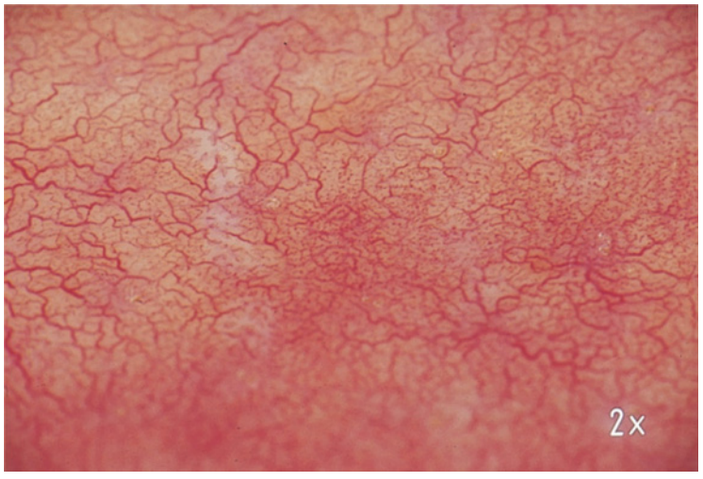


Fig. 60.13 Prominent telangiectasia in an area of necrobiosis.



Fig. 60.14 Ulcerated necrobiosis lipoidica.

cell granuloma' for these lesions. A similarity to granuloma multiforme (p. 60.17) is also apparent. The relationship of these disorders to each other, and to the necrobiotic granulomas, has provoked debate [3,33].

Differential diagnosis. Lesions with marked fatty infiltration, particularly when not on the legs, may be mistaken for xanthomas. Necrobiotic xanthogranuloma is a rare destructive xanthogranuloma, in which red-orange or yellowish indurated plaques most frequently involve the periorbital regions and trunk [34,35]. It is associated with systemic lesions and a monoclonal gammopathy (Chapter 62).



Fig. 60.15 'Burnt out' necrobiosis lipoidica—marked atrophy is evident.

References

1 Muller SA, Winkelmann RK. Necrobiosis lipoidica diabeticorum. A clinical and pathological investigation of 171 cases. *Arch Dermatol* 1966; **93:** 272–81.
2 Boulton AJM, Cutfield RG, Abouganem D *et al*. Necrobiosis lipoidica diabeticorum. A clinicopathologic study. *J Am Acad Dermatol* 1988; **18:** 530–7.
3 Lowitt MH, Dover JS. Necrobiosis lipoidica. *J Am Acad Dermatol* 1991; **25:** 735–48.
4 Shall L, Millard LG, Stevens A *et al*. Necrobiosis lipoidica: 'the footprint not the footstep'. *Br J Dermatol* 1990; **123** (Suppl. 37): 47.
5 Chernosky ME, Guin JD. Necrobiosis lipoidica in a three-year-old girl. *Arch Dermatol* 1961; **84:** 135–6.
6 Verrotti A, Chiarelli F, Amerio P, Morgese G. Necrobiosis lipoidica diabeticorum in children and adolescents: a clue for underlying renal and retinal disease. *Pediatr Dermatol* 1995; **12**: 220–3.
7 Ho KK, O'Loughlin S, Powell FC. Familial non-diabetic necrobiosis lipoidica. *Australas J Dermatol* 1992; **33**: 31–4.
8 Findlay GH, Morrison JGL, De Beer HA. Non-diabetic necrobiosis lipoidica. *S Afr Med J* 1981; **59:** 323–6.
9 Mann RJ, Harman RRM. Cutaneous anaesthesia in necrobiosis lipoidica. *Br J Dermatol* 1984; **110:** 323–5.
10 Hatzis J, Varelzidis A, Tosca A, Stratigos J. Sweat gland disturbances in granuloma annulare and necrobiosis lipoidica. *Br J Dermatol* 1983; **108:** 705–9.
11 Parra CA. Transepithelial elimination in necrobiosis lipoidica. *Br J Dermatol* 1977; **96:** 83–6.
12 Dwyer CM, Dick D. Ulceration in necrobiosis lipoidica—a case report and study. *Clin Exp Dermatol* 1993; **18:** 366–9.
13 Clement M, Guy R, Pembroke AC. Squamous cell carcinoma arising in long standing necrobiosis lipoidica. *Arch Dermatol* 1985; **121:** 24–5.
14 Kossard S, Collins E, Wargon O, Downie D. Squamous carcinomas developing in bilateral lesions of necrobiosis lipoidica. *Australas J Dermatol* 1987; **28:** 14–7.
15 Beljaards RC, Groen J, Starink TM. Bilateral squamous cell carcinomas arising in long-standing necrobiosis lipoidica. *Dermatologica* 1990; **180:** 96–8.
16 Gudi VS, Campbell S, Gould DJ, Marshall R. Squamous cell carcinoma in an area of necrobiosis lipoidica diabeticorum: a case report. *Clin Exp Dermatol* 2000; **25:** 597–9.

17 Imtiaz KE, Kaleeli AA. Squamous cell carcinoma developing in necrobiosis lipoidica. *Diabet Med* 2001; **18:** 325–8.
18 Santos-Juanes J, Galache C, Curto JR *et al*. Squamous cell carcinoma arising in long-standing necrobiosis lipoidica. *J Eur Acad Dermatol Venereol* 2004; **18:** 199–200.
19 Vanhooteghem O, André J, de la Brassinne M. Epidermoid carcinoma and perforating necrobiosis lipoidica: a rare association. *J Eur Acad Dermatol Venereol* 2005; **19:** 756–8.
20 Lim C, Tschuchnigg M, Lim J. Squamous cell carcinoma arising in an area of long-standing necrobiosis lipoidica. *J Cutan Pathol* 2006; **33:** 581–3.
21 Kavanagh GM, Novelli M, Hartog M, Kennedy CTC. Necrobiosis lipoidica—involvement of atypical sites. *Clin Exp Dermatol* 1993; **18**: 543–4.
22 España A, Sánchez-Yus E, Serna MJ *et al*. Chronic balanitis with palisading granuloma: an atypical genital localisation of necrobiosis lipoidica responsive to pentoxifylline. *Dermatology* 1994; **188**: 222–5.
23 Velasco-Pastor AM, del Pino Gil-Mateo M, Martinéz-Aparicio A, Aliaga-Boniche A. Necrobiosis lipoidica of the glans penis. *Br J Dermatol* 1996; **135:** 154–5.
24 Imakado S, Satomi H, Ishikawa M *et al*. Diffuse necrobiosis lipoidica diabeticorum associated with non-insulin dependent diabetes mellitus. *Clin Exp Dermatol* 1998; **23:** 271–3.
25 Gebauer K, Armstrong M. Koebner phenomenon with necrobiosis lipoidica diabeticorum. *Int J Dermatol* 1993; **32:** 895–6.
26 Sahl WJ Jr. Necrobiosis lipoidica diabeticorum. Localization in surgical scars. *J Cutan Pathol* 1978; **5:** 249–53.
27 Miller RA. Koebner phenomenon in a diabetic with necrobiosis lipoidica diabeticorum. *Int J Dermatol* 1990; **29:** 52–3.
28 Ghate JV, Williford PM, Sane DC, Hitchcock MG. Necrobiosis lipoidica associated with Köbner's phenomenon in a patient with diabetes. *Cutis* 2001; **67:** 158–60.
29 Wilson Jones E. Necrobiosis lipoidica presenting on the scalp and face: an account of 29 patients and a detailed consideration of recent histochemical findings. *Trans St John's Hosp Dermatol Soc* 1971; **57**: 202–20.
30 Mehregan AH, Altman J. Miescher's granuloma of the face. *Arch Dermatol* 1973; **107:** 62–4.
31 O'Brien J. Actinic granuloma. An annular connective tissue disorder affecting sun- and heat-damaged (elastotic) skin. *Arch Dermatol* 1975; **111:** 460–6.
32 Hanke CW, Bailin PL, Roenigk HH Jr. Annular elastolytic giant cell granuloma. A clinicopathologic study of five cases and a review of similar entities. *J Am Acad Dermatol* 1979; **1:** 413–21.
33 Weedon D. *Skin Pathology*, 2nd edn. London: Churchill Livingstone, 2002: 208–10.
34 Finan MC, Winkelmann RK. Necrobiotic xanthogranuloma with paraproteinemia. A review of 22 cases. *Medicine (Baltimore)* 1986; **65:** 376–88.
35 Finan MC, Winkelmann RK. Histopathology of necrobiotic xanthogranuloma with paraproteinemia. *J Cutan Pathol* 1987; **14:** 92–9.

Associations. Although it is accepted that there is a relationship between necrobiosis lipoidica and diabetes mellitus, there is some disagreement about the closeness of this association. In Muller and Winkelmann's large series of cases, 111 of 171 patients with necrobiosis lipoidica (65%) had diabetes, and several of the non-diabetic patients subsequently had abnormal glucose tolerance tests, whereas in a study from Ireland [2], of 65 individuals with necrobiosis lipoidica only seven (11%) were known to have diabetes at the time of presentation. Necrobiosis lipoidica is relatively uncommon in diabetic patients, with reported prevalences of 0.3% [1] and 1.2% [3], and appears to be rare (0.06%) in childhood diabetes [4].

It is most commonly seen in patients with type 1 diabetes [3,5], but also occurs in type 2 diabetes, and in recent years has been reported in children and adolescents with type 2 diabetes [6–9], including diabetes associated with Prader–Willi syndrome [10]. A survey of the records of 178 patients fitting the clinical criteria for maturity-onset diabetes of the young (MODY), which is a subtype of non-insulin-dependent diabetes, showed a prevalence of necrobiosis lipoidica of 2.8% [8].

There is some evidence that diabetic patients who have necrobiosis lipoidica are at higher risk of retinopathy and nephropathy than diabetics who do not [5,11,12]. In the past, it was noted that good control of diabetes did not appear to have a significant effect on the course of necrobiosis lipoidica [1], but it would be of interest to reassess this aspect of the disease in the context of advances in diabetes care in recent years.

Necrobiosis lipoidica has also been reported as occurring in association with ulcerative colitis [13] and Crohn's disease [14], ataxia–telangiectasia [15], and after jejunal bypass surgery [16]. Reports of its occurrence with granuloma annulare have been mentioned previously (p. 60.9). It has also been reported in association with sarcoidosis [17,18].

Magro *et al*. [19] have demonstrated histopathological evidence of an 'active vasculopathy' in the majority of a series of cases of necrobiosis lipoidica associated with systemic disease.

References

1 Muller SA, Winkelmann RK. Necrobiosis lipoidica diabeticorum. A clinical and pathological investigation of 171 cases. *Arch Dermatol* 1966; **93:** 272–81.
2 O'Toole EA, Kennedy U, Nolan JJ *et al*. Necrobiosis lipoidica: only a minority of patients have diabetes mellitus. *Br J Dermatol* 1999; **140:** 283–6.
3 Shall L, Millard LG, Stevens A *et al*. Necrobiosis lipoidica: 'the footprint not the footstep'. *Br J Dermatol* 1990; **123** (Suppl. 37): 47.
4 de Silva BD, Schofield OMV, Walker JD. The prevalence of necrobiosis lipoidica diabeticorum in children with type 1 diabetes. *Br J Dermatol* 1999; **140:** 283–6.
5 Boulton AJM, Cutfield RG, Abouganem D *et al*. Necrobiosis lipoidica diabeticorum: a clinicopathologic study. *J Am Acad Dermatol* 1988; **18:** 530–7.
6 Szabo RM, Harris GD, Burke WA. Necrobiosis lipoidica in a 9-year-old girl with new-onset type II diabetes mellitus. *Pediatr Dermatol* 2001; **18:** 316–9.
7 Yigit S, Estrada E. Recurrent necrobiosis lipoidica diabeticorum associated with venous insufficiency in an adolescent with poorly controlled type 2 diabetes mellitus. *J Pediatr* 2002; **141:** 280–2.
8 Stride A, Lambert P, Burden ACF *et al*. Necrobiosis lipoidica is a clinical feature of maturity-onset diabetes of the young. *Diabetes Care* 2002; **25:** 1249–50.
9 Marchetti F, Gerarduzzi T, Longo F *et al*. Maturity-onset diabetes of the young with necrobiosis lipoidica and granuloma annulare. *Pediatr Dermatol* 2006; **23:** 247–50.
10 Walker JD, Warren RE. Necrobiosis lipoidica in Prader–Willi-associated diabetes mellitus. *Diabet Med* 2002; **19:** 884–5.
11 Kelly WF, Nicholas J, Adams J, Mahmood R. Necrobiosis lipoidica diabeticorum: association with background retinopathy, smoking, and proteinuria. A case controlled study. *Diabet Med* 1993; **10:** 725–8.
12 Verrotti A, Chiarelli F, Amerio P, Morgese G. Necrobiosis lipoidica diabeticorum in children and adolescents: a clue for underlying renal and retinal disease. *Pediatr Dermatol* 1995; **12:** 220–3.
13 Whorwell PJ, Haboubi NY, Du Boulay C. Nodular necrobiosis in association with ulcerative colitis. *Gut* 1986; **27:** 1517.
14 Du Boulay C, Whorwell PJ. 'Nodular necrobiosis': a new cutaneous manifestation of Crohn's disease? *Gut* 1982; **23:** 712–5.
15 Götz A, Eckert F, Landthaler M. Ataxia-telangiectasia (Louis–Bar syndrome) associated with ulcerating necrobiosis lipoidica. *J Am Acad Dermatol* 1994; **31:** 124–6.
16 Clegg DO, Zone JJ, Piepkorn MW. Necrobiosis lipoidica ssociated with jejunoileal bypass surgery. *Arch Dermatol* 1982; **118:** 135–6.
17 Graham-Brown RAC, Shuttleworth D, Sarkany I. Coexistence of sarcoidosis and necrobiosis lipoidica of the legs—a report of two cases. *Clin Exp Dermatol* 1985; **10:** 274–8.
18 Monk BE, Du Vivier AWP. Necrobiosis lipoidica and sarcoidosis. *Clin Exp Dermatol* 1987; **12:** 294–5.

19 Magro CM, Crowson AN, Regauer S. Granuloma annulare and necrobiosis lipoidica tissue reactions as a manifestation of systemic disease. *Hum Pathol* 1996; **27:** 50–6.

Treatment. Potent topical corticosteroids, particularly if applied beneath an occlusive dressing, and changed weekly, may help [1]. Locally injected triamcinolone, delivered by needle or jet injector [2], can improve the appearance, but atrophy usually remains. As there is evidence of extension of the inflammatory infiltrate into apparently normal skin surrounding active lesions, injection of steroids into perilesional areas might help to limit progression [3]. The use of oral steroids may be of benefit [4,5]. Petzelbauer *et al*. [5] employed short-course steroid therapy that resulted in cessation of disease activity in six patients, and no recurrence in a mean follow-up period of 7 months.

There are reports of benefit from PUVA therapy [6–12], UVA1 phototherapy—some patients improved but there was a poor response in others [13], topical tacrolimus [14], fumaric acid esters [15], thalidomide [16], chloroquine [17], photodynamic therapy [18], a combination of split-thickness autografting and immunomodulatory therapy [19], and etanercept [20].

Other treatments that have been employed in the past, with varying degrees of success, include fibrinolytic agents [21], high-dose nicotinamide [22], clofazimine [23], pentoxifylline [24–27], tretinoin (0.05%) [28], prostaglandin E1 [29,30], and aspirin or an aspirin/dipyridamole combination [31–33]. Aspirin alone was subsequently shown to be ineffective [34,35], and in a randomized, double-blind comparison with placebo, patients treated with an aspirin/dipyridamole combination did not show any significant improvement [36].

Pulsed dye laser has been employed, and may improve the telangiectatic and erythematous components [37], but skin breakdown can occur [38]. Ulcerated necrobiosis has been treated by excision and grafting [39–41], although recurrence tends to occur unless the excision is deep [41]. Other treatments employed include oral steroid [42], ciclosporin [43–45], mycophenolate mofetil [46], topical granulocyte-macrophage colony stimulating factor [47,48], infliximab [49], intravenous immunoglobulin [50], hyperbaric oxygen [51,52], topically applied bovine collagen [53], and grafting with bioengineered dermal tissue [54,55].

References

1 Volden G. Successful treatment of chronic skin diseases with clobetasol propionate and hydrocolloid occlusive dressing. *Acta Derm Venereol (Stockh)* 1992; **72**: 69–71.
2 Sparrow G, Abell E. Granuloma annulare and necrobiosis lipoidica treated by jet injector. *Br J Dermatol* 1975; **93**: 85–9.
3 Boulton AJM, Cutfield RG, Abouganem D *et al*. Necrobiosis lipoidica diabeticorum: a clinicopathologic study. *J Am Acad Dermatol* 1988; **18:** 530–7.
4 Taniguchi Y, Sakamoto T, Shimizu M. A case of necrobiosis lipoidica treated with systemic corticosteroid. *J Dermatol* 1993; **20**: 304–7.
5 Petzelbauer P, Wolff K, Tappeiner G. Necrobiosis lipoidica: treatment with systemic corticosteroids. *Br J Dermatol* 1992; **126**: 542–5.
6 Patel GK, Rashid A, Mills CM. Topical photochemotherapy: a ray of hope for the treatment of necrobiosis lipoidica. *Br J Dermatol* 1999; **141**(Suppl. 55): 118 (Abstr).
7 McKenna DB, Cooper EJ, Tidman MJ. Topical psoralen plus ultraviolet A treatment for necrobiosis lipoidica. *Br J Dermatol* 2000; **143:** 1333–5.
8 Patel GK, Harding KG, Mills CM. Severe disabling koebnerizing ulcerated necrobiosis lipoidica successfully treated with topical PUVA. *Br J Dermatol* 2000; **143:** 668–9.
9 Patel GK, Mills CM. A prospective open study of topical psoralen-UV-A therapy for necrobiosis lipoidica. *Arch Dermatol* 2001; **137:** 1658–60.
10 de Rie MA, Sommer A, Hoekzema R, Neumann HAM. Treatment of necrobiosis lipoidica with topical psoralen plus ultraviolet A. *Br J Dermatol* 2002; **147:** 743–7.
11 Ling TC, Thomson KF, Goulden V, Goodfield MJD. PUVA therapy in necrobiosis lipoidica diabeticorum. *J Am Acad Dermatol* 2002; **46:** 3129–20.
12 Narbutt J, Torzecka JD, Sysa-Jedrzejowska A, Zalewska A. Long-term results of topical PUVA in necrobiosis lipoidica. *Clin Exp Dermatol* 2006; **31:** 65–7.
13 Beattie PE, Dawe RS, Ibbotson SH, Ferguson J. UVA1 phototherapy for treatment of necrobiosis lipoidica. *Clin Exp Dermatol* 2006; **31:** 235–8.
14 Harth W, Linse R. Topical tacrolimus in granuloma annulare and necrobiosis lipoidica. *Br J Dermatol* 2004; **150:** 792–4.
15 Kreuter A, Knierim C, Stücker M *et al*. Fumaric acid esters in necrobiosis lipoidica: results of a prospective noncontrolled study. *Br J Dermatol* 2005; **153:** 802–7.
16 Kukreja T, Petersen J. Thalidomide for the treatment of refractory necrobiosis lipoidica. *Arch Dermatol* 2006; **142:** 20–2.
17 Nguyen K, Washenik K, Shupack J. Necrobiosis lipoidica diabeticorum treated with chloroquine. *J Am Acad Dermatol* 2002; **46** (Suppl. 2): S34–6.
18 Heidenheim M, Jemec GBE. Successful treatment of necrobiosis lipoidica diabeticorum with photodynamic therapy. *Arch Dermatol* 2006; **142:** 1548–50.
19 Cummins DL, Hiatt KM, Mimouni D *et al*. Generalized necrobiosis lipoidica treated with a combination of split-thickness autografting and immunomodulatory therapy. *Int J Dermatol* 2004; **43:** 852–4.
20 Zeichner JA, Stern DWK, Lebwohl M. Treatment of necrobiosis lipoidica with the tumor necrosis factor antagonist etanercept. *J Am Acad Dermatol* 2006; **54** (Suppl. 2): S120–1.
21 Rhodes EL. Fibrinolytic agents in the treatment of necrobiosis lipoidica. *Angiology* 1978; **29:** 60–4.
22 Handfield-Jones S, Jones S, Peachey R. High dose nicotinamide in the treatment of necrobiosis lipoidica. *Br J Dermatol* 1988; **118:** 693–6.
23 Mensing H. Clofazimine—therapeutische Alternative bei Necrobiosis lipoidica und Granuloma anulare. *Hautarzt* 1989; **40:** 99–103.
24 Littler CM, Tschen EH. Pentoxifylline for necrobiosis lipoidica diabeticorum. *J Am Acad Dermatol* 1987; **17:** 314–6.
25 España A, Sánchez-Yus E, Serna MJ *et al*. Chronic balanitis with palisading granuloma: an atypical genital localisation of necrobiosis lipoidica responsive to pentoxifylline. *Dermatology* 1994; **188**: 222–5.
26 Noz KC, Korstanje MJ, Vermeer BJ. Ulcerating necrobiosis lipoidica effectively treated with pentoxifylline. *Clin Exp Dermatol* 1993; **18**: 78–9.
27 Basaria S, Braga-Basaria M. Necrobiosis lipoidica diabeticorum: response to pentoxiphylline. *J Endocrinol Invest* 2003; **26:** 1037–40.
28 Boyd AS. Tretinoin treatment of necrobiosis lipoidica diabeticorum. *Diabetes Care* 1999; **22:** 1753–4.
29 Sawada Y. Successful treatment of ulcerated necrobiosis lipoidica diabeticorum with prostaglandin E1 and skin flap transfer—a case report. *J Dermatol* 1985; **12:** 449–54.
30 Kuwert C, Abeck D, Steinkraus V *et al*. Prostaglandin E1 improves necrobiosis lipoidica. *Acta Derm Venereol (Stockh)* 1995; **75**: 319–20.
31 Heng MC, Song MK, Heng MK. Healing of necrobiotic ulcers with antiplatelet therapy. Correlation with plasma thromboxane levels. *Int J Dermatol* 1989; **28:** 195–7.
32 Quimby SR, Muller SA, Shroeter AL *et al*. Necrobiosis lipoidica diabeticorum: platelet survival and response to platelet inhibitors. *Cutis* 1989; **43:** 213–6.
33 Eldor A, Diaz EG, Naparstek E. Treatment of diabetic necrobiosis with aspirin and dipyridamole. *N Engl J Med* 1978; **298**: 1033.
34 Beck HI, Bjerring P, Rasmussen I *et al*. Treatment of necrobiosis lipoidica with low-dose acetylsalicylic acid. A randomized double-blind trial. *Acta Derm Venereol* 1985; **65:** 230–4.
35 Beck HI, Bjerring P. Skin blood flow in necrobiosis lipoidica during treatment with low-dose acetylsalicylic acid. *Acta Derm Venereol (Stockh)* 1988; **68:** 364–5.
36 Statham B, Finlay AY, Marks R. A randomised double blind comparison of an aspirin dipyridamole combination versus a placebo in the treatment of necrobiosis lipoidica. *Acta Derm Venereol (Stockh)* 1981; **61**: 270–1.

37 Moreno-Arias GA, Camps-Fresneda A. Necrobiosis lipoidica diabeticorum treated with the pulsed dye laser. *J Cosmet Laser Ther* 2001; **3:** 143–6.
38 Currie CL, Monk BE. Pulsed dye laser treatment of necrobiosis lipoidica: report of a case. *J Cutan Laser Ther* 1999; **1:** 239–41.
39 Cawley EP, Dingman RO. Necrobiosis lipoidica diabeticorum: its surgical treatment. *Arch Dermatol Syphilol* 1951; **63**: 764–7.
40 Nylen BO, Skoog T. Surgical treatment of necrobiosis lipoidica. *Acta Derm Venereol (Stockh)* 1958; **38**: 366–71.
41 Dubin BJ, Kaplan EN. The surgical treatment of necrobiosis lipoidica diabeticorum. *Plast Reconstr Surg* 1977; **60:** 421–8.
42 Dwyer CM, Dick D. Ulceration in necrobiosis lipoidica—a case report and study. *Clin Exp Dermatol* 1993; **18:** 366–9.
43 Darvay A, Acland KM, Russell-Jones R. Persistent ulcerated necrobiosis lipoidica responding to treatment with cyclosporin. *Br J Dermatol* 1999; **141:** 725–7.
44 Stinco G, Parlangeli ME, De Francesco V *et al*. Ulcerated necrobiosis lipoidica treated with cyclosporin A. *Acta Derm Venereol (Stockh)* 2003; **83:** 151–3.
45 Stanway A, Rademaker M, Newman P. Healing of severe ulcerative necrobiosis lipoidica with cyclosporin. *Australas J Dermatol* 2004; **45:** 119–22.
46 Reinhard G, Lohmann F, Uerlich M *et al*. Successful treatment of ulcerated necrobiosis lipoidica with mycophenolate mofetil. *Acta Derm Venereol (Stockh)* 2000; **80:** 312–3.
47 Remes K, Rönnemaa T. Healing of chronic leg ulcers in diabetic necrobiosis lipoidica with local granulocyte-macrophage colony stimulating factor. *J Diabetes Complications* 1999; **13:** 115–8.
48 Evans AV, Atherton DJ. Recalcitrant ulcers in necrobiosis lipoidica diabeticorum healed by topical granulocyte-macrophage colony-stimulating factor treatment. *Br J Dermatol* 2002; **147:** 1023–5.
49 Kolde G, Muche JM, Schulze P *et al*. Infliximab: a promising new treatment option for ulcerated necrobiosis lipoidica. *Dermatology* 2003; **206:** 180–1.
50 Batchelor J, Todd PM. Improvement of ulcerated necrobiosis lipoidica with intravenous immunoglobulin. *Br J Dermatol* 2007; **157** (Suppl. 1)**:** 66.
51 Weisz G, Ramon Y, Waisman D, Melamed Y. Treatment of necrobiosis lipoidica diabeticorum by hyperbaric oxygen. *Acta Derm Venereol (Stockh)* 1993; **73**: 447–8.
52 Bouhanick B, Vervet JL, Guello JP *et al*. Necrobiosis lipoidica: treatment by hyperbaric oxygen and local corticosteroids. *Diabetes Metab* 1998; **24:** 156–9.
53 Spenceri EA, Nahass GT. Topically applied bovine collagen in the treatment of ulcerative necrobiosis lipoidica diabeticorum. *Arch Dermatol* 1997; **133:** 817–8.
54 Owen CM, Murphy H, Yates VM. Tissue-engineered dermal skin grafting in the treatment of ulcerated necrobiosis lipoidica. *Clin Exp Dermatol* 2001; **26:** 176–8.
55 Stuart L, Wiles PG. Management of ulcerated necrobiosis lipoidica: an innovative approach. *Br J Dermatol* 2001; **144:** 907–8.

Granuloma multiforme

Definition. A chronic granulomatous skin condition, characterized clinically by firm papules aggregated into plaques or forming the edges of annular lesions, and histologically by focal necrobiosis and histiocytic granulomas. It has been reported from Africa, Indonesia and India [1–8]. Leiker *et al*. [1–3] first described granuloma multiforme and distinguished it from tuberculoid leprosy. Leiker called it Mkar disease, after the town where it was first studied. The condition is endemic in certain villages in eastern Nigeria, where the local inhabitants refer to it in the Ibo tongue as 'Ununo Enyi' (elephant ringworm) [4,7].

The disease appears to occur predominantly in females over the age of 40 years [4,7,9].

Aetiology. The morphology and histological features of lesions, and their distribution predominantly on exposed parts of the body, indicate that this disorder may be granuloma annulare on light-exposed areas. It has been suggested that the primary event may be sun-induced damage to dermal connective tissue [9].

Pathology [4,10]. There are focal areas of necrobiosis, with loss of elastic tissue, surrounded by histiocytes. Multinucleated giant cells are usually a prominent feature. There is a perivascular lymphocytic infiltrate with variable numbers of plasma cells and eosinophils.

Clinical features. The upper, uncovered parts of the body are predominantly affected. The initial lesions are small, flesh-coloured papules which become aggregated into plaques or form the elevated rims of annular lesions. In larger annular lesions the central area is often hypopigmented. Pruritus may be prominent. The condition lasts for many months or years, and may persist indefinitely.

Differential diagnosis. Leprosy is endemic in the same regions where granuloma multiforme is found, and can look very similar. However, there is no loss of sensation or sweating, or other evidence of neural involvement in granuloma multiforme. In addition, the histological changes are different.

Treatment. None is known to be effective.

References

1 Leiker DL, Kok SH, Spaas JAJ. Granuloma multiforme: a new skin disease resembling leprosy. *Int J Lepr* 1964; **32**: 368–76.
2 Marshall J, Weber HW, Kok SH. Granuloma multiforme (Leiker). *Dermatologica* 1967; **134**: 193–207.
3 Leiker DL, Ziedses des Plantes M. Granuloma multiforme in Kenya. *East Afr Med J* 1967; **44**: 429–36.
4 Allenby CF, Wilson Jones E. Granuloma multiforme. *Trans St John's Hosp Dermatol Soc* 1969; **55:** 88–98.
5 Cherian S. Granuloma multiforme in India. *Int J Lepr* 1990; **58:** 719–21.
6 Verhagen ARHB, Koten JW, Chaddah VK, Patel RI. Skin diseases in Kenya: a clinical and histopathological study of 3168 patients. *Arch Dermatol* 1968; **98**: 577–86.
7 Garrett AS. Granuloma multiforme (called Nkanu disease in the 1940s and Mkar disease in 1964). *Int J Lepr* 1999; **67:** 172–4.
8 Sandhu K, Saraswat A, Gupta S *et al*. Granuloma multiforme. *Int J Dermatol* 2004; **43:** 441–3.
9 Cherian S. Is granuloma multiforme a photodermatosis? *Int J Dermatol* 1994; **33:** 21–2.
10 Meyers WM, Connor DH, Shannon R. Histologic characteristics of granuloma multiforme (Mkar disease). Including a comparison with leprosy and granuloma annulare. Report of first case from Congo (Kinshasa). *Int J Lepr* 1970; **38**: 241–9.

CHAPTER 61
Sarcoidosis

D.J. Gawkrodger
Royal Hallamshire Hospital, Sheffield, UK

Definition, 61.1
Main features, 61.1
History, 61.1
Epidemiology, 61.2
Aetiology, 61.2
Histopathology, 61.3
Immunological aspects, 61.5
General manifestations of sarcoidosis, 61.6
Staging of the disease, 61.6
Systemic features, 61.6
Sarcoidosis of the skin, 61.8
Classical forms, 61.9
Unusual and atypical forms, 61.14
Associated diseases, 61.17
Course and prognosis, 61.18
Investigations, 61.19
Biopsy, 61.19
Kveim test, 61.19
Other investigations, 61.20
Treatment, 61.20
Topical therapy, 61.21
Systemic therapy 61.21
Other sarcoidal reactions, 61.21
Infections, 61.22
Foreign materials, 61.22
Crohn's disease, 61.23
Whipple's disease, 61.23
Farmer's lung, 61.23
Other conditions, 61.23

Definition

There is no universally accepted definition of sarcoidosis. Many attempts have been made, but as long as its cause is unknown, definitions must be empirical and may also be inaccurate. Current definitions still have to avoid aetiological implications and the illogicalities that may result from them.

Scadding and Mitchell [1], after a full discussion of the difficulties, suggested the following: 'Sarcoidosis is a disease characterized by the formation in all or several affected organs or tissues of epithelioid cell tubercles, without caseation, although fibrinoid necrosis may be present at the centre of a few, proceeding either to resolution or to conversion of the epithelioid cell tubercles into hyaline fibrous tissue.'

The characteristic histology should be present in all affected tissue and similar in all parts of it. This excludes the sarcoid-like histology found in tuberculosis, brucellosis or leprosy. It is characterized by non-caseating epithelioid granulomas.

Main features

The most important features of sarcoidosis are as follows.

1 The disease process is usually generalized. The term is seldom applicable to a localized granulomatous reaction even though it may have similar histological findings.
2 The clinical manifestations are protean; the disease process is usually widespread; the course is protracted and usually benign, though sometimes with dangerous and disabling sequelae and complications.
3 The disease may affect any organ of the body (the adrenal gland possibly excluded). The lymph nodes, lungs, liver, spleen, skin, eyes, small bones of hands and feet, and salivary glands are most frequently affected.
4 All affected organs conform to a similar histological pattern.
5 Other changes present to a varying and inconstant degree include suppression or weakening of tuberculin and other intradermal responses, an increase in the serum gamma-globulins and a raised serum calcium level.
6 The Kveim reaction is positive in most active cases. This test is no longer available.

History [2–4]

The earliest description of a case which would now be categorized as sarcoidosis was probably Besnier's report in 1889 [5] of an association between reddish-blue lesions of the face and nose with swellings of the fingers [4]; the name 'lupus pernio' reflected his view that this might be a variant of lupus vulgaris. Tenneson in 1892 added the histological description [6]. In 1898 Hutchinson described two more cases of a skin eruption, probably sarcoidosis, to which he gave the name of 'Mortimer's malady' after one of his patients [7]. Boeck in 1899 [8] recorded his 'multiple benign sarkoid of the skin', and the current term 'sarcoidosis' stems from his misinterpretation of the histological changes. However, it was Boeck who first developed the concept of a disease involving both the skin and internal organs—a concept taken further by Schaumann [9], who again emphasized the generalized nature of the disease and showed that skin changes were not a necessary feature of it. The disease was further expanded by the inclusion of 'osteitis tuberculosa multiplex cystica' [10], uveoparotid fever [11], and pulmonary and other manifestations [12,13]. The introduction of mass radiography led to the recognition of hilar lymphadenopathy, with or without erythema nodosum, as an early benign form [14,15] and this has altered the whole concept

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

of the disease, which is now seen more often by chest and general physicians than by dermatologists.

References

1 Scadding JG, Mitchell DN, eds. *Sarcoidosis*, 2nd edn. London: Chapman & Hall, 1985: 1–12.
2 Epstein WL. What begot Boeck. *Arch Dermatol* 1982; **118**: 721–2.
3 Hutchinson J, ed. *Illustrations of Clinical Surgery*, Vol. 1. London: Churchill, 1878: 42–3.
4 Scadding JG. The eponymy of sarcoidosis. *J R Soc Med* 1981; **74**: 147–57.
5 Besnier E. Lupus pernio de la face: synovites fongueuses symétriques des extrémités supérieures. *Ann Dermatol Syphil* 1889; **10**: 333–6.
6 Tenneson M. Lupus pernio. *Bull Soc Fr Dermatol Syphil* 1892; **3**: 417–9.
7 Hutchinson J. Mortimer's malady (a form of lupus). *Arch Surg* 1898; **9**: 307–21.
8 Boeck C. Multiple benign sarkoid of the skin. *J Cutan Genitourin Dis* 1899; **17**: 543–50.
9 Schaumann J. Etude sur le lupus pernio et ses rapports avec les sarcoïdes et la tuberculose. *Ann Dermatol Syphil* 1917; **6**: 357–73.
10 Jungling O. Osteitis tuberculosa multiplex cystica. *Fortschr Röntgenstr* 1920–21; **27**: 375–83.
11 Heerfordt CF. Über eine Febrid Uveo-Parotidea Subchronica und der Glandula Parotis und der Uvea des Auges lokalisiert und häufig mit paresen cerebrospinaler Nerven kompliziert. *Arch Ophthalmol* 1909; **70**: 254–73.
12 Kusnitsky E, Bittord A. Boecksches Sarkoid mit Beteiligung innerer Organe. *Münch Med Wochenschr* 1915; **62**: 1349–53.
13 Leitner SJ, ed. *Der Morbus Besnier–Boeck–Schaumann*. Basle: Schwabe, 1949: 6.
14 James DG. Dermatological aspects of sarcoidosis. *Q J Med* 1959; **28**: 109–24.
15 Kerley P. The significance of the radiological manifestations of erythema nodosum. *Br J Radiol* 1942; **15**: 155–65.

Epidemiology [1]

The apparent increase in sarcoidosis over the last 40 years has been due partly to better detection, especially by mass radiography. However, even in countries with compulsory notification of the disease, there are bound to be many cases in an early, asymptomatic stage that remain undetected. For this reason, prevalence and incidence figures have to be interpreted with caution, though it is now clear that the disease has a worldwide distribution.

Sarcoidosis seems to be most prevalent (more than 10 per 100 000 population) in developed countries, but 'each succeeding world congress brings to the fore yet another country which has achieved manhood by joining in the world recognition of sarcoidosis' [2].

The danger of drawing inferences from unrepresentative collections of patients is well known [3], but certain groups do seem to be especially prone to sarcoidosis. It is, for example, more common in Afro-Caribbeans than in white inhabitants of the same area [4,5]. Other especially vulnerable groups include Puerto Ricans in New York and Irish immigrants to England. A useful study of 401 consecutive patients presenting to a district general hospital in the UK [6] gives a view of ethnic representation: Irish and Afro-Caribbean patients were disproportionately common in the material, but no attempt was made to assess incidence or prevalence in the population covered. Erythema nodosum was particularly common in the British and Irish; other skin manifestations occurred in 30 patients, 80% of whom were under 45 years of age.

Overall, sarcoidosis may be slightly more common in women than in men, and usually presents between the ages of 20 and 40 years. It is rare in young children [7]. The fact remains, however, that despite the voluminous data available, the factors influencing the prevalence and incidence of sarcoidosis remain obscure. Occupational, socioeconomic and climatic factors may be more important than have been recognized so far.

References

1 Sharma OP. Epidemiology of sarcoidosis: a report of the papers and posters presented at the Tenth International Conference on Sarcoidosis, Baltimore, USA, 1984. *Sarcoidosis* 1985; **2**: 9–11.
2 James DG. Sarcoidosis around the world. *Postgrad Med J* 1988; **64**: 177–9.
3 Scharkoff T. Apropos of the present level of epidemiologic knowledge on sarcoidosis. *Sarcoidosis* 1987; **4**: 152–4.
4 Benatar SR. A comparative study of sarcoidosis in white, black and coloured South Africans. In: Jones Williams W, Davies BH, eds. *Proceedings of the VIIIth International Conference on Sarcoidosis.* Cardiff: Alpha Omega, 1980: 508–13.
5 Sartwell PE. Racial differences in sarcoidosis. *Ann NY Acad Sci* 1976; **278**: 368–70.
6 Mikhail JR. Ethnicity and sarcoidosis. In: Jones Williams W, Davies BH, eds. *Proceedings of the VIIIth International Conference on Sarcoidosis.* Cardiff: Alpha Omega, 1980: 532–5.
7 O'Driscoll JB, Beck MH, Lendon M *et al.* Cutaneous presentation of sarcoid in an infant. *Clin Exp Dermatol* 1990; **15**: 60–2.

Aetiology

Despite intensive investigation, the cause of sarcoidosis remains unknown; it is not even clear whether the condition has only one or many causes. Most of the earlier theories have been discarded; others remain unproven. Evidence from genetic and environmental sources has been inconclusive, and immunological studies have, perhaps, raised more questions than they have solved. Speculations now lie in two main areas: infectious causes and genetic factors. Both may be interlinked.

Infectious agents

Many infectious agents have been put forward as the cause of sarcoidosis, but cultures are always negative and responses to treatment have not supported these beliefs. However, it remains possible that the disease represents an unusual host reaction to one or more infective agents—as yet unknown. Diagnostic confusion with tuberculosis led to speculation that *Mycobacterium tuberculosis*, perhaps in some transmuted form, might be responsible for the symptom complex of sarcoidosis. Recent evidence has lent some support for this. Serological studies have shown that patients with sarcoidosis have raised levels of antibodies to *M. paratuberculosis*, similar to those seen with Crohn's disease [1]. A polymerase chain reaction study revealed the presence of various subtypes of mycobacterial DNA (including *M. avium–intracellulare*) in 16 of 20 cases of cutaneous sarcoidosis [2]. In addition, it was reported that acid-fast cell-wall-deficient forms of *M. tuberculosis* have been grown from the blood of patients with active sarcoidosis [3]. However, a recent study failed to detect *M. tuberculosis* ribosomal RNA in fresh tissue specimens [4]. The significance of these findings is unclear at present, and the contribution of any mycobacteria to the pathogenesis of sarcoidosis is unknown. The onset of cutaneous sarcoidosis has been described following *M. marinum* infection [5]. It has been questioned as to whether *Propionibacterium acnes* may be involved in the aetiology of sarcoidosis, as *P. acnes* has been isolated from bronchial lavage in subjects with pulmonary sarcoidosis. However, it is known that *P. acnes* is a commensal in peripheral lung tissues and the findings do not appear to be specific for sarcoidosis [6].

Histoplasmosis and other fungi, which can produce granulomas exactly mimicking sarcoidosis, also have been suspected as possible causes, but their geographical limitations rule them out. Finally, it is always tempting to consider a viral cause for an obscure disease, but there is still no evidence to take this beyond mere speculation.

Genetic and familial factors

Familial sarcoidosis is well recognized and occurs more commonly than chance would predict. In ethnic groups known to have a high prevalence of sarcoidosis, the probability that an index case will have a sibling with sarcoidosis is about 10% [7]. In one study of 645 cases of sarcoidosis, 26 came from 12 families [8]. A literature search [9] found 182 affected sibling pairs; the excess of like-sex pairs was thought to reflect the effects of environmental exposure, which they are more likely to share than unlike-sex pairs. Far fewer examples of husband/wife sarcoidosis have been recorded [10] and this suggests that family aggregates occur either on a mainly genetic basis, or require a common environmental exposure during childhood. No consistent mode of inheritance has been found, although a recessive pattern may be more common [11].

Studies of human leukocyte antigens (HLAs) have not clarified the matter [12]. Differences between black and white subjects exist. Among black patients in the USA, sarcoidosis occurred significantly more frequently in individuals with BW15—but so did tuberculosis [13]. In London, white people with HLA-B8 were especially likely to have arthritis or erythema nodosum [14]. A recent Japanese study of 63 patients with sarcoidosis suggested that susceptibility for the disease may reside in the HLA-DRB1 locus, with resistance being conferred by the HLA-DRB1*1302 locus [15].

It seems likely that the HLA type can influence the pattern of the disease, rather than determine its occurrence. Recent studies suggest that the genes influencing clinical presentation of sarcoidosis in African Americans are different from those that underlie disease susceptibility [16].

Interferon-alpha (IFN-α) therapy

In more than 65 case reports [17], sarcoidosis has developed 15 days to 30 months after commencing IFN-α treatment. Some patients [18,19] had chronic myelogenous leukaemia and cutaneous lymphoma, conditions known to be associated with sarcoidosis on occasions. Others have had chronic hepatitis C [20]. Fifty per cent of cases have skin signs [19]. It is suggested that IFN-α might stimulate Th1 immune responses that are thought to be involved in sarcoidosis.

References

1 Reid JD, Chiodini RJ. Serologic reactivity against *Mycobacterium paratuberculosis* antigens in patients with sarcoidosis. *Sarcoidosis* 1993; **10**: 32–5.

2 Li N, Bajoghli A, Kubba A, Bhawan J. Identification of mycobacterial DNA in cutaneous lesions of sarcoidosis. *J Cutan Pathol* 1999; **26**: 271–8.

3 Almenoff PL, Johnson A, Lesser M, Mattman LH. Growth of acid-fast L forms from the blood of patients with sarcoidosis. *Thorax* 1996; **57**: 530–3.

4 Marcoval J, Benitez MA, Alcaide F, Mana J. Absence of ribosomal RNA of *Mycobacterium tuberculosis* complex in sarcoidosis. *Arch Dermatol* 2005; **141**: 57–9.

5 Gudit VS, Campbell SM, Gould D *et al.* Activation of cutaneous sarcoidosis following *Mycobacterium marinum* infection of the skin. *J Eur Acad Dermatol Venereol* 2000; **14**: 296–7.

6 Ishige I, Eishi Y, Takemura T *et al*. *Propionibacterium acnes* is the most common bacterium commensal in peripheral lung tissue and mediastinal lymph nodes from subjects without sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2005; **22**: 33–42.

7 Carmichael AK, Tan CY, Smith AG. Familial sarcoidosis: high ethnic prevalence. *Acta Derm Venereol (Stockh)* 1989; **69**: 531–2.

8 Turiaf J, Battesti JP, Jeanjean Y *et al*. Sarcoidose familiale, 26 cas dans 12 familles. *Nouv Presse Med* 1978; **7**: 913–5.

9 Grufferman S, Barton JW, Eby N. Increased sex concordance of sibling pairs with Behçet's disease, Hashimoto's disease, multiple sclerosis and sarcoidosis. *Am J Epidemiol* 1987; **126**: 365–9.

10 Gange RW. Sarcoidosis in husband and wife. *Clin Exp Dermatol* 1979; **4**: 107–9.

11 Luisetti M, Beretta A, Casali I. Genetic aspects in sarcoidosis. *Eur Respir J* 2000; **16**: 768–80.

12 Mehra NK, Bovornkitti S. HLA and sarcoidosis. *Sarcoidosis* 1988; **5**: 87–9.

13 Al-Arif L, Goldstein RA, Affronti LF *et al.* HLA antigens and susceptibility to tuberculosis in a black population. *Clin Res* 1977; **25**: 321.

14 Neville E, James DG, Brewerton DA *et al.* HLA antigens and clinical features of sarcoidosis. In: Jones Williams W, Davies BH, eds. *Proceedings of the VIIIth International Conference on Sarcoidosis.* Cardiff: Alpha Omega, 1980: 201–3.

15 Ishihara M, Ohno S, Ishida T *et al.* Molecular genetic studies of HLA class II alleles in sarcoidosis. *Tissue Antigens* 1994; **43**: 238–41.

16 Rybicki BA, Sinha R, Iyengar S *et al*. Genetic linkage analysis of sarcoidosis phenotypes: the sarcoidosis genetic analysis (SAGA) study. *Genes Immun* 2007; **8**: 379–86.

17 Alazemi S, Campos MA. Interferon-induced sarcoidosis. *Int J Clin Pract* 2006; **60**: 201–11.

18 Kidawada M, Ichinose Y, Kunisawa A *et al.* Sarcoidosis induced by interferon therapy for chronic myelogenous leukaemia. *Respirology* 1998; **3**: 41–4.

19 Schmuth M, Prior C, Illersperger B *et al.* Systemic sarcoidosis and cutaneous lymphoma: is the association fortuitous? *Br J Dermatol* 1999; **140**: 952–5.

20 Cogrel O, Doutre MS, Maliere V *et al.* Cutaneous sarcoidosis during interferon alfa and ribavirin treatment of hepatitis C virus infection. *Br J Dermatol* 2002; **146**: 320–4.

Histopathology [1]

The histological changes are similar in all organs affected and are remarkably constant. The essential feature is a monotonous repetition of aggregates of epithelioid cells with pale-staining nuclei, which form the characteristic, discrete sarcoidal granulomas (Fig. 61.1). Multinucleate giant cells are usually, but not invariably, present. An inconstant and variable rim of lymphoid cells surrounds the granuloma but this is never well developed—hence the term 'naked tubercle'. Caseation is absent, although an inconspicuous focus of fibrinoid necrosis or coagulation may occur within the granuloma. A fine reticulin network encircles the granuloma and may penetrate it (Fig. 61.2). The infiltrate tends to occur lower in the dermis than that of lupus vulgaris; in erythrodermic sarcoidosis, the granulomas are looser and less well defined. Epidermal changes can include hyperkeratosis, parakeratosis, acanthosis, atrophy and spongiosis: occasionally a lichenoid reaction is seen [2].

During the development of the granuloma, the loosely packed epithelioid cells of the early stage become more numerous and compact (their development is stimulated by IFN-γ produced by Th1 lymphocytes), and giant cells appear by their fusion. Reticulum appears and hyalinization becomes progressively more apparent as fibrosis gradually obliterates the characteristic features of the granulomas. This is the cause of the irreversible tissue scarring of the late stage of the disease. Polarizable foreign bodies were

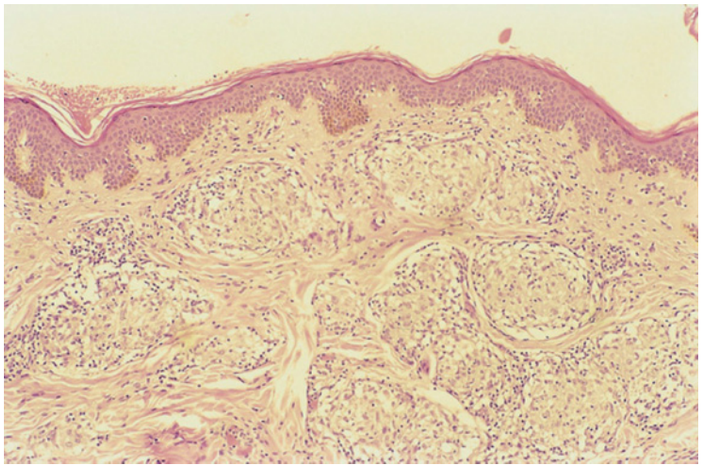


Fig. 61.1 Sarcoidosis. The epidermis is normal, while the superficial and mid-dermis contain numerous small granulomas without caseous necrosis. (Courtesy of Dr T.J. Stephenson, Royal Hallamshire Hospital, Sheffield, UK.)

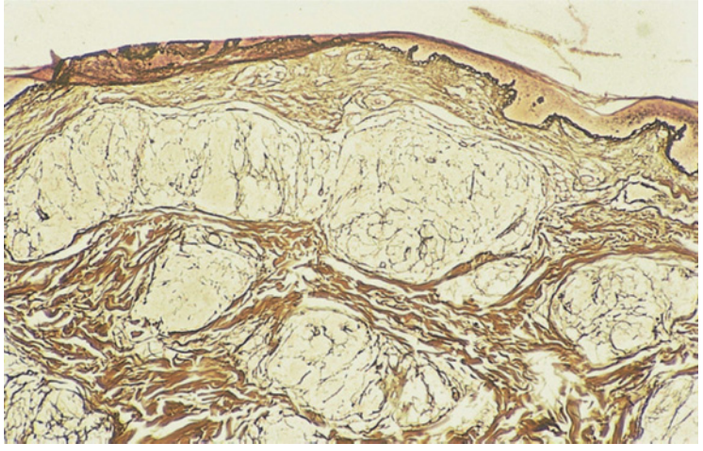


Fig. 61.2 Sarcoidosis. Reticulin stain of the section in Fig. 61.1, showing that the granulomas contain strands of staining reticulin, indicating that they lack caseous necrosis. (Courtesy of Dr T.J. Stephenson, Royal Hallamshire Hospital, Sheffield, UK.)

found in 12 of 50 cases of cutaneous sarcoidosis (all of whom also had systemic granulomatous disease), suggesting that, in some patients, a foreign body may be an inciting stimulus for granuloma formation [1,3].

Inclusion bodies

These are often found in the giant cells in sarcoidosis and other sarcoidal granulomas, but are not specific. Their numbers increase as lesions age. The following types are recognized.

1 *Schaumann (conchoid) bodies* (Fig. 61.3a) are basophilic concentric lamellar structures, 100 μm in diameter, composed of lipomucoglycoproteins impregnated with calcium and iron, and they show central, birefringent crystals.
2 *Asteroid (stellate) bodies* (Fig. 61.3b) are between 10 and 15 μm in size; their central core is surrounded by radiating spicules (the 'open umbrella frame'). They consist of collagen [4].

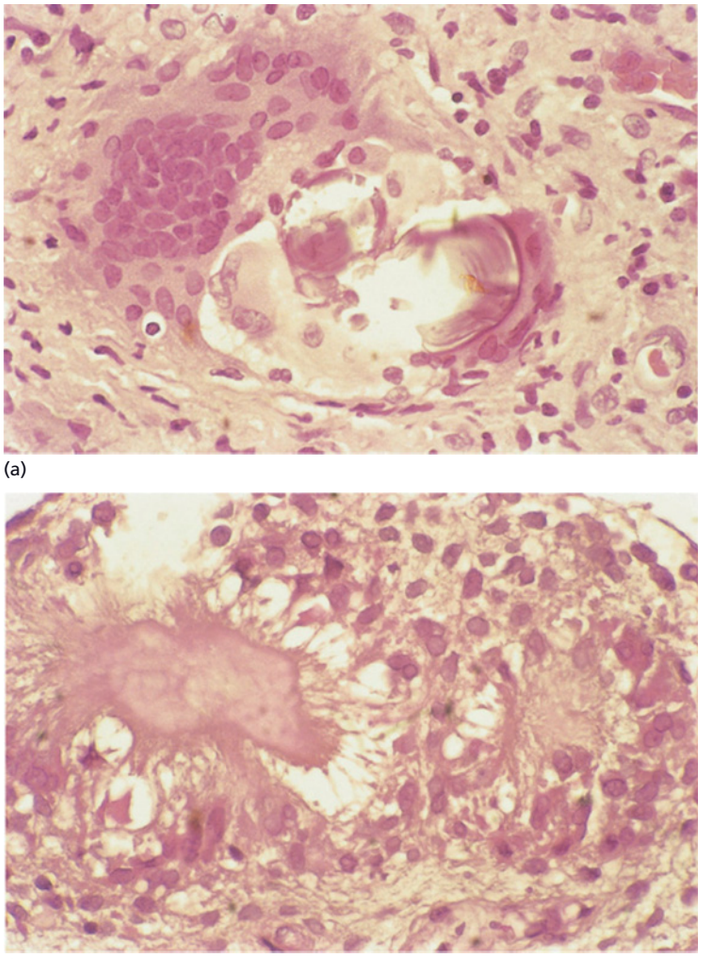


Fig. 61.3 (a) A Schaumann or conchoid body. These laminated calcospherites tend to fracture and to cause score marks. They stain basophilically. They are thought to arise from dystrophic calcification and it is suggested that they indicate chronicity. (b) High-power view of a granuloma in sarcoidosis showing an asteroid body within a giant cell. (Courtesy of Dr T.J. Stephenson, Royal Hallamshire Hospital, Sheffield, UK.)

Development of the granuloma [5]

Several strands of research have combined to increase our understanding of the complex cascade of cellular and mediator interactions involved in granuloma formation.

1 The technique of bronchoalveolar lavage, allowing easy harvesting of cells involved in the inflammatory process within the lungs.
2 Studies of evolving Kveim antigen-induced granulomas.
3 The use of monoclonal antibodies to characterize the cells found within the sarcoidal lesions.
4 The study of local immunological changes in cutaneous sarcoidosis, including the use of the techniques of molecular biology.

The architecture of a cutaneous sarcoid granuloma follows a pattern in which the centre consists of activated macrophages and epithelioid cells, surrounded by dendritic cells. Many activated CD4 helper/inducer T lymphocytes are present at the centre of the granuloma with a smaller population of CD8 suppressor/cytotoxic T lymphocytes at the periphery [6]. The antigen in

Table 61.1 Main histological features of sarcoidosis and tuberculosis.

Feature	Sarcoidosis	Tuberculosis
General structure	Monomorphic tubercles	Caseating tubercles
Form	Discrete, sharply defined 'naked tubercles'	Confluent, diffuse
Epithelioid cells	Large, grouped, predominant	Massed, irregular or at margin of caseation, less than 50%
Giant cells	Large, usually sparse Langhans' and foreign body cells	More numerous, Langhans' cells predominate
Lymphocytes	Sparse cuffing	More numerous and scattered
Inclusion bodies	Frequent	Occasional
Blood vessels	Usually normal or dilated	May show fibrinoid changes
Reticulin	Fine and abundant around tubercles	Destroyed
Caseation	No	Yes (but not lupus vulgaris)
Fibrinoid	Sometimes at centre of tubercle	Vascular and perivascular (late)
Healing process	Progressive hyalinization from periphery; gradual dissolution	Dense collagen mesh Retraction, fibrosis, calcification

sarcoidosis remains unknown, but the arrangements within the granuloma suggest an active immunological process. In addition, most workers have been able to demonstrate immune deposits within cutaneous granulomas, presumably as a consequence of the presence of circulating immune complexes known to occur in some patients with sarcoidosis. The most usual finding has been of immunoglobulin M (IgM) in the walls of dermal blood vessels or at the dermo-epidermal junction.

In the lung, an alveolitis precedes granuloma formation. Circulating blood monocytes appear in the lung, presumably in response to local chemotactic factors, and these aggregate into epithelioid cell granulomas. Pulmonary macrophages are induced by an unknown trigger mechanism to secrete interleukin-1 (IL-1), which is responsible for the migration of T lymphocytes to the site of disease activity. IL-1 also activates T cells and stimulates T-cell release of IL-2, which further amplifies local inflammatory activity. Activated T cells secrete chemotactic factors for monocytes and migration inhibitory factors. Fibrosis is enhanced by fibronectin and growth factors derived from alveolar macrophages.

Differential diagnosis

Typical tuberculosis is usually distinguishable by the histological features listed in Table 61.1. Sarcoidosis may be particularly hard to separate from lupus vulgaris if lymphocytes are more abundant than usual. In tuberculoid leprosy, epithelioid cells surround and are associated with the nerves, and there is more central necrosis. However, the histology of true sarcoidosis cannot always be distinguished from that of sarcoidal granulomas due to other causes—the key to the diagnosis of sarcoidosis lies in the uniformity of the histological changes in all affected organs.

Lupoid leishmaniasis, granulomatosis disciformis, rosacea and Crohn's disease may pose difficulties. Plasma cells and coagulation necrosis are features of syphilis. The granulomas of cat scratch fever are said to be larger than those of sarcoidosis. When sarcoid-like reactions occur in a scar, the possibility of a foreign-body reaction must be considered. Talc may be recognized by its refractile nature.

References

1 Ball NJ, Kho GT, Martinka M. The histopathologic spectrum of cutaneous sarcoidosis: a study of twenty-eight cases. *J Cutan Pathol* 2004; **31**: 160–8.

2 Okamoto H. Epidermal changes in cutaneous sarcoidosis. *Am J Dermatopathol* 1999; **21**: 229–33.

3 Kim YC, Triffet MK, Gibson LE. Foreign bodies in sarcoidosis. *Am J Dermatopathol* 2000; **22**: 408–12.

4 Azar HA, Lunardelli C. Collagen nature of asteroid bodies of giant cells in sarcoidosis. *Am J Pathol* 1959; **57**: 81–92.

5 Thomas PD, Hunninghake GW. Current concepts of the pathogenesis of sarcoidosis. *Am Rev Respir Dis* 1987; **135**: 747–60.

6 Fazel SB, Howie SE, Krajewski AS, Lamb D. Increased CD45RO expression on T lymphocytes in mediastinal lymph node and pulmonary lesions of patients with pulmonary sarcoidosis. *Clin Exp Immunol* 1994; **95**: 509–13.

Immunological aspects [1,2]

Important advances have been made in our understanding of the immunology of sarcoidosis in recent years; yet the paradox of the disease remains. How is it that granulomas can evolve, presumably as a consequence of a local T-cell-mediated immune response to antigenic insult (e.g. a superantigen or a particulate antigen ingested by macrophages), in a condition apparently characterized by reduced cell-mediated immunity? Even if the cutaneous anergy of sarcoidosis is partly explained by a movement of activated helper T cells to sites of disease activity, leaving in the circulation an excess of anergic suppressor cells, then it still has to be accepted that Kveim-induced granulomas, at least, can develop during a state of depressed immune responsiveness.

Cell-mediated immunity

Depression of cell-mediated immunity is the hallmark of sarcoidosis; indeed, the first immunological defect to be demonstrated was lack of reactivity to tuberculin. Sensitivity to tuberculin is depressed to a variable degree and becomes negative in about two-thirds of patients [3]. However, there is no absolute correlation between reactivity and the state of the disease, and some failure of immunological response may persist despite apparent clinical resolution. Later, this anergy was shown to extend to other intradermal allergens such as candidine, strepkokinase–streptodornase and trichophytin antigens [4]. The combination of a depressed reaction to mumps antigen with normal circulating antibody responses is characteristic of, but not specific for, sarcoidosis.

The levels of circulating T lymphocytes expressing the γ/δ T-cell marker are increased in sarcoidosis, and correlate with the defect in cellular immunity [5]. T-cell receptor gene studies from blood and sarcoid lesions are consistent with an oligoclonal expansion of T cells from an antigen-driven response [6]. The formation of sarcoid granulomas, like tuberculoid, is characterized by the expression of a Th1 cytokine profile, i.e. the T-lymphocytes secrete IL-2, IFN-γ, and tumour necrosis factor-α (TNF-α) [7]; there is inactivation of Th2 lymphocytes. Th2-type granulomas have a prevalence of eosinophils and are seen, for example, in schistosomiasis.

The onset of sarcoidosis in HIV-positive patients after commencement of highly active antiretroviral therapy has been reported in 11 cases, leading to the suggestion that immune reconstitution was involved [8]. However, it is significant that sarcoidosis has developed in some patients with low $CD4^+$ counts (126–1080, mean 373 cells/mm^3) [8].

Humoral immunity

All classes of serum immunoglobulins are increased. Activated T lymphocytes release B-cell growth factor and a B-cell differentiation factor, which together increase immunoglobulin production at the sites of disease. Significantly raised levels of circulating antibodies may be found to rubella, measles, herpes simplex, the Epstein–Barr virus and cytomegalovirus [9]. With regard to atopy as defined by personal history, skin prick tests and total IgE levels, a recent Turkish study of 41 patients with sarcoidosis found that only four (10%) were atopic compared with the expected 25% [10]. Interpretation of a small series such as this is difficult.

References

1 Baumer I, Zissel G, Sclaak M, Muller-Quernheim J. Th1/Th2 cell distribution in pulmonary sarcoidosis. *Am J Respir Cell Biol* 1997; **16**: 171–7.
2 Moller DR. Etiology of sarcoidosis. *Clin Chest Med* 1997; **18**: 695–706.
3 Siltzbach LE. Course and prognosis of sarcoidosis around the world. *Am J Med* 1974; **57**: 847–52.
4 Morell F, Levy G, Orriols R *et al*. Delayed cutaneous hypersensitivity tests and lymphopenia as activity makers in sarcoidosis. *Chest* 2002; **121**: 1239–44.
5 Nakata K, Sugie T, Cohen H *et al*. Expansion of circulating gamma delta T cells in active sarcoidosis closely correlates with defects in cellular immunity. *Clin Immunol Immunopathol* 1995; **74**: 217–22.
6 Moller DR. T-cell receptor genes in sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 1998; **15**: 158–64.
7 Agostini C, Semenzato G. Biology and immunology of the granuloma. In: James DG, Zumla A, eds. *The Granulomatous Disorders*. Cambridge: Cambridge University Press, 1999: 3–16.
8 Roustan G, Yebra M, Rodriguez-Braojos O *et al*. Cutaneous and pulmonary sarcoidosis in a patients with HIV after highly active antiretroviral therapy. *Int J Dermatol* 2007; **46**: 68–71.
9 Byrne EB, Evans AS, Fouts DW *et al*. A sero-epidemiological study of Epstein–Barr virus and other viral antigens in sarcoidosis. *Am J Epidemiol* 1973; **97**: 355–63.
10 Kokturk N, Han ER, Turktas H. Atopic status in patients with sarcoidosis. *Allergy Asthma Proc* 2005; **26**: 121–4.

General manifestations of sarcoidosis [1–3]

There is no disease with more varied manifestations. Its course is unpredictable. Several years may separate one manifestation from another, and any organ of the body may be involved. Symptoms result from invasion and replacement, pressure, anaemia, hypercalcaemia and fibrosis.

A full history must include details of race, area of residence, previous tuberculin testing and bacille Calmette–Guérin (BCG) vaccination, industrial exposure to beryllium and any previous disease, such as erythema nodosum, that may be related, even distantly.

Staging of the disease

Pulmonary sarcoidosis is classically divided into four stages on the basis of the chest radiograph:



Fig. 61.4 Chest radiograph showing bilateral hilar lymphadenopathy typical of sarcoidosis.

1 Stage 0: 5–10% of patients with sarcoidosis have a normal chest radiograph.
2 Stage I: bilateral hilar lymphadenopathy alone—seen on the presenting radiograph of 35–45% of patients (Fig. 61.4).
3 Stage II: bilateral hilar lymphadenopathy with parenchymal lung involvement of fine 'fluffy' or coarse type.
4 Stage III: late stage of pulmonary infiltration with fibrosis and pulmonary insufficiency.

Extrapulmonary manifestations of sarcoidosis cannot be staged in this way, although some generalizations are possible. Erythema nodosum is, *par excellence*, an early feature, occurring with stage I pulmonary disease, and carrying a good prognosis. Iridocyclitis and anterior uveitis are usually associated with the later stages and more persistent forms of the disease. An attempt can be made to classify sarcoidosis on the basis of the degree of internal involvement, and on the type of skin lesions, as 'early' (e.g. erythema nodosum and bilateral hilar lymphadenopathy), 'intermediate' (e.g. papular and nodular forms) and 'late' (e.g. plaque, subcutaneous or lupus pernio). However, this may be unreliable, as the prognosis mostly depends upon the extent of internal disease, and this may not become apparent until treatment is too late to be effective. Of this disease, it has been aptly said: 'One of its most singular details . . . is the frequency of its clinical silence'.

Systemic features

General symptoms

The onset is often marked by lethargy, loss of weight and general malaise, but may be symptomless. A dry cough, dyspnoea and chest pain are present in half the patients.

Bone and joint changes

An acute polyarthralgia may accompany erythema nodosum. A more chronic polyarthritis may appear later in the disease, chiefly

in Afro-Caribbeans. Bone changes, often asymptomatic, were found in 8% of 260 patients routinely examined radiologically [4]. Classically, they involve the small bones of the hands and feet in middle-aged women with lupus pernio. The most common change is lysis with bone cysts. The nasal bones, and occasionally the calvarium, may be involved in a way that mimics metastatic deposits [5].

Cardiac involvement [6]

Granulomatous infiltration of the conducting system may lead to heart block, papillary muscle dysfunction, congestive cardiac failure, pericarditis, chest pain, arrhythmias or even sudden death. The patients are often young, and the condition may be revealed only at post-mortem. Cardiac involvement is more common than was once believed, being found in 20–50% of autopsies on patients with sarcoid [6]. An abnormal electrocardiogram (ECG) was found in 14% of 401 patients examined routinely [4]. A careful cardiac examination should be a routine procedure in all cases of established sarcoidosis.

Muscle involvement

Polymyositis and myopathy occur rarely, and even muscle weakness and tenderness are uncommon despite the fact that random muscle biopsies in patients with sarcoidosis are positive in 50–80%. Tumour-type muscle sarcoidosis is very rare [7].

Nervous system involvement [8,9]

About 5% of patients with sarcoidosis have nervous system involvement and a wide variety of syndromes may result, including optic nerve lesions, cranial nerve palsies, meningoencephalitis, multiple sclerosis-like changes, peripheral neuropathy, mononeuritis multiplex and psychiatric changes. The facial nerve is frequently affected, with or without Heerfordt's syndrome (see below). Involvement of the hypothalamus or brain stem is rare but important. Sarcoidosis may also present as diabetes insipidus, hypopituitarism or endocrine abnormalities. The cerebrospinal fluid can show elevated protein and/or cells. Magnetic resonance imaging (MRI) may reveal abnormalities. Peripheral neuropathies often settle, but central nervous system manifestations seldom do so.

Ocular involvement [10]

The eyes are involved at some time in 25–50% of patients with sarcoidosis; eye disease is the first feature of sarcoidosis in about 10% of patients. The main types of ocular involvement are as follows:

1. *Uveitis*. Anterior and posterior uveitis are the most important and serious manifestations. Acute and chronic forms occur. The onset is usually insidious and 'mutton-fat' precipitates are found on the corneal epithelium. Iridocyclitis may be severe and recurrent. Complications include glaucoma, cataract and iris synechiae.
2. *Iris nodules*. These represent granulomatous infiltration of the stroma of the iris.
3. *Retinochoroiditis*. This usually occurs with chronic uveitis.
4. *Conjunctivitis*. Conjunctival nodules are common and are opaque, grey, slightly elevated lesions. 'Millet-seed' nodules may involve the eyelid margins. Biopsy will help to confirm the diagnosis of sarcoidosis; even 'blind' biopsies may reveal the disease.
5. *Lacrimal gland involvement*. Decreased lacrimal gland secretion is not uncommon (keratoconjunctivitis sicca is a presenting feature in about 10% of cases). Sarcoidosis is one cause of Mikulicz's syndrome (bilateral swelling of the lacrimal and salivary glands). Sjögren's syndrome can coexist with sarcoidosis and poses particular diagnostic problems.
6. *Optic nerves*. These may be involved as part of a widespread involvement of the central nervous system or as unilateral retrobulbar disease. Papilloedema, retrobulbar neuritis and optic atrophy may result.
7. *Orbital involvement*. This may cause unilateral proptosis.
8. *Other ocular syndromes*.
   (a) Lofgren's syndrome (erythema nodosum, bilateral hilar lymphadenopathy and acute iridocyclitis) is usually self-limiting.
   (b) Heerfordt's syndrome includes uveitis, parotid gland enlargement, fever and cranial nerve palsies, usually of the facial nerve.
   (c) Keratoconjunctivitis sicca with parotid and lacrimal gland enlargement.
   (d) Lupus pernio, chronic iridocyclitis, bone cysts and pulmonary fibrosis.

Pulmonary and upper respiratory changes [11]

Pulmonary changes dominate the later stages of the disease, and progressive diminution of respiratory function is the most common cause of incapacity. All patients with clinical or radiographic evidence of pulmonary involvement should be referred to a chest physician, who will decide on the need for and timing of treatment.

Upper respiratory involvement is often associated with chronic pulmonary disease and may be asymptomatic. Nasal stuffiness or blockage, with crusting and a nasal discharge, are common [12]. Cartilage or bone may be destroyed.

Renal involvement [13]

Symptoms are rare, but scattered granulomas can be found at autopsy in up to 40% of patients. Renal failure may be secondary to granulomatous invasion or to hypercalcaemia.

Reticuloendothelial system involvement

Lymph nodes are enlarged in about 50% of patients and may provide a convenient site for biopsy. An enlarged spleen can be felt in about 15% of cases [14]; hypersplenism may cause thrombocytopenia [15].

Involvement of the liver and other organs

It is evident that no organ is exempt from the occasional deposit of sarcoidal granuloma, and the dermatologist, as much as the general physician, should attempt to delineate the full extent of the disease in all patients. In no disease is it more important to look repeatedly 'under the skin' for other signs. Liver granulomas

are found in 63–87% of patients with sarcoidosis and mild elevation of the serum alkaline phosphatase or bilirubin is seen in up to 80% of cases [16], although the liver is only palpable in about 20% of patients.

Hypercalcaemia and hypercalciuria [17]

The frequency of hypercalcaemia varies greatly (from 2% to 40% in different series), but it is less common than hypercalciuria. In one series, 11% of 1760 sarcoid patients had hypercalcaemia, while 40% had hypercalciuria [18]. Persistent hypercalcaemia is manifest clinically as polyuria, nocturia or polydipsia in the absence of hypertension. It can cause nephrocalcinosis and renal failure. The details of the abnormal calcium metabolism in sarcoidosis are still debated: sarcoid granulomas can themselves produce 1,25-dihydroxyvitamin D [19], which may increase calcium absorption via the gut. Persistent hypercalcaemia is one indication for systemic steroid therapy.

Sarcoidosis and pregnancy

The condition may improve during pregnancy, only to relapse thereafter. Miscarriages and congenital abnormalities are not especially common [20].

References

1 Johns CJ, Scott PP, Schonfeld SA. Sarcoidosis. *Ann Rev Med* 1989; **40**: 353–71.
2 Baughman RP, Teirstein AS, Judson MA *et al.* Clinical characteristics of patients in a case control study of sarcoidosis. *Am J Respir Crit Care Med* 2001; **164**: 1885–9.
3 Zax RH, Callen JP. Sarcoidosis. *Dermatol Clin* 1989; **7**: 505–15.
4 Mickhail JR. Ethnicity and sarcoidosis. In: Jones Williams W, Davies BH, eds. *Proceedings of the VIIIth International Conference on Sarcoidosis.* Cardiff: Alpha Omega, 1980: 532–5.
5 Zimmermann R, Leeds NE. Calvarial and vertebral sarcoidosis. *Radiology* 1976; **119**: 384.
6 Veinot JP, Johnston B. Cardiac sarcoidosis: an occult cause of sudden death: a case report and literature review. *J Forensic Sci* 1998; **43**: 715–7.
7 Nemoto I, Shimizu T, Fujita Y *et al*. Tumour-like muscular sarcoidosis. *Clin Exper Dermatol* 2007; **32**: 298–300.
8 Stern BJ, Krumholtz A, Johns CJ *et al*. Sarcoidosis and its neurological manifestations. *Arch Neurol* 1985; **42**: 909–17.
9 Zajicek JP, Scolding NJ, Foster O *et al*. Central nervous system sarcoidosis: diagnosis and management. *Q J Med* 1999; **92**: 103–17.
10 Liggett PE. Ocular sarcoidosis. *Clin Dermatol* 1986; **4**: 129–35.
11 Bower JS. Pulmonary evaluation of patients presenting with dermatological manifestations of sarcoidosis. *Int J Dermatol* 1981; **20**: 385–9.
12 Wilson R, Lund V, Sweatman M *et al.* Upper respiratory tract involvement in sarcoidosis and its management. *Eur Respir J* 1988; **1**: 269–72.
13 Nuther RS, McCarron DA, Bennett WM. Renal manifestations of sarcoidosis. *Arch Intern Med* 1981; **141**: 643–7.
14 Selroos O. Sarcoidosis of the spleen. *Acta Med Scand* 1976; **200**: 337–40.
15 Larner AJ. Life threatening thrombocytopenia in sarcoidosis. *BMJ* 1990; **300**: 317–9.
16 Sharma OP, Izumi T. Sarcoidosis. In: Cannon GW, Zimmerman GA, eds. *The Lung in Rheumatic Diseases*. New York: Dekker, 1990: 433–59.
17 Fine RM. The mechanism of hypercalcaemia in sarcoidosis. *Int J Dermatol* 1987; **26**: 22–3.
18 James DG, Williams WG, eds. *Sarcoidosis*. Philadelphia: Saunders, 1985: 163.
19 Adams JS, Gacad MA. Characterisation of the 1-α hydroxylation of vitamin D3 by cultured alveolar macrophages from patients with sarcoidosis. *J Exp Med* 1985; **161**: 755–65.
20 Weinberger SE, Weiss ST, Cohen WR *et al*. Pregnancy and the lung. *Am Rev Respir Dis* 1980; **121**: 559–81.

Sarcoidosis of the skin

Between 20% and 35% of patients with systemic sarcoidosis have skin lesions [1], but cutaneous sarcoidosis can also occur without systemic disease. Significant pulmonary disease may be silent [2]. In six of 13 patients with cutaneous sarcoidosis, but without a past history of sarcoidosis, no other systemic signs of the disease were detected during prolonged follow-up [3]; in another series of 188 patients with cutaneous sarcoid, 50 had no systemic involvement [4]. Finally, the extent of any cutaneous lesions does not correlate with the extent of systemic disease.

References

1 Kerdel FA, Moschella SL. Sarcoidosis; an updated review. *J Am Acad Dermatol* 1984; **11**: 1–19.
2 Collins P, Evans AT, Gray W, Levison DA. Pulmonary sarcoidosis presenting as a granulomatous tattoo reaction. *Br J Dermatol* 1994; **130**: 658–62.
3 Hanno R, Needelman A, Eiferman RA *et al.* Cutaneous sarcoidal granulomas and the development of systemic sarcoidosis. *Arch Dermatol* 1981; **117**: 203–7.
4 Veien NK, Stahl D, Brodthagen H. Cutaneous sarcoidosis in Caucasians. *J Am Acad Dermatol* 1987; **16**: 534–40.

Classification. This has been made more difficult by the use of eponyms that are no longer appropriate and which should now be discarded. A simple morphological classification is shown in Table 61.2, but more than one type of lesion may exist at the same time. The differences between the main patterns lie in the manner and extent of the involvement of the skin or subcutaneous tissues.

The specific lesions of sarcoidosis take the form of granulomatous infiltrates: erythema nodosum stands out from these as a non-specific accompaniment of early sarcoidosis without the characteristic sarcoidal granulomas.

Clinical features. The features of the specific cutaneous lesions arise from a dense accumulation of epithelioid cell granulomas in the dermis. In the deep nodular and infiltrative types, the

Table 61.2 Classification of sarcoidosis of the skin.

Type of cutaneous lesions	Stage of disease
Erythema nodosum	Acute ('benign')
Erythematous and erythematopapular	Acute and subacute
'Scar sarcoidosis'	Acute and subacute
Papular ('small nodular')	Acute and subacute
(Boeck) lichenoid variety	
Erythrodermic (Schaumann)	Subacute and chronic
Nodular	Subacute and chronic
Annular (or circinate)	
Angiolupoid (Brocq–Pautrier)	
Subcutaneous	
Plaque	Chronic
Lupus pernio	
Miscellaneous	Usually chronic
Ulcerative, psoriasiform, palmoplantar, ungual, mucosal	
Sarcoidosis of black Africans	

subcutaneous tissue is involved by extension. The lesions of sarcoidosis are generally recognizable as nodules or plaques with a greater degree of infiltration than would be expected from their surface appearance. Their colour ranges from yellow ochre to the livid violaceous hue which is most marked in lupus pernio. On diascopy, a pale yellowish-grey colour remains; sometimes, individual nodules are apparent. There is a tendency to form annular lesions. The epidermis is rarely affected, except for a light scaling, but some degree of vascular dilatation is frequent, especially in angiolupoid sarcoid. Scarring is unusual except in the papular and annular forms.

There is no characteristic distribution, though the small nodular type tends to involve the extensor aspects of the limbs, and rarely the trunk, while the large nodular type affects predominantly the face, hands and trunk. The manifestations of the disease vary from country to country: mucosal involvement, for instance, is rare in France but common in Scandinavia.

Classical forms

Angiolupoid form

A rare but characteristic variety. It affects women predominantly, almost always occurring at the side of the bridge of the nose towards the corner of the eye, below the inner edge of the eyebrow, or on the adjacent area of cheek. There are seldom more than two tumours. They are soft and hemispherical, with a well-marked orange-red or reddish-brown colour and of a more livid hue than other forms. This is due to the marked telangiectatic component, which alters the normal grey-yellow appearance on diascopy. There is little tendency to spontaneous resolution.

Annular forms (Fig. 61.5)

Annular lesions were seen in 32 of 188 white subjects with cutaneous sarcoid lesions [1] and occurred mainly in the chronic stage. They are formed by peripheral evolution and central clearing. They occur particularly on the forehead, face and neck. The central area may become depigmented and scarred. Ulceration is rare. The lesions may resemble annular necrobiosis of the scalp [2], but can be differentiated histologically. Diffuse papular forms may also show an annular configuration.

Erythema nodosum

Sarcoidosis is but one of the many causes of erythema nodosum—a subject dealt with in detail in Chapter 50. It occurs most often in the spring, in young women, and signals an early and usually 'benign' variety of sarcoidosis, with bilateral hilar lymphadenopathy and a tendency to involute spontaneously. Most cases resolve completely within 2 years.

The frequency with which erythema nodosum is reported in sarcoidosis varies from series to series, no doubt depending upon the selection of material. This was well shown in a worldwide survey of sarcoidosis [3] in which erythema nodosum pinpointed the onset of the disease in 600 (17%) of 3676 patients. The distribution was uneven between the countries studied, the condition affecting one-third of British patients and being less evident elsewhere. In a Danish series [1], 25 out of 188 patients with cutaneous sarcoidosis had erythema nodosum which tended to affect younger patients (mean age 30 years) than did infiltrative sarcoidal lesions (mean age 48 years).



Fig. 61.5 Annular sarcoidosis of the face.

Lupus pernio [4]

This is a relatively common skin manifestation of sarcoidosis. In a Danish series of 188 patients with cutaneous sarcoidosis, 22 had lupus pernio [1]. In contrast, in a Turkish series of 516 patients with various skin lesions only 14 had lupus pernio [4]. Lupus pernio tends to affect older patients, is twice as common in women as in men, and is more common in Afro-Caribbeans than in their white counterparts.

Large bluish-red and dusky violaceous infiltrated nodules and plaques occur more or less symmetrically on the nose (Fig. 61.6), cheeks, ears, fingers, hands and toes (Fig. 61.7). The lesions may feel soft, doughy or indurated. Discrete nodules with a typical appearance on diascopy may be found at the edge sometimes. The surface is often glistening, and the epidermis stretched, with large pilosebaceous follicles. Ulceration rarely occurs in the skin, gross mutilation, as in lupus vulgaris, never. Involved ear lobes may become massive ('turkey ears'). Other chronic skin lesions, including plaques and subcutaneous nodules, may accompany lupus pernio. Scarring alopecia may occur on the scalp.

Nasal involvement is associated with swelling, ulceration or crusting of the nasal vestibule, and patients may present with difficulty in breathing. Submucous resection carries the risk of nasal septal perforation and collapse of the nose.

Lupus pernio tends to be associated particularly with other forms of chronic fibrotic sarcoidosis, including upper respiratory

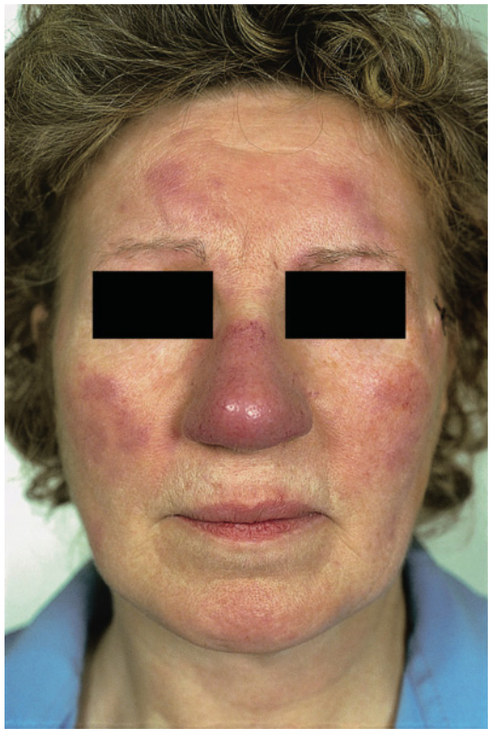


Fig. 61.6 Lupus pernio. (Courtesy of Dr F.A. Ive, Dryburn Hospital, Durham, UK.)

tract sarcoidosis, bone cysts, lacrimal gland and renal sarcoidosis, and with hyperglobulinaemia and hypercalcaemia [4].

Lupus pernio tends to persist: lesions of more than 2 years standing seldom resolve [4]. The facial disfigurement it causes may lead to emotional scarring, which may justify aggressive lines of therapy including plastic surgery [5]. Topical camouflage is an important adjunct to this therapy.

Maculopapular and erythematous forms (Fig. 61.8)

This is separate from the papular form (see below). Transient 'prodromal' maculopapular eruptions were noted in the early stages of sarcoidosis in no less than 8 of 33 patients who showed cutaneous signs of the disease [6] and are apparently seen most commonly by chest and general physicians. Diffuse forms of papular sarcoidosis do occur but are uncommon. Even less common are ill-defined patches of a lavender colour, sometimes slightly scaly or lightly infiltrated. On the face, these simulate rosacea. Sand-like lupoid grains are sometimes seen on diascopy, but more frequently there is a yellow discoloration. Transient parotid swellings and hepatosplenomegaly may be seen [7]. Such cases pursue a long course, fluctuating in severity. Pruritic maculopapular lesions have been described [8].

Nodular forms (Fig. 61.9)

Here the lesions are larger than 5 mm, usually single or relatively few, and remain circumscribed. Red or yellowish-red at first, becoming violaceous or purplish-brown later, they are soft or firm, round and most often affect the proximal parts of the limbs, the trunk and the face. Dilated vessels may be seen on the surface of the lesions which are extremely indolent. As they involute, the centre may become depressed, and the lesions are eventually replaced by brownish telangiectatic marks, or yellowish-white atrophic and fibrotic patches.

Papular (small nodular type) (Figs 61.10 & 61.11)

The papules are hemispherical and vary in size from 1 to 5 mm. Orange or yellowish-brown at first, they later become brownish-red or violaceous, painless and torpid. Only a few lesions or several hundred may appear, arising in crops but eventually becoming stationary. They particularly affect the face (especially in Afro-Caribbeans) and extensor aspects of the limbs, but rarely the trunk or mucous membranes.

On diascopy, the lupoid grains are of a more opaque appearance and colour than those of lupus vulgaris, resembling grains of sand. If probed with a needle they feel firm. When lesions disappear they often leave a pale, yellowish-white or telangiectatic scar. Occasionally they become confluent, merging into an erythematous plaque (Fig. 61.12). A ringed nummular configuration was present in the second of Schaumann's four cases [9].

Widely disseminated, hard, shotty, subcutaneous papules can appear with the granulomas lying in the deep subcutaneous tissues and fascial planes. A lichenoid variety is discussed separately on p. 61.14.

In general, the papular type carries a more favourable prognosis than do other types of infiltration. Confirmatory biopsy of other organs should be carried out, although this form may occur without other manifestations of the disease.

Histopathology. The infiltrate is in the high and mid-dermis. It may be hard to distinguish from acne agminata in which, however, caseation can be seen.

Differential diagnosis. Lupus erythematosus can be mimicked. Papular forms of secondary syphilis are distinguished by the course and associated features of this disease. Occasionally, acne agminata (Chapter 43) presents difficulties.

Plaque form (Fig. 61.13)

It is convenient to keep this form distinct. It involves chiefly the limbs, shoulders, buttocks and thighs. The lesions are characteristically diffuse, and extend further than is apparent on the surface. They may form placards of an irregular shape with more superficial nodules superimposed, sometimes having a crescentic or serpiginous outline resembling tertiary syphilis. On the legs, they may closely resemble necrobiosis lipoidica (Fig. 61.14). They are very persistent.

Scar sarcoidosis (Fig. 61.15)

Sarcoidosis appearing in a scar may be the only cutaneous sign of the disease, and is therefore of diagnostic importance. Scar involvement was seen in 26 of 188 white patients with sarcoidosis [1], and may represent a form of Koebner phenomenon. Long-standing scars, often on the knees, become inflamed and infiltrated, giving rise to typical purplish-red lesions which turn brown as they fade. There is some resemblance to a keloid, but the lesions do not itch. This form of sarcoidosis is as common in men as in women [10].



(a)



(b)



(c)



(d)

Fig. 61.7 (a) Typical fusiform appearance of the fingers from bone involvement. (Courtesy of Dr F.A. Ive, Dryburn Hospital, Durham, UK.) (b) Sarcoidosis of the terminal phalanx of the toe. (Courtesy of Dr F.A. Ive, Dryburn Hospital, Durham, UK.) (c) Sarcoidosis of the terminal phalanx involving the nail. (d) Radiograph of the hand in a patient with finger involvement by sarcoidosis, showing lucent areas in the bones of the phalanges.



Fig. 61.8 Confluent scaly macules of the trunk due to sarcoidosis. (Courtesy of the late Dr R.H. Champion, Addenbrooke's Hospital, Cambridge, UK.)



(a)



(b)

Fig. 61.9 (a) Nodular sarcoidosis on the upper back; (b) close-up of the same patient, showing the grouped nodules. (Courtesy of Dr D.A. Burns, Leicester, UK.)



Fig. 61.10 Papular sarcoid of the buttocks. (Courtesy of Professor J.A.A. Hunter, Royal Infirmary, Edinburgh, UK.)

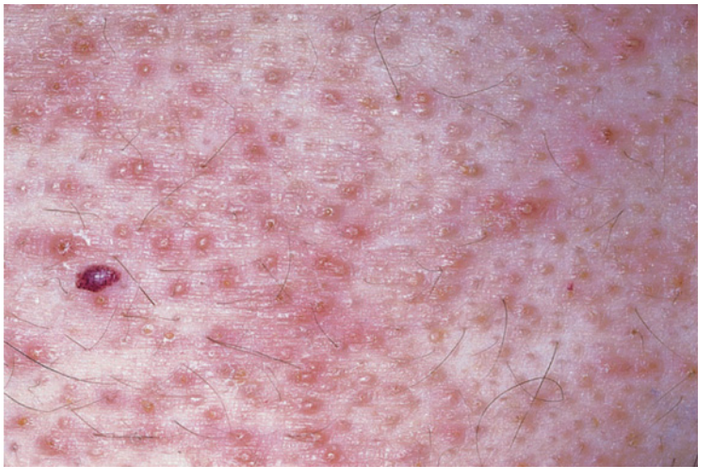


Fig. 61.11 Micropapular sarcoidosis. (Courtesy of the late Dr R.H. Champion, Addenbrooke's Hospital, Cambridge, UK.)



Fig. 61.12 Plaque-type sarcoidosis affecting the face in a black African. (Courtesy of Dr J.E. Bothwell, Barnsley District General Hospital, Barnsley, UK.)

Scar sarcoidosis occurs in three situations:

1 In the acute eruptive phase, following erythema nodosum, or in the scars of biopsies taken at that time.
2 At any later stage of the disease, sometimes moving in parallel with pulmonary changes and slightly in advance of iritis [6]. Exacerbation of the systemic disease may be preceded by this warning sign.



Fig. 61.13 Sarcoidosis. Lesions of the plaque type are present on the upper back. (Reproduced with permission from Elsevier, Ltd.)



Fig. 61.14 Sarcoidosis of the plaque type on the shins, resembling necrobiosis lipoidica.

3 At inoculation sites—for example, after venepuncture [11], BCG or tuberculin tests. The involvement of tribal scarification marks is the commonest presentation of sarcoidosis in Nigeria [12,13].

The histology is typical. Confirmatory evidence of sarcoidosis should be sought (by chest radiograph, and biopsy from other organs), as local sarcoidal reactions may occur in scars contaminated with silica. A silica granuloma in a scar may, rarely, progress into scar sarcoidosis [14]. Tattoos may also show sarcoidal reactions.



Fig. 61.15 Scar sarcoidosis on the presternal area. (Courtesy of Dr D.A. Burns, Leicester, UK.)

Subcutaneous sarcoidosis [15]

It seems likely that the first case report of subcutaneous sarcoidosis was indeed that of Darier and Roussy in 1904 [16], although they considered that their patient had tuberculosis. However, the term 'sarcoid of Darier–Roussy' has been used so often for granulomatous conditions other than sarcoidosis that it has become devalued and should be discarded.

Nevertheless, subcutaneous sarcoidosis does exist, although it is rare, especially in white people. It takes the form of tender or painless persistent nodules, most often on the extremities of middle-aged patients, usually women [17]. Systemic involvement is usually present, sometimes as hilar lymphadenopathy [18], although usually not severe and not associated with chronic fibrotic disease [15]. Spontaneous resolution can occur [15].

Histopathology. The infiltrate is naturally greater in nodular lesions but remains circumscribed. In the subcutaneous form, the sarcoid process may at first be located in the septa and at the periphery of the fat lobules, eventually replacing the lobules with granulomatous nodules. In the angio-lupoid form, vascular dilatation is prominent.

Differential diagnosis. Lymphocytoma cutis can be separated by its histology. Four other diseases cause particular difficulty, and serial sectioning and cultures of biopsy material may be necessary. They are as follows:

1 *Tuberculoid leprosy*. Distinguished by loss of thermal appreciation and of the histamine flare, a positive Mitsuda test and invasion of nerves.
2 *Lupus vulgaris*. In its exuberant form, this can scarcely be distinguished, although vitropression is said to reveal more translucent nodules of an 'apple jelly' rather than a greyish-yellow colour. Ulceration and scarring ultimately occur. Histology helps, but does not decide: a therapeutic test with antituberculous drugs does.
3 *Lupoid leishmaniasis*. The same difficulties exist clinically and histologically. Leishman–Donovan bodies are rarely found. The Kveim test is negative.

4 *Local sarcoid reaction*. By definition, this is confined to local areas or sites of trauma. There are no other signs of sarcoidosis, and the Kveim test is negative.

References

1 Veien NK, Stahl D, Brodthagen H. Cutaneous sarcoidosis in Caucasians. *J Am Acad Dermatol* 1987; **16**: 534–40.
2 Dowling GB, Wilson Jones E. Atypical (annular) necrobiosis lipoidica of the face and scalp. *Dermatologica* 1967; **135**: 11–26.
3 James DG, Siltzbach TE. A world-wide review of sarcoidosis. *Ann NY Acad Sci* 1976; **278**: 321–34.
4 Yanardag H, Pamuk ON, Pamuk GE. Lupus pernio in sarcoidosis: clinical features and treatment outcomes of 14 patients. *J Clin Rheumatol* 2003; **9**: 72–6.
5 Shaw M, Black MM, David PKB. Disfiguring lupus pernio successfully treated with plastic surgery. *Clin Exp Dermatol* 1984; **9**: 614–7.
6 James DG. Dermatological aspects of sarcoidosis. *Q J Med* 1959; **28**: 109–24.
7 Barnes HM, Calnan CD. Erythematous sarcoid. *Proc R Soc Med* 1975; **68**: 651–2.
8 Fong YW, Sharma OP. Pruritic maculopapular skin lesions in sarcoidosis. *Arch Dermatol* 1975; **111**: 362–4.
9 Schaumann J. Lymphogranulomatosis benigna in the light of prolonged clinical observations and autopsy findings. *Br J Dermatol* 1936; **48**: 399–446.
10 Scadding JG, Mitchell DN, eds. *Sarcoidosis*, 2nd edn. London: Chapman & Hall, 1985: 181–206.
11 Burgdorf WH, Hoxtell EO, Bart BJ. Sarcoid granulomas in venepuncture sites. *Cutis* 1979; **24**: 52–3.
12 Alabi GO, George AO. Cutaneous sarcoidosis and tribal scarifications in West Africa. *Int J Dermatol* 1990; **28**: 29–31.
13 Olumide YM, Bandele EO, Elesha SO. Cutaneous sarcoidosis in Nigeria. *J Am Acad Dermatol* 1989; **21**: 1222–4.
14 Rowland-Payne CME, Meyrick-Thomas RH, Black MM. From silica granuloma to scar sarcoidosis. *Clin Exp Dermatol* 1983; **8**: 171–5.
15 Marcoval J, Mana J, Moreno A, Peyri J. Subcutaneous sarcoidosis-clinicopathological study of 10 cases. *Br J Dermatol* 2005; **153**: 790–4.
16 Darier J, Roussy G. Un cas de tumeurs benignes multiples (sarcoides sous-cutanées ou tuberculides nodulaires hypodermiques). *Ann Dermatol Syphil* 1904; **5**: 144–9.
17 Ahmed I, Harshad SR. Subcutaneous sarcoidosis: is it a specific subset of cutaneous sarcoidosis frequently associated with systemic disease? *J Am Acad Dermatol* 2006; **54**: 55–60.
18 Shidrawi RG, Paradinas F, Murray-Lyon IM. Sarcoidosis presenting as multiple subcutaneous nodules. *Clin Exp Dermatol* 1994; **19**: 356–8.

Unusual and atypical forms

In addition to the 'classical' forms of the disease described above, a wide variety of unusual forms have been recorded, particularly in Afro-Caribbeans.

Alopecia

Alopecia of the scalp due to sarcoidosis is well recognized [1,2]. Alopecia of the shin has been a presenting sign of the disease [3]. Sarcoidal granulomas were found on histology, and the Kveim test was positive.

Atrophic forms

The rare atrophic types of cutaneous sarcoidosis may be localized to the legs [4,5] or generalized [6,7]. It is usually accompanied by ulceration.

Erythrodermic sarcoidosis

This is extremely rare. Red scaling patches extend and merge into infiltrated brownish-red sheets. Lymphadenopathy is usually pronounced. During resolution, typical papules and nodules may separate from the plaque, which gradually loses its infiltration and disappears. A reticulate yellowish stippling may be seen as it resolves. One unique case was associated with periarteritis and ulceration [8]; in another patient, a 6-year-old boy, the eruption resembled pityriasis rubra pilaris [9].

Hypopigmentation

Macular hypopigmentation or hypopigmented areas around a central indurated lesion were first recorded in eight of 145 patients (mostly Afro-Caribbeans) with sarcoidosis [10]. There have been several subsequent reports [11–13]. Lesions vary from 0.2 cm to 1 cm in diameter and occur mainly on the limbs [13]. They may be tender, but are not anaesthetic, and may be the first sign of the disease [14].

Histologically, epithelioid cell granulomas are usually present in the dermis; occasionally the changes are non-specific [11,14]. The melanocytes show degenerative changes but electron-microscopy studies have not been helpful [11]. The differential diagnosis includes leprosy, post-inflammatory hypopigmentation, idiopathic guttate hypomelanosis and pityriasis lichenoides chronica [15]. The condition does not respond to corticosteroids [11], but may repigment after prolonged psoralen and UVA (PUVA) therapy [14].

Ichthyosiform sarcoidosis [16–18]

More than 19 cases of ichthyosiform sarcoidosis have been reported [18]. It usually occurs on the lower legs as large, thick, polygonal adherent scales that may or may not overlie dark red papules and nodules. Biopsy reveals epidermal changes consistent with ichthyosis vulgaris, as well as non-caseating epithelioid granulomas in the dermis, even in the absence of clinically detectable dermal abnormality. Almost all patients with ichthyosiform sarcoidosis have systemic involvement. In patients with acquired ichthyosis, biopsy may be worthwhile to exclude occult sarcoidosis.

Lichenoid forms (Fig. 61.16)

The lichenoid variety of sarcoidosis consists of pinhead-sized papules, skin-coloured, erythematous or yellowish in hue, that can be follicular or closely grouped in round or oval clusters and show slight scaling [18]. It constitutes 1–2% of skin sarcoidosis and may pose difficulties in diagnosis [19]. Although the lichenoid form resembles lichen planus or lichen scrofulosorum, the tuberculin test is negative, the course is indolent and the histology characteristic. Arguments have, however, been adduced in favour in a mycobacterial cause, because of atypical features that are sometimes present [20].

Miscellaneous forms

Many have been described, including the following: pseudotumoral [21], psoriasiform [22,23] and pruriginous varieties [24]; lupus erythematosus-like and lupoid forms; a bizarre polymorphous light eruption type; perifollicular pustules and papules widely scattered over the body; keratotic lesions of the palms simulating psoriasis or syphilis [25], thrombophlebitis [26]; vulval disease [27]; and breast mass [28,29]. Hyperpigmentation may occur, particularly in Afro-Caribbeans [10]. Oedema of the lower leg, usually unilateral, is an uncommon manifestation of sarcoidosis [30]. It may occur due to vascular or lymphatic compression



Fig. 61.16 Lichenoid sarcoidosis. (Courtesy of Pro. Dr P. Frosch, Dortmund, Germany)

from enlarged inguinal or parailiac lymph nodes, or from direct granulomatous infiltration of the skin. Calcinosis with subcutaneous plaques was present in one unusual patient [31]. Pain after alcohol or showering has also been described.

References

1 Maurice PDL, Goolamali SK. Sarcoidosis of the scalp presenting as scarring alopecia. *Br J Dermatol* 1988; **119**(Suppl. 33): 116–7.
2 Golitz LE, Shapiro L, Hurwitz E *et al.* Cicatricial alopecia of sarcoidosis. *Arch Dermatol* 1973; **107**: 758–60.
3 Felix RH. Alopecia of the shin. *Br J Dermatol* 1983; **109**(Suppl. 24): 66–7.
4 Basex A, Dupré A, Christol B *et al.* Sarcoidosis with atrophic lesions and ulcers, and the presence in some sarcoid granulomata of orceinophil fibres. *Br J Dermatol* 1970; **83**: 255–62.
5 Yoo SS, Mimouni D, Nikolskaia OV *et al.* Clinicopathologic features of ulcerative-atrophic sarcoidosis. *Int J Dermatol* 2004; **43**: 108–12.
6 Chevrant-Breton J, Revillon L, Pony JC *et al.* Sarcoidose à manifestations cutanées extensives ulcéreuses et atrophiantes (de type Pick–Herxheimer) avec complications cardiaques et musculaires: à propos d'un cas. *Ann Dermatol Vénéréol* 1977; **104**: 805–10.
7 Hruza GJ, Kerdel FA. Generalised atrophic sarcoidosis with ulcerations. *Arch Dermatol* 1986; **122**: 320–2.
8 Simpson JR. Sarcoidosis with erythroderma and ulceration. *Br J Dermatol* 1963; **75**: 193–8.
9 Morrison JG. Sarcoidosis in a child presenting with keratotic spines and palmar pits. *Br J Dermatol* 1976; **95**: 93–7.
10 Maycock RL, Bertrand P, Morrison CE *et al.* Manifestations of sarcoidosis. *Am Med* 1963; **35**: 67–89.
11 Clayton R, Breathnach A, Martin B *et al.* Hypopigmented sarcoidosis in the Negro: report of eight cases with ultrastructural observations. *Br J Dermatol* 1977; **96**: 119–25.
12 Cornelius CE, Stein KM, Hansaw WJ *et al.* Hypopigmentation and sarcoidosis. *Arch Dermatol* 1973; **108**: 249–51.
13 Thomas MRH, McKee PH, Black MM. Hypopigmented sarcoidosis. *J R Soc Med* 1981; **74**: 921–3.
14 Patterson JW, Fitzwater E. Treatment of hypopigmented sarcoidosis with 8-methoxypsoralen and long wave ultraviolet light. *Int J Dermatol* 1982; **21**: 476–80.
15 Clayton R, Warin A. Pityriasis lichenoides chronica presenting as hypopigmentation. *Br J Dermatol* 1979; **100**: 297–302.
16 Banse-Kupin L, Pelachyk JM. Ichthyosiform sarcoidosis: report of two cases and review of the literature. *J Am Acad Dermatol* 1987; **17**: 616–20.
17 Cather JC, Cohen PR. Ichthyosiform sarcoidosis. *J Am Acad Dermatol* 1999; **40**: 862–5.
18 Seo SK, Yeum JS, Suh JC, Na GY. Lichenoid sarcoidosis in a 3-year-old girl. *Pediatr Dermatol* 2001; **18**: 384–7.
19 Pinkus H. How useful is biopsy in a lichenoid eruption? *Cutis* 1977; **20**: 651–8.
20 Ridgway HA, Ryan T. Is micropapular sarcoidosis tuberculosis? *J R Soc Med* 1981; **74**: 140–4.
21 Bélaich S, Blanchet P, Crickx B *et al.* Sarcoidose pseudo-tumorale dermo-hypodermique du menton. *Ann Dermatol Vénéréol* 1982; **109**: 741–2.
22 Burgoyne JS, Wood MG. Psoriasiform sarcoidosis. *Arch Dermatol* 1972; **106**: 896–8.
23 Fulton RA. Psoriasiform sarcoidosis. *Br J Dermatol* 1984; **111**(Suppl. 26): 52.
24 Degos R, ed. *Dermatologie.* Paris: Flammarion, 1981: 533.
25 Scadding JG, Mitchell DN, eds. *Sarcoidosis*, 2nd edn. London: Chapman & Hall, 1985: 195–6.
26 Rowland Payne CME, McGibbon DH. Sarcoidosis presenting as widespread thrombophlebitis. *Clin Exp Dermatol* 1985; **10**: 592–4.
27 Tatnall FM, Barnes HM, Sarkany I. Sarcoidosis of the vulva. *Clin Exp Dermatol* 1985; **10**: 384–5.
28 Ojeda H, Sardi A, Totoonchie A. Sarcoidosis of the breast: implications for the general surgeon. *Am Surg* 2000; **66**: 1144–8.
29 Mingins C, Williams MR, Cox NH. Subcutaneous sarcoidosis mimicking breast carcinoma. *Br J Dermatol* 2002; **146**: 924–5.
30 Hoover RD Jr, Stricklin G, Curry TW, Carmichael LC. Unilateral lower limb edema caused by infiltrative sarcoidosis. *J Am Acad Dermatol* 1994; **30**: 498–500.
31 Kroll JJ, Shapiro L, Kaplan BS *et al.* Subcutaneous sarcoidosis with calcification. *Arch Dermatol* 1972; **106**: 894–5.

Mucosal involvement

Buccal lesions or tongue involvement are occasionally found when sought [1]. The nasal mucosa is often affected in lupus pernio [2,3] and is a convenient site for biopsy. Difficulty in breathing, or a purulent catarrh, may be the presenting symptom. Yellowish-brown nodules or a diffuse infiltration with crusting occurs [4]. The nasal bones may be involved; or the nasal cartilage may collapse [5]. Nodules with a hyperpigmented halo, diffuse pale-yellow plaques or ulceration may be found on the buccal mucosa, palate, larynx or tongue.

Nail involvement [6]

This is rare, affecting only one in 400 patients with sarcoidosis in one series [7]. Changes recorded have included the following: thickening, opacity, fragility, layering, convexity, longitudinal ridging, pitting, atrophy, nail loss, pterygium and red or brown discoloration of the nail beds. Surrounding skin changes may be minimal, but in almost every case the nail abnormalities will be accompanied by cysts in the bone of the underlying terminal phalanx and a chronic disease course, often with lupus pernio.

Sarcoidosis in black Africans and African Americans (Fig. 61.17)

The lesions are often exuberant and bizarre, and the skin is especially affected, although erythema nodosum is uncommon [8,9]. Psoriasiform or lupus erythematosus-like lesions [10], verrucous

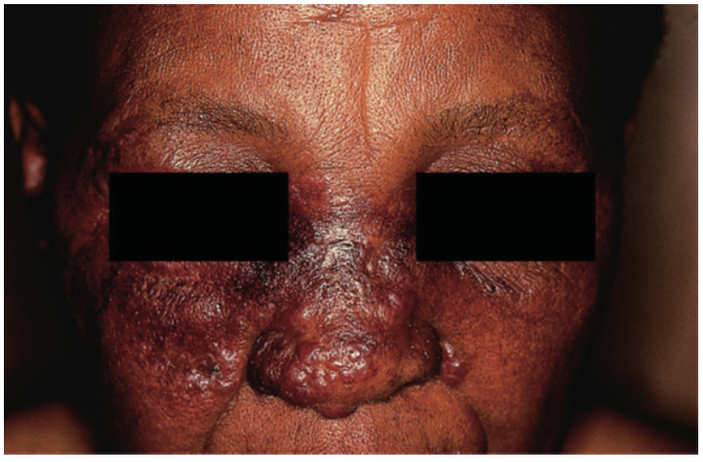


Fig. 61.17 Sarcoidosis in a black African, showing typical verrucous changes. (Courtesy of Dr J.E. Bothwell, Barnsley District General Hospital, Barnsley, UK.)



Fig. 61.18 Extensive ulceration of the foot and ankle due to sarcoidosis. (Courtesy of the late Dr R.H. Champion, Addenbrooke's Hospital, Cambridge, UK.)

and keloid-like forms [11,12], 'atypical' plaques or nodules [13], ulcerative lesions resembling papulonecrotic tuberculides [11], giant nodular forms and other atypical lesions occur, with more typical manifestations elsewhere. Shiny, waxy papules are a particular presentation [8]. The histological features may be equivocal and tuberculosis is a common cause of death. When the lesions are annular, histoplasmosis must be excluded [14].

Small ulcerating nodules, sometimes associated with deep, softer non-ulcerative lesions, have been described [10]. The histology is that of sarcoidosis but the infiltrate is diffuse, fibroblasts are numerous and the vessel walls in the subcutis are thickened.

Skin lesions in children [15,16]

Sarcoidosis in children is uncommon; a presentation with erythema nodosum is especially so. In one series of 48 children [15], 15 had erythema nodosum, 6 had other skin lesions, 12 developed uveitis or iridocyclitis and 2 had arthritis. Though papular forms of skin sarcoidosis are seen in older children, younger ones may present with uveitis or keratitis, progressive joint disease and skin lesions consisting of maculopapules, reddish-brown confluent plaques or eczema-like lesions [17,18]. Other reported cases have shown unusual features: follicular [19], miliary [20] or erythrodermic lesions with keratotic pitting [21]. The chest radiograph is often normal. The severity of eye or joint involvement may justify corticosteroid therapy, often for several years, despite the risks at this early stage.

The Blau syndrome, in which asymptomatic, red–brown papules (showing granulomas in histology) on the face, trunk and limbs are associated with arthritis and ocular disease in a child, has recently been identified, with mutations in the *NOD2* gene [23].

Ulcerated sarcoidosis [22,23] (Fig. 61.18)

This is a rare presentation: more than 35 cases have now been described, most of which were reported individually [24,25]. It usually occurs in women and black people. Ulcers develop most often on the legs [26] and may be punched-out and apparently appearing *de novo*, or arising on existing nodules and plaques, or, rarely, on extensive atrophic areas [27]. The possibility of necrobiosis lipoidica should be kept in mind, particularly in patients with diabetes [25]. The distribution of the ulcers may be unusual: a flexural distribution in one patient resembled that of metastatic Crohn's disease [28]. The granuloma may be of necrotizing type, with caseation or minimal fibrinoid necrosis [29]. True primary vasculitic changes are usually absent.

Verrucose forms [30]

Papular lesions may progress to crusted verrucose and sometimes ulcerative lesions [31], which may mimic halogen eruptions, fungal infections or tuberculosis.

References

1 Nagata Y, Kanekura T, Kawabata H *et al.* A case of sarcoidosis of the tongue. *J Dermatol* 1999; **26**: 666–70.
2 Holmes R, Black MM. Sarcoidosis (lupus pernio) with involvement of the nasal bones. *Br J Dermatol* 1981; **105**: 35–7.
3 Neville E, Mills RGS, Jash DK *et al.* Sarcoidosis of the upper respiratory tract and its association with lupus pernio. *Thorax* 1976; **31**: 660–4.
4 Degos R, ed. *Dermatologie.* Paris: Flammarion, 1981: 533.
5 Allen BR. Sarcoid of nose with collapse of nasal cartilage. *Br J Dermatol* 1978; **99** (Suppl. 16): 54–5.
6 Cox NH, Gawkrodger DJ. Nail dystrophy in chronic sarcoidosis. *Br J Dermatol* 1988; **118**: 697–701.
7 Patel KB, Sharma OP. Nails in sarcoidosis: response to treatment. *Arch Dermatol* 1983; **119**: 277–8.
8 Minus HR, Grimes PE. Cutaneous manifestations of sarcoidosis in blacks. *Cutis* 1983; **32**: 361–3.
9 Jacyk WK. Cutaneous sarcoidosis in black South Africans. *Int J Dermatol* 1999; **38**: 841–5.
10 Irgang S. Ulcerative cutaneous lesions in sarcoidosis. *Br J Dermatol* 1955; **67**: 255–60.
11 Klauder JV, Weidman FD. Multiple sarcoid-like granulomas of the skin of undetermined nature. *Arch Dermatol Syphilol* 1926; **13**: 675–6.
12 Schmunes E, Lantis LR, Hurley H. Verrucose sarcoidosis. *Arch Dermatol* 1970; **102**: 665–9.
13 Cronin E. Skin changes in sarcoidosis. *Postgrad Med J* 1970; **46**: 507–9.
14 Lucas AD. Cutaneous manifestations of histoplasmosis. *Br J Dermatol* 1970; **82**: 435–47.
15 Hoffmann AL, Milman N, Byg KE. Childhood sarcoidosis in Denmark 1979–94: incidence, clinical features and laboratory results at presentation in 48 children. *Acta Paediatr* 2004; **93**: 30–6.

16 Kendig EL. The clinical picture of sarcoidosis in children. *Paediatrics* 1974; **54**: 289–92.
17 Rasmussen JE. Sarcoidosis in young children. *J Am Acad Dermatol* 1981; **5**: 566–70.
18 O'Driscoll JB, Beck MH, Lendon M *et al.* Cutaneous presentation of sarcoidosis in an infant. *Clin Exp Dermatol* 1990; **15**: 60–2.
19 Appleyard WJ. Sarcoidosis in a young child. *Proc R Soc Med* 1976; **69**: 345–6.
20 Siltzbach LE, James DG, Neville E *et al.* Course and prognosis of sarcoidosis around the world. *Am J Med* 1974; **57**: 847–52.
21 Morrison JG. Sarcoidosis in a child presenting as an erythroderma with keratotic spines and palmar pits. *Br J Dermatol* 1976; **95**: 93–7.
22 Verdegem TD, Sharma OP. Cutaneous ulcers in sarcoidosis. *Arch Dermatol* 1987; **123**: 1531–4.
23 Schaffer JV, Vhandra P, Keegan BR *et al*. Widespread granulomatous dermatitis of infancy: an early sign of Blau syndrome. *Arch Dermatol* 2007; **143**: 386–91.
24 Albertini JG, Tyler W, Miller OF 3rd. Ulcerative sarcoidosis: case report and review of the literature. *Arch Dermatol* 1997; **133**: 215–9.
25 Gupta AK, Haberman HF, From GLA *et al.* Sarcoidosis with extensive cutaneous ulceration. *Dermatologica* 1987; **174**: 135–9.
26 Schwartz RA, Robertson DB, McNutt NS. Generalised ulcerative sarcoidosis. *Arch Dermatol* 1982; **118**: 931–3.
27 Hruza GJ, Kerdel FA. Generalized atrophic sarcoidosis with ulcerations. *Arch Dermatol* 1986; **122**: 320–2.
28 Neill SM, Smith NP, Eady RAJ. Ulcerative sarcoidosis: a rare manifestation of a common disease. *Clin Exp Dermatol* 1984; **9**: 277–9.
29 Herzlinger DC. Verrucous ulcerative lesions in sarcoidosis: an unusual clinical presentation. *Cutis* 1979; **23**: 569–72.
30 Schmunes E, Lantis LR, Hurley HJ. Verrucose sarcoidosis. *Arch Dermatol* 1970; **102**: 665–9.
31 Golitz LE, Shapiro L, Hurwitz E *et al.* Cicatricial alopecia of sarcoidosis. *Arch Dermatol* 1973; **107**: 758–60.

Associated diseases

Some associated diseases are understandable against the background of depressed immunological responses; some are due to a simple blocking of the activity of an organ by granulomatous infiltration, and others are uncommon and poorly understood associations. In a disease as common as sarcoidosis, coincidental associations can be expected from time to time.

Infections

A critical review of previous reports of invasive fungal infections such as cryptococcosis [1] has suggested that in many of these the entire cause of the granulomatous illness was infection, rather than sarcoidosis complicated by infection. In the series which accompanied the review, 122 patients with sarcoidosis were, in fact, found to be remarkably free of infections: three had *Aspergillus* mycetomas in cystic areas in the lung and another also had pulmonary tuberculosis, but the only extrathoracic manifestation was one case of disseminated herpes zoster. Patients with sarcoidosis, however, are prone to extensive and stubborn wart virus infections, despite an unusually high prevalence of circulating antibodies to wart antigen [2].

Immunologically mediated conditions

In a series of 190 female patients with sarcoidosis, four had hyperthyroidism and four had Hashimoto's thyroiditis with antibodies [3]. Another patient in the same series had myxoedema and Addison's disease. Chronic urticaria may occur more frequently than would be expected by chance [4]. At least 14 cases of associated sarcoidosis and connective tissue disorders have been described [5].

Effects of infiltration

Granulomas, especially in the pituitary or thyroid gland, may cause endocrine disease. Invasion of the thyroid may be without effect or, if massive, can cause hypothyroidism [6]. Cushing's syndrome and diabetes insipidus, secondary to involvement of the pituitary, have been reported. The list of such cases may be extended to cover most endocrine diseases.

Vasculitis with sarcoidosis

There are occasional but well-authenticated reports of cutaneous vasculitis occurring in the course of sarcoidosis, usually early in the disease. In a series of six patients, five of them children, the vasculitis was associated with systemic illness including fever, lymphadenopathy, musculoskeletal and eye disease, and systemic steroids were given [7]. Three of these patients, all African Americans, had large-vessel disease on angiography. Erythema nodosum itself may be regarded as a form of vasculitis. Skin biopsy may show foci of epithelioid cell granulomas centred on damaged vessels [8]. An apparently unique case of leukocytoclastic vasculitis with epithelioid cell granulomas has been described [9] and annular forms documented [10]. The occurrence of vasculitis fits with the presence of circulating immune complexes in the early stages of sarcoidosis.

Malignancy

An analysis of 131 cases of coincident sarcoidosis and malignancy suggests an increased risk of developing lymphoproliferative disease [11]. The relationship between sarcoidosis and solid tumours was less clear-cut, but most marked with carcinoma of the cervix, lung, testis and uterus [12]. Sarcoidosis may precede the development of a lymphoma (the 'sarcoidosis–lymphoma syndrome') by 18 months to 28 years [13]. All types of lymphoma may develop [12], and there is an increased incidence of thyroid cancer and leukaemia. Five patients with sarcoidosis developed multiple myeloma (four several years later and one at the time of diagnosis of the sarcoidosis) [14].

Necrobiosis lipoidica and granuloma annulare

There have been several reports of patients with sarcoidosis and necrobiosis lipoidica [15,16], and with sarcoidosis and granuloma annulare [17]. To complete the circle of association, patients with both necrobiosis lipoidica and granuloma annulare have also been described. In one African American woman with pulmonary sarcoid, fresh lesions of histologically typical granuloma annulare were adjacent to histologically classic sarcoid papules, suggesting that the former progressed to the latter [18].

These associations may be fortuitous, but histological overlap between sarcoidosis and necrobiosis may occasionally be seen [19]. Granuloma annulare is important in the differential diagnosis of sarcoidosis, as is necrobiosis, particularly of the scalp and face. Granuloma annulare shares some aspects of collagen metabolism with sarcoidosis [20], but in granuloma annulare the Kveim test is negative [21,22].

Other associations

Associations with psoriasis and gout [23], pyoderma gangrenosum [24,25] and secondary syphilis [26] have been reported, but seem likely to have been coincidental. Two Kveim-positive patients were found to have primary biliary cirrhosis [27], and a sarcoidal plaque on the face has been described in a woman with primary biliary cirrhosis [28]. Two cases of porphyria cutanea tarda have also been reported [29,30].

References

1 Winterbauer RH, Kraemer KG. The infectious complications of sarcoidosis. *Arch Intern Med* 1976; **136**: 1356–62.
2 Morison WL. Wart immunity, autoantibodies and Australia antigen in sarcoidosis. *Br J Dermatol* 1975; **93**: 717–8.
3 Karlish AJ, MacGregor GA. Sarcoidosis, thyroiditis and Addison's disease. *Lancet* 1970; **ii**: 330–3.
4 Doeglas HMG. *Chronic urticaria.* [thesis]. Druk Rijkstr Niemager, Groningen: 1975: 86.
5 Aaronson PA, Fretzin DF, Morgan NE. A unique case of sarcoidosis with coexistent collagen vascular disease. *J Am Acad Dermatol* 1985; **13**: 886–91.
6 Cohen JD. Sarcoidosis and thyrotoxicosis. *Proc R Soc Med* 1974; **67**: 220–1.
7 Fernandes SR, Singsen BH, Hoffman GS. Sarcoidosis and systemic vasculitis. *Semin Arthritis Rheum* 2000; **30**: 33–46.
8 Kennedy C. Sarcoidosis with cutaneous vasculitis. *Br J Dermatol* 1979; **101**: 47–9.
9 Chouvet B, Del Grande P, Enay G *et al.* Vascularité leucocytoclastique et sarcoidose. *Ann Dermatol Vénéréol* 1980; **107**: 279–84.
10 Branford WA, Farr PM, Porter DI. Annular vasculitis of the head and neck in a patient with sarcoidosis. *Br J Dermatol* 1982; **106**: 713–6.
11 Brincker H. Coexistence of sarcoidosis and malignant disease: causality or coincidence? *Sarcoidosis* 1989; **6**: 31–43.
12 Cohen PR, Kurzrock R. Sarcoidosis and malignancy. *Clin Dermatol* 2007; **25**: 326–33.
13 Karakantza M, Matutes E, MacLennan K *et al.* Association between sarcoidosis and lymphoma revisited. *J Clin Pathol* 1996; **49**: 208–12.
14 Pettersson T, Koivunen E, Ilvonen M *et al.* Sarcoidosis and multiple myeloma: an association. *BMJ* 1987; **295**: 958.
15 Monk B, Du Vivier A. Necrobiosis lipoidica and sarcoidosis. *Clin Exp Dermatol* 1987; **12**: 294–5.
16 Igawa K, Maruyama R, Satoh T *et al.* Necrobiosis lipoidica-like skin lesions in systemic sarcoidosis. *J Dermatol* 1998; **25**: 653–6.
17 Umbert P, Winkelmann RK. Granuloma annulare and sarcoidosis. *Br J Dermatol* 1977; **77**: 481–6.
18 Lupton JR, Figueroa P, Berberian BJ, Sulica VI. Can granuloma annulare evolve into cutaneous sarcoidosis? *Cutis* 2000; **66**: 390–2.
19 Mehregan A, Pinkus H. Necrobiosis lipoidica with sarcoid reaction. *Arch Dermatol* 1961; **83**: 143–5.
20 Oikarinen A, Kinnunen T, Kallioinen M. Biochemical and immunohistochemical comparison of collagen in granuloma annulare and skin sarcoidosis. *Acta Derm Venereol (Stockh)* 1989; **69**: 277–83.
21 Harrison P, Shuster S. Granuloma annulare and sarcoidosis. *Br J Dermatol* 1979; **100**: 231.
22 Rhodes EL. Granuloma annulare and sarcoidosis. *Br J Dermatol* 1979; **100**: 231.
23 Ecks L. Über das gemeinsame Vorkommen von Psoriasis, Sarkoidose und Gicht. *Hautarzt* 1975; **26**: 357–61.
24 Powell FC, Schroeter AL, Su WPD *et al.* Pyoderma gangrenosum and sarcoidosis. *Arch Dermatol* 1984; **120**: 959–60.
25 Hardwick N, Cerio R. Superficial granulomatous pyoderma: a report of two cases. *Br J Dermatol* 1993; **129**: 718–22.
26 Laugier P. Secondary syphilis and sarcoidosis. *Arch Dermatol* 1976; **112**: 261.
27 Karlish AJ, Thompson RPH, Williams R. A case of sarcoidosis and primary binary cirrhosis. *Lancet* 1969; **ii**: 599.
28 Harrington AC, Fitzpatrick JE. Cutaneous sarcoidal granulomas in a patient with primary biliary cirrhosis. *Cutis* 1992; **49**: 271–4.
29 Lockman DS. Porphyria cutanea tarda and sarcoidosis. *J Am Acad Dermatol* 1980; **2**: 62–5.
30 Mann RJ, Harman RRM. Porphyria cutanea tarda and sarcoidosis. *Clin Exp Dermatol* 1982; **7**: 619–23.

Course and prognosis [1]

The prognosis of sarcoidosis is difficult to assess because of its frequent 'clinical silence' and the uncertainty of its onset. Several attempts have been made to list favourable and unfavourable factors [2–4], most of which have been mentioned elsewhere in this chapter. Table 61.3 is an attempt to summarize the course of sarcoidosis. The prognosis is generally better in females, in those with less severe pulmonary disease at the onset, and in patients with a positive tuberculin test and normal globulin levels [4]. HLA-B8 may be associated with a tendency to spontaneous resolution [5]. In the African American, the course may be fulminant.

Table 61.3 The course of sarcoidosis.

Prognosis	Stage	Cardinal features*	Unfavourable events
? Abortive cases, or may be absent 60% subside in 6–18 months	Prodromal	Malaise, fatigue, fever, depression, polyarthralgia	—
	Acute	*Erythema nodosum*, *scar sarcoidosis*, *erythematopapular rashes*, polyarthralgia, iridocyclitis, lymphadenopathy	? Sudden cardiac death
	Subacute	*Papular*, *nodular* or *scar*, pulmonary changes, lymphadenopathy, recurrent iritis, parotitis, spleen, liver	May be cardiac death
Prolonged intermission or resolution	Intermittent Chronic		
Gradual, often slow	Progressive	*Lupus pernio*, *erythrodermic*, bone cysts, cataracts, hypersplenism	Blindness
Irreversible but often extremely slow and patient survives, though disabled	Fibrotic regression	Progressive pulmonary fibrosis, nephritis, nephrosis, cataracts, glaucoma	Blindness, death
	Functional failure	Emphysema, cor pulmonale, nephrolithiasis, renal failure, tuberculosis	Death

* Skin signs are in *italics*.

About 60% of patients with stage I pulmonary disease will have recovered within 2 years [6,7]. The presence of erythema nodosum does not alter the prognosis. In the classic forms of the disease, the prognosis is quite different: only a small proportion of those in pulmonary stage II and beyond resolve spontaneously [7]. Morbidity from blindness, pulmonary disease, renal failure and the cosmetic and social effects of a disfiguring skin lesion are the not inconsiderable burdens of a disease that follows a relentless course of smouldering activity [8]. Despite corticosteroid therapy, half the patients continue to have abnormal respiratory function.

Most types of cutaneous sarcoidosis occur in the subacute and chronic stages, and their course is usually prolonged. Many papules and nodules tend to resolve within months or years, but plaques are even more resistant. Lupus pernio is especially persistent and is often accompanied by the involvement of other organs, further modifying the prognosis.

Mortality in sarcoidosis [9] has been estimated at 3–6% [4,7]. However, this may ignore undiagnosed deaths from cardiac involvement. Renal involvement is also a potential cause of death as, rarely, is progressive pulmonary disease.

References

1 Turiaf J, Battesti JP, Sharma OP *et al*. Course and prognosis of sarcoidosis around the world. *Am J Med* 1974; **57**: 847–52.

2 Deremee A, Zinsmeister AR. *Proceedings of the IXth International Conference on Sarcoidosis*. Paris: Pergamon, 1983: 457.

3 von Wurm K, ed. *Sarkoidose*. Stuttgart: Thième, 1983: 228.

4 von Wurm K, Rosner R. Prognosis of chronic sarcoidosis. *Ann NY Acad Sci* 1976; **278**: 732–5.

5 Smith MJ, Turton CW, Mitchell DN. Association of HLA-B8 with spontaneous resolution in sarcoidosis. *Thorax* 1981; **36**: 296–8.

6 James DC. The early diagnosis of sarcoidosis. *Postgrad Med J* 1958; **34**: 240–4.

7 Siltzbach LE, James DC, Neville E *et al*. Course and prognosis of sarcoidosis around the world. *Am J Med* 1974; **57**: 847–52.

8 Hanno R, Callen JP. Sarcoidosis: a disorder with prominent cutaneous features, and their inter-relationship with systemic disease. *Med Clin North Am* 1980; **64**: 847–66.

9 Huang CT. Mortality in sarcoidosis: a changing pattern of causes of death. *Eur J Respir Dis* 1981; **62**: 231–8.

Investigations

The most important single criterion for the diagnosis of sarcoidosis is the finding of typical granulomas histologically [1], but the need for histological support varies with the pattern of clinical features. For example, in the UK, patients with erythema nodosum and bilateral hilar gland enlargement may not require biopsy, although this is necessary in other forms of the disease. Other investigations may add weight to the diagnosis, and may be useful in monitoring the activity of the disease.

Biopsy

The involvement of several organs will allow the clinician to select the biopsy site best suited to the individual patient. The dermatologist has the advantage of dealing with a site easily accessible for biopsy, but it may still be necessary to confirm the presence of sarcoidosis as opposed to a sarcoidal reaction, and biopsies from other organs are then needed. In one series [2] involving 292 biopsies from 10 sites, 87% were positive, but biopsies from the skin proved less reliable than those from lymph nodes, parotid gland or nasal mucosa. Scars that become infiltrated provide acceptable histological evidence of sarcoidosis. A mucosal biopsy is an alternative to skin biopsy in lupus pernio. A conjunctival biopsy should be considered, and may be positive even if no obvious lesions can be seen [3], as may a biopsy of the lower lip [4].

A range of techniques is now available to obtain biopsy material from other areas. These include the removal of epitrochlear or scalene lymph nodes, mediastinoscopy with mediastinal node biopsy, liver biopsy, gastrocnemius muscle biopsy (even when there are no muscle symptoms) [5], and transbronchial lung biopsy or mediastinal node biopsy through a flexible fibrescope [6]. The last may be the most helpful and least disturbing for patients with suspected systemic sarcoidosis and intrathoracic manifestations, but carries some risk of pneumothorax. Bronchoalveolar lavage in patients with active pulmonary involvement shows an increase in the number of helper T lymphocytes present, but this is not specific for sarcoidosis.

Kveim test [7,8]

Fifty years after Kveim described it, the test that bears his name is still something of an immunological puzzle. Until relatively recently, it was a simple and useful way of supporting a diagnosis of sarcoidosis. The Kveim test is no longer available due to the infective risk of injecting human tissue, but nevertheless details of the test are of interest and will be outlined.

The test depends upon the ability of sarcoidal tissue, usually from the spleen of an affected individual, to evoke epithelioid cell granulomas like those of sarcoidosis when injected intradermally into a patient with sarcoidosis. Positive results were found in a high proportion of patients with active early disease, but became less common in chronic disease.

The technique used is important. An easily relocated site, usually on the forearms, was injected intradermally with 0.1–0.2 mL of shaken antigen using a 1-mL tuberculin syringe and a narrow-gauge needle. In a positive reaction, a papule usually appeared within 2–3 weeks and slowly increased in size. It was best excised at 6 weeks for histology.

A positive result was the unequivocal presence of an epithelioid granuloma, exactly mimicking the natural disease, though usually less profuse. Histological interpretation was difficult in 10–20% of responses; epithelioid cells may be diffusely scattered in the dermis or granulomatous aggregates of histiocytes may not be arranged in the usual circumscribed foci of an epithelioid granuloma. The occasional presence of birefringent particles can make interpretation more complicated. False-positive foreign body-type reactions had to be disregarded.

An adequate Kveim antigen had to be sensitive enough to detect at least 60% of cases of active sarcoidosis and specific enough to exclude all but 2–3% of non-sarcoid cases [9]. To achieve this, the antigen had to be validated by extensive tests on normal subjects and on patients with other conditions, such as Crohn's disease, in which false-positive reactions are known to occur [10]. The safety of the Kveim test with regard to it being free from infective agents, for example human immunodeficiency virus, cannot be guaranteed and hence it is no longer available. The active principle in Kveim material was heat stable, and also stable on storage, though

some loss of sensitivity was observed over a period of years [11]. The active material is particulate and probably lies within the membrane-containing elements of the sarcoidal tissue [12], although its exact constitution has not been established. It is not known whether the active ingredient is an antigen derived from the aetiological agent of sarcoidosis or whether a positive Kveim response is a manifestation of host predisposition to form granulomas on antigenic stimulation. These two hypotheses are not mutually exclusive.

Other investigations

A chest radiograph should be taken in all cases, no matter what the clinical presentation. Hand radiographs show cystic changes only in chronic disease, and usually only when there are clinical abnormalities in the fingers. Sputum should be examined and cultured for acid-fast bacilli, and a weak or negative tuberculin response may add weight to the diagnosis of sarcoidosis. An ECG is needed to exclude cardiac involvement. Pulmonary function tests may also be indicated. High-resolution computed tomography of the chest is helpful to define lung field involvement.

The erythrocyte sedimentation rate (ESR) is usually raised in active phases, and a rise in the ESR 6–8 weeks after the onset of erythema nodosum may indicate lung involvement [13]. Slight anaemia, neutropenia or lymphopenia are often noted, but these changes, and the hypergammaglobulinaemia that occurs in over half the chronic cases, are not of proven diagnostic or prognostic significance. Serum calcium should be checked, as an increase may lead to chronic renal failure.

Angiotensin-converting enzyme (ACE) [14] is produced by sarcoidal granulomas. Raised serum levels are found in some 60% of patients with sarcoidosis, but are also present in other conditions such as diabetes and alcoholic liver disease. This limits the value of the test as a diagnostic aid, although it remains a useful monitor of disease activity.

Other markers of disease activity [15] vary in their usefulness in sarcoidosis. They include lysozyme, β_2-microglobulin, neopterin, collagenase and fibronectin levels. The serum level of soluble intercellular adhesion molecule 1 (ICAM-1), which is shed from cell surfaces and is a measure of the inflammatory response, mirrors disease activity in active sarcoidosis [16]. Hydroxyprolinuria may indicate disease activity. Radioactive gallium-67 uptake occurs in some pulmonary infections and neoplasms as well as sarcoidosis, but if these can be excluded it provides a way of separating active from fibrotic pulmonary disease.

References

1 Poole GW. The diagnosis of sarcoidosis. *BMJ* 1982; **285**: 321–2.
2 Israel HL, Sones M. Selection of biopsy procedures for sarcoidosis diagnosis. *Arch Intern Med* 1964; **113**: 255–60.
3 Khan F, Wessely Z, Chezin SR *et al*. Conjunctival biopsy in sarcoidosis: a simple, safe and specific diagnostic procedure. *Ann Ophthalmol* 1977; **9**: 761.
4 Nessan VS, Jacoway JR. Biopsy of minor salivary glands in the diagnosis of sarcoidosis. *N Engl J Med* 1979; **301**: 922–4.
5 Andrnopoulos AP, Papadimitriou C, Melachrinou M *et al*. Asymptomatic gastrocnemius muscle biopsy: an extremely sensitive and specific test in the pathologic confirmation of sarcoidosis presenting with hilar adenopathy. *Clin Exp Rheumatol* 2001; **19**: 569–72.
6 Wang KP, Johns CJ, Fuenning C *et al*. Flexible transbronchial needle aspiration for the diagnosis of sarcoidosis. *Ann Otol Rhinol Laryngol* 1989; **98**: 298–300.
7 Munro CS, Mitchell DN. The Kveim response: still useful, still a puzzle. *Thorax* 1987; **42**: 321–31.
8 Teirstein AS. The Kveim–Siltzbach test. *Clin Dermatol* 1986; **4**: 154–64.
9 Siltzbach LE. Qualities and behaviour of satisfactory Kveim suspensions. *Ann NY Acad Sci* 1976; **278**: 665–6.
10 James DG. Kveim revisited, reassessed. *N Engl J Med* 1975; **292**: 859–60.
11 Hurley TH, Sullivan JR, Hurley JV. Reaction to Kveim test material in sarcoidosis and other diseases. *Lancet* 1985; **i**: 494–6.
12 Middleton WG, Douglas AC. Further experience with Edinburgh prepared Kveim–Siltzbach test suspensions. In: Jones Williams W, Davies BH, eds. *Proceedings of the VIIIth International Conference on Sarcoidosis*. Cardiff: Alpha Omega, 1980: 655–9.
13 Vesey CMR, Wilkinson DS. Erythema nodosum. *Br J Dermatol* 1959; **71**: 139–55.
14 Callen JP, Hanno R. Serum angiotensin converting enzyme in patients with cutaneous sarcoidosis. *Arch Dermatol* 1982; **118**: 232–3.
15 Pozzi E, Ghio P, Albera A. Sarcoid activity markers. *Sarcoidosis* 1988; **5**: 162–5.
16 Ishii Y, Kitamura S. Elevated levels of soluble ICAM-1 in serum and BAL fluid in patients with active sarcoidosis. *Chest* 1995; **107**: 1636–40.

Treatment [1,2]

The chance of spontaneous remission favours a conservative approach to systemic therapy, which will usually carry the hazards of long-term immunosuppression, such as opportunistic mycobacterial infection [3] or a gross proliferation of viral warts [4]. At any time the pattern of the disease may change, but an expectant policy is often best if the course is not progressive and if vital structures are not involved.

Johns *et al*. [1] list the most frequent indications for systemic treatment:

1. symptomatic pulmonary disease
2. progressive or persistent parenchymal lung disease after 2 years
3. posterior ocular disease or anterior disease not responding to local steroids
4. persistent fever or weight loss
5. liver disease with significant dysfunction or hepatosplenomegaly
6. disfiguring skin disease or lymphadenopathy
7. nervous system disease
8. hypercalcaemia
9. myocardial disease
10. myopathy or myositis
11. thrombocytopenia
12. other significant organ involvement—for example, kidneys.

A major determinant is the degree to which a patient's normal life is disrupted by the disease, but objective measurements, such as pulmonary function tests, may be a more valuable way of monitoring therapy than symptoms alone.

A few patients with severe cardiac or pulmonary disease have come to transplantation; the sarcoidosis does not necessarily recur in the graft, perhaps due to the use of potent immunosuppressive agents [5].

In the skin clinic any decisions about the use of systemic therapy must take into account the seriousness of the accompanying internal involvement and the natural history of the particular type of skin lesion. Papular lesions, for example, are likely to fade without treatment, whereas lupus pernio is not.

Topical therapy

High-potency topical corticosteroids may sometimes prove helpful, as may intralesional triamcinolone injections. Tacrolimus, which inhibits hapten-induced production of Th1 cytokines and TNF-α by T cells, has been reported to be beneficial when used topically in cutaneous sarcoidosis [6]. Cryotherapy and radiotherapy have occasionally been used [2]. PUVA therapy has been successful in hypopigmented sarcoidosis [7] and in erythrodermic sarcoidosis [2]. In certain types of cutaneous sarcoidosis, for example lupus pernio, cosmetic camouflage advice is helpful.

Systemic therapy [8]

Corticosteroids are usually the most effective treatment, given at first in a relatively high dose, possibly 30 or 40 mg prednisolone daily, and then tapered over a period of several weeks to a lower maintenance dose of possibly 15 mg on alternate days. The length of the course of treatment will vary from case to case but is usually at least 6 months. Intravenous 'pulse' methylprednisolone, for example 1 g/week for 8 weeks, may be effective in those with the most severe neurological disease [5].

Immunosuppressive drugs may be tried if corticosteroids are contraindicated or have been ineffective. Methotrexate has been used with some success [9] and has been recommended for use with corticosteroids for lupus pernio [10]. Azathioprine, and mycophenolate mofetil (45 mg/kg/day), have been used for their steroid-sparing effects [11,12].

Biologic agents have recently been employed. The anti-TNF drugs infliximab and etanercept have been used successfully in cutaneous sarcoidosis—resistance to anti-TNF agents may require a switch to an alternative drug [13,14]. The anti-T-cell agent alefacept is described as beneficial in lupus pernio [15].

Other drugs which have been tried with some success include allopurinol, doxycycline and chloroquine [11,16]. Minocycline, 200 mg daily for 12 months, produced complete resolution in eight and partial improvement in two out of 12 patients with cutaneous sarcoidosis [17]. Levamisole is not recommended [18]. The response to ciclosporin has been variable [5]. Isotretinoin induced complete resolution in one case of cutaneous sarcoidosis [19]. Treatment with thalidomide (100–200 mg/day) in 12 patients with cutaneous sarcoidosis induced complete remission in four cases, partial improvement in six and no change in two [20]. Fumaric acid esters (FAEs) may give variable benefit [21]. In a small series of three patients with recalcitrant cutaneous sarcoidosis, all cleared after 4–12 months treatment with FAEs [22].

Laser, ultraviolet radiation and photodynamic therapies

Lupus pernio has been improved using the carbon dioxide laser [23]. UVA1 (340–440 nm) has been effective for forehead plaque sarcoid [24]. The use of photodynamic therapy can also be considered [25].

References

1 Johns CJ, Scott PP, Schonfled SA. Sarcoidosis. *Ann Rev Med* 1989; **40**: 353–71.
2 Veien NK. Cutaneous sarcoidosis: prognosis and treatment. *Clin Dermatol* 1986; **4**: 75–87.
3 Grice K. Sarcoidosis and *Mycobacterium avium–intracellulare* cutaneous abscesses. *Clin Exp Dermatol* 1983; **8**: 323–7.
4 MacKie RM. Extensive warts treated with etretinate. *Br J Dermatol* 1982; **107** (Suppl. 22): 97–8.
5 Mitchell DM. Sarcoidosis. In: Mitchell DM, ed. *Recent Advances in Respiratory Medicine*. Edinburgh: Churchill Livingstone, 1991: 185–202.
6 Katoh N, Mihara H, Yasuno H. Cutaneous sarcoidosis successfully treated with topical tacrolimus. *Br J Dermatol* 2002; **147**: 154–6.
7 Patterson JW, Fitzwater JE. Treatment of hypopigmented sarcoidosis with 8-methoxypsoralen and longwave ultraviolet light. *Int J Dermatol* 1982; **21**: 476–80.
8 Badgwell C, Rosen T. Cutaneous sarcoidosis therapy updated. *J Am Acad Dermatol* 2007; **56**: 69–83.
9 Veien NK, Brodthagen H. Cutaneous sarcoidosis treated with methotrexate. *Br J Dermatol* 1977; **97**: 213–6.
10 Spiteri MA, Matthey F, Carstairs LS *et al.* Lupus pernio: a clinicoradiological study of 35 cases. *Br J Dermatol* 1985; **112**: 315–22.
11 Mosam A, Morar N. Recalcitrant cutaneous sarcoidosis: an evidence-based sequential approach. *J Dermatol Treat* 2004; **15**: 353–9.
12 Kouba DJ, Mimouni D, Rencic A, Nousari HC. Mycophenolate mofetil may serve as a steroid-sparing agent for sarcoidosis. *Br J Dermatolol* 2003; **148**: 147–8.
13 Yee AMF, Pochapin MB. Treatment of complicqated sarcoidosis with infliximab anti-TNF-alfa therapy. *Ann Intern Med* 2001; **135**: 27–31.
14 Khanna D, Leibling M, Louie J. Etanercept ameliorates sarcoidosis arthritis and skin disease. *J Rheumatol* 2003; **30**: 1864–5.
15 Garcia-Zuazaga J, Korman NJ. Cutaneous sarcoidosis successfully treated with alefacept. *J Cutan Med Surg* 2006; **10**: 300–3.
16 Bregnhoej A, Jemec GB. Low-dose allopurinol in the treatment of cutaneous sarcoidosis: response in four of seven patients. *J Dermatol Treat* 2005; **16**: 125–7.
17 Bachelez H, Senet P, Cadranel J *et al.* The use of tetracyclines for the treatment of sarcoidosis. *Arch Dermatol* 2001; **137**: 69–73.
18 Veien NK. Cutaneous sarcoidosis treated with levamisole. *Dermatologica* 1977; **154**: 185–9.
19 Georgiou S, Monastirli A, Pasmatzi E, Tsamboas D. Cutaneous sarcoidosis: complete resolution after oral isotretinoin therapy. *Acta Derm Venereol (Stockh)* 1998; **78**: 457–9.
20 Nguyen YT, Dupuy A, Cordoliani F *et al.* Treatment of cutaneous sarcoidosis with thalidomide. *J Am Acad Dermatol* 2004; **50**: 235–51.
21 Breuer K, Gutzmer R, Volker B *et al.* Therapy of non-infectious granulomatous skin disease with fumaric acid esters. *Br J Dermatol* 2005; **152**: 1290–5.
22 Nowack U, Gambichler T, Henefeld C *et al.* Successful treatment of recalcitrant cutaneous sarcoidosis with fumaric acid esters. *BMC Dermatol* 2002; **2**: 15.
23 O'Donoghue NB, Barlow RJ. Laser remodelling of nodular nasal lupus pernio. *Clin Exper Dermatol* 2006; **31**: 27–9.
24 Graefe T, Konrad H, Barta U *et al.* Successful ultraviolet A1 treatment of cutaneous sarcoidosis. *Br J Dermatol* 2001; **145**: 354–5.
25 Gilaberte Y, Serra-Guillen C, de las Heras ME *et al.* Photodynamic therapy in dermatology. *Actas Dermosifiliogr* 2006; **97**: 83–102.

Other sarcoidal reactions

A number of infections and chemicals may cause sarcoid-like granulomas, although their features are seldom as clear-cut histologically [1,2]. Such reactions differ from sarcoidosis in several important respects:

1 They involve only those organs normally affected by the disease in question, or on the route of absorption or deposition of the chemical.
2 The Kveim test when performed has been negative.
3 The tuberculin reaction is usually not depressed.

The following text describes reactions which should be borne in mind in the differential diagnosis of sarcoidosis.

Infections

The problem of differentiating tuberculosis and leprosy from sarcoidosis has been dealt with on p. 16.13. Syphilis, brucellosis, fungus infections and some bacterial or viral diseases may produce a sarcoidal type of tissue response but any clinical resemblance is usually superficial.

Foreign materials

Silicates occur in many common materials—for example, in talc, kaolin, quartz and as a constituent of slate, brick, gravel and coal. Silicosis from the inhalation of silica dust is an important industrial hazard, but wounds containing crystals of silica normally remain unchanged indefinitely. Talc has been the cause of granulomas in surgical wounds when used as a glove powder. The long delay between the implantation of silica and the appearance of the granuloma suggests that the silica may not be the immediate cause of the reaction. In one case, a silica granuloma has progressed to scar sarcoidosis [3]. It is wise to examine all sarcoidal reactions under polarized light: silica particles are doubly refractile and differ from Schaumann bodies in that the crystalline material is spiculated but not laminated.

Beryllium reactions [2] are rarely seen now that beryllium is no longer used in the manufacture of fluorescent lights. The cutaneous lesions of systemic berylliosis are indistinguishable histologically from those of sarcoidosis, whereas the granulomas due to local beryllium implantation show marked central necrosis.

Zirconium granulomas may form in the axillae as a delayed hypersensitivity reaction to the zirconium content of deodorants [1,4].

Sea-urchin spines may induce foreign-body or sarcoidal granulomas [5]. The exact cause of the reaction is unknown. Intralesional triamcinolone may help speed resolution if excision is not practicable [6].

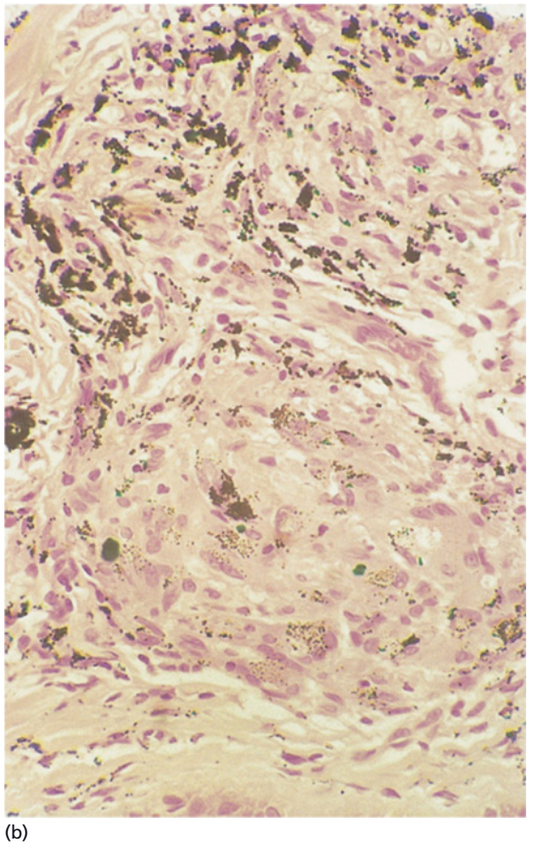
Foreign-body reactions to lipids (fat granulomas, epidermal cysts) and reactions to other lipid and non-lipid extraneous matter are variable and often show many giant cells.

Thesaurosis [7] is a pulmonary infiltration occurring in those heavily exposed to polyvinyl–pyrrolidine hair sprays in hairdressing procedures.

Sarcoidal reactions in tattoos (Fig. 61.19). A granulomatous dermal infiltrate may accompany sensitization reactions to any pigment of the tattoo, or may occur alone [8]. Less commonly, a pure sarcoidal reaction is present as an indolent lump within a tattooed area. Regional lymph nodes may also show a sarcoidal reaction [9]. Such lesions may be accompanied by other signs of sarcoidosis or a positive Kveim test [10] and are occasionally the only skin manifestation of the disease [11]. The pulmonary disease may be silent [8]. The association of a sarcoidal reaction in a cobalt tattoo with uveitis in three cases and with erythema nodosum in one [12] emphasizes the need for a thorough investigation of all cases showing a sarcoidal type of infiltrate.



(a)



(b)

Fig. 61.19 (a) Sarcoidal reaction to pigment in a tattoo. (Courtesy of Dr P. Collins, St Vincent's Hospital, Dublin, Eire.) (b) Histology of a sarcoidal reaction to two varieties of tattoo pigment, one opaque and one green. (Courtesy of Dr T.J. Stephenson, Royal Hallamshire Hospital, Sheffield, UK.)

Cosmetic fillers. Sarcoidal granulomas developed in the skin of a woman with pulmonary sarcoidosis who had had facial skin treated with a cosmetic filler [13].

Other reactions. A sarcoid-like reaction has been reported from exposure to acrylic or nylon fibres, either as dust or from walking

on acrylic carpets [14]. The significance of a sarcoidal reaction to ear piercing [15] was not clear in the presence of a positive Kveim test.

Crohn's disease

The similarity between the histological and immunological features of Crohn's disease and sarcoidosis led to speculation about a common aetiology. However, the rarity of sarcoidosis of the intestine makes this unlikely, and earlier reports of positive Kveim tests in patients with Crohn's disease have not been fully substantiated [16].

Whipple's disease [17]

Sarcoid-like changes have been recorded in the skin and lymphatic glands [17]. Diarrhoea is an important distinguishing clinical feature and jejunal biopsy will confirm the correct diagnosis (Chapter 62).

Farmer's lung [18]

This is caused by the inhalation of mouldy hay containing fungal spores: sarcoid-type granulomas sometimes develop slowly around the air passages and the condition then runs a course not unlike pulmonary sarcoidosis.

Other conditions

Sarcoid-like granulomas can occur in the skin and lymph nodes of patients with lymphoma: most commonly in Hodgkin's disease [19], but also in non-Hodgkin's lymphoma [20,21]. Sarcoid reaction is described with other malignancies, for example papillary thyroid carcinoma [22].

Epithelioid cell granulomas may also be a feature of rosacea [23]. In one unusual case [24], rosacea-like facial lesions, with a sarcoidal histology, were seen in a patient with a poorly differentiated lymphoma.

An epithelioid cell granuloma histology is found in granulomatous cheilitis and the Melkersson–Rosenthal syndrome, sometimes in necrobiosis lipoidica [25] and in granulomatosis disciformis, and has been reported in giant cell and other forms of arteritis [26].

References

1 Shelley WB, Hurley HJ. The allergic origin of zirconium deodorant granulomas. *Br J Dermatol* 1958; **70**: 75–101.

2 Sprince NL, Kazemi H, Hardy HL. Current problem of differentiating between beryllium disease and sarcoidosis. *Ann NY Acad Sci* 1976; **278**: 654–64.

3 Rowland-Payne CME, Meyrick-Thomas RH, Black MM. From silica granuloma to scar sarcoidosis. *Clin Exp Dermatol* 1983; **8**: 171–5.

4 Epstein WL, Skahen JR, Krasnobrod H. Granulomatous hypersensitivity to zirconium. *J Dermatol* 1962; **38**: 223–32.

5 Kinmont PDC. Sea urchin sarcoidal granuloma. *Br J Dermatol* 1965; **77**: 335–43.

6 Warin AP. Sea urchin granuloma. *Clin Exp Dermatol* 1977; **2**: 405–7.

7 Herrero EU, Feigelson HH, Becker A. Sarcoidosis in a beautician. *Am Rev Respir Dis* 1965; **92**: 280–3.

8 Antonovich DD, Callen JP. Development of sarcoidosis in cosmetic tattoos. *Arch Dermatol* 2005; **141**: 869–72.

9 Hanada K, Chiyoya S, Katebira Y. Systemic sarcoidal reaction in a tattoo. *Clin Exp Dermatol* 1985; **10**: 479–84.

10 Kennedy C. Sarcoidosis presenting in tattoos. *Clin Exp Dermatol* 1976; **1**: 395–9.

11 Dickinson JA. Sarcoidal reactions in tattoos. *Arch Dermatol* 1969; **100**: 315–9.

12 Rorsman H, Dahlquist I, Jacobsson S *et al.* Tattoo granuloma and uveitis. *Lancet* 1969; **ii**: 27–8.

13 Sidwell RU, Johnson NMcL, Francis N, Bunker CB. Cutaneous sarcoidal granulomas developing after facial cosmetic filler in a patient with newly diagnosed systemic sarcoidosis. *Clin Exper Dermatol* 2006; **31**: 208–11.

14 Pimental JC. Sarcoid granulomas of the skin produced by acrylic and nylon fibres. *Br J Dermatol* 1977; **96**: 673–7.

15 Mann RJ, Peachey RDC. Sarcoidal tissue reaction: another complication of ear piercing. *Clin Exp Dermatol* 1983; **8**: 199–200.

16 Middleton WG, Douglas AC. Further experience with Edinburgh prepared Kviem–Siltzbach test suspensions. In: Jones Williams W, Davies BH, eds. *Proceedings of the VIIIth International Conference on Sarcoidosis.* Cardiff: Alpha Omega, 1980, 655–9.

17 James DG, Lipman MC. Whipple's disease: a granulomatous masquerader. *Clin Chest Med* 2002; **23**: 513–9.

18 Rankin J, Jaersche WH, Callies QC *et al.* Farmer's lung. *Ann Intern Med* 1962; **57**: 606–26.

19 Kadin ME, Donaldson SS, Dorfman RF. Isolated granulomas in Hodgkin's disease. *N Engl J Med* 1970; **283**: 859–61.

20 Dupre A, Bolinelli BC, Biart M *et al.* Reactions sarcoidosiques au cours d'une réticulose histiomonocytaire: présentation de deux observations. *Bull Soc Fr Dermatol Syphilol* 1974; **82**: 162–3.

21 Kavin LB, Gordon W, Camp R. Florid sarcoid reaction associated with lymphoma of the skin. *Cancer* 1974; **33**: 1117–22.

22 Yamauchi M, Inoue D, Fukunaga Y *et al.* A case of sarcoid reaction associated with papillary thyroid carcinoma. *Thyroid* 1997; **7**: 901–3.

23 Laymon CW, Schoch EP. Micropapular tuberculid and rosacea: a clinical and histologic comparison. *Acta Derm Venereol (Stockh)* 1948; **58**: 286–98.

24 Sherertz EF, Westwitk TJ, Flowers FP. Sarcoidal reaction to lymphoma presenting as granulomatous rosacea. *Arch Dermatol* 1986; **122**: 1303–5.

25 Mehregan A, Pinkus H. Necrobiosis lipoidica with sarcoid reaction. *Arch Dermatol* 1961; **83**: 143–5.

26 Kinmont PDC, McCallum DI. Skin manifestations of giant cell arteritis. *Br J Dermatol* 1964; **76**: 299–308.

CHAPTER 62

Systemic Disease and the Skin

N.H. Cox[1] *& I.H. Coulson*[2]

[1]Department of Dermatology, Cumberland Infirmary, Carlisle, UK
[2]Dermatology Unit, Burnley General Hospital, Burnley, UK

Endocrine disorders, 62.2
Pituitary syndromes, 62.2
Adrenal syndromes, 62.3
Thyroid diseases, 62.7
Parathyroid disease, 62.12
Multiple endocrinopathy syndromes, 62.12
Autoimmune polyendocrine syndromes, 62.13
Cutaneous markers of internal malignancy, 62.14
Introduction and classification, 62.14
Investigation for internal malignancy, 62.14
Multisystem and haemopoietic tumours that involve the skin, 62.14
Direct tumour spread from adjacent and deeper tissues, 62.15
Cutaneous metastasis from tumours affecting other organs, 62.17
Genodermatoses associated with internal malignancies, 62.19
Paraneoplastic disorders, 62.29
Indirect cutaneous markers of internal malignancy, 62.46
The gastrointestinal tract, 62.47
Oesophagus and stomach, 62.48
Crohn's disease (regional ileitis), 62.48
Ulcerative colitis, 62.50
Collagenous colitis, 62.53
Bowel-associated dermatosis–arthritis syndrome, 62.53
Skin complications of stomas, 62.53
Coeliac disease, 62.55
Whipple's disease, 62.55
Skin disorders associated with gastrointestinal bleeding, 62.55
Intestinal polyposis, 62.56
Liver disease, 62.58
Hepatitis and acute liver disease, 62.58
Cirrhosis of the liver, 62.60
Drugs and the liver, 62.62
Systemic diseases and the liver, 62.63
Dermatological features and dermatoses associated with liver disease, 62.63
Pancreatic disease, 62.65
Acute pancreatitis, 62.65
Subcutaneous fat necrosis, 62.65
Migratory thrombophlebitis, 62.66
Necrolytic migratory erythema, pancreatic islet cell tumours and glucagonoma syndrome, 62.66
Renal disease, 62.68
Hereditary syndromes and malformations, 62.68
Metabolic and systemic disorders, 62.70
Infective dermatoses causing renal disease, 62.71
Renal failure and dialysis, 62.72
Skin changes in renal transplant recipients, 62.74
Cardiac disease, 62.75
Consequences of cardiac disease, 62.77
Congenital and inherited disorders, 62.77
Coronary artery disease, 62.78
Connective tissue and systemic diseases, 62.78
Infections, 62.78
Cardiac myxoma syndromes, 62.78
Miscellaneous, 62.79
Respiratory system, 62.80
Congenital and inherited disorders, 62.80
Infections, 62.80
Connective tissue diseases, 62.80
Vasculitis and neutrophilic dermatoses, 62.82
Other systemic diseases, 62.83
Miscellaneous, 62.83
Haematology, 62.85
Erythrocyte disorders, 62.85
Leukocyte disorders, 62.86
Haematological malignancies, 62.88
Platelet and clotting disorders, 62.90
Paraproteins and multiple myeloma, 62.92
Miscellaneous haematological diseases with cutaneous manifestations, 62.95
Graft-versus-host disease, 62.96
Bone and joint diseases, 62.99
Inflammatory conditions, 62.101
Metabolic conditions, 62.105
Infections, 62.105
Annular and figurate reactive erythemas, 62.106

Introduction

The systemic associations of skin diseases have been stressed throughout this book. In this chapter many of these associations are listed again, along with some other important conditions. They are grouped so as to be helpful to the general physician or internist. It is hoped that such a presentation will also be useful to the dermatologist who is asked to help in the diagnosis of obscure internal disease. Many further references may be found by turning to the chapter in which the relevant dermatosis is considered in detail.

The texts listed below [1–5] provide much more information than it is possible to give here, and are also a source of additional references.

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

References

1 Braverman IM. *Skin Signs of Systemic Disease*, 3rd edn. Philadelphia: Saunders, 1998.
2 Callen JP, Jorrizo JL, eds. *Dermatological Signs of Internal Disease*, 3rd edn. Philadelphia: Saunders, 2003.
3 Jones JH, Mason DK, eds. *Oral Manifestations of Systemic Disease*, 2nd edn. Philadelphia: Baillière Tindall, 1990.
4 Provost TT, Flynn JA, eds. *Cutaneous Medicine: Cutaneous Manifestations of Systemic Disease*. Hamilton, Ontario: Decker, 2001.
5 Lebwohl MG. *The Skin and Systemic Disease. A Color Atlas and Text*, 2nd edn. London: Churchill Livingstone, 2004.

Endocrine disorders

The physiological effects of hormones on pigmentation, hair growth, sebaceous glands and connective tissue have been described in other chapters. This section is limited to discussion of specific endocrine pathology with cutaneous features. Additional detail is provided in several general references [1–6].

References

1 Feingold KR, Elias PM. Endocrine–skin interactions. *J Am Acad Dermatol* 1987; **17**: 921–40.
2 Feingold KR, Elias PM. Endocrine–skin interactions. *J Am Acad Dermatol* 1988; **19**: 1–20.
3 Boyne M, Dobs AS, Krasner AS, Provost TT. Evaluation and treatment of endocrine disorders. In: Provost TT, Flynn JA, eds. *Cutaneous Medicine: Cutaneous Manifestations of Systemic Disease*. Hamilton, Ontario: Decker, 2001: 413–51.
4 Braverman IM. *Skin Signs of Systemic Disease*, 3rd edn. Philadelphia: Saunders, 1998: 438–91.
5 Wass JAH, Shalet SM. *Oxford Textbook of Endocrinology and Diabetes*. Oxford: Oxford University Press, 2002.
6 Jabbour SA. Cutaneous manifestations of endocrine disorders. A guide for dermatologists. *Am J Clin Dermatol* 2003; **4**: 315–31.

Pituitary syndromes

Hyperpituitarism [1–3]

Excessive secretion of growth hormone (GH, somatotrophin) causes an increase in plasma insulin-like growth factor-1 (IGF-1). These hormones stimulate synthesis of collagen and glycosaminoglycan in the skin and skeleton, leading to insidious hypertrophy of skin, subcutaneous tissues and viscera, and to periosteal bone growth. This causes acromegaly in the adult (most cases), and gigantism in children whose bony epiphyses have not yet closed.

*Acromegaly (MIM *102200)* [4] *and gigantism*

Aetiology. The usual cause (over 95%) is a benign adenoma or hyperplasia of the eosinophilic cells of the adenohypophysis, producing GH and often prolactin [4]. Other tumours, such as bronchial carcinoma, may occasionally cause acromegaly, usually by ectopic secretion of GH-releasing hormone (GH-RH). Individual, viable epidermal cells are larger than normal, and epidermal cell turnover is increased.

Clinical features. Periosteal new bone formation of the facial bones and skin causes the characteristic facies. Features are prognathism, frontal bossing, widely spaced teeth and acral hypertrophy, which causes elongated, blunt and thickened fingers. Dermatological features include a protruding, thickened lower lip, oedematous thick eyelids, a large and furrowed tongue (Fig. 62.1), triangular large ears, numerous skin tags ('fibroma molluscum'), widened skin pores, wet and oily skin due to hyperhidrosis and increased sebum production, acne and cutis gyrata of the scalp in more extreme cases. Eruptive seborrhoeic keratoses mimicking the sign of Leser–Trélat have been reported in acromegaly [5]. Hyperpigmentation develops in about half of the affected individuals due to increased levels of melanocyte-stimulating hormone (MSH), and acanthosis nigricans may occur. The scalp hair is initially coarse and there may be hirsutism, but later in the disease there is a decrease in gonadotrophin production, which causes the hair to become finer, with loss of secondary sexual hair. The nails are flat and wide and grow fast. Pachydermoperiostosis (Chapter 15) is an important differential diagnosis. In this disease, there is no macroglossia or prognathism, and the fingers are characteristically clubbed.



Fig. 62.1 Acromegalic macroglossia.

Non-cutaneous features include macroglossia, visual field defect and headache due to the neoplasm, arthropathy, carpal tunnel syndrome and proximal myopathy. Cardiovascular morbidity and mortality is markedly increased due to associated hypertension, left ventricular hypertrophy, cardiomyopathy, sleep hypoxia and apnoea, and hyperlipidaemia. Acromegalic subjects have an increased incidence of colonic adenomas and carcinomas [6].

Diagnosis. The clinical picture is, in most cases, suggestive of the diagnosis. Serum GH and prolactin levels are generally elevated, but vary considerably both in normal subjects and in those with acromegaly [4]; plasma IGF-1 is a more reliable test of chronically elevated GH levels [7]. Failure of GH levels to suppress during glucose challenge, and GH-RH stimulation tests, help to confirm the diagnosis. Magnetic resonance imaging (MRI) of the pituitary gland with contrast confirms the site and size of the tumour in most cases; three-quarters of subjects have a macroadenoma (>10 mm) at presentation but microadenomas as small as 2 mm can be identified using current imaging techniques.

Treatment. Neurosurgical removal of the tumour is the preferred treatment. Patients in whom this fails to achieve a cure may be treated with somatostatin analogues such as octreotide and lanreotide, dopamine agonists such as bromocriptine and cabergoline, GH receptor antagonists such as pegvisomant, or radiotherapy [1–3,7,8,10]. Colonoscopy surveillance is recommended as there is an increased risk of colonic polyps, carcinomas and tubulovillous adenomas.

Pituitary insufficiency [1–3,9,11]

Insufficiency of the adenohypophysis (anterior pituitary) may involve individual or multiple hormones. In classical hypopituita-

Table 62.1 The causes of anterior pituitary deficiency.

Neoplasia—adenomas (most), craniopharyngioma, metastases
Infection—tuberculosis, abscess
Trauma, surgical, iatrogenic
Congenital—familial, 'empty sella syndrome'
Vascular—Sheehan's syndrome (postpartum) and other infarction, bleeding, diabetes mellitus, vasculitis, antiphospholipid syndrome
Idiopathic
Hypothalamic—due to hypothalamic tumours, trauma, infiltration (Langerhans' cell histiocytosis, sarcoidosis), congenital causes of hypothalamic failure

rism, all endocrine cell functions of the pituitary gland are involved to a varying degree. However, the clinical picture is influenced by the cause of hypopituitarism; for example, adenomas may produce GH or prolactin, but may also cause compression atrophy of cells producing gonadotrophins. Concurrent loss of function of the posterior pituitary may occur if there is a hypothalamic lesion, such as Langerhans' cell histiocytosis.

Aetiology. Over 95% of cases of hypopituitarism are due to pituitary cell destruction [8]. Familial hypopituitarism has a genetic basis due to mutations in Pit-1 or its precursor Prop-1, resulting in deficient production of GH, prolactin and thyrotrophin. Causes of insufficiency of the anterior pituitary are listed in Table 62.1.

Clinical features. The various endocrine dysfunctions are typically insidious and less impressive than those seen in the primary glandular disorders. Pallor of the skin due to decreased MSH secretion results in generalized hypopigmentation, most apparent in the skin of the nipple areola and genitalia; in contrast with anaemia, the mucous membranes retain their normal colour. There is an increased sunburn tendency and lack of tanning, and there may be a degree of carotenaemia due to hypothyroidism. Loss of terminal hair due to decreased gonadotrophin secretion is observed in all patients, first in the axillae and later, but not invariably, in the pubic area. Fine wrinkling and dryness of the skin simulates advanced age. The face appears expressionless due to diminution of the facial skinfolds. The activity of sebaceous and sweat glands is reduced. Onycholysis, longitudinal ridging and brownish discoloration of the nail plate may be seen.

Pituitary dwarfism is characterized by proportionate retardation of somatic growth in conjunction with normal mental development. The cutaneous changes of old age may develop prematurely from the third decade onwards.

Erythromelalgia with non-healing skin ulcers has been reported as a presenting feature of GH deficiency in a child.

Diagnosis and treatment. Measurement of hormone levels—prolactin, IGF-1, thyroid-stimulating hormone (TSH) and thyroxine (T_4), cortisol, gonadotrophins—is required to detect subnormal levels; prolactin or IGF-1 may be elevated if the cause of hypopituitarism is a pituitary tumour. Posterior pituitary function should also be assessed, and visual field testing and MRI should be performed. Treatment is of the primary cause, together with hormone replacement [8,9].

References

1 Braverman IM. *Skin Signs of Systemic Disease*, 3rd edn. Philadelphia: Saunders, 1998: 438–40.
2 Feldman SR, Jorizzo JL. Adrenal, androgen-related, and pituitary disorders. In: Callen JP, Jorizzo JL, eds. *Dermatological Signs of Internal Disease*, 3rd edn. Philadelphia: Saunders, 2003: 187–91.
3 Boyne M, Dobs AS, Krasner AS, Provost TT. Evaluation and treatment of endocrine disorders. In: Provost TT, Flynn JA, eds. *Cutaneous Medicine: Cutaneous Manifestations of Systemic Disease*. Hamilton, Ontario: Decker, 2001: 413–51.
4 Melmed S. Acromegaly. *N Engl J Med* 2006; **355**: 2258–73.
5 Kilmer SL, Berman B, Morhenn VB. Eruptive seborrheic keratoses in a young woman with acromegaly. *J Am Acad Dermatol* 1990; **23**: 991–4.
6 Jenkins PJ. Cancers associated with acromegaly. *Neuroendocrinology* 2006; **83**: 218–23.
7 Melmed S, Ho K, Klibanski A *et al*. Recent advances in pathogenesis, diagnosis and management of acromegaly. *J Clin Endocrinol Metab* 1995; **80**: 3395–402.
8 Orrego JJ, Barkan AL. Pituitary disorders: drug treatment options. *Drugs* 2000; **59**: 93–106.
9 Lamberts SWJ, de Herder WW, van der Lely AJ. Pituitary insufficiency. *Lancet* 1998; **352**: 127.
10 Melmed S. Medical progress: Acromegaly. *N Engl J Med* 2006; **355**: 2558–73.
11 Geller JL, Braunstein GD. Dermatologic manifestations of hypopituitarism. *Clin Dermatol* 2006; **4**: 266–75.

Adrenal syndromes

Cushing's disease and syndrome [1–8]

Chronic glucocorticoid excess may occur due to increased secretion of adrenocorticotrophic hormone (ACTH, corticotrophin), usually from the pituitary (MIM *219090), due to glucocorticoid hypersecretion of adrenal origin (ACTH-independent, MIM *219080) or due to exogenous administration of glucocorticoids.

Aetiology. The commonest ACTH-dependent cause is that due to a pituitary adenoma (Cushing's disease or pituitary-dependent Cushing's syndrome), which accounts for about 70% of spontaneous cases; pituitary overproduction of ACTH leads to adrenal hyperplasia and thus to glucocorticoid excess. Other ACTH-dependent causes include the ectopic ACTH syndrome (for example, from small cell lung cancer or bronchial carcinoids) and, rarely, ectopic corticotrophin-releasing hormone (CRH) syndrome. ACTH-independent causes include cortisol-producing adrenocortical adenomas and carcinomas, various types of bilateral adrenal hyperplasia (including the Carney complex), and, most commonly, iatrogenic causes such as results from long-term administration of glucocorticoids, either systemically or from excessive use of topical, inhaled or intralesional steroids [4]. The glucocorticoid hormones, among other effects, impair synthesis of collagen and mucopolysaccharides and thus lead to atrophy and vascular fragility of the skin.

Clinical features. The cutaneous manifestations are quite similar whether caused by endogenous or iatrogenic hypercorticism, although there are additional effects mediated by androgens in patients with adrenal disease. The features are enumerated in Table 62.2; the thin skin and easy bruising are helpful in distinguishing Cushing's syndrome from simple obesity.

About 6–10% of patients with pituitary Cushing's disease have addisonian-like pigmentation [1], as oversecretion of the common

Table 62.2 Cutaneous manifestations of Cushing's disease.

Truncal obesity (classically deposits of fat over the clavicles and back of the neck, the 'buffalo hump')
Facial fullness and plethora ('moon facies') are most frequent
Slender limbs
Skin atrophy
Fragility, bruising and poor healing
Telangiectasia
Striae (typically wide and red)
Hirsuties
Hypertrichosis (downy facial hair in iatrogenic hypercorticism)
Acneiform lesions (often monomorphic and devoid of comedones and cysts)
Male-pattern baldness in women
Dermatophyte and yeast infections

precursor pro-opiomelanocortin causes overproduction of both ACTH and MSH.

Diagnosis. A 24-hour urinary cortisol and/or a 1-mg overnight dexamethasone suppression test are generally considered to be satisfactory screening tests. However, the 24-hour urinary cortisol is now felt to be least sensitive, and may miss mild or cyclical disease; it may be falsely low if there is renal impairment or an incomplete collection. Mildly elevated levels overlap with other causes of hypercortisolaemia, but values above fourfold greater than normal are indicative of Cushing's syndrome [8]. A midnight plasma cortisol level (100% specific if over 50 nmol/L) or a 2-day low-dose (0.5 mg 6-hourly) dexamethasone suppression test may resolve equivocal results. Additional tests may be required [2], as atypical presentations, other illnesses and various laboratory factors may influence interpretation of tests [6–8]. Venous sampling to measure ACTH levels is also performed in order to differentiate between ACTH-dependent and ACTH-independent Cushing's syndrome, the best available (but technically difficult) test being bilateral inferior petrosal sinus sampling (BIPSS) [7,8]. Additional investigations may include an MRI scan of pituitary to detect a microadenoma, and CT or MRI scan of chest and abdomen to detect a source of ectopic ACTH secretion.

Treatment. Trans-sphenoidal selective adenomectomy is the treatment of choice for pituitary-dependent Cushing's disease in adults, with radiotherapy as second choice; radiotherapy is more effective in children. Surgery only leads to long-term remission in about 60% of cases. Bilateral adrenalectomy is the third-choice definitive cure for pituitary Cushing's syndrome, and is the treatment of choice when the disease is caused by bilateral adrenal hypersecretion; lifelong replacement therapy with glucocorticoids and mineralocorticoids is then required. A substantial number of such patients eventually develop a pituitary macroadenoma and cutaneous hyperpigmentation (Nelson's syndrome, Fig. 62.2); this is best treated by pituitary surgery [5]. Unilateral adrenal disease (adenoma or carcinoma) is treated by unilateral adrenalectomy. Medical treatments may act at hypothalamic–pituitary level (serotonin antagonists, dopamine or GABA agonists, somatostatin analogues), at corticosteroid receptors (mifepristone) or on adrenal glands (metyrapone, aminoglutethimide, ketoconazole and others). Most of these agents have significant potential side effects.



Fig. 62.2 Diffuse pigmentation in Nelson's syndrome.

Pseudo-Cushing's disease [9,10]

A clinical and biochemical mimic of Cushing's disease has been described in alcoholics. The biochemical parameters are not as severe as seen in true disease, and the condition can resolve on alcohol abstinence [9]. Pseudo-Cushing's syndrome may represent a state of stress-induced hypercortisolaemia secondary to multiple episodes of subacute withdrawal from ethanol [10].

References

1 Braverman IM. *Skin Signs of Systemic Disease*, 3rd edn. Philadelphia: Saunders, 1998: 438–91.
2 Newell-Price J, Bertagna X, Grossman AB, Nieman LK. Cushing's syndrome. *Lancet* 2006; **367**: 1605–17.
3 Shibli-Rahhal A, Van Beek M, Schlechte JA. Cushing's syndrome. *Clin Dermatol* 2006; **24**: 260–5.
4 Gilbertson EO, Spellman MC, Piacquadio DJ, Mulford MI. Super potent topical corticosteroid use associated with adrenal suppression: clinical considerations. *J Am Acad Dermatol* 1998; **38**: 318–21.
5 Kemink SA, Grotenhuis JA, de Vries J *et al*. Management of Nelson's syndrome: observations in fifteen patients. *Clin Endocrinol* 2001; **54**: 45–52.
6 Boscaro M, Barzon L, Fallo F, Sonino N. Cushing's syndrome. *Lancet* 2001; **357**: 783–1.
7 Arnaldi G, Angeli A, Atkinson AB *et al*. Diagnosis and complications of Cushing's syndrome: a consensus statement. *J Clin Endocrinol Metab* 2003; **88**: 5593–602.
8 Newell-Price J. Cushing's syndrome. *Clin Med* 2008; **8**: 204–8.
9 Rees LH, Besser GM, Jeffcoate WJ *et al*. Alcohol-induced pseudo-Cushing's syndrome. *Lancet* 1977; **2**: 726–8.
10 Elias AN, Meshkinpour H, Valenta LJ, Grossman MK. Pseudo-Cushing's syndrome: the role of alcohol. *J Clin Gastroenterol* 1982; **4**: 135–7.

Adrenal insufficiency [1–8]

Synonyms
- Addison's disease
- Hypocorticism
- Hypoadrenalism

This condition is due to insufficient secretion or supply of adrenocortical hormones or hormonal compounds—mainly cortisol and mineralocorticoids.

Aetiology. Most cases of adrenal insufficiency occur due to prolonged supraphysiological glucocorticoid therapy for a variety of inflammatory and other diseases; this suppresses ACTH production, so abrupt discontinuation of treatment may cause acute adrenal insufficiency.

Primary adrenal insufficiency (Addison's disease) in developed countries is most commonly due to autoimmune adrenalitis. Most such patients show circulating antibody to the cortex cells; about 40% of adults and virtually all children with Addison's disease have other autoimmune-related disorders as part of a polyglandular syndrome [2,4–8]. There are also several genetic disorders that cause primary adrenal failure [8]. Other causes of primary adrenal damage include infections (tuberculosis is the commonest cause, others include HIV, CMV, cryptococcus, histoplasmosis and viral infections), metastatic malignant disease or (rarely) haemorrhage. The latter is of some dermatological importance, as it may rarely occur due to sepsis (Waterhouse–Friderichsen syndrome); this is classically described as a consequence of meningococcaemia, but in a study of paediatric deaths due to sepsis with bilateral adrenal haemorrhage the commonest cause was *Pseudomonas* infection.

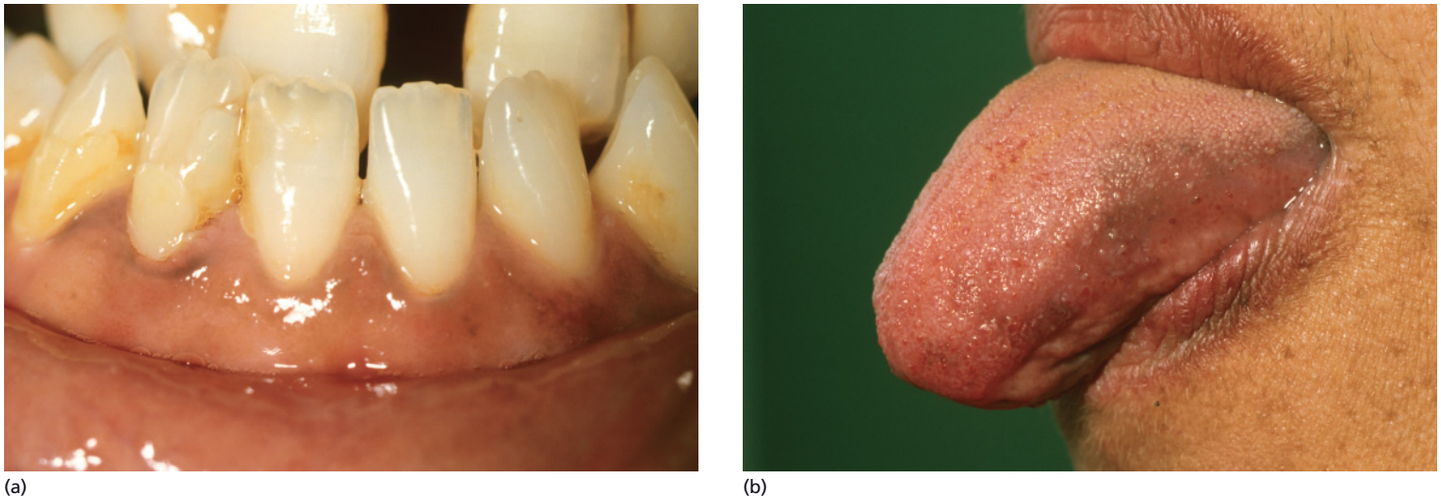
Secondary adrenal insufficiency may occur due to hypothalamic or pituitary disease, leading to insufficient secretion of ACTH; patients with pituitary hyposecretion of ACTH lack the pigmentary changes that are characteristic of primary adrenal insufficiency, and mineralocorticoid production is generally maintained.

Clinical features [1–8]. General symptoms include wasting, fatigue, orthostatic hypotension, dizziness, anorexia, abdominal pain and amenorrhoea. Self-mutilation, presenting as gouges in the skin, has been reported as a result of psychiatric symptoms [9]. However, hyperpigmentation of the skin, due to increased secretion of pituitary MSH and ACTH as a response to low adrenal corticosteroid levels, is the cardinal dermatological feature. This develops insidiously and is often not recognized as abnormal by the patient. Patterns of increased pigmentation are enumerated in Table 62.3.

Mucous membrane lesions are usually spots or patches rather than diffuse pigmentation (Fig. 62.3), and the oral pigmentation may persist after glucocorticoid replacement therapy. Scar pigmentation only occurs in scars acquired during adrenal insufficiency and is permanent—scars that precede the disorder or occur during therapy are unaffected [6]. In women, in whom the adrenal gland is the main source of androgens, there may be loss of axillary and pubic hair and improvement in acne. Features of associated autoimmune disease may be present, notably vitiligo in 15% of patients with autoimmune causation. Calcification of the pinna has been described [10], but may occur in other endocrine conditions and is more commonly the result of frostbite or injury.

Table 62.3 Patterns of addisonian pigmentation.

Light-exposed areas—face, dorsa of hands
Areas subject to friction—elbows, knees, waistline, under bra straps
Accentuation of normally high pigmentation areas—genital, perineum, axillae, areolae, umbilicus
Palmar creases
Tongue and mucous membranes (Fig. 62.3)
Scars
Hair and nails—longitudinal melanonychia.
Darkening existing pigmented lesions (such as café-au-lait patches)
Eruptive lentigines



(a) (b)

Fig. 62.3 Pigmentation of (a) the gingivae and (b) the tongue in a woman who presented with darkening skin due to Addison's disease.

Similar pigmentation may be seen in Nelson's syndrome and in tumours causing ectopic ACTH secretion; in the latter case, cortisol production is increased, so the clinical picture and electrolyte changes may be those of Cushing's syndrome.

Rarely pigmentation is absent in Addison's disease, making diagnosis difficult, and patients with 'white' Addison's disease may present in addisonian crisis. They have metabolic Addison's disease, with low cortisol, flat short Synacthen responses, and elevated circulating ACTH and MSH levels. Absence of hyperpigmentation is explained by a high degree of melanosome degradation in secondary lysosomes called 'compound melanosomes', which overwhelm the increased stimulation of the skin pigmentation [11].

Diagnosis. Anaemia, lymphocytosis, hyponatraemia, hyperkalaemia and hypoglycaemia are expected. A short Synacthen test demonstrates impaired cortisol secretion in response to corticotrophin, and ACTH and cortisol production are subnormal in response to an insulin stress test. Adrenal calcification may be present in autoimmune or tuberculous disease. Primary adrenal failure can be identified by demonstrating elevated ACTH levels, presence of adrenal autoantibodies, and by stimulation tests such as the metyrapone test or CRH test. In acute presentation, where there may be severe hypotension, weakness and clinical shock, baseline blood tests should include serum cortisol and plasma ACTH, which can be assayed later to confirm the diagnosis, but intravenous fluids and cortisol replacement should be commenced without waiting for results. Associated coeliac disease has been reported in five (12.2%) of 41 subjects, in a study that suggested that coeliac serology should be performed as part of an autoimmune screen in any patient with Addison's disease [12].

Treatment. Primary adrenal failure requires glucocorticoid and mineralocorticoid replacement [5–8]. In secondary cases related to pituitary insufficiency, usually only cortisol is required [3]. During stress, such as when undergoing major surgery and in severe systemic infections, the need for cortisol is increased. The hyperpigmentation may start to regress within days, but generally takes weeks to months to fully resolve—the process is slower in hair and nails, and pigmented scars remain pigmented [6].

References

1 Feldman SR, Jorizzo JL. Adrenal, androgen-related, and pituitary disorders. In: Callen JP, Jorizzo JL, eds. *Dermatological Signs of Internal Disease*, 3rd edn. Philadelphia: Saunders, 2003: 187–91.

2 Baker JR. Autoimmune endocrine disease. *JAMA* 1997; **278**: 1931–7.

3 Braverman IM. *Skin Signs of Systemic Disease*, 3rd edn. Philadelphia: Saunders, 1998: 438–91.

4 Feingold KR, Elias PM. Endocrine–skin interactions. *J Am Acad Dermatol* 1987; **17**: 921–40.

5 Ten S, New M, Maclaren N. Clinical review 130: Addison's disease 2001. *J Clin Endocrinol Metab* 2001; **86**: 2909–22.

6 Orth DN, Kovacs WJ. The adrenal cortex. In: Wilson JD, Foster DW, Kronenberg HM, Larsen PR, eds. *Williams Textbook of Endocrinology*, 9th edn. Philadelphia: Saunders, 1998: 517–664.

7 Betterle C, Dal Pra C, Mantero F, Zanchetta R. Autoimmune adrenal insufficiency and autoimmune polyendocrine syndromes, autoantibodies, autoantigens, and their applicability in diagnosis and disease prediction. *Endocrin Rev* 2002; **23**: 327–64.

8 Arit W. Adrenal insufficiency. *Clin Med* 2008; **8**: 211–5.

9 Rajathurai A, Chazan BI, Jeans JE. Self mutilation as a feature of Addison's disease. *BMJ* 1983; **287**: 1027.

10 Chadwick JM, Downham TF. Auricular calcification. *Int J Dermatol* 1978; **17**: 799–801.

11 Kendereski A, Micic D, Sumarac M *et al*. White Addison's disease: what is the possible cause? *J Endocrinol Invest* 1999; **22**: 395–400.

12 O'Leary C, Walsh CH, Wieneke P *et al*. Coeliac disease and autoimmune Addison's disease: a clinical pitfall. *QJM* 2002; **95**: 79–82.

Congenital adrenal hyperplasia [1,2]

Congenital adrenal hyperplasia (CAH) is a family of autosomal recessive disorders caused by mutations that encode for enzymes involved in one of the various steps of adrenal steroid synthesis. These defects result in the absence or the decreased synthesis of cortisol from its cholesterol precursor. The anterior pituitary secretes excess adrenocorticotrophic hormone (ACTH) via feedback regulation by cortisol, which results in overstimulation of the adrenals and causes hyperplasia. Six variants are recognized, but only two will be discussed here as they are more likely to be seen by dermatologists. Symptoms due to CAH can vary from mild to severe depending on the degree of enzymatic defect.

21-hydroxylase deficiency

In the classical form of CAH, there is a severe enzymatic defect owing to mutations in the *CYP21* gene. This results in deficient 21-hydroxylase levels, and deficient cortisol synthesis, as they cannot convert 17-hydroxy progesterone to 11-deoxycortisol. Negative feedback results in increased CRF and ACTH secretion and adrenal gland hyperplasia. Rather than produce cortisol, the adrenal produces excess sex hormone precursors, and these are further converted to active androgens. Approximately 75% of patients cannot synthesize enough aldosterone as they cannot convert progesterone to deoxycorticosterone, and they may present with 'salt wasting' episodic hyponatraemic dehydration.

Classically, affected female fetuses undergo virilization of the genitalia prenatally and present with genital ambiguity at birth; however, prenatal treatment of CAH with dexamethasone to prevent ambiguity has been successfully utilized for over a decade. There are reports of neonatal acanthosis nigricans arising in classical disease [3].

Of greater relevance to dermatologists (as it is common) is the less severe, late-onset form of CAH; prenatal virilization does not occur. The milder enzyme deficiency was termed non-classical 21-hydroxylase deficiency (NC21OHD) in 1979 and was later found to be the most common autosomal recessive disorder in humans. Disease frequency of NC21OHD varies between ethnic groups with the highest ethnic-specific disease frequency in Ashkenazi Jews at 1 in 27. Similar to classical CAH, non-classical 21-hydroxylase deficiency may cause premature development of pubic hair, advanced bone age, accelerated linear growth velocity and diminished final height in both males and females. Severe cystic acne has also been attributed to non-classical CAH. Women may present with symptoms of androgen excess, including hirsutism, temporal baldness, and infertility. Menarche in females may be normal or delayed and secondary amenorrhoea is a frequent occurrence. Polycystic ovary syndrome may also be seen in these patients. In males, early beard growth, acne [4], and growth spurt may prompt the diagnosis of NC21OHD. Although many males appear to be asymptomatic, they may present with oligozoosper-

mia or diminished fertility. Non-classical CAH may be seen in both early-onset prepubertal acne [5], persisting acne in women [6] and in acne fulminans [7]. Some authors have questioned the importance of this finding, arguing that it is one of many factors in the eventual expression of clinical acne [8].

Diagnosis. In the classic disease, there is marked elevation of 17-hydroxyprogesterone. In the non-classical disease, resting 17-hydroxyprogeserone levels may be normal, but stimulation of the adrenal with low-dose intravenous ACTH will result in elevated levels of 17-hydroxyprogesterone. Gene markers can now be identified. Low-dose glucocorticoid treatment may then be a useful adjunct to treatment.

11-hydroxylase deficiency

This comprises 5–8% of CAH cases, affecting about 1 in 100 000 births. The 11-hydroxylase enzyme is coded for by the *CYP11B1* gene. There is an inability to convert 11-deoxycortisol to cortisol. A parallel defect exists in the synthesis of 17-deoxysteroids, so that deoxycorticosterone is not converted to corticosterone, and it accumulates. As some of its metabolites have mineralocorticoid activity, sodium retention, potassium loss and hypertension develop. A non-classical variant is not associated with hypertension. It may rarely account for the development of infantile acne in boys [9], and precocious puberty. It causes virilization and ambiguous genitalia in girls.

Diagnosis. Elevated deoxycorticosterone and 11-deoxycortisol confirms the diagnosis.

References

1 New MI. An update of congenital adrenal hyperplasia. *Ann N Y Acad Sci* 2004; **1038**: 14–43.
2 Speiser PW, White PC. Congenital adrenal hyperplasia. *N Engl J Med* 2003; **349**: 776–88.
3 Kurtoğlu S, Atabek ME, Keskin M, Canöz O. Acanthosis nigricans in association with congenital adrenal hyperplasia: resolution after treatment. Case report. *Turk J Pediatr* 2005; **47**: 183–7.
4 Degitz K, Placzek M, Arnold B *et al*. Congenital adrenal hyperplasia and acne in male patients. *Br J Dermatol* 2003; **148**: 1263–6.
5 De Raeve L, De Schepper J, Smitz J. Prepubertal acne: a cutaneous marker of androgen excess? *J Am Acad Dermatol* 1995; **32**: 181–4.
6 McLaughlin B, Barrett P, Finch T, Devlin JG. Late onset adrenal hyperplasia in a group of Irish females who presented with hirsutism, irregular menses and/or cystic acne. *Clin Endocrinol (Oxf)* 1990; **32**: 57–64.
7 Placzek M, Degitz K, Schmidt H, Plewig G. Acne fulminans in late-onset congenital adrenal hyperplasia. *Lancet* 1999; **354**: 739–40.
8 Ostlere LS, Rumsby G, Holownia P *et al*. Carrier status for steroid 21-hydroxylase deficiency is only one factor in the variable phenotype of acne. *Clin Endocrinol (Oxf)* 1998; **48**: 209–15.
9 Harde V, Muller M, Sippell WG *et al*. [Acne infantum as presenting symptom of congenital adrenal hyperplasia due to 11-beta-hydroxylase deficiency]. *J Dtsch Dermatol Ges* 2006; **4**: 654–7.

Thyroid diseases

General reviews of thyroid disease and the skin can be found in the following references [1–4].

References

1 Heymann WR, ed. *Thyroid diseases with cutaneous manifestations*. New York: Springer, 2008.
2 Rosen T, Kleman GA, Jorizzo JL. Thyroid and the skin. In: Callen JP, Jorizzo JL, eds. *Dermatological Signs of Internal Disease*, 3rd edn. Philadelphia: Saunders, 2003: 175–9.
3 Leonhardt JM, Heymann WR. Thyroid disease and the skin. *Dermatol Clin* 2002; **20**: 473–81.
4 Burman KD, McKinley-Grant L. Dermatologic aspects of thyroid disease. *Clin Dermatol* 2006; **24**: 247–55.

Hyperthyroidism [1–4]

Synonym
- Thyrotoxicosis

This is a hypermetabolic state that results from excessive production or administration of thyroid hormones—thyroxine (T_4) and triiodothyronine (T_3). It is most common in women.

Aetiology. Hyperthyroidism is usually due to Graves' disease (diffuse toxic goitre, Basedow's disease), but 10–15% of cases are due to other causes, including toxic multinodular goitre, adenoma, thyroiditis, and iatrogenic or factitious ingestion of T_4, iodine and iodine-containing drugs, such as amiodarone. Secondary hyperthyroidism may occur due to production of TSH or thyrotrophin-releasing hormone (TRH) from the pituitary or from tumours at other sites. Graves' disease is an autoimmune disorder in which there is a high incidence of antithyroid antibodies and of other autoimmune diseases. Thyroid-stimulating immunoglobulins (TSIs) such as long-acting thyroid stimulator (LATS, a 7S immunoglobulin) are typically present in Graves' disease. These bind to TSH receptors, acting as thyroid gland agonists.

Clinical features. Most of the features of hyperthyroidism (Table 62.4) are not specific to the cause. Increased sympathetic nervous

Table 62.4 Cutaneous features of hyperthyroidism.

Skin
Soft, smooth, velvety
Increased skin temperature
Palmar erythema, facial flushing
Increased sweating
Pruritus
Hyperpigmentation
Pretibial myxoedema*
Vitiligo*
Cutaneous signs of goitre: Pemberton sign and Maroni sign
Others—urticaria*, palmoplantar pustulosis*
Nails
Fast nail growth
Soft nails, koilonychia
Distal onycholysis (Plummer's nails)
Thyroid acropachy*
Hair
Fine thin hair, diffuse alopecia
Alopecia areata*

* Associated with autoimmune thyroid disease; not a feature of hyperthyroidism *per se*.

system activity causes vasodilatation, leading to warm skin, flushing, palmar erythema and increased sweating (especially of palms and soles). Hair is fine, with diffuse alopecia in about a third of patients. Nails may be thin, with koilonychia and onycholysis (Plummer's nails); the onycholysis typically commences on the fourth digit of the hands [5]. Hyperpigmentation, similar to that of Addison's disease, may occur due to increased corticotrophin (ACTH) levels, and may be diffuse or localized to scars, but usually spares the buccal mucosa. Hyperpigmented eyelids have been described (Jellinek's sign).

Facial suffusion may be provoked in patients with a large substernal goitre (Pemberton sign), and erythema (sometimes with pruritus) may occur in the skin overlying a toxic goitre (Maroni sign).

Pretibial myxoedema, thyroid acropachy (both discussed separately below) and exophthalmos are features of Graves' disease (collectively known as Diamond's triad), although pretibial myxoedema can also occur in Hashimoto's thyroiditis. The combination of *e*xophthalmos, pretibial *m*yxoedema and hypertrophic *o*steoarthropathy has also been termed the EMO syndrome. In addition to these linked conditions, cutaneous features of associated autoimmune disease may be present, especially vitiligo.

The associations between thyroid diseases and other dermatoses are considered separately below.

Diagnosis [6]. In most instances, negative feedback mechanisms cause suppressed serum TSH levels before T_4 or T_3 levels are elevated. The exception is when hyperthyroidism is of secondary type, due to increased TRH or TSH levels. Thyroid antibodies are less helpful, as they are common in euthyroid individuals, and TSI levels are not usually measured. Isotope scanning can confirm the cause (diffuse goitre, adenoma, etc.).

Treatment. Beta-blockers may be used in the initial phase of therapy to suppress the increased sympathetic activity. The hyperthyroid state can be reversed by surgery, radioactive iodine or therapy with antithyroid drugs (propylthiouracil and carbimazole). However, changes that are unrelated to the hormone production tend to persist. Ophthalmopathy is not influenced by a return to euthyroidism, and the prognosis in severe cases is doubtful.

References

1 Heymann WR. Cutaneous manifestations of thyroid disease. *J Am Acad Dermatol* 1992; **26**: 885–902.

2 Rosen T, Kleman GA, Jorizzo JL. Thyroid and the skin. In: Callen JP, Jorizzo JL, eds. *Dermatological Signs of Internal Disease*, 3rd edn. Philadelphia: Saunders, 2003: 175–9.

3 Boyne M, Dobs AS, Krasner AS, Provost TT. Evaluation and treatment of endocrine disorders. In: Provost TT, Flynn JA, eds. *Cutaneous Medicine: Cutaneous Manifestations of Systemic Disease*. Hamilton, Ontario: Decker, 2001: 413–51.

4 Leonhardt JM, Heymann WR. Thyroid disease and the skin. *Dermatol Clin* 2002; **20**: 473–81.

5 Tosti A, Baran R, Dawber RPR. The nail in systemic diseases and drug-induced changes. In: Baran R, Dawber RPR, Deberker DAR, Haneke E, Tosti A, eds. *Diseases of the Nails and Their Management*. Oxford: Blackwell Science, 2001: 223–329.

6 O'Reilly DS. Thyroid function tests: time for a reassessment. *BMJ* 2000; **320**: 1332–4.

Pretibial myxoedema

Synonym
- Localized myxoedema

Localized oedematous and thickened pretibial plaque formation occurs in 1–10% of patients with hyperthyroidism. It is usually a late feature, occurring after ophthalmopathy and diagnosis of hyperthyroidism (sometimes only becoming evident after antithyroid treatment has been initiated), but it can occasionally precede other features [1,2]. Almost all patients with pretibial myxoedema have ophthalmopathy [1]. The same process often occurs on the dorsum of the hallux, and may affect other sites, including the lower abdomen, arms, shoulders, neck and pinnae [3]. Pretibial myxoedema in euthyroid individuals is very rare [4], and must be distinguished from a recently described entity called chronic obesity lymphoedematous mucinosis [5], which arises on the calves and shins of the obese.

Aetiology. It is unclear whether circulating or local factors are the main determinant of pretibial myxoedema. It was demonstrated over two decades ago that serum of pretibial myxoedema patients caused a two- to threefold increase in hyaluronic acid production by cultured fibroblasts from the pretibial area of patients and normal subjects, but had no effect on those from the shoulder or prepuce [6]. Most patients with pretibial myxoedema, whether thyrotoxic or not, have elevated levels of LATS in their serum, so this specific antibody does not seem to be causally involved [7]. A role for TSI was proposed, as fibroblasts from the pretibial and orbital regions have TSH receptors; TSIs have agonist effects on TSH receptors. Ribonucleic acid sequences encoding parts of the TSH receptor, and TSH receptor-like immunoreactivity, have been demonstrated in fibroblasts from these sites in affected patients [8]. There is, however, no obvious association between the clinical manifestations and the presence of TSH receptor autoantibodies. Recent research demonstrated that patients with pretibial myxoedema, but not control subjects, have circulating immunoglobulin A2 (IgA2) fibroblast antibodies capable of binding to a 54-kDa antigen of dermal fibroblast cell lines [9]. IGF-1 has also been suggested to have a role in the pathogenesis [10]. However, the occurrence of pretibial myxoedema in both the donor and recipient site in a patient who had excision of pretibial myxoedema, with normal skin grafted into the area, suggests that there are local factors operative which are not explained by site-specific properties of the dermal fibroblasts [11].

Pretibial myxoedema also occurs in other situations, especially in chronic stasis dermatitis [12].

Histopathology. The dermis is thickened, especially in the middermis and deeper part, by extensive deposits of acid mucopolysaccharides, which may cause separation of the collagen fibres. Stellate, mucin-producing fibroblasts may be prominent.

Clinical features. In many instances, the lesions first appear on the anterolateral aspect of the lower limbs and only later extend to the back of the legs, and feet (Fig. 62.4). The nodules are pink or skin-coloured, sometimes yellow-brown and waxy, with promi-



Fig. 62.4 Elephantiasic pretibial myxoedema.

nent hair follicles giving a 'peau d'orange' appearance. They may occur in old or recent scars [11,13,14]; localized pruritus or hypertrichosis over the lesions may be a feature, and localized hyperhidrosis has also been reported [15,16]. Three clinical types are recognized:

1 Sharply circumscribed, in which both nodular and tuberous lesions appear on the shins and toes
2 Diffuse, producing solid non-pitting oedema of the shins and feet
3 Elephantiasic, in which there is both oedema and nodule formation

Treatment. Topical glucocorticoids, with or without occlusive dressings, or intralesional glucocorticoid injections, may be useful [1,17]. The long-term benefits of surgery vary, although debulking procedures may be of benefit (for example, for lesions on the toes) [18]. Octreotide [19,20], plasmapheresis (perhaps acting by removal of TSIs, although not all patients respond) [21], photochemotherapy and intravenous immunoglobulin [22] have been advocated. Graduated compression bandaging can be used as an addition to all therapies provided there is no vascular contraindication; pneumatic compression [23] has also been used.

References

1 Fatourechi V. Pretibial myxedema: pathophysiology and treatment options. *Am J Clin Dermatol* 2005; **6**: 295–309.
2 Srebnik A, Ophir J, Brenner S. Euthyroid pretibial myxedema. *Int J Dermatol* 1992; **31**: 431–2.
3 Noppakun N, Bancheun K, Chandraprasert S. Unusual locations of localized myxoedema in Graves' disease. *Arch Dermatol* 1986; **122**: 85–8.
4 Buljan-Cvijanovic M, Neal JM, Zemtsov A. Euthyroid pretibial myxedema. *Endocr Pract* 1998; **4**: 375–7.
5 Tokuda Y, Kawachi S, Murata H, Saida T. Chronic obesity lymphoedematous mucinosis: three cases of pretibial mucinosis in obese patients with pitting oedema. *Br J Dermatol* 2006; **154**: 157–61.
6 Cheung HS, Nickoloff JT, Kamiel MB *et al.* Stimulation of fibroblast biosynthetic activity by serum of patients with pretibial myxedema. *J Invest Dermatol* 1978; **71**: 12–7.
7 Lynch PJ, Maize JC, Sisson JC. Pretibial myxedema and nonthyrotoxic thyroid disease. *Arch Dermatol* 1973; **107**: 107–11.
8 Stadlmayr W, Spitzweg C, Bichlmair AM, Heufelder AE. TSH receptor transcripts and TSH receptor-like immunoreactivity in orbital and pretibial fibroblasts of patients with Graves' ophthalmopathy and pretibial myxedema. *Thyroid* 1997; **7**: 3–12.
9 Arnold K, Metcalfe R, Weetman AP. Immunoglobulin A class fibroblast antibodies in patients with Graves' disease and pretibial myxedema. *J Clin Endocrinol Metab* 1995; **80**: 3430–7.
10 Kriss JP. Pathogenesis and treatment of pretibial myxedema. *Endocrinol Metab Clin North Am* 1987; **16**: 409–15.
11 Rapoport B, Alsabeh R, Aftergood D, McLachlan SM. Elephantiasis—pretibial myxedema: insight into and a hypothesis regarding the pathogenesis of the extrathyroid manifestations of Graves' disease. *Thyroid* 2000; **10**: 629–30.
12 Somach SC, Helm TN, Lawlor KB. Pretibial mucin: histologic patterns and clinical correlation. *Arch Dermatol* 1993; **129**: 1152–6.
13 Wright AL, Buxton PK, Menzies D. Pretibial myxedema localized to scar tissue. *Int J Dermatol* 1990; **29**: 54–5.
14 Tong DW, Ho KK. Pretibial myxoedema presenting as a scar infiltrate. *Australas J Dermatol* 1998; **39**: 255–7.
15 Kato N, Ueno H, Matsubara M. A case report of EMO syndrome showing localised hyperhidrosis in pretibial myxedema. *J Dermatol* 1991; **18**: 598–604.
16 Gitter DG, Sato K. Localized hyperhidrosis in pretibial myxedema. *J Am Acad Dermatol* 1990; **23**: 250–4.
17 Boyne M, Dobs AS, Krasner AS, Provost TT. Evaluation and treatment of endocrine disorders. In: Provost TT, Flynn JA, eds. *Cutaneous Medicine: Cutaneous Manifestations of Systemic Disease*. Hamilton, Ontario: Decker, 2001: 413–51.
18 Derrick EK, Tanner B, Price ML. Successful surgical treatment of severe pretibial myxoedema. *Br J Dermatol* 1995; **133**: 317–8.
19 Chang TC, Kao SCS, Huang KM. Octreotide and Graves' ophthalmopathy and pretibial myxoedema. *BMJ* 1992; **304**: 158.
20 Shinohara M, Hamasaki Y, Katayama I. Refractory pretibial myxoedema with response to intralesional insulin-like growth factor 1 antagonist (octreotide): downregulation of hyaluronic acid production by the lesional fibroblasts. *Br J Dermatol* 2000; **143**: 1083–6.
21 Dandona P, Marshall NJ, Bidey SP *et al.* Successful treatment of exophthalmos and pretibial myxoedema with plasmapheresis. *BMJ* 1979; **1**: 374–6.
22 Antonelli A, Saracino A, Agostini S *et al.* [Results of high-dose intravenous immunoglobulin treatment of patients with pretibial myxedema and Basedow's disease: preliminary findings; in Italian]. *Clin Ter* 1992; **141**: 63–8.
23 Schleicher SM, Milstein HJ. Treatment of pretibial mucinosis with gradient pneumatic compression. *Arch Dermatol* 1994; **130**: 842–4.

Thyroid acropachy [1,2]

Clubbing of the fingers and toes in Graves' disease, associated with soft-tissue swelling of hands and feet and with periosteal new bone formation, is termed thyroid acropachy. It occurs in less than 1% of thyrotoxic patients, and is usually associated with exophthalmos and pretibial myxoedema (Diamond's triad), occurring in about 5% of patients with these other features. Acropachy usually appears some time after the other components of the syndrome, usually after treatment of Graves' disease. Pathologically, there is periosteal new bone formation involving the phalanges and other distal long bones, which is manifest radiologically as a

feathery pattern of lamellar new bone parallel to the diaphyses, sometimes with perpendicularly orientated new bone spicules, and which can be demonstrated as osteoblastic activity using a bone scan [2]. The proximal phalanges and first or second metacarpals are most commonly affected. Most patients have minimal or no symptoms, but in those with symptoms, stiffness is the most frequent; by comparison with hypertrophic pulmonary osteoarthropathy, pain and heat are absent. Pachydermoperiostosis (Chapter 15) shows some resemblance to acropachy, but other features of the syndrome are absent.

References

1 Kinsella RA, Bach DK, Lynch PJ. Thyroid acropachy. *Med Clin North Am* 1968; **52**: 393–5.

2 Leonhardt JM, Heymann WR. Thyroid disease and the skin. *Dermatol Clin* 2002; **20**: 473–81.

Hypothyroidism [1–3]

Synonyms
- Myxoedema
- Hypothyreosis

In hypothyroidism, there is a slowed metabolic rate involving all organs. It is caused by a decreased concentration of free thyroid hormone in the blood, or target cell resistance to thyroid hormone.

Aetiology. The most common cause is idiopathic (primary) hypothyroidism, which is an autoimmune disease, usually affecting women from the fourth decade; the prevalence rate is almost 2% in females but a tenth of this in males. A high percentage of patients with Hashimoto's thyroiditis (who may initially be thyrotoxic) eventually develop hypothyroidism, and iatrogenic hypothyroidism may occur as a late effect of radio-iodine treatment of thyrotoxicosis. Secondary hypothyroidism due to pituitary disease is uncommon, TSH production being relatively spared compared to sex hormone and ACTH production, but pituitary infarction, haemorrhage or neoplasm may lead to hypothyroidism in some cases. Severe iodine deficiency, or drugs such as lithium and bexarotene, may cause hypothyroidism. Congenital hypothyroidism (cretinism), usually due to absence of the thyroid, is rare. Tertiary hypothyroidism is due to hypothalamic failure of TRH production.

Clinical features. Cutaneous changes of hypothyroidism (Table 62.5) [1–7] were well known in the latter part of the 19th century [4]. The most prominent manifestation of hypothyroidism is related to dermal accumulation of mucopolysaccharides, in particular chondroitin sulphate and hyaluronic acid, which bind water in the tissue and lead to puffiness of the skin. Whilst characteristic, the features may be insidious in development, and some are of low specificity. For example, loss of the outer third of the eyebrow (madarosis, Hertog's sign) is common in many euthyroid elderly individuals. The yellowish skin colour is due to a combination of alterations in connective tissue of the dermis, carotenaemia and vasoconstriction (due to the slowed metabolic rate). The connective tissue changes also cause loss of support of dermal vessels and, along with decreased levels of clotting factors, predispose to purpuric lesions or bruising. Asteatotic eczema [5] and keratoderma of palms and soles [6] may occur, sometimes as the presenting feature. Features of previous autoimmune thyrotoxicosis, or of associated autoimmune diseases, may also be present. The hypometabolic state and low core temperature may cause cold extremities due to reflex vasoconstriction. Loss of hair is common, occurring in about 50% of affected individuals (Fig. 62.5).

Table 62.5 Cutaneous and oral features of hypothyroidism.

Skin
Pale, cold, scaly and wrinkled skin
Xerosis, asteatotic eczema, itch
Palmoplantar keratoderma
Absence of sweating
Ivory-yellow skin colour
Puffy oedema of hands, face and eyelids
Purpura and ecchymoses
Punctate telangiectases on arms and fingertips
Delayed wound healing
Xanthomatosis (secondary to hyperlipidaemia)
Nails
Brittle and striated nails
Slow nail growth
Hair
Coarse sparse scalp hair
Loss of pubic, axillary and facial hair
Loss of lateral eyebrows (madarosis)
Oral
Large tongue
Gingival swelling (in congenital hypothyroidism)
Oral candidosis



Fig. 62.5 Diffuse alopecia and coarse hair due to hypothyroidism.

In congenital hypothyroidism ('cretinism'), coarseness of features, lethargy, periorbital puffiness, swelling of hands and feet, macroglossia, cold and dry skin with livedo, umbilical hernia and poor muscle tone are pathognomic, but may not be apparent until a few months of age. Cutis marmorata occurs due to vasoconstriction. Without treatment, physical and mental development is retarded. The scalp hair is coarse, and the eyebrows may be confluent.

In juvenile hypothyroidism, abnormal physical and mental development is the principal manifestation of the disease. Some children develop hypertrichosis of the upper back and shoulders. The waxy, yellowish skin changes may be prominent, but the puffiness may be less apparent than in older individuals. Rarely, juvenile hypothyroidism is associated with sexual precocity; the penis and scrotum enlarge in males, or menstruation and galactorrhoea occur in females, but axillary and pubic hair do not develop.

Diagnosis. Protein-bound iodine, T_4 and T_3 levels are low. In primary hypothyroidism, the TSH level is elevated; in pituitary failure, it is low or undetectable. The histological changes in the dermis may be helpful in difficult cases [8]. Recognition of hypothyroidism in the elderly may be difficult. Symptoms and signs develop insidiously and may easily be taken as evidence of arteriosclerotic disease. Serum TSH is recommended as the primary investigation for screening of elderly patients.

References

1 Heymann WR. Cutaneous manifestations of thyroid disease. *J Am Acad Dermatol* 1992; **26**: 885–902.
2 Rosen T, Kleman GA, Jorizzo JL. Thyroid and the skin. In: Callen JP, Jorizzo JL, eds. *Dermatological Signs of Internal Disease*, 3rd edn. Philadelphia: Saunders, 2003: 175–9.
3 Boyne M, Dobs AS, Krasner AS, Provost TT. Evaluation and treatment of endocrine disorders. In: Provost TT, Flynn JA, eds. *Cutaneous Medicine: Cutaneous Manifestations of Systemic Disease*. Hamilton, Ontario: Decker, 2001: 413–51.
4 Doyle L. Myxoedema: some early reports and contributions by British authors, 1873–1898. *J R Soc Med* 1991; **84**: 103–6.
5 Warin RP. Eczéma craquelé as the presenting feature of myxoedema. *Br J Dermatol* 1973; **89**: 289–91.
6 Good JM, Neill SM, Rowland Payne CME. Keratoderma of myxoedema. *Clin Exp Dermatol* 1988; **13**: 339–41.
7 Crotty CP, Dicken CH. Blue fingertips associated with myxedema. *Arch Dermatol* 1981; **117**: 158–9.
8 Means MA, Dobson RL. Cytological changes in the sweat gland in hypothyroidism. *JAMA* 1963; **186**: 113–5.

Thyroid disease and other dermatoses

Thyroglossal cysts are in the differential diagnosis of other congenital cysts in the neck, such as branchial cysts or ectopic bronchial mucosa.

Thyroid cancer may give rise to cutaneous metastases, or to thyroxine-producing metastases which therefore cause features of thyrotoxicosis. Thyroid cancer is also a feature of syndromes such as Cowden's disease and multiple endocrine neoplasia (MEN) type 2, discussed elsewhere in this chapter.

Table 62.6 Some skin disorders and other diseases with prominent cutaneous manifestations that have been associated with thyroid dysfunction or with the presence of antithyroid antibodies.

Bullous diseases	*Others*
Dermatitis herpetiformis	Chronic urticaria
Bullous pemphigoid	Palmoplantar pustulosis
Pemphigus	Psoriasis
Pemphigoid gestationis	Atopic dermatitis
Endocrine diseases	Sweet's syndrome
Pernicious anaemia	Sarcoidosis
Diabetes mellitus	POEMS syndrome
Addison's disease	Granuloma annulare
Acanthosis nigricans with insulin resistance	Pseudoxanthoma elasticum
Autoimmune polyglandular syndromes I–III	Polyostotic fibrous dysplasia
Other autoimmune conditions	Melasma
Alopecia areata	Melanoma
Vitiligo	Lichen sclerosus
Premature greying (canities)	Xanthelasma
Connective tissue diseases	
Lupus erythematosus	
Scleroderma	
Dermatomyositis	
Sjögren's syndrome	

POEMS, *p*olyneuropathy, *o*rganomegaly, *e*ndocrinopathy, *M* protein and *s*kin changes (syndrome).

There are associations between either the presence of antithyroid antibodies, or of overt thyroid dysfunction or thyroiditis, with a number of other skin diseases and disorders with cutaneous manifestations (Table 62.6) [1–13]. Some of these associations are based on small studies, but associations with disorders such as dermatitis herpetiformis and chronic urticaria are strongly supported by the available literature. About 20% of children with alopecia areata have thyroid antibodies, although clinical thyroid dysfunction is rare [13]. It is debatable to what extent management is altered by routinely testing for thyroid antibodies or thyroid dysfunction in the absence of other clinical symptoms, although there are reported instances where chronic urticaria, for example, has resolved after treatment of associated thyrotoxicosis; it has also been recommended that T_4 treatment should be considered in euthyroid patients with chronic urticaria if they have evidence of thyroid autoimmunity [7]. An increased incidence of hypothyroidism is reported in melanoma [14,15].

References

1 Heymann WR. Cutaneous manifestations of thyroid disease. *J Am Acad Dermatol* 1992; **26**: 885–902.
2 Rosen T, Kleman GA, Jorizzo JL. Thyroid and the skin. In: Callen JP, Jorizzo JL, eds. *Dermatological Signs of Internal Disease*, 3rd edn. Philadelphia: Saunders, 2003: 175–9.
3 Agner T, Sindrup JH, Høier-Madsen M *et al*. Thyroid disease in pustulosis palmoplantaris. *Br J Dermatol* 1989; **121**: 487–91.

4 Rosén K, Mobacken H, Nilsson L. Increased prevalence of antithyroid antibodies and thyroid disease in pustulosis palmoplantaris. *J Am Acad Dermatol* 1981; **18**: 666–71.
5 Lanigan SW, Short P, Moult P. The association of chronic urticaria and thyroid autoimmunity. *Clin Exp Dermatol* 1987; **12**: 335–8.
6 Leznoff A, Sussman GL. Syndrome of idiopathic chronic urticaria and angioedema with thyroid autoimmunity: a study of 90 patients. *J Allergy Clin Immunol* 1989; **84**: 66–71.
7 Heymann WR. Chronic urticaria and angioedema associated with thyroid autoimmunity: review and therapeutic implications. *J Am Acad Dermatol* 1999; **40**: 229–32.
8 Cunningham MJ, Zone JJ. Thyroid abnormalities in dermatitis herpetiformis: prevalence of clinical thyroid disease and thyroid autoantibodies. *Ann Intern Med* 1985; **102**: 194–6.
9 Peréz B, Kraus A, Lopez G *et al*. Autoimmune thyroid disease in primary Sjögren's syndrome. *Am J Med* 1995; **99**: 480–4.
10 Goolamali SK, Barnes EW, Irvine WJ, Shuster S. Organ specific antibodies in patients with lichen sclerosus. *BMJ* 1974; **iv**: 78–9.
11 Harrington CI, Dunsmore IR. An investigation into the incidence of autoimmune disorders in patients with lichen sclerosus et atrophicus. *Br J Dermatol* 1981; **104**: 563–6.
12 Kalmus K, Kovatz S, Shilo L *et al*. Sweet's syndrome and subacute thyroiditis. *Postgrad Med J* 2000; **76**: 229–30.
13 Milgraum SS, Mitchell AJ, Bacon GE *et al*. Alopecia areata, endocrine function, and autoantibodies in patients 16 years of age or younger. *J Am Acad Dermatol* 1987; **17**: 57–61.
14 Ellerhorst JA, Cooksley CD, Broemeling L *et al*. High prevalence of hypothyroidism among patients with cutaneous melanoma. *Oncol Rep* 2003; **10**: 1317–20.
15 Shah M, Orengo IF, Rosen T High prevalence of hypothyroidism in male patients with cutaneous melanoma. *Dermatol Online J* 2006; **28**: 12:1.

Parathyroid disease

Skin changes are not a particular feature of hyperparathyroidism, although subcutaneous calcification may occur (especially in hyperparathyroidism secondary to renal failure; see below) [1–4].

Itch is thought to be related to hyperparathyroidism [5], although this is poorly documented [6] and some of the documentation is inferred (from resolution in some instances of renal itch after parathyroidectomy, or paraneoplastic itch after resection of parathormone (PTH)-producing bronchial tumours). Hyperparathyroidism has also been linked to cutaneous T-cell lymphoma [7].

Hypoparathyroidism may cause skin changes somewhat similar to those of hypothyroidism—the skin may be dry, keratotic and puffy, with sparse, coarse hair. Nails are brittle and ridged, with cracking at the free margin, or crumbling of the distal nail plate. Chloasma or pellagra-like pigmentary disturbance is less common [3,8].

There are numerous reports of pustular psoriasis of the von Zumbusch type being provoked by hypocalcaemia, with resolution of the pustulation and erythroderma with resolution of the skin eruption on restoring normocalcaemia [9,10] and one of the authors has personal experience of a patient presenting with a severe pustular exacerbation of chronic plaque psoriasis associated with hypocalcaemic tetany due to primary hypoparathyroidism.

Calciphylaxis of the skin, resulting in localized necrosis due to vascular calcific occlusion, is usually seen in renal failure, but there are occasional reports of it occurring in the setting of normal renal function and hyperparathyroidism [11].

Chronic mucocutaneous candidiasis, especially of the nails and oral mucosa, may occur in conjunction with hypoparathyroidism when this occurs as part of the polyglandular autoimmune syndrome (see below) or in association with immunological defects such as Di George's syndrome (in which there is parathyroid gland agenesis) [1], but it is not a feature of post-thyroidectomy iatrogenic hypoparathyroidism.

Subcutaneous ossification is a feature of Albright's hereditary osteodystrophy, which encompasses both pseudohypoparathyroidism type Ia and pseudopseudohypoparathyroidism [1,12–14]. The somatic features include obesity, short stature and short metacarpals—Albright's sign is dimpling over the knuckle of the typically affected fourth metacarpal. The dominant condition occurs due to a heterozygous functional defect of the α-subunit of the stimulatory G protein (G_s α protein) of adenylate cyclase, with which PTH interacts at the cell surface. This is encoded by the *GNAS1* gene on chromosome 20q13.3, but there are tissue-specific differences in expression of G_s α and other *GNAS1* transcripts that are different for the maternal and paternal alleles [13]. It is now known that pseudopseudohypoparathyroidism is the same disorder as pseudohypoparathyroidism type Ia, but with the genetic defect inherited from the father; patients have the somatic features of pseudohypoparathyroidism, but with normal hormone responses [14].

References

1 Marx SJ. Hyperparathyroid and hypoparathyroid disorders. *N Engl J Med* 2000; **343**: 1863–75.
2 Walsh JS, Fairley JA. Calcifying disorders of the skin. *J Am Acad Dermatol* 1995; **33**: 693–706.
3 Braverman IM. *Skin Signs of Systemic Disease*, 3rd edn. Philadelphia: Saunders, 1998: 438–91.
4 Khafif RA, Delima C, Silverberg A *et al*. Acute hyperparathyroidism with systemic calcinosis. *Arch Intern Med* 1989; **149**: 681–4.
5 Gartner R. Itching in hyperparathyroidism. *Med Wochenschr* 2001; **126**: 190.
6 Bernhard JD. Endocrine and metabolic itches. In: Bernhard JD. *Itch: Mechanisms and Management of Pruritus*. New York: McGraw-Hill, 1994: 251–60.
7 Owen CM, Blewitt RW, Harrison PV, Yates VM. Two cases of primary hyperparathyroidism associated with primary cutaneous lymphoma. *Br J Dermatol* 2000; **142**: 120–3.
8 Kawamura A, Kinoshita MT, Suzuki H. Generalized pustular psoriasis with hypoparathyroidism. *Eur J Dermatol* 1999; **9**: 574–6.
9 Tercedor J, Rodenas JM, Munoz M *et al*. Generalized pustular psoriasis and idiopathic hypoparathyroidism. *Arch Dermatol* 1991; **127**: 1418–9.
10 Hirano K, Ishibashi A, Yoshino Y. Cutaneous manifestations in idiopathic hypoparathyroidism. *Arch Dermatol* 1974; **109**: 242–4.
11 Mirza I, Chaubay D, Gunderia H *et al*. An unusual presentation of calciphylaxis due to primary hyperparathyroidism. *Arch Pathol Lab Med* 2001; **125**: 1351–3.
12 Trueb RM, Panizzon RG, Burg G. Cutaneous ossification in Albright's hereditary osteodystrophy. *Dermatology* 1993; **186**: 205–9.
13 Bastepe M, Juppner H. Pseudohypoparathyroidism: new insights into an old disease. *Endocrinol Metab Clin North Am* 2000; **29**: 569–89.
14 Simon A, Koppeschaar HP, Roijers JF *et al*. Pseudohypoparathyroidism type Ia—Albright hereditary osteodystrophy: a model for research on G protein-coupled receptors and genomic imprinting. *Neth J Med* 2000; **56**: 100–9.

Multiple endocrinopathy syndromes

It is common that autoimmune conditions may occur simultaneously—due to, for example, human leukocyte antigen (HLA) linkage. Some of these produce an overlap between endocrine disease and:

- Other autoimmune conditions, e.g. polyglandular autoimmune syndrome (see below), various combinations of Sjögren's syndrome and sarcoidosis with endocrine autoimmune conditions [1,2]
- Infections, such as in autoimmune polyglandular syndrome type I (see below)
- Ectodermal changes, e.g. alopecia areata (commonly), ANOTHER syndrome (*a*lopecia, *n*ail dystrophy, *o*phthalmic complications, *t*hyroid dysfunction, *h*ypohidrosis, *e*phelides and enteropathy, *r*espiratory tract infections) [3]
- Gastrointestinal disease, e.g. the triple A syndrome (Allgrove's syndrome) of achalasia, addisonianism and alacrima (MIM #231550); IPEX syndrome (*i*mmune dysregulation, *p*olyendocrinopathy, *e*nteropathy, *X*-linked syndrome) in which diarrhoea is a significant feature with an icthyosiform dermatitis, and also diabetes, throiditis and haemolytic anaemia [4]
- Pigmentary change, e.g. vitiligo (commonly), Carney complex (see cardiac disease, below), POEMS syndrome (see cardiac disease, below)
- Alopecia areata—associated with thyroid disease and other autoimmune conditions
- Bone disease, e.g. McCune–Albright syndrome (MIM #174800); G protein mutations cause dysregulation of cyclic adenosine monophosphate (cAMP), leading to growth and hyperfunction of many organs—features include hypophosphataemic osteodystrophy, hyperparathyroidism, hyperthyroidism, large irregularly shaped café-au-lait macules, Cushing's syndrome, acromegaly and hyperprolactinaemia
- Cerebral disease, e.g. triple H syndrome—*h*ippocampus (anterograde memory loss), *h*air follicle (alopecia areata), *h*ypothalamic–pituitary–adrenal axis (isolated ACTH deficiency) [5].

Autoimmune polyendocrine syndromes [6–13]

Three types of autoimmune polyendocrine (polyglandular) syndrome (APS) are described—types 1 to 3—although there may also be other, incomplete forms [13]. The pathogenesis of these disorders is discussed in detail in [8,13]. The most important example dermatologically is APS type 1 (MIM 240300), which is usually due to the R257X mutation of the *AIRE* gene on chromosome 21q22.3 [11] and is associated with about 13% of cases of Addison's syndrome [13]. It is also termed mucocutaneous candidiasis–endocrinopathy syndrome, multiple endocrinopathy syndrome, *a*utoimmune *p*olyendocrinopathy–*c*andidiasis–*e*ctodermal *d*ystrophy (APECED) syndrome, or Whitaker's syndrome. Table 62.7 outlines the diagnostic criteria; the dermatological features include mucocutaneous candidiasis, nail dystrophy, alopecia areata, vitiligo and cutaneous features of Addison's disease [9,11,13].

An interesting feature of vitiligo in this condition, which does not occur in isolated vitiligo or in other autoimmune combinations, is the presence of complement-fixing melanocyte autoantibodies [11]. Most patients also have adrenal cortex autoantibodies, and those with gonadal failure have steroid-producing cell antibodies. Nail dystrophy and tooth enamel defects comprise the ectodermal dystrophy component. Epidermolysis bullosa acquisita has also been reported in type 1 syndrome [12].

Patients with APS types 2 and type 3 more commonly have diabetes, but less commonly have alopecia or vitiligo, and do not have chronic mucocutaneous candidiasis. Addison's disease is present in all patients with APS type 2, which has been further divided by some authors according to the specific endocrinopathies present; thus, Addison's disease with autoimmune thyroid disease is termed Schmidt's syndrome, Addison's disease with immune-mediated diabetes (with or without thyroid disease) is Carpenter's syndrome. APS type 3 is defined as co-occurrence of autoimmune thyroid disease with two other autoimmune disorders in the absence of Addison's disease [14]. APS type 2 is due to defects in the *HLA* region on 6p21 or in *CTLA4* on 2q33. It should be noted that not all of the autoimmune components are actually endocrine in type; vitiligo is not uncommon, and Schmidt's multiple endocrine insufficiency syndrome has been reported with alopecia areata and the stiff man syndrome (due to autoantibodies to glutamic acid decarboxylase).

The MEN syndromes are discussed later in this chapter.

Table 62.7 Type 1 autoimmune polyglandular syndrome diagnostic criteria (defined by the presence of two or more of the three major features).

Major features
Chronic mucocutaneous candidiasis (usually by age 5 years, present in about 80%)
Chronic hypoparathyroidism (usually by age 10 years, present in about 90%)
Autoimmune adrenal insufficiency (usually by age 15 years, present in about 70%, frequently autoantibody positive)
Other features
Hypergonadotrophic hypogonadism (45%)
Diabetes mellitus
Thyroid antibodies or overt thyroid dysfunction
Alopecia areata (25%)
Vitiligo (10%)

References

1 Seinfeld ED, Sharma OP. TASS syndrome: unusual association of thyroiditis, Addison's syndrome, Sjögren's syndrome and sarcoidosis. *J R Soc Med* 1983; **76**: 883–5.

2 Cox NH, McCrea J. The association of Sjögren's syndrome, sarcoidosis, ulcerative colitis and other autoimmune disorders. *Br J Dermatol* 1996; **134**: 1138–40.

3 Pike MG, Baraitser M, Dinwiddie R *et al*. A distinctive type of hypohidrotic ectodermal dysplasia featuring hypothyroidism. *J Pediatr* 1986; **108**: 109–11.

4 Baud O, Goulet O, Canioni D *et al*. Treatment of the Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked syndrome (IPEX) by allogeneic bone marrow transplantation. *N Engl J Med* 2001; **344**: 1758–62.

5 Farooqi IS, Jones MK, Evans M *et al*. Triple H syndrome: a novel autoimmune endocrinopathy characterised by dysfunction of the hippocampus, hair follicle, and hypothalamic–pituitary–adrenal axis. *J Clin Endocrinol Metab* 2000; **85**: 2644–8.

6 Feingold KR, Elias PM. Endocrine–skin interactions. *J Am Acad Dermatol* 1988; **19**: 1–240.

7 Baker JR. Autoimmune endocrine diseases. *JAMA* 1997; **278**: 1931–7.

8 Eisenbarth GS, Gottlieb PA. Autoimmune polyendocrine syndromes. *N Engl J Med* 2004; **350**: 2068–79.

9 Ahonen P, Myllarniemi S, Sipila I *et al*. Clinical variation of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) in a series of 68 patients. *N Engl J Med* 1990; **332**: 1829–36.

10 Betterle C, Dalpra C, Greggio N *et al*. Clinical review 93: autoimmune polyglandular syndrome type 1. *J Clin Endocrinol Metab* 1998; **83**: 1049–55.

11 Collins SM, Dominguez M, Ilmarinen T *et al*. Dermatological manifestations of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome. *Br J Dermatol* 2006; **154**: 1088–93.

12 Burke WA, Briggaman RA, Gammon WR. Epidermolysis bullosa acquisita in a patient with multiple endocrinopathies syndrome. *Arch Dermatol* 1986; **122**: 187–9.
13 Betterle C, Dal Pra C, Mantero F, Zanchetta R. Autoimmune adrenal insufficiency and autoimmune polyendocrine syndromes: autoantibodies, autoantigens, and their applicability in diagnosis and disease prediction. *Endocrin Rev* 2002; **23**: 327–64.
14 Ten S, New M, Maclaren N. Clinical review 130: Addison's disease 2001. *J Clin Endocrinol Metab* 2001; **86**: 2909–22.

Cutaneous markers of internal malignancy [1–11]

Introduction and classification

The different types of skin change associated with internal malignancy, and the links between systemic neoplasia and consequent or associated skin conditions, are so numerous that to report all documented associations here is impracticable. We suggest some broad categories for consideration; this includes disorders in those with a known internal malignancy but the emphasis is on skin manifestations that provide clues to internal malignancy or that indicate a need for malignancy screening. The main categories are:

1 Multisystem and haemopoietic tumours that involve the skin
2 Direct tumour spread from adjacent or deeper tissues
3 Cutaneous metastasis from internal tumours (indirect tumour spread to the skin)
4 Genetically determined syndromes with cutaneous manifestations, where there is a recognized predisposition to internal malignancy (also termed 'genodermatoses with malignant potential')
5 Paraneoplastic disorders—cutaneous reaction patterns that have an association with neoplasia involving various internal organ systems
6 Indirect cutaneous markers of internal malignancy (markers of exposure to carcinogens, cancers of the skin related to immunosuppression, infections, etc., in which those affected have a higher risk of internal malignancy).

Investigation for internal malignancy

Potential cutaneous markers of internal malignancy vary in their reliability for predicting underlying neoplasia. Additionally, other factors such as malaise, weight loss, non-specific or non-cutaneous focal symptoms may all play a part in deciding which patients to investigate and how extensively. There may be non-specific cutaneous markers of disease (such as purpura, stigmata of liver disease, etc.) that influence a decision; these are discussed elsewhere in this chapter. A clinical decision on the extent of investigation and screening, if any, must therefore be based on the strength of the association and on the clinical history and examination in the individual patient. It is helpful to consider various skin eruptions in terms of the likelihood of the cutaneous features suggesting the presence of internal malignancy—this may be obvious in some situations (e.g. internal tumours metastatic to the skin), but the strength of associations between some paraneoplastic dermatoses and internal malignancy varies hugely (as discussed later).

In some situations, simple investigations, such as chest radiography, full blood count, liver enzymes, non-specific markers of disease (such as erythrocyte sedimentation rate) or of possible tumour burden (such as lactate dehydrogenase), urine analysis and stool examination for occult blood, may be sufficient. Rapid changes in investigative techniques, such as the speed and accuracy of magnetic resonance imaging (MRI), emerging techniques such as positron emission tomography (PET scan), use of serological tumour markers (such as CA-125 for ovarian tumours, prostate-specific antigen, etc.) and, in inherited cancer susceptibility, the ability to identify individuals who have genes linked with malignant disease, are all altering the ease and extent of investigation that may be appropriate. Thus advice that was once very appropriate (such as the conclusion by many authors that investigation in dermatomyositis should be guided by careful clinical history and examination, and by pursuit of any abnormality of simple tests) must be viewed in the context not only of the tests that were readily available at the time, but also in the light of new tests that may help to identify subgroups with a higher than average risk of a malignancy being found.

Cutaneous adverse reactions to drugs used to treat malignancy are a related topic that will not be considered here, but is covered in Chapter 75 and in [11].

References

1 Braverman IM. *Skin Signs of Systemic Disease*, 3rd edn. Philadelphia: Saunders, 1998.
2 Callen JP, Jorizzo JL, eds. *Dermatological Signs of Internal Disease*, 3rd edn. Philadelphia: Saunders, 2003.
3 Waldenstrom JG. *Paraneoplasia: Biological Signals in the Diagnosis of Cancer*. New York: Wiley, 1978.
4 Poole S, Fenske NA. Cutaneous markers of internal malignancy, 1: malignant involvement of the skin and the genodermatoses. *J Am Acad Dermatol* 1993; **28**: 1–13.
5 Poole S, Fenske NA. Cutaneous markers of internal malignancy, 2: paraneoplastic dermatoses and environmental carcinogens. *J Am Acad Dermatol* 1993; **28**: 147–64.
6 Lookingbill DP, Spangler N, Helm KF. Cutaneous metastases in patients with metastatic carcinoma: a retrospective study of 4020 patients. *J Am Acad Dermatol* 1993; **29**: 228–36.
7 Chung VQ, Moschella SL, Zembowicz A, Liu V. Clinical and pathologic findings of paraneoplastic dermatoses. *J Am Acad Dermatol* 2006; **54**: 745–62.
8 Provost TT, Laman SD, Bell WR. Paraneoplastic dermatoses. In: Provost TT, Flynn JA, eds. *Cutaneous Medicine: Cutaneous Manifestations of Systemic Disease*. Hamilton, Ontario: Decker, 2001: 367–88.
9 Boyce S, Harper J. Paraneoplastic dermatoses. *Dermatol Clin* 2002; **20**: 523–32.
10 Cohen PR, Kurzrock R, eds. Genodermatoses with malignant potential. *Dermatol Clinics* 1995; **13**: 1–243.
11 Thomas VD, Thomas CR, eds. Internal malignancy and the skin: paraneoplastic and cancer treatment-related cutaneous disorders. *Dermatol Clinics* 2008; **26**: 1–182.

Multisystem and haemopoietic tumours that involve the skin [1–3]

This category includes a number of tumours, discussed in other chapters, in which the skin is involved as part of a multisystem neoplasm. The importance for dermatologists is that the diagnosis may present due to skin lesions, or that the skin may be the most accessible site for histological diagnosis.

The type of skin involvement that may occur in such disorders ranges from very non-specific (such as purpura, which may reflect

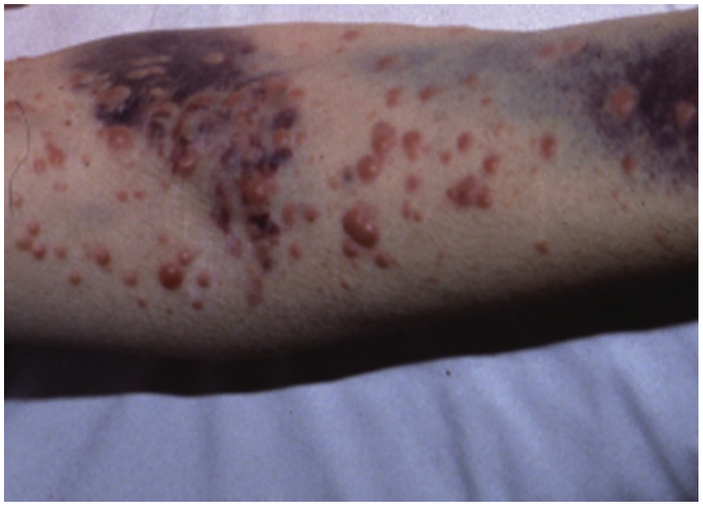


Fig. 62.6 Leukaemia cutis (acute myelogenous leukaemia) and purpura.



Fig. 62.7 Carcinoma erysipeloides. (Courtesy of Dr R. Emmerson, Royal Berkshire Hospital, Reading, UK.)

abnormal platelet numbers or function or both, or susceptibility to unusual infections in disorders where immunosurveillance is compromised), through to highly specific features such as cutaneous deposits of the malignancy (for example, lesions of leukaemia cutis). In some instances, there may be features that suggest a particular diagnosis (such as oral leukaemic deposits, which are most typically seen in myelomonocytic leukaemia), or other cutaneous disease associations (such as the rare association of neurofibromatosis type 1 with juvenile xanthogranuloma and juvenile myelomonocytic leukaemia).

This type of involvement of the skin as part of a multisystem tumour is somewhat different from metastases from solid tumours in both mechanism and in the fact that lesions are often widespread. Most relevant conditions are discussed in other chapters, but, as examples, skin involvement is an important component of many haemopoietic tumours, particularly lymphomas (Chapter 57); similarly, Langerhans' cell histiocytosis (Chapter 55) and Kaposi's sarcoma (Chapter 56) characteristically cause skin lesions.

Specific cutaneous infiltrations of the skin may occur with myeloproliferative disorders; this is commonly recognized with lymphoma, but can occur with leukaemia (Fig. 62.6) [4]. Some skin infiltrates that are characteristic of specific disorders are discussed elsewhere in this section.

References

1 Provost TT, Flynn JA, eds. *Cutaneous Medicine: Cutaneous Manifestations of Systemic Disease*. Hamilton, Ontario: Decker, 2001.

2 Lebwohl MG. *The Skin and Systemic Disease. A Color Atlas and Text*, 2nd edn. London: Churchill Livingstone, 2004: 185–214.

3 Callen JP, Jorizzo JL, eds. *Dermatological Signs of Internal Disease*, 3rd edn. Philadelphia: Saunders, 2003.

4 Vardy DA, Sion N, Grunswald MH. Specific cutaneous infiltrates in chronic myelogenous leukaemia. *Cutis* 1989; **44**: 53–5.

Direct tumour spread from adjacent and deeper tissues [1,2]

Other than primary skin neoplasms, the skin may be involved by tumour as a result of cutaneous metastases from an internal tumour (see below), or by direct involvement in continuity with an adjacent organ. This may be the presenting feature of the underlying malignancy, as occurs in Paget's disease [2] (Chapter 52 and below), but more commonly occurs when an underlying tumour has been neglected (e.g. some breast carcinomas) or is refractory to treatment. It is a particular feature of malignant lymph node metastases (e.g. breast carcinoma, melanoma), and occasionally arises after diagnostic or therapeutic interventions such as needle aspiration of a tumour, pleural biopsy, drainage of malignant ascites or placement of other drains in the vicinity of a tumour. 'Tumour spillage', direct contamination of wounds with tumour cells during a laparoscopy or surgical procedure, was once a problem in nearly 20% of cases but is now uncommon; laparoscopic port site metastasis rates and laparotomy wound metastasis rates due to direct tumour inoculation are both in the order of 0.8% [3]. However, skin involvement may still occur from an abdominal viscus neoplasm or peripheral lung tumour that directly invades the skin.

Local and in-transit metastases from primary epidermal tumours are discussed in relevant chapters; melanoma is the most important tumour to behave in this fashion.

Direct invasion of the skin from a deeper tumour usually causes tumid ulceration or inflammation, but may present in less obvious ways; dermal infiltration causing sclerosis (carcinoma en cuirasse), vascular changes (carcinoma telangiectoides), a peau d'orange appearance, and more rarely a carcinoma erysipeloides (inflammatory metastatic carcinoma) pattern (Fig. 62.7) may all occur, especially with carcinoma of the breast. Although these patterns may occur as distant metastases, they most commonly occur in the skin in the vicinity of the primary tumour, all being most commonly associated with breast cancer, and are therefore usefully considered as a rather different pattern to those tumours that metastasize to distant sites.

All of these patterns may be difficult to diagnose unless there is clinical suspicion. *Carcinoma en cuirasse* may have an early inflammatory stage, and may include some nodularity, but at a later stage is very sclerodermoid in appearance. A particular diagnostic problem arises when a breast cancer has been treated with

radiotherapy, as this may cause post-irradiation morphoea; the latter is relatively well documented but the early inflammatory phase of post-irradiation morphoea that occurs in some patients is much less well recognized and may be very alarming clinically. Carcinoma en cuirasse may also occur with lung, gastrointestinal, renal and other malignancies [2]. *Carcinoma erysipeloides* resembles erysipelas but without the pyrexia or toxaemia; tumour cells lie within dilated lymphatic vessels in the skin. This pattern is again most commonly seen in breast carcinoma, but occurs due to melanoma and pelvic cancers (when it affects the lower abdomen or thigh); it can also occur due to carcinomas of the oral cavity or associated glands, as well as with upper abdominal cancers (stomach, pancreas) or lung cancer. *Telangiectatic metastatic carcinoma* is typically associated with breast cancer and may be difficult to diagnose as tumour cells may be quite scanty and telangiectasia quite subtle, although it may be more florid and resemble angiosarcoma. Less common patterns of direct tumour invasion include breast carcinoma presenting as an inframammary intertrigo-like pattern, and lymphatic obstruction by pelvic tumours or lymphadenopathy which may be accompanied by extensive tumour cells within the lymphatics, presenting as skin nodules. Oral tumours, usually squamous cell carcinoma, may extend to directly involve the skin of the face.

Paget's disease

Paget's disease occurs in mammary and extramammary forms. Paget's disease of the breast occurs due to an underlying ductal tumour; extramammary Paget's disease may occur without an underlying tumour, or distant to a tumour, and so does not have the close link with direct tumour spread of the mammary pattern but is conveniently discussed here.

Paget's disease of the breast [2,4–6]

This condition presents with scaling and erythema, sometimes with oozing and crusting, on or around the nipple (Fig. 62.8). It is generally viewed as a direct epidermal extension of an underlying ductal adenocarcinoma, and is important as the underlying tumour is usually small and superficial so early recognition may allow curative intervention. However, of the 30–50% with a palpable underlying lesion, half will have axillary lymph node involvement. The reason for the epidermotropic spread of tumour cells is uncertain but may involve a keratinocyte-derived chemoattractant for Paget cells, termed heregulin-α [5]. The main pathogenetic hypothesis for those cases that do not have an underlying carcinoma is derivation from Toker cells within the epidermis of the nipple and areola [2,5].



Fig. 62.8 Paget's disease of the breast causing destruction of the right nipple.

Clinically, eczemas, psoriasis, hyperkeratosis of the nipple and erosive adenomatosis are in the differential diagnosis of mammary Paget's disease. Histologically, there may be differential diagnosis problems from other disorders with Pagetoid spread, such as some melanomas or Bowen's disease, and also from a benign proliferation of Toker cells termed clear cell papulosis. Useful histopathological markers for mammary Paget's disease include epithelial membrane antigen (EMA), carcinoembryonic antigen (CEA), cytokeratins CK7 and CK8/18, as well as mucins such as MUC1 [5,6]. CD23, a lymphoid and apocrine/eccrine marker, is uniformly positive in mammary or extramammary Paget's disease [7].

Extramammary Paget's disease [2,5–10]

This rarer form of Paget's disease occurs in apocrine gland-bearing areas such as anogenital and axillary sites. About 60% of cases are vulval, 20% perianal and 15% penile or scrotal; there is thus a female predominance (although some populations, such as the Japanese [10], have a male predominance). Its histogenesis is less certain, and only about 25% of patients appear to have an underlying cancer. When the vulva is affected, cancers comprise about 10% in whom the cancer is locally arising (from apocrine sweat glands or Bartholin's glands) and about 15% in whom the carcinoma arises in the vagina, cervix, bladder, ovary, colon or rectum, or occasionally from more distant sites such as breast or gallbladder. Perianal Paget's disease is associated with an adnexal tumour in about 10% and a distant tumour in about 25% (rectum, stomach, ureter, breast); male genital Paget's disease is associated with a carcinoma of prostate, bladder, ureter, kidney or testes in about 10% of cases. In other cases, extramammary Paget's disease arises locally in the epidermis.

Most patients are over 60 years of age; clinical features include itch, burning sensation, oedema, bleeding and reddish-brown (or sometimes hypopigmented) plaques which may have a slightly more prominent margin. The margin may be obscured by secondary infection, and may be difficult to define in vaginal mucosa. Genital Paget's disease is often mistaken for an eczematous process, psoriasis or tinea. Histological and immunohistochemical features are similar to those of mammary Paget's disease; the antigen RCAS1 is particularly sensitive [5]. The prognosis is determined by the underlying tumour, if present, and the ability to adequately excise it; for those with a local epidermal origin, the depth of invasion and lymphatic spread dictate the prognosis, serum CEA being a useful indicator of survival [10].

References

1 Poole S, Fenske NA. Cutaneous markers of internal malignancy, 1: malignant involvement of the skin and the genodermatoses. *J Am Acad Dermatol* 1993; **28**: 1–13.

2 Rolz-Cruz G, Kim CC. Tumor invasion of the skin. *Dermatol Clin* 2008; **26**: 89–102.
3 Shoup M, Brennan MF, Karpeh MS *et al*. Port site metastasis after diagnostic laparoscopy for upper gastrointestinal tract malignancies: an uncommon entity. *Ann Surg Oncol* 2002; **9**: 632–6.
4 Paget J. On disease of mammary areola preceding cancer of mammary gland. *St Bartholomew's Hosp Rep* 1874; **10**: 87–9.
5 Kanitakis J. Mammary and extramammary Paget's disease. *J Eur Acad Dermato-Venereol* 2007; **21**: 581–90.
6 Liegl B, Liebl S, Gogg-Kamerer M *et al*. Mammary and extramammary Paget's disease: an immunohistochemical study of 83 cases. *Histopathology* 2007; **50**: 439–47.
7 Carvalho J, Fullen D, Lowe L *et al*. The expression of CD23 in cutaneous non-lymphoid neoplasms. *J Cutan Pathol* 2007; **34**: 693–8.
8 Neumann R. Extramammärer Morbus Paget assoziiert mit einem Magen-Karzinom. *Hautarzt* 1986; **37**: 568–70.
9 Chandra JJ. Extramammary Paget's disease: prognosis and relationship to internal malignancy. *J Am Acad Dermatol* 1985; **13**: 1009–14.
10 Hatta N, Yamada M, Hirano T *et al*. Extramammary Paget's disease: treatment, prognostic factors and outcome in 76 patients. *Br J Dermatol* 2008; **158**: 313–8.

Cutaneous metastasis from tumours affecting other organs [1–12]

Frequency of skin metastases

The skin is a relatively uncommon site for distant metastatic deposits, compared with organs such as liver, lung and bone. However, autopsy studies suggest a higher frequency of skin metastasis than may be apparent from clinical studies; in some studies up to 9% of patients with internal cancer have had skin metastases, a large analysis suggesting that 5% is usual [4], and in about 0.5–1% a metastasis is the presenting feature of internal cancer [1,2]. Of patients with metastatic cancer, 10% have cutaneous metastases [8]. Studies vary in cited frequency of skin metastases in part because some include metastasis from cutaneous melanoma whilst others exclude this and only refer to internally originating tumours; additionally, it can sometimes be difficult to know whether skin involvement is in contiguity or close proximity with a primary tumour of a different organ (direct invasion) or not (metastasis [12]). The most common sources of cutaneous metastases are (in generally accepted order of frequency): breast, (melanoma), lung, colon, stomach, upper aerodigestive tract, uterus and kidney; the most common skin metastases from a previously unknown primary tumour originate from the kidney, lung, thyroid or ovary [2,9,11].

Appearance of skin metastases

Cutaneous metastases generally present as solitary or multiple painless, firm to hard nodules, which may be skin-coloured, blue-brown or reddish-purple (Fig. 62.9); presentation with a solitary nodule is more common than with multiple nodules [9]. Ulceration of nodules may occur but is not usually a feature at initial presentation. They may also present as palpable subcutaneous nodules, often multiple (from a few to several hundred) in such instances. Other patterns include a morphoea-like sclerotic pattern, plaque morphology, scar infiltration, erysipelas-like pattern, infiltrated areas of alopecia (alopecia neoplastica), zosteriform metastases, embolic metastasis to digits (Fig. 62.10), and others.

The commonest, nodular, pattern presents with a solitary nodule about twice as frequently as with multiple nodules, although huge numbers of small dermal or subcutaneous nodules may be palpable in some such cases, even if not initially apparent or symptomatic.



Fig. 62.9 Subcutaneous metastasis from lung carcinoma; such metastases are typically multiple and many more firm nodules can usually be palpated if the patient is carefully examined.



Fig. 62.10 Embolic metastasis to the little finger of each hand from carcinoma of oesophagus.

Mechanisms and distribution [1]

Metastasis to the skin occurs as a result of lymphatic or haematogenous dissemination of tumour; direct infiltration of the skin by an underlying tumour is especially notable with breast carcinomas, and is discussed above. The reason for metastasis to specific organs is complex, involving both properties of the tumour cells, tumour cytokines (such as lymphangiogenic factors) and their interaction with host defences and tissues, and the distribution pattern within the skin is not random [2,12]. Indeed, 75% of metastases are found in the 25% of body surface area that comprises the head, neck and upper trunk [2].



Fig. 62.11 Metastasis to the groin in a patient with extensive pelvic prostatic carcinoma.

The clinical pattern of metastases may provide clues to the route of metastasis. For example, metastases to extremities suggest intra-arterial embolic spread, widespread skin metastases suggest that tumour cells are present in the general circulation, whilst metastases to the skin in the vicinity of the affected organ (for example, prostatic tumour metastases are often on the lower abdomen, Fig. 62.11) is more suggestive of dissemination by lymphatic vessels or by veins. Retrograde lymphatic spread may occur from pelvic tumours, causing metastases in the perineal area or on the legs. In general, the head, neck and upper trunk are disproportionately commonly affected by tumours that metastasize to the skin [2,7–9,11], possibly because of the high vascularity of this area. Some of the tumour and host factors involved in metastasis, both generally and organ-specific, are reviewed in [13–17]; in particular, chemokine receptors on tumour cells may influence the organs involved in metastatic spread [18,19].

Other than the scalp, notable sites for skin metastasis include the umbilicus (Sister Mary Joseph's nodule, related to bowel tumours most commonly) [11,20,21] and recent operative scars. Scar metastasis is most often related to surgery for the primary tumour, and, in view of the low frequency of 'tumour spillage' documented previously, presumably represents spread by local lymphatic or venous drainage; however, recent but distant scars (for example, skin graft donor sites [22,23]) may be a site for metastases, suggesting a role of adhesion molecules, metalloproteinases or cytokines related to angiogenesis and tissue repair. Metastases have also been reported that are localized to a site of irradiation of the skin [24]. An additional, unusual phenomenon is 'tumour-to-tumour metastasis', in which metastases localize to another (usually benign) tumour [25]. A postulated mechanism is the trapping effect of fibrin in the vessels of recipient tumour; most such metastases occur within quite vascular neoplasms, such as thyroid or adrenal adenomas, but metastasis to lipoma and to basal cell carcinoma [26] have both been reported and are relevant to dermatologists.

Metastases to the scalp may give rise to focal alopecia, carcinomas of breast, lung and kidney being the commonest tumours to metastasize to the scalp. Renal and thyroid cancer metastases may be quite vascular in appearance, both clinically and pathologically [27], and are occasionally misdiagnosed as benign haemangiomas or pyogenic granulomas; hypernephroma metastases may even be pulsatile. Generally, cutaneous metastases may be mistaken for cysts or inflammatory lesions, although alopecia over a scalp 'cyst' should give rise to suspicion regarding the true nature of the lesion.

Histopathology and investigations

Biopsy of skin metastases is generally helpful in confirming a metastatic tumour, but is not always useful in determining the organ of origin if the tumour cells are poorly differentiated. Occasionally, it may be difficult, even with use of immunohistochemical tumour markers, to confidently distinguish between primary skin tumours and metastatic disease. Although, in general, the cells of a metastasis resemble the cells of the primary tumour, some patterns may prove diagnostically difficult. Spindle cell tumours, and tumours comprising 'small blue cells', cause particular difficulty and may need a panel of immunohistochemical markers to aid in diagnosis both between primary skin lesions and metastases, or between different origins of an internal tumour. For example, small cell neoplasms may occur in primary skin tumours (Merkel cell tumour), in skin or systemic lymphomas, and in metastases from small cell carcinoma of lung, from carcinoid or visceral neuroendocrine tumours, and in rarer metastatic tumours such as neuroblastoma or retinoblastoma. Immunohistochemistry may help in determining the diagnosis of the primary tumour, especially in the case of prostatic metastases (prostate-specific antigen) or thyroid metastases (thyroglobulin); where a specific site of origin cannot be determined, cytokeratin stains may help to distinguish between squamous cell carcinomas (e.g. from lung) and adenocarcinomas. Melanoma metastases may mimic many cell types, and melanoma markers such as MART-1 are not always expressed. Pathological diagnosis of specific metastases and immunohistochemical markers are discussed in [11,28]. In some instances, there may be marked oedema or dilated lymphatic vessels, which may make diagnosis difficult. In some specific tumours such as hypernephroma, or in some clinical patterns such as carcinoma telangiectoides, the tumour cells may either be scanty or the vascular proliferation may dominate the histopathological appearance. Lymphatic spread of tumour cells may lead to an 'Indian filing' appearance in some cases, sometimes with fibrosis.

Implications and prognosis

Cutaneous metastases usually occur in subjects with a known cancer, but may be the first indication of an internal neoplasm, especially in the case of lung cancers. They are usually indicative of disseminated disease and indicate a correspondingly poor prognosis; survival is typically only about 3 months in patients with disseminated skin metastases [4]. Patients with solitary metastases without other evidence of dissemination may have a better survival [29]. Infrequent cases of tumour regression after primary tumour removal are documented [30]. It is noteworthy that cutaneous metastases do not necessarily relate to a prior, documented tumour; the histological pattern, localization and

temporal relationship may occasionally point to a second primary [31]. Treatment options, depending on the primary tumour, may include excision or other destructive therapy (e.g. laser destruction, radiotherapy, photodynamic therapy) for limited numbers of lesions, and chemotherapy or other systemic treatment for disseminated lesions.

References

1 Provost TT. Cutaneous metastasis. In: Provost TT, Flynn JA, eds. *Cutaneous Medicine: Cutaneous Manifestations of Systemic Disease*. Hamilton, Ontario: Decker, 2001: 357–66.
2 Schwartz RA. Cutaneous metastatic disease. *J Am Acad Dermatol* 1995; **33**: 161–82.
3 Smoller BR. Metastatic carcinoma. In: Morgan MB, Smoller BR, Somach SC. *Deadly Dermatologic Diseases. Clinicopathologic Atlas and Text*. New York: Springer, 2007: 38–42.
4 Reingold IM. Cutaneous metastasis from internal carcinoma. *Cancer* 1966; **19**: 162–8.
5 Lookingbill DP, Spangler N, Helm KF. Cutaneous metastases in patients with metastatic carcinoma: a retrospective study of 7316 cancer patients. *J Am Acad Dermatol* 1990; **22**: 19–26.
6 Spencer PS, Helm TN. Skin metastases in cancer patients. *Cutis* 1987; **39**: 119–21.
7 Brownstein MH, Helwig EB. Patterns of cutaneous metastasis. *Arch Dermatol* 1972; **105**: 862–8.
8 Lookingbill DP, Spangler N, Helm KF. Cutaneous metastases in patients with metastatic carcinoma: a retrospective study of 4020 patients. *J Am Acad Dermatol* 1993; **29**: 228–36.
9 Marcoval J, Moreno A, Peyri J. Cutaneous infiltration by cancer. *J Am Acad Dermatol* 2007; **57**: 577–80.
10 Poole S, Fenske NA. Cutaneous markers of internal malignancy, 1: malignant involvement of the skin and the genodermatoses. *J Am Acad Dermatol* 1993; **28**: 1–13.
11 Weedon D. *Skin Pathology*, 2nd edn. London: Churchill Livingstone, 2002: 1045–56.
12 Rolz-Cruz G, Kim CC. Tumor invasion of the skin. *Dermatol Clin* 2008; **26**: 89–102.
13 Cao Y, Zhong W. Tumor-derived lymphangiogenic factors and lymphatic metastasis. *Biomed Pharmacother* 2007; **61**: 534–9.
14 Dittmar T, Heyder C, Gloria-Maercker E *et al*. Adhesion molecules and chemokines: the navigation system for circulating tumor (stem) cells to metastasize in an organ-specific manner. *Clin Exp Metastasis* 2008; **25**: 11–32.
15 Pedraza-Fariña LG. Mechanisms of oncogenic cooperation in cancer initiation and metastasis. *Yale J Biol Med* 2006; **79**: 95–103.
16 Ramsay AG, Marshall JF, Hart IR. Integrin trafficking and its role in cancer metastasis. *Cancer Metastasis Rev* 2007; **26**: 567–78.
17 Leong SPL, Cady B, Jablons DM *et al*. Clinical patterns of metastasis. *Cancer Metastasis Rev* 2006; **25**: 221–32.
18 Dai CY, Haqq CM, Puzas JE. Molecular correlates of site-specific metastasis. *Semin Radiat Oncol* 2006; **16**: 102–10.
19 Kakinuma T, Hwang ST. Chemokines, chemokine receptors, and cancer metastasis. *J Leukoc Biol* 2006; **79**: 639–51.
20 Clements AB. Metastatic carcinoma of the umbilicus. *JAMA* 1952; **150**: 556–9.
21 Duperrat B, Duperrat N. Les métastases ombilicales. A propos de 20 pièces personnelles. *Bull Soc Franc Dermatol Syphiligr* 1968; **75**: 638–9.
22 Taylor CD, Snelling CF, Nickerson D, Trotter MJ. Acute development of invasive squamous cell carcinoma in a split-thickness skin graft donor site. *J Burn Care Rehab* 1998; **19**: 382–5.
23 Serrano OS, Buendia EA, Ortega DRM, Linares SJ. Melanoma metastasis in donor site of full-thickness skin graft. *Dermatology (Basel)* 2000; **201**: 377–8.
24 Diehl LF, Hurwitz MA, Johnson SA *et al*. Skin metastases confined to a field of previous irradiation. Report of two cases and review of the literature. *Cancer* 1984; **53**: 1864–8.
25 Richardson JF, Katayama I. Neoplasm to neoplasm metastasis, an acidophil adenoma harbouring metastatic carcinoma: a case report. *Arch Pathol* 1971; **91**: 135–9.
26 Cowley GP, Gallimore A. Malignant melanoma metastasizing to a basal cell carcinoma. *Histopathol* 1966; **29**: 469–70.
27 Rosenthal AL, Lever WF. Involvement of the skin in renal carcinoma: report of two cases with review of the literature. *AMA Arch Dermatol* 1957; **76**: 96–102.
28 Sariya D, Ruth K, Adams-McDonnell R *et al*. Clinicopathologic correlation of cutaneous metastases. Experience from a cancer center. *Arch Dermatol* 2007; **143**: 613–20.
29 Menter A, Boyd AS, McCaffree DM. Recurrent renal cell carcinoma presenting as skin nodules: two case reports and review of literature. *Cutis* 1989; **44**: 305–8.
30 Braren V, Taylor JN, Pace W. Regression of metastatic renal carcinoma following nephrectomy. *Urology* 1974; **3**: 777–8.
31 Brownstein MH, Helwig EB. Spread of tumours to the skin. *Arch Dermatol* 1973; **107**: 80–6.

Genodermatoses associated with internal malignancies [1–10]

Most cutaneous signs of neoplasia do not involve direct spread of tumour to the skin but are paraneoplastic. Genodermatoses account for a significant minority of paraneoplastic skin lesions; some including both cutaneous and internal neoplasms as part of the syndrome, both benign and malignant. The most important are listed in Table 62.8; non-cancer aspects of these disorders are discussed more fully in earlier chapters. A number of mechanisms underlie the association of genodermatoses with internal malignancy; these include chromosomal instability, faulty DNA repair mechanisms, abnormal lymphocyte function and immunosurveillance, and in some cases a combination of these. More precise genetic diagnosis, understanding of mechanisms, awareness of the benefits and ability to focus screening of family members for genetic abnormalities or for cancers, is a constantly evolving area within dermatology and paediatric medicine in particular.

Genodermatoses that predispose to skin but not to internal cancers are not discussed here; examples include disorders such as albinism, epidermodysplasia verruciformis, dystrophic epidermolysis bullosa, porokeratosis of Mibelli and KID syndrome.

References

1 Braverman IM. *Skin Signs of Systemic Disease*, 3rd edn. Philadelphia: Saunders, 1998.
2 Callen JP. Skin signs of internal malignancy. In: Callen JP, Jorizzo JL, eds. *Dermatological Manifestations of Internal Disease*, 3rd edn. Philadelphia: Saunders, 2003: 95–104.
3 Lynch HT, Fusaro RM, eds. *Cancer-Associated Genodermatoses*. New York: Van Nostrand Reinhold, 1982.
4 Callen JP. Skin signs of internal malignancy. *Australas J Dermatol* 1987; **28**: 106–14.
5 Poole S, Fenske NA. Cutaneous markers of internal malignancy, 1: malignant involvement of the skin and the genodermatoses. *J Am Acad Dermatol* 1993; **28**: 1–13.
6 Provost TT, Laman SD, Bell WR. Paraneoplastic dermatoses. In: Provost TT, Flynn JA, eds. *Cutaneous Medicine: Cutaneous Manifestations of Systemic Disease*. Hamilton, Ontario: Decker, 2001: 367–88.
7 Cohen PR, Kurzrock R, eds. Genodermatoses with malignant potential. *Dermatologic Clinics* 1995; **13**: 1–243.
8 Tsao H. Update on familial cancer syndromes and the skin. *J Am Acad Dermatol* 2000; **42**: 939–46.
9 Palayoor S, Harper J. Genetic diseases that predispose to malignancy. In: Harper J, Oranje A, Prose N. *Textbook of Pediatric Dermatology*, 2nd edn. Oxford: Blackwell, 2006: 1596–604.
10 Somoano B, Tsao H. Genodermatoses with cutaneous tumors and internal malignancies. *Dermatol Clinics* 2008; **26**: 69–87.

Table 62.8 Examples of genodermatoses associated with internal malignancies.

Main organ affected or usual mode of presentation (many are multisystem disorders)	Genodermatosis	Main neoplasms (may be limited to some families in some of the disorders listed)
Gastrointestinal tract	Gardner's syndrome	Gastrointestinal polyposis and carcinomas (p. 62.56), central nervous system tumours
	Bannayan–Riley–Ruvalcaba syndrome	
	Turcot syndrome (mismatch repair cancer syndrome)	
	Peutz–Jeghers syndrome	Gastrointestinal polyposis and carcinomas (p. 62.56), pancreatic carcinoma, genital tumours (especially Sertoli cell, sex cord and cervix), breast cancers, lung cancers
Neurological	Ataxia–telangiectasia	Lymphomas, leukaemias
	Neurofibromatosis	Neurological tumours, sarcomas, phaeochromocytoma
Skin	Xeroderma pigmentosum	Skin cancers, sarcomas, central nervous system tumours, leukaemia, various solid organ tumours
	Naevoid basal cell carcinoma syndrome (Gorlin)	Basal cell carcinomas of skin, medulloblastoma
	Basex–Dupré–Christol syndrome	Basal cell carcinomas of skin, possible leukaemia
	Porphyria cutanea tarda	Hepatocellular carcinoma
	Tylosis	Oesophageal carcinoma
	Sclerotylosis (Huriez syndrome)	Squamous cell carcinoma of skin; oral and bowel cancers also reported
	Muir–Torre syndrome	Colorectal tumours, sebaceous carcinoma
	Birt–Hogg–Dube syndrome and Hornstein–Knickenberg syndrome	Medullary carcinoma of thyroid, renal cell carcinoma
	Familial leiomyomas (also uterine)	Renal cell carcinoma, others (see text)
	Incontinentia pigmenti	Wilms' tumour, rhabdomyosarcomas (renal, paratesticular), retinoblastoma, leukaemias
	Familial atypical naevi and melanoma	Pancreatic carcinoma, cutaneous and ocular melanoma
	Melanoma–astrocytoma syndrome	Melanomas, astrocytomas and other central nervous system tumours
	Supernumerary nipples	Genitourinary tumours—renal cell carcinoma, Wilms' tumour, bladder, testicular, prostate
	Ichthyoses (autosomal dominant and X-linked)	Testicular carcinoma
Endocrine	Multiple endocrine neoplasia syndromes	Medullary carcinoma of thyroid, phaeochromocytoma
Growth/skeletal	Werner's syndrome	Many, especially sarcomas
	Rothmund–Thomson syndrome	Skin, osteosarcoma
	Bloom's syndrome	As general population but early onset
	Maffucci syndrome	Chondrosarcomas, gliomas, ovarian cancers
	Goltz syndrome	Chondrosarcomas, giant cell tumour of bone
	Fanconi's anaemia (usually presents due to congenital malformations)	Myelodysplastic syndrome, acute myelogenous leukaemia, hepatic carcinoma
Haemopoietic	Dyskeratosis congenita	Mucosal squamous cell carcinoma, haemopoietic malignancy, and others
Immunological	Wiskott–Aldrich syndrome	Lymphoreticular malignancies
	Chediak–Higashi syndrome	Lymphoreticular malignancies
Multisystem	Cowden's (multiple hamartoma and neoplasia) syndrome	Breast, thyroid, gastrointestinal, cerebellum, endometrial and renal carcinomas
	Carney complex	Myxomas, Schwannomas, testicular Sertoli cell tumour, pituitary adenomas, thyroid cancer
	Von Hippel–Lindau disease	Phaeochromocytoma, renal carcinoma, haemangioblastoma, pancreatic carcinoma
	Beckwith–Wiedermann syndrome (EMG syndrome)	Wilms' tumour, adrenal carcinoma, hepatoblastoma, pancreatoblastoma, others (especially in patients with hemihypertrophy)

Focal palmoplantar keratoderma (Howel-Evans syndrome; tylosis; MIM 148500) and other palmoplantar keratodermas (Chapter 19)

Howel-Evans syndrome is the association of autosomal dominantly inherited focal palmoplantar keratoderma (tylosis) with the eventual development of oesophageal carcinoma in most cases [1]. Since the original description, other families linked with inherited tylosis and carcinoma of the oesophagus have been described [2,3]. The genetic locus is at chromosome 17q25. However, in diffuse familial palmoplantar kerato-

derma starting in infancy, there is no genetic susceptibility to neoplasia.

A possible familial association has been described between palmoplantar keratoderma and gastrointestinal malignancy [4], diffuse epidermolytic palmoplantar keratoderma has been linked with increased risk of breast and ovarian cancer [5] and punctate porokeratotic keratoderma has been tentatively associated with internal neoplasia [6,7]. However, it is likely that such cases represent a separate, inherited tendency as most such reports relate to one specific family [8].

Acquired palmar hyperkeratosis may also occur as a marker of carcinogen ingestion (pp. 62.46–62.47), principally linked with arsenic. The relationship between arsenic-induced keratosis or punctate keratoderma and internal malignancy is controversial.

Palmoplantar punctate keratoses may be present in Cowden's disease (p. 62.25), in which there is a predisposition to several malignancies.

References

1 Harper PS, Harper RM, Howel-Evans AW. Carcinoma of the oesophagus with tylosis. *QJM* 1970; **155**: 317–33.
2 Shine I, Allison PR. Carcinoma of the oesophagus with tylosis. *Lancet* 1966; **i**: 951–3.
3 Zultak M, Blanc D, Merle C *et al.* Erythème annulaire centrifuge et leucémie aiguë myéloblastique. *Ann Dermatol Vénéréol* 1989; **116**: 477–80.
4 Bennion SD, Patterson JW. Keratosis punctata palmaris et plantaris and adenocarcinoma of the colon: a possible familial association of punctate keratoderma and gastrointestinal malignancy. *J Am Acad Dermatol* 1984; **10**: 587–91.
5 Blanchet-Bardon C, Nazzaro V, Chevrant-Breton J *et al*. Hereditary epidermolytic palmoplantar keratoderma associated with increased breast and ovarian cancer in a large kindred. *Br J Dermatol* 1987; **117**: 363–70.
6 Bianchi L, Orlandi A, Iraci S *et al.* Punctate porokeratotic keratoderma: its occurrence with internal neoplasia. *Clin Exp Dermatol* 1994; **19**: 139–41.
7 Bennion SD, Patterson JW. Keratosis punctata palmaris et plantaris and adenocarcinoma of the colon: a possible familial association of punctate keratoderma and gastrointestinal malignancy. *J Am Acad Dermatol* 1984; **10**: 587–91.
8 Moore RL, Devere TS. Epidermal manifestations of internal malignancy. *Dermatol Clinics* 2008; **26**: 17–29.

Naevoid basal cell carcinoma syndrome (NBCCS; Gorlin's syndrome, MIM #109400) (Chapter 52)

This is an autosomal dominant condition with prevalence of about 1/100 000 (about half being due to *de novo* mutations), the main features being multiple basal cell carcinomas (BCCs), mandibular odontogenic keratocysts, skeletal anomalies, abnormal calcification and dyskeratotic pits of palms and soles [1–6]. Diagnostic criteria are documented in [5,6]. The most commonly reported internal malignancies are medulloblastoma [7] and ovarian tumours (mainly benign fibromas, but also desmoids and sarcomas); astrocytomas, meningiomas, craniopharyngiomas, fibrosarcomas and ameloblastomas have occasionally been reported [2]. It is important to note that individuals may have only the family history, without themselves having developed BCC. However, neoplasia may also commence early in life, with a median age of onset of BCC by 20 years; most patients will have at least one BCC before age 30 years. The BCCs may present as small, subtle, tan-coloured or brown papules or acrochordon-like lesions on the face, neck, back, chest and upper limbs. They may become more aggressive as the patient ages, with both deep local invasion and metastases being possible. Facial milia also occur, and multiple skin cysts (some with a corrugated internal surface similar to odontogenic keratinocysts) have been reported. An acral distribution of skin cysts may be suggestive of NBCCS [8].

The gene for NBCCS has been mapped to chromosome 9q22.3, with a high percentage (about 60% of pedigrees) having germ-line mutations in the *PTCH* gene [5,6,9], part of the Sonic Hedgehog (SHH) signalling pathway which is involved in transcription and cell cycle regulation.

References

1 Andreev VC, Petkov I. Skin manifestations associated with tumours of the brain. *Br J Dermatol* 1975; **92**: 675–8.
2 Jackson R, Gardere S. Nevoid basal cell carcinoma syndrome. *Can Med Assoc J* 1971; **105**: 850–9.
3 Gorlin SJ. Nevoid basal cell carcinoma syndrome. *Dermatol Clin* 1995; **13**: 113–25.
4 Kimonis VE, Goldstein AM, Pastakia B *et al*. Clinical manifestations in 105 persons with nevoid basal cell carcinoma syndrome. *Am J Hum Genet* 1997; **69**: 299–308.
5 Somoano B, Tsao H. Genodermatoses with cutaneous tumors and internal malignancies. *Dermatol Clinics* 2008; **26**: 69–87.
6 Farndon PA. The Gorlin (naevoid basal cell carcinoma) syndrome. In: Harper J, Oranje A, Prose N. *Textbook of Pediatric Dermatology*, 2nd edn. Oxford: Blackwell Publishing, 2006: 1514–31.
7 Southwick GT, Schwartz RA. The basal cell nevus syndrome: disasters occurring among a series of 36 patients. *Cancer* 1979; **44**: 2294–305.
8 Motegi S, Nagai Y, Tamura A, Ishikawa O. Multiple skin cysts in nevoid basal cell carcinoma syndrome: a case report and review of the literature. *Dermatology* 2008; **21**: 159–62.
9 Tsao H. Update on familial cancer syndromes and the skin. *J Am Acad Dermatol* 2000; **42**: 939–46.

Familial melanoma and internal malignancy syndromes

Familial melanoma, and metastases from melanoma, are discussed in more detail in Chapter 54, but links between melanoma and other internal neoplasms are detailed here [1–6].

Familial melanoma syndrome (B-K mole syndrome, familial atypical multiple-mole and melanoma, dysplastic naevus syndrome; MIM 155600)

This is a variable group of disorders, probably polygenic in inheritance, in which multiple melanomas are the main feature. Typically, there is one or more of a family history of melanoma, a personal or family background of multiple atypical ('dysplastic') melanocytic naevi, or all of these. Large multiple and irregular naevi are the norm, with an early onset of melanoma, potentially multiple primary melanomas, and in some pedigrees an increase in non-cutaneous malignancies such as pancreatic, gastrointestinal, lung, breast and laryngeal cancers, as well as ocular melanoma and cutaneous SCC of the head and neck. The *CDKN2A* germline mutation in the 9p21 gene region has been implicated in most cases [1,2]. The molecular genetics of *CDKN2A* has been extensively studied [2]; it encodes proteins that are involved in regulation of cell cycle progression (p16 and p14ARF). Those mutations that impair p16 function are linked with increased risk (22-fold) in pancreatic cancer, and specific mutations have been linked with breast cancer in some populations [2]. However, other gene mutations are also involved in familial melanoma, and external factors such as sunlight may alter the likelihood of cutaneous melanoma.

Melanoma–astrocytoma syndrome (melanoma–nervous system tumours syndrome, melanoma-NST syndrome; MIM 155755)

This syndrome comprises an association of melanomas with astrocytomas specifically, or with astrocytomas, other central nervous system tumours, meningiomas, ependymomas and peripheral nerve tumours such as malignant schwannoma [3–6]. Deletions of chromosome 9p21, which includes tumour suppressor and cell cycle regulating genes, are implicated. Several genetic loci have been implicated in different families, including all or parts of the p16, p19 and p15 gene cluster (*INK4* locus) which includes *CDKN2A* and *CDKN2B* (suggesting contiguous suppressor gene deletion) [3–5], and more recently a specific deletion of p14(ARF) [6]. In one study, a kindred with melanomas and nervous system tumours (melanoma/NST syndrome) had a large germline deletion of the *INK4* locus, whilst a more circumscribed gene disruption was associated with a melanoma–astrocytoma family [5].

References

1 Tsao H. Update on familial cancer syndromes and the skin. *J Am Acad Dermatol* 2000; **42**: 939–46.
2 Somoano B, Tsao H. Genodermatoses with cutaneous tumors and internal malignancies. *Dermatol Clinics* 2008; **26**: 69–87.
3 Azizi E, Friedman J, Pavlotsky F *et al*. Familial cutaneous malignant melanoma and tumours of the nervous system. A hereditary cancer syndrome. *Cancer* 1995; **76**: 1571–8.
4 Bahuau M, Vidaud D, Kujas M *et al*. Familial aggregation of malignant melanoma/dysplastic naevi and tumours of the nervous system: an original syndrome of tumour proneness. *Ann Genet* 1997; **40**: 78–91.
5 Bahuau M, Vidaud D, Jenkins RB *et al*. Germline mutation involving the INK4 locus in familial proneness to melanoma and nervous system tumours. *Cancer Res* 1998; **58**: 2298–303.
6 Randerson-Moore JA, Harland M, Williams S *et al*. A germline deletion of p14(ARF) but not CDKN2A in a melanoma-neural system tumour family. *Hum Mol Genet* 2001; **1**: 55–62.

Xeroderma pigmentosum (XP; MIM 194400, 133510, 278700–278800) [1–4]

This group of disorders with autosomal recessive inheritance are discussed in more detail in Chapter 15. XP characteristically presents at an early age with severe photosensitivity, marked reduction in threshold for sunburn and myriads of lentigines, principally in a sun-exposed distribution. Early onset of photoageing is found in infants, followed by sun-induced dysplasias, BCC, SCC and malignant melanomas, commencing in the first decade of life, which occur with a 2000-fold increased risk; SCC of the tip of the tongue has a 10 000-fold increased risk compared with individuals of the same age [3]. Ocular neoplasms, both melanoma and non-melanoma, occur in 10–20%. However, it is not only neoplasms linked with solar exposure that are increased in frequency; there is also a 10- to 20-fold increased incidence of internal malignancy, including central nervous system (CNS) sarcomas, leukaemia, and carcinomas of lung, breast, pancreas, stomach and testes [4]. The mutations causing XP cause abnormal fibroblast sensitivity to ultraviolet radiation, in most cases (complementation groups A–G) resulting from a defective DNA nucleotide excision repair process; the eighth form, termed XP variant, codes for a post-replication repair polymerase. Inactivation of tumour suppressors and activation of oncogenes due to these mutations results in development of multiple tumours [2].

References

1 Kraemer KH, Lee MM, Scotto J. Xeroderma pigmentosum: cutaneous, ocular and neurologic abnormalities in 830 published cases. *Arch Dermatol* 1987; **123**: 241–50.
2 Tsao H. Update on familial cancer syndromes and the skin. *J Am Acad Dermatol* 2000; **42**: 939–46.
3 Bootsma D, Kraemer KH, Cleaver JE *et al*. Nucleotide excision repair syndromes: xeroderma pigmentosum, Cockayne syndrome, and trichothiodystrophy. In: Vogelstein BV, Kinzler K, eds. *The Genetic Basis of Human Cancer*. New York: McGraw-Hill, 1998: 245–74.
4 Somoano B, Tsao H. Genodermatoses with cutaneous tumors and internal malignancies. *Dermatol Clinics* 2008; **26**: 69–87.

Von Hippel–Lindau disease (VHL; MIM *193300)

A rare, autosomal dominantly inherited condition, characterized by benign and malignant tumours of various systems, particularly haemangioblastomas of the CNS, angiomatosis of the retinae, phaeochromocytoma [1] (which may be bilateral), renal carcinoma [2], pancreatic adenoma, carcinoma and cysts [3], and epididymal cystadenomas. Endolymphatic sac tumours are rarely found other than in von Hippel–Lindau disease [4]. The non-specific cutaneous manifestations include haemangiomas and café-au-lait spots [5]. The VHL gene has been located on chromosome 3p26-p25; although different mutations have been found to be causative, the gene is a tumour-suppressor gene following the Knudson two-hit model. Families may be characterized by the presence (type 2, missense mutations) or absence (type 1, deletions/protein-truncating mutations) of phaeochromocytoma; in those with a predominance of familial phaeochromocytoma, analysis of VHL mutations may be useful to identify asymptomatic subjects at risk of von Hippel–Lindau disease. Type 2b has, in addition to an association with phaeochromocytoma, a high incidence of renal cell carcinoma and haemangioblastomas, whereas in type 2a there is a lower incidence of renal cell carcinoma and in type 2c an exclusive association with phaeochromocytoma [6]. However, genetic investigation of patients with apparently sporadic phaeochromocytoma rarely identifies subjects with mutations in *VHL* or in the *RET* proto-oncogene (mutations in which cause multiple endocrine neoplasia type 2, another cause of familial phaeochromocytoma) and is not routinely indicated [7].

References

1 Kiechle-Schwartz M, Neuman HP, Decker HH *et al.* Cytogenetic studies on three pheochromocytomas derived from patients with von Hippel–Lindau syndrome. *Hum Genet* 1989; **82**: 127–30.
2 Saranya R, Matzkin H, Papo J *et al.* Von Hippel–Lindau syndrome with unusual presentations in 2 brothers. *Urology* 1989; **34**: 301–4.
3 Neumann HP. Basic criteria for clinical diagnosis and genetic counselling in von Hippel–Lindau syndrome. *Vasa* 1987; **16**: 220–6.
4 Manski TJ, Heffner DK, Glenn GM *et al*. Endolymphatic sac tumors. A source of morbid hearing loss in von Hippel–Lindau disease. *JAMA* 1997; **277**: 1461–6.
5 Lynch HT, Fusaro RM, eds. *Cancer-Associated Genodermatoses*. New York: Van Nostrand Reinhold, 1982.
6 Eamonn ER, Kaelin WG. Von Hippel–Lindau Disease. *Medicine (Baltimore)* 1997; **76**: 381–91.
7 Bar M, Friedman E, Jakobovitz O *et al*. Sporadic phaeochromocytomas are rarely associated with germline mutations in the von Hippel-Lindau and *RET* genes. *Clin Endocrinol* 1997; **47**: 707–12.

Neurofibromatosis types 1 and 2 (NF1, von Recklinghausen's disease, MIM *162200; NF2, MIM *101000) (Chapter 15) [1–5]

There are two main forms of neurofibromatosis, type 1 (NF1) and type 2 (NF2). Both have an autosomal dominant inheritance but in a large proportion of affected individuals the condition is due to a *de novo* mutation (which may be mosaic). The abnormal neural crest cell function in NF1 leads to development of multiple peripheral neurofibromas, as well as CNS tumours (notably optic glioma, which is one of the diagnostic criteria for NF1 [4]) and café-au-lait macules [1–5]. Patients with a deletion of the whole gene have earlier development of neurofibromas and an apparent higher frequency of malignant peripheral nerve sheath tumours [5].

NF1 is the commonest form of neurofibromatosis, with a prevalence of approximately 1/3000, about tenfold that of NF2. There are several different clinical presentations, depending on the localization of the lesions. Clinical overlap between NF1 and NF2 occurs particularly in children, who may have café-au-lait macules and peripheral nerve tumours; flexural freckling is indicative of NF1. Café-au-lait macules occur in NF2, but only in half of affected subjects and usually fewer than six in number (six or more being one of the diagnostic criteria for NF1).

Lisch nodules (pigmented iris hamartomas) are found with slit-lamp analysis in 90% of adult patients with NF1 and are fairly specific for NF1; two or more such lesions are one of the diagnostic criteria. Around 80% of patients with NF2 have posterior subcapsular cataracts, including about a third of affected children.

The associations with benign tumours, malignancy and systemic manifestations are varied but patients with NF1 have an overall 2.5-fold increase in risk of developing a malignancy [4]. In general, NF2 patients have fewer skin lesions than in those with NF1, and the lesions that occur are mainly schwannomas, but more severe disease in NF2 is linked with greater prevalence of skin tumours [3,4].

NF2 patients develop vestibular and peripheral nerve schwannomas (the vestibular schwannomas characteristically being bilateral), together with CNS tumours such as meningiomas. Spinal schwannomas (mainly), astrocytomas or ependymomas eventually occur in about three-quarters of patients with NF2. If meningiomas occur in children, NF2 should be suspected. Perhaps the commonest neoplasm developing in patients with neurofibromatosis is a malignant neurofibrosarcoma [6]. Most superficial neurofibromas have a low malignant potential, change occurring more often in the deep plexiform neurofibromas and those more in continuity with nerves, designated schwannomas. Benign tumours such as acoustic neuromas, dumb-bell tumours and optic gliomas can result in disastrous sequelae when occurring in confined, pressure-sensitive sites. The commonest CNS malignancy is an astrocytoma. Other malignancies include nephroblastoma (Wilms' tumour), fibrosarcoma, rhabdomyosarcoma and leukaemia, especially in children [3–8]; there is an association between NF1, juvenile myelomonocytic leukaemia and juvenile xanthogranulomas [9]. Monosomy 7 myelodysplastic syndrome may also occur [10]. There is an increased frequency of phaeochromocytomas and carcinoid tumours [4], and ocular melanoma has been reported [11].

The *NF1* gene, located on chromosome 17q11.2, has a role as a tumour-suppressor gene; its protein product, neurofibromin, regulates cell growth, including an effect of accelerating inactivation of the p21 *ras* proto-oncogene [4,12]. Transformation of benign neurofibromas to malignant peripheral nerve sheath tumours involves the loss of other tumour-suppressor genes such as p53 and p16.

The *NF2* gene locus is on chromosome 22q12.2; the product of this gene, termed merlin, has an uncertain effect on tumour suppression [3,4].

References

1 Riccardi VM. *Neurofibromatosis: Phenotype, Natural History, and Pathogenesis*, 2nd edn. Baltimore: Johns Hopkins University Press, 1992: 213–23.
2 Ferner RE, Huson SM, Thomas N *et al*. Guidelines for the diagnosis and management of individuals with neurofibromatosis 1. *J Med Genet* 2007; **44**: 81–8.
3 Tsao H. Update on familial cancer syndromes and the skin. *J Am Acad Dermatol* 2000; **42**: 939–46.
4 Somoano B, Tsao H. Genodermatoses with cutaneous tumors and internal malignancies. *Dermatol Clinics* 2008; **26**: 69–87.
5 Huson SM, Ruggieri M. The neurofibromatoses. In: Harper J, Oranje A, Prose N. *Textbook of Pediatric Dermatology*, 2nd edn. Oxford: Blackwell Publishing, 2006: 1467–90.
6 Hope DG, Mulvill JJ. Malignancy in neurofibromatosis. *Adv Neurol* 1981; **29**: 33–56.
7 McKeen EA, Bodurtha J, Meadows AT *et al*. Rhabdomyosarcoma complicating multiple neurofibromatosis. *J Pediatr* 1977; **93**: 992–3.
8 Stay EJ, Vawter G. The relationship between nephroblastoma and neurofibromatosis (von Recklinghausen's disease). *Cancer* 1977; **39**: 2550–5.
9 Zvulunov A, Barak Y, Metzker A. Juvenile xanthogranuloma, neurofibromatosis, and juvenile chronic myelogenous leukemia. World statistical analysis. *Arch Dermatol* 1995; **131**: 904–8.
10 Maris JM, Wiersma SR, Mahgoub N *et al*. Monosomy 7 myelodysplastic syndrome and other second malignant neoplasms in children with neurofibromatosis type 1. *Cancer* 1997; **79**: 1438–46.
11 Wiznia RA, Freeman JK, Mancini AD *et al*. Malignant melanoma of the choroid in neurofibromatosis. *Am J Ophthalmol* 1978; **86**: 684–7.
12 Parisi MA, Sybert VP. Molecular genetics in pediatric dermatology. *Curr Opin Pediatr* 2000; **12**: 347–53.

Tuberous sclerosis complex (TSC; Bourneville's disease; TSC1, MIM #191100 and TSC2, MIM *191092) (Chapter 15) [1–5]

An autosomal dominant condition of angiokeratomas, epilepsy and mental retardation; a high spontaneous mutation rate accounts for over half of cases. It may be associated with multisystem tumour involvement, mostly hamartomatous. There are two known causative genes—*TSC1* on chromosome 9q34, encoding hamartin, and *TSC2* on chromosome 16p13.3, encoding tuberin; both genes function as tumour suppressor genes. There are large numbers of different mutations, *TSC2* mutations being more common, and causing more severe disease, than *TSC1* mutations.

Other than skin lesions (Chapter 15), the CNS, renal and cardiopulmonary systems are most significantly affected [1–3]. Angiomyolipomas (of vessels, fat and smooth muscle) all show the same loss of heterozygosity at the *TSC1* or *TSC2* loci, with hyperphosphorylation of ribosomal protein S6; the smooth muscle component of these lesions is identical to that of the smooth muscle in lymphangiomyomatosis, which is also a feature of tuberous sclerosis [5]. Malignant sarcomatous change can occur, particularly with angiomyolipomas and rhabdomyomas, but is uncommon,

and metastases are unusual [4]. Renal cell carcinoma is a recognized, infrequent complication [3,6].

References

1 Callen JP. Skin signs of internal malignancy. In: Callen JP, Jorizzo JL, eds. *Dermatological Manifestations of Internal Disease*, 3rd edn. Philadelphia: Saunders, 2003: 95–104.

2 Somoano B, Tsao H. Genodermatoses with cutaneous tumors and internal malignancies. *Dermatol Clinics* 2008; **26**: 69–87.

3 Osborne JP. Tuberous sclerosis. In: Harper J, Oranje A, Prose N. *Textbook of Pediatric Dermatology*, 2nd edn. Oxford: Blackwell Publishing, 2006: 1491–502.

4 Lynch HT, Fusaro RM, eds. *Cancer-Associated Genodermatoses*. New York: Van Nostrand Reinhold, 1982.

5 Crino PB, Nathanson KL, Henske EP. The tuberous sclerosis complex. *N Engl J Med* 2006; **355**: 1345–56.

6 Lynne CM, Carrion HM, Baskshandeh K *et al.* Renal angiomyolipoma: polycystic kidney and renal cell carcinoma in a patient with tuberous sclerosis. *Urology* 1979; **14**: 174–6.

Multiple endocrine neoplasia syndrome (multiple endocrine adenomatosis, MEA)

This section actually includes three conditions, MEN1, MEN2A and MEN2B (previously termed MEN3).

Multiple endocrine neoplasia type 1 (MEN1; Wermer syndrome; MIM *131100). This is an autosomal dominant familial cancer syndrome, with parathyroid, pancreatic islet cell and pituitary gland tumours, as well as cutaneous findings. It is caused by mutations in the *MEN1* gene, located on chromosome 11q12-13, which codes for the production of a protein named menin. The cutaneous findings in MEN1 are mostly multiple facial angiofibromas and collagenomas. Café-au-lait macules and lipomas are also encountered [1,2].

MEN1 is, at least in part, a tumour-suppressor gene. MEN1 is characterized by tumours of the parathyroid, anterior pituitary, pancreatic islet cells, neuroendocrine origin, foregut carcinoid and adrenal cortex. It is associated with 20–25% of cases of Zollinger–Ellison syndrome (ZES). In MEN1, 60–100% of cases have gastroenteropancreatic (GEP) lesions, especially pancreatic islet endocrine tumours (pancreatic polypeptidomas or non-functional 80–100%, ZES 54%, insulinoma 21%, glucagonoma 3% and vasoactive intestinal peptide (VIP)oma 1%). Glucagonoma may be difficult to diagnose as even subjects with MEN1 without a pancreatic endocrine tumour may have glucagon levels above the normal basal level. Associated endocrine disease consists of parathyroid hyperplasia >95%, anterior pituitary adenomas around 60% (range 14–100%), adrenal adenomas about 30%, lung carcinoids 7% and gastric carcinoids 13–30%. The pituitary adenomas are prolactinomas in 14–76% and cause acromegaly in 11–33% and Cushing's syndrome in 5–19%. The commonest tumours in MEN1 secrete PTH or gastrin; hyperparathyroidism is present in 95–100% of affected individuals. However, screening patients with sporadic pituitary adenomas for other features of MEN1 yields few cases of MEN1, the greatest number being in patients with prolactinoma. Screening patients with hyperparathyroidism yields 1–16% with MEN1, whilst screening those with GEP tumours identifies 10–50% as having other features of MEN1.

Metastases from malignant neuroendocrine tumours (carcinoid) may be one of the commonest causes of mortality in MEN1; most of these, unlike non-MEN1 cases, arise from the embryological foregut (bronchi, thyroid, stomach, duodenum and pancreas) [3–5].

Multiple endocrine neoplasia type 2A (MEN2A, Sipple syndrome; MIM #171400—mucosal neuromas, medullary thyroid carcinoma and phaeochromocytoma) [5–7]. This shares some features with MEN2B. Both principally involve the thyroid and parathyroid glands, and the adrenal medulla, and are linked with familial medullary thyroid carcinoma (FMTC) [8,9]. They are caused by mutations of the *RET* proto-oncogene locus (10q11.2) [10–12]. Both are autosomal dominant, but 50% of cases with MEN2B are due to spontaneous mutations. In the same vicinity, near the centromere of chromosome 10, are the genes for Hirschprung disease (which may occur in both MEN2A and 2B) and for FMTC. Thickened corneal nerves occur in both MEN2 syndromes.

Type 2A is linked to a mutation of the *RET* oncogene, located on chromosome 10, compared to a sporadic *RET* oncogene in 2B; *RET* testing has replaced calcitonin screening to diagnose *MEN2* carrier status. The specific *RET* codon mutation will delineate the course of the disease and degree of aggression; details of the genetic aspects underlying MEN2 are provided in [3,4,6,11,12].

MEN2A lacks the mucosal neuromas and skin lipomas of MEN1 and MEN2B, and café-au-lait macules are only present in those with a combined phenotype of MEN2A with neurofibromatosis type 1. By contrast, symmetrical, bilateral pruritic skin lesions are found overlying the scapular area, with hyperpigmentation and hyperkeratosis clinically suggestive of macular amyloidosis; deposits of keratin-derived amyloid are typically found histologically [3,5,7]. Lesions suggestive of notalgia paraesthetica have been reported prior to recognition of the syndrome. Reflecting the genetic background, lichen amyloidosis also occurs in FMTC.

The main internal disorders in MEN2A, described as the triad of cardinal manifestations, are medullary thyroid carcinoma (MTC), phaeochromocytoma and hyperparathyroidism (due to either hyperplasia or adenomas). Other hamartomas and tumours include cerebellar haemangioblastomas, cervical neuroblastoma, pituitary adenomas and pinealomas [7]; Cushing's syndrome also occurs.

Multiple endocrine neoplasia type 2B (MEN type 2B or 3, MIM #162300). This is characterized by mucosal neuromas that are apparent at birth or in the first years of life. Neuromas manifest as asymptomatic, soft, flesh-coloured papules or nodules. They cause a characteristic facial appearance with soft, lumpy ('blubbery'), protuberant lips; everted, thickened, bumpy eyelids; and prominent eyebrows. Neuromas typically affect mucosal surfaces, especially the anterior border of the tongue and the buccal mucosa inside the commissures of the lips; gingival, palatal and pharyngeal surfaces may occasionally be affected. Medullated corneal nerve fibres are seen on slit lamp examination, and there may be conjunctival and, rarely, corneal neuromas. Perioral lentiginosis, pigmentation of hands and feet, and café-au-lait macules may occur and, rarely, a progressive striated pigmentary change of hyperplastic dermal nerves on the trunk [13]. Prognathism or retrognathism can be evident, and there may be a high-arched palate. About 75% of patients have a marfanoid appearance; muscle

weakness and musculoskeletal anomalies (especially kyphoscoliosis, pes cavus and (often bilateral) slipped upper femoral epiphysis) may also be present [10].

MEN2B is also associated with MTC (in 75%) and phaeochromocytoma (in almost 50%), the MTC in type 2B presenting earlier and more aggressively than in type 2A. The MTC is often multicentric and bilateral, occurring in a background of calcitonin-producing cell hyperplasia; it may be found in children as young as 3 years. Diarrhoea is a common symptom. Early lymphatic spread may occur, 75% having metastases at presentation [10]. Prophylactic thyroidectomy may be indicated. Phaeochromocytomas are often bilateral, but the mortality is greater from MTC than from phaeochromocytoma. Hyperparathyroidism due to parathyroid hyperplasia or adenomatosis is much less common than in MEN types 1 and 2A. Intestinal ganglioneuromatosis is more common in type 2B than 2A, occurring in 30% and often presenting early in life due to constipation or abdominal pain.

References

1 Guo SS, Sawicki MP. Molecular and genetic mechanism of tumorigenesis in multiple endocrine neoplasia. *Mol Endocrinol* 2001; **15**: 1653–64.
2 Darling TN, Skarulis MC, Steinberg SM *et al.* Multiple facial angiofibromas and collagenomas in patients with multiple endocrine neoplasia type 1. *Arch Dermatol* 1997; **133**: 853–7.
3 Tsao H. Update on familial cancer syndromes and the skin. *J Am Acad Dermatol* 2000; **42**: 939–46.
4 Brandi ML, Gagel RF, Angeli A *et al.* Guidelines for diagnosis and therapy of MEN type 1 and type 2. *J Clin Endocrin Metab* 2001; **86**: 5658–71.
5 Stratakis CA. Clinical genetics of multiple endocrine neoplasias, Carney's complex and related syndromes. *J Endocrinol Invest* 2001; **24**: 370–83.
6 Callen JP. Skin signs of internal malignancy. In: Callen JP, Jorizzo JL, eds. *Dermatological Manifestations of Internal Disease*, 3rd edn. Philadelphia: Saunders, 2003: 95–104.
7 Kousseff BG. Multiple endocrine neoplasia 2 (MEN 2)/MEN 2A (Sipple syndrome). *Dermatol Clinics* 1995; **13**: 91–7.
8 Sipple JH. The association of phaeochromocytoma with carcinoma of the thyroid gland. *Am J Med* 1961; **31**: 163–6.
9 Cunliffe WJ, Hudgson P, Fulthorpe JJ *et al.* A calcitonin secreting medullary thyroid carcinoma, associated with mucosal neuromas, marfanoid features, myopathy and pigmentation. *Am J Med* 1970; **48**: 120–6.
10 Holloway KB, Flowers FP. Multiple endocrine neoplasia 2B (MEN 2B)/MEN 3. *Dermatol Clinics* 1995; **13**: 99–103.
11 Lee NC, Norton JA. Multiple endocrine neoplasia type 2B: genetic basis and clinical expression. *Surg Oncol* 2000; **9**: 111–8.
12 Huang SC, Torres-Cruz J, Pack SD *et al*. Amplification and overexpression of mutant RET in multiple endocrine neoplasia type 2-associated medullary thyroid carcinoma. *J Clin Endocrinol Metab* 2003; **88**: 459–63.
13 Guillett G, Gauthier Y, Tamisier JM *et al.* Linear cutaneous neuromas (dermatoneurie en stries): a limited phakomatosis with striated pigmentation corresponding to cutaneous hyperneury (featuring multiple endocrine neoplasia syndrome?). *J Cutan Pathol* 1987; **14**: 43–8.

Carney complex (CNC; Carney syndrome; NAME syndrome; LAMB syndrome; myxoma syndrome. Type I MIM #160980, type II MIM *605244) [1–5] (see also p. 62.78)

This is a group of disorders in which there are cutaneous pigmented lesions associated with cutaneous, subcutaneous and internal myxomas at various sites, and associated endocrinopathy (mainly tumours) which typically includes involvement of one or more of the adrenal cortex, thyroid, pituitary, and gonads. NAME syndrome consists of *n*aevi (congenital melanocytic), *a*trial myxomas, *m*yxoid neurofibromas and *e*phelides. LAMB syndrome consists of *l*entigines, *a*trial myxomas, *m*ucocutaneous myxomas and *b*lue naevi. The association with myxomas has led to many other names; some prefer to use '*myxoma syndrome*', or the combined term *Carney complex/myxoma syndrome* [5]. Cardiac myxomas occur in 61% [1] and are the most important internal myxomas, due to the causation of cardiac symptoms and potentially life-threatening effects (see also the section on cardiac disease later in this chapter). Likewise with endocrine involvement, adrenal-linked Cushing's syndrome can have critical, life-threatening effects; the adrenal tumours in Carney complex are typically of primary pigmented nodular type, an otherwise rare condition. Various other gonadal and endocrine hormone-secreting tumours, including pituitary tumours producing GH, prolactin or ACTH, occur; ovarian tumours are associated, and both benign and malignant thyroid tumours (usually of follicular type) also occur [2,3]. Testicular tumours, often large-cell calcifying Sertoli cell tumours, occur in about 30% of males, and are often bilateral and multicentric. Psammomatous melanotic schwannoma, usually of the upper gastrointestinal tract or of paravertebral sympathetic nerves, is very suggestive of this syndrome. Myxoid fibroadenomas of the breast, and mammary ductal adenomas, may be found [5], and myxoid leiomyomas and uterine tumours are described. Lentiginosis and blue naevi occur in two-thirds, typically on the face, lips and conjunctivae [5], and skin myxomas occur in over a third of cases [1].

Over half of patients with Carney complex have mutations in genes coding for a regulatory subunit type 1A of protein kinase A. CNC is clinically and probably genetically heterogeneous. At least two gene locations have been proposed, one on chromosome 2p16 (type 2) and another on 17q23-24 (type 1) [3,4].

References

1 Carney JA. Carney complex: the complex of myxomas, spotty pigmentation, endocrine overactivity, and schwannomas. *Semin Dermatol* 1995; **14**: 90–8.
2 Stratakis CA. Clinical genetics of multiple endocrine neoplasias, Carney's complex and related syndromes. *J Endocrinol Invest* 2001; **24**: 370–83.
3 Lee NC, Norton JA. Multiple endocrine neoplasia type 2B: genetic basis and clinical expression. *Surg Oncol* 2000; **9**: 111–8.
4 Tsao H. Update on familial cancer syndromes and the skin. *J Am Acad Dermatol* 2000; **42**: 939–46.
5 Cullen MK. Carney complex. In: Nordlund JJ, Boissy RE, Hearing VJ *et al.*, eds. *The Pigmentary System*, 2nd edn. Oxford: Blackwell Publishing, 2006: 851–63.

PTEN hamartoma tumour syndrome (Cowden's disease, multiple hamartoma and neoplasia syndrome; MIM #158350) [1–6]

This rare, cancer-associated genodermatosis was first described by Lloyd and Dennis and named after their patient Rachel Cowden [1]. Inheritance is as an autosomal dominant trait with incomplete penetrance. It is due to germline mutations in the *PTEN* (protein tyrosine phosphatase with homology to tensin; *MMAC1*) gene on chromosome 10q23.3. *PTEN* is a tumour suppressor gene; mutations may produce their effects in Cowden's disease and allied hamartomatous disorders due to a failure to regulate cell death [2–4]. The spectrum of the disorder has increased with understanding of the genetic aspects [5], and has not only led to development of diagnostic criteria by the International Cowden Disease Consortium [3,5,6] but also to inclusion within the PTEN hamartoma neoplasia syndrome of several other hamartomatous

disorders including Bannayan–Riley–Ruvalcaba syndrome (Bannayan–Zonana syndrome; MIM 153480) and Lhermitte–Duclos disease [5], in which hamartomatous outgrowths of the cerebellum occur. Bannayan–Riley–Ruvalcaba syndrome, as originally described, has many features in common with Cowden's disease, but lacks the extent of the malignant lesions of the latter; it is characterized by microcephaly, vascular anomalies, lipomas, thyroid disease, gastrointestinal polyposis and speckled genital pigmentation; it is discussed further with other gastrointestinal polyposis syndromes (p. 62.56). A family history of features of Bannayan–Riley–Ruvalcaba syndrome is typical in patients with Cowden's disease, the latter having a stronger association with internal malignancy. Also of dermatological importance is an overlap with Proteus syndrome (MIM 176920); up to 20% of patients with Proteus syndrome have *PTEN* mutations, and 50% of patients with Proteus-like syndrome (in which some features of Proteus syndrome are present, but not sufficient to meet formal diagnostic criteria) [5].

Pathognomonic criteria for Cowden's disease are mucocutaneous lesions, facial trichilemmomas (at least three), acral keratosis (at least six palmar lesions), papillomatous lesions and mucosal lesions. These are found in over 90% of patients. The mucosal lesions (Fig. 62.12) comprise a warty, 'cobblestone' hyperplasia of the mucosal surfaces, particularly affecting the tongue and buccal mucosa; periorificial facial papules, acral warty keratoses and palmoplantar semitranslucent, punctate keratosis are characteristic. The lesions, which are grouped especially around the mouth, nose and ears, have a hyperkeratotic, flat-topped, wart-like appearance, as do many lesions elsewhere; these are mostly trichilemmomas or related benign tumours of the follicular infundibulum [3–7]. Multiple hamartomatous lesions of ectodermal, endodermal and mesodermal origin occur. The other cutaneous lesions include ganglioneuromas, lipomas, fibromas, angiomas, angiolipomas, epidermoid cysts and a variety of pigmentary changes. Craniomegaly is common; there may be an adenoid facies, kyphoscoliosis and a high-arched palate.

Benign internal anomalies are numerous, most commonly affecting the breast (severe fibrocystic disease occurs in the majority of women) and the thyroid (mainly multinodular goitres and adenomas). Gastrointestinal polyposis and cysts or polyps of the female genitourinary system are also frequent. Seizures and mental retardation occur (the latter is a minor diagnostic criterion) and there may be an association with meningioma.

The predisposition to neoplasia includes almost any internal malignancy, but particularly cancers of the breast [8], colon and thyroid (especially follicular thyroid carcinoma). Adenocarcinoma of the breast occurs in about 50% of women. Fibrocystic breast disease and cancers may have an early onset, and screening of at-risk family members is therefore recommended. Even prophylactic mastectomy has been suggested [8]. Benign gynaecomastia has been reported in the male, but malignancy of the breast or thyroid is exceptional. Breast, endometrial and thyroid cancers all contribute to a higher mortality in females. Renal carcinomas have more recently been linked with this syndrome, and an increased likelihood of melanoma has been suggested.



Fig. 62.12 Warty papillomatosis of the hard palate in Cowden's disease. (Courtesy of Dr R. Emmerson, Royal Berkshire Hospital, Reading, UK.)

References

1 Lloyd KM, Dennis M. Cowden's disease: a possible new system complex with multiple system involvement. *Ann Intern Med* 1963; **58**: 136–42.
2 Tsao H. Update on familial cancer syndromes and the skin. *J Am Acad Dermatol* 2000; **42**: 939–46.
3 Eng C. Will the real Cowden syndrome please stand up: revised diagnostic criteria. *J Med Genet* 2000; **37**: 828–30.
4 Mallory S, Mallory SB. Cowden syndrome (multiple hamartoma syndrome). *Dermatol Clin* 1995; **13**: 27–31.
5 Pilarski R, Eng C. Will the real Cowden syndrome please stand up (again)?: expanding mutational and clinical spectra of the PTEN hamartoma tumour syndrome. *J Med Genet* 2004; **41**: 323–6.
6 Uppal S, Mistry D, Coatesworth AP. Cowden disease: a review. *Int J Clin Pract* 2007; **61**: 645–52.
7 Graham RM, Emmerson RW. Multiple hamartoma and neoplasia syndrome. *Clin Exp Dermatol* 1985; **10**: 262–8.
8 Brownstein MH, Wolf M, Bikowski J. Cowden's disease: a cutaneous marker of breast cancer. *Cancer* 1978; **41**: 2393–8.

Sebaceous tumours, keratoacanthomas and visceral malignancy (Muir–Torre syndrome, MTS, Torre syndrome; MIM 158320) [1–6]

This is a cancer-associated genodermatosis in which there is an association between sebaceous lesions and, to a lesser extent, keratoacanthomas and internal malignancy. Inheritance is autosomal dominant with variable expression, males being affected more commonly than females. MTS has been considered to be a variant of the 'cancer family syndrome' [3]; it is currently viewed as a phenotypic variant of the hereditary non-polyposis colon cancer syndrome (HNPCC; Lynch syndrome). Both syndromes are due to mutations at the same region of chromosome 2p22-p21 in the genes *MLH1* and *MSH2*, which are DNA mismatch repair enzymes. Defects result in microsatellite instability, a finding in HNPCC which has also been documented in many MTS-associated keratoacanthomas and sebaceous tumours [6]. About 1% of patients with HNPCC have features of MTS, although this may be an underestimate as the cutaneous features may occur after the development of internal malignancy, or may go unrecognized.

Sebaceous tumours are usually multiple, but occasionally solitary. Although sebaceous adenoma is the commonest, sebaceous carcinoma and epithelioma frequently occur, and within the same patient a variety of different pilosebaceous-derived skin lesions

including keratoacanthomas may arise. Most skin tumours occur in middle age, keratoacanthomas occurring in a quarter of affected subjects. Multiple or early onset of keratoacanthomas are suggestive of this diagnosis, as are multiple (especially eyelid) sebaceous tumours. Multiple or solitary keratoacanthomas associated with SCC of the larynx and lower gastrointestinal tract [7,8] probably represent a variant of MTS in which expression of sebaceous tumours and adenocarcinomas is not exhibited. The cutaneous manifestations of MTS have been reported to be exacerbated by immunosuppression.

The most important internal malignancy is colonic adenocarcinoma, which occurs in almost 50%, often at a relatively young age—around 10 years earlier than in the normal population—and most commonly in the region of the splenic flexure; rectal adenocarcinomas also occur but only in about 5% [4,5]. Urogenital malignancies are also common, occurring in 25% [4]; bladder, renal pelvis and endometrial cancers each account for about 5% of cancers in MTS. The proband in the first family described with HNPCC died of endometrial carcinoma, and gynaecological cancers of various types occur both in HNPCC patients [9] and in those with MTS [4]. Nearly half of affected patients have two or more internal malignancies [10]; other notable malignancies are breast cancers and haematological malignancies (each in about 5% of subjects) [4]. Despite the high risk of malignancy, both the malignant cutaneous sebaceous tumours and the colonic tumours tend to have relatively indolent behaviour (the 50% survival time for colonic cancers is about 12 years [2]) and the incidence of metastases is relatively low. Criteria for diagnosis (Amsterdam and Bethesda criteria), and recommendations for screening of patients and relatives, have been reviewed [11].

References

1 Lynch HT, Fusaro RM, eds. *Cancer-Associated Genodermatoses*. New York: Van Nostrand Reinhold, 1982.
2 Schwarz RA, Torre DP. The Muir–Torre syndrome: a 25-year retrospect. *J Am Acad Dermatol* 1995; **33**: 90–104.
3 Hall NR, Williams AT, Murday VA *et al.* Muir–Torre syndrome: a variant of the cancer family syndrome. *J Med Genet* 1994; **31**: 627–31.
4 Cohen PR, Kohn SR, Davis DA, Kurzrock R. Muir–Torre syndrome. *Dermatol Clinics* 1995; **13**: 79–89.
5 Smoller BR. Muir–Torre syndrome. In: Morgan MB, Smoller BR, Somach SC. *Deadly Dermatologic Diseases. Clinicopathologic Atlas and Text*. New York: Springer, 2007: 53–8.
6 Somoano B, Tsao H. Genodermatoses with cutaneous tumors and internal malignancies. *Dermatol Clinics* 2008; **26**: 69–87.
7 Chapman RS, Finn OA. Carcinoma of the larynx in two patients with keratoacanthoma. *Br J Dermatol* 1974; **90**: 685–8.
8 Stewart WM, Lauret P, Hemet J *et al.* Kératoacanthomes multiples et carcinomes viscéraux: syndrome de Torre. *Ann Dermatol Vénéréol* 1977; **104**: 622–6.
9 Offit K, Kauff ND. Reducing the risk of gynecologic cancer in the Lynch syndrome. *N Engl J Med* 2006; **354**: 293–5.
10 Serleth HJ, Kisken WA. A Muir–Torre syndrome family. *Am Surgeon* 1998; **64**: 365–9.
11 Jones B, Oh C, Mangold E, Egan CA. Muir–Torre syndrome: diagnostic and screening guidelines. *Austral J Dermatol* 2006; **47**: 266–9.

Bloom's, Rothmund–Thomson's and Werner's syndromes

These conditions are considered together as they are all caused by RecQ helicase gene mutations, and they all predispose to abnormal growth, premature ageing and increased incidence of site-specific malignancies [1].

Reference

1 Lindor NM, Furuichi Y, Kitao S *et al.* Rothmund–Thomson syndrome due to RECQ4 helicase mutations: report and clinical and molecular comparisons with Bloom syndrome and Werner syndrome. *Am J Med Genet* 2000; **90**: 223–8.

Bloom's syndrome (MIM *210900) (Chapter 15) [1–4]. This is an autosomal recessive disorder that affects principally the Ashkenazi Jewish ethnic group, nearly 1% of whom are carriers. Affected subjects have small stature and slight build, a sun-sensitive telangiectatic facial rash and café-au-lait macules. Minor congenital anatomical abnormalities commonly occur. Levels of IgA and IgM are low and bacterial infections frequent. Mutations of the gene designated *BLM* on chromosome 15q26.1 lead to inhibition of the function of the protein product, a DNA helicase enzyme. This loss of function allows genomic instability with the occurrence of significantly increased exchanges between DNA strands during the S phase of mitosis, including a tenfold increase in sister chromatid exchanges, such that mutations occur throughout the genome.

The occurrence of lymphoproliferative neoplasia (approximately equally divided between leukaemias and lymphomas) and epithelial tissue cancers, particularly of the aerodigestive tract and lower gastrointestinal tumours, is very high; they typically occur at an early age, and the mean age of death is 23 years [3]. Cervical cancer and Wilms' tumour are additional risks. There is a predisposition to malignancy through mutations in other target genes [4].

References

1 Gretzula JC, Hevia O, Weber PJ. Bloom's syndrome. *J Am Acad Dermatol* 1987; **17**: 479–88.
2 Clark LW. Genetic diseases associated with DNA and chromosomal instability. *Dermatol Clin* 1987; **5**: 85–108.
3 German J. Bloom's syndrome. *Dermatol Clinics* 1995; **13**: 7–18.
4 Tsao H. Update on familial cancer syndromes and the skin. *J Am Acad Dermatol* 2000; **42**: 939–46.

Rothmund–Thomson syndrome (RTS; poikiloderma congenitale; MIM #268400) (Chapter 15) [1–3]. This is a rare autosomal recessive genetic disease, characterized by developmental abnormalities in the skin and skeletal systems, with photosensitivity, poikiloderma, small stature and juvenile cataracts. Premature ageing and a predisposition to certain malignancies occur, notably an approximate 30% incidence of osteosarcoma. Fibrosarcoma, myelodysplasia and non-melanoma skin cancer also occur. A mutation of genes for RecQ helicase is thought to be responsible for at least some, if not all, cases of RTS.

References

1 Lindor NM, Furuichi Y, Kitao S *et al.* Rothmund–Thomson syndrome due to RECQ4 helicase mutations: report and clinical and molecular comparisons with Bloom syndrome and Werner syndrome. *Am J Med Genet* 2000; **90**: 223–8.
2 Narayan S, Fleming C, Trainer AH *et al.* Rothmund–Thomson syndrome with myelodysplasia. *Pediatric Dermatol* 2001; **18**: 210–2.
3 Wang LL, Levy ML, Lewis RA *et al.* Clinical manifestations in a cohort of 41 Rothmund–Thomson syndrome patients. *Am J Med Genet* 2001; **102**: 11–7.

Werner's syndrome (adult progeria; MIM #277700) [1–4]. This is an autosomal-recessive condition of premature ageing, with onset in the second to third decade of life. It is due to mutation of the *WRN* gene on chromosome 8p12-p11.2. The normal gene product

is a DNA helicase belonging to the RecQ family which unwinds double-stranded DNA and is able to resolve aberrant DNA structures, so that aberrations occurring during repair, recombination and replication are made good, together with those that result from direct DNA damage [1–4]. Neoplasms develop in about 10% of cases, although the commonest cause of death is arteriosclerosis. Sarcomas, melanomas, leukaemia and a variety of epithelial-derived carcinomas have been reported [1–6]. Meningiomas are a recognized association, and an astrocytoma has been documented [7]. Werner's syndrome is a chromosome-instability syndrome and, as with XP, ataxia–telangiectasia, Bloom's syndrome and Fanconi's anaemia, is associated with a high incidence of neoplasia [2,3].

References

1 Duvic M, Lemak NA. Werner's syndrome. *Dermatol Clin* 1995; **13**: 163–8.
2 Callen JP. Skin signs of internal malignancy. In: Callen JP, Jorizzo JL, eds. *Dermatological Manifestations of Internal Disease*, 3rd edn. Philadelphia: Saunders, 2003: 95–104.
3 Tsao H. Update on familial cancer syndromes and the skin. *J Am Acad Dermatol* 2000; **42**: 939–46.
4 Shen J, Loeb LA. Unwinding the molecular basis of the Werner syndrome. *Mech Ageing Dev* 2001; **122**: 921–44.
5 Hrabko RP, Milgrom H, Schwartz RA. Werner's syndrome with associated malignant neoplasms. *Arch Dermatol* 1982; **118**: 106–8.
6 Usui M, Ishii S, Yamawaki S *et al.* The occurrence of soft tissue sarcomas in three siblings with Werner's syndrome. *Cancer* 1984; **54**: 2580–6.
7 Laso FJ, Vasquez G, Pastor I *et al.* Werner's syndrome and astrocytoma. *Dermatologica* 1989; **178**: 118–20.

Immunodeficiency and neoplasia syndromes: Wiskott–Aldrich syndrome, Chediak–Higashi syndrome, ataxia–telangiectasia, dyskeratosis congenita, Fanconi's anaemia

Wiskott–Aldrich syndrome (MIM #301000) (Chapter 15) [1]. This is an X-linked recessive immunodeficiency syndrome due to mutations at Xp11.23-p11.22; the Wiskott–Aldrich syndrome protein (WASP) is expressed in all haemopoietic cells, and mutations cause defective T-cell function and thrombocytopenia. Infections are the commonest cause of death but lymphoreticular malignancy occurs in 18% and is the cause of death in about 10% [1,2]. Non-Hodgkin's lymphoma occurs in almost all subjects who survive infections or bleeding due to thrombocytopenia, usually by the age of 30 years. Lymphoma (especially large cell or immunoblastic) and leukaemia occur; the small intestine is a particular site for lymphomatous involvement. Cerebral tumours such as astrocytoma, and various sarcomas, have also been reported [1–4].

References

1 Paller AS. Immunodeficiency syndromes. In: Harper J, Oranje A, Prose N. *Textbook of Pediatric Dermatology*, 2nd edn. Oxford: Blackwell Publishing, 2006: 2052–73.
2 Ormerod AD. The Wiskott–Aldrich syndrome. *Int J Dermatol* 1985; **24**: 77–81.
3 Model LM. Primary reticulum cell sarcoma of the brain in Wiskott–Aldrich syndrome. *Arch Neurol* 1977; **34**: 633–5.
4 Heidelberger KP, Le Golvan DP. Wiskott–Aldrich syndrome and cerebral neoplasia: report of a case with localised reticulum cell sarcoma. *Cancer* 1974; **24**: 280–4.

Chediak–Higashi syndrome (MIM #214500) (Chapter 15) [1,2]. This is a fatal autosomal recessive illness, with features of partial albinism, photophobia, neurological abnormalities and severe, recurrent bacterial infections. About 85% of patients develop a terminal, accelerated 'lymphomatous' phase, which may be triggered by viral infections, especially due to Epstein–Barr virus [2]. There is extensive organ infiltration with lymphoid and histiocytic cells; patients develop fever, jaundice, hepatosplenomegaly, lymphadenopathy, leukaemia-like gingival lesions and sloughing of the oral mucosa, pancytopenia and a deterioration of neurological changes. Death may result from bleeding due to thrombocytopenia and reduced synthesis of clotting factors, or from infection due to neutropenia. Although strongly suggestive of lymphoma, the infiltrate of affected organs is reported to be of a reactive, diffuse, mononuclear cell type, rather than neoplastic [1].

Ataxia–telangiectasia syndrome (AT; Louis–Bar syndrome; MIM *208900) (Chapter 15) [3–9]. This is a condition with autosomal recessive inheritance, characterized by progressive cerebellar ataxia and oculocutaneous telangiectasia. Like XP, the condition has different complementation groups defined by fibroblast fusion and irradiation studies. Most families have one of many different germ-line mutations in the large *ATM* gene at chromosome 11q22.3; the product, ATM protein (phosphatidylinositol-3-kinase p53 checkpoint regulation), is involved in the handling of chromosome strand breaks and activation of the p53 oncogene [6], and has been considered to be a 'caretaker' of the genome and tumour suppressor. Mutations are mainly inactivating in type but may be missense [9]; they allow unregulated DNA synthesis, with DNA that is predisposed to instability and hypersensitive to ionizing radiation [6]. Peripheral blood lymphocytes are abnormal, having translocations mainly involving chromosomes 7 and 14, and abnormal function, and there is a variable but progressive immune deficiency of both the cell-mediated and humoral types, which results in frequent infections and a reduction in immune surveillance [3]. As a result, there is a high incidence of neoplasia, approximately 30% lifetime risk, usually in or before the teenage years, and being the cause of death in 15% of affected individuals [3–8].

The majority (around 80%) of tumours are lymphoproliferative or leukaemic, although carcinomas of various sites also occur, the latter usually in older subjects [5,7,8]. Most haematological malignancies are B-cell lymphomas but 25% are leukaemias, notably chronic T-cell leukaemia with chromosome 14 translocations, occurring in older patients. However, T-cell leukaemias do occur in younger patients, and both T-cell lymphomas and B-cell leukaemias are also encountered. Most tumours have early onset, and may precede diagnosis of AT from the cutaneous features; this is of considerable importance as standard radiotherapy doses are contraindicated. Heterozygotes (carriers) have a five to tenfold increased risk of tumours, usually not lymphoid, including a fivefold increase in risk of breast malignancy in females [4,6]. Atm-deficient mice also develop lymphomas.

Dyskeratosis congenita (Zinsser–Cole–Engman syndrome; MIM #305000) (Chapter 15) [10]. This is a multisystem ectodermal dysplasia, in which a triad of cutaneous abnormalities are the most consistent and diagnostic feature, comprising reticulate hyperpigmentation of the skin, nail dystrophy and leukokeratosis of mucous

membranes. Dental, skeletal, ocular and gastrointestinal abnormalities are common; mental retardation, short stature and premature ageing also occur. Most cases have X-linked recessive inheritance (linked to Xq28) but autosomal recessive and autosomal dominant forms also occur [10].

Aplastic anaemia occurs in 50%, typically in early teens. Oropharyngeal carcinomas secondary to the mucous membrane lesions are the commonest form of malignancy; there is also increased incidence of internal malignancy, particularly gastrointestinal, including pancreatic adenocarcinoma and other haematological disorders, similar to those found in Fanconi's anaemia and Hodgkin's disease, which may evolve into leukaemia [11,12]. A defect in cell-mediated immunity involving suppressor T cells may be linked to the premature ageing sometimes associated with this syndrome [13].

Fanconi's anaemia (MIM #227650 and others). This is an autosomal recessive disorder characterized dermatologically by pigmentary abnormalities which may be diffuse (with accentuation around the neck and over joints), mottled, often with scattered darker macules, and sometimes just exhibiting localized café-au-lait macules. Scattered areas of hypopigmentation are a common finding. The main abnormality is progressive pancytopenia, which may lead eventually to development of leukaemia. Multiple skeletal abnormalities occur, including digital hypoplasias, scoliosis and short stature. The underlying defect is one of increased DNA cross-linkage (especially radiation-induced) and defective DNA repair.

References

1 Stolz W, Graubner U, Gerstmeier J *et al*. Chediak–Higashi syndrome: approaches in diagnosis and treatment. *Curr Probl Dermatol* 1989; **18**: 93–100.
2 Paller AS. Immunodeficiency syndromes. In: Harper J, Oranje A, Prose N. *Textbook of Pediatric Dermatology*, 2nd edn. Oxford: Blackwell Publishing, 2006: 2052–73.
3 Spector BD, Fillipivich AH, Perry SS *et al*. Epidemiology of cancer in ataxia telangiectasia. In: Bridges BA, Harnden DG, eds. *Ataxia Telangiectasia: a Cellular and Molecular Link Between Cancer Neuropathy and Immune Deficiency*. New York: Wiley, 1982: 103–38.
4 Gatti RA. Ataxia-telangiectasia. *Dermatol Clinics* 1995; **13**: 1–6.
5 Swift M, Morrell D, Massey RB *et al*. Incidence of cancer in 161 families affected by ataxia–telangiectasia. *N Engl J Med* 1991; **325**: 1831–6.
6 Tsao H. Update on familial cancer syndromes and the skin. *J Am Acad Dermatol* 2000; **42**: 939–46.
7 Morgan MB. Lethal hereditary vascular disorders: Osler-Weber-Rendu, ataxia telangiectasia, and Fabry's disease. In: Morgan MB, Smoller BR, Somach SC. *Deadly Dermatologic Diseases. Clinicopathologic Atlas and Text*. New York: Springer, 2007: 145–9.
8 Callen JP. Skin signs of internal malignancy. In: Callen JP, Jorizzo JL, eds. *Dermatological Manifestations of Internal Disease*, 3rd edn. Philadelphia: Saunders, 2003: 95–104.
9 Boultwood J. Ataxia telangiectasia gene mutations in leukaemia and lymphoma. *J Cutan Pathol* 2001; **54**: 512–6.
10 Drachtman RA, Alter BP. Dyskeratosis congenita. *Dermatol Clinics* 1995; **13**: 33–9.
11 Clark Lambert W. Genetic diseases associated with DNA and chromosomal instability. *Dermatol Clin* 1987; **5**: 85–108.
12 Connor JM, Teague RH. Dyskeratosis congenita: report of a large kindred. *Br J Dermatol* 1981; **105**: 321–5.
13 Fudenberg HH, Goust JM, Vesole DH, Salinas CF. Active and suppressor T cells: diminution in a patient with dyskeratosis congenita and in first-degree relatives. *Gerontology* 1979; **25**: 231–7.

Follicular atrophoderma (Bazex–Dupré–Christol syndrome; MIM *301845)** [1]

A rare, X-linked, dominant condition of follicular atrophoderma, milia, epidermoid cysts, hypotrichosis, basal cell epitheliomas and occasional generalized or localized hypohidrosis, which appears to have an association with leukaemia. Pigmented, perioral, follicular atrophoderma is characteristic [2].

References

1 Colomb D, Ducros B, Boussuge N. Le syndrome de Bazex, Dupré et Christol. A propos d'un cas avec leucémie prolymphocytaire. *Ann Dermatol Vénéréol* 1989; **116**: 381–7.
2 Inoue Y, Ono T, Kayashima K *et al*. Hereditary perioral pigmented follicular atrophoderma associated with milia and epidermoid cysts. *Br J Dermatol* 1998; **139**: 713–8.

Hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome (MIM #605839)

A syndrome comprising multiple cutaneous leiomyomas with uterine leiomyomas (Reed syndrome, MIM #150800); in some cases (2% in one series [1]) there is also an association with aggressive renal cell carcinoma, mainly of papillary cell type. Numerous different fumarate hydratase (FH) mutations on chromosome 1q 42.1 have been identified; patients who have renal cell carcinomas are usually female and have truncating or frameshift mutations [1]. One study of 40 such renal carcinomas found that the presence of a large nucleus, with a prominent orangiophilic or eosinophilic nucleolus surrounded by a clear halo, appeared to be characteristic and was seen even in the renal carcinomas that were not papillary or tubulopapillary in type [2]. Most women with HLRCC develop uterine leiomyomas ('fibroids'). Benign ovarian mucinous cystadenomas, renal cysts and adrenal gland adenomas, as well as uterine leiomyosarcomas, have also been linked with FH mutations; there is also some evidence for an association with breast and bladder cancers [3] and a suggested association with Leydig cell carcinoma of testis.

References

1 Alam NA, Olpin S, Leigh IM. Fumarate hydratase mutations and predisposition to cutaneous leiomyomas, uterine leiomyomas and renal cancer. *Br J Dermatol* 2005; **153**: 11–7.
2 Merino MJ, Torres-Cabala C, Pinto P, Linehan WM. The morphologic spectrum of kidney tumors in hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome. *Am J Surg Pathol* 2007; **31**: 1578–85.
3 Lehtonen HJ, Kiura M, Ylisaukko-Oja SK *et al*. Increased risk of cancer in patients with fumarate hydratase germline mutation. *J Med Genet* 2006; **43**: 523–6.

Paraneoplastic disorders [1–14]

Paraneoplastic dermatoses are skin conditions that have an association with internal malignancy but are not themselves malignant. They may be classified in a variety of ways; some authors include genodermatoses within the spectrum of paraneoplastic disorders [1] whilst others view these as a separate group [2,3], or distinguish between paraneoplastic dermatoses [4], hereditary paraneoplastic syndromes [5] and hormonally mediated paraneoplastic syndromes [6]. They may be classified according to strength of association with malignancy, association with certain types of malignancy [13,14], by the type of eruption that occurs (papulosquamous, vascular, etc.) or by the apparent mechanism (hormone

secretion, autoimmune, cytokine/growth factor, etc.). Paraneoplastic conditions occur in other organ systems as well, but whatever system is affected there are general principles that can be applied to determine a relationship.

Helen Ollendorff Curth proposed criteria for diagnosis of a paraneoplastic dermatosis (discussed in [7]):

1 Both conditions start at approximately the same time
2 Both conditions follow a parallel course
3 In syndromes, neither the onset nor the course of either condition is dependent on the other
4 A specific tumour occurs with a specific skin manifestation
5 The dermatosis is not common in the general population
6 A high percentage of association between the two conditions is noted

These criteria were quite specific and some conditions that would now be viewed as potentially paraneoplastic, such as acquired ichthyosis, would fail to meet several of the above criteria.

A less rigid definition that has been in common use is as follows [1]:

1 The malignancy and the cutaneous disorder may occur concurrently
2 The two disorders may follow a parallel course
3 There can be a specific tumour site or cell type associated with the cutaneous disease
4 There may be a statistical association between the two processes
5 There may be a genetic association between the two processes

Those disorders with a genetic link between the dermatological features and internal malignancy are discussed above; this section discusses other paraneoplastic dermatoses. Specific tumour sites are discussed in the following sections although this text is arranged in categories of types of presentation. In terms of the intensity of investigation required, it is also helpful to divide paraneoplastic disorders into groups depending on the likelihood of an underlying neoplasm being discovered. Thus, the likelihood of finding a neoplasm may be graded as high, intermediate or low for some of the better known paraneoplastic disorders (Table 62.9), as derived from several reviews [1–15].

References

1 Callen JP. Skin signs of internal malignancy. In: Callen JP, Jorizzo JL, eds. *Dermatological Manifestations of Internal Disease*, 3rd edn. Philadelphia: Saunders, 2003: 95–104.
2 Poole S, Fenske NA. Cutaneous markers of internal malignancy, 1: malignant involvement of the skin and the genodermatoses. *J Am Acad Dermatol* 1993; **28**: 1–13.

Table 62.9 Strength of correlation of some potentially paraneoplastic dermatoses with internal malignancy.

Strength of correlation	Type of reaction pattern	Examples
Strong	Papulosquamous and figurate eruptions	Bazex syndrome
		Erythema gyratum repens
		Necrolytic migratory erythema
	Deposition disorders	Primary amyloidosis
		Scleromyxedema
		Necrobiotic xanthogranuloma
		POEMS syndrome
	Others	Acquired hypertrichosis lanuginosa
		Paraneoplastic pemphigus
		Tripe palms
		Carcinoid syndrome
		Trousseau's syndrome
Moderate	Papulosquamous and neutrophilic eruptions	Sweet's syndrome
		Pyoderma gangrenosum
		Dermatomyositis
	Others	Multicentric reticulohistiocytosis
		Pityriasis rotunda
Weak	Epidermal conditions	Acanthosis nigricans in isolation
		Acquired ichthyosis (unless widespread, deeply fissured, truncal pattern)
		Eruptive seborrhoeic keratoses (sign of Leser–Trélat)
	Deposition disorders	Scleredema
		Calcinosis cutis
	Others	Vasculitis, Raynaud's phenomenon, digital ischaemia
		Erythromelalgia
		Relapsing polychondritis
		Erythroderma/exfoliative dermatitis
		Digital clubbing (unless with hypertrophic osteoarthropathy)
		Pruritus
		Erythema annulare centrifugum
		Cushing's syndrome

3 Poole S, Fenske NA. Cutaneous markers of internal malignancy, 2: paraneoplastic dermatoses and environmental carcinogens. *J Am Acad Dermatol* 1993; **28**: 147–64.
4 Provost TT, Laman SD, Bell WR. Paraneoplastic dermatoses. In: Provost TT, Flynn JA, eds. *Cutaneous Medicine: Cutaneous Manifestations of Systemic Disease*. Hamilton, Ontario: Decker, 2001: 367–88.
5 Provost TT, Laman SD, Giardiello FM. Hereditary paraneoplastic syndromes. In: Provost TT, Flynn JA, eds. *Cutaneous Medicine: Cutaneous Manifestations of Systemic Disease*. Hamilton, Ontario: Decker, 2001: 389–400.
6 Provost TT, Gordon AH, Laman SD. Hormonally mediated paraneoplastic syndromes. In: Provost TT, Flynn JA, eds. *Cutaneous Medicine: Cutaneous Manifestations of Systemic Disease*. Hamilton, Ontario: Decker, 2001: 401–12.
7 Chung VQ, Moschella SL, Zembowicz A, Liu V. Clinical and pathologic findings of paraneoplastic dermatoses. *J Am Acad Dermatol* 2006; **54**: 745–62.
8 Boyce S, Harper J. Paraneoplastic dermatoses. *Dermatol Clin* 2002; **20**: 523–32.
9 Thomas VD, Thomas CR, eds. Internal malignancy and the skin: paraneoplastic and cancer treatment-related cutaneous disorders. *Dermatol Clinics* 2008; **26**: 1–182.
10 Pipkin CA, Lio PA. Cutaneous manifestations of internal malignancies: an overview. *Dermatol Clin* 2008; **26**: 1–15.
11 Stone SP, Buescher LS. Life-threatening paraneoplastic cutaneous syndromes. *Clinics Dermatol* 2005; **23**: 301–6.
12 Thomas I, Schwartz RA. Cutaneous paraneoplastic syndromes: uncommon presentations. *Clinics Dermatol* 2005; **23**: 593–600.
13 Roumm A, Medsger TJ. Cancer in connective tissue disease. *Arthritis Rheum* 1982; **25**: 1130–3.
14 Cohen PR. Paraneoplastic dermatopathology: cutaneous paraneoplastic syndromes. *Adv Dermatol* 1996; **11**: 215–52.
15 Zappasodi P, Del Forna C, Corso A, Lazzarino M. Mucocutaneous paraneoplastic syndromes in hematologic malignancies. *Int J Dermatol* 2006; **45**: 14–22.

Acanthotic, epidermal and ichthyotic conditions

Acanthosis nigricans [1–5]

Acanthosis nigricans may be simply divided into two important categories, benign (see also Chapter 19) and malignant, although Schwartz [1] described eight types of acanthosis nigricans: benign, obesity-associated, syndromic, malignant, acral, unilateral, medication-induced (especially nicotinic acid) and mixed types. Benign acanthosis nigricans is actually fairly common, especially in obesity or in individuals with insulin resistance, and is usually relatively mild; it has been documented in up to 7% of children, mainly in teenage years, and virtually all childhood cases are of benign type.

Malignancy-associated acanthosis nigricans is much less common than the non-malignancy-associated types. It may have a rapid onset and progression to produce symmetrical, hyperpigmented, rugose velvety plaques [1–5]. The axillae and other flexures are particularly affected, along with the areolar area, and the nape of the neck. There may be prominent acrochordon-like papillomatosis arising from the plaques; the sign of Leser–Trélat, and acanthosis palmaris (tripe palms) may coexist [5]. *De novo* development of acanthosis nigricans in adults, especially if progressive and associated with weight loss (most patients with insulin resistance having a rather stocky build), is strongly suspicious that there is an underlying neoplasm, although cases have been described in which acanthosis nigricans has preceded a malignancy by 10 years or more [2]. If there is also generalized pruritus or the skin changes of tripe palms (see below), then a malignancy is even more likely; mucosal involvement is a useful pointer to the diagnosis of paraneoplastic acanthosis nigricans as it occurs in over half of cases [6]. Production by tumour cells of either transforming growth factor-alpha, or cytokines that activate insulin-like growth factors or their cutaneous receptors, have been suggested as the pathogenetic mechanism.

By far the commonest site of underlying neoplasm is the gastrointestinal tract (70–90%); gastric adenocarcinoma is most frequent [1–5]. A number of different malignancies have been reported, nearly all being adenocarcinomas, at sites including other parts of the intestine, liver or bile duct; other tumour sites include lung, breast, endometrium, kidney, bladder, prostate, testis, cervix, thyroid and adrenal. Most are solid organ tumours but lymphoma has been recorded [7]. Sarcomas occur rarely. The prognosis with malignant acanthosis nigricans is generally poor, which at least in part is related to the low survival rate from the neoplasia concerned. However, the changes may resolve with eradication of the cancer [8]. Malignancy-associated acanthosis nigricans has rarely been associated with other paraneoplastic conditions including pachydermoperiostosis, paraneoplastic pemphigus and acquired hypertrichosis lanuginosa.

An additional, indirect link between acanthosis nigricans and internal malignancy is that it may be associated with ataxia–telangiectasia (p. 62.28).

References

1 Schwartz RA. Acanthosis nigricans. *J Am Acad Dermatol* 1994; **31**: 1–19.
2 Thomas I, Schwartz RA. Cutaneous paraneoplastic syndromes: uncommon presentations. *Clinics Dermatol* 2005; **23**: 593–600.
3 Stone SP, Buescher LS. Life-threatening paraneoplastic cutaneous syndromes. *Clinics Dermatol* 2005; **23**: 301–6.
4 Curth HO. Classification of acanthosis nigricans. *Int J Dermatol* 1976; **15**: 592–3.
5 Moore RL, Devere TS. Epidermal manifestations of internal malignancy. *Dermatol Clinics* 2008; **26**: 17–29.
6 Longshore SL, Taylor JS, Kennedy A, Nurko S. Malignant acanthosis nigricans and endometrial carcinoma of the parametrium: the search for malignancy. *J Am Acad Dermatol* 2003; **49**: 541–3.
7 Janier M, Blanchet-Bardon C, Bonvalet D *et al.* Malignant acanthosis nigricans associated with non-Hodgkin's lymphoma. *Dermatologica* 1988; **176**: 133–7.
8 Moller H, Eriksson S, Holen O *et al.* Complete reversibility of paraneoplastic acanthosis nigricans after operation. *Acta Med Scand* 1978; **203**: 245–6.

Acanthosis palmaris (Tripe palms, pachydermatoglyphy) [1–4]

Tripe palms describes thickened skin of the palms and occasionally the soles, with an enhanced dermatoglyphic change, causing a velvety or, less commonly, a pitted honeycombed pattern of the hand. It is associated with neoplasia in about 90% of cases; it may be the only paraneoplastic manifestation in 30–40% or it may occur with one or both of malignant acanthosis nigricans or the sign of Leser–Trélat [1–3]. It occurs particularly in men, especially when it occurs in isolation or when the underlying tumour is a lung cancer [2]. However, it can occur in isolation without neoplasia, or as a pattern of exfoliative psoriasis or eczema [1,2], and has been reported with bullous pemphigoid.

As the condition is usually associated with an internal neoplasm, usually of solid organ type (but rarely lymphoma), it requires appropriate evaluation and investigation. Most commonly the underlying tumour is bronchial or gastric, together accounting for over half of associated malignancy, but many sites are reported including tumours of genitourinary tract, breast and others [2]. One study found that acanthosis palmaris occurring alone was more often associated with bronchial carcinoma (53%) compared with combined acanthosis nigricans and acanthosis

palmaris, in which 35% had gastric carcinoma and only 11% had bronchial neoplasia [4]. If nail clubbing is also present (18% of patients [2]), then bronchial carcinoma is very likely. Thus, tripe palms alone, especially if the patient is male and also has clubbing, very strongly suggests an underlying lung cancer, whilst tripe palms with acanthosis nigricans is more suggestive of an underlying gastric carcinoma. Resolution of the palmar changes has been described with resection of the tumour [4].

References

1 Breathnach SM, Wells GC. Acanthosis palmaris: tripe palms—a distinctive pattern of palmar keratoderma frequently associated with internal malignancy. *Clin Exp Dermatol* 1980; **5**: 181–9.
2 Moore RL, Devere TS. Epidermal manifestations of internal malignancy. *Dermatol Clinics* 2008; **26**: 17–29.
3 Cohen PR, Grossman ME, Silvers DN *et al*. Tripe palms and cancer. *Clin Dermatol* 1993; **11**: 165–73.
4 Votion V, Mineur P, Mirgaux M *et al*. Hyperkératose palmoplantaire associée à un adénocarcinome gastrique. *Dermatologica* 1982; **165**: 660–3.

The sign of Leser–Trélat [1–4]

This is the sudden development of numerous seborrhoeic keratoses, in an eruptive fashion, with or without pruritus, as an indicator of internal malignancy. However, the significance of eruptive seborrhoeic keratoses remains unclear, with strong proponents and opponents of its importance [2,3]. Multiple seborrhoeic keratoses are extremely common, especially in elderly people, and may be pruritic or rapidly erupting, without any apparent cause; they may also occur in other situations [4] such as HIV infection, acromegaly, and in the resolving phase of erythrodermic dermatoses [5].

Of the cases reported with a neoplasm, half of the tumours are adenocarcinomas, most of which (one-third of the associated tumours) arise in the gastrointestinal tract; this is similar to the distribution of tumours in acanthosis nigricans, which may coexist. Carcinomas of the breast are also frequent, although this may just reflect the incidence of these tumours in an age group who are also likely to have seborrhoeic keratoses. Rare associations have been documented with a variety of other neoplasms, including malignant haemangiopericytoma [6], malignant melanoma [7], renal carcinoma [4] and transitional cell carcinoma of the bladder [8]. Lymphoproliferative disorders, which are rarely associated with acanthosis nigricans, have been more commonly reported with the sign of Leser–Trélat, accounting for about 20% of associated tumours [4].

Truly sudden development of multiple seborrhoeic keratosis, especially in younger patients, and especially if associated with pruritus or with acanthosis nigricans, does warrant investigation, but the mere presence of many seborrhoeic keratoses is unlikely to be linked with malignancy and the strength of this sign as a marker of internal malignancy must be viewed as uncertain.

References

1 De Bersaques J. Sign of Leser–Trélat. *J Am Acad Dermatol* 1985; **12**: 724.
2 Holdiness MR. On the classification of the sign of Leser–Trélat. *J Am Acad Dermatol* 1988; **19**: 754–7.
3 Rampen FH, Schwengle LE. The sign of Leser–Trélat: does it exist? *J Am Acad Dermatol* 1989; **21**: 50–5.
4 Moore RL, Devere TS. Epidermal manifestations of internal malignancy. *Dermatol Clinics* 2008; **26**: 17–29.
5 Williams MG. Acanthomata appearing after eczema. *Br J Dermatol* 1956; **68**: 268–71.
6 Mayou SC, Benn JJ, Sonksen PH *et al*. Paraneoplastic rhinophyma and the Leser–Trélat sign. *Clin Exp Dermatol* 1989; **14**: 253–5.
7 Fanti PA, Metri M, Patrizi A. The sign of Leser–Trélat associated with malignant melanoma. *Cutis* 1989; **44**: 39–41.
8 Yaniv R, Servadio Y, Feinstein A *et al*. The sign of Leser–Trélat associated with transitional cell carcinoma of the urinary bladder: a case report and short review. *Clin Exp Dermatol* 1994; **19**: 142–5.

Acquired ichthyosis [1–5] *and pityriasis rotunda*

Acquired ichthyosis usually has gradual onset, consists of a mild dryness or asteatosis pattern, and is not associated with underlying malignancy. Other systemic diseases associated with acquired ichthyosis include nutritional deficiencies, sarcoidosis, leprosy, HIV infection, hypothyroidism, lupus erythematosus, graft-versus-host disease and drug reactions [2]. Some of these cause particular problems in differential diagnosis as well, especially sarcoidosis which may itself have an association with lymphoma (p. 62.40). Asteatosis is a common problem cause, especially in elderly people, and does not warrant an extensive search for malignancy unless there are other suggestive features such as weight loss or focal symptoms.

However, more sudden onset of ichthyosis similar to the pattern of ichthyosis vulgaris in adult life, or with a generalized eczema craquelé appearance, does suggest the possibility of internal malignancy, particularly if it occurs in a younger age group. The strongest association is with Hodgkin's disease (accounting for over 70% of cases) and other lymphoreticular tumours, including T-cell lymphomas, leukaemias, myelodysplastic syndrome, multiple myeloma and polycythaemia rubra vera [1–4], although cases linked with solid tumours are also well documented [4], including cancers of ovary, kidney, liver and breast [5] as well as leiomyosarcoma [2]. Paraneoplastic ichthyosis is typically very extensive, affecting the trunk and having quite prominent fissuring; a parallel course with the underlying lymphoma (including resolution related to treatment) is also usual. Other paraneoplastic signs have been reported to be present in conjunction with acquired ichthyosis, including erythema gyratum repens, Bazex syndrome and dermatomyositis [4].

Pityriasis rotunda [4,6] is a fixed, annular, scaling, dry-skin change more often seen in the African and Asian races—it has been associated with neoplasia, particularly hepatocellular carcinoma. However, it may also be seen in other systemic diseases and in leprosy [4,6].

References

1 Elewski BE, Gilgor RS. Eruptive lesions and malignancy. *Int J Dermatol* 1985; **24**: 617–29.
2 Patel N, Spencer LA, English JC 3rd, Zirwas MJ. Acquired ichthyosis. *J Am Acad Dermatol* 2006; **55**: 647–56.
3 Moore RL, Devere TS. Epidermal manifestations of internal malignancy. *Dermatol Clinics* 2008; **26**: 17–29.
4 Griffin LJ, Massa MC. Acquired ichthyosis and pityriasis rotunda. *Clin Dermatol* 1993; **11**: 27–32.
5 Polisky RB, Bronson DM. Acquired ichthyosis in a patient with adenocarcinoma of the breast. *Cutis* 1986; **38**: 359–60.
6 Leibowitz MR, Weiss R, Smith EH. Pityriasis rotunda: a cutaneous sign of malignant disease in two patients. *Arch Dermatol* 1983; **119**: 607–9.

Other epidermal conditions

Transient acantholytic dermatosis has been linked with internal malignancy, particularly with myelogenous leukaemia and carcinoma of the genitourinary tract. However, this may be linked in part with therapy, or simply because it may go unrecognized unless it is specifically considered [1].

Seed-like keratoses of the palms and soles, an acquired pattern of punctate keratoses of the palms and soles, are a common normal finding in healthy subjects (36%) over 50 years old, but are apparently more common in individuals with carcinoma of the bladder (87%) and bronchus (71%) [2]. Punctate keratoderma occurring in Cowden's syndrome (Chapter 12 and p. 62.25) and seed-like keratoses with arsenic ingestion may also be associated with internal malignancy (p. 62.47). Inherited palmoplantar keratodermas were discussed on p. 62.20.

Café-au-lait macules (spots) [3] **and lentigines** (see also Table 62.10). Café-au-lait macules are common, but increased numbers of such lesions are a component of many disorders, some of which are associated with internal malignancy.

Some of these have been discussed above (Genodermatoses associated with internal malignancies); these include neurofibromatosis, Bloom's syndrome, Fanconi's anaemia, Cowden's disease and (variably) ataxia–telangiectasia. An association between café-au-lait macules and early-onset colorectal neoplasia has been proposed to represent a variant of the HNPCC (Lynch) syndrome [4].

Lentiginosis is a feature of the Carney complex (pp. 62.25 and 62.78). Lentigines of the palms and/or soles have recently been described as a paraneoplastic syndrome in four patients, two with previously undiagnosed tumours (one small bowel lymphoma and one carcinoma of stomach) and the other two with known breast cancer [5].

References

1 Guana AL, Cohen PR. Transient acantholytic dermatosis in oncology patients. *J Clin Oncol* 1994; **12**: 1703–9.

2 Cuzick J, Harris R, Mortimer PS. Palmar keratoses and cancers of the bladder and lung. *Lancet* 1984; **i**: 530–3.

3 Landau M, Krafchik BR. The diagnostic value of café-au-lait macules. *J Am Acad Dermatol* 1999; **40**: 877–90.

4 Trimbath JD, Petersen GM, Erdman SH *et al*. Café-au-lait spots and early onset colorectal neoplasia: a variant of HNPCC? *Fam Cancer* 2001; **1**: 101–5.

5 Wolf R, Orion E, Davidovici B. Acral lentigines: a new paraneoplastic syndrome. *Int J Dermatol* 2008; **47**: 168–70.

Pigmentation

Many aspects of generalized or localized pigmentation that can be associated with internal malignancy have been discussed in relation to specific disorders. However, it is potentially useful to summarize the most important or characteristic types here, and to comment on those that are not discussed elsewhere in this chapter. A summary is provided in Table 62.10; the mechanisms of pigmentation are discussed in more detail in Chapter 58.

The *ectopic ACTH syndrome* (extracutaneous neuroendocrine melanoderma) occurs due to production of an ACTH-like hormone from tumours; small cell bronchial carcinoma is the cause in over 50%, other reports have described the same condition resulting from gastric, pancreatic, oesophageal and ovarian cancers, as well as in thymoma, phaeochromocytoma, carcinoid syndrome and in various APUD (amine precursor uptake and decarboxylation) tumours. Pituitary and adrenal ACTH production and its effects are discussed in the section describing Cushing's syndrome (p. 62.3). The pigmentation in ectopic ACTH syndrome is addisonian in distribution, diffuse but with photoaccentuation and more prominent over pressure points and in flexures, genital skin, scars and the oral mucosa [1].

Hyperpigmentation with scleromyxoedema and gammopathy [2] has been reported. One patient had pigmentation of the face and V of the neck; the other had generalized pigmentation with accentuation in thickened skin, at acral sites and of genitalia. A similar picture has been seen by one of the authors in a patient without gammopathy.

In Carney complex (p. 62.25), lentiginosis is typically centrofacial but may be widespread at almost any body site; the buccal mucosa is only affected in 5%, rarer sites include the conjunctivae and labia minora, but palms, soles and penis are rarely affected. Blue naevi, usually few in number, occur on the face, trunk or limbs but rarely on the extremities.

References

1 Levine N, Burk C. Extracutaneous neuroendocrine melanoderma. In: Nordlund JJ, Boissy RE, Hearing VJ *et al.*, eds. *The Pigmentary System,* 2nd edn. Oxford: Blackwell Publishing, 2006: 938–9.

2 Urabe K, Nakayama J, Hori Y. Hyperpigmentation associated with scleromyxedema and gammopathy. In: Nordlund JJ, Boissy RE, Hearing VJ *et al.*, eds. *The Pigmentary System*, 2nd edn. Oxford: Blackwell Publishing, 2006: 965.

Pruritus [1]

Internal carcinoma is a non-specific, rare, but important cause of pruritus. Many mechanisms may be involved, including secondary metabolic effects such as uraemia or cholestasis, or itch related to iron-deficiency anaemia, acquired ichthyosis or xerosis. Other mechanisms, such as that linking brain tumours with pruritus, are less well understood. Unfortunately, senile pruritus and asteatosis are not uncommonly encountered in elderly patients, a group who are more at risk from malignancy. It is therefore difficult to dissociate chance from true association, which can lead to difficulties in deciding whether screening is indicated on a cost-effective basis [2].

Generalized pruritus

In a 6-year study of 125 patients with generalized pruritus, Paul *et al*. [2] found no significant increase in malignancy, although of the eight patients with malignancy detected, two had lymphoma—a higher than expected incidence.

Other studies support the likelihood of a genuine association of haematological disorders and lymphoma with generalized pruritus; in particular, itch may be a severe problem in patients with Hodgkin's disease and may indicate a poorer prognosis [3]. Other haematological disorders, including Sézary syndrome, mycosis fungoides, myelomatosis and leukaemia, may also cause generalized pruritus [4,5]; the mechanisms in these conditions are poorly understood. In polycythaemia rubra vera (PRV), the initiating factor appears to be rapid cooling of the skin, as encountered after bathing. This is thought to be due to the release of pruritogens by

Table 62.10 Pigmentary abnormalities associated with internal malignancy.

Pigmentary change	Pattern	Examples
Hyperpigmentation	Diffuse, or diffuse with localized accentuation (addisonian pattern of pigmentation)	Melanoma (rarely causes diffuse slate grey pigmentation) Phaeochromocytoma (addisonian pattern) Ectopic ACTH syndrome (addisonian pattern) POEMS syndrome (p. 62.94) (diffuse or semiconfluent speckled pattern) Hyperpigmentation with scleromyxoedema and gammopathy Diffuse mastocytosis Lymphomas (uncommon) Ependymoma (mild increase in pigmentation) Werner's syndrome (localized or diffuse pigmentation; p. 62.24) Cachexia due to neoplasia
	Patchy or reticulated	Fanconi's anaemia (various pigmentary changes, p. 62.28) Dyskeratosis congenita (reticulate pigmentation; p. 62.28)
	Other distributions	Carcinoid syndrome (photodistributed) Pancreatic, gastric and renal tumours (erythema ab igne due to local application of heat)
	Lentigines and freckles	Peutz–Jeghers syndrome (p. 62.56) (lentigines) Carney complex (pp. 62.25 and 62.78) (lentiginosis is characteristic, freckles also occur) Xeroderma pigmentosum (Chapter 15) (freckles) Neurofibromatosis (Chapter 15 and p. 62.23) (flexural freckle-like macules) Cowden's disease and Bannayan–Riley–Ruvalcaba syndrome (genital lentigines) Gardner's syndrome (p. 62.56) (freckles) Paraneoplastic acral lentiginosis (p. 62.33)
	Café-au-lait macules	Neurofibromatosis (p. 62.23) Bloom's syndrome (p. 62.27) Multiple endocrine neoplasia types 1 and 2B Fanconi's anaemia von Hippel–Lindau disease
	With epidermal hyperplasia	Acanthosis nigricans (p. 62.31)
	Melanocytic naevi and melanoma	Associated with pancreatic neoplasia, astrocytomas and other cerebral neoplasms in some families Blue naevi and ordinary naevi occur in Carney complex
Mixed hyper- and hypopigmentation	Poikiloderma	Dermatomyositis (speckled pigmentation on hypopigmented background) Rothmund–Thomson syndrome (photodistributed poikiloderma)
Hypopigmentation	Generalized	Chediak–Higashi syndrome (p. 62.28)
	Localized, multiple	Tuberous sclerosis complex (ash leaf macules) Mycosis fungoides (hypopigmented variant)
	Melanoma-associated (other than regression within the primary lesion)	Halo depigmentation around primary tumour or metastases Distant leukoderma, usually with centrifugal spread starting on the trunk

POEMS, polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes.

degranulated mast cells [6]. However, patients with PRV can also develop intractable itching unrelated to bathing.

Many other visceral carcinomas can cause pruritus, including breast and gastrointestinal cancers, and carcinoid syndrome [7]; again, the mechanisms are frequently poorly understood.

Localized pruritus

Nerve damage by a tumour at any site can cause neuropathic pain or pruritus. The patterns that are most likely to present to a dermatologist are brachioradial pruritus and localized facial or nasal pruritus.

Brachioradial pruritus [8] most commonly affects the lateral upper arm or dorsum of the forearm. Although solar damage has been implicated as a cause, most cases appear to be due to neuropathic damage between C5 and C8. Most of these cases are mechanical due to bony abnormalities but a case due to a spinal tumour has been reported, with rapid resolution of symptoms after treatment [9].

Brain tumours are an uncommon cause of pruritus localized to the face [8,10]. Variations that have been recorded include unilateral pruritus and pruritus limited to the nostril. The latter is particularly linked with tumours invading the floor of the fourth ventricle but tumours elsewhere in the brain, and other cerebral lesions (e.g. abscesses) as well as trigeminal neuralgia can also produce this distribution of pruritus. Generalized itching can also sometimes occur with intracranial neoplasia [10].

References

1 Goldman BD, Koh HK. Pruritus and malignancy. In: Bernhard JD, ed. *Itch. Mechanisms and Management of Pruritus*. New York: McGrawHill, 1994: 299–319.

2 Paul R, Paul R, Jansen CT. Itch and malignancy prognosis in generalized pruritus: a 6-year follow-up of 125 patients. *J Am Acad Dermatol* 1987; **16**: 1179–82.

3 Feiner AS, Mahmood T, Wallner SF. Prognostic importance of pruritus in Hodgkin's disease. *JAMA* 1978; **240**: 2738–40.
4 Graham RM. Aspects of itching. In: Verbov JL, ed. *New Clinical Applications in Dermatology*. Lancaster: MTP Press, 1987: 49–70.
5 Thomas I, Schwartz RA. Cutaneous paraneoplastic syndromes: uncommon presentations. *Clinics Dermatol* 2005; **23**: 593–600.
6 Jackson N, Burt D, Crocker J *et al*. Skin mast cells in polycythaemia vera: relationship to the pathogenesis and treatment of pruritus. *Br J Dermatol* 1987; **116**: 21–9.
7 Pipkin CA, Lio PA. Cutaneous manifestations of internal malignancies: an overview. *Dermatol Clin* 2008; **26**: 1–15.
8 Yosipovitch G. Pruritus: an update. *Curr Prob Dermatol* 2003; **15**: 135–64.
9 Johnson RE, Kanigsberg ND, Jimenez CL. Localized pruritus: a presenting symptom of a spinal cord tumor in a child with features of neurofibromatosis. *J Am Acad Dermatol* 2000; **43**: 958–61.
10 Andreev VC, Petkov I. Skin manifestations associated with tumours of the brain. *Br J Dermatol* 1975; **92**: 675–8.

Hair, nails and skin appendages

Paraneoplastic hypertrichosis lanuginosa acquisita [1–4]

This is a rare but important condition; cases reported in the medical literature up to 2007 have recently been reviewed [1]. About 70% of cases occur in women, usually aged 40–70 years, and most patients have metastatic tumours at presentation, with correspondingly poor prognosis. The commonest tumour sites in men are lung, followed by colorectal, and in women are colorectal, followed by lung and breast. Other reported sites or tumour types include endometrium (about 7–8% of cases), ovary, cervix, renal, prostate, bladder, adrenal gland, stomach, gallbladder, skin (including melanoma), parotid gland, sarcoma, lymphoma and leukaemia [1,3].

There may be associated acanthosis nigricans, hypertrophy of papillae of the tongue, and glossitis [2]; disturbances of taste or smell also occur [3]. However, the glossitis in at least some patients may be a manifestation of vitamin deficiency rather than a specifically related condition [4]. Development of paraneoplastic hypertrichosis lanuginosa acquisita tends to affect the face initially, extending down the body with time. The mechanism is unclear but the hair is of fine, downy, lanugo type; prolongation of the anagen growth phase has been proposed to explain this. Resolution of hypertrichosis lanuginosa occurs after treatment of the underlying tumour, and regrowth related to recurrence of the neoplasm.

References

1 Slee PHTJ, van der Waal RIF, Schagen van Leeuwen JH *et al*. Paraneoplastic hypertrichosis lanuginosa acquisita: uncommon or overlooked? *Br J Dermatol* 2007; **157**: 1087–92.
2 Wendolin DS, Pope DN, Mallory SB. Hypertrichosis. *J Am Acad Dermatol* 2003; **48**: 161–79.
3 Stone SP, Buescher LS. Life-threatening paraneoplastic cutaneous syndromes. *Clinics Dermatol* 2005; **23**: 301–6.
4 Callen JP. Skin signs of internal malignancy. In: Callen JP, Jorizzo JL, eds. *Dermatological Manifestations of Internal Disease*, 3rd edn. Philadelphia: Saunders, 2003: 95–104.

Clubbing of nails

This nail abnormality is discussed in more detail in Chapter 65. Both clubbing and associated hypertrophic osteoarthropathy (HOA) have been documented with many neoplasms, the commonest being carcinoma of the bronchus. In patients with lung cancer, clubbing has been reported to be present in 29%, especially in females; most lung tumours are squamous cell carcinoma or adenocarcinoma [1]. A high incidence of HOA occurs particularly with mesothelioma, but it may also occur with malignancies of the pulmonary, cardiovascular, gastrointestinal and hepatobiliary systems [2]; it is much less common than clubbing, occurring in perhaps 5% of patients with clubbing.

References

1 Sridhar KS, Lobo CF, Altman RD. Digital clubbing and lung cancer. *Chest* 1998; **114**: 1535–7.
2 Caldwell DS, McCallum RM. Rheumatological manifestations of cancer. *Med Clin North Am* 1986; **70**: 385–417.

Sebaceous neoplasms

Sebaceous neoplasms of various types are strongly linked with Muir–Torre syndrome (p. 62.26).

Hyperhidrosis [1]

Generalized hyperhidrosis may rarely be associated with malignant disease. It is an almost consistent finding in phaeochromocytoma (PCC; see below), in which it may be limited to night-time or occur at any time. Nocturnal hyperhidrosis ('night sweats') may occur in PCC, lymphoma and carcinoid syndrome, as well as in non-neoplastic conditions such as thyrotoxicosis, chronic infections and others. Localized hyperhidrosis may occur in POEMS syndrome.

Specific distributions of localized hyperhidrosis may also be important. Hyperhidrosis with autonomic dysreflexia is associated with spinal cord lesions above T6, and is characterized by episodic sweating of the face, neck and upper trunk with vasodilatation in the same distribution, headache, hypertension and piloerection; most cases are due to injury or cord compression but intracranial posterior fossa neoplasms can produce similar symptoms. Paroxysmal unilateral hyperhidrosis of the face and neck, usually severe and unrelated to stimuli such as eating, may be due to an ipsilateral thoracic tumour (adenocarcinoma, squamous cell carcinoma or mesothelioma) compressing or infiltrating the sympathetic trunk; associated features may include Horner's syndrome, facial weakness, sensory disturbance, and other features of the primary tumour.

Phaeochromocytomas (PCCs) may be present in 0.3–1.9% of individuals, based on post-mortem studies and biochemical screening, but only 10% are malignant in nature [2]. Standard teaching is that 10% of PCC are familial, including those occurring in MEN syndromes (p. 62.24), neurofibromatosis, von Hippel–Lindau disease, hereditary paragangliomatosis and tuberous sclerosis; however, screening PCCs for germline mutations demonstrated that 24% of apparently sporadic PCC had mutations of *VHL*, *RET*, *SDHD* or *SDHB* genes [3]. Patients with PCC that have *SDHD* or *SDHB* mutations have a 20–30% risk of developing glomus tumours (these genes confer susceptibility to both extra-adrenal PCC (paragangliomas) and glomus tumours, as both have a common neural crest origin) [4]. Genetic aspects of PCC and other adrenal tumours are reviewed in [5].

Presentation of PCC is often incidental due to discovery of labile hypertension, but the classical triad of features in PCC is episodic

headache with palpitations (tachycardia) and hyperhidrosis due to release of catecholamines [2,4]. Numerous other symptoms may occur, including hyper- and hypoglycaemia, pallor with rebound flushing, diarrhoea, fatigue, dyspnoea, chest pain, abdominal pain and malaise.

References

1 Sato K, Kang WH, Saga K, Sato KT. Biology of sweat glands and their disorders. II. Disorders of sweat gland function. *J Am Acad Dermatol* 1989; **20**: 713–26.
2 Werbel SS, Ober KP. Phaeochromocytoma. Update on diagnosis, localization, and management. *Med Clin N Am* 1995; **79**: 131–53.
3 Neumann HPH, Bausch B, McWhinney SR *et al*. Germ-line mutations in nonsyndromic phaeochromocytoma. *N Engl J Med* 2002; **346**: 1459–66.
4 Dluhy RG. Phaeochromocytoma—death of an axiom. *N Engl J Med* 2002; **346**: 1486–8.
5 Bertherat J, Gimenez-Roqueplo AP. New insights in the genetics of adrenocortical tumors, pheochromocytomas and paragangliomas. *Horm Metab Res* 2005; **37**: 384–90.

Dermatoses

Several dermatoses have a significant association with internal malignancy; in other conditions there is just a minor statistical link documented, as discussed below.

Acrokeratosis paraneoplastica (Bazex syndrome) [1–5]

This is a rare condition, much commoner in males than females [3–5], which is associated particularly with squamous cell carcinoma of the upper respiratory or gastrointestinal tracts, particularly when there are metastases in the cervical lymph nodes. An underlying malignancy is a required criterion for the diagnosis; the cutaneous features are predominantly acral in distribution and papulosquamous lesions, hyperpigmentation, keratoderma, paronychia and nail dystrophy (at least one of which is also required for diagnosis) [3]. More than 60% of tumours arise in the oropharynx, larynx or are cervical squamous cell carcinoma metastases with an unknown primary site; lung, oesophageal and other primary or metastatic lesions above the diaphragm make up most of the remainder [5]. Rare associations, such as metastatic adenocarcinoma of the prostate and transitional cell carcinoma of the bladder, have been reported [6,7]. The cutaneous changes develop gradually, often in several phases, initially with violaceous erythema and scaling on the peripheries, especially helices of the ears, tip of the nose, hands and feet (especially the distal portion of digits). The eruption then becomes more hyperkeratotic, with a keratoderma on hands and feet. Subsequently, the eruption may become more generalized. Nail dystrophy and paronychia are often present. Changes on the face may appear more eczematous or lupus erythematosus-like, whereas acral changes are often psoriasiform. The differential diagnosis can include dermatitis, especially seborrhoeic or contact-allergic types. Alternatively, acral psoriasis with the possibility of Reiter's syndrome may be considered. The course mostly parallels the underlying neoplasm; resolution may occur with successful tumour resection, and recurrence may develop on relapse of malignancy. When resection is felt inappropriate or impracticable, systemic retinoids may improve the cutaneous changes [8]. The histological changes are non-diagnostic, but essentially reflect the clinical appearance with hyperkeratosis, parakeratosis, focal spongiosis and a mixed, inflammatory cell infiltrate [4,5,9].

References

1 Bazex A, Griffiths A. Acrokeratosis paraneoplastica: a new cutaneous marker of malignancy. *Br J Dermatol* 1980; **102**: 301–6.
2 Richard M, Giroux JM. Acrokeratosis paraneoplastica. *J Am Acad Dermatol* 1987; **16**: 178–83.
3 Bolognia JL. Bazex syndrome: acrokeratosis paraneoplastica. *Semin Dermatol* 1995; **14**: 84–9.
4 Moore RL, Devere TS. Epidermal manifestations of internal malignancy. *Dermatol Clinics* 2008; **26**: 17–29.
5 Stone SP, Buescher LS. Life-threatening paraneoplastic cutaneous syndromes. *Clinics Dermatol* 2005; **23**: 301–6.
6 Obasi OE, Garg SK. Bazex paraneoplastic acrokeratosis in prostate carcinoma. *Br J Dermatol* 1987; **117**: 647–51.
7 Arregui MA, Raton JA, Landa NI *et al*. Bazex's syndrome (acrokeratosis paraneoplastica): first case report of association with a bladder carcinoma. *Clin Exp Dermatol* 1993; **18**: 445–8.
8 Wishart JM. Bazex paraneoplastic acrokeratosis: a case report and response to Tigason. *Br J Dermatol* 1986; **115**: 595–9.
9 Pecora AL, Landsman L, Imgrund SP *et al*. Acrokeratosis paraneoplastica (Bazex's syndrome). *Arch Dermatol* 1983; **119**: 820–6.

Dermatomyositis (Chapter 51) [1–5]

Both dermatomyositis (Fig. 62.13) and polymyositis in adults may be associated with internal malignancy. The reported likelihood of finding a neoplasm varies between 6% (in polymyositis) [6] and 50% [7]; overall, about 25–30% is probably a representative proportion for the various reported studies of dermatomyositis, making this a condition with a significant association with underlying malignancy. The association with neoplasia is much stronger for dermatomyositis than for polymyositis or dermatomyositis/autoimmune disease overlap conditions. Conventional teaching has been that malignancy is an uncommon cause of dermatomyositis in subjects less than 40 years of age; however, paediatric cases with neoplasia are reported [8]. As there is a lower incidence of malignancy in the younger age group, and there are no age-matched comparative studies against a control population in children, it is difficult to judge the strength of the association in this age group [3].



Fig. 62.13 Dermatomyositis in a patient with ovarian carcinoma.

The temporal association of dermatomyositis with neoplasia varies; in one report approximately equal proportions had a known malignancy at the time that dermatomyositis presented, had a malignancy found due to investigation when dermatomyositis was diagnosed, or had a malignancy found during follow-up (usually in the first 6 months after diagnosis of dermatomyositis) [4]. Others report a four to five times increased incidence of malignancy in the first 2 years [9] or even 5 years [5] after diagnosis. Accounts of specific malignant associations may be subject to bias by rare-case reporting, and in larger series the malignancies identified generally reflect tumour prevalence in the general population; lung cancer in men, breast and gynaecological tumours in women, and colorectal cancers in both sexes. In South-East Asia, there is a higher frequency of nasopharyngeal carcinoma, that probably also reflects the background risk of this type of neoplasm. The one exception to this generalization is ovarian carcinoma, which appears to be significantly overrepresented and potentially overlooked [2,4,5,10].

The value of extensive screening for neoplasia in dermatomyositis is questionable. Several authors have stressed that the emphasis should be attached to thorough clinical evaluation, simple investigations and then specific investigations as indicated [1,4,10]. However, all of these studies were performed before easy availability of CT or MRI scanning, and the quality of such imaging has increased hugely in recent years, so radiological screening should be included in the investigation of patients with dermatomyositis. 'Blind' (i.e. not symptom-directed) CT scanning of chest, abdomen and pelvis increased the yield of malignancies in one study, although the number of patients in whom a tumour might have been missed was small, and one was an ovarian tumour which has been documented above as worthy of greater suspicion. There should certainly be a low threshold for further or repeated investigations at the time of diagnosis or during follow-up if previous neoplasia has been present, when the therapeutic response is poor, or if new symptoms develop; there is also an argument for ongoing screening for ovarian cancers throughout follow-up of female patients without any initial screening test abnormalities, using clinical examination, trans-vaginal ultrasound and tumour markers (CA125) [2].

In general, subjects with dermatomyositis who truly have amyopathic dermatomyositis (dermatomyositis sine myositis) [12], or who have a connective tissue overlap syndrome, appear less likely to have an underlying malignancy; however, some patients with amyopathic dermatomyositis do actually develop myositis, some studies document similar tumour rates in those with or without myositis [13], and tumours have been reported in all such variants, so screening investigations should still be performed [14]. In one study, patients with malignancy were found to have a more rapid onset of dermatomyositis, higher mean creatine kinase and erythrocyte sedimentation rates, and a lower frequency of Raynaud's phenomenon compared with patients without an underlying malignancy [11]. However, a low creatine kinase has also been linked with a higher frequency of malignancy. Vasculitis or necrosis, manifest clinically or in histopathology specimens, has also been associated with an increased risk of an associated neoplasm [13,15–17].

Whilst no clinical pattern reliably excludes the possibility of an underlying malignancy, a greater understanding of the immunopathogenesis of paraneoplastic dermatomyositis may be instructive [18–20]. A recent report documented that subjects with a myositis-specific autoantibody reactive with 155-kDa and 140-kDa nuclear antigens (anti-155/140 Ab) had a much higher risk of malignancy (71%) than those without this antibody (11%) [19]. Patients with this antibody had a higher frequency of heliotrope rash, Gottron's papules and flagellate erythema than those with negative results, but none with anti-155/140 Ab had interstitial lung disease. No patients with systemic lupus erythematosus, systemic sclerosus or healthy controls had this antibody. A novel myositis-specific antibody (anti-CADM 140) has recently been demonstrated in amyopathic dermatomyositis, and some myositis-specific antibodies are expressed both in regenerating muscle cells and in some cancers [20]. Such insights may in the future help to determine which patients require investigation for malignancy.

References

1 Callen JP. Skin signs of internal malignancy. In: Callen JP, Jorizzo JL, eds. *Dermatological Manifestations of Internal Disease*, 3rd edn. Philadelphia: Saunders, 2003: 95–104.

2 Provost TT, Flynn JA. Dermatomyositis. In: Provost TT, Flynn JA, eds. *Cutaneous Medicine: Cutaneous Manifestations of Systemic Disease*. Hamilton, Ontario: Decker, 2001: 82–103.

3 Callen JP. Malignancy in polymyositis/dermatomyositis. *Clin Dermatol* 1988; **6**: 55–63.

4 Cox NH, Lawrence CM, Langtry JA *et al*. Dermatomyositis: disease associations and evaluation of screening investigations for malignancy. *Arch Dermatol* 1990; **126**: 61–5.

5 Sigurgeiersson B, Lindelöf B, Edhag O, Allander E. Risk of cancer in patients with dermatomyositis or polymyositis. A population-based study. *N Engl J Med* 1992; **326**: 363–7.

6 Henriksson KG, Sandstedt P. Polymyositis—treatment and prognosis: a study of 107 patients. *Acta Neurol Scand* 1982; **65**: 280–300.

7 Vesterager L, Worm AM, Thomsen K. Dermatomyositis and malignancy. *Clin Exp Dermatol* 1980; **5**: 31–5.

8 Kalmanti M, Athanasion A. Neuroblastoma occurring in a child with dermatomyositis. *Am J Pediatr Hematol Oncol* 1985; **7**: 387–8.

9 Masi AT, Hochberg MC. Temporal associations of polymyositis–dermatomyositis with malignancy: methodologic and clinical considerations. *Mt Sinai J Med* 1988; **55**: 471–8.

10 Richardson JB, Callen JP. Dermatomyositis and malignancy. *Med Clin North Am* 1989; **73**: 1211–20.

11 Sparsa A, Liozon E, Herrmann F *et al*. Routine vs extensive malignancy search for adult dermatomyositis and polymyositis. A study of 40 patients. *Arch Dermatol* 2002; **138**: 885–90.

12 Caproni M, Carinali C, Parodi A *et al*. Amyopathic dermatomyositis. A review by the Italian Group of Immunodermatology. *Arch Dermatol* 2002; **138**: 23–7.

13 Gallais V, Crickx B, Belaich S. Prognostic factors and predictive signs of malignancy in adult dermatomyositis. *Ann Dermatol Venereol* 1996; **123**: 722–6.

14 Callen JP. When and how should the patient with dermatomyositis or amyopathic dermatomyositis be assessed for possible cancer? *Arch Dermatol* 2002; **138**: 969–71.

15 Feldman D, Hochenberg MC, Zizic TM, Stevens MB. Cutaneous vasculitis in adult polymyositis/dermatomyositis. *J Rheumatol* 1983; **10**: 85–9.

16 Hunger RE, Durr D, Brand CU. Cutaneous leukocytoclastic vasculitis in dermatomyositis suggests malignancy. *Dermatology* 2001; **202**: 123–6.

17 Burnouf M, Mahé E, Verpillat P *et al*. Cutaneous necrosis is predictive of cancer in adult dermatomyositis. *Ann Dermatol Venereol* 2003; **130**: 313–6.

18 Levine SM. Cancer and myositis: new insights into an old association. *Curr Opin Rheumatol* 2006; **18**: 620–4.

19 Kaji K, Fujimoto M, Hasegawa M *et al*. Identification of a novel autoantibody reactive with 155 and 140 kDa nuclear proteins in patients with dermatomyositis: an association with malignancy. *Rheumatology (Oxford)* 2007; **46**: 25–8.

20 Mimori T, Imura Y, Nakashima R, Yoshifuji H. Autoantibodies in idiopathic inflammatory myopathy: an update on clinical and pathophysiological significance. *Curr Opin Rheumatol* 2007; **19**: 523–9.

Migratory erythemas

This descriptive term is applied to a variety of annular and figurate eruptions, which are discussed in more detail on pp. 62.106–62.113. Two variants, erythema gyratum repens and necrolytic migratory erythema, have a clear association with internal neoplasia. Others, such as erythema annulare centrifugum and some unspecified figurate erythemas, also have a very variable association with neoplasia. There are also reports of subacute lupus erythematosus-like annular and figurate rashes, linked with myeloproliferative disorders and carcinoma of lung, liver, breast, larynx and oesophagus in individual cases.

Erythema gyratum repens (see also p. 62.107) is a rare, bizarre cutaneous eruption consisting of mobile concentric, often palpable, erythematous, wave-like bands, which give a 'wood-grain' appearance to the skin (Fig. 62.14). A peripheral scale or collarette may be present. The complete torso is frequently affected. There is often associated severe pruritus, sometimes ichthyosis, and sometimes bullae within the erythema. The lesions migrate from day to day, usually changing position by about 1 cm daily. It has a strong association with internal malignancy (over 80% of cases), particularly lung cancer [1,2] which is present in about a third of cases; other cancer sites include oesophagus, breast, bowel, uterus, cervix, kidney, pancreas and haematological neoplasia [2]. Occasional cases without associated malignancy have been reported [3] but it is important to be aware that 6% are found to have a tumour of unknown primary origin [2]. Identification and resection of the tumour often results in resolution of the eruption.

Necrolytic migratory erythema (glucagonoma syndrome) is the characteristic eruption associated with an α-cell tumour of the pancreas. It is discussed in the section on pancreatic disease later in this chapter (p. 62.66).

Erythema annulare centrifugum [4,5] is the term used to describe one of the commoner annular erythemas, which is usually not associated with neoplasia (p. 62.110). If an underlying malignancy is found, it is usually a myeloproliferative disorder [5]. Clinical examination and routine screening tests are the only investigation required, rather than an exhaustive search for malignancy, unless there are additional clinical pointers.



Fig. 62.14 Erythema gyratum repens of the arm secondary to carcinoma of the bronchus. (Courtesy of Dr A.W. McKenzie, Norfolk and Norwich Hospital, Norwich, UK.)

References

1 Solomon H. Erythema gyratum repens. *Arch Dermatol* 1969; **100**: 639.
2 Stone SP, Buescher LS. Life-threatening paraneoplastic cutaneous syndromes. *Clinics Dermatol* 2005; **23**: 301–6.
3 Juhlin L, Lacour JP, Larrouy JC *et al*. Episodic erythema gyratum repens with ichthyosis and palmoplantar hyperkeratosis without signs of internal malignancy. *Clin Exp Dermatol* 1989; **14**: 223–6.
4 Lazar P. Cancer, erythema annulare centrifugum, autoimmunity. *Arch Dermatol* 1963; **87**: 247–51.
5 Mahood JM. Erythema annulare centrifugum: a review of 24 cases, with special reference to its association with underlying disease. *Clin Exp Dermatol* 1983; **8**: 383–7.

Other dermatological disorders

Lichen planus may rarely be induced by neoplasia [1]. There is also an increased risk, particularly in males, of oral squamous cell carcinoma (SCC); this may be due to a combined direct effect and co-factors such as smoking [2]. The strength of the association may however have been overestimated, as some of the reports are those that have collected patients presenting with oral SCC and have then looked for histological evidence of lichen planus as a background factor.

Urticaria; with the exception of cold urticaria and peripheral gangrene as a result of circulating cryoglobulins, where there is a possible, but uncommon, link with myeloma and lymphoma [3], associations of urticaria and neoplasia are difficult to evaluate. Certainly it cannot be regarded as an established paraneoplastic phenomenon, other than in Schnitzler's syndrome (a distinct disorder of chronic urticaria, bone pain, hyperostosis, high erythrocyte sedimentation rate and monoclonal IgM gammopathy, usually IgMκ; see Chapter 22). Histologically, there is neutrophilic inflammation within dermal venules with some perivascular involvement, rarely extending to a leukocytoclastic vasculitis. Although the overall prognosis is reasonable, around 10–15% of patients develop lymphoplasmacytic lymphoma [4].

Erythroderma (Chapter 23) and exfoliative dermatitis have both been linked with malignancy [5,6]. In most such cases (around 10% in most reported series), the neoplasm is mycosis fungoides or its leukaemic variant, Sézary syndrome; these are really a representation of a systemic neoplasm rather than a truly paraneoplastic disorder. However, there are a small number of patients who have neither condition, but present with erythroderma and eventually develop lymphoma or leukaemia. The incidence is uncertain and rare; a report in an Asian population failed to demonstrate one association in 80 patients [7]. Immunophenotypic studies do not appear to help distinguish benign from malignant cases. There are additionally reported cases of erythroderma with cancers of liver, lung, colon, stomach, pancreas, thyroid, prostate and cervix [5,6,8]. *Ofuji papuloerythroderma* has also been associated with peripheral T-cell non-epidermotrophic cutaneous lymphoma [9].

Granuloma annulare has been reported in association with lymphomas, other haematological malignancies, and uncommonly

with solid tumours [10]; however, a causal relationship in such cases is uncertain. It has been suggested that the subcutaneous pattern of granuloma annulare may carry a greater risk of malignancy, but this may reflect the more extensive investigation that is usually performed to establish the diagnosis in such cases by comparison with more typical granuloma annulare.

'*Insect bite-like' reactions* are reported in haematological malignancy, usually chronic lymphocytic leukaemia [11].

Cutis verticis gyrata may occasionally occur as a paraneoplastic phenomenon [12].

Mental neuropathy ('numb chin syndrome') has several benign causes, but may occur as a feature of metastatic disease and is considered an indicator of poor prognosis [13]. Relevant tumours include breast, thyroid, renal, lung, prostate, lymphomas and melanoma.

Non-melanoma skin cancer has been linked with increased risk and poor prognosis of non-Hodgkin's lymphoma [14].

References

1 Helm TN, Camisa C, Liu AY *et al.* Lichen planus associated with neoplasia: a cell-mediated immune response to tumor antigens? *J Am Acad Dermatol* 1994; **30**: 219–24.
2 Sigurgeirsson B, Lindelof B. Lichen planus and malignancy. *Arch Dermatol* 1991; **127**: 1684–8.
3 Neittaanmaki H. Cold urticaria: clinical findings in 220 patients. *J Am Acad Dermatol* 1985; **13**: 636–44.
4 Daoud MS, Lust JA, Kyle RA *et al.* Monoclonal gammopathies and associated skin disorders. *J Am Acad Dermatol* 1999; **40**: 507–35.
5 Boyce S, Harper J. Paraneoplastic dermatoses. *Dermatol Clin* 2002; **20**: 523–32.
6 Thomas I, Schwartz RA. Cutaneous paraneoplastic syndromes: uncommon presentations. *Clinics Dermatol* 2005; **23**: 593–600.
7 Abel EA, Lindae ML, Hoppe RT *et al.* Benign and malignant forms of erythroderma: cutaneous immunophenotypic characteristics. *J Am Acad Dermatol* 1988; **19**: 1089–95.
8 Nicolis GD, Helwig EB. Exfoliative dermatitis: a clinicopathologic study of 135 cases. *Arch Dermatol* 1973; **108**: 788–97.
9 Grob JJ, Collet-Villete AM, Horchowski N *et al.* Ofuji papulo-erythroderma: report of a case with T cell skin lymphoma and discussion of the nature of this disease. *J Am Acad Dermatol* 1989; **20**: 927–31.
10 Cohen PR. Granuloma annulare, relapsing polychondritis, sarcoidosis, and systemic lupus erythematosus: conditions whose dermatologic manifestations may occur as hematologic malignancy-associated mucocutaneous paraneoplastic syndromes. *Int J Dermatol* 2006; **45**: 70–80.
11 Davis MD, Perniciaro C, Dahl PR *et al*. Exaggerated arthropod-bite lesions in patients with chronic lymphocytic lekaemia: a clinical, histopathologic, and immunopathologic study of eight patients. *J Am Acad Dermatol* 1998; **39**: 27–35.
12 Ross JB, Tompkins MG. Cutis verticis gyrata as a marker of internal malignancy. *Arch Dermatol* 1989; **125**: 434–5.
13 Burt RK, Sharfman WH, Karp B, Wilson WH. Mental neuropathy (numb chin syndrome). A harbinger of tumor progression or relapse. *Cancer* 1992; **70**: 877–81.
14 Hjalgrim H, Frisch M, Storm HH *et al.* Non-melanoma skin cancer may be a marker of poor prognosis in patients with non-Hodgkin's lymphoma. *Int J Cancer* 2000; **85**: 639–42.

Connective tissue and rheumatological disorders

Malignancies have been reported in association with many disorders that overlap between dermatology and rheumatology. Those that fall into the collagen vascular group are discussed here; dermal deposition disorders, neutrophilic infiltrates, paraneoplastic vasculitis and other vascular conditions are discussed later.

Systemic lupus erythematosus

The possibility of an increased risk of internal malignancy in systemic (SLE) and subacute cutaneous lupus erythematosus has been debated for many years, and still remains controversial. There are individual cases in which a close temporal relationship has been documented [1], and large cohort and population studies have mainly produced results in favour of an increased risk [2,3]. Studies that have supported an association with malignancy have suggested increases in lymphomas, monoclonal gammopathy, cervical, lung, hepatobiliary and breast cancer [3–6], although the latter is disputed [4]. The majority of large studies suggest an increase in non-Hodgkin's lymphoma [3], particularly diffuse large B-cell lymphoma (DLBCL) [5]. The mechanism may be a T-cell defect in SLE, or may be a result of immunosuppressive medication used in treatment (especially implicated in the increased risk of haematological malignancies [7]). The evidence for an association between autoimmune conditions and lymphoma is supported by a large study of 3055 patients with non-Hodgkin's lymphoma and matched controls; significant associations were found with rheumatoid arthritis, primary Sjögren's syndrome, and SLE, again documenting the specific association with DLBCL [8]. The increased tumour risk in patients with Sjögren's syndrome has been noted in other reviews [9]. Treatment with antimalarials has been suggested to have a protective effect against development of cancers in SLE [10].

Rare patterns of lupus erythematosus, such as lupus erythematosus gyratum repens, may carry a higher risk of internal malignancy [11], although this condition is generally reported as isolated cases, so this conclusion is uncertain. Individual reports suggest an association of a subacute cutaneous lupus erythematosus (SCLE)-like eruption with tumours of various organs (including myeloproliferative disorders causing a neutrophilic lupus-like figurate erythema, and SCLE-like rash associated with tumours of lung, liver, larynx, breast and oesophagus [12,13]. Potential clues to this association are an SCLE-like rash in males, in an older age-group than usual, and with resistance to therapy.

References

1 Chaudhry SI, Murphy LA, White IR. Subacute cutaneous lupus erythematosus: a paraneoplastic dermatosis? *Clin Exp Dermatol* 2005; **30**: 655–8.
2 Bernatsky S, Boivin JF, Joseph L *et al*. An international cohort study of cancer in systemic lupus erythematosus. *Arthritis Rheum* 2005; **52**: 1481–90.
3 Tarr T, Gyorfy B, Szekanecz E *et al*. Occurrence of malignancies in Hungarian patients with lupus erythematosus: results from a single center. *Ann N Y Acad Sci* 2007; **1108**: 76–82.
4 Kontos M, Fentiman IS. Systemic lupus erythematosus and breast cancer. *Breast J* 2008; **14**: 81–6.
5 Löfström B, Backlin C, Sundström C *et al*. A closer look at non-Hodgkin's lymphoma cases in a national Swedish systemic lupus erythematosus cohort: a nested case-control study. *Ann Rheum Dis* 2007; **66**: 1627–32.
6 Ali YM, Urowitz MB, Ibanez D, Gladman DD. Monoclonal gammopathy in systemic lupus erythematosus. *Lupus* 2007; **16**: 426–9.
7 Bernatsky S, Joseph L, Boivin JF *et al*. The relationship between cancer and medication exposures in systemic lupus erythematosus: a case-cohort study. *Ann Rheum Dis* 2008; **67**: 74–9.
8 Smedby KE, Hjalgrim H, Askling J *et al*. Autoimmune and chronic inflammatory disorders and risk of non-Hodgkin lymphoma by subtype. *J Natl Cancer Inst* 2006; **98**: 51–60.
9 Bernatsky S, Ramsay-Goldman R, Clarke A. Malignancy and autoimmunity. *Curr Opin Rheum* 2006; **18**: 129–34.

10 Ruiz-Irastorza G, Ugarte A, Egurbide MV *et al*. Antimalarials may influence the risk of malignancy in systemic lupus erythematosus. *Ann Rheum Dis* 2007; **66**: 815–7.
11 Kreft B, Marsch WC. Lupus erythematosus gyratum repens. *Eur J Dermatol* 2007; **17**: 79–82.
12 Dawn G, Wainwright NJ. Association between subacute cutaneous lupus erythematosus and epidermoid carcinoma of the lung: a paraneoplastic phenomenon? *Clin Exp Dermatol* 2002; **27**: 714–22.
13 Yasim ZF, Walsh MY, Armstrong DKB. Subacute lupus erythematosus-like rash associated with oesophageal carcinoma *in situ*. *Clin Exp Dermatol* 2007; **32**: 443–4.

Scleroderma, fasciitis, panniculitis and similar sclerodermoid conditions

Like SLE, scleroderma/systemic sclerosis has been linked with occurrence of internal malignancy [1,2], and a possible role of fibrogenic peptides has been proposed [3], although overall the association is probably not strong [4]. Likewise, eosinophilic fasciitis has occasionally been linked with contemporaneous diagnosis of a neoplasm [5]. Many of the cases described are not entirely classical of 'usual' scleroderma, some cases having a more aggressive course of fibrosis than anticipated, an unusual distribution, extensive fibrotic changes in the subcutaneous fat, or progressive arthritis. To reflect these features, more recent cases have been described under the terms palmar fibrosis/arthritis [6,7] or cancer-associated fasciitis–panniculitis syndrome [8,9]. The commonest tumour types documented are ovarian and lung; breast, prostate and pancreatic tumours have also been reported.

A more typical panniculitis process resembling Weber–Christian disease may occur in patients with acinar cell carcinoma of the pancreas, in whom a syndrome of panniculitis, polyarthritis and eosinophilia can occur. Eosinophilic panniculitis has also been reported in association with other solid tumours or pre-leukaemia [10,11].

Scleroderma-like skin changes may also be a cutaneous manifestation of carcinoid syndrome, the differential diagnosis from collagen vascular scleroderma processes being suggested by the presence of flushing and the absence of Raynaud's phenomenon.

Post-irradiation morphoea is a phenomenon seen after treatment of breast cancer [12]; its importance is not as a marker of underlying malignancy, but in the differential diagnosis of carcinoma en cuirasse (or occasionally carcinoma erysipeloides), discussed above.

References

1 Duncan S, Winkelmann R. Cancer and scleroderma. *Arch Dermatol* 1979; **115**: 950–5.
2 Roumm A, Medsger TJ. Cancer in connective tissue disease. *Arthritis Rheum* 1982; **25**: 1130–3.
3 Gruber BL, Miller F, Kaufman LD. Simultaneous onset of systemic sclerosis (scleroderma) and lung cancer: a case report and histologic analysis of fibrogenic peptides. *Am J Med* 1992; **92**: 705–8.
4 Bernatsky S, Ramsey GM, Clarke A. Malignancy and autoimmunity. *Curr Opn Rheumatol* 2006; **18**: 129–34.
5 Chan LS, Hanson CA, Cooper KD. Concurrent eosinophilic fasciitis and cutaneous T-cell lymphoma. *Arch Dermatol* 1991; **127**: 862–5.
6 Naschitz JE, Yeshurun D, Rosner I. Rheumatic manifestations of occult cancer. *Cancer* 1995; **12**: 2954–8.
7 Cohen PR. Paraneoplastic dermatopathology: cutaneous paraneoplastic syndromes. *Adv Dermatol* 1996; **11**: 215–52.
8 Naschitz JE, Yeshuran D, Zuckerman E *et al*. Cancer-associated fasciitis–panniculitis. *Cancer* 1994; **73**: 231–5.
9 Cox NH, Ramsay B, Dobson C, Comaish JS. Woody hands in a patient with pancreatic carcinoma: a variant of cancer-associated fasciitis–panniculitis syndrome. *Br J Dermatol* 1996; **135**: 995–8.
10 Winkelmann RK, Frigas E. Eosinophilic panniculitis: a clinicopathologc study. *J Cutan Pathol* 1986; **13**: 1–12.
11 Marullo S, Dallot A, Carelier-Balloy B *et al*. Subcutaneous eosinophilic necrosis associated with refractory anaemia with an excess of myeloblasts. *J Am Acad Dermatol* 1989; **20**: 320–3.
12 Colver GB, Rodger A, Mortimer PS *et al*. Post-irradiation morphoea. *Br J Dermatol* 1989; **120**: 831–5.

Relapsing polychondritis

It is increasingly recognized that relapsing polychondritis may be linked with malignancy. Myelodysplastic syndrome and other haematological malignancies are much the commonest association [1,2], but a variety of solid tumours have also been reported including lung, breast, colorectal, pancreas, prostate and others [1]. Concurrence with malignancy-associated Sweet's syndrome is discussed in Chapter 50.

References

1 Cohen PR. Granuloma annulare, relapsing polychondritis, sarcoidosis, and systemic lupus erythematosus: conditions whose dermatologic manifestations may occur as hematologic malignancy-associated mucocutaneous paraneoplastic syndromes. *Int J Dermatol* 2006; **45**: 70–80.
2 Somach SC. Relapsing polychondritis. In: Morgan MB, Smoller BR, Somach SC. *Deadly Dermatologic Diseases. Clinicopathologic Atlas and Text*. New York: Springer, 2007: 161–4.

Sarcoidosis

Several studies document an association of sarcoidosis with malignant disease [1–4]; the suggested mechanism relates to abnormal immune function in sarcoidosis [1,4]. The strongest link reported is with lymphomas, to the extent that the term 'sarcoidosis–lymphoma syndrome' is used by some authors [1,3]. In most such cases, lymphoma has followed sarcoidosis, but the rationale for any association is less clear in cases in which sarcoidosis has developed after a cutaneous lymphoma. An apparent aetiological relationship is suggested in a quarter of cases [4]. Testicular tumours, carcinomas of skin (including melanoma), multiple myeloma, lung cancer, female genitourinary tract and other tumours have also been reported. However, large studies have found no evidence to support any significant association between sarcoidosis and malignant disease (or lymphoma specifically) [5,6].

References

1 Linnenberg HS, Medici TC, Rhyner K. The sarcoidosis-lymphoma syndrome—a lymphocyte dysregulation? *Pneumologie* 1992; **46**: 229–35.
2 Caras WE, Dillard T, Baker T, Pluss J. Coexistence of sarcoidosis and malignancy. *South Med J* 2003; **96**: 918–22.
3 Schmuth M, Prior C, Illersperger B *et al*. Systemic sarcoidosis and cutaneous lymphoma: is the association fortuitous? *Br J Dermatol* 1999; **140**: 952–5.
4 Cohen PR. Granuloma annulare, relapsing polychondritis, sarcoidosis, and systemic lupus erythematosus: conditions whose dermatologic manifestations may occur as hematologic malignancy-associated mucocutaneous paraneoplastic syndromes. *Int J Dermatol* 2006; **45**: 70–80.
5 Rømer FK, Hommelgaard P, Schou G. Sarcoidosis and cancer revisited: a long-term follow-up study of 555 Danish sarcoidosis patients. *Eur Respir J* 1998; **12**: 906–12.
6 Smedby KE, Hjalgrim H, Askling J *et al*. Autoimmune and chronic inflammatory disorders and risk of non-Hodgkin lymphoma by subtype. *J Natl Cancer Inst* 2006; **98**: 51–60.



Fig. 62.15 Pyoderma gangrenosum of the lower leg in a patient with myelodysplastic syndrome.

Pyoderma gangrenosum and neutrophilic dermatoses. These are discussed in greater depth in Chapter 50 and are only briefly noted here. Pyoderma gangrenosum, particularly in a superficial and bullous form, has been associated with myeloproliferative diseases, including acute and chronic myeloid leukaemia, acute lymphocytic leukaemia, myeloid metaplasia, PRV, multiple myeloma, lymphoma and myelofibrosis (Fig. 62.15) [1]. The association of pyoderma gangrenosum with monoclonal gammopathy is uncertain, but it does occur at a frequency higher than expected in the general population and is usually of IgA type, whereas IgG gammopathy is the commonest type overall. Solid tumours reported include carcinoid, colon, bladder, prostate, breast, bronchus, ovary and adrenocortical carcinoma.

Sweet's syndrome has likewise been associated with several malignancies, especially haemopoietic. Chronic recurrent Sweet's syndrome [2] appears to have a particularly strong link with myelodysplastic disorders.

References

1 Powell FC, Daniel Su WP, Perry HO. Pyoderma gangrenosum: classification and management. *J Am Acad Dermatol* 1996; **34**: 395–409.

2 Vignon-Pennamen MD, Juillard C, Rybojad M *et al*. Chronic recurrent lymphocytic Sweet syndrome as a predictive marker of myelodysplasia: a report of 9 cases. *Arch Dermatol* 2006; **142**: 1170–6.

***Multicentric reticulohistiocytosis* (lipoid dermatoarthritis; reticulocytoma cutis)** [1,2]

This is a rare condition, usually occurring in adult life, and characterized by papulonodular lesions of the fingers or other extremities, the face, and sometimes mucous membranes. Papules around the nail fold have been termed the 'coral bead sign'. A severe symmetrical polyarthritis, especially affecting the hands, is frequently associated [3]. Approximately 25% of cases are associated with internal neoplasia, virtually always solid tumours such as those of the breast, lung, colon, pancreas, stomach, ovary or cervix [1–3], although haematological malignancies have also been reported [4].

References

1 Aldridge RD, Main RA, Daly BM. Multicentric reticulohistiocytosis and cancer. *J Am Acad Dermatol* 1984; **10**: 296–7.

2 Nunnink JC, Krusinski PA, Yates JW. Multicentric reticulohistiocytosis and cancer: a case report and review of the literature. *Med Ped Oncol* 1985; **13**: 273–9.

3 Weenig RH, Mehrany K. Dermal and pannicular manifestations of internal malignancy. *Dermatol Clin* 2008; **26**: 31–43.

4 Cox NH, West NC, Popple AW. Multicentric reticulohistiocytosis associated with idiopathic myelofibrosis. *Br J Dermatol* 2001; **145**: 1033–4.

Vascular disorders

Raynaud's phenomenon and digital ischaemia (paraneoplastic acral vascular syndrome) [1–3]

Persistent, painful digital ischaemia, with an unusual Raynaud's syndrome-type appearance but often progressing to gangrene, has been linked to a variety of solid tumours and reticuloendothelial neoplasms [1–3]. The process may have a vasculitic element [4] (see below).

Hyperviscosity syndromes such as polycythaemia rubra vera, leukaemias or myeloma-linked cryoglobulinaemia may give rise to cutaneous ischaemia and phlebitis by microvascular occlusion; cancer-associated coagulopathy may also cause vascular occlusion [5].

Hypereosinophilic syndrome, for which there is increasing evidence of a malignant clonal proliferation, has also been associated with acrocyanosis, cutaneous microthrombi, digital infarction and gangrene [6–8]. In some instances, there is a clonal T-cell production of interleukin-5, a major controlling cytokine in production release and differentiation of eosinophils. In other cases, there is clonal expansion of eosinophils with hepatosplenomegaly and thrombocytopenia; this condition appears to be due to a cytogenetic defect t(9;22)(q34;q11) in which there is chromosomal breakage and reciprocal exchange of chromosomal fragments that leads to formation of a fusion tyrosine kinase FIP1L1–PDGFRα.

Erythromelalgia

This condition is linked with myeloproliferative disorders, most commonly polycythaemia rubra vera or essential thrombocythaemia, in over a third of adult cases. In a large series of patients with erythromelalgia linked with haematological malignancy, the feet were most commonly affected, with severe burning pain and erythema; symptoms may occur 2 years or more before the haematological disorder is documented [9]. The mechanism involves microvascular occlusion (typically with platelet aggregates, termed 'white thrombi'); Raynaud's phenomenon may also occur.

Palmar erythema

This is rarely linked with malignancy, but an interesting association was observed in a series of patients with cerebral malignancies, in whom nearly 20% had palmar and (to a lesser extent) plantar erythema, either diffuse or mottled. This occurrence seemed to be linked with the vascularity of the tumour, and was particularly seen with high-grade astrocytomas and glioblastomas; a role for vascular endothelial growth factor was proposed [10].

Vasculitis and malignancy [4,11]

There appears to be an association of cutaneous vasculitis with neoplasia, particularly in myeloproliferative disorders [11–13] and

myeloma [14,15], although solid tumours have also been reported [4,16,17]. Hairy cell leukaemia appears to be especially associated with vasculitis, which may be of leukocytoclastic or polyarteritis nodosa pattern. Of the solid tumours reported with malignancy, the most common would appear to be approximately the sites expected in an average population, including breast, lung, colon, oesophageal, renal, prostatatic and head and neck tumours. As noted above, there is overlap with paraneoplastic digital ischaemia. In a study of 200 patients with ANCA-positive vasculitis (Wegener's granulomatosis or microscopic polyangiitis), the relative risk of malignancy preceding or concurrent with vasculitis was sixfold greater than that for the local population; patients with Henoch–Schönlein purpura (n = 129) had a fivefold relative risk, but only five of 333 patients with SLE had a malignancy [18].

The dermatological manifestations include palpable purpura, maculopapular, urticarial and petechial lesions; these presumably reflect a small-vessel vasculitis or even, when ulceration occurs, a necrotizing vasculitis [4,11]. When linked with a haematological malignancy, vasculitis often antedates bone marrow involvement, as opposed to the more predictable purpura due to thrombocythaemia, which reflects bone marrow infiltration by myeloproliferative disease or carcinoma. It is difficult in some reports to distinguish between microvascular occlusion (for example, by a monoclonal type I cryoglobulin) versus primary vasculitis or therapy-related vessel injury.

Chilblain-like lesions

Lesions resembling perniosis may be a manifestation of leukaemias and myeloproliferative disorders (Fig. 62.16; see also p. 62.88) [19,20]. They are persistent rather than episodic, which would be expected in idiopathic perniosis, refractory to treatments for perniosis, such as calcium channel blockers, and biopsies may show blast cells. Metastasis from breast carcinoma has also been documented as resembling chilblains [21].

References

1 El Tal AK, Tannous Z. Cutaneous vascular disorders associated with internal malignancy. *Dermatol Clin* 2008; **26**: 45–57.

2 Hawley PR, Johnston AW, Rankin JT. Association between digital ischaemia and malignant disease. *BMJ* 1967; **iii**: 208–12.

3 Palmer HM. Digital vascular disease and malignant disease. *Br J Dermatol* 1974; **91**: 476–7.

4 Greer JM, Longley S, Lawrence-Edwards N *et al.* Vasculitis associated with malignancy: experience with 13 patients and literature review. *Medicine* 1988; **67**: 220–30.

5 Boyce S, Harper J. Paraneoplastic dermatoses. *Dermatol Clin* 2002; **20**: 523–32.

6 Jang K-A, Lim Y-S, Choi J-H *et al.* Hypereosinophilic syndrome presenting as cutaneous necrotizing eosinophilic vasculitis and Raynaud's phenomenon complicated by digital gangrene. *Br J Dermatol* 2000; **143**: 641–4.

7 Hamada T, Kimura Y, Hayashi S *et al.* Hypereosinophilic syndrome with peripheral circulatory insufficiency and cutaneous microthrombi. *Arch Dermatol* 2007; **143**: 812–3.

8 Oppliger R, Gay-Crosier F, Dayer E, Hauser C. Digital necrosis in a patient with hypereosinophilic syndrome in the absence of cutaneous eosinophilic vasculitis. *Br J Dermatol* 2001; **144**: 1087–90.

9 Kurzrock R, Cohen PR. Erythromelalgia and myeloproliferative disorders. *Arch Intern Med* 1989; **149**: 105–9.

10 Noble JB, Boisnic S, Branchet-Gumila MC, Poisson M. Palmar erythema: cutaneous marker of neoplasm. *Dermatology* 2002; **204**: 209–13.

11 Kurzrock R, Cohen PR. Vasculitis and cancer. *Clin Dermatol* 1993; **11**: 175–67.

12 Longley S, Caldwell Pannish RS. Paraneoplastic vasculitis: unique syndrome of cutaneous angiitis and arthritis associated with myeloproliferative disorders. *Am J Med* 1986; **80**: 1027–30.

13 Zappasodi P, Del Forna C, Corso A, Lazzarino M. Mucocutaneous paraneoplastic syndromes in hematologic malignancies. *Int J Dermatol* 2006; **45**: 14–22.

14 Seelen MAJ, de Meijer PHEM, Arnoldus EPJ *et al*. A patient with multiple myeloma presenting with severe polyneuropathy caused by necrotizing vasculitis. *Am J Med* 1997; **102**: 485–6.

15 Daoud MS, Lust JA, Kyle RA *et al.* Monoclonal gammopathies and associated skin disorders. *J Am Acad Dermatol* 1999; **40**: 507–35.

16 Mita T, Nakanishi Y, Ochiai A *et al*. Paraneoplastic vasculitis associated with esophageal carcinoma. *Pathol Internat* 1999; **49**: 643–7.

17 Lotti T, Ghersetich I, Comacchi C, Jorizzo JL. Cutaneous small-vessel vasculitis. *J Am Acad Dermatol* 1998; **39**: 667–87.

18 Pankhurst T, Savage COS, Gordon C, Harper L. Malignancy is increased in ANCA-associated vasculitis. *Rheumatology (Oxford)* 2004; **43**: 1532–5.

19 Yazawa H, Saga K, Omori F *et al*. The chilblain-like eruption as a diagnostic clue to the blast crisis of chronic myelocytic leukaemia. *J Am Acad Dermatol* 2004; **50** (Suppl.): S42–4.

20 Affleck AG, Ravenscroft JC, Leach IH. Chilblain-like leukemia cutis. *Pediatr Dermatol* 2007; **24**: 38–41.

21 Tan BB, Lear JT, English JSC. Metastasis from carcinoma of breast masquerading as chilblains. *J Roy Soc Med* 1997; **90**: 162.



Fig. 62.16 Chilblain-like lesions in acute myeloid leukaemia.

Cancer-associated thrombosis

Three main patterns need to be considered: migratory thrombophlebitis, deep venous thrombosis, and Mondor's disease (a specific pattern of thrombophlebitis, but sufficiently distinctive that it is described separately). Arterial thrombosis may also occur as a paraneoplastic entity but is much less common. The aetiology of cancer-associated thrombosis is multifactorial. Interaction of macrophages with cancer cells causes release of tumour necrosis factor and interleukin-6 which damage endothelium, creating a pro-thrombotic situation; the same interaction causes activation of platelets, and of clotting factors X and XII [1]. Some tumour proteases are also procoagulant, especially 'tissue factor' which activates factor VII, and sialic acid moieties of mucin (released from adenocarcinomas) which activate factor X [1].

Migratory thrombophlebitis (Trousseau's sign) [2–7]. Unlike superficial thrombophlebitis confined to the lower limbs, thrombophlebitis associated with neoplasia is often recurrent and migra-

tory. A variety of sites, especially the upper extremities and trunk, can be involved, and lesions are usually multiple. Migratory thrombophlebitis is associated with malignancy in 50% of cases. The mechanism in most cases is an intravascular, low-grade hypercoagulation, which responds poorly to anticoagulant therapy; heparin is usually more effective than warfarin [8]. As well as altered level or function of prothrombotic and anticoagulant proteins, the coagulation and thrombotic process may involve cytokines, angiogenic factors or mucin secretion by tumours, altered blood viscosity, vascular endothelial changes and production of small tumour emboli. Migratory thrombophlebitis can be associated with any cancer, but particularly occurs with carcinomas of the pancreas, stomach, colon and lung; pancreatic carcinoma accounts for about half of all cases. Leukaemias and lymphomas are less commonly associated with migratory thrombophlebitis. Causative tumours are often highly malignant and metastatic with a poor prognosis.

Deep vein thrombosis (DVT). This is not commonly the presenting feature of malignancy [4,7], although cancers have a significant risk of causing thrombosis. The likelihood of finding a malignancy is increased by about fourfold in patients with a deep venous thrombosis of the leg compared with expected population rates, the overall risk of such an association is about 10%. By contrast, DVT of the upper limb is more commonly linked with neoplasia (in some cases, the reason is obstruction by an apical lung tumour), and DVT is identified post-mortem in half of patients who have died due to cancer. Tumours associated with DVT are usually adenocarcinomas in the gastrointestinal tract, urogenital tract, breast or lung; mucin secretion, as noted above, causes non-enzymatic activation of factor X to factor Xa, initiating the thrombotic cascade. Older age of patients with a DVT has been proposed as a factor that should be associated with a lower threshold for malignancy screening.

Mondor's disease. This is a rare condition in which a cord-like lesion is palpable in the subcutaneous tissue of the anterior or lateral thorax, or sometimes abdomen. The underlying lesion is a thrombophlebitis of thoracic or epigastric veins, usually unilateral but occasionally bilateral, which may occur as a result of trauma, inflammation or post-surgery. However, 10–15% of patients may have an associated breast carcinoma [4,7,9] so careful examination and mammography are indicated unless an alternative cause is obvious.

References

1 Bick RL. Cancer-associated thrombosis. *N Engl J Med*; **349**: 109–11.

2 Callen JP. Skin signs of internal malignancy. In: Callen JP, Jorizzo JL, eds. *Dermatological Manifestations of Internal Disease*, 3rd edn. Philadelphia: Saunders, 2003: 95–104.

3 Braverman IM. *Skin Signs of Systemic Disease*, 3rd edn. Philadelphia: Saunders, 1998.

4 El Tal AK, Tannous Z. Cutaneous vascular disorders associated with internal malignancy. *Dermatol Clin* 2008; **26**: 45–57.

5 Sack GH, Levin J, Bell WR. Trousseau's syndrome and other manifestations of chronic disseminated coagulopathy in patients with neoplasms: clinical, pathophysiologic, and therapeutic features. *Medicine* 1977; **56**: 1–37.

6 James WD. Trousseau's syndrome. *Int J Dermatol* 1984; **23**: 205–6.

7 Samlaska CP, James WD. Superficial thrombophlebitis. II. Secondary hypercoagulable states. *J Am Acad Dermatol* 1990; **23**: 1–18.

8 Walsh-McMonagle D, Green D. Low molecular-weight heparin in the management of Trousseau's syndrome. *Cancer* 1997; **80**: 649–55.

9 Catania S, Zurrida S, Veronesi P *et al*. Mondor's disease and breast cancer. *Cancer* 1992; **69**: 2267–70.

Flushing

This is a normal physiological response and may be a problematic menopausal symptom. However, it may be a feature of carcinoid syndrome, mastocytosis, phaeochromocytoma, medullary carcinoma of thyroid, hypogonadism in males, pancreatic tumours producing vasoactive intestinal peptide (VIPomas), basophilic leukaemia, horseshoe kidney (Rovsing's syndrome) and renal cell carcinoma [1,2]; it is also a feature of POEMS syndrome which is associated with myeloma (discussed on pp. 62.92 and 62.94). Plethora, but not flushing, may be apparent in polycythaemia rubra vera.

Carcinoid syndrome may be difficult to diagnose at an early stage, as flushing is typically provoked by common triggers of physiological flushing, such as emotional stress or alcohol ingestion. Only about 10% of patients with a carcinoid tumour have a malignant carcinoid syndrome, and paroxysmal flushing is present in virtually all cases; episodes typically last a few minutes and may be more widespread than emotional flushing, sometimes involving the whole body. Nearly 75% of carcinoid tumours are gastrointestinal (especially involving the appendix and ileum), 25% are bronchial, and a small number arise at other sites including the larynx, pancreas, gallbladder and ovary [3]. Flushing is described as varying according to the site of the neoplasm; the most common midgut tumours (appendix and ileum) are associated with gradual development of fixed cyanotic erythema in the flushing distribution, whereas foregut tumours (stomach, pancreas, lung) are associated with a brighter pink flush. This may reflect production of different mediators; gastric carcinoids typically cause flushing by production of histamine, whereas midgut carcinoids produce serotonin, bradykinin and prostaglandins. Other symptoms, such as diarrhoea, abdominal pain, dyspnoea, wheezing and occasionally syncope, may occur with progression of the tumour, usually not occurring until liver metastases have developed. Persistent erythema with or without telangiectasia, scleroderma-like change, pigmentary anomalies and a pellagra-like dermatitis eventually develop.

Mastocytosis [1,4,5] is discussed in more detail in Chapter 22. It is most commonly limited to the skin but may be systemic, in which event it can be classified into four groups: indolent, associated with a clonal haematological non-mast cell lineage disease (myeloproliferative or myelodysplastic disorders), aggressive (lymphadenopathic with eosinophilia), and mast cell leukaemia. It may be associated with mutations in the gene for c-kit. The more aggressive forms tend not to be associated with cutaneous mast cell lesions but flushing, dyspnoea, chest pain, abdominal cramps, palpitations, syncope and other systemic reactions due to mast cell degranulation may occur. Serum tryptase is a useful screening test that may suggest systemic disease. However, the proportion of bone marrow mast cells, eosinophilia (especially in bone marrow) and alkaline phosphatase level are of greater prognostic importance than levels of mast cell mediators [6].

Phaeochromocytomas (PCC) may cause pallor with rebound flushing [1,2], but the more typical dermatological feature is

hyperhidrosis, discussed above. *Medullary carcinoma of thyroid*, like PCC, may occur as part of a MEN syndrome (p. 62.24) but may occur in isolation. They may produce several other hormones such as ACTH, as well as prostaglandins and amines, which may cause other symptoms such as diarrhoea.

References

1 El Tal AK, Tannous Z. Cutaneous vascular disorders associated with internal malignancy. *Dermatol Clin* 2008; **26**: 45–57.
2 Hemann WR. Flushing, pheochromocytoma, and the dermatologist. *J Am Acad Dermatol* 2006; **55**: 1075–7.
3 Modlin IM, Sandor A. An analysis of 8305 cases of carcinoid tumors. *Cancer* 1997; **79**: 13–29.
4 Beck LA, Provost TT. Mastocytosis. In: Provost TT, Flynn JA, eds. *Cutaneous Medicine: Cutaneous Manifestations of Systemic Disease*. Hamilton, Ontario: Decker, 2001: 367–88.
5 Tharp MD, Chan IJ. Mastocytosis. *Adv Dermatol* 2003; **19**: 207–36.
6 Pardanani A, Baek J-Y, Li C-Y *et al.* Systemic mast cell disease without associated hematologic disorder: a combined retrospective and prospective study. *Mayo Clin Proc* 2002; **77**: 1169–75.

Venous or lymphatic obstruction

In addition to vasculitis and the thrombotic intravascular occlusion described above, vessels of different types may become occluded by intravascular tumour cells, or may be compressed by an adjacent tumour. The facial and upper limb suffusion of superior vena caval obstruction is well known. Obstruction of venous flow from the head and neck may also occur due to benign retrosternal thyroid gland enlargement and is typically seen when the arms are elevated (Pemberton sign). Lymphatic obstruction typically occurs at the main lymph node sites, such as in the axilla due to a breast carcinoma, lymphoma or limb melanoma. Apical lung neoplasms may also cause damage to sympathetic nerves, leading to anhidrosis and sometimes hyperhidrosis and flushing of the contralateral, unaffected side. Arterial obstruction by tumours is much less common, although tumour emboli may occur.

Other vascular disorders

Various other angiomatous lesions have been linked with internal malignancy, including *eruptive angiomas* [1] and *telangiectasia* [2]. The latter may occur as a direct tumour infiltration of vessels (carcinoma telangiectoides, p. 62.16) but has also been described secondary to lung cancer. Painful telangiectatic plaques are a feature of malignancy angioendotheliomatosis. *Glomeruloid angiomas* are a feature of POEMS syndrome, in which a monoclonal paraprotein is a feature. Telangiectasia occurs in several genodermatoses described earlier, such as Bloom's syndrome and Rothmund–Thomson syndrome, and is a feature of more advanced cases of carcinoid syndrome.

References

1 Pembroke AC, Grice K, Levantine AV *et al.* Eruptive angiomata in malignant disease. *Clin Exp Dermatol* 1978; **3**: 147–55.
2 El Tal AK, Tannous Z. Cutaneous vascular disorders associated with internal malignancy. *Dermatol Clin* 2008; **26**: 45–57.

Deposition disorders: mucinoses, xanthomas, amyloidosis and calcification

Dermal deposition disorders may be linked with internal malignancy [1]; in particular, there are a number of diverse cutaneous manifestations of paraproteinaemia and myeloma (p. 62.92) [2]. Some of these are rare conditions, and their occurrence should prompt a search for an underlying internal cause. Some of the most important deposition disorders, and their potentially associated internal malignancy, are listed in Table 62.11; all listed are discussed in detail in other chapters.

Paraproteinaemia is associated with many of the deposition disorders listed in Table 62.11. Other manifestations of paraproteinaemia are discussed in more detail in the section on haematological disorders (pp. 62.92–62.94). Pathology of disorders such as sclero-myxoedema and necrobiotic xanthogranuloma is discussed in [2–4].

Calcinoisis cutis is a rare complication of internal carcinoma. However, it should be noted that many cancers cause hypercalcaemia, and that metastatic calcification may occur in other organs, such as the lung or kidney, even if not in the skin. The commonest underlying tumours are carcinoma of oesophagus, myeloma, breast cancer, lymphoma and osteolytic metastases; mechanisms include production of parathyroid hormone, parathyroid hormone-related peptide, vitamin D, cytokines, up-regulation of NFκB ligand (RANKL) or down-regulation of RANKL antagonist (osteoprotegerin) [2].

References

1 Touart DM, Sau P. Cutaneous deposition disorders. Part I. *J Am Acad Dermatol* 1998; **39**: 149–71.
2 Weenig RH, Mehrany K. Dermal and pannicular manifestations of internal malignancy. *Dermatol Clin* 2008; **26**: 31–43.
3 Cohen PR. Paraneoplastic dermatopathology: cutaneous paraneoplastic syndromes. *Adv Dermatol* 1996; **11**: 215–52.
4 Chung VQ, Moschella SL, Zembowicz A, Liu V. Clinical and pathologic findings of paraneoplastic dermatoses. *J Am Acad Dermatol* 2006; **54**: 745–62.

Bullous disorders

Paraneoplastic pemphigus (PNP; neoplasia-associated pemphigus) [1–6]

This is a heterogeneous, multiorgan, autoimmune syndrome in which patients may display a spectrum of mucocutaneous manifestations including pemphigus-like, pemphigoid-like, erythema multiforme-like, graft-versus-host disease-like or lichen planus-like patterns, characteristically with oral involvement; in addition, there is an association with small-airways occlusion [5] and deposition of autoantibody complexes in different organs. The mucosal disease is often severe and progressive.

Associated neoplasms in one large review series were mainly B-cell proliferations and thymoma or thymoma-like neoplasms; specific neoplasms included Hodgkin's lymphoma (42%), chronic lymphocytic leukaemia (29%), Castleman's tumour (10%), thymoma (6%), spindle cell neoplasms (6%) and Waldenström's macroglobulinaemia (6%) [1]. PNP is distinguished from pemphigus by its clinical features and by the presence of serum autoantibodies to a range of antigens of 250, 230, 210, 190 and 170 kDa (which include bullous pemphigoid antigen, as well as desmosomal and hemidesmosomal proteins including desmoglein 1, desmoglein 3, envoplakin and periplakin); direct immunofluorescence of skin biopsies is usually positive for IgG and C3 but may be negative in some cases. High sensitivity and specificity for this differential diagnosis has recently been reported by taking account

Table 62.11 Some deposition disorders that are linked with internal malignancy.

Material deposited	Disorder	Associated internal malignancies	Comments
Amyloid proteins [1] (see Chapter 59)	Primary and myeloma-associated systemic amyloidosis (AL protein deposition)	Paraproteinaemia, myeloma	Amyloidosis occurs in about 15% of patients with myelomatosis
	Secondary amyloidosis (AA protein deposition)	Lymphomas, especially Hodgkin's lymphoma Hypernephroma Other solid tumours	
Mucin/proteoglycans and fibromucinoses	Scleromyxedema/lichen myxoedematosus	Paraproteinaemia, typically a 'slow gamma region'	Paraprotein is present in most cases
	Papular mucinosis	Paraproteinaemia	Uncommon
	Scleredema	Paraproteinaemia	More commonly associated with diabetes or streptococcal infection
	POEMS syndrome	Paraproteinaemia	Features are polyneuropathy, organomegaly, endocrinopathy, M-protein, skin changes
Lipids (as foamy macrophages)	Necrobiotic xanthogranuloma	Paraproteinaemia, usually monoclonal IgGκ, present in about 70% of cases	Also associated with cryoglobulinaemia, myeloma, marrow dyscrasias and rarely leukaemia; some cases apparently occur in isolation
	Normolipaemic plane xanthomatosis	Myeloma	Usually IgG paraprotein
	Xanthoma disseminatum	Gammopathy, bone marrow dyscrasias	Usually IgG paraprotein
Calcium	Metastatic calcification	Lung and other squamous carcinomas Due to primary hyperparathyroidism; may be associated with multiple endocrine neoplasia syndromes	Due to ectopic parathyroid-like hormone secretion See p. 62.24
	Dystrophic calcification	Pancreatic carcinoma	Calcification of fat

of the association with a lymphoproliferative disorder, indirect immunofluorescence of rat bladder urothelium (antibodies to desmoplakin), and envoplakin and/or periplakin bands on immunoblotting [6].

References

1 Anhalt GJ. Paraneoplastic pemphigus. *Adv Dermatol* 1997; **12**: 77–96.
2 Thomas I, Schwartz RA. Cutaneous paraneoplastic syndromes: uncommon presentations. *Clinics Dermatol* 2005; **23**: 593–600.
3 Stone SP, Buescher LS. Life-threatening paraneoplastic cutaneous syndromes. *Clinics Dermatol* 2005; **23**: 301–6.
4 Nguyen VT, Ndoye A, Bassler KD *et al*. Classification, clinical manifestations and immunopathological mechanisms of epithelial variant of paraneoplastic autoimmune multiorgan syndrome. *Arch Dermatol* 2001; **137**: 193–206.
5 Nousari HC, Deterding R, Wojtczack H *et al*. The mechanism of respiratory failure in paraneoplastic pemphigus. *N Engl J Med* 1999; **340**: 1406–10.
6 Joly P, Richard C, Gilbert D *et al*. Sensitivity and specificity of clinical, histologic, and immunologic features in the diagnosis of paraneoplastic pemphigus. *J Am Acad Dermatol* 2000; **43**: 619–26.

Bullous pemphigoid

Isolated reports have suggested an association between bullous pemphigoid and underlying neoplasia [1–3]. However, larger series do not support a significant association with malignant disease [4,5]. Despite this, the issue remains controversial, and more selective studies have shown there may be a correlation when immunofluorescent findings are negative and mucosal involvement is present [4,6]. Historical reports are difficult to evaluate with certainty, as some cases may actually have been epidermolysis bullosa acquisita, or even bullous pemphigoid-like PNP, which can now be separated from bullous pemphigoid by current immunological techniques. Malignancies have been reported from breast, lung, thyroid, larynx, skin, soft tissue, stomach, colon, lymphoreticular system, prostate, cervix, bladder, kidney and uterus.

References

1 Hodge L, Marsden RA, Black MM *et al*. Bullous pemphigoid: the frequency of mucosal involvement and concurrent malignancy related to indirect immunofluorescence findings. *Br J Dermatol* 1981; **105**: 65–9.
2 Schroeter AL. Pemphigoid and malignancy. *Clin Dermatol* 1987; **5**: 60–3.
3 Tanaka T, Ogino A, Ogura K *et al*. A case of bullous pemphigoid and transitional cell carcinoma of the bladder: demonstration of a circulating factor reactive with basement membrane zone of skin and of bladder carcinoma. *Arch Dermatol* 1983; **119**: 704–5.
4 Lindelof B, Islam N, Eklund G *et al*. Pemphigoid and cancer. *Arch Dermatol* 1990; **126**: 66–8.
5 Stone SS, Schroeter AL. Bullous pemphigoid and associated malignant neoplasms. *Arch Dermatol* 1975; **111**: 991–4.
6 Person JR, Rogers RS. Bullous and cicatricial pemphigoid: clinical, histopathologic and immunopathologic correlations. *Mayo Clin Proc* 1977; **52**: 54–66.

Pemphigus

Historically, pemphigus has been linked with various tumours; some cases, such as those associated with thymoma and Castleman's tumour, would probably now be found to have the features of PNP. Pemphigus foliaceus has been associated with acanthosis nigricans-like lesions and hepatocellular carcinoma [7], and pemphigus in Japanese subjects has been associated with lung cancer. The concurrence of internal malignancy and pemphigus, as with bullous pemphigoid, may be a true association [8], although some suggest this to be coincidence [9].

7 Muramatsu T, Matsumoto H, Yamashina Y *et al.* Pemphigus foliaceus associated with acanthosis nigricans-like lesions and hepatocellular carcinoma. *Int J Dermatol* 1989; **28**: 462–3.
8 Krain LS, Bierman SM. Pemphigus vulgaris and internal malignancy. *Cancer* 1974; **33**: 1091–9.
9 Callen JP. Internal disorders associated with bullous disease of the skin: a critical review. *J Am Acad Dermatol* 1980; **3**: 107–19.

Other blistering disorders

Dermatitis herpetiformis (DH) has been documented in some studies to have a link with internal malignancy of various types, especially lymphoma [1–4], although some studies suggest that the risk is actually quite low and confined to a small increase in likelihood of lymphoma [3]. Review of a single-institution large cohort of patients with DH documented a low frequency of lymphoproliferative disorders (seven of 270 patients, including two with small bowel and one with gastric lymphoma) and although 10.4% of the series had some form of documented malignant disease at some time, there was no apparent tumour type that was overrepresented, no control population to know whether this represented an increased risk, and the interval between DH and lymphoma varied widely [5]. There is logic for an indirect link with lymphoma; DH is always associated with some degree of gluten-sensitive enteropathy, and the latter has a well documented association with small bowel lymphoma. One group of authors who initially found an increased risk of lymphoma in DH [4] later, in a larger study, documented that the overall risk of mortality in DH was lower than in the general population [6], although the risk of non-Hodgkin's lymphoma was increased with a standardized incidence ratio of 6.0. In this study, one of seven lymphomas in DH was an enteropathy-associated T-cell lymphoma, associated with inadequate dietary compliance [6], supporting the earlier documentation that a gluten-free diet (GFD) reduces the risk of small bowel lymphoma in patients with DH [7].

It therefore appears that there is an increased risk of lymphoma in DH but that the overall risk is small; additionally, the lymphoma risk, particularly of bowel lymphoma, is decreased by adherence to a GFD.

Linear IgA disease also appears to have a higher-than-predicted association with lymphoproliferative malignancy although this is much less well documented [8].

Epidermolysis bullosa acquisita (EBA) is commonly linked with autoimmune diseases but has also been reported to occur in association with neoplasia (Fig. 62.17), particularly myeloma and lymphoma [9–11]. An interesting possible explanation is partial homology of a 105-kDa basement membrane antigen with a 90-kDa tumour antigen [12]. The difficulties in separating EBA from other subepidermal blistering disorders such as cicatricial pemphigoid and bullous pemphigoid have already been alluded to, and make evaluation of earlier reports uncertain.

Porphyria cutanea tarda and *variegate porphyrias* have been associated with hepatocellular carcinoma [13]. Myeloma and visceral carcinoma have also been reported [14].

Erythema multiforme is most commonly related to herpes simplex or other infections, or to medications; if it occurs in the context of neoplasia it can be difficult to prove an association. The association is certainly weak and does not warrant investigation routinely.



Fig. 62.17 Paraneoplastic epidermolysis bullosa acquisita in a patient with metastatic breast carcinoma; irregular erosions on the abdomen resulting from fragile blisters.

References

1 Leonard JN, Tucker WF, Fry JS *et al.* Increased incidence of malignancy in dermatitis herpetiformis. *BMJ* 1983; **286**: 16–18.
2 Swerdlow AJ, Whittaker S, Carpenter LM *et al*. Mortality and cancer incidence in patients with dermatitis herpetiformis: a cohort study. *Br J Dermatol* 1993; **129**: 140–4.
3 Sigurgeirsson B, Agnarsson BA, Lindelof B. Risk of lymphoma in patients with dermatitis herpetiformis. *BMJ* 1994; **308**: 13–5.
4 Collin P, Pukkala E, Reunala T. Malignancy and survival in dermatitis herpetiformis: a comparison with coeliac disease. *Gut* 1996; **38**: 528–30.
5 Alonso LJ, Gibson LE, Rogers RS 3rd. Clinical, pathologic, and immunopatholgic features of dermatitis herpetiformis: review of the Mayo clinic experience. *Int J Dermatol* 2007; **46**: 910–9.
6 Viljamaa M, Kaukinen K, Pukkala E *et al*. Malignancies and mortality in patients with coeliac disease and dermatitis herpetiformis: 30-year population-based study. *Dig Liver Dis* 2006; **38**: 374–80.
7 Lewis HM, Reunala TL, Garioch JJ *et al*. Protective effect of gluten-free diet against development of lymphoma in dermatitis herpetiformis. *Br J Dermatol* 1996; **135**: 363–7.
8 Godfrey KM, Wojnarowska FJ, Leonard J. Disease associations of linear IgA disease. *Br J Dermatol* 1989; **121**: 48.
9 Aractingi S, Bachmeyer C, Prost C *et al*. Subepidermal autoimmune bullous skin diseases associated with B-cell lymphoproliferative disorders. *Medicine (Baltimore)* 1999; **78**: 228–35.
10 Baler GR. Epidermolysis bullosa acquisita associated with lymphoma. *J Am Acad Dermatol* 1987; **17**: 856–9.
11 Engineer L, Dow EC, Braverman IM, Ahmed AR. Epidermolysis bullosa acquisita and multiple myeloma. *J Am Acad Dermatol* 2002; **47**: 943–6.
12 Chan LS, Woodley DT. The 105-kDa basement membrane autoantigen p105 is N-terminally homologous to a tumor-associated antigen. *J Invest Dermatol* 1996; **107**: 209–14.
13 Tidman MJ, Higgins EM, Elder GH *et al*. Variegate porphyria associated with hepatocellular carcinoma. *Br J Dermatol* 1989; **121**: 503–5.
14 Dandurand M, Guillot B, Guilhou JJ. Porphyrie cutanée tardive et néoplasies: à propos de deux observations. *Ann Dermatol Vénéréol* 1986; **113**: 679–83.

Indirect cutaneous markers of internal malignancy

Exposure to carcinogens [1]

Nicotine staining of the fingers is one of the commonest signs that a patient may be predisposed to bronchial carcinoma, together with other tobacco-linked neoplasia.



Fig. 62.18 Arsenical keratoses on the hand.

Radiotherapy damage to the skin may indicate that underlying tissues are at increased risk of neoplasia; this is particularly relevant for neck and thyroid carcinoma. Radiotherapy damage and/or multiple BCCs over the spine following radiotherapy for ankylosing spondylitis may indicate the patient is predisposed to leukaemia.

Arsenic-induced pigmentation, keratoses (Fig. 62.18), Bowen's disease, superficial BCCs and multiple sebaceous tumours can be linked to an increased risk of internal neoplasia (especially bronchial). The relationship between Bowen's disease of non-sun-exposed skin and an increased risk of internal neoplasia has been a long-standing controversy; a meta-analysis of published studies did not confirm a significant association [2], and if the link with arsenic is excluded, the association appears unsubstantiated [3,4]. A further study of 1147 patients found the overall incidence of internal cancers in patients with Bowen's disease to be slightly increased (115 cancers versus 103 expected, standardized incidence ratio (SIR) 1.1) but not significant [5]. However, there was an SIR of 3.2 for leukaemia in men and of 4.6 for lung cancer in men with Bowen's disease before age 60 years (the overall lung cancer SIR for both sexes and all ages was 1.3). There are various sources of potential bias in many studies of this type, and available evidence would still suggest that routine investigation for internal malignancy in patients with Bowen's disease is not justified [6].

Vinyl chloride-related acrosclerosis, acro-osteolysis and papular skin changes are variable markers of heavy industrial exposure in polyvinyl chloride manufacture. A link with angiosarcoma of the liver has been noted [7].

Immunosuppression

Patients on immunosuppressive therapy have an increased risk of internal malignancy. Some such patients have no specific cutaneous features but some may have a combination of features of their underlying disease (e.g. signs of renal failure), side effects of their treatment (e.g. hypertrichosis and gingival changes due to ciclosporin; frequent, severe or unusual infections), and other features linked with immunosuppression (e.g. sebaceous hyperplasia, viral warts, skin cancers or precursors). These issues are discussed in the section on organ transplantation (p. 62.74).

Several inherited immunodeficiency syndromes also carry an increased risk of internal neoplasia, the most important of which are discussed above.

A variety of viral, bacterial and fungal infections may occur as a result of compromised immune response as a consequence of internal malignancy, particularly in haematological malignancies or in those with a large tumour burden. Occasionally, such infection may be the presenting feature—in particular, herpes zoster occurs more severely, with higher incidence and wider dissemination, in patients with reticuloendothelial or myeloproliferative neoplasia [8]. More than 20 disseminated (chickenpox-like) lesions, or involvement of two or more dermatomes, are suggestive of immune compromise and possible underlying malignancy, although involvement of adjacent sacral dermatomes is not uncommon and does not warrant extensive investigation. Chronic herpes-virus infections may also be a feature of immunosuppression and therefore indirectly linked with neoplasia (such as Kaposi's sarcoma in AIDS).

References

1 Poole S, Fenske NA. Cutaneous markers of internal malignancy, 2: paraneoplastic dermatoses and environmental carcinogens. *J Am Acad Dermatol* 1993; **28**: 147–64.

2 Lycka BAS. Bowen's disease and internal malignancy. A meta-analysis. *Int J Dermatol* 1989; **28**: 531–3.

3 Chuang TY, Reizner GT. Bowen's disease and internal malignancy. *J Am Acad Dermatol* 1988; **19**: 47–51.

4 Arbesman H, Ransohoff DF. Is Bowen's disease a predictor for the development of internal malignancy? A methodological critique of the literature. *JAMA* 1987; **257**: 516–8.

5 Jaeger AB, Gramkow A, Hjalgrim H *et al*. Bowen disease and risk of subsequent malignant neoplasms: a population-based cohort study of 1147 patients. *Arch Dermatol* 1999; **135**: 790–3.

6 Cox NH, Eedy DJ, Morton CA. Guidelines for management of Bowen's disease: 2006 update. *Br J Dermatol* 2007; **156**: 11–21.

7 Anonymous. Vinyl chloride and cancer. *BMJ* 1974; **i**: 590–1.

8 Shanbrom E, Miller S, Haar H. Herpes zoster in hematologic neoplasias: some unusual manifestations. *Ann Intern Med* 1960; **53**: 523–33.

The gastrointestinal tract

This section concentrates on bowel, hepatic and pancreatic diseases in which cutaneous associations or consequences are prominent [1–4]. Skin changes related to more general effects of gastrointestinal diseases, such as nutritional defects, are discussed in Chapter 59; oral disease is described in Chapter 69. Links between skin disorders and abdominal pain are not specifically considered, but many of the disorders in this section may cause this symptom; other causes of skin eruption with abdominal pain include disorders such as hereditary angio-oedema (Chapter 22), vasculitides (Chapter 50), porphyrias (Chapter 59), and autoinflammatory diseases (periodic fevers; see the section on bone and joint disease later). Cutaneous metastases and paraneoplastic eruptions due to gastrointestinal malignancy are discussed in the preceding section of this chapter.

References

1 Gregory B, Ho VC. Cutaneous manifestations of gastrointestinal disorders, I and II. *J Am Acad Dermatol* 1992; **26**: 371–83.
2 Braverman IM. *Skin Signs of Systemic Disease*, 3rd edn. Philadelphia: Saunders, 1998: 405–37.
3 Herron MD, Zone JJ. Cutaneous diseases associated with gastrointestinal abnormalities. In: Callen JP, Jorrizo JL, eds. *Dermatological Signs of Internal Disease*, 3rd edn. Philadelphia: Saunders, 1995: 219–32.
4 Boh EE, al-Smadi RMF. Cutaneous manifestations of gastrointestinal diseases. *Dermatol Clin* 2002; **20**: 533–46.

Oesophagus and stomach

Bleeding from the oesophagus or stomach may be associated with skin and nail changes of iron deficiency, such as koilonychia, smooth tongue and angular cheilitis (Chapter 59). Iron deficiency is associated with dysphagia and development of a postcricoid web as in the Paterson–Brown–Kelly (Plummer–Vinson) syndrome. Skin disorders that are associated with gastrointestinal bleeding, or with polyps, are discussed later. Cutaneous metastases may occur from tumours of the oesophagus or stomach. Paraneoplastic eruptions linked to the upper gastrointestinal tract, such as tylosis with oesophageal carcinoma (Howell–Evans syndrome), acrodermatitis and nail dystrophy with upper gastrointestinal carcinoma (Bazex syndrome), or acanthosis nigricans with gastric carcinoma, are discussed earlier in this chapter.

Bullous diseases may affect the pharynx, oesophagus or stomach. Epidermolysis bullosa (EB) is of particular relevance; dystrophic EB may cause oesophageal scarring [1], with a risk of SCC, and gastric outflow is affected in junctional EB, resulting in pyloric atresia [2,3]. Several inflammatory disorders such as lichen planus may affect the mouth, pharynx or oesophagus [4,5]. Immunobullous diseases, particularly those with an IgA basement membrane zone immunoreactant, may cause mucosal blistering and erosions—examples include cicatricial pemphigoid, linear IgA disease and the IgA variant of epidermolysis bullosa acquisita. Cicatricial pemphigoid may also cause oesophageal scarring and stenosis.

Sclerodermatous processes also affect the oesophagus, in particular CREST (*c*alcinosis, *R*aynaud's phenomenon, *o*esophagus, *s*clerodactyly, *t*elangiectasia). This disorder is discussed more fully in Chapter 51. The oesophageal abnormality consists of decreased and disordered peristalsis. Scleroderma is also associated with decreased peristalsis throughout the bowel, leading to malabsorption, constipation and diverticulae. Sjögren's syndrome may also cause dysphagia, as may dermatomyositis in cases in which there is involvement of the pharyngeal musculature.

Helicobacter pylori has been implicated as an aetiological factor in some cases of urticaria, rosacea, vasculitis, Sweet's syndrome, erythema multiforme, alopecia areata, chronic itch and prurigo nodularis, and atopic and nummular dermatitis [6–8]. Although there are some individuals in whom eradication therapy coincides with resolution of a dermatosis, most larger studies in which there is adequate control for confounding factors such as age and social class have failed to demonstrate either a higher prevalence of *H. pylori* infection, higher titres on ^{13}C urea breath test, or a higher rate of response to eradication therapy in infected individuals compared with controls [9–12].

References

1 Orlando RC, Bozymski EM, Briggaman RA *et al.* Epidermolysis bullosa: gastrointestinal manifestations. *Ann Intern Med* 1974; **81**: 203–6.
2 Shaw DW, Fine JD, Piacquadio DJ *et al.* Gastric outflow obstruction and epidermolysis bullosa. *J Am Acad Dermatol* 1997; **36**: 304–10.
3 Nakano A, Pulkkinen L, Murrell D *et al.* Epidermolysis bullosa with congenital pyloric atresia: novel mutations in the beta 4 integrin gene (*ITGB4*) and genotype/phenotype correlations. *Pediatr Res* 2001; **49**: 618–26.
4 Harewood GC, Murray JA, Cameron AJ. Esophageal lichen planus: the Mayo Clinic experience. *Dis Esoph* 1999; **12**: 309–11.
5 Evans AV, Fletcher CL, Owen WL, Hay RJ. Oesophageal lichen planus. *Clin Exp Dermatol* 2000; **25**: 36–7.
6 Shiotani A, Okada K, Yanaoka K *et al.* Beneficial effect of *Helicobacter pylori* eradication in dermatologic diseases. *Helicobacter* 2001; **6**: 60–5.
7 Di Campli C, Gasbarrini A, Nucera E *et al.* Beneficial effects of *Helicobacter pylori* eradication on chronic idiopathic urticaria. *Dig Dis Sci* 1998; **43**: 1226–9.
8 Utas S, Ozbakir O, Turasan A, Utas C. *Helicobacter pylori* eradication treatment reduces the severity of rosacea. *J Am Acad Dermatol* 1999; **40**: 433–5.
9 Leontiadis GI, Sharma VK, Howden CW. Non-gastrointestinal tract associations of *Helicobacter pylori* infection. *Arch Intern Med* 1999; **159**: 925–40.
10 Hook-Nikanne J, Varjonen E, Harvima RJ, Kosunen TU. Is *Helicobacter pylori* infection associated with chronic urticaria? *Acta Derm Venereol* 2000; **80**: 425–6.
11 Dauden E, Jimenez-Alonso I, Garcia-Diez A. *Helicobacter pylori* and idiopathic chronic urticaria. *Int J Dermatol* 2000; **39**: 446–52.
12 Bamford JT, Tilden RL, Blankush JL, Gangeness DE. Effect of treatment of *Helicobacter pylori* infection on rosacea. *Arch Dermatol* 1999; **135**: 659–63.

Crohn's disease (regional ileitis)

Crohn's disease is now known to be one of a group of diseases caused by mutations in the caspase recruitment domain 15 gene (*CARD15*), also termed *NOD2* [1]. Other disorders in which *CARD15* mutations are involved include several with dermatological aspects, including Muckle–Wells syndrome, IPEX (immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome), and PAPA (pyogenic arthritis, pyoderma gangrenosum and acne).

Skin lesions are frequently seen in Crohn's disease [2–5]. These include:

- Crohn's disease occurring as direct extension from the bowel
- Cutaneous lesions of Crohn's disease at other skin sites
- Reactive lesions that are associated with Crohn's disease, but which do not have granulomatous histology
- Skin lesions related to malabsorption (Chapter 59)
- Skin lesions related to treatment: drug reactions, stoma dermatoses, etc.
- Psoriasis
- Other associated dermatoses.

Direct skin and mucosal involvement in continuity with the bowel

Cutaneous Crohn's disease may occur at sites in continuity with the bowel, such as the lip, stoma sites (see later section) or, commonly, the perineal skin including the vulva in females. Orofacial granulomatosis and the overlap with Crohn's disease is discussed in Chapter 69. The umbilicus, a site connected to the bowel by a vestigial tract, may also be involved [6]. Rarely, there may be frank enterocutaneous fistulae due to underlying Crohn's disease, sometimes with multiple lesions.

Perineal abscesses and multiple fissures and fistulae occur in about a quarter of patients ('watering-can perineum'). This is more frequent in individuals with colonic disease [7] and may affect

about 60% of patients, although symptoms may be absent. By contrast, such lesions are rare in ulcerative colitis. Anal tags, which may be oedematous or have granulomatous histology, are common.

Oral Crohn's disease is manifest as a thickened, corrugated appearance of the oral mucosa and lips. Granulomatous cheilitis may precede other features of Crohn's disease (Chapter 69).

Cutaneous Crohn's disease at other sites ('metastatic Crohn's disease')

Cutaneous Crohn's disease may also occur at sites separated from the bowel by normal tissues—a situation that is termed 'metastatic Crohn's disease', although not technically correct [8–11]. Lesions may parallel gastrointestinal disease activity, or may occur with a totally separate temporal pattern.

Lesions of cutaneous Crohn's disease may be solitary or multiple, and may have varied morphology, including intact or eroded plaques and nodules, or sinus formation. The lower legs are involved in half of the cases, with lesions sometimes mimicking erythema nodosum, but cutaneous Crohn's disease may affect the abdominal wall, groin and inframammary flexures, face and other sites. Genital involvement may be a presenting feature, affecting the perineum [11], vulva [12], scrotum or penis [4,13]. Unusual patterns include perifollicular papules [14], erysipelas-like lesions [15] and necrobiotic lesions [16]. In any of these morphological variants, there is a granulomatous histology in the dermis and subcutis. Lymphoedema, typically of the genital area, perineum or face, are also well documented and presumably related to local lymphatic obstruction by granulomatous inflammation.

Treatments for both contiguous and 'metastatic' Crohn's disease include topical and intralesional corticosteroids, agents used to treat the bowel disease (oral corticosteroids, sulphasalazine and split products such as mesalamine, immunosuppressive agents), oral metronidazole, and hyperbaric oxygen. Antitumour necrosis factor-α (anti-TNF) monoclonal antibodies, specifically infliximab and adalimumab, have been increasingly used for Crohn's disease, in which they may heal fistulae, both bowel–bowel and bowel–skin or bowel–vagina. A particular problem in such cases is being certain that infection is not playing a part in fistulation or sinuses, as this may worsen. Anti-TNF therapy is also effective for cutaneous associations, especially psoriasis and pyoderma gangrenosum but also hidradenitis suppurativa, so may have dual benefit in Crohn's disease. The benefit in ulcerative colitis is less clear. This and other cytokine treatments are discussed in [17,18]. Serum sickness-like reactions have been reported with infliximab.

Reactive dermatoses associated with Crohn's disease

These include oral aphthae, erythema nodosum and a variety of neutrophilic dermatoses. As most of the reactive processes can occur with either type of inflammatory bowel disease, but most are more commonly associated with ulcerative colitis than with Crohn's disease, they are discussed later in this section.

Other dermatoses that have been associated with Crohn's disease

Epidermolysis bullosa acquisita (EBA) has been associated with both Crohn's disease and ulcerative colitis, mainly the former [19] (see also Chapter 40 and Fig. 62.19). In most instances, Crohn's disease had been established for several years prior to development of EBA, although EBA may precede diagnosis of the bowel disease [20]. This condition may be very refractory to treatment; drugs that may improve both the bowel disease and the cutaneous lesions of EBA include corticosteroids, azathioprine and ciclosporin.



Fig. 62.19 Epidermolysis bullosa acquisita associated with a flare of inflammatory bowel disease.

Other bullous disorders that have been linked with Crohn's disease include *oral intraepidermal IgA pustulosis* [21] and *subcorneal pustular dermatosis* [22]; it has been suggested that the latter eruption was actually pustular pyoderma gangrenosum [23].

Polyarteritis nodosa (PAN) has been associated with Crohn's disease, but not specifically with ulcerative colitis [24,25]. It may be difficult to distinguish PAN from 'metastatic' Crohn's disease in patients with both disorders, as the histological features include a granulomatous component with the arteritis [26]; PAN may also resemble erythema nodosum or early pyoderma gangrenosum. The presence of livedo may suggest the diagnosis, but this can also occur due to cryoglobulinaemia. Other patterns of vasculitis associated with inflammatory bowel disease are discussed in the section on ulcerative colitis.

Psoriasis has been associated with Crohn's disease in several studies [27], and involvement of TNF in the pathogenesis of the two disorders has strengthened the view that they are linked. *Vitiligo* may also be associated.

In patients with Crohn's disease, apparently unrelated skin disorders may develop granulomas, for example hidradenitis suppurativa [28]. The presence of granulomas within predominantly neutrophilic infiltrates may cause diagnostic difficulty [29]; distinguishing between perineal sinuses of either disorder can be very difficult.

Disorders of keratinization that have been linked to Crohn's disease include *porokeratosis* [30] and *parakeratotic horns* [31].

Acrodermatitis enteropathica due to secondary zinc deficiency is a well-documented consequence of Crohn's disease [32] (Chapter 59).

References

1 Rose CD, Martin TM. Caspase recruitment domain 15 mutations and rheumatic diseases. *Curr Opin Rheumatol* 2005; **17**: 579–85.
2 Gregory B, Ho VC. Cutaneous manifestations of gastrointestinal disorders, 2. *J Am Acad Dermatol* 1992; **26**: 371–83.
3 Braverman IM. *Skin Signs of Systemic Disease*, 3rd edn. Philadelphia: Saunders, 1998: 405–37.
4 Herron MD, Zone JJ. Cutaneous diseases associated with gastrointestinal abnormalities. In: Callen JP, Jorrizo JL, eds. *Dermatological Signs of Internal Disease*, 3rd edn. Philadelphia: Saunders, 2003: 199–210.
5 Harris ML, Provost TT. Ulcerative colitis and Crohn's disease. In: Provost TT, Flynn JA, eds. *Cutaneous Medicine: Cutaneous Manifestations of Systemic Disease*. Hamilton, Ontario: Decker, 2001: 473–8.
6 McLelland J, Griffin SM. Metastatic Crohn's disease of the umbilicus. *Clin Exp Dermatol* 1996; **21**: 318–9.
7 Rankin GB, Watts HD, Melnyck CS *et al.* National cooperative Crohn's disease study: extraintestinal manifestations and perianal complications. *Gastroenterology* 1979; **77**: 914–20.
8 Lebwohl M, Fleischmajer R, Janowitz H *et al.* Metastatic Crohn's disease. *J Am Acad Dermatol* 1984; **10**: 33–8.
9 Shum DT, Guenther L. Metastatic Crohn's disease. *Arch Dermatol* 1990; **126**: 645–8.
10 Ploysangam T, Heubi JE, Eisen D *et al.* Cutaneous Crohn's disease in children. *J Am Acad Dermatol* 1997; **36**: 697–704.
11 Guest GD, Fink RL. Metastatic Crohn's disease: case report of an unusual variant and review of the literature. *Dis Colon Rectum* 2000; **43**: 1764–6.
12 Virgili A, Corazza M. Crohn's disease of the vulva: a case report. *J Reprod Med* 1994; **39**: 115–7.
13 Acker SM, Sahn EE, Rogers HC *et al.* Genital cutaneous Crohn's disease: two cases with unusual clinical and histopathologic features in young men. *Am J Dermatopathol* 2000; **22**: 443–6.
14 Buckley C, Bayoumi AH, Sarkany I. Metastatic Crohn's disease. *Clin Exp Dermatol* 1990; **15**: 131–3.
15 Dippel E, Rosenberger A, Zouboulis CC. Distant cutaneous manifestation of Crohn's disease presenting as a granulomatous erysipelas-like lesion. *J Eur Acad Dermatol Venereol* 1999; **12**: 65–6.
16 Perret CM, Bahmer FA. Extensive necrobiosis in metastatic Crohn's disease. *Dermatologica* 1987; **175**: 208–12.
17 Podolsky DK. Inflammatory bowel disease. *N Engl J Med* 2002; **347**: 417–28.
18 Brooklyn TN, Dunnill MGS, Shetty A *et al.* Infliximab for the treatment of pyoderma gangrenosum: a randomized, double blind, placebo controlled trial. *Gut* 2006; **55**: 505–9.
19 Ray TL, Levine JB, Weiss W *et al.* Epidermolysis bullosa acquisita and inflammatory bowel disease. *J Am Acad Dermatol* 1982; **6**: 242–52.
20 Labeille B, Gineston JL, Denoeux JP, Capron JP. Epidermolysis bullosa acquisita and Crohn's disease: a report with immunological and electron microscopic studies. *Arch Intern Med* 1988; **148**: 1457–9.
21 Borradori L, Saada V, Rybojad M *et al.* Oral intraepidermal IgA pustulosis and Crohn's disease. *Br J Dermatol* 1992; **126**: 383–6.
22 Delaporte E, Colombel JF, Nguyen-Mailfer C *et al.* Subcorneal pustular dermatosis in a patient with Crohn's disease. *Acta Derm Venereol* 1992; **72**: 301–2.
23 Powell FC, Su WPD, Perry HO. Pyoderma gangrenosum: classification and management. *J Am Acad Dermatol* 1996; **34**: 395–409.
24 Kahn EI, Daum E, Aiges HW *et al.* Cutaneous polyarteritis nodosa associated with Crohn's disease. *Dis Colon Rectum* 1980; **23**: 258–62.
25 Gudbjornsson B, Hallgren R. Cutaneous polyarteritis nodosa associated with Crohn's disease: report and review of the literature. *J Rheumatol* 1990; **17**: 386–90.
26 Chalvardijan A, Nethercott JR. Cutaneous granulomatous vasculitis associated with Crohn's disease. *Cutis* 1982; **30**: 645–55.
27 Najaian DJ, Gottlieb AB. Connections between psoriasis and Crohn's disease. *J Am Acad Dermatol* 2003; **48**: 805–21.
28 Attanoos RL, Appleton MA, Hughes LE *et al.* Granulomatous hidradenitis suppurativa and cutaneous Crohn's disease. *Histopathology* 1993; **23**: 111–5.
29 Yosipovitch G, Hodak E, Feinmesser D, David M. Acute Crohn's colitis with lobular panniculitis: metastatic Crohn's? *J Eur Acad Dermatol Venereol* 2000; **14**: 405–6.
30 Morton CA, Shuttleworth D, Douglas WS. Porokeratosis and Crohn's disease. *J Am Acad Dermatol* 1995; **32**: 894–7.
31 Aloi FG, Molinero A, Pippione M. Parakeratotic horns in a patient with Crohn's disease. *Clin Exp Dermatol* 1989; **14**: 79–81.
32 Krasovec M, Frenk E. Acrodermatitis enteropathica secondary to Crohn's disease. *Dermatology* 1996; **193**: 361–3.

Ulcerative colitis [1–4]

Skin lesions are reported in up to a third of patients with ulcerative colitis [2], although the cited frequency is usually in the region of 10–15%. As with Crohn's disease, these fall into several categories:

- Reactive lesions (a similar spectrum, but commoner in ulcerative colitis than in Crohn's disease)
- Direct involvement contiguous with the bowel (fissures and fistulae; rare)
- Skin lesions related to malabsorption (Chapter 59)
- Skin lesions related to treatment: drug reactions, stoma dermatoses, etc.
- Other associated dermatoses.

Reactive lesions associated with ulcerative colitis and Crohn's disease

A variety of non-specific eruptions may occur with either ulcerative colitis or Crohn's disease, usually paralleling the activity of inflammatory bowel disease [5]. However, all of these may occur for other reasons or in isolation. They include:

- Erythema nodosum—this occurs in about 5% of patients with ulcerative colitis (usually extensive rather than of limited extent) and in about 2% with Crohn's disease. It is the predominant pattern of reactive skin lesions in children, and in adults is most common in women. It is frequently associated with articular and other extragastrointestinal manifestations of the underlying bowel disease [6].
- Aphthous ulceration [1]—this occurs in about 5–8% of patients with ulcerative colitis and a rather smaller proportion with Crohn's disease. In some instances, the mechanism may be malabsorption, leading to iron and vitamin deficiency. Oral aphthae also occur in isolation, in association with numerous medications and in other medical disorders (including other bowel disorders, such as coeliac disease).
- Erythema multiforme [7,8]—this may occur in either disorder, usually associated with active disease (or as a side effect of treatment).
- Urticaria and angio-oedema.
- Neutrophilic dermatoses—these also occur in association with other disorders, but pyoderma gangrenosum and pyostomatitis vegetans in particular are strongly associated with inflammatory bowel disease. These disorders are discussed in more detail below.
- Vasculitis and intravascular coagulation disorders—these also occur as a consequence of inflammatory bowel disease, most commonly active ulcerative colitis, and are discussed separately below.

Neutrophilic dermatoses

Pyoderma gangrenosum [9–12]. Pyoderma gangrenosum occurs as a complication of inflammatory bowel disease, haematological disorders, inflammatory arthritides and other medical conditions [9] (it is discussed more fully in Chapter 50). It is estimated to occur in about 2–5% of patients with ulcerative colitis, this disor-

der being the single commonest cause of pyoderma gangrenosum; it is three to five times commoner in patients with ulcerative colitis than in those with Crohn's disease. The ulcerative and pustular variants in particular are associated with inflammatory bowel disease. It may also occur in other bowel diseases, such as the bowel-associated dermatosis–arthritis syndrome (see below) and diverticular disease [13], as a peristomal dermatosis [14] and in patients with hepatitis. The characteristic lesions are rapidly progressive necrotic skin ulcers with a bluish-coloured undermined border, but nodular and pustular lesions may occur, especially in early disease. Trauma is sometimes a predisposing factor. Pyoderma gangrenosum generally parallels the activity of the colitis [1–4], but may precede the diagnosis [15] or occur many years after complete removal of the diseased bowel [16]. Treatments for pyoderma gangrenosum include corticosteroids (topical, oral, intralesional), dapsone, azathioprine, ciclosporin, mycophenolate mofetil, tacrolimus (topical, oral), chlorambucil, intravenous immunoglobulin, and antitumour necrosis factor-α monoclonal antibodies such as infliximab [10,17–19].

Pyodermatitis–pyostomatitis vegetans [20,21] is a rare disorder of the oral mucosa and skin; the skin lesions were previously termed pyodermite végétante. The oral lesions consist of multiple pustules, plaques and erosions, which may have a 'snail's-track' appearance. The skin lesions are crusted papules and plaques, which coalesce into annular lesions, mainly affecting the major flexures and the scalp. There are similarities to pemphigus vegetans, but this is associated with strongly positive direct immunofluorescence of lesional skin, which is either negative or weak in pyodermatitis–pyostomatitis vegetans. Oral and skin lesions show the same histological features, having intraepidermal and superficial dermal microabscesses containing neutrophil and eosinophil polymorphs, and a more mixed, deeper dermal inflammatory infiltrate. Acanthosis, acantholysis and pseudoepitheliomatous hyperplasia occur, especially in the oral lesions. Most cases of pyodermatitis–pyostomatitis vegetans are associated with inflammatory bowel disease, usually ulcerative colitis, although the condition has also been reported with sclerosing cholangitis and in isolation. It is difficult to control; high-dose, systemic corticosteroids are the first-line therapy, but dapsone or azathioprine may be of benefit. Remission may occur following colectomy.

Acute febrile neutrophilic dermatosis (Sweet's syndrome). This has been associated with inflammatory bowel disease, especially ulcerative colitis [22–25]. It may coexist with pyoderma gangrenosum [22,24], and may also occur after colectomy in patients with inflammatory bowel disease. It is discussed more fully in Chapter 50. Treatment options include corticosteroids, dapsone, non-steroidal anti-inflammatory drugs, colchicine, tetracyclines, ciclosporin and other immunosuppressive agents and, in the context of inflammatory bowel disease, metronidazole [25]. A neutrophilic colitis in a patient with Sweet's syndrome and acute myeloid leukaemia, and with previous Crohn's disease, was felt to be histologically distinct from Crohn's disease or ulcerative colitis [26].

Vesicopustular eruption and other neutrophilic dermatoses. A vesicopustular eruption may occur in ulcerative colitis [1,2,27,28], or less commonly in Crohn's disease [29]. The lesions consist of a dense neutrophilic infiltrate similar to that of pyoderma gangrenosum or Sweet's syndrome, and may be a variation of these [2,9]. In practice, many of the group of neutrophilic dermatoses may overlap, coexist or evolve from smaller papular or pustular lesions. Morphologically similar lesions in the bowel-associated dermatosis–arthritis syndrome may have vasculitic histology; features of this syndrome may also occur in patients with inflammatory bowel disease [30]. Treatment is similar to that of the other neutrophilic dermatoses.

Erythema elevatum diutinum has been reported with both Crohn's disease and with ulcerative colitis [31,32], as has oral intraepidermal IgA pustulosis [33,34].

An important recent issue in the field of neutrophilic dermatoses has been a general view that the spectrum of conditions in this category is greater than previously thought. Some of the internal manifestations of neutrophilic dermatoses may cause diagnostic difficulties in patients with Crohn's disease, particularly features such as mesenteric lymphadenitis or aseptic abscesses [35,36]. Most such abscesses are internal but vulval and other cutaneous lesions have occurred.

Vasculitis and intravascular coagulation disorders

Vasculitis and purpura [1,2,37–39] may occur in either ulcerative colitis or Crohn's disease, most commonly in ulcerative colitis. The clinical picture is of a leukocytoclastic vasculitis with palpable purpura, typically affecting the lower legs and sometimes causing nodules or ulceration. Pustular lesions may have vasculitic histology. Joint pain and malaise may be prominent. Polyarteritis nodosa in Crohn's disease is discussed above.

Antineutrophil cytoplasm antibodies (ANCA) are present in 60–70% of patients with ulcerative colitis and 5–10% with Crohn's disease [40].

Cutaneous gangrene and focal thrombosis [41–43] is a rare complication. Patients with ulcerative colitis have significant coagulation defects; in one large early series, this was sufficient to complicate the clinical course in more than 1% of patients [41]. Thrombosis of internal vessels affects younger patients, unusual vascular sites, is associated with active inflammatory Crohn's disease but apparently quiescent ulcerative colitis, and has significant mortality of 5–10%. Abnormalities underlying this tendency are unclear—some reports implicate thrombocythaemia, elevated levels of fibrinogen, factor VIII and factor V, and decreased levels of antithrombin III whilst others have excluded common thrombophilic states such as factor V Leiden, deficiencies of protein C, protein S or antithrombin III, or presence of anticardiolipin antibodies. Microvascular thrombosis of the skin may result in cutaneous gangrene. High-dose systemic steroids have no effect on the thrombotic complications, which should be treated with anticoagulant therapy. Similar features have been reported due to cryoglobulinaemia associated with inflammatory bowel disease.

Other cutaneous disorders associated with ulcerative colitis

Linear IgA disease. Linear IgA disease may be relatively common in patients with ulcerative colitis, which usually precedes the dermatosis by several years [44]. Linear IgA disease may resolve after

colectomy has been performed for ulcerative colitis [45]. Whether these patients actually have ulcerative colitis or a specific colitis associated with linear IgA disease is uncertain; two recent patients with preceding bowel symptoms developed oral ulceration and were found to have linear IgA deposition in mouth and colon. The bowel histology was that of a lymphocytic colitis or Crohn's disease [46]. Linear IgA disease has also been associated with Crohn's disease [47].

Epidermolysis bullosa acquisita, discussed above in relation to Crohn's disease, also occurs in some patients with ulcerative colitis; an erythema gyratum repens-like pattern has been described in such a case [48].

Hermansky–Pudlak syndrome (MIM #203300) (Chapter 39). This may be associated with an inflammatory colitis that resembles ulcerative colitis but has a granulomatous infiltrate histologically; this appears to be distinct from either ulcerative colitis or Crohn's disease [1,49].

Ulcerative colitis has been linked with a variety of autoimmune disorders and with sarcoidosis [50,51], although the strength of this association is not clear. Finger clubbing may be associated with inflammatory bowel disease, particularly ulcerative colitis [52], as well as with several other gastrointestinal diseases, including tumours, chronic infections, protein-losing enteropathy and laxative abuse [53]. Acne fulminans has also been reported in association with inflammatory bowel disease [54].

References

1 Gregory B, Ho VC. Cutaneous manifestations of gastrointestinal disorders, 2. *J Am Acad Dermatol* 1992; **26**: 371–83.

2 Braverman IM. *Skin Signs of Systemic Disease*, 3rd edn. Philadelphia: Saunders, 1998: 405–37.

3 Herron MD, Zone JJ. Cutaneous diseases associated with gastrointestinal abnormalities. In: Callen JP, Jorrizo JL, eds. *Dermatological Signs of Internal Disease*, 3rd edn. Philadelphia: Saunders, 2003: 199–210.

4 Harris ML, Provost TT. Ulcerative colitis and Crohn's disease. In: Provost TT, Flynn JA, eds. *Cutaneous Medicine: Cutaneous Manifestations of Systemic Disease*. Hamilton, Ontario: Decker, 2001: 473–8.

5 Greenstein AJ, Janowitz HD, Sachar DB. The extraintestinal complications of Crohn's disease and ulcerative colitis: a study of 700 patients. *Medicine (Baltimore)* 1976; **55**: 401–12.

6 Areias E, Garcia e Silva L. Érythème noueux au cours de la rectocolite hémorrhagique et de la maladie de Crohn. *Ann Dermatol Venereol* 1986; **113**: 197–206.

7 Chapman RS, Forsyth A, MacQueen A. Erythema multiforme in association with active ulcerative colitis and Crohn's disease. *Dermatologica* 1977; **154**: 32–8.

8 Cameron AJ, Baron JH, Priestley BL. Erythema multiforme, drugs and ulcerative colitis. *BMJ* 1966; **ii**: 1174–8.

9 Powell FC, Su WPD, Perry HO. Pyoderma gangrenosum: classification and management. *J Am Acad Dermatol* 1996; **34**: 395–409.

10 Jackson JM, Callen JP. Pyoderma gangrenosum: an expert commentary. *Expert Rev Dermatol* 2006; **1**: 391–400.

11 Basler RSW. Ulcerative colitis and the skin. *Med Clin North Am* 1980; **64**: 941–54.

12 Levitt MD, Ritchie JK, Lennard-Jones JE *et al.* Pyoderma gangrenosum in inflammatory bowel disease. *Br J Surg* 1991; **78**: 676–8.

13 Klein S, Mayer L, Present D *et al.* Extraintestinal manifestations in patients with diverticulitis. *Ann Intern Med* 1988; **108**: 700–2.

14 Lyon CC, Smith AJ, Beck MH *et al*. Parastomal pyoderma gangrenosum: clinical features and management. *J Am Acad Dermatol* 2000; **42**: 992–1002.

15 Powell FC, Perry HO. Pyoderma gangrenosum in childhood. *Arch Dermatol* 1984; **120**: 757–61.

16 Cox NH, Peebles-Brown DA, MacKie RM. Pyoderma gangrenosum occurring ten years after proctocolectomy for ulcerative colitis. *Br J Hosp Med* 1986; **36**: 363.

17 Chow RK, Ho VC. Treatment of pyoderma gangrenosum. *J Am Acad Dermatol* 1996; **34**: 1047–60.

18 Tan MH, Gordon M, Lebwohl O *et al.* Improvement of pyoderma gangrenosum and psoriasis associated with Crohn disease with anti-tumor necrosis factor alpha monoclonal antibody. *Arch Dermatol* 2001; **137**: 930–3.

19 Brooklyn TN, Dunnill MGS, Shetty A *et al*. Infliximab for the treatment of pyoderma gangrenosum: a randomized, double blind, placebo controlled trial. *Gut* 2006; **55**: 505–9.

20 Storwick GS, Prihoda MB, Fulton RJ, Wood WS. Pyodermatitis–pyostomatitis vegetans: a specific marker for inflammatory bowel disease. *J Am Acad Dermatol* 1992; **31**: 336–41.

21 Soriano ML, Martinez N, Grilli R *et al.* Pyodermatitis–pyostomatitis vegetans: report of a case and review of the literature. *Oral Surg Oral Med Oral Pathol* 1999; **87**: 322–6.

22 Cohen PR, Kurzrock R. Sweet's syndrome revisited: a review of disease concepts. *Int J Dermatol* 2003; **42**: 761–78.

23 Travis S, Innes N, Davies MG *et al*. Sweet's syndrome: an unusual cutaneous feature of Crohn's disease or ulcerative colitis. The South West Gastroenterology Group. *Eur J Gastroenterol Hepatol* 1997; **9**: 715–20.

24 Benton EC, Rutherford D, Hunter JAA. Sweet's syndrome and pyoderma gangrenosum associated with ulcerative colitis. *Acta Derm Venereol* 1985; **65**: 77–80.

25 Banet DE, McClave SA, Callen JP. Oral metronidazole, an effective treatment for Sweet's syndrome in a patient with associated inflammatory bowel disease. *J Rheumatol* 1994; **21**: 1766–8.

26 Fain O, Mathieu E, Feton N *et al.* Intestinal involvement in Sweet's syndrome. *J Am Acad Dermatol* 1996; **35**: 989–90.

27 Fenske NA, Gern JE, Pierce D *et al.* Vesicopustular eruption of ulcerative colitis. *Arch Dermatol* 1983; **119**: 664–9.

28 O'Loughlin S, Perry HO. A diffuse pustular eruption associated with ulcerative colitis. *Arch Dermatol* 1978; **114**: 1061–4.

29 Matheson BK, Gilbertson EO, Eichenfield LF. Vesicopustular eruption of Crohn's disease. *Pediatr Dermatol* 1996; **13**: 127–30.

30 Delaney TA, Clay CD, Randell PL. The bowel-associated dermatosis–arthritis syndrome. *Australas J Dermatol* 1989; **30**: 23–7.

31 Buahene K, Hudson M, Mowat A *et al.* Erythema elevatum diutinum: an unusual association with ulcerative colitis. *J Am Acad Dermatol* 1990; **22**: 948–52.

32 Planaguma M, Puig L, Alomar A *et al*. Erythema elevatum diutinum in a patient with Crohn's disease. *Cutis* 1992; **49**: 201–6.

33 Borradori L, Saada V, Rybojad M *et al.* Oral intraepidermal IgA pustulosis and Crohn's disease. *Br J Dermatol* 1992; **126**: 383–6.

34 Wright S, Philipps T, Ryan J, Leigh IM. Intra-epidermal neutrophilic IgA dermatosis with colitis. *Br J Dermatol* 1989; **120**: 113–9.

35 André M, Aumaître O, Papo T *et al*. Disseminated aseptic abscesses associated with Crohn's disease: a new entity? *Dig Dis Sci* 1998; **43**: 420–8.

36 André MFJ, Piette JC, Kémény JL *et al*. Aseptic abscesses: a study of 30m patients with or without inflammatory bowel disease and review of the literature. *Medicine (Baltimore)* 2007; **86**: 145–61.

37 Callen JP. Severe cutaneous vasculitis complicating ulcerative colitis. *Arch Dermatol* 1979; **115**: 226–7.

38 Saulsbury FT, Hart MH. Crohn's disease presenting with Henoch–Schönlein purpura. *J Pediatr Gastroenterol Nutr* 2000; **31**: 173–5.

39 Castanet J, Lacour JP, Perrin C *et al.* Cutaneous vasculitis with lesions mimicking Degos' disease and revealing Crohn's disease. *Acta Derm Venereol* 1995; **75**: 408–9.

40 Galperin C, Gershwin ME. Immunopathogenesis of gastrointestinal and hepatobiliary diseases. *JAMA* 1997; **278**: 1946–55.

41 Bargen JA, Barker NW. Extensive arterial and venous thrombosis complicating chronic ulcerative colitis. *Arch Intern Med* 1936; **58**: 17–31.

42 Stapleton SR, Curley RK, Simpson WA. Cutaneous gangrene secondary to focal thrombosis: an important cutaneous manifestation of ulcerative colitis. *Clin Exp Dermatol* 1989; **14**: 387–9.

43 Jackson LM, O'Gorman PJ, O'Connell J *et al*. Thrombosis in inflammatory bowel disease: clinical setting, procoagulant profile and Factor V Leiden. *QJM* 1997: **90**: 183–8.

44 Paige DG, Leonard JN, Wojnarowska F, Fry L. Linear IgA disease and ulcerative colitis. *Br J Dermatol* 1997; **134**: 779–82.

45 Walker SL, Banerjee P, Harland CC, Black MM. Remission of linear IgA disease associated with ulcerative colitis following panproctocolectomy. *Br J Dermatol* 2000; **143**: 1341–2.

46 Cowan CG, Lamey PJ, Walsh M *et al*. Linear IgA disease (LAD): immunoglobulin deposition in oral and colonic lesions. *J Oral Pathol Med* 1995; **24**: 374–8.
47 Barberis C, Doutre MS, Bioulac-Sage P. Linear IgA bullous dermatosis associated with Crohn's disease. *Gastroenterol Clin Biol* 1988; **12**: 76–7.
48 España A, Sitaru C, Pretel M *et al*. Erythema gyratum repens-like eruption in a patient with epidermolysis bullosa acquisita associated with ulcerative colitis. *Br J Dermatol* 2007; **156**: 773–5.
49 Sherman A, Genuth L, Hazzi CG *et al*. Perirectal abscess in the Hermansky–Pudlak syndrome. *Am J Gastroenterol* 1989; **84**: 552–6.
50 Cox NH, McCrea J. The association of Sjögren's syndrome, sarcoidosis, ulcerative colitis and other autoimmune disorders. *Br J Dermatol* 1996; **134**: 1138–40.
51 Porter WM, Hardman CM, Leonard JN, Fry L. Sarcoidosis in a patient with linear IgA disease. *Clin Exp Dermatol* 1999; **24**: 67–70.
52 Kitis G, Thompson H, Allan RN. Finger clubbing in inflammatory bowel disease, its prevalence and pathogenesis. *BMJ* 1979; **2**: 825–8.
53 Tosti A, Baran R, Dawber RPR. The nail in systemic diseases and drug-induced changes. In: Baran R, Dawber RPR, deBerker DAR, Haneke E, Tosti A, eds. *Diseases of the Nails and Their Management*. Oxford: Blackwell Science, 2001: 223–329.
54 McAuley D, Miller RA. Acne fulminans with inflammatory bowel disease. *Arch Dermatol* 1985; **121**: 91–3.

Collagenous colitis

This, with lymphocytic colitis, is a type of microscopic colitis characterized clinically by diarrhoea and histologically by a thickened subepithelial collagen layer. Cases have been described that have evolved to, or from, ulcerative colitis; it has also been reported to have evolved to Crohn's disease and, of dermatological relevance, to have coexisted with systemic sclerosis and to have possibly been triggered by isotretinoin. There are now several reports of associated pyoderma gangrenosum [1,2], including peristomal and vulval involvement; lymphocytic venulitis of adjacent bowel, but not of the skin, has also been reported.

References

1 Davis MDP, Nakamura KJH. Peristomal pyoderma gangrenosum associated with collagenous colitis. *Arch Dermatol* 2007; **143**: 669–70.
2 Koch D, Sinha A, Greenaway JR, Carmichael AJ. Pyoderma gangrenosum associated with collagenous colitis. *Clin Exper Dermatol* 2007; **32**: 329–31.

Bowel-associated dermatosis–arthritis syndrome [1–6]

Synonyms
- Blind loop syndrome
- Bowel bypass syndrome
- Intestinal bypass arthritis–dermatitis syndrome

This is a serum sickness-like illness which is related to bacterial overgrowth in the bowel. Bacterial antigens in the form of peptidoglycans are probably released from the intestinal flora, particularly *Escherichia coli* [2]. Circulating immune complexes can be demonstrated in most patients actively developing skin lesions [3].

It was originally linked with bowel bypass surgery for obesity [1–4], which created a 'blind loop' of bowel. Most cases now are related to other causes of a blind loop, or simply to areas of stasis, and the condition has attracted the name 'bowel bypass syndrome without bowel bypass' [6]. Causes include achalasia [7], strictures and inflammatory bowel disease [5], as well as surgical procedures that create a defunctioning segment of bowel [8]. Pyoderma gangrenosum secondary to diverticular disease [9] is probably in the same spectrum of disease.

The characteristic skin lesions are crops of erythematous papules, sterile vesicopustules similar to those associated with ulcerative colitis, or overtly indurated or necrotic vasculitic lesions. Erythema nodosum-like and panniculitis-like lesions may occur. Associated constitutional symptoms include fever, polyarthritis, tenosynovitis, myalgia and nephritis. Raynaud's phenomenon has been described, as has Sweet's syndrome. The joint involvement is variable and similar to the type of arthritis recognized in regional ileitis and ulcerative colitis. The bypass enteropathy may manifest itself as acute massive abdominal distension resembling intestinal obstruction, but milder and chronic forms have been described.

Histological examination shows dilated dermal venules and capillaries with a marked perivascular neutrophilic infiltrate. This is most pronounced in vesicopustular lesions, in which the resulting dermal oedema may lead to dermal–epidermal separation. Epidermal necrosis may be found. Treatments include oral corticosteroids, antibiotics such as metronidazole, a variety of immunosuppressive medications and restorative surgery.

References

1 Dicken CH, Seehafer JR. Bowel bypass syndrome. *Arch Dermatol* 1979; **115**: 837–9.
2 Ely PH. The bowel bypass syndrome: a response to bacterial peptidoglycans. *J Am Acad Dermatol* 1980; **2**: 473–87.
3 Kennedy C. The spectrum of inflammatory skin disease following jejuno-ileal bypass for morbid obesity. *Br J Dermatol* 1981; **105**: 425–36.
4 Simon S, Sikka JV, Lynfield YL. Bowel bypass syndrome. *Cutis* 1981; **28**: 545–7.
5 Delaney TA, Clay CD, Randell PL. The bowel-associated dermatosis–arthritis syndrome. *Australas J Dermatol* 1989; **30**: 23–7.
6 Jorizzo JL, Apisarnthanarax P, Subrt P *et al*. Bowel bypass syndrome without bowel bypass: bowel associated dermatosis–arthritis syndrome. *Arch Intern Med* 1983; **143**: 457–61.
7 Tucker SC, Chalmers RJG, Andrew SM, Odom NJ. Pustular vasculitis secondary to achalasia of the cardia. *Br J Dermatol* 2000; **142**: 373–4.
8 Cox NH, Palmer JG. Bowel-associated dermatitis-arthritis syndrome associated with ileo-anal pouch anastamosis, and treatment with mycophenolate mofetil. *Br J Dermatol* 2003; **149**: 1296–7.
9 Klein S, Mayer L, Present D *et al*. Extraintestinal manifestations in patients with diverticulitis. *Ann Intern Med* 1988; **108**: 700–2.

Skin complications of stomas [1,2]

Dermatoses associated with a stoma include those related to its function (irritation from faecal leakage, infections, contact dermatitis), Koebner reaction of existing or new dermatoses (psoriasis, lichen sclerosus) and disorders related to bowel disease (peristomal pyoderma gangrenosum, cutaneous Crohn's disease) [1,2].

The skin around a gastrointestinal or urinary tract stoma is liable to irritation from the effluent, the wafer and pouch, and substances applied as barriers, adhesives and cleaners. The collection pouch is either attached to a wafer or directly to the skin; a barrier/sealant may be applied before adhesion. The sealant is either a gelatine–pectin formulation, karaya (a hygroscopic partially acetylated polysaccharide), or a flexible plastic, applied in liquid form. The adhesives are usually acrylic, silicone or latex. Ideally, the wafer should adhere perfectly to the skin, with a rim of skin 1–2 mm between the stoma and the appliance. If this rim is too narrow, chafing against the stomal mucosa will occur, and if it is too wide there is a higher risk of dermatitis. Any surface

irregularities beneath the attachment surface will allow effluent to track beneath. This may occur if there are changes in body weight, or if there is incorrect or unavoidable siting of the stoma in body folds or adjacent to scars.

Enzyme-degradation dermatitis, caused by proteolytic enzymes in an alkaline fluid medium, is commonest with ileostomies [3], and presents with maceration, erythema and erosions. Because of the tracking of the fluid downwards, the pattern of dermatitis depends on the patient's predominant position. Diversion of the urinary stream also causes problems because of stagnation and ammonia production.

Treatment. Most peristomal skin disease is irritant and is treated by judicious use of topical corticosteroids together with soothing and barrier preparations. Infections such as *Candida* or pyogenic bacterial infection should be treated with an appropriate specific antimicrobial agent. Many types of protective wafer and protective powders are available. These contain gelatine, pectin, polyisobutylene and sodium carboxy-methylcellulose. They adhere to moist skin and allow healing to take place if they are left for about 3 days. Creases and crevices around a stoma or fistula can be filled using pastes, which generally consist of gelatine, sodium carboxy-methylcellulose, triacetin, fixin and ethanol. They are applied in layers, moulded into the creases with a moist finger and built up to the required level. If the drainage application can then remain in position for several days, this will usually allow the damaged skin to heal. Other topical treatments for irritant peristomal dermatoses include soothing compresses (for example, saline or 1:40 aluminium acetate), karaya and sucralfate [3]. In the case of very painful conditions such as pyoderma gangrenosum, instillation of a suitable topical local anaesthetic under the appliance 40–60 min before changing it can make a great difference to patient comfort.

Allergic contact dermatitis can occur to the adhesive [4], the barrier or any part of the appliance. Epoxy resins have been a problem in pouch materials, even though they are often present in small amounts only [5]. It has been suggested that patch testing should be carried out on the symmetrically opposite part of the abdomen [1]. It is usually possible to provide substitutes for materials causing the allergic reaction.

Urostomy encrustations and acanthotic chronic papillomatous dermatitis (pseudoverrucous lesions). The encrustations are crystals of phosphates and sometimes uric acid that form on the stoma and can damage the mucosa and even the bag. Pseudoverrucous lesions are grey or reddish-brown, warty papules at the mucocutaneous junction. They are more common around urostomies than around gastrointestinal stomas, occurring in about 20% of urostomy patients. There may be a non-specific erythematous and erosive change [6]. Stagnation and urinary infection are important in the aetiology of both encrustations and pseudoverrucous lesions and, as well as treating infection, acidification of the urine is helpful—for example, with cranberry juice or vitamin C in large doses [1]. Peristomal viral warts are a particular differential-diagnostic problem.

Parastomal fistulae and ulcers [7]. These are particularly associated with ileostomy for Crohn's disease and may represent or herald recurrent disease. Fistulae are often preceded by abscesses, and may be multiple. The parastomal ulcer is defined as a defect in the surface 1.5 cm or more across. It is typically accompanied by severe burning pain and erythema, and often associated with induration and erythema of the stoma [8]. Low-grade infection should be considered as a possible cause in parastomal ulcers that occur early after formation of the stoma, but in late-appearing ulcers, recurrent Crohn's disease is probably the most important underlying cause. Treatment of both parastomal ulcers and fistulae is usually surgical.

Dermatoses. Psoriasis and pemphigus have been described as a result of the Koebner reaction around 'ostomies' [9], and pyoderma gangrenosum can localize to the peristomal skin after colectomy for inflammatory bowel disease [10,11], and much less commonly in relation to urostomies. A papular, erythematous condition similar to granuloma inguinale infantum has been described following intensive use of a potent fluorinated steroid around a colostomy site [12].

Neoplasms. Basal cell carcinoma has been described as a long-term complication of colostomy [13]. Metastatic carcinoma at the stoma site, sometimes invading the surrounding skin, has been reported following ureterosigmoidostomy [14] and in patients who have had colectomy for ulcerative colitis [15–18].

References

1 Rothstein MS. Dermatologic considerations to stoma care. *J Am Acad Dermatol* 1986; **15**: 411–32.
2 Lyon CC, Smith AJ, Griffiths CEM, Beck MH. The spectrum of skin disorders in abdominal stoma patients. *Br J Dermatol* 2000; **143**: 1248–60.
3 Lyon CC, Stapleton M, Smith AJ *et al*. Topical sucralfate in the management of peristomal skin disease: an open study. *Clin Exp Dermatol* 2000; **25**: 584–8.
4 Bergman B, Lowhagen GB, Mobacken H. Irritant skin reactions to urostomal adhesives. *Urol Res* 1982; **10**: 153–5.
5 Beck MH, Burrows D, Fregert S *et al*. Allergic contact dermatitis to epoxy resin in colostomy bags. *Br J Surg* 1985; **72**: 202–3.
6 Borglund E, Nordström G, Nyman CR. Classification of peristomal skin changes in patients with urostomy. *J Am Acad Dermatol* 1988; **19**: 623–32.
7 Greenstein AJ, Dicker A, Meyer S *et al*. Peri-ileostomy fistulae in Crohn's disease. *Ann Surg* 1982; **197**: 179–82.
8 Last M, Fazio V, Lavery I *et al*. Conservative management of paraileostomy ulcers in patients with Crohn's disease. *Dis Colon Rectum* 1984; **27**: 779–86.
9 Rodriguez DB. Treatment for three ostomy patients with systemic skin disorders. *J Enterostom Ther* 1981; **8**: 31–2.
10 McGavity WC, Robertson DB, McKeown PP. Pyoderma gangrenosum at the parastomal site in patients with Crohn's disease. *Arch Surg* 1984; **119**: 1186–8.
11 Lyon CC, Smith AJ, Beck MH *et al*. Parastomal pyoderma gangrenosum: clinical features and management. *J Am Acad Dermatol* 2000; **42**: 992–1002.
12 Hjorth N, Sjolin K. Multiple inflammatory acanthomas around a colostomy. *J Cutan Pathol* 1981; **8**: 361–4.
13 Didolkar MS, Douglass HO, Holyoke ED. Basal cell carcinoma originating at the colostomy site. *Dis Colon Rectum* 1975; **18**: 399–402.
14 Carswell JJ, Skeel DA, Witherington R. Neoplasia at the site of ureterosigmoidostomy. *J Urol* 1976; **115**: 750–2.
15 Baciewicz K, Sparberg M, Lawrence JB *et al*. Adenocarcinoma of an ileostomy site with skin invasion. *Gastroenterology* 1983; **84**: 168–70.
16 Cuesta MA, Donner R. Adenocarcinoma arising at an ileostomy site. *Cancer* 1976; **37**: 949–52.
17 Johnson WR, McDermott FT, Pihl E. Adenocarcinoma of an ileostomy in a patient with ulcerative colitis. *Dis Colon Rectum* 1980; **23**: 351–2.
18 Morgan MN. Carcinoma in a caecostomy in longstanding ulcerative colitis. *Proc R Soc Med* 1966; **59**: 427.

Coeliac disease [1]

Coeliac disease usually presents with malabsorption and diarrhoea. The pathogenesis is discussed in detail elsewhere [1,2]; a digestion-resistant peptide in gliadin (mer-33) may be the initiator of the disease [3].

There are associations with numerous other autoimmune diseases, notably type 1 diabetes and thyroid disease [1], and strong HLA associations; 95% of patients have the HLA-DQ(α1*501,β1*02) heterodimer (HLA-DQ2) and almost all the remainder have HLA DQ8. A significant increase in the frequency of coeliac disease in patients with inflammatory bowel disease has been suggested recently, and it has been reported following interferon treatment for hepatitis C and other disorders [4].

Diagnosis of coeliac disease can be made by serological tests for IgA antiendomysial antibodies (sensitivity is 85–98% and specificity 97–100%) or IgA tissue transglutaminase (sensitivity 91–95% and negative predictive value nearly 100%) [1,2]. Tissue transglutaminase acts as an autoantigen—it deaminates glutamine residues in gliadin to create negatively charged glutamic acid residues that activate T cells. IgA antigliadin antibodies are less specific but are useful in younger children. Antigliadin, antiendomysial and tissue transglutaminase antibody levels all become undetectable after a period of 3–6 months on a strict gluten-free diet (GFD). Other tests include documentation of malabsorption and small-bowel biopsy.

Dermatological features of coeliac disease include cutaneous features of malabsorption of nutrients (Chapter 59), and features of associated autoimmune conditions. Darkening of previously white hair has been reported after starting GFD to treat coeliac disease [5]. Other documented dermatological features include follicular keratosis and alopecia. The most important dermatological association is with dermatitis herpetiformis (DH) which occurs in 25% of subjects (Chapter 40); the enteropathy of DH seems to be the same as that of coeliac disease, and some degree of abnormality of small-bowel mucosa is present, even if minimal and asymptomatic, in all patients with DH. However, it is unclear why DH only occurs in some subjects, often with mild enteropathy; there may be factors that alter disease expression. A recent study showed a significant linkage of coeliac disease chromosome 19p13, but investigation of a candidate gene, myosin IXB, showed no association with coeliac disease but a weak association with DH. The precise genetic aspects of coeliac disease and DH may therefore not be identical [6]. There is an association between DH and internal malignancies, the most important being lymphoma of the small bowel (enteropathy-associated lymphoma) [7,8], as in coeliac disease. GFD exerts a protective effect [8].

Improvement of psoriasis in a small number of patients who were treated with GFD suggested the possibility that coeliac disease and psoriasis might be associated. Patients with psoriasis have a high frequency of positive IgA antigliadin antibodies, which correlate with lymphocytic infiltration of the duodenal mucosa, but do not have an increased incidence of coeliac disease, and there is no increase in either antireticulin or antiendomysial antibodies [9,10].

Vasculitis, sometimes with cryoglobulinaemia, may occur in association with coeliac disease [11].

References

1 Farrell RJ, Kelly CP. Celiac sprue. *N Engl J Med* 2002; **346**: 180–8.
2 Hopper A, Hadjivassiliou M, Butt S, Sanders S. Adult celiac disease. *BMJ* 2007; **335**: 558–62.
3 McManus R, Kelleher D. Celiac disease—the villain unmasked? *N Engl J Med* 2003; **348**: 2573–4.
4 Bardella MT, Marino R, Meroni PL. Celiac disease during interferon treatment. *Ann Intern Med* 1999; **131**: 157–8.
5 Hill LS. Reversal of premature hair greying in adult coeliac disease. *BMJ* 1980; **281**: 115.
6 Koskinen LL, Korponay-Szabo IR, Viiri K *et al.* Myosin IXB gene region and gluten intolerance: linkage to coeliac disease and a putative dermatitis herpetiformis association. *J Med Genet* 2008; **45**: 222–7.
7 Renaula TL, Leonard JN. Malignant disease in dermatitis herpetiformis. *Clin Dermatol* 1991; **9**: 369–73.
8 Lewis HM, Renaula TL, Garioch JJ *et al.* Protective effect of gluten-free diet against lymphoma in dermatitis herpetiformis. *Br J Dermatol* 1996; **135**: 363–7.
9 Michaelsson G, Gerden B, Ottosson M *et al.* Patients with psoriasis often have increased serum levels of IgA antibodies to gliadin. *Br J Dermatol* 1993; **129**: 667–73.
10 Michaelsson G, Kraaz W, Gerden B *et al.* Increased lymphocyte infiltration in duodenal mucosa from patients with psoriasis and serum IgA antibodies to gliadin. *Br J Dermatol* 1995; **133**: 896–904.
11 Lie JT. Vasculitis and the gut: unwitting partners or strange bedfellows? *J Rheumatol* 1991; **18**: 647–8.

Whipple's disease

This disorder, another cause of malabsorption and diarrhoea, may be accompanied by skin manifestations. Diffuse pigmentation is frequent, and may resemble Addison's disease, but buccal pigmentation is not a feature. Subcutaneous nodules may occur, resembling rheumatoid nodules or sarcoidosis [1–3]. The disorder usually presents with arthralgia and general malaise; abdominal features (pain, diarrhoea and malabsorption leading to weight loss) occur in most individuals with more advanced disease. Cardiac, pleural, ophthalmological or neurological symptoms also occur, and there may be generalized lymphadenopathy. The diagnosis has historically been confirmed by demonstration of periodic acid–Schiff-positive particles in biopsies from infected tissue (usually bowel mucosa). The diagnosis can now be made using polymerase chain reaction (PCR) amplification of sequences from the causative organism, *Tropheryma whippelii*, in infected tissue [4,5] and the organism has been cultured [6].

References

1 Durand DV, Lecomte C, Cathebras P *et al*. Whipple disease: clinical review of 52 cases. The SNFMI Research Group on Whipple disease. *Medicine* 1997; **76**: 170–84.
2 Ratnaike RN. Whipple's disease. *Postgrad Med J* 2000; **76**: 760–6.
3 Frenk E, Merot Y, Perez I *et al*. Whipple's disease with sarcoidosis-like cutaneous manifestations. *Ann Dermatol Venereol* 1991; **118**: 115–8.
4 Misbah SA, Mapstone MP. Whipple's disease revisited. *J Clin Pathol* 2000; **53**: 750–5.
5 Dutly F, Altwegg M. Whipple's disease and '*Tropheryma whippelii*'. *Clin Microbiol Rev* 2001; **14**: 561–83.
6 Raoult D, Birg ML, La Scola B *et al*. Cultivation of the bacillus of Whipple's disease. *N Engl J Med* 2000; **342**: 620–5.

Skin disorders associated with gastrointestinal bleeding

These are listed in Table 62.12. Most are discussed elsewhere in this section, or in other chapters. In addition, gastrointestinal tumours may metastasize to skin (see earlier in this chapter), some

Table 62.12 Skin lesions associated with gastrointestinal disorders that may present with bleeding.

Disease	Gastrointestinal lesion	Skin symptom
Vascular defects and inherited		
Osler–Weber–Rendu disease (Chapter 47)	Telangiectasia	Telangiectasia
Blue rubber bleb naevus (Chapter 18)	Haemangiomas	Haemangiomas
Pseudoxanthoma elasticum (Chapter 45)	Involvement of visceral arteries	Yellowish papules and plaques
Ehlers–Danlos syndrome (type IV) (Chapter 45)	Fragility of visceral arteries	Hyperelasticity of skin and joints
Polyposis (see text in this chapter)		
Neurofibromatosis (von Recklinghausen)	Neurofibromas	Café-au-lait spots, neurofibromas
Cronkhite–Canada syndrome	Gastrointestinal polyposis	Diffuse hyperpigmentation, alopecia, nail defects
Gardner's syndrome	Polyposis of colon (cancer)	Lipomas, epidermoid cysts
Peutz–Jeghers syndrome	Polyposis, especially small intestine	Hyperpigmentation on lips, circumoral area and fingertips
Cowden's disease	Polyposis	Papules, lipomas, angiomas
Inflammatory bowel disease		
Crohn's disease, ulcerative colitis	Inflammatory changes of the intestinal wall	Erythema nodosum Aphthous stomatitis Pyoderma gangrenosum, other neutrophilic dermatoses Necrotizing vasculitis Epidermolysis bullosa acquisita Erythema multiforme
Vasculitis and systemic disease		
Henoch–Schönlein purpura and other vasculitides (Chapter 50)	Mesenteric vasculitis, gastric ulcers (polyarteritis nodosa)	Purpura, livedo, nodules, necrosis
Cholesterol emboli (Chapter 49)	Intestinal arterial occlusion	Vasculitis, necrosis, livedo
Degos' disease (Chapter 49)	Intestinal perforation	White atrophic lesions
Amyloidosis (Chapter 59)	Vascular fragility	Purpuric lesions
Neoplasia		
Primary gastrointestinal cancers	Neoplasm	Metastases, paraneoplastic eruptions, features of polyposis syndromes
Kaposi's sarcoma (Chapter 35)	Kaposi's sarcoma of bowel	Kaposi's sarcoma of skin

tumours may affect the skin and gastrointestinal tract (e.g. Kaposi's sarcoma), and skin tumours may rarely metastasize to the gastrointestinal tract (e.g. melanoma).

Several patterns of cutaneous vasculitis or collagen vascular disease may be associated with mesenteric vasculitis and/or thrombosis, leading to bleeding or ulceration. Various radiological signs of mesenteric vasculitis seen on computed tomography (CT) have been reviewed in relation to systemic lupus erythematosus, and include a palisade and comb-like pattern of vessels, peritoneal enhancement of ascitic fluid, thickening of the bowel wall, and a 'double-halo' or 'target sign' [1,2].

References

1 Hallegua DA, Wallace DJ. Gastrointestinal manifestations of systemic lupus erythematosus. *Curr Opin Rheumatol* 2000; **12**: 379–85.

2 Ko SF, Lee TY, Cheng TT *et al.* CT findings at lupus mesenteric vasculitis. *Acta Radiol* 1997; **38**: 115–20.

Intestinal polyposis [1,2]

A number of, usually inherited, gastrointestinal polyposis disorders also have cutaneous features. The most important are:

- Peutz–Jeghers syndrome
- Gardner's syndrome
- Cowden's disease (multiple hamartoma and neoplasia syndrome, p. 62.25)
- Bannayan–Riley–Ruvalcaba syndrome (Ruvalcaba–Myhre–Smith syndrome, Bannayan–Zonana syndrome)
- Cronkhite–Canada syndrome (non-inherited)
- Birt–Hogg–Dubé syndrome
- Naevoid basal cell carcinoma syndrome (p. 62.21) [3]
- Neurofibromatosis (Chapter 15).

Additionally, ganglioneuromas of the gastrointestinal tract and oral mucosal neuromas may be associated with Hirschsprung's disease, and colonic diverticula as features of MEN type 2B syndrome.

Peutz–Jeghers syndrome (MIM #175200) [4]. This is an autosomal-dominant or sporadic condition due to mutations in the serine/threonine kinase *STK11* (*LKB1*) gene on chromosome 19p13.3 [5–7]. This appears to be a tumour suppressor gene—loss of heterozygosity at this site has been shown to be associated with malignant transformation of polyps. Polyps occur mainly in the small intestine, but also in the stomach and colon. The usual presentation is with intussusception or melaena. Polyps can also be found in the genitourinary and respiratory tracts, and occasionally in the gallbladder.

The cutaneous feature is lentiginosis, with a predominantly perioral, periorbital and intraoral distribution; perianal and acral lentiginosis (occasionally causing longitudinal melanonychia) also occurs. The pigmented macules appear in early childhood and may fade with increasing age, although the mucosal lesions persist [4]. The pigmented lip lesions may be confused with those of Laugier–Hunziker syndrome (a benign, non-polyposis, disorder with onset in later years).

Cancers may occur in the gastrointestinal tract, but the frequency is relatively low, as the polyps are hamartomatous; additional mutations of the β-catenin gene or the p53 gene appear to be needed to convert them into adenomas or carcinomas. However, there is an increased risk of non-gastrointestinal cancers, with an overall risk estimated at 18-fold greater than that of the general population [8]. Other associated neoplasias include pancreatic adenocarcinoma (100-fold more common than expected [8]), and less commonly breast and pulmonary adenocarcinoma. Multiple myeloma may occur more frequently than expected. Precocious puberty may occur in either sex, and a variety of genital cancers have been associated with Peutz–Jeghers syndrome, including Sertoli cell tumours; there is a particular link with multifocal sex-cord tumours and an aggressive variant of adenocarcinoma of the cervix [1]. Finger clubbing may occur in conjunction with the ovarian sex-cord tumours.

Gardner's syndrome (MIM +175100) [6,7,9]. This condition is allelic with adenomatous polyposis of the colon. Both are caused by mutations in the *APC* gene, which has an important role as part of a signalling pathway involving β-catenin and E-cadherin, thereby influencing cell division, migration, adhesion and apoptosis; the wild-type gene also antagonizes a tumour suppressor gene *WNT1*. There is very high penetrance but marked variation in expression.

The syndrome is the association of adenomatous colonic polyposis with large numbers of subcutaneous fibromas, epidermoid cysts (both mainly on the upper trunk and head), desmoid tumours (mainly abdominal wall), retinal pigmentary changes, osteomas (especially of the facial bones), odontomas and other dental abnormalities, including supernumerary teeth [9]. The onset of cysts is generally prepubertal. Multiple pilomatricomas, or pilomatricoma-like areas within the epidermoid cysts, have also been recorded. The occurrence of fibromas may involve a general tendency to fibromatosis, including desmoid tumours, mesenteric and retroperitoneal fibrosis. Nuchal-type fibromas [10], especially if multiple or at unusual sites [11], may be an early sign of the syndrome. Leiomyomas, lipomas, neurofibromas and BCCs may also occur [9].

It is an autosomal dominant condition with variable expression, and is caused by mutations in the same APC gene on chromosome 5q21 that also causes familial polyposis coli without associated cutaneous abnormalities [1,6,7]. The phenotype is not simply determined by different mutations of the gene, as exactly the same mutation may on occasions give rise to a phenotype with or without skin lesions—suggesting that other genes influence the disease expression. There are also subsets of this condition in which skin lesions may be limited in type; for example, epidermoid cysts and colonic polyposis without the other features has been termed Oldfield's syndrome [12]. Skin lesions are usually the earliest manifestation of this group of diseases, although the retinal pigmented lesions (hypertrophy of the pigment epithelium) occur in 90% and are probably congenital. The latter are dark, roughly oval-shaped lesions, at the periphery of the retina; they are generally multiple, bilateral, and also occur in first-degree relatives [13].

The bowel polyps are premalignant, and virtually all untreated cases will eventually develop colonic cancer, even in childhood occasionally, so regular colonoscopy and early colectomy is advised for affected individuals. The colon and rectum are the main cancer sites, but gastric and small-bowel polyps may occur. There is also an increased incidence of other neoplasia, which may be gastrointestinal (especially duodenal), bony (osteosarcoma and chondrosarcoma), hepatic (hepatoblastoma), neurological (medulloblastoma), endocrine (thyroid and adrenal) or soft tissue (liposarcoma) [8]. The diagnosis is usually suspected from the family history, can be supported by funduscopy and dental radiological studies and is confirmed by genetic testing.

Cowden's disease (multiple hamartoma and neoplasia syndrome; MIM #158350) [1,2,14–17]. Gastrointestinal polyposis and less commonly malignant change occur. However, the main neoplastic condition in Cowden's disease is breast cancer, and numerous other sites of cancer may be associated; this condition is therefore discussed in more detail in the section on genodermatoses associated with neoplasia (p. 62.25). A Cowden-like syndrome has also been reported in which the mutation is in the *BMPR1A* gene rather than in *PTEN1* as in Cowden's syndrome.

Bannayan–Riley–Ruvalcaba syndrome (Ruvalcaba–Myhre–Smith syndrome; Bannayan–Zonana syndrome, MIM #153480). This multiply named syndrome comprises gastrointestinal polyposis with vascular malformations, lipomas, penile café-au-lait spots, macrocephaly and thyroid disease. There is considerable overlap with Cowden's disease; both conditions involve mutations in *PTEN1* [18,19], and it has been suggested that they may be best grouped together as the *PTEN* hamartoma tumour syndrome.

Birt–Hogg–Dubé syndrome (Hornstein–Knickenberg syndrome; MIM #135150) [20–22]. These two conditions probably represent the same entity, in which there is autosomal-dominant inheritance. The gene locus is on chromosome 17p11.2, coding a presumed tumour suppressor 64-kDa protein, folliculin. Birt–Hogg–Dubé syndrome consists of multiple fibrofolliculomas, trichodiscomas and acrochordons; several cases have also had intestinal polyposis. Hornstein–Knickenberg syndrome is the association of perifollicular fibromas with intestinal polyposis. Lipomas (which may be large), angiolipomas, oral fibromas, parathyroid adenomas, renal tumours (especially oncocytomas), lung cysts and flecked choroidoretinopathy have also been linked with these conditions. Individual cases with meningioma and neurothekeoma have also been described. The odds ratio of renal tumours has been calculated at 6.9, and of pneumothorax (due to the lung cysts) at 50.3 [23].

Cronkhite–Canada syndrome (MIM 175500) [24–26]. This rare syndrome is characterized by skin pigmentation, alopecia,

nail-plate defects and polyposis of the gastrointestinal tract, from oesophagus to anus. The cause is unknown, and only sporadic cases have been reported. Affected patients are middle-aged or elderly, with a male/female incidence ratio of 3:2.

Chronic diarrhoea due to protein-losing enteropathy associated with the intestinal polyposis is the usual presenting feature, leading to hypoalbuminaemia, hypokalaemia and hypocalcaemia. There is diffuse macular pigmentation of the skin (but not intraorally) with accentuation over the face, neck and extremities; histologically, there is an increased number of melanin granules in keratinocytes and an increased number of melanosomes in melanocytes, with marked hyperkeratosis and a perivascular inflammatory infiltrate in the dermis. The palms and volar aspects of the fingers are also involved. The scalp hair becomes thin and sparse, initially resembling alopecia areata; later, total loss of hair occurs. All fingernails and toenails are dystrophic, undergoing onycholysis, onychoschizia and onychomadesis with a peculiar, triangular, residual nail plate. The course is usually slowly progressive; therapy is symptomatic and non-specific.

Acrochordons (fibroepithelial polyps, 'skin tags'). Several studies have suggested a link between acrochordons and colonic polyposis [1,2]. However, most of these studies were either small or examined only a population who were being investigated for bowel disease. A meta-analysis that divided patients into those with colonic symptoms and those who were asymptomatic demonstrated that the association was only sustained in the former group, and that this was therefore an artefact of patient selection [27].

References

1 Braverman IM. *Skin Signs of Systemic Disease*, 3rd edn. Philadelphia: Saunders, 1998: 58–60, 405–8.
2 Gregory B, Ho VC. Cutaneous manifestations of gastrointestinal disorders, 1. *J Am Acad Dermatol* 1992; **26**: 153–66.
3 Schwartz RA. Basal-cell-nevus syndrome and gastrointestinal polyposis. *N Engl J Med* 1978; **299**: 49.
4 Kitigawa S, Townsend BL, Hebert AA. Peutz–Jeghers syndrome. *Dermatol Clin* 1995; **13**: 127–33.
5 Stratakis CA. Clinical genetics of multiple endocrine neoplasias, Carney complex and related syndromes. *J Endocrinol Invest* 2001; **24**: 370–83.
6 Tsao H. Update on familial cancer syndromes and the skin. *J Am Acad Dermatol* 2000; **42**: 939–69.
7 Wirtzfeld DA, Petrelli NJ, Rodriguez-Bigas MA. Hamartomatous polyposis syndromes: molecular genetics, neoplastic risk, and surveillance recommendations. *Ann Surg Oncol* 2001; **8**: 319–27.
8 Giardiello FM, Welsh SB, Hamilton SR *et al.* Increased risk of cancer in the Peutz–Jeghers syndrome. *N Engl J Med* 1987; **316**: 1511–4.
9 Perniciaro C. Gardner's syndrome. *Dermatol Clin* 1995; **13**: 51–6.
10 Michal M, Fetsch JF, Hes O, Miettinen M. Nuchal-type fibroma: a clinicopathologic study of 52 cases. *Cancer* 1999; **85**: 156–63.
11 Wehrli BM, Weiss SW, Yandow S, Coffin CM. Gardner-associated fibromas (GAF) in young patients: a distinct fibrous lesion that identifies unsuspected Gardner syndrome and risk for fibromatosis. *Am J Surg Pathol* 2001; **25**: 645–51.
12 Oldfield MC. Association of familial polyposis of colon with multiple sebaceous cysts. *Br J Surg* 1954; **41**: 534.
13 Traboulsi EI, Krush AJ, Gardner EJ *et al.* Prevalence and importance of pigmented ocular fundus lesions in Gardner's syndrome. *N Engl J Med* 1987; **316**: 661–7.
14 Salem OS, Steck WD. Cowden's disease (multiple hamartoma and neoplasia syndrome): a case report and review of the English literature. *J Am Acad Dermatol* 1983; **8**: 686–96.
15 Mallory SB. Cowden syndrome (multiple hamartoma syndrome). *Dermatol Clin* 1995; **13**: 27–31.
16 Starink TM, van der Veen JPW, Arwet F *et al.* The Cowden syndrome: a clinical and genetic study in 21 patients. *Clin Genet* 1986; **29**: 222–33.
17 Eng C. Will the real Cowden syndrome please stand up: revised diagnostic criteria. *J Med Genet* 2000; **37**: 828–30.
18 Marsh DJ, Kum JB, Lunetta KL *et al.* PTEN mutation spectrum and genotype–phenotype correlations in Bannayan–Riley–Ruvalcaba syndrome suggest a single entity with Cowden syndrome. *Hum Mol Genet* 1999; **8**: 1461–72.
19 Zhou XP, Woodford-Richens K, Lehtonen R *et al.* Germline mutations in *BMPR1A/ALK3* cause a subset of cases of juvenile polyposis syndrome and of Cowden and Bannayan–Riley–Ruvalcaba syndromes. *Am J Hum Genet* 2001; **69**: 704–11.
20 Rongioletti F, Hazini R, Gianotti G, Rebora A. Folliculomas, trichodiscomas and acrochordons (Birt–Hogg–Dubé) associated with intestinal polyposis. *Clin Exp Dermatol* 1989; **14**: 72–4.
21 Schachtschabel AA, Kuster W, Happle R. Perifollicular fibroma of the skin and colonic polyps: Hornstein–Knickenberg syndrome. *Hautarzt* 1996; **47**: 304–6.
22 Hornstein OP, Knickenberg M. Perifollicular fibromatosis cutis with polyps of the colon: a cutaneo-intestinal syndrome sui generis. *Arch Dermatol Res* 1975; **253**: 161–75.
23 Zbar B, Alvord WG, Glenn G *et al.* Risk of renal and colonic neoplasms and spontaneous pneumothorax in the Birt-Hogg-Dube syndrome. *Cancer Epidemiol Biomarkers Prev* 2002; **11**: 393–400.
24 Daniel ES, Ludwig SL, Lewin KJ *et al.* The Cronkhite–Canada syndrome: an analysis of clinical and pathologic features and therapy in 55 patients. *Medicine (Baltimore)* 1982; **61**: 293–309.
25 Herzberg AJ, Kaplan DL. Cronkhite–Canada syndrome. *Int J Dermatol* 1990; **29**: 121–5.
26 Ward EM, Wolfsen HC. Review article: the non-inherited gastrointestinal polyposis syndromes. *Alimentary Pharmacol Ther* 2002; **16**: 333–42.
27 Piette AM, Meduri B, Fritsch J *et al.* Do skin tags constitute a marker for colonic polyps? A prospective study of 100 patients and metaanalysis of the literature. *Gastroenterology* 1988; **95**: 1127–9.

Liver disease

Hepatobiliary diseases are frequently associated with abnormalities of the skin, nails and hair. However, most are non-specific, as they may be present in other diseases and absent even in patients with advanced liver dysfunction—jaundice, for example, may occur due to haemolysis rather than due to liver damage. Additionally, many diseases may share the same cutaneous features (for example, most causes of cirrhosis have a commonality of clinical signs), and there is no clear correlation between the degree of the skin changes and the severity of liver dysfunction. However, there may be constellations of features that suggest specific diagnoses (e.g. pigmentation, jaundice and xanthomas in primary biliary cirrhosis). The overall picture of the patient may therefore be as useful as the presence of particular cutaneous signs.

This section will discuss some of the main groups of hepatobiliary disease, followed by some of the more important symptoms and signs.

Hepatitis and acute liver disease

Acute hepatic damage is most often due to viral hepatitis, alcohol or other drugs. Cutaneous features may be absent, or there may be jaundice. Other features may occur, depending on the cause. Most of the cutaneous features of alcohol excess are related to chronic abuse and are considered later; flushing and, uncommonly, urticaria may occur as short-term effects. This section considers the dermatological associations of infective hepatitis.

Hepatitis A virus infection is usually asymptomatic and transient. Dermatological features, if present, are jaundice, urticaria (less than 2%) and exanthema [1]. Chronic liver disease is not a feature, but a relapsing variant has been described in which itch, purpura and urticarial lesions occur [2]. Histology in such cases demonstrates a small-vessel vasculitis. More severe vasculitis or panniculitis is rare.

Hepatitis B virus (HBV) infection [1,3–5] is of major relevance to health-care workers, as it may be transmitted parenterally. It is also transmitted sexually, and HBV infection may be associated with other sexually transmitted diseases. HBV screening and vaccination are recommended for all health-care workers; routine HBV screening may be recommended for patients attending genitourinary medicine clinics, but at present is usually targeted to high-risk groups (human immunodeficiency virus (HIV)-positive individuals and parenteral drug abusers). Vaccination is not without dermatological side effects—provocation of granuloma annulare, lichen planus, Gianotti–Crosti syndrome, urticaria and contact reactions to excipients have all been reported [6–9].

Dermatological features of acute HBV infection include:

- Urticaria, non-specific erythema or a serum sickness-like picture (generalized malaise, fever and arthralgia)—this occurs in 20–30% of patients with hepatitis [3]. Angio-oedema, erythema multiforme or erythema nodosum-like lesions may occur. Circulating immune complexes are probably involved [10], and skin biopsy shows small vessel vasculitis with positive direct immunofluorescence for IgG, IgM, complement C3 and hepatitis B surface antigen (HB_sAg). This eruption may precede other features of infection, or may occur as recurrent urticaria after infection.
- Gianotti–Crosti syndrome (papular acrodermatitis of childhood, papulovesicular acrolocated syndrome)—this eruption was originally linked with HBV infection, although accumulated knowledge documents that it is a feature of numerous viral infections. Lesions consist of small, umbilicated papules, often affecting the knees, buttocks, cheeks and extremities; the lesions usually last about 6–8 weeks and are associated with non-specific malaise in the early phase.
- Polyarteritis nodosa (PAN)—about 20% of patients with PAN may have positive HBV serology, but the frequency has decreased considerably over the last 20 years, some units that previously expected HBV positivity in 30–50% of cases only finding this in less than 5% now. PAN is discussed in Chapter 50. In relation to the link with hepatitis, it is of interest that cases have been reported after vaccination. Additionally, cases are described in which PAN has resolved after treatment of the HBV infection with lamivudine (and interferon in one case), although the patients concerned had also received corticosteroids or other immunosuppressive therapy. Hepatitis viruses do not seem to provoke larger vessel vasculitides, and one study of patients with Behçet's disease demonstrated a lower frequency of antibodies to HBV than in controls.
- Cryoglobulinaemic vasculitis—about 15% of patients with HBV have detectable cryoglobulins, although most have no symptoms. The association is more important in hepatitis C.
- Other skin lesions—pyoderma gangrenosum, lichen planus and dermatomyositis have been reported with HBV infection. However, at least in the case of lichen planus, this may reflect high geographical prevalence rather than being a true association.

Hepatitis C virus (HCV) infection is usually transmitted parenterally. Acute HCV infection is usually only mildly symptomatic; chronic hepatitis occurs in about 75%, but progression varies considerably [11,12]. Its importance in dermatology is increasingly recognized; dermatological features [13–20] include mixed cryoglobulinaemia, PAN, acral necrolytic erythema, red fingers syndrome, porphyria cutanea tarda, pruritus, lichen planus, features of chronic liver disease in some cases, and various treatment-related eruptions. Some of these warrant more detailed discussion:

- Mixed cryoglobulinaemia, usually type II (polyclonal IgG and monoclonal IgM rheumatoid factor) and less commonly type III (polyclonal IgG and polyclonal IgM rheumatoid factor) is strongly linked with HCV infection; 70%–90% of type II cryoglobulinaemia is HCV-associated. Features include small vessel vasculitis, livedo reticularis, acrocyanosis, arthralgia, glomerulonephritis, peripheral neuropathy, hepatosplenomegaly and hypocomplementaemia [17,18]. Other patterns of vasculitis may also occur. A high frequency of autoimmune thyroid disorders and antibody tests has been reported in patients with HCV-related mixed cryoglobulinaemia. Treatment is discussed in detail in references [11,12].
- Necrolytic acral erythema is a relatively recently described and apparently specific, if rare, feature of acute HCV infection [19–21]. Well demarcated, acral (mainly hands and feet but can affect forearms, knees, lower legs), dusky discoloration with peripheral blister formation progresses to form keratotic erythrokeratoderma-like chronic inflammation. Histology is that of a necrolytic process but the distribution and laboratory tests (positive HCV, normal glucagon) confirm the diagnosis. The relationship to zinc deficiency has been debated—typically, zinc deficiency has been excluded by the lack of periorificial rash and by normal serum zinc levels. However, some cases improve with empirical administration of zinc supplements, including two treated with zinc alone—one of these had a baseline zinc level that was only just in the normal range [21], but the other had frank deficiency and improvement in the necrolytic acral erythema correlated with restoration of serum zinc levels [22]. More commonly, treatment has usually been with interferon, usually combined with ribavirin [23].
- Red fingers syndrome—an earlier description of red fingers syndrome in patients with HIV and HCV infection [24] may have represented the same entity, and was felt to be due to the HCV infection, although skin histology (only obtained in one of nine cases) just showed capillary dilatation.
- PAN—in patients with 'classic' PAN in whom hepatitis virus is of relevance, the association is usually with HBV rather than HCV infection, but preceding HCV infection has been reported in up to 30% of patients with the cutaneous variant of PAN [25]. Hypocomplementaemia seems to be more common in patients with cutaneous PAN who also have HCV infection, but the numbers of patients studied is small.
- Porphyria cutanea tarda (PCT)—the most important risk factors for PCT are alcoholic liver disease and hereditary

haemochromatosis (see later). However, in some countries where there is a low prevalence of the gene mutations that cause haemochromatosis, chronic HCV infection may assume greater importance in the aetiology of PCT; the prevalence of positive HCV serology in PCT varies from about 10% to 90%, depending on geography [26]. HCV has also been linked to variegate porphyria. A case–control study in the USA found that 16 of 17 patients with PCT were HCV-positive (94%), compared with 0.17% of nearly 150 000 volunteer blood donors (although these may not be fully representative of the general population) [26]. HCV is therefore best viewed as an important independent risk factor in development of PCT [27,28]. Overall, PCT appears to be uncommon as a manifestation of HCV positivity. A large study of patients with HCV or HIV infection, or both, only found one of 177 patients to have a PCT porphyrin excretion pattern and did not support a direct role of HCV in provoking PCT. However, the mean coproporphyrin level was significantly raised in HCV-positive patients and especially in those who were also HIV-positive [29].

- Autoimmune disorders. There are associations between HCV infection and lichen planus, autoimmune thrombocytopenic purpura, Behçet's disease, vitiligo and a Sjögren's syndrome-like sialadenitis. However, as with HBV, the association with lichen planus is questionable as there is marked geographical variation; in an area of low HCV prevalence, no association could be demonstrated [30].
- Other dermatological symptoms. Pruritus may be a presenting symptom of HCV infection, and persistent itch may occur [16]. Urticaria, erythema multiforme, erythema nodosum and papuloerythroderma [31] have been reported.
- Treatment related dermatoses—interferon and antiviral agents have many potential side effects, including urticaria and exanthematous reactions. Discoid eczema and Meyerson's phenomenon (halo eczema around naevi) have been reported. Potentially more severe or less apparent reactions include a thrombotic microangiopathy reported due to pegylated-interferon-α-2b [32], and sarcoidosis (which may self-resolve, or may be treated with judicious oral corticocosteroid) associated with use of pegylated-interferon-α plus ribavirin [33].

Hepatitis D causes cutaneous features similar to those of HBV. *Hepatitis E* is generally mild, but may cause disseminated intravascular coagulation [1]. *Hepatitis F* is disputed, and *hepatitis G* is usually transmitted parenterally.

References

1 Geyer AS, Rosenburg DS, Herlong HF, Provost TT. Hepatitis. In: Provost TT, Flynn JA, eds. *Cutaneous Medicine: Cutaneous Manifestations of Systemic Disease*. Hamilton, Ontario: Decker, 2001: 452–63.

2 Glikson M, Galune E, Oren R *et al*. Relapsing hepatitis A: review of 14 cases and literature survey. *Medicine* 1992; **71**: 14–23.

3 McElgunn PS. Dermatologic manifestations of hepatitis B virus infection. *J Am Acad Dermatol* 1983; **8**: 539–48.

4 D'Souza R, Foster GR. Diagnosis and treatment of chronic hepatitis B. *J Roy Soc Med* 2004; **97**: 318–21.

5 Aggarwal R, Ranjan P. Preventing and treating hepatitis B infection. *BMJ* 2004; **329**: 1080–6.

6 Wolf F, Grezard P, Berard F *et al*. Generalized granuloma annulare and hepatitis B vaccination. *Eur J Dermatol* 1998; **8**: 435–6.

7 Tay YK. Gianotti–Crosti syndrome following immunization. *Pediatr Dermatol* 2001; **18**: 262.

8 Al-Khenaizan S. Lichen planus occurring after hepatitis B vaccination: a new case. *J Am Acad Dermatol* 2002; **45**: 614–5.

9 Rietschel RL, Adams RM. Reactions to thimerosal in hepatitis B vaccines. *Dermatol Clin* 1990; **8**: 161–4.

10 Neumann HAM, Berretty PJM, Reinders Folmer SSC *et al*. Hepatitis B surface antigen deposition in the blood vessel walls of urticarial lesions in acute hepatitis B. *Br J Dermatol* 1981; **104**: 383–8.

11 Hayes PC, ed. Consensus conference on hepatitis C. *J Viral Hepatitis* 2004; **11** (Suppl. 1); 1–39.

12 Lauer GM, Walker BD. Hepatitis C virus infection. *N Engl J Med* 2001; **345**: 41–52.

13 Pawlotsky JM, Dhumeaux D, Bagot M. Hepatitis C virus in dermatology. *Arch Dermatol* 1995; **131**: 1185–93.

14 Schwaber MJ, Zlotogorski A. Dermatologic manifestations of hepatitis C infection. *Int J Dermatol* 1997; **36**: 251–4.

15 Bonkovsky HL, Mehta S. Hepatitis C. Review and update. *J Am Acad Dermatol* 2001; **44**: 159–79.

16 Fisher DA, Wright TL. Pruritus as a symptom of hepatitis C. *J Am Acad Dermatol* 1994; **30**: 629–32.

17 Cacoub P, Costedoat-Chalumeau N, Lidove O, Alric L. Cryoglobulinemia vasculitis. *Curr Opin Rheumatol* 2002; **14**: 29–35.

18 Ferri C, Mascia MT. Cryoglobulinemic vasculitis. *Curr Opin Rheumatol* 2006; **18**: 54–63.

19 Darouti ME, Ala ME. Necrolytic acral erythema: a cutaneous marker of hepatitis C. *Int J Dermatol* 1996; **35**: 252–6.

20 Crawford GH, Kim S, James WD. Skin signs of systemic disease: an update. *Adv Dermatol* 2003; **18**: 1–27.

21 Abdallah MA, Hull C, Horn TD. Necrolytic acral erythema. A patient from the United States successfully treated with oral zinc. *Arch Dermatol* 2005; **141**: 85–7.

22 Najarian DJ, Lefkowitz I, Balfour E *et al*. Zinc deficiency associated with necrolytic acral erythema. *J Am Acad Dermatol* 2006; **55**: S108–10.

23 Hivnor CM, Yan AC, Junkins-Hopkins JM, Honig PJ. Necrolytic acral erythema: response to combination therapy with interferon and ribavirin. *J Am Acad Dermatol* 2004; **50**: S121–4.

24 Pechère M, Krishner J, Rosay A, Hirschel B, Saurat J-H. Red fingers syndrome in patients with HIV and hepatitis C infection. *Lancet* 1996; **348**: 196–7.

25 Soufir N, Descamps V, Crickx B *et al*. Hepatitis C virus infection in cutaneous polyarteritis nodosa: a retrospective study of 16 cases. *Arch Dermatol* 1999; **135**: 1001–2.

26 Chuang TY, Brashear R, Lewis C. Porphyria cutanea tarda and hepatitis C virus: a case–control study and meta-analysis of the literature. *J Am Acad Dermatol* 1999; **41**: 31–6.

27 Bulaj ZJ, Phillips JD, Ajioka RS *et al*. Hemochromatosis genes and other factors contributing to the pathogenesis of porphyria cutanea tarda. *Blood* 2000; **95**: 1565–71.

28 Stuart KA, Busfield F, Jazwinska EC *et al*. The C282Y mutation in the hemochromatosis gene (HFE) and hepatitis C virus infection are independent cofactors for porphyria cutanea tarda in Australian patients. *J Hepatol* 1998; **28**: 404–9.

29 Cribier B, Rey D, Uhl G *et al*. Abnormal urinary coproporphyrin levels in patients infected by hepatitis C virus with or without human immunodeficiency virus. *Arch Dermatol* 1996; **132**: 1448–52.

30 Tucker SC, Coulson IH. Lichen planus is not associated with hepatitis C virus infection in patients from north west England. *Acta Derm Venereol* 1999; **79**: 378–9.

31 Ota M, Sato-Matsumura KC, Sawamura D, Shimizu H. Papuloerythroderma associated with hepatitis C virus infection. *J Am Acad Dermatol* 2005; **52**: S61–2

32 Creput C, Auffret N, Samuel D *et al*. Cutaneous thrombotic microangiopathy during treatment with alpha-interferon for chronic hepatitis C. *J Hepatol* 2002; **37**: 871–2.

33 Hurst EA, Mauro T. Darcoidosis associated with pegylated interferon alpha and ribavirin treatment for chronic hepatitis C. *Arch Dermatol* 2005; **141**: 865–8.

Cirrhosis of the liver

Assessing the degree of liver disease is not the remit of dermatologists, but measurement of hepatic fibrosis warrants discussion as this has importance with regard to monitoring of methotrexate therapy (see 'Drugs and the liver' below, and Chapters 20 and 74).

Progression to cirrhosis, whatever the cause, is often avoided if fibrosis is detected at an early stage. Increasingly, measurement of serum levels of the amino-terminal propeptide of collagen III (PIIINP) is being used as a substitute for liver biopsy in methotrexate monitoring [1–3], and, if performed three or four times annually, a consistently normal result appears to indicate a negligible risk of significant fibrosis. It does however have limitations—it can only detect active fibrosis, and can be elevated in other situations (notably psoriatic arthritis). Biopsy also has limitations—one study showed that, in 25% of cases where each liver lobe was biopsied, there was at least one fibrosis stage difference between the samples. Algorithms based on an increased number of parameters may help to improve non-invasive accuracy—a study that used biopsy as the gold standard in 1021 subjects and analysed nine other factors determined that four of these (age, hyaluronic acid, PIIINP and tissue inhibitor of matrix metalloproteinase I) had 90% sensitivity and a negative predictive value of 92% for significant fibrosis [4].

References

1 Zachariae H, Heickendorff L, Søgaard H. The value of amino-terminal propeptide of type III procollagen in routine screening for methotrexate-induced liver fibrosis: a 10-year follow-up. *Br J Dermatol* 2001; **144**: 100–3.

2 Zachariae H. Have methotrexate-induced liver fibrosis and cirrhosis become rare? A matter for reappraisal of routine liver biopsies. *Dermatology (Basel)* 2005; **211**: 307–8.

3 Chalmers RJG, Kirby B, Smith A *et al*. Replacement of routine liver biopsy by procollagen III aminopeptide for monitoring patients with psoriasis receiving long-term methotrexate: a multicentre audit and health economic analysis. *Br J Dermatol* 2005; **152**: 444–50.

4 Rosenberg WM, Voelker M, Thiel R *et al*. Serum markers detect the presence of liver fibrosis: a cohort study. *Gastroenterology* 2004; **127**: 1704–13.

Cutaneous features of chronic liver disease

Cutaneous features of chronic liver disease are listed in Table 62.13 [1,2]. Causes include chronic hepatitis (above), alcohol abuse and others—some of the idiopathic causes are discussed below, as each has some specific features in addition to those that occur in liver failure of any cause.

Table 62.13 Skin lesions associated with chronic liver disease.

Spider angiomas, telangiectasia
Palmar erythema
Dilated abdominal/chest veins (including periumbilical caput medusae)
Jaundice
Increased melanin pigmentation
Thin 'paper-money' skin, striae
Excoriations
Loss of secondary sexual hair in males
Bruising, purpura
Nail changes: clubbing, pallor, Muehrcke's bands, Terry's nail
Features of malnutrition (see Chapter 59)
Associated lesions
Xanthomas (primary biliary cirrhosis)
Porphyria cutanea tarda (alcoholic liver disease)
Vasculitis/capillaritis/pyoderma gangrenosum (chronic active hepatitis)
Lichen planus (primary biliary cirrhosis)

References

1 Smith KE, Fenske NA. Cutaneous manifestations of alcohol abuse. *J Am Acad Dermatol* 2000; **43**: 1–16.

2 Ruocco V, Psilogenis M, Lo Schiavo A, Wolf R. Dermatological manifestations of alcoholic cirrhosis. *Clin Dermatol* 1999; **17**: 463–8.

Haemochromatosis

There are at least five hereditary (idiopathic) types of haemochromatosis ('bronze diabetes') [1–7], a disorder in which iron overload is associated with arthropathy, endocrine failure, cardiovascular disease and some infections. By far the commonest is 'classic' autosomal recessive haemochromatosis, which is due to mutations of the *HFE* gene (chromosome 6p21.3); mutations C282Y (cysteine 282 tyrosine) and H63D (histidine 63 asparagine) account for about 80% of cases, and mutations in S65C for perhaps 10% (all vary considerably between populations). The genotype combinations that may occur influence the risk of some associated disorders such as PCT (below). The 'classic' haemochromatosis phenotype also occurs due to mutations in the hemojuvulin gene (chromosome 1q21, also autosomal recessive). Haemochromatosis type 2 (HFE2, juvenile haemochromatosis) also occurs as a result of mutations in two different genes, HFE2A is due to hemojuvulin gene mutations and HFE2B due to mutation in *HAMP* (was *LEAP1*) which encodes hepcidin antimicrobial peptide (hepcidin). Other genes in which mutations cause haemochromatosis include *TFR2*, the gene for transferrin receptor-2 (causing haemochromatosis type 3, usually mutation Y250X) and *SCL40A1*, the gene for ferroportin (causing hemochromatosis type 4, HFE4). Classic idiopathic haemochromatosis usually presents in males over the age of 40 years. An acquired form also occurs, secondary to haemosiderosis or alcohol abuse.

There is increased iron absorption leading to iron deposition in various organs, including the liver, pancreas, heart, pituitary and endocrine organs. Skin pigmentation, diabetes, hepatic cirrhosis and cardiac failure are prominent features [8–10]. Dryness of the skin and koilonychia may have been underestimated in the past [11]; stigmata of chronic hepatic failure may also be present. Deposition of iron in the skin has been used as a surrogate for deposition in other organs [12,13]; in idiopathic haemochromatosis, iron deposition includes deposition in eccrine sweat glands [11]. However, the pigmentation of haemochromatosis is due to melanin rather than to haemosiderin [8–10]. It typically has a grey hue, and is most prominent on exposed skin, similar to addisonian pigmentation. Keratin cysts with a black colour [14], and black stasis dermatitis [15], have also been reported.

There is a 200-fold increase in the risk of hepatocellular carcinoma compared with the general population [8].

Porphyria cutanea tarda has been linked with haemochromatosis [10,16,17]. It has subsequently been shown that homozygosity for the C282Y mutation and seropositivity for HCV are the greatest risk factors for expression of PCT [18] and that they appear to act as independent co-factors [19]. In patients with mutations in uroporphyrinogen decarboxylase, which leads to PCT, coinheritance of C282Y homozygosity is associated with earlier age of onset of the porphyria [20].

References

1 Online Mendelian Inheritance in Man. *Haemochromatosis*. www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=235200

2 Bacon BR. Hemochromatosis: diagnosis and management. *Gastroenterology* 2001; **120**: 718–25.
3 Njajou OT, Vaessen N, Joosse M *et al.* A mutation in *SLC11A3* is associated with autosomal dominant hemochromatosis. *Nature Genet* 2001; **28**: 213–4.
4 Kotze MJ, de Villiers JNP, Bouwens CSH *et al*. Molecular diagnosis of hereditary hemochromatosis: application of a newly-developed reverse-hybridization assay in the South African population. *Clin Genet* 2004; **65**: 317–23.
5 Milet J, Dehais V, Bourgain C *et al*. Common variants in the BMP2, BMP4 and HJV genes of the hepcidin regulation pathway modulate HFE hemochromatosis penetrance. *Am J Hum Genet* 2007; **81**: 799–807.
6 Wallace DF, Subramanion VN. Non-HFE haemochromatosis. *World J Gastroenterol* 2007; **13**: 4690–8.
7 Griffiths WJH. Review article: the genetic basis of haemochromatosis. *Aliment Pharmacol Ther* 2007; **26**: 331–42.
8 Braverman IM. *Skin Signs of Systemic Disease*, 3rd edn. Philadelphia: Saunders, 1998: 405–37.
9 Bloom PD, Gordeuk VR, MacPhail AP. HLA-linked hemochromatosis and other forms of iron overload. *Dermatol Clin* 1995; **13**: 57–63.
10 Tavill AS, Sharma BK, Bacon BR. Iron and the liver: genetic hemochromatosis and other hepatic iron overload disorders. *Prog Liver Dis* 1990; **9**: 281–305.
11 Chevrant-Breton J, Simon M, Bourel M, Ferrand B. Cutaneous manifestations of idiopathic hemochromatosis. *Arch Dermatol* 1977; **113**: 161–5.
12 Tsuji T. Experimental hemosiderosis: relationship between skin pigmentation and hemosiderin. *Acta Derm Venereol* 1980; **60**: 109–14.
13 Farquharson MJ, Bagshaw AP, Porter JB, Abeysinghe RD. The use of skin Fe levels as a surrogate marker for organ Fe levels, to monitor treatment in cases of iron overload. *Phys Med Biol* 2000; **45**: 1387–96.
14 Leyden JJ, Lockshin NA, Krebel S. The black keratinous cyst: a sign of hemochromatosis. *Arch Dermatol* 1972; **106**: 379–81.
15 Soderberg KI, Sharp M, Carrington PR. Brown and black scaly patches on the lower leg. *Arch Dermatol* 2007; **143**: 1441–6.
16 Seymour DG, Elder GH, Fryer A *et al*. Porphyria cutanea tarda and haemochromatosis: a family study. *Gut* 1990; **31**: 719–21.
17 Kushner JP, Edwards CQ, Dadone MM, Skolnick MH. Heterozygosity for HLA-linked hemochromatosis as a likely cause of the hepatic siderosis associated with sporadic porphyria cutanea tarda. *Gastroenterology* 1985; **88**: 1232–8.
18 Bulaj ZJ, Phillips JD, Ajioka RS *et al*. Hemochromatosis genes and other factors contributing to the pathogenesis of porphyria cutanea tarda. *Blood* 2000; **95**: 1565–71.
19 Stuart KA, Busfield F, Jazwinska EC *et al.* The C282Y mutation in the hemochromatosis gene (*HFE*) and hepatitis C virus infection are independent cofactors for porphyria cutanea tarda in Australian patients. *J Hepatol* 1998; **28**: 404–9.
20 Brady JJ, Jackson HA, Roberts AG *et al*. Co-inheritance of mutations in the uroporphyrinogen decarboxylase and hemochromatosis genes accelerates the onset of porphyria cutanea tarda. *J Invest Dermatol* 2000; **115**: 868–74.

Primary biliary cirrhosis and biliary tract disease

From the dermatological standpoint, primary biliary cirrhosis (PBC) is the most important biliary tract disease. The cutaneous features of significance are marked itch (discussed in more detail below), excoriation, hyperpigmentation and various xanthomatous lesions due to secondary hyperlipidaemia [1,2]. Xanthelasma, palmar crease, tuberous and tendinous xanthomas may all occur. PBC occurs mainly in middle-aged women as an autoimmune disease, is strongly associated with the presence of antimitochondrial antibodies (AMA), and has been associated with numerous other autoimmune conditions, including CREST, morphoea and other scleroderma spectrum disorders, lichen planus and lichen sclerosus [1–7]. The constellation of CREST with PBC is also known as Reynolds' syndrome, and is usually associated with M2 antibodies. Sarcoidosis [8] and other patterns of granulomatous disease such as granuloma annulare are also reported. There is a strong link with Sjögren's syndrome—about 10% of patients with Sjögren's syndrome have AMA, sometimes with abnormal liver function tests or liver histology, and over half of patients with PBC have some evidence of Sjögren's syndrome [9]. Itch is often the first symptom of PBC, so serology to detect AMA is a useful screening test in women with unexplained pruritus; AMA-negative PBC causes particular diagnostic difficulty.

Cholestasis and bile stones may cause acute or chronic jaundice and other features of liver disease. Pigment bile stones may occur due to erythropoietic protoporphyria.

Congenital biliary tract hypoplasia is a feature of Alagille's syndrome (MIM #118450) [10], a dominantly inherited disorder due to a gene mutation on chromosome 20p12. Affected individuals have a characteristic facies, jaundice, pruritus and retardation of growth and mental development. Various skeletal, ocular and vascular defects are associated. A report of 38 children documented firm xanthomas in 28%, mainly flexural but also affecting palms and ears; the xanthomas resolved in those individuals treated by liver transplantation [11].

Biliary tract abnormalities are also common in hereditary haemorrhagic telangiectasia, resembling either a congenital malformation of the ductal plate, or appearing similar to the changes seen in sclerosing cholangitis [12].

References

1 Kaplan MM. Primary biliary cirrhosis. *N Engl J Med* 1996; **335**: 1570–80.
2 Heathcote J. The clinical expression of primary biliary cirrhosis. *Semin Liver Dis* 1997; **17**: 23–33.
3 Powell FC, Rogers RS, Dickson ER. Primary biliary cirrhosis and lichen planus. *J Am Acad Dermatol* 1983; **9**: 540–5.
4 Powell FC, Schroeter AL, Dickson ER. Primary biliary cirrhosis and the CREST syndrome: a report of 22 cases. *QJM* 1987; **62**: 75–82.
5 Akimoto S, Ishikawa O, Muro Y *et al.* Clinical and immunological characterization of patients with systemic sclerosis overlapping with primary biliary cirrhosis: a comparison with systemic sclerosis alone. *J Dermatol* 1999; **26**: 18–22.
6 Meyrick Thomas RH, Ridley CM, McGibbon DH, Black MM. Association between lichen sclerosus et atrophicus and primary biliary cirrhosis. *Br J Dermatol* 1986; **114**: 514–5.
7 Reed JR, De Luca N, McIntyre AS, Wilkinson JD. Localised morphoea, xanthomatosis and primary biliary cirrhosis. *Br J Dermatol* 2000; **143**: 652–3.
8 Harrington AC, Fitzpatrick JE. Cutaneous sarcoidal granulomas in a patient with primary biliary cirrhosis. *Cutis* 1992; **49**: 271–4.
9 Martin DR, Provost TT. Sjögren's syndrome. In: Provost TT, Flynn JA, eds. *Cutaneous Medicine: Cutaneous Manifestations of Systemic Disease*. Hamilton, Ontario: Decker, 2001: 127–46.
10 Alagille D, Estrada A, Hadchouel M *et al.* Syndromic paucity of interlobular bile ducts (Alagille syndrome or arteriohepatic dysplasia): review of 80 cases. *J Pediatr* 1987; **110**: 195–200.
11 Garcia MA, Ramonet M, Ciocca M *et al*. Alagille syndrome: cutaneous manifestations in 38 children. *Pediatr Dermatol* 2005; **22**: 11–4.
12 Garcia-Tsao G, Korzenik JR, Young L *et al*. Liver disease in patients with hereditary haemorrhagic telangiectasia. *N Engl J Med* 2000; **343**: 931–6.

Drugs and the liver

Drug-related links between the skin and the liver include the following:

- Drugs used to treat the skin, whose hepatic metabolism is altered by liver disease or by other drugs that are also metabolized in the liver, e.g. ciclosporin
- Drugs used to treat skin disease that may cause hepatitis or other liver damage, e.g. azathioprine, methotrexate
- Drugs used to treat liver disease that may have cutaneous side effects, e.g. local reactions to vitamin K (Texier's syndrome),

elastosis perforans serpiginosa due to penicillamine for Wilson's disease
- Drugs used to prevent liver disease that may have cutaneous side effects, e.g. local reactions due to thimerosal or other preservatives in hepatitis vaccines
- Drugs that cause liver changes with secondary cutaneous signs, e.g. oestrogens leading to PCT
- Drugs that may cause concurrent hepatitis and rash, e.g. phenytoin and other anticonvulsants.

Systemic diseases and the liver

A large number of systemic diseases may affect the liver, many with cutaneous features. Most are discussed in other chapters. For example, sarcoidosis is associated with subclinical hepatic involvement in over 50% of patients, but may cause overt hepatomegaly or abnormalities of liver function in conjunction with skin lesions.

Porphyrias, especially PCT, may occur as a consequence of liver disease (see Chapter 59 and the discussion of PCT below); severe liver disease is also a feature in some patients with erythropoietic protoporphyria.

Hereditary haemorrhagic telangiectasia, mentioned earlier as a cause of gastrointestinal bleeding, is associated with portal hypertension due mainly to portosystemic shunting, so bleeding in such patients may be from varices.

Dermatological features and dermatoses associated with liver disease

Pruritus

Pruritus is the most common skin symptom associated with liver disease. It may precede the onset of jaundice of any cause, and may be a feature of hepatitis, as discussed above. Liver diseases in which itch is most prominent are PBC, sclerosing cholangitis and any other biliary tract obstruction, and disorders causing cholestasis; itch is less prominent in haemochromatosis, alcoholic cirrhosis and autoimmune chronic active hepatitis [1]. The symptoms are generally most severe at acral sites and at areas of tight clothing, and are more prominent nocturnally. Disappearance of pruritus may accompany severe deterioration in hepatic function [2].

The precise mechanism of itch in obstructive liver disease remains unclear. It was believed to be due to the presence of bile salts in the skin [3,4], but the intensity of itch does not reliably correlate with bilirubin or bile acid levels in chronic liver failure, and this theory is not supported by more recent research [1,5]. Other proposed mediators of cholestatic itch include alternative liver metabolites, histamine or other mast cell mediators, and endogenous opiates. Although patients with cholestasis may have elevated plasma histamine levels, the therapeutic response to antihistamines is limited, and it is unlikely that release of histamine plays an important role in the pathogenesis of hepatobiliary itch [1]. Improvement in hepatic itch after administration of drugs that block the action of endogenous opiates suggests that the latter may have an important role in cholestatic itch [6–8].

Treatment, where possible, is for the underlying cause—for example, drug withdrawal in drug-induced cholestasis, surgery for mechanical biliary obstruction, interferon and ribavirin for chronic HCV infection, etc. Less specific options include ursodeoxycholic acid, cholestyramine, phenobarbital, anabolic steroids such as stanozolol, rifampicin, antihistamines and dietary manipulation to supplement polyunsaturated fatty acids [1,9,10]. Phototherapy of various types—daylight, ultraviolet A (UVA), ultraviolet B (UVB), photoirradiation of plasma and extracorporeal photophoresis—can be effective, but ongoing treatment is generally required [1,11,12]. Other treatments that have been used with success include haemoperfusion or plasma perfusion through charcoal-coated beads (which can produce benefit lasting several weeks), plasmapheresis, infusions of albumin (benefit for a few days) and slow injection of intravenous lidocaine (lignocaine) (which produces short-term benefit only). On the basis that endogenous opiates play a role in this symptom, and that these have a circadian rhythm regulated by light, bright-light therapy to the eyes was studied and found to reduce cholestatic itch in a short-term study [13]. Oral opiate antagonists are effective but may cause opioid withdrawal-like reactions—this may be reduced by use of very low dose naloxone infusions prior to gradual increase in dose of an oral opiate antagonist [14]. Gabapentin was ineffective in a double-blind, controlled trial [15].

References

1 Ghent CN. Cholestatic pruritus. In: Bernhard JD. *Itch: Mechanisms and Management of Pruritus*. New York: McGraw-Hill, 1994: 229–42.
2 Bernhard JD, Jorizzo JL, Callen JP. Pruritus. In: Callen JP, Jorizzo JL, eds. *Dermatological Signs of Internal Disease*, 3rd edn. Philadelphia: Saunders, 2003: 65–8.
3 Kirby J, Heaton KW, Burton JL *et al*. The pruritic effect of bile salts. *Br J Dermatol* 1974; **91** (Suppl. 10): 11–2.
4 Varadi DP. Pruritus induced by crude bile and purified bile acids: experimental production of pruritus in human skin. *Arch Dermatol* 1974; **109**: 678–81.
5 Ghent CN. Pruritus of cholestasis is related to effects of bile salts on the liver, not the skin. *Am J Gastroenterol* 1987; **82**: 117–8.
6 Bergasa NV, Talbot TL, Alling DW *et al*. A controlled trial of naloxone infusions for the pruritus of cholestasis. *Gastroenterology* 1992; **102**: 544–9.
7 Borgeat A, Wilder-Smith OHG, Mentha G. Subhypnotic doses of propofol relieve pruritus associated with liver disease. *Gastroenterology* 1993; **104**: 244–7.
8 Bergasa NV, Alling DW, Talbot TL *et al*. Oral nalmefene therapy reduces scratching activity due to the pruritus of cholestasis: a controlled study. *J Am Acad Dermatol* 1999; **41**: 431–4.
9 Smith KE, Fenske NA. Cutaneous manifestations of alcohol abuse. *J Am Acad Dermatol* 2000; **43**: 1–16.
10 Garden JM, Ostrow JD, Roenigk HH. Pruritus in hepatic cholestasis: pathogenesis and therapy. *Arch Dermatol* 1985; **121**: 1415–20.
11 Rosenthal E, Diamond E, Benderly A, Etzioni A. Cholestatic pruritus: effect of phototherapy on pruritus and excretion of bile acids in urine. *Acta Paediatr* 1994; **83**: 888–91.
12 Greaves MW, Provost TT. Pruritus as a manifestation of systemic disease. In: Provost TT, Flynn JA, eds. *Cutaneous Medicine: Cutaneous Manifestations of Systemic Disease*. Hamilton, Ontario: Decker, 2001: 1–8.
13 Bergasa NV, Link MJ, Keogh M *et al*. Pilot study of bright-light therapy reflected towards the eyes for the pruritus of chronic liver disease. *Am J Gastroenterol* 2001; **96**: 1563–70.
14 Jones EA, Neuberger J, Bergasa NV. Opiate antagonist therapy for the pruritus of cholestasis: the avoidance of opioid withdrawal-like reactions. *QJM* 2002; **95**: 947–52.
15 Bergasa NV, McGee M, Ginsburg IH, Engler D. Gabapentin in patients with the pruritus of cholestasis: a double-blind, randomized, placebo-controlled trial. *Hepatology* 2006; **44**: 1317–23.

Skin pigment changes in liver disease [1–3]

Jaundice (icterus) is first visible as a yellowish hue of the sclerae and soft palate before it becomes generalized. It is due to

hyperbilirubinaemia. Carotenaemia may have a similar appearance but does not affect sclerae; skin discoloration following mepacrine or busulphan therapy may simulate jaundice, but these usually also cause subungual pigmented bands.

Green-coloured sweat [4] and green discoloration of the gingivae may occur due to jaundice.

A muddy-grey coloured hyperpigmentation occurs in chronic liver disease of any cause. It is due to hypermelanosis with normal numbers of melanocytes, but the precise mechanism is uncertain. There may be a yellowish tinge due to associated jaundice. Usually, pigmentation is more prominent in sun-exposed areas. It may be blotchy or diffuse, and may be exaggerated in the perioral and periorbital areas (resembling chloasma); in other cases it may resemble freckling and it can also localize to palmar creases. Males frequently show increased pigmentation of the areola in association with gynaecomastia and testicular atrophy.

Spotty hypomelanosis may occur on the back, buttocks and thighs, often in relation to spider angiomas.

Associated dietary deficiency may cause the pigmentary changes of pellagra (Chapter 59).

Vascular changes

Spider angiomas are a characteristic feature in patients with severe chronic liver disease (Fig. 62.20). Contributory factors [5] include decreased hepatic metabolism of oestrogen leading to hyperoestrogenaemia (which also accounts for loss of secondary male-pattern hair, gynaecomastia and testicular atrophy); alcohol-induced vasodilatation and altered central vasomotor control may also be involved. The same factors lead to palmar erythema ('liver palms'), which is most pronounced on the thenar and hypothenar regions and may also affect the soles of the feet, and also to facial plethora. None of these vascular features are specific for liver disease. Diffusely scattered tiny telangiectatic vessels are referred to as 'paper money skin'. Increased peripheral blood flow with dilatation of digital pulp arteriovenous anastomoses is thought to be the cause of finger clubbing, which occurs in about 15% of patients with hepatic cirrhosis.



Fig. 62.20 Telangiectasia in alcoholic liver cirrhosis.

Purpuric lesions including scurvy may occur as a result of poor nutrition, especially in alcoholic liver disease (see Chapter 59). Altered production of prothrombin and deficiency of vitamin K may lead to frank ecchymoses.

In progressive liver disease with portal hypertension, collateral blood flow creates visible coiled varicose veins on the abdominal wall. When these are in a pattern radiating from the umbilicus, the appearance is termed 'caput Medusae'.

Hair, nail and collagen changes [1–3]

The body hair is often thinned or partially lost, and males tend to develop a female pubic-hair pattern. There is both increased production and decreased metabolism of oestrogens, as well as decreased production and increased metabolism of testosterone. When there is severe loss of scalp hair, zinc deficiency should be suspected (Chapter 59).

Nail changes include a diffuse white colour with an invisible lunula, proximal white colour with distal pink colour (Terry's nails) and white bands (Muehrke's bands [6]). Altered digital blood flow, soft-tissue overgrowth and hypoalbuminaemia may all contribute. Lunulae may be red in patients with hepatic cirrhosis, and occasionally an azure-blue colour in hepatolenticular degeneration (Wilson's disease). Nail-plate changes include clubbing (see above) and its milder variant, the 'watch-glass' deformity; flattened nails or koilonychia may occur if there is poor nutrition or altered iron metabolism (e.g. haemochromatosis).

Striae occur in both sexes, especially on the lower abdomen, thighs and buttocks. Chronic alcoholism also alters metabolism of corticosteroids, leading to 'pseudo-Cushing's syndrome'.

Porphyria cutanea tarda

Chronic liver disease is involved in the skin changes of porphyria cutanea tarda. Lesions consist of bullae, scarring and hyperpigmentation of sun-exposed skin areas and hypertrichosis of the face. This is discussed in more detail in Chapter 59.

Other cutaneous lesions associated with liver disease

Lichen planus has been reported in a number of diseases with abnormal immune function. The association of erosive oral lesions in PBC [7] and chronic active hepatitis [8] may be related to a common immunological pathogenesis. Most reported patients have received penicillamine therapy which is believed by some to trigger the eruption [9–11]. HCV infection is associated with lichen planus [12].

In chronic active hepatitis (juvenile cirrhosis, lupoid hepatitis) and in PBC, firm reddish papules resembling pityriasis lichenoides chronica or lymphomatoid papulosis have been reported [8,13]. The lesions erupt on the trunk and extremities and may heal leaving slightly depressed atrophic scars. Histological examination reveals a capillaritis of the skin. Pityriasis lichenoides has also been reported in association with HCV seropositivity.

Pyoderma gangrenosum has also been reported in chronic active hepatitis [14]. The Gianotti–Crosti syndrome has been discussed in relation to hepatitis. Skin changes simulating classical glucagonoma syndrome have been reported in cirrhosis and termed the 'pseudoglucagonoma syndrome' [15].



Fig. 62.21 Scaling rash on the trunk in chronic zinc deficiency.

Acquired zinc deficiency (Fig. 62.21) may occur in chronic alcoholic liver disease due to increased loss of urinary zinc in cirrhosis and poor nutrition [16,17]. Clinical features are a crackled and reticulate eczema on the trunk and extensor aspects of the limbs, erosive crusted changes in the perianal and genital areas, cheilitis, hair loss and multiple Beau's lines on the nails. Increased hair growth, often with a deeper pigmentation, may occur. Beer, wine and spirits are practically free of zinc, but most beer brands contain vitamin B in significant amounts and the typical zinc-deficient beer-drinker does not show additional clinical signs of vitamin B depletion [17].

References

1 Smith KE, Fenske NA. Cutaneous manifestations of alcohol abuse. *J Am Acad Dermatol* 2000; **43**: 1–16.
2 Ruocco V, Psilogenis M, Lo Schiavo A, Wolf R. Dermatological manifestations of alcoholic cirrhosis. *Clin Dermatol* 1999; **17**: 463–8.
3 Braverman IM. *Skin Signs of Systemic Disease*, 3rd edn. Philadelphia: Saunders, 1998: 405–37.
4 Allegue F, Hermo JA, Fachal C, Alfonsín N. Localised green pigmentation in a patient with hyperbilirubinemia. *J Am Acad Dermatol* 1996; **35**: 108–9.
5 Malpas SC, Robinson BJ, Maling TJ. Mechanism of ethanol-induced vasodilation. *J Appl Physiol* 1990; **68**: 731–4.
6 Muehrcke RC. The finger-nails in chronic hypoalbuminaemia: a new physical sign. *BMJ* 1956; **i**: 1327–8.
7 Graham-Brown RAC, Sarkany I, Sherlock S. Lichen planus and primary biliary cirrhosis. *Br J Dermatol* 1982; **106**: 699–703.
8 Sarkany I. Juvenile cirrhosis and allergic capillaritis of the skin. *Proc R Soc Med* 1970; **63**: 819.
9 Powell FC, Rogers RS III, Dickson ER. Lichen planus, primary biliary cirrhosis and penicillamine. *Br J Dermatol* 1982; **107**: 616.
10 Seehafer JR, Rogers RS III, Fleming R *et al.* Lichen planus-like lesions caused by penicillamine in primary biliary cirrhosis. *Arch Dermatol* 1981; **117**: 140–2.
11 Rebora A, Rongioletti F, Canepa A. Chronic active hepatitis and lichen planus. *Acta Derm Venereol* 1982; **62**: 351–2.
12 Pawlotsky JM, Dhumeaux D, Bagot M. Hepatitis C in dermatology. *Arch Dermatol* 1995; **131**: 1185–93.
13 Rai GS, Hamlyn AN, Dahl MGC *et al.* Primary biliary cirrhosis, cutaneous capillaritis and IgM-associated membranous glomerulonephritis. *BMJ* 1977; **i**: 817.
14 Byrne JP, Newitt M, Summerley R. Pyoderma gangrenosum associated with chronic active hepatitis. *Arch Dermatol* 1976; **112**: 1297–301.
15 Doyle JA, Schroeter AL, Rogers RS II. Hyperglucagonaemia and necrolytic migratory erythema in cirrhosis: possible pseudoglucagonoma syndrome. *Br J Dermatol* 1979; **101**: 581–7.
16 Gaveau D, Piette F, Cortot A *et al.* Manifestations cutanées du déficit en zinc dans la cirrhose éthylique. *Ann Dermatol Vénéréol* 1987; **114**: 39–53.
17 Weismann K, Verdich J. Acquired zinc deficiency in alcoholics with malnutrition. In: Wilkinson DS, Mascaró JM, Orfanos CE, eds. *The CMD Case Collection*, Vol. 37: *World Congress of Dermatology, Berlin 1987*. Stuttgart: Schattauer, 1987: 379–81.

Pancreatic disease

Apart from jaundice and panniculitis, skin changes associated with pancreatic disease are uncommon. As with other causes of chronic, localized pain, erythema ab igne has been described in the skin overlying the pancreas in cases of chronic pancreatitis. The glucagonoma syndrome is a rare but highly characteristic skin disorder, which is discussed below. The pancreas is often involved in haemochromatosis (see the section on liver disease, above). Skin disorders associated with diabetes mellitus are discussed in Chapter 59.

Acute pancreatitis [1–3]

Jaundice and fat necrosis (see below) may both be prominent. Purpura or bruising may occur in about 5% of patients with acute pancreatitis; note however that neither are specific for this cause, they may occur due to retroperitoneal haemorrhage, or bleeding from sources such as splenic rupture, ectopic pregnancy, metastatic tumour or aortic aneurysm. Four eponymous signs occur with retroperitoneal bleeding, the tracking of haemorrhagic fluid being:

1 Grey Turner sign (Turner sign)—tracks from the pararenal space to the edge of the quadratus lumborum muscle then through a defect in the fascia to the subcutaneous tissues of the flank (left sided in pancreatitis)
2 Cullen's sign—tracks into the falciparum ligament then through the connective tissues of the round ligament to the periumbilical area
3 Fox's sign—tracks along the fascia of the psoas and iliac muscles to the subcutaneous tissues of the upper thigh
4 Bryant's sign—tracks to the scrotum to produce the 'blue scrotum' sign.

Features of causative factors of pancreatitis may also be present, such as signs of alcohol abuse or hepatic cirrhosis, or xanthomas due to hypertriglyceridaemia.

Subcutaneous fat necrosis [1–7]

Synonym
- Nodular panniculitis

Systemic nodular fat necrosis is a rare condition that affects 2–3% of patients with pancreatic disease [6]. It may be associated with acute or chronic pancreatitis, post-traumatic pancreatitis or pancreatic carcinoma [1–3]. Pancreatitis accounts for about two-thirds and carcinoma one-third of reported cases [4]. Most of the reported

pancreatic neoplasms are acinous adenocarcinoma, which is rare. Subcutaneous fat necrosis associated with acute pancreatitis in a newborn has been reported [5].

The mechanism of fat necrosis is not fully understood, but the condition is probably due to the effect of enzymes released from damaged pancreatic tissue. However, the condition does not simply relate to release of amylase or lipase from the pancreas. Not only is fat necrosis relatively uncommon in pancreatitis, but the eruption does not correlate with enzyme levels—it may occur in patients with normal lipase levels, or fail to occur in subjects with grossly elevated levels. Furthermore, incubation of skin with lipase or with patient's serum *in vitro* fails to demonstrate fat necrosis [4]. Thus, other enzymes are presumably involved.

Clinical features. Pancreatic nodular fat necrosis is accompanied by fever, abdominal pain (less common in those with underlying carcinoma), blood eosinophilia and synovitis of the small joints. Either the nodules or the arthralgia may predominate. Nodular lesions are usually 1–3 cm in diameter and tender or symptomless. The areas of predilection are the trunk and the lower extremities, especially the anterior shins, but lesions may occur anywhere. Lesions persist for 2–3 weeks and usually heal without scar formation, leaving slightly depressed, hyperpigmented spots. More severe changes due to periarticular fat necrosis may occur. Polyserositis may be part of the syndrome [7]. Increased serum amylase or lipase levels can be demonstrated in most cases, but may be normal in cases due to carcinoma.

Histopathology. There are foci of subcutaneous fat necrosis, with ghost cells and a surrounding inflammatory infiltrate of neutrophils and eosinophils. At the periphery of the lesion histiocytes, foam cells and foreign-body giant cells are seen. Secondary calcification may be observed in necrotic areas.

Migratory thrombophlebitis [1–3,8–11]

Pancreatic cancer is one of the classical associations with Trousseau's sign, in which multiple, migratory, superficial thromboses occur. Recent studies indicate that lung cancer is the most common associated neoplasm in men aged over 40 years, but pancreatic cancer is still an important cause; historically, pancreatic cancer accounts for about 25–30% of cases of migratory thrombophlebitis. Cancers elsewhere in the gastrointestinal tract may also cause this condition. The usual interval to diagnosis is about 4 months from onset, but pancreatic neoplasia may present later than this [9]. The phlebitis is distributed on the trunk, neck and extremities and is usually limited to a short segment of the vein. A significantly increased frequency of deep venous thrombosis is also found. The cause is unknown, but probably related to increased levels of clotting factors and disordered fibrinolysis, a form of disseminated intravascular coagulopathy. The combination of thrombotic change with haemorrhage (purpura fulminans) may also occur as a paraneoplastic phenomenon. Thrombotic change may coexist with other paraneoplastic features; it was demonstrated in the skin of a patient with malignancy-associated fasciitis due to a pancreatic carcinoma [11]. Other signs of pancreatic carcinoma include cutaneous metastasis; about 10% of cases of Sister Mary Joseph's nodule (metastasis to the umbilicus) are due to pancreatic carcinoma [2].

Other dermatological features of pancreatitis

The main dermatological features of acute and chronic pancreatitis have been described above, or are the result of malabsorption in the chronic disease (Chapter 59). Livedo reticularis has also been described in both acute and chronic pancreatitis as 'Walzel's sign' [12,13].

References

1 Sibrack LA, Gouterman IH. Cutaneous manifestations of pancreatic diseases. *Cutis* 1978; **21**: 763–8.
2 Greer KE, Jorizzo JL. Pancreatic disease. In: Callen JP, Jorrizo JL, eds. *Dermatological Signs of Internal Disease*, 3rd edn. Philadelphia: Saunders, 2003: 217–20.
3 Braverman IM. *Skin Signs of Systemic Disease*, 3rd edn. Philadelphia: Saunders, 1998.
4 Berman B, Conteas C, Smith B, Leong S, Hornbeck L 3rd. Fatal pancreatitis presenting with subcutaneous fat necrosis: evidence that lipase and amylase alone do not induce lipocyte necrosis. *J Am Acad Dermatol* 1987; **17**: 359–64.
5 Dawson TSJ, Slattery C. Subcutaneous fat necrosis of the newborn and acute pancreatitis. *Br J Dermatol* 1979; **101**: 359.
6 Fine RM. Subcutaneous fat necrosis, pancreatitis and arthropathy. *Int J Dermatol* 1983; **22**: 575–6.
7 Polts DE, Iseman MD. Syndrome of pancreatic disease, subcutaneous fat necrosis and polyserositis: case report and review of literature. *Am J Med* 1975; **58**: 417–23.
8 Sproul EE. Carcinoma and venous thrombosis: the frequency of association of carcinoma in the body or tail of the pancreas with multiple venous thrombosis. *Am J Cancer* 1938; **34**: 566.
9 Sack GH, Levin J, Bell WR. Trousseau's syndrome and other manifestations of chronic disseminated coagulopathy in patients with neoplasms: clinical, pathophysiologic, and therapeutic features. *Medicine* 1977; **56**: 1–37.
10 James WD. Trousseau's syndrome. *Int J Dermatol* 1984; **23**: 205–6.
11 Cox NH, Ramsay B, Dobson C, Comaish JS. Woody hands in a patient with pancreatic carcinoma: a variant of cancer-associated fasciitis–panniculitis syndrome. *Br J Dermatol* 1996; **135**: 995–8.
12 Sigmund WJ, Shelley WB. Cutaneous manifestations of acute pancreatitis, with special reference to livedo reticularis. *N Engl J Med* 1954; **251**: 851–3.
13 Gould JW, Helms SE, Schulz SM, Stevens SR. Relapsing livedo reticularis in the setting of chronic pancreatitis. *J Am Acad Dermatol* 1998; **39**: 1035–6.

Necrolytic migratory erythema, pancreatic islet cell tumours and glucagonoma syndrome [1–6]

Necrolytic migratory erythema

Aetiology. Necrolytic migratory erythema is a cutaneous reaction that occurs in the context of hyperglucagonaemia. The syndrome was described in 1941 [1] and there have been several subsequent reviews [2–7]. The same condition occurs in dogs and other animals. It is usually due to a glucagonoma, an α-cell tumour, which is usually in the tail of the pancreas [4,8], and which secretes excessive amounts of proglucagon-like material [7]. However, it may also occur due to other causes such as pancreatic insufficiency [9], intestinal causes of malabsorption [6,9,10], intestinal protein loss (for example, secondary to lymphatic disease—Waldmann's syndrome [11]), hepatic cirrhosis [12,13], and aberrant glucagon-secreting tumours such as bronchial or nasopharyngeal carcinoma [14,15]. It has also been documented as an iatrogenic condition after administration of glucagon [6] and in a heroin abuser [16]. MEN (discussed below) is associated with glucagonoma, which occurs in about 3% of cases and accounts for about 20% of glucagonomas.

Hyperglucagonaemia also causes diabetes; the 'diabetico-dermatogenic syndrome' occurs in almost 60% of patients with glucagonoma [4], but when only some of the features are present this may lead to delay in diagnosis. Glucagon production and metabolism are discussed in [7].

The pathogenetic mechanism of the skin eruption is not certain, but the condition is probably due to hypoaminoacidaemia caused by high glucagon levels [5] or by intestinal protein loss or malabsorption. There may be a contributory role of essential fatty acid and zinc deficiencies, but abnormal zinc levels or response to zinc supplementation are not consistent, and correction of amino acid levels does not reliably lead to resolution of the skin eruption [16]. It is characteristic that all skin changes disappear after complete surgical removal of the tumour in cases in which this is the cause [17].

Clinical features. The typical patient with glucagonoma is a woman 45–65 years of age. The usual features are weight loss (67%), anaemia (33%), glucose intolerance (56%) and necrolytic migratory erythema (72%) [8]. The rash is itchy or burning and particularly affects flexural sites on the lower abdomen, groin, buttocks and thighs (Fig. 62.22). It is initially macular, extending to form superficially eroding areas of erythema that progress to fragile vesicle and bullae formation. Irregular centrifugal extension of the annular lesions causes a marginated, often crusted, polycyclic or geographical pattern. It has a prolonged, fluctuating course or cyclical pattern; the central part heals over 7–14 days, leaving postinflammatory pigmentation, while the erythematous periphery becomes crusted. Perianal and genital lesions are common. Angular cheilitis and a painful, beefy-coloured glossitis occur in about one-third of patients with glucagonoma [8].



Fig. 62.22 Glucagonoma syndrome. (Courtesy of Dr Kristian Thomsen, Finsen Institute, Copenhagen, Denmark.)

The clinical spectrum also includes diarrhoea (20%), weakness, venous thromboses (10%) and psychiatric disturbances. The plasma glucagon level is generally elevated several-fold above the upper limit of the normal range, but may show only minor elevation. The systemic features, such as weight loss, anaemia and hypoaminoacidaemia, are all more frequent in patients with glucagonoma with the diabetico-dermatogenic syndrome than in those without [4]. The same pattern of eruption has been described due to zinc deficiency with normal glucagon levels, usually in the context of liver disease.

Histopathology [2,3]. Biopsy should be taken from the edge of early lesions. The characteristic histological feature is well-demarcated necrolysis of the outer cell layers in the Malpighian stratum. Early lesions may present as a 'dyskeratotic dermatitis' with superficial perivascular inflammation in the dermis, and minor spongiosis and dyskeratotic or vacuolated epidermal cells [3,18]. Clefts and separation occur, associated with necrotic keratinocytes and cellular debris surrounding the cleft. In the dermis, a mild perivascular lymphocytic and histiocytic infiltrate is seen. Older lesions show various degrees of dyskeratosis, acanthosis and a lymphocytic infiltrate in the dermis. The histological changes are similar to those observed in acute zinc deficiency, in which cell degeneration and the formation of clefts and vesicles are predominant at the level of the basal cells.

Diagnosis. Pancreatic and hepatic scans and arteriography are helpful in locating a primary pancreatic tumour and its metastases if present. Serum amino acid, glucose, zinc and plasma glucagon levels should be determined. In cases with an elevated plasma glucagon level and a clinical and histological picture suggestive of the disease, surgical exploration should be performed.

Treatment. Where there is a glucagonoma, surgical resection is indicated, with embolization of hepatic metastases, which are present in the majority at the time of diagnosis. Various forms of chemotherapy have been used [2,5,19–21], such as streptozocin (a nitrosourea compound used for the ablation of β-cell adenoma) with 5-fluorouracil. Somatostatin is an inhibitor of glucagons but has a half life of just a few minutes, so analogues such as lanreotide, which is active for up to 2 weeks after intramuscular injection, are used therapeutically. Octreotide, a somatostatin analogue, rapidly improves symptoms, especially the rash, by altering glucagon metabolism, but it does not influence tumour growth [7,21]; dacarbazine is also useful [22]. Parenteral amino-acid infusions and correction of any essential fatty acid deficiency may be helpful [19], although the benefit of amino-acid infusions does not appear to be sustained long term [17]. In the rare cases related to malabsorption, correction of this (for example, GFD in coeliac disease) is usually effective [4,10].

Other non-insulin-secreting pancreatic endocrine tumours

Although glucagonoma is more important dermatologically, the most common islet cell tumours are insulinoma of β-cells and gastrinoma of δ-cells (Zollinger–Ellison syndrome, ZES). These do not have specific skin changes, but they may occur together with other tumours that secrete ACTH, MSH and serotonin; severe

diarrhoea in ZES may cause secondary hypovitaminosis and other nutritional deficiencies, giving rise to skin and hair changes. Both of these tumours occur sporadically or as part of the autosomal-dominant MEN type 1 syndrome (Wermer syndrome, MIM *131100), which is due to a mutation in the *MEN1* gene on chromosome 11q13. In this condition, as well as the endocrine tumours, other cutaneous features include angiofibromas, collagenomas, café-au-lait macules, lipomas and gingival macules [21]. MEN1 was associated with 13% of glucagonomas in one large series [4], and glucagonoma has also been reported in MEN2.

Tumours that produce vasoactive intestinal polypeptide (VIPomas) cause flushing (discussed in Chapter 43) with watery diarrhoea, hypokalaemia and achlorhydria [23]. A macular rash that resolved after tumour resection was reported in a patient with a pancreatic polypeptide-producing tumour of the pancreas (PPoma) [24].

References

1 Becker SW, Kahn D, Rothman S. Cutaneous manifestations of internal malignant tumors. *Arch Dermatol Syphilol* 1941; **45**: 1069–80.
2 Guillausseau PJ, Villet R, Kalloustian E *et al.* Les glucagonomes. Aspects cliniques, biologiques, anatomopathologiques et thérapeutiques (revue générale de 130 cas). *Gastroenterol Clin Biol* 1982; **6**: 1029–41.
3 Hashizumet T, Kiryu H, Noda K *et al.* Glucagonoma syndrome. *J Am Acad Dermatol* 1988; **19**: 377–83.
4 Soga J, Yakuwa Y. Glucagonomas/diabetico-dermatogenic syndrome (DDS): a statistical evaluation of 407 reported cases. *J Hepatobiliary Pancreat Surg* 1998; **5**: 312–9.
5 Chastain MA. The glucagonoma syndrome: a review of its features and discussion of new perspectives. *Am J Med Sci* 2001; **321**: 306–20.
6 Mullens EA, Cohen PR. Iatrogenic necrolytic migratory erythema: a case report and review of nonglucagonoma-associated necrolytic migratory erythema. *J Am Acad Dermatol* 1998; **38**: 866–73.
7 van Beek AP, de Haas ERM, van Vloten WA *et al.* The glucagonoma syndrome and necrolytic migratory erythema: a clinical review. *Eur J Endocrinol* 2004; **151**: 531–7.
8 Frankton S, Bloom SR. Glucagonomas. *Baillière's Clin Gastroenterol* 1996; **10**: 697–705.
9 Thorisdottir K, Camisa C, Tomecki KJ, Bergfeld WF. Necrolytic migratory erythema: a report of three cases. *J Am Acad Dermatol* 1994; **30**: 324–9.
10 Goodenberger DM, Lawley TJ, Strober W *et al.* Necrolytic migratory erythema without glucagonoma: a report of two cases. *Arch Dermatol* 1979; **115**: 1429–32.
11 Bancault S, Soubrane JC, Courville P *et al*. Necrolytic migratory erythema in Waldmann's disease. *Ann Dermatol Venereol* 2006; **133**: 693–6.
12 Doyle JA, Schroeter AL, Rogers RS III. Hyperglucagonaemia and necrolytic migratory erythema in cirrhosis: possible pseudoglucagonoma syndrome. *Br J Dermatol* 1979; **101**: 581–7.
13 Blackford S, Wright S, Roberts DL. Necrolytic migratory erythema without glucagonoma: the role of dietary essential fatty acids. *Br J Dermatol* 1991; **125**: 460–2.
14 Hunstein W, Trumper LH, Dummer R *et al.* Glucagonoma syndrome and bronchial carcinoma. *Ann Intern Med* 1988; **109**: 920–1.
15 Mohrenschlager M, Kohler LD, Bruckbauer H *et al*. Squamous epithelial carcinoma-associated necrolytic migratory erythema. *Hautarzt* 1999; **50**: 198–202.
16 Bencini PL, Vigo GP, Caputo R. Necrolytic migratory erythema without glucagonoma in a heroin-dependent patient. *Dermatology* 1994; **189**: 72–4.
17 Abraira C, DeBartolo M, Katzen R, Lawrence AM. Disappearance of glucagonoma rash after surgical resection but not during dietary normalization of serum amino acids. *Am J Clin Nutr* 1984; **39**: 351–5.
18 Hunt SJ, Narus VT, Abell E. Necrolytic migratory erythema: dyskeratotic dermatitis, a clue to early diagnosis. *J Am Acad Dermatol* 1991; **24**: 473–7.
19 Bewley AP, Ross JS, Bunker CB, Staughton RCD. Successful treatment of a patient with octreotide-resistant necrolytic migratory erythema. *Br J Dermatol* 1996; **134**: 1101–4.
20 Jockenhovel F, Lederbogen S, Olbricht T *et al.* The long-acting somatostatin analogue octreotide alleviates symptoms by reducing posttranslational conversion of prepro-glucagon to glucagon in a patient with malignant glucagonoma, but does not prevent tumour growth. *Clin Invest* 1994; **72**: 127–33.
21 Loos van der TLJM, Lambrecht ER, Lambers ICCA. Successful treatment of glucagonoma related necrolytic migratory erythema with dacarbazine. *J Am Acad Dermatol* 1987; **16**: 468–72.
22 Darling TN, Skarulis MC, Steinberg SM *et al.* Multiple facial angiofibromas and collagenomas in patients with multiple endocrine neoplasia type 1. *Arch Dermatol* 1997; **133**: 853–7.
23 Park SK, O'Dorisio MS, O'Dorisio TM. Vasoactive intestinal polypeptide-secreting tumours: biology and therapy. *Baillière's Clin Gastroenterol* 1996; **10**: 673–96.
24 Choski UA, Sellin RV, Hickey RC *et al.* An unusual skin rash associated with a pancreatic polypeptide-producing tumor of the pancreas. *Ann Intern Med* 1988; **108**: 64–5.

Renal disease [1–4]

The skin and renal systems may be affected not uncommonly by the same disease processes. The more important of these renocutaneous syndromes are listed in Table 62.14.

Hereditary syndromes and malformations

Angiokeratoma corporis diffusum (Fabry's disease; MIM *301500; Chapter 59). Affected individuals often show proteinuria, microscopic haematuria and lipiduria. Renal disease eventually develops in most male patients, and as lipid deposition in the form of glycosphingolipids occurs, renal function deteriorates. The premature mortality in the condition is often a result of renal failure. Renal transplantation can supply a source of the deficient enzyme lysosomal hydrolase, α-galactosidase A, and results in an improvement in the condition; commercial preparations of this enzyme are

Table 62.14 Renocutaneous syndromes.

Hereditary syndromes
Angiokeratoma corporis diffusum
Neurofibromatosis
Tuberous sclerosis
Nail–patella syndrome
Birt–Hogge–Dubé syndrome
Sickle cell disease
Pseudoxanthoma elasticum
Oral–facial–digital syndrome
von Hippel–Lindau disease
Hereditary haemorrhagic telangiectasia
Metabolic disorders
Primary systemic amyloidosis
Calcinosis
Inflammatory and miscellaneous
Allergic vasculitis
Systemic lupus erythematosus
Polyarteritis nodosa
Scleroderma
Nephrogenic fibrosing dermopathy (nephrogenic systemic fibrosis)
Wegener's granulomatosis
Erythema multiforme
Anaphylactoid purpura
Drug-induced toxic epidermal necrolysis

also now available (see Chapter 59). Other enzyme defects may give rise to the same clinical phenotype.

Neurofibromatosis (NF1, MIM *162200; NF2, MIM *101000; von Recklinghausen's disease) (Chapter 15). Urinary outflow obstruction may develop secondary to an impinging neurofibroma. Vascular lesions can result in renal artery thrombosis and subsequent hypertension. In patients with hypertension, normal plasma and urine catecholamine levels—especially those under the age of 20 years—renal artery stenosis should be suspected [5]. Raised blood pressure may also develop as a result of an associated phaeochromocytoma. Causes of hypertension in neurofibromatosis should be fully investigated [5]. Nephroblastoma is a recognized association in neurofibromatosis [6] and renal polycystic disease.

Tuberous sclerosis complex (TSC1, MIM #191100; TSC2, MIM *191092; Bourneville's disease; Chapter 15). An increased incidence of rhabdomyomas and carcinoma may occur in this condition [7]. Malignant renal tumours may include renal cell carcinoma, malignant angiomyolipoma and Wilms' tumour [8]. The classical renal lesion associated with tuberous sclerosis is an angiomyolipoma. Renal cysts also occur in conjunction with these, or as isolated findings [9].

Nail–patella syndrome (Fong's syndrome; hereditary osteo-onychodysplasia; MIM #161200; Chapters 15, 65). The defective gene *LMX1B* is located on the long arm of chromosome 9 (9q34.1); this gene regulates type IV and VI collagen expression, which in turn affects skeletal and basement membrane structure and function [10]. *LMXIB* is expressed in the kidney, primarily in podocytes, and regulates many crucial podocyte proteins. Renal dysplasia presenting as chronic glomerulonephritis occurs in some cases, and characteristic electron-microscopic glomerular abnormalities are present in most cases of nail–patella syndrome. The ultrastructural features consist of thickening and splitting of the glomerular basement membrane and fibrillar α3(IV) and α4(IV) collagen deposits. Renal lesions are asymptomatic; patients show proteinuria, haematuria and reduced creatinine clearance. Although there is often a progressive course to renal failure, many patients with the complication do surprisingly well. Helpful diagnostic signs include small, defective nails that do not reach the free nail border, triangular lunulae, the thumbnails being the most frequently and severely affected nails and the severity of the defect reducing from the index to little finger nails. There is absence of the skin creases on the dorsal interphalyngeal joints [11]. The patellae are less well developed, potentially giving stability problems for the knee and there is instability of the radial head; other indicators include (radiologically) posterior iliac horns and (ophthalmically) irregular hyperpigmented pupillary borders. There is a tendency to glaucoma.

Birt–Hogge–Dubé syndrome (BHD; Hornstein–Knickenberg syndrome; MIM #135150). Hereditary renal cell cancer syndromes include BHD, von Hippel–Lindau disease, as well as hereditary papillary renal cell carcinoma, familial oncocytoma and hereditary renal cell carcinoma of various types [12].

The cutaneous features of BHD include trichofolliculomas, trichidiscomas and skin tags. Pulmonary cysts, predominantly basilar, may cause spontaneous pneumothorax. A variety of coding sequence mutations have been linked to the 17p11.2 chromosome [12].

Hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome (MIM #605839). Multiple cutaneous leiomyomas, which have an inherited predisposition, are linked to uterine leiomyoma (Reed syndrome, MIM #150800) and also appear to be associated with an increased incidence of renal cell carcinoma, usually aggressive and of papillary cell type. Numerous different fumarate hydratase mutations have been identified, but the patients who have renal cell carcinomas associated (only 2% in one series) are more likely to have truncating or frameshift mutations and be female [13]; see also the section 'Cutaneous markers of internal malignancy' above, p. 62.29.

Multiple hamartoma and neoplasia syndrome (Cowden's disease; MIM #158350). This is associated with an increased incidence of renal cell carcinoma, liposarcoma and transitional cell carcinoma of the bladder [8]. It is discussed earlier in this chapter.

von Hippel–Lindau syndrome (VHL; MIM *193300; see earlier in this chapter and Chapter 15). Renal lesions in VHL are either simple cysts or adenocarcinomas; usually they are a late manifestation. Renal carcinoma may present with cutaneous metastases several years in advance of the systemic malignancy; alternatively, cutaneous deposits may indicate a recurrence of previously treated neoplasia [3]. von Hippel–Lindau syndrome represents one of the hereditary kidney cancer syndromes in which a two-hit model of tumour genesis occurs, explaining the often late development of this complication.

The other tumours linked to VHL are dealt with in Chapter 15, but phaeochromocytomas and pancreatic tumours can occur with increased frequency in close anatomical association with each other.

Familial Mediterranean fever with urticaria (FMFU), Muckle–Wells syndrome (MWS) and tumour necrosis receptor associated periodic syndrome (TRAPS) [14,15]. These 'autoinflammatory syndromes' are all associated with a significant risk of renal failure secondary to amyloidosis, frequently resulting in premature death (see also later in this chapter).

Oral–facial–digital syndrome [16]. Oral–facial–digital syndrome type I (OFD1) is characterized by the following abnormalities: oral (lobed tongue, hamartomas or lipomas of the tongue, cleft of the hard or soft palate, accessory gingival frenulae, hypodontia and other dental abnormalities); facial (ocular hypertelorism or telecanthus, hypoplasia of the alae nasi, median cleft or pseudocleft upper lip, micrognathia); digital (brachydactyly, syndactyly of varying degrees, and clinodactyly of the fifth finger; duplicated hallux [great toe]; preaxial or postaxial polydactyly of the hands) and brain (intracerebral cysts, corpus callosum agenesis, cerebellar agenesis with or without Dandy–Walker malformation). Polycystic disease of the kidneys and liver occurs commonly in this

condition. As many as 50% of individuals with OFD1 have some degree of mental retardation, which is usually mild. Almost all affected individuals are female. However, males with OFD1 have been described, mostly as malformed fetuses born to women with OFD1.

References

1 Gupta AK, Gupta MA, Cardella CJ *et al.* Cutaneous associations of chronic renal failure and dialysis. *Int J Dermatol* 1986; **25**: 498–504.
2 Dymock RB. Skin disease associated with renal transplantation. *Australas J Dermatol* 1979; **20**: 61–7.
3 Christianson HB, Birchall R. Nephrocutaneous syndromes. *South Med J* 1964; **57**: 1043–50.
4 Callen JP. Cutaneous nephrology. In: Callen JP, Jorizzo JL, eds. *Dermatological Signs of Internal Disease*, 3rd edn. Philadelphia: Saunders, 2003: 271–4.
5 Riccardi VM. *Neurofibromatosis: Phenotype, Natural History, and Pathogenesis*, 2nd edn. Baltimore: Johns Hopkins University Press, 1992.
6 Stay EJ, Vawter G. The relationship between nephroblastoma and neurofibromatosis (von Recklinghausen's disease). *Cancer* 1977; **39**: 2550–5.
7 Lynne CM, Carrion HM, Bakshandeh K *et al.* Renal angiomyolipoma, polycystic kidney and renal cell carcinoma in patients with tuberous sclerosis. *Urology* 1979; **14**: 174–6.
8 Tsao H. Update on familial cancer syndromes and the skin. *J Am Acad Dermatol* 2000; **42**: 939–69.
9 Stillwell TJ, Gomez MR, Kelalis PP. Renal lesions in tuberous sclerosis. *J Urol* 1987; **138**: 477–81.
10 Stratigos AJ, Baden HP. Unraveling the molecular mechanisms of hair and nail genodermatoses. *Arch Dermatol* 2001; **137**: 1465–71.
11 Itin PH, Eich G, Fistarol SK. Missing creases of distal finger joints as a diagnostic clue of nail-patella syndrome. *Dermatology* 2006; **213**: 153–5.
12 Choyke PL, Sharma N, Peterson J *et al*. Germline BHD-mutation spectrum and phenotype analysis of a large cohort of families with Birt-Hogg-Dube syndrome. *Am J Hum Genet* 2005; **76**: 1023–33.
13 Alam NA, Olpin S, Leigh IM. Fumarate hydratase mutations and predisposition to cutaneous leiomyomas, uterine leiomyomas and renal cancer. *Br J Dermatol* 2005; **153**: 11–7.
14 Ozen S, Hoffman HM, Frenkel J, Kastner D. Familial Mediterranean fever (FMF) and beyond: a new horizon. Fourth International Congress on the Systemic Autoinflammatory Diseases held in Bethesda, USA, 6–10 November 2005. *Ann Rheum Dis* 2006; **65**: 961–4.
15 Dinc A, Erdem H, Rowczenio D *et al*. Autosomal dominant periodic fever with AA amyloidosis: tumor necrosis factor receptor-associated periodic syndrome (TRAPS) in a Turkish family. *J Nephrol* 2000; **18**: 626–9.
16 Thauvin-Robinet C, Cossée M, Cormier-Daire V *et al*. Clinical, molecular, and genotype-phenotype correlation studies from 25 cases of oral-facial-digital syndrome type 1: a French and Belgian collaborative study. *J Med Genet* 2006; **43**: 54–61.

Metabolic and systemic disorders

Partial lipodystrophy

Renal disorders occur frequently in this condition (25%), usually as a membranoproliferative glomerulonephritis; subsequent renal failure is common at an early age. There is a circulating C3 nephritic factor and reduced levels of complement (C3) [1]. An association with hereditary angio-oedema (C1 inhibitor deficiency) has been reported [2].

Primary and myeloma-associated systemic amyloidosis (Chapter 59)

Up to 40% of patients have waxy, purpuric cutaneous or mucosal changes, periocular lesions are the most recognizable [3] and diagnostically useful. Typically, patients may also have macroglossia, hepatomegaly, oedema and carpal tunnel syndrome. Cutis laxa-like clinical changes have also been reported [4]. Without dialysis, renal failure is often fulminant and fatal; peritoneal dialysis may be the most appropriate approach. Although renal amyloid may recur after transplantation, this is not completely contraindicated [5]. Primary cutaneous amyloid does not appear to have renal associations. Nodular or tumid amyloidosis was said to represent an early phase of systemic amyloid, but recent studies have reported only a 7% progression to systemic disease after long follow up [6].

Calcification and calcific uraemic arteriolopathy (calciphylaxis) (see also Chapter 49)

Calcifying panniculitis has been reported occasionally in renal failure, a disorder now termed calcific uraemic arteriolopathy [7–9]. It is usually, but not invariably, associated with a high serum calcium phosphate product. Metastatic skin calcification is a rare phenomenon in uraemic patients; it usually presents as papular or nodular cutaneous lesions around large joints or flexural sites. Non-cutaneous metastatic calcification is, by comparison, much commoner. Metastatic calcification in blood vessel walls associated with hyperparathyroidism and renal failure (calcific uraemic vasculopathy, calciphlaxis) may lead to cutaneous necrosis or gangrene as a result of thrombosed vessels (Fig. 62.23); however, calcification does not always need to be present, and vascular damage may be triggering a premature haemostatic cascade. This carries a poor prognosis, in one series, only 40% of patients survived a year after diagnosis. Risk factors included obesity, liver disease, systemic steroid use, and a high calcium phosphate product and high serum aluminium [9]. Treatments include low phosphate dialysate fluids, non-calcium phosphate binders, parathyroidectomy, and more recently drugs such as sodium thiosulphate or cinacalcet which alter calcium metabolism.

References

1 Misra A, Peethambaram A, Garg A. Clinical features and metabolic and autoimmune derangements in acquired partial lipodystrophy: report of 35 cases and review of the literature. *Medicine (Baltimore)* 2004; **83**: 18–34.



Fig. 62.23 Calcific uraemic arteriolopathy of the thighs in a patient with renal failure. (Courtesy of Dr C. Owen, Royal Blackburn Hospital, Lancashire.)

2 Frank MM, Gelfand JA, Atkinson JP. Hereditary angio-edema: the clinical syndrome and its management. *Ann Intern Med* 1976; **84**: 580–93.
3 Breathnach SM. Amyloid and amyloidosis. *J Am Acad Dermatol* 1988; **18**: 1–16.
4 Newton JA, McKee PH, Black MM. Cutis laxa associated with amyloidosis. *Clin Exp Dermatol* 1986; **11**: 87–91.
5 Wong CK. Cutaneous amyloidoses. *Int J Dermatol* 1987; **26**: 273–7.
6 Woollons A, Black MM. Nodular localized primary cutaneous amyloidosis: a long-term follow-up study. *Br J Dermatol* 2001; **145**: 105–9.
7 Laurent R, Thiery F, Saint-Hillier Y *et al.* Panniculite calcificante associée à une insuffisance rénale: un syndrome de calciphylaxie tissulaire. *Ann Dermatol Vénéréol* 1987; **14**: 1073–81.
8 Richens G, Piepkorn MW, Krueger GG. Calcifying panniculitis associated with renal failure. *J Am Acad Dermatol* 1982; **6**: 537–9.
9 Weenig RH, Sewell LD, Davis MD *et al*. Calciphylaxis: natural history, risk factor analysis, and outcome. *J Am Acad Dermatol* 2007; **56**: 569–79.

Sarcoidosis and the kidney [1,2]

Nephrolithiasis and nephrocalcinosis occur in patients with sarcoidosis with a 20% higher frequency than in the normal population. Hypercalcaemia which occurs in sarcoidosis may cause polyuria and polydipsia, and may even precipitate acute renal failure. Renal sarcoidosis can give rise to diffuse interstitial nephritis, but it is seldom that there are identifiable granulomas or direct renal involvement. Rarely, cases of outflow obstruction from retroperitoneal sarcoidal masses and sarcoid of the urethra have been reported [3].

References

1 English JC 3rd, Patel PJ, Greer KE. Sarcoidosis. *J Am Acad Dermatol* 2001; **44**: 725–43.
2 Berliner AR, Haas M, Choi MJ. Sarcoidosis: the nephrologist's perspective. *Am J Kidney Dis* 2006; **48**: 856–70.
3 Carr LK, Honey RJ, Sugar L. Diagnosis and management of urethral sarcoidosis. *J Urol* 1995; **153**: 1612–3.

Vasculitis (Chapter 50)

Renal involvement commonly occurs in various types of vasculitis that present with cutaneous changes and is the main cause of mortality in many of these syndromes. This should be considered particularly in classical Henoch–Schönlein purpura (anaphylactoid purpura), especially in adults, where IgA nephropathy has become recognized as a fairly common form of glomerulonephritis [1]. An association between anaphylactoid purpura and familial IgA nephropathy has also been described [2]. Patients labelled as having allergic vasculitis and arteritis with livedo reticularis [3] should also be regarded as being at risk of kidney damage.

Renal failure is a recognized, but rare, complication of Behçet's syndrome, usually with immune-complex deposition [4]. Concomitant or delayed renal involvement is common in Wegener's granulomatosis, usually as a focal necrotizing glomerulitis. Deposits of IgM and IgG are present in renal vessels and circulating immune complexes are also frequently detected [5]. Renal changes that occur in these conditions, and in collagen vascular disorders such as polyarteritis nodosa, systemic lupus erythematosus and scleroderma, are considered in Chapters 50 and 51.

References

1 Saulsbury FT. Clinical update: Henoch-Schönlein purpura. *Lancet* 2007; **24**; 369, 976–8.
2 Miyagawa S, Dohi K, Hanatani M *et al.* Anaphylactoid purpura and familial IgA nephropathy. *Am J Med* 1989; **86**: 340–2.
3 Cream JS, Gumpel JM, Peachy RD. Schönlein–Henoch purpura in the adult: a study of 77 adults with anaphylactoid or Schönlein–Henoch purpura. *QJM* 1970; **39**: 461–84.
4 Wilkey D, Yocum DE, Oberley TD *et al.* Budd–Chiari syndrome and renal failure in Behçet disease. *Am J Med* 1983; **75**: 541–50.
5 Aasarød K, Iversen BM, Hammerstrøm J *et al*. Wegener's granulomatosis: clinical course in 108 patients with renal involvement. *Nephrol Dial Transplant* 2000; **15**: 611–8.

Renal disease in bullous disorders

Bullous pemphigoid. Renal disease, including membranous glomerulopathy, diffuse proliferative and mesangioproliferative glomerulonephritis, has been infrequently reported in patients with pemphigoid [1].

Toxic epidermal necrolysis (TEN) [2]. Deteriorating renal function is a poor prognostic factor in TEN, and is one of the parameters used in the SCORTEN prognostic score.

Epidermolysis bullosa (EB). Renal failure was the second most common cause of death (with a mean age of 35) in 12% of adults with recessive dystrophic EB of the Hallepeau–Siemens type [3]. It was surpassed as a cause of death only by metastatic squamous cell carcinoma. Renal failure due to IgA nephropathy, and post-infectious membranoproliferative glomerulonephritis, has complicated recessive dystrophic EB. Obstructive uropathy has been seen in junctional EB. Surveillance for early renal involvement should become part of the routine evaluation of all adults with RDEB and JEB [4].

References

1 Ross EA, Ahmed AR. Bullous pemphigoid-associated nephropathy: report of two cases and review of the literature. *Am J Kidney Dis* 1989; **14**: 225–9.
2 Blum L, Chosidow O, Rostoker G *et al*. Renal involvement in toxic epidermal necrolysis. *J Am Acad Dermatol* 1996; **34**: 1088–90.
3 Fine JD, Johnson LB, Weiner M *et al*. National Epidermolysis Bullosa Registry. Inherited epidermolysis bullosa and the risk of death from renal disease: experience of the National Epidermolysis Bullosa Registry. *Am J Kidney Dis* 2004; **44**: 651–60.
4 Chan SM, Dillon MJ, Duffy PG, Atherton DJ. Nephro-urological complications of epidermolysis bullosa in paediatric patients. *Br J Dermatol* 2007; **156**: 143–7.

Infective dermatoses causing renal disease

Streptococcal impetigo. An acknowledged cause of acute glomerulonephritis, particularly when streptococcal infection occurs secondary to scabies [1], but most cases of acute nephritis are not the sequel of streptococcal infection.

Secondary syphilis. A rare cause of the nephrotic syndrome.

Herpes zoster. If affecting the appropriate dermatomes, herpes zoster cause neurogenic bladder dysfunction and pain [2], leading to acute urinary retention.

References

1 Svartman M, Potter EV, Poon-King T, Earle DP. Streptococcal infection of scabetic lesions related to acute glomerulonephritis in Trinidad. *J Lab Clin Med* 1973; **81**: 182–93.
2 Izumi AK, Edwards J Jr. Herpes zoster with neurogenic bladder dysfunction. *Arch Dermatol* 1974; **109**: 692–4.

Renal failure and dialysis [1–3]

Cutaneous signs of renal failure are mainly related to chronicity of disease. Urea frosting, in which crystalline urea is deposited on the skin, is now very rare, but dry, pigmented skin with excoriations is typical.

Uraemic patients tend to have a dry skin, sometimes with fine scaling. A reduction in the size of eccrine sweat glands in uraemia may contribute to this effect [4], although high-dose diuretic regimens are a co-factor [5].

Pigmentation. Anaemia presenting as pallor is an early and common sign in renal failure, resulting from reduced erythropoiesis and increased haemolysis.

A muddy brown hyperpigmentation develops in many cases, attributed to retention of chromogens and deposition of melanin, possibly due to impaired renal processing of melanocyte-stimulating hormone [6]. Increased nail pigmentation, usually confined to the distal aspect, occurs in a proportion of patients [7]. This distal brown or more normal red colour, combined with a proximal white appearance gives rise to the 'half-and-half' nails, a distinctive pattern seen in about 10% of patients with renal failure [8].

Purpura due to a mild thrombocytopenia or more marked platelet dysfunction is common and may be partly corrected by dialysis [9]. Wound healing is prolonged and patients may be more susceptible to pressure sores.

Pruritus. Generalized, severe pruritus occurs in about one-third of renal failure cases, less troublesome involvement occurs in many more. Unfortunately, haemodialysis can initiate the symptom as well as improve it. Up to 85% of patients on haemodialysis suffered from itching in one study [10], one-third before dialysis, the others after; 12% had reduced pruritus after 6 months' dialysis. There seems to be an association with predialysis blood urea levels, and a less clear correlation with dry skin and secondary hyperparathyroidism [11]. Subtotal parathyroidectomy may be very helpful [12], but the problem can subsequently recur, and many cases are not related to secondary hyperparathyroidism. Moreover, many patients with this finding do not itch. A complete explanation for pruritus in renal failure is obscure, as pruritus is unusual in acute renal failure and a reduction in uraemia often does not improve the symptom. Slowly accumulated or deposited pruritogen(s), of as yet uncertain nature, are the likely cause. In dialysis, lowering the magnesium concentration of the dialysate has been reported as helpful [13]. In intractable itching, UVB radiation is an effective therapy [14], benefit being associated with a reduction of skin phosphorus to normal values. Ultraviolet A (without psoralen) has been reported nearly as effective [15]; oral cholestyramine and activated charcoal are alternatives [16,17]. Erythropoietin therapy can alleviate pruritus in some cases of renal failure. Naltrexone (and other opioids such as nalmefene) and odansetron have also been reported to help uraemic pruritus [11]. Gabapentin has recently been demonstrated to be effective in uraemic pruritus [18].

Perforating disorders. A perforating disorder variously described as acquired reactive perforating collagenosis, Kyrle's disease or perforating folliculitis occurs in renal failure; often there is diabetes, diabetic nephropathy and/or retinopathy. Pruritus is nearly always present, and up to 10% of dialysis patients may be affected. The condition seems to have a higher incidence in Afro-Caribbeans. The cutaneous lesions consist of hyperpigmented papules up to 1 cm in diameter with a central keratinous plug (Fig. 62.24). The extensor surfaces of the limbs are more commonly affected but the trunk and face may be involved. The pathogenesis is uncertain, but there is some histological evidence that it is a perforating collagenosis [19,20].



Fig. 62.24 Reactive perforating collagenosis in end-stage renal failure.

Other cutaneous features. Uraemic neuropathy affects some 60% of patients with renal failure or on long-term haemodialysis. This appears to be a predominantly sensorimotor neuropathy [20].

Up to 40% of patients with renal failure may develop gynaecomastia while receiving dialysis [21]. Calcinosis cutis may occur in 1% of patients with end-stage renal disease [22]. It may be reversed by a low phosphorus diet and aluminium hydroxide gel.

Features related to treatment. Premature ageing of the skin and actinic keratoses have been described, a reason for avoiding excessive ultraviolet therapy for pruritus. This should be distinguished from the numerous viral, dysplastic and frankly malignant skin lesions which may develop in immunosuppressed renal allograft recipients.

Cutaneous complications affecting the limb of patients in which their haemodialysis arteriovenous shunt is situated include infection, phlebitis and haematoma. However, both irritant and allergic contact eczema may also develop [23]. Vascular complications of arteriovenous fistula construction are relatively uncommon, but include digital ischaemia and aneurysm formation. The venous hypertension syndrome with or without ulceration may occur; pseudo-Kaposi's sarcoma [24], and pyoderma gangrenosum [25], are both rare developments.

Bullous eruptions mimicking PCT (pseudoporphyria of haemodialysis) are well recognized, with an incidence reported at between 2 and 18%. True porphyria cutanea tarda due to defi-

ciency of uroporphyrin decarboxylase is reported but uncommon. Distinguishing these two conditions can be difficult as many patients on haemodialysis have elevated blood porphyrin levels slightly above what is regarded as the normal range due to their reduced excretion; the importance of accurate assays is emphasized [26,27]. Photosensitizing drugs such as furosemide, oestrogens and non-steroidal anti-inflammatory agents may also induce a pseudoporphyria picture. In all cases, UV protection is important. *N*-acetylcysteine, which acts as an antioxidant, may help reduce the blistering [28]. Treatment of true PCT in patients with end-stage renal failure is limited as antimalarials work by binding porphyrins and renal excretion of the complexes formed (which will not occur in many patients with renal failure, as the complexes will not be excreted by anuric subjects and will not cross dialysis membranes), and venesection is limited by anaemia; treatment with erythropoietin to increase conversion of porphyrin to haem is the usual approach.

Nephrogenic systemic fibrosis. A condition termed nephrogenic fibrosing dermopathy, or, more recently, nephrogenic systemic fibrosis, was initially linked with haemodialysis but occurs in other patients with renal failure [29–31]. Clinical features include indurated plaques, sometimes with finger-like projections, that may be erythematous, yellowish or skin-coloured. Nodules and contractures occur in more advanced disease. Scleral plaques may also occur, although the face is usually spared (by contrast with scleromyxoedema). There may be internal organ involvement (hence the more modern term nephrogenic systemic fibrosis), and death and severe disability can ensue. Involvement of the diaphragm is frequently the event that leads to death and 10% of patients have a fulminant course. Histology shows increased mucin deposition and spindle cells and compact collagen bundles. There has been a strong association with the use of radio-contrast agents that contain gadolinium, such as gadodiamide, which are used to enhance magnetic resonance imaging of vessels [32,33]. Such contrast media are now not recommended for use in patients with a GFR less than 30 ml/min [32,33] as they are renally excreted and have a tissue half-life about 10-fold longer in those with severe renal impairment compared to normal subjects. The resulting prolonged high tissue levels may be pro-fibrotic. A recent study using quantitative scanning electron microscopy/energy-dispersive X-ray spectroscopy demonstrated the presence of gadolinium in the skin of 20 patients with nephrogenic systemic fibrosis but not in the skin of a gadodiamide-exposed patient with renal failure but without fibrosis; importantly, where repeat biopsies were examined, gadolinium levels increased for almost 2 years in 60% of subjects [34]. On the basis that the toxic Gd^{3+} ion is retained in apatite-like structures, the findings suggested that there might be gradual mobilization of gadolinium from bone stores, explaining the variability in timing and extent of fibrosis.

References

1 Gupta AK, Gupta MA, Cardella CJ *et al*. Cutaneous associations of chronic renal failure and dialysis. *Int J Dermatol* 1986; **25**: 498–504.
2 Dymock RB. Skin disease associated with renal transplantation. *Australas J Dermatol* 1979; **20**: 61–7.
3 Callen JP. Cutaneous nephrology. In: Callen JP, Jorizzo JL, eds. *Dermatological Signs of Internal Disease*, 3rd edn. Philadelphia: Saunders, 2003: 271–4.
4 Landing BH, Wells TR, Williamson ML. Anatomy of eccrine sweat glands in children with chronic renal failure, insufficiency and other fatal chronic disease. *Am J Clin Pathol* 1970; **54**: 15–21.
5 Graham RM. Aspects of itching. In: Verbov JL, ed. *New Approaches in Dermatology*. Lancaster: MTP Press, 1987: 49–70.
6 Gilkes JJ, Eady RA, Rees LH *et al*. Plasma immunoreactive melanotrophic hormones in patients on maintenance haemodialysis. *BMJ* 1975; **i**: 656–7.
7 Kint A, Bussels L, Fernandes M *et al*. Skin and nail disorders in relation to chronic renal failure. *Acta Derm Venereol* 1974; **54**: 137–40.
8 Baran R, Dawber RP, eds. *Diseases of the Nails and Their Management*. Oxford: Blackwell Scientific Publications, 1984.
9 Stewart JH, Castaldi PA. Uraemic bleeding: a reversible platelet defect corrected by dialysis. *QJM* 1967; **36**: 409–23.
10 Young AW Jr, Sweeney EW, David DS *et al*. Dermatologic evaluation of pruritus in patients on hemodialysis. *N Y State J Med* 1973; **73**: 2670–4.
11 Murphy M, Carmichael AJ. Renal itch. *Clin Exp Dermatol* 2000; **25**: 103–6.
12 Massry SG, Popovtzer MM, Coburn JW *et al*. Intractable pruritus as a manifestation of secondary hyperparathyroidism in uraemia: disappearance of itching after subtotal parathyroidectomy. *N Engl J Med* 1968; **279**: 697–700.
13 Graf H, Kovarik J, Stummvoll HK *et al*. Disappearance of uraemic pruritus after lowering dialysate magnesium concentration. *BMJ* 1979; **2**: 1478–9.
14 Blachley JD, Blankenship DM, Menter A *et al*. Uremic pruritus, skin divalent ion content and response to ultra-violet phototherapy. *Am J Kidney Dis* 1985; **1**: 752–93.
15 Hindson C, Taylor A, Martin A *et al*. UVA—light relief of uraemic pruritus. *Lancet* 1981; **i**: 215.
16 Pederson JA, Matter BJ, Czerwinski AW *et al*. Relief of idiopathic generalized pruritus in dialysis patients with activated oral charcoal. *Ann Intern Med* 1980; **93**: 446–8.
17 Silverberg DS, Iaina A, Reisin E *et al*. Cholestyramine in uraemic pruritus. *BMJ* 1977; **1**: 215.
18 Faver IR, Daoud MS, Su WP. Acquired reactive perforating collagenosis. Report of six cases and review of the literature. *J Am Acad Dermatol* 1994; **30**: 575–80.
19 Prioleau PG, Varghese M. The perforating dermatoses. In: Lebwohl M, ed. *Difficult Diagnoses in Dermatology*. New York: Churchill Livingstone, 1988.
20 Dellantonio R, Paladini D, Carletti P *et al*. Sympathetic skin response in chronic renal failure and correlation with sensorimotor neuropathy. *Funct Neurol* 1989; **4**: 173–5.
21 Freeman RM, Lawton RL, Fearing MO. Gynecomastia: an endocrinologic complication of hemodialysis. *Ann Intern Med* 1968; **69**: 67–72.
22 Rivet J, Lebbé C, Urena P *et al*. Cutaneous calcification in patients with end-stage renal disease: a regulated process associated with in situ osteopontin expression. *Arch Dermatol* 2006; **142**: 900–6.
23 Goh CL, Phay KL. Arteriovenous shunt dermatitis in chronic renal failure patients on maintenance haemodialysis. *Clin Exp Dermatol* 1988; **13**: 379–81.
24 Irvine C, Holt P. Hand venous hypertension complicating arteriovenous fistula construction for haemodialysis. *Clin Exp Dermatol* 1989; **14**: 289–90.
25 Sangiray H, Nguyen JC, Turiansky GW, Norwood C. Pyoderma gangrenosum occurring near an arteriovenous dialysis shunt. *Int J Dermatol* 2006; **45**: 851–3.
26 Poh-Fitzpatrick MB, Sosin AE, Bemis J. Porphyria levels in plasma and erythrocytes of chronic hemodialysis patients. *J Am Acad Dermatol* 1982; **7**: 100–4.
27 Topi GC, D'Alessandro GL, Cancarini GC *et al*. Porphyria cutanea tarda in a haemodialysis patient. *Br J Dermatol* 1981; **104**: 579–80.
28 Cooke NS, McKenna K. A case of haemodialysis-associated pseudoporphyria successfully treated with oral N-acetylcysteine. *Clin Exp Dermatol* 2007; **32**: 64–6.
29 Cowper S, Robin H, Steinberg S *et al*. Scleromyxedema-like cutaneous diseases in renal-dialysis patients. *Lancet* 2000; **356**: 1000–1.
30 Streams BN, Liu V, Liégeois N, Moschella SM. Clinical and pathologic features of nephrogenic fibrosing dermopathy: a report of two cases. *J Am Acad Dermatol* 2003; **48**: 42–7.
31 Mackay-Wiggan JM, Cohen DJ, Hardt MA *et al*. Nephrogenic fibrosing dermopathy (scleromyxedema-like illness of renal disease). *J Am Acad Dermatol* 2003; **48**: 55–60.
32 High WA. Nephrogenic systemic fibrosis and gadolinium-based contrast agents. *Expert Rev Dermatol* 2007; **2**: 593–605.

33 Marckmann P, Skov L, Rossen K *et al*. Nephrogenic systemic fibrosis: suspected causative role of gadodiamide used for contrast-enhanced magnetic resonance imaging. *J Am Soc Nephrol* 2006; **17**: 2359–62.
34 Abraham JL, Thakral C, Skov L *et al*. Dermal inorganic gadolinium concentrations: evidence for *in vivo* transmetallation and long-term persistence in nephrogenic systemic fibrosis. *Br J Dermatol* 2008; **158**: 273–80.

Skin changes in renal transplant recipients

To prevent graft rejection after renal transplantation, immunosuppressive therapy with corticosteroids, and either azathioprine, ciclosporin, tacrolimus or sirolimus will be required for the duration of the graft survival. The long-term consequences of this are best documented after kidney transplant, but similar problems arise after other organ transplants; the degree of immunosuppression needed after liver transplants is not so great, whilst that required after cardiac or heart–lung transplantation is greater. The effects of these drugs on the skin include:

Corticosteroid effects. These include skin atrophy, fragility and purpura; see Cushing's syndrome (p. 62.3) for details.

Infections [1]. Some infections, such as candidal infection, herpes simplex infection, and impetigo are prominent during the first post-transplant year. Dermatomycoses, herpes zoster and folliculitis are more common after the first post-transplant year [2]; infections with unusual organisms (e.g. cutaneous alternariosis) should always be considered, as discussed below. The incidence of warts increased steadily after transplant, such that of patients transplanted for more than 5 years, 92% were found to have warts and 65% had more than five each [3]. Warts may become unusually florid (Fig. 62.25) [4], and recalcitrant to therapy [5].

Exotic and aggressive opportunistic infections are a challenge to both diagnose and treat, and may be caused by virus (disseminated herpes simplex and varicella zoster infection, cytomegalovirus [6]), bacteria (tuberculosis and atypical acid-fast infections [7]), fungi, yeasts and moulds (aspergillus [8], altenaria [9], nocardia [10], invasive candidiasis, cryptococcus [11], sporotrichosis [12], histoplasmosis [13], mucormycosis [14]) and protozoa (leishmaniasis [15] and acanthamoebiasis [16]). Abscesses, nodules or cellulitic lesions need biopsy, with appropriate culture as well as histological examination, and close microbiological liaison.

Skin tumours. Transplant recipients are at greatly increased risk of developing skin cancers, particularly squamous cell carcinoma (SCC; Fig. 62.26) [17–19]. The pathogenesis of post-transplant skin cancer is reviewed in detail in [19]; SCC is discussed in Chapter 52. Renal recipients are at particular risk as the survival period is now so prolonged. Liver transplant recipients may not be as susceptible due to the less profound immunosuppression they require [20]. In a series of nearly a thousand recipients from the south of England followed for over 20 years, 61% of patients developed a skin cancer, and SCC was the most frequent. The cancer may behave aggressively, particularly on the ear and scalp, and have a spindle cell morphology. The mean time to first cancer development post transplant was 8 years, and 60% of patients had multiple cancers, with as many as 50 lesions recorded. The risk of BCC was also increased [20]. The same group has reported melanomas occurring at approximately eight times the rate in the general population [21]. Due to regular surveillance of their skin, melanomas were identified with relatively thin Breslow thickness, so prognosis was good.

An important issue in post-transplantation skin cancers is the reversal of the expected ratio of BCCs compared with SCCs. Whilst the incidence of BCC may be increased 10-fold compared to the normal population, that of SCC is increased 65- to 250-fold. Thus SCC is at least four times as common as BCC in post-transplant patients [22]. The risk of tumours is multifactorial—as well as skin type, sun exposure history and degree of immunosuppression, genetic factors may play a part. These include polymorphisms in genes coding for glutathione-S-transferase, interleukin-10, p53,



Fig. 62.25 Viral warts and multiple dysplastic lesions on the arms in a renal transplant recipient.



Fig. 62.26 Squamous cell carcinoma and semi-confluent dysplastic lesions on the trunk of a patient immunosuppressed after organ transplantation.

retinoblastoma, folate metabolism, melanocortin-1 receptor and vitamin D receptor [23]. Human papilloma virus (HPV) may also be co-oncogenic; HPV DNA can be detected in 65–90% of SCCs in immunosuppressed subjects, often several types of HPV are within a single tumour [22].

Kaposi's sarcoma affecting the skin as well as other organs is well recognized after transplantation; it was reported in 3% of kidney recipients in one series [24], and has been documented as being between 84- and 500-fold commoner in subjects with a transplant compared to the normal population [22]. Some series report Kaposi's sarcoma confined to the skin [25]—this is possibly as a result of surveillance and early detection in at-risk individuals, as earlier series suggested internal involvement in 50%. Merkel cell tumours also seem to be more frequent and carry a poor prognosis [22,26]; increased risk up to 80-fold greater than the normal population has been suggested. Appendageal tumours are common, as is sebaceous gland hyperplasia. Sebaceous carcinomas are overrepresented in organ recipients [27]. Lymphomas of both B (associated with Epstein–Barr virus) and T–cell lineage (often $CD30^+$) are reported [28]. Sirolimus (rapamycin) may be less likely to provoke skin cancers [19], and a change from immunosuppression with ciclosporin and mycophenolate mofetil to sirolimus has been described to cause regression of Kaposi's sarcoma [25]. Oral retinoids (notably acitretin) appear to reduce the rate at which skin cancers develop [29,30]; some renal physicians have reservations as the manufacturer's product information states that renal disease is a contraindication to use of acitretin, but, although there is a possible increased tendency to mucocutaneous side effects, none of the studies reported have shown any unexpected renal adverse effect. Topical imiquimod is useful in reducing skin dysplasia in patients at high risk of developing skin neoplasms [31].

References

1 Carucci JA. Management of skin cancer in organ transplant recipients. In: Rigel DS, Friedman RJ, Dzubow LM *et al*. *Cancer of the skin*. Philadelphia: Elsevier Saunders, 2005: 631–40.

2 Hogewoning AA, Goettsch W, van Loveren H *et al*. Skin infections in renal transplant recipients. *Clin Transplant* 2001; **15**: 32–8.

3 Dyall-Smith D, Trowell H, Dyall-Smith ML. Benign human papillomavirus infection in renal transplant recipients *Int J Dermatol* 1991; **30**: 785–9.

4 Yu HC, Cho BH, Chung MJ *et al*. A case of giant condylomata acuminata involving anus after renal transplantation. *Clin Nephrol* 2003; **59**: 235–6.

5 Harwood CA, Perrett CM, Brown VL *et al*. Imiquimod cream 5% for recalcitrant cutaneous warts in immunosuppressed individuals. *Br J Dermatol* 2005; **152**: 122–9.

6 Trimarchi H, Casas G, Jordan R *et al*. Cytomegalovirus maculopapular eruption in a kidney transplant patient. *Am J Nephrol* 2000; **20**: 38–41.

7 Jie T, Matas AJ, Gillingham KJ *et al*. Mycobacterial infections after kidney transplant. *Transplant Proc* 2005; **37**: 937–9.

8 Park SB, Kang MJ, Whang EA *et al*. A case of primary cutaneous aspergillosis in a renal transplant recipient. *Transplant Proc* 2004; **36**: 2156–7.

9 Gallelli B, Viviani M, Nebuloni M *et al*. Skin infection due to Alternaria species in kidney allograft recipients: report of a new case and review of the literature. *J Nephrol* 2006; **19**: 668–72.

10 Wong KM, Chak WL, Chan YH *et al*. Subcutaneous nodules attributed to nocardiosis in a renal transplant recipient on tacrolimus therapy. *Am J Nephrol* 2000; **20**: 138–41.

11 Basaran O, Emiroglu R, Arikan U *et al*. Cryptococcal necrotizing fasciitis with multiple sites of involvement in the lower extremities. *Dermatol Surg* 2003; **29**: 1158–60.

12 Gullberg RM, Quintanilla A, Levin ML *et al*. Sporotrichosis: recurrent cutaneous, articular, and central nervous system infection in a renal transplant recipient. *Rev Infect Dis* 1987; **9**: 369–75.

13 McGuinn ML, Lawrence ME, Proia L, Segreti J. Progressive disseminated histoplasmosis presenting as cellulitis in a renal transplant recipient. *Transplant Proc* 2005; **37**: 4313–4.

14 Adriaenssens K, Jorens PG, Meuleman L *et al*. A black necrotic skin lesion in an immunocompromised patient. Diagnosis: cutaneous mucormycosis. *Arch Dermatol* 2000; **136**: 1165–70.

15 Mirzabeigi M, Farooq U, Baraniak S *et al*. Reactivation of dormant cutaneous Leishmania infection in a kidney transplant patient. *J Cutan Pathol* 2006; **33**: 701–4

16 Steinberg JP, Galindo RL, Kraus ES *et al*. Disseminated acanthamebiasis in a renal transplant recipient with osteomyelitis and cutaneous lesions: case report and literature review. *Clin Infect Dis* 2002; **35**: e43–9.

17 Carucci JA. Management of skin cancer in organ transplant recipients. In: Rigel DS, Friedman RJ, Dzubow LM, Reintgen DS, Bystryn J-C, Marks R, eds. *Cancer of the Skin*. Philadelphia: Elsevier, 2005: 631–40.

18 Perera GK, Child FJ, Heaton N *et al*. Skin lesions in adult liver transplant recipients: a study of 100 consecutive patients. *Br J Dermatol* 2006; **154**: 868–72.

19 Ho WL, Murphy GM. Update on the pathogenesis of post-transplant skin cancer in renal transplant recipients. *Br J Dermatol* 2007; **158**: 217–24.

20 Bordea C, Wojnarowska F, Millard PR *et al*. Skin cancers in renal-transplant recipients occur more frequently than previously recognized in a temperate climate. *Transplantation* 2004; **77**: 574–9.

21 Le Mire L, Hollowood K, Gray D *et al*. Melanomas in renal transplant recipients. *Br J Dermatol* 2006; **154**: 472–7.

22 Euvrard S, Kanitakis J, Claudy A. Skin cancers after organ transplantation. *N Engl J Med* 2003; **348**: 1681–91.

23 Laing ME, Kay E, Conlon P, Murphy GM. Genetic factors associated with skin cancer in renal transplant patients. *Photoderm Photoimmunol Photomed* 2007; **23**: 62–7.

24 Berber I, Altaca G, Aydin C *et al*. Kaposi's sarcoma in renal transplant patients: predisposing factors and prognosis. *Transplant Proc* 2005; **37**: 967–8.

25 Stallone G, Schena A, Infante B *et al*. Sirolimus for Kaposi's sarcoma in renal-transplant recipients. *N Engl J Med* 2005; **352**: 1317–23.

26 Penn I, First MR. Merkel's cell carcinoma in organ recipients: report of 41 cases. *Transplantation* 1999; **68**: 1717–21.

27 Harwood CA, McGregor JM, Swale VJ *et al*. High frequency and diversity of cutaneous appendageal tumors in organ transplant recipients. *J Am Acad Dermatol* 2003; **48**: 401–8.

28 Ravat FE, Spittle MF, Russell-Jones R. Primary cutaneous T-cell lymphoma occurring after organ transplantation. *J Am Acad Dermatol* 2006; **54**: 668–75.

29 Harwood CA, Leedham-Green M, Leigh IM, Proby CM. Low-dose retinoids in the prevention of cutaneous squamous cell carcinomas in organ transplant recipients: a 16-year retrospective study. *Arch Dermatol* 2005; **141**: 456–64.

30 Chen K, Craig JC, Shumack S. Oral retinoids for the prevention of skin cancers in solid organ transplant recipients: a systematic review of randomized controlled trials. *Br J Dermatol* 2005; **152**: 518–23.

31 Brown VL, Atkins CL, Ghall L *et al*. Safey and efficacy of 5% imiquimod cream for the treatment of skin dysplasia in high-risk renal transplant recipients: randomized, double-blind, placebo-controlled trial. *Arch Dermatol* 2005; **141**: 985–93.

Cardiac disease

There are several diseases in which both cardiac and skin involvement may be found (Table 62.15). Most of these are part of a syndrome or are systemic disorders affecting other organs as well [1,2]; most are discussed in other chapters, but some are briefly described below. Disorders of blood vessels are not included here. The effects of skin disease on the heart (e.g. cardiac failure due to erythroderma) and indirect effects, such as anaemia due to immunosuppressive agents used to treat the skin, are not discussed. Numerous infections may occasionally cause myocardial disease

Table 62.15 Conditions that affect the heart and skin.

Disease	Main cardiac feature, or comment
Congenital/inherited	
Ehlers–Danlos syndrome	Dilated main vessels, mitral or tricuspid insufficiency, cardiac/vascular rupture (type IV)
Cutis laxa	Early CAD, aortic aneurysm, mitral valve prolapse
Marfan syndrome	Aortic aneurysm, aortic regurgitation, mitral valve prolapse or regurgitation
Pseudoxanthoma elasticum	Arterial calcification, CAD, mitral valve prolapse
Werner's disease	Early CAD
Progeria	Early CAD
Cockayne's syndrome	Early CAD
Cornelia de Lange's syndrome	Septal defects, persistent ductus arteriosus, pulmonary stenosis
Fabry's disease	Conduction defects, arrhythmias, hypertension, left ventricular hypertrophy, mitral valve prolapse
Noonan's syndrome	Pulmonary stenosis, septal defects, hypertrophic cardiomyopathy, aortic abnormalities, others
Rubinstein–Taybi syndrome	Aortic coarctation, persistent ductus arteriosus, pulmonary stenosis, septal defects
LEOPARD syndrome	E, ECG abnormalities (various forms of heart block); P, pulmonary stenosis; also subaortic stenosis and hypertrophic cardiomyopathy
Tuberous sclerosis	Cardiac rhabdomyomas
Neurofibromatosis	Hypertension (renovascular or phaeochromocytoma)
Incontinentia pigmenti	Patent ductus arteriosus, tricuspid insufficiency
Alagille's syndrome	Pulmonary artery hypoplasia/stenosis
Di George's syndrome	Tetralogy of Fallot, aortic arch defects
Lymphoedema–distichiasis syndrome	Tetralogy of Fallot, patent ductus arteriosus
Naxos disease	Arrhythmogenic right ventricular cardiomyopathy
Chromosomal syndromes	Various—includes Down's syndrome, Turner's syndrome, trisomy 13, trisomy 18
Inflammatory diseases, connective tissue disease, vasculitis	
Systemic lupus erythematosus	Vegetations (especially mitral, Libman–Sacks endocarditis), pericarditis, myocarditis, aortic/mitral regurgitation
Neonatal lupus erythematosus	Neonatal heart block (various patterns), septal defects, persistent ductus arteriosus, tricuspid/mitral insufficiency
Systemic sclerosis	Pericarditis and effusion, conduction defects, myocardial fibrosis, cardiomyopathy, cor pulmonale
CREST	Pulmonary hypertension
Polyarteritis nodosa	Coronary artery vasculitis, ECG abnormalities, hypertension
Behçet's disease	Pericarditis, pulmonary and coronary artery aneurysm
Antiphospholipid syndrome	Vegetations, valvular heart disease, coronary artery thrombosis, pericardial effusion, CCF
Degos's disease	Pericarditis, pericardial effusion
Churg–Strauss disease	Pericarditis, cardiac fibrosis, pericardial effusion
Wegener's granulomatosis	Cardiomyopathy
Cholesterol emboli	Coronary artery occlusion
Other vasculitides	Coronary artery vasculitis
Dermatomyositis	Conduction defects, arrhythmias, cardiomyopathy, CCF, (rarely) pulmonary hypertension
Relapsing polychondritis	Mitral or aortic insufficiency, dissecting aortic aneurysm, pericarditis, myocardial ischaemia, heart block, aortitis
Rheumatic fever	Mitral and aortic valve disease
Kawasaki disease	Conduction defects, coronary artery aneurysms, pericardial effusion, cardiomegaly
Multicentric reticulohistiocytosis	Pericarditis, cardiomegaly, CAD, CCF
Hypereosinophilic syndrome	Eosinophilic endomyocarditis, valvular scarring, CCF, restrictive cardiomyopathy
Sarcoidosis	Conduction defects, arrhythmias, CCF
Reiter's disease	Conduction defects, aortic regurgitation
Deposition, metabolic and endocrine disorders	
Amyloidosis	Conduction defects, cardiomegaly, CCF
Haemochromatosis	Arrhythmias, cardiomyopathy, CCF
Wilson's disease	Arrhythmias, cardiomyopathy
Mucinoses: scleromyxoedema	Cardiomyopathy, CCF
Atrial myxoma syndromes	See text
Hyperlipidaemias	CAD
Diabetes mellitus	CAD, cardiomyopathy
Hyperthyroidism	Tachycardia, atrial fibrillation, mitral regurgitation
Hypothyroidism	Bradycardia, CAD, pericardial effusion
Acromegaly	Left ventricular hypertrophy, CCF
Carcinoid syndrome	Tricuspid or pulmonary stenosis, right heart failure
Phaeochromocytoma	Variable heart rate, hypertension/hypotension
Mastocytosis	Tachycardia, hypotension, arrhythmia, angina
Homocystinuria	Atherosclerosis

(Continued)

Table 62.15 *Continued*

Disease	Main cardiac feature, or comment
Embolic diseases	
Subacute bacterial endocarditis	Vegetations, valvular incompetence
Cholesterol emboli	Usually from proximal arteries rather than cardiac
Atrial myxomas	See text
Infections	
Lyme disease	Myocarditis, heart block
Syphilis	Aortitis, aortic aneurysm, aortic and mitral regurgitation, obstructed coronary arteries
Varicella	Myocarditis
Septicaemia	Pustules, infarcts, disseminated intravascular coagulopathy
Congenital rubella	Pulmonary artery and valve stenosis, patent ductus arteriosus
Whipple's disease	Pericarditis, myocarditis, valve deformity (especially mitral valve endocarditis)
Drugs	
Used in cardiology, causing rash	e.g. amiodarone (photosensitivity, pigmentation)
Cardiotoxic and cause skin eruptions	e.g. doxorubicin (cardiotoxic, anagen effluvium, pigmentation)
Used for skin disease, cardiovascular side effects	e.g. ciclosporin (hypertension)
Teratogenic, causing both skin and cardiac defects	e.g. alcohol, phenytoin, retinoids
Miscellaneous	
Earlobe crease	CAD
POEMS syndrome	Cardiac failure
Mycosis fungoides, Sézary syndrome	Heart is infiltrated in advanced disease
Kaposi's sarcoma	Heart is commonly involved
Diffuse neonatal haemangiomatosis	High output cardiac failure
Erythroderma, any cause	High output cardiac failure
Pacemaker reactions	Infection, contact dermatitis, mechanical issues
Clubbing of nails	Cyanotic congenital heart defects
Red lunulae	Occur in CCF

CAD, coronary artery disease; CCF, congestive cardiac failure; CREST, calcinosis, *R*aynaud's phenomenon, *e*sophageal disease, *s*clerodactyly, *t*elangiectasia; ECG, electrocardiogram; LEOPARD, *l*entigines, *E*CG abnormalities, *o*cular hypertelorism, *p*ulmonary stenosis, *a*bnormalities of genitalia, *r*etardation of growth, and *d*eafness (syndrome); POEMS, *p*olyneuropathy, *o*rganomegaly, *e*ndocrinopathy, *M* protein, *s*kin changes (syndrome).

and may have an exanthem (for example, parvovirus B19), but these are not discussed individually. Drug reactions due to cardiac medications are described in Chapter 75.

Consequences of cardiac disease

Dermatological consequences of cardiac disease include skin colour changes such as cyanosis, erythema due to secondary polycythaemia, and a combination of the two that may occur in congenital heart disease (and which has been termed erythremia). Finger clubbing is a consequence of congenital cyanotic heart disease, but occurs in other situations as well. Applying pressure on the tip of the nail in subjects with aortic regurgitation reveals visible flushing of the nail bed in time with the pulse, due to the wide pulse pressure in this disorder (Quincke pulsation) [2].

Congenital and inherited disorders

Cardiac involvement occurs in several congenital and inherited conditions, such as the LEOPARD syndrome, Anderson–Fabry disease, Alagille's syndrome and the cardiofaciocutaneous and Noonan's syndromes [1–8], as well as in chromosomal abnormalities such as Turner's syndrome and trisomy 13 or 18 [1]. The lymphoedema–distichiasis syndrome, due to mutations in *FOXC2* (*MFH-1*) on chromosome 16q24.3, has been linked to cardiac anomalies such as tetralogy of Fallot and patent ductus arteriosus [9,10]; spinal arachnoid cysts also occur. Cardiac rhabdomyomas occur in about 50% of patients with tuberous sclerosis (see Chapter 15).

In the LEOPARD syndrome (multiple lentigines syndrome; MIM *151100) [3] there are widespread *l*entigines, *e*lectrocardiographic abnormalities, *o*cular hypertelorism, *p*ulmonary stenosis, *a*bnormal genitals, *r*etardation of growth and *d*eafness. The cardiac involvement includes left-axis deviation on the electrocardiogram (ECG), ventricular hypertrophy and arrhythmia.

In angiokeratoma corporis diffusum (Anderson–Fabry disease; MIM *301500) [4], cardiac involvement may be manifest as arrhythmias, an abnormal P–R interval on ECG and left-ventricular hypertrophy. ECG abnormalities may also be found in heterozygotes. Manufactured α-galactosidase is now available to treat this condition [4] and appears to be more beneficial for the renal and cardiac lesions than for the cutaneous angiokeratomas, although accumulated globotriaosylceramide in the skin decreases during treatment.

Coronary artery disease

Coronary artery disease and ischaemic heart disease may occur in premature ageing syndromes such as progeria and Werner's syndrome, and premature myocardial ischaemia has also been reported in pseudoxanthoma elasticum, although it seems to be less common than the presence of a calcifying vascular pathology might suggest [2,11]. Coronary artery disease may be associated with xanthelasma or xanthomas due to hyperlipidaemia [2]. Both all-cause and cardiac-specific morbidity and mortality have been linked with the presence of a unilateral or bilateral diagonal earlobe skin crease [12,13], although others suggest that the association is with older age rather than with coronary artery disease *per se*. Both antinuclear [14] and high-titre anticardiolipin antibodies [15] have been demonstrated in a high proportion of patients with coronary artery disease; the significance of these is uncertain.

Connective tissue and systemic diseases

Cardiac involvement is common in systemic disorders such as sarcoidosis [16], connective tissue diseases [17–19], vasculitides (Chapter 50) [20,21], dermatomyositis (Chapter 51), relapsing polychondritis (Chapter 68) [22] and the hypereosinophilic syndrome [23,24], although it may be underestimated if symptoms are absent. Sudden death due to conduction defects and ventricular arrhythmias is the most important complication, and is particularly well recognized in sarcoidosis [16]; cardiomyopathy may also occur. The major vasculitides that affect the heart are Wegener's granulomatosis, polyarteritis nodosa, Churg–Strauss syndrome, temporal arteritis and Takayasu arteritis. Cardiac involvement is commoner in Churg–Strauss syndrome than in Wegener's granulomatosis, but has low discriminatory value—this is discussed in more detail in Chapter 50 and in the section on respiratory disease and the skin, below.

A number of cardiac complications occur in systemic lupus erythematosus (SLE), especially pericarditis, which may be present in 60–80% of patients at autopsy (Chapter 51) [2,25]. Neonatal LE is a particularly important entity, as about two-thirds of affected children have congenital heart block, although the frequency of this manifestation varies between countries [18,19]. Mothers of affected children generally express the 52-kDa and 60-kDa anti-SS-A (Ro) antibodies, even if they have no other features of LE. This antibody group is particularly associated with subacute cutaneous LE, but also with systemic LE. Mothers of children with neonatal LE with heart block tend to have higher titres of anti-SS-A but lower titres of anti-SS-B (La) antibody than mothers of children with neonatal LE rash alone [19].

Cardiac involvement occurs in 80% of patients with systemic sclerosis, but is not always clinically apparent; pericarditis, pericardial effusion, myocardial fibrosis, endothelial damage to coronary arteries and heart failure due to pulmonary arterial hypertension all occur [2,26,27]. Symptoms include heart failure, palpitations and myocardial infarction. Vasospasm may occur due to Raynaud's phenomenon. Pulmonary hypertension is particularly associated with CREST.

In the antiphospholipid syndrome (APLS) [28], about 50% of patients have valvular heart disease, either vegetations or thickening. The mitral valve is most frequently affected. About 5% require cardiac valve surgery, but many have no symptoms. There is also an increased incidence of coronary artery disease. Intracardiac thrombus is a rare complication. Unrecognized APLS may explain some cases of valvular heart disease in SLE.

Cardiac involvement is frequent in primary and in familial amyloidosis [29], causing features of cardiomyopathy such as congestive heart failure, low voltage on the ECG and conduction disturbances. Cardiomegaly is present in about one-third of the patients. Cutaneous signs, macroglossia and demonstration of amyloid deposition on skin histology support the diagnosis.

Kawasaki disease (mucocutaneous lymph-node syndrome) is an acute febrile disease of unknown aetiology, with accepted diagnostic criteria [30]. Coronary artery aneurysms may develop in up to 25% of patients, more commonly in children; conduction defects, pericardial effusion and cardiomegaly also occur. Symptoms and signs may include murmurs, gallop rhythm, angina and myocardial infarction [25,30]. Echocardiography and ECG are indicated. Treatment consists of acetylsalicylates and high doses of intravenous gammaglobulin.

Infections

Subacute bacterial endocarditis (SBE) [31–33] typically occurs in patients with a past history of heart disease (rheumatic fever, congenital heart disease, heart valve operation) or of parenteral drug addiction. About 75–80% of cases are caused by *Staphylococcus aureus* or streptococcal species, predominantly *Streptococcus viridans*. Cutaneous lesions may represent either septic emboli or immune complex disease due to the bacterial focus [31]; organisms can occasionally be cultured from skin lesions [32]. The skin lesions may be purpuric, pustular or erythematous, and various patterns are described. A non-specific small vessel vasculitis with splinter haemorrhages of the nail fold or nail bed occurs in about half of affected individuals. Similar small haemorrhages occur on the conjunctivae and retina (Roth spots). Osler's nodes are small, tender, red papules situated mainly on the distal finger and toe pads; Janeway lesions are faint, red, macular lesions on the thenar and hypothenar eminences. Both rheumatoid factor and cANCA can be demonstrated in some patients with SBE; these are of uncertain significance, but may erroneously suggest that the diagnosis is of systemic ANCA-associated vasculitis rather than of infective aetiology [33].

Rheumatic fever is a complication of streptococcal infection [34]. It causes arthritis, carditis, neuromuscular disease (Sydenham's chorea, dysphagia, dysarthria, distal weakness) and cutaneous lesions. The latter include erythema marginatum and papular lesions on the extensor surface of the extremities, particularly near the joints—both of these manifestations are usually transient, typically resolving after a few weeks. Erythema marginatum is a transitory gyrate erythema situated mainly on the trunk and proximal parts of the extremities. Urticaria, erythema nodosum and purpura are described in about 2% of patients. Cardiac features include valvular disease, pericarditis, myocarditis and congestive cardiac failure.

Cardiac myxoma syndromes

Carney complex (type I, MIM #160980; type II, MIM *605244). A number of atrial myxoma syndromes have been described, with various eponyms and acronyms and overlapping features [35–39].

These include LAMB syndrome, NAME syndrome, Danoff syndrome and the Carney complex. LAMB is an acronym for *l*entigines, *a*trial myxoma, *m*ucocutaneous myxoma and *b*lue naevi. The NAME syndrome indicates blue *n*aevi, *a*trial myxoma, *m*yxoid neurofibromas and *e*phelides. The inheritance is autosomal-dominant. In the Danoff syndrome there are, apart from atrial myxomas, adrenocortical dysplasia, lentigines and spindle cell tumours.

About 50% of cases of bilateral, pigmented, micronodular adrenal hyperplasia—a rare cause of ACTH-independent Cushing's syndrome—are associated with the Carney complex; anti-ACTH receptor antibodies are present and stimulate adrenal growth and secretion. Other features include cardiac myxomas (in one-third of patients), skin myxomas (two-thirds), skin pigmentation (96%), myxoid fibroadenomas of the breast (in one-third of women, uncommon in men), GH-secreting pituitary tumours (acromegaly occurs in 8% of patients), Sertoli cell (in 10%) and Leydig cell testicular tumours (which cause male precocious puberty), thyroid cysts, hyperplasia and tumours (10%), and ovarian cysts and tumours (which are felt to be underestimated in frequency) [37–39]. Psammomatous melanotic schwannoma is rare, but is usually part of this syndrome when it occurs [40].

The genetic background of these disorders has been extensively investigated. Carney complex type 1 (CNC1) is linked to a susceptibility gene for the protein kinase A type 1α regulatory subunit gene (*PRKAR1A*) and has loci on chromosomes 2p16 and 17q23–24, whilst CNC2 links to a currently unknown gene on chromosome 2p. Genetic evaluation has demonstrated that this disorder is related to PJS. Any patient with multiple melanocytic and myxomatous tumours of the skin and mucosa (including vulval melanotic macules) should have a cardiac evaluation.

From a dermatological aspect, atrial myxomas may present due to embolic infarction of the skin. They may mechanically interfere with cardiac function and can also lead to pericarditis. Systemic malaise, pleurisy, Raynaud's phenomenon and the occasional occurrence of ANCA [41] may suggest other forms of vasculitis as the cause of skin lesions.

Miscellaneous

Cardiac pacemaker and implantable defibrillator dermatoses. Cutaneous reactions over the site of implanted cardiac pacemakers have been reported [42–45]. Most of these are either infections or mechanical issues (erosions, extrusions, capsular contracture, exposed generator or electrodes, bronchopleural cutaneous fistulae) and may respond to antibiotics or altered positioning of the pacemaker [42,43]. However, contact dermatitis to epoxy resins, nickel or chromium may occur, in which event removal of the implanted material and use of titanium pacemaker casings may be appropriate [44,45]. A reticular telangiectatic pattern of erythema overlying pacemaker or defibrillator sites may occur [46,47]. Cardiac pacemakers also have dermatological surgical relevance, as they may malfunction during the use of electrosurgery [48].

References

1 Abdelmalek NF, Gerber TL, Menter A. Cardiocutaneous syndromes and associations. *J Am Acad Dermatol* 2002; **46**: 161–83.

2 McDonnell JK. Cardiac disease and the skin. *Dermatol Clin* 2002; **20**: 503–11.

3 Gorlin RJ, Anderson RC, Blaw M. Multiple lentigines syndrome. *Am J Dis Child* 1969; **117**: 652–62.

4 Desnick RJ, Ioannou YA, Eng CM. α-galactosidase A deficiency: Fabry disease. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic and Molecular Bases of Inherited Disease*, 8th edn. New York: McGraw-Hill, 2001: 3733–74.

5 Eng CM, Guffon N, Wilcox WR *et al.* International Collaborative Fabry Disease Study Group. Safety and efficacy of recombinant human alpha-galactosidase A replacement therapy in Fabry's disease. *N Engl J Med* 2001; **345**: 9–16.

6 Alagille D, Estrada A, Hadchouel M *et al.* Syndromic paucity of interlobular bile ducts (Alagille syndrome or arteriohepatic dysplasia): review of 80 cases. *J Pediatr* 1987; **110**: 195–200.

7 Ward KA, Moss C, McKeown C. The cardio-facio-cutaneous syndrome: a manifestation of the Noonan syndrome? *Br J Dermatol* 1994; **131**: 270–4.

8 Daoud MS, Dahl PR, Su WPD. Noonan syndrome. *Semin Dermatol* 1995; **14**: 140–4.

9 Bell R, Brice G, Child AH *et al.* Analysis of lymphoedema–distichiasis families for *FOXC2* mutations reveals small insertions and deletions throughout the gene. *Hum Genet* 2001; **108**: 546–51.

10 Chen E, Larabell SK, Daniels JM, Goldstein S. Distichiasis–lymphedema syndrome: tetralogy of Fallot, chylothorax and neonatal death. *Am J Med Genet* 1996; **66**: 273–5.

11 Neldner KH. Pseudoxanthoma elasticum. *Clin Dermatol* 1988; **6**: 45–64.

12 Wyre H. The diagonal ear-lobe crease: a cutaneous manifestation of coronary artery disease. *Cutis* 1979; **23**: 328–31.

13 Elliott WJ, Karrison T. Increased all-cause and cardiac morbidity and mortality associated with the diagonal earlobe crease: a prospective cohort study. *Am J Med* 1991; **91**: 247–54.

14 Grainger DJ, Bethell HW. High titres of serum antinuclear antibodies, mostly directed against nucleolar antigens, are associated with the presence of coronary atherosclerosis. *Ann Rheum Dis* 2002; **61**: 110–4.

15 Yilmaz E, Adalet K, Yilmaz G *et al.* Importance of serum anticardiolipin antibody levels in coronary heart disease. *Clin Cardiol* 1994; **17**: 117–21.

16 English JC 3rd, Patel PJ, Greer KE. Sarcoidosis. *J Am Acad Dermatol* 2001; **44**: 725–43.

17 Petri M, Perez-Gutthann S, Spence D *et al.* Risk factors for coronary artery disease in patients with systemic lupus erythematosus. *Am J Med* 1992; **93**: 513–9.

18 Petri M, Watson R, Hochberg MC. Anti-Ro antibodies and neonatal lupus. *Rheum Dis Clin North Am* 1989; **5**: 335–60.

19 Yukiko N. Immune responses to SS-A 52-kDa and 60kDa proteins and to SS-B 50-kDa protein in mothers of children with neonatal lupus erythematosus. *Br J Dermatol* 2000; **142**: 908–12.

20 Guillevin L, Lhote F, Casassus P. Polyarteritis nodosa: clinical aspects. In: Ansell BM, Bacon PA, Lie JT, Yazici H, eds. *The Vasculitides: Science and Practice.* London: Chapman & Hall Medical, 1996: 121–34.

21 Chakravarty K. Vasculitis by organ systems. *Baillière's Clin Rheumatol* 1997; **11**: 357–93.

22 Del Rosso A, Petix NR, Pratesi M *et al.* Cardiovascular involvement in relapsing polychondritis. *Semin Arthritis Rheum* 1997; **26**: 840–4.

23 Weller PF, Bubley GJ. The idiopathic hypereosinophilic syndrome. *Blood* 1994; **83**: 2759–79.

24 Leiferman KM. Hypereosinophilic syndrome. *Semin Dermatol* 1995; **14**: 122–8.

25 Sondheimer HM, Lorts A. Cardiac involvement in inflammatory disease: systemic lupus erythematosus, rheumatic fever, and Kawasaki disease. *Adolesc Med* 2001; **12**: 69–78.

26 Tuffanelli DL. Systemic sclerosis. In: Sontheimer RD, Provost TT, eds. *Cutaneous Manifestations of Rheumatic Diseases*. Baltimore: Williams and Wilkins, 1996: 115–39.

27 Wigley FM, Provost TT. Scleroderma. In: Provost TT, Flynn JA, eds. *Cutaneous Medicine: Cutaneous Manifestations of Systemic Disease*. Hamilton, Ontario: Decker, 2001: 104–26.

28 Cuadrado MJ, Hughes GRV. Hughes (antiphospholipid) syndrome: clinical features. *Rheum Dis Clin* 2001; **27**: 507–24.

29 Breathnach SM. Amyloid and amyloidoses. *J Am Acad Dermatol* 1988; **18**: 1–16.

30 Wortmann DW, Nelson AM. Kawasaki syndrome. *Rheum Dis Clin North Am* 1990; **16**: 363–75.

31 Brown M, Griffin GE. Immune responses in endocarditis. *Heart* 1998; **79**: 1–2.

32 Parikh SK, Lieberman A, Colbert DA *et al*. The identification of methicillin-resistant *Staphylococcus aureus* in Osler's nodes and Janeway lesions of acute bacterial endocarditis. *J Am Acad Dermatol* 1996; **35**: 767–8.

33 Choi HK, Lamprecht P, Niles JL *et al*. Subacute bacterial endocarditis with positive cytoplasmic antineutrophil cytoplasmic antibodies and anti-proteinase 3 antibodies. *Arthritis Rheum* 2000; **43**: 226–31.

34 Flynn JA, Provost TT. Rheumatic fever. In: Provost TT, Flynn JA, eds. *Cutaneous Medicine: Cutaneous Manifestations of Systemic Disease*. Hamilton, Ontario: Decker, 2001: 205–7.

35 Atherton DJ, Pitcher DW, Wells RS, MacDonald DM. A syndrome of various cutaneous pigmented lesions, myxoid neurofibromata and atrial myxoma: the NAME syndrome. *Br J Dermatol* 1980; **103**: 421–9.

36 Rhodes AR, Silverman RA, Harrist TJ, Perez-Atayde AR. Mucocutaneous lentigines, cardiomucocutaneous myxomas, and multiple blue nevi: the 'LAMB' syndrome. *J Am Acad Dermatol* 1984; **10**: 72–82.

37 Stratakis CA, Carney JA, Lin JP *et al*. Carney complex, a familial multiple neoplasia and lentiginosis syndrome: analysis of 11 kindreds and linkage to the short arm of chromosome 2. *J Clin Invest* 1996; **97**: 599–607.

38 Kirschner LS, Carney JA, Pack SD *et al*. Mutations of the gene encoding the protein kinase A type I-alpha regulatory subunit in patients with the Carney complex. *Nat Genet* 2000; **26**: 89–92.

39 Malchoff CD. Carney complex: clarity and complexity [editorial]. *J Clin Endocrinol Metab* 2000; **85**: 4010–2.

40 Utiger CA, Headington JT. Psammomatous melanocytic schwannoma: a new cutaneous marker for Carney's complex. *Arch Dermatol* 1993; **129**: 202–4.

41 Savige JA, Yeung SP, Davies DJ *et al*. Anti-neutrophil cytoplasmic antibodies associated with atrial myxoma. *Am J Med* 1988; **85**: 755–6.

42 Chua FS, Leininger BJ, Hamouda FA, Pifarre RF. Bronchopleural cutaneous fistula from infected pacemaker electrodes. *Chest* 1973; **63**: 284–6.

43 Har-Shai Y, Amikam S, Bolous M, Peled IJ. The management of soft tissue complications related to pacemaker implantations. *J Cardiovasc Surg* 1994; **35** (Suppl. 1): 211–7.

44 Andersen EK. Cutaneous reaction to an epoxy-coated pacemaker. *Arch Dermatol* 1979; **115**: 97–8.

45 Romaguera C, Grimalt F. Pacemaker-dermatitis. *Contact Derm* 1981; **7**: 33.

46 Kint A, Vermander F. Reticular telangiectatic erythema after implantation of a pacemaker. *Dermatologica* 1983; **166**: 651–4.

47 Krasagakis K, Vogt R, Tebbe B, Goerdt S. Persistent telangiectatic erythema associated with an implantable cardioverter defibrillator. *Br J Dermatol* 1997; **136**: 633–5.

48 Sebben JE. Electrosurgery and cardiac pacemakers. *J Am Acad Dermatol* 1983; **9**: 457–63.

Respiratory system

Pulmonary disease rarely occurs as a direct consequence of a primary skin disease, except for instances such as metastasis from a primary skin tumour (e.g. melanoma). Similarly, there are relatively few instances in which skin abnormalities occur as a direct consequence of respiratory pathology. Examples include cyanosis due to severe pulmonary disease or intrapulmonary right-to-left shunts, and finger clubbing due to chronic cyanotic lung disease or neoplasm. Dermatomyositis may occur as a paraneoplastic phenomenon due to lung cancer (but, as discussed below, lung disease also occurs as a consequence of dermatomyositis). Amyloidosis may occur secondary to chronic respiratory diseases such as bronchiectasis or cystic fibrosis, but cutaneous signs in secondary amyloidosis are generally few, even though aspiration of subcutaneous fat for histological examination can be diagnostic. Tumours may cause direct nerve damage and abnormalities of sweating [1,2].

However, in most instances in which the skin and respiratory tract exhibit the same disease process, this is as part of a multisystem disorder. This section on the respiratory system concentrates on this diverse group of disorders (Table 62.16).

Congenital and inherited disorders

Examples are listed in Table 62.16. NF1 (Chapter 15) is not uncommonly associated with the development of restrictive lung disease if there is severe scoliosis. Intrathoracic, intra-abdominal or retroperitoneal diffuse plexiform neurofibromas can also compromise pulmonary function [3]. Fibrosis is found in around 10% of patients with NF1, mainly in the lower lobes, and bullous changes may occur in the upper lobes [4]. Pleural effusions have been reported in tuberous sclerosis [5] (Chapter 12). Pulmonary involvement is uncommon but, especially in adult female patients, there may be numerous small cysts which represent lymphangioleiomyomatosis [6]. These may be mistaken for tuberculosis or sarcoidosis radiologically. Diffuse lower lobe fibrosis and laryngeal involvement has been reported in Darier's disease [7] (Chapter 19). α_1-Antitrypsin deficiency, particularly the ZZ genotype, links cutaneous panniculitis with emphysema and hepatic cirrhosis [8]. In familial dysautonomia (Riley–Day syndrome), there are acute episodes of bronchopneumonia, with profuse mucous secretion causing dyspnoea. Skin changes include multiple excoriations, and erythematous mottling associated with fever and sweating [9]. Radiological features of lung disease [10] may be accompanied by abdominal distension as the 'chest–abdomen' sign [11]. Ataxia–telangiectasia (Louis–Bar syndrome) may be associated with pulmonary problems, including recurrent pneumonia, bronchiectasis and pulmonary fibrosis [12].

Infections

Numerous infections may be associated with both respiratory and skin disease, and only a selection of these have been listed. Many viral infections, for example, may cause upper and sometimes lower respiratory tract symptoms in association with either a non-specific exanthem or with erythema multiforme. *Mycoplasma* infection is particularly associated with erythema multiforme with mucosal involvement (Stevens–Johnson syndrome). *Psittacosis (ornithosis)* may be accompanied by erythema nodosum and erythema multiforme (Bateman's syndrome).

Associations between *tuberculosis* and the skin include non-specific reactions such as erythema nodosum or erythema multiforme, as well as several patterns of specific skin lesion such as lichen scrofulosorum, Bazin's disease or papulonecrotic tuberculide (Chapter 31). Several *systemic mycoses* are caused by inhalation but may subsequently cause skin lesions (Table 62.16)—either non-specific reactions such as erythema multiforme or erythema nodosum, or specific lesions caused by haematogenous dissemination. Other mycoses may have primary cutaneous lesions with occasional spread to internal organs, including the lung (e.g. sporotrichosis). *Pulmonary melioidosis* may run a subacute course and last for one to several weeks. It may be contracted by inhalation, causing early pneumonic symptoms, or via skin defects, in which case abscess formation precedes the septic stage. Urticaria may occur in chronic melioidosis [13].

Connective tissue diseases

This group of disorders has a variety of respiratory features.

Respiratory disease is frequent in the various forms of *scleroderma* [14,15]. Systemic sclerosis is associated with fibrosing alveolitis and interstitial fibrosis, causing a restrictive defect. This occurs

Table 62.16 Conditions that affect the skin and respiratory system.

Disease	Respiratory tract features or comment
Congenital/inherited	
Atopic disease	Asthma, hay fever
Cutis laxa	Emphysema, cor pulmonale
Tuberous sclerosis	Rhabdomyomas
Neurofibromatosis	Kyphoscoliosis, intrathoracic neuromas, lung fibrosis, bullae
Ataxia–telangiectasia	Pneumonia, bronchiectasis, pulmonary fibrosis
Hereditary haemorrhagic telangiectasia	Haemoptysis, dyspnoea, cyanosis due to arteriovenous shunting
α_1-antitrypsin deficiency	Emphysema
Darier's disease	Lower lobe fibrosis, laryngeal involvement
Dyskeratosis congenital	Interstitional pneumonia, fibrosis
Lipoid proteinosis	Laryngeal involvement
Riley–Day syndrome	Lung infiltrate, pneumonia
Birt–Hogg–Dubé syndrome	Lung cysts, pneumothorax
Hyper-IgE syndrome	Abscesses, pneumonia
Infections and infestations	
Tuberculosis	Specific skin lesions, erythema nodosum
Mycobacterium avium–intracellulare infection	May disseminate to skin (usually in HIV infection)
Leprosy	Laryngeal involvement
Mycoplasma infection	Causes erythema multiforme (often mucosal)
Dissemination of pulmonary fungal infections	Blastomycosis, coccidioidomycosis, cryptococcosis, aspergillosis, histoplasmosis, melioidosis
Scrub typhus	Pneumonia (common)
Varicella	Pneumonia
Measles	Pneumonia
Larva migrans	Asthma/bronchitis with eosinophilia
Chronic mucocutaneous candidiasis	Bronchiectasis
Whipple's disease	Cough, pleural effusion, pulmonary infiltrate, hilar lymphadenopathy
Infiltrations and metabolic	
Histiocytoses (Langerhans' cell histiocytosis, Rosai–Dorfman disease, haematophagocytic syndrome, necrobiotic xanthogranuloma, sea-blue histiocytosis, others)	Pulmonary nodules and fibrosis, upper respiratory tract infiltration disease, xanthoma disseminatum
Amyloidosis	Cutaneous amyloid deposition secondary to chronic lung disease, lung infiltration in primary amyloidosis
POEMS	Pleural effusion, bronchospasm
Carcinoid syndrome	Bronchospasm
Hypothyroidism	Laryngeal involvement
Myxoma	Pleurisy
Inflammatory	
Sarcoidosis	Pulmonary fibrosis, hilar lymphadenopathy, laryngeal involvement, necrotizing sarcoid granulomatosis
Pulmonary vasculitides	See text (this section)
Systemic sclerosis	Interstitial fibrosis, pneumothorax, pulmonary hypertension (especially in CREST)
Sjögren's syndrome	Decreased secretions, sinusitis, bronchoalveolitis, interstitial lung disease
Lupus erythematosus	Pleuritis, pleural effusion, shrinking lungs syndrome
Mixed connective tissue disease	Fibrosing alveolitis (especially U_1 ribonucleoprotein antibody-positive)
Antiphospholipid syndrome	Pulmonary embolism, infarction, thrombosis, haemorrhage
Dermatomyositis	Muscular weakness, pharyngeal dysfunction (aspiration pneumonia), interstitial lung disease, bronchiolitis obliterans
Relapsing polychondritis	Tracheal collapse
Multicentric reticulohistiocytosis	May be associated with bronchial neoplasia, also lung infiltration, pleural effusion
Bullous diseases (epidermolysis bullosa, pemphigus, erythema multiforme/Stevens–Johnson syndrome/toxic epidermal necrolysis)	Upper respiratory tract involvement; paraneoplastic pemphigus is associated with intrathoracic disease, especially Castleman's disease, thymoma
Graft-versus-host disease	Restrictive defect, fibrosis
Pyoderma gangrenosum	Neutrophilic nodules in lung, tracheal pyoderma
Familial Mediterranean fever	Pleuritis

(*Continued p. 62.82*)

Table 62.16 *Continued*

Disease	Respiratory tract features or comment
Drugs	
Used in respiratory disease, causing rash	e.g. co-trimoxazole (drug eruptions)
May cause skin eruptions and respiratory tract disease	e.g. antibiotic-induced toxic epidermal necrolysis, cisplatin (bronchospasm, pigmentation)
Used for skin disease, respiratory side effects	e.g. isotretinoin (bronchospasm)
Miscellaneous	
Angio-oedema	Upper airway obstruction
Anaphylaxis	Bronchospasm
Pancreatitis	May cause basal pleural reaction, and cutaneous fat necrosis
Yellow nail syndrome	Pleural effusion, bronchiectasis
Mastocytosis	Rhinorrhoea, laryngeal oedema, bronchospasm
Tumours	Metastatic disease, Kaposi's sarcoma, lymphomatoid granulomatosis, extensive mycosis fungoides/Sézary syndrome, others

HIV, human immunodeficiency virus; POEMS, *p*olyneuropathy, *o*rganomegaly, *e*ndocrinopathy, *M* protein, *s*kin changes (syndrome).

in at least 50% of patients. Symptoms (exertional dyspnoea and cough) may be relatively late in presenting—pulmonary function tests including transfer factor should be measured. Pneumothorax, pleural effusion, respiratory muscle involvement and 'splinting' of the chest by sclerotic skin may all occur. Pulmonary vascular disease leading to pulmonary hypertension is a particular concern in CREST syndrome; this may be identified by transoesophageal echocardiography and treated with bosanten.

Over 50% of anti-U1RNP-positive patients with *systemic lupus erythematosus* (SLE) and about a quarter of those with *mixed connective tissue disease* may have pleurisy [16]. Involvement of the respiratory muscles may lead to diaphragmatic elevation and the *'shrinking lungs' syndrome* [17]. These conditions are discussed in more detail in Chapter 51. Pulmonary embolism, haemorrhage, infarction and hypertension may occur in patients with the *antiphospholipid syndrome* [18].

Relapsing polychondritis [19] is due to autoantibodies against type II collagen, and is a potentially fatal disease. Dyspnoea and inspiratory stridor occur due to swelling of the respiratory tract, and collapse of cartilages of the larynx and trachea, in over 50%. Costal cartilage is involved in one-third of cases. Inflamed nasal and auricular cartilages are present in most patients, with nasal obstruction, arthropathy and high erythrocyte sedimentation rate (ESR). The disorder may therefore mimic one of the vasculitides, such as Wegener's granulomatosis. The non-cartilaginous lobe of the ear is classically spared in relapsing polychondritis.

In *dermatomyositis,* there are three main mechanisms that provide a link with respiratory disease [20–22]. Firstly, dermatomyositis may occur as a consequence of bronchial carcinoma, the commonest malignancy associated with dermatomyositis in males [20]. Muscular weakness due to myositis may affect either the intercostal and thoracic musculature, or the larynx and pharynx—the latter may lead to aspiration pneumonia as a complication. Finally, interstitial lung disease or bronchiolitis obliterans may occur due to dermatomyositis. The lung disease is typically associated with the presence of antiaminoacyl-tRNA synthetase antibodies, notably anti-Jo-1, and with anti-tRNA antibodies such as anti-$tRNA^{his}$. Patients with these antibodies only comprise 15–20% of individuals with dermatomyositis, but most patients with lung disease have one of these antibodies. The antisynthetase syndrome consists of dermatomyositis (or polymyositis) with interstitial lung disease, arthritis and Raynaud's phenomenon [22]. Presence of antisynthetase antibodies is also associated with the clinical entity of 'mechanic's hands' in dermatomyositis, but they are not usually a feature of paraneoplastic dermatomyositis. Dermatomyositis may also indirectly be associated with lung disease as a consequence of treatment—either infection due to immunosuppression, or rarely drug-induced pneumonitis (methotrexate).

In *Sjögren's syndrome,* alveolitis can be demonstrated in about 50% of patients, but is often asymptomatic. Inspissated secretions may predispose to pneumonia; obstructive and interstitial lung disease may occur [23].

Vasculitis and neutrophilic dermatoses (see also Chapter 50)

Vasculitis of many types may affect the lung. The major pulmonary vasculitides are Wegener's granulomatosis, Churg–Strauss disease, polyarteritis nodosa and Behçet's disease [24].

Behçet's disease (Chapter 50). The frequency of lung involvement in Behçet's disease may be as high as 19%, although 5–10% is a more frequent estimate. Pleurisy or perihilar radiological opacities may be found [23], and pulmonary arterial aneurysm is an important feature, which can be fatal [25]. About 90% of patients with Behçet's disease complicated by pulmonary artery aneurysm also have thrombophlebitis.

Small-vessel vasculitis (Chapter 50). Any form of small-vessel vasculitis can also affect the lung, even urticarial vasculitis. In one large series, over 20% of patients with urticarial vasculitis had pulmonary disease, either chronic obstructive pulmonary disease or asthma. Although it is not clear that these were always causally related to the vasculitis, obstructive pulmonary disease was more frequent in the group of patients with hypocomplementaemia [26], and lung vasculitis or serological evidence of LE was demonstrated in over 50% of patients with lung disease.

Wegener's granulomatosis [27,28]. This is an uncommon disease. The 'classic' syndrome is characterized by necrotizing granulomatous vasculitis of the upper and lower respiratory tracts, necrotizing glomerulonephritis and disseminated vasculitis of various organs. Skin lesions are frequent, including vasculitis with purpura, subcutaneous nodules and ulcers (see also Chapter 50). Upper airway disease causes nasal discharge, ulceration and bleeding, and oral ulceration. Pulmonary changes are typical with bilateral infiltrate, nodules or cavities. Subglottic or tracheobronchostenosis may also occur. There is no hilar or mediastinal lymphadenopathy. Prognosis is poor in patients with lung or renal disease; chronic nasal staphylococcal carriage is also associated with a poorer prognosis. Treatment consists of immunosuppressive agents (cyclophosphamide, azathioprine, chlorambucil and methotrexate). Trimethoprim–sulfamethoxazole (co-trimoxazole) also appears to be of benefit in induction of remission [29]. Diffuse alveolar haemorrhage, due to extensive pulmonary capillaritis, is a life-threatening complication of Wegener's granulomatosis—it also occurs in microscopic polyangiitis, and more rarely in SLE, antiphospholipid syndrome, Behçet's disease and secondary to drugs such as D-penicillamine [30].

Churg–Strauss syndrome (allergic granulomatous angiitis) [27,28]. This rare condition comprises rhinitis, asthma, pneumonitis, fever, malaise, eosinophilia (usually over 10%) and widespread vasculitis, which may cause skin lesions, neuropathy and cardiac or less commonly renal disease. Cutaneous lesions include palpable purpura and nodular lesions. Distinction from Wegener's granulomatosis or microscopic polyangiitis may be difficult in the early stages—peripheral eosinophilia is the most useful discriminatory feature [31], but eosinophils in inflammatory infiltrates may occur in all three disorders (also in SLE and Sjögren's syndrome), as may mononeuritis multiplex. Cardiac disease is more frequent in Churg–Strauss syndrome than in Wegener's granulomatosis, but is not specific; a history of asthma and other allergies with the other features suggest Churg–Strauss syndrome [24,27]. There is some concern that leukotriene receptor antagonists may provoke Churg–Strauss syndrome in patients with asthma, although an alternative explanation is simply that disease progression or altered corticosteroid therapy allowed additional clinical features to become apparent [32,33]. Therapy consists of high-dose corticosteroids, if necessary with other immunosuppressive agents such as cyclophosphamide, azathioprine or chlorambucil.

PAN and microscopic polyangiitis (microscopic polyarteritis) [27]. These conditions are distinguished by the size of vessels affected and by the usual absence of antineutrophil cytoplasm antibodies against myeloperoxidase (MPO-ANCA) in 'classic' PAN. The term 'polyangiitis' is preferred to polyarteritis for the microscopic disease, as arterioles, venules and capillaries may all be affected. Lung disease is not a particular feature of classic PAN, although bronchial arteries can be affected. By contrast, microscopic polyangiitis has many similarities to Wegener's granulomatosis, including nasopharyngeal involvement, renal vasculitis and tendency to cause alveolar haemorrhage [27,30]. However, the presence of granulomas and proteinase 3-ANCA (which suggest the diagnosis of Wegener's granulomatosis) help to distinguish these disorders.

Neutrophilic dermatoses (Chapter 50). Pulmonary and major airway involvement have been described with pyoderma gangrenosum and neutrophilic dermatoses [34–38], usually comprising focal, dense neutrophilic infiltrates with scattered radiological opacities. Tracheal lesions may occur. Endobronchial involvement may also occur in eosinophilic states such as the hypereosinophilic syndrome, although cardiac disease is more important in this condition.

Other systemic diseases

Sarcoidosis [39] is discussed in Chapter 61. Hilar lymphadenopathy occurs with erythema nodosum in acute sarcoidosis. Pulmonary involvement is the major feature in chronic sarcoidosis, about 30% of such patients also having skin lesions. *Necrotizing sarcoid granulomatosis* (also termed necrotizing sarcoid angiitis and granulomatosis) is a rare disorder that is in the differential diagnosis of Wegener's granulomatosis but is currently felt to be an arteritic variant of sarcoidosis [40]. In the respiratory system, a nodular pulmonary infiltrate is typical; extrapulmonary involvement is most commonly ophthalmological (uveitis or ophthalmoplegia) but other organs including the skin [41] may be involved and necrosis due to arteritic vascular occlusion may be a feature.

Multicentric reticulohistiocytosis is associated with pleural effusion and hilar lymphadenopathy [42]; it may also occur as a paraneoplastic phenomenon.

Scleromyxoedema has been associated with lung disease, causing dyspnoea, in a sixth of reported cases [43]. Pulmonary hypertension has been reported.

Amyloidosis (Chapter 59); involvement of the respiratory tract is common in primary amyloidosis. It may cause dyspnoea, but is often asymptomatic.

Lymphomatoid granulomatosis [44,45] is a rare lymphoproliferative disease which primarily affects the lung; radiology shows multiple, small nodules that predominantly affect the periphery of the lower lung fields. Cutaneous lesions are present in about 50% of cases, typically on the face, and consist of infiltrated flat or nodular lesions that may become necrotic and ulcerated. Histologically, there are necrotizing angiocentric lesions of various organs, with an infiltrate of atypical lymphocytes. Epstein–Barr virus infection has been demonstrated [46]. The condition behaves as a lymphoma with poor prognosis; corticosteroids and cyclophosphamide may help in some cases.

Miscellaneous

Yellow nail syndrome (MIM #153300). Associated respiratory features include recurrent pleural effusion, bronchiectasis and chronic infections such as empyema [47,48].

Paraneoplastic pemphigus (PNP). Respiratory failure in PNP is particularly important as it is frequently the cause of death in patients with this disorder. Pathologically, there is a diffuse segmental constrictive bronchiolitis of small bronchioles causing a bronchiolitis obliterans clinical picture. The mechanism may be due to autoantibody-mediated damage as direct immunofluorescence

of bronchial mucosal biopsies may demonstrate linear deposition of IgG and complement in the lamina propria [49], although $CD8^+$ T lymphocytes may have a key role in this process [50], and underlying neoplasms, toxic effects of immunosuppressive therapy, and secondary infections may all be involved in some cases.

Hoarseness as a sign of systemic disease [51]. Hoarseness from laryngeal or tracheal involvement is an important audible sign of certain systemic diseases with skin involvement. Examples are pachyonychia congenita, de Lange's syndrome, Farber's disease, lipoid proteinosis, sarcoidosis, secondary syphilis, epidemic typhus, hypothyroidism, relapsing polychondritis, LE and dermatomyositis. Several inherited or acquired bullous diseases may affect the pharyngeal or laryngeal mucosa. Carcinoma of the larynx may complicate chronic inflammation.

References

1 Chan PH. Pulmonary carcinoma and provocative sweat testing. *Arch Dermatol* 1983; **119**: 185.
2 McCoy BP. Apical pulmonary adenocarcinoma with contralateral hyperhidrosis. *Arch Dermatol* 1981; **117**: 659–61.
3 Riccardi VM. *Neurofibromatosis*, 2nd edn. Baltimore: Johns Hopkins University Press, 1992.
4 Prakash UB. Respiratory manifestations of systemic disease: lower airways in systemic disease, 3. *Postgrad Med* 1984; **76**: 143–52.
5 Broughton RBK. Pulmonary tuberous sclerosis presenting with pleural effusion. *BMJ* 1970; **i**: 477–8.
6 Costello LC, Hartman TE, Ryu JH. High frequency of pulmonary lymphangioleiomyomatosis in women with tuberous sclerosis complex. *Mayo Clin Proc* 2000; **75**: 591–4.
7 Dellon AL, Peck GL, Chretien PB. Hypopharyngeal and laryngeal involvement with Darier disease. *Arch Dermatol* 1975; **111**: 744–6.
8 Edmunds BK, Hodge JA, Rietschel RL. Alpha-1-antitrypsin deficiency-associated panniculitis: case report and review of the literature. *Pediatr Dermatol* 1991; **8**: 296–9.
9 Fellner MJ. Manifestations of familial autonomic dysautonomia: report of a case with an analysis of 125 cases in the literature. *Arch Dermatol* 1964; **89**: 190–5.
10 Fishbein D, Grossman RF. Pulmonary manifestations of familial dysautonomia in an adult. *Am J Med* 1986; **80**: 709–13.
11 Grunebaum M. The 'chest–abdomen sign' in familial dysautonomia. *Br J Radiol* 1975; **48**: 23–7.
12 Canny GJ, Roifman C, Weitzman S *et al.* A pulmonary infiltrate in a child with ataxia telangiectasia. *Ann Allergy* 1988; **61**: 466–8.
13 Steck WD, Byrd RB. Urticaria secondary to pulmonary melioidosis: report of a case. *Arch Dermatol* 1969; **99**: 80–1.
14 Tuffanelli DL. Systemic sclerosis. In: Sontheimer RD, Provost TT, eds. *Cutaneous Manifestations of Rheumatic Diseases*. Baltimore: Williams and Wilkins, 1996: 115–39.
15 Wigley FM, Provost TT. Scleroderma. In: Provost TT, Flynn JA, eds. *Cutaneous Medicine: Cutaneous Manifestations of Systemic Disease*. Hamilton, Ontario: Decker, 2001: 104–26.
16 Provost TT, Flynn JA. Lupus erythematosus. In: Provost TT, Flynn JA, eds. *Cutaneous Medicine: Cutaneous Manifestations of Systemic Disease*. Hamilton, Ontario: Decker, 2001: 41–81.
17 Cavallasca JA, Dubinsky D, Nasswetter GG. Shrinking lungs syndrome, a rare manifestation of systemic lupus erythematosus. *Int J Dermatol* 2006; **60**: 1683–6.
18 Cuadrado MJ, Hughes GRV. Hughes (antiphospholipid) syndrome: clinical features. *Rheum Dis Clin* 2001; **27**: 507–24.
19 Braverman IM. *Skin Signs of Systemic Disease*, 3rd edn. Philadelphia: Saunders, 1998: 501–2.
20 Cox NH, Langtry JAA, Lawrence CM, Ive FA. Dermatomyositis: disease associations and an evaluation of screening investigations for malignancy. *Arch Dermatol* 1990; **126**: 61–5.
21 Euwer RL, Sontheimer RD. Dermatomyositis. In: Sontheimer RD, Provost TT, eds. *Cutaneous Manifestations of Rheumatic Diseases*. Baltimore: Williams and Wilkins, 1996: 73–114.
22 Hengstman GJD, van Engelen BGM, Vree Egberts WTM, van Venrooij WJ. Myositis-specific autoantibodies: overview and recent developments. *Curr Opin Rheumatol* 2001; **13**: 476–82.
23 Fox RI. Clinical features, pathogenesis, and treatment of Sjögren's syndrome. *Curr Opin Rheumatol* 1996; **8**: 438–45.
24 Chakravarty K. Vasculitis by organ systems. *Baillière's Clin Rheumatol* 1997; **11**: 357–93.
25 Hamuryudan H, Yurdakal S, Moral F *et al.* Pulmonary artery aneurysms in Behçet's syndrome: a report of 24 cases. *Br J Rheumatol* 1994; **33**: 48–51.
26 Mehregan DR, Hall MJ, Gibson LE. Urticarial vasculitis: a histopathologic and clinical review of 72 cases. *J Am Acad Dermatol* 1992; **26**: 441–8.
27 Gross WL. Systemic necrotizing vasculitis. *Baillière's Clin Rheumatol* 1997; **11**: 259–84.
28 Mouthon L, Lhote F, Guillevin L. Pulmonary vasculitides. In: Ansell BM, Bacon PA, Lie JT, Yazici H, eds. *The Vasculitides*: *Science and Practice.* London: Chapman & Hall Medical, 1996: 222–45.
29 Stegeman CA, Cohen Tervaert JW, de Jong PE, Kallenberg CGM. Trimethoprim-sulphamethoxazole (co-trimoxazole) for the prevention of relapses of Wegener's granulomatosis. *N Engl J Med* 1996; **335**: 16–20.
30 Specks U. Diffuse alveolar haemorrhage syndromes. *Curr Opin Rheumatol* 2001; **13**: 12–7.
31 Sorenson SF, Slot O, Tvede N *et al.* A prospective study of vasculitis patients collected in a five year period: evaluation of the Chapel Hill nomenclature. *Ann Rheum Dis* 2000; **59**: 478–82.
32 Wechsler ME, Garpestad E, Kocher O *et al*. Pulmonary infiltrates, eosinophilia and cardiomyopathy in patients with asthma receiving zafirlukast. *JAMA* 1988; **279**: 455–7.
33 Wechsler ME, Finn D, Gunawardena D *et al*. Churg–Strauss syndrome in patients receiving montelukast as treatment for asthma. *Chest* 2000; **117**: 708–13.
34 Vignon-Pennamen MD, Zelinsky-Gurung A, Janssen F *et al.* Pyoderma gangrenosum with pulmonary involvement. *Arch Dermatol* 1989; **125**: 1239–42.
35 Brown TS, Marshall GS, Callen JP. Cavitating pulmonary infiltrate in an adolescent with pyoderma gangrenosum: a rarely recognized extracutaneous manifestation of a neutrophilic dermatosis. *J Am Acad Dermatol* 2000; **43**: 108–12.
36 Merke DP, Honig PJ, Potsic WP. Pyoderma gangrenosum of the skin and trachea in a 9-month-old boy. *J Am Acad Dermatol* 1996; **34**: 681–2.
37 Lazarus AA, McMillan M, Miramadi A. Pulmonary involvement in Sweet's syndrome (acute febrile neutrophilic dermatosis). *Chest* 1986; **90**: 922–4.
38 Bourke SJ, Quinn AG, Farr PM *et al.* Neutrophilic alveolitis in Sweet's disease. *Thorax* 1992; **47**: 572–3.
39 English JC 3rd, Patel PJ, Greer KE. Sarcoidosis. *J Am Acad Dermatol* 2001; **44**: 725–43.
40 Quaden C, Tillie-Leblond I, Delobbe A *et al*. Necrotising sarcoid granulomatosis: clinical, functional, endoscopical and radiographical evaluations. *Eur Respir J* 2005; **26**: 778–85.
41 Shirodaria CC, Nicholson AG, Hansell DM *et al*. Lesson of the month: necrotising sarcoid granulomatosis with skin involvement. *Histopathology* 2003; **43**: 91–3.
42 Lesher JL Jr, Allen BS. Multicentric reticulohistiocytosis. *J Am Acad Dermatol* 1984; **11**: 713–23.
43 Rongioletti F, Rebora A. Updated classification of papular mucinosis, lichen myxedematosus, and scleromyxedema. *J Am Acad Dermatol* 2001; **44**: 273–81.
44 Braverman IM. *Skin Signs of Systemic Disease*, 3rd edn. Philadelphia: Saunders, 1998: 117.
45 James WD, Odom RB, Katzenstein AL. Cutaneous manifestations of lymphomatoid granulomatosis: report of 44 cases and a review of literature. *Arch Dermatol* 1981; **117**: 196–202.
46 Guinee D Jr, Jaffe E, Kingma D *et al.* Pulmonary lymphomatoid granulomatosis: evidence for a proliferation of Epstein–Barr virus infected B lymphocytes with a prominent T-cell component and vasculitis. *Am J Surg Pathol* 1994; **18**: 753–64.
47 Tosti A, Baran R, Dawber RPR. The nail in systemic diseases and drug-induced changes. In: Baran R, Dawber RPR, Deberker DAR, Haneke E, Tosti A, eds. *Diseases of the Nails and Their Management*. Oxford: Blackwell Science, 2001: 249–51.
48 Lodge JP, Hunter AM, Saunders NR. Yellow nail syndrome associated with empyema. *Clin Exp Dermatol* 1989; **14**: 328–9.

49 Nousari HC, Deterding R, Wotjczack H *et al*. The mechanism of respiratory failure in paraneoplastic pemphigus. *New Engl J Med* 1999; **340**: 1406–10.
50 Hoffman MA, Qiao X, Anhalt GJ. CD8+ T lymphocytes in bronchiolitis obliterans, paraneoplastic pemphigus, and solitary Castleman's disease. *New Engl J Med* 2003; **349**: 407–8.
51 Bernhard JD. Non-rashes, 4: audible signs of cutaneous disease. *Cutis* 1983; **31**: 189–90.

Haematology [1]

Disorders of the blood components and the coagulation system may have striking cutaneous and mucosal signs and symptoms and sometimes are the presenting features of haematological disease, and these will be elaborated in this section.

Erythrocyte disorders

Anaemia

Anaemia from any cause will result eventually in pallor of the skin and mucous membranes, traditionally appreciated in the palmar creases of the hand and mucous membranes of the palpebral conjunctivae and mouth. Constitutional symptoms such as fatigue, breathlessness, dizziness and postural hypotension are more likely to occur the more acutely that the anaemia has developed. Many nutritional anaemias (see also Chapter 59) develop slowly, and physiological adaptation may account for the relatively minor symptoms despite marked reduction in the haemoglobin concentration in some instances. Palmar crease erythema will be evident until the haemoglobin concentration is around 7 g/dl.

Iron deficiency. This results from an inability to absorb sufficient iron to match bodily iron losses. Many cases result from both increased losses, either overtly, as in heavy menstrual blood loss or frequent and heavy nose bleeds, or covertly, such as with intestinal blood loss from hook worm infestation, tumours or other vessel abnormalities such as angiodyspasia, coupled with inadequate dietary iron intake. Intestinal malabsorbtion due to coeliac disease (coeliac sprue) often produces a mixed iron and folic acid deficiency.

The mucocutaneous signs [2,3] of iron deficiency include pallor, koilonychia or spooning of the nail plate, diffuse hair thinning and pruritus. A burning sensation of the tongue (glossodynia) and cravings for eating unpalatable substances (pica) are described in iron deficiency.

Iron deficiency is particularly liable to develop in hereditary haemorrhagic telangiectasia and the blue rubber bleb naevus syndrome due to either nasal or gastrointestinal blood loss from vascular abnormalities in these conditions. Chronic blood loss from vascular abnormalities in the gut in pseudoxanthoma elasticum results in iron deficiency, though blood loss may be more acute and present with melaena [4]. Anaemia may occur in dermatitis herpetiformis due to both iron and folic acid malabsorbtion complicating the associated gluten sensitive enteropathy, compounded also by dapsone-induced haemolysis [5].

Megaloblastic anaemias. These are due to impaired DNA synthesis, and the most common causes are either vitamin B_{12} or folic acid deficiency. Antimetabolite drugs are a potential cause, macrocytosis due to hydroxcarbamide being the most familiar to the dermatologist; drugs such as folate antagonists (trimethoprim) and anticonvulsants are less common causes.

As the onset of megaloblastic anaemias is insidious, symptoms may only be evident when anaemia is marked. A mild haemolysis resulting in a type of jaundice may give the patient a lemon yellow hue. Hyperpigmentation of the feet, hands and face is reported. Megaloblastic anaemia due to vitamin B_{12} deficiency has been reported to produce a partially reversible poikiloderma. Premature greying of the hair (canities) is associated with pernicious anaemia [6]. Loss of lingual filiform papillae and cheilitis are common. Neurological symptoms, leading ultimately to subacute combined degeneration of the spinal cord, may prompt cutaneous symptoms such as paraesthesiae and loss of sensation in the skin.

Vitamin B_{12} deficiency usually results from pernicious anaemia; antiparietal cell antibodies (present in 70% of cases) destroy the cells that produce intrinsic factor needed to absorb the vitamin. There is an association between other autoimmune disorders, such as vitiligo and Addison's disease, and dermatological manifestations; these diseases, and testing for their relevant antibodies, should always be considered. Rarely, vitamin B_{12} deficiency is the result of terminal ileal disease, such as Crohn's disease, fish tape worm or ileal resection.

Folic acid deficiency is usually the result of inadequate dietary intake due to poor nutrition, but may occur in times of increased metabolic requirement, such as pregnancy. Dermatological causes of folate deficiency include erythroderma, particularly due to psoriasis [7], and in such situations it is prudent to check folate levels prior to administering folate antagonists such as methotrexate (discussed further in Chapters 20 and 74).

Haemoglobinopathies and haemolytic anaemias

Both sickle cell disease and thalassaemia have important cutaneous manifestations due to the underlying diseases and their therapies. Lower leg ulceration, which may start in childhood and be both recalcitrant and recurrent, is a major burden; ulcers may be the first manifestation of milder disease [8,9]. Ulceration occurs with a prevalence of 2.5% in sickle disease, being more common in sickle and sickle thalassaemia, but does not occur in sickle C disease. Ulcers are more common in men and prevalence increases with age. In sickle disease there is a strong association with venous incompetence; leg elevation and compression hosiery are thus important aspects of treatment. Spherocytosis may also be complicated by leg ulcers [10].

Thalassaemia requires multiple blood transfusions and haemosiderosis with slate-grey skin pigmentation may be a consequence.

Both chronic sickle cell anaemia and thalassaemia can be associated with a condition similar to familial pseudoxanthoma elasticum (PXE) [11]. As well as the characteristic features of PXE, including yellow papular and plaque lesions on the neck (the 'plucked chicken skin'), axillae and antecubital fossae, retinal angioid streaks may be present. Associated mitral valve prolapse indicates the general and widespread nature of the elastin disorder seen in haemoglobinopathy-associated PXE-like disease.

Hydroxcarbamide has become an important therapy for sickle disease. Its chronic use has numerous dermatological complications, including a dermatomyositis-like eruption affecting the dorsal hands and face (hydroxycarbamide dermopathy), painful ulcers on feet and ankles, nail pigmentation and cutaneous malignancies [12].

Polycythaemia

Defined as an increase in the red cell mass, polycythaemia can be a primary disorder (polycythaemia vera; PV) or secondary. The secondary form is usually due to chronic hypoxaemia, but rarely may be due to erythropoietin production by renal tumours or exogenous administration of erythropoietin (such as illicit use by athletes). Polycythaemia vera is believed to be a stem cell disorder due to mutation of the Janus kinase 2 gene (*JAK2*). Splenomegaly and an elevation of both the total white cell and platelet counts usually develop; this, and an elevated leukocyte alkaline phosphatase, help distinguish PV from other causes of polycythaemia. As *JAK2* mutations occur in 95% of cases, and can now be readily identified, genotyping has replaced more complex tests previously used to estimate total red cell mass. *JAK2* mutations are also found in about 50% of cases of essential thrombocythaemia and chronic myeloid leukaemia.

The most important consequences of PV are an increased tendency to thrombosis (resulting in stroke and hepatic vein thrombosis) or bleeding. Hyperhomocysteinaemia is a risk factor for thrombosis. Dermatological features may include skin changes due to peripheral vascular disease and deep vein thrombosis, leg ulcers, digital gangrene and erythromelalgia (burning erythema of the extremities, usually the feet, on warming).

Pruritus is common in PV [13], and aquagenic pruritus, an intense disabling itching after water exposure, may antedate the onset of polycythaemia by several years [14]. Itching may persist even after restoration of the red cell mass to normal. Venesection is used to reduce the red cell mass followed by the use of hydroxycarbamide to maintain blood parameters. However this drug may induce dermopathy. Therapy with either radioactive phosphorus, or alkylating agents, is used less than previously, as both treatments are associated with the development of leukaemia. Aquagenic and spontaneous pruritus may improve with emollients, topical antipruritics, oral antihistamines, UVB or PUVA phototherapy, recombinant interferon-α or opioid antagonists such as naltrexone. Repeated venesection may lead to iron deficiency, and this should be excluded as a cause of itch. A superficial pustular dermatosis, nosologically thought to be a superficial variant of Sweet's syndrome, has been described in PV [15].

References

1 Hoffbrand AV, Pettit JE. *Clinical Haematology Illustrated.* Edinburgh: Churchill Livingstone, 1987.
2 Vickers CF. Nutrition and skin: iron deficiency. In: Ledingham JC, ed. *Proceedings of the Tenth Symposium on Advanced Medicine*. London: Pitman, 1974: 311–6.
3 Sato S. Iron deficiency: structural and microchemical changes in hair, nails, and skin. *Semin Dermatol* 1991; **10**: 313–9.
4 Spinzi G, Strocchi E, Imperiali G *et al*. Pseudoxanthoma elasticum: a rare cause of gastrointestinal bleeding. *Am J Gastroenterol* 1996; **91**: 1631–4.
5 Cream JJ, Scott L. Anaemia in dermatitis herpetiformis: the role of dapsone induced haemolysis and malabsorption. *Br J Dermatol* 1970; **82**: 333–42.
6 Noppakun N, Swasdikul D. Reversible hyperpigmentation of skin and nails with white hair due to vitamin B12 deficiency. *Arch Dermatol* 1986; **122**: 896–9.
7 Shuster S, Marks J. *The Systemic Effects of Skin Disease*. London: Heinemann, 1970.
8 Clare A, FitzHenley M, Harris J *et al*. Chronic leg ulceration in homozygous sickle cell disease: the role of venous incompetence. *Br J Haematol* 2002; **119**: 567–71.
9 Gimmon Z, Wexler MR, Rachmilewitz EA. Juvenile leg ulceration in beta-thalassemia major and intermedia. *Plast Reconstr Surg* 1982; **69**: 320–5.
10 Lawrence P, Aronson I, Saxe N, Jacobs P. Leg ulcers in hereditary spherocytosis. *Clin Exp Dermatol* 1991; **16**: 28–30.
11 Aessopos A, Farmakis D, Loukopoulos D. Elastic tissue abnormalities resembling pseudoxanthoma elasticum in beta thalassemia and the sickling syndromes. *Blood* 2002; **99**: 30–5.
12 Young HS, Khan AS, Kendra JR, Coulson IH. The cutaneous side-effects of hydroxyurea. *Clin Lab Haematol* 2000; **22**: 229–32.
13 Diehn F, Tefferi A. Pruritus in polycythaemia vera: prevalence, laboratory correlates and management. *Br J Haematol* 2001; **115**: 619–21.
14 du Peloux Menage H, Greaves MW. Aquagenic pruritus. *Semin Dermatol* 1995; **14**: 313–6.
15 Grob JJ, Mege JL, Prax AM, Bonerandi JJ. Disseminated pustular dermatosis in polycythemia vera. Relationship with neutrophilic dermatosis of myeloproliferative disorders: study of neutrophil function. *J Am Acad Dermatol* 1988; **18**: 1212–8.

Leukocyte disorders

Neutrophils

Neutrophilia commonly occurs with infections and as a response to a variety of skin disorders including erythroderma, pustular psoriasis and erythema multiforme, and as a result of systemic corticosteroid administration.

Acute febrile neutrophilic dermatosis (Sweets's syndrome; Chapter 50) [1] has neutrophilia as one of its diagnostic criteria, and may be associated with infection, myelodysplasia, polycythaemia, leukaemia, lymphomas, myeloma and paraproteinaemia as well as solid cancers. Superficial pustular variants have been reported in chronic myeloid leukaemia, and the dorsal hand variety in polycythaemia vera. Sweet's syndrome, subcorneal pustular dermatosis, superficial bullous pyoderma gangrenosum, conventional pyoderma gangrenosum and erythema elevatum diutinum are felt to be a continuum of neutrophilic disorders that may be associated with a neutrophilia or with myelodysplasia, myelofibrosis and myeloid leukaemia.

Eosinophils

Eosinophilia of the blood is a frequent finding in parasitic helminth infestation of the gut and the skin (for example, in larva migrans or onchocerciasis) and in non-helminth infestations such as scabies. Worldwide, infestations are the commonest cause of eosinophilia. In developed areas of the world, allergic causes predominate. Severe atopic dermatitis is often accompanied by a marked eosinophilia; immunobullous diseases such as pemphigoid and pemphigus, even in their prebullous phase, may be accompanied by an eosinophilia, as may allergic drug reactions. Conditions of particular dermatological interest associated with eosinophilia are listed in Table 62.17, and are discussed below.

Churg–Strauss syndrome (Chapter 50) [2]. Asthma and rhinitis, haemorrhagic palpable purpuric lesions and granulomatous

Table 62.17 Some dermatologically relevant causes of peripheral blood eosinophilia.

Category	Examples
Infestation and infection	Scabies Strongyloides Helminths Other parasitic infections Insect bites, reactions to stings HIV/AIDS (especially if late stage)
Allergic/atopic	Atopic dermatitis Allergic reactions Episodic angioedema with eosinophilia Other urticaria and angioedema
Immunobullous	Bullous pemphigoid Pemphigoid gestationis
Vasculitis (Chapter 50)	Churg-Strauss syndrome Wegener's granulomatosis (some) Polyarteritis nodosa (some) Eosinophilic vasculitis Drug-induced vasculitis Granuloma faciale (some)
Other inflammatory conditions	Eosinophilic cellulitis (Wells' syndrome) Eosinophilic fasciitis (Shulman syndrome) Eosinophilic panniculitis Eosinophilic mastitis Eosinophilia myalgia syndrome Toxic oil syndrome Chronic graft-versus-host disease Eosinophilic pustular folliculitis (Ofuji disease) Eosinophilic folliculitis of HIV infection Connective tissue disorders (some) Sarcoidosis (rarely) Erythema annulare centrifugum and annular erythema of infancy (some cases) Incontinentia pigmenti Pyoderma vegetans
Medications	Many cutaneous drug reactions (Chapter 75) Granulocyte-monocyte colony stimulating factor Other cytokine infusions Capillary leak syndrome
Neoplastic/clonal/proliferative	Hypereosinophilic syndrome (Gleich syndrome) Cutaneous T cell lymphoma Hodgkin's lymphoma Myeloproliferative disorders/leukaemias Systemic mastocytosis
Idiopathic/miscellaneous	Cholesterol emolization syndrome Angiolymphoid hyperplasia with eosinophilia Addison's disease (some)

plaques on the elbows and knees, weight loss, arthralgias and pulmonary infiltrates are the characteristic findings. p-ANCA is frequently but not always positive; eosinophilia in excess of 10% is a diagnostic criterion.

Eosinophilic fasciitis (Chapter 51) [3]. A fibrosing condition usually affecting the limbs, due to inflammation and fibrosis of the fascia, associated with an eosinophilic infiltration of the fascia and a circulating eosinophilia. The absence of Raynaud's phenomenon differentiates it from scleroderma.



Fig. 62.27 Eosinophilic cellulitis. Lesions may be bullous and often resolve to leave a green discoloration of the skin.

Eosinophilia myalgia syndrome [4]. A fibrotic condition similar to eosinophilic fasciitis, but induced by ingestion of tryptophan.

Eosinophilic cellulitis (Wells' syndrome; Fig. 62.27) [5]. This typically presents as an indurated erythematous plaque, which sometimes blisters, mimicking bacterial cellulitis; histologically, it is characterized by a dense, eosinophilic dermal infiltrate and eosinophilic flame figures. Eosinophilia is usual during episodic exacerbations of the cellulitis, and usually resolves to the normal range between attacks.

Hypereosinophilic syndrome (HES; Gleich syndrome) [6,7]. This condition is characterized by an eosinophilia in excess of 1500/μl (but usually greatly in excess of this), with no apparent cause, for greater than 6 months, and with presumptive signs of multiple organ involvement. Although traditionally viewed as idiopathic, recent evidence suggests that the entity may include more than one form of haematological malignancy [8]. In some instances, there is a clonal T-cell production of interleukin (IL)-5, a major controlling cytokine in production, release and differentiation of eosinophils. In other cases, there is clonal expansion of eosinophils with hepatosplenomegaly and thrombocytopenia; this condition appears to be due to a cytogenetic defect t(9;22)(q34;q11) in which there is chromosomal breakage and reciprocal exchange of chromosomal fragments that leads to formation of a fusion tyrosine kinase FIP1L1–PDGFRα.

The disease most commonly affects middle-aged men and the morbidity and mortality is related to endomyocardial fibrosis, eosinophilic vasculitis, thrombosis and embolic phenomena [9–12]. Skin lesions are varied and include vesicles, petechiae, papules and papulonodules, angio-oedema, livedo reticularis, erythema annulare, Raynaud's phenomenon, digital ischaemia, acrocyanosis, cutaneous microthrombi and gangrene. The pathology of the skin lesions may be non-specific with variable eosinophilic infiltration; cutaneous microthrombi may be a clue to the disease.

Eosinophilic cellulitis with florid eosinophilic infiltration and flame figures has been reported.

Newer treatments combined with identification of the causative abnormality may allow targeted therapy; imatinib mesylate, used mainly in treatment of chronic myelogenous leukaemia, targets the platelet-derived growth factor receptor (PDGFR) in the fusion tyrosine kinase of HES [13], described above, and mepolizumab, an anti-IL-5 monoclonal antibody, has also been used recently to treat HES [14].

Haematological malignancies

Leukaemia

Leukaemias can cause a huge array of cutaneous symptoms and signs, some of which are common and non-specific (e.g. purpura due to thrombocytopenia), some of which are relatively uncommon but specific (e.g. leukaemia cutis), and some of which are both rare and non-specific (e.g. numb chin due to acute lymphoblastic leukaemic cells infiltrating the mental nerve). Some of the dermatologically relevant features of leukaemia are listed in Table 62.18.

Leukaemia can infiltrate the skin, where it is termed leukaemia cutis [15]. This is uncommon, and although it may occur in any leukaemia, it is commoner in acute monocytic and myelomonocytic disease. Skin infiltration can occur in any chronic leukaemia, including chronic myeloid, chronic lymphocytic, hairy cell and the leukaemic phase of non-Hodgkin's lymphoma. It tends to be a late manifestation of acute leukaemias, and may herald a blast transformation of chronic leukaemia. There is a strong association of leukaemia cutis with other extramedullary disease. Lesions are usually painless, evolving from patches to plaques and nodules and may ulcerate (see Fig. 62.6).

Aleukaemic leukaemia cutis, where there is evidence of leukaemic skin infiltration before evidence of leukaemia in the peripheral blood, is reported, and lesions may be mistaken initially for a high-grade lymphoma. Congenital leukaemia cutis is more common in congenital myeloid leukaemia where purple 'blueberry muffin' lesions may mimic congenital infection [16]. An important differential diagnosis occurs in neonates with Down's syndrome, who may develop a leukaemic blood picture and vesicopustular skin eruption as a transient myeloproliferative disorder (leukaemoid reaction) [17,18]. Vasculitis has been noted in some lesions of leukaemia cutis with vascular injury being mediated by blast cells [19]. Leukaemia cutis due to juvenile myelomonocytic leukaemia has been reported to mimic chilblains [20], and chilblain-like lesions have been reported in various forms of adult leukaemia [21]. Non-specific skin lesions and reactions (such as erythroderma) can occur as a paraneoplastic phenomenon in leukaemia; a variety of paraneoplastic syndromes associated with haematological malignancy are summarized in [22].

Table 62.18 Skin lesions in leukaemia.

Category	Examples
Specific lesions	Leukaemia cutis Chloroma Granulocytic sarcoma
Paraneoplastic phenomena	Sweet's syndrome (including GCSF-induced and ATRA-induced) [23,24] Neutrophilic dermatosis of the dorsal hands (Fig. 62.28) [25] Pyoderma gangrenosum [23] Subcorneal pustular dermatosis [22] Erythema elevatum diutinum [26] Neutrophilic eccrine hidradenitis [27] Vasculitis [19,28] Eosinophilic pustular folliculitis [29] Erythroderma [22]
Secondary to disordered immune or white cell function	Infections: bacterial e.g. echthyma gangrenosum viral e.g. herpetic infections (especially chronic herpes simplex or disseminated herpes zoster) fungal e.g. candidosis, zygomycosis
Due to other haematological parameters	Bruising, purpura
Conditions associated with leukaemias	Increased incidence of basal cell carcinoma and squamous cell carcinoma in chronic lymphocytic leukaemia [29] Association of juvenile chronic myelomonocytic leukaemia with juvenile xanthogranuloma and neurofibromatosis type 1 (pp. 62.23 and 62.96)
Due to treatment	Drug eruptions Neutrophilic eccrine hidradenitis Graft-versus-host disease (p. 62.96) Effects of cytopenia, infections etc as above

Myelodysplastic syndrome (MDS)

This refers to a closely related group of disorders characterized by ineffective blood cell production that may affect either erythrocytic, granulocytic or megakaryocytic cell lines. Myelodysplastic syndrome can occur at any age but is more common in older men. It represents a clonal haematopoietic disorder and after a variable time may progress to an acute myelogenous leukaemia.

A variety of skin disorders are associated with MDS, neutrophilic dermatoses (Fig. 62.28) being the best known [22,23]



Fig. 62.28 Neutrophilic dermatosis of the dorsal hands in a patient with myelodysplastic syndrome.



Fig. 62.29 Cutaneous extramedullary haematopoiesis in myelofibrosis. (Courtesy of Dr C. Blasdale, Sunderland Royal Infirmary, UK.)

(Chapter 50). Vasculitis [30], extramedullary haemopoiesis (Fig. 62.29) [31], reactive angioendotheliomatosis [32] and prurigo [33] have been reported. A significant proportion of patients with relapsing polychondritis have MDS [34]. Erythroderma [22] and erythromelalgia [22] may both occur.

References

1 Neoh CY, Tan AW, Ng SK. Sweet's syndrome: a spectrum of unusual clinical presentations and associations. *Br J Dermatol* 2007; **156**: 480–5.
2 Vogel PS, Nemer J, Sau P, Hnatiuk O. Churg–Strauss syndrome. *J Am Acad Dermatol* 1992; **27**: 821–4.
3 Helfman T, Falanga V. Eosinophilic fasciitis. *Clin Dermatol* 1994; **12**: 449–55.
4 Blackburn WD Jr. Eosinophilia myalgia syndrome. *Semin Arthritis Rheum* 1997; **26**: 788–93.
5 Ling TC, Antony F, Holden CA *et al*. Two cases of bullous eosinophilic cellulitis. *Br J Dermatol* 2002; **146**: 160–1.
6 Weller PF. The idiopathic hypereosinophilic syndrome. *Arch Dermatol* 1996; **132**: 583–5.
7 Fujii K, Tanabe H, Kanno Y *et al*. Eosinophilic cellulitis as a cutaneous manifestation of idiopathic hypereosinophilic syndrome. *J Am Acad Dermatol* 2003; **49**: 1174–7.
8 Schwartz RS. The hypereosinophilic syndrome and the biology of cancer. *N Engl J Med* 2003; **348**: 1199–200.
9 Jang K-A, Lim Y-S, Choi J-H *et al*. Hypereosinophilic syndrome presenting as cutaneous necrotizing eosinophilic vasculitis and Raynaud's phenomenon complicated by digital gangrene. *Br J Dermatol* 2000; **143**: 641–4.
10 Hamada T, Kimura Y, Hayashi S *et al*. Hypereosinophilic syndrome with peripheral circulatory insufficiency and cutaneous microthrombi. *Arch Dermatol* 2007; **143**: 812–3.
11 Oppliger R, Gay-Crosier F, Dayer E, Hauser C. Digital necrosis in a patient with hypereosinophilic syndrome in the absence of cutaneous eosinophilic vasculitis. *Br J Dermatol* 2001; **144**: 1087–90.
12 Kim SH, Kim TB, Yun YS *et al*. Hypereosinophilia presenting as eosinophilic vasculitis and multiple peripheral artery occlusions without organ involvement. *J Korean Med Sci* 2005; **20**: 677–9.
13 Cools J, DeAngelo DJ, Gotlib J *et al*. A tyrosine kinase created by fusion of the PDGFRA and FIP1L1 genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. *N Engl J Med* 2003; **348**: 1201–14.
14 Rothenberg ME, Klion AD, Roufosse FE *et al*. Treatment of patients with the hypereosinophilic syndrome with mepolizumab. *N Engl J Med* 2008; **358**: 1215–28.
15 Desch JK, Smoller BR. The spectrum of cutaneous disease in leukemias. *J Cutan Pathol* 1993; **20**: 407–10.
16 Bresters D, Reus AC, Veerman AJ *et al*. Congenital leukaemia: the Dutch experience and review of the literature. *Br J Haematol* 2002; **117**: 513–24.
17 Solky BA, Yang FC, Xu X, Levins P. Transient myeolproliferatve disorder causing a vesicopustular eruption in a phenotypically normal neonate. *Pediatr Dermatol* 2004; **21**: 551–4.
18 Burch JM, Weston WL, Rogers M, Morelli JG. Vutaneous pustular leukaemoid reactions in trisomy 21. *Pediatr Dermatol* 2003; **20**: 232–7.
19 Jones D, Dorfman DM, Barnhill RL, Granter SR. Leukemic vasculitis: a feature of leukemia cutis in some patients. *Am J Clin Pathol* 1997; **107**: 637–42.
20 Affleck AG, Ravenscroft JC, Leach IH. Chilblain-like leukemia cutis. *Pediatr Dermatol* 2007; **24**: 38–41.
21 Yazawa H, Saga K, Omori F *et al*. The chilblain-like eruption as a diagnostic clue to the blast crisis of chronic myelocytic leukaemia. *J Am Acad Dermatol* 2004; **50** (Suppl.): S42–4.
22 Zappasodi P, Del Forno C, Corso A, Lazzarino M. Mucocutaneous paraneoplastic syndromes in hematologic malignancies. *Int J Dermatol* 2006; **45**: 14–22.
23 Lear JT, Atherton MT, Byrne JP. Neutrophilic dermatoses: pyoderma gangrenosum and Sweet's syndrome. *Postgrad Med J* 1997; **73**: 65–8.
24 Cox NH, O'Brien HAW. Sweet's syndrome associated with *trans*-retinoic acid treatment in acute promyelocytic leukemia. *Clin Exp Dermatol* 1994; **19**: 51–2.
25 Walling HW, Snipes CJ, Gerami P, Piette WW. The relationship between neutrophilic dermatosis of the dorsal hands and Sweet syndrome: report of 9 cases and comparison to atypical pyoderma gangrenosum. *Arch Dermatol* 2006; **142**: 57–63.
26 Delaporte E, Alfandari S, Fenaux P *et al*. H Erythema elevatum diutinum and chronic lymphocytic leukemia. *Clin Exp Dermatol* 1994; **19**: 188.
27 Pierson JC, Helm TN, Taylor JS *et al*. Neutrophilic eccrine hidradenitis heralding the onset of acute myelogenous leukemia. *Arch Dermatol* 1993; **129**: 791–2.
28 Bachmeyer C, Wetterwald E, Aractingi S. Cutaneous vasculitis in the course of hematologic malignancies. *Dermatology* 2005; **210**: 8–14.
29 Agnew KL, Ruchlemer R, Catovsky D *et al*. Cutaneous findings in chronic lymphocytic leukaemia. *Br J Dermatol* 2004; **150**: 1129–35.
30 O'Donnell BF, Williams HC, Carr R. Myelodysplastic syndrome presenting as cutaneous vasculitis. *Clin Exp Dermatol* 1995; **20**: 439–42.
31 Haniffa MA, Wilkins BS, Blasdale C, Simpson NB. Cutaneous extramedullary hemopoiesis in chronic myeloproliferative and myelodysplastic disorders. *J Am Acad Dermatol* 2006; **55**: S28–31.
32 del Pozo J, Martinez W, Sacristan F *et al*. Reactive angioendotheliomatosis associated with myelodysplastic syndrome. *Acta Derm Venereol* 2005; **85**: 269–70.
33 Aractingi S, Bachmeyer C, Miclea JM *et al*. Unusual specific cutaneous lesions in myelodysplastic syndromes. *J Am Acad Dermatol* 1995; **33**: 187–91.
34 Myers B, Gould J, Dolan G. Relapsing polychondritis and myelodysplasia: a report of two cases and review of the current literature. *Clin Lab Haematol* 2000; **22**: 45–8.

Lymphoma

After the gastrointestinal tract, the skin is the commonest organ to be affected by malignant lymphomas. Most lymphomas are of the cutaneous T-cell variety, but the cutaneous B cell form constitutes up to a third of primary skin lymphomas.

The skin may be infiltrated by metastatic nodal lymphoma; in Hodgkin's disease direct infiltration from underlying nodes may produce a scrofuloderma-like appearance [1,2].

Lymphoma may produce a number of paraneoplastic phenomena; itch, which may be intractable and severe, was found in 8% of a large series of patients with Hodgkin's disease and it purported a relatively poor prognosis. Mild itch was present in almost a quarter of the patients at diagnosis [3]. Eczema, excoriations, prurigo and reactive perforating collagenosis have also been reported [4]. Cutaneous T-cell lymphoma appears to be more common in Hodgkin's disease [5]. Acrokeratosis paraneoplastic (Bazex syndrome), more commonly associated with solid respiratory tract neoplasia, may occur with Hodgkin's disease [6].



Fig. 62.30 Paraneoplastic pemphigus of the mouth and lips in Castleman's disease.

The development of acquired ichthyosis is most strongly associated with either Hodgkin's disease [7], non-Hodgkin's lymphoma [8] or anaplastic large cell lymphoma [9]. It is important to distinguish this from the increasingly well recognized ichthyotic variant of cutaneous T-cell lymphoma [10].

Paraneoplastic pemphigus (Chapter 40) is most associated with B cell malignancies (lymphoma, chronic lymphatic leukaemia and Castleman's disease; Fig. 62.30) and may manifest as a severe mucositis with an acral lichenoid eruption, ranging to a more widespread eruption, even mimicking toxic epidermal necrolysis. An associated obliterative pneumonitis is a major cause of mortality [11,12].

Other reported associated dermatological conditions or paraneoplastic phenomena in lymphomas include Sweet's syndrome, subcorneal pustular dermatosis, pemphigus foliaceous and vulgaris (some of these in retrospect possibly representing paraneoplastic pemphigus), pemphigoid, erythroderma, exfoliative dermatitis, acanthosis nigricans, dermatomyositis, dermatitis herpetiformis and vasculitis [13].

References

1 O'Bryan-Tear CG, Burke M, Coulson IH, Marsden RA. Hodgkin's disease presenting in the skin. *Clin Exp Dermatol* 1987; **12**: 69–71.

2 Takagawa S, Maruyama R, Yokozeki H *et al*. Skin invasion of Hodgkin's disease mimicking scrofuloderma. *Dermatology* 1999; **199**: 268–70.

3 Gobbi PG, Attardo-Parrinello G, Lattanzio G *et al*. Severe pruritus should be a B-symptom in Hodgkin's disease. *Cancer* 1983; **51**: 1934–6.

4 Eigentler TK, Metzler G, Brossart P, Fierlbeck G. Acquired perforating collagenosis in Hodgkin's disease. *J Am Acad Dermatol* 2005; **52**: 922.

5 Rubenstein M, Duvic M. Cutaneous manifestations of Hodgkin's disease. *Int J Dermatol* 2006; **45**: 251–6.

6 Lucker GP, Steijlen PM. Acrokeratosis paraneoplastica (Bazex syndrome) occurring with acquired ichthyosis in Hodgkin's disease. *Br J Dermatol* 1995; **133**: 322–5.

7 Rizos E, Milionis HJ, Pavlidis N, Elisaf MS. Acquired icthyosis: a paraneoplastic skin manifestation of Hodgkin's disease. *Lancet Oncol* 2002; **3**: 727.

8 Kato N, Yasukawa K, Kimura K, Yoshida K. Anaplastic large-cell lymphoma associated with acquired ichthyosis. *J Am Acad Dermatol* 2000; **42**: 914–20.

9 Estines O, Grosieux-Dauger C, Derancourt C *et al*. Paraneoplastic acquired ichthyosis revealing non-Hodgkin's lymphoma. *Ann Dermatol Venereol* 2001; **128**: 31–4.



Fig. 62.31 Non-palpable purpura in thrombocytopenia.

10 Hodak E, Amitay I, Feinmesser M *et al*. Ichthyosiform mycosis fungoides: an atypical variant of cutaneous T-cell lymphoma. *J Am Acad Dermatol* 2004; **50**: 368–74.

11 Wade MS, Black MM. Paraneoplastic pemphigus: a brief update. *Australas J Dermatol* 2005; **46**: 1–8

12 Mimouni D, Anhalt GJ, Lazarova Z *et al*. Paraneoplastic pemphigus in children and adolescents. *Br J Dermatol* 2002; **147**: 725–32.

13 Zappasodi P, Del Forno C, Corso A, Lazzarino M. Mucocutaneous paraneoplastic syndromes in hematologic malignancies. *Int J Dermatol* 2006; **45**: 14–22.

Platelet and clotting disorders

Purpura and bruising

Purpura is discussed in more detail in Chapter 49. A brief overview and details of some specific disorders of platelet numbers or function, and of impaired blood clotting, are listed here.

Non-palpable purpura or macular haemorrhages are suggestive of low platelet count or abnormal platelet function (Fig. 62.31). Petechiae are red-purple lesions less than 4 mm in diameter, and are usually due to a significant reduction in absolute platelet numbers (less than 50 000/microlitre), or abnormal platelet function (hereditary, salicylates, renal and hepatic disease). Less commonly, petechiae are the result of intermittent, severe elevation of intravascular pressure due to paroxysmal coughing, straining, stasis or strangulation. Viral exanthems, often enteroviral, may be purpuric. Macular haemorrhage is a term applied to larger lesions, between 4 and 10 mm. Causes include many of the same conditions that cause petechiae, although lesions of this size are uncommonly due to vascular leakage. Larger, non-palpable macules may recur in crops on the lower legs in Waldenstrom's hyperglobulinaemic purpura. This occurs most commonly in women, and may be associated with the sicca syndrome, SLE and rheumatoid arthritis.

Ecchymoses (bruises) are lesions larger than 10 mm in diameter. They are less likely to be due to platelet disorders, but can result from procoagulant defects, such as anticoagulant use, vitamin K deficiency, diffuse intravascular coagulopathy, or from inadequate dermal vasculature support, as occurs in severe actinic disease, corticosteroid use, scurvy, systemic amyloidosis, and ecchymotic (type IV) Ehlers–Danlos syndrome (Fig. 62.32).



Fig. 62.32 Bruising in type IV Ehlers–Danlos syndrome; the hyperextensibility of skin and joints is also apparent.



Fig. 62.33 Palpable purpura with haemorrhagic bullae in small vessel vasculitis.

Palpable or reticulate purpura

Palpable purpura is usually the result of vasculitis, most commonly of the small vessel leukocytoclastic type (Fig. 62.33). Inflammatory vascular changes produce an early erythematous change so that lesions remain red–pink when compressed. They are usually discrete macules or plaques rather than reticulate (compare with microvascular occlusive disorders, below) and they may progress to produce haemorrhagic blisters. Causes include ANCA-positive diseases (Wegener's granulomatosis, microscopic polyangiitis and Churg–Strauss disease) and non-ANCA syndromes (benign cutaneous polyarteritis nodosum) and small vessel vasculitis (Chapter 50).

This may be contrasted with the palpable purpura that is associated with non-inflammatory processes which result in occlusion of small dermal vessels (microvascular occlusion, Chapter 49), for example following platelet or crystal plugging, embolization (due to cholesterol, atrial myxoma, or endocarditis), cold-related gelling or agglutination, or abnormal coagulation control (coumarin necrosis, thrombophilic disorders). In these disorders, initial erythema is minimal (early lesions may fade on compression) and development of a reticulate morphology is common.

Essential thrombocythaemia shares many of the cutaneous signs seen with PV, with livedo reticularis and erythromelalgia being the best recognized.

Table 62.19 The thrombophilic disorders.

Lupus anticoagulant/antiphospholipid disease
Protein S and protein C deficiency
Factor V Leiden mutation
Antithrombin III deficiency
Hyperhomocysteinaemia
Plasminogen activator inhibitor-1 level elevation
Prothrombin gene mutation

Table 62.20 Dermatological conditions resulting from thrombophilia.

Livedo reticularis, Sneddon's syndrome [1,2]
Degos malignant atrophic papulosis [3]
Livedoid vasculomathy [4]
Acrocyanosis
Splinter haemorrhages
Capillaritis
Coumarin necrosis [5]
Thrombophlebitis
Mondor's disease [6]
Deep venous thrombosis and post phlebitic syndrome
Leg ulcers, cutaneous infarcts [7,8]
Cutaneous nodules and plaques with histological evidence of intravascular thrombosis [9]
Purpura fulminans [10]
Anetoderma [11]

Thrombophilic disorders

The thrombophilic disorders (Tables 62.19 and 62.20; also discussed in more detail in Chapter 49) cause a tendency for blood to clot; they are due to deficiencies of, or resistance to, anticoagulant factors, either inherited or acquired, and may present as a single factor disorder or due to several deficiencies coexisting in the same individual (Table 62.19). Many such factors have now been identified. Thrombophilias may present in the neonate (homozygous factor S or C deficiency) with neonatal purpura fulminans, during infection (heterozygous protein S or C deficiency), or in later childhood or adult life with an increased

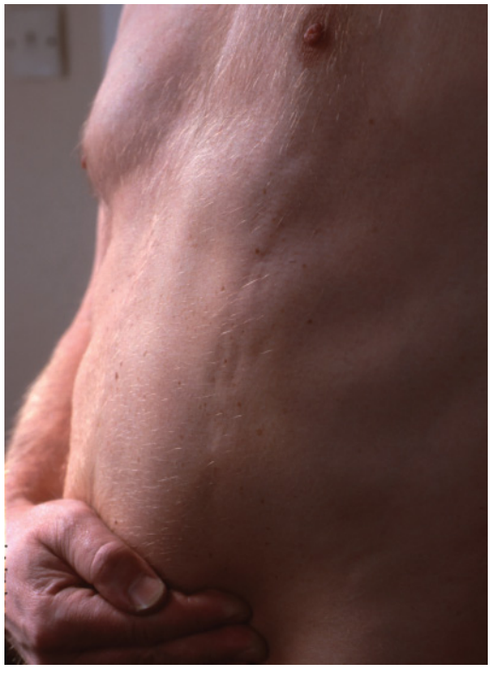


Fig. 62.34 Mondor's disease (thrombophlebitis of the superficial chest wall veins) associated with protein S deficiency.



Fig. 62.35 Cutaneous necrosis after initiation of warfarin treatment in protein C deficiency.

tendency to superficial (Fig. 62.34) and deep venous thrombosis, pulmonary embolism, and less commonly arterial thrombosis. Some disorders, particularly the presence of antiphospholipid antibodies/lupus anticoagulant, may be identified due to recurrent spontaneous abortions. Table 62.20 outlines the range of dermatological disorders with which they may manifest. Most can be explained as arising as a result of intravascular thrombosis in cutaneous vessels of different sizes.

Coumarin necrosis

This is an uncommon but serious complication arising within the first week of coumarin anticoagulation. Well-circumscribed, haemorrhagic necrosis of the skin, usually of the breasts, buttocks, abdomen or thighs develops (Fig. 62.35). Histologically, fibrin occlusion of the small veins and postcapillary venules in the skin and fat is seen. The condition is more common in women, and occurs in 0.1 to 0.01% of individuals anticoagulated. Coumarin necrosis arises as a result of temporary reduction in levels of the vitamin K-dependent natural anticoagulants such as proteins C and S, prior to reduction in the levels of the procoagulant factors in the clotting cascade; this results in a temporary state of thrombophilia when coumarins are commenced. In a minority of patients it is a manifestation of familial protein S or C deficiency. Heparin-induced skin necrosis is rarer, appears to be immunologically mediated and often associated with heparin-induced thrombocytopenia.

References

1 Naldi L, Locati F, Marchesi L *et al*. Cutaneous manifestations associated with antiphospholipid antibodies in patients with suspected primary antiphospholipid syndrome: a case-control study. *Ann Rheum Dis* 1993; **52**: 219–22.

2 Gibson GE, Su WP, Pittelkow MR. Antiphospholipid syndrome and the skin. *J Am Acad Dermatol* 1997; **36**: 970–82.

3 Hohwy T, Jensen MG, Tottrup A *et al*. A fatal case of malignant atrophic papulosis (Degos' disease) in a man with factor V Leinden mutation and lupus anticoagulant. *Acta Derm Venereol* 2006; **86**: 245–7.

4 Hairston BR, Davis MD, Pittelkow MR, Ahmed I. Livedoid vasculopathy: further evidence for procoagulant pathogenesis. *Arch Dermatol* 2006; **142**: 1413–8.

5 Harenberg J, Hoffmann U, Huhle G *et al*. Cutaneous reactions to anticoagulants. Recognition and management. *Am J Clin Dermatol* 2001; **2**: 69–75.

6 de Godoy JM, Godoy MF, Batigalia F, Braile DM. The association of Mondor's disease with protein S deficiency: case report and review of literature. *J Thromb Thrombolysis* 2002; **13**: 187–9.

7 Kolbach DN, Veraart JC, Hamulyak K *et al*. Recurrent leg ulcers in a young man with hyperhomocysteinemia, factor V Leiden and impaired fibrinolysis. *Acta Derm Venereol* 2002; **82**: 52–4.

8 Meiss F, Marsch WC, Fischer M. Livedoid vasculopathy. The role of hyperhomocysteinemia and its simple therapeutic consequences. *Eur J Dermatol* 2006; **16**: 159–62.

9 Ishikawa O, Takahashi A, Tamura A, Miyachi Y. Cutaneous papules and nodules in the diagnosis of the antiphospholipid syndrome. *Br J Dermatol* 1999; **140**: 725–9.

10 Nakayama T, Matsushita T, Hidano H *et al*. A case of purpura fulminans is caused by homozygous delta8857 mutation (protein C-nagoya) and successfully treated with activated protein C concentrate. *Br J Haematol* 2000; **110**: 727–30.

11 Hodak E, Feuerman H, Molad Y *et al*. Primary anetoderma: a cutaneous sign of antiphospholipid antibodies. *Lupus* 2003; **12**: 564–8.

Paraproteins and multiple myeloma [1–6]

There are numerous cutaneous associations with monoclonal gammopathy of uncertain significance and multiple myeloma. Several of these are discussed in more detail in other chapters and are listed in Tables 62.21 and 62.22, without additional discussion; selected disorders that are not discussed elsewhere are noted below. A classification according to mechanisms has suggested

Table 62.21 Categories of paraprotein-related disorders by mechanism (adapted from text of [6]).

Category/mechanism	Examples
Cutaneous extravascular deposition of paraproteins	Nodular and other cutaneous amyloidosis (Chapter 59) Plasmacytoma Papules of macroglobulinaemia (IgM) Hyperkeratotic spicules Acquired cutis laxa Cutaneous light chain deposition
Intravascular paraproteinaemia	Vascular occlusion/cutaneous necrosis (Chapter 49) Type I cryoglobulinaemia (Chapter 49) Reactive angiomas, glomeruloid angiomas in POEMS syndrome (reactive post-thrombosis)
Cutaneous lesions due to biological activity of the paraprotein	Normolipaemic plane xanthoma (anti-LDL activity) Acquired C1 esterase deficiency Bullous lesions of Waldenström's macroglobulinaemia (dermo-epidermal deposition) Schnitzler syndrome (Chapter 22) Mucinoses associated with gammopathy (e.g. scleromyxoedema, acral papuar mucinosis) may also belong in this category
Conditions resulting from abnormal cytokine secretion	AESOP syndrome POEMS syndrome
Unknown mechanism	Telangiectasia, oedema, capillary leak syndrome (may be due to capillary deposition of monoclonal protein) Necrobiotic xanthogranuloma Neutrophilic dermatoses (Chapter 50)

AESOP, *a*denopathy and *e*xtensive *s*kin patch *o*verlying a *p*lasmacytoma; LDL, low density lipoprotein; POEMS, *p*olyneuropathy, *o*rganomegaly, *e*ndocrine disorders, *m*onoclonal gammopathy, *s*kin changes.

Table 62.22 Skin lesions and conditions associated with paraproteinaemias and multiple myeloma [1–6].

Amyloidosis AL type (Chapter 59; Fig. 62.36)
Cryoglobulinaemias, especially Type 1 cryoglobulinaemia (Fig. 62.37) [4,7]
Crystalglobulinaemia [8]
POEMS syndrome [9,10]
AESOP [11,12]
Livedo reticularis [7]
Small vessel vasculitis [13]
Neutrophilic disorders [3]—pyoderma gangrenosum, subcorneal pustular dermatosis [14], Sweet's syndrome, erythema elevatum diutinum (Chapter 50)
Mucinoses—scleredema, papular mucinosis and scleromyxoedema [15]
Xanthomatous disorders [3]—necrobiotic xanthogranuloma, normolipaemic plane xanthoma, and xanthoma disseminatum
Immunobullous disorders [5,16]—IgA pemphigus, linear IgA disease, epidermolysis bullosa aquisita (Chapter 40)
Schnitzler syndrome [17]
Nasal spicules [18]
Acquired cutis laxa [19]
Acquired ichthyosis, acanthosis nigricans, pityriasis rotunda [20]
Calcinosis cutis [3]
Plasmacytomas, myeloma skin metastases (Fig. 62.39) [21]
Systemic lupus erythematosus [22]
Dermatomyositis [5]

AESOP, *a*denopathy, *e*xtensive *s*kin patch *o*verlying a *p*lasmacytoma; POEMS, *p*olyneuropathy, *o*rganomegaly, *e*ndocrine disorders, *m*onoclonal gammopathy, *s*kin changes.



Fig. 62.36 Waxy plaques and periorbital purpura in paraprotein-associated systemic amyloidosis.

five categories (Table 62.21) [6]. A fuller list, including consequences of paraproteinaemia and selected references, is provided in Table 62.22.

The manifestations of systemic amyloid are discussed in Chapter 59. Waxy yellow plaques into which bruising easily occurs are typical, particularly on the eyelids (Fig. 62.36).

Cryoproteinaemias are associated with multiple myeloma. Monoclonal gammopathy-associated cryoglobulinaemia (type 1 cryoglobulinaemia; Chapter 49) may produce haemorrhagic, vasculitis-like lesions, often in a livedo distribution on the limbs.



(a) (b)

Fig. 62.37 (a,b) Reticulate purpura and small infarcts in type I cryoglobulinaemia, shown on the knees and ear (a cold site).

Although types II and III cryoglobulinaemia damage vessels in part by immune complex deposition and ensuing vasculitis, type I monoclonal cryoglobulinaemia causes physical obstruction of blood vessels (Figs 62.37 & 62.38) [4,7]. Areas sensitive to the cold, such as the ear lobe and nasal tip, are particularly affected. Livedo reticularis and leg ulcers may be seen in both cryoglobulinaemia and cryofibrinogenaemia (Chapter 49). Crystalglobulinaemia [8] has similar features.

POEMS syndrome [9,10] is a rare multisystem disorder characterized by *p*olyneuropathy, *o*rganomegaly of liver, spleen and lymph nodes, *e*ndocrine disorders, *m*onoclonal gammopathy and a variety of *s*kin changes. It has also been associated with the multicentric variant of Castleman's disease. Raynaud's phenomenon, scleroderma, oedema, generalized pigmentation and hypertrichosis are the most common skin changes. Angiomas and angioendotheliomatosis (particularly glomeruloid haemangiomas), alopecia, flushing reactions, whitening of the proximal nail, Sweet's syndrome-like lesions and vasculitis have all been reported in POEMS syndrome. The associated paraprotein is usually of the IgG or A type.

AESOP syndrome (*a*denopathy and *e*xtensive *s*kin patch *o*verlying a *p*lasmacytoma) [11,12] is a rarely described disorder in which mucinosis and angiomatosis occur over a bony or other plasmacytoma, with or without associated regional lymphadenopathy. Several of the few reported cases have also had, or have developed, concurrent POEMS syndrome [11].

Nasal spicules (small follicular keratin horns) and anetodermas are rare pointers to paraproteins, but can also occur in other haematological disorders.

Schnitzler's syndrome (Chapter 22) is an urticarial eruption associated with fever, and there is an underlying IgM paraproteinaemia; it has recently been incorporated into the group of 'autoinflammatory syndromes'.

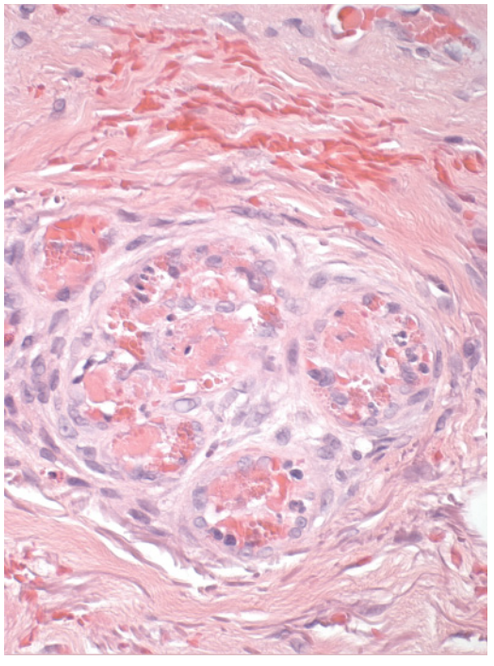


Fig. 62.38 Histological features of type I cryoglobulinaemia showing deposition of immunoglobulin obstructing small vessels.

References

1 Bayer-Garner IB, Smoller BR. The spectrum of cutaneous disease in multiple myeloma. *J Am Acad Dermatol* 2003; **48**: 497–507.

2 Daoud MS, Lust JA, Kyle RA, Pittelkow MR. Monoclonal gammopathies and associated skin disorders. *J Am Acad Dermatol* 1999; **40**: 507–35.

3 Weenig RH, Mehrany K. Dermal and pannicular manifestations of internal malignancy. *Dermatol Clin* 2008; **26**: 31–43.

4 Dammacco F, Sansonno D, Piccoli C *et al.* The cryoglobulins: an overview. *Eur J Clin Invest* 2001; **31**: 628–38.



Fig. 62.39 Cutaneous deposits of multiple myeloma.

5 Zappasodi P, Del Forno C, Corso A, Lazzarino M. Mucocutaneous paraneoplastic syndromes in hematologic malignancies. *Int J Dermatol* 2006; **45**: 14–22.

6 Lipsker D, Boeckler P. Cutaneous manifestations of paraproteinaemia and their mechanisms. *Presse Med* 2007; **36**: 1135–40.

7 Requena L, Kutzner H, Angulo J, Renedo G. Generalized livedo reticularis associated with monoclonal cryoglobulinemia and multiple myeloma. *J Cutan Pathol* 2007; **34**: 198–202.

8 Ball NJ, Wickert W, Marx LH, Thaell JF. Crystalglobulinemia syndrome. A manifestation of multiple myeloma. *Cancer* 1993; **15**; 71: 1231–4.

9 Perniciaro C. POEMS syndrome. *Semin Dermatol* 1995; **14**: 162–5.

10 Nordlund JJ. Polyneuropathy, Organomegaly, Endocrinopathy, M protein, and Skin changes; POEMS syndrome. In: Nordlund JJ, Boissy RE, Hearing VJ, King RA, Oetting WS, Ortonne J-P, eds. *The Pigmentary System*, 2nd edn. Oxford: Blackwell Publishing, 2006: 951–4.

11 Lipsker D, Rondeau M, Massard G, Grosshans E. The AESOP (adenopathy and extensive skin patch overlying a plasmacytoma) syndrome: report of four cases of a new syndrome revealing POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes) syndrome at a curable stage. *Medicine (Baltimore)* 2003; **82**: 51–9.

12 Rongioletti F, Romanelli P, Rebora A. Cutaneous mucinous angiomatosis as a presenting sign of bone plasmacytoma: a new case of (A)ESOP syndrome. *J Am Acad Dermatol* 2006; **55**: 909–10.

13 Bayer-Garner IB, Smoller BR. Leukocytoclastic (small vessel) vasculitis in multiple myeloma. *Clin Exp Dermatol* 2003; **28**: 521–4.

14 Kasha EE Jr, Epinette WW. Subcorneal pustular dermatosis (Sneddon-Wilkinson disease) in association with a monoclonal IgA gammopathy: a report and review of the literature. *J Am Acad Dermatol* 1988; **19**: 854–8.

15 Pomann JJ, Rudner EJ. Scleromyxedema revisited. *Int J Dermatol* 2003; **42**: 31–5.

16 Morita E, Horiuchi K, Yamamoto S, Hashimoto T. A case of acquired autoimmune bullous disease associated with IgM macroglobulinaemia. *J Dermatol* 1999; **26**: 671–6.

17 Lipsker D, Veran Y, Grunenberger F *et al*. The Schnitzler syndrome. Four new cases and review of the literature. *Medicine (Baltimore*) 2001; **80**: 37–44.

18 Requena L, Sarasa JL, Ortiz Masllorens F *et al.* Follicular spicules of the nose: a peculiar cutaneous manifestation of multiple myeloma with cryoglobulinemia. *J Am Acad Dermatol* 1995; **32**: 834–9.

19 Tan S, Pon K, Bargman J, Ghazarian D. Generalized cutis laxa associated with heavy chain deposition disease. *J Cutan Med Surg* 2003; **7**: 390–4.

20 Ikada J, Oki M. Concurrent pityriasis rotunda and acquired ichthyosis with IgG myeloma. *Br J Dermatol* 1974; **91**: 585–6.

21 Requena L, Kutzner H, Palmedo G *et al* Cutaneous involvement in multiple myeloma: a clinicopathologic, immunohistochemical, and cytogenetic study of 8 cases. *Arch Dermatol* 2003; **139**: 475–86.

22 Ali YM, Urowitz MB, Ibanez D, Gladman DD. Monoclonal gammopathy in systemic lupus erythematosus. *Lupus* 2007; **16**: 426–9.

Miscellaneous haematological diseases with cutaneous manifestations

Dyskeratosis congenita [1]

A genetically heterogeneous disorder with recessive, X-linked and dominant heredity, thought to be due to telomerase dysfunction. The skin changes are a mottled or reticulate macular hyperpigmentation, hypopigmentation or a mixture of both in a light-exposed distribution. Alopecia, premature hair greying, hyperhidrosis and adermatoglyphia are less common. A progressive nail dystrophy starts with ridging and splitting, and ends with atrophic rudimentary nails. There is leukoplakia of the tongue and buccal mucosa, and malignancy may develop within these sites. Bone marrow failure develops at a mean age of 10 years and is the major cause of mortality.

Fanconi's anaemia [2]

This rare disorder presents in early childhood with generalized increased pigmentation, particularly on the lower trunk, flexures and neck; more discrete café-au-lait type lesions are associated. A progressive hypoplastic marrow failure develops within 2 to 5 years of the onset; the disease often terminates with leukaemia or other neoplasia, or with infection resulting from leukopenia.

Chediak–Higashi syndrome [3]

This syndrome includes vitiligo-like depigmentation, blond or silvery grey hair and blue eyes, due to melanosome autophagocytosis. Polymorphonuclear cell dysfunction leads to oral and cutaneous infections, abscesses and pyodermas, usually due to staphylococcal infection. A lymphoma-like process is a frequent cause of early mortality.

Hermansky–Pudlak syndrome [4]

An autosomal recessive disorder characterized by oculocutaneous albinism, bleeding due to platelet dysfunction and ceroid accumulation in lysosomes. The skin is pale and the hair blond. Freckles and lentigines are common, as are atypical naevi. Trichomegaly and acanthosis nigricans-like flexural pigmentation has been described. Lack of melanin increases the risk of non-melanoma skin cancer as well as of melanoma. It is common in Puerto Rico, but rare elsewhere. Pulmonary fibrosis at the age of 40–50 years is the most common cause of death.

Griscelli syndrome [5]

Partial albinism is associated with immunodeficiency (a variety of defects are reported, including deficiency or dysfunction of T and B cells, natural killer cells, cell mediated immunity and hypogammaglobulinaemia). Silver or grey hair in infancy may be the clue to the diagnosis.

Wiskott–Aldrich syndrome [6]

An X-linked recessive disorder characterized by thrombocytopenia, an atopic eczema-like dermatitis and recurrent infections due to an inherited defect of T-cell function caused by the WASP gene

mutation. Purpura and eccymoses may occur in the eczematous areas and be a diagnostic clue.

Neurofibromatosis, juvenile xanthogranuloma and juvenile chronic myeloid leukaemia [7]

The finding of juvenile xanthogranuloma and NF1 type neurofibromatosis is estimated to be associated with a 30 to 40-fold increased risk of juvenile chronic myeloid leukaemia.

References

1 Vulliamy T, Dokal I. Dyskeratosis congenita. *Semin Hematol* 2006; **43**: 157–66.
2 Auerbach AD. Fanconi anemia. *Dermatol Clin* 1995; **13**: 41–9.
3 Al-Khenaizan S. Hyperpigmentation in Chediak-Higashi syndrome. *J Am Acad Dermatol* 2003; **49**: S244–6.
4 Toro J, Turner M, Gahl WA. Dermatologic manifestations of Hermansky-Pudlak syndrome in patients with and without a 16-base pair duplication in the HPS1 gene. *Arch Dermatol* 1999; **135**: 774–80.
5 Malhotra AK, Bhaskar G, Nanda M *et al*. Griscelli syndrome. *J Am Acad Dermatol* 2006; **55**: 337–40.
6 Peacocke M, Siminovitch KA. The Wiskott-Aldrich syndrome. *Semin Dermatol* 1993; **12**: 247–54.
7 Zvulunov A, Barak Y, Metzker A. Juvenile xanthogranuloma, neurofibromatosis, and juvenile chronic myelogenous leukemia. World statistical analysis. *Arch Dermatol* 1995; **131**: 904–8.

Graft-versus-host disease [1–5]

Graft-versus-host disease (GVHD) occurs when T lymphocytes from an allograft exert immunological activity against cells of the graft recipient (host). Historically, it was the advent of bone marrow transplantation 50 years ago that brought GVHD to prominence, but it also occurs in the settings of solid organ allografting (renal, liver, etc.), non-irradiated blood or blood product transfusion and maternofetal transfusion (typically in an immunodeficient fetus).

Haemopoietic stem cell transplantation (HSCT) is now used rather than bone marrow transplantation; the main indication is haematological malignancies (leukaemias, lymphoproliferative disorders, aplastic anaemia, etc.) but HSCT is also used in the treatment of various immunological deficiency disorders, metabolic disorders (e.g. congenital erythropoietic porphyria, some mucopolysaccharidoses) and increasingly as a treatment for some solid tumours [2]. A major issue in haematological transplantation has been how to separate the beneficial graft-versus-tumour effects from the deleterious graft-versus-host effects of transplantation [6].

The conditioning regimen used for myeloablation in leukaemias, the type of transplantation performed, treatments used in preparation of the cells to be grafted (e.g. depletion of T cells using antithymocyte globulin) and a number of host factors (e.g. HLA disparity of host and donor, age, previous episodes of GVHD) all influence the likelihood that GVHD will occur [4]. Stem cells are now usually derived from peripheral blood treated with granulocyte colony-stimulating factor, rather than from bone marrow; some reports suggest that this may have increased the risk of chronic GVHD, but this may in part be due to better survival such that patients survive long enough to develop GVHD, coupled with an increased use of transplantation in older subjects in whom GVHD is more likely to occur.

All organs are affected, but are not discussed here although they are important in diagnosis and scoring of GVHD [3]. From a dermatological perspective, there are three main manifestations [1,2,4,5]; early GVHD causes acute rashes (which may have infections or drug eruptions in the differential diagnosis), later eruptions are often lichenoid (see also Chapter 4), and finally there is a sclerodermoid phase in which several morphologies occur (see also Chapter 51). The lichenoid and sclerodermoid manifestations may occur together.

Acute GVHD

Acute GVHD occurs in 60% of HLA-identical sibling HSCT and in 80% of unrelated HSCT, with a mortality of 50% if graded moderate or severe [2]. It develops in three phases—epithelial cell injury and cytokine release due to the conditioning regimen is followed by antigen presentation (by host dendritic cells) to donor T lymphocytes, resulting in cell death caused by activated cytotoxic T cells and cytokines [5–8]. Tumour necrosis factor (TNF) plays a key role in this process [2,8], activating dendritic cells, recruiting effector cells, and directly causing apoptosis and cell death; the interaction of Fas with its ligand FasL is also critical. Experimental blocking of TNF inhibits both GVHD and graft-versus-leukaemia (GVL) reactions, whilst blocking Fas inhibits GVHD but not GVL [8].

The cutaneous features of acute GVHD usually occur 2–6 weeks after transplant, typically at 4 weeks but a severe 'hyperacute' form with high mortality can occur within a week of HSCT. There may be early pain, itch or folliculocentric lesions; generally the rash of acute GVHD is rather morbilliform in distribution, affecting mainly the face and upper trunk, as well as palms and soles (Fig. 62.40). More extensive erythroderma, blistering and necrosis resembling toxic epidermal necrolysis (TEN) characterize the more severe forms of acute GVHD, and are associated with diarrhoea and abnormal liver function; in the hyperacute form there is erythroderma, hepatitis, fever and shock [1,2,4,5]. Mucositis also



Fig. 62.40 Acute GVHD; (a) morbilliform exanthem-like rash , and peeling on the neck, and (b) acute palmar erythema and desquamation. (Courtesy of Dr C. Kennedy, Bristol Royal Infirmary, UK.)

occurs, but is difficult to differentiate from the effects of chemotherapy and irradiation used for conditioning regimens for marrow ablation. The differential diagnosis includes drug eruptions (chemotherapeutic drugs, antimicrobials, etc.) and infections, especially viral. A TEN-like pattern, and palmoplantar disease, are particularly problematic as both can occur due to drugs; the morbilliform rash may be difficult to distinguish from potentially important viral infections. Other patterns of acute GVHD skin eruption include ichthyosis, scarlatiniform rash, varicelliform rash and pustular acral chemotherapy rash. Purpura and haemorrhagic conjunctivitis may occur due to thrombocytopenia in association with capillary leak syndrome.

Reactivation of human herpesviruses (HHV) is a difficult diagnostic issue, as it occurs in both GVHD and in severe drug-induced hypersensitivity syndrome. HHV-6 is commonly reactivated, but cytomegalovirus, Epstein–Barr virus and HHV-7 reactivation may all occur; the sequence in GVHD is the same as that in severe drug hypersensitivity [9].

Skin biopsy is important in diagnosis of GVHD. Both acute and chronic GVHD cause an interface dermatitis which may be a lichenoid lymphocytic infiltrate or predominantly vacuolar damage of basal cells. Lymphocytic 'satellitosis' (lymphocytes encircling necrotic keratinocytes) is particularly suggestive of GVHD, although no single histological feature is pathognomonic. For many years, a system of four histological grades has been used where grade I is characterized by basal cell vacuolation; grade II by keratinocyte dyskeratosis or eosinophilic degeneration; grade III by more frank keratinocyte necrosis leading to basal epidermal clefts; and grade IV by frank epidermal loss [2,4]. Recent criteria have emphasized that keratinocyte necrosis also occurs in the outer root sheath of the hair follicle and in the acrosyringium, and used the degree of apoptotic activity as a marker of severity [10]. However, in situations where the risk of acute GVHD is high (over 30%, as in HSCT), it has been shown that treatment on suspicion gives a better outcome than performing a biopsy; by contrast, if acute GVHD is unlikely, basing treatment on the results of a skin biopsy is preferable [11]. Documentation of macrochimerism (determining the presence of donor cells in the host) has been performed on blood and in skin biopsies [12,13] and may be helpful in identifying or predicting GVHD.

Chronic GVHD

Chronic GVHD may develop without a preceding acute GVHD phase, after acute GVHD with an intervening symptom-free period, or as a continuum from prior acute GVHD. The pathophysiology is different from that of acute GVHD, and is reminiscent of that seen in autoimmune disorders; indeed, several autoantibodies (antinuclear, anti-dsDNA, antinucleolar, anti-smooth muscle and others) may be found in up to 60% of subjects, vitiligo has been reported in several cases, and the hepatic disease of chronic GVHD is very similar to primary biliary cirrhosis. Donor alloreactive T lymphocytes, with a predominance of cytotoxic $CD8^+$ cells, and autoreactive $CD4^+$ T lymphocytes arising due to defective thymic deletion, damage tissues directly, lead to disordered cytokine synthesis and regulation. Chronic GVHD is usually a multisystem disease in which the skin is affected in 90–100% of subjects; localized chronic GVHD also occurs, in which individual organs (usually skin or liver) are affected. The multiorgan involvement has allowed development of 'organ scoring' from which severity grades (mild, moderate or severe) can be derived [3,4]; the percentage of skin involved is part of this scoring system [3,4]. Chronic GVHD of the skin is sometimes provoked by trauma, sunlight or infections such as herpes zoster.

The lichenoid form of chronic GVHD typically occurs as an earlier form of the disorder, and is conventionally defined as occurring more than 100 days after transplantation although the timing varies considerably; it is unlikely before day 80 but may occur after many months. Papules or plaques resembling lichen planus develop, usually less well defined and more scaly than true lichen planus; initially they affect acral sites (distal limbs, including palms and soles), ears and the periorbital area, before becoming generalized. Oral mucosa and oesophagus may also be affected. In some cases, the eruption may be more lupus erythematosus-like [1,2,4]. Like drug-induced lichenoid eruptions, the lymphocytic infiltrate of this form of chronic GVHD is usually rather less tightly band-like than that of standard lichen planus, and may contain eosinophils.

The sclerodermoid spectrum of chronic GVHD may follow the lichenoid form, or may develop without preceding rash—it usually presents between days 150 and 300. Profibrotic cytokines (IL-4 and transforming growth factor-β) are increased, as well as IL-5, which may cause tissue and blood eosinophilia [4]. Early sclerodermoid chronic GVHD is usually lichen sclerosus-like or morphoeaform, later becoming deeper with involvement of fascia and resemblance to eosinophilic fasciitis. The lichen sclerosus lesions frequently occur at areas of trauma (a predilection for sites of central venous lines has been reported), and typically involve the neck, upper trunk and genitalia. The morphoeaform lesions tend to involve the lower trunk; histologically, fibrosis is more superficial than in sporadic morphoea although lesions may progress and coalesce to form a deeper and firmer scleroderma-like picture (Fig. 62.41).

The scleroderma-like and eosinophilic fasciitis-like fibrotic reactions tend to affect the limbs [14]. Septal panniculitis and fibrosis may lead to a puckered ('ripply' [1]) appearance of the skin [15], and blisters, erosions, ulceration and scarring (including scarring alopecia and nail dystrophy) occur [1,4]. Other features include eczema craquelé, eczematoid reactions [16], nodular fibromas, cutaneous mucinosis, eruptive angiomas, dermatomyositis-like rash [17], cicatricial pemphigoid-like conjunctival involvement, poikiloderma, vitiligo, leukotrichia and other pigmentary disturbance (increased, decreased or both; sometimes termed 'leopard-skin' eruption) [1,2,4,5]. Skin changes associated with GVHD affecting other organs also need to be considered, for example plane xanthomas due to cholestasis [18].

Treatment [1,2,4,5,13]

Management of GVHD typically involves treatments that might be used in autoimmune conditions, such as prednisolone, ciclosporin, mycophenolate mofetil, azathioprine, hydroxychloroquine, methotrexate, cyclophosphamide, clofazimine, cladribine, tacrolimus, sirolimus, dacluzimab and thalidomide; the most common regimen is corticosteroid with ciclosporin, thalidomide is generally too toxic and azathioprine may contribute to further malignancies. Antithymocyte globulin has been used in acute GVHD



(a)



(b)

Fig. 62.41 (a,b) Chronic GVHD showing extensive sclerodermoid changes. (Courtesy of Dr C. Kennedy, Bristol Royal Infirmary, UK.)

but has no benefit in the chronic form. Prophylaxis for acute GVHD typically consists of ciclosporin, tacrolimus or mycophenolate mofetil for about 6 months post-transplantation. Photochemotherapy (PUVA) and UVB have been used for both the acute and the lichenoid lesions, and PUVA, UVA1 and extracorporeal photopheresis (ECP) for deeper sclerodermoid lesions [19]. Acitretin appears to be beneficial for sclerodermoid lesions, as does denileukin diftitox. Biological agents such as dacluzimab have been disappointing but rituximab appears to be helpful in treatment of sclerodermoid lesions; aletuzumab, infliximab and etanercept have also been used. Recent guidance on the use of extracorporeal photopheresis (ECP) in the UK [20] suggests that it should be reserved for those who have GVHD refractory to corticosteroids (prednisolone 1 mg kg^{-1} daily for at least 4 weeks, or prednisolone dosed consistently at >10 mg daily), and achieves best results for skin, mucous membrane and hepatic GVHD; however, its best effects in improving survival are seen if treatment is started early, and there is no easy way to predict which patients will require ECP.

Other aspects of transplantation

Dermatologists have an important role in the management of skin cancers arising due to immunosuppression following solid organ transplantation [21]. Such concerns are most prominent after cardiac transplantation, and least after liver transplants, but are discussed in this chapter in the context of renal disease and the skin on the basis that renal transplantation is the commonest such procedure, this post-transplant complication is discussed on p. 62.74.

Hypothyroidism occurs in about 25% of stem cell transplant recipients in whom whole body radiotherapy has been part of the conditioning regimen [22]. As discussed in the section on renal disease, ongoing immunosuppression increases the risk of many infections after HSCT [1,22]; herpes zoster is of particular importance dermatologically as lichen sclerosus-like sclerodermoid GVHD reactions may localize to sites of recent zoster.

The transfer of donor diseases to a recipient of a solid organ transplant or of an SCT is a potential disaster. Transfer of viral infections such as cytomegalovirus is well recognized; transfer of tumours can also occur. Of dermatological relevance, peanut allergy [23], psoriasis [24] and psoriatic arthritis [25] have also been documented post-transplant. There is also evidence of donor stem cells causing a skin cancer in a female recipient of a renal transplant from a male donor, in whom most epithelial (cytokeratin-positive) cells within a basal cell carcinoma were demonstrated to be XY and thus of male origin [26].

References

1 Johnson ML, Farmer ER. Graft-versus-host reactions in dermatology. *J Am Acad Dermatol* 1998; **38**: 369–92.

2 Vargas-Díaz E, García-Díaz A, Marín A, Fernández-Herrera J. Life-threatening graft-vs-host disease. *Clinics Dermatol* 2005; **23**: 285–300.

3 Filipovich AH, Weisdorf P, Pavletic S *et al*. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease. I. Diagnosis and Staging Working Group Report. *Biol Blood Marrow Transplant* 2005; **11**: 945–56.

4 Schaffer JV. The changing face of graft-versus-host disease. *Semin Cutan Med Surg* 2006; **25**: 190–200.

5 Farmer EF. Graft-versus-host disease. In: Provost TT, Flynn JA, eds. *Cutaneous Medicine: Cutaneous Manifestations of Systemic Disease*. Hamilton, Ontario: Decker, 2001: 651–61.

6 Parkman R. Getting a handle on graft-versus-host disease. *N Engl J Med* 2004; **350**: 614–5.

7 Socié G. Graft-versus-host disease—from the bench to the bedside? *N Engl J Med* 2005; **353**: 1396–7.

8 Contassot E, Gaide O, French LE. Death receptors and apoptosis. *Dermatol Clin* 2007; **25**: 487–501.

9 Kano Y, Hiraharas K, Sakuma K, Shiohara T. Several herpesviruses can reactivate in a severe drug-induced multiorgan reaction in the same sequential order as in graft-versus-host disease. *Br J Dermatol* 2006; **155**: 301–6.

10 Shulman HM, Kleiner D, Lee SJ *et al*. Histopathologic diagnosis of chronic graft-versus-host disease: National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease. II. Pathology Working Group Report. *Biol Blood Marrow Transplant* 2006; **12**: 31–47.

11 Firoz BF, Lee SJ, Nghiem P, Quereshi AA. Role of skin biopsy to confirm acute graft-vs-host disease. *Arch Dermatol* 2006; **142**: 175–82.

12 Taylor AI, Gibbs P, Bradley JL. Acute graft versus host disease following liver transplantation: the enemy within. *Am J Transplant* 2004; **4**: 466–74.

13 Meves A, el-Azhary RA, Talwalkar JA *et al*. Acute graft-versus-host disease after liver transplantation diagnosed by fluorescent in situ hybridization testing of skin biopsy specimens. *J Am Acad Dermatol* 2006; **55**: 642–6.
14 White JML, Creamer D, du Vivier AWP *et al*. Sclerodermatous graft-versus-host disease: clinical spectrum and therapeutic challenges. *Br J Dermatol* 2007; **156**: 1032–8.
15 Peñas PF, Jones-Caballero M, Fernández-Herrera J *et al*. Sclerodermatous graft-vs-host disease: clinical and pathological study of 17 patients. *Arch Dermatol* 2004; **138**: 924–34.
16 Creamer D, Martyn-Simmons CL, Osborne G *et al*. Eczematoid graft-vs-host disease: a novel form of chronic cutaneous graft-vs-host disease and its response to psoralen-UV-A therapy. *Arch Dermatol* 2007; **143**: 1157–62.
17 Ollivier I, Wolkenstein P, Gherardi R *et al*. Dermatomyositis-like graft-versus-host disease. *Br J Dermatol* 1998; **138**: 558–9.
18 Moriue T, Yoneda K, Katsuura J *et al*. Planar xanthoma due to cholestasis in graft versus host disease. *Br J Dermatol* 2007; **156**: 1374–6.
19 Brenner M, Herzinger T, Berking C *et al*. Phototherapy and photochemotherapy of sclerosing skin diseases. *Photodermatol Photoimmunol Photomed* 2005; **21**: 157–65.
20 Scarisbrick JJ, Taylor P, Holtick U *et al*. U.K. consensus statement on the use of extracorporeal photophoresis for treatment of cutaneous T-cell lymphoma and chronic graft-versus-host disease. *Br J Dermatol* 2008; **158**: 659–78.
21 Carucci JA. Management of skin cancer in organ transplant recipients. In: Rigel DS, Friedman RJ, Dzubow LM, Reintgen DS, Bystryn J-C, Marks R, eds. *Cancer of the Skin*. Philadelphia: Elsevier, 2005: 631–40.
22 Antin JH. Long-term care after haemopoietic-cell transplantation in adults. *N Engl J Med* 2002; **347**: 36–42.
23 Legendre C, Caillat-Zucman S, Samuel D *et al*. Transfer of symptomatic peanut allergy to the recipient of a combined liver-and-kidney transplant. *N Engl J Med* 1997; **337**: 822–3.
24 Hubiche T, Leaute-Labreze C, Lepreux S *et al*. Psoriasis after cord blood stem cell transplantation. *Br J Dermatol* 2007; **156**: 386–8.
25 Daikeler T, Günaydin I, Einsele H *et al*. Transfer of psoriatic arthritis by allogeneic bone marrow transplantation for chronic myelogenous leukaemia from an HLA-identical donor. *Rheumatology* 1999; **38**: 89–90
26 Aractingi S, Kanitakis J, Sylvie E *et al*. Skin carcinoma arising from donor cells in a kidney transplant recipient. *Cancer Res* 2005; **65**: 1755–60.

Bone and joint diseases

There are several diseases in which bone or joint abnormalities occur together with skin changes (Tables 62.23 & 62.24) [1–3]. In some instances, as occurs in several inflammatory diseases (for example, gout or psoriatic arthropathy), or due to localized tumours (such as glomus tumour), the bone or joint disease may be obvious; in other conditions, skeletal changes may be asymptomatic but demonstrated radiologically. For example, more than half of adults with *mastocytosis* may have diffuse bone disease detected radiologically [4], and the osteopoikilosis of *Buschke–Ollendorf syndrome* (Fig. 62.42) is asymptomatic and usually only demonstrated as an incidental finding or if the patient presents with cutaneous elastomas.

Bony changes may be an important factor in diagnosis of several *genodermatoses* (Chapter 15) [1,2] and underlying bony or neural defects should always be considered in midline *congenital lesions* such as faun tail or on the head and neck (e.g. facial or scalp nodules and pits) [5,6]. The genetic and metabolic basis for some of these are now well understood—for example, the role of G proteins in *McCune–Albright syndrome* [7]. Vascular or lymphatic proliferations or malformations of limbs should also generate suspicion of possible associated bony abnormality, such as asymmetry of growth in *Klippel–Trenaunay* syndrome, or osteolysis due to lymphatic proliferation in *Gorham–Stout* disease [8,9].

Soft-tissue calcification, and less commonly ossification, occurs in numerous disorders [10]. It is particularly prominent in *childhood dermatomyositis* and is discussed in more detail in Chapter 51. *Progressive systemic sclerosis* and *CREST* (Chapter 51) are characterized by atrophy and dystrophic calcifications in the soft tissues, ultimately leading to joint deformities and resorption of the terminal tufts of the phalanges. Resorption of bone occurs at other sites as well in these individuals, and marginal erosions may develop in the metacarpophalangeal and interphalangeal joints of the hands [11]. Calcification of cerebral blood vessels may be associated with facial haemangiomas (Chapter 18). Both calcification and ossification of the cartilage of the ear can occur following repeated cold injury, and may present with symptoms of chrondrodermatitis nodularis helicis (Fig. 62.43). Osteoma cutis affecting the face can occur spontaneously, but may follow acne.

Skin lesions may also occur as a direct consequence of bone disease. Neuropathic ulcers, an important cause of morbidity in type I diabetes, have a strong association with bony deformity of the foot and typically occur at bony pressure points. Bone infection, in the form of osteomyelitis, is closely linked with chronic skin ulceration and has a risk of development of squamous cell carcinoma. Less obviously, as there is no obvious local body site correlation, *fat emboli*, particularly caused by fractures of the long bones, may present cutaneously with petechiae, usually 2 or 3 days after trauma; other symptoms may include respiratory distress and cerebral impairment. The intensity of the petechiae may indicate the severity of other organ involvement. Fat globules may be observed histologically in affected tissue, including the skin, when suitably processed. The distribution of skin petechiae is principally on the anterior trunk; they are seldom found on the back or face [12].

References

1 Orlow SJ, Watsky KL, Bolognia JL. Skin and bones, 1. *J Am Acad Dermatol* 1991; **25**: 205–21.
2 Orlow SJ, Watsky KL, Bolognia JL. Skin and bones, 2. *J Am Acad Dermatol* 1991; **25**: 447–62.
3 Freyschmidt J, Freyschmidt G. *SKIBO-diseases. Disorders Affecting the Skin and Bones.* Berlin, Germany: Springer-Verlag, 1999.
4 Tharp MD, Longley BJ. Mastocytosis. *Dermatol Clin* 2001; **19**: 679–96.
5 Drolet B. Birthmarks to worry about: cutaneous markers of dysraphism. *Dermatol Clin* 1998; **16**: 447–53.
6 Nijhawan A, Lyon VB, Drolet BA. Pediatric dermatology: cutaneous markers of malformations and selected syndromes—what do you see, when do you see it, and how do you find it? *Curr Probl Dermatol* 2001; **13**: 249–300.
7 Levine MA. Clinical implications of genetic defects in G proteins: oncogenic mutations in G alpha s as the molecular basis for McCune–Albright syndrome. *Arch Med Res* 1999; **30**: 522–31.
8 Bastarrika G, Redondo P, Sierra A *et al*. New techniques for the evaluation and therapeutic planng of patients with Klippel-Trenaunay syndrome. *J Am Acad Dermatol* 2007; **56**: 242–9
9 Bruch-Gerharz D, Gerharz C-D, Stege H *et al*. Cutaneous lymphatic malformations in the disappearing bone (Gorham-Stout) syndrome: a novel clue to the pathogenesis of a rare syndrome. *J Am Acad Dermatol* 2007; **56**: S21–5.
10 Touart DM, Sau P. Cutaneous deposition diseases, 2. *J Am Acad Dermatol* 1998; **39**: 527–44.
11 Gold RH, Bassett LW, Seeger LL. The other arthritides: roentgenologic features of osteoarthritis, erosive osteoarthritis, ankylosing spondylitis, psoriatic arthritis, Reiter's disease, multicentric reticulohistiocytosis, and progressive systemic sclerosis. *Radiol Clin North Am* 1988; **26**: 1195–212.
12 Tachakra SS. Distribution of skin petechiae in fat embolism rash. *Lancet* 1976; **i**: 284–5.

Table 62.23 Skin disorders that are commonly associated with bony abnormalities.

Disorder	Skin lesions	Bony change
Congenital/inherited		
Ectodermal dysplasias and keratodermas	Various	Chapter 19
Conradi–Hünermann syndrome	Chapter 19	Chondrodysplasia punctata
Neurofibromatosis	Neurofibromas, café-au-lait patches	Kyphoscoliosis, vertebral erosions, partial absence of sphenoid bone, cystic lesions, pseudarthroses
Tuberous sclerosis	Angiofibromas, ash leaf macules, collagenomas	Intracerebral calcification, bony sclerosis (especially skull), cortical thickening, bone cysts (especially phalanges)
Klippel–Trenaunay syndrome	Port-wine stains, other vascular lesions, lymphangioma	Bony hypertrophy, macrocephaly, polydactyly/syndactyly
Proteus syndrome	Soft-tissue overgrowth, epidermal naevi	Partial gigantism (usually hand/foot), scoliosis and vertebral abnormalities, exostoses, osteochondromas
Maffucci's syndrome	Haemangiomas, lymphangiomas	Enchondromas (especially hands), chondrosarcoma
Sturge–Weber syndrome	Port-wine stain	Calcification of meningeal vessels, hemiatrophy
Gorham (Gorham–Stout) syndrome (osteovascular dysplasia)	Lymphatic vascular proliferations	Lytic lesions, 'disappearing bones'—usually unilateral
Gardner's syndrome	Cysts, lipomas, fibromas	Osteomas, exostoses
Ehlers–Danlos syndrome	Skin laxity, atrophic scars, molluscoid pseudotumours	Kyphoscoliosis (especially type IV), abnormalities of long bones, short clavicles, occipital exostoses (all in type IX)
Osteogenesis imperfecta	Atrophic skin	Brittle bones, otosclerosis
Marfan syndrome	Arachnodactyly	Increased limb length, arachnodactyly, chest deformities, joint laxity
Focal dermal hypoplasia (Goltz's syndrome)	Dermal atrophy, telangiectasia, fatty herniation	Syndactyly, scoliosis, skeletal asymmetry, osteopathia striata, bony tumours, dental abnormalities
Rothmund–Thomson syndrome	Poikiloderma	Hypoplasia of thumbs or forearm bones, dental abnormalities, osteosarcoma
Linear naevus sebaceus syndrome	Sebaceous naevi (often facial or widespread)	Asymmetry (especially skull), spinal abnormalities, hypophosphataemic rickets
Linear epidermal naevus syndrome	Epidermal naevi	Asymmetry, kyphoscoliosis, bone cysts, equinovarus deformity
Incontinentia pigmenti	Atrophic streaks, fatty herniations	Dental abnormalities (conical teeth), spina bifida occulta, skeletal asymmetry, vertebral/rib abnormalities, phalangeal lytic lesions
Hypomelanosis of Ito	Pale, whorled streaks	Kyphoscoliosis, spina bifida occulta, skeletal asymmetry, various digital anomalies
Buschke–Ollendorf syndrome	Elastomas	Osteopoikilosis
McCune–Albright syndrome	Pigmented macules	Fibrous dysplasia, asymmetry, scoliosis, sclerosis of base of skull, fractures, rickets, osteomas
Lipoid proteinosis	Confluent waxy papules, alopecia	Intracranial calcification
Disseminated lipogranulomatosis	Nodules on digits	Destructive arthropathy
Pseudoxanthoma elasticum	'Plucked chicken' appearance of neck, flexures	Calcification of soft tissues, falx cerebri, dura, choroid plexus
Nail–patella syndrome	Hypoplastic nails	Absent or small patellae, iliac horns, scoliosis, hypoplasia of first rib, absent fibulae
Fabry disease	Angiokeratomas	Necrosis of femoral head, arthritis of distal interphalangeal joints
Werner's syndrome	Premature ageing	Osteoporosis, sclerodactyly, joint contractures, sarcomas
Progeria	Aged appearance	Skeletal dysplasia, osteolysis, osteoporosis, dislocation or avascular necrosis of hip, non-union of fractures
Gaucher disease	Pigmentation	Bone pain, fractures, cortical destruction
Naevus of Ota	Facial naevus	Posterior cranial fossa defects
Midline lesions	Various, includes scalp nodules/cysts, nasal gliomas, pits and sinuses, faun tail	Various; connections between skin and CNS may be associated with bony defects, e.g. spina bifida
Infection		
Local		
Dental sinus	Localized nodule, may discharge	Usually periapical abscess, may be retained root, cyst
Chronic ulcer	Skin ulcer	Underlying osteomyelitis
Systemic		
Syphilis	Various; see Chapter 34	Periostitis, osteitis, focal osteolysis or sclerosis
Leprosy	Various; see Chapter 32	Acral bone resorption, osteitis leprosa multiplex cystica
Cryptococcosis	Skin nodules	Osteolytic lesions
Blastomycosis	Skin nodules	Osteomyelitis
Hyper-IgE syndrome with recurrent infections	Abscesses, eczema-like rash	Fractures, scoliosis, abnormal facies

(Continued)

Table 62.23 *Continued*

Disorder	Skin lesions	Bony change
Inflammatory and systemic diseases		
Psoriasis and Reiter's syndrome	See Chapter 20	Erosive arthritis, sacroiliitis
Palmoplantar pustulosis	Palm and sole pustules	See text (this section)
Sarcoidosis	See Chapter 61	Honeycomb change and bone cysts (especially hands), acrosclerosis
Scleroderma	See Chapter 51	Resorption of terminal phalanges (acronecrosis), soft-tissue calcification, erosive arthritis Linear scleroderma may show underlying linear hyperostosis Acro-osteolysis is typical of vinyl chloride disease
Scleromyxoedema	Mucinosis	Arthralgia, carpal tunnel syndrome, acro-osteolysis
Granuloma annulare	Aggressive nodular/subcutaneous type	Subperiostial involvement, 'vanishing bones'
Acne fulminans/ conglobata	See Chapter 42	Lytic lesions, especially clavicles; clavicular hyperostosis
SAPHO	Acne, pustules	Hyperostosis, osteomyelitis
Neutrophilic dermatoses	See Chapter 49	Periosteal reaction adjacent to pyoderma gangrenosum, osteomyelitis-like lesions (chronic recurrent multifocal osteomyelitis)
Gout	Tophi	Erosive arthritis
Multicentric reticulohistiocytosis	Skin and subcutaneous nodules	Destructive polyarthritis, especially terminal interphalangeal joints (similar to rheumatoid disease), atlantoaxial disease
POEMS syndrome	Pigmentation, sclerosis, hypertrichosis	Sclerotic lesions, may have central lucency
Neoplastic		
Naevoid basal cell carcinoma syndrome (Gorlin syndrome, Gorlin-Goltz syndrome)	Basal cell carcinomas	Cysts of jaw and other bones, frontal bossing, calcification of falx cerebri, bifid ribs, spina bifida and other spinal abnormalities, polydactyly/syndactyly, shortened metacarpals
Histiocytoses (Langerhans' cell histiocytosis, Rosai–Dorfman disease, Erdheim–Chester disease, juvenile xanthogranuloma, others)	See Chapter 55	Lytic lesions, defects of skull and mandible, vertebral lesions
Mastocytosis	See Chapter 22	Diffuse or focal osteoporosis or sclerosis
Fibromatoses	See Chapter 56	Various; most characteristic are cystic lesions of skull and long bones in infantile myofibromatosis
Subungual tumours	Glomus, squamous cell carcinoma, others	Osteolysis
Other		
Subungual exostosis	Hard subungual nodule	Underlying exostosis
Osteoma cutis	Hard plaque(s)	Focal bone formation, possibly primary or within a preceding lesion
Becker's naevus	Pigmented hairy lesion	Scoliosis, spina bifida
Thyroid acropachy	Finger clubbing	Expanded distal phalangeal tuft
Acromegaly	(See p. 62.2)	Increased periosteal bone growth
Pachydermoperostosis	Clubbing, thickened digits, cutis verticis gyrata	Periosteal new bone affecting all segments of bone, acro-osteolysis
Complex regional pain syndrome (reflex sympathetic dystrophy, Sudek's atrophy)	Soft tissue swelling (usually limb or acral), hyperhidrosis/hypohidrosis, vasomotor changes	Patchy osteoporosis, bone atrophy
Scurvy	Ecchymosis, 'corkscrew' hairs, gingival lesions	Increased bone density ('white line' of scurvy, Wimberger's sign), lucent bands, metaphyseal corner breaks, pseudo-double epiphysis, periosteal new bone due to haemorrhages
Fat embolism	Petechial rash on anterior trunk	Causative fracture(s)

POEMS, *p*olyneuropathy, *o*rganomegaly, *e*ndocrinopathy, *M* protein, *s*kin changes (syndrome); SAPHO, synovitis, *a*cne, *p*ustulosis, *h*yperostosis, *o*steomyelitis.

Inflammatory conditions [1,2]

Arthralgia and/or arthritis is frequent in a number of inflammatory and metabolic conditions which also affect the skin, such as psoriasis and sarcoidosis (Table 62.24). Most of these individual diseases are discussed in more detail elsewhere in this text; some of the multisystem disorders are briefly described here.

Palmoplantar pustulosis (Chapter 20). A group of overlapping joint diseases occur in conjunction with palmoplantar pustulosis, and less frequently with psoriasis, acne and non-dermatological conditions such as inflammatory bowel disease. The various patterns have been brought together under the acronym SAPHO (*s*ynovitis, *a*cne, *p*ustulosis, *h*yperostosis and *o*steitis). Individual components include predominant sternoclavicular disease (variously termed intersternocostoclavicular osteitis, sternoclavicular pustulotic osteitis, sternocostoclavicular hyperostosis, pustulotic arthro-osteitis or anterior chest wall syndrome; Fig. 62.44) and a more widespread non-purulent chronic recurrent multifocal osteo-

Table 62.24 Some inflammatory and metabolic disorders that affect skin and joints.

Dermatoses
Psoriasis, Reiter's syndrome, palmoplantar pustulosis
Acne fulminans and conglobata, SAPHO
Connective tissue diseases
Lupus erythematosus (especially systemic and subacute cutaneous)
Mixed connective tissue disease
Sclerodermas
Still's disease
Rheumatic fever
Rheumatoid disease
Relapsing polychondritis
Granulomatous disorders
Sarcoidosis
Interstitial granulomatous dermatitis with plaques and cords
Blau syndrome (granulomatous arthritis, uveitis, campylodactyly)
Vasculitis and neutrophilic vascular reactions (see Chapter 50)
Vasculitis (any; notably Henoch–Schönlein purpura)
Behçet's disease and related disorders
Neutrophilic dermatoses (notably Sweet's syndrome)
Bowel-associated dermatosis–arthritis syndrome
Metabolic, endocrine and deposition disorders
Gout
Pancreatic panniculitis
Amyloidosis
Scleromyxoedema, cardiac myxoma
Ochronosis
Haemochromatosis
Acromegaly
Fabry's disease
Infections
Whipple's disease
Lyme disease
Disseminated gonococcal infection, chronic meningococcal infection, others
Miscellaneous
Ehlers–Danlos syndrome
Hyper-IgE syndrome
Multicentric reticulohistiocytosis
Autoinflammatory disorders (periodic fevers), e.g. familial Mediterranean fever, PAPA

PAPA, *p*yogenic *a*rthritis, *p*yoderma gangrenosum, *a*cne; SAPHO, *s*ynovitis, *a*cne, *p*ustulosis, *h*yperostosis, *o*steomyelitis.



Fig. 62.42 Osteopoikilosis in Buschke–Ollendorf syndrome. (Courtesy of Dr C. Blasdale, Sunderland Royal Infirmary, UK.)

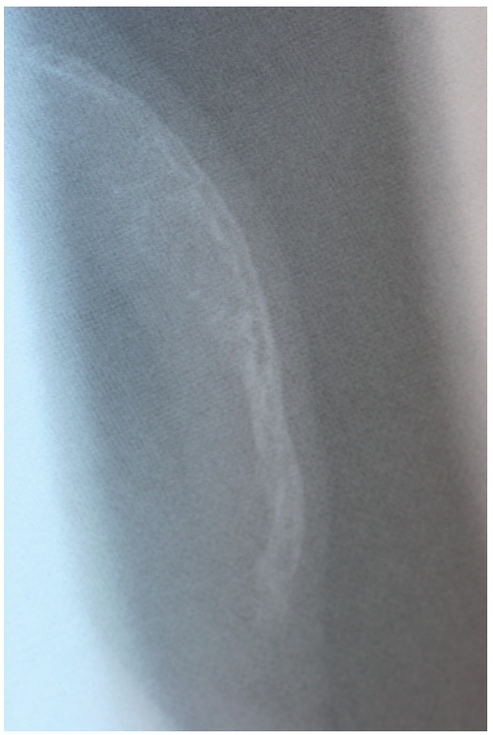


Fig. 62.43 Calcification of the ear due to cold injury.

myelitis [1–5]. Diagnostically, scintigraphy is more sensitive than radiographic examination. Hidradenitis suppurativa and pyoderma gangrenosum have been linked with similar bone and joint changes. Therapeutic options include non-steroidal anti-inflammatory drugs and doxycycline; if infection has been excluded then oral or intra-articular corticosteroids, methotrexate and infliximab may also be considered.

Acne. In addition to the SAPHO pattern described above, arthritis of larger joints occurs in about a third of patients with acne fulminans—most have arthralgia. This is associated with fever, systemic malaise and weight loss, and can usually be controlled with short-term oral corticosteroids. Other skeletal manifestations linked to acne are those secondary to therapeutic agents (skeletal hyperostosis due to isotretinoin, usually only if given long term, and arthralgia in the lupus-like syndrome caused by minocycline); infectious arthritis due to *Propionibacterium acnes* may also occur [6].

Vasculitides (Chapter 50). Arthralgia or arthritis is a common feature of many disorders in this spectrum, occurring for example in about 90% of patients with systemic lupus erythematosus, two-thirds of those with Henoch–Schönlein purpura and about 40% of those with Behçet's disease.

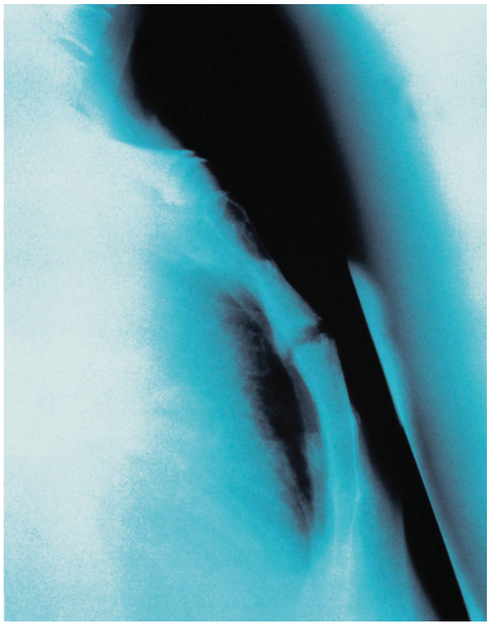


Fig. 62.44 Tomogram showing inflammatory changes of the sternal synchondrosis with widening and 'woolly' appearance in a patient with palmoplantar pustulosis.

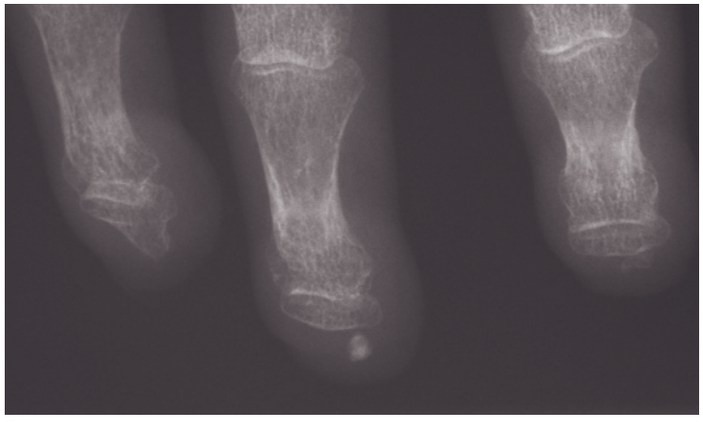
Neutrophilic dermatoses. This group of disorders is discussed in relation to gastrointestinal and haematological disease in this chapter, and in more detail in Chapter 50. Sweet's syndrome may be associated with arthralgia, with a frequency of around one-third to over 60%. Patterns include a seronegative polyarthritis, a chronic axial and peripheral destructive polyarthritis, and acute aseptic monoarthritis [7,8]. Multifocal osteomyelitis, which may be chronic or recurrent, is increasingly recognized as one of the systemic manifestations of this syndrome, and localized osteitis may occur in association with pyoderma gangrenosum [9,10].

Connective tissue diseases (Chapter 51) **and rheumatological disorders.** Arthralgia is a major feature in many conditions in this category, such as lupus erythematosus, progressive systemic sclerosis (PSS) and localized acral variants, mixed connective tissue disease and dermatomyositis. Interstitial calcinosis in these disorders has already been briefly discussed. In most cases, radiological studies show no major changes as the arthritis is typically non-erosive, but acral or periarticular osteoporosis may be apparent. In PSS, resorption of distal phalanges may be apparent (Fig. 62.45), as well as osteolytic foci and 'cysts' in bones such as ribs, spinous processes and in the wrists [1]. Melorrheostosis is also linked with scleroderma, usually localized in type.

Rheumatoid arthritis (RA) is associated with potentially severe bone changes, as is psoriatic arthropathy (Chapter 20). Rheumatoid disease is also associated with several skin disorders, including vasculitis, pyoderma gangrenosum and other potentially severe complications. *Fibroblastic rheumatism*, a less well known condition, causes polyarthritis of medium-size joints, together with skin nodules that typically affect the hands and areas adjacent to joints [1]. An unusual but distinctive feature in RA is marked skin redness around the elbows, associated with joint



(a)



(b)

Fig. 62.45 Progressive systemic sclerosis; (a) tight skin, dyspigmentation, shortening and distortion of phalanges, and (b) X-ray image of the same patient showing bony resorption and some soft tissue calcium deposition.

swelling and raised inflammatory markers—skin histology shows massive aggregates of histiocytes in dilated vessels, with a mixed dermal inflammatory infiltrate [11]. This has been termed *intravascular or intralymphatic histiocytosis associated with RA*.

Interstitial granulomatous dermatitis. This histological pattern may occur in many situations including infections (such as borreliosis or hepatitis C infection), lymphoreticular malignancies, drug eruptions and autoimmune disease. Various skin lesions have been described in *palisading neutrophilic and granulomatous dermatitis (PNGD) of immune complex disease*, including papulonodules, urticaria, vasculitis and granuloma annulare-like lesions. Arthralgia may occur due to systemic vasculitis, and PNGD may occur in rheumatoid arthritis [12]. There are also several reports of a related disorder in which arthritis occurs together with cutaneous lesions that may be plaques or subcutaneous cords ('rope

sign'), which are linear or arciform and typically on the trunk or proximal limbs; this disorder is usually termed *interstitial granulomatous dermatitis with plaques* [13,14].

Relapsing polychondritis (Chapter 68). Migratory arthritis of small and large joints, usually sparing the hands, is a frequent feature [1,15]. It probably occurs in about two-thirds of patients. Chondritis affecting spinal vertebra may cause chronic back pain.

Still's disease. Evanescent rash (typically erythema marginatum pattern, occurring in about 80%), spiking high fever and arthralgia/arthritis are seen. It is often reasonably characteristic in children, but frequently a less easy diagnosis in the rarer cases in older individuals. Different diagnostic criteria have been proposed for adult-onset Still's disease (AOSD), of which the most sensitive are those of Yamaguchi [16]. Additional cutaneous findings in AOSD are persistent widespread papules and plaques in up to two-thirds of patients, in some cases forming confluent sheets [17] or with a lichenoid or linear patterning [18], vesicopustules and post-inflammatory pigmentation. Marked elevation of ferritin levels is a helpful diagnostic clue in active AOSD.

Multicentric reticulohistiocytosis (Chapter 55). Polyarthritis, especially affecting the interphalangeal joints of the hands, occurs as the first manifestation of the disorder in half to two-thirds of patients. It is typically rapidly progressive, and all of the synovium-lined joints may become affected, with arthritis mutilans the end result in one-third to half of cases. The erosions are strikingly symmetrical and well circumscribed, and accompanying osteoporosis is disproportionately mild. The arthritis may burn out, but residual hypertrophic osteoarthropathy may persist [1,19]. A disorder reported as familial histiocytic dermatoarthritis [20] has been described in which there is early onset of a papulonodular eruption, a symmetrical destructive arthritis and ocular lesions such as cataract and glaucoma. Subsequent cases and electron microscopy studies [21] suggest that this may be part of the spectrum of multicentric reticulohistiocytosis.

Autoinflammatory syndromes (periodic fevers). The most important 'classical' periodic fevers are familial Mediterranean fever (FMF; MIM *249100), FMF with amyloidosis (MIM *134610), Hibernian fever—now redesignated as *t*umour necrosis factor (TNF) *r*eceptor–*a*ssociated *p*eriodic *s*yndrome, TRAPS, MIM #142680—and the hyperimmunoglobulin D and periodic fever syndrome (HIDS; MIM #260920). All are characterized by recurrent fever with serositis (peritonitis-like abdominal pain, pleurisy, pericarditis), headache and arthralgia or arthritis [22–26]. In FMF, there may be urticarial lesions, subcutaneous nodules, purpura, leukocytoclastic vasculitis (described, probably incorrectly, as Henoch–Schönlein purpura), or transient cellulitis-like erythematous plaques [22–25]. Both the articular symptoms [26], and erysipelas-like skin lesions predominantly affect the lower leg [23]. Erythematous macules and nodules, but not the erysipelas-like lesions, may occur in HIDS [22]. In TRAPS, the cutaneous features include migratory patches, oedematous plaques and periorbital oedema [23]. FMF is due to a variety of mutations in the *MEFV* gene [27]; classic-type HIDS is due to mutations in the *MVK* gene leading to deficient activity of mevalonate kinase [28,29]; and TRAPS is due to mutations in *TNFRSF1A,* which codes for the 55-kDa TNF receptor [26].

This spectrum has recently been expanded by the addition of some hereditary syndromes that may not include fever, but which have related mutations in genes that regulate innate immunity. Dermatologically, this includes several 'connective tissue' diseases, as well as a number of syndromes that include both skin and bone components [30]. Some of these have already been discussed above or are discussed in other chapters, including sarcoidosis, PAPA (pyogenic arthritis, pyoderma gangrenosum, acne) syndrome (now known to be due to a mutation of *PSTPIP1*), chronic recurrent multifocal osteomyelitis (linked with acne and hidradenitis suppurativa) and psoriatic arthropathy. *Blau syndrome* is also included with the above conditions. It is a familial condition in which there is granulomatous arthritis, granulomatous skin rash and uveitis, with synovial cysts and camptodactyly [31]; the underlying defect is a mutation in *NOD2* which is an intracellular toll-like receptor. Increasingly, defects of handling microbial agents are being demonstrated in these conditions.

Sarcoidosis is discussed in detail in Chapter 61. The classical constellation of features in acute sarcoidosis includes erythema nodosum, arthralgia of medium sized joints and hilar lymphadenopathy [32]. The main differential diagnoses for the joint symptoms include Lyme disease, gonococcal infection and Reiter's syndrome. Less recognized is an acute periarticular ankle inflammation [32], which may occur alone or with erythema nodosum, is more common in men, and in which skin biopsy from the periarticular subcutis shows a non-specific inflammation or panniculitis. Chronic sarcoidosis is associated with both articular symptoms and bone cysts [33], often affecting the hands and occasionally presenting to dermatologists initially [34].

Inherited conditions associated with hypermobility of joints include Ehlers–Danlos syndrome, of which there are several types, and hyper-IgE syndrome in which two-thirds of patients have hyperextensible joints together with a triad of abscesses, pneumonia and elevated IgE levels [35].

References

1 Freyschmidt J, Freyschmidt G. *SKIBO-Diseases. Disorders Affecting the Skin and Bones.* Berlin, Germany: Springer-Verlag, 1999.

2 Orlow SJ, Watsky KL, Bolognia JL. Skin and bones, 2. *J Am Acad Dermatol* 1991; **25**: 447–62.

3 Hayem G, Bouchard-Chabot A, Benali K *et al.* SAPHO syndrome: a long-term follow-up study of 120 cases. *Semin Arthritis Rheum* 1999; **29**: 159–71.

4 Schilling F, Kessler S. [SAPHO syndrome: clinico-rheumatologic and radiologic differentiation and classification of a patient sample of 86 cases; in German]. *Z Rheumatol* 2000; **59**: 1–28.

5 Hyodoh K, Sugimoto H. Pustulotic arthro-osteitis: defining the radiologic spectrum of the disease. *Semin Musculoskelet Radiol* 2001; **5**: 89–93.

6 Hustache-Mathieu L, Brousse A, Lohse A *et al.* Infectious osteoarthritis due to *Propionibacterium* acnes: two new cases. *Rev Méd Interne* 2000; **21**: 547–9.

7 Smolle J, Kresbach H. Acute febrile neutrophilic dermatosis (Sweet syndrome): a retrospective clinical and histological analysis. *Hautarzt* 1990; **41**: 549–56.

8 Wallach D, Vignon-Pennamen M-D. From acute febrile neutrophilic dermatosis to neutrophilic disease: forty years of clinical research. *J Am Acad Dermatol* 2007; **55**: 1066–71.

9 Marie I, Boyer A, Heron F *et al.* Focal aseptic osteitis underlying neutrophilic dermatosis. *Br J Dermatol* 1998; **139**: 744–5.

10 Rodot S, Lacour JP, Van Elslande L *et al*. Manifestations extra-cutanées des dermatoses neutrophiliques. *Ann Dermatol-Venereol* 1996; **123**: 129–34.
11 Takiwaki H, Adachi A, Kohno H, Ogawa Y. Intravascular or intralymphatic histiocytosis associated with rheumatoid arthritis: a report of 4 cases. *J Am Acad Dermatol* 2004; **50**: 585–90.
12 Sangueza O, Caudell MD, Mengesha YM *et al*. Palisaded neutrophilic and granulomatous dermatitis in rheumatoid arthritis. *J Am Acad Dermatol* 2002; **47**: 251–7.
13 Tomasini C, Pippione M. Interstitial granulomatous dermatitis with plaques. *J Am Acad Dermatol* 2002; **46**: 892–9.
14 Verneuil L, Dompmartin A, Comoz F *et al*. Interstitial granulomatous dermatitis with cutaneous cords and arthritis: a disorder associated with autoantibodies. *J Am Acad Dermatol* 2001; **45**: 286–91.
15 O'Hanlan M, McAdam LP, Bluestone R *et al*. The arthropathy of relapsing polychondritis. *Arthritis Rheum* 1976; **19**: 191–4.
16 Masson C, Le Loet X, Liote F *et al*. Comparative study of 6 types of criteria in adult Still's disease. *J Rheumatol* 1996; **23**: 495–7.
17 Lee JY-Y, Yang C-C, Hsu MM-L. Histopathology of persistent papules and plaques in adult-onset Still's disease. *J Am Acad Dermatol* 2005; **52**: 1003–8.
18 Perez C, Montes M, Gallego M, Loza E. Atypical presentation of adult Still's disease with generalized rash and hyperferritinaemia. *Br J Dermatol* 2001; **145**: 187–8.
19 Lesher JL Jr, Allen BS. Multicentric reticulohistiocytosis. *J Am Acad Dermatol* 1984; **11**: 713–23.
20 Zayid I, Farraj S. Familial histiocytotic dermatoarthritis. *Am J Med* 1973; **54**: 793–800.
21 Valente M, Parenti A, Cipriani R, Peserico A. Familial histiocytotic dermatoarthritis: histologic and ultrastructural findings in two cases. *Am J Dermatopathol* 1987; **9**: 491–6.
22 Braverman IM. *Skin Signs of Systemic Disease*, 3rd edn. Philadelphia: Saunders, 1998: 412–3.
23 Sohar E, Gafni J, Pras M *et al*. Familial Mediterranean fever: a survey of 470 cases and review of the literature. *Am J Med* 1967; **43**: 227–53.
24 Majeed HA, Quabazard Z, Hijazi Z *et al*. The cutaneous manifestations in children with familial Mediterranean fever (recurrent hereditary polyserositis): a six-year study. *QJM* 1990; **278**: 607–16.
25 Uthman I, Hajj-Ali RA, Arayssi T, Masri AF, Nasr F. Arthritis in familial Mediterranean fever. *Rheumatol Int* 2001; **20**: 145–8.
26 Toro JR, Aksentijevitch I, Hull K *et al*. Tumour necrosis factor receptor-associated periodic syndrome. *Arch Dermatol* 2000; **136**: 1487–94.
27 Touitou I. The spectrum of familial Mediterranean fever (FMF) mutations. *Eur J Hum Genet* 2001; **9**: 473–83.
28 Houten SM, Koster J, Romeijn GJ *et al*. Organization of the mevalonate kinase (*MVK*) gene and identification of novel mutations causing mevalonic aciduria and hyperimmunoglobulinaemia D and periodic fever syndrome. *Eur J Hum Genet* 2001; **9**: 253–9.
29 Simon A, Cuisset L, Vincent MF *et al*. Molecular analysis of the mevalonate kinase gene in a cohort of patients with the hyper-IgD and periodic fever syndrome: its application as a diagnostic tool. *Ann Intern Med* 2001; **135**: 338–43.
30 Kanazawa K, Furukawa F. Autoinflammatory syndromes: a dermatological perspective. *J Dermatol* 2007; **34**: 601–18.
31 Schaffer JV, Chandra P, Keegan BR *et al*. Widespread granulomatous dermatitis of infancy: an early sign of Blau syndrome. *Arch Dermatol* 2007; **143**: 386–91.
32 Mañá J, Gómez-Vaquero C, Montero A *et al*. Löfgren's syndrome revisited: a study of 186 patients. *Am J Med* 1999; **107**: 240–5.
33 Torralba KD, Quismorio FP Jr. Sarcoid arthritis: a review of clinical features, pathology and therapy. *Sarcoidosis Vasc Diffuse Lung Dis* 2003; **20**: 95–103.
34 Cox NH, Gawkrodger DJ. Nail dystrophy in chronic sarcoidosis. *Br J Dermatol* 1988; **118**: 697–701.
35 Grimbacher B, Holland SM, Gallin JI *et al*. Hyper-IgE syndrome with recurrent infections—an autosomal dominant multisystem disorder. *N Engl J Med* 1999; **340**: 692–702.

Metabolic conditions

Gout may present to dermatologists due to tophi, but is generally diagnosed due to acute arthropathy or chronic erosive joint disease [1,2]. Tophi may be small and occurring in clusters, but may be large and deforming, and may be associated with lytic bone lesions. They may be detected within the carpal tunnel using CT or MRI. Medullary tophi cause subchondral osteolytic areas [1].

Haemochromatosis—arthropathy is a frequent complication, probably due to abnormal accumulation of metal ions [3,4]; other aspects are discussed elsewhere in this chapter.

Ochronosis is discussed in Chapter 68. Calcium crystal deposition accompanies the cartilage degradation characteristic of this disease [4].

Amyloidosis (Chapter 59) is closely linked to joint disease, as rheumatoid arthritis is the commonest cause of secondary amyloidosis [5]. Amyloid A has cytokine-like properties and may be actively involved in inflammatory processes.

Scleromyxoedema causes arthralgia or arthritis in 10% of patients, and is also associated with rheumatoid arthritis and sicca syndrome. Carpal tunnel syndrome and acroosteolysis may also occur [6].

Other metabolic disorders that may have skin and bony or joint symptoms include Fabry's disease, Gaucher's disease and Farber's disease [4]. Bone symptoms are an important part of *Gaucher's disease* [4,7]. Bone crises may be related in part to haemorrhage; they may be treated with prednisolone, bisphosphonates or with prophylactic enzyme replacement therapy. Avascular necrosis, pathological fractures and cortical destruction of bones with extraosseous extension also occur.

Xanthomas at acral sites can be associated with prominent defects in underlying phalanges.

Scurvy is discussed in Chapter 59; bony features are listed in Table 62.23.

Infections

Numerous infective conditions may affect both the skin and joints. Arthralgia is associated with the exanthem of viral infections such as parvovirus, hepatitis B or rubella. *Reiter's syndrome* may be provoked by genital infections such as *Chlamydia*, or by various enteritic organisms such as *Yersinia*, *Shigella* or *Campylobacter*. Arthralgia is frequent, with constitutional symptoms and a non-specific exanthem, in brucellosis. Other bacterial causes of arthritis with pustular or vasculitis skin lesions include disseminated *gonococcal infection* and *chronic meningococcal septicaemia*. Arthralgia may be prominent in spirochaetal diseases such as *Lyme disease* or *secondary syphilis*. In the latter, the flat bones of the skull are frequently involved, causing headache. Osteomyelitis is a feature of tertiary syphilis. Arthralgia is the presenting feature in two-thirds of patients in the early stage of *Whipple's disease* [8,9].

References

1 Freyschmidt J, Freyschmidt G. *SKIBO-Diseases. Disorders Affecting the Skin and Bones.* Berlin, Germany: Springer-Verlag, 1999.
2 Agudelo CA, Wise CM. Gout: diagnosis, pathogenesis, and clinical manifestations. *Curr Opin Rheumatol* 2001; **13**: 234–9.
3 von Kempis J. Arthropathy in hereditary hemochromatosis. *Curr Opin Rheumatol* 2001; **13**: 80–3.
4 Rooney PJ. Hyperlipidemias, lipid storage disorders, metal storage disorders, and ochronosis. *Curr Opin Rheumatol* 1991; **3**: 166–71.
5 Cunnane G. Amyloid precursors and amyloidosis in inflammatory arthritis. *Curr Opin Rheumatol* 2001; **13**: 67–73.
6 Rongioletti F, Rebora A. Updated classification of papular mucinosis, lichen myxedematosus, and scleromyxedema. *J Am Acad Dermatol* 2001; **44**: 273–81.

7 Ida H, Rennert OM, Kato S *et al*. Severe skeletal complications in Japanese patients with type 1 Gaucher disease. *J Inherit Metab Dis* 1999; **22**: 63–73.
8 Durand DV, Lecomte C, Cathebras P, Rousset H, Godeau P. Whipple disease: clinical review of 52 cases. The SNFMI Research Group on Whipple disease. *Medicine* 1997; **76**: 170–84.
9 Puechal X. Whipple disease and arthritis. *Curr Opin Rheumatol* 2001; **13**: 74–9.

Annular and figurate reactive erythemas

Numerous dermatoses produce annular lesions, in some cases leading to a specific diagnosis (for example, tinea corporis or granuloma annulare). The aim of this section is not to discuss all annular eruptions that may be part of a systemic disease (such as annular sarcoidosis). However, there are a group of, often chronic, annular and figurate eruptions that do not easily lead to a specific diagnosis. This rather vague group, collectively termed 'annular erythemas', and some of their more important differential diagnoses, may have systemic causes and may pose diagnostic and therapeutic problems. The nomenclature of this group of disorders has been discussed in detail elsewhere [1] but most of the descriptive and eponymous terms that are applied do not help greatly in management of the patient. Equally, although the pathological features can be divided into those cases with superficial or deep perivascular lymphohistiocytic infiltrate ('superficial or deep gyrate erythema' [2], clinically corresponding to annular erythema with scaling or with smooth surface respectively), the clinical relevance of this is not clear. Some of these annular erythemas that have a specific clinical pattern or clinical course related to their aetiology are discussed separately; the remainder are conveniently grouped with erythema annulare centrifugum (EAC) although it should be appreciated that this latter group are undoubtedly a heterogeneous mixture.

For the purposes of this section, the following will be discussed:

1 Erythema (chronicum) migrans
2 Erythema marginatum (rheumaticum)
3 Erythema gyratum repens
4 Annular erythema of infancy
5 Annular erythema associated with extractable nuclear antigens
6 Erythema annulare centrifugum and other 'annular erythemas'
7 Neutrophilic and vasculitic annular eruptions.

References

1 Bressler GS, Jones RE. Erythema annulare centrifugum. *J Am Acad Dermatol* 1981; **4**: 597–602.
2 Ackerman AB. *Histologic Diagnosis of Inflammatory Skin Diseases*. Philadelphia: Lea & Febiger, 1978: 1784–5, 231–3, 283–4.

Erythema migrans (Chapter 30)

Synonym
- Erythema chronicum migrans

Erythema (chronicum) migrans is the term applied to the commonest skin lesion of Lyme borreliosis. This condition is caused by infection with *Borrelia burgdorferi sensu lato*, *B. afzellii* or *B. garinii*, which are spirochaetes transmitted by bites from *Ixodes* ticks [1]. The primary lesion of erythema migrans at the site of a tick bite is usually solitary and usually essentially flat with mild inflammation, but may be urticated or haemorrhagic (lesions of *B. burgdorferi* are usually more inflammatory and more rapid in evolution than those caused by the other species). The shape may be an expanding annular morphology, a homogeneous macule, or less often may consist of concentric target-like rings. Non-annular erythema migrans is more frequent in infections with *B. afzellii* or *B. garinii* in parts of Europe. Malaise, flu-like symptoms and lymphadenopathy are common at this stage. The lesion expands slowly over a period of weeks to a median size of about 15 cm with central clearing (the early-localized, or first, stage) [2–6]. Although erythema migrans accounts for 85% of skin lesions of Lyme disease, a 'borrelial lymphocytoma' is another manifestation of this stage, consisting of a small (up to 5 mm) plaque, usually on the earlobe, nose, areola, scrotum or over bony prominences. The two disorders together are pathognomic for Lyme borreliosis.

In the early disseminated (or second) stage, which occurs within one to a few weeks, additional, usually multiple, annular plaques may develop in up to half of patients. These are usually smaller than the first stage lesion, and may have a polycyclic pattern that resembles erythema annulare centrifugum or an annular erythema multiforme-like appearance. The term 'erythema migrans chronicum' is something of a misnomer as the early stages are of quite short duration, although Lyme disease itself may become chronic if untreated, and a chronic (third, or late disseminated, stage) skin lesion termed acrodermatitis chronicum atrophicans may occur in such cases. Rarely, lesions typical of erythema migrans may occur in the third stage [7]; there may also be lesions clinically resembling morphoea and having histological features of an interstitial granulomatous dermatitis with histiocytic pseudorosettes [7].

Histology of early localized or disseminated stage erythema migrans shows a superficial perivascular lymphocytic infiltrate, which may contain plasma cells, and which may extend more deeply around vessels or appendages. The diagnosis can be confirmed serologically, but serology after treatment is not useful for predicting the clinical course—persistence of IgG antibody is linked with size and duration of erythema migrans, rather than with other clinical variables [8].

Treatment is usually with tetracyclines (generally doxycycline 100 mg b.d. for 2–3 weeks, although a single dose has been reported as being effective in 87%) or ampicillin; third-generation cephalosporins such as ceftiaxone are the alternative. Vaccination was also available in the USA but, due to high cost and uncertainty about safety and efficacy, was withdrawn from the market. It should be noted that coinfection with the organism of human granulocytic anaplasmosis (was human granulocytotropic ehrlichiosis) has been reported in up to 20% of cases, both organisms being carried by deer ticks [9].

Associated systemic manifestations in the disseminated stages include arthralgia and arthritis, myalgia, cardiac involvement (especially atrioventricular block or pericarditis) and a variety of neurological manifestations (cranial nerve palsies, peripheral neuropathy, meningitis, encephalitis). These same features are seen in canine infection. Treatments for Lyme disease with heart block, facial palsy or meningitis have recently been reviewed [10].

References

1 Burgdorfer W. Vector/host relationships of the Lyme disease spirochaete, *Borrelia burgdorferi*. *Rheum Dis Clin North Am* 1989; **15**: 775–87.
2 Berger BW. Cutaneous manifestations of Lyme borreliosis. *Rheum Dis Clin North Am* 1989; **15**: 627–34.
3 Steere AC. Lyme disease. *N Engl J Med* 2001; **345**: 115–25.
4 Singh-Behl D, La Rosa SP, Tomecki KJ. Tick-borne infections. *Dermatol Clin* 2003; **21**: 237–44.
5 Hercogová J. Lyme borreliosis up-to-date. *G Ital Dermatol Venereol* 2005; **140**: 321–3.
6 Feder HM Jr, Abeles M, Bernstein M, Whitaker-Worth D, Grant-Kels JM. Diagnosis, treatment and prognosis of erythema migrans and Lyme disease. *Clin Dermatol* 2006; **24**: 509–20.
7 Moreno C, Kützner H, Palmedo G, Goerttier E, Carrasco L, Reguena L. Interstitial granulomatous dermatitis with histiocytic pseudorosettes: a new histopathologic pattern in cutaneous borreliosis. Detection of *Borrelia burgdorferi* DNA sequences by a highly sensitive PCR-ELISA. *J Am Acad Dermatol* 2003; **48**: 376–84.
8 Glatz M, Golestani M, Kerl H, Müllegger RR. Clinical relevance of different IgG and IgM serum antibody responses to *Borrelia burgdorferi* after antibiotic therapy for erythema migrans. *Arch Dermatol* 2006; **142**: 862–8.
9 McJunkin JE, Irazutza J, Thompson AE. Coinfection with *Borrelia burgdorferi* and the agent of human granulocytic ehrlichiosis. *N Eng J Med* 2001; **345**: 150–1.
10 Wormser GP. Early Lyme disease. *N Eng J Med* 2006; **354**: 2794–801.

Erythema marginatum (rheumaticum)

Synonym
- Erythema annulare rheumaticum

Rashes of various morphologies can occur in rheumatic fever and Still's disease, erythema marginatum being the most classical and distinctive, but now rare, pattern. Along with carditis, migratory polyarthritis, chorea and subcutaneous nodules, it is one of the Duckett Jones major criteria for the diagnosis of rheumatic fever, and is probably specific for this diagnosis (two major, or one major and two minor, criteria are strictly required for the diagnosis but newer echocardiography techniques and Doppler colour flow mapping may extend the diagnostic criteria). However, erythema marginatum may be subtle, and only occurs in about 10% of patients (especially in children) with active rheumatic fever [1–3]; one study of 126 children (80 first attacks and 46 recurrences) did not identify any with erythema marginatum [4].

The eruption consists of rings or segments of rings, pale or dull red in colour, flat or palpably thickened. The rings may be discrete, or may enlarge and merge to produce a polycyclic or reticular pattern.

Characteristically, the lesions fade in a few hours or at most in 2–3 days, and tend to be more prominent in the afternoon. Recurrent crops, often in different sites, may appear at intervals for many weeks. The lesions occur most frequently on the trunk, especially on the abdomen, but are occasionally seen on the limbs. They are asymptomatic.

Histologically, an infiltrate of polymorphs can help to distinguish this disease from other annular erythemas [5], but is not always found.

A similar eruption has been reported with psittacosis [6], and erythema marginatum has been reported preceding attacks of hereditary angioneurotic oedema [7,8].

References

1 Abt AF. Erythema annulare rheumaticum. *Am J Med Sci* 1935; **190**: 824–33.
2 Keil H. The rheumatic erythemas; a critical survey. *Ann Intern Med* 1937–38; **11**: 2223–72.
3 Rullan E, Sigal LH. Rheumatic fever. *Curr Rheumatol Rep* 2001; **3**: 445–52.
4 Jamal M, Abbas KA. Clinical profile of acute rheumatic fever in children. *J Trop Pediatr* 1989; **35**: 10–3.
5 Troyer C, Grossman ME, Silvers DN. Erythema marginatum in rheumatic fever: early diagnosis by skin biopsy. *J Am Acad Dermatol* 1983; **8**: 724–8.
6 Green ST, Hamlet NW, Willocks L *et al*. Psittacosis presenting with erythema marginatum-like lesions—a case report and a historical review. *Clin Exp Dermatol* 1990; **15**: 225–7.
7 Starr JC, Brasher GW. Erythema marginatum preceding hereditary angioedema. *J Allergy Clin Immunol* 1974; **53**: 352–5.
8 Farkas H, Harmat G, Fáy A *et al*. Erythema marginatum preceding an acute oedematous attack of hereditary angioneurotic oedema. *Acta Dermatovenereol* 2001; **81**: 376–7.

Erythema gyratum repens [1–8]

The first description of this condition in 1953 is attributed to Gammel, who reported a case associated with breast carcinoma [1]. It is exceptionally rare but clinically distinctive (see Fig. 62.14). It is more common in men than in women, and usually occurs in or after the seventh decade of life.

Clinical features [1–8]. Regular waves of erythema spread over the body to produce a series of concentric, figurate bands in a pattern resembling the grain of wood (see Fig. 62.14). The characteristic feature is the way rings, swirls or waves appear within existing lesions to form a concentric pattern of sequential eruptions, with day-to-day migration of the leading edge by about 1 cm. Scaling, usually at the trailing edge, and itch are usually prominent. This is by contrast to the more common 'annular erythemas' of erythema annulare centrifugum pattern, in which each lesion is usually a distinct ring or arc with variable but usually without prominent scale, and not in a concentric arrangement. Hyperkeratosis of palms occurs in about 10% and has been reported in both paraneoplastic and idiopathic cases.

Aetiology. This eruption has been briefly discussed earlier (p. 62.38) as a paraneoplastic eruption; about 80% of reported cases are associated with an internal tumour [4,6–9], most commonly of the lung. Other tumour sites include bowel, oesophagus, urogenital tract, breast, pancreas and haematological neoplasia.

However, not all cases are paraneoplastic. Since the report of a case associated with tuberculosis [10], several cases have been reported in apparently well patients or associated with other disorders such as CREST syndrome (reviewed in [4,7]). Drug hypersensitivity has also been implicated. Some of these non-paraneoplastic cases are questionable in the absence of photographic documentation, but some cases appear very convincing, such as a patient with recurrent pregnancy-associated episodes [11]. An infant was reported in whom lesions were controlled by long-term systemic ketoconazole [12].

Pathology [13]. There is a superficial, and occasionally deep, perivascular lymphocytic infiltrate associated with acanthosis, spongiosis and parakeratosis. Deposition of C3 or IgG in the sublamina densa region supports the concept that the eruption is

immunologically mediated, possibly by immune complex deposition [5,14].

Investigation. The paramount issue is a detailed search for underlying malignancy. Fungal infection should be excluded, especially tinea imbricata in relevant populations. Skin biopsy is important as a similar gyrate eruption may be a prodromal manifestation of pemphigoid [15], and similar but rather localized lesions have been reported due to vasculitis, especially in lupus erythematosus [16] and in neutrophilic dermatoses; a morphologically similar disorder termed lupus erythematosus gyratum repens has been reported, related to either medications or internal malignancy [17,18]. Necrolytic migratory erythema (p. 62.66) and erythrokeratoderma variabilis (Chapter 19) may produce very similar lesions, as may the subacute annular (Lapière) variant of psoriasis, although none of these typically have multiple concentric lesions. Cases of apparent idiopathic erythema gyratum repens have also been suggested to represent a stage in the evolution of pityriasis rubra pilaris [19,20]. A patient with EBA associated with ulcerative colitis has been reported due to occurrence of erythema gyratum repens-like lesions, but PCT-like erosions and milia on the dorsum of hands and feet were also present [21].

References

1 Gammel JA. Erythema gyratum repens. *AMA Arch Dermatol Syphilol* 1953; **66**: 494–505.
2 Thomson J, Stankler L. Erythema gyratum repens. *Br J Dermatol* 1970; **82**: 406–11.
3 Thomas I, Schwartz RA. Cutaneous paraneoplastic syndromes: uncommon presentations. *Clinics Dermatol* 2005; **23**: 593–600.
4 Boyd AS, Neldner KH, Menter A. Erythema gyratum repens: a paraneoplastic eruption. *J Am Acad Dermatol* 1992; **26**: 757–62.
5 Holt PJA, Davies MG. Erythema gyratum repens—an immunologically mediated dermatosis? *Br J Dermatol* 1977; **96**: 343–7.
6 Stone SP, Buescher LS. Life-threatening paraneoplastic cutaneous syndromes. *Clinics Dermatol* 2005; **23**: 301–6.
7 Tyring SK. Reactive erythemas: erythema annulare centrifugum and erythema gyratum repens. *Clin Dermatol* 1993; **11**: 135–9.
8 Eubanks LE, McBurney E, Reed R. Erythema gyratum repens. *Am J Med Sci* 2001; **321**: 302–5.
9 Kawakami T, Saito R. Erythema gyratum repens unassociated with underlying malignancy. *J Dermatol* 1995; **22**: 587–9.
10 Barber PV, Doyle L, Vickers DM *et al*. Erythema gyratum repens with pulmonary tuberculosis. *Br J Dermatol* 1978; **98**: 465–8.
11 Garrett SJ, Roenigk HH. Erythema gyratum repens in a healthy woman. *J Am Acad Dermatol* 1992; **26**: 121–2.
12 Saurat JH, Janin-Mercier A. Infantile epidermodysplastic erythema gyratum responsive to imidazoles. A new entity? *Arch Dermatol* 1984; **120**: 1601–3.
13 Weedon D. *Skin Pathology*, 2nd edn. London: Churchill Livingstone, 2002: 245–6.
14 Caux F, Lebbe C, Thomine E *et al*. Erythema gyratum repens: a case studied with immunofluorescence, immunoelectron microscopy and immunohistochemistry. *Br J Dermatol* 1994; **131**: 102–7.
15 Breathnach SM, Wilkinson JD, Black MM. Erythema gyratum repens-like figurate eruption in bullous pemphigoid. *Clin Exp Dermatol* 1982; **7**: 401–6.
16 Piqué E, Palacios S, Santana Z. Leukocytoclastic vasculitis presenting as an erythema gyratum repens-like eruption on a patient with systemic lupus erythematosus. *J Am Acad Dermatol* 2002; **47** (5 Suppl.): S254–6.
17 Blanc D, Kienzler J-L. Lupus erythematosus gyratus repens. Report of a case associated with lung carcinoma. *Clin Exp Dermatol* 1982; **77**: 129–34.
18 Kreft B, Marsch WC. Lupus erythematosus gyratum repens. *Eur J Dermatol* 2007; **17**: 79–82.
19 Cheesbrough MJ, Williamson DM. Erythema gyratum repens, a stage in the evolution of pityriasis rubra pilaris? *Clin Exp Dermatol* 1985; **10**: 466–71.
20 Gebauer K, Singh G. Resolving pityriasis rubra pilaris resembling erythema gyratum repens. *Arch Dermatol* 1993; **129**: 917–8.
21 España A, Sitaru C, Pretel M *et al*. Erythema gyratum repens-like eruption in a patient with epidermoysis bullosa acquisita associated with ulcerative colitis. *Br J Dermatol* 2007; **156**: 773–5.

Annular erythema of infancy

This term was first applied by Peterson and Jarratt [1] although infantile onset of a similar eruption had been reported previously [2]; numerous cases have been reported subsequently [3–8]. Although the age group does not define a category that can be distinguished from other cases of EAC, and probably also represents a range of disorders, the implications for investigation are somewhat different. For example, cutaneous fungal infection and malignant diseases are unlikely causes, whereas other (systemic) infections and lupus erythematosus-related antibodies (see below) are important to exclude. However, the fact that some cases started in teenage years and others in infancy in a family with autosomal dominantly inherited annular erythema [9] argues against there being a specific infantile variant.

Clinical features. The clinical morphology of lesions is generally as described for EAC.

Pathology. Histological appearances are typically the same as in cases of EAC. However, some authors have reported eosinophils to be prominent [7,8] and they may be the predominant cell type and associated with peripheral eosinophilia [10]. A neutrophilic variant has also been reported [6,11,12].

Aetiology. As in EAC (below), no cause can be identified in many patients, often despite extensive investigation. Some childhood cases may be discovered to have lupus erythematosus or have had transplacental transfer of maternal antibodies against extractable nuclear antigens, as discussed below; a clinical pattern described as erythema gyratum atrophicans transiens neonatale is now felt to be a variant of neonatal lupus erythematosus [13]. Heavy intestinal colonization with *Candida albicans* has been documented as a cause [14], and concurrent Epstein–Barr virus infection has been reported in an infant [15]. *Pityrosporum* infection in an infant has been reported as a mimic of EAC [16]; other differential diagnoses that may apply in children are listed in the section on EAC. A recently described 'annular lichenoid dermatitis of youth' [17] appears to be distinct, although it may include lesions resembling annular erythema; 'lymphomatoid annular erythema' [18] has also been described as a childhood presentation of mycosis fungoides.

Treatment. Any associated infection should be treated as discussed in the section on aetiology. Treatments are otherwise symptomatic, as for EAC. In one case, lesions resolved during febrile episodes but reappeared 2 weeks later [12]. Responses to sodium cromoglycate and to IFN-α have been reported, but in many cases new lesions continue to erupt over many years.

References

1 Peterson AO, Jarratt MD. Annular erythema of infancy. *Arch Dermatol* 1981; **117**: 145–8.

2 Fried R, Schonberg IL, Litt JZ. Erythema annulare centrifugum (Darier) in a newborn infant. *J Pediatr* 1957; **50**: 66–7.
3 Herbert A, Esterly NB. Annular erythema in infancy. *J Am Acad Dermatol* 1986; **14**: 339–43.
4 Helm TN, Bass J, Chang LW, Bergfield WF. Persistent annular erythema in infancy. *Pediatr Dermatol* 1993; **10**: 46–8.
5 Toonstra J, de Witt RFE. 'Persistent' annular erythema of infancy. *Arch Dermatol* 1984; **120**: 1069–72.
6 Cox NH, McQueen A, Evans TJ *et al.* An annular erythema of infancy. *Arch Dermatol* 1987; **123**: 510–3.
7 Helm TN, Bass J, Chang LW *et al.* Persistent annular erythema of infancy. *Pediatr Dermatol* 1993; **10**: 46–8.
8 Hebert AA, Esterly NB. Annular erythema of infancy. *J Am Acad Dermatol* 1986; **14**: 339–43.
9 Beare JM, Frogatt P, Jones JH *et al*. Familial annular erythema. An apparently new dominant mutation. *Br J Dermatol* 1966; **78**: 59–68.
10 Kunz M, Hamm K, Brocker EB *et al.* Annular erythema in childhood—a new eosinophilic dermatosis. *Hautarzt* 1998; **49**: 131–4.
11 Annessi G, Signoretti S, Angelo C *et al*. Neutrophilic figurate erythema of infancy. *Am J Dermatopathol* 1997; **19**: 403–6.
12 Patrizi A, Savoia F, Varotti E *et al*. Neutrophilic figurate erythema of infancy. *Ped Dermatol* 2008; **25**: 255–60.
13 Puig L, Moreno A, Alomar A *et al.* Erythema gyratum atrophicans transiens neonatale: a variant of cutaneous neonatal lupus erythematosus. *Pediatr Dermatol* 1988; **5**: 112–6.
14 Stachowitz S, Abeck D, Schmidt T *et al.* Persistent annular erythema of infancy associated with intestinal *Candida* colonization. *Clin Exp Dermatol* 2000; **25**: 404–5.
15 Hammar H. Erythema annulare centrifugum coincident with Epstein–Barr virus infection in an infant. *Acta Paediatr Scand* 1974; **63**: 788–92.
16 Kikuchi I, Ogata K, Inoue S. *Pityrosporum* infection in an infant with lesions resembling erythema annulare centrifugum. *Arch Dermatol* 1984; **120**: 380–2.
17 Annessi G, Paradisi M, Angelo C *et al*. Annular lichenoid dermatitis of youth. *J Am Acad Dermatol* 2003; **49**: 1029–6.
18 Cogrel O, Boralevi F, Lepreux S *et al*. Lymphomatoid annular erythema: a new form of juvenile mycosis fungoides. *Br J Dermatol* 2005; **152**: 565–6.

Annular erythema associated with extractable nuclear antigens

It has been recognized for many years that annular lesions in neonatal lupus erythematosus are related to maternal antibodies against SSA(Ro) [1]. Neonatal lupus erythematosus with annular lesions but without anti-SSA antibodies may be explained by the demonstration that some patients have anti-U1RNP antibodies instead [2].

More recently, it has been recognized that annular lesions may occur in anti-SSA(Ro)-positive patients with Sjögren's syndrome, lupus erythematosus (or both together), and less commonly in otherwise well patients who do not fit criteria for either of these diagnoses [3–6]. In a group of 15 patients with anti-SSA antibodies and annular erythema, all sera were positive for the anti-60kDa-SSA and 11 for the anti-52-kDa-SSA [7]. It has been suggested that patients with annular lesions in Sjögren's syndrome actually have lupus erythematosus, although a more recent review of 93 patients with Sjögren's syndrome demonstrated that annular erythema was a more common feature in primary Sjögren's syndrome (6.5%) than in secondary Sjögren's syndrome (3.2%) [8], and was associated with anti-SSA and anti-SSB(La) antibodies in 75%. A role for anti-SSB(La) antibodies has also been proposed in patients with a rather more tumid-appearing pattern of annular erythema [9]. Further investigation has shown that patients with Sjögren's syndrome and/or lupus erythematosus who have anti-tRNA antibodies as well as anti-SSA or anti-SSB antibodies are more likely to have recurrent papulosquamous annular erythema than are those with anti-SSA or anti-SSB alone [10]. Conversely, anti-alpha-fodrin antibodies (which are most common in primary Sjögren's syndrome) do not appear to be linked with annular erythema [11].

Affected patients are usually young adults, although childhood onset occurs [12], and they are usually female; individuals of Japanese origin seem to be particularly likely to develop annular lesions. Although the edge of the lesions is often broader than in many cases of EAC, and the distribution is often photosensitive and limited to the face, it is likely that some cases previously classified as EAC may be explained by this mechanism.

In some cases, there may be residual central atrophy or telangiectasia. Such cases usually have granular IgG deposition at the dermoepidermal junction. This pattern is felt to be a variant of neonatal lupus erythematosus, termed erythema gyratum atrophicans transiens neonatale [13].

Treatment is usually determined by the underlying disease; topical treatments such as corticosteroids have limited benefit. Phototherapy, used for some patients with EAC, is probably not advisable as anti-SSA antibodies are linked with photosensitivity. However, as has been demonstrated in discoid lupus erythematosus, topical tacrolimus may be beneficial in annular erythema associated with Sjögren's syndrome [14].

References

1 Watson RM, Lane AT, Barnett NK *et al*. Neonatal lupus erythematosus. *Medicine (Baltimore)* 1984; **63**: 362–78.
2 Gugan EM, Tunnessen WW, Honig PJ *et al.* U1RNP antibody-positive neonatal lupus. A report of two cases with immunogenetic studies. *Arch Dermatol* 1992; **128**: 1490–4.
3 Teramoto N, Katayama I, Arai H *et al.* Annular erythema: a possible association with primary Sjögren's syndrome. *J Am Acad Dermatol* 1989; **20**: 596–601.
4 Ruzicka T, Faes J, Bergner T *et al.* Annular erythema associated with Sjögren's syndrome: a variant of systemic lupus erythematosus. *J Am Acad Dermatol* 1991; **25**: 557–70.
5 Miyagawa S, Kitamura W, Sakamoto K. Skin lesions associated with Sjögren's syndrome and anticytoplasmic antibodies in SLE patients. *J Dermatol* 1983; **10**: 495–500.
6 Ostlere LS, Harris D, Rustin MH. Urticated annular erythema: a new manifestation of Sjögren's syndrome. *Clin Exp Dermatol* 1993; **18**: 50–1.
7 Miyagawa S, Fukumoto T, Hachiya T, Shirai T. Anti-Ro/SSA associated recurrent annular erythema: autoimmune response to recombinant 60- and 52-kDa Ro/SSA proteins. *J Dermatol Sci* 1996; **12**: 127–31.
8 Bernacchi E, Amoto L, Parodi A *et al*. Sjögren's syndrome: a retrospective review of the cutaneous features of 93 patients by the Italian Group of Immunodermatology. *Clin Exp Rheumatol* 2004; **22**: 55–62.
9 Hoshino Y, Hashimoto T, Mimori T *et al.* Recurrent annular erythema associated with anti-SS-B/La antibodies: analysis of the disease-specific epitope. *Br J Dermatol* 1992; **127**: 608–13.
10 Ohosone Y, Ishida M, Takahashi Y *et al.* Spectrum and clinical significance of autoantibodies against transfer RNA. *Arthritis Rheum* 1998; **41**: 1625–31.
11 Watanabe T, Tsuchida T, Kanda N *et al.* Anti-alpha-fodrin antibodies in Sjögren syndrome and lupus erythematosus. *Arch Dermatol* 1999; **135**: 535–9.
12 Miyagawa S, Iida T, Fukumoto T *et al.* Anti-Ro/SSA-associated annular erythema in childhood. *Br J Dermatol* 1995; **133**: 779–82.
13 Puig L, Moreno A, Alomar A *et al.* Erythema gyratum atrophicans transiens neonatale: a variant of cutaneous neonatal lupus erythematosus. *Pediatr Dermatol* 1988; **5**: 112–6.
14 Yokota K, Shichinohe R, Havasaka T. Topical tacrolimus in the treatment of annular erythema in association with Sjögren's syndrome. *Clin Exp Dermatol* 2005; **30**: 450–1.

Erythema annulare centrifugum (EAC) and other 'annular erythemas'

The term EAC was originally used by Darier [1], who delineated EAC from a more scaly and itchy eruption described earlier by Colcott Fox as erythema gyratum perstans. The term EAC is conveniently applied to the annular erythemas that do not obviously fall into one of the more specific categories discussed previously, although the 'diagnostic' term EAC probably identifies a mixed group of disorders with similar clinical appearance and histological features. Annular erythema of infancy is discussed separately, as it can be defined by the age group, and annular erythemas associated with anti-SSA (anti-Ro) and anti-SSB (anti-La) antibodies are viewed as a separate group as their aetiology is more defined; EAC usually has no identifiable cause, although many anecdotal triggers are reported.

Clinical features. EAC has been reviewed by several authors [2–6]. It is commonest in young and middle-aged adults, although onset may occur in infancy (discussed previously). Some authors suggest a female preponderance [5]. A small, pink, infiltrated papule slowly enlarges and forms a ring, as the central area flattens and fades (Figs 62.46 & 62.47). The rate of extension is variable; although a diameter of 6–8 cm may be achieved in less than 2 weeks, extension is usually much slower (typically 2–3 mm/day), especially in the cases with epidermal involvement. Extension may be irregular, to leave arciform segments. Lesions may be solitary or, more often, multiple. The edge may be quite flat or easily palpable with a superficial cord-like quality, and lesions may be smooth or show slight scaling behind the advancing edge. Rarely, vesiculation occurs. Itching is variable, but seldom intense. The commonest sites are the buttocks, thighs and upper arms, but any areas may be involved. Sometimes lesions are mainly on the extremities, but the face is seldom affected.

Individual lesions last for a few days, more often a few weeks, or slowly extend for a few months. Further lesions usually occur, and the disease is usually chronic with periodic fluctuations over many years. Purpura and pigmentation may rarely occur within the lesions [7].

Pathology. The characteristic feature in EAC is a perivascular 'sleeve-like' lymphohistiocytic infiltrate, referred to as a 'gyrate erythema', which may be mainly superficial, mainly deep, or mixed. The pathological changes may be entirely within the dermis, whereas in other cases there is much more obvious epidermal change (spongiosis and parakeratosis) [8,9]. There is dispute about whether these represent two separate diseases or a continuous range.

A study of 82 biopsies from 73 patients suggested that EAC with a superficially situated infiltrate is different to that with a deeper dermal infiltrate [10]. The superficial pattern was associated clinically with a collarette of scale, that was not seen in the deeper pattern. Histologically, the superficial pattern was more likely to have spongiosis, parakeratosis, epidermal hyperplasia and papillary dermal oedema, whilst the deeper pattern more commonly had a sleeve-like infiltrate, melanophages and individual necrotic keratinocytes. However, neither pattern appeared to have any consistent systemic disease association, so the clinical utility of this histological distinction is unclear.

Eosinophils may occasionally be seen around superficial vessels. Significant peripheral eosinophilia raises the possibility of parasitic infection as the underlying cause. A very rare eruption that has clinical features of EAC but with a frankly eosinophilic infiltrate has been described under the name 'eosinophilic annular erythema' [11,12]. It has been suggested that this may actually be a variant of Wells' syndrome (eosinophilic cellulitis).

Aetiology. A broad range of associations has been described as causes of EAC (Table 62.25) [13–31]; however, some 'associations' that have been described may be coincidental, and some may be more properly categorized as unusual presentations of diseases mimicking EAC. A seasonally recurrent form has been reported and described as having received little attention [28], although the image of seasonally recurrent EAC in this textbook (Fig. 62.46) had already been published in the previous edition. Drug- and infection-induced cases are well documented although only in a small minority of cases. Underlying malignancy is an important



Fig. 62.46 Erythema annulare centrifugum; an expanding lesion with central clearing and scaling at the 'trailing edge'. This case was seasonally recurrent.



Fig. 62.47 Erythema annulare centrifugum; cases with deeply situated inflammation feel more tumid and exhibit less scaling.

Table 62.25 Possible causes and associations of erythema annulare centrifugum.

Category	Examples
Idiopathic	Including annually recurrent forms [13]
Familial	Dominant inheritance [14], twins [15]
Infantile onset	(see p. 62.108)
Fungi	Cutaneous tinea [5], intestinal *Candida* [16,17], ingested fungi (cheese) [16]
Other infections [2–6]	Molluscum contagiosum, Epstein–Barr virus, genital herpes, herpes zoster, Q fever, recurrent appendicitis, *E. coli* urinary tract infection, tuberculosis, *Ascaris* infection, trypanosomiasis, *Phthirus pubis* infestation, *Borrelia* spp.
Drugs [2–6]	Aldactone, amitryptiline, ampicillin, cimetidine, etizolam, granulocyte colony-stimulating factor, gold, hydrochlorthiazide, hydroxychloroquine, penicillin, piroxicam, salicylates, thiacetazone, vitamin K, finasteride
Endocrine	Hyperthyroidism [18], Hashimoto's thyroiditis, autoimmune progesterone dermatitis, oestrogen dermatitis, pregnancy, polyglandular autoimmune syndrome type I (the latter possibly mediated by *Candida* infection)
Haematological disorders	Lymphomas (various) [4,5,19,20], leukaemias [21,29–31], thrombocythaemia [22], polycythaemia rubra vera, myelodysplastic syndrome, hypereosinophilic syndrome [23], myeloma, dysproteinaemia, cryoglobulinaemia
Other neoplastic conditions [4,5,24]	Carcinomas of bronchus, prostate, nasopharynx, ovary, rectum and liver; carcinoid tumour
Immunological	Relapsing polychondritis [25,26], sarcoidosis [27], autoimmune hepatitis, linear IgA disease, lupus erythematosus
Miscellaneous	Liver disease, following biliary surgery, localized at pacemaker site, seasonal

consideration—for example, both 'standard' and eosinophilic variants of EAC have recently been reported in association with underlying chronic lymphocytic leukaemia [29–31]. In the large majority of cases the aetiology remains obscure, even after prolonged observation and investigation.

One study of 66 cases identified cutaneous fungal infection as the most important aetiological factor (in 72%), other causes being internal neoplasm in 13%, other skin diseases in 18% and other internal diseases in 21% [5]. However, a causal association could not always be proven, and the high frequency of fungal infection may have been influenced by the geographical location of the study in Korea.

A retrospective study of 90 cases suggested alternative diagnoses (urticaria, vasculitis, psoriasis) in 22%; the others were felt to be LE tumidus (32%), spongiotic dermatitides (28%) and pseudolymphoma (18%); in the latter group, 81% had *Borrelia* sequences detected [32].

Investigations. These are aimed at excluding alternative diagnoses, and search for an underlying cause (see section on Aetiology, above).

Fungal infections are the commonest differential diagnosis and should be excluded by microscopy and culture of skin scrapings. Other skin infections are less likely to mimic EAC but leprosy and leishmaniasis have both been reported to cause similar lesions, and an annular presentation of cutaneous *Pseudomonas* infection has been described in an immunosuppressed child. Granuloma annulare can usually be distinguished on clinical and/or histological features, and has slower evolution of individual lesions, but can cause diagnostic difficulty in some cases. Lymphomas, especially mycosis fungoides (MF), may produce annular lesions very similar to those of annular erythemas; these usually have a broader edge, but a very EAC-like appearance over 10 years prior to diagnosis has been reported [20] as well as a case of juvenile MF resembling EAC and termed 'lymphomatoid annular erythema' [33]. Pseudolymphomas also pose a diagnostic dilemma, as they may be both clinically and histologically similar to EAC—especially a disorder termed palpable migratory arciform erythema of Clark, which may be a variant of Jessner's lymphocytic infiltrate [34]. Genodermatoses such as erythrokeratoderma variabilis and erythrokeratoderma en cocardes should be considered in children, and similar lesions may be seen in carriers of chronic granulomatous disease. Several immunobullous diseases have been reported to have EAC-like lesions, especially in the prodromal phase, including bullous pemphigoid, pemphigus, dermatitis herpetiformis and linear IgA disease. Sarcoidosis, Still's disease, necrolytic migratory erythema, subacute annular psoriasis, pityriasiform seborrhoeic dermatitis, neutrophilic dermatoses, vasculitides, acute haemorrhagic oedema of childhood, leprosy, leishmaniasis and trypanosomiasis may all cause clinical confusion at times, but should be identifiable by histology and evolution of the eruption. Cases of pityriasis rosea in which there are few and large lesions may cause confusion but are self-limiting. Lupus erythematosus and Sjögren's syndrome need to be excluded, particularly cases with a dermatosis mediated by extractable nuclear antigens (see above).

Otherwise, it is seldom possible to establish an underlying cause. A search for a neoplasm should be made, especially in those with older age of onset, but exhaustive investigations are not recommended in the absence of other clues. Tinea pedis, *Candida* infection of the gut and other underlying infections are always worth excluding.

Treatment. Discovery and elimination of the cause are seldom possible. Numerous other treatments have been used including antihistamines, oral or topical corticosteroids, vitamin D analogues such as calcipotriol [35] or calcitriol, narrow-band UVB, various types of allergen avoidance, and systemic immunosuppressive therapies. Two patients with topical corticosteroid-resistant annular erythema responded promptly to use of topical tacrolimus [36]. Cases that have responded to antimicrobials such as sulphonamides or metronidazole may suggest that there was in fact an underlying infective cause. However, most empirical treatments appear to be relatively unsuccessful. The eosinophilic variant of annular erythema has been reported to respond to chloroquine [12] or hydroxychloroquine.

References

1 Darier J. De l'erytheme annulaire centrifuge. *Ann Dermatol Syphilol* 1916; **6**: 57–76.
2 Harrison PV. The annular erythemas. *Int J Dermatol* 1979; **18**: 282–90.
3 Litoux P. Essai sur la physiopathologie des érythèmes annulaires centrifuge. *Ann Dermatol Syphiligr* 1987; **114**: 709–15.
4 Tyring SK. Reactive erythemas: erythema annulare centrifugum and erythema gyratum repens. *Clin Dermatol* 1993; **11**: 135–9.
5 Kim KJ, Chang SE, Choi JH *et al*. Clinicopathologic analysis of 66 cases of erythema annulare centrifugum. *J Dermatol* 2002; **29**: 61–7.
6 Mahmood JM. Erythema annulare centrifugum: a review of 24 cases with some reference to its association with underlying disease. *Clin Exp Dermatol* 1983; **8**: 383–7.
7 Degos R, Guillaine J. Erytheme annulaire centrifuge purpurique et pigmentaire. *Bull Soc Fr Dermatol Syphiligr* 1964; **71**: 450–2.
8 Ackerman AB. *Histologic Diagnosis of Inflammatory Skin Diseases*. Philadelphia: Lea & Febiger, 1978: 231–2.
9 Weedon D. *Skin Pathology*, 2nd edn. London: Churchill Livingstone, 2002: 245–6.
10 Weyers W, Diaz-Cascajo C, Weyers I. Erythema annulare centrifugum: results of a clinicopathologic study of 73 patients. *Am J Dermatopathol* 2003; **25**: 451–62.
11 Kahofer P, Grabmaier E, Aberer E. Treatment of eosinophilic annular erythema with chloroquine. *Acta Dermatovenereol* 2000; **80**: 70–1.
12 Dereure O, Guilhou JJ. Eosinophilic-like erythema: a clinical subset of Well's eosinophilic cellulitis responding to antimalarial drugs? *Ann Dermatol Venereol* 2002; **129**: 720–3.
13 Betti R, Gualandri L, Inselvini E *et al*. Annual recurrent annular acroerythema without lactate dehydrogenase M-subunit deficiency. *J Eur Acad Dermatol Venereol* 1999; **12**: 270–2.
14 Beare JM, Frogatt P, Jones JH *et al*. Familial annular erythema. *Br J Dermatol* 1966; **78**: 59–68.
15 Watsky KL, Hansen T. Annular erythema in identical twins. *Cutis* 1989; **44**: 139–40.
16 Shelley WB. Erythema annulare centrifugum. *Arch Dermatol* 1964; **90**: 54–8.
17 Shelley WB. Erythema annulare centrifugum due to *Candida albicans*. *Br J Dermatol* 1965; **77**: 383–4.
18 Launay P, Blanc D, Paris B *et al*. Erythema annulare centrifugum disclosing hyperthyroidism. *Ann Dermatol Venereol* 1988; **115**: 721–3.
19 Yaniv R, Shpielberg O, Shpiro D *et al*. Erythema annulare centrifugum as the presenting sign of Hodgkin's disease. *Int J Dermatol* 1993; **32**: 59–61.
20 Lim DS, Murphy GM, Egan CA. Mycosis fungoides presenting as annular erythema. *Br J Dermatol* 2003; **148**: 591.
21 Anzai H, Kikuchi A, Kinoshita A *et al*. Recurrent annular erythema in juvenile chronic myelogenous leukaemia. *Br J Dermatol* 1998; **138**: 1058–60.
22 Motohashi N, Satoh T, Yokozeki H *et al*. Annular erythema associated with essential thrombocythemia. *Acta Dermatovenereol* 2002; **82**: 390.
23 Woskoff A, Daneziger E, Zamparo DI. Hypereosinophilic syndrome. Centrifugal annular erythema as an initial manifestation. *Med Cutan Ibero Lat Am* 1978; **6**: 267–72.
24 Summerly R. The figurate erythemas and neoplasia. *Br J Dermatol* 1964; **76**: 370–3.
25 Inger-Housz S, Venutolo E, Pinquier L *et al*. Erythema annulare centrifugum and relapsing polychondritis. *Ann Dermatol Venereol* 2000; **127**: 735–9.
26 Ramos JM, Blazquez RM, Climent A *et al*. Aseptic meningitis, erythema nodosum and centrifugal annular erythema as first manifestations of recurrent polychondritis. *Med Clin (Barc)* 2000; **12**: 196–7.
27 Altomare GF, Capella GL, Frigerio E. Sarcoidosis presenting as erythema annulare centrifugum. *Clin Exp Dermatol* 1995; **20**: 502–3.
28 Garcia-Muret MP, Pujol RM, Gimene-Arnau AM *et al*. Annually recurring erythema annulare centrifugum: a distinct entity? *J Am Acad Dermatol* 2006; **54**: 1091–5.
29 Helbling I, Walewska R, Dyer MJS *et al*. Erythema annulare centrifugum associated with chronic lymphocytic leukaemia. *Br J Dermatol* 2007; **157**: 1044–5.
30 Stokkermans-Dubois J, Beylot-Barry M, Vergier B *et al*. Erythema annulare centrifugum revealing chronic lymphocytic leukaemia. *Br J Dermatol* 2007; **157**: 1045–7.
31 Miljkovic J, Bartenjev I. Hypereosinophilic dermatitis-like erythema annulare centrifugum in a patient with chronic lymphocytic leukaemia. *J Eur Acad Dermatol Venereol* 2005; **19**: 228–31.
32 Ziemer M, Eisendle K, Zelger B. New concepts on erythema annulare centrifugum: a clinical reaction pattern that does not represent a specific clinicopathological entity. *Br J Dermatol* 2009; **160**: 119–26.
33 Cogrel O, Boralevi F, Lepreux S *et al*. Lymphomatoid annular erythema: a new form of juvenile mycosis fungoides. *Br J Dermatol* 2005; **152**: 565–6.
34 Steinmann A, Gummer M, Agathos M *et al*. Palpable migratory arciform erythema and lymphocytic infiltration of the skin—different presentations of the same entity? *Hautarzt* 1999; **50**: 270–4.
35 Gniadecki R. Calcipotriol for erythema annulare centrifugum. *Br J Dermatol* 2002; **146**: 317–9.
36 Rao NG, Pariser RJ. Annular erythema responding to tacrolimus ointment. *J Drugs Dermatol* 2003; **4**: 421–4.

Neutrophilic and vasculitic annular eruptions

A variety of vasculitides or neutrophilic dermatoses have been documented as causing annular or figurate lesions, sometimes consistently in some individuals. These include acute haemorrhagic oedema of infancy, erythema elevatum diutinum and chronic recurrent annular neutrophilic dermatosis, which may clinically resemble the annular erythemas described above.

Examples of annular vasculitis were summarized by Nousari and colleagues [1], and included acute haemorrhagic oedema of infancy, erythema elevatum diutinum, urticarial vasculitis, Henoch–Schönlein purpura, and some cases of leukocytoclastic vasculitis associated with myeloma, inflammatory bowel disease or pregnancy. These are discussed in Chapter 50. A disorder described as recurrent annular erythema with purpura is noted here rather than within the spectrum of EAC, as it has vasculitic histology and response to dapsone, consistent with a form of leukocytoclastic vascultis [2]; the three cases included one each with ulcerative colitis and a benign IgA monoclonal gammopathy, all had monthly episodes of multiple, purpuric, centrifugally-spreading lesions. Subsequent similar cases have been reported [3], as well as annular purpuric lesions in a patient with lymphoma [4]. Large, annular purpuric lesions with histology of leukocytoclastic vasculitis have been reported in a patient with Sjögren's syndrome and carcinoma of the cervix [5]. Eosinophilic vasculitis may present with annular lesions [6], and both drugs [7] and infections [8] may cause annular leukocytoclastic vasculitis. Sarcoidosis itself can present as vascular lesions, but there are also reports of annular leukocytoclastic vasculitis in patients with sarcoidosis, distinct from cutaneous sarcoid lesions [9,10]. Figurate erythema with an erythema gyratum repens clinical morphology but leukocytoclastic vasculitis on histology has been reported in a patient with lupus erythematosus [11].

Sweet's syndrome often includes some annular lesions [12,13] but these seem to be a particular feature of a chronic variant of Sweet's syndrome [14–16]; in one series of nine cases of recurrent Sweet's syndrome characterized by erythematosus and annular plaques, with an initially lymphocytic histology, all developed myelodysplastic syndrome [16]. Annular lesions have also been reported in neutrophilic eccrine hidradenitis [17] (Chapter 50).

References

1 Nousari HC, Kimyai-Asadi A, Stone JH. Annularleukocytoclastic vasculitis associated with monoclonal gammopathy of unknown significance. *J Am Acad Dermatol* 2000; **43**: 955–7.

2 Cribier B, Cuny JF, Schubert B *et al*. Recurrent annular erythema with purpura; a variant of leukocytoclastic vascultis responsive to dapsone. *Br J Dermatol* 1996; **135**: 972–5.
3 Ruiz Villaverde R, Blasco Melguizo J, Martin Sanchez MC, Naranto Sintes R. Annular leukocytoclastic vascultis: response to dapsone. *J Eur Acad Dermatol Venereol* 2002; **16**: 544–6.
4 Yasukawa K, Kato N, Hamasaka A, Hata H. Unusual annular purpura and erythema in a patient with malignant lymphoma accompanied by hyperglobulinaemia. *Int J Dermatol* 2008; **47**: 302–4.
5 Nakajima H, Ikeda M, Yamamoto Y, Kodama H. Large annular purpura and paraneoplastic purpura in a patient with Sjögren's syndrome and cervical carcinoma. *J Dermatol* 2000; **27**: 40–3.
6 Tsunemi Y, Saeki H, Ihn H, Tamaki K. Recurrent cutaneous eosinophilic vasculitis presenting as annular urticarial plaques. *Acta Derm Venereol* 2005; **85**: 380–1.
7 Chiu CS, Chang YC, Chung WH *et al*. Annular leukocytoclastic vasculitis induced by chorzoxazone. *Br J Dermatol* 2004; **150**: 153.
8 Meissner M, Beier C, Gille J, Kaufmann R. Annular leukocytoclastic vasculitis in association with chronic hepatitis B. *J Eur Acad Dermatol Venereol* 2007; **21**: 135–6.
9 Branford WA, Farr PM, Porter DI. Annular vasculitis of the head and neck in a patient with sarcoidosis. *Br J Dermatol* 1982; **106**: 713–6.
10 Cecchi R, Giomi A. Annular vasculitis in association with sarcoidosis. *J Dermatol* 1999; **26**: 334–6.
11 Piqué E, Palacios S, Santana Z. Leukocytoclastic vasculitis presenting as an erythema gyratum repens-like eruption on a patient with systemic lupus erythematosus. *J Am Acad Dermatol* 2002; **47** (5 Suppl.): S254–6.
12 von den Driesch P. Sweet's syndrome: acute febrile neutrophilic dermatosis. *J Am Acad Dermatol* 1994; **31**: 535–56.
13 Wallach D, Vignon-Pennamen M-D. From acute febrile neutrophilic dermatosis to neutrophilic disease: forty years of clinical research. *J Am Acad Dermatol* 2006; **55**: 1066–71.
14 Christensen OB, Holst R, Svensson A. Chronic recurrent annular neutrophilic dermatosis. An entity? *Acta Derm Venerel* 1989; **69**: 415–8.
15 Cabanillas M, Suárez-Amor O, Sánchez-Aguilar D *et al*. Chronic recurrent neutrophilic dermatosis: a possible variant in the spectrum of neutrophilic dermatoses. *Actas Dermosifiliogr* 2008; **99**: 61–3.
16 Vignon-Pennamen MD, Juillard C, Rybojad M *et al*. Chronic recurrent lymphocytic Sweet syndrome as a predictive marker of myelodysplasia: a report of 9 cases. *Arch Dermatol* 2006; **142**: 1170–6.
17 Scong VY, Appell ML, Omura EF *et al*. Annular plaques on the dorsa of the hands. *Arch Dermatol* 1991; **127**: 1398–402.

CHAPTER 63

The Skin and the Nervous System

C.B. Archer[1] *& D.J. Eedy*[2]

[1]Bristol Dermatology Centre, Bristol Royal Infirmary, Bristol, UK
[2]Department of Dermatology, Craigavon Area Hospital, Northern Ireland

Skin innervation, 63.1
Sensory innervation, 63.1
Autonomic nervous system, 63.3
Wound healing and trophic effects, 63.4
Neuroimmunology, 63.4
Neurophysiological testing for skin innervation, 63.4
Post-herpetic neuralgia, 63.6
Pathophysiology of pain, 63.6
Prevention of post-herpetic neuralgia, 63.6
Management of established post-herpetic neuralgia, 63.7
Neuropathic ulcers, 63.8
Peripheral neuropathy, 63.11
Human immunodeficiency (HIV) neuropathy, 63.12
Trigeminal trophic syndrome, 63.13
Peripheral nerve injury, 63.13
Syringomyelia, 63.14
Tabes dorsalis, 63.15
Spinal dysraphism, 63.15
Spinal cord injury, 63.17
Disorders associated with autonomic abnormalities, 63.18
Hereditary sensory and autonomic neuropathies (HSANs), 63.18
Sympathetic nerve injury, 63.20
Complex regional pain syndrome (CRPS), 63.20
Horner's syndrome, 63.22
Gustatory hyperhidrosis, 63.22
Chronic skin pain, 63.23
Notalgia paraesthetica, 63.23
Brachioradial pruritus, 63.23
Skin-ache syndrome, 63.24
Restless legs syndrome (RLS), 63.24
Burning feet syndrome (BFS), 63.25

Introduction

The relationship between the nervous system and the skin is complex, and the aim of this chapter is to outline the physiology and pathophysiology of the interactions. Nervous system disorders may be divided broadly into those associated with sensory abnormalities and those associated with autonomic abnormalities, although there is overlap between these two groups. Skin manifestations may occur when the pathology is predominantly located either in the central nervous system (CNS), such as the spinal cord, or in the peripheral nervous system.

The sensory innervation of the skin allows the detection of a number of stimuli from the surrounding environment and the transmission of this information to the CNS (Chapter 4).

Groups of disorders affecting the skin and nervous system simultaneously might include genetic conditions (e.g. neurofibromatosis and tuberous sclerosis, Chapter 15), metabolic abnormalities (e.g. the mucopolysaccharidoses and Tangier disease, Chapter 59), Refsum's disease (Chapter 19), vitamin deficiency states (e.g. pellagra, Chapter 59) and exposure to toxins (e.g. arsenic poisoning) or infective agents (e.g. *Meningococcus*).

Skin innervation

The skin is innervated by a dense, three-dimensional network of highly specialized afferent sensory and efferent autonomic nerve branches. The sensory system contains receptors for touch, temperature, pain, itch and various other physical and chemical stimuli [1,2]. The autonomic system comprises post-ganglionic cholinergic parasympathetic nerves and adrenergic and cholinergic sympathetic nerves. It plays a crucial role in maintaining cutaneous homeostasis by regulating vasomotor function, pilomotor activity and eccrine gland secretion. As many as 1000 such afferent neurones may innervate 1 cm^2 of skin. The afferent sensory neurones are unipolar and branch off with a single axon travelling towards the skin. The autonomic nerves innervate the skin in a different pattern. Post-ganglionic fibres originate in the sympathetic chain and are co-distributed with the sensory neurones until they arborize into plexuses around sweat glands, blood vessels and arrector pili muscles [1,2]. Skin nerves may contain myelinated and/or unmyelinated fibres: subgroups of sensory neurones are myelinated A fibres, whereas unmyelinated C fibres contain sensory and autonomic fibres. The sensory myelinated fibres can be further subdivided, on the basis of diameter, into rapidly conducting Aα and slowly conducting Aδ nerves, which transmit tactile sensitivity or temperature, noxious sensation and itch, respectively [2–4]. In the upper dermis, small myelinated nerves lose their nerve sheaths and, together with the unmyelinated nerves, end in either free nerve endings or in association with receptors, such as Merkel cells or nerve ending organs [2,3].

Sensory innervation

Sensory innervation follows well-defined dermatomes with some overlap between adjacent dermatomes. Sensory nerves not only function as an afferent system to conduct stimuli back from the skin to the CNS, but also act in an efferent neurosecretory fashion,

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

releasing neuropeptides with important visceromotor, inflammatory and trophic effects on skin (see below). Unmyelinated type C fibres terminate as either free nerve receptor endings or in association with receptors such as the pacinian or Meissner's corpuscles. Pacinian corpuscles, innervated by a single myelinated sensory axon, are most densely located on the palms and soles, where they act as mechanoreceptors. Meissner's corpuscles also occur in greatest density on the palms and soles; being innervated by one or more sensory nerve endings, they also act as mechanoreceptors, and in addition transmit touch sensation. Merkel cells, which occur at low density generally, with an increased density around hair follicles and at the palms, nail beds and lips, are innervated by synaptic nerve endings. Merkel cells produce and contain a wide range of neuropeptides, which may be important in the local regulation of inflammation [2].

Afferent sensory nerves, either unmyelinated C fibres or myelinated Aδ fibres, derive from the dorsal root ganglion and are capable of the release of a variety of neuropeptides in response to noxious stimuli [2–4]. Sensory impulses are conducted in the peripheral and central axon of the spinal ganglion cell in the dorsal root ganglion, and pass via the lateral spinothalamic tract and the lemniscus spinalis to the thalamus [4]. From the thalamus the information reaches consciousness via the thalamic radiation to the post-central gyrus of the parietal lobe.

C and Aδ fibres not only conduct nociceptive information to the dorsal root ganglion but also have an important efferent function, in that they stimulate target tissues by releasing a range of neuropeptides in response to noxious stimuli, such as chemical, electrical, thermal and mechanical injury, or UV radiation. Over 20 neuropeptides have been identified and more or less characterized in the skin of various species [5]. Neuropeptides with an important neurotransmitter function contained in primary sensory neurones include three tachykinins, substance P, (SP), neurokinin A (NKA) and calcitonin gene-related peptide (CGRP) [6]. These neuropeptides most frequently coexist in the same subpopulation of primary sensory neurones, the Aδ and C fibres, and are involved in the nerve transmission of impulses initiated by noxious stimuli. They usually occur in free nerve endings in the upper dermis (Fig. 63.1) and epidermis throughout the body, but are at greatest density on the palms and soles, where some end in a plexus around Meissner's corpuscles (Fig. 63.2) [6].

Capsaicin, a vanilloid alkaloid found in red pepper fruit [7], functions in nociception by binding to a specific receptor called the vanilloid receptor, the name referring to a homovanillyl group found in ligands of the receptor. Vanilloid receptors have been found on the unmyelinated C and thinly myelinated Aδ fibre types, which transmit painful stimuli. When capsacin stimulates the transient receptor potential vanilloid receptor 1 (TRP-V1), one of the vanilloid receptors particularly implicated in neurogenic inflammation [7], this causes cation influx which is rapidly followed by receptor desensitization. If calcium overload is sufficient, this can lead to cell death [7,8].

Release of neuropeptides often leads to neurogenic inflammation. The key components of neurogenic inflammation are precapillary vasodilation, plasma protein extravasation and leukocyte infiltration, which follow antidromic stimulation of peripheral nerves. Neuropeptides can regulate both acute and chronic

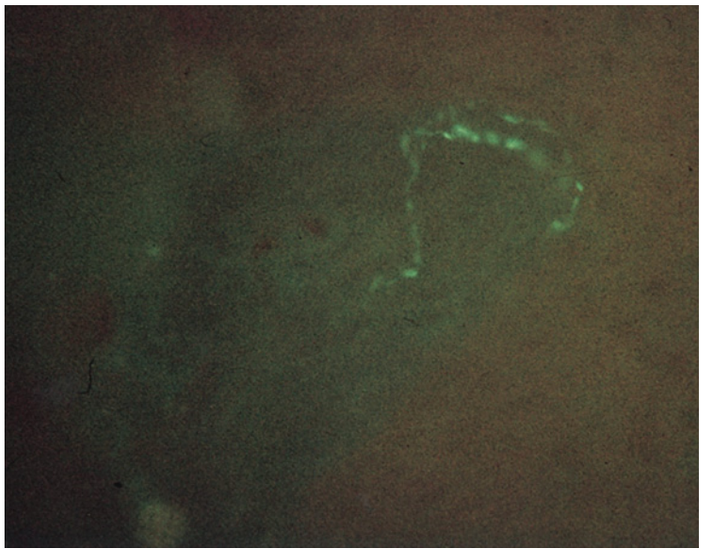


Fig. 63.1 Substance P immunoreactive nerve endings in the epidermis of human skin.

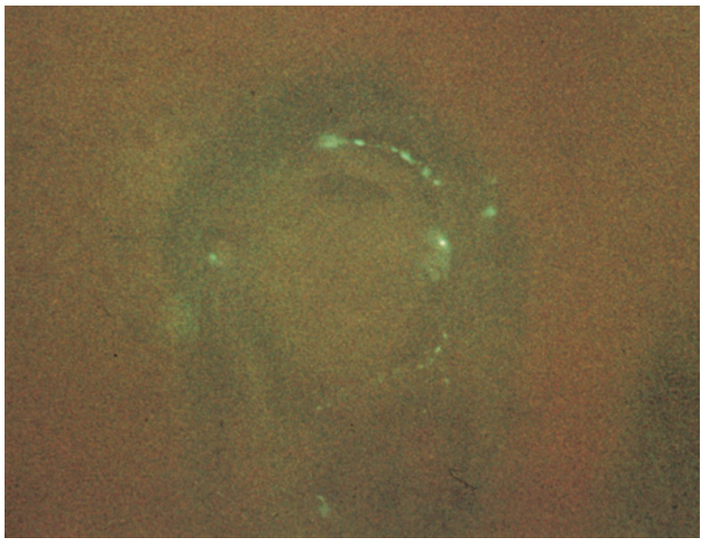


Fig. 63.2 Substance P fibres ending in Meissner's corpuscles of skin.

inflammation by influencing vascular motility and cellular trafficking. After release, neuropeptides are metabolized by membrane-bound endopeptidases that occur on target structures such as blood vessels and eccrine sweat glands in skin [9]. Neutral endopeptidase (NEP) and angiotensin converting enzyme (ACE) in particular seem to play an important role in terminating the action of neuropeptide agonists [5].

A key receptor on sensory nerves which is involved in neurogenic inflammation is the proteinase-activated receptor 2 (PAR-2). PAR-2, bound to G-protein, occurs on keratinocytes (especially in the stratum granulosum), endothelial cells, hair follicles, and in the myoepithelial cells of the sweat glands [7]. Tryptase released from degranulated mast cells cleaves PAR-2 in the sensory nerve endings. This leads to its activation and stimulates the release of

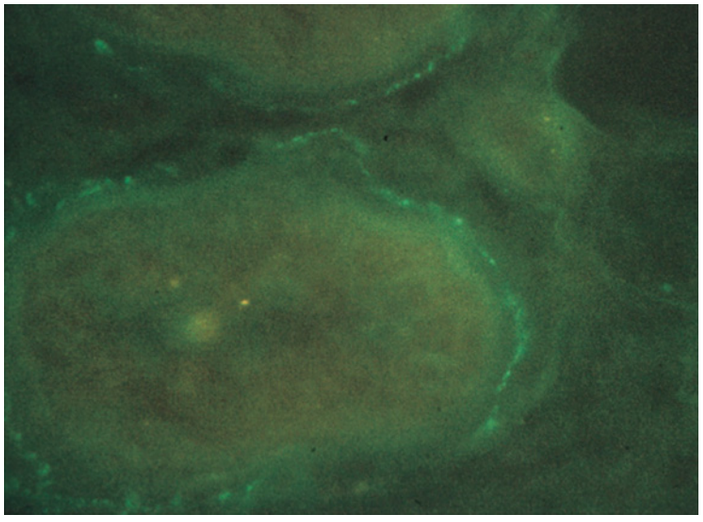


Fig. 63.3 Vasoactive intestinal peptide immunoreactive fibres surround secretory cells of eccrine sweat gland.

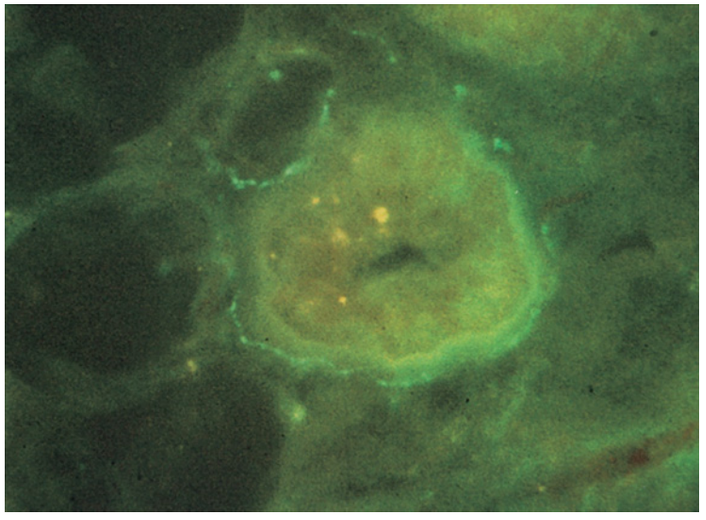


Fig. 63.4 Peptide histidine methionine immunoreactive fibres surround eccrine sweat glands.

CGRP and neurokinin—SP and NKA from sensory nerve endings. CGRP interacts with CGRP-1 receptor to induce arteriolar dilation and hyperaemia; SP interacts with NKA-1 receptor on the endothelial cells of postcapillary venules, to induce plasma extravasation; the overall result is tissue oedema. SP may also stimulate degranulation of mast cells, leading to release of tryptase, which produces positive feedback. Tryptase degrades CGRP and reduces its effects, CGRP inhibits SP degradation by neutral endopeptidase and enhances SP release. Other mediators from mast cells and other inflammatory cells stimulate the release of vasoactive peptides from sensory nerves [5,7].

It can be seen that close interaction between the different neuromediators, target cells and neuropeptide-degrading enzymes is critical for the control of cutaneous neurogenic inflammation [5].

Autonomic nervous system

The autonomic nervous system innervates the skin through post-ganglionic fibres originating in sympathetic ganglia, and terminating in autonomic plexuses that supply sweat glands, blood vessels and arrector pili muscles [1]. Histochemically there are two main groups of post-ganglionic nerve fibre in the skin. Firstly, adrenergic fibres synthesize and store catecholamines and norepinephrine (noradrenaline). The second major group consists of the cholinergic fibres containing acetylcholine. Co-localizing with acetylcholine are 'secretory' neuropeptides such as vasoactive intestinal peptide (VIP) and peptide histidine methionine (PHM). Nerves containing these should be regarded, at least physiologically, as parasympathetic. The secretory portion of the eccrine sweat glands, myoepithelial cells and nearby blood vessels are innervated by a basket-weave pattern of nerves, containing predominantly acetylcholine but also significant numbers of fibres containing 'secretory neuropeptides' including VIP (Fig. 63.3), PHM (Fig. 63.4), neuropeptide Y (NPY), CGRP, galanin, atrial natriuretic peptide (ANP) and norepinephrine. Secretory neuropeptides, mainly VIP and ANP, together with norepinephrine, are not as effective as acetylcholine at sweat production, and probably synergistically amplify acetylcholine-induced adenosine 3′,5′-cyclic monophosphate (cAMP) accumulation, which is the most important secondary messenger in sweat production. ANP may be responsible, at least in part, for regulation of sodium and other electrolytes released in sweat [6]. NPY has been identified in the periarteriolar nerve fibres of the deep and superficial vascular plexus, and in eccrine sweat glands, and is likely to play a role in regulation of skin blood flow and eccrine sweating [6]. Pituitary adenylate cyclase-activating polypeptide (PACAP) also plays a significant role in modulating cutaneous inflammation. It belongs to the VIP family and is capable of binding identical receptors to VIP in the same tissue but with different affinities. Therefore it is possible that there is some differential, fine-tuned interaction between these two peptides [5]. PACAP leads to mast cell degranulation and dilatation of small blood vessels [10]. PACAP may have a proinflammatory effect on endothelial cells during acute inflammation, yet it exerts anti-inflammatory effects under chronic inflammatory conditions [5].

Blood vessels in the skin are innervated by adrenergic fibres, which are vasoconstrictor, while acetylcholine and neuropeptides, such as VIP and PHM, act as vasodilators and increase vascular permeability [6,11]. Thus, by increasing release of acetylcholine and secretory neuropeptide, the body has a mechanism of increasing blood flow to the skin and increasing sweating, both of which act to reduce body temperature. If body temperature falls, this is detected in the preoptic region of the hypothalamus, which activates the sympathetic nervous system, which in turn reduces skin blood flow and sweating. Conversely, if warmer blood is detected in the hypothalamus, inhibition of sympathetic response allows skin sweating and blood flow to increase, thereby reducing core temperature [12,13].

Adrenergic fibres mediate strong vasoconstriction and arrector pili muscle activity, thus diverting blood from the skin, and pulling hairs into the upright position, in the classical 'fight or flight' reaction [1].

The digital nerves in patients with Raynaud's phenomenon and with systemic sclerosis are deficient in CGRP fibres [14], and intravenous infusions of CGRP increase digital blood flow in such patients. A similar depletion of CGRP fibres has been described in digital nerves of patients with vibration white finger, and this may be responsible for both the vasoconstriction and sensory abnormalities characteristic of this condition [15].

Wound healing and trophic effects

Impaired wound healing is often found in patients suffering from peripheral neuropathies, spinal cord lesions or after peripheral nerve trauma. Depletion of neuropeptides in animal models using capsaicin, and *in vitro* studies demonstrating that certain neuropeptides such as substance P, neurokinin A, CGRP and VIP stimulate DNA synthesis in fibroblasts, keratinocytes, melanocytes and endothelial cells, suggest that they are likely to act as mitogens, stimulating proliferation of tissue cells and thereby aiding the healing process [6,15–18]. The sprouting of sensory nerve endings, containing large amounts of substance P, occurs in wounds during the first 3 weeks, and is probably important in wound healing. Substance P has also been shown to up-regulate the synthesis of interleukin-1 (IL-1), IL-6 and transforming growth factor-α (TGF-α) in keratinocytes [18]. Nerve growth factor (NGF) is a neurotrophic factor released from sensory neurones, as well as fibroblasts, mast cells, lymphocytes and keratinocytes, which may act as a major controller of cutaneous wound healing and inflammation [18].

CGRP has a trophic effect in the regeneration of UV-damaged skin, and synthesis of CGRP increases after nerve injury, suggesting that this peptide may have a role in nerve regeneration [19].

Neuroimmunology

There is significant evidence of a close interaction between the nervous system and the immune system. Substance P, neurokinin A and CGRP predominantly function as pro-inflammatory mediators, whereas VIP, somatostatin and α-melanocyte-stimulating hormone (α-MSH) largely have anti-inflammatory properties [20].

Substance P *in vivo* and *in vitro* enhances the proliferation and function of B and T cells and induces cytokine secretion from monocytes, including IL-1, IL-6, tumour necrosis factor-α (TNF-α) and interferon-γ (IFN-γ) [21]. Substance P influences inflammatory responses by enhancing macrophage and leukocyte activity, and acts to release histamine, prostaglandin and leukotriene from mast cells [22]. Furthermore, it activates human dermal microvascular endothelial cells to express vascular adhesion molecule 1 [23].

While VIP is a potent releaser of histamine for mast cells, a mechanism that is independent of IgE activation, it also has anti-inflammatory effects, suppressing delayed hypersensitivity *in vitro* and inhibiting phospholipase A2 [24]. VIP inhibits natural killer cell activity and may have an inhibitory effect in inflammatory processes, such as contact dermatitis, an effect which may be mediated through an increased production of IFN-γ in peripheral blood monocytes [24].

Neuropeptides can activate a number of target cells, including keratinocytes, Langerhans' cells, mast cells, epithelial cells, granulocytes, eosinophils, macrophages and lymphocytes, all of which have been shown to have receptors for neuropeptides. Recent evidence shows that many of these cells may also synthesize these neuropeptides. In addition cytokines, including IL-1, TNF-α and NGF are potent stimulators of neuropeptide production [20]. The release of substance P, CGRP and other neuropeptides may ultimately hold the link between psychological stress and the flaring of inflammatory skin diseases [25–27]. Substance P, neurokinin A and CGRP are all up-regulated by UV light exposure of human skin, and may contribute to the inflammation of acute UV exposure, while in the longer term CGRP inhibits Langerhans' cell activity, thus leading to immunosuppression as a result of UV exposure [28]. Similarly, α-MSH is produced in the skin as a result of UV irradiation, and has been shown to induce the production of IL-10 and inhibit the production of IL-1 and IL-12, thereby inhibiting the chemokine-mediated migration of antigen-presenting cells [29].

In addition to their role as neurotransmitters, neuropeptides can modulate immune responses, leading to the concept of the neuro-immuno-cutaneous system, representing an interrelationship between the nervous system, immunity and skin. This may explain the link between the flare up of inflammatory diseases, such as atopic dermatitis [30] and psoriasis [25,26,31], during periods of emotional stress.

Neurophysiological testing for skin innervation

Sympathetic skin response

Sympathetic skin response (SSR) is a safe, simple and non-invasive electrophysiological test used to evaluate sudomotor function in a variety of clinical settings [32–34]. It can be used to assess autonomic function in patients with suspected sympathetic nerve dysfunction. The SSR is a polysynaptic reflex associated with the activation of sweat glands. It is usually performed by electrical stimulation of the median, ulnar, peroneal or sural nerves and measuring the change in galvanic resistance on glabrous skin brought about by sweating using a conventional electromyograph apparatus. The afferent component may be activated by non-specific sensory stimuli or repeated electrical stimulation; the efferent component depends on the functioning of the sympathetic-cholinergic fibres from the sympathetic chain to the sweat glands. In autonomic failure the SSR cannot be elicited.

Cold-induced vasodilation

Hand cooling is a cold pressor test in which an extremity is placed in cold water, leading to a rapid decrease in skin temperature, accompanied by initial strong vasoconstriction aimed at limiting heat transfer to the environment [35–39]. After a few minutes, skin temperature starts increasing as a consequence of cold-induced vasodilation. The precise mechanism of this reflex is unknown, but it is thought to be mediated through an increase in sympathetic stimulation, although factors independent of the sympathetic nervous system may also play a role. Exposure of the human body to cold stress elicits generalized cutaneous vasoconstriction. This is a response mediated by a sympathetic control process, triggered partly by stimulation of cutaneous cold receptors and partly by cold blood returning to the general circulation and stimulating the temperature-regulating centre in the hypothalamus. The tone of cutaneous vessels is controlled mainly by

vasoconstrictor skin sympathetic nerve activity. A reduction in this response has been reported in diabetic and neuropathic patients, and in the immature and elderly, probably resulting from reduced skin sympathetic nerve vasoconstriction [38,39].

Triple response of Lewis

Lewis described the capacity of the cutaneous microcirculation to vasodilate in response to direct stimulation with a firm mechanical stroke or with a dermographometer (the axon reflex) [39–41]. The amount of vasodilation can be measured by Doppler flow meter. The axon reflex, known as 'antidromic vasodilation', does not occur in chronically denervated skin or skin in which neuropeptides have been depleted by capsaicin. The antidromic vasodilation and plasma extravasation, which occurs in the skin following stimulation of the dorsal nerve roots or peripheral sensory nerves, can be mimicked by intra-arterial infusion of substance P.

Histamine is known to be a principal mediator of the triple response of Lewis, and to act via H_1 and H_2 receptors to produce vasodilation and increased vascular permeability. However, it is known that substance P, neurokinin A and CGRP from primary sensory fibres are also mediators in the skin flares of the triple response of Lewis [42,43].

Laser evoked potentials (LEPs)

Sensory evoked potentials (SEPs) are used for standard clinical neurophysiological assessment of somatosensory pathways, and can detect dysfunction in the tactile and proprioceptive systems, consisting of large fibres in the peripheral nerve, the dorsal columns of the spinal cord and the medial lemniscus in the brainstem. However, lesions in the nociceptive and thermoreceptive pathways of the somatosensory system are not detectable by these means. In recent years, studies have confirmed the usefulness of laser evoked potentials (LEPs), which can be produced by rapid heating of the skin with infrared laser pulses. These latter specifically activate such pathways, which consist of small fibres in the peripheral nerves and the anterolateral spinothalamic tract in the spinal cord and brainstem. Unlike standard SEPs, the LEP technique can be applied to non-glabrous skin in any dermatome. The late components of the LEPs allow the assessment of the functional status of nociceptive Aδ-fibre afferents and so provide complementary information to the standard SEPs, which assess the functional status of tactile Aβ-fibre afferents [44].

Thus this technique, performed carefully, allows the assessment of the functional status of the nociceptive pathways within the somatosensory system. Additional information beyond that obtainable with standard SEPs may be expected particularly in those patients who present with a dissociated sensory loss of pain and temperature sensitivity and preserved tactile and proprioceptive sensitivity. Its potential usefulness lies in documenting clinically relevant sensory deficits, detecting subclinical lesions, and differentiating axonal and demyelinating lesions [44].

References

1 Metze D, Luger T. Nervous system in the skin. In: Freinkel RK, Woodley DT, eds. *The Biology of the Skin*. New York: Parthenon, 2000: 153–76.

2 Lynn B. Cutaneous sensation. In: Goldsmith LA, ed. *Physiology, Biochemistry and Molecular Biology of the Skin*. New York: Oxford University Press, 1991: 779–815.

3 Sternberg EM. Neuroendocrine regulation of autoimmune/inflammatory disease. *J Endocrinol* 2001; **169**: 429–35.

4 Bridges B, Thompson SWN, Rice ASC. Mechanisms of neuropathic pain. *Br J Anaesth* 2001; **87**: 12–26.

5 Steinhoff M, Ständer S, Seeliger S *et al*. Modern aspects of cutaneous neurogenic inflammation. *Arch Dermatol* 2003; **139**: 1479–88.

6 Eedy DJ. Neuropeptides in skin. *Br J Dermatol* 1993; **128**: 597–605.

7 Zegarska B, Leliñska A, Tyrakowski T. Clinical and experimental aspects of cutaneous neurogenic inflammation. *Pharmacolog Reports* 2006; **58**: 13–21.

8 Garle MJ, Fry JR. Sensory nerves, neurogenic inflammation and pain: missing components of alternative irritation strategies? A review and a potential strategy. *Altern Lab Anim* 2003; **31**: 295–316.

9 Pincelli C, Fantini F, Giannetti A. Neuropeptides and skin inflammation. *Dermatology* 1993; **189**: 156–8.

10 Peters EMJ, Ericson ME, Hosoi J *et al*. Neuropeptide control mechanisms in cutaneous biology: physiological and clinical significance. *J Invest Dermat* 2006; **126**: 1937–47.

11 Bonelli RM, Költringer P. Autonomic nervous function assessment using thermal reactivity of microcirculation. *Clin Neurophysiol* 2000; **111**: 1880–8.

12 Delis KT, Lennox AF, Nicolaides AN, Wolfe JH. Sympathetic autoregulation in peripheral vascular disease. *Br J Surg* 2001; **88**: 523–8.

13 Joyner MJ, Halliwill JR. Sympathetic vasodilation in humans. Topical review. *J Physiol* 2000; **526**: 471–80.

14 Bunker CB, Foreman J, O'Shaugnessy D *et al.* Calcitonin gene-related peptide in the treatment of severe Raynaud's phenomenon. *Br J Dermatol* 1989; **121**: 43–4.

15 Goldsmith PC, Bunker CB, Leslie TA *et al.* Cutaneous nerve fibre depletion in vibration finger. *Br J Dermatol* 1992; **127**: 424 [Abstract].

16 Matucci-Cerinic M, Giacomelli R, Pignone A *et al.* Nerve growth factor and neuropeptide circulating levels in systemic sclerosis (scleroderma). *Ann Rheum Dis* 2001; **60**: 487–94.

17 Ansel JC, Kaynard AH, Armstrong CA *et al.* Skin–nervous system interactions. *J Invest Dermatol* 1996; **106**: 198–204.

18 Scholzen TE, Kalden DH, Brozoska T *et al.* Expression of proopiomelanocortin peptides in human dermal microvascular endothelial cells: evidence for regulation by ultraviolet and interleukin-1. *J Invest Dermatol* 2000; **115**: 1021–8.

19 Benrath J, Eschenfender C, Zimmermann M, Gillardon F. Calcitonin gene-related peptide, substance P and nitric oxide are involved in cutaneous inflammation following ultraviolet irradiation. *Eur J Pharmacol* 1995; **293**: 87–96.

20 Brain SD. Sensory neuropeptides: their role in would healing and inflammation. *Immunopharmacology* 1997; **37**: 133–52.

21 Ansel JC, Brown JR, Payan DG, Brown MA. Substance P selectively activates TNF-alpha gene expression in murine mast cells. *J Immunol* 1993; **150**: 4478–85.

22 Payan DG, Levine JD, Goetzl EJ. Modulation of immunity and hypersensitivity by sensory neuropeptides. *J Immunol* 1984; **132**: 1601–4.

23 Ansel JC, Armstrong CA, Song I *et al.* Interactions of the skin and nervous system. *J Investig Dermatol Symp Proc* 1997; **2**: 23–6.

24 Umeda Y, Takamiya M, Yoshizaki H, Arisawa M. Inhibition of mitogen-stimulated T lymphocyte proliferation by calcitonin gene-related peptide. *Biochem Biophys Res Commun* 1988; **154**: 227–35.

25 Naukkarinen AN, Nickoloff BJ, Farber EM. Quantification of cutaneous sensory nerves and their substance P content in psoriasis. *J Invest Dermatol* 1989; **92**: 126–9.

26 Raychaudhuri SP, Farber EM. Neuroimmunologic aspects of psoriasis. *Cutis* 2000; **66**: 357–62.

27 Arck PC, Slominski A, Theoharides TC *et al*. Neuroimmunology of stress: skin takes center stage. *J Invest Dermat* 2006; **126**: 1697–704.

28 Rossi R, Johansson O. Cutaneous innervation and the role of neuronal peptides in cutaneous inflammation: a mini review. *Eur J Dermatol* 1998; **8**: 299–306.

29 Lindsey KQ, Caughman SW, Olerud JE *et al.* Neural regulation of endothelial cell-mediated inflammation. *J Invest Dermatol* 2000; **5**: 74–8.

30 Toyoda M, Morimatsu S, Morohashi M. The alterations of cutaneous innervation and neuropeptide expression by cyclosporin A treatment in atopic dermatitis: an immunohistochemical study. *Jpn J Dermatol B* 1997; **107**: 1275–9.

31 Pinicilli C, Fantina F, Romualdi P *et al*. Substance P is diminished and vasoactive intestinal peptide is augmented in psoriatic lesions and these peptides exert disparate effects on the proliferation of cultured human keratinocytes. *J Invest Dermatol* 1992; **98**: 421–7.

32 Delius W, Hagbarth K-E, Hongell A, Wallin BG. Manoeuvres affecting sympathetic outflow in human skin nerves. *Acta Physiol Scand* 1972; **84**: 177–86.
33 Shahani BT, Halperin JJ, Boulu P, Cohen J. Sympathetic skin response—a method of assessing unmyelinated axon dysfunction in peripheral neuropathies. *J Neurol Neurosurg Psychiatry* 1984; **47**: 536–42.
34 Vetrugno R, Liguori R, Cortelli P, Montagna P. Sympathetic skin response. Basic mechanisms and clinical applications. *Clin Auton Res* 2003; **13**: 256–70.
35 Sawasaki N, Iwase S, Tadaaki M. Effect of skin sympathetic response to local or systemic cold exposure on thermoregulatory functions in humans. *Auton Neurosci* 2001; **87**: 274–81.
36 Scott AR, MacDonald IA, Bennett T, Tattersall RB. Abnormal thermoregulation in diabetic autonomic neuropathy. *Diabetes* 1988; **37**: 961–8.
37 Inoue Y, Araki T, Tsujita J. Thermoregulatory responses of prepubertal boys and young men in changing temperature linearly from 28 to 15°C. *Eur J Appl Physiol* 1996; **72**: 204–8.
38 Khan F, Spence VA, Belch JJF. Cutaneous vascular responses and thermoregulation in relation to age. *Clin Sci* 1992; **82**: 521–8.
39 Sendowski I, Savourey G, Launay JC *et al*. Sympathetic stimulation induced by hand cooling alters cold-induced vasodilatation in humans. *Eur J Appl Physiol* 2000; **81**: 303–9.
40 Lewis T. *Blood Vessels of the Human Skin and Their Responses*. London: Shaw & Sons, 1927.
41 Baraniuk JN. Neuropeptides and the skin. In: Bos JD, ed. *Skin Immune System*, 2nd edn. Boca Raton: CRC Press, 1997: 311–23.
42 Greaves MW, Sabroe RA. Histamine: the quintessential mediator. *J Dermatol* 1996; **23**: 735–40.
43 Anand P, Bannister R, McGregor GP *et al*. Marked depletion of dorsal spinal cord substance P and calcitonin gene-related peptide with intact skin flare responses in multiple system atrophy. *J Neurol Neurosurg Psychiatry* 1988; **51**: 192–6.
44 Treede R-D. Neurophysiological studies of pain pathways in peripheral and central nervous system disorders. *J Neurol* 2003; **250**: 1152–61.

Post-herpetic neuralgia

Herpes zoster (Chapter 33) is itself painful, and is sometimes followed by neuralgia. The risk of developing post-herpetic neuralgia (PHN) rises with age, which influences both the duration and the severity of the neuralgia once it appears [1]. Post-herpetic neuralgia, defined as pain persisting beyond 4 weeks, occurred in 16% of patients younger than 60 years but in 47% of those older than 60 years [2]. Only about one-quarter of those with pain 4 weeks after the vesicles have healed still have pain a year later, but this pain, which is chronic and debilitating, especially in the elderly, can be so severe that it interferes with sleep, and causes depression or even suicidal tendencies.

Patients may report a variety of painful sensations with different components, including spontaneous and continuous deep aching and throbbing pain, burning, lancinating pain, or paroxysms of burning pain, sometimes provoked by non-noxious stimuli, such as contact with clothing or changes in temperature [3]. The pain is accompanied by autonomic instability and its intensity is exacerbated by physical and emotional stress and alleviated by relaxation. Some patients with PHN have profound sensory loss in the area of maximum pain (anaesthesia dolorosa), while others have pronounced allodynia with minimal sensory loss. Another group of patients has areas of sensory loss surrounded by a 'transition zone', within which a noxious stimulus can elicit a particularly unpleasant pain that radiates widely [3]. The patient may go to extraordinary lengths to protect the area from innocuous stimuli, while firm compression of the skin may actually produce pain relief.

Why some patients develop PHN is incompletely understood. There is, for example, no consistent relationship between this type of pain and a loss of large fibres in the damaged nerves, but *in vitro* studies [4] suggest that the virus itself may cause normally silent neurones to produce spontaneous action potentials. In only 70% of PHN patients is it possible to demonstrate loss of function within punch biopsies of the affected tissues, with degeneration of small fibre afferents in the affected dermatome [5].

Pathophysiology of pain

Post-herpetic neuralgia may be caused by neurological lesions at all levels of the nervous system including peripheral, central and autonomic components.

In pain associated with peripheral damage in the dorsal root ganglion, spinal cord and afferent neurones, ectopic impulse generation may occur at the site of damage, and these impulses can be evoked by mechanical or thermal stimuli in the local environment (tactile allodynia) [3]. For this type of disorder, membrane-stabilizing drugs are likely to work best. There is also some evidence that nociceptors in painful skin of post-herpetic neuralgia patients have enhanced adrenergic sensitivity [3].

When sensory deficits are present, suggesting destruction of dorsal root ganglion cells, the pain is primarily sustained by processes in the CNS, resulting in what is known as 'deafferentation pain' [3].

With the realization that several pain mechanisms may be operating in any one individual, it is unrealistic to expect any one drug to completely alleviate the pain in all neuropathic pain disorders, or to significantly reduce the pain in all patients suffering from the same neuropathic condition.

Prevention of post-herpetic neuralgia

Two controlled studies [6,7] suggested that the use of systemic corticosteroids during the acute episode of herpes zoster might reduce the risk of developing post-herpetic neuralgia, and in neither was generalized herpes zoster a problem. However, a systematic review [8] concluded that corticosteroids are not of proven efficacy, and this was borne out in a randomized, open trial [9]. Given its immunosuppressive effects, and potential for serious complications, systemic corticosteroids are not recommended.

In older adults with localized herpes zoster, oral aciclovir (800 mg five times daily for 7 days) reduces acute pain and healing times if treatment is initiated within 72 h of the onset of the eruption [10]. A reduction in ocular complications, particularly keratitis and anterior uveitis, occurs with treatment of herpes zoster ophthalmicus [11]. A systematic review of four placebo-controlled trials of oral aciclovir showed only marginal evidence for pain reduction after herpes zoster. Famciclovir and valaciclovir significantly reduced the duration but not the incidence of post-herpetic neuralgia, in one placebo-controlled trial for each agent. Famciclovir (500 mg three times daily for 7 days) or valaciclovir (1000 mg three times daily for 7 days) may provide more prompt relief of zoster-associated pain than aciclovir in acute herpes zoster in older adults (over 50 years of age) [12].

In immunocompromised patients with herpes zoster, intravenous aciclovir (500 mg/m^2/8 h for 7 days) reduces viral shedding, healing times, the risks of cutaneous dissemination and visceral

complications, as well as the length of hospital stay in disseminated zoster [13].

A vaccine has been developed which decreases the incidence both of herpes zoster reactivation and post-herpetic neuralgia. In a placebo-controlled primary prevention study of the vaccine, men and women age 60 and over had a significant reduction in the burden of illness due to both clinical herpes zoster and of post-herpetic neuralgia [14].

Management of established post-herpetic neuralgia [15]

In mild and moderate cases of established post-herpetic neuralgia, simple analgesics help, but in severe cases they may have little effect. Opioids should probably be prescribed for resistant pain not coming under control with other drugs (below). Controlled-release oxycodone at a dose of 10–30 mg 12-hourly was shown to be effective in a randomized, placebo-controlled study for steady-state, paroxysmal spontaneous pain and allodynia [16]. Tramadol, a centrally acting analgesic with both opioid and non-opioid activities, seemed to work well in a pilot study up to a maximum dose of 600 mg daily [17].

The most effective drugs include antidepressants and anticonvulsants (membrane-stabilizing drugs). In a placebo-controlled trial, amitriptyline was shown to be superior to placebo, with about 60% of patients experiencing a good response to the active drug [18]. Pain relief was achieved with a relatively low dose. At a dose of around 70 mg/day, some 60% of patients experienced a good result with reduction of pain from severe to mild, and 14% had no pain. Most patients complained of side effects including dry mouth, drowsiness, constipation or urinary hesitancy. Other antidepressants recommended for post-herpetic neuralgia include desipramine, nortriptyline and maprotiline. Of these, nortriptyline [19] and desipramine [20] were shown to be effective in randomized controlled trials, whereas a controlled trial showed no advantage of maprotiline over amitriptyline [21]. While anticonvulsants such as sodium valproate, phenytoin, carbamazepine and clonazepam are frequently advocated for shooting or lancinating pain, others have claimed that these drugs are unproven and relatively ineffective [22]. The new anticonvulsant drug, gabapentin, has been shown in a randomized, double-blind placebo-controlled trial to reduce post-herpetic neuralgia pain [22], and has recently been licensed for the treatment of peripheral neuropathic pain such as painful diabetic neuropathy and PHN. Gabapentin, an analogue of γ-aminobutyric acid (GABA), does not interact with any known neurotransmitter receptors and specifically it is not a GABA agonist, unlike its close relative, baclofen. Data suggest that it exerts an effect on the presynaptic calcium channels of primary nociceptive endings and it is now widely used in neuropathic pain [5]. To date, there are no studies directly comparing gabapentin with antidepressants, but it is considered at least as effective and safe as the antidepressants but with fewer side effects [3]. The results of these studies support the use of gabapentin as a first-line medication in the treatment of chronic neuropathic pain syndromes such as post-herpetic neuralgia. A successor drug, pregabalin, has also been shown to be efficacious but with superior bioavailability, making it easier to use without the need for long titration periods [5,23]. Other drugs reported to be of help are clonidine and lamotrigine, although, as yet, no controlled trials have been carried out on these drugs [3]. Randomized, controlled trials of capsaicin, at either 0.025 or 0.077% applied three to four times per day, have been shown to be effective [24]. The use of topical 5% lidocaine (lignocaine) patches either worn for around 12 h/day [25], or applied up to four times per day [26], has been shown to be efficacious, well tolerated and associated with low systemic absorption. Surprisingly, clinical response to topical lidocaine was seen in the group of patients shown by Quantitative Sensory Testing to have predominant degeneration of nociceptive neurones rather than in those with sensitized nociceptors. It may be appropriate to consider topical lidocaine before capsacin since the latter produces burning pain and hyperalgesia, which often leads to discontinuation [5]. Other treatments that have been reported to produce benefit in some patients include baclofen [27] and weekly lumbar intrathecal injections of methylprednisolone [28].

Surgical treatments have been tried in the past, including division of the dorsal root or tractotomy, or ablation by injection of the ganglion or sensory root, but these are not advocated due to limited efficacy and the high rate of morbidity [3]. Spinal cord stimulators have been used with variable results, and transcutaneous stimulation (TENS) may be helpful, but proper trials are lacking [29]. There seems to be no good evidence to support a role for acupuncture in treating post-herpetic neuralgia [30].

References

1 Russell K, Portenoy RK, Duma C *et al.* Acute herpetic and postherpetic neuralgia: clinical review and current management. *Ann Neurol* 1986; **20**: 651–64.

2 Watson PN, Evans RJ. Post-herpetic neuralgia. *Arch Neurol* 1986; **43**: 836–46.

3 Bonizzi C, Demartini L. Treatment options in postherpetic neuralgia. *Acta Neurol Scand Suppl* 1999; **173**: 25–35.

4 Schon F, Mayer ML, Kelly JS. Pathogenesis of post-herpetic neuralgia. *Lancet* 1987; **ii**: 366–8.

5 Wasner G, Fleetwood-Walker SM, Garry EM *et al.* Postherpetic neuralgia: basic research and clinical implications. *Reviews in Analgesia* 2007; **9**: 71–86.

6 Eaglestein WH, Katz R, Brown JA. The effects of early corticosteroid therapy on the skin eruptions of herpes zoster. *JAMA* 1970; **211**: 1681–3.

7 Keczkes K, Basheer AM. Do corticosteroids prevent post-herpetic neuralgia? *Br J Dermatol* 1980; **102**: 511–5.

8 Alper BS, Lewis PR. Does treatment of acute herpes zoster prevent or shorten postherpetic neuralgia? *J Fam Pract* 2000; **49**: 255–64.

9 Calza AM, Schmied E, Harms M. Systemic corticosteroids do not prevent postherpetic neuralgia. *Dermatology* 1992; **184**: 314–6.

10 Wood MJ, Ogan PH, McKendrick MW *et al.* Efficacy of oral acyclovir treatment of acute herpes zoster. *Am J Med* 1988; **85** (Suppl. 2A): 79–83.

11 Cobo LM, Foulks GN, Liesegang T *et al.* Oral acyclovir in the treatment of acute herpes zoster ophthalmicus. *Ophthalmology* 1986; **93**: 763–70.

12 Beutner KR, Friedman DJ, Forszpaniack C *et al.* Valaciclovir compared with acyclovir for improved therapy for herpes zoster in immunocompetent adults. *Antimicrob Agents Chemother* 1995; **39**: 1546–53.

13 Whitley RJ, Gnann JW Jr, Hinthorn D *et al.* Disseminated herpes zoster in the immunocompromised host: a comparative trial of acyclovir and vidarabine. *J Infect Dis* 1992; **165**: 450–5.

14 Oxman MB, Levin MJ, Johnson GR *et al.* A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults *N Engl J Med* 2005; **352**: 2271–84.

15 Ladhani S, Williams HC. The management of established postherpetic neuralgia: a comparison of the quality and content of traditional vs. systematic reviews. *Br J Dermatol* 1998; **139**: 66–72.

16 Watson CP, Babul N. Efficacy of oxycodone in neuropathic pain: a randomized trial in postherpetic neuralgia. *Neurology* 1998; **50**: 1837–41.

17 Gobel H, Stadler T. Treatment of post-herpes zoster pain with tramadol: results of an open pilot study versus clomipramine with or without levomepromazine. *Drugs* 1997; **53**: 34–9.
18 Watson CP, Evans RJ, Reed K *et al*. Amitriptyline versus placebo in post-herpetic neuralgia. *Neurology* 1982; **32**: 670–3.
19 Watson CP, Vernich L, Chipman M, Reed K. Nortriptyline versus amitriptyline in postherpetic neuralgia: a randomized trial. *Neurology* 1998; **51**: 1166–71.
20 Kishore-Kumar R, Max MB, Schafer SC *et al*. Desipramine relieves postherpetic neuralgia. *Clin Pharmacol Ther* 1990; **47**: 305–12.
21 Watson CPN, Chipman M, Reed K *et al*. Amitriptyline versus maprotiline in post herpetic neuralgia: a randomized, double-blind crossover trial. *Pain* 1992; **48**: 29–36.
22 Rowbotham M, Harden N, Stacy B *et al*. Gabapentin for the treatment of postherpetic neuralgia: a multicentre double-blind, placebo-controlled study. *JAMA* 1998; **280**: 1837–42.
23 Gilron I, Flatters SJL. Gabapentin and pregabalin for the treatment of neuropathic pain: a review of laboratory and clinical evidence. *Pain Res Manage* 2006; **11** (Suppl. a): 16A–29A.
24 Watson PN, Tyler KL, Bickers DR *et al*. A randomized vehicle-controlled trial of topical capsaicin in the treatment of postherpetic neuralgia. *Clin Ther* 1993; **15**: 510–26.
25 Devers A, Galer BS. Topical lidocaine patch relieves a variety of neuropathic pain conditions: an open-label study. *Clin J Pain* 2000; **16**: 205–8.
26 Gammaitoni AR, Alvarez NA, Galer BS. Safety and tolerability of the lidocaine patch 5%, a targeted peripheral analgesic: a review of the literature. *J Clin Pharmacol* 2003; **43**: 111–7.
27 Steordo L, Leo A, Marano E. Efficacy of baclofen in trigeminal neuralgia and other painful conditions: a clinical trial. *Eur Neurol* 1984; **23**: 51–5.
28 Pappagallo M, Campbell N. Chronic opioid therapy as an alternative treatment for post-herpetic neuralgia. *Ann Neurol* 1994; **35**: S54–6.
29 Yamashiro H, Hara K, Gotoh Y. Relief of intractable post-herpetic neuralgia with gasserian ganglion block using methyprednisolone acetate and with TENS. *Masui* 1990; **39**: 1239–44.
30 Lewith GT, Field J, Machin D. Acupuncture compared with placebo in postherpetic neuralgia. *Pain* 1983; **17**: 361–8.

Neuropathic ulcers

Neuropathic ulcer is a form of chronic ulceration, also known as 'perforating ulcer', which develops in anaesthetic skin. Characteristically neuropathic ulcers are painless, persistent and uninflamed, appearing on areas subject to trauma or pressure.

Aetiology. While a number of neurological disorders may cause neurotrophic ulcers, the vast majority occur in patients with type II diabetes [1,2]. Other causes include leprosy, peripheral neuropathy, alcoholism, vitamin deficiencies, pernicious anaemia, syringomyelia, tabes dorsalis, spinal dysraphism, spinal cord injury and hereditary sensory and autonomic neuropathies [3,4].

Neuropathic ulcers result from a distal polyneuropathy encompassing motor, sensory and autonomic components.

Motor involvement leads to weakness of the intrinsic muscles of the feet and an imbalance between the long flexor and extensor tendons, leading to a typical cavus or high arched foot along with clawing of the toes (Fig. 63.5) [5]. This, combined with arch collapse, leads to the 'rocker-bottom foot', which is prone to tissue breakdown and ulceration. The plantar aspect of the foot is protected by fat pads, which anticipate weight-bearing forces in all directions. Increased pressure under the metatarsal heads and heel, the sites of around 90% of such ulcers, results in high pressure with initial callosity leading to ulceration. In the majority of patients, a palpable pulse in the affected foot is an indication of good vascular supply. However, the presence of rest pain, diminished or absent pulses, pallor on elevation and sluggish refilling of toe capillaries, together with trophic signs in the skin, are highly indicative of ischaemic ulcers. The associated sensory neuropathy allows the patient to injure the foot, either suddenly by standing on sharp objects such as pins or glass, or gradually, for example from pressure within a poorly fitting shoe, without the patient being aware of the damage. Autonomic neuropathy leads to a foot with loss of sweating, leading to dryness with fissuring and cracking and changes in the normal microcirculation autoregulation. Such cracks or fissures allow a portal of entry of infection. In the diabetic foot there is an impairment of the neurogenic vasodilator response, or flare, which correlates with the clinical diminution in pain sensation. It is likely that loss of both components of the nociceptive C-fibre function, both neurological inflammation and pain sensation, is an important factor in the development of foot complications in diabetes. Diabetics have been demonstrated as having a defect of unmyelinated nociceptive C fibres on the soles of their feet, leading to loss of nociceptive function and the development of both neuropathic plantar ulcers and neuroarthropathy. As sympathetic tone is lost, increased peripheral blood flow leads to arterial venous shunting, with blood bypassing the capillary bed, thereby reducing nutritive skin blood flow [6].



Fig. 63.5 Clawing of feet occurring in neuropathic foot with painless damage to skin on great toe.

Clinical features. Primary neuropathic limbs tend to be warm, insensitive and prone to ulceration on the sole of the foot, while neuroischaemic limbs are usually cool, discoloured and prone to ulceration on the foot margins [2]. Neuropathic ulcers typically occur under the metatarsal heads or heel, surrounded by thick hyperkeratosis, and have a pink punched out base that bleeds easily and is painless (Figs 63.6 & 63.7). The foot is warm with palpable pulses and the changes include pes cavus, warm, dry and insensitive foot with dilated veins, clawed toes and hyperkeratosis under the forefoot and heel [2]. In diabetic patients, there may be



Fig. 63.6 Typical neuropathic ulcers with surrounding hyperkeratosis under metatarsal heads.



Fig. 63.7 Neuropathic ulcer with hyperkeratosis removed.

a complex interplay of neuropathy and ischaemia, and when the latter is present, the foot may be cold with absent pulses, hyperkeratosis and a dark fibrotic base that does not bleed easily and is painful to touch. Continuing mechanical overload on established callus can result in fissures and increases the risk of future ulcer formation [7]. In the neuropathic ulcer, the sensations of light touch and vibration and sharp–blunt discrimination are reduced, which can be demonstrated using a Bailey® nylon monofilament (Fig. 63.8), which buckles in response to 10 g force, neurotheissometer and Neurotip® [8], respectively. Absent pulses suggest ischaemia. Falsely high ankle–brachial pressure indices may occur, especially in diabetics, as a result of non-compressible calcified vessels.

A frequent complication is the presence of cellulitis or deep infection with abscess formation or osteomyelitis. One study found that Gram-positive, aerobic bacterial colonization predominates (84%), with *Staphylococcus aureus* being the commonest organism (79%). Methicillin-resistant *S. aureus* (MRSA) was isolated in 30% of patients, which was almost double the proportion of MRSA-infected patients 3 years previously [9]. Bacterial colonization of the ulcer does not necessarily indicate infection. By contrast, infection may be present, especially in diabetics, without a very apparent pyrexia; leukocytosis, elevation of erythrocyte sedimentation rate and local signs may be less than expected. Cellulitis should alert one to the possibility of underlying osteomyelitis; plain X-rays may exhibit periosteal reactions or osteolysis. Probing a wound to find palpable bone at the base of an ulcer is an excellent predictor of osteomyelitis [10] (Fig. 63.9). A plain X-ray of the foot should be done to check for foreign bodies, tissue gas or bony abnormalities. A sinogram may be required to show communication of the sinus with a joint or a subfascial plantar abscess. A radioisotope bone scan, or magnetic resonance imaging (MRI) scan, may help to establish the diagnosis [11].



Fig. 63.8 Bailey® nylon monofilament assessing sensory loss on neuropathic foot.

Treatment. The prevention of ulceration in neuropathic patients is of the utmost importance [11]. Persons at risk should receive instruction on basic foot care, preferably from a podiatrist, with education on regular self-inspection of feet and correct nail-cutting techniques. Shoes should accommodate any deformity, have broad rounded or square toes, adequate toe depth and a low heel to avoid excessive pressure on the forefoot [12,13]. They should fasten securely to prevent movement within the shoe. Orthotic devices such as cushioned insoles may also be beneficial in preventing ulceration. Management with urea-based products may be helpful in managing callus [7]. Patients should be discouraged from removing callus themselves; this should be done by a podiatrist. Control of hypertension, cessation of smoking, prescription of aspirin in patients with atherosclerosis and meticulous control



(a)



(b)

Fig. 63.9 Probing a neuropathic wound. (a) Probe in position. (b) With probe removed.

of hyperglycaemia can slow or even reverse the signs of peripheral neuropathy [14].

In the treatment of a neuropathic foot ulcer, a multidisciplinary approach is most effective, and has been shown to significantly reduce amputation [15]. Typically, the ulcer is debrided surgically or treated using a hydrogel followed by the application of a hydrocolloid dressing. Randomized, controlled trials have shown benefit from the use of the platelet-derived growth factor becaplermin [16], cultured dermis (Dermograft®) [17] and hyaluronic acid dressings (Hyalofill®) [17,18] in promoting wound healing in clean wounds.

An essential part of treatment is the offloading of areas of abnormal pressure on the foot [15]. Contact casting is useful for healing ulceration over metatarsal heads but requires expertise in application and should not be used in patients whose ulcers are infected, or where there is a significant ischaemic component [15]. An example of such a casting is the Aircast Walkers® foam boot (Fig. 63.10). A modified non-weight-bearing boot made out of layers of adhesive foam padding may achieve complete removal of pressure points [19]. Boots made of plaster of Paris (with a rocker base) seem popular in some centres, especially with orthopaedic practitioners. The plaster boot is applied, initially weekly, and every 3 weeks, until ulceration is healed [20].



Fig. 63.10 Aircast Walkers® boot.

References

1 Boulton A. Peripheral neuropathy and the diabetic foot. *Foot* 1992; **2**: 67–72.
2 Boulton A. The pathogenesis of diabetic foot problems: an overview. *Diabet Med* 1996; **13**: S12–6.
3 Sumpio BE. Foot ulcers. *N Engl J Med* 2000; **343**: 787–93.
4 Phillips TJ. Leg ulcers. *Postgrad Med* 1999; **105**: 165–73.
5 Laing P. The development and complications of diabetic foot ulcers. *Am J Surg* 1998; **176** (Suppl. 2A): S11–9.
6 Parkhouse N, Le Quesne PM. Impaired neurogenic vascular response in patients with diabetes and neuropathic foot lesions. *N Engl J Med* 1988; **318**: 1306–9.
7 Pavicic T, Korting HC. Xerosis and callus formation as a key to the diabetic foot syndrome: dermatologic view of the problem and its management. *J Deutsch Dermatol Gesell* 2006; **4**: 935–41.
8 Klenerman L, McCabe C, Cogley D *et al.* Screening for patients at risk of diabetic foot ulceration in a general diabetic outpatient clinic. *Diabet Med* 1996; **13**: 561–3.
9 Dang CN, Prasad YD, Boulton AJ, Jude EB. Methicillin-resistant *Staphylococcus aureus* in the diabetic foot clinic: a worsening problem. *Diabet Med* 2003; **20**: 159–61.
10 Grayson ML, Gibbons GW, Balogh K *et al.* Probing to bone in infected pedal ulcers: a clinical sign of underlying osteomyelitis in diabetic patients. *JAMA* 1995; **273**: 721–3.
11 Malone JM, Snyder M, Anderson G *et al.* Prevention of amputation by diabetic education. *Am J Surg* 1989; **158**: 520–3.
12 Catanzariti AR, Haverstock BD, Grossman JP, Mendicino RW. Off-loading techniques in the treatment of diabetic plantar neuropathic foot ulceration. *Adv Wound Care* 1999; **12**: 452–8.
13 Armstrong DG, Nguyen HC, Lavery LA *et al.* Off-loading the diabetic foot wound: a randomized clinical trial. *Diabetes Care* 2001; **24**: 1019–22.

14 Moss SE, Klein R, Klein BE. The 14-year incidence of lower-extremity amputations in a diabetic population. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. *Diabetes Care* 1999; **22**: 951–9.
15 Larsson J, Apelqvist J, Agardh CD, Stenstrom A. Decreasing incidence of major amputation in diabetic patients: a consequence of a multidisciplinary foot care team approach? *Diabet Med* 1995; **12**: 770–6.
16 Bennett SP, Griffiths GD, Schor AM *et al.* Growth factors in the treatment of diabetic foot ulcers. *Br J Surg* 2003; **90**: 133–46.
17 Edmonds M, Bates M, Doxford M *et al.* New treatments in ulcer healing and wound infection. *Diabetes Metab Res Rev* 2000; **16** (Suppl. 1): S51–4.
18 Vazquez JR, Short B, Findlow AH *et al.* Outcomes of hyaluronan therapy in diabetic foot wounds. *Diabetes Res Clin Pract* 2003; **59**: 123–7.
19 Myerly SM, Stavosky JW. An alternative method for reducing plantar pressures in neuropathic ulcers. *Adv Wound Care* 1997; **10**: 26–9.
20 Laing P. Diabetic foot ulcers. *Am J Surg* 1994; **167** (Suppl. 1A): S31–6.

Peripheral neuropathy

Peripheral neuropathy may be sensory, motor or mixed [1]. In most types of peripheral neuropathy, the involvement is symmetrical and symptoms begin in the extremities with sensory loss in a glove and stocking distribution. In contrast to this, is the patchy involvement of peripheral nerves in mononeuritis multiplex seen, for example, in polyarteritis nodosa, or sarcoidosis (Chapter 61). The causes of peripheral neuropathy are numerous and include diabetes mellitus, carcinomatous neuropathy, vitamin B group deficiency and drugs or chemicals (Table 63.1).

The typical picture of polyneuropathy occurs with acquired, toxic or metabolic neuropathic states, and it is these that will usually be seen by a dermatologist. The first symptoms tend to be sensory, consisting of tingling, prickling, burning or band-like dysaesthesia in the balls of the feet or tips of the toes, or in a general distribution over the soles. Symptoms and findings are usually symmetrical and graded distally. If the polyneuropathy remains mild, objective motor or sensory signs may not be detectable. With progression, the dysaesthesia spreads up the legs, pan-sensory loss is found over the feet and the ankle reflexes are lost. Sensory loss moves centripetally in a graded 'stocking' fashion. The patient may complain that the feet have a numb or 'wooden' feeling. Neuropathy is usually less severe in the arms, and spreads in a centripetal, symmetrically graded manner with palmar sensory loss and areflexia. Overall, nerve fibres are affected according to axon length, without regard to the root or nerve trunk distribution, giving rise to the term 'stocking and glove' distribution to describe the pattern of the sensory deficit. Mononeuritis multiplex refers to sequential involvement of individual non-contiguous nerve trunks. This leads to a patchy, multifocal neurological defect, and is often caused by an immunological or toxin-mediated disease process. Lightning pains may be a feature of tabes dorsalis and angiokeratoma corporis diffusum (Fabry's disease).

Autonomic neuropathies can be a manifestation of a more generalized polyneuropathy, but may also occur in isolation, when structural changes in the pre- and post-ganglionic neurones occur. Autonomic neuropathy is characterized by symptoms of postural hypotension, anhidrosis, hypothermia, bladder atonia, constipation, dry mouth and eyes, failure of salivary and lacrimal glands to secrete, blurring of vision from lack of pupillary and ciliary regulation, and sexual impotence in males [1].

Carpal tunnel syndrome is caused by an entrapment mononeuropathy of the median nerve at the wrist. It may be secondary to excessive use of the wrist, tenosynovitis, or local infiltration with connective tissue such as in acromegaly, amyloid or mucopolysaccharidosis. The main symptoms are nocturnal paraesthesiae of the thumb, index and middle fingers.

Table 63.1 List of causes of peripheral neuropathy.

Metabolic	Diabetes mellitus, alcohol, porphyria, myxoedema, acromegaly, uraemia, POEMS syndrome, hypoglycaemia
Neoplastic	Paraneoplastic neuropathy, lymphoma, Hodgkin's disease, multiple myeloma
Nutritional	Deficiencies of vitamins B_1, B_{12} or E and malabsorption syndromes including coeliac disease
Toxic	Alcohol, heavy metals (e.g. lead, mercury, gold, thallium), drugs (e.g. amiodarone, cisplatin, hydralazine isoniazid, dapsone, nitrofurantoin, disulfiram, phenytoin, vincristine, metronidazole, antiretroviral nucleoside analogues), other toxic agents (e.g. organophosphates, acrylamide)
Trauma	Pressure neuropathy, ischaemia, pressure from tumours, electrical shock
Infective	Diphtheria, leprosy, mumps, Guillain–Barré syndrome, HIV infection, Lyme disease
Inflammatory	Rheumatoid arthritis, polyarteritis nodosa, sarcoidosis, systemic lupus erythematosus, primary biliary cirrhosis, primary systemic amyloidosis, chronic obstructive airways disease, Churg–Strauss syndrome, critical illness
Genetic	Charcot–Marie–Tooth disease, Refsum's disease, HSANs, Fabry's disease, Roussy–Levy syndrome, metachromatic leukodystrophy

HIV, human immunodeficiency virus; HSANs, hereditary sensory autonomic neuropathies; POEMS, polyneuropathy, organomegaly, endocrinopathy, M-protein, skin changes.

Investigations. The investigations variably appropriate in peripheral neuropathy are shown in Table 63.2 [1].

Despite the complaints of pain and burning due to degeneration of thin myelinated Aδ fibres and unmyelinated C fibres, neurological examination, including sensory nerve conduction studies, may be normal in small-fibre neuropathy. In such cases, skin biopsy

Table 63.2 Investigation of peripheral neuropathy [1].

Urine	Glucose, protein, Bence Jones protein
Haematology	Full blood count, erythrocyte sedimentation rate, vitamin B_{12} and folate
Biochemistry	Fasting blood glucose, renal function, liver function, thyroid function, glucose tolerance test, serum protein electrophoresis, serum angiotensin-converting enzyme, prostate-specific antigen
Radiology	Chest X-ray, abdominal or pelvic ultrasound, chest and abdominal computed tomography, mammography, PET
Immunology	Antinuclear factor, antibodies to extractable nuclear antigen (Ro, La), neutrophilic cytoplasmic antigen, HIV, gliadin, neuronal (Hu, Yo)
Neurophysiology	Proximal and distal nerve conduction studies
Cerebrospinal fluid	Cells, protein, immunoglobulin oligoclonal bands

HIV, human immunodeficiency virus; PET, positron emission tomography.

may prove helpful. The technique is safe, almost painless, cheap and repeatable. In centres trained in the technique, the density of small fibres can be measured easily using bright field microscopy in sections cut from the specimen and appropriately immunostained with antibodies against markers expressed by peripheral nerve fibres, such as protein gene product 9.5, microtubules and neuropeptides. Location of these fibres either in the epidermis or around sweat glands, arrector pili muscles and blood vessels, helps distinguish somatic from autonomic neuropathies [2].

Treatment. Treatment of neuropathic pain and neuropathic foot, sexual dysfunction and bowel or bladder control are dealt with in the relevant sections in this chapter.

Human immunodeficiency (HIV) neuropathy

With the effectiveness of antiretroviral treatment and the decline in opportunistic infections and HIV-induced dementia, HIV-associated neuropathies have become the most common neurological disorder associated with acquired immune deficiency syndrome (AIDS). They present as acute or chronic demyelinating neuropathies, mononeuritis multiplex, cytomegalovirus (CMV)-related polyradiculoneuropathy, autonomic neuropathy or distal painful sensory neuropathy [3–5]. They are multifactorial in aetiology, occurring in all stages of the illness, and take a variety of courses. Early in the course of HIV infection, acute inflammatory demyelinating polyneuropathy resembles Guillan–Barré syndrome. In other patients, a progressive or relapsing inflammatory neuropathy, resembling chronic inflammatory demyelinating polyneuropathy and mononeuritis multiplex, occurs. The most common peripheral neuropathy in patients with HIV infection is distal sensory polyneuropathy (DSP), which may be either a direct consequence of HIV infection, or a side effect of antiretroviral therapy, antiretroviral toxic neuropathy (ATN), or both [3,5].

Aetiology. DSP is characterized by axonal degeneration of long nerves in the extremities. The virus, which is not found within ganglionic neurones or Schwann cells but only within the endoneurial macrophages, may generate a tissue-specific autoimmune attack by secretion of cytokines that promote trafficking of activated T cells and macrophages within the endoneurial parenchyma [6–8].

Studies of skin biopsies of patients with HIV-associated sensory neuropathy, developing during treatment with didanosine or zalcitabine, have shown a reduction in the density of epidermal fibres in distal lower extremities, with an inverse correlation between reduced nerve density and neuropathic pain [8,9]. Mononeuritis multiplex in AIDS may be due to immune complex necrotizing vasculitis, resulting from associated hepatitis B or C infection or cryoglobulinaemia [10,11]. In patients with opportunistic infection and AIDS, extension of CMV cytopathic effects may involve endothelial cells and Schwann cells in the nerve roots, dorsal root ganglia or spinal cord [3].

Clinical features. Distal sensory neuropathy and ATN lead to sensory loss and neuropathic pain in the extremities. Presenting symptoms are usually painful burning sensations in the feet and lower extremities. When due to antiretroviral therapy, patients may complain of a sensation that they are walking on ice. Findings on examination would include a stocking type sensory loss of pin prick, temperature and touch sensation and loss of ankle reflexes. Patients may develop a progressive weakness in the distal muscle groups in limbs [3–5]. Two-thirds of patients with AIDS may have electrophysiological studies showing some evidence of peripheral nerve disease. Progressive, relapsing inflammatory neuropathy, mononeuritis multiplex and CMV-related neuronal damage give rise to sensorimotor neuropathies. Xerosis is common in HIV infection, occurring in around 20% of seropositive patients. This may be related to a decrease in immunoreactive substance P and CGRP fibres occurring around the tubules of the eccrine sweat glands [12].

Treatment. In the acute stage of demyelination, plasma exchange or intravenous immunoglobulins may have been tried with variable success. Gabapentin [13], carbamazepine [14], tricyclic antidepressants or analgesics may be effective for dysaesthesia [3–5].

A multicentre, placebo-controlled, randomized trial has been carried out using recombinant human NGF, which is trophic for small sensory neurones and stimulates the regeneration of damaged nerve fibres [15,16]. The treatment was shown to be efficacious in reduction of neuropathic pain and increase in pin prick sensitivity. Side effects of treatment included pain at the site of injection and transient myalgic pain.

References

1 Hughes RAC. Peripheral neuropathy: regular review. *BMJ* 2002; **324**: 466–9.
2 Lauria G, Lombardi R. Skin biopsy: a new tool for diagnosing peripheral neuropathy. *BMJ* 2007; **334**: 1159–62.
3 Pardo CA, McArthur JC, Griffin JW. HIV neuropathy: insights in the pathology of HIV peripheral nerve disease. *J Peripher Nerv Syst* 2001; **6**: 21–7.
4 Dalakas MC, Cupler EJ. Neuropathies in HIV infection. *Baillières Clin Neurol* 1996; **5**: 199–218.
5 Fuller GN, Jacobs JM, Guiloff RJ. Nature and incidence of peripheral nerve syndromes in HIV infection. *J Neurol Neurosurg Psychiatry* 1993; **56**: 372–81.
6 Said G, Goulon-Goeau C, Lacroix C *et al.* Inflammatory lesions of the peripheral nerve in a patient with human T-lymphocyte virus type 1-associated myelopathy. *Ann Neurol* 1988; **24**: 275–7.
7 Vital C, Vital A, Lagueny A *et al.* Chronic inflammatory demyelinating polyneuropathy: immunopathological and ultrastructural study of peripheral nerve biopsy in 42 cases. *Ultrastruct Pathol* 2000; **24**: 363–9.
8 Cherry CL, McArthur JC, Hoy JF, Wesselingh SL. Nucleoside analogues and neuropathy in the era of HAART. *J Clin Virol* 2003; **26**: 195–207.
9 Polydefkis M, Yiannoutsos CT, Cohen BA *et al.* Reduced intraepidermal nerve fiber density in HIV-associated sensory neuropathy. *Neurology* 2001; **57**: 1313–6.
10 Stricker RB, Sanders KA, Owen WF *et al.* Mononeuritis multiplex associated with cryoglobulinemia in HIV infection. *Neurology* 1992; **42**: 2103–5.
11 Cacoub P, Renou C, Rosenthal E *et al.* Extrahepatic manifestations associated with hepatitis C virus infection. A prospective multicenter study of 321 patients. *Medicine (Baltimore)* 2000; **79**: 47–56.
12 Rowe A, Mallon E, Rosenberger P *et al.* Depletion of cutaneous peptidergic innervation in HIV-associated xerosis. *J Invest Dermatol* 1999; **112**: 284–9.
13 La Spina I, Porazzi D, Maggiolo F *et al.* Gabapentin in painful HIV-related neuropathy: a report of 19 patients, preliminary observations. *Eur J Neurol* 2001; **8**: 71–5.
14 Backonja MM. Use of anticonvulsants for treatment of neuropathic pain. *Neurology* 2002; **59** (Suppl. 2): S14–7.
15 McArthur JC, Yiannoutsos C, Simpson DM *et al.* A phase II trial of nerve growth factor for sensory neuropathy associated with HIV infection. AIDS Clinical Trials Group Team 291. *Neurology* 2000; **54**: 1080–8.

16 Schifitto G, Yiannoutsos C, Simpson DM *et al*. Long-term treatment with recombinant nerve growth factor for HIV-associated sensory neuropathy. *Neurology* 2001; **57**: 1313–6.

Trigeminal trophic syndrome

This is an uncommon disorder in which trophic ulceration follows minor, repetitive trauma to anaesthetic skin within the trigeminal area. Neurotrophic changes in the trigeminal area may follow the destruction of fibres conveying pain and temperature sensation [1]. Causes of this disorder include central sensory neuronal damage (post-encephalitic parkinsonism, syringobulbia, posterior fossa tumour or occlusion of the posterior inferior cerebellar artery [2,3], leprous neuritis and brain stem infarcts [4]) or damage to the trigeminal nerve by attempts to relieve intractable trigeminal neuralgia (by surgery or alcohol injections into the gasserian ganglion [5]) or herpes zoster [6] or simplex-related neuritis [7]. Trigeminal trophic syndrome is usually a disease of adults, although recently a case has been described in a 14-year-old child secondary to herpes simplex trigeminal neuritis [8].

Clinical features. The patient complains of paraesthesiae or a sensation of itch on the ala nasi. This is then picked, rubbed or scratched and, because the trauma is painless, the erosion increases in size and may extend to destroy the nasal cartilage [1,9]. The patients freely admit to traumatizing the area in an attempt to relieve the uncomfortable sensation. A clinical similarity to a basal cell carcinoma may be striking, often requiring a biopsy, which in trigeminal trophic syndrome simply shows inflammatory reaction [9] (Fig. 63.11). The pattern of ulceration may be sufficiently bizarre to suggest dermatitis artefacta. The ulcer spreads towards the cheek and the upper lip and, apart from the problems of control of secondary infection, subsequent scar formation in the area of the ala can result in the elevation of the lip resulting in a disfiguring sneer [9]. Characteristically, the alar rim is involved and the tip of the nose spared. Sites less frequently involved include the forehead, scalp and cheeks. Neurological examination should reveal decreased perception of light touch and pain over the area, and sometimes an absent corneal reflex on the same side [9].



Fig. 63.11 Trigeminal trophic syndrome resembling basal cell carcinoma of the right ala nasi.

Treatment. Surgical approaches in the past have included cervical sympathectomy [10], transcutaneous electrical stimulation [11] and grafting or the use of innervated transposition flaps [12], although these can fail if trauma to the area continues. Wearing gloves can be of some help, but the ulceration commonly persists, particularly in the elderly or in confused patients who compulsively pick at the skin. Protection through dressings such as Aquaplast thermoplastic dressing has been shown to promote ulcer healing [13]. Medical treatments which have resulted in improvement have included amitriptyline [5], diazepam [5], chlorpromazine [1] and pimozide, presumably through influencing the paraesthesiae and behavioural factors involved in the syndrome. Carbamazepine was found to be very effective in one reported case [9], although less so in others [1].

References

1 Kavanagh GM, Tidman NJ, McLaren KM *et al*. The trigeminal trophic syndrome: an under-recognised complication. *Clin Exp Dermatol* 1996; **21**: 299–301.
2 Freeman AG. Neurotrophic ulceration of the face with erosion of the ala nasi in vascular disorders of the brain. *Br J Dermatol* 1966; **78**: 322–31.
3 Walton SL, Keczkes K. Trigeminal neurotrophic ulceration—a report of four patients. *Clin Exp Dermatol* 1985; **10**: 485–90.
4 Ferrara G, Argenziano G, Cicarelli G *et al*. Post-apopletic trigeminal trophic syndrome. *J Eur Acad Dermatol Venereol* 2000; **15**: 153–5.
5 Finlay AY. Trigeminal trophic syndrome. *Arch Dermatol* 1979; **115**: 1118.
6 Tada J, Ueda M, Abe Y *et al*. Trigeminal trophic syndrome—a report of three patients. *J Dermatol* 1991; **18**: 613–15.
7 Shea CR, Scott RA, Tompkins SD. Herpetic trigeminal trophic syndrome. Treatment with acyclovir and sublesional triamcinolone. *Arch Dermatol* 1996; **132**: 613–4.
8 Lyon CC, Mughal MZ, Muston HL. Herpetic trigeminal trophic syndrome in an infant. *J R Soc Med* 2001; **94**: 135–7.
9 Bhushan M, Parry EJ, Telfer NR. Trigeminal trophic syndrome: successful treatment with carbamazepine. *Br J Dermatol* 1999; **141**: 758–9.
10 McKenzie KG. Observations on the operative treatment of trigeminal neuralgia. *Can Med Assoc J* 1933; **29**: 492–6.
11 Westerhof W, Bos JD. Trigeminal trophic syndrome: a successful treatment with transcutaneous electrical stimulation. *Br J Dermatol* 1983; **108**: 601–4.
12 Abyholm FE, Eskeland G. Defect of the ala nasi following trigeminal denervation. *Scand J Plast Reconstr Surg* 1977; **11**: 87–8.
13 Preston PW, Orpin SD, Tucker WFG, Zaki I. Successful use of thermoplastic dressing in two cases of the trigeminal trophic syndrome. *Clin Exp Derm* 2006; **31**: 525–7.

Peripheral nerve injury

Lesions of the peripheral nerve may cause permanent denervation with paralysis and disability, and represent a challenging problem in neurosurgery. The slow rate of nerve regeneration conspires together with atrophy and degeneration of the denervated organs

to increase the risk of permanent disability after peripheral nerve injury, emphasizing the importance of rapid and timely intervention [1,2]. Neurotrophic factors are secreted polypeptides that control the survival, differentiation and maintenance of neurones. Sectioning of peripheral nerves results in the almost total loss of immunoreactivity for both low- (p75) and high-affinity (TrkA-like) receptors for NGF [3]. Meissner's and Pacinian corpuscles, after nerve section, lose immunohistochemical antigens such as S100 protein, epithelial membrane antigen and vimentin, strongly suggesting that the structure and integrity of the nerve axis is essential in maintaining some immunohistochemical characteristics of the human sensory corpuscles [4].

Section or severe contusion of a peripheral nerve has been held responsible for a variety of cutaneous changes. Skin manifestations are found in some 20% of patients with the carpal tunnel syndrome [5], and include a reddish discoloration of the fingers with bullae, small foci of necrosis and nail dystrophy [6]. Nail dystrophy and other trophic changes are also sometimes caused by a cervical rib [7]. In one report, injury to the lateral femoral cutaneous nerve during appendicectomy [8] was followed 6 days later by the development of bullae on the outer aspect of the right lower leg, with subsequent ulceration and scarring.

Cooling also affects conduction in peripheral nerves. Loss of sensation in the feet has been reported after prolonged immersion in cold seawater [9]. Areas of skin looking like partial-thickness burns and blistering were found on the feet of 25 out of 160 participants in a barefoot run: a temporary cold-induced neuropathy of the feet had allowed subjects to continue running despite these injuries [10]. Neuropathy may be induced by cryotherapy, and in one series of 183 lesions treated in this way, some subsequent sensory loss was demonstrated in 28%. This was usually mild and transient, although rarely long lasting [11].

References

1 Funakoshi H, Risling M, Carlstedt T *et al.* Targeted expression of a multifunctional chimeric neurotrophin in the lesioned sciatic nerve accelerates regeneration of sensory and motor axons. *Proc Natl Acad Sci USA* 1998; **95**: 5269–74.

2 Ahcan U, Arnez SM, Bajrovic F, Janko M. Contribution of collateral sprouting to the sensory and sudomotor recovery in the human palm after peripheral nerve injury. *Br J Plast Surg* 1998; **51**: 436–43.

3 Lopez SM, Perez-Perez M, Marquez JM *et al.* P75 and TrkA neurotrophin receptors in human skin after spinal cord and peripheral nerve injury, with special reference to sensory corpuscles. *Anat Rec* 1998; **251**: 371–83.

4 Marquez J, Perez-Perez M, Naves FJ, Vega JA. Effect of spinal cord and peripheral nerve injury on human cutaneous sensory corpuscles. An immunohistochemical study. *J Peripher Nerv Syst* 1997; **2**: 49–59.

5 Aratari E, Regesta G, Rebora A. Carpal tunnel syndrome appearing with prominent skin symptoms. *Arch Dermatol* 1984; **120**: 517–9.

6 Pfister PR. Zur Klinik der Haut- und Nagelveränderungen beim Carpal-Tunnel syndrome. *Hautarzt* 1954; **5**: 440–5.

7 Rubin LC, Cipollaro AC. Onychodystrophy caused by cervical rib. *Arch Dermatol* 1939; **39**: 430–3.

8 Wagner W. Skin changes caused by damage of the lateral femoral cutaneous nerve. *Dermatol Wochenschr* 1957; **136**: 971–3.

9 Ungley CC, Channell GD, Richards RL. Immersion foot syndrome. *Br J Surg* 1945; **33**: 17–31.

10 Reichl M. Neuropathy of the feet due to running on cold surfaces. *BMJ* 1987; **294**: 348–9.

11 Faber WR, Naafs B, Smitt JHS. Sensory loss following cryosurgery of skin lesions. *Br J Dermatol* 1987; **117**: 343–7.

Syringomyelia

This is a rare disorder characterized by a longitudinal cyst in the cervical cord and/or medulla (syringobulbia) immediately anterior to the central canal, which spreads, usually asymmetrically, to each side. The majority of lesions occur in association with type 1 Chiari's syndrome where there is a congenital extension of the cerebellar tonsils below the foramen magnum [1]. Other causes include trauma and tumours [1]. MRI scanning of the hindbrain and upper spinal cord is best for delineation of the syrinx [1–3]. An association with other abnormalities, such as a short neck and a low hairline, suggests a developmental origin. Symptoms usually appear in young adults and the disease is generally slowly progressive over 20–30 years, although limited resolution of symptoms has occurred in adults [1] and children [2,3].

Early involvement of pain and temperature fibres, where they cross the midline anteriorly, leads to a characteristic dissociated sensory loss, in which pain and temperature sensation is lost early in the upper limbs, while other sensory modalities carried in the posterior columns (e.g. touch, vibration and position sense) may remain relatively intact. These changes are responsible for the earliest manifestation of the disease, a tendency to sustain painless burns and cuts on the hands and forearms. Later, upper motor neurone signs in the legs may accompany weakness, wasting and loss of reflexes in the arms. Occasionally a combination of progressive pain loss, resultant skin ulceration, loss of soft tissue, resorption of the phalanges and muscular atrophy (Morvan's syndrome) occurs.

Body asymmetry or hemi-hypertrophy is known to occur in syringomyelia and can occur on the head and face. Hypertrophy of the hands and feet, together with hypertrophy of the bones and muscles in the same limb (especially in the upper limbs), has been described with syringomyelia [4].

Many of the skin changes accompanying syringomyelia are the result of repeated burns or other injuries, particularly of the hands, where the skin over the fingers and knuckles may become thickened, swollen, cyanotic and keratotic. Analgesia renders the patient liable to minor injuries, which heal slowly. Gangrene rarely occurs, but damage to, or loss of, terminal phalanges or nails is not uncommon. The French term '*la main succulente*' refers to the swollen and oedematous hands of syringomyelia sufferers. Syringomyelia is responsible for dyshidrosis with hyperhidrosis or hypohidrosis, this being more common than previously recognized, with one series showing dyshidrosis in 60% of patients [5]. The dyshidrosis, usually occurring over the face and upper arms, may be spontaneous or occur reflexly, when the patient consumes hot or highly seasoned food. Its distribution, which can be studied by thermography, correlates with the location of the syrinx and other neurological manifestations [5]. Hyperhidrosis is probably caused by stimulation of the sympathetic preganglionic neurones and, as the disease progresses, hyper-reactivity gradually decreases and is replaced by hypoactivity. This may be important, as focal hyperhidrosis can be regarded as a hallmark of a relatively intact, even though slightly damaged, spinal cord [5]. Asymmetry of scalp hair can also occur in syringomyelia, with the denervated areas having less abundant hair, which grows more slowly [6].

Extension of the syrinx into the medulla may disrupt the vestibular pathways, the descending root of the trigeminal nerve, the sympathetic and taste pathways, and the hypoglossal nerve. The symptoms and signs may then include vertigo with nystagmus, dissociated sensory loss over the face, loss of taste, a wasted tongue, Horner's syndrome and sometimes paralysis of the vocal cords. Facial oedema confined to areas of sensory loss has been described [7].

References

1 Kastrup A, Nägele T, Topka H. Spontaneous resolution of idiopathic syringomyelia. *Neurology* 2001; **57**: 1519–20.
2 Jack CRJ, Kokmen E, Onofrio BM. Spontaneous decompression of syringomyelia: magnetic resonance imaging findings. Case report. *J Neurosurg* 1991; **74**: 283–6.
3 Yeager BA, Lusser MA. Spontaneous resolution of idiopathic syringomyelia: MR features. *J Comput Assist Tomogr* 1992; **16**: 323–4.
4 Sudo K, Owada Y, Yabe I *et al.* Syringomyelia as a cause of body hypertrophy. *Lancet* 1996; **347**: 1593–5.
5 Sudo K, Fujiki N, Tsuji S *et al.* Focal (segmental) dyshidrosis in syringomyelia. *J Neurol Neurosurg Psychiatry* 1999; **67**: 106–8.
6 Soria E, Fine E, Paroski M. Asymmetrical growth of scalp hair in syringomyelia. *Cutis* 1989; **43**: 33–6.
7 McFadden JP, Handfield-Jones SE, Harman RRM. Hemi-facial oedema complicating a case of syringomyelia. *Clin Exp Dermatol* 1988; **13**: 42–5.

Tabes dorsalis

This is still the most common form of neurosyphilis and is the one with the longest incubation period (usually 10–20 years: range 5–50 years), affecting men more often than women. The main symptoms are due to degeneration of the afferent fibres of the dorsal roots. It is characterized by a triad of symptoms (lightning pains, dysuria and ataxia) and a triad of signs (Argyll Robertson pupils, areflexia and loss of proprioceptive sense) [1].

Usually, sensory symptoms precede ataxia by months or years. Lightning pains are the most characteristic early symptom, and occur in 90% of cases at some stage, most often affecting the legs. Pain sensibility is also impaired early, the deep tissues becoming insensitive before the skin does. This may be demonstrated by squeezing the Achilles tendon. Argyll Robertson pupils, miotic pupils that fail to react to direct light, are found in about half of the patients. Originally associated with tabes dorsalis, the sign is now recognized as being common to a number of conditions causing lesions in the area of the nucleus of Edinger–Westphal. Thus, MRI studies have localized lesions to this region in patients with sarcoidosis and multiple sclerosis [2]. With the declining incidence of neurosyphilis, the sign is increasingly likely to indicate another cause, although an assiduous search for syphilis should also be undertaken.

Later features may include ataxia, with a wide-based gait, made worse by the elimination of visual clues, dribbling overflow incontinence, visceral crises, optic atrophy and a painless distortion of the hips, knees or ankles (Charcot's joints).

The commonest trophic change in the skin is a neuropathic ulcer. Symptomatic herpes zoster may occur, as in other conditions affecting dorsal roots.

The clinical features and laboratory findings may be modified by the widespread use of antibiotics and corticosteroids for treating unrelated diseases [3]. This sometimes leads to difficulty in deciding whether tabes dorsalis is active or 'burned-out', with a neurological deficit due to fixed structural damage. Penicillin treatment will arrest the course of the disease, but residual lightning pains, gastric crises and urinary incontinence are likely to persist.

References

1 Simon R. Neurosyphilis. *Arch Neurol* 1985; **42**: 606–13.
2 Dacso CC, Bortz DL. Significance of the Argyll Robertson pupil in clinical medicine. *Am J Med* 1989; **86**: 199–202.
3 Kolar OJ, Burkhart JE. Neurosyphilis. *Br J Vener Dis* 1977; **53**: 221–5.

Spinal dysraphism

Spinal cord development occurs between weeks 2 and 6 of embryonic life. A raphe is a line of junction between symmetrical embryological structures: dysraphism is a failure of this type of fusion [1]. Spinal dysraphism leads to malformations of midline dorsal structures [2]. Defects in the early embryonic stages produce spinal dysraphisms, which can be categorized clinically into two subsets. Open spinal dysraphisms are exposed to the environment (e.g. spina bifida, myelomeningocoele), while closed spinal dysraphisms are covered by intact skin.

A review of 200 published cases of spinal dysraphism [3] included 102 with cutaneous abnormalities, often in combination. A dermatologist may be the first physician to see such patients, and should be aware of possible associations with underlying neurological abnormalities. Spinal sonography is a useful screening method in newborns in the presence of a suggestive cutaneous lesion, while progressive ossification makes spinal ultrasound less relevant after 4 months of age. Indications for referral for ultrasound or MRI have recently been reviewed [4]. While lumbosacral dimples are indications for further investigation, a clinical dilemma relates to cutaneous dimples. Coccygeal dimples may represent a normal variation unrelated to spinal dysraphism and may not need as aggressive an investigation, whereas the presence of lumbosacral dimples is higher risk for underlying problems [4,5].

Patients with giant congenital melanocytic naevi overlying the scalp or dorsal spine can, on MRI, have abnormalities of the leptomeninges, the amygdala, cerebellum and pons [6].

Many skin abnormalities overlying the lumbosacral region have been reported to be associated with spinal dysraphism and cord tethering, including lipomas [7], port-wine stains, haemangiomas [8,9], 'faun tail' (hypertrichosis) [10], pigmented macules and pits or dimples. Because tethered spinal cord is a treatable condition and, if left untreated, can lead to progressive neurological degeneration, spinal MRI scanning of infants with giant melanocytic naevi involving the lumbosacral area is advocated [11,12]. Approximately 20% of patients with large congenital naevi in this region will have associated neurological or developmental abnormalities on MRI scanning [13].

Spina bifida

Several varieties of spina bifida are described, differing in the nature and severity of the spinal defect. In the severe form, a sac



Fig. 63.12 Tuft of hair in association with spina bifida.

protrudes through the vertebral opening and transmits an impulse on crying or coughing. In the least severe cases (spina bifida occulta) there is no such protrusion, but a defect in the vertebral lamina may be felt as a depression, and is sometimes covered by a tuft of hair or a dimple (Fig. 63.12). The likelihood of a mid-line fusion defect is increased when the cutaneous findings are associated with a subcutaneous lesion such as a lipoma [4]. Spina bifida occulta may give rise to no symptoms, and be a chance finding in the course of a routine examination. However, lesions preventing the ascent of the spinal cord, which occurs during normal growth, can lead to undue traction on the lower end of the cord and cauda equina.

The neurological changes will then be those of a chronic lesion of the cauda equina. Such patients may have been slow to learn to walk. Sensation may be impaired over the areas innervated by the lowest sacral segments, leading to a characteristic saddle-shaped area of analgesia over the buttocks and dorsa of the thighs. Trophic changes are conspicuous in some cases, and are rarely lacking altogether. In milder cases, the feet are usually cold and cyanosed: cutaneous injuries are slow to heal and tend to ulcerate, not only on the feet but also in the analgesic skin of the buttocks and thighs. The most severe neurological abnormality is a flaccid paraparesis with sphincter paralysis.

The diagnosis is confirmed by radiography [14], showing defective fusion of the laminae in the affected region, usually the first sacral and fifth lumbar vertebrae. An MRI scan or myelography may be helpful. Estimation of α-fetoprotein in the amniotic fluid or in the maternal serum may successfully identify a fetus with a severe malformation of the CNS such as spina bifida cystica or anencephaly.

Patients with spina bifida are at risk of latex sensitivity [15] due to exposure to latex products, both at the time of surgery and also with indwelling catheters, etc. Such patients should be assessed using latex-specific serum IgE, radioallergosorbent test (RAST), skin prick testing to latex suspension and latex glove usage test [15,16]. Patients allergic to latex may display urticaria, conjunctivitis, angio-oedema, rhinitis and bronchial asthma. They are at risk of anaphylaxis during procedures when healthcare workers are using latex gloves during bladder catheterization and, because of cross-sensitivity to food allergens, can be allergic to fresh foods including kiwi, pear, orange, pineapple, tomato and banana.

The treatment of spina bifida lies in the domain of the paediatrician or neurologist, but the dermatologist may be asked for advice on the trophic ulcers.

Congenital dermal sinuses

These lie close to the midline and may be no more than 1 or 2 mm in diameter [1]. Hairs may protrude from the opening, but these sinuses differ from pilonidal sinuses in that they connect directly to the contents of the spinal canal and so serve as a portal of entry for infection. Probing is therefore unwise. Such sinuses may expand into cysts deeply, and these may press on the spinal cord. The outcome over a 30-year period in a cohort of children with congenital dermal sinuses was reviewed. Cutaneous markers, such as sinus ostea, pigmentation changes, erythema, skin tags and subcutaneous masses, were seen in 15 of 28 cases. Patients over 1 year old at presentation were more likely to have a neurological deficit than younger patients, and delay in diagnosis was identified as a risk factor for developing neurological damage [17].

References

1 Storer JS, Hawk RJ. Cutaneous signs of spinal dysraphism. In: Schachner LA, Hansen RC, eds. *Paediatric Dermatology*, Vol. 1. New York: Churchill Livingstone, 1988: 275–7.

2 Lichtenstein BW. Spinal dysraphism. Spina bifida and myelodysplasia. *Arch Neurosurg Psychiatry* 1940; **44**: 792–809.

3 Tavafoghi V, Ghandchi A, Hambrick GW *et al.* Cutaneous signs of spinal dysraphism. *Arch Dermatol* 1978; **114**: 573–7.

4 Schenk J-P, Herweh C, Günther P *et al*. Imaging of congenital anomalies and variations of the caudal spine and back in neonates and small infants. *Eur J Radiol* 2006; **58**: 3–14.

5 Guggisberg D, Hadj-Rabia S, Viney C *et al*. Skin markers of occult spinal dysraphism in children. *Arch Dermatol* 2004; **140**: 1109–15.

6 Drolet B. Birthmarks to worry about. Cutaneous markers of dysraphism. *Dermatol Clin* 1998; **16**: 447–53.

7 Pierre-Kahn A, Zerah M, Renier D *et al.* Congenital lumbosacral lipomas. *Child Nerv Syst* 1997; **13**: 298–334.

8 Boyvat A, Yazar T, Ekmekci P, Gurgey E. Lumbosacral vascular malformation: a hallmark for occult spinal dysraphism. *Dermatology* 2000; **201**: 374–6.

9 Tubbs RS, Wellons JC, Iskandar BJ, Oakes WJ. Isolated flat capillary midline lumbosacral hemangiomas as indicators of occult spinal dysraphism. *J Neurosurg (Pediatrics 2)* 2004; **100**: 86–9.

10 Laurent I, Leaute-Labreze C, Maleville J, Taieb A. Faun tail and sacral hemangioma associated with occult spinal dysraphism. *Ann Dermatol Venereol* 1998; **125**: 414–6.

11 Foster RD, Williams ML, Barovich AJ *et al.* Giant congenital melanocytic naevi: the significance of neurocutaneous melanosis in neurologically asymptomatic children. *Plast Reconstr Surg* 2001; **107**: 933–41.

12 Dawson HA, Atherton DJ, Mayou B. A prospective study of congenital melanocytic naevi: progress report and evaluation after 6 years. *Br J Dermatol* 1996; **134**: 617–23.

13 Tortori-Donati P, Rossi A, Brancheri R, Cama A. Magnetic resonance imaging of spinal dysraphism. *Top Magn Reson Imaging* 2001; **12**: 375–409.
14 Drugan A, Weissman A, Evans MI. Screening for neural tube defects. *Clin Perinatol* 2001; **28**: 279–87.
15 Mertes PM, Mouton C, Fremont S *et al.* Latex hypersensitivity in spinal cord injured adult patients. *Anaesth Intensive Care* 2001; **29**: 393–9.
16 Bernardini R, Novembre E, Lombardi E *et al.* Risk factors for latex allergy in patients with spina bifida and latex sensitization. *Clin Exp Allergy* 1999; **29**: 681–6.
17 Ackerman LL, Menezes AH. Spinal congenital dermal sinuses: a 30-year experience. *Pediatrics* 2003; **112**: 641–7.

Spinal cord injury

The spinal cord may be injured directly by penetrating wounds or, more frequently, it suffers indirectly as a result of dislocations or fracture dislocations of the vertebral column. Damage may not necessarily be as a result of direct trauma but because of surrounding tissue damage, causing the spinal cord to swell and occupy the entire diameter of the spinal cord at the level of the injury. Causes include motor vehicle accidents (36–48%), violence (5–29%), falls (17–21%) and recreational activities (7–16%) [1]. Conventional radiography on its own should not be depended on to define the damage, and dynamic views in flexion–extension movement may provide additional information; where these are not deemed safe, MRI is necessary [1]. Rare dermatological causes of spinal cord injury have included a neglected basal cell carcinoma on the back [2], an adenocystic carcinoma in overlying skin [3] and multiple myeloma in a man presenting with primary cutaneous plasmacytomas, resulting in spinal cord compression [4].

Seborrhoea and seborrhoeic dermatitis have been reported in quadriplegia patients [5,6]. In one study [6] of 20 patients with spinal injury but no seborrhoeic dermatitis on admission, 13 developed the condition on the face and trunk within a few weeks. Nummular eczema may also occur below the level of the lesion [5]. Twenty-one patients with complete paralysis below levels varying from C5 to T12 were investigated for sebum excretion rate, skin temperature and the presence of acne [7]. An increased incidence of acne was found on the back and buttocks, often occurring for the first time after the onset of paralysis. Sebum excretion on the forehead did not differ from that of normal, but was significantly increased below the neurological lesion. This could not be explained by changes in skin temperature.

The changes in eccrine sweating after spinal cord injuries are complex [8]. Episodes of profuse sweating on the face, neck and upper trunk in patients with lesions at or above T6 may occur as an exaggerated response to stimuli such as bowel or bladder distension (autonomic dysreflexia). Facial flushing and headache may be associated with these episodes. Other patients develop sweating of the face and arms after dizziness due to postural hypotension. Finally, post-traumatic syringomyelia can lead to hyperhidrosis [9]. Dryness of the skin, particularly noticeable on the soles, is an effect of anhidrosis.

Chronic decubitus ulceration can be a problem, and local osteomyelitis rarely leads to secondary amyloidosis. Excellent nursing, prevention of pressure and attention to the patient's general health are essential. There should be frequent review of pressure ulcer prevention and management strategies, and patients should be supplied with aids such as ripple mattresses to help reduce localized pressure. Pressure sore closure is frequently a reconstructive challenge and in itself can be deforming. The use of an inferiorly based vertical rectus abdominis myocutaneous flap for both recalcitrant ischial and trochanteric pressure sores has been shown to be useful [10].

Early decompression and high-dose methylprednisolone may reduce further spinal cord damage following injury. Small gains in neurological regeneration can lead to a disproportionate gain in function, since, for example, fewer than 10% functional long-tract connections are needed to enable good locomotor action. Adequate rehabilitation will prevent many complications and improve outcome [1]. Tendon transfer can improve hand grip and transcutaneous electrical stimulation can help muscles, including the diaphragm, facilitate erection and ejaculation and control pain. Bladder and bowel control may be helped with implantable electrical stimulators or botulinum toxin [11]. Sexual dysfunction can be treated by mechanical (vacuum pumps, penile implants, electrical stimulation) or pharmacological interventions (sildenafil, intracavernosus injection) [1,12], the latter depending on the sparing of either the sacral (S2–S4) or thoraco–lumbar (T10–L2) spinal segments. Exciting new treatment opportunities have emerged through the use of NGFs, creation of neuronal 'bridges' using peripheral nerves and the use of stem cells [1], and future development is likely through collaboration between scientists and clinical specialists [1].

References

1 McDonald JW, Sadowsky C. Spinal cord injury. *Lancet* 2002; **359**: 417–25.
2 Cohen B, Weiss G, Yin H. Basal cell carcinoma (BCC) causing spinal cord compression. *Dermatol Online J* 2000; **6**: 12.
3 Gelabert-Gonzalez M, Febles-Perez C, Martinez-Rumbo R. Spinal cord compression caused by adjacent adenocystic carcinoma of the skin. *Br J Neurosurg* 1999; **13**: 601–3.
4 Lallemand F, Fritsch L, Cywiner-Golenzer C, Rozenbaum W. Multiple myeloma in an HIV-positive man presenting with primary cutaneous plasmascytomas and spinal cord compression. *J Am Acad Dermatol* 1998; **38**: 506–8.
5 Reed WB, Pidgeon J, Becker SW. Patients with spinal cord injury: clinical cutaneous studies. *Arch Dermatol* 1961; **83**: 379–85.
6 Wilson CL, Walshe M. Incidence of seborrhoeic dermatitis in spinal injury patients. *Br J Dermatol* 1988; **119** (Suppl. 33): 48.
7 Thomas SE, Conway J, Ebling FJG *et al.* Measurement of sebum excretion rate and skin temperature above and below the neurological lesion in paraplegic patients. *Br J Dermatol* 1985; **112**: 569–73.
8 Sato K, Kang WH, Saga K *et al.* Biology of sweat glands and their disorders. II. Disorders of sweat gland function. *J Am Acad Dermatol* 1989; **20**: 713–26.
9 Stanworth PA. The significance of hyperhidrosis in patients with posttraumatic syringomyelia. *Paraplegia* 1982; **20**: 282–7.
10 Kierney PC, Cardenas DD, Engrav LH *et al.* Limb-salvage in reconstruction of recalcitrant pressure sores using the inferiorly based rectus abdominis myocutaneous flap. *Plast Reconstr Surg* 1998; **102**: 111–6.
11 Schurch B, Schmid DM, Stohrer M. Treatment of neurogenic incontinence with botulinum toxin A. *N Engl J Med* 2000; **342**: 665.
12 Schmid DM, Schurch B, Hauri D. Sildenafil in the treatment of sexual dysfunction in spinal cord-injured male patients. *Eur Urol* 2000; **38**: 184–93.

Disorders associated with autonomic abnormalities

Hereditary sensory and autonomic neuropathies (HSANs)

The classification of HSAN was modified by Dyck [1] into five main groups of syndromes with common clinical, pathophysiological and genetic phenotypes. The considerable advances made in identifying the specific loci and genes implicated in the different types of HSANs [2] and the resulting mechanisms of disease [3] are reviewed below.

Hereditary sensory and autonomic neuropathy type I (HSAN I)

HSAN type I differs from all other HSANs in that its symptoms appear late, rather than congenitally. It is an autosomal dominant disorder, mapping to chromosome 9q22.1–q22.3 [4,5], and the affected gene has been identified as serine palmitoyltransferase long-chain base subunit-1 (SPTLC1) [2], leading to an impact on enzyme systems critical for sphingolipid synthesis [6]. It is the most common HSAN, resulting in progressive degeneration of sensory dorsal root ganglia, with loss of both small myelinated and unmyelinated nerves leading to a distal sensory and motor loss, particularly in the lower limbs [4,7]. HSAN type I presents in late childhood or adolescence with progressive loss of all modalities of sensation in the lower extremities, particularly pain and temperature. This often results in chronic trophic ulceration on weight-bearing areas of the feet, associated osteomyelitis and mutilating deformity [7,8]. Later manifestations include muscle wasting, weakness and lancinating pain in the lower limbs and extension of sensory symptoms to the upper limbs. Neural deafness is frequent, and congenital cataracts and mental retardation have been reported [7].

Treatment is supportive, with good fitting shoes and alleviation of weight bearing if ulcers form [8].

Hereditary sensory and autonomic neuropathy type II (HSAN II)

HSAN type II is an autosomal recessive disorder with a congenital or early onset, with marked loss of sensory, motor and autonomic motor neurones and marked loss of unmyelinated nerves [1,9–11]. Linkage analysis has identified a locus mapping to 12p13.33 with subsequent isolation of a possible HSN2 gene, although as yet the biological activity of its gene product is not clear [12]. A high urinary excretion of sphingomyelin and lecithin suggest that the primary mechanism may be a disorder of phospholipid metabolism [7].

Infantile hypotonia is common. Unlike HSAN I, which primarily affects the feet, HSAN II results in loss of sensation equally in hands and feet, leading to ulceration at sites such as the forehead, trunk, tongue and lips as a result of repeated injury. Fingers can show ainhum-like constriction bands and spontaneous amputations. Loss of deep sensation results in deep ulceration, osteomyelitis, stress fractures and injury to long bones [9–11]. Tendon reflexes and anhidrosis occur in areas of decreased sensation, although anhidrosis is less prominent than in HSAN IV.

Associated features include mental retardation, neural deafness, impaired taste and smell, retinitis pigmentosa and cataracts.

Hereditary sensory and autonomic neuropathy type III (HSAN III) (familial dysautonomia)

HSAN type III (previously familial dysautonomia; Riley–Day syndrome) is the most common of the sensory and autonomic neuropathies [13–17]. The disorder is transmitted as an autosomal recessive trait, mapping to 9q31–q33 [18–20], involving the gene inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein (IKBKAP) [2], and is prevalent in Ashkenazi Jews, in whom the frequency is 1:10 000. Scattered cases in non-Jewish patients have been reported. Prenatal diagnosis is now possible [19].

Onset is congenital, and hypotonia, sucking difficulties, a poor cry and vomiting are present at birth. Autonomic features are prominent, with impaired production of tears, unstable temperature control, postural hypotension and excessive sweating, especially during infection, all being major features. Impaired oesophageal motility, with resultant pneumonia, together with bouts of apnoea, are causes of death in childhood. Blotchy erythema occurs during overheating, and erythematous macules 2–5 cm in diameter may occur on the trunk and limbs in response to emotional upsets [17].

A diagnosis is sometimes made in infancy because the child cries without producing tears. Other diagnostic criteria include absent fungiform papillae on the tongue, absent tendon and corneal reflexes, lack of axon flare after intradermal histamine, and miosis following instillation of methacholine. Later, the child may show delayed growth and invariably displays postural hypotension. Intelligence remains normal, but emotional lability is common. Progressive abnormalities of cutaneous temperature discrimination and nociception are found in most patients [15]. Mortality rates remain high but have improved with better supportive measures, and 50% of patients now survive to adulthood [21]. Death may follow inhalation during attacks of vomiting, and hypotension and cardiac arrest are risks with a general anaesthetic [22].

Treatment is symptomatic. Attention to feeding must be meticulous and gastrostomy may be required. Diazepam and chlorpromazine can be used to treat acute autonomic crises and intranasal midazolam can be used for patients at home [23].

Hereditary sensory and autonomic neuropathy type IV (HSAN IV)

HSAN type IV probably comprises a heterogeneous group of patients and is transmitted by autosomal dominant inheritance [24]. Defects in the human neurotrophic tyrosine kinase receptor type 1 (*NTRK1*) gene (previously known as *TRKA*) located on chromosome 1 (1q21–q22), which encodes a receptor tyrosine kinase (RTK), have been shown [25]. The action of nerve growth factor on RTK seems to be crucial for the correct development of nociceptive neurones and sweating as a means of thermal regulation [2]. Clinically, the boundary between HSAN II and IV can be difficult to delineate. HSAN IV is an autosomal recessive disorder characterized by recurrent episodic fevers, anhidrosis, absence of reaction to noxious stimuli, self-mutilating behaviour and mental

retardation [24,25]. Infants are hypotonic and areflexic. High fever related to an inability to sweat, especially in the summer, can be associated with seizures [24–26]. Insensitivity to pain with self-inflicted injury results in multiple scars and bone fractures, autoextraction of teeth and ulceration of tongue, lips and buccal mucosa.

The anomalous pain and temperature sensation and anhidrosis in HSAN IV are due to the absence of afferent neurones activated by tissue-damaging stimuli and a loss of innervation of eccrine sweat glands, respectively [27]. These patients have recently been shown to have a decrease in skin nerve fibres positive for PGP 9.5, CGRP, substance P, NPY, nitric oxide and VIP [26,27], and innervation is almost completely absent around eccrine sweat glands [27].

Treatment is limited; oral shields may prevent damage to the oral tissues [28].

Hereditary sensory and autonomic neuropathy type V (HSAN V)

Synonym

- Congenital insensitivity to pain

HSAN type V is a rare, autosomal, recessive, hereditary sensory autonomic neuropathy characterized by insensitivity to pain, self-mutilating behaviour, anhidrosis with recurrent hyperpyrexia and mental retardation [29,30].

This autosomal recessive condition results in a defect in the development of sensory and autonomic peripheral nerves [30]. It has been reported as being caused by mutations of the human *TRKA* (*NTRK1*) gene located on chromosome 1q21–q22, which codes for the receptor for NGF and tyrosine kinase [31–34], although the locus 1;13.1 and the associated gene *NGFB* have also been implicated [2,3]. Nociceptive and sympathetic Aδ-fibre and C-fibre nerve activity is reduced or absent in the skin, S100 protein and neurone-specific enolase are reduced or absent in the vicinity of eccrine sweat glands, and substance P receptors are absent from nerve fibres and the epidermis [35]. This is consistent with the loss of unmyelinated and small myelinated fibres, as seen in sural nerve biopsies [36].

Patients present in early childhood when they start to crawl; they fail to learn the consequences of injury and do not cry with soft-tissue injury. There is associated heat intolerance due to anhidrosis, with episodes of hyperpyrexia. Death from hyperpyrexia has been recorded in up to 10% of patients in the first 3 years of life. Sunburn and frostbite may occur. There is a striking absence of the SSR. Congenital insensitivity to pain with anhidrosis is characterized by multisystem involvement. Skin ulcerations on the fingers and toes are common from self-biting, and neurological examination often reveals complete analgesia, although tactile discrimination, sensation of cold, heat and vibration may be normal. Corneal reflexes are usually present but deep tendon reflexes are abolished. Neonatal hypotonia and psychomotor retardation are common, as are slow healing fractures, joint deformities, osteomyelitis, avascular necrosis and acro-osteolysis of fingers [37].

References

1 Dyck PJ. Neuronal atrophy and degeneration predominantly affecting peripheral sensory and autonomic neurones. In: Dyck PJ, Thomas PK, Griffin JW *et al*., eds. *Peripheral Neuropathy*. Philadelphia: Saunders, 1993: 1065–93.

2 Auer-Grumbach M, Mauko B, Auer-Grumbach P, Pieber TR. Molecular genetics of hereditary sensory neuropathies. *NeuroMol Med* 2006; **8**: 147–58.

3 Verpoorten N, De Jonghe P, Timmerman V. Disease mechanisms in hereditary sensory and autonomic neuropathies. *Neurobiol Dis* 2006; **21**: 247–55.

4 Nicholson GA, Dawkins JL, Blair IP *et al.* The gene for hereditary sensory neuropathy type I (HSN-1) maps to chromosome 9q22.1–q22.3. *Nat Genet* 1996; **13**: 101–4.

5 Dawkins JL, Hulme DJ, Brahmbhatt SB *et al.* Mutations in *SPTLC1*, encoding serine palmitoyltransferase, long chain base subunit-1, cause hereditary sensory neuropathy type I. *Nat Genet* 2001; **27**: 309–12.

6 Bejaoui K, Uchida Y, Yasuda S *et al*. Hereditary sensory neuropathy type 1 mutations confer dominant negative effects on serine palmitoyltransferase, critical for sphingolipid synthesis. *J Clin Invest* 2002; **110**: 1301–8.

7 Axelrod FB. Autonomic and sensory disorders. In: Emory AEH, Rimoin DL, eds. *Principles of Medical Genetics*. Edinburgh: Churchill Livingstone, 1996: 397–411.

8 Berginer V, Baruchin A, Ben-Yakar Y, Mahler D. Plantar ulcers in hereditary sensory neuropathy: a plea for conservative treatment. *Int J Dermatol* 1984; **23**: 664–8.

9 Heckmann JM, Carr JA, Bell N. Hereditary sensory and autonomic neuropathy with cataracts, mental retardation and skin lesions: five cases. *Neurology* 1995; **45**: 1405–8.

10 Bockers M, Benes P, Bork K. Persistent skin ulcers, mutilations and acro-osteolysis in hereditary sensory and autonomic neuropathy with phospholipid excretion. Report of a family. *J Am Acad Dermatol* 1989; **21**: 736–9.

11 Ferriére G, Guzzetta F, Kulakowski S *et al.* Nonprogressive type II hereditary sensory autonomic neuropathy: a homogeneous clinicopathologic entity. *J Child Neurol* 1992; **7**: 364–70.

12 Lafrenière RG, MacDonald MLE, Dubé M-P *et al*. Identification of a novel gene (*HSN2*) causing hereditary sensory and autonomic neuropathy type II through the study of Canadian genetic isolates. *Am J Hum Genet* 2004; **74**: 1064–73.

13 Axelrod FB, Iver K, Fish I *et al.* Progressive density loss in dysautonomia. *Pediatrics* 1981; **67**: 517–22.

14 Brunt PW, McKusick VA. Familial dysautonomia: a report of genetic and clinical studies with a review of the literature. *Medicine (Baltimore)* 1970; **49**: 343–74.

15 Mahloudji M, Brunt PW, McKusick VA. Clinical neurological aspects of familial dysautonomia. *J Neurol Sci* 1970; **11**: 383–95.

16 Riley CM, Day RL, Greeley DM *et al.* Central autonomic dysfunction with defective lacrimation: report of five cases. *Pediatrics* 1949; **3**: 468–78.

17 Fellner MJ. Manifestations of familial autonomic dysautonomia. Report of a case with an analysis of 125 cases in the literature. *Arch Dermatol* 1964; **89**: 190–5.

18 Blumenfeld A, Slaugenhaupt SA, Axelrod FB *et al.* Localization of the gene for familial dysautonomia on chromosome 9 and definition of DNA markers for genetic diagnosis. *Nat Genet* 1993; **4**: 160–4.

19 Eng CM, Slaugenhaupt SA, Blumenfeld A *et al.* Prenatal diagnosis of familial dysautonomia by analysis of linked CA-repeat polymorphisms on chromosome 9q31–q33. *J Med Genet* 1995; **59**: 349–55.

20 Slaugenhaupt SA, Blumenfeld A, Gill SP *et al.* Tissue-specific expression of a splicing mutation in the *IKBKAP* gene causes familial dysautonomia. *Am J Hum Genet* 2001; **68**: 598–605.

21 Axelrod FB, Abularrage JJ. Familial dysautonomia: a prospective study of survival. *J Pediatr* 1982; **101**: 234–6.

22 Meridy HW, Creighton RE. General anaesthesia in eight patients with familial dysautonomia. *Can Anaesth Soc J* 1971; **18**: 563–70.

23 Lahat E, Goldman M, Barr J *et al.* Intranasal midazolam as a treatment of autonomic crisis in patients with familial dysautonomia. *Pediatr Neurol* 2000; **22**: 19–22.

24 Rosemberg S, Marie SKN, Kliemann S. Congenital insensitivity to pain with anhidrosis (hereditary sensory neuropathy type IV). *Pediatr Neurol* 1994; **11**: 50–6.

25 Indo Y. Genetics of congenital insensitivity to pain with anhidrosis (CIPA) or hereditary sensory and autonomic neuropathy type IV. Clinical, biological and

molecular aspects of mutations in *TRKA* (*NTRK1*) gene encoding the receptor tyrosine kinase for nerve growth factor. *Clin Auton Res* 2002; **12** (Suppl. 1): 120–32.
26 Verzé L, Viglietti-Panzica C, Plumari L *et al.* Cutaneous innervation in hereditary sensory and autonomic neuropathy type IV. *Neurology* 2000; **55**: 126–8.
27 Langer J, Goebel HH, Veit S. Eccrine sweat glands are not innervated in hereditary sensory neuropathy type IV. An electron-microscopy study. *Acta Neuropathol (Berl)* 1981; **54**: 199–202.
28 Edem TL, Ozcan I, Ilguy D, Sirin S. Hereditary sensory and autonomic neuropathy: review and case report with dental implications. *J Oral Rehabil* 2000; **27**: 180–3.
29 Sztriha L, Lestringant GG, Hertecant J *et al.* Congenital insensitivity to pain with anhidrosis. *Pediatr Neurol* 2001; **25**: 63–6.
30 Shorer Z, Moses SW, Hershkovitz E *et al.* Neurophysiological studies in congenital insensitivity to pain with anhidrosis. *Pediatr Neurol* 2001; **25**: 397–400.
31 Holden H, King RH, Hashemi-Nejad A *et al.* A novel *TRKA* (*NTRK1*) mutation with hereditary sensory and autonomic neuropathy type V. *Ann Neurol* 2001; **49**: 521–4.
32 Indo Y, Tsuruta M, Hayashida Y *et al.* Mutations in the *TRKA/NGF* receptor gene in patients with congenital insensitivity to pain with anhidrosis. *Nat Genet* 1996; **13**: 485–8.
33 Indo Y, Mardy S, Miura Y *et al.* Congenital insensitivity of pain with anhidrosis (CIPA): novel mutations of the *TRKA* (*NTRK1*) gene, a putative uniparental disomy, and a linkage of the mutant *TRKA* and *PKLR* genes in a family with CIPA and pyruvate kinase deficiency. *Hum Mutat* 2001; **18**: 308–18.
34 Toscano E, della Casa R, Mardy S *et al.* Multisystem involvement in congenital insensitivity to pain with anhidrosis (CIPA), a nerve growth factor receptor (TRK A)-related disorder. *Neuropediatrics* 2000; **31**: 39–41.
35 Misery L, Hermier M, Staniek V *et al.* Congenital insensitivity to pain with anhidrosis: absence of substance P receptors in the skin. *Br J Dermatol* 1999; **140**: 190–1.
36 Nolano M, Crisci C, Santoro L *et al.* Absent innervation of skin and sweat glands in congenital insensitivity to pain with anhidrosis. *Clin Neurophysiol* 2000; **111**: 1596–601.
37 Schulman H, Tsodikow V, Einhorn M *et al.* Congenital insensitivity to pain with anhidrosis (CIPA): the spectrum of radiological findings. *Pediatr Radiol* 2001; **31**: 701–5.

Sympathetic nerve injury [1]

When the sympathetic supply of the skin is interrupted, loss of vasoconstrictor impulses leads to erythema. There is passive vasodilation and the denervated area is anhidrotic. The skin may become noticeably dry with scaliness and fine fissures. The affected area heals only slowly following minor trauma, and some patients complain that it is hyperaesthetic. It has been shown that after sympathetic ganglionectomy there can be dissociation of sudomotor and pilomotor activity [2]. In the denervated areas, there is no loss of cutaneous sensation, and the phenomenon may be due to the regeneration of post-ganglionic cholinergic fibres. In general, the areas of vasodilation correspond to the areas of anhidrosis, suggesting a close correspondence of sudomotor and vasoconstrictor fibres [3]. Measurements of sweating and vasomotor responses can help to determine the extent of autonomic denervation [4].

As discussed earlier in this chapter, when sympathetic denervation is combined with a loss of somatic sensation, as, for instance, in peripheral nerve injury or severe peripheral neuropathy, neurotrophic ulcers may be encountered. These result from local minor trauma and are characteristically painless and slow to heal. Sympathetic denervation may also slow or prevent the normal greying of hair that takes place with increasing age [5,6], and in one case it seemed to cause hyperpigmentation of the skin in the affected area [7].

References
1 Munro PAG. *Sympathectomy. An Anatomical and Physiological Study with Clinical Applications*. Oxford: Oxford University Press, 1959.
2 Brown GE, Adson AW. Physiologic effects of thoracic and of lumbar sympathetic ganglionectomy or section of the trunk. *Arch Neurol Psychiatry* 1929; **22**: 322–57.
3 Silver A, Versaci A, Montagna W. Studies of sweating and sensory function in cases of peripheral nerve injuries of the hand. *J Invest Dermatol* 1963; **40**: 243–58.
4 Longmire DR. An electrophysiological approach to the evaluation of regional sympathetic dysfunction: a proposed classification. *Pain Physician* 2006; **9**: 69–82.
5 Lerner AB. Grey hair and sympathectomy: report of a case. *Arch Dermatol* 1966; **93**: 235–6.
6 Ortonne J-P, Thivolet J, Guillet R. Greying of hair with age and sympathectomy. *Arch Dermatol* 1982; **118**: 876–7.
7 Samuel C, Bird DR, Burton JL. Hyperpigmentation after sympathectomy. *Clin Exp Dermatol* 1980; **5**: 349–50.

Complex regional pain syndrome (CRPS)

Complex regional pain syndrome (CRPS Type I, previously known as reflex sympathetic dystrophy, or Type II, previously known as causalgia) is a heterogeneous group of conditions resulting in neuropathic pain that is characterized by pain and dysfunction of the sympathetic nervous system [1–3]. CRPS is a painful disorder typically involving the distal portion of a limb, represented by spontaneous and evoked pain as well as autonomic, motor and trophic abnormalities. It commonly occurs in the 30–50 age group and women predominate with a ratio of 4:1, with upper limbs being twice as frequently involved as lower limbs; fractures are the most common initiating triggering factor, occurring in nearly half of patients. CRPS I is much more prevalent and typically develops after minor trauma with either no obvious or only a small nerve lesion, while CRPS II is usually associated with an identifiable nerve injury [4]. It has been recommended that the diagnostic criteria include at least one event from each of four groups: (i) a syndrome that develops after a noxious event; (ii) spontaneous pain or allodynia/hyperalgesia not limited to the territory of a single nerve and disproportionate to the initiating stimulus; (iii) past or present oedema, abnormal skin blood flow or sudomotor activity; and (iv) absence of conditions that might otherwise account for pain and dysfunction [1,2].

Aetiology. Complex regional pain syndrome commonly develops after trauma, with at least 50% of cases involving a fracture (most often a Colles' fracture), but it can be induced by sprains, contusion or lacerations. It usually involves a distal limb site. Other antecedent factors have included injury to the central or peripheral nervous system, stroke, myocardial infarction, tuberculosis and certain drugs [1]. Dermatologically associated causes of CRPS are listed in Table 63.3 [1,5–8].

The pathogenesis of CRPS is not well understood, although pathologies in peripheral nerves and abnormalities in the CNS have been described in patients with both CRPS I and II [4]. Hypotheses include release from peripheral unmyelinated fibres of neuropeptides, including substance P, CGRP and neurokinins which cause pain and vasodilation, enhanced α-adrenergic receptor activity, and up-regulation of afferent nocioreceptors in response to norepinephrine release from sympathetic efferents. Other theories suggest excessive inflammation at the site of injury and involvement of the immune system or the CNS [1].

Table 63.3 Dermatologically associated causes of complex regional pain syndrome (CRPS) [1,4–7].

Acrodermatitis continua of Hallopeau
Chronic venous ulceration
Dupuytren's contracture
Epithelioid haemangioendothelioma
Herpes zoster
Human parvovirus B19
Minor surgery (nail, skin biopsy)
Osteogenesis imperfecta
Psoriatic arthritis
Systemic lupus erythematosus
Vasculitis
Weber–Christian panniculitis

Table 63.4 Dermatological manifestations of complex regional pain syndrome (CRPS) [1].

Sudomotor changes and oedema
Erythema and warmth
Pallor or cyanosis
Hypertrichosis or hypotrichosis
Hypohidrosis or hyperhidrosis
Beau's lines or nail notching, leukonychia, onychodystrophy
Factitious ulcers
Bullae

Symptoms. It is common to divide the symptoms of CRPS into three stages [1].

The first stage begins several days or weeks after the injury and lasts about a month. During this first stage, the symptoms are those of spontaneous burning and stinging pain, tearing or shooting pain precipitated by mechanical stimuli such as bathing, clothing resting on the skin or draughts blowing on a limb [2]. The second stage occurs from 1 to 7 months after injury and lasts 3–6 months. The symptoms relate to sympathetic hyperactivity and include cool, oedematous skin, hyperhidrosis and cyanosis or livedo-like changes. Hair may show decreased growth and nails become brittle. Pain is variable and the neuralgia may either spread or decrease.

In the third stage, starting some 8 months after injury, there is progressive tissue damage, which can become permanent. The skin becomes shiny, atrophic and dry and fingertips may diminish in size. When pain is made worse by a variety of stimuli, the patient may protect the limb, leading to trophic changes in bone, muscle and skin (Sudeck's atrophy).

Dermatological manifestations of CRPS are listed in Table 63.4 [1].

Diagnosis. By definition, electrodiagnostic studies (needle electromyography and nerve conduction studies) are normal in CRPS type I, but demonstrate a peripheral nerve lesion in CRPS II [9]. While patchy osteoporosis may be seen on plain radiographs in CRPS I, some patients may have no changes. CT scan or MRI may show signs of atrophy or swelling of soft tissues and changes in bone mineralization. Bone scintigraphy using three-phase bone scans may be of more value in picking up changes early in the disease process. Other tests include: pain relief on α_1-adrenergic blockade with intravenous phentolamine; pain exacerbation on α_2 stimulation by clonidine; and elicitation of severe pain on cold stimulation, induced by evaporation of a drop of acetone or ethyl chloride on the skin. These tests help identify those patients with sympathetically maintained pain (SMP). Despite having similar clinical signs and symptoms, only a proportion of patients with CRPS type I show alleviation of the pain by selective blockage of the sympathetic nervous system or of α-adrenoreceptors. SMP can also be shown in patients with CRPS II, although the mechanism subsequent to trauma with a nerve lesion is unlikely to be identical [4].

Treatment. While many CRPS patients improve spontaneously, for others the syndrome may deteriorate and become devastating. Interdisciplinary pain management techniques should include the use of occupational therapy and physiotherapy to aid active movement and allow graded increase in activity. Early mobilization of 'at risk' extremities or joints, for example the wrist after Colles' fracture or surgery, can be preventative. This can be accomplished by a series of exercises using devices; for example, in the case of Colles' fracture a rubber ball progressing to spring grip strengtheners and mat exercises [2,10]. Desensitization techniques, such as rubbing the skin with silk, then cotton, then towelling, or baths of contrasting temperature, can be particularly useful [2,10].

Drug treatment may include tricyclic antidepressants, or newer antidepressants such as venlafaxine and mirtazapine, especially in the setting of associated depression [2]. Gabapentin [11], lamotrigine and carbamazepine have proved useful, although randomized control trials in CRPS are lacking [2]. Both α- (phentolamine) and β- (propranolol) blockers have been found useful in some patients [1]. A eutectic mixture of local anaesthetics (EMLA) or capsaicin creams have not generally proved beneficial [2,12]. Where inflammation is considered to have an aetiological role, ketoprofen or even a short course of oral steroids may be of help [2]. Interestingly, calcitonin is one of the best-studied drugs in the management of CRPS and produced significant pain relief in almost 60% of patients in a randomized clinical trial [13].

There has been a recent report of resolution of CRPS with thalidomide therapy [14]. Although sympathectomy has been a traditional first line of treatment in CRPS, there is little evidence to support its use, and it does not seem to have a long-term effect [15,16]. Intravenous regional sympathetic blockade using guanethidine [2] or bretylium [2,17], use of a spinal cord stimulator [18] and subcutaneous lidocaine infusions [19] may be helpful.

Psychological interventions, including biofeedback, cognitive-behavioural and relaxation techniques are of crucial importance, although are often overlooked.

References

1 Phelps RG, Wilentz S. Review. Reflex sympathetic dystrophy. *Int J Dermatol* 2000; **39**: 481–6.

2 Harden RN. Complex regional pain syndrome. *Br J Anaesth* 2001; **87**: 99–106.

3 Baron R, Wasner G. Complex regional pain syndrome. *Curr Pain Headache Rep* 2001; **5**: 114–23.

4 Jänig W, Baron R. Complex regional pain syndrome: mystery explained? *Lancet Neurol* 2003; **2**: 687–97.

5 Prager JP, Sete M. An unusual cause of pain after nevus excision: complex regional pain syndrome. *J Am Acad Dermatol* 1997; **37**: 652–3.
6 Ingram GJ, Scher RK, Lally EV. Reflex sympathetic dystrophy following nail biopsy. *J Am Acad Dermatol* 1987; **16**: 253–6.
7 Malane SL, Sau P, Benson M. Epithelioid haemangioendothelioma associated with reflex sympathetic dystrophy. *J Am Acad Dermatol* 1992; **26**: 325–8.
8 Mullins PA. Postsurgical rehabilitation of Dupuytren's disease. *Hand Clin* 1999; **15**: 167–74.
9 Moroz A, Leali A, Lee M, Liu A. Reflex sympathetic dystrophy: a comprehensive review. *Crit Rev Physical Rehab Med* 2002; **14**: 291–306.
10 Rovetta G, Baratto L, Farinelli G, Monteforte P. Three-month follow-up of shoulder–hand syndrome induced by phenobarbital and treated with gabapentin. *Int J Tissue React* 2001; **23**: 39–43.
11 Mellegers MA, Furlan AD, Mailis A. Gabapentin for neuropathic pain: systematic review of controlled and uncontrolled literature. *Clin J Pain* 2001; **17**: 284–95.
12 Hautkappe M, Roizen MF, Toledano A *et al.* Review of the effectiveness of capsaicin for painful cutaneous disorders and neural dysfunction. *Clin J Pain* 1998; **14**: 97–106.
13 Perez RS, Kwakkel G, Zuurmond WW, de Lange JJ. Treatment of reflex sympathetic dystrophy (CRPS type 1): a research synthesis of 21 randomized clinical trials. *J Pain Symptom Manage* 2001; **21**: 511–26.
14 Rajkumar SV, Fonseca R, Witzig TE. Complete resolution of reflex sympathetic dystrophy with thalidomide treatment. *Arch Intern Med* 2001; **161**: 2502–3.
15 Furlan AD, Mailis A, Papagagpion N. Are we paying too high a price for surgical sympathectomy? A systematic literature review of late complications. *J Pain* 2000; **1**: 245–57.
16 Furlan AD, Lui PW, Mailis A. Chemical sympathectomy for neuropathic pain: does it work? Case report and systematic literature review. *Clin J Pain* 2001; **17**: 327–36.
17 Kingery WS. A critical review of controlled clinical trials for peripheral neuropathic pain and pain complex regional pain syndromes. *Pain* 1997; **73**: 123–7.
18 Kemler MA, Barendse GA, van Kleef M, Egbrink MG. Pain relief in complex regional pain syndrome due to spinal cord stimulation does not depend on vasodilation. *Anesthesiology* 2000; **92**: 1653–60.
19 Linchitz RM, Raheb JC. Subcutaneous infusion of lidocaine provides effective pain relief for CRPS patients. *Clin J Pain* 1999; **15**: 67–72.

Horner's syndrome [1]

This follows partial or complete interruption of the sympathetic pathways of the face. It is characterized by ptosis, miosis and anhidrosis.

Aetiology. The fibres responsible for the sympathetic nerve supply to the skin of the face travel from the hypothalamus via the spinal cord, to relay at the level of the first and second thoracic segments in the lateral column of the spinal grey matter. The preganglionic fibres emerge from the cord in the anterior rami of the first and second thoracic spinal nerves, and pass up the cervical sympathetic chain to relay in the superior cervical ganglion. From here, post-ganglionic fibres pass to supply the eye and the skin of a small central area of the face via the internal carotid sympathetic plexus. Other fibres pass along the external carotid artery and its branches to innervate the greater part of the facial skin with vasomotor and sudomotor fibres.

This pathway can be interrupted centrally in the spinal cord; for example, by medullary infarction, syringomyelia, multiple sclerosis or intraspinal tumours. The peripheral fibres can be damaged by an aortic aneurysm, cervical lymphadenopathy, surgery, regional anaesthetic procedures or tumours. Horner's syndrome may follow sympathectomy for the treatment of palmar and axillary hyperhidrosis, and occurs in up to 40% of patients having cervical sympathectomy by conventional open surgery and in up to 8% of those having transthoracic endoscopic sympathectomy [2]. In such cases, there may be resolution of long-standing pompholyx-type hand eczema on the ipsilateral side, suggesting a neurological pathogenesis for endogenous pompholyx in some patients [3,4].

Clinical features. An irritative phase is described, but rarely seen, in which there is transient unilateral hyperhidrosis and vasoconstriction. The paralytic phase is characterized by drooping of the eyelid (ptosis) with narrowing of the palpebral fissure. The pupil is small, but shows normal reflex constriction to light and accommodation, and sweating is absent on the ipsilateral side of the face. There may be slight retraction of the globe of the eye into the orbit (enophthalmos). Cases of bilateral Horner's syndrome are rarely encountered. Sweat glands on the medial and lateral parts of the forehead are innervated separately, with the medial forehead being supplied by nerve fibres from the sympathetic plexus of the internal carotid artery, while the lateral forehead derives its sympathetic nerve supply from the plexus surrounding the external carotid artery [5]. This accounts for the findings in Raeder's syndrome, where damage involving the perivascular plexus of the internal carotid artery leads to anhidrosis medially but not laterally on the forehead [6].

Treatment. This should be directed to the underlying cause; usually, however, this is not amenable to therapy.

References

1 Smith SA. Pupillary function in autonomic failure. In: Bannister R, ed. *Autonomic Failure*, 2nd edn. Oxford: Oxford Medical Publications, 1988: 393–412.
2 Chowdhury MM, Hedges R, Lanigan SW. Unilateral resolution of palmar eczema and hyperhidrosis complicated by Horner's syndrome following ipsilateral endoscopic cervical sympathectomy. *Br J Dermatol* 2000; **143**: 653–4.
3 Chowdhury MM, Hedges R, Lanigan SW. Intact nerve supply for eczema. *Br J Dermatol* 2001; **144**: 1270–1.
4 Möller H. Intact nerve supply for eczema. *Br J Dermatol* 2001; **144**: 1270.
5 Salvesen R. Innervation of sweat glands in the forehead. A study in patients with Horner's syndrome. *Neurol Sci* 2001; **183**: 39–42.
6 Sjaastad O, Elsäs T, Shen JM *et al.* Raeder's syndrome: anhidrosis, headache and a proposal for a new classification. *Funct Neurol* 1994; **9**: 215–34.

Gustatory hyperhidrosis

The autonomic nervous system has a propensity for regrowth [1]. Damage to adjacent preganglionic parasympathetic fibres and post-ganglionic sympathetic fibres may be followed by parasympathetic fibres regrowing into the sympathetic nerves, thereby directly controlling sweat gland function. In the neck, for example, following damage to the sympathetic cervical trunk and the vagus (parasympathetic) at the time of thyroidectomy or after trauma, such reinnervation may result in gustatory hyperhidrosis even after eating bland foods [2]. A similar event may occur on the cheeks or chin following surgery to the parotid or submandibular glands—the so-called auriculotemporal syndrome (Frey's syndrome) [3]. Secretory sweating is now more frequently seen after endoscopic trans-thoracic sympathectomy [4,5]. A recent review of 918 procedures in 458 patients reports a rate of gustatory hyperhidrosis of 1.1% [6].

Treatment. Fortunately, topical preparations such as those containing aluminium chloride hexahydrate often control these

symptoms well, but may themselves produce an irritant dermatitis. Botulinum toxin has been shown to be effective and safe in gustatory sweating [7]. A further option is the use of a 0.5% aqueous solution of glycopyrronium bromide topically, which has been shown to be effective, safe, well tolerated and convenient in diabetes-associated gustatory sweating [8].

References

1 Murray JG, Thompson JW. The occurrence and function of collateral sprouting in the sympathetic nervous system of the cat. *J Physiol* 1957; **135**: 133–62.
2 Cunliffe WJ, Johnson CE. Gustatory hyperhidrosis. A complication of thyroidectomy. *Br J Dermatol* 1967; **79**: 519–26.
3 Bloor K. Post-parotidectomy gustatory sweating. *BMJ* 1958; **ii**: 1295.
4 Cartier B, Cartier P. Thoracoscopic cervicodorsal sympathectomy with diathermy. *Ann Vasc Surg* 1999; **13**: 582–5.
5 Collin J. Compensatory hyperhidrosis after thoracic sympathectomy. *Lancet* 1998; **351**: 1136.
6 Moya J, Ramos R, Morera R *et al*. Thoracic sympathicolysis for primary hyperhidrosis. A review of 918 procedures. *Surg Endosc* 2006; **20**: 598–602.
7 Naumann M. Evidence-based medicine: botulinum toxin in focal hyperhidrosis. *J Neurol* 2001; **248**: 31–3.
8 Urman JD, Bobrove AM. Diabetic gustatory sweating successfully treated with topical glycopyrrolate: report of a case and review of the literature. *Arch Intern Med* 1999; **159**: 877–8.

Chronic skin pain

The diagnosis of dysmorphophobia or dermatological non-disease [1,2] should always be considered when patients present with chronic skin pain, especially when areas important to body image are involved. These include the burning vulva syndrome (vulvodynia) and the burning scrotum syndrome (Chapter 71) as well as orodynia (Chapter 69). However, one should keep an open mind about other entities including notalgia paraesthetica, brachioradial pruritus (BRP) and skin–ache syndrome. Postherpetic neuralgia is discussed earlier in this chapter.

Scalp dysaesthesia

Cutaneous dysaesthesia syndrome is a disorder characterized by chronic cutaneous symptoms without objective findings. Patients complain of burning, stinging or itching, which is often triggered or exacerbated by psychological or physical stress. These symptoms may be manifestations of an underlying psychiatric disorder or may represent a type of chronic pain syndrome. Patients are typically middle-aged or older women who experience debilitating scalp pain and/or pruritus. The sensations of both pain and itch are carried on the same unmyelinated (slow), afferent, group C nerve fibres. Treatment is low-dose antidepressants but it has been noted that patients with only pruritus were less responsive or unresponsive to such therapy [3].

Notalgia paraesthetica

Notalgia paraesthetica was first described in 1934 by Astwazaturow [4]. It is characterized by episodes of itch and skin pain, usually close to the medial border of the scapula, corresponding to the posterior primary rami of the thoracic nerves T2–T6. The condition may be caused by entrapment of the posterior rami of these spinal nerves as they pass through muscle, and may be predisposed to by back injury or back trauma from prolonged sitting [5]. Patients present with localized discomfort or pruritus on the back; the condition runs a chronic course, and is probably more frequent than previously thought. Examination often reveals a speckled or uniform area of pigmentation, which may be associated with lichenification. There may be hypoaesthesia or hyperaesthesia to pin prick, often localized to the centre of the area [6]. Histopathology characteristically shows intraepithelial necrotic keratinocytes with melanin and macrophages in the papillary dermis [7]. One study found increased substance P immunoreactive fibres in the skin [8].

The relationship of this condition to primary localized cutaneous amyloidosis of macular type [6] is unclear; but in most cases amyloid has been found to be absent, although it may have been missed because deposits were sparse [4,9]. Cases with classical features of notalgia paraesthetica have been reported in which macular amyloid was present on skin biopsy [4]. It is well known that prolonged scratching and rubbing can give rise to friction-related amyloid deposits (Chapter 59); the intractable pruritus characteristic of notalgia paraesthetica may thus explain the association with localized cutaneous amyloidosis.

In one study, 70% of patients treated with topical capsaicin and 30% of patients receiving vehicle, reported some degree of improvement, but it was difficult to maintain the double-blind design of the study because of the symptoms produced by capsaicin itself [10]. In a series of three patients, all patients were reported as improved by application of topical EMLA (2.5% lidocaine and 2.5% prilocaine) [6]. A small open study has also found useful results with oral oxcarbazepine 300–600 mg twice daily for a minimum of 6 months in three of five patients, although one patient discontinued early due to side effects [11]. Recently, case reports on two subjects pointed to the possibility of long-lasting relief after only one or two injections with botulinum toxin A [12].

In addition to pharmacological approaches, Wallengren and Sundler [13] explored cutaneous field stimulation (CFS) in patients with a variety of pruritic conditions, using a 0.8-mA current applied locally to the point of maximal itch for 20 min each day for 5 weeks. Some symptom improvement was noted in patients with notalgia paraesthetica and brachioradial pruritus (see below). This was accompanied by structural changes shown by immunostaining of baseline and post-treatment biopsy material for calcitonin gene related peptide and protein gene product 9.5. After treatment a decrease in epidermal nerve fibres was noted, and the appearance of thick bundles of protein gene product immunoreactive nerve fibres just beneath the epidermis was taken potentially to indicate nerve regeneration. The effect did not, however, persist indefinitely after discontinuing CFS, and over time the itch gradually reappeared [13].

Brachioradial pruritus

Brachioradial pruritus (BRP) is a localized itch in a dermatomal distribution, which usually occurs on the lateral aspect of the arm and elbow, or less commonly on the shoulders, neck or upper thorax [14]. It was originally described in patients from Florida, USA, and the Transvaal, South Africa. A strong seasonal variation, with symptoms being worse in summer months, improvement

with photoprotection and the fact that case reports have come mainly from tropical areas, have all been cited as evidence that BRP is a photodermatosis [14–18]. In other cases, cervical root damage (C5–C8) from degenerative arthropathy, cervical rib or spinal tumours may have been important aetiological factors [19]. It is likely that both cervical spine disease and sunlight-induced damage to cutaneous nerve endings are important underlying contributors and triggering factors [17]. Specific staining with neuronal markers has shown brachioradial pruritus to be associated with a reduction in epidermal and dermal nerve fibres, which normalizes during the symptom-free period [20]. Dermal pin prick hyperaesthesia may be present in a cervical nerve distribution [18]. MRI scanning should be performed to define cervical nerve-root compression [21].

Unlike normal itch, which tends to be relieved by scratching, in BRP scratching seems to potentiate the sensation of itch transmitted by the C fibres [14,22]. BRP is often refractory to topical or oral steroids and antihistamines [19]. Reports of response to topical capsaicin have been variable [10,22,23]. Gabapentin may be useful for BRP [24] and its use in a number of chronic skin syndromes has recently been reviewed [25] A small open study suggested a possible long-lasting beneficial effect from the use of deep intramuscular stimulation acupuncture to the para-vertebral muscles in the dermatomal segments of the body affected by the pruritus [26].

Skin-ache syndrome

Bassoe [27] suggested the term 'skin-ache syndrome' for a situation in which patients experience pain of unknown aetiology characterized by cutaneous trigger points, although this is not widely used. Relief of symptoms was reported after injection of lidocaine or surgical removal of the skin trigger point. This is in contrast to fibromyalgia, from which it must be distinguished, and where pain is more refractory.

References

1 Cotterill JA. Dermatological non-disease: a common and potentially fatal disturbance of cutaneous body image. *Br J Dermatol* 1981; **104**: 611–8.
2 Cotterill JA. Clinical features of patients with dermatological non-disease. *Semin Dermatol* 1983; **2**: 203–5.
3 Hoss D, Segal S. Scalp dysesthesia. *Arch Dermatol* 1998; **134**: 327–30.
4 Astwazaturow M. Der paresthetische Neuralgien und eine bezondere Form derselben-Nothalgia paresthetica. *Nervenarzt* 1934; **133**: 88–96.
5 Massey EW, Pleet AB. Notalgia paraesthetica. *Arch Dermatol* 1979; **115**: 982–3.
6 Goulden V, Highet AS, Shamy HK. Notalgia paraesthetica—report of an association with macular amyloidosis. *Clin Exp Dermatol* 1994; **19**: 356–9.
7 Layton AM, Cotterill JA. Notalgia paraesthetica—report of three cases and their treatment. *Clin Exp Dermatol* 1991; **16**: 197–8.
8 Weber PJ, Poullos EG. Notalgia paraesthetica. *J Am Acad Dermatol* 1988; **18**: 25–30.
9 Springall DR, Kranth SS, Kirkham N *et al.* Symptoms of notalgia paraesthetica may be explained by increased dermal innervation. *J Invest Dermatol* 1991; **97**: 555–61.
10 Wallengren J, Klinker M. Successful treatment of notalgia paresthetica with topical capsaicin: vehicle-controlled, double-blind, crossover study. *J Am Acad Dermatol* 1995; **32**: 287–9.
11 Savk E, Bolukbasi O, Akyol A, Karaman G. Open pilot study on oxcarbazepine for the treatment of notalgia paresthetica. *J Am Acad Dermatol* 2001; **45**: 630–2.
12 Weinfeld PK. Successful treatment of notalgia paresthetica with botulinum toxin type A. *Arch Dermatol* 2007; **143**: 980–2.
13 Wallengren J, Sundler F. Cutaneous field stimulation in the treatment of severe itch. *Arch Dermatol* 2001; **137**: 1323–5.
14 Wallengren J. Brachioradial pruritus: a recurrent solar dermopathy. *J Am Acad Dermatol* 1998; **39**: 803–6.
15 Waisman M. Solar pruritus of the elbows (brachioradial summer pruritus). *Arch Dermatol* 1968; **98**: 481–5.
16 Heyl T. Brachioradial pruritus. *Arch Dermatol* 1983; **119**: 115–6.
17 Orton DI, Wakelin SH, George SA. Brachioradial photopruritus—a rare chronic photodermatosis in Europe. *Br J Dermatol* 1996; **135**: 486–7.
18 Fisher DA. Brachioradial pruritus: a recurrent solar dermopathy. *J Am Acad Dermatol* 1999; **41**: 656–7.
19 Kavak A, Dosoglu M. Can a spinal cord tumor cause brachioradial pruritus? *J Am Acad Dermatol* 2002; **46**: 437–40.
20 Wallengren J, Sundler F. Brachioradial pruritus is associated with a reduction in cutaneous innervation that normalizes during the symptom-free remissions. *J Am Acad Dermatol* 2005; **52**: 142–5.
21 Bernhard JD. Brachioradial pruritus: a recurrent solar dermopathy. *J Am Acad Dermatol* 1999; **41**: 658.
22 Goodless DR, Eaglstein WH. Brachioradial pruritus: treatment with capsaicin. *J Am Acad Dermatol* 1993; **29**: 783–4.
23 Wallengren J. Brachioradial pruritus: a recurrent solar dermopathy. *J Am Acad Dermatol* 1999; **41**: 657–8.
24 Bueller HA, Bernhard JD, Dubroff LM. Gabapentin treatment for brachioradial pruritus. *J Eur Acad Dermatol Venereol* 1999; **13**: 227–8.
25 Scheinfeld N. The role of gabapentin in treating diseases with cutaneous manifestations and pain. *Int J Dermatol* 2003; **42**: 491–5.
26 Stellon A. Neurogenic pruritus: an unrecognized problem? A retrospective case series of treatment by acupuncture. *Acupuncture Med* 2002; **20**: 186–90.
27 Bassoe C-F. Skinache syndrome. *J R Soc Med* 1995; **88**: 565–9.

Restless legs syndrome (RLS)

RLS is a common sleep and movement disorder. A large population based study in over 15 000 subjects estimated 7.2% to have had RLS symptoms during the preceding year: in 5.0% this was at least weekly and 2.7% reported moderately or severely distressing RLS symptoms at least two times per week [1]. RLS is a clinically pleomorphic syndrome, probably reflecting multiple genetic and acquired factors. A significant linkage was established to chromosome 12q [2], and it has long been felt that it represented a subclinical sensory neuropathy [3]. Others have related it to a dopamine imbalance, due to the presence of dyskinetic movements and response to levodopa [4]. Studies of the basal ganglia using positron emission tomography (PET) scanning techniques have shown a decreased binding of dopamine to its receptor [1]. More recently, involvement of the endogenous opioid system has been implicated in the pathogenesis of RLS [5]. Up to 30% of patients have iron deficiency, with consequent reduced levels in brain tissue and cerebrospinal fluid [1]. RLS is a common disorder in haemodialysis patients [6] and associations have also been noted with pregnancy, fibromyalgia, rheumatoid arthritis and multiple sclerosis [5].

Clinical features. Two subtypes are recognized. The first, with an early onset, accounts for some 25% of cases, is more commonly familial and is associated with a history of 'growing pains' in childhood [7]. Those with a late onset (idiopathic RLS) have less painful paraesthesiae or dysaesthesiase, insomnia and lack a family history of the condition. RLS is characterized by leg paraesthesiae, associated with an irresistible urge, occurring at rest, to move the

legs, which is relieved by movement [3,8,9]. These symptoms are worse at night, with both circadian rhythms and recumbency being shown to play a role [5], and often lead to disruption of life and chronic sleep deprivation. Children may struggle at school and present with symptoms of attention deficit hyperactivity disorder [5]. Sensory symptoms include painful legs and arms, and pain at 'internal' sites. Many patients will have a previous diagnosis of a musculoskeletal disorder, such as joint and back pains, and there is a significant association with depression and other neuropsychiatric symptoms [7,8]. Headache on awakening and daytime headache occurs frequently, while in men, hypertension and heart problems have been reported [9].

Treatment. Some believe the first choice of treatment for RLS should be dopaminergic agents such as levodopa [3] or the longer-acting cabergoline [3]. However, a recent evidence-based review including newer treatment options suggested a greater rate of augmentation with levodopa compared to other dopaminergics. Non-ergot dopaminergic derivatives, such as pramipexole, ropinirole or rotigotine, were preferable to ergot derivatives with their risk of heart or lung fibrosis [10], for patients where side effects such as nausea and daytime somnolence could be tolerated [11]. In recent randomized, double-blind studies of gabapentin, significant improvement occurred in both idiopathic RLS [12] and haemodialysis patients [6]. Other second-line options suggested included opioids such as oxycodone, codeine and methadone, and benzodiazepines such as clonazepam or diazepam [5]. Ferrous sulphate, which had been felt to be effective as an empirical treatment, was not shown to have an effect in a randomized, double-blind, placebo-controlled trial [13]. It penetrates the blood–brain barrier poorly and is not suitable as monotherapy. It should only be given in the presence of relative iron deficiency (serum ferritin <50 ug/L) [5].

Burning feet syndrome (BFS)

BFS is a poorly recognized and often underdiagnosed condition [14,15]. It may occur as a result of diabetic neuropathy, but in most cases it is idiopathic. Families with an autosomal dominant inheritance for BFS have been described [16]. A kindred of 21 patients with familial BFS has been described; BFS was often associated with minor foot abnormalities such as high arches or reduced toe fanning [16]. Loss of small fibre sensory nerves has been found both in type 2 diabetics [14] and idiopathic cases. Tests on the autonomic system have shown predominantly cholinergic defects, unlike other autonomic neuropathies. There is a close correlation between quantitative abnormalities in the sudomotor axon reflex test and the loss of small nerve fibres in the skin [14].

Clinical features. The main clinical features are of a burning sensation on the feet with accentuation by heat or cold. Other autonomic associated features may include dry skin, eyes and mouth, vasomotor symptoms with peripheral coldness, burning or flushing, hypertension and impotence. Orthostatic hypotension does not appear to be an association [14,15].

Treatment. Treatment options for BFS appear less defined than for RLS, but treatments efficacious for the latter would probably also help in the BFS.

References

1 Allen RP, Walters AS, Montplaisir J *et al*. Restless legs syndrome prevalence and impact: REST general population study. *Arch Intern Med* 2005; **165**: 1286–92.
2 Desautels A, Turecki G, Montplaisir J *et al*. Identification of a major susceptibility locus for restless legs syndrome on chromosome 12q. *Am J Hum Genet* 2001; **69**: 1266–70.
3 Polydefkis M, Allen RP, Hauer P *et al*. Subclinical sensory neruopathy in late-onset restless legs syndrome. *Neurology* 2000; **55**: 1115–21.
4 Stiasny K. Clinical data on restless legs syndrome: a dose-finding study with cabergoline. *Eur Neurol* 2001; **46** (Suppl. S1): 24–6.
5 Walters AS. Restless legs syndrome and periodic limb movements in sleep. *Continuum Lifelong Learning Neurol* 2007; **13**: 115–38.
6 Thorp ML, Morris CD, Bagby SP. A crossover study of gabapentin in treatment of restless legs syndrome among haemodialysis patients. *Am J Kidney Dis* 2001; **38**: 104–8.
7 Allen RP, Earley CJ. Restless legs syndrome: a review of clinical and pathophysiological features. *J Clin Neurophysiol* 2001; **18**: 128–47.
8 Bassetti CL, Mauerhofer D, Gugger M *et al*. Restless legs syndrome: a clinical study of 55 patients. *Eur Neurol* 2001; **45**: 67–74.
9 Ulfberg J, Nystrom B, Carter N, Edling C. Prevalence of restless legs syndrome among men aged 18–64 years: an association with somatic disease and neuropsychiatric symptoms. *Mov Disord* 2001; **16**: 1159–63.
10 Montagna P. The treatment of restless legs syndrome. *Neurol Sci* 2007; **28**: S61–6.
11 Weimerskirch PR, Ernst ME. Newer dopamine agonists in the treatment of restless legs syndrome. *Ann Pharmacother* 2001; **35**: 627–30.
12 Garcia-Borreguero D, Larrosa O, de la Llave Y *et al*. Treatment of restless legs syndrome with gabapentin: a double-blind cross-over study. *Neurology* 2002; **59**: 1573–9.
13 Davis BJ, Rajput A, Rajput ML *et al*. A randomized, double-blind placebo-controlled trial of iron in restless legs syndrome. *Eur Neurol* 2000; **43**: 70–5.
14 Holland NR, Crawford TO, Hauer P *et al*. Small-fibre sensory neuropathies: clinical course and neuropathology of idiopathic cases. *Ann Neurol* 1998; **44**: 47–59.
15 Novak V, Freimer ML, Kissel JT *et al*. Autonomic impairment in painful neuropathy. *Neurology* 2001; **56**: 861–8.
16 Kuhlenbaumer G, Young P, Kiefer R *et al*. A second family with autosomal dominant burning feet syndrome. *Ann NY Acad Sci* 1999; **883**: 445–8.

CHAPTER 64
Psychocutaneous Disorders

L.G. Millard[1] *& J. Millard*[2]

[1]Rotherham District Hospitals Trust, Rotherham, UK
[2]The Becklin Centre, Leeds, UK

The psychological and symbolic importance of skin, 64.1
Psychodermatology, 64.2
Psychosomatics, 64.4
Self-esteem, 64.5
Stigma, 64.6
Psychoneuroimmunology, 64.8
Disability and quality of life, 64.10
Classification, 64.11
Disorders of dermatological beliefs, 64.12
Delusions of parasitosis, 64.13
Olfactory delusions, 64.16
Morgellons syndrome, 64.17
Disorders of body awareness, 64.17
Body dysmorphic disorder, 64.17
Anorexia nervosa and bulimia, 64.21
Psychogenic pruritus, 64.23
Cutaneous phobias, 64.24
Dirt, infection and wart phobias, 64.24
Molephobia and cancerphobia, 64.24
Topical steroid phobia, 64.25
Group and mass population reactions, 64.25
Sick building syndrome and building-related illness, 64.26
Harmful cutaneous habits, 64.26
Lichen simplex and neurodermatitis, 64.27
Pathological skin picking, 64.27
Acne excoriée, 64.29
Trichotillomania, 64.30
Trichobezoar and the Rapunzel syndrome, 64.31
Onychotillomania and onychophagia, 64.33
Psychogenic purpuras and painful bruising syndrome, 64.33
Factitious skin disease, 64.34
Dermatitis factitia, 64.35
Dermatological pathomimicry, 64.42
Dermatitis simulata, 64.42
Dermatitis passivata, 64.43
Malingering, 64.43
Pseudologica fantastica and Münchausen's syndrome, 64.44
Fabricated and induced illness (Münchausen's syndrome by proxy), 64.44
Medicolegal issues in suspected factitious dermatitis, 64.45
Self-mutilation, 64.45
Cutaneous disease and alcohol misuse, 64.46
Depression in dermatological patients, 64.47
Suicide in dermatological patients, 64.48
Isotretinoin and mood changes, 64.49
Psychiatric treatments, 64.49
Drug treatments, 64.50
Psychological therapies, 64.52
Alternative therapies, 64.54

The psychological and symbolic importance of skin [1,2]

We call our emotions our feelings. The metaphors of everyday language emphasize the ingrained influence that touch [3,4] has in our experience and psyche. We talk about 'getting in touch', our feelings are 'hurt', we are 'touched' when an unexpected kindness is given, we 'handle' a problem 'with kid gloves'. Madness is described as being 'touched'. *Noli me tangere* translates literally as 'don't touch me', but it is legal Latin, meaning 'do not interfere' and, significantly, was the original term for ulcerated cutaneous lupus vulgaris.

The significance of the skin as a substance, as a vehicle and in descriptive language gives it a unique position in human life. Beliefs, true or erroneous, attitudes and responses are commonly based upon mythological and cultural values which have persisted despite the rise of science and reason. This unique position has emphasized the inviolability of the skin, the need to remain whole and to guarantee this by maintaining it in a smooth and immaculate state. The flayed or abstracted skin was the bearer of special powers; Hercules dressing in the hide of the slain lion to assume the mantle of peerless courage or the Aztecs honouring the spirit of vanquished enemies by wearing their inverted flayed skin. The ancient Greeks, the Syrians and later, medieval anatomists regarded the skin as a dried form of the excrescence of impurities and as such an indicator of inner impurities, both physical and sinful. The use of the term complexion changed from being an indicator of the interaction of the four humours (blood, phlegm, black and yellow bile), to that signifying colour, texture and condition of the skin but retaining the meanings and relationship to dirt and sin. This concept of the 'complexion' related to all of an individual's body and character until the mid 16th century when the skin came to be taken as the most direct and readable indicator of a person's physical and emotional state. The secretions of the pores, the colour, and texture of skin were signifiers of disease of the body and by implication of the moral and virtuous standing of an individual. The aesthetic immaculateness of the 18th century, with smooth white complexion of the ladies, pure neo-classical sculpture and portraiture, was in direct contrast to the rotting, eruptive, crusty skin of syphilis, plague and smallpox. The skin would be the first sign of contagion and usually eventual death, and thus the simplistic belief that a clear skin would ward off the dangers was paramount, particularly to the ruling classes. This thinking continues in cosmetic advertising where the culture

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

of skincare [5] means not only an indication of health and vigour but particularly sexual attractiveness, the largely unspoken issue in most dermatological consultations.

Closely allied to the visual disgust of rashes is the fear of those who itch. Intrinsic to our responses is the reaction to scratch when we see others itch and indeed to scratch ourselves when we read or think about itch. Again the implication is of contagion and transferable disease, not only mites but also worms and in the case of those with delusions (see below) the unique products of their own distorted imagination. To scratch brings distress and pain and in psychoanalytic terms the guilt and pleasure of self touching.

Touch is the oldest sense because it is the first sensation of the newborn [6]. It is their introduction to the world and continues to be essential for development, both physically and emotionally. The nocioceptors are capable of recognizing an enormous variety of sensations through a combination of responses to produce sensations as diverse as intense pain, erotic pleasure or the minute differentiations of texture and structure. Massaged babies gain weight appreciably quicker than non-massaged ones. In some cultures it is the norm for any family member, not necessarily solely the mother, to take turns massaging the newborn and infant. Emotionally deprived children are more likely to suffer psychosocial dwarfism with lack of growth, delayed milestones and emotional blunting. Furthermore, a beneficial change in social circumstances alone produced an acceleration of growth if applied soon enough. Deprivation of social touch affects the bonding process between individuals. Distorted sensation, either because of sensory loss or disease of the skin, may significantly affect the intended response in both toucher and touched. The diseased child has a relative sensory deprivation if, for example, they are enclosed in a curasse of ichthyosis. The family may feel a reluctance and repulsion to touch a child who feels unpleasant as well as being physically changed. The maturing child with widespread skin disease develops an awareness of stigmatization and a disinclination to be invited into peer group contact play. Emotional stunting and isolation can be a permanent consequence unless this is recognized and active interventions initiated.

For young and old adults alike the violation of tactile memories by disease may impair the continuation of relationships within family, the forging of new alliances especially sexual, and the corruption of tactile skills in work or leisure. There is a human need for touch and to be touched, to feel safe and supported and the unwelcome touch of a person with visible skin disease is treated as a boundary violation by the touched and as personal rejection by the diseased. Professional touchers are given permission to engage in an intimacy reserved usually for only those close to a patient. This 'laying on of hands' is not confined to the qualified doctor or nurse but equally to any healer, legitimate or not. The success of alternative medicine practitioners such as aromatherapists, reflexologists or shiatsu massage may, in part, be due to the element of touch rather than any other elaborate quasi scientific explanations. Reduction in experimental stress-induced blood cortisol levels was found to be greater in those who had forms of relaxation massage than a control group who were not touched.

Disfigurement has always been associated with rejection of the afflicted, guilt and stigma. Guilt for a birthmark has been traditionally visited upon the mother for some misdemeanour that is implied by others or ruminated upon by the woman herself. Positively assuaging this reaction should be standard advice for all families who seek the reasons for the imperfections, not only in scientific terms but also to dispel these arcane beliefs. It may seem paradoxical that the decorated body with tattoos and piercings, which are in themselves violations of the body, should continue to flourish [7]. They are regarded as marks of enhancement and tokens of bonding in groups, and only rarely as forms of concealment, for example over a birthmark, or as self-mutilation, for example found particularly in those with hundreds of metal piercings.

It is impossible to manage a patient's distress about skin disease without in some part addressing the metaphors and myths surrounding it. These myths remain a part of every culture, no matter how ancient their origins, but need demystifying to manage the disease which is neither curse, nor punishment but usually treatable [8].

References

1 Connor S. *The Book of Skin*. London: Reaktion Books, 2004.
2 Benthien C. *Skin*. New York: Columbia University, 1999.
3 Miller WI. *The Anatomy of Disgust*. Cambridge, MA: Harvard University, 1998: 39–66.
4 Montagu A. *Touching The Human Significance of Skin*, 2nd edn. New York: Harper & Row, 1978.
5 Wolf N. *The Beauty Myth*. London: Vintage, 1990.
6 Autton N. *Touch: An Exploration*. London: Darton & Longman, 1989.
7 Caplan J, ed. *Written on the Body. The Tattoo in European and American History*. London: Reaktion, 2000.
8 Sontag S. *Illness as Metaphor and AIDS and its Metaphors*. New York: Picador, 1988.

Psychodermatology

Psychodermatology covers all aspects of how the mind and body interact in relation to the onset, form and progression of skin disease. The subject is best regarded as a global term, used to encompass the wide and diverse relationships that have been recognized to exist between the two disciplines, psychology and dermatology.

Historically, clinicians [1,2] have noted the apparent influence of the emotions on skin disease. Eminent dermatologists of the past have related clinical associations of the nervous system with dermatological disease but it is important to realize that what were described as dermatological neuroses was to define some dysfunction of the nervous system which subserves those affections of sense and emotion, some of which are prominent symptoms in skin disease. Thus, for example, Erasmus Wilson [2] ascribed leukoderma to a physical weakening of the innervation of the skin. To quote Hunter and Macalpine [3,4], 'The term neurosis retained its essential meaning of a disordered nerve function without a structural pathology until, 100 years later, the prefix "psycho" was added for nervous disease caused psychologically'.

This is not to undermine the observations that rosacea, urticaria or eczema were sometimes the result of 'affections of the nervous system as mental emotions especially of the depressive kind'. The diagnostic problem for dermatologists was clear since mental

illness was mainly classified as the major organic and functional psychosis. There are pertinent, if cautious, references to the influence of melancholia and depression but not the psychoneuroses until late in the 19th century. Hebra [5] (1866) was sceptical of a relationship saying that 'I have neither seen myself or read nor heard from physicians who have charge of lunatics that cutaneous affections are particularly common in such cases'.

When Brocq described localized and disseminated neurodermatitis he also proposed a deep disorder he called nervosism. Later, in association with Besnier and Jacquet [6] they referred to the neurasthenia of eczema more as a result of the distress of the disease than as a significant cause. By this time (1901) they were still of the belief that 'particularities of a nervous pathological state that would make eczema more likely must be taken into account'.

This time was a significant one for medicine with the twin rise of scientific medicine and an excitement of observable physiological, microbiological and pathological knowledge. The emergence of the concepts of neurasthenia and hysteria, and redefinitions of psychiatric illness were hampered by a lack of objective scientific evidence and charges of quackery based on the disreputable practitioners such as Mesmer and his followers. In psychiatry, there were two significant developments relevant to assessment of illness in general. Firstly, the concepts of psychosomatic medicine and, secondly, the development of psychoanalysis.

The term psychosomatic disorder refers to a physical condition caused or aggravated by psychological factors. At this time, medicine was passing through a descriptive era where morbid pathology had identified changes in organs and tissues and which were recorded in great detail. Unfortunately, certain long-term diseases defied resolution by these methods and alternative explanations based on early psychosomatic research influenced medical thinking.

Clinicians who suggested that they had no doubt that in some cases the patient's mind operates through the endocrine system and in others via the vasomotor system were denounced as unscientific and discreditable [7]. Dunbar [8] (1954) catalogued the psychosomatic dermatology research during the first 50 years of the 20th century from 1910 to 1953, during which it became clearer that the contribution of the understanding of 'functional diseases' of the World Wars in particular could be extended to understanding the effects of stress and deprivation in specific disease states of organ systems such as the skin.

At this time, controlled studies from psychiatrists and psychoanalytically trained researchers attempted to apply some stringency to a field fraught with difficulties [9,10]. Psychophysiological measurements of parameters in certain skin disorders continued to establish the credibility of psychosomatic relationships in skin disease [11], but the history of development has been phasic, marked by advances punctuated by lulls in activity. Dermatology moves from its original exemplary, clinical expertise with limited aetiological understanding into new scientific clarity where disease complexity is more understandable. At these times the alleged role of psychogenesis in disease is undervalued and there is a contemporary dismissal of skin–psyche relationships. This was not helped by an apparent failure of psychological therapies in psychosomatic dermatoses. Whitlock wrote that 'it is worth noting that improved biochemical and immunological understanding does not rule out contributory psychological factors whose importance will vary from time to time and case to case' [11]. This astute observation ushered in further developments for psychodermatology.

The term 'psychoimmunology' was introduced in 1964 by Solomon and Moses [12], but the real expansion of psychoneuroimmunology did not begin until the demonstration of behaviourally conditioned immunosuppression in 1975 by Adler and Cohen [13]. For further consideration of psychoneuroimmunology, see below.

It is encouraging that the development of a multidisciplinary approach to psychodermatology continues to validate the relationships between skin disease and psychological mechanisms.

References

1 Cullen W. *First Lines on the Practice of Physic*, 4th edn, Vol. 2. Edinburgh: Bell and Bradfute, 1774: 133–5.
2 Wilson E. *Lectures on Dermatology*, Vol. 1. London: J&A Churchill, 1871: 106–13.
3 Hunter R, Macalpine I. *Three Hundred Years of Psychiatry 1535–1860*. London: Oxford University Press, 1963.
4 McKenna RMB, Macalpine I. Applications of psychology to dermatology. *Lancet* 1951; **i**: 65–8.
5 Hebra F. *On Diseases of the Skin*. London: New Sydenham Society, 1866.
6 Brocq L, Jacquet L. Notes pour servir a l'histoire les neurodermatites. *Ann Dermatol Syphil* 1891; **97**: 193–9.
7 O'Donovan WJ. *Dermatological Neuroses*. London: Keegan Paul, 1927: 7–9.
8 Dunbar HF. *Emotions and Bodily Change*. New York: Columbia University, 1954.
9 Macalpine A. A critical evaluation of psychosomatic medicine in relation to dermatology. In: McKenna RMB, ed. *Modern Trends in Dermatology*, series 2. London: Butterworth, 1954: 18–25.
10 Hamilton M. *Psychosomatics*. London: Chapman and Hall, 1954: 136–71.
11 Whitlock FA. *Psychophysiological Aspects of Skin Disease*. London: W.B. Saunders, 1976.
12 Solomon GF, Moses RH. Emotions, immunity and disease. *Arch Gen Psychiatry* 1964; **11**: 657–74.
13 Adler R, Cohen N. Behaviourly conditioned immunosuppression. *Psychosom Med* 1975; **37**: 333–40.

Skin–psyche interactions

An essential component of dermatological illness is the relationship that somatic dermatology has to psychological status of the sufferer at the time. The influence that these psychological, psychosocial and sometimes psychiatric factors play can be conveniently assessed as:

1 Multifactorial dermatological disorders which can be substantially influenced by psychological factors, e.g. psoriasis
2 Dermatological disorders as a result of psychiatric illness, e.g. factitious dermatoses, body dysmorphic disorder
3 Psychiatric illness developing as a result of skin disease, e.g. depression, adjustment disorder
4 Co-morbidity with another psychiatric disorder, e.g. alcoholism.

In large centres, this work can be refined and developed in specific clinics for psychosomatic dermatology [1]. Ideally, liaison psychiatry should be available together with help from clinical psychologists and social workers [2]. Research and dissemination of further knowledge in psychosomatic dermatology is supported in Europe by the European Society for Investigative

Dermatology and Psychiatry (ESDaP) and in North America by the Association for Psychodermatological Medicine of North America (APMNA).

The dermatological consultation is substantially different from the psychiatric one. However, for those who feel intimidated, the consultation process and descriptive psychopathology of psychological medicine is well described for non-psychiatrists [3,4].

References

1 Schneider G, Geiler U. Psychosomatic dermatology—state of the art. *Z Psychosom Med Psychother* 2001; **47**: 307–31.

2 Fritzche K, Ott J, Augusti M. Psychosomatic liaison service. *Dermatology* 2002; **203**: 27–31.

3 Neighbour R. *The Inner Consultation*. Lancaster: MTP Press, 1989.

4 Sims A. *Symptoms in the Mind. An Introduction to Descriptive Psychopathology*, 2nd edn. London: W.B. Saunders, 1995.

Psychosomatics

A common folk belief is that there is an influence of 'mind over matter' and this can influence the onset, progression and resolution of disease. In other words, that the state of mind can, to some extent, have a significant bearing not only upon how an illness is perceived but also on its severity and content. The narrative of clinical anecdote and experience held for a long time that emotional stress could be counted as an integral cause of skin disease or at least an exacerbating factor leading to increased disease morbidity.

The concept of 'well being' is common to all cultures and associated with declarations of 'life forces', 'vital life energies', chi in Chinese, ki in Japanese and prana in Sanskrit. In the presence of physical symptoms and disease, psychosomatic theories have given insight into the effects of stress on the onset of disease, for example: psoriasis, on the persistence of symptoms; glossodynia, and the effects of anxiety and depression on the rate of disease recovery; and atopic dermatitis. The therapeutic value of the 'talking therapies' and the effect they have on physical recovery in skin disease are well established [1,2]. Chronic illness requires a series of psychological adjustments and these can differ depending on the patterns of illness. Thus an acute relapsing illness with full recovery between episodes, such as recurrent genital herpes, will produce different stress influences than a chronic illness with gradual linear decline, for example peripheral vascular disease or the stepwise decline of psoriatic arthritis with increasing disability after each episode. The effectiveness of coping strategies relates directly to the degree of psychological morbidity experienced and thereafter the stress effect on disease expression [3]. Those patients who use problem-focused coping strategies are better at seeking information, learning new skills and participating in treatment. Disease control is better with fewer exacerbations and less anxiety and depression. Emotion-focused coping strategies help patients to share their feelings, express anger and become realistic about prognosis. Adverse psychological responses to illness are related to chronicity, to increasing disability and poorer prognosis. Examples of this form of thinking are the vain belief that the condition will cure itself spontaneously, denial of the disease (and thus poor treatment acceptance) and seeking to blame others.

Atopic dermatitis

The complex psychological issues have been admirably summarized by Koblenzer [4]. The child is distressed from an early age, uncomfortable, exhausted and restless. The comfort from parental touching is limited, either by the irritation produced or the reluctance of parents to cuddle the imperfect infant. The parents' anxiety is transferred to the child and this leads to increased itching and scratching. Some children may become the sole focus of parental attention, resulting in elaborate regimens which prolong the infantilization of the child, promote sibling rivalry and even marital disharmony and divorce. Atopic children and adolescents show more anxiety, handle situations less well and are provoked to anger more readily. In school and college, the psychosocial issues of mixing in peer groups and making personal relationships may be blighted by feelings of stigmatization and disfigurement (see below). Regression and/or paradoxical aggressive behaviour are related to increased psychological morbidity, which has been shown to be commoner in boys than girls [5]. Stress makes atopic dermatitis worse [6]. Psychometric and immunological measures of change (see below) have emphasized that this is no longer an arcane clinical whim. Furthermore, psychotherapies have a part to play in the treatment plan [1,7]. Analysis of the effect of psychological interventions in atopic dermatitis is encouraging rather than conclusive because of the different types of approach employed. These therapies had a significant ameliorating effect on clinical severity, itching intensity and scratching in adults [8] and to a lesser extent in children [9] where correction of psychosocial and educational factors were more helpful.

Psoriasis

There have been many reviews of the psychosomatic aspects of psoriasis [10,11]. The imposition of a disfiguring, scaly and obvious disease in young adults has a profound effect upon body image and self-esteem at the very time when the independence of the personality is being established. The physical limitations introduced by widespread involvement as well as the stigma of visible disease make team games less likely. Sexual relationships are stunted by facial and flexural psoriasis because of shame and fear. Anxiety, depression and suicidal ideation (see below) are commoner than in eczema, acne or alopecia [11]. Depression is particularly significant and may remain undetected but is important because untreated it may contribute to therapy resistant disease and increased pruritus [12]. Patients with significant stress in the previous 6 months were found to be at increased risk for acute guttate psoriasis [13], as were those with diffuse plaque psoriasis [12]. The latent period between a significant life stress and the onset of an exacerbation of psoriasis has been difficult to assess. One study [10] suggested a 3-month delay was significant but this could not be confirmed by others. The response to PUVA therapy in highly worried individuals was almost half that of those who were deemed low worry and was constant for disease severity, gender, age, duration and skin type [14].

Chronic urticaria

The urticarias are a heterogeneous group of conditions. Chronic urticaria which is largely 'idiopathic' has a significant effect on quality of life [15,16]. It is significantly associated with depression,

dysthymia and anxiety [16,17]. Psychological factors may be prominent at onset, and contribute to disease progression [18] and negative coping may be associated with exacerbations. Psychotherapies are not well developed for chronic urticaria and are not as effective as for atopic dermatitis.

Alopecia areata

There has always been a strong anecdotal belief that the onset and recurrence of alopecia areata is related to stress and major life events; the few major controlled studies have failed to produce conclusive evidence [19]. First episodes of alopecia areata tended to be associated with avoidance of personal binding relationships, poor social support and high alexithymic personality characteristics. That is, a difficulty identifying and expressing internal emotions. Recurrent attacks were more frequent in these personality types and also those with trait anxiety and high stress perception [20]. Although the finding of stress mediators such as substance P and nerve growth factor (NGF) in the immunoreactivity of alopecia areata are suggestive of a remedial mechanism of therapy [21], large controlled studies of psychotherapy or psychoactive drugs are absent. Individual case reports continue to record success with individual psychotherapy, or antidepressants, either imipramine or SSRIs, not always in the presence of clinical depression [4].

References

1 Koblenzer CS. The emotional impact of chronic and disabling skin disease: a psychoanalytic perspective. *Dermatolog Clin* 2005; **23**: 619–27.
2 Picardi A, Pasquini P, Abeni D. Psychosomatic assessment of skin diseases in clinical practice. *Psychother Psychosom* 2005; **74**: 315–22.
3 Royal College of Physicians. Psychological responses to illness. In: *The Psychological Care of Medical Patients. A Practical Guide*, 2nd edn. London: Royal College of Physicians, 2003: 26–9.
4 Koblenzer CS. The psychological aspects of atopic dermatitis. In: Bieber T, Leung D, eds. *Atopic Dermatitis*. New York: Marcell Decker, 2002: 519–39.
5 Saunes M, Smidesang I, Holmen T. Atopic dermatitis in adolescent boys is associated with great psychological morbidity compared with girls. *Br J Dermatology* 2007; **156**: 283–8.
6 Linnet J, Jemec GB. Anxiety level and severity of skin condition predicts outcome of psychotherapy in atopic dermatitis. *Int J Dermatol* 2001; **40**: 632–6.
7 Fried R. Nonpharmacological treatments in psychodermatology. In: Koo J, Lee C, eds. *Psychocutaneous Medicine*. New York: Marcel Dekker, 2003: 411–27.
8 Chida Y, Steptoe A, Hirakawa N. The effects of psychological intervention on atopic dermatitis. A systematic review. *Int Arch Allergy Immunol* 2007; **144**: 1–9.
9 Ersser S, Latter S, Sibley A *et al*. Psychological and educational interventions for atopic eczema in children. *Cochrane Database of Systematic Reviews* 2003; **3**: 1–33.
10 Fortune D, Richards HL, Griffiths CEM. Psychological factors in psoriasis. *Dermatolog Clin* 2005; **23**: 681–94.
11 Picardi A, Pasquini P, Abeni D *et al*. Stress, social support, emotional regulation, and exacerbation of diffuse plaque psoriasis. *Psychosomatics* 2005; **46**: 556–64.
12 Vedhara K, Morris R, Booth R. Changes in mood predict disease activity and QOL in patients with psoriasis following emotional disclosure. *J Psychosom Research* 2007; **62**: 611–9.
13 Naldi L, Peli L, Parazzini F. Risk factors for first episode of acute guttate psoriasis: a case control study. *J Am Acad Dermatol* 2001; **44**: 433–8.
14 Fortune DS, Richards HL, Kirby B *et al*. Psychological distress impairs clearance of psoriasis in patients treated with photochemotherapy. *Arch Dermatol* 2003; **139**: 752–6.
15 Greaves M. Chronic idiopathic urticaria. *Curr Opinion Allergy* 2003; **3**: 363–8.
16 Staubach P, Eckhardt A *et al*. QOL in patients with chronic urticaria is differentially determined by psychiatric co-morbity. *Br J Dermatology* 2006; **154**: 294–8.
17 Ozkan M, Oflaz SB. Psychiatric morbidity and QOL in patients with chronic urticaria. *Ann Allergy Immunol* 2007; **99**: 29–33.
18 Baiardini I, Giardini A *et al*. QOL and patient satisfaction in chronic urticaria. *Allergy* 2003; **58**: 621–3.
19 Picardi A, Pasquini P, Catarruzi M *et al*. Psychosomatic factorms in first onset alopecia areata. *Psychosomatics* 2003; **44**: 374–88.
20 Brajac I, Tkalcic M. Roles of stress perception and trait anxiety in the onset and course of alopecia areata. *J Dermatol* 2003; **30**: 871–8.
21 Peters E, Liotiri S, Bodo E *et al*. The effects of stress mediators on the human hair. *Am J Pathol* 2007; **171**: 1872–86.

Self-esteem [1]

Self-esteem is a widely used concept both in popular language and in psychology. It refers to an individual's sense of his or her value or worth, or the extent to which a person values, approves of, appreciates, prizes, or likes him or herself [2]. The most broad and frequently cited definition of self-esteem within psychology is Rosenberg's [3], who described it as a favourable or unfavourable attitude toward the self.

Self-esteem is generally considered the evaluative component of the self-concept, a broader representation of the self that includes cognitive and behavioural aspects as well as evaluative or affective ones [2]. While the construct is most often used to refer to a global sense of self-worth, narrower concepts such as self-confidence or body-esteem are used to imply a sense of self-esteem in more specific domains. It is also widely assumed that self-esteem functions as a trait—that is, it is stable across time within individuals. Self-esteem is an extremely popular construct within psychology, and has been related to virtually every other psychological concept or domain, including personality (e.g. shyness), behavioural (e.g. task performance), cognitive (e.g. attributional bias) and clinical concepts (e.g. anxiety and depression). While some researchers have been particularly concerned with understanding the nuances of the self-esteem construct, others have focused on the adaptive and self-protective functions of self-esteem (for a review of conceptual and methodological issues see [3]).

The concept of self-esteem has expanded and therefore the previous understanding should be clarified. The expanded definition [1] states that there are many different concepts of self-esteem, some primarily psychological and others sociological, all dealing with different dimensions of the phenomenon. Various perspectives on self-esteem lead us to emphasize one or other policy direction. Self-esteem has been related both to socioeconomic status and to various aspects of health and health-related behaviour, as has a related construct, self-efficacy. Self-efficacy refers to an individual's sense of competence or ability in general or in particular domains. The sociological perspective leads us to support policies which will increase self-esteem by reducing environmental pressures on vulnerable persons. The psychological perspective tends to support policies which will increase self-esteem by changing individuals within themselves, for example counselling and psychotherapy.

Each perspective involves a different vision of what the self means in self-esteem and how to understand it. The psychological approach to the self and self-esteem focuses largely on the individual developmental intrapsychic processes, the role of the individual in the creation of the self through decision making, and

specific behaviours, particularly those involving success, mastery of tasks and achievement. This defines self-esteem as a component of competence within the self, the family and the workplace. The more sociological approach to self began to emphasize how others react to us, how we respond to these reactions and how these reactions lead to the development of self and one's worth or value in a social context. This sociological view was developed by Rosenberg [3] and others who emphasized the worthiness component of self-esteem.

Self-esteem was assumed to be a relatively stable characteristic akin to intelligence or personality type which gave it the form of a *trait*, measurable in unidimensional terms of degrees high or low. The scales of worthiness generally function in this way. Self-esteem functions appear to work in a more multidimensional way [4], involving the stability or instability of the self-esteem, defined as the *self-esteem state*. Measures of this component are essential because it is more dynamic than trait self-esteem. That is, it assesses the quality of self-esteem at a particular time relevant to, perhaps, treatment or other influences. The measurement of self-esteem is therefore more complex than originally assumed and thus multidimensional tools are now used to measure the changing dynamic situation presented by treatment and patient responses [1].

References

1 Mruk CJ. *Self Esteem Research, Theory and Practice*. New York: Springer, 2006.
2 Blascovich J, Tomaka J. Measures of self-esteem. In: Robinson JP, Shaver PR, Wrightsman LS, eds. *Measures of Personality and Social Psychological Attitudes*, Vol. 1. San Diego, CA: Academic Press, 1991: 176–89.
3 Rosenberg M. *Society and the Adolescent Self-image*. Princeton, NJ: Princeton University Press, 1965.
4 Hill SE, Buss DM. The evolution of self esteem. In: Kernis MH, ed. *Self Esteem: Issues and Answers*. New York: Psychology Press, 328–33.

Stigma [1,2]

The word *stigma* referred originally to a mark or brand on Greek slaves, distinguishing them from free men. The term describes the situation of an individual who is disqualified from full social acceptance. It is a social state initiated by others but with extensive and possibly long-lasting repercussions. The routines of social intercourse when meeting new people are the anticipation that we have an expected and normal response. These anticipations are shaped by the extended views and models of our experience of an accepted norm. The stigmatized individual is normal until abnormalized by the societal views around him or her. These events may occur early, for example in those afflicted by congenital deformities, or later with an acquired deformation, for example following trauma.

Stigma is not just confined to the alterations in the visible body. There are implications of character such as stigmatization in those who have deficiencies of will, passions or beliefs inferred from mental disorder, alcoholism, drug addiction, unemployment and imprisonment. In addition there are the population prejudices of ethnicity and religion.

For dermatologists the commonest situations where stigma is encountered may be:

1 Physical deformities
- i Congenital naevae, e.g. port-wine stain [3]
- ii Acquired deformities from developmental disorders, e.g. tuberose sclerosis
- iii Widespread inflammatory skin disease [4]
- iv Surgical or post-traumatic deformities

2 Implications of inferred character deficiencies
- i Psychiatric disorder, i.e. their views on the skin disease are disqualified because they also have a psychiatric diagnosis
- ii Learning disability, i.e. they have limited emotional capacity to respond to their dermatosis, e.g. Down's syndrome
- iii Persistent treatment non–compliance, i.e. an assumption of a fickleness of character, e.g. depressive illness
- iv Alcoholism and drug addiction, e.g. the cutaneous signs of substance abuse are a labelling of character weakness
- v Unemployment
- vi Imprisonment
- vii HIV status

3 Stigma of
- i Race, e.g. implications of vitiligo for marriage [5]
- ii Religion, e.g. allowing the naked body to be seen by a stranger.

Stigma is therefore an undesired difference from what was anticipated. Thus society constructs a theory based on, amongst other things, sociocultural beliefs to account for that difference. Cultural beliefs abound, relating a physical difference to an assumed association with an inferior or degenerate form or action.

The commonest are those of dirt and contagiousness whose roots are based on arcane skin beliefs related to leprosy, disfiguring and deadly dermatoses such as smallpox and morally reprehensible dermatoses of syphilis. The further beliefs are imported on the visible and represent an assumption of inferior and degenerate action and behaviour upon the visible imperfection. Thus 'dirty thoughts' are a prelude to dirty skin, acne is occasioned by self abuse and chronic ulcers (especially leg ulceration in men) are a sign of a dissolute past. There is the perception that all skin conditions are contagious, with imputations of an unclean house, and rashes are described as 'poxy', 'scabby', 'plecky' or 'wormy' in everyday conversation.

The stigmatized person may be victimized or exploited because of their vulnerable status. The stigmatized person becomes exposed to fraudulent merchandisers offering youth restoration, skin lightening, blemish removal etc, of an ever more sophisticated and allegedly technically advanced variety. Dermatologists are regularly assailed by desperate patients with a new therapy they have found. This is not because they are particularly gullible but is a reflection of a deeper unhappiness.

After a time, stigma can be used by patients for secondary gain. It is used as a hook to hang the failures and inadequacies of life after the effect on self-esteem has been made concrete over time. There is a danger that these patients accommodate to a subachievement status that develops into a compensatory hypochondriasis, anxiety state or illness complication syndrome, for example chronic somatic pain. The stigmatized patient is uncertain what category he/she will be placed in. A sense of insecurity exists, a feeling of not knowing what people really think. It is important in

children, especially, that they are encouraged to be open about their positive qualities and not focusing on the defect or the bad skin whilst being open about it to others. There is a small risk of inducing the bravado approach to the stigma which is counterproductive and may be seen as aggressive behaviour. The advice of a child psychologist in these situations is invaluable.

Help for the stigmatized begins with information control from both physician and family. Thus the child is protected from the derogatory and the hurtful by association with children of informed friends. Information about new therapies can be sifted to sort the real from the quack. Self help or disease clubs can be invaluable. A tolerant and informed grouping allows the expression of the normal developmental skills of the individual. The very act of offering treatment for birthmarks increases self-esteem in children even though treatment is not perfect [3].

The emergence of the patient into a more unprotected life means anticipating and neutralizing expected reactions such as teasing, taunting and bullying. One such response is that of naming and overtness techniques [2]. A particular difficulty arises from both congenital and acquired skin stigmata with the trauma of sports teams (and changing rooms) and the first experience of partner relationships [6]. Disfiguring conditions have significant effects upon depression, anxiety and self-esteem. There is a weak relationship between the severity of a condition and its social and personal effects. In clinic, this is one of the reasons for the patient with minimal lesions who is particularly distressed and insistent on aggressive therapy. In addition, whilst treatment can reduce and improve quality of life, social improvements and adjustments are not closely related to clinical improvement [6]. There is a significant difference between those who develop skin disease whilst in a relationship and those with stigma who attempt to make a new relationship.

Stigmatization in later life presents a different perspective because the patient has become a physical stranger to themselves. This is most striking and obvious in those who have developed disfiguring facial scarring but is also as valid for the patient with a late-onset dermatosis or those who suffer the odour of hidradenitis suppurativa. These patients have the unease not only of meeting and explaining their disease to new associates but how to relate to old associates.

The ordinary, the routine and the normal generate social anticipations which are then transformed into 'normative expectations, into righteously presented demands' [1]. There is the transformation into moral claims on others not to upset the reliable smooth running of life. There is the imposition of a shame morality upon the afflicted which relates to what you are and physically appear to be rather than, as in guilt morality, to what you may have done. The minimal demand on the stigmatized is not to make undue claims on people's fears or trigger their embarrassment or disgust. Thus, not to attempt to hide a significant facial scar, to expose widespread skin disease in a public place or to present with extensive acne in an intimate crowd leaves the individual open to claims of shame and disgust from others who are 'normal'. A form of attribution theory would suggest that the sufferer has brought retribution upon themselves [2].The stigmatized patient has an imposition from others to make themselves as unobtrusive as possible. This has been described as being *civilly disattendable*. To disregard this social rule is to be judged as being shamed for being unaware of the sensitivity of others and guilty for taking no action to minimize the effect on the observer. A distinction has been drawn within the broad term of stigma between felt stigma and enacted stigma. Felt stigma refers to the shame and expectation of discrimination, that is internal self-stigmatization that prevents people from talking about their experience and inhibits them from seeking help. Enacted stigma refers to unfair treatment by others, that is external stigma [7].

In the past, there would have been little guilt on the observer's part for the emotions the stigmatized provoke. Nowadays, in most societies the guilt of the observer is mollified by the respect given to the stigmatized. However, one of the mechanisms proposed for the continued avoidance of the stigmatized is that there is still a feeling that good deeds may be motivated by an uneasy self-congratulation rather than open respect for patients [8].

Stigma in psychiatry [9]

Many people hold negative stereotypes of those with mental illness. As with skin disease there is a traditional stereotyping from historical attitudes towards psychiatric patients. They are portrayed traditionally as unpredictable, unreliable and uneconomic. In addition there is a 'perceived dangerousness' that sets them apart from the normal social intercourse of everyday interactions. These concerns are modern. Images of mental illness on television focused on violence in 66% of items and 50% of patients with psychiatric problems reported that negative media coverage had a significant adverse effect on recovery. Health professionals who do not work with psychiatric patients have difficulty in accommodating to the needs of this group and tend to hold a range of attitudes towards individuals similar to the general public. With increasing education and contact, medical practitioners become less stigmatizing. The problem with all non-psychiatric specialisms, including dermatology, is that the demands of the consultation in terms of time, knowledge and therapy place unique demands for them on the doctor–patient relationship.

The importance in reducing the impact of stigmatization [10] is better understood in relation to Social Exclusion Theory (SET) which holds that:

1. Humans possess a fundamental motive to avoid exclusion from social groupings
2. Much social behaviour attempts to improve the chances of inclusion
3. Negative effect (including loneliness and depression) results when a person does not or cannot achieve a desired level of social inclusion.

The experience of involvement in groups, not necessarily 'Disease Clubs', helps to improve a sense of well-being and to determine physical and psychological fitness.

Measurement of stigma in dermatology and psychiatry has tended to rely on general measures of mental health with depression and anxiety scores but also with psychometric measures of self-esteem such as the Rosenberg Self-esteem Scale. This has been used to assess stigmatization in psoriasis and eczema as well as mental illness. Further the Stigma Scale for mental illness [11], developed to examine discrimination, disclosure and potential positive reactions to mental illness, demonstrated that Stigma

Scale scores were negatively correlated with global self-esteem. Interventions in dermatological physical visual stigmata are concentrated on firstly the reduction in visibility and secondly the psychologically based approaches to forestall stigmatization. Skilful cosmetic camouflage [2] and the use of cosmetic surgery and laser therapy [12] have all shown that patients gain a better self-image and sense of well-being.

Psychological therapies using social skills training, cognitive behavioural therapy and an interventional method to directly challenge staring and rejection behaviour increased self-esteem and reduced automatic negative thinking [2].

Methods to change entrenched reactions within society to physical and psychological difference are more difficult to evaluate. Frances studied children with visible differences at school and developed programmes of community inclusiveness to reduce discrimination [13].

References

1 Goffman E. *Stigma. Notes on the Management of Spoiled Identity*. New Jersey: Prentice Hall, 1963.
2 Kent G. Stigmatisation and skin conditions. In: Walker C, Papadopoulos L, eds. *Psychodermatology*. Cambridge: Cambridge University Press, 2005: 44–52.
3 Lanigan S, Cotterill J. Psychological disabilities amongst patients with portwine stains. *Br J Dermatol* 1989; **121**: 209–15.
4 Schmid-Ott G, Burchard R *et al*. Stigmatisation and QOL of patients with psoriasis and atopic dermatitis. *Hautarzt* 2003; **54**: 852–7.
5 Schmid-Ott G, Kunsebeck HW, Jech E *et al*. Stigmatisation experience, coping and sense of coherence in vitiligo patients. *Eur Acad Dermatol Venereol* 2007; **21**: 456–61.
6 Anthis L. Skin disease and relationships. In: Walker C, Papadopoulos L, eds. *Psychodermatology*. Cambridge: Cambridge University Press, 2005: 72–84.
7 Weiner B, Perry R, Magnusson I. An attributional analysis of reactions to stigma. *J Social Psychol* 1988; **55**: 738–48.
8 Miller WI. *The Anatomy of Disgust*. Cambridge: Harvard Press, 1997: 197–205.
9 Gray AJ. Stigma in psychiatry. *J R Soc Med* 2002; **95**: 72–7.
10 Baumeister R, Twenge J, Nuss C. Effect of social exclusion on cognitive processes. *J Social Clin Psychol* 2002; **8**: 17–27.
11 King M, Dinos S, Shaw J *et al*. The stigma scale of mental illness. *Br J Psychiatry* 2007; **190**: 248–54.
12 Troilius A, Wrangsjo B, Ljungrenn B. Potential psychological benefits from early treatment of port-wine stains in children. *Br J Dermatology* 1998; **139**: 59–65.
13 Frances J. *Educating Children with Facial Disfigurement*. London: Routledge Falmer, 2004.

Psychoneuroimmunology [1]

It has been consistently recorded that patients with depression suffer more physical illness and conversely patients with chronic physical illness more often suffer major depressive illness [2]. Much recent research reflects the potential shared mechanisms of inflammation mediated by the known immune mechanisms.

The anatomy of the structures in brain, nerve and skin are embryologically derived from the ectoderm. They show their origins from the neural plate where both the CNS and peripheral nerves develop from the neural crest as do the cutaneous structures, melanocytes and Merkel cells [3]. The functional relationships between brain and immune system are linked by the autonomic nervous system and the neuroendocrine outflow via the hypothalamus and the pituitary gland. Communication between the immune system and the brain is bi-directional and probably largely mediated by neuropeptides released within nerves and also locally at tissue sites, in this case the skin. This neuro-immuno-cutaneous-endocrine system (NICE) [4] seems to form part of an integrated system, relating behaviour to neuroendocrine and immune function.

The skin has a critical immune function, employing a large number of cell populations in a coordinated manner to respond to both extrinsic and intrinsic challenge (see Chapter 13).

The clinical links between psychosomatic factors and skin disease are amply demonstrated by the fluctuations of remission and relapse which are seen in dermatological disorders as a result of stress and psychological events in patients' lives. There is a substantial body of evidence detailing the neural innervation of the skin with nerve fibres extending from the subcuticular tissue through the dermis and into the epidermis. The contact between nerve cells and epidermal cells, as first recorded by Langerhans and Merckel, is well documented.

Interactions between the immune and the neuroendocrine systems: bidirectional communication pathways [5,6]

Sickness behaviour is a common and not trivial experience, accompanying infectious or inflammatory illnesses. Individuals are lethargic, lose interest in surroundings and have depressed mood. This apathy is accompanied by hyperalgesia. Peripheral inflammation results in the production of various inflammatory mediators including cytokines, which signal to the brain by various routes. Peripherally generated cytokines, for example by infections, induce monocytes and macrophages to secrete pro-inflammatory cytokines centrally, which modulate brain function and can produce fever and sickness behaviour (malaise, lethargy, depressed mood). Because of the large size of cytokines, those produced in peripheral inflammation do not readily cross the blood–brain barrier. However, three mechanisms have been suggested by which cytokines may have access to the brain [7,8]: firstly, via the circumventricular organs; secondly, by binding to specific binding proteins on brain endothelium; and, thirdly, activation of vagal afferent fibres which transmit cytokine signals to specific brain nuclei [9]. The CNS cytokine networks have an effect on neurotransmitter and corticotrophin-releasing hormone (CRH) functions to produce a sickness behaviour syndrome of lethargy, anorexia and impaired sleep patterns [5].

The symptoms of sickness can be reproduced experimentally by induction of pro-inflammatory cytokines or measured from activated monocytes and macrophages during illness. Cytokine receptors are present in the brain and are activated by cytokines produced locally in response to peripheral cytokines. These brain cytokines are produced in macrophage-like cells in the meninges and microglial cells in the brain parenchyma. This sickness response is both physically and psychologically apparent and is reversible in acute illness by potent endogenous factors such as the glucocorticoid system and the production of anti-inflammatory cytokines. However, with disease chronicity there is a blunting of the HP axis response (see below) and the pro-inflammatory cytokine activity leads to the symptoms of sickness becoming chronic. This results in cognitive changes and

depression of chronic disease. Structural changes can occur in the brain as astrogliosis and degeneration of the oligodendrocytes in the myelin sheath, leading to neuronal death. Experimentally, the parenteral injection of the pro-inflammatory cytokines interleukin-1 (IL-1) and tumour necrosis factor (TNF) α resulted in depressed social and feeding activity in rats; this did not occur with IL-6 [8].

CNS stress response: effects on the immune system

The nervous system regulates the immune system through hormonal effects, regionally via immune organ secretion and locally at sites of inflammation [6,8]. Endogenous glucocorticoids are essential in the regulation of the immune response and resultant degree and type of inflammation. The hypothalamic–pituitary–adrenal (HPA) axis activates CRH which activates CRH type 1 receptors in the anterior pituitary to release propiomelanocortin (POMC)-derived peptides adrencorticotropin, α-melanocyte stimulating hormone and β endorphin. It has been proposed that the physiological levels of glucocorticoids secreted via the HPA axis feedback mechanism have a significant immunomodulatory role and result in a shift of cytokine production from a primarily pro- to an anti-inflammatory pattern.

The activation of stress responses results in increased neural output to peripheral tissues. The sympathetic and parasympathetic nervous systems modulate inflammatory responses through regional innervation of organs including spleen, thymus and lymph nodes.

The parasympathetic nerves modulate inflammatory responses at the regional level via efferent fibres of the vagus nerve. The afferent fibres signal the presence of peripheral inflammation to the brain via cytokines such as IL-1, which bind to paraganglial cells to increase activity in vagal brain stem centres. This increased vagal tone results in increased acetylcholine release, which suppresses cytokine release; this is known as the cholinergic inflammatory reflex [9]. The peripheral nervous system affects inflammation through neuropeptides such as substance P (SP) and vasoactive intestinal peptide (VIP) released from peripheral sensory neurones. These neuropeptides may be pro-inflammatory, particularly SP, or anti-inflammatory, particularly VIP.

Stress and immunity [5,6,8]

The mechanisms by which stress can influence the progress, continuity and severity of skin disease can usefully be grouped into three areas: firstly, as mentioned previously, the effect on the immune system of steroid hormones and catecholamines; secondly, the induced alterations in the normal feedback mechanisms of the HPA axis; and, thirdly, the peripheral influence of neuropeptides and inflammatory mediators on skin function. Stress, whether it be emotional, physical or an infective challenge, induces cortisol secretion via corticotrophin-releasing factor from the hypothalamus to adrenocorticotrophin hormone from the pituitary and stimulation of the adrenal cortex. The sympathetic system is activated via the limbic system to release norepinephrine and peripheral neuropeptides. These act on the immune system by influencing the expression of T helper cells and tissue macrophages. Norepinephrine can stimulate Th2 cells through induction of IL-10 and suppression of macrophage IL-12.

Influences on skin disease [5,10–14]

The many influences on the immune system, both known and unknown, cannot give a wholly predictable picture of response of skin disease to stress and adverse psychological influences. The balance between Th1 and Th2 responses can vary enormously and may account for the fluctuations seen in the commoner chronic inflammatory disease such as atopic dermatitis and psoriasis [14]. Endocrine and immune responses to experimental stress showed that there was significant attenuated responsiveness of the HPA axis and increased sympathetic activity in atopic dermatitis patients, leading to increased eosinophil numbers, increased IgE levels and elevation of pro-inflammatory cytokines, particularly IFN-γ. Similar studies in psoriasis demonstrated a significant rise in monocytes and $CD4^+$ cells. Pro-inflammatory IFN-γ and IL-2 levels were elevated whilst IL-10, an anti-inflammatory cytokine, decreased. This mimics the changes found in active psoriasis.

There are many anecdotal reports of stress-induced exacerbations in other dermatoses, but fuller immunological evidence is not available. However, many studies support the role of stress in the pathogenesis of chronic urticaria, recurrent herpes simplex and delayed wound healing [15,16].

References

1 Alder R, ed. *Psychoneuroimmunology*, 4th edn. New York: Elsevier, 2007.
2 Evans DL. Mood disorders in the medically ill: scientific review and recommendations. *Biol Psychiatry* 2005; **58**: 175–89.
3 Bernstern JE. Neuropeptides and the skin. In Goldsmith LE, ed. *Biochemistry and Physiology of the Skin*. New York: Oxford University Press, 1983: 1217–33.
4 O'Sullivan RL, Lipper G, Lerner EA. The neuro-immuno-cutaneous-endocrine network. *Arch Dermatol* 1998; **134**: 1431–5.
5 Danzer R, Bluthe R, Castanon N *et al*. Cytokines, sickness behaviour and depression. In: Alder R, ed. *Psychoneuroimmunology*, 4th edn. New York: Elsevier, 2007: 281–318.
6 Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends Immunol* 2006; **27**: 24–31.
7 Maier SF, Watkins LR. Cytokines for psychologists: implications of bi-directional immune to brain communications for behaviour, mood and cognition. *Psychol Rev* 2002; **105**: 83–107.
8 Arck PC, Slominski A, Theoharides TC *et al*. Neuroimmunology of stress: skin takes center stage. *J Invest Dermatol* 2006; **126**: 1697–704.
9 Tracey KJ, Pavlov VA. The cholinergic anti-inflammatory pathway. *Brain Behav Immunity* 2005; **19**: 493–9.
10 Miller AH, Raison CL. Cytokines, p38MAP kinase and the pathophysiology of depression. *Neuropsychopharmacology* 2006; **31**: 2089–90.
11 Pariante CM. Glucocorticoid receptors in major depression: relevance to pathophysiology and treatment. *Biol Psychiatry* 2001; **49**: 391–404.
12 Revicki D,Willian MK, Seurat J *et al*. Impact of adulimumab on health related quality of life and other patient related outcomes in moderate to severe plaque psoriasis. *Br J Dermatol* 2008; **158**: 149–57.
13 Stern R, Wolfe F. Infliximab dose and clinical status: results of 2 studies in 1642 patients with rheumatoid arthritis. *J Rheumatol* 2004; **31**: 1538–45.
14 Buske-Kirchebaum A, Kern S, Hellhammer D. Altered distribution of leucocyte subsets and cytokine production in response to acute psychosocial stressing patients with psoriasis vulgaris. *Brain Behav Immunol* 2007; **21**: 92–9.
15 Bonneau RH. Stress induced modulation of the immune response to herpes simplex virus. In: Alder R, ed. *Psychoneuroimmunology*, 4th edn. New York: Elsevier, 2007: 1077–97.
16 Marucha PT. Stress and wound healing. In: Alder R, ed. *Psychoneuroimmunology*, 4th edn. New York: Elsevier, 2007: 825–37.

Disability and quality of life [1]

This aspect of dermatology is covered in more detail in Chapter 72.

Quality of life (QOL) is defined as an individual's perception of their position in life in the context of the culture and value system in which they live and in relation to their goals, expectations standards and concerns. It is a broad-ranging concept, affected in a complex way by the person's physical heath, psychological state, level of independence, social relationships and their relationship to salient features of their environment.

Established dermatological medicine describes skin disorders in tightly defined diagnostic criteria, which takes little account of the individual patient's responses. The patient with disease needs to be understood not only in terms of objective outcomes of the kind usually assessed in clinical practice but also those composed of the psychosocial structures that are assessed from the patient's self-reports. It is important to try and determine these disparate degrees of disability that a particular skin disease confers because their recognition leads to greater patient compliance and a more positive response.

The effect on QOL induced by psoriasis, eczema and acne have been assessed using disability indices which are readily accessible [2]. These scales can also be used to quantify reduction in disability before and after treatment. The newer indices of disability have successfully combined the physical and psychological measures to produce a more holistic assessment of disease, as exemplified by the Salford Psoriasis Index [3]. For instance the presence of relatively trivial amounts of psoriasis on an individual's face may induce disparate depression. The concept of a person's QOL includes measures of the psychological impact of the disease including stigma and its corollary self-esteem. Questions clarifying the contributions of embarrassment, helplessness, anger and depression are reflected in social, sexual and occupational life. The further development of these instruments has indicated that at similar objective levels of clinical severity QOL may differ significantly between individuals because of the psychological impact. In acne the QOL measures indicated that neither clinical severity scores nor the presence of scarring correlated with psychological morbidity [4]. The use of specific instruction in skin care make up in acne improved the psychological components of the World Health Authority QOL 26 questionnaire in patients compared to controls [5]. The same groups showed no significant differences with the Dermatology Life Quality Index (DLQI). In a study of 936 patients using the Skindex-29, the DLQI and Psoriasis Disability Index, the authors concluded that the Skindex-29 showed higher scores, and was more sensitive to psychological distress in women over 65 years of age. Further work in childhood atopic eczema [6] suggested that the three measuring instruments SCORAD (scoring atopic dermatitis), NESS (Nottingham Eczema Severity Scores) and CDLQI (Children's DLQI) measured differing elements of disease activity and should be regarded as intercalated and not mutually exclusive measurements. This may be related to the different scoring, which can be objective by the physician or subjective by the patient. Patient reported outcome (PRO) measures are increasingly used both for present state assessment and also as a measure of treatment response. Comparisons of DLQI, the Short Form SF-36 and EuroQOL 5D in psoriasis demonstrated that the SF-36 was more valuable in measuring bodily pain and impairments in psychosocial functioning [7]. This sensitivity to mental health issues was true also for different types of psoriasis. Nevertheless, the DLQI identified the significant psychosocial distress in women with vitiligo compared to men [8] when used as the sole measure and specifically for Muslim women compared to men comparing psychological health and sexual activity.

The assessment of the effect of the disease on the family of the patient has been a new use of QOL measures [9,10] in atopic eczema and psoriasis [11]. The demonstration that significant emotional distress occurs in parents and partners is not new but allows the evidence to be used to negotiate for increased resources for family care. It is clear that the different QOL instruments may be general measures of disability; other disease-specific instruments may also vary in the emphasis they bring to assess disability, be it physical or psychological. They may also help to identify gender and ethnic differences in disease and response to therapy [2]. Measurements of psychosocial predictors of disease activity have been used, particularly in management of cancer. The baseline psychosocial predictors of survival in localized melanoma have been estimated with QOL measures and showed shorter survival with anger repression, hopelessness and depression. A better prognosis was associated with reality recognition and minimizing response [12].

QOL assessments are not related to health but to disease and are usually specific to a particular diagnosis. This is very different from the non-medical connotation of the meaning of the phrase which is accepted to relate to a non-ill state of contentedness of 'having a good time'. It has been proposed that in future the QOL of ill people may need to take account of this difference because the patient's abnormal physiological state (cytokines and other mediators) may affect the psychological state and responses to questionnaires [13].

References

1 Bowling A. *Measuring Disease. A Review of Disease Specific Quality of Life Scales.* Buckingham: Open University Press, 2001.

2 Sampogna F, Chren MM, Melchi FF *et al*. Age, gender, quality of life and psychological distress in patients hospitalized with psoriasis. *Br J Dermatol* 2006; **154**: 325–31.

3 Kirby B, Fortune DG, Bhushan M *et al*. The Salford Psoriasis Index: an holistic measure of psoriasis. *Br J Dermatol* 2000; **142**: 728–32.

4 Ilgen E, Derya A. There is no correlation between acne severity and AQUOLS/DLQI scores. *J Dermatol* 2005; **32**: 705–10.

5 Matsuoka Y, Yoneeda K, Sadahira C. Effects of skin care and makeup on the quality of life of female patients with acne vulgaris. *J Dermatol* 2006; **33**: 745–52.

6 Hon KL. CDLQI, SCORAD, and NESS: are they correlated? *Qual Life Res* 2006; **15**: 1551–8.

7 Shiklar R, William M. The validity and responsiveness of three QOL measures in the assessment of psoriasis. *Health Qual Life Outcomes* 2006; **4**: 71–9.

8 Ongenae K, Van Geel N. Effect of vitiligo on self-reported health related quality of life. *Br J Dermatol* 2005; **152**: 1165–72.

9 Ganemo A, Svensson A, Linberg M. Quality of life in Swedish children with eczema. *Acta Dermat Venereol* 2007; **87**: 345–9.

10 Basra M, Finlay A. The family impact of skin disease. *Br J Dermatol* 2007; **156**: 929–37.

11 Eghlileb A, Davies E, Finlay AY. Psoriasis has a major secondary impact on the lives of family members and partners. *Br J Dermatol* 2007; **156**: 1245–50.

12 Lehto U, Ojanen M, Dyba T. Baseline psychosocial predictors of survival in localized melanoma. *J Psychosom Res* 2007; **63**: 9–15.
13 Koller M, Lorenz W. Quality of life: a deconstruction for clinicians. *J R Soc Med* 2002; **95**: 451–88.

Classification

The classification of diseases serves to describe the speciality and place the categories within the speciality such that they are inclusive and relate to each other to facilitate diagnosis and treatment. The difficulties inherent in a joint classification of diseases within dermatology and psychiatry have been fully explored [1,2]. There are fundamental differences in nosology, morphology, phenomenology and thus diagnostic clustering. Consequently, the psychiatry in psychodermatology has been classified by dermatologists in generalizations because they have limited familiarity with the diagnostic and classification difficulties in psychiatry, for example the nuances of disorders of belief which stretch from an episodic rumination through to a fixed psychotic delusion. For psychiatrists the dermatological lesion such as excoriation may represent a consistent physical sign of self-harm but which for dermatologists may be on the spectrum from pure itchy dermatosis to fabricated and induced disease.

There are two main internationally recognized classifications of psychiatric disorders. The first is produced by the American Psychiatric Association, with disorders defined by diagnostic criteria which describe their essential features. The Diagnostic and Statistical Manual of Mental Disorders (DSM) is modified regularly, the current revision DSM-IV dating from 2000 with DSM-V due for publication in 2012 [3]. The text revision version of DSM-IV gives extra information on diagnostic categories. The second is the current International Statistical Classification and nomenclature system for medical and psychiatric disorder (ICD-10), published by the World Health Organization [4] and in many respects is similar to DSM. However, these classifications are probably not particularly easy for dermatologists to use in everyday practice. There are very good textbooks which are much more user friendly [5]. These classifications are part of the essential practice of psychiatry where the language and symptoms of disease, and thus its subsequent treatment, is to identify, for example, organic syndromes, schizophrenia, bipolar disorders, somatic and personality disorders. But whatever the presenting features to dermatologists it is important to remember that the symptoms are not a diagnosis and therefore should not be assumed to be treatable in the same way. Therefore, for example, dermatitis factitia may be a symptom of depression, personality disorder or an abnormal psychosocial situation. Each requires a different treatment.

The diagnosis in psychiatry has become more dynamic to encompass the present state of a patient's vulnerability according to the type and intensity of stress factors. These dimensional diagnostics [1,6] are no different in concept from assessing an atopic and their eczema activity at any one time.

The classification is necessarily psychiatrically based because the treatment is primarily directed to the mental disorder and not the dermatological one. However, the classification crosses the borderlines of those divisions between the psychoses, thought and mood disorders, and the classical neuroses representing the ultimately inappropriate reactions to stress in emotion and behaviour.

This classification is therefore pragmatic with an emphasis on usefulness for dermatologists and modified from the Vienna Diagnoses Schedule for Psychodermatological Disorders [1].

1 Psychiatric disorders without significant dermatological disease
- **1.1** Delusional syndromes
  - Parasitosis
  - Smell
  - Impregnation and contamination
  - *Folie à deux*
  - Other hypochondriasis, e.g. so-called Morgellons
- **1.2** Disorders of awareness of the body
  - Phobias and obsessive compulsive disorders
    - Disorders of body image: body dysmorphic disorder (BDD) (synonyms dysmorphophobia, dermatological non-disease)
    - Disturbance of body size and eating, e.g. anorexia nervosa, bulimia
    - Phobias, e.g. mole phobia, venereophobia, wart phobia, erythrophobia, electrophobia and steroid phobia
    - Obsessive–compulsive behaviours, e.g. hand washing, hair plucking
    - Atypical pain disorders, e.g. glossodynia, vulvodynia and scrotodynia, anodynia
    - Pruritis sine materia
    - Other dermatologic hypochondriases: botoxophilia, tanorexia, cyberchondria

2 Mental disorders and dermatological disorders
- **2.1** Classical psychosomatic disorders
  - Dermatoses in which emotional precipitating or perpetuating factors may be important
    - Vesicular eczema of the palms and soles
    - Atopic dermatitis
    - Seborrhoeic dermatitis
    - Psoriasis
    - Some cases of localized or generalized pruritus
    - Alopecia areata
    - Aphthosis
    - Flushing reactions and rosacea
    - Hyperhidrosis
    - Urticarias
- **2.2** Dermatoses primarily factitious in origin
  - Dermatitis factitia
  - Artefact by proxy
  - Witchcraft syndrome
  - Dermatological pathomimicry
  - Dermatitis simulata
  - Malingering
  - Compensation neurosis
  - Münchausen's syndrome
  - Fabricated and induced illness (Münchausen's syndrome by proxy)
  - Deliberate self-cutting
  - Self-mutilation

2.3 Dermatoses in association with harmful habits and compulsions
- Lichen simplex
- Neurotic excoriations
- Prurigo nodularis
- Acne excoriée
- Hair plucking
- Trichotillomania
- Trichophagia
- Nail destruction
- Onychotillomania
- Lip-licking cheilitis
- Knuckle biting

2.4 The psychogenic purpura syndromes
- Autoerythrocyte sensitization (Gardner–Diamond syndrome)
- Autosensitivity to DNA
- Psychogenic purpura (idiopathic)
- Stigmata

2.5 Disorders of neglect of self-care (synonym Diogenes syndrome)

2.6 Drug-dependence syndromes
- Alcohol-related syndromes
- Substance abuse

2.7 Mental disorders due to dermatological treatment
- Cortisone psychosis
- Interferon depression

2.8 Dermatological disorders due to psychopharmacological treatment
- Lithium-induced psoriasis
- Tranquillizer hyperpigmentation
- Anti-depressant hyperhidrosis

2.9 Dual non-associated disease, dermatological and psychiatric disorders
- Skin cancer in patients with major psychosis

3 Dermatological patients with psychic symptoms not amounting to a disorder
- 'Troublesome patients'
- Dysthymic responses to illness
- Cosmetology associated worries

4 Group and mass population reactions
- Sick building syndrome
- Epidemic hysteria

Disorders of dermatological beliefs [1–10]

The classical reports of patients who erroneously believed that they were infested by parasites were first reported by Thibierge in 1894 [11] and reiterated by Perrin in 1896 [12]. The 'Nervodermies Parasitophobiques' as they were called perhaps led to the misnomer that these patients suffered from a phobia which is an irrational fear and anxiety reaction when what they really suffer from is a disorder of thought and belief.

The many reports and reviews since Ekbom series in 1938 [10] have emphasized the psychiatric heterogeneous nature of the cases [2–8]. The heterogeneity of the group was recognized by Lyell [13] who commented that it is hard to know where eccentricity ends and psychiatric illness begins. Musalek [3,4] and others [5,6] stressed the importance of the nosology and classification which is critical when most of these patients are presenting to dermatologists.

The content of this form of hypochondriasis (or excessive preoccupation with health) is usually a preoccupation with infestation, especially parasites, but may take the form of a belief about smell, halitosis, or impregnation. In so-called Morgellon's syndrome (see below) fibres are extruded from the skin. The intensity of the belief depends on the psychopathology of the hypochondriasis. The expressed belief is a symptom and needs to be positioned within a diagnostic psychiatric classification to make a judgement about treatment and prognosis.

A true primary delusion is a judgement made by others about a false unshakeable belief which arises from internal morbid processes in a patient and which are not amenable to logic and are out of keeping with the person's educational and cultural background. Primary delusions can be an isolated phenomenon as in a monosymptomatic hypochondriacal psychosis as described by Munro in the cases of delusions of parasitosis [9] or as part of a broader psychosis for example schizophrenia which has other features such as paranoia. A secondary delusion more commonly occurs with affective disorder such that the belief is understood in terms of the underlying depressed mood. The nihilistic delusions may influence the patient to believe that her skin is rotting and infested.

Depressive thinking to a lesser degree may take the form of depressive ruminations which are insistent recurring thoughts which the patient may try to resist because of its compulsive nature. Patients may therefore say that they 'keep thinking they (might) have parasites'. To some extent the belief is shakeable and amenable to reason. Similarly obsessional ruminations about infestations arise as recurrent thoughts but without depressive moods.

Ideas of infestation, smell or impregnation may arise as an overvalued idea. This is more commonly seen as an extension of an acceptable comprehensible thought pursued by the patient beyond the bounds of reason [1]. It is distinguishable from an obsessional belief and a delusion because the former is subjectively felt to be 'senseless' and the latter qualitatively different with irrational meanings given to events. An overvalued idea is an isolated notion, in this case ideas of infestation associated with strong affect and an abnormal personality. These patients with beliefs of infestation have a degree of conviction similar in quality to politi-

References

1 Musalek M, Hoble B, Mossbacher U. Diagnostics in psychodermatology. *Dermatol Psychosom* 2001; **2**: 110–5.

2 Gieler U, Bosse KA. *Seeliche Faktoren bei Hautkrankheiten. Beitrag zur Psychosomatiscen Dermatologie*. Bern: Huber, 1996.

3 American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn, Text Revision. Washington, DC: American Psychiatric Association, 2000.

4 World Health Organization. *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*. Geneva: World Health Organization, 1992.

5 Sims A. *Symptoms in the Mind*, 3rd edn. London: Saunders, 2006.

6 Medansky RS, Handler RM. Dermatopsychosomatics: classification, physiology and therapeutic approaches. *J Am Acad Dermatol* 1981; **5**: 125–36.

cal or religious zealotry. They assert that their ideas 'stand to reason'.

Some anxious mildly depressed patients with psychosocial isolation may form the notion they have an infestation as a way of interpreting patients' symptoms provoked by an itchy dermatosis. These ideas are usually shakeable and the patients persuadable about the error of their belief.

Delusions of parasitosis [4–8]

Synonyms
- Beliefs of infestation
- Delusions of infestation
- Psychogenic parasitosis

Definition. The patient with delusions of parasitosis (DP) has an unshakeable conviction that his or her skin is infested by parasites (this must be differentiated from parasitophobia—the *fear* of becoming infested).

Table 64.1 summarizes the secondary organic causes of DP [14]. Delusions of perception may follow disease in the non-dominant hemisphere, thus DP are sometimes seen in patients after a cerebrovascular accident involving that side of the brain. Similarly, DP may be part of the picture of dementia and should be considered when examining the elderly patient. DP have also been described in pellagra, vitamin B_{12} deficiency, following coronary bypass surgery, as a side-effect of phenelzine and in severe renal disease. Delusions of parasitosis in a young adult suggest illicit exposure to recreational drugs, in particular amphetamine, cannabis (skunk) or cocaine [15].

Table 64.1 Organic medical disorders associated with delusional parasitosis.

Neurological
Cerebrovascular disease
Dementia and neurodegenerative diseases
Parkinson's disease
Huntingdon's disease
CNS tumours
Head injury
Encephalitis
Meningitis
Multiple sclerosis
Learning disability

Cardiovascular disorders
Arrhythmias
Heart failure
Coronary artery bypass

Renal disease
Chronic renal failure
Dialysis

Liver disease
Hepatitis

Endocrine disease
Diabetes mellitus
Hyperthyroidism
Hypothyroidism
Panhypopituitarism
Hypoparathyroidism
Acromegaly

Nutritional disorders
Pellagra
Folate deficiency
Vitamin B_{12} deficiency
Anorexia nervosa

Infectious diseases
Syphilis
AIDS
Tuberculosis (pulmonary)
Leprosy

Malignancy
Breast cancer
Colon cancer
Lung cancer
Lymphoma
Chronic lymphatic leukaemia

Substance abuse
Amphetamines
Cannabis
Cocaine
Ecstasy
Opiates

Medicines
Corticosteroids
Ciprofloxacin
Mefloquine
Pemoline
Phenelzine
Pargyline

Detailed analysis of these cases cannot always determine whether the aetiology is primary delusional, secondary to depression or a toxic effect. Huber [16] has proposed that decreased striatal dopamine transportation (DAT) corresponding with an increased level of extracellular dopamine would account for the aetiology in primary DAT inhibitors such as cocaine, pemoline and amphetamine. Several other associated causes of secondary DAT dysfunction, for example Parkinson's disease, brain injury and HIV/AIDS may also be relevant.

It is particularly important to exclude the possibility of a real infestation. In 6% of one series, patients developed DP following real infestation [13] and 3% had been in contact with an infestation, usually scabies, at some time in their life. For 12% this was part of a delusion shared with another member of the family (*folie à deux*), see below.

Pseudodelusory syndromes have been recorded with thrips infestation [17], bird mites and fir tree pollen (personal observations).

Incidence. Patients with DP are rare but the true prevalence is unknown. The condition affects both sexes equally below the age of 50 years, but after that age three times as many women are affected as men [3,8,18]. Although patients with delusions of parasitosis are relatively easily recognized, it is possible to spend a lifetime as a dermatologist and never see a new case. The average age of onset varies from 55 to 68 years; at this age the patient is more likely to be female. The age group 20 to 40 years with DP should be regarded with the utmost concern for they may be regular users of recreational drugs especially cocaine and/or amphetamines, particularly crystal meth and ecstasy (methylenedioxymethylamphetamine). The symptom may be the earliest sign of a major psychotic illness in young patients [15].

Clinical features. The presenting episode of DP to the dermatologist may be extremely variable. It can be as an urgent appeal from the primary care practitioner to see a patient with an established delusion of infestation because they are disrupting everyone's life with their constant demands. Patient and relatives may be regular and vociferous visitors to the emergency room refusing to leave until 'something is done'. Colleagues in other specialities, such as infectious diseases, public health and tropical medicine, call in despair and exasperation to take over the patient's care. Fellow dermatologists in public and private practice are relieved if they can refer on to a psychodermatology team. By contrast, the patient can present with an ill-defined, persistent itching with no immediate, obvious delusional thoughts. These may only become apparent on closer questioning.

In the most established case the patient has consulted a series of specialist services to eradicate the imagined infestation. The family doctor is consulted repeatedly for even 'stronger' medicines to treat the 'bugs', the public health authorities called on many occasions to disinfest the home, and the veterinary services recruited to scrutinize and treat pets as a *proxy folie* [19]. Eminent university personnel may have been consulted—both medical, in infectious disease departments, and scientific, in zoology specialities. Specimens are sent to international institutions such as the British Museum for the ultimate examination. By the time the patient reaches the clinic there is always an inevitable degree of frustration, anger and impatience which makes the first consultation both difficult and vital. The situation can be complicated by previous consultations where unwittingly various complexities have been added. In the pressure of the situation some physicians and scientists claim to see an offending organism, others give a 'new treatment' to get the patient out of the consulting room, and some collude with the patient and suggest they can see the parasite in the skin and then refer to 'someone who is more expert'.

The patient, usually female, is tense, expectant and beneath the simmering frustration has a certainty of demeanour. The presenting symptoms are variable and not consistent amongst patients. It may be a feeling of creeping, crawling, burrowing, biting, burning and stinging. Some speak of a sensation in their skin as though an insect or worm is crawling around, followed by a prolonged and elaborate description of the pathway the organism is taking. In addition, elaborate life cycles are constructed involving the different 'stages' of maturity. This agent may not be confined to the skin but also involve the genital, oral [20] or ocular [21] areas. They may describe and draw the insect or worm concerned but can describe the infestation as invisible or dissolved in orificial secretions.

No obvious skin disease may be present, but excoriations are usual and can be both extensive and very destructive (Fig. 64.1).

These are produced in an attempt to extricate the organism using fingernails to produce deep excoriations and resultant scarring. Most resort to instrumentation with nail files, scissors, needles, penknives, tweezers and nail clippers. Significantly, the most disturbed patients use surgical implements, handicraft knives and chemical corrosives which inflict significant damage, occasionally endangering their eyesight [22]. These follow attempts by the patient to extract the 'parasites' and are therefore not fabricated lesions but produced in an apparently legitimate attempt at cure. Usually, the patient will bring samples to the clinic but not always offer them unless asked directly. Commonly they reveal a small container, such as a matchbox or pill container enclosing their insects. More often they produce a sealed plastic bag or Ziplock (Fig. 64.2). Other samples which have been brought are collections of scales and crust, sellotape strippings of skin, folded elastoplast impregnated with debris and liquid samples collected from orifices. Debris collected as it 'falls' from the body or clothes, collected in the bath or shower tray and gathered at the hairdresser can amount to bags of detritus. On microscopy these offerings are usually found to be fragments of skin and hair, samples of fabric, and coagulated elements of serum, dust and dirt. The samples may include actual organisms such as ants, flies and sundry isolated fleas.

The purification rituals become rapidly established and are more frequent and elaborate. Patients are compelled to cleanse the skin and their environment with ever-increasing zeal. Their skin may smell of organic solvents such as benzyl benzoate or horticultural insecticide spray and the hands of bleach and disinfectant. A secondary general or localized, chemically induced insult dermatitis is a feature. This itchy dermatitis is a further reinforcement of the delusional belief. Clothes and soft furnishings are jettisoned, rooms cleared and mothballed, daily clothing and towels limited to two sets, one of which is used, the other in a sealed bag, after stringent cleaning, ready for use. These details are usually kept



Fig. 64.1 Excoriations in delusions of parasitosis in an amphetamine addict.



Fig. 64.2 Container of imaginary insects—from a patient with delusional parasitosis.

secret but as an important indicator of disease severity discreet enquires need to be made.

In 12% of cases delusions are shared with another individual [2,9,23], so-called *folie à deux*. This is defined in DSM-IV as a delusion developing in an individual in the context of a close relationship with another person, who has an established delusion. This does not refer to a close partner or friend who believes the patient's account but who crucially does not imagine they too have the infestation. The separate phenomenon of induced pruritus is a common sympathetic accompaniment in those close to the patient but does not mean induced secondary delusion. Again, this phenomenon is reported more often in women [23] and therefore the relationship between subjects is more often between sisters (34%), wife and husband (20%) and mother and child (20%). This contrasts with that reported between brothers (9%) and fathers and sons (2%). The disorder may rarely involve most or even whole families.

Diagnosis. Although it is unlikely the first task is to exclude scabies, bed bugs, insect mites, fabric or fibreglass impregnation. Rarely, onchocerciasis may confuse the unwary although the rash is usually prominent. In most cases the history, clinic behaviour, physical examination and presentation of specimens makes the diagnosis of DP obvious. It is also important to rule out underlying secondary organic disease, although this is rare. A clinical examination will exclude most organic disease but full biochemical investigation is advisable and most patients are happy to have 'tests'. Musalek *et al*. [3] have emphasized the importance of establishing the psychiatric diagnosis before instituting treatment. However, presentations in patients with secondary delusions as part of a depression or dementia may present in a more subtle fashion. The nature of depression may make the patient less communicative, and more guilt ridden. A short inquiry about features of depression can clarify this element of the diagnosis. Questions about widowhood, the empty nest syndrome, social isolation because of physical disability or retirement can be folded into the history. There may be a need to actively enquire about beliefs of infestation in a patient who complains of itching alone. Clinically, there may be a need to distinguish between a true delusion and an overvalued idea [3,4]. This latter is an acceptable comprehensible idea carried on beyond the bounds of reason.

Management. It should be remembered that suicide is an ever-attendant risk in these patients [1,4]. The management of patients with delusional parasitosis is always difficult. The basis of the consultation is to change the agenda from one of dermatological infestation as seen by the patient to one of psychiatric intervention. The shakeability of the belief depends on the psychiatric assessment. It is therefore essential to maintain a cohesive doctor–patient relationship. The first consultation is crucial. It is important to look, listen and be empathetic; to defuse the anger and tension but never to collude with the belief, nor to mention the parasites directly. It is preferable to mention 'the problem', 'the itch', 'the discomfort'. The full consultation process should be pursued, with adequate time given for the history, and proper care taken in the physical examination. All samples should be examined at the time and under the microscope. If none are volunteered encourage them to bring or send examples. Report truthfully what you see and invite the patient to look also. If you are perfunctory about this the patient will be less likely to continue with the same cooperation. Neither is it helpful to say directly on the first visit that he or she has a mental problem.

Listen politely without interruption and resist the temptation to question the singular interpretation of events. This non-judgemental acceptance of events does much to reduce the often fevered nature of the first consultation and reduce the isolation and fervency of the patient's feelings. Do not get drawn into the criticism of past consultations of others. This is an opportunity to reassure them that the consultation is 'new' with no strings but also gives the time when an assessment of the psychiatric state can be made (see above), particularly the presence of features of depression.

If the patient has been told previously that they are 'imagining it' they need to be reassured that to them the symptoms are real and that you recognize this. This does not imply an alliance on thought content. It is necessary to say that you have seen this problem before, that sometimes the reason for the symptoms is not always clear. After two to three visits and examination of more samples both in the consulting room and the laboratory there comes an opportunity to discuss further the 'whole illness', meaning the skin symptoms and the distress, anxiety and depression. If there is a history of using recreational drugs this needs mentioning also. At this time it is also useful to remind the patient of the dominance this illness plays in their life and the need to treat them even though there are differences in interpretation of the sensations. Some psychodermatologists have suggested that perhaps the sensations remain in the skin in very sensitive and aware individuals even though the precipitating event has receded. These feelings can be more intense and sometimes out of control the more the illness 'gets you down' and makes you depressed. Explain that this is an illness that torments otherwise sane individuals and that this does not make them 'irredeemably crazy'.

It is at this stage that there are indications as to the shakeability or not of the belief. For those with a recognized anxiety, social isolation or depression it is possible to discuss the next stage of psychotherapy, or antidepressants such as doxepin, citalopram or venlafaxine. Referral to a psychiatrist can be offered for consideration either then or in the immediate future. The very difficult problem of the truly deluded patient with an unshakeable belief needs the help of a psychiatrist, ideally as part of a psychodermatology team or failing that a liaison psychiatrist who is familiar with the work in the dermatology department and can see the patient on site. The failure and non-attendance rate for paper and distant referrals to psychiatry is enormous and it is better to continue attendance at the skin department in the expectation that the situation may change under the influence of relatives and input of a primary care physician [4,5].

A surprising number of patients will accept medication to help their distress even though it is not directed at the eradication of the 'parasites'. If broached in terms of using a medication which 'has helped others before' and 'getting started to help in some way' you can suggest an antidepressant if there are significant signs of depression but it is mandatory to refer to a psychiatrist if there is any indication of risk of suicide [24]. Initially, it is often best to admit the patient to hospital. This reduces pressure at

home on other family members and ensures compliance with medication. A psychiatric colleague can more easily be asked to see the patient in the dermatology ward. The further management is ideally a joint consultation with liaison psychiatry but the inevitable difficulty is to convince the patient that this is a psychiatric problem.

The response to pimozide is often good in these patients and the initial dose, 2 mg, is increased weekly by 2 mg increments as necessary to a maximum of 12 mg daily. On higher doses, patients may develop extrapyramidal symptoms which requires addition of benztropine 1– 2 mg up to four times per day. In addition, with higher doses of pimozide there is a definite risk of ventricular arrhythmias and other electrocardiogram (ECG) abnormalities such as prolongation of the Q–T interval and T-wave changes. An ECG should be performed before pimozide therapy, and the drug should not be given to patients with a prolonged Q–T interval or to patients with a history of cardiac arrhythmia. Patients taking long-term pimozide should have an ECG at least once a year and if the Q–T interval is prolonged, treatment should be reviewed or withdrawn [18]. Moreover, concurrent treatment with other antipsychotics, tricyclic antidepressants and drugs that prolong the Q–T interval, such as the antihistamines terfenadine and astemizole, antimalarials, or drugs such as diuretics that alter the electrolyte status, should be avoided. Hypokalaemia may predispose to the cardiotoxic effects of pimozide and care should be taken in patients with hepatic or renal dysfunction.

Many physicians, including the authors, have found that the usefulness of pimozide is outweighed by the possible complications. Other equally effective treatments exist with the availability of other antipsychotics. The so-called atypical antipsychotics have a better side-effect profile and in case reports are effective. Alternative effective therapy with a better side-effect profile includes sulpiride 200–400 mg per day and amisulpride [6], which are selective dopamine antagonists. Extrapyramidal side effects are rare with no risk of arrhythmias. The antipsychotic respiridone is both a dopamine blocker and a serotonin antagonist and has proved of further use in doses of 1–8 mg per day [24]. Olanzapine has a higher affinity as a serotonin blocker than a dopamine antagonist and can be effective in surprisingly small doses. The side-effect profile is significant in high doses, including weight gain and disturbed glucose tolerance. When compliance is a problem, depot neuroleptics such as haloperidol may be used [6], but these are best reserved for specialist psychiatric use.

Patients frequently defect from follow-up clinics with the consequent risk of relapse. Therefore strenuous efforts should be made to maintain contact either via the general practitioner or community psychiatric services.

References

1 Sims A. Delusions and other erroneous ideas. In: Sims A, *Symptoms in the Mind*. London: W.B. Saunders, 1995: 101–11.

2 Munro A. Delusional parasitosis paranoia or delusional disorder. In: Bhugra D, Munro A, eds. *Troublesome Disguises. Underdiagnosed Psychiatric Syndromes*. Oxford: Blackwell, 1997: 24–51.

3 Musalek M, Bach M, Passweg V, Jaeger S. The position of delusional parasitosis in psychiatric nosology and classification. *Psychopathology* 1990; **23**: 115–24.

4 Musalek M. Delusional parasitosis. In: Koo J, Lee CS, eds. *Psychocutaneous Medicine*. Basel: Decker, 2003: 143–52.

5 Zanol K, Slaughter J, Hall R. An approach to the treatment of psychogenic parasitosis. *Int J Dermatol* 1998; **37**: 56–63.

6 Lepping P, Russell I, Freundenmann RW. Antipsychotic treatment of primary delusional parasitosis. *Br J Psychiatry* 2007; **191**: 198–205.

7 Trabert W. 100 years of delusional parasitosis. Meta analysis of 1223 case reports. *Psychopathology* 1995; **28**: 238–46.

8 Skott A. Delusions of infestation. *Reports from the Psychiatric Research Centre*, University of Goteborg, Sweden 1978; **13**: 1–118.

9 Munro A. Delusional parasitosis: a form of monosymptomatic hypochondriacal psychosis. *Semin Dermatol* 1983; **2**: 197–202.

10 Ekbom KA. Presenile delusional parasitosis. *Acta Psych Neurol Scand* 1938; **13**: 227–59.

11 Thibierge G. Les acarophobes. *Revue Generale de Clinique et de Therepeutique* 1894; **32**: 373–6.

12 Perrin L. Des nevrodermies parasitophobiques. *Ann Derm Syphil* 1896; **7**: 129–38.

13 Lyell A. Delusions of parasitosis. *Br J Dermatol* 1983; **108**: 485–99.

14 Driscoll MS, Rothe MJ, Grant-Kels JM, Hale MS. Delusional parasitosis: a dermatologic, psychiatric, and pharmacologic approach. *J Am Acad Dermatol* 1993; **29**: 1023–33.

15 Mitchell J, Vierkant AD. Delusions and hallucinations of cocaine abusers and paranoid schizophrenics: a comparative study. *J Psychol* 1991; **125**: 301–10.

16 Huber M. Delusional parasitosis and the dopamine transporter. *Med Hypotheses* 2007; **68**: 1351–8.

17 Guaneri F, Guaneri C. Pseudodelusory syndrome caused by Limothrips cerealllum. *Int J Dermatol* 2006; **43**: 197–9.

18 Reilly TM, Batchelor DH. The presentation and treatment of delusional parasitosis: a dermatological perspective. *Clin Psychopharmacol* 1986; **1**: 340–53.

19 Nel M, Schoeman JP, Lobetti RG. Delusions of parasitosis in clients presenting pets for veterinary care. *J South African Vet Assoc* 2001; **72**: 167–9.

20 Maeda K, Yamamoto Y, Yasuda M, Ishii K. Delusions of oral parasitosis. *Prog Neuropsychol Psychiatry* 1998; **22**: 243–8.

21 Sherman MD, Holland GN, Holsclaw DS *et al*. Delusions of ocular parasitosis. *Am J Ophthalmol* 1998; **125**: 852–6.

22 Lim GC, Chen YF, Lui L. Camphor related self-inflicted keratoconjunctivitis in delusions of parasitosis. *Cornea* 2006; **25**: 1254–6.

23 Hughes TA, Sims A. Folie a deux. In: Bhugra D, Munro A, eds. *Troublesome Disguises. Underdiagnosed Psychiatric Syndromes*. Oxford: Blackwell, 1997: 168–94.

24 Koo J, Lee CS. Delusions of parasitosis. A dermatologist's guide to treatment. *Am J Clin Dermatol* 2001; **2**: 285–90.

Olfactory delusions [1–3]

Synonyms

- Delusions of smell
- Olfactory delusional syndrome
- Olfactory reference syndrome
- Bromidrosiphobia

This complaint is important for dermatologists because they are more likely than any other speciality to see patients who complain of unpleasant body odour. This is usually assumed to be related to either sweating or sebum excretion. The cultural significance of body odour varies with ethnic group but an excessive or unpleasant body smell carries with it social and psychological significance and judgements.

Patients who do have intense body odour because of self-neglect, beliefs of natural existence without washing or phobias about washing are easily identified. There are patients who smell because of disease [4]. Nevertheless those who emit a strong smell, whether it be for the reasons above or from wounds, exfoliative skin or contaminated dressings, will suffer from the self-righteous opprobrium of a section of society such that they will feel guilty and be stigmatized.

As with patients with erroneous beliefs of infestation, the false belief about body smell can represent various psychiatric aetiologies [3,5,6]. As a monosymptomatic hypochondriacal delusion it may be difficult to differentiate an olfactory hallucination from a delusion as this is also a symptom of a schizophrenic illness. Men are more likely than women to develop this belief in a ratio of 4–5:1 [3–6]. Schizophrenic patients are more likely to be young men with severe, disabling beliefs accompanied by personality deterioration and paranoid features [6]. Others with beliefs of delusional intensity have compensatory, excessive cleansing rituals and associated social avoidance patterns which may be a monosymptomatic delusion or body dysmorphic disorder (see below) of delusional intensity. In depression the symptom is an expression of feelings of worthlessness and negative self-evaluation and accompanied by the other vegetative signs of sleep, appetite and behaviour alterations. Patients may voice an association between the unpleasant odours and disgust or guilt, especially of a sexual nature.

The patient 'knows' that they are emitting a foul odour. They believe that the origin of the smell is usually flatus and may have seen a gastroenterologist. Occasionally, they believe that foul sweat is produced in excess from body folds and orifices. Most patients complain that the smell comes from the groin or sometimes the armpit. Those with paranoid features believe that other people avoid them and talk about them with evident disgust [1,6]. A subgroup of patients complain of unbearable halitosis and plague dentists. This delusion is commonly related to a chronic avoidant paranoid personality trait [7].

Organic syndromes should be noted. Delusions of smell have been associated with cerebral tumours, epilepsy, alcoholism and substance abuse [8,9]. Konuk [10] also showed that frontotemporal hypoperfusion could be a feature. Psychotherapy may occasionally be successful but antidepressants and antipsychotics are indicated, as for delusions of parasitosis.

References

1 Videbech T. Chronic olfactory paranoid syndromes. *Acta Scand Psychiat* 1966; **42**: 183–212.
2 Pryse-Phillips W. An olfactory reference syndrome. *Acta Psych Scand* 1971; **47**: 485–509.
3 Malasi TH, El-Hilu SR, Mirza IA. Olfactory delusional syndrome with various aetiologies. *Br J Psychiatry* 1990; **156**: 256–60.
4 Senol M, Fireman P. Body odour in dermatological diagnosis. *Cutis* 1999; **63**: 107–11.
5 Osman A. Monosymptomatic hypochondriacal psychosis in developing countries. *Br J Psychiatry* 1991; **159**: 428–31.
6 Bourgeois M. Autodysmorphobia and olfactory reference syndrome. *Ann Medico-Psychol* 1973; **2**: 353–76.
7 Iwu CO, Akpata O. Delusional halitosis. Review of the literature and analysis of 32 cases. *Br Dent J* 1990; **168**: 294–6.
8 Devinsky O. Olfactory reference syndrome in a patient with partial epilepsy. *Neuropsychiatry* 1998; **11**: 103–5.
9 Warnecke M, Bahlmann M. Olfactory delusional syndrome and alcoholism. *Psychiatr Prax* 2002; **4**: 211–3.
10 Konuk N. Frontotemporal hypoperfusion in a patient with olfactory reference syndrome. *Gen Hosp Psychiatry* 2006; **28**: 174–7.

Morgellons syndrome [1,2]

In 2002, a biologist whose 2-year-old child developed sores on the skin 'discovered' that the multicoloured fibres coming from her child's lesions were undiagnosable by the multitude of physicians she consulted. The Morgellons were described by Sir Thomas Browne in 1674 as a population in the Languedoc, one of whose characteristics was the development of a hairy back. Nevertheless this misnomer was coined to name a syndrome, set up a research foundation, raise funding and generate vast media and Internet interest.

The phenomenon comprises:

- Sensations of crawling, stinging and biting under the skin
- Sores that do not heal
- Fibre-like filaments, granules and crystals that appear on or under the skin lesions
- Joint and muscle pain and fibromyalgia
- Debilitating fatigue
- Cognitive dysfunction, poor concentration and memory.

Most dermatologists recognize the familiarity between this constellation of symptoms and patients with delusions of parasitosis but more particularly of delusions of impregnation and extrusions who have presented more rarely. An examination of the Internet website shows the disparate and heterogeneous nature of the respondents, similar to the websites dedicated to the treatment of non-identifiable parasites. It has been described as a rapport-enhancing term for delusions of parasitosis [2]. Researchers at the Morgellons Foundation have suggested Lyme disease is to blame as well as agricultural filamentous yeasts [3]. The US Center for Disease Control has set up an independent study to evaluate the phenomenon. Treatment responses to pimozide and risperidone have been recorded [4].

References

1 Kellet CE. Sir Thomas Browne and the disease called Morgellons. *Ann Hist Med* 1935; **7**: 467–79.
2 Murase JE, Koo J. Morgellons disease: a rapport enhancing term for delusions of parasitosis. *J Am Acad Dermatol* 2006; **55**: 913–4.
3 Elkan D. Morgellons disease: real or delusion. *New Scientist* 2007; **195**: 45–9.
4 Koblenzer C. The challenge of Morgellon's disease. *J Am Acad Dermatol* 2006; **55**: 920–2.

Disorders of body awareness

Body dysmorphic disorder [1–3]

Synonyms

- Dermatological non-disease
- Dysmorphophobia

In 1886, Morselli [4] described dysmophophobia as a distortion of psychological body image and more recently 'dermatological non-disease' [5] has been used to describe patients who are rich in symptoms (especially in areas important in the body image) but poor in signs of organic skin disease [1,2]. All dermatology clinics contain these distressed patients whose chronic attendance is a reflection of their impaired family, social and occupational functioning. This disorder is defined in DSM-IV as body dysmorphic disorder (BDD) a preoccupation with an imagined defect in appearance; if a slight defect is present the person's concern is markedly excessive. In DSM-IV (TR) the revision separates the

distress caused by the apparent physical defect (B1) from the impairment in social, occupational and domestic functioning. Although BDD is classified as a somatoform disorder, there is a variant in which the belief is of delusional intensity and as such is regarded as a psychotic disorder and may have been included as another manifestation of monosymptomatic hypochondriacal psychosis [6]. There is significant evidence to classify BDD as one of the obsessive–compulsive disorders [2,7] based on similarities between OCD and BDD, the increased rates of OCD-related disorders in BDD [8], and OCD samples which show increased rates of BDD [9]. Those who disagree would point to the fact that insight is poor in BDD not only among the delusional type but also the non-delusional [10] whereas insight is usually good in OCD.

Prevalence. This condition was originally thought to be uncommon, but it is now clear that concern about the body image and some particular facet of self is remarkably common. The prevalence in the general population has been difficult to measure and therefore results vary from 12% [2] in a community, whilst a study of German students revealed a prevalence of 5.3% [11]. A point-prevalence study of a community sample of women in the USA showed a frequency of 0.75% [12]. A very thorough, large point-prevalence study found a prevalence of 1.7% of the population conforming to BDD criteria [11]. Previous studies with estimates of 0.7% were confounded by selective populations, for example students or geography. This is more often a female disorder, though marginally so with a female:male ratio of 3:2 to 2:1 [1,2,10,11]. Studies of body dissatisfaction not amounting to BDD suggest that 27% of men and 40% of women are unhappy about at least one part of their body [2,9,11]. In dermatology clinics, 8.5–12% have diagnosable BDD [13,14] and 9% of mild acne patients fulfil the criteria for BDD. Aesthetic clinics show a prevalence of 6% [9,15] for BDD with 18% at a subthreshold level. In a plastic surgery clinic those who conform to BDD criteria vary from 3.2 to 20% [2,9]. These rates may be underestimates because BDD is often a secret illness, revealed only to relatives or to physicians when under severe duress. Grant *et al*. [16] reported that 13% of psychiatry in-patients had BDD symptoms but these were only demonstrable on direct inquiry.

Aetiology. Theories on the aetiology of BDD reflect the knowledge of disease characteristics and treatment response. The cognitive behavioural theory suggests that sufferers from BDD have self-defeating thoughts, cognitive distortions and aberration and destructive beliefs about themselves and their appearance [17]. The development of selective processing of emotional information about body image, physical appearance and interpersonal contact may be related to anxiety disorders and social phobias. BDD patients exhibit more perfectionist thinking and maladaptive attractiveness beliefs [18] and it is assumed that these are aetiological rather than symptomatic [18]. In support, it has been suggested that childhood abusive experiences may result in body dissatisfaction, bodily shame, low self-esteem and body image distortion [19–21].

Neurobiological theories relate BDD to acquired brain abnormalities and parietal lobe function. Neurochemical and psychopharmacological evidence suggests that abnormal serotonin metabolism also contributes to BDD [22]. By contrast, social and cultural influences are assuming an increasing importance of personal bodily appearance because of the pressures that the perceived concepts of beauty and the quest for perfection play at present in public and media-driven societies. These pressures shape the attitudes of both women and men. Women are socially driven to view and treat themselves as objects [19] whilst men are pushed towards an often unattainable body image, the Adonis complex [23] of muscular perfection even though they use illegal oral steroid supplements. This sociocultural model opens up further therapeutic pathways, particularly postmodern narrative therapy [19].

BDD is often co-morbid with other mental disorders. For instance depression may occur in 60% and a lifetime rate of up to 80% has been reported [1,24]. The depressive symptoms may be subclinical but are revealed on direct questioning. An obsessional premorbid personality is not unusual [2,8] and co-morbidity with obsessional compulsive disorder may be found in 30% [2,9]. Dysmorphophobic symptoms in a teenager or adult may be the presentation of schizophrenia, while in an elderly patient dementia should be considered. Co-morbid psychiatric conditions have also included social phobia, that is fear of a negative impact (37%), substance abuse (40%), and avoidant personality disorder [10,25]. In a study of patients with anorexia nervosa, 39% were diagnosed with co-morbid BDD unrelated to concerns about weight. These individuals had higher levels of delusionality and lower levels of social functioning than those with eating disorders alone [26]. There is usually no evidence of any underlying organic disease.

Clinical features. The problem of BDD is disturbing for dermatologists because their clinical expectations are confounded and they are disenfranchized from participation because there is little or nothing to see. For the patient there exists a state of stigmatization and all the personal dread, loathing and discontent that goes with these insistent compulsive thoughts.

Affected individuals are more often solitary, unmarried or divorced. As a whole they socialize poorly and do not like contact with other people [1,2,10]. Those with severe symptoms are more likely to be unemployed. Their symptoms may appear after severe emotional, especially marital, or sexual problems.

Most patients are in their third decade although reported ages are from 5 to 80 years. The duration of symptoms is long, from 11 to 18 years [8,10]. Women are affected slightly more often than men [2,11] although referral sources may affect the statistics. Dermatological non-disease presents with symptoms that appear to have gender differences. For women the sites of dominance were skin, mainly face, breasts, hair, nose and stomach, whereas men presented with concerns about hair (usually thinning), nose, ears, genitals and body build [27]. Facial symptoms include complaints of excessive redness, blushing, a burning feeling, scarring, large pores, excessive facial hair and facial greasiness. Scalp symptoms include a feeling of intense burning, unremitting by day or night, and excessive hair loss. Those patients with facial and scalp problems are more often female than male, but those with perineal

symptoms are more likely to be male than female. Perineal symptoms in males include complaints of an excessively red scrotum, discomfort in the genital area, often spreading to the anterior thighs making the wearing of clothes uncomfortable. This is described rather cumbersomely as the dysthaesic penoscrotal syndrome [28]. Women had more concerns about perceived flaws than men, sometimes up to four areas in 40%, the effect being additive with time. Women develop BDD earlier than men, although men more often show severe delusional forms [29].

A consultation with a patient with dermatological non-disease always takes much longer than with a patient with organic disease. The content of the consultation is dominated by complaints of ugliness, unattractiveness and irreconcilable deformity. It is important to remember that this long consultation can consume vast amounts of time to no great purpose unless it is used to assess, firstly, the effect of personal behaviours induced by the illness on life quality and, secondly, the impaired functioning of the patient's daily social, family and work life. Their thoughts are dominated by the abnormality for up to 8 h per day, the distress is intense, self-esteem poor and insight minimal. They perform repetitive, almost compulsive, behaviours with excessive grooming, repeatedly applying makeup to hide the 'defect', changing hairstyles and altering clothes to disguise the problem. Inappropriate dress such as veils, or coats with high collars or long gloves on hot days are not unusual. Dark glasses, huge wigs and excessive tans are other devices used to hide the defect; 'mirror gazing' is irresistible and time-consuming as part of continual checking behaviours [3]. Patients are driven by the desire to know what they look like, a desire that is made worse if they resist the urge. BDD patients invariably feel worse after mirror watching but cannot resist looking in other reflective surfaces such as shop windows, chromed surfaces, cutlery and shiny CDs. This continual mirror watching may be to show the 'best face' to the public and avoiding the feared adverse attention. Other activities and behaviour may be stimulated by these beliefs with diet regimes, the purchase of enormous quantities of beauty products and the seeking of unending aesthetic treatments. Muscle dysmorphia describes men who use illicit anabolic steroids and obsessive weight training to develop their body, so called 'bigorexia'.

Patients with BDD touch, tease, adjust, squeeze and pick their skin. The picking may become pathological, intense and time consuming. The episodes begin as a minor peel and pick at a small lesion and progress to a prolonged 'binge'. Some confess to eating the scabs. After hours the damage done is so appalling that the patient can no longer go out, and is more distressed than before. When picking reaches this stage the effect on family, social and work life is significant. At first, the patient arrives late for work, has significant absences for toilet room breaks, and then eventually misses days at work. They may become unemployed. An increasing reclusiveness curtails social life and family, friends and partners become estranged. Alcoholism and drug abuse may follow.

Patients with dermatological non-disease are 'doctor shoppers' and will have often seen many doctors about their many problems over the years. An individual patient is likely to return to the clinic within a few minutes of being seen and may repeatedly telephone the doctor asking questions that have already been answered many times in the immediate past. Uncommonly, the delusional type of BDD gives rise to familial BDD where a parent imposes a delusional idea upon a child who in turn develops BDD [30] or even more rarely the patient believes that their child has a bodily defect, BDD by proxy [31].

There is a definite risk of suicide in patients with BDD [1,8–11]. High rates of suicidal ideation (78%) and suicide attempts (27.5%) in some series may have been because of co-morbid factors such as lifetime depression or eating disorder [8,29]. Significant but lower estimates of ideation (20%) and attempts (7%) were found by Reif *et al*. [11]. They also found that a group with subthreshold BDD features, that is body concerns not reaching BDD criteria, had a 1% rate of attempted suicide. A prospective study [32] over 4 years in 185 subjects with BDD showed 58.7% reported suicide ideation, 2.6% attempted suicide per year and 0.3% completed suicide per year. The risk is very real. A transcultural study of BDD [33] showed no significant variations in features between Brazilian, North-American and European populations.

Dermatological and plastic-surgical treatment [9]. Most patients with dysmorphophobia perceive the solution to their problems as dermatological, aesthetic or plastic-surgical treatment. They 'shop' between doctors to find one who will perform the procedure which is the answer to their problem, and so come to haunt dermatologists and plastic surgeons rather than psychiatrists. Some patients demand repeated medical cosmetic treatments such as botulinum toxin, so called botulophilia, and repeated face peels. In a series of 130 patients, it was found that 30% had received previous cosmetic surgery, with a mean of 2.0 ± 1.3 procedures and as many as six procedures had occurred in individual patients. Two international studies reported rates of 6.3 and 9% BDD amongst cosmetic surgery patients [9,15]. A perfect cosmetic result may be perceived by a depressed, dysmorphophobic patient as worse than the situation before surgery. In a large study 91% of patients reported no improvement in symptoms [9] and furthermore, 81% of patients with body dysmorphic disorder were either dissatisfied or very dissatisfied with their consultation and results of surgery [8]. A study of patients who had either BDD or sub-BDD concerns showed that after 5 years most were dissatisfied with the operative result despite earlier, immediate postoperative satisfaction. In addition, half of those with sub-BDD concerns developed full BDD criteria despite operative intervention [34]. If aesthetic or plastic surgery is planned in this group of patients it is very important to have careful preoperative psychiatric assessment. Those contemplating surgery should remember that some patients with body dysmorphic disorder are angry and easily progress to litigation. One-third of aesthetic surgeons [35] had threats of legal action from BDD patients. More crucially, 2% of BDD patients threaten their physicians and surgeons physically and at least two cosmetic surgeons have been murdered by patients with BDD. Photography before and after surgery is important to refute legal claims objectively. However, plastic surgery in carefully selected cases may be deemed helpful, assessment with preoperative questionnaires may temper the surgical decision. There is always a risk that the patients may then move their preoccupation to another part of the body.

Diagnosis [1–3]. BDD is often diagnosed late, up to 11 years after initial symptoms. This is possibly because patients are reluctant to disclose their distress, shame and embarrassment. The clinical clue for dermatologists may be a persistent return to the clinic for a harmless, small lesion or presentation as a persistent picker. These patients make up a large proportion of the querulous and disenchanted complainers. Most experienced dermatologists have a well developed 'BDD radar' but the trainee will always be vulnerable to the demands of these patients. BDD should be asked about; brief questionnaires to expose BDD-related thoughts and behaviours [2,3] and a longer structured instrument, the BDD Examination [35], which includes measures of severity, are available.

Management. The management of patients with dermatological delusional disease is always difficult and should not be done by the inexperienced. The most difficult task is to make the transfer from a primary dermatological illness of perceived flaws to one which requires psychiatric care. This is not unlike the management of primary skin delusions. There is nothing to be gained by talking about either the non-existence or minimal nature of the lesions. The way forward is to talk about the presentation of *illness* about which both patient and physician are agreed. Demonstration of the distress, disability and impairment of function as a consequence of the illness will show an empathetic response. The next step is to talk about differences in interpretation which does not invalidate any of the profound distress and dysfunction this has caused. It is valid to explain that nobody knows why the patient, their partners and friends and physicians see the problem differently, but the aim is to use treatment which has been proven to help. There are a number of useful texts and websites which can serve as 'homework' for patients between consultations [3].

Treatments that have been shown to be successful are pharmacotherapy with specific serotonin reuptake inhibitors (SSRIs) [1], or psychological treatments such as cognitive behavioural therapy, or a combination of both [21].

Treatment with SSRIs. Early open studies showed that nearly 50% of patients may respond completely or partially to fluoxetine or clomipramine, whereas there was only a 5% response to all other medications. A systematic review of trials [36] confirmed that over 60% of patients have a significant improvement in symptoms. It is important that the medication be continued long term, as discontinuation precipitates relapse in 80%. All SSRIs are equally effective and the choice depends on tolerability. Those most studied have been fluoxetine, fluvoxamine and citalopram. A randomized, controlled trial of fluoxetine showed it was superior to placebo [1]. In many patients there is a significant improvement in the social prognosis evidenced by an ability to return to school or work, and this is accompanied by a reduction in ritualistic behaviour, such as mirror checking and skin picking. Only a small proportion of patients responding to SSRI drugs experience any change in insight. A review of the addition of anti-psychotic drugs such as pimozide or olanzepine demonstrated inconclusive benefits [9].

It is important to note that sometimes the effective dosage of SSRI drugs is higher than the dosage conventionally used to treat depression, for fluoxetine 50 mg/day and for fluvoxamine 260 mg/day. The dose of SSRI needs to be high and the duration of treatment is also long term, with response taking, on average, 2–4 months. The duration of treatment is usually at least a year. Venlafaxine 37.5 mg/day can be substituted for the SSRI. The help of the liaison psychiatry services should be used at this stage.

Cognitive behavioural therapy [2,21]. Simple behavioural treatment, such as encouraging patients to avoid ritualistic behaviour and mirror checking, and urging them to give up unnecessary cosmetic camouflage, while gradually exposing them to the most feared social situations, can be helpful. This is especially true if combined with a cognitive approach involving self-esteem building and modification of distorted thinking, coupled with coping strategies. All these techniques are more likely to be effective when combined with SSRI treatment, and initially some patients may be too ill to benefit from a cognitive behavioural approach. This needs the help of a skilled clinical psychologist but has the advantage that it is often more acceptable to the patient. Stress and symptom reduction may be as much as 77%.

Supportive psychotherapy can be helpful in patients with overvalued ideas and who are not truly deluded, but it is very time consuming and emotionally demanding. Patients with body dysmorphic disorder are poor communicators and difficulty with interpersonal relationships may be one of the central, crucial and earliest features of this disorder. The physician undertaking supportive psychotherapy has to be patient and realize that further skilled directive intervention will eventually be needed from psychiatrists or clinical psychologists. Body dysmorphic patients are poor attenders at clinics, but the consultation may in some cases be the only opportunity that a patient has to talk to another human being, a reflection of the isolated life these patients often lead. The dermatologist's essential role is to recognize the problem and sympathetically steer the patient on the correct path to help.

Narrative therapy [19]. Narrative therapy addresses the sociocultural causes which may establish beliefs, in this case about the body. The change process in narrative therapy involves helping patients replace these influences by more preferred stories about their problems and lives. Single case studies have been encouraging.

References

1 Castle DJ, Phillips KA, eds. *Disorders of Body Image*. Philadelphia: Wrightson Biomedical Publishing, 2002.
2 Veale D. Body dysmorphic disorder. *Postgrad Med J* 2004; **80**: 67–75.
3 Phillips KA. *The Broken Mirror*. New York: Oxford University Press, 2005.
4 Morselli E. Sulla Dismorfofobia et sulla tafefobia. *Bull Acad Sci Med Genova* 1886; **6**: 110–5.
5 Cotterill JA. Dermatological non-disease: a common and potentially fatal disturbance of cutaneous body image. *Br J Dermatol* 1981; **104**: 611–8.
6 Munro A. Delusional parasitosis: a form of monosymptomatic hypochondriacal psychosis. *Semin Dermatol* 1983; **2**: 197–202.
7 Mataix-Cols D, Pertusa A, Leckman JF. Issues for DSM-V: classification of obsessive–compulsive and related disorders. *Am J Psychiatry* 2007; **164**: 1313–7.
8 Veale D, Boocock A, Gournay K *et al*. Body dysmorphic disorder: a survey of fifty cases. *Br J Psychiatry* 1996; **168**: 196–201.

9 Crerand CE, Franklin ME, Sarwer D. Body dysmorphic disorder and cosmetic surgery. *Plastic Reconstruct Surg* 2006; **118**: 167–80.
10 Phillips K. The presentation of body dysmorphic disorder in medical settings. *Primary Psychiat* 2006; **13**: 51–9.
11 Reif W, Buhlmann U, Wilhelm S *et al*. The prevalence of body dysmorphic disorder: a population-based study. *Psycholog Med* 2006; **36**: 877–85.
12 Otto MW, Wilhelm S, Cohen LS. Prevalence of body dysmorphic disorder in a community sample of women. *Am J Psychiatry* 2001; **158**: 2061–3.
13 Phillips KA, Dufresne RG. Rate of body dysmorphic disorder in dermatology patients. *J Am Acad Dermatol* 2000; **42**: 436–41.
14 Vulink NC, Sigurdsson V, Kon M *et al*. Body dysmorphic disorder in outpatient dermatology and plastic surgery clinics. *Ned Tijdschr Geneeskd* 2006; **150**: 97–100.
15 Altamura C, Paluello MM, Mundo E. Clinical and subclinical body dysmorphic disorder. *Eur Arch Psychiatry* 2001; **251**: 105–8.
16 Grant JE, Kim SW, Crow SJ. Prevalence and clinical features of body dysmorphic disorder in adolescent and adult psychiatry inpatients. *J Clin Psychiatry* 2001; **62**: 517–22.
17 Osman S, Cooper M, Hackman A, Veale D. Spontaneously occurring images and early memories in people with body dysmorphic disorder. *Memory* 2004; **12**: 428–34.
18 Buhlmann U, Etcoff NL, Wilhelm S. Facial attractiveness ratings and perfectionism in body dysmorphic disorder and obsessive-compulsive disorder. *J Anxiety Disorder* 2007; **21**: 289–98.
19 da Costa D, Nelson TM, Rudes J, Guterman JT. A narrative approach to body dysmorphic disorder. *J Mental Health* 2007; **29**: 67–81.
20 Didie E, Tortolani C, Pope CG *et al*. Childhood abuse and neglect in body dysmorphic disorder. *Child Abuse* 2006; **30**: 1105–15.
21 Veale D. Advances in the cognitive–behavioural model of body dysmorphic disorder. *Body Image* 2004; **1**: 113–25.
22 Hadley S, Newcorn J, Hollander E. The neurobiology and psychopharmacology of body dysmorphic disorder. In: Castle DJ, Phillips KA, eds. *Disorders of Body Image*. Philadelphia: Wrightson Biomedical Publishing, 2001: 139–57.
23 Pope HG, Phillips KA, Olivardia R. *The Adonis Complex*. New York: Free Press, 2000.
24 Gunstad J, Phillips KA. Axis 1 comorbidity in body dysmorphic disorder. *Compr Psychiatry* 2003; **44**: 270–5.
25 Phillips KA, McElroy SL. Personality disorders and traits in patients with body dysmorphic disorder. *Compr Psychiatry* 2000; **41**: 229–36.
26 Grant JE, Kim SW, Eckert ED. Body dysmorphic disorder in patients with anorexia nervosa: prevalence, clinical features and delusions of body image. *Int J Eating Dis* 2002; **32**: 291–300.
27 Phillips KA. Gender differences in body dysmorphic disorder. *Compr Psychiatry* 2006; **47**: 77–87.
28 Markos AR. The male genital skin burning syndrome (dysthaesic peno/scrotodynia). *Int J STD-AIDS* 2002; **13**: 271–4.
29 Phillips KA, Menard W, Pagano ME *et al*. Delusional versus nondelusional body dysmorphic disorder. *J Psychiatry Res* 2006; **40**: 95–104.
30 Seaton ED, Baxter KF, Cunliffe WJ. Familial dysmorphophobia. *Br J Dermatol* 2001; **144**: 439–40.
31 Atiullah M, Phillips KA. Fatal body dysmorphic disorder by proxy. *J Clin Psych* 2001; **62**: 204–5.
32 Phillips KA, Menard W. Suicidality in body dysmorphic disorder: a prospective study. *Am J Psychiatry* 2006; **163**: 1280–2.
33 Fontanelle LF, Telles LL, Nazar BP *et al*. A sociodemographic, phenomenological, and long term follow up of patients with body dysmorphic disorder in Brazil. *Int J Psychiatry* 2006; **36**: 243–59.
34 Tignol J, Baraben L, Martin C *et al*. Body dysmorphic disorder and cosmetic surgery. *Eur Psychiatry* 2007; **33**: 520–4.
35 Sarwer DB. Awareness and identification of body dysmorphic disorder by aesthetic surgeons. *Aesthetic Surg* 2002; **22**: 531–8.
36 Phillips KA. Treating body dysmorphic disorder using medication. *Psychiatr Ann* 2004; **34**: 945–52.

Anorexia nervosa and bulimia [1–5]

Eating disorders are considered primarily psychiatric illnesses which have significant physical complications. Anorexia nervosa (AN), bulimia nervosa (BN) and a third group classified as eating disorders not classified (EDNOS) are particularly common among young women and are increasing in incidence. Anorexia nervosa now has an incidence of up to 1% and bulimia up to 5% [1]. Reviews [6–8] suggest a lifetime prevalence of 2.2% with over half the cases not detected initially in the health care system. The annual prevalence is about 0.3% for AN and 1% for BN, although this may be higher in women aged 15–24 years. The incidence is 270 per 100 000 person years in this group of younger women compared to 8 per 100 000 person years in the group of women as a whole.

Definitions. Anorexia nervosa must satisfy the criteria for:

1 An inability to maintain the normal or minimum weight for age and height coupled with an intense fear of gaining weight; the BMI is less than 17.5 kg/m^2
2 A distorted perception of weight, size and body configuration
3 Amenorrhoea

Bulimia nervosa [9] is defined by the following:

1 Recurrent and compulsive overeating episodes (binge eating)
2 Recurrent and inappropriate compensatory behaviour in order to avoid gaining weight; these include induced vomiting and abuse of diuretics and laxatives
3 Binge eating and weight reduction behaviours occurring at least twice per week for 3 months
4 Self-esteem affected by weight and body configuration.

In the definition in ICD-10, body image distortion is one of the essential features. There is a dread of fatness as an intrusive, overvalued idea and the patient imposes a low weight threshold upon herself or himself. Anorexia occurs earlier in life, usually adolescence, whilst bulimia has its peak in later teens and early twenties. The majority are young women, the proportion of men being 1 in 20. White races predominate in published studies. The prevalence in Afro-Caribbean and Asian women is rare [6,10]. It is commoner in industrialized societies and much more frequent in those of high social class. There is a clear association between body image disturbance and eating disorder. The lower the weight the greater the degree of body image abnormality. There are descriptions of 'nervous consumption' in the 18th century as fashion dictated women wear wire bodices and bustles which emphasized the fashionable tiny waist. Fashion models are particularly newsworthy as a group suffering eating disorders, sometimes aggravated by substance abuse. Illness and death are not uncommon. Gymnasts, athletes and jockeys are other vulnerable groups. 'Fashionable' thinness is one of the precipitating factors for the disease.

There are associations with other psychodermatoses, body dysmorphic disorder and self-injurious behaviours, trichotillomania, severe onychophagia and fabricated dermatitis. Self-cutting, excoriations and bruising occurred in 44% of 134 female patients [11]. The suicide risk is higher than in the normal population [12].

The significant metabolic effects of these eating disorders have a marked effect upon all major body systems but particularly the skin. Signs are detectable earlier in the skin and the astute physician may well detect disease long before severe medical complications supervene, particularly in anorexia nervosa where illness from inanition is a real risk.

Table 64.2 Cutaneous manifestations of eating disorders.

Cutaneous manifestations	Frequency (%)
Xerosis	60–70
Hair loss	25–50
Angular cheilitis	42–75
Nail fragility and dystrophy	45
Acneform eruption	40
Gingivitis aphthae	35
Diffuse hypertrichosis	25–60
Acrocyanosis	30
Knuckle abrasions and calluses, Russell's sign (bulimia only)	4–60
Carotenoderma	20
Hyperpigmentation	12
Generalized pruritus	15
Seborrhoeic dermatitis	8
Follicular hyperkeratosis	5
Striae, scurvy, pellagra, peripheral oedema, pili torti, acquired acrodermatitis enteropathica	Rarely



Fig. 64.3 Russell's sign: callosities of the knuckles from manual forced vomiting in bulimia.

The nutritional and physical consequences of anorexia nervosa and bulimia are frequent with many dermatological sequelae. Gupta and Gupta [13] showed that patients with eating disorders were more concerned with dermatological problems than the normal population and thus would be more likely to attend for consultation (Table 64.2). Although reviews show some variation in the frequency of cutaneous signs in eating disorders [1–5], in general they are consistent.

The most frequent skin manifestation is xerosis with a particular form of branny scaling developing on the extensor surfaces of the limbs and flexures, often described as 'dirty skin'. Hair effluvium occurred in 50% and is slow to recover, even on weight gain. Nails are fragile, discoloured and patchily white. Angular cheilitis reflects iron and vitamin deficiency in half the patients. Diffuse lanugo hypertrichosis has been related to a reduction in 5α-reductase secondary to thyroid hypofunction. The abrasions and callosities of the knuckles (Russell's sign; Fig. 64.3), caused by the forcible contact with the incisor teeth during self-induced vomiting, may be present as an early sign.

As the bulimia becomes more chronic, vomiting may be provoked by manual abdominal pressure. An acneform eruption is frequent and may be pruritic, resembling acne excoriée. Paradoxically, food fads are common in anorexia and can cause carotenaemia following dietary loading with green vegetables and yellow/orange discoloration of carotenoderma. Poor wound healing and striae distensae were more common in the restrictive type of anorexia as opposed to the bulimic type, where hair and nail changes, seborrhoeic dermatitis and generalized pruritus were more prominent. Severe perniosis is also seen in individuals with anorexia nervosa [14]. Drenching night sweats during weight recovery, possibly due to secondary changes in thermoregulation which occur with rapid refeeding, have also recently been described in patients with eating disorders [15].

Russell's sign, hand dermatitis, interdigital intertrigo and brittle nails with dystrophy are highly suggestive of bulimia. In the mouth, there may be dental enamel erosion, caries and gingivitis. Some patients develop a Sjögren-like syndrome.

Other cutaneous features may result from the use of laxatives, such as phenolphthalein, producing a fixed drug reaction, and thiazide diuretics, producing photosensitivity, while the use of the emetic ipecac can be associated with a dermatomyositis-like syndrome. Compulsive hand washing and trichotillomania may result from accompanying psychiatric illness.

The alert dermatologist should suspect anorexia nervosa when presented with these suggestive signs, particularly hair loss, angular cheilitis and xerosis in an underweight girl. A simple screening questionnaire (SCOFF) [16] is helpful for detecting eating disorders. Eating disorders are largely undetected in the community. Patients are not resistant to the suggestion of specialist care and should be referred to a psychiatrist.

References

1 Strumia R. Dermatologic signs in patients with eating disorders. *Am J Clin Dermatol* 2005; **6**: 165–73.
2 Tyler I, Wiseman M, Crawford R. Cutaneous signs of eating disorders. *J Cutan Med Surg* 2002; **6**: 345–53.
3 Hediger C, Rost B, Itin P. Cutaneous manifestations of anorexia nervosa. *Scheeitz Med Wocheschr* 2000; **130**: 565–75.
4 Gupta MA, Gupta AK. Dermatologic signs in anorexia nervosa and bulimia nervosa. *Arch Derm* 1987; **123**: 1386–90.
5 Marshman GM, Hanna MJ, Ben-Tovin DI, Walker MK. Cutaneous abnormalities in anorexia nervosa. *Australas J Dermatol* 1990; **31**: 9–12.
6 Hoek H. Incidence, prevalence and mortality of anorexia nervosa and other eating disorders. *Curr Opin Psychiat* 2006; **19**: 389–94.
7 Keski-Rahkonnen A, Hoek H, Susser E *et al*. Epidemiology and course of anorexia nervosa in the community. *Am J Psychiatry* 2007; **164**: 1259–64.
8 Steinhausen H. The outcome of anorexia nervosa in the 20th century. *Am J Psychiatry* 2002; **159**: 1283–93.
9 Russell G. Bulimia nervosa: an ominous form of anorexia nervosa. *Psychological Med* 1979; **9**: 429–48.
10 Dolan B, Lacey J, Evans C. Eating behaviour in British women from three ethnic groups. *Br J Psychiatry* 1990; **157**: 523–8.
11 Claes L, Vandereycken W, Vertommen H. Self-injurious behaviours in eating disordered patients. *Eating Behav* 2001; **2**: 263–72.

12 Pompili M, Mancinelli I. Suicide in anorexia nervosa: a meta analysis. *Int J Eating Disorders* 2003; **36**: 99–103.
13 Gupta MA, Gupta AK. Dissatisfaction with skin appearance amongst patients with eating disorders. *Br J Dermatol* 2001; **145**: 110–3.
14 Luck P, Wakerling A. Increased cutaneous vasoreactivity to cold in anorexia nervosa. *Clin Sci* 1981; **61**: 559–67.
15 Anderson AE. Drenching nocturnal sweats during weight recovery in eating disordered patients: a new syndrome. Paper presented at the *6th International Conference on Eating Disorders*, New York, April 1994.
16 Luck AJ, Morgan JF, Reid F *et al*. The SCOFF Questionnaire and clinical interview for eating disorders in general practice. *BMJ* 2002; **325**: 755–6.

Psychogenic pruritus [1,2]

Psychogenic pruritus is a poorly defined disorder. In the past it has commonly been applied to a subgroup of the psychopruritic disorders, representing those with intractable or persistent itch for which no pruritic physical illness or dermatological illness can be found [1]. The definition cannot solely be confined to this simple group since itch can be a major debilitating symptom, both psychologically and physically.

The psychological parameters of itch should be considered as:

1 Predominant psychological pruritus classified as a somatoform or dissociative disorder
2 Pruritus in dermatological illness for which psychological factors play a role in the development or course
3 Problems in coping with chronic pruritus in the sense of an adjustment disorder, so called helpless/hopelessness reactions
4 Co-morbidity with other psychiatric conditions, particularly substance abuse, anxiety reactions and depression.

It is a *sine qua non* that pruritus is a multifactorial symptom. Dermatological, neurological, iatrogenic illness and internal disease are well-recognized causes [1,2]. These must be taken into account in any evaluation of persistent itch. A proposed clinical classification of itch has been produced to serve as a diagnostic pathway for better evaluation of patients [2]. However, the propensity for normal subjects to sense itch after psychological provocation by pictures of insects, rashes and watching other subjects scratching demonstrates the ready ability of simple measures to induce psychosomatic pruritus. Histamine release in skin may be influenced by psychiatric factors and in normal subjects the sensation of itch and cutaneous sensory symptoms was correlated with major life events [3]. Musaph [4] pointed out that one mechanism for relieving everyday irritations is to scratch a little. The motorist stopped at a red traffic light almost invariably scratches some accessible site such as the neck, arms or scalp. Grooming behaviours such as adjustments of hair, clothing or makeup may be associated with an accompanying scratch for transient itch.

Functional itch disorder has been studied by Misery and colleagues who have proposed diagnostic criteria for psychogenic pruritus. There are three compulsory criteria: (i) localized or generalized pruritus *sine materia*; (ii) chronic pruritus (>6 weeks); and (iii) the absence of a somatic cause. Three additional criteria from the following seven should be present: a chronological relationship of pruritus with one or several life events that could have psychological repercussions; variations of intensity associated with stress; nocturnal variation; predominance during rest or inaction; associated psychological disorders; pruritus that is improved by psychogenic drugs; pruritus that is improved by psychotherapy [5].

In individuals who develop localized or generalized neurodermatitis it may begin as a stress response. Patterns of itching and scratching may predominantly occur during periods of relaxation or non-occupied time. Pruritic episodes may be unpredictable in onset and present with abrupt and sudden termination. The quality of itch may be unusual, described as crawling, stinging or burning. Sites of predilection in two-thirds of subjects were legs, arms and back. Furthermore, localized itching may lead to generalized body itch within a short time. The activity may mimic the chronology of depressive symptoms as a depression equivalent with early morning waking and exacerbations at times of agitation [6]. In some individuals, intense scratching can induce an ultimate feeling of pleasure and this may be related to the release of opioids centrally. Enkephalins and endorphins are important as neurotransmitters in the CNS in mediating the sensation of itch because itch and pain are thought to share common neurological pathways. The central elicitation of itch by morphine may result from binding to opioid receptors and this may mimic the normal physiological binding of endorphins and enkephalins at these receptor sites [7]. Paroxysmal intense scratching to produce pain instead of itch has been described as 'orgasm cutanee'. Patients with generalized pruritus who had responded well to placebo reported greater itching after naloxone, probably due to the abolition of the placebo response. Conversely, the placebo non-responders reported less itch after naloxone than the placebo responders, suggesting that naloxone may be competing with an endorphin system, thus modulating the individual perception of itch.

Patients with psychogenic itch tend to be introverted and there may be a history of recent major psychological stress [8]. A psychiatric and psychodynamic investigation of patients with prurigo nodularis demonstrated an extraordinary propensity for these patients to suffer from psychological trauma, and a distinct correlation was claimed between the outbreak of the disease and the preceding loss of a human relationship detrimental to self-esteem [9]. A significant proportion of patients with generalized pruritus may be suffering from depression. Using the Beck Depression Inventory, significantly more patients with generalized pruritus (32.4%) had depressive symptomatology than did controls [10]. Recent studies of psychosomatic co-factors and psychiatric co-morbidity have confirmed these earlier observations with psychosomatic stress factors exhibiting a marked influence on severity of pruritus in skin disease. Severity of itch was related to the failure of psychosocial coping, with 39% suffering from feelings of helplessness and lack of control [11]. In most studies the prevalence of anxiety and depression is 10% for outpatients and 20% for inpatients [12].

Treatment with antihistamines is disappointing although those which have phenothiazine activity, such as hydroxyzine 50 to 75 mg daily, may produce more relief. However, even those patients with proven depression may respond disappointingly to antidepressants. Doxepin, used in doses up to 125 mg/day, is more effective probably because of the combined effect of both antipruritic and antidepressant actions. Selective serotonin reuptake inhibitors can also afford relief, used for up to 1 year. Typical doses are paroxetine 20–40 mg/day, fluvoximine 100–200 mg/

day or citalopram 20–40 mg/day [13]. Psychiatric referral is indicated in non-responders for the expertise in the use of higher doses of these antidepressants and the use of alternative antidepressants such as trazadone or duloxetine. Behaviour-orientated therapy is useful for those with high psychosocial morbidity. The benefit depends upon the availability of therapists and does rely upon a receptive patient. Success may be limited and disappointing in those with significant mood shift or personality disorder [14].

References

1 Schneider D, Dresch G, Evers S *et al*. Psychosomatic cofactors and psychiatric comorbidity in patients with chronic itch. *Clin Exp Dermatol* 2006; **31**: 762–7.
2 Stander S, Weisshaar F, Mettang T *et al*. Clinical classification of itch. *Acta Dermatovenereol* 2007; **87**: 291–4.
3 Gupta MA, Gupta A. Stressful major life events associated with a higher frequency of cutaneous sensory symptoms. *J Eur Acad Dermatol* 2004; **18**: 560–5.
4 Musaph H. Psychogenic pruritus. *Semin Dermatol* 1983; **2**: 217–22.
5 Misery L, Alexandre S, Dutray S *et al*. Functional itch disorder or psychogenic pruritus: suggested diagnostic criteria. *Acta Dermatovenereol* 2007; **87**: 341–4.
6 Gupta MA, Gupta K, Kirkby S *et al*. Pruritus associated with night time waking. *J Am Acad Dermatol* 1989; **21**: 479–84.
7 Summerfield JA. Naloxone modulates the perception of itching. *Br J Clin Pharmacol* 1980; **10**: 180–3.
8 Radmanesh M, Shafei S. Underlying psychopathologies of psychogenic pruritic disorders. *Dermatol Psychosom* 2001; **2**: 130–3.
9 Valtola J. A psychiatric and psychodynamic investigation of LCO (prurigo nodularis Hyde) patients. *Acta Derm Venereol (Stockh)* 1991; **156** (Suppl.): 49–52.
10 Sheehan-Dare RA, Henderson MJ, Cotterill JA. Anxiety and depression in patients with chronic urticaria and generalized pruritus. *Br J Dermatol* 1990; **123**: 769–74.
11 Vanos H, Eland P, Grypdonck M. Prevalence and predictors of psychosocial morbidity in patients with chronic pruritic skin diseases. *J Eur Acad Dermatol* 2006; **20**: 810–7.
12 Gieler U, Neimeir V. Psychosomatic aspects of pruritus. *Dermatol Psychosomat* 2002; **3**: 6–13.
13 Gupta MA, Gupta AK. The use of antidepressant drugs in dermatology. *J Eur Acad Dermatol* 2001; **15**: 512–8.
14 Freid RG. Non-pharmacologic treatments in psychodermatology. *Dermatol Clin* 2002; **20**: 177–85.

Cutaneous phobias

Phobias are irrational fears which cause anxiety. These fears are unreasonable and inappropriate. The fear is out of proportion to the demands of the situation and cannot be explained or reasoned away. Phobias are overwhelming and compelling and tend to distort the conduct of everyday life. They can be regarded as *obsessional fears* whereas not all obsessions, thoughts or actions are associated with these anxieties. There is a loss of voluntary control and the feared situation leads to avoidance behaviour. Dermatology patients may present with focused anxieties about the development of a variety of cutaneous diseases. These are usually based upon either a fear of contamination and infection, or of impending malignancy and cancer. Occasionally, there is a fear of showing emotion or embarrassment. Predominant cutaneous phobias can be divided into:

1 Fear of contamination, e.g. dirt phobia, germ phobia, wart phobia
2 Fear of malignancy, e.g. cancer phobia, mole phobia
3 Fear of emotional display, e.g. blushing, sweating.

Dirt, infection and wart phobias

Studies of obsessive–compulsive behaviour in dermatology outpatients [1,2] estimate that OCD is present in up to 25% but this may include some with body dysmorphic disorder. However, excluding this group there were still up to 15% who had *fears* of contamination or malignancy half of whom showed compulsive washing behaviours. Hand washing leading to dermatitis is common but up to 10% will admit to compulsive body washing also. The precipitating factors are fears of dirt and contamination from others who have been infected with real organisms, for example MRSA, or those who might have been, that is those recently discharged from hospital. Situational exposure in work to dirt and waste may initiate the fear. Hand washing may occur up to 100 times per day and compulsive showering and bathing 10–20 times daily. Irritant dermatitis which does not resolve with adequate advice should prompt inquiry, not only about washing compulsions but also checking behaviours.

Wart phobia is a specific contamination fear and usually follows an index case in family or acquaintances, often children. Patients with imagined wart infection are sent with real lesions such as milia, normal anatomical variations, for example pearly papules or milia, or even no lesions at all. Fear and guilt is associated with genital wart phobia. Avoidance behaviours such as cleaning of door handles, chairs and toilet seats are associated with carriage and excess usage of boxes of antiseptic wipes. Underwear, socks and gloves may be discarded to avoid the possibility of contamination in the wash. Parents who are unwilling to wait for natural resolution of viral warts may insist on aggressive treatment to prevent other members becoming infected and complain to managers and the media if it is not forthcoming.

Mole phobia and cancer phobia

For dermatologists these are usually related. Occasionally, a dislike of moles and freckles may be a manifestation of BDD but for most patients who repeatedly demand mole examinations, and sometimes excision, there is an underlying cancer phobia. This is in response to various stimuli. They may have had a malignant lesion removed and need constant reassurances. This is a 'normal' response to disease. There may have been malignancy or unfortunately death from melanoma in the family or friends, or concern repeatedly triggered by media or commercial pressure. These patients present regularly and acutely to screening clinic or primary physicians. They may demand removal of some or all their moles [3,4] or even attempt to multiple self-surgery. Mole phobia by proxy is not uncommon in parents who worry about their children and their moles to such an extent that normal play activities are curtailed because of the sun, and family holidays are compromised also. Screening programmes *per se* are not shown consistently to increase cancer anxiety, nor to attract a disproportionate number of phobic patients although the vulnerable attendees are the young, those with low education and social class and high doctor dissatisfaction [5]. The management of these patients is difficult because they usually present with an instant demand to be seen and the consultation is a form of crisis management. It is preferable to organize regular reassuring appointments, gradually extending the period between visits to a reasonable interval. Nor is it reasonable to regularly take off normal naevi to 'reassure'

the patient who will see this as a form of definitive therapy. Many of these patients are seen in private clinics where their fears are reinforced by repeated, expensive operations.

Topical steroid phobia

Topical corticosteriod preparations were introduced in the 1960s and by the 1970s most dermatologists were familiar with patients who expressed fears about the use of these drugs. A few examples of gross abuse were published in the media, fuelling a continuing irrational concern, predominantly about skin thinning [6] and to a lesser extent stunting of growth in children. These families present in the clinic as angry resentful parents suspicious of conventional therapy, significantly disillusioned and poorer from repeated expensive, useless alternative therapy. Their child is miserable, undertreated and suspicious of all therapists, riven by discord between parents and physicians. Management is extremely difficult because the fears are so dominant. However, cognitive assessment of needs, rational explanation of effects of safe therapy and frequent, regular, open review of progress with interactive discussion does much to alleviate anxieties. It may take many months to reach a state of equanimity with parents in particular, whose fears may remain to some degree.

References

1 Demet MM, Deveci A, Taskin E *et al*. Obsessive–compulsive disorder in a dermatology outpatient clinic. *Gen Hosp Psychiatry* 2005; **27**: 426–30.
2 Fineberg N, O'Doherty C, Rajagopol S *et al*. How common is obsessive–compulsive disorder in a dermatology out patient clinic? *J Clin Psychiatry* 2003; **64**: 152–5.
3 Allan S, Doherty VR. Naevophobia. *Clin Exp Dermatol* 1995; **20**: 499–501.
4 Williams H. Early diagnosis of malignant melanoma: surgical excision of 37 moles. *Br J Dermatol* 1998; **138**: 202–3.
5 Hay J, Buckley T, Ostroff J. The role of cancer worry in cancer screening: a theoretical and empirical review of the literature. *Psycho-oncology* 2004; **14**: 517–34.
6 Charman CR, Morris A, Williams H. Topical steroid phobia in dermatology outpatients with atopic eczema. *Br J Dermatol* 1999; **141**: 105.

Group and mass population reactions [1,2]

Synonyms

- Epidemic hysteria syndrome
- Mass psychogenic illness
- Mass sociogenic illness
- Occupational mass psychogenic illness (OMPI)

The modern nomenclature for hysteria is conversion or dissociation disorder. This disorder has been defined as a constellation of symptoms suggestive of organic illness, but without an identifiable cause, that occurs between two or more people who share beliefs related to those symptoms [2]. The implications from this classification are that the symptoms are psychogenic, that the causation is unconscious, and that symptoms may carry some advantage either primary, such as debilitating symptoms, or secondary, by being exempted from community responsibility or gaining public attention. It can be seen as a social phenomenon or cultural and ethnic stress reaction occurring in otherwise normal populations. Conversion implies the behaviour of physical illness without evidence of organic pathology, the patient being unaware of the psychopathology. The prime examples of this group response are epidemics occurring in the closed communities of the workplace or in schools. It has been called a culture bound stress reaction with two recognizable variants. Firstly, those associated with anxiety, namely headache, nausea, dizziness, flushing, fainting, abdominal pain and hyperventilation. Secondly, the motor variant, mainly tics, pseudoseizures and convulsions.

Two large reviews of epidemic hysteria, one covering 78 outbreaks between 1872 and 1972 [3], and another the 70 incidents between 1973 and 1993 [2], found limited cutaneous symptoms. The earlier reports emphasize the motor symptoms whilst the latter lists more widespread symtomatology including a 9% incidence of a rash. These occurred usually in factories or schools with a minority within a family group. Skin-related symptoms have been reported in widespread reaction to contamination of a community water supply where there was anxiety but no long-term effects on health [4]. In the 1981 food poisoning outbreak caused by adulterated rapeseed oil, where 20 000 people were affected by well-defined symptoms, some cutaneous, more than 6000 people with symptoms of 'reactive psychological disaster syndrome' were allowed compensation in the absence of specific physical illness [5]. The fear of skin illness or contagion led to two separate outbreaks of skin disorders among factory workers in a small northern English town. In each outbreak a central female figure with non-industrial dermatological problems fuelled an epidemic of what was thought to be dermatitis among several employees in a ceramics factory and a second epidemic in a textile factory. In the first outbreak, 10 employees were affected and 17 in the second. No significant dermatological pathology of industrial origin was found [6]. A similar outbreak occurred in a warehouse, triggered by two severe cases of non-occupational dermatitis, combined with the idea that incoming aircraft parts to the warehouse from foreign countries might be 'dirty' in some way. This caused a heightened perception of the risk of skin disease with increased frequency of hand washing. Over-frequent hand washing in a few employees resulted in a dermatitis with a false reinforcement of the fear of industrial dermatitis [7]. The presence of proven dermatitis may stimulate a response from the remainder of the workforce. An outbreak in the pottery industry which began as isolated gum arabic sensitivity developed into a more widespread epidemic described as 'epidemic hysteria dermatologica' in eight female workers [8]. There was also a female preponderance in the outbreak at a textile factory where the skin problems were common dermatoses unrelated to work [9].

Most of these mass reactions involve female workers in stressful situations with boring, low-paid, repetitive jobs. Women are more likely to externalize their discontent as a conversion symptom than a direct complaint which may jeopardize their job [2]. Surveys of OMPI episodes stress that many outbreaks occur in dehumanizing jobs with poor management communication. Secondary compensation neurosis may follow to prolong the epidemic from those who feel particularly injured. It is clearly important, if possible, to visit a factory very early and examine all the complainants in an outbreak of alleged 'epidemic' industrial dermatitis.

The other common closed communities are schools, where epidemic complaints of itch, dry skin and transient rash were predominant [2,10–12]. These outbreaks involved 50 to 100 children aged 7 to 12 years. The symptoms lasted 2 weeks and no cause

was found. Girls outnumbered boys by 3 to 1. It has been suggested that the precipitating factors may be illness in a favourite teacher or student, rigid teaching regimes and parental pressure for academic success.

References

1 Bartholomew RE. *Little Green Men, Meowing Nuns and Head-Hunting Panics. A Study in Mass Psychogenic Illnesses*. North Carolina: MacFarland, 2001: 25–78.
2 Boss LP. Epidemic hysteria. *Epidemiol Rev* 1997; **19**: 233–43.
3 Sirois F. Epidemic hysteria. *Acta Scand Psychiatr* 1974; **252** (Suppl.): 1–46.
4 David AS, Wessely S. The legend of camelford. Medical consequences of a water pollution accident. *J Psychosom* 1995; **39**: 1–9.
5 Lopez-Ibor JJ, Soria J. Psychopathological aspects of the toxic oil syndrome catastrophe. *Br J Psychiatry* 1985; **147**: 352–65.
6 McGuire A. Psychic possession among industrial workers. *Lancet* 1978; **i**: 376–8.
7 Ashworth J, Rycroft RJ, Waddy RS, Irvine D. Irritant contact dermatitis in warehouse employees. *Occup Med* 1993; **43**: 32–4.
8 Ilchyshyn A, Smith AG. Gum arabic sensitivity and epidemic hysteria dermatologica. *Contact Dermatitis* 1985; **13**: 282–3.
9 Cunliffe WJ. Psychic possession amongst textile workers. *Lancet* 1978; **ii**: 44.
10 Levine RJ. An outbreak of psychogenic illness at a rural elementary school. *Lancet* 1974; **I**: 1500–3.
11 Polk LD. Mass hysteria in an elementary school. *Clin Paediatrics* 1974; **13**: 1013–4.
12 Robinson P, Haddy L, Jones P. Outbreak of itching and rash. *Arch Int Med* 1984; **144**: 159–62.

Sick building syndrome and building-related illness [1–4]

The concept of sick building syndrome (SBS) and building-related illness (BRI) [1] is used to define a group of symptoms that appear to be due to a range of apparent allergic, toxic, irritant and possibly infectious causes within non-industrial and non-residential buildings [5]. Both SBS and BRI refer to illnesses related particularly to non-industrial premises such as large blocks of flats or offices where people spend a large quantity of time in close association. In a minority of cases these syndromes consist of a specific homogeneous illness caused by identifiable vapours, for example formaldehyde, or identifiable allergens, such as pollens. A series of heterogeneous complaints, such as irritable dry skin, facial flushing, pruritus, dryness and cracking of mucous membranes of mouth, nose and eyes, recurrent sore throat, headache, fatigue and loss of concentration exist, for which no cause can be found. In over half the patients the symptoms are dermatological but the lack of demonstrable biological correlates together with vague aetiological attributes makes precise definition of the problem difficult [2]. Patch testing was negative. In large reviews [2,6,7] symptoms were significantly associated with signs of dampness, condensation, water leakage, high humidity, and mouldy odour. Furthermore, the symptomatology could be related more to mechanical ventilation systems and internal air conditioning than in buildings where there was efficient natural ventilation [6]. In addition, changing from artificial ventilation to a natural one reduced skin symptoms by one-third [8].

Workers may feel ill when exposed to odours from xenobiotic sources (cacosmia) [9]. The presence of a strange smell at work may precipitate symptoms in a significant number of previously healthy individuals. Patients develop headaches, itchy eyes, transient rash, and congested nose or throat followed by sweating, faintness and tachycardia. In most cases the odour is chemically harmless. The medical and social prognosis of SBS in a long-term follow-up study showed that fatigue, irritation of the eyes and facial erythema were the most common persistent symptoms [10]. Personal factors such as atopy and photosensitive skin, psychosocial conditions and physical factors prolong symptomatology. A significant psychological component was postulated when 24 workers reported sensitivity to electricity in the workplace causing itchy wealing of face and limbs [11]. The patients reported increased symptoms not only when they were exposed to an experimental electromagnetic field but also when they believed they were exposed even though the field was turned off. Patients with visual display-related skin symptoms and hypersensitivity to electricity who complained of continuing problems were female, had poor self-image and limited capacity for coping [12].

Not surprisingly therefore, work stress, manifested by role conflict, work overload, managerial difficulties and workplace building renovations have all been significantly associated with perceptions of poor workplace air quality and increased dermatological symptoms of SBS [8].

Symptoms were more common in those lower down the office hierarchy than in managers because they had no authority or power to tackle the perceived stresses but women had more symptoms than men, irrespective of their status [2,12,13].

References

1 Menzies D, Bourbeau J. Building related illnesses. *New Eng J Med* 1997; **337**: 1524–31.
2 Worgocki PM, Sindell J, Bischoff W *et al*. Sick building syndrome a review of 105 papers. *Indoor Air* 2002; **12**: 113–28.
3 Eriksson NM, Berndt G, Stenberg T. Baseline prevalence of symptoms related to indoor environment. *Scand J Pub Health* 2006; **34**: 387–98.
4 Marmot AF, Ely J, Stafford M *et al*. Building health: an epidemiological study of 'sick building syndrome'. *Occ and Environ Med* 2006; **63**: 283–9.
5 Wittczak T, Walusiak J. 'Sick building syndrome': a problem of occupational medicine. *Med Pr* 2001; **52**: 369–73.
6 Seppanen O, Fisk WJ. Association of ventilation system type with SBS symptoms in the office worker. *Indoor Air* 2002; **12**: 98–112.
7 Engvall K, Norrby C, Norbaek D. Sick building syndrome in relation to building dampness. *Int Arch Occ Environ Health* 2001; **74**; 270–8.
8 Bourbeau J, Brisson C, Allaire S. Prevalence of sick building syndrome before and after improved office ventilation. *Occ Environ Med* 1996; **53**: 204–10.
9 Magnavita M. Cacosmia in healthy workers. *Br J Med Psychol* 2001; **74**: 121–7.
10 Edvardsson B, Sternberg B, Bergdahl J *et al*. Medical and social prognoses of non-specific building related symptoms (sick building syndrome): a follow-up study of hospital patients. *Int Arch Occ Envir Health* 2007; **80**: 247–59.
11 Lonne RS, Andersson B, Melin I *et al*. Provocation with stress and electricity of patients with 'sensitivity to electricity'. *J Occp Environ Med* 2000; **42**: 512–6.
12 Bergdahl J, Sternberg B, Erisson M *et al*. Coping and self image in patients with visual display terminal related skin symptoms and perceived hypersensitivity to electricity. *Int Arch Occ Environ Health* 2004; **77**: 538–47.
13 Mendelson MB, Catano VM, Kelloway K. The role of stress and social support in sick building syndrome. *Work Stress* 2000; **14**: 137–55.

Harmful cutaneous habits

There are certain everyday habits which are non-destructive and can be regarded as an extension of grooming behaviours. These are seen in the general population as autocontact and displacement activities. These are commonly seen as hair adjustments,

non-excoriative scratching of face, neck or genital areas, nose touching and clearing and ear cleaning [1].

In past editions of this text a number of skin conditions have been defined as harmful habits, for example knuckle biting, or considered in isolation as a primary destructive condition, for example acne excoriée. It is clear that a redefinition of these is overdue because they represent a continuum of disease from a simple harmless stress-induced (and therefore relieving) habit with no other psychiatric overtones, for example nail biting, to a severe self-destructive process, for example trigeminal trophic syndrome which can result in massive tissue destruction as part of a depressive disorder, OCD or dementia [2,3].

Pathological rubbing and picking behaviours producing visible change represents a more informative grouping for the following activities:

1 Repeated, localized skin rubbing: lichen simplex, knuckle biting, neurodermatitis
2 Pathological excoriation and picking producing scarring, previously called neurotic excoriations, acne excoriée
3 Nail sucking, picking, biting, eating and instrumentation onychotillomania
4 Pathological picking of a localized area of skin, e.g. acne excoriée des jeunes filles
5 Trichotillomania of one or more areas of hair-bearing skin
6 Pathological picking representing a psychiatric disorder, e.g. 'corrective picking' in BDD or investigative picking in delusional disorder
7 Fabricated disease.

References

1 Morris D. *Manwatching: A Field Guide to Human Behaviour*. London: Grafton, 1978.
2 Bohne A, Keuthen N, Wilhelm S. Pathologic hair-pulling, skin picking and nail biting. *Ann Clin Psychiat* 2005; **17**: 227–32.
3 Lochner C, Simpson D. Trichotillomania and skin picking. A phenomenological comparison. *Depress Anxiety* 2002; **15**: 83–6.

Lichen simplex and neurodermatitis

(see also Chapter 23)

Lichenification describes the characteristic pattern of response of the predisposed skin to repeated rubbing. In some instances, a minor initiating event, such as trauma, infection or insect bite, precipitates episodic insistent scratching and rubbing. Irresistible itching is the major complaint, scratching the chronic accompaniment. This behaviour takes the form of rubbing with either the hands, back of nails or knuckles and in extreme cases sometimes with the use of a convenient instrument such as hairbrush, pen or some other domestic implement. The actions may be subconscious. However, in some cases patients subject themselves to frenetic, prolonged spasms of uncontrollable self-damage which proceeds with increasing rapidity until the pruritus is relieved, to be replaced by soreness and pain. The change from itch to pain is quite sudden and this abrupt cessation has been described as 'orgasm cutanée'. Nodular pruriginous lesions probably represent two populations: an early-onset atopic group with mean age 19 years, and a later, non-atopic group with mean age 48 years [1]. The early-onset group was associated with hypersensitivity reactions whereas the later group, predominantly female, show more habit-induced responses. Lichen simplex and neurodermatitis are much rarer in the elderly and may be related to a reduced capacity to lichenification.

Regular rubbing and pressure on the skin produces characteristic thickened, coarsely grained papules and nodules with hyperpigmentation. The classic sites of involvement are within easy reach, particularly on the nape and sides of the neck, elbows, thighs, knees and ankles. It is unknown why these areas remain so discrete. These areas may be in varying stages of evolution, from early small violaceous papules with surface excoriations to chronic areas that present as hyperkeratotic plaques with pigment changes, described as 'dermatological worry beads'. Localized patches of lichen simplex presenting as pruritus ani and vulvae are more often found in females and occur predominantly after puberty. They are found, very rarely, as isolated phenomena in children, even in atopics. It is more often seen in Afro-Caribbean and oriental races.

Most authors have commented on the relationship of emotional tension to bouts of scratching [2]. Patients are usually described as stable but anxious individuals, whose reactions to stress are relieved by ritualized behaviour such as rubbing [3]. Aggression and hostility related to anxiety caused by emotional disturbance may lead to itching. This maladaptive response has been treated successfully with behaviour therapy [4–6] to break the itch–scratch cycle.

Treatment with antihistamines is helpful, but antidepressants, particularly tricyclic compounds such as doxepin in doses as low as 25–50 mg/day, may be more effective. Non-psychotropic medication is also sometimes effective, using thalidomide 50–100 mg daily for up to 2 months at a time [7].

References

1 Tanaka M, Alba S, Matsumura M. Prurigo nodularis consists of two forms: early onset atopic and late onset non atopic. *Dermatology* 1995; **190**: 269–76.
2 Allerhand ME, Gough HG, Grais ML. Personality factors in neurodermatitis. *Psychosom Med* 1950; **12**: 386–9.
3 Freid RG. Evaluation and treatment of psychogenic pruritis and self excoriation. *J Am Acad Dermatol* 1994; **30**: 993–9.
4 Fried RG. Nonpharmacologic treatment in psychodermatology. *Dermatol Clin* 2002; **20**: 177–85.
5 van-Os H, Eland P, Kennedy C. Effectiveness of nursing programme coping with itch. *Br J Dermatol* 2007; **156**: 1235–44.
6 Melin L, Noren P. Behavioural treatment of scratching in patients with atopic dermatitis. *Br J Dermatol* 1986; **115**: 467–74.
7 Lan C, Lin C, Wu C. Treatment of idiopathic prurigo nodularis with low dose thalidomide. *J Dermatol* 2007; **34**: 237–42.

Pathological skin picking [1,2]

Synonyms

- Psychogenic excoriations
- Neurotic excoriations
- Compulsive skin picking
- Dermatotillomania
- Acne excoriée

Epidemiology and pathogenesis. Pathological skin picking is defined as recurrent picking accompanied by visible tissue damage and functional impairment [1]. The DSM-IV classification does not

include a category for skin picking, which has been previously described as an impulse control disorder, stereotypic movement disorder or obsessive compulsive disorder. Body dysmorphic disorder and delusional skin disease are separated by the primary psychiatric pathology. The commonest of the self-inflicted dermatoses have previously been called neurotic excoriations, psychogenic excoriations or compulsive skin picking. The lesions differ from other artefactual disorders as those who suffer admit to an urge to pick and gouge at their skin. Not uncommonly, there may be an initial reluctance to confess to the self-damage but patients are willing to discuss the 'response to itch' or the 'relief of tension' as a mechanism of guilt dissociation. There may be an associated involvement of the face and neck as acne excoriée. It is unknown why particular areas are involved but may relate to the occurrence of the site of the initial lesion, for example acne trauma or an insect bite. Picking occurs in 2% of dermatology clinic patients [3] and 4.6% of college students [1,4]. Pathological picking can be seen before 10 years of age through to middle age. Curiously, the elderly are spared. Childhood onset [5] may progress into adulthood in up to 47%. This group had similar characteristics to those who begin primarily in their late 30s [3]. All of these clinical syndromes are characterized by the preponderance of females, even in childhood and adolescence. Destructive excoriations are seen most frequently in middle-aged women, the average age of onset being between 30 and 50 years [2,6], but significantly the average duration of disease before presentation can be up to 10 years. This group makes up the most severe cases, where the problem tends to be persistent and unremitting. Picking intensity coincided with menstruation in 44% [7], although it is common for activity to wax and wane. On average patients spend up to 3 h per day picking, thinking about picking or resisting the urge to pick [1,2,7]. These bouts can be ritualized to a set time and place, often the bathroom, frequently at bedtime. These activities are done in full consciousness although in children, particularly, a fugue or trance state can be apparent [5].

These patients are described as rather rigid and obsessional individuals with repressed emotions [5]. They have difficulty in verbalizing their problems and are aggressive but also insecure [6]. Depression is a very common feature [1,2,6,7]. There is a compulsive quality about the need to continue until pain is produced. Psychosocial stresses have been reported to precede exacerbations of excoriations in 30–90% of patients [1–4]. Studies indicate that increasingly severe skin picking is related to greater levels of anxiety, depression and experiential avoidance, defined simply as the tendency of an individual to avoid or escape negative events or emotions [1,8].

Clinical features. Lesions can be seen in all stages of development, the appearance depending on chronicity and degree of instrumentation. Clinically, the lesions are polymorphic, the newer lesions are angular excoriated erosions with a serosanguineous crust found predominantly on the face, hair margins, sides of the neck, chin, upper chest, shoulders, upper arms and thighs. The healing lesions are erythematous, eventually becoming white and atrophic centrally and commonly hypertrophic and hyperpigmented at the periphery. They may be quite deep, extending into dermis, and are distributed symmetrically within reach of the hands. Significant bouts of cellulitis and ulceration are common, leading to hospitalization [9]. Older lesions show pink or red scars, some of which may be hypertrophic. Chronic lesions may also show atrophic scars, which merge and are eventually seen as linear, coalescent areas. Lesions appear at all stages of development and may number from a few to several hundred (Fig. 64.4).



Fig. 64.4 Acute excoriations and chronic, scarred, atrophic lesions due to pathological picking on face, neck and shoulders.

Characteristically, these lesions appear as discrete islands in a sea of normal skin. Concealment behaviour, for example by make-up and clothing, was present in 65% of chronic cases and active avoidance of social situations in 40%. Up to one-quarter of patients may increase alcohol, tobacco or recreational substance habits to counter the burden of disease [1].

Differential diagnosis. It is important to exclude excoriations caused by generalized pruritus, bullous disorders, such as pemphigus, and linear excoriated lesions, which may be the presenting signs of lichen planus or lupus erythematosus. Rarities such as self-healing keratoacanthomas or mucinoses which cause scarring are usually distinguishable entities.

Treatment. Simple, empathetic, supportive psychotherapy can produce significant improvement, particularly in children. Crucially, the parents need to be convinced they are part of the therapeutic team. Cognitive behavioural therapy alone has improved some patients, although the management of underlying personality difficulties may require the specific skills of a psychotherapist [1,8–10]. Habit reversal programmes may also help [11]. The compulsive nature of this disorder responds well to antidepressants and in particular to serotonin re-uptake inhibitor drugs, such as fluoxetine, fuvoxamine and citalopram [2,12]. Clomipramine and doxepin [13] have been reported to work well. The A-B-C model of habit disorders, that is Affect regulation, Behavioural regulation and Cognitive control [14], makes use of all modalities to help patients conceptualize and manage skin picking behaviours. An open study of lamotrigine used as a mood stabilizer improved two-thirds of patients, mean age 3 years, over a period of 3 months [15]. Whilst the condition eventually resolves, the most difficult

cases are middle-aged women with established patterns of excoriation, which may have been continuing for decades. It may be necessary to continue antidepressants in these patients for some years.

References

1 Flessner C, Woods D. Phenomenological characteristics, social problems, and economic impact of chronic skin picking. *Behaviour Modification* 2006; **30**: 944–63.
2 Gupta M, Gupta A, Haberman H. Neurotic excoriations: a review and some new perspectives. *Compr Psychiatry* 1986; **27**: 381–6.
3 Arnold LM, Auchenbach MB, McElroy SL. Psychogenic excoriation. Clinical features, proposed diagnostic criteria, epidemiology and approaches to treatment. *CNS Drugs* 2001; **5**: 351–9.
4 Bohne A, Keuthen N, Wilhelm S. Pathologic hair-pulling, skin picking and nail biting. *Ann Clin Psychiatry* 2005; **17**: 227–32.
5 Odlaug B, Grant J. Childhood-onset pathological skin picking: clinical characteristics and psychiatric comorbidity. *Compr Psychiatry* 2007; **48**: 388–93.
6 Fruensgaard K. Neurotic excoriations. *Int J Dermatol* 1987; **17**: 761–7.
7 Wilhelm S, Keuthen N, Deckersbach T. Self injurious skin picking: clinical characteristics and comorbidity. *J Clin Psych* 1999; **60**: 654–9.
8 Calikusu C, Yucel B. The relationship of psychogenic excoriation to psychiatric disorders. *Compr Psych* 2003; **44**: 256–61.
9 Odlaung B, Grant J. Clinical characteristics and medical complications of pathological skin picking. *Gen Hosp Psychiatry* 2008; **30**: 61–6.
10 Deckersbach T, Wilhelm S, Keuthen N. Cognitive behaviour therapy for self-injurious skin picking. *Behaviour Modification* 2002; **26**: 361–77.
11 Fried RG. Nonpharmacologic treatment in psychodermatology. *Dermatol Clin* 2002; **20**: 177–85.
12 Bloch M, Elliott M. Fluoxetine in pathological skin picking. *Psychosomatics* 2001; **42**: 314–8.
13 Harris BA, Sheretz EF, Flowers FP. Improvement of chronic neurotic excoriations with oral doxepin therapy. *Int J Dermatol* 1983; **26**: 541–3.
14 Stein D, Chaimberlain S, Fineberg N. An A-B-C model of habit disorders. *CNS Spectr* 2006; **11**: 824–7.
15 Grant J, Odlaug B. Lamotrigine treatment of pathological skin picking. *J Clin Psych* 2007; **68**: 1384–91.

Acne excoriée (see Chapter 42) [1,2]

There is not one patient with acne who can resist squeezing and pinching the lesions. Brocq in 1891 [3] described acne excoriée particularly in adolescent girls under emotional stress who picked and squeezed acne lesions. Although some patients develop these lesions after picking acne, most had no acne at all [2]. The condition should be considered a variant of psychogenic (neurotic) excoriation [2], with the lesions largely confined to the face. Acne excoriée is commoner in women [1–4] and seen in an older age group than acne vulgaris, with a mean age of about 30 years [1,2,4]. Psychological studies have shown no diagnosable DSM-IV-R disorder such as body dysmorphic disorder or obsessive compulsive disorder [4,5]. An immature personality or narcissistic personality disorder were commented upon. Sneddon and Sneddon described associated phobic states [1] and specifically excluded monosymptomatic hypochondriasis as a diagnostic category. However, the depressive and delusional disorders [6,7], which have been described in the past in association with acne excoriée, may have represented patients with excoriations as a result of pathological picking in BDD.

The clinical lesions resemble those of chronic excoriations. They are found predominantly around the hairline, forehead, preauricular cheek and chin areas (Fig. 64.5). Extension to the neck and occipital hairline is common. Chronic lesions characteristically show white, atrophic scarring with peripheral hyperpigmentation. Lesions are picked as a ritual, apparently as a response to itch or throbbing. The lesions are excoriated until 'emptied' [1].



Fig. 64.5 Acne excoriée; habitual scarring lesions of cheek and chin.

Although patients with acne excoriée sometimes respond to simple acne therapy, most require systemic antibiotics and isotretinoin. The tetracyclines, in particular doxycycline, are better than the other antibiotics [1] and topically the patients prefer antibiotic roll-on preparations to the benzoyl peroxide creams, which are too irritant. Whilst this may modify the development of new lesions and scarring, the course of the disease is poor without psychological support [1]. These patients tend to be psychologically dependent on the effects of the disfigurement to provide them with an excuse not to go out. The benefits of simple supportive consultation and psychotherapy should not be underestimated [8]. Habit-reversal therapy and hypnosis has worked well [9,10] but combined laser resurfacing and cognitive psychotherapy had prolonged success [11].

References

1 Sneddon J, Sneddon I. Acne excoriée; a protective device. *Clin Exp Dermatol* 1983; **8**: 65–8.
2 Wrong NM. Excoriated acne of young females. *Arch Dermatol Syphiligr* 1954; **70**: 574–82.
3 Brocq L, Jacquet L. Notes pour servir a' l'histoire des neurodermites. *Arch Derm Syph* 1891; **97**: 193–5.
4 Zadro-Jaeger S, Musalek M. Acne excoriée psychiatric studies. *Abstracts of the Third International Congress on Dermatology and Psychiatry*. Florence: Tipographia, 1991.
5 Bach M, Bach D. Psychiatric and psychometric issues in acne excoriée. *Psychother Psychosom* 1993; **60**: 207–8.
6 Koo JM, Smith LL. Psychologic aspects of acne. *Pediatr Dermatol* 1991; **8**: 185–9.
7 Ginsburg IH. The psychosocial impact of skin disease. *Dermatol Clin* 1996; **14**: 473–84.
8 Freid RG. Evaluation and treatment of psychogenic pruritus and self excoriation. *J Am Acad Dermatol* 1994; **30**: 993–9.
9 Sheefelt P. Use of hypnosis in acne excoriée. *Am J Clin Hypnosis* 2004; **46**: 439–45.
10 Kent A, Drummond LM. Acne excoriée: a case report using habit reversal. *Clin Exp Dermatol* 1989; **14**: 163–4.
11 Bower L, Alster T. Treatment of facial scarring from acne excoriée with pulse dye laser and cognitive psychotherapy. *Dermatol Therapy* 2004; **30**: 934–8.

Trichotillomania [1–3]

Definition. The term was first used by Hallopeau in 1889 and is derived from the Greek *thrix* hair, *tillein* pull out and *mania* madness. Literally it means a morbid craving to pull out hair. Originally DSM-IV [4] lists trichotillomania under impulse-control disorders in company with compulsive gambling. It is now clear that the definition must encompass the probability of a broader spectrum of additional psychopathologies [1] such as OCD, BDD and mood disorders. The revised DSM-IV [5] diagnostic criteria for trichotillomania are:

A Recurrent pulling out of one's own hair resulting in hair loss
B An increasing sense of tension immediately before pulling out the hair or when attempting to resist the behaviour
C Pleasure, gratification or relief when pulling out the hair
D The disturbance is not better accounted for by another mental disorder and
E The disturbance provokes clinically marked distress and/or impairment in occupational, social or other areas of functioning.

The ICD-10 definition [6] is consistent with this but does not mention either distress or loss of functioning.

Aetiology and pathogenesis [1,2]. The epidemiology of this complaint is not absolutely clear, probably for the reason that this physical sign and response is a product of various complex psychopathologies. The grouping includes both paediatric and adult patients and the latter in particular may have additional classifiable psychiatric illnesses, which contaminate any attempt to make this a homogeneous entity as has been attempted previously. Studies of frequency show a wide variation. There is an estimated lifetime prevalence of 0.6% in college students [7] with equal sex incidence. If the criteria are based on ICD-10 then the prevalence increased to 3.4% in females and 1.5% in men. Another study, again in students, found that 11% plucked their hair for other than cosmetic reasons and that 1% satisfied DSM criteria [8]. There is great difficulty in assessing the true incidence. Firstly, adult patients have been reluctant to present themselves for treatment because of shame and exposure, preferring instead to disguise the problem with hats and wigs and makeup. Secondly, the diagnosis may have been missed. Thirdly, any apparent increase in frequency may be the product of media attention, particularly when patients die of complications of trichobezoar. Lastly, infants and children with hair loss are more likely to be seen because of parental concern.

In a study of unselected populations, the incidence varied from below 1 per 1000 to more than 1 in 200 below the age of 18 years [6]. However, there appear to be two distinct populations: those who present in childhood [2,9] mainly between the ages of 5 and 12 years and more chronic cases who present as adults who have continued hair-pulling activity from adolescence or developed the disorder in early adult life [2]. One study has suggested that over 40% of adult cases have continued from adolescence. Nevertheless, the number of affected children may be seven times that of adults [8] and there is evidence of a bimodal distribution with peaks in the preschool years and in adolescence. The preschool children are more likely to be boys (62%) although after this older boys and adolescents are only 30% of the group [9]. There is some difficulty in meeting the diagnostic criteria for DSM-IV in young children because of the need to satisfy criteria B (a pattern of rising tension prior to pulling) and C (relief after pulling). This early-onset group, usually between the ages of 2 and 10 years, show benign, self-limiting behaviour and most are probably suffering a habit disorder, perhaps as an extension of hair twirling activity and childhood stress [8,10]. The association with nail biting and thumb sucking, skin picking, nose picking, lip biting and cheek chewing is well documented [11,12]. In children, there is an association with anxiety and dysthymia [13], learning disability and iron deficiency [14]. Emotional problems in the pre-adolescent group tend to be less severe, more a reflection of a stressful life event rather than serious psychopathology [15].

The adolescent group are much more likely to be female, with ratios of up to 3.5:1 [3]. The psychopathology may be related to parent relationships, school difficulties (commonly bullying), body image changes and, increasingly, parental and sexual abuse [16]. It is more likely that there is an accompanying anxiety disorder, although depression in children may be missed because the features are of somatic complaints and irritability.

In adults, there is greater psychopathology and a distinct female preponderance [1,2,9,16], usually 4:1, but 15:1 being most evident in the oldest group [17]. These statistics may be skewed because women are more likely to seek treatment and comprise the majority of those in clinical trial data. This remains true for different racial groups [18–20]. Adult patients show more diverse psychopathology with depression, anxiety disorder and obsessive–compulsive disorder (OCD). Depression was present in 14% and anxiety in 15% [21]. Substance abuse (6%) and eating disorders may also be evident [2,3]. There is a significant debate about the relationship of trichotillomania to obsessive–compulsive disorder [1,16]. An extensive review discusses the similarities between trichotillomania and OCD, in particular the compulsive urges and ritualistic behaviours. Whilst it has been proposed that adult chronic trichotillomania is a variant of obsessive–compulsive disorder, with positive correlation in family studies [22], this definition is too narrow for many patients [2], and has not been supported by psychometric testing [11]. OCD compulsions are ego dystonic, that is are performed to avoid increased anxiety, are not pleasurable and are performed in full awareness. That is they have the compulsion to perform an act to prevent something which they feel may happen. Whereas for those with trichotillomania the act is performed to release tension, may be pleasurable and not always performed in full awareness. Patients with OCD have an explanation for their responses whereas those with trichotillomania rarely justify their actions. In addition, the activity relieves stress for those with trichotillomania although a small subset may have the typical disabling compulsive conscious behaviours [23]. A family history of trichotillomania is present in 5–8% of cases and also higher rates of OCD, which may represent either a genetic predisposition or, more likely, a continuing family psychosocial response [22].

Clinical features [1]. The hair pulling activity is usually not as a response to any skin symptoms but is either a conscious deliberate

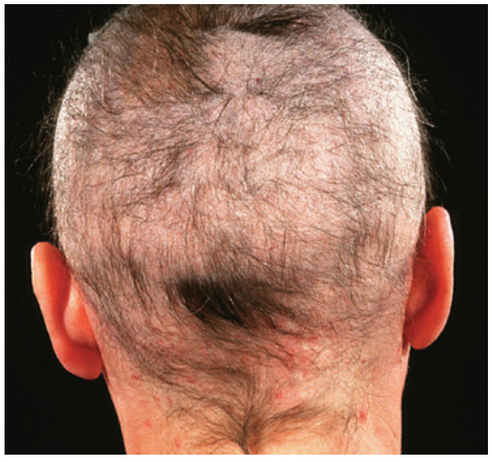


Fig. 64.6 Adult trichotillomania; extensive hair loss with a preserved tuft over the occiput.



Fig. 64.7 Childhood trichotillomania showing eyelash involvement with hair loss and broken-off hairs. This child also had scalp involvement.

act or more often a subconscious act, almost in some children being part of a hypnogogic (dreamlike) state. Some patients may have incomplete awareness until the pattern has been established [24].

Hair pulling and plucking is commonest from the scalp, but is only occasionally as a response to scalp symptoms. Some patients select an apparently abnormal hair by feel or texture and extend into an adjacent area. Most pull hair from the vertex, but temporal, occipital and frontal hair loss in children may be more obvious on the side of manual dominance. The hair loss may be minimal, commonly a solitary patch but visible hair thinning may progress to virtual total depilation, significantly so in adult women (Fig. 64.6).

Typically, the hairs are short, irregular, broken and distorted. The hair feels like stubble because of the broken, fractured hair shafts by contrast to alopecia areata which is much smoother. The patterns of plucking activity are centrifugal from a single starting point or linear, in wave-like activity. In extreme cases, the centrifugal pattern removes all hair except the most difficult to access namely the occiput. This shows as a 'tonsure pattern' [25] or 'Friar Tuck' [26] distribution. The eyelashes, eyebrows [27], facial and pubic hair may also be primarily affected. Children will also pluck eyebrows and eyelashes but adults almost exclusively pluck hair on the torso. Two-thirds of adults pulled hair from two or more sites and one-third from three areas [2,3]. Involvement of a second area began after an average of 8 years [1]. Body and pubic hair plucking, commoner in males [28], may become a ritualized activity either alone or as a conjugal activity and can indicate a personality or psychotic disorder. Hair is plucked from the scalp on average two to three times per day and daily from other areas. The duration and frequency of activity is variable but adults in general have longer and more frequent activity.

Children tend to manipulate hair at times of leisure for example watching TV, when tired and in the evening (Fig. 64.7). Adults have a more conscious structured activity initially seeking thicker or distorted hair and then progressing to larger areas, taking more and more time over the activity. This may become similar to a compulsion with elaboration of the rituals using instruments such as tweezers. The more frequent the plucking episodes, the greater the body image dissatisfaction and the more likely the patient will suffer depression and anxiety. There are similarities and overlap with body dysmorphic disorder in some cases.

Patients use wigs, hair weaving, false eyelashes and semipermanent use of hats and scarves to disguise the defects. The psychosocial effects of hair loss, for example reluctance to swim, date and participate in sports, cause significant disability. Chronic folliculitis of the neck, chin, chest, pubic areas or thighs as a result of plucking activity may also be the presenting complaint.

Once removed the hair may be licked or stroked against the cheeks and lips. The children may pluck the hair, stroke or suck the hair root before chewing and swallowing the remainder. The hair root alone may be eaten (trichorhizophagia) as a secretive activity and in a few patients the whole hair is eaten (trichophagia). Occasionally, hair may be seen stuck between the teeth. Patients who eat more hair tend to swallow the longer strands and a small percentage develops gastrointestinal bezoars.

Trichobezoar and the Rapunzel syndrome

Bezoar is derived from the Arabic word *badzahr*, meaning an antidote or counter poison. It also relates to the hardened contents of the fourth stomach of the Syrian goat, much prized as a cure for many diseases. Bezoars are ball-like aggregations of vegetable or fibre-like materials in the stomach and small intestine. The true incidence of trichobezoar is unknown. It is seen almost exclusively in girls and young women. It is rare but its importance is that morbidity is high with chronicity and severe complications which can lead to death. The aetiology has been linked to iron deficiency and pica where the tendency to swallow non-organic materials is reduced by iron replacement. Swallowed hair is retained within the folds of the gastric mucosa. The longer the hair, the more likely the action of peristalsis to stimulate the hair to become enmeshed into a ball which then becomes too large to easily leave the stomach

via the pylorus. The larger the ball becomes, the more likely it is that gastric atony will develop, leading to symptoms of nausea, indigestion, bloating and pain. The hair ball may eventually completely fill the stomach. Gastric erosions are common in chronic cases leading to anorexia and weight loss. The hair ball is decomposed to a degree by gastric acidity and fermentation of fats and food in the interstices of the hair gives a putrid smell and significant halitosis. These effects darken the hair in the bezoar no matter what the original hair colour. Children with trichotillomania who present with a combination of any of the following: abdominal pain; weight loss; nausea; vomiting; anorexia; and foul breath should be investigated [9,14]. Gastric trichobezoars may cause intestinal bleeding, pancreatitis or obstructive symptoms [1,18], particularly if the hair bolus extends down the small intestine. The Rapunzel syndrome [29] described this particular group after the character in the Grimm Brothers fairy tales. The syndrome is now defined as those with a trichobezoar with a tail that extends at least to the jejunum and in whom gastrointestinal obstructive symptoms are highly likely [30]. In a review of 27 cases which included only one male, the mean age at presentation was 10.8 years. Most patients ingested their own long hair although cases have been recorded of *Bezoar by proxy* where another person's hair has been eaten by the patient, one a hairdresser (personal observation) and another a nit picker [31]. The sole male in this study ate his sister's hair. In this group 37% had abdominal pain, 33% nausea and vomiting, 26% obstruction and 18.5% developed peritonitis. The hair ball can have a tail as long as 195 cm. The tail may also be broken up into numerous segments distributed throughout the small bowel. Recurrent Rapunzel syndrome has been reported. Life-threatening intestinal obstruction necessitates surgical intervention.

Investigations. Scalp biopsy has been shown to be the most useful investigation [1,8,9]. There are normally growing hairs amongst empty hair follicles in a non-inflamed dermis. This is the product of mechanical traction of hairs. Follicular plugging with keratin debris is evident. Many of the empty hair follicles show evidence of changing into the catagen phase with transformation of the lower follicular epithelium into a cord of undifferentiated basiloid cells. The hair shafts are often broken or reduced to little dark bodies. Trichomalacia is seen as deep distortion and curling of the hair bulb. In severe damage there is intraepithelial and perifollicular damage.

Clinically, gastrointestinal bezoars may be palpated as a non-tender, mobile mass in the upper abdomen. Barium contrast shows a filling defect in a lace-like, mottled pattern (Fig. 64.8).

The most accurate diagnostic tool is CT scan which in one study diagnosed at least 65% of cases in both stomach and small intestine [32]. Conventional X-ray was least helpful. Gastric endoscopy is confirmatory and laparoscopic endoscopy has been successfully used for removal [12].

Treatment. Clinical assessment scales are helpful in the fuller evaluation of treatments but remain largely research tools. Treatment is based on either some form of behavioural therapy or pharmacotherapy with tricyclic or SSRI antidepressants [33–35]. For many adolescents and children, identification of stressful episodes with accompanying support and parent education is usually all that is necessary. Teaching awareness and relaxation training and the introduction of coping strategies needs the expertise of a clinical psychologist. It is essential to present the harmful habit in an atmosphere of non-blame or fault but to change the agenda to a positive one to negotiate change. Habit reversal is effective as is behaviour therapy. Systematic reviews [33,34] showed that cognitive behavioural therapy (CBT) was effective alone and combined CBT and SSRIs were possibly more effective. Clomipramine was more useful than SSRI alone. One study showed that tricyclic antidepressants were effective and that clomipramine was more effective than desipramine [17] although relapse may be common unless treatment is continued for at least a year. All therapy is time consuming and needs expert clinical psychology support to maintain progress.



Fig. 64.8 Gastric trichobezoar on barium contrast examination showing a lace-like pattern of the mass of hairs.

References

1 Hautmann G, Hercogova J, Lotti T. Trichotillomania. *J Am Acad Dermatol* 2002; **46**: 807–21.

2 Christenson GA, Mackenzie TB, Mitchell JE. Characteristics of 60 adult chronic hair pullers. *Am J Psychiatry* 1991; **148**: 365–70.

3 Swedo SE, Rapoport JL. Trichotillomania. *J Clin Psychol Psychiatry* 1991; **32**: 401–9.

4 American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders; DSM-IV*, 4th edn. Washington DC: American Psychiatric Press, Inc., 1994.

5 American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders; DSM-IV*, 4th edn. Text revision. Washington DC: American Psychiatric Press, Inc., 2000.

6 Greenberg HR, Sarner CA. Trichotillomania. *Arch Gen Psychiatry* 1965; **12**: 482–9.

7 Christenson GA, Pyle RL, Mitchell JE. Estimated lifetime prevalence of trichotillomania in college students. *J Clin Psychiatry* 1991; **52**: 415–7.

8 Bruce T, Barwick L, Wright H. Diagnosis and management of trichotillomania in children and adolescents. *Paediatr Drugs* 2005; **7**: 365–76.

9 Muller SA. Trichotillomania: a histopathologic study in sixty six patients. *J Am Acad Dermatol* 1990; **23**: 56–62.

10 Deaver C, Miltenberger RG, Stricker JM. Functional analysis and treatment of hair twirling in children. *J App Behav Analysis* 2001; **34**: 535–8.
11 Stanley MA, Prather RC, Wagner AL *et al*. Can the Yale–Brown Obsessive Compulsive Scale be used to assess trichotillomania? *Behav Res Ther* 1993; **31**: 171–7.
12 Shami S, Jamaa A, Hamade A. Laparoscopic removal of a huge gastric trichobezoar. *Surg Laparoscopy Tech* 2007; **17**: 197–200.
13 Reeve EA, Bernstein GA, Christenson GA. Clinical characteristics and psychiatric comorbidity in children with trichotillomania. *J Am Acad Child Adolesc Psychiatry* 1992; **31**: 132–8.
14 Oranje AP, Peereboom-Wynia JD, DeRaeymacker DM. Trichotillomania in childhood. *J Am Acad Dermatol* 1986; **15**: 614–9.
15 Krishnan RRK, Davidson JRT, Guajardo C. Trichotillomania: a review. *Compr Psychiatry* 1985; **26**: 123–8.
16 Lochner C, Seedat S, du Toit P *et al*. Obsessive-compulsive disorder and trichotillomania. *Psychiatry* 2005; **5**: 2–16.
17 Birmaher B, Ryan ND, Williamson DE *et al*. Childhood and adolescent depression: a 10 year review. *J Am Acad Child Adolesc Psychiatry* 1996; **35**: 1427–39.
18 Bhatia MS, Singhal PK, Rastogi V, Dhar NK. Clinical profile of trichotillomania. *J Ind Med Assoc* 1991; **89**: 137–9.
19 Chang CH, Lee MB, Chiang YC, Lu YC. Trichotillomania: a clinical study of 36 patients. *J Formosan Med Assoc* 1991; **90**: 176–80.
20 Hussein SH. Trichotillomania. *Psychopathology* 1992; **25**: 289–93.
21 Simeon D, Cohen LJ, Stein DJ. Co-morbid self injurious behavior in 71 female hair pullers. *J Nerv Ment Dis* 1997; **185**: 117–9.
22 Lenane MC, Swedo SE, Rapoport JL *et al*. Rates of obsessive compulsive disorder in first degree relatives of patients with trichotillomania. *J Clin Psychiatry* 1992; **33**: 925–33.
23 Baer L. Behaviour therapy for OCD and trichotillomania. In: Chase TN, ed. *Advances in Neurology*. New York: Raven Press, 1992: 333–40.
24 Demaret A. Onychophagia, trichotillomania and grooming. *Ann Med Psychol (Paris)* 1973; **1**: 235–42.
25 Sanderson KV, Hall-Smith P. Tonsure trichotillomania. *Br J Dermatol* 1970; **82**: 343–50.
26 Dimino-Emme L, Camisa C. Trichotillomania associated with the 'Friar Tuck' sign and nail biting. *Cutis* 1991; **47**: 107–10.
27 Radmanesh M, Shafiel S, Naderi A. Isolated eyebrow and eyelash trichotillomania mimicking alopecia areata. *Int J Dermatol* 2006; **45**: 557–60.
28 Mazuecos J. Pubic trichotillomania in a man. *Br J Dermatol* 2001; **145**: 1034–5.
29 Vaughan E, Sawyers J, Scott H. The Rapunzel syndrome. An unusual complication of intestinal bezoar. *Surgery* 1968; **63**: 339–43.
30 Naik S, Gupta V. Rapunzel syndrome reviewed and redefined. *Dig Surg* 2007; **24**: 157–61.
31 Memon S, Mondham P. Recurrent Rapunzel syndrome. *Med Sci Monit* 2003; **9**: 92–7.
32 Ripolles T, Garcia AJ, Martinez MJ. Gastrointestinal bezoars: sonographic and CT characteristics. *Am J Roentgenol* 2001; **177**: 65–9.
33 Dougherty D, Loh B, Jenike M. Single modality versus dual modality treatment for trichotillomania. *J Clin Psychiatry* 2006; **67**: 1086–92.
34 Block M, Landero S, Dombranski P *et al*. Systematic review: pharmacological and behavioural treatment for trichotillomania. *Biol Psychiatry* 2007; **62**: 839–46.
35 Gupta MA, Gupta AK. Use of psychotropic drugs in dermatology. *Dermatol Clin* 2000; **18**: 711–25.

Onychotillomania and onychophagia [1]

(see also Chapter 65)

The compulsive habits of nail picking and nail biting have been shown to be common in children and adolescents [2,3]. The aetiologies suggested include stress, imitation of family members and transference from the thumb sucking habit. Nail biting is usually confined to the fingernails, but nail picking, especially in adults, may involve all digits. Damage to cuticles and nails causes paronychia, nail dystrophy and longitudinal melanonychia [4]. In chronic cases, there is an association with trichotillomania [1]. Compulsive biting, tearing or picking with instruments such as scissors, knives or razorblades may lead to permanent destruction [5].

Onychotillomania may be a feature of developmental problems in children and is a component of self-destructive behaviours in Tourette's and Prader–Willi syndromes. In adults, chronic nail biting is most commonly an isolated self-destructive habit which may respond to cognitive behavioural training [6]. The other common problem is a compulsive action as a part of OCD, not always at times of stress. Rarely, onychotillomania is a manifestation of a major depressive disorder which has a suicide risk [7]. Self-induced anonychia of the toenails was produced by one man who plucked out the nails with pliers rather than suffer recurrent paronychia from previously crushed toes [8]. Delusions of parasitosis may provoke self-destruction of the nails [9] as can a *folie à deux* in the confused elderly [10]. Successful drug response to treatment has been shown with clomipramine [9] and pimozide [10].

References

1 Demaret A. Onychophagia, trichotillomania and grooming. *Ann Med Psychol (Paris)* 1973; **1**: 235–42.
2 Leung AK, Robson WL. Nailbiting. *Clin Paediatr* 1990; **29**: 690–2.
3 Odenrick B, Fattstrom V. Nailbiting: frequency and association with root resorption during orthodontic treatment. *Br J Orthod* 1985; **12**: 78–81.
4 Baran R. Nail biting and picking as a cause of longitudinal melanonychia. *Dermatologica* 1990; **181**: 126–8.
5 Sait MA, Reddy BSN, Garg BR. Onychotillomania. *Dermatologica* 1985; **171**: 200–2.
6 Twohig H, Woods D. Evaluating the efficacy of habit reversal in chronic nail biting. *J Clin Psychiatry* 2003; **64**: 40–8.
7 Lin C. Onychotillomania, major depressive disorder and suicide. *Clin Exp Dermatol* 2006; **31**: 897–9.
8 Hurley PT, Balu V. Self inflicted anonychia. *Arch Dermatol* 1982; **118**: 956–7.
9 Alkiewicz J. Uber Onychotillomanie. *Dermatol Wochenschr* 1934; **98**: 519–21.
10 Hamman K. Onychotillomania treated with pimozide. *Acta Derm Venereol (Stockh)* 1982; **62**: 346–8.

Psychogenic purpuras and painful bruising syndrome

This group of disorders continues to present an enigma. The common features are the presence of purpura, bruising or frank bleeding in patients who often have a history of psychological disturbance. Patients are almost always female. Reports of male involvement are extremely rare since the original description of the syndrome over 50 years ago. For clarification it is helpful to consider the following separate categories, although some overlap is apparent:

1 Autoerythrocyte sensitization syndromes (Gardner–Diamond syndrome)
2 Purpura factitia.

Autoerythrocyte sensitization syndromes [1–3]

In this rare but well-recognized condition, exquisitely tender bruises arise after minimal trauma with or without a history of emotional disorders. In the original cases, it was noted there was a preceding history of an injury involving extensive bruising or major surgery. These bizarre, tender lesions are most commonly located on the arms and legs [4,5]. Bruising is heralded by a burning or stinging sensation followed after a few hours by

oedema, and erythema and appears a day or so later. There are reports of severe, deep bruising mimicking cellulitis of the leg [6] and also resembling compartment syndrome [7]. Magnetic resonance imaging shows subcutaneous swelling and histology oedema and erythrocyte extravasation [8]. Abdominal pain, bleeding from internal organs and neurological symptoms may occur [1]. The characteristics of the clinical picture have remained consistent in young adolescents [9] and in the few men reported [10]. However, the pathognomonic autosensitivity testing by injection of autologous red cells is not consistently positive. Other abnormalities may be found [3,11,12] including abnormalities of platelet aggregation. Typical ecchymoses can be reproduced by the intradermal injection of the patient's own erythrocytes and in some cases red-cell phosphatidyl-L-serine [13]. Gomi and Miura [14] described a case with associated thrombocytosis where busulphan therapy induced a reduction in attacks. Increased fibrinolytic activity has also been noted at the onset of fresh lesions in some patients [11,15]. One case seemed to have been made worse by a copper-containing intrauterine contraceptive [16].

Psychiatric symptoms were present in 21 of 30 cases reported [17]. All reported cases emphasize the severe emotional disturbances as a constant feature. Anxiety, depression and psychosocial isolation are consistent findings. The possible relationship of stress to altered fibrinolysis is conjectural but measurable effects have been found [18] and the relationship to religious stigmatization has been discussed [1,14,18,19]. Psychotherapy [1,4,8] is a more successful treatment than psychotropic drugs and should be offered early in the course of the disease.

Purpura factitia

Bleeding, bruising and purpura have all been reported as factitious disease. A case of autoerythrocyte sensitivity associated with dermatitis artefacta has been recorded [20]. Anticoagulant malingerers, dicoumarol eaters and superwarfarin ingesters [21,22] misuse anticoagulants to produce bruising and bleeding. Child abuse has also been induced by surreptitious warfarin ingestion [23]. High-dose aspirin has also been taken by adults and given to children to produce similar but milder effects. Mechanical suction purpuras are ingenious and usually found on the chin in children as a result of sucking on a cup or glass. Adults may produce the purpura using machinery [24,25].

References

1 Ratnoff OD. The psychogenic purpuras: a review of autoerythrocyte sensitization, autosensitization to DNA, 'hysterical' and factitious bleeding, and the religious stigmata. *Semin Hematol* 1980; **17**: 192–213.

2 Gardner FH, Diamond LK. Autoerythrocyte sensitization: a form of purpura producing painful bruising following autosensitization to red blood cells in certain women. *Blood* 1955; **10**: 675–90.

3 Uthman IW, Moukarbel GV, Salman SM *et al*. Autoerythrocyte sensitization (Gardner Diamond) syndrome. *Eur J Haematol* 2000; **65**: 144–7.

4 Berman DA, Roenigk HH, Green D. Autoerythrocyte sensitization syndrome (psychogenic purpura). *J Am Acad Dermatol* 1992; **27**: 829–32.

5 Verstraete M. Psychogenic haemorrhages. *Verhandelingen* 1991; **53**: 5–28.

6 Ingen S, Viguier M, Guitera P *et al*. Painful bruising syndrome resembling cellulites of the leg. *Ann Dermatol Vener* 2002; **129**: 1029–32.

7 Karatosun V. Autoerythrocyte sensitivity (Gardner–Diamond syndrome) mimicking compartment syndrome. *Arch Orth Trauma Surg* 2003; **123**: 370–3.

8 Boussault P, Doutre MS. Painful bruising syndrome: a psychogenic disease. *Rev Med Intern* 2005; **26**: 744–7.

9 Sorenson R, Newman A, Gordon EM. Psychogenic purpura in adolescent patients. *Clin Paed* 1985; **24**: 700–4.

10 Ingber A, Alcalay J. Autoerythrocyte sensitivity (Gardner–Diamond syndrome) in men. Review of the literature. *Postgrad Med J* 1985; **61**: 823–6.

11 Rowell NR. A painful bleeding syndrome with increased fibrinolytic activity. *Br J Dermatol* 1974; **91**: 591–3.

12 Peutz J, Fete T. Platelet function disorder in Gardner–Diamond syndrome. *J Paed Haematol Oncol* 2005; **27**: 323–5.

13 Strunecka A, Krpejsova L, Palecek J *et al*. Transbilayer redistribution of phosphatidylserine in erythrocytes of a patient with autoerythrocyte sensitization syndrome (psychogenic purpura). *Folia Haematol* 1990; **117**: 829–41.

14 Gomi H, Miura T. Autoerythrocyte sensitization syndrome with thrombocytosis. *Dermatology* 1994; **188**: 160–2.

15 Lotti T, Benci M, Sarti MG *et al*. Psychogenic purpura with abnormally increased tPA dependent cutaneous fibrinolytic activity. *Int J Dermatol* 1993; **32**: 521–3.

16 Grossman RA. Autoerythrocyte sensitization worsened by a copper containing IUD. *Obstet Gynecol* 1987; **70**: 526–8.

17 Hersle K, Mobacken H. Autoerythrocyte sensitization syndrome (psychogenic purpura): report of two cases and review of the literature. *Br J Dermatol* 1969; **81**: 574–87.

18 Panconesi E, Hautman G. Stress, stigmatisation and psychosomatic purpuras. *Int Angiol* 1995; **14**: 130–7.

19 Whitlock FA. Self inflicted and related dermatoses. In: Whitlock FA, ed. *Psychophysiological Aspects of Skin Disease*. London: WB Saunders, 1976: 98–107.

20 Sawhney MP, Arora G. Undiagnosed purpura: autoerythrocyte sensitization syndrome associated with dermatitis artefacta and pseudo-ainhum. *Int J Dermatol* 2006; **72**: 379–81.

21 Agle D, Ratnoff OD, Spring GK. The anticoagulant malingerer. *Ann Intern Med* 1970; **73**: 67–72.

22 Oreilly RA, Aggeler PM. Covert anticoagulant ingestion: a study of 25 patients and review of the world literature. *Medicine (Baltimore)* 1976; **55**: 389–99.

23 White ST, Voter K, Perry J. Surreptitious warfarin ingestion. *Child Abuse Negl* 1985; **9**: 349–52.

24 Sneddon IB. Simulated disease: problems in diagnosis and management. *J R Coll Physicians Lond* 1983; **17**: 199–205.

25 Yates VM. Factitious purpura. *Clin Exp Dermatol* 1992; **17**: 238–9.

Factitious skin disease [1,2]

Doctors are trained to believe what the patient says. The unwritten contract of the consultation process is that the patient will relate the details of the illness as truthfully as they see it and respond to the physician's questions as openly as possible, neither deliberately hiding nor distorting the facts. The physician makes these assumptions in assessing the combination of signs and symptoms of the illness. It is also assumed that the patient will not do anything to hinder or interfere with the course of treatment and recovery. The anxious and apprehensive patient will commonly exaggerate or occasionally minimize symptoms in order to press their case in the alien and unique atmosphere of the consulting room. 'My skin was literally on fire and I had to throw myself into the bath' is the dramatic expression of the effects of skin disease on a patient driven to hyperbolic and dramatic language rather than by any real belief she had to convince her dermatologist that she had suffered spontaneous combustion of the skin. Patients may mis-attribute causation on the basis of experience, culture and a need to place the illness in a context. They may have mistaken beliefs because of other advice from other medical or increasingly media- or Internet-inspired sources. These consultation behaviours are common and do not really constitute a fabrication, although as persistent conduct can alienate a clinician's objectivity.

The clinician can be deceived by somatizing illness which has an unconscious basis, for example pain syndromes, the dynias, psychogenic itch or rarely for a dermatologist a conversion phenomenon which has a wholly psychogenic cause. These were previously grouped as hysteria.

Clinical deception refers to a spectrum of illness that lies in a continuum depending on the level of intention to deceive at the time of the act and the motivation for the induced illness. The definition of factitious behaviour is not completely clear since the level of intention may vary but for the dermatologist the definition by DSM-IV-TR [3] criteria maintains the difference from malingering. The DSM-IV-TR criteria for factitious disorder include:

A Intentional feigning of physical or psychological signs or symptoms

B The motivation is to assume the sick role

C External incentives for the behaviour (such as economic gain, avoiding legal responsibility, or improving physical well-being, as in malingering) are absent.

Criterion A supposedly excludes disorders characterized by unintentional production of symptoms, thereby marking a distinction between factitious disorders and somatoform, conversion and dissociative disorders. Criterion B assumes an internal incentive but a conscious one and criterion C excludes the intentional production of symptoms for external gain, thereby marking a distinction with malingering. There is much debate about this imperfect definition but it serves to helpfully distinguish most categories of factitious illness found in dermatology.

Dermatologists will encounter the DSM-IV subtype 300.19 presenting with predominantly physical signs and symptoms.

The nomenclature for dermatological lesions produced by patients as defined above is multifarious. Artifice is a noun meaning the use of cunning plans or devices in order to trick or deceive whilst an artefact is defined as man-made and artistic or decorative. A fabrication is an invention often in certain contexts meaning with deceitful intent, whilst factitious is an adjective meaning artificial or contrived. The term factitious dermatitis will be used preferentially here in keeping also with the revised definition of Münchausen's syndrome by proxy as factitious or induced illness (FII) [4].

Most physicians will maintain an endearing and undiscerning naïvety even in the face of strong evidence of simulated or fraudulent illness. The dilemma for the clinician is to determine the degree of intention present in the patient for the consciousness of the action which may not equate with the consciousness of the motive.

Factitious falsification of information, that is lying, is a consequence of the manufacture of skin lesions, the occult use of others (proxy disease) and disease produced for material profit or retribution. The lying may have a different quality in these cases such that the psychosocial lies of the impulsive, immature, young girl are mainly used to avoid the shame and denigration of exposure whereas the pathological lies (pseudologica fantastica) of the accomplished malingerer are used to embellish his performance.

There are a series of recognized skin diseases characterized by the essential features that, firstly, they are caused by the fully aware patient and, secondly, there is a desire to hide the cause from their doctors. This definition includes dermatitis factitia, dermatological pathomimicry, dermatitis simulata and dermatitis passivata. These syndromes are additionally distinguishable from others where there is overt secondary gain, such as Münchausen's syndrome, Münchausen by proxy and malingering.

References

1 Cunnien AJ. Psychiatric and medical syndromes associated with deception. In: Rogers R, ed. *Clinical Assessment of Malingering and Deception*. New York: Guildford Press, 1997: 23–46

2 Halligan P, Bass C, Oakley D, eds. *Malingering and Illness Deception*. Oxford: Oxford University Press, 2003.

3 American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn, Text Revision. Washington, DC: American Psychiatric Press, Inc., 2000.

4 Bass C, Jones DP. Fabricated or induced illness. *Psycholog Med* 2006; **5**: 60–5.

Dermatitis factitia

Definition. Dermatitis factitia is a skin disease caused entirely by the actions of the fully aware (i.e. not consciously impaired) patient on the skin, hair, nails or mucosae. These patients hide the responsibility for their actions from their doctors.

Epidemiology and aetiology. In adults all studies have shown a female preponderance, the ratio of female to male varying from 20:1 to 4:1 [1–5]. Lesions have been found in children from the age of 8 years [5], pre-pubertal children having an equal sex ratio, rising to 3:1 female predominance by early teenage years [5,6]. These series confirm that the majority of cases begin in adolescence and in adults under 30 years of age, although there is an important subgroup whose age of onset is significantly older. This subgroup is distinguished by being more likely to be male (male to female ratio 2:1), to produce more subtle skin lesions [1,2] and to have a past history of somatizing illness [1,5,7]. These complaints may take the form of pseudoseizures, abdominal pain, syncope, chronic fatigue and backache. Previous work has suggested that factitious dermatitis is more common in health-care workers and their families [8,9] because this environment provides not only a ready 'model to copy' but also a social structure where illness is always sympathetic and allowed for. However, this bias may now be less obvious [2–4] in a well-informed society whose medical symptoms, pathology and disease are more available via the media and the Internet.

The motivation to assume the sick role [10] depends on understanding the lexicon of medical anthropology. There is a distinction between disease, illness and sickness. Disease refers to primarily biological forms of pathology, illness to the subjective experience of being diseased and sickness involves the *process* of being ill. People differ in the way that they perceive, assess, act or fail to act upon the symptoms that they experience. This is recognized as a personal 'illness behaviour' [11] and shapes the role, firstly, within the family and, secondly, with professional health advisors. Those who assume the sick role [10] are exempted from responsibility for their illness but should do all in their power to get better. The psychopathology underlying the production of factitious lesions [1,2,12,13] suggests that the patient *wants* the *sickness role* as the essential pathology since the primary gain of *being a patient* is usually to be suspected of all illness. It is suggested that these patients have strong masochistic needs, for

example self-hate and guilt, and an illness which allows inappropriate regression and avoidance of adult (especially sexual) responsibilities, for example marital trauma. Factitious illness symbolizes both anger at, or conflict with, authority figures, for example school phobia and attempts at mastery of past trauma. Psychiatric or medical care fulfils massive dependency needs, for example inadequate coping strategies.

In many cases, the psychosocial stress of a major life event may be apparent. Children and adolescents commonly show anxiety and immaturity of coping styles in response to a dysfunctional parent–child relationship, bullying, physical body changes, or sexual and substance abuse. Adults may be neurotic and react to adverse situations in an immature, impulsive manner [3,12]. However, there may also be significant depression [2,3]. The more chronic patients tend to have a demonstrable personality disorder, more particularly borderline or hysterical in females and paranoid in males [2,12,14]. There is a significant literature on the relationship between factitious disorder and illness falsification in both children and adults and previous factitious and induced illness (FII; see below).

The development of factitious illness is commoner in those with memorable early (and sometimes continuing) experience of illness. There is a frequent association with medicine and these patients may have a grudge against medicine because of perceived mismanagement to them or their family. Alternatively, there may have been a close relationship to a physician in the past which is now loosened. It is part of the doctor–patient relationship that as an acute, active illness passes into a more chronic, enduring phase, some patients perceive that they are less important to both family and physician and a sort of 'emotional fatigue' is apparent in their responses to them.



Fig. 64.9 Factitious dermatitis; symmetrical and predominantly monomorphic.



Fig. 64.10 Factitious disease of skin on the chin and 'Mona Lisa smile'.

Clinical features. The two characteristics of the illness are, firstly, the physical signs and, secondly, the fabricated story that accompanies it. Because this story is essentially a compendium of lies, the nature of the clinical symptomatology in factitious dermatitis is the 'hollow history' [15]. The patient often describes the sudden appearance of complete lesions with little or no prodrome. There is no complete description of the genesis of individual skin lesions. The signs appear or are 'discovered' on waking, or in a lunch break, or on the way home from school or work. Lesions appear at an identical stage in development, in crops or groups, more often symmetrically but rarely scattered apparently at random (Fig. 64.9).

There is a significant lack of a history of progression of each lesion from its initial appearance to its fully developed state. By contrast there is a prolonged and elaborate description of complications and the failure to heal. Characteristically, established lesions may undergo sudden deterioration at the same time as new areas appear. Only rarely do patients use more than one method to produce lesions. It has been suggested that the patients show a 'belle indifference' to their predicament as part of a dissociative state and that, in the presence of visible disease, manifest a nonchalance and innocence transmitted through an enigmatic 'Mona Lisa smile' (Fig. 64.10).

This is more likely to represent a characteristic gesture of liars under questioning [15]. It is probably truer to say that the patients are more often passive than aggressive, even though they have a widespread disfigurement. However, considerable anger is commonplace from parents, carers, husbands or partners, who complain at the incompetence of a succession of doctors. This may extend further to recruiting other doctors, university academics, nurses and social workers to support their case [2]. More than one person may be involved, as in the *folie à deux* of two patients with factitious ulcers [16]. Official complaints to hospital management and to local government officials may follow.

Clinical signs [4,9,17]. For all age groups the commonest site of involvement is the face, particularly cheeks, representing over half the presentation in children [2,5,6]. The dorsa of the hands rather than the palms are the next commonest site, then the forearms,



Fig. 64.11 Crude, linear, angulated and destructive factitious dermatitis.



Fig. 64.12 Persistent ulceration of the breast from covert injections of milk and talcum powder.

most frequently of the non-dominant limb. There is a particular covert pattern on covered skin where the clothes hide significant mutilation of the breasts, abdominal areas and sometimes the genitalia. These areas of damage in young girls should prompt inquiry about sexual abuse. Involvement of the back, axillae and external ear is uncommon.

Cutaneous lesions have been produced by every known means of damaging the skin and are thus polymorphic, bizarre and mimic any of the known inflammatory reactions in the skin. Factitial dermatitis should enter the differential diagnosis of every chronic, puzzling and recurrent dermatosis. Most patients have simple 'models to copy', mainly acute inflammatory, traumatic or infective. The lesions are crude, angulated, destructive processes with a tendency to a linear configuration, as the result of thermal, chemical or instrumental injury (Fig. 64.11).

Circular erosions or blisters of a uniform size can be manufactured by cigarette burns or cryodamage from a closely applied pressurized aerosol such as an antiperspirant or asthma inhaler [18]. Perfume may remain detectable in the lesions for some days (personal observations). Less commonly, dermal lesions from blunt trauma presenting as odd haemorrhages or dramatic dermal indurations and necrosis are found from foreign body injections of milk, cosmetic oil or industrial grease. These are found more often in the breasts (Fig. 64.12), thighs or penis, the latter as covert body augmentation.

Oedema of limbs from constricting bands and hysterical dependent posture has been described [19] (Secretan's syndrome). It is characteristic that one digit, usually a toe, will be constricted at a time whilst all others are healthy. A repeated series of single, different ischaemic toes, whilst all others are healthy, should raise suspicion of external banding. Embolic disease can be excluded by vascular scan.

Excoriations may be made with nail files, sanding boards, cheese graters or wire brushes to produce raw, crusty, linear or arciform lesions with characteristic geometrical edges (Fig. 64.13). Punched-out necrotic areas, sometimes with blisters developing into indurated scars, are typical of thermal burns from cigarettes, soldering irons or ovens. These lesions are usually uniform in size and scattered haphazardly. Urticarial lesions are initially produced by chemical damage and progress subsequently to blistering, crusting and scarring.



Fig. 64.13 Dermatitis factitia: note the straight edges and sharp angulation of some of the lesions.

Characteristically, these areas may show the 'drip-sign', where corrosive liquids have been uncontrolled and allowed to run over



Fig. 64.14 Dermatitis factitia showing the drip sign.

the skin (Fig. 64.14). Bleaches, soaps and household cleaners are most commonly employed by women; industrial acids and automotive fluids by men. These chemicals may produce a persistent, detectable smell on the skin. Purpura and bruising are seen after suction, friction or blunt trauma. Children produce purpura on the chin by sucking on cups and on limbs by direct mouth suction or with the use of a toy or tool. Shearing stress also produces purpura, tending to present as linear limb lesions. Extensive bruising and bleeding in a child means that factitious and induced illness (see below) should be excluded, caused not only by trauma but also drug-induced by anticoagulants (see above, factitious purpura).

Subtle factitious skin lesions [2] are seen as fixed urticaria, vasculitic dermal nodules, panniculitis-type lesions and boggy fluctuant swellings. Considerable atrophy and pigment change occur with resolution. Careful examination of an acute lesion may reveal the presence of a needle track where milk, air, faeces, urine, cooking oil, silicone, grease or engine oil has been injected [20,21]. Access to needles and syringes may be via medical or paramedical family and friends. In other medical specialities, such as ophthalmology, oral medicine and otolaryngology, factitious disease presents as non-healing, infected wounds and excoriations [22–24].

There is a group that presents with a non-healing, post-surgical wound. This may follow a small operation after minor skin trauma, breast biopsy or instrumentation such as a laparoscopy (Fig. 64.15).

Wounds 'burst' after the sutures are removed, become recurrently infected and real organisms such as MRSA appear. Unfortunately, further 'wound repairs' exacerbate and legitimize the continuing wound. It is not unusual to see patients who have had up to eight operative revisions before a further referral is made to a dermatologist. Real complications arise, such as osteomyelitis or fistulae, provoking the need for further intervention [25]. There may be unexpected complications to the induced damage, leading to severe infection such as cerebral abscess [26], osteomyelitis and peritonitis, which may be life threatening [25,27].

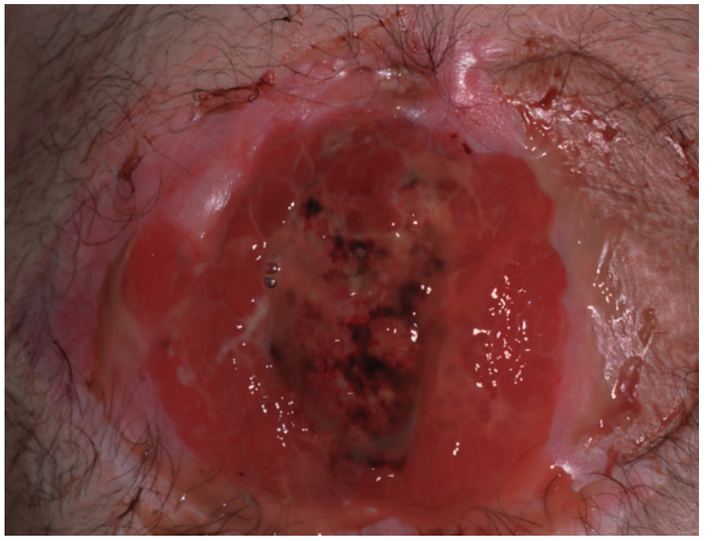


Fig. 64.15 Non-healing wound after surgery with characteristic central 'interference haemorrhage'.

Fabricated skin disease in children can begin from the age of 5 years (personal cases), is significantly more common in girls [5,6] and has an additional emphasis on certain imaginative presentations. Makeup, skin painting and application of glue have been skilfully used to simulate port-wine stains, other naevi, scaly dermatoses and even religious stigmata (personal series) (Fig. 64.16). Widespread, destructive eroded lesions can be an indicator of past or present sexual abuse [28].

The disease becomes self-generating as a perpetual circle of laboratory tests and investigations compounded by the voluble distress of the patient about the effect of the wound and the complaints of the relatives about medical incompetence. The primary reason for the appearance of the wound is obscured. The reason for the medical journey becomes lost because the accompanying emotional and investigative luggage has become so heavy and obstructive.

Differential diagnosis. The distribution and physical characteristics of the crude dermatitis are almost diagnostic. However, blistering, crusty lesions may simulate ecthyma, herpes simplex and bullous disorders. More subtle facial blisters may simulate porphyria cutanea tarda. Rare disorders, such as epidermolysis bullosa acquisita or amyloid, are a trap for the unwary. The collagen–vascular diseases including vasculitis and pyoderma gangrenosum must be excluded in non-healing wounds as must atypical mycobacterial infections and imported tropical infections. The curious linear dermatoses such as Nékam's syndrome, cuta-



Fig. 64.16 Glue applied to look like herpes zoster.

neous lymphomas, epidermolysis bullosa pruriginosa and linear drug eruptions [29] must be excluded. The diverse hereditary sensory neuropathies can show chronic non-healing ulcers and be mistaken for factitious wounds as can the cutaneous changes of reflex sympathetic dystrophy [30,31]. Drug addicts develop extensive ulceration and scarring at injection sites after extravasation of drug 'cocktails' into the skin. The purpuras and tissue purpuric reactions such as cutaneous amyloid can be perplexing and should be excluded [32].

References

1 Lyell A. Dermatitis artefacta in relation to the syndrome of contrived disease. *Clin Exp Dermatol* 1976; **1**: 109–26.
2 Millard L. Dermatitis artefacta in the 1990s. *Br J Dermatol* 1996; **135** (Suppl. 47): 27.
3 Koblenzer C. Dermatitis artefacta: clinical features and approaches to treatment. *Am J Clin Dermatol* 2000; **1**: 47–55.
4 Verraes S, Derancourt C, Poot F *et al*. Dermatitis artefacta: a retrospective study of 31 patients. *Ann Dermatol Venereol* 2006; **133**: 235–8.
5 Rogers M, Fairley M, Santhaman R. Artefactual skin disease in children and adolescents. *Australas J Dermatol* 2001; **42**: 264–70.
6 Saez M, Orozco L, Mora I *et al*. Dermatitis artefacta in paediatric patients. *Paediatr Dermatol* 2004; **21**: 205–11.
7 Millard LG. Factitious dermatological disorders in the somatising patient. *Abstracts of the Fifth International Meeting European Society for Dermatology and Psychiatry*. Bordeaux: ESDaP, 1993.
8 Fras I. Factitial disease. An update. *Psychosomatics* 1978; **19**: 119–22.
9 Sneddon I, Sneddon J. Self inflicted injury: a follow-up study of 43 patients. *BMJ* 1975; **3**: 527–30.
10 Prior L, Wood F. Characteristics of the sick role. In: Halligan P, Bass C, Oakley D, eds. *Malingering and Illness Deception*. Oxford: Oxford University Press, 2003: 122–31.
11 Mechanic D. The concept of illness behaviour: culture, situation and predisposition. *Psycholog Med* 1986; **16**: 1–7.
12 Fabisch W. Psychiatric aspects of dermatitis artefacta. *Br J Dermatol* 1980; **102**: 29–34.
13 Overholser JC. Differential diagnosis of malingering and factitious disorders with physical symptoms. *Behavioural Sciences and the Law* 1990; **8**: 55–65.
14 Sneddon IB. Simulated disease: problems in diagnosis and management. *J R Coll Physicians Lond* 1983; **17**: 199–205.
15 Vrij A, Mann S. Non verbal and verbal characteristics of lying. In: Halligan P, Bass C, Oakley D, eds. *Malingering and Illness Deception*. Oxford: Oxford University Press, 2003: 351–4.
16 Hubler WR, Hubler WR Sr. Folie à deux factitious ulcers. *Arch Dermatol* 1980; **116**: 1303–4.
17 Lyell A. Cutaneous artefactual disease. *J Am Acad Dermatol* 1979; **1**: 391–407.
18 Ikenaga S, Nakano H. Bullous dermatitis artefacta induced by deodorant spray. *J Dermatol* 2006; **33**: 40–2.
19 Smith RJ. Factitious lymphoedema of the hand. *J Bone Joint Surg* 1975; **57**: 89–94.
20 Aduan RP, Fauci AS, Dale DC *et al*. Factitious fever and self-induced infection. *Ann Intern Med* 1979; **90**: 230–42.
21 Behar TA, Anderson EE, Barwick WJ *et al*. Sclerosing lipogranulomatosis. A literature review of subcutaneous injection of oils. *Plast Reconst Surg* 1993; **91**: 352–61.
22 Ugurlu S, Bartley GB, Otley SCC. Factitious disease of periocular and facial skin. *Am J Ophthalmol* 1999; **127**: 196–201.
23 Ebeling O, Ott S, Michel O. Self-induced illness ENT medical practice. *HNO* 1996; **44**: 526–31.
24 Svirsky JA, Sawyer DR. Dermatitis artefacta of the paraoral region. *Oral Surg* 1987; **64**: 259–63.
25 Angus J, Affleck A, Leach IH, Millard L. Factitious disease presenting as non-healing wounds. *J Eur Acad Dermatol Venereol* 2005; **19**: 70.
26 Reed DH, Martin I. Dermatitis artefacta complicated by cerebral abscess. *Postgrad Med J* 1988; **64**: 976–8.
27 Murray SJ, Ross JB, Murray AH. Life threatening dermatitis artefacta. *Cutis* 1987; **39**: 387–8.
28 Harth W, Linse R. Dermatological symptoms and sexual abuse. *J Eur Acad Dermatol Venereol* 2000; **14**: 489–94.
29 Miori L, Vignini M, Rabbiosi G. Flagellate dermatitis after bleomycin. *Am J Dermatopathol* 1990; **12**: 598–602.
30 Buijs EJ, Klijn FA, Lindeman E. Reflex sympathetic dystrophy vs. a factitious disorder. *Ned Tijdschr Geneeskd* 2000; **144**: 1614–20.
31 Phelps R, Wilentz S. Reflex sympathetic dystrophy. *Int J Dermatol* 2000; **39**: 481–6.
32 Mahood JM. Familial amyloid neuropathy. *Postgrad Med J* 1980; **56**: 658–9.

Factitious cheilitis

Synonym
- *Le tic des levres*

The production of artefactual lesions of the lips is not common. Studies are small but a personal review of cases reported over the last 10 years shows that it is commonest in girls and young women but the incidence is equal in older groups [1,2]. Simulation of cheilitis has been produced by applying a crust of paper, glue and colorant. There is a significant debate about the role of factitious behaviour in the pathogenesis of exfoliative cheilitis. Reactions of the lips are limited and appear particularly as persistent inflammation with crusting and variable haemorrhage. The crusts may be very thick with a succession of layers of congealed haemorrhagic exudates resembling a carapace or oyster shell. The haemorrhage can also be impressive with coagulated blood and serum extruding over the lips. This is caused by picking, biting, rubbing and licking [3,4]. Occasionally, young adolescents will develop a disuse crusting of the lips because they become dysmorphic about cleaning and washing their mouth [5]. Removal of the crusts leaves a relatively normal lip although with time there is some superficial erosion.

Differential diagnosis includes contact dermatitis, actinic damage, chronic lip-licking habit and causes of granulomatous cheilitis.

Secondary candidiasis is not uncommon and treatment containing an antifungal is helpful as well as addressing the problem of self-trauma (see below).

References

1 Jeanmougin M, Civatte J, Bertail MA. Factitious crusting cheilitis. *Ann Dermatol Venereol* 1984; **111**: 1007–11.
2 Crotty CP, Dicken CH. Factitious lip crusting. *Arch Dermatol* 1981; **117**: 338–40.
3 Thomas JR, Greene SL, Dicken CH. Factitious cheilitis. *J Am Acad Dermatol* 1983; **3**: 368–72.
4 Kuffer R. Cheilitis and lip lesions artificially induced. *Ann Dermatol Vénéréol* 1990; **117**: 477–86.
5 Calobrisi S, Baselga E, Miller ES. Factitious cheilitis in an adolescent. *Paed Derm* 1999; **31**: 128–33.

Factitious nail disease

Traumatic and chemical damage to both the nail and nail fold have been seen in children and adults [1]. The paediatric cases show chronic paronychia caused by the insertion of nails, pins or splinters [2]. Soldiers avoiding duty have habitually used caustics to damage their fingers. The characteristic lesions show purpura and haemorrhage around the nail fold but also subungual haemorrhage and pustules. Similarly, Lyell [3] described a patient who induced haemorrhagic nail loss using a nail file. A significant sign is repeated traumatic nail loss occurring singly or multiply on one hand only. The differential diagnosis is described in Chapter 65.

References

1 Sneddon IB. Simulated disease: problems in diagnosis and management. *J R Coll Physicians Lond* 1983; **17**: 199–205.
2 Lesher J, Peterson C, Lane JE. An unusual case of factitious onychodystrophy. *Paed Dermatol* 2004; **21**: 239–41.
3 Lyell A. Dermatitis artefacta and self-inflicted disease. *Scot Med* 1972; **17**: 187–95.

Hair artefact

A distinctive pattern of hair loss may occur after cutting or shaving. It differs from the plucked appearance of trichotillomania with obvious gross changes such as rough, cropped areas of hair loss or unnatural, patterned shaved alopecia of scalp or eyebrows.

Differential diagnosis. See Chapter 66.

Witchcraft syndrome [1,2]

Artefact dermatitis can be provoked on an unknowing and unsuspecting victim by proxy. As an act of revenge, the daughter of a hairdresser applied benzyl ether of nicotinic acid to a customer's skin. This induced hyperaemia with some oedema within 10 min but not on the perpetrator since absorption of the agent is very low on the palm of the hand so she could easily apply it to the customer's skin without harm to herself.

References

1 Bandmann HJ, Wahl B. Contact urticaria artefacta (witchcraft syndrome). *Contact Dermatitis* 1982; **8**: 145–6.
2 Simani VK. Witchcraft syndrome. *Int J Dermatol* 1998; **37**: 229–31.

Dermatitis artefacta with artefact of patch tests

Bullous dermatitis artefacta in a female veterinary assistant healed with occlusive dressings [1]. New bullae on the other arm prompted the parents to demand 'allergy' tests. Ten patch tests to yellow petrolatum were applied to the back, which provoked a non-inflammatory bulla on one of the sites 2 days later. In another case the patch test reaction was mimicked by scarification in an attempt to claim compensation [2].

References

1 Maurice PDL, Rivers JK, Jones C, Cronin E. Dermatitis artefacta with artefact of patch tests. *Clin Exp Dermatol* 1987; **12**: 204–6.
2 Meigel WN, Koops DH. Scarification artifacts in the test reaction in an expert opinion of occupational dermatosis. *Hautarzt* 1976; **27**: 349–51.

Investigations. The primary suspicion of factitious dermatitis is clinical. The diagnosis is on the weight of evidence, both clinical and investigational, over a period of time. The clinical evidence is as much a finding of fact as the finding of, for instance, talc injected in a wound, provided that this has demonstrable objectivity. Clinical evidence is based on the physical appearance, distribution and evolution of lesions. Other clinical diagnostic clues may be seen such as the sparing of decorative marks and the areas of skin on the back [1]. Suspicions are aroused by the presence of physiologically impossible symptoms, observably incompatible lesions, contradictory objective evidence and non-response to reasonable treatment. However, certain investigations may produce supportive information. Dressings or underlying skin lesions may test unusually acid or alkaline with litmus [2]. Odd discoloured areas, brown, red or green, may dissolve with alcohol swabs and the pigment analysed by chromatography [3].

A skin biopsy will provide essential supportive information [4] but may not be necessary in all cases such as suction purpura (see above) on the chin. Trunk and limb lesions are easier to biopsy than facial areas but if there is a solitary lesion a diagnostic biopsy is indicated. Indurated areas need a deep incisional section to include deep tissues down to subcutaneous fat [4]. The epidermis is most damaged by friction or chemicals with a vacuolar dermatitis and lymphocyte around degenerating keratinocytes. The superficial acute and dramatic epidermal necrosis from physical and chemical damage is characteristic of crude damage to the skin. Additional subepidermal blistering can be produced by thermal and cryodamage. In contrast, the subjacent deeper dermal tissues can appear spared. Some chemicals, for example toothpaste, can induce unusual inflammatory reactions suggestive of cutaneous lymphoma [5] simply as a response to continuous rubbing and a foreign body reaction. Lesions produced by injections into subcutaneous tissues produce deeper lesions which show as vasculitis or an odd panniculitis. Careful examination may show injection tracks and foreign material [6–8]. Ink shows as pigment with limited inflammation, and talc excites a macrophage reaction with giant cells. Injected oils and greases produce deep continuing panniculitis. An alarming form of squamous syringometaplasia was seen after covert injections [9]. Special stains can reveal silver from silver nitrate caustic damage. Examination under polarized light can identify foreign material and further refinement can be found with energy dispersive X-ray analysis and infrared spectrometry [10]. Unlike disease states, the histopathology of factitious disease may vary with time and it has been shown that serial biopsy may be diagnostically helpful in sophisticated artefact [4] because

differing patterns of change may be present on each occasion. Occasionally, patients will bury needles completely into their skin to produce recurrent abscesses. A straight X-ray will visualize these. Some patients have inserted hundreds of these throughout the skin. Identification in one area needs X-rays of other body areas also. Wooden skewers may also be inserted, these are best seen via MRI scanning (personal cases).

There are psychometric tests which can be used for the assessment of factitial disorders, but these are essentially research tools [11,12].

References

1 Joe EK, Li VW, Magro CM *et al*. Diagnostic clues to dermatitis artefacta. *Cutis* 1999; **63**: 209–14.
2 Sneddon IB. Simulated disease: problems in diagnosis and management. *J R Coll Physicians Lond* 1983; **17**: 199–205.
3 McSween R, Millard L. A green man: a case of artefact. *Arch Dermatol* 2000; **136**: 115–8.
4 McSween R, Stevens A, Millard L. Sex, lies and dermatopathology. *Br J Dermatol* 1996; **135**: 27.
5 Angus J, Ravenscroft J, Leach I *et al*. Dermatitis artefact in a child mimicking cutaneous T-cell lymphoma. *Paed Dermatol* 2007; **24**: 327–9.
6 Raquena L, Sanchez YE. Panniculitis. *J Am Acad Dermatol* 2001; **45**: 325–61.
7 Ackerman BA, Mosher DT, Schwamm HA. Factitial Weber–Christian syndrome. *JAMA* 1966; **198**: 155–60.
8 Winkelmann RK, Barker SM. Factitial traumatic panniculitis. *J Am Acad Dermatol* 1985; **13**: 988–94.
9 Cribier B, Lipsker D, Grosshans E. Squamous syringometaplasia: an original manifestation of pathomimesis. *Ann Dermatol Venereol* 1993; **120**: 900–3.
10 Kwon EJ. Dermatitis artefacta. *J Cut Med Surg* 2006; **10**: 108–13.
11 Greene RL. Assessment of malingering and defensiveness. In: Rogers R, ed. *Clinical Assessment of Malingering and Deception*. New York: Guildford Press, 1997: 169–207.
12 Vrij A, Mann S. Deceptive responses and detecting deceipt. In: Halligan P, Bass C, Oakley D, eds. *Malingering and Illness Deception*. Oxford: Oxford University Press, 2003: 348–60.

Co-morbidity. Twenty per cent of patients have a somatization disorder and hypochondriasis [1,2]. These are co-morbid with anxiety, depression and substance abuse [3]. Borderline personality disorder is a factor for chronicity in both sexes [4]. True hysteria where there is dissociation between the act of self-damage and the awareness of performing the action is debated at length based on the premise that the patient may be performing a conscious act for unconscious reasons [5].

References

1 Sharpe M. Distinguishing malingering from psychiatric disorders. In: Halligan P, Bass C, Oakley D, eds. *Malingering and Illness Deception*. Oxford: Oxford University Press, 2003: 156–69.
2 Fink P. Physical complaints and symptoms of somatising patients. *J Psychosom Research* 1992; **36**: 125–36.
3 Barsky AJ. Overview: hypochondriasis, bodily complaints, and somatic styles. *Am J Psychiatry* 1992; **140**: 101–8.
4 Kapfhammer HP, Dobmeir P. Artefactual disorders between deception and self mutilation. *Nervenartzt* 1998; **69**: 401–9.
5 Bass C. Factitious disorders and malingering. In: Halligan P, Bass C, eds. *Contemporary Approaches to Hysteria*. Oxford: Oxford University Press, 2001: 127–42.

Treatment. The management of factitious dermatitis is not an interrogation. There are three therapeutic aims. First, the skin damage may be extensive, disfiguring and infected. It is a mistake to assume that the perpetrator, that is the patient, does not wish treatment. There is always significant skin damage which will be both inflamed and infected with the potential for scarring and residual pigmentation. The process of tissue repair may take time but allows the opportunity for patient contact and relationship building. Topical and systemic antibiotics, analgesics and anti-inflammatories establish the doctor–patient relationship and underline to the patient that the physician has a helpful, non-aggressive, sympathetic approach. Efficient occlusive bandaging will allow most lesions to heal except for those of the most devious and determined.

Secondly, time should be taken to identify the nature and extent of the psychological problem. The dilemma has always been whether patients should be confronted or not [1–7]. In most cases the urge to confrontation is stimulated by the aggression the physician feels because the doctor–patient relationship has apparently been betrayed. The doctor must avoid personalizing the episode and needs to consider the approach which is likely to change the patient's behaviour.

For many years a non-confrontational and non-punitive approach has been favoured. This passive acceptance of 'a cry for help' has the merit of a non-aggressive interview in the short term. The psychological problems should be approached in a non-intrusive manner [5–9], allowing the patient freedom to express their difficulties in a passive, confidential environment. Children usually respond well to this approach, particularly if a cause of psychosocial pressure is identifiable. However, chronic persistent self-damage is predictive of long-term emotional illness and referral to a child psychiatrist is imperative [4]. Paradoxically, too passive an approach gives the patient consent to continue in the abnormal sickness role [4,10]. Although this approach has been unsuccessful, for a dermatologist it is the most comfortable since there is no confrontation.

Thirdly, adult patients may respond to a different type of non-confrontational approach which also displays surprising robustness. This is the 'narrow escape', 'quasi-confession', 'recovery', 'face-saving' or 'escape with honour' strategy. This mechanism works by suggesting that the patient does some 'personal homework' to find a solution to their illness by offering a rationale for recovery. The patient may claim that alternative medicine such as hypnosis, homeopathy or fringe methods such as manipulation and aromatherapy has 'cured' them. It is important to follow up the patient to establish that psychological and social factors were intrinsic to the remission.

One additional technique is the double-blind strategy where the physician explains that the treatment carries an expectation for recovery. If this does not occur then they will be forced to conclude that failure to improve constituted conclusive evidence that the problem is psychological or factitious [10]. A study of behavioural interventions of this type in acute and chronic non-organic (conversion/factitious) motor disorders showed that this produced positive resolution in chronic cases resistant to more passive techniques. This strategy worked particularly well where members of the family were angry or sceptical about the nature of the symptoms.

In addition, the physician can reformulate the physical problem as a synthesis of both the physical and the psychological effects of

discovered stressful events. This deliberate change of agenda provides a basis for an 'inexact explanation', relating the stress to the appearance of physical lesions without direct confrontation. This is a form of *indirect* confrontation.

Direct confrontation is a highly charged strategy and should only be used if the deliberate act is certain (e.g. if the self-damage has been witnessed) and there is sufficient support and advice available at the consultation. In certain paediatric cases early intervention with confrontation has been advised [11]. This will need the assistance of psychiatric advice and to effect a transference to psychiatric care if necessary. This catharsis can be achieved in a manner which allows the patient to express a positive decision to change without dwelling on the deception and precipitating an aggressive defensive response [1,4,10–12]. Not surprisingly, other workers disagree with this approach citing the high failure rate and the risk that the patient may strive even harder to legitimize the illness and himself by consulting other doctors [2,7].

The management and prognosis in adults is that of the primary psychological disorder [8]. Acute stress reaction can be addressed in a series of short consultations at the time when the dressings are changed. Depression responded well in two series to tricyclics, or SSRI antidepressants [7,8] even when no precipitating event was identifiable. Tacit acceptance that the cause of the rash has been identified, without further challenge, helps to make the transfer to formal psychiatric care easier if needed [10]. Between one-third and a half of patients continue to develop chronic lesions [6,7–9]. Such cases usually have a personality disorder, commonly hysterical, paranoid or borderline [10], and need psychiatric assessment [13]. Unfortunately, this is frequently unacceptable to the patients who default the clinic or are referred elsewhere.

References

1 Bass C, May S. Chronic multiple functional somatic symptoms. In: Mayou R, Sharp M, eds. *The ABC of Psychological Medicine*. London: BMJ, 2002: 325–7.
2 Rogers R. Psychiatric and medical syndromes associated with deception. In: Rogers R, ed. *Clinical Assessment of Malingering and Deception*. New York: Guildford Press, 1997: 390–7.
3 van der Feltz CCM. Confronting patients about a factitious disorder. *Ned Tidjschr Geneeskd* 2000; **144**: 545–8.
4 Feldman MD, Ford CV. Factitious disorders. In: Sadock BJ, Sadock VA, eds. *Comprehensive Psychiatry*, 7th edn. Baltimore: American Psychiatric Press, 1996: 175–94.
5 Lyell A. Dermatitis artefacta in relation to the syndrome of contrived disease. *Clin Exp Dermatol* 1976; **1**: 109–26.
6 Sneddon I, Sneddon J. Self inflicted injury: a follow-up study of 43 patients. *BMJ* 1975; **3**: 527–30.
7 Consoli S. Dermatitis artefacta: a general review. *Eur J Dermatol* 1995; **5**: 5–11.
8 Fabisch W. Psychiatric aspects of dermatitis artefacta. *Br J Dermatol* 1980; **102**: 29–34.
9 Millard L. Dermatitis artefacta in the 1990s. *Br J Dermatol* 1996; **135** (Suppl. 47): 27.
10 Shapiro AP, Teassell RW. Behavioural interventions in the rehabilitation of acute vs chronic non-organic (conversion/factitious disorders). *Br J Psychiatry* 2004; **185**: 140–6.
11 Libow JA. Child and adolescent illness falsification. *Paediatrics* 2000; **105**: 336–42.
12 Libow JA. Beyond collusion: active illness falsification. *Child Abuse Neglect* 2002; **26**: 525–36.
13 van Moffaert MM. Integration of medical and psychiatric management in self-mutilation. *Gen Hosp Psychiatry* 1991; **13**: 59–67.

Dermatological pathomimicry [1]

Some patients may intentionally aggravate an existing dermatosis using the explanation of its genesis given by their dermatologist. It is distinguishable from dermatitis factitia because the disease appears like an exacerbation of established skin disease with none of the bizarre physical signs typical of mechanical, chemical or thermal interference. This is also to be differentiated from self-inflicted delayed healing of surgical and traumatic wounds which is achieved by external damage. The clinical suspicion should arise when patients suffer unexplained exacerbations of disease or are particularly unresponsive to adequate supervised therapy. A group of 13 patients who had deliberately caused recurrence of their existing skin disease by reintroducing the precipitating factor and invoking the original pathogenic mechanism have also been described [1,2]. Atopic patients reintroduced allergens, for example animal danders, and patients with proven allergic contact dermatitis used the allergen on their skin, for example lanolin, local anaesthetics. Those patients with systemic drug sensitivities were found to have the drug detectable in their blood or urine on representation. Known past irritants were applied to chronic leg disorders and a married couple swapped contaminated dressings to continue mutual skin sepsis. Since the original description there have been numerous reports of contrived exacerbations of common dermatoses. A patient with psoriasis covertly retook atenolol which previously had caused problems (personal communication). Other reports have described irritant contact dermatitis [3], allergic perianal dermatitis [4] and artificial oedema of an arm or leg [5]. The largest group were young women who had lost support from within their family group. A smaller sample were elderly who had lost social contact and felt isolated.

More direct confrontational discussion without recrimination proved helpful and follow-up showed only minor recurrence in two patients 5 years later [2].

References

1 Millard LG. Dermatological pathomimicry: a form of patient maladjustment. *Lancet* 1984; **2**: 969–71.
2 Millard LG. Dermatological pathomimicry—a follow up study. *Proceedings of the First International Symposium on Dermatology and Psychiatry*. Vienna: ESDaP, 1987.
3 Condé-Salazar L, Gomez J, Meza B. Artefactual irritant dermatitis. *Contact Dermatitis* 1993; **28**: 246.
4 Cunha A, Barros M, Azevado F. Perianal contact eczema: an unusual presentation of dermatitis artefacta. *Derm Psychosomatics* 2003; **4**: 219–22.
5 Stoberi C, Musalek M, Partsch H. Artificial oedema of the extremity. *Hautarzt* 1994; **45**: 149–53.

Dermatitis simulata

Apparent skin disease can be represented by patients who are ingenious enough to use external disguise to simulate disease. These patients do not significantly damage their skin. Makeup has been used to paint on a rash [1] or simulate a birthmark. This is most common in children. Glue and crystallized sugar can produce a coagulum to simulate a desquamating rash or chronic cheilitis, drugs to induce skin discoloration [2] and topical printing dyes to produce discoloured sweat [3]. These discolorations can be removed by aqueous or alcohol swabs and analysed if necessary [3]. Sugar crusts dissolve easily in water, keratin ones

do not. Red makeup has been used to simulate a port-wine stain on the face. Localized red facial rashes seen on two young girls disappeared after treatment with erythromycin but no analysis of the pigment or skin biopsy was possible to confirm the source of the pigment in this bizarre distribution [4]. An acute blue patch on the arm of a diabetic in an injection site was diagnosed on biopsy as self-injected printer ink rather than an injection haematoma [5].

These deceptions were clever enough to confuse their doctors for months. Most of these patients were young and immature, but a somatizing illness was recorded in one older patient and previous treated depression in another. The main differential diagnosis is from apocrine and eccrine chromhidrosis or pseudochromhidrosis after accidental absorption of dyes through the skin.

References

1 King MC, Chalmers RJG. Another aspect of contrived disease: 'dermatitis simulata'. *Cutis* 1984; **34**: 463–4.

2 Sneddon IB. Simulated disease: problems in diagnosis and management. *J R Coll Physicians Lond* 1983; **17**: 199–205.

3 McSween R, Millard L. A green man: a case of artefact. *Arch Dermatol* 2000; **136**: 115–8.

4 Singal A, Thami G. Red pseudochromatosis of the neck. *Clin Exp Dermatol* 2004; **29**: 548–9.

5 Heydendael V, Hoekzema R. Acute blue patch on the forearm. *Arch Dermatol* 2007; **143**: 937–42.

Dermatitis passivata

The cessation of normal skin cleansing will produce an accumulation of keratinous crusts. This is commonly seen in geriatric or demented patients who suffer from self-neglect and in its extreme form has been called the Diogenes syndrome [1,2]. The lesions are the result of self-neglect and comprise cumulative accretions of keratin and dirty debris which forms a thick carapace with time. Lesions are usually found on the upper central chest, over the back and accumulated as coagulated debris in the groins. These elderly patients may be paranoid, have mood disorders or have temporofrontal dementia. Alcohol abuse is a co-factor. Characteristically, they are hoarders and live in extreme squalor. However, a group of younger patients have been described [3] who showed lesions on the scalp, face or arms. They were young adults who were invariably accompanied by parents or family (Fig. 64.17).

Significant psychopathology was schizoid thought disorder and social withdrawal. Occasionally, patients with a dissociative hysterical limb palsy will present with mild but significant hyperkeratosis on the affected limb. Specialist psychological therapy was usually necessary either as day care or community psychiatric support [2,4].

References

1 Clark ANG, Mankikar GD, Gray I. Diogenes syndrome: a study of neglect in old age. *Lancet* 1975; **i**: 366–8.

2 Hanon C, Pinquier C, Gaddour N. Diogenes syndrome: a transnosographic approach. *Encephale* 2004; **30**: 315–22.

3 Millard LG. Dermatitis passivata: the young Diogenes syndrome. *Cutis* 1997; **47**: 124–7.

4 Reyes-Ortiz CA. Diogenes syndrome: the self-neglect elderly. *Compr Ther* 2001; **27**: 117–21.



Fig. 64.17 Young Diogenes syndrome; accretions of facial keratin and debris.

Malingering

Asher [1] defined malingering as the imitation, production or encouragement of illness for a deliberate end. The American Psychiatric Association DSM-IV definition states that the 'essential feature of malingering is the intentional production of false or grossly exaggerated physical or psychological symptoms, motivated by external incentives such as avoiding military duty, avoiding work, seeking financial compensation, evading criminal prosecution, or obtaining drugs'. However, the taxonomy of malingering is difficult because of the moralistic overtones of criminality and false compensation litigation [2–5].

Malingering may be co-morbid with conversion disorders, personality disorders and other factitial behaviour. However, usually it differs from most factitial disease in being short-term and opportunistic whereas other illness falsification is chronic and persistent. Fear, desire and escape are the three main motives to produce false or grossly exaggerated physical or psychological symptoms. Soldiers feigning disease and disability hope to avoid duty, suspend transfer or be discharged from the service [6,7]. Workers can prolong sick leave, delay corporate change of job or seek to obtain early retirement with an apparently extended illness [8]. Some patients may seek compensation for some contrived illness, for example alleged burns, or aggravate and continue an existing disease, for example industrial dermatitis, out of a sense of grievance or retribution. Active intervention to introduce policies and procedures to reduce the risk of illness deception at work are recommended [9]. Prolonged legal cases of supposed medical negligence are common in those with manufactured illness whose dissatisfaction with their doctors or the care they have been given may lead to a financial settlement as a reward [10].

Chronic, non-healing, post-operative scars are manipulated with instruments, or even faecal injection to maintain sepsis [11,12]. Hand dermatitis, both irritant and allergic contact, may be perpetuated to seek higher compensation awards [13,14].

Treatment depends on the underlying psychiatric illness if significant psychopathology can be found but the opportunist

response in patients with an underlying personality disorder is poor.

References

1 Asher R. Malingering. *Talking Sense*. Bath: Pitman Press, 1973: 145–7.
2 Bass C. Factitious disorders and malingering. In: Halligan P, Bass C, eds. *Contemporary Approaches to Hysteria*. Oxford: Oxford University Press, 2001: 127–42.
3 Raine A. Malingering and criminal behaviour as psychopathology. In: Halligan P, Bass C, Oakley D, eds. *Malingering and Illness Deception*. Oxford: Oxford University Press, 2003: 93–107.
4 Hutchinson GL. *Disorders of Simulation*. Madison: Psychosocial Press, 2001: 53–63.
5 Cunnien AJ. Psychiatric and medical syndromes associated with deception. In: Rogers R, ed. *Clinical Assessment of Malingering and Deception*. New York: Guildford Press, 1997: 33–46.
6 Palmer I. War based hysteria: the military perspective. In: Halligan P, Bass C, eds. *Contemporary Approaches to Hysteria*. Oxford: Oxford University Press, 2001: 12–35.
7 Cohen A, Vardy D. Dermatitis artefacta in soldiers. *Mil Med* 2006; **171**: 497–9.
8 Meneghini C, Angelini G. Occupational dermatitis artefacta. *Derm Beruf Umvelt* 1979; **27**: 163–5.
9 Barron C, Poole J. How can organizations prevent illness deception among employees? In: Halligan P, Bass C, Oakley D, eds. *Malingering and Illness Deception*. Oxford: Oxford University Press, 2003: 156–69.
10 Eisendrath SJ. When Munchausen becomes malingering. Factitious disorders that penetrate the legal system. *Bulletin of American Academy of Psychiatry and the Law* 1996; **24**: 471–81.
11 Lyell A. Cutaneous artefactual disease. *J Am Acad Dermatol* 1979; **1**: 391–407.
12 Reich P, Gottfreid LA. Factitious disorders in a teaching hospital. *Ann Intern Med* 1983; **99**: 240–7.
13 Condé-Salazar L, Gomez J, Meza B. Artefactual irritant dermatitis. *Contact Dermatitis* 1993; **28**: 246–7.
14 Hutchinson GL. *Disorders of Simulation*. Madison: Psychosocial Press, 2001: 195–221.

Pseudologica fantastica and Münchausen's syndrome [1–4]

Asher used this term to describe the notorious hospital hopper who presents with a dramatic and untruthful story of illness. This is a chronic, severe and dramatic subtype of factitious disease [1]. The essential elements are the recurrent nature of the illness, and the frequency and similarity of the repetitive pattern of the complaint in different hospitals (peregrination). The simulated illnesses may be esoteric and rare with the patient often presenting a dossier to the doctors. Whilst dermatological complaints are uncommon in Münchausen's syndrome, simulated porphyria and connective tissue disease, for example, may present to the dermatologist. The last element in the syndrome is pseudologica fantastica (pathological lying) [3]. This describes the telling of lies about past social history and connections, exploits, wealth and invention of an alias. The patients are usually male, over 30 years of age and travel widely from hospital to hospital. They complain of abdominal pain, haemorrhage or some neurological incapacity. Skin lesions are rare. The commonest signs are non-healing wounds, widespread blistering or multiple excoriations associated with other somatic complaints [5]. Serious consequences such as septicaemia and paraplegia have occurred [6] from induced cutaneous ulceration. Characteristically, patients take their own discharge if they sense their deception has been discovered. The Internet provides access to those interested in health and medicine and is a rich resource for the expansive personality of the Münchausen patient. Because the Internet offers 'virtual support groups' these individuals may offer 'virtual' factitious disorders. Four cases have been reported showing the facility with which they can attract attention, mobilize sympathy and control others [7].

References

1 Menninger K. Polysurgery and polysurgical addiction. *Psychoanal Quart* 1934; **4**: 173–99.
2 Asher R. Munchausen's syndrome. *Lancet* 1951; **1**: 339–41.
3 Newmark N, Adityanjee KJ. Pseudologica fantastica and factitious disorder. Review of the literature. *Compr Psychiatry* 1999; **40**: 89–95.
4 Bass C. Factitious disorders and malingering. In: Halligan P, Bass C, eds. *Contemporary Approaches to Hysteria*. Oxford: Oxford University Press, 2001: 127–42.
5 Eisendrath SJ. When Munchausen becomes malingering. *Bull Am Acad of Psych* 1996; **24**: 471–81.
6 Burket JM, Burket BA. Factitial dermatitis resulting in paraplegia. *J Am Acad Dermatol* 1987; **17**: 306–7.
7 Feldman MD. Munchausen by internet. Detecting factitious illness and crisis on the Internet. *South Med J* 2000; **93**: 669–72.

Fabricated and induced illness (Münchausen's syndrome by proxy) [1,2]

In 1977, Meadow [1] had the clinical acuity and personal courage to describe the syndrome of Münchausen by proxy where the illness in the child is fabricated by the parent, usually mother, or someone *in loco parentis*. This phenomenon has been redefined as fabricated and induced illness (FII). Other carers may be involved and that may include health professionals. Doctors and others may not only fail to understand the origins of a child's symptoms but also institute further harm by inappropriate investigations, treatment and surgery [2]. The guidelines to identifying cases [3] mirror many of those discussed for factitious dermatitis. The history is 'hollow' with a lack of detail. Most parents and carers can give a clear account of an accident. Risk factors include single parent, previous abuse, frequent visits to GP or Accident and Emergency departments, poverty, overcrowding and young parents. The victims have a persistent or recurrent illness that cannot be readily explained. The previous diagnoses remain descriptive and not stringent. Symptoms do not respond and laboratory tests are incongruous. The reported symptoms are inconsistent with presenting health and the symptoms fail to appear in the absence of a certain parent (usually the mother). The perpetrator is reluctant to leave the child even for a few minutes, but remains oddly impassive even in an emergency. They refuse treatments and hospital admission and may become hostile and abusive. Characteristically, these carers attempt to make close relationships with some medical staff, usually nurses, with a blurring of the professional–parent objective relationship. There may be fabrication of family details and a disturbed marital and social structure. Rarely, the parent exhibits the syndrome herself and produces proxy lesions on the child [4].

The victims are usually infants or toddlers with a mean age at diagnosis of 40 months [5,6,7]. The mean delay between presentation and diagnosis was 15 months. The most common presentations in a literature review were bleeding and bruising (44%), CNS depression (19%), apnoea (15%), diarrhoea (11%), vomiting (10%), fever (10%) and rash (9%) [6]. A list of 105 symptom presentations showed dermatological lesions were amongst the five commonest signs [7]. Skin lesions are very commonly bruising, often blistering

and burns. Bruises in children are common on the lower legs and arms but certain sites should raise concern. These are the face and head of a child less than 1 year old, sides of the face and ears, black eyes, and bruising on buttocks/lower back and outer thighs. These are the 'punishment' sites. The pattern of bruising may show fingertip marks, striate finger stripe effect from slapping, or pinch marks as opposing crescent shaped lesions. Kicks to the lower body show as irregular, large, deep bruises. Belt and strap damage appears on the trunk as parallel curved marks. The other skin lesions are usually crude forms of factitious dermatitis [6,8] produced by thermal burns or caustic corrosives on the skin [9]. On one occasion the rash was the result of drug poisoning. A large review of countries outside English speaking industrialized populations produced similar results in rather older children [10]. The long-term consequences of childhood victimization might contribute to the development of factitious disease in adult life. Elements of the child victim experience, including feelings of powerlessness, lack of control and disappointment in the physician, are the suggested dynamics for the development of independent illness falsification [11]. A full discussion of the issues in these cases with the paediatric services is essential [12–14].

Münchausen by proxy may also rarely be seen in the elderly, mentally handicapped or other dependent persons [14,15] perpetrated by relatives, nurses and care-home personnel.

References

1 Meadow R. Munchausen syndrome by proxy. The hinterland of child abuse. *Lancet* 1977; **2**: 343–5.
2 McLure RJ, Davis PM, Meadow SR. Epidemiology of Munchausen syndrome by proxy. *Arch Dis Child* 1996; **75**: 57–61.
3 Parnell TF. Guidelines for identifying cases. In: Parnell TF, Day DO, ed. *Munchausen by Proxy Syndrome*. California: Sage Publications, 1998: 47–67.
4 Verity CM, Winkworth C, Bruman D. Polle syndrome: children of Munchausen. *BMJ* 1979; **2**: 422–3.
5 Siebel MA. The physicians role in confirming the diagnosis. In: Parnell TF, Day DO, eds. *Munchausen by Proxy Syndrome*. California: Sage Publications, 1998: 68–95.
6 Rosenberg D. Web of deceipt: Munchausen by proxy. A literature review. *Child Abuse Neglect* 1987; **11**: 547–63.
7 Schreier H, Libow J. *Hurting for Love. Munchausen by Proxy*. New York: Guilford, 1993.
8 Meadow SR. Who's to blame—mothers, Munchausen or medicine? *J R Coll Physicians Lond* 1994; **28**: 332–7.
9 Tamay Z, Ackay A. Corrosive poisoning mimicking cicatricial pemphigoid: Munchausen by proxy. *Child Care Health* 2007; **33**: 496–9.
10 Feldman MD, Brown RMA. Munchausen by proxy in an international context. *Child Abuse Neglect* 2002; **26**: 509–24.
11 Libow JA. Beyond collusion. Active illness falsification. *Child Abuse Neglect* 2002; **26**: 525–36.
12 Schreier H. Munchausen by proxy defined. *Paediatrics* 2002; **110**: 985–9.
13 David T. Child abuse and paediatrics. *J R Soc Med* 2005; **96**: 229–31.
14 Galvin H, Newton A, Vandeven A. Update on Munchausen syndrome by proxy. *Curr Op Paediatr* 2005; **17**: 252–7.
15 Sigal MD, Altmark D, Carmel I. Munchausen syndrome by adult proxy. *J Nerv Mental Dis* 1986; **186**: 696–8.

Medicolegal issues in suspected factitious dermatitis [1]

The most important action for the physician who suspects factitious disease is to share the suspicion with colleagues at a very early stage. Case conference discussion and involvement of the institution's management and legal services after these group discussions help to avoid isolation and persecution of the physician. Structures will differ according to health providers in each country but the solitary physician may find disappointing support if an acrimonious dispute arises and legal action has been taken.



Fig. 64.18 Scarring from deliberate self-cutting over a birthmark.

Reference

1 Jones MA. Medico-legal and occupational perspectives. In: Halligan P, Bass C, Oakley D, eds. *Malingering and Illness Deception*. Oxford: Oxford University Press, 2003: 209–54.

Self-mutilation

Self-mutilation of the skin, sometimes termed self-injury or self-harm, may present with a wide range of lesions. Cutting and scratching are frequent, but other methods, such as grazing, burning with fire or chemicals or insertion of foreign bodies under the skin are also seen. The damage can be to a wide range of body parts, including face and genitals. Cases of self-mutilation may present to accident departments with acute damage in need of treatment, or present with chronic lesions or scarring in clinic (Fig. 64.18).

The relationship between such self-harming behaviours and suicide is complex and varies widely amongst cases [1]. Authors have made a distinction between repetitive cases of self-mutilation that occur in the context of suicidal ideation, or ambivalence towards suicide, and those cases that clearly occur outside the context of suicidal ideation [2–4]. It should be noted, however, that there is a potential for overlap between the two, both due to the difficulty in measuring or categorizing 'intent' [5] and cases of repetitive self-mutilation, apparently without suicidal intent, progressing to completed suicide [3].

Self-mutilation with suicidal ideation

Self-mutilating behaviour is often grouped with other behaviours, such as self-poisoning, attempted hanging or jumping from heights, as 'parasuicide' or 'deliberate self-harm'. The patient describes suicidal ideation, or ambivalence about continuing to live, at mental state examination. The most frequent lesions are caused by self-cutting, often to the wrists. Burns and ligature marks, and their scars, may also be seen.

The predisposing and precipitating factors for this behaviour are numerous [1,6]. The act may be in response to the symptoms of an underlying psychiatric illness, such as depression, substance misuse or schizophrenia. Vulnerable individuals may respond with parasuicidal behaviour to social or interpersonal stressors. Often a combination of the psychiatric and social is elicited from history.

Patients often present to Accident and Emergency departments with acute lesions. In many areas, psychiatric screening of such cases by specialist services is standard. Some patients, however, commit these acts and do not present for emergency medical treatment. Patients may present with chronic lesions or scarring when this behaviour has become a frequent response to stressors, and such stressors are chronic, such as untreated illness or continuing social problems.

Referral for treatment of underlying psychiatric illnesses is indicated where one is present. There is evidence that social intervention is of benefit in improving outcome where these factors are precipitants [7].

Repetitive self-mutilation without suicidal intent

A number of authors have made the case for a distinct syndrome of self-injurious behaviour, or self-mutilation, occurring outside the context of conscious suicidal ideation [2,4,5,8]. Currently, a disorder of self-mutilation does not occur in either the ICD-10 or DSM-IV classifications of mental disorders, although ICD-10 contains the category 'Other habit and impulse disorder' (F63.8) and DSM-IV 'Impulse control disorder, not otherwise specified' (312.30) and it has been suggested that repetitive self-mutilation meets the criteria for these categories [2,3].

A further attempt has been made to classify the syndrome into categories based on degree of tissue damage and rate and pattern of the destructive behaviour, yielding the categories Major, Stereotypic and Superficial/Moderate [3,8]. When described as a syndrome, onset is reported as typically in early life, below the age of 30 years. Increased prevalence in women is reported by the same authors. The mean duration of the syndrome is 12 years [2]. Recent work has demonstrated a potential genetic link [9].The syndrome has been associated with numerous other psychiatric conditions. Personality disorders, especially borderline type, are found in numerous studies and reviews. There is an association with childhood trauma, including abuse. Eating disorders, depressive and bipolar affective disorders, anxiety disorders, somatoform disorders, OCD, substance misuse disorders and schizophrenia have also been described in association with the syndrome. Another major group of patients who self-mutilate is found in those with learning disability [3,8,10,11].

Psychological symptoms described by repetitive self-mutilators include dysphoria, anxiety, depersonalization and aggression. The patient may experience and describe a strong compulsion to self-harm, similar to compulsion in OCD. The act of self-mutilation may provide relief from the unpleasant emotions or compulsion to self-mutilate, and may also induce feelings of self-control, power or euphoria. Relief may last from several hours to several weeks. In addition, a marked reduction in pain sensation, or increase in pain tolerance, is described in self mutilators, although is not uniform. The act is often performed in private [4,8].

Reviews of biological correlates of self-injurious behaviour have suggested changes in opiate, dopaminergic and serotonin systems. One study found reduced imipramine binding sites at platelets, a marker for serotinergic dysfunction, associated with self-mutilation [10]. Other proposed biological mechanisms are reinforcement of self-mutilating behaviour due to dysregulation of the dopamine system.

Treatment should include appropriate referral where the syndrome is associated with another psychiatric diagnosis. There are no clear guidelines for pharmacological treatment of self-mutilation syndrome itself, and a lack of randomized trials. Indeed some authors do not feel there are any general recommendations for the use of psychotropic medication [8]. Where suggestions have been made, SSRIs have been used, in line with the serotonergic hypofunction hypothesis. Dopamine antagonists and opiate antagonists have also been suggested. Mood stabilizers, β-blockers and analgesics have all been used [3].

Psychological approaches to treatment are varied. Behavioural and psychodynamic techniques are used, in group and individual settings. Dialectical behaviour therapy (DBT) has been described as successful, but access to this therapy varies regionally. Authors make the point that therapy can be long term, difficult and, in serious cases, involve periods of in-patient care.

Patients presenting with self-mutilation are a heterogeneous group, and likely to have complex problems in any of the biological, psychological and social domains. An understanding of the aetiological factors behind an individual's presentation is a key first step to deciding upon a programme of treatment. This may include pharmacological strategies, but there is as yet no clear core medication recommendation for these cases, and treatment is often complex and specialized.

References

1 Isacsson G, Rich C. Management of patients who deliberately harm themselves. *BMJ* 2001; **322**: 213–5.

2 Pattison EM, Kahan J. The deliberate self harm syndrome. *Am J Psychiat* 1983; **140**: 867–72.

3 Favazza AR. The coming of age of self mutilation. *J Nervous Mental Dis* 1998; **18**: 259–68.

4 Winchel RM, Stanley M. Self-injurious behaviour: a review of the behaviour and biology of self-mutilation. *Am J Psychiat* 1991; **148**: 306–17.

5 Herpertz S. Psychopathological and nosological characteristics in subtypes of self-injurers. *Acta Psychiatrica Scand* 1995; **91**: 57–68.

6 Boyce P, Oakley-Browne MA, Hatcher S. The problem of deliberate self-harm. *Curr Opin Psychiat* 2001; **14**: 107–11.

7 House A, Owens D, Storer D. Psycho-social intervention following attempted suicide: is there a case for better services? *Int Rev Psychiat* 1992; **4**: 15–22.

8 Kocalevent RD, Fliege H, Rose M *et al*. Autodestructive syndromes. *Psychoth Psychosomat* 2005; **74**: 202–11.

9 Joyce PR, McKenzie JM, Mulder RT *et al*. Genetic, developmental and personality correlates of self-mutilation in depressed patients. *Aust NZ J Psychiat* 2006; **4**: 225–9.

10 Simeon D, Stanley B, Frances A *et al*. Self mutilation in personality disorder: psychological and biological correlates. *Am J Psychiat* 1992; **149**: 221–6.

11 Starr D. Understanding those who self mutilate. *J Psychosocial Nursing Mental Health Services* 2004; **42**: 32–40.

Cutaneous disease and alcohol misuse [1,2]

Alcohol dependence and alcohol abuse are on the increase. They rank among the three commonest psychiatric disorders in the

Table 64.3 CAGE questionnaire.

1. Have you ever felt you should Cut down on your drinking?
2. Have people Annoyed you by criticizing your drinking?
3. Have you ever felt bad or Guilty about your drinking?
4. Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover (Eye opener)?
Item responses are scored 0 or 1 with a higher score over 2 clinically significant

community. The prevalence of DSM-IV alcohol abuse and dependence rose to 4.65% and 3.8% respectively [3]. There are significant medical and economic consequences because of differing effects of alcohol on metabolism, health, treatment behaviour and motivation [4]. Alcohol abuse can be missed as a diagnosis by experienced physicians even though the problem is common. Mechanisms for screening and brief interventions are well established and show robust stringency. The four-question CAGE questionnaire used as part of a general health enquiry is a consistent indicator of alcohol problems (Table 64.3). A two-question screen consisting of, firstly, enquiry about past alcohol problems and, secondly, significant drinking within the last 24 h is also a sensitive index. The combined sensitivity shows a 90% accuracy [5]. Up to 15% of admissions to hospital are directly or partially related to alcohol intake. Alcohol abuse is also co-morbid with psychiatric disorders such as depression, OCD and anxiety states.

The cutaneous manifestations of alcohol abuse are reviewed elsewhere [1,2]. Other studies show small variations in common manifestations with a different emphasis such as the prominence of seborrhoeic dermatitis and nail and oral changes according to race [6,7].

The psychosocial effects of chronic and disfiguring skin disease commonly produce feelings of stigma and rejection. Recreational substances such as alcohol are commonly used by affected patients [8]. Discoid dermatitis appears to be more frequent in alcohol abusers and is a more reliable indicator of alcohol dependence with significantly abnormal biochemistry and immunology related to alcohol excess. Atopic dermatitis appears to be unaffected by alcohol to the same degree. Seborrhoeic dermatitis is twice as common with alcohol abuse and this may be related to immunosuppression and the effect on cutaneous microflora.

A study of a large urban population suggested that male as well as female psoriatics showed an excess rate of alcoholism [9,10]. However, further studies suggested that, whilst alcohol abuse was not a factor in the onset of psoriasis, it became significant in women after the disease was present and was associated with the area of skin surface involvement [11] and severity particularly in men [12]. Up to 30% of patients thought they had difficulties with alcohol and 13% a current drinking problem [13]. Furthermore, a prospective study [14] showed that a daily intake of alcohol of more than 80 g was more frequently associated with less treatment-induced in-patient improvement in the percentage of the total body surface area affected by psoriasis. It also appears that the changed character and distribution of psoriasis make it more difficult to treat [1,2]. In studies of patients with psoriasis, alcohol abuse was not marked by elevated liver function tests. Alcohol abstinence helped to induce remission and relapse was induced by re-consumption. The effects of alcohol on immune function and skin vasculature are thought to precipitate exacerbations of rosacea and post-adolescent acne.

Infestations of the skin and superficial skin infections were found more often in alcoholic vagrants than in non-alcoholics and those with other psychiatric disorders. This also suggests that more specific alcohol-related immune factors were active [15].

References

1 Smith KE, Fenske NA. Cutaneous manifestations of alcohol abuse. *J Am Acad Dermatol* 2000; **43**: 1–16.
2 Higgins E, du Vivier A. Alcohol intake and other skin disorders. *Clin Dermatol* 1999; **17**: 437–41.
3 Grant BF, Dawson D, Stinson F *et al*. The 12-month prevalence and trends in DSM-IV alcohol abuse and dependence. *Drug Alcohol Depend* 2004; **74**: 224–34.
4 Volpicelli JR. Alcohol abuse and alcoholism: an overview. *J Clin Psychiatry* 2001; **62** (Suppl. 20): 4–10.
5 Fleming MF, Graham AW. Screening and brief interventions for alcohol use disorders in managed care settings. *Rec Dev Alcohol* 2001; **15**: 393–416.
6 Rao GS. Cutaneous changes in chronic alcoholics. *Ind J Dermatol Venereol Leprol* 2004; **70**: 79–84.
7 Kostovic K, Lipozecik J. Skin disease in alcoholics. *Acta Dermatovenereol Croat* 2004; **12**: 181–90.
8 Ginsburg IH, Link BG. Feelings of stigmatization in patients with psoriasis. *J Am Acad Dermatol* 1989; **20**: 53–60.
9 Lidegaard B. Disease associated with psoriasis in a population of middle aged urban native Swedes. *Dermatologica* 1986; **172**: 298–304.
10 Hill L, Kennedy P. The role of coping strategies in mediating subjective disability in psoriasis. *Psych Health Med* 2002; **7**: 261–9.
11 Poikolinen K, Reunala T, Karvonen J. Smoking, alcohol and life events related to psoriasis among women. *Br J Dermatol* 1994; **130**: 473–7.
12 Monk BE, Neill SM. Alcohol consumption and psoriasis. *Dermatologica* 1986; **173**: 57–60.
13 Kirby B, Richards HL, Mason DL *et al*. Alcohol consumption and psychological distress in patients with psoriasis. *Br J Dermatol* 2008; **158**: 138–40.
14 Gupta MA, Schnork NJ, Gupta AK, Ellis CN. Alcohol intake and treatment responsiveness in psoriasis. *J Am Acad Dermatol* 1993; **28**: 730–5.
15 Arfi C, Dela L, Benassia E. Dermatologic consultation in a precarious situation. *Ann Dermatol Venereol* 1999; **126**: 682–6.

Depression in dermatological patients

The concept of depression is frequently used loosely to mean disillusion, disenchantment, helplessness, frustration or mental fatigue. Depression has also been called 'melancholia without its charms'. For all its public profile, true depressive illness is one of the most frequently missed diagnoses for non-specialist psychiatrically trained physicians. Up to one-third of medically ill patients have depressive symptoms and depression has a greater impact on mean health scores than angina, asthma or diabetes and more so when combined with chronic physical illness [1]. This is also true for dermatology [2]. Depression, and to a lesser extent all forms of substance abuse, were the most overlooked diagnoses by dermatologists in 500 unselected dermatology patients examined by Musalek [3]. Screening for depressive diseases in patients with skin disease showed a prevalence of major depressive disorder in 8.4% and dysthymic disorder in 6.3% [4].

DSM-IV criteria for major depressive disorders are:

1 Depressed mood most of the day every day, subjective feelings of sadness, objective evidence of tearfulness; in children irritability may predominate
2 Diminished pleasure or interest in the activities of the day (anhedonia)

3 >5% change in weight
4 Insomnia or hypersomnia every day
5 Psychomotor retardation or agitation every day
6 Fatigue or loss of energy every day
7 Feelings of worthlessness or inappropriate guilt (which may be delusional)
8 Diminished ability to think or concentrate nearly every day
9 Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a suicide plan.

Five or more symptoms must be present in the same 2 weeks with one of the symptoms being depressed mood.

Dysthymia is a chronic state of depression that may not be severe enough to meet the criteria for major depression. Depressed mood must be present for most of the day for at least 2 years. The patient must not have gone more than 2 months without experiencing at least two of the following symptoms:

1 Poor appetite or overeating
2 Insomnia or hypersomnia
3 Low energy or fatigue
4 Low self-esteem
5 Poor concentration
6 Feelings of hopelessness.

Such chronic forms of depression are at risk of subsequent major depression, considerable social disability and unhealthy lifestyle choices such as poor diet, alcohol abuse and smoking.

Depression in the elderly may be more manifested by irritability, self-neglect, somatic complaints or forgetfulness than conventional symptoms. In children, depression may be insidious and present as disruptive behaviour, irritability, truancy or somatic complaints [5].

A number of robust screening instruments have been developed and validated to detect depression either administered by the physician, for example Beck Depression Inventory, Hospital Anxiety and Depression Scale [6], or self-reported [7]. One- and two-question screening tools have the merit of speed but a high false positivity. The Patient Health Questionnaire-9 for depression appears well validated as a diagnostic and treatment outcome measure [7].

References

1 Editorial. Depression is worse than angina or diabetes. *Lancet* 2007; **370**: 851.
2 Freid R. Depression and skin disease. *Dermatol Clinics* 2005; **23**: 657–64.
3 Musalek M. Psychopathology in dermatological patients. *11th Int Conference Dermatology and Psychiatry (ESDAP)*. Giessen, 2005.
4 Picardi A, Adler D, Abeni D *et al*. Screening for depressive disorders in patients with skin diseases. *Acta Dermatol Vener* 2005; **65**: 414–9.
5 Hazell P. Depression in children and adolescents. In: Barton S, ed. *Clinical Evidence*. Issue 6. BMJ Publishing, 2002: 278–84.
6 Royal College of Physicians and the Royal College of Psychiatrists. Management of psychological problems. In: *The Psychological Care of Medical Patients*. Report of a joint working party of the Royal College of Physicians and the Royal College of Psychiatrists, 2nd edn. London: Royal College of Physicians, 2003: 52–64.
7 Lowe B. Monitoring depression treatment outcomes with Patient Health Questionnaire-9. *Medical Care* 2004; **42**: 1194–201.

Suicide in dermatological patients

Suicide refers to a range of self-destructive behaviours ranging from non-lethal acts, which have been called suicidal gestures, attempted suicide, parasuicide and more recently self-injury, to a lethal action in which a patient dies, defined as a completed suicide. The rates of completed suicide in the UK are 8–10 per 100 000 people and in the US a little higher. The rate is rising in young men particularly in those with behavioural disturbance, substance misuse (25%) and persistent psychosocial difficulties. Suicide is an essential feature of depressive disease and 15% of patients with major depression kill themselves. It is therefore one of the 10 most common causes of death in Great Britain [1]. Psychiatric disorders are the main risk factors but numerous studies have also identified physical illness as an important contributory factor [1,2].

Chronic illness is a risk factor in suicidal ideation and 50% of patients who attempt suicide have a physical illness, especially chronic debility and pain. Not surprisingly, disfiguring chronic dermatoses have been shown to put patients at risk.

In a study of 217 patients with psoriasis, 10% of patients reported a death wish and 6% reported active suicidal ideation at the time of the study [3]. In another group, 2.5% of outpatients and 7.2% of in-patients with psoriasis expressed suicidal ideas. The severity of the psoriasis was reflected in the frequency of suicidal ideation and also measurable clinical depression [4]. Facial acne was also associated with significant risk (5.6%) of suicidal ideation, which is also higher than the levels reported in general medical patients [1]. Suicidal ideation was found in seven of 11 patients with Darier's disease related to the disfigurement, the intractability, social exclusion and smell of the dermatosis [5].

Some dermatological patients become so disturbed that they commit suicide successfully [6–8]. A group of 16 patients—seven males and nine females—who committed suicide successfully after presenting with dermatological problems to two dermatologists working in the same skin department, have been described [6]. The majority of these patients had either body-image disorders (dysmorphophobia, body dysmorphic disorder) or acne. It is important to recognize that patients with dermatological non-disease, and particularly females with facial complaints, may be extremely depressed and at risk of suicide. Even more strikingly, body dysmorphic disorder in children and adolescents carries a much larger risk, 67% experiencing suicidal ideation and 21% had attempted suicide [7]. Acne scarring can have just as profound an effect, or even a more profound effect, on body image, self-esteem and confidence as inflammatory acne. The positive therapeutic role of isotretinoin was emphasized [1,8].

Assessment of risk

Dermatologists are not accustomed to asking patients about their intentions for self-harm. However, it is essential in some circumstances where the indications are such that a depressed patient has opened up and confided their distress that they should be asked about suicidal thoughts. It is appropriate to ask 'How difficult have things become? Do you wonder whether you can go on?', gradually pressing to 'Have you ever thought you can't go on, or even don't want to go on?', and eventually 'Have you ever thought about harming yourself, or even ending your life?' It is important not to try and persuade the patient out of their suicidality by false reassurance but to assess whether they just have suicidal thoughts, have an intention to act, have plans and have the

means to implement the plan. Record the interview and seek permission to call a psychiatrist.

References

1 Diekstra RFW. The epidemiology of suicide and parasuicide. *Acta Psychiatr Scand* 1993; **371**; 9–20.
2 Carson AJ, Best S, Warlow C. Suicidal ideation among outpatients at general clinics. *BMJ* 2000; **320**: 1311–3.
3 Gupta MA, Schork NJ, Gupta AK *et al*. Suicidal ideation in psoriasis. *Int J Dermatol* 1993; **33**: 188–90.
4 Gupta MA, Gupta AK. Depression and suicidal ideation in dermatology patients with acne, alopecia areata, atopic dermatitis and psoriasis. *Br J Dermatol* 1998; **139**: 846–50.
5 Denicoff KD, Lehman ZA, Rubinow DR *et al*. Suicidal ideation in Darier's disease. *J Am Acad Dermatol* 1990; **22**: 196–8.
6 Cotterill JA, Cunliffe WJ. Suicide in dermatological patients. *Br J Dermatol* 1997; **137**: 246–50.
7 Albertini RS, Phillips KA. Thirty three cases of BDD in children and adolescents. *J Am Acad Child Adolesc Psych* 2006; **38**: 453–9.
8 Kellett SC, Gawkroger DJ. The psychological and emotional impact of acne and the effect of treatment with isotretinoin. *Br J Dermatol* 1999; **140**: 273–82.

Isotretinoin and mood changes [1–3]

Since the introduction of oral isotretinoin for the systemic treatment of acne in 1982 there has been increasing controversy over the relationship of this treatment to the apparent development of depression and suicidality. Shortly after the introduction of oral isotretinoin there were isolated case reports of mood change and depression. Large doses of vitamin A have well-recognized toxic effects including fatigue, confusion, headache and diplopia. Psychological effects include aggression, personality changes, poor concentration, tearfulness, depression, ruminations of guilt and psychosis [3]. These neuropsychological adverse effects have been suggested as a general model for retinoid side effects. The relationship between the drug and depressive illness was made more acute by reports of suicide in isolated rare cases. Many case reports have described depression developing during treatment, some with resolution during the discontinuation of the drug, so-called positive dechallenge, and a few with the recurrence of symptoms on rechallenging with the drug. In addition, there have been descriptions of an increase in frequency and/or severity with increased dosage, simulating a dose–response relationship [2].

Grouped case reports showed some patients who developed depression whilst on isotretinoin who recovered whilst off the medication and further groups who tolerated re-exposure without depression. A very small minority redeveloped mood change on retaking the drug. Secondary analysis of large data sets did not support any association between isotretinoin and mood change but was criticized for being industry based and for methological inaccuracies. A systematic literature search [4] for studies reporting primary data on depression and suicidal behaviour in patients treated with isotretinoin for acne could only analyse nine studies which met the inclusion criteria of 214 examined [3]. Rates of depression varied from 1% to 11%. A period prevalence of 11% was found in a 4-month treatment period in one study and monthly prevalence of 4% in another. These rates are similar to those seen in 12-month prevalence rates of 10% in the US, of 6% in Canada and 9% in Europe. The incidence of newly diagnosed depression whilst taking isotretinoin was 1.5% over 20 weeks [4]. The annual incidence rate of depression varies from 1.6% to 7.5% by country [5]. In other controlled studies the low self-esteem and measurable depression were improved by therapy with isotretinoin and comparisons of mood changes before and after in matched groups of patients receiving either antibiotics or isotretinoin also showed no difference in mood change.

The data on suicidality is hampered by the need for a large population study to examine the statistics and accuracy of the rarity of attempted and completed suicide in patients with acne. No difference was found in one study [6] but methodological criticisms were cited particularly as attempted suicide and completed suicide are fundamentally different behaviours. The frequency of mood change in a normal population of this age is probably more than would be identified by a dermatologist in routine practice. However, monitoring an individual patient represents a different clinical scenario from assessment of the risk in a group. There still remains enough doubt about the validity of a relationship between isotretinoin and mood changes to suggest that clinicians need specifically to enquire about depression at each outpatient visit. Most national dermatology associations have produced guidelines to assess this risk of mood change in patients on isotretinoin. Most dermatologists will now routinely ask about mood change at each clinic visit and if indicated use a depression inventory, for example Beck Depression Inventory (BDI) or Hospital Anxiety and Depression Scale (HAD). Positive scores (BDI > 10) should prompt withdrawal of the drug and referral to the psychiatry team.

References

1 Magin P, Pond D. Isotretinoin, depression and suicide: a review of the evidence. *Br J Gen Pract* 2004; **55**: 134–8.
2 Hull P, Darcy C. Isotretinoin use and subsequent depression and suicide; presenting the evidence. *Am J Clin Dermatol* 2003; **4**: 493–505.
3 Marqueling A, Zane L. Depression and suicidal behaviour in acne patients treated with isotretinoin: a systematic revue. *Sem Cutan Med Surg* 2005; **24**: 92–102.
4 Serrano A, Rodriguez L. Isotretinoin and depression. *Acta Dermo Sifilog* 2003; **94**: 535–8.
5 Waraich P, Goldner E *et al*. Prevalence and incidence studies of mood disorders: a systematic review. *Can J Psychiat* 2004; **49**: 124–38.
6 Jick S, Kremers H, Vasilakis C. Isotretinoin use and risk of depression, psychotic symptoms, suicide and attempted suicide. *Arch Dermatol* 2000; **136**: 1231–40.

Psychiatric treatments

Psychiatric treatments are traditionally divided into physical and psychological. Physical treatments now most often refer to medication, but also include some other infrequently used modalities, such as electroconvulsive therapy, light box treatment and even psychosurgery. Psychological treatments cover a wide range of interventions, including anxiety management techniques, cognitive behavioural therapies and psychoanalytic therapies.

It should also be noted that the treatment of psychiatric conditions often involves social interventions, such as attention to housing, occupational or educational interventions and arranging appropriate access to benefits or resources.

The synthesis of the three approaches is often termed the bio-psycho-social approach.

Clearly, the specialist dermatologist who is presented with a psychiatric case in the dermatology clinic would not be expected to have knowledge of or access to a full range of specialist interventions. However, if a diagnosis can be made in dermatological clinic, and there is a working therapeutic rapport with the dermatologist, there is clearly an opportunity for both the initialization of appropriate prescribing, and also recommendation and referral for further treatments if indicated. Useful guidance to this is found in the NICE recommendations so far published for psychiatric interventions that cover primary care and secondary care. At the time of writing, such guidelines have been produced for anxiety, bipolar affective disorder, dementia, depression (both in adults and children), drug misuse, eating disorders, obsessive compulsive disorder (which contains specific guidelines for body dysmorphic disorder), post-traumatic stress disorder, pre- and post-natal mental health disorders, schizophrenia and self-harm.

These guidelines provide information about recommended treatments across the biological, psychological and social domains.

Drug treatments

Antidepressants

Antidepressants are widely used, not only in depression [1,2] but also anxiety [3], obsessive–compulsive disorder and body dysmorphic disorder [4], post-traumatic stress disorder [5] and also in bulimia nervosa [6]. They are also occasionally used cautiously in depression in the context of bipolar affective disorder [7]. The introduction of antidepressants with a better safety profile in over-dosage has led to an increase in their prescription in recent years. Arguments have been made both that there is now over-prescription [8], especially with concerns about associations with suicide and certain agents [9] particularly in adolescents. These concerns have been contested [10] but guidelines for treatment now reflect an increased caution in the prescribing of antidepressants.

The precise mechanism of action of antidepressants is not yet fully established, nor is it yet fully understood why antidepressant action takes a number of weeks to take effect. Most theories postulate effects through the monoamine system.

When starting an antidepressant, it is necessary, due to the delay in therapeutic action, to counsel the patient that side effects may appear before response. Otherwise, the patient can discontinue medication in the early stages. A particular caution is the use of potentially toxic medications in patients who have suicidal ideation, who may be at risk of over-dosage in the window before therapeutic effects are noticed. In addition, patients are often concerned that reports of withdrawal reactions from antidepressants indicate that they are addictive, causing tolerance or craving, and it can be helpful to pre-empt this by discussing this fully. Antidepressants do need to be withdrawn gradually, but are not associated with tolerance or craving.

Caution is advised when starting antidepressants, with review after 1 week of starting for those felt to be at high risk of self-harm, or those under 30 years of age, and review after 2 weeks for others. It is also recommended that antidepressants be continued for at least 6 months past the remission of symptoms, as this helps reduce the risk of relapse.

Table 64.4 Use of SSRI antidepressants.

Name	Dose (adult under 65 years)	Indications [1,2]	Notes
Fluoxetine	20–60 mg/day	Depression OCD Bulimia nervosa	Long half-life SSRI with most experience of use in pregnancy
Paroxetine	10–60 mg/day	Depression OCD Panic disorder PTSD Social anxiety disorder Generalized anxiety disorder	Marked withdrawal syndrome Associated with extrapyramidal side effects Recommended as good choice in liver impairment [13] Recommended as good choice in breast feeding [11]
Sertraline	50–200 mg/day	Depression OCD PTSD (women)	Recommended as good choice in hepatic impairment [11] Recommended as good choice in breastfeeding
Fluvoxamine	50–300 mg/day	Depression OCD	Split dosing if above 150 mg/day
Citalopram	10–60 mg/day	Depression Panic disorder	Recommended as good choice in hepatic impairment [11]
Escitalopram	5–20 mg/day	Depression Panic disorder Social anxiety disorder	Isomer of citalopram

All antidepressants have been associated with hyponatraemia, especially in the elderly [11].

Serotonin reuptake inhibitors (SRIs, SSRIs) (Table 64.4) are now recommended as first-choice use in depression [1], obsessive–compulsive disorder, specifically including body dysmorphic disorder [4] and anxiety disorders [3], due to their relatively low side-effect profile and lower toxicity in over-dosage when compared with the older tricyclic antidepressants.

They are not entirely free from side-effects, the most common of which include nausea, dyspepsia and gastrointestinal upset, headache, agitation and anxiety, sweating and rashes, insomnia, and sexual dysfunction. In some cases, purpura occur. In the under-18-years age group, the association with agitation leading to increased suicidal behaviour and hostility has led to the recommendation that SSRIs be only used by specialists [2].

Tricyclic antidepressants

The tricyclic antidepressants are no longer recommended for first-line use in depression (Table 64.5) [1]. They are still useful when sedation is required, as this can provide some immediate relief from the insomnia of depressive states, and aid concordance. Their usefulness has been limited by their toxicity in over-dosage, and by side effects. They are most often now used by specialists in treatment-resistant cases.

Side-effects can be marked, and include dry mouth, blurred vision, constipation, sedation, urinary retention and postural

Table 64.5 Use of tricyclic antidepressants.

Name	Dose (adult under 65 years)	Uses [12]	Notes
Amitriptyline	10–200 mg/day	Depression Neuropathic pain	Noted cardiotoxicity
Clomipramine	10–250 mg/day	Depression Phobic states Obsessional states	
Dosulepin	75–225 mg/day	Depression	Previous name dothiepin
Imipramine	75–300 mg/day	Depression	Less sedating Split dose twice daily above 150 mg/day
Lofepramine	140–210 mg/day	Depression	Split dose twice daily Less toxic in overdose Occasionally hepatotoxic
Nortriptyline	10–150 mg/day	Depression Neuropathic pain	Plasma level monitoring often available
Trimipramine	50–300 mg/day	Depression	Regarded as most sedating

hypotension. Cardiac effects, including heart block, are known, and also reduction of the seizure threshold and an association with convulsions. They can precipitate angle-closure glaucoma.

They are often used in low doses for treatment of anxiety or insomnia. Some tricyclics are also used adjunctively for the management of pain, and have also been used in pruritus.

Other antidepressants

A number of other antidepressant drugs are available, they are also believed to act through changes in monoamine activity (Table 64.6). None are recommended for first-line use, although all have a role in specialist treatment of resistant cases. Mirtazipine has been suggested as a second choice of drug if the first choice is unsuccessful.

Switching antidepressant drugs

The need to switch between antidepressant drugs is common, not only because response rates to the first drug are around 60%, but also due to intolerance of side effects or troublesome interactions. When switching from drug to drug, it is necessary both to consider the potential for withdrawal reactions from the first drug, and also the possibility of interactions between the old and new agent. It has been recommended that antidepressants be withdrawn gradually if prescribed for longer than 6 weeks, and that doses of new drugs are cross-tapered upwards if possible [11]. Interactions described on switching include serotonin syndrome, cholinergic rebound, elevated levels of drugs due to pharmacokinetic interactions and excessive side effects due to pharmacodynamic interactions. Tabulated guides to switching antidepressants have been produced [11,13].

Certain drugs are particularly troublesome in switches, such as monoamineoxidase inhibitors (due to their mechanism of action) and fluoxetine (due to a long half-life).

Table 64.6 Other antidepressants in use.

Name	Dose (adult under 65 years)	Uses	Notes
Mirtazipine	15–45 mg/day	Depression	Relatively free of anticholinergic side effects, but appetite increase and weight gain Sedating, often used if sleep poor
Venlafaxine	75–375 mg/day	Depression Generalized anxiety disorder	Serotonin and norepinephrine reuptake inhibitor Previously quite widely prescribed; now recommended if two other drugs unsuccessful Split dosing, or up to 225 mg/day can be given as a modified release form
Duloxetine	60 mg/day	Depression (also diabetic neuropathy and stress incontinence)	Serotonin and norepinephrine reuptake inhibitor
Trazadone	150–600 mg/day	Depression Anxiety	Sedating, often used if sleep poor Fewer antimuscarinic effects than tricyclics; can cause nausea Doses above 300 mg/day in hospitalized patients Split dosing above 300 mg/day
Mianserin	30–90 mg/day	Depression	Tetracyclic Fewer antimuscarinic effects than tricyclics Associated with blood dyscrasias and blood count monitoring recommended
Reboxetine	8–12 mg/day	Depression	Not sedating Split dosing

Antipsychotic medication

Dermatologists may occasionally find themselves in a position where the prescribing of antipsychotic drugs is indicated, such as psychoses presenting with cutaneous symptoms. There may be a delay before the patient can see a psychiatrist or, in some cases, the patient may be reluctant to see a psychiatrist at all. Although the British National Formulary indications for antipsychotic drugs often list schizophrenia solely, their use in the related conditions such as delusional disorder and acute and transient psychotic disorders, including those related to stimulant drug use, is recognized. NICE guidelines suggest the consideration of early treatment of symptoms with antipsychotic medication by general medical practitioners and the dermatologist may find themselves in a similar position [14]. Early referral to and advice from psychiatry is recommended if possible.

Table 64.7 Use of atypical antipsychotics.

Name	Dose (adult under 65 years)	Uses [12]	Notes
Amisulpiride	400–1200 mg/day	Schizophrenia	Potent raiser of prolactin Split dosing
Aripiprazole	10–30 mg/day	Schizophrenia	Can cause nausea
Olanzapine	5–20 mg/day	Schizophrenia Mania	Weight gain Sedating Avoid in stroke disease in elderly
Quetiepine	25–800 mg/day	Schizophrenia Mania	Split dosing or available in MR form
Risperidone	2–16 mg/day	Acute and chronic psychoses Mania	Avoid in stroke disease in elderly
Sertindole	4–24 mg/day	Schizophrenia	Low EPSE Associated with arrhythmias Limited use in many countries including UK
Zotepine	75–300 mg/day	Schizophrenia	Three times per day split dosing

Atypical antipsychotics [15]

The agents of choice are the 'atypical antipsychotics', the more recently developed agents, which have a lower incidence of extrapyramidal side-effects (Table 64.7). These side effects, which include parkinsonian symptoms, dystonia and tardive dyskinsia, are less common than in the older 'typical' antipsychotics.

Other side-effects are frequent with antipsychotics, such as drowsiness and weight gain, hyperprolactinaemia and QT interval prolongation. There is an association with impaired glucose tolerance with antipsychotics, especially the atypical.

Clozapine, although atypical, is reserved for specialist use due to the association with severe agranulocytosis which requires close monitoring of the full blood count.

Typical antipsychotics

A wide number of typical antipsychotics are still available, although are unlikely to be prescribed by a dermatologist. Chlorpromazine, the first of the antipsychotics, is still available. It can cause a contact sensitivity rash in patients and health-care workers who handle the tablets. Haloperidol has a wide range of uses, not only in psychoses, but also in tic disorders, hiccup and nausea. Many dermatologists may have used it in the early part of their medical career to treat agitation in the elderly in-patient. Sulpiride is very similar in structure to amisulpiride, and is less expensive.

Flupentixol, in low doses, has a licence for adjunctive treatment in depression.

Some dermatologists may be familiar with pimozide, which is listed in the British National Formulary for treatment of monosymptomatic hypochondriacal psychosis, and was often used in Ekbom's syndrome [16]. Increasing concerns about cardiotoxicity and sudden death related to lengthened QTc have limited its use, and use of atypicals has been suggested [17].

Anxiolytics

The benzodiazepine anxiolytics can appear initially very effective in alleviating anxiety symptoms and states, but problems with tolerance and dependence rapidly develop, and they are frequently misused. They should be avoided.

Buspirone has low dependence potential and is rarely misused, and is licensed for short-term use in anxiety. β-blockers are used for autonomic anxiety symptoms but do not affect psychic symptoms or muscle tension. As mentioned before, the use of low-dose antipsychotics or tricyclic antidepressants is widespread.

Mood stabilizers

Few dermatologists would expect to prescribe a mood-stabilizing drug, although they may be familiar with some of the agents from other indications.

Lithium is the oldest of the mood stabilizers, but still widely used and effective in acute mania, prophylaxis of bipolar disorder and augmentation of treatment in refractory depression. It has a narrow therapeutic index and a wide array of side effects, especially on the kidneys and thyroid, and requires careful monitoring through blood tests. It is also known for causing exacerbations of psoriasis.

Valproate in various forms is very frequently used. Semisodium valproate has a licence for treatment of acute mania. Modified-release forms of valproate are frequently used off licence for prophylaxis.

Carbamazepine is licensed for the prophylaxis of bipolar disorder, and is also used in augmentation strategies for refractory depression.

Other antiepileptic drugs have been used off licence for treatment and for prophylaxis. Use of lamotrigine has become widespread, and topiramate and gabapentin have also been used.

Psychological therapies

The use of psychotherapies in disorders that combine somatic and psychological factors is widespread, but there is often confusion about how these conditions are defined, and the evidence base is incomplete [18]. An example of the difficulties in this area is given by a recent Cochrane review of conversion disorder [19] in which all but three of only 43 identified references were excluded on grounds of quality.

There is more evidence for specific therapies in certain psychiatric illnesses, and recommendations for use of therapies have been included in clinical guidelines [1–4].

The therapeutic relationship

The relationship between clinician and patient has a potentially powerful therapeutic (or sometimes counter therapeutic) effect, even before formal psychological techniques are considered.

The effect of an empathic and patient approach can be very powerful in those cases presenting with emotional distress related to dermatological presentation. Although efforts are constantly made to reduce stigma, some patients may feel stigmatized by both their skin and psychiatric symptoms. The opportunity to

express their anxieties and fears may provide significant relief. It may be necessary for the clinician to gently question defensive explanations that patients use for their symptoms, which at first may appear spurious and even obstructive. The effect of touch during examination has been described as relieving the anxiety of patients who feel stigmatized by their skin lesions. The effect of actively listening within a therapeutic relationship in allowing patients to express their feelings has been described as helpful in allowing patients to address their own problems, and is the basis of client-centred counselling, described by Rogers [20]. Of course, the dermatologist will need to give clinical advice, but a confident, authoritative rather than authoritarian approach, where the clinician offers explanation and clinical advice when indicated, but is able to tolerate this advice initially being partially taken or prevaricated on, will aid sustained engagement.

It should also be noted that a small, but significantly morbid, population of patients can have a marked negative effect through the therapeutic relationship. With such patients, who usually have severe neurotic or personality pathologies, the clinician can find themselves feeling pressed into making unusual decisions, ordering unusual investigations and going to extreme lengths to manage the patient's anxiety, anger or demands. It is not unusual for such patients to initially present with the impression that the clinician is 'the best they have seen' or 'the only one who has understood', a relationship that can rapidly change to one of dissatisfaction, complaint or litigation. In such patients, although presenting as seeking 'a cure', there may be an unspoken or unconscious need to remain in the sick role, and the clinician has an apparently impossible task. It is important for the clinician to recognize when such dynamics are potentially distorting practice, and seek appropriate advice if severe neurosis or personality disorder are suspected.

Cognitive behavioural therapy (CBT)

Increasingly, CBT has become the first line psychological therapy in depression and anxiety disorders, including BDD [1–4]. Randomized trials have shown its efficacy in BDD [21] and it is recommended in national guidelines for treatment of BDD.

CBT was developed by Beck [22] for the treatment of depression. The theory of CBT is that the patient automatically responds to certain situations and stimuli with ingrained negative thoughts. These thoughts in turn lead to negative emotions such as fear or depression, and behavioural consequences such as avoidance or rituals. Treatment in CBT is based around the process of sympathetically, through the development of a treatment alliance, challenging these negative automatic thoughts and exploring alternative responses that may not lead to behavioural and emotional pathology. The therapeutic process may include exposure and response prevention, wherein the patient is exposed to a troubling thought or stimulus (often, initially, in imagination or abstract) and encouraged to explore alternative thoughts and responses to their ingrained pathological reaction. Often, adjunctive relaxation and anxiety management techniques are an integral part of the therapy. CBT techniques are very widely used, and have been published in 'self-help' formats, for example *Mind Over Mood* [23] and *Overcoming Depression and Low Mood* [24]. The clinician can incorporate CBT principles and techniques in their clinical practice, for example when working with BDD [25]. Computer packages have been developed to deliver CBT, although guidelines state the evidence is better in depression and anxiety than in OCD [26]. Formal CBT treatment, when provided by a trained therapist, can consist of from six to 20 or more hour-long sessions, depending on severity of the case, complexity, co-morbidities and response. The main concern for many health-care providers is insufficient therapist hours to meet demand, resulting in lengthy waiting lists. The therapy can be provided in group as well as individual settings. Group therapy in a cognitive behavioural model has been used in eczema [27]. Although widely researched with good efficacy, and now most often considered, CBT is not suitable for all cases, and alternate modalities of therapy still need to be considered.

Interpersonal psychotherapy (IPT) and interpersonal counselling (IPC)

These forms of therapy are based on the work of Klerman and associates [28]. The focus of IPT is on the relationships of the patient and how they affect mood states. Problems in relationships are categorized as one of dispute, change in role, grief or deficit. The therapist then assists the patient in working through the problems using techniques such as role play and analysis of communications within relationships. Like CBT, the therapy takes place over a number of hour-long sessions, usually 12 to 16.

IPC is a modification of IPT, of a simpler form that can be integrated into the work of health professionals. It was designed for primary care, but can be used in other health settings. IPT has been shown to be effective, and equivalent to CBT in depression and also eating disorders. Unlike CBT, it has not yet been shown to be effective in OCD or BDD. It has been suggested that IPT be offered as an alternative to CBT for patients who prefer the approach. However, provision, especially outside the US, is often limited by a shortage of trained practitioners.

Dynamic psychotherapies and psychoanalysis

There is not scope here to fully describe the range of varieties of these psychotherapies available. Some awareness of, or even familiarity with, the concepts first described by Freud are common in Western and European cultures. There have been numerous therapist, theorists and writings on the subject. Psychodynamic concepts such as transference, counter transference, projection and identification can help the clinical interview, and good descriptions can be found for the interested in textbooks such as *Introduction to Psychotherapy* [29].

Short-term forms of dynamic therapies (defined as fewer than 40 sessions) have been shown to have efficacy in a wide range of common mental health disorders [30]. Many forms of dynamic therapies and psychoanalytic therapy are long lasting and intensive, with three or more sessions weekly. Due to the complexity of the longer forms of therapy, especially around conducting controlled studies and defining outcomes, there are difficulties with an evidence-based approach to demonstrating efficacy [31,32]. Whilst this is acknowledged by practitioners writing in this field, the point is often made that these forms of therapy are complex, and used in complex conditions where the 'drug paradigm' or

'single intervention for single condition' approach may not be strictly relevant. Others have proposed the view that such long-term therapies can be shown to have better outcomes [33].

Varieties of psychiatric syndrome presenting to the dermatologist, either as part of or alongside a cutaneous presentation, can be effectively treated by the clinician familiar with the stratagems used in primary care. Although specialist knowledge and training is required to deliver formal psychotherapy, techniques from psychotherapy, especially the commonalities of empathy, understanding, patience and reflection can be used to augment safe prescribing where indicated [27]. Specialist referral is indicated where symptoms are severe or specialist drugs or therapies needed.

References

1 National Institute for Health and Clinical Excellence. *Depression. Management of Depression in Primary and Secondary Care*, London: National Institute of Health & Clinical Excellence, 2004.
2 National Institute for Health and Clinical Excellence. *Depression in Children and Young People. Identification and Management in Primary, Community and Secondary Care*, London: National Institute of Health & Clinical Excellence, 2005.
3 National Institute for Health and Clinical Excellence. *Anxiety. Management of Anxiety (Panic Disorder, with or without Agoraphobia, and Generalised Anxiety Disorder) in Adults in Primary, Secondary and Community Care*, London: National Institute of Health & Clinical Excellence, 2004.
4 National Institute for Health and Clinical Excellence. *Obsessive-Compulsive Disorder. Obsessive–Compulsive Disorder: Core Interventions in the Treatment of Obsessive–Compulsive Disorder and Body Dysmorphic Disorder*, London: National Institute of Health & Clinical Excellence, 2005.
5 National Institute for Health and Clinical Excellence. *Post-Traumatic Stress Disorder (PTSD). The Management of PTSD in Adults and Children in Primary and Secondary Care*, London: London: National Institute of Health & Clinical Excellence, 2005.
6 National Institute for Health and Clinical Excellence. *Eating Disorders. Core Interventions in the Treatment and Management of Anorexia Nervosa, Bulimia Nervosa and Related Eating Disorders*, London: National Institute of Health & Clinical Excellence, 2004.
7 National Institute for Health and Clinical Excellence. *Bipolar Disorder. The Management of Bipolar Disorder in Adults, Children and Adolescents, in Primary and Secondary Care*, London: National Institute of Health & Clinical Excellence, 2006.
8 Manninen B. Medicating the mind: a Kantian analysis of overprescribing psychoactive drugs. *Medical Ethics* 2006; **32**: 100–5.
9 Fergusson D, Doucette S, Glass K *et al*. Association between suicide attempts and selective serotonin reuptake inhibitors: systematic review of randomised controlled trials. *BMJ* 2005; **330**: 396–404.
10 Gregory E, Simon M, Savarino J, Operskalski B. Suicide risk during antidepressant treatment. *Am J Psychiat* 2006; **163**: 41–7.
11 Taylor D, Paton C, Kerwin R. *The Maudsley Prescribing Guidelines*, 9th edn. London: Informa Healthcare, 2007.
12 Mehta D, ed. *British National Formulary 54*. London: Pharmaceutical Press, 2007.
13 Bazire S. *Psychotropic Drug Directory*. Salisbury: HealthComm UK Limited, 2007.
14 National Institute for Health and Clinical Excellence. *Schizophrenia. Core Interventions in the Treatment and Management of Schizophrenia in Primary and Secondary Care*, London: National Institute of Health & Clinical Excellence, 2002.
15 Adams C, Wilson P, Gilbody S, Bagnall A. Drug treatments for schizophrenia. *Quality Health Care* 2000; **9**: 73–9.
16 Zomer S, De-Wit R, Van-Bronswijk J, Nabarro G. Delusions of parasitosis. A psychiatric disorder to be treated by dermatologists? An analysis of 33 patients. *Br J Dermatol* 1998; **138**: 10–6.
17 Meehan W, Badreshia S, Mackley C. Successful treatment of delusions of parasitosis with olanzapine. *Arch Dermatol* 2006; **142**: 352–5.
18 Henningsen P, Zipfel S, Herzog W. Management of functional somatic syndromes. *Lancet* 2007; **369**: 944–56.
19 Ruddy R, House A. Psychosocial interventions for conversion disorder (Review). *Cochrane Library* 2007, Issue 4.
20 Rogers C. *On Becoming a Person*. London: Houghton Mifflin, 1961.
21 Veale D, Gournay K, Dryden W *et al*. Body dysmorphic disorder: a cognitive behavioural model and pilot randomised controlled trial. *Behav Res Therapy* 1996; **34**: 717–29.
22 Beck A. *Cognitive Therapy of Depression*. New York: Guilford Publications, 1979.
23 Padesky C, Greenberger D. *Mind Over Mood: Change How You Feel By Changing the Way You Think*. New York: Guilford Publications, 1995.
24 Williams C. *Overcoming Depression and Low Mood: A Five Areas Approach*. London: Hodder Arnold, 2006.
25 Allen A. Cognitive-behavioral treatment of body dysmorphic disorder. *Prim Psychiat* 2006; **13**: 70–6.
26 National Institute for Health and Clinical Excellence. *Computerised Cognitive Behaviour Therapy for Depression And Anxiety. Review of Technology Appraisal 51*, London: National Institute of Health & Clinical Excellence, 2006.
27 Cole C, Roth H, Sachs L. Group psychotherapy as an aid in the medical treatment of eczema. *J Am Acad Derm* 1988; **18**: 286–9.
28 Klerman G, Weissman M, Rounsaville B. *Interpersonal Psychotherapy of Depression: A Brief, Focused, Specific Strategy*. New York: Jason Aronson, 1994.
29 Brown D, Pedder J, Bateman A. *Introduction to Psychotherapy: An Outline of Psychodynamic Principles and Practice*. London: Routledge, 2000.
30 Abbass A, Hancock J, Henderson J, Kisely S. Short-term psychodynamic psychotherapies for common mental disorders (Review). *Cochrane Library*, Issue 4, 2007.
31 Holmes J. All you need is cognitive behaviour therapy? *BMJ* 2002; **324**: 288–94.
32 Fonagy P, Roth A, Higgitt A. Psychodynamic psychotherapies: evidence-based practice and clinical wisdom. *Bull Menninger Clinic* 2005; **69**: 1–25.
33 Seligman M. The effectiveness of psychotherapy. The consumer reports study. *Am Psychol* 1995; **50**: 965–74.

Alternative therapies

There has been a long tradition of the use of complementary therapies in dermatology but especially for those diseases where there is a psychological component. Most reports of therapy are anecdotal, often single cases with no randomized controlled trials. Therapies with a neurogenic basis are claimed to work by the neuroimmune mechanisms although no hard evidence is available. Acupuncture, biofeedback and hypnosis in skin disease are summarized by Shenefelt [1] and Freid [2]. The mechanisms of action may be related to the beneficial effects of supportive psychotherapy and relaxation rather than any specific therapeutic component measurable for each treatment type. Hypnotherapy has been the most frequently studied in Western literature. Despite the lack of trials there are strong advocates for the use of hypnosis as an adjunct to control itch [3] and pain [4]. Hypnotherapy for warts in children showed a 53% success at 3 months compared to none in the control group [5]. The practicality and cost was not assessed.

Alternative herbal medications are used both topically and systemically. In an evidence-based review of the literature [6] there was no compelling evidence for the efficacy of diet, herbal medicine or dietary supplements in atopic eczema. The authors suggested promising data for treatments with a psychological component such as hypnosis, autogenic training and biofeedback. For chronic venous insufficiency oral horse chestnut seed extract appeared to have a real effect as opposed to topical aloe vera gel or tea tree oil. Two fuller reviews of phytopharmaceutical agents explored not only the therapeutic uses of herbs but also the toxic and allergic skin reactions [7,8].

References

1 Shenefelt P. Complementary psychocutaneous therapies in dermatology. *Dermatol Clinics* 2005; **23**: 723–34.

2 Freid R. Non pharmacologic treatments in psychodermatology. In: Koo JYM, Lee CS, eds. *Psychocutaneous Medicine*. New York: Marcel Dekker, 2003: 427–51.

3 Stewart A, Thomas SE. Hypnotherapy as a treatment for atopic eczema. *Br J Dermatol* 1995; **132**: 778–83.

4 Shenefeld P. Hypnosis facilitated relaxation during self-guided imagery during dermatological procedures. *Am J Clin Hypnosis* 2003; **45**: 225–32.

5 Surman OS. Hypnosis in the treatment of warts. *Arch Gen Psychiatry* 1973; **28**: 439–41.

6 Ernst E, Pittler M. Complementary/alternative medicine in dermatology: evidence assessed efficacy. *Am J Clin Derm* 2002; **3**: 341–8.

7 Meyer S, Vogt T, Karrer S. Use of phytopharmaceutical agents in dermatology. *Hautarzt* 2005; **56**: 483–99.

8 Bedi MK, Shenefelt P. Herbal therapy in dermatology. *Arch Dermatol* 2002; **138**: 332–42.

CHAPTER 65
Disorders of Nails

D.A.R. de Berker[1] *& R. Baran*[2]

[1]Bristol Dermatology Centre, Bristol Royal Infirmary, Bristol, UK
[2]Nail Disease Centre, Le Grand Palais, Cannes, France

Anatomy and biology of the nail unit, 65.1
Structure, 65.1
Blood supply, 65.4
Nail growth and morphology, 65.5
Nails in childhood and old age, 65.6
Nail signs and systemic disease, 65.7
Abnormalities of shape, 65.7
Abnormalities of nail attachment, 65.9
Changes in nail surface, 65.12
Changes in colour, 65.14
Developmental abnormalities of the nails, 65.18
Infections of the nail and nail folds, 65.21
Dermatoses affecting the nails, 65.23
Tumours under or adjacent to the nail, 65.30
Benign tumours, 65.30
Other bone tumours, 65.34
Vascular tumours, 65.34
Myxoid cyst, 65.36
Squamous cell carcinoma, 65.37
Epithelioma cuniculatum, 65.38
Keratoacanthoma, 65.38
Melanocytic lesions, 65.38
Nail surgery, 65.41
Patterns of nail biopsy, 65.44
Lateral matrix phenolization, 65.48
Other surgical modalities, 65.48
Traumatic nail disorders, 65.49
Acute trauma, 65.49
Chronic repetitive trauma, 65.50
The nail and cosmetics, 65.54

Introduction

The epithelial part of the nail apparatus develops *in utero* from the primitive epidermis. In generalized integumentary diseases, such as psoriasis, the nail apparatus, hair follicle and epidermis may all be structurally and functionally affected, presumably because of their common tissue of origin.

The main function of the nail apparatus is to produce a strong, relatively inflexible, keratinous nail plate over the dorsal surface of the end of each digit. The nail plate acts as a protective covering for the fingertip. By exerting counter-pressure over the volar skin and pulp, the flat nail plate allows precision and delicacy when picking up small objects and in many other subtle finger functions [1–3]. Fingernails typically cover approximately one-fifth of the dorsal surface, whereas on the great toe the nail may cover up to 50% of the dorsum of the digit.

The nail apparatus develops and matures from the primitive epidermis between the ninth and 20th weeks of intrauterine growth. At 20 weeks, the matrix cells show postnatal-type cell division, differentiation and keratinization, and the nail plate begins to form and move distally [4,5]; the nail bed loses its granular layer at this stage [6]. By 36 weeks, the complete nail plate reaches the tip of the digit and is surrounded by prominent lateral nail folds and a well-formed cuticle.

References

1 Baran R, Dawber RPR, de Berker DAR, Haneke E, Tosti A, eds. *Baran and Dawber's Diseases of the Nails and Their Management*, 3rd edn. Oxford: Blackwell Science, 2001.
2 Scher RK, Daniel CR, eds. *Nails: Therapy, Diagnosis, Surgery*, 2nd edn. Philadelphia: Saunders, 1997.
3 Baran R, Dawber RPR, Haneke E, Tosti A, Bristow I. *A Text Atlas of Nail Disorders. Techniques in Investigation and Diagnosis*, 3rd edn. London: Martin Dunitz, 2003.
4 Zaias N. Embryology of the human nail. *Arch Dermatol* 1963; **87**: 37–42.
5 Zaias N. *The Nail in Health and Disease*. New York: Spectrum Press, 1990.
6 Baden HP, Kubilus J. A comparative study of the immunologic properties of hoof and nail fibrous proteins. *J Invest Dermatol* 1984; **83**: 327–31.

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

Anatomy and biology of the nail unit

Structure

Gross anatomy [1–5]

The component parts of the nail apparatus are shown diagrammatically in Fig. 65.1. The rectangular nail is firmly attached to the nail bed; it is less adherent proximally, apart from the posterolateral corners. Approximately one-quarter of the nail is covered by the proximal nail fold, and a narrow margin of the sides of the nail plate is often occluded by the lateral nail folds. Underlying the proximal part of the nail is the white lunula (half-moon, lunule); this area represents the most distal region of the matrix [6]. It is most prominent on the thumb and great toe and may be partly or completely concealed by the proximal nail fold in other digits. The reason for the white colour is not known [7–9]. The natural shape of the free margin of the nail is the same as the contour of the distal border of the lunula. The nail plate distal to the lunula usually appears pink, due to its translucency, which allows the redness of the vascular nail bed to be seen through it. The proximal nail fold has two epithelial surfaces, dorsal and ventral; at the junction of the two, the cuticle projects distally onto the nail surface. The lateral nail folds are in continuity with the skin on the sides of the digit laterally, and medially they are joined by the nail bed. Some authorities term the lateral nail fold and adjacent tissue lateral to the nail fold the 'nail wall'.

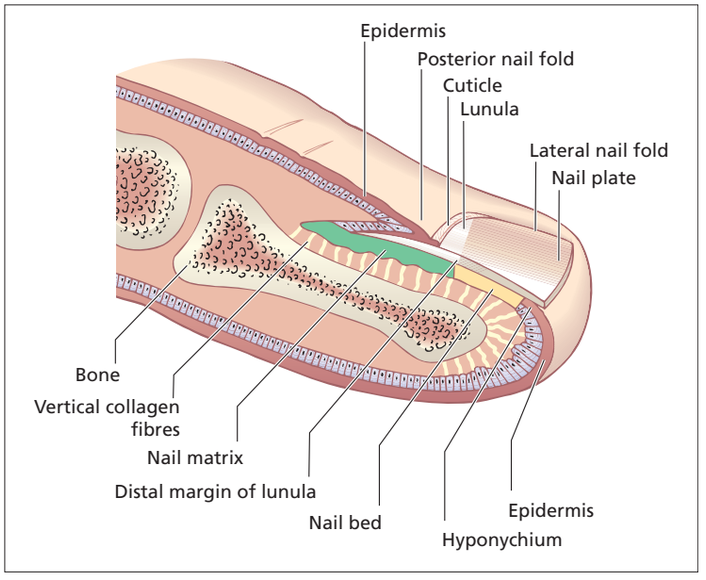


Fig. 65.1 Longitudinal section of a digit showing the dorsal nail apparatus.

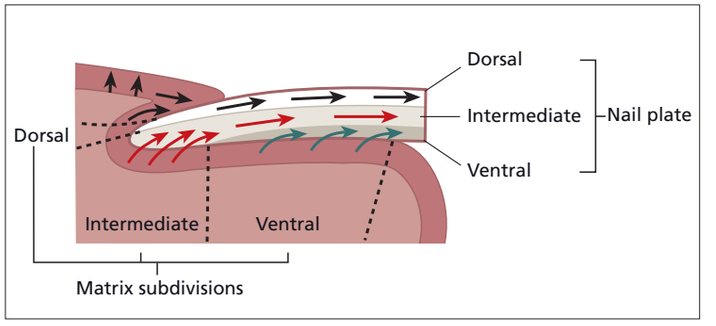


Fig. 65.2 Direction of differentiation and cell movement within the nail apparatus.

The definition of nail matrix is controversial [10]. There is common acceptance that there is a localized region beneath proximal nail which produces the major part of the normal nail plate. For those who consider this the sole source of nail it is termed simply the matrix, or germinal matrix. However, there is some evidence that other epithelial parts of the nail unit also contribute to the nail plate, and these are then also attributed matrix status (Fig. 65.2). The matrix can be subdivided into dorsal (ventral aspect of the proximal nail fold), intermediate (germinal matrix or matrix) and ventral (nail bed) sections. The nail bed is also termed the sterile matrix and its role in the production of nail is unclear. Although it appears that the nail plate may thicken by up to 30% as it passes from the distal margin of the lunula to the end of the nail bed [3], this is not associated with an increase in cell numbers and may represent compaction of the nail from distal tip trauma rather than nail bed or nail plate production [11]. The situation may change in disease, where the nail bed changes its histological appearance to gain a granular layer [12] and may contribute a false nail of cornified epithelium to the undersurface of the nail [5]. The gap beneath the free edge is known as the hyponychium.

When the attached nail plate is viewed from above, two distinct areas may be visible: the proximal lunula and the larger pink zone. On close examination, two further distal zones can often be identified: the distal yellowish-white margin and immediately proximal to this the onychodermal band [13]. Histologically, it is defined as the most distal attachment of cornified epithelium to the undersurface of the nail. As such, it is structurally significant for the adherence of nail plate to the nail bed. Once breached, as in conditions such as psoriasis, separation of the nail bed from the nail plate can be progressive.

Microscopic anatomy [14]

Nail folds

The proximal nail folds are similar in structure to the adjacent skin but are normally devoid of dermatoglyphic markings and pilosebaceous glands. There is a normal granular layer. From the distal area of the proximal nail fold the cuticle adheres to the upper surface of the nail plate; it is composed of modified stratum corneum and serves to protect the structures at the base of the nail, particularly the germinal matrix, from environmental insults such as irritants, allergens, and bacterial and fungal pathogens.

Nail matrix (intermediate matrix)

Nail matrix produces the nail plate in the absence of disease (Fig. 65.2). The basal compartment of the matrix is broader than the same region in normal epithelium or in other parts of the nail unit, such as the nail bed [10]. There is no granular layer, and cells differentiate with the expression of trichocyte 'hard' keratin as they become incorporated into the nail plate, alongside normal epithelial keratins [15,16]. During this process, they may retain their nuclei until more distal in the nail plate. These retained nuclei are called *pertinax bodies*. Apart from this, the detailed cytological changes seen in the matrix epithelium under the electron microscope are essentially the same as in the epidermis [17,18].

The nail matrix contains melanocytes in the lowest three cell layers and these donate pigment to the keratinocytes. The presence of 6.5 melanocytes per millimetre of matrix basement membrane can be used as a guide to a normal matrix melanocyte population [19]. The appearance of melanocytes separate from the basement membrane distinguishes them from those found in the nail folds, which are primarily basal [20]. Unlike melanocytes in the proximal nail fold and most other sites, nail matrix melanocytes do not express HLA-A/B/C antigens [21]. Matrix melanocytes are further distinguished from those elsewhere by their failure to produce melanin in normal circumstances in white people. This can change, with melanotic streaks presenting in local inflammatory, naevoid or neoplastic disease. In non-white people, brown streaks are common and are almost universal in Afro-Caribbeans by the age of 60 years.

Langerhans' cells are detectable in the matrix by CD1a staining, and the matrix appears to contain basement membrane components indistinguishable from normal skin [22].

Nail bed

Nail bed consists of epidermis with underlying connective tissue closely apposed to the periosteum of the distal phalanx. There is no subcutaneous fat in the nail bed, although scattered dermal fat cells may be visible microscopically.

The nail bed epidermis is usually no more than two or three cells thick, although there may be tongues of epithelium that extend obliquely down. The transitional zone from living keratinocyte to dead ventral nail plate cell is abrupt, occurring in the space of one horizontal cell layer; in this regard it closely resembles the Henle layer of the internal root sheath of the epidermis [23]. Nail bed cells do not have any independent movement, and it is yet to be clearly demonstrated whether they are incorporated into an overlying nail plate as it grows distally [24]. The process of nail bed keratinization has been likened to that seen in rat-tail epidermis, possibly being affected by pressure changes. The loss of the overlying nail results in the development of a granular layer, which is otherwise present only in disease states [11,25,26].

The nail bed dermal collagen is mainly orientated vertically, being directly attached to the phalangeal periosteum and the epidermal basal lamina. Within the connective tissue network lie blood vessels, lymphatics, a fine network of elastic fibres and scattered fat cells; at the distal margin, eccrine sweat glands have been seen [1].

Nail plate

The nail plate comprises three horizontal layers: a thin dorsal lamina, the thicker intermediate lamina and a ventral layer from the nail bed [4]. This is not always apparent with normal light microscopy using routine stains, where the nail demonstrates a transition between flattened cells dorsally and thicker cells on the ventral aspect. Electron microscopy shows squamous cells with tortuous interlocking plasma membranes [18,19]. At high magnification, the contents of each cell show a uniform fine granularity similar to the hair cuticle [23]. Nail plate thickness can be measured in health and disease using ultrasound or optical coherence tomography [27].

The nail plate contains significant amounts of phospholipid, mainly in the dorsal and intermediate layers, which contributes to its flexibility. The detectable free fats and long-chain fatty acids may be of extrinsic origin. For further details of these and other histochemical changes in the components of the nail apparatus, the reader is referred to more detailed texts [8].

The nail plate is rich in calcium, found as the phosphate in hydroxyapatite crystals; it is bound to phospholipids intracellularly [28]. The relevance of other metals (copper, manganese, zinc, iron and others), which are present in smaller amounts, is not known [25]. Calcium is present in a concentration of 0.1% by weight, 10 times greater than its concentration in hair. It is possible that calcium is not an intrinsic part of the nail but is incorporated from extrinsic sources. Calcium does not significantly contribute to the hardness of the nail [6].

Nail keratin

Nail keratin analysis shows essentially the same fractions as in hair, but amino acid analysis shows higher cysteine, glutamic acid and serine, and less tyrosine in nail compared with hair and wool [17,29].

One classification of keratins is to divide them into 'soft' epithelial keratins or 'hard' trichocyte keratins. The latter are characteristic of hair and nail differentiation, where their high sulphur content is responsible for their rugged physical qualities. This is matched by the resistance of trichocyte keratins to dissolution in strong solvent.

Trichocyte and epithelial keratins are intermediate filaments representing the major cytoskeletal protein of epithelial cells. They share the normal classification into type I or type II based on gene hybridization, which reflects segregation on two-dimensional electrophoresis into acidic and basic proteins. Each acidic keratin is expressed in a tissue with a corresponding basic keratin to form specific heterodimers, which are assembled into higher-order protofibrils and protofilaments.

Keratin distribution in the nail and associated epithelium has been studied in adult [16,30], infant [17] and embryonic [31,32] digits. Immunohistochemistry of the epithelial structures of normal nail demonstrates that the suprabasal keratin pair K1/K10 is found on both aspects of the proximal nail fold and to a lesser degree in the matrix. However, it is absent from the nail bed. This is reversed when there is nail bed disease, such as onychomycosis or psoriasis, where a granular layer develops and K1/K10 becomes expressed at corresponding sites [23]. The nail bed contains keratin synthesized in normal basal layer epithelium, K5/K14, which is also found in nail matrix. An antibody marking the epitope characteristically associated with keratin expressed in the basal layer is found throughout the thickness of the nail bed, but only basally in the matrix [26].

Recent examination of the nail bed using monospecific monoclonal antibodies to the keratin pair K6/K16 demonstrates these proteins in the nail bed but not the germinal matrix [16]. This is paradoxical given our understanding that K6/K16 is characteristic of psoriasis and wound healing, where proliferation is a prominent feature. It has been shown that the nail bed has very low rates of proliferation [10,33], and it may be that K6/K16 more precisely illustrates a loss of differentiation, often associated with proliferation in skin but representing the resting state of nail bed epithelium.

The location of K6/K16 is reflected in the localization of the features of pachyonychia congenita. In this group of autosomal dominant disorders, there is thickening of the nail plate attributed to disease of the nail bed. In some forms of pachyonychia congenita, there is a missense mutation of the initiation peptide of K16 [34].

Trichocyte keratins can also be detected immunohistochemically within the epithelial structures of the nail unit. A monospecific antibody to Ha-1 has been created and characterized on nail, hair and skin. In the nail, it demonstrates a well-demarcated suprabasal region corresponding to the matrix [16]. Proximally, it does not extend onto the ventral aspect of the proximal nail fold, sometimes described as the dorsal matrix. Distally, the keratin expression is limited to a margin taken as corresponding to the lunula. Ha-1 is only one of at least 10 trichocyte keratins, but quantitatively it probably represents a large fraction of nail keratin. According to its distribution it appears to define a matrix consistent with the classic description of the germinal matrix.

Improved understanding of the distribution of keratins in the nail bed and matrix has accompanied further understanding of the molecular basis of pachyonychia congenita, where the various nail manifestations correlate with mutations within the keratin genes and corresponding phenotypes [35].

References

1 Zook EG. Anatomy and physiology of the perionychium. *Hand Clin* 2002; **18**: 553–9.
2 Haneke E. Surgical anatomy of the nail apparatus. *Dermatol Clin* 2006; **24**: 291–6.
3 Johnson M, Comaish JS, Shuster S. Nail is produced by the normal nail bed: a controversy resolved. *Br J Dermatol* 1991; **125**: 27–9.
4 Lewin K. The normal fingernail. *Br J Dermatol* 1965; **77**: 421–4.
5 Samman PD. Anatomy and physiology. In: Samman PD, Fenton D, eds. *The Nails in Disease*. London: Heinemann, 1986: 1–20.
6 Cohen PR. The lunula. *J Am Acad Dermatol* 1996; **34**: 943–53.
7 Achten G. L'ongle normal et pathologique. *Dermatologica* 1963; **126**: 229–34.
8 Dawber RPR, de Berker D, Baran R. Science of the nail apparatus. In: Baran R, Dawber RPR, eds. *Diseases of the Nails and Their Management*, 2nd edn. Oxford: Blackwell Science, 1994: 1–34.
9 Burrows MT. The significance of the lunula of the nail. *Johns Hopkins Hosp Rep* 1919; **18**: 357–61.
10 de Berker D, Angus B. Markers of epidermal proliferation are limited to nail matrix in normal nail. *Br J Dermatol* 1996; **135**: 555–9.
11 de Berker DAR, MaWhinney B, Sviland L. Quantification of regional matrix nail production. *Br J Dermatol* 1996; **134**: 1083–6.
12 Fanti PA, Tosti A, Cameli N, Varotti C. Nail matrix hypergranulosis. *Am J Dermatopathol* 1994; **16**: 607–10.
13 Terry RB. The onychodermal band in health and disease. *Lancet* 1955; **i**: 179–81.
14 Lewis BL. Microscopic studies of foetal and mature nail and surrounding soft tissue. *Arch Dermatol* 1954; **70**: 732–6.
15 de Berker D, Wojnarowska F, Sviland L *et al*. Keratin expression in the normal nail unit: markers of regional differentiation. *Br J Dermatol* 2000; **142**: 89–96.
16 Perrin C, Langbein L, Schweizer J. Expression of hair keratins in the adult nail unit: an immunohistochemical analysis of the onychogenesis in the proximal nail fold, matrix and nail bed. *Br J Dermatol* 2004; **151**: 362–71.
17 Hashimoto K. Ultrastructure of the human toenail. 1. Proximal nail matrix. *J Invest Dermatol* 1971; **56**: 235–46.
18 Hashimoto K. Ultrastructure of the human toenail. *Ultrastruct Res* 1971; **36**: 391–410.
19 Tosti A, Cameli N, Piraccini BM *et al*. Characterisation of nail matrix melanocytes with anti-PEP1, anti-PEP8, TMH-1 and HMB-45 antibodies. *J Am Acad Dermatol* 1994; **31**: 193–6.
20 de Berker D, Graham A, Dawber RPR, Thody A. Melanocytes are absent from the normal nail bed: the basis of a clinical dictum. *Br J Dermatol* 1996; **134**: 564.
21 Ito T, Ito N, Saathoff M *et al*. Immunology of the human nail apparatus: the nail matrix is a site of relative immune privilege. *J Invest Dermatol* 2005; **125**: 1139–48.
22 Sinclair RD, Wojnarowska F, Leigh IM, Dawber RPR. The basement membrane zone of the nail. *Br J Dermatol* 1994; **131**: 499–505.
23 Achten G. L'ongle normal. *J Med Esth Chir Dermatol* 1988; **XV**: 193–200.
24 Zaias N. The movement of the nail bed. *J Invest Dermatol* 1967; **48**: 402–3.
25 Zaias N. *The Nail in Health and Disease*. New York: Spectrum Press, 1990: 6–7.
26 de Berker D, Sviland L, Angus BA. Suprabasal keratin expression in the nail bed: a marker of dystrophic nail bed differentiation. *Br J Dermatol* 1995; **133**(Suppl. 45): 16.
27 Mogensen M, Thomsen JB, Skovgaard LT, Jemec GB. Nail thickness measurements using optical coherence tomography and 20-MHz ultrasonography. *Br J Dermatol* 2007; **157**: 894–900.
28 Cane AK, Spearman RIC. A histochemical study of keratinisation in the domestic fowl. *J Zool* 1967; **153**: 337–44.
29 Baden HP, Goldsmith LA, Flemming BC. A comparative study of the physicochemical properties of human keratinised tissue. *Biochim Biophys Acta* 1973; **322**: 269–78.
30 Haneke E. The human nail matrix: flow cytometric and immuno-histochemical studies. In: *Clinical Dermatology in the Year 2000*. London: Book of Abstracts, 1990.
31 Heid WH, Moll I, Franke WW. Patterns of expression of trichocytic and epithelial cytokeratins in mammalian tissues. II. Concomitant and mutually exclusive synthesis of trichocytic and epithelial cytokeratins in diverse human and bovine tissues. *Differentiation* 1988; **37**: 215–30.
32 Moll I, Heid HW, Franke WW, Moll R. Patterns of expression of trichocytic and epithelial cytokeratins in mammalian tissues. *Differentiation* 1988; **39**: 167–84.
33 Zaias N, Alvarez J. The formation of the primate nail plate. An autoradiographic study in the squirrel monkey. *J Invest Dermatol* 1968; **51**: 120–36.
34 McLean WHI, Rugg EL, Lunny DP *et al*. Keratin 16 and keratin 17 mutations cause pachyonychia congenita. *Nat Genet* 1995; **9**: 273–8.
35 McLean WH; Epithelial Genetics Group. Genetic disorders of palm skin and nail. *J Anat* 2003; **202**: 133–41.

Blood supply [1]

There is a rich arterial blood supply to the nail bed and matrix derived from paired digital arteries, a large palmar and small dorsal digital artery on either side. The palmar arteries are supplied from the large superficial and deep palmar arcades [2]. The main supply passes into the pulp space of the distal phalanx before reaching the dorsum of the digit (Fig. 65.3). Distally, the arteries are extremely tortuous and coiled, which allows them to be distorted without occluding supply by kinking. There are two main arterial arches (proximal and distal) supplying the nail bed and matrix, formed from anastomoses of the branches of the digital arteries. In the event of damage to the main supply in the pulp space, such as may occur with infection or scleroderma, there may be sufficient blood from the accessory vessels to permit normal growth of the nail. At a microvascular level, there are three patterns. Within the matrix, vessels are longitudinal with a helicoidal twisting. This becomes more definably longitudinal in the nail bed without the tortuosity—a pattern that is also seen in the distal proximal nail fold. This orientation is reflected in the appearance of splinter haemorrhages. In the digit pulp, vessels follow the pattern of the dermatoglyphics [3–5].

There are many arteriovenous anastomoses beneath the nail—glomus bodies—which are concerned with heat regulation. Glomus bodies are important in maintaining acral circulation under cold conditions: arterioles constrict with cold but glomus bodies dilate [6]. These occupy the subdermal tissues and increase in number in a gradient towards the distal nail bed [7].

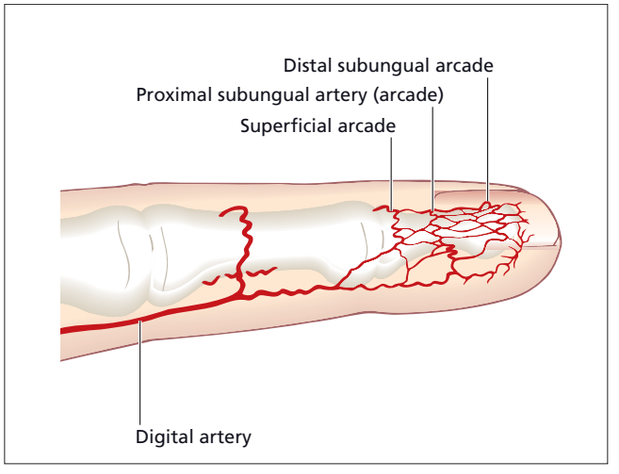


Fig. 65.3 Arterial supply of the distal finger.

References

1 Dawber RPR, de Berker DAR, Baran R. Science of the nail apparatus. In: Baran R, Dawber RPR, de Berker DAR, Haneke E, Tosti A, eds. *Diseases of the Nails and Their Management*, 3rd edn. Oxford: Blackwell Science, 2001: 1–47.
2 Smith DO, Oura C, Kimura C, Toshimuri K. Arterial anatomy and tortuosity in the distal finger. *J Hand Surg* 1991; **16A**: 297–302.
3 Sangiorgi S, Manelli A, Congiu T *et al*. Microvascularization of the human digit as studied by corrosion casting. *J Anat* 2004; **204**: 123–31.
4 Samman PD. The human toenail. Its genesis and blood supply. *Br J Dermatol* 1959; **71**: 296–301.
5 Hasegawa K, Pereira BP, Pho RW. The microvasculature of the nail bed, nail matrix, and nail fold of a normal human fingertip. *J Hand Surg* 2001; **26A**: 283–90.
6 Ryan TJ. The arteriovenous anastomoses. In: Jarrett A, ed. *The Physiology and Pathophysiology of the Skin*, Vol. 2. London: Academic Press, 1973: 612–4.
7 Wolfram-Gabel R, Sick H. Vascular networks of the periphery of the fingernail. *J Hand Surg* 1995; **20B**: 488–92.

Nail growth and morphology

Clinicians used to observing the slow rate of growth of diseased or damaged nails are apt to view the nail apparatus as inert, although it is biochemically and kinetically active throughout life. In this respect, it differs from the hair follicle, which undergoes periods of quiescence as part of the follicular cycle.

Cell kinetics

The kinetic activity of the matrix has been examined using many techniques. These include immunohistochemistry, autoradiography and direct measurement of matrix product (i.e. nail plate) by ultrasound [1], micrometer or histology.

There is a broad basal compartment of proliferating cells in the matrix, which can be detected immunohistochemically with antibodies to proliferating cell nuclear antigen and Ki-67 (Fig. 65.4); both antigens are associated with proliferating cells [2]. The matrix is also the site of maximal inclusion of tritiated thymidine if injected into the peritoneum of squirrel monkeys and followed subsequently by autoradiography [3]. Although there was some inclusion of thymidine into the nail bed, Zaias and Alvarez interpreted the findings as indicating that the nail bed had no role in creation of the nail plate. Norton [4] drew a similar conclusion from work with live human subjects where labelled thymidine and glycine were injected locally to act as markers of proliferating and metabolically active keratinocytes, and both primarily labelled the matrix.

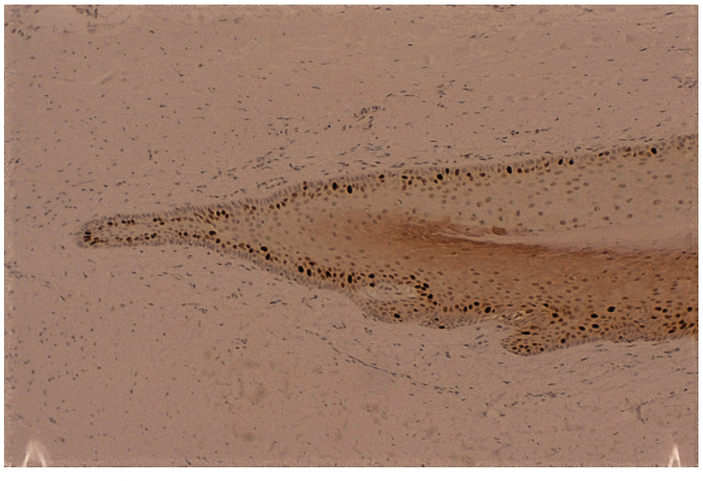


Fig. 65.4 Proliferating epithelial cells of the matrix and ventral aspect of the proximal nail fold, staining with the antibody MIB-1.

However, the earlier work of Lewis [5] suggested on histological grounds that the nail plate is a trilaminar structure originating from three separate matrix zones: the dorsal matrix (ventral aspect of proximal nail fold), intermediate matrix (germinal matrix) and ventral matrix (nail bed). In support of this, Johnson *et al*. [6,7] demonstrated that 21% of the nail thickness is gained as it passes over the nail bed, implying that the nail bed is generating this fraction of the nail plate. De Berker *et al*. [2] noted that the increase in nail thickness did not coincide with corresponding increases of nail plate cells. This challenges the interpretation that nail thickens over the nail bed because of a contribution from underlying structures. An alternative explanation may be appropriate, such as compaction arising from repetitive distal trauma. Others have also debated this issue [8] and, although the nail bed may have a significant contribution to make in disease [9], the evidence for its contribution at other times is conflicting.

Nail morphology

Why the nail grows flat, rather than as a heaped-up keratinous mass, has generated much thought and discussion [10–14]. Several factors probably combine to produce a relatively flat nail plate: the orientation of the matrix rete pegs and papillae; the direction of cell differentiation [15]; and moulding of the direction of nail growth between the proximal nail fold and distal phalanx [16]. Containment laterally within the lateral nail folds assists this orientation, and the adherent nature of the nail bed is likely to be important. In diseases such as psoriasis, the nail bed can lose its adherent properties, exhibiting onycholysis. In addition, there may be subungual hyperkeratosis. These combined factors make psoriasis the most common pathology in which up-growing nails are seen. Onychogryphosis is characterized by upward growth of thickened nail. In this condition, the nail matrix may become bucket-shaped and the effect of the overlying proximal nail fold is lost.

Linear nail growth [17–19]

Over the last century, many studies have been carried out on the linear growth of the nail plate in health and disease; these have been reviewed [20,21] and are listed in Tables 65.1 and 65.2 [22]. Most of these studies have been performed by observing the distal movement of a reference mark etched on the nail plate over a fixed

Table 65.1 Physiological and environmental factors affecting the rate of nail growth.

Faster	Slower
Daytime	Night
Pregnancy [25]	First day of life [14]
Right-hand nails	Left-hand nails [28,29]
Youth, increasing age	Old age [18,23,30]
Fingers	Toes [31]
Summer [18]	Winter or cold environment [32,33]
Middle, ring and index fingers	Thumb and little finger [28,31,34,35]
Male gender	Female gender [27,35]
Minor trauma/nail biting [26,27]	

Table 65.2 Pathological factors affecting the rate of nail growth.

Faster	Slower
Psoriasis [36] Normal nails [23] Pitting Onycholysis [37]	Finger immobilization [41]
Pityriasis rubra pilaris [21,38]	Fever [42] Beau's lines [43]
Etretinate, rarely [39]	Methotrexate [24], azathioprine [24], etretinate [39]
Idiopathic onycholysis of women [37]	Denervation [44]
Bullous ichthyosiform erythroderma [13]	Poor nutrition Kwashiorkor [45]
Hyperthyroidism [28]	Hypothyroidism [28]
Levodopa [40]	Yellow nail syndrome [13]
Arteriovenous shunts [28]	Relapsing polychondritis [46]

period of time; this may well correlate with matrix germinative cell kinetics but there is no direct proof that it does. However, studies on nail growth in psoriasis, and its inhibition by cytostatic drugs [23,24], suggest that cell kinetics and linear growth rate do have a direct correlation.

Fingernails grow approximately 1 cm every 3 months and toenails at one-third of this rate.

References

1 Finlay AY, Moseley H, Duggan TC. Ultrasound transmission time: an *in vivo* guide to nail thickness. *Br J Dermatol* 1987; **117**: 765–70.
2 de Berker D, MaWhinney B, Sviland L. Quantification of regional matrix nail production. *Br J Dermatol* 1996; **134**: 1083–6.
3 Zaias N, Alvarez J. The formation of the primate nail plate. An autoradiographic study in squirrel monkeys. *J Invest Dermatol* 1968; **51**: 120–36.
4 Norton LA. Incorporation of thymidine ^{3}H and glycine-2 ^{3}H in the nail matrix and bed of humans. *J Invest Dermatol* 1971; **56**: 61–8.
5 Lewis BL. Microscopic studies of foetal and mature nail and surrounding soft tissue. *Arch Dermatol* 1954; **70**: 732–7.
6 Johnson M, Comaish JS, Shuster S. Nail is produced by the normal bed: a controversy resolved. *Br J Dermatol* 1991; **125**: 27–9.
7 Johnson M, Shuster S. Continuous formation of nail along the bed. *Br J Dermatol* 1993; **128**: 277–80.
8 Pinkus F. In: Jasassohn J, eds. *Handbuch der Haut und Geschlechtskrankheiten*. Berlin: Springer, 1927: 267–89.
9 Samman PD. The ventral nail. *Arch Dermatol* 1961; **84**: 192–5.
10 Baran R. Nail growth direction revisited. Why do nails grow out instead of up? *J Am Acad Dermatol* 1981; **4**: 78–84.
11 Kligman AM. Nail growth direction revisited. Why do nails grow out instead of up? Response. *J Am Acad Dermatol* 1981; **4**: 78–84.
12 Kligman AM. Why do nails grow out instead of up? *Arch Dermatol* 1961; **84**: 181–3.
13 Samman PD. *The Nails in Disease*, 3rd edn. London: Heinemann, 1978: 14.
14 Schmiegelow P, Lindner J, Puschmann M. Autoradiographische Quantifizierung dosisabhängiger 35S CystinbZW. *Aktuelle Dermatol* 1983; **2**: 62.
15 Hashimoto K. Ultrastructure of the human toenail. *Arch Dermatol Forsch* 1971; **240**: 1–22.
16 Kelikian H. *Congenital Deformities of the Hand and the Forearm*. Philadelphia: Saunders, 1974: 210–2.
17 Baran R, Dawber RPR, eds. *Guide Médico-Chirurgical des Onychopathies*. Paris: Arnette, 1990: 12.
18 Bean WB. Nail growth: 30 years of observations. *Arch Intern Med* 1974; **134**: 497–502.
19 Dawber R, Baran R. Nail growth. *Cutis* 1987; **39**: 99–102.
20 Dawber RPR, de Berker D, Baran R. Science of the nail apparatus. In: Baran R, Dawber RPR, eds. *Diseases of the Nails and Their Management*, 2nd edn. Oxford: Blackwell Science, 1994: 1–34.
21 Runne U, Orfanos CE. The human nail. *Curr Probl Dermatol* 1981; **9**: 102–49.
22 de Doncker P, Pierard GE. Acquired nail beading in patients receiving itraconazole: an indicator of faster nail growth? A study using optical profilometry. *Clin Exp Dermatol* 1994; **19**: 404–6.
23 Dawber RPR. Fingernail growth in normal and psoriatic subjects. *Br J Dermatol* 1970; **82**: 454–7.
24 Dawber RPR. The effect of methotrexate, corticosteroids and azathioprine on fingernail growth in psoriasis. *Br J Dermatol* 1970; **83**: 680–8.
25 Hewitt D, Hillman RW. Relation between rate of nail growth in pregnant women and estimated previous general growth rate. *Am J Clin Nutr* 1966; **19**: 436–9.
26 Gilchrist ML, Buxton LHD. The relation of fingernail growth to nutritional status. *J Anat* 1939; **73**: 575–81.
27 Hamilton JB, Tereda H, Mestler GE. Studies of growth throughout the lifespan in Japanese. *Gerontology* 1955; **10**: 401–10.
28 Orentreich N, Markofsky J, Vogelman JH. The effect of ageing on the rate of linear nail growth. *J Invest Dermatol* 1979; **73**: 126–30.
29 Pfister R. Das normale Onychodiagramm. *Z Haut Geschlechtskr* 1955; **18**: 132–7.
30 Lavelle CE. Nail growth. *Curr Probl Dermatol* 1981; **9**: 102–4.
31 Pfister R, Henera J. Wachstum und Gestaltung der Zehennagel bei Gesunden. *Arch Klin Exp Dermatol* 1965; **223**: 263–74.
32 Donovan KM. Antarctic environment and nail growth. *Br J Dermatol* 1977; **96**: 507–10.
33 Roberts DF, Sandford MR. A possible climatic effect on nail growth. *Appl Physiol* 1958; **13**: 135–7.
34 Knobloch VH. Das normale Wachstum der Fingernagel. *Dtsch Med Wochenschr* 1953; **78**: 743–5.
35 Le Gros-Clark WE, Buxton LHD. Studies in nail growth. *Br J Dermatol* 1938; **50**: 221–9.
36 Landherr G, Braun-Falco O, Hofmann C *et al*. Fingernagel Wachstum bei Psoriatitern unter PUVA-Therapie. *Hautarzt* 1982; **33**: 210–3.
37 Dawber RPR, Samman PD, Bottoms E. Fingernail growth in idiopathic and psoriatic onycholysis. *Br J Dermatol* 1971; **85**: 558–67.
38 Dawber RPR. The ultrastructure and growth of human nails. *Arch Dermatol Res* 1980; **269**: 197–204.
39 Baran R. Action thérapeutique et complications du rétinoid aromatique sur l'appareil unguéal. *Ann Dermatol Vénéréol* 1982; **109**: 367–70.
40 Miller E. Levodopa and nail growth. *N Engl J Med* 1973; **288**: 916–9.
41 Dawber RPR. Effects of immobilisation on fingernail growth. *Clin Exp Dermatol* 1981; **6**: 1–4.
42 Sibinger MS. Observations on growth of fingernails in health and disease. *Pediatrics* 1959; **24**: 225–33.
43 Weismann K. Beau and his description of transverse depressions on nails. *Br J Dermatol* 1977; **97**: 571–2.
44 Head H, Sherrin J. The consequence of injury to peripheral nerves in man. *Brain* 1905; **28**: 116–8.
45 Babcock MJ. Methods of measuring fingernail growth in nutritional studies. *J Nutr* 1955; **55**: 323–38.
46 Estes SA. Relapsing polychondritis. *Cutis* 1983; **32**: 471–6.

Nails in childhood and old age

Childhood [1]

In early childhood, the nail plate is relatively thin and may show temporary koilonychia. This is particularly prominent on the great toes. Under the age of 5 years, nails are also prone to terminal onychoschizia (lamellar splitting). This can be most prominent on the sucked thumb, but is also seen on the toes. Sucking may also lead to paronychia, which can be a troublesome condition in childhood, with pain and nail dystrophy. Ingrowing can also cause pain

and may present in different forms. At birth, there is often a degree of distal ingrowing, particularly in the great toe, as the nail has not surmounted the tip of the digit in its development [2]. In a more gross form, this may present as congenital hypertrophic lip of the hallux, where soft tissue overgrowth may resemble fibrous tumours of the digit before spontaneously disappearing [3]. Painful distal embedding can lead to infection, but as long as the toenail is properly orientated with respect to the underlying phalanx, the condition usually subsides. In one series of seven children, two needed surgery due to painful persistence of the problem [4]. The changes associated with congenital malalignment of the great toe may also subside within 5–10 years in about 50% of children. In this condition, there is deviation of the tip of the great toe nail laterally, rotating on the distal phalanx. The nail is yellow, triangular, thickened and has transverse ridges [5].

Fungal infection is relatively uncommon in children, with a prevalence of 0.3% [6] to 0.44% [7]. Terbinafine is not licensed for use in children in most countries, although there is evidence of its efficacy and it is sometimes used [7].

Beau's lines can be seen in up to 92% of normal infants between 8 and 9 weeks of age [8]. Normal surface markings of the nail can differ in children from those seen in adults. A herringbone pattern is common and gradually diminishes with time [9], which may reflect a gradual change in the pattern of matrix maturation.

Old age

With age, altered arterial and venous supply and cumulative trauma affect the feet more than most other body sites [10]. Elastic tissue changes diffusely affecting the nail bed epidermis are often seen histologically. The whole subungual area in old age may show thickening of blood vessel walls with vascular elastic tissue fragmentation [11]. Nail growth is inversely proportional to age [12].

The nail plate becomes paler, dull and opaque with advancing years, and white nails similar to those seen in cirrhosis, uraemia and hypoalbuminaemia may be seen in normal subjects. Longitudinal ridging is present to some degree in most people after 50 years of age and this may give a 'sausage links' or beaded appearance.

For details of the common traumatic abnormalities and changes due to inadequate pedicure or neglect, detailed texts should be consulted [1,12]. Nail problems in the elderly are often associated with more widespread mechanical changes of the foot, and it is often more important to direct treatment at maintaining mobility rather than the restoration of normal nails [13,14].

Onychomycosis is one of the most common nail diseases of the elderly, and is often combined with an element of traumatic dystrophy that will predispose to relapse after treatment. There are concerns that drug interactions in this group might make systemic therapy a poor choice [15]. This is not borne out by one large study designed to examine the effects of terbinafine. But the study also revealed that complete cure at the conclusion of the trial occurred in only 28% of cases, which should be considered before instigating therapy [16].

References

1 Baran R, Barth J, Dawber RPR, eds. *Nail Disorders*. London: Dunitz, 1991: 78–101.

2 de Berker D. Childhood nail diseases. *Dermatol Clin* 2006; **24**: 355–63.

3 Hammerton MD, Shrank AB. Congenital hypertrophy of the lateral nail folds of the hallux. *Pediatr Dermatol* 1988; **5**: 243–5.

4 Piraccini BM, Parente GL, Varotti E, Tosti A. Congenital hypertrophy of the lateral nail folds of the hallux: clinical features and follow-up of seven cases. *Pediatr Dermatol* 2000; **17**: 348–51.

5 Baran R. Congenital malalignment of the toe nail. *Arch Dermatol* 1980; **116**: 1346.

6 Gupta AK, Skinner AR, Baran R. Onychomycosis in children: an overview. *J Drugs Dermatol* 2003; **2**: 31–4.

7 Gupta AK, Skinner AR. Onychomycosis in children: a brief overview with treatment strategies. *Pediatr Dermatol* 2004; **21**: 74–9.

8 Turano AF. Beau's lines in infancy. *Pediatrics* 1968; **41**: 996–4.

9 Parry EJ, Morley WN, Dawber RPR. Herringbone nails: an uncommon variant of nail growth in childhood. *Br J Dermatol* 1995; **132**: 1021–2.

10 Singh G, Haneef NS, Uday A. Nail changes and disorders among the elderly. *Indian J Dermatol Venereol Leprol* 2005; **71**: 386–92.

11 Baran R. Nail care in the 'golden years' of life. *Curr Med Res Opin* 1982; **7**: 96–101.

12 Brauer E, Baran R. Cosmetics: the care and adornment of the nail. In: Baran R, Dawber RPR, de Berker DAR, Haneke E, Tosti A, eds. *Diseases of the Nails and Their Management*, 3rd edn. Oxford: Blackwell Science, 2001: 366–8.

13 Woodrow P, Dickson N, Wright P. Foot care for non-diabetic older people. *Nurs Older People* 2005; **17**: 31–2.

14 Helfand AE. Assessing onychial disorders in the older patient. *Clin Podiatr Med Surg* 2003; **20**: 431–42.

15 Loo DS. Onychomycosis in the elderly: drug treatment options. *Drugs Aging* 2007; **24**: 293–302.

16 Tavakkol A, Fellman S, Kianifard F. Safety and efficacy of oral terbinafine in the treatment of onychomycosis: analysis of the elderly subgroup in Improving Results in Onychomycosis Concomitant Lamisil and Debridement (IRONCLAD), an open-label, randomized trial. *Am J Geriatr Pharmacother* 2006; **4**: 1–13.

Nail signs and systemic disease

It is important for clinicians to understand and accurately describe nail findings if they are to communicate accurately with their colleagues and avoid the vagueness that often surrounds nail pathology. Signs fall into categories of shape, surface and colour.

Abnormalities of shape

Clubbing

In clubbing there is increased transverse and longitudinal nail curvature with hypertrophy of the soft-tissue components of the digit pulp. Hyperplasia of the fibrovascular tissue at the base of the nail allows the nail to be 'rocked', and in causes associated with cardiopulmonary disease there may be local cyanosis.

There are three forms of geometric assessment that can be performed. *Lovibond's angle* is found at the junction between the nail plate and the proximal nail fold, and is normally less than 160°. This is altered to over 180° in clubbing (Fig. 65.5). *Curth's angle* at the distal interphalangeal joint is normally about 180°. This is diminished to less than 160° in clubbing (Fig. 65.6). *Schamroth's window* is seen when the dorsal aspects of two fingers from opposite hands are apposed, revealing a window of light, bordered laterally by the Lovibond angles. As this angle is obliterated in clubbing, the window closes [1]. Assessment of clubbing at the bedside shows poor agreement between examiners [2] in milder cases and there are problems in firm morphometric analysis that do not lend themselves to routine clinical solutions [3].

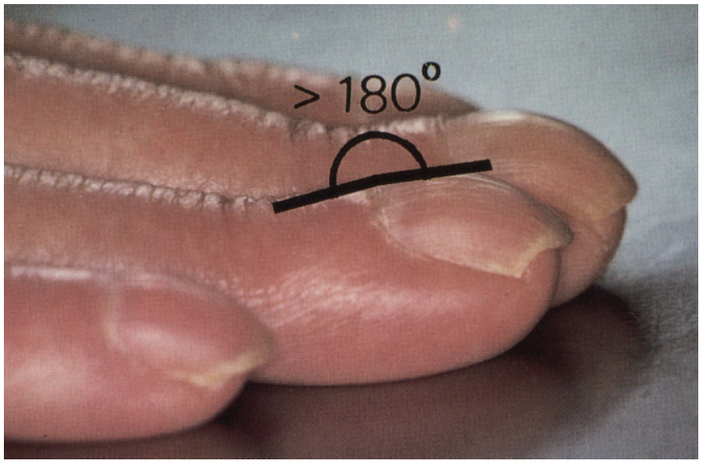


Fig. 65.5 Clubbing: Lovibond's profile sign. The angle is normally less than 160° but exceeds 180° in clubbing.

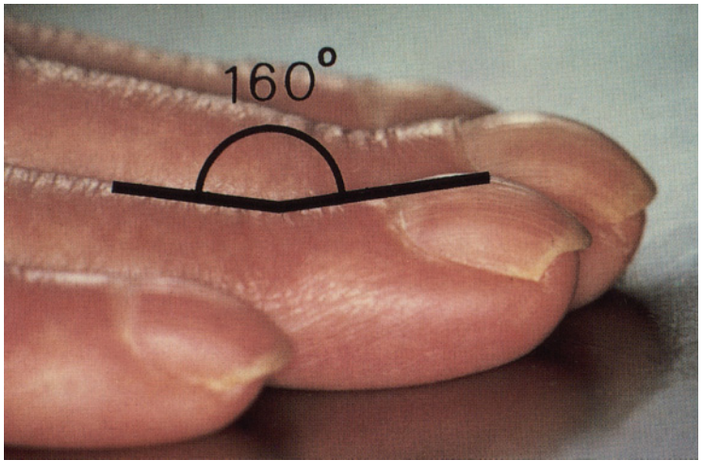


Fig. 65.6 Clubbing: Curth's modified profile sign.

Clubbing appears to be related more to increased blood flow through the vasodilated plexus of nail unit vasculature than to vessel hyperplasia. Altered vagal tone and microvascular infarcts have been implicated [4,5].

Pathological associations of clubbing include inflammatory bowel disease, carcinoma of the bronchus and cirrhosis. In forms associated with bronchiectasis or neoplasm, prominent inflammatory joint signs may also be seen, resulting in hypertrophic pulmonary osteoarthropathy. It has also been reported as a common finding in hemiplegic limbs [6] and can be a presenting feature of a subungual tumour when in a single digit [7]. In some cases of bronchiectasis, a variant of clubbing, *shell nail syndrome*, can be seen. This is distinguished from clubbing by the presence of atrophy of underlying bone and nail bed [8] and may have more in common with yellow nail syndrome than with clubbing. Rare cases of association with medication leave the matter open to doubt [9].

References

1 Lampe RM, Kagan A. Detection of clubbing: Schamroth's sign. *Clin Pediatr* 1983; **22**: 125.
2 Myers KA, Farquhar DR. The rational clinical examination. Does this patient have clubbing? *JAMA* 2001; **286**: 341–7.
3 Goyal S, Griffiths AD, Omarouayache S, Mohammedi R. An improved method of studying fingernail morphometry: application to the early detection of fingernail clubbing. *J Am Acad Dermatol* 1998; **39**: 640–2.
4 Currie AE, Gallagher PJ. The pathology of clubbing: vascular changes in the nail bed. *Br J Dis Chest* 1988; **82**: 382–5.
5 Silveri F, Carlino G, Cervini C. The endothelium/ platelet unit in hypertrophic osteoarthropathy. *Clin Exp Rheumatol* 1992; **10** (Suppl. 7): 61–6.
6 Siragusa M, Schepis C, Cosentino FI *et al*. Nail pathology in patients with hemiplegia. *Br J Dermatol* 2001; **144**: 557–60.
7 Baran R, Perrin C. Subungual perineurioma: a peculiar location. *Br J Dermatol* 2002; **146**: 125–8.
8 Cornelius CE, Shelley WB. Shell nail syndrome associated with bronchiectasis. *Arch Dermatol* 1967; **96**: 694–5.
9 Packard KA, Arouni AJ, Hilleman DE, Gannon JM. Fingernail clubbing and chromonychia associated with the use of angiotensin II receptor blockers. *Pharmacotherapy* 2004; **24**: 546–50.

Koilonychia

In koilonychia (Greek: *koilos*, hollow; *onyx*, nail), there is reverse curvature in the transverse and longitudinal axes giving a concave dorsal aspect to the nail [1]. Fingers and toes may be affected, with signs most prominent in the thumb or great toe. The nail may be thickened, thinned, softened or unchanged in quality. Koilonychia is common in infancy as a benign feature of the great toenail, although in some infants its persistence may be associated with a deficiency of cysteine-rich keratin [2] in trichothiodystrophy. The most common systemic association is with iron deficiency [3] and haemochromatosis, although the majority of adults with koilonychia demonstrate a familial pattern which may be autosomal dominant [4]. In dermatoses such as psoriasis and dermatophyte infection, nail bed hyperkeratosis may push the nail up distally to produce a spoon-shaped nail. In mechanics, softening of the nail with oil may be a factor [5], and in hairdressers, permanent wave solutions may be causal [6].

References

1 Stone OJ. Spoon nails and clubbing: significance and mechanisms. *Cutis* 1975; **16**: 235–41.
2 Jalili MA, Al-Kassab S. Koilonychia and cystine content of nails. *Lancet* 1959; **ii**: 108–10.
3 Hogan GR, Jones B. The relationship of koilonychia and iron deficiency in infants. *J Pediatr* 1970; **77**: 1054.
4 Bergeron JR, Stone OJ. Koilonychia. A report of familial spoon nails. *Arch Dermatol* 1967; **95**: 351.
5 Dawber RPR. Occupational koilonychia. *Br J Dermatol* 1974; **91**(Suppl. 10): 11.
6 Alanko K, Kanerva L, Estlander T *et al*. Hairdresser's koilonychia. *Am J Contact Dermatitis* 1997; **8**: 177–8.

Pincer nail

Synonyms
- Involuted nail
- Trumpet nail

Pincer nail describes a dystrophy where nail growth is pitched towards the midline, combined with increased transverse curvature. It presents in three patterns [1–3]. Probably the most common is in association with psoriasis, where the thumbs and big toes are the most likely to be affected, although the pattern is not as orga-

nized and symmetrical as that seen in the inherited version. In the latter there is often a gradient of involvement, radiating from the thumbs and big toes outwards, which progresses with time. The third variant is the individual nail which develops a pincer deformity. In this instance careful imaging and surgical exploration should be undertaken to exclude an isolated space-occupying lesion beneath the matrix [4–6]. Although the changes in matrix geometry may only be slight, their effect is amplified by longitudinal growth of the nail such that the free edge may take on the shape of the apex of a cone in extreme cases. Pain may arise due to embedding of the pincer nail in the lateral nail folds and nail bed, which becomes most pronounced distally. It is seen as an isolated familial abnormality that usually becomes manifest in adulthood.

Imaging can be helpful in all variants. Treatment is usually by surgery to relieve the pain. In toes it is usually best to perform a lateral ablation of the most embedded margin. This will sometimes lead to a shift of the nail such that the other side no longer embeds. If both sides require ablation, the dimensions of the toenail may mean that it is better to ablate the entire matrix rather than to leave a central zone of nail. The alternative of corrective surgery in toes has less chance of success, although successful case series are reported. Ablation may ultimately be required as a definitive procedure. When treating the thumbs or fingers, the chance of success with corrective surgery is higher and the cosmetic and functional handicap of ablation may not be acceptable. Again, a lateral ablation may be adequate, but more complex procedures entail altering the alignment of the matrix [2,7,8], level of the nail bed [9], and addressing any midline hypertrophy of the distal phalanx. Some surgeons advocate a combination of reconstruction and ablation [10]. Nail braces rarely produce long-term benefit, although promising outcomes have been reported [11].

References

1 Baran R, Haneke E, Richert B. Pincer nails: definition and surgical treatment. *Dermatol Surg* 2001; **27**: 261–6.
2 Haneke E. Ingrown and pincer nails: evaluation and treatment. *Dermatol Ther* 2002; **15**: 148–58.
3 Mimouni D, Ben-Amitai D. Hereditary pincer nail. *Cutis* 2002; **69**: 51–3.
4 Hwang SM, Lee SH, Ahn SK. Pincer nail deformity and pseudo-Kaposi's sarcoma: complications of an artificial arteriovenous fistula for haemodialysis. *Br J Dermatol* 1999; **141**: 1129–32.
5 Vanderhooft SL, Vanderhooft JE. Pincer nail deformity after Kawasaki's disease. *J Am Acad Dermatol* 1999; **41**: 341–2.
6 Jemec GB, Thomsen K. Pincer nails and alopecia as markers of gastrointestinal malignancy. *J Dermatol* 1997; **24**: 479–81.
7 Plusje LG. Pincer nails: a new surgical treatment. *Dermatol Surg* 2001; **27**: 41–3.
8 Brown RE, Zook EG, Williams J. Correction of pincer-nail deformity using dermal grafting. *Plast Reconstr Surg* 2000; **105**: 1658–61.
9 Mutaf M, Sunay M, Isk D. A new surgical technique for the correction of pincer nail deformity. *Ann Plast Surg* 2007; **58**: 496–500.
10 Aksakal AB, Akar A, Erbil H, Onder M. A new surgical therapeutic approach to pincer nail deformity. *Dermatol Surg* 2001; **27**: 55–7.
11 Ozawa T, Yabe T, Ohashi N *et al*. A splint for pincer nail surgery: a convenient splinting device made of an aspiration tube. *Dermatol Surg* 2005; **31**: 94–8.

Macronychia and micronychia

Macronychia and micronychia are conditions where a nail is considered too large or too small in comparison with other nails on nearby digits. The nail disorder is usually associated with an abnormal digit, arising from underlying bony abnormalities such as local gigantism causing macronychia or megadactyly [1]. This is also the basis of racket thumb (Fig. 65.7), the most common form of benign, dominantly inherited macronychia. Plexiform neurofibromas may cause nail changes, and duplication of the terminal phalanges may cause bifid or small nails [2].



Fig. 65.7 Racket nail associated with clubbing.

References

1 Barsky AJ. Macrodactyly. *J Bone Joint Surg* 1967; **49**: 1255–6.
2 Millman AJ, Strier RP. Congenital onychodysplasia of the index fingers. *J Am Acad Dermatol* 1982; **7**: 57–65.

Anonychia

Anonychia is absence of all or part of one or several nails [1]. It may be congenital, acquired or transient. The underlying genetic abnormality of the congenital form has recently been identified as a mutation in the R-spondin 4 gene, which plays a part in Wnt signalling within the cell [2]. There may be a biological interaction with the underlying phalanx in embryogenesis [3]. Acquired forms are due to scarring of the nail matrix. This can arise as a result of burns, surgery or trauma, or be due to inflammatory dermatoses such as lichen planus where the entire nail matrix is scarred and lost [4]. Similar scarring can occur in variants of epidermolysis bullosa, with irreversible nail loss. The transient variant is due to nail shedding. This can occur due to an intense physiological or local inflammatory process, in the absence of scarring.

References

1 Solammadivi SV. Simple anonychia. *South Med J* 1981; **74**: 1555.
2 Blaydon DC, Ishii Y, O'Toole EA *et al*. The gene encoding R-spondin 4 *(RSPO4)*, a secreted protein implicated in Wnt signaling, is mutated in inherited anonychia. *Nat Genet* 2006; **38**: 1245–7.
3 Baran R, Juhlin L. Bone dependent nail formation. *Br J Dermatol* 1986; **114**: 371–5.
4 Pall A, Gupta RR, Gulati B, Goyal P. Twenty nail anonychia due to lichen planus. *J Dermatol* 2004; **31**: 146–7.

Abnormalities of nail attachment

Nail shedding

Nails can be lost through different mechanisms:

1 Complete loss of the nail plate due to proximal nail separation extending distally [1] is called onychomadesis and is a progression of profound Beau's lines. This may reflect local or systemic disease and in the latter may result in temporary loss of all nails.
2 Local dermatoses, such as the bullous disorders and paronychia, may cause nail loss. Generalized dermatoses may be manifest, for example toxic epidermal necrolysis (TEN) and severe/rapid onset of pustular psoriasis. Scarring of the nail unit is seen in lichen planus and following TEN, which may both provoke nail loss.
3 Trauma is a common cause of recurrent loss and may reflect the nature of the activity, such as football, or some underlying abnormality of footwear [2] or pedal mechanics. It is often associated with subungual haemorrhage [3]. In the long term, athletes often develop thickened dystrophic nails matching a history of recurrent shedding.
4 Temporary loss has also been described due to retinoids [4], and large doses of cloxacillin and cephaloridine during the treatment of two anephric patients [5].
5 Onychoptosis defluvium or alopecia unguium describes atraumatic, familial, non-inflammatory nail loss [6]. It may be periodic and associated with dental amelogenesis imperfecta.
6 Nail shedding can be part of an inherited structural defect, most obviously in epidermolysis bullosa [7], although at times the diagnosis may be occult [8].
7 Nail degloving [9]: this refers to partial or total avulsion of the nail and surrounding tissue (perionychium). Typically, it appears as thimble-shaped nail shedding or total loss of the nail organ with soft tissue. Nail degloving represents the end result of a variety of insults to the nail apparatus, including trauma, dermatological diseases and drug reactions.

References

1 Runne U, Orfanos CE. The human nail. *Curr Probl Dermatol* 1981; **9**: 102–49.
2 Almeyda J. Platform nails. *BMJ* 1973; **i**: 176.
3 Baran R, Barth J, Dawber RPR. *Nail Disorders*. London: Dunitz, 1991: 84–8.
4 Baran R. Retinoids and the nails. *J Dermatol Treat* 1990; **1**: 151–4.
5 Eastwood JB, Curtin JR, Smith EKM *et al*. Shedding of the nails apparently induced by large amounts of cephaloridine and cloxacillin in 2 anephric patients. *Br J Dermatol* 1969; **81**: 750–2.
6 Oliver WJ. Recurrent onychoptosis occurring as a family disorder. *Br J Dermatol* 1927; **26**: 59–68.
7 Bruckner-Tuderman L, Schnyder UW, Baran R. Nail changes in epidermolysis bullosa: clinical and pathogenetic considerations. *Br J Dermatol* 1995; **132**: 339–44.
8 Dharma B, Moss C, McGrath JA *et al*. Dominant dystrophic epidermolysis bullosa presenting as familial nail dystrophy. *Clin Exp Dermatol* 2001; **26**: 93–6.
9 Baran R, Perrin Ch. Nail degloving: a polyetiological condition with three main patterns. A new syndrome. *J Am Acad Dermatol* 2008; **58**: 232–7.

Onycholysis

Onycholysis is the distal and/or lateral separation of the nail from the nail bed [1] and can be graded for the purposes of clinical documentation or therapeutic trials [2]. Psoriatic onycholysis can be considered the reference point for other forms of onycholysis where it is typically distal, with variable lateral involvement. Areas of separation appear white or yellow due to air beneath the nail and sequestered debris, shed squames and glycoprotein exudate. Isolated islands of onycholysis present as 'oily spots' or 'salmon patches' in the nail bed. At the border of onycholysis, the nail bed is usually reddish-brown, reflecting the underlying psoriatic inflammatory changes. All the common causes are associated with diminished adherence of nail to nail bed as a primary (idiopathic) or secondary event and include trauma, fungal infection, eczema, drug reactions and photo-onycholysis [3].



Fig. 65.8 Onycholysis: idiopathic type.

Idiopathic onycholysis

This is a painless separation of the nail from its bed, which occurs without apparent cause. Overzealous manicure, frequent wetting and cosmetic 'solvents' may be the cause but may not be admitted by the patient. There may, however, be a minor traumatic element, as the condition occurs rather more often in persons who keep their nails abnormally long. Maceration with water may also be a factor [3]. It must be distinguished from other causes of onycholysis (see below). The affected nails grow very quickly [4].

The condition usually starts at the tip of one or more nails and extends to involve the distal third of the nail bed (Fig. 65.8). Persistent manicure is attempted to remove the debris which accumulates within the onycholytic space, and this can result in a crescentic margin of onycholysis matching the onychocorneal band and appearing similar in all involved digits. Pain occurs only if there is further extension as a result of trauma or if active infection supervenes. More often there is microbial colonization of a mixed nature, including *Candida albicans* and several bacteria, of which *Pseudomonas pyocyanea* is the most common. If the condition persists for several months, the nail bed becomes dark and irregularly thickened. The condition is mostly seen in women and many cases return to normal after a few months. The longer it lasts, the less likely is the nail to become reattached, due to keratinization of the exposed nail bed.

Treatment [5]. The patient should be advised to cut away as much as possible of the loosened nail and to apply a topical steroid preparation containing broad-spectrum antimicrobials, effective against both yeasts and bacteria. Reattachment is slow, and the loosened nail should be recut several times if necessary. The object



Fig. 65.9 Photo-onycholysis with a uniform pattern of discoloured onycholysis in the midline.

of treatment is to prevent infection becoming established beneath the loosened nail, because this leads to thickening of the nail bed and prevents reattachment. Some authorities still recommend 4% thymol in chloroform (not available in the USA) as a means of preventing infection and further maceration of the nail bed; however, 2% thymol is often as strong as the patient can tolerate and is usually effective. Where antimicrobial therapy is needed for *Pseudomonas*, gentamicin eye drops can be useful. Drying under the onycholytic nails with a hair dryer has been advocated in order to desiccate the environment in which *Pseudomonas* would otherwise grow. Soaking the finger tips several nights a week in vinegar or sodium hypochlorite solution (Milton™) for 5 minutes can be useful to prevent recurrence.

Secondary onycholysis

There are many causes of secondary onycholysis [5,7–8]. Psoriasis, fungal infections, dermatitis and trauma are among the most common. Onycholysis occurs in general medical conditions, including impaired peripheral circulation, hypothyroidism [8], hyperthyroidism [9], hyperhidrosis, yellow nail syndrome and shell nail syndrome. Minor trauma is a common cause, and many occupational cases are due to trauma [10]. Immersion of the hands in soap and water may be considered traumatic, as also may the use of certain nail cosmetics. It has also been described after the application of 5% 5-fluorouracil to the fingertips [11]. There is a condition of hereditary partial onycholysis associated with hard nails [12]. Photo-onycholysis (Fig. 65.9) may occur during treatment with psoralens, demethylchlortetracycline and doxycycline [13,14], and rarely other antibiotics. This is sometimes associated with cutaneous photosensitivity (see Chapter 29). Drugs such as retinoids [15] and cancer chemotherapy can also be implicated, with taxanes eliciting nail changes in between 19 and 44% of patients, depending on the chemotherapy regimen [16]. Cooling the hand with a specialized glove has been demonstrated to help diminish or delay onset of the side effects [17].

References

1 Ray L. Onycholysis: a classification and study. *Arch Dermatol* 1963; **88**: 181–5.
2 Daniel CR 3rd, Iorizzo M, Piraccini BM, Tosti A. Grading simple chronic paronychia and onycholysis. *Int J Dermatol* 2006; **45**: 1447–8.
3 Baran R, Juhlin L. Drug-induced photo-onycholysis. Three subtypes identified in a study of 15 cases. *J Am Acad Dermatol* 1987; **17**: 1012–6.
4 Dawber RPR, Samman PD, Bottoms E. Fingernail growth in idiopathic and psoriatic onycholysis. *Br J Dermatol* 1971; **85**: 558–60.
5 Wilson JW. Paronychia and onycholysis: aetiology and therapy. *Arch Dermatol* 1965; **92**: 726–30.
6 Baran R, Dawber RPR, Richert B. Physical signs. In: Baran R, Dawber RPR, eds. *Diseases of the Nails and Their Management*. Oxford: Blackwell Science, 2001: 76–7.
7 Kechijian P. Onycholysis of the fingernails: evaluation and management. *J Am Acad Dermatol* 1985; **12**: 552–60.
8 Fox EC. Diseases of the nails: report of cases of onycholysis. *Arch Dermatol Syphilol* 1940; **44**: 426–8.
9 Luria MN, Asper SP. Onycholysis in hyperthyroidism. *Ann Intern Med* 1958; **42**: 102–8.
10 Heinmann H, Silverberg MG. Onycholysis in fur workers. *Arch Dermatol Syphilol* 1941; **44**: 426–8.
11 Shelley WB. Onycholysis due to 5-fluorouracil. *Acta Derm Venereol (Stockh)* 1972; **52**: 320–2.
12 Schultz HD. Hereditary partial onycholysis and hard nails. *Dermatol Wochenschr* 1966; **152**: 766–8.
13 Franks SB, Coton HJ, Mirkin W. Photo-onycholysis due to tetracycline. *Arch Dermatol* 1971; **103**: 520.
14 Baran R, Juhlin L. Photoonycholysis. *Photodermatol Photoimmunol Photomed* 2002; **18**: 202–7.
15 Onder M, Oztas MO, Oztas P. Isotretinoin-induced nail fragility and onycholysis. *J Dermatol Treat* 2001; **12**: 115–6.
16 Minisini AM, Tosti A, Sobrero AF *et al*. Taxane-induced nail changes: incidence, clinical presentation and outcome. *Ann Oncol* 2003; **14**: 333–7.
17 Scotte F, Tourani JM, Banu E *et al*. Multicenter study of a frozen glove to prevent docetaxel-induced onycholysis and cutaneous toxicity of the hand. *J Clin Oncol* 2005; **23**: 4424–9.

Pterygium [1]

The term 'pterygium' describes the winged appearance achieved when a central fibrotic band divides a nail proximally in two. However, the fibrotic tissue may not always grossly alter the nail, and can extend from the lateral nail fold as well as the more typical proximal nail fold origin. A large pterygium may destroy the whole nail.

An inflammatory destructive process precedes pterygium formation. There is fusion between the nail fold and underlying nail bed and matrix. The fibrotic band then obstructs normal nail growth. Superficial abnormal vessels may be seen and there are no skin markings. It most typically develops in trauma or lichen planus and its variants, including idiopathic atrophy of the nail [2] and graft-versus-host disease [3]. It can also occur in leprosy, where it may represent scarring secondary to neuropathic damage and secondary purulent infection [4].

References

1 Richert BJ, Patki A, Baran RL. Pterygium of the nail. *Cutis* 2000; **66**: 343–6.
2 Samman PD. Idiopathic atrophy of the nails. *Br J Dermatol* 1969; **81**: 746–9.
3 Little BJ, Cowan MA. Lichen planus-like eruption and nail changes in a patient with graft-versus-host disease. *Br J Dermatol* 1990; **122**: 841–3.
4 Patki AH, Mehta JM. Pterygium unguis in a patient with recurrent type 2 lepra reaction. *Cutis* 1989; **44**: 311–2.

Ventral pterygium [1]

Ventral pterygium or pterygium inversum unguis [2] occurs on the distal undersurface of the nail, with forward extension of the

nail bed epithelium dislocating the hyponychium and obscuring the distal groove. Causes include trauma, systemic sclerosis [2,3], Raynaud's phenomenon, lupus erythematosus, familial [4] and infective [5]. The overlying nail may be normal, but adjacent soft tissues can be painful.

References

1 Drake L. Pterygium inversum unguis. *Arch Dermatol* 1976; **112**: 255–6.
2 Caputo R, Cappio F, Rigoni C *et al*. Pterygium inversum unguis. Report of 19 cases and review of the literature. *Arch Dermatol* 1993; **129**: 1307–9.
3 Patterson JW. Pterygium inversum unguis-like changes in scleroderma. *Arch Dermatol* 1977; **113**: 1429–30.
4 Amblard P, Reymond JL. Familial subungual pterygium. *Ann Dermatol Vénéréol* 1980; **107**: 949–50.
5 Patki AH. Pterygium inversum unguis in a patient with leprosy. *Arch Dermatol* 1990; **126**: 1110.

Subungual hyperkeratosis

Subungual hyperkeratosis entails hyperkeratosis of the nail bed and hyponychium and may occur in a range of conditions, including those where the primary diagnosis is not clear. Nail plate changes are variable, but thickening is common. Dry, white or yellow hyperkeratosis may crumble away from the overhanging nail. Hyperkeratosis may extend onto the digit pulp. Features of onychomycosis and wart virus infection (mainly toes) or psoriasis, pityriasis rubra pilaris and eczema (mainly fingers) may be found elsewhere to indicate the aetiology.

The nail bed is an epithelium of low proliferative turnover. Any disease process that affects it is likely to result in an excess of squamous debris. The overlying nail prevents simple loss. The initial outcome is compaction of debris into layers of subungual hyperkeratosis. The only route of loss is by emerging distally with the growing nail.

Focal subungual keratoses are seen with Darier's disease, and keratotic debris beneath the nail in Norwegian (crusted) scabies may contain mites and eggs.

Nail thickening

Isolated thickening of the nail is associated with yellow discoloration as the nail bed vasculature is obscured. Common causes include psoriasis, eczema, trauma and onychomycosis, some of which may be associated with subungual hyperkeratosis. The shape of the nail may alter depending on the underlying cause, such as in yellow nail syndrome, where there is increased curvature in the longitudinal and transverse axes.

In the elderly and in yellow nail syndrome, retarded longitudinal growth of the toenail is compensated for by increased thickness [1]. Yellow nail may also develop where the nail bed produces abnormal nail [2]. Onychogryphosis describes thickened nails, usually the great toenails, which commonly grow upwards in a spiral. It is attributed to chronic distorting trauma and can be treated surgically or by conservative methods. These include trimming with an electric drill, chemical destruction with 40% urea paste, phenolization of the matrix to achieve total ablation (phenol time reduced to 2 min) or carbon dioxide laser.

References

1 Higashi N, Matsumura T. The aetiology of onychogryphosis of the great toe nail and of ingrowing nail. *Hifu* 1988; **30**: 620–3.
2 Schönfeld PH. The pachyonychia congenita syndrome. *Acta Derm Venereol (Stockh)* 1980; **60**: 45–9.

Changes in nail surface

Longitudinal grooves

Longitudinal grooves may run all or part of the length of the nail in the longitudinal axis, and need to be distinguished from ridges that are proud of the nail surface [1]. Grooves may be full or partial thickness.

The median canaliform dystrophy of Heller [2] is the most distinctive form [3]. The nail is split, usually in the midline, with a fir-tree-like appearance of ridges angled backwards. The thumbs are most commonly affected and the involvement may be symmetrical. The cuticle may be normal, as distinct from the cuticle in habit tic deformity (washboard nails). After a period of months or years the nails often return to normal, but relapse may occur [4] and a ridge may replace the original defect. Some patients give a definite history of trauma [1], or the disorder can be attributed to oral retinoids [5]. Familial cases have been recorded. Sutton [6] described involvement of a toenail in which a flabby filament of fleshy tissue was present in the canal. Treatment is unnecessary, although the patient should be advised to apply an emollient cream to the nail fold.

Physiological furrows and ridges are accentuated in lichen planus, rheumatoid arthritis, peripheral vascular disease, old age and Darier's disease. *Onychorrhexis* may occur where there are superficial grooves in the nail that lead to a distal split.

Tumours (warts, myxoid cysts) pressing on the matrix, or a proximal nail fold pterygium, may produce a longitudinal groove.

References

1 Ronchese F. Peculiar nail anomalies. *Arch Dermatol* 1951; **63**: 565–9.
2 Heller J. Dystrophia unguium mediana canaliformis. *Dermatol Z* 1928; **51**: 416–7.
3 Zelger J, Wohlfarth P, Putz R. Dystrophia unguium mediana canaliformis Heller. *Hautarzt* 1974; **25**: 629.
4 Sweet RD. Dystrophia unguium mediana canaliformis. *Arch Dermatol Syphilol* 1951; **64**: 61–2.
5 Bottomley W, Cunliffe W. Median canaliform dystrophy associated with isotretinoin therapy. *Br J Dermatol* 1992; **127**: 447.
6 Sweeney SA, Cohen PR, Schulze KE, Nelson BR. Familial median canaliform nail dystrophy. *Cutis* 2005; **75**: 161–5.

Transverse grooves and Beau's lines [1,2]

Transverse grooves may be full or partial thickness through the nail. When they are endogenous they have an arcuate margin matching the lunula. If exogenous, such as those due to manicure, the margin may match the proximal nail fold and the grooves may be multiple as in washboard nails associated with a habit tic [3]. When multiple, it may be difficult to distinguish a habit tic from psoriasis. Transverse grooves may occur on isolated diseased digits (trauma, inflammation or neurological events) [4] or may be generalized, reflecting a systemic event such as drug reaction [5], coronary thrombosis, measles, mumps or pneumonia. If endogenous, they are usually referred to as *Beau's lines* [2]. They arise through temporary interference with nail formation and become visible on the nail surface (Fig. 65.10) some weeks after the precipitant. The distance of the groove from the nail fold is related to the time since the onset of growth disturbance. The depth and



Fig. 65.10 Beau's lines present as transverse grooves in the nail, matching the proximal margin of the nail matrix and lunula.

width of the groove may be related to the severity and duration of disturbance, respectively. In many cases, grooves are seen on all 20 nails but are most prominent on the thumb and great toenail, and are deeper in the midline of the nail. Full-thickness grooves can be associated with distal extension of the plane of separation of the nail plate. This can lead to nail loss, termed *onychomadesis*.

References

1 de Berker DAR. What is a Beau's line? *Int J Dermatol* 1994; **33**: 545–6.
2 Beau JHS. Note sur certain caractères de séméiologie rétrospective présentés par les ongles. *Arch Gén Méd* 1846; **11**: 447–9.
3 Macaulay WL. Transverse ridging of the thumbnails. *Arch Dermatol* 1966; **93**: 421–3.
4 Lee YJ, Yun SK. Unilateral Beau's lines associated with a fingertip crushing injury. *J Dermatol* 2005; **32**: 914–6.
5 Piraccini BM, Iorizzo M, Starace M, Tosti A. Drug-induced nail diseases. *Dermatol Clin* 2006; **24**: 387–91.

Pitting

Pitting presents as punctate erosions in the nail surface. Individual pits may be shallow or deep, with a regular or irregular outline. The individual pits of psoriasis are said to be less regular in form and in overall pattern than those of alopecia areata, but this is not always the case. When numerous, they appear randomly distributed upon the nail surface or have a geometric pattern. The latter may cause rippling or create a grid of pits. Extensive pitting combined with other surface irregularities results in the appearance of *trachyonychia*. An isolated large pit may produce a localized full-thickness defect in the nail plate termed *elkonyxis*, which is found in Reiter's disease, psoriasis and following trauma.



Fig. 65.11 Trachyonychia: roughened surface of up to 20 nails.

Histologically, pits represent foci of parakeratosis, reflecting isolated nail malformation [1].

Reference

1 Zaias N. Psoriasis of the nail. A clinicopathologic study. *Arch Dermatol* 1969; **99**: 567–79.

Trachyonychia

Trachyonychia presents as a rough surface affecting all of the nail plate and up to 20 nails (20-nail dystrophy) [1]. The original French term was 'sand-blasted nails', which evokes the main clinical feature of a grey, roughened surface (Fig. 65.11). It is mainly associated with alopecia areata [2], psoriasis and lichen planus, although the most common presentation is as an isolated nail abnormality. In the isolated form, histology shows spongiosis and a lymphocytic infiltrate of the nail matrix [3]. It may present as a self-limiting condition in childhood or as a more chronic problem in adulthood. There is some response to potent topical, locally injected and systemic steroids, but this may be temporary. Topical 5-fluorouracil has also been used to good effect [4], although it is important to be wary of associated onycholysis where the diagnosis is psoriasis, as onycholysis can be exacerbated by 5-fluorouracil. Childhood forms normally resolve spontaneously.

References

1 Samman PD. Trachyonychia (rough nails). *Br J Dermatol* 1979; **101**: 701–5.
2 Baran R. Twenty nail dystrophy of alopecia areata (letter). *Arch Dermatol* 1981; **117**: 1.
3 Tosti A, Fanti PA, Morelli R *et al*. Spongiotic trachyonychia. *Arch Dermatol* 1991; **127**: 584–5.
4 Schissel DJ, Elston DM. Topical 5-fluorouracil treatment for psoriatic trachyonychia. *Cutis* 1998; **62**: 27–8.

Onychoschizia

Onychoschizia is also known as lamellar dystrophy and is characterized by transverse splitting into layers at or near the free edge (Fig. 65.12) in fingers and toes, especially in infants [1]. There is a subtle distinction between the static features, such as types of split, and the subjective experience of having brittle nails. Usually these characteristics coincide, although clinicians and patients may



Fig. 65.12 Onychoschizia (lamellar dystrophy).

prefer to use one term in preference to the other. The different features can be assessed within a scoring system [2]. Variants include splitting at the lateral margins alone and multiple crenellated splits at the free edge. It is seldom associated with any systemic disorder, although it has been reported with polycythaemia [3], human immuno-deficiency virus (HIV) infection [4] and glucagonoma [5], and recently it has been referred to as a 'syndrome' [2].

Scanning electron microscopy illustrates the tendency of the lamellar structure of nail to separate after repeated immersion in water [6], although case–control studies show that occupation is not a major determinant of the condition [7]. However, efforts at retaining hydration (gloves, emollient and base coat with nail varnish) may help reverse clinical changes. Biotin has been used as systemic therapy, but the evidence for its efficacy is weak [8].

References

1 Scher RK. Brittle nails. *Int J Dermatol* 1989; **28**: 515–6.
2 van de Kerkhof PC, Pasch MC, Scher RK *et al*. Brittle nail syndrome: a pathogenesis-based approach with a proposed grading system. *J Am Acad Dermatol* 2005; **53**: 644–51.
3 Graham-Brown RAC, Holmes R. Lamellar nail dystrophy with polycythaemia. *Clin Exp Dermatol* 1980; **5**: 209–12.
4 Cribier B, Mena ML, Rey D *et al*. Nail changes in patients infected with human immunodeficiency virus. A prospective controlled study. *Arch Dermatol* 1998; **134**: 1216–20.
5 Chao SC, Lee JY. Brittle nails and dyspareunia as first clues to recurrences of malignant glucagonoma. *Br J Dermatol* 2002; **146**: 1071–4.
6 Wallis MS, Bowen WR, Guin JR. Pathogenesis of onychoschizia (lamellar dystrophy). *J Am Acad Dermatol* 1991; **24**: 44–8.
7 Lubach D, Beckers P. Wet working conditions increase brittleness of nails but do not cause it. *Dermatology* 1992; **185**: 120–2.
8 Colombo VE, Gerber F, Bronhofer M *et al*. Treatment of brittle fingernails and onychoschizia with biotin: scanning electron microscopy. *J Am Acad Dermatol* 1990; **23**: 1127–32.

Beading and ridging

Beading and ridging have been described as occurring more often than normal in patients with rheumatoid arthritis [1]. More recently, increased beading has been examined using optical profilometry in patients taking itraconazole for onychomycosis [2]. Itraconazole is known to increase the rate of nail growth, and it was proposed that beading may be a feature of this increase. As beading is more commonly a feature of old age, when nail growth rate slows down, one would not expect beading to correspond directly to faster linear nail growth. Both beading and ridging are common signs in normal ageing patients and at present their significance remains unclear.

References

1 Hamilton EDB. Nail studies in rheumatoid arthritis. *Ann Rheum Dis* 1960; **19**: 167–73.
2 de Doncker P, Pierard GE. Acquired nail beading in patients receiving itraconazole: an indicator of faster nail growth? A study using optical profilometry. *Clin Exp Dermatol* 1994; **19**: 404–6.

Changes in colour [1–7]

Alteration in nail colour may occur because of changes affecting the dorsal nail surface, the substance of the nail plate, the undersurface of the nail or the nail bed.

Exogenous pigment

Exogenous pigment on the upper surface is easy to demonstrate by scraping the nail. If the proximal margin of the pigment is an arc matching the proximal nail fold, this is a further clue confirming an exogenous source. Often, the cuticle is less absorbent than nail and there will be a narrow proximal margin of unstained nail. This margin will broaden as the period since exposure lengthens. Hence the 'quitters' nail, which demonstrates the cessation of smoking and nicotine-free fingers for 2 months.

Exogenous pigment on the undersurface of the nail is less easy to demonstrate and may mean that part or all of the nail needs to be avulsed in order to scrape the undersurface and examine it separately from the nail bed. The green pigment of *Pseudomonas* infection [6] in association with onycholysis is a typical situation where partial avulsion is the best way to demonstrate the site of pigmentation, although it may not always be the best treatment.

Nail plate changes

The nail plate can be changed by the addition of pigment or the alteration of the normal cellular and intercellular organization such that there is loss of normal lucency. Pigment is typically added in the form of melanin produced by matrix melanocytes during nail formation. This produces a brown longitudinal streak the entire length of the nail. In white people this is abnormal and requires thorough assessment and, in some instances, biopsy. In darker-skinned people it is a common variant. The incorporation of heavy metals and some drugs into the nail via the matrix can also produce altered nail plate colour, such as the grey colour associated with silver. The disruption of normal nail plate formation by disease, chemotherapy, poisons or trauma can result in waves of parakeratotic nail cells or small splits between cells within the nail. Both make the nail less lucent and produce the white marks of true *leukonychia.* Transmission electron microscopy suggests that there is a change in collagen fibre organization, which might provide an intracellular basis for altered diffractive properties. This disruption can be achieved at nail formation or subsequently in the case of fungal nail infection, where discoloration may start distolaterally rather than via the matrix.

Dermoscopy can be very helpful in the assessment of nail plate pigmentation and underlying nail bed changes [7].

Nail bed changes

In addition to generalized vascular changes in the nail bed, there can be localized changes, as seen with nail bed tumours. In the instance of a glomus tumour, this may be the sole method of localization and arises because of the differential blood supply in the tumour and surrounding nail bed. Subungual hyperkeratosis or the incorporation of drugs (antimalarials, phenothiazines) may also change the apparent colour of the nail. Splinter haemorrhages, representing ruptured nail bed vessels, deposit haemoglobin on the undersurface of the nail, which grows out. Cyanosis makes the nail bed blue and carbon monoxide poisoning makes it bright red.

References

1 Baran R. Longitudinal melanotic streaks as a clue to Laugier–Hunziker syndrome. *Arch Dermatol* 1979; **115**: 1448–9.
2 Daniel CR. Nail pigmentation abnormalities. *Dermatol Clin* 1985; **3**: 431–43.
3 Daniel CR, Zaias N. Pigmentary abnormalities of the nails with emphasis on systemic diseases. *Dermatol Clin* 1988; **6**: 305–13.
4 Higashi N. Melanonychia due to tinea unguium. *Hifu* 1990; **32**: 379–80.
5 Lovemann AB, Fliegelman MT. Discoloration of the nails. *Arch Dermatol* 1955; **72**: 153–6.
6 Shellow WVR, Koplon BS. Green striped nails: chromonychia due to *Pseudomonas aeruginosa*. *Arch Dermatol* 1963; **97**: 149–53.
7 Thomas L, Dalle S. Dermoscopy provides useful information for the management of melanonychia striata. *Dermatol Ther* 2007; **20**: 3–10.

True leukonychia

White discoloration of the nail attributable to matrix dysfunction occurs in a variety of patterns [1,2]. There is the rare, inherited form called total leukonychia, in which all nails are milky porcelain white [3]. In subtotal leukonychia, the proximal two-thirds are white, becoming pink distally. This is attributed to a delay in keratin maturation, and the nail may still appear white at the distal overhang (Fig. 65.13).

Transverse leukonychia (Mees' line) reflects a systemic disorder, such as chemotherapy or poisoning [4], or systemic infection [5] affecting matrix function. The 1- to 2-mm-wide transverse band is in the arcuate form of the lunula and is analogous to a Beau's line, with which it is occasionally found. Punctate leukonychia comprises white spots of 1–3 mm diameter attributed to minor matrix trauma (e.g. manicure) and is also seen in alopecia areata. The pattern and number of spots may change as the nail grows. With longitudinal leukonychia, there is a parakeratotic focus in the matrix, sometimes attributable to Darier's disease or a small tumour.



Fig. 65.13 True leukonychia with white nail in the distal free edge.

References

1 Norgett EE, Wolf F, Balme B *et al*. Hereditary 'white nails': a genetic and structural study. *Br J Dermatol* 2004; **151**: 65–72.
2 Grossman M, Scher RK. Leukonychia: review and classification. *Int J Dermatol* 1990; **29**: 535–41.
3 Baran R, Dawber RPR. Physical signs. In: Baran R, Dawber RPR, eds. *Diseases of the Nails and Their Management*, 2nd edn. Oxford: Blackwell Science, 1994: 72.
4 Marino MT. Mees' lines. *Arch Dermatol* 1990; **126**: 827–8.
5 Mautner GH, Lu I, Ort RJ, Grossman ME. Transverse leukonychia with systemic infection. *Cutis* 2000; **65**: 318–20.

Apparent leukonychia

In apparent leukonychia, changes in the nail bed are responsible for the white appearance [1,2]. Nail bed pallor may be a non-specific sign of anaemia, oedema or vascular impairment. It may occur in particular patterns that have become associated with certain conditions.

Terry's nail

This is white proximally and normal distally and is attributed to cirrhosis, congestive cardiac failure and adult-onset diabetes mellitus [3]. Nail bed biopsy reveals only mild changes of increased vascularity. This is similar to *half-and-half nails*, where there is a proximal white zone and distal (20–60%) brownish sharp demarcation, the histology of which suggests an increase of vessel wall thickness and melanin deposition. It is seen in 9–50% of patients with chronic renal failure and after chemotherapy. It is unclear whether the variant *Neapolitan nails*, where there are bands of white, brown and red, is a version of half-and-half or Terry's nails, or a feature of old age.

Muehrcke's paired white bands

These bands are parallel to the lunula in the nail bed, with pink between two white lines. They are commonly associated with hypoalbuminaemia, the correction of which by albumin infusion can reverse the sign. They have also been reported following placement of a left ventricular assist device in a patient with congestive heart failure [4].

References

1 Albright SD, Wheeler CE. Leukonychia: total and partial leukonychia in a single family with review of the literature. *Arch Dermatol* 1964; **90**: 392–9.
2 Grossman M, Scher RK. Leukonychia: review and classification. *Int J Dermatol* 1990; **29**: 535–41.
3 Holzberg M, Walker HK. Terry's nails: revised definition and new correlations. *Lancet* 1984; **i**: 896–9.
4 Alam M, Scher RK, Bickers DR. Muehrcke's lines in a heart transplant recipient. *J Am Acad Dermatol* 2001; **44**: 316–7.

Colour changes due to drugs [1]

There are a number of colour changes due to drugs. Yellowing of the nail is a rare occurrence in prolonged tetracycline therapy, which can also produce a pattern of dark distal photo-onycholysis associated with photosensitivity [2]. The whole nail is affected and returns to normal when the drug is discontinued. A similar effect, but of a bluish colour, is seen with mepacrine [3], the nails fluorescing yellow–green or white when viewed under Wood's light. Normal nails show slight fluorescence of violet–blue colour. Hydroxyurea has been reported to result in blue lunulae [4].

Chloroquine may produce blue–black pigmentation of the nail bed [5]. Other antimalarials may produce longitudinal or vertical bands of pigmentation on the nail bed or in the nail [6]. A fixed drug eruption of the nail bed can be dark blue [7]. Argyria may discolour the nails slate blue [8], and inorganic arsenic may produce longitudinal bands of pigment or transverse white stripes (*Mees' stripes*) across the nail.

Hyperpigmentation due to increased melanin in the nail and nail bed has been noted in children after 6 weeks of treatment with doxorubicin (Adriamycin) [9,10]. Other, similar cytotoxic drugs may cause a variety of patterns of increased pigmentation [1]. However, in acquired immune deficiency syndrome (AIDS), longitudinal melanonychia may be seen in untreated cases [11,12] as well as in those receiving zidovudine [9,13].

References

1 Baran R, Dawber RPR, Richert B. Physical signs. In: Baran R, Dawber RPR, de Berker DAR, Haneke E, Tosti A, eds. *Diseases of the Nails and Their Management*, 3rd edn. Oxford: Blackwell Science, 2001: 86–103.

2 Orentreich N, Harber LC, Tromovitch TH. Photosensitivity and photoonycholysis due to demethylchlortetracycline. *Arch Dermatol* 1961; **83**: 730–7.

3 Mallon E, Dawber RPR. Longitudinal melanonychia induced by minocycline. *Br J Dermatol* 1994; **130**: 794–5.

4 Jeevankumar B, Thappa DM. Blue lunula due to hydroxyurea. *J Dermatol* 2003; **30**: 628–30.

5 Tuffanelli D, Abraham RK, Dubois E. Pigmentation from antimalarial drugs. *Arch Dermatol* 1963; **88**: 419–26.

6 Maguire A. Antimalarial nail pigmentation. *Lancet* 1963; **i**: 667–71.

7 Wise F, Sulzberger MB. Drug eruptions. *Arch Dermatol Syphilol* 1933; **27**: 549–67.

8 Ramelli G. Argyria. *Cutis* 1972; **10**: 155–9.

9 Goark SP, Hood AF, Nelson K. Nail pigmentation associated with zidovudine. *J Am Acad Dermatol* 1984; **5**: 1032–3.

10 Pratt CB, Shanks EC. Hyperpigmentation of the nails due to doxorubicin. *JAMA* 1974; **228**: 460.

11 Fisher BK, Warner LC. Cutaneous manifestations of AIDS. *Int J Dermatol* 1987; **16**: 615–30.

12 Panwalker A. Nail pigmentation in AIDS. *Ann Intern Med* 1987; **107**: 943–4.

13 Gallais V, Lacour JPh, Perrin C *et al*. Acral hyperpigmented macules and longitudinal melanonychia in AIDS patients. *Br J Dermatol* 1992; **126**: 387–91.

Yellow nail syndrome

The nails in yellow nail syndrome are yellow due to thickening, sometimes with a tinge of green possibly due to secondary infection. The lunula is obscured and there is increased transverse and longitudinal curvature and loss of cuticle (Fig. 65.14). Occasionally, there is chronic paronychia with onycholysis and transverse ridging [1]. The condition usually presents in adults, but may occur as early as the age of 8 years [2]. Although an autosomal dominant inheritance was initially suggested, detailed modern family trees suggest that it is not heritable [3]. Some of the clinical features may overlap with lichen planus [4], although the latter does not have the other systemic features normally seen in this syndrome. The features are usually accompanied by lymphoedema [5] at one or more sites and respiratory or nasal sinus disease. The nails grow at a greatly reduced rate: 0.1–0.25 mm/week for fingernails compared with the lowest normal rate of 0.5 mm/week. All 20 nails may be involved, although often a few are spared. Histologically, in the nail bed and matrix, dense fibrous tissue is found replacing subungual stroma, with numerous ectatic endothelium-lined vessels [6]. A foreign-body reaction has been noted [7]. It has been suggested that obstruction of lymphatics by this dense stroma leads to the abnormal lymphatic function found in the affected digits in some [8] but not all [9] cases.



Fig. 65.14 Yellow nail syndrome.

The oedema most frequently affects the legs, and may not be seen for some months after the nail change has been noted. Less often it affects the face or hands, and occasionally it is universal. In some instances the oedema has been shown to be due to abnormalities of the lymphatics, either atresia or, in some cases, varicosity [10]. Other cases have normal lymphatics, suggesting that a functional rather than an anatomical defect may be present [11], or perhaps only the smallest lymph vessels are defective. Although the nail changes may draw attention to the underlying lymphatic abnormality, they are found only in a minority of patients with congenital abnormality of the lymphatics. Recurrent pleural effusions have been noted in a few cases [12,13]. Chronic bronchitis and bronchiectasis may also occur [12]. The condition may be associated with an increased incidence of malignant neoplasms [10,14,15]. Other associations include D-penicillamine therapy [5] and nephrotic syndrome [16]. In hypothyroidism and AIDS [17] there may be yellow nails, but it is debatable whether these represent yellow nail syndrome or simply the discoloration of nail associated with retarded growth [18].

Although the nail changes, once established, are usually permanent, complete reversion to normal may occur spontaneously. Attempted treatments include oral [19] and topical [20] vitamin E, oral zinc [21] and treatment of chronic infection at other sites [22]. There is debate as to whether itraconazole is of value as treatment. The drug has been demonstrated to increase the rate of longitudi-

nal growth, but an open trial in eight patients demonstrated that half gained no benefit with respect to nail changes [23]. It is reported that results are better when itraconazole or fluconazole is combined with oral vitamin E [24].

References

1 Samman PD, White WF. The 'yellow nail' syndrome. *Br J Dermatol* 1964; **76**: 153–7.
2 Magid M, Esterly NB, Prendiville J, Fujisaki C. The yellow nail syndrome in an 8 year old girl. *Pediatr Dermatol* 1987; **4**: 90–3.
3 Hoque SR, Mansour S, Mortimer PS. Yellow nail syndrome: not a genetic disorder? Eleven new cases and a review of the literature. *Br J Dermatol* 2007; **156**: 1230–4.
4 Baran R. Lichen planus of the nails mimicking the yellow nail syndrome. *Br J Dermatol* 2000; **143**: 1117–8.
5 Ilchyshin A, Vickers CFH. Yellow nail syndrome associated with penicillamine therapy. *Acta Derm Venereol (Stockh)* 1983; **63**: 554–5.
6 De Coste SD, Imber MJ, Baden HP. Yellow nail syndrome. *J Am Acad Dermatol* 1990; **22**: 608–11.
7 Mallon E, Dawber RPR. Nail unit histopathology in the yellow nail syndrome. *Br J Dermatol* 1995; **133**(Suppl. 45): 55.
8 Fenton DA, Bull R, Gane J *et al*. Abnormal lymphatic function assessed by quantitative lymphoscintigraphy in the yellow nail syndrome. *Br J Dermatol* 1990; **123** (Suppl. 37): 32.
9 Ellis JP, Marks R, Pery BJ. Lymphatic function: the disappearance rate of ^{131}albumin from the dermis. *Br J Dermatol* 1970; **82**: 593–9.
10 Miller E, Rosenow EC, Olsen AM. Pulmonary manifestations of the yellow nail syndrome. *Chest* 1972; **61**: 452–8.
11 Bull RH, Fenton DA, Mortimer PS. Lymphatic function in the yellow nail syndrome. *Br J Dermatol* 1996; **134**: 307–12.
12 Emerson PA. Yellow nails, lymphoedema and pleural effusions. *Thorax* 1966; **21**: 247–53.
13 Dilley JJ, Kierland RR, Randall RV, Schick RM. Primary lymphoedema associated with yellow nails and pleural effusions. *JAMA* 1968; **203**: 670–3.
14 Burrows NP, Russell Jones R. Yellow nail syndrome in association with carcinoma of the gall bladder. *Clin Exp Dermatol* 1991; **16**: 471–3.
15 Stosiek N, Peters KP, Hiller D *et al*. Yellow nail syndrome in a patient with mycosis fungoides. *J Am Acad Dermatol* 1993; **28**: 792–4.
16 Cockram CS, Richards P. Yellow nails and nephrotic syndrome. *Br J Dermatol* 1979; **101**: 707–9.
17 Chernosky ME, Finley VK. Yellow nail syndrome in patients with AIDS. *J Am Acad Dermatol* 1985; **13**: 731–6.
18 Scher RK. Acquired immunodeficiency syndrome and yellow nails. *J Am Acad Dermatol* 1988; **18**: 758–9.
19 Ayres S, Mihan R. Yellow nail syndrome. Response to vitamin E. *Arch Dermatol* 1973; **108**: 267–8.
20 Williams HC, Buffham R, du Vivier A. Successful use of topical vitamin E solution in the treatment of nail changes in yellow nail syndrome. *Arch Dermatol* 1991; **127**: 1023–8.
21 Arroyo JF, Cohen ML. Yellow nail syndrome cured by zinc supplementation. *Clin Exp Dermatol* 1993; **18**: 62–4.
22 Pang SM. Yellow nail syndrome resolution following treatment of pulmonary tuberculosis. *Int J Dermatol* 1993; **32**: 605–6.
23 Tosti A, Piraccini BM, Iorizzo M. Systemic itraconazole in the yellow nail syndrome. *Br J Dermatol* 2002; **146**: 1064–7.
24 Baran R. The new oral antifungal drugs in the treatment of the yellow nail syndrome. *Br J Dermatol* 2002; **147**: 189–91.

Red lunulae

Erythema of all or part of the lunula may affect all digits, but most prominently the thumb. Erythema is less intense in the distal lunula, where it can merge with the nail bed or be demarcated by a pale line, and can be obliterated by pressure on the nail plate. The appearance can fade over a few days. A single report of histological features did not reveal any vascular or epidermal changes [1]. Dotted red lunulae have been reported in psoriasis and alopecia areata, but otherwise the list of associations is so broad that it is unconvincing [2].

The exception to this is a red lunula seen in a single digit. In this setting, it often indicates a local disturbance of vascular flow, which is most likely to be a benign tumour. Glomus tumours and subungual myxoid cysts are the most common [3] and the colour may vary between blue and red.

References

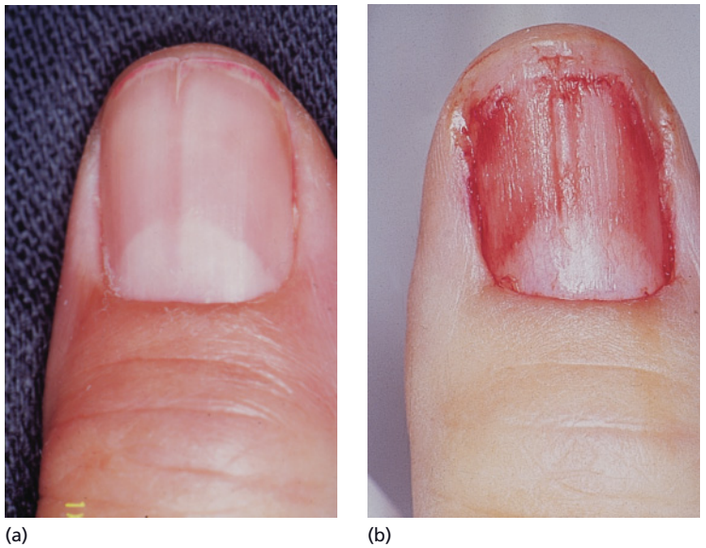
1 Cohen PR. Red lunulae: case report and review of the literature. *J Am Acad Dermatol* 1992; **26**: 292–4.
2 Wilkerson MG, Wilkin JK. Red lunulae revisited: a clinical and histopathologic examination. *J Am Acad Dermatol* 1989; **20**: 453–7.
3 de Berker D, Goettmann S, Baran R. Subungual myxoid cysts: clinical manifestations and response to therapy. *J Am Acad Dermatol* 2002; **46**: 394–8.

Longitudinal erythronychia (Fig. 65.15)

A longitudinal red streak in the nail can have several causes [1,2]. All will have a corresponding band of thinned nail plate as part of the defect. The effect of this is a strip where the nail bed is less compressed by the overlying nail so that blood pools and is more apparent. Equally, the colour is more easily seen because the nail is thinner in this line. Splinter haemorrhages may lie longitudinally within the erythronychia.

A strip of thinned nail arises because of focal reduction of matrix function. This can be due to direct matrix disease, such as an epidermal pathology, or as a result of pressure on the matrix with secondary loss of function. This second category contains the full range of dermal tumours as well as tumours of bone and cartilage that arise from the distal phalanx.

Matrix epidermal disease covers a spectrum of pathologies. The most common are lichen planus and Darier's disease, where thin longitudinal red streaks may terminate at the free edge with a split. In Darier's disease there may be a small subungual keratosis



(a) (b)

Fig. 65.15 (a) Longitudinal erythronychia. (b) The longitudinal ridge in the nail bed corresponds to the groove on the undersurface of the nail plate.

[3]. Acantholytic dyskeratotic naevus and warty subungual dyskeratoma [4] may both represent localized forms of Darier's disease. Acrokeratosis verruciformis of Hopf has a greater focus on nail fold disease, but also demonstrates longitudinal erythronychia and both clinical and pathological overlap with Darier's disease. In some instances there does not appear to be any primary disease to provide an explanation for multiple areas of erythronychia and in this setting the term 'idiopathic polydactylous erythronychia' has been suggested [5].

Baran has coined the term 'onychopapilloma' to describe the isolated, benign warty distal nail bed lesions found in association with longitudinal erythronychia where the diagnosis lies outside those described above [6]. The papilloma is a secondary element, given that it is found distally in the nail bed while the cause lies proximally within the matrix. However, there is a category of this disease where the matrix disease remains unclear and the distal papilloma represents the identifiable entity. At other times, despite a similar clinical presentation with erythronychia and splinter haemorrhages, the matrix pathology may reveal a specific alternative diagnosis such as Bowen's disease [6] or basal cell carcinoma [7]. This means that isolated longitudinal erythronychia needs careful assessment, and biopsy may be warranted if there is evolution.

Not all causes of longitudinal erythronychia conform to these rules. This is particularly the case where there are multiple red streaks associated with a dermatosis and additional nail changes. It can be a feature of lichenoid diseases of the nail unit, discoid lupus erythematosus, psoriasis, Langerhans' cell histiocytosis and a number of other diseases where there is patchy nail atrophy.

References

1 de Berker DA, Perrin C, Baran R. Localized longitudinal erythronychia: diagnostic significance and physical explanation. *Arch Dermatol* 2004; **140**: 1253–7.
2 Baran R, Perrin C. Localized multinucleate distal subungual keratosis. *Br J Dermatol* 1995; **133**: 77–82.
3 Zaias N, Ackerman AB. The nail in Darier–White disease. *Arch Dermatol* 1973; **107**: 193–9.
4 Baran R, Perrin C. Focal subungual warty dyskeratoma. *Dermatology* 1997; **195**: 278–80.
5 Baran R, Dawber RP, Perrin C, Drape JL. Idiopathic polydactylous longitudinal erythronychia: a newly described entity. *Br J Dermatol* 2006; **155**: 219–21.
6 Baran R, Perrin C. Longitudinal erythronychia with distal subungual keratosis: onychopapilloma of the nail bed and Bowen's disease. *Br J Dermatol* 2000; **143**: 132–5.
7 Gee BC, Millard PR, Dawber RP. Onychopapilloma is not a distinct clinicopathological entity. *Br J Dermatol* 2002; **146**: 156–7.

Splinter haemorrhages

Splinter haemorrhages represent longitudinal haemorrhages in the nail bed conforming to the pattern of subungual vessels [1–4]. They are most frequently seen in the distal nail bed and on the fingers of the dominant hand, reflecting trauma as the cause. In dermatological practice, they are often found in association with psoriasis, dermatitis and fungal infection of the nails. As they occur under so many conditions, their importance as a sign of disease is often exaggerated. Focal pathology may also represent a cause, as in longitudinal erythronychia and onychomatricoma (see pp. 65.17 and 65.32).

Large numbers of proximal haemorrhages with no obvious traumatic origin may indicate a systemic cause [5], such as bacterial endocarditis or antiphospholipid syndrome [6]. Unilateral splinter haemorrhages may arise after arterial catheterization on the involved side. Examination under oil or gel with a dermatoscope may reveal greater detail.

References

1 Heath D, Williams DR. Nail haemorrhages. *Br Heart J* 1978; **40**: 1300–5.
2 Kilpatrick ZM, Greenberg PA, Sanford JP. Splinter haemorrhages, their clinical significance. *Arch Intern Med* 1965; **115**: 730–5.
3 Monk BE. The prevalence of splinter haemorrhages. *Br J Dermatol* 1980; **103**: 183–5.
4 Young JB, Will EJ, Mulley GP. Splinter haemorrhages: facts and fiction. *J R Coll Phys Lond* 1988; **22**: 240–3.
5 Gross NJ, Tall R. Clinical significance of splinter haemorrhages. *BMJ* 1963; **ii**: 1496–8.
6 Ames DE, Asherson RA, Aynes B *et al*. Bilateral adrenal infarction, hypoadrenalism and splinter haemorrhages in the primary antiphospholipid syndrome. *Br J Rheumatol* 1994; **31**: 117–20.

Developmental abnormalities of the nails [1,2]

Congenital anonychia

Absence of the nails from birth is a rare congenital anomaly. It may occur as an isolated sign or be accompanied by other defects of the digits and other structures. In many of the affected families there is a mix of anonychia with hyponychia. In several pedigrees, mutations in the gene for R-spondin 4 have been identified, which play a part in the Wnt signalling pathway [3]. This has been shown to have significance in the early stages of nail embryogenesis, with expression of the signalling protein in the distal dorsal digit ridge which acts as a landmark for early nail unit formation. This is deficient in those with the mutation—with the implication that loss of signalling results in a failure of nail unit formation.

Anonychia with ectrodactylia [4] has been shown to be inherited as a dominant trait without sex linkage. In this condition, there is usually complete absence of the nails on the index and middle fingers, and when there is any nail on the thumb it is often present on the proximal lateral corners of the nail fold. On the ring fingers, the radial half of the nail is often absent, and the nail bed is also missing. In a minority of affected individuals there are striking and bizarre defects of the digits, sometimes restricted to one hand or foot. The defects usually take the form of absence of one or more digits. Two sisters in a sibship of five, whose parents were first cousins, are recorded as having rudimentary nails associated with congenital deafness. The parents showed neither abnormality [5]. Bart *et al*. [6] described a family with congenital absence of areas of skin, blistering of skin and mucous membranes, and absence or deformity of the nails, inherited as an autosomal dominant trait. It is now classified as a subtype of dominantly inherited dystrophic epidermolysis bullosa, with the responsible gene mapped to chromosome 3p [7]. Verbov [8] described a case with bizarre flexural pigmentation and anonychia, thought to be an autosomal dominant condition.

References

1 Juhlin L, Baran R. Hereditary and congenital nail disorders. In: Baran R, Dawber RPR, de Berker DAR, Haneke E, Tosti A eds. *Diseases of the Nails and Their Management*, 3rd edn. Oxford: Blackwell Science, 2001; 370–424.
2 Telfer NR, Barth JH, Dawber RPR. Congenital and hereditary nail dystrophies: an embryological approach to classification. *Clin Exp Dermatol* 1988; **13**: 160–3.
3 Blaydon DC, Ishii Y, O'Toole EA *et al*. The gene encoding R-spondin 4 *(RSPO4)*, a secreted protein implicated in Wnt signaling, is mutated in inherited anonychia. *Nat Genet* 2006; **38**: 1245–7.
4 Lees DH. Anonychia and ectrodactylia. *Ann Hum Genet* 1957; **22**: 69–71.
5 Feinmesser M, Zelig S. Anonychia and congenital deafness. *Arch Otolaryngol* 1962; **74**: 507–10.
6 Bart BJ, Gorlin RJ, Anderson E *et al*. Congenital localised absence of skin: associated abnormalities resembling epidermolysis bullosa. *Arch Dermatol* 1966; **93**: 296–304.
7 Zelickson B, Matsumara K, Kist D *et al*. Bart's syndrome. *Arch Dermatol* 1995; **131**: 663–8.
8 Verbov J. Anonychia with bizarre flexural pigmentation: an autosomal dominant dermatosis. *Br J Dermatol* 1975; **92**: 469–74.

Nail–patella syndrome

This uncommon condition is of special interest because it involves abnormalities of ectodermal and mesodermal structure. It is inherited as an autosomal dominant trait. The disorder is caused by mutations in the LIM-homeodomain transcription factor β1 protein (LMX1B). This protein plays an important role in dorsoventral limb patterning during embryogenesis [1]. Gradients of expression of the protein determine the dominance of dorsal or ventral axon growth with concomitant trophic effects on mesoderm and ectoderm [2]. The gene maps to chromosome 9q34.1, with affected families showing a wide range of deletions and mutations [3]. In a typical case, the nails are grossly defective, being only one-third or half the normal size and never reaching the free edge of the finger [4]. In other cases, the thumbnails alone may be defective or only the ulnar half of each may be missing [5]. In every case, the thumbnails are most affected [6] and the remaining nails, if involved, are progressively less damaged from index to little finger. The lunulae may be triangular, with a distal peak (Fig. 65.16) in the midline [7]. Missing dorsal creases of distal finger joints is also a diagnostic clue of nail–patella syndrome [8]. Even when the nail is completely missing, the nail bed is present. In addition to the nail changes, the patellae are smaller than normal and may be rudimentary, so that the knees are unstable. There are also bony spines arising from the posterior aspect of the iliac bones, visible on X-ray examination.

Other recorded features include hyperextension of the joints, skin laxity, hyperhidrosis [9], renal abnormalities [10,11], and open angle glaucoma. LMX1B is known to influence transcription of genes affecting collagen IV in the glomerular basement membrane [12].

In 1965, there were 255 patients with this syndrome known to be living in the UK. The mutation rate is estimated at 1 per 1.9 million alleles per generation [13].

Screening entails examination of knee, hip and elbow X-rays for characteristic changes, renal assessment and measurement of intraocular pressures in case of glaucoma. Once the diagnosis is established, the last two aspects should be reviewed annually. The condition must be distinguished from congenital ectodermal defects and pachyonychia congenita.



Fig. 65.16 Nail–patella syndrome with triangular lunula.

References

1 McIntosh I, Dunston JA, Liu L et *al*. Nail patella syndrome revisited: 50 years after linkage. *Ann Hum Genet* 2005; **69**: 349–63.
2 Chen H, Lun Y, Ovchinnikov D *et al*. Limb and kidney defects in Lmx1b mutant mice suggest an involvement of LMX1B in human nail patella syndrome. *Nat Genet* 1998; **19**: 51–5.
3 Dreyer SD, Zhou G, Baldini A *et al*. Mutations in LMX1B cause abnormal skeletal patterning and renal dysplasia in nail patella syndrome. *Nat Genet* 1998; **19**: 47–50.
4 Renwick JH, Izatt MM. Some genetic parameters of the nail–patella locus. *Ann Hum Genet* 1965; **28**: 369–78.
5 Levan NE. Congenital defect of thumbnails. *Arch Dermatol Syphilol* 1961; **83**: 938–40.
6 Guidera KJ, Satterwhite Y, Ogden JA *et al*. Nail patella syndrome: a review of 44 orthopaedic patients. *J Paediatr Orthop* 1991; **11**: 737–42.
7 Daniel CR, Osment LS, Noojin RO. Triangular lunulae: a clue to nail patella syndrome. *Arch Dermatol* 1980; **116**: 448–9.
8 Itin PH, Eich G, Fistarol SK. Missing creases of distal finger joins as a diagnostic clue of nail-patella syndrome. *Dermatology* 2006; **213**: 153–5.
9 Pechman KJ, Bergfield WF. Hyperhidrosis in nail–patella syndrome. *J Am Acad Dermatol* 1980; **3**: 627–30.
10 Ben Bassat M. The glomerulo-basement membrane in nail–patella syndrome. *Arch Pathol* 1971; **92**: 350–5.
11 Goodman RM. Hereditary congenital deafness with onychodystrophy. *Arch Otolaryngol* 1959; **90**: 474–7.
12 Morello R, Zhou G, Dreyer SD *et al*. Regulation of glomerular basement membrane collagen expression by LMX1B contributes to renal disease in nail patella syndrome. *Nat Genet* 2001; **27**: 205–8.
13 Renwick JH, Lawler SD. Genetic linkage between the ABO and nail–patella loci. *Ann Hum Genet* 1955; **19**: 312–31.

Congenital onychodysplasia of the index fingers [1,2]

Synonym
- Iso-Kikuchi syndrome

In this condition, the nail of the index finger is absent, small or represented by two nails of unequal size. There may be a family history suggestive of autosomal dominant inheritance, although there is frequently no clear genetic pattern, and involvement of other digits has been reported [1,3,4]. Underlying changes in the distal phalanx can usually be demonstrated by lateral radiography, where bifurcation of the distal phalanx is the norm [4]. Syndactyly is an associated hand anomaly in some cases [2].

Variants include a similar form of onychodysplasia affecting other digits, including toes [5].

References

1 Baran R. Syndrome d'Iso Kikuchi (COIF syndrome): 2 cas avec revue de la litérature. *Acta Derm Venereol (Stockh)* 1980; **107**: 431–5.
2 Miura T, Nakamura R. Congenital onychodysplasia of the index fingers. *J Hand Surg* 1990; **15A**: 793–7.
3 Kikuchi I, Horikawa S, Amano F. Congenital onychodysplasia of the index fingers. *Arch Dermatol* 1974; **110**: 743–6.
4 Kikuchi I. Congenital onychodysplasia of the index fingers: a case involving the thumb nails. *Semin Dermatol* 1991; **10**: 7–11.
5 Youn SH, Kwon OS, Park KC *et al*. Congenital onychodysplasia of the index fingers: Iso-Kikuchi syndrome. A case involving the second toenail. *Clin Exp Dermatol* 1996; **21**: 457–8.

Pachyonychia congenita (Fig. 65.17)

Pachyonychia congenita (PC) is a rare, autosomal dominant genodermatosis in which hypertrophy of the nails occurs, in some cases associated with nail bed and hyponychial hyperkeratosis [1,2]. A recessive form has been reported [3].

The two variants of PC arise through mutations affecting the genes encoding keratins 6a and 16 in PC-1 [4,5] and 6b and 17 in PC-2 [6,7]. In some instances, onset can be delayed into adult life and be more subtle in appearance. This is designated PC tarda [8].



Fig. 65.17 Pachyonychia congenita.

PC-1 (Jadassohn–Lewandosky type). The nails are normal at birth but within months they become discoloured and progressively thicken, more so on the hands than feet. Typical associated findings include palmar and plantar hyperkeratosis and warty skin lesions at various sites: knees, elbows, buttocks, legs, ankles and popliteal region. Acral bullae may be crippling and hyperhidrosis may be severe. Mouth and corneal dyskeratosis are less common findings.

PC-2 (Jackson–Lawler type). In this type, with less severe nail thickening and keratoses than type 1, many associations have been described: teeth may be present at birth; multiple epidermal cysts; sebocystomatosis; dry, lustreless and kinky scalp hair; eyebrows that stand straight out; and hamartomas.

The thickened nails can be treated surgically in some instances [9]. This is most likely to be warranted in PC-1. The localization of the four implicated keratins to the nail bed underlines that this is the main site of pathology [10]. Affected nails viewed end-on can appear almost normal, but with a dense wedge of subungual keratin, representing the focus of nail bed disease.

A range of associated features have been reported, including amyloidosis in one pedigree [11] and a case where PC coincided with tuberous sclerosis [12]. Treatments are based on focal complaints such as ingrowing or paronychia. There are no established therapies [13].

References

1 Leachman SA, Kaspar RL, Fleckman P *et al*. Clinical and pathological features of pachyonychia congenita. *J Invest Dermatol Symp Proc* 2005; **10**: 3–17.
2 Smith FJ, Liao H, Cassidy AJ *et al*. The genetic basis of pachyonychia congenita. *J Invest Dermatol Symp Proc* 2005; **10**: 21–30.
3 Haber RM, Rose TH. Autosomal recessive pachyonychia congenita. *J Am Acad Dermatol* 1986; **122**: 919–23.
4 Bowden PE, Haley JL, Kansky A *et al*. Mutation of a type II keratin gene (K6a) in pachyonychia congenita. *Nat Genet* 1995; **10**: 363–78.
5 McLean WHI, Rugg EL, Lunny DP *et al*. Keratin 16 and keratin 17 mutations cause pachyonychia congenita. *Nat Genet* 1995; **9**: 273–8.
6 Smith FJD, Jonkman MF, van Goor H *et al*. A mutation in human keratin K6b produces a phenocopy of the K17 disorder pachyonychia congenita type 2. *Hum Mol Genet* 1998; **7**: 1143–8.
7 Covello SP, Smith FJD, Sillevis Smitt JH *et al*. Keratin 17 mutations cause either steatocystoma multiplex or pachyonychia congenita type 2. *Br J Dermatol* 1998; **138**: 475–80.
8 Hannaford RS, Stapleton K. Pachyonychia congenita tarda. *Australas J Dermatol* 2000; **41**: 175–7.
9 Thomsen RJ, Zuehlke RL, Beckman BL. Pachyonychia congenita. Surgical management of the nail changes. *J Dermatol Surg Oncol* 1982; **8**: 24–8.
10 de Berker D, Wojnarowska F, Sviland L *et al*. Keratin expression in the normal nail unit: markers of regional differentiation. *Br J Dermatol* 2000; **142**: 89–96.
11 Tidman MJ, Wells RS, MacDonald DM. Pachyonychia congenita with cutaneous amyloidosis and hyperpigmentation: a distinct variant. *J Am Acad Dermatol* 1987; **16**: 935–40.
12 Sharma VK, Sharma R, Kaus S. Pachyonychia congenita with tuberous sclerosis. *Int J Dermatol* 1989; **28**: 332–3.
13 Milstone LM, Fleckman P, Leachman SA *et al*. Treatment of pachyonychia congenita. *J Invest Dermatol Symp Proc* 2005; **10**: 18–20.

Infections of the nail and nail folds

Fungal nail infections

See Chapter 36.

Paronychia

Bacterial paronychia

Acute paronychia is a common complaint usually due to staphylococcal infection. It may result from local injuries, splits, splinters or nail biting. It also occurs frequently as a complication of chronic paronychia, when other organisms may be involved, including streptococci, *Pseudomonas pyocyanea*, coliform organisms and *Proteus vulgaris*.

The condition presents as a painful swelling of the nail fold. If superficial it may point close to the nail and can easily be drained by incision with a size 11 scalpel, without anaesthesia [1]. Deeper lesions are best treated by antibiotics initially, but if they do not improve within 2 days, incision under local anaesthesia is required, particularly in childhood. A broad-spectrum antibiotic is preferred because it is unlikely that the organisms can be identified in advance. Some authorities recommend removing the proximal one-third of the nail plate without initial incisional drainage. This gives more rapid relief and more sustained drainage. There may be a place for treatment with topical steroid at the same time as antibiotic therapy [2].

References

1 Keyser JJ, Littler JW, Eaton RG. Surgical treatment of infections and lesions of the perionychium. *Hand Clin* 1990; **6**: 137–53.

2 Wollina U. Acute paronychia: comparative treatment with topical antibiotic alone or in combination with corticosteroid. *J Eur Acad Dermatol Venereol* 2001; **15**: 82–4.

Chronic paronychia

This is an inflammatory dermatosis of the nail folds, with secondary effects on the nail matrix, nail growth and soft-tissue attachments. It may be associated with infection on the background of the dermatosis. The dermatosis may be directly due to an irritant associated with wet work or caustic materials. Alternatively, it may be on the background of atopy or psoriasis, where minor provocation can result in active disease.

Wet, cold hands are predisposed to chronic paronychia [1,2]. Wet foods are a combined source of factors, where the food may be an irritant [3]. It is predominantly a disease of domestic workers, bar staff, canteen workers and fishmongers [4]. The majority of cases are in patients between 30 and 60 years of age [1], although chronic paronychia is also seen in children, especially as a result of finger- or thumb-sucking [5].

Any finger may be involved, most often the index and middle fingers of the right hand and the middle finger of the left [4]. These fingers may be more subject to minor trauma than the remainder. The condition begins as a slight swelling at the base of one or more nails (Fig. 65.18), which is tender but much less so than in acute paronychia. The cuticle is soon lost and pus may form below the nail fold. Inflammation adjacent to the matrix disturbs nail growth, resulting in irregular transverse ridges and other surface irregularities, which may be combined with discoloration (Fig. 65.18).



Fig. 65.18 Chronic paronychia with nail plate discoloration due to *Pseudomonas pyocyanea*.

There is some evidence that the darkening is due to the pigment from *Pseudomonas* infection of the nail [6]. In long-standing cases, the size of the nail may be reduced, and this reduction is exaggerated by bolstering of the fold all around the nail. Most of the nail deformity is due to the inflammation interfering with the formation of the nail, but a true *Candida* infection of the nail plate is occasionally seen.

There is a complex relationship with *Candida*, usually *Candida albicans* [7], which may be identified by swabs or scraping. Stone and Mullins [8] showed that chronic paronychia can be produced by non-viable *C. albicans* introduced into a relatively sterile nail fold. Much of the chronic inflammation seen in this disorder probably arises from an irritant reaction to material sequestered beneath the proximal nail fold. The loss of the cuticle means that detergent and other solvents may gain access to this tight space and act like a prolonged irritant patch test. This chronic, non-infective, inflammatory component is why topical steroids are useful in addition to antimicrobials as part of the treatment [9]. Acute exacerbations occur from time to time and are due to secondary bacterial infection. Various organisms may be found, including *Staphylococcus aureus* or *albus*, *Proteus vulgaris*, *Escherichia coli* and *Pseudomonas pyocyanea*. Barlow *et al*. [9] consider that *S. aureus* plays a more active part in initiating the process by penetrating the keratin at the base of the nail and opening up the nail fold. The role of *S. aureus* as a superantigen may also be relevant. Ingested allergens may also play a part [10].

Pemphigus [11] and squamous cell carcinoma [12] can present as chronic paronychia. The latter usually involves a single digit, and underlines the need for biopsy in isolated periungual

conditions where the diagnosis is unclear. Cancer chemotherapy, antiretroviral medication and retinoids can provoke acute paronychia with features of pyogenic granuloma, which may become chronic.

Treatment. Treatment is a combination of avoidance of precipitants, hand care and medication. Perhaps the most important part of the treatment, but the one most difficult to achieve, is to keep the hands dry. For all wet work the patient should be advised to wear cotton gloves under rubber or plastic gloves and avoid manicure of the proximal nail folds. Covering the affected fingers with porous surgical tape may afford some protection, but normal occlusion aggravates the problem. General hand care with emollient and protection during rough work is useful. If this stage of the therapy is not adequately pursued, the condition is likely to fail to settle whatever medical treatment is provided.

Topical therapy requires a combination of steroid [13] and antimicrobial. A potent steroid may be used for short periods when there is adequate antimicrobial cover. Injected triamcinolone (2.5 mg/mL) is useful in some instances. Topical imidazoles are usually sufficient to treat *Candida* and may provide a modest therapy against some bacteria. More potent topical antibacterials may be needed. Barlow *et al*. [9] suggest using gentamicin ointment during the day and nystatin ointment at night. When features are marked, oral antibiotics appropriate for *S. aureus* should be used. Because of the 'mixed' aetiology of the inflammation, many clinicians use antiseptic or antibiotic/anti-*Candida*/steroid creams in the chronic phase.

Incision is not indicated unless the condition enters an acute tender purulent phase, where removal of the proximal third of the nail may help. Attempting to clean out the nail fold with a sharp instrument is not recommended. If there is obvious candidal infection elsewhere, or *Candida* onychomycosis, this should be treated. Surgical removal of the proximal nail fold and adjacent part of the lateral nail folds may cure recalcitrant cases [14].

In societies in which mechanical dishwashers and washing machines have become common household appliances, chronic paronychia is now rarely encountered.

References

1 Esteves J. Chronic paronychia. *Dermatologica* 1959; **119**: 229–31.
2 Hellier FF. Chronic paronychia: aetiology and treatment. *BMJ* 1955; **ii**: 1358–60.
3 Tosti A, Buerra L, Mozelli R *et al*. Role of food in the pathogenesis of chronic paronychia. *J Am Acad Dermatol* 1992; **27**: 706–10.
4 Frain-Bell W. Chronic paronychia. Short review of 590 cases. *Trans St John's Hosp Dermatol Soc* 1957; **38**: 29–35.
5 Stone OJ, Mullins JF. Chronic paronychia in childhood. *Clin Pediatr* 1968; **7**: 104–7.
6 Samman PD. Management of disorders of the nails. *Clin Exp Dermatol* 1982; **7**: 189–94.
7 Marten RH. Chronic paronychia: a mycological and bacteriological study. *Br J Dermatol* 1959; **71**: 422–6.
8 Stone OJ, Mullins JF. Role of *Candida albicans* in chronic disease. *Arch Dermatol* 1965; **91**: 70–2.
9 Barlow AJE, Chattaway FW, Holgate ML *et al*. Chronic paronychia. *Br J Dermatol* 1970; **82**: 448–53.
10 Zaias N. *The Nail in Health and Disease*. Stanford, NJ: Appleton & Lange, 1990.
11 Engineer L, Norton LA, Ahmed AR. Nail involvement in pemphigus vulgaris. *J Am Acad Dermatol* 2000; **43**: 529–35.
12 Betti R, Vergani R, Inselvini E, Tolomio E, Crosti C. Guess what! Subungual squamous cell carcinoma mimicking chronic paronychia. *Eur J Dermatol* 2000; **10**: 149–50.
13 Tosti A, Piraccini BM, Ghetti E, Colombo MD. Topical steroids versus systemic antifungals in the treatment of chronic paronychia: an open, randomized double-blind and double dummy study. *J Am Acad Dermatol* 2002; **47**: 73–6.
14 Baran R, Bureau H. Surgical treatment of recalcitrant chronic paronychias of the fingers. *J Dermatol Surg Oncol* 1981; **7**: 106–9.

Pseudomonas infection

This is almost always a complication of onycholysis or chronic paronychia and is usually restricted to one or two nails (see Fig. 65.18). The nail plate has a characteristic bluish-black or green colour [1–3] due to accumulation of debris beneath the nail and the pigment pyocyanin adhering to the undersurface of the nail plate. Pigment may remain after the organism has been removed. In some cases, the nail plate appears to be invaded by the bacillus [2]. Subjects with nail extensions and nail wraps are susceptible to *Pseudomonas* colonization beneath the extensions. This has been documented as a risk factor for passing infection to patients in the medical setting [4]. Treatment [5] is as described for onycholysis or paronychia, whichever appears to be the prominent predisposing state. In addition, it is possible to treat with gentamicin or sulfacetamide (sulphacetamide) eye drops to eradicate the colonization where onycholysis is resistant to therapy. Once treated, if the onycholysis persists, prevention of further *Pseudomonas* infection can be achieved with nightly soaks of the finger tips in dilute hypochorite solution (Milton™) or vinegar.

References

1 Bauer MF, Cohen BA. The role of *Pseudomonas aeruginosa* infections about the nails. *Arch Dermatol* 1957; **75**: 394–6.
2 Chernosky ME, Dukes CD. Green nails: importance of *Pseudomonas aeruginosa* in onychia. *Arch Dermatol* 1963; **88**: 548–53.
3 Goldman L, Fox H. Greenish pigmentation of nail plates from *Bacillus pyocyaneus*. *Arch Dermatol* 1944; **49**: 136–7.
4 Foca M, Jakob K, Whittier S *et al*. Endemic *Pseudomonas aeruginosa* infection in a neonatal intensive care unit. *N Engl J Med* 2000; **343**: 695–700.
5 Samman PD. Topical sulphacetamide for onycholysis. *Clin Exp Dermatol* 1982; **7**: 189–90.

Herpetic paronychia [1,2]

Synonym
- Herpetic whitlow

This uncommon condition is due to primary inoculation of the herpes simplex virus and presents as single or grouped blisters close to the nail; it may give a honeycomb appearance. Clear at first, the blisters soon become purulent and may break and be replaced by crusts. It is usually very painful and takes about 3 weeks to resolve, with pain settling in half that time. Lymphangitis sometimes occurs and may precede vesiculation. Diagnosis may be established by recovering the virus from a recent blister and by cytological examination of the blister floor. Contact cases may occur.

Treatment probably does little to shorten the course of the disorder, but cleaning with 1/6000 potassium permanganate followed by application of a bland cream is recommended. Relapse may occur as with other primary herpetic infections. The value of

thymidine analogues, such as oral aciclovir, famciclovir and valaciclovir, is unproven, but use for other forms of recurrent herpes suggests that they might be useful in shortening the duration and severity of an episode.

Numbness of the finger has been reported following infection [1], and persistent lymphoedema may occur. Persistent cases may have an atypical presentation in patients with HIV infection [3].

References

1 Chang T, Gorbach SL. Primary and recurrent herpetic whitlow. *Int J Dermatol* 1977; **16**: 752–4.
2 Stern H, Elek SD, Millar DM *et al*. Herpetic whitlow: cross-infection in hospitals. *Lancet* 1958; **ii**: 871–4.
3 Robayna MG, Herranz P, Rubio FA *et al*. Destructive herpetic whitlow in AIDS: report of three cases. *Br J Dermatol* 1997; **137**: 812–5.

HIV infection

The most common nail changes in individuals with HIV infection are clubbing, transverse lines, onychoschizia, leukonychia and longitudinal melanonychia [1]. In addition, there is a lower threshold for infection with dermatophytes, yeasts, human papillomavirus and herpesvirus [1]. Severe scabies infection, in the form of crusted scabies, is more common in HIV infection, with chronic paronychia and subungual hyperkeratosis [2]. Proximal subungual white fungal infection is said to be a pointer to HIV infection [3]. There may be erythema of the proximal nail folds [4], and paronychia may occur during antiretroviral therapy [5]. The nail can also manifest various patterns of melanonychia, which is usually ascribed to zidovudine therapy [6] but has also been attributed to hydroxycarbamide (hydroxyurea) [7].

Terbinafine is effective for most dermatophyte onychomycosis in HIV infection [8].

References

1 Cribier B, Mena ML, Rey D *et al*. Nail changes in patients infected with human immunodeficiency virus. A prospective controlled study. *Arch Dermatol* 1998; **134**: 1216–20.
2 Fuchs BS, Sapadin AN, Phelps RG, Rudikoff D. Diagnostic dilemma: crusted scabies superimposed on psoriatic erythroderma in a patient with acquired immunodeficiency syndrome. *Skinmed* 2007; **6**: 142–4.
3 Gupta AK, Taborda P, Taborda V *et al*. Epidemiology and prevalence of onychomycosis in HIV-positive individuals. *Int J Dermatol* 2000; **39**: 746–53.
4 Itin PH, Gilli L, Nüesch R *et al*. Erythema of the proximal nail fold in HIV-infected patients. *J Am Acad Dermatol* 1996; **35**: 631–3.
5 Tosti A, Piraccini BM, D'Antuono A *et al*. Paronychia associated with antiretroviral therapy. *Br J Dermatol* 1999; **140**: 1165–8.
6 Bendick C, Heinrich R, Steigleder GK. Azidothymidine induced pigmentation of skin and nails. *Arch Dermatol* 1989; **125**: 1285–6.
7 Laughon SK, Shinn LL, Nunley JR. Melanonychia and mucocutaneous hyperpigmentation due to hydroxyurea use in an HIV-infected patient. *Int J Dermatol* 2000; **39**: 928–31.
8 Cribier BJ, Bakshi R. Terbinafine in the treatment of onychomycosis: a review of its efficacy in high-risk populations and in patients with nondermatophyte infections. *Br J Dermatol* 2004; **150**: 414–20.

Dermatoses affecting the nails

Psoriasis

Psoriatic dystrophy is probably the most common disorder affecting fingernails. Between 1.5 and 3% of the population have psoriasis, and up to 50% of psoriatics have nail involvement [1]. Over a lifetime, this may cumulatively increase to 80–90% [2]. In children, nail involvement ranges from 7% [3] to 39% [4], and pitting has been observed in the first week of life in the offspring of a mother severely affected with psoriasis [5]. Psoriatic nail changes are prominent in the childhood nail disease of parakeratosis pustulosa. Approximately one-third of these children will develop other features of psoriasis in time, a smaller fraction will have variants of eczema and half of the total will get better [6]. De Jong *et al*. [7] reported that 93% of those with nail psoriasis considered it a significant cosmetic handicap, 58% found that it interfered with their job and 52% described pain as a symptom.

Clinical features. In order of reducing frequency, nail signs of psoriasis include pits, onycholysis, subungual hyperkeratosis, nail plate discoloration, uneven nail surface, splinter haemorrhages, acute and chronic paronychia, and transverse midline depressions in the thumbnails. These features can be recorded using a Nail Psoriasis Severity Index (NAPSI), which can be of value in trials of drug treatment [8]. Baran's nail psoriasis severity index has also been validated by a Polish team [9,10].

Pits. Pits more commonly affect fingers than toes (Fig. 65.19). They represent punctate surface depressions arising from proximal matrix disease (Table 65.3). Zaias [1,11] has demonstrated small columns of pathological parakeratotic nail falling off the upper surface of the nail plate to produce a pit. Some authorities advocate nail plate histology as a means of diagnosing nail psoriasis [12]. This can be useful for exclusion of fungal infection, although the specificity of nail plate changes in psoriasis is yet to be established. The origin of pits means that they can be influenced by disease in the proximal nail fold and it is thought that injection of triamcinolone into the nail fold alone can suppress this

Table 65.3 Relationship between clinical features and site of disease activity in psoriasis of the nail. (From Zaias [1].)

Clinical feature	Area of disease	Duration of disease
Changes in nail plate	*Matrix*	
Pits	Proximal matrix	Episodic: short
Transverse furrows	Proximal matrix; distal extension depends on depth of furrow	1–2 weeks
Crumbling nail plate	Entire matrix	Prolonged
Leukonychia with rough surface	Proximal matrix; leukonychia may involve distal matrix	Variable
Changes in nail bed and hyponychium	*Nail bed*	
Splinter haemorrhages	Nail bed dermal ridge haemorrhage	Short
Oily spot/onycholysis	Nail bed psoriasis	Prolonged
False nail following onychomadesis	Nail bed psoriasis	Prolonged
Subungual hyperkeratosis	Nail bed psoriasis	Prolonged
Yellow/ green discoloration of nail bed	Secondary infection by yeasts or *Pseudomonas*	Prolonged

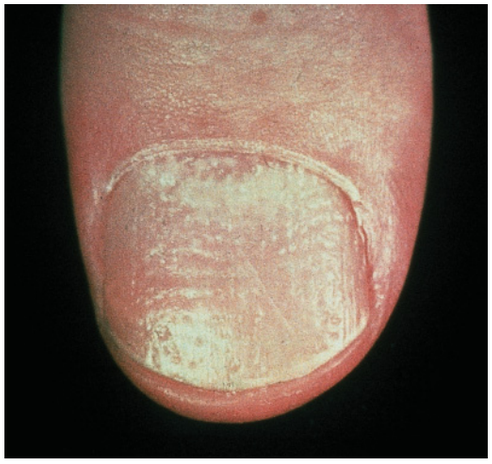


Fig. 65.19 Psoriasis: diffuse pitting.



Fig. 65.20 Psoriasis: onycholysis.

clinical feature. The pattern of pitting may be disorganized or occur in transverse/ longitudinal rows as seen in alopecia areata [2]. Pits may be shallow or large [11], to the point of leaving a punched-out hole in the nail plate (elkonyxis).

Onycholysis. Focal nail bed parakeratosis produces an 'oily spot' or 'salmon patch'. Extension of this area to the free edge produces onycholysis, which typically has a reddish-brown margin. Alternatively, onycholysis may commence at the distal edge (Fig. 65.20), representing disruption of the onychocorneal band [13]. Once this band of firm attachment has been breached, the condition is often progressive. Minor manicure, wet work and leverage from long nails exacerbate the condition.

Discoloration. Discoloration in psoriasis is multifactorial. The major factors are nail thickening and subungual hyperkeratosis. Both of these contribute to a yellow appearance, particularly common in the toes. It is possible that at this site repeated trauma elicits the isomorphic reaction (Köbner phenomenon), with local exacerbation of psoriasis. The coincidence of onychomycosis and psoriasis is also seen in the toenails [14] and can add to the pathological appearance. *Candida* spp. and *Pseudomonas* infection can result in green discoloration. While non-dermatophytes and bacteria are common, dermatophytes are rare [1].



Fig. 65.21 Psoriasis: subungual hyperkeratosis.

Subungual hyperkeratosis. Subungual hyperkeratosis represents nail bed disease (Fig. 65.21). Substantial nail plate thickening may result from subungual hyperkeratosis, which is most marked distally and extends proximally. The fingertip may become very tender where there is gross subungual hyperkeratosis, as the nail plate attachment is greatly reduced and the nail can easily be caught and tug on the matrix attachment. Subungual hyperkeratosis is a prominent feature when pityriasis rubra pilaris affects the nail and is often accompanied by splinter haemorrhages [14,15].

Nail plate abnormalities. Splits, atrophy and fragility may be seen. The nail may also thicken, independent of subungual hyperkeratosis. Transverse midline depressions resembling the nail changes seen in 'washboard nails' [16] are also seen. Usually, these are a consequence of the habit tic of picking the cuticle (Fig. 65.22) and, although this may play a part in psoriasis, it appears that there is a lower threshold for the development of this midline feature in the presence of psoriasis.

Splinter haemorrhages. Splinter haemorrhages are seen in the nail bed of 42% of fingernails and 6% of toenails [17]. This may be due to the increased capillary prominence and fragility in nail bed dermis in psoriasis and the presence of dystrophy. Where trans-



Fig. 65.22 Multiple transverse grooves of the thumbnails.

verse overcurvature occurs for reasons other than psoriasis, splinter haemorrhages are also common, suggesting that mechanical factors may contribute to splinter haemorrhage formation.

Subacute and chronic paronychia. Periungual involvement may be dramatic and inflammatory, giving rise to gross disruption of nail matrix. Loss of the nail may follow, with scaling of the nail bed or a deep transverse furrow.

Chronic psoriatic paronychia causes loss of the cuticle. The nail plate can become thin [18], although this may be offset by matrix disease, which can result in thickened nail. The nail fold may be scaly, in the form of psoriasis seen elsewhere.

Acropustulosis. This form of psoriasis involves destructive pustulation of the nail unit. It may present as part of pustular psoriasis, palmoplantar pustulosis [19], acrodermatitis continua of Hallopeau [20] or parakeratosis pustulosa (typically in young girls) on isolated digits. The nail plate may be lifted off by sterile pustules in the nail bed and matrix. There is associated erythema and discomfort of the end of the digit. There may be long-term nail loss, except in parakeratosis pustulosa, which usually resolves spontaneously. Parakeratosis pustulosa may affect only part of one digit—there is pitting and ridging combined with fine scaling erythema of the periunguium and only very rarely pustules. It is usually interpreted as a form of psoriasis [6], although it shares histological features with eczema [21], and some consider it a variant of eczema [22].

Acrodermatitis continua of Hallopeau can be very aggressive and result in resorptive osteolysis [23] or loss of toes and distal parts of fingers [24]. In a study of 20 patients with the condition, seven were male and 13 female, with a mean age of 46 years, and all had involvement of only one digit, with no features of psoriasis elsewhere [25].

Differential diagnosis. When the diagnosis of psoriatic nail dystrophy is in doubt, the main differential diagnoses are onychomycosis and lichen planus. In onychomycosis, the features usually present in the toes, whereas the fingernails are more commonly affected in psoriasis. Equally, there are often changes on the nail surface alone in psoriasis, whereas in onychomycosis features are usually within or beneath the nail plate. If there is fingernail involvement in onychomycosis, it is usually of only one or a minority of digits, in contrast with psoriasis where there are usually several digits affected.

Some forms of fingernail lichen planus and psoriasis are very difficult to distinguish. Both may result in roughened nails (trachyonychia) with subungual hyperkeratosis. If pits are prominent the diagnosis of psoriasis can be made, but if they are subtle and difficult to distinguish from other surface changes, they may be part of lichen planus. The nails in Reiter's disease and pityriasis rubra pilaris can also be difficult to distinguish from psoriasis [26,27], where distal subungual hyperkeratosis and splinter haemorrhages are common [8]. Aggressive forms of atypical nail psoriasis presenting in later life may represent acrokeratosis paraneoplastica. The patient is usually male, with subungual hyperkeratosis and scaling of the periunguium, ears and nose associated with malignancies of the upper gastrointestinal or respiratory tract [28–30].

Arthritis of the distal interphalangeal joint suggests a psoriatic cause of any associated dystrophy [31], with the exception of changes due to a myxoid pseudocyst associated with adjacent osteoarthritis. Baker *et al*. [32] found that there was no strict relationship between which joints are arthritic and which nails are dystrophic, although Jones *et al*. [33] noted that in a group of 100 psoriatics with arthritis, where there was nail involvement there was a significantly greater chance of joint disease in the adjacent distal interphalangeal joint. There was also a significant correlation between PASI (Psoriasis Area and Severity Index) score and scoring of nail disease, and nail disease increased with the duration of psoriasis. A variant of nail psoriasis presents with pain and soft-tissue swelling of the distal part of the digit associated with psoriatic nail changes, and underlying bone erosion and periosteal reaction. This can be in the absence of joint involvement and has been termed 'psoriatic onycho-pachydermo-periostitis' [34].

Histopathology. Histopathology varies according to the clinical focus of the disease [1,35]. The matrix and nail bed develop a granular layer, whereas the hyponychium, where a granular layer is normally present, no longer has one [1]. Where there is subungual hyperkeratosis, there are mounds of parakeratotic keratinocytes beneath the nail plate. Neutrophils may be found throughout these mounds and Munro microabscesses may form. Similar features are seen in acrodermatitis continua of Hallopeau [25]. Amorphous material, interpreted as glycoprotein, may accumulate within the keratotic mass [1]. Acanthosis and elongation of the rete ridges are present, with dilatation and tortuosity of the capillaries of the dermal papillae. Where the nail is lost, the nail bed may form a false nail of compacted hyperkeratosis [36]. The matrix can become quiescent, which can be demonstrated immunohistochemically by the absence of synthesis of the hard keratin Ha-1, which is normally a major constituent of nail [37].

The nail plate may show faults, clinically manifest as transverse splits and pits, which are lined with parakeratotic cells. These probably originate from the most proximal part of the matrix, or the ventral aspect of the proximal nail fold [1].

Treatment [38–40]. General hand care is important to avoid provocation of the isomorphic (Köbner) response, whereby minor trauma may elicit psoriasis. These measures include avoiding manicure, keeping the nails short, wearing gloves for wet work and heavy or greasy manual work, avoiding direct exposure to solvents and encouraging emollient usage. Concealment with nail lacquer is a reasonable approach to milder forms of psoriasis, and surface irregularities can be smoothed by the use of nail gel. This is a polymer, applied by a beautician and hardened by exposure to a table-top UVA source. The gel can then be shaped and buffed. Gel or other forms of sculptured or adherent artificial nails have the potential for aggravating onycholysis and are not usually recommended if this is a prominent feature.

Active treatments are mainly directed at the more dystrophic forms of nail involvement and may sometimes help with onycholysis. Often the focus of therapy is the proximal nail fold, where active psoriasis is disturbing the underlying matrix and lack of cuticle is promoting chronic paronychia. Medical treatments include the following.

Local steroids. Clobetasol propionate ointment may be used without occlusion, rubbed into the nail fold. Duration of treatment is limited by local atrophy. It is useful for psoriatic paronychia where there are secondary nail plate changes. Onycholysis may benefit if the nail is clipped back to the point of nail plate attachment and the nail bed treated topically. *Candida* is a frequent colonizer of this space and warrants treatment at the same time. Triamcinolone acetonide may be used by injection into the nail fold or nail bed with regional or digital ring block. Using 0.1-mL injections of 10 mg/mL triamcinolone acetonide at matrix and nail bed sites, on no more than two or three occasions, de Berker and Lawrence [41] report a good response in subungual hyperkeratosis, nail plate thickening and ridging. However, onycholysis and pitting improved in only 50% of nails. Alternative regimens employ more dilute triamcinolone (2.5–5 mg/mL) and are routinely used more than two or three times per digit, infiltrating the proximal nail fold alone, and making a ring block optional. The Dermojet™ is rarely used in nail fold injections now due to the risk of blood splashback and an account of bone damage.

Topical vitamin D analogues. Calcipotriol can be useful where there is subungual hyperkeratosis and nail thickening [42]. It has also been used in combination with topical steroid on an alternating basis (AM/PM) [43] and it is now possible to use it as a combined steroid and calcipotriol ointment. Calcipotriol has the advantage of avoiding the risk of atrophy with long-term use, but it is not as beneficial in treating the nail fold inflammation and consequent changes in proximal matrix function, which manifest as ridging and pitting.

Maintenance treatment with calcipotriol may also be one of the most effective topical therapies for pustular nail psoriasis [44].

Photochemotherapy. Subjects may improve as part of their general psoralen and UVA (PUVA) therapy or may have local PUVA to the nail unit. This can be done with topical or systemic psoralen. Specific high-dose handsets of UVA lamps have been advocated. As part of whole-body PUVA, 18 of 26 patients showed a greater than 50% improvement in nail changes, although pitting was unresponsive [45]. With local therapy, four of five patients improved: onycholysis was more responsive than pitting, but one patient with severe pitting showed improvement [46].

Retinoids. The nail plate is made thin by acitretin and etretinate. This reduces subungual hyperkeratosis. Pitting or onycholysis may be exacerbated [47,48]. Pustulation may be improved. Topical tazarotene 0.1% can be helpful for the treatment of onycholysis and pitting when applied under occlusion [49].

Others. Systemic methotrexate and ciclosporin (cyclosporin) may both help the nail unit but would not usually be advocated as therapy for disease affecting this area alone. Biological agents can also be effective, whilst usually being given in the context of severe disease elsewhere [50], although there are additional reports of psoriasis precipitated by them when given for rheumatological diseases [51]. Acrodermatitis continua of Hallopeau and psoriatic onychopachydermo-periostitis [52] are exceptions, and may respond to methotrexate.

Topical ciclosporin has been reported as useful in a single case report [53]. 5-Fluorouracil 1% has been used topically in 20% urea [54] and also in propylene glycol [55]. Pitting and subungual hyperkeratosis were thought to respond well to the former. Both are contraindicated in onycholysis.

Superficial radiotherapy [56] and electron-beam therapy [57] have been shown to be only of temporary benefit and are not usually recommended.

Treatment of coincident fungal infection may provide clinical benefit, although it is seldom a dermatophyte and positive cultures may only represent colonization.

References

1 Zaias N. Psoriasis of the nail. A clinical–pathologic study. *Arch Dermatol* 1969; **99**: 567–79.
2 Samman PD. *The Nails in Disease*, 3rd edn. London: Heinemann, 1978.
3 Puissant A. Psoriasis in children under the age of 10: a study of 100 observations. *Gaz Sanita* 1970; **19**: 191.
4 Nanda A, Kaur S, Kaur I *et al*. Childhood psoriasis: an epidemiologic survey of 112 patients. *Pediatr Dermatol* 1990; **7**: 19–21.
5 Stankler L. Foetal psoriasis. *Br J Dermatol* 1988; **119**: 684.
6 Tosti A, Peluso AM, Zucchelli V. Clinical features and long-term follow-up of 20 cases of parakeratosis pustulosa. *Pediatr Dermatol* 1998; **15**: 259–63.
7 de Jong EM, Seegers BA, Gulinck MK *et al*. Psoriasis of the nails associated with disability in a large number of patients: results of a recent interview with 1,728 patients. *Dermatology* 1996; **193**: 300–3.
8 Rich P, Scher RK. Nail Psoriasis Severity Index: a useful tool for evaluation of nail psoriasis. *J Am Acad Dermatol* 2003; **49**: 206–12.
9 Baran R. A nail psoriasis severity index. *Br J Dermatol* 2004; **150**: 568–9.
10 Chruściel A, Karlinska-Jachowska M, Młynek A *et al*. Application of R.L. Baran scale in nail plates evaluation in psoriasis. *Dermatol Klin* 2007; **9**: 84–8.
11 Zaias N. Psoriasis of the nail unit. *Dermatol Clin* 1984; **2**: 493–505.
12 Grammer-West NY, Corvette DM, Giandoni MB, Fitzpatrick JE. Clinical pearl: nail plate biopsy for the diagnosis of psoriatic nails. *J Am Acad Dermatol* 1998; **38**: 260–2.
13 Sonnex TS, Griffiths WAD, Nicol WJ. The nature and significance of the transverse white band of human nails. *Semin Dermatol* 1991; **10**: 12–16.
14 Gupta AK, Lynde CW, Jain HC *et al*. A higher prevalence of onychomycosis in psoriatics compared with non-psoriatics: a multicentre study. *Br J Dermatol* 1997; **136**: 786–9.

15 Cohen PR, Prystowsky JH. PRP: a view of diagnosis and treatment. *J Am Acad Dermatol* 1989; **20**: 801–7.
16 Macaulay WL. Transverse ridging of the thumbnails. *Arch Dermatol* 1966; **93**: 421–3.
17 Calvert HT, Smith MA, Wells RS. Psoriasis and the nails. *Br J Dermatol* 1963; **75**: 415–8.
18 Ganor S. Chronic paronychia and psoriasis. *Br J Dermatol* 1975; **92**: 685–8.
19 Burden AD, Kemmett D. The spectrum of nail involvement in palmoplantar pustulosis. *Br J Dermatol* 1996; **134**: 1079–82.
20 Baran R. Hallopeau's acrodermatitis. *Arch Dermatol* 1979; **115**: 815–8.
21 Dulanto P, Armijo-Morens M, Camacho-Martinez F. Histological finding in parakeratosis pustulosa. *Acta Derm Venereol (Stockh)* 1974; **54**: 365–7.
22 Hjorth N, Thomsen K. Parakeratosis pustulosa. *Br J Dermatol* 1967; **79**: 527–32.
23 Miller JL, Soltani K, Toutellotte CD. Psoriatic acro-osteolysis without arthritis. *J Bone Joint Surg* 1971; **53A**: 371–4.
24 Mahowald ML, Parrish RM. Severe osteolytic arthritis mutilans pustular psoriasis. *Arch Dermatol* 1982; **118**: 434–7.
25 Pirracini BM, Fanti PA, Morelli R, Tosti A. Hallopeau's acrodermatitis continua of the nail apparatus: a clinical and pathological study of 20 patients. *Acta Derm Venereol (Stockh)* 1994; **74**: 65–7.
26 Lovy M, Bluhm G, Morales A. The occurrence of nail pitting in Reiter's syndrome. *J Am Acad Dermatol* 1980; **2**: 66–8.
27 Sonnex TS, Dawber RPR, Zachary CB *et al*. The nails in adult type I pityriasis rubra pilaris. A comparison with Sézary syndrome and psoriasis. *J Am Acad Dermatol* 1986; **15**: 956–60.
28 Bazex A, Griffiths A. Acrokeratosis paraneoplastica. A new cutaneous marker of malignancy. *Br J Dermatol* 1980; **103**: 301–6.
29 Richard M, Giroux JM. Acrokeratosis paraneoplastica (Bazex syndrome). *J Am Acad Dermatol* 1987; **16**: 178–83.
30 Handfield-Jones S, Matthews CNA, Ellis JP *et al*. Acrokeratosis paraneoplastica of Bazex. *J R Soc Med* 1992; **85**: 548–50.
31 Wright V, Roberts MC, Hill AGS. Dermatological manifestations in psoriatic arthritis. A follow up study. *Acta Derm Venereol (Stockh)* 1979; **59**: 235–40.
32 Baker H, Golding DN, Thompson M. The nails in psoriatic arthritis. *Br J Dermatol* 1964; **76**: 549–54.
33 Jones SM, Armas JB, Cohen MG *et al*. Psoriatic arthritis: outcome of disease subsets and relationship of joint disease to nail and skin disease. *Br J Rheumatol* 1994; **33**: 834–9.
34 Boisseau-Garsaud AM, Beylot-Barry M, Doutre MS *et al*. Psoriatic onycho-pachydermo-periostitis. *Arch Dermatol* 1996; **132**: 176–80.
35 Lewin K, Dewit S, Ferrington RA. Pathology of the fingernail in psoriasis. *Br J Dermatol* 1972; **86**: 555–63.
36 Samman PD. The ventral nail. *Arch Dermatol* 1961; **84**: 192–5.
37 de Berker D, Westgate G, Leigh I. Patterns of hard keratin (Ha-1) expression in nail matrix correspond to nail plate morphology (abstract). *Br J Dermatol* 1996; **134**: 584–5.
38 de Berker D. Management of nail psoriasis. *Clin Exp Dermatol* 2000; **25**: 357–62.
39 Jiaravuthisan MM, Sasseville D, Vender RB *et al*. Psoriasis of the nail: anatomy, pathology, clinical presentation, and a review of the literature on therapy. *J Am Acad Dermatol* 2007; **57**: 1–27.
40 Cassell S, Kavanaugh AF. Therapies for psoriatic nail disease. A systematic review. *J Rheumatol* 2006; **33**: 1452–6.
41 de Berker DA, Lawrence CM. A simplified protocol of steroid injection for psoriatic nail dystrophy. *Br J Dermatol* 1998; **138**: 90–5.
42 Tosti A, Piraccini BM, Cameli N *et al*. Calcipotriol ointment in nail psoriasis: a controlled double-blind comparison with betamethasone dipropionate and salicylic acid. *Br J Dermatol* 1998; **139**: 655–9.
43 Rigopoulos D, Ioannides D, Prastitis N, Katsambas A. Nail psoriasis: a combined treatment using calcipotriol cream and clobetasol propionate cream. *Acta Derm Venereol (Stockh)* 2002; **82**: 140.
44 Piraccini BM, Tosti A, Iorizzo M, Misciali C. Pustular psoriasis of the nails: treatment and long-term follow-up of 46 patients. *Br J Dermatol* 2001; **144**: 1000–5.
45 Marx JL, Scher RK. The response of psoriatic nails to photochemotherapy. *Arch Dermatol* 1980; **116**: 1023–4.
46 Handfield-Jones SE, Boyle J, Harman RRM. Local PUVA treatment for nail psoriasis. *Br J Dermatol* 1987; **116**: 280–1.
47 Baran R. Retinoids and the nails. *J Dermatol Treat* 1990; **1**: 151–4.
48 Ellis IN, Voorhees JJ. Etretinate therapy. *J Am Acad Dermatol* 1987; **16**: 291–9.
49 Scher RK, Stiller M, Zhu YI. Tazarotene 0.1% gel in the treatment of fingernail psoriasis: a double blind, randomized, vehicle-controlled study. *Cutis* 2001; **68**: 355–8.
50 Lawry M. Biological therapy and nail psoriasis. *Dermatol Ther* 2007; **20**: 60–7.
51 Sfikakis PP, Iliopoulos A, Elezoglou A *et al*. Psoriasis induced by anti-tumor necrosis factor therapy: a paradoxical adverse reaction. *Arthritis Rheum* 2005; **52**: 2513–8.
52 Bauza A, Redondo P, Aquerreta D. Psoriatic onycho-pachydermo periostitis: treatment with methotrexate. *Br J Dermatol* 2000; **143**: 901–2.
53 Tosti A, Guerra L, Bardazzi F, Lanzarini M. Topical cyclosporin in nail psoriasis. *Dermatologica* 1990; **180**: 110.
54 Fritz K. Psoriasis of the nail. Successful topical treatment with 5-fluorouracil. *Z Hautkr* 1988; **64**: 1083–8.
55 Friedriekson T. Topically applied fluorouracil in the treatment of psoriatic nails. *Arch Dermatol* 1974; **110**: 735–6.
56 Yu RCH, King CM. A double blind study of superficial radiotherapy in psoriatic nail dystrophy. *Acta Derm Venereol (Stockh)* 1992; **72**: 134–6.
57 Kwang TY, Nee TS, Seng KTH. A therapeutic study of nail psoriasis using electron beams. *Acta Derm Venereol (Stockh)* 1995; **75**: 90.

Darier's disease [1–5]

Nail involvement is common in Darier's disease; 96% of patients are reported to have acral changes, of which nail changes are the most common [2]. These include red and/or white longitudinal streaks in the nail, often terminating in a V-shaped notch (Fig. 65.23). The streak may represent a zone of fragile or thinned nail, which makes it prone to fragmentation at the tip, with the consequent notch at the free edge. In severe cases, the nails are almost lost by extension of the fragmentation process to involve the entire matrix. Subungual hyperkeratotic papules can be found in the hyponychium. Histologically, matrix and nail bed changes resemble the acantholysis seen in involved skin, with the addition of multinucleate giant cells and epithelial hyperplasia in the nail bed



Fig. 65.23 Darier's disease: white and red longitudinal lines and distal notching.

[5]. These histological features make it possible to diagnose Darier's disease when it is confined to the nail [1]. Excess ridging and a rough nail surface may also be found, as may total leukonychia. Occasionally, marked thickening of the nail plate occurs. It is probable that the nail is sometimes affected in the absence of disease elsewhere [1].

Hailey–Hailey disease has some histological similarities and may also present with longitudinal white streaks [2]. However, the disease does not have the same destructive effect and is not associated with hyperkeratoses or symptoms of the nail apparatus.

A case of squamous cell carcinoma developing in a nail bed with chronic changes of Darier's disease has been reported [6]. Pain or conspicuous, uncharacteristic features in a nail apparatus affected by Darier's disease may therefore be indications for biopsy.

References

1 Bingham EA, Burrows D. Darier's disease. *Br J Dermatol* 1984; **111**(Suppl. 26): 88–9.

2 Burge SM, Wilkinson JD. Darier–White disease: a review of the clinical features in 163 patients. *J Am Acad Dermatol* 1992; **27**: 40–50.

3 Ronchese F. The nail in Darier's disease. *Arch Dermatol* 1965; **91**: 617–8.

4 Schubert H. Darier's disease. *Z Haut Geschlechskr* 1966; **41**: 239–44.

5 Zaias N, Ackerman AB. The nail in Darier–White disease. *Arch Dermatol* 1973; **107**: 193–9.

6 Downs AM, Ward KA, Peachey RD. Subungual squamous cell carcinoma in Darier's disease. *Clin Exp Dermatol* 1997; **22**: 277–9.

Eczema

Nail changes may accompany eczema elsewhere or occur as an isolated finding. Endogenous and exogenous factors may contribute. The nail changes may reflect this division, in that they may be in response to a systemic atopic disposition, with pitting in the absence of inflammation, or may demonstrate the effects of local eczema in the nail unit influencing nail formation.

The common allergens, such as nickel, fragrance and medicaments, rarely have particular bearing on nail abnormalities. However, allergic contact sensitivity to rubber and chromate, and irritant dermatitis are significant factors in hand dermatitis. These materials, and hand dermatitis in general, are associated with particular occupations. Selective exposure to such allergens or strong irritants is as important as chronic low-grade irritation from milder agents, such as water, seen in catering workers.

Cyanoacrylates used in prosthetic nails can provoke local and distant allergic reactions. Formaldehyde, occasionally used as a nail hardener, can provoke painful onycholysis if the patient becomes sensitized, or sometimes when acting solely as an irritant. Some allergens may cause nail dystrophy without associated inflammation.

A combination of atopy and an exogenous irritant or allergic contact reaction is common.

Clinical features. Nail matrix disturbance is reflected in thickening, pits, nail loss, transverse ridges and furrows in a pattern similar to psoriatic nail disease (Table 65.4).

Nail bed disease can produce subungual hyperkeratosis, splinter haemorrhages, onycholysis and pain. Allergens and irritants can be sequestered beneath the free edge of the nail to achieve high concentrations and prolonged exposure.

Nail changes may betray eczema elsewhere and the nails may be buffed smooth and shiny, indicating their use as a tool for rubbing itchy skin.

Associated hand dermatitis may show vesicles, scaling, erythema, cracks and swollen fingers, although the presence of vesicles will not always distinguish the condition from psoriasis, which should be sought at other sites. The distribution on the hand or foot may give some clues as to possible local causes, such as gloves, shoes, prosthetic nails or nail varnish. Hands and feet should always be examined together, as the presence of disease in both diminishes the likelihood of a contact dermatitis.

Defining the presence of atopy, or patch testing, can be useful even in the absence of active eczema, as subungual hyperkeratosis and discomfort may be disproportionate to the cutaneous features [1].

Treatment. General hand care is important, with the avoidance of soap, irritants, wet work and any identified cause. Protective gloves should be used, with copious emollient application. Barrier creams are not usually adequate protection once features have developed. Potent topical steroids may be needed, sometimes with additional topical or systemic antimicrobial therapy. These should be rubbed in around the nail folds. In the young, steroids may precipitate premature closure of the phalangeal epiphyses if too potent or used for too long [2]. Osteomyelitis has also been reported in children using potent topical steroids in this area. Hand or foot PUVA can help.

Table 65.4 Differential diagnosis between four common nail disorders: fungal infections, psoriasis, chronic paronychia and dermatitis.

	Fungal infections	Psoriasis	Chronic paronychia	Dermatitis
Colour	Often yellow or brown; part or whole of nail	May be normal or yellow or brown	Edge of nail often discoloured brown or black	May be normal
Onycholysis	Frequent	Frequent	Usually absent	Confined to tip or absent
Pitting	Infrequent	Often present and fine	Uncommon	Coarse pits frequent
Filaments or spores in potash preparations	Filaments, usually abundant	Absent	May be spores in edge of nail; filaments and spores in scrapings from nail fold	Absent
Cross-ridging	Absent	Uncommon	Frequent	Frequent
Other	Associated fungal infections elsewhere	Associated psoriasis elsewhere or family history of psoriasis	Predominantly women; wet work and cold hands cause predisposition	Recent history of dermatitis on hands

References

1 Marren P, de Berker DAR, Powell S. Occupational contact dermatitis due to Quaternium 15 presenting as nail dystrophy. *Contact Dermatitis* 1991; **25**: 253–5.

2 Boiko S, Kaufman RA, Lucky AW. Osteomyelitis of the distal phalanges in three children with severe atopic dermatitis. *Arch Dermatol* 1988; **124**: 418–23.

Lichen planus

Nails are involved in about 10% of cases of disseminated lichen planus [1]. In a study of 24 adults with nail lichen planus, nail changes were the sole manifestation of the disease in 75% [2,3], and the figure may be higher in children [4,5], in whom lichen planus of all types is rare. This suggests only a modest degree of overlap between the disease process in the nail unit and at other sites. Although the skin lesions may itch intensely, nail disease may be relatively asymptomatic except when nails are shed.

Clinical features. The disease can involve the proximal nail folds with bluish-red discoloration. Nail plate changes include thinning, onychorrhexis, brittleness, crumbling or fragmentation, and accentuation of surface longitudinal ridging. All these features are secondary to disease affecting the matrix, which can also produce transient or permanent longitudinal melanonychia [6] or leukonychia as a post-inflammatory phenomenon (Fig. 65.24). When inflammation is intense and widespread within the nail apparatus, nails may be shed. Single longitudinal depressions in the nail, with a distal notch or entire split, may arise from a pterygium. This is a fibrotic band of tissue fusing the proximal nail fold with the nail bed and matrix, following destructive local inflammation. Surviving proximal matrix is unable to push growing nail through the scar tissue, with a consequent split. Thickening, with features resembling yellow nail syndrome, is a less common pattern of presentation [7]. Where this occurs there is usually little difficulty in making the distinction in the fingernails as the prominent surface changes and/or atrophy of lichen planus are seen. However, these changes are less obvious in the toes, where yellow discoloration due to thickening can be marked [8].

Nail bed disease can produce subungual hyperkeratosis and onycholysis. Bullous lichen planus may affect the soles of the feet and in particular the toenails. Permanent anonychia may follow [9] (Fig. 65.25).

Twenty-nail dystrophy, with stippling of the nail plate (see Fig. 65.11) in up to 20 nails, is seen in a range of autoimmune diseases [10], alopecia areata [3], primary biliary cirrhosis and possibly in pemphigus [11]. In itself, it does not indicate the diagnosis of lichen planus, but is one of the recognized forms of the disease. It is one of the more common childhood patterns of presentation in which the nails feel rough and lose their lustre [12]. It has a reasonably good prognosis, in contrast with idiopathic atrophy of the nails, which may also occur in children. In the latter, the surface change is less marked and the change in overall nail morphology greater, with thinning and disintegration of the nail plate. Although nail biopsy is seldom undertaken in children, it may be warranted when lichen planus is suspected, because if destructive lichen planus is not treated in childhood, there will be lifelong loss of nails.

In the related disorder, lichen nitidus, numerous pits giving a fine rippling effect have been reported [13]. Longitudinal ridging, beads and thickening may occur and nails become brittle.

In keratosis lichenoides chronica, although the skin condition may resemble hyperkeratotic lichen planus the nail changes may mimic psoriasis; 30% have nail involvement, with hyperkeratotic hypertrophy of periungual tissues.

Lichen planus nail changes are seen in graft-versus-host disease [14] and in the disseminated lichenoid papular dermatosis of AIDS. There can be an overlap between lichen planus and discoid lupus erythematosus, in both the skin and the nails. Coexistence of skin and nail lichen sclerosus has been reported [15]. Lichen striatus may extend down a limb to the nails [16].



Fig. 65.24 Lichen planus with longitudinal melanonychia.



Fig. 65.25 Anonychia following lichen planus.

The differential diagnosis for the range of appearances of lichen planus in the nail unit includes Stevens–Johnson syndrome, infection, peripheral vascular disease, trauma and radiodermatitis.

Histology. In 20-nail dystrophy, there is a granular layer in the nail bed and matrix, with marked spongiosis [3]. The hypergranulosis is believed to reflect the disordered keratinization that causes both subungual hyperkeratosis and the poor nail plate formation. In other forms of nail lichen planus, in addition to hypergranulosis, there is occasionally saw-toothing of the rete pattern, and colloid bodies are rarely seen [2,17,18].

In 20-nail dystrophy it may be useful to perform a screen for organ-specific antibodies because of the association with alopecia areata and the related autoimmune diathesis [3].

Treatment. Potent topical steroids may help when rubbed into the nail folds in the active stage. Triamcinolone acetonide may be instilled into the proximal nail fold under local anaesthetic. In children, potent steroid therapy puts them at risk of premature closure of the phalangeal epiphyses. Oral steroids at up to 60 mg/day have been used to arrest severe scarring nail lichen planus [2]. Triamcinolone acetonide can be given intramuscularly at a dose of 0.5–1 mg/kg per month for 3–6 months [12]. Failure to deliver effective treatment in progressive disease may result in permanent nail loss or dystrophy. Ciclosporin can also be of benefit and azathioprine has been used to good effect in erosive disease [19]. Ulcerative lichen planus of the nail unit may benefit from grafting the nail bed.

References

1 Samman PD. The nails in lichen planus. *Br J Dermatol* 1961; **73**: 288–92.
2 Tosti A, Peluso AM, Fanti PA *et al*. Nail lichen planus. Clinical and pathological study of 24 patients. *J Am Acad Dermatol* 1993; **28**: 724–30.
3 Tosti A, Fanti PA, Morelli R *et al*. Trachyonychia associated with alopecia areata. A clinical and pathological study. *J Am Acad Dermatol* 1991; **25**: 266–70.
4 de Berker D, Dawber RPR. Childhood lichen planus. *Clin Exp Dermatol* 1991; **16**: 233.
5 Milligan A, Graham-Brown RAC. Lichen planus in childhood: a review of six cases. *Clin Exp Dermatol* 1990; **15**: 340–2.
6 Baran R, Jancovici E, Sayag J, Dawber RPR. Longitudinal melanonychia in lichen planus. *Br J Dermatol* 1985; **113**: 369–74.
7 Baran R. Lichen planus of the nails mimicking the yellow nail syndrome. *Br J Dermatol* 2000; **143**: 1117–8.
8 Tosti A, Piraccini BM, Cameli N. Nail changes in lichen planus may resemble those of yellow nail syndrome. *Br J Dermatol* 2000; **142**: 848–9.
9 Cornelius CE, Shelley WB. Permanent anonychia due to lichen planus. *Arch Dermatol* 1967; **96**: 434–5.
10 Samman PD. Idiopathic atrophy of the nails. *Br J Dermatol* 1985; **81**: 746–9.
11 de Berker D, Dalziel K, Dawber RPR, Wojnarowska F. Pemphigus associated with nail dystrophy. *Br J Dermatol* 1993; **129**: 461–4.
12 Tosti A, Piraccini BM, Cambiaghi S, Jorizzo M. Nail lichen planus in children: clinical features, response to treatment, and long-term follow-up. *Arch Dermatol* 2001; **137**: 1027–32.
13 Munro CS, Cox NH, Marks JM *et al*. Lichen nitidus presenting as palmoplantar hyperkeratosis and nail dystrophy. *Clin Exp Dermatol* 1993; **18**: 381–3.
14 Saurat JH, Gluckman E. Lichen planus-like eruption following bone marrow transplantation: a manifestation of the graft-versus-host disease. *Clin Exp Dermatol* 1977; **2**: 335–44.
15 Ramrakha-Jones VS, Paul M, McHenry P, Burden AD. Nail dystrophy due to lichen sclerosus? *Clin Exp Dermatol* 2001; **26**: 507–9.
16 Tosti A, Peluso AM, Misciali C, Cameli N. Nail lichen striatus: clinical features and long-term follow-up of five patients. *J Am Acad Dermatol* 1997; **36**: 908–13.
17 Barth JH, Millard PR, Dawber RPR. Idiopathic atrophy of the nails. A clinicopathological study. *Am J Dermatopathol* 1988; **10**: 514–7.
18 Zaias N. The nail in lichen planus. *Arch Dermatol* 1970; **101**: 264–71.
19 Lear JT, English JS. Erosive and generalized lichen planus responsive to azathioprine. *Clin Exp Dermatol* 1996; **21**: 56–7.

Tumours under or adjacent to the nail

Tumours of the nail apparatus and adjacent structures are relatively common. Neoplasms of the nail area can be divided into benign, benign but aggressive lesions (e.g. keratoacanthoma, recurring digital fibrous tumours of childhood and some warts) and malignant tumours [1].

Clinical diagnosis is often difficult because of traumatic factors, infection and pigmentation, and because the translucent nail plate masks physical signs in the nail bed. Also, common tumours, easily recognized at other sites, may behave differently in the nail apparatus. An X-ray investigation should be carried out on all swellings in or around the nail apparatus, particularly those affecting a single digit, to exclude osteoma. Where changes are primarily in soft tissues, magnetic resonance imaging (MRI) may be preferable [2].

Benign tumours

Viral warts

This is the most common tumour involving the nail, usually found in one of the nail folds but also seen in the digit pulp and less commonly on the nail bed. In the lateral nail folds, there may be no nail plate changes, although proximal nail fold warts can result in longitudinal ridging and nail plate distortion (Fig. 65.26), and nail bed warts may cause onycholysis (Fig. 65.27). Erosion of underlying bone has also been reported.



Fig. 65.26 The entire periunguium is affected by wart, with secondary nail changes.



Fig. 65.27 Nail bed warts can cause onycholysis and nail plate disruption.



Fig. 65.28 Garlic clove fibroma.

The causal human papillomavirus is usually type 1, 2 or 4. Nail biting and certain occupations, such as butcher, may predispose to warts and complicate therapy. Warts are more common and difficult to eradicate in the immunosuppressed, particularly in organ-transplant recipients.

The most significant lesion from which warts need to be distinguished is squamous cell (epidermoid) carcinoma. However, this malignancy often destroys part of the matrix and nail bed and is usually painful; both features are uncommon in benign viral warts, unless aggressive cryosurgery has been used or there has been bacterial infection. Other disorders, such as syringometaplasia, amyloid, subungual corn and verrucous epidermal naevus, may mimic viral warts.

Although most warts remit spontaneously, a wide range of therapies is available [3], including topical salicylic acid (paste, on plaster or in collodion), salicylic acid combined with abrasion [4], cryosurgery [4–7], bleomycin [8,9], cantharidin [10], imiquimod [11], curettage and carbon dioxide laser therapy [12,13], pulsed dye laser [14] and interferon [15]. Immunotherapy can be successful using sensitization to diphencyprone [16], or relying on naturally acquired immune sensitivity to pathogens such as mumps or *Candida* [17].

References

1 Baran R, Richert B. Common nail tumors. *Dermatol Clin* 2006; **24**: 297–311.

2 Drapé JL, Idy-Peretti I, Goettmann S *et al*. Standard and high resolution MRI in glomus tumours of toes and fingertips. *J Am Acad Dermatol* 1996; **35**: 550–5.

3 Gibbs S, Harvey I, Sterling J, Stark R. Local treatments for cutaneous warts: systematic review. *BMJ* 2002; **325**: 461.

4 Bunney MH, Nolan MW, Williams DA. An assessment of methods of treating viral warts by comparative trials based on a standard design. *Br J Dermatol* 1976; **94**: 667–79.

5 Colver GB, Dawber RPR. Cryosurgery: the principles and simple practice. *Clin Exp Dermatol* 1989; **14**: 1–6.

6 Dawber RPR, Colver GB, Jackson A. *Cutaneous Cryosurgery*, 2nd edn. London: Dunitz, 1997: 38–48.

7 Kuflik E. Cryosurgical treatment of periungual warts. *J Dermatol Surg Oncol* 1984; **10**: 673–6.

8 Munn SE, Higgins E, Marshall M, Clement M. A new method of intralesional bleomycin therapy in the treatment of recalcitrant warts. *Br J Dermatol* 1996; **135**: 969–72.

9 Shelley WB, Shelley ED. Intralesional bleomycin sulphate therapy for warts: a novel bifurcated needle puncture technique. *Arch Dermatol* 1991; **127**: 234–6.

10 Tkach JR. Finding and inventing alternative therapies. How I do it. *Dermatol Clin* 1989; **7**: 1–18.

11 Grussendorf-Conen EI, Jacobs S, Rubben A, Dethlefsen U. Topical 5% imiquimod long-term treatment of cutaneous warts resistant to standard therapy modalities. *Dermatology* 2002; **205**: 139–45.

12 Logan RO, Zachary CB. Outcome of carbon dioxide laser therapy for persistent cutaneous warts. *Br J Dermatol* 1989; **121**: 99–105.

13 Street ML, Roenigk RK. Recalcitrant periungual verrucae: the role of carbon dioxide laser vaporisation. *J Am Acad Dermatol* 1990; **23**: 115–20.

14 Kenton-Smith J, Tan ST. Pulsed dye laser therapy for viral warts. *Br J Plast Surg* 1999; **52**: 554–8.

15 Stadler R, Mayer-da-Silva A, Bratzke B *et al*. Interferons in dermatology. *J Am Acad Dermatol* 1989; **20**: 650–6.

16 Buckley DA, Keane FM, Munn SE *et al*. Recalcitrant viral warts treated by diphencyprone immunotherapy. *Br J Dermatol* 1999; **141**: 292–6.

17 Johnson SM, Roberson PK, Horn TD. Intralesional injection of mumps or *Candida* skin test antigens: a novel immunotherapy for warts. *Arch Dermatol* 2001; **137**: 451–5.

Fibrous tumours

There are several types of fibrous tumours of the nail apparatus, which can be differentiated on clinical and histological grounds [1,2]. Koenen tumours are associated with tuberous sclerosis and present at puberty as periungual fibromas. They are often multiple, large or small, elongated or nodular, and may produce a longitudinal groove in the nail plate due to matrix compression. Histologically, they show loose collagen with numerous small vessels distally, but with dense collagen and few vessels proximally.

Acquired periungual fibrokeratoma [3] is probably the same as acquired digital fibrokeratoma and garlic clove fibroma (Fig. 65.28). They are all benign asymptomatic fibromas with a hyperkeratotic tip and narrow base arising in the periunguium, especially at the proximal aspect of the matrix. They grow out along the nail, resulting in a longitudinal groove. There are three histological variants:

1 thick, dense, closely packed collagen bundles
2 similar to type 1, but with increased fibroblasts in the cutis
3 oedematous and loose dermis.

Fibrous dermatofibroma is a true fibroma presenting as a smooth-edged tumour, commonly in the periungual tissues rather than within the nail unit. There is no collar of elevated skin as is often seen in acquired fibrokeratomas and it lacks the hyperkeratotic tip. It is hypocellular but with prominent collagen bundles, and rarely has a histiocytic dermal component. Occasionally, fibromas can be confused with other lesions, such as Bowen's disease, exostosis, keloid, dermatofibrosarcoma, eccrine poroma, neurofibroma and verruca. Multiple soft fibromas presenting on the dorsal aspect of digits in childhood may be infantile digital fibromatosis. These are benign and resolve with age [4,5]. Periungual fibromas may act as a diagnostic clue for tuberous sclerosis, although they normally occur in association with at least one other feature such as hypomelanotic macules that allows corroboration [6]. They are rarely seen before the age of 5 years, but are present in 23% of subjects with tuberous sclerosis at 14 years, rising to 88% over 30 [6]. Presentation with a single periungual fibroma should lead to a full history and examination to establish whether it is a feature of undiagnosed tuberous sclerosis. However, if nothing else is found, it is unlikely that the tumour has broader significance [7].

Treatment is by excision. In acquired periungual fibrokeratoma arising in the proximal matrix, great care is needed to remove the origin of the tumour without damaging the matrix: there is a fine balance between allowing recurrence and producing long-term nail dystrophy. Koenen tumours are particularly prone to relapse, probably because of their dermal origin.

References

1 Baran R, Perrin C, Baudet J, Requena L. Clinical and histological patterns of dermatofibromas (true fibromas) of the nail apparatus. *Clin Exp Dermatol* 1994; **19**: 31–5.
2 Kint A, Baran R. Histopathologic study of Koenen tumours. *J Am Acad Dermatol* 1988; **18**: 369–72.
3 Bart RS, Andrade R, Kopf AW, Leider M. Acquired digital fibrokeratomas. *Arch Dermatol* 1968; **97**: 120–9.
4 Cohen MM, Hayden PW. A newly recognised hamartomatous syndrome. *Birth Defects* 1979; **15**: 291–6.
5 Reye RDK. Recurring fibrous digital tumours of childhood. *Arch Pathol* 1965; **80**: 228–31.
6 Webb DW, Clarke A, Fryer A, Osborne JP. The cutaneous features of tuberous sclerosis: a population study. *Br J Dermatol* 1996; **135**: 1–5.
7 Zeller J, Friedmann D, Clerici T, Revuz J. The significance of a single periungual fibroma: report of seven cases. *Arch Dermatol* 1995; **131**: 1465–6.

Onychomatricoma

Onychomatricoma [1] may be considered a form of fibroma of the proximal nail fold [2,3], closely associated with the matrix. Its location means that the main features are those of altered nail, which becomes thickened, with increased longitudinal ridging (Fig. 65.29). There may be increased transverse and longitudinal curvature in larger tumours. Splinter haemorrhages within the zone of altered nail are common. When the onychomatricoma is small it may occupy only a narrow band of altered nail which is thickened and grey or yellow. As it enlarges, the band broadens and thickens. When avulsed, the proximal aspect of the nail reveals multiple, honeycomb channels corresponding to the digitations of the matrix, which has changed shape in response to the dermal matrix tumour. The tumour has normal immunohistochemical markers for a benign fibroma [3,4]. The matrix epithelium is normal in cytology and differentiation with respect to keratins [4].



(a)



(b)

Fig. 65.29 (a) Subtle longitudinal thickening and opacity of the nail plate due to an onychomatricoma. (b) Onychomatricoma on MRI.

Electron microscopy demonstrates decreased amounts of tonofilaments and desmosomes in basal epithelial cells [5]. It is the marked change in shape that leads to the altered nail and characteristic clinical presentation.

Less classical presentations of the tumour may have nail features of melanonychia and onychomycosis [6].

Treatment is by excision. The margins need to include a proximal element of the proximal nail fold, and extend down to bone and into proximal nail bed to obtain the whole tumour. This typically sacrifices a significant fraction of the matrix and may mean that total matrix excision is the best option.

References

1 Baran R, Kint A. Onychomatrixoma. Filamentous tufted tumour in the matrix of a funnel-shaped nail: a new entity. *Br J Dermatol* 1992; **126**: 510–15.
2 Perrin C, Goettmann S, Baran R. Onychomatricoma: clinical and histopathologic findings in 12 cases. *J Am Acad Dermatol* 1998; **39**: 560–4.
3 Fraga GR, Patterson JW, McHargue CA. Onychomatricoma: report of a case and its comparison with fibrokeratoma of the nailbed. *Am J Dermatopathol* 2001; **23**: 36–40.
4 Perrin C, Baran R, Pisani A *et al*. The onychomatricoma: additional histologic criteria and immunohistochemical study. *Am J Dermatopathol* 2002; **24**: 199–203.
5 Kint A, Baran R, Geerts ML. The onychomatricoma: an electron microscopic study. *J Cutan Pathol* 1997; **24**: 183–8.
6 Fayol J, Baran R, Perrin C, Labrousse F. Onychomatricoma with misleading features. *Acta Derm Venereol (Stockh)* 2000; **80**: 370–2.

Subungual exostosis

A subungual exostosis is a benign bony outgrowth of the terminal phalanx. It is usually found on the great toe [1] or rarely a finger [2] in subjects between the ages of 10 and 35 years (Fig. 65.30). It is not clear whether trauma is causal or contributory. Where there are hereditary multiple exostoses, the problem is inherited in a dominant pattern and attributable to mutations of the *EXT1* and *EXT2* genes on chromosomes 8q and 11p, respectively. These genes encode the proteins exostosin 1 and 2, which are part of a family of glycosyltransferases required for the synthesis of heparan sulphate chains. Heparan sulphate is integral to the expression of proteoglycans on the cell surface and in the extracellular matrix [3]. Mutations of *EXT1* and *EXT2* are also found in specimens of solitary exostoses [3]. This corresponds to the absence of heparan sulphate in the chondrocyte zones of exostosis growth plates [4], consistent with the proposal that such changes in chondrocyte biology are associated with abnormal cell signalling.



Fig. 65.30 Subungual exostosis.

Pain as a presenting feature is common. It is usually associated with trauma, but is also caused by ingrowing of the nail plate as it is displaced by the tumour [5]. The nail plate is elevated laterally but rarely damaged by the tumour. Radiography reveals an outgrowth of trabeculated bone [6], which may seem modest in comparison with the clinical complaint because of the large radiolucent cartilaginous cap. The X-ray examination should include a lateral view, as typically a view from above will miss the pathology.

Distinction from a subungual osteochondroma may be possible histologically because fibrous cartilage caps the bony outgrowth in exostosis and hyaline cartilage in osteochondroma [7]. Although this rule is often stated, it is not clear whether an absolute distinction can be made between the two lesions.

Where multiple exostoses exist, autosomal dominant multiple exostosis syndrome must be considered. The tumours in this condition are 'near the knee and far from the elbow' and can be destructive to nail [8]. The importance of making the diagnosis lies in the remote possibility of transformation of individual tumours to chondrosarcoma—an estimated figure for malignant change is 0.5% [9]. Older patients may have a different variety of exostosis, which represents hyperostosis of the distal tuft. This can cause elevation of the nail and pincer deformity, whereby the distal and lateral borders of the nail curve downward and inward to act as a pincer upon the nail bed.

Treatment. Treatment of subungual exostosis is by partial nail avulsion or fish-mouth elevation of nail bed and plate and removal of the tumour using bone nibblers or a chisel [7]. A margin of normal bone should be removed at the base to prevent recurrence. There is a 10% relapse rate following surgery, and children are more prone to relapse than adults [5]. Permanent matrix damage may follow surgery if tumours undermine the matrix. Rates of postoperative nail deformity or loss as high as 56% have been reported, but our experience suggests a figure in the order of 15% with residual abnormality.

References

1 Landon GC, Johnson KA, Dahlin DC. Subungual exostoses. *J Bone Joint Surg* 1979; **61A**: 256–9.
2 Carroll RE, Chance JT, Inan Y. Subungual exostoses of the hand. *J Hand Surg* 1992; **17B**: 569–74.
3 Hall CR, Cole WG, Haynes R, Hecht JT. Reevaluation of a genetic model for the development of exostosis in hereditary multiple exostosis. *Am J Med Genet* 2002; **112**: 1–5.
4 Hecht JT, Hall CR, Snuggs M *et al*. Heparan sulfate abnormalities in exostosis growth plates. *Bone* 2002; **31**: 199–204.
5 de Berker DA, Langtry J. Treatment of subungual exostoses by elective day case surgery. *Br J Dermatol* 1999; **140**: 915–8.
6 Evison G, Price CHG. Subungual exostoses. *Br J Radiol* 1966; **39**: 451–5.
7 Dumontier CA, Abimelec P. Nail unit enchondromas and osteochondromas: a surgical approach. *Dermatol Surg* 2001; **27**: 274–9.

8 Baran R, Bureau H. Multiple exostoses syndrome presenting with anonychia on a single finger. *J Am Acad Dermatol* 1991; **25**: 333–5.
9 Voutsinas S, Wynne-Davies R. The infrequency of malignant disease in diaphyseal aclasis and neurofibromatosis. *J Med Genet* 1983; **20**: 345–9.
10 Suga H, Mukouda M. Subungual exostosis: a review of 16 cases focusing on postoperative deformity of the nail. *Ann Plast Surg* 2005; **55**: 272–5.

Other bone tumours

Enchondroma

An enchondroma is a cartilage tumour, which may present as a painful solitary tumour of the distal phalanx with clubbing, paronychia, nail thickening, discoloration, ridging and elevation of the nail, and pathological fractures [1]. In Ollier's disease, multiple digits are usually affected. In Maffuci's syndrome there are multiple subcutaneous angiomas and hard cartilaginous nodules of the epiphyseal line, which may distort the entire hand or foot [2].

X-ray shows lucent expansion of distal phalanges alone, with spotty calcification in simple enchondromas. In Maffuci's syndrome there is widespread lucency in many phalanges of all the digits. Treatment is by enucleation of the tumour and autologous cancellous bone grafting. All these tumours can be associated with chondrosarcoma, angiosarcoma being an additional risk in Maffuci's syndrome [3].

Osteoid osteoma [4–6]

Osteoid osteomas of the distal phalanx present with enlargement of the entire digit tip in a young adult, with thickening of the nail, clubbing, increased local sweating and violaceous skin changes. A tender tumour may be palpated within the diffuse swelling, and the tumour may cause a nagging pain, characteristically relieved by non-steroidal anti-inflammatory drugs.

X-ray reveals a small area of rarefaction surrounded by sclerosis, although symptoms may precede this appearance and an isotope bone scan or MRI may show the focus earlier. Arteriography and thermography demonstrate the hypervascularity. Surgical treatment of this benign condition is by *en bloc* resection through a fish-mouth incision.

Implantation epidermoid cyst

Implantation epidermoid cyst may produce gradual enlargement of the tip of the digit, with the appearance of clubbing, or pincer nail. Pain may arise due to disturbance of the underlying bone where there is erosion, with distortion of cortical bone seen on X-ray, or a cyst may be demarcated on MRI. There is sometimes a history of previous trauma or surgery. Surgery is generally curative [7,8].

Metastases

Metastatic tumours present as inflamed swellings at the tip of a digit, with relatively few symptoms. X-ray reveals an osteolytic lesion, and systemic examination and investigation may reveal the primary focus; 50% will be from carcinoma of the lung [9,10].

References

1 Yaffee HW. Peculiar nail dystrophy caused by an enchondroma. *Arch Dermatol* 1965; **91**: 361.
2 Monses B, Murphy WA. Distal phalangeal erosive lesions. *Arthritis Rheum* 1984; **27**: 449–55.
3 Lewis RJ, Ketcham AS. Maffuci's syndrome: functional and neoplastic significance. *J Bone Joint Surg* 1973; **55A**: 1465–79.
4 Bowen CVA, Dzus AK, Hardy DA. Osteoid osteomata of the distal phalanx. *J Hand Surg* 1987; **12B**: 387–90.
5 Brown RE, Russel JB, Zook EG. Osteoid osteoma of the distal phalanx of the finger: a diagnostic challenge. *Plast Reconstr Surg* 1991; **90**: 1016–21.
6 Jaffé HL. Osteoid osteoma. A benign osteoblastic tumour composed of osteoid and atypical bone. *Arch Surg* 1935; **31**: 709–28.
7 Baran R, Broutard JC. Epidermoid cyst of the thumb presenting as a pincer nail. *J Am Acad Dermatol* 1989; **19**: 143–4.
8 Schajowicz F, Alello CA, Slullitel I. Cystic and pseudo-cystic lesions of the terminal phalanx with special reference to epidermoid cyst. *Clin Orthop Rel Res* 1970; **68**: 84–92.
9 Baran R, Tosti A. Metastatic carcinoma to the terminal phalanx of the big toe: report of two cases and review of the literature. *J Am Acad Dermatol* 1994; **31**: 259–63.
10 Cohen PR. Metastatic tumors to the nail unit: subungual metastases. *Dermatol Surg* 2001; **27**: 280–93.

Vascular tumours

Glomus tumour

Glomus tumours are the most characteristic of vascular nail bed tumours. There is pain, which may be spontaneous or evoked by mild trauma or temperature change. Nail plate changes depend on the location of the tumour. Matrix tumours cause splitting and distortion of the nail plate. Nail bed lesions are most likely to appear as bluish or red foci, 1–5 mm in diameter, beneath the nail [1]. On X-ray, 36% show a depression in the underlying phalanx [1]; MRI can reveal the exact site of the tumour, but can miss tumours of less than 3 mm across. Such cases will still need surgical exploration on the basis of signs and symptoms, which undermines its value as a baseline investigation [2]. However, it can be of value when there is pain after excision in order to help determine whether the pain is a complication of surgery or due to recurrent tumour [3]. High-resolution ultrasound has also been used with some success [4].

Histology is the definitive investigation and reveals vascular channels lined with endothelium and cuboidal glomus cells. These have dark nuclei and pale cytoplasm. Myelinated and non-myelinated nerves are found, which may account for the associated symptoms; neuromas must be considered in the differential diagnosis [5].

Treatment. Excision is the treatment of choice. Some surgeons advocate approaching the pathology by a fish-mouth incision, expecially when the tumour is in the nail bed [6]. However, this assumes a clear knowledge as to the location and nature of the tumour before surgery. Often it is necessary to remove the nail for preliminary assessment and this also facilitates matrix repair [5,7]. Where there is persistent pain after treatment, it may be due to the earlier surgery or further tumour. MRI can help in assessing this [2]. Residual scarring of the nail may remain, depending on the nature of the surgery and the extent of preoperative damage.

References

1 Van Geertruyden J, Lorea P, Goldschmidt D *et al*. Glomus tumours of the hand. A retrospective study of 51 cases. *J Hand Surg* 1996; **21B**: 257–60.

2 Al-Qattan MM, Al-Namla A, Al-Thunayan A *et al*. Magnetic resonance imaging in the diagnosis of glomus tumours of the hand. *J Hand Surg [Br]* 2005; **30**: 535–40.
3 Theumann NH, Goettmann S, Le Viet D *et al*. Recurrent glomus tumors of fingertips: MR imaging evaluation. *Radiology* 2002; **223**: 143–51.
4 Fornage BD, Schernberg FL, Rifkin MD, Touche DH. Sonographic diagnosis of glomus tumour of the finger. *J Ultrasound Med* 1984; **3**: 523–4.
5 Shelley ED, Shelley WB. Exploratory nail plate removal as a diagnostic aid in painful subungual tumours: glomus tumour, neurofibroma and squamous cell carcinomas. *Cutis* 1986; **38**: 310–12.
6 Wegener EE. Glomus tumors of the nail unit: a plastic surgeon's approach. *Dermatol Surg* 2001; **27**: 240–1.
7 Takata H, Ikuta Y, Ishida O, Kimori K. Treatment of subungual glomus tumour. *Hand Surg* 2001; **6**: 25–7.

Pyogenic granuloma and periungual vascular lesions

Pyogenic granulomas are benign eruptive haemangiomas. They may involve the nail fold, with a prominent collar of epithelium, or be subungual and penetrate the nail plate (Fig. 65.31). In this location, they almost invariably arise from the matrix and produce a localized deformity of the nail plate, visible as the nail grows distally. Mild penetrating injury, friction [1] and immobilization of the limb in a cast [2] are physical causes. Medication can also be relevant. Retinoids [3], ciclosporin [4], cancer chemotherapy and antiretroviral treatment for HIV infection are all potential initiating factors. With these medications, the presentation is often of excessive granulation tissue on more than one digit as part of an ingrowing nail, rather than the classic isolated lesion puncturing the matrix and emerging from beneath the proximal nail fold. There may be features that blur the distinction between focal lesions and areas of hyperaemia with inflammation [5] and onycholysis [5–7]. Pain can be a significant feature [7] and docetaxel, used in breast and prostate cancer, has been implicated in such cases. Where antiretroviral medication is implicated, it is usually in association with nucleoside reverse transcriptase inhibitors [8,9].



Fig. 65.31 Pyogenic granuloma penetrating the nail plate.

A pyogenic granuloma bleeds easily and must be distinguished from an amelanotic malignant melanoma, histiocytoid haemangioma [10], granulation tissue reaction to ingrowing nail and cavernous angioma. Where the clinical evolution is slow, the differential diagnosis includes squamous cell carcinoma and a range of benign tumours [11]. The possibility of malignancy and other progressive tumours makes histological examination important. Bacteriology is also required and may help with the diagnosis of coccal nail fold angiomatosis, which may resemble a pyogenic granuloma arising from the matrix. This can relapse locally and on other digits [12].

Treatment. Once histology is available, if the lesion persists, destructive therapy such as carbon dioxide laser or suppressive therapy such as a potent topical steroid can be used. The latter is preferable and adequate for matrix lesions where infection has been adequately treated. Potassium permanganate soaks, or local or systemic antibiotics, may be needed if there is secondary infection with excessive oozing.

References

1 Richert B. Frictional pyogenic granuloma of the nail bed. *Dermatology* 2001; **202**: 80–1.
2 Tosti A, Piraccini BM, Camacho-Martinez F. Onychomadesis and pyogenic granuloma following cast immobilization. *Arch Dermatol* 2001; **137**: 231–2.
3 Baran R. Retinoids and the nails. *J Dermatol Treat* 1990; **1**: 151–4.
4 Higgins EM, Hughes JR, Snowden S, Pembroke AC. Cyclosporin-induced periungual granulation tissue. *Br J Dermatol* 1995; **132**: 829–30.
5 Nicolopoulos J, Howard A. Docetaxel-induced nail dystrophy. *Australas J Dermatol* 2002; **43**: 293–6.
6 Wasner G, Hilpert F, Schattschneider J *et al*. Docetaxel-induced nail changes: a neurogenic mechanism. A case report. *J Neurooncol* 2002; **58**: 167–74.
7 Minisini AM, Tosti A, Sobrero AF *et al*. Taxane-induced nail changes: incidence, clinical presentation and outcome. *Ann Oncol* 2003; **14**: 333–7.
8 Ward HA, Russo GG, Shrum J. Cutaneous manifestations of antiretroviral therapy. *J Am Acad Dermatol* 2002; **46**: 284–93.
9 Heim M, Schapiro J, Wershavski M, Martinowitz U. Drug-induced and traumatic nail problems in the haemophilias. *Haemophilia* 2000; **6**: 191–4.
10 Tosti A, Peluso AM, Fanti PA *et al*. Histiocytoid haemangioma with prominent fingernail involvement. *Dermatology* 1994; **189**: 87–9.
11 Hassanein A, Telang G, Benedetto E, Spielvogel R. Subungual myxoid pleomorphic fibroma. *Am J Dermatopathol* 1998; **20**: 502–5.
12 Davies MG. Coccal nail fold angiomatosis. *Br J Dermatol* 1995; **132**: 162–3.

Arteriovenous abnormalities

Periungual and subungual arteriovenous tumours (cirsoid aneurysms) are firm, bluish, non-pulsatile nodules in a nail fold or penetrating the nail [1]. Following excision, histology shows thick-walled vascular channels with fibrous tissue boundaries and no internal elastic lamina. In the presence of a digital arteriovenous malformation, the digit and nail bed are purple, with gradual shrinkage and overcurvature of the nail plate [2]. Growth may be rapid in young people, in whom the digit may become bulbous and painful. X-ray may reveal aneurysmal destruction of the terminal phalanx, and more precise detail may be gained by MRI.

References

1 Burge SM, Baran R, Dawber RPR, Verret JL. Periungual and subungual arteriovenous tumours. *Br J Dermatol* 1986; **115**: 361–6.

2 Enjolras O, Riché MC. *Hémangiomes et Malformations Vasculaires Superficielles*. New York: Medsi/McGraw-Hill, 1990.

Myxoid cyst

Synonym

- Myxoid or mucoid pseudocyst

This benign cystic swelling has many names and is often termed a pseudocyst because a cellular cyst wall can seldom be demonstrated. It is usually located between the crease of the distal interphalangeal joint on the dorsal surface and the proximal nail fold. Less commonly it is found between the proximal nail fold and the nail plate, beneath the nail matrix or in the digit pulp. Pressure on the matrix results in a longitudinal groove or gutter in the nail plate (Fig. 65.32), which may have transverse ridges within it, reflecting episodes of decreased matrix pressure when the cyst is decompressed as a result of discharge of its contents. When it occupies the space between the nail and proximal nail fold, it may protrude from beneath the nail fold with what appears to be a keratotic tip, mimicking a fibrokeratoma. When located beneath the matrix, the nail becomes misshapen, with increased transverse curvature, and the lunula appears red [1].

Myxoid cysts are more common in the fingers than the toes. They contain a clear gelatinous fluid that may discharge spontaneously or on minor trauma. This fluid may be the product of mucoid degeneration of connective tissue or be derived directly from the adjacent distal interphalangeal joint with which a communication is usually demonstrable by injection of methylene blue into the joint [2,3]. The condition of the joint is a major factor in the origin of the cyst, with osteoarthritic osteophytes damaging the joint capsule and provoking the flaw through which synovial fluid escapes. Infection of the ruptured pseudocyst may cause septic arthritis or local paronychia, although this is uncommon.



Fig. 65.32 Nail plate groove due to proximal myxoid cyst.

High-resolution ultrasound or MRI provides non-invasive visualization to confirm the diagnosis or to localize the pedicle in recurrent cases. However, it may be more practical to attempt transillumination with a pen torch. This will distinguish it from a giant cell tendon sheath tumour, which is usually found overlying the dorsal distal interphalangeal crease in women with osteoarthritis [4,5]. Giant cell tendon sheath tumours are often rubbery and fail to transilluminate. Alternatively, a myxoid cyst will easily puncture using a size 11 scalpel, with sterile technique, revealing the diagnostic gelatinous contents.

Histology usually reveals a pseudocyst cavity within a fibrous capsule containing a myxomatous stroma with scattered fibroblasts. Areas of myxomatous change may merge to form a multilobular pseudocyst. Some workers report a mesothelial lining to the pseudocyst, consistent with continuity with the synovial joint space. This is not always confirmed and may mean that there are different histological forms of myxoid pseudocysts.

Treatment. There are many conservative approaches to cure [6,7], none of which is definitive. These include incision and drainage (pricking with a sterile blade or needle) and which may be repeated by the patient [8], injected sclerosant [9] or steroid [10,11], cryosurgery [12,13], laser [14] and infrared photocoagulation [15].

Surgical therapy may entail removal of osteophytes involving the distal interphalangeal joint [16–19], excising the distal margin of the proximal nail fold if the lesion is located there [20], or tracing the communication between the joint and cyst with methylene blue and tying it off [3,21].

There is a high relapse rate after single treatments with less invasive therapies. More detailed surgical therapies are more effective [19,21].

References

1 de Berker D, Goettman S, Baran R. Subungual myxoid cysts: clinical manifestations and response to therapy. *J Am Acad Dermatol* 2002; **46**: 394–8.

2 Kleinert HE, Kutz JE, Fishman JH *et al*. Etiology and treatment of the so-called mucous cyst of the finger. *J Bone Joint Surg* 1972; **54A**: 1455–8.

3 Newmeyer WL, Kilgore ES, Graham WP. Mucous cyst: the dorsal distal interphalangeal joint ganglion. *Plast Reconstr Surg* 1974; **53**: 313–5.

4 Averill RM, Smith RJ, Campbell CJ. Giant cell tumours of the bones of the hand. *J Hand Surg* 1980; **5**: 39–50.

5 Wright CJE. Benign giant-cell synovioma. An investigation of 85 cases. *Br J Surg* 1951; **38**: 257–71.

6 Baran R, Haneke E. Tumours of the nail apparatus and adjacent tissues. In: Baran R, Dawber RPR, eds. *Diseases of the Nails and Their Management*, 2nd edn. Oxford: Blackwell Science, 1994: 474–6.

7 de Berker DAR. Treatment of myxoid cysts. *J Dermatol Treat* 1995; **6**: 55–7.

8 Epstein E. A simple technique for managing digital mucous cysts. *Arch Dermatol* 1979; **115**: 1315–6.

9 Audebert C. Treatment of mucoid cysts of fingers and toes by injection of sclerosant. *Dermatol Clin* 1989; **7**: 179–81.

10 Epstein E. Steroid injection of myxoid finger cysts. *JAMA* 1965; **194**: 98–9.

11 Johnson WC, Graham JH, Helwig EB. Cutaneous myxoid cyst. A clinicopathological and histochemical study. *JAMA* 1965; **191**: 15–20.

12 Dawber RPR, Colver G, Jackson A. *Cutaneous Cryosurgery. Principles and Clinical Practice*. London: Dunitz, 1992: 71–2.

13 Dawber RPR. Myxoid cysts of the finger: treatment by liquid nitrogen spray cryosurgery. *Clin Exp Dermatol* 1983; **8**: 153–7.

14 Huerter CJ, Wheeland RG, Bailin PL, Ratz JL. Treatment of digital myxoid cysts with carbon dioxide laser vaporization. *J Dermatol Surg Oncol* 1987; **13**: 723–7.
15 Lonsdale-Eccles AA, Langtry JA. Treatment of digital myxoid cysts with infrared coagulation: a retrospective case series. *Br J Dermatol* 2005; **153**: 972–5.
16 Brown RE, Zook EG, Russell RC *et al*. Fingernail deformities secondary to ganglions of the distal interphalangeal joint (mucous cysts). *Plast Recontr Surg* 1991; **87**: 718–25.
17 Gingrass MK, Brown RE, Zook EG. Treatment of fingernail deformities secondary to ganglions of the distal interphalangeal joint. *J Hand Surg* 1995; **20A**: 502–5.
18 Kasdan ML, Stallings SP, Leis V, Wolens D. Outcome of surgically treated mucous cysts of the hand. *J Hand Surg* 1994; **19A**: 504–7.
19 Mani-Sundaram D. Surgical correction of mucous cysts of the nail unit. *Dermatol Surg* 2001; **27**: 267–8.
20 Salasche SJ. Myxoid cysts of the proximal nail fold, a surgical approach. *J Dermatol Surg Oncol* 1984; **10**: 35–9.
21 de Berker D, Lawrence C. Ganglion of the distal interphalangeal joint (myxoid cyst): therapy by identification and repair of the leak of joint fluid. *Arch Dermatol* 2001; **137**: 607–10.

Squamous cell carcinoma

Synonym
- Epidermoid carcinoma

Squamous cell carcinoma of the nail unit includes *in situ* (Bowen's disease) and invasive forms (Fig. 65.33). A single biopsy may fail to make a distinction between them. A tumour that appears *in situ* at one site may be invasive elsewhere [1]. Periungual features include hyperkeratotic warty changes, erosions and fissuring, macerated cuticle, periungual swelling, erythema and occasional secondary infection. Subungual changes include onycholysis with a friable or warty nail bed, longitudinal melanonychia, nail dystrophy, ingrowing or loss. Some cases may be as subtle as a single, red longitudinal streak [2] (see p. 65.18). Nodular change with ulceration and bleeding is a late development. The condition may affect many digits [3]. Common misdiagnoses include onychomycosis, periungual warts, recurrent paronychia, pyogenic granuloma and subungual exostosis. As some of these conditions do not warrant biopsy and clinicians seldom think of squamous cell carcinoma at this site, the diagnosis is frequently delayed. Mean periods of 52 months [4], 9 years [5] and 5 years [6] have been reported. This slow progression may mean that the diagnosis is never made on older people, with the consequent impression that the disease is less common than is the case [7].



Fig. 65.33 Bowen's disease with melanonychia.

Predisposing factors include radiation exposure [3,8], human papillomaviruses 16, 18 and 34 [4,5,8–10], and possibly ectodermal dysplasias and chronic trauma. Features of chronic radiation damage to the periunguium may precede the onset of malignancy [11]. History and examination should include a note of genital wart infection or cervical dysplasia in the patient or partner [8]. Appropriate investigation includes X-ray and biopsy of a large and representative area. Prognosis is good, with few cases of metastatic disease in the literature [9], two of which were in patients with ectodermal dysplasia [12,13].

Treatment. Mohs' micrographic surgery is the treatment of choice for ill-defined lesions, as long as there is no evidence of bone involvement [1,6,14]. The technique allows the digit to be preserved in most instances. Horizontal sections in the context of the complex three-dimensional anatomy and histology of the nail unit require careful and experienced interpretation [15]. Alternative treatments include local excision, digit amputation and radiotherapy [16].

References

1 Mikhail G. Subungual epidermoid carcinoma. *J Am Acad Dermatol* 1984; **11**: 291–8.
2 Baran R, Perrin C. Longitudinal erythronychia with distal subungual keratosis: onychopapilloma of the nail bed and Bowen's disease. *Br J Dermatol* 2000; **143**: 132–5.
3 Baran RL, Gormley DE. Polydactylous Bowen's disease of the nail. *J Am Acad Dermatol* 1987; **17**: 201–4.
4 Sau P, McMarlin S, Sperling LC, Katz R. Bowen's disease of the nail bed and periungual area. *Arch Dermatol* 1994; **130**: 204–9.
5 Moy RL, Eliezri YD, Nuovo GJ *et al*. Human papillomavirus type 16 DNA in periungual squamous cell carcinomas. *JAMA* 1989; **261**: 2669–73.
6 Godlminz D, Bennett RG. Mohs micrographic surgery of the nail unit. *J Dermatol Surg Oncol* 1992; **18**: 721–6.
7 Virgili A, Rosaria Zampino M, Bacilieri S *et al*. Squamous cell carcinoma of the nail bed: a rare disease or only misdiagnosed? *Acta Derm Venereol (Stockh)* 2001; **81**: 306–7.
8 Guitart J, Bergfeld WF, Tuthull RJ *et al*. Squamous cell carcinoma of the nail bed: a clinicopathological study of twelve cases. *Br J Dermatol* 1990; **123**: 215–22.
9 Ashinoff R, Jumli J, Jacobson M *et al*. Detection of HPV DNA in squamous cell carcinoma of the nail bed and finger determined by polymerase chain reaction. *Arch Dermatol* 1991; **127**: 1813–8.
10 McHugh RW, Hazen P, Eliezri YD, Nuovo GJ. Metastatic periungual squamous cell carcinoma: detection of human papillomavirus type 35 RNA in the digital tumour and axillary lymph node metastases. *J Am Acad Dermatol* 1996; **34**: 1080–2.
11 Richert B, de la Brassine M. Subungual chronic radiodermatitis. *Dermatology* 1993; **186**: 290–3.
12 Campbell J, Keokarn T. Squamous cell carcinoma of the nail bed in epidermal dysplasia. *J Bone Joint Dis* 1966; **48**: 92–9.
13 Mauro JA, Maslyn R, Stein AA. Squamous cell carcinoma of the nail bed in hereditary ectodermal dysplasia. *N Y State J Med* 1972; **72**: 1065–6.

14 de Berker DAR, Dahl MGC, Malcolm AJ, Lawrence CM. Micrographic surgery for subungual squamous cell carcinoma. *Br J Plast Surg* 1996; **49**: 414–9.
15 Zaiac MN, Weiss E. Mohs micrographic surgery of the nail unit and squamous cell carcinoma. *Dermatol Surg* 2001; **27**: 246–51.
16 Attiyeh FF, Shah J, Booker RJ *et al*. Subungual squamous cell carcinoma. *JAMA* 1979; **241**: 262–3.

Epithelioma cuniculatum [1,2]

Epithelioma cuniculatum is a slow-growing, locally destructive, low-grade tumour, histologically related to squamous cell carcinoma [1,2]. It is typically found on the sole of the foot, but may involve the periunguium, mucosal surfaces and other locations [3]. It is warty, with discharge of foul-smelling yellow material from nail bed sinuses. The overlying nail is disrupted by onycholysis or destruction at the matrix, and there may be paronychia. The underlying bone is usually affected and X-ray reveals destruction of the terminal phalanx in most cases. Biopsy confirms the diagnosis. A system of epithelium-lined channels within the tumour forms fistulae extruding keratinous debris. Mitoses and dyskeratotic cells are rare and the benign appearance may lead to the misdiagnosis of pseudoepitheliomatous hyperplasia. Mohs' micrographic surgery is a useful treatment.

References

1 McKee P, Wilkinson JD, Black MM *et al*. Carcinoma (epithelioma) cuniculatum: a clinicopathological study of nineteen cases and review of the literature. *Histopathology* 1986; **5**: 425–36.
2 Tosti A, Morelli R, Fanti PA *et al*. Carcinoma cuniculatum of the nail apparatus: report of 3 cases. *Dermatology* 1993; **186**: 217–21.
3 Schwartz RA. Verrucous carcinoma of the skin and mucosa. *J Am Acad Dermatol* 1995; **32**: 1–21.

Keratoacanthoma

Subungual or periungual keratoacanthomas are typically painful, rapidly enlarging lesions that are usually solitary [1,2]. They are often referred to by the acronym SUKA. Keratoacanthoma is a misleading term as it is very uncommon for the tumour to involute [3] as seen in keratoacanthomas elsewhere. There is no apparent relationship to sun exposure. Although trauma and wire wool have been implicated [4], in most cases there is no obvious precipitating factor. Erosion of bone is seen on X-ray, which is an essential preliminary investigation [3,5–7]. This feature is likely to represent a reversible pressure effect of rapid subungual expansion, rather than bone invasion [3]. The diagnosis is made partly on the history but largely from the histology, which closely resembles that of a keratoacanthoma seen elsewhere, but showing little or no squamous dysplasia [5]. Subungual wart, squamous cell carcinoma and subungual exostosis are among the differential diagnoses. Clinically, subungual keratotic incontinentia pigmenti tumours fall between the appearance of fibroma and keratoacanthoma [8,9]. They resemble the latter in often being painful and causing underlying bone changes. They are commonly multiple and seen with the other features of incontinentia pigmenti, which is usually lethal in males. These tumours can be treated with oral retinoids [10], but may eventually require surgery.

Treatment. Treatment of subungual keratoacanthoma can be by Mohs' micrographic surgery or curettage. More aggressive treatments, including amputation of the digit, have been employed in the past, but are rarely warranted [11]. Given the concern that the tumour may represent a form of squamous cell carcinoma, confirmation of excision margins is important.

References

1 Baran R, Mikhail G, Costini B *et al*. Distal digital keratoacanthoma: two cases with a review of the literature. *Dermatol Surg* 2001; **27**: 575–9.
2 Baran R, Goettmann S. Distal digital keratoacanthoma: a report of 12 cases and a review of the literature. *Br J Dermatol* 1998; **139**: 512–5.
3 Sinha A, Marsh R, Langtry J. Spontaneous regression of subungual keratoacanthoma with reossification of underlying distal lytic phalaynx. *Clin Exp Dermatol* 2005; **30**: 20–2.
4 Fisher AA. Subungual keratoacanthoma: possible relationship of exposure to steel wool. *Cutis* 1990; **46**: 26–8.
5 Keeney GL, Banks PM, Linscheid RL. Subungual keratoacanthoma. Report of a case and review of the literature. *Arch Dermatol* 1990; **124**: 1074–6.
6 Oliwiecki S, Peachey RDG, Bradfield JWB *et al*. Subungual keratoacanthoma: a report of four cases and review of the literature. *Clin Exp Dermatol* 1994; **19**: 230–5.
7 Patel MR, Desai SS. Subungual keratoacanthoma in the hand. *J Hand Surg* 1989; **14A**: 139–42.
8 Adeniran A, Townsend PLG, Peachey RDG. Incontinentia pigmenti (Bloch–Sulzberger syndrome) manifesting as painful periungual and subungual tumours. *J Hand Surg* 1993; **18B**: 667–9.
9 Bessems PJM, Jagtman BA, Van de Staak W. Progressive, persistent, hyperkeratotic lesions in incontinentia pigmenti. *Arch Dermatol* 1988; **124**: 29–30.
10 Malvehy J, Palou J, Mascaro JM. Painful subungual tumour in incontinentia pigmenti. Response to treatment with etretinate. *Br J Dermatol* 1998; **138**: 554–5.
11 de Berker D. Hold on the amputation. *Br J Dermatol* 2003; **148**: 1077–8.

Melanocytic lesions

Benign and malignant melanocytic lesions present as longitudinal melanonychia (LM). This means that a careful approach needs to be take to the evaluation of a pigmented nail streak [1]. An understanding of the causes of benign nail pigmentation is important in order to judge when biopsy is indicated to exclude melanoma. Dermoscopy can be useful in assessment [2], although different patterns of melanin deposition within the nail may not allow confident clinical distinction between melanocytic lesions. The presence of blood droplets can enable distinction between melanocytic lesions and haemorrhage, usually related to trauma.

Benign causes of LM

Laugier–Hunziker syndrome

Laugier–Hunziker syndrome features pale-brown LM on one or more digits [3]. There may be periungual involvement resembling Hutchinson's sign, and the oral and genital mucosae may be affected with pigmented macules. The macules are amenable to laser treatment [4].

Subungual naevi

Subungual naevi may present in adulthood or early in life with LM or with naevoid melanosis of the nail plate [5] (Fig. 65.34). This has been described in European [6,7] and Japanese [8] adults and children.

Drug therapy

Drug therapy with hydroxyurea, minocycline, zidovudine [9] and antimalarials may produce brown streaks in the nail (see p. 65.16), as may dermatoses such as lichen planus [10] and onychomycosis [11], trauma [12] and non-melanocytic tumours such as squamous



Fig. 65.34 Benign longitudinal melanonychia due to a subungual naevus.



Fig. 65.35 Malignant melanoma arising in the nail matrix and invading the nail bed.

cell carcinoma *in situ* [13] (see Fig. 65.33). Subungual blood pigment may resemble melanin, but associated features in the history, dermoscopy and gross appearance usually make it possible to distinguish between the two.

Benign racial pigmentation

The most common cause of LM is racial variation; 77% of Afro-Caribbeans over 20 years of age have LM and this prevalence rises to almost 100% by the age of 50 years [14]. It is present in 10–20% of Japanese [15] and is more common in Mediterranean races than in northern Europeans. However, in this context, the percentage of malignant melanomas presenting in the nail unit is higher in Afro-Caribbeans (15–20%) [14] than in any other group (3% in white populations [16]). This contrasts with the low incidence of malignant melanoma at other skin sites in Afro-Caribbeans.

Malignant melanoma [17–20]

There are many features of LM that should suggest the possibility of malignant melanoma. Trauma may be described early in the evolution of the pathology, although a definite association with melanoma is difficult to establish [18]. Variation within the melanonychia and a darker range of pigments can be significant. This is of particular note if the pigment spreads onto the adjacent nail fold or digit pulp (Hutchinson's sign) [21], especially in a single digit in adult life, with a clear history of evolution. Hutchinson's sign is a risk factor, but does not necessarily carry a bad prognosis [2,22]. Dermatoscopic examination through the nail, and end on at the free edge, may help with diagnosis [1,2, 23,24]. The suspicion of melanoma is raised further if the individual has any other risk factors for melanoma, if the involved digit is a thumb, great toe or index finger, and if the nail has become dystrophic.

Despite the importance of LM as a warning sign, 30% of subungual melanomas present as amelanotic tumours. This exceeds the percentage of melanomas presenting as an amelanotic tumour elsewhere. It is difficult to determine whether these tumours were always amelanotic [25] or whether loss of pigment is due to development of the disease process (Fig. 65.35). This form of melanoma usually has associated nail plate damage and easily bleeds. With this appearance, the differential diagnosis includes pyogenic granuloma, chronic paronychia and vascular tumour.

The assessment of pigmented streaks in children is complex. The earlier dictum that they were all benign and could be left has some ramifications. Indeed they are almost all benign [7], although very rare cases of melanoma are reported [26]. This alone may make diagnostic biopsy warranted in some. In addition, it is documented that pigmented streaks arising in childhood can evolve into melanoma, even after an initial biopsy with benign histology (S. Goettmann-Bonvallot, personal communication). The implication of this is that repeated biopsies may be needed as a pigmented streak evolves, and lifelong monitoring is required for children with such signs. Faced with this, complete excision of the matrix origin can sometimes be the best option, even when there is permanent loss of all or part of the nail.

The significance of preceding trauma is unclear [25]. Such a history is present in a large number of cases. It is thought that primary malignant melanoma of the nail unit arises only from within the matrix and not from the nail bed. This is consistent with the absence of antigenically identifiable melanocytes in the nail bed [27,28] and can provide some reassurance when assessing pigmented lesions not arising from the matrix. However, such lesions may arise from the nail folds, or be secondary malignant melanomas.

Biopsy of LM

Given the potential gravity of isolated longitudinal melanonychia, there should be a low threshold for biopsy. The type of biopsy can be determined by a range of factors [1].

1 Periungual pigmentation present. This indicates high risk of malignancy. If there are no other factors to account for this pigmentation, the whole area of affected nail unit should be removed *en bloc* down to bone with a 1-mm margin of normal tissue. Cosmetic considerations are secondary.
2 Lateral third of nail plate involved. This indicates lateral longitudinal biopsy. The cosmetic outcome is reasonable and the assurance provided by complete removal of the affected area is usually worthwhile.
3 Mid-portion of the nail plate involved. The cosmetic outcome of complete excision at this site is potentially bad. This is particularly so if the origin of melanocytes is proximal in the matrix. This may be determined by sampling the free edge of the nail plate and performing a Masson–Fontana stain, or undertaking end-on nail dermoscopy at the free edge. Pigment in the lower part of the nail reflects a distal matrix origin, compared with ventral nail pigment reflecting an origin in the proximal matrix. The latter carries a high risk of scarring following excision.

For lesions less than 3 mm wide. It is usually possible to undertake a full excision and repair of a longitudinal ellipse extending into the nail bed.

For lesions 3–6 mm wide. If the pigment arises from distal matrix, a transverse matrix biopsy can be performed. Proximal matrix pigment requires an en bloc removal and repair using a Schernberg and Amiel flap.

For lesions greater than 6 mm wide. Matrix punch or transverse biopsy is usually adequate as the preliminary investigation. Where the clinical suspicion of a melanocytic lesion is high, it is reasonable to undertake complete matrix and nail bed excision as a single procedure. A benign histology on sampling a band of this size will not provide total reassurance in the long term, and it may therefore be preferable to undertake a curative and preventive excision at the outset.

Treatment and prognosis. Nail unit melanoma has a record of delayed treatment and poor prognosis [29]. It affects light- and dark-skinned people, with those of African origin representing 12% of patients in one North American series [30]. The most common pattern is of acral lentiginous melanoma [17], although one series reported the superficial spreading type as being marginally more common [31]. In the acral lentiginous form, there is lentiginous spread of pleomorphic, often dendritic, atypical melanocytes in the basal and suprabasal layers of the epidermis. Epidermal melanoma cells may be incorporated into the nail plate and seen on stained clippings of nail taken from the free edge. Dermal melanoma cells are pleomorphic, with spindle, epithelioid, polygonal, dendritic and bizarre shapes.

Hutchinson's sign is represented histologically by atypical melanocytes mainly in the basal layer, with a few higher in the epidermis. *In situ* subungual melanoma has junctional nests of melanoma cells. Nodular patterns of melanoma are rare.

Amputation of the digit is the routine treatment, although local excision is occasionally practised for small shallow lesions and is an accepted mode of treatment for *in situ* melanoma [1]. Mohs' micrographic surgery is used in some centres, but is still at a relatively early stage of evaluation [32]. In one series of 14 patients, three had recurrence at the margins of treatment. Adjuvant isolated limb perfusion has failed to show benefit in stage 1 subungual melanoma [33], although use of a more aggressive regimen has possibly been associated with improved survival [34].

British surveys [31,35,36] suggest that the poor prognosis of subungual melanoma is related to the depth of invasion at diagnosis (4.7 mm). This reflects late diagnosis (3 months to 12 years). The mean 5-year survival was 41% compared with 61% for a control group of primary cutaneous malignant melanomas in the same study [35]. In comparison, in a French study of 146 patients with acral lentiginous melanoma there was a mean Breslow thickness of 2.51 mm and 76% 5-year survival [20]. Japanese evidence supports the idea that diagnosing subungual melanoma early, with a lower Breslow thickness, improves prognosis, with an 87% 5-year survival rate [34].

References

1 Braun RP, Baran R, Le Gal FA *et al*. Diagnosis and management of nail pigmentations *J Am Acad Dermatol* 2007; **56**: 835–47.
2 Thomas L, Dalle S. Dermoscopy provides useful information for the management of melanonychia striata. *Dermatol Ther* 2007; **20**: 3–10.
3 Baran R, Bariere H. Longitudinal melanonychia with spreading pigmentation in Laugier–Hunziker syndrome: a report of 2 cases. *Br J Dermatol* 1986; **115**: 707–10.
4 Papadavid E, Walker NP. Q-switched Alexandrite laser in the treatment of pigmented macules in Laugier–Hunziker syndrome. *J Eur Acad Dermatol Venereol* 2001; **15**: 468–9.
5 Tosti A, Baran R, Piraccini BM *et al*. Nail matrix naevi: a clinical and histopathologic study of twenty-two patients. *J Am Acad Dermatol* 1996; **34**: 765–71.
6 Léauté-Labrèze C, Bioulac-Sage P, Taïeb A. Longitudinal melanonychia in children. *Arch Dermatol* 1996; **132**: 167–9.
7 Goettmann-Bonvallot S, Andre J, Belaich S. Longitudinal melanonychia in children: a clinical and histopathologic study of 40 cases. *J Am Acad Dermatol* 1999; **41**: 17–22.
8 Kikuchi I, Inoue S, Sakaguchi E *et al*. Nevoid nail area melanosis in childhood (cases which showed spontaneous regression). *Dermatology* 1993; **186**: 88–93.
9 Gallais V, Lacour JPH, Perrin C *et al*. Acral hyperpigmented macules and longitudinal melanonychia in AIDS patients. *Br J Dermatol* 1992; **126**: 387–91.
10 Juhlin L, Baran R. Longitudinal melanonychia after healing of lichen planus. *Acta Derm Venereol (Stockh)* 1989; **69**: 338–9.
11 Matsumoto T, Matsuda T, Padhye AA *et al*. Fungal melanonychia: ungual phaeohyphomycosis caused by *Wangiella dermatitidis*. *Clin Exp Dermatol* 1992; **17**: 83–6.
12 Haneke E, Baran R. Longitudinal melanonychia. *Dermatol Surg* 2001; **27**: 580–4.
13 Baran R, Simon C. Longitudinal melanonychia: a symptom of Bowen's disease. *J Am Acad Dermatol* 1988; **6**: 1359–6.
14 Monash S. Normal pigmentation in the nails of the negro. *Arch Dermatol* 1932; **25**: 876–81.
15 Kopf AW, Waldo E. Melanonychia striata. *Australas J Dermatol* 1980; **21**: 59–70.
16 Collins RJ. Melanomas in the Chinese among south western Indians. *Cancer* 1984; **55**: 2899–902.
17 Blessing K, Kernohan NM, Park KGM. Subungual malignant melanoma: clinicopathological features of 100 cases. *Histopathology* 1991; **19**: 425–9.
18 Bormann G, Marsch WC, Haerting J, Helmbold P. Concomitant traumas influence prognosis in melanomas of the nail apparatus. *Br J Dermatol* 2006; **155**: 76–80.

19 Daly JM, Berlin R, Urmacher C. Subungual melanoma. *Ann Surg* 1987; **161**: 545–52.
20 Phan A, Touzet S, Dalle S *et al*. Acral lentiginous melanoma: a clinicoprognostic study of 126 cases. *Br J Dermatol* 2006; **155**: 561–9.
21 Kopf AW. Hutchinson's sign of subungual malignant melanoma. *Am J Dermatopathol* 1981; **3**: 201–2.
22 Baran R, Kechijian P. Hutchinson's sign: a reappraisal. *J Am Acad Dermatol* 1996; **34**: 87–90.
23 Ronger S, Touzet S, Ligeron C *et al*. Dermoscopic examination of nail pigmentation. *Arch Dermatol* 2002; **138**: 1327–33.
24 Kawabata Y, Ohara K, Hino H, Tamaki K. Two kinds of Hutchinson's sign, benign and malignant. *J Am Acad Dermatol* 2001; **44**: 305–7.
25 Miura S, Jimbow K. Clinical characteristics of subungual melanomas in Japan. *J Dermatol* 1985; **12**: 393–402.
26 Kiryu H. Malignant melanoma in situ arising in the nail unit of a child. *J Dermatol* 1998; **25**: 41–4.
27 de Berker D, Dawber RPR, Thody A, Graham A. Melanocytes are absent from normal nail bed: the basis of a clinical dictum. *Br J Dermatol* 1996; **134**: 564.
28 Perrin C, Michiels JF, Pisani A, Ortonne JP. Anatomic distribution of melanocytes in normal nail unit: an immunohistochemical investigation. *Am J Dermatopathol* 1997; **19**: 462–7.
29 Thai KE, Young R, Sinclair RD. Nail apparatus melanoma. *Australas J Dermatol* 2001; **42**: 71–83.
30 O'Leary JA, Berend KR, Johnson JL *et al*. Subungual melanoma. A review of 93 cases with identification of prognostic variables. *Clin Orthop* 2000; **78**: 206–12.
31 Rigby HS, Briggs JC. Subungual melanoma: a clinicopathological study of 24 cases. *Br J Plast Surg* 1992; **45**: 275–8.
32 Brodland DG. The treatment of nail apparatus melanoma with Mohs micrographic surgery. *Dermatol Surg* 2001; **27**: 269–73.
33 Vrouenraets BC, Kroon BBR, Klaase JM *et al*. Regional isolated perfusion with melphalan for patients with subungual melanoma. *Eur J Surg Oncol* 1993; **19**: 37–42.
34 Kato T, Suetake T, Sugiyama Y *et al*. Epidemiology and prognosis of subungual melanoma in 34 Japanese patients. *Br J Dermatol* 1996; **134**: 383–7.
35 McLaren KM, Hunter JAA, Smyth JF *et al*. The Scottish Melanoma Group: a progress report. *J Pathol* 1989; **158**: 335A.
36 Banfield CC, Redburn JC, Dawber RP. The incidence and prognosis of nail apparatus melanoma. A retrospective study of 105 patients in four English regions. *Br J Dermatol* 1998; **139**: 276–9.

Nail surgery [1,2]

Nail surgery is delicate and requires attention to detail. It is important that anyone performing a nail biopsy appreciates the principles outlined in the preliminary section of this chapter on anatomy and physiology, and that they obtain tuition in detailed technique. Once in this position, the outcome of nail unit surgery is usually excellent and provides useful and definitive diagnostic material [3].

For many procedures, the routine skin surgery pack needs to be supplemented by specialized instruments. These include a Freer septum elevator for finger work and a larger elevator for the great toenail. English nail splitters are essential for performing partial avulsion. They have a flat undersurface, which can be introduced beneath the nail to act as an anvil and a sharp upper part that cuts down upon the nail to meet the other half of the instrument. For bone surgery, such as removal of exostoses, bone rongeurs and McKindoes are needed.

Indications

A nail biopsy may perform several functions. It can provide useful positive diagnostic information or help exclude a malignant condition, such as squamous cell carcinoma of the nail bed. Painful conditions may be relieved by the drainage of pus with proximal hemi-avulsion, or ablation of an ingrowing toenail. Focal pathology, such as a glomus tumour or the origin of melanonychia, can be completely excised and provide the diagnosis. If a positive diagnostic and therapeutic attitude is taken to the nail disorder, a good outcome can be expected.

Diagnostic nail biopsy may be undertaken as part of the investigation of nail dystrophy of unknown cause in the presence of more than one negative mycology sample.

Biopsy of the nail plate alone, or with associated nail bed and occasionally matrix biopsy, may be needed to confirm fungal infection in atypical cases, although biopsies are more commonly directed at distinguishing between dermatoses affecting the nail, such as lichen planus, psoriasis or infiltrative disease. In instances of nail dystrophy of a single digit, it is appropriate to biopsy to exclude a neoplasm once necessary imaging has been performed.

Caution is needed in patients with relevant medical and circulatory problems. The latter are subject to poor reperfusion following the tourniquet and it may be necessary to abbreviate the procedure to ensure no inadvertent damage is done. The wound must be seen to bleed and the digit colour return before the dressing is applied in these cases, and this can take several minutes. This contrasts with the usual pace at which dressings are applied to prevent bleeding in a healthy digit. Diabetics may have ischaemia combined with immune impairment and frequently need attention to toenail problems. Paradoxically, they are cited as a group in whom cold steel surgery for nail problems is preferable to other techniques such as phenolic ablation or cryosurgery. This is because the course of healing in these wounds is predictable and often shorter than wounds produced by other therapies.

Preoperatively

It is advisable to prepare the patient for the procedure by a discussion on a day other than that on which the surgery is performed. In this discussion, the patient must appreciate the potential benefits and problems of the biopsy. It is useful to make it clear that it will be painful and that they will have a degree of disability postoperatively for which they must make provision at home and at work. The best surgical technique can be utterly confounded by a patient who goes back to a dirty workplace the next day. Much of the information concerning scarring, the need for elevation, dressings and analgesia has to be repeated on the day of the procedure. The patient should have a means of transport home that does not involve them driving or standing for prolonged periods.

The affected digit should be soaked in warm antiseptic and scrubbed in a manner similar to that used by the surgeon prior to gloving. This will diminish the bacterial load beneath the free edge of the nail, which is a source of potential pathogens. Soaking for 10 min softens the nail and facilitates removal of parts of the nail plate, so avoiding complete avulsion. During this period, the local anaesthetic can take effect.

Anaesthetic (Fig. 65.36)

Lidocaine (lignocaine) 2% or equivalent can be used [4]. Bupivacaine can be used to provide prolonged analgesia. The use of

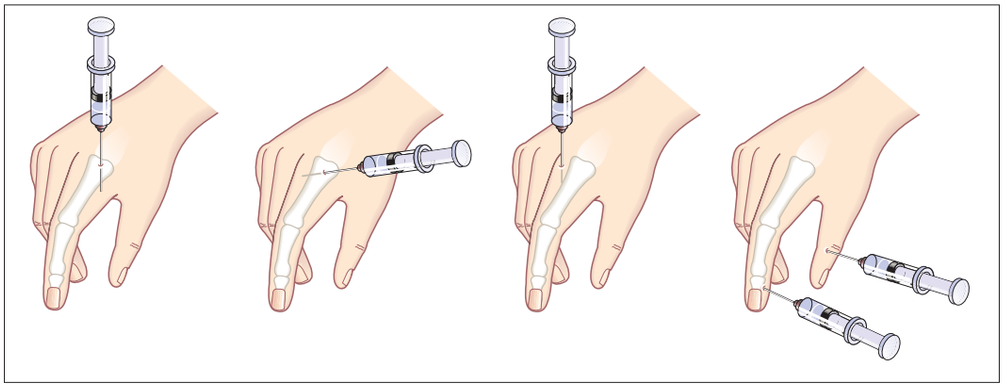


Fig. 65.36 Digital sites of injection for a ring block.

epinephrine (adrenaline) in anaesthetic remains controversial. There are several publications illustrating how anaesthetic containing 1 in 200 000 epinephrine has been used safely [5]. The ischaemia and prolongation of anaesthesia is a potential advantage. If subjects with peripheral ischaemic or vasospastic disease are avoided, anaesthetic with 1 in 200 000 epinephrine appears safe. An alternative is to use ropivacaine. This local anaesthetic has physiological and pharmacological properties somewhere between bupivacaine and lidocaine. It has a moderately quick onset of action and can produce anaesthesia for over 12 h, combined with a modest short-term vasoconstrictive effect [6]. We use ropivacaine 7.5 mg/mL in the same way as lidocaine, with very good results. A 30-gauge needle causes less discomfort during injection than larger needles, and minimizes the risk of damage to digital nerves when inserting a ring block. Risk of nerve trauma may be reduced further by the use of nerve-block needles, which have less traumatic tips.

The most common form of anaesthesia is a ring block (digital nerve block), which is delivered by injection of anaesthetic into the dorsolateral aspect of the digit at the base, with about 1–2 mL on each side of the phalanx. Greater than 5 mL may impair circulation, but this can be assessed visually during the procedure and is very variable according to the bulk of individual digits. Anaesthesia may take 10–20 min to become total. In the great toe, additional anaesthetic should be placed ventrally. After 10 min, efficacy of the block can be assessed at the digit tip with the same needle; if the anaesthesia is incomplete, it can be supplemented by a small local injection at the site of surgery. However, this can increase tissue turgor and render fine manipulation difficult.

Other ring block techniques can be employed, including a method that aims to infiltrate the anaesthetic via the flexor tendon as a transthecal block [7,8]. An alternative is the distal 'wing' block given 2–3 mm proximal to the junction of the proximal and lateral nail folds. The injection is first directed distally into the lateral nail fold. After partial withdrawal, it is redirected over the proximal nail fold. Sufficient is used to produce blanching in both nail folds. The procedure is repeated on the other side to achieve complete block. The digit is more sensitive distally than proximally and it is often more comfortable to provide the traditional proximal digital nerve block.

For invasive procedures on many digits concurrently, more proximal or regional blocks can be employed [9]. In children it can be worthwhile to use a topical anaesthetic as a preliminary measure before ring block. Evidence of its efficacy in adults is mixed [10,11].

Tourniquet

It is important that the area of applied pressure beneath the tourniquet is as broad as possible to avoid pressure damage to underlying structures. In particular, neuritis may be a long-term complication of prolonged application of a narrow, tight tourniquet. This effect can be exacerbated by topping up anaesthetic near the tourniquet after it is in place. Ischaemia can be tolerated in a normal digit for 20 min and possibly longer, with no complications as long as there is no local trauma from the tourniquet.

The standard tourniquet for local anaesthetic is the Penrose drain (Fig. 65.37), which may be wound around the digit from the tip proximally. This exsanguinates the digit and provides a tourniquet effect that can be maintained with a pair of artery forceps. A sterile glove is an alternative. It is worn by the patient and the tip of the glove digit at the site of surgery is snipped off. It is then rolled back to the base of the digit, exsanguinating it, providing a tourniquet and avoiding contamination from adjacent digits peroperatively. With general anaesthetic, an exsanguinating cuff can be used on the forearm or calf.

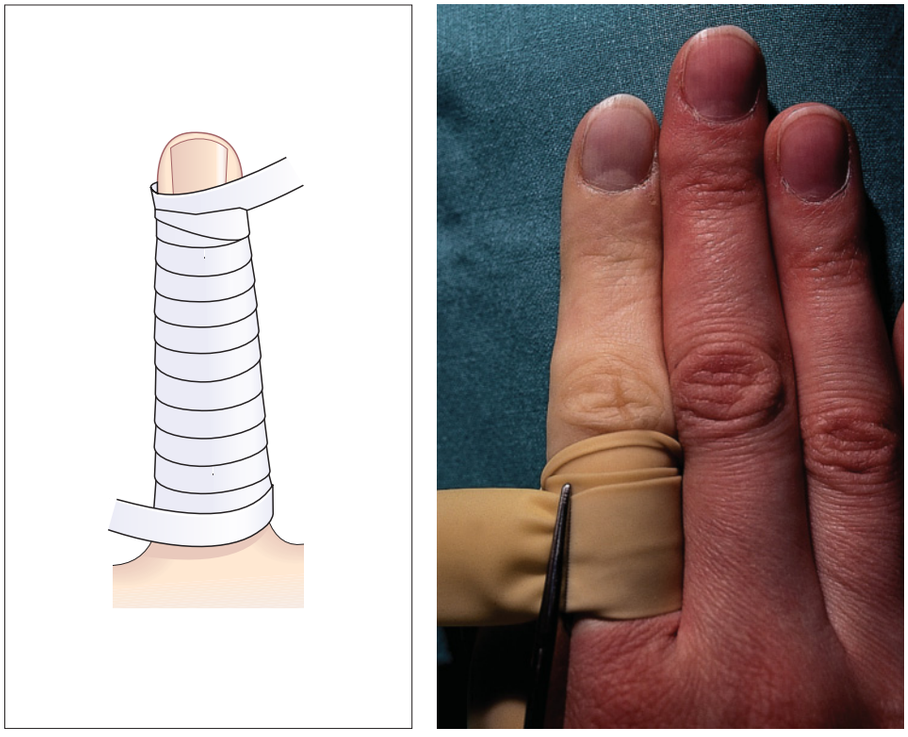
It is our practice to remove the tourniquet before sutured repairs, to detect bleeding points and achieve haemostasis with electrocautery. For some reconstructions it may be necessary to re-apply the tourniquet.

Specimen

The specimen must be delivered to the pathologist undistorted and with the maximum of clinical and operative information. It is useful to allow the specimen to adhere lightly to a piece of paper before immersion in fixative, or to enclose it in a small plastic mesh cassette. This should be matched with a detailed drawing on the histopathology request form. It is helpful to work regularly with the same pathologist for nail specimens, as processing requires specialized understanding of specimen preparation and histological interpretation.

Postoperatively

Dressings should be ready before removal of the tourniquet. They must be firm and moderately bulky. An acceptable dressing



(a) (b)

Fig. 65.37 (a) A Penrose drain is applied from the tip and wound down the digit achieving exsanguination. (b) The drain is then unwound from the top, with the base maintained secure with artery forceps.

includes an antimicrobial ointment under a greasy tulle, padding and a small bandage. Calcium alginate dressings can also be useful if there is an area that needs to heal by secondary intention. Dressings should be held in place with oblique or longitudinal sticky tape to avoid a tourniquet effect if the digit swells. A sling or plastic overshoe should be provided.

The frequency of change of dressings is determined by the nature of the procedure and the patient. An antiseptic soak is normally needed to remove the dressing and clean the wound. Infection should be treated vigorously with systemic antibiotics combined with daily antiseptic soaks.

It is good practice to provide a moderately strong analgesic and to recommend taking it regularly in the first 48 h. It may prove unnecessary, but the distress of unrelieved pain in the few who suffer warrants caution. Some patients need night-time sedation.

In most cases, it is wise to arrange review within 2 days of surgery to change the dressing, assess the wound and answer any questions that have arisen.

Complications

Pain can sometimes be disproportionate to the wound [12]. When it is severe, the patient is at risk of reflex sympathetic dystrophy [13]. They should receive regular potent analgesics, including non-steroidal anti-inflammatory agents, amitriptyline and sometimes an anxiolytic such as diazepam.

Bleeding is common and should be accommodated by firm, bulky dressings. Once blood has clotted in these dressings they can be rock-like and represent an infection risk—good reasons for an early dressing change.

Infection is a potential problem and can be devastating to the matrix. Prophylactic antibiotics are a reasonable precaution when the surgical site is likely to be heavily colonized due to skin changes or a dystrophic nail. Surgery to the toenail matrix, children or patients with poor hygiene may also warrant antibiotics.

Longer term, complications are mainly related to scarring dystrophy and loss of function. The former is always a potential risk of any surgery involving the matrix and should be discussed preoperatively as part of the risk assessment with the patient. Loss of function can be modest, with a tendency for the nail to catch, or more significant if associated with pain or marked paraesthesia. Mild paraesthesia is quite common in the short term and is sometimes seen with cold sensitivity. Complications involving the tendons of the distal interphalangeal joint are very rare and usually related to more proximal surgery.

References

1 Zook EG, Baran R, Haneke E, Dawber RPR. Nail surgery and traumatic abnormalities. In: Baran R, Dawber RPR, de Berker DAR, Haneke E, Tosti A, eds. *Diseases of the Nails and Their Management*, 3rd edn. Oxford: Blackwell Science, 2001: 425–514.

2 Salasche SJ, Peters VJ. Tips on nail surgery. *Cutis* 1985; **35**: 428–38.

3 de Berker D, Dahl MGC, Comaish JS, Lawrence CM. The value of nail unit surgery in dermatology. *Acta Derm Venereol (Stockh)* 1996; **76**: 484–7.

4 Abadir A. Use of local anaesthetics in dermatology. *J Dermatol Surg* 1975; **1**: 68–72.

5 Wilhelmi BJ, Blackwell SJ, Miller J *et al*. Epinephrine in digital blocks: revisited. *Ann Plast Surg* 1998; **41**: 410–14.

6 Moffitt DL, de Berker DA, Kennedy CT, Shutt LE. Assessment of ropivacaine as a local anesthetic for skin infiltration in skin surgery. *Dermatol Surg* 2001; **27**: 437–40.

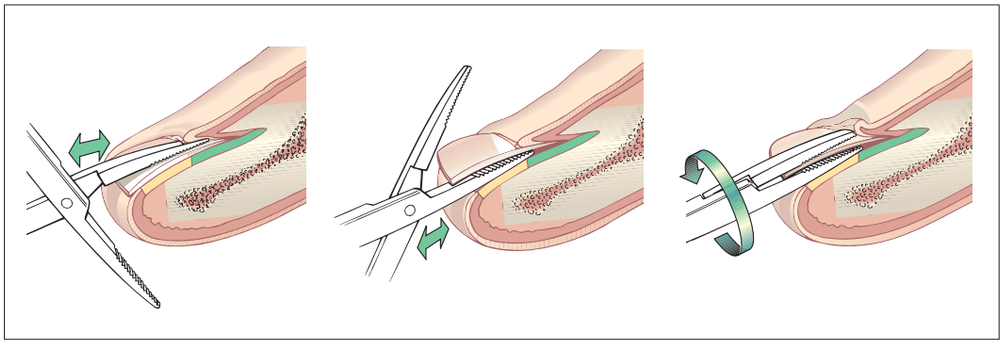


Fig. 65.38 The three stages of standard nail avulsion.

7 Chiu DTW. Transthecal digital block: flexor tendon sheath used for anaesthetic infusion. *J Hand Surg* 1990; **15A**: 471–3.
8 Brutus JP, Baeten Y, Chahidi N *et al*. Single injection digital block: comparison between three techniques. *Chir Main* 2002; **21**: 182–7.
9 Cohen SJ, Roegnik RK. Nerve blocks for cutaneous surgery on the foot. *J Dermatol Surg Oncol* 1991; **17**: 527–34.
10 Serour F, Ben-Yehuda Y, Boaz M. EMLA cream prior to digital nerve block for ingrown nail surgery does not reduce pain at injection of anesthetic solution. *Acta Anaesthesiol Scand* 2002; **46**: 203–6.
11 Browne J, Fung M, Donnelly M, Cooney C. The use of EMLA reduces the pain associated with digital ring block for ingrowing toenail correction. *Eur J Anaesthesiol* 2000; **17**: 182–4.
12 Moossavi M, Scher RK. Complications of nail surgery: a review of the literature. *Dermatol Surg* 2002; **27**: 225–8.
13 Ingram GJ, Scher RK, Lally EV. Reflex sympathetic dystrophy following nail biopsy. *J Am Acad Dermatol* 1987; **16**: 253–6.

Patterns of nail biopsy

Nail avulsion [1,2]

Nail avulsion can be performed in order to examine underlying tissues or to provide temporary relief in cases of soft-tissue trauma. In isolation, it is not a treatment for ingrowing toenails. The procedure requires a distal or ring block, and an elevator in addition to the routine instrument pack. For a partial avulsion, nail splitters are also needed.

To minimize the trauma of the procedure, soft-tissue nail attachments should be loosened at all sites prior to removal. This minimizes tearing damage to the nail folds. The cuticle may need disrupting with fine scissors or a blade, but all other detachments can be performed with a septum elevator. Once this is done, the nail is gripped with a pair of rugged artery forceps and removed by a mixed twisting and lifting action (Fig. 65.38).

With a lateral partial avulsion, the nail splitter is used to define the medial margin and only the attachments of the piece of nail to be removed need to be interrupted. Proximal hemi-avulsion of the nail plate entails the following technique.

1 The origin of the nail and its proximal lateral aspects are undermined with a septum elevator.
2 In nails with a shallow lateral nail fold, a nail splitter may be inserted and the nail transversely bisected.
3 In nails with a deep lateral nail fold, a deep transverse score is placed with a scalpel across the nail halfway along its length.
4 The septum elevator is then fully inserted through the transverse score to loosen and elevate the proximal nail.

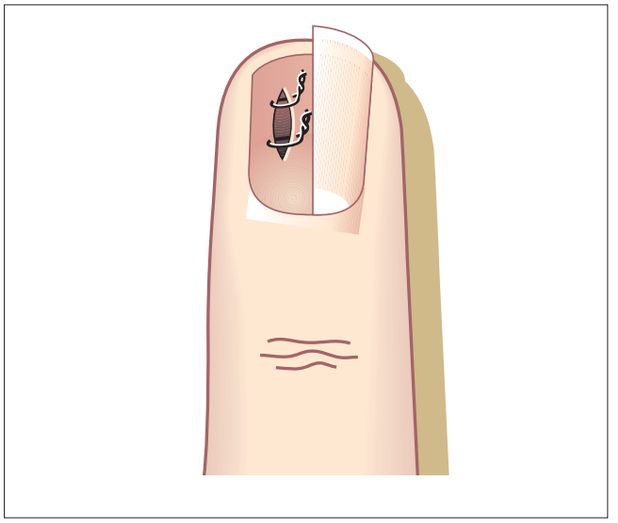


Fig. 65.39 After partial nail avulsion, the nail bed can be seen and biopsied along the longitudinal access.

References

1 Albom MJ. Avulsion of a nail plate. *J Dermatol Surg Oncol* 1977; **3**: 34–5.
2 Baran R. More on avulsion of nail plate. *J Dermatol Surg Oncol* 1981; **7**: 854.

Nail bed biopsy [1–4]

Biopsy of the nail bed is usually performed to investigate a focal abnormality of the nail bed or changes in the nail plate arising distally. Occasionally, it may be appropriate to biopsy through the nail plate where the histological relationship between nail bed and plate is under investigation. More commonly, the nail bed is visualized first, following complete or partial avulsion. A thin ellipse is taken down to bone in the long axis of the digit (Fig. 65.39). An alternative is to employ a double punch technique, where a 6-mm hole can be made in the nail plate with a biopsy punch over the area of nail bed to be examined, and the nail bed sampled using a smaller punch.

If there has been nail avulsion, it is possible to close the wound, which may require gentle undermining. In small biopsies this may be unnecessary, and the wound will heal well by secondary inten-

tion. When the nail is left *in situ* or if the double punch technique is used, closure is not possible. After a double punch, as long as there is complete haemostasis, the original disc of nail plate can be returned after soaking in antiseptic; it may reattach or at least provide a natural dressing during the early healing phase.

No scarring is anticipated from this biopsy if it is small and does not extend into the nail matrix.

References

1 Baran R, Sayag J. Nail biopsy. Why, when, where, how? *J Dermatol Surg Oncol* 1976; **2**: 322–4.
2 Haneke E. Surgical anatomy of the nail apparatus. *Dermatol Clin* 2006; **24**: 291–6.
3 Hanno R, Mathes BM, Krull EA. Longitudinal nail biopsy in evaluation of acquired nail dystrophies. *J Am Acad Dermatol* 1986; **14**: 803–9.
4 Jellinek NJ. Nail surgery: practical tips and treatment options. *Dermatol Ther* 2007; **20**: 68–74.

Matrix biopsy

Lateral longitudinal nail biopsy [1,2]

Lateral longitudinal nail biopsy is the definitive method for sampling all the tissues of the nail unit. It is most commonly required when there is dystrophy affecting the whole nail or for the excision of a melanonychia. If focal matrix pathology occurs laterally, longitudinal biopsy may be warranted to preserve the shape of the nail, which can otherwise be altered by local matrix surgery. Early literature suggested that longitudinal biopsies of less than 3 mm in width could be taken from the midline of the nail without scarring [3] but it is now accepted that this may produce long-term nail dystrophy.

The first incision starts in the lateral nail sulcus, between the nail and nail fold. The distal limit is just beneath the distal groove, in the tip of the digit. Proximally, the incision extends almost to the first of the transverse skin markings of the distal interphalangeal joint. The medial margin of the ellipse is formed by an incision through the nail plate, which has been softened by an antiseptic soak. Both incisions are down to bone and separated by 3 mm at the widest point. The specimen is released from its deep attachment from the distal point proximally. The nail can be lifted at the free edge with forceps, allowing the bottom of the specimen to be released with curved iris scissors. Particular care is needed at the proximal end to ensure that the matrix is fully sampled without damage.

A 3/0 or 4/0 monofilament suture is used for closure. One suture closes the wound through the proximal nail fold. One or two further sutures are needed through the nail plate and lateral nail fold. The suture is designed to elevate the lateral nail fold and enhance the embedding of the new nail edge in the nail fold (Fig. 65.40).

The nail will be permanently narrowed following this procedure and the contour of the lateral and proximal nail fold intersection is altered to provide a more acute angle. In spite of the specialized suture to elevate the lateral nail fold, the nail is seldom fully embedded in a new lateral sulcus. Where biopsies of greater than 3 mm width are taken, the nail may develop malalignment, with distal deviation towards the side of the biopsy [4].

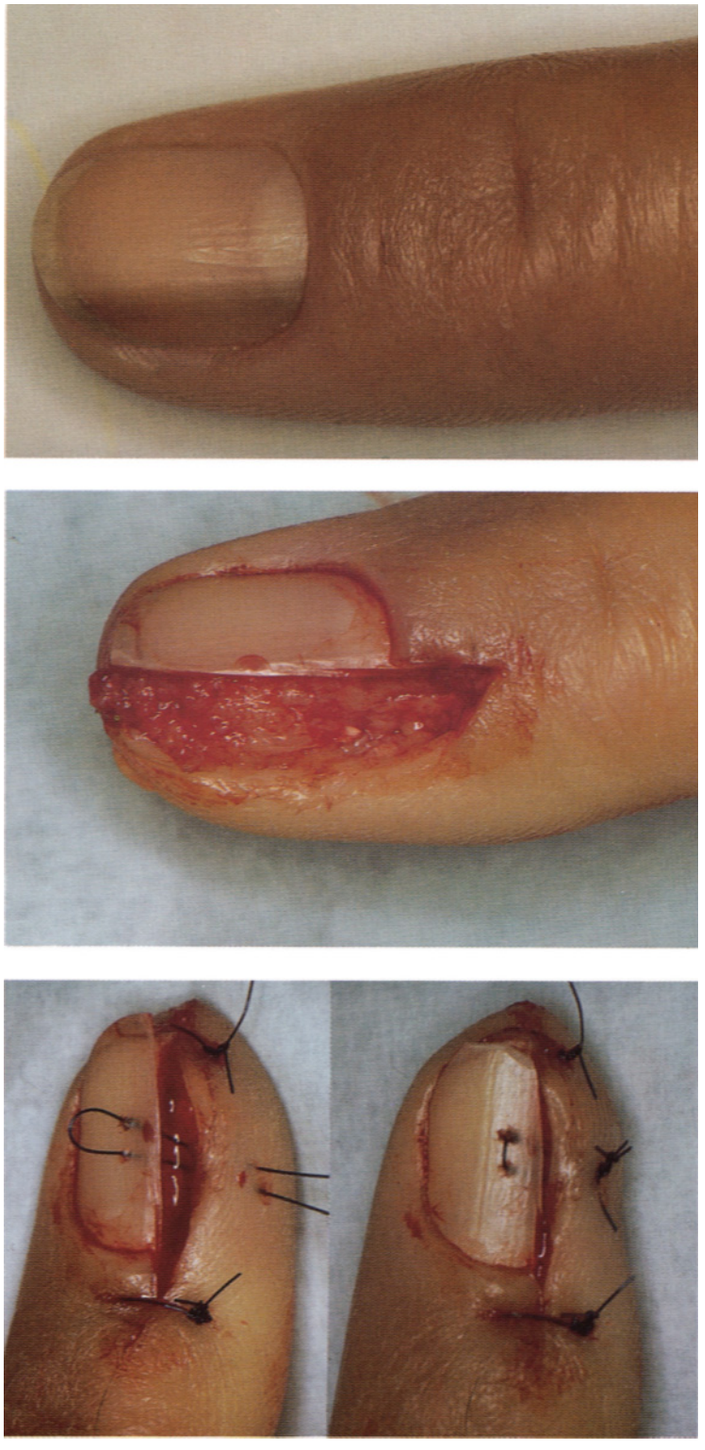


Fig. 65.40 A large, lateral, longitudinal nail biopsy is closed with sutures designed to reconstruct the lateral nail fold.

References

1 Rich P. Nail biopsy: indications and methods. *J Dermatol Surg Oncol* 1992; **18**: 673–82.
2 Salasche SJ, Peters VJ. Tips on nail surgery. *Cutis* 1985; **35**: 428–38.
3 Zaias N. The longitudinal nail biopsy. *J Invest Dermatol* 1967; **49**: 406–8.
4 de Berker D, Baran R. Acquired malalignment of the nail following broad lateral longitudinal nail biopsy. *Acta Derm Venereol (Stockh)* 1998; **78**: 468–70.

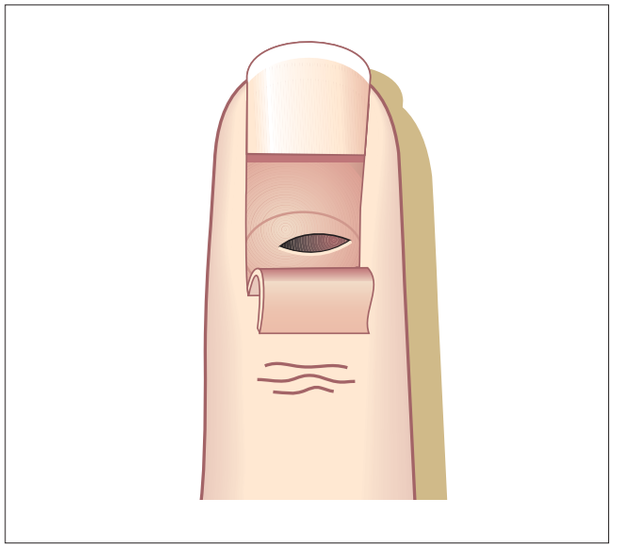


Fig. 65.41 Crescentic or narrow elliptical transverse matrix biopsy, which can be performed after removal of the proximal half of the nail plate alone.

Transverse matrix biopsy (Fig. 65.41)
A transverse matrix biopsy may be performed to investigate focal abnormality of a nail dystrophy arising from the matrix.

The proximal nail fold is reflected following an oblique incision at the junction with the lateral nail folds and gentle separation of the proximal nail fold from the dorsal aspect of the nail plate. The matrix is then visualized by performing a proximal hemi-avulsion. A thin ellipse is taken from the distal matrix with the distal margin of the excision matching the shape of the lunula.

The wound may be gently undermined, taking care with the extremely fragile matrix epithelium and undermining most on the distal nail bed margin. Loose sutures with resorbable 6/0 monofilament can be used.

Once healed, a blemish may remain in the margin of the lunula. The nail plate will show changes in thickness proportional to the extent of the biopsy.

Matrix shave or tangential biopsy
Haneke has described a technique of obtaining a diagnostic shave biopsy from nail matrix in longitudinal melanonychia [1,2]. When successful, it can also represent an excision specimen. The matrix needs to be exposed, with clear identification of the origin of the melanonychia. The origin is then scored with a scalpel, 1 mm beyond the edge of the pathology. This score mark is then used as a guide for a shave sample to be obtained, extending the excision into the dermis so as to avoid leaving a remnant of the matrix epidermis rete pattern or superficial melanocytic naevus. Incomplete excision may occur with deeper naevi or biopsies of irregular depth. The nail plate is replaced to prevent contact between the wound and ventral aspect of the nail fold, and suture repair is not required. Secondary intention healing can result in normal or only slightly abnormal nail, but there are insufficient published cases to give clear guidance.

References
1 Haneke E, Baran R. Longitudinal melanonychia. *Dermatol Surg* 2001; **27**: 580–4.
2 Jellinek N. Nail matrix biopsy of longitudinal melanonychia: diagnostic algorithm including the matrix shave biopsy. *J Am Acad Dermatol* 2007; **56**: 803–10.

Nail fold biopsy [1–4]

Proximal nail fold biopsy
It may be necessary to biopsy the proximal nail fold to investigate a local dermatosis, connective tissue disease or focal tumour. The biopsy can be taken in different axes, but preservation of the symmetry and curvature of the proximal nail fold is a priority. If sutures are to be used, a distal wing block should be avoided, as the tissues will become turgid and difficult to manipulate.

Transverse nail fold biopsy
A transverse ellipse (for connective tissue disease), a 2-mm punch (far from the free edge) or a shave biopsy are simple nail fold procedures. The transverse ellipse and punch biopsies are down to the dorsal aspect of the nail plate. The matrix may require protection from cutting trauma and this can be achieved by inserting a septum elevator between the nail fold and the nail.

The transverse biopsy requires 4/0 monofilament suture. Wounds from other biopsy methods can be left to heal by secondary intention. Postoperatively, a thin line may remain in the nail fold after the transverse biopsy; otherwise, these techniques leave little or no scarring. There is no nail plate change.

Crescentic nail fold biopsy (Fig. 65.42)
A larger nail fold biopsy can be taken as a distal crescentic wedge. A crescentic incision is performed just proximal to the cuticle with the blade angled to direct trauma away from the proximal matrix if the nail is penetrated. Additional matrix protection may be provided by inserting a septum elevator beneath the proximal nail fold. The distal fraction of the proximal nail fold (including the cuticle) can be removed, although the width of the specimen should not exceed 4–5 mm in the midline. The contour is aimed at recreating a new edge to the entire nail fold. The wound heals by secondary intention and a new cuticle usually reforms, depending upon the original problem. The amount of exposed nail is permanently enlarged, but the nail surface is unchanged unless ridging or grooves produced by the original pathology are reversed.

This technique can be used for the excision of chronic paronychia resistant to routine therapy. It has also been recommended for the excision of digital mucus cysts occupying the most distal margin of the nail fold. At this site, it is argued that the lesions are solely degenerative and do not communicate with the joint space [3,4].

Focal nail fold biopsy
Focal pathology in the nail fold can be excised by a V-shaped incision into the nail fold. The excision is through the entire thickness of the nail fold, but should not penetrate underlying nail. Relaxing incisions are made at one or both of the lateral margins of the proximal nail fold (Fig. 65.43). The primary defect is closed with 4/0 monofilament suture and the relaxing incisions heal by sec-



Fig. 65.42 Crescentic shave of the distal proximal nail fold and cuticle as treatment for chronic paronychia. Also provides histological specimen where biopsy relevant.

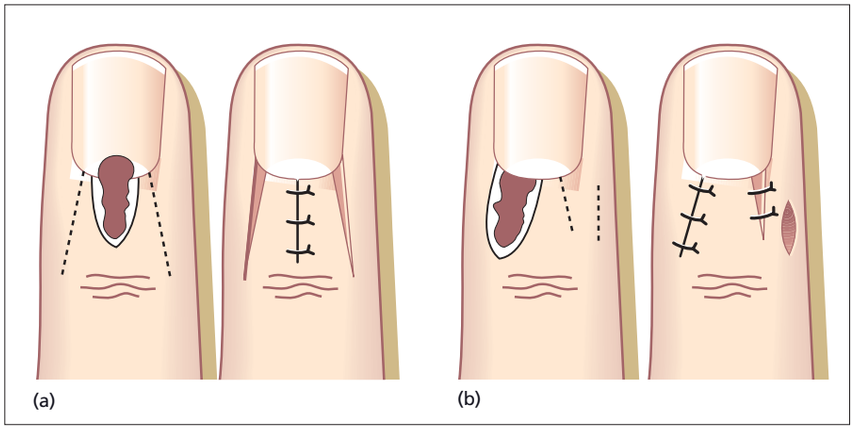


Fig. 65.43 Method for removing a small lesion from the proximal nail fold.

ondary intention. Wounds in the midline of the nail fold can leave some scarring, but the nail plate is usually unaffected.

References

1 Baran R. Removal of the proximal nail fold. Why, when, how? *J Dermatol Surg Oncol* 1986; **12**: 234–6.

2 Zook EG, Baran R, Haneke E, Dawber RPR. Nail surgery and traumatic abnormalities. In: Baran R, Dawber RPR, de Berker DAR, Haneke E, Tosti A, eds. *Diseases of the Nails and Their Management*, 3rd edn. Oxford: Blackwell Science, 2001: 425–514.

3 Salasche SJ. Myxoid cysts of the proximal nail fold: a surgical approach. *J Dermatol Surg Oncol* 1984; **10**: 35–9.

4 Schnitzler L, Baran R, Civatte J *et al*. Biopsy of the proximal nail fold in collagen diseases. *J Dermatol Surg Oncol* 1976; **2**: 313–5.

Nail plate biopsy [1,2]

It is sometimes useful to biopsy the nail plate, with or without a small piece of the hyponychium. This may help differentiate between onychomycosis and psoriasis. If hyponychium is included, a small bleb of anaesthetic will be needed or a distal wing block can be performed. A chunk of distal nail plate of at least 3 mm width is then removed with large nail clippers. Subungual debris should also be obtained and a scalpel may be needed if hyponychium is attached. Hyponychial wounds heal by secondary intention after cautery haemostasis, and leave no scarring.

References
1 Cabral A, Berger TH, Middag-Broekman JH, Boon ME. Unequivocal morphological diagnosis of fungi in morphologically abnormal nails. *Histopathology* 2006; **48**: 862–7.
2 Grammer-West NY, Corvette DM, Giandoni MB, Fitzpatrick JE. Clinical pearl: nail plate biopsy for the diagnosis of psoriatic nails. *J Am Acad Dermatol* 1998; **38**: 260–2.

Lateral matrix phenolization [1,2]

Ingrowing nails, particularly toenails, can be treated in many different ways [1–4]. However, phenolization is quick, relatively painless and has a high success rate [5]. Any area of matrix may be phenolized, including total ablation. In some centres sodium hydroxide is used in place of phenol. This is reported to produce good results and possibly a shorter period of postoperative ooze [6].

After anaesthetic, antiseptic soak and tourniquet, the margin of lateral ingrowing nail is avulsed using nail splitters to separate it from the rest of the nail plate. The nail folds are then protected with a layer of yellow soft paraffin, and 85% aqueous phenol is applied on the end of an orange stick to the exposed matrix. This is done for 3 min (one stick per min), before douching with 70% alcohol to neutralize the chemical cautery. Although 3 min is common practice [1], in one series of 537 ingrowing nails, phenol was applied for 5–6 min and a 99% 1-year cure rate was achieved, with a mean healing period of 20 days [2]. As a result of the chemical burn, there is some ooze from the wound, which can occasionally last several weeks, but it is seldom infected and is often pain-free. If the ooze is prominent, the toe should receive daily potassium permanganate or povidone–iodine soaks, or be irrigated directly to remove debris. It is advisable to culture for specific microbes. The nail is permanently narrowed.

There is occasionally a small element of lateral nail regrowth, although further surgery is indicated only if there is repeated symptomatic ingrowing. Complete nail ablation can be achieved using the same technique applied to the entire matrix.

References
1 Kimata Y, Uetake M, Tsukada S, Harii K. Follow up study of patients treated for ingrown nails with the nail matrix phenol method. *Plast Reconstr Surg* 1995; **95**: 719–24.
2 Bose B. A technique for excision of nail fold for ingrowing toenail. *Surg Gynecol Obstet* 1971; **132**: 511–2.
3 Haneke E. Ingrown and pincer nails: evaluation and treatment. *Dermatol Ther* 2002; **15**: 148–58.
4 Bostanci S, Kocyigit P, Gurgey E. Comparison of phenol and sodium hydroxide chemical matricectomies for the treatment of ingrowing toenails. *Dermatol Surg* 2007; **33**: 680–5.
5 Johnson DB, Ceilley RI. A revised technique for the ablation of the matrix of a nail. *J Dermatol Surg Oncol* 1979; **5**: 642.
6 Rounding C, Hulm S. Surgical treatments for ingrowing toenails. *Cochrane Database Systematic Review* 2000; (2): CD001541.

Other surgical modalities

Mohs micrographic surgery

This technique applied to the nail unit exploits the principle of maximum conservation of healthy tissue while ensuring tissue clearance of tumour. It is particularly useful in squamous cell carcinoma of the nail unit (see p. 65.37), where it should be offered as an alternative to digit amputation when there is no evidence of invasion of bone by tumour [1,2]. At this site, the conservation of normal tissue is of considerable functional significance. The place of Mohs' surgery in treatment of pigmented lesions of the nail apparatus remains to be fully explored. There is limited experience of its use in nail melanoma [3].

Cryosurgery

Cryosurgery is widely used for the treatment of periungual warts. There is a small risk of damage to the tendons in the finger with aggressive freezing techniques. It is also used for myxoid cysts [4,5]. The cysts should be evacuated of their mucoid contents before a double 20-s freeze–thaw cycle. EMLA (eutectic mixture of local anaesthetics) or injected local anaesthetic may sometimes be needed. This regimen produces cure in approximately 25% of cases [5], although more aggressive freezing can produce better results [4].

Infrared photocoagulation

This has been used as a treatment for myxoid cysts of the proximal nail fold [6,7]. The contents are evacuated through a puncture wound before treatment.

Carbon dioxide laser

There is a range of indications for carbon dioxide laser [8–10], and its virtue may be in provision of a bloodless wound which allows a good view of the surgical procedure. This can normally be provided only in cold-steel surgery by an effective tourniquet.

The bulk of laser work on the nail unit is for subungual and periungual warts. This uses the defocused mode with a 1–2 mm spot at 5–10 W output and can be intermittent, in 0.05-s bursts, or continuous. Haemostasis may not be complete, and both anaesthetic and tourniquet are usually used with the laser.

It is also used in the treatment of myxoid cysts [11] and ablation of abnormal nail in irreversible nail disorders. This includes partial destruction of the matrix in ingrowing nails [12–14] and in pachyonychia congenita to reduce nail thickness.

References
1 de Berker DAR, Dahl MGC, Malcolm AJ, Lawrence CM. Micrographic surgery for subungual squamous cell carcinoma. *Br J Plast Surg* 1996; **49**: 414–9.
2 Zaiac MN, Weiss E. Mohs micrographic surgery of the nail unit and squamous cell carcinoma. *Dermatol Surg* 2001; **27**: 246–51.
3 Brodland DG. The treatment of nail apparatus melanoma with Mohs micrographic surgery. *Dermatol Surg* 2001; **27**: 269–73.
4 Dawber RPR, Sonnex T, Leonard J, Ralfs I. Myxoid cysts of the finger: treatment by liquid nitrogen spray cryosurgery. *Clin Exp Dermatol* 1983; **8**: 153.
5 de Berker DAR, Lawrence CM. Cryosurgery for myxoid cysts. *Br J Dermatol* 1997; **137**(Suppl. 50): 27.
6 Kemmett D, Colver GB. Myxoid cysts treated by infra-red coagulation. *Clin Exp Dermatol* 1994; **19**: 118–20.
7 Lonsdale-Eccles AA, Langtry JA. Treatment of digital myxoid cysts with infrared coagulation: a retrospective case series. *Br J Dermatol* 2005; **153**: 972–5.
8 Apfelberg D, Maser M, Lash H, White D. Efficacy of the carbon dioxide laser in hand surgery. *Ann Plast Surg* 1984; **13**: 320–6.
9 Street M, Roegnik R. Recalcitrant periungual verrucae: the role of carbon dioxide laser vaporization. *J Am Acad Dermatol* 1990; **12**: 115–20.
10 Bennett G. Laser use in foot surgery. *Foot Ankle* 1989; **10**: 110–14.
11 Karrer S, Hohenleutner U, Szeimies RM, Landthaler M. Treatment of digital mucous cysts with a carbon dioxide laser. *Acta Derm Venereol (Stockh)* 1999; **79**: 224–5.

Table 65.5 Classification of acute trauma. (From Van Beek *et al.* [1].)

Type	Effect	Therapy
I	Small haematoma associated with a small break in the nail bed	Fenestration of nail over the haematoma
II	Large haematoma with significant nail bed injury	Remove nail in order to identify site and nature of subungual damage
III	Large haematoma, nail plate displaced	X-ray may reveal fracture of terminal phalanx, usually in association with nail bed laceration which requires resorbable 6/0 suture
IV	Severe crush injury	Avulsion needed to reveal matrix, with multiple lacerations requiring careful reconstruction
V	Amputation of tip of digit, may include parts of matrix	If tip can be retrieved, it should be used as a graft. Otherwise nail bed from other sites may provide autologous grafts

12 Lin YC, Su HY. A surgical approach to ingrown nail: partial matricectomy using CO_2 laser. *Dermatol Surg* 2002; **28**: 578–80.
13 Ozawa T, Nose K, Harada T *et al*. Partial matricectomy with a CO_2 laser for ingrown toenail after nail matrix staining. *Dermatol Surg* 2005; **31**: 302–5.
14 Orenstein A, Goldan O, Weissman O *et al*. A comparison between CO^2 laser surgery with and without lateral fold vaporization for ingrowing toenails. *J Cosmet Laser Ther* 2007; **9**: 97–100.

Traumatic nail disorders

Nails may show signs of acute trauma, scars following acute trauma or chronic repetitive trauma.

Acute trauma

Acute trauma is classified with respect to severity, ranging from a small haematoma to digit amputation (Table 65.5).

Nail bed laceration

The nail bed may be lacerated by different forms of trauma, including incisions, and crush and avulsion injuries. In simple injuries there is displacement of the nail plate, which may be found proximally avulsed but retaining distal attachment to the nail bed. In this form of trauma, and in many others, the nail plate can be employed as a useful splint [2]. Initially, the nail bed damage should be assessed by avulsion, and then the nail can be replaced after any necessary nail bed repair has been performed; a small window for drainage of blood and exudate is made in the nail [3]. More complicated injuries may require flap or graft reconstructions and, in some instances, vascularized composite nail grafts are used with microvascular anastomoses. When the wounds arise from crush injury, fracture is relatively common. If the distal tuft has been fractured to leave fragments of bone dispersed in the soft tissues, it may prevent long-term morbidity if these are removed [4].

References

1 Van Beck AL, Kassan MA, Adson MH *et al*. Management of acute fingernail injuries. *Hand Clin* 1990; **6**: 23–38.
2 Brown RE. Acute nail bed injuries. *Hand Clin* 2002; **18**: 561–75.
3 Zook EG. Discussion of 'Management of acute nail bed avulsions'. *Hand Clin* 1990; **6**: 57–8.
4 Zook EG. Understanding the perionychium. *J Hand Ther* 2000; **13**: 269–75.

Delayed trauma

The most common kind of chronic deformity following an acute injury is a split nail or reduction in the length of the nail bed with consequent overcurvature of the tip of the nail. Cure of a split-nail deformity is difficult, with only a modest chance of success [1]. Sometimes, there is an associated pterygium. Treatment entails excision of the nail bed and matrix scar and, in the case of a pterygium, a split-skin graft may be placed on the ventral aspect of the proximal nail fold to help prevent recurrence of the pterygium. It is important to keep the wounded aspects of nail bed or matrix separate from the overlying nail fold after surgery, and this is often best done by returning the nail plate after soaking it in antiseptic during the procedure.

If treatment is required for a shortened distal phalanx with nail bed changes, there are two choices [2]: the entire nail can be phenolized, or a V–Y advancement flap can be performed based on two neurovascular pedicles.

References

1 Hoffman S. Correction of a split nail deformity. *Arch Dermatol* 1973; **108**: 568–9.
2 Zook EG, Baran R, Haneke E, Dawber RPR. Nail surgery and traumatic abnormalities. In: Baran R, Dawber RPR, de Berker DAR, Haneke E, Tosti A, eds. *Diseases of the Nails and Their Management*, Oxford: Blackwell Science, 2001: 425–514.

Haematoma [1,2]

Subungual bleeding is a common sign. It may present as a feature of acute trauma, with pain due to the recent event in combination with pain arising from the pressure exerted by the subungual accumulation of blood. A haematoma arising within the matrix will be incorporated into the nail plate [3]. Where the haematoma is associated with acute trauma, there is usually pain and the diagnosis is obvious. However, with less extreme trauma, a haematoma may not develop immediately and may be painless. This is most common in the toes and may give rise to clinical uncertainty as to whether it represents early subungual melanoma. A history of traumatic sporting hobbies is useful, and signs of symmetrical nail trauma and inappropriate footwear all point towards trauma as the cause of the appearance. Dermoscopy will nearly always resolve the situation [2], but if it does not, making a small punch in the surface of the nail may reveal old blood as the source of pigment. Malignancies can bleed and so confirmation of blood does not refute the possibility of a tumour; however, as an isolated finding in the absence of other clues, this test should be sufficient to obviate the need for surgical exploration. An alternative is to score a transverse groove in the nail at the proximal margin of the pigment and observe over a few weeks as the discoloration grows out. If pigment continues to spread proximal to the groove, surgical exploration is needed.

The only treatment that can be offered is to relieve the pressure, and if seen soon after the injury this can be done by puncturing the nail, for instance with a hot pointed implement, cautery or a small drill. This procedure will relieve pain and may save the nail.

The possibility of an underlying fracture must be considered for larger haematomas [1].

It is stated that if more than 50% of the visible nail is affected, the nail plate should be removed. However, there is evidence to challenge this rule. A comparison between two groups of children having exploration and repair or trephination alone showed fewer complications in the latter group and considerably less investment in medical time [4]. A literature review failed to find clear evidence for avulsion [5].

References

1 Farrington H. Subungual haematoma: an evaluation of treatment. *BMJ* 1964; **i**: 742–4.

2 Braun RP, Baran R, Le Gal FA *et al*. Diagnosis and management of nail pigmentations. *J Am Acad Dermatol* 2007; **56**: 835–47.

3 Stone OJ, Mullins JF. The distal course of nail haemorrhage. *Arch Dermatol* 1963; **88**: 186–7.

4 Roser SE, Gellman H. Comparison of nail bed repair versus nail trephination for subungual hematomas in children. *J Hand Surg* 1999; **24A**: 1166–70.

5 Batrick N, Hashemi K, Freij R. Treatment of uncomplicated subungual haematoma. *Emerg Med J* 2003; **20**: 65.

Chronic repetitive trauma

Chronic repetitive trauma may take several forms. Some have been considered in other sections detailing transverse ridges produced by a habit tic (Fig. 65.22; p. 65.25), the canaliform dystrophy of Heller (Fig. 65.44; p. 65.50) and chronic paronychia (Fig. 65.18; p. 65.21).

Nail biting

The nail plate, periunguium and nail bed are all subject to biting and picking. Although fingers are most commonly involved, rarely toenails are also bitten [1]. This produces distinctive features, which are found in 60% of children, 45% of adolescents and 10% of adults [2]. The majority of moderate nail biters have no associated psychiatric disorder [3,4]. Focal abnormalities, such as viral warts, are often a complication, whether as a cause or as a result of the Koebner effect after biting. Severe damage may be associated with self-mutilating disorders such as Lesch–Nyhan syndrome.

The nails are typically short, with up to 50% of the nail bed exposed. The free edge may be even or ragged. Surface change may include splitting of the nail into layers or a sand-papered effect, and the nail may acquire a brown longitudinal streak [5]. The most aggressive nail biting (onychotillomania/onychophagia) can produce subungual haemorrhage, strips of nail loss with residual spurs, or loss of the entire nail (Fig. 65.45). Onychotillomania may be allied to delusions of parasitosis when the patient picks off pieces claiming that they contain parasites [6]. A rough and irregular nail and nail fold may result. Many fingernails are involved. Oral pimozide may be beneficial [7].

Direct damage and secondary infection may make nail loss permanent or result in pterygium formation. The nail folds are sometimes bitten in addition to, or as a substitute for, the nail. This can lead to bleeding and chronic paronychia, with acute infective exacerbations. This in turn may lead to nail plate damage or ridging and nail fold scarring. In cases associated with infection, osteomyelitis of the terminal phalanx can develop [8,9]. Subjects will sometimes deny nail biting and attribute the appearance to a disease that stops nail growth. Transverse grooves scored proximally in the nail plate will confirm that the nail is growing by moving distally with time. In aggressive nail biting, the groove may be eroded from the surface.



Fig. 65.44 Median canaliform dystrophy of Heller.



Fig. 65.45 Nail biting can be extensive, with damage to the nail folds and nail plate causing subungual haemorrhage.

Trauma is sometimes inflicted by other nails, with pushing back of the proximal nail fold as part of a habit tic (see p. 65.24 and Fig. 65.22). This results in serial transverse ridges and depressions running up the midline of the nail, associated with loss of the cuticle. In more conscious forms of self-damage, sharp instruments are used to produce dermatitis artefacta of the nail unit, and the nail fold is commonly preserved [10].

Treatment. Treatment is often unsuccessful and cure relies largely on the motivation of the patient. Local antiseptics and antimicrobial ointments may help settle infection secondary to nail unit damage. Those with the most bitter taste are often prescribed in the belief that this will discourage biting. This is seldom the case. Antidepressants [11] and behavioural therapy [12] have been used with some success in limited studies.

References

1 Hurley PT, Balu V. Self-inflicted anonychia. *Arch Dermatol* 1982; **118**: 956–7.
2 Malone AJ, Massler M. Index of nail biting in children. *J Abnorm Social Psychol* 1952; **47**: 193–202.
3 Ballinger BR. The presence of nail-biting in normal and abnormal populations. *Br J Psychol* 1970; **117**: 445–6.
4 Colver GB. Onychotillomania. *Br J Dermatol* 1987; **117**: 397–9.
5 Baran R. Nail biting and picking as a possible cause of longitudinal melanonychia. *Dermatologica* 1990; **181**: 126–8.
6 Combes FC, Scott MJ. Onychotillomania. *Arch Dermatol Syphilol* 1951; **63**: 778–80.
7 Hamann K. Onychotillomania treated with pimozide (Orap). *Acta Derm Venereol (Stockh)* 1982; **62**: 364–7.
8 Tosti A, Peluso AM, Bardazzi F *et al*. Phalangeal osteomyelitis due to nail biting. *Acta Derm Venereol (Stockh)* 1994; **74**: 206–7.
9 Waldmann BA. Osteomyelitis caused by nail biting. *Pediatr Dermatol* 1991; **7**: 189–90.
10 Norton L. Self-induced trauma to the nails. *Cutis* 1987; **40**: 223–7.
11 Leonard HL, Lenane MC, Swedo SC *et al*. A double blind comparison of clomipramine and desipramine treatment of severe onychophagia (nail biting). *Arch Gen Psychiatry* 1991; **48**: 821–7.
12 Silber KP, Haynes CE. Treating nailbiting: a comparative analysis of mild aversion and competing response therapies. *Behav Res Ther* 1992; **30**: 15–22.

Hang nails

These are due to hard pieces of epidermis breaking away from the lateral nail folds. Although often due to nail biting, they may result from many other minor injuries. The splits may be painful when they penetrate to the underlying dermis. They should be removed with sharp pointed scissors.

Nutcracker nails

Under this heading, Cohen [1] described splitting and onycholysis caused by the habit of separating the two halves of cracked walnuts over a period of 10 years.

Reference

1 Cohen BH. Nutcracker nails. *Cutis* 1975; **16**: 141.

Damage from nail manicure instruments

Metal instruments, such as a nail file or scissors, wooden or plastic orange sticks, or nail whitener pencils may create acute or chronic injuries in the nail area. Onycholysis may result from using the sharp point for cleaning under the nail plate. Nails, however, are best cleaned with a nail brush and soap, because overzealous manicure, pushing back the cuticles, may result in white streaks across several nails. Cleaning around the nail with contaminated instruments may lead to acute or chronic paronychia. According to Brauer and Baran [1], it is not advisable to cut or clip the nail plate, as this produces a shearing action that weakens the natural layered structure and promotes fracturing and splitting. An emery board is preferred for shaping the fingernail by filing from the sides of the nail towards the centre.

Reference

1 Brauer E, Baran R. Cosmetics: the care and adornment of the nail. In: Baran R, Dawber RPR, de Berker DAR, Haneke E, Tosti A, eds. *Diseases of the Nails and Their Management*, 3rd edn. Oxford: Blackwell Science, 2001: 358–69.

Trauma from footwear

Onychogryphosis and nail hypertrophy [1–5]

Onychogryphosis is an acquired dystrophy usually affecting the great toenail, which is thickened, yellow and twisted. It is most commonly seen in the elderly [1,2,4], although trauma and biomechanical foot problems may precipitate similar changes in middle age or earlier.

At one time, onychogryphosis was known as ostlers' nail, owing to the fact that some cases could be traced to injury caused by a horse trampling on the foot of the ostler. Competitive sport is a more contemporary cause. The injury, once sustained, is aggravated by footwear. As the nail becomes longer and thicker, the damage from the footwear becomes progressively more important. Nail hypertrophy implies thickening and increase in length, whereas onychogryphosis implies curvature also.

Some cases of nail hypertrophy are intrinsic, and this applies especially to toenails other than the nail of the great toe. The nail becomes thick and circular in cross-section instead of flat, and thus comes to resemble a claw. There are two possible explanations for this formation.

1 There is insufficient matrix under cover of the posterior fold to exert a flattening effect. The altered relationship between matrix and proximal nail fold in postmortem specimens supports this.
2 The nail bed is contributing a greater quantity of keratin to the nail than usual. It is usually possible to exclude this on clinical grounds as there is often an element of onycholysis that separates the dystrophic nail from the nail bed.

Hypertrophy of fingernails is usually traumatic in origin and is often the result of a single injury.

In onychogryphosis, one or more nails become greatly thickened (Fig. 65.46) and, with neglect, increase in length, becoming curved like a ram's horn. The nails of the great toes are most often involved, but no toenail is exempt. It is possible that the nail plate distortion produced by chronic untreated onychomycosis may be partly responsible for onychogryphosis at a later stage. In extreme cases, the free edge may press on or even re-enter the soft tissues of the foot.

Treatment of onychogryphosis and nail hypertrophy is either radical or palliative. Radical treatment consists of surgical removal of the nail and matrix and is recommended in those with good circulation (Fig. 65.47). Palliative treatment requires regular paring



Fig. 65.46 Early onychogryphosis of the left great toenail.



(a)



(b)



(c)

Fig. 65.47 (a–c) Onychogryphosis is often best treated by ablation of the nail matrix.

and trimming of the affected nails, usually by a podiatrist using nail clippers and a file or mechanical burr. The thickened nails are extremely hard and trimming is difficult. Not infrequently, the nail is invaded by granulation tissue from the nail bed, and incision of this during trimming will result in pain and haemorrhage.

Other causes of thickened nails are psoriasis, pityriasis rubra pilaris, Darier's disease, fungal infections, pachyonychia congenita, congenital ectodermal defects and congenital malalignment of the great toenails [6].

References

1 Cohen PR, Scher RK. Geriatric nail disorders: diagnosis and management. *J Am Acad Dermatol* 1992; **26**: 521–31.
2 Dawber RPR, Bristow I, Mooney J. *The Foot: Problems in Podiatry and Dermatology*. London: Dunitz, 1996.
3 Douglas MA, Krull EA. Diseases of the nails. In: Conn WB, ed. *Current Therapy*. Philadelphia: Saunders, 1981: 712.
4 Gilchrist AK. Common foot problems in the elderly. *Geriatrics* 1979; **34**: 67–70.
5 Lubach D. Erbliche onychogryphosis. *Hautarzt* 1982; **33**: 331–3.
6 Baran R, Bureau H. Congenital malalignment of the great toenail as a cause of ingrowing toenail in infancy. *Clin Exp Dermatol* 1983; **6**: 619–23.

Ingrowing toenail [1–3]

Synonym
- Onychocryptosis

The soft tissue at the side of the nail (lateral nail fold) is penetrated by the edge of the nail plate, resulting in pain, sepsis and, later, the formation of granulation tissue [4]. Penetration is often caused by spicules of nail at the edge of the nail plate, which have been separated from the main portion of the nail. The great toes are those most often affected. The main cause of the deformity is compression of the toe from the side due to ill-fitting footwear, and the main contributory cause is cutting the toenails in a half-circle instead of straight across. Anatomical features, such as an abnormally long great toe and prominent lateral nail folds, are important in some cases. Sport, with the toe impacting on the inside of the shoe through kicking or other movements, can also be contributory.

In infancy, ingrowing toenail most commonly occurs before shoes are worn, associated with crawling, 'pedalling' or wearing undersized 'jumpsuits' [5]; acute paronychia may be associated [6]. Rarely, it is congenital [7] and even familial [2]. In children, ingrowing is commonly distal rather than lateral. Management is conservative in most instances, with topical steroid and antiseptic preparations. Surgery is occasionally required [8].

The first features are pain and redness, shortly followed by swelling and pus formation. Granulation tissue then forms and adds to the swelling and discharge. More severe infection may follow. There is seldom any difficulty with diagnosis. Excess nail fold granulation tissue can also be a feature of amelanotic melanoma and reactions to medications such as retinoids, ciclosporin, antiretroviral drugs and chemotherapy [9–15].

Treatment. Treatment may be difficult and prolonged. The first essential is to insist on the patient wearing shoes that are sufficiently wide, high and pliable to remove lateral pressure [16]. Any abnormality of foot/toe function should be corrected. The patient must also be instructed to cut the nail straight across instead of in a semicircle. The nail must be allowed to grow until its edges are clear of the end of the toe before it is cut; this prevents the further formation of marginal spicules. In the early stages, the infection may be overcome by the application of antiseptics and by inserting a pledget of cotton-wool under the edge of the nail. Taping the toe or applying plastic gutters between nail edge and nail fold are alternatives [17]. These can be supplemented with acrylic nail to build up a smooth surface able to push the nail fold away and relieve ingrowing [18]. Twice-daily warm-water baths followed by careful drying and powdering are helpful. Potent topical steroid can be useful to diminish inflammation and suppress granulation tissue – but can only be used when infection is ruled out or being actively managed. If the infection is more severe and there is local cellulitis, an appropriate systemic antibiotic should be administered. When granulation tissue forms this should be destroyed by cauterization with a silver nitrate stick. It is important that an amelanotic melanoma is not missed [19], and if there are atypical features a biopsy should be performed.

If conservative measures fail, operative intervention will be necessary. Removing the nail alone is likely to result in recurrence of ingrowing when the nail returns [20] and so should be combined with a curative procedure such as phenolization of the relevant part of the matrix [4,21]. Although surgical excision of matrix can provide an excellent result, it is more dependent than phenolization on the skill of the practitioner. In large studies, phenol treatment results in a greater cure rate and less morbidity [21]. The prolonged period of ooze from the wound after phenolic ablation leads to suspicion of infection, but this has not been confirmed by formal research [22]. Recent reports of the use of 10% sodium hydroxide suggest that it may be equally effective but with a shorter period of postoperative ooze [23]. Where there is diabetes or impaired peripheral circulation, surgery may require avoidance of prolonged or tight tourniquet application, and close follow-up. Phenolization can be undertaken safely in diabetics [24]. Carbon dioxide laser has been used, although it lacks the analgesic properties intrinsic to phenol [25].

References

1 Baran R, Bureau H. Congenital malalignment of the great toenail as a cause of ingrowing toenail in infancy. *Clin Exp Dermatol* 1983; **6**: 619–23.
2 Cambiaghi S, Pistritto G, Gelmeti C. Congenital hypertrophy of the lateral nail folds of the hallux in twins. *Br J Dermatol* 1997; **136**: 635–6.
3 Samman PD. Nail deformities due to trauma. In: Samman PD, Fenton DA, eds. *The Nails in Disease*. London: Heinemann, 1986: 148–9.
4 Baran R, Haneke E, Richert B. Pincer nails: definition and surgical treatment. *Dermatol Surg* 2001; **27**: 261–6.
5 Verbov J. Ingrowing toenails in infancy. *BMJ* 1978; **ii**: 1087.
6 Walker S. Paronychia of the great toe of infants. *Clin Pediatr* 1979; **18**: 247–8.
7 Katz A. Congenital ingrown toenails. *J Am Acad Dermatol* 1996; **34**: 519–20.
8 Piraccini BM, Parente GL, Varotti E, Tosti A. Congenital hypertrophy of the lateral nail folds of the hallux: clinical features and follow-up of seven cases. *Pediatr Dermatol* 2000; **17**: 348–51.
9 Baran R. Retinoids and the nails. *J Dermatol Treat* 1990; **1**: 151–4.
10 Higgins EM, Hughes JR, Snowden S, Pembroke AC. Cyclosporin-induced periungual granulation tissue. *Br J Dermatol* 1995; **132**: 829–30.
11 Nicolopoulos J, Howard A. Docetaxel-induced nail dystrophy. *Australas J Dermatol* 2002; **43**: 293–6.

12 Wasner G, Hilpert F, Schattschneider J *et al*. Docetaxel-induced nail changes: a neurogenic mechanism. A case report. *J Neurooncol* 2002; **58**: 167–74.
13 Stemmler HJ, Gutschow K, Sommer H *et al*. Weekly docetaxel (Taxotere) in patients with metastatic breast cancer. *Ann Oncol* 2001; **12**: 1393–8.
14 Ward HA, Russo GG, Shrum J. Cutaneous manifestations of antiretroviral therapy. *J Am Acad Dermatol* 2002; **46**: 284–93.
15 Heim M, Schapiro J, Wershavski M, Martinowitz U. Drug-induced and traumatic nail problems in the haemophilias. *Haemophilia* 2000; **6**: 191–4.
16 Wernick J, Gibbs RC. Pedal biomechanics and toenail disease. In: Scher RK, Daniel CR, eds. *Nails: Therapy, Diagnosis, Surgery*. Philadelphia: Saunders, 1990: 244–9.
17 Schulte KW, Neumann NJ, Ruzicka T. Surgical pearl: nail splinting by flexible tube—a new noninvasive treatment for ingrown toenails. *J Am Acad Dermatol* 1998; **39**: 629–30.
18 Arai H, Arai T, Nakajima H, Haneke E. Formable acrylic treatment for ingrowing nail with gutter splint and sculptured nail. *Int J Dermatol* 2004; **43**: 759–65.
19 Lemont H, Brady J. Amelanotic melanoma masquerading as an ingrown toenail. *J Am Podiatr Med Assoc* 2002; **92**: 306–7.
20 Rounding C, Hulm S. Surgical treatments for ingrowing toenails. *Cochrane Database Systematic Review* 2005; **18**;(2):CD001541.
21 de Berker DA. Phenolic ablation of the nail matrix. *Australas J Dermatol* 2001; **42**: 59–61.
22 Bos AM, van Tilburg MW, van Sorge AA, Klinkenbijl JH. Randomized clinical trial of surgical technique and local antibiotics for ingrowing toenail. *Br J Surg* 2007; **94**: 292–6.
23 Bostanci S, Kocyigit P, Gurgey E. Comparison of phenol and sodium hydroxide chemical matricectomies for the treatment of ingrowing toenails. *Dermatol Surg* 2007; **33**: 680–5.
24 Giacalone VF. Phenol matricectomy in patients with diabetes. *J Foot Ankle Surg* 1997; **36**: 264–7.
25 Lin YC, Su HY. A surgical approach to ingrown nail: partial matricectomy using CO_2 laser. *Dermatol Surg* 2002; **28**: 578–80.

The nail and cosmetics

The main areas of medical involvement with nail cosmetics are:

1 where nail cosmetics cause alteration or damage to the nails and periunguium [1,2]
2 where nail cosmetics cause allergic contact dermatitis locally and ectopically, such as of the eyelids [1,2]
3 where nail disease has limited therapeutic options and nail cosmetics can provide an important supplement to dermatological management [3].

To understand these areas it is helpful to have some knowledge of the agents and techniques used in cosmetic nail care. Nail coatings represent an attractive nail enhancement. They may harden upon evaporation (nail polish) or polymerize (sculptured nails, gels, preformed artificial nails).

Coatings that harden upon evaporation

Nail polish

The term 'nail lacquer' is sometimes used to include enamels, top coats and base coats, either as separate entities or combined in one product. Although chemically similar, they contain different ratios of the same constituents to lend different characteristics. The base coat is used to improve the adhesion or bonding of enamel to the nail. A top coat improves the depth and lustre of the enamel and increases its resistance to chipping and abrasion. Nail polishes consist of solids and solvent ingredients, the former representing about 30%, the latter 70% of the product. The ingredients can be divided into six principal groups.

1 cellulose film formers (e.g. nitrocellulose): provide gloss, body and gel structure
2 resins (e.g. tosylamide formaldehyde resin [previously known as toluene sulphonamide formaldehyde resin]): improve the gloss and adhesion of the film
3 plasticizers (e.g. dibutylphthalate): give the film pliability, minimize shrinkage, and soften and plasticize the cellulose
4 thixotropic suspending agents (e.g. bentonite) for non-settling and flow: keep pigments in suspension on shaking
5 solvents and diluents (e.g. toluene): keep nitrocellulose, resin and plasticizer in the liquid state and control the application and drying time
6 colour substances: these are either inorganic (iron oxides) or a variety of certified organic colours (D and C yellow A1 lakes).

Recently, there has been a move away from toluene and formaldehyde resin, and most recently avoidance of dibutylphthalate due to potential health risk.

'Pearls' or 'frosts' are produced by bismuth oxychloride and titanium dioxide coated with mica and guanine (obtained from fish scales). 'Clears' contain a small tint.

The base coat is formulated in a manner similar to standard lacquer, but it has a lower non-volatile content (less nitrocellulose) and lower viscosity, because a thinner film is desirable; it may also contain hydrolysed gelatine. In the top coat the nitrocellulose content is increased and the resin is reduced. A slight increase in plasticizer content improves elasticity of the film. There is no pigment. The top coat often has an added sunscreen.

Reactions such as an allergic contact dermatitis to nail polish frequently appear on any part of the body accessible to the nails, with paradoxically no signs in or around the nail apparatus [4]. The commonest areas involved are the eyelids, the lower half of the face, the sides of the neck and the upper chest. Generalized dermatitis may rarely occur. Sometimes the use of nail polish on stockings to stop 'runs' or on nickel-plated costume jewellery to prevent nickel dermatitis may induce nail-polish dermatitis on the legs or at the site of metal contact. Nail-polish dermatitis may occur in the user's partner or other close contacts. Although any ingredient may account for distant allergic contact dermatitis, tosylamide formaldehyde resin is the most common culprit. After the nail polish is removed, the dermatitis usually clears rapidly unless secondary infection or lichenification has occurred. Metal pellets present in some bottles to maintain a liquid state may cause nickel reactions and onycholysis.

Nail plate staining from the use of polish is most commonly yellow/ orange in colour. It typically starts near the cuticle, extends to the nail tip and becomes progressively darker from base to tip. With time, the dyes penetrate the nail too deeply to be removed. Injury to the nail plate from nail lacquers is rare. However, 'granulation' of nail keratin, a superficial friability, can be observed in some instances where individuals leave nail lacquer on for many weeks or where there is poor formulation of the product. For patch testing, several nail lacquers should be used and tested 'as is'; they should be allowed to dry for 15 min because the solvents and diluents may cause false-positive reactions. The following substances should be included in the test battery.

- tosylamide formaldehyde resin (10% in petrolatum)
- nickel (5% in petrolatum); dimethylglyoxime spot test for nickel
- glyceryl phthalate resin (polymer resin) (10% in petrolatum)
- pearly material: guanine powder (pure)
- formaldehyde (1% aqueous)
- colophony (20% in petrolatum); drometrizole (Tinuvin P) (1–5% in petrolatum).

The resin contains no free formaldehyde. Formaldehyde is merely the chemical moiety on which the resin is formed. Usually, formaldehyde-sensitive individuals do not cross-react with this resin. However, it has been suggested that there is always a small amount of free formaldehyde present in many preparations. Various cosmetic companies now make varnishes that are formulated without the sensitizing resin.

Nail polish removers. These are composed of various solvents such as acetone. Occasionally, nail polish removers cause trouble by excessive drying of the nail plate, and may be responsible for some inflammation of nail folds.

Coatings that polymerize [5]

Sculptured nails

The basic kit of sculptured nails is sold as a set containing a template, a liquid monomer and a powdered polymer. Self-curing acrylic resins are created by polymerization of methyl methacrylate monomer and polymethyl methacrylate powder with an organic peroxide and an accelerator. They harden at room temperature. The compound has to be moulded on the natural nail. The acrylic compound is applied to the nail, which has been roughened on the surface. When hardened, the compound produces a prosthetic nail that is enlarged and elongated by repeated applications. The prosthesis can be filed and manicured to shape; as the plate grows out, further applications of acrylic can be made to maintain a regular contour.

Technicians who sculpt nails should be instructed to wash their hands before touching the face or eye area. Usually, the area involved is the chin, which technicians tend to rest in their hands. Additionally, they should be warned to avoid contact with the dust of freshly applied product and to avoid using the wet product.

Allergic reactions. Allergic reactions due to sculptured nails may occur 2–4 months, and even as long as 16 months, after the first application. The first indication is an itch in the nail bed. Paronychia, which is usually present in allergic reactions, is associated with excruciating pain in the nail area, and sometimes with paraesthesia. The nail bed is dry and thickened, and there is usually onycholysis. The natural nail plate becomes thinner, split and sometimes discoloured. It takes several months for the nails to return to normal. Permanent nail loss is exceptional, as is intractable prolonged paraesthesia [6].

Patch tests most commonly show reactions to the acrylic liquid monomer and not to the polymer; this is similar to denture allergy (see Chapter 26).

Improper application and maintenance. With continued wear, the edges of the sculptured nails become loose. These must be clipped and then rebuilt to prevent the development of an environment prone to bacterial and, beneath the nail plate, candidal infection. In fact, this is a result of improper application and maintenance. Failure to file the prosthetic nail every 2 weeks will result in the creation of a lever arm that predisposes to traumatic onycholysis or damage to the natural nail. Onycholysis is very common with nail extensions that are too long.

Irritant reactions. Irritant reactions to monomers are possible. These manifest as a thickening of the nail bed's keratin layer, which can sometimes cause the entire nail bed to thicken with or without onycholysis. Nonetheless, the overwhelming majority of cases result from physical trauma or abuse.

Damage to the natural nail is not unusual after 2–4 months of wear of a sculptured nail. If it becomes yellow or crumbly, this means that the product was applied and maintained incorrectly. The patient should find a better-qualified nail technician. The problem may well not be the acrylic nail materials but rather the thinning of the nail due to excessive filing with heavy abrasives.

Primer (methacrylic acid) is a strong irritant, which may produce third-degree burns. It is hazardous if the cuticles are flooded or spills are not washed out immediately. Primer can permeate the plate and soak into the nail bed if the nails are too thin. Soap or baking soda, used with water, are excellent neutralizers. If primer gets into the eye, it should be flushed with water for at least 15 min, and a Poisons Information Centre should be contacted.

Premixed acrylic gels

Gel system products are premixed and either acrylic-based (14% of the market) or cyanoacrylate-based (1% or less of the market). Their virtual lack of odour makes gels popular in full-service beauty salons. UV light-cured gels are the best known of the different gel technologies. These gels contain urethanes and (meth)acrylate compounds, a photoinitiator and cellulose, which necessitates antiyellowing agents and a UV light unit. The gel remains in a semiliquid form until cured in a photobonding box. The proportion of resins to monomers determines the gel consistency. When the gel is exposed to light of an appropriate wavelength, polymerization occurs, resulting in hardening of the gel. UV gels never involve catalysts and often do not employ primers.

Gel enhancement products shrink by up to 20%, which may result in lifting and tip cracking. As an effect of excessive shrinkage, clients may comment that the enhancement feels tight on the nail bed. Other symptoms include throbbing or warmth below the nail plate. This may lead to tender, sore fingertips. Photobonded acrylate has been observed to cause nail reactions, sometimes with nail loss and paraesthesia. Hemmer *et al*. [7] have patch tested 'hypoallergenic' commercial products in patients wearing photobonded acrylic nails who had perionychial and subungual eczema. Triethyleneglycol dimethacrylate, hydroxyfunctional methacrylates, and (meth)-acrylated urethanes proved to be relevant allergens in photobonded nail preparations. Meth-acrylated epoxy resin sensitization was not observed. The omission of irritant methacrylic acid in UV-curable gels does not reduce the high sensitizing potential of new acrylates. Contrary to the manufacturers' declarations, all 'hypoallergenic' products continue to include

acrylate functional monomers and therefore continue to cause allergic sensitization. Gels and acrylics, being chemically distinct entities, will not necessarily cross-react.

Unreacted UV gel in the dusts and filings may produce distant allergic reactions. Although sensitization to butyl-hydroxytoluene is possible, gels usually contain acrylated oligomers and monomers. Acrylates are far more likely to cause sensitization than methacrylates or stabilizers.

Finally, thick ornately painted gel false nails that may be difficult to remove present a real challenge to pulse oximetry. It appears to be the polish more than the sculpted nail that interferes with the readings [8,9].

Preformed plastic nails

Preformed plastic nails are packaged in several shapes and sizes to conform to the normal nail plate configuration. Such nails are trimmed to fit the fingertip and are fixed with cyanoacrylate adhesive supplied with the kit. The usefulness of these prosthetic nails is limited by the need for some normal nail to be present for attachment. Normal physical and chemical insults to the nails cause the preformed plastic nails to loosen. If the preformed nails remain in place for more than 3 or 4 days, they may cause onycholysis and nail-surface damage. Eczematous, painful paronychia due to cyanoacrylate nail preparations may be observed after about 3 months. Dystrophy and discoloration of the nails may become apparent and last for several months. In some cases, distant contact dermatitis of the face and eyelids occurs. On patch testing, the patients react far more often to the adhesive than to the prosthetic nails. Suggested test substances are *p*-tertiary-butylphenol resin (1% in petrolatum), tricresyl ethyl phthalate (5% in petrolatum), cyanoacrylates and other glues (5% in methylethylketone).

Nail-mending kits

These include paper strips of a basic film-forming product to create a 'splint' for the partially fractured nail plate. The split is first bonded with cyanoacrylate glue, then the nail is painted with fibred clear nail polish. A piece of wrap fabric is cut and shaped to fit over the nail surface. This is then embedded in polish of high solid content, and several coats are applied.

Nail wrapping

In nail wrapping, the free edge of the nail should be long enough to be splinted with paper, silk, linen, plastic film or fibreglass, and fixed with cyanoacrylate glue. After drying, the edge is shaped, and the nail is coated with enamel.

Removal of nail coatings that polymerize. The most commonly used solvent for removal of nail products is acetone. Warming the solvent with great care can cut product removal time in half. However, most gels are difficult to remove because they are highly cross-linked and resistant to many solvents. Therefore, if gel enhancements have to be removed, slowly file (not drill) the enhancement with a medium-grit file, leaving a very thin layer of product. Soak in warm product remover and, once softened, scrape the remaining product away with a wooden pusher stick.

Cuticle removers

These are lotions or gels containing approximately 0.4% sodium or potassium hydroxide. The lotion is left in place for 1–3 min and then washed off. Creams containing 1–5% lactic acid (pH 3–3.7) are also used.

Nail hardeners

Nail keratin can be hardened by tissue fixatives such as formaldehyde. These are not commercially available in the USA because of their toxic effects. Nail changes caused by such nail hardeners may include pain, subungual haemorrhage and bluish discoloration of the nail. The nail returns to normal when the offending agent is discontinued. Formaldehyde nail hardeners have been reported as causing onycholysis and allergic contact dermatitis; they may also act as irritants. Patch testing should be with formaldehyde (1% aqueous). Because of its irritant qualities, reactions should be interpreted with caution.

Silicone rubber nail prosthesis [10]

In a wide variety of cases, ranging from deformed nail to complete loss of the terminal phalanx, a silicone rubber, thimble-shaped finger cover may be indicated. This prosthesis is easily fitted on the finger stump, encasing the entire distal phalanx; it must be fine and flexible to maintain pulp sensitivity and must have the same marking and colouring as the finger. The fixation is excellent and the nail form takes nail varnish well.

Nail cream

This is an ordinary water-in-oil moisturizing cream, with low water (30%) and high lipid content. It is applied, after cleaning the hands, to prevent or diminish brittleness.

Nail buffing

Weekly buffing may be indicated for removing small particles of nail debris, thus enhancing the lustre and smoothness of the nail plate. Buffing creams, which contain waxes and finely ground pumice, and buffing powders are abrasive and should not be overused on thin nails.

Nail whitener

This is a pencil-like device with a white clay (kaolin) core used to deposit colour on the undersurface of the free edge of the nail.

Infection risks

Secondary infection with *Candida* or bacteria is a hazard for anyone with an irritant or allergic contact dermatitis of the periunguium. Where this is associated with artificial nails, the prosthetic nails may be longer than usual and so reduce the ability to keep the area clean. Prosthetic nails are sometimes worn because there are underlying problems with the natural nails, such as cracks or onycholysis. These features may also lower the threshold to certain types of infection.

Medical staff with artificial nails or nail extensions may put patients at risk through carriage of pathogens [11]. Guidelines in the UK now require medical staff not to wear such embellishments [12]. Nail varnish is also thought to be associated with bacterial

carriage when it becomes chipped, although the evidence for this is less strong [13]. Infection through nail salons and the manicuring process is a further factor that adds to the risks for those with artificial nails [14].

Conclusion

Nail beauty therapy may certainly produce an attractive enhancement and disguise unsightly nail conditions but it may also represent a potential hazard due to instrument damage, and is not recommended for psoriatic nails as it may provoke the Koebner phenomenon.

References

1 Baran R, Andre J. Side effects of nail cosmetics. *J Cosmet Dermatol* 2005; **4**: 204–9.

2 Rich P. Nail cosmetics. *Dermatol Clin* 2006; **24**: 393–9.

3 Iorizzo M, Piraccini BM, Tosti A. Nail cosmetics in nail disorders. *J Cosmet Dermatol* 2007; **6**: 3–8.

4 Liden C, Berg M, Färv G, Wrangsjö K. Nail varnish allergy with far-reaching consequences. *Br J Dermatol* 1993; **68**: 57–62.

5 Schoon D, Baran R. Cosmetics for nails. In: Barel AO, Paye M, Maibach HI, eds. *Handbook of Cosmetic Science and Technology*. New York: Marcel Dekker, 2001: 685–7.

6 Slodownik D, Williams JD, Tate BJ. Prolonged paresthesia due to sculptured acrylic nails. *Contact Dermatitis* 2007; **56**: 298–9.

7 Hemmer W, Focke M, Wantke F *et al*. Allergic contact dermatitis to artificial fingernails prepared from UV light-cured acrylates. *J Am Acad Dermatol* 1996; **35**: 377–80.

8 Cote CJ, Goldstein EA, Fuchsman WH, Hoaglin DC. The effect of nail polish on pulse oximetry. *Anesth Analg* 1988; **67**: 683–6.

9 Peters SM. The effect of acrylic nails on the measurement of oxygen saturation as determined by pulse oximetry. *AANA J* 1997; **65**: 361–3.

10 Pillet J, Didierjean-Pillet A. Ungual prosthesis. *J Dermatol Treat* 2001; **12**: 41–6.

11 Hedderwick SA, McNeil SA, Lyons MJ, Kauffman CA. Pathogenic organisms associated with artificial fingernails worn by healthcare workers. *Infect Control Hosp Epidemiol* 2000; **21**: 505–9.

12 Pratt RJ, Pellowe CM, Wilson JA *et al*. epic2: National evidence-based guidelines for preventing healthcare-associated infections in NHS hospitals in England. *J Hosp Infect* 2007; **65**(Suppl. 1): S1–64.

13 Arrowsmith VA, Maunder JA, Sargent RJ, Taylor R. Removal of nail polish and finger rings to prevent surgical infection. *Cochrane Database Systematic Review* 2001: CD003325.

14 Winthrop KL, Abrams M, Yakrus M *et al*. An outbreak of mycobacterial furunculosis associated with footbaths at a nail salon. *N Engl J Med* 2002; **346**: 1366–71.

CHAPTER 66
Disorders of Hair

A.G. Messenger[1], *D.A.R. de Berker*[2] *& R.D. Sinclair*[3]

[1]Department of Dermatology, Royal Hallamshire Hospital, Sheffield, UK
[2]Bristol Dermatology Centre, Bristol Royal Infirmary, Bristol, UK
[3]Department of Dermatology, St Vincent's Hospital, Melbourne, Australia

Anatomy and physiology, 66.1
Types of hair, 66.2
Development and distribution of hair follicles, 66.2
Anatomy of the hair follicle, 66.2
The hair cycle, 66.7
Androgens and hair growth, 66.13
Alopecia, 66.16
Common baldness and androgenetic alopecia, 66.16
Disturbances of hair cycle, 66.27
Alopecia areata, 66.31
Acquired cicatricial alopecia, 66.38
Developmental defects and hereditary disorders, 66.50
Infections, 66.52
Artefactual alopecia, 66.53
Scaling disorders of the scalp, 66.56
Thickened scalp disorders, 66.58
Congenital alopecia and hypotrichosis, 66.59
Abnormalities of the hair shaft, 66.61
Structural defects with increased fragility, 66.61
Structural defects without increased fragility, 66.69
Excessive growth of hair, 66.75
Hypertrichosis, 66.75
Hirsutism, 66.80
Hair pigmentation, 66.89
Variation in hair colour, 66.91
Hair cosmetics, 66.95
Shampoos, 66.96
Conditioners, 66.96
Cosmetic hair colouring, 66.96
Permanent waving, 66.98
Hair straightening (relaxing), 66.99
Hair setting, 66.100
Complications, 66.100

Anatomy and physiology

A.G. Messenger, pp. 66.1–66.16

Introduction

Hair has no vital function in humans, yet its psychological functions are extremely important, as any clinical dermatologist or cosmetician can readily attest from routine daily practice. If the inevitability of scalp baldness makes it reluctantly tolerable to genetically disposed men, in women, loss of hair from the scalp is distressing as is the growth of body or facial hair in excess of the culturally accepted norm.

The evolutionary history of hair is no less enigmatic. Mammals probably evolved from Therapsid reptiles during the Late Triassic period over 200 million years ago (MyA). The earliest direct evidence of hair in mammals comes from fossilized casts and impressions in coprolites and pellets from the Late Paleocene beds of Inner Mongolia [1]. Hairs from at least four extinct mammalian taxa were identified, notably the multituberculate *Lambdopsalis bulla*, all showing striking preservation of the cuticular scale pattern. The three extant mammalian groups—monotremes, marsupials and placental mammals—all possess hair, indicating its presence prior to the divergence of therian mammals from monotremes, which probably took place between 170 and 230 MyA [2,3]. The multituberculate lineage extends back into the Triassic, suggesting that hair is a very ancient and possibly defining feature of mammals. Whatever its origin, it is clear that the warm-blooded mammals owe much of their evolutionary success to the properties of the hairy pelage as a heat insulator. Paradoxically, Man's movement from the ancestral forest home to populate the globe is linked with a reversion to relative nudity and an ability to keep cool. Moreover, hair serves other purposes: in particular, it is concerned with sexual and social communication by constructing adornments such as the mane of the lion or the beard of the human male, or assisting in the dispersal of scents secreted by complexes of sebaceous or apocrine glands.

For these evolutionary reasons, hair follicles are not all under identical control mechanisms. To match the animal coat to seasonal changes in ambient temperature or environmental background requires moulting and replacement of the hairs. The process appears to involve an inherent follicular rhythm, modified by circulating hormones such as melatonin, prolactin, androgens or thyroxine, whose secretion is geared to environmental cues through the pineal gland, hypothalamus and pituitary.

The control of sexual hair growth must be clearly differentiated from that of the moult cycle. The development of pubic, axillary and other body hair is delayed until puberty because it is dependent upon androgens in both sexes; that 'male' hormones are, in contrast, also a prerequisite for the manifestation of androgenetic alopecia still defies adequate explanation.

In all mammals, including humans, but with the possible exception of the merino sheep and the poodle dog, hair follicles show intermittent activity. Thus, each hair grows to a maximum length, is retained for a time without further growth, and is eventually shed and replaced.

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

Types of hair

Different types of hair may be produced by different kinds of follicle, and the type of hair produced in any particular follicle can change with age or under the influence of hormones. Animals characteristically have both an overcoat of stiff guard hairs and an undercoat of fine hairs [4], but many kinds of follicle and fibre have been described. Many species also have large vibrissae or sinus hairs, which are sensory and are produced from special follicles containing erectile tissue, but there are no strictly comparable follicles in humans. In humans, a prenatal coat of fine, soft, unmedullated and usually unpigmented hair, known as *lanugo*, is normally shed *in utero* in the eighth to ninth month of gestation. Postnatal hair may be divided at the extreme into two kinds: vellus, which is soft, unmedullated, occasionally pigmented and seldom more than 2 cm long; and terminal hair, which is longer, coarser and often medullated and pigmented. However, there is a range of intermediate kinds. Before puberty, terminal hair is normally limited to the scalp, eyebrows and eyelashes. After puberty, secondary sexual 'terminal' hair is developed from vellus hair in response to androgens.

Development and distribution of hair follicles

Human hair follicles appear first in the regions of the eyebrows, upper lip and chin at about 9 weeks of embryonic development, and in other regions in the fourth month [5]. Hair over most of the scalp passes through a complete cycle and is shed *in utero*, and follicles in these regions have re-entered anagen by the time of birth. In the occipital scalp, telogen is delayed until after birth and this may give rise to a patch of hair loss in this region in the neonatal period. A fuller account of embryonic development is given in Chapter 3.

In humans, the full complement of hair follicles is probably established by the time of birth. Follicle density is highest in the fetus, when it may be similar across the skin surface. With growth there is a progressive reduction in follicle density, which continues until adult life, as skin surface area increases (Table 66.1). This occurs to a greater degree over the trunk and limbs than over the head so that the reduction in follicle density is less marked on the head than elsewhere [6]. The highest hair follicle densities, in the region of 800/cm^2, are found on the forehead and cheeks, with rather lower values for visible vellus hairs on the forehead in young adults of both sexes, and on the cheeks in women (400–450/cm^2) [7]. Lower hair densities of 50–100/cm^2 are found on the chest and back in both sexes [7,8], and follicle densities of approximately 50/cm^2 on the thigh and leg [6]. Published values for the average scalp hair density in white people vary between 250 and 320 hairs/cm^2 [9–12]. Scalp hair density shows a normal distribution in the population, with a wide range [12]. There is also racial variation in scalp hair density: average hair density in Africans (187/cm^2) [13] and African Americans (171/cm^2) [14] is lower than in white people, and it is lower still in Koreans (128/cm^2) [15].

Table 66.1 Hair follicle density in human fetal and adult skin. In adults, hair follicle density is highest on the head and much lower on the trunk and limbs. At 24 weeks' gestational age hair follicle density is similar in forehead and thigh skin. There is a pronounced reduction in thigh hair follicle density by adult life but only a small fall on the forehead. (Adapted from Szabo [6].)

	Fetal skin				Adult	
	24 weeks		Full term			
	Mean	±	Mean	±	Mean	±
Cheek					830	40
Forehead	1060		1060	110	765	20
Scalp					350	50
Forearm					95	15
Thigh	1010	250	480	40	55	5
Lower leg					45	10
Abdomen					70	15
Chest					75	25

References

1 Meng J, Wyss AR. Multituberculate and other mammal hair recovered from Palaeogene excreta. *Nature* 1997; **385**: 712–4.
2 Belov K, Hellman L, Cooper DW. Characterisation of echidna IgM provides insights into the time of divergence of extant mammals. *Dev Comp Immunol* 2002; **26**: 831–9.
3 van Rheede T, Bastiaans T, Boone DN *et al.* The platypus is in its place: nuclear genes and indels confirm the sister group relation of monotremes and Therians. *Mol Biol Evol* 2006; **23**: 587–97.
4 Dry FW. The coat of the mouse (*Mus musculus*). *J Genet* 1925; **16**: 287–340.
5 Pinkus H. Embryology of hair. In: Montagna W, Ellis RA, eds. *The Biology of Hair Growth*. New York: Academic Press, 1958: 1–32.
6 Szabo G. The regional anatomy of the human integument with special reference to the distribution of hair follicles, sweat glands and melanocytes. *Philos Trans R Soc Lond B Biol Sci* 1967; **252**: 447–85.
7 Blume U, Verschoore M, Poncet M *et al.* The vellus hair follicle in acne: hair growth and sebum excretion. *Br J Dermatol* 1993; **129**: 23–7.
8 Blume U, Ferracin J, Verschoore M *et al.* Physiology of the vellus hair follicle: hair growth and sebum excretion. *Br J Dermatol* 1991; **124**: 21–8.
9 Barman JM, Astore I, Pecoraro V. The normal trichogram of the adult. *J Invest Dermatol* 1965; **44**: 233–6.
10 Rushton DH, Ramsay ID, James KC *et al.* Biochemical and trichological characterization of diffuse alopecia in women. *Br J Dermatol* 1990; **123**: 187–97.
11 Whiting DA. Diagnostic and predictive value of horizontal sections of scalp biopsy specimens in male pattern androgenetic alopecia. *J Am Acad Dermatol* 1993; **28**: 755–63.
12 Birch MP, Messenger JF, Messenger AG. Hair density, hair diameter and the prevalence of female pattern hair loss. *Br J Dermatol* 2001; **144**: 297–304.
13 Loussouarn G. African hair growth parameters. *Br J Dermatol* 2001; **145**: 294–7.
14 Sperling LC. Hair density in African Americans. *Arch Dermatol* 1999; **135**: 656–8.
15 Lee HJ, Ha SJ, Lee JH *et al.* Hair counts from scalp biopsy specimens in Asians. *J Am Acad Dermatol* 2002; **46**: 218–21.

Anatomy of the hair follicle (Fig. 66.1)

Hair is the keratinized product of the hair follicle, a tube-like structure continuous with the epidermis at its upper end. The follicles are sloped in the dermis, and longer follicles extend into the subcutaneous layer. An oblique muscle, the arrector pili, runs from the mid-region of the follicle wall to a point in the papillary dermis close to the dermal–epidermal junction. Above the muscle, one or more sebaceous glands, and in some regions of the body an apocrine gland also, open into the follicle. The hair fibre is made up of three cell layers: an outer cuticle, the cortex (which forms the bulk of the fibre in most hair types) and a variable central medulla, all of which derive from highly proliferative cells in the hair bulb

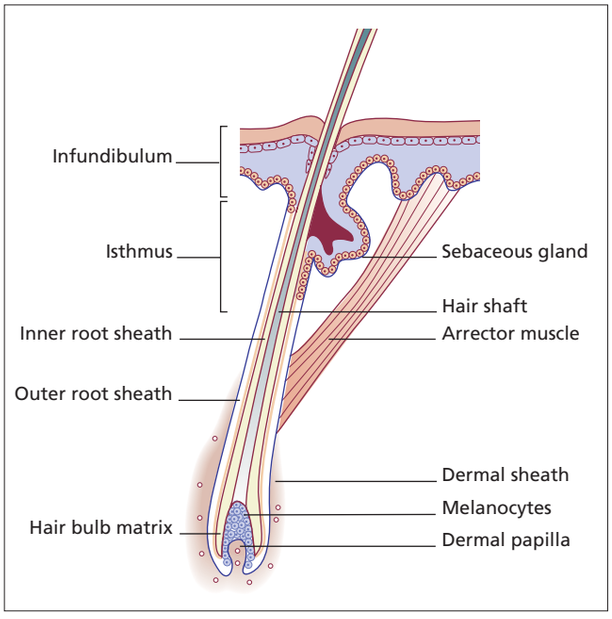


Fig. 66.1 Diagram of an anagen hair follicle.

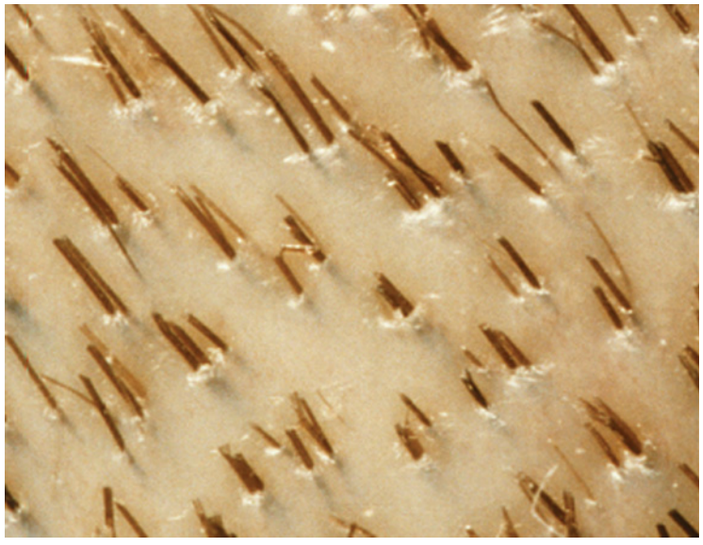


Fig. 66.2 Grouping of hairs in follicular units on human scalp. In some groups, multiple hairs emerge from a single follicular opening.

at the base of the follicle. Cells in the hair bulb also give rise to the inner root sheath which surrounds the hair fibre and which disintegrates before the hair emerges from the skin. The inner root sheath is itself enclosed by the outer root sheath, which forms a continuous structure extending from the hair bulb to the epidermis, although the functions and microscopic structure of the outer root sheath vary along the length of the follicle. The hair follicle also has a specialized dermal component, which includes the dermal or connective tissue sheath surrounding the follicle, and the dermal papilla which invaginates the hair bulb.

The hair follicle is conventionally divided into two regions: the upper part consisting of the infundibulum and isthmus and the lower part comprising the hair bulb and suprabulbar region. The upper follicle is a relatively constant structure, whereas the lower follicle undergoes repeated episodes of regression and regeneration during the hair cycle. On the scalp, and some other regions of the skin, hair follicles are arranged in groups of three or more follicles known as follicular units (Fig. 66.2). Several follicles within a follicular unit may coalesce so that hairs emerge through a common infundibulum.

The infundibulum

The infundibulum extends from the skin surface, where it merges with the epidermis, to the opening of the sebaceous duct at the junction with the isthmus. Infundibular epithelium differentiates in a similar manner to epidermis, producing a granular layer and stratum corneum which desquamates into the follicular lumen.

The isthmus

The isthmus extends from the opening of the sebaceous gland duct to the insertion of the arrector pili muscle. It consists of a multilayered outer root sheath that is continuous with the infundibulum but differs in its structure. The innermost cells lack a granular layer and undergo a pattern of differentiation known as trichilemmal keratinization. The keratinized inner root sheath, which lies within the outer root sheath, disintegrates at or about the level of the sebaceous duct. The arrector muscle loops around the follicle in the manner of a sling [1]. Each follicular unit is supplied by a single arrector muscle, which splits to encircle each follicle within the follicular unit [2].

Hair follicle stem cells reside in the lower part of the isthmus close to the insertion of the arrector muscle [3]. During embryogenesis, and in adult follicles in other species, this region shows a distinctive bulge, although a clearly defined bulge is often not seen in human adult hair follicles. Hair follicle stem cells show distinctive biochemical properties, they are slow cycling and proliferate only during the onset of anagen. Daughter cells, known as transient amplifying cells, input into the outer root sheath of the lower part of the hair follicle whence they migrate in a downward direction. On entering the hair bulb matrix, they proliferate and undergo terminal differentiation to form the hair shaft and inner root sheath [4]. The progeny of hair follicle stem cells may also migrate distally to form the sebaceous gland and, under certain circumstances such as wound healing, the epidermis.

The suprabulbar region (Fig. 66.3)

The suprabulbar region of the follicle, below the isthmus and above the hair bulb, is comprised of three layers from outermost to innermost: outer root sheath, inner root sheath and hair shaft. The outer root sheath is a multilayered epithelium enclosing the inner root sheath which, at this level, is a fully keratinized structure. Cells of the hair shaft, at the centre of the follicle, undergo terminal differentiation within the keratogenous zone in the middle part of the suprabulbar region. Keratinization of the inner root sheath precedes that of the hair shaft, suggesting that the inner root sheath has a role in 'moulding' the shape of the hair fibre.

The hair bulb (Fig. 66.4)

In large terminal follicles, the deepest part of the follicle, the hair bulb, is situated in the subcutaneous fat. The hair bulb is

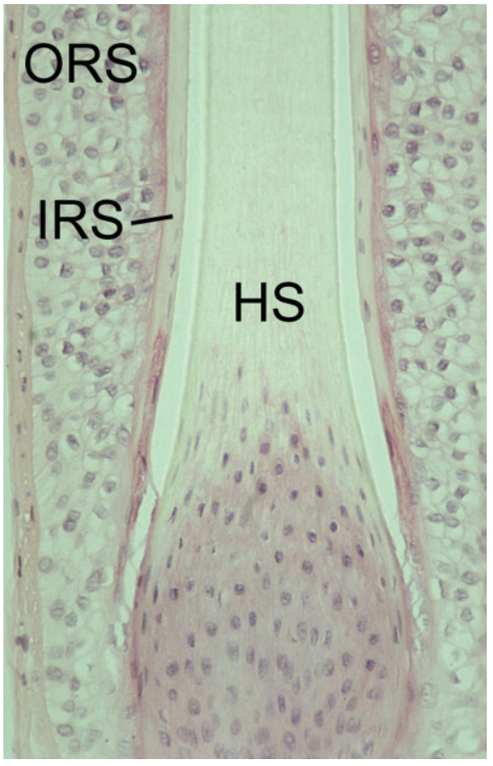


Fig. 66.3 Longitudinal section through the suprabulbar region of an anagen follicle showing the keratogenous region of the hair shaft (HS). The inner root sheath (IRS) is keratinized at this level. ORS, outer root sheath.

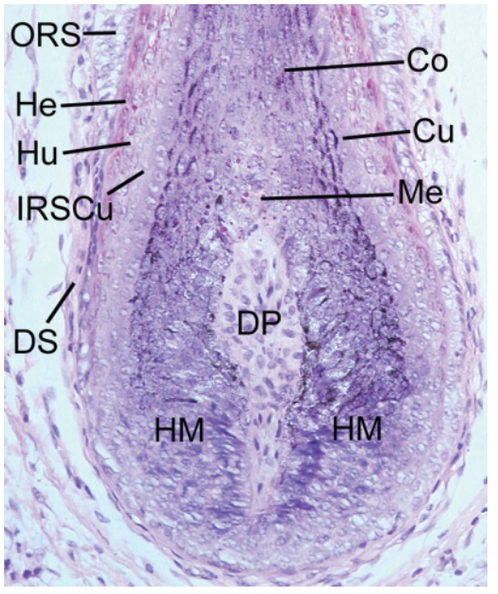


Fig. 66.4 Anagen hair bulb. Co, hair cortex; Cu, hair cuticle; DP, dermal papilla; DS, dermal sheath; He, Henle's layer; HM, hair matrix; Hu, Huxley's layer; IRSCu, inner root sheath cuticle; ORS, outer root sheath.

invaginated at its base by the dermal papilla, which is connected to the perifollicular dermal sheath by a narrow stalk. The hair shaft and the inner root sheath are derived from epithelial cells surrounding the dermal papilla, a region known as the hair bulb matrix or germinative epithelium. These cells have a high mitotic rate, with a rate of cell turnover similar to that in the bone marrow. Daughter cells migrate in an upward direction and differentiate in a highly ordered fashion to form the concentric layers of the inner root sheath and the hair shaft. The inner root sheath derives from cells in the lower, more lateral part of the matrix, whereas the hair shaft is formed from the upper, centrally situated cells. In pigmented hair follicles, highly melanized melanocytes are situated amongst cells destined to form the hair cortex. Occasional Langerhans' cells may also be found in the matrix region. The outer root sheath surrounds the inner root sheath. At the level of the hair bulb it consists of a single layer of cells, which can be followed almost to the lower tip of the hair follicle.

The dermal papilla

In anagen follicles, the dermal papilla is a flask-shaped structure that invaginates the base of the hair follicle. It is made up of specialized fibroblast-like cells embedded in an extracellular matrix rich in basement-membrane proteins and proteoglycans, and in large follicles the dermal papilla often contains a loop of capillary blood vessels. It is connected to the dermal sheath surrounding the follicle by a narrow stalk. Both the dermal papilla and the dermal sheath are derived from a condensation of mesenchymal cells, which appear at an early stage in follicular embryogenesis. Tissue recombinant studies have shown that the dermal papilla plays an essential part in the induction and maintenance of follicular epithelial differentiation [5–8]. It is responsible for determining the follicle type, so that cultured dermal papilla cells derived from the rat vibrissae follicle induce the formation of a vibrissa-like follicle when implanted into ear skin [9]. The volume of the dermal papilla may also be responsible for controlling the size of the hair follicle, and that of the hair fibre [10,11]. This is of particular relevance to androgen-dependent changes in human hair growth, as the dermal papilla is probably the primary target of androgen action in the hair follicle.

The dermal sheath

The lower part of the hair follicle is enveloped by a collagenous layer known as the dermal or connective tissue sheath. Like dermal papilla cells, fibroblasts of the dermal sheath are specialized. In experimental circumstances, these cells can reconstitute the dermal papilla and induce the formation of new hair follicles in adult human skin [12]. As we move distally along the hair follicle, above the level of the arrector insertion, the dermal sheath becomes less distinct, both structurally and functionally, as it merges with the interfollicular dermis.

The inner root sheath

The inner root sheath consists of three layers (from outermost to innermost): Henle's layer, Huxley's layer and the inner root sheath cuticle. Inner root sheath cells accumulate filaments approximately 7 nm thick and, in contrast with the hair cortex, amorphous trichohyalin granules appear in the cytoplasm. As the cells move up the follicle towards the surface, the filaments become more abundant and the number and size of the granules increase. Each of the three layers of the inner root sheath undergoes abrupt keratinization.

This occurs at different levels in each layer, although the patterns of change are identical. In the hardened cytoplasm, however, only filaments can be seen. The changes occur first in the outermost Henle's layer, then in the innermost cuticle and lastly in Huxley's layer, which is situated between them. Cells of the inner root sheath cuticle become flattened and overlap, with their free edges pointing downwards to interdigitate with the upwards-pointing cells of hair shaft cuticle, thus anchoring the hair shaft within the hair follicle. The inner root sheath hardens before the presumptive hair within it, and it is consequently thought to control the definitive shape of the hair shaft.

The outer root sheath

The outer root sheath forms the most peripheral layer of hair follicle epithelium, enclosing the inner root sheath. At the lower tip of the hair bulb it consists of a single layer of cuboidal cells, becoming multilayered in the region of the upper hair bulb. The cytoplasm of outer root sheath cells is rich in glycogen, giving a clear appearance with routine histological stains. In some follicles, particularly large beard follicles, there is a distinct single cell layer interposed between the outer and inner root sheaths, known as the companion layer [13]. Companion layer cells are flattened along the axis of the follicle and are relatively devoid of glycogen. They show numerous intercellular connections to the inner root sheath and are thought to migrate distally along with the inner root sheath to be lost in the isthmus region. The direction of movement of outer root sheath cells is unclear but they may migrate downwards towards the hair bulb, the companion layer forming the plane of slippage between the inner and outer root sheaths. The outer root sheath of the suprabulbar region merges imperceptibly with the isthmus where the innermost cells undergo tricholemmal keratinization.

The cuticle

The hair cuticle is formed initially as a single cell layer, but the cells become progressively imbricated (tile-like) as they move peripherally. The cells become flattened, first in a direction at right angles to the plane of the follicle, and then becoming progressively angulated so that the outer edges of the cells point in an upward direction. The flattened cells overlap, their free edges directed towards the tip (Fig. 66.5) and interlocking with the cuticle of the surrounding inner root sheath. In the fully formed hair shaft, the cuticle consists of 5–10 overlapping cell layers, each 350–450 nm thick (Fig. 66.6). The mature cells are thin scales consisting of compact cuticular keratin, associated with ultra-high sulphur proteins, which show three distinct layers by transmission electron microscopy: the outer A-layer, which is particularly rich in cystine; the exocuticle (also cystine-rich); and the inner endocuticle, which is virtually devoid of sulphur. The endocuticle has an irregular substructure of membrane-like elements which are probably the remnants of cytoplasmic structures [14]. The outer surface of the cuticle is thought to be coated with long-chain (straight and branched) fatty acids linked to an underlying lipid–protein matrix [15]. This layer is 2–7 nm thick and is known as the fibre cuticle surface membrane or epicuticle. The cuticle has important protective properties. It acts as a barrier to physical and chemical insults, and also maintains the integrity of the hair shaft. Wear and tear

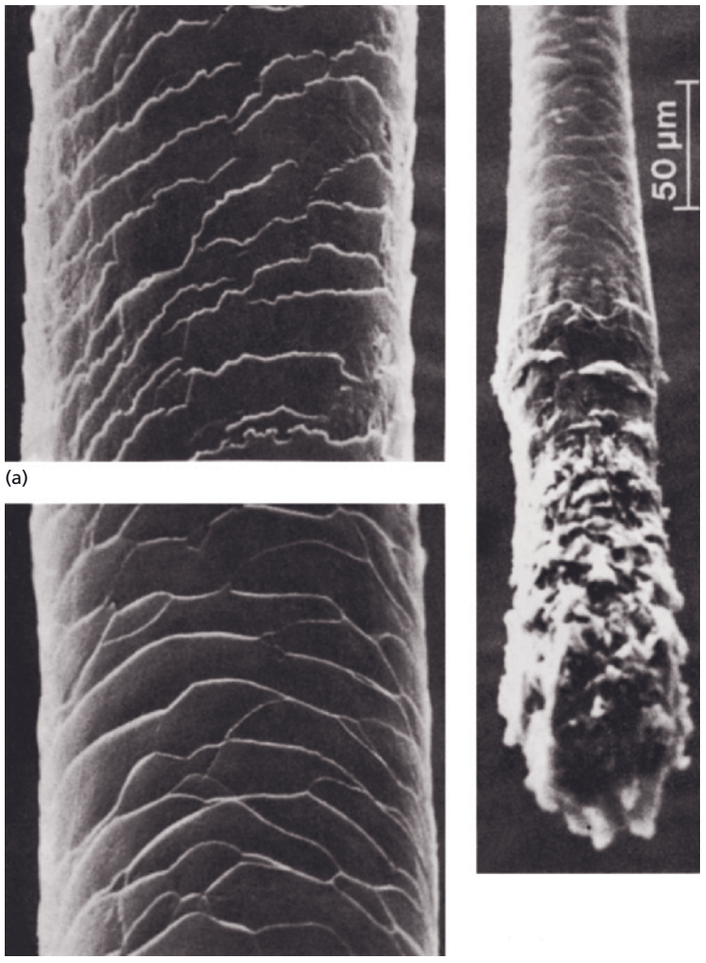


Fig. 66.5 (a) Surface view of weathered cuticular scales in the distal portion of the hair shaft. (b) Surface view of undamaged cuticular scales in proximal part of hair shaft. (Courtesy of Dr D. Jackson, University of Sheffield, Sheffield, UK.)

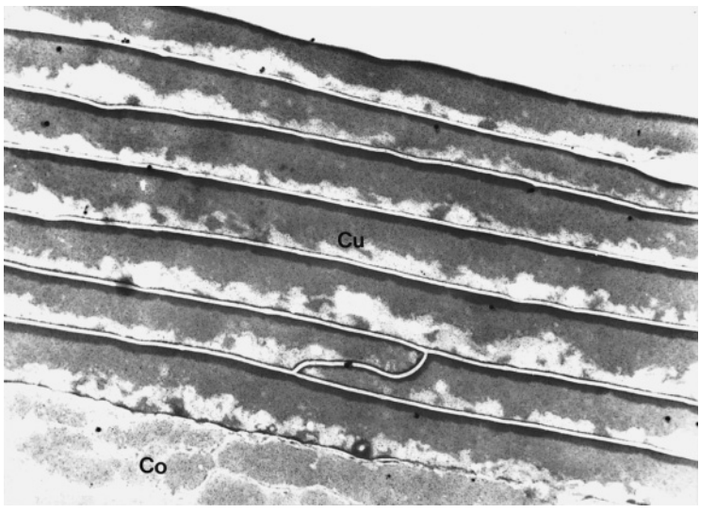


Fig. 66.6 Cross-section through hair shaft showing cuticle layers (Cu) surrounding the central cortex (Co). (Transmission electron micrograph, silver methenamine stain.)

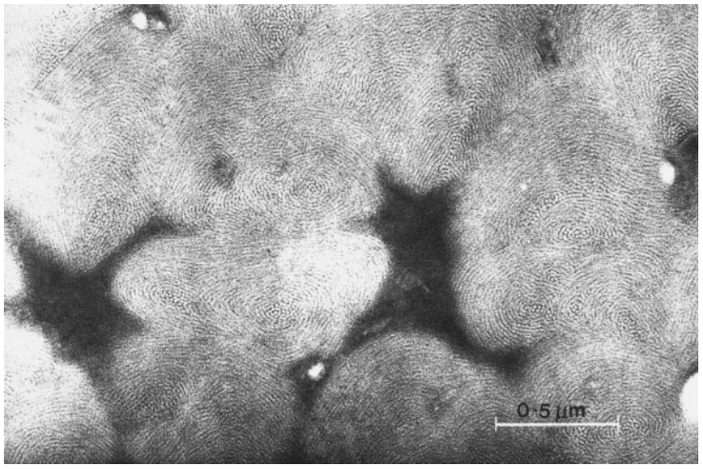


Fig. 66.7 Cross-section of transformed cortical cells of human hair. The relatively translucent filaments, set in a more dense sulphur-rich matrix, appear as concentric lamellae (macrofibrils), giving a characteristic fingerprint pattern.

(e.g. from cosmetic procedures) leads to gradual degradation of the cuticle ('weathering'), with breaking and lifting of the free margins of cuticular cells. Eventually this process may lead to exposure of the cortex and fracture of the hair shaft.

The cortex

Cells destined to form the cortex gradually become more fusiform in shape as they migrate upwards from the hair bulb. They develop a dense filamentous cytoskeleton in the upper hair bulb to become fully hyalinized in the suprabulbar region (the keratogenous zone) (Fig. 66.7). The hard α-keratin intermediate filaments (α-KIF) are the major structural component of the mammalian hair cortex. The molecule in α-KIF is an obligate heteropolymer containing a type I and a type II polypeptide chain [16–18], in which right-handed α-helices coil round one another in a left-handed manner to form a rod-like dimeric structure (a 'coiled coil') (Fig. 66.8). The 8-nm keratin filaments (microfibrils) are formed from multiple α-KIF molecules, on average 16 molecules or 32 chains in cross-section [19]. Keratin filaments are cross-linked to keratin-associated proteins, which form a matrix between the filaments. More than 60 hair keratin-associated proteins have been found in various species. They are classified into three major families: high sulphur, ultra-high sulphur and high glycine–tyrosine proteins [20]. In some species, notably the sheep, the cortex can be divided into two regions: the orthocortex and paracortex, which differ in the arrangement of KIFs and the proportion of keratin-associated proteins. In humans, the hair cortex appears to contain mixtures of KIF arrangements within each cell.

The medulla

The medulla is a variable structure in human hairs, where it may be continuous, discontinuous or absent. Large-diameter hairs are more likely to contain a medulla, although the relationship between hair diameter and medullation is not clear-cut. The medulla develops quite abruptly around the upper pole of the dermal papilla, without any obvious precursor cell population. Medullary cells contain distinctive eosinophilic granules that eventually form internal coatings within the membranes of mature cells. As these

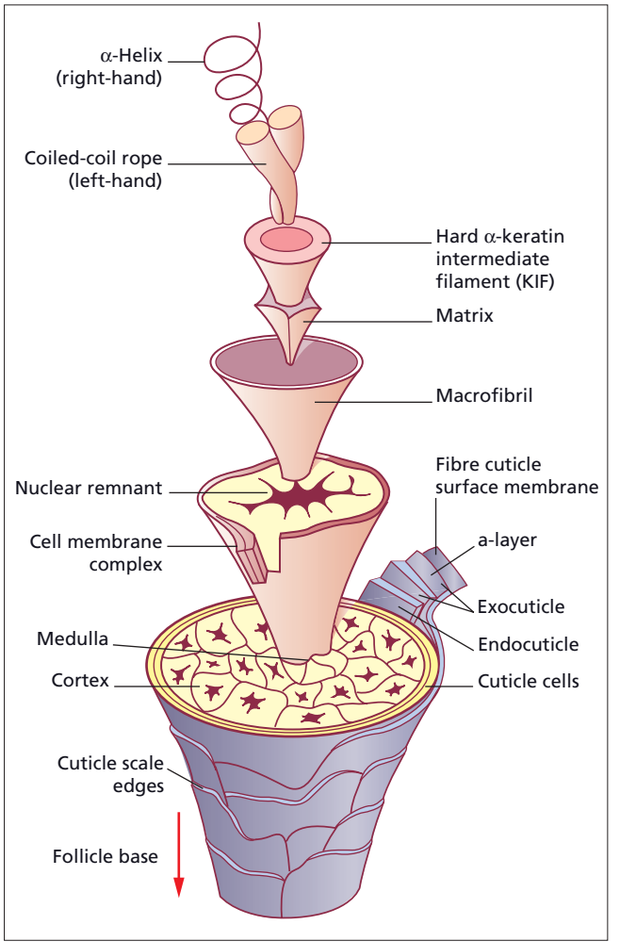


Fig. 66.8 Diagram showing an exploded view of the major structural components comprising a human hair fibre. Pigment granules that are normally dispersed throughout the cortex are not included. (Courtesy of Dr L. Jones [14].)

cells develop, arginine residues are converted to citrulline, and isopeptide bonds are formed to yield a highly insoluble protein complex [21]. Mature medulla cells have a spongy structure, with amorphous material bounding air spaces of varying sizes.

Hair follicle innervation

A plexus of longitudinally aligned sensory nerve fibres surrounds the isthmus region. Small nerve fibres may also be arranged in a circular fashion outside the longitudinal fibres. Several different types of nerve endings are found around human hair follicles, including free nerve endings, pilo-Ruffini nerve endings and Merkel nerve endings [22,23]. In other species, lamellated nerve endings are found in richly innervated sinus hair follicles (e.g. vibrissae follicles), which have specialized sensory function [23]. Merkel cells, with or without associated nerve endings, may be found within the bulge region epithelium and the surrounding connective tissue sheath, and it has been postulated that their secretions are involved in regulating the hair cycle [24].

References

1 Narisawa Y, Kohda H. Arrector pili muscles surround human facial vellus hair follicles. *Br J Dermatol* 1993; **129**: 138–9.

2 Poblet E, Ortega F, Jimenez F. The arrector pili muscle and the follicular unit of the scalp: a microscopic anatomy study. *Dermatol Surg* 2002; **28**: 800–3.
3 Cotsarelis G, Sun TT, Lavker RM. Label-retaining cells reside in the bulge area of pilosebaceous unit: implications for follicular stem cells, hair cycle, and skin carcinogenesis. *Cell* 1990; **61**: 1329–37.
4 Oshima H, Rochat A, Kedzia C *et al.* Morphogenesis and renewal of hair follicles from adult multipotent stem cells. *Cell* 2001; **104**: 233–45.
5 Oliver RF. Whisker growth after removal of the dermal papilla and lengths of follicle in the hooded rat. *J Embryol Exp Morphol* 1966; **16**: 231–44.
6 Oliver RF. The experimental induction of whisker growth in the hooded rat by implantation of dermal papillae. *J Embryol Exp Morphol* 1967; **18**: 43–51.
7 Oliver RF. The induction of hair follicle formation in the adult hooded rat by vibrissa dermal papillae. *J Embryol Exp Morphol* 1970; **23**: 219–36.
8 Jahoda CA, Horne KA, Oliver RF. Induction of hair growth by implantation of cultured dermal papilla cells. *Nature* 1984; **311**: 560–2.
9 Jahoda CA, Reynolds AJ, Oliver RF. Induction of hair growth in ear wounds by cultured dermal papilla cells. *J Invest Dermatol* 1993; **101**: 584–90.
10 Van Scott EJ, Ekel TM. Geometric relationships between the matrix of the hair bulb and its dermal papilla in normal and alopecic scalp. *J Invest Dermatol* 1958; **31**: 281–7.
11 Ibrahim L, Wright EA. A quantitative study of hair growth using mouse and rat vibrissal follicles. I. Dermal papilla volume determines hair volume. *J Embryol Exp Morphol* 1982; **72**: 209–24.
12 Reynolds AJ, Lawrence C, Cserhalmi-Friedman PB *et al.* Trans-gender induction of hair follicles. *Nature* 1999; **402**: 33–4.
13 Rothnagel JA, Roop DR. Hair follicle companion layer: reacquainting an old friend. *J Invest Dermatol* 1995; **104**: 42–3S.
14 Jones LN. Hair structure anatomy and comparative anatomy. *Clin Dermatol* 2001; **19**: 95–103.
15 Jones LN, Rivett DE. The role of 18-methyleicosanoic acid in the structure and formation of mammalian hair fibres. *Micron* 1997; **28**: 469–85.
16 Langbein L, Rogers MA, Winter H *et al.* The catalog of human hair keratins. I. Expression of the nine type I members in the hair follicle. *J Biol Chem* 1999; **274**: 19874–84.
17 Langbein L, Rogers MA, Winter H *et al.* The catalog of human hair keratins. II. Expression of the six type II members in the hair follicle and the combined catalog of human type I and II keratins. *J Biol Chem* 2001; **276**: 35123–32.
18 Schweizer J, Langbein L, Rogers MA *et al.* Hair follicle-specific keratins and their diseases. *Exp Cell Res* 2007; **313**: 2010–20.
19 Jones LN, Simon M, Watts NR *et al.* Intermediate filament structure: hard alpha-keratin. *Biophys Chem* 1997; **68**: 83–93.
20 Rogers GE, Powell BC. Organization and expression of hair follicle genes. *J Invest Dermatol* 1993; **101**: 50–5S.
21 Harding HW, Rogers GE. Epsilon-(gamma-glutamyl)lysine cross-linkage in citrulline-containing protein fractions from hair. *Biochemistry* 1971; **10**: 624–30.
22 Hashimoto K, Ito M, Suzuki Y. Innervation and vasculature of the hair follicle. In: Orfanos CE, Happle R, eds. *Hair and Hair Diseases*. Berlin: Springer-Verlag, 1990: 117–47.
23 Halata Z. Specific nerve endings in vellus hair, guard hair and sinus hair. In: Orfanos CE, Happle R, eds. *Hair and Hair Diseases*. Berlin: Springer-Verlag, 1990: 149–64.
24 Narisawa Y, Hashimoto K, Nakamura Y *et al.* A high concentration of Merkel cells in the bulge prior to the attachment of the arrector pili muscle and the formation of the perifollicular nerve plexus in human fetal skin. *Arch Dermatol Res* 1993; **285**: 261–8.

The hair cycle (Fig. 66.9)

Hair follicles undergo a repetitive sequence of growth and rest known as the hair cycle. The timing of the phases of the hair cycle and its overall duration varies between species, between follicles in different regions of the skin in the same species and, in some animals, between different follicle types, such as guard hairs and underhairs, in the same region of the skin.

The period of active hair growth is known as *anagen* and the duration of this phase is responsible for determining the final length of the hair. In most hair follicles in most animals, anagen

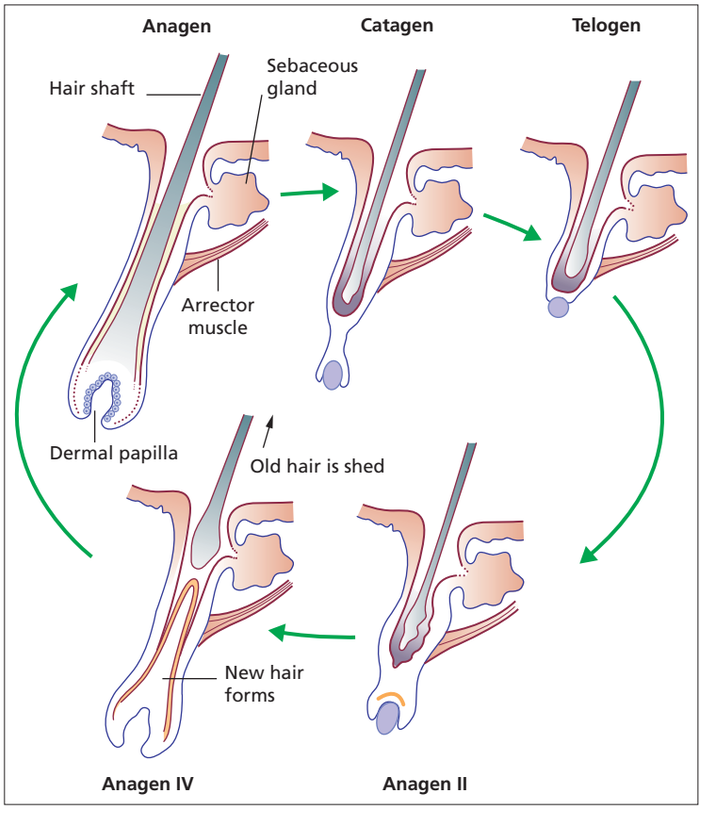


Fig. 66.9 The hair cycle. (From *Disorders of Hair Growth*, McGraw-Hill.)

is relatively brief, lasting a few weeks at most. In some hair follicles, such as those on human scalp, the horse's tail and wool follicles in the merino sheep, anagen may continue for several years, so that very long hairs are produced. Under normal circumstances, 80–90% of hair follicles on the human scalp are in anagen at any one time.

The entry of a resting hair follicle into anagen is heralded by the onset of mitotic activity in epithelial cells overlying the dermal papilla at the base of the follicle (the secondary epithelial germ). In most follicle types (vibrissa follicles are an exception), the lower part of the follicle elongates downwards along a preformed dermal tract (the stele). The developing hair bulb partly envelops the dermal papilla, and epithelial cells start to differentiate to form the inner root sheath and the hair shaft (Fig. 66.10). The dermal papilla expands from a tightly packed ball of cells into a flask-shaped structure where the cells become separated by an extracellular matrix rich in proteoglycans and basement-membrane proteins. A network of capillary blood vessels develops around the lengthening follicle, extending into the dermal papilla in larger follicles. In the fully developed anagen follicle, epithelial cells in the hair bulb undergo vigorous proliferative activity. Their progeny move distally and differentiate in an ordered fashion to form the layers of the inner root sheath and the hair shaft. At the end of anagen, epithelial cell division declines and ceases, and the follicle enters an involutionary phase known as *catagen*. During catagen, the proximal end of the hair shaft keratinizes to form a club-shaped structure and the lower part of the follicle involutes by apoptosis (Fig. 66.11). The basement membrane surrounding the follicle

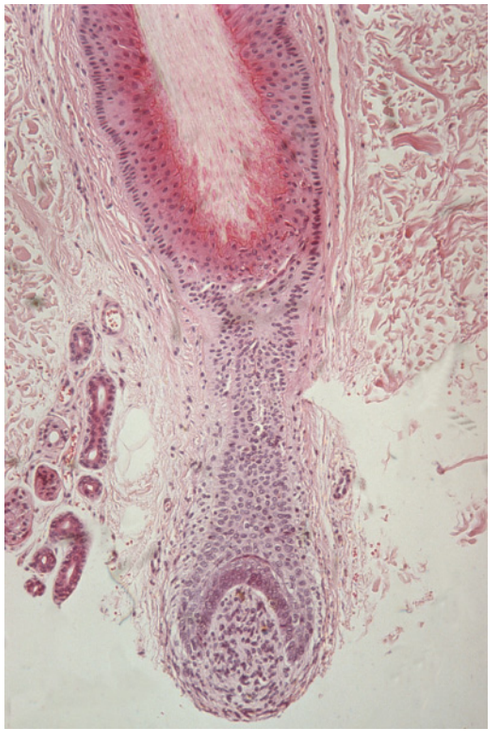


Fig. 66.10 Scalp hair follicle in Anagen 2 stage of development. The club hair from the previous cycle is still present within the follicle. (Courtesy of Dr A.J.G. McDonagh, Royal Hallamshire Hospital, Sheffield, UK.)

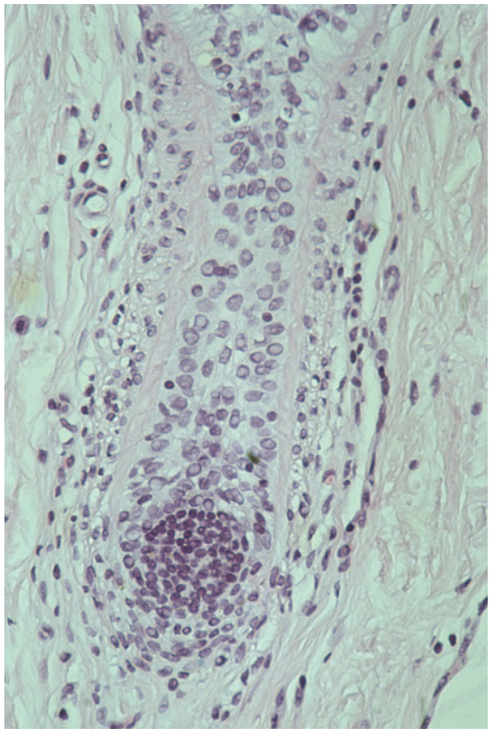


Fig. 66.11 Human hair follicle in mid-catagen. There is a prominent glassy membrane surrounding the regressing epithelial column. The dermal papilla has rounded and condensed. (Courtesy of McGraw-Hill.)

becomes thickened and corrugated to form the 'glassy membrane'. The base of the follicle, together with its dermal papilla, moves upwards, eventually to lie just below the level of the arrector insertion. The period between the completion of follicular regression and the onset of the next anagen phase is termed *telogen*. The club hair lies within an epithelial sac to which it is attached by tricholemmal keratin. The club hair is eventually shed through an active process termed *exogen*. In many species, follicles re-enter anagen prior to shedding of the club hair so that the old hair is not shed until the follicle is well into its next growth phase. This may also be seen in human follicles although it is unusual for a club hair to be retained much beyond the mid-stage of anagen development. In human scalp, hair follicles may remain in a state of latency, also known as *kenogen*, for a prolonged period after the club hair is shed [1].

Control of the hair cycle

It is thought that hair cycling is controlled primarily within individual hair follicles but that this intrinsic rhythmic behaviour may be modulated by both local and systemic factors. In most mammals, including humans, hair cycles are coordinated in a wave-like fashion (moult waves) across regions of the skin in the neonatal period. Moult waves are regulated within the skin and are accompanied by changes in other skin structures, such as epidermal and dermal thickness. In many mammals, living in their natural environment in temperate and higher latitudes, moult waves continue into adult life and occur on a seasonal basis. This allows adaptation of the thickness of the coat, and sometimes its colour, to different climatic conditions in summer and winter (Fig. 66.12). In humans, synchronous hair cycling is lost rapidly with increasing age so that, beyond the neonatal period, hair follicles cycle independently of their neighbours. In these circumstances, hair cycling must be regulated by mechanisms intrinsic to the hair follicle.

Seasonal hair growth

Seasonal moulting is regulated by the endocrine system under the influence of environmental signals. The most important of these



Fig. 66.12 Bactrian camel in spring moult.

is change in day length (the photoperiod) [2,3]. Temperature may act as a modifying factor in some species. Changing levels of melatonin production by the pineal gland have a key role in orchestrating endocrine control of seasonal hair growth [4–6]; pinealectomy prevents seasonal moulting, whereas administration of melatonin advances onset of the growth of the winter coat and prevents growth of the summer coat. Prolactin production by the pituitary correlates inversely with melatonin levels, being raised during the summer and falling during the winter. Pinealectomy abolishes the fall in prolactin level in animals kept in short day length conditions and prevents the development of the winter coat [7]. The same response is seen in animals treated with prolactin. Prolactin receptors have been identified in the hair follicle, suggesting that prolactin can affect hair growth directly [8]. Pineal and pituitary hormones may also act indirectly by modulating the activity of peripheral endocrine glands. In rats, oestradiol, testosterone and adrenal steroids delay the onset of anagen, whereas gonadectomy and adrenalectomy have the opposite effect [9]. Conversely, thyroid hormones accelerate the onset of follicular activity, whereas thyroidectomy or treatment with propylthiouracil delays it. Seasonal moults are also delayed by testosterone and accelerated by thyroxine in other species [10]. Hormones also act on the anagen phase of hair growth [9]. Oestradiol and thyroxine both reduce the duration of anagen in rats, but oestradiol decreases the rate of hair growth, whereas thyroxine has the opposite effect, suggesting these hormones have different points of action. In the mouse, oestrogen receptors are expressed in the dermal papilla and the inhibitory effect of exogenous oestrogen on hair growth is prevented by topical treatment with an oestrogen receptor antagonist [11].

Vestiges of seasonal variation in hair growth are present in humans [12], although the magnitude is seldom sufficient to be noticeable. The best example of a systemic influence on the human hair growth cycle is pregnancy (Fig. 66.13) [13]. During pregnancy,

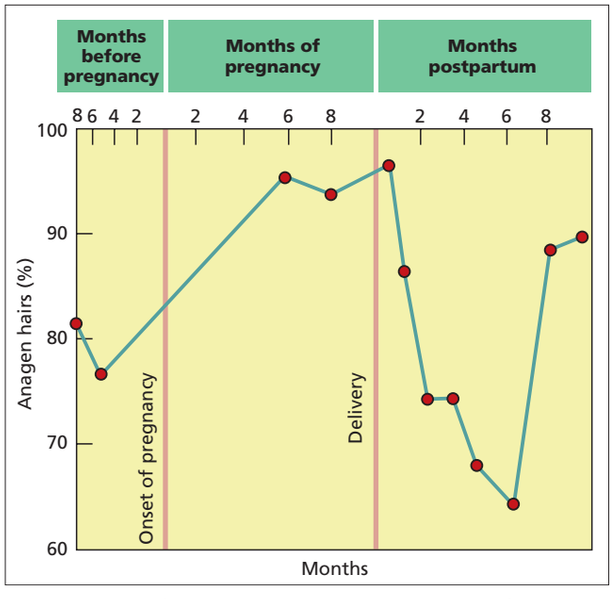


Fig. 66.13 Percentage of anagen hairs in a 25-year-old woman before, during and after pregnancy. (From Lynfield [13].)

there is an increase in the proportion of follicles in anagen, although it is not clear whether this is caused by prolongation of anagen or more rapid shedding of telogen hairs, as there is also a reduction in hair density during the second and third trimesters [14]. Following childbirth, large numbers of follicles enter telogen, leading to increased shedding from about 3 months postpartum (postpartum telogen effluvium). Telogen shedding may also be caused by a number of drugs and by febrile and other catabolic illnesses [15].

Intrinsic control of the hair growth cycle

Although local and systemic factors modulate the hair cycle in some species, in humans and some other mammals hair cycling is asynchronous. Hair follicles in different regions of the skin may also cycle differently. In humans, for example, the duration of anagen on the scalp may last several years, whereas on the eyebrows anagen is very brief. Even in animals showing seasonal hair growth, hair cycles in different follicle types in the same skin region are not necessarily in phase. When scalp hair follicles are transplanted into other regions of the skin they retain the cyclical behaviour of the donor site, indicating that cycle control is determined within the follicle or its immediate tissue environment. Interactions between two key cell populations in the hair follicle, epithelial stem cells in the outer root sheath and mesenchymal cells in the dermal papilla and dermal sheath, are thought to underlie intrinsic control of hair cycling, and a large number of molecules have been implicated in this process. However, the location and the nature of the 'switch' that initiates and terminates anagen growth are unknown.

It has been known for many years that plucking of resting hairs from telogen follicles advances the onset of anagen. This led to the idea that the hair cycle is controlled by a locally active inhibitor which accumulates during anagen causing entry into catagen when present in sufficient concentration (the chalone hypothesis) [16]. The putative inhibitor would disperse during telogen, and plucking resting hairs could accelerate this process. The chalone hypothesis has been disputed because the plucking of resting hairs from follicles that have already entered anagen does not prolong the anagen in progress, although it does advance the onset of the next anagen cycle [9]. There is one report that murine skin contains a factor that inhibits hair growth *in vivo* and *in vitro* [17]. This inhibitory factor appeared to be derived from the epidermis and was present in telogen skin but not in anagen skin.

Cotsarelis *et al.* [18] suggested that anagen is initiated by signals from the dermal papilla which stimulate mitosis in stem cells in the bulge region of the outer root sheath (the bulge activation hypothesis). As transient amplifying cells, daughter cells have a limited mitotic potential. When this is exhausted, hair growth ceases and the follicle enters catagen, thus determining the duration of anagen and the onset of catagen.

Molecular control of hair cycling [19]

A large number of molecular signals are involved in controlling the hair cycle (Table 66.2). These include developmental genes, several families of growth factors and their receptors, transcription factors, nuclear receptors, neurotrophins, cytokines and intracellular signalling pathways. These factors interact to form

Table 66.2 Molecular mediators of hair cycle control.

Growth factor	Location	Function
FGF5	ORS	Terminates anagen [21]
FGF7 (KGF)	DP	Induces hair growth in athymic nude mice [32]
		Hair shaft defect in KGF-deficient mice [33]
EGF/TGF-α		Inhibits hair development and growth [34,35]
		Stimulates ORS proliferation *in vitro* [36]
EGF-R	Hair bulb and ORS	Wavy hair in EGF-R deficient mice [37]
TGF-α		Wavy hair in TGF-α deficient mice [38]
TGF-β1, 2, 3		Inhibits hair growth *in vitro* [39]
		TGF-β mRNA expressed in skin during anagen/catagen transition [24]
TGF-β receptors		TGF-β receptors expressed in hair follicle—maximal during anagen/catagen transition [40]
		Delayed catagen in TGF-β1 null mice [41]
IGF-1	DP, hair bulb	Maintains hair follicle growth *in vitro* [42]
IGF-1 receptors	DP, pre-cortex, ORS	Down-regulated in catagen [43]
IGF BP-3, -4, -5	DP and DS [44]	
HGF		Stimulates hair growth when injected into mouse skin [45]
		Expression in skin varies during hair cycle: high in anagen, low in telogen [46]
VEGF	DP, ORS	Probably regulates perifollicular angiogenesis; increased follicle size in transgenic mice which overexpress VEGF in ORS; systemic VEGF antibody retards hair growth in mice [47]
IL-1α, IL-1β		Inhibits hair growth *in vitro* [48]
TNF-α		Inhibits hair growth *in vitro* [48]; TNF-α receptor mRNA expression increased in late anagen [43]
Sonic hedgehog (SHH)		Overexpression in skin accelerates entry into anagen [49]
		SHH antibody inhibits pelage (but not vibrissae) follicle development in mice; inhibits anagen in postnatal cycles [50]
Hairless		Required for normal catagen [25]
PTHrp	Follicle epithelium	Inhibits initiation and maintenance of anagen; PTHrp antagonist induces and prolongs anagen [51]
RXR		Required for normal catagen? [29]
Vitamin D receptor	DP, ORS	Variable expression during hair cycle [52]
		Alopecia in vitamin D receptor knockout mice [28] and in human vitamin D-resistant rickets [53]
Oestrogen receptor	DP	Oestrogen inhibits hair growth in mice [11]
		ER-beta expressed in human hair follicles [54]
Neurotrophins	Follicle epithelium	NGF, brain-derived neurotrophic factor, neurotrophin-3, neurotrophin-4, and p75 neurotrophin receptor, TrkB receptors promote progression of catagen [55]
Mast cells		Increased degranulation at end of anagen and fall in number during telogen; may be involved in control of catagen [56]

DP, dermal papilla; DS, dermal sheath; EGF, epidermal growth factor; FGF, fibroblast growth factor; HGF, hepatocyte growth factor; IGF, insulin-like growth factor; IGF BP, IGF binding proteins; IL-1, interleukin-1; KGF, keratinocyte growth factor; ORS, outer root sheath; PTHrp, parathyroid hormone-related peptide; RXR, retinoid X receptor; TGF, transforming growth factor; TNF, tumour necrosis factor; VEGF, vascular endothelial growth factor.

signalling networks and their activity may also be modulated by interactions with extracellular matrix molecules that serve to increase or reduce the biological response.

Telogen. The growth factor bone morphogenetic protein-4 (BMP-4) appears to play an important role in suppressing follicular growth and differentiation during telogen, and it may be the inhibitor identified by Paus [17]. BMP-4 is produced in the dermal papilla and may interact with the receptor BMPR-IA, which is expressed by keratinocytes in the secondary epithelial germ. BMP-4 treatment prevents entry into anagen of murine follicles induced by plucking, whereas administration of the BMP-4 antagonist noggin accelerates the onset of anagen [20]. In the mouse, there is also increased expression of oestrogen receptors in the dermal papilla during telogen, and topical administration of an oestrogen receptor antagonist causes premature entry of resting follicles into anagen [11], suggesting that oestrogen is involved in maintaining telogen, presumably acting by a paracrine or autocrine mechanism.

Anagen. The transition of telogen follicles into anagen is associated with activation of Wnt/beta-catenin/Lef1, Sonic Hedgehog (Shh) and STAT3 pathways, and down-regulation of BMP signalling [19]. Other growth factors involved in promoting anagen include insulin-like growth factor 1 (IGF-1), hepatocyte growth factor, keratinocyte growth factor and vascular endothelial growth factor. Anagen development is a time of extensive remodelling of the follicle and its tissue environment. Follicles grown *in vitro* synthesize a variety of metalloproteinases, suggesting that this process involves degradation of the surrounding extracellular matrix. Hair follicles also express tissue inhibitor of matrix metalloproteinase 3 (TIMP-3) in the outer root sheath during anagen, implying that remodelling involves a carefully controlled sequence of positive and negative influences.

Catagen. The end of anagen and transition into catagen is a key period in the hair cycle, as its timing determines the final length of the hair. Catagen may be initiated as a passive process through exhaustion of the mitotic potential of transient amplifying cells in the hair bulb or the loss of action of growth promoting agents. Also, several growth factors and cytokines, including transforming growth factor-β (TGF-β), interleukin-1α (IL-1α) and tumour necrosis factor-α (TNF-α) have an inhibitory effect on hair growth and may be actively involved in triggering catagen. Transgenic mice with a null mutation in the gene for fibroblast growth factor 5 (*FGF5*) show a delay in the onset of catagen and grow abnormally long hair. The phenotype is identical to the naturally occurring *angora* mouse which has a mutation in the *FGF5* gene, suggesting that this growth factor has an active role in terminating anagen [21]. *FGF5* is expressed in the outer root sheath towards the end of anagen, in keeping with this idea. However, although anagen is delayed in *FGF5*-deficient mice, it is not delayed indefinitely, indicating that other factors must also be involved. The ectodysplasin signalling pathway is involved in regulating apoptosis during catagen, in addition to its role in hair follicle development [22].

Catagen proceeds in an orderly fashion as cells are deleted from the regressing epithelial column by apoptosis. The expression levels of several proto-oncogenes associated with apoptosis, including c-*myc*, c-*jun* and c-*myb*, change immediately prior to or coincident with the onset of catagen [23]. The apoptosis-inhibitory proto-oncogene *bcl*-2 is expressed in cycling follicular epithelium during anagen, disappears during catagen and is absent in telogen. *Bcl*-2 is expressed in the dermal papilla throughout the hair cycle, suggesting a possible protective role in this site [24]. For the follicle to maintain the ability to cycle, it must maintain its integrity during catagen regression. In the *hairless* mouse, the first coat develops normally but the pelage is then lost. Towards the end of the first anagen phase, cells in the hair bulb undergo extensive premature apoptosis, and formation of the epithelial column is disrupted during catagen. The dermal papilla loses contact with the base of the hair follicle epithelium and the follicle is unable to re-enter anagen. Follicular remnants subsequently undergo cystic degeneration [25]. A similar pattern of hair loss is seen in the human disorder atrichia with papular lesions, in which there is a mutation in the human homologue of the mouse *hairless* gene [26]. The function of *hairless* in the hair follicle is not fully established but there is some evidence that it acts as a co-repressor of the thyroid receptor (TR) [27]. Atrichia with papules also occurs in some families with vitamin D-resistant rickets [28], which is caused by a mutation in the vitamin D receptor (VDR) gene. Like the TR, the VDR is a transcription factor and a member of the nuclear hormone receptor superfamily. Both TR and VDR bind to response elements in target genes as heterodimers with the retinoid X receptor (RXR), another nuclear hormone receptor. Transgenic mice with a null mutation in the RXR gene also show a *hairless* phenotype [29], suggesting there is a common pathway involving nuclear hormone receptors that regulates entry into catagen.

Exogen. Release of the club hair from the follicle, a process that has been termed *exogen* [30], does not necessarily coincide with re-entry of the follicle into anagen, and this has led to the idea that shedding is controlled separately from the hair cycle. The club root lies embedded in tricholemmal keratin and its release presumably requires local proteolysis. The cells surrounding the club root are also rich in desmosomes. Transgenic mice with a null mutation in the gene for the desmosomal protein desmoglein 3 show defective anchorage of the club hair [31].

Role of the immune system in hair cycling

Cells in the lower part of the hair follicle, below the arrector insertion, show reduced or absent expression of class I major histocompatibility complex (MHC) molecules [57]. In rat skin the expression of class I MHC in follicular epithelium increases during catagen, and this is associated with a perifollicular accumulation of activated macrophages and loss of the proteoglycan-rich extracellular matrix [58]. These observations led to the suggestion that an immune process mediated by macrophages contributes to control of the hair cycle, but other studies have failed to confirm these findings [59]. However, there is experimental support for the idea that the lower part of the hair follicle is an immunologically 'privileged' site not subject to classic immune surveillance [60,61]. This is relevant to disease states, such as alopecia areata, which may be explained by a breakdown of putative immune privilege.

Rate of hair growth

The rate of hair growth varies from species to species, and within one species from region to region, as well as with sex and age. For example, in the rat it can be more than 1 mm/24 h [62] and in the guinea pig up to 0.6 mm/24 h, whereas in humans it is much less. The rate has been determined by direct measurement of marked hairs *in situ* [63], by shaving and clipping at selected intervals [64,65] or by pulse labelling with ^{35}S-cysteine [66,67]. Most investigators now use macrophotographic methods (phototrichography), which may be analysed using computerized systems. Comparable measurements are obtained by all methods. The average rate of growth of human hair has been stated to be approximately 0.03 mm/24 h for the vellus on the male forehead [68], 0.21 mm/24 h on the female thigh and 0.38 mm/24 h on the chin of a young male. On the crown of the scalp it averaged approximately 0.5 mm/24 h, being slightly less on the margins. In another study in which graduated capillary tubes were fitted around the growing hairs, the average growth in males was as follows: vertex 0.44 mm/24 h; temple 0.39 mm/24 h; chest 0.44 mm/24 h; beard 0.27 mm/24 h [69]. The average rate on the vertex of women was 0.45 mm/24 h, and there were no variations diurnally or during the menstrual cycle. Although scalp hair grows faster in women than in men [69,70], the rate before puberty is greater in boys than in girls [71].

There is agreement that shaving has no effect on the rate of growth [69,72]. Various endocrine factors have been shown to influence the rate of hair growth in animals; for example, oestrogens reduce it [62,73] and thyroxine increases it [74].

References

1 Courtois M, Loussouarn G, Hourseau C. Aging and hair cycles. *Br J Dermatol* 1995; **132**: 86–93.

2 Bissonnette TH. Relations of hair cycles in ferrets to changes in the anterior hypophysis and to light cycles. *Anat Rec* 1936; **63**: 159–68.

3 Harvey NE, MacFarlane VW. The effects of day length on the coat-shedding cycles, body weight, and reproduction of the ferret. *Aust J Biol Sci* 1958; **11**: 187–99.
4 Allain D, Rougeot J. Induction of autumn moult in mink (*Mustela vison* Peale and Beauvois) with melatonin. *Reprod Nutr Dev* 1980; **20**: 197–201.
5 Rose J, Stormshak F, Oldfield J *et al.* Induction of winter fur growth in mink (*Mustela vison*) with melatonin. *J Anim Sci* 1984; **58**: 57–61.
6 Rose J, Oldfield J, Stormshak F. Apparent role of melatonin and prolactin in initiating winter fur growth in mink. *Gen Comp Endocrinol* 1987; **65**: 212–5.
7 Badura LL, Goldman BD. Prolactin-dependent seasonal changes in pelage: role of the pineal gland and dopamine. *J Exp Zool* 1992; **261**: 27–33.
8 Nixon AJ, Ford CA, Wildermoth JE *et al.* Regulation of prolactin receptor expression in ovine skin in relation to circulating prolactin and wool follicle growth status. *J Endocrinol* 2002; **172**: 605–14.
9 Ebling FJ. The hormonal control of hair growth. In: Orfanos CE, Happle R, eds. *Hair and Hair Diseases.* Berlin: Springer Verlag, 1990: 267–99.
10 Maurel D, Coutant C, Boissin J. Thyroid and gonadal regulation of hair growth during the seasonal molt in the male European badger, *Meles meles* L. *Gen Comp Endocrinol* 1987; **65**: 317–27.
11 Oh HS, Smart RC. An estrogen receptor pathway regulates the telogen-anagen hair follicle transition and influences epidermal cell proliferation. *Proc Natl Acad Sci U S A* 1996; **93**: 12525–30.
12 Randall VA, Ebling FJ. Seasonal changes in human hair growth. *Br J Dermatol* 1991; **124**: 146–51.
13 Lynfield YL. Effect of pregnancy on the human hair cycle. *J Invest Dermatol* 1960; **35**: 323–7.
14 Pecoraro V, Barman JM, Astore I. The normal trichogram of pregnant women. In: Montagna W, Dobson RL, eds. *Advances in Biology of the Skin*, Vol. 9. Oxford: Pergamon Press, 1967: 203–10.
15 Kligman AM. Pathologic dynamics of human hair loss. *Arch Dermatol* 1961; **83**: 175–98.
16 Chase HB. Growth of the hair. *Physiol Rev* 1954; **34**: 113–26.
17 Paus R, Stenn KS, Link RE. Telogen skin contains an inhibitor of hair growth. *Br J Dermatol* 1990; **12**: 777–84.
18 Cotsarelis G, Sun TT, Lavker RM. Label-retaining cells reside in the bulge area of pilosebaceous unit: implications for follicular stem cells, hair cycle, and skin carcinogenesis. *Cell* 1990; **61**: 1329–37.
19 Botchkarev VA, Kishimoto J. Molecular control of epithelial-mesenchymal interactions during hair follicle cycling. *J Investig Dermatol Symp Proc* 2003; **8**: 46–55.
20 Botchkarev VA, Botchkareva NV, Nakamura M *et al.* Noggin is required for induction of the hair follicle growth phase in postnatal skin. *FASEB J* 2001; **15**: 2205–14.
21 Hebert JM, Rosenquist T, Gotz J *et al.* FGF5 as a regulator of the hair growth cycle: evidence from targeted and spontaneous mutations. *Cell* 1994; **78**: 1017–25.
22 Fessing MY, Sharova TY, Sharov AA *et al.* Involvement of the Edar signaling in the control of hair follicle involution (catagen). *Am J Pathol* 2006; **169**: 2075–84.
23 Seiberg M, Marthinuss J, Stenn KS. Changes in expression of apoptosis-associated genes in skin mark early catagen. *J Invest Dermatol* 1995; **104**: 78–82.
24 Stenn KS, Lawrence L, Veis D *et al.* Expression of the bcl-2 protooncogene in the cycling adult mouse hair follicle. *J Invest Dermatol* 1994; **103**: 107–11.
25 Panteleyev AA, Botchkareva NV, Sundberg JP *et al.* The role of the hairless (hr) gene in the regulation of hair follicle catagen transformation. *Am J Pathol* 1999; **155**: 159–71.
26 Ahmad W, Panteleyev AA, Christiano AM. The molecular basis of congenital atrichia in humans and mice: mutations in the hairless gene. *J Investig Dermatol Symp Proc* 1999; **4**: 240–3.
27 Potter GB, Beaudoin GM 3d, DeRenzo CL *et al.* The hairless gene mutated in congenital hair loss disorders encodes a novel nuclear receptor corepressor. *Genes Dev* 2001; **15**: 2687–701.
28 Miller J, Djabali K, Chen T *et al.* Atrichia caused by mutations in the vitamin D receptor gene is a phenocopy of generalized atrichia caused by mutations in the hairless gene. *J Invest Dermatol* 2001; **117**: 612–7.
29 Li M, Chiba H, Warot X *et al.* RXR-alpha ablation in skin keratinocytes results in alopecia and epidermal alterations. *Development* 2001; **128**: 675–88.
30 Stenn KS, Paus R. Controls of hair follicle cycling. *Physiol Rev* 2001; **81**: 449–94.
31 Koch PJ, Mahoney MG, Cotsarelis G *et al.* Desmoglein 3 anchors telogen hair in the follicle. *J Cell Sci* 1998; **111**: 2529–37.
32 Danilenko DM, Ring BD, Yanagihara D *et al.* Keratinocyte growth factor is an important endogenous mediator of hair follicle growth, development, and differentiation. Normalization of the nu/nu follicular differentiation defect and amelioration of chemotherapy-induced alopecia. *Am J Pathol* 1995; **147**: 145–54.
33 Guo L, Degenstein L, Fuchs E. Keratinocyte growth factor is required for hair development but not for wound healing. *Genes Dev* 1996; **10**: 165–75.
34 Moore GP, Panaretto BA, Robertson D. Epidermal growth factor delays the development of the epidermis and hair follicles of mice during growth of the first coat. *Anat Rec* 1983; **205**: 47–55.
35 Hollis DE, Chapman RE, Panaretto BA *et al.* Morphological changes in the skin and wool fibres of Merino sheep infused with mouse epidermal growth factor. *Aust J Biol Sci* 1983; **36**: 419–34.
36 Philpott MP, Kealey T. Effects of EGF on the morphology and patterns of DNA synthesis in isolated human hair follicles. *J Invest Dermatol* 1994; **102**: 186–91.
37 Luetteke NC, Phillips HK, Qiu TH *et al.* The mouse waved-2 phenotype results from a point mutation in the EGF receptor tyrosine kinase. *Genes Dev* 1994; **8**: 399–413.
38 Luetteke NC, Qiu TH, Peiffer RL *et al.* TGF alpha deficiency results in hair follicle and eye abnormalities in targeted and waved-1 mice. *Cell* 1993; **73**: 263–78.
39 Philpott MP, Green MR, Kealey T. Human hair growth in vitro. *J Cell Sci* 1990; **97**: 463–71.
40 Paus R, Foitzik K, Welker P *et al.* Transforming growth factor-beta receptor type I and type II expression during murine hair follicle development and cycling. *J Invest Dermatol* 1997; **109**: 518–26.
41 Foitzik K, Lindner G, Mueller-Roever S *et al.* Control of murine hair follicle regression (catagen) by TGF-beta1 in vivo. *FASEB J* 2000; **14**: 752–60.
42 Philpott MP, Sanders DA, Kealey T. Effects of insulin and insulin-like growth factors on cultured human hair follicles: IGF-I at physiologic concentrations is an important regulator of hair follicle growth in vitro. *J Invest Dermatol* 1994; **102**: 857–61.
43 Little JC, Redwood KL, Granger SP *et al.* In vivo cytokine and receptor gene expression during the rat hair growth cycle. Analysis by semi-quantitative RT-PCR. *Exp Dermatol* 1996; **5**: 202–12.
44 Batch JA, Mercuri FA, Werther GA. Identification and localization of insulin-like growth factor-binding protein (IGFBP) messenger RNAs in human hair follicle dermal papilla. *J Invest Dermatol* 1996; **106**: 471–5.
45 Jindo T, Tsuboi R, Takamori K *et al.* Local injection of hepatocyte growth factor/scatter factor (HGF/SF) alters cyclic growth of murine hair follicles. *J Invest Dermatol* 1998; **110**: 338–42.
46 Yamazaki M, Tsuboi R, Lee YR *et al.* Hair cycle-dependent expression of hepatocyte growth factor (HGF) activator, other proteinases, and proteinase inhibitors correlates with the expression of HGF in rat hair follicles. *J Investig Dermatol Symp Proc* 1999; **4**: 312–5.
47 Yano K, Brown LF, Detmar M. Control of hair growth and follicle size by VEGF-mediated angiogenesis. *J Clin Invest* 2001; **107**: 409–17.
48 Philpott MP, Sanders DA, Bowen J *et al.* Effects of interleukins, colony-stimulating factor and tumour necrosis factor on human hair follicle growth in vitro: a possible role for interleukin-1 and tumour necrosis factor-alpha in alopecia areata. *Br J Dermatol* 1996; **135**: 942–8.
49 Sato N, Leopold PL, Crystal RG. Induction of the hair growth phase in postnatal mice by localized transient expression of Sonic hedgehog. *J Clin Invest* 1999; **104**: 855–64.
50 Wang LC, Liu ZY, Gambardella L *et al.* Conditional disruption of hedgehog signaling pathway defines its critical role in hair development and regeneration. *J Invest Dermatol* 2000; **114**: 901–8.
51 Schilli MB, Ray S, Paus R *et al.* Control of hair growth with parathyroid hormone (7–34). *J Invest Dermatol* 1997; **108**: 928–32.
52 Reichrath J, Schilli M, Kerber A *et al.* Hair follicle expression of 1,25-dihydroxyvitamin D3 receptors during the murine hair cycle. *Br J Dermatol* 1994; **131**: 477–82.
53 Li YC, Pirro AE, Amling M *et al.* Targeted ablation of the vitamin D receptor: an animal model of vitamin D-dependent rickets type II with alopecia. *Proc Natl Acad Sci U S A* 1997; **94**: 9831–5.
54 Thornton MJ, Taylor AH, Mulligan K *et al.* Oestrogen receptor beta is the predominant oestrogen receptor in human scalp skin. *Exp Dermatol* 2003; **12**: 181–90.
55 Botchkarev VA, Yaar M, Peters EM *et al.* Neurotrophins in skin biology and pathology. *J Invest Dermatol* 2006; **126**: 1719–27.

56 Maurer M, Fischer E, Handjiski B *et al.* Activated skin mast cells are involved in murine hair follicle regression (catagen). *Lab Invest* 1997; **77**: 319–32.
57 Harrist TJ, Ruiter DJ, Mihm MC *et al.* Distribution of major histocompatibility antigens in normal skin. *Br J Dermatol* 1983; **109**: 623–33.
58 Westgate GE, Craggs RI, Gibson WT. Immune privilege in hair growth. *J Invest Dermatol* 1991; **97**: 417–20.
59 Paus R, van der Veen C, Eichmuller S *et al.* Generation and cyclic remodeling of the hair follicle immune system in mice. *J Invest Dermatol* 1998; **111**: 7–18.
60 Barker CF, Billingham RE. Analysis of local anatomic factors that influence the survival times of pure epidermal and full-thickness skin homografts in guinea pigs. *Ann Surg* 1972; **176**: 597–604.
61 Reynolds AJ, Lawrence C, Cserhalmi-Friedman PB *et al.* Trans-gender induction of hair follicles. *Nature* 1999; **402**: 33–4.
62 Hale PA, Ebling FJ. The effects of epilation and hormones on the activity of rat hair follicles. *J Exp Zool* 1975; **191**: 49–62.
63 Trotter M. The life cycles of hair in selected regions of the body. *Am J Phys Anthropol* 1924; **7**: 427–37.
64 Ebling FJ, Thomas AK, Cooke ID *et al.* Effect of cyproterone acetate on hair growth, sebaceous secretion and endocrine parameters in a hirsute subject. *Br J Dermatol* 1977; **97**: 371–81.
65 Pelfini C, Cerimele D, Pisanu G. Aging of the skin and hair growth in man. In: Montagna W, Dobson RL, eds. *Advances in Biology of the Skin*. Oxford: Pergamon Press, 1969: 153–60.
66 Munro DD. Hair growth measurement using intradermal sulfur 35 cystine. *Arch Dermatol* 1966; **93**: 119–22.
67 Comaish S. Autoradiographic studies of hair growth in various dermatoses: investigation of a possible circadian rhythm in human hair growth. *Br J Dermatol* 1969; **81**: 283–8.
68 Blume U, Ferracin J, Verschoore M *et al.* Physiology of the vellus hair follicle: hair growth and sebum excretion. *Br J Dermatol* 1991; **124**: 21–8.
69 Saitoh M, Uzuka M, Sakamoto M *et al.* Rate of hair growth. In: Montagna W, Dobson RL, eds. *Advances in Biology of the Skin, Vol. 9 Hair Growth*. Oxford: Pergamon, 1969: 183–201.
70 Myers RJ, Hamilton JB. Regeneration and rate of growth of hairs in man. *Ann N Y Acad Sci* 1951; **53**: 562–8.
71 Pecoraro V, Astore I, Barman JM *et al.* The normal trichogram in the child before the age of puberty. *J Invest Dermatol* 1964; **42**: 427–30.
72 Lynfield YL, MacWilliam P. Shaving and hair growth. *J Invest Dermatol* 1970; **55**: 170–2.
73 Johnson E. Quantitative studies of hair growth in the albino rat. II. The effect of sex hormones. *J Endocrinol* 1958; **16**: 351–9.
74 Ebling FJ, Johnson E. The action of hormones on spontaneous hair growth cycles in the rat. *J Endocrinol* 1964; **29**: 193–201.

Androgens and hair growth

Androgens influence hair growth in several ways. Firstly, they participate in the endocrine control of moulting in animals that show seasonal hair growth [1]. Secondly, in some mammals, androgens stimulate the growth of hair follicles in certain regions of the skin following sexual maturity. Thirdly, in humans and some other primates, androgens are necessary for the development of balding on the scalp.

Androgen-stimulated hair growth

The growth of obvious facial, trunk and extremity hair in the male, and of pubic and axillary hair in both sexes, is dependent on androgens. The development of such hair at puberty is, in broad terms and at least initially, in parallel with the rise in levels of androgen from testicular, adrenocortical and ovarian sources, which occurs in both sexes and is somewhat steeper in males. That testosterone from the interstitial cells of the testis is responsible for growth of beard and body hair in male adolescence and that testicular activity is itself initiated by gonadotrophic hormones of the pituitary is unquestioned. However, the findings that growth-hormone-deficient boys and girls are less than normally responsive to androgens, and that growth hormone is necessary as a synergistic factor to allow testosterone to be fully effective with respect to hair growth [2], as well as protein anabolism and growth promotion, suggest that hypophysial hormones also have a more direct role. Direct evidence of the role of testicular androgen is that castration reduces growth of the human beard [3], whereas testosterone stimulates it in eunuchs and elderly men. The role of androgen is further demonstrated in the treatment of hirsute women with the antiandrogen cyproterone acetate [4], which reduces the definitive length, rate of growth, diameter and extent of medullation of the thigh hairs [5].

At puberty, terminal hair gradually replaces vellus, starting in the pubic regions. In both sexes the first pubic hair is sparse, long, downy, slightly pigmented and almost straight. It later becomes darker, coarser, more curled and extends in area to form an inverse triangle. A British study showed that boys had the first recognizable pubic hair at an average age of 13.4 years, and the full adult 'male' pattern at 15.2 years, approximately 3.5 years after the start of development of the genitalia [6]. The corresponding mean ages for girls were considerably earlier, namely 11.7 years and 13.5 years [7]. In approximately 80% of men and 10% of women the pubic hair continues spreading until the mid-twenties or later; there is no absolute distinction between male and female patterns, only one of degree.

Axillary hair first appears approximately 2 years after the start of pubic hair growth. The amount, as measured by the weight of the fully grown mass, continues to increase until the late twenties in males as well as in females, in whom, however, it is less at any age [3]. The mean amounts grown per day increase from late puberty until the mid-twenties and thereafter decrease steadily.

Facial hair in boys first appears at about the same time as the axillary hair, starting at the corners of the upper lip, and spreading medially to complete the moustache and then the cheeks and beard.

Terminal hair development is continued in regular sequence on the legs, thighs, forearms, abdomen, buttocks, back, arms and shoulders [8]. The extent of terminal hair tends to increase throughout the years of sexual maturity, but most patterns occur over a wide age range. The adult pattern is not achieved until the fourth decade, when the androgen levels are already somewhat lower than in early adult life. Moreover, aural hairs do not appear until late middle age, and a study of coarse sternal hair in men showed that the hairs continue to increase in length and number from puberty to the fifth or sixth decade.

There is considerable racial variability in androgen-dependent hair growth. The growth of facial and body hair is greater in European men than in Chinese men [3] and there is also variation within these broad racial categories—southern European men tend to be hairier than men from northern Europe [9].

Androgenetic alopecia

It has been known since ancient times that eunuchs do not go bald. Hippocrates noted that 'eunuchs are not subject to gout nor do they become bald' (Aphorisms VI, 28). The role of testosterone in male balding was first recognized by James Hamilton, an American anatomist [10]. He observed that men castrated before puberty

retain a prepubertal hairline and do not go bald. Of 12 such men who were treated with testosterone, four developed typical male hair loss. Castration later in life halted the progression of hair loss but did not result in regrowth of hair.

The prevalence and severity of male balding increase with age. All races are affected but the prevalence is higher in white males, reaching at least 80% in men aged over 70 years, than in African American [11] and in Japanese men [12]. Chinese and Korean men are also less likely to show frontal recession [13,14].

It has long been recognized that male balding runs in families. Twin studies confirm there is a strong genetic element to male balding with concordance rates of 80–90% in monozygotic twins and consistently lower rates in dizygotic twins [15–17]. There is an association between male balding and a variant region in the androgen receptor gene (AR) [18,19], but this does not explain the strong paternal influence on balding [20] as the AR gene is on the X chromosome and inherited from the mother.

The loss of hair in male balding is the result of a gradual reduction in the duration of anagen and a prolongation of the latent period of the hair cycle [21], and miniaturization of terminal hair follicles [22].

Androgen synthesis and metabolism

The initial stages in the synthesis of steroid hormones from cholesterol occur exclusively in the gonads and the adrenal glands. Circulating androgens are also derived from the peripheral conversion of weak precursor hormones into potent androgens, a process that takes place in many tissues including the skin and hair follicles. The majority of androgens in the circulation are bound to plasma proteins, principally sex hormone-binding globulin (SHBG), with approximately 20% bound to albumin. The remaining 1–2% circulates in a free unbound form and this comprises the biologically active pool. Androgen bound to albumin dissociates readily and can replenish the free pool. SHBG binds androgen with high affinity and its plasma concentration therefore has an important effect on the free and albumin-bound pools. High levels of SHBG reduce the biologically active androgen level and low levels of SHBG have the reverse effect. Free androgen is thought to enter cells by passive diffusion, where it binds to a specific intracellular androgen receptor.

Testosterone is the major circulating androgen, but in most body sites the effect of testosterone on hair growth is mediated by its more potent metabolite 5α-dihydrotestosterone (DHT). The conversion of testosterone to DHT is catalysed by the enzyme 5α-reductase. There are two isoforms of 5α-reductase, which are encoded by different genes [23]. Although both enzymes catalyse the conversion of testosterone to DHT they differ in their pH optima, substrate affinities and tissue distributions. Type 1 5α-reductase is widely distributed in the skin, but expression of the type 2 isoform is restricted to androgen target tissues such as the prostate and the epididymis. Much of our knowledge of the biological role of DHT in hair growth comes from studies of men with 5α-reductase deficiency (type II pseudohermaphroditism, pseudovaginal perineoscrotal hypospadias) [18,19], which is caused by mutations in the 5α-reductase 2 gene [24]. In this autosomal recessive disorder, genetic males (46XY) are born with normally differentiated but usually undescended testes. The external genitalia are ambiguous, with a small hypospadic phallus, a bifid scrotum and a blind vagina. Partial virilization of the genitalia occurs at puberty, the voice deepens and the musculature assumes a typical male distribution. Circulating testosterone levels are within or above the normal male range but DHT levels remain low, with testosterone : DHT ratios 3.5–5 times higher than normal. Subjects show a female pattern of androgen-dependent hair growth, with terminal hair largely restricted to the axillae and the lower pubic triangle, suggesting that hair growth in these sites responds to less potent androgens. In the large group of subjects studied in the Dominican Republic, beard growth was absent or sparse. More facial hair has been observed in affected men from other parts of the world, perhaps reflecting underlying racial differences in normal androgen-dependent hair growth, although this was reduced compared with normal males in the same communities. None of the cases studied has shown temporal recession of the hairline or balding. A role for DHT in balding is supported by studies in macaques in which treatment with 5α-reductase inhibitors prevented the development of balding [25] or increased scalp hair growth in balding animals [26], and a large clinical trial of the 5α-reductase type 2 inhibitor finasteride in balding men. This latter study showed that the progression of balding was prevented in almost all men taking finasteride orally, and about two-thirds showed an increase in hair growth [27].

Hair follicles possess 5α-reductase activity, suggesting that DHT acts as a paracrine or intracrine hormone (it is synthesized within or close to the target cell). It is possible that circulating DHT also contributes to androgen effects on hair growth. Other steroid-metabolizing enzymes, including 3β- and 17β-hydroxysteroid dehydrogenase which interconvert weak and potent androgens, and aromatase which converts androgens to oestrogens, are also expressed in the hair follicle [28,29], but their role in hair growth is not currently known.

The androgen receptor

The tissue effects of androgens are mediated through binding to the intracellular androgen receptor. The androgen receptor is a nuclear hormone receptor [30], and like other members of the nuclear hormone receptor superfamily it acts as a gene transcription factor following ligand binding. Mutations in the androgen receptor gene are responsible for the androgen insensitivity syndrome [31]. Individuals with the complete form of the syndrome, in which there is failure of functional androgen receptor expression, have intra-abdominal testes but female external genitalia, breast development and psychosocial development. After puberty, circulating testosterone is in the normal or elevated male range but pubic and axillary hair fail to develop, there is no beard growth and no balding.

Mechanism of androgen action on the hair follicle

Hamilton [10] reported that balding did not progress following castration in older men but neither did it promote regrowth of hair. Similarly, although beard growth was prevented by castration before puberty and stimulated by subsequent treatment with testosterone, there was only partial regression of the beard in postpubertal men castrated before the age of 20 years and no effect in older men [3]. Hamilton's observations were relatively crude

by modern standards and it is now clear from clinical trials of 5α-reductase inhibitors that some reversal of male balding is possible. However, the response is far from complete, indicating that androgens induce changes in gene expression in hair follicles that are only partially reversible in the absence of androgen and probably not at all once these changes are fully expressed.

The specificity of the response of hair follicles to androgens is determined within the skin. Hair follicles in occipital skin, a site that shows little or no response to androgens, retain their site-specific behaviour when transplanted into balding areas on the frontal scalp [32]. Conversely, hair follicles from balding scalp continue to regress when transplanted into skin of the forearm [33]. The success of micrografting techniques, in which individual follicles are transplanted, shows that androgen responsiveness is determined at the level of the follicle or its immediate tissue environment. Three lines of evidence suggest that the dermal papilla is the primary target of androgen action in the hair follicle.

1 Androgen receptor expression in the lower part of the follicle is restricted to dermal papilla cells [34,35].
2 The size of the hair follicle is probably determined by the volume of the dermal papilla [36,37].
3 Dermal papillae express 5α-reductase type 2 whereas hair follicle epithelium expresses only 5α-reductase type 1 [38].

Androgens may act on hair growth by altering the number of cells in the dermal papilla and its extracellular matrix [37]. Cells cultured from dermal papillae of human beard hair follicles also release growth factors in response to androgens that stimulate proliferation of keratinocytes [35,39], and the pattern of androgen metabolism by cultured and intact dermal papilla cells is consistent with that expected from their site of origin [40,41]. There is one report that dermal papilla cells grown from balding scalp follicles secrete TGF-β in the presence of testosterone [42]. TGF-β is a growth factor known to inhibit hair growth [43]. Hence the variable response of hair growth to androgens may reflect site-dependent differences in the types of growth factors produced by the dermal papilla.

References

1 Ebling FJ. The hormonal control of hair growth. In: Orfanos CE, Happle R, eds. *Hair and Hair Diseases*. Berlin: Springer Verlag, 1990: 267–99.
2 Blok GJ, de Boer H, Gooren LJ *et al.* Growth hormone substitution in adult growth hormone-deficient men augments androgen effects on the skin. *Clin Endocrinol (Oxf)* 1997; **47**: 29–36.
3 Hamilton JB. Age, sex and genetic factors in the regulation of hair growth in men: a comparison of Caucasian and Japanese populations. In: Montagna W, Ellis RA, eds. *The Biology of Hair Growth*. New York: Academic Press, 1958: 399.
4 Hammerstein J, Meckies J, Leo-Rossberg I *et al.* Use of cyproterone acetate (CPA) in the treatment of acne, hirsutism and virilism. *J Steroid Biochem* 1975; **6**: 827–36.
5 Ebling FJ, Thomas AK, Cooke ID *et al.* Effect of cyproterone acetate on hair growth, sebaceous secretion and endocrine parameters in a hirsute subject. *Br J Dermatol* 1977; **97**: 371–81.
6 Marshall WA, Tanner JM. Variations in pattern of pubertal changes in boys. *Arch Dis Child* 1970; **45**: 13–23.
7 Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. *Arch Dis Child* 1969; **44**: 291–303.
8 Reynolds EL. The appearance of adult patterns of body hair in man. *Ann N Y Acad Sci* 1951; **53**: 576–84.
9 Danforth CH, Trotter M. The distribution of body hair in white subjects. *Am J Phys Anthropol* 1922; **5**: 259–65.
10 Hamilton JB. Male hormone stimulation is prerequisite and an incitant in common baldness. *Am J Anat* 1942; **71**: 451–80.
11 Setty LR. Hair patterns of scalp of white and Negro males. *Am J Phys Anthropol* 1970; **33**: 49–55.
12 Takashima I, Iju M, Sudo M. Alopecia androgenetica—its incidence in Japanese and associated conditions. In: Orfanos CE, Montagna W, Stuttgen G, eds. *Hair Research Status and Future Aspects*. Berlin: Springer-Verlag, 1981: 287–302.
13 Hamilton JB. Patterned loss of hair in man: types and incidence. *Ann N Y Acad Sci* 1951; **53**: 708–28.
14 Paik JH, Yoon JB, Sim WY *et al.* The prevalence and types of androgenetic alopecia in Korean men and women. *Br J Dermatol* 2001; **145**: 95–9.
15 Hayakawa K, Shimizu T, Ohba Y *et al.* Intrapair differences of physical aging and longevity in identical twins. *Acta Genet Med Gemellol (Roma)* 1998; **41**: 177–85.
16 Nyholt DR, Gillespie NA, Heath AC *et al.* Genetic basis of male pattern balding. *J Invest Dermatol* 2003; **121**: 1561–64.
17 Rexbye H, Petersen I, Iachina M *et al.* Hair loss among elderly men: etiology and impact on perceived age. *J Gerontol A Biol Sci Med Sci* 2005; **60**: 1077–82.
18 Ellis JA, Stebbing M, Harrap SB. Polymorphism of the androgen receptor gene is associated with male pattern baldness. *J Invest Dermatol* 2001; **116**: 452–5.
19 Hillmer AM, Hanneken S, Ritzmann S *et al.* Genetic variation in the human androgen receptor gene is the major determinant of common early-onset androgenetic alopecia. *Am J Hum Genet* 2005; **77**: 140–8.
20 Ellis JA, Stebbing M, Harrap SB. Genetic analysis of male pattern baldness and the 5a-reductase genes. *J Invest Dermatol* 1998; **110**: 849–53.
21 Courtois M, Loussouarn G, Hourseau C. Aging and hair cycles. *Br J Dermatol* 1995; **132**: 86–93.
22 Whiting DA. Diagnostic and predictive value of horizontal sections of scalp biopsy specimens in male pattern androgenetic alopecia. *J Am Acad Dermatol* 1993; **28**: 755–63.
23 Jenkins EP, Andersson S, Imperato McGinley J *et al.* Genetic and pharmacological evidence for more than one human steroid 5-alpha-reductase. *J Clin Invest* 1992; **89**: 293–300.
24 Imperato-McGinley J. 5alpha-reductase-2 deficiency and complete androgen insensitivity: lessons from nature. *Adv Exp Med Biol* 2002; **511**: 121–31; discussion 31–4.
25 Rittmaster RS, Uno H, Povar ML *et al.* The effects of *N,N*-diethyl-4-methyl-3-oxo-4-aza-5a-androstane-17b-carboxamide, a 5a-reductase inhibitor and antiandrogen, on the development of baldness in the stumptail macaque. *J Clin Endocrinol Metab* 1987; **65**: 188–92.
26 Diani AR, Mulholland MJ, Shull KL *et al.* Hair growth effects of oral administration of finasteride, a steroid 5 alpha-reductase inhibitor, alone and in combination with topical minoxidil in the balding stumptail macaque. *J Clin Endocrinol Metab* 1992; **74**: 345–50.
27 Kaufman KD, Olsen EA, Whiting D *et al.* Finasteride in the treatment of men with androgenetic alopecia. *J Am Acad Dermatol* 1998; **39**: 578–89.
28 Schweikert HU, Wilson JD. Regulation of hair growth by steroid hormones. I Testosterone metabolism in isolated hairs. *J Clin Endocrinol Metab* 1974; **38**: 811–9.
29 Schweikert HU, Milewich L, Wilson JD. Aromatization of androstenedione by isolated human hairs. *J Clin Endocrinol Metab* 1975; **40**: 413–7.
30 Williams GR, Franklyn JA. Physiology of the steroid-thyroid hormone nuclear receptor superfamily. *Baillieres Clin Endocrinol Metab* 1994; **8**: 241–66.
31 Patterson MN, McPhaul MJ, Hughes IA. Androgen insensitivity syndrome. *Baillieres Clin Endocrinol Metab* 1994; **8**: 379–404.
32 Orentreich N. Autografts in alopecias and other selected dermatological conditions. *Ann N Y Acad Sci* 1959; **83**: 463–79.
33 Nordstrom REA. Synchronous balding of scalp and hair-bearing grafts of scalp transplanted to the skin of the arm in male pattern baldness. *Acta Derm Venereol (Stockh)* 1979; **59**: 266–8.
34 Choudhry R, Hodgins MB, Van der Kwast TH *et al.* Localization of androgen receptors in human skin by immunohistochemistry: implications for the hormonal regulation of hair growth, sebaceous glands and sweat glands. *J Endocrinol* 1992; **133**: 467–75.

35 Itami S, Kurata S, Sonoda T *et al.* Interaction between dermal papilla cells and follicular epithelial cells in vitro: effect of androgen. *Br J Dermatol* 1995; **132**: 527–32.
36 Van Scott EJ, Ekel TM. Geometric relationships between the matrix of the hair bulb and its dermal papilla in normal and alopecic scalp. *J Invest Dermatol* 1958; **31**: 281–7.
37 Elliott K, Stephenson TJ, Messenger AG. Differences in hair follicle dermal papilla volume are due to extracellular matrix volume and cell number: implications for the control of hair follicle size and androgen responses. *J Invest Dermatol* 1999; **113**: 873–7.
38 Asada Y, Sonoda T, Ojiro M *et al.* 5 alpha-reductase type 2 is constitutively expressed in the dermal papilla and connective tissue sheath of the hair follicle in vivo but not during culture in vitro. *J Clin Endocrinol Metab* 2001; **86**: 2875–80.
39 Itami S, Kurata S, Takayasu S. Androgen induction of follicular epithelial cell growth is mediated via insulin-like growth factor 1 from dermal papilla cells. *Biochem Biophys Res Commun* 1995; **212**: 988–94.
40 Itami S, Kurata S, Sonoda T *et al.* Characterization of 5 alpha-reductase in cultured human dermal papilla cells from beard and occipital scalp hair. *J Invest Dermatol* 1991; **96**: 57–60.
41 Thornton MJ, Laing I, Hamada K *et al.* Differences in testosterone metabolism by beard and scalp hair follicle dermal papilla cells. *Clin Endocrinol (Oxf)* 1993; **39**: 633–9.
42 Inui S, Fukuzato Y, Nakajima T *et al.* Androgen-inducible TGF-beta1 from balding dermal papilla cells inhibits epithelial cell growth: a clue to understand paradoxical effects of androgen on human hair growth. *FASEB J* 2002; **16**: 1967–9.
43 Foitzik K, Lindner G, Mueller-Roever S *et al.* Control of murine hair follicle regression (catagen) by TGF-beta1 in vivo. *FASEB J* 2000; **14**: 752–60.

Alopecia

Introduction

When assessing a patient for alopecia it is important to establish whether the hair loss is due to loss of hair follicles, alteration in hair cycling or fracture of the hair shaft.

Fractured hair shafts are usually visible as a short stubble of hair on the surface of the scalp. It may be patchy or generalized. Most hair shaft disorders are congenital, but may not be clinically apparent until the second or third post-natal moult wave when the child is around 12 months old. Tinea capitis is an acquired form of hair shaft fracture.

Alterations in the hair cycle with premature termination of anagen growth is a feature of alopecia areata, androgenetic alopecia, telogen effluvium and anagen effluvium. Follicular ostia remain visible on close inspection of the scalp and are best seen with a hand-held epiluminescent microscope. In alopecia areata there are patches of hair loss where the scalp is completely bald with the exception of the occasional exclamation mark hair. In androgenetic alopecia hairs shorten and ultimately disappear in a characteristic pattern across the scalp. Telogen effluvium leads to generalized hair shedding and a diffuse reduction in hair volume, but the shedding is never so severe as to render the scalp bald. In contrast, the shedding associated with anagen effluvium commonly leads to total alopecia.

Complete loss of hair follicles is a feature of scar tissue following wounding, primary cicatricial alopecias and congenital follicular agenesis. Follicullar ostia are lost and the scalp is smooth and shiny. Most acquired cicatricial alopecias produce patches of baldness.

Common baldness and androgenetic alopecia

R.D. Sinclair, pp. 66.16–66.31

Synonyms
- Male pattern hair loss
- Female pattern hair loss
- Patterned or premature baldness

Nomenclature. Common baldness is the result of a progressive, patterned hair loss that occurs when genetically predisposed individuals are exposed to androgens. The lack of balding in eunuchs, pseudohermaphrodites and individuals with androgen insensitivity syndrome confirms that androgens are a prerequisite for common baldness. As the pattern of hair loss differs between men and women, the terms male pattern hair loss and female pattern hair loss are also commonly used [1]. Whether someone is considered bald, and in particular prematurely bald, is in part a subjective assessment. The process by which common baldness occurs is androgen-mediated conversion of susceptible terminal hairs into vellus hairs, and has been termed androgenetic alopecia (AGA).

Aetiology. Four separate but interrelated factors determine whether an individual will become bald: susceptibility to AGA, age of onset, rate of progression and pattern of hair loss. Among men, susceptibility to AGA is near universal, and variations in baldness are largely explained by the other three factors.

Hamilton [2] defined the progressive pattern of male baldness and produced the first useful grading scale. This classification was modified by Norwood [3], who added grades IIIa, III vertex, IVa and Va (Fig. 66.14). Although the grades are imprecise measures of the continuum of hair patterns that are seen in adult males, they are useful as diagnostic aids and in the classification of extent of hair loss in clinical investigations.

Prepubertal boys universally have a straight frontal hairline. By the age of 20 over 90% of men demonstrate some degree of frontoparietal recession of the hairline [2]. As the histology of this hair loss shows increased vellus hairs, and as Hamilton observed that three males castrated at the age of 15 and 16 years failed to develop even minimal recession along the frontal hairline, it is likely that this hair loss occurs by androgen-mediated miniaturization of terminal follicles, and by definition is AGA [4]. However, 6% of 80-year-old men still have stage I hair density. Therefore, limited frontoparietal AGA does not always progress, and may be a benign manifestation of sexual maturity rather than a precursor of male pattern baldness (MPB).

The lifetime risk of MPB (as opposed to AGA) can be defined by studying hair patterns in men aged 80 years and above. In Norwood's cohort [3], 16% had a type I hair pattern, and by definition are not bald despite many demonstrating at least some degree of bitemporal AGA. Fourteen per cent had a type 2 hair pattern, with a moderate degree of bitemporal AGA, but would not be considered bald. The remaining 70% had a type III (16%), IV (12%), V (12%), VI (13%) or VII (17%) pattern of hair loss and would be considered to be balding.

The age of onset of MPB is highly variable. If early MPB is defined as stage II hair pattern, then 40% begin to develop MPB

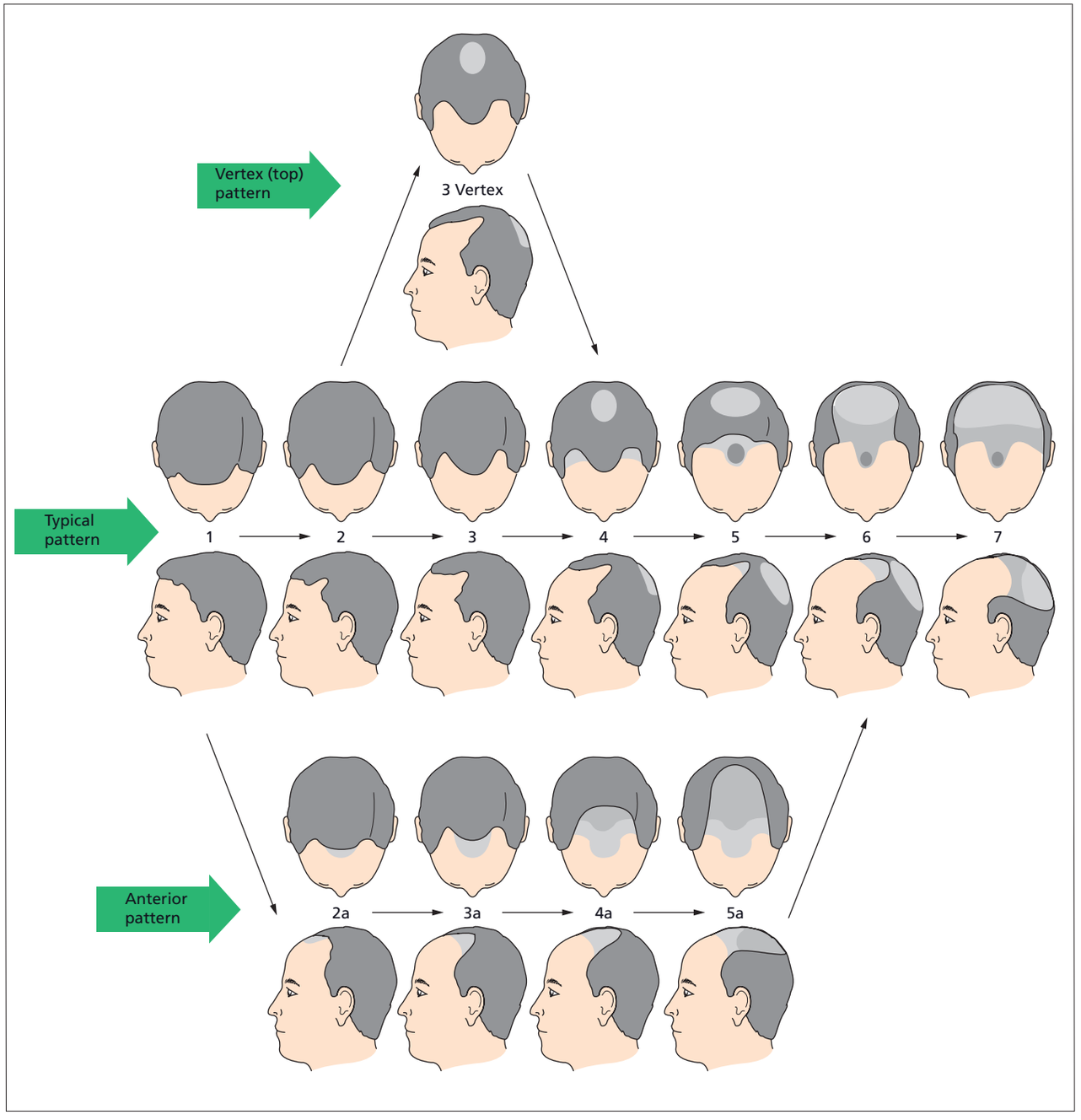


Fig. 66.14 Hamilton–Norwood scale for grading male pattern hair loss [3].

between the ages of 18 and 29, a further 24% first develop MPB in their thirties, 3% in their forties, 5% in their fifties, 9% in their sixties, 2% in their seventies and 1% at or beyond the age of 80 years [3].

There is wide individual variation in the rate of progression of hair loss in MPB. A small number of men achieve type V or VI hair loss in their twenties, indicating a very rapid rate of progression. In contrast, approximately 25% of men with MPB show no visible hair loss on standardized clinical photographs over a 5-year period [5]. Early-onset MPB progresses more rapidly. Men who develop MPB in their twenties tend to advance one to two stages per decade, whereas men with late-onset MPB may take two decades to progress a single stage [3]. Not every man with AGA goes bald. Although 40% of men start losing their hair in their twenties, only 30% ever reach stage VI or VII. Hence, even for those with early-onset AGA complete baldness is not inevitable.

Twin studies in males indicate that susceptibility, age of onset, pattern and rate of progression of MPB are all under genetic influence [6,7]. The lower age-related prevalence of MPB and higher proportion of men with a Ludwig pattern hair loss among Koreans also confirms the profound influence of genes on susceptibility, age of onset and pattern of hair loss [8].

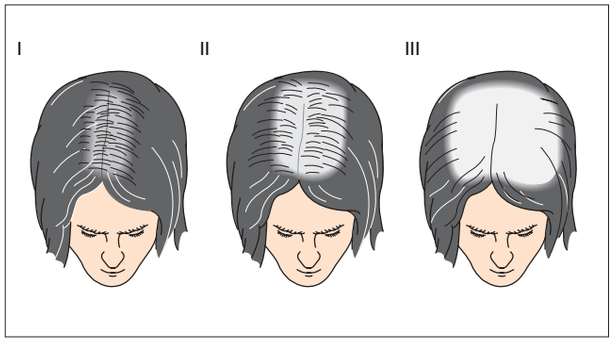


Fig. 66.15 Ludwig scale for grading female pattern hair loss [11].

Patterned balding occurs in women, but the susceptibility, age of onset, rate of progression and pattern are different from men. Thirty-two per cent of women aged 80 years and above show no visible evidence of female pattern hair loss (FPHL). The age of onset of FPHL is later than that seen in men. Only 3% first develop clinically detectable FPHL by age 29 years, a further 13% first develop it by age 49 years, a further 8% by age 69 years and a further 6% after the age of 70 years [9,10].

As many women wear their hair long, they are more aware of fluctuations in daily hair shedding. Women with AGA-related hair shedding often present prior to the development of reduction in hair volume over the crown (FPHL), making early diagnosis problematic.

Fewer than 1% of women progress to Hamilton–Norwood stage IV or above (equivalent to Ludwig stage III). Severe bitemporal recession (Hamilton–Norwood III) is uncommon and, as Ludwig pointed out, the most common pattern of hair loss seen in women is diffuse reduction of hair density over the crown, with complete or near complete preservation of the frontal hairline [11]. Olsen observed the so-called Christmas-tree pattern, with widening of the central parting line most noticeably in the mid-frontal scalp. She also pointed out that the hair loss in women is often not confined to the crown but may extend ear to ear (Figs 66.15 & 66.16) [12].

The histology of FPHL is indistinguishable from MPB. The process of FPHL involves androgen-mediated miniaturization of terminal hair follicles and therefore is AGA. Miniaturization of terminal hair follicles is also seen in alopecia areata, traction alopecia and secondary syphilis. In contrast with the uniform miniaturization of alopecia areata, miniaturization in FPHL spares one or two hairs within each follicular unit. The net result is that follicular units that normally have three to five terminal hairs only have one to two terminal hairs. Hair follicle miniaturization together with diffuse hair loss over the frontal scalp has also been observed in a female without androgens, indicating that other non-androgen-dependent mechanisms can miniaturize terminal hairs in a pattern that mimics AGA [13].

Minor bitemporal recession also occurs in more than 25% of women in their twenties and, as in men, is not necessarily a precursor of frontal baldness, even though biopsy from these areas reveals AGA [14].

Inheritance. Twin studies confirm the long-held belief that there is a genetic predisposition to MPB [7]. Of the 54 father–son relationships in the Victorian Family Heart Study, 81.5% of balding sons had fathers who had cosmetically significant balding. The

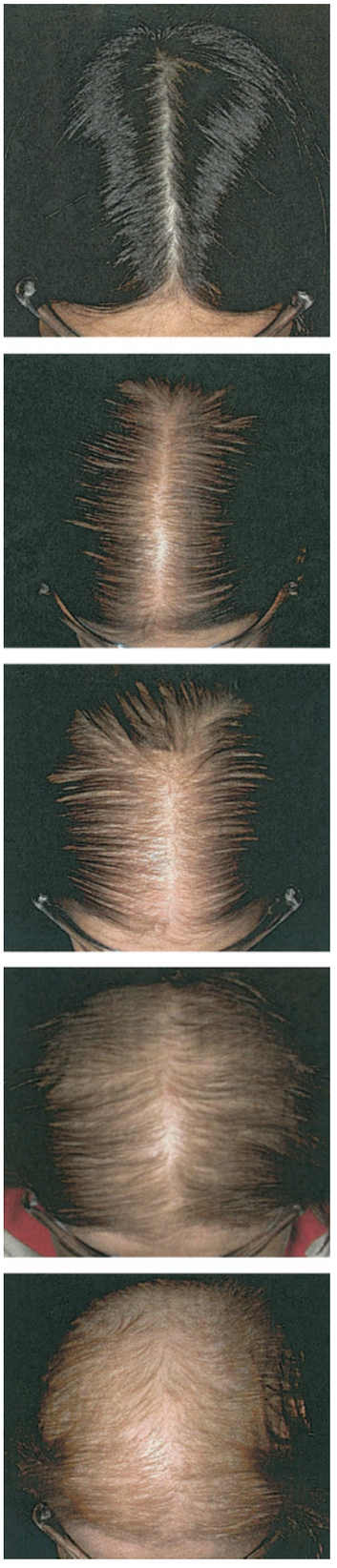


Fig. 66.16 Pattern of frontal hair loss in women with androgenetic alopecia. Stage 1 is normal.

high prevalence of MPB in the population, racial variation in the age-related prevalence of balding, the finding that baldness risk increases with the number of affected family members and the high frequency of baldness in the fathers of balding men can all be explained by polygenic inheritance [15].

Gene association studies comparing DNA from young bald men with that of old non-bald men have identified an association of MPB with a polymorphism of the androgen receptor gene on the X chromosome [16]. The androgen receptor gene *Stu1* restriction fragment length polymorphism (RFLP) was found in almost all (98.1%) young bald men, and most older bald men (92.3%), but only in 77% of non-bald men. This polymorphism appears to be necessary for the development of AGA, but its presence in non-bald men indicates that it is not sufficient for the development of AGA. This association has been confirmed by other groups in different patient cohorts [17,18]. However, other genes must be involved as the androgen receptor gene is located on the X chromosome and is inherited exclusively from the mother.

Current modelling suggests the involvement of at least four genes that combine to modify the age of onset, pattern of loss and rate of progression of MPB [19]. Other candidate gene and chromosomal regions have been examined. They include *SRDA1* and *SRDA5*, coding for the two variants of the 5α-reductase enzymes [20], the insulin gene [21], the aromatase gene, the gene for the ER-α oestrogen receptor, the non-recombinant area of the Y chromosome and the type II IGF genes [19]. Thus far, no association has been found between any of the above-mentioned genetic areas and MPB. Recently, Hillmer and colleagues, in a genome-wide linkage study of 95 families, have identified an additional gene locus for androgenetic alopecia on chromosome 3q26. The putative gene has not yet been disclosed [22].

Although a positive association between vertex balding and prostate cancer [23] has been identified, there is no clear association between MPB and dense hair patterns on the trunk [24] or number of children [25]. Several studies have reported an association between male balding and coronary artery disease [26–28]. In the largest of these, a retrospective study conducted amongst 22 071 US male physicians, there was a weak association between coronary heart disease and vertex balding [27].

To date there are no comparable genetic studies in female pattern hair loss.

References

1 Sinclair R. Male pattern androgenetic alopecia. *BMJ* 1998; **317**: 865–9.
2 Hamilton JB. Patterned loss of hair in man: types and incidence. *Ann N Y Acad Sci* 1951; **53**: 708–28.
3 Norwood OT. Male pattern baldness: classification and incidence. *South Med J* 1975; **68**: 1359–65.
4 Hamilton JB. Effect of castration in adolescent and young adult males upon further changes in the proportions of bare and hairy scalp. *J Clin Endocrinol Metab* 1960; **20**: 1309–18.
5 Kaufman K. Long-term (5-year) multinational experience with finasteride 1 mg in the treatment of men with androgenetic alopecia. *Eur J Dermatol* 2002; **12**: 38–49.
6 Stough DB, Rao NA, Kaufman KD *et al.* Finasteride improves male pattern hair loss in a randomized study in identical twins. *Eur J Dermatol* 2002; **12**: 32–7.
7 Nyholt DR, Gillespie NA, Heath AC *et al.* Genetic basis of male pattern balding. *J Invest Dermatol* 2003; **121**: 1561–4.
8 Paik JH, Yoon JB, Sim WY *et al.* The prevalence and types of androgenetic alopecia in Korean men and women. *Br J Dermatol* 2001; **145**: 95–9.
9 Birch MP, Messenger JF, Messenger AG. Hair density, hair diameter and the prevalence of female pattern hair loss. *Br J Dermatol* 2001; **144**: 297–304.
10 Norwood OT. Incidence of female androgenetic alopecia (female pattern alopecia). *Dermatol Surg* 2001; **27**: 53–4.
11 Ludwig E. Classification of the types of androgenetic alopecia (common baldness) occurring in the female sex. *Br J Dermatol* 1977; **97**: 247–54.
12 Olsen E. Androgenetic alopecia. In: Olsen E, ed. *Disorders of Hair Growth*. New York: McGraw-Hill, 1994: 257–84.
13 Orme S, Cullen DR, Messenger AG. Diffuse female hair loss: are androgens necessary? *Br J Dermatol* 1999; **141**: 521–3.
14 Venning VA, Dawber RP. Patterned androgenic alopecia in women. *J Am Acad Dermatol* 1988; **18**: 1073–7.
15 Kuster W, Happle R. The inheritance of common baldness: Two B or not two B? *J Am Acad Dermatol* 1984; **11**: 921–6.
16 Ellis JA, Stebbing M, Harrap SB. Polymorphism of the androgen receptor gene is associated with male pattern baldness. *J Invest Dermatol* 2001; **116**: 452–5.
17 Hillmer AM, Hanneken S, Ritzmann S *et al.* Genetic variation in the human androgen receptor gene is the major determinant of common early-onset androgenetic alopecia. *Am J Hum Genet* 2005; **77**: 140–8.
18 Hayes VM, Severi G, Eggleton SA *et al.* The E211 G > A androgen receptor polymorphism is associated with a decreased risk of metastatic prostate cancer and androgenetic alopecia. *Cancer Epidem Biomar* 2005; **14**: 993–6.
19 Ellis JA, Sinclair R, Harrap SB. Androgenetic alopecia: pathogenesis and potential for therapy. *Expert Rev Mol Med* 2002; **4**: 1–11.
20 Ellis JA, Stebbing M, Harrap SB. Genetic analysis of male pattern baldness and the 5α-reductase genes. *J Invest Dermatol* 1998; **110**: 849–53.
21 Ellis JA, Stebbing M, Harrap SB. Insulin gene polymorphism and premature male pattern baldness in the general population. *Clin Sci* 1999; **96**: 659–62.
22 Hillmer AM, Flaquer A, Hanneken S *et al.* Genome-wide scan and fine-mapping linkage study of androgenetic alopecia reveals a locus on chromosome 3q26. *Am J Hum Genet* 2008; **82**: 737–43.
23 Giles GG, Severi G, Sinclair R *et al.* Androgenetic alopecia and prostate cancer: findings from an Australian case-control study. *Cancer Epidem Biomar* 2002; **11**: 549–53.
24 Ellis JA, Stebbing M, Harrap SB. Male pattern baldness is not associated with established cardiovascular risk factors in the general population. *Clin Sci* 2001; **100**: 401–4.
25 Burton JL, Halim MM, Meyrick G *et al.* Male-pattern alopecia and masculinity. *Br J Dermatol* 1979; **100**: 567–71.
26 Herrera CR, D'Agostino RB, Gerstman BB *et al.* Baldness and coronary heart disease rates in men from the Framingham Study. *Am J Epidemiol* 1995; **142**: 828–33.
27 Lotufo PA, Chae CU, Ajani UA *et al.* Male pattern baldness and coronary heart disease: the Physicians' Health Study. *Arch Intern Med* 2000; **160**: 165–71.
28 Matilainen VA, Makinen PK, Keinanen-Kiukaanniemi SM. Early onset of androgenetic alopecia associated with early severe coronary heart disease: a population-based, case-control study. *J Cardiovasc Risk* 2001; **8**: 147–51.

Pathogenesis. Any unifying hypothesis for AGA has to explain the following: the occurrence in humans and simian species; strong familial tendency; the involvement of both sexes; geographical patterning of hair loss on the scalp; the diffuse nature of initial hair loss; the paradoxical effect of circulating and local androgens on scalp and body hairs; the phenomenon of donor dominance in hair transplantation; the alteration of hair cycle dynamics; follicular miniaturization; perifollicular inflammation; and the coexistence of greasy skin, acne and hirsutism in some women.

Hormonal influences

Systemic hormonal effects (see p. 66.13)

The key role of androgens in the pathogenesis of male AGA was revealed by the observations of the American anatomist James Hamilton. He noted that men castrated before puberty did not develop balding unless treated with testosterone [1]. A number of studies have tried to determine whether balding males have

increased circulating androgens, but no differences between patients and controls have been consistently found. Absolute levels of serum dihydroepiandrosterone sulphate (DHEA) and testosterone [2], free testosterone [3,4], the ratio of DHT : testosterone [5], and IGF-1 [6] have all been measured in bald men. All these studies suffer from a lack of reproducibility, and although differences in mean levels have been variously detected, the substantial overlap in the absolute levels of all androgens between cases and controls demonstrates that normal male levels of androgen are sufficient to make manifest the degree of baldness determined genetically for the individual.

While the role of androgens is well established in the pathogenesis of male pattern hair loss, their role in female pattern hair loss has been recently questioned. On the one hand, scalp hair loss and hirsutism are undoubtedly features of hyperandrogenism in women; indeed, loss of hair was reported in women with androgen-secreting tumours prior to Hamilton's observations in men [7,8]. Several investigators have noted that women with hair loss are more likely to have elevated androgen levels, although usually of minor degree, or show an increased frequency of other features of androgen excess than women without hair loss [9–11]. However, on the other hand, several investigators have failed to find evidence of raised androgen levels in women with FPHL [12], and in all studies there is a variable proportion of women with hair loss who do not show clinical or biochemical signs of androgen excess. It is not yet known whether hair loss in this latter group relates to a high level of sensitivity of scalp hair follicles to normal female levels of androgens or is due to another, non-androgenic mechanism.

It would seem that for women, androgens in the normal female range are sufficient to induce early baldness in women with a strong genetic predisposition. In women without a strong predisposition, balding will not occur until later in life unless endogenous androgen production is increased or drugs with androgen-like activity are taken. Some women with even grossly abnormal levels of androgen do not develop clinically significant baldness, although such patients are generally hirsute.

Local hormonal effects

Androgens do not affect all hairs equally. Body hair grows, scalp hair is lost whereas the eyebrows remain essentially unchanged at puberty. On the scalp there is a hierarchy of sensitivity, with the most anterior of the hairs at the temples being lost first, and subsequent hairs miniaturizing in a highly ordered fashion to produce patterned baldness. Similarly on the male beard, hairs first appear on the upper lip at the lateral corners and then over the rest of the face in a highly ordered fashion. On the chest, hairs first appear centrally and then around the areolae before migrating across the rest of the torso.

In men, where circulating androgens are surplus to the requirements of the hair follicles for maximal stimulation, local factors determine individual susceptibility and severity of baldness. This intrinsic regulation is best demonstrated in hair transplantation experiments; occipital hairs maintain their resistance to AGA when transplanted to the vertex [13], and scalp hairs from the vertex transplanted to the forearm miniaturize at the same pace as hairs neighbouring the donor site [14]. In females, where circulating androgens are not sufficient to maximally stimulate hair follicles, local factors still determine susceptibility, but severity is influenced by both local factors and levels of systemic hormone.

Beard dermal papilla cells are known to secrete growth-inducing autocrine growth factors including IGF-1 in response to testosterone, leading to an increase in dermal papilla size and enlargement of the hair follicle and hair cortex [15–17]. Similar investigations performed on dermal papilla cells from the balding scalp of the stump-tailed macaque showed that testosterone inhibited the growth and proliferation of keratinocytes [18]. TGF-β1 has been identified as a major component of the secreted cytokines in the vertex scalp and neutralizing anti-TGF-β1 antibody reversed the androgen-induced inhibition of keratinocyte proliferation. It has been postulated that the androgen-induced anti-TGF-β1 derived from the dermal papilla cells mediates hair growth suppression in androgenetic alopecia [19]. Studies examining distribution and expression of androgen receptors have shown varying results. Two studies showed that androgen receptors are only found in the nuclei of dermal papilla cells [15,20]. However, another study found more extensive follicular distribution of receptors, including the hair bulb [21]. Comparing different anatomical sites, there appear to be higher numbers of androgen receptors in the pubic hair follicles and beard dermal papilla cells, with occipital scalp follicles expressing lower levels [22].

Hair cycle dynamics

In AGA, the duration of anagen decreases with each successive cycle, whereas the length of telogen remains constant or is prolonged. Prolongation of telogen occurs particularly in the latent phase of telogen (also known as kenogen) that follows release of the club hair (exogen). This leads to a reduction of the anagen : telogen ratio and corresponds to periods of excessive hair shedding, most noticeable while combing or washing. Prolongation of the latent phase increases the proportion of empty hair follicles on the scalp, further contributing to the balding process [23].

As the hair growth rate remains relatively constant, the duration of anagen growth determines hair length. Thus, with each successively foreshortened hair cycle, the length of each hair shaft is reduced. Ultimately, anagen duration becomes so short that the growing hair fails to achieve sufficient length to reach the surface of the skin, leaving an empty follicular pore.

Hair follicle miniaturization

The population density of hair follicles per unit area of the scalp does not change with balding. Rather there is a gradual diminution in the size of follicles that results from the transformation of terminal follicles into vellus-type follicles.

Hair follicle miniaturization leads to finer hair that is often lighter in colour. On the balding scalp, transitional indeterminate hairs represent the bridge between full-sized and miniaturized terminal hairs [24].

Although smaller follicles tend to cycle more quickly there is no absolute correlation between hair follicle size and anagen duration. Eyebrow, eyelash and nasal follicles are large but the hair is relatively short. It is likely that separate factors control the miniaturization and hair cycle changes. Consequently, baldness and increased hair shedding do not necessarily go hand in hand. Many balding men and women are never aware of increased hair shed-

ding, and increased hair shedding occurs without associated follicular miniaturization in chronic telogen effluvium.

The dermal papilla is central to the maintenance and control of hair growth and is likely to be the target of androgen-mediated events leading to follicle miniaturization and hair cycle changes [18,25,26]. The constant geometric relationship between the dermal papilla size and the size of the hair matrix [27] suggests that the size of the dermal papilla determines the size of the hair bulb and ultimately the hair shaft produced.

The cross-sectional area of individual hair shafts remains constant throughout fully developed anagen [28], indicating that the hair follicle, and its dermal papilla, remain the same size through each individual anagen stage of the cycle. Thus, miniaturization occurs between rather than within cycles. Follicular miniaturization has been traditionally thought to occur in a stepwise fashion although there have been suggestions that it occurs rapidly, possibly in the space of a single hair cycle [29].

Follicular miniaturization leaves behind stellae as dermal remnants of the full-sized follicle. These stellae, also known as fibrous tracts or streamers, extend from the subcutaneous tissue up the old follicular tract to the miniaturized hair and mark the formal position of the original terminal follicle. Arao–Perkins bodies may be seen with elastic stains within the follicular stellae. An Arao–Perkins body begins as a small cluster of elastic fibres in the neck of the dermal papilla. These clump in catagen and remain situated at the lowest point of origin of the follicular stellae. With the progressive shortening of anagen hair seen in AGA, multiple elastic clumps may be found in stellae, like the rungs of a ladder [30].

References

1 Hamilton JB. Male hormone stimulation is prerequisite and an incitant in common baldness. *Am J Anat* 1942; **71**: 451–80.

2 Pitts RL. Serum elevation of dehydroepiandrosterone sulfate associated with male pattern baldness in young men. *J Am Acad Dermatol* 1987; **16**: 571–3.

3 Demark-Wahnefried W, Lesko SM, Conaway MR *et al.* Serum androgens: associations with prostate cancer risk and hair patterning. *J Androl* 1997; **18**: 495–500.

4 Platz EA, Pollak MN, Willett WC *et al.* Vertex balding, plasma insulin-like growth factor 1, and insulin-like growth factor binding protein 3. *J Am Acad Dermatol* 2000; **42**: 1003–7.

5 Sreekumar GP, Pardinas J, Wong CQ *et al.* Serum androgens and genetic linkage analysis in early onset androgenetic alopecia. *J Invest Dermatol* 1999; **113**: 277–9.

6 Signorello LB, Wuu J, Hsieh C *et al.* Hormones and hair patterning in men: a role for insulin-like growth factor 1? *J Am Acad Dermatol* 1999; **40**: 200–3.

7 Baldwin LG, Gafford JA. Arrhenoblastoma case report. *Endocrinology* 1936; **20**: 373–82.

8 Kantner AE, Ragins AB. Arrhenoblastoma of the ovary. *Am J Obstet Gynecol* 1941; **42**: 1061–6.

9 Futterweit W, Dunaif A, Yeh HC *et al.* The prevalence of hyperandrogenism in 109 consecutive female patients with diffuse alopecia. *J Am Acad Dermatol* 1988; **19**: 831–6.

10 Vexiau P, Chaspoux C, Boudou P *et al.* Role of androgens in female-pattern androgenetic alopecia, either alone or associated with other symptoms of hyperandrogenism. *Arch Dermatol Res* 2000; **292**: 598–604.

11 Cela E, Robertson C, Rush K *et al.* Prevalence of polycystic ovaries in women with androgenic alopecia. *Eur J Endocrinol* 2003; **149**: 439–42.

12 Schmidt JB, Lindmaier A, Trenz A *et al.* Hormone studies in females with androgenic hair loss. *Gynecol Obstet Invest* 1991; **31**: 235–9.

13 Orentreich N. Autografts in alopecias and other selected dermatological conditions. *Ann N Y Acad Sci* 1959; **83**: 463–79.

14 Nordstrom REA. Synchronous balding of scalp and hair-bearing grafts of scalp transplanted to the skin of the arm in male pattern baldness. *Acta Derm Venereol (Stockh)* 1979; **59**: 266–8.

15 Itami S, Kurata S, Sonoda T *et al.* Interaction between dermal papilla cells and follicular epithelial cells in vitro: effect of androgen. *Br J Dermatol* 1995; **132**: 527–32.

16 Thornton MJ, Hamada K, Messenger AG *et al.* Androgen-dependent beard dermal papilla cells secrete autocrine growth factor(s) in response to testosterone unlike scalp cells. *J Invest Dermatol* 1998; **111**: 727–32.

17 Itami S, Kurata S, Takayasu S. Androgen induction of follicular epithelial cell growth is mediated via insulin-like growth factor-I from dermal papilla cells. *Biochem Biophys Res Commun* 1995; **212**: 988–94.

18 Obana N, Chang C, Uno H. Inhibition of hair growth by testosterone in the presence of dermal papilla cells from the frontal bald scalp of the postpubertal stumptailed macaque. *Endocrinology* 1997; **138**: 356–61.

19 Inui S, Fukuzato Y, Nakajima T *et al.* Androgen-inducible TGF-beta1 from balding dermal papilla cells inhibits epithelial cell growth: a clue to understand paradoxical effects of androgen on human hair growth. *FASEB J* 2002; **16**: 1967–9.

20 Choudhry R, Hodgins MB, Van der Kwast TH *et al.* Localization of androgen receptors in human skin by immunohistochemistry: implications for the hormonal regulation of hair growth, sebaceous glands and sweat glands. *J Endocrinol* 1992; **133**: 467–75.

21 Liang T, Hoyer S, Yu R *et al.* Immunocytochemical localization of androgen receptors in human skin using monoclonal antibodies against the androgen receptor. *J Invest Dermatol* 1993; **100**: 663–6.

22 Thornton MJ, Laing I, Hamada K *et al.* Differences in testosterone metabolism by beard and scalp hair follicle dermal papilla cells. *Clin Endocrinol (Oxf)* 1993; **39**: 633–9.

23 Courtois M, Loussouarn G, Hourseau C *et al.* Hair cycle and alopecia. *Skin Pharmacol* 1994; **7**: 84–9.

24 Sinclair R. Male pattern androgenetic alopecia. *BMJ* 1998; **317**: 865–9.

25 Oliver RF, Jahoda CAB. The dermal papilla and the maintenance of hair growth. In: Rogers GE, Reis PJ, Ward KA *et al.*, eds. *The Biology of Wool and Hair*. London: Chapman & Hall, 1989: 51–67.

26 Randall VA. The use of dermal papilla cells in studies of normal and abnormal hair follicle biology. *Dermatol Clin* 1996; **14**: 585–94.

27 Van Scott EJ, Ekel TM. Geometric relationships between the matrix of the hair bulb and its dermal papilla in normal and alopecic scalp. *J Invest Dermatol* 1958; **31**: 281–7.

28 Elliott K, Stephenson TJ, Messenger AG. Differences in hair follicle dermal papilla volume are due to extracellular matrix volume and cell number: implications for the control of hair follicle size and androgen responses. *J Invest Dermatol* 1999; **113**: 873–7.

29 Birch MP, Messenger JF, Messenger AG. Hair density, hair diameter and the prevalence of female pattern hair loss. *Br J Dermatol* 2001; **144**: 297–304.

30 Pinkus H. Differential patterns of elastic fibers in scarring and non-scarring alopecias. *J Cutan Pathol* 1978; **5**: 93–104.

Clinical features. The essential clinical feature of balding in both sexes is patterned hair loss over the crown. Pigmented terminal hairs are progressively replaced by finer hairs, which are short and virtually non-pigmented. This process may begin at any age after the onset of adrenarche and may precede pubarche.

Males. The clinical appearance of male androgenetic alopecia is instantly recognizable in most cases. The progression of the hair loss occurs in an orderly manner and has been well documented by Hamilton [1] and Norwood [2] (Fig. 66.14). The posterior and lateral scalp margins are relatively spared, and only affected in the most advanced cases and with old age. Twin concordance studies indicate that variations in the pattern are governed, at least in part, by genetic factors, as is the rate of progression [3].

The main significance of hair relates to socialization, and hair is an essential part of an individual's self-image. Thus, the consequences of AGA are predominantly psychological. Despite an identical libido, bald men are likely to have fewer lifetime sexual

partners than non-bald men, reflecting reduced physical attractiveness to potential partners [4]. In Germany, where it is customary to include a photograph in job applications, otherwise identical applications accompanied by a photograph that had been digitally altered to make the applicant bald were less likely to lead to interview. Several studies have shown that the negative self-perception of balding patients appears to be consistent between Western [5,6] and Asian cultures [7]. The negative impact of AGA is often trivialized or ignored by the non-bald [8]. However, there is evidence that perception by others may compound the psychological problems suffered by balding men. A Korean study of the perception of balding men by women and non-balding men found that their negative perception of men with AGA was similar to the psychosocial effects reported by the patients themselves [7]. Of note was that a perception of bald men looking less attractive was found in more than 90% of subjects surveyed. Importantly, this view was more common in women than non-balding men. Such negative perceptions may further impair the social functioning of balding men.

However, it is important to note that most affected men cope well with AGA, and it does not have significant impact on their psychosocial function. Thus, those who do seek help are likely to be in greater emotional distress and to have been dissatisfied with any treatment they have received. The most distressed balding men are those with more extensive hair loss, those who have very early onset, and those who regard their balding as progressive (often arising from observation of their father) and socially noticeable [5].

Females. The pattern of hair loss and the clinical presentation of AGA in women differ from men. Women may present with either an episodic or continuous increase in hair shedding without any noticeable reduction in hair volume, increased hair shedding with loss of hair volume over the crown, or diffuse thinning over the crown with no history of hair shedding [9]. The most informative question to ask balding women is about change in the thickness of their ponytail. This enables women to estimate their degree of hair loss. Loss of volume or thinning over the crown is best detected when the hair is parted centrally. Widening of the central parting may follow a 'Christmas tree' pattern and is used to score the hair loss [10].

Ludwig described the earliest change (Ludwig grade I) as rarefaction of the hair on the crown [11]. This produces an oval area of alopecia encircled by a band of variable breadth with normal hair density. Frontally the fringe is narrow (1–3 cm) and at the sides the margin is 4–5 cm wide. Progression to Ludwig grade II results in further rarefaction of the crown, with preservation of the fringe. Grade III is near-complete baldness of the crown. As Ludwig only produced three illustrations (Fig. 66.15), other validated scales with more images have proved to be more useful for patient grading (Fig. 66.16) [12].

Not all women who develop FPHL maintain their frontal hair line. Bitemporal recession occurs in 13% of premenopausal women and 37% of postmenopausal women [13].

In many women the hair loss is confined to the vertex scalp, but in a significant proportion hair loss also occurs diffusely over the parietal scalp. Generalized hair loss often precludes women from hair transplantation procedures because of a diminished donor population.

Most women who present with hair loss have no other evidence of virilization. However, if the hair loss is of sudden onset, rapidly progressive and advanced, a full medical history and examination, and endocrinological investigation are desirable to exclude virilization, which can rarely be caused by a virilizing tumour. Investigation is also indicated in women with AGA of gradual onset accompanied by menstrual disturbance, hirsutism or recrudescence of acne [14].

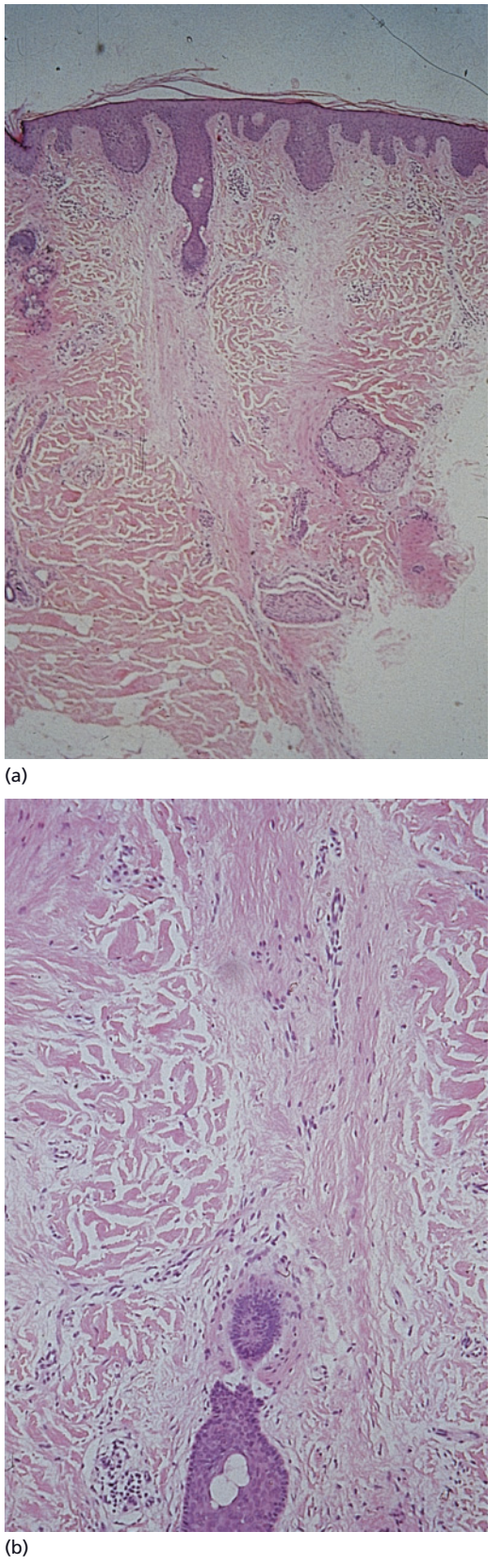
The principal differential diagnosis of early AGA is chronic telogen effluvium (CTE) [15]. Women with CTE present with chronic diffuse hair shedding without noticeable widening of the central parting. They may describe a loss in volume of the ponytail of up to one-third, and there is commonly mild bitemporal recession. Scalp biopsy of women who present in this fashion reveals AGA in approximately 60% of cases and CTE in 40% [12]. Scalp biopsy is not required in women who present with loss of hair volume either alone or associated with increased hair shedding.

References

1 Hamilton JB. Patterned loss of hair in man: types and incidence. *Ann N Y Acad Sci* 1951; **53**: 708–28.
2 Norwood OT. Male pattern baldness: classification and incidence. *South Med J* 1975; **68**: 1359–65.
3 Nyholt DR, Gillespie NA, Heath AC *et al.* Genetic basis of male pattern balding. *J Invest Dermatol* 2003; **121**: 1561–4.
4 Severi G, Sinclair R, Hopper JL *et al.* Androgenetic alopecia in men aged 40–69 years: prevalence and risk factors. *Br J Dermatol* 2003; **149**: 1207–13.
5 Cash TF. The psychology of hair loss and its implications for patient care. *Clin Dermatol* 2001; **19**: 161–6.
6 Budd D, Himmelberger D, Rhodes T *et al.* The effects of hair loss in European men: a survey in four countries. *Eur J Dermatol* 2000; **10**: 122–7.
7 Lee HJ, Ha SJ, Kim D *et al.* Perception of men with androgenetic alopecia by women and nonbalding men in Korea: how the nonbald regard the bald. *Int J Dermatol* 2002; **41**: 867–9.
8 Passchier J. Quality of life issues in male pattern hair loss. *Dermatology* 1998; **197**: 217–8.
9 Sinclair RD, Dawber RP. Androgenetic alopecia in men and women. *Clin Dermatol* 2001; **19**: 167–78.
10 Olsen EA. The midline part: an important physical clue to the clinical diagnosis of androgenetic alopecia in women. *J Am Acad Dermatol* 1999; **40**: 106–9.
11 Ludwig E. Classification of the types of androgenetic alopecia (common baldness) occurring in the female sex. *Br J Dermatol* 1977; **97**: 247–54.
12 Sinclair R, Jolley D, Mallari R *et al.* The reliability of horizontally sectioned scalp biopsies in the diagnosis of chronic diffuse telogen hair loss in women. *J Am Acad Dermatol* 2004; **51**: 189–99.
13 Venning VA, Dawber RP. Patterned androgenic alopecia in women. *J Am Acad Dermatol* 1988; **18**: 1073–7.
14 Futterweit W, Dunaif A, Yeh HC *et al.* The prevalence of hyperandrogenism in 109 consecutive female patients with diffuse alopecia. *J Am Acad Dermatol* 1988; **19**: 831–6.
15 Whiting DA. Chronic telogen effluvium. *Dermatol Clin* 1996; **14**: 723–31.

Pathology. The key elements of the histology of AGA are a reduction in terminal hairs, an increase in secondary vellus hair with associated angiofibrotic streamers, a variable increase in telogen and catagen hairs, and a mild or moderate perifollicular lymphohistiocytic infiltrate, with or without concentric layers of perifollicular collagen deposition (Fig. 66.17) [1].

A mild lymphohistiocytic inflammation is found in approximately one-third of cases of AGA and a similar number of controls, and is non-specific. In contrast, a moderate lymphohistiocytic inflammation is found in another one-third of cases of AGA, but



(a)

(b)

Fig. 66.17 Histology of androgenetic alopecia on a vertically sectioned scalp biopsy. (a) The low-power photomicrograph shows a reduction in follicle number and size. (b) The high-power photomicrograph shows the follicular streamer and a light perifollicular inflammatory infiltrate.

in only 10% of controls [2]. Occasional eosinophils and mast cells can be seen. The cellular inflammatory changes also occur around lower follicles in some cases and occasionally involve follicular stellae. The diagnostic and prognostic significance of the degree of the inflammation is not known.

Many of these changes are best seen on horizontally sectioned scalp biopsies. Horizontal sections reveal numerous pseudovellus hair follicles in the papillary dermis, reflecting a miniaturization process. In the vast majority of cases there is no genuine reduction in the number of follicles, and follicular fibrosis is seen in less than 10% of cases. The presence of arrector pili muscles and angiofibrotic streamers distinguishes them from true vellus hairs. There is a change in the ratio of terminal : vellus hairs from greater than 8 : 1 to less than 4 : 1. Also, the anagen : telogen hair ratio reduces from 12 : 1 to 5 : 1 [3]. The increased proportion of catagen and telogen hairs reflects the shortened duration of anagen and the relative increase in telogen hairs.

As the balding scalp loses its protective covering of hair, solar degenerative changes may be seen. A reduction of blood supply has been observed [4], but whether it follows or precedes the hair loss is unknown.

References

1 Kligman AM. The comparative histopathology of male-pattern baldness and senescent baldness. *Clin Dermatol* 1988; **6**: 108–18.

2 Whiting DA. Diagnostic and predictive value of horizontal sections of scalp biopsy specimens in male pattern androgenetic alopecia. *J Am Acad Dermatol* 1993; **28**: 755–63.

3 Whiting DA. Scalp biopsy as a diagnostic and prognostic tool in androgenetic alopecia. *Dermatologic Therapy* 1998; **8**: 24–33.

4 Klemp P, Peters K, Hansted B. Subcutaneous blood flow in early male pattern baldness. *J Invest Dermatol* 1989; **92**: 725–6.

Treatment. There are now a number of effective treatments to arrest the progression of the hair loss, that will also stimulate partial regrowth. Complete regrowth of a bald scalp is not yet feasible. Although epithelial stem cells in the bulge region contribute to wound healing they generally do not stimulate new hair follicle formation in adult mammals in any meaningful way. However, transgenic mice overexpressing certain WNT molecules do generate large numbers of new hair follicles following wounding [1].

As baldness is not life-threatening and the morbidity is variable, most people do not seek treatment. Some patients simply attend for a diagnosis, and when the currently available therapies are discussed, decline treatment. Without therapy baldness is progressive, although the rate of progression is extremely variable. Twenty-five per cent of men will have no visible progression after 5 years. Some will achieve Hamilton stage VII within 5 years, whereas others may take 50 years.

Before a patient embarks on therapy they should be counselled carefully and made aware of the requirement for maintenance therapy for sustained effect. It is preferable that advice is given by qualified medical practitioners who are fully aware of all the treatment options so that vulnerable individuals are protected from dubious Internet sites and profit-driven hair loss clinics.

Surgery. All surgical procedures involve the redistribution of terminal hair follicles from hairy into balding regions of the scalp.

Hair can be redistributed using autografts or flaps. Either procedure can be performed alone or in combination with reduction of the bald area by excision and closure. Grafts may be as large as 4 mm in diameter, but better results are achieved with much smaller 'mini' and 'micrografts', which can be manipulated to produce a natural-looking frontal hairline. Maintaining hair follicle unit groupings enhances graft survival and is the favoured approach. Reduction of the bald area by removal of an ellipse from the vault or repeated such operations may cover the top of the head by stretching the remaining parietal scalp. Expansion techniques have been used successfully to restore post-traumatic alopecia [2]. The implantation of artificial fibres may be complicated by foreign body reactions and infection [3,4] and its use has been banned in a number of countries.

Surgery is often performed long before the ultimate pattern of hair loss is clear. Without adjunctive medical therapy to prevent progression of the balding process, an unnatural appearance can evolve over time that may require further surgery to correct.

Hair transplantation techniques are constantly undergoing revision and improvement; they have been reviewed [5].

Camouflage and wigs. Camouflage is the simplest, easiest and cheapest way of dealing with mild AGA. Balding becomes most noticeable when the scalp can be seen through the hair. Camouflage treatments involve either adding small fibres held in place electrostatically or dyeing the scalp the same colour as the hair to create the illusion of thicker hair. Numerous brands are available, each in a range of colours. Although many of the newer agents are water-resistant, if the hair becomes wet in the rain the dye may still run.

Wigs are an alternative to scalp surgery. For many women, an alternative to a full wig is a smaller hair piece that can either be interwoven with existing hair or worn over the top of existing hair. Because interwoven wigs lift as the hair beneath grows, they require periodic adjustment.

Wig hair is composed of either a synthetic acrylic fibre that withstands wear and tear very well, or natural fibre (usually Asian or European human hair). Natural fibre wigs look better, are easier to style and last longer, but are considerably more expensive. Wigs can be styled and washed, and modern wigs provide excellent coverage that looks natural. A drawback of wigs is that the head may be hot in the summer, and some patients find them difficult to wear for this reason.

Advice on wigs is available from alopecia patient support groups in the UK, USA and Australia. In the UK, the National Health Service subsidizes wigs for 'medical hair loss'.

Medical management. Medical management for women consists of oral antiandrogens, topical minoxidil or a combination of both. Antiandrogens feminize males and are therefore not appropriate for men. They are also potential teratogens, and women should be advised to avoid pregnancy while taking these medications. Pharmacological therapy for men includes topical minoxidil and the 5α-reductase inhibitors finasteride and dutasteride. Finasteride and dutasteride are both teratogens with very long biological half-lives. Finasteride should be ceased at least 6 months prior to a woman contemplating pregnancy, and dutasteride should be avoided completely in women of childbearing age as its teratogenic potential might persist for years.

Although improvement may be seen after as soon as 4 months, 1 year of treatment may be required before a clinical response is observed. Maintenance therapy is required to sustain the effect. Monitoring of clinical response can be problematic. Patients are often anxious about their hair and inspect it frequently. Subtle fluctuations are often overinterpreted, and patients' subjective assessment of hair density is commonly unreliable. Serial photography at 6- to 12-monthly intervals helps to encourage patient adherence to treatment in the medium and long term [6].

Management of male pattern baldness

Minoxidil lotion. Minoxidil is a piperidinopyrimidine derivative and a potent vasodilator that is effective orally for severe hypertension. When applied topically in a lotion or foam vehicle, minoxidil increases terminal hair density in up to 30% of individuals [7,8]. Terminal hair appeared to regrow at the margins, but complete covering of the bald areas was seen in less than 10% of responders. De Villez [9] suggested that men who responded best to minoxidil were those in whom the balding process was at an early stage, with a maximum diameter of the bald area of less than 10 cm, and in whom the pre-treatment hair density was in excess of 20 hairs/cm^2. There is a slight increase in benefit if the concentration is increased to 5%. The benefit is most pronounced in the first 6 months of therapy and thereafter is marginal.

Topical minoxidil appears to be a safe therapy with side effects only of local irritation and hypertrichosis of the temples, and there is a low incidence of contact dermatitis [10]. If treatment is stopped, clinical regression occurs within 6 months, to the state of baldness that would have existed if treatment had not been applied [11]. Patients should be warned that in order to maintain any beneficial effect, applications must continue twice daily for the rest of their lives.

Finasteride. Finasteride is a synthetic aza-steroid that is a potent and highly selective antagonist of 5α-reductase type 2. It inhibits the conversion of testosterone to DHT. A scalp biopsy study of patients with AGA found that after 12 months of finasteride treatment, terminal hair counts increase and vellus hair counts decrease, demonstrating the ability of finasteride to reverse the miniaturization process and to encourage the growth of terminal hairs [12].

An oral dosage of 1 mg/day reduces scalp DHT by 64% and serum DHT by 68% [13]. Clinical trial data showed that, after 1 year, patients on finasteride have a 10% increase in the mean number of terminal hairs compared with baseline counts [14]. After 5 years of continuous therapy, hair counts remained close to the 1-year level, whereas the counts in the placebo patients had dropped by 30%. Using global photography to assess scalp coverage, 48% of patients taking finasteride had increased hair density, compared with 7% of the placebo group at the end of 1 year. At 2 years, coverage continued to improve in the finasteride group, with 66% having increased density, whereas only 7% of the placebo subjects had increased coverage. By 5 years [15], 10% of treated patients had a lowered hair density, 42% had no change, and 22%, 21% and 5% were assessed as moderately, markedly and greatly improved, respectively. In contrast, 19%, 31% and 25% of patients

in the placebo group were greatly, markedly or moderately worse. Nevertheless, 25% of the patients in the placebo group showed no deterioration over the 5-year period, reflecting the variable rate of progression of balding among males.

These data suggest that the maximal number of finasteride-responsive follicles are recruited by the end of 1 year, and further improvement in scalp coverage results from increase in hair length, diameter and pigmentation [15]. At the end of the first year, some finasteride patients were changed to placebo, resulting in a decrease in their hair counts after 12 months. Some in the placebo group were also crossed over, receiving finasteride for the second year; these subjects had an increase in their hair counts, although the average increase was less than that seen in the original group, indicating the potential for regrowth diminishes as the AGA progresses.

Studies using hair weight as the objective measure of outcome indicate that men on placebo had a reduction in hair weight of 9.2% at 48 weeks and 15.4% at 96 weeks, compared with the men on active treatment who had an increase of 25.6% at 48 weeks and 35.8% at 96 weeks. Factors that affect hair weight include the number of hairs, hair growth rate and hair thickness [16]. Work examining the effect of finasteride on frontal hair loss also confirmed efficacy here, although the magnitude of regrowth appears less [17].

Few adverse effects were reported in the phase III studies [14,15]. In the finasteride group, loss of libido was reported in 1.8% and erectile dysfunction in 1.3%. The placebo groups reported these same events, with frequencies of 1.3% and 0.7%, respectively. These events appeared to resolve on cessation of the drug and, in some cases, with continued treatment. It has been suggested that even these figures overstate the true incidence of sexual dysfunction [18].

Of note is that older men on finasteride experienced a 50% reduction in serum prostate-specific antigen (PSA) levels, which could result in an underestimation of prostatic cancer risk. It has been shown in the urology literature that PSA levels remain valid while patients are taking finasteride, but the value should be doubled to correct for the finasteride effect [19,20]. Men between 18 and 41 years of age have a negligible decrease in measured PSA [21].

Finasteride is a teratogen. Male rats exposed to finasteride *in utero* develop hypospadias with cleft prepuce, decreased anogenital distance, reduced prostate weight and altered nipple formation [22]. As the drug is secreted in the semen and can be absorbed through the vagina during intercourse, it was originally advocated that men taking finasteride should avoid unprotected intercourse with pregnant women. In practice, the concentration of finasteride in the semen is well below the minimum effect dosage, and no recommendations regarding the use of condoms are made in the product information leaflet. There are no reports of adverse pregnancy outcomes among women exposed to finasteride taken by their partners [23]. Finasteride has no effect on spermatogenesis or semen production [24].

Finasteride has now been in widespread use for over 10 years. Many recipients are elderly men taking 5 mg/day for prostate hyperplasia. Very few side effects have been observed [25]. There is no effect of long-term use on bone mineral density [15,26]. Reversible painful gynaecomastia has been reported [27] and the incidence is thought to be approximately 0.001% [28]. The prostate cancer prevention trial has demonstrated that 5 mg daily of finasteride will reduce the incidence of prostate cancer by 25% among men aged 55 and over. More of the reduction occurred in low-grade prostate cancers (Gleason stage 2–6), whereas the incidence of high-grade cancers (Gleason stage 7–10) was increased [29]. As this increase in Gleason score has not yet been shown to adversely affect patient survival it is not known whether it accurately reflects the biology of the tumour or is an artefact of the scoring system [30].

Dutasteride is a combined type 1 and 2 5α-reductase inhibitor. It produces a dose-dependent reduction in serum and scalp DHT levels to a greater degree than that seen with finasteride, and is more effective than finasteride in stimulating hair regrowth in MPB [31]. Dutasteride is currently marketed at a 0.5 mg dosage for benign prostatic hypertrophy and it is not licensed for treatment of MPB. Sexual side effects are more common with dutasteride than with finasteride, and are also dose related, but appear to be reversible on cessation.

Management of female pattern hair loss

Minoxidil. Topical minoxidil has been shown to arrest hair loss or to induce mild to moderate hair regrowth in approximately 60% of women with FPHL [32]. A clinical trial comparing 5% and 2% formulations of minoxidil found a mean increase in non-vellus hair counts after 48 weeks of 18% and 14%, respectively [33].

Antiandrogens. Oral antiandrogen therapy with cyproterone acetate, spironolactone or flutamide is widely used in the treatment of FPHL although there is a dearth of clinical trial data.

Spironolactone is a synthetic steroid, structurally related to aldosterone, which acts by competitively blocking androgen receptors. It also weakly inhibits androgen biosynthesis. Its primary use is as a diuretic and antihypertensive, and many of its side effects and numerous drug interactions relate to this. Several studies have demonstrated the efficacy of spironolactone in the treatment of hirsutism [34]. There are no controlled trials in FPHL. There is one report that women treated for 1 year with spironolactone showed less hair loss than in an untreated group [35]. Dosage ranges from 100 to 300 mg/day. Side effects are dose related and include menstrual irregularities, postmenopausal bleeding, breast tenderness or enlargement, and fatigue [36]. Spironolactone has the potential to feminize a male fetus and women should not become pregnant while taking spironolactone. Concomitant use of oral contraceptives will reduce the hormonal side effects. The antialdosterone effect can result in an elevation of serum potassium and a slight reduction in blood pressure, although this is rarely significant in the absence of renal impairment. Rare cases of hepatocellular carcinoma and hepatitis have been reported, but with substantially higher doses [37,38].

Cyproterone acetate is an androgen receptor blocker and potent progestin [39]. It also has an antigonadotrophic effect. It has been in common usage for over 40 years in the treatment of hirsutism but the limited controlled trial evidence has shown little evidence of efficacy in FPHL. In a study comparing cyproterone acetate with topical minoxidil lotion hair density had declined after 1 year

in the cyproterone acetate group but had improved in those using minoxidil [40]. However, subset analysis showed some increase in hair density in women with clinical evidence of androgen excess taking cyproterone acetate, suggesting that antiandrogens may be more effective in women with hyperandrogenism. There are no dose-ranging studies, but most practitioners use cyproterone acetate 50–100 mg/day for the first 10 days of each menstrual cycle. For postmenopausal women, cyproterone acetate may be used continuously, with or without oestrogens.

The side effects of cyproterone acetate are dose dependent and include lassitude, weight gain, breast tenderness, loss of libido, depression and nausea [41]. Shortness of breath is an uncommon side effect [42]. Feminization of a male fetus may occur and so patients should be advised to cease the medication before conception. The combination of cyproterone acetate and oral oestrogen therapy provides effective contraception and stabilizes menstrual irregularities.

Flutamide is a non-steroidal antiandrogen that acts by inhibiting androgen uptake and by inhibiting nuclear binding of androgen within the target tissue. One study suggested that flutamide is superior to cyproterone acetate and finasteride in the treatment of androgenetic alopecia [43]. However, rare but potentially fatal hepatotoxicity limits the use of flutamide for this condition [34].

In a double-blind, placebo-controlled study involving almost 100 postmenopausal women with FPHL, 1 mg finasteride was found to be no better than placebo [44]. Subsequent case reports and a case series have reported benefits in both pre- and postmenopausal women, but teratogenicity remains a relative contraindication to use in premenopausal women [45,46].

References

1 Ito M, Yang Z, Andl T *et al.* Wnt-dependent de novo hair follicle regeneration in adult mouse skin after wounding. *Nature* 2007; **447**: 316–20.

2 Masser MR. A twin tissue expander used in the elimination of alopecia. *Plast Reconstr Surg* 1988; **81**: 444–9.

3 Auerback R. Dangers of synthetic fiber implantation for male pattern baldness. *Cutis* 1980; **26**: 416.

4 Lepaw MI. Therapy and histopathology of complications from synthetic fiber implants for hair replacement. A presentation of one hundred cases. *J Am Acad Dermatol* 1980; **3**: 195–204.

5 Unger WP. Surgical approach to hair loss. In: Olsen EA, ed. *Disorders of Hair Growth: Diagnosis and Treatment*. New York: McGraw-Hill, 1994: 353–74.

6 Trueb RM, Itin P. [Photographic documentation of the effectiveness of 1 mg. oral finasteride in treatment of androgenic alopecia in the man in routine general practice in Switzerland]. *Schweiz Rundsch Med Prax* 2001; **90**: 2087–93.

7 Rietschel RL, Duncan SH. Safety and efficacy of topical minoxidil in the management of androgenetic alopecia. *J Am Acad Dermatol* 1987; **16**: 677–85.

8 Olsen EA, Weiner MS, Amara IA *et al.* Five-year follow-up of men with androgenetic alopecia treated with topical minoxidil. *J Am Acad Dermatol* 1990; **22**: 643–6.

9 De Villez RL. Topical minoxidil therapy in hereditary androgenetic alopecia. *Arch Dermatol* 1985; **121**: 197–202.

10 Tosti A, Bardazzi F, De Padova MP *et al.* Contact dermatitis to minoxidil. *Contact Dermatitis* 1985; **13**: 275–6.

11 Olsen EA, DeLong ER, Weiner MS. Long-term follow-up of men with male pattern baldness treated with topical minoxidil. *J Am Acad Dermatol* 1987; **16**: 688–95.

12 Whiting DA, Waldstreicher J, Sanchez M *et al.* Measuring reversal of hair miniaturization in androgenetic alopecia by follicular counts in horizontal sections of serial scalp biopsies: results of finasteride 1 mg treatment of men and postmenopausal women. *J Investig Dermatol Symp Proc* 1999; **4**: 282–4.

13 Drake L, Hordinsky M, Fiedler V *et al.* The effects of finasteride on scalp skin and serum androgen levels in men with androgenetic alopecia. *J Am Acad Dermatol* 1999; **41**: 550–4.

14 Kaufman KD, Olsen EA, Whiting D *et al.* Finasteride in the treatment of men with androgenetic alopecia. *J Am Acad Dermatol* 1998; **39**: 578–89.

15 Finasteride Male Pattern Hair Loss Group. Long-term (5-year) multinational experience with finasteride 1 mg in the treatment of men with androgenetic alopecia. *Eur J Dermatol* 2002; **12**: 38–49.

16 Price VH, Menefee E, Sanchez M *et al.* Changes in hair weight and hair count in men with androgenetic alopecia after treatment with finasteride, 1 mg, daily. *J Am Acad Dermatol* 2002; **46**: 517–23.

17 Leyden J, Dunlap F, Miller B *et al.* Finasteride in the treatment of men with frontal male pattern hair loss. *J Am Acad Dermatol* 1999; **40**: 930–7.

18 Tosti A, Pazzaglia M, Soli M *et al.* Evaluation of sexual function with an international index of erectile function in subjects taking finasteride for androgenetic alopecia. *Arch Dermatol* 2004; **140**: 857–8.

19 Matzkin H, Barak M, Braf Z. Effect of finasteride on free and total serum prostate-specific antigen in men with benign prostatic hyperplasia. *Br J Urol* 1996; **78**: 405–8.

20 Keetch DW, Andriole GL, Ratliff TL *et al.* Comparison of percent free prostate-specific antigen levels in men with benign prostatic hyperplasia treated with finasteride, terazosin, or watchful waiting. *Urology* 1997; **50**: 901–5.

21 Andriole GL, Guess HA, Epstein JI *et al.* Treatment with finasteride preserves usefulness of prostate-specific antigen in the detection of prostate cancer: results of a randomized, double-blind, placebo-controlled clinical trial. PLESS Study Group. Proscar Long-term Efficacy and Safety Study. *Urology* 1998; **52**: 195–201; discussion 1–2.

22 Clark RL, Anderson CA, Prahalada S *et al.* Critical developmental periods for effects on male rat genitalia induced by finasteride, a 5 alpha-reductase inhibitor. *Toxicol Appl Pharmacol* 1993; **119**: 34–40.

23 Pole M, Koren G. Finasteride. Does it affect spermatogenesis and pregnancy? *Can Fam Physician* 2001; **47**: 2469–70.

24 Overstreet JW, Fuh VL, Gould J *et al.* Chronic treatment with finasteride daily does not affect spermatogenesis or semen production in young men. *J Urol* 1999; **162**: 1295–300.

25 Marberger MJ. Long-term effects of finasteride in patients with benign prostatic hyperplasia: a double-blind, placebo-controlled, multicenter study. PROWESS Study Group. *Urology* 1998; **51**: 677–86.

26 Matsumoto AM, Tenover L, McClung M *et al.* The long-term effect of specific type II 5alpha-reductase inhibition with finasteride on bone mineral density in men: results of a 4-year placebo controlled trial. *J Urol* 2002; **167**: 2105–8.

27 Wade MS, Sinclair RD. Reversible painful gynaecomastia induced by low dose finasteride (1 mg/day). *Australas J Dermatol* 2000; **41**: 55.

28 Ferrando J, Grimalt R, Alsina M *et al.* Unilateral gynecomastia induced by treatment with 1 mg of oral finasteride. *Arch Dermatol* 2002; **138**: 543–4.

29 Thompson IM, Goodman PJ, Tangen CM *et al.* The influence of finasteride on the development of prostate cancer. *N Engl J Med* 2003; **349**: 215–24.

30 Lucia MS, Epstein JI, Goodman PJ *et al.* Finasteride and high-grade prostate cancer in the Prostate Cancer Prevention Trial. *J Natl Cancer Inst* 2007; **99**: 1375–83.

31 Olsen EA, Hordinsky M, Whiting D *et al.* The importance of dual 5alpha-reductase inhibition in the treatment of male pattern hair loss: results of a randomized placebo-controlled study of dutasteride versus finasteride. *J Am Acad Dermatol* 2006; **55**: 1014–23.

32 De Villez RL, Jacobs JP, Szpunar CA *et al.* Androgenetic alopecia in the female. Treatment with 2% topical minoxidil solution. *Arch Dermatol* 1994; **130**: 303–7.

33 Lucky AW, Piacquadio DJ, Ditre CM *et al.* A randomized, placebo-controlled trial of 5% and 2% topical minoxidil solutions in the treatment of female pattern hair loss. *J Am Acad Dermatol* 2004; **50**: 541–53.

34 Young R, Sinclair R. Hirsutes. II: Treatment. *Australas J Dermatol* 1998; **39**: 151–7.

35 Rushton DH, Futterweit W, Kingsley D *et al.* Quantitative assessment of spironolactone treatment in women with diffuse androgen-dependent alopecia. *J Soc Cosmet Chem* 1991; **42**: 317–25.

36 Shaw JC. Spironolactone in dermatologic therapy. *J Am Acad Dermatol* 1991; **24**: 236–43.

37 Barker DJP. The epidemiological evidence relating to spironolactone and malignant disease in man. *J Drug Develop* 1987; **1** (Suppl. 2): 22–5.

38 Thai KE, Sinclair RD. Spironolactone-induced hepatitis. *Australas J Dermatol* 2001; **42**: 180–2.
39 Neumann F. Pharmacological basis for clinical use of antiandrogens. *J Steroid Biochem* 1983; **19**: 391–402.
40 Vexiau P, Chaspoux C, Boudou P *et al.* Effects of minoxidil 2% vs. cyproterone acetate treatment on female androgenetic alopecia: a controlled, 12-month randomized trial. *Br J Dermatol* 2002; **146**: 992–9.
41 van Wayjen RG, van den Ende A. Experience in the long-term treatment of patients with hirsutism and/or acne with cyproterone acetate-containing preparations: efficacy, metabolic and endocrine effects. *Exp Clin Endocrinol Diabetes* 1995; **103**: 241–51.
42 Mallari R, Sinclair RD. Shortness of breath: an uncommon side-effect of cyproterone acetate in the treatment of androgenetic alopecia. *Int J Dermatol* 2002; **41**: 946–7.
43 Carmina E, Lobo RA. Treatment of hyperandrogenic alopecia in women. *Fertil Steril* 2003; **79**: 91–5.
44 Price VH, Roberts JL, Hordinsky M *et al.* Lack of efficacy of finasteride in postmenopausal women with androgenetic alopecia. *J Am Acad Dermatol* 2000; **43**: 768–76.
45 Thai KE, Sinclair RD. Finasteride for female androgenetic alopecia. *Br J Dermatol* 2002; **147**: 812–3.
46 Shum KW, Cullen DR, Messenger AG. Hair loss in women with hyperandrogenism: four cases responding to finasteride. *J Am Acad Dermatol* 2002; **47**: 733–9.

Disturbances of hair cycle

Telogen effluvium

Synonym
- Telogen defluvium

Definition. The term telogen effluvium, first coined by Kligman in 1961 [1], refers to the loss of club (telogen) hair in disease states of the follicle. Kligman's hypothesis was that whatever the cause of the hair loss, the follicle tends to behave in a similar way—the premature termination of anagen. 'The follicle is precipitated into catagen and transforms into a resting stage that mimics telogen.' The observation of increased telogen hair shedding does not infer a cause. To establish a cause, one requires a history to identify known triggers, biochemical investigation to exclude endocrine, nutritional or autoimmune aetiologies and, in persistent cases, histology to identify the earliest stages of AGA. The duration of the hair shedding at presentation helps predict those patients in whom further investigation will have the greatest yield.

Follicular cycling within anatomical regions is synchronous in infancy, in that all neighbouring hairs grow together, involute together and are shed together, producing a moult wave. Whereas the moult wave persists indefinitely in many animals, in humans synchronous hair growth disappears in childhood. Rather than periodically shedding all 100 000 scalp hairs over the course of a few months, adult humans tend to lose a few hairs each day [2].

Scalp trichography reveals that an average of 86% of plucked hairs are in anagen, 1% in catagen and 13% are in telogen, whereas data from analysis of horizontal scalp biopsies puts these figures at 93% of follicles in anagen and 7% in telogen [3]. Based on biopsy data, if the average number of scalp hairs is 100 000, then 7000 hairs should be in telogen at any one time. As the approximate duration of telogen is 100 days, 77 hairs should be shed each day, but most people are not aware of shedding anywhere near this amount. Although this number is likely to correspond to the absolute number of hairs that are shed each day, it still remains to be defined what amount is normally noticed and how introspection heightens one's powers of detection [4]. When people are concerned they are losing hair, they look harder and find more.

Pathogenesis. Headington [5] described five functional types of telogen effluvium, based on different phases of the follicular cycle: immediate anagen release, delayed anagen release, short anagen syndrome, immediate telogen release and delayed telogen release. Immediate anagen release is a short-onset effluvium where follicles are stimulated to leave anagen and enter telogen prematurely, resulting in increased hair shedding at the end of telogen, approximately 2–3 months later. It is common after a physiological stress such as severe illness, and with drug-induced hair loss. Reversal is associated with resumption of the normal cycle. Delayed anagen release is the cause of postpartum hair loss. During pregnancy, hairs remain in prolonged anagen rather than cycling into telogen. If a large number of follicles are involved, postpartum telogen conversion will be accompanied by increased shedding some months later. Short anagen syndrome is caused by an idiopathic shortening of the duration of anagen and can cause a persistent telogen hair shedding in some individuals [5].

It is not known precisely how long a telogen hair remains in the follicle, but it is believed that club hairs are released 4–6 weeks after the onset of anagen. This may explain the different anagen : telogen rates seen on trichogram versus biopsy. Immediate telogen release results from a shortening of normal telogen, with release of club hairs as the follicles are stimulated to re-enter anagen. Drugs such as minoxidil can precipitate immediate telogen release. Delayed telogen release occurs after a prolonged telogen followed by transition to anagen. It occurs in animals with synchronous hair cycles during shedding of their winter coats. It may occur seasonally in some humans.

Acute telogen effluvium. Acute telogen effluvium is an acute-onset scalp hair loss that occurs 2–3 months after a triggering event such as a high fever, surgical trauma, sudden starvation or haemorrhage [1,4–6]. In approximately a third of cases of acute telogen effluvium, no trigger can be identified. Acute telogen effluvium is commonly attributed to emotional stress, but the evidence for this is weak and there is no evidence that suggests the stresses of everyday life are sufficient to induce diffuse hair loss. The functional mechanism of shedding is immediate anagen release.

The patient may be particularly aware of increased loss on the brush or comb, or during shampooing. The daily loss ranges from under 100 to over 1000. If the lower rates of shedding are continued for only a short period there may be no obvious baldness, but if shedding occurs at higher rates, diffuse reduction in hair density is produced (Fig. 66.18). It may be severe but is never total. Unless the trigger is repeated, spontaneous complete regrowth occurs within 3–6 months. The proportion of follicles affected, and hence the severity of the subsequent alopecia, depends partly on the duration and severity of the precipitating cause and partly on unexplained individual variations in susceptibility.

Telogen gravidarum refers to the telogen hair loss seen 2–3 months after childbirth [7,8]. It is an example of delayed anagen



Fig. 66.18 Acute telogen effluvium.

release. It is universal to some degree, but is often subclinical. Most cases of telogen gravidarum resolve; however, a small proportion of women may experience persistent episodic shedding that may be diffuse or localized. It has been suggested that after pregnancy some hairs may not revert to an asynchronous growth pattern seen in normal adult hair follicles [5]. A similar state of affairs prevails when the contraceptive pill is discontinued after it has been taken continuously for some time [8,9].

Diagnosis. The diagnosis is usually simple. Abrupt-onset telogen effluvium is likely to be related to a specific event or trigger 6–16 weeks earlier. The hair pull test is positive, with normal club hairs. The hair loss is always diffuse and never total. Gradual onset or prolonged hair loss is more difficult to assess. Increased shedding of club hairs is a variable but often very obvious symptom of early AGA. Other differential diagnoses are discussed below under the heading of chronic diffuse telogen hair loss.

The hair pull test is notoriously difficult to interpret. In acute telogen effluvium, it is usually strongly positive for telogen hairs at the vertex and the scalp margins. However, a negative hair pull test does not exclude the diagnosis of telogen effluvium. The trichogram from a hair pluck sample usually shows more than 25% of telogen hairs in acute telogen effluvium [1]. When an obvious explanation exists for a recent-onset telogen effluvium, expectant management and observation is appropriate. Shedding can be expected to cease within 3–6 months and thereafter recovery should be complete. Histological examination shows no abnormality other than an increase in the proportion of follicles in telogen.

References

1 Kligman AM. Pathologic dynamics of human hair loss. I. Telogen effuvium. *Arch Dermatol* 1961; **83**: 175–98.
2 Kligman AM. The human hair cycle. *J Invest Dermatol* 1959; **33**: 307–16.
3 Whiting DA. Chronic telogen effluvium. *Dermatol Clin* 1996; **14**: 723–31.
4 Harrison S, Sinclair R. Telogen effluvium. *Clin Exp Dermatol* 2002; **27**: 389–5.
5 Headington JT. Telogen effluvium. New concepts and review. *Arch Dermatol* 1993; **129**: 356–63.
6 Dawber RPR, Simpson NB, Barth JH. Diffuse alopecia: endocrine, metabolic and chemical influences on the follicular cycle. In: Dawber RPR, ed. *Diseases of the Hair and Scalp*. Oxford: Blackwell Science, 1997: 123–50.
7 Schiff BL, Kern AB. Study of postpartum alopecia. *Arch Dermatol* 1963; **87**: 609–11.
8 Dawber RP, Connor BL. Pregnancy, hair loss, and the pill. *BMJ* 1971; **4**: 234.
9 Griffiths WA. Diffuse hair loss and oral contraceptives. *Br J Dermatol* 1973; **88**: 31–6.

Chronic diffuse telogen hair loss. A short-lived insult usually produces a sudden-onset diffuse shedding. If the insult is prolonged or repeated, shedding can develop insidiously. Chronic diffuse telogen hair loss refers to telogen hair shedding persisting for longer than 6 months. It can be a result of a primary chronic telogen effluvium or be secondary to a variety of causes including FPHL. To be a true cause of chronic diffuse telogen hair loss, the relationship between the trigger and the hair loss must be reversible and reproducible. The requirements of proof include exclusion of other known causes of shedding, in particular AGA, reversal of the hair loss following correction of the causative factor, and relapse on rechallenge.

Accepted causes of chronic diffuse telogen hair loss are thyroid disorders (Fig. 66.19), profound iron deficiency anaemia, acrodermatitis enteropathica and malnutrition [1]. Both hyperthyroidism and hypothyroidism (including drug-induced hypothyroidism) may cause a diffuse telogen hair loss [2,3]. The mechanism of telogen hair shedding in thyroid disorders is unclear [4]. Hair loss is reversible when the euthyroid state is restored, except in long-standing cases. If replacement therapy fails to correct the hair loss, alternate causes should be sought [5].

Profound iron-deficiency anaemia can cause a diffuse telogen hair loss that is corrected by iron replacement. The relationship between iron deficiency with no anaemia or only mild anaemia and chronic diffuse hair loss is, however, more complex and controversial [6–8]. Depending on how it is defined, low iron stores are a common finding in women of child-bearing age. AGA is also common in this age group and the shedding in the early stages of female AGA can be diffuse and episodic, and mimic a telogen effluvium. It is important not to focus on the treatment of a subclinical iron deficiency while neglecting the underlying AGA, especially when therapy for female AGA is more reliable in arresting hair loss than stimulating regrowth. It is not uncommon for women presenting with increased telogen hair shedding caused by AGA to coincidentally have low iron stores. As the telogen hair loss in AGA can be episodic, it may even appear to abate with iron replacement. However, in patients with AGA the shedding tends to be chronic and relapsing, and recovery is generally incomplete. A punch biopsy can usually clarify the diagnosis.

Acrodermatitis enteropathica and acquired zinc deficiency (Fig. 66.20) brought about by long-standing parenteral nutrition can lead to a severe telogen effluvium [1,9]. However, low zinc levels



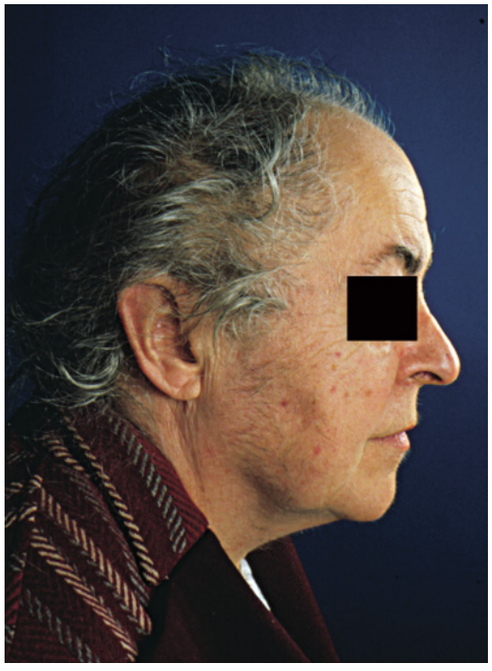


Fig. 66.19 Diffuse alopecia in association with hypothyroidism.



Fig. 66.20 Acquired zinc deficiency resulting from prolonged parenteral feeding and inadequate zinc supplementation.

found on routine blood biochemistry screening in patients being investigated for diffuse telogen hair loss are probably an incidental finding. Diffuse hair loss alone, with no other symptoms or signs, is never a result of dietary zinc deficiency [8].

Crash dieting with severe protein–calorie restriction can precipitate hair loss [10,11]. Chronic starvation, especially marasmus, causes a diffuse telogen hair loss often accompanied by hair shaft abnormalities [12]. Hypoproteinaemia of metabolic as well as dietary origin can cause hair loss [1]. Pancreatic disease and other forms of malabsorption also cause a diffuse telogen hair loss [13], as do the essential fatty acid deficiencies seen in prolonged parenteral nutrition and hypervitaminosis A [14,15]. Metabolic disturbances such as liver disorders [1,16] and chronic renal failure can produce sparse scalp hair [17]. Hair loss in advanced malignant disease may be a result of hypoproteinaemia rather than the malignancy itself, but alopecia has occurred as an early sign of Hodgkin's disease [18]. Systemic lupus erythematosus (Fig. 66.21) and dermatomyositis can also cause telogen hair loss [19]. Diffuse hair loss may occur in secondary syphilis, but the characteristic moth-eaten appearance is not always present [20].

Drug-induced diffuse telogen hair loss usually starts 6–12 weeks after instigation of treatment and is progressive while the drug is continued [21,22]. It is most commonly a result of immediate anagen release [23]. The diagnosis of drug-induced telogen hair loss is made by demonstrating compatible chronology of drug exposure and the onset of the hair loss, and exclusion of the other causes of alopecia. Shedding can recur with drugs that are chemically unrelated, suggesting that true cross-reactivity is rare, and individual susceptibility exists to drug-induced telogen effluvium. Chronic telogen effluvium and AGA are important differential diagnoses. If a particular drug is suspected, testing involves stopping it for at least 3 months. Regrowth following discontinuation and recurrence on re-exposure to the drug supports the conclusion that the drug caused the alopecia. Many drugs have been said to cause a diffuse telogen hair loss but few have fulfilled the above criteria. A dose-related diffuse telogen hair loss is common with etretinate [24] and acitretin, but less common with isotretinoin. The retinoids appear to cause a telogen anchorage defect and reduce the duration of anagen. Occasionally, continued shedding



Fig. 66.21 Hair loss and photosensitivity caused by systemic lupus erythematosus.

is noted after retinoid-induced telogen effluvium, but such cases may be caused by coincidental AGA. Minoxidil has been reported to cause a short-lived telogen shedding by immediate telogen release [23,25].

References

1 Dawber RPR, Simpson NB, Barth JH. Diffuse alopecia: endocrine, metabolic and chemical influences on the follicular cycle. In: Dawber RPR, ed. *Diseases of the Hair and Scalp*. Oxford: Blackwell Science, 1997: 123–50.

2 Rook A. Endocrine influences on hair growth. *BMJ* 1965; **1**: 609–14.

3 Freinkel RK, Freinkel N. Hair growth and alopecia in hypothyroidism. *Arch Dermatol* 1972; **106**: 349–52.

4 Messenger AG. Thyroid hormone and hair growth. *Br J Dermatol* 2000; **142**: 633–4.

5 Sinclair R. Diffuse hair loss. *Int J Dermatol* 1999; **38** (Suppl. 1): 8–18.

6 Rushton DH, Ramsay ID, James KC *et al*. Biochemical and trichological characterization of diffuse alopecia in women. *Br J Dermatol* 1990; **123**: 187–97.

7 Hard S. Non-anemic iron deficiency as an etiologic factor in diffuse loss of hair of the scalp in women. *Acta Derm Venereol (Stockh)* 1963; **43**: 562–9.

8 Sinclair R. There is no clear association between low serum ferritin and chronic diffuse telogen hair loss. *Br J Dermatol* 2002; **147**: 982–4.

9 Weismann K. Zinc metabolism and the skin. In: Rook A, Savin J, eds. *Recent Advances in Dermatology*. 5th edn. Edinburgh: Churchill Livingstone, 1980: 109–29.

10 Goette DK, Odom RB. Alopecia in crash dieters. *JAMA* 1976; **235**: 2622–3.

11 Kaufman JP. Letter: Telogen effluvium secondary to starvation diet. *Arch Dermatol* 1976; **112**: 731.

12 Bradfield RB, Bailley MA. Hair root response to protein undernutrition. In: Montagna W, Dobson RC, eds. *Advances in Biology of the Skin*, Vol. 9 Hair Growth. Oxford: Pergamon, 1968: 109–11.

13 Wells GC. Skin disorders in relation to malabsorption. *BMJ* 1962; **2**: 937–43.

14 Skolnik P, Eaglstein WH, Ziboh VA. Human essential fatty acid deficiency: treatment by topical application of linoleic acid. *Arch Dermatol* 1977; **113**: 939–41.

15 Stimson WH. Vitamin A intoxication in adults: report of a case with a summary of the literature. *N Engl J Med* 1961; **265**: 369–73.

16 Starzl TE, Putnam CW, Groth CG *et al*. Alopecia, ascites, and incomplete regeneration after 85 to 90 per cent liver resection. *Am J Surg* 1975; **129**: 587–90.

17 Scoggins RB, Harlan WR Jr. Cutaneous manifestations of hyperlipidemia and uremia. *Postgrad Med* 1967; **41**: 537–45.

18 Klein AW, Rudolph RI, Leyden JJ. Telogen effluvium as a sign of Hodgkin disease. *Arch Dermatol* 1973; **108**: 702–3.

19 Dawber RPR, Simpson NB. Hair and scalp in systemic disease. In: Dawber RPR, ed. *Diseases of the Hair and Scalp*. Oxford: Blackwell Science, 1997: 483–527.

20 Kennedy C. Syphilis presenting as hair loss. *BMJ* 1976; **2**: 854.

21 Brodin MB. Drug-related alopecia. *Dermatol Clin* 1987; **5**: 571–9.

22 Fiedler VC, Gray AC. Diffuse alopecia: telogen hair loss. In: Olsen EA, ed. *Disorders of Hair Growth: Diagnosis and Treatment*, 2nd edn. New York: McGraw-Hill, 2003: 303–20.

23 Headington JT. Telogen effluvium. New concepts and review. *Arch Dermatol* 1993; **129**: 356–63.

24 Gupta AK, Goldfarb MT, Ellis CN *et al*. Side-effect profile of acitretin therapy in psoriasis. *J Am Acad Dermatol* 1989; **20**: 1088–93.

25 Bardelli A, Rebora A. Telogen effluvium and minoxidil. *J Am Acad Dermatol* 1989; **21**: 572–3.

Chronic telogen effluvium. Chronic telogen effluvium (CTE) is a primary, idiopathic and often self-limiting condition affecting middle-aged women that is distinct from androgenetic hair loss and chronic diffuse telogen effluvium secondary to organic causes [1]. Women describe a sudden onset of increased hair shedding persisting for at least 6 months. There is no associated visible widening of the central parting line, and no miniaturization of hair follicles on scalp biopsy. CTE contrasts with acute telogen effluvium by its prolonged fluctuating course and much less frequent occurrence. It occurs mainly in females between 30 and 50 years of age. Hair shedding is much less obvious in males with short hair, and for unknown reasons few males with long hair present with increased hair shedding [2]. Although some cases of CTE follow an acute telogen effluvium with an identified trigger, such as pregnancy or systemic illness, in most cases no trigger can be identified. Any of the functional types of telogen effluvium could account for CTE, but it is believed to be related to shortening of the anagen phase of the hair cycle [3].

The diagnosis of CTE is made by exclusion of other causes of diffuse telogen hair loss. A thorough history is required, including a detailed drug and dietary history. A full clinical examination should be performed, including scalp examination and hair pull testing. The routine work-up includes full blood count and thyroid function tests. Syphilis serology, antinuclear antibody titre, serum zinc levels and other investigations of nutritional status should be performed if clinically warranted.

Affected women present with persistent severe shedding that runs a fluctuating course over several years [3] (Fig. 66.22). They often give a history of the ability to grow their hair very long in childhood, suggestive of a long anagen phase, and report a high hair density prior to the onset of hair loss [4,5]. They usually have a negative family history of AGA. Clinical examination reveals bitemporal recession, but no widening of the central hair parting, which if present would support the diagnosis of AGA. However, these criteria are not absolute, and AGA can mimic this presentation. A positive hair pull test is common over the vertex and occipital scalp, and patients may describe a reduction in the thickness of their ponytail volume, stating it has decreased by up to 50% [3]. A negative hair pull test on any one given day does not exclude the diagnosis of CTE.



Fig. 66.22 Idiopathic chronic telogen effluvium.

CTE has to be distinguished clinically from AGA, as women with early AGA may present with periods of increased hair shedding without a discernible pattern to the loss. In an evaluation of 600 women presenting with chronic diffuse telogen hair shedding with little or no reduction of visible hair density, 60% were found on scalp biopsy to have hair miniaturization consistent with a diagnosis of AGA and 40% had CTE [6].

The diagnosis of CTE can usually be suspected from the history and examination, but scalp biopsy may be required to differentiate it from early AGA [1]. The optimal scalp biopsy is a 4-mm punch biopsy taken from the vertex of the scalp for horizontal embedding. A terminal : vellus ratio below 8 : 1 is suggestive of AGA [1].

Despite the assertion that CTE is a self-limiting process that does not evolve into AGA, its natural history remains poorly characterized, with only one published longitudinal study [7].

References

1 Whiting DA. Chronic telogen effluvium. *Dermatol Clin* 1996; **14**: 723–31.
2 Thai KE, Sinclair RD. Chronic telogen effluvium in a man. *J Am Acad Dermatol* 2002; **47**: 605–7.
3 Headington JT. Telogen effluvium. New concepts and review. *Arch Dermatol* 1993; **129**: 356–63.
4 Sinclair R. Diffuse hair loss. *Int J Dermatol* 1999; **38** (Suppl. 1): 8–18.
5 Rushton DH, Ramsay ID, James KC *et al.* Biochemical and trichological characterization of diffuse alopecia in women. *Br J Dermatol* 1990; **123**: 187–97.
6 Sinclair R, Jolley D, Mallari R *et al.* The reliability of horizontally sectioned scalp biopsies in the diagnosis of chronic diffuse telogen hair loss in women. *J Am Acad Dermatol* 2004; **51**: 189–99.
7 Sinclair R. Chronic telogen effluvium: a study of 5 patients over 7 years. *J Am Acad Dermatol* 2005; **52**: 12–6.

Alopecia areata

A.G. Messenger, pp. 66.31–66.38

Alopecia areata is a chronic inflammatory disease that involves the hair follicle and sometimes the nails. Current evidence indicates that hair follicle inflammation in alopecia areata is caused by a T-cell-mediated autoimmune mechanism occurring in genetically predisposed individuals. Environmental factors may be responsible for triggering the disease.

In the only formal population study of alopecia areata, from Olmsted County, Minnesota, USA, the incidence rate was 0.1–0.2% with a projected lifetime risk of 1.7% [1]. Several large case series of alopecia areata have been reported from Europe [2], North America [3,4] and Asia [5,6], but these have generally been drawn from hospital clinic attenders and no accurate indication of variation in disease rates between populations is available.

Aetiology.

Genetic factors

The importance of genetic factors in alopecia areata is underlined by the high frequency of a positive family history in affected individuals [7]. In most reports, this ranges from 10 to 20% of cases, but mild cases are often overlooked or concealed and the true figure may be greater. The lifetime risk of alopecia areata in the children of a proband is approximately 6% [8,9]. Price and Colombe [10] found a family history of alopecia areata was more common in those with disease onset before the age of 30 years (37% compared with 7.1% in patients with onset after 30 years). There are several case reports of alopecia areata in twins [11–13]. A study in monozygotic and dizygotic pairs found a concordance rate of 55% for alopecia amongst monozygotic twins with no concordance among the dizygotic pairs [14]. The numbers studied were insufficient to allow a precise estimate of the genetic contribution in alopecia areata. Except in occasional families, alopecia areata is not inherited in a simple Mendelian fashion and the genetic basis appears to be multifactorial.

Gene associations. Case–control studies have reported associations between alopecia areata and a variety of genes involved in regulating immune and inflammatory responses (reviewed in [15]). The strongest associations to date have been with genes of the major histocompatibility complex (MHC), particularly the Class II alleles *HLA-DQB1*0301* [16–18] and *HLA-DRB1*1104* [18,19]. A genome-wide scan performed on 20 families confirmed the linkage between alopecia areata and the MHC region on chromosome 6p [20]. This study also showed susceptibility loci on chromosomes 10, 16 and 18. The loci on 16 and 18 are also associated with psoriasis.

Atopy. Several studies have reported an association between alopecia areata and atopic disease [4,5,21,22], and have suggested that alopecia areata in atopic subjects tends to have an earlier age of onset and be more severe than in non-atopic subjects. However, none of these studies has used a control group to which the same criteria for defining atopy have been applied, and the association has been disputed in a study from India [23].

Autoimmunity

The idea that alopecia areata is an autoimmune disease was first suggested by Rothman following a paper presented by Van Scott [24]. Alopecia areata is associated with other autoimmune diseases, such as myxoedema and pernicious anaemia [4,25].

The frequency of type 1 diabetes mellitus is increased in the relatives of patients with alopecia areata but not in the patients themselves [26], suggesting that the predisposition to alopecia areata protects against the development of diabetes. In most published series, patients with alopecia areata have had an increased frequency of circulating organ-specific and non-organ-specific autoantibodies compared with normal subjects, and a variety of non-specific abnormalities in peripheral T-cell numbers and function have also been reported (reviewed in [7]). Circulating autoantibodies to hair follicle tissue have been found in patients with alopecia areata [27] but their pathogenic role is uncertain. Passive immunization with alopecia areata serum failed to induce hair loss in human skin grafted on to nude mice [28].

The most convincing evidence implicating circulating immune factors in the pathogenesis of alopecia areata comes from the transplantation experiments carried out by Gilhar *et al.* They first showed that hair growth recovered in alopecic skin transplanted on to athymic nude mice [29]. In their later experiments alopecia was induced in grafted skin by the injection of autologous T lymphocytes incubated with hair follicle extracts and antigen-presenting cells [30]. T cells not incubated with hair follicle extracts failed to cause hair loss.

Immune privilege

The low or absent expression of MHC proteins by cells in the lower part of the hair follicle has led to the concept that the hair follicle is an immunologically privileged site, an idea that has some experimental support [31]. It has been suggested that the development of a hair follicle-targeted immune response in alopecia areata is the consequence of impairment in this putative immune privilege status, but this has yet to be confirmed [15].

Environmental factors

The idea that alopecia areata is caused by infection, either directly or as a consequence of a remote 'focus of infection', has a long history and still cannot be ruled out. It was the predominant aetiological theory until well into the 20th century, and sporadic reports connecting alopecia areata with infective agents continue to appear. Skinner *et al.* [32] reported finding mRNA for cytomegalovirus in alopecic lesions, but this was not confirmed in a subsequent study from Italy [33]. There are also reports of alopecia areata in husband and wife, although this may be coincidence [34,35]. The 'external' factor most frequently implicated in triggering alopecia areata is psychological stress [36–38]. The significance of such an association is difficult to establish because of the problems in performing a controlled investigation. The published evidence is also conflicting, with some studies failing to show any relationship between stressful events and onset of hair loss [39,40], to the extent that no firm conclusion can be reached.

Despite the anecdotal nature of much of the evidence it is possible that environmental factors are responsible for triggering alopecia areata in some patients. If so, it seems likely that a diversity of factors can operate in this way.

References

1 Safavi KH, Muller SA, Suman VJ *et al.* Incidence of alopecia areata in Olmsted County, Minnesota, 1975 through 1989. *Mayo Clin Proc* 1995; **70**: 628–33.

2 Gip L, Lodin A, Molin L. Alopecia areata: a follow-up investigation of outpatient material. *Acta Derm Venereol (Stockh)* 1969; **49**: 180–8.

3 Walker SA, Rothman S. Alopecia areata: a statistical study and consideration of endocrine influences. *J Invest Dermatol* 1950; **14**: 403–13.

4 Muller SA, Winkelmann RK. Alopecia areata. *Arch Dermatol* 1963; **88**: 290–7.

5 Ikeda T. A new classification of alopecia areata. *Dermatologica* 1965; **131**: 421–45.

6 Ro BI. Alopecia areata in Korea (1982–1994). *J Dermatol* 1995; **22**: 858–64.

7 McDonagh AJG, Messenger AG. The pathogenesis of alopecia areata. *Dermatol Clin* 1996; **14**: 661–70.

8 van der Steen P, Traupe H, Happle R *et al.* The genetic risk for alopecia areata in first degree relatives of severely affected patients. An estimate. *Acta Derm Venereol (Stockh)* 1992; **72**: 373–5.

9 Blaumeiser B, van der Goot I, Fimmers R *et al.* Familial aggregation of alopecia areata. *J Am Acad Dermatol* 2006; **54**: 627–32.

10 Price VH, Colombe BW. Heritable factors distinguish two types of alopecia areata. *Dermatol Clin* 1996; **14**: 679–89.

11 Omens DV, Omens HD. Alopecia areata in twins. *Arch Dermatol* 1946; **53**: 193.

12 Hendren OS. Identical alopecia areata in identical twins. *Arch Dermatol* 1949; **60**: 793–5.

13 Weidmann AI, Ziion LS, Mamelok AE. Alopecia areata occurring simultaneously in identical twins. *Arch Dermatol* 1956; **74**: 424–6.

14 Jackow C, Puffer N, Hordinsky M *et al.* Alopecia areata and cytomegalovirus infection in twins: genes versus environment? *J Am Acad Dermatol* 1998; **38**: 418–25.

15 Gilhar A, Paus R, Kalish RS. Lymphocytes, neuropeptides, and genes involved in alopecia areata. *J Clin Invest* 2007; **117**: 2019–27.

16 Morling N, Frentz G, Fugger L *et al.* DNA polymorphism of HLA class II genes in alopecia areata. *Dis Markers* 1991; **9**: 35–42.

17 Welsh EA, Clark HH, Epstein SZ *et al.* Human leukocyte antigen-DQB1*03 alleles are associated with alopecia areata. *J Invest Dermatol* 1994; **103**: 758–63.

18 Colombe BW, Price VH, Khoury EL *et al.* HLA class II antigen associations help to define two types of alopecia areata. *J Am Acad Dermatol* 1995; **33**: 757–64.

19 de Andrade M, Jackow CM, Dahm N *et al.* Alopecia areata in families: association with the HLA locus. *J Investig Dermatol Symp Proc* 1999; **4**: 220–3.

20 Martinez-Mir A, Zlotogorski A, Gordon D *et al.* Genomewide scan for linkage reveals evidence of several susceptibility loci for alopecia areata. *Am J Hum Genet* 2007; **80**: 316–28.

21 Penders AJM. Alopecia areata and atopy. *Dermatologica* 1968; **136**: 395–9.

22 Young E, Bruns HM, Berrens L. Alopecia areata and atopy. *Dermatologica* 1978; **156**: 306–8.

23 Sharma VK, Muralidhar S, Kumar B. Reappraisal of Ikeda's classification of alopecia areata: analysis of 356 cases from Chandigarh, India. *J Dermatol* 1998; **25**: 108–11.

24 Van Scott EJ. Morphologic changes in pilosebaceous units and anagen hairs in alopecia areata. *J Invest Dermatol* 1958; **31**: 35–43.

25 Cunliffe WJ, Hall R, Stevenson CJ *et al.* Alopecia areata, thyroid disease and autoimmunity. *Br J Dermatol* 1969; **81**: 877–81.

26 Wang SJ, Shohat T, Vadheim C *et al.* Increased risk for type I (insulin-dependent) diabetes in relatives of patients with alopecia areata (AA). *Am J Med Genet* 1994; **51**: 234–9.

27 Tobin DJ, Orentreich N, Fenton DA *et al.* Antibodies to hair follicles in alopecia areata. *J Invest Dermatol* 1994; **102**: 721–4.

28 Gilhar A, Pillar T, Assay B *et al.* Failure of passive transfer of serum from patients with alopecia areata and alopecia universalis to inhibit hair growth in transplants of human scalp skin grafted on to nude mice. *Br J Dermatol* 1992; **126**: 166–71.

29 Gilhar A, Krueger GG. Hair growth in scalp grafts from patients with alopecia areata and alopecia universalis grafted onto nude mice. *Arch Dermatol* 1987; **123**: 44–50.

30 Gilhar A, Ullmann Y, Berkutzki T *et al.* Autoimmune hair loss (alopecia areata) transferred by T lymphocytes to human scalp explants on SCID mice. *J Clin Invest* 1998; **101**: 62–7.

31 Reynolds AJ, Lawrence C, Cserhalmi-Friedman PB *et al.* Trans-gender induction of hair follicles. *Nature* 1999; **402**: 33–4.

32 Skinner RB Jr, Light WH, Bale GF *et al.* Alopecia areata and presence of cytomegalovirus DNA [letter]. *JAMA* 1995; **273**: 1419–20.

33 Tosti A, La Placa M, Placucci F *et al.* No correlation between cytomegalovirus and alopecia areata [letter]. *J Invest Dermatol* 1996; **107**: 443.
34 Swift S. Folie a deux? Simultaneous alopecia areata in a husband and wife. *Arch Dermatol* 1961; **84**: 94–6.
35 Zalka AD, Byarlay JA, Goldsmith LA. Alopecia à deux: simultaneous occurrence of alopecia in a husband and wife [letter]. *Arch Dermatol* 1994; **130**: 390–2.
36 Greenberg SI. Alopecia areata: a psychiatric survey. *Arch Dermatol* 1955; **72**: 454–7.
37 De Waard-van der Spek FB, Oranje AP, De Raeymaecker DM *et al.* Juvenile versus maturity-onset alopecia areata—a comparative retrospective clinical study. *Clin Exp Dermatol* 1989; **14**: 429–33.
38 Gupta MA, Gupta AK, Watteel GN. Stress and alopecia areata: a psychodermatologic study. *Acta Derm Venereol (Stockh)* 1997; **77**: 296–8.
39 MacAlpine I. Is alopecia areata psychosomatic? *Br J Dermatol* 1958; **70**: 117–31.
40 van der Steen P, Boezeman J, Duller P *et al.* Can alopecia areata be triggered by emotional stress? An uncontrolled evaluation of 178 patients with extensive hair loss. *Acta Derm Venereol (Stockh)* 1992; **72**: 279–80.

Pathology. Anagen follicles at the margins of expanding patches of alopecia areata characteristically show a perifollicular and intrafollicular inflammatory cell infiltrate, concentrated in and around the hair bulb (Fig. 66.23). The inflammatory infiltrate is composed mainly of activated T lymphocytes, with a preponderance of CD4 cells, and an admixture of macrophages and Langerhans' cells [1,2]. In contrast to the inflammatory scarring alopecias, little or none of the inflammatory infiltrate is seen around the isthmus of the hair follicle, the site of hair follicle stem cells [3]. This may explain why follicles are not destroyed in alopecia areata. Lymphocytic infiltration of the dermal papilla and bulbar epithelium may be accompanied by increased expression of HLA class I and II antigens and of intercellular adhesion molecule-1 (ICAM-1) [4–6], which are thought to be secondary to the local release of T-cell cytokines. Normal numbers of follicles are found in established bald patches and in alopecia universalis. Both anagen and telogen follicles are found in these sites, with a higher proportion in telogen than in normal scalp. Follicles are smaller than normal and anagen follicles do not develop beyond the Anagen 3–4 stage, when the hair shaft starts to be formed [7]. The inflammatory infiltrate tends to be less pronounced than in early lesions and is associated mainly with anagen follicles.

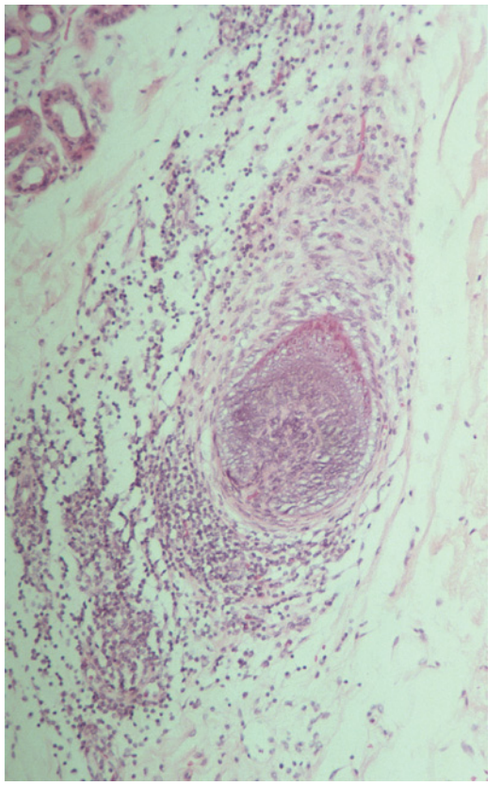


Fig. 66.23 Lymphocytic inflammatory infiltrate surrounding an anagen hair bulb in alopecia areata.

Alopecia areata causes a disturbance in the normal dynamics of the hair cycle. Anagen follicles are precipitated into telogen. This may occur as a centrifugal wave, reminiscent of a moult wave [8]. Follicles are able to re-enter anagen but, whilst the disease is active, are unable to progress beyond the Anagen 3–4 stage [7]. It has been suggested that they then return prematurely to telogen and that these truncated cycles continue until disease activity wanes [9] (Fig. 66.24).

The inflammatory infiltrate in alopecia areata is concentrated in and around the bulbar region of anagen hair follicles. Cells of several different types and differentiation pathways are found in the hair bulb, but which of these is the primary focus of the pathology is unknown. Trichocytes in the hair bulb matrix undergoing early cortical differentiation may show vacuolar degeneration (Fig. 66.25) [10,11] and are also the predominant cell type showing aberrant class I and II MHC expression. However, it is possible that changes in the epithelial compartment of the hair follicle are secondary to dysfunction of the dermal papilla. The sparing of white hair sometimes seen in alopecia areata has also raised the possibility that alopecia areata is primarily a disease of hair bulb melanocytes. Alopecia areata may show other pigmentary features, including reduced pigmentation in regrowing hairs and an association with vitiligo. However, the melanocyte hypothesis does not explain why sparing of white hair is often a relative phenomenon and is sometimes absent.

Alopecia areata in other species

Alopecia areata occurs in mammals other than humans, including chimps, dogs, horses, rats and mice. Two rodent strains, in which alopecia areata is common, the Dundee experimental bald rat (DEBR) and the CH3/HeJ mouse, have been used as experimental models of the disease. Extensive studies using the CH3/HeJ mouse have demonstrated a central role for T cells in mediating the follicular pathology in alopecia areata (reviewed in [12]).

References

1 Perret C, Wiesner-Menzel L, Happle R. Immunohistochemical analysis of T-cell subsets in the peribulbar and intrabulbar infiltrates of alopecia areata. *Acta Derm Venereol (Stockh)* 1984; **64**: 26–30.
2 Wiesner-Menzel L, Happle R. Intrabulbar and peribulbar accumulation of dendritic OKT 6-positive cells in alopecia areata. *Arch Dermatol Res* 1984; **276**: 333–4.
3 Cotsarelis G, Sun TT, Lavker RM. Label-retaining cells reside in the bulge area of pilosebaceous unit: implications for follicular stem cells, hair cycle, and skin carcinogenesis. *Cell* 1990; **61**: 1329–37.
4 Messenger AG, Bleehen SS. Expression of HLA-DR by anagen hair follicles in alopecia areata. *J Invest Dermatol* 1985; **85**: 569–72.

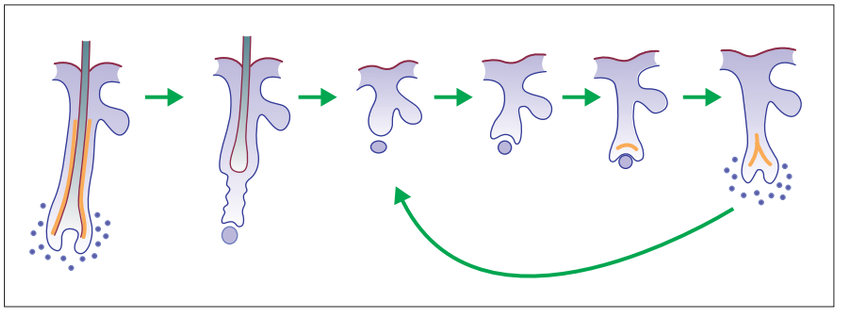


Fig. 66.24 Proposed pathodynamic changes in alopecia areata. An inflammatory attack on anagen follicles precipitates follicles into telogen. Follicles re-enter anagen but development is halted in Anagen 3–4 and follicles return to telogen prematurely.

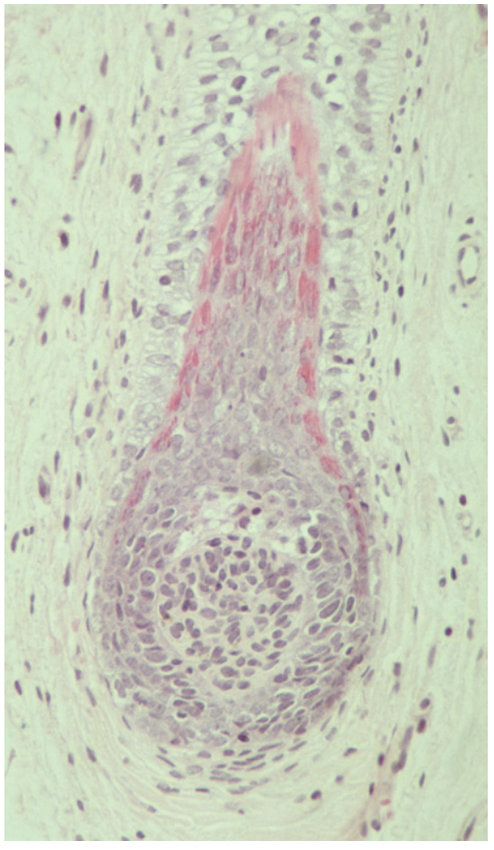


Fig. 66.25 An early anagen follicle in alopecia totalis, showing vacuolation in the hair matrix epithelium around the upper pole of the dermal papilla.

5 Bröcker EB, Echternacht-Happle K, Hamm H *et al.* Abnormal expression of class I and class II major histocompatibility antigens in alopecia areata: modulation by topical immunotherapy. *J Invest Dermatol* 1987; **88**: 564–8.

6 McDonagh AJG, Snowden JA, Stierle C *et al.* HLA and ICAM-1 expression in alopecia areata in vivo and in vitro: the role of cytokines. *Br J Dermatol* 1993; **129**: 250–6.

7 Van Scott EJ. Morphologic changes in pilosebaceous units and anagen hairs in alopecia areata. *J Invest Dermatol* 1958; **31**: 35–43.

8 Eckert J, Church RE, Ebling FJ. The pathogenesis of alopecia areata. *Br J Dermatol* 1968; **80**: 203–10.

9 Messenger AG, Slater DN, Bleehen SS. Alopecia areata: alterations in the hair growth cycle and correlation with the follicular pathology. *Br J Dermatol* 1986; **114**: 337–47.

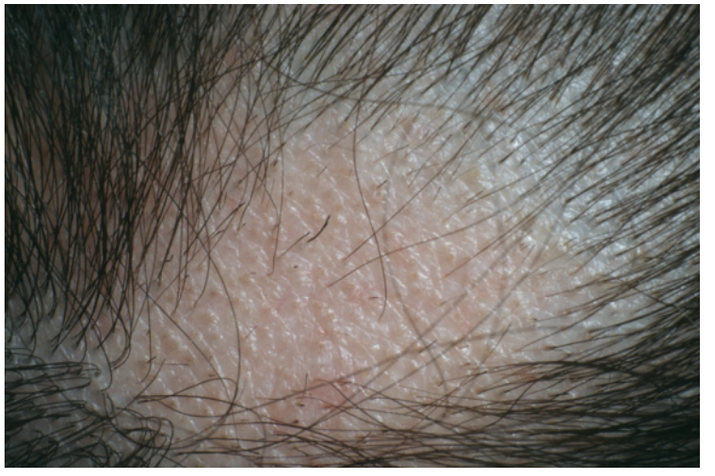


Fig. 66.26 Patch of alopecia areata. Broken 'exclamation mark hairs' are seen towards the margins of the patch.

10 Thies W. Vergleichende histologische Untersuchungen bei Alopecia areata und narbig-atrophisierenden. *Arch Klin Exp Dermatol* 1966; **227**: 541–9.

11 Messenger AG, Bleehen SS. Alopecia areata: light and electron microscopic pathology of the regrowing white hair. *Br J Dermatol* 1984; **110**: 155–62.

12 McElwee KJ, Yu M, Park SW *et al.* What can we learn from animal models of alopecia areata? *Dermatology* 2005; **211**: 47–53.

Clinical features. The onset of alopecia areata may be at any age, peaking between the second and fourth decades. The sex incidence is probably equal. The characteristic initial lesion is a circumscribed, totally bald, smooth patch (Fig. 66.26). It is often noticed by chance by a parent, hairdresser or friend. The skin within the bald patch appears normal or slightly reddened. Short, easily extractable broken hairs, known as exclamation mark hairs, are often seen at the margins of the bald patches during active phases of the disease (Fig. 66.27). Subsequent progress is very varied; the initial patch may regrow within a few months, or further patches may appear after an interval of 3–6 weeks and then in a cyclical fashion. These intervals are of varying duration. A succession of discrete patches may rapidly become confluent by the diffuse loss of remaining hair. In some cases the initial hair loss is diffuse, and total denudation of the scalp has been reported within 48 h. However, diffuse hair loss may occur over part or the whole of the scalp without the development of bald areas.



Fig. 66.27 Exclamation mark hairs.



Fig. 66.28 Alopecia areata affecting the beard.

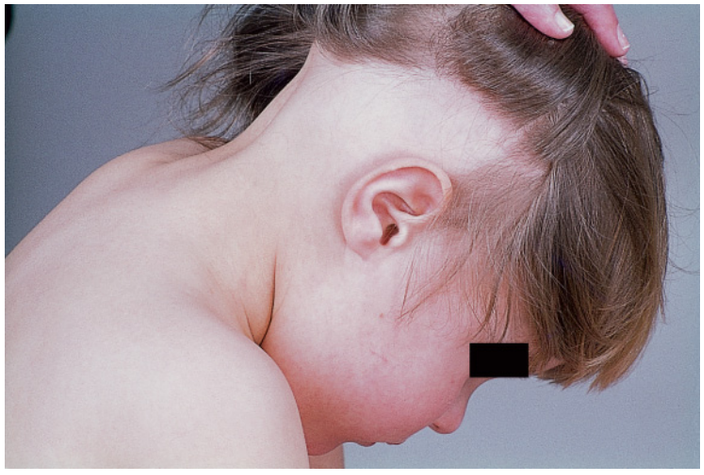


Fig. 66.29 The ophiasis pattern of alopecia areata.



Fig. 66.30 Regrowth of hypopigmented hair in alopecia areata.

Regrowth is often at first fine and unpigmented, but usually the hairs gradually resume their normal calibre and colour. Regrowth in one region of the scalp may occur while the alopecia is extending in others.

The scalp is the first affected site in most cases, but any hair-bearing skin can be affected. In dark-haired men, patches in the beard are conspicuous and in such individuals are often the first to be noticed (Fig. 66.28). The eyebrows and eyelashes are lost in many cases of alopecia areata and may be the only sites affected. The term alopecia totalis is applied to total or almost total loss of scalp hair, and alopecia universalis is the loss of all body hair. The extension of alopecia along the scalp margin is known as ophiasis (Fig. 66.29).

An intriguing feature of alopecia areata is the sparing of white hairs. In patients with grey hair, which is an admixture of pigmented and non-pigmented hair, the disease process appears preferentially to affect pigmented hair, so that non-pigmented or white hair is spared. This may result in a dramatic change in hair colour if the alopecia progresses rapidly, and is probably the explanation for historical accounts of people 'going white overnight'. Sparing of white hair is a relative phenomenon and it is clear that the white hairs, although less susceptible to the disease, are not immune. During the regrowth phase hairs may be non- or hypopigmented (Fig. 66.30) but hair pigmentation usually recovers completely. In exceptional cases where regrowing hairs remain non-pigmented the possibility of concurrent vitiligo should be considered.

In 10–15% of cases referred for specialist opinion alopecia areata also involves the nails, usually in the context of severe hair loss. Classically, alopecia areata causes fine, stippled pitting of the nails (Fig. 66.31), but some cases show less well-defined roughening of the nail plate (trachyonychia) or a non-specific atrophic dystrophy. For some patients, the latter problem is the most troublesome aspect of the disease.

Differential diagnosis. In children the main sources of diagnostic difficulty are tinea capitis and trichotillomania. Tinea capitis should always be considered in children presenting with patchy hair loss. There is usually evidence of scalp inflammation but this may be limited to mild scaling. The hair loss in trichotillomania may be asymmetrical or occur in artificial shapes. Broken hairs are usually present across the areas of hair loss, giving a bristly texture and, unlike exclamation mark hairs, are firmly anchored in the



Fig. 66.31 An organized pattern of pitting present on all fingernails 8 months prior to the onset of alopecia areata. Pits are highlighted with mascara.

scalp. In most cases the true diagnosis will become evident with time; a biopsy is useful when doubt remains. Occasionally, the early stages of scarring alopecia can resemble alopecia areata. The diffuse form of alopecia areata is perhaps the most difficult to identify. A history of previous episodes of hair loss, nail dystrophy and the usually rapid progression may provide clues, but other causes of diffuse hair loss, such as SLE, may need to be excluded by appropriate serological tests and a scalp biopsy. Secondary syphilis sometimes presents with diffuse or patchy hair loss.

Prognosis. Alopecia areata does not destroy hair follicles, and the potential for regrowth of hair is retained for many years, and is possibly lifelong. In some patients, patches of hair loss occur at infrequent intervals interspersed with long periods of normal hair growth. In others, alopecia areata is more persistent, so that new patches of hair loss continue to develop at the same time as regrowth occurs elsewhere. In a relatively small number of patients, hair loss progresses to involve all of the scalp (alopecia totalis) or the entire skin surface (alopecia universalis); in these cases, spontaneous recovery is the exception rather than the rule.

Data from secondary and tertiary referral centres indicate that 34–50% of patients will recover within 1 year, although almost all will experience more than one episode of the disease, and 14–25% progress to alopecia totalis or alopecia universalis, from which full recovery is unusual (less than 10%) [1–3]. One study from Japan reported that spontaneous remission within 1 year occurred in 80% of patients with a small number of circumscribed patches of hair loss [4]. The prognosis is less favourable when onset occurs during childhood [3,5] and in ophiasis [5]. The concurrence of atopic disease has been reported to be associated with a poor prognosis [4,5], but this was not found in a study from India [6].

References

1 Walker SA, Rothman S. Alopecia areata: a statistical study and consideration of endocrine influences. *J Invest Dermatol* 1950; **14**: 403–13.

2 Gip L, Lodin A, Molin L. Alopecia areata: a follow-up investigation of outpatient material. *Acta Derm Venereol (Stockh)* 1969; **49**: 180–8.

3 Tosti A, Bellavista S, Iorizzo M. Alopecia areata: a long term follow-up study of 191 patients. *J Am Acad Dermatol* 2006; **55**: 438–41.

4 Ikeda T. A new classification of alopecia areata. *Dermatologica* 1965; **131**: 421–45.

5 De Waard-van der Spek FB, Oranje AP, De Raeymaecker DM *et al*. Juvenile versus maturity-onset alopecia areata—a comparative retrospective clinical study. *Clin Exp Dermatol* 1989; **14**: 429–33.

6 Sharma VK, Dawn G, Kumar B. Profile of alopecia areata in Northern India. *Int J Dermatol* 1996; **35**: 22–7.

Management. A number of treatments can induce hair growth in alopecia areata, but none has been shown to alter the course of the disease, and the response rate in patients with extensive hair loss is low. Few treatments have been subjected to randomized controlled trials and, except for contact immunotherapy, there are few published data on long-term outcomes. These difficulties mean that counselling of the patient and, where relevant, of their family, are of paramount importance. This should include discussion of the nature of the disease and its natural history, the treatments available and their chances of success. Some patients have great difficulty coping with alopecia areata and require considerable support. Sources of support may include the physician, other patients, formal patient support groups and, in some circumstances, professional counselling services.

Treatment. Leaving alopecia areata untreated is a legitimate option for many patients. Spontaneous remission occurs in up to 80% of patients with limited patchy hair loss of short duration (less than 1 year) [1]. Such patients may be managed by reassurance alone, with advice that regrowth cannot be expected within 3 months of the development of any individual patch. The prognosis in long-standing extensive alopecia is less favourable. However, all treatments have a high failure rate in this group and some patients prefer not to be treated, other than wearing a wig if appropriate.

Corticosteroids. Potent topical steroids are widely used to treat alopecia areata. Two controlled trials have demonstrated modest benefit in limited disease, one using the steroid under occlusion [2] and the other using a foam formulation [3]. Topical steroids are not effective in alopecia totalis/universalis.

Intralesional depot corticosteroids can be used to accelerate regrowth in a circumscribed patch of alopecia areata that is cosmetically disfiguring or difficult to conceal [4,5]. They can also be useful to stimulate regrowth of the eyebrows, but care must be exercised to avoid steroid side effects in the eye. Hydrocortisone acetate (25 mg/mL) and triamcinolone acetonide (5–10 mg/mL) are commonly used, either by needle injection or jet injection; 1–3 ml can be injected in a session, each injection of 0.05–0.1 ml,

and repeated at intervals as necessary. Localized atrophy is a common complication, particularly if triamcinolone is used, but this is temporary and recovers within a few months. Repeated injections into the same site should be avoided.

Long-term daily treatment with oral corticosteroids will produce regrowth of hair in some patients. One small, partly controlled study reported that 30–47% of patients treated with a 6-week tapering course of oral prednisolone (starting at 40 mg/day) showed more than 25% hair regrowth [6]. Unfortunately, in most patients, continued treatment is needed to maintain hair growth and the response is usually insufficient to justify the risks. There are several case series reporting a favourable response to high-dose pulsed corticosteroid treatment using different oral and intravenous regimens [7–9]. In the only controlled trial, patients receiving prednisolone 200 mg once a week for 3 months showed better hair regrowth at 6 months than those taking placebo [10], but this was not statistically significant [11].

Contact immunotherapy. Contact immunotherapy is the most effective and best-documented treatment for alopecia areata, but problems associated with its use mean that it is available in only a few centres. The patient is sensitized to a potent allergen and the same allergen is then applied to the scalp, usually at weekly intervals, in a concentration sufficient to induce a mild contact dermatitis. The contact allergens that have been used in the treatment of alopecia areata include dinitrochlorobenzene (DNCB), squaric acid dibutylester (SADBE) and diphenylcyclopropenone (DPCP). Most centres now use DPCP [12]. A review of all the published studies of contact immunotherapy concluded that 50–60% of patients achieve a worthwhile response, but the range of response rates was very wide (9–87%) [13]. Patients with extensive hair loss are less likely to respond [14,15]. Other reported adverse prognostic features include the presence of nail changes, early onset and a positive family history [13]. In most studies treatment was discontinued after 6 months if no response was obtained. In one case series from Canada, clinically significant regrowth occurred in approximately 30% of patients after 6 months' treatment, but this increased to 78% after 32 months of treatment, suggesting that more prolonged treatment is worthwhile [16]. The response in patients with alopecia totalis and universalis was less favourable at 17% and this was not improved by treatment beyond 9 months. Relapses may occur following or during treatment. In the Canadian series, relapse following successful treatment occurred in 62% of patients. Two case report series of contact immunotherapy in children with alopecia areata reported response rates of 33% [17] and 32% [18]. A third study found a similar short-term response in children with severe alopecia areata, but less than 10% experienced sustained benefit [19].

Most patients will develop occipital and/or cervical lymphadenopathy during contact immunotherapy. This is usually temporary but may persist throughout the treatment period. Severe dermatitis is the most common adverse event, but the risk can be minimized by careful titration of the concentration. Uncommon adverse effects include urticaria [20] and vitiligo [21]. Cosmetically disabling pigmentary complications, both hyper- and hypopigmentation (including vitiligo), may occur if contact immunotherapy is used in patients with racially pigmented skin. Contact immunotherapy has been in use for 20 years and no long-term side effects have been reported.

The mode of action of contact immunotherapy is unknown. Happle [22] suggested that the contact allergen competes for CD4 cells, attracting them away from the perifollicular region ('antigenic competition'). Other suggested mechanisms include the non-specific stimulation of a local T-suppressor-cell response [23] and increased expression of TGF-β in the skin, which acts to suppress the immune response [24].

Photochemotherapy. There are several uncontrolled studies of photochemotherapy (PUVA) for alopecia areata, using all types of PUVA (oral or topical psoralen, local or whole body UVA irradiation) [25–27], claiming success rates of up to 60–65%. Two retrospective reviews have reported low response rates [28] or suggested that the response was no better than the natural course of the disease [29], although these observations were also uncontrolled. The relapse rate following treatment is high and continued treatment is usually needed to maintain hair growth, which may lead to an unacceptably high cumulative UVA dose.

Minoxidil. An early double-blind study reported a significantly greater frequency of hair regrowth in patchy alopecia areata in patients treated with topical 1% minoxidil compared with placebo [30]. Subsequent controlled trials in patients with extensive alopecia areata using 1% or 3% minoxidil failed to confirm these results [31–33]. Two of these studies reported a treatment response during an extended but uncontrolled part of the trial [32,33]. In one study comparing 5% and 1% minoxidil in extensive alopecia areata, regrowth of hair occurred more frequently in those receiving 5% minoxidil, but few subjects obtained a cosmetically worthwhile result [34]. Topical minoxidil is ineffective in alopecia totalis and universalis.

Dithranol. There are a small number of case report series of the use of dithranol (anthralin) or other irritants in the treatment of alopecia areata. The lack of controls makes the response rates difficult to evaluate, but only a small proportion of patients seem to achieve cosmetically worthwhile results. In one open study, 18% of patients with extensive alopecia areata achieved cosmetically worthwhile hair regrowth [35]. The published data indicate that dithranol needs to be applied sufficiently frequently and in a high enough concentration to produce a brisk irritant reaction in order to be effective.

Summary

Alopecia areata is difficult to treat and few treatments have been tested in randomized, controlled trials. The tendency to spontaneous remission and the lack of adverse effects on general health are important considerations in management, and counselling, with no treatment, is the best option in many cases. Topical and intralesional corticosteroids can be helpful in disease of limited extent. Minoxidil lotion and dithranol are widely used but there is little convincing evidence of efficacy. Contact immunotherapy is the most effective treatment for extensive alopecia areata, although it is not widely available, and the response rate in alopecia totalis

and universalis is low. The place of systemic corticosteroids is controversial.

Alopecia areata may cause considerable psychological and social disability and, in some cases, particularly those seen in secondary care, it may be a chronic and persistent disease causing extensive or universal hair loss. If the prognosis is poor (e.g. in a prepubertal atopic child with total alopecia), a full explanation and help in adjusting to the problems of hair loss will be of far greater value than the raising of unwarranted hopes.

References

1 Ikeda T. A new classification of alopecia areata. *Dermatologica* 1965; **131**: 421–45.
2 Tosti A, Piraccini BM, Pazzaglia M *et al.* Clobetasol propionate 0.05% under occlusion in the treatment of alopecia totalis/universalis. *J Am Acad Dermatol* 2003; **49**: 96–8.
3 Tosti A, Iorizzo M, Botta GL *et al.* Efficacy and safety of a new clobetasol propionate 0.05% foam in alopecia areata: a randomized, double-blind placebo-controlled trial. *J Eur Acad Dermatol Venereol* 2006; **20**: 1243–7.
4 Abell E, Munro DD. Intralesional treatment of alopecia areata with triamcinolone acetonide by jet injector. *Br J Dermatol* 1973; **88**: 55–9.
5 Kubeyinje EP. Intralesional triamcinolone acetonide in alopecia areata amongst 62 Saudi Arabs. *East Afr Med J* 1994; **71**: 674–5.
6 Olsen EA, Carson SC, Turney EA. Systemic steroids with or without 2% topical minoxidil in the treatment of alopecia areata. *Arch Dermatol* 1992; **128**: 1467–73.
7 Sharma VK. Pulsed administration of corticosteroids in the treatment of alopecia areata. *Int J Dermatol* 1996; **35**: 133–6.
8 Friedli A, Labarthe MP, Engelhardt E *et al.* Pulse methylprednisolone therapy for severe alopecia areata: an open prospective study of 45 patients. *J Am Acad Dermatol* 1998; **39**: 597–602.
9 Nakajima T, Inui S, Itami S. Pulse corticosteroid therapy for alopecia areata: study of 139 patients. *Dermatology* 2007; **215**: 320–4.
10 Kar BR, Handa S, Dogra S *et al.* Placebo-controlled oral pulse prednisolone therapy in alopecia areata. *J Am Acad Dermatol* 2005; **52**: 287–90.
11 Sladden MJ, Hutchinson PE. Is oral pulsed prednisolone useful in alopecia areata? Critical appraisal of a randomized trial. *J Am Acad Dermatol* 2005; **53**: 1100–1; author reply 01.
12 Happle R, Hausen BM, Wiesner-Menzel L. Diphencyprone in the treatment of alopecia areata. *Acta Derm Venereol (Stockh)* 1983; **63**: 49–52.
13 Rokhsar CK, Shupack JL, Vafai JJ *et al.* Efficacy of topical sensitizers in the treatment of alopecia areata. *J Am Acad Dermatol* 1998; **39**: 751–61.
14 van der Steen PH, van Baar HM, Happle R *et al.* Prognostic factors in the treatment of alopecia areata with diphenylcyclopropenone. *J Am Acad Dermatol* 1991; **24**: 227–30.
15 Gordon PM, Aldrige RD, McVittie E *et al.* Topical diphencyprone for alopecia areata: evaluation of 48 cases after 30 months' follow-up. *Br J Dermatol* 1996; **134**: 869–71.
16 Wiseman MC, Shapiro J, MacDonald N *et al.* Predictive model for immunotherapy of alopecia areata with diphencyprone. *Arch Dermatol* 2001; **137**: 1063–8.
17 MacDonald Hull S, Pepall L, Cunliffe WJ. Alopecia areata in children: response to treatment with diphencyprone. *Br J Dermatol* 1991; **125**: 164–8.
18 Schuttelaar ML, Hamstra JJ, Plinck EP *et al.* Alopecia areata in children: treatment with diphencyprone. *Br J Dermatol* 1996; **135**: 581–5.
19 Tosti A, Guidetti MS, Bardazzi F *et al.* Long-term results of topical immunotherapy in children with alopecia totalis or alopecia universalis. *J Am Acad Dermatol* 1996; **35**: 199–201.
20 Tosti A, Guerra L, Bardazzi F. Contact urticaria during topical immunotherapy. *Contact Dermatitis* 1989; **21**: 196–7.
21 Macdonald Hull S, Norris JF, Cotterill JA. Vitiligo following sensitization with diphencyprone. *Br J Dermatol* 1989; **120**: 232.
22 Happle R. Antigenic competition as a therapeutic concept for alopecia areata. *Arch Dermatol Res* 1980; **267**: 109–14.
23 Bröcker EB, Echternacht-Happle K, Hamm H *et al.* Abnormal expression of class I and class II major histocompatibility antigens in alopecia areata: modulation by topical immunotherapy. *J Invest Dermatol* 1987; **88**: 564–8.
24 Hoffmann R, Wenzel E, Huth A *et al.* Growth factor mRNA levels in alopecia areata before and after treatment with the contact allergen diphenylcyclopropenone. *Acta Derm Venereol (Stockh)* 1996; **76**: 17–20.
25 Claudy AL, Gagnaire D. PUVA treatment of alopecia areata. *Arch Dermatol* 1983; **119**: 975–8.
26 Lassus A, Eskelinen A, Johansson E. Treatment of alopecia areata with three different PUVA modalities. *Photodermatol* 1984; **1**: 141–4.
27 Mitchell AJ, Douglass MC. Topical photochemotherapy for alopecia areata. *J Am Acad Dermatol* 1985; **12**: 644–9.
28 Taylor CR, Hawk JL. PUVA treatment of alopecia areata partialis, totalis and universalis: audit of 10 years' experience at St John's Institute of Dermatology. *Br J Dermatol* 1995; **133**: 914–8.
29 Healy E, Rogers S. PUVA treatment for alopecia areata—does it work? A retrospective review of 102 cases. *Br J Dermatol* 1993; **129**: 42–4.
30 Fenton DA, Wilkinson JD. Topical minoxidil in the treatment of alopecia areata. *BMJ (Clin Res Ed)* 1983; **287**: 1015–7.
31 Vestey JP, Savin JA. A trial of 1% minoxidil used topically for severe alopecia areata. *Acta Derm Venereol (Stockh)* 1986; **66**: 179–80.
32 Price VH. Double-blind, placebo-controlled evaluation of topical minoxidil in extensive alopecia areata. *J Am Acad Dermatol* 1987; **16**: 730–6.
33 Ranchoff RE, Bergfeld WF, Steck WD *et al.* Extensive alopecia areata. Results of treatment with 3% topical minoxidil. *Cleve Clin J Med* 1989; **56**: 149–54.
34 Fiedler-Weiss VC. Topical minoxidil solution (1% and 5%) in the treatment of alopecia areata. *J Am Acad Dermatol* 1987; **16**: 745–8.
35 Fiedler-Weiss VC, Buys CM. Evaluation of anthralin in the treatment of alopecia areata. *Arch Dermatol* 1987; **123**: 1491–3.

Acquired cicatricial alopecia

R.D. Sinclair, pp. 66.38–66.52

Cicatricial alopecia is the generic term applied to permanent areas of hair loss that are associated with destruction of hair follicles. Following recovery from the initial injury or inflammatory insult, there is little if any potential for hair regrowth. Histologically, the follicles are replaced by fibrous stellae.

One of the earliest descriptions of cicatricial alopecia was by Brocq in 1885 [1]. He described what later became known eponymously as pseudopelade of Brocq [2], which is now regarded as a syndrome in which destruction of follicles leading to permanent patchy baldness is not accompanied by any clinically evident inflammatory pathology. Quainquad [3] described folliculitis decalvans, a form of scarring alopecia in which pustular folliculitis of the advancing margin was a conspicuous feature.

Cicatricial alopecia may result from a disease that affects the follicles primarily or a disease process external to the follicle that damages them secondarily. Secondary causes include trauma, as in burns or radiodermatitis, infections such as favus, tuberculosis or syphilis, or benign or malignant tumours. Chemicals used to straighten or curl hair may also cause a secondary cicatricial alopecia in susceptible persons.

Once the preliminary diagnosis of cicatricial alopecia has been made, the scalp should be examined for other clues as to the cause of the hair loss such as folliculitis, follicular plugging or broken hairs. These signs may help to establish the cause of a cicatricial alopecia, but no single sign is pathognomonic for a particular disease, and clinico-pathological correlation is usually needed to make a specific diagnosis. An occasional sterile pustule can even be seen in some cases of lichen planopilaris and chronic cutaneous lupus. Hairs, even if grossly normal in appearance, should be extracted from the edge of the bald area for microscopy and culture. Any pustule should be swabbed and the fluid cultured.

If no firm diagnosis is achieved, general examination of the skin, nails and oral mucosa should be carried out. Up to 40% of patients with scalp lichen planus and 30% of patients with discoid lupus of the scalp will have cutaneous disease elsewhere either at presentation or during follow-up.

In most cases, a diagnostic biopsy is indicated. The site for biopsy must be carefully selected and an early lesion is preferable. Several punch biopsies are preferable to a single elliptical biopsy; in this way, the biopsies can be orientated along follicles, and different stages of the disease process can be investigated. Ideally, at least one 4-mm biopsy should be taken from a clinically active area, prepared for horizontal section and stained with haematoxylin and eosin. If vertical sections or immunofluorescence are desired, a second 4-mm biopsy specimen from an area of similar clinical activity should be obtained. Additional biopsies from the centre of a patch of alopecia to establish whether follicular loss has occurred or to assess potential regrowth are optional, as are further biopsies for special stains (e.g. elastin, mucin, periodic acid–Schiff [PAS]) [4].

Classification of the primary causes of cicatricial alopecia is difficult because of changing clinical and histological features as these conditions evolve. The most common identifiable causes among white people are lichen planopilaris (LPP), folliculitis decalvans and discoid lupus erythematosus. Among black people, especially in North America and Europe, the most common cause is central centrifugal alopecia (see p. 66.46). Tumours, in particular metastatic nodules from renal, breast and lung carcinomas, should not be forgotten as a rare but important cause of cicatricial alopecia.

Despite multiple investigations a specific diagnosis is not always possible and a generic diagnosis of cicatricial alopecia is the best that can be offered. In such cases, a trial of oral steroids or antimalarials may be considered to assess the potential for regrowth. Surgical correction of small areas can be considered once the underlying disorder has burned out. This can be done either by follicle transplantation or excision of the area. Larger areas may require the prior use of tissue expanders [5].

Classification [4]. The causes of cicatricial alopecia are classified here into broad groups, and the individual causes then considered in greater detail (Table 66.3). Many of the causes are discussed in other chapters where appropriate.

References

1 Brocq L. Alopecia. *J Cutan Vener Dis* 1885; **3**: 49–56.
2 Brocq L, Lenglet E, Ayrignac J. Recherches sur l'alopecie atrophiante, variete pseudo-pelade. *Ann Dermatol Syphil (France)* 1905; **6**: 1–32, 97–127, 209–37.
3 Quainquad E. Folliculite epilante decalvante. *Ann Dermatol Syphiligr* 1889; **10**: 99–105.
4 Olsen EA, Bergfeld WF, Cotsarelis G *et al.* Summary of North American Hair Research Society (NAHRS)-sponsored Workshop on Cicatricial Alopecia, Duke University Medical Center, February 10 and 11, 2001. *J Am Acad Dermatol* 2003; **48**: 103–10.
5 Roenigk RK, Wheeland RG. Tissue expansion in cicatricial alopecia. *Arch Dermatol* 1987; **123**: 641–6.

Non-specific cicatricial alopecia

Aetiology. This is by far the most common diagnosis made among patients presenting with cicatricial alopecia. In Whiting's series of 358 patients who were biopsied because of cicatricial alopecia this was the diagnosis made in 32% of cases [1]. Although often called pseudopelade, this term is best avoided because of confusion with pseudopelade of Brocq, a specific and distinct clinical disease. This entity of non-specific cicatricial alopecia encompasses a range of idiopathic, non-inflammatory, irregular, permanent alopecias that are often slowly progressive. Many primary cicatricial alopecias ultimately burn out and the final common pathway is an irregular area of cicatricial hair loss of the scalp with no distinguishing clinical or histological features. Various authorities have estimated that between 15% and 90% of cases of non-specific cicatricial alopecia result from LPP, but there is no way of confirming this. That a small minority of patients initially diagnosed as having non-specific cicatricial alopecia later develop associated cutaneous lichen planus confirms significant overlap between this condition and LPP.

Pathology. The histology is variable and non-specific. Scalp biopsies taken from hairy skin at the edge of a scarred patch may be either completely normal or show a non-specific lymphocytic infiltrate around follicular infundibulum and mid-follicle, with or without a light, superficial perivascular infiltrate. Follicles may be depleted and replaced by fibrous tracts, and sebaceous glands and follicular units may be disrupted. In the centre of areas of alopecia, follicles are absent or dramatically diminished in number and the epidermis is atrophic. Concentric lamellar fibrosis and follicular atrophy is seen around residual follicles. The adjacent dermis is sclerotic. Follicle rupture can produce hair granulomas or pustules that may lead to an erroneous diagnosis of folliculitis decalvans.

Clinical features. The initial patch often occurs over the crown, but may occur anywhere on the scalp. The lesions tend to be oval, and several foci may coalesce to form irregular bald areas. There is usually no erythema and the patches are smooth, shiny and slightly depressed. Within any patch, a small number of terminal hairs may persist. These are often irregularly twisted and sometimes easily extracted. Folliculitis is rarely seen. The hairs at the edge of the patch of alopecia are also often irregularly twisted and easily extracted, even when in anagen, which indicates active extension of the alopecia.

Prognosis. The prognosis is extremely variable and unpredictable. Some patches extend almost imperceptibly over many years, whereas others enlarge rapidly. Whether this condition ever truly burns out, or merely extends too slowly to be noticed, is uncertain.

Treatment. Much has been tried empirically, but nothing has been shown to be effective.

Lichen planus (see Chapter 41)

Synonyms
- Lichen planopilaris
- Frontal fibrosing alopecia

Table 66.3 Classification of cicatricial alopecia.

Primary cicatricial alopecia			
Inflammatory	Lymphocytic	Chronic cutaneous lupus erythematosus	
		Lichen planopilaris (LPP)	
			Classic LPP
			Graham-Little syndrome
			Frontal fibrosing alopecia
		Pseudopelade of Brocq	
		Central centrifugal cicatricial alopecia	
		Alopecia mucinosa	
		Keratosis pilaris spinulosa decalvans	
	Neutrophilic	Folliculitis decalvans (including tufted folliculitis)	
		Dissecting cellulitis/folliculitis	
	Mixed	Acne keloidalis	
		Acne necrotica	
		Erosive pustular dermatosis	
	Non-specific or end-stage cicatricial alopecia		
Secondary cicatricial alopecia			
Traumatic	Radiodermatitis		
	Mechanical trauma		
	Postoperative (e.g. flap necrosis)		
	Burns		
	Accidental alopecia		
	Dermatitis artefacta		
	Traction alopecia		
	Hot comb alopecia		
Sclerosing disorders	Morphoea		
	Scleroderma		
	Lichen sclerosus		
	Sclerodermoid porphyria cutanea tarda		
	Chronic graft-versus-host disease		
Granulomatous	Sarcoidosis		
	Necrobiosis lipoidica		
	Infectious granulomas		
Infectious	Bacterial	Folliculitis	
		Carbuncle/furuncle	
	Fungal	Kerion	
		Favus	
		Tinea capitis (rarely scarring)	
	Viral	Shingles	
		Varicella	
		HIV	
	Protozoal	Leishmaniasis	
	Treponemal	Syphilis	
	Mycobacterial	Tuberculosis	
Neoplastic	Benign	Cylindroma	
		Other adnexal tumours	
	Malignant	Primary	Basal cell carcinoma
			Squamous cell carcinoma
			Cutaneous T-cell lymphoma
		Secondary	Renal, breast, lung, gastrointestinal
			Lymphoma, leukaemia
Developmental defects and hereditary disorders			
	Aplasia cutis		
	Facial hemiatrophy (Romberg's syndrome)		
	Epidermal naevi		
	Hair follicle hamartomas		
	Incontinentia pigmenti		
	Focal dermal hypoplasia of Goltz		
	Porokeratosis of Mibelli		
	Ichthyosis		
	Epidermolysis bullosa		
	Polyostotic fibrous dysplasia		
	Conradi–Hünermann syndrome (chondrodysplasia punctata)		

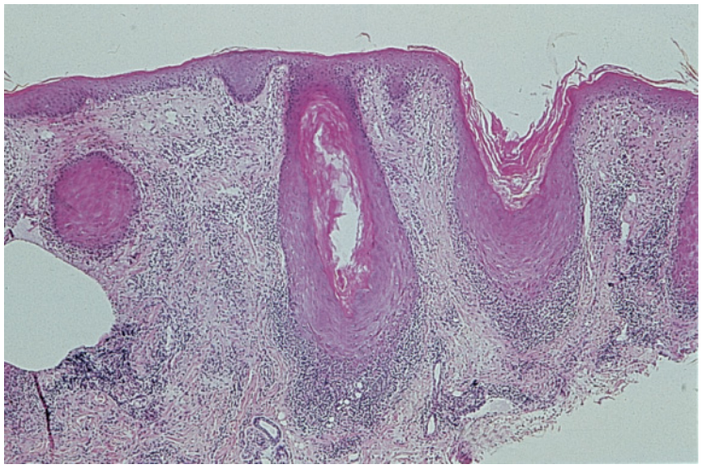


Fig. 66.32 Low-power photomicrograph showing lichen planopilaris. There is follicular plugging and a periappendageal inflammatory infiltrate.

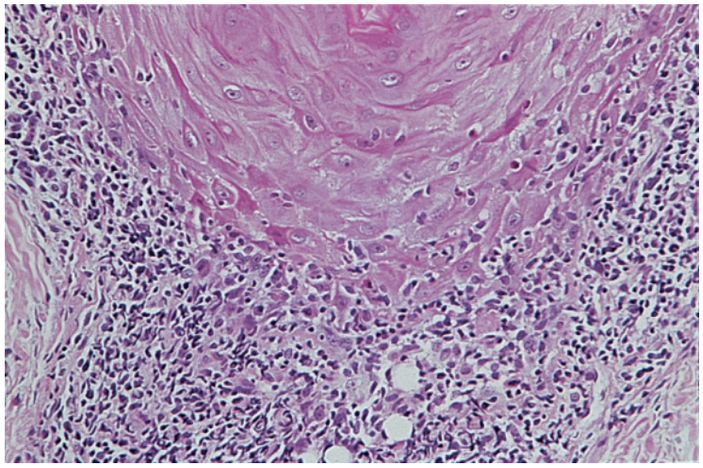


Fig. 66.33 Base of the hair follicle shows hydropic degeneration of the basal layer and a lichenoid mononuclear cell infiltrate.

Aetiology. Lichen planus is an idiopathic inflammatory disease that may affect the skin, hair and nails. There are numerous cutaneous variants of lichen planus. On the scalp it tends to produce a cicatricial alopecia. Three variants of cicatricial alopecia resulting from lichen planus are recognized: LPP, Graham-Little syndrome and frontal fibrosing alopecia. In each of these conditions the scalp may be affected alone or in conjunction with lichen planus elsewhere.

Lichen planus occurs throughout the world, although there are no data on its frequency in different ethnic groups.

Pathology [2]. The initial abnormality is in the epidermis; fibrillar changes in the basal cells lead to the formation of colloid bodies and at an early stage these, and macrophages containing pigment, may be seen in the dermis. By immunofluorescence, fibrin and immunoglobulin M (IgM) may be detected in the upper dermis, and various components of complement in the basement-membrane zone. The damaged basal cells are continually replaced by the migration of cells from neighbouring normal epidermis. In the established lesion, the horny layer and granular layer are thickened and there is irregular acanthosis. Flattening of the rete pegs gives rise to a saw-tooth configuration. There is liquefaction degeneration of the basal cells. Close up against the epidermis is a dense infiltrate of lymphocytes and some histiocytes. In many sections, colloid bodies can be seen. If the process involves hair follicles, the infiltrate extends around them and the hairs are replaced by keratin plugs. The follicles may ultimately be totally destroyed (Figs 66.32 & 66.33).

AGA with associated fibrosis may be confused with patterned LPP, especially as mild to moderate lymphohistiocytic inflammation is commonly seen in AGA [3].

Clinical features [4]. Lichen planus occurs at any age, but in over 80% of cases the onset is between 30 and 70 years [5]. Significant involvement of the scalp is relatively infrequent—only 10 of 807 patients in one series [5]—but the incidence is probably rather higher than such figures suggest, because they tend to exclude those patients in whom alopecia, classified as pseudopelade, was the only manifestation of the disease. Scalp involvement occurs in over 40% of patients with either of two unusual variants of lichen planus: the bullous or erosive form and LPP.



Fig. 66.34 Scarring alopecia caused by lichen planus, showing active lesions.

Recent scalp lesions may show violaceous papules, erythema and scaling (Fig. 66.34). These papules are replaced quickly by follicular plugs and scarring (Fig. 66.35). Eventually, the plugs are shed from the scarred area, which remains white, smooth and atrophic. Follicular orifices are absent within the area of alopecia. If the patch is extending, horny plugs may still be present in follicles around its margins, and the hair pull will be positive at the margins, with twisted anagen hairs being easily extracted by gentle traction.

Patients commonly present with pseudopelade-like patches of scarring that are non-specific. The diagnosis of lichen planus can be made only in the presence of unquestionable lesions elsewhere and lichen planus histology. These may take the form of bullous lichen planus with shedding of nails [6], of bullous lesions associated with typical lichen planus of the skin and mucous membranes, or of lichen planus of very limited extent involving, for example, the nails only.



Fig. 66.35 More advanced lichen planus, showing follicular plugs and scarring.

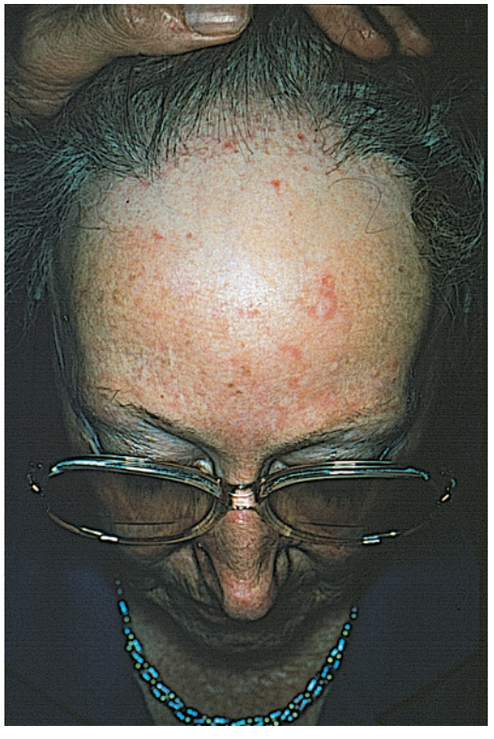


Fig. 66.36 Frontal fibrosing alopecia of Kossard.

One clinical variant of LPP is frontal fibrosing alopecia (Fig. 66.36) [7]. This condition superficially resembles AGA with frontal recession, but on close inspection there is loss of follicular orifices, and perifollicular erythema and hyperkeratosis at the marginal hairline. It typically occurs in postmenopausal women, although it can occur earlier. In contrast with AGA, the frontal hairline recedes in a straight line rather than bitemporally.

The natural history of frontal fibrosing alopecia is slow progression over many years. There is no effective treatment [7].

Prognosis. In some patients, the course of lichen planus of the scalp is slow and only a few inconspicuous patches are present after many years. However, particularly if the skin lesions are of bullous or planopilaris type, they may rapidly result in extensive and permanent baldness.

Treatment. In some cases, a short course of systemic treatment with a corticosteroid may be desirable. In other cases, intralesional corticosteroids are helpful, but only at a stage when active inflammatory changes are still present. Potent topical steroids such as clobetasol propionate ointment twice daily usually relieve associated symptoms such as itch or pain, and may slightly inhibit the process [8]. Hydroxychloroquine and acitretin have been tried with variable success. Ciclosporin is very effective for cutaneous lichen planus, and has been reported as useful in Graham-Little syndrome [9], as has thalidomide [10,11].

The lack of a clearly defined natural history, the permanency of the hair loss, the absence of any proven effective treatment to arrest disease progression, and the difficulty in monitoring clinical response, conspire to make treatment of this condition particularly frustrating for both patient and doctor.

References

1 Whiting DA. Cicatricial alopecia: clinico-pathological findings and treatment. *Clin Dermatol* 2001; **19**: 211–25.

2 Headington JT. Cicatricial alopecia. *Dermatol Clin* 1996; **14**: 773–82.

3 Zinkernagel MS, Trueb RM. Fibrosing alopecia in a pattern distribution: patterned lichen planopilaris or androgenetic alopecia with a lichenoid tissue reaction pattern? *Arch Dermatol* 2000; **136**: 205–11.

4 Mehregan DA, Van Hale HM, Muller SA. Lichen planopilaris: clinical and pathologic study of forty-five patients. *J Am Acad Dermatol* 1992; **27**: 935–42.

5 Altman J, Perry HO. The variations and course of lichen planus. *Arch Dermatol* 1961; **84**: 179–91.

6 Cram DL, Kierland RR, Winkelmann RK. Ulcerative lichen planus of the feet. Bullous variant with hair and nail lesions. *Arch Dermatol* 1966; **93**: 692–701.

7 Kossard S, Lee MS, Wilkinson B. Postmenopausal frontal fibrosing alopecia: a frontal variant of lichen planopilaris. *J Am Acad Dermatol* 1997; **36**: 59–66.

8 Chieregato C, Zini A, Barba A *et al.* Lichen planopilaris: report of 30 cases and review of the literature. *Int J Dermatol* 2003; **42**: 342–5.

9 Bianchi L, Paro Vidolin A, Piemonte P *et al.* Graham Little-Piccardi-Lassueur syndrome: effective treatment with cyclosporin A. *Clin Exp Dermatol* 2001; **26**: 518–20.

10 George SJ, Hsu S. Lichen planopilaris treated with thalidomide. *J Am Acad Dermatol* 2001; **45**: 965–6.

11 Boyd AS, King LE Jr. Thalidomide-induced remission of lichen planopilaris. *J Am Acad Dermatol* 2002; **47**: 967–8.

Graham-Little syndrome

In 1915, Graham-Little reported the case of a woman aged 55 years who had suffered for 10 years from slowly progressive cicatricial alopecia and for 5 months from groups of horny papules [1]. Since then many further cases have been reported. Whether this syndrome is or is not a form of lichen planus is still unresolved, although the immunofluorescence in typical cases strongly suggests lichen planus [2]. However, whatever its cause or causes, the syndrome is distinctive. It is known eponymously and variously as the Graham-Little, Lassueur–Graham-Little or Piccardi–Lassueur–Little syndrome.

Pathology. In the scalp, the mouths of affected follicles are filled by horny plugs. The underlying follicle is progressively destroyed and eventually an atrophic epidermis covers sclerotic dermis. In

the axillae and pubic region, the follicles are likewise destroyed, although the skin does not appear clinically to be atrophic.

Clinical features. Most patients are women between the ages of 30 and 70 years. The essential features of the syndrome are progressive cicatricial alopecia of the scalp, loss of pubic and axillary hair without clinically evident scarring, and the rapid development of keratosis pilaris [3].

In most patients, the earliest change has been patchy cicatricial alopecia of the scalp. In general, the scalp alopecia precedes the widespread keratosis pilaris by months or years [4]. In some patients, the alopecia and the keratosis pilaris appear to have developed more or less simultaneously, or the keratosis pilaris has preceded the discovery of the alopecia [5].

The scalp changes are commonly described simply as patches of cicatricial alopecia. Some authors specifically mention associated follicular plugging of the scalp [6]; others refer to 'scaly red patches'.

The keratosis pilaris is referred to in early case reports as lichen spinulosus, which emphasizes that the horny papules are prolonged into conspicuous spines. In most cases they have developed aggressively over a period of weeks or months and have been grouped into plaques, often on the trunk, or the trunk and limbs, but occasionally involving the eyebrows and the sides of the face. Pruritus is an inconstant symptom; it was noted in several reported cases [7]. Thinning and ultimately total loss of pubic and axillary hair has been noted in many cases.

Treatment. None is universally effective. Ciclosporin was reported as useful in a single case [6].

References

1 Graham-Little EG. Folliculitis decalvans et atrophicans. *Br J Dermatol* 1915; **27**: 183–5.

2 Horn RT Jr, Goette DK, Odom RB *et al.* Immunofluorescent findings and clinical overlap in two cases of follicular lichen planus. *J Am Acad Dermatol* 1982; **7**: 203–7.

3 Rongioletti F, Ghigliotti G, Gambini C *et al.* Agminate lichen follicularis with cysts and comedones. *Br J Dermatol* 1990; **122**: 844–5.

4 Pages F, Lapeyre J, Misson R. [Lassueur-Graham Little syndrome.]. *Ann Dermatol Syphiligr (Paris)* 1961; **88**: 272–8.

5 Reiss F, Reisch M, Buncke CM. Keratodermatitis follicularis decalvans. *AMA Arch Derm* 1958; **78**: 619–24.

6 Bianchi L, Paro Vidolin A, Piemonte P *et al.* Graham Little-Piccardi-Lassueur syndrome: effective treatment with cyclosporin A. *Clin Exp Dermatol* 2001; **26**: 518–20.

7 Kubba R, Rook A. The Graham-Little syndrome: follicular keratosis with cicatricial alopecia. *Br J Dermatol* 1975; **93** (Suppl. 11): 53–5.

Discoid lupus erythematosus [1]

Lupus erythematosus (LE) is an autoimmune connective tissue disease characterized by the presence of circulating non-organ-specific autoantibodies to cell nuclear antigens. Three different forms of LE are described: systemic (SLE), subacute and discoid (DLE) lupus. However, only DLE regularly produces cicatricial alopecia. Inflammation of the infundibular region of the hair follicle that contains the stem cells is thought to be the basis of the scarring alopecia that occurs in DLE, but this does not explain why the identical pattern of inflammation seen in SLE does not scar.

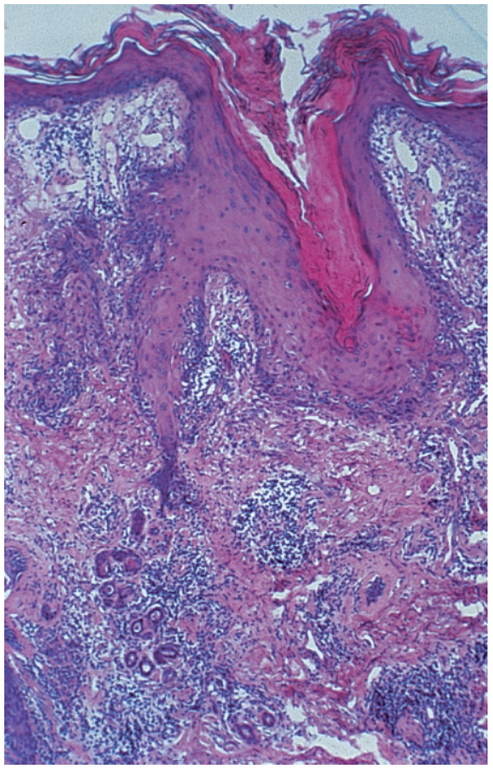


Fig. 66.37 Discoid lupus erythematosus. Low-power photomicrograph showing follicular plugging, superficial and deep perivascular and periappendageal lymphocytic infiltrate. (Courtesy of Dr G. Mason, Melbourne, Australia.)

The diffuse hair shedding that accompanies SLE is believed to be an acute telogen effluvium.

Pathology [2]. The histology of DLE, in common with SLE, shows hyperkeratosis with follicular plugging, a perivascular and periadnexal lymphoid infiltrate, which may be sparse, moderate or heavy, and the essential feature of focal basal layer vacuolar degeneration (Figs 66.37–66.39). This may be associated with colloid body formation, pigmentary incontinence, papillary dermal oedema, thickening of the basement-membrane zone and exocytosis of lymphocytes into the epidermis and follicular epithelium. Mucin can be seen in the dermis as a faint blue tinge between widely separated collagen bundles. Scarring only occurs in DLE and manifests as homogenized collagen fibres running parallel to the surface, a loss of appendages and lone arrector pili muscles. Staining for elastin shows that elastic fibres are absent from the scar.

Hypergranulosis, saw-toothed rete ridges, perifollicular fibrosis and clefts are not seen in lupus, and this helps to distinguish it from lichen planus. However, frequently it is not possible to separate these two conditions on routine histological examination and in such cases immunofluorescence may be decisive. There is linear staining of deposits of complement (C3), IgM and IgG on the basement membrane in more than 80% of cases of LE, but not in lichen planus. Direct immunofluorescence is also positive in non-lesional skin in approximately 50–75% of cases of SLE, depending on

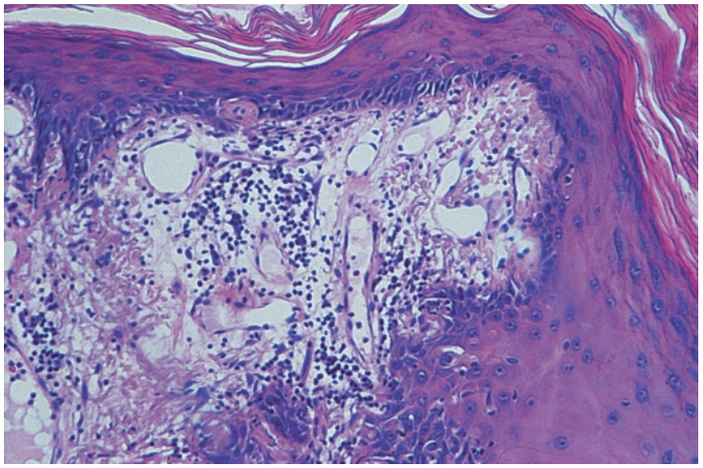


Fig. 66.38 Discoid lupus erythematosus. High-power photomicrograph showing the hydropic degeneration of the basal layer and the mononuclear cell infiltrate. (Courtesy of Dr G. Mason, Melbourne, Australia.)

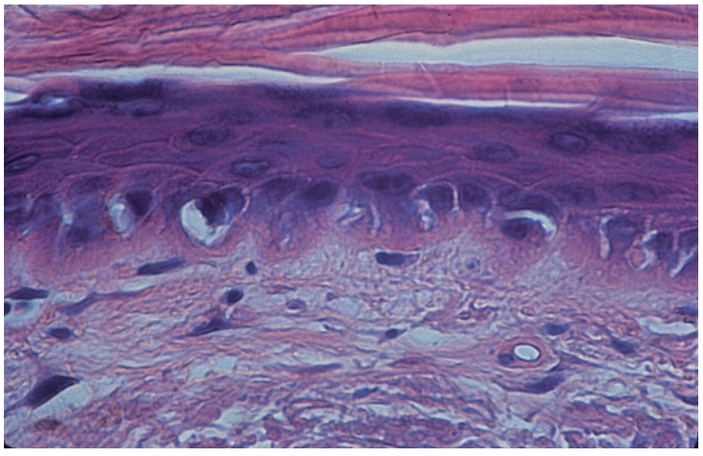


Fig. 66.39 Discoid lupus erythematosus. High-power photomicrograph showing the hydropic degeneration of the basal layer. (Courtesy of Dr G. Mason, Melbourne, Australia.)

whether sun-exposed or non-exposed skin is chosen. Only approximately 20% of cases of DLE will have positive immunofluorescence of uninvolved skin. A weak false-positive immunofluorescence to IgM can occur on the head and neck and is a source of confusion. Only positivity to IgG or very strong positivity to IgM (Fig. 66.40) should be used as supportive evidence of lupus on the scalp, as this only rarely occurs in the absence of lupus.

In old, burnt-out lesions, the histology and immunofluorescence may be inconclusive, and in such cases a non-specific diagnosis such as scarring alopecia is all that can be made.

Clinical features [2]. DLE occurs most commonly in women (8:1 for SLE and 2:1 for DLE), and is about three times more common in African Americans than in white people. The incidence is approximately 1 in 2000. Familial cases occur in approximately 10%. The peak age of onset is around 40 years.

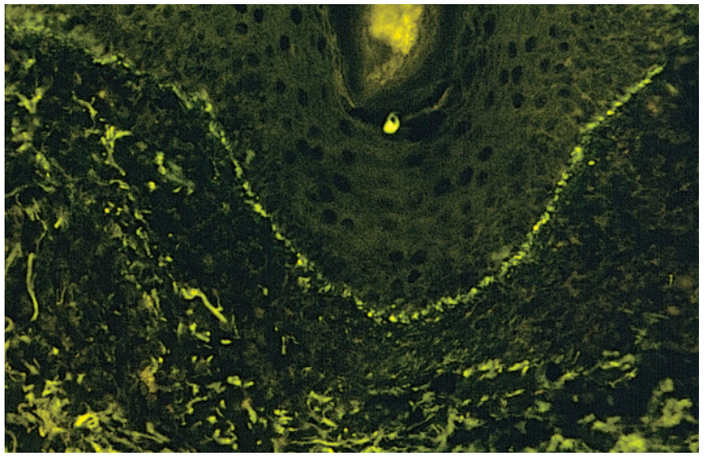


Fig. 66.40 Positive linear immunofluorescence to IgG: the lupus band test. (Courtesy of Dr G. Mason, Melbourne, Australia.)



Fig. 66.41 Discoid lupus erythematosus producing cicatricial alopecia.

Scarring alopecia occurs in 20% of men and 50% of women affected with DLE, and the scalp is the only area affected in a significant number of patients. Patches on the scalp are often itchy. Areas of erythema and scaling with follicular plugging extend irregularly across the scalp and produce scarring (Fig. 66.41). Sometimes patches of scarring alopecia develop with little in the way of preceding inflammation, and then resemble pseudopelade of Brocq. Ultimately, large areas of alopecia may form. Some cases burn out after 1–2 years, but others continue to progress for many years.

Pigmentary disturbance, particularly in dark-skinned people, is common. Rarely, calcification occurs in the patches. Squamous

cell carcinoma has been reported in chronic cicatricial LE of the scalp [3].

Antinuclear antibody (ANA) is positive in approximately 35% of patients with DLE. Anti-Ro antibodies are found in 10%. DLE may occur on its own or associated with SLE. If the initial DLE is confined to the head and neck, the risk is 1–2%, whereas if the lesions are generalized the risk is 22%. SLE first presents with DLE in 10% of cases and DLE can be found at some stage during the course of SLE in 33%.

Treatment [4]. Potent topical corticosteroids, intralesional triamcinolone and systemic prednisolone (1 mg/kg) may halt progression of active DLE. Antimalarials form the mainstay of treatment in chronic cases refractory to topical steroids. Hydroxychloroquine in a regimen of 200–400 mg/day produces a remission within 3 months in the majority and the dosage can then be tapered gradually. Scarring is permanent, but early treatment may produce a surprising amount of regrowth. Chloroquine, acitretin, dapsone, thalidomide or a combination of these medications may be useful in refractory cases. Cyclophosphamide, methotrexate and ciclosporin have also been used in severe, rapidly progressive cases where all other treatments have failed.

References

1 Drake LA, Dinehart SM, Farmer ER *et al.* Guidelines of care for cutaneous lupus erythematosus. American Academy of Dermatology. *J Am Acad Dermatol* 1996; **34**: 830–6.

2 Whiting DA. Cicatricial alopecia: clinico-pathological findings and treatment. *Clin Dermatol* 2001; **19**: 211–25.

3 Onayemi O, Soyinka F. Squamous cell carcinoma of the scalp following a chemical burn and chronic discoid lupus erythematosus. *Br J Dermatol* 1996; **135**: 342–3.

4 Ter Pooten M, Theirs B. Discoid lupus erythematosus. In: Lebwohl M, Heymann WR, Berth Jones J *et al.*, eds. *Treatment of Skin Disease*. London: Mosby, 2002: 166–8.

Pseudopelade of Brocq [1]

Pseudopelade of Brocq is an idiopathic, chronic, slowly progressive, patchy cicatricial alopecia that occurs without any evidence of inflammation. It is primarily an atrophy rather than an inflammatory folliculitis. The term pseudopelade was first used by Brocq to distinguish this condition from the 'pelade' of alopecia areata. The French term pelade had been in use at that time for more than 200 years and is derived from *pelage*—the fur, hair, wool, etc. of a mammal. In recent times, the term pseudopelade has been used to describe a generic scarring alopecia, the end result of any number of different pathological processes, and the interchangeable use by some of 'pseudopelade' and 'pseudopelade of Brocq' has led to confusion in the literature.

Pathology [2]. Early lesions may have a light lymphocytic infiltrate around the upper two-thirds of the hair follicle (including the hair bulge) that spares the epidermis and eccrine glands [3]. This infiltrate invades the walls of the follicles and sebaceous glands and eventually destroys the entire pilosebaceous unit. Single hairs may survive within a patch for many years.

Later patches are smooth, soft and slightly depressed, and histological examination reveals only a thin atrophic epidermis overlying a sclerotic dermis containing fibrotic streams extending into the subcutis. There are no inflammatory changes at this stage. These fibrotic streams are follicular 'ghosts'. Arrector pili muscles may be seen inserting into these fibrous remnants of hair follicles. Elastic stains are important in differentiating pseudopelade of Brocq from lichen planus, DLE and other scarring alopecias. With an acid–alcohol orcein stain, elastic fibres are seen around the lower part of the follicle, whereas in all the other scarring alopecias the scar tissue consists of collagen devoid of elastin.



Fig. 66.42 Pseudopelade of Brocq.

Clinical features [1]. Pseudopelade of Brocq may occur in both sexes at any age. Most commonly, women over 40 years are affected. Childhood cases are rare. The aetiology and pathogenesis are unknown. The condition is almost always sporadic, but the occurrence in two brothers suggests a genetic factor may be important. There is no doubt that lichen planus can produce a very similar clinical picture and there are some authorities who maintain, on the basis of associated skin lesions and histopathological findings, that 90% of cases of 'pseudopelade' are caused by lichen planus [4].

The alopecia is asymptomatic and is often discovered by chance. It always remains confined to the scalp. The initial patch is often on the vertex but may occur anywhere (Fig. 66.42). On examination, the affected patches are smooth, soft and slightly depressed. At an early stage in the development of any individual patch there may be some erythema. The patches tend to be small and round or oval, but irregular bald patches may be formed by the confluence of many lesions. The hair in uninvolved scalp is normal, but if the process is active the hairs at the edges of each patch are very easily extracted.

The course is extremely variable. Most often there is slow development over many years of small round patches of alopecia that ultimately converge to produce larger irregular areas of hair loss. The hair in the uninvolved scalp is normal and the progression is sufficiently slow that even after 15–20 years patients may still be able to arrange their hair in such a way as to conceal the bald areas. The entire process can burn out spontaneously at any stage, leaving behind only relatively small areas of alopecia.

Table 66.4 Diagnostic criteria for pseudopelade of Brocq. (After Braun-Falco *et al.* [1]).

Clinical criteria
Irregularly defined and confluent patches of alopecia
Moderate atrophy (late stage)
Mild perifollicular erythema (early stage)
Female : male ratio 3 : 1
Long course (more than 2 years)
Slow progression with spontaneous termination possible
Direct immunofluorescence
Negative (or only weak IgM on sun-exposed skin)
Histological criteria
Absence of marked inflammation
Absence of widespread scarring (best seen with elastin stain)
Absence of significant follicular plugging
Absence, or at least a decrease, of sebaceous glands
Presence of normal epidermis (only occasional atrophy)
Fibrotic streams into the dermis

The diagnostic criteria of Braun-Falco *et al.* [1] shown in Table 66.4, and based on the histological criteria of Pinkus [5], should be fulfilled before this specific diagnosis is made. Cases that do not fulfil these criteria should be diagnosed generically as scarring alopecia.

Treatment. The alopecia is irreversible and does not respond to topical or intralesional corticosteroids. No treatment is known to arrest progression. If the disfigurement is considerable and no active inflammatory changes are present, autografting from unaffected to scarred scalp may be considered [6], or surgical 'expansion' techniques in severe cases.

References

1 Braun-Falco O, Imai S, Schmoeckel C *et al.* Pseudopelade of Brocq. *Dermatologica* 1986; **172**: 18–23.
2 Degos R, Rabut R, Duperrat B *et al.* [Pseudopeladic state; comments on one hundred cases of circumscribed cicatricial alopecia, apparently primary, of pseudopelade type]. *Ann Dermatol Syphiligr (Paris)* 1954; **81**: 5–26.
3 Pincelli C, Girolomoni G, Benassi L. Pseudopelade of Brocq: an immunologically mediated disease? *Dermatologica* 1987; **174**: 49–50.
4 Gay Prieto J. Pseudopelade of Brocq: its relationship to some forms of cicatricial alopecias and to lichen planus. *J Invest Dermatol* 1955; **24**: 323–35.
5 Headington JT. Cicatricial alopecia. *Dermatol Clin* 1996; **14**: 773–82.
6 Stough DB 3rd, Berger RA, Orentreich N. Surgical improvement of cicatricial alopecia of diverse etiology. *Arch Dermatol* 1968; **97**: 331–4.

Follicular degeneration syndrome [1]

This condition begins as a single focus of cicatricial alopecia over the vertex scalp in black women that gradually spreads outwards in a centrifugal pattern, but remains unifocal. It was originally called hot comb alopecia, but many patients have no preceding history of hot comb usage. A possible relationship to other hair-straightening procedures is postulated, but not conclusively proven. The name 'central centrifugal alopecia' has also been proposed, and this focuses attention on the clinical appearance of the hair loss rather than the histological identification of premature degeneration of the inner root sheath, which is variable and not entirely specific [2].

Pathology. A superficial perivascular and perifollicular lymphocytic infiltrate is seen in active areas. There is no associated interface change. Sebaceous glands are lost early, but eccrine glands are spared. Premature disintegration of the inner root sheath epithelium has been emphasized, but is not always found. Hair follicle destruction is severe and widespread and leaves prominent concentric lamellar fibrosis. Release of hair fragments into the dermis results in granulomatous inflammation.

Clinical features. Most patients are middle-aged black females who chemically straighten their hair. The alopecia is slowly progressive and the symmetrical forward progression follows a pattern similar to female pattern hair loss.

Treatment. Minimal hair grooming is recommended, but many patients find this difficult. No treatment has been found to help. Many patients resort to wearing a suitable hair piece.

References

1 Sperling LC, Sau P. The follicular degeneration syndrome in black patients. 'Hot comb alopecia' revisited and revised. *Arch Dermatol* 1992; **128**: 68–74.
2 Whiting DA. Cicatricial alopecia: clinico-pathological findings and treatment. *Clin Dermatol* 2001; **19**: 211–25.

Folliculitis decalvans and tufted folliculitis [1]

Under the general term folliculitis decalvans we group the various syndromes in which clinically evident chronic folliculitis leads to progressive scarring. This is probably a heterogeneous group.

Aetiology. The cause of folliculitis decalvans is still uncertain. *Staphylococcus aureus* may be grown from the pustules. In the vast majority of people who develop a bacterial pustular folliculitis of the scalp it is transient, resolves with antibiotics and heals without scarring. In some, the folliculitis is more persistent, penetrates more deeply within the hair follicle, tends to recur in the same site after apparently successful treatment with antibiotics and produces a scarring alopecia. Spread tends to only occur to neighbouring follicles so that the condition presents as a slowly enlarging solitary area of cicatricial alopecia. It is rarely multifocal.

Failure to confine the *Staph. aureus* to the infundibulum of the hair follicle and to completely eradicate it from the isthmus is postulated, which may be due to disruption by bacterial proteases of the protective barrier provided by the inner root sheath. No consistent defect in cell-mediated immunity or inner root sheath keratinization has been identified in patients with folliculitis decalvans.

Douwes *et al.* [2] reported simultaneous occurrence in identical twins, with no identifiable immune abnormality [2].

Pathology [1,3,4]. Histology reveals follicular abscesses, with a dense perifollicular polymorphonuclear infiltrate, and scattered eosinophils and plasma cells. Foreign-body granulomas occur in response to follicular disruption, which is succeeded by scarring. Eventually all that remains of the follicle is extensive fibrosis.

Clinical features [1]. Men may be affected from adolescence onwards, whereas women tend not to develop this condition until



Fig. 66.43 Folliculitis decalvans, showing active pustulation and scarring.

their thirties. Following a pustular folliculitis of the scalp, usually one, but occasionally more, rounded patches of alopecia develop, each surrounded by crusting and a few follicular pustules. Successive crops of pustules appear and are followed by progressive destruction of the affected follicles (Fig. 66.43). In some cases the folliculitis spreads along the scalp margin in a coronal pattern, or along the edge of an AGA. The severity of the inflammatory changes fluctuates, but the course is prolonged.

Tufted folliculitis is a variant of folliculitis decalvans where circumscribed areas of scalp inflammation heal with scarring characterized by tufts of up to 15 hairs emerging from a single orifice (Fig. 66.44) [5–7]. The tufts consist of a central anagen hair surrounded by telogen hairs, each arising from independent follicles, converging towards a common dilated follicular infundibulum. Cases in which the tufts were comprised of only anagen hairs have also been described. Based on an animal model, it is suggested that erythema and scaling are the initial events and the tufting is a consequence of the emergence of hairs from beneath the free edge of the scales.

A scalp biopsy is required to confirm the diagnosis and swabs should be taken of any pustules. Investigation for an underlying defect in cell-mediated immunity is generally unrewarding, and only indicated when there is additional evidence of impaired immunity. As fungal kerion may mimic folliculitis decalvans, hairs should be plucked for fungal culture and a PAS stain should be performed on the scalp biopsy.

Treatment [1]. Essentially, treatment consists of attempts to eradicate *Staph. aureus* from the scalp. Prolonged courses of flucloxacillin induce remission, but relapse occurs when the antibiotics are stopped. For localized areas, topical clindamycin is useful. Tetracyclines are also commonly effective. Isotretinoin has been used to alter the follicular environment to make it less suitable for *Staph. aureus* colonization, but it may increase cutaneous carriage of this organism and make the condition worse. The only treatment shown to induce prolonged remission is rifampicin in a dosage of 300 mg twice daily. This should be given in combination with other antibiotics to prevent the emergence of resistant organisms. Drugs commonly used in combination include clindamycin 300 mg twice daily, fucidic acid 150 mg three times daily, ciprofloxacin, doxycycline and clarithromycin.



Fig. 66.44 Tufted folliculitis.

Tufting may be reduced by measures directed at reducing the scale, such as the use of tar shampoos and topical keratolytics.

References

1 Powell JJ, Dawber RP, Gatter K. Folliculitis decalvans including tufted folliculitis: clinical, histological and therapeutic findings. *Br J Dermatol* 1999; **140**: 328–33.
2 Douwes KE, Landthaler M, Szeimies RM. Simultaneous occurrence of folliculitis decalvans capillitii in identical twins. *Br J Dermatol* 2000; **143**: 195–7.
3 Headington JT. Cicatricial alopecia. *Dermatol Clin* 1996; **14**: 773–82.
4 Whiting DA. Cicatricial alopecia: clinico-pathological findings and treatment. *Clin Dermatol* 2001; **19**: 211–25.
5 Dalziel KL, Telfer NR, Wilson CL *et al.* Tufted folliculitis. A specific bacterial disease? *Am J Dermatopathol* 1990; **12**: 37–41.
6 Tong AK, Baden HP. Tufted hair folliculitis. *J Am Acad Dermatol* 1989; **21**: 1096–9.
7 al-Jawamis FM, Khalifeh L, Todd DJ. Tufted hair folliculitis in Jordanian patients. *Int J Dermatol* 1996; **35**: 280–1.

Dissecting cellulitis of the scalp [1]

Synonyms
- Dissecting folliculitis
- Perifolliculitis capitis abscedens et suffodiens

This rare condition manifests with a perifolliculitis of the scalp, deep and superficial abscesses in the dermis, sinus tract formation and extensive scarring. It occurs predominantly in black males aged between 18 and 40 years. Familial cases are exceptional, as is childhood onset.



Fig. 66.45 Dissecting cellulitis of the scalp. (Courtesy of Dr D. Dyall-Smith and the *Australasian Journal of Dermatology* [4].)

Aetiology. The aetiology of this inflammatory condition is unknown. Although staphylococci, streptococci and *Pseudomonas* may be cultured from various lesions, no specific causative organism has been isolated. Dissecting cellulitis associates with hidradenitis suppurativa and acne conglobata in the follicular occlusion triad [2]. Other reported associations include pilonidal sinus and spondyloarthropathy. The activity of the arthritis parallels the activity of the skin.

Clinical features. Painful, firm, skin-coloured nodules develop near the vertex of the scalp and later become softer and fluctuant (Fig. 66.45). Confluent nodules form tubular ridges with an irregular cerebriform pattern, on a red and oedematous background. Thin blood-stained pus exudes from crusted sinuses, and pressure on one region of the scalp may cause discharge of pus from a neighbouring intercommunicating ridge. Cervical adenitis is present in some cases, but is more remarkable for its absence in many others. Progressive scarring and permanent alopecia occur. Characteristically, hair is lost from the summits of these inflammatory lesions and retained in the valleys. The condition is chronic, with frequent acute exacerbations. Fatal squamous cell carcinoma has developed within the areas of scarring after many years [3].

Pathology [5]. Histology shows a perifolliculitis with a heavy infiltrate of lymphocytes, histiocytes and polymorphonuclear cells. Abscess formation results, and leads to destruction of the pilosebaceous follicles initially, and eventually the other cutaneous appendages. Keratin fragments induce a granulomatous reaction, with foreign-body giant cells, lymphoid and plasma cells. Special stains for bacteria, fungi and mycobacteria are negative.

Investigations. Culture from affected areas often grows bacterial organisms. Fungal cultures and a scalp biopsy for routine histology and direct immunofluorescence will exclude other causes of scarring alopecia.

Treatment. Although systemic antibiotics and topical or intralesional corticosteroids are sometimes helpful, relapses are frequent and the course is usually protracted. Isotretinoin in full dosage (1 mg/kg), in combination with prednisolone (1 mg/kg) and erythromycin 500 mg four times daily, may induce a rapid remission and significant hair regrowth in areas not yet irreversibly damaged [4]. Because the inflammation is predominantly perifollicular, a surprising amount of regrowth may occur. The antibiotics can be stopped after 4 weeks and the prednisolone gradually tailed off and replaced by topical steroids. The isotretinoin should be continued for at least 6 months, and reintroduced if the condition relapses. In recalcitrant cases, widespread excision and grafting may be considered, or alternatively in an older patient, X-ray epilation has been used with success [6]. Improvement has also been noted following laser-assisted hair removal [7].

The benefit of isotretinoin in this condition contrasts with the frequent worsening seen with oral isotretinoin in folliculitis decalvans and suggests that these two conditions are distinct entities rather than different points along a spectrum of the same disease.

References

1 Wise F, Parkhurst HJ. A rare form of suppurating cicatrizing disease of the scalp (perifolliculitis capitis abscedens et suffodiens). *Arch Dermatol Syphilol* 1921; **4**: 750–8.

2 Chicarilli ZN. Follicular occlusion triad: hidradenitis suppurativa, acne conglobata, and dissecting cellulitis of the scalp. *Ann Plast Surg* 1987; **18**: 230–7.

3 Camisa C. Squamous cell carcinoma arising in acne conglobata. *Cutis* 1984; **33**: 185–7, 90.

4 Dyall-Smith D. Signs, syndromes and diagnoses in dermatology. Dissecting cellulitis of the scalp. *Australas J Dermatol* 1993; **34**: 81–2; quiz 83–4.

5 Whiting DA. Cicatricial alopecia: clinico-pathological findings and treatment. *Clin Dermatol* 2001; **19**: 211–25.

6 Scheinfeld NS. A case of dissecting cellulitis and a review of the literature. *Dermatol Online J* 2003; **9**: 8.

7 Chui CT, Berger TG, Price VH *et al.* Recalcitrant scarring follicular disorders treated by laser-assisted hair removal: a preliminary report. *Dermatol Surg* 1999; **25**: 34–7.

Circumscribed scleroderma and linear morphoea

Circumscribed scleroderma is rare in the scalp, but may occur there as single or multiple lesions. The hair is shed at an early stage to leave a cicatricial alopecia. The diagnosis must be confirmed histologically. Linear circumscribed morphoea in the frontal region—'en coup de sabre' morphoea (Fig. 66.46)—is slightly more common (see Chapter 51). It has been suggested that lesions may follow the lines of Blaschko [1]. Histological examination of both conditions shows chronic inflammation of the upper and mid-follicle, and prominent fibrosis [2]. Linear morphoea has been associated with hereditary deficiency of complement C2 [3].

References

1 McKenna DB, Benton EC. A tri-linear pattern of scleroderma 'en coup de sabre' following Blaschko's lines. *Clin Exp Dermatol* 1999; **24**: 467–8.

2 Whiting DA. Cicatricial alopecia: clinico-pathological findings and treatment. *Clin Dermatol* 2001; **19**: 211–25.

3 Hulsmans RF, Asghar SS, Siddiqui AH *et al.* Hereditary deficiency of C2 in association with linear scleroderma 'en coup de sabre'. *Arch Dermatol* 1986; **122**: 76–9.



Fig. 66.46 Linear morphoea (en coup de sabre). After having this lesion since adolescence this lady later developed biopsy-proven lichen sclerosus of the vulva.



Fig. 66.47 Erosive pustular dermatosis of the scalp occurring on a sun-exposed bald scalp.

Cicatricial pemphigoid

Synonym
- Benign mucosal pemphigoid

Cicatricial pemphigoid affects predominantly the elderly, and women more than men [1,2]. It is associated with autoantibodies to the basement-membrane-zone adhesion complex (see Chapter 40).

Bullae are formed at the dermal–epidermal junction. Direct immunocytochemical studies show that linear deposits of IgG, IgA, C3 and C4 may be found in the basement-membrane zone, but circulating basement-membrane-zone antibodies (IgG or IgA) are not always demonstrable [3,4].

Although the disease predominantly affects the ocular and/or genital mucous membrane, the skin is involved in 40–50% of cases, and skin lesions may precede the mucosal lesions by months or years [5]. The skin lesions repeatedly recur and leave scars. The favoured sites are the face and upper trunk, the scalp being involved in approximately 10% of cases [6]. Skin lesions, predominantly on the head and neck, are the major feature of the Brunsting–Perry variant.

Management is often dictated by the need to control mucosal lesions. If recurrent bullae in a localized area of skin are troublesome, excision and grafting may be successful [6]. Whether to prescribe oral corticosteroids or immunosuppressive drugs for skin lesions alone is controversial, but topical clobetasol propionate cream may inhibit the process to some degree.

References

1 Pearson RW. Advances in the diagnosis and treatment of blistering diseases: a selective review. In: Malkinson F, Pearson RW, eds. *Year Book of Dermatology*. Chicago: Year Book Medical Publishers 1977.

2 Kurzhals G, Stolz W, Maciejewski W *et al*. Localized cicatricial pemphigoid of the Brunsting-Perry type with transition into disseminated cicatricial pemphigoid. Report of a case proved by preembedding immunogold electron microscopy. *Arch Dermatol* 1995; **131**: 580–5.

3 Holubar K, Honigsmann H, Wolff K. Cicatricial pemphigoid. Immunofluorescence investigations. *Arch Dermatol* 1973; **108**: 50–2.

4 Whiting DA. Cicatricial alopecia: clinico-pathological findings and treatment. *Clin Dermatol* 2001; **19**: 211–25.

5 Leenutaphong V, von Kries R, Plewig G. Localized cicatricial pemphigoid (Brunsting-Perry): electron microscopic study. *J Am Acad Dermatol* 1989; **21**: 1089–93.

6 Slepyan AH, Burks JW, Fox J. Persistent denudation of the scalp in cicatricial pemphigoid: treatment by skin grafting. *Arch Dermatol* 1961; **84**: 444–51.

Erosive pustular dermatosis of the scalp

This clinical entity particularly affects the elderly [1,2]. Its cause is unknown but Grattan *et al*. [3], in their study of 12 cases, suggested that local trauma and sun damage are important. Surgery, cryosurgery, skin grafting and radiation therapy may all precipitate this condition [4].

Pathology. Histological examination shows areas of epidermal erosion, a chronic inflammatory cell infiltration in the dermis consisting predominantly of lymphocytes and plasma cells, and sometimes small foci of foreign-body giant cells where hair follicles have been destroyed.

Clinical features. This condition almost always occurs in association with AGA. Initially, a small area of scalp becomes red, crusted and irritable; crusting and superficial pustulation overlie a moist, eroded surface (Fig. 66.47). As the condition extends, areas of activity coexist with areas of scarring. Squamous carcinoma has developed in the scars [5].

Differential diagnosis. Pyogenic and yeast infection is excluded by bacteriological examination and the lack of response to antibacterial or antifungal agents. Biopsy may be necessary to exclude pustular psoriasis, cicatricial pemphigoid, 'irritated' solar keratosis or squamous cell carcinoma.

Treatment. The stronger topical corticosteroids (e.g. 0.05% clobetasol propionate) will suppress the inflammatory changes. Gradual reduction in the potency of topical steroid over a 6-month period may result in cure. Maintenance therapy with sun protection and intermittent moderate potency steroid can provide

long-term relief. Ikeda *et al.* [6] suggested oral zinc sulphate, and Boffa [7] suggested topical calcipotriol can be curative in some cases.

References

1 Caputo R, Veraldi S. Erosive pustular dermatosis of the scalp. *J Am Acad Dermatol* 1993; **28**: 96–8.
2 Pye RJ, Peachey RD, Burton JL. Erosive pustular dermatosis of the scalp. *Br J Dermatol* 1979; **100**: 559–66.
3 Grattan CE, Peachey RD, Boon A. Evidence for a role of local trauma in the pathogenesis of erosive pustular dermatosis of the scalp. *Clin Exp Dermatol* 1988; **13**: 7–10.
4 Rongioletti F, Delmonte S, Rossi ME *et al.* Erosive pustular dermatosis of the scalp following cryotherapy and topical tretinoin for actinic keratoses. *Clin Exp Dermatol* 1999; **24**: 499–500.
5 Lovell CR, Harman RR, Bradfield JW. Cutaneous carcinoma arising in erosive pustular dermatosis of the scalp. *Br J Dermatol* 1980; **103**: 325–8.
6 Ikeda M, Arata J, Isaka H. Erosive pustular dermatosis of the scalp successfully treated with oral zinc sulphate. *Br J Dermatol* 1982; **106**: 742–3.
7 Boffa MJ. Erosive pustular dermatosis of the scalp successfully treated with calcipotriol cream. *Br J Dermatol* 2003; **148**: 593–5.

Necrobiosis lipoidica, granuloma annulare and sarcoidosis

Necrobiosis lipoidica occurs in 0.2–0.3% of cases of diabetes mellitus, and approximately 70% of patients with necrobiosis have diabetes. The diabetic cases begin in childhood or early adult life, and the non-diabetic cases rather later and usually in women.

The oval atrophic plaques classically occur on the shins but may be seen on other parts of the body, including the scalp. The patches are glazed and yellowish, often with conspicuous telangiectases. Scarring may be dense. The clinical features in the scalp vary from large plaques of cicatricial alopecia to multiple small areas of scarring [1].

An atrophic form affecting predominantly the forehead and the scalp has been described [2]. In general, the differential diagnosis is from sarcoidosis and granuloma annulare [3,4].

Cutaneous sarcoidosis may produce plaques or nodules on the scalp as well as both cicatricial and non-cicatricial alopecia (Fig. 66.48) [5]. Affected areas may itch. There is a marked preponderance of females amongst reported cases. The histology is distinctive, with non-caseating granulomatous inflammation [3].

References

1 Gartmann H, Dickmans-Burmeister D. [Unusual skin changes in a 4 year old child with diabetes mellitus 'necrobiosis diabetica acuta parvimaculata']. *Hautarzt* 1969; **20**: 265–70.
2 Jones EW. Necrobiosis lipoidica presenting on the face and scalp. An account of 29 patients and a detailed consideration of recent histochemical findings. *Trans St Johns Hosp Dermatol Soc* 1971; **57**: 202–20.
3 Katta R, Nelson B, Chen D *et al.* Sarcoidosis of the scalp: a case series and review of the literature. *J Am Acad Dermatol* 2000; **42**: 690–2.
4 Wong GA, Verbov JL. Subcutaneous granuloma annulare of the scalp in a diabetic child. *Pediatr Dermatol* 2002; **19**: 276–7.
5 Sinclair RD, Banfield C, Dawber RPR. *Handbook of Diseases of the Hair and Scalp*. Oxford: Blackwell Science, 1999.

Lichen sclerosus

Lichen sclerosus of the scalp is rare (Fig. 66.49). It may cause an extensive cicatricial alopecia that is relatively nondescript clinically, but which has all the characteristic histological features. Associated lesions are usually found on the trunk and vulva [1,2].



Fig. 66.48 Sarcoidosis of the scalp.



Fig. 66.49 Lichen sclerosus.

References

1 Foulds IS. Lichen sclerosus et atrophicus of the scalp. *Br J Dermatol* 1980; **103**: 197–200.
2 Sinclair RD, Banfield C, Dawber RPR. *Handbook of Diseases of the Hair and Scalp*. Oxford: Blackwell Science, 1999.

Developmental defects and hereditary disorders

Scarring follicular keratosis

Numerous syndromes have been described and elaborately named, all of them characterized by keratosis pilaris associated with some degree of inflammatory change leading to destruction of the affected follicles [1].

Only detailed clinical and genetic studies can provide the essential facts to allow reliable differentiation of syndromes that some authorities regard as forms or degrees of a single state and others accept as distinct entities. For the time being, the reported cases can be conveniently classified in three groups; in addition, certain apparently well-defined entities can be recognized.

1 *Atrophoderma vermiculata* (acne vermiculata, folliculitis ulerythematosa reticulata). There is honeycomb atrophy of the cheeks. Scarring alopecia may occur, but rarely.
2 *Keratosis pilaris atrophicans faciei* (ulerythema oophryogenes). The process is more or less confined to the eyebrow region.
3 *Keratosis follicularis spinulosa decalvans*. Keratosis pilaris of variable extent is associated with cicatricial alopecia [2].

All these conditions are assumed to be genetically determined, although many cases occur sporadically. Such genetic data as are available are considered under the individual forms.

Clinical features. Atrophoderma vermiculata usually begins in childhood. Follicular plugs, often in the pre-auricular regions, are gradually shed to leave reticulate atrophy. On the face, the extent of the process is variable. Exceptionally, cicatricial alopecia of the scalp may be associated [3].

Keratosis pilaris atrophicans faciei (ulerythema oophryogenes) is present from early infancy. Erythema and horny plugs begin in the outer halves of the eyebrows, which they eventually destroy, and then advance medially and to a variable extent on the cheeks. Involvement of the scalp has apparently not been reported in cases in which the eyebrows are predominantly involved. However, there are reports of cases to which this diagnosis has been applied, but which appear to be more rationally classified in one of the other categories, in which alopecia has occurred. Such cases emphasize the need for improved diagnostic criteria.

Keratosis follicularis spinulosa decalvans is also a genetically heterogeneous syndrome. In some families it is inherited in an X-linked fashion with a mutation in the spermidine/spermine N(1)acetyltransferase gene (*SSAT*) at Xp22.1 [4,5]. In other families it appears to follow autosomal dominant inheritance [6]. The clinical presentation includes extensive keratosis pilaris and progressive cicatricial alopecia. Keratosis pilaris begins in infancy or childhood, often on the face. Ultimately, it may be confined to the face or to face and limbs, or may be more or less universal. The cicatricial alopecia may occur from early childhood or later, and may be localized or extensive, involving eyebrows and eyelashes as well as the scalp. Other features may include facial erythema, photophobia and ophthalmitis, and palmar–plantar keratoderma [2,7,8].

Treatment. Only symptomatic measures are available. Topical and systemic retinoids, topical steroids, antibiotics and methotrexate have been tried but without notable success. Retinoic acid deserves a trial. The status of oral retinoids remains controversial, although anecdotal response has been noted.

References

1 Rand RE, Arndt KA. Follicular syndromes with inflammation and atrophy. In: Fitzpatrick TB, Eisen AZ, Wolff K *et al.*, eds. *Dermatology in General Medicine*, 3rd edn. New York: McGraw-Hill, 1987: 717–32.
2 Rand R, Baden HP. Keratosis follicularis spinulosa decalvans. Report of two cases and literature review. *Arch Dermatol* 1983; **119**: 22–6.
3 Fisher AA. Keratosis pilaris rubra atrophicans faciei with diffuse alopecia of the scalp. *Arch Dermatol* 1957; **75**: 283–9.
4 Oosterwijk JC, Nelen M, van Zandvoort PM *et al.* Linkage analysis of keratosis follicularis spinulosa decalvans, and regional assignment to human chromosome Xp21.2-p22.2. *Am J Hum Genet* 1992; **50**: 801–7.
5 Gimelli G, Giglio S, Zuffardi O *et al.* Gene dosage of the spermidine/spermine N(1)-acetyltransferase (SSAT) gene with putrescine accumulation in a patient with a Xp21.1p22.12 duplication and keratosis follicularis spinulosa decalvans (KFSD). *Hum Genet* 2002; **111**: 235–41.
6 Oosterwijk JC, Richard G, van der Wielen MJ *et al.* Molecular genetic analysis of two families with keratosis follicularis spinulosa decalvans: refinement of gene localization and evidence for genetic heterogeneity. *Hum Genet* 1997; **100**: 520–4.
7 Baden HP, Byers HR. Clinical findings, cutaneous pathology, and response to therapy in 21 patients with keratosis pilaris atrophicans. *Arch Dermatol* 1994; **130**: 469–75.
8 Bellet JS, Kaplan AL, Selim MA *et al.* Keratosis follicularis spinulosa decalvans in a family. *J Am Acad Dermatol* 2008; **58**: 499–502.

Porokeratosis of Mibelli

Porokeratosis of Mibelli commonly begins in childhood but may first appear at any age. It is most frequent on the limbs, particularly the hands and feet, the neck, the shoulders and the face, but may occur anywhere, including the scalp [1]. The initial lesion is a crateriform horny papule that gradually extends to form a circinate or irregular atrophic plaque with a raised horny margin, which may be surmounted by a furrow from which the lamina of horn projects. In the scalp there is loss of hair in the atrophic phase.

Reference

1 Sehgal VN, Dube B. Porokeratosis (Mibelli) in a family. *Dermatologica* 1967; **134**: 219–24.

Incontinentia pigmenti

Cicatricial alopecia has been present in at least 25% of reported cases of incontinentia pigmenti; it appears in early infancy and ceases to extend after a variable period of up to 2 years, but the loss of hair is permanent. Other hair defects present in some cases have been hypoplasia of the eyebrows and eyelashes, and woolly hair naevus of the scalp [1].

Reference

1 Wiklund DA, Weston WL. Incontinentia pigmenti. A four-generation study. *Arch Dermatol* 1980; **116**: 701–3.

Generalized follicular hamartoma

Cicatricial alopecia beginning in childhood was a feature of a syndrome described by Mehregan and Hardin [1]. Their patient was a woman aged 23 years. From infancy, she had widespread horny plugs over the trunk and limbs and small pits on the palms and soles. She later developed cicatricial alopecia, in which, from the age of 8 years, appeared follicular tumours. The tumours of the scalp were proliferating trichilemmal cysts. The lesions of palms and soles showed funnel-shaped dilatation of sweat ducts, which were plugged with parakeratotic material containing acid mucopolysaccharide. Ridley and Smith [2] described this entity with alopecia and myasthenia gravis.

References

1 Mehregan AH, Hardin I. Generalized follicular hamartoma. Complicated by multiple proliferating trichilemmal cysts and palmar pits. *Arch Dermatol* 1973; **107**: 435–8.

2 Ridley CM, Smith N. Generalized hair follicle hamartoma associated with alopecia and myasthenia gravis: report of a second case. *Clin Exp Dermatol* 1981; **6**: 283–9.

Epidermolysis bullosa

The term epidermolysis bullosa is applied to a group of distinct, genetically determined disorders characterized by the formation of bullae of skin, and often also of mucous membranes, in response to trauma, or spontaneously (see Chapter 39). Atrophic alopecia is a feature of generalized atrophic benign epidermolysis bullosa (GABEB) [1,2], a group of non-lethal hemidesmosomal forms. Mutations in several genes may cause GABEB including *COL17A1*, *LAMA3*, *LAMB3* and *LAMC2* (MIM #226650). Cicatricial alopecia may also occur in recessive dystrophic epidermolysis bullosa.

References

1 Hintner H, Wolff K. Generalized atrophic benign epidermolysis bullosa. *Arch Dermatol* 1982; **118**: 375–84.

2 Darling TN, Bauer JW, Hintner H *et al*. Generalized atrophic benign epidermolysis bullosa. *Adv Dermatol* 1997; **13**: 87–119; discussion 20.

Cleft lip-palate, ectodermal dysplasia and syndactyly

This rare or rarely recognized syndrome is probably hereditary, and determined by an autosomal recessive gene. The constant features of the syndrome are mental retardation, cleft palate, genital hypoplasia, cicatricial alopecia, defective teeth and syndactyly [1].

Reference

1 Bowen P, Armstrong HB. Ectodermal dysplasia, mental retardation, cleft lip/palate and other anomalies in three sibs. *Clin Genet* 1976; **9**: 35–42.

Polyostotic fibrous dysplasia

The progressive enlargement over a period of 10 years of a bald patch present since childhood was shown histologically to be caused by the replacement of the follicles by coils of fibrous tissue. The patient had polyostotic fibrous dysplasia [1].

Reference

1 Shelley WB, Wood MG. Alopecia with fibrous dysplasia and osteomas of skin. A sign of polyostotic fibrous dysplasia. *Arch Dermatol* 1976; **112**: 715–9.

Infections

A.G. Messenger, pp. 66.52–66.53

Tinea capitis

See Chapter 36.

Infestations

See Chapter 38.

Syphilis

Hair loss occurs in approximately 10% of cases of secondary syphilis and may be the presenting feature [1,2]. The hair loss typically has a 'moth-eaten' appearance but may be diffuse in nature [3]. Other features of secondary syphilis are present in most cases, particularly lymph node enlargement and hepatomegaly, but hair loss has been reported as the only sign of the disease [4]. Histological features include an increase in catagen and telogen forms, and a peribulbar lymphocytic infiltrate, similar to the changes seen in alopecia areata [3]. Additional features in syphilis include lymphocytic infiltration of the isthmus region, parabulbar lymphoid aggregates and the presence of plasma cells within the infiltrate.

The serpiginous nodulo-squamous syphilide of tertiary syphilis may affect the scalp, and the syphilitic gumma is a cause of scarring alopecia.

Human immunodeficiency virus (see Chapter 35)

A variety of alterations in hair growth have been described in patients with HIV infection. Telogen effluvium is a common cause of hair loss [5]. Causes include chronic HIV-1 infection itself, secondary infections, nutritional deficiencies and drugs. Hair loss on the body as well as the scalp has been reported with several antiretroviral drugs, particularly indinavir [6] and other protease inhibitors. There are also reports of alopecia areata occurring in patients with HIV infection [7–9].

There are several reports of hypertrichosis of the eyelashes (eyelash trichomegaly) in HIV infection [9–11]. The cause of this striking and unusual feature is not known. It is usually associated with advanced disease and has been noted to regress with antiretroviral treatment [11].

Straightening of the hair is a common feature of HIV infection in black patients [12].

Various forms of folliculitis are seen in HIV infection, including acneiform eruptions, staphylococcal folliculitis and eosinophilic pustular folliculitis.

Leprosy

Loss of eyebrow and body hair may occur in lepromatous leprosy but the scalp is rarely involved.

References

1 Kennedy C. Syphilis presenting as hair loss. *BMJ* 1976; **2**: 854.

2 Hira SK, Patel JS, Bhat SG *et al*. Clinical manifestations of secondary syphilis. *Int J Dermatol* 1987; **26**: 103–7.

3 Lee JY, Hsu ML. Alopecia syphilitica, a simulator of alopecia areata: histopathology and differential diagnosis. *J Cutan Pathol* 1991; **18**: 87–92.

4 Cuozzo DW, Benson PM, Sperling LC *et al*. Essential syphilitic alopecia revisited. *J Am Acad Dermatol* 1995; **32**: 840–3.

5 Smith KJ, Skelton HG, DeRusso D *et al*. Clinical and histopathologic features of hair loss in patients with HIV-1 infection. *J Am Acad Dermatol* 1996; **34**: 63–8.

6 Calista D, Boschini A. Cutaneous side effects induced by indinavir. *Eur J Dermatol* 2000; **10**: 292–6.

7 Ostlere LS, Langtry JA, Staughton RC *et al*. Alopecia universalis in a patient seropositive for the human immunodeficiency virus. *J Am Acad Dermatol* 1992; **27**: 630–1.

8 Stewart MI, Smoller BR. Alopecia universalis in an HIV-positive patient: possible insight into pathogenesis. *J Cutan Pathol* 1993; **20**: 180–3.

9 Grossman MC, Cohen PR, Grossman ME. Acquired eyelash trichomegaly and alopecia areata in a human immunodeficiency virus-infected patient. *Dermatology* 1996; **193**: 52–3.

10 Casanova JM, Puig T, Rubio M. Hypertrichosis of the eyelashes in acquired immunodeficiency syndrome. *Arch Dermatol* 1987; **123**: 1599–601.

11 Kaplan MH, Sadick NS, Talmor M. Acquired trichomegaly of the eyelashes: a cutaneous marker of acquired immunodeficiency syndrome. *J Am Acad Dermatol* 1991; **25**: 801–4.

12 Leonidas JR. Hair alteration in black patients with the acquired immunodeficiency syndrome. *Cutis* 1987; **39**: 537–8.

Artefactual alopecia

D.A.R. de Berker, pp. 66.53–66.54

Cosmetic alopecia

Cosmetic practices can result in damage to the hair shaft or the scalp. The application of heat (e.g. from heated tongs) to damp hair may cause breakage due to the formation of bubbles in the hair shaft ('bubble hair') [1]. Fracture of hair shafts, which can be extensive, may also be caused by overuse of chemical treatments such as permanent waves and relaxers.

Traction alopecia

Traction alopecia is brought about by hair styles that impose sustained pulling on the hair roots. The clinical features in the many variants of this syndrome include folliculitis, hair casts [2], reduction in hair density with vellus hairs and sometimes broken hairs in the affected areas, and eventually scarring alopecia. It can be associated with headache, relieved when the hair is loosened [3]. The pattern of the hair loss is often distinctive and reflects the distribution of the traction.

Traction alopecia is seen most commonly in Afro-Caribbean hair styles where the hair is tightly braided. The hair loss commonly begins in the temporal regions and in front of and above the ears, but may involve other parts of the scalp (Fig. 66.50), particularly where 'corn row' patterns are adopted. Problems typically start in childhood, where they may initially be reversible [4]. A degree of temporal thinning may also be part of a genetic hair pattern seen in those with no traction.

Pony tails, hair twisting in Sikh boys [5], and tight scarf styles can all result in hair loss [6].

Treatment. The patient, or parents of affected children, need to be educated to adopt hair styles that do not pull the hair tight [7]. Where there is inflammation, a mild topical steroid can be helpful, but is not a substitute for a non-traction hair style.



Fig. 66.50 Traction alopecia from braiding.

References

1 Gummer CL. Bubble hair: a cosmetic abnormality caused by brief, focal heating of damp hair fibres. *Br J Dermatol* 1994; **131**: 901–3.
2 Rollins TG. Traction follicultis with hair casts and alopecia. *Am J Dis Child* 1961; **101**: 639–40.
3 Blau JN. Ponytail headache: a pure extracranial headache. *Headache* 2004; **44**: 411–3.
4 Hantash BM, Schwartz RA. Traction alopecia in children. *Cutis* 2003; **71**: 18–20.
5 Singh G. Letter: Traction alopecia in Sikh boys. *Br J Dermatol* 1975; **92**: 232–3.
6 Malhotra YK, Kanwar AJ. Tractional alopecia among Libyan women. *Arch Dermatol* 1980; **116**: 987.
7 Wilborn WS. Disorders of hair growth in African Americans. In: Olsen E, ed. *Disorders of Hair Growth*, 2nd edn. New York: McGraw-Hill, 2003: 497–518.

Medical trauma

There are instances where medical intervention may result in scalp trauma and be implicated in scarring alopecia. Scalp electrodes or infusion [1] or forceps delivery in the neonate can result in trauma. Uterine rings have also been reported as a cause of infant scalp problems [2]. Marks from such interventions need to be distinguished from aplasia cutis which can sometimes be the underlying diagnosis [3].

Interventions in adulthood, directly through scalp and brain surgery or indirectly through local embolization procedures, can result in scarring. Adler *et al.* [4] described a case in which ischaemic necrosis of the occipital scalp occurred following embolization and surgery for a large convexity meningioma.

Pressure ischaemia can occur during intensive care or gynaecological surgery in the Trendelenburg position [5]. In one large clinic, over a period of 3 years, 60 cases of occipital pressure alopecia were observed after open-heart surgery [6]. In 29 of these cases, the hair loss was permanent. Temporary alopecia followed prolonged pressure on the scalp by a foam rubber ring used to prevent such an occurrence [7].

References

1 Strong AM. Extensive cicatrical alopecia following scalp vein infusion. *Clin Exp Dermatol* 1979; **4**: 197–9.
2 Prendiville JS, Esterly NB. Halo scalp ring: a cause of scarring alopecia. *Arch Dermatol* 1987; **123**: 992–3.
3 Brown ZA, Jung AL, Stenchever MA. Aplasia cutis congenita and the fetal scalp electrode. *Am J Obstet Gynecol* 1977; **129**: 351–2.
4 Adler JR, Upton J, Wallman J *et al.* Management and prevention of necrosis of the scalp after embolization and surgery for meningioma. *Surg Neurol* 1986; **25**: 357–60.
5 Abel RR. Postoperative (Pressure) Alopecia. *Anesthesiology* 1964; **25**: 869–71.
6 Lawson NW, Mills NL, Ochsner JL. Occipital alopecia following cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 1976; **71**: 342–7.
7 Patel KD, Henschel EO. Postoperative alopecia. *Anesth Analg* 1980; **59**: 311–3.

Chronic radiodermatitis [1,2]

Roentgen discovered X-rays in 1895. X-ray epilation of the face for hirsutism was frequently employed during the first two decades of the 20th century and, although Schultz [3] condemned this treatment, it continued to be so widely used that Cipollaro and Einhorn [4] entitled their paper: 'The use of X-rays for the treatment of hypertrichosis is dangerous'.

X-ray epilation for the treatment of scalp ringworm was introduced in Paris in 1904. The discovery of griseofulvin in 1958 gradually made X-ray epilation unnecessary, but it has been estimated that between 1904 and 1959 some 300 000 children throughout the

world were treated with X-rays for ringworm of the scalp. Correct dosage did not cause toxicity; however, technical errors were frequent, from inadequate and poorly calibrated apparatus. The treatment produced complete epilation in approximately 3 weeks and regrowth after 2 months. The follow-up of 2043 patients treated in childhood showed a higher incidence of cancer in the patients than in a control group [1]. Radiodermatitis of the scalp may occur also as an unavoidable consequence of skin damage during the treatment of both internal malignant disease and malignant disease of the skin.

In chronic radiodermatitis, the epidermis is generally atrophic, with loss of hair follicles and sebaceous glands, but there are also irregular areas of acanthosis. Degenerative changes and nuclear abnormalities are frequent in the epidermis. Dermal collagen stains irregularly. Superficial small vessels are telangiectatic, but deeper vessels are partially or completely occluded by fibrosis.

Clinical features. The development of a basal cell carcinoma in middle age or later in an area of the scalp should lead the dermatologist to enquire about X-ray epilation for ringworm in childhood [5]. In other cases, the patient complains of hair loss, which is apparently accentuated in certain areas, and these areas are found to show both AGA and reduction of follicle population as a result of the earlier radiation.

Chronic radiodermatitis produced by radiation therapy of a malignant tumour of the scalp presents a circumscribed area of cicatricial alopecia. Radiation necrosis may simulate a recurrence of carcinoma, but the edges of the necrotic ulcer are not raised. The diagnosis should be confirmed by a biopsy. Superficial X-ray of Grenz ray type does not penetrate deeply enough to damage scalp follicles. Malignant tumours arising in radiodermatitis should be excised [6].

References

1 Albert RE, Omran AR. Follow-up study of patients treated by X-ray epilation for tinea capitis. I. Population characteristics, posttreatment illnesses, and mortality experience. *Arch Environ Health* 1968; **17**: 899–918.

2 Getzrow PL. Chronic radiodermatitis and skin cancer. In: Andrade R, Gumport SL, Popkin GL *et al.*, eds. *Cancer of the Skin*. Philadelphia: Saunders, 1976: 458–67.

3 Schultz F. *The X-ray Treatment of Skin Diseases*. London: Rebman, 1912.

4 Cipollaro AC, Einhorn MB. The use of X-rays for the treatment of hypertrichosis is dangerous. *JAMA* 1947; **135**: 349–54.

5 Ridley CM. Basal cell carcinoma following X-ray epilation of the scalp. *Br J Dermatol* 1962; **74**: 222–3.

6 Conway H, Hugo NE. Radiation dermatitis and malignancy. *Plast Reconstr Surg* 1966; **38**: 255–68.

Trichotillomania (see also Chapter 64)

A.G. Messenger, pp. 66.54–66.57

Trichotillomania is a behavioural disorder characterized by compulsive hair pulling. It presents as a pattern of hair loss, often bizarre, with no clear biological or overt traumatic explanation [1]. Compulsive hair rubbing (trichoteiromania [2]) and hair cutting (trichotemnomania [3]) fall into the same general category.

Pathology. Microscopy may be undertaken of the hair or of a scalp biopsy. Hairs may be of different length in an affected area.

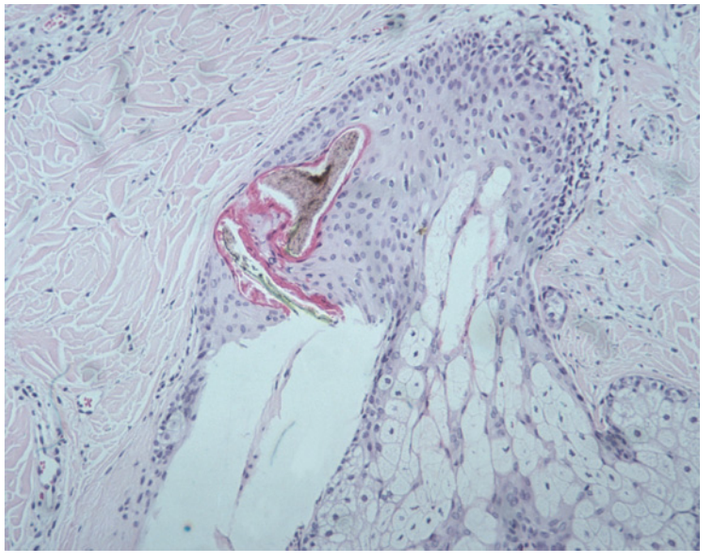


Fig. 66.51 Histology of trichotillomania, showing fragmentation of the hair shaft.

They may be broken, where trauma has snapped the shaft, or be tapered, where trauma is in the form of plucking. The scalp itself is usually clinically normal except in the instances where the trauma is rubbing or scratching. In these instances there are often scalp signs and the problem may present primarily as a scalp dermatosis—even if it is wholly artefactual. Rubbing can also lead to hair breakage or interfere with the normal anagen cycle without specifically altering the hair shaft.

Dermoscopy of the scalp may help differentiate between trichotillomania and alopecia areata, where follicular orifices may appear as yellow dots [4].

Scalp histology varies according to the severity and duration of the hair plucking. Numerous empty canals are the most consistent feature. Some follicles are severely damaged; there are clefts in the hair matrix, the follicular epithelium is separated from the connective tissue sheath, and there are intraepithelial and perifollicular haemorrhages and intrafollicular pigment casts (Fig. 66.51) [5]. Injured follicles may form only soft, twisted hairs—a process that has been described as a separate entity under the name of trichomalacia [6]. Many follicles are in catagen, with very few or no follicles in telogen. Some dilated follicular infundibula contain horny plugs [7].

Aetiology and psychopathology. Trichotillomania occurs in two main forms. In infants and young children it is usually a habit akin to thumb-sucking and nail biting. It seems slightly more common in boys and usually resolves spontaneously or with minimal treatment. Parents who have not noticed hair-pulling behaviour in their offspring may deny the diagnosis. In older age groups, adolescents and adults, trichotillomania is seen predominantly in females, with women outnumbering men by up to 7:1, and evidence of some form of psychological or behavioural stress is often apparent [8]. The American Psychiatric Association classifies trichotillomania as an impulse control disorder, in which there is an irresistible desire to pull out the hair. This process results in an

Table 66.5 DSM-IV criteria for trichotillomania.

Recurrent pulling out of one's hair resulting in noticeable hair loss
An increasing sense of tension immediately before pulling out the hair or when attempting to resist the behaviour
Pleasure, gratification or relief when pulling out the hair
The disturbance is not better accounted for by another mental disorder and is not due to a general medical condition (e.g. a dermatological condition)
The disturbance causes clinically significant distress or impairment in social, occupational or other important areas of functioning

instant release of tension and sense of relief. The diagnostic criteria are given in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), and are listed in Table 66.5, although not all patients with trichotillomania fit these criteria.

Trichotillomania shares some features of obsessive–compulsive disorder (OCD), but some authorities consider it may be the result of a number of psychopathologies including OCD, personality disorders, body dysmorphophobic disorders, mental retardation and psychosis. There is an extensive psychiatric literature on trichotillomania, but this may be biased because psychiatric help is likely to be sought only in those patients who accept that it is a self-inflicted problem. This is not true of all patients presenting to dermatologists.

Clinical features. In young children, the hair-pulling tic develops gradually and unconsciously. Hair is plucked most frequently from one frontoparietal region. This results in a patch of hair loss, often in a bizarre or angular pattern, in which the hairs are twisted and broken at various distances from the clinically normal scalp. Older patients present with an area of scalp on which the hair has been reduced to coarse stubble uniformly 2.5–3 mm long. The plucked area may be asymmetrical or cover the entire scalp apart from the margin (Fig. 66.52). It is unusual for hair to be lost completely within the affected area (in contrast with alopecia areata). The scalp skin appears normal. Over time the extent of hair loss can vary, and hair growth may recover temporarily.

Hair in sites other than the scalp can also be affected, such as eyelashes, eyebrows and beard. Exceptionally, the patient may pluck hair also, or only, from other regions of the body, such as the mons pubis and perianal region.

A hairball (trichobezoar) is a rare accompaniment of trichotillomania in those who also eat the plucked hair (trichophagia) [9].

Differential diagnosis. The minor form in young children can be confused with ringworm or with alopecia areata. In ringworm, the texture of the infected hairs is abnormal and the scalp surface may be scaly. Alopecia areata may be difficult to exclude with certainty at the first examination, but the course of the condition usually establishes the correct diagnosis. Unlike alopecia areata, it is unusual for hair to be lost completely in trichotillomania and, in contrast with exclamation mark hairs, the broken hairs of trichotillomania are firmly anchored in the scalp. Where doubt remains, dermoscopy [4] or a skin biopsy will usually establish the correct diagnosis. However, there are reports of the coexistence of alopecia areata and trichotillomania [8,10]. In rare cases, genetic disorders characterized by increased hair fragility, such as monilethrix, may resemble trichotillomania and should be excluded by hair microscopy.



Fig. 66.52 Trichotillomania. Characteristic 'tonsure' pattern with scalp margin hair spared.

Treatment. The establishment of a relationship between the physician and the patient, or with the parents of an affected child, is an important step in management of trichotillomania. A confident diagnosis is essential, but this is not always easy and may require observation over time and sometimes a scalp biopsy. The habit tic in young children is often self-limiting, but input from a paediatric psychologist can be very helpful. Trichotillomania in adolescents and adults is a different proposition, and can be intractable [11]. Patients with insight should be referred to a psychiatrist or clinical psychologist. A number of psychotherapeutic approaches have been used, particularly behavioural therapy aimed at habit reversal, and pharmacotherapy using clomipramine or selective serotonin-reuptake inhibitors (SSRIs), but none is uniformly successful. A systematic review of published studies found that habit-reversal therapy is superior to drug treatment [12]. Clomipramine is more effective than placebo but there was no convincing benefit from treatment with SSRIs.

Some patients are helped by contact with fellow sufferers, and there are several patient support groups and Internet websites devoted to trichotillomania. Patients who fail to admit the self-inflicted nature of the hair loss present particular difficulties, as they are unlikely to accept psychiatric referral and, like dermatitis artefacta, a confrontational approach will probably be unsuccessful. Management should be aimed at helping the patient recognize the cause for themselves. This can be a long and slow process requiring skill and empathy on the part of the physician.

References

1 Hautmann G, Hercogova J, Lotti T. Trichotillomania. *J Am Acad Dermatol* 2002; **46**: 807–21; quiz 22–6.
2 Freyschmidt-Paul P, Hoffmann R, Happle R. Trichoteiromania. *Eur J Dermatol* 2001; **11**: 369–71.
3 Happle R. Trichotemnomania: obsessive-compulsive habit of cutting or shaving the hair. *J Am Acad Dermatol* 2005; **52**: 157–9.
4 Ross EK, Vincenzi C, Tosti A. Videodermoscopy in the evaluation of hair and scalp disorders. *J Am Acad Dermatol* 2006; **55**: 799–806.
5 Mehregan AH. Trichotillomania. A clinicopathologic study. *Arch Dermatol* 1970; **102**: 129–33.
6 Lachapelle JM, Pierard GE. Traumatic alopecia in trichotillomania: a pathogenic interpretation of histologic lesions in the pilosebaceous unit. *J Cutan Pathol* 1977; **4**: 51–67.
7 Muller SA. Trichotillomania: a histopathologic study in sixty-six patients. *J Am Acad Dermatol* 1990; **23**: 56–62.
8 Tay YK, Levy ML, Metry DW. Trichotillomania in childhood: case series and review. *Pediatrics* 2004; **113**: e494–8.
9 Bouwer C, Stein DJ. Trichobezoars in trichotillomania: case report and literature overview. *Psychosom Med* 1998; **60**: 658–60.
10 Trueb RM, Cavegn B. Trichotillomania in connection with alopecia areata. *Cutis* 1996; **58**: 67–70.
11 Cohen LJ, Stein DJ, Simeon D *et al*. Clinical profile, comorbidity, and treatment history in 123 hair pullers: a survey study. *J Clin Psychiatry* 1995; **56**: 319–26.
12 Bloch MH, Landeros-Weisenberger A, Dombrowski P *et al*. Systematic review: pharmacological and behavioral treatment for trichotillomania. *Biol Psychiatry* 2007; **62**: 839–46.

Scaling disorders of the scalp

Scaling of the scalp is a feature of a number of clinical disorders, including dandruff (pityriasis capitis), seborrhoeic dermatitis, psoriasis and pityriasis amiantacea. These disorders show overlapping clinical and histological features and, when confined to the scalp, it can be difficult to distinguish between them. Scalp scaling is also seen in other inflammatory dermatoses such as atopic dermatitis, tinea capitis, discoid lupus erythematosus and cutaneous T-cell lymphoma.

Pityriasis capitis

Pityriasis capitis, or dandruff, and seborrhoeic dermatitis confined to the scalp are generally regarded as the same entity, with dandruff representing the mild non-inflammatory end of a spectrum of scalp scaling. Its peak incidence and severity are reached at the age of approximately 20 years, and it becomes less frequent after 50 years of age. At age 20 years, some 50% of white people are affected to some degree. Although previously thought to be uncommon in children, an epidemiological study from Australia found that approximately 40% of children under the age of 6 years showed at least mild pityriasis capitis, and 10% of neonates had seborrhoeic dermatitis of the scalp [1].

Aetiology [2]. It is reasonably well established that pityriasis capitis and seborrhoeic dermatitis are related, in some way, to the presence on the skin of lipophilic yeasts of the genus *Malassezia*, previously known as *Pityrosporum*. This idea, which evolved in the 19th century when these organisms were first identified [3–5], is based largely on the clinical observations of improvement with antifungal treatment. For a time during the 1960s and 1970s the microbial hypothesis was disputed [6], but it became re-established with the advent of azole antifungal agents [7–9]. Although there is no numerical relationship between colonization of the scalp by *Malasezzia* and seborrhoeic dermatitis the treatment of patients with seborrhoeic dermatitis with azole antifungal agents such as ketoconazole is associated with improvement of the rash, a reduction in *Malassezia*, and relapse as the skin is recolonized following treatment [10]. As *Malassezia* is present on normal skin there must be other factors involved that lead to scalp scaling. Possible explanations have included a direct inflammatory effect of free fatty acids released by the organisms from metabolism of sebaceous triglycerides and individual susceptibility [10].

Clinical features. Small, white or grey scales accumulate on the surface of the scalp in localized, more or less segmental patches or more diffusely. After removal with an effective shampoo, the scales form again within 4–7 days. The condition first becomes a cosmetic problem during the second and third decades, but there are long- and short-term variations in its severity, without obvious cause. There are also variations in the ease with which the scales become detached and drift unaesthetically among the hair shafts or fall on the collar and shoulders. Although pityriasis usually clears spontaneously during the fifth or sixth decade, it may persist in old age. Pityriasis merges, almost imperceptibly, into seborrhoeic dermatitis where signs of inflammation and itching are also present, and other skin sites may be involved. Pruritus is not a feature of simple pityriasis.

Diagnosis. Asymptomatic scalp scaling in children also occurs in pediculosis and in tinea capitis. The latter is typically associated with broken hair shafts and patchy hair loss, but these features may be absent in carriers of anthropophilic dermatophyte infections. Pediculosis should also be considered in adults with scalp scaling. Other than in the neonatal period, seborrhoeic dermatitis is uncommon in children, and psoriasis should be considered in the presence of significant scalp inflammation. Differentiation between seborrhoeic dermatitis and scalp psoriasis can be difficult at any age. Psoriasis is suggested by more demarcated plaques, extension of lesions beyond the hairline and the silvery character of the scaling. Occasionally, atopic dermatitis is confined to the scalp, when pruritus is usually a major feature. Profuse, adherent silvery scale should suggest pityriasis amiantacea.

Treatment. Pityriasis in its milder forms is a physiological process. The object of treatment is to control it at the lowest possible cost and inconvenience to the patient, appreciating that any procedure found to be effective will need to be repeated at regular intervals.

Shampoos containing the antiyeast agents ketoconazole or zinc pyrithione are effective in most cases of pityriasis capitis. One controlled trial reported an excellent response in 88% of subjects using ketoconazole [11]. Another study showed a 71% reduction in the dandruff score after 4 weeks of treatment with ketoconazole shampoo and a 67% reduction in subjects using a shampoo containing zinc pyrithione [12]. The scaling will return if treatment is discontinued, but the frequency of relapse can be reduced by prophylactic treatment (e.g. once-weekly treatment with ketoconazole shampoo [11]). Shampoos containing selenium sulphide or

tar have also been widely used to treat pityriasis capitis. Topical steroids may be used in patients with seborrhoeic dermatitis who do not respond to a shampoo. Salicylic acid-containing preparations (e.g. sulphur and salicylic acid cream) can be helpful for heavy scaling.

References

1 Foley P, Zuo Y, Plunkett A *et al.* The frequency of common skin conditions in preschool-aged children in Australia: seborrheic dermatitis and pityriasis capitis (cradle cap). *Arch Dermatol* 2003; **139**: 318–22.
2 Hay RJ, Graham-Brown RA. Dandruff and seborrhoeic dermatitis: causes and management. *Clin Exp Dermatol* 1997; **22**: 3–6.
3 Malassez L. Notes sur le champignon de la pilade. *Arch Physiol Normal Pathol* 1874; 1.
4 Unna PG. Seborrhoeic eczema. *J Cutan Dis* 1887; **5**.
5 Moore M, Kile RL, Engman MF. *Pityrosporum ovale* (Bacillus of Unna, Spore of Malassez). Cultivation and possible role in seborrhoeic dermatitis. *Arch Dermatol Syphilogr* 1936; **33**.
6 Leyden JJ, McGinley KJ, Kligman AM. Role of microorganisms in dandruff. *Arch Dermatol* 1976; **112**: 333–8.
7 Aron-Brunetiere R, Dompmartin-Pernot D, Drouhet E. Treatment of pityriasis capitis (dandruff) with econazole nitrate. *Acta Derm Venereol* 1977; **57**: 77–80.
8 Ford GP, Farr PM, Ive FA *et al.* The response of seborrhoeic dermatitis to ketoconazole. *Br J Dermatol* 1984; **111**: 603–7.
9 Shuster S. The aetiology of dandruff and the mode of action of therapeutic agents. *Br J Dermatol* 1984; **111**: 235–42.
10 DeAngelis YM, Gemmer CM, Kaczvinsky JR *et al.* Three etiologic facets of dandruff and seborrheic dermatitis: *Malassezia* fungi, sebaceous lipids, and individual sensitivity. *J Investig Dermatol Symp Proc* 2005; **10**: 295–7.
11 Peter RU, Richarz-Barthauer U. Successful treatment and prophylaxis of scalp seborrhoeic dermatitis and dandruff with 2% ketoconazole shampoo: results of a multicentre, double-blind, placebo-controlled trial. *Br J Dermatol* 1995; **132**: 441–5.
12 Pierard-Franchimont C, Goffin V, Decroix J *et al.* A multicenter randomized trial of ketoconazole 2% and zinc pyrithione 1% shampoos in severe dandruff and seborrheic dermatitis. *Skin Pharmacol Appl Skin Physiol* 2002; **15**: 434–41.

Pityriasis amiantacea

Pityriasis amiantacea is an inflammatory scaling reaction of the scalp, often without evident cause. One Scandinavian follow-up study reported that psoriasis occurred in 15% of patients with pityriasis amiantacea [1]. Another study failed to show an association with psoriasis but suggested that seborrhoeic dermatitis was more common [2]. In Knight's study of 71 patients, two had associated psoriasis and nine had eczema [3]; he pointed out that pityriasis amiantacea may occur at any age, but the average age was 25 years (range 5–40 years).

Pathology. Biopsies from 18 patients were examined by Knight [3]. The most consistent findings were spongiosis, parakeratosis, migration of lymphocytes into the epidermis and a variable degree of acanthosis. The essential features responsible for the asbestos-like scaling are diffuse hyperkeratosis and parakeratosis together with follicular keratosis, which surrounds each hair with a sheath of horn.

Clinical features. Masses of adherent silvery scales, overlapping like the tiles on a roof, adhere to the scalp and are attached in layers to the shafts of the hairs, which they surround (Fig. 66.53). The underlying scalp is usually reddened. The disease may be confined to discrete areas of the scalp, or may be very extensive, either involving a large area diffusely or affecting a number of small patches. The majority of patients notice some hair loss in areas of severe scaling. The hair regrows when the scaling is effectively treated, although scarring alopecia has been reported following pityriasis amiantacea [4].

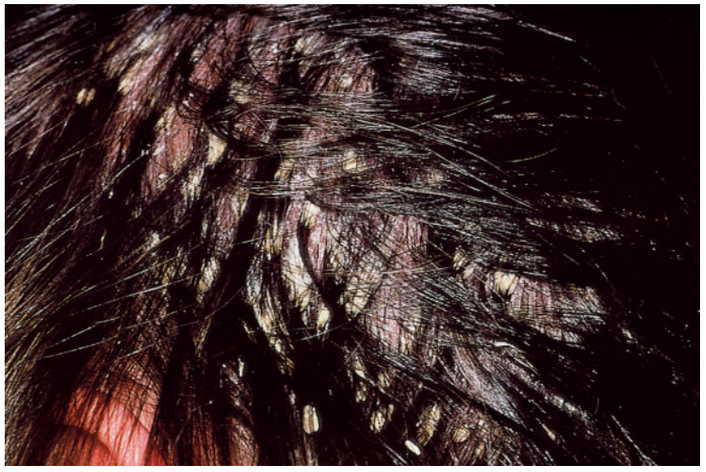


Fig. 66.53 Pityriasis amiantacea.

Diagnosis. The distinctive clinical appearance usually makes the diagnosis easy, but the identification of the underlying disease may not be straightforward; indeed, none may be established.

Treatment. Generous applications of an oil-based product are needed to remove the scales. Tar or salicylic acid ointments are commonly used. The preparation is left on the scalp for several hours and then washed out. The scales may be gently removed using a metal-toothed comb. Once the scaling is controlled an antidandruff or tar-based shampoo may help to maintain remission, but most patients will need to re-treat with an ointment from time to time. Potent topical corticosteroid lotions are beneficial in some cases, but are not effective in removing thick scales.

References

1 Hansted B, Lindskov R. Pityriasis amiantacea and psoriasis. A follow-up study. *Dermatologica* 1983; **166**: 314–5.
2 Hersle K, Lindholm A, Mobacken H *et al.* Relationship of pityriasis amiantacea to psoriasis. A follow-up study. *Dermatologica* 1979; **159**: 245–50.
3 Knight AG. Pityriasis amiantacea: a clinical and histopathological investigation. *Clin Exp Dermatol* 1977; **2**: 137–43.
4 Langtry JA, Ive FA. Pityriasis amiantacea, an unrecognized cause of scarring alopecia, described in four patients. *Acta Derm Venereol (Stockh)* 1991; **71**: 352–3.

Folliculitis

See Chapter 30.

Acne keloidalis nuchae

See Chapter 30.

Pseudofolliculitis

See Chapter 30.

Thickened scalp disorders

David de Berker, pp. 66.58–66.59

Cutis verticis gyrata

The term cutis verticis gyrata (CVG) describes a morphological syndrome in which there is hypertrophy and folding of the skin of the scalp to present a gyrate or cerebriform appearance. Polan and Butterworth established the classification of CVG, dividing it into primary and secondary forms [1]. The classification was later modified by Garden and Robinson [2], who subdivided the primary form into primary essential CVG, in which there are no associated features, and primary non-essential CVG, which is associated with a wide range of mental, cerebral and ophthalmological abnormalities.

Primary CVG. The aetiology of primary CVG is not known. Most cases appear to be sporadic although familial forms have been reported in the context of complex syndromes [3,4]. The skin changes typically develop after puberty and usually before 30 years of age. It is more common in men, with a male : female ratio of 5 : 1 or 6 : 1. There is a strong association with mental retardation. Akesson [5] found 47 cases (3.4%) of CVG in institutionalized mentally retarded subjects in Sweden, and CVG was observed in 22 out of 494 (4.5%) patients in an Italian psychiatric institution [6]. Cytogenetic analyses in the latter study showed chromosome fragile sites in nine subjects (chromosomes 9, 12 and X).

Secondary CVG. This has been described with a wide range of underlying causes. Congenital melanocytic naevi appear to be the most common but other naevoid abnormalities, such as naevus lipomatosus and connective tissue naevi, and acquired lesions such as neurofibroma, may also cause CVG [7–9]. CVG has been described in association with a variety of endocrine and genetic disorders, including acromegaly [10,11], myxoedema [12], insulin resistance [13], Turner's syndrome [14,15] and eczema [16]. The age of onset is more variable than in primary CVG and, in the naevoid forms, it may be present at birth.

The differential diagnosis includes pachydermoperiostosis and 'lumpy scalp syndrome'. The former is genetically determined and occurs mainly in men. It differs from CVG in several particulars. The scalp is folded but the skin of the face is also affected, as is that of the hands and feet. The cutaneous changes, which are accompanied by thickening of the phalanges and of the long bones of the limbs, progress for 10–15 years, then become static.

Pathology. The essential abnormality appears to be overgrowth of the scalp in relation to the underlying skull. In primary CVG, the histology appears normal in most cases. The histopathology in the secondary form depends on the nature of the underlying pathology.

Clinical features. CVG typically affects the vertex and occipital scalp but it may involve the entire scalp. The folds are usually arranged in an anteroposterior direction but may be transverse over the occiput. Hair density may be reduced over the convexities of the folds.

Treatment. Investigations are aimed at identifying underlying causes. These may include neurological, endocrine, ophthalmological and cytogenetic studies. In early-onset CVG, a biopsy is advisable to identify those cases caused by a structural lesion, such as a melanocytic naevus. In the majority of cases treatment is symptomatic. Patients should be educated in scalp hygiene to avoid accumulation of skin debris and secretions in the furrows. Surgical correction can be helpful in selected cases [17,18], and may be indicated in cerebriform naevi.

References

1 Polan S, Butterworth T. Cutis verticis gyrata. A review with report of seven new cases. *Am J Ment Defic* 1953; **57**: 613–31.
2 Garden JM, Robinson JK. Essential primary cutis verticis gyrata. Treatment with the scalp reduction procedure. *Arch Dermatol* 1984; **120**: 1480–3.
3 Rosenthal JW, Kloepfer HW. An acromegaloid, cutis verticis gyrata, corneal leukoma syndrome. *Arch Ophthal* 1962; **68**: 722–6.
4 Megarbane A, Waked N, Chouery E *et al.* Microcephaly, cutis verticis gyrata of the scalp, retinitis pigmentosa, cataracts, sensorineural deafness, and mental retardation in two brothers. *Am J Med Genet* 2001; **98**: 244–9.
5 Akesson HO. Cutis verticis gyrata and mental deficiency in Sweden. I Epidemiologic and clinical aspects. *Acta Med Scand* 1964; **175**: 115–27.
6 Schepis C, Palazzo R, Cannavo SP *et al.* Prevalence of primary cutis verticis gyrata in a psychiatric population: association with chromosomal fragile sites. *Acta Derm Venereol (Stockh)* 1990; **70**: 483–6.
7 Commens CA, Greaves MW. Cutis verticis gyrata due to an intradermal naevus with an underlying neurofibroma. *Clin Exp Dermatol* 1978; **3**: 319–22.
8 Orkin M, Frichot BC 3rd, Zelickson AS. Cerebriform intradermal nevus. A cause of cutis verticis gyrata. *Arch Dermatol* 1974; **110**: 575–82.
9 Jeanfils S, Tennstedt D, Lachapelle JM. Cerebriform intradermal nevus. A clinical pattern resembling cutis verticis gyrata. *Dermatology* 1993; **186**: 294–7.
10 Zeisler EP, Wieder LJ. Cutis verticis gyrata and acromegaly. *Arch Dermatol Syphilogr* 1940; **42**: 1092–9.
11 O'Reilly FM, Sliney I, O'Loughlin S. Acromegaly and cutis verticis gyrata. *J R Soc Med* 1997; **90**: 79.
12 Corbalan-Velez R, Perez-Ferriols A, Aliaga-Bouiche A. Cutis verticis gyrata secondary to hypothyroid myxedema. *Int J Dermatol* 1999; **38**: 781–3.
13 Woollons A, Darley CR, Lee PJ *et al.* Cutis verticis gyrata of the scalp in a patient with autosomal dominant insulin resistance syndrome. *Clin Exp Dermatol* 2000; **25**: 125–8.
14 Parolin Marinoni L, Taniguchi K, Giraldi S *et al.* Cutis verticis gyrata in a child with Turner syndrome. *Pediatr Dermatol* 1999; **16**: 242–3.
15 Larralde M, Gardner SS, Torrado MV *et al.* Lymphedema as a postulated cause of cutis verticis gyrata in Turner syndrome. *Pediatr Dermatol* 1998; **15**: 18–22.
16 Larsen F, Birchall N. Cutis verticis gyrata: three cases with different aetiologies that demonstrate the classification system. *Australas J Dermatol* 2007; **48**: 91–4.
17 Tani T, Miyamoto Y, Kurozumi N. Surgical treatment of cutis verticis gyrata: a report of 2 cases. *Br J Plast Surg* 1977; **30**: 235–9.
18 Ulrich J, Franke I, Gollnick H. Cutis verticis gyrata secondary to acne scleroticans capitis. *J Eur Acad Dermatol Venereol* 2004; **18**: 499–502.

Lipedematous alopecia

Lipedematous alopecia is a rare condition of unknown aetiology. It is characterized by a thick, boggy scalp with varying degrees of hair loss [1,2]. Although originally reported in black women, lipedematous alopecia also occurs in white women [3,4] and in men [5]. There is slowly progressive, diffuse alopecia and boggy thickening of the scalp. There are no associated medical or physiological conditions. The fundamental pathological finding consists of an approximate doubling in scalp thickness resulting from expansion of the subcutaneous fat layer in the absence of adipose tissue hypertrophy or hyperplasia. There is associated atrophy and fibrous replacement of many hair follicles. Light and electron

microscopy suggests that the increase in scalp thickness is caused by localized oedema, with disruption and degeneration of adipose tissue. Mucin is not seen [6].

References

1 Coskey RJ, Fosnaugh RP, Fine G. Lipedematous alopecia. *Arch Dermatol* 1961; **84**: 619–22.
2 Curtis JW, Heising RA. Lipedematous alopecia associated with skin hyperelasticity. *Arch Dermatol* 1964; **89**: 819–20.
3 Martin JM, Monteagudo C, Montesinos E *et al.* Lipedematous scalp and lipedematous alopecia: a clinical and histologic analysis of 3 cases. *J Am Acad Dermatol* 2005; **52**: 152–6.
4 Yasar S, Mansur AT, Goktay F *et al.* Lipedematous scalp and lipedematous alopecia: report of three cases in white adults. *J Dermatol* 2007; **34**: 124–30.
5 Piraccini BM, Voudouris S, Pazzaglia M *et al.* Lipedematous alopecia of the scalp. *Dermatol Online J* 2006; **12**: 6.
6 Fair KP, Knoell KA, Patterson JW *et al.* Lipedematous alopecia: a clinicopathologic, histologic and ultrastructural study. *J Cutan Pathol* 2000; **27**: 49–53.

Congenital alopecia and hypotrichosis

R.D. Sinclair, pp. 66.59–66.61

Total or partial absence of hair of developmental origin occurs in a bewildering variety of clinical forms, either as an apparently isolated defect or in association with a wide range of other anomalies. A logical classification must be based on detailed histological and genetic investigations and these, unfortunately, are seldom carried out. Provisionally, a purely clinical classification is useful to enable the clinician at least to understand the clearly defined types [1].

Total alopecia

Synonym
- Atrichia congenita

As an isolated abnormality

Aetiology. Total alopecia as an apparently isolated defect is usually determined by an autosomal recessive gene. Some pedigrees have been traced back to the early 19th century [1]. Dominant or irregular dominant inheritance has occurred in some families [2,3]. The two genotypes seem to be phenotypically indistinguishable, but detailed investigation would probably reveal differences. The term 'total' is relative, but if any hairs are present they are extremely few. Many isolated cases and families reported under the diagnosis of congenital alopecia are found on review of the original reports to be unquestionably examples of other syndromes; many were hidrotic ectodermal dysplasia.

Pathology. The hair follicles are absent in adult life, even when the fetal hair coat has been normal. Sebaceous glands are smaller than normal. When a few stray hairs have survived, the structure of the shaft appears to be normal.

Clinical features [3,4]. The scalp hair is often normal at birth but is shed between the first and sixth months, after which no further growth occurs. In some cases the scalp has been totally hairless at birth and has remained so [4]. Eyebrows, eyelashes and body hair may also be absent [5], but more often there are a few straggling pubic and axillary hairs and scanty eyebrows and eyelashes. Teeth and nails are normal, and general health, intelligence and life expectancy are unimpaired.

With associated defects

Total or almost total alopecia is unusual in hereditary syndromes.

Papular atrichia [6]. This rare, autosomal recessive syndrome is associated with mutations in the zinc finger domain of the hairless gene [7]. Patients are born with hair that falls out and is not replaced. They are completely devoid of eyebrows, eyelashes, and axillary and pubic hair. Histological studies show the presence of the infundibular portion of the hair follicles, but the middle and lower portions of the follicle are replaced by small, keratinizing epithelial cysts. No hair shafts are formed. At any age between 1 and 10 years, numerous small, horny papules appear, first on the face, neck and scalp, and then gradually over the greater part of the limbs and trunk. Histologically, the papules are thick-walled keratin cysts [6]. Whitish, hypopigmented streaks can be found on the scalp. Nails, teeth, sweating, growth and development are normal.

The underlying disorder in papular atrichia appears to be that towards the end of the first anagen phase the hair bulb, proximal inner root sheath and outer root sheath all undergo premature and massive apoptosis and disintegrate into separate cell clusters that lose contact with the dermal papilla. As a result, the dermal papilla fibroblasts fail to migrate upward, and break up into clusters of shrunken cells stranded in the reticular dermis as dermal cyst precursors, and the follicle loses the ability to cycle [8].

The genetics are complex. Apart from cases of pseudodominant inheritance [9], there is phenotypic and genetic heterogeneity in inherited atrichias caused by mutations in the *hr* gene, suggesting different roles for the regions mutated in atrichia with papular lesions and in other forms of congenital atrichia during hair development [10]. Furthermore, mutations in the gene for the vitamin D receptor, causing vitamin D-dependent rickets, Type II, cause a similar clinical and histological phenotype in some families [11,12].

Progeria. There is progressive loss of scalp and body hair in this rare, premature ageing disorder, which is caused by mutation in the lamin A gene [13].

Hidrotic ectodermal dysplasia. Total or almost total alopecia is associated with palmoplantar keratoderma and thickened, discolored nails. Any hairs that are present are structurally normal but are often finer than the average. Mutations in the *GJB6* gene encoding the gap junction protein connexin 30 have been shown to cause this disorder [14].

Moynahan's syndrome. This autosomal recessive syndrome is associated with mental retardation, epilepsy and total baldness of the scalp; the hair may regrow in childhood between 2 and 4 years of age [15]. A similar clinical presentation in an inbred family was reported by Baraitser and colleagues [16]. In a large

consanguineous Pakistani family with alopecia and mental retardation the disease locus was mapped to 3q26.33-q27.3 [17].

References

1 Sinclair R, de Berker D. Hereditary and congenital alopecia and hypotrichosis. In: Dawber RPR, ed. *Diseases of the Hair and Scalp*. 3rd edn. Oxford: Blackwell Science, 1997: 252–397.
2 Birke G. Uber Atrichia Congenita und ihren Erbgang. *Arch Klin Exp Dermatol* 1954; **197**: 322–43.
3 Tillman WG. Alopecia congenita: report of two families. *BMJ* 1952; **2**: 428.
4 Linn HW. Congenital atrichia. *Aust J Dermatol* 1964; **7**: 223–4.
5 Friederich HC. Zur Kenntnis der kongenitalen Hypotrichosis (Familiäre Hypotrichosis mit und ohne Nageldystrophie, Anidrosis hypotrichotica, Progerie.) *Dermatol Wochenschr* 1950; **121**: 409–17.
6 Zlotogorski A, Panteleyev AA, Aita VM *et al.* Clinical and molecular diagnostic criteria of congenital atrichia with papular lesions. *J Invest Dermatol* 2002; **118**: 887–90.
7 Ahmad W, Irvine AD, Lam H *et al.* A missense mutation in the zinc-finger domain of the human hairless gene underlies congenital atrichia in a family of Irish travellers. *Am J Hum Genet* 1998; **63**: 984–91.
8 Panteleyev AA, Botchkareva NV, Sundberg JP *et al.* The role of the hairless (hr) gene in the regulation of hair follicle catagen transformation. *Am J Pathol* 1999; **155**: 159–71.
9 Zlotogorski A, Martinez-Mir A, Green J *et al.* Evidence for pseudodominant inheritance of atrichia with papular lesions. *J Invest Dermatol* 2002; **118**: 881–6.
10 Klein I, Bergman R, Indelman M *et al.* A novel missense mutation affecting the human hairless thyroid receptor interacting domain 2 causes congenital atrichia. *J Invest Dermatol* 2002; **119**: 920–2.
11 Miller J, Djabali K, Chen T *et al.* Atrichia caused by mutations in the vitamin D receptor gene is a phenocopy of generalized atrichia caused by mutations in the hairless gene. *J Invest Dermatol* 2001; **117**: 612–7.
12 Zlotogorski A, Hochberg Z, Mirmirani P *et al.* Clinical and pathologic correlations in genetically distinct forms of atrichia. *Arch Dermatol* 2003; **139**: 1591–6.
13 Eriksson M, Brown WT, Gordon LB *et al.* Recurrent de novo point mutations in lamin A cause Hutchinson-Gilford progeria syndrome. *Nature* 2003; **423**: 293–8.
14 Smith FJ, Morley SM, McLean WH. A novel connexin 30 mutation in Clouston syndrome. *J Invest Dermatol* 2002; **118**: 530–2.
15 Moynahan EJ. Familial congenital alopecia, epilepsy, mental retardation with unusual electroencephalograms. *Proc R Soc Med* 1962; **55**: 411–2.
16 Baraitser M, Carter CO, Brett EM. A new alopecia/mental retardation syndrome. *J Med Genet* 1983; **20**: 64–5.
17 John P, Ali G, Chishti MS *et al.* Localization of a novel locus for alopecia with mental retardation syndrome to chromosome 3q26.33-q27.3. *Hum Genet* 2006; **118**: 665–7.

Hypotrichosis [1,2]

Hypotrichosis is also a relatively common feature of many hereditary syndromes, usually in association with other ectodermal defects. In the majority, the hair is not only sparse but is structurally abnormal. Where hypotrichosis is the most prominent manifestation and the structural defect is distinctive and well characterized, it has given its name to the syndrome, as in monilethrix and pili torti. In other syndromes, the scanty scalp hair is a minor and sometimes inconstant manifestation, and the shaft defect is usually less specific.

Hypotrichosis simplex. In this autosomal dominant condition hair is usually normal at birth but thins progressively during childhood to become very sparse or absent by the third decade. Hair loss may be confined to the scalp (hypotrichosis simplex of scalp) with normal growth of facial and body hair [3]. This disorder is associated with mutations in the *CDSN* gene located on 6p21.3 [4]. *CDSN* encodes a protein called corneodesmosin that is exclusively expressed in cornified squamous epithelia. A second form of hypotrichosis simplex, in which there is reduced hair growth on the scalp and body, although eyelashes, eyebrows and male beards are normal, maps to 18p11.32-p11.23 [5].

Marie–Unna hereditary hypotrichosis [6–8]. In this rare but distinctive syndrome the hair in affected individuals is typically coarse and wiry in early childhood and is then progressively lost during childhood and early adulthood. Unna described two patterns of alopecia. In the more severe form, the child's hair is always sparse and is progressively lost, so that alopecia is advanced by puberty. In the other, milder form, the hair is initially thick and the hair loss only commences in the second or third decade. The hair loss predominantly affects the frontal, mid-scalp and vertex regions and ultimately may resemble Hamilton stage VIII androgenetic alopecia. There is usually also a subtle, simultaneous loss from around the scalp margins. Scattered, coarse, twisted hairs may remain within the alopecic regions.

The eyelashes, eyebrows and body hair are typically absent from birth, and after puberty any axillary or pubic hair that develops is also sparse. General physical and mental development is normal. Scanning electron microscopy shows that the hair shafts are coarse, irregularly twisted and fluted [6].

Marie–Unna hypotrichosis maps to chromosome 8p, close to the *hairless* locus, but the gene has not yet been identified [9]. Other disorders clinically very similar to Marie–Unna hypotrichosis, but genetically distinct, are now recognized and indicate that more than one form of progressive patterned alopecia with wiry hair exists [10].

Hypohidrotic ectodermal dysplasia [11]. Affected males show hypotrichosis, abnormal teeth and absent sweat glands. The hair is fine and silky but thin and short. Both X-linked and autosomal dominant forms exist. The X-linked condition is caused by mutations in the ectodysplasin gene; the autosomal dominant form is due to mutation of the gene encoding the ectodysplasin receptor. Mutations in either the ectodysplasin gene or its receptor disrupt ectodysplasin-mediated cell–cell signalling, which regulates the morphogenesis of ectodermal appendages.

Hypotrichosis resulting from short anagen [12]. This autosomal dominant condition is characterized by hair that is fine and short from birth. While the growth rate is normal, shortening of the duration of the anagen phase limits hair length to a few centimetres.

Hypotrichosis with keratosis pilaris [13]. The hair is apparently normal at birth, but after the birth coat has been shed, between the second and sixth months, it fails to grow satisfactorily and remains sparse, short, brittle and poorly pigmented. Eyebrows and eyelashes may be normal or sparse. Keratosis pilaris is present on the occipital region and neck, and sometimes on the trunk and limbs. Nails, teeth and general physical development are normal. The hairs show no beading or other distinctive abnormality.

Hypotrichosis with keratosis pilaris and lentiginosis [13]. Seven females in three generations in a family of three males and 13

females developed hypotrichosis at or just after puberty, which progressed until the menopause. Axillary and pubic hair was completely lost. There was keratosis pilaris of the scalp and axillae, brittleness and longitudinal striation of the nails, and centrofacial lentiginosis.

Eyelid cysts, hypodontia and hypotrichosis. See [14].

Hypomelia, hypotrichosis, facial haemangioma syndrome [15]. This 'pseudothalidomide' syndrome, which is probably determined by an autosomal recessive gene, associates gross reduction defects of the limbs, a mid-facial capillary naevus and sparse silver–blonde hair.

Hypotrichosis in disorders of amino acid metabolism. In many disorders with aminoaciduria, the hair is hypopigmented and is often also fine, friable and sometimes sparse. Fine, sparse hair has been reported in phenylketonuria, arginosuccinic aciduria and hyperlysinaemia.

A number of case reports associate hypotrichosis with a variety of ectodermal defects. Some such cases may represent partial forms of recognized syndromes but it is probable that many additional distinct syndromes remain to be identified and characterized.

Differential diagnosis. Microscopy of plucked hairs will exclude the more distinctive structural defects (pili torti, monilethrix and pili annulati). Other ectodermal defects should be carefully sought and relatives should be examined.

References

1 Happle R. Genetic defects involving the hair. In: Orfanos CE, Happle R, eds. *Hair and Hair Diseases*. Berlin: Springer-Verlag, 1989: 325–62.
2 Sinclair R, de Berker D. Hereditary and congenital alopecia and hypotrichosis. In: Dawber RPR, ed. *Diseases of the Hair and Scalp*, 3rd edn. Oxford: Blackwell Science, 1997: 252–397.
3 Toribio J, Quinones PA. Hereditary hypotrichosis simplex of the scalp. Evidence for autosomal dominant inheritance. *Br J Dermatol* 1974; **91**: 687–96.
4 Levy-Nissenbaum E, Betz RC, Frydman M *et al*. Hypotrichosis simplex of the scalp is associated with nonsense mutations in CDSN encoding corneodesmosin. *Nat Genet* 2003; **34**: 151–3.
5 Baumer A, Belli S, Trueb RM *et al*. An autosomal dominant form of hereditary hypotrichosis simplex maps to 18p11.32-p11.23 in an Italian family. *Eur J Hum Genet* 2000; **8**: 443–8.
6 Peachey RD, Wells RS. Hereditary hypotrichosis (Marie-Unna type). *Trans St John's Hosp Dermatol Soc* 1971; **57**: 157–66.
7 Solomon LM, Esterly NB, Medenica M. Hereditary trichodysplasia: Marie Unna's hypotrichosis. *J Invest Dermatol* 1971; **57**: 389–400.
8 Stevanovic DV. Hereditary hypotrichosis congenita: Marie Unna type. *Br J Dermatol* 1970; **83**: 331–7.
9 Lefevre P, Rochat A, Bodemer C *et al*. Linkage of Marie-Unna hypotrichosis locus to chromosome 8p21 and exclusion of 10 genes including the hairless gene by mutation analysis. *Eur J Hum Genet* 2000; **8**: 273–9.
10 Green J, Fitzpatrick E, de Berker D *et al*. Progressive patterned scalp hypotrichosis, with wiry hair, onycholysis, and intermittently associated cleft lip and palate: clinical and genetic distinction from Marie Unna. *J Investig Dermatol Symp Proc* 2003; **8**: 121–5.
11 Barsh G. Of ancient tales and hairless tails. *Nat Genet* 1999; **22**: 315–6.
12 Barraud-Klenovsek MM, Trueb RM. Congenital hypotrichosis due to short anagen. *Br J Dermatol* 2000; **143**: 612–7.
13 Greither A. [On 3 generations of congenital keratosis follicularis with alopecia, hyperhidrosis and abortive palmar-plantar keratoses limited to women and its relation to congenital hereditary hypotrichosis.]. *Arch Klin Exp Dermatol* 1960; **210**: 123–40.
14 Burket JM, Burket BJ, Burket DA. Eyelid cysts, hypodontia, and hypotrichosis. *J Am Acad Dermatol* 1984; **10**: 922–5.
15 Hall BD, Greenberg MH. Hypomelia-hypotrichosis-facial hemangioma syndrome (pseudothalidomide, SC syndrome, SC phocomelia syndrome). *Am J Dis Child* 1972; **123**: 602–4.

Abnormalities of the hair shaft

D.A.R. de Berker, pp. 66.61–66.100

Structural defects of the hair shaft may be sufficient in degree to cause significant cosmetic disability, or they may render the hair abnormally susceptible to injury by minor degrees of trauma (excessive weathering). Hair microscopy can be a useful part of clinical assessment in some situations [1], including a range of hereditary or acquired metabolic disorders, where the hair shaft can sometimes provide clues to the diagnosis [2,3] (Table 66.6).

Price [4] classified anomalies of the shaft into those that are associated with increased fragility, and those that are not. This distinction is useful because only the former present clinically as patchy or diffuse alopecia. Price's classification will be followed throughout the present section.

References

1 Whiting DA, Dy LC. Office diagnosis of hair shaft defects. *Semin Cutan Med Surg* 2006; **25**: 24–34.
2 de Berker D. Clinical relevance of hair microscopy in alopecia. *Clin Exp Dermatol* 2002; **27**: 366–72.
3 Smith VV, Anderson G, Malone M *et al*. Light microscopic examination of scalp hair samples as an aid in the diagnosis of paediatric disorders: retrospective review of more than 300 cases from a single centre. *J Clin Pathol* 2005; **58**: 1294–8.
4 Price VH. Strukturanomalien des Haarschaftes. In: Orfanos CE, ed. *Haar und Haarkrankheiten*. Stuttgart: Fischer, 1979: 387–446.

Structural defects with increased fragility

Monilethrix (beading of hair)

Smith initially called this condition 'a rare nodose condition of the hair' [1]. Radcliffe Crocker subsequently suggested the term monilethrix. Nevertheless, some early reports, and even some more recent ones, confuse monilethrix with other shaft defects (e.g. trichorrhexis nodosa) when 'weathering' is severe.

Aetiology. Autosomal dominant transmission has been demonstrated in numerous large pedigrees [2]. The alleged occurrence of normal carriers of the dominant gene has not been proven, as a parent with only 5% of abnormal follicles is easily passed as normal [3]. The abnormality is attributable to mutations in the genes coding for the human hair keratins hHb1 and hHb6 [4]. There is no clear correlation between the severity of the phenotype and the mutation responsible [5]. A variant of monilethrix, with scalp erosions and the appearance of congenital alopecia, is attributed to a mutation in the gene for desmoglein 4, which can be recessively inherited [6].

Pathology. The hair shaft is beaded and breaks easily (Fig. 66.54). Elliptical nodes 0.7–1 mm apart, are separated by narrower

Table 66.6 Terms used to define hair shaft pathology.

Term	Meaning	Associations
Trichorrhexis nodosa (Fig. 66.63)	A circumferential break in the hair cuticle, with cortical fibres extruding through the fracture	Physical and chemical trauma to the hair elicits this appearance at a threshold dependent upon the age and fragility of the hair; seen in normal hair
Brush end	When a trichorrhexis node breaks it leaves the proximal end looking like a chimney sweep's brush	As above
Trichoclasis	A 'greenstick' fracture of the hair, where the cuticle is partly stripped in continuity with the fracture	Trauma and moderate fragility
Trichoptilosis	Split ends—in continuity with the tip	Common outcome of cumulative brushing and chemical trauma
Circle hairs	Circle and spiral hairs on the thigh and abdomen; usually trapped beneath the stratum corneum; in males	Normal in more hirsute males; not the same as scurvy
Trichomalacia	Softened hair residue with keratin in open scalp follicular orifice	Trichotillomania
Trichoschisis	Clean transverse fracture across hair	Typically associated with sulphur-deficient hair of trichothiodystrophy
Pohl-Pinkus constriction	Zone of constriction within the hair shaft, possibly due to transient physiological compromise of hair growth; comparable with a Beau's line	Period of ill health or cytotoxic medication, where not sufficient to precipitate telogen effluvium or anagen effluvium
Tapered hairs	The tip of a hair that has been generated *de novo* at the commencement of anagen will be tapered	Characteristic of hair that is regrowing after shedding or of hair with a short anagen phase, e.g. eyebrow
Bayonet hair	Slight kink in hair within 1–2 mm of tapered tip	Variant of normal
Trichonodosis	Knots in hair	Usually a simple reef knot, seen where hair is rubbed or where the hair is markedly curly and predisposed to knotting; can contribute to fragility; most common in African hair
Bubble hair (Fig. 66.74)	Bubbles within hair shaft	Arises due to extreme heat or singeing of hair; attributed to leaning over a fire, or hot hair treatments where thermostatic controls are faulty
Hair casts (Fig. 66.75)	Keratin cylinders moving freely on the proximal hair shaft and arising from the upper part of the internal root sheath	May be associated with scaling scalp conditions or hair styling where there is tension on the hair; sometimes referred to as 'pseudonits'
Tiger tail (Fig. 66.65)	Light and dark transverse stripes on a hair shaft when viewed with cross-polarization, preferably in histological medium	Sulphur deficient hair has a weakened cortex which loses its longitudinal rigidity and tends to become wavy; this alters light polarization characteristics
Nit	The egg case of a head louse adherent to the shaft	The egg case may be empty or still contain the louse nymph; only nits proximal on the shaft are likely to represent active infestation, which needs to be confirmed by identification of a live head louse
Pili torti (Figs 66.56–66.58)	Twisting of hair through 180° within the long axis of the hair	Although this is a sign, it is sometimes used as a diagnosis; it is associated with the specific diagnosis of Menkes' syndrome, but also presents as an isolated autosomal dominant condition

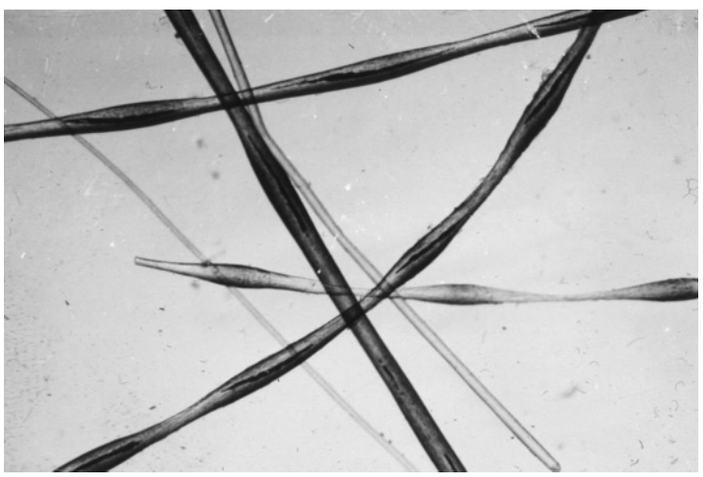


Fig. 66.54 Monilethrix with the swollen (node) and narrow (internode) fluctuations in hair bore.

internodes with a form resembling the body and neck of a skittle. The widths of the nodes and the distances between them vary between the hairs of an individual and between members of the same family. The nodes and some of the internodes show a normal imbricated scale pattern, but most internodes show longitudinal ridging [7,8]. True monilethrix must be distinguished from pseudomonilethrix, an artefact produced by tweezers or compressing overlapping hairs between two glass slides.

Histologically, the follicle shows wide and narrow zones corresponding to the nodes and internodes [9]. Attempts have been made to investigate the mechanism of node formation and to relate it to the diurnal rate of hair growth, but with no overall conclusion [7,10,11]. Intermittent administration of an antimitotic agent can give rise to zones of constriction alternating with zones of normal diameter [12].

Clinical features. Monilethrix shows considerable variation in age of onset, severity and course [13]. Hair loss or broken hair is accompanied by follicular keratoses most commonly on the nape



Fig. 66.55 Monilethrix. Nape of the neck, showing follicular keratoses and short, broken hairs.

and occiput (Fig. 66.55). In some cases, the eyebrows and eyelashes, pubic and axillary hair and general body hair may be affected.

In many patients, the condition persists with little change throughout life [2]. Spontaneous improvement or complete recovery has occurred [1] and has been reported during pregnancy [14].

Treatment. Three reports support the use of oral retinoids, providing a reversible benefit [15–17]. This may result from a therapeutic effect on the keratosis pilaris, which lessens in combination with a reduction of shaft beading and modest increase in overall hair length [17]. Improvement has been attributed to the hormone changes of menarche in one report [18]; male and female cases may both improve at puberty. Griseofulvin also has temporarily restored normal hair growth [19]. Iron supplementation has been reported to be of value in the presence of iron deficiency [20]. Reduction of hairdressing trauma may be followed by some improvement, by lessening the 'weathering' from chemical and physical insults.

References

1 Smith WG. A rare nodose condition of the hair. *BMJ* 1879; **11**: 291–6.
2 Solomon IL, Green OC. Monilethrix: its occurrence in seven generations, with one case that responded to endocrine therapy. *N Engl J Med* 1963; **269**: 1279–82.
3 Deraemaeker R. Monilethrix: report of a family with special reference to some problems concerning inheritance. *Am J Hum Genet* 1957; **9**: 195–9.
4 Schweizer J, Langbein L, Rogers MA *et al*. Hair follicle-specific keratins and their diseases. *Exp Cell Res* 2007; **313**: 2010–20.
5 Horev L, Glaser B, Metzker A *et al*. Monilethrix: mutational hotspot in the helix termination motif of the human hair basic keratin 6. *Hum Hered* 2000; **50**: 325–30.
6 Zlotogorski A, Marek D, Horev L *et al*. An autosomal recessive form of monilethrix is caused by mutations in DSG4: clinical overlap with localized autosomal recessive hypotrichosis. *J Invest Dermatol* 2006; **126**: 1292–6.
7 Comaish S. Autoradiographic studies of hair growth and rhythm in monilethrix. *Br J Dermatol* 1969; **81**: 443–7.
8 Dawber RPR. Weathering of hair in some genetic hair shaft abnormalities. In: Brown A, Crosin RG, eds. *Hair: Trace Elements and Human Illness*. New York: Praeger, 1980: 95–102.



Fig. 66.56 Pili torti. Light micrograph showing 180° twists.

9 De Berker DA, Ferguson DJ, Dawber RP. Monilethrix: a clinicopathological illustration of a cortical defect. *Br J Dermatol* 1993; **128**: 327–31.
10 Klingmuller G. [Monilethrix with 48 hour rhythm.]. *Hautarzt* 1954; **5**: 23–4.
11 Baker H. An investigation of monilethrix. *Br J Dermatol* 1962; **74**: 24–30.
12 Van Scott EJ, Reinertson RP, Steinmuller R. The growing hair roots of the human scalp and morphologic changes therein following amethopterin therapy. *J Invest Dermatol* 1957; **29**: 197–204.
13 Amichai B, Metzker A. Hair loss in a 6-month-old child. Monilethrix. *Arch Dermatol* 1996; **132**: 574–5, 77–8.
14 Summerly R, Donaldson EM. Monilethrix. A family study. *Br J Dermatol* 1962; **74**: 387–91.
15 Tamayo L. Monilethrix treated with the oral retinoid Ro 10–9359 (Tigason). *Clin Exp Dermatol* 1983; **8**: 393–6.
16 Karincaoglu Y, Coskun BK, Seyhan ME *et al*. Monilethrix: improvement with acitretin. *Am J Clin Dermatol* 2005; **6**: 407–10.
17 de Berker D, Dawber RP. Monilethrix treated with oral retinoids. *Clin Exp Dermatol* 1991; **16**: 226–8.
18 Gebhardt M, Fischer T, Claussen U *et al*. Monilethrix—improvement by hormonal influences? *Pediatr Dermatol* 1999; **16**: 297–300.
19 Keipert JA. The effect of griseofulvin on hair growth in monilethrix. *Med J Aust* 1973; **1**: 1236–8.
20 Karaman GC, Sendur N, Basar H *et al*. Localized monilethrix with improvement after treatment of iron deficiency anaemia. *J Eur Acad Dermatol Venereol* 2001; **15**: 362–4.

Pili torti (twisting of hair)

In pili torti, the hairs are flattened and at irregular intervals completely rotated through 180° around their long axis (Fig. 66.56). This rotation runs for three to five twists before the shaft normalizes [1]. True pili torti of Menkes' syndrome and the isolated expression of the abnormality in an otherwise unaffected person, demonstrate the same distinct twisting (Figs 66.57 & 66.58). Scanning electron microscopy has made it clear that twisted hairs occur in many different forms, and that not all twisted hairs are pili torti.

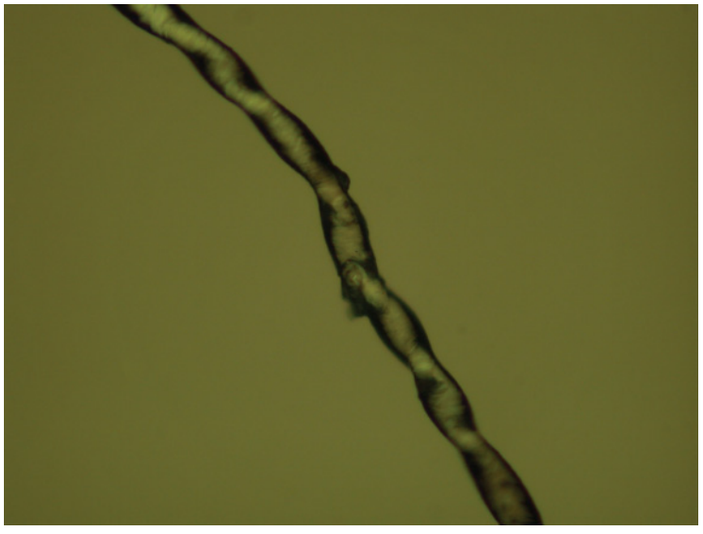


Fig. 66.57 Pili torti in a 6-month-old boy with Menkes' syndrome.

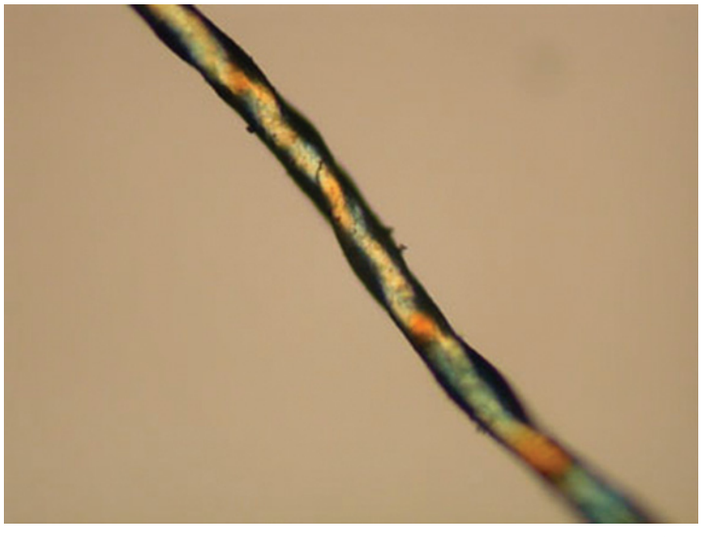


Fig. 66.58 Pili torti in a 27-year-old woman with no personal or family history of associated disorders.

Occasional twists of varying angle should not be taken to be this distinctive genetically 'fixed' abnormality of pili torti—many dystrophies and distortions of the follicular zone of keratinization will vary the hair shaft 'bore', sometimes showing less than 180° irregular twists.

Syndromes in which twisted hair is a feature

Menkes' syndrome. Light-coloured, twisted hair is a manifestation of a hereditary defect of intestinal copper transport; the inheritance is of sex-linked recessive type. Accumulation of copper in the neonatal period leads to brain damage, mental retardation and fitting. Fits may be the presenting complaint, with the diagnosis made later on hair microscopy. The twisting of the hair microscopically is generally exactly the same as in pili torti [2,3]. The disorder is caused by a mutation in the gene encoding Cu^2 transporting ATPase, α-polypeptide. The occipital horn syndrome is caused by mutation in the same gene.

Differential diagnosis (Table 66.7). The main differential is Björnstad's syndrome with sensorineural deafness. Other diagnoses found in the literature are probably erroneous and based on a loose interpretation of the term pili torti. The spiral is either too low-pitched or it is around an axis that is not within the long axis of the hair.

Aetiology. In those cases in which classic pili torti of early onset appears to have occurred as an isolated defect, examples suggesting autosomal dominant and recessive inheritance can be found.

Pathology. The earlier reports emphasized that the affected hairs were flattened and twisted through 180° around their long axis at irregular intervals along the shaft. Hairs can manifest fragility with the shape making them more vulnerable to the effects of weathering.

Clinical features. The hair is usually normal at birth, but is gradually replaced by abnormal hair, which becomes clinically evident as early as the third month, or not until the second or third year. There is a wide variation from case to case in the fragility of the hair, and hence in the clinical picture. Affected hairs are brittle and may break off at a length of 5 cm or less, or grow longer in areas of the scalp less subject to trauma. There may therefore be only a short, coarse stubble over the whole scalp or there may be circumscribed baldness, irregularly patchy or occipital. Affected hairs have a spangled appearance in reflected light. The cosmetic appearance of isolated pili torti can improve greatly with transition from childhood to early adulthood [4].

References

1 Ronchese F. Twisted hairs (pili torti). *Arch Dermatol Syphilol* 1932; **26**: 98–104.
2 Menkes JH, Alter M, Steigleder GK *et al.* A sex-linked recessive disorder with retardation of growth, peculiar hair, and focal cerebral and cerebellar degeneration. *Pediatrics* 1962; **29**: 764–79.
3 Dupre A, Enjolras O. [Menkes' syndrome with alternating pili torti]. *Ann Dermatol Venereol* 1980; **107**: 269–71.
4 Telfer NR, Cutler TP, Dawber RP. The natural history of 'dystrophic' pili torti. *Br J Dermatol* 1989; **120**: 323–5.
5 Hinson JT, Fantin VR, Schonberger J *et al.* Missense mutations in the *BCS1L* gene as a cause of the Bjornstad syndrome. *N Engl J Med* 2007; **356**: 809–19.
6 Selvaag E. Pili torti and sensorineural hearing loss. A follow-up of Bjornstad's original patients and a review of the literature. *Eur J Dermatol* 2000; **10**: 91–7.
7 Oley CA, Sharpe H, Chenevix-Trench G. Basal cell carcinomas, coarse sparse hair, and milia. *Am J Med Genet* 1992; **43**: 799–804.
8 Vabres P, Lacombe D, Rabinowitz LG *et al.* The gene for Bazex-Dupre-Christol syndrome maps to chromosome Xq. *J Invest Dermatol* 1995; **105**: 87–91.
9 Bentley-Phillips B, Bayliss MA. Letter: Pseudo-monilethrix. *Br J Dermatol* 1975; **92**: 113–4.
10 Itin PH, Sarasin A, Pittelkow MR. Trichothiodystrophy: update on the sulfur-deficient brittle hair syndromes. *J Am Acad Dermatol* 2001; **44**: 891–920; quiz 21–4.
11 Lurie R, Danziger Y, Kaplan Y *et al.* Acquired pili torti—a structural hair shaft defect in anorexia nervosa. *Cutis* 1996; **57**: 151–6.
12 Hays SB, Camisa C. Acquired pili torti in two patients treated with synthetic retinoids. *Cutis* 1985; **35**: 466–8.
13 Berth-Jones J, Shuttleworth D, Hutchinson PE. A study of etretinate alopecia. *Br J Dermatol* 1990; **122**: 751–5.

Table 66.7 Diseases where pili torti and other twisted hair abnormalities are found.

Name	Genetics	Mechanism	Features
Pili torti—isolated [1]	Both dominant and recessive reported	Not known	Pili torti, fragile hair, sometimes with hypoplastic dental enamel; could be female carrier of Menkes' syndrome
Menkes' syndrome [2]	X-linked recessive carried on Xq12-q13	Mutation in gene encoding the Cu^{2+} transporting ATPase, alpha protein	Blond fine hair in boys, with poor neonatal development, evolving into status epilepticus and brain damage as cumulative copper metabolism damage progresses
Female carrier of Menkes' syndrome	Ditto	Ditto	Pili torti in 43% of obligate female carriers
Björnstad's syndrome [5,6]	Autosomal recessive disease due to mutation in BC1SL gene on 2q33	Altered function of mitochondrial respirasome protein, in turn affecting transmission of inner ear neurosensory hair responses	Neurosensory deafness with hypogonadism in some instances (Crandall's syndrome)
Twisted hairs—poor evidence for true pili torti			
Bazex syndrome [7,8]	X-linked dominant Xq24-q27	Possible loss of efficacy of a DNA repair protein produced by the UBE2A gene	Hypotrichosis, follicular atrophoderma, and multiple basal cell neoplasms; hypohidrosis also reported
Pseudomonilethrix [9]	Putative dominant inheritance	Probably an artefact in hair plucking or twisting	Intermittent nodes and internodes in hair shafts that mimic monilethrix, but may be in the form of a flattened spiral
Trichothiodystrophy [10]	Autosomal recessive 19q13.2-q13.3, 6p25.3, 2q21	Transcription syndrome with defects in transcription factors II H and possibly others	Multiple phenotypes and subtypes, with flattened fragile hair that can twist; common factor is sulphur deficiency in hair amino acid constituents
Anorexia nervosa [11]	Acquired	May be mediated through lack of vitamin C	Wiry hair
Retinoid hair [12,13]	Acquired	Secondary to systemic retinoid therapy	Wiry hair with hair loss and dry skin
Scarring alopecia [14]	Acquired	Secondary to scarring inflammation, most common with folliculitis decalvans	Wiry hair at the margins of active scarring follulitis
Tuberous sclerosis complex [15]	Autosomal dominant	16p13.3, 12q14, 9q34	Corkscrew hairs, multiple hamartomas, renal cysts and epilepsy

14 Kurwa AR, Abdel-Aziz AH. Pili torti–congenital and acquired. *Acta Derm Venereol (Stockh)* 1973; **53**: 385–92.
15 Argenziano G, Monsurro MR, Pazienza R *et al*. A case of probable autosomal recessive ectodermal dysplasia with corkscrew hairs and mental retardation in a family with tuberous sclerosis. *J Am Acad Dermatol* 1998; **38**: 344–8.

Netherton's syndrome (bamboo hair) [1–3]

Netherton [4] observed bamboo-like nodes in the fragile hairs of a girl with 'erythematous scaly dermatitis'. It has gradually become apparent that ichthyosis linearis circumflexa (ILC) and 'bamboo hairs' (trichorrhexis invaginata) (Fig. 66.59) are two features of a single syndrome [5]. Most cases of Netherton's syndrome have had ILC but some have ichthyosis vulgaris [6] or both conditions, or ichthyosiform erythroderma. Features of ILC may be seen in variants of psoriasis. It is controversial as to whether it occurs as an isolated disease in the absence of Netherton's syndrome, or whether it is the fluctuating prevalence of the hair shaft changes that leads to difficulty in detecting both characteristics at the same time in some patients.

ILC is thus an almost constant feature of the syndrome, with hair shaft defects of various types and degrees of severity. The inheritance of Netherton's syndrome appears to be determined by an autosomal recessive gene of variable expressivity. Girls are affected more than boys. The underlying defect has been localized to a gene on chromosome 5q32, known as *SPINK5*, an acronym for serum protease inhibitor [7]. The gene product is termed LEKTI (lymphoepithelial kazal-type-related inhibitor). The protein has antitrypsin and antichymotrypsin-like activities, which serve to inhibit the natural proteolytic activity of serine proteases. Where a mutation removes this inhibition, the proteases degrade cadherins of the corneodesmosome, desmoglein 1 and desmocollin 1 in



Fig. 66.59 Light microscopy revealing a trichorrhexis invaginata node likened to bamboo.

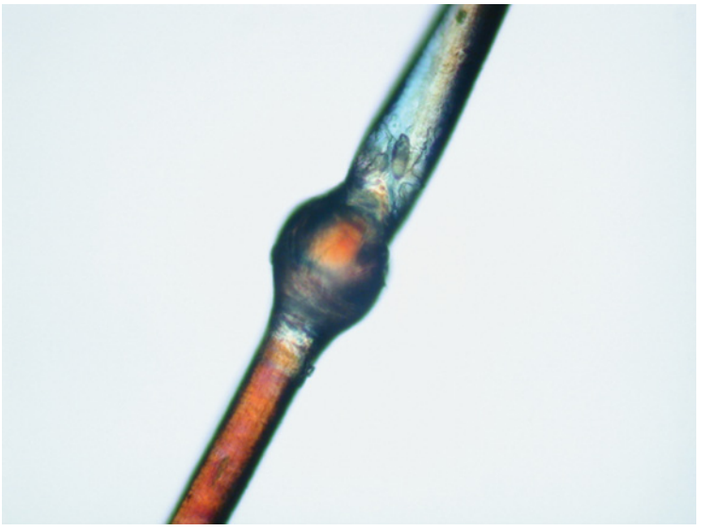


Fig. 66.60 Netherton's syndrome with an invaginate node showing partial twisting of the hair at the upper pole.

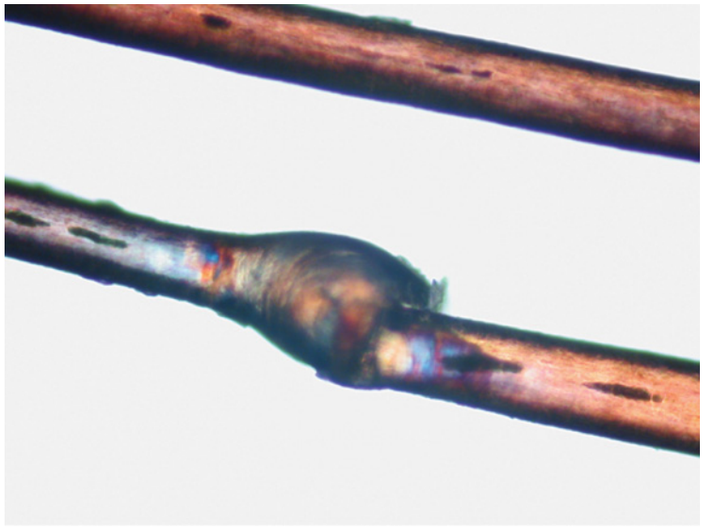


Fig. 66.61 Netherton's syndrome with the invaginate node acting as a point of weakness in the hair shaft.

the upper epidermis, with additional loss of filaggrin. This reduction of the epidermal barrier represents the pathology of the associated skin disease, typically with features of atopic dermatitis [8,9]. Immunohistochemical techniques are under development to allow tissue diagnosis of Netherton's syndrome on the basis of absence of LEKTI immunostaining. Identification of the gene has allowed prenatal diagnosis [10].

Pathology. As Netherton's syndrome results in fragile hair, samples should be cut at the scalp surface, thus reducing the chances that the hair will break at the point of diagnostic interest, making diagnosis more difficult. Light microscopy is the best tool for detecting features of Netherton's syndrome in hair. However, an individual may have multiple hairs with characteristic changes in one sample and then no features in another sample taken some months later. Because of this it is important that samples of at least 100 hairs are carefully examined on several occasions before a definite negative is asserted. Alternatively, finding a single trichorrhexis invaginata node in a single hair is a conclusive positive (Figs 66.60 & 66.61).

To assess such large numbers of hairs it is necessary to use the light microscope, as electron microscopy will only allow assessment of small lengths of a small number of hairs. Detail of the surface features is enhanced using partially crossed polarizing filters, and the cortical anatomy of the hair is revealed if the hair is prepared on a slide in histological mounting medium. Scanning electron microscopy of the hair shafts shows focal defects that produce the development of torsion nodules, invaginated nodules (trichorrhexis invaginata) and trichorrhexis nodosa [11,12].

Where diagnosis is difficult, sampling the eyebrows may provide confirmation [13]. The proximal remnant of an invaginate node may resemble a golf tee and can allow diagnosis where classic nodes are absent [3].

Clinical features [14]. The patient may present primarily either with cutaneous changes or complaining of sparse and fragile hairs. Generalized scaling and erythema are present from birth or early infancy, but the degree, extent and persistence of the erythema are very variable. In some cases, the erythema may be slight and transient. In many it has the characteristics of atopic eczema accompanied by an elevated IgE. On the trunk and limbs, the fine, dry scales are associated with a polycyclic and serpiginous eruption whose horny margin slowly changes its pattern.

The hair defects may be detected only if deliberately sought, but in most cases are readily apparent clinically [14]. The hair is short, dry, lustreless and brittle, and the eyebrows and lashes are sparse or absent. Jones *et al.* [15] described two cases in which neonatal hypernatraemia occurred. The severity of the phenotype does not show strict correlation with the mutation, and members of the same kindred may share a mutation but have different degrees of disease [16].

Treatment. Management of Netherton's syndrome is discussed in Chapter 19. There is no specific treatment for the hair dystrophy other than avoidance of physical and chemical trauma.

References

1 Altman J, Stroud J. Netherton's syndrome and ichthyosis linearis circumflexa. *Arch Dermatol* 1969; **100**: 550–8.

2 Ito M, Ito K, Hashimoto K. Pathogenesis in trichorrhexis invaginata (bamboo hair). *J Invest Dermatol* 1984; **83**: 1–6.

3 de Berker DA, Paige DG, Ferguson DJ *et al.* Golf tee hairs in Netherton disease. *Pediatr Dermatol* 1995; **12**: 7–11.

4 Netherton EW. A unique case of trichorrhexis nodosa; bamboo hairs. *AMA Arch Derm* 1958; **78**: 483–7.

5 Mevorah B, Frenk E. Ichthyosis linearis circumflexa comel with trichorrhexis invaginata (Netherton's syndrome). A light microscopical study of the skin changes. *Dermatologica* 1974; **149**: 193–200.

6 Brodin MB, Porter PS. Netherton's syndrome. *Cutis* 1980; **26**: 185–8, 91.

7 Chavanas S, Bodemer C, Rochat A *et al.* Mutations in SPINK5, encoding a serine protease inhibitor, cause Netherton syndrome. *Nat Genet* 2000; **25**: 141–2.

8 Descargues P, Deraison C, Prost C *et al.* Corneodesmosomal cadherins are preferential targets of stratum corneum trypsin- and chymotrypsin-like hyperactivity in Netherton syndrome. *J Invest Dermatol* 2006; **126**: 1622–32.

9 Hachem JP, Wagberg F, Schmuth M *et al.* Serine protease activity and residual LEKTI expression determine phenotype in Netherton syndrome. *J Invest Dermatol* 2006; **126**: 1609–21.
10 Ong C, O'Toole EA, Ghali L *et al.* LEKTI demonstrable by immunohistochemistry of the skin: a potential diagnostic skin test for Netherton syndrome. *Br J Dermatol* 2004; **151**: 1253–7.
11 Murphy GM, Griffiths WA, Grice K. Netherton's syndrome. *J R Soc Med* 1989; **82**: 683–4.
12 Orfanos CE, Mahrle G, Salamon T. [Netherton's syndrome. Ichthyosis-like changes in the skin and trichorrhexis invaginata. Demonstration of pathologically changed cortex keratin in the hair]. *Hautarzt* 1971; **22**: 397–409.
13 Powell J, Dawber RP, Ferguson DJ *et al.* Netherton's syndrome: increased likelihood of diagnosis by examining eyebrow hairs. *Br J Dermatol* 1999; **141**: 544–6.
14 Judge MR, Morgan G, Harper JI. A clinical and immunological study of Netherton's syndrome. *Br J Dermatol* 1994; **131**: 615–21.
15 Jones SK, Thomason LM, Surbrugg SK *et al.* Neonatal hypernatraemia in two siblings with Netherton's syndrome. *Br J Dermatol* 1986; **114**: 741–3.
16 Bitoun E, Chavanas S, Irvine AD *et al.* Netherton syndrome: disease expression and spectrum of SPINK5 mutations in 21 families. *J Invest Dermatol* 2002; **118**: 352–61.

Trichorrhexis nodosa

Trichorrhexis is best regarded as a distinctive response of the hair shaft to injury [1]. If the degree or frequency of the injury is sufficient, it can be induced in normal hair, and this is probably the most common scenario. The cuticular cells become disrupted, allowing the cortical cells to splay out to form nodes [2]. If, however, the hair is abnormally fragile, trichorrhexis may follow relatively trivial injury. The trauma of hairdressing procedures has often been incriminated [3]. Scratching may produce identical changes in pubic hairs [3]. The cumulative effect of shampooing, brushing, sea bathing and sunlight has led to seasonal summer recurrences [4].

Congenital and hereditary defects of the hair shaft resulting in fragility can predispose to trichorrhexis nodosa.

Trichorrhexis nodosa is a feature of the rare metabolic defect argininosuccinic aciduria, in which it is associated with mental retardation [5]; there is a deficiency of the enzyme argininosuccinase. Some 20 patients have been reported [6,7]. The hair tends to be dry, brittle and lustreless and may show trichorrhexis nodosa, but it does not occur in all patients with this metabolic disorder.

Trichorrhexis nodosa may occur in certain families as an apparently isolated defect of the hair; node formation and fracture are induced by minimal trauma and develop during the early months of life. Wolff *et al.* [8] described as 'trichorrhexis congenita' the presence from birth of trichorrhexis nodosa confined to the scalp, with normal teeth and nails.

Localized autosomal recessive hypotrichosis. This recently described disorder presents with brittle hair which fractures readily leading to extensive loss of hair. The hair may appear unusually stiff. Hair microscopy shows trichorrhexis nodosa. Monilethrix-like beading may also be seen [9]. Localized autosomal recessive hypotrichosis is due to mutations in the gene for the desmosomal protein desmoglein 4 (*dsg4*) [10,11] (Fig. 66.62).



Fig. 66.62 Localized autosomal recessive hypotrichosis due to *dsg4* mutation.



Fig. 66.63 Trichorrhexis nodosa. Polarized light examination demonstrates the splayed cortical fibres radiating from the transverse fracture in a trichorrhexis node.

Pathology. In simple trichorrhexis nodosa, the shaft may appear normal with the light or electron microscope, except at the nodes; or the shaft, apart from the proximal 1 cm, may show signs of abnormal wear and tear [2]. At the nodes, the cuticle bulges and is split by longitudinal fissures (Fig. 66.63). If fracture occurs transversely through a node (trichoclasis), the end of the hair resembles a small paintbrush.

Clinical features. In trichorrhexis nodosa complicating a congenital defect of the hair shaft, the hair breaks so easily that large or small portions of the scalp show only broken stumps and alopecia may be gross. However, the common situation is where trauma plays a major part and predisposition has a relatively minor role. In this setting there are three principal clinical presentations [12].

1 Distal trichorrhexis nodosa occurs in all races. Often it is discovered incidentally, and only a few whitish nodules are seen near the ends of scattered hairs. If many hairs are affected, the patient may complain that the hair is dry, dull or brittle. The longer the hair, the more likely it is to occur.

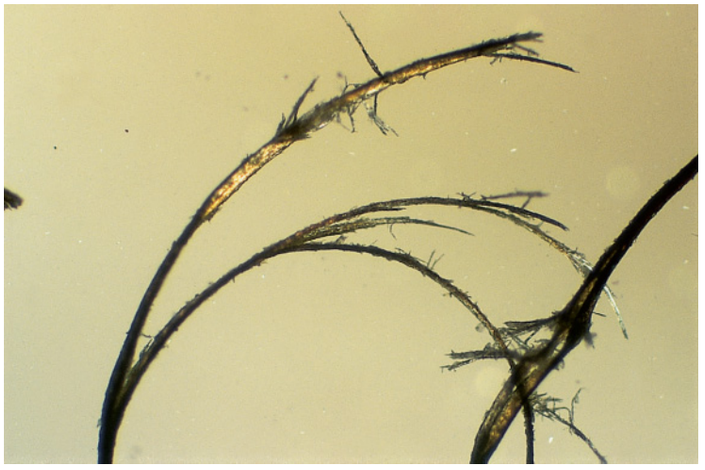


Fig. 66.64 Proximal trichorrhexis nodes and dramatic split ends (trichoptilosis) are visible in hair from an Afro-Caribbean woman.

2 There is a generalized variant seen in Afro-Caribbean women called proximal trichorrhexis nodosa. The scalp hair is universally short and brittle and demonstrates severe weathering on light microscopic examination (Fig. 66.64). There may be an association with the follicular degeneration syndrome where there is a central scarring alopecia in the absence of an overt inflammatory process [13].

3 The third clinical form was well described by Sabouraud [14] but it appears now to be rare. In a localized area of scalp, moustache or beard, some hairs are broken and others show from one to five or six nodules [15].

Diagnosis. The congenital forms must be differentiated from other shaft defects. The distal acquired form may simulate dandruff or even pediculosis. In all cases, diagnosis depends on careful microscopy. Excessive physical and chemical (cosmetic) trauma must be avoided, apart from shampooing.

References

1 Whiting DA, Dy LC. Office diagnosis of hair shaft defects. *Semin Cutan Med Surg* 2006; **25**: 24–34.

2 Dawber R, Comaish S. Scanning electron microscopy of normal and abnormal hair shafts. *Arch Dermatol* 1970; **101**: 316–22.

3 Chernosky ME, Owens DW. Trichorrhexis nodosa. Clinical and investigative studies. *Arch Dermatol* 1966; **94**: 577–85.

4 Papa CM, Mills OH Jr, Hanshaw W. Seasonal trichorrhexis nodosa. Role of cumulative damage in frayed hair. *Arch Dermatol* 1972; **106**: 888–92.

5 Allan JD, Cusworth DC, Dent CE *et al.* A disease, probably hereditary characterised by severe mental deficiency and a constant gross abnormality of aminoacid metabolism. *Lancet* 1958; **1**: 182–7.

6 Brenton DP, Cusworth DC, Hartley S *et al.* Argininosuccinicaciduria: clinical, metabolic and dietary study. *J Ment Defic Res* 1974; **18**: 1–13.

7 Shih VE. Early dietary management in an infant with argininosuccinase deficiency: preliminary report. *J Pediatr* 1972; **80**: 645–8.

8 Wolff HH, Vigl E, Braun-Falco O. [Trichorrhexis congenita. Scanning electron microscopic studies on a congenital disorder of hair growth]. *Hautarzt* 1975; **26**: 576–80.

9 Zlotogorski A, Marek D, Horev L *et al.* An autosomal recessive form of monilethrix is caused by mutations in DSG4: clinical overlap with localized autosomal recessive hypotrichosis. *J Invest Dermatol* 2006; **126**: 1292–6.

10 Rafiq MA, Ansar M, Mahmood S *et al.* A recurrent intragenic deletion mutation in DSG4 gene in three Pakistani families with autosomal recessive hypotrichosis. *J Invest Dermatol* 2004; **123**: 247–8.

11 Moss C, Martinez-Mir A, Lam H *et al.* A recurrent intragenic deletion in the desmoglein 4 gene underlies localized autosomal recessive hypotrichosis. *J Invest Dermatol* 2004; **123**: 607–10.

12 Price V. Office diagnosis of structural hair anomalies. *Cutis* 1975; **15**: 213–39.

13 Sperling LC. Scarring alopecia and the dermatopathologist. *J Cutan Pathol* 2001; **28**: 333–42.

14 Sabouraud R. Trichoclasie, trichorrhexie et trichopilose. *Ann Dermatol Syphiligr* 1921; **2**: 445–50.

15 Camacho-Martinez F. Localized trichorrhexis nodosa. *J Am Acad Dermatol* 1989; **20**: 696–7.

Trichothiodystrophy

The term trichothiodystrophy (TTD) was coined [1] to describe brittle hair with abnormally low sulphur content. The term covers a range of phenotypes, with low sulphur fragile hair representing the central defining criterion [2–5]. TTD can be classified according to the constellation of features that accompany the hair changes [4].

Using current criteria, approximately 50% of those with TTD are photosensitive. In this group, there is phenotypic and genetic crossover with xeroderma pigmentosum (XP). Of the different complementation groups within XP, most of the photosensitive TTDs share features with XP complementation group D, some with XP complementation group B and a small group represent an isolated photosensitive category, termed TTD-A [6]. The common genetic defect in XPD and photosensitive TTD is within the *ERCC2* (excision repair cross-complementation 2) gene on chromosome 19q as defined by *in vitro* complementation studies. Mutations of the *ERCC3* gene on chromosome 2q have a corresponding role in XPB. These genes code for a transcription factor TFIIH, which has a dual function. First it acts as a helicase, which unravels the double helix of segments of photodamaged DNA as part of nucleotide excision and repair (NER). Secondly, it acts to enable transcription of segments of DNA to produce RNA and gene expression. A range of mutations in this gene can lead to changes in function of TFIIH. Where defects in NER occur, there is cumulative photodamage to the DNA, which is clinically expressed as photoageing and dysplasia. In XP, this ultimately predisposes to skin cancer, but not in TTD. Equally, the genetic basis for TTD can result in neuroectodermal changes that are not part of XP. A further mystery is that the genetic defect in Cockayne's syndrome arises within the same gene and affects the same transcription factor, but results in a different phenotype.

Pathology. The hair is brittle and weathers badly [5], with abnormalities inversely proportional to the sulphur content [2]. With trauma it may fracture with a clean transverse break (trichoschisis) or may form nodes somewhat resembling trichorrhexis nodosa. The hairs are flattened and can be twisted into various appearances—rather like a ribbon or shoe lace. Details of these changes are clarified by scanning electron microscopy [5]. The shaft is irregular, with ridging and fluting, and the cuticular scales are patchily absent. Transmission electron microscopy demonstrates a decrease in high-sulphur protein staining in the hair shaft and a reduction of this protein in the exocuticular part of the cuticle cells [7].

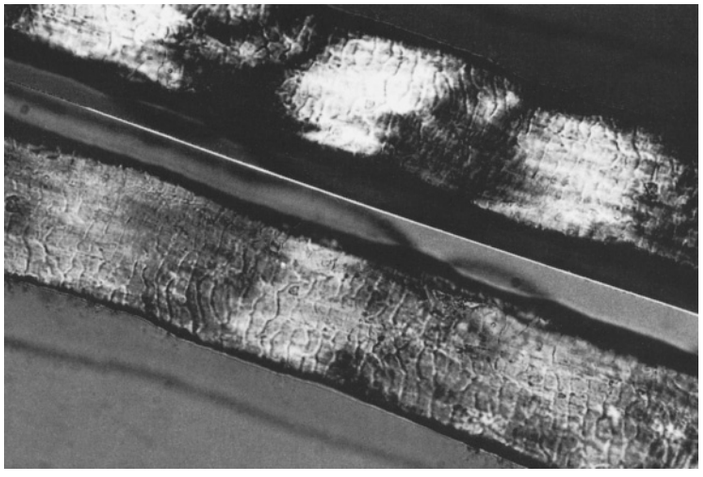


Fig. 66.65 Trichothiodystrophy. Alternating bright and dark zones in the polarizing microscope. (Courtesy of D. Van Neste, Brussels.)

Using crossed polarizing filters with a light microscope the hairs show alternating bright and dark zones (Fig. 66.65). This feature is sensitive for TTD [2,8], but not specific. It may occur in a range of genetic and acquired disorders where the longitudinal organization of cortical fibres within the hair is thrown into a sine wave pattern through loss of rigidity [9]. As a sign, it may arise at different stages in infancy. In one instance it has been used prognostically when identified in a fetal eyebrow biopsy obtained *in utero* [10]. Other cases illustrate that the sign may fail to develop until a few months of age [11].

Clinical features. There is a wide range of phenotypic characteristics, depending on the variant of TTD (Table 66.8). The hair is sparse, short and brittle, but the degree of alopecia varies considerably. There may be lamellar ichthyosis. The nails may be dystrophic. Mental and physical development may be normal but one or both may be slightly, moderately or severely retarded. The central feature of altered hair remains the basis of diagnosis, but the mechanism linking the associated features requires further elucidation.

Table 66.8 Classification of trichothiodystrophy.

Type	Findings	Eponym/acronym
A	Hair ± nails	
B	Hair ± nails + mental retardation	Sabinas
C	Hair ± nails + mental retardation, folliculitis, retarded bone age ± caries	Pollitt
D	Brittle hair ± nails, infertility, developmental delay, short stature	BIDS
E	Ichthyosis, BIDS, hair ± nails, mental retardation, short stature ± decreased gonadal function ± lenticular opacities/cataracts + failure to thrive/ 'progeria' + microcephaly ± ataxia ± calcifications of the basal ganglia + erythroderma and scale	Tay and IBIDS
F	Photosensitivity and IBIDS	PIBIDS
G	TTD with immune defects; hair ± mental retardation + chronic neutropenia or immunoglobulin deficiency	Itin
H	Trichothiodystrophy with severe intrauterine growth retardation and failure to thrive, developmental delay, recurrent infections, cataracts, hepatic angioendotheliomas	

References

1 Price VH, Odom RB, Ward WH *et al.* Trichothiodystrophy: sulfur-deficient brittle hair as a marker for a neuroectodermal symptom complex. *Arch Dermatol* 1980; **116**: 1375–84.

2 Liang C, Morris A, Schlucker S *et al.* Structural and molecular hair abnormalities in trichothiodystrophy. *J Invest Dermatol* 2006; **126**: 2210–6.

3 Itin PH, Sarasin A, Pittelkow MR. Trichothiodystrophy: update on the sulfur-deficient brittle hair syndromes. *J Am Acad Dermatol* 2001; **44**: 891–920; quiz 21–4.

4 Bergmann E, Egly JM. Trichothiodystrophy, a transcription syndrome. *Trends Genet* 2001; **17**: 279–86.

5 Venning VA, Dawber RP, Ferguson DJ *et al.* Weathering of hair in trichothiodystrophy. *Br J Dermatol* 1986; **114**: 591–5.

6 Giglia-Mari G, Coin F, Ranish JA *et al.* A new, tenth subunit of TFIIH is responsible for the DNA repair syndrome trichothiodystrophy group A. *Nat Genet* 2004; **36**: 714–9.

7 Gummer CL, Dawber RP. Trichothiodystrophy: an ultrastructural study of the hair follicle. *Br J Dermatol* 1985; **113**: 273–80.

8 Liang C, Kraemer KH, Morris A *et al.* Characterization of tiger-tail banding and hair shaft abnormalities in trichothiodystrophy. *J Am Acad Dermatol* 2005; **52**: 224–32.

9 Sperling LC, DiGiovanna JJ. 'Curly' wood and tiger tails: an explanation for light and dark banding with polarization in trichothiodystrophy. *Arch Dermatol* 2003; **139**: 1189–92.

10 Quintero RA, Morales WJ, Gilbert-Barness E *et al.* In utero diagnosis of trichothiodystrophy by endoscopically-guided fetal eyebrow biopsy. *Fetal Diagn Ther* 2000; **15**: 152–5.

11 Brusasco A, Restano L. The typical 'tiger tail' pattern of the hair shaft in trichothiodystrophy may not be evident at birth. *Arch Dermatol* 1997; **133**: 249.

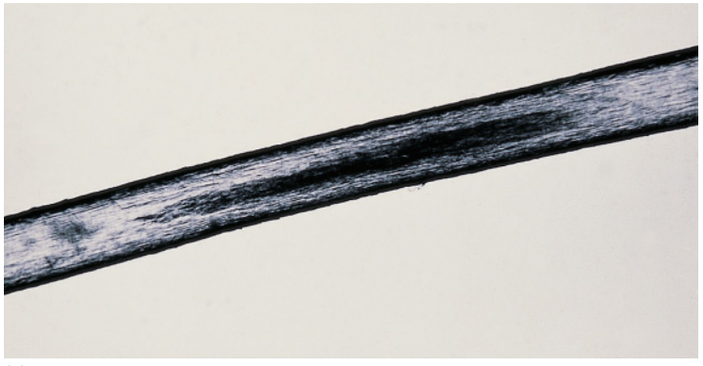
Structural defects without increased fragility

Pili annulati (ringed hair) [1,2]

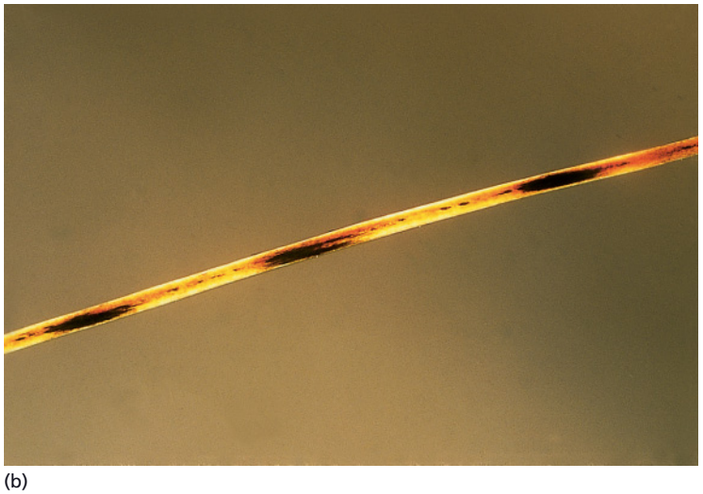
Aetiology. This abnormality is characterized by hair showing alternate light and dark bands along its length. In extreme cases there may be some additional fragility as the lighter areas seen with light microscopy represent a split in the hair cortex. The condition is inherited as an autosomal dominant, and although the molecular basis of the abnormality remains unknown, the genetic defect maps to chromosome 12q [2,3].

Pathology and pathogenesis [2]. With the light microscope the abnormal dark bands alternating with normal light bands are reversed. The bright appearance of the abnormal bands in reflected light is caused by air spaces in the cortex (Fig. 66.66) [4]. Detection of the cortical defect is made easier if the hair is mounted in histological mounting medium because this enhances transmission of light through the hair. Although this illustrates that the pathology can result in structural weakness, it only rarely leads to a clinical complaint of fragility [5].

Electron microscopic studies [5,6] showed that the clusters of air-filled cavities, randomly distributed throughout the cortex in the abnormal bands, lie partly within cortical cells and between



(a)



(b)

Fig. 66.66 (a) Pili annulati. Hair shaft by transmitted light showing an abnormal dark band (central part) caused by multiple cortical air spaces. This corresponds to a bright region as seen by reflected light. (b) The abnormality is intermittent, causing the beaded or ringed appearance.

macrofibrils, or in the case of larger cavities appear to replace cortical cells.

Clinical features. Pili annulati is normally diagnosed as a coincidental finding or as part of pursuance of the unusual, but quite attractive, spangled appearance. The condition has been reported in association with alopecia areata on several occasions. It is uncertain whether this represents a genuine association or if medical scrutiny reveals the otherwise subtle diagnosis [7]. The axillary hair is occasionally affected [8].

The diagnosis is readily established on microscopy of affected hair. A defect in which partially twisted shafts have an elliptical cross-section has been named pseudo-pili annulati because such hair may give an impression of alternating light and dark bands [9].

Prognosis and treatment. The prognosis is good in the sense that the severity of the defect does not increase with age.

References

1 Karsch A. De Capillitiri humani coloiebus quardan. Cited in Landois L. Das plötzliche Ergrauen der Haupthaare. *Arch Pathol Anat Physiol* 1866; **35**: 575–99.

2 Giehl KA, Ferguson DJ, Dawber RP *et al.* Update on detection, morphology and fragility in pili annulati in three kindreds. *J Eur Acad Dermatol Venereol* 2004; **18**: 654–8.

3 Green J, Fitzpatrick E, de Berker D *et al.* A gene for pili annulati maps to the telomeric region of chromosome 12q. *J Invest Dermatol* 2004; **123**: 1070–2.

4 Cady LOP, Trotter M. Study of ringed hair. *Arch Dermatol Syphilol* 1922; **6**: 301–11.

5 Feldmann KA, Dawber RP, Pittelkow MR *et al.* Newly described weathering pattern in pili annulati hair shafts: a scanning electron microscopic study. *J Am Acad Dermatol* 2001; **45**: 625–7.

6 Price VH, Thomas RS, Jones FT. Pili annulati. Optical and electron microscopic studies. *Arch Dermatol* 1968; **98**: 640–7.

7 Green J, Sinclair RD, de Berker D *et al.* Disappearance of pili annulati following an episode of alopecia areata. *Clin Exp Dermatol* 2002; **27**: 458–60.

8 Montgomery RM, Binder AI. Ringed hair. *Arch Dermatol Syphilol* 1948; **58**: 177–91.

9 Price VH, Thomas RS, Jones FT. Pseudopili annulati; an unusual variant of normal hair. *Arch Dermatol* 1970; **102**: 354–8.

Woolly hair

Woolly hair is more or less tightly coiled hair occurring over the entire scalp or part of it. In those of African origin, woolly hair is the norm. Tight coiling, knots and fractures are common [1]. Woolly hair in non-African individuals may be generalized or localized. The generalized forms may be inherited. The investigation by Hutchinson *et al.* [2] was important in delineating the clinical types.

Hair microscopy in all the woolly hair disorders reveals nonspecific features that are consistent with a woolly, stiff hair phenotype. This usually arises in association with grooves, partial twists, irregularity of bore and sometimes features of trauma. When a hair shaft has an irregular shape and is stiffer, it is more prone to damage. The changes are often subtle, and are better appreciated on assessment of at least 20 and preferably 50 hairs or more. Isolated reports describing hair morphology often fall into the trap of describing individual hairs rather than the population of hairs as a whole. This mistake can be compounded by using scanning electron microscopy for the main assessment rather than as a supplementary tool. Although electron microscopy is excellent for revealing great detail in a small number of hairs, it is very poor at showing the characteristics of a population of hairs, which is the usual determinant of a phenotype.

Autosomal dominant woolly hair. This was reported in six generations of a German family [3]. A dominant form of woolly hair in an English family was associated with ichthyosis and deafness [4]. Additional features in a Dutch family with woolly hair included dental caries, acral keratoderma and facial abnormalities [5].

Naxos disease [6]. This autosomal recessive disorder is due to a mutation in the plakoglobin gene [7]. In addition to woolly or bristly hair, Naxos disease is characterized by palmar–plantar keratoderma and cardiomyopathy.

Carvajal disease [8]. The phenotype is similar to Naxos disease, with woolly hair, palmar–plantar keratoderma and cardiomyopathy. Carvajal disease is a recessive disorder due to a mutation in the gene for desmoplakin [9,10].

Acquired woolly hair. This is a heterogeneous group. It occurs most commonly in the context of patterned hair loss [11]. It may also be caused by drugs such as valproate and retinoids [12,13].

Woolly hair naevus [14–16]. This is a naevoid condition with a circumscribed patch of hair showing altered colour and texture. The hair may be fine in infancy, becoming coarser with age, especially at puberty. It is commonly associated with melanocytic or epidermal naevi elsewhere on the skin. Ocular defects and precocious puberty have also been reported [17,18].

References

1 Khumalo NP, Doe PT, Dawber RP *et al.* What is normal black African hair? A light and scanning electron-microscopic study. *J Am Acad Dermatol* 2000; **43**: 814–20.
2 Hutchinson PE, Cairns RJ, Wells RS. Woolly hair. Clinical and general aspects. *Trans St John's Hosp Dermatol Soc* 1974; **60**: 160–77.
3 Hoffmann E. Uber einen Kräuselnaevus innerhalb sonst glatten Kopfhaares im Vergleich zum erblichen Kraushaar und zur Lockenbildung nach Róntgenepilation. *Dermatologica* 1953; **107**: 281–92.
4 Verbov J. Woolly hair—study of a family. *Dermatologica* 1978; **157**: 42–7.
5 van Steensel MA, Koedam MI, Swinkels OQ *et al.* Woolly hair, premature loss of teeth, nail dystrophy, acral hyperkeratosis and facial abnormalities: possible new syndrome in a Dutch kindred. *Br J Dermatol* 2001; **145**: 157–61.
6 Protonotarios N, Tsatsopoulou A, Patsourakos P *et al.* Cardiac abnormalities in familial palmoplantar keratosis. *Br Heart J* 1986; **56**: 321–6.
7 McKoy G, Protonotarios N, Crosby A *et al.* Identification of a deletion in plakoglobin in arrhythmogenic right ventricular cardiomyopathy with palmoplantar keratoderma and woolly hair (Naxos disease). *Lancet* 2000; **355**: 2119–24.
8 Carvajal-Huerta L. Epidermolytic palmoplantar keratoderma with woolly hair and dilated cardiomyopathy. *J Am Acad Dermatol* 1998; **39**: 418–21.
9 Norgett EE, Hatsell SJ, Carvajal-Huerta L *et al.* Recessive mutation in desmoplakin disrupts desmoplakin-intermediate filament interactions and causes dilated cardiomyopathy, woolly hair and keratoderma. *Hum Mol Genet* 2000; **9**: 2761–6.
10 Whittock NV, Wan H, Morley SM *et al.* Compound heterozygosity for non-sense and mis-sense mutations in desmoplakin underlies skin fragility/woolly hair syndrome. *J Invest Dermatol* 2002; **118**: 232–8.
11 Mortimer PS, Gummer C, English J *et al.* Acquired progressive kinking of hair. Report of six cases and review of literature. *Arch Dermatol* 1985; **121**: 1031–3.
12 Bunker CB, Maurice PD, Dowd PM. Isotretinoin and curly hair. *Clin Exp Dermatol* 1990; **15**: 143–5.
13 Berth-Jones J, Shuttleworth D, Hutchinson PE. A study of etretinate alopecia. *Br J Dermatol* 1990; **122**: 751–5.
14 Reda AM, Rogers RS 3rd, Peters MS. Woolly hair nevus. *J Am Acad Dermatol* 1990; **22**: 377–80.
15 Lantis SD, Pepper MC. Woolly hair nevus. Two case reports and a discussion of unruly hair forms. *Arch Dermatol* 1978; **114**: 233–8.
16 Amichai B, Grunwald MH, Halevy S. A child with a localized hair abnormality. Woolly hair nevus. *Arch Dermatol* 1996; **132**: 573–4, 77.
17 Jacobsen KU, Lowes M. Woolly hair naevus with ocular involvement. Report of a case. *Dermatologica* 1975; **151**: 249–52.
18 Tay YK, Weston WL, Ganong CA *et al.* Epidermal nevus syndrome: association with central precocious puberty and woolly hair nevus. *J Am Acad Dermatol* 1996; **35**: 839–42.

Uncombable hair syndrome

Synonyms
- Spun-glass hair
- Cheveux incoiffables
- Pili trianguli et canaliculi

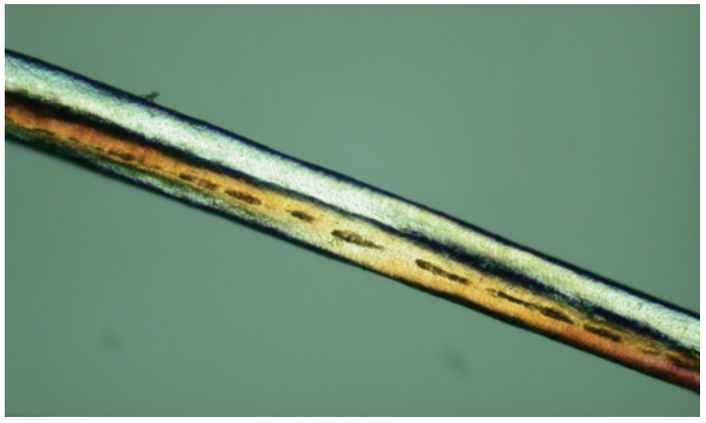


Fig. 66.67 Triangular cross-section of the hair contributes to stiffness.

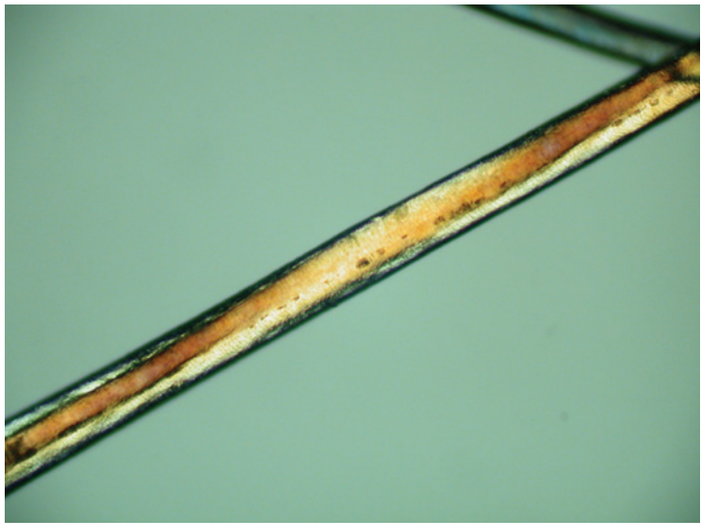


Fig. 66.68 Light microscopy reveals grooving when using partially crossed polarizing filters.

Aetiology [1]. This is a combination of a striking clinical presentation and distinctive hair shaft defect first described by Dupré *et al.* [2]. Since then, many more cases have been reported, some of them under the name of 'spun-glass hair'. Others have preferred the term pili trianguli et canaliculi, with emphasis on the triangular cross-section and longitudinal groove that is commonly found on microscopy. The mode of inheritance is probably autosomal dominant [3].

Pathology. Light microscopy reveals the features in a hair shaft that make it rigid: the triangular cross-section (Fig. 66.67) and longitudinal grooving (Fig. 66.68). Twisting can also be present and contributes to stiffness to a minor degree. Scanning electron microscopy can be helpful on selected hairs (Fig. 66.69) [4–6]. The term 'pili trianguli et canaliculi' has been proposed for these defects. The pili canaliculi are present in all cases, pili trianguli in the majority and pili torti in a few [6]. Van Neste *et al.* [7] have suggested that the misshapen dermal papilla alters the shape of

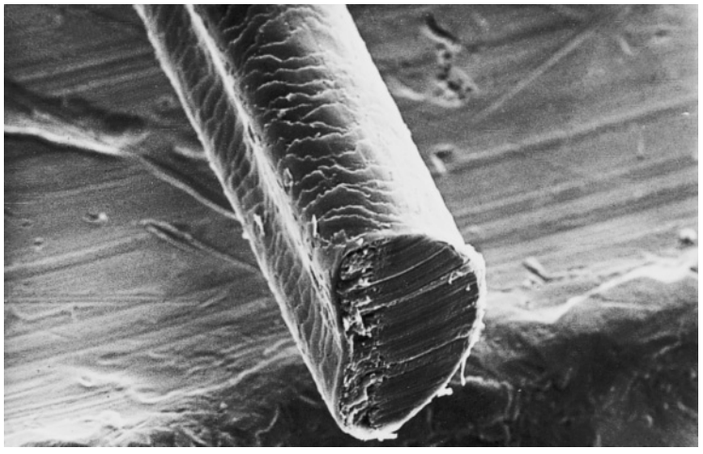


Fig. 66.69 Uncombable hair syndrome. Scanning electron micrograph showing triangular cross-section and canalicular depression or gutter along one side.

the internal root sheath, which hardens (before the hair within) in a triangular cross-sectional shape; the hair then hardens into a shape complementing the root sheath. The defect resembles the 'straight hair naevus' of which it may be a diffuse form.

Clinical features [4,5]. The abnormality may first become obvious from 3 months to 12 years of age. The hair is normal in quantity and sometimes also in length, but the wild, disorderly appearance totally resists all efforts to control it with brush or comb. In some cases, these efforts lead to the hair breaking, but increased fragility is not a constant feature [8]. The hair is often a silvery blonde colour. The eyebrows and eyelashes are normal. The appearance becomes less marked with time [9]. Some people with loose anagen syndrome may have a similar appearance [10].

With light microscopy the diagnosis is dependent upon the experience of the microscopist as the three-dimensional aspect of the shaft changes can be difficult to establish. No treatment is known, although oral biotin therapy has been suggested [11].

References

1 Mallon E, Dawber RP, De Berker D *et al.* Cheveux incoiffables—diagnostic, clinical and hair microscopic findings, and pathogenic studies. *Br J Dermatol* 1994; **131**: 608–14.

2 Dupré A, Rochiccidi P, Bonafe J-L. 'Cheveux incoiffables': anomalie congenitale des cheveux. *Bulletin de la Societe Francaise de Dermatologie et de Syphiligraphie* 1973; **80**: 111–7.

3 Hebert AA, Charrow J, Esterly NB *et al.* Uncombable hair (pili trianguli et canaliculi): evidence for dominant inheritance with complete penetrance based on scanning electron microscopy. *Am J Med Genet* 1987; **28**: 185–93.

4 Dupre A, Bonafe J-L, Litoux F *et al.* [Uncombable hair syndrome. Pili trianguli et canaliculi (author's transl.)]. *Ann Dermatol Venereol* 1978; **105**: 627–30.

5 Dupre A, Bonafe J-L. A new type of pilar dysplasia. The uncombable hair syndrome with pili trianguli et canaliculi. *Arch Dermatol Res* 1978; **261**: 217–8.

6 Ferrando J, Fontarnau R, Gratacos MR *et al.* [Pili canaliculi (uncombable hair syndrome or spun glass hair syndrome). A scanning electron microscope study of ten new cases (author's transl.)]. *Ann Dermatol Venereol* 1980; **107**: 243–8.

7 Van Neste D, Armijo-Subieta F, Tennstedt D *et al.* The uncombable hair syndrome: four non-familial cases of pili trianguli et canaliculi. *Arch Dermatol Res* 1981; **271**: 223–7.

8 Baden HP, Schoenfeld RJ, Stroud JD *et al.* Physicochemical properties of 'spun glass' hair. *Acta Derm Venereol* 1981; **61**: 441–4.

9 Garty B, Metzker A, Mimouni M *et al.* Uncombable hair: a condition with autosomal dominant inheritance. *Arch Dis Child* 1982; **57**: 710–2.

10 Lee AJ, Maino KL, Cohen B *et al.* A girl with loose anagen hair syndrome and uncombable, spun-glass hair. *Pediatr Dermatol* 2005; **22**: 230–3.

11 Shelley WB, Shelley ED. Uncombable hair syndrome: observations on response to biotin and occurrence in siblings with ectodermal dysplasia. *J Am Acad Dermatol* 1985; **13**: 97–102.

Loose anagen hair syndrome [1]

This condition features anagen hairs that are loosely anchored and easily pulled from the scalp [2–4]. The majority of cases are fair-haired children, aged 2–9 years, mostly girls. There is usually a pattern of autosomal dominant inheritance. They typically have slightly unruly hair, which is of uneven length and patchy in quality. Variants of this include those with stiff, uncombable hair and those in whom shedding is the primary complaint. All three phenotypes may coexist within the same family [5]. The children may present with patchy alopecia, leading to a misdiagnosis of alopecia areata, but which, in fact, represents modest hair pulling. The child is well, and there are no other ectodermal abnormalities.

Hair is usually easily and painlessly plucked with the hair-pull test, although this is not a constant or specific finding [6]. Microscopy of plucked hair may show ruffling of the cuticle adjacent to the anagen bulb, giving the appearance of a 'floppy sock' (Fig. 66.70). The hair shaft may have twists and grooves, and be angular in cross-section. The root sheath is absent or there may be a small everted remnant.

The hair becomes more normal with age, although the pull test may still yield abnormally large numbers of hairs into adulthood [7].

There have been isolated reports of loose anagen syndrome associated with hypohidrotic ectodermal dysplasia [8] and ocular coloboma [9].

Histological examination shows premature keratinization of the inner root sheath layers of Huxley and Henle. Trichograms show 98–100% anagen hairs. Keratin K6irs is an inner root sheath keratin proposed as a protein that might control manifestations of the disorder [10]. In one report, mutations in the gene coding for such a keratin supported this possibility [11].

Some authorities have had good results with 5% topical minoxidil [11], although it is not commonly employed and is not of clear value.

References

1 Tosti A, Piraccini BM. Loose anagen hair syndrome and loose anagen hair. *Arch Dermatol* 2002; **138**: 521–2.

2 Price VH, Gummer CL. Loose anagen syndrome. *J Am Acad Dermatol* 1989; **20**: 249–56.

3 Hamm H, Traupe H. Loose anagen hair of childhood: the phenomenon of easily pluckable hair. *J Am Acad Dermatol* 1989; **20**: 242–8.

4 Baden HP, Kvedar JC, Magro CM. Loose anagen hair as a cause of hereditary hair loss in children. *Arch Dermatol* 1992; **128**: 1349–53.

5 Chong AH, Sinclair R. Loose anagen syndrome: a prospective study of three families. *Australas J Dermatol* 2002; **43**: 120–4.

6 Chapman DM, Miller RA. An objective measurement of the anchoring strength of anagen hair in an adult with the loose anagen hair syndrome. *J Cutan Pathol* 1996; **23**: 288–92.

7 Tosti A, Peluso AM, Misciali C *et al.* Loose anagen hair. *Arch Dermatol* 1997; **133**: 1089–93.



Fig. 66.70 Plucked anagen hair in loose anagen syndrome, showing absence of root sheaths and ruffled cuticle.

8 Azon-Masoliver A, Ferrando J. Loose anagen hair in hypohidrotic ectodermal dysplasia. *Pediatr Dermatol* 1996; **13**: 29–32.
9 Murphy MF, McGinnity FG, Allen GE. New familial association between ocular coloboma and loose anagen syndrome. *Clin Genet* 1995; **47**: 214–6.
10 Porter RM, Corden LD, Lunny DP *et al.* Keratin K6irs is specific to the inner root sheath of hair follicles in mice and humans. *Br J Dermatol* 2001; **145**: 558–68.
11 Chapalain V, Winter H, Langbein L *et al.* Is the loose anagen hair syndrome a keratin disorder? A clinical and molecular study. *Arch Dermatol* 2002; **138**: 501–6.

Trichostasis spinulosa

This is probably a normal, age-related phenomenon—easily overlooked—in which successive telogen hairs are retained in predominantly sebaceous follicles [1]. When it was specifically sought, 51 cases were seen in 1 month in Madras [2].

Aetiology. Trichostasis is found most commonly in the middle-aged or elderly and is said by most authors to occur particularly on the nose and face [3]. Other sites were perhaps not always examined, for others have found it to be not uncommon on the trunk, limbs [4] and interscapular area [5].

Pathology. The affected follicles contain up to 50 vellus hairs embedded in a keratinous plug. A mild perifolliculitis is often present. The condition must be differentiated from the 'multiple hairs' of Flemming–Giovannini in which up to seven hairs grow from a composite papilla with a common outer root sheath [6]. Follicles may contain *Malassezia* yeasts and *Propionibacterium acnes* [5].

Clinical features [7]. It is reported at all adult ages, although it appears more common in the elderly. The lesions, which closely resemble comedones, may occur predominantly on the nose, forehead and cheeks, or the face may be spared and the nape, back, shoulders, upper arms and chest may be affected. The lesions vary greatly in number. On inspection with a hand lens, the 'comedones' seem to be unusually prominent and in some cases a tuft of hairs may be seen projecting through the horny plug.

Treatment. Keratolytic preparations have often been recommended but we have found them of little value. The most effective treatment is topical retinoic acid [8], which should be used as in the treatment of acne. Depilatory wax [7], specialized cleaning pads [9] and pulsed diode laser [10] have been advocated.

References

1 Goldschmidt H, Hajyo-Tomoka MJ, Kligman AM. Trichostasis spinulosa: a common inapparent follicular disorder of the aged. In: Brown AC, ed. *First Human Hair Symposium*. New York: Medcom Press, 1974: 50–6.
2 Kailasam V, Kamalam A, Thambiah AS. Trichostasis spinulosa. *Int J Dermatol* 1979; **18**: 297–300.
3 Ladany E. Trichostasis spinulosa. *J Invest Dermatol* 1954; **23**: 33–41.
4 Young MC, Jorizzo JL, Sanchez RL *et al.* Trichostasis spinulosa. *Int J Dermatol* 1985; **24**: 575–80.
5 Chung TA, Lee JB, Jang HS *et al.* A clinical, microbiological, and histopathologic study of trichostasis spinulosa. *J Dermatol* 1998; **25**: 697–702.
6 Pinkus H. Multiple hairs (Flemming–Giovannini); report of two cases of pili multigemini and discussion of some other anomalies of the pilary complex. *J Invest Dermatol* 1951; **17**: 291–301.
7 Sarkany I, Gaylarde PM. Trichostasis spinulosa and its management. *Br J Dermatol* 1971; **84**: 311–5.
8 Mills OH Jr, Kligman AM. Topically applied tretinoin in the treatment of trichostasis spinulosa. *Arch Dermatol* 1973; **108**: 378–80.
9 Elston DM, White LC. Treatment of trichostasis spinulosa with a hydroactive adhesive pad. *Cutis* 2000; **66**: 77–8.
10 Manuskiatti W, Tantikun N. Treatment of trichostasis spinulosa in skin phototypes III, IV, and V with an 800-nm pulsed diode laser. *Dermatol Surg* 2003; **29**: 85–8.

Pili multigemini

Synonym
- Pili bifurcati

The term pili multigemini [1] describes an uncommon developmental defect of hair follicles as a result of which multiple matrices and papillae form hairs that emerge through a single pilosebaceous canal. The incidence of multigeminate hairs in the general population is unknown. Numerous follicles showing this defect have been seen in a patient with cleidocranial dysostosis [2].

Pathology. From two to eight matrices and papillae, each with its internal root sheath, form hairs that are often flattened, ovoid or triangular in configuration and may be grooved. In the follicular canal, contiguous hairs may adhere, bifurcate and then re-adhere.

Clinical features. Multigeminate follicles occur mainly on the face, especially along the lines of the jaw. Tufts of hair may be seen emerging from a few or many follicles. Their discovery is often a matter of chance, but the patient may complain of recurrent inflammatory nodules, leaving scars.

Treatment. If the hairs are plucked, they regrow [2]. A single report of ablation after three treatments with a ruby laser may indicate that this is a therapeutic option [3].

References

1 Pinkus H. Multiple hairs (Flemming–Giovannini): report of two cases of pili multigemini and discussion of some other anomalies of the pilary complex. *J Invest Dermatol* 1951; **17**: 291–301.

2 Mehregan AH, Thompson WS. Pili multigemini. Report of a case in association with cleidocranial dysostosis. *Br J Dermatol* 1979; **100**: 315–22.

3 Naysmith L, De Berker D, Munro CS. Multigeminate beard hairs and folliculitis. *Br J Dermatol* 2001; **144**: 427–8.

Weathering of the hair shaft [1,2]

All hair fibres undergo some degree of cuticular and secondary cortical breakdown from root to tip before being shed during the telogen or early anagen phase of the hair cycle. The term 'weathering' of hair has been limited by some authorities to structural changes in the hair shaft resulting from cosmetic procedures; indeed, both *in vivo* and *in vitro* studies carried out by cosmetic scientists have shown the type of damage that factors such as combing, brushing, bleaching and permanent waving can cause [3,4]. Scalp hair, having a long anagen phase and being subject to more frictional damage and cosmetic treatment, shows more deep cuticular and cortical degeneration than fibres from other sites.

Weathering of scalp hair has been studied in greater detail than hair from other sites. At the root end, surface cuticle cells are closely apposed to deeper layers. Within a few centimetres of the scalp, the free margin of these cells lifts up and breaks irregularly [5]. Increasing scale loss leads to surface areas denuded of cuticle. Many fibres show complete loss of overlapping scales well proximal to the tip (Fig. 66.71). This is particularly common on long hair shafts, which frequently have a frayed tip. Proximal to terminal fraying, longitudinal fissures may be present between exposed cortical cells. Hairs subjected to considerable friction damage may show transverse fissures and some nodes of the type seen in trichorrhexis nodosa [6,7]. Hair that has been bleached or permanently waved may show shaft distortion. The most severe changes are mostly seen near the distal part of the hair shaft in normal scalp hair.

Hair knotting (Fig. 66.72) and braids (Fig. 66.73) are a significant source of hair shaft trauma, with loss of cuticle and damage to cortical fibres.

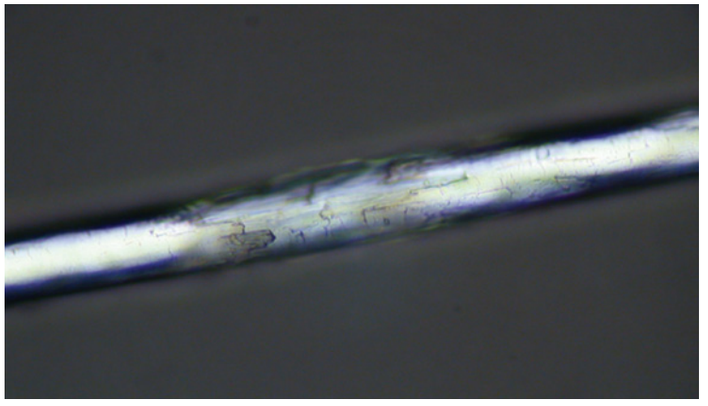


Fig. 66.71 Focal loss of cuticle in a weathered hair.

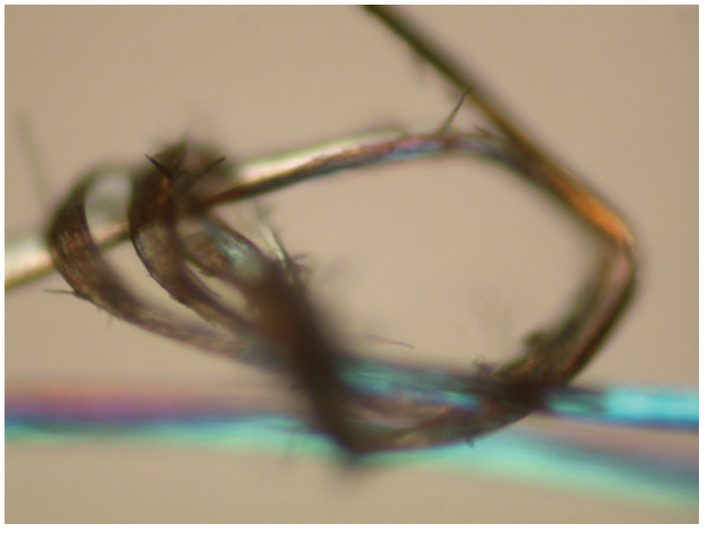


Fig. 66.72 Knotting of single and multiple hairs contributes to hair shaft trauma.

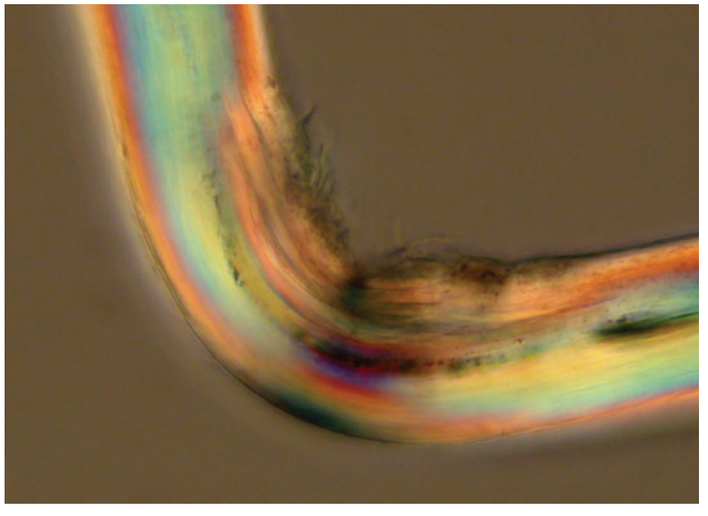


Fig. 66.73 Braiding damages hair shaft cuticle.

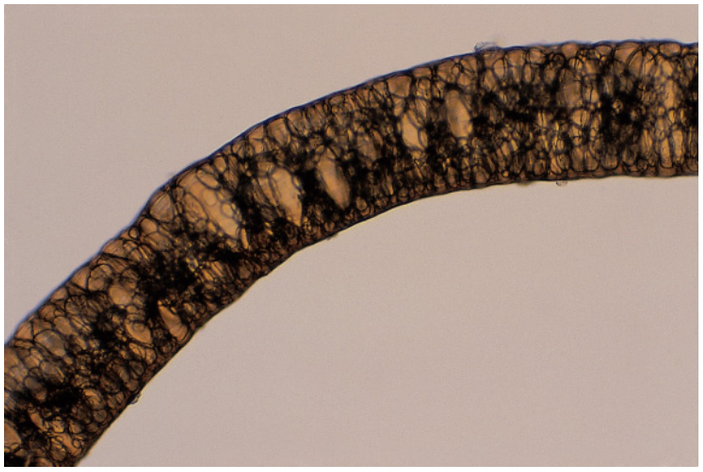


Fig. 66.74 Appearance of normal scalp hair after exposure to naked flame. Bubbles form within the cortex.



Fig. 66.75 Circumferential keratin cast resembling a cuff around the hair shaft.

Trichorrhexis nodosa is the most severe form of weathering. Many of the changes seen in normal hair towards the tip are visible more proximally in congenitally weakened hair [8,9] and in trichorrhexis nodosa caused by overuse of cosmetic treatments [10]. In some hair structural abnormalities, such as monilethrix and pili torti, specific weathering patterns may be seen.

References

1 de Berker D, Sinclair R. Defects of the hair shaft. In: RPR Dawber, ed. *Diseases of the Hair and Scalp*, 3rd edn. Oxford: Blackwell Science, 1997: 427–9.
2 Dawber RPR. Weathering of hair in some genetic hair shaft abnormalities. In: Brown A, Crosin RG, eds. *Hair: Trace Elements and Human Illness*. New York: Praeger, 1980: 95–102.
3 Brown AG, Swift JA. Hair breakage; the scanning electron microscope as a diagnostic tool. *J Soc Cosmet Chem* 1985; **26**: 289–98.
4 Robinson VNE. A study of damaged hair. *J Soc Cosmet Chem* 1976; **27**: 155–62.
5 Garcia ML, Epps JH, Yare RS. Normal cuticle wear patterns in human hair. *J Soc Cosmet Chem* 1978; **29**: 155–64.
6 Chernosky ME. Acquired trichorrhexis nodosa. In: Brown AC, ed. *The First Human Hair Symposium*. New York: Medcom Press, 1974.
7 Dawber R, Comaish S. Scanning electron microscopy of normal and abnormal hair shafts. *Arch Dermatol* 1970; **101**: 316–22.
8 Pollitt RJ, Jenner FA, Davies M. Sibs with mental and physical retardation and trichorrhexis nodosa with abnormal amino acid composition of the hair. *Arch Dis Child* 1968; **43**: 211–6.
9 Lyon JB, Dawber RP. A sporadic case of dystrophic pili torti. *Br J Dermatol* 1977; **96**: 197–8.
10 Camacho-Martinez F. Localized trichorrhexis nodosa. *J Am Acad Dermatol* 1989; **20**: 696–7.

Excessive growth of hair [1–3]

Growth of hair that in any given site is coarser, longer or more profuse than is normal for the age, sex and race of the individual is regarded as excessive. The terms hirsutism and hypertrichosis are often confused. The term hirsutism will be restricted to androgen-dependent hair patterns of typically terminal hair, and the term hypertrichosis will be applied to other patterns of excessive hair growth. In some areas it is difficult to make the distinction, such as in the excess facial hair in porphyria cutanea tarda. This is typically referred to as hypertrichosis, but the point can be argued.

References

1 Barth JH, Dawber RPR. Hypertrichosis. In: Dawber RPR, ed. *Diseases of the Hair and Scalp*, 3rd edn. Oxford: Blackwell Science, 1997: 490–3.
2 Rittmaster RS. Hirsutism. *Lancet* 1997; **349**: 191–5.
3 Dawber RP, Sinclair RD. Hirsuties. *Clin Dermatol* 2001; **19**: 189–99.

Hypertrichosis

The terminology used in describing different patterns of hypertrichosis is inconsistent, as reports have given synonymous terms to clinically different forms of the problem. Baumeister *et al.* [1] sought to unravel the matter. Hypertrichosis usually conforms to the classification of localized or generalized of congenital or acquired pattern, where congenital is loosely interpreted as that seen in early infancy.

Reference

1 Baumeister FA, Schwarz HP, Stengel-Rutkowski S. Childhood hypertrichosis: diagnosis and management. *Arch Dis Child* 1995; **72**: 457–9.

Congenital generalized hypertrichosis

Hypertrichosis lanuginosa

In congenital hypertrichosis, the fetal pelage is not replaced by vellus and terminal hair but persists, grows excessively and is constantly renewed throughout life. In the acquired form, the previously normal follicles of all types revert at any age to the production of hair with lanugo characteristics [1].

Aetiology. Traditionally, cases of congenital hypertrichosis have been classified into two groups—'dog faced' and 'simian'—but a survey [2] suggests that there may be only a single genotype, with considerable interfamily variation in the phenotype. With one exception [3], all published pedigrees suggest autosomal dominant inheritance.

Clinical features [2,4–7]. The child is usually noticed to be excessively hairy at birth (Fig. 66.76). The hair gradually lengthens until by early childhood the entire skin, apart from the palms and soles, is covered by silky hair, which may be 10 cm or more long. Long eyelashes and thick eyebrows are conspicuous features. Some affected individuals are normal at birth and sometimes for the first few years of life, before the universal replacement of other hair types by lanugo. Once established, the hypertrichosis is permanent, but some diminution of hairiness of trunk and limbs may be noted in later childhood. At puberty, axillary, pubic and beard



Fig. 66.76 Congenital hypertrichosis lanuginosa. (Courtesy of Dr Partridge, Leamington, UK.)

hairs retain their downy character. Hypodontia or anodontia and deformities of the external ear are apparently associated in some families, but the physical and mental development of most patients has been normal. In a Mexican family, hypertrichosis was associated with an osteochondral dysplasia [8].

The status of the apparently recessive form is still more uncertain. Three children of a normal mother were densely hairy at birth and died within a week. Neonatal shaving was of cosmetic benefit in one rare case [6].

Treatment of children with long-pulsed ruby laser can result in a useful reduction of hair, although the benefits tend to wane over 6–12 months. Morley reported a 63% reduction in hair counts at 6 months [9].

Universal hypertrichosis

Not all people with congenital universal hypertrichosis will represent the same entity. If it is possible to make the distinction between lanugo and vellus hair, those with vellus hair may be classified as a form of universal hypertrichosis known as the Ambras syndrome, in which there are dysmorphic features. There is a debate concerning the distinction between Ambras syndrome and other forms of generalized hypertrichosis. Baumeister [10] argues that the uniformity of facial growth and the hypertrichosis of the external ear help set Ambras syndrome apart from other extreme forms of universal hypertrichosis where facial hair is not uniformly distributed and the ear hair growth is less marked. Although those outside the diagnosis of Ambras syndrome may have other associated features, such as gingival hyperplasia [11], there are some areas of overlap with respect to rearrangements on chromosome 8 [12,13].

There are also individuals who might be classified as demonstrating universal hypertrichosis, but with less extreme manifestations and without associated or dysmorphic features. The hair pattern is normal, but in any site the hairs are larger and coarser than usual. The eyebrows may be double. Inheritance is determined by an autosomal dominant gene. The features begin to merge into what is considered the normal spectrum.

References

1 Barth JH, Dawber RPR. Hypertrichosis. In: Dawber RPR, ed. *Diseases of the Hair and Scalp*, 3rd edn. Oxford: Blackwell Science, 1997: 490–3.
2 Felgenhauer WR. [Hypertrichosis lanuginosa universalis]. *J Genet Hum* 1969; **17**: 1–44.
3 Jansen TAE, De Lange C. Familial hypertrichosis totalis. *Acta Paediatr Scand* 1945; **33**: 69–85.
4 Barth JH, Wilkinson JD, Dawber RP. Prepubertal hypertrichosis: normal or abnormal? *Arch Dis Child* 1988; **63**: 666–8.
5 Beighton P. Congenital hypertrichosis lanuginosa. *Arch Dermatol* 1970; **101**: 669–72.
6 Partridge JW. Congenital hypertrichosis lanuginosa: neonatal shaving. *Arch Dis Child* 1987; **62**: 623–5.
7 Tourain A, ed. *L'Hérédité en Médecine*. Paris: Masson, 1995.
8 Cantu JM, Garcia-Cruz D, Sanchez-Corona J *et al.* A distinct osteochondrodysplasia with hypertrichosis—individualization of a probable autosomal recessive entity. *Hum Genet* 1982; **60**: 36–41.
9 Morley S, Gault D. Hair removal using the long-pulsed ruby laser in children. *J Clin Laser Med Surg* 2000; **18**: 277–80.
10 Baumeister FA. Differentiation of Ambras syndrome from hypertrichosis universalis. *Clin Genet* 2000; **57**: 157–8.
11 Lee IJ, Im SB, Kim DK. Hypertrichosis universalis congenita: a separate entity, or the same disease as gingival fibromatosis? *Pediatr Dermatol* 1993; **10**: 263–6.
12 Tadin M, Braverman E, Cianfarani S *et al.* Complex cytogenetic rearrangement of chromosome 8q in a case of Ambras syndrome. *Am J Med Genet* 2001; **102**: 100–4.
13 Baumeister FA. Diagnosis of Ambras syndrome: comments on complex cytogenetic rearrangement of chromosome 8q in a case of Ambras syndrome. *Am J Med Genet* 2002; **109**: 77–8.

Congenital generalized hypertrichosis associated with other syndromes

Hurler's syndrome and other mucopolysaccharidoses (see Chapter 15). Hypertrichosis is usually present from early infancy or early childhood on the face, trunk and limbs and may be a conspicuous feature. The eyebrows are often bushy and confluent. In abortive forms, the hair growth may first appear after puberty and be more limited in extent.

Congenital macrogingivae (see Chapter 69) [1]. Exuberant overgrowth of the gingivae as an isolated congenital defect is not uncommon. The association with profuse hypertrichosis of trunk, limbs and lower face has been reported on several occasions. Some patients have markedly acromegaloid features [2] or thyroid disease [3].

Cornelia de Lange syndrome (see Chapter 15). These mildly microcephalic, mentally defective children have a low hairline and profuse overgrowth of the eyebrows. The forehead is covered with long fine hair. Hypertrichosis is usually also conspicuous on the lower back, and may be generalized.

Winchester syndrome. This rare hereditary disorder is characterized by dwarfism, joint destruction and corneal opacities. The skin in many parts of the body becomes thickened, hyperpigmented and hypertrichotic [4,5].

Berardinelli's syndrome [6]. From early life, growth and maturation are accelerated and there is lipodystrophy with muscular hypertrophy. Enlargement of the liver and hyperlipidaemia are other constant features. The skin is coarse and often hypertrichotic.

Trisomy 18 (see Chapter 15). Generalized hypertrichosis of variable degree is present in these patients.

Hypertrichosis has been reported in the rare hereditary globoid leukodystrophy, Krabbe's disease. Most patients die in infancy [4].

Teratogenic syndromes

Fetal alcohol syndrome [7]. Mental and physical retardation affects the infants of many mothers with chronic alcoholism. The cutaneous changes include hypertrichosis and capillary haemangiomatosis.

References

1 Byars LT, Jurkiewicz M. Congenital macrogingivae and hypertrichosis with subsequent giant fibroadenomas of the breasts. *Plast Reconstr Surg* 1962; **27**: 608–12.
2 Vontobel F. Idiopathic gingival hyperplasia and hypertrichosis associated with acromegaloid features. *Helv Paediatr Acta* 1973; **28**: 401–11.
3 Gohlich-Ratmann G, Lackner A, Schaper J *et al.* Syndrome of gingival hypertrophy, hirsutism, mental retardation and brachymetacarpia in two sisters: specific entity or variant of a described condition? *Am J Med Genet* 2000; **95**: 241–6.
4 Cohen AH, Hollister DW, Reed WB. The skin in the Winchester syndrome. *Arch Dermatol* 1975; **111**: 230–6.
5 Winchester P, Grossman H, Lim WN *et al.* A new acid mucopolysaccharidosis with skeletal deformities simulating rheumatoid arthritis. *Am J Roentgenol* 1969; **106**: 121–8.
6 Berardinelli W. An undiagnosed endocrinometabolic syndrome: report of 2 cases. *J Clin Endocrinol Metab* 1954; **14**: 193–204.
7 Hanson JW, Jones KL, Smith DW. Fetal alcohol syndrome. Experience with 41 patients. *JAMA* 1976; **235**: 1458–60.

Congenital localized hypertrichosis

Naevoid hypertrichosis

The growth of hair abnormal for the site and the age of the patient in its length, shaft diameter and colour and may occur as a circumscribed developmental defect, either isolated or associated with other naevoid abnormalities [1], such as duplication of the thumb [2].

Melanocytic naevi (see Chapter 54) may be accompanied by a vigorous growth of coarse hair. The hair may be present from infancy or may develop at puberty. Less often, circumscribed hypertrichosis may occur as the only clinical abnormality. Histologically, the epidermis is acanthotic and the follicles are large, but there is no excess of melanocytes.

Hypertrichosis is a characteristic feature of Becker's naevus (see Chapter 18). The coarse hairs develop in the same body regions as the pigmentation, usually the thoracic or pelvic girdle, but pigmentation and hypertrichosis are not coextensive. It has been suggested that this naevus is a functional one, being androgen dependent; acne may also occur in the same site [3]. It has also rarely been reported in association with limb asymmetry and other ipsilateral anatomical abnormalities [4].

True linear hypertrichotic naevi are rare and hair growth may not be sustained [5].

A tuft of hair in the lumbosacral region, the so-called faun-tail naevus, is often associated with diastematomyelia (Fig. 66.77).



Fig. 66.77 Lumbosacral hypertrichosis ('faun tail'), here associated with diastematomyelia.

References

1 Rupert LS, Bechtel M, Pellegrini A. Nevoid hypertrichosis: multiple patches associated with premature graying of lesional hair. *Pediatr Dermatol* 1994; **11**: 49–51.
2 Taskapan O, Dogan B, Cekmen S *et al.* Nevoid hypertrichosis associated with duplication of the right thumb. *J Am Acad Dermatol* 1998; **39**: 114–5.
3 Downs AM, Mehta R, Lear JT *et al.* Acne in a Becker's naevus: an androgen-mediated link? *Clin Exp Dermatol* 1998; **23**: 191–2.
4 Crone AM, James MP. Giant Becker's naevus with ipsilateral areolar hypoplasia and limb asymmetry. *Clin Exp Dermatol* 1997; **22**: 240–1.
5 Dudding TE, Rogers M, Roddick LG *et al.* Nevoid hypertrichosis with multiple patches of hair that underwent almost complete spontaneous resolution. *Am J Med Genet* 1998; **79**: 195–6.

Acquired generalized hypertrichosis

Acquired hypertrichosis lanuginosa associated with malignancy

Aetiology. In its most dramatic severe form, this syndrome is rare. It usually accompanies a serious, and often terminal, illness. Fine downy hair grows over a large area of the body, replacing normal hair and primary and secondary vellus. Approximately 60 cases have been reported and all except two (in which there was no follow-up) were suffering from malignant disease of the gastrointestinal tract, bronchus, breast, gall bladder, uterus, bladder or other organs [1–5]. One patient with lymphatic leukaemia had acquired ichthyosis as well as hypertrichosis, and one had a lymphoma. The hypertrichosis may precede the diagnosis of a neoplasm by several years [6].

Pathology. In one case [7] the lanugo follicles lay almost parallel to the surface, and were apparently derived from mantle follicles.

Clinical features [8–10]. In the milder forms ('malignant down' [7]), hair is confined to the face, where it attracts attention by its appearance on the nose and eyelids and other sites that normally are clinically hairless. As the growth of hair continues, it may ultimately involve the entire body, apart from the palms and soles. Existing terminal hair of scalp, beard and pubes may not be replaced, and may contrast in colour and texture with the very fine, white or blonde lanugo. Such hair may grow abundantly, even on the previously bald scalp. The hair may grow exceedingly rapidly, up to 2.5 cm/week, and may be more than 10 cm long.

References

1 Hegedus SI, Schorr WF. Acquired hypertrichosis lanuginosa and malignancy. A clinical review and histopathologic evaluation with special attention to the 'mantle' hair of Pinkus. *Arch Dermatol* 1972; **106**: 84–8.
2 Hensley GT, Glynn KP. Hypertrichosis lanuginosa as a sign of internal malignancy. *Cancer* 1969; **24**: 1051–6.
3 Jemec GB. Hypertrichosis lanuginosa acquisita. Report of a case and review of the literature. *Arch Dermatol* 1986; **122**: 805–8.
4 Knowling MA, Meakin JW, Hradsky NS *et al*. Hypertrichosis lanuginosa acquisita associated with adenocarcinoma of the lung. *Can Med Assoc J* 1982; **126**: 1308–10.
5 Ricken KH. [Hypertrichosis lanuginosa et terminalis acquisita and pseudoichthyosis acquisita as paraneoplastic syndromes in chronic lymphatic leukemia (CLL)]. *Z Hautkr* 1979; **54**: 869–72.
6 Farina MC, Tarin N, Grilli R *et al*. Acquired hypertrichosis lanuginosa: case report and review of the literature. *J Surg Oncol* 1998; **68**: 199–203.
7 Davies RA, Newman DM, Phillips MJ *et al*. Acquired hypertrichosis lanuginosa as a sign of internal malignant disease. *Can Med Assoc J* 1978; **118**: 1090, 1095–6.
8 Gonzalez JJ, Ungaro PC, Hooper JW *et al*. Acquired hypertrichosis lanuginosa. Rare manifestation of urinary bladder carcinoma. *Arch Intern Med* 1980; **140**: 969–70.
9 Goodfellow A, Calvert H, Bohn G. Hypertrichosis lanuginosa acquisita. *Br J Dermatol* 1980; **103**: 431–3.
10 Sindhuphak W, Vibhagool A. Acquired hypertrichosis lanuginosa. *Int J Dermatol* 1982; **21**: 599–601.

Non-malignant acquired generalized hypertrichosis

There is a range of non-malignant systemic diseases in which hypertrichosis may develop. Generally, the hair is coarser and less profuse than the lanugo hair associated with systemic malignancy. However, at any single point early in the process, the distinction may not always be obvious.

Endocrine disturbances

Hypothyroidism [1]. A profuse growth of hair on the back and the extensor aspects of the limbs develops in some children with hypothyroidism.

Hyperthyroidism. Coarse hair often grows over the plaques of pretibial myxoedema as it may over other forms of inflammation on the anterior shin.

Possible diencephalic or pituitary mechanisms. Severe, generalized hypertrichosis has been reported in young children after encephalitis [2] and after mumps followed by the sudden onset of obesity [3]. A diencephalic disturbance is postulated. Generalized hypertrichosis occurred in a girl after traumatic shock [4] and remitted in 6 months. There are many reports of hypertrichosis after head injuries, especially in children. The hair growth is first noticed 4–12 weeks after the injury (which seems to be of no consistent type) and appears as fine silky hair on the forehead, cheeks, back, arms and legs, and may be asymmetrical. It is sometimes shed after a few months, but may persist.

Other conditions

Malnutrition [5]. Gross malnutrition, which may be primary or occur in coeliac disease or other malabsorption states or in severe infections, may cause profuse generalized hypertrichosis in children.

Anorexia nervosa. An increased growth of fine downy hair on the face, trunk and arms, sometimes of severe degree, has been reported in 20–77% of adult cases [6,7], and is also seen in children [8]. The prevalence of hypertrichosis in bulimia is reported to be half of that in anorexia, and both are associated with approximately 60% prevalence of scalp alopecia [6].

Dermatomyositis [9]. Excessive hair growth has been noted mainly in children and principally on the forearms, legs and temples, but it may be more extensive.

Epidermolysis bullosa. Gross hypertrichosis of the face and limbs has occurred in association with epidermolysis bullosa of the dystrophic type, although this is rare (see Chapter 39).

Hypertrichosis is seen affecting the extensor surface of the arm (Fig. 66.78) in a sporadic or familial form in children, resolving in adolescence. Although associations with other disorders have been sought, it appears as a largely isolated finding [10].

References

1 Perloff WH. Hirsutism; a manifestation of juvenile hypothyroidism. *JAMA* 1955; **157**: 651–2.
2 Stegagno G, Vignetti P. [Case of hypertrichosis with cerebropathy in a two and one-half year old girl]. *Arch Ital Pediatr Pueric* 1955; **17**: 421–32.
3 Lesne E. Mumps hypertrichosis. *Bull Soc Pediatr* 1930; **28**: 94–6.
4 Robinson RC. Temporary acquired hypertrichosis following traumatic shock. *AMA Arch Derm* 1955; **71**: 401–2.
5 Holzel A. Hypertrichosis in childhood; a clinical study. *Acta Paediatr* 1951; **40**: 59–69.



Fig. 66.78 Hypertrichosis of the elbows in a child.

Table 66.9 Iatrogenic hypertrichosis.

Drug	Comment
Steroid—systemic, injected and topical [1]	Analogous to Cushing's syndrome, with additional local effects with injection or topical use
Diphenylhydantoin [2]	Takes 2–3 months to be apparent
Psoralen [3]	Possibly linked to degree of photosensitization and only shortly outlasts treatment
Diazoxide [2]	
Minoxidil [2,4]	Systemic and topical effect; after only a few weeks—may affect forehead when applied to scalp
Ciclosporin [5,6]	Associated with sebaceous hyperplasia
Latanoprost and bimatoprost [7,8]	Increases growth of eyelashes and adjacent vellus hairs when used as eye drops—analogue of prostaglandin F2α

Table 66.10 Causes of local hypertrichosis.

Example	Comment
Carrying sacks [1]	Hypertrichosis on one shoulder
Carrying religious artefacts [2]	Hypertrichosis on one shoulder
Self-harm [3]	Mentally retarded patient with arm-chewing
Vaccination	Upper arm
Post-surgery [4]	After excision of warts
Chronic inflammation [5–8]	At site of chronic venous insufficiency or thrombophlebitis; following burns and insect bites; chronic eczema
Epidermolysis bullosa [9]	In chronically involved skin
Post-fracture [10]	At site of plaster cast on arms and legs

6 Glorio R, Allevato M, De Pablo A *et al.* Prevalence of cutaneous manifestations in 200 patients with eating disorders. *Int J Dermatol* 2000; **39**: 348–53.
7 Hediger C, Rost B, Itin P. Cutaneous manifestations in anorexia nervosa. *Schweiz Med Wochenschr* 2000; **130**: 565–75.
8 Schulze UM, Pettke-Rank CV, Kreienkamp M *et al.* Dermatologic findings in anorexia and bulimia nervosa of childhood and adolescence. *Pediatr Dermatol* 1999; **16**: 90–4.
9 Reich MG, Reinhart JB. Dermatomyositis associated with hypertrichosis. *Arch Dermatol Syphilol* 1948; **57**: 725–32.
10 Escalonilla P, Aguilar A, Gallego M *et al.* A new case of hairy elbows syndrome (Hypertrichosis cubiti). *Pediatr Dermatol* 1996; **13**: 303–5.

Iatrogenic hypertrichosis

Iatrogenic hypertrichosis is almost universally due to medication, and can be from systemic, injected or local topical use [1] (Table 66.9).

References

1 Hengge UR, Ruzicka T, Schwartz RA *et al.* Adverse effects of topical glucocorticosteroids. *J Am Acad Dermatol* 2006; **54**: 1–15; quiz 16–8.
2 Parker LN, Lifrak ET, Odell WD. Lack of a gonadal or adrenal androgenic mechanism for the hypertrichosis produced by diazoxide, phenytoin and minoxidil. *Biochem Pharmacol* 1982; **31**: 1948–50.
3 Singh G, Lal S. Hypertrichosis and hyperpigmentation with systemic psoralen treatment. *Br J Dermatol* 1967; **79**: 501–3.
4 Burton JL, Marshall A. Hypertrichosis due to minoxidil. *Br J Dermatol* 1979; **101**: 593–5.
5 Tsuji Y, Iwabuchi T, Hamada C *et al.* Effects of cyclosporin A, FK506 and steroid hormones on hair growth. *Exp Dermatol* 1999; **8**: 366–7.
6 de Berker DA, Taylor AE, Quinn AG *et al.* Sebaceous hyperplasia in organ transplant recipients: shared aspects of hyperplastic and dysplastic processes? *J Am Acad Dermatol* 1996; **35**: 696–9.
7 Demitsu T, Manabe M, Harima N *et al.* Hypertrichosis induced by latanoprost. *J Am Acad Dermatol* 2001; **44**: 721–3.
8 Tosti A, Pazzaglia M, Voudouris S *et al.* Hypertrichosis of the eyelashes caused by bimatoprost. *J Am Acad Dermatol* 2004; **51**: S149–50.

Acquired localized hypertrichosis

Cutting or shaving the hair influences neither its rate of growth nor the calibre of the hair shaft. However, any chronic local inflammatory or traumatic process may influence hair growth (Table 66.10, Fig. 66.79).



Fig. 66.79 Circumscribed hypertrichosis in an area of steroid-treated lichen simplex.

Porphyria (see Chapter 59). Hypertrichosis of exposed skin is a common feature of the very rare congenital erythropoietic porphyria; appearing first on the forehead, it later extends to the cheeks and chin and, to a lesser degree, to other exposed areas. It is also present in many cases of the much more common erythropoietic protoporphyria [11].

In porphyria cutanea tarda, hypertrichosis is a common finding [12], and may accompany the pigmentation, plethora, blistering and scleroderma-like changes on exposed skin. Darkening of scalp hair in a subject with white hair at the onset of porphyria cutanea tarda has been reported [13], and hypertrichosis has been reported as the presenting complaint in one subject in whom porphyria cutanea tarda was the underlying cause [14]. In black people, hypertrichosis and pigmentation may be present without blistering [15].

The most extreme degree of hypertrichosis is seen in children with hepatic porphyria induced by hexachlorobenzene or other chemicals. Hypertrichosis is frequent in porphyria variegata. The temples, forehead and cheeks are covered with downy hair. There is also increased pigmentation.

Some forms of localized hypertrichosis are caused by the local application or effect of drugs and are discussed in the section on iatrogenic causes of hypertrichosis (see above).

References

1 Csillag J. Über Beruishypertricose. *Arch Dermatol Syphilol* 1921; **134**: 147–8.
2 Camacho F. Acquired circumscribed hypertrichosis in the 'costaleros' who bear the 'pasos' during Holy Week in Seville, Spain. *Arch Dermatol* 1995; **131**: 361–3.
3 Ressmann AC, Butterworth T. Localized acquired hypertrichosis. *AMA Arch Derm Syphilol* 1952; **65**: 458–63.
4 Friederich HC, Gloor M. [Postoperate 'irritative' hypertrichosis]. *Z Haut Geschlechtskr* 1970; **45**: 419–26.
5 Schraibman IG. Localized hirsuties. *Postgrad Med J* 1967; **43**: 545–7.
6 Shafir R, Tsur H. Local hirsutism at the periphery of burned skin. *Br J Plast Surg* 1979; **32**: 93.
7 Tisocco LA, Del Campo DV, Bennin B *et al.* Acquired localized hypertrichosis. *Arch Dermatol* 1981; **117**: 127.
8 Soyuer U, Aktas E, Ozesmi M. Postphlebitic localized hypertrichosis. *Arch Dermatol* 1988; **124**: 30.
9 Cofano AR. [A case of dystrophic bullous epidermolysis with severe hypertrichosis.]. *Ann Ital Dermatol Sifilogr* 1955; **10**: 195–212.
10 Veldman PH, Reynen HM, Arntz IE *et al.* Signs and symptoms of reflex sympathetic dystrophy: prospective study of 829 patients. *Lancet* 1993; **342**: 1012–6.
11 Dean G, ed. *The Porphyrias*. London: Pitman, 1963.
12 Grossman ME, Bickers DR, Poh-Fitzpatrick MB *et al.* Porphyria cutanea tarda. Clinical features and laboratory findings in 40 patients. *Am J Med* 1979; **67**: 277–86.
13 Shaffrali FC, McDonagh AJ, Messenger AG. Hair darkening in porphyria cutanea tarda. *Br J Dermatol* 2002; **146**: 325–9.
14 Boffa MJ, Reed P, Weinkove C *et al.* Hypertrichosis as the presenting feature of porphyria cutanea tarda. *Clin Exp Dermatol* 1995; **20**: 62–4.
15 Zeligman I. Patterns of porphyria in the American Negro. *Arch Dermatol* 1963; **88**: 616–26.

Hirsutism

Perception of hirsutism is by definition subjective, and women present with a wide variation in severity [1]. Both the severity of the hirsutism and the degree of its acceptance are dependent on racial, cultural and social factors. Even the criteria for the definition of hirsutism used by physicians vary widely [2–6]. In order to resolve this issue, different groups have evolved different grading schemes for body hair growth. The scheme employed in the study by Ferriman and Gallwey [3], which has become the standard grading system, defined hirsutism purely on quantitative grounds. Hirsutism is graded as numerical scores beyond an upper limit of twice the standard deviation from the mean. Scoring can be on a global basis assessing 8–11 body sites, or it can be based on a single site. Others have examined women complaining of hirsutism and compared them with controls; they have demonstrated that there is a considerable overlap in the grades of hirsutism between the two groups [4,6]. Hair on the face, chest or upper back is a good discriminating factor between hirsute women and controls with similar hair growth scores. In clinical practice, it has often been suggested that 'real' hirsutism is simply that which the woman in question thinks is excessive.

Facial and body hair is less commonly seen on oriental people [7], black people and native Americans than on white people [8]. Even among white people there are differences; hair growth is heavier on those of Mediterranean than those of Nordic ancestry [9]. The pattern of hair growth in hirsutism within different racial groups is identical [3–6]. However, different criteria have made the determination of the comparative incidence and severity within these groups difficult to assess. Only one study of a random population stated how many women considered themselves to be hirsute. McKnight [5] examined 400 unselected students, 60% of whom were Welsh: 9% were considered by both the women and investigator to be hirsute and 4% were considered to be disfigured by their facial hair growth. This investigation also included studies of hair growth in women who were not complaining of hirsutism. It is important to the definition of hirsutism that a sizeable proportion of normal women have some terminal hairs on their face, breasts and lower abdomen.

Lorenzo [10] studied 90 hirsute women and found an increased incidence of hirsutism in their female relatives compared with control populations. McKnight [5] reported that 14% of hirsute Welsh women gave a positive family history. This tendency to familial clustering in hirsutism might be anticipated, as some of the underlying disorders that result in hyperandrogenism have a familial basis. For example, congenital adrenal hyperplasia is autosomal recessive and linked to MHC [11], and a very strong family relationship has been reported in the polycystic ovary syndrome (PCOS) [12].

Studies of the psychological burden of hirsutism among women seeking medical treatment suggest that it has a significant impact [13,14] and adversely affects quality of life [15].

References

1 Hughes CL. Hirsutism. In: Olsen EA, ed. *Disorders of Hair Growth*. New York: McGraw-Hill, 2003: 431–52.
2 Editorial: endocrine treatment hirsutism. *BMJ* 1975; **2**: 461.
3 Ferriman D, Gallwey JD. Clinical assessment of body hair growth in women. *J Clin Endocrinol Metab* 1961; **21**: 1440–7.
4 Lunde O, Grottum P. Body hair growth in women: normal or hirsute. *Am J Phys Anthropol* 1984; **64**: 307–13.
5 McKnight E. The prevalence of 'hirsutism' in young women. *Lancet* 1964; **1**: 410–3.
6 Shah PN. Human body hair: a quantitative study. *Am J Obstet Gynecol* 1957; **73**: 1255–65.
7 Hamilton JE. Age, sex and genetic factors in the regulation of hair growth in men: a comparison of Caucasian and Japanese populations. In: Montagna W, Ellis RA, eds. *The Biology of Hair Growth*. New York: Academic Press, 1958: 399–417.
8 Danforth CH, Trotter M. The distribution of body hair in white subjects. *Am J Phys Anthropol* 1922; **5**: 259–65.
9 Greenblatt RB. Hirsutism: ancestral curse or endocrinopathy. In: Mahesh VB, Greenblatt RB, eds. *Hirsutism and Virilism: Pathogenesis, Diagnosis and Management*. Boston: John Wright, 1983: 1–9.
10 Lorenzo EM. Familial study of hirsutism. *J Clin Endocrinol Metab* 1970; **31**: 556–60.
11 Gordon MT, Conway DI, Anderson DC *et al.* Genetics and biochemical variability of variants of 21 hydroxylase deficiency. *J Med Genet* 1985; **22**: 354–60.
12 Hague WM, Adams J, Reeders ST *et al.* Familial polycystic ovaries: a genetic disease? *Clin Endocrinol (Oxf)* 1988; **29**: 593–605.
13 Rabinowitz S, Cohen R, Le Roith D. Anxiety and hirsutism. *Psychol Rep* 1983; **53**: 827–30.
14 Lipton MG, Sherr L, Elford J *et al.* Women living with facial hair: the psychological and behavioral burden. *J Psychosom Res* 2006; **61**: 161–8.
15 Coffey S, Mason H. The effect of polycystic ovary syndrome on health-related quality of life. *Gynecol Endocrinol* 2003; **17**: 379–86.

Endocrine factors and hirsutism [1]

Hirsutism attracts a wide range of endocrine investigations, which differ according to the presentation and the specialty background of the clinician. However, the assumption that hirsutism is wholly related to androgens can be challenged on an individual and general level. The increasing awareness of insulin metabolism and

hirsutism has highlighted this and, on an individual level, it is very clear that many women with unwanted hair have no endocrinological disturbance.

There have been several attempts to correlate hair growth in women with plasma androgen levels but these reports have yielded conflicting results. Reingold and Rosenfield [2] noted a considerable variability between hair growth scores and free testosterone, but no significant relationship. Ruutiainen *et al.* [3] have calculated a complex formula for multiple plasma androgen levels:

$$\text{Testosterone/SHBG} + \text{androstenedione}/100 + \text{dehydroepiandrosterone sulphate}/100$$

This correlates with hair growth only in women with idiopathic hirsutism. In a further study, the same group [4] found a relationship between hair growth and salivary testosterone levels, but in this study no selection of patients was required. The equation demonstrates the significance of sex hormone binding globulin (SHBG) as a factor modifying the effects of circulating androgen.

The first sign of androgen production in women occurs 2–3 years before the menarche and is caused by adrenal secretion [5]. The major androgens secreted by the adrenal are androstenedione, dehydroepiandrosterone (DHA) and DHA sulphate (DHAS). Their control during postpubertal life is unknown, but it is thought that androstenedione and DHA may be controlled by adrenocorticotrophic hormone (ACTH), as their serum levels mirror those of cortisol [6].

Ovarian androgen production begins under the influence of the pubertal secretion of luteinizing hormone (LH) and takes place in the theca cells. The predominant androgen secreted by the ovaries is androstenedione during the reproductive years, and testosterone after the menopause [7].

In normal women, the majority of testosterone production (50–70%) is derived from peripheral conversion of androstenedione in skin and other extrasplanchnic sites [8,9]. The remaining proportion is secreted directly by the adrenals and ovaries. The relative proportion estimated from each gland varies between reported studies: 5–20% from the ovary and 0–30% from the adrenal [10]. DHA is the source of less than 10% of circulating androstenedione and 1% of circulating testosterone [11,12].

Androgen transport proteins

In non-pregnant women, the majority of circulating androgens are bound to a high-affinity β-globulin, sex hormone-binding globulin (SHBG). A further 20–25% is transported loosely bound to albumin, and approximately 1% circulates freely. The free steroid is believed to be active, and the binding protein is therefore of paramount importance. The affinity of androgens for SHBG is proportional to their biological activity.

The function of SHBG is unknown. It is probable that its main role is to buffer acute changes in unbound androgen levels and to protect androgens from degradation. Burke and Anderson [13] suggested that it also acts as a biological amplifier. High oestrogen levels increase SHBG and therefore reduce available androgen; high androgen levels reduce SHBG and increase available free androgen.

References

1 Rosenfield RL. Clinical practice. Hirsutism. *N Engl J Med* 2005; **353**: 2578–88.
2 Reingold SB, Rosenfield RL. The relationship of mild hirsutism or acne in women to androgens. *Arch Dermatol* 1987; **123**: 209–12.
3 Ruutiainen K, Erkkola R, Kaihola HL *et al.* The grade of hirsutism correlated to serum androgen levels and hormonal indices. *Acta Obstet Gynecol Scand* 1985; **64**: 629–33.
4 Ruutiainen K, Sannikka E, Santti R *et al.* Salivary testosterone in hirsutism: correlations with serum testosterone and the degree of hair growth. *J Clin Endocrinol Metab* 1987; **64**: 1015–20.
5 Reiter EO, Fuldauer VG, Root AW. Secretion of the adrenal androgen, dehydroepiandrosterone sulfate, during normal infancy, childhood, and adolescence, in sick infants, and in children with endocrinologic abnormalities. *J Pediatr* 1977; **90**: 766–70.
6 Rosenfeld RS, Rosenberg BJ, Fukushima DK *et al.* 24-Hour secretory pattern of dehydroisoandrosterone and dehydroisoandrosterone sulfate. *J Clin Endocrinol Metab* 1975; **40**: 850–5.
7 Baird DT, Burger PE, Heavon-Jones GD *et al.* The site of secretion of androstenedione in non-pregnant women. *J Endocrinol* 1974; **63**: 201–12.
8 Horton R, Tait JF. Androstenedione production and interconversion rates measured in peripheral blood and studies on the possible site of its conversion to testosterone. *J Clin Invest* 1966; **45**: 301–13.
9 Kirschner MA, Bardin CW. Androgen production and metabolism in normal and virilized women. *Metabolism* 1972; **21**: 667–88.
10 Moltz L, Sorensen R, Schwartz U *et al.* Ovarian and adrenal vein steroids in healthy women with ovulatory cycles—selective catheterization findings. *J Steroid Biochem* 1984; **20**: 901–5.
11 Horton R, Tait JF. In vivo conversion of dehydroisoandrosterone to plasma androstenedione and testosterone in man. *J Clin Endocrinol Metab* 1967; **27**: 79–88.
12 Kirschner MA, Sinhamahapatra S, Zucker IR *et al.* The production, origin and role of dehydroepiandrosterone and delta 5-androstenediol as androgen prehormones in hirsute women. *J Clin Endocrinol Metab* 1973; **37**: 183–9.
13 Burke CW, Anderson DC. Sex-hormone-binding globulin is an oestrogen amplifier. *Nature* 1972; **240**: 38–40.

Androgen pathophysiology in hirsutism [1,2]

The growth of normal secondary sexual hair is a response of the hair follicles to androgens. Abnormal degrees of hair growth are therefore often seen in endocrine disorders characterized by hyperandrogenism. However, not all women with greater amounts of secondary sexual hair will have abnormal androgens. Many will lie within the range of normal for their age and ethnic origin—albeit possibly at an extreme of the spectrum. For those objectively classified as hirsute, many will have underlying polycystic ovary syndrome (PCOS). Most of the others will have no detectable hormonal abnormality and are usually classified as having 'idiopathic' hirsutism. This subgroup is gradually becoming smaller as diagnostic techniques for PCOS become more refined.

Polycystic ovary syndrome [1,2]. There are currently two prevalent diagnostic consensus criteria for PCOS:

1 1990 National Institutes of Health criteria [2]—the two criteria below need to be fulfilled for the diagnosis of PCOS
   — Clinical (acne or hirsutism) and/or biochemical hyperandrogenaemia (measured elevated androgen levels)
   — Menstrual irregularity
2 2003 Rotterdam criteria [3]—two of the three criteria below need to be fulfilled for the diagnosis of PCOS
   — Clinical (acne or hirsutism) and/or biochemical hyperandrogenaemia (measured elevated androgen levels)
   — Menstrual irregularity
   — Polycystic ovarian morphology on ultrasonography

In both instances it is necessary to exclude other specific disorders, such as non-classical adrenal 21-hydroxylase deficiency, Cushing's syndrome, hyperprolactinaemia and androgen-producing tumours. The 1990 criteria lack the presence of polycystic ovaries as a requirement for diagnosis. The reasoning behind this is that a woman may have the metabolic syndrome of PCOS in the absence of the ultrasonically detected abnormal ovaries. Failure to detect such cystic ovaries should not undermine management of the metabolic syndrome. It is equally true that there are polycystic ovaries in normal women [4] or mildly polycystic ovaries in hirsute women with normal menses [5]. The latter finding has led to the inclusion of women who were previously labelled as having idiopathic hirsutism under the diagnosis of PCOS by some clinical groups. An estimated one-third of women in the UK have polycystic ovaries—defined as 10 or more follicles/ovary detected on ultrasound [6]. One-third of these women will suffer from PCOS. The pattern of these features will depend upon the presenting complaint, be it dermatological, endocrinological or gynaecological. In a gynaecology service, Conway *et al.* [7] found the following clinical features in a series of 556 patients: hirsutism (61%), acne (24%), alopecia (8%), acanthosis nigricans (2%), obesity (35%), menorrhagia (1%), oligomenorrhoea (45%), amenorrhoea (26%) and infertility (over 29%). However, those patients who present to a dermatologist almost invariably have acne and/or hirsutism.

Laboratory investigations in PCOS usually reveal an elevated level of luteinizing hormone (LH), often with an increased LH : follicle-stimulating hormone (FSH) ratio. Testosterone, androstenedione and oestradiol levels are also often raised [7], although these tests are neither wholly sensitive nor specific.

Ideas concerning the pathogenesis of PCOS have been as controversial as the diagnosis, and different authorities embrace beliefs that it is primarily caused by an ovarian abnormality with excess androgen secretion, inappropriate gonodotrophin secretion with abnormal LH pulses, a disorder of the adrenal glands and cortisol production or a defect in insulin action and secretion with hyperinsulinaemia and insulin resistance. In addition to the presence of elevated testosterone, commonly in the range of 2.6–4.8 nmol/L [8], 50% or more of patients will have hyperinsulinaemia of varying degrees [9]. This appears to be the case for both the classically obese and the non-obese PCOS patient [10]. Insulin acts to inhibit production of SHBG and stimulates ovarian testosterone production. Both effects amplify androgenic features in PCOS. Excess insulin production is related to the feedback loop of peripheral insulin resistance which increases in PCOS. This is characteristic of type 2 diabetes mellitus, which is a disease that is more common in PCOS. Consistent with this association, PCOS patients are also at higher risk of dyslipidaemias and coronary artery disease [11]. Altered glucose tolerance, hyperinsulinaemia and hirsutism are all exacerbated by obesity, and the relationship between diabetes and hyperandrogenism in women, or 'diabetes of bearded women', has been recognized for many years [12].

Such features are not invariably part of PCOS. Hyperinsulinaemia may be an autonomous process causing acanthosis nigricans (AN), which acts as a cutaneous marker for the insulin resistance (IR). The combination of AN and IR occurs in 5% of women with hyperandrogenism (HA) [13] and in 7% of women presenting with hirsutism [14]. Women with HAIR-AN have marked features of virilism: muscular physique, acne, alopecia and hidradenitis suppurativa [15]. The cause of hyperinsulinaemia is not always apparent, but its effects can be partly reversed by troglitazone [16], and its significance is illustrated by the evolution of HAIR-AN syndrome with an insulin-secreting tumour, cured by partial pancreatectomy [17].

Leptin is a protein secreted by adipocytes that increases energy expenditure and decreases appetite [18]. In genetically obese *ob/ob* mice, leptin is functionally deficient and the mice develop obesity, insulin resistance, diabetes and infertility. In recent years, there has been much interest in determining the role of this protein in PCOS. High serum levels appear primarily related to obesity rather than the diagnosis of PCOS alone [18] and there is evidence that its fluctuations are synchronized with those of luteinizing hormone [19]. However, although there is some correlation between polymorphisms of the leptin gene and insulin regulation, no mutation specific to PCOS has yet been identified [20].

Family studies of PCOS suggest there is a strong heritable component. However, to date 70 candidate genes have been evaluated with no conclusive result [21], possibly consistent with the multifactorial mechanism and variability of the disease.

SAHA syndrome. The term SAHA syndrome is used by some to describe the constellation of features that arise with cutaneous virilization [22]. The acronym stands for *s*eborrhoea, *a*cne, *h*irsutism and *a*ndrogenetic alopecia. The term does not suggest any specific aetiology; all the causes of hirsutism need to be considered and investigated where clinically indicated. As with all women with hirsutism, androgen-receptor sensitivity can be implicated where there are no apparent endocrine abnormalities. The four features exist together in only 20% of women embraced by this diagnosis, but the concept is favoured by some as a clinical label encompassing the range of problems associated with the diagnosis of hirsutism.

Ovarian tumours. Hirsutism is an almost universal feature in virilizing ovarian tumours; however, functioning tumours that cause virilization represent approximately 1% of ovarian tumours [23]. Amenorrhoea or oligomenorrhoea develop in all premenopausal patients, and alopecia, clitoromegaly, deepening of the voice and a male habitus develop in approximately half of the patients [24,25]. The majority of patients with virilizing ovarian tumours have raised plasma testosterone levels [23,25]. As a rule, these levels exceed double the upper limit of normal and combine with the more extreme and evolving clinical picture to distinguish these women from those with PCOS.

Hirsutism in pregnancy. Hirsutism has only rarely been reported to develop during pregnancy; it may be caused by the development of PCOS or a virilizing tumour. PCOS has been reported to present with virilization during the first or third trimester and may regress postpartum [26]. Androgens freely cross the placenta and virilization of a female fetus may occur [27]. The range of tumours occurring during pregnancy has been reviewed by Novak *et al.* [28].

Congenital adrenal hyperplasia. Cholesterol is metabolized in the adrenal cortex, via a complex pathway, into aldosterone, cortisol, androgens and oestrogens. A defect in cortisol synthesis results in redistribution of the precursors to other pathways, which results in overproduction of the other hormones. In approximately 95% of cases, 21-hydroxylation is impaired [29] so that 17-hydroxyprogesterone (17-OHP) is not converted to 11-deoxycortisol. Because of defective cortisol synthesis, ACTH levels increase, resulting in overproduction and accumulation of cortisol precursors, particularly 17-OHP. This causes excessive production of androgens, resulting in virilization.

Congenital adrenal hyperplasia (CAH) is divided into four categories:

1 Salt-losing, which presents in infancy with dehydration
2 Simple virilizing, in which children present with precocious puberty and short stature
3 Non-classical, attenuated or acquired; and it is this variant that is likely to present to the dermatologist with degrees of hirsutism in otherwise well women
4 Cryptic.

The diagnosis of non-classical late-onset CAH (LO-CAH) cannot be made clinically, and dynamic endocrine investigations are required to differentiate between it, PCOS and idiopathic hirsutism. These women may have only mild degrees of hirsutism, normal physique, normal menses and no metabolic sequelae to the changes in cortisol pathways; however, approximately 80% will have polycystic ovaries [30].

21-Hydroxylase deficiency is the most common defect found with (more than 90%) LO-CAH. As many as 3–6% of women presenting with hirsutism may be affected with this form. It is an allelic variant of the classical childhood salt-wasting type. It is associated with a mutation of the gene controlling cytochrome P-450, *CYP 21*, on chromosome 6 [31]. Among a group of 56 women with LO-CAH, a range of mutations was found. Some put the woman at risk of progeny with classical salt-losing CAH if the father is heterozygous for the same mutation. This raises the significance of detailed analysis of this pathway in such women and the genotypic basis in the woman and male partner [32]. 3β- and 11β-hydroxylase deficiencies are less common forms of CAH and are consequently less frequently found in hirsute women [33].

Acquired adrenocortical disease. Adrenal carcinomas usually present with abdominal swelling or pain; however, 10% of both adenomas and carcinomas may present with isolated virilization [34]. The combination of virilization and Cushing's syndrome strongly suggests the presence of a carcinoma. The testosterone level is usually markedly raised in the latter.

Patients with Cushing's syndrome are said to have both hypertrichosis, a generalized diffuse growth of fine hair resulting from hypercortisolaemia, and androgen-induced coarse hair in the usual male pattern [35].

Hyperprolactinaemia. The exact relationship between prolactin and hirsutism is not clear. The incidence of hirsutism in the amenorrhoea–galactorrhoea syndrome has been reported as 22–60% [36]. This may be caused by a direct effect of prolactin on adrenal androgen production or by PCOS, with which it is frequently associated; prolactin has also been reported to attenuate cutaneous 5α-reductase activity both *in vivo* and *in vitro* [37].



Fig. 66.80 Facial hirsutism: in this case not associated with any systemic disease or detectable biochemical endocrine abnormality.

Idiopathic hirsutism (Fig. 66.80). Idiopathic hirsutism is the diagnostic label given to those hirsute women in whom no overt underlying endocrine disorder can be detected. There are a number of subtle dynamic alterations in the androgen metabolism of some hirsute women compared with non-hirsute women: daily testosterone production can be increased 3.5- to 5-fold; the majority of androgen is secreted as testosterone (hirsute 75%, versus normal <40%) rather than as androstenedione [38]; increased androgens in hirsute women are associated with lower levels of SHBG, which binds less testosterone and increases its free level [39]. More free testosterone is therefore available for peripheral metabolism and clearance; these two factors disguise the increased rates of testosterone production.

Normal values for total testosterone are found in 25–60% of hirsute women and in 80% of those with regular menstrual cycles [40]. This may be a result of the effect of SHBG or the wide fluctuations in plasma testosterone seen in hirsute women, or it may reflect the role of androgen receptor sensitivity. The finding of a small elevation of testosterone is not a holy grail, and the tendency to repeat the test many times in the setting of hirsutism is only warranted in progressive or extreme cases where a neoplasm is suspected. Although many women classified as having idiopathic hirsutism may have subtle PCOS, others may be completely normal.

References

1 Tsilchorozidou T, Overton C, Conway GS. The pathophysiology of polycystic ovary syndrome. *Clin Endocrinol (Oxf)* 2004; **60**: 1–17.
2 Zawadeski JK, Dunaif A. Diagnostic criteria for PCOS: towards a more rational approach. In: Dunaif A, Givens JR, Haseltine FP *et al.*, eds. *PCOS*. Boston: Blackwell Scientific, 1992: 377–84.
3 Rotterdam ESHRE/ASRM-sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod* 2004; **19**: 41–7.
4 Polson DW, Adams J, Wadsworth J *et al.* Polycystic ovaries—a common finding in normal women. *Lancet* 1988; **1**: 870–2.

5 Carmina E, Lobo RA. Polycystic ovaries in hirsute women with normal menses. *Am J Med* 2001; **111**: 602–6.
6 Balen A. Pathogenesis of polycystic ovary syndrome—the enigma unravels? *Lancet* 1999; **354**: 966–7.
7 Conway GS, Honour JW, Jacobs HS. Heterogeneity of the polycystic ovary syndrome: clinical, endocrine and ultrasound features in 556 patients. *Clin Endocrinol (Oxf)* 1989; **30**: 459–70.
8 Coney P. Polycystic ovarian disease: current concepts of pathophysiology and therapy. *Fertil Steril* 1984; **42**: 667–82.
9 Balen AH, Conway GS, Kaltsas G *et al.* Polycystic ovary syndrome: the spectrum of the disorder in 1741 patients. *Hum Reprod* 1995; **10**: 2107–11.
10 Pugeat M, Ducluzeau PH, Mallion-Donadieu M. Association of insulin resistance with hyperandrogenia in women. *Horm Res* 2000; **54**: 322–6.
11 Marsden PJ, Murdoch AP, Taylor R. Tissue insulin sensitivity and body weight in polycystic ovary syndrome. *Clin Endocrinol (Oxf)* 2001; **55**: 191–9.
12 Conway GS, Jacobs HS. Clinical implications of hyperinsulinaemia in women. *Clin Endocrinol (Oxf)* 1993; **39**: 623–32.
13 Achard C, Thiers S. Insuffisance glycolytique associée au virilisme pilaire (diabète des femmes à barbe). *Bull Acad Nat Méd* 1921; **136**: 58–63.
14 Flier JS, Eastman RC, Minaker KL *et al.* Acanthosis nigricans in obese women with hyperandrogenism. Characterization of an insulin-resistant state distinct from the type A and B syndromes. *Diabetes* 1985; **34**: 101–7.
15 Barth JH, Ng LL, Wojnarowska F *et al.* Acanthosis nigricans, insulin resistance and cutaneous virilism. *Br J Dermatol* 1988; **118**: 613–9.
16 Elkind-Hirsch KE, McWilliams RB. Pregnancy after treatment with the insulin-sensitizing agent troglitazone in an obese woman with the hyperandrogenic, insulin-resistant acanthosis nigricans syndrome. *Fertil Steril* 1999; **71**: 943–7.
17 Pfeifer SL, Wilson RM, Gawkrodger DJ. Clearance of acanthosis nigricans associated with the HAIR-AN syndrome after partial pancreatectomy: an 11-year follow-up. *Postgrad Med J* 1999; **75**: 421–2.
18 Jacobs HS, Conway GS. Leptin, polycystic ovaries and polycystic ovary syndrome. *Hum Reprod Update* 1999; **5**: 166–71.
19 Takeuchi T, Tsutsumi O. Basal leptin concentrations in women with normal and dysfunctional ovarian conditions. *Int J Gynaecol Obstet* 2000; **69**: 127–33.
20 Sir-Petermann T, Piwonka V, Perez F *et al.* Are circulating leptin and luteinizing hormone synchronized in patients with polycystic ovary syndrome? *Hum Reprod* 1999; **14**: 1435–9.
21 Urbanek M. The genetics of the polycystic ovary syndrome. *Nat Clin Pract Endocrinol Metab* 2007; **3**: 103–11.
22 Orfanos CE, Adler YD, Zouboulis CC. The SAHA syndrome. *Horm Res* 2000; **54**: 251–8.
23 Woodruff JD, Parmley TH. Virilizing ovarian tumors. In: Mahesh VB, Greenblatt RB, eds. *Hirsutism and Virilism: Pathogenesis, Diagnosis and Management*. Boston: John Wright, 1983: 129–45.
24 Sandberg EC, Jackson JR. A clinical analysis of ovarian virilizing tumors. *Am J Surg* 1963; **105**: 784–92.
25 Moltz L, Pickartz H, Sorensen R *et al.* Ovarian and adrenal vein steroids in seven patients with androgen-secreting ovarian neoplasms: selective catheterization findings. *Fertil Steril* 1984; **42**: 585–93.
26 Shortle BE, Warren MP, Tsin D. Recurrent androgenicity in pregnancy: a case report and literature review. *Obstet Gynecol* 1987; **70**: 462–6.
27 Fayez JA, Bunch TR, Miller GL. Virilization in pregnancy associated with polycystic ovary disease. *Obstet Gynecol* 1974; **44**: 511–21.
28 Novak DJ, Lauchlan SC, McCawley JC *et al.* Virilization during pregnancy. Case report and review of literature. *Am J Med* 1970; **49**: 281–90.
29 Dewailly D, Vantyghem-Haudiquet MC, Sainsard C *et al.* Clinical and biological phenotypes in late-onset 21-hydroxylase deficiency. *J Clin Endocrinol Metab* 1986; **63**: 418–23.
30 Hague WM, Adams J, Rodda C *et al.* The prevalence of polycystic ovaries in patients with congenital adrenal hyperplasia and their close relatives. *Clin Endocrinol (Oxf)* 1990; **33**: 501–10.
31 Blanche H, Vexiau P, Clauin S *et al.* Exhaustive screening of the 21-hydroxylase gene in a population of hyperandrogenic women. *Hum Genet* 1997; **101**: 56–60.
32 Deneux C, Tardy V, Dib A *et al.* Phenotype-genotype correlation in 56 women with nonclassical congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *J Clin Endocrinol Metab* 2001; **86**: 207–13.
33 Pang SY, Lerner AJ, Stoner E *et al.* Late-onset adrenal steroid 3 beta-hydroxysteroid dehydrogenase deficiency. I. A cause of hirsutism in pubertal and postpubertal women. *J Clin Endocrinol Metab* 1985; **60**: 428–39.
34 King DR, Lack EE. Adrenal cortical carcinoma: a clinical and pathologic study of 49 cases. *Cancer* 1979; **44**: 239–44.
35 Griffing GT, Melby JC. Cushing's syndrome. In: Mahesh VB, Greenblatt RB, eds. *Hirsutism and Virilism: Pathogenesis, Diagnosis and Management*. Boston: John Wright, 1983: 63–78.
36 Robyn C, Tukumbane M. Hyperprolactinemia and hirsuties. In: Mahesh VB, Greenblatt RB, eds. *Hirsutism and Virilism: Pathogenesis, Diagnosis and Management*. Boston: John Wright, 1983: 189–211.
37 Serafini P, Lobo RA. Prolactin modulates peripheral androgen metabolism. *Fertil Steril* 1986; **45**: 41–6.
38 Kirschner MA, Bardin CW. Androgen production and metabolism in normal and virilized women. *Metabolism* 1972; **21**: 667–88.
39 Hauner H, Ditschuneit HH, Pal SB *et al.* Fat distribution, endocrine and metabolic profile in obese women with and without hirsutism. *Metabolism* 1988; **37**: 281–6.
40 Cumming DC, Wall SR. Non-sex hormone-binding globulin-bound testosterone as a marker for hyperandrogenism. *J Clin Endocrinol Metab* 1985; **61**: 873–6.

Diagnostic approach to the hirsute woman (Table 66.11)

Most women consulting with concern over hirsutism will provide two key clues. The first will be the appearance and the second the history. The main area of patient concern is usually the face, but this is not always easy to assess. The patient may spend hours every day plucking or otherwise managing the excess hair and so appear to be someone with no clinical problem. The account of such self care leads the examination to other body sites, where the most sensitive is the chest and back for pathological hirsutism. Although there are scoring systems, these are mainly of scientific interest or as a means of monitoring response to treatment. The presence or absence of terminal hair at specific sites is important to document. This can be supplemented by an approximation of how dense the growth is—ranging from a few scattered hairs to confluence. Other features of androgenization to be noted are acne, androgenetic alopecia, acanthosis nigricans and obesity. Malignant androgen-secreting tumours may also lead to clitoromegaly, increased muscle bulk and a deeper voice.

If the clinician is able to corroborate the complaint of hirsutism, the history becomes important as a means of determining whether it is likely to have broader biological significance. Of primary importance is the duration of the problem and its rate of evolution. A short history of a dramatic change raises concern that there might be an androgen-secreting tumour. A slow evolution during puberty would make such a diagnosis unlikely. Menstrual regularity is a further important detail, where lifelong menstrual disturbance suggests PCOS, recent marked alteration suggests a new evolving diagnosis, and the absence of any menstrual problem is likely to mean that there is no hormonal basis to the hirsutism. A drug history may point to an ingested source of androgens (e.g. glucocorticoid or anabolic steroids) and those used to enhance athletic performance. The progestogenic components of many contraceptive preparations are relatively androgenic and this is often cited as a cause of hirsutism, but it has not been a major factor in our experience.

The extent to which it is necessary for hirsute women without suspicious signs or history to be investigated is debatable. If the primary concern is to exclude an androgen-secreting tumour, a measure of serum testosterone is a good screening tool. This might

Table 66.11 Investigations where hirsutism suggests an endocrinological origin (after Setji & Brown [1]).

Test	Looking for	Comment
Total testosterone	Androgen-secreting tumour	This is a useful screening test. If it is more than twice the upper limit of normal then it should trigger more extensive investigation for an androgen-secreting tumour. Up to that level above normal, it probably represents PCOS, but this should be clarified.
Dehydroepiandrosterone sulphate	Androgen-secreting tumour of the adrenal glands	DHEAS is a supplementary test if there is a raised testosterone or other reason to pursue the possibility of an androgen-secreting tumour. Although modest elevations in dehydroepiandrosterone sulphate can be seen in polycystic ovary syndrome, greater elevations should prompt a complete evaluation for an adrenal androgen-secreting tumour.
Morning 17-hydroxyprogesterone	Late-onset congenital adrenal hyperplasia	This screens for non-classical congenital adrenal hyperplasia which in turn might be suggested by a family history or the more complete variant of CAH.
24-h urine for cortisol and creatinine	Cushing's syndrome	Look for the classic features of Cushing's syndrome with hypertension, abdominal striae, central abdominal weight gain and moon face.
Prolactin	Hyperprolactinaemia	There may be associated galactorrhoea. Some advocate this test in all women with irregular menstrual cycles.
Thyroid function studies	Hyper- or hypothyroidism	May help explain altered menstruation, but will rarely be a cause of hirsutism.
Imaging	Localizing abnormality within ovaries or adrenals	Choice of imaging needs to be directed by specific line of enquiry by someone expert in endocrinological or gynaecological tumours.

need to be repeated, and if there is heightened concern it can be supplemented by measurement of the dehydroepiandrosterone sulphate (DHEAS). Clarifying the diagnosis of PCOS may be appropriate (Table 66.12) or further investigation arranged in collaboration with a primary care physician or gynaecologist. Pursuing the diagnosis of LO-CAH is controversial. In some hands the diagnosis will not alter management. Others advocate the use of dexamethasone indefinitely, with all the attendant risks of osteoporosis and other metabolic sequelae [2].

However, there may be reduced fertility [3] and if the woman is heterozygous for a mutation that predisposes to the salt-losing variant, her progeny may be at risk if their father is heterozygous for the same mutation [4]. This last point raises the question of whether the diagnosis should be sought more rigorously. Although it may not alter clinical management of the hirsutism, it may be of significance to the reproductive plans of the woman. At present, defining whether the woman is heterozygous for a mutation of the CYP21 gene that can lead to the salt-losing variant of CAH in offspring is limited to gene analysis. The phenotype and endocrine investigations are not sufficiently sensitive to distinguish between heterozygosity for a range of CAH mutations of differing significance. The standard screening test for such mutations is estimation of the basal (early morning) plasma 17-hydroxyprogesterone level.

It remains an overriding priority to exclude a virilizing tumour if this is suggested by the history and examination [1,5]. The clinician can then determine which investigations are indicated.

References

1 Setji TL, Brown AJ. Polycystic ovary syndrome: diagnosis and treatment. *Am J Med* 2007; **120**: 128–32.

2 New MI. Extensive clinical experience: nonclassical 21-hydroxylase deficiency. *J Clin Endocrinol Metab* 2006; **91**: 5044–50.

3 Premawardhana LD, Hughes IA, Read GF *et al.* Longer term outcome in females with congenital adrenal hyperplasia (CAH): the Cardiff experience. *Clin Endocrinol (Oxf)* 1997; **46**: 327–32.

4 Deneux C, Tardy V, Dib A *et al.* Phenotype–genotype correlation in 56 women with nonclassical congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *J Clin Endocrinol Metab* 2001; **86**: 207–13.

5 Barth JH. Investigations in the assessment and management of patients with hirsutism. *Curr Opin Obstet Gynecol* 1997; **9**: 187–92.

Treatment [1–4]

Treatment can be as simple as giving clear advice on how to use products available at the chemist, to a complex mix of topical, laser and systemic therapies alongside management of related endocrinological pathology. In all settings there is usually an element of psychological support needed, which may amount to a requirement for counselling or other specialist services. The schema for management of PCOS addresses the core elements of management of all women with hirsutism (Table 66.13).

Cosmetic measures

Where a woman has failed to make full use of physical methods of hair removal it is helpful if the dermatologist is familiar with what is available [4] or can direct her to a reliable beautician or other expert in cosmetic care for advice (Table 66.14). The easiest measure is to bleach the hair with hydrogen peroxide. This produces a yellow hue because of the native colour of keratin. Hair plucking is widely performed, but the act of plucking not only removes the hair shaft but also stimulates the root into anagen and there is only a brief delay while the shaft grows through the epidermis. Shaving avoids this problem by removing all the hairs but is followed by growth only of the hairs that were previously in anagen. Negative aspects of shaving the face are that it is seen as a masculine activity and also that the regrowing hair has a sharp bevel, accentuating the rough feel.

Depilatory creams contain thioglycolates that dissolve sulphur bonds within keratin molecules, making the hair gelatinous. They are irritant and require care in terms of strength of preparation and duration of exposure. It is often the case that the patient has used a depilatory cream once and given up because she became

Table 66.12 Options for investigation and assessment directed to the diagnosis of PCOS.

Test	Normal range (may vary with local laboratory assays)	Comment
Pelvic ultrasound	To assess ovarian morphology and endometrial thickness	Ultrasound criteria are 10 or more cysts, 2–8 mm in diameter, arranged either peripherally around a dense core of stroma or scattered throughout an increased amount of stroma
Testosterone	0.50–3.5 nmol/L	It is unnecessary to measure other androgens unless total testosterone is >5 nmol/L, in which case comprehensive assessment is indicated
Luteinizing hormone	2–10 IU/L	FSH and LH best measured during days 1–3 of a menstrual bleed; if oligo-/amenorrhoeic then random samples are taken
Follicle stimulating hormone	2–8 IU/L	
Fasting glucose	<5.5 mmol/L	Fasting level below 5.5 mmol/L makes impaired glucose tolerance very unlikely
Fasting lipid profile		

Table 66.13 Management of polycystic ovary syndrome.

Aspects of PCOS	Points for the dermatologist to cover	Points for multidisciplinary involvement
Psychosocial	Address body image and eating behaviours Screen for depression Discuss stress management Provide non-judgmental support	Specialist counselling or behavioural therapy
Cosmetic	Discuss depilatory products available over the counter: bleaching, thioglycolate, waxing Discuss use of eflornithine hydrochloride 13.9% cream, laser therapy, and electrolysis Discuss use of oestrogen-containing oral contraceptives to suppress androgens if no contraindications Consider spironolactone 50–100 mg twice daily for refractory hirsutism or acne Discuss other aspects of androgenization—acne, androgenetic alopecia, acanthosis Discuss obesity, if relevant, and direct to local services	
Metabolic	*Consider referral to primary care physician or general physician*	Assess diabetes and cardiovascular disease risk Assess risk for non-alcoholic fatty liver disease Discuss lifestyle therapies such as nutrition and physical activity
Cycle control	*Consider referral to gynaecologist or work with primary care physician*	Assess bleeding pattern and risk for endometrial hyperplasia Provide therapies to prevent endometrial hyperplasia: oestrogen-progestin therapy
Ovulation	*Consider referral to gynaecologist or work with primary care physician*	Discuss fertility goals Discuss therapies to increase ovulation frequency: weight loss, metformin Consider referral to reproductive endocrinology for assisted reproductive technologies
Sleep apnoea	*Consider referral to respiratory physician or work with primary care physician*	Screen for sleep apnoea Refer for sleep study if indicated

Table 66.14 Physical and topical measures in the management of hirsutism.

Method	Practitioner	Cost	Efficacy	Longevity	Side effects
Pluck	Self	Zero	+	2–4 weeks	Soreness; folliculitis
Shave	Self	Low	++	1–2 weeks	Folliculitis; stubble
Bleaching	Self	Low	+	1–3 weeks	Good for concealing modest amounts of hair
Waxing, sugaring	Self or beautician	Medium	++	2–4 weeks	Can treat larger areas, but then more soreness
Depilatory creams	Self or beautician	Medium	++	1–2 weeks	Irritant dermatitis; needs care on sensitive areas
Eflornithine cream	Self on prescription	Medium	+/–	4 weeks	Folliculitis; can be used in conjunction with laser or IPL therapy
Electrolysis	Beautician	High	++(+)	weeks–months	Long-term therapy; folliculitis and scarring
Intense pulsed light	Technician	High	++(+)	?6–9 months after course of treatment	Course of multiple treatments with top-ups in following years Can be painful, burn and scar, especially on dark skin, and no use for light hair
Laser	Technician	High	+++	?6–12 months after course of treatment	As above

Table 66.15 The principal systemic treatments in hirsutism.

Drug	Dose	Duration	Side effects
Dianette™ [12–14]	As in oral contraceptive pill (OCP)	>6 months	OCP side effects plus additional thromboembolic risk?
Cyproterone acetate [12,13,15]	50–100 mg in postmenopausal or as supplement to Dianette	>12 months	As above
Spironolactone [16–21]	50–200 mg daily	>6 months	Menstrual irregularities, breast tenderness, diuretic effects
	As in OCP with withdrawal bleed or continuous		
Other drugs			
Finasteride [22–25]			
Metformin [26–28]			
Flutamide [29,30]			
GnRH [30–32]			

sore or it did not work. Results can be improved by employing the cream in the same way that one might use dithranol when treating psoriasis, using small test areas to gain experience.

Waxing is performed by the application of a sheet of soft wax to the skin and, as soon as it has hardened with the hair shafts embedded, abruptly peeling it off, removing all the shafts. This is a painful method and is often complicated by folliculitis. Certain natural sugars, long used in parts of the Middle East, are becoming popular in place of waxes, as they appear to depilate as effectively but with less trauma. Both methods require the hair to be long enough for the wax, resin or sugar to gain sufficient purchase on the hair shaft.

Electrolysis is a more permanent method of hair removal [4]. A fine electrical wire is introduced down the hair shaft to the papilla, which is destroyed by an electrical current. Laser thermolytic hair removal is now widely used. Although its long-term efficacy is not yet known, laser-assisted hair removal has been in use for sufficient time to allow a reasonable estimate of its efficacy and safety. A Cochrane review observed that the data to support laser and intense pulse light treatment were poor, but favoured alexandrite and diode lasers over others. Lack of follow-up data was a particular shortcoming [5]. Most practitioners will select patients for dark hair and light skin. This maximizes the absorption of laser energy by the hair and minimizes absorption by the skin. Nevertheless, it is still possible for soreness and crusting to occur following treatment. In darker skin this can be associated with post-inflammatory pigmentary changes. Treatments are usually administered as part of a course of at least three visits separated by intervals of several weeks. This reflects the biology of the follicle, which is most responsive to abalation when in anagen. The gap between treatments allows those hairs initially in telogen to move into anagen. Sommer *et al.* [6] compared the hair counts 36 weeks after four treatments to the face with a normal pulse ruby laser with the effects of a single pulse. Hair counts were reduced by 61% and 41%, respectively. A randomized trial in hirsute PCOS women examined the effects of alexandrite laser therapy given monthly for 6 months, demonstrating a reduction in hair growth, patient anxiety scores, time spent on other depilatory activities and an improvement in quality of life score [7]. There was no follow-up period and the treatment was provided free. There is some evidence that supplementing laser therapy with eflornithine cream results in a greater benefit sooner than with either treatment alone [8]. Broad-band intense pulsed light (IPL) represents a cheaper technology with less restriction on the licensing of those who use it. It is likely to achieve some of the benefits of laser therapy [9].

Drug therapy [10]

The main systemic therapies for hirsutism are antiandrogens (Table 66.15). These can be effective in the absence of abnormal androgen levels. Any benefits are lost within months of stopping treatment [11]. Hence, the patient and the person with responsibility for prescribing need to be aware of the following parameters when medication is commenced:

1. All medications have potential side effects and they may need monitoring by blood tests and other measures.
2. Pregnancy is contraindicated with these drugs, and a pregnancy prevention plan is required for the duration of therapy—which may be long term.
3. Not everyone will respond to treatment and therefore some semi-objective measure of efficacy and timescale for assessment need to be discussed, e.g. frequency of use of depilatory aids at outset and 6 months, or photographs.
4. At what point is it envisaged that the treatment will be stopped?
5. Who will take responsibility for long-term prescribing and monitoring, where medication is being used outside the licensed indication?

When the hirsute woman has PCOS, prescribing may cross boundaries with treatment of other aspects of the disease and care may be shared with other clinicians. When the woman is otherwise completely healthy, the issues of using unlicensed medication in the absence of disease have to be weighed against the loss of function arising from the hirsutism. Our preferences are spironolactone or an oral contraceptive with a non-androgenic progestagen—Dianette™, Marvelon™ and Yasmin™ are examples. Cyproterone acetate, present in Dianette™, can be prescribed alone in post-menopausal women, but its use raises some concerns, cited below.

Cyproterone acetate [12]. Cyproterone acetate (CPA) is a synthetic progestogen that acts as both an antiandrogen and an inhibitor of gonadotrophin secretion. It reduces androgen production, increases the metabolic clearance of testosterone and binds to the

androgen receptor; in addition, long-term therapy is associated with a reduction in the activity of cutaneous 5α-reductase. Although CPA is a potent progestogen it does not reliably inhibit ovulation. It is usually administered with cyclical oestrogens in order to maintain regular menstruation and to prevent conception in view of the risk of feminizing a male fetus.

A Cochrane review found that cyproterone acetate has only poor quality data to support its use, although subjective improvements are recorded [12]. Several regimens have been advocated. Low-dose therapy (Dianette; Schering AG) is an oral contraceptive containing 35 µg ethinylestradiol and 2 mg CPA, taken daily for 21 in every 28 days. However, many of the dose-ranging and efficacy studies have been performed using the preparation that contained 50 µg ethinylestradiol; this may be relevant, as only the higher dose of oestrogen increases SHBG. Current dosage recommendations for CPA usually advise that 50 mg or 100 mg CPA should be administered for 10 days/cycle (e.g. day 1–10 or 5–15). However, there have now been many dose-ranging studies that suggest that there is no dose effect. Objective studies comparing Dianette with and without extra CPA found no difference in the reduction of overall hirsutism grades, although the rate of onset of benefit was faster with the additional cyproterone [13].

Side effects of CPA include weight gain, fatigue, loss of libido, breast tenderness, nausea, headaches and depression. All these side effects are more frequent with higher dosage. As with all medication for a cosmetic problem, safety can be a concern for those needing long-term treatment. Contraindications to its use are the same as for the contraceptive pill and include cigarette smoking, age, obesity and hypertension. Venous thromboembolism is the adverse effect of greatest medical significance. A case–controlled study indicated that risk of this was four times greater in women taking an oral contraceptive containing CPA as the progestogen in comparison with those containing levonorgestrel [14].

One retrospective study of 188 women taking CPA 50–100 mg/day described side effects in 23%. Nine per cent of the total group stopped therapy because of these effects, but it is difficult to discern whether the problems were a result of the CPA or ethinylestradiol that many also took. Most of the problems were related to mood, weight or menstrual disturbance. Within the group, 24 had been treated for 5 years or more, nine for 10 years or more and two for 15 years [15].

Spironolactone [16,17]. Spironolactone is a popular and relatively safe treatment for hirsutism. Formal proof of its efficacy is not to the highest standards, although a Cochrane review concluded that it was of some value [18]. The discovery of its benefit in hirsutism was serendipitous—a 19-year-old hirsute woman with PCOS was treated with spironolactone (200 mg/day) for concurrent hypertension and she noted after 3 months the need to shave less frequently.

Spironolactone has several antiandrogenic pharmacological properties. It reduces the bioavailability of testosterone by interfering with its production and increases its metabolic clearance. It binds to the androgen receptor and, like CPA, long-term therapy is associated with a reduction in cutaneous 5α-reductase activity [19]. Different regimens of spironolactone have been studied, varying between 50 and 200 mg taken either daily or cyclically (daily for 3 weeks in every 4). Within this dosage range, the one chosen will depend on the severity of the hirsutism. A 3 out of 4 week cycle will result in a withdrawal bleed in the fourth week, which is similar to that seen with the oral contraceptive. However, spironolactone cannot be relied on as a contraceptive and care must be taken to avoid conception while taking the drug.

Spritzer *et al.* [20] compared the relative benefits of a combination of CPA 50 mg/day and ethinylestradiol 35 µg/day with spironolactone 200 mg/day over 12 months. Both groups were stratified for those with PCOS and idiopathic hirsutism. In both groups, those with idiopathic hirsutism did equally well. However, those with PCOS did significantly better with the CPA/ethinylestradiol combination. Where spironolactone is used in combination with ethinylestradiol 35 µg and CPA 2 mg, there may be some modest advantage [21].

When compared with finasteride 5 mg, spironolactone 100 mg produced a significantly greater improvement during a 9-month trial [22]. Spironolactone may feminize a male fetus. Long-term high-dose spironolactone has been shown to produce tumours in rodents. Some clinicians feel that this finding makes long-term use inappropriate in healthy young patients with hirsutism.

5α-Reductase inhibitors. 5α-Reductase inhibitors are a potential systemic therapy for hirsutism. Finasteride inhibits the type 2 isoenzyme of 5α-reductase and has been assessed in small placebo-controlled trials, with some benefit after 6 months' therapy. Small, randomized, head-to-head trials suggest that finasteride works over a 6–12-month period, but is probably not quite as good as Dianette or spironolactone [22,23]. Supplementing spironolactone with finasteride might result in a greater improvement than treatment with finasteride alone [24]. Trials of topical finasteride have had mixed results [25]. Other systemic and topical 5α-reductase inhibitors are likely to be available in the near future. This group of drugs feminizes a male fetus, which is a drawback in the therapy of women of child-bearing potential and has precluded a drug licence for the treatment of hirsutism.

Corticosteroids. Corticosteroids have a logical place in the treatment of LO-CAH. However, any benefits that they may have in this setting need to be balanced against their well-described side effects. Although their use is justified on the basis of physiological replacement, it is likely that pharmacological regimens will far exceed this, with consequent problems. Spritzer *et al.* [33] demonstrated the superiority of ethinylestradiol 35 µg with CPA 2 mg over hydrocortisone in the treatment of hirsutism associated with LO-CAH.

Metformin. Metformin is a biguanide originally used in the treatment of type 2 diabetes mellitus. It has found a place in the treatment of hirsutism associated with hyperinsulinaemia and insulin resistance. In this setting, it can reduce levels of insulin, increase insulin sensitivity and, particularly when associated with a low-calorie diet, result in weight loss [26]. In many, this constellation of problems will be part of PCOS, and metformin has also been shown to assist in normalization of menstruation and improvement in lipid profiles [27]. These broader metabolic effects can

make it a useful therapy where hirsutism is not the only problem, and it is not a drug likely to be prescribed by a dermatologist [28].

Eflornithine. Eflornithine was originally used orally in the treatment of hyperactivity in childhood. It is an inhibitor of ornithine decarboxylase and is able to delay the initiation of anagen, leaving the follicle in telogen. Limited studies show some reduction in hirsutism when used as a cream on women's faces [34]. It may also supplement the efficacy of laser when used as combined therapy [8].

Flutamide [29]. This acts as a pure antiandrogen and works by binding to androgen receptors. However, it has no antigonadotrophic effect, and the result of binding to central androgen receptors is that it prevents the negative feedback effect of testosterone, and consequently androgen levels rise. There has been a single study in hirsutism in which flutamide (250 mg twice daily) was administered with an oral contraceptive for 7 months; 12 out of 13 patients demonstrated a subjective reduction in hair growth and improvement in acne [30]. Flutamide is potentially hepatotoxic and requires close monitoring to avoid liver complications. It is not used in the UK.

Gonadotrophin-releasing hormone agonists. Gonadotrophin-releasing hormone (GnRH) agonists inhibit LH production and this results in profound suppression of ovarian androgen production. These agents are presently under investigation, but preliminary studies suggest that they effectively reduce hair growth and acne in women with PCOS [31], and may be superior to finasteride [32]. Drawbacks are cost and the need for monthly injections.

References

1 Young R, Sinclair R. Hirsutes. II: Treatment. *Australas J Dermatol* 1998; **39**: 151–7.
2 Bergfeld WF. Hirsutism in women. Effective therapy that is safe for long-term use. *Postgrad Med* 2000; **107**: 93–4, 99–104.
3 Lanigan SW. Management of unwanted hair in females. *Clin Exp Dermatol* 2001; **26**: 644–7.
4 Olsen EA. Methods of hair removal. *J Am Acad Dermatol* 1999; **40**: 143–55; quiz 56–7.
5 Haedersdal M, Gotzsche PC. Laser and photoepilation for unwanted hair growth. *Cochrane Database Syst Rev* 2006: CD004684.
6 Sommer S, Render C, Sheehan-Dare R. Facial hirsutism treated with the normal-mode ruby laser: results of a 12-month follow-up study. *J Am Acad Dermatol* 1999; **41**: 974–9.
7 Clayton WJ, Lipton M, Elford J *et al.* A randomized controlled trial of laser treatment among hirsute women with polycystic ovary syndrome. *Br J Dermatol* 2005; **152**: 986–92.
8 Hamzavi I, Tan E, Shapiro J *et al.* A randomized bilateral vehicle-controlled study of eflornithine cream combined with laser treatment versus laser treatment alone for facial hirsutism in women. *J Am Acad Dermatol* 2007; **57**: 54–9.
9 Sadick NS, Weiss RA, Shea CR *et al.* Long-term photoepilation using a broad-spectrum intense pulsed light source. *Arch Dermatol* 2000; **136**: 1336–40.
10 Rittmaster RS. Antiandrogen treatment of polycystic ovary syndrome. *Endocrinol Metab Clin North Am* 1999; **28**: 409–21.
11 Yucelten D, Erenus M, Gurbuz O *et al.* Recurrence rate of hirsutism after 3 different antiandrogen therapies. *J Am Acad Dermatol* 1999; **41**: 64–8.
12 Van der Spuy ZM, le Roux PA. Cyproterone acetate for hirsutism. *Cochrane Database Systematic Reviews* 2003: CD001125.
13 Barth JH, Cherry CA, Wojnarowska F *et al.* Cyproterone acetate for severe hirsutism: results of a double-blind dose-ranging study. *Clin Endocrinol (Oxf)* 1991; **35**: 5–10.
14 Vasilakis-Scaramozza C, Jick H. Risk of venous thromboembolism with cyproterone or levonorgestrel contraceptives. *Lancet* 2001; **358**: 1427–9.
15 van Wayjen RG, van den Ende A. Experience in the long-term treatment of patients with hirsutism and/or acne with cyproterone acetate-containing preparations: efficacy, metabolic and endocrine effects. *Exp Clin Endocrinol Diabetes* 1995; **103**: 241–51.
16 Barth JH, Cherry CA, Wojnarowska F *et al.* Spironolactone is an effective and well tolerated systemic antiandrogen therapy for hirsute women. *J Clin Endocrinol Metab* 1989; **68**: 966–70.
17 Ober KP, Hennessy JF. Spironolactone therapy for hirsutism in a hyperandrogenic woman. *Ann Intern Med* 1978; **89**: 643–4.
18 Farquhar C, Lee O, Toomath R *et al.* Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne. *Cochrane Database of Systematic Reviews* 2003: CD000194.
19 Serafini PC, Catalino J, Lobo RA. The effect of spironolactone on genital skin 5 alpha-reductase activity. *J Steroid Biochem* 1985; **23**: 191–4.
20 Spritzer PM, Lisboa KO, Mattiello S *et al.* Spironolactone as a single agent for long-term therapy of hirsute patients. *Clin Endocrinol (Oxf)* 2000; **52**: 587–94.
21 Kelestimur F, Sahin Y. Comparison of Diane 35 and Diane 35 plus spironolactone in the treatment of hirsutism. *Fertil Steril* 1998; **69**: 66–9.
22 Beigi A, Sobhi A, Zarrinkoub F. Finasteride versus cyproterone acetate-estrogen regimens in the treatment of hirsutism. *Int J Gynaecol Obstet* 2004; **87**: 29–33.
23 Lumachi F, Rondinone R. Use of cyproterone acetate, finasteride, and spironolactone to treat idiopathic hirsutism. *Fertil Steril* 2003; **79**: 942–6.
24 Kelestimur F, Everest H, Unluhizarci K *et al.* A comparison between spironolactone and spironolactone plus finasteride in the treatment of hirsutism. *Eur J Endocrinol* 2004; **150**: 351–4.
25 Lucas KJ. Finasteride cream in hirsutism. *Endocr Pract* 2001; **7**: 5–10.
26 Pasquali R, Gambineri A, Biscotti D *et al.* Effect of long-term treatment with metformin added to hypocaloric diet on body composition, fat distribution, and androgen and insulin levels in abdominally obese women with and without the polycystic ovary syndrome. *J Clin Endocrinol Metab* 2000; **85**: 2767–74.
27 Ibanez L, Valls C, Potau N *et al.* Sensitization to insulin in adolescent girls to normalize hirsutism, hyperandrogenism, oligomenorrhea, dyslipidemia, and hyperinsulinism after precocious pubarche. *J Clin Endocrinol Metab* 2000; **85**: 3526–30.
28 Harborne L, Fleming R, Lyall H *et al.* Descriptive review of the evidence for the use of metformin in polycystic ovary syndrome. *Lancet* 2003; **361**: 1894–901.
29 Erenus M, Gurbuz O, Durmusoglu F *et al.* Comparison of the efficacy of spironolactone versus flutamide in the treatment of hirsutism. *Fertil Steril* 1994; **61**: 613–6.
30 Cusan L, Dupont A, Belanger A *et al.* Treatment of hirsutism with the pure antiandrogen flutamide. *J Am Acad Dermatol* 1990; **23**: 462–9.
31 Rittmaster RS. Differential suppression of testosterone and estradiol in hirsute women with the superactive gonadotropin-releasing hormone agonist leuprolide. *J Clin Endocrinol Metab* 1988; **67**: 651–5.
32 Bayhan G, Bahceci M, Demirkol T *et al.* A comparative study of a gonadotropin-releasing hormone agonist and finasteride on idiopathic hirsutism. *Clin Exp Obstet Gynecol* 2000; **27**: 203–6.
33 Spritzer P, Billaud L, Thalabard JC *et al.* Cyproterone acetate versus hydrocortisone treatment in late-onset adrenal hyperplasia. *J Clin Endocrinol Metab* 1990; **70**: 642–6.
34 Wolf JE Jr, Shander D, Huber F *et al.* Randomized, double-blind clinical evaluation of the efficacy and safety of topical eflornithine HCl 13.9% cream in the treatment of women with facial hair. *Int J Dermatol* 2007; **46**: 94–8.

Hair pigmentation [1–3]

In humans, hair pigmentation depends entirely on the presence of melanin from melanocytes. The perceived colour will depend also on physical phenomena. The range of colours produced by melanins is limited to shades of grey, yellow, brown, red and black,



Fig. 66.81 Human anagen follicle, showing pigment donation to the hair cortex. There is pigment incontinence in the dermal papilla (Masson–Fontana stain).

depending on the amount and ratio of eumelanin (black) and phaeomelanin (red).

It is important to remember that much of the research on melanogenesis and its cellular control is in relation to epidermis outside the follicle. Many aspects of hair bulb melanogenesis are likely to be the same. Hair melanin is formed by melanocytes situated in the hair bulb epithelium around the upper half of the dermal papilla amongst cells destined to form the hair cortex. Ultrastructurally, hair bulb melanocytes appear more melanogenic than epidermal melanocytes, and their population density is much greater than in the epidermis (approximately one melanocyte to four basal keratinocytes in the upper hair bulb compared with a ratio of 1 : 25 in the basal layer of the epidermis [4]). Melanocytes are also present in the basal layer of the infundibulum and, in small numbers, in the outer root sheath of the lower part of the follicle. These latter cells are DOPA-negative and non-melanized and are thought to form a melanocyte reservoir in the skin. Under certain circumstances (e.g. during repigmentation of vitiligo), outer root sheath melanocytes proliferate and migrate to the epidermis [5]. In humans, hair bulb melanocytes donate pigment almost exclusively to cells undergoing early differentiation to form the hair cortex (Fig. 66.81). Therefore there is a close spatial and functional relationship between hair bulb melanocytes and the cells that act as pigment receptors (cortical keratinocytes).

Melanogenic activity in the hair follicle is closely linked to the hair cycle. In the telogen follicle, non-melanogenic melanocytes are found in the basal layer of the outer root sheath and in the secondary germ region [6]. These cells are assumed to be the precursors of active melanocytes during the next anagen phase, and either migrate or are carried into the hair bulb in early anagen development. They congregate in the upper part of the anagen hair bulb amongst cells destined to form the hair cortex. Melanogenesis begins well after epithelial proliferation has started and coincides with the onset of morphological evidence of cortical differentiation. Tyrosinase activity becomes apparent in Anagen 3, and pigment transfer to cortical epithelium begins in the Anagen 4 stage of development [7–9]. In pigmented hair follicles, intense melanogenesis continues throughout the remainder of anagen (Anagen 5 and 6), and then ceases with the onset of catagen. The close anatomical and functional association of hair bulb melanocytes with cells to which pigment is donated, cells destined to form the hair cortex, suggests that interaction between these two cell types has a key role in regulating pigmentary activity. The fate of hair bulb melanocytes during catagen is uncertain. Non-melanizing melanocytes have been observed in the regressing epithelial column in human catagen follicles [10], but apoptotic deletion of follicular melanocytes has also been described during this stage of the hair cycle [11].

References

1 Slominski A, Wortsman J, Plonka PM *et al.* Hair follicle pigmentation. *J Invest Dermatol* 2005; **124**: 13–21.

2 Bolognia JL, Pawelek JM. Biology of hypopigmentation. *J Am Acad Dermatol* 1988; **19**: 217–55.

3 Van Neste D, Tobin DJ. Hair cycle and hair pigmentation: dynamic interactions and changes associated with aging. *Micron* 2004; **35**: 193–200.

4 Cesarini JP. Hair melanin and hair color. In: Orfanos CE, Happle R, eds. *Hair and Hair Diseases*. Berlin: Springer-Verlag, 1990: 165–97.

5 Cui J, Shen LY, Wang GC. Role of hair follicles in the repigmentation of vitiligo. *J Invest Dermatol* 1991; **97**: 410–6.

6 Silver AF, Chase HB, Potten CS. Melanocyte precursor cells in the hair follicle germ during the dormant stage (telogen). *Experientia* 1969; **25**: 299–301.

7 Kukita A. Changes in tyrosinase activity during melanocyte proliferation in the hair growth cycle. *J Invest Dermatol* 1957; **28**: 273–4.

8 Fitzpatrick TB, Brunet P, Kukita A. The nature of hair pigment. In: Montagna W, Ellis RA, eds. *The Biology of Hair Growth*. New York: Academic Press, 1958: 255–303.

9 Slominski A, Paus R. Melanogenesis is coupled to murine anagen: toward new concepts for the role of melanocytes and the regulation of melanogenesis in hair growth. *J Invest Dermatol* 1993; **101**: 90S–7S.

10 Commo S, Bernard BA. Melanocyte subpopulation turnover during the human hair cycle: an immunohistochemical study. *Pigment Cell Res* 2000; **13**: 253–9.

11 Tobin DJ, Hagen E, Botchkarev VA *et al.* Do hair bulb melanocytes undergo apoptosis during hair follicle regression (catagen)? *J Invest Dermatol* 1998; **111**: 941–7.

Melanogenesis [1–3]

Functional melanocytes respond to the peptide hormones α-melanocyte stimulating hormone (α-MSH) or ACTH through the MC1R receptor to stimulate melanin production. This receptor is a transmembrane G-protein. When bound to melanocortin peptides, intracellular cyclic adenosine monophosphate (AMP) rises, resulting in tyrosinase gene expression, melanocyte proliferation and increased dendricity. There may also be switching of melanin type. Loss-of-function mutations in the *MC1R* gene are associated with a switch from eumelanin (dark) to phaeomelanin (red) production [4,5]. The phaeomelanosome, containing the key enzyme of the tyrosinase pathway, produces light red-yellowish melanin,

whereas the eumelanosome produces darker melanins via induction of additional TYRP1, TYRP2, SILV enzymes, and the P-protein. Intramelanosomal pH, governed by the P-protein, may act as a critical determinant of tyrosinase enzyme activity. There is significant genetic variation in the genes from which these proteins arise. Over 30 variant alleles have been identified in the *MC1R* gene alone. Functional correlation of *MC1R* alleles with skin and hair colour provides evidence that this receptor molecule is a principal component underlying normal human pigment variation.

In black hair follicles, deposition of melanin within melanosomes continues until the whole unit is uniformly dense. Lighter coloured hair shows less melanin deposition, and blonde hair follicles show melanosomes with a moth-eaten appearance. Red and blonde hair follicles have spherical melanosomes; those in brown and black hair are ellipsoidal.

Pigment is incorporated into hair cortex. No pigment is donated to presumptive cuticular and internal root sheath cells, although pigment granules have been detected in the cuticle of human nostril hair and in the coats of many animals [6]. Melanocytes are functional only during the anagen phase of the hair cycle. Some melanocytes undergo apoptotic deletion during catagen, but amelanotic melanocytes can be found in telogen hair bulb epithelium, possibly derived from the melanocyte reservoir in the outer root sheath [7,8]. In murine follicles, melanocytes are also present in the dermal papilla during telogen [8].

Hair colour resulting from physical phenomena

The whiteness of hair seen when melanin is absent is an optical effect resulting from reflection and refraction of incident light from various interfaces at which zones of different refractive index meet. Thus, in general, non-pigmented hair with a broad medulla appears paler than non-medullated hair. Normal 'weathering' of hair along its length may lead to the terminal part appearing lighter than the rest as a result of a similar mechanism—the cortex and cuticle become disrupted and form numerous interfaces from internal reflection and refraction of light. This also applies in trichorrhexis nodosa (excessive 'weathering'), in which patients often note a lightening in colour of the brittle hair, and in the white bands of pili annulati. Because these optical lightening effects are caused by reflection and refraction of incident light, when such hairs are viewed by transmitted light microscopy they appear dark. Newly formed, unpigmented hair with no medulla appears yellowish rather than white. This is probably the intrinsic colour of dense keratin as orientated in hair fibres. Findlay [9] showed that the perceived colour is affected by the physical characteristics of the hair shaft and may bear little relationship to the true chromaticity of the shaft.

Hair fibre tryptophan content increases with age and within age groups, and is higher in dark hair than fair hair. The exception is with white hair and the significance of these findings is uncertain [10].

Lanugo hair present *in utero* is unpigmented. Vellus hair is also typically unpigmented but, in men in particular, some vellus fibres may pigment slightly after puberty. Hair colour varies according to body site in most people. Eyelashes are usually the darkest. Scalp hair is generally lighter than genital hair, which often has a reddish tint even in subjects having essentially brown hair. Apart from individuals with red scalp hair, a red tint to axillary hair is most common in brown-haired individuals.

Hairs on exposed parts may be bleached by sunlight. Very dark hair first lightens to a brownish-red colour but rarely becomes blonde even after strong sunlight exposure; brown hair, however, may be bleached white.

References

1 Montagna W, Parakkal PK. *The Structure and Function of Skin*. New York: Academic Press, 1974.
2 Orfanos C, Ruska H. [Fine structure of human hair. 3. Hairpigment]. *Arch Klin Exp Dermatol* 1968; **231**: 279–92.
3 Rees JL. The melanocortin 1 receptor (MC1R): more than just red hair. *Pigment Cell Res* 2000; **13**: 135–40.
4 Schaffer JV, Bolognia JL. The melanocortin-1 receptor: red hair and beyond. *Arch Dermatol* 2001; **137**: 1477–85.
5 Sturm RA, Teasdale RD, Box NF. Human pigmentation genes: identification, structure and consequences of polymorphic variation. *Gene* 2001; **277**: 49–62.
6 Swift JA. The histology of keratin fibres. In: Asquith RS, ed. *The Chemistry of Natural Protein Fibres*. London: Wiley, 1977.
7 Commo S, Bernard BA. Melanocyte subpopulation turnover during the human hair cycle: an immunohistochemical study. *Pigment Cell Res* 2000; **13**: 253–9.
8 Sharov A, Tobin DJ, Sharova TY *et al*. Changes in different melanocyte populations during hair follicle involution (catagen). *J Invest Dermatol* 2005; **125**: 1259–67.
9 Findlay GH. An optical study of human hair colour in normal and abnormal conditions. *Br J Dermatol* 1982; **107**: 517–27.
10 Bertazzo A, Biasiolo M, Costa CV *et al*. Tryptophan in human hair: correlation with pigmentation. *Farmaco* 2000; **55**: 521–5.

Variation in hair colour

Genetic and racial aspects [1–3]

Ethnic differences in hair colour are very conspicuous, as are the differences in hair morphology, although colour and hair form are inherited separately [4]. Dark hair predominates in the world. Among white people there is wide variation in colour within geographical regions. Blonde hair is most frequent in northern Europe and black hair in southern and eastern Europe; foci of blondeness are to be found even in North Africa, the Middle East and in some Australoids. Congoid, Capoid, Mongoloid and Australoid hair is mainly black.

Red hair

This has attracted more attention than other colours because it is less common, so distinctive and, to date, is the only hair colour for which the genetic basis is known. The incidence of red hair varies from 0.3% in northern Germany to as high as 11% in parts of Scotland. In mice the synthesis of eumelanin or phaeomelanin is determined by activation or blockade, respectively, of the melanocortin receptor-1 (MC1R). The receptor is activated by α-MSH and blocked by agouti signalling protein derived from the dermal papilla. It is not yet clear whether there is a human equivalent for agouti. However, three variant regions within the highly polymorphic human *MC1R* gene confer reduced function of the receptor and are associated with red hair. Most red-haired individuals are homozygous or compound heterozygous for these *MC1R* polymorphisms.

Heterochromia

This implies the growth of hair of two distinct colours in the same individual. A colour difference between scalp and moustache is

not uncommon. In fair-haired individuals, pubic and axillary hair, eyebrows and eyelashes are much darker than scalp hair. In humans, eyelashes are generally the most darkly pigmented hairs. Variation in colour of individual hair shafts is also seen in normal human scalp. More rarely, discrete patches of lighter or darker hair may occur, which may occur in a Blaschko's distribution [5,6].

There are several case reports of segmental heterochromia, in which demarcated variations in colour occur along a single hair shaft [7–9]. This usually takes the form of intermittent loss of pigmentation. Some cases have been associated with iron deficiency anaemia and have recovered following treatment with an iron supplement [7,8].

Greying of hair (canities)

Greying of hair is usually a manifestation of the ageing process. In white races, white hair first appears at the age of 34.2 ± 9.6 years, and by the age of 50 years 50% of the population have at least 50% grey hairs [10]. The onset in black people is 43.9 ± 10.3 years, and in Japanese between 30 and 34 years in men and between 35 and 39 years in women. The beard and moustache areas commonly become grey before scalp or body hair. On the scalp, the temples usually show greying first, followed by a wave of greyness spreading to the crown and later to the occipital area.

The visual impression of greying is due to an admixture of pigmented and white hairs. Melanization of pigmented hairs on a grey scalp may be reduced compared with normally pigmented hairs but it is not known if a decline in pigmentation occurs along the length of a hair shaft, that is during a single anagen cycle, or whether the level of reduced or absent pigmentation is established at the onset of an anagen cycle. Loss of hair pigmentation is associated with a decrease and eventual cessation of tyrosinase activity in the lower bulb [11]. Melanocytes are absent from the bulbs of white hairs [12,13] although non-melanized melanocytes are still present in the outer root sheath [14].

Rapid onset, allegedly 'overnight', greying of the hair has excited the literary, medical and anthropological worlds for centuries [15]. Historical examples include Sir Thomas More and Marie Antoinette, whose hair became grey over the night preceding their executions. The probable mechanism for rapid greying is the selective shedding of pigmented hairs in diffuse alopecia areata, the non-pigmented hairs being retained (Figs 66.82 & 66.83).

In general, greying of hair is progressive and permanent, but there are occasional reports of repigmentation of previously non-pigmented hair [16–18].

Premature greying (Fig. 66.84)

The association between premature greying and certain organ-specific autoimmune diseases is well recognized although there are limited published data. In a controlled study of 125 patients with pernicious anaemia, 11% had premature greying, defined as onset before the age of 20, compared with 2% in the control group [19].

Premature greying is a feature in a number of genetic diseases. It occurs in the early ageing disorders, Werner's and Rothmund–Thomson syndromes, which are due to defects in DNA helicases [20]. In progeria, premature greying is associated with marked

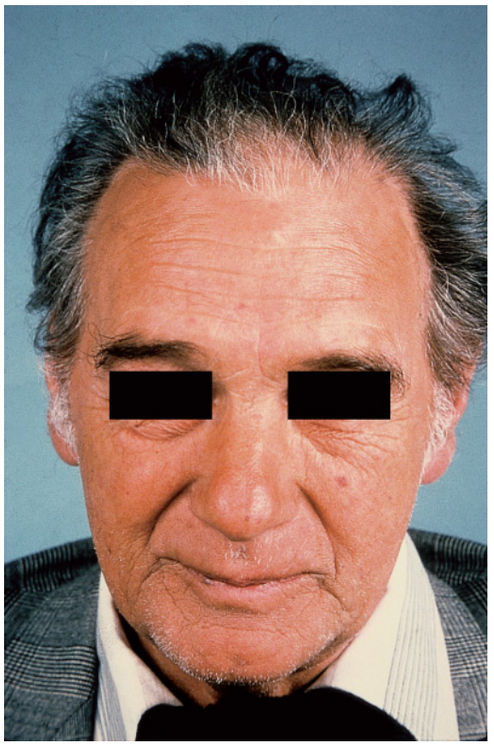


Fig. 66.82 Slight greying of hair. (Courtesy of Dr D. Fenton, St Thomas' Hospital, London, UK.)

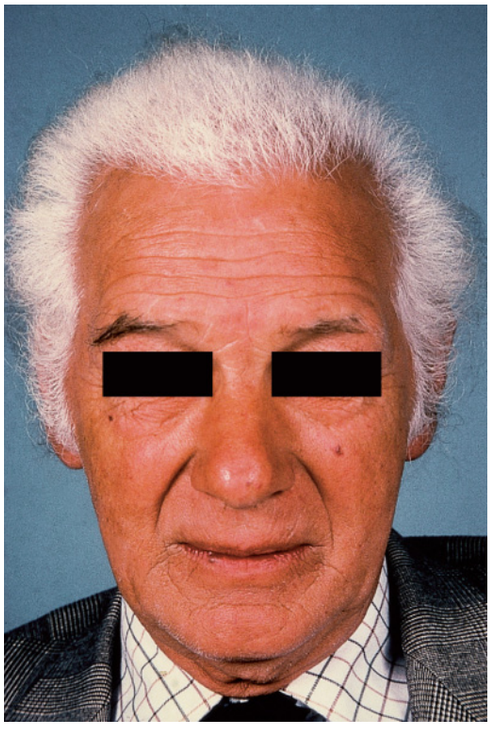


Fig. 66.83 Rapid greying of the hair. Same patient as Fig. 66.82 taken 1 week later. Caused by alopecia areata. (Courtesy of Dr D. Fenton, St Thomas' Hospital, London, UK.)



Fig. 66.84 Premature greying of hair, which commenced at 19 years of age in this individual.

loss of scalp hair as early as 2 years of age. In Book's syndrome, an autosomal dominant trait, premature greying is associated with premolar hypodontia and palmoplantar hyperhidrosis [21]. One-third of patients with chromosome 5p syndrome (cri du chat syndrome) have prematurely grey hair [22].

Poliosis

Poliosis is defined as the presence of a localized patch of white hair resulting from the absence or deficiency of melanin in a group of neighbouring follicles. Pigment absence can be congenital or acquired. In many cases of the former it is brought about by physically or functionally abnormal melanocytes from birth, or abnormal migration during embryogenesis. Such migratory defects may be restricted to the skin, but there can be associated abnormalities in other organs such as the ear or eye, where melanocytes or related neural crest cells have an important role.

Acquired forms of poliosis are due to vitiligo or to regrowth of non-pigmented hair following alopecia areata.

Hereditary defects [21]

Piebaldism (white spotting or partial albinism) is an autosomal dominant abnormality with patches of skin totally devoid of pigment, which remain unchanged throughout life. The borders of unpigmented areas are hyperpigmented. Heterochromia iridis occurs in some. Most commonly, a frontal white patch occurs—the white forelock—which may be the only sign. Melanocytes are decreased in number, but are morphologically abnormal and contain normal non-melanized premelanosomes, and also premelanosomes and melanosomes of abnormal appearance [23]. In most cases, piebaldism is caused by mutation in the *KIT* proto-oncogene [24] mapping to chromosome 4q12. In one kindred with a severe and progressive phenotype, the *KIT* mutation affected function of tyrosine kinase [25]. Piebaldism may also be due to deletions of the gene for the neural crest transcription factor *SNA12* [26].

Waardenburg's syndrome (WS) [27] is a heterogeneous condition, usually divided into four types, with absence of melanocytes from cochlear, skin, eye, hair and other structures. Features are present at birth. Type 1 WS is characterized by dystopia canthorum, with lateral displacement of the medial canthi, hypertrophy of the nasal root and hyperplasia of the inner third of the eyebrows with confluent brows [28]. Total or partial iridial heterochromia may occur, as may perceptive deafness. The white forelock is present in 20% of cases. Premature greying may develop with or without the white forelock [29]; a minority have piebaldism and congenital nerve deafness but no other overt signs of WS, suggesting that this association may be genetically distinct. Type 1 WS is caused by loss-of-function mutations in the *PAX3* gene which plays a part in control of neural crest cells during embryogenesis. Type 3 WS (Klein–Waardenburg syndrome, with abnormalities of the arms) is an extreme presentation of type 1, and affected individuals are usually homozygotes. Type 4 WS (Shah–Waardenburg syndrome with Hirschsprung's disease) can be caused by mutations in the genes for endothelin-3 or one of its receptors, EDNRB. Type 2 WS is a heterogeneous group, approximately 15% of whom are heterozygous for mutations in the *MITF* (microphthalmia-associated transcription factor) gene. All these forms show marked variability, even within families, and at present it is not possible to predict the severity, even when a mutation is detected. A mutation in *MITF* is also responsible for Tietz syndrome, in which complete deaf mutism and eyebrow hypoplasia are associated with generalized hypopigmentation rather than the localized pigment loss of WS [30].

Poliosis of scalp hair and eyelashes [31] occurs in tuberous sclerosis complex. Depigmented hair may be the earliest sign of the disease [32].

The pathognomonic signs of Von Recklinghausen's neurofibromatosis relate to hyperpigmented areas—café-au-lait macules and axillary and perineal freckling. Scalp hypopigmented patches must not be mistaken for vitiliginous changes.

Acquired defects [33]

In vitiligo, the white patches of skin may have white hairs within them. In alopecia areata, regrowing hair is frequently white. It may remain so, although in most cases hair pigmentation recovers.

The Vogt–Koyanagi–Harada syndrome [34,35] is a post-febrile condition comprising bilateral uveitis, labrynthine deafness, tinnitus and vitiligo, poliosis and alopecia areata [34,35]. It is likely to be an autoimmune disease, with the melanocyte, tyrosinase or tyrosinase-related protein as targets.

Alezzandrini's syndrome, which shows some similarity to Vogt–Koyanagi–Harada syndrome, combines unilateral facial vitiligo, retinitis, hypoacusis and poliosis of eyebrows and eyelashes [36].

Permanent loss of hair pigment may be induced by inflammatory processes that damage melanocytes (e.g. herpes zoster). X-irradiation often causes permanent hair loss, but less intense treatment leads to hypopigmented and, rarely, hyperpigmented hair.

Albinism [37,38]

The term albinism is applied to a group of genetic disorders characterized by generalized absence or reduced pigmentation in skin, hair and eyes. They are caused by mutations in genes involved in

Table 66.16 Clinical and genetic features of albinism.

	Cutaneous features	Associated abnormalities	Gene	Gene function
Oculocutaneous albinism Type 1 (OCA1)	Absence or near absence of skin and hair pigmentation	Photophobia, nystagmus, reduced visual acuity	Tyrosinase 11q14.3	Melanin synthesis
Oculocutaneous albinism Type 2 (OCA2)	Reduced pigmentation of skin and hair. Freckles and naevi may occur with age	Nystagmus, reduced visual acuity	*OCA2* (P gene) 16q24.3 15q11.2-12	Melanosome membrane protein
Oculocutaneous albinism Type 3 (OCA-3)	Minimal reduction in skin and hair pigmentation ('Rufous' albinism)	Mild ocular abnormalities	Tyrosinase-related protein-1 9p23	Melanin synthesis
Oculocutaneous albinism Type 4 (OCA-4)	Similar to OCA-2		Membrane-associated transporter protein 5p13.3	Unknown
Ocular albinism (OA)	None	Ocular depigmentation, nystagmus, reduced visual acuity	Xp22.3-22.2	Unknown
Hermansky–Pudlak syndrome	Variable absence of pigment in skin, hair and eyes	Variable ocular features Bleeding diathesis due to platelet dysfunction	*HPS* 8 genetically distinct variants	Trafficking from Golgi
Chediak–Higashi syndrome	Silver hair Large pigment granules in hair shafts	Ocular abnormalities Immunodeficiency Lymphoma	Lysosomal trafficking regulator gene 1q42.1-2	Translocation from Golgi
Griscelli syndrome	Silver hair Large pigment granules in hair shafts	Type 1 (MYO5A) Neurological abnormalities Type 2 (RAB27A) Immunodeficiency, haemophagocytosis	*MYO5A* 15q21 *RAB27A* 15q21	Translocation of melanosomes

the production and transport of melanin and may be accompanied by a variety of associated disorders. Apart from ocular albinism, which is X-linked, all are inherited in an autosomal recessive fashion. The clinical and genetic features are summarized in Table 66.16.

Colour changes induced by drugs and other chemicals

Some topical agents temporarily change hair colour. Dithranol and chrysarobin stain light-coloured or grey hair mahogany brown. Resorcin, formerly used a great deal in a variety of skin diseases, colours black or white hair yellow or yellowish-brown. The prostaglandin (PGF2α) analogues, such as latanoprost, used in the treatment of glaucoma, cause darkening of the iris and the eyelashes [39].

Some systemic drugs alter hair colour by interfering with the eumelanin or phaeomelanin pathway; in others, the mechanism is not known. Chloroquine interferes with phaeomelanin synthesis [40] and affects only blonde and red-haired individuals; the changes are completely reversible. Mephenesin, a glycerol ether muscle relaxant, causes pigmentary loss in dark-haired people [41]. The tyrosine kinase inhibitor imatinib, which inhibits the KIT and PDGF receptors, has diverse effects on pigmentation, causing both skin hypopigmentation [42] and reversal of hair greying [43].

Colour changes induced by nutritional deficiencies

Because specific dietary deficiencies are rare in humans, most clinical knowledge of their effects is derived from laboratory and animal studies. Copper deficiency in cattle causes achromotrichia because it is the prosthetic group of tyrosinase; loss of hair colour from this mechanism occurs in humans as Menkes' kinky hair syndrome. In protein malnutrition, exemplified by kwashiorkor, hair colour changes are a prominent feature; normal black hair becomes brown or reddish, and brown hair becomes blonde [44]. Intermittent protein malnutrition leads to the 'flag' sign of kwashiorkor (signe de la bandera). Alternating white (abnormal) and dark bands occur along individual hairs. Changes similar to those in kwashiorkor have been described in severe ulcerative colitis and after extensive bowel resection.

The lightening of hair colour from black to brown described in severe iron-deficiency anaemia may be an effect on keratinization rather than on melanocytic function [7].

Noppakun and Swasdikul [45] described a case of reversible white hair in vitamin B_{12} deficiency and commented on a variety of reversible and other hair colour changes in adult coeliac disease.

Hair colour in metabolic disorders

Phenylketonuria is an autosomal recessive disorder in which the tissues are unable to metabolize phenylalanine to tyrosine because of phenylalanine hydroxylase deficiency. Mental retardation, fits and decreased pigmentation of the skin, eyes and hair occur with eczema and dermographism. Black hair may become brown, and older institutionalized patients with phenylketonuria may have pale blonde or grey hair. Tyrosine treatment causes darkening towards normal colour within 1–2 months.

The pale hair colour seen in homocystinuria is probably caused by keratinization changes resulting from the error in methionine metabolism.

Light, almost white hair and recurrent oedema are manifestations of the hair condition 'oast house' disease. Methionine concentration in the blood is raised.

Darkening of grey hair has been reported in porphyria cutanea tarda [18].

Accidental hair discoloration

Hair avidly binds many inorganic elements and thus hair colour changes are occasionally seen after exposure to certain substances.

Exposure to high levels of copper in industry or inadvertently high concentrations in tap water [46] or in swimming pools may cause green hair, which is particularly visible in blonde-haired subjects [47,48]. A yellowish hair colour is not uncommon in white- or grey-haired heavy smokers, resulting from the tar in cigarette smoke; yellow staining may also occur from picric acid and dithranol. Trinitrotoluene (TNT) workers sometimes develop yellow skin and reddish-brown hair.

References

1 Castanet J, Ortonne J-P. Hair melanin and hair colour. In: Jollès P, Zahn H, eds. *Formation and Structure of Human Hair*. Basel: Birkhäuser Verlag, 1997: 209–25.
2 Rees JL. The melanocortin 1 receptor (MC1R): more than just red hair. *Pigment Cell Res* 2000; **13**: 135–40.
3 Sturm RA, Teasdale RD, Box NF. Human pigmentation genes: identification, structure and consequences of polymorphic variation. *Gene* 2001; **277**: 49–62.
4 Trotter M, Duggins OH. Age changes in head hair from birth to maturity. *Am J Phys Anthropol* 1950; **8**: 467–84.
5 Restano L, Barbareschi M, Cambiaghi S *et al.* Heterochromia of the scalp hair: a result of pigmentary mosaicism? *J Am Acad Dermatol* 2001; **45**: 136–9.
6 Iorizzo M, Piraccini BM, Tosti A. Heterochromia of the scalp hair following Blaschko lines. *Pediatr Dermatol* 2007; **24**: 69–70.
7 Sato S, Jitsukawa K, Sato H *et al.* Segmented heterochromia in black scalp hair associated with iron-deficiency anemia. Canities segmentata sideropaenica. *Arch Dermatol* 1989; **125**: 531–5.
8 Yoon KH, Kim D, Sohn S *et al.* Segmented heterochromia in scalp hair. *J Am Acad Dermatol* 2003; **49**: 1148–50.
9 Faulkner C, Godbolt AM, Messenger AG *et al.* Nonsynchronized segmented heterochromia in black scalp hair. *Clin Exp Dermatol* 2003; **28**: 280–2.
10 Keogh EV, Walsh RJ. Rate of greying of human hair. *Nature* 1965; **207**: 877–8.
11 Kukita A, Fitzpatrick TB. Demonstration of tyrosinase in melanocytes of the human hair matrix by autoradiography. *Science* 1955; **121**: 893–4.
12 Herzberg J, Gusek W. Das ergrauen des kopfhaares: eine histo-und fermentschemische sowie elektronen-mikroskopische Studie. *Archiv Klin Exp Dermatol* 1970; **236**: 368–84.
13 Sato S, Kukita A, Jimbow K. Electron microscopic studies of dendritic cells in the human gray and white hair matrix during anagen. In: McGovern VJ, Russel P, eds. *Pigment Cell*. Basel: Karger, 1973: 20–7.
14 Commo S, Gaillard O, Bernard BA. Human hair greying is linked to a specific depletion of hair follicle melanocytes affecting both the bulb and the outer root sheath. *Br J Dermatol* 2004; **150**: 435–43.
15 Jelinek JE. Sudden whitening of the hair. *Bull N Y Acad Med* 1972; **48**: 1003–13.
16 Comaish S. White scalp hairs turning black—an unusual reversal of the ageing process. *Br J Dermatol* 1972; **86**: 513–4.
17 Verbov J. Erosive candidiasis of the scalp, followed by the reappearance of black hair after 40 years. *Br J Dermatol* 1981; **105**: 595–8.
18 Shaffrali FC, McDonagh AJ, Messenger AG. Hair darkening in porphyria cutanea tarda. *Br J Dermatol* 2002; **146**: 325–9.
19 Dawber RP. Integumentary associations of pernicious anaemia. *Br J Dermatol* 1970; **82**: 221–3.
20 Mohaghegh P, Hickson ID. Premature aging in RecQ helicase-deficient human syndromes. *Int J Biochem Cell Biol* 2002; **34**: 1496–501.
21 Book JA. Clinical and genetical studies of hypodontia. I. Premolar aplasia, hyperhidrosis, and canities prematura; a new hereditary syndrome in man. *Am J Hum Genet* 1950; **2**: 240–63.
22 Mainardi PC, Pastore G, Castronovo C *et al.* The natural history of Cri du Chat Syndrome. A report from the Italian Register. *Eur J Med Genet* 2006; **49**: 363–83.
23 Mosher DB, Fitzpatrick TB. Piebaldism. *Arch Dermatol* 1988; **124**: 364–5.
24 Giebel LB, Spritz RA. Mutation of the KIT (mast/stem cell growth factor receptor) protooncogene in human piebaldism. *Proc Natl Acad Sci U S A* 1991; **88**: 8696–9.
25 Richards KA, Fukai K, Oiso N *et al.* A novel KIT mutation results in piebaldism with progressive depigmentation. *J Am Acad Dermatol* 2001; **44**: 288–92.
26 Sanchez-Martin M, Perez-Losada J, Rodriguez-Garcia A *et al.* Deletion of the SLUG (SNAI2) gene results in human piebaldism. *Am J Med Genet A* 2003; **122**: 125–32.
27 Read AP, Newton VE. Waardenburg syndrome. *J Med Genet* 1997; **34**: 656–65.
28 Waardenburg PJ. A new syndrome combining developmental anomalies of the eyelids, eyebrows and nose root with pigmentary defects of the iris and head hair and with congenital deafness. *Am J Hum Genet* 1951; **3**: 195–253.
29 Rugel SJ, Keates EU. Waardenburg's syndrome in six generations of one family. *Am J Dis Child* 1965; **109**: 579–83.
30 Smith SD, Kelley PM, Kenyon JB *et al.* Tietz syndrome (hypopigmentation/deafness) caused by mutation of MITF. *J Med Genet* 2000; **37**: 446–8.
31 Awan KJ. Leaf-shaped lesions of ocular fundus and white eyelashes in tuberous sclerosis. *South Med J* 1982; **75**: 227–8.
32 McWilliam RC, Stephenson JB. Depigmented hair. The earliest sign of tuberous sclerosis. *Arch Dis Child* 1978; **53**: 961–3.
33 Prunieras M. Melanocytes, melanogenesis, and inflammation. *Int J Dermatol* 1986; **25**: 624–8.
34 Read RW, Rao NA, Cunningham ET. Vogt-Koyanagi-Harada disease. *Curr Opin Ophthalmol* 2000; **11**: 437–42.
35 Tsuruta D, Hamada T, Teramae H *et al.* Inflammatory vitiligo in Vogt-Koyanagi-Harada disease. *J Am Acad Dermatol* 2001; **44**: 129–31.
36 Alezzandrini AA. [Unilateral manifestations of tapeto-retinal degeneration, vitiligo, poliosis, grey hair and hypoacousia]. *Ophthalmologica* 1964; **147**: 409–19.
37 Oetting WS, King RA. Molecular basis of albinism: mutations and polymorphisms of pigmentation genes associated with albinism. *Hum Mutat* 1999; **13**: 99–115.
38 Gronskov K, Ek J, Brondum-Nielsen K. Oculocutaneous albinism. *Orphanet J Rare Dis* 2007; **2**: 43.
39 Grierson I, Jonsson M, Cracknell K. Latanoprost and pigmentation. *Jpn J Ophthalmol* 2004; **48**: 602–12.
40 Saunders TS, Fitzpatrick TB, Seiji M *et al.* Decrease in human hair color and feather pigment of fowl following chloroquine diphosphate. *J Invest Dermatol* 1959; **33**: 87–90.
41 Spillane JD. Brunette to blonde. Depigmentation of human hair during oral treatment with mephenesin. *BMJ* 1963; **1**: 997–1000.
42 Tsao AS, Kantarjian H, Cortes J *et al.* Imatinib mesylate causes hypopigmentation in the skin. *Cancer* 2003; **98**: 2483–7.
43 Robert C, Spatz A, Faivre S *et al.* Tyrosine kinase inhibition and grey hair. *Lancet* 2003; **361**: 1056.
44 Bradfield RB, Jelliffe DB. Letter: Hair-colour changes in kwashiorkor. *Lancet* 1974; **1**: 461–2.
45 Noppakun N, Swasdikul D. Reversible hyperpigmentation of skin and nails with white hair due to vitamin B12 deficiency. *Arch Dermatol* 1986; **122**: 896–9.
46 Goldschmidt H. Green hair. *Arch Dermatol* 1979; **115**: 1288.
47 Blanc D, Zultak M, Rochefort A *et al.* [Green hair: clinical, chemical and epidemiologic study. Apropos of a case]. *Ann Dermatol Venereol* 1988; **115**: 807–12.
48 Melnik BC, Plewig G, Daldrup T *et al.* Green hair: guidelines for diagnosis and therapy. *J Am Acad Dermatol* 1986; **15**: 1065–8.

Hair cosmetics [1–3]

People have always been concerned about their hair, and have sought to modify it by grooming, colouring, cutting and wigs.

There are references in Egyptian papyruses to the importance of arranging the hair prior to seduction [4,5]. Now, hair care and hair cosmetics are big business and many of the advances have come from cosmetic science laboratories [6,7]. Some aspects of cosmetic management can lead to scalp and hair shaft problems.

References

1 Draelos ZD. The biology of hair care. *Dermatol Clin* 2000; **18**: 651–8.
2 Bolduc C, Shapiro J. Hair care products: waving, straightening, conditioning, and coloring. *Clin Dermatol* 2001; **19**: 431–6.
3 Bouillon C, Wilkinson J, eds. *The Science of Hair Care,* 2nd edn. London: Taylor & Francis, 2005.
4 Pomey-Rey D. Hair and psychology. In: Zviak C, ed. *The Science of Hair Care*. New York: Marcel Dekker, 1986: 571–86.
5 Gummer C, Dawber RPR. Hair cosmetics. In: Dawber RPR, ed. *Diseases of the Hair and Scalp,* 3rd edn. Oxford: Blackwell Science, 1997: 732–59.
6 Zviak C, Dawber RPR. Hair structure, function, and physicochemical properties. In: Zviak C, ed. *The Science of Hair Care*. New York: Marcel Dekker, 1986: 1–48.
7 Schoen LA, ed. *Skin and Hair Care,* 1st UK edn. Harmondsworth: Penguin, 1978.

Shampoos [1–6]

A shampoo may be defined as a suitable detergent for washing hair that leaves the hair in good condition. It must remove grease, as it is the latter that attracts dirt and other particulate matter. The polar group of a detergent achieves this by displacing oil from the hair surface. The evaluation of shampoo detergency is difficult and complicated. The consumer tends to equate detergency with foaming; in Western society, few shampoos sell unless they possess good foaming power. In the evaluation of detergents as shampoos no single criterion can be used, although instrumental methods have been devised. Efficacy can be based only on the subjective impression of the consumer.

Shampoo formulations

These vary enormously, but the basic ingredients can be resolved into a few groups: water, detergent and fatty material. Soap shampoos are made from vegetable or animal fats and remove dirt and grease as efficiently as detergents; however, a scum forms with hard water and most shampoos contain detergents as the principal washing ingredient. Detergents are synthetic petroleum products.

Shampoos contain:

1 Principal surfactants for detergency and foaming power
2 Secondary surfactants to improve and 'condition' hair
3 Functional additives to control pH and viscosity, or ingredients such as tar or antifungal agents
4 Preservatives
5 Aesthetic additives such as colorants and fragrance.

Shampoo safety

Shampoos must be non-toxic, and at concentrations used by the consumer not irritate either skin or eyes. New shampoo formulations are tested exhaustively prior to marketing, particularly to assess their propensity to cause eye irritation, scarring and corneal opacities. Skin irritation is not usually encountered from shampoos that have low eye irritancy potential. In general, the eye irritancy of detergents is greatest with cationics, followed by anionics, and least with non-anionics. There are exceptions to this, suggesting that shampoo irritancy may be caused by properties other than detergency, including surface activity, pH, wetting power, foaming power (Ross–Miles test), and wetting and foaming power together. Most shampoos are, in fact, irritant but not dangerously so. Allergic contact dermatitis resulting from biocides does occur (see Chapters 26 and 27).

Conditioners

Dry hair lacks gloss and lustre and is difficult to style. This results from natural weathering and is worsened by chemical and physical processes applied to the hair. Conditioners have a range of characteristics that may contribute to shine, reduction of static electricity, protection from ultraviolet radiation and possibly increased hair strength [7]. Conditioners comprise fatty acids and alcohols: natural triglycerides (e.g. almond, avocado, corn and olive oil); waxes (e.g. beeswax, jojoba oil, mink oil, lanolin); phospholipids (e.g. egg yolk and soya bean); vitamins A, B and E, protein hydrolysates of silk, collagen, keratin (horn and hoof), gelatine and other proteins; and cationic polymers. Conditioners are available in a variety of forms and are widely used. They provide lubrication and gloss, and render the hair easier to comb and style. The most commonly used are those combined with a shampoo as a 2-in-1 preparation. These cationic chemicals bind with the hair at the negatively charged surface and areas of weathering. In so doing they reduce static by electrically neutralizing the hair, and provide a physical coating to the areas of damaged hair shaft with materials such as dimethicone. Other forms of conditioner may be applied as a separate procedure, and can take the form of creams and emulsions applied for a few minutes after washing and then rinsed off. Deep conditioners are left on for up to 30 min, often with damp heat. Fluids, gels and aerosol foams aid styling. Hair oils are traditional conditioners. Men may use brilliantines, greases or oils to leave the hair glossy and sleek [3].

Where the hair is significantly dry or damaged, or the scalp is inflamed or eczematous, conditioner may be used as a shampoo substitute in the same manner that one might advocate an emollient as soap substitute on the skin of someone with eczema. The conditioner will mix with water to remove surface dirt and odour, but will not subject the hair and scalp to the powerful solvent effects of the shampoo.

References

1 Corbett JP. The chemistry of hair-care products. *J Soc Dyers Colourists* 1976; **92**: 285–93.
2 Robbins CR, ed. *Chemical and Physical Behaviour of Human Hair,* 1st edn. New York: Van Nostrand Reinhold, 1979.
3 Zviak C, Bouillon C. Hair treatment and hair care products. In: Zviak C, ed. *The Science of Hair Care*. New York: Marcel Dekker, 1986: 210–24.
4 Zviak C, Vanderberghe G. Scalp and hair hygiene: shampoos. In: Zviak C, ed. *The Science of Hair Care*. New York: Marcel Dekker, 1986: 224–41.
5 Bouillon C. Shampoos. *Clin Dermatol* 1996; **14**: 113–21.
6 Spoor HJ. Shampoos and hair dyes. *Cutis* 1977; **20**: 189–90.
7 Fox C. An introduction to the formulation of shampoos. *Cosmet Toilet* 1988; **103**: 25–38.

Cosmetic hair colouring [1–4]

Since the days of the pharaohs, women in particular have used hair dyes to hide grey hair. Use has increased enormously during the past 50 years and now men are using hair dyes. Or perhaps they always did!

The penetration of dyes into hair depends on molecular size and the aqueous swelling of the hair at the time of application of the dye; basicity of the dye is also important. The most successful dyes are relatively small molecules.

Excluding bleaches, hair-colouring materials can be divided into three groups: vegetable, metallic and synthetic organic dyes. Synthetic organic materials are thought to give more 'natural' colours than those obtained with vegetable and metallic hair colorants.

Vegetable dyes

Henna may be used to give reddish auburn shades. It is obtained from shrubs found in North Africa and the Middle East: *Lawsonia alba*, *L. spinosa* and *L. inermis*. The dye is produced from dried leaves, which are removed before the plant flowers. The active principle is an acidic naphthoquinone (lawsone). Traditionally, it is applied as a thick paste 'pack', which is left *in situ* for 5–60 min. The effects last for up to 10 weeks. This process is non-toxic but messy, and fingernails may become stained. Henna rinses are mixtures of henna and powdered indigo leaves that produce blue-black shades. A wide range of products containing compound henna exist [5]. Ground flower heads of a Roman or German chamomile yield a yellow dye, 1,3,4,-trihydroxyflavone (apigenin). It stains only the cuticle and can be used to lighten or brighten hair. Other vegetable dyes include extracts from logwood and walnut shell, and these can be used by patients who are paraphenylenediamine sensitive. These products are obtainable at herbalists and beauty shops.

Metallic dyes

Traditionally, hair dyes for men have been of this type, as the colour changes occur less rapidly and are not as immediately obvious as with the oxidative dyes. Inorganic salts are used, which are altered by the hair and coat the surface as either oxides from reduction of the metal salts by keratin, or sulphides from the action of the sulphur in keratin on the metal. They all give a rather dull (metallic) appearance and may cause brittle or damaged hair if used too often.

Lead acetate, with precipitated sulphur or sodium thiosulphate, gives brown to black shades; grey hair may be changed through yellow to brown or black. Silver nitrate used alone produces a greenish-black colour; pyrogallol is used as developer. Colours from ash-blonde to black are possible by mixing silver nitrate variously with copper, cobalt or nickel; brownish-black skin staining is the great disadvantage. Bismuth salts give shades of brown. Newer metallic dyes, containing a metal plus an organic ligand, are used on textile fibres and in some hair-dye patents. Metallic dyes cannot be removed without hair damage, and should be left to grow out.

Synthetic organic dyes

This group has now been in use for more than 60 years. They are the most important type because of the comprehensive range of 'natural' colours that can be obtained. Most penetrate the hair cuticle so are potentially permanent, but in recent years less permanent types have been introduced.

Synthetic organic colorants are of three types:

1. *Temporary*. These wash out with one shampoo and last no longer than 1 week. Many temporary rinses belong to this group, including fashionable unnatural colours used by avant-garde sects and groups. They are available in aerosol sprays by incorporation into transparent polymeric plastics such as PVP; the disadvantage of such vehicles is their tendency to flake off on to clothing.
2. *Semipermanent*. In the UK, these have the widest appeal. They are used frequently at home and also in salons to brighten or subdue a natural colour, modify a permanent or bleached colour, or modify white or grey. They are of sufficiently small molecular size to penetrate the cortex. They are intrinsically coloured; no developing is required (see the oxidative permanent group). They are relatively easy to wash out with shampoos containing ammonia; other shampoos must be used 6–10 times to remove them. Some semipermanent dyes have an affinity for thioglycollate-waved hair. Many are now used in colour shampoos.
3. *Permanent* (developed or oxidation dyes). These do not rely on the natural colour of a single chemical dye-stuff (see semipermanents), but require an oxidative developer—hydrogen peroxide—to produce the final colour:

Paraphenylenediamine (PPD) and/or paratoluenediamine (PTD)
+
Hydrogen peroxide
↓
Applied to hair
↓
Quinone diamine (small molecule)
↓
Penetrate hair—to cortex
↓
Large molecules produced
(by diamine 'self' condensation and modifiers, e.g. pyrogallol)

Other substances may be included in specific formulations to give greater intensity to the dye (e.g. resorcinol and polyhidric phenols).

Oxidative dyes are potentially hazardous. The need for hydrogen peroxide enables lighter shades to be obtained and is chiefly responsible for the structural damage to hair that may occur if care is not exercised. Additives such as pyrogallol and resorcinol are potential irritants. The greatest problem is the potential of PPD (less so with PTD) to cause allergic dermatitis. Up to 10% of users may develop type IV allergy [6,7]. All dyes in this group are therefore sold with instructions to carry out preliminary patch testing 24–48 h before the proposed dye is used. Thus, the dye system is applied to skin either behind one ear or on the forearm—any redness, swelling or blistering implies allergy and the dyeing should not therefore proceed. A negative patch test does not mean that subsequent allergy cannot develop; it simply shows the subject is not allergic at the time the test is carried out. If allergy is shown, it is not sufficient merely to stop all future use of oxidative dyes; unfortunately, cross-sensitization also occurs with other aromatic benzenes (e.g. sulphonamides and some local anaesthetics), which must also be avoided for life. Modern formulations seem to cause less problems with allergy [8]. Hair dyes of this

group have been incriminated as possible carcinogens [9]. Chromosome breaks have occurred under experimental conditions [10] and an increased incidence of tumours [11] and aplastic anaemia [12] has been suggested and contested [13,14]. None of these reports is sufficiently conclusive to warrant the withdrawal of such dyes.

Permanent dyes last for several months; they must not be applied more frequently than every 2–3 weeks because hair damage will occur. Permanently dyed hair must therefore be allowed to grow out. However, if a light shade has been produced and the subject wishes a darker shade, then temporary rinses may safely be used as these only coat the hair surface and have no propensity to cause structural damage.

For less commonly used permanent dye formulations, such as 'highlights', the reader is referred to specialized texts [4].

Bleaches [15–17]

Bleaching is used both to lighten hair and to prepare it to take up hair dyes. Bleaching is an oxidative alkaline treatment that oxidizes and bleaches melanin. The hair lightens to reddish or yellow tones, depending on the underlying hair colour, and ultimately to platinum. Bleaching is very damaging to the hair, rendering it dry, porous and more prone to tangle. Overuse may cause disruption and fracture of the hair. Thus, it is advisable to perform permanent waving before bleaching. Home bleaching is usually performed with 6% hydrogen peroxide (20 volumes) with ammonia to speed the reaction, which otherwise takes 12 h. Salons use more powerful bleaching creams, powders and pastes, which are much faster. They are often applied to individual strands of hair, others being left untreated to give highlights, which lessens the problem of the darkened roots. Bleaching is terminated by shampooing or an acid rinse. The human eye perceives a more aesthetically acceptable blonde ('platinum' blonde) when the bleached hair is treated with a blue or lilac colorant.

References

1 Corbett JF. Hair coloring. *Clin Dermatol* 1988; **6**: 93–101.
2 Kalopesis G. Toxicology and hair dyes. In: Zviak C, ed. *The Science of Hair Care*. New York: Marcel Dekker, 1986: 287–305.
3 Zviak C. Hair coloring: non-oxidation coloring. In: Zviak C, ed. *The Science of Hair Care*. New York: Marcel Dekker, 1986: 235–62.
4 Zviak C. Oxidation coloring. In: Zviak C, ed. *The Science of Hair Care*. New York: Marcel Dekker, 1986: 263–86.
5 Natow AJ. Henna. *Cutis* 1986; **38**: 21.
6 Blohm SG, Rajka G. The allergenicity of paraphenylendiamine. I. *Acta Derm Venereol (Stockh)* 1970; **50**: 49–50.
7 Lubowe I. Allergic dermatitis and cosmetics. *Cutis* 1973; **11**: 431–5.
8 Calnan C. Adverse reactions to hair products. In: Zviak C, ed. *The Science of Hair Care*. New York: Marcel Dekker, 1986: 409–24.
9 Burnett C, Jacobs MM, Seppala A *et al*. Evaluation of the toxicity and carcinogenicity of hair dyes. *J Toxicol Environ Health* 1980; **6**: 247–57.
10 Kirkland DJ, Lawler SD, Venitt S. Chromosomal damage and hair dyes. *Lancet* 1978; **2**: 124–7.
11 Burnett CM, Menkart J. Hair dyes and breast cancer. *N Engl J Med* 1978; **299**: 1253.
12 Burnett CM, Corbett JF, Lanman BM. Hair dyes and aplastic anemia. *Drug Chem Toxicol* 1977; **1**: 45–61.
13 Benavente Y, Garcia N, Domingo-Domenech E *et al*. Regular use of hair dyes and risk of lymphoma in Spain. *Int J Epidemiol* 2005; **34**: 1118–22.
14 Nohynek GJ, Fautz R, Benech-Kieffer F *et al*. Toxicity and human health risk of hair dyes. *Food Chem Toxicol* 2004; **42**: 517–43.
15 Natow AJ. Hair bleach. *Cutis* 1986; **37**: 28–30.
16 Wolfram LJ, Hall K, Hui I. The mechanism of hair bleaching. *J Soc Cosmet Chem* 1970; **21**: 875–85.
17 Zviak C, Millequant J. Hair bleaching. In: Bouillon C, Wilkinson J, eds. *The Science of Hair Care*, 2nd edn. London: Taylor & Francis, 2005: 229–50.

Permanent waving [1–3]

Permanent waving is often referred to as 'a perm'. It has been defined as the process of changing the shape of the hair so that the new shape persists through several shampoos. During the last 70 years, increasing knowledge of keratin chemistry has enabled semipermanent chemical methods to be developed. Whatever the process used, three stages are involved in hair waving:

1 Physical or chemical softening of the hair
2 Reshaping
3 Hardening of fibres to retain the reshaped position.

Softening

Water can extend the hydrogen bonds between adjacent polypeptides in the keratin molecule, allowing temporary reshaping to be carried out—exposure to high humidity or rewetting immediately reverses the process. To obtain a more durable effect from water, steam may be used which, in a limited way, disrupts disulphide bonds. Heat and steam alone are rarely acceptable to modern women because their effects are temporary and the treatment is uncomfortable. Heat can be more effectively employed in conjunction with ammonium hydroxide and potassium bisulphite or triethanolamine as agents to reduce disulphide bonds; great skill is involved in this process as failure to judge the time of application of chemicals and heat may cause severe damage.

Since 1945, cold wave processes using substituted thiosulphates (thioglycolates) have largely superseded hot waving. Thioglycolates are potent reducers of disulphide bonds in the keratin molecule:

$$—S{=}S \rightarrow 2—SH$$

A typical cold waving lotion contains thioglycolic acid plus ammonia or monoethanolamine.

Acid permanent waves have recently become popular for salon use. They contain glyceryl monothioglycolate and produce a softer curl, and can be used on damaged and bleached hair. Their disadvantage is the high frequency of sensitization in the hairdressers using the product and, occasionally, sensitization of the client [4].

Reshaping

The type of rollers or curlers used to reshape the softened hair depends on the training of the hairdresser and the fashion desired. The degree of curl or tightness of the permanent wave depends both on the diameter of the roller and the size of the strand wound round the roller. Increasing the time of the exposure to the perming solution up to 20 min increases the curl, but longer times do not give a further increase. The strength of the solution used depends on the hair type, texture and previous bleaching. Home permanent waves are weaker and cannot achieve the same degree of curl. 'Tepid' waving involves using a weaker thioglycolate solu-

tion plus warm air. Neutralization is carried out initially with the curlers in place and again after they have been carefully removed. The reshaping stage is thus a great test of hairdressing skill and experience.

Hardening (neutralizing or setting)

In general, this process involves a reversal of the softening (reduction) stages:
oxidation

$$2\text{—SH} \rightarrow \text{—S=S—}$$

It is important to note that complete reversal to presoftened 'strength' cannot occur because many free SH groups may not be in a position for oxidation to be effective, for example:

$$2\text{—SH} \rightarrow \text{—S—C—S—} \quad (\text{C} = \text{carbon})$$

$$2\text{—SH} \rightarrow \text{—S—Ba—S—} \quad (\text{Ba} = \text{barium})$$

Atmospheric oxidation may efficiently neutralize the waving process. This method is slow and rollers must be left in position for several hours overnight. Chemical oxidation is now the rule. Hairdressers generally use hydrogen peroxide, whereas most solutions for home use contain sodium perborate or percarbonate (UK), or sodium or potassium bromate (USA). This is why hair is lighter after permanent waving. Some neutralizers contain shellac, which may react with alcohol groups to cause hair discoloration.

Practical procedures

Hot waving

This is almost never used. The procedure is:

1 Shampooing
2 Hair divided and rollers or curlers applied under slight tension
3 Waving solution applied
4 Heating.

Heating varies according to the solution used or the type of wave required. Electric rollers or exothermic reactive chemicals may be used. The latter allow free head movement during the waving. The skill of this procedure lies in good hair sectioning, judging the right amount of solution, correct winding tension and appropriate steaming time.

Cold waving

This also involves initial shampooing, hair division into locks, moistening with waving lotion and application of croquignole curlers. Further solution may then be applied. The softening time is 10–20 min. Occasionally, mild heat is included, using exothermic chemicals or the natural heat from the head by enclosing the scalp in a plastic bag. These may add to the comfort of the process. Rinsing then takes place, followed by neutralization with the oxidizing solution for up to 10 min. After removing the curlers, further 'hardening' solution is usually applied. 'Loose' curl waves last for no more than a few weeks but 'tight' curl styles may persist for 4–12 months.

References

1 Zviak C. Permanent waving and hair straightening. In: Bouillon C, Wilkinson J, eds. *The Science of Hair Care,* 2nd edn. London: Taylor & Francis, 2005: 201–8.
2 Wickett RR. Permanent waving and straightening of hair. *Cutis* 1987; **39**: 496–7.
3 Bolduc C, Shapiro J. Hair care products: waving, straightening, conditioning, and coloring. *Clin Dermatol* 2001; **19**: 431–6.
4 Morrison LH, Storrs FJ. Persistence of an allergen in hair after glyceryl monothioglycolate-containing permanent wave solutions. *J Am Acad Dermatol* 1988; **19**: 52–9.

Hair straightening (relaxing) [1,2]

In principle, the methods used to straighten hair are similar to those used in permanent waving. The practice is almost exclusively used to straighten negroid hair and is also called relaxing. One survey found that relaxing formulations were used in 45% of black American women [3]. These practices are associated with a range of problems and ultimately may contribute to scarring alopecia [4].

Pomades

These are mostly used by men with relatively short hair. They are greasy and act by 'plastering' hair into position.

Hot-comb methods

Shampooing is carried out and the hair is towelled dry; oil is then applied (e.g. petroleum jelly or liquid paraffin), which acts as a heat-transferring agent. Heat pressing with hot combing is then used (148–260°F), causing breakage and reforming of disulphide bonds, allowing the hair to be moulded straight. Structural damage (and breakage) of hair is common with this process and scarring alopecia may occur as a result of hot waxes entering the follicles. Sweating and rain reverse this procedure.

Cold methods

The chemical methods employed use alkaline reducing agents (caustics), thioglycolates, ammonium carbonate or sodium bisulphite. Caustic soda preparations are usually creams and require the application of protective scalp oil or wax. They are combed through the hair and left for 15–20 min; the hair is combed and straightened again, then rinsed and neutralized. These preparations are limited to salon use because of their potential to cause irritant dermatitis and damage to the hair. Thioglycolate creams are the most common agents used; the cream is applied liberally to the hair, which is then combed until it is straight. The cream is then washed off and a neutralizer (oxidizing agent) applied. Other straighteners ('relaxers') do not contain thioglycolates (e.g. sodium bisulphite and ammonium carbonate, acidic ethylene glycol or 1,3-propylene glycol). Bisulphite straighteners are suitable for home use in combination with alkaline stabilizers.

References

1 Wickett RR. Permanent waving and straightening of hair. *Cutis* 1987; **39**: 496–7.
2 Zviak C, Sabbagh A. Permanent waving and hair straightening. In: Bouillon C, Wilkinson J, eds. *The Science of Hair Care*, 2nd edn. USA: Informa Healthcare, 2005: 201–28.
3 Grimes PE. Skin and hair cosmetic issues in women of color. *Dermatol Clin* 2000; **18**: 659–65.
4 Wilborn WS. Disorders of hair growth in African Americans. In: Olsen E, ed. *Disorders of Hair Growth, Diagnosis and Treatment*. New York: McGraw Hill, 1994: 389–407.

Hair setting [1]

Setting lotions have changed considerably in recent years. The traditional semiliquid gels based on water-soluble gums (e.g. tragacanth, karaya and acasia) have been replaced by various synthetic polymers in a bewildering array of forms—aerosol foams and sprays, liquids and gels. Most are based on PVP in a gelled aqueous solution and give an attractive glossy, non-greasy appearance [2]. Some preparations incorporate other ingredients to condition or to add antistatic action, lustre or sheen.

Setting lotion and spray formulations are considered safe, after early reports of foreign body granulomatous inflammation [3,4] had been questioned and not supported by further cases. Hair sprays were incriminated as a possible cause of peripilar casts [5], but this was not confirmed by later work [6].

References

1 Zviak C. Hair setting. In: Zviak C, ed. *The Science of Hair Care*. New York: Marcel Dekker, 1986: 149–82.
2 Friefeld M, Lyons J, Martinelli AT. Polyvinylpyrrolidone in cosmetics. *Am Perfumery* 1962; **77**: 25.
3 Edelston BG. Thesaurosis following inhalation of hair spray. *Lancet* 1959; **2**: 112–3.
4 Bergmann M, Flance IJ, Blumenthal HT. Thesaurosis following inhalation of hair spray; a clinical and experimental study. *N Engl J Med* 1958; **258**: 471–6.
5 Scott MJ. Peripilar keratin casts. *AMA Arch Derm* 1959; **79**: 654–5.
6 Dawber RP. Hair casts. *Br J Dermatol* 1979; **100**: 417–21.

Methylolated compounds

Many cosmetic preparations, by their action on the keratin molecule, irreversibly weaken the hair. The cosmetic scientist has produced chemicals that attempt to combat this problem. The formulations contain methylolated compounds of varying strength depending on the type of hair under treatment and the solubility of the compound. Most preparations containing alkylated methylol compounds have greater stability and release very little formaldehyde [1].

Reference

1 Zviak C, Bouillon C. Hair treatment and hair care products. In: Zviak C, ed. *The Science of Hair Care*. New York: Marcel Dekker, 1986: 210–24.

Complications

Hair loss is often attributed to cosmetics, with relatively little evidence in support [1]. Matting of scalp hair is most commonly a sudden, usually irreversible, tangling of scalp hair resulting from shampooing of weathered hair [2]. Excessive bleaching, permanent waving and straightening procedures may induce excessive weathering and fragility of hair as well as irritant and allergic reactions of the scalp. Hairdressers suffer a high rate of occupational reactions to the agents used in hair care [3].

Complications from the use of synthetic hair fibre implantation for male pattern balding can be severe [4].

References

1 Gummer CL. Cosmetics and hair loss. *Clin Exp Dermatol* 2002; **27**: 418–21.
2 Wilson CL, Ferguson DJ, Dawber RP. Matting of scalp hair during shampooing—a new look. *Clin Exp Dermatol* 1990; **15**: 139–42.
3 Khumalo NP, Jessop S, Ehrlich R. Prevalence of cutaneous adverse effects of hairdressing: a systematic review. *Arch Dermatol* 2006; **142**: 377–83.
4 Lepaw MI. Complications of implantation of synthetic fibers into scalps for 'hair' replacement: experience with fourteen cases. *J Dermatol Surg Oncol* 1979; **5**: 201–4.

CHAPTER 67
The Skin and the Eyes

J.N. Leonard[1] *& J.K.G. Dart*[2]

[1]Department of Dermatology, St Mary's Hospital, London, UK
[2]Moorfields Eye Hospital NHS Foundation Trust, London, UK

Anatomy and physiology of the eye, 67.1
The eyebrows, 67.1
The eyelids, 67.1
The lacrimal glands, 67.2
The precorneal tear film, 67.3
Glossary of ophthalmological terms, 67.3
Disorders affecting the eyebrows and eyelashes, 67.3
Disorders of the eyebrows, 67.3
Disorders of the eyelashes, 67.4
Abnormality of the eyelids, 67.5
Skin diseases affecting the eyelids, 67.5
Chronic blepharitis, rosacea and seborrhoeic dermatitis, 67.6
Description, 67.6
Epidemiology, 67.6
Immunopathogenesis, 67.6
Treatment, 67.11
Atopy and atopic eye disease, 67.13
Description and epidemiology, 67.13
Diagnosis, 67.15
Immunopathogenesis, 67.15
Management, 67.15
The interaction of drugs used for the management of atopic eye disease and atopic dermatitis, 67.16
Cicatrizing conjunctivitis and the immunobullous disorders, 67.16
Description and epidemiology, 67.16
Mucous membrane pemphigoid (MMP), 67.17
Other subepithelial immunobullous disorders and conjunctivitis, 67.20
Erythema multiforme major and toxic epidermal necrolysis, 67.20
Graft-versus-host disease, 67.22
Treatment of cicatrizing conjunctivitis and the ocular complications of the immunobullous disorders, 67.22
Systemic diseases with skin and eye involvement, 67.24
Infections, 67.24
Viral infections, 67.24
Bacterial infection, 67.26
Parasitic infection, 67.27
Inherited disorders, 67.28
Ocular complications of dermatological therapy, 67.31
Tumours, 67.33
Benign tumours of the eyelid, 67.33
Malignant tumours of the eyelid, 67.34

Introduction

This chapter is not intended to be a comprehensive account of all diseases that affect the skin and eyes, for which there are several reviews [1–7]. The main focus is on those conditions that commonly occur in clinical practice and that present a problem with management. It is also intended to alert the dermatologist to conditions that might threaten visual acuity and require urgent referral to an ophthalmologist. Also, many systemic diseases affect both the skin and eyes, and ophthalmic assessment will be of help in making the correct diagnosis and in long-term management of such patients.

References

1 Easty DI, Sparrow JM, eds. *Oxford Textbook of Ophthalmology*. Oxford: Oxford University Press, 1999.
2 Hoang-Xuan T, Baudouin C, Creuzot-Garcher C, eds. *Inflammatory Diseases of the Conjunctiva*. Stuttgart: Thieme, 2001.
3 Kanski JJ. *Clinical Ophthalmology. A Systematic Approach*, 4th edn. Oxford: Butterworth–Heinemann, 1999.
4 Pepose JS, Holland GN, Wilhelmus KR, eds. *Ocular Infection and Immunity*. St Louis: Mosby, 1996.
5 Theirs BH, Grant-Kels JM, Rothe MJ *et al*., eds. *Dermatology Clinics—Oculocutaneous Diseases, I & II*, Vol. 10; Nos 3 & 4. Philadelphia: WB Saunders, 1992.
6 Mannis MJ, Macsai MS, Huntley AC, eds. *Eye and Skin Disease*. New York: Lippincott-Raven, 1996.
7 Ostlere HB, Maibach HI, Hoko AW, Swab IR, eds. *Diseases of the Eye and Skin: a Color Atlas*. Philadelphia: Lippincott, Williams & Wilkins, 2004.

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

Anatomy and physiology of the eye [1,2]

The eye and skin share a common embryological origin. The structure of the lid, conjunctiva, the lacrimal gland and associated drainage apparatus are of surface ectodermal origin while the remainder of the eye arises from epithelium of the ectodermal neural plate. The only mesodermal contribution to the eye is the myoblasts of the extraocular muscles. The anatomy of the eye is shown in Fig. 67.1. The eye appendages are as follows.

The eyebrows

This hair-bearing area rests on a very mobile fat and muscle pad overlying the superior orbital ridge. Its mobility is important as a means of facial expression. The eyebrows help protect the eye from bright light and sweat.

The eyelids

The eyelids have distinct anatomical layers, comprising the skin with subcutaneous tissue, the tarsal plate and conjunctiva, and striated muscles that effect lid movement (Fig. 67.2).

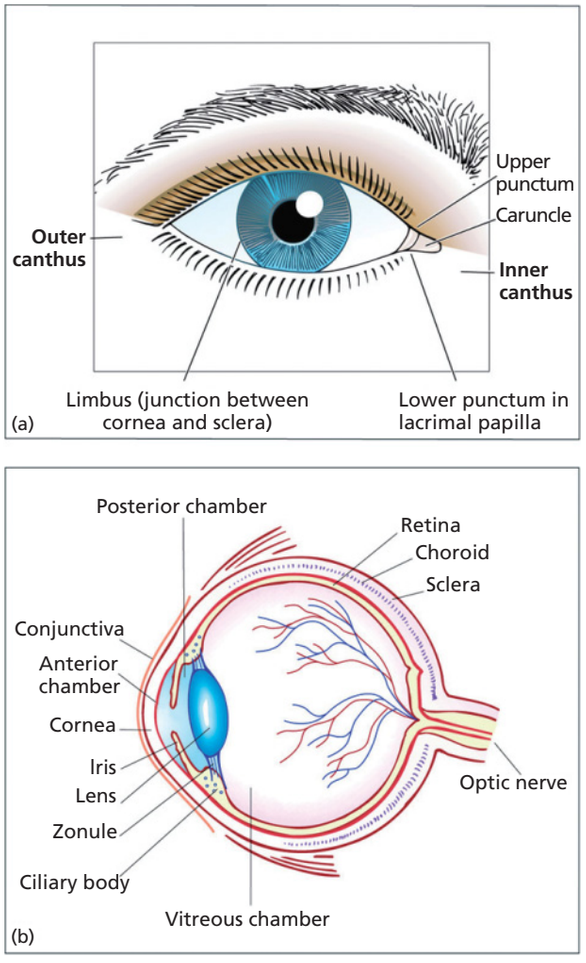


Fig. 67.1 Anatomy of normal eye. (a) The external appearance of the right eye. (b) Cross-section of the human eye.

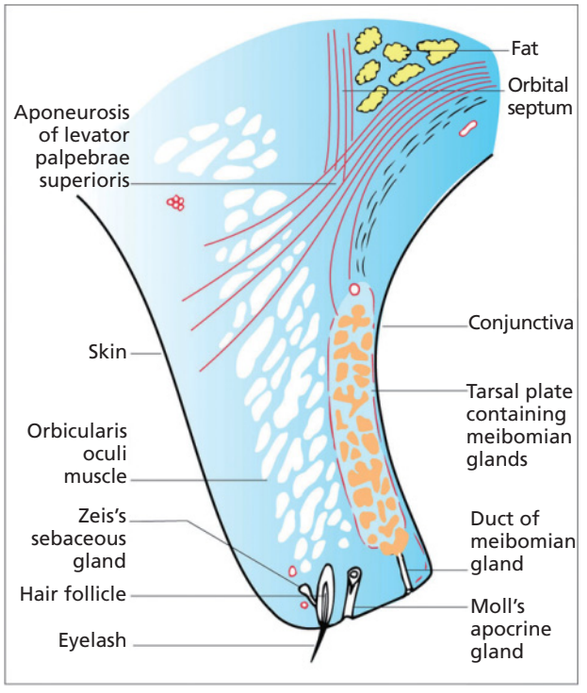


Fig. 67.2 Cross-section of upper eyelid.

The skin is thin and modified in several ways to protect the eyeball. It contains sebaceous glands associated with the fine hairs of the eyelashes (cilia) and both apocrine and eccrine sweat glands. There are about 300 eyelashes, arising in two rows along the eyelid margin, two-thirds of which are in the upper lid. They have no associated erector muscles, but rudimentary sebaceous glands (of Zeis) are present. Some lashes, particularly those of the lower lid, are associated with ancillary apocrine sweat glands (of Moll). The ducts of these glands open both into the lash follicles and directly onto the anterior lid margin between the lashes. The eyelashes help to protect foreign bodies from impinging on the eyeball. Each lash follicle has a rich nerve plexus, which is easily excited—light touch initiates reflex closure.

The tarsal plate of each eyelid gives the palpebral aperture shape and stability. They comprise dense, fibrous tissue surrounding modified sebaceous glands (meibomian glands). These secrete the outer lipid layer of the precorneal tear film through openings along the mucocutaneous junction of the eyelid margin. This lipid helps to stabilize the tear film and reduce evaporation. There are about 30 glands in the upper tarsal plate and 20 in the lower. Meibomian glands have up to 20 acini surrounding a central vertical duct and are visible through the conjunctiva.

The eyelids are lined by a mucous membrane called the palpebral conjunctiva. It is reflected over the anterior portion of the eyeball up to the edge of the cornea as the bulbar conjunctiva. The folds formed by the reflection of the conjunctiva from the lids onto the eyeball are called the superior and inferior palpebral fornices. The conjunctiva contains numerous goblet cells secreting mucin into the tear film. It also contains about 50 accessory lacrimal glands and its substantia propria contains neural tissue, mast cells, lymphocytes and lymphoid follicles, which are important in mediating local immunological reactions.

The striated muscle of the levator palpebrae superioris opens the eye, and the striated orbicularis oculi muscle closes it. Both are innervated by the facial nerve. Two divisions of the trigeminal nerve supply sensation to the eyelids; the upper lid and medial canthus are supplied by the ophthalmic division, and the remainder of the lower lid by the maxillary division.

The eyelid has a rich blood supply, mainly through the medial and lateral palpebral arteries, which are branches of the ophthalmic artery. There is also a rich anastomosis between adjacent arteries arising from the internal and external carotid. The blood drains through a network of veins to the facial and orbital veins and the cavernous sinus. Lymphatics drain the conjunctiva and tarsal plate to the post-tarsal plexus and the skin and orbicularis to the pre-tarsal plexus. The medial canthus and lower lid subsequently drain to the submandibular nodes whilst the lateral canthus and upper lid drain to the parotid and preauricular nodes.

The lacrimal glands

The main lacrimal gland is a modified sweat gland located in the lacrimal fossa, a bony depression just under the upper and outer

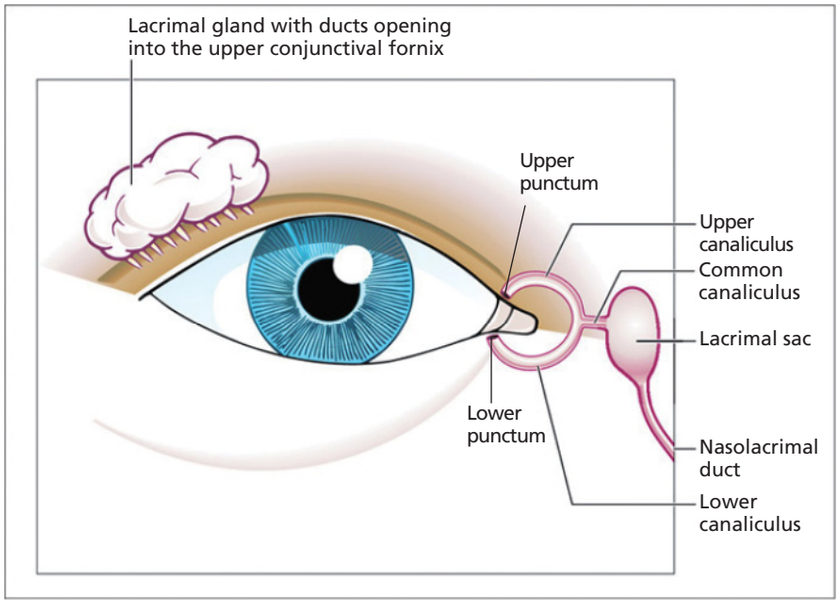


Fig. 67.3 The lacrimal apparatus of the right eye.

margin of the orbit. It produces an aqueous secretion, which discharges through a network of ductules onto the conjunctiva of the palpebral conjunctiva. In addition, there are a variable number of accessory lacrimal glands in the upper and lower conjunctival fornices. The lacrimal gland is innervated whereas the accessory glands are not.

The precorneal tear film

The eyelids make a vital contribution to the composition and stability of the precorneal tear film, which is about 40 µm thick. It is a three-layered structure consisting of a lower hydrophilic mucin layer secreted by goblet cells of the conjunctiva, a central aqueous layer secreted by the lacrimal gland, and a surface hydrophobic lipid layer secreted by the meibomian glands (as discussed above). Blinking consists of a lateral to medial movement of the eyelids, which enables resurfacing of the tear film of the cornea and propels the tears to the punctum of the tear duct; from here, they are actively removed by the lacrimal pump mechanism through the lacrimal canaliculi into the common canaliculus and lacrimal sac, and then via the nasolacrimal duct into the nose (Fig. 67.3).

The tear film has a number of functions:

1 To supply oxygen and other nutrients to the cornea
2 To remove particulate matter from the surface of the eye
3 To prevent drying of the eye
4 To act as a lubricant and prevent adhesion of the palpebral to the bulbar conjunctiva
5 To protect the eye surface through its antibacterial role; it contains white blood cells, various proteins, lysozyme and immunoglobulins.

References

1 Burns RP. Eyelids lacrimal apparatus and conjunctiva. *Arch Ophthalmol* 1968; **79**: 211–25.
2 Dickinson AJ. Anatomy physiology and malformation of the eyelids. In: Easty DL, Sparrow JM, eds. *Oxford Textbook of Ophthalmology*. Oxford: Oxford University Press, 1999: 355–60.

Glossary of ophthalmological terms

A glossary is provided in Table 67.1.

Disorders affecting the eyebrows and eyelashes

There is a wide variation in the colour, distribution and density of the eyebrow hairs. The inheritance of the appearance of the eyebrows is polygenic. Some hereditary variations are of no known significance, but others are associated with other development defects or are part of a recognized syndrome.

Disorders of the eyebrows [1]

Synophrys

This term is applied when the eyebrows are profuse with a tendency to meet in the centre of the face. Synophrys is a feature of some genodermatoses (Chapter 15). The eyebrows also tend to become more bushy in the ageing male for reasons that are unknown. Bushy eyebrows may also occur in other acquired forms of hypertrichosis, for example due to drugs such as diazoxide, and fusion of the eyebrows has been reported in kwashiorkor.

Hypoplasia of eyebrows

Some inherited diseases are characterized by hypoplasia of the eyebrows (Chapter 15). Acquired conditions can cause sparsity or sometimes complete loss of the eyebrows. They may be the only site affected in alopecia areata. Thinning of the eyebrows occurs in hypothyroidism, erythroderma, follicular mucinosis and secondary syphilis. Lepromatous leprosy causes thinning of the outer third of the eyebrows in the early stages, often with depigmentation, progressing to total loss of the brows and lashes. Tuberculoid

Table 67.1 Glossary of ophthalmological terms.

Anophthalmia	Absence of eye
Astichiasis	Absence of lashes
Blepharitis	Inflammation of the eyelid margin
Blepharochalasis	Elastic tissue atrophy causing loose eyelid skin
Bruch's membrane	The retinal layer sandwiched between the retinal pigment epithelium and the vascular choroid
Coloboma	Congenital cleft created by failure of development of a portion of the eye or adnexal structures
Dermatochalasis	Laxness of the skin of the eyelids
Distichiasis	Accessory row of eyelashes
Ectropion	Eversion of the eyelid
Entropion	Inversion of the eyelid
Epicanthal fold	Accessory fold of skin at the inner canthal region of the eye
Epicanthus inversus	Lower lid fold larger than upper lid fold
Epiphora	Excess tearing
Episcleritis	Inflammation of the superficial scleral tissues
Hypertelorism	Increased distance between the two eyes measured radiologically
Hypopyon	The presence of pus in the anterior chamber
Keratitis	Inflammation of the cornea—various types are recognized, including: *filamentary keratitis*—the development of epithelialized mucous filaments on the corneal surface; *interstitial keratitis*—inflammation of the corneal stromal layer
Keratoconjunctivitis sicca	Corneal and conjunctival inflammation associated with impaired tear secretion and ocular dryness
Keratoconus	Conical distortion of the central cornea as a result of a degenerative process in the stroma
Keratopathy	Corneal abnormalities including: *exposure keratopathy*—from corneal exposure and drying of the cornea
Lagophthalmos	Persistent exposure of the eyeball despite closure of the eyelid
Limbus	Boundary between the cornea and sclera
Madarosis	Loss of the eyelashes
Pannus	Vascularized corneal scar
Phlyctenule	Wedge-shaped, peripheral corneal or conjunctival, nodule
Preseptal cellulitis	Cellulitis of the eyelids that has not penetrated through the orbital septum to involve the orbit
Symblepharon	Adhesions between the bulbar and palpebral conjunctiva resulting in complete or partial obliteration of the eyelid fornices
Telecanthus	Increased distance between the inner canthi
Trichiasis	Lashes that turn inward toward the cornea usually as a result of entropion
Uveitis	Inflammation of the uveal tract. It is subdivided into anterior uveitis, which is the most common, intermediate uveitis, posterior uveitis and pan uveitis. *Anterior uveitis* is subdivided into iritis, in which the inflammation predominantly affects the iris, and iridocyclitis, in which both the iris and the anterior part of the ciliary body (pars plicata) are equally involved. *Intermediate uveitis* involves the posterior part of the ciliary body (pars plana) and the extreme periphery of the choroid and retina. *Posterior uveitis* is inflammation located behind the vitreous base. *Pan uveitis* is involvement of the entire uveal tract.

leprosy, by contrast, does not cause loss of the eyebrows. Plucking the eyebrows for cosmetic reasons is common, but true trichotillomania of the eyebrows is unusual.

Inflammatory disorders affecting the eyebrows

The eyebrows are often involved in seborrhoeic dermatitis and psoriasis. Post-inflammatory cicatricial alopecia from discoid lupus erythematosus, folliculitis decalvans, lupus vulgaris or tertiary syphilis may cause loss of eyebrow hairs. Scarring with loss of eyebrows may also follow chemical and thermal burns or radiation. Loss of eyebrows can be camouflaged by the use of eyebrow pencils, permanent tattooing or by a hair prosthesis glued in place daily.

Disorders of the eyelashes

Trichomegaly [2–5]

This may be due to a genetic trait. Increased growth of the eyelashes has also been described in human immunodeficiency virus (HIV) infection and related to various drugs including ciclosporin, zidovudine, interferon and topical xalatan. Long lashes also occur in some patients with phenylketonuria.

Madarosis [1]

Madarosis is a decrease in the number or complete loss of lashes. A number of causes have been recognized and include alopecia areata, chronic anterior lid margin blepharitis, infiltrating tumours of the lid, burns, cryotherapy and radiotherapy, trichotillomania and discoid lupus erythematosus. Systemic diseases such as hypothyroidism and syphilis may also be responsible.

References

1 Draelos ZK, Yeatts RP. Eyebrow loss, eyelash loss and dermatochalasis. *Dermatol Clin* 1992; **10**: 793–8.
2 Casanova JM, Puig T, Rubro M. Hypertrichosis of the eyelashes in acquired immunodeficiency syndrome. *Arch Dermatol* 1987; **123**: 1599–601.
3 Klutman NE, Hinthorn DR. Excessive growth of eyelashes in a patient with AIDS being treated with zidovudine. *N Engl J Med* 1991; **324**: 1896.
4 Foon KA, Dougher G. Increased growth of the lashes in a patient given leukocyte A interferon. *N Engl J Med* 1984; **311**: 1259.
5 Tosti A, Pazzaglia M, Stylanios V, Tosti G. Hypertrichosis of the eyelashes caused by bimatoprost. *J Am Acad Dermatol* 2004; **51**: S149–50.

Abnormality of the eyelids

These include dermatochalasis, blepharochalasis and lid laxity. Numerous developmental defects can affect the palpabral fissure or size and shape of the eyelids. A number of hereditary dermatoses affect the eyelids (Chapter 15).

Ptosis

Drooping of the eyelids on one or both sides is a common genetic defect. Mild ptosis commonly develops in the elderly due to the laxity of the connective tissue. There are many important acquired causes, such as third nerve palsy, Horner's syndrome and myasthenia gravis, which require neurological referral. Ptosis may be associated with other ocular abnormalities.

Skin diseases affecting the eyelids

A large number of dermatological conditions can affect the eyelids as part of a generalized process. Usually there is little diagnostic difficulty as the diagnosis is made by examination of the rest of the skin. Psoriasis and lichen planus can both involve the lids and cause considerable irritation. These are chronic diseases and management can become a problem with use of potent topical corticosteroids on the eyelids over a prolonged period of time. Use of the new topical immunosuppressants, such as tacrolimus and pimecrolimus, may offer some promise for the future in reducing topical corticosteroid exposure. Unilateral involvement of an eyelid raises the possibility of infective conditions, including tinea and mycobacterial infections.

Psoriasis [1]

Eyelid involvement can occur in about 10% of patients with psoriasis. Men are more susceptible to ocular disease. Involvement of the eyelid gives rise to blepharitis, madarosis and development of psoriatic plaques. Chronic non-specific conjunctivitis may occur over time and lead eventually to keratoconjunctivitis sicca with symblepharon formation and trichiasis. Conjunctivitis usually complicates eyelid margin involvement; white or yellow psoriatic plaques can spread from the lid on to the conjunctiva itself. Corneal changes are rare and are most commonly related to exposure and trichiasis. Anterior uveitis is rare but has been reported in patients with psoriatic arthritis and is similar to that seen in Reiter's syndrome. Ocular psoriasis is treated with use of lubricants and topical corticosteroids. Patients with chronic eyelid involvement should be referred for ophthalmological assessment.

Contact dermatitis [2–8]

Contact dermatitis is the responsible cause in approximately half of patients with an eyelid dermatitis. The remainder have manifestations of atopic or seborrhoeic dermatitis. The eyelid skin is very sensitive to primary irritants. These can cause a dermatitis in their own right or can aggravate an underlying constitutional tendency in patients with either atopic or seborrhoeic dermatitis.

Allergic contact dermatitis can present after many years of exposure to the culpable allergen. Clinically it is characterized by severe itching, erythema and swelling of the eyelid, progressing to formation of vesicles. A large variety of allergens have been reported as causing an allergic contact dermatitis of the lid and include preservatives (used in cosmetics, topical medications and contact lens cleaning solutions), fragrances and the resin used in nail polish. Patients with suspected contact dermatitis of the eyelids should be patch tested. Careful history taking is of paramount importance to make sure the relevant allergens are included in the test battery. The possibility of transferring antigen from the hands to the eyelids needs to be considered. Maibach described the upper eyelid dermatosis syndrome in which patients have discomfort of the eyelids with or without dermatitis; it is thought to be unrelated to use of cosmetics.

Periorbital oedema [9,10]

The subcutaneous tissue of the eyelids is lax and prone to oedema. There are many systemic and dermatological causes of eyelid oedema that need to be considered. Systemic causes include angio-oedema, glomerulonephritis, hypoalbuminaemia (especially nephrotic syndrome), cardiac failure, superior venocaval obstruction and thyroid disease. Some systemic infections, such as infectious mononucleosis and scarlatina, cause periorbital oedema. It may be the presenting feature of dermatomyositis and has been reported in systemic lupus erythematosus.

The most common dermatological causes of periorbital oedema are angio-oedema, lymphoedema, allergic contact dermatitis and blepharochalasis; they are usually distinguished by the history. Angio-oedema is transient and often part of a more generalized urticarial eruption. Lymphoedema is permanent and tends to be worse first thing in the morning and improves during the day; it may be associated with underlying sinus disease or a chronic inflammatory condition such as granulomatous rosacea. Allergic contact dermatitis presents acutely with swelling, redness and itching. Blepharochalasis is an uncommon condition which may be inherited (autosomal dominant) or sporadic; it presents in the second decade with recurrent episodes of painless lid oedema, resulting in the development of excess skin and thickened subcutaneous tissue which may require treatment by blepharoplasty. Senile orbital fat prolapse through a deficient orbital septum may mimic periorbital oedema but is differentiated by the fact that there is minimal fluctuation in the associated swelling. Periorbital oedema may be the presenting feature of rosacea.

Changes in pigmentation [11–15]

There are considerable racial and familial variations of the degree of pigmentation of the eyelids (Chapter 58). Marked periorbital melanosis is seen as a genetic trait. Pigmentation of the periorbital skin can also be post-traumatic, post-inflammatory or can accompany melanocyte-stimulating hormone-induced melanosis of any cause. Chemical pigmentation can occur from prolonged use of a mercurial or silver preparation, producing a slate-blue or grey-brown discoloration. Mauve discoloration of the eyelids and periorbital area is an early part of chrysiasis from parenteral gold therapy. A grey discoloration can complicate long-term treatment with minocycline. Local increase in pigmentation may also be due to cosmetics containing phototoxic agents, usually psoralens. Increased pigmentation can also follow inflammatory dermatoses such as eczema and lichen planus. The eyelids may be involved in vitiligo. Hypopigmentation can complicate the use of topical medications including thiotepa eye drops and mercurial ointments.

References

1 Steiner G, Arffa RC. Psoriasis, ichthyosis and porphyria. *Int Ophthalmol Clin* 1997; **37**: 41–61.
2 Guin JD. Eyelid dermatitis: experience in 203 cases. *J Am Acad Dermatol* 2002; **47**: 755–65.
3 Nethercott JR, Nield G, Holmes DL. A review of 79 cases of eyelid dermatitis. *J Am Acad Dermatol* 1989; **21**: 223–30.
4 Valecchi R, Imberti G, Martinod D, Carnelli T. Eyelid dermatitis—an evaluation of 150 patients. *Contact Dermatitis* 1992; **27**: 143–7.
5 Shah M, Lewis FM, Gawkrodger DJ. Facial dermatitis and eyelid dermatitis—a comparison of patch tests results and final diagnosis. *Contact Dermatitis* 1992; **27**: 143–7.
6 Rapaport M. Contact dermatitis secondary to chlorhexidine in contact lens cleansing solution. *Am J Contact Dermat* 1991; **2**: 65–6.
7 Herbst RA, Maibach HI. Contact dermatitis caused by allergy to ophthalmic drugs and contact lens solutions. *Contact Dermatitis* 1991; **25**: 305–12.
8 Maibach HI, Engasser P, Ostler B. Upper eyelid dermatosis syndrome. *Dermatol Clin* 1992; **10**: 549–54.
9 Jarek MJ, Finger DR, Gillil UR, Giandoni MB. Periorbital oedema and Mees' lines in systemic lupus erythematosus. Non-specific but disease-related skin lesions. *J Clin Rheumatol* 1996; **2**: 156–9.
10 Chen DM, Crosby DL. Periorbital edema as an initial presentation of rosacea. *J Am Acad Dermatol* 1997; **37**: 346–8.
11 Hunzinger N. Apropos of familial hyperpigmentation of the eyelid. *J Genet Hum* 1962; **11**: 16–21.
12 Aguilera Diaz L. Hyperpigmentation of the eyelids. *Ann Dermatol Syphiligr (Paris)* 1972; **99**: 43–6.
13 Smith RW, Leppard B, Barnett NL *et al*. Chrysiasis revisited: a clinical and pathological study. *Br J Dermatol* 1995; **133**: 671–8.
14 Cowan CI, Halder RM, Grimes PE. Ocular disturbances in vitiligo. *J Am Acad Dermatol* 1986; **15**: 17–24.
15 Harben DJ, Cooper PH, Rodman OG. Thiotepa induced leucoderma. *Arch Dermatol* 1979; **115**: 973–4.

Chronic blepharitis, rosacea and seborrhoeic dermatitis [1–4]

Description

Chronic blepharitis is a term that is used to describe a group of disorders in which the lid margin is always involved. These disorders often occur simultaneously. Not all of them result in inflammation of the lid margin. They are frequently associated with a conjunctivitis or keratoconjunctivitis. Chronic blepharitis may occur in the absence of any significant dermatological association, and its classification is further complicated both by the variable association of chronic blepharitis with rosacea and seborrhoeic dermatitis, and also by the term ocular rosacea, a condition which may occur in the absence of dermatological rosacea.

It is hardly surprising that this classification causes confusion amongst practitioners. This situation has arisen partly because there is no consensus about the terminology (although most modern authors use similar classifications based on McCulley's modification of Thygeson's classification) and, more probably, because the pathogenesis is very poorly understood, with few unifying concepts.

Table 67.2 summarizes a current classification, associations and features. It includes ocular rosacea amongst the meibomian gland disorders, with which it is always associated. Table 67.2 classifies the five types of blepharitis (including ocular rosacea) into those that principally affect the anterior lid margin structures (cutaneous margin with lash-bearing skin and associated glands) and those affecting the posterior lid margin (mucocutaneous junction, meibomian orifices). This classification corresponds with, and simplifies understanding of, the treatment of the different conditions, which differs between the anterior- and posterior-lid margin disorders but not between the individual conditions within each of these two groups. The commoner clinical signs of staphylococcal blepharitis are shown in Fig. 67.4. Ocular rosacea (Table 67.3, Fig. 67.5) is an important condition because of its severity and wide spectrum of clinical features.

In addition to these very common types of blepharitis, there are other chronic causes in which the pathogenesis is clear. These are all uncommon and are often misdiagnosed as one of the types of chronic blepharitis described in Table 67.2. They include fungal infection (e.g. *Candida*), parasitic infection (e.g. phthiriasis), protozoal infection (e.g. leishmaniasis), some neoplasms, and autoimmune conditions such as lupus erythematosus; some of these are illustrated in Fig. 67.6. They should be considered when therapy for conventional blepharitis fails.

Acute blepharitis is a clearly defined group of conditions, for which the causes are summarized in Table 67.4.

Epidemiology

The epidemiology has been dogged by difficulties of disease definition and the different perspectives of dermatologists and ophthalmologists. Chronic blepharitis is one of the commonest disorders in both ophthalmic and general medical practice. In general medical practice it makes up about 70% of ophthalmic referrals, which themselves account for between 2 and 7% of all outpatient consultations. Meibomian gland dysfunction is probably the commonest type of blepharitis and affects 20–40% of all patients consulting ophthalmologists for routine eye examinations. Between 3 and 58% of patients with rosacea have ocular involvement; this wide variation in cited frequency largely reflecting differences in disease definition. Approximately half of patients with rosacea have signs of ocular rosacea, whilst one-quarter of patients with ocular rosacea have no dermatological disease.

Immunopathogenesis [5]

There is some evidence to support hypotheses of pathogenesis in staphylococcal blepharitis and in meibomian dysfunction, but the pathogenesis is even more poorly understood in the other types of chronic blepharitis.

Staphylococcal blepharitis

In staphylococcal blepharitis [6–13] there is an association with *Staphylococcus aureus* and *S. epidermidis* colonization of the lid margins, although colonization by *S. aureus* is often transient and the numbers of either organism are often no greater than in normal controls. Although folliculitis, styes and lid margin ulcers may be due to infection by *S. aureus*, the persistence of lid inflammation after treatment and the sterile marginal ulcers are not explained by infection alone. The importance of cell-mediated immunity in the pathogenesis of the disease was shown by experimental studies in rabbits; when these were immunized with either whole *S. aureus* or with cell wall ribitol–teichoic acid, both ulcerative keratitis, phlyctenules and marginal corneal ulcers developed after second-

Table 67.2 Classification of types of chronic blepharitis (lid margin disorders).

Anterior lid margin*		**Posterior lid margin***		
Staphylococcal blepharitis	**Seborrhoeic blepharitis**	**Meibomitis/ocular rosacea**	**Meibomian gland dysfunction**	**Meibomian seborrhoea**
Associations with other types of blepharitis				
Secondary meibomitis	Any posterior lid margin condition	Staphylococcal and seborrhoeic blepharitis	Seborrhoeic blepharitis	Seborrhoeic blepharitis
Associated skin disease				
Atopic eczema Impetigo Rosacea (rare)	Seborrhoea Rosacea (rare)	Acne rosacea in up to 50% of cases	Acne rosacea in up to 50% of cases	
Associated eye disease				
Dry eye Atopic keratoconjunctivitis		Scleritis and episcleritis in ocular rosacea		
Main features				
Symptoms				
Burning Itching Photophobia	Minimal	Foreign body sensation Burning Discomfort Photophobia with ocular rosacea	Variable: Foreign body sensation Burning Discomfort	Variable: Foreign body sensation Burning Discomfort
Lid signs				
Unilateral/patchy lid margin involvement (Fig. 67.4d) Brittle fibrinous scales bleed when detached, form collarettes at lash base (Fig. 67.4a) Dilated vessels, styes Poliosis and madarosis (Fig. 67.4b)	Bilateral greasy scales (not fibrinous)	Chalazia (Fig. 67.5b) Irregular lid margins Distorted meibomian orifices Inspissated secretions Expression difficult Surrounding inflammation For lid signs in ocular rosacea see Table 67.3		Plugged and elevated orifices without inflammation
Conjunctival and corneal signs				
Follicles, papillae and hyperaemia of lower tarsal conjunctiva and fornix (Fig. 67.4c)		Early tear break up time Foam/debris in tears Punctate keratitis (dry eye)		Minimal injection
Coarse punctate keratitis in lower third of cornea. Marginal keratitis (Fig. 67.4e) and vascularization. Conjunctival scarring (Fig. 67.5a)		For conjunctival and corneal signs in ocular rosacea see Table 67.3		±Foamy tear film

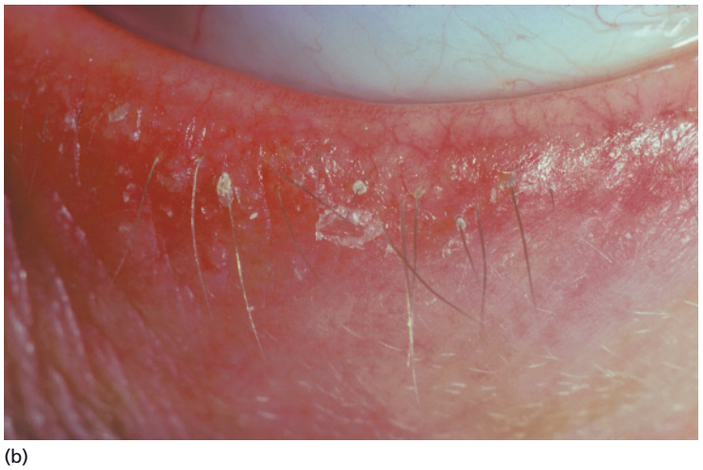
* The anterior lid margin is the portion anterior to the meibomian gland orifices and the posterior lid margin is behind this, including the meibomian glands. Anterior and posterior lid margin disorders are commonly mixed; frequent associations are shown in the table.

Table 67.3 Clinical signs of ocular rosacea.

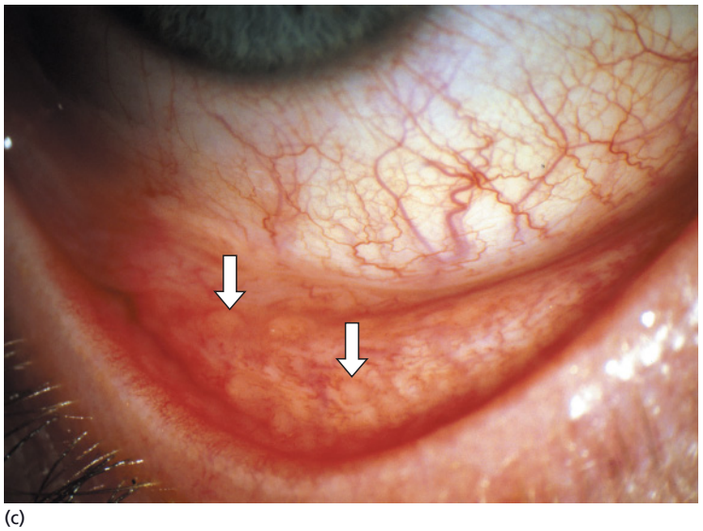
Signs	**Common**	**Uncommon**	**Rare**
Lid	Meibomitis (Fig. 67.5a) Seborrhoeic blepharitis Lid margin telangiectasia Lid notching Retroplacement of the mucocutaneous junction Chalazia (Fig. 67.5b) Hordeoleum	Entropion	
Conjunctiva	Conjunctival hyperaemia Papillary conjunctivitis	Reticular and linear tarsal scarring and fornix shortening (Fig. 67.5a)	
Cornea	Phlyctenular keratoconjunctivitis Marginal corneal infiltration and ulceration (Fig. 67.5d,e)	Pseudopterygium (Fig. 67.5d)	Corneal perforation
Sclera and episclera		Episcleritis	Scleritis



(a)



(b)



(c)



(d)

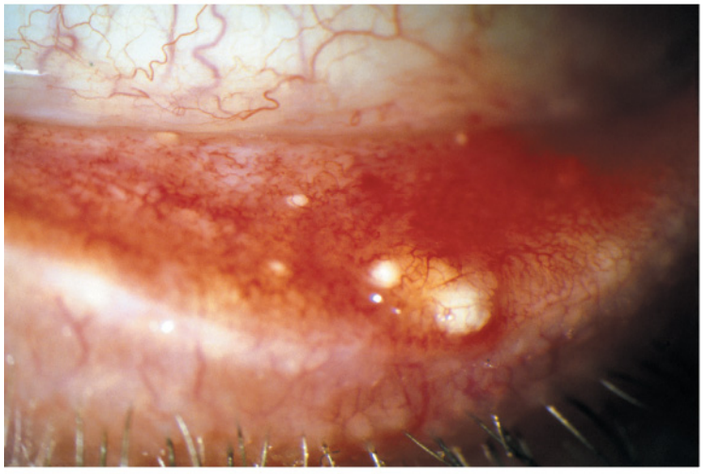


(e)

Fig. 67.4 Staphylococcal blepharitis. (a) Fibrinous 'collarettes' lifting away from the skin as the lashes grow. (b) Fibrinous scales on the anterior lid margin with the madarosis (loss of lashes) and poliosis (white lashes) that accompanies chronic blepharitis. (c) Follicular conjunctivitis with arrows showing the white/yellow follicles. (d) Localized ulcerative blepharitis. Sectoral disease like this is quite common in staphylococcal blepharitis which can also be largely unilateral. (e) Marginal ulceration, a common corneal complication of staphylococcal blepharitis.



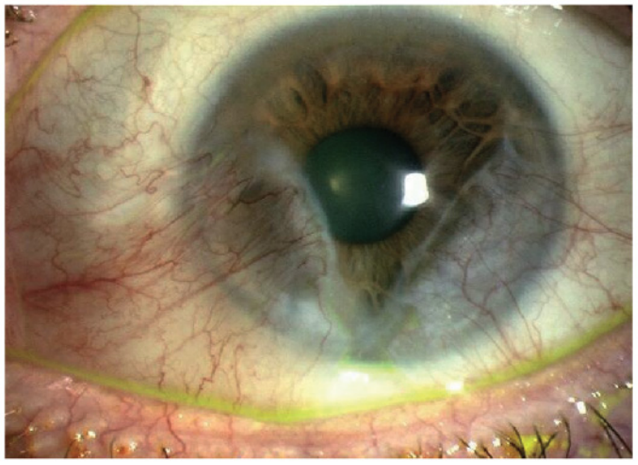
(a)



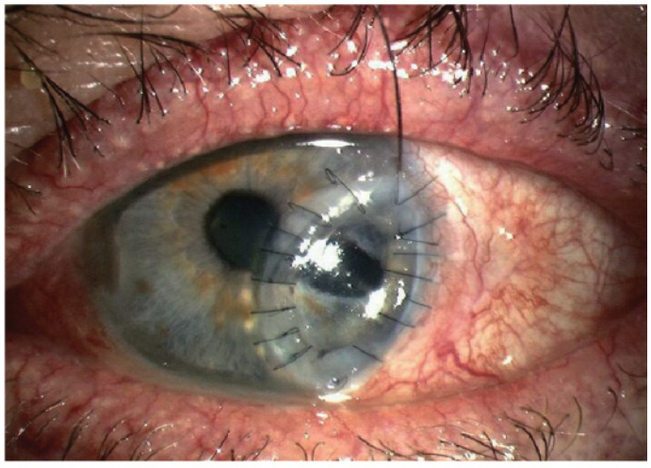
(b)



(c)



(d)

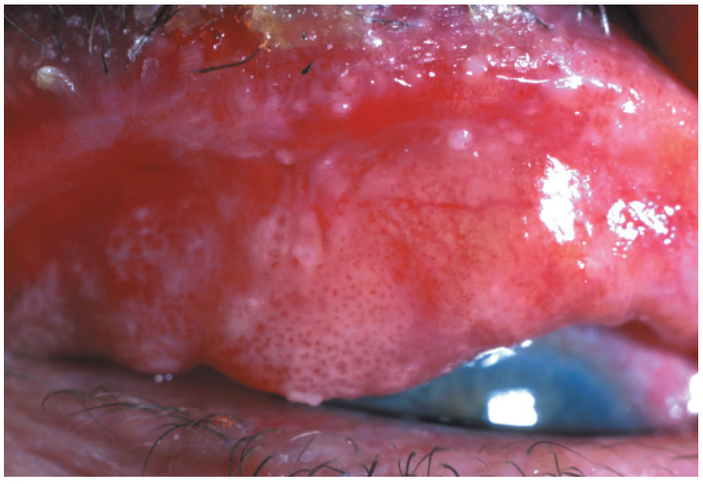


(e)

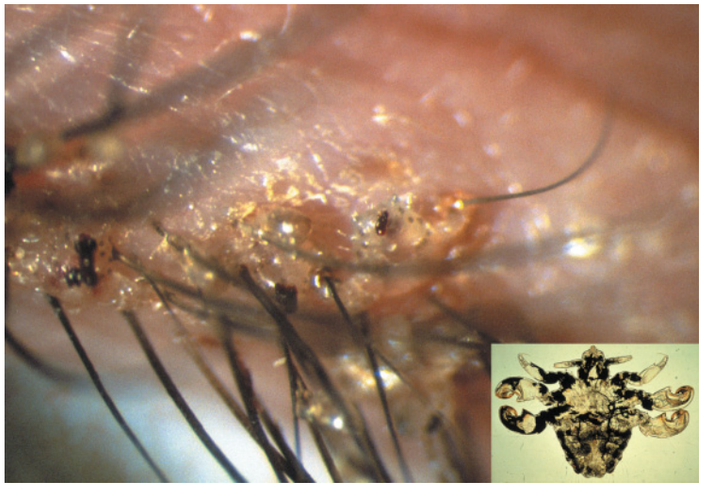
Fig. 67.5 Ocular rosacea. (a) Scales on the anterior lid margin, meibomitis with posterior migration of the orifices associated with loss of the normal posterior lid margin architecture and scarring in the superior tarsal marginal sulcus. Entropion and trichiasis may result from this degree of scarring. (b) Meibomian dysfunction with blocked glands and small chalazia. (c) Marginal ulceration complicated by frank bacterial superinfection with an hypopyon ulcer. (d) Severe marginal ulcers with pseudopterygia. (e) Corneal transplant following perforation of a marginal ulcer; also shows meibomitis.



(a)



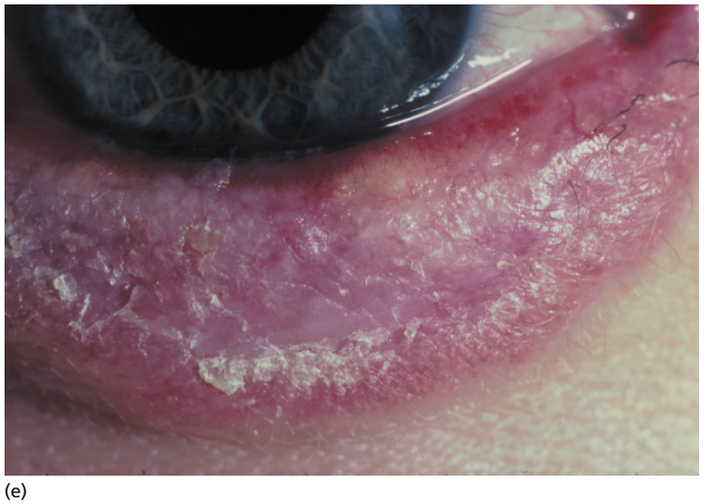
(b)



(c)



(d)



(e)

Fig. 67.6 Rarer causes of chronic blepharitis. (a,b) Sebaceous carcinoma of the upper lid. Basal cell carcinomas (BCCs) may also 'masquerade' as chronic blepharitis. (c,d) Blepharitis due to *Phthirus pubis*, showing the louse in (c) and the eggs ('nits') in (d). (e) Typical lid lesion of discoid lupus.

Table 67.4 Causes of acute blepharitis.

Acute anterior lid margin	Folliculitis (infected lash follicles)
	External hordeoleum (stye)
	Angular (at lateral canthus)
	Impetigo
	Pustular (herpes infections)
Acute posterior lid margin	Chalazion
	Internal hordeoleum
Generalized anterior and posterior	Necrotizing fasciitis

ary challenge, providing evidence for the hypothesis that these changes were due to the development of hypersensitivity to both viable and killed organisms. These findings could not be reproduced for *S. epidermidis*. However, evidence for a similar pathogenesis in humans is lacking; the relationship between the clinical signs of staphylococcal blepharitis and hypersensitivity to subcutaneous injections of either whole *S. aureus* or of *S. aureus* cell wall protein A is poor. *Staphylococcus epidermidis* is more often isolated than *S. aureus* from the lids of patients with staphylococcal blepharitis, but the role of a hypersensitivity response is assumed and not supported by any firm data. The pathogenesis of the, often severe, follicular and papillary conjunctivitis that accompanies this condition is assumed to be due to a combination of transient infection and hypersensitivity.

Meibomian gland disease (MGD) [14–16]

The meibomian lipids (meibum) are a complex mixture of cholesterol esters and esterified unsaturated fatty acids. These lipids are responsible for maintaining a stable tear film, reducing tear film evaporation (and, therefore, preventing drying of the ocular surface), preventing tear spill over the lid margins by lowering surface tension and reducing ocular surface contamination by sebum from the cutaneous surface of the lids, which otherwise forms dry spots.

Three factors have been invoked as contributing to MGD: (i) keratinization of the meibomian ductules; (ii) the effect of bacterial lipases on the meibum at the lid margin; and (iii) primary abnormalities in the production of meibum by individuals with MGD.

Normal meibomian gland ducts open just anterior to the mucocutaneous junction. As the duct lining is partially keratinized, abnormalities of keratinization, analogous to those present in the sebaceous glands of patients with rosacea, may be important in the pathogenesis of MGD by altering gland function. Bacterial lipases are produced by all the bacteria that colonize the lid margin and have the potential to break down meibum into free fatty acids, which will destabilize the tear film. These bacteria colonize the gland orifices and expression of lipid from deeper within the glands can stabilize the tear film. Meibomian lipids differ between individuals and, as analytical methods increase in sensitivity, the relative roles of primary abnormalities of meibum and those secondary to the effects of bacterial lipases in the pathogenesis of MGD are likely to become clearer.

Neither the pathogenesis of the conjunctival inflammation that is common in meibomitis (and which is a feature of ocular rosacea), nor that of the keratitis in ocular rosacea, has been explained.

Treatment [17–25]

The treatment of blepharitis is that of the underlying cause, if a specific cause can be identified. Treatment for the principal causes of chronic blepharitis is outlined in Table 67.5. The blepharitis should initially be classified into either anterior or posterior lid disease or both (Table 67.2). It is important to decide whether blepharitis is the cause of the symptoms; seborrhoea rarely causes symptoms and should not be used as a scapegoat to explain away symptoms possibly due to other, or undiagnosable, conditions. Other conditions that give rise to similar symptoms and signs (Table 67.2) should be excluded or treated. Symptoms of dry eye, and associated skin disorders, should also be treated.

Diffuse folliculitis is generally caused by *S. aureus* and requires a course of an appropriate systemic antibiotic. Laboratory investigations are of limited value—bacteriology samples can be taken from lid margins using swabs dipped in trypsin digest broth, but are usually only performed for recurrent disease that has not responded to initial therapy.

Chalazion will resolve in time; approximately 60% of lesions will resolve in 6 months and the remainder will resolve spontaneously, given longer. Resolution of chalazia can be hastened by incision and curettage; the lid is incised, usually from the conjunctival surface, under local anaesthesia, and the necrotic granulomatous tissue in the centre of the lesion removed with a curette. This leaves a linear conjunctival and tarsal scar. It is only recommended for cosmetic reasons or to improve vision in large lesions affecting the upper lid, which can cause temporary astigmatism.

Practice points for dermatologists are that the association between blepharitis and skin disease is variable, that treatment with tetracyclines may be beneficial for both the ocular and dermatological manifestations of these disorders, and that ocular rosacea and staphylococcal blepharitis may produce sight-threatening complications.

References

1 McCulley JP, Dougherty JM, Deneau DG. Classification of chronic blepharitis. *Ophthalmology* 1982; **89**: 1173–80.
2 Browning DJ, Proia AD. Ocular rosacea. *Surv Ophthalmol* 1986; **31**: 145–58.
3 Akpek EK, Merchant A, Pinar V, Foster CS. Ocular rosacea. *Ophthalmology* 1997; **104**: 1863–7.
4 Erzurum SA, Feder RS, Greenwald MJ. Acne rosacea with keratitis in childhood. *Arch Ophthalmol* 1993; **111**: 228–30.
5 Huang-Xuan T, Rodriguez A, Zaltas MM *et al*. Ocular rosacea. A histologic and immunopathologic study. *Ophthalmology* 1990; **97**: 1468–75.
6 Mondino BJ, Brawman-Mintsev O, Adamu S. Corneal antibody levels to ribitol teichoic acid in rabbits immunised with staphylococcal antigen using various routes. *Invest Ophthalmol Vis Sci* 1987; **28**: 1553–8.
7 Mondino BJ, Caster AI, Dethlefs B. A rabbit model of staphylococcal blepharitis. *Arch Ophthalmol* 1987; **105**: 409–12.
8 Mondino BJ, Dethlefs B. Occurrence of phylctenules after immunisation with ribitol teichoic acid of *S. aureus*. *Arch Ophthalmol* 1984; **102**: 461–3.
9 Mondino BJ, Kowalski R, Ratajczak HV *et al*. Rabbit model of phylctenulosis and catarrhal infiltrates. *Arch Ophthalmol* 1981; **99**: 891–5.
10 Shine WE, Silvany R, McCulley JP. Relation of cholesterol stimulated *Staphylococcus aureus* growth to chronic blepharitis. *Invest Ophthalmol Vis Sci* 1993; **34**: 2291–6.
11 Dougherty JM, McCulley JP. Comparative bacteriology of chronic blepharitis. *Br J Dermatol* 1984; **68**: 524–8.
12 Dougherty JM, McCulley JP. Bacterial lipases and chronic blepharitis. *Invest Ophthalmol Vis Sci* 1986; **27**: 484–91.

Table 67.5 Treatment of chronic blepharitis.

Aims of treatment	Therapeutic guidelines
For anterior lid margin disease (ALMD)	
Treat infection	Staphylococcal and mixed staphylococcal/seborrhoeic groups Topical antibiotics—chloramphenicol or fucidic acid—4 times daily to lid margins Oral oxytetracycline or erythromycin 500 mg twice daily for 10 days
Clean lid margins	'Lid scrubs': 1–2 times daily with cotton wool bud dampened in boiled water or with proprietary lid cleaning pads, to remove debris
Lid hyperaemia and exudate	Topical chloramphenicol and hydrocortisone 0.5–1.0% to lid margins 2–4 times daily for 1 month
For posterior lid margin disease (PLMD)	
Mechanically unblock meibomian glands	Apply hot compresses for 3–5 min to liquefy meibomian secretions, followed by massage* of tarsal plate with cotton wool bud (or finger), to express lipid from glands, 1–2 times daily
Alter meibomian secretions	Oral tetracycline (e.g. doxycycline 100 mg once daily) or erythromycin 250–500 mg twice daily for 12 weeks minimum
For the tear film	
Restore tear film	Artificial tears—drops 2–4 hourly, or Viscotears 3–4 times daily
For associated conjunctivitis (papillary or mixed follicular and papillary)	
Reduce inflammation	Fluoromethalone 0.1% four times daily for 1 week, progressively reducing to one time daily over a further 4 weeks
Treat associated skin disease	Seborrhoea—medicated soap and shampoo (ideally containing glycolic acid 10–15%) Rosacea—oral oxytetracycline (or doxycycline 100 mg) or erythromycin 250–500 mg twice daily for 12 weeks
For keratitis	
Coarse punctate keratitis and/or marginal keratoconjunctivitis	Fluoromethalone 0.1% four times daily for 1 week, progressively reducing to once daily over a further four weeks†
Corneal thinning and perforation	Exclude and treat any concomitant microbial keratitis and establish disease control by methods summarized above, apply tissue glue to perforations. Carry out tectonic keratoplasty, if necessary, once the inflammation is controlled.

* Lid scrubs, lid massage and low-dose systemic antibiotics take about 4–6 weeks to start to work. DO NOT assume treatment has failed until at least 8 weeks on treatment has elapsed, and continue the regime for a minimum of 2–3 months if benefit is shown. Then advise a maintenance regime of lid scrubs (for ALMD), hot compresses and tarsal massage (for PLMD), ± artificial tears. In the case of relapse, repeat a 3-month course of oral antibiotic treatment.

† More prolonged courses of corticosteroid or more potent corticosteroids may be needed under specialist ophthalmological supervision. Topical ciclosporin has recently been shown to be effective for controlling inflammation in posterior blepharitis in one randomized trial and another case series [24,25]. The author's experience with topical ciclosporin in ocular rosacea has been promising.

13 Thygeson P. Complications of staphylococcal blepharitis. *Am J Ophthalmol* 1969; **68**: 446–9.

14 McCulley JP, Scialis GF. Meibomian keratoconjunctivitis. *Am J Ophthalmol* 1977; **84**: 788–93.

15 Mathers WD. Ocular evaporation in meibomian gland dysfunction and dry eye. *Ophthalmology* 1993; **10**: 347–51.

16 Yokoi N, Mossa F, Tiffany JM, Bron AJ. Assessment of meibomian gland function in dry eye using meibometry. *Arch Ophthalmol* 1999; **117**: 723–9.

17 Huber-Spitzy V, Baumgartner I, Bohler-Sommeregger K, Grabner G. Blepharitis—a diagnostic and therapeutic challenge: a report on 407 consecutive cases. *Graefes Arch Clin Exp Ophthalmol* 1991; **229**: 224–7.

18 Thygeson S. Etiology and treatment of blepharitis: a study in military personnel. *Arch Ophthalmol* 1946; **36**: 445–77.

19 Brown SI, Shahinian L Jr. Diagnosis and treatment of ocular rosacea. *Ophthalmology* 1978; **85**: 779–86.

20 Bartholomew RS, Reid BJ, Cheeseborough MJ *et al*. Oxytetracycline in the treatment of ocular rosacea: a double blind trial. *Br J Ophthalmol* 1982; **66**: 386–8.

21 Frucht-Pery J, Sagi E, Hemo I, Ever-Hadani P. Efficacy of doxycycline and tetracycline on ocular rosacea. *Am J Ophthalmol* 1993; **116**: 88–92.

22 Dougherty JM, McCulley JP, Silvany RE, Meyer DR. The role of tetracycline in chronic blepharitis. Inhibition of lipase production in staphylococci. *Invest Ophthalmol Vis Sci* 1991; **32**: 2970–5.

23 Lemp MA, Mahmood MA, Weiler HH. Association of ocular rosacea and keratoconjunctivitis sicca. *Arch Ophthalmol* 1984; **102**: 556–7.

24 Rubin M, Rao SN. Efficacy of topical cyclosporin 0.05% in the treatment of posterior blepharitis. *J Ocul Pharmacol Ther* 2006; **22**: 47–53.

25 Perry HD, Doshi-Carnevale S, Donnenfeld ED *et al*. Efficacy of commercially available topical cyclosporine A 0.05% in the treatment of meibomian gland dysfunction. *Cornea* 2006; **25**: 171–5.

Atopy and atopic eye disease

Description and epidemiology [1–5]

This group of disorders, usually known as the allergic eye diseases, is better termed the atopic eye diseases to distinguish them from disorders that result from other hypersensitivity mechanisms. The atopic eye diseases comprise a group of disorders that have in common a papillary conjunctivitis and evidence of a type 1 allergic mechanism; the immunopathogenesis has recently been shown to be more complex than this. All of these diseases are uncommon, and only a small proportion of patients with atopic dermatitis have ocular disease. Table 67.6 summarizes these disorders and Fig. 67.7 shows the commoner clinical signs.

Of these disorders only atopic keratoconjunctivitis (AKC) (Fig. 67.7b,g), atopic blepharoconjunctivitis (ABC) and vernal keratoconjunctivitis (VKC) (Fig. 67.7c,d) are of interest to the dermatolo-

Table 67.6 Clinical characteristics and distinguishing features and diagnosis of the atopic eye diseases.

Disease	Disease course	Conjunctival signs	Corneal signs	Disease associations	Diagnostic tests
Seasonal allergic conjunctivitis (SAC)	Onset 5–20 years Spontaneous remissions common Rare in old age Strikingly seasonal	Hyperaemia. Stringy white discharge. Oedema Micropapillae if severe	None	Personal or family history of atopy including atopic dermatitis	*Cytology*: usually normal. Serum and tear IgE often elevated but not diagnostic
Perennial allergic conjunctivitis (PAC)	As for SAC but symptoms all year round with seasonal exacerbations	Hyperaemia, stringy white discharge, micropapillae common	None	Personal or family history of atopy including atopic dermatitis	
Atopic keratoconjunctivitis (AKC)	Onset between 20 and 50 years. Chronic course over many years (Fig. 67.7g). Spontaneous resolution in old age Non-seasonal	Micropapillae with intense infiltrate (Fig. 67.7b). Reticular and sheet scarring. Shortened fornices in some cases Trantas' dots*	Punctate epithelial keratopathy, pannus, macroerosion† and plaque‡ Pseudogerontoxon§. Herpes keratitis and bacterial keratitis (Fig. 67.7f) common	*Systemic*: atopy and atopic dermatitis in all cases *Ocular*: staphylococcal lid disease, cataract, keratoconus, herpes simplex keratitis (often bilateral)	*Cytology*: shows eosinophils and mast cells. Serum IgE elevated. Skin prick tests positive to many allergens but not diagnostic *Upper tarsal conjunctival punch biopsy*: the gold standard for disease confirmation after a 2-week abstention from use of topical corticosteroids *Tear IgE*: useful unless the serum IgE is very high
Atopic blepharoconjunctivitis (ABC)	As for AKC	Micropapillae with intense infiltrate, reticular scarring	None	Personal or family history of atopy	
Vernal keratoconjunctivitis (VKC)—*palpebral, limbal and mixed forms*	Onset between 5 and 15 years. Spontaneous resolution in 95% after 10 years Seasonal exacerbations usual	*Palpebral form*: giant upper tarsal papillae (Fig. 67.7c) often bilaterally asymmetrical *Limbal form*: micropapillae on upper tarsus but gelatinous macropapillae at limbus (Fig. 67.7d). Trantas' dots in both *Mixed form*: combines features of both diseases	*Palpebral form*: punctate epithelial keratopathy affecting upper half of cornea. Adherent mucus appearing as superficial syncytial opacity progressing to macroerosion and vernal plaque (Fig. 67.7e) *Limbal form*: keratopathy extending in from limbus with associated epithelial dysplasia	*Ocular*: keratoconus and cataract *Systemic*: atopy in variable proportions from 0–100% depending on geographical location (atopy common in Northern Europe but rare in Middle East)	

* Trantas' dots: white, pinhead sized dots consisting of eosinophils and necrotic epithelial cells usually at the limbus.
† Macroerosion: large epithelial erosions usually in upper half of cornea.
‡ Plaque (vernal plaque): laminated structure of protein and polysaccharide adherent to the anterior stroma with destruction of Bowman's layer.
§ Pseudogerontoxon: arcus-like appearance in relation to limbal pannus; may disappear in remissions.



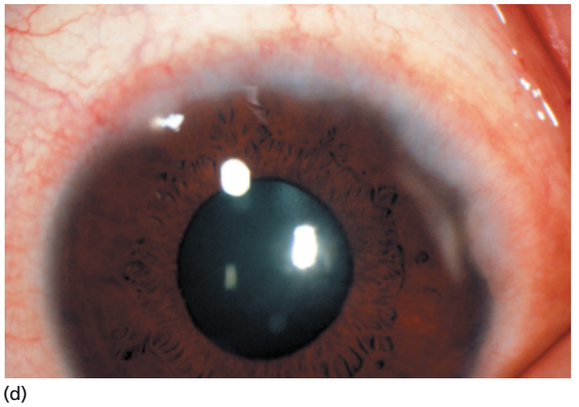
(a)



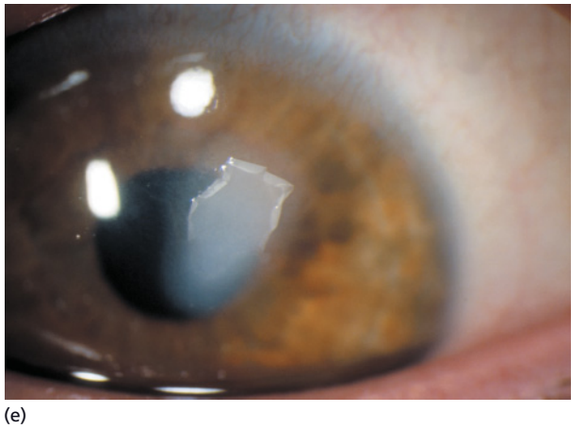
(b)



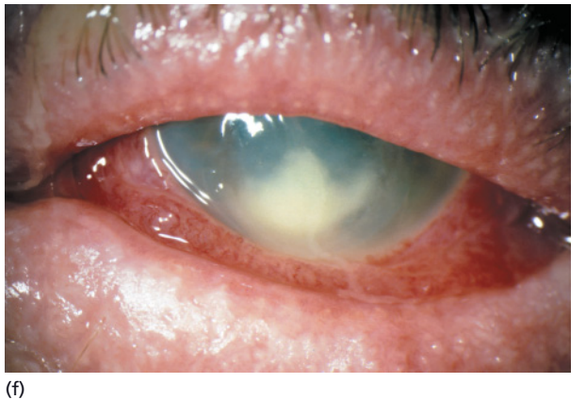
(c)



(d)



(e)



(f)



(g)

Fig. 67.7 Atopic eye disease. (a) Normal upper tarsal conjunctiva; the tarsal vessels are clearly visible through the healthy conjunctival epithelium and substantia propria. (b) Atopic keratoconjunctivitis with an infiltrated, papillary, upper tarsal conjunctiva. Compare with the normal tarsal conjunctiva in (a). (c) Showing 'giant' or compound upper tarsal papillae and the mucous exudate that develops during an exacerbation. (d) Vernal keratoconjunctivitis (VKC) (limbal form) showing the typical pale limbal papillae. (e) Fully developed vernal plaque. (f) Bacterial keratitis complicating atopic keratoconjunctivitis (AKC) showing a corneal infiltrate. The eyes of this patient are shown in (g), with atopic eczema localized to the eyelids; the eczema is often generalized. The right eye shows the infection in (f).

gist because of their association with atopic dermatitis and will be described here. Of these, AKC and VKC are sight-threatening disorders that are often difficult to treat, although VKC occurs in children and 90% of cases resolve in adult life. The severity of symptoms is closely related to disease activity, and patients with minimal symptoms will respond to simple treatment with antihistamines and/or mast cell stabilizers, which have an excellent safety profile. However, acute exacerbations of AKC and VKC must be recognized and treated promptly as these may develop within hours and can lead to blinding corneal complications within 1–2 days.

Symptoms are similar for all of these atopic eye diseases. Typically there is itching, watering and the production of a sticky white and stringy mucous discharge. During exacerbations the symptoms increase in severity very rapidly—the itching may be superseded by extreme discomfort with soreness and a foreign body sensation, and the vision deteriorates. The lids may be difficult to open in the morning because of a combination of discomfort and discharge.

Signs that can be seen without a slit-lamp examination are thickened lids; in AKC and ABC the lid margins are usually inflamed, crusted and excoriated with madarosis (Fig. 67.7g). Lid margin signs are uncommon in VKC. The bulbar conjunctiva is inflamed during exacerbations but otherwise grossly normal except for the limbal region, which may be thickened and nodular (Fig. 67.7d) with the presence of pinpoint Trantas' dots at the apices of the nodules; these may be present in AKC and in the limbal type of VKC. The distinction between limbal and palpebral VKC is principally of interest to the ophthalmologist; in the UK the limbal form of the disease is generally easier to manage, although this may not be the case in Africa. The lower tarsal conjunctiva is usually less abnormal than that of the upper lid, which can be seen to be thickened and velvety when the lid is everted. In VKC, and in some cases of AKC, 'giant' compound papillae are easily seen (Fig. 67.7c). In adults with long-standing disease, there is sheet-like scarring of the upper tarsal conjunctiva and shortening of the lower conjunctival fornix. During exacerbations the tarsal conjunctiva becomes very inflamed and covered in adherent mucous. The corneal signs, with the exception of plaque (Fig. 67.7e) or ulceration due to superadded infection (Fig. 67.7f), are difficult to see without a slit lamp but fluorescein staining is diffuse during flare-ups of disease.

Diagnosis

The clinical features, together with a personal or family history of atopy, are usually sufficient for diagnosis. Laboratory investigations are only needed in patients who do not respond to therapy or who require topical (or systemic) immunosuppressive therapy for relief of symptoms, or when the diagnosis is uncertain. Serum IgE and skin prick tests have no value in the diagnosis of atopic conjunctivitis as the results do not indicate the antigens precipitating the eye disease. Ophthalmic investigations are the province of the ophthalmologist and are summarized in Table 67.6.

Immunopathogenesis [6–9]

Recent advances in the understanding of these diseases have come from investigations of the humoral mediators of inflammation in the tears, and analysis of the cellular components by immunostaining and *in situ* hybridization. These techniques have shown that seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC) are primarily typical type 1 hypersensitivity diseases, whereas the others show varying degrees of a coexisting type 4 hypersensitivity response. SAC and PAC show mast cells and eosinophils in the conjunctival mucosa and submucosa, with high levels of locally produced IgE to specific allergens being present in the tears. The diseases can be mimicked by topical instillation of antigen; this reaction is blocked by drugs that are active against mast cells. AKC and VKC show both the cellular components present in SAC and VKC but also connective tissue hyperplasia, $CD4^+$ T lymphocytes and plasma cells, together with different subsets of mast cells. The T cells are probably important inducers of the cellular inflammatory response in these diseases. Differences in AKC and VKC phenotypes may be explained by differences in the predominance of T-helper subsets; the Th1 subset, predominant in delayed type hypersensitivity responses and inactivated by ciclosporin, is more predominant in AKC than in VKC, in which the Th2 subset, with a B-cell-helper role, may be more important. Mast cells and eosinophils are found in larger numbers in VKC than in AKC and functional heterogeneity in their populations may also be determinants of disease phenotype.

These effector cell types are known to cause atopic eye diseases by the following mechanisms. Mast cells release preformed mediators by exocytosis when they degranulate in response to binding of IgE with allergen. The important mediators released are histamine, resulting in hyperaemia, oedema and mucus production, and prostaglandins. Histamine has been detected in the tears in these diseases. Eosinophils release cationic proteins including major basic protein, which is epitheliotoxic and has been identified in the tears in VKC. It is probably a major factor responsible for the development of corneal epithelial erosions and macroerosion. The presence of the latter, with the mucus and debris present in an acute exacerbation of keratopathy, accounts for the formation of plaque. B cells produce IgE locally in atopic conjunctivitis; locally produced IgE is an important factor in the pathogenesis of SAC, PAC and some cases of VKC, but less so in AKC and ABC.

Management [10–15]

The management of VKC and AKC requires specialized ophthalmological care, as these diseases are uncommon, and some of the management strategies are outside the remit of the general ophthalmologist. Topical cromones (sodium cromoglycate 2–4%, or the more recently introduced nedocromil or lodoxamide) are the first-line treatment, given one to four times daily depending on symptoms. Topical olapatadine and Ketotifen combine the effects of a cromone with that of an antihistamine and are probably currently used more widely than cromones as first line drugs. Addition of a potent topical antihistamine (levocabastine or emedastine) or a systemic antihistamine may help relieve itch. These treatments are very safe and do not require ophthalmological supervision but are only effective for very mild disease. Cromones are often not tolerated until the inflammation is brought under control with high-dose topical corticosteroids, such as dexamethasone 0.1% or prednisolone acetate 1%. These will precipitate glaucoma

in 10% of patients as well as contributing to cataract; as soon as the disease is brought under control, a 'safe' corticosteroid with a lower risk of precipitating glaucoma (about 1% risk) should be substituted (fluoromethalone, rimexolone or clobetasone). Cromones are used topically, whenever possible, as corticosteroid-sparing drugs.

Topical ciclosporin is not yet available as a licensed preparation for any ocular indication in Europe, although a preparation designed for use in dry eye is available in the USA (Restasis®, Allergan, USA). However, a veterinary preparation is available (Optimmune®, Schering) in addition to preparations made up in hospital pharmacies (through the NHS Medicines Manufacturing Service). Topical ciclosporin has shown promise in two randomized trials for AKC, and in both randomized trials and in case series for VKC, and is used by the authors for these indications. Adverse effects, apart from stinging, are infrequent and introduction of the drug as a corticosteroid sparing agent, for patients requiring high doses of topical corticosteroids, has allowed reduction or complete withdrawal of corticosteroids in many cases. Topical ciclosporin is most successfully tolerated if introduced during remissions.

Systemic immunosuppression is needed in severe exacerbations of disease; a 3–4 week course of systemic corticosteroids, starting at a prednisolone dose of 60 mg daily, may be necessary to bring the disease under control while topical therapy is introduced. Systemic steroids also carry a risk of glaucoma. Patients with a previous history of labial or ocular herpes simplex (HSV), or with serological evidence of previous exposure to HSV, should be aware that they may develop herpetic keratitis while on systemic or topical corticosteroids. Patients who have had previous episodes of ocular HSV should receive prophylaxis with oral aciclovir 400 mg twice daily (or valaciclovir 500 mg once daily); topical prophylaxis is unnecessary and may complicate the clinical signs in patients with a complex keratoconjunctivitis. Patients with AKC are predisposed to bilateral herpes keratitis and prophylactic antivirals are advisable when they are using corticosteroids.

For a small number of patients, systemic ciclosporin (usually starting at 5 mg/kg) can be very helpful. Patients who need systemic ciclosporin for management of their atopic eczema will usually obtain substantial collateral ocular benefits.

Severe staphylococcal blepharitis often accompanies AKC and ABC and can be treated with a course of azithromycin followed by local therapy with an antibiotic ointment to which the skin flora is sensitive, usually chloramphenicol, together with a topical ophthalmic corticosteroid ointment such as hydrocortisone 0.5% or 1.0%. Combined preparations often contain aminoglycosides, which frequently cause toxicity or allergy and should be avoided.

The management of the corneal complications that often accompany these conditions (vernal plaque, bacterial keratitis and herpes keratitis) is beyond the scope of this summary but presents challenging management problems in the context of these conditions.

Practice points for dermatologists are that the dermatologist should be aware that any sudden deterioration in vision may herald one of the blinding complications of these diseases and should be treated as an emergency. Good control of the underlying condition aims to reduce the frequency with which the blinding corneal complications develop, whilst minimizing the potentially serious side effects of corticosteroid treatment.

The interaction of drugs used for the management of atopic eye disease and atopic dermatitis

Most cases of atopic eye disease are managed with topical ocular therapy which has no effect on the dermatological aspects of the disorder. However, treatment with courses of systemic corticosteroid and/or ciclosporin, when needed either for the dermatological or ophthalmological aspects of atopy, are beneficial to the management of both. The risk of glaucoma from systemic corticosteroids, while occurring, is very low whereas topical application of corticosteroid around the eyelids probably constitutes a higher risk; patients who chronically use corticosteroid cream around the eyes should have glaucoma screening.

References

1 Friedlander MH. Conjunctivitis of allergic origin: clinical presentation and differential diagnosis. *Surv Ophthalmol* 1993; **38**: 105–14.
2 Tuft SJ, Kemeney DM, Dart JKG, Buckley RJ. Clinical features of atopic keratoconjunctivitis. *Ophthalmology* 1991; **98**: 150–8.
3 Power WJ, Tughal-Tutkun I, Foster CS. Long-term follow up of patients with atopic keratoconjunctivitis. *Ophthalmology* 1998; **105**: 637–42.
4 Tuft SJ, Dart JKG. Limbal vernal keratoconjunctivitis. Clinical characteristics and IgE expression compared with palpebral vernal. *Eye* 1989; **3**: 420–7.
5 Dart JKG, Buckley RJ, Monnickendam M, Prasad J. Perennial allergic conjunctivitis. Definition, clinical characteristics and prevalence. *Trans Ophthalmol Soc UK* 1986; **105**: 513–20.
6 Abelson M, Schaefer K. Conjunctivitis of allergic origin: immunologic mechanisms and current approaches to therapy. *Surv Ophthalmol* 1993; **38**: 115–32.
7 Tuft SJ, Ramakrishnan M, Seal DV, Kemeny DM, Buckley RJ. Role of *Staphylococcus aureus* in chronic allergic conjunctivitis. *Ophthalmology* 1992; **99**: 180–4.
8 Montan PG, van Hage-Hamsten M. Eosinophil cationic protein in tears in allergic conjunctivitis. *Br J Ophthalmol* 1996; **80**: 556–60.
9 Whitcup SM, Chan CC, Luyo DA *et al*. Topical cyclosporine inhibits mast cell mediated conjunctivitis. *Invest Ophthalmol Vis Sci* 1996; **37**: 2686–93.
10 Hoang-Xuan T, Prisant O, Hannouche D, Robin H. Systemic cyclosporine A in severe atopic keratoconjunctivitis. *Ophthalmology* 1997; **104**: 1300–5.
11 Bleik JH, Tabbara KF. Topical cyclosporine in vernal keratoconjunctivitis. *Ophthalmology* 1991; **98**: 1679–84.
12 Akpek EK, Dart JK, Watson S *et al*. A randomized trial of topical cyclosporin 0.05% in topical steroid-resistant atopic keratoconjunctivitis. *Ophthalmology* 2004; **111**: 476–82.
13 Kilic A, Gurler B. Topical 2% cyclosporine A in preservative-free artificial tears for the treatment of vernal keratoconjunctivitis. *Can J Ophthalmol* 2006; **41**: 693–8.
14 Pucci N, Novembre E, Cianferoni A *et al*. Efficacy and safety of cyclosporine eyedrops in vernal keratoconjunctivitis. *Ann Allergy Asthma Immunol* 2002; **89**: 298–303.
15 Hingorani M, Calder VL, Buckley RJ, Lightman S. The immunomodulatory effect of topical cyclosporin A in atopic keratoconjunctivitis. *Invest Ophthalmol Vis Sci* 1999; **40**: 392–9.

Cicatrizing conjunctivitis and the immunobullous disorders

Description and epidemiology [1–4]

Cicatrizing conjunctivitis, although uncommon, is one of the most difficult management problems in ophthalmology because of the widespread effects on the ocular surface, leading to corneal blind-

Table 67.7 Immunobullous diseases (those associated with conjunctivitis are shown in italics).

Intraepithelial	Subepithelial
• Pemphigus *vulgaris* vegetans • Pemphigus foliaceous • Pemphigus erythematosis • Brazilian pemphigus • *Paraneoplastic pemphigus* • *Lichen planus* *Graft-versus-host disease* *Erythema multiforme* • Minor • *Major (Stevens–Johnson syndrome)* *Toxic epidermal necrolysis (Lyell syndrome)*	• Pemphigoid *Bullous* *Mucous membrane* (Fig. 67.8a–f) • Pemphigoid gestationis • *Epidermolysis bullosa aquisita* • Bullous systemic lupus erythematosis • *Linear IgA disease* • *Dermatitis herpetiformis*

ness in many victims. The classification of the conjunctival disorders follows the dermatological classification although not all of the dermatological disorders are associated with conjunctivitis (Table 67.7).

The severity of the conjunctival involvement varies but is mild, without scarring, in pemphigus vulgaris, and with variable degrees of scarring and severity in the remainder.

Mucous membrane pemphigoid (MMP) [5–11]

Synonym
- Cicatricial pemphigoid (CP)

MMP is the commonest of these uncommon disorders. It has also been termed cicatricial pemphigoid (CP) and benign MMP (but its effects on the eye are sight-threatening, so 'benign' has been dropped). It is a systemic disease that may be localized to one site or may affect multiple sites. The proportion of patients with ocular involvement alone has varied in recent series from 18 to 50%; these differences are likely to reflect differences in the referral base for each series. About 60% of patients presenting to a dermatology clinic will have conjunctival involvement, in addition to skin disease.

Epidemiology of MMP

Unambiguous data on the epidemiology of the disease is difficult to obtain because studies have been based on the site of involvement. However, the incidence of dermatological disease is about 1/million/year. This is likely to be an underestimate of the disease as a whole because mucosal presentations are more common. In ophthalmology centres, MMP affects between 1:8000 and 1:46 000 patients. The male:female ratio is 1:3 and the age range is 30–90 years with peak onset in the seventh decade, although patients may rarely present in childhood and in extreme old age. At presentation, between 25 and 38% of patients with ocular disease have significant visual loss and about 30% become legally blind. Treatment has been shown to slow disease progression. A genetic predisposition has been found in an association with the *DQw7* gene and expression of the HLA-DR4 antigen.

Clinical features [12]

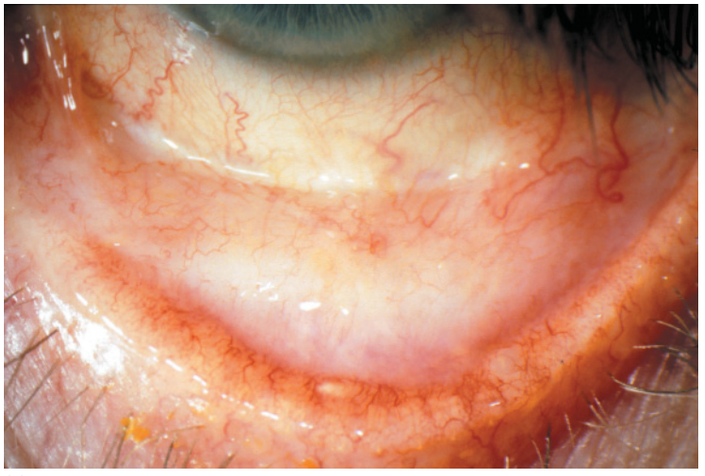
Most patients with ocular MMP (ocMMP) have progressive disease. However, early-presenting disease is usually milder and progresses more slowly than late-presenting disease. Current aggressive treatment regimens, with systemic immunosuppression, have been shown to reduce the rate of progression by about 50%. Because patients can occasionally progress to blindness within months from the onset, both early diagnosis and effective treatment are critical in improving the prognosis.

In most patients the onset is insidious, with non-specific conjunctival symptoms including irritation, hyperaemia and discharge. Dry eye and mucous deficiency are late signs. Acute disease occurs in about 20% of new patients with severe inflammation and conjunctival ulceration; this presentation may follow lid surgery for entropion on undiagnosed cases.

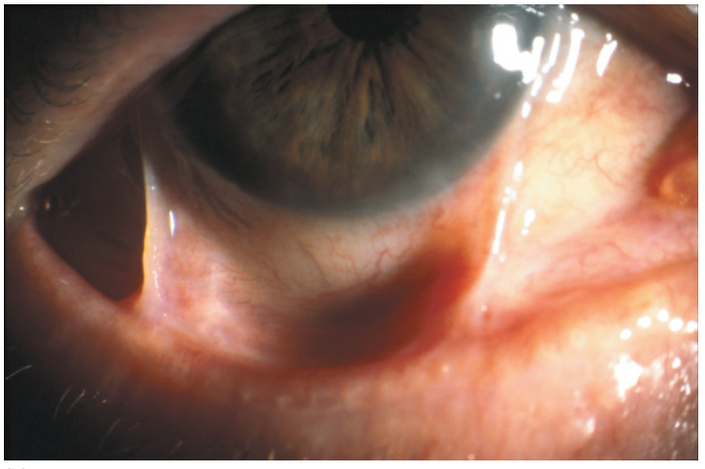
Signs, in order of progression, often start at the medial canthus with loss of the plica and later of the caruncle (Fig. 67.8f), subepithelial reticular fibrosis of tarsal conjunctiva (Fig. 67.8a), conjunctival infiltrate due to increased cellularity and collagen formation (Fig. 67.8c,d), hyperaemia, shortening of the fornices (Fig. 67.8a), symblepharon (Fig. 67.8b), blepharitis, trichiasis and entropion, punctate keratopathy, limbitis, conjunctival and corneal keratinization, and corneal surface failure (Fig. 67.8e). Late disease results in fusion of the lids and globe (Fig. 67.8f), and may obscure the cornea completely. Persistent epithelial defect, microbial keratitis and corneal perforation are common and, with the corneal surface failure, account for the management challenges posed by the disease. Mucous membrane pemphigoid is associated with the autoimmune diseases rheumatoid arthritis, systemic lupus erythematosus and polyarteritis nodosa.

Diagnostic problems in predominantly ocular MMP [9,10,13–18]

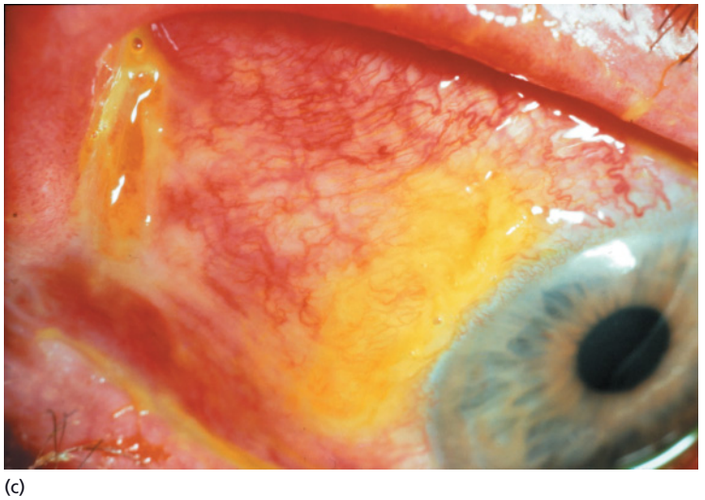
The diagnosis of predominantly ocular MMP (ocMMP) has been complicated by the definition of MMP used by the first International Consensus Statement on mucous membrane pemphigoid in which the disease is defined as 'a group of putative autoimmune, chronic inflammatory, subepithelial blistering diseases predominantly affecting mucous membranes that is characterized by linear deposition of IgG, IgA or C3 along the epithelial basement membrane zone (BMZ)'. Whilst it has done much to harmonize the various definitions of MMP in terms of the clinical and diagnostic characteristics, and also to encourage both careful clinical phenotyping and the application of diagnostic immunopathology tests, the necessity of positive direct immunofluorescence (DIF) raises important issues for ocMMP. It is well recognized that DIF is invariably positive from at least one site when MMP affects the oropharynx and skin as well as the eyes; compliance with a definition that requires positive DIF is therefore usually straightforward in such cases with multiple sites affected. However, from the perspective of clinicians caring for patients with MMP affecting the eyes alone, the Consensus Statement has resulted in a substantial proportion of patients (from 14 to 40% having negative DIF) failing to meet these immunopathological criteria for diagnosis. As a



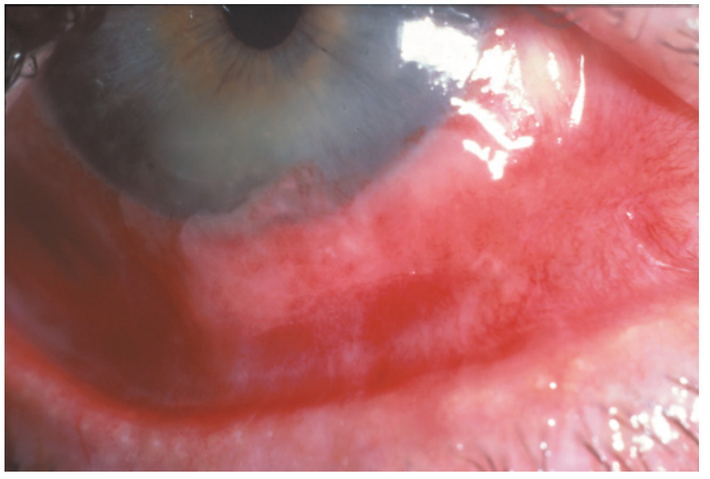
(a)



(b)



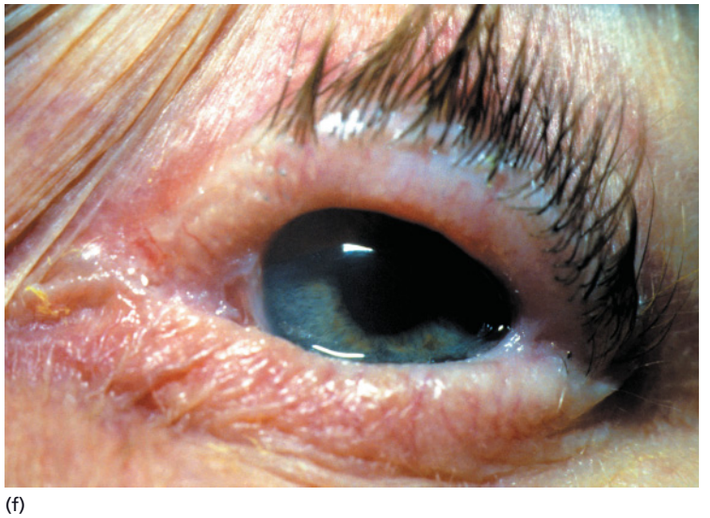
(c)



(d)



(e)



(f)

Fig. 67.8 Ocular signs of mucous membrane pemphigoid (MMP). (a) Inferior fornix shortening and subconjunctival scarring. (b) Conjunctival symblepharon tethering the globe to the lower lid. (c) Acute exacerbation of conjunctival MMP showing conjunctival ulceration. This occurs in only 10% of patients presenting with MMP affecting the eye. (d) Severe conjunctival inflammation and limbitis. This leads rapidly to the ocular surface failure and corneal blindness shown in (e) unless it is promptly controlled with adequate immunosuppressive therapy. (e) Ocular surface failure and keratinization (the white area) in advanced pemphigoid. This eye is blind. (f) Advanced ocular pemphigoid showing loss of the medial canthal structures (plica and caruncle) with a reduced interpalpebral aperture secondary to shortening of the fornices (as in (a)) and fusion of the tarsal and bulbar conjunctivae.

result, despite having a typical MMP phenotype and response to treatment, they fall outside the Consensus Statement diagnostic criteria. Subsequent to the publication of the Consensus Statement, peer reviewers of studies on ocMMP have suggested that this group of patients be omitted from studies on MMP; extending this to clinical settings, the resulting uncertainty about the diagnosis has meant that immunosuppressive therapy has been delayed or deferred in some patients.

Sensitivity and specificity of direct immunofluorescence for MMP

However, DIF is not a specific test for MMP and a positive result does not exclude other immunobullous disorders as is made clear in the Consensus Statement.

In effect, a positive DIF test is used as a surrogate to provide evidence for an autoimmune pathogenesis. For DIF to be integral to a diagnosis of ocMMP, the test should ideally be both highly sensitive and specific. Not only is DIF of low sensitivity in ocMMP, it is also of low specificity. Conjunctival biopsies may have a positive DIF test in a range of disorders, including bullous pemphigoid, skin-dominated linear IgA bullous dermatosis, skin-dominated epidermolysis bullosa acquisita, drug-induced pemphigoid, Stevens–Johnson syndrome, rosacea and ulcerative colitis; most of these are immunobullous disorders with an autoimmune basis, but not all. Furthermore, some must be differentiated from each other by the clinical phenotype or may require more sophisticated tests to reliably distinguish them from each other (indirect immunofluorescence studies on salt-split skin, immunoblotting, immunoelectron microscopy, etc.; see Chapter 40). In addition, DIF may not be consistently positive and may change with time. With regard to the low sensitivity of DIF, studies have shown that there is a well-recognized DIF-negative subgroup comprising up to 14–40% of patients with ocMMP, these subjects having scarring conjunctival inflammation that is phenotypically indistinguishable from MMP, and which responds identically to immunosuppressive therapy.

Indirect immunofluorescence in MMP

Indirect immunofluorescence (IIF) was not included amongst the criteria for MMP in the Consensus Statement because this investigation is often negative in MMP. However, positive IIF also provides evidence for an underlying autoimmune pathology and may be positive in ocMMP when DIF is negative.

Recommended criteria for the diagnosis of predominantly ocular MMP

More workable, and clinically useful, criteria for ocMMP used in our clinical service are as follows:

Predominantly ocular MMP (ocMMP). This is a term that we use for those cases without any evidence of MMP affecting other systems. The term 'predominantly' is used to recognize the fact that, even with the most careful phenotyping, it is not possible to exclude asymptomatic involvement of, for example, the oesophagus.

Criteria for the diagnosis of ocMMP. Patients with positive conjunctival DIF or positive DIF from another uninvolved site meet currently agreed criteria for the diagnosis of MMP and can be reported as such. Patients with negative DIF from any site and positive IIF can be diagnosed as having MMP. Patients with negative immunopathology can be diagnosed as ocMMP providing that they have a typical phenotype of progressive conjunctival scarring and providing that other diseases that may cause this same phenotype have been excluded (Sjögren's syndrome, ocular rosacea, Stevens–Johnson syndrome, atopic keratoconjunctvitis, ectodermal dysplasia, sarcoidosis, scleroderma and drug-induced pseudopemphigoid). When ocular cases are reported in studies we believe that the detailed immunopathology findings should be recorded for each case so that the diagnosis can be interpreted in the light of future modifications to diagnostic criteria.

In ocMMP patients (without extraocular disease) the laboratory investigations are outside the scope of many ophthalmology services and ideally such patients should be referred to specialist corneal and external eye disease departments. However, many patients are elderly, for whom distant referral is unwelcome. For such cases a diagnosis, based on a history of progressive conjunctival scarring, the presence of the typical clinical signs and exclusion of other ocular causes, is adequate for clinical purposes.

Taking conjunctival biopsies for DIF

Conjunctival biopsies for DIF should be taken from the bulbar conjunctiva and the presence of IgA, IgG, and the C3 component of complement confirm the diagnosis of MMP when positive. Fornix biopsies should be avoided as biopsying this site may cause exacerbations of disease. The biopsy can be taken using topical anaesthesia with tetracaine, the conjunctiva can be tented up and a piece about 2 mm in diameter cut off with spring scissors. This can be done in the outpatient department using magnification from the slit lamp microscope. Routine histopathology of conjunctival biopsies is of little value in the diagnosis because the conjunctiva is fragile and detection of basement membrane zone cleavage is unreliable. However, it should be done to exclude surface neoplasia, particularly in unilateral disease, as this can present with scarring and inflammation. Squamous metaplasia of the conjunctival epithelium and a reduction in goblet cells are non-specific findings, as is an increased inflammatory cell infiltrate. In acute disease there is a neutrophil-rich infiltrate.

Differential diagnosis

The conjunctival signs in MMP may be identical to those produced by the other immunobullous disorders that are summarized in Table 67.7. However, in these conditions the skin disease precedes the ocular disease so that there is rarely any confusion. In erythema multiforme major, exacerbations of conjunctival inflammation can occur many years after the acute disease, leading to a condition indistinguishable from MMP both in terms of the clinical signs and immunopathology. The principal problems in differential diagnosis relate to diseases other than the immunobullous disorders that may also cause cicatrizing conjunctivitis (Table 67.8). Patients with conjunctival cicatrization secondary to infective causes are sometimes referred for investigation of what has been longstanding conjunctival scarring, following a long-forgotten episode of infection, in whom the absence of a recent history of inflammation, or of progressive symptoms, usually

Table 67.8 Causes of non-autoimmune cicatrizing conjunctivitis.

Infective conjunctivitis
Trachoma
Corynebacterium diphtheriae conjunctivitis
Streptococcal conjunctivitis
Adenoviral keratoconjunctivitis
Systemic diseases
Sarcoidosis
Progressive systemic sclerosis
Sjögren's syndrome
Atopic keratoconjunctivitis
Trauma
Iatrogenic conjunctivitis (pseudopemphigoid)
Chemical, thermal or mechanical trauma
Factitious (self-induced) conjunctival trauma
Others
Ocular rosacea
Staphylococcal blepharoconjunctivitis

indicates static disease. Patients with sarcoidosis or systemic sclerosis normally have a well-established diagnosis by the time conjunctival scarring develops. Sjögren's syndrome may mimic early MMP but can usually be differentiated by the presence of Sjögren's specific antibodies and/or a positive labial biopsy. Atopic keratoconjunctivitis can occasionally be difficult to differentiate from slowly progressive MMP but the history and clinical signs of severe eczema, and a tarsal conjunctival biopsy (performed after withdrawal of topical corticosteroids for 2 weeks) that shows excessive numbers of mast cells and eosinophils can confirm the diagnosis. Iatrogenic conjunctivitis is non-progressive, except in the case of drug-induced MMP, which is indistinguishable from classical MMP. Awareness that conjunctival scarring can occur in ocular rosacea and in staphylococcal blepharoconjunctivitis (Fig. 67.5a) is usually enough to distinguish these conditions from MMP. Factitious conjunctival trauma is rare and usually more focal than classical MMP but can mimic MMP while the self-trauma is active.

Pathogenesis [19,20]

MMP is an autoimmune disease directed at components of the conjunctival basement membrane; progression occurs as a result of inflammatory disease and cicatrization, secondary ocular surface disease, infection and treatment toxicity. Drug-induced pemphigoid (pseudopemphigoid), and Stevens–Johnson syndrome, lead to an identical situation, suggesting that conjunctival damage may precipitate MMP, which may be the final common pathway following one type of conjunctival insult.

Inflammatory mechanisms in MMP are reasonably well understood and provide a rationale for immunosuppressive therapy. In chronic disease, macrophages and T cells are present, of which the Th1 subset is active, as demonstrated by the presence of the cytokines IL2 and interferon-γ, as opposed to the Th2 subset that is involved in B-cell activation. This, coupled with the low numbers of B cells but increased number of plasma cells, suggests that B-cell activation must be occurring in the extraocular tissues with homing of mature plasma cells to the conjunctiva. MHC Class II expression is increased, suggesting the potential for local antigen presentation to T helper cells. There is a slight increase in activated T cells, which are involved in the recruitment of fibroblasts and macrophages. In acute disease, neutrophils and antigen-presenting (dendritic) cells are also present, together with an increase in CD4 (helper) T cells, which probably reflects their role in recruiting other inflammatory cells.

Growth factors including FGF (fibroblast growth factor), PDGF (platelet-derived growth factor) and TGF-β (transforming growth factor-beta) are all present in MMP. PGDF upregulates the extracellular matrix component (ECM) thrombospondin, which is itself important in activating latent TGF-β. PDGF is a powerful chemoattractant for macrophages and fibroblasts and is probably pivotal to the scarring response. However, only TGF-β is capable of stimulating fibroblasts to produce collagen and ECM components. It also blocks matrix degradation by decreasing protease synthesis and increasing protease inhibition. In acute disease, TGF-β is significantly increased and is produced by macrophages and fibroblasts in ocMMP conjunctiva. Once macrophages and fibroblasts are present in large numbers and activated they may become self regulating; T-cell-deficient models have shown that T cells are not necessary for wound healing to occur, and fibroblasts from ocMMP conjunctiva display abnormal activity in cell culture after several passages.

Implications of immunopathological findings for therapy

Inflammation is important in acute disease; severe inflammation is associated clinically with rapid scarring and therefore demands effective immunosuppression to reduce scarring. Inflammation may also play a role in chronic disease although scarring often continues even in the presence of minimal inflammation, suggesting that growth factor production by macrophages and fibroblasts is relatively independent of the other inflammatory cells. Therefore, modulation of growth factor activity, collagen metabolism or fibroblast activity may be necessary to halt the disease process. Of these, growth factor activity can potentially be specifically blocked or inhibited, thus holding promise for new treatments.

Other subepithelial immunobullous disorders and conjunctivitis [21]

Other immunobullous disorders are much less frequently associated with conjunctival cicatrization. As a result, little is known about the pathogenesis of the conjunctival disease as opposed to the events in the skin. Bullous pemphigoid generally results in mild conjunctivitis although severe cicatrization has been reported. Epidermolysis bullosa aquisita, linear IgA disease, dermatitis herpetiformis and lichen planus may all be associated with progressive conjunctival scarring indistinguishable from that of MMP.

Erythema multiforme major and toxic epidermal necrolysis [22–26]

The ocular complications of these two conditions are identical (Table 67.9); about 70–80% of patients admitted for treatment of these diseases will develop eye disease. It is the eye disease which leads to the most profound, long-term morbidity in many such patients. In addition, the eye disease, unlike the lesions affecting the remaining mucosal surfaces, may progress years after the

Table 67.9 Ocular effects of Stevens–Johnson syndrome and toxic epidermal necrolysis.

Ocular effects	Resulting symptoms and signs
Loss of goblet cells	Disrupted tear film leading to poor vision and punctate keratopathy (Fig. 67.9b)
Loss of accessory lacrimal glands	
Scarring of meibomian gland orifices	
Metaplasia of meibomian gland epithelium with development of metaplastic lashes	Trichiasis secondary to metaplastic lashes (Fig. 67.9b)
Conjunctival scarring and obliteration of lacrimal gland ductules	Very dry eye with secondary conjunctival and corneal squamous metaplasia (Fig. 67.9b)
Keratinization due to squamous metaplasia	Exacerbates drying and discomfort
Conjunctival scarring with fornix shortening and symblepharon formation leading to lid shortening	May cause lagophthalmos and corneal exposure
Retroplacement of meibomian gland orifices	Disrupts tear film
Entropion of upper and lower lids with trichiasis of both metaplastic and normal lashes	Corneal punctate keratopathy and ulceration
Corneal epithelial failure secondary to limbal inflammation	Blindness

acute episode has resolved. Acute ocular complications usually occur concurrently with the skin disease but may sometimes precede it by several days. The conjunctivitis varies from a papillary reaction with watery discharge (Fig. 67.9a) to a membranous conjunctivitis with sloughing of the conjunctival epithelium. Corneal epithelial defects are common and may progress to corneal ulceration with or without bacterial superinfection. The morbidity of the disease may be due to the acute corneal complications but is more usually due to conjunctival scarring.

Chronic ocular complications are numerous. The severe conjunctival inflammation leads to loss of goblet cells and the accessory conjunctival lacrimal glands as well as disruption of the meibomian gland orifices leading to MGD. This results in a disrupted tear film and a secondary punctate keratopathy. In mildly affected patients this causes chronic mild discomfort, photophobia and slightly reduced vision. In more severely affected patients, the conjunctival inflammation leads to cicatrization of the lacrimal ductules, resulting in a severely dry eye accompanied by squamous metaplasia and keratinization of both the conjunctival and corneal components of the ocular surface, thereby causing more severe discomfort and loss of vision (Fig. 67.9b). In addition, the meibomian gland ductal epithelium undergoes metaplasia, resulting in the development of fine metaplastic lashes which are not a feature of MMP. The conjunctival shortening leads both to entropion, resulting in ocular surface abrasion by normal as well as by metaplastic lashes, and may also cause lid shortening, leading to reduced eye closure (lagophthalmos), which is easily overlooked. Lash abrasion and trichiasis lead to the development of corneal epithelial defects which, as a result of the poor tear film, may persist. Persistent epithelial defect predisposes to corneal stromal melts and perforation, which are often precipitated by infection. This evolution of changes is not the direct consequence of the acute disease but is secondary to the effects on the tear film and lids.



(a)



(b)

Fig. 67.9 Ocular disease in Stevens–Johnson syndrome. (a) Acute conjunctivitis in a patient with mild Stevens–Johnson syndrome. The conjunctiva is hyperaemic with a papillary reaction and mucopurulent discharge. (b) The late ocular complications of Stevens–Johnson syndrome showing entropion, a dry eye with ocular surface failure (in this case an opaque keratinized epithelium).

The severe inflammation may also lead to blinding opacity of the corneal epithelium, not only as a result of squamous metaplasia, but also by loss of corneal epithelial progenitor cells (stem cells). Because of prolonged survival of transient amplifying cells, the progeny of stem cells, stem cell failure may not be manifest for 12 to 18 months after the onset of the disease.

An additional problem for patients with ocular complications of Stevens–Johnson syndrome is the development of severe conjunctival inflammation with progressive scarring that may be indistinguishable from MMP and may also be DIF-positive. This can occur as a continuation of the acute episode or may occur many years after the onset of disease. Other inflammatory complications are recurrent conjunctival inflammation following Stevens–Johnson syndrome and necrotizing sclerokeratitis. All of these severe inflammatory problems can precipitate stem cell failure and demand rapid control, usually requiring systemic immunosuppressive therapy. The cause of these late inflammatory complications is not understood.

Graft-versus-host disease [27–35]

Ocular complications are common in patients with graft-versus-host disease (GVHD) and result from involvement of both the conjunctiva and the lacrimal gland. In acute GVHD, conjunctivitis ranges from hyperaemia through chemosis to a pseudomembranous conjunctivitis, with or without corneal epithelial sloughing. Severe conjunctival involvement is a marker for the severity of acute GVHD and was found to occur in 12% of patients in one study; this subset had 90% mortality [26]. In chronic GVHD the same study found conjunctival involvement in 11% of patients for whom it was also associated with disease severity. Some of these patients develop a severe scarring response like that of MMP. Lacrimal gland involvement occurs in about 50% of patients with chronic GVHD who develop a Sjögren's syndrome-type picture of dry eyes. The pathogenesis of the conjunctival disease has been examined in a few cases and appears to be similar to that in the skin.

Although dry eye and cicatrizing conjunctivitis are the commonest ocular findings in GVHD, choroiditis, retinitis and scleritis may also occur.

Treatment of cicatrizing conjunctivitis and the ocular complications of the immunobullous disorders [11,36–47]

The same strategies can be used to treat the ocular aspects of all these disorders. The aim of treatment is the successful management of each of the three principal components that underlie the pathogenesis of these diseases: (i) the ocular surface disease, (ii) the treatment toxicity, and (iii) inflammation. These components of disease are present to variable degrees in different diseases. For example, in Stevens–Johnson syndrome, most patients have relatively little inflammation once the surface disease has been treated and any treatment toxicity eliminated, so that it is the minority of these patients, with recurrent inflammation or progressive cicatrization, who require suppression of inflammation with systemic therapy. On the other hand most, but not all, MMP patients require management of all three components of disease, with 80% of patients requiring systemic immunosuppressive therapy to control the inflammation that persists once the surface disease and toxicity has been controlled.

Successful management demands identification and treatment of all of the components of the disorder, including surface disease, treatment toxicity and inflammation related to activity of the underlying disease, as well as the early detection and treatment of secondary corneal infection.

Management of the ocular surface disease

The ocular surface disease is secondary to previous or current lid and conjunctival scarring and inflammation. The surface disease causes much of the damage to the cornea and is responsible for additional inflammation. Trichiasis and entropion, blepharitis, dry eye and filamentary keratitis, keratinization, persistent epithelial defect, microbial keratitis and corneal perforation may all result from a combination of a poor tear film, poor lid closure, and corneal damage secondary to trichiasis. These are treated as follows:

Trichiasis: epilate in the short term, use electrolysis or laser for odd lashes, cryotherapy for misdirected lashes and surgery for entropion (inferior retractor plication for lower lid and anterior lamellar reposition for upper lid).

Blepharitis: use oral tetracyclines and institute a lid hygiene regimen.

Dry eye and filaments: use non-preserved lubricants, topical acetylcysteine 5–10% as a mucolytic, and punctal occlusion to conserve tears (once any blepharitis has been controlled).

Keratinization: topical retinoic acid is effective in 30% but is only available in specialized centres.

Persistent corneal epithelial defect: exclude infection, treat ingrowing lashes, use non-preserved lubricants, therapeutic lenses (silicone hydrogel if the eyes are not too dry) and, if these measures are unsuccessful, close the eye with a botulinum toxin protective ptosis or with a temporary tarsorraphy. Other more specialized treatments may be needed.

Corneal perforation: temporize with therapeutic contact lenses and/or corneal glue, followed by keratoplasty only if absolutely necessary.

Eliminating or minimizing treatment toxicity

Treatment toxicity results principally from the preservative benzalkonium chloride, a component of most reusable bottles of eye drop preparations as well as of topical glaucoma medications and aminoglycoside eye drops.

Unnecessary topical treatment should therefore be avoided and unpreserved drops or saline used as far as possible. The effects of topical treatment toxicity are hard to distinguish from those of the ocular surface disease. After withdrawal of toxic topical therapy, the mean recovery period is 2 weeks but may extend to 3 months.

Suppressing inflammation/immunosuppressive therapy

Monitoring and side effects of the main immunosuppressive agents are discussed in Chapter 74 and are not repeated here.

In *mild disease* (*hyperaemia and oedema*), low-dose topical corticosteroid may be helpful, particularly in the alleviation of the symptoms of very dry eye. Topical ciclosporin preparations are being widely used for dry eye in the USA where there is a well-tolerated preparation (Restasis®, Allergan) that has been licensed for use in dry eye. This preparation is not licensed in Europe where less-well-tolerated preparations are available from hospital pharmacies. The role of topical ciclosporin for the severe dry eye associated with cicatrizing eye disease is currently uncertain but may provide benefits for this group of patients without the risks associated with topical steroid use. Comparative studies or randomized controlled trials comparing topical ciclosporin and steroids for dry eye are not available.

For *moderate disease* (*hyperaemia, intense infiltration*), sulphapyridine 500 mg daily for 2 weeks then 1 g daily (sulfasalazine 1–2 g daily is an alternative); 55% of patients respond in 1–2 months, but 15% develop an allergic reaction. If response is poor, dapsone 75 mg daily, increased each month by 25 mg daily to 125 mg,

can be used; there is a 70% response in 1–2 months, reducing to 50% after 1 year. Other agents that may be considered are azathioprine (1–2 mg/kg/day; effective in about 60%), methotrexate (7.5–25.0 mg once weekly) or mycophenolate mofetil (1–2 g daily) (each effective in about 80% depending on the severity of the disease).

For *severe disease* (*hyperaemia, limbitis, conjunctival ulceration*), start prednisolone 1 mg/kg/day, reduce the dose after 2 weeks and tail off after 2–4 months. This is ineffective at low doses in the long term and a steroid-sparing immunosuppressive agent is generally added for long-term disease control. The most effective currently is cyclophosphamide 1 mg/kg/day. The dose is adjusted until the lymphocyte count is between 0.5 and 1.0×10^9/L; other haematological parameters should remain normal. Cyclophosphamide therapy is usually discontinued after 1 year and substituted by sulphonamides or immunosuppressive agents as described above.

Most of this therapy is empirical and a sulphonamide (dapsone or sulphapyridine) is often used together with an alkylating agent (cyclophosphamide) or an antimetabolite (azathioprine, methotrexate or mycophenolate mofetil) to control inflammation. This immunosuppressive strategy is summarized in Fig. 67.10, and can be modified as necessary for all these disorders; generally any systemic therapy will benefit the underlying disease. This approach is summarized in a recent case series [11].

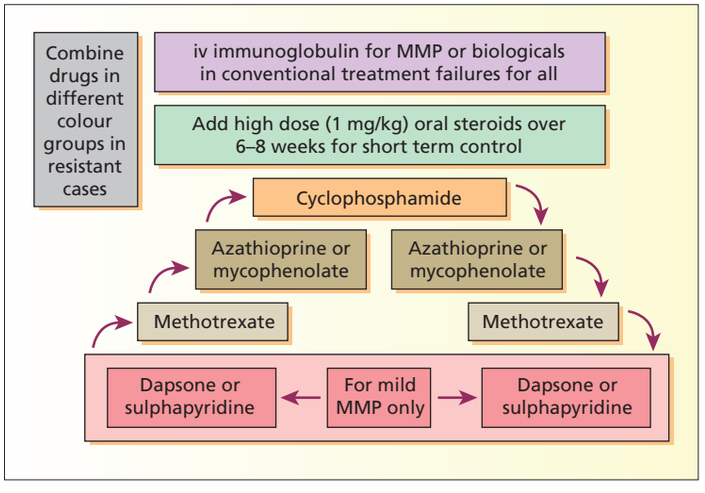


Fig. 67.10 Systemic immunosuppression stepladder for progressive conjunctival cicatrization. Immunosuppression can be carried out using a 'stepladder' approach for the introduction of systemic drugs. Dapsone or sulphapyridine (given as sulphasalazine) are only used in MMP and mild disease may respond well to these. If there is no response after 2–3 months, treatment is 'stepped up' to azathioprine or mycophenolate mofetil (methotrexate is an alternative, which the authors have little experience of using). If these drugs are not effective in another 2–3 months then cyclophosphamide is the drug of choice. For severe and rapidly progressive disease, cyclophosphamide is the drug of choice. Patients are started on this with a 2-month course of systemic steroids, which speeds up the control of inflammation, while the cyclophosphamide takes effect (2–3 months). When the disease has been controlled for several months, treatment can be 'stepped down' to a less toxic drug. Steroids, the sulphones (dapsone and sulphapyridine) and the bone marrow suppressive immunosuppressants (methotrexate, mycophenolate, azathioprine and mycophenolate) can be combined although neutrophil count, in particular, must be monitored. About 10% of patients with severe disease will not be fully controlled with cyclophosphamide. For these patients, intravenous immunoglobulin OR a biological agent (anti-TNF or anti-B cell) may be effective. Ciclosporin has been little used in cicatrizing conjunctivitis because of concern about potential fibrogenic side effects as well as likely renal toxicity in the elderly subset of patients.

References

1 Bernauer W, Elder MJ, Dart JKG, eds. *Cicatrising Conjunctivitis. Developments in Ophthalmology*, Vol. 28. Basel: Karger, 1997.
2 Bernauer W, Elder MJ, Dart JK. Introduction to cicatrising conjunctivitis. *Dev Ophthalmol* 1997; **28**: 1–10.
3 Saw VP, Dart JK. Ocular mucous membrane pemphigoid: diagnosis and management strategies. *Ocul Surf* 2008; **6**: 128–42.
4 Meyers SJ, Varley GA, Meisler DM *et al*. Conjunctival involvement in paraneoplastic pemphigus. *Am J Ophthalmol* 1992; **114**: 621–4.
5 Foster CS. Cicatricial pemphigoid. *Trans Am Ophthalmol Soc* 1986; **84**: 527–663.
6 Fiore PM, Jacobs IH, Goldberg DB. Drug induced ocular pemphigoid. A spectrum of disease. *Arch Ophthalmol* 1987; **105**: 1660–3.
7 Hoang-Xuan T, Robin H, Demers PE *et al*. Pure ocular cicatricial pemphigoid. A distinct immunopathologic subset of cicatricial pemphigoid. *Ophthalmology* 1999; **106**: 355–61.
8 Frith PA, Venning VA, Wojnarowska F *et al*. Conjunctival involvement in cicatricial and bullous pemphigoid: a clinical and immunopathological study. *Br J Ophthalmol* 1989; **73**: 52–6.
9 Chan LS, Ahmed AR, Anhalt GJ *et al*. The first international consensus on mucous membrane pemphigoid. *Arch Dermatol* 2002; **138**: 370–9.
10 Thorne JE, Anhalt GJ, Jabs DA. Mucous membrane pemphigoid and pseudopemphigoid. *Ophthalmology* 2004; **111**: 45–52.
11 Saw VP, Dart JK, Rauz S *et al*. Immunosuppressive therapy for ocular mucous membrane pemphigoid strategies and outcomes. *Ophthalmology* 2008; **115**: 253–61.
12 Elder MJ, Bernauer W, Leonard J, Dart JKG. Progression of disease in ocular cicatricial pemphigoid. *Br J Ophthalmol* 1996; **80**: 292–6.
13 Bernauer W, Elder M, Leonard JN *et al*. The value of biopsies in the evaluation of chronic progressive conjunctivial cicatrisation. *Graefes Arch Clin Exp Ophthalmol* 1994; **232**: 533–7.
14 Tauber J. Ocular cicatricial pemphigoid. *Ophthalmology* 2008; **115**(9): 1639–40. Author reply 1640–1.
15 Patten JT, Cavanagh HD, Allansmith MR. Induced ocular pseudopemphigoid. *Am J Ophthalmol* 1976; **82**: 272–6.
16 Chan LS, Soong HK, Foster CS. Ocular cicatricial pemphigoid occurring as a sequela of Stevens–Johnson syndrome. *JAMA* 1991; **266**: 1543–6.
17 Brown SI, Shahinian L Jr. Diagnosis and treatment of ocular rosacea. *Ophthalmology* 1978; **85**: 779–86.
18 Bernauer W, Itin PH. Immunological investigations in the evaluation of patients with cicatrising conjunctivitis. *Dev Ophthalmol* 1997; **28**: 102–10.
19 Elder MJ, Dart JK, Lightman S. Conjunctival fibrosis in ocular cicatricial pemphigoid—the role of cytokines. *Exp Eye Res* 1997; **65**: 165–76.
20 Bernauer W, Wright P, Dart JKG *et al*. The conjunctiva in acute and chronic mucous membrane pemphigoid: an immunohistochemical analysis. *Ophthalmology* 1993; **100**: 339–46.
21 Leonard JN, Wright P, Williams DDM. The relationship between linear IgA disease and benign mucous membrane pemphigoid. *Br J Dermatol* 1984; **110**: 307–14.
22 Wright P, Collin JRO. The ocular complications of erythema multiforme (Stevens–Johnson syndrome) and their management. *Trans Ophthalmol Soc UK* 1983; **103**: 338–41.
23 Foster CS, Fong LP, Azar D, Kenyon KR. Episodic conjunctival inflammation after Stevens–Johnson syndrome. *Ophthalmology* 1988; **95**: 453–62.
24 Mondino BJ. Cicatricial pemphigoid and erythema multiforme. *Ophthalmology* 1990; **97**: 939–52.
25 Power WJ, Ghorashi M, Merayo-Lloves J *et al*. Analysis of the acute ophthalmic manifestations of the erythema multiforme/Stevens–Johnson syndrome/toxic epidermal necrolysis disease spectrum. *Ophthalmology* 1995; **102**: 1669–76.
26 De Rojas MV, Dart JK, Saw VP. The natural history of Stevens Johnson syndrome: patterns of chronic ocular disease and the role of systemic immunosuppressive therapy. *Br J Ophthalmol* 2007; **91**: 1048–53.
27 Kim SK. Update on ocular graft versus host disease. *Curr Opin Ophthalmol* 2006; **17**: 344–8.

28 Couriel D, Carpenter PA, Cutler C *et al*. Ancillary therapy and supportive care of chronic graft-versus-host disease: National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: V. Ancillary Therapy and Supportive Care Working Group Report. *Biol Blood Marrow Transplant* 2006; **12**: 375–96.
29 Franklin RM, Kenyon KR, Tutschka PJ *et al*. Ocular manifestations of graft-vs-host disease. *Ophthalmology* 1983; **90**: 4–13.
30 Hirst LW, Jabs DA, Tutschka PJ *et al*. The eye in bone marrow transplantation. I. Clinical study. *Arch Ophthalmol* 1983; **101**: 580–4.
31 Jabs DA, Hirst LW, Green WR *et al*. The eye in bone marrow transplantation. II. Histology. *Arch Ophthalmol* 1983; **101**: 585–90.
32 Jack MK, Jack GM, Sale GE *et al*. Ocular manifestations of graft-vs-host disease. *Arch Ophthalmol* 1983; **101**: 1080–4.
33 Jabs DA, Wingard JR, Green WR *et al*. The eye in bone marrow transplantation. III. Conjunctival graft-vs-host disease. *Arch Ophthalmol* 1989; **107**: 1342–8.
34 Bray LC, Carey PJ, Proctor SJ *et al*. Ocular complications of bone marrow transplantation. *Br J Ophthalmol* 1991; **75**: 611–4.
35 Lopez PF, Sternberg P, Dabbs CK *et al*. Bone marrow transplant retinopathy. *Am J Ophthalmol* 1991; **112**: 635–46.
36 Elder MJ, Bernauer W, Dart JK. General considerations in the management of chronic progressive conjunctival cicatrisation. *Dev Ophthalmol* 1997; **28**: 192–5.
37 Elder MJ, Bernauer W, Dart JK. The management of ocular surface disease. *Dev Ophthalmol* 1997; **28**: 219–27.
38 Elder MJ, Lightman SL, Dart JK. The role of cyclophosphamide and high dose steroid in ocular cicatricial pemphigoid. *Br J Ophthalmol* 1995; **79**: 264–6.
39 Elder MJ, Leonard J, Dart JKG. Sulphapyridine—a new agent for the treatment of ocular cicatricial pemphigoid. *Br J Ophthalmol* 1996; **80**: 549–52.
40 Foster CS, Neumann R, Tauber J. Long-term results of systemic chemotherapy for ocular cicatricial pemphigoid. *Doc Ophthalmol* 1992; **82**: 223–9.
41 Shimazaki J, Shimmura S, Fujishima H *et al*. Association of preoperative tear function with surgical outcome in severe Stevens–Johnson syndrome. *Ophthalmology* 2000; **107**: 1518–23.
42 Dart JKG. Corneal toxicity. The epithelium and stroma in iatrogenic and factitious disease. *Eye* 2003; **17**: 886–92.
43 Marsh P, Pflugfelder SC. Topical nonpreserved methylprednisolone therapy for keratoconjunctivitis sicca in Sjogren syndrome. *Ophthalmology* 1999; **106**: 811–6.
44 Sall K, Stevenson OD, Mundorf TK, Reis BL. Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease. CsA Phase 3 Study Group. *Ophthalmology* 2000; **107**: 631–9.
45 Pflugfelder SC. Antiinflammatory therapy for dry eye. *Am J Ophthalmol* 2004; **137**: 337–42.
46 Dogru M, Tsubota K. New insights into the diagnosis and treatment of dry eye. *Ocul Surf* 2004; **2**: 59–75.
47 McCluskey P, Chang JH, Singh R, Wakefield D. Methotrexate therapy for ocular cicatricial pemphigoid. *Ophthalmology* 2004; **111**: 796–801.

Systemic diseases with skin and eye involvement

Some multisystem diseases affect both the skin and the eye [1–23]. It is not possible to catalogue every complication of all these diseases but the most frequent are summarized in Table 67.10.

References

1 Callen JP, Mahl CF. Oculocutaneous manifestation observed in multisystem disorders. *Dermatol Clin* 1992; **10**: 709–16.
2 Krzystolik M, Power WJ, Foster CS. Diagnostic and therapeutic challenges of sarcoidosis. *Int Ophthalmol Clin* 1998; **38**: 61–76.
3 Smith JA, Foster CS. Sarcoidosis and its ocular manifestations. *Int Ophthalmol Clin* 1996; **36**: 109–25.
4 Newman LS, Rose CS, Maier LA. Sarcoidosis. *N Engl J Med* 1997; **336**: 1224–34.
5 Ghabral R, McCluskey FJ, Wakefield D. Spectrum of sarcoidosis involving the eye and brain. *Aust NZ J Ophthalmol* 1997; **25**: 221–4.
6 English JC, Patel PJ, Greer KE. Sarcoidosis. *J Am Acad Dermatol* 2001; **44**: 725–43.
7 Giuffrida TJ, Kerdel FA. Sarcoidosis. *Dermatol Clin* 2002; **20**: 435–47.
8 Burgess SM, Frith PA, Frith RP *et al*. Mucosal involvement in systemic and chronic lupus erythematosus. *Br J Dermatol* 1989; **121**: 727–41.
9 Foster CS. Systemic lupus erythematosus, discoid lupus erythematosus and progressive systemic sclerosis. *Int Ophthalmol Clinic* 1997; **37**: 93–110.
10 Quan DN, Foster CS. Systemic lupus erythematosus and the eye. *Int Ophthalmol Clin* 1998; **38**: 33–60.
11 Friedlander MH. Ocular manifestations of Sjögren syndrome: keratoconjunctivitis sicca. *Rheum Dis Clin North Am* 1992; **18**: 591–608.
12 Whallett AJ, Thurairajan G, Hamburger J *et al*. Behçet's syndrome: a multidisciplinary approach to clinical care. *QJM* 1999; **92**: 727–40.
13 Ando K, Fujino Y, Hijikata K *et al*. Epidemiological features and visual prognosis of Behçet's disease. *Jpn J Ophthalmol* 1999; **43**: 312–7.
14 Bernstein CN, Blanchard JF, Rawsthorne P, Yu N. The prevalence of extra-intestinal diseases in inflammatory bowel disease: a population-based study. *Am J Gastroenterol* 2001; **96**: 1116–22.
15 Orchard TJ, Chua CN, Ahmed T *et al*. Uveitis and erythema nodosum in inflammatory bowel disease: clinical features and the role of *HLA* genes. *Gastroenterology* 2002; **123**: 714–8.
16 Blumenkranz MS, Penneys NS. Acquired immunodeficiency syndrome and the eye. *Dermatol Clin* 1992; **10**: 777–91.
17 Neves RA, Rodriguez A, Power WJ *et al*. Herpes zoster peripheral ulcerative keratitis in patients with the acquired immunodeficiency syndrome. *Cornea* 1996; **15**: 446–50.
18 Sarraf D, Ernest JT. AIDS and the eyes. *Lancet* 1996; **348**: 525–8.
19 Cunningham ET, Margolis TP. Ocular manifestations of HIV infection. *N Engl J Med* 1998; **339**: 236–44.
20 Mansour AM, Saad AJ, Haque AK *et al*. Ocular pathology in acquired immunodeficiency syndrome. *Ann Ophthalmol* 2002; **34**: 137–41.
21 Sober AJ, Grove AS Jr, Muhlbauer JE. Cicatricial ectropion and lacrimal obstruction with porphyria cutanea tarda. *Am J Ophthalmol* 1984; **91**: 396–400.
22 DeFrancisco M, Savino PJ, Schatz NJ. Optic atrophy in acute intermittent porphyria. *Am J Ophthalmol* 1976; **87**: 221–4.
23 Vassallo M, Shepherd RJ, Iqbal P, Feehally I. Age related variations in presentation and outcome in Wegener's granulomatous. *J R Coll Physicians Lond* 1977; **31**: 396–400.

Infections

A number of infections involve the eyelids, but the following are important to recognize because they are common or require urgent therapy or referral to an ophthalmologist [1].

Viral infections

Warts

These are common and are found on the eyelid margins, often as a long thin ('filiform') projection. Lesions in this site are best treated with careful cryotherapy and accurate application of liquid nitrogen to the tip of the lesion using a cotton wool bud rather than cryospray.

Molluscum contagiosum [2]

This condition mainly affects children and young adults. It is also prevalent in patients with acquired immune deficiency syndrome (AIDS), who may develop multiple lesions around the eyelids. Lesions may grow in the lash line as well as on the lid skin and, occasionally, on the mucocutaneous junction. Lesions can be easily overlooked or mistaken for a sebaceous cyst; this condition must

Table 67.10 Systemic diseases with skin and eye involvement.

Systemic disease	Eye disease
Sarcoidosis *Epidemiology*: ocular involvement the presenting feature in 10%; 20–30% of patients have eye disease at some stage [1–7]	*Lids and orbital findings*: clusters of granulomatous eyelid swellings. Proptosis from orbital granulomas. Dry eye from lacrimal gland involvement *Heerfordt's syndrome*: (uveo-parotid fever) consists of uveitis and parotid gland enlargement, fever and facial nerve palsy. *Lofgren's syndrome*: acute iritis, bilateral hilar lymphadenopathy, erythema nodosum and arthralgia. *Mikulicz's syndrome*: bilateral swelling of lacrimal and salivary glands *Anterior segment findings*: *conjunctivitis*: occasionally a granulomatous conjunctivitis mimicking a follicular conjunctivitis. *Uveitis*: usually, but not always, bilateral granulomatous anterior uveitis in 80% of patients with eye manifestations with redness, pain, photophobia and blurred vision with floaters *Posterior segment findings*: rare
Systemic lupus erythematosus [8–10]	*Anterior segment findings*: dry eye, peripheral corneal ulcers. Scleritis is rare. Episcleritis occurs in 10% causing a red eye *Posterior segment findings*: retinal vasculitis common during exacerbations of systemic disease with flame shaped haemorrhages and cotton wool spots. May be associated with severe central nervous system vasculitis or lupus nephritis
Sjögren's syndrome [11]	*Lids and orbital findings*: lacrimal gland inflammation causing dry eye *Anterior segment findings*: *symptoms*: often severe with chronic discomfort, foreign body sensation, dryness and blurred vision. *Conjunctiva*: conjunctivitis and scarring in some cases. *Cornea*: punctate keratopathy, persistent corneal epithelial defects leading to corneal ulceration and perforation or corneal infection
Reiter's syndrome *Epidemiology*: ocular involvement in about 30% of patients [1]	*Anterior segment findings*: *symptoms*: red irritable eyes resolving spontaneously within 7–10 days *Conjunctiva*: bilateral mucopurulent conjunctivitis is the most frequent manifestation affecting approximately 30% of patients; this usually follows a urethritis by about 2 weeks and precedes the onset of arthritis. *Cornea*: keratitis may occur in isolation and is rare. *Uveitis*: anterior uveitis (iritis) occurs in about 20% of patients either with the first attack of Reiter's syndrome or during a recurrence
Behçet's syndrome *Epidemiology*: ocular involvement in 60% to 70% of patients [12,13]	*Anterior segment findings*: *external eye diseases*: conjunctivitis, keratitis and episcleritis may occur but are not specific for the condition. *Uveitis*: is the commonest manifestation of the disease *Posterior segment findings*: visual impairment or blindness is a frequent complication of Behçet's syndrome as a result of the retinal ischaemia
Inflammatory bowel disease *Epidemiology*: ocular manifestations in about 5% of patients [14,15]	*Anterior segment findings*: *external eye diseases*: conjunctivitis, limbitis, peripheral corneal infiltrates and episcleritis may occur *Uveitis*: acute iritis in about 5% of patients which may occur at the same time as exacerbation of colitis
Acquired immune deficiency syndrome (AIDS) *Epidemiology*: ocular complications occur in about 75% of patients [16,19]	*Common features*: (i) opportunistic infections with viruses, mycobacteria and fungi; (ii) malignancies e.g. Kaposi's sarcoma; (iii) retinal microangiopathy; and (iv) neuro-ophthalmic lesions with intracranial infections and tumours *Anterior segment findings*: *external eye diseases*: *Molluscum contagiosum* is a common ocular finding in patients with AIDS, they tend to be large and when located on the lid margin can give rise to follicular conjunctivitis. The lesions can be complicated by epithelial keratitis with associated pannus formation. Kaposi's sarcoma may involve the lids and conjunctiva. *Herpes simplex* keratitis tends to be severe with more frequent relapses. The peripheral cornea is more often involved in contrast to central disease in immunocompetent patients. *Herpes zoster ophthalmicus* is common and may be a presenting feature of HIV infection, especially if severe disease presents in young patients *Posterior segment findings*: retinal microangiopathy is common and characterized by retinal haemorrhages, microaneurysms and cotton wool spots. *Cytomegalovirus* retinitis and *Pneumocystis carinii* choroiditis are serious ophthalmic complications signifying severe systemic involvement
Porphyria [20,21]	*Common feature*: ocular involvement results from either photosensitization and/or neurological dysfunction. Photosensitization can affect the eyelids, conjunctiva, cornea, sclera and possibly the retina *Lids and orbital findings*: inflammation can lead to vesicle and bulla formation, secondary infection scarring with ectropion and hyperpigmentation *Neuro-ophthalmic complications*: include optic neuritis, optic atrophy, ptosis and cranial nerve palsies
Wegener's granulomatosis [22]	Episcleritis is very common in active stages. Also retinal vasculitis, optic neuritis, orbital pseudotumour
Polyarteritis nodosa	Episcleritis, scleritis and keratitis

HIV, human immunodeficiency virus.

always be considered in the differential diagnosis of patients with unilateral or bilateral follicular conjunctivitis. There is associated conjunctival discharge and a variable, often severe, follicular conjunctival response (Fig. 67.11). A superficial epithelial keratitis may develop in longstanding cases, which can progress to pannus formation across the cornea. Treatment involves removal of the lesions by curettage. Cryotherapy is also effective, but these will cause depigmentation in pigmented skins. In a cooperative adult this can be done under local anaesthetic, but for children a general anaesthetic is required.

Herpes simplex virus [3–5]

Primary HSV infection is asymptomatic in many patients; in others it causes blepharoconjunctivitis. However, most of the ocular manifestations of HSV infection are due to reactivation of latent infection in the trigeminal ganglion. Both the primary infection,



Fig. 67.11 Molluscum contagiosum at medial aspect of the upper lid margin with an associated follicular conjunctivitis.

and reactivation of latent disease, may be particularly severe in patients with atopic dermatitis or with immunodeficiency. The blepharoconjunctivitis of HSV usually results in crops of small vesicles, which may be associated with mild oedema of the lids with or without associated conjunctivitis. As with HSV elsewhere, the vesicles dry to a crust and heal within a few days. The conjunctivitis can be treated with aciclovir ointment five times daily for 5 days or with oral aciclovir 400 mg three times daily. Neither the blepharitis nor conjunctivitis present a serious problem for most patients. The serious and sight-threatening ocular complications of HSV infection of the eye are due to recurrent keratitis or keratouveitis. Herpetic keratitis may affect the epithelium alone (dendritic keratitis), the stroma (in stromal herpetic keratitis, geographical corneal ulceration and metaherpetic keratitis), or the endothelium (disciform keratitis or herpetic endotheliitis). Dendritic keratitis is in itself a benign disease unless treated with topical corticosteroids when the disease will rapidly spread, resulting in geographical keratitis, which may cause destructive corneal disease. Most cases of corneal disease represent reactivation of latent HSV and patients may develop any of the corneal manifestations. Stromal and endothelial disease can progress to blinding corneal vascularization, scarring and ulceration. Fortunately the disease is normally unilateral, except in atopic individuals when it may often be bilateral. The management of the stromal and endothelial keratitis is beyond the scope of this review except to state that this involves the judicious use of topical corticosteroids with systemic or topical antivirals. Keratouveitis involves the endothelium and stroma and may also be associated with secondary glaucoma. Dendritic keratitis may occur during treatment with topical corticosteroids. Because of the difficulties of managing the ocular manifestations of this disease, patients with suspected HSV involvement of the eye should be referred for urgent ophthalmological assessment. Topical corticosteroids must not be used alone as these will mask the symptoms and signs, leading to spread of the ulcer and corneal perforation with catastrophic consequences for the patient's vision.

Herpes zoster [6–9]

Herpes zoster of the ophthalmic division (HZO) of the trigeminal nerve is an important condition to recognize. As occurs when it affects other sites, it often presents with a non-specific, flu-like illness with fever and malaise and symptoms of unilateral neuralgia. This develops over the distribution of the affected nerve and varies in severity from a mild tingling in the skin to a deep, severe pain. The characteristic lesions of herpes zoster may appear up to a week after the initial symptoms. Erythematous macules develop into clusters of papules and vesicles becoming pustular and haemorrhagic after 3–4 days. The lesions then scab and are dry by 7–14 days, separating to leave pitted scars. Involvement of the nasociliary nerve, which supplies the skin on the side of the nose, occurs in about 35% of patients and vesicles at this site (Hutchinson's sign) are associated with a high risk of ophthalmic complications. Ocular involvement may occur in the absence of nasociliary involvement but it is usually milder. Herpes zoster sine eruptione can cause ocular complications without the cutaneous eruption. It is rare but evidence of the infection can be found by polymerase chain reaction analysis of the aqueous fluid or sequential titres of HZO antibodies. Patients whose eyes cannot be examined due to persistent lid oedema, or those with ocular signs and symptoms, should be referred for urgent ophthalmological assessment. The disease can affect any part of the eye, including the orbit, extraocular muscles, optic nerve and cornea, and may give rise to long-term complications including severe relapsing keratitis, glaucoma and cataract. The commonest ocular complications are dendritiform keratopathy, stromal keratitis and uveitis.

Antiviral drugs reduce the duration and severity of acute herpes zoster but must be given within the first 3 days of the onset of the rash to be effective. Oral aciclovir has been the standard therapy at doses of 800 mg five times a day for 7–10 days. Valaciclovir (1000 mg three times per day) or famciclovir (500 mg three times per day for 7 days) are now preferred because of simpler dosing regimens and superior pharmacokinetics. Topical aciclovir is not indicated unhelpful. Topical corticosteroid therapy is needed to control the numerous corneal manifestations of the disease and may need to be continued for several years. Some of these complications may be delayed and occur months after the initial skin eruption.

Prolonged or severe post-herpetic neuralgia is a painful and unpleasant sequel to herpes zoster infection. It occurs in about half of elderly patients but is rare in children. There is some evidence that the use of amitriptyline in the early stages of infection is helpful in reducing the incidence and severity. Oral corticosteroids given concurrently with the antivirals may reduce the severity of post-herpetic neuralgia in some patients.

Bacterial infection

Staphylococcal infection

Impetigo

Impetigo is a common skin infection that mainly affects children. It can involve the eyelids, but usually as part of a general infection over the face. It presents as rapidly spreading erythematous macules, developing into flaccid vesicles that subsequently rupture to give rise to surface crusting. The lesions need to be swabbed for bacteriology and appropriate oral and topical antibiotics given.

Hordeolum

External hordeolum (stye) is caused by staphylococcal infection of an eyelash follicle and its associated glands. It presents with a

tender, red, inflamed swelling on the lid margin, which subsequently points anteriorly and discharges close to the lash roots. No treatment is usually required beyond the application of local soothing compresses and removal of the affected lash. If there is a local cellulitis then systemic antibiotics should be given. An internal hordeolum is a staphylococcal abscess of the meibomian glands and needs incision and drainage.

Streptococcal infection

Erysipelas [10]

This represents subcutaneous spreading cellulitis, usually caused by β-haemolytic *Streptococcus*. It usually presents with a rigor followed by a red, raised, erythematous plaque with a well-demarcated edge that spreads rapidly over the skin. Erysipelas is a serious skin infection that needs to be treated urgently with appropriate systemic antibiotics.

Necrotizing fasciitis [11]

This is a very rare condition, most commonly caused by *Streptococcus*, which mainly affects elderly or debilitated patients. A spreading purple discoloration of the eyelid rapidly progresses to gangrene. Unlike erysipelas, the periorbital tissue is not usually affected. Early recognition, immediate institution of intravenous antibiotics and referral to an ophthalmic plastic surgeon for debridement of the necrotic tissue are mandatory as the condition carries a high mortality.

Mycobacterial infection

Tuberculosis

There are no specific ocular findings in tuberculosis, and diagnosis is often based on indirect evidence such as intractable uveitis that is unresponsive to corticosteroid therapy, with negative findings for other causes of uveitis, and in the presence of tuberculosis at a distant body site. Chronic iridocyclitis, which is usually granulomatous, is the commonest feature. Choroiditis and retinal vasculitis may occur.

Leprosy [12,13]

Ocular complications of leprosy are common, most frequently madarosis, conjunctivitis, episcleritis or scleritis. Keratitis results from a combination of corneal anaesthesia, lagophthalmus, trichiasis and secondary infection. Iritis and its complications are the most common causes of blindness and leprosy. Lepromatous disease is more commonly associated with uveitis than is tuberculoid leprosy.

Treponemal infection

Syphilis [14]

Ocular syphilis is very rare and there are no pathognomonic signs. Eye involvement mainly occurs during the secondary and tertiary stages, though primary chancre of the conjunctiva may occur. External features include madarosis, scleritis and interstitial keratitis. Uveitis and chorioretinitis are rare but serious complications of syphilis and lead to blindness. Neuro-ophthalmic features include Argyll Robertson pupils, optic nerve lesions, and palsies of the third and sixth cranial nerves. Gummatous involvement of the brain can cause visual field defects.

Lyme disease [15,16]

Ocular manifestations of Lyme disease involve all parts of the eye. As with syphilis, the ocular manifestations vary according to the stage of the disease. In stage 1, a localized conjunctivitis with photophobia occurs in 10% of patients. This is mild and brief and ophthalmologists are rarely consulted. In stage 2, various ophthalmic complications have been described including cranial nerve palsies; these may occur within 1 month of the rash appearing. It is in the late stage 3 that most of the severe ocular complications are seen, including episcleritis, symblepharon, interstitial keratitis, uveitis, chorioretinitis and retinal vasculitis.

Parasitic infection

Phthiriasis (lice) [17,18]

An infestation of the eyelashes by the pubic louse, *Phthirus pubis*. It mainly affects children and causes chronic itching, irritation and rubbing of the lids. As with louse infection elsewhere, the adult lice can be difficult to see, though nits (eggs) and their shells are visible, adhering to the eyelashes (see Fig. 67.6c,d). The skin nearest to the base of the lashes may show small bluish spots due to the louse bites (maculae caeruleae). A number of measures have been used to treat louse infestation of the eyelids, including mechanical removal with forceps, epilation and trimming of infested lashes, and application of fluorescein, occlusive ointments (e.g. petrolatum) or aqueous malathion for 7 to 10 days.

Filariasis (onchocerciasis) [19]

Onchocerciasis or river blindness is caused by the filarial organism, *Onchocerca volvulus*. It is the second most common cause of preventable blindness in sub-Saharan Africa with an estimated prevalence of 500 000 cases with visual impairment and 270 000 with blindness. It appears that *Wolbachia endobacteria*, a bacterial symbiont, produces an endotoxin-like product which constitutes a major pro-inflammatory stimulus in the eye, causing corneal inflammation and sclerosing keratitis.

Protozoal infection

Ocular disease may complicate leishmaniasis. In *Leishmania donovani* infection, bilateral retinal haemorrhages may be a feature. In *L. tropica* and *L. braziliasis* infection, eyelid and corneal lesions occur, and subsequent destruction may lead to loss of the eye. In trypanosomiasis, unilateral oedema of the lids may occur.

References

1 Holzberg M, Stulting RD, Drake LA. Ocular and periocular infections. *Dermatol Clin* 1992; **10**: 741–61.

2 Vannas S, Lapinleimu K. Molluscum contagiosum in the skin, caruncle and conjunctiva. *Acta Ophthalmol (Copenh)* 1967; **45**: 314–6.

3 Liesegang TJ, Melton J, Daly PJ. Epidemiology of herpes simplex: incidence in Rochester, Minnesota 1950 through 1982. *Arch Ophthalmol* 1987; **107**: 1160–5.

4 Herpetic Eye Disease Study Group. Oral acyclovir for herpes simplex virus eye disease. Effect on prevention of epithelial keratitis and stromal keratitis. *Arch Ophthalmol* 2000; **118**: 1030–6.

5 Fatezadeh M, Schwartz RA. Human herpes simplex viral infections: epidemiology, pathogenesis, symptomatology, diagnosis and management. *J Am Acad Dermatol* 2007; **57**: 737–63.

6 Marsh RJ. Ophthalmic zoster. *Lancet* 1991; **338**: 1527.

7 Weinberg JM. Herpes zoster: epidemiology, natural history and common complications. *J Am Acad Dermatol* 2007; **57**: S130–5.
8 Tyring SK. Management of herpes zoster and post-herpetic neuralgia. *J Am Acad Dermatol* 2007; **57**: S136–42.
9 Negasako EM, Johnson RW, Griffin DRJ, Dworkin RH. Rash severity in herpes zoster: correlates and relationship to postherpetic neuralgia. *J Am Acad Dermatol* 2002; **46**: 834–9.
10 Jackson K, Baker SR. Periorbital cellulitis. *Head Neck Surg* 1987; **9**: 227–34.
11 Walters R. A fatal case of necrotizing fasciitis of the eyelid. *Br J Ophthalmol* 1988; **72**: 428–31.
12 John D, Daniel E. Infectious keratitis in leprosy. *Br J Ophthalmol* 1999; **83**: 173–6.
13 Dana MR, Hochman MA, Viana MA *et al*. Ocular manifestations of leprosy in the USA. *Arch Ophthalmol* 1994; **112**: 626–9.
14 Schlaegel TF Jr, Kao SF. A review (1970–1980) of 28 presumptive cases of syphilis uveitis. *Am J Ophthalmol* 1982; **93**: 412–4.
15 Zaidman GW. The ocular manifestation of Lyme disease. *Int Ophthalmol Clin* 1997; **37**: 13–28.
16 Lesser RI. Ocular manifestations of Lyme disease. *Am J Med* 1995; **98**: 605–25.
17 Burns DA. The treatment of phthirus pubis infestation of the eyelashes. *Br J Dermatol* 1987; **117**: 741–3.
18 Jacobson CC, Abel EA. Parasitic infections. *J Am Acad Dermatol* 2007; **56**: 1026–43.
19 Hoerauf A, Buttner DW, Adjei O, Pearlman E. Onchocerciasis. *BMJ* 2003; **326**: 207–10.

Inherited disorders

A large number of inherited disorders affect the skin and eyes. Major reference texts are cited [1–3]. The main ocular features are summarized in Table 67.11 [4–51].

References

1 Harper J, ed. *Inherited Skin Disorders—the Genodermatoses*. Oxford: Butterworth–Heinemann, 1996.
2 Wiedemann HR, Kunze J, eds. *Clinical Syndromes*. London: Mosby Wolfe, 1997.
3 Grant-Kels JM, Rothe MJ, Kels BD, eds. *Oculocutaneous Disease*, Vol. 10. Philadelphia: WB Saunders, Dermatologic Clinics, 1992.
4 Neldener KH, Hambridge KM, Walravens PA. Acrodermatitis enteropathica. *Int J Dermatol* 1978; **17**: 380–7.
5 Beighton P. Serious ophthalmological complications in the Ehlers–Danlos syndrome. *Br J Ophthalmol* 1970; **54**: 263–8.
6 Maumenee IH. The eye in the Marfan syndrome. *Trans Am Ophthalmol Soc* 1981; **79**: 684–733.
7 Neldner KH. Pseudoxanthoma elasticum. *Int J Dermatol* 1988; **27**: 98–100.
8 Pellegrino JE, Schnurr RE, Boghosian-Sell LE *et al*. Ablepharon macrostomia syndrome with associated cutis laxa: possible localisation to 18q. *Hum Genet* 1996; **97**: 532–6.
9 Leung RSC, Beer WE, Menta HK. Aplasia cutis congenita presenting as a familial triad of atrophic alopecia, ocular defects and a peculiar scarring tendency of the skin. *Br J Dermatol* 1988; **118**: 715–20.
10 Oley C, Baraitser M. Blepharophimosis, ptosis, epicanthus inversus syndrome. (BPES syndrome). Syndrome of the month. *J Med Genet* 1988; **25**: 47–51.
11 Nance MA, Berry SA. Cockayne syndrome. Review of 140 cases. *Am J Med Genet* 1992; **42**: 68–84.
12 Davidson HR, Connor JM. Dyskeratosis congenita. *J Med Genet* 1988; **25**: 843–6.
13 Pinheiro M, Freire-Maia N. Ectodermal dysplasias. In: Harper J, ed. *Inherited Skin Disorders—the Genodermatoses*. Oxford: Butterworth–Heinemann, 1996: 126–45.
14 Thomas JV, Yoshizumi MO, Beyer CK *et al*. Ocular manifestations of focal dermal hypoplasia syndrome. *Arch Ophthalmol* 1977; **95**: 1997–2001.
15 Gattuso J, Patton MA, Baraitser M. The clinical spectrum of the Fraser syndrome. *J Med Genet* 1987; **24**: 549–55.
16 Frydman M, Curran HA, Carmon G, Savir H. Autosomal recessive blepharophimosis ptosis V—esotrophic syndactyly and short stature. *Clin Genet* 1992; **41**: 57–61.
17 11th Annual David W. Smith Workshop on Malformations and Morphogenesis. Symposium on the Hallerman–Streiff syndrome. *Am J Med Genet* 1991; **41**: 487–523.
18 Happle R, Daniels D, Koopman RJJ. Midas syndrome (microphthalmia dermal aplasia and sclerocornea): an X-linked phenotype distinct from Golz syndrome. *Am J Med Genet* 1993; **47**: 710–3.
19 Su WPD, Chun IS, Hammond DL *et al*. Pachyonychia congenita. A clinical study of 12 cases and review of the literature. *Pediatr Dermatol* 1990; **7**: 33–8.
20 Jackson LG. Lange syndrome (editorial). *Am J Med Genet* 1992; **42**: 377–8.
21 Solomon IL, Green OC. Monilethrix. *N Engl J Med* 1963; **269**: 1279–85.
22 Galewsky E. Pili torti. *Arch Dermatol Syphilol* 1932; **26**: 659–66.
23 Bennett CP, Berry AC, Maxwell DJ, Seller MJ. Chondrodysplasia punctata: another possible X-linked recessive case. *Am J Med Genet* 1992; **44**: 795–9.
24 Joy B, Black RK, Wells RS. Ocular manifestations of ichthyosis. *Br J Ophthalmol* 1968; **52**: 217–26.
25 Skinner BA, Greist MC, Norins AL. The keratitis ichthyosis and deafness (KID) syndrome. *Arch Dermatol* 1981; **117**: 285–9.
26 Refsum S. Herdopathia atactica polyneuritiformis phytanic acid storage disease (Refsum's disease) with a particular reference to ophthalmological disturbances. *Metab Ophthalmol* 1977; **1**: 73–9.
27 Gilbert WR, Smith JL, Nyhan WY. The Sjögren–Larsson syndrome. *Arch Ophthalmol* 1968; **80**: 308–16.
28 Burnett JW, Schwartz MF, Berbian BJ. Ulerythema ophryogenes with multiple congenital abnormalities. *J Am Acad Dermatol* 1988; **18**: 437–40.
29 O'Brien WM, La Du BN, Bunim JJ. Biochemical pathologic and clinical aspects of alkaptonuria, ochronosis and ochronotic arthropathy. Review of world literature. *Am J Med* 1963; **34**: 813–38.
30 Wallace HJ. Anderson–Fabry disease. *Br J Dermatol* 1973; **88**: 1–23.
31 Carson NAJ, Cusworth DC, Dent CE *et al*. Homocystinuria. *Arch Dis Child* 1963; **38**: 425–36.
32 Burk RD, Valle D, Thomas GH *et al*. Early manifestations of multiple sulphatase deficiency. *J Pediatr* 1984; **104**: 574–8.
33 Goldsmith LA, Reed J. Tyrosine induced eye and skin lesions: a treatable genetic disease. *JAMA* 1976; **236**: 382–4.
34 Brownstein S, Little JM. Ocular neurofibromatosis. *Ophthalmology* 1983; **90**: 1595–9.
35 Greenwald MJ, Weiss A. Ocular manifestations of the neurocutaneous syndromes. *Pediatr Dermatol* 1984; **2**: 98–117.
36 Gorlin RJ. The naevoid basal cell carcinoma syndrome. *Medicine* 1987; **66**: 98–113.
37 Gretzula JC, Hevia O, Weber PJ. Bloom's syndrome. *J Am Acad Dermatol* 1987; **17**: 479–88.
38 Moss C. Rothmund–Thomson syndrome. A report of two patients and review of the literature. *Br J Dermatol* 1990; **122**: 821–3.
39 Kraemer KH, Lee MM, Scotto J. Xerodermo pigmentosum cutaneous ocular and neurologic abnormalities in 830 published cases. *Arch Dermatol* 1987; **123**: 241–50.
40 Blume RS, Wolff SM. The Chediak–Higashi syndrome. *Br J Dermatol* 1971; **85**: 336–47.
41 Cross HE, McKusick VA, Breen W. A new oculocerebral syndrome with hyperpigmentation. *J Pediatr* 1967; **70**: 396–406.
42 Rogers M, McCrossin I, Commons C. Epidermal naevi and the epidermal naevus syndrome. A review of 131 cases. *J Am Acad Dermatol* 1989; **20**: 476–88.
43 Berlin AL, Paller AS, Chan LS. Incontinentia pigmenti. A review and update on the molecular basis of pathophysiology. *J Am Acad Dermatol* 2002; **47**: 169–87.
44 Glover MT, Brett EM, Atherton DJ. Hypomelanosis of Ito: spectrum of the disease. *J Pediatr* 1989; **115**: 75–80.
45 Witkop CJ, Hill CW, Desnick S *et al*. Ophthalmologic biochemical platelet and ultrastructural defects in the various types of oculocutaneous albinism. *J Invest Dermatol* 1973; **60**: 443–56.
46 Winship I, Young K, Martell R *et al*. Piebaldism: an autonomous autosomal dominant entity. *Clin Genet* 1991; **39**: 330–7.
47 Goldberg MF. Waardenburg's syndrome with fundus and other anomalies. *Arch Ophthalmol* 1966; **76**: 797–810.
48 Pehr K, Moroz B. Cutis marmorata telangiectatica congenita. Long term follow up review of the literature and report of a case in conjunction with congenital hypothyroidism. *Pediatr Dermatol* 1993; **10**: 6–11.
49 Auerbach AD. Fanconi's anaemia. *Dermatol Clin* 1995; **13**: 41–9.

Table 67.11 Inherited disorders affecting the skin and eyes.

Group	Condition	Inheritance	Ocular features
Bullous disorders	Acrodermatitis enteropathica [4]	AR (MIM #201100)	Loss of eyebrows and eyelashes, conjunctivitis, blepharitis, photophobia
Connective tissue disorder	Ehlers–Danlos syndrome [5]	Mainly AD (see MIM 130000)	Lax eyelid skin with redundant folds, epicanthal folds, hypertelorism, strabismus, blue sclera, corneal abnormalities including keratoconus, angioid streaks, ectopic lens. Retinal detachments occasionally occur
	Marfan's syndrome [6]	AD (MIM #154700)	Subluxation of lens—60–80% of patients in early childhood. Amblyopia, myopia, cataract, corneal abnormalities, glaucoma. Retinal detachment is most serious complication
	Pseudoxanthoma elasticum [7]	Types I & II AR (MIM #264800, 264810) Types III & IV AD (MIM #177850, 177860)	Angioid streaks (breaks in Bruch's membrane) in majority. Haemorrhagic maculopathy after trauma may cause visual loss
Dysplasias, hyperplasia, atrophies and aplasias	Ablepharon macrostomia [8] syndrome	Unknown (MIM 200110)	Absent eyelids and ectropion
	Aplasia cutis congenita [9]	AD (MIM #107600) AR (MIM 207700)	Congenital absence of skin leading to eyelid colobomas, corneal opacities, scleral dermoids and lamellar cataracts
	Blepharophimosis ptosis epicanthus inversus syndrome [10]	AD (MIM #110100)	Blepharophimosis, ptosis, epicanthus inversus, telecanthus. Amblyopia in 50% of patients
	Cockayne's syndrome [11]	AR (MIM *216400)	Corneal opacities, cataracts in 30%, retinitis pigmentosa, optic atrophy, strabismus, photophobia
	Dyskeratosis congenita [12]	XR (MIM #305000)	Obliteration of the lacrimal puncta in 80% of cases, conjunctivitis, blepharitis, ectropion, loss of eyelashes and eyebrows
	Ectodermal dysplasias—a complex group of disorders with various inheritance patterns and a variety of ocular findings [13]		
	Examples are given:		
	(i) Christ–Siemans–Touraine syndrome	XR (MIM #305100)	Photophobia, dry eye
	(ii) Fischer–Jacobson–Clouston syndrome	AD	Usually normal
	(iii) Ellis–van Cleveld syndrome	AR (MIM #225500)	Coloboma of iris, microphthalmia, occasional cataract
	Focal dermal hypoplasia (Goltz's syndrome) [14]	XD (MIM *305600)	40% have ocular abnormalities, the commonest being colobomas of iris, choroid, retina or optic nerve
	Fraser's syndrome [15]	AR (MIM *219000)	Bilateral or unilateral absence of palpebral fissure with loss of eyebrows, anophthalmia, microphthalmia
	Frydman's syndrome [16]	AR	Synophrys, blepharophimosis, weakness of extra-ocular and frontal muscles
	Hallerman–Streiff syndrome [17]	Unknown (MIM *264090)	Loss of hair of eyebrows and eyelashes, microphthalmos, cataracts, amblyopia and nystagmus
	MIDAS syndrome (MCOPS7) [18]	XD (MIM #309801)	Microphthalmia, sclerocorneal
	Pachyonychia congenita [19]	AD (PC1 MIM #167200 PC2 MIM #167210)	Cataract and corneal dyskeratosis
Hair disorders	Brachmann–Lang syndrome [20]	AR	Synophrys, long thick eyelashes, narrow palpebral fissure, myopia, nystagmus and strabismus
	Monilethrix [21]	AD (MIM #158000)	Loss of eyebrows and lashes
	Pili torti [22]	AR (MIM 261900)	Loss of eyebrows and lashes
	Chondrodysplasia punctata [23]	AD (MIM 215105) XR (MIM #302950)	Cataracts Ocular albinism, cataracts, microphthalmia
Keratinization disorders	The ichthyoses [24]		
	(i) Ichthyosis congenita gravis	AR (MIM *242500)	Severe ectropion
	(ii) Ichthyosiform erythroderma	AD (MIM 242100)	Early development of ectropion is characteristic
	(iii) Lamellar ichthyosis	AR (various types)	Cicatricial ectropion with exposure keratitis Direct conjunctival involvement may occur

(Continued)

Table 67.11 *Continued*

Group	Condition	Inheritance	Ocular features
	(iv) X-linked ichthyosis	XL (MIM *308100)	Deep corneal opacities
	KID syndrome [25]	XD (MIM #148210)	Keratitis
	Refsum's syndrome [26]	AR (MIM #266500)	Night blindness, posterior subcapsular cataracts develop in most cases
	Sjögren–Larson syndrome [27]	AR (MIM *270200)	Blepharitis, conjunctivitis, punctate corneal erosions and pigmentary degeneration of the retina
	Ulerythema ophryogenes [28]	AD	Erythema and perifollicular papules on eye to eyebrows spreading medially causing thinning of eyebrows (occurs in keratosis pilaris, Noonan syndrome, cardiofacialcutaneous syndrome)
Metabolic disorders	Alkaptonuria [29]	AR (MIM #203500)	Scleral pigmentation is early sign, eyelid pigmentation
	Angiokeratoma corporis diffusum [30]	XL (MIM *301500)	Angiokeratomas of conjunctiva, corneal opacities, posterior capsular cataracts
	Homocystinuria [31]	AR (MIM *236200)	Myopia, cataracts, subluxation of lens, secondary glaucoma, retinal detachment
	Hurler's syndrome [32]	AR (MIM *252800)	Early clouding of cornea
Neurocutaneous syndromes	Richner–Hanhart syndrome [33]	AR (MIM 276600)	Corneal lesions vary from erosions to deep ulcers Nystagmus and lens opacities
	Neurofibromatosis type I [34]	AD (MIM *162200)	Neurofibromas of eyelid, corneal clouding, Lisch nodules of iris, optic nerve glioma, palsies from cranial nerve involvement
	Neurofibromatosis type II	AD (MIM #101000)	Cataract fundus lesions, extraocular motility abnormalities
	Tuberous sclerosis [35]	AD (MIM #191100)	Tumours of the lids or nodules on conjunctiva and retina
Photosensitive disorders	Basal cell naevus syndrome [36]	AD (MIM #109400)	Basal cell carcinoma of eyelid and periorbital area, hypertelorism, strabismus, colobomas of the choroid, cataracts, glaucomas in 5–10%
	Bloom's syndrome [37]	AD (MIM #210900)	Telangiectasis on lower lids, blistering and scarring lower eyelids
	Rothmund–Thomson syndrome [38]	AR (MIM #268400)	Sparse eyebrows and eyelashes, degenerative changes in cornea, 50% of patients have bilateral cataracts which develop in childhood, strabismus
	Xeroderma pigmentosum [39]	AR (various types)	Angiomas, keratoses, papillomas, carcinomas develop on eyelids, sometimes extending on to conjunctiva and cornea, scarring and atrophy of lids with exposure keratitis leading to corneal ulceration symblepharon formation; ocular melanoma
	Chediak–Higashi syndrome [40]	AR (MIM #214500)	Oculocutaneous albinism, corneal opacities
Pigmentation disorders	Cross syndrome [41]	AR (MIM *257800)	Microphthalmia, small opaque cornea, coarse nystagmus
	Epidermal naevus syndrome [42]	Sporadic	Ocular melanocytic naevi, coloboma of the lids, iris and choroid; lipodermoid of conjunctiva or choroid
	Incontinentia pigmenti [43]	XD (MIM #308300)	35% of patients have eye abnormalities including strabismus, cataract and microphthalmia; retinal detachment may occur
	Hypomelanosis of Ito [44]	Sporadic (MIM *300337)	Hypertelorism, strabismus, myopia
	Oculocutaneous albinism [45]	AR (various types; Chapter 58)	Total loss of pigment in eyes, nystagmus, absence of binocular vision
	Piebaldism [46]	AD (MIM #172800)	Absent pigmentation medially of eyebrows, eyelids and eyelashes, heterochromia of iris
	Waardenberg's syndrome [47]	AD (MIM #193150)	Telecanthus, synophrys, partial albinism, heterochromia of iris
Vascular and haematological syndromes	Congenital telangiectatic cutis marmorata [48]	Unknown (MIM 219250)	Clouding of cornea, glaucoma
	Fanconi pancytopenia syndrome [49]	AR (MIM #227650)	Microphthalmia strabismus, nystagmus and colobomas
	Lymphoedema–distichiasis syndrome [50]	AD (MIM #153400)	Double row of eyelashes on upper and lower eyelids
	Sturge–Weber syndrome [51]	Sporadic (MIM 185300)	50% of patients have angiotomatous changes of the ipsilateral choroid causing glaucoma

AD, autosomal dominant; AR, autosomal recessive; XD, X-linked dominant; XL, X-linked; XR, X-linked recessive.

50 Kolin T, Johns KJ, Wadlington WB *et al*. Hereditary lymphoedema and distichiasis. *Arch Ophthalmol* 1991; **109**: 980–1.
51 Phelps CD. The pathogenesis of glaucoma in Sturge–Weber syndrome. *Ophthalmology* 1978; **85**: 276–8.

Ocular complications of dermatological therapy

A number of drugs used by dermatologists have significant side effects on the eye and require careful monitoring.

Corticosteroids [1–15]

The use of corticosteroids can cause significant side effects on the eye. Both systemic and topical corticosteroids are responsible, though the greatest risk is to those receiving prednisolone at a dose of 10–15 mg/day for over a year. Continuous therapy is more likely to cause side effects than intermittent therapy.

Posterior subcapsular cataracts are induced by long-term systemic corticosteroids in as many as 30% of patients. They rarely occur at doses less than 10 mg/day and for less than 1 year. Children are particularly vulnerable. Reversibility of cataracts is not common and progression of cataracts may occur in spite of reduction or discontinuation of corticosteroid therapy.

Patients also risk developing open angle glaucoma, particularly if genetically predisposed. The precise mechanism is unknown, though it is thought to be due to decreased aqueous outflow. Particular risk factors include type 1 diabetes, high myopia, connective tissue disorders and a family history of glaucoma. Topical corticosteroids induce a rise in intraocular pressure more quickly than systemic corticosteroids. Medium- or high-potency dermatological corticosteroids applied for long periods to, or near, the eyelids may spread over the lid margin and are absorbed through the cornea, reaching sufficient concentrations to elevate ocular pressures. Patients on long-term topical or systemic corticosteroids need to have their eye pressures monitored regularly at 1–6 monthly intervals depending on their degree of risk.

Topical corticosteroids predispose patients to cataract, glaucoma and secondary surface infection. Injudicious use in HSV infection masks the clinical signs of dendritic ulcer and risks perforation. Wearing a soft contact lens is a contraindication to topical ocular corticosteroid usage. Other ocular complications from corticosteroids include angioneurotic oedema, papilloedema from raised intracranial pressure and toxic amblyopia. Systemic treatment with corticosteroids may cause serous chorioretinopathy or diffuse retinal pigment epitheliopathy.

Oral retinoids [16–22]

Both isotretinoin and acitretin can cause ocular side effects. The most common is dry eye with associated conjunctivitis and blepharoconjunctivitis, giving rise to blurred vision. The blepharoconjunctivitis is frequently associated with staphylococcal infection. Exposure keratopathy and corneal ulceration rarely occur; asymptomatic corneal opacities may develop but resolve after 6–8 weeks. Patients should be warned that they may be unable to tolerate contact lenses whilst on retinoid therapy. Use of tear substitutes, humidification of the environment and lid hygiene measures help. Retinal abnormalities may also occur, with poor night vision and increased sensitivity to glare, and can be a significant problem in those who drive at night; pilots are not allowed to fly whilst taking isotretinoin due to the potential effects on night vision. The cause is unknown but may be due to competitive inhibition of ocular retinol dehydrogenase causing local vitamin A deficiency and reduction in rhodopsin formation. More serious side effects include papilloedema from raised intracranial pressure, optic atrophy and cataract. Although these are rare, a history of visual disturbance should be asked for when patients come for follow-up. Severe headache early in the course of treatment is significant. The ocular manifestations are dose-dependent and usually reversible, provided they are recognized and the treatment regimen adjusted. However, there have been reports of the dry eye syndrome and night blindness persisting after retinoids have been discontinued.

Antimalarials [23–27]

The most serious potential side effect of antimalarial drugs is retinopathy. The mechanism is uncertain but seems to depend on the ability of the drug to bind the retinal pigment epithelium. Ocular side effects from antimalarials are much less common now that hydroxychloroquine rather than chloroquine is the drug of choice. However, both drugs should be used with caution in patients with hepatic or renal impairment. The Royal College of Ophthalmologists and American Academy of Ophthalmologists have issued clear guidelines on screening protocols for use of chloroquine and hydroxychloroquine. Baseline ophthalmic assessment of patients, for whom these drugs are proposed, is carried out by the dermatologist and requires questioning the patient about any known visual impairment (uncorrected by spectacles) and the recording of near visual acuity using a test type. If visual impairment is reported or detected then referral to an optometrist is advised; the optometrist will refer any patient with abnormal findings to an ophthalmologist. Patients should not be treated with more than the maximum daily dosage (hydroxychloroquine at a maximum dosage of 6.5 mg/kg or chloroquine phosphate not exceeding 4 mg/kg daily) and should have this visual screening repeated annually and recorded in their notes. Referral to an ophthalmologist is appropriate if visual impairment is detected at baseline, if changes are detected on the annual screening or if the patient develops visual symptoms. The ophthalmologist will then carry out a range of tests, including visual acuity, colour vision, visual fields, Amsler fields, corneal and retinal examinations. If long-term treatment is required, for more than 5 years, the risks of ocular complications are increased; in this instance, individual arrangements for screening should be agreed with a local ophthalmologist. No screening is recommended for mepacrine as it is not associated with ophthalmological side effects.

Antibiotics for acne [28–32]

Oxytetracycline, minocycline and doxycycline can all cause raised intracranial pressure. The mechanism is unknown but is thought to be related to interference with energy-dependent absorption mechanism of cerebrospinal fluid, which is mediated by cyclic adenosine monophosphate (AMP) at the arachnoid granulations. Patients who complain of headache should be examined carefully

with fundoscopy through dilated pupils to look for papilloedema, and should have formal testing of visual acuity and of visual fields. The condition is far from benign; permanent visual field loss can occur if the condition is not recognized early and the drug stopped. Sometimes treatment with acetazolamide is required to reduce the pressure. Erythromycin or trimethoprim may cause erythema multiforme and associated ocular changes. Pigmentation due to minocycline can occur in the skin (Chapter 58) and has also been reported in the sclera.

Psoralens [33–46]

Psoralens have been shown to bind to the lens proteins, and some animal studies have shown induction of anterior cortical opacities though others have not. 8-Methoxypsoralen can be detected in the human lens 12 h after oral ingestion. There has been a longstanding concern about the risk of cataract in patients having psoralen and long-wave UV radiation (PUVA) therapy. Although PUVA has been used in treatment of skin diseases for 30 years, and clinical studies have not yet shown any convincing evidence of an increase in cataract as compared with the general population, it is still recommended that ultraviolet light A (UVA)-filtered spectacles are used for 12 h after ingestion of psoralens in case significant long-term sequelae eventually develop. Failure to do so may result in other signs of ocular toxicity such as conjunctival hyperaemia, decreased lacrimation and pinguecula formation, which represents elastotic degeneration of the cornea. Care must be taken to ensure that the spectacles are suitable for ultraviolet protection.

Botulinum toxin [47]

With the increased use of botulinum toxin for the treatment of facial wrinkling and eyebrow position dermatologists need to be aware of the potential side effects. These include haematoma, ptosis, ectropion, diplopia and eyelid drooping, and are often related to poor injection technique.

References

1 David D, Berkowitz J. Ocular effects of topical and systemic corticosteroids. *Lancet* 1969; **i**: 149–51.
2 Agaarwal RK, Potamitis T, Chong NHV. Extensive visual loss with topical facial steroids. *Eye* 1993; **7**: 664–6.
3 Black RL, Oglesby RB, von Sallman L *et al*. Posterior subcapsular cataracts induced by corticosteroids in patients with rheumatoid arthritis. *JAMA* 1960; **174**: 166–71.
4 Giles C, Mason G, Dugg I *et al*. The association of cataract formation and systemic corticosteroid therapy. *JAMA* 1962; **182**: 719–22.
5 Shiono H, Oonishi M, Yamaguchi M *et al*. Posterior subcapsular cataracts associated with long term oral corticosteroids therapy. *Clin Pediatr (Phila)* 1977; **16**: 726–8.
6 Branco N, Branco BC, Maibach HI. Cutaneous corticosteroids therapy and cataract in men. *J Toxicol Cutaneous Ocul Toxicol* 2002; **21**: 161–8.
7 First C, Smiley WK, Arsell BM. Steroid cataract. *Ann Rheum Dis* 1983; **25**: 364–8.
8 Armaly MF. Effect of corticosteroids on intraocular pressure and fluid dynamics. I. The effect of dexamethasone in the normal eye. *Arch Ophthalmol* 1963; **70**: 482–6.
9 Rentro L, Snow JS. Ocular effects of topical and systemic steroids. *Dermatol Clin* 1992; **10**: 505–12.
10 Kwok AKH, Lam DJC, Ng JSK *et al*. Ocular hypertensive response to topical steroids in children. *Ophthalmology* 1997; **104**: 2112–6.
11 Chua JK, Fan DS, Leung AT, Lam DS. Accelerated ocular hypertensive response after application of corticosteroid ointment to a child's eye. *Mayo Clin Proc* 2000; **75**: 539–48.
12 Cubey RB. Glaucoma following the application of corticosteroids. *Br J Dermatol* 1976; **95**: 207–9.
13 Zigerman C, Saunders D, Levit F. Glaucoma from topically applied steroids. *Arch Dermatol* 1976; **112**: 1362–6.
14 Brown SI, Blomfield S, Pearce DB, Tragakis M. Infections with the therapeutic soft lens. *Arch Ophthalmol* 1973; **91**: 275–7.
15 Sprawl CW, Lang GE, Lang GK. Retinal pigment epithelial changes associated with systemic corticosteroids treatment. Report of cases and review of the literature. *Ophthalmologica* 1998; **212**: 142–8.
16 Palestine AG. Transient acute myopia resulting from isotretinoin (acutane) therapy. *Ann Ophthalmol* 1984; **16**: 660–2.
17 Bigby M, Stein RSL. Adverse reactions to isotretinoin. A report from the adverse drug reaction reporting system. *J Am Acad Dermatol* 1988; **18**: 543–52.
18 Goulden V, Layton AM, Cunliffe WJ. Long term safety of isotretinoin as a treatment for acne vulgaris. *Br J Dermatol* 1994; **131**: 360–3.
19 Lerman S. Ocular side effects of accutane therapy. *Lens Eye Toxic Res* 1992; **9**: 429–38.
20 Leyden JJ. The role of isotretinoin in the treatment of acne: personal observation. *J Am Acad Dermatol* 1998; **39**: 545–9.
21 Weleber R, Denman S, Hanifin J, Cunningham WJ. Abnormal retinal function associated with isotretinoin therapy for acne. *Arch Opthalmol* 1986; **104**: 831–7.
22 Fraunfelder FT, Fraunfelder FW, Edwards R. Ocular side effects possibly associated with isotretinoin usage. *Am J Ophthalmol* 2001; **132**: 299–305.
23 Easterbrook M. Ocular side effects and safety of antimalarial agents. *Am J Med* 1988; **85**: 23–9.
24 Cox NH, Paterson WD. Ocular toxicity of antimalarials in dermatology: a survey of current practice. *Br J Dermatol* 1994; **131**: 878–82.
25 Browning DJ. Hydroxychloroquine and chloroquine retinopathy: screening for drug toxicity. *Am J Ophthalmol* 2002; **135**: 649–56.
26 Fielder A, Graham E, Jones S *et al*. Royal College of Ophthalmologists guidelines: ocular toxicity and hydroxychloroquine. *Eye* 1998; **12**: 907–9.
27 Marmor MF, Carr RE, Easterbrook M *et al*. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy. A report by the American Academy of Ophthalmology. *Ophthalmology* 2002; **109**: 1377–82.
28 Digre KB. Not so benign intracranial hypertension. *BMJ* 2003; **326**: 613–4.
29 Elston J, Lochhead J. Doxycycline induced intracranial hypertension. *BMJ* 2003; **326**: 641–2.
30 Sabroe RA, Archer CB, Harlow D *et al*. Minocycline induced discolouration of the sclerae. *Br J Dermatol* 1996; **135**: 314–6.
31 Fraunfelder FT, Randall JA. Minocin induced scleral pigmentation. *Ophthalmology* 1997; **104**: 936–8.
32 Morrow GL, Abbott RL. Minocycline—induced scleral dental and dermol pigmentation. *Am J Ophthalmol* 1998; **125**: 396–7.
33 Boettner EA, Woffer JR. Transmission of the ocular media. *Invest Ophthalmol Vis Sci* 1962; **i**: 776–83.
34 Parrish JA, Chylack LT, Woehler ME *et al*. Dermatological and ocular examination in rabbits chronically photosensitised with methoxsalen. *J Invest Dermatol* 1979; **73**: 256–8.
35 Basis O, Hollstrom E, Lidor S *et al*. Absence of cataract 10 years after treatment with 8-methoxypsoralen. *Acta Derm Venereol Suppl (Stockh)* 1980; **60**: 79–80.
36 Hammershoy O, Jessen F. A retrospective study of cataract formation in 96 patients treated with PUVA. *Acta Derm Venereol Suppl (Stockh)* 1982; **62**: 444–6.
37 Stern RC, Parrish JA, Fitzpatrick TB. Ocular findings in patients treated with PUVA. *J Invest Dermatol* 1985; **85**: 269–73.
38 Lerman S, Megaw J, Gardner K *et al*. PUVA therapy and human cataractogenesis. *Invest Ophthalmol Vis Sci* 1982; **23**: 801–4.
39 Calzavara-Pinton PG, Carlino A, Manfredi E *et al*. Ocular side effects of PUVA treated patients refusing eye sun protection. *Acta Derm Venereol Suppl (Stockh)* 1994; **186**: 164–5.
40 Stern RS. Ocular lens findings in patients treated with PUVA. *J Invest Dermatol* 1994; **103**: 534–8.
41 See JA, Weller P. Ocular complications of PUVA therapy. *Australas J Dermatol* 1993; **34**: 1–4.

42 Prytowsky JH, Keen MS, Rabinowitz AU *et al*. Present status of eyelid phototherapy: clinical efficacy and transmittance of ultra violet and visible radiation through human eyelids. *J Am Acad Dermatol* 1992; **26**: 607–13.
43 Moseley H, Cox NH, MacKie RM. The suitability of sunglasses used by patients following ingestion of psoralens. *Br J Dermatol* 1988; **118**: 247–53.
44 Moseley H, Jones SK. Clear ultraviolet blocking lenses for use by PUVA patients. *Br J Dermatol* 1990; **123**: 775–81.
45 Malanos D, Stern RN. Psoralen plus ultraviolet A does not increase the risk of cataracts: a 25 year prospective study. *J Am Acad Dermatol* 2007; **57**: 231–7.
46 Garg A, Loosemore M. Pinguecula following psoralen and ultraviolet A therapy. *J Am Acad Dermatol* 2007; **57**: 177–8.
47 Huang W, Foster JA, Rogachefsky AJ. Pharmacology of botulinum toxin. *J Am Acad Dermatol* 2000; **43**: 249–50.

Tumours

Benign tumours of the eyelid

As would be expected of such complex tissue, the eyelid gives rise to a large number of skin tumours. Tumours can arise from the epidermis and dermis in addition to the adnexal structures, which include the meibomian and Zeis sebaceous glands, eccrine and Moll's apocrine sweat glands, and the specialized hair follicles of the eyelashes. They may also originate from lymphoid neural and vascular tissue found in the preseptal tissues of the eyelid. Although optimal treatment of the tumours begins with accurate diagnosis, many are rather non-specific in their appearance and are only diagnosed with certainty by histology.

Keratoses

Both seborrhoeic and actinic keratoses occur on the eyelid. They have similar clinical features to those elsewhere on the skin and are treated in the same way with local destructive measures, using carefully applied cryotherapy, curettage and cautery or laser ablation under local anaesthetic. Recurrent actinic keratosis should be biopsied and sent for histological examination to make sure it is not a deceptive manifestation of an early skin cancer.

Xanthelasma [1,2]

These present as yellowish cutaneous plaques, most commonly located on the medial part of the eyelids. They are usually bilateral and are much more common in elderly patients. About 60% of patients have an associated hypercholesterolaemia and lipid levels should be measured. Patients often request treatment for cosmetic reasons. Although 90% trichloroacetic acid applied with a cotton wool bud is used there is a significant risk of spillage into the eye. More effective treatment is by surgical excision or ablation with carbon dioxide laser. Necrobiotic xanthogranuloma may look similar to xanthelasma but they are thicker and more nodular. These lesions may involve the conjunctiva and sclera. On the rare occasions that they infiltrate the orbit they may cause proptosis.

Juvenile xanthogranuloma [3]

These lesions occasionally involve the eyelid, conjunctiva or uveal tract. They may be associated with glaucoma and threaten sight. Patients need screening by an ophthalmologist (Fig. 67.12).

Adnexal tumours [4]

Syringomas, milia, trichoepitheliomas and tricholemmomas present as small papules around the eyelids. They can be very difficult to distinguish from each other. Syringomas are the most common, but histology from a biopsy is the only way to make a definite diagnosis. Treatment is by local destruction of the lesions. Eccrine hidrocystomas can present in an eruptive fashion on the face and eyelids; they may respond to topical atropine.

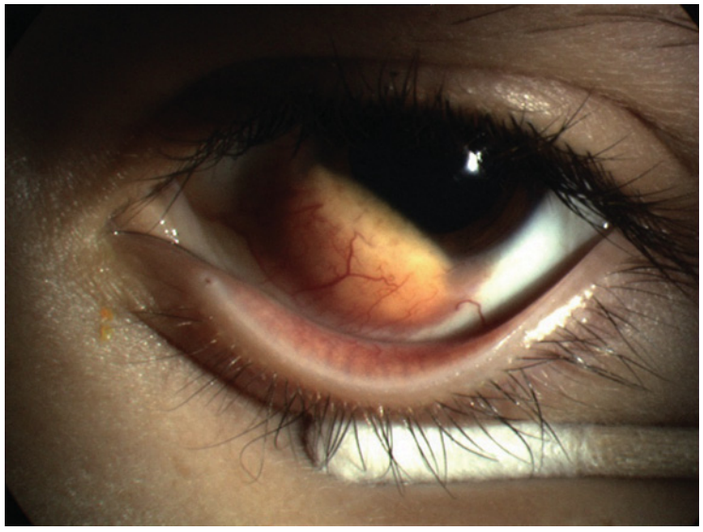


Fig. 67.12 Juvenile xanthogranuloma.

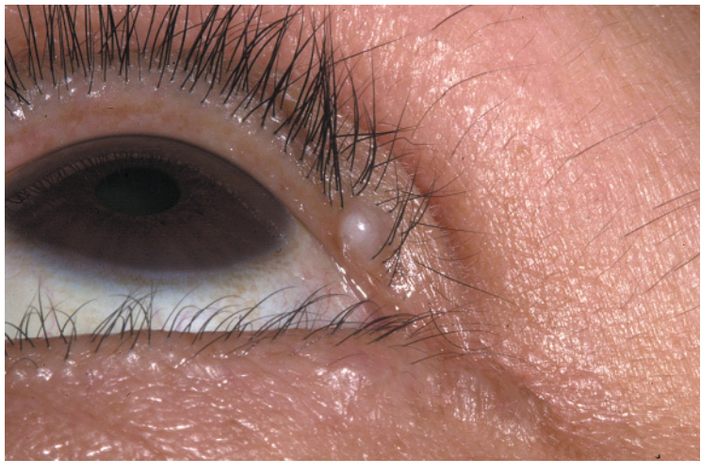


Fig. 67.13 Cyst of Moll. Small translucent cyst on anterior lid margin. (Courtesy of Mr N. Joshi, Chelsea & Westminster Hospital/Medical Illustration UK, London, UK.)

Benign cysts of the eyelid

Retention cysts may arise from either the glands of Moll or of Zeis. A cyst of Moll usually presents as a small translucent lesion on the anterior lid margin close to the lacrimal punctum (Fig. 67.13). Glands of Zeis are sebaceous glands and their retention cysts contain oily secretions and are more opaque than a cyst of Moll. An eccrine gland hidrocystoma is similar in appearance to a cyst of Moll but is not confined to the lid margin. These cysts are easily confused with a basal cell carcinoma clinically and are treated by excision and submission for histology.

Chalazion [5]

This lesion represents a chronic granulomatous inflammatory reaction around a blocked sebaceous gland. Patients with seborrhoeic dermatitis and rosacea are at increased risk of chalazion formation. A chalazion presents as a firm lump in the eyelid, which is clearly visible when the lid is everted; an association with chronic posterior blepharitis is common. Chalazia will usually resolve spontaneously but large and troublesome lesions can be treated by everting the lid with a special clamp, incising the cyst and curetting the contents through the tarsal plate. Patients who develop recurrent chalazion associated with seborrhoeic dermatitis and rosacea benefit from long-term antibiotic treatment using tetracyclines. Hot saline compresses reduce the inflammation.

Pigmented naevi [6,7]

The skin on the eyelid can develop pigmented naevi. Their appearance, classification and potential malignant change applies as elsewhere on the skin. Patients with dysplastic naevus syndrome should be referred to an ophthalmologist for ocular assessment. Melanocytic lesions of the conjunctiva extending onto the cornea or pigmented lesions of the conjunctiva, which change in character, should also be referred with a view to excision biopsy.

Naevus of Ota [8]

This lesion affects the eyelids, conjunctiva and sclera. Occasionally, the pigmentation is confined to the eye with no cutaneous involvement. Naevus of Ota carries an increased risk of ocular melanoma and glaucoma and patients need to be referred for ophthalmic examination and long-term review.

Melanoacanthoma [9]

These are small, shining, black papules situated along the line of the lashes and are a form of dermatosis papulosa nigricans.

Vascular naevi [10–13]

Strawberry naevus (capillary haemangioma) can affect the eyelids. It is more common on the upper lid and presents as a unilateral, red, raised lesion, which grows quickly during the first year of life (Fig. 67.14). Spontaneous involution occurs usually by age 9 years. Amblyopia is the main complication of larger periorbital lesions and results either from physical closure of the eye and occlusion of the pupil, giving rise to stimulus deprivation, or from refractive errors caused by corneal distortion due to lid pressure. Both systemic and intralesional corticosteroids can reduce the bulk of the haemangioma. Surgical resection or laser therapy is helpful in certain cases.

Port-wine stain

This is a rare, congenital, vascular lesion, which may affect the eyelids. It presents as a sharply demarcated red patch. Extensive lesions involving the periocular region have a high risk of central nervous involvement and of ipsilateral glaucoma (especially if the upper lid is involved), which may not develop until adult life.

Keratoacanthoma

Keratoacanthomas may develop on the eyelid. They present as a small papule, which grows rapidly developing a characteristic keratin-filled crater and may reach up to 3 cm in diameter (Fig. 67.15). The lesions then stop growing and remain static for 2 or 3 months before spontaneously involuting, which can lead to significant scarring of the eyelid. Because of this, the lesion should be excised at an early stage.



Fig. 67.14 Capillary haemangioma. Enlarging lesion on right upper lid starting to occlude vision. (Courtesy of Mr N. Joshi, Chelsea & Westminster Hospital/Medical Illustration UK, London, UK.)



Fig. 67.15 Keratoacanthoma. Keratin-filled crater on lid margin. (Courtesy of Mr N. Joshi, Chelsea & Westminster Hospital/Medical Illustration UK, London, UK.)

Malignant tumours of the eyelid [14–16]

Basal cell carcinomas (BCCs), squamous cell carcinomas (SCCs) and malignant melanomas all occur on the eyelid as on other areas of the skin. The same rules for management apply on the eyelid as at any site, but the eyelid poses specific problems in preserving good cosmesis and residual function. Clinical examination is an unreliable way of determining the extent of many of these lesions, particularly sclerosing BCC. Early referral to an oculoplastic surgeon is advisable with a view to Mohs micrographic surgery if appropriate.

Basal cell carcinomas [17–19]

These are the most common skin malignancy and in most series account for 90% of malignant tumours. They rarely metastasize but cause problems by local tissue destruction and invasion of periorbital tissue. Over 70% arise on the lower eyelid, followed in order of frequency by the medial canthus, upper eyelid and lateral

canthus. Tumours located near to the medial canthus can invade the orbit and sinuses. They are more difficult to excise than those elsewhere, because of the high risk of damaging the tear duct. The majority of BCCs are solid or cystic and fairly straightforward to recognize (Fig. 67.16). Sclerosing or morphoeic BCCs are less common and can be difficult to diagnose as they infiltrate beneath the epidermis, forming a flat indurated plaque with indistinct margins, which may simulate a localized area of chronic dermatitis. The paucity of reticular dermis and subcutaneous fat to resist deep invasion presents a particular problem with the eye. Once the orbital septum is penetrated the BCC can rapidly invade, threatening the orbit. At the medial canthus the lacrimal sac and the rich anastomosis of blood vessels offers little barrier. Curettage and cautery is generally not advised for the treatment of eyelid lesions. The skin is thin and tears easily and the sensitivity of the curette is lost in the soft tissue. Successful initial treatment with surgery and accurate margin assessment to ensure complete excision is mandatory in management of these tumours. Mohs micrographic surgery is usually the treatment of choice where margins are in doubt. Radiotherapy damages and scars the eyelid tissues and lacrimal system and should be reserved for situations when surgery is otherwise inappropriate. Cryotherapy is best avoided due to the risk of leaving residual tumour.

Squamous cell carcinomas [20]

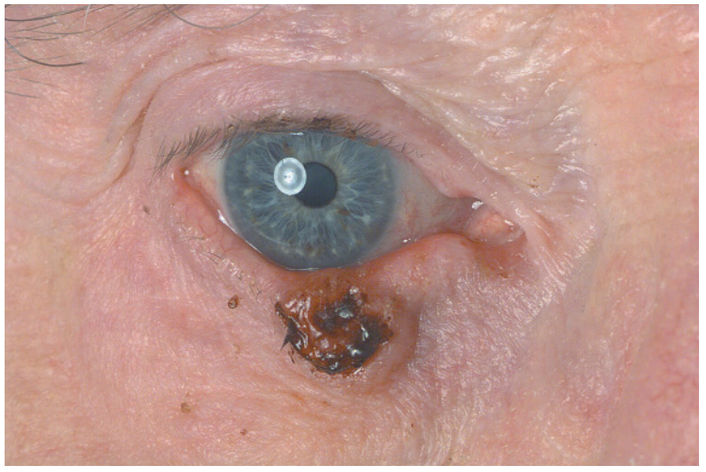
This is much less common than BCCs, accounting for between 5 and 10% of eyelid malignancies. SCCs occur on a background of marked actinic damage. They mainly affect the lower eyelid and lid margin, and may arise *de novo* or from pre-existing actinic keratoses. SCC of the eyelids may be nodular, plaque like or ulcerated (Fig. 67.17). Excision with adequate margins is the treatment of choice. Tumours greater than 2 cm in diameter and those with deep penetration have a higher risk of metastasis. Histological evidence of poor differentiation or of perineural invasion are also poor prognostic factors requiring more aggressive treatment. Mohs micrographic surgery is indicated where the initial margins are not free of tumour, and offers a good long-term prognosis. As with BCC, cryotherapy and radiotherapy are reserved for situations where surgery is inappropriate.

Malignant melanoma

This may occur on the eyelids or conjunctiva. As elsewhere, melanomas are characterized by a change in size, shape or colour of a pigmented lesion (Fig. 67.18). However, a significant proportion of lid melanomas are amelanotic and this may give rise to difficulties with clinical diagnosis.

Sebaceous gland carcinoma and epithelioma [21,22]

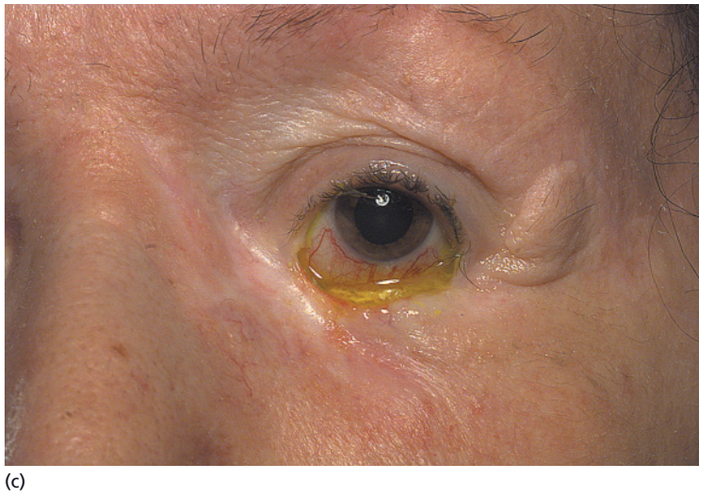
These are very rare tumours, accounting for less than 1–5% of malignant tumours of the eyelid. Sebaceous gland carcinoma usually arises from the meibomian glands, occasionally from the glands of Zeis. In contrast to BCC or SCC, the majority of lesions affect the upper lid. Most lesions are nodular and look very much like a chalazion (see Figs 67.6a,b & 67.19), causing delay in diagnosis; a sebaceous tumour should always be suspected if a 'chalazion' lasts for more than 6 months, and a 'chalazion' that recurs should be viewed with great suspicion, excised and sent for histol-



(a)



(b)



(c)

Fig. 67.16 Basal cell carcinoma (BCC). (a) Ulcerated BCC on lower lid. (b) Poorly defined BCC at medial canthus. (c) Morphoeic BCC along lower lid. (Courtesy of Mr N. Joshi, Chelsea & Westminster Hospital/Medical Illustration UK, London, UK.)



Fig. 67.17 Squamous cell carcinoma (SCC). Infiltrating ulcerated SCC on lower lid. (Courtesy of Mr N. Joshi, Chelsea & Westminster Hospital/Medical Illustration UK, London, UK.)

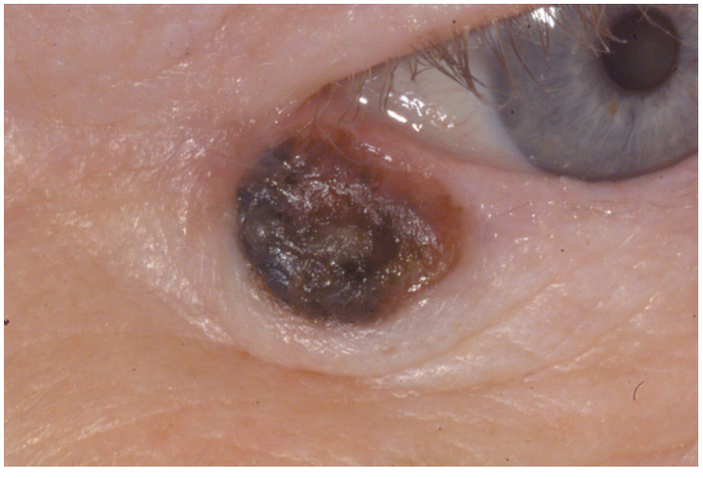


Fig. 67.18 Malignant melanoma. Irregularly pigmented lesion on lower lid. (Courtesy of Mr N. Joshi, Chelsea & Westminster Hospital/Medical Illustration UK, London, UK.)

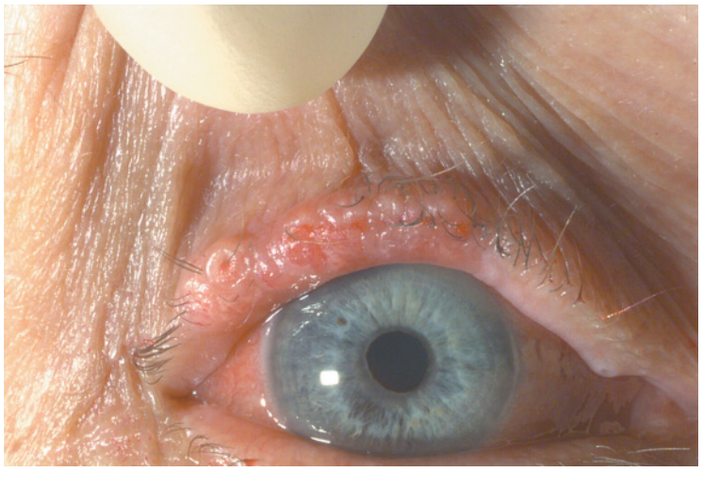


Fig. 67.19 Sebaceous gland carcinoma. Infiltrating lesion on upper lid. (Courtesy of Mr N. Joshi, Chelsea & Westminster Hospital/Medical Illustration UK, London, UK.)

ogy. Because of late diagnosis, sebaceous gland carcinoma carries a significant mortality. Wide local excision is the treatment of choice. The multicentric nature of the tumour may limit the use of Mohs surgery.

Eccrine carcinoma [23]

These are rare cancers of the eye and may present as an indurated thickening of the lid or with a signet-ring appearance. They are commonest in middle-aged or elderly men and recur after excision.

Merkel cell carcinoma

A very rare tumour. It can also mimic a chalazion in its early stages, with delay in diagnosis. It is highly malignant and has often metastasized by the time of excision.

Kaposi's sarcoma

A vascular malignancy. It presents as a purple lesion on the eyelid or conjunctiva and can be mistaken for a benign haemangioma. However, it grows rapidly and may ulcerate and bleed. When it presents on the eyelid it is associated with AIDS, of which it may be the sole manifestation at the time of presentation. These lesions are very radiosensitive, and this is the preferred mode of treatment once a biopsy has been taken to confirm the diagnosis.

References

1 Watanabe A. Serum lipids lipoprotein lipids and coronary heart disease in patients with xanthelasma palpebrarum. *Atherosclerosis* 1981; **38**: 283–90.
2 Codere F, Lee RD, Anderson RL. Necrobiotic xanthogranuloma of the eyelid. *Arch Ophthalmol* 1983; **101**: 60–3.
3 Dapling RB, Nelson ME. Ocular lesions in patients with juvenile xanthogranuloma. *Br J Dermatol* 1994; **130**: 260–1.
4 Armstrong DK, Walsh MY, Corbet JR. Multiple facial eccrine hidrocystomas—effective topical treatment with atropine. *Br J Dermatol* 1998; **139**: 558–9.
5 Coskey RJ, Liroi J, Rossini T. Diagnosis and treatment of chalazia. *J Am Acad Dermatol* 1986; **15**: 345–7.
6 Farber M, Schutzer P, Mihm MC. Pigmented lesions of the conjunctiva. *J Am Acad Dermatol* 1998; **38**: 971–8.
7 Grin JM, Grant-Kiels JM, Grin CM *et al*. Ocular melanomas and melanocytic lesions of the eye. *J Am Acad Dermatol* 1998; **38**: 716–30.
8 Patel BCK, Egon CA, Lucius RW *et al*. Cutaneous malignant melanoma and oculodermal melanocytosis (nevus of Ota): report of a case and review of the literature. *J Am Acad Dermatol* 1998; **38**: 862–5.
9 Spott D, Heaton CL, Word MG. Melanoacanthoma of the eyelid. *Arch Dermatol* 1972; **105**: 898–9.
10 Goldberg NS, Rosanova M. Periorbital haemangioma. *Dermatol Clin* 1992; **10**: 653–61.
11 Stigmar G, Crawford JS, Ward CM *et al*. Ophthalmological sequelae of infantile haemangiomas of the eyelids and orbit. *Am J Ophthalmol* 1978; **85**: 806–13.
12 Bruckner AL, Frieden IJ. Haemangiomas of infancy. *J Am Acad Dermatol* 2003; **48**: 477–93.
13 Boyd MJ, Collin JRO. Capillary haemangiomas: an approach to their management. *Br J Ophthalmol* 1991; **75**: 298–300.
14 Salasche SJ, Shore JW, Olbricht SM. Periocular tumours. *Dermatol Clin* 1992; **10**: 669–85.
15 Char DH. The management of lid and conjunctival malignancies. *Surv Ophthalmol* 1980; **24**: 679–80.
16 Tesluk GC. Eyelid lesions. Incidence and comparison of benign and malignant lesions. *Ann Ophthalmol* 1985; **17**: 704–7.
17 Anderson RL. A warning on cryosurgery for eyelid malignancies. *Arch Ophthalmol* 1978; **96**: 1289–90.

18 Mohs FE. Microscopically controlled excision of medial canthal carcinomas. *Ann Plast Surg* 1981; **7**: 308–11.
19 Mohs FE. Micrographic surgery for the microscopically controlled excision of eyelid cancers. *Arch Ophthalmol* 1986; **104**: 901–9.
20 Rosin P, Drubow LM, Rigel DJ. Squamous cell carcinoma healed by Mohs' surgery: an experience with 414 cases in a period of 15 years. *J Dermatol Surg Oncol* 1981; **7**: 800–1.
21 Rao NA, Hidyet A, McClean JW *et al*. Sebaceous carcinoma of the ocular adnexae. A clinicopathologic study of 104 cases with a 5-year follow up date. *Hum Pathol* 1982; **13**: 113–22.
22 Spencer JM, Nossa R, Tse DT, Sequerra M. Sebaceous carcinoma of the eyelid treated with Mohs' micrographic surgery. *J Am Acad Dermatol* 2001; **45**: 1004–9.
23 Ni C, Dryja TP, Albert DM. Sweat gland tumours of the eyelids. A clinicopathological analysis of 55 cases. *Int Ophthalmol Clin* 1982; **22**: 1–22.

CHAPTER 68
The External Ear

C.T.C. Kennedy
Bristol Dermatology Centre, Bristol Royal Infirmary, Bristol, UK

Anatomy and physiology, 68.1
Examination, 68.3
Developmental defects, 68.3
Ageing changes, 68.5
Traumatic conditions, 68.6
Dermatoses and the external ear, 68.14
Systemic disease and the external ear, 68.17
Infection, 68.18
Tumours of the pinna and external auditory canal, 68.28
Miscellaneous conditions, 68.35

Anatomy and physiology [1–3]

The external ear consists of the auricle, the external auditory canal and the outer layer of the tympanic membrane.

The auricle, or pinna (Fig. 68.1), is a convoluted, elastic and cartilaginous plate covered by skin which is continuous medially with the lining of the external auditory canal. Except on the non-cartilaginous lobe and at the back of the ear, the skin is bound firmly to the cartilage. The auricle is attached to the head by fibrous ligaments and three vestigial auricularis muscles. The size and general detail of the auricle can vary greatly between individuals, and may be characteristically affected in a number of congenital syndromes. In humans, the auricle is largely functionless and motionless.

The epidermis of the ear has a complex dermal–epidermal junction, a conspicuous stratum granulosum and a thick, compact stratum corneum [4]. The dermis contains abundant elastic tissue. Sebaceous glands are numerous, particularly on the tragus and lobe, and fine vellus or terminal hairs occur over the entire surface, but are especially prominent on the helix and tragus. Coarser terminal hair is seen in some men, possibly as a Y-linked and androgen-dependent inherited trait (OMIM 425500) (Fig. 68.2). Eccrine sweat glands are sparsely and irregularly distributed except in the external auditory canal, which has, instead, a large number of modified apocrine or ceruminous glands. The pinna has a variably thick fatty layer that extends between the perichondrium and the reticular dermis and that also forms the main fibrofatty core of the lobe of the ear.

The blood supply to the auricle is provided by anastomosing branches of the superficial temporal and posterior auricular arteries, which drain via posterior auricular and superficial temporal veins into the external jugular vein and via the superficial temporal, maxillary and facial veins into the internal jugular vein. Lymphatic drainage is to the superficial parotid, retroauricular and superficial cervical lymph nodes. Embryonic fusion planes and minute deficiencies in the cartilaginous portion of the external auditory canal provide potential pathways for the spread of infection and tumours.

There is a complex nerve supply to the ear involving elements of the Vth, VIIth, IXth and Xth cranial nerves as well as cervical branches of the greater and lesser auricular nerves. The back of the ear is supplied by the greater auricular nerve (C2,3), the concha by the auricular branch of the vagus (Xth) and the anterior part of the pinna and the external auditory canal by the auriculotemporal branch of the Vth cranial nerve. Intercommunicating branches of the VIIth, IXth and Xth supply the deeper parts of the ear. With this complicated nerve supply, otalgia is more commonly due to referred pain than to disease in the ear itself [4]. Within the dermis, the nerve supply is abundant, especially around hair follicles where there are complicated basket-like networks of acetylcholinesterase and butyrylcholinesterase nerve fibres [5]. Free nerve endings are also present, but there are no organized nerve endings as occur on glabrous skin elsewhere.

The external auditory canal extends upwards and backwards in an S-shaped curve from the concha to the tympanic membrane. The angle of curvature varies between races and individuals, being more marked in white people than in black people or Polynesians. This has a bearing on trauma, infection and the retention of moisture. The length of the canal is 2.5 cm as measured from the concha to drum. The outer third of the canal is cartilaginous and is lined by a thicker layer of skin than the inner portion within the temporal bone. Anteroinferiorly there are two horizontal fissures in the cartilaginous canal, the fissures of Santorini. These can allow infection or tumour to pass beyond the external auditory canal, for example to the parotid gland. Subcutaneous tissue is scanty, and the epithelium is firmly bound to the perichondrium. Sebaceous glands are plentiful, and open into the follicles of extremely fine vellus hairs. Occasionally, larger terminal hairs (tragi) arise in the canal or around the meatus and these, if they become matted with

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

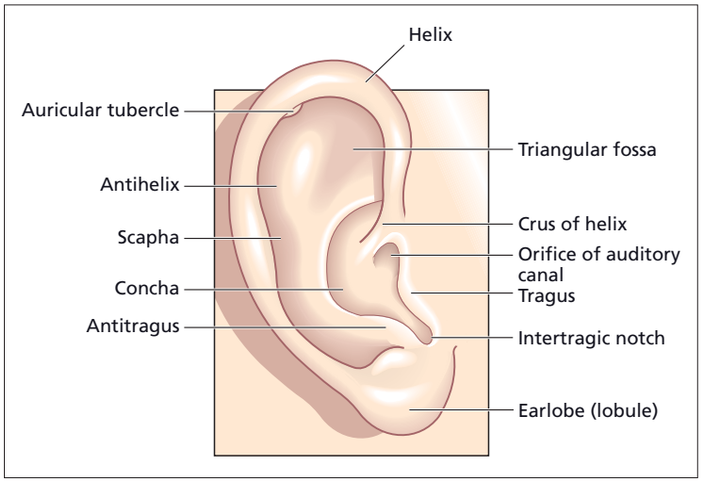


Fig. 68.1 Anatomical landmarks of the auricle.



Fig. 68.2 Coarse terminal hair on the auricle: a trait possibly associated with the Y chromosome.

wax or debris, may interfere with normal epidermal 'migration' and ventilation of the ear and hence may play a part in the development of 'hot-weather ear' (see p. 68.21).

Eccrine sweat glands are not present in the auditory canal but modified apocrine (ceruminous) glands are numerous. They increase in size and activity at puberty. There is great individual and racial variability, and although concentrated in the cartilaginous part of the canal, they may also occur, albeit sparsely, in the osseous portion.

The inner osseous part of the acoustic canal constitutes two-thirds of its total length. The skin is firmly bound to the periosteum, subcutaneous tissue being nearly absent and only 30–50 µm thick. The epidermis here is thin and easily traumatized, and rete ridges are absent [1]. The skin of the external auditory canal and tympanic membrane is unique in that there is no frictional loss of stratum corneum; cerumen (wax) and epithelial debris have therefore to be removed by a special 'migratory' property of the external ear canal epithelium [5]. A slight narrowing of the canal, the isthmus, occurs at or just medial to the junction of the two parts. When marked, it may impede the flow of cerumen to the exterior. Just medial to the isthmus, inferiorly and anteriorly, is the tympanic sulcus. Debris often collects here, especially in patients with chronic external otitis.

The surface pH of the auditory canal varies from 5.6–5.8 at the concha to 7.3–7.5 at 5–10 mm within the canal. With inflammation, the pH becomes slightly more acid.

Microbiology

The skin of the external auditory canal in most healthy individuals supports the growth of multiple bacterial species, especially *Staphylococcus epidermidis*, *Corynebacterium* spp., *Bacillus* spp. and less often *Staphylococcus aureus*. *Pseudomonas aeruginosa*, often relevant to external otitis, and fungi are not normally found [2]. The normal flora can include organisms such as *Turicella otidis*, which can cause otitis media [6].

Cerumen (wax) [7]

Cerumen is the combined product of sebaceous and apocrine glands. It contains both squalene and insoluble fatty acids. Analysis by flash pyrolysis–gas chromatography/mass spectrometry has shown numerous diterpenoids [8]. Its main function is to waterproof the external auditory canal. Extrusion is aided by mastication and by the peripheral movement and desquamation of the epithelial cells of the canal. It is impeded if the ear canal is too narrow or tortuous, or when inflammation interferes with the normal process of 'migration'.

There are genetically determined differences in cerumen composition and character: so-called 'dry' ear wax is light grey, dry and flaky; 'wet' ear wax is golden brown and sticky. The former is very common in Asians. Wax phenotype is determined by a single gene pair, the wet wax allele being dominant [7]. Cerumen darkens with exposure to air.

Although not bactericidal, cerumen does not encourage bacterial or fungal growth. It is likely that antimicrobial peptides play a role [9]; other possible reasons include the presence of lysozyme, immunoglobulins and polyunsaturated fatty acids.

Two populations have been shown to have excessive production and/or impaction of cerumen: individuals with mental retardation and the elderly [7]. An increased secretion of cerumen occurs in patients treated with aromatic retinoids [10,11].

If wax becomes impacted or adherent, it can cause various symptoms such as hearing loss, tinnitus, vertigo, pain and itching, and can be a contributory factor to external otitis. It may be removed by irrigation techniques or by suction under direct vision

[12,13]. A systematic review found no clear evidence that pharmaceutical agents have any proven value over irrigation with water [14]. It is possible that simple solutions such as 10% aqueous sodium bicarbonate or 2.5% aqueous acetic acid can be helpful in children [15]. Regular use of an emollient liquid may have a role in prevention of impaction [16]. Inflammation interferes with normal epidermal migration and tends therefore both to induce and to encourage the retention of scale. The pruritus associated with excess cerumen, and the low-grade inflammation that often accompanies this, frequently leads to a persistent form of low-grade neurodermatitis. Recently, 1% pimecrolimus has been shown to be effective when other measures have failed [17].

Contact dermatitis from medicaments or irritant cerumenolytics [18] is well recognized.

References

1 Lucente FE. Anatomy, histology and physiology. In: Lucente FE, Lawson W, Novick NL, eds. *The External Ear*. Philadelphia: Saunders, 1995: 1–17.
2 Kelly KE, Mohs DC. The external auditory canal: anatomy and physiology. *Otolaryngol Clin North Am* 1996; **29**: 725–9.
3 Montagna W, Giacometti L. Histology and cytochemistry of human skin. XXXII. The external ear. *Arch Dermatol* 1969; **99**: 757–67.
4 Al-Sheikhli ARJ. Pain in the ear: with special reference to referred pain. *J Laryngol Otol* 1980; **94**: 1433–40.
5 Alberti PWRM. Epithelial migration on the tympanic membrane. *J Laryngol Otol* 1964; **78**: 808–30.
6 Stroman DW, Roland PS, Dohar J, Burt W. Microbiology of normal external auditory canal. *Laryngoscope* 2001; **111**: 2054–9.
7 Roeser RJ, Ballachanda BB. Physiology, pathophysiology, and anthropology/epidemiology of human ear canal secretions. *J Am Acad Audiol* 1997; **8**: 391–400.
8 Burkhart CN, Kruge MA, Burkhart CG, Black C. Cerumen composition by flash pyrolysis–gas chromatography/mass spectrometry. *Otol Neurotol* 2001; **22**: 715–22.
9 Stoeckelhuber M, Matthias C, Andratschke M, *et al*. Human ceruminous gland: ultrastructure and histochemical analysis of antimicrobial and cytoskeletal components. *Anat Rec* 2006; **288**: 877–84.
10 Burge SM, Wilkinson JD, Miller AJ *et al*. The efficacy of an aromatic retinoid, Tigason, in the treatment of Darier's disease. *Br J Dermatol* 1981; **104**: 675–9.
11 Kramer M. Excessive cerumen production due to the aromatic retinoid Tigason in a patient with Darier's disease. *Acta Derm Venereol (Stockh)* 1981; **62**: 267–8.
12 Grossan M. Cerumen removal: current challenges. *Ear Nose Throat J* 1998; **77**: 541–8.
13 Browning G. Ear wax. *Clin Evid* 2005; **14**: 650–8.
14 Burton MJ, Doree CJ. Ear drops for the removal of ear wax. *Cochrane Database Syst Rev* 2003; CD004400.
15 Carr MM, Smith RL. Ceruminolytic efficacy in adults versus children. *J Otolaryngol* 2001; **30**: 154–6.
16 Saloranta K, Westermarck T. Prevention of cerumen impaction by treatment of ear canal skin. A pilot randomized controlled study. *Clin Otolaryngol* 2005; **30**: 112–4.
17 Djalilian HR, Memar O. Topical pimecrolimus 1% for the treatment of pruritic external auditory canals. *Laryngoscope* 2006; **116**: 1809–12.
18 Holmes RC, Johns AN, Wilkinson JD *et al*. Medicament contact dermatitis in patients with chronic inflammatory ear disease. *J R Soc Med* 1982; **75**: 27–30.

Examination [1]

As well as examining the pinna, the dermatologist may need to examine the ear canal. Equipment available should include a headlight or equivalent, otoscope, several sizes of ear speculae, ear curettes, metal applicators, bayonet forceps, ear irrigation apparatus and cotton.

General inspection of the auricles should take account of their symmetry, size, shape and position, and completeness of development.

The ear canal is best inspected when the auricle is pulled gently upwards, outwards and backwards, and the largest possible speculum is used. It is essential to avoid traumatizing the thin skin of the canal, particularly beyond the isthmus. If inspection reveals accumulation of cerumenous debris, this can sometimes be removed carefully using a curette or wire loop along the posterior wall. If the material is against the drum, gentle suction may be feasible. Irrigation should only be used if the drum is known to be intact.

Samples may need to be taken for bacteriology, mycology and histology. If a biopsy is required from the canal, this should be devolved to a surgeon with the necessary expertise.

Reference

1 Lucente FE. Techniques of examination. In: Lucente FE, Lawson W, Novick NL, eds. *The External Ear*. Philadelphia: Saunders, 1995: 18–24.

Developmental defects

The auricle begins to develop at the end of the fifth week of embryonic life in the first branchial groove, contributed to by the first (mandibular) and second (hyoid) arches [1]. Six hillocks appear on these arches and later fuse to form the complex shape of the fully developed auricle. Inspection of the external ear at birth is important in the overall assessment of the neonate but interpretation can be complicated by the effects of birth trauma [2].

Developmental defects are considered in detail in Chapter 18. Only those defects of the ear sufficiently common to constitute a part of general dermatological practice are therefore considered here, together with some general principles relating to congenital ear abnormalities and their more important medical and otological associations [3–7]. Pinna abnormalities are associated sufficiently often with conductive hearing loss that screening tests should be carried out [8].

About 30% of infants with external ear anomalies have a renal anomaly identifiable by ultrasound examination, and this combination is a strong pointer towards a multiple congenital anomaly syndrome, in particular Townes–Brocks, CHARGE, branchio-oto-renal, Nager and diabetic embryopathy syndromes [9].

Many developmental defects are of unknown aetiology. Some, however, are associated with chromosomal abnormalities, for example those occurring in Down's syndrome, or are associated with syndromes that have well-recognized Mendelian inheritance patterns, for example the *e*ctrodactyly, *e*ctodermal dysplasia and *c*left lip–palate (EEC) syndrome. Environmental factors may be implicated as in fetal alcohol syndrome and fetal hydantoin syndrome, and maternal exposure to isotretinoin and thalidomide.

Congenital ear abnormalities exhibit great variability, even within syndromes or families, and any one aetiological factor may be associated with a variety of ear malformations. External ear malformations as part of a genetic syndrome account for less than 10% of all external ear abnormalities; isolated cases of ear malformation may either be non-genetic in origin or may have a genetic basis but with poor gene penetrance [10].

Microtia (small ears) [11]

Microtia designates a spectrum of underdevelopment of the pinna, from small ears to absence of an ear or ears. Small ears are often associated with hearing deficit and may be a feature of many syndromes. In addition to being small, the pinna may be rudimentary, resembling the hillocks from which it is embryologically derived. The more primitive the appearance, the greater the likelihood of hearing abnormalities, in most cases due to defects or atresia of the ossicles. There may also be a narrowing or atresia of the auditory canal [10–13] and various abnormalities of the middle ear [14] and inner ear [6]. A wide variety of non-aural abnormalities are associated with small ears, multiple malformations occurring in 56% in one large series [15]. Small ears are a feature of many syndromes, including Down's syndrome, Treacher Collins syndrome, Goldenhar's syndrome, Apert's syndrome, various first and second branchial arch and first branchial cleft syndromes, Mohr's orofaciodigital syndrome, Duane's retraction syndrome and thalidomide embryopathy [6,7,16].

Familial microtia inherited as an autosomal dominant trait has been described [17]. Microtia is one of the birth defects that occurs more on the right than the left side [18].

Macrotia (large ears)

Macrotia is a developmental variation in which the amount of tissue between the helix and antihelix is increased, causing the ears to wing out. The ear may also be diffusely enlarged, or elongated. Such changes are common in Turner's syndrome, and there may be associated sensorineural deafness. Large ears are well described in fragile X syndrome [19] and Kabuki's syndrome, although in the latter they may also be smaller than normal [20]. Generally enlarged ears are sometimes seen in patients with the XXXXY chromosome defect. The cartilaginous parts of the ears are enlarged and soft in Laband's syndrome [21,22]. In this rare disorder the ears are large and floppy, in association with a bulbous soft nose, gingival fibromatosis and a variety of other findings including absence or dysplasia of nails and/or of terminal phalanges, hyperextensibility of joints, hepatosplenomegaly, and rarely hypertrichosis and mental retardation.

Low-set ears

Normally, the top of the helix is at the same level as the eyebrow, the earlobe is above the angle of the mandible and the external auditory meatus is at the level of the ala nasi. Low-set ears may in addition be posteriorly rotated, and are often small. The condition is usually bilateral. Although it may be isolated, it is often associated with major middle-ear or systemic malformations, appearing for example in Turner's, Noonan's, Patau's and Crouzon's syndromes.

Periauricular anomalies

Pre-auricular pits, sinuses (Fig. 68.3) and tags are relatively common, with an incidence of approximately 1% [10,23]. Lesions on or near the tragus are probably best termed 'accessory tragus' [24]. The term 'accessory auricle' is sometimes used for this, and for similar firm elevations of skin and cartilage just near the ascending crus of the helix. They may be single or multiple, and may occur anywhere in a line from the tragus to the angle of the mouth. Accessory auricles, congenital fistulae and other external ear manifestations may occur alone or may be associated with more widespread first and second branchial arch abnormalities, for example Treacher Collins and Goldenhar's syndromes [4,5,9,23], or with developmental abnormalities of the genitourinary tract [9,23], as well as with isolated hearing defects. Because of the association with renal abnormalities, it has been recommended that a renal ultrasound scan should be performed if there is a pre-auricular pit or sinus associated with one or more of the following: another malformation or dysmorphic feature, a family history of deafness, auricular and/or renal malformations, or a maternal history of gestational diabetes [25].



Fig. 68.3 Pre-auricular sinus.

Variations in the shape of the pinna

Minor variations in size and shape are common and not usually associated with any other abnormality. These include *bat ear* or protruding ear, in which the antihelix lacks the usual bulge; *lop ear*, in which there is an unrolled helix, a poorly developed antihelix and scapha, and a large concha resulting in a somewhat floppy ear; and *prominent auricular* (*Darwin's*) *tubercle.* Variations in the contour of the helix and antihelix to produce a bulge of the anterosuperior part of the pinna account for so-called *Mozart's ear*, and in *Wildemuth's ear* the antihelix is prominent and the formation of the helix is poor. These minor ear anomalies can be a syndromic feature or can be associated with conductive and occasionally sensorineural hearing loss, but in most instances they are isolated. They may, however, be inherited, as in the Mozart family. A distinctive *railroad track abnormality* with marked prominence of the crus of the helix is said to occur in up to 30% of children with fetal

alcohol syndrome [12,16] and a protruding auricle may, rarely, be a sign of neuromuscular disease [26]. Various abnormalities of the configuration of the pinna have been described in the distinctive *lumpy scalp syndrome* [27], in which other features include absent or rudimentary nipples and dermal nodules on the scalp [28]. The lobule can show isolated abnormalities, for example pits and clefts. Absence of the lobule is, however, usually associated with a syndrome of a more serious nature [7]. Diagonal linear creases in the lobule are seen in Beckwith–Wiedemann syndrome, and in adult life in association with some degenerative diseases (see p. 68.6), although they are also a common finding in normal individuals.

Developmental anomalies of ear hair

Hypertrichosis of the pinnae (OMIM 425500) was originally described as a Y chromosome-linked trait [29]. An autosomal dominant genetic basis for hairy ears has also been noted in South Indians [30] and Maltese [31]. Acquired hairy ears have been described in infants born of diabetic mothers [32,33] and in association with human immunodeficiency virus (HIV) infection [34].

Management [11,35]

The infant with obvious malformation of the pinna that might have auditory system or other associations should be assessed by a paediatrician. The history may reveal exposure to a teratogen (e.g. isotretinoin) or family history of a syndrome and examination may show evidence of other anomalies. Investigations may include radiological evaluation [36], an auditory brainstem evoked response hearing test and a renal ultrasound. It may be appropriate for an ear, nose and throat (ENT) specialist and plastic surgeon [37,38] to become involved with correction of complications and the physical deformity, respectively.

References

1 Bowden REM. Development of the middle and external ear in man. *Proc R Soc Med* 1977; **70**: 807–15.
2 Spilman L. Examination of the external ear. *Adv Neonatal Care* 2002; **2**: 72–80.
3 Anson BJ, Donaldson JA, eds. Clinical significance of developmental anatomy. In: *Surgical Anatomy of the Temporal Bone and Ear, Part II. The Ear: Developmental Anatomy*, 2nd edn. Philadelphia: Saunders, 1973: 17–50.
4 Bellucci RJ. Congenital aural malformations: diagnosis and treatment. Symposium on Congenital Disorders in Otolaryngology. *Otolaryngol Clin North Am* 1981; **14**: 95–124.
5 Melnick M. The etiology of external ear malformations and its relation to abnormalities of the middle ear, inner ear, and other organ systems. *Birth Defects* 1980; **16**: 303–31.
6 Bergstrom LB. Anomalies of the ear. In: English GM, ed. *Otolaryngology*, Vol. 1. Philadelphia: Lippincott, 1990: 1–35.
7 Sakashita T, Sando I, Kamerer DB. Congenital anomalies of the external and middle ears. In: Bluestone CD, Stool SE, Kenna MA, eds. *Pediatric Otolaryngology*, 3rd edn. Philadelphia: Saunders, 1996: 333–70.
8 Jaffe BF. Pinna anomalies associated with congenital conductive hearing loss. *Pediatrics* 1976; **57**: 332–41.
9 Wang RY, Earl DL, Ruder RO, Graham JM. Syndromic ear anomalies and renal ultrasounds. *Pediatrics* 2001; **108**: E32.
10 Melnick M, Myrianthopoulos NC. External ear malformations: epidemiology, genetics and natural history. *Birth Defects* 1979; **15**: 1–139.
11 Kelley PE, Scholes MA. Microtia and congenital aural atresia. *Otolaryngol Clin North Am* 2007; **40**: 61–80.
12 Jahrsdoerfer RA. Congenital atresia of the ear. *Laryngoscope* 1978; **88** (Suppl. 13): 1–48.
13 Okajima H, Takeichi Y, Umeda K, Baba S. Clinical analysis of 592 patients with microtia. *Acta Otolaryngol (Stockh)* 1996; **525**: 18–24.
14 Kountakis SE, Helidonis E, Oahrsdoerfer RA. Microtia grade as an indicator of middle ear development in aural atresia. *Arch Otolaryngol Head Neck Surg* 1995; **121**: 885–6.
15 Jafek BW, Nager GT, Stife J *et al.* Congenital aural atresia: an analysis of 311 cases. *Trans Am Acad Ophthalmol Otolaryngol* 1975; **80**: 588–95.
16 Aase JM. Microtia: clinical observations. *Birth Defects* 1980; **16**: 289–97.
17 Balci S, Boduroglu K, Kaya S. Familial microtia in four generations with variable expressivity and incomplete penetrance in association with type I syndactyly. *Turkish J Pediatr* 2001; **43**: 362–5.
18 Paulozzi LJ, Lary JM. Laterality patterns in infants with external birth defects. *Teratology* 1999; **60**: 265–71.
19 Loesch DZ, Sampson ML. Effect of the fragile X anomaly on body proportions estimated by pedigree analysis. *Clin Genet* 1993; **44**: 82–8.
20 Fong C-T, Wang M, Young EC *et al.* Microtia associated with the Kabuki (Niikawa–Kuraki) syndrome. *Otolaryngol Head Neck Surg* 2001; **125**: 557–8.
21 Laband PF, Habib G, Humphreys GC. Hereditary gingival fibromatosis. Report of an affected family with associated splenomegaly and soft tissue abnormalities. *Oral Surg Oral Med Oral Pathol* 1964; **17**: 339–51.
22 Bazopoulou-Kyrkanidou E, Papagianoulis L, Papanicolaou S, Mavrou A. Laband syndrome: a case report. *J Otol Pathol Med* 1990; **19**: 385–7.
23 Melnick M. Hereditary hearing loss and ear dysplasia–renal adysplasia syndromes: syndrome delineation and possible pathogenesis. *Birth Defects* 1980; **16**: 59–72.
24 Jansen T, Romiti R, Altmeyer MD. Accessory tragus: report of two cases and review of the literature. *Pediatr Dermatol* 2000; **17**: 391–4.
25 Scheinfeld NS, Silverberg NB, Weinberg JM, Nozad V. The preauricular sinus: a review of its clinical presentation, treatment, and associations. *Pediatr Dermatol* 2004; **21**: 191–6.
26 Smith DW, Takashima H. Protruding auricle: a neuromuscular sign. *Lancet* 1978; **i**: 747–9.
27 Steinberg RD, Ethington J, Esterly NB. Lumpy scalp syndrome. *Int J Dermatol* 1990; **29**: 657–8.
28 Finlay AY, Marks R. An hereditary syndrome of lumpy scalp, odd ears and rudimentary nipples. *Br J Dermatol* 1978; **99**: 423–30.
29 Dronamrajn KR. Hypertrichosis of the pinnae of the human ear, Y-linked pedigrees. *J Genet* 1961; **51**: 230–43.
30 Kamalan A, Thambiah AS. Genetics of hairy ears in South Indians. *Clin Exp Dermatol* 1990; **15**: 192–4.
31 Ruggles Gates R, Vella F. Hairy pinnae in Malta. *Lancet* 1962; **ii**: 357.
32 Woods DL, Malan AF, Coetzee EJ. Intra-uterine growth in infants of diabetic mothers. *S Afr Med J* 1980; **58**: 441–3.
33 Rafaat M. Hypertrichosis pinnae in babies of diabetic mothers. *Pediatrics* 1981; **68**: 745–6.
34 Tosti A, Gaddoni G, Peluso AM *et al.* Acquired hairy pinnae in a patient infected with the human immunodeficiency virus. *J Am Acad Dermatol* 1993; **28**: 513.
35 Eavey RD. Ear malformations. What a pediatrician can do to assist with auricular reconstruction. *Pediatr Otolaryngol* 1996; **43**: 1233–43.
36 Calzolari F, Garani G, Sensi A, Martini A. Clinical and radiological evaluation in children with microtia. *Br J Audiol* 1999; **33**: 303–12.
37 Meyer R, de Goumoens R, Derder S. Combined aesthetic and functional treatment of microtia. *Aesthetic Plast Surg* 1997; **21**: 159–67.
38 Aguilar EF. Auricular reconstruction in congenital anomalies of the ear. *Facial Plast Surg Clin North Am* 2001; **9**: 159–69.

Ageing changes

Many changes seen on the skin of the pinna attributed to ageing are a result of its exposure to environmental factors, especially UV radiation, cold (perniosis) and infrared radiation. The elderly exposed pinna often shows varying degrees of dermal and epidermal atrophy, solar keratoses and lentigines, solar elastosis, telangiectasia and venous lakes. If the pinna is at least partially

light-protected, as in many women, the skin may still appear somewhat thinned due to intrinsic ageing changes.

Ear length

It is recognized in Chinese culture that length of the ear in men is a predictor for longevity [1]. Two studies would appear to confirm this: one from Kent, UK [2], and one from Japan [3]. The increase in length of the male ear from the age of 30 years onwards may have a 7-year periodicity [4].

Earlobe creases

First described in 1973 [5], and now known as Frank's sign, a diagonal crease in the earlobes of adults has been associated in many studies with an increased risk for atherosclerotic coronary artery disease. A meta-analysis in 1983 gave a relative risk of 2.06 for heart disease if there are bilateral creases [6] and there is approximately double the risk for death from heart disease [7,8]. The crease can be graded in terms of length and depth, and deeper, longer creases have the strongest association. The ear crease appears to be separate from other risk factors for coronary artery disease, and is not simply a function of age [9]. A more recent case–control series suggested a relative risk of 1.37 for myocardial infarction [10]. The positive predictive value of the diagonal ear crease sign remains controversial: in one series of patients from London it was only 16% [11] whereas in another from Turkey it was 89% [12]. It is probably of greater significance in people under age 40 years [13].

Diagonal earlobe creases are seen in other contexts, for example Beckwith–Wiedemann syndrome [14] (Fig. 68.4), and do not seem to be associated with coronary artery disease in Hawaiians [15], native Americans [16] or Chinese [17].

Earlobe creases have also been associated with primary open-angle glaucoma [18].

References

1 Woo Pick-Ngor, Lip Peck-Lin. Why do old men have big ears? *BMJ* 1996; **312**: 586.
2 Heathcote JA. Why do old men have big ears? *BMJ* 1996; **311**: 1668.
3 Asai Y, Yoshimura M, Nago N, Yamada T. Correlation of ear length with age in Japan. *BMJ* 1996; **312**: 582.
4 Verhulst J, Onghena P. Circaseptennial rhythm in ear growth. *BMJ* 1996; **313**: 1597–8.
5 Frank ST. Aural sign of coronary artery disease. *N Engl J Med* 1973; **289**: 327–8.
6 Elliott WJ. Earlobe crease and coronary artery disease: 1000 patients and review of the literature. *Am J Med* 1983; **75**: 1024–32.
7 Kirkham N, Murrells T, Melcher DH, Morrison EA. Diagonal earlobe creases and fatal cardiovascular disease: a necropsy study. *Br Heart J* 1989; **61**: 361–4.
8 Patel V, Champ C, Andrews PS *et al.* Diagonal earlobe creases and atheromatous disease: a post mortem study. *J R Coll Physicians Lond* 1992; **26**: 274–7.
9 Tranchesi B, Barbosa V, de Albuquerque CP *et al.* Diagonal earlobe creases as a marker of the presence and extent of coronary atherosclerosis. *Am J Cardiol* 1992; **70**: 1417–20.
10 Miric D, Fabijanic D, Giunio L *et al.* Dermatological indicators of coronary risk: a case–control study. *Int J Cardiol* 1998; **67**: 251–5.
11 Motamed M, Pelekoudas N. The predictive value of diagonal ear-lobe crease sign. *Int J Clin Pract* 1998; **52**: 305–6.
12 Evrengul H, Dursunoglu D, Kaftan A *et al.* Bilateral diagonal earlobe crease and coronary artery disease: a significant association. *Dermatology* 2004; **209**: 271–5.
13 Edston E. The earlobe crease, coronary artery disease, and sudden cardiac death: an autopsy study of 520 individuals. *Am J Forensic Med Pathol* 2006; **27**: 129–33.
14 Wiedemann HR. Earlobe creases, congenital and acquired. *N Engl J Med* 1979; **301**: 111.
15 Rhoads GG, Klein K, Yano K, Preston H. The earlobe crease sign of obesity in middle-aged Japanese men. *Hawaii Med J* 1977; **36**: 74–7.
16 Fisher JR, Sievers ML. Earlobe crease in American Indians. *Ann Intern Med* 1980; **93**: 512.
17 Cheng TO. Diagonal earlobe creases. *J R Coll Physicians Lond* 1992; **26**: 460.
18 Hawksworth NR. Diagonal earlobe creases: an association with primary open angle glaucoma. *J R Coll Physicians Lond* 1992; **26**: 459–60.



Fig. 68.4 Diagonal earlobe crease in an infant with Beckwith–Wiedemann syndrome.

Traumatic conditions

Contusion and haematoma

Bruises of the ear are usually due to blunt trauma and are common in contact sports, such as boxing, wrestling and rugby. In children, physical abuse may need to be excluded [1,2]. A distinctive condition known as *tin ear syndrome* has been considered pathognomonic of child abuse: a triad of isolated ear bruising, haemorrhagic retinopathy and a small, ipsilateral subdural haematoma [3].

Following trauma, blood and serum collects in the plane between perichondrium and cartilage, and will undergo fibrosis if not removed early. The patient should be carefully examined for concurrent auditory canal, middle ear, parotid and central nervous system trauma.

Repeated trauma may result in the distorted nodular deformity known as *cauliflower ear*, which is due to varying degrees of cartilage necrosis, fibrosis and dystrophic calcification.

Treatment. Subperichondrial haematomas must be treated promptly, with full aseptic technique to avoid secondary perichondritis. Small collections of fluid can sometimes be aspirated by syringe, but usually need to be drained through a small incision and a laterally placed pressure dressing applied to prevent reaccumulation [4,5]. Another useful technique is to use a through-and-through suture technique to maintain bolsters over the area where the haematoma has been evacuated [6]. Other approaches include a posterior incision and suction drainage [7], or fenestrations in the cartilage to promote adhesion of the opposing perichondrial layers [8]. Prophylactic antibiotics are sometimes given.

Improvement of cauliflower ear usually requires multiple corrective procedures.

References

1 Manning SC, Casselbrant M, Lammers D. Otolaryngolic manifestations of child abuse. *Int J Pediatr Otorhinolaryngol* 1990; **20**: 7–16.
2 Willner A, Ledereich PS, de Vries EJ. Auricular injury as a presentation of child abuse. *Arch Otolaryngol Head Neck Surg* 1992; **118**: 634–7.
3 Hanigan WC, Peterson RA, Njus G. Tin ear syndrome: rotational acceleration in pediatric head injuries. *Pediatrics* 1987; **80**: 618–22.
4 Germon WH. The care and management of acute haematoma of the external ear. *Laryngoscope* 1980; **90**: 881–5.
5 Lee D, Sperling N. Initial management of auricular trauma. *Am Fam Physician* 1996; **53**: 2339–44.
6 Schuller DE, Dankle SD, Strauss RH. A technique to treat wrestler's auricular hematoma without interrupting training or competition. *Arch Otolaryngol Head Neck Surg* 1989; **115**: 202–6.
7 Bull PD, Lancer JM. Treatment of auricular haematoma by suction drainage. *Clin Otolaryngol* 1984; **9**: 355–60.
8 Tenta LT, Keyes GR. Reconstructive surgery of the external ear. *Otolaryngol Clin North Am* 1981; **14**: 917–38.

Laceration and avulsion

Lacerations of the pinna vary from the trivial to amputation [1]. Because of the risk of cartilage infection, potentially dirty wounds should always be carefully cleaned and a course of prophylactic antibiotic given. It is probably best to avoid suturing the cartilage itself unless pieces overlap or are severely displaced [2]. Injuries that expose cartilage will need to be covered with a skin graft, for example taken from behind the ear or the upper eyelid. If the anterior perichondrium is destroyed, cartilage may need to be excised so that the graft can be placed on the posterior perichondrium. If the post-auricular area is not injured, a pedicled island flap of post-auricular skin may be pulled through the area of excised cartilage and sutured into place. If the helix or antihelix is exposed, it may be possible to cover it with an advancement or rotation flap from the posterior surface of the auricle. Large areas may need to be covered with a pedicled flap of temporoparietal fascia, which in turn is covered with a split-skin graft. The lobule of the ear can be repaired by direct closure, although a cosmetically superior result may be obtained by a broken line repair or Z-plasty [3]. Many techniques have been described for repair of major trauma, including even complete avulsion of the pinna [1,4,5], but these are likely to be beyond the scope of the dermatologist. Following total ear replantation there is lack of cutaneous sensation and this may explain the cold intolerance that can occur [6].

References

1 Templer J, Renner GJ. Injuries of the external ear. *Otolaryngol Clin North Am* 1990; **23**: 1003–18.
2 Mladick RA. Salvage of the ear in acute trauma. *Clin Plast Surg* 1978; **5**: 427–35.
3 Walike J, Larrabee WF. Repair of the cleft earlobe. *Laryngoscope* 1985; **95**: 876–7.
4 Lawson W. Management of acute trauma. In: Lucente FE, Lawson W, Norvick NL, eds. *The External Ear*. Philadelphia: Saunders, 1996: 177–82.
5 Kind GM, Buncke GM. Total ear replantation. *Plast Reconstr Surg* 1997; **99**: 1858–67.
6 Finical SJ, Keller KM, Lovett JE. Postoperative ramifications of total ear replantation. *Ann Plast Surg* 1998; **41**: 667–70.

Dermatitis artefacta

The ear is occasionally the sole site for self-mutilation and there may be underlying psychodynamic reasons for this [1].

Reference

1 Paar GH. Excerpt from the treatment of a patient with otitis externa artefacta. *Psychother Psychosom* 1994; **62**: 135–9.

Ear piercing

Earrings have been worn by men and women since antiquity, and tend to follow the dictates of fashion. Current trends include using rings or studs in almost all parts of the body, the use of up to 10 or more in a single ear, and the piercing of cartilage. Body piercings other than earlobes represent a marker for risky behaviour [1–3].

Complications of ear piercing are very common, with rates of about 30% whether the procedure is carried out by medical personnel, friend or relative, or in a store; they are also independent of technique, there being little difference in frequency of complications from piercing by needle, staple gun or sharpened stud [4]. Minor infection is the most common adverse effect, with contact dermatitis, keloid and traumatic tear occurring less often [5]; other consequences occur occasionally. Although case series indicate that so-called 'high' ear piercing, that is through cartilage, has a significant risk for perichondritis [6,7] and chondritis [8], such events were not found in a population study of 1000 nurses [5]. Embedding of the earring seems to be a common problem in children [9].

The ear is also pierced in acupuncture as used in traditional medicine, and complications have been reported [10,11].

Complications. Various infections and reactions may occur after ear piercing.

Bacterial infection, usually with Gram-positive cocci, is common; predisposing factors include skin disease, such as atopic or contact dermatitis. Life-threatening septicaemia has been described [12]. Infants with unsuspected immunodeficiency and individuals with valvular heart disease may be at particular risk [13]. When cartilage is pierced the usual bacterial infection is with *Ps. aeruginosa*, which causes perichondritis [6] or chondritis [8], and for which the best treatment is ciprofloxacin [7]. Any purulent material should be cultured, since other pathogens have been described (e.g. *Lactobacillus* [14]). There is a report of pyogenic spondylitis [15]. Primary tuberculosis has been described [16].

Viral hepatitis may also be a hazard [17,18].

Oedema and haematoma [1,19] usually respond to cold compresses, pressure and removal of the earring. Haematoma may require incision and drainage [20].

Trauma can occur from pressure on the lobe and post-auricular skin, or from inaccurate insertion of the post of the earring. Heavy earrings can tear the earlobe, sometimes making it bifid. Repair of the latter is probably best by excision of the cleft and simple closure with eversion of the edges [21], although a staggered repair such as a Z-plasty may be appropriate in some cases.

Sensitization to nickel from earrings remains a major problem, and ear piercing is one explanation for the higher incidence of nickel allergy in females [22]. Even stainless steel studs and clasps, which can produce irritant as well as allergic effects, may release sufficient nickel to elicit contact dermatitis [23]. Gold sensitization, although less common [24], can be a protracted cause of dermatitis even after the earrings are removed [25]. Contact dermatitis from

other materials used in earrings, such as olive wood [26], copper [27], cobalt [28,29] and chromium [30], has been described, and may also occur from the use of topical antiseptics, antibiotics and dressings used to treat infection. When nickel in ear piercings has been banned, as in Denmark in 1992, there has been a substantial fall in nickel sensitization [31].

Granulomatous and lymphoid reactions. Reddish brown and purple papules and nodules at sites of ear piercing may denote a granulomatous response to gold [32,33] and a lymphocytoma cutis-like reaction has been described [34–36]. Similar reactions have been associated with palladium [37] and titanium [38]. Sarcoidosis has presented after ear piercing [39,40].

Embedded earrings. The spring-loaded gun method of ear piercing can result in the earring backing becoming embedded in the back of the ear [41]. The 'vanishing earring' [42] can resemble a keloid [43]. The embedded metal can usually be pulled out, or if necessary an incision can be made to locate it.

Epidermoid cyst formation. Implantation epidermoid cysts due to ear piercing often present as tender, chronic, inflammatory swellings, sometimes with drainage. There is usually an epithelial lined track as well as cysts, and all epithelial tissue must be removed, for example with a skin punch [44].

Keloids quite commonly follow ear piercing, especially in those ethnic groups with a predisposition (Fig. 68.5). Piercing before the age of 11 years is more likely to be followed by keloid than after that age [45]. The keloids seem to occur more on the back surface than the front of the earlobe [46]. As well as being unsightly, they can itch and be painful.

Treatment options include intralesional steroid, pressure [47], excision alone [48], with or without concurrent use of intralesional steroid [49] and radiotherapy (see Chapter 79) [50]. Combinations of these methods are often advocated [51,52]. Prospective, controlled trials are needed to assess these approaches. A relatively simple and safe method which has shown efficacy and acceptability is injection of intralesional steroid followed by Zimmer splints which can be decorated to look like earrings [53].

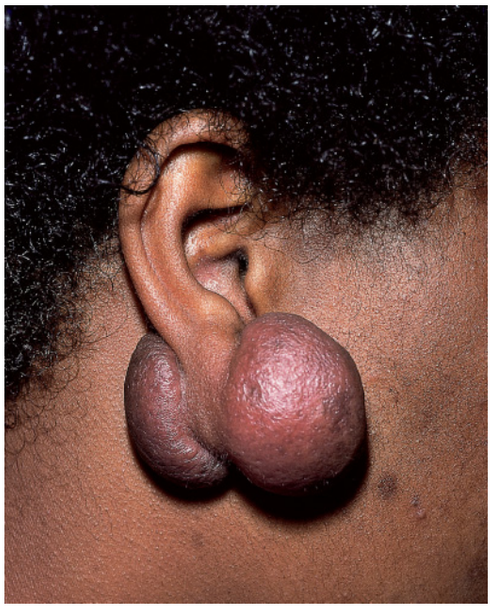


Fig. 68.5 Keloids following ear piercing.

Localized argyria. Bluish macules have been described on the posterior surface of the earlobe [54,55].

Frostbite has followed the use of ethyl chloride topical anaesthesia [56].

Systemic disease. A case of severe relapsing polychondritis following ear piercing has been reported [57].

Measures to prevent complications [58]. Many of the complications of ear piercing are avoidable. The procedure is best not carried out on children, or in those with immunodeficiency, valvular heart disease or sarcoidosis, and there is clearly a risk if the individual has a tendency to keloid formation. For a dermatologist who wishes to pierce ears or instruct others, a simple method with a low likelihood of complications has been described [59]. The use of a surgical-grade, stainless steel, one-piece earring with an interlocking groove has been recommended. Gold-plated or gold-alloy earrings should be avoided for at least 6 weeks after the ear has been pierced. Sterile technique is important. Piercing of cartilage should be avoided. Only nickel-free earrings should be used. Large or heavy earrings should be removed prior to activities that may result in tearing the earlobes. A technique using a piece of intravenous catheter to avoid reactions in metal-sensitive individuals has been described [60].

References

1 Deschesnes M, Fines P, Demers S. Are tattooing and body piercing indicators of risk-taking behaviours among high school students? *J Adolesc* 2006; **29**: 379–93.
2 Laumann AE, Derick AJ. Tattoos and body piercings in the United States: a national data set. *J Am Acad Dermatol* 2006; **55**: 413–21.
3 Suris JC, Jeannin A, Chossis I, Michaud PA. Piercing among adolescents: Body art as risk marker: A population-based survey. *J Fam Pract* 2007; **56**: 126–30.
4 Biggar RJ, Haughie GE. Medical problems of ear piercing. *N Y State J Med* 1975; **75**: 1460–2.
5 Simplot TC, Hoffman HT. Comparison between cartilage and soft tissue ear piercing complications. *Am J Otol* 1998; **19**: 305–10.
6 Cumberworth VL, Hogarth TB. Hazards of ear-piercing procedures which traverse cartilage: a report of *Pseudomonas* perichondritis and review of other complications. *Br J Clin Pract* 1990; **44**: 512–3.
7 Hanif J, Frosh A, Marnane C *et al*. 'High' ear piercing and the rising incidence of perichondritis of the pinna. *BMJ* 2001; **322**: 906–7.
8 Turkeltaub SH, Habal MB. Acute *Pseudomonas* chondritis as a sequel to ear piercing. *Ann Plast Surg* 1990; **24**: 279–82.
9 Macgregor DM. The risks of ear piercing in children. *Scott Med J* 2001; **46**: 9–10.
10 Allison G, Kravitz E. Auricular chondritis secondary to acupuncture. *N Engl J Med* 1975; **293**: 780.
11 Davis O, Powell M. Auricular perichondritis secondary to acupuncture. *Arch Otolaryngol* 1985; **111**: 770–1.
12 Lovejoy FH Jr, Smith DH. Life-threatening staphylococcal disease following ear piercing. *Pediatrics* 1970; **46**: 301–3.
13 Kovarik A, Setina M, Sulda M *et al*. Infective endocarditis of the tricuspid valve caused by *Staphylococcus aureus* after ear piercing. *Scand J Infect Dis* 2007; **39**: 266–8.
14 Razavi B, Schilling M. Chondritis attributable to *Lactobacillus* after ear piercing. *Diagn Microbiol Infect Dis* 2000; **37**: 75–6.

15 Sewnath M, Faber T, Castelein R. Pyogenic spondylitis as a complication of ear piercing: differentiating between spondylitis and discitis. *Acta Orthop Belg* 2007; **73**: 128–32.
16 Morgan LG. Primary tuberculosis inoculation of an earlobe: report of an unusual case and review of the literature. *J Pediatr* 1952; **40**: 482–5.
17 Van Sciver AE. Hepatitis from ear piercing. *JAMA* 1969; **207**: 2285.
18 Johnson CJ, Anderson H, Spearman J. Viral hepatitis in young women after ear piercing. *MMWR* 1973; **22**: 390–5.
19 Jay AL. Ear piercing problems. *BMJ* 1977; **2**: 574–5.
20 Ellis DAF. Complication and correction of the pierced ear. *J Otolaryngol* 1976; **5**: 247–50.
21 Apesos J, Kane M. Treatment of traumatic earlobe clefts. *Aesthetic Plast Surg* 1993; **17**: 253–5.
22 Larsson-Stymne B, Widstrom L. Ear piercing: a cause of nickel allergy in school girls? *Contact Dermatitis* 1985; **13**: 289–93.
23 Fischer T, Fregert S, Gruvberger B. Nickel release from ear-piercing kits and earrings. *Contact Dermatitis* 1984; **10**: 39–41.
24 Nakada T, Iijima M, Nakayama H, Maibach HI. Role of ear piercing in metal allergic contact dermatitis. *Contact Dermatitis* 1997; **36**: 233–6.
25 Fisher AA. Allergic contact dermatitis due to gold earrings. *Cutis* 1990; **39**: 473–5.
26 Hausen BM, Rothenborg HW. Allergic contact dermatitis caused by olive wood jewelry. *Arch Dermatol* 1981; **17**: 732–4.
27 Karlberg AT, Boman A, Wahlberg JE. Copper: a rare sensitizer. *Contact Dermatitis* 1983; **9**: 134–9.
28 Menné T. Relationship between cobalt and nickel sensitization in females. *Contact Dermatitis* 1980; **3**: 337–40.
29 Lammintausta K, Pitkanen OP, Kalino K *et al.* Interrelationship of nickel and cobalt contact sensitization. *Contact Dermatitis* 1985; **13**: 148–52.
30 Burrows D. The dichromate problem. *Int J Dermatol* 1984; **23**: 215–20.
31 Jensen CS, Lisby S, Baadsgaard O *et al.* Decrease in nickel sensitization in a Danish schoolgirl population with ears pierced after implementation of a nickel-exposure regulation. *Br J Dermatol* 2002; **146**: 636–42.
32 Fisher AA. Metallic gold: the cause of a persistent allergic 'dermal' contact dermatitis. *Cutis* 1974; **14**: 177–80.
33 Aoshima T, Oguchi M. Intracytoplasmic crystalline inclusions in dermal infiltrating cells of granulomatous contact dermatitis due to gold earrings. *Acta Derm Venereol (Stockh)* 1988; **68**: 261–4.
34 Iwatsuki K, Tagami H, Moriguichi T *et al.* Lymphadenoid structure induced by gold hypersensitivity. *Arch Dermatol* 1982; **118**: 608–11.
35 Iwatsuki K, Yamada M, Tagigawa M *et al.* Benign lymphoplasia of the earlobes induced by gold earrings: immunohistologic study on the cellular infiltrates. *J Am Acad Dermatol* 1987; **16**: 83–8.
36 Zilinsky I, Tsur H, Trau H, Orenstein A. Pseudolymphoma of the earlobes due to ear piercing. *J Dermatol Surg Oncol* 1989; **15**: 666–8.
37 Goossens A, De Swerdt A, De Coninck K *et al*. Allergic contact granuloma due to palladium following ear piercing. *Contact Dermatitis* 2006; **55**: 338–41.
38 High WA, Ayers RA, Adams JR *et al*. Granulomatous reaction to titanium alloy: an unusual reaction to ear piercing. *J Am Acad Dermatol* 2006; **55**: 716–20.
39 Masel G. Copper-induced cutaneous sarcoidosis. *Australas J Dermatol* 2005; **46**: 38–41.
40 Mann RJ, Peachey RDG. Sarcoidal tissue reaction: another complication of ear piercing. *Clin Exp Dermatol* 1983; **8**: 199–200.
41 Muntz HR, Cui DJ, Asher BA. Embedded earrings: a complication of the ear-piercing gun. *Int J Pediatr Otorhinolaryngol* 1990; **19**: 73–6.
42 de San Lazaro C, Jackson RH. Vanishing earrings. *Arch Dis Child* 1986; **61**: 606–7.
43 Saleeby ER, Rubin MG, Youshock E *et al.* Embedded foreign bodies presenting as earlobe keloids. *J Dermatol Surg Oncol* 1984; **10**: 902–4.
44 Ellis DAF. Complications and corrections of the pierced ear. *J Otolaryngol* 1976; **5**: 247–50.
45 Lane JE, Waller JL, Davis LS. Relationship between age of ear piercing and keloid formation. *Pediatrics* 2005; **115**: 1312–4.
46 Slobodkin D. Why more keloids on back than front of earlobe? *Lancet* 1990; **335**: 335–6.
47 Brent B. The role of pressure therapy in the management of earlobe keloids: a preliminary report of a controlled study. *Ann Plast Surg* 1978; **1**: 579–81.
48 Kim DY, Kim ES, Eo SR *et al*. A surgical approach for earlobe keloid: keloid fillet flap. *Plast Reconstr Surg* 2004; **113**: 1668–74.
49 Chowdri NA, Mattoo MMA, Darzi MA. Keloids and hypotrophic scars: results with intra-operative and serial post-operative corticosteroid injection therapy. *Aust N Z J Surg* 1999; **69**: 655–9.
50 Chaudry MR, Akhtar S, Duvalsaint F *et al.* Ear lobe keloids, surgical excision followed by radiation therapy: a 10-year experience. *Ear Nose Throat J* 1994; **73**: 779–81.
51 Akoz T, Gideroglu K, Akan M. Combination of different techniques for the treatment of earlobe keloids. *Aesthetic Plast Surg* 2002; **26**: 184–8.
52 Yencha MW, Oberman JP. Combined therapy in the treatment of auricular keloids. *Ear Nose Throat J* 2006; **85**: 93–4, 96–7.
53 Russell R, Horlock N, Gault D. Zimmer splintage: a simple effective treatment for keloids following ear-piercing. *Br J Plast Surg* 2001; **54**: 509–10.
54 van den Nieuwenhuijsen IJ, Calame JJ, Brynzeel DP. Localised argyria caused by silver earrings. *Dermatologica* 1988; **177**: 189–91.
55 Shall L, Stevens A, Millard LG. An unusual case of acquired localised argyria. *Br J Dermatol* 1990; **123**: 403–7.
56 Noble DA. Another hazard of pierced ears. *BMJ* 1979; **1**: 125.
57 Serratrice J, Ene N, Granel B *et al*. Severe relapsing polychondritis occurring after ear piercing. *J Rheumatol* 2003; **30**: 2716–7.
58 Hendricks WM. Complications of ear piercing: treatment and prevention. *Cutis* 1991; **48**: 386–94.
59 Landeck A, Newman N, Breadon J *et al.* A simple technique for ear piercing. *J Am Acad Dermatol* 1998; **39**: 795–6.
60 Cornetta AJ, Reiter D. Ear piercing for individuals with metal hypersensitivity. *Otolaryngol Head Neck Surg* 2001; **125**: 93–5.

Acanthoma fissuratum

This chronic response to friction and pressure from the spectacle frame can present with papules or nodules, sometimes with ulceration, in the supra-auricular or retro-auricular folds (Fig. 68.6); even when bilateral, basal cell carcinoma is a differential diagnosis. Acanthoma fissuratum is discussed in Chapter 28.



Fig. 68.6 Acanthoma fissuratum. Nodular thickening behind the pinna superficially resembling basal cell carcinoma.



Fig. 68.7 Perniosis. Purple discoloration, soft-tissue loss and crusting due to acute-on-chronic cold injury.



Fig. 68.8 Venous lakes on a sun-damaged pinna.

Cold injury

The ears are extremely susceptible to cold, and the pinna may be affected by chilblains in winter (Fig. 68.7). Extreme cold will cause frostbite (see Chapter 28). Similar changes have also been reported as a consequence of using excessive amounts of ethylchloride spray for ear piercing [1]. Frostbite may result in vesiculation, blisters and ischaemic necrosis of both skin and cartilage. Ears that have previously been damaged by cold may subsequently become calcified and even ossified [2–4].

Cold is also a provoking factor in many conditions that can affect the ear, for example chondrodermatitis nodularis, chilblain lupus erythematosus and cryoglobulinaemia.

The ear subjected to frostbite should be thawed rapidly by the application of wet, sterile cotton pledgets warmed to 38–42°C for about 20 min [5] with adequate analgesic cover.

Emollients have traditionally been thought to protect against frostbite [6], at least in Finland. However, those who use them experience more frostbite, probably through conferring a false sense of safety, and only thermal protection from clothing can be expected to have protective value [7].

References

1 Noble DA. Another hazard of pierced ears (use of ethylchloride spray anaesthetic with children). *BMJ* 1979; **1**: 125.

2 Di Bartolomeo JR. The petrified auricle: comments on ossification, calcification and exostoses of the external ear. *Laryngoscope* 1985; **95**: 566–75.

3 Yeatman JM, Varigos GA. Auricular ossification. *Australas J Dermatol* 1999; **39**: 268–70.

4 High WA, Larson MJ, Hoang MP. Idiopathic bilateral auricular ossificans: a case report and review of the literature. *Arch Pathol Lab Med* 2004; **128**: 1432–4.

5 Sessions DG, Stallings JO, Mills WJ, Beal DD. Frostbite of the ear. *Laryngoscope* 1971; **81**: 1223–32.

6 Lehmuskallio E. Cold protecting ointments and frostbite. *Acta Derm Venereol (Stockh)* 1999; **79**: 67–70.

7 Lehmuskallio E. Emollients in the prevention of frostbite. *Int J Circumpolar Health* 2000; **59**: 122–30.

Solar damage

The external ear is often exposed to solar radiation and is therefore liable to acute and chronic sequelae. A significant hazard from severe sunburn is the development of perichondritis (see below). Many photosensitivity disorders will present on the ear, for example polymorphic light eruption, juvenile spring eruption, lupus erythematosus and porphyria (see Chapter 29).

The full gamut of chronic solar damage is frequently seen on the ears, including erythema, telangiectasia, atrophy, blotchy pigmentation, solar keratoses and cutaneous malignancies. As on the lower lip, venous lakes may be seen (Fig. 68.8). Solar elastosis is often evident, and distinctive elastotic nodules may be seen particularly on the anterior crus of the antihelix [1–3]. These lesions are usually bilateral and asymptomatic, and present as pale papules or nodules. Occasionally, they can occur on the helix and be painful, simulating chondrodermatitis nodularis. They differ from 'weathering' nodules (Fig. 68.9), which, like chondrodermatitis nodularis, occur on the helix of the ear [4]. A distinctive combination of elastosis with vellous hair cysts on the pinna has been described [5].

For treatment of mild acute sunburn, cold compresses may be sufficient. More severe cases may benefit from a course of systemic corticosteroid, given for 5 days and then tapered. Preventive measures are discussed in Chapter 29.



Fig. 68.9 Several firm, white, 'weathering' nodules on the helical rim.

References

1 Carter VH, Constantine VS, Poole WL. Elastotic nodules of the antihelix. *Arch Dermatol* 1969; **100**: 282–5.
2 Kocsard E, Ofner F, Turner B. Elastotic nodules of the antihelix. *Arch Dermatol* 1970; **101**: 370.
3 Weedon D. Elastotic nodules of the ear. *J Cutan Pathol* 1980; **8**: 429–33.
4 Kavanagh GM, Bradfield JWB, Collins CMP, Kennedy CTC. Weathering nodules of the ear: a clinicopathological study. *Br J Dermatol* 1996; **135**: 550–4.
5 Morgan MB, Stevens GL, Somach S. Multiple follicular cysts, infundibular type with vellus hairs and solar elastosis of the ears: a new dermatoheliosis? *J Cutan Pathol* 2003; **30**: 29–31.

Altitude injury

A distinctive presentation of petechiae and haemorrhagic bullae in the skin of the external auditory canal and tympanic membrane has been described in air pilots descending from high altitudes or in pressure chambers while wearing well-sealed earplugs as noise protectors [1].

For treatment, a steroid–antibiotic ear drop has been advised, and if sizeable clots are present they can be gently dislodged by suction after the application of hydrogen peroxide. Preventive methods include the use of perforated earplugs on high-altitude descent.

Reference

1 Senturia BH, Peugnet HB. Aero-otitis externa. *Laryngoscope* 1946; **56**: 225–36.

Radiation injury

Therapeutic use of radiation may result in characteristic acute and chronic changes (see Chapter 79). The cartilage can be susceptible to destruction if inappropriate techniques are used. Post-radiation changes on the external auditory canal include thickening of the canal epithelium, subepithelial fibrosis and resorption of underlying bone, as well as ulceration of the epithelium and the development of cholesteatoma [1].

Reference

1 Adler M, Hawke M, Berger G *et al*. Radiation effects on the external auditory canal. *J Otolaryngol* 1985; **14**: 226–32.

Foreign bodies

A variety of vegetable, animal and mineral substances may be encountered lodged in the external ear and external auditory canal, and are frequently unsuspected. Presenting symptoms include pain, hearing loss, inflammation and discharge.

Vegetable matter, such as beans, peas and cotton, tends to absorb water and swell, impacting in the ear canal. Arthropods are the commonest animal material. While alive, their motion within the ear can produce distinctive symptoms, even vertigo. Flies can deposit eggs in the external auditory canal and the resulting myiasis has produced severe complications [1]; larvae in the triangular fossa of the pinna can also cause marked inflammation [2]. Mineral materials include beads, sand and pebbles, fragments of plaster and metallic substances. Even batteries have been found lodged in the ear and can produce serious consequences [3–5]. Impacted cerumen can behave like a foreign body in the ear canal. Loose hairs in the ear canal have been reported as a cause of noise [6].

Retrieval of foreign bodies should only be undertaken if appropriate instrumentation and expertise is available. The outcome is generally better if the procedure is done by an otolaryngologist [7]. For children, with whom the problem is more common, general anaesthesia is required. Small foreign bodies can usually be extracted with a curette or alligator forceps. Live insects should first be killed by drowning, for example in 2% lidocaine (lignocaine) [8], ether, chloroform or spirit. If some vegetable materials have absorbed water and become impacted, it may be necessary to divide the foreign body *in situ* and remove the fragments. It may be necessary to control bleeding from the skin of the canal, for example with epinephrine (adrenaline)-soaked gauze, and the canal should then be packed with an antibiotic-impregnated dressing. In cases of a battery lodged in the ear canal, it is essential that an ENT surgeon is involved in the management, because of the likelihood of serious destructive change to the middle ear and beyond.

References

1 Mendivil JA, El Shammaa NA. Aural myiasis caused by *Cochliomyia homini-vorax*: case report. *Milit Med* 1979; **144**: 261–2.
2 Kron MA. Human infestation with *Cochliomyia hominivorax*, the New World screwworm. *J Am Acad Dermatol* 1992; **27**: 264–5.
3 Rachlin LS. Assault with battery. *N Engl J Med* 1984; **311**: 921–2.
4 Kavanagh KT, Litovitz T. Miniature battery foreign bodies in auditory and nasal cavities. *JAMA* 1986; **255**: 1470–2.
5 Capo JM, Lucente FE. Alkaline battery foreign bodies of the ear and nose. *Arch Otolaryngol Head Neck Surg* 1986; **112**: 562–3.
6 Goldman G, Toher L. A hair in the ear as a cause of noise (letter). *N Engl J Med* 1982; **306**: 1553.
7 Singh GB, Sidhu TS, Sharma A *et al*. Management of aural foreign body: an evaluative study in 738 consecutive cases. *Am J Otolaryngol* 2007; **28**: 87–90.
8 Schittek A. Insect in the external auditory canal: a new way out. *JAMA* 1980; **243**: 331.

Chondrodermatitis nodularis

This painful condition usually involves the superior portion of the helix, but may appear on the antihelix, concha, tragus and antitragus.

Aetiology. The principal factors in its pathogenesis are pressure and a compromised local blood supply. It is much more common in patients who habitually sleep on one side at night but can be triggered off by other factors, including cold, and by other types of pressure (e.g. from headgear, earphones). Alteration of connective tissue by chronic sun exposure may also be a factor in some cases [1]. The age of onset is over 40 years in most cases and the condition is commoner in males than females. We have encountered chondrodermatitis nodularis (CDN) in juveniles, but only when there is an abnormality such as marked prominence of the antihelix or a history of injury (e.g. from contact sports). Paediatric CDN is reviewed by Grigoryants [2]. Chondrodermatitis nodularis has been reported in a series of patients with systemic sclerosis [3] and in childhood dermatomyositis [4].

Pathology [5,6]. A typical lesion of chondrodermatitis nodularis consists of a nodule of degenerate homogeneous collagen surrounded by vascular granulation tissue with an overlying acanthotic epidermis, and there may be a central ulcer through which the damaged collagen is extruded. In nearly all cases there is inflammation and fibrosis of the underlying perichondrium, and degenerative changes may be seen in the cartilage. Although many authors view the condition as an example of transepidermal elimination of altered connective tissue, it has been suggested that the infundibular portion of the hair follicle is primarily involved, with perforation of the follicular contents into the dermis [7,8]. There is an increased number of small nerves [9].

Clinical features. The patient, usually a middle-aged to elderly man, seeks advice on account of pain. The more stoical may postpone consultation until the lesion interferes with sleep. The pain, which is sometimes severe, is initiated by pressure and occasionally by cold. It may be brief but can persist and throb for an hour or more. Occasionally, and particularly in women, there is little discomfort. The lesion is a globular or oval nodule, about 0.5–2 cm in diameter, raised above the often hyperaemic surrounding skin (Fig. 68.10). The surface is frequently scaly or crusted, concealing a small ulcer.

In men, nearly 90% of nodules are situated on the helix, usually at the upper pole and more frequently on the right, but may occur on the antihelix [10], tragus, concha and antitragus, in order of decreasing frequency [11]. Occasionally, there are multiple nodules or lesions, and they may occur bilaterally [12]. In women, the left and right ears are affected equally and the proportion of lesions on the antihelix and tragus is greater [13]. The nodules attain a maximum size in a few months and then remain unchanged indefinitely.

Diagnosis. Although the associated pain and tenderness are characteristic, the lesion is often misdiagnosed. Differential diagnosis includes basal and squamous cell carcinomas, solar keratosis, calcification of the pinna, elastotic nodules and 'weathering nodules' [14].



Fig. 68.10 Chondrodermatitis nodularis of the helix. A superficially ulcerated, exquisitely tender nodule.

Treatment. For symptomatic CDN, treatment options include strategies to relieve pressure, intralesional steroid injection, surgical removal, cryotherapy, and laser destruction. There are no satisfactory comparative trials between these approaches. Removal of the abnormal cartilage leaving most or all of the overlying skin [15] has superseded wedge excision, giving higher cure rates, sustained over lengthy follow up, and a better cosmetic outcome than the older technique [16,17]. Removal of cartilage only can not only be used for lesions on the helix but also for other sites such as the antihelix [15,16] and tragus. If surgery is not considered suitable, a useful conservative approach is to strap a pressure-relieving sponge over the ear at night time for 4 weeks; this can heal CDN in the short term in a high proportion of cases [18]. A similar approach is to use a doughnut shaped pillow [19]. Other treatments include intralesional steroid therapy which can help about a third of cases [20], liquid nitrogen cryotherapy and carbon dioxide laser [21]. Whenever possible, efforts must be made to reduce pressure or trauma to the helix.

References

1 Goette DK. Chondrodermatitis nodularis chronica helicis: a perforating necrobiotic granuloma. *J Am Acad Dermatol* 1980; **2**: 148–54.

2 Grigoryants V, Qureshi H, Patterson JW, Lin KY. Pediatric chondrodermatitis nodularis helicis. *J Craniofac Surg* 2007; **18**: 228–31.

3 Bottomley WW, Goodfield MDJ. Chondrodermatitis nodularis helicis occurring with systemic sclerosis: an under-reported association? *Clin Exp Dermatol* 1994; **19**: 219–20.

4 Sasaki T, Nishizawa H, Sugita Y. Chondrodermatitis nodularis helicis in childhood dermatomyositis. *Br J Dermatol* 1999; **141**: 363–5.

5 Shuman R, Helwig EB. Chondrodermatitis nodularis helicis chronica. *Am J Clin Pathol* 1954; **24**: 126–44.

6 Santa Cruz DJ. Chondrodermatitis nodularis helicis: a transepidermal perforating disorder. *J Cutan Pathol* 1980; **7**: 70–6.

7 Hurwitz RM. Painful papule of the ear: a follicular disorder. *J Dermatol Surg Oncol* 1987; **13**: 270–4.

8 Hurwitz RM. Pseudocarcinomatous or infundibular hyperplasia. *Am J Dermatopathol* 1989; **11**: 189–91.
9 Cribier B, Scrivener Y, Peltre B. Neural hyperplasia in chondrodermatitis nodularis chronica helicis. *J Am Acad Dermatol* 2006; **55**: 844–8.
10 Burns DA, Calnan CD. Chondrodermatitis nodularis antihelicis. *Clin Exp Dermatol* 1978; **3**: 207–8.
11 Barker LP, Young AW, Sachs W. Chondrodermatitis of the ears: a differential study of nodules of the helix and antihelix. *Arch Dermatol* 1960; **81**: 53–63.
12 Cannon CR. Bilateral chondrodermatitis helicis: case presentation and review of the literature. *Am J Otol* 1985; **6**: 164–6.
13 Yaffee HS. Perichondritis in nuns caused by a change of head-dress. *Arch Dermatol* 1963; **87**: 735.
14 Kavanagh GM, Bradfield JWB, Collins CMP, Kennedy CTC. Weathering nodules of the ear: a clinicopathological study. *Br J Dermatol* 1996; **135**: 550–4.
15 Lawrence CM. The treatment of chondrodermatitis nodularis with cartilage removal alone. *Arch Dermatol* 1991; **127**: 530–5.
16 Hudson-Peacock MJ, Cox NH, Lawrence CM. The long-term results of cartilage removal alone for the treatment of chondrodermatitis nodularis. *Br J Dermatol* 1999; **141**: 703–5.
17 de Ru JA, Lohuis PJ, Saleh HA, Vuyk HD. Treatment of chondrodermatitis nodularis with removal of the underlying cartilage alone: retrospective analysis of experience in 37 lesions. *J Laryngol Otol* 2002; **116**: 677–81.
18 Moncrieff M, Sassoon EM. Effective treatment of chondrodermatitis nodularis chronica helicis using a conservative approach. *Br J Dermatol* 2004; **150**: 892–4.
19 Sanu A, Koppana R, Snow DG. Management of chondrodermatitis nodularis chronica helicis using a 'doughnut pillow'. *J Laryngol Otol* 2007; **24**: 1–3
20 Cox NH, Denham PF. Intralesional triamcinolone for chondrodermatitis nodularis: a follow-up study of 60 patients. *Br J Dermatol* 2002; **146**: 712–3.
21 Taylor MB. Chondrodermatitis nodularis chronica helicis: successful treatment with the carbon dioxide laser. *J Dermatol Surg Oncol* 1991; **17**: 862–4.



Fig. 68.11 Pseudocyst. Asymptomatic fluctuant swellings on the upper pinna.

Pseudocyst of the ear

Synonyms
- Endochondrial pseudocyst
- Idiopathic cystic chondromalacia

A non-inflammatory, fluid-filled cavity within the cartilage of the ear.

Aetiology. Although the cause is unknown in most cases, trauma is likely to be important at least in some, as in fracture in the ear cartilage [1], habit-twisting of the ears [2] and rubbing due to atopic eczema [3]. Most speculations about the pathogenesis include an underlying malformation of the cartilage [4] and degeneration due to release of lysosomal enzymes from chondrocytes. A role for cytokines has also been suggested [5].

Pathology. There is a cavity within the cartilage, the walls of which show the presence of eosinophilic amorphous material [6,7]. There may be focal fibrosis, especially in older lesions.

Clinical features. Most cases are young men, although the condition is seen over a wide age range [8] including infants [9]. Occasional cases have been recorded in females [4]. All races are affected [10]. There may be a predilection for Chinese, although this could be reporting bias [11,12]. The condition is usually unilateral and presents as an asymptomatic swelling, which is non-tender and fluctuant. Occasionally, there are signs of inflammation and some tenderness. The commonest location is on the upper half of the ear (Fig. 68.11), on the scapha, less commonly over the helix and antihelix. Sometimes, coalescent swellings are seen. Aspiration usually yields serous fluid, which soon reaccumulates.

Diagnosis. The differential diagnosis includes traumatic perichondritis, relapsing polychondritis (see Chapter 45), haematoma, dermoid cyst and epidermoid cyst, and various benign and malignant tumours; any of these can if necessary be excluded by histological examination.

Treatment. There are no adequate studies comparing various treatments that have been proposed. Aspiration followed by pressure is simple and can be effective, for example the use of a simple bandage, or perhaps better a thermoplastic material as used for mobilizing extremities can be used to provide the pressure [13,14]. After aspiration the introduction of a few drops of 1% tincture of iodine [10] or corticosteroid [15] and then application of a contour pressure bandage has been suggested but the value of such measures is unproven. A suture has also been recommended to prevent re-filling [16,17] as has a fibrin glue [18].

For recurrences, excision of the anterior wall of the cyst, suturing the skin flap back and use of a pressure dressing can produce a cosmetically satisfactory result in most cases [12].

References

1 Grabski WJ, Salasche SJ, McCollough ML, Angeloni VL. Pseudocyst of the auricle associated with trauma. *Arch Dermatol* 1989; **125**: 528–30.
2 Gonzales M, Raton JA, Manzano D *et al*. Pseudocyst of the ear. *Acta Derm Venereol (Stockh)* 1993; **73**: 212–3.
3 Devlin J, Harrison CJ, Whitby DJ, David TJ. Cartilaginous pseudocyst of the external auricle in children with atopic eczema. *Br J Dermatol* 1990; **122**: 699–704.

4 Santos VB, Polisar IA, Ruffy ML. Bilateral pseudocysts of the auricle in a female. *Ann Otol Rhinol Laryngol* 1974; **83**: 9–11.
5 Yamamoto T, Yokoyama A, Umeda T. Cytokine profile of bilateral pseudocyst of the auricle. *Acta Derm Venereol (Stockh)* 1995; **76**: 92–3.
6 Glamb R, Kim R. Pseudocyst of the auricle. *J Am Acad Dermatol* 1984; **11**: 58–63.
7 Heffner DK, Hyams VJ. Cystic chondromalacia (endochondral pseudocyst) of the auricle. *Arch Pathol Lab Med* 1986; **110**: 740–3.
8 Lazar RH, Heffner DK, Hughes GB, Hyams VK. Pseudocyst of the auricle: a review of 21 cases. *Otolaryngol Head Neck Surg* 1986; **94**: 360–1.
9 Santos AD, Kelley PE. Bilateral pseudocyst of the auricle in an infant girl. *Pediatr Dermatol* 1995; **12**: 152–5.
10 Cohen PR, Grossman ME. Pseudocyst of the auricle: case report and world literature review. *Arch Otolaryngol Head Neck Surg* 1990; **116**: 1202–4.
11 Engel D. Pseudocyst of the auricle in Chinese. *Arch Otolaryngol* 1996; **83**: 29–34.
12 Choi S, Lam K, Chan K, Ghadially F. Enchondral pseudocyst of the auricle in Chinese. *Arch Otolaryngol Head Neck Surg* 1984; **110**: 792–6.
13 Salgado CJ, Hardy JE, Mardini S *et al*. Treatment of auricular pseudocyst with aspiration and local pressure. *J Plast Reconstr Aesthet Surg* 2006; **59**: 1450–2.
14 Schulte KW, Neumann NJ, Ruzicka T. Surgical pearl: the close-fitting ear cover cast. A noninvasive treatment for pseudocyst of the ear. *J Am Acad Dermatol* 2001; **44**: 285–6.
15 Myamoto H, Dida M, Onuma S, Uchiyama M. Steroid injection therapy for pseudocyst of the auricle. *Acta Derm Venereol (Stockh)* 1994; **74**: 140–2.
16 Lim CM, Goh YH, Chao SS, Lynne L. Pseudocyst of the auricle. *Laryngoscope* 2002; **112**: 2033–6.
17 Han A, Li LJ, Mirmirani P. Successful treatment of auricular pseudocyst using a surgical bolster: a case report and review of the literature. *Cutis* 2006; **77**: 102–4.
18 Truncer S, Basterzi Y, Yavuzer R. Recurrent auricular pseudocyst: a new treatment recommendation with curettage and fibrin glue. *Dermatol Surg* 2003; **29**: 1080–3.

Dermatoses and the external ear

Atopic dermatitis

A crusted eczematous fissure at the junction of the earlobe and the face is a common finding in atopics, and can be regarded as a reliable feature of atopy [1–3]. In the series of Tada *et al*. [3], 45 of their 46 patients with severe atopic dermatitis had infra-auricular fissures. In addition to involvement of the infra-auricular crease, the tragal notch and sometimes the whole of the pinna may be commonly involved. Treatment of eczema and the secondary infection that often accompanies it is discussed in Chapter 24.

Seborrhoeic dermatitis

In its mildest form, seborrhoeic dermatitis simply causes a little scaling and inflammation at the entrance to the external auditory meatus, in the concha or in the auricular folds. When severe, the whole pinna may be affected and there may be infective eczematoid dermatitis both in and around the ear or post-auricularly. The relationship between seborrhoeic dermatitis and otitis externa is discussed in Chapter 23.

Asteatotic eczema

The exposed position of the ear renders it vulnerable to the climatic changes that can induce asteatotic eczema (see Chapter 23). This common cause of a dry, itchy ear is mainly seen in the elderly. Aggravating factors include overzealous cleansing, cold, windy weather, low humidity indoors and air-conditioned air during the summer. There may be little to see other than slight scaling. Similar changes can occur in the ear canal, where additional factors include drying vehicles used in ear drops, for example alcohol and acetone. Management will include avoidance of provocative factors, and use of emollients.

Contact dermatitis

The external ear is commonly affected by both irritant and allergic contact dermatitis [4]. Causes of contact allergy may be grouped as follows.

1 Products used for the hair and scalp: hairspray, shampoos, hair dyes, hair nets, bathing caps.
2 Items worn or placed in or on the ear: jewellery, especially nickel alloys (see p. 68.23).
3 Plastic, rubber or metal ear appliances, for example hearing aids, spectacles, headphones, telephone receivers including cellular phones, earplugs, hair nets.
4 Objects used to clean or scratch the ear, for example hairpins, matches.
5 Cosmetics and toiletries: make-up, perfumes, soaps and creams.
6 Topical medicaments
7 Others (transferred to the ear by fingers), e.g. nail varnish, plant resins (e.g. poison ivy, oak or sumac).

The role of occult allergic contact dermatitis in patients with otitis externa is discussed on p. 68.23.

Psoriasis

Both guttate and plaque psoriasis involve the external ear. Sometimes this is by extension from the scalp, face or neck. Like seborrhoeic dermatitis, psoriasis often involves the concha and distal part of the external auditory canal, but usually its colour, the nature of the scaling and the presence of psoriasis elsewhere allow it to be differentiated. Sometimes both conditions appear to coexist.

Acne

Comedones frequently involve the concha, and are occasionally found on the helix, tragus or earlobe. Inflammatory cysts may be found on the lobe, at the entrance to the external auditory canal, or in both the pre- and post-auricular areas. Pressure from spectacle frames, telephone receivers or headsets can aggravate acne lesions.

Darier's disease

Occasionally, Darier's disease can present with involvement of the external ear as the principal affected site, with erythema, oedema and crusting mimicking an eczematous reaction [5].

Transepithelial elimination disorders

The ear may occasionally be the site for lesions of Kyrle's disease, elastosis perforans serpiginosa, perforating folliculitis and perforating papules of diabetic dialysis patients. These conditions are discussed in Chapter 45.

Lupus erythematosus (Fig. 68.12)

Although most parts of the pinna may be involved in lupus erythematosus (LE), pits and scarring in the concha are distinctive



Fig. 68.12 Cutaneous lupus erythematosus. Acute erythema and erosions following sun exposure.



Fig. 68.13 Angiolymphoid hyperplasia with eosinophilia. Firm red-brown nodules at the entrance to the external auditory canal.

features [6,7]. Atrophy often occurs, and even perforation of the pinna [8]. LE profundus can involve the lobe [9].

Lymphocytoma cutis

When the ear is involved, the lobe is characteristically affected, often with a large, single nodule. Possible causative factors include *Borrelia burgdorferi* infection [10] and gold earrings [11,12].

Lichen planus

There is a single case report of conductive deafness due to erosive lichen planus in both ear canals causing stenosis [13].

Jessner's benign lymphocytic infiltration

This condition occasionally involves the ear and post-auricular region, and sunlight may precipitate or worsen the eruption.

Granuloma annulare

Typical papular and annular dermal lesions of granuloma annulare may involve the pinna, sometimes in the absence of lesions elsewhere [14].

Primary cutaneous amyloidosis

Asymptomatic papules on the helix and concha of the ear have been described as the sole manifestation of cutaneous amyloidosis [15]; such lesions can also occur with more generalized papular amyloid [16] and with macular amyloid of the back [17].

Angiolymphoid hyperplasia with eosinophilia

Synonyms
- Pseudopyogenic granuloma
- Nodular angioblastic hyperplasia with eosinophilia

This is a reactive proliferative disorder of blood vessels with a variable component of inflammatory cells [18]. Opinions vary as to whether it is identical with Kimura's disease, a condition mainly found in Eastern Orientals (see Chapter 56). Angiolymphoid hyperplasia with eosinophilia occurs in both a dermal [19] and a subcutaneous [20] form, and is most commonly found on the head and neck. The two forms are regarded as variants of the same condition [21–23].

Aetiological factors include trauma, pregnancy and immunization procedures [24].

Histology. There are circumscribed collections of vessels whose endothelial cells are epithelioid, that is have abundant eosinophilic cytoplasm and large nuclei. These cells sometimes proliferate into the lumen, and may occur in solid clumps. The associated inflammatory infiltrate consists of lymphocytes, sometimes lymphoid follicles, and there are varying numbers of eosinophils. At least in some cases there may be an underlying associated arteriovenous malformation [25]. In typical Kimura's disease there is more prominent lymphoid hyperplasia.

Clinical features. The dermal form commonly affects the pinna, external auditory meatus (Fig. 68.13) and post-auricular area. The

lesions are red-brown papules or nodules. Occasionally, they itch and can be painful or pulsatile [24]. The condition mainly affects young to middle-aged adults, and in some series there is a female preponderance [26].

Kimura's disease has been reported as involving the ears [27,28] but more commonly produces subcutaneous, lymph node and salivary gland-related masses in the head and neck.

Differential diagnosis includes pyogenic granuloma (rare at this site), bacillary angiomatosis and angiosarcoma.

Treatment. The treatment of choice is surgical excision, although there is often recurrence. Intralesional corticosteroids, pulsed dye laser [29], radiotherapy or oral immunosuppressive agents have been used in some cases with benefit.

Skin reactions to osseo-integrated implants

Restoration of the pinna following traumatic loss or congenital absence may be achieved using an osseointegrated skin-penetrating titanium fixture. About 10% of such patients have skin reactions [30,31]. The reaction consists of erythema and crusting, sometimes with significant infection, which should be adequately treated.

Elephantiasis of the external ears

Chronically red swollen ears may occur for a number of reasons, including long-standing eczema, psoriasis [32] and chronic streptococcal infection. Long-standing head louse infection has also been reported as a cause [33].

Psychocutaneous disorders

Dermatitis artefacta and delusions of parasitosis (see Chapter 64) may occasionally result in self-induced lesions on the ears and even in the ear canals.

Granuloma faciale

The ear is an occasional site for this distinctive disorder [34].

Bullous diseases

Pemphigus, pemphigoid, dermatitis herpetiformis and epidermolysis bullosa aquisita may all involve the ear, and occasionally the auditory canal. Blistering of the pinna and stenosis of the canal can occur in dystrophic epidermolysis bullosa [35].

Verruciform xanthoma

This uncommon condition is typically found in the mouth but has been reported on the ear, where it can mimic squamous cell carcinoma [36].

Adult-onset xanthogranuloma

Symmetrical, yellow-red, nodular lesions with the same histology as juvenile xanthogranuloma have been described on the earlobes [37].

Mudi-chood

This distinctive dermatosis, which typically affects the nape of the neck and upper shoulders of girls and young women in the state of Kerala in South India, can occur on the ears. It is thought to be the result of the frictional and occlusive effects of moist, oily hair in a hot and humid environment. Individual lesions are hyperpigmented papules with a thin surrounding rim of scale, occurring on the posterolateral aspects of the pinnae [38,39].

References

1 Voss M, Voss E, Schubert H. Schuppung der Ohren: ein Leitsymtom der Ichthyosis gruppe? *Dermatol Monatsschr* 1982; **168**: 394–7.
2 Sampson HA. Atopic dermatitis. *Ann Allergy* 1992; **69**: 469–81.
3 Tada J, Toi Y, Akiyama H, Arata J. Infra-auricular fissures in atopic dermatitis. *Acta Derm Venereol (Stockh)* 1994; **74**: 129–31.
4 Jones EH. Allergy of the external ear and canal. *Otolaryngol Clin North Am* 1974; **7**: 735–48.
5 Thompson AC, Shall L, Moralee SJ. Darier's disease of the external ear. *J Laryngol Otol* 1992; **106**: 725–6.
6 Shuster S. A simple sign of discoid lupus erythematosus. *Br J Dermatol* 1981; **104**: 350–1.
7 Rebora A. Scarring of the concha as a sign of lupus erythematosus. *Br J Dermatol* 1982; **106**: 122.
8 Lucky PA. Lupus erythematosus with perforation of the pinna. *Cutis* 1983; **32**: 554–7.
9 Sardana K, Mendiratta V, Koranne RV *et al*. Lupus erythematosus profundus involving the ear lobe. *J Eur Acad Dermatol Venereol* 2003; **17**: 727–9.
10 Albrecht A, Hofstadter S, Artsob H *et al*. Lymphadenosis benigna cutis resulting from *Borrelia* infection (*Borrelia* lymphocytoma). *J Am Acad Dermatol* 1991; **24**: 621–5.
11 Murata J, Toyoda H, Nogita T *et al*. A case of lymphadenosis benigna cutis of the earlobe: an immunohistochemical study. *J Dermatol* 1992; **19**: 186–9.
12 Kobayashi J, Nanko H, Nakamura J, Mizoguchi M. Lymphocytoma cutis induced by gold earrings. *J Am Acad Dermatol* 1992; **27**: 457–8.
13 Martin L, Moriniere S, Machet MC *et al*. Bilateral conductive deafness related to erosive lichen planus. *J Laryngol Otol* 1998; **112**: 365–6.
14 Muhlbauer JE. Granuloma annulare. *J Am Acad Dermatol* 1980; **3**: 217–30.
15 Hicks BC, Weber PJ, Hashimoto K *et al*. Primary cutaneous amyloidosis of the auricular concha. *J Am Acad Dermatol* 1988; **18**: 19–25.
16 Bakos L, Weissbluth ML, Pires AKS, Muller LFB. Primary amyloidosis of the concha (letter). *J Am Acad Dermatol* 1989; **20**: 524–5.
17 Barnadas M, Perez M, Esquius J *et al*. Papules in the auricular concha: lichen amyloidosus in a case of biphasic amyloidosis. *Dermatologica* 1990; **181**: 149–51.
18 Rosai J. Angiolymphoid hyperplasia with eosinophilia of the skin. *Am J Dermatopathol* 1982; **4**: 175–84.
19 Wilson Jones E, Bleehen SS. Inflammatory angiomatous nodules with abnormal blood vessels occurring about the ears and scalp (pseudo and atypical pyogenic granuloma). *Br J Dermatol* 1969; **81**: 804–16.
20 Wells GC, Whimster IW. Subcutaneous lymphoid hyperplasia with eosinophilia. *Br J Dermatol* 1969; **81**: 1–15.
21 Kandil E. Dermal angiolymphoid hyperplasia with eosinophilia versus pseudopyogenic granuloma. *Br J Dermatol* 1970; **83**: 405–8.
22 Mehregan AH, Shapiro L. Angiolymphoid hyperplasia with eosinophilia. *Arch Dermatol* 1971; **103**: 50–7.
23 Reed RJ, Terezakis N. Subcutaneous angioblastic lymphoid hyperplasia with eosinophilia (Kimura's disease). *Cancer* 1972; **29**: 489–97.
24 Olsen TG, Helwig EB. Angiolymphoid hyperplasia with eosinophilia. A clinicopathologic study of 116 patients. *J Am Acad Dermatol* 1985; **12**: 781–96.
25 Onishi Y, Ohara K. Angiolymphoid hyperplasia with eosinophilia associated with arteriovenous malformation: a clinicopathological correlation with angiography and serial estimation of serum levels of renin, eosinophil cationic protein and interleukin 5. *Br J Dermatol* 1999; **140**: 1153–6.
26 Henry PG, Burnett JW. Angiolymphoid hyperplasia with eosinophilia. *Arch Dermatol* 1978; **114**: 1168–72.
27 Chan KM, Mok JSW, Ng SK, Abdullah V. Kimura's disease of the auricle. *Otolaryngol Head Neck Surg* 2001; **124**: 598–9.
28 Hiwatashi A, Hasuo K, Shiina T *et al*. Kimura's disease with bilateral auricular masses. *Am J Neuroradiol* 1999; **20**: 1976–8.
29 Lertzman BH, McMeekin T, Gaspari AA. Pulsed dye laser treatment of angiolymphoid hyperplasia with eosinophilia lesions. *Arch Dermatol* 1997; **133**: 920–1.
30 Jacobsson M, Tjellstrom A, Fine L, Andersson H. A retrospective study of osseointegrated skin-penetrating titanium fixtures used for retaining facial prostheses. *Int J Oral Maxillofac Implants* 1992; **7**: 523–8.

31 Gitto CA, Plata WG, Schaaf NG. Evaluation of the peri-implant epithelial tissue of percutaneous implant abutments supporting maxillofacial prostheses. *Int J Oral Maxillofac Implants* 1994; **9**: 197–206.
32 Grant JM. Elephantiasis nostras verrucosa of the ears. *Cutis* 1982; **29**: 441–4.
33 Mahzoon S, Azadeh B. Elephantiasis of external ears: a rare manifestation of pediculosis capitis. *Acta Derm Venereol (Stockh)* 1983; **63**: 363–5.
34 Foss MH. Granuloma faciale: report on a case. *Acta Derm Venereol (Stockh)* 1957; **37**: 473–82.
35 Kastanioudakis I, Bassioukas K, Ziavra N, Skevas A. External ear involvement in epidermolysis bullosa. *Otolaryngol Head Neck Surg* 2000; **122**: 618.
36 Jensen JL, Liao SY, Jeffes EW III. Verruciform xanthoma of the ear with coexisting epidermal dysplasia. *Am J Dermatopathol* 1992; **14**: 426–30.
37 Sueki H, Saito T, Iijima M, Fujisawa R. Adult onset xanthogranuloma appearing symmetrically on the ear lobes. *J Am Acad Dermatol* 1995; **32**: 372–4.
38 Sugathan P. Mudi-chood on the pinnae. *Br J Dermatol* 1976; **95**: 197–8.
39 Sugathan P. Mudi-chood disease. *Dermatol Online J* 1999; **5**: 5.

Systemic disease and the external ear

Many conditions described more fully elsewhere will occasionally present on the external ear with lesions of diagnostic value.

Granulomatous disorders

These include sarcoidosis [1,2], especially the lupus pernio variety. Metastatic Crohn's disease may rarely involve the ear [3]. Atypical facial necrobiosis may involve the ear, as well as the more typical location on the face and scalp. Wegener's granulomatosis can present with serous or suppurative otitis and conductive or sensorineural deafness [4,5]. A similar allergic granulomatosis affected both ears in a young black South African who died from glomerulonephritis [6]. Infective granulomatous diseases involve the ear, notably leprosy, in which the earlobe is a valuable site for taking smears [7]. Lupus vulgaris, other manifestations of tuberculosis, atypical mycobacterial infection (e.g. *Mycobacterium marinum* from swimming-pool injuries), deep fungal infections and even syphilis [8] can involve the ear.

Collagen vascular diseases

As well as discoid lupus, subacute cutaneous lupus erythematosus and systemic lupus erythematosus may also involve the ears. Scleroderma can produce pallor and telangiectasia of the auditory canal. Rheumatoid disease is characterized by nodules, which can occur on the ear, where they may ulcerate due to pressure from the pillow or spectacles. Redness, tenderness and swelling of the ear, but sparing the lobe, is characteristic of relapsing polychondritis (see Chapter 45).

Pyoderma gangrenosum

The ear is an occasional presenting site [9] for this primary ulcerative disorder, discussed in Chapter 50. Vasculitis and factitial disease may be mimicked.

Metabolic disorders

Xanthomas occasionally occur on the ears, presenting as yellow nodules. Gouty tophi frequently involve the pinna (Fig. 68.14), and may antedate the onset of joint disease or appear decades after the initial attack. The helix and antihelix are typical sites. Histology is distinctive. Porphyria cutanea tarda (Fig. 68.15) may present with

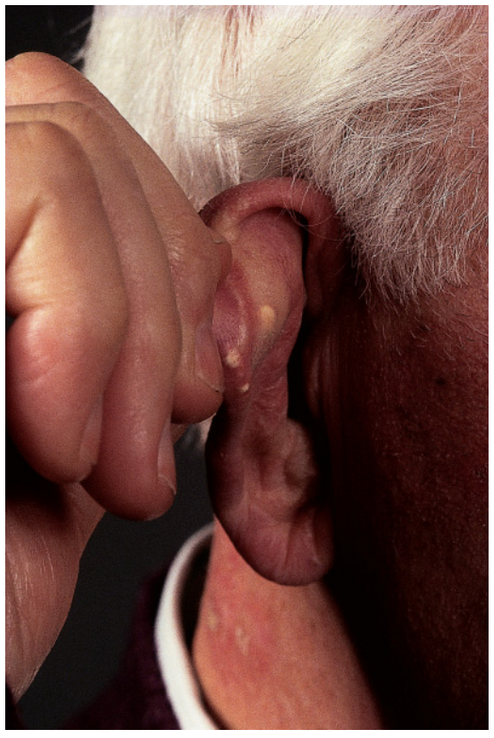


Fig. 68.14 Gouty tophi. Yellowish dermal nodules.



Fig. 68.15 Porphyria cutanea tarda. Firm, whitish, sclerodermoid changes at the site of repeated blistering.

vesicles and bullae, often on a background of scarring, hyperpigmentation, milia, sclerodermoid plaques and hypertrichosis. Pseudocysts of the auricle and perichondritis may be simulated [10].

Diseases of connective tissue

Cutis laxa may result in distinctive pendulous earlobes [11].

Alkaptonuria

Synonym
- Ochronosis

This is typically associated with a bluish discoloration of the auricular cartilage due to oxidation of bound homogentisic acid (Fig. 68.16). The cerumen in such patients may be very dark, a finding that can precede other clinical manifestations.

Calcium deposition

Calcium deposition may occur in many circumstances (see Chapter 59) and occasionally the ear is involved. The so-called petrified ear has been described in association with diabetes mellitus [12]. Usually, calcium deposits in the ear occur for local reasons, for example degenerative changes in the cartilage. In infants, congenital nodular calcification of Winer should be considered [13].

Endocrine disorders

In Addison's disease, the pigmentary changes may involve the ear, and ossification of the auricular cartilage may occur [14]. In acromegaly, there is usually enlargement of the auricular cartilage and coarsening of the overlying skin.

Paraneoplastic syndromes

Bazex's syndrome (acrokeratosis paraneoplastica) (see Chapter 62) commonly affects the ears and is an important marker for internal malignancy [15].



Fig. 68.16 Alkaptonuria. The auricular cartilage has a distinctive blue colour. (Courtesy of Dr P. Hollingworth, Southmead Hospital, Bristol, UK.)

Drug-related effects

Purpura of the ears has been described in a series of children receiving levamisole for nephritic syndrome [16]. Both vasculitis and thrombotic changes occurred, and there was an association with circulating autoantibodies.

Hypertrophy of the retro-auricular folds may be seen as a consequence of phenytoin therapy [17]. Hypertrichosis of the ear canal due to minoxidil therapy can be a predisposing factor for external otitis [18].

Lymphoma

Systemic lymphoma can occasionally present as an isolated lesion on the ear [19].

References

1 Nova A. Sarcoidosis of the ear. *Ear Nose Throat J* 1981; **60**: 307–8.
2 Swansson-Beck H, Goos M, Christophers E. Ohrlappchengranuloma. *Hautarzt* 1982; **33**: 115–6.
3 McCallum DI, Gray WM. Metastatic Crohn's disease. *Br J Dermatol* 1976; **95**: 551–4.
4 McCaffrey TU, McDonald TJ, Facer GW *et al.* Otologic manifestation of Wegener's granulomatosis. *Otolaryngol Head Neck Surg* 1980; **88**: 586–93.
5 Kornblut AD, Wolffs M, Fauci AS. Ear disease in patients with Wegener's granulomatosis. *Laryngoscope* 1982; **92**: 713–7.
6 Bentley-Phillips B, Bayler MA. Destructive granuloma of the ear. *Int J Dermatol* 1980; **19**: 336–9.
7 Mansfield RE, Storkan MA, Cliff IS. Evaluation of the earlobe in leprosy. A clinical and histopathological study. *Arch Dermatol* 1969; **100**: 407–12.
8 Wilcox JR. An atypical case of secondary syphilis. *Br J Venere Dis* 1981; **57**: 30–2.
9 Lysy J, Zimmerman J, Ackerman Z, Reifen E. Atypical auricular pyodermagangrenosum simulating fungal infection. *J Clin Gastroenterol* 1989; **11**: 561–4.
10 Bukachevsky R, Kimmelman CP. Otolaryngologic manifestations of porphyria cutanea tarda. *Otolaryngol Head Neck Surg* 1989; **101**: 402–3.
11 Ghigliotti G, Parodi A, Borgiani L *et al.* Acquired cutis laxa confined to the face. *J Am Acad Dermatol* 1991; **24**: 504–5.
12 Strumia R, Lombardi AR, Altieri E. The petrified ear: a manifestation of dystrophic calcification. *Dermatology* 1997; **194**: 371–3.
13 Azon-Masoliver A, Ferrando J, Navarra E, Mascaro JE. Solitary congenital nodular calcification of Winer located on the ear: report of two cases. *Pediatr Dermatol* 1989; **6**: 191–3.
14 Chadwick JM, Downham TF. Auricular calcification. *Int J Dermatol* 1978; **17**: 799–801.
15 Bazex A, Griffiths A. Acrokeratosis paraneoplastica: a new cutaneous marker of malignancy. *Br J Dermatol* 1980; **102**: 301–6.
16 Rongioletti F, Ghio L, Ginevri F *et al.* Purpura of the ears: a distinctive vasculopathy with circulating autoantibodies complicating long-term treatment with levamisole in children. *Br J Dermatol* 1999; **140**: 948–51.
17 Trunnell TN, Waisman M. Hypertrophied retroauricular folds attributable to diphenylhydantoin therapy. *Cutis* 1982; **30**: 207–9.
18 Toriumi DM, Konior RJ, Berktold RE. Severe hypertrichosis of the external ear canal during minoxidil therapy. *Arch Otolaryngol Head Neck Surg* 1988; **114**: 918–9.
19 Darvay A, Russell-Jones R, Acland KM *et al.* Systemic B-cell lymphoma presenting as an isolated lesion on the ear. *Clin Exp Dermatol* 2001; **26**: 166–9.

Infection

The anatomy of the ear, with its many folds and the semi-occluded nature of the external auditory canal, make it particularly susceptible to intertriginous infection, especially with Gram-negative organisms. The close anatomical relationship between the middle

and external ear means that infections can pass relatively easily from one to the other, and the eardrum should always be examined. The cartilaginous and bony structures close to the skin are particularly vulnerable to infection. Although chondritis and perichondritis may have other causes, they are included in this section.

Infections of the pinna

Staphylococcus aureus, alone or in association with group A β-haemolytic *Streptococcus*, may cause impetigo contagiosum of the ear. This is a relatively common site for infection in infants and young children. *Staphylococcus aureus* is also the most common causative organism of furuncles (boils) and carbuncles, which are more common in the external auditory canal than on the pinna. Cracks and fissures around the auricle are often the portal of entry for β-haemolytic streptococcal infection manifesting as erysipelas. This is more common in the elderly, the newborn and those suffering from malnutrition, disability, alcoholism, diabetes or immune deficiency states.

Erysipelas typically begins with high fever and constitutional upset, including malaise, vomiting and headache, and there is rapidly spreading erythema and oedema from the pinna on to the face. There is often lymphadenopathy. Recurrent attacks of cellulitis of the face may have the same predisposing factors as at other body sites. Recurrent attacks of cellulitis lead to fibrosis and lymphoedema. Treatment of erysipelas and cellulitis is discussed in Chapter 30.

Necrotizing fasciitis has rarely been described arising from an initial infection of the pinna [1].

The term *infective eczematoid dermatitis* is still sometimes used for an oozing, crusted, eczematous condition occurring on and often below the pinna in association with chronic discharge from the ear. Coagulase-positive staphylococci are the most frequently isolated bacteria. The ear canal is oedematous and erythematous, and purulent discharge may be seen coming from a perforated tympanic membrane. The condition should be differentiated from impetigo, secondarily infected contact dermatitis, seborrhoeic dermatitis and atopic dermatitis.

Treatment. Primary infection of the ear must be treated appropriately, usually with a systemic antibiotic; any associated chronic otitis media or mastoiditis is likely to be managed by an otologist. Involved skin can be cleansed with saline, 1 in 10 000 potassium permanganate or dilute aluminium acetate soaks and then treated with a topical steroid. Surgical intervention will be required for necrotizing fasciitis.

Perichondritis and chondritis

Inflammation of the cartilage itself (chondritis), or more commonly the vascularized lining (perichondritis), can be indistinguishable from infection of these structures, and infection is a common complication whatever the cause [2,3].

Aetiology. There are many causes, including physical trauma (Fig. 68.17), thermal and chemical burns, frostbite, pressure (e.g. from tight headphones and head-dresses [4]) and ear piercing, especially so called high piercing (i.e. through the cartilage; see p. 68.7). Acupuncture is also a risk factor [5,6]. Perichondritis may occasionally follow superficial infections of the ear such as furunculosis or otitis externa. The most common infecting organism is *Ps. aeruginosa*, although other Gram-negative organisms or staphylococci may at times be responsible.



Fig. 68.17 Pressure ulcer exposing cartilage, a potential cause of chondritis.

Clinical features. Chondritis and perichondritis are typically painful. The pinna becomes hot, painful and swollen, with loss of normal contour due to oedema, and there may be accumulation of pus in the subperichondrial layer. Constitutional symptoms are common. The inflammation can spread back to the adjoining face. The destruction of cartilage results in deformity of the ear, which may be severe. Necrotizing fasciitis can follow perichondritis of the pinna [1], and if suspected must be treated by urgent debridement.

Diagnosis. Perichondritis may be difficult to distinguish from cellulitis, although perichondritis is usually more painful and does not involve the lobule of the ear, which lacks cartilage. Relapsing polychondritis (see Chapter 45) usually also involves cartilage at other body sites, and is often recurrent.

Treatment. Treatment should be instituted promptly. If an abscess has developed, early drainage is necessary. Surgery is necessary if perichondritis is secondary to malignant external otitis [7]. Ciprofloxacin or other quinolones are probably the treatment of choice [8,9]. Necrotic cartilage may subsequently need to be excised, and fluid collections aspirated.

References

1 Skorina J, Kaufman D. Necrotizing fasciitis originating from pinna perichondritis. *Otolaryngol Head Neck Surg* 1995; **113**: 467–73.

2 Martin R, Yonkers AJ, Yarington CT Jr. Perichondritis of the ear. *Laryngoscope* 1976; **86**: 664–73.

3 Bassiouny A. Perichondritis of the auricle. *Laryngoscope* 1981; **91**: 422–31.
4 Williams HC. Turban ear. *Arch Dermatol* 1994; **130**: 117–9.
5 Allison G, Kravitz E. Auricular chondritis secondary to acupuncture. *N Engl J Med* 1975; **293**: 780.
6 Davis O, Powell M. Auricular perichondritis secondary to acupuncture. *Arch Otolaryngol* 1985; **111**: 770–1.
7 Prasad HK, Sreedharan S, Prasad HS *et al*. Perichondritis of the auricle and its management. *J Laryngol Otol* 2007; **121**: 530–4.
8 Noel SB, Scattan P, Meadors MC *et al*. Treatment of *Pseudomonas aeruginosa* auricular perichondritis is with oral ciprofloxacin. *J Dermatol Surg Oncol* 1989; **15**: 633–7.
9 Thomas JN, Swanson N. Treatment of perichondritis with a quinolone derivative: norfloxacin. *J Dermatol Surg Oncol* 1988; **14**: 447–9.

Other bacterial infections of the pinna

Mycobacterial infection can rarely involve the external ear. Lupus vulgaris can produce extensive destruction [1] and may mimic other conditions [2]. Secondary involvement from underlying lymph node disease (scrofuloderma) can present with hearing loss, tinnitus and periauricular lymphadenopathy, with only minimal secretion in the ear canal [3].

Atypical mycobacteria that may involve the ear include *M. marinum* acquired from swimming-pool injuries.

In leprosy, the ear is almost always involved in the lepromatous type, and there may be evident infiltration of the skin. The earlobe is often used for taking smears [4].

Syphilis may occasionally involve the ear, usually in the secondary stage [5].

References

1 Fasal P. But it was not leprosy. *Cutis* 1975; **15**: 499–509.
2 Okazaki M, Sakurai MD. Lupus vulgaris of the earlobe. *Ann Plast Surg* 1997; **39**: 643–6.
3 Hunsaker DH. Conchomeatoplasty for chronic otitis externa. *Arch Otolaryngol Head Neck Surg* 1988; **114**: 395–8.
4 Mansfield RE, Storkan MA, Cliff IS. Evaluation of the earlobe in leprosy. A clinical and histopathological study. *Arch Dermatol* 1969; **100**: 407–12.
5 Wilcox JR. An atypical case of secondary syphilis. *Br J Venereol Dis* 1981; **57**: 30–2.

Viral infections

Herpes simplex occasionally involves the ear. It is often transmitted during contact sports such as rugby and wrestling. Herpes zoster may present as an isolated herpetiform eruption of the external ear or may be associated with ipsilateral facial palsy and auditory symptoms (Ramsay–Hunt syndrome; geniculate herpes). The condition usually begins with pain and may initially be mistaken for erysipelas. Vesicles usually appear on about the fifth day and involve the pinna, the external auditory meatus and, rarely, the tympanic membrane. There is usually malaise, pyrexia and lymphadenopathy. Facial palsy, when it occurs, is usually transient, but more severe and persistent cases do occur. Taste and lacrimation may also be affected. Compression damage to the VIIIth cranial nerve may lead to tinnitus, vertigo, nystagmus, nausea and deafness. Management of herpes zoster is discussed in Chapter 33. Orf affecting the ear has been described, presenting as an inflammatory nodule on the tragus [1].

Reference

1 Shinkwin CA, Holmes AH, Freeland AP. Orf of the pinna. *J Laryngol Otol* 1991; **105**: 947–9.

Superficial and deep mycoses

Dermatophyte fungi may rarely involve the ear, and when present can simulate granulomatous disease [1,2] and chondritis [3].

Pityriasis versicolor may involve the ears, but is usually easy to diagnose.

In cases of ulcerative granulomatous disease of the ear, deep fungal infections, for example sporotrichosis [4], should be considered. Biopsy, examination of smears, cultures and serological studies should enable accurate diagnosis. Deep fungal infection may prompt an enquiry for underlying immune deficiency.

Otomycosis is discussed below (Otitis externa).

References

1 Verbov J. Granulomatous *Trichophyton rubrum* infection of the pinnae. *Br J Dermatol* 1973; **89**: 212–3.
2 Gong JQ, Liu XQ, Xu HB *et al*. Deep dermatophytosis caused by *Trichophyton rubrum*: report of two cases. *Mycoses* 2007; **50**: 102–8.
3 Bishop M, Rist TE. Tinea of the ear mimicking chondritis. *Cutis* 1979; **23**: 638–9.
4 Cox RL, Reller LB. Auricular sporotrichosis in a brick mason. *Arch Dermatol* 1979; **115**: 1229–30.

Infections of the external auditory canal and meatus

External otitis

Synonym
- Otitis externa

Otitis externa [1] is a loose term that embraces more than one disease process. Aetiologically, it is rarely unifactorial [2]; constitutional, traumatic, environmental and microbial factors usually coexist. The condition is characterized by inflammation of the canal epithelium and by varying degrees of pain, itch, deafness and discharge. It may be acute, usually lasting less than 6 weeks, or chronic if lasting more than 3 months. The term 'external otitis' sometimes includes furunculosis of the ear canal, and is then subclassified as acute localized external otitis; furunculosis is described separately below. Invasive (necrotizing) external otitis, which involves the temporal bone, is described later (p. 68.25).

Incidence. Tha annual incidence of acute otitis externa is probably between 1:100 and 1:250 of the general population, with regional variations depending on age and geographical factors [3].

Pathogenesis. Otitis externa can be divided, for convenience, into two main groups [4]: (i) a *reactive* group consisting of patients suffering from eczema, psoriasis or seborrhoeic dermatitis; and (ii) a predominantly *infective* group in which either bacteria or fungi are involved. However, the two components often coexist. The cause in many cases is not apparent [5] but the following predisposing factors appear to be important.

Genetic and constitutional. There are significant racial and individual differences in susceptibility to otitis externa. This may be due to anatomical differences in the curvature of the external auditory canal or narrowing of the isthmus—natives of New Guinea with wide, straight canals only rarely suffer from external otitis [6]—or, possibly, to differences in the type, amount or composition

of cerumen, whose waxy consistency and low pH are protective against bacteria. Lack of ear wax is associated with external otitis. An alkaline pH is associated with chronicity [7]. *Pseudomonas aeruginosa*, the commonest bacterial pathogen in external otitis, binds to cells by a lectin-mediated process, and binding occurs more in individuals expressing blood group A on their epithelial cells [8]. Increased levels of proteases may also be associated with chronicity [9].

Abundant tragal hair or plugs of wax and debris increase the relative humidity and reduce ventilation of the external auditory canal so that the canal epithelium becomes macerated and more susceptible to infection. Hypertrichosis of the canal due to minoxidil has been associated with external otitis [10]. Dental abnormalities and poor mastication [11] may also retard expulsion of wax and epithelial squames.

The atopic and seborrhoeic states predispose to external otitis not only by interfering with the integrity of the auricular epithelium but also by encouraging scratching and secondary infection. Both too much and too little cerumen and alterations in skin pH have at times been held responsible [12].

Environmental. Heat, humidity and moisture are undoubtedly important in 'hot-weather ear' or 'swimmer's ear' [13]. This condition is common, especially among white people in tropical and subtropical regions. High temperature, high relative humidity and swimming [14] all encourage maceration and secondary bacterial or fungal infections of the canal epithelium. Freshwater swimming appears to be a particular risk factor [15]. Failure to dry the ears completely after swimming, shampooing or showering may also be a factor in some cases [5].

Traumatic. Trauma, in the opinion of many investigators [2,14,16,17], is one of the prime factors in both the initiation and the persistence of many cases. In one series of 113 patients, 58 admitted using wool-tipped matches, two admitted using bare matches and seven used hairgrips to relieve itching [2]. Patients suffering from eczema or those with neurodermatitis tend to scratch, rub or 'fiddle' with their ears; other patients appear obsessed about cleaning their ears and by doing so excessively they interfere with the normal homeostatic and self-cleaning properties [18]. Impacted cerumen may cause irritation, which is often increased by inexpert attempts to remove it. Pressure from hearing aids and in-the-ear auditory equipment may also cause irritation and, especially with the 'internal' hearing aid, a combination of pressure and occlusion often leads to the development of external otitis.

Bacterial and mycotic infection. The epidermis of the external auditory canal is normally fairly resistant to infection. The bacterial flora, although varying with race, geography and season, tends to resemble that of the skin but with a higher likelihood of finding *Ps. aeruginosa* [19]. In hot humid environments, however, and particularly among swimmers, whose ears are habitually wet, the incidence of *Ps. aeruginosa* and other Gram-negative infections rises substantially [20,21] as does the frequency with which *Aspergillus* or *Candida* species are isolated [16]. An outbreak of *Pseudomonas* otitis has been reported in association with contaminated pool water [22] but a source has rarely been found in other series, and it is assumed that *Pseudomonas* infections are of endogenous origin. Some strains may be more pathogenic [23].

In more temperate climates, *S. aureus* is often isolated. This may be associated with evidence of skin disease elsewhere or with staphylococcal carriage. Methicillin-resistant *S. aureus* (MRSA) infections are becoming more common, especially when the patient has recently had hospital exposure [24]. Certainly, patients with recurrent staphylococcal otitis externa should have nasal and perianal swabs sent for bacterial culture; occasionally it may be necessary to swab and 'de-Staph' the whole family. In other cases, there may be an underlying tympanic perforation or coexistent otitis media. The eardrums should therefore always be examined, especially in patients with unilateral or recurrent disease. Occasionally, infection spreads out from the ear canal and causes impetigo or infective eczema of the auricle and surrounding skin.

In the tropics, mycotic infections of the external ear canal are relatively common [25,26]. *Aspergillus*, *Candida*, *Penicillium* and *Mucor* spp. are the organisms most often incriminated, most cases being due to either *Aspergillus niger* or *Candida albicans*. There is some debate, however, as to whether these fungi are pathogenic, opportunistic, saprophytic or simply commensal [26–29].

References

1 Lucente FE. Diseases due to infection. In: Lucente FE, Lawson W, Novick NL, eds. *The External Ear*. Philadelphia: Saunders, 1996: 48–97.
2 McKelvie M, McKelvie P. Some aetiological factors in otitis externa. *Br J Dermatol* 1966; **78**: 227–31.
3 Rowlands S, Devalia H, Smith C *et al*. Otitis externa in UK general practice: a survey using the UK General Practice Research Database. *Br J Gen Pract* 2001; **51**: 533–8.
4 Mawson SR, Ludman H, eds. *Diseases of the Ear*, 4th edn. London: Arnold, 1979.
5 Russell JD, Donnelly M, McShane DP *et al*. What causes acute otitis externa? *J Laryngol Otol* 1993; **107**: 898–901.
6 Quayle AF. Otitis externa in New Guinea. *Med J Aust* 1944; **2**: 228–31.
7 Martinez Devesa P, Willis CM, Capper JW. External auditory canal pH in chronic otitis externa. *Clin Otolaryngol Allied Sci* 2003; **28**: 320–4.
8 Steuer MK, Hofstadter F, Probster L *et al*. Are ABH antigenic determinants on human outer ear canal epithelium responsible for Pseudomonas aeruginosa infections? *Otorhinolaryngology* 1995; **57**: 148–52.
9 Antonelli PJ, Schultz GS, Cantwell JS *et al*. Inflammatory proteases in chronic otitis externa. *Laryngoscope* 2005; **115**: 651–4.
10 Toriumi DM, Konior RJ, Berktold RE. Severe hypertrichosis of the external ear canal during minoxidil therapy. *Arch Otolaryngol Head Neck Surg* 1988; **114**: 918–9.
11 Dunn B. Otitis externa and malposed third molars. *J Laryngol Otol* 1962; **76**: 981–4.
12 McLaurin JW, Raggio TP, Simmons M. Persistent external otitis. *Laryngoscope* 1965; **75**: 1699–707.
13 Calderon R, Mood EW. An epidemiological assessment of water quality and 'swimmers' ear'. *Arch Environ Health* 1982; **37**: 300–5.
14 Strauss NB, Dierker RL. Otitis externa associated with aquatic activities (swimmer's ear). *Clin Dermatol* 1987; **5**: 103–11.
15 Springer GL, Shapiro EA. Fresh water swimming as a risk factor for otitis externa: a case–control study. *Arch Environ Health* 1985; **40**: 202–6.
16 Wright DN, Alexander JM. Effect of water on the bacterial flora of swimmers' ears. *Arch Otolaryngol* 1974; **99**: 15–8.
17 Hirsch BE. Infections of the external ear. *Am J Otolaryngol* 1992; **13**: 145–55.
18 Alberti PWRM. Epithelial migration on the tympanic membrane. *J Laryngol* 1964; **78**: 808–30.

19 Brook I. Microbiological studies of bacterial flora of the external auditory canal in children. *Acta Otolaryngol (Stockh)* 1981; **91**: 285–7.
20 Hoadley AW, Knight DE. External otitis among swimmers and nonswimmers. *Arch Environ Health* 1975; **30**: 445–8.
21 Lambert IJ. A comparison of the treatment of otitis externa with 'Otosporin' and aluminium acetate: a report from a services practice in Cyprus. *J R Coll Gen Pract* 1981; **31**: 291–4.
22 Weingarten MA. Otitis externa due to *Pseudomonas* in swimming pool bathers. *J R Coll Gen Pract* 1977; **27**: 359–60.
23 Matar GM, Harakeh HS, Ramlawi F *et al*. Comparative analysis between *Pseudomonas aeruginosa* genotypes and severity of symptoms in patients with unilateral or bilateral otitis externa. *Curr Microbiol* 2001; **42**: 190–3.
24 Walshe P, Rowley H, Timon C. A worrying development in the microbiology of otitis externa. *Clin Otolaryngol* 2001; **26**: 218–20.
25 Beaney GRE, Broughton A. Tropical otomycosis. *J Laryngol Otol* 1967; **81**: 987–97.
26 Youssef YA, Abdou MH. Studies on fungus infection of the external ear. I. Mycological and clinical observations. *J Laryngol Otol* 1967; **81**: 401–12.
27 Haley LD. Etiology of otomycosis II. Bacterial flora of the ear. *Arch Otolaryngol* 1950; **52**: 208–13.
28 Gregson AEW, La Touche CJ. Otomycosis: a neglected disease. *J Laryngol Otol* 1961; **75**: 45–69.
29 Smyth GDL. Fungal infection in otology. *Br J Dermatol* 1964; **76**: 425–8.

Histopathology. In most cases of external otitis, there is acanthosis, elongation of the rete ridges and an increase in orthokeratosis and parakeratosis. Spongiosis occurs in eczematous and seborrhoeic forms. The nature of the dermal infiltrate varies with both cause and chronicity. The histopathology is seldom diagnostic except when fungal mycelia are seen.

Clinical features. The condition can be acute, subacute or chronic. In patients seen at hospital, it tends to be severe, chronic or chronic relapsing, but in the community it is less severe and recalcitrant [1,2].

Mild attacks may present with pain or itching without discharge and with a minimally congested or swollen meatus. The degree of irritation or discomfort is often out of all proportion to the appearance. This stage probably represents early damage to the meatal skin [3]. Most cases of this type will resolve with simple therapeutic measures, but a minority, perhaps due to trauma, secondary infection or failure to keep the ear dry and clean, progress to more severe disease.

Fully developed, acute external otitis (diffuse otitis externa) is characterized by a sudden onset of ear pain, itching, a sense of fullness or stuffiness if there is significant oedema, and a variable degree of hearing loss. The otalgia is often exacerbated by jaw movements. With progression, there is usually drainage of malodorous pus, which tends to be bluish-green in colour if *Ps. aeruginosa* is the dominant infecting organism. Examination shows erythema and swelling, which may spread from the external auditory meatus to involve the concha or beyond. The external auditory canal shows erythema and oedema, and there is macerated debris and perhaps greenish pus present. In severe cases, inflammation can extend to involve the tympanic membrane. Hearing loss is due to oedema of the canal, and this may be sufficient to obscure vision of its full length. Traction on the pinna to examine the canal and pressure over the tragus characteristically elicit pain. There may be associated fever, malaise and regional lymphadenopathy. *Pseudomonas* is the commonest cause of acute external otitis [4].

It is important to gently remove debris in the process of a full examination, and to try to determine whether the disease is secondary to otitis media and whether or not the tympanic membrane is intact.

Bullous external otitis [5] is an uncommon variant in which there is a sudden onset of severe pain followed by discharge of blood from the ear canal. Bluish-red haemorrhagic bullae are visible on the osseous canal walls.

In granular external otitis the lining of the meatus and canal is replaced in part or whole by granulation tissue, which can project inwards as pedunculated masses. These are usually found near the tympanic membrane, arising from the osseous end of the canal. Granular external otitis is associated with a severe or neglected course [6,7].

The term 'chronic external otitis' is sometimes used for cases that have had persistent symptoms for more than 2 months [8]. Microbiological assessment demonstrated a significant organism in 82% of cases in one series [9]: *S. aureus* in one-third, *Pseudomonas* in one-third and various other Gram-negative and Gram-positive organisms in the remainder; in addition, 17 of the 99 patients had fungal disease alone. There is often a dry canal due to lack of cerumen. It is likely that in most cases of chronic otitis externa, particularly when treatment has been used for the acute attack and symptoms have continued, concurrent dermatological disorders are present (Fig. 68.18). In patients in whom the disorder behaves in a recalcitrant manner it is important to consider the possibility that they may have an underlying systemic disease, such as acquired immune deficiency syndrome (AIDS), malnutrition or



Fig. 68.18 Chronic otitis externa. There is longstanding eczematous change, in part due to contact allergic reactions to ear drops, and induration causing narrowing of the canal.

uncontrolled diabetes mellitus; a poor therapeutic response is also seen in patients treated with high-dose steroids or chemotherapeutic agents [10].

Seborrhoeic dermatitis, atopic dermatitis and psoriasis usually occur only at the meatus but may sometimes extend further into the canal. Seborrhoeic otitis externa is extremely common and has been regarded by some dermatologists as the basis for most cases of otitis externa. The symptoms and signs, however, are normally mild unless complicated by secondary factors and usually consist of no more than superficial scaling and a little discomfort or itching. Signs of pityriasis capitis or seborrhoeic dermatitis elsewhere are usually present. The condition may deteriorate at times of stress or fatigue. Secondary bacterial infection is common. In this 'reactive' group the appearance is often that of a dermatitis spreading into the ear, in contrast with those cases with a primarily 'infective' aetiology where infection and/or inflammation often appears to be spreading out from the ear and where the entire length of the canal is often affected. The clinical appearance, however, is often non-diagnostic.

In infective eczema there is usually intense pruritus associated with exudate. The condition may complicate both otitis media and otitis externa and is usually associated with some degree of otorrhoea. In others, it appears to develop from seborrhoeic dermatitis that has become secondarily infected. The condition may affect the meatus, concha, lobe and periauricular skin and often spreads widely. The post-auricular fold is commonly affected. The symptoms and signs are those of eczema with an accompanying or preceding aural discharge. In seborrhoeic individuals, other areas may be involved at the same time. Fissures and cellulitis are common complications.

Contact dermatitis is often occult [11] and easily overlooked. It is both a complication (see below) and a contributory factor to chronicity. Sensitivity to topically applied medicaments is common in chronic external otitis. Neomycin and the related aminoglycosides are likely to be the commonest sensitizers [12–14]. As well as drops, medicated gauze should be considered [15]. Occlusion, the recurrent nature of the disease and frequent use of antibiotics on an already damaged skin probably account for the high incidence of contact dermatitis at this site. Other sensitivities include nickel from hair pins, metal implements, chromate and phosphorus sesquisulphide in matches, and nail varnish. It is characteristic that the degree of itching and burning is often markedly out of proportion to the amount of erythema and oedema present. Contact dermatitis may also rarely occur with ear moulds [16]. Clinically, it is often difficult to differentiate neurodermatitis from contact dermatitis.

Lichen simplex (neurodermatitis) may be localized to one area of the meatus or may occur more diffusely over the tragus, triangular fossa and adjoining skin. The condition is usually diagnosed by the history rather than the signs. Itching is intense, but often intermittent. The need to scratch or rub is compulsive, although often denied. Signs of inflammation are often minimal, but some degree of oedema and scaling is common. Complications from trauma, infection and sensitization are frequent. Intermittent itching of the external auditory canal (non-specific external otitis) can also occur, irregularly and over a long period, without any obvious cause and with minimal signs of disease.

Whatever the primary aetiology, with the passage of time chronic external otitis becomes an increasingly complex diagnostic and therapeutic problem.

References

1 Rowlands S, Devalia H, Smith C *et al*. Otitis externa in UK general practice: a survey using the UK General Practice Research Database. *Br J Gen Pract* 2001; **51**: 533–8.

2 Osguthorpe JD, Nielsen DR. Otitis externa: Review and clinical update. *Am Fam Physician* 2006; **74**: 1510–6.

3 Wright DN, Alexander JM. Effect of water on the bacterial flora of swimmers' ears. *Arch Otolaryngol* 1974; **99**: 15–8.

4 Roland PS, Stroman DW. Microbiology of acute otitis externa. *Laryngoscope* 2002; **112**: 1166–77.

5 Senturia BH. External otitis, acute diffuse. *Ann Otol Rhinol Laryngol* 1973; **82** (Suppl. 8): 1–23.

6 Moffett AJ. Granulating myringitis: unusual affection of the eardrum. *J Laryngol Otol* 1943; **58**: 453–6.

7 Lucente FE. Diseases due to infection. In: Lucente FE, Lawson W, Novick NL, eds. *The External Ear*. Philadelphia: Saunders, 1996: 48–97.

8 Hirsch BE. Infections of the external ear. *Am J Otolaryngol* 1992; **13**: 145–55.

9 Hawke M, Wong J, Krajden S. Clinical and microbiological features of otitis externa. *J Otolaryngol* 1984; **13**: 289–95.

10 Selesnick SH. Otitis externa: management of the recalcitrant case. *Am J Otol* 1994; **15**: 408–12.

11 Holmes RC, Wilkinson JD, Johns AN *et al*. Medicament contact dermatitis in patients with chronic inflammatory ear disease. *J R Soc Med* 1982; **75**: 27–30.

12 Sood S, Strachan DR, Tsikoudas A, Stables GI. Allergic otitis externa. *Clin Otolaryngol Allied Sci* 2002; **27**: 233–6.

13 Devos SA, Mulder JJ, van der Valk PG. The relevance of positive patch test reactions in chronic otitis externa. *Contact Dermatitis* 2000; **42**: 354–5.

14 Millard TP, Orton DI. Changing patterns of contact allergy in chronic inflammatory ear disease. *Contact Dermatitis* 2004; **50**: 83–6.

15 Roest MA, Shaw S, Orton DI. Allergic contact otitis externa due to iodoform in BIPP cavity dressings. *Contact Dermatitis* 2002; **46**: 360.

16 Cockerill D. Allergies to ear moulds. A study of reactions encountered by hearing aid users to some ear mould materials. *Br J Audiol* 1987; **21**: 145.

Differential diagnosis. The part played by trauma, environment, infection, sensitization and altered physiology and anatomy must be assessed and evaluated as accurately as possible. Difficulties often arise in the interpretation of bacteriological and mycological findings. 'Hearing-aid dermatitis' is more often due to traumatic and physical factors than to allergic sensitivity. Sensitivity to topical antibiotics may be occult, especially when they are prescribed in combination with corticosteroids, and are one cause of chronicity. Contact hypersensitivity to aural treatments (see below) may produce eczema that extends onto facial skin anterior to, or below, the ear. The importance of perineal and nasal transfer of infection should not be underestimated, and mechanical interference with the external auditory canal in patients with otitis externa tends to be the rule rather than the exception.

External otitis is unlikely to be confused with any other condition except perhaps psoriasis and eczema, and these, of course, may coexist. Middle-ear disease, past and present, should always be excluded.

Swabs should be taken for bacteriological culture and epithelial debris examined and sent for mycological culture. Potassium hydroxide preparations showing evidence of epithelial invasion with hyphae are probably more important in this respect than a positive culture, which may simply indicate commensal or saprophytic infection.

In any long-standing or resistant case, patch testing with a special 'ear battery' [1] should be undertaken to rule out unsuspected contact dermatitis. If there is excess granulation, middle-ear disease should be ruled out, and if the patient is diabetic, debilitated, very young, elderly or immunosuppressed, malignant otitis externa must also be excluded.

Another condition that may need to be considered is *bullous myringitis*, an uncommon condition probably due to upper respiratory tract viral infection (e.g. influenza), which presents with single or multiple bullae on the tympanic membrane and adjacent canal wall. It can resemble bullous external otitis, which is usually due to *Pseudomonas*. Sudden, severe pain is a feature, but this resolves rapidly after rupture of the bullae. Furuncles of the external auditory canal are described below. Other bacteria may be a rare cause, for example gonococcal otitis externa [2].

Complications. Recurrent otitis externa may also develop into hypertrophic otitis externa or localized elephantiasis nostra [3] of the ears as a result of the effects of chronic lymphatic obstruction. The resultant narrowing of the external acoustic canal coupled with the underlying lymphoedema makes recurrent and repeated infections even more likely.

Secondary trauma. Once an irritable focus occurs in the canal, energetic attempts to remove wax or debris or to satisfy the urge to rub or scratch the infected area often intensify the inflammation. Cotton buds, although frequently regarded as safe, are a common cause of tympanic perforation [4].

Secondary sensitization. This is usually a consequence of treatment or a reaction to objects placed in the ear to alleviate itching. Therapeutic agents may therefore enhance and perpetuate the condition for which they were prescribed. The commonest causes are neomycin, framycetin (Soframycin®) and gentamicin, with quinoline mix, which includes iodoform, and the caine mix giving a much lower level of positive reactions in a recent series [1]; allergy to topical corticosteroids used in the ear may also occur [5]. Allergy to topical medicaments is found in as many as 40% of patients with chronic or treatment-resistant otitis externa [6]. In only about 20% of cases is there improvement after discontinuing topical agents to which patients have been shown to be allergic [5].

Sensitivity to nail varnish may be misconstrued as lichen simplex and, in women who are nickel sensitive, otitis externa may be aggravated by using metal objects to alleviate itching or to clear the ear. Otoscopes themselves may release nickel. Another source of contact dermatitis is chromate [7] or phosphorus sesquisulphide in match heads, which some people use to scratch their ears.

Benign non-necrotizing otitis externa. This usually presents as chronic, non-painful otorrhoea with an ulcer present in the floor of the external canal. Surgery may be a better alternative than long-term medical management [8].

Allergic and 'ide' reactions [9,10]. A few well-documented cases have been reported in which recurrent pruritus, oedema and scaling of the ear canal have occurred in response to fungal infection at a distant body site, or associated with food or drug allergies. Some such cases also have an 'ide' reaction affecting the hands or other areas.

References

1 Millard TP, Orton DI. Changing patterns of contact allergy in chronic inflammatory ear disease. *Contact Dermatitis* 2004; **50**: 83–6.
2 Pareek SS. Gonococcal otitis externa. *N Engl J Med* 1979; **300**: 1490.
3 Grant JM. Elephantiasis nostra verrucosa of the ears. *Cutis* 1982; **29**: 441–4.
4 Robertson MS. A critical comment on the use of cotton buds. *N Z Med J* 1971; **86**: 102–3.
5 Devos SA, Mulder JJS, van der Valk PGM. The relevance of positive patch test reactions in chronic otitis externa. *Contact Dermatitis* 2000; **42**: 354–5.
6 Fraki JE, Kalimo K, Tuohimaa P *et al.* Contact allergy to various components of topical preparations for treatment of external otitis. *Acta Otolaryngol (Stockh)* 1985; **100**: 414–8.
7 McKelvie M, McKelvie P. Some aetiological factors in otitis externa. *Br J Dermatol* 1966; **78**: 227–31.
8 Wormald PJ. Surgical management of benign necrotizing otitis externa. *J Laryngol Otol* 1994; **108**: 101–5.
9 Brown WH. Some observations on neurodermatitis of the scalp, with particular reference to tinea amiantacea. *Br J Dermatol Syphil* 1948; **60**: 81–90.
10 Jones EH. *External Otitis*. Springfield, IL: Thomas, 1965.

Treatment [1–4]. The general principles of treatment of otitis externa are to relieve pain [4], reduce itching, prevent trauma and avoid known sensitizers. Significant infective organisms should be identified and treated appropriately, although in practice treatment will be initiated before results are available.

Many mild cases of otitis externa will respond to simple aural toilet, optimally with careful suction and under direct vision, followed by the use of an acidifying and drying agent. Flushing of the ear canal should not be attempted unless the tympanic membrane has been clearly visualized. Moderately severe cases are likely to require topical treatment as outlined below. Systemic antibiotics are not usually needed [4].

When there is coexistent eczema, combined steroid–antiseptic or steroid–antibiotic drops or wicks can be used. In chronic cases, a great variety of treatments will already have been given and medicament contact dermatitis will therefore be more likely. Because this is often occult, patch testing should be done in all patients with chronic disease.

Pain is often severe, especially with acute staphylococcal infections, and strong analgesics may be required. Local heat also often helps. Bed rest and daily wicks or dressing may be needed in the more severe case.

If there is significant pyrexia (>38.3°C), lymphadenopathy, concurrent otitis media or failure to improve with topical therapy, an oral antibiotic should be used, for example a cephalosporin or fluoroquinolone. If pain is very severe, granulations are present in the canal or the patient is diabetic or immunocompromised, there should be suspicion for invasive (necrotizing) otitis (see p. 68.25).

Topical treatment. This is the essential part of therapy and the most difficult to carry out satisfactorily. Ear drops are of less value than regular cleaning of the ear, and this initially needs to be done daily by a doctor or an experienced nurse. Less severe cases may be treated once a week. Having cleaned the ear of debris and wax,

preferably by suction under direct vision, a wick may be inserted or the patient instructed to apply ear drops regularly. When the cartilaginous portion of the canal alone is involved, the patient can be shown how to apply the prescribed medicament by holding a loose wool-tipped orange stick 2.5 cm from its end and inserting this until the fingers touch the tragus.

If wax is impacted, this can be softened with oil, glycerine or sodium bicarbonate eardrops and then removed either manually or by syringing, as long as the drum can be visualized and there is no perforation. Obstinate cases should be referred to an otologist. Some proprietary cerumenolytics are irritant and should be left in the ear for only 15–30 min before syringing.

In most chronic or complicated cases, treatment must be continued regularly for some weeks after apparent cure. Care must be taken to prevent cross-infection from other body sites, especially from the anterior vestibule of the nose or the perineum, and the ear should be kept as dry and as clean as possible.

A very large number of medicaments have been used in the treatment of uncomplicated, acute otitis externa and there is a dearth of good quality, randomized controlled trials (RCTs) on which to base a choice of treatment [3,4]. Simple antiseptics have an important role, aluminium acetate solution being especially useful against the expected pathogens [5,6] and as effective as hydrocortisone/neomycin/polymyxin drops [7]. Other antiseptics used include 70–85% isopropyl alcohol, 1–2% acetic acid, and 2% salicylic acid in 60% spirit. If acidic ear drops cause a burning sensation, ophthalmic hydrogen peroxide drops are a practical substitute. Wicks with 8–13% aluminium acetate, 0.25–0.5% silver nitrate, or glycerine and ichthyol are used to treat hypertrophic otitis externa. Corticosteroids with or without antimicrobials are commonly used as first line treatment. Only one RCT has shown a topical steroid to be better than placebo [8], and interestingly hydrocortisone, a weak steroid, may be as effective as hydrocortisone butyrate, classed as potent [9]. Topical steroids are more commonly used with antibiotics, usually neomycin, framycetin (Soframycin®), gentamicin, polymyxin or a quinolone such as ofloxacin. The combination of neomycin and polymyxin will cover both *S. aureus* and *Ps. aeruginosa*. Topical ofloxacin is as effective and only has to be used twice daily [10]. There is probably no difference in efficacy between these many preparations [3,11], except with regard to the risk of sensitization and cross-sensitization, the quinolones probably representing less risk. Long term continuous use is therefore best avoided. For patients with chronic or chronic relapsing otitis externa, an antiseptic such as iodochlorhydroxyquinoline (Vioform®, chinoform) can be used alone or in combination with corticosteroids and aluminium acetate has the advantage of a lack of sensitizing potential.

The role of antifungals is not clear [3], but if fungi are thought to be contributory the imidazoles have largely replaced nystatin and amphotericin as they are active against *Aspergillus* as well as against *Candida*, although acetic acid, boric acid and 25% *m*-cresyl acetate may still at times be useful; 2% salicylic acid in spirit is useful for prophylaxis.

Several ear-drops, for example the aminoglycosides, chlorhexidine, polymyxin and chloramphenicol, are potentially ototoxic [12,13] and should be avoided in the presence of tympanic perforation.

In all cases of external otitis, treatment should be prolonged beyond the time of apparent recovery and patients should be advised how best to avoid recurrence and about the dangers of indiscriminate or prolonged self-medication.

Surgical treatments. Occasionally, chronic otitis externa is due to narrowing of the external auditory meatus. Surgical enlargement of the meatus can then bring about resolution [14–16].

References

1 Roland PS. External otitis: a challenge in management. *Curr Infect Dis Rep* 2000; **2**: 160–7.
2 Sander R. Otitis externa: a practical guide to treatment and prevention. *Am Fam Physician* 2001; **63**: 927–36, 941–2.
3 Hajioff D. Otitis externa. *BMJ Clinical Evidence* [online] 2006 [accessed Sept. 1, 2008]. http://clinicalevidence.bmj.com/ceweb/conditions/ent/0510/0510.jsp
4 Rosenfeld RM, Brown L, Cannon CR *et al*. Clinical practice guideline: acute otitis externa. *Otolaryngol Head Neck Surg* 2006; **134**: S4–23.
5 Thorpe MA, Kruger J, Oliver S *et al.* The antibacterial activity of acetic acid and Burow's solution as topical otological preparations. *J Laryngol Otol* 1998; **112**: 925–8.
6 Kashiwamura M, Chida E, Matsumura M *et al*. The efficacy of Burow's solution as an ear preparation for the treatment of chronic ear infections. *Otol Neurotol* 2004; **25**: 9–13.
7 Lambert IJ. A comparison of the treatment of otitis externa with 'Otosporin' and aluminium acetate: a report from a services practice in Cyprus. *J R Coll Gen Pract* 1981; **31**: 291–4.
8 Jacobsson S, Karlsson G, Rigner P *et al*. Clinical efficacy of budesonide in the treatment of eczematous external otitis. *Eur Arch Otorhinolaryngol* 1991; **248**: 246–9.
9 Buch-Rasmussen A. Hydrocortisone alcoholic solution in eczematous external otitis. *J Int Med Res* 1979; **7**: 449–51.
10 Ruben RJ. Efficacy of ofloxacin and other otic preparations for otitis externa. *Pediatr Infect Dis J* 2001; **20**: 108–10.
11 Rosenfeld RM, Singer M, Wasserman JM, Stinnett SS. Systematic review of topical antimicrobial therapy for acute otitis externa. *Otolaryngol Head Neck Surg* 2006; **134**: S24–48.
12 Brummett RE, Harris RF, Lindgren JA. Detection of ototoxicity from drugs applied topically to the middle ear space. *Laryngoscope* 1976; **86**: 1177–87.
13 Mittelman H. Ototoxicity of 'ototopical' antibiotics: past, present, and future. *Trans Am Acad Ophthalmol Otolaryngol* 1977; **76**: 1432–43.
14 Hunsaker DH. Conchomeatoplasty for chronic otitis externa. *Arch Otolaryngol Head Neck Surg* 1988; **114**: 395–8.
15 Roland PS. Chronic external otitis. *Ear Nose Throat J* 2001; **80** (6 Suppl.): 12–6
16 Jacobsen N, Mills R. Management of stenosis and acquired atresia of the external auditory meatus. *J Laryngol Otol* 2006; **120**: 266–71.

Invasive external otitis [1,2]

Synonyms
- Malignant external otitis
- Necrotizing external otitis

This is an infection of the skin of the external ear canal that spreads to deeper structures and causes necrosis.

Aetiology. In most cases, the infecting organism is *Ps. aeruginosa*, although occasionally other organisms have been involved: *S. aureus* [3], *S. epidermidis* [4], *Klebsiella oxytoca* [5], and fungi such as mucormycosis [6], *Candida glabrata* [7], *Aspergillus* [8,9], *Malassezia sympodialis* [10], *Scedosporium apiospermum* [11] and *Actinomycetes.* The condition characteristically occurs in elderly diabetics [12,13] but is also seen with some frequency in the immunocompromised,

including patients with HIV infection [1,13,14]; it has also been reported in association with diabetes insipidus [15]. Cases have been reported in children [16–18] in whom chronic illness or immunosuppression is usually present. In diabetics, microangiopathy may be important in the pathogenesis [1]. It is possible that abnormalities of cellular immunity and polymorphonuclear function are important in some cases [19,20], but in many instances the pathogenesis is poorly understood.

Pathology. In most cases, there is evidence of osteomyelitis [5]. An early event is acellular necrosis of cartilage [21].

Clinical features. Quite often there is a preceding history of irrigation of the ear. The commonest presenting symptom is pain, which is usually very severe and persistent. It may spread from the region of the ear to the vertex, temporal or occipital areas, and there may be temporomandibular joint pain. Pain progresses more quickly in children than adults. The second most common symptom is discharge from the ear. In up to 50% there is some degree of hearing loss. Systemic symptoms, including fever, are uncommon [1]. There may be symptoms due to involvement of cranial nerves, particularly dysphagia.

On examination the external auditory canal is always abnormal, with varying degrees of oedema and erythema, and extensive granulation tissue formation is evident. This is particularly seen on the posterior and inferior aspect of the wall and at the junction between the bony and cartilaginous segments of the canal. There may be swelling of the soft tissues around the ear. The tympanic membrane is frequently necrotic in children but characteristically spared in adults [18]. Cranial neuropathies may be found in up to 40% of patients [1,14]. Facial palsy is the most common finding but involvement of cranial nerves IV, VI, VIII, IX, X and XII may be variably present. When such nerve involvement is found, the disease is more extensive.

Investigations usually show elevation of the erythrocyte sedimentation rate, but the white-cell count is often normal.

Diagnosis. Invasive external otitis is usually diagnosed on clinical suspicion. It is essential to obtain material for culture to determine the infective cause, and samples should be taken from the ear canal, granulations, soft tissue and bone, depending on the case. Blood cultures may also be valuable.

Imaging techniques can be helpful, particularly in diagnosing bony involvement and following progress of the disease, and should enable granular external otitis to be distinguished from the much more serious invasive external otitis. Plain films, computed tomography (CT), bone scans, magnetic resonance imaging (MRI) and single-photon emission tomography (SPECT) have all been used. MRI with or without gadolinium enhancement is probably the best technique for imaging soft-tissue involvement, and for evaluation of the meninges and changes within the osseous medullary cavity, although CT is preferred for the initial diagnosis and recognition of cortical bone erosion [22,23]. When available, SPECT is probably the best method for initial diagnosis of the distinctive bony changes, and gallium scintigraphy most useful for assessing response to treatment [24].

Complications. Spread of the disease can produce parotitis, mastoiditis or osteomyelitis of the base of the skull and thence spread to the contralateral side. Meningitis can occur, and is an important cause of death. Cranial nerve paralysis may result in aspiration pneumonia. A rare complication is destructive osteomyelitis of the temporomandibular joint [25]. Overall, there is a mortality of 10–20%; in the presence of cranial neuropathies the mortality has been high [1,14] but with prolonged courses of appropriate antibiotics is less nowadays [26]. Facial nerve palsy is less likely to recover than that of other cranial nerves [26].

Treatment. Because of the range of possible infections, it is essential to base treatment on the result of culture. For *Pseudomonas*, the traditional approach has been to use an extended-spectrum antipseudomonal penicillin for 4–8 weeks and an aminoglycoside for 4–6 weeks [1]. Ciprofloxacin [27,28] can be successful if used early in the course of disease but drug resistance is increasing [29]. When there is evidence of extensive bone destruction, removal of necrotic material is necessary. Some cases fail to respond to antibiotic therapy and, if the facility is available, hyperbaric oxygen can improve the outlook [30]. Ascorbic acid has also been recorded as an adjuvant therapy [19].

When the infective cause is bacteria other than *Pseudomonas* or is a fungus, advice on the choice of antimicrobial agent should be taken from a microbiologist.

References

1 Doroghazi RM, Nadol JB Jr, Hyslop NE Jr *et al.* Invasive external otitis. Report of 21 cases and review of the literature. *Am J Med* 1981; **71**: 603–14.

2 Rubin Grandis J, Branstetter BF 4th, Yu VL. The changing face of malignant (necrotising) external otitis: clinical, radiological, and anatomic correlations. *Lancet Infect Dis* 2004; **4**: 34–9.

3 Keay DG, Murray AM. Clinical records: malignant external otitis due to *Staphylococcus* infection. *J Laryngol Otol* 1988; **102**: 926–7.

4 Barrow HN, Levenson MJ. Necrotizing 'malignant' external otitis caused by *Staphylococcus epidermidis*. *Arch Otolaryngol Head Neck Surg* 1992; **118**: 94–6.

5 Bernheim J, Sade J. Histopathology of the soft parts in 50 patients with malignant external otitis. *J Laryngol Otol* 1989; **103**: 366–8.

6 Parfrey NA. Improved diagnosis and prognosis of mucormycosis. A clinicopathologic study of 33 cases. *Medicine* (Baltimore) 1986; **65**: 113–23.

7 Bae WK, Lee KS, Park JW *et al.* A case of malignant otitis externa caused by *Candida glabrata* in a patient receiving haemodialysis. *Scand J Infect Dis* 2007; **39**: 370–2.

8 Gordon G, Giddings NA. Invasive otitis externa due to *Aspergillus* species: case report and review. *Clin Infect Dis* 1994; **19**: 866–70.

9 Anderson LL, Giandoni MB, Keller RA, Grabski WJ. Surgical wound healing complicated by *Aspergillus* infection in a non-immunocompromised host. *Dermatol Surg* 1995; **21**: 799–801.

10 Chai FC, Auret K, Christiansen K *et al.* Malignant otitis externa caused by *Malassezia sympodialis*. *Head Neck* 2000; **22**: 87–9.

11 Yao M, Messner AH. Fungal malignant otitis externa due to *Scedosporium apiospermum*. *Ann Otol Rhinol Laryngol* 2001; **110**: 377–80.

12 Lang R, Goshen S, Kitzes-Cohen R *et al.* Successful treatment of malignant external otitis with oral ciprofloxacin: report of experience with 23 patients. *J Infect Dis* 1990; **161**: 537–40.

13 Kielhofner M, Atmar RL, Hamill RJ. Life-threatening *Pseudomonas aeruginosa* infections in patients with human immunodeficiency virus infection. *Clin Infect Dis* 1992; **14**: 403–11.

14 Rubin J, Yu VL. Malignant external otitis: insights into pathogenesis, clinical manifestations, diagnosis and therapy. *Am J Med* 1988; **85**: 391–8.

15 Giguere P, Rouillard G. Otite externe maligne bilatérale chez une fillete de 10 ans. *J Otolaryngol* 1976; **5**: 159–66.

16 Coser PL, Stamm AEC, Lobo RC *et al.* Malignant external otitis in infants. *Laryngoscope* 1980; **90**: 312–6.
17 Joachims HZ. Malignant external otitis in children. *Arch Otolaryngol* 1976; **102**: 236–7.
18 Rubin J, Yu VL, Stool SE. Malignant external otitis in children. *J Pediatr* 1988; **113**: 965–70.
19 Corberand J, Nguyen F, Fraysse B *et al.* Malignant external otitis and polymorphonuclear leukocyte migration impairment: improvement with ascorbic acid. *Arch Otolaryngol* 1982; **108**: 122–4.
20 Yust I, Radiano C, Tartakovsky B *et al.* Impairment of cellular immunity in patients with malignant external otitis. *Acta Otolaryngol* 1980; **90**: 398–403.
21 Ostfeld E, Segal M, Czernobilsky B. Malignant external otitis: early histopathologic changes and pathogenic mechanism. *Laryngoscope* 1981; **91**: 965–70.
22 Gherini SG, Brackmann DE, Bradley WG. Magnetic resonance imaging and computerized tomography in malignant otitis externa. *Laryngoscope* 1986; **96**: 542–8.
23 Grandis JR, Curtin HD, Yu VL. Necrotizing (malignant) external otitis: prospective comparison of CT and MR imaging in diagnosis and follow-up. *Radiology* 1995; **196**: 499–504.
24 Okpala NC, Siraj QH, Nilssen E, Pringle M. Radiological and radionuclide investigation of malignant otitis externa. *J Laryngol Otol* 2005; **119**: 71–5.
25 Midwinter KI, Gill KS, Spencer JA, Fraser ID. Osteomyelitis of the temporomandibular joint in patients with malignant otitis externa. *J Laryngol Otol* 1999; **113**: 451–3.
26 Mani N, Sudhoff H, Rajagopal S *et al*. Cranial nerve involvement in malignant external otitis: implications for clinical outcome. *Laryngoscope* 2007; **117**: 907–10.
27 Brody T, Pensak ML. The fluoroquinolones. *Am J Otol* 1991; **12**: 477–9.
28 Morrison GAJ, Bailey CM. Relapsing malignant otitis externa successfully treated with ciprofloxacin. *J Laryngol Otol* 1988; **102**: 872–6.
29 Berenholz L, Katzenell U, Harell M. Evolving resistant pseudomonas to ciprofloxacin in malignant otitis externa. *Laryngoscope* 2002; **112**: 1619–22.
30 Davis JC, Gates GA, Lerner C *et al.* Adjuvant hyperbaric oxygen in malignant external otitis. *Arch Otolaryngol Head Neck Surg* 1992; **118**: 89–93.

Furunculosis

Synonym
- Acute localized external otitis

A furuncle is a staphylococcal infection of a hair follicle [1]. A common site is between the junction of the tragus and the anterior crus of the helix. Furuncles also may occur in the skin of the external auditory canal at the junction with the concha. Coalescence of adjacent infected follicles results in a carbuncle.

The patient presents with pain, which can be aggravated by chewing if there is involvement of the anterior wall of the canal. There may be sufficient swelling to obstruct the entrance to the canal. There is often regional lymphadenopathy and sometimes fever.

Furunculosis can usually be distinguished from external otitis by the normal appearance of the canal epithelium and an absence of discharge; the two conditions can, however, coexist. If possible the tympanic membrane should be examined, in order to exclude otitis media and mastoiditis.

Localized lesions associated with mild swelling usually respond to an oral antistaphylococcal antibiotic [1]. If an abscess or carbuncle is present, incision and drainage is usually necessary. The latter can be achieved with a wick. Any draining material should be sent for culture and antibacterial sensitivities.

Reference

1 Hirsch BE. Infection of the external ear. *Am J Otolaryngol* 1992; **13**: 145–55.

Otomycosis

Otomycosis is an inflammatory process due to a variety of yeast and fungal organisms as the primary aetiological agent. The same range of fungi may be found in patients with multifactorial or bacterial external otitis (see above).

Aetiology. The species of fungus and yeast involved vary somewhat depending on ambient climate. In most tropical regions of the world *Aspergillus* species account for the majority of isolates, whereas in temperate areas *Candida albicans* is the most frequent [1]. Others include phycomycetes, *Rhizopus*, *Actinomyces* and *Penicillium*. The fact that these organisms can be pathogenic as well as saprophytic has been confirmed in a number of studies [2–5].

The factors that convert organisms that are normally saprophytic into pathogens are similar to those that apply to bacterial external otitis. Local trauma, heat and humidity are foremost, and account for the frequency of otomycosis in the tropics and in those using hearing aids or occlusive ear moulds. Diabetes mellitus, immunosuppression, systemic and topical antibiotics, and steroids are also important.

Clinical features. The principal symptom is usually itching, which can have a quality of being deep inside the ear. This is often accompanied by a sensation of fullness. Pain is uncommon, in contrast to bacterial external otitis. Discharge, if any, is usually slight. There may be hearing loss of a conductive type. Because of the irritation, patients are liable to traumatize the canal and may then initiate the symptoms and signs of bacterial external otitis. The most important complication is perforation of the eardrum [6].

On examination the dominant feature is the presence of wispy filamentous masses, which may be isolated or diffusely present in the canal. These masses are white, grey or stippled black if *Aspergillus* is present. Inflammation of the canal epithelium is usually mild. There may be some epithelial debris, which may be either moist or dry.

Diagnosis. The clinical appearance is usually distinctive. As always with external canal disorders it is important to check for other pathology. Material can be taken for mycological examination and culture.

Treatment [7]. Careful cleaning followed by drying is a prerequisite to successful management. The canal can then be wiped out, for example with *m*-cresyl acetate or 1% thymol in 70% alcohol, and the specific treatment applied on a wick. Treatment should be changed daily until a satisfactory result has been achieved. Many agents have been advocated for otomycosis, but there is little evidence to promote one above the others. They include aluminium acetate, acetic acid, *m*-cresyl acetate, thiomersal, gentian violet, clioquinol, nystatin, amphotericin and the imidazoles.

In rare situations, usually in immunosuppressed patients, there may be cellulitis of the surrounding soft tissues directly due to fungal infection. In such cases, itraconazole is likely to be the treatment of choice. Oral terbinafine has also been used when other treatments have failed [8].

References

1 Lucente FE. Fungal infections of the external ear. *Otolaryngol Clin North Am* 1993; **26**: 995–1006.
2 Nielsen PG. Fungi isolated from chronic external ear disorders. *Mykosen* 1985; **28**: 234–7.
3 Sood VB, Sinha A, Mohaoatra LN. Otomycosis: a clinical entity—clinical and experimental study. *J Laryngol Otol* 1988; **81**: 999–1173.
4 Stern JC, Lucente FE. Otomycosis. *Ear Nose Throat J* 1988; **67**: 804–10.
5 Talwar P, Chakrabarti A, Kaur P *et al.* Fungal infection of ear with special reference to chronic suppurative otitis media. *Mycopathologia* 1988; **104**: 47–50.
6 Hurst WB. Outcome of 22 cases of perforated tympanic membrane caused by otomycosis. *J Laryngol Otol* 2001; **115**: 879–80.
7 Lucente FE. Diseases due to infection. In: Lucente FE, Lawson W, Novick NL, eds. *The External Ear*. Philadelphia: Saunders, 1995: 81–6.
8 Rotoli M, Sascaro G, Cavalier S. *Aspergillus versicolor* infection of the external auditory canal successfully treated with terbinafine. *Dermatology* 2001; **202**: 143.

HIV, AIDS and the external ear

The consequences of HIV infection will at times be seen on the pinna and in the external auditory canal [1,2]. The ear is a relatively common site for manifestation of Kaposi's sarcoma. Florid seborrhoeic dermatitis is often a presenting feature of AIDS. The occurrence of molluscum contagiosum lesions in an adult should prompt a suspicion of immunodeficiency; on the ear the lesions can resemble basal cell carcinoma. Bacillary angiomatosis may produce vascular papules and nodules on the ear. Herpes simplex and zoster can be more florid in patients with AIDS. Polyps in the external auditory canal due to *Pneumocystis carinii* have been described [3,4] and can invade the middle ear and middle cranial fossa [5]. Invasive external otitis (see p. 68.25) is a well-recognized consequence of HIV-related immunosuppression [6]. Cryptococcosis of the external ear can be a presenting sign of AIDS [7]. Excessive growth of ear hair has been noted [8].

References

1 Lucente FE. Diseases due to infection. In: Lucente FE, Lawson W, Novick NL, eds. *The External Ear*. Philadelphia: Saunders, 1995: 95–6.
2 Truitt TO, Tami TA. Otolaryngologic manifestations of human immunodeficiency virus infection. *Med Clin North Am* 1999; **83**: 303–15.
3 Gherman CR, Ward RR, Bassis ML. *Pneumocystis carinii* otitis media and mastoiditis as the initial manifestation of the acquired immunodeficiency syndrome. *Am J Med* 1988; **85**: 250–2.
4 Praveen CV, Terry RM, Elmahallawy M, Horsfield C. Pneumocystis carinii infection in bilateral aural polyps in a human immunodeficiency virus-positive patient. *J Laryngol Otol* 2002; **116**: 288–90.
5 Patel SK, Philpott JM, McPartlin DW. An unusual case of *Pneumocystis carinii* presenting as an aural mass. *J Laryngol Otol* 1999; **113**: 555–7.
6 Hern JD, Almeyda J, Thomas DM *et al.* Malignant otitis externa in HIV and AIDS. *J Laryngol Otol* 1996; **110**: 770–5.
7 Velesrubio F, Walters D, Fulcher J *et al*. Auricular cryptococcosis as the initial presentation of AIDS. *Otolaryngol Head Neck Surg* 2007; **136**: 493–4.
8 Tosti A, Gaddoni G, Peluso AM *et al.* Acquired hairy pinnae in a patient infected with the human immunodeficiency virus. *J Am Acad Dermatol* 1993; **28**: 513.

Tumours of the pinna and external auditory canal [1]

Benign tumours

On the pinna, these will present as papules or nodules, sometimes with distinctive morphology. In the external auditory canal, benign tumours tend to present with hearing loss and may predispose to infection [2].



Fig. 68.19 Seborrhoeic keratosis (basal cell papilloma) of the pinna.



Fig. 68.20 Lobulated capillary haemangioma (pyogenic granuloma). A bright-red nodule with a surrounding collarette of keratin.

Benign tumours found on the pinna include melanocytic naevus, seborrhoeic keratosis (Fig. 68.19), squamous cell papilloma, pilomatrixoma [3,4], trichoepithelioma [5], trichofolliculoma [6,7], Winer's dilated pore [8], myoma, chondroma, osteoma, fibroma [9], neurofibroma [10], neurilemmoma [11], granular cell tumour, haemangioma (Fig. 68.20) and lymphangioma [12]. Benign glandular tumours may occur on the pinna, but are more common in the canal, especially sebaceous adenoma. Occasional unique lesions have been described [13].

Benign mass lesions in the canal include exostosis and osteoma, fibrous dysplasia both monostotic and polyostotic (Albright's syndrome), eosinophilic granuloma, cholesteatoma and keratosis obturans (see p. 68.35), benign ceruminous gland tumours

(see below), cartilaginous choristomas [14] and temporomandibular joint herniation [15].

Papillomatosis of the external auditory canal presents with multiple rounded papules; it has been associated with human papillomavirus (HPV) 6 [16].

Extra-adrenal paraganglioma (glomus jugulare tumour) of the temporal bone can manifest in the external ear canal as a friable haemorrhagic neoplasm and can cause conductive hearing loss [1]. This tumour can be locally aggressive, and there are rare instances of metastasis.

Various conditions can mimic benign tumours. On the pinna, these include cysts of various types, viral warts and molluscum contagiosum, chondrodermatitis, elastotic and weathering nodules, keloids, congenital malformations such as accessory tragi, nodular calcinosis, gouty tophi, deposits of amyloid, angiolymphoid hyperplasia with eosinophilia and 'pseudolymphoma', inflammatory polyps, hamartomas [17], choristomas [18] and congenital cysts of branchial arch origin in the external auditory canal. Cholesteatoma (see p. 68.35) may also occur in the external canal.

References

1 Hyams VJ. Pathology of tumours of the external ear. In: Lucente FE, Lawson W, Novick NL, eds. *The External Ear*. Philadelphia: Saunders, 1995: 108–48.
2 Tran LP, Grundfast KM, Selesnick SH. Benign lesions of the external auditory canal. *Otolaryngol Clin North Am* 1996; **29**: 807–25.
3 Vinayak BC, Cox GJ, Ashton-Key M. Pilomatrixoma of the external auditory meatus. *J Laryngol Otol* 1993; **107**: 333–4.
4 Sevin K, Can Z, Yilmaz S *et al*. Pilomatrixoma of the earlobe. *Dermatol Surg* 1995; **21**: 245–6.
5 Ferlito A, Recher G, Polidero F *et al*. Solitary trichoepithelioma and epithelioma adenoides cysticum of Brooke involving the external auditory meatus. *J Laryngol Otol* 1981; **95**: 835–41.
6 O'Mahony JJ. Trichofolliculoma of the external auditory meatus. Report of a case and review of the literature. *J Laryngol Otol* 1981; **95**: 623–5.
7 Srivastava RN, Ajwani KD. Trichofolliculoma. *Ear Nose Throat J* 1979; **58**: 159–60.
8 Ayoub OM, Timms MS, Mene A. Winer's dilated pore: rare presentation in the external ear canal. *Auris Nasus Larynx* 2001; **28**: 349–52.
9 Varletzides E, Grigoriades S, Tsiliguri E. An unusual localization of fibroma on the lobe of the ear. *Panminerva Med* 1980; **22**: 37–9.
10 Trevisani TP, Pohl AL, Matloub HS. Neurofibroma of the ear: function and aesthetics. *Plast Reconstr Surg* 1982; **70**: 217–9.
11 Fodor RI, Pastore PN, Frable MA. Neurilemmoma of the auricle: a case report. *Laryngoscope* 1977; **87**: 1760–4.
12 Grabb WC, Dingman RO, Oneal RM *et al*. Facial hamartomas in children: neurofibroma, lymphangioma and hemangioma. *Plast Reconstr Surg* 1980; **66**: 509–27.
13 Donati P, Balus L. Folliculosebaceous cystic hamartoma: reported case with a neural component. *Am J Dermatopathol* 1993; **15**: 277–9.
14 Lee FP. Cartilaginous choristoma of the bony external auditory canal: a study of 36 cases. *Otolaryngol Head Neck Surg* 2005; **133**: 786–90.
15 Tran LP, Grundfast KM, Selesnick SH. Benign lesions of the external auditory canal. *Otolaryngol Clin North Am* 1996; **29**: 807–25.
16 Xia M-Y, Zhu W-Y, Lu J-Y *et al*. Ultrastructure and human papillomavirus DNA in papillomatosis of external auditory canal. *Int J Dermatol* 1996; **35**: 337–9.
17 Hansen KK, Segura AD, Esterly NB. Solitary congenital nodule on the ear of an infant. *Pediatr Dermatol* 1993; **10**: 88–90.
18 Braun GA, Lowry D, Meyers A. Bilateral choristomas of the external auditory canals. *Arch Otolaryngol* 1978; **104**: 467–8.

Exostosis and osteoma

Exostoses of the external auditory canal are usually bilateral, symmetrical, multiple, diffuse, broadly based growths of bone arising from the tympanic bone in the external auditory canal [1,2]. Frequent exposure to cold water is an aetiological factor in nearly all cases [3]. Exostoses are very common in surfers, risk factors including years spent surfing and exposure to cold water [4–7]. A male who has been surfing more than 20 years has a 1 in 2 chance of having exostoses that impair hearing [7].

Osteomas can usually be differentiated by their solitary and unilateral distribution, although they may be similar to exostoses histologically [8]. They are often attached by a narrow pedicle to the tympanosquamous or tympanomastoid suture line [1].

Occasionally other fibro-osseous lesions are found which are neither exostosis nor osteoma [9,10].

Osteomas and exostoses are normally asymptomatic unless they enlarge sufficiently to block the external auditory canal [11]. Surgical removal may be indicated [12–15].

References

1 Graham MD. Osteomas and exostoses of the external auditory canal. A clinical, histopathologic and scanning electron microscopic study. *Ann Otol Rhinol Laryngol* 1979; **88**: 566–72.
2 Sheehy JL. Diffuse exostoses and osteomata of the external auditory canal: a report of 100 operations. *Otolaryngol Head Neck Surg* 1982; **90**: 337–42.
3 di Bartolomeo JR. Exostoses of the external auditory canal. *Ann Otol Rhinol Laryngol* 1979; **88** (Suppl. 61): 2–20.
4 Chaplin JM, Stewart IA. The prevalence of exostoses in the external auditory meatus of surfers. *Clin Otolaryngol* 1998; **23**: 326–30.
5 Wong BJ, Cervantes W, Doyle KJ *et al*. Prevalence of external auditory canal exostoses in surfers. *Arch Otolaryngol Head Neck Surg* 1999; **125**: 969–72.
6 Kroon DF, Lawson ML, Derkay CS *et al*. Surfer's ear: external auditory exostoses are more prevalent in cold water surfers. *Otolaryngol Head Neck Surg* 2002; **126**: 499–504.
7 Hurst W, Bailey M, Hurst B. Prevalence of external auditory canal exostoses in Australian surfboard riders. *J Laryngol Otol* 2004; **118**: 348–51.
8 Fenton JE, Turner J, Fagan PA. A histopathologic review of temporal bone exostoses and osteomata. *Laryngoscope* 1996; **106**: 624–8.
9 Tran LP, Grundfast KM, Selesnick SH. Benign lesions of the external auditory canal. *Otolaryngol Clin North Am* 1996; **29**: 807–25.
10 Ramirez-Camacho R, Vicente J, Berrocal JRG *et al*. Fibro-osseous lesions of the external auditory canal. *Laryngoscope* 1999; **109**: 488–91.
11 Kemink JL, Graham MD. Osteomas and exostoses of the external auditory canal: medical and surgical management. *J Otolaryngol* 1982; **11**: 101–6.
12 Whitaker SR, Cordier A, Kosjakov S, Charbonneau R. Treatment of external auditory canal exostoses. *Laryngoscope* 1998; **108**: 195–9.
13 Timofeev I, Notkina N, Smith IM. Exostoses of the external auditory canal: a long-term follow-up study of surgical treatment. *Clin Otolaryngol Allied Sci* 2004; **29**: 588–94.
14 Sanna M, Russo A, Khrais T *et al*. Canalplasty for severe external auditory meatus exostoses. *J Laryngol Otol* 2004; **118**: 607–11.
15 Vasama JP. Surgery for external auditory canal exostoses: a report of 182 operations. *ORL J Oto-Rhino-Lary* 2003; **65**: 189–92.

Glandular tumours

Tumours of the ceruminous glands are rare. It is often difficult to distinguish between adenoma and carcinoma on histological grounds [1,2]. The tumours comprise benign and pleomorphic adenomas, adenocarcinomas, adenoid cystic carcinomas and perhaps others including mucoepidermoid carcinomas. The glandular tissue of a ceruminous adenoma has myoepithelial basal cells which are positive for CK5/6, S100 and p63 and luminal ceruminous cells which stain for CK7 [3]. Tumours of the cerumen glands have been reported in association with other sweat gland tumours elsewhere [4].

Isolated cases of syringocystadenoma papilliferum, apocrine cystadenoma, benign eccrine cylindroma, hidradenoma papilliferum and carcinomas of eccrine and sebaceous origin have also been reported [5,6].

Extramammary Paget's disease of the external ear and/or canal resembles Bowen's disease or a dermatosis [7].

Benign tumours produce symptoms of obstruction and hearing loss. Pain is the usual presenting feature of the more malignant tumours. They are usually seen as polypoid masses in the canal. Other symptoms include bleeding, otorrhoea and, with spread of the neoplasm, nerve palsies.

Treatment is the province of the otorhinolaryngologist. Because of the potential for malignant behaviour, all ceruminous gland tumours should be fully excised with an adequate margin of normal tissue [8].

References

1 Lynde CW, McLean DI, Wood WS. Tumors of the ceruminous glands. *J Am Acad Dermatol* 1984; **11**: 841–7.
2 Lassaletta L, Patron M, Oloriz J *et al*. Avoiding misdiagnosis in ceruminous gland tumours. *Auris Nasus Larynx* 2003; **30**: 287–90.
3 Thompson LD, Nelson BL, Barnes EL. Ceruminous adenomas: a clinicopathologic study of 41 cases with a review of the literature. *Am J Surg Pathol* 2004; **28**: 308–18.
4 Habib MA. Ceruminoma in association with other sweat gland tumours. *J Laryngol Otol* 1981; **95**: 415–20.
5 Dehner LP, Chen KTK. Primary tumours of the external and middle ear: benign and malignant glandular neoplasms. *Arch Otolaryngol* 1980; **106**: 13–9.
6 Nissim F, Czernobilsky B, Ostfeld E. Hidradenoma papilliferum of the external auditory canal. *J Laryngol Otol* 1981; **95**: 843–8.
7 Gonzalez-Castro J, Iranza P, Palou J, Mascaro JM. Extramammary Paget's disease of the external ear. *Br J Dermatol* 1998; **138**: 914–5.
8 Mansour P, George MK, Pahor AL. Ceruminous gland tumours: a reappraisal. *J Laryngol Otol* 1992; **106**: 727–32.

Premalignant epithelial neoplasms of the auricle

Because of its high level of exposure to UV radiation [1], especially in men, the auricle is a common site for premalignant and malignant lesions of epidermal origin. Other predisposing factors include prior ionizing radiation, a chronic dermatosis such as lupus vulgaris, and genetic factors such as xeroderma pigmentosum and Gorlin's syndrome.

The commonest premalignant lesion is the solar keratosis, which can occur on all sun-exposed aspects of the auricle, but is especially common on the upper surface of the helix [2,3]. The clinical presentations include an erythematous telangiectatic patch, a focal area of scaling or hyperkeratosis, or a cutaneous horn. Solar keratoses on the auricle are often multiple. Solar elastosis may be evident in the surrounding skin. On the auricle, progression to squamous carcinoma from solar keratosis may occur more readily than at other sites [4].

Other premalignant lesions include Bowen's disease, radiation and tar keratoses and, rarely, keratoacanthoma [5,6].

Treatment. Several forms of treatment can eradicate premalignant lesions from the auricle, but there are no adequate data to compare them. They include excision, curettage, electrosurgery, cryotherapy, 5-fluorouracil and photodynamic therapy. The choice will depend on a number of factors, including the need for a tissue diagnosis, size and location of the lesion, likely cosmetic outcome and the available facilities. Follow-up is important for detection of recurrences and the appearance of new lesions. Lesions closely resembling squamous carcinoma, such as keratoacanthoma, should probably be totally excised to ensure accurate diagnosis [6].

References

1 Green A, Williams G. Ultraviolet radiation and skin cancer: epidemiological data from Australia. In: Young AR, Moan J, Bjorn LO, Nultsch W, eds. *Environmental UV Photobiology*. New York: Plenum Press, 1993: 233–54.
2 Byers R, Kesler K, Redman B *et al.* Squamous carcinoma of the external ear. *Am J Surg* 1983; **146**: 447–50.
3 Freedlander E, Chung FF. Squamous cell carcinoma of the pinna. *Br J Plast Surg* 1983; **36**: 171–5.
4 Blake GB, Wilson SP. Malignant tumours of the ear and their treatment: 1. Tumours of the auricle. *Br J Plast Surg* 1974; **27**: 67–76.
5 Patterson HC. Facial keratoacanthoma. *Otolaryngol Head Neck Surg* 1983; **91**: 263–70.
6 Moriyama M, Watanabe T, Sakamoto N *et al.* A case of giant keratoacanthoma of the auricle. *Auris Nasus Larynx* 2000; **27**: 185–8.

Squamous cell carcinoma of the auricle

Although the ratio of basal cell carcinoma (BCC) to squamous cell carcinoma (SCC) is about 4:1 on the head and neck generally, on the ear SCC is relatively more common (BCC:SCC, 1.3 : 1) [1].

In most instances, SCC evolves from a premalignant lesion, usually a solar keratosis, and occurs predominantly in elderly white men, although at a younger age in the immunosuppressed. The most common site is the helix [2]. Early SCC may be suspected when there is induration of the base of a scaly papule, nodule or cutaneous horn. With progression, SCC usually ulcerates and with invasion of cartilage can become grossly destructive (Fig. 68.21). Local spread along perichondrial, periosteal and neurovascular planes can make SCC of the auricle very difficult to control. With the exception of the lip, auricular SCC is more likely to metastasize



Fig. 68.21 Squamous carcinoma of the auricle. An advanced tumour with extensive destruction of the ear cartilage. (Courtesy of Mr D. Baldwin, Southmead Hospital, Bristol, UK.)

than is SCC at any other sun-exposed site (11% compared with 2%) [3]. There is a small but significant mortality [2,4,5]. Adverse prognostic factors for both local recurrence and metastasis of SCC include size (>2 cm), depth of invasion (>4 mm, Clark levels 4 and 5), perineural involvement and poor differentiation of the tumour [6,7]. The pre-auricular site may also confer a poor prognosis [8]. It is not clear, however, to what extent these are independent variables; shallow lesions with large surface area (i.e. >2 cm diameter) do not seem to have a poor prognosis. There is an increased risk for a poor prognosis for SCC of the ear in renal transplant recipients [9–11]. If SCC recurs after primary treatment, there is a much greater risk for further recurrence and metastasis [6].

Treatment. It is important to achieve control of the disease with the initial treatment for SCC. For small, minimally invasive lesions, simple excision, cryotherapy or curettage with cautery/electrodesiccation may be adequate. Excellent results have been reported from the combination of curettage and cryotherapy for carefully selected cases [12]. For larger lesions, and especially for those with adverse prognostic factors, the choice is likely to be between wide margin excision, Mohs' micrographic surgery and radiation therapy.

The surgical procedure used will depend on the location and extent of the tumour. Smaller lesions can often be removed by wedge excision with primary repair by advancement flaps. Larger and ill-defined lesions are best closed by temporary grafts pending a histopathological assessment of the margins before definitive repair is carried out [13]. Partial or total amputation may be needed for large tumours. If there is spread beyond the pinna, resection of the parotid, temporal bone, temporomandibular joint or mandibular ramus may be required, with appropriate repair.

Several authors have recommended minimal resection margins, for example 1 cm [14], 6 mm with frozen section control [15], 8 mm for 1-cm-diameter tumours and 1.5 cm for 3-cm-diameter tumours [16], all with removal of the underlying cartilage. Overall, there is an incidence of 18.7% recurrence during follow-up for 5 years or more with non-Mohs' modalities compared with 5.3% for Mohs' micrographic surgery, suggesting that the latter is the treatment of choice [6,17].

SCCs in the tragal and pretragal location appear to have a greater tendency to spread along embryonic fusion planes and may only be curable by radical surgery, for example parotidectomy in association with removal of the tumour [8,18].

Various techniques are needed to reconstruct the ear after curative surgery [19–26].

Radiotherapy can be successful as a primary treatment for SCC of the auricle, megavoltage electron-beam therapy having therapeutic and cosmetic advantages over conventional orthovoltage X-ray treatment [27]. There may, however, be a higher recurrence rate [28] compared with surgery, particularly for large tumours [2,29,30]. Radiation therapy can be complicated by damage to the cartilage and associated chronic infection; deformity of the pinna is another long-term consequence. Radiotherapy may improve the outlook for cases with extensive local spread requiring radical surgery.

In renal transplant recipients, reducing the degree of immunosuppression can improve survival in poor prognosis SCC without necessarily jeopardizing the transplant [31].

The management of SCC with metastasis to regional lymph nodes and beyond is outside the scope of the dermatologist.

References

1 Ahmad I, Das Gupta AR. Epidemiology of basal cell carcinoma and squamous cell carcinoma of the pinna. *J Laryngol Otol* 2001; **115**: 85–6.
2 Thomas SS, Matthews RN. Squamous cell carcinoma of the pinna: a 6-year study. *Br J Plastic Surg* 1994; **47**: 81–5.
3 Johnson TM, Rowe DE, Nelson BR, Swanson NA. Squamous carcinoma of the skin (excluding lip and oral mucosa). *J Am Acad Dermatol* 1992; **26**: 467–84.
4 Byers R, Kesler K, Redman B *et al.* Squamous carcinoma of the external ear. *Am J Surg* 1983; **146**: 447–50.
5 Freedlander E, Chung FF. Squamous cell carcinoma of the pinna. *Br J Plast Surg* 1983; **36**: 171–5.
6 Rowe DE, Carroll RJ, Day CL. Prognostic factors for local recurrence, metastasis and survival rates in squamous carcinoma of the skin, ear and lip. *J Am Acad Dermatol* 1992; **26**: 976–90.
7 Veness MJ, Palme CE, Morgan GJ. High-risk cutaneous squamous cell carcinoma of the head and neck: results from 266 treated patients with metastatic lymph node disease. *Cancer* 2006; **106**: 2389–96.
8 Lee D, Nash M, Har-El G. Regional spread of auricular and periauricular cutaneous malignancies. *Laryngoscope* 1996; **106**: 998–1001.
9 Cooper JZ, Brown MD. Special concern about squamous cell carcinoma of the scalp in organ transplant recipients. *Arch Dermatol* 2006; **142**: 755–8.
10 Moloney FJ, Comber H, O'Lorcain P *et al*. A population-based study of skin cancer incidence and prevalence in renal transplant recipients. *Br J Dermatol* 2006; **154**: 498–504.
11 Lindelof B, Dal H, Wolk K, Malmborg N. Cutaneous squamous cell carcinoma in organ transplant recipients: a study of the Swedish cohort with regard to tumor site. *Arch Dermatol* 2005; **141**: 447–51.
12 Nordin P, Stenquist B. Five-year results of curettage-cryosurgery for 100 consecutive auricular non-melanoma skin cancers. *J Laryngol Otol* 2002; **116**: 893–8.
13 Reddy LV, Zide MF. Reconstruction of skin cancer defects of the auricle. *J Oral Maxillofac Surg* 2004; **62**: 1457–71.
14 Pless J. Carcinoma of the external ear. *Scand J Plast Reconstr Surg* 1976; **10**: 147–51.
15 Kitchens GG. Auricular wedge resection and reconstruction. *Ear Nose Throat J* 1989; **68**: 673–4, 677–9, 683.
16 Levine HL, Kinney SE, Bailin PL, Roberts JK. Cancer of the periauricular region. *Dermatol Clin* 1989; **7**: 781–95.
17 Mohs F, Larson P, Iriondo M. Micrographic surgery for the microscopically controlled excision of carcinoma of the external ear. *J Am Acad Dermatol* 1988; **19**: 729–37.
18 Niparko JK, Swanson NA, Baker SR *et al*. Local control of auricular, periauricular, and external canal malignancies with Mohs' surgery. *Laryngoscope* 1990; **100**: 1047–51.
19 Menick FJ. Reconstruction of the ear after tumor excision. *Clin Plast Surg* 1990; **17**: 405–15.
20 Johnson TM, Fader DJ. The staged retroauricular to auricular direct pedicle (interpolation) flap for helical ear reconstruction. *J Am Acad Dermatol* 1997; **37**: 975–8.
21 Yotsuyanagi T, Nihei Y, Sawada Y. Reconstruction of defects involving the upper one-third of the auricle. *Plast Reconstr Surg* 1998; **102**: 988–92.
22 Martinez JM, Alconchel MD, Olivares C, Cimorra GA. Reconstruction of the tragus after tumour excision. *Br J Plast Surg* 1997; **50**: 552–4.
23 van der Lei B, Spronk CA. Reconstruction of non-marginal ear defect by a postauricular wedge transposition flap. *Br J Plast Surg* 1998; **51**: 14–6.
24 Majumdar A, Townend J. Helix rim advancement for reconstruction of marginal defects of the pinna. *Br J Oral Maxillofac Surg* 2000; **38**: 3–7.
25 Dagregorio G, Darsonval V. Peninsular conchal axial flap to reconstruct the upper or middle third of the auricle. *Dermatol Surg* 2005; **31**: 350–5.
26 Redondo P, Lloret P, Sierra A, Gil P. Aggressive tumors of the concha: treatment with postauricular island pedicle flap. *J Cutan Med Surg* 2003; **7**: 339–43.
27 Hunter RD, Pereira DTM, Pointon RCS. Megavoltage electron beam therapy in the treatment of basal and squamous cell carcinomata of the pinna. *Clin Radiol* 1982; **33**: 341–5.

28 Blake GB, Wilson JSP. Malignant tumours of the ear and their treatment: 1. Tumours of the auricle. *Br J Plast Surg* 1974; **27**: 67–76.
29 Mazeron JJ, Ghalie R, Zeller J *et al.* Radiation therapy for carcinoma of the pinna using iridium 192 wires: a series of 70 patients. *Int J Radiat Oncol Biol Phys* 1986; **12**: 1757–63.
30 Silva JJ, Tsang RW, Panzarella T *et al.* Results of radiotherapy for epithelial skin cancer of the pinna: the Princess Margaret Hospital experience, 1982–1993. *Int J Radiat Oncol Biol Phys* 2000; **47**: 451–9.
31 Moloney FJ, Kelly PO, Kay EW *et al*. Maintenance versus reduction of immunosuppression in renal transplant recipients with aggressive squamous cell carcinoma. *Dermatol Surg* 2004; **30**: 674–8.

Basal cell carcinoma of the auricle

BCC of the auricle is somewhat less common than SCC (Fig. 68.22). It is also mainly due to the effects of solar radiation, but is much less liable to metastasize [1,2]. Presentation is generally as for BCC elsewhere, although could be missed when resembling a cleft earlobe [3].

The approach to treatment is essentially similar to that outlined for SCC. Mohs' micrographic surgery is the most likely modality to achieve cure with lesions that are extensive, deeply invasive or recurrent, or which have a morphoeic growth pattern.

References

1 Blake GB, Wilson JSP. Malignant tumours of the ear and their treatment: 1. Tumours of the auricle. *Br J Plast Surg* 1974; **27**: 67–76.
2 Small CS, Hawkins FD. Basal cell carcinoma with metastases. *Arch Pathol* 1949; **47**: 196–204.
3 Altchek ED. Basal cell carcinoma presenting as a cleft earlobe. *Plast Reconstr Surg* 1998; **102**: 1758.

Squamous and basal cell carcinoma of the external auditory canal

Non-glandular carcinomas of the external auditory canal are uncommon. Most are squamous in type (Fig. 68.23). They affect a younger age group (50–65 years) and, in contrast to SCC of the auricle, there is much less of a male preponderance. A preceding history of chronic otitis is common [1,2]. Pseudoepitheliomatous hyperplasia secondary to chronic infection or inflammation can sometimes be difficult to distinguish from SCC [3]. *In situ* squamous carcinoma has been described [4]. Rarely, the tumour is bilateral [5].

Most squamous carcinoma of the canal has an infiltrative growth pattern. It tends to grow along the canal, escaping anteriorly through Santorini's fissures in the cartilaginous segment and Huschke's foramen in the bony portion, into the temporomandibular joint and parotid. Spread also occurs posteriorly into the mastoid, and through the tympanic membrane into the middle ear and thence to the carotid canal, apex of the petrous temple bone, the internal auditory canal, base of the skull and the dura. Metastasis to lymph nodes and distantly is common.

Overall, there is a much poorer prognosis than for SCC of the pinna, with 5-year survival rates of about 65% [6,7] but the proportion surviving depends on tumour staging—see below. Adverse factors are a large lesion, invasion of cartilage or bone, facial nerve palsy, spread to the middle ear and beyond, and lymph node metastasis. The extent of the disease can be determined accurately by CT [8]. The University of Pittsburgh staging using clinical and



Fig. 68.22 Basal cell carcinoma. Translucent ulcerated nodules in the retro-auricular fold.



Fig. 68.23 Squamous carcinoma of the external auditory canal. Purulent discharge, inflammation and destruction of the meatus. (Courtesy of Mr D. Baldwin, Southmead Hospital, Bristol, UK.)



Fig. 68.24 Basal cell carcinoma of the external auditory canal. An erythematous tumour presenting as obstruction at the entrance of the canal. (Courtesy of Mr M. Birchill, Southmead Hospital, Bristol, UK.)

imaging data [8,9] is important for assessing prognosis [10] and the likelihood of benefit from adjuvant radiotherapy; patients with more advanced stages are unlikely to be cured [11].

Verrucous carcinoma of the external auditory canal is an uncommon variant that can appear cytologically banal but nevertheless invade bone, by a pushing rather than an infiltrative growth pattern [12,13]. Mucoepidermoid carcinoma is also encountered rarely [14].

BCC of the external auditory canal can be locally destructive (Fig. 68.24) and can be difficult to fully remove surgically [15], but does not metastasize and usually has a better prognosis than SCC [16].

The most common symptoms of invasive SCC of the canal are purulent and bloody discharge from the ear, followed by pain, hearing loss and facial paralysis. Examination reveals a friable tumour, partially or completely obstructing the external auditory canal.

Treatment. Surgery has been regarded as the treatment of choice, the extent determined by an assessment of the limits of tumour growth. However, radiotherapy alone may be as effective if the disease is limited to the site of origin, that is there is no evidence of nerve or bone involvement [17,18]. Post-operative radiotherapy improves the outlook [6,7,19–22], but for lesions that have spread deeply or have metastasized cure is most unlikely.

References

1 Lederman M. Malignant tumours of the ear. *J Laryngol Otolaryngol* 1965; **79**: 85–119.

2 Paaske PB, Witten J, Schwer S, Hansen HS. Results in treatment of carcinoma of the external auditory canal and middle ear. *Cancer* 1987; **59**: 156–60.

3 Gacek MR, Gacek RR, Gantz B *et al.* Pseudoepitheliomatous hyperplasia versus squamous cell carcinoma of the external auditory canal. *Laryngoscope* 1998; **108**: 620–3.

4 Shu MT, Lin HC, Yang CC, Chang KM. Squamous cell carcinoma in situ of the external auditory canal. *J Laryngol Otol* 2006; **120**: 684–6.

5 Wolfe SG, Lai SY, Bigelow DC. Bilateral squamous cell carcinoma of the external auditory canals. *Laryngoscope* 2002; **112**: 1003–5.

6 Chen KTK, Dehner LP. Primary tumors of the external and middle ear. I. Introduction and clinicopathologic study of squamous cell carcinoma. *Arch Otolaryngol* 1978; **104**: 244–52.

7 Yin M, Ishikawa I, Honda K *et al*. Analysis of 95 cases of squamous cell carcinoma of the external and middle ear. *Auris Nasus Larynx* 2006; **33**: 251–7.

8 Arriaga M, Curtin H, Takashi H *et al.* Staging proposal for external auditory meatus carcinoma based on pre-operative clinical examination and computed tomography findings. *Ann Otol Rhinol Laryngol* 1990; **99**: 714–21.

9 Moody SA, Hirsch BE, Myers EN. Squamous cell carcinoma of the external auditory canal: an evaluation of a staging system. *Am J Otol* 2000; **21**: 582–8.

10 Testa JRG, Fukuda Y, Kowalski LP. Prognostic factors in carcinoma of the external auditory canal. *Arch Otolaryngol Head Neck Surg* 1997; **123**: 720–4.

11 Nyrop M, Grøntved A. Cancer of the external auditory canal. *Arch Otolaryngol Head Neck Surg* 2002; **128**: 834–7.

12 Stafford DN, Frootko NJ. Verrucous carcinoma in the external auditory canal. *Am J Otol* 1986; **7**: 443–5.

13 Proops DW, Hawke WM, Van Nostrand AW *et al.* Verrucous carcinoma of the ear. Case report. *Ann Otol Rhinol Laryngol* 1984; **93**: 385–8.

14 Bared A, Dave SP, Garcia M, Angeli SI. Mucoepidermoid carcinoma of the external auditory canal (EAC). *Acta Otolaryngol* 2007; **127**: 280–4.

15 Vandeweyer E, Thill MP, Deraemaecker R. Basal cell carcinoma of the external auditory canal. *Acta Chir Belg* 2002; **102**: 137–40.

16 Stell PM. Basal cell carcinoma of the external auditory meatus. *Clin Otolaryngol* 1984; **9**: 187–90.

17 Hashi N, Shirato H, Omatsu T *et al.* The role of radiotherapy in treating squamous cell carcinoma of the external auditory canal, especially in early stages of disease. *Radiother Oncol* 2000; **56**: 221–5.

18 Pemberton LS, Swindell R, Sykes AJ. Primary radical radiotherapy for squamous cell carcinoma of the middle ear and external auditory canal—an historical series. *Clin Oncol* 2006; **18**: 390–4.

19 Hahn SS, Kim JA, Goodchild N, Constable WD. Carcinoma of the middle ear and external auditory canal. *Int J Radiat Oncol Biol Phys* 1983; **9**: 1003–7.

20 Lewis JS. Cancer of the ear. *Cancer* 1987; **37**: 78–87.

21 Kinney SE. Squamous cell carcinoma of the external auditory canal. *Am J Otol* 1989; **10**: 111–6.

22 Shih L, Crabtree JA. Carcinoma of the external auditory canal: an update. *Laryngoscope* 1990; **100**: 1215–8.

Malignant melanoma

Malignant melanoma of the external ear is relatively uncommon, constituting about 1% of all cutaneous melanomas [1,2]. It accounted for 4.8% of all auricular malignancies in one series [3] and represented 7% of all melanomas in another series [4]. Melanomas at this site are about three times more common in males than females [4,5]. Melanoma is found in a similar frequency distribution on the ear as SCC and its precursors, that is about half occur on the helix and one-quarter on the antihelix [4], but they are rarely found in the external auditory canal [6,7]. Most melanomas on the ear are of superficial spreading or nodular type, the latter being relatively more common than at other head and neck sites [8,9]. The major determinant for prognosis is Breslow thickness [5,10].

Treatment is in principle no different from malignant melanoma elsewhere (see Chapter 54), and relatively conservative excision followed by reconstruction can be safe [2,10,11]. Sentinel lymph

node mapping may be valuable for accurate staging, particularly for melanoma of the ear, since its lymphatic drainage is notoriously unpredictable [12,13], but whether prognosis will be altered is uncertain.

References

1 Hudson DA, Krige JEJ, Strover RM, King HS. Malignant melanoma of the external ear. *Br J Plast Surg* 1990; **43**: 608–11.
2 Ravin AG, Pickett N, Johnson JL *et al*. Melanoma of the ear: treatment and survival probabilities based on 199 patients. *Ann Plast Surg* 2006; **57**: 70–6.
3 Blake GB, Wilson SP. Malignant tumours of the ear and their treatment: 1. Tumours of the auricle. *Br J Plast Surg* 1974; **27**: 67–76.
4 Pack GT, Conley J, Oropeza R. Melanoma of the external ear. *Arch Otolaryngol* 1970; **92**: 106–13.
5 Cox NH, Aitchison TC, Sirel JM, MacKie RM. Comparison between lentigo maligna melanoma and other histogenetic types of malignant melanoma of the head and neck. *Br J Cancer* 1996; **73**: 940–4.
6 Langman AW, Yarington T, Patterson SD. Malignant melanoma of the external auditory canal. *Otolaryngol Head Neck Surg* 1996; **114**: 645–8.
7 Milbrath MM, Campbell BH, Madiedo G, Janjan NA. Malignant melanoma of the external auditory canal. *Am J Clin Oncol* 1998; **21**: 28–30.
8 Davidson A, Hellquist HB, Villman K, Westman G. Malignant melanoma of the ear. *J Laryngol Otol* 1993; **107**: 798–802.
9 Cox NH, Jones SK, MacKie RM. Malignant melanoma of the head and neck in Scotland: an eight year analysis of trends in prevalance, distribution and prognosis. *QJM* 1987; **64**: 661–70.
10 Jahn V, Breuninger H, Garbe C, Moehrle M. Melanoma of the ear: prognostic factors and surgical strategies. *Br J Dermatol* 2006; **154**: 310–8.
11 Narayan D, Ariyan S. Surgical considerations in the management of malignant melanoma of the ear. *Plast Reconstr Surg* 2001; **107**: 20–4.
12 Wey PD, de la Cruz C, Goydos JS *et al*. Sentinel lymph node mapping in melanoma of the ear. *Ann Plast Surg* 1998; **40**: 506–9.
13 Carlson GW, Murray DR, Lyles RH *et al*. Sentinel lymph node biopsy in the management of cutaneous head and neck melanoma. *Plast Reconstr Surg* 2005; **115**: 721–8.

Other malignant tumours

Other malignant tumours involving the external ear or the external auditory canal are all rare. The pathology is reviewed in Friedman and Arnold's monograph [1]. The dermatologist may encounter sebaceous carcinoma [2], atypical fibroxanthoma (Fig. 68.25), trichilemmal carcinoma [3], Merkel cell tumour [4], carcinosarcoma [5], Kaposi's sarcoma [6,7] or rhabdomyosarcoma (mainly in children) [8–10]. Angiosarcoma of the pinna has the same gloomy outlook as it does on the scalp [11]. Other sarcomas have been recorded but are exceptionally rare. Lymphomas may occur on the external ear [12], particularly mycosis fungoides [13]. Perichondritis can be mimicked by non-Hodgkin's lymphoma [14,15], and both lymphoma [16,17] and myeloma [18] can present with an external auditory canal tumour. The ear may be involved by direct extension from tumours nearby, for example the parotid, and also by metastases from distant sites [19].



Fig. 68.25 Atypical fibroxanthoma. A firm fleshy tumour of the pinna.

References

1 Friedman I, Arnold W. *Pathology of the Ear*. Edinburgh: Churchill Livingstone, 1993.
2 Ray J, Schofield JB, Shotton JC, Al-Ayoubi A. Rapidly invading sebaceous carcinoma of the external auditory canal. *J Laryngol Otol* 1999; **113**: 578–80.
3 Billingsley EM, Davidowski TA, Maloney ME. Trichilemmal carcinoma. *J Am Acad Dermatol* 1997; **36**: 106–7.
4 Hanna GS, Ali MH, Akosa AB, Maher EJ. Merkel-cell carcinoma of the pinna. *J Laryngol Otol* 1988; **102**: 607–11.
5 Vincek V, Mirzabeigi M, Jewett BS, Goodwin WJ. Primary carcinosarcoma of the helix of the ear. *Ear Nose Throat J* 2005; **84**: 712–5.
6 Gnepp DR, Chandler W, Hyams VJ. Primary Kaposi's sarcoma of the head and neck. *Ann Med* 1984; **100**: 107–14.
7 Delbrouck C, Kampouridis S, Chantrain G. An unusual localisation of Kaposi's sarcoma: the external auditory canal. *Acta Otorhinolaryngol Belg* 1998; **52**: 29–36.
8 Jaffe N, Fuller RM, Farber S. Rhabdomyosarcoma in children: improved outlook with a multidisciplinary approach. *Am J Surg* 1973; **125**: 482–7.
9 Maurer HM. Rhabdomyosarcoma in childhood and adolescence. *Curr Probl Cancer* 1978; **2**: 3–36.
10 Feldman BA. Rhabdomyosarcoma of the head and neck. *Laryngoscope* 1982; **92**: 424–40.
11 Leighton SE, Levine TP. Angiosarcoma of the external ear: a case report. *Am J Otol* 1991; **12**: 54–6.
12 Darvay A, Russell-Jones R, Acland KM *et al*. Systemic B-cell lymphoma presenting as an isolated lesion on the ear. *Clin Exp Dermatol* 2001; **26**: 166–9.
13 Baumgartner BJ, Eusterman V, Myers J, Massengill P. Initial report of a cutaneous T-cell lymphoma appearing on the auricular helix. *Ear Nose Throat J* 2000; **79**: 391–4.
14 Levin RJ, Henick DH, Cohen AF. Human immunodeficiency virus associated non-Hodgkin's lymphoma presenting as an auricular perichondritis. *Otolaryngol Head Neck Surg* 1995; **112**: 493–5.
15 Indudharan R, Arni T, Myint KK, Jackson N. Lymphoblastic lymphoma/leukaemia presenting as perichondritis of the pinna. *J Laryngol Otol* 1998; **112**: 592–4.
16 Kieserman SP, Finn DG. Non-Hodgkin's lymphoma of the external auditory canal in an HIV-positive patient. *J Laryngol Otol* 1995; **109**: 751–4.
17 Angeli SI, Brackmann DE, Xenellis JE *et al*. Primary lymphoma of the internal auditory canal. *Ann Otol Rhinol Laryngol* 1998; **107**: 17–21.
18 Quinodoz D, Dulguerov P, Kurt AM *et al*. Multiple myeloma presenting with external ear canal mass. *J Laryngol Otol* 1998; **112**: 469–71.
19 Golding-Wood DG, Quiney RE, Cheesman AD. Carcinoma of the ear: retrospective analysis of 61 patients. *J Laryngol Otol* 1989; **103**: 653–6.

Miscellaneous conditions

Petrified ear

This is a rare clinical entity in which the cartilage of the ear is replaced by ectopic calcification or ossification [1]. The clinical presentation is of a partially or wholly rigid auricle, which may be uncomfortable with pressure over it. One or both ears may be involved. Causes include frostbite, trauma, including radiation therapy, and several systemic diseases. Addison's disease seems the commonest; others include diabetes mellitus, hypopituitarism acromegaly and hypothyroidism.

Reference

1 Stites PC, Boyd AS, Zic J. Auricular ossificans (ectopic ossification of the auricle). *J Am Acad Dermatol* 2003; **49**: 142–4.

Cholesteatoma of the external auditory canal

Cholesteatoma of the middle ear space is accumulation of keratinous debris within a sac-like squamous epithelial lining. It can grow at the expense of normal structures and if it ruptures, the associated foreign body-type inflammatory reaction can produce serious damage.

A similar condition occurs rarely in the external auditory canal, although its status as a true cholesteatoma is disputed [1,2]. The accumulation of stratum corneum occurs within a cyst-like penetration of the bony portion of the canal wall by the epithelial lining. There is localized ulceration of the skin of the floor of the canal, with underlying osteitis and sometimes necrosis of bone. A necrotic sequestrum may become incorporated into the cholesteatoma. The cause is unknown, although trauma, for example from hard wax and manipulation of the canal, seems important in some cases [3].

Cholesteatoma usually occurs in patients over the age of 40 years. Symptoms are a dull pain in one ear and otorrhoea. Examination shows a white cystic mass protruding into the canal. The main differential diagnosis is from neoplasms and keratosis obturans [4,5]. External auditory canal cholesteatoma can occasionally behave aggressively, and may erode into the mastoid cavity, middle ear, temporomandibular joint and adjacent soft tissue. CT can be useful to assess the extent of the disease. Treatment is within the province of the otorhinolaryngologist.

Keratosis obturans

In this uncommon condition there is a localized accumulation of desquamated keratin in the ear canal. It may be due to a defect in the normal epithelial migration [6]. It is usually bilateral and typically occurs in younger patients than those presenting with external auditory canal cholesteatoma, which it can resemble. There is conductive hearing loss, sometimes with otalgia. Keratosis obturans can be associated with paranasal sinus disease and bronchitis; it has also been described in association with the yellow nail syndrome [7]. Treatment consists of careful removal of the accumulated keratin. Irrigation with water should be avoided [4,5].

References

1 Friedman I, Arnold W. *Pathology of the Ear*. Edinburgh: Churchill Livingstone, 1993: 30–1.
2 Sismanis A, Williams GH, Abedi E. External auditory meatus cholesteatoma. In: Tos M, Thomas J, Peitersen E, eds. *Cholesteatoma and Mastoid Surgery*. Amsterdam: Kugler and Ghedini, 1984: 577–82.
3 Holt JJ. Ear canal cholesteatoma. *Laryngoscope* 1992; **102**: 608–13.
4 Corbridge RJ, Michaels L, Wright T. Epithelial migration in keratosis obturans. *Am J Otol* 1996; **17**: 411–4.
5 Armitage JM, Lane DJ, Stradling JR, Burton M. Ear involvement in the yellow nail syndrome. *Chest* 1990; **98**: 1534–5.
6 Piepergerdes JC, Kramer BM, Behnke EE. Keratosis obturans and external auditory canal cholesteatoma. *Laryngoscope* 1980; **90**: 383–90.
7 Shire JR, Donegan JO. Cholesteatoma of the external auditory canal and keratosis obturans. *Am J Otol* 1986; **7**: 361–4.

Referred pain [1]

Due to the complicated nerve supply to the ear, referred pain is commoner than pain due to lesions in the ear itself [2]. Non-otological causes of such pain include the otomandibular syndrome [3] due to dysfunction of the temporomandibular joint, cervical arthritis with involvement of the cervical nerves, tonsillitis and carcinoma of the pharynx. Hair in the ear canal is an occasional cause [4]. Psychogenic otalgia has also been reported [5].

References

1 Shah RK, Blevins NH. Otalgia. *Otolaryngol Clin North Am* 2003; **36**: 1137–51.
2 Sheikhi AARJ. Pain in the ear: with special reference to referred pain. *J Laryngol Otol* 1980; **94**: 1433–40.
3 Arlen H. The otomandibular syndrome: diagnosis. *Ear Nose Throat J* 1978; **57**: 553–6.
4 Papay FA, Levine HL, Schiavone WA. Facial fuzz and funny feelings. *Cleve Clin J Med* 1989; **56**: 273–6.
5 Dight R. Psychogenic earache. An unusual cause of otalgia. *Med J Aust* 1980; **i**: 76–7.

CHAPTER 69
The Oral Cavity and Lips

C. Scully[1] *& A. Hegarty*[2]

[1]Eastman Dental Institute, University College London, London, UK
[2]The Charles Clifford Dental Hospital, Sheffield, UK

Biology of the mouth, 69.1
Oral epithelium, 69.1
Lips, 69.1
Oral mucosa, 69.2
Teeth, 69.2
Junction of the mucosa with the teeth, 69.3
Immunity in the oral cavity, 69.3
Examination of the mouth and perioral region, 69.3
Lymph nodes, 69.4
Temporomandibular joints and muscles of mastication, 69.4
Jaws, 69.5
Salivary glands, 69.5
Intraoral examination, 69.5
Anatomical variants, 69.6
Disorders affecting the teeth, 69.7
Disorders of tooth eruption, 69.7
Loosening and early loss of teeth, 69.7
Malformed and discoloured teeth, 69.8
Taurodontism, 69.9
Ectodermal dysplasia, 69.10
Disorders affecting the periodontium, 69.12
Gingival disorders affecting the periodontium, 69.12
Genetic disorders affecting the periodontium, 69.14
Acquired disorders affecting the periodontium, 69.17
Disorders affecting the oral mucosa or lips, 69.21
Genetic disorders affecting the oral mucosa or lips, 69.22
White or whitish lesions, 69.22
Pigmented lesions, 69.26
Red lesions, 69.29
Vesiculoerosive disorders, 69.31
Lumps and swellings, 69.33
Other congenital anomalies, 69.36
Various orocutaneous syndromes, 69.37
Acquired disorders of the oral mucosa or lips, 69.42
Mouth ulcers, 69.42
Oral soreness, 69.85
White lesions, 69.87
Pigmented lesions, 69.95
Red lesions, 69.100
Loss of elasticity of oral tissues, 69.106
Lumps and swellings, 69.107
Oral manifestations of systemic diseases, 69.115
Acquired lip lesions, 69.119
Cheilitis, 69.119
Lupus erythematosus, 69.128
Sarcoidosis, 69.129
Lip fissure, 69.129
Lip ulcer due to calibre-persistent artery, 69.129
Reactive perforating collagenosis, 69.129

Introduction

Oral lesions are usually the result of local disease but may be the early signs of systemic disease, including dermatological disorders, and in some instances may cause the main symptoms. This chapter mainly discusses disorders of the dental, periodontal and mucosal tissues that may be related to skin disease and that may present at a dermatology clinic. It should be borne in mind that the professionals most competent in diagnosing and treating oral diseases are dentally qualified; few without this formal training and education are in a position to understand the full complexities of the region.

The chapter is an overview only and is divided into a brief discussion of the biology of the mouth, an overview of the more common signs and symptoms affecting specific oral tissues, discussion of the disorders of the oral mucosa of most relevance to dermatology and a tabulated review of oral manifestations of systemic diseases. Diseases affecting the salivary glands, or jaws or temporomandibular joints are not discussed in any depth.

Only the more classic oral lesions are illustrated. About 20 of the colour illustrations are from the *Colour Atlas of Oral and Maxillofacial Diseases*, 2004 (reproduced by kind permission of C. Scully, S. Flint, S.R. Porter and K. Moos, and publishers Taylor and Francis, London). More detail of histology is available elsewhere [1].

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

Biology of the mouth

Oral epithelium

The oral epithelium consists of a *functional compartment*—the progenitor cells (basal and parabasal cells)—which is the site of cell division; a *maturation compartment* (spinous and granular cells) where the cells become more terminally differentiated; and a superficial *cornified compartment* of squames and areas of keratinization, either orthokeratotic or parakeratotic. In the non-keratinized regions such as the buccal (cheek) and floor-of-mouth mucosae, overt keratinization and granular cells are absent and the surface cells are flattened, with elongated nuclei [2].

Lips

The lips extend from the lower end of the nose to the upper end of the chin. They mainly consist of bundles of striated muscle, particularly the *orbicularis oris* muscle, with skin on the external surface and mucous membrane on the inner surface, which has a profusion of minor salivary glands.

The vermilion zone, the transitional zone between the glabrous skin and the mucous membrane, is found only in humans. The vermilion zone contains no hair or sweat glands but does contain

sebaceous glands (Fordyce spots, see below). The epithelium of the vermilion is distinctive, with a prominent stratum lucidum and a very thin stratum corneum. The dermal papillae are numerous at this site, with a rich capillary supply, which produces the reddish-pink colour of the lips in white people. Melanocytes are abundant in the basal layer of the vermilion of pigmented skin, but are infrequent in white skin.

The *oral commissures* are the angles where the upper and lower lip meet. The upper lip includes the *philtrum*, a midline depression, extending from the columella of the nose to the superior edge of the vermilion zone [3].

Oral mucosa

The mucosa is divided into masticatory, lining and specialized types. *Masticatory mucosa* (hard palate, gingiva) is adapted to the forces of pressure and friction and is keratinized, with numerous tall rete ridges and connective tissue papillae and little submucosa. *Lining mucosa* (buccal, labial and alveolar mucosa, floor of mouth, ventral surface of tongue, soft palate, lips) is non-keratinized, with broad rete ridges and connective tissue papillae and abundant elastic fibres in the lamina propria [4,5].

Specialized mucosa on the dorsum of the tongue, adapted for taste and mastication, is keratinized, with numerous rete ridges and connective tissue papillae, abundant elastic and collagen fibres in the lamina propria and no submucosa. The tongue is divided by a V-shaped groove, the *sulcus terminalis*, into an anterior two-thirds and a posterior third. Various papillae on the dorsum include the *filiform papillae*, which cover the entire anterior surface and form an abrasive surface to control the food bolus as it is pressed against the palate, and the *fungiform papillae*. The latter are mushroom-shaped, red structures covered by non-keratinized epithelium. They are scattered between the filiform papillae and have taste buds on their surface. Adjacent and anterior to the sulcus terminalis are eight to twelve large *circumvallate papillae*, each surrounded by a deep groove into which open the ducts of serous minor salivary glands. The lateral walls of these papillae contain taste buds.

The *foliate papillae* consist of four to eleven parallel ridges, alternating with deep grooves in the mucosa, on the lateral margins on the posterior part of the tongue. There are taste buds on their lateral walls. The *lingual tonsils* are round or oval prominences with intervening lingual crypts lined by non-keratinized epithelium. They are part of *Waldeyer's oropharyngeal ring* of lymphoid tissue. The lingual tonsil is a mass of lymphoid tissue in the posterior third of the tongue, between the epiglottis posteriorly and the circumvallate papillae anteriorly. It is usually divided in the midline by a ligament.

Teeth

The teeth develop from neuroectoderm [6]. Tooth development begins in the fetus, at about 28 days *in utero*. Indeed, all the deciduous and some of the permanent dentition commence development in the fetus. At around the sixth week of intrauterine life the oral epithelium proliferates over the maxillary and mandibular ridge areas to form primary epithelial bands that project into the mesoderm, and produce a dental lamina in which discrete swellings appear—the enamel organs of developing teeth. Each enamel organ eventually produces tooth enamel, and the mesenchyme, which condenses beneath the enamel organ (actually neuroectoderm), forms a dental papilla that produces the dentine and pulp of the tooth. The enamel organ together with the dental papilla constitute the tooth germ, and this becomes surrounded by a mesenchymal dental follicle, from which the periodontium forms, ultimately to anchor the tooth in its bony socket. Mineralization of the primary dentition commences at about 14 weeks *in utero* and all primary teeth are mineralizing by birth. Permanent incisor and first molar teeth begin to mineralize at, or close to, the time of birth, mineralization of other permanent teeth starting later. Tooth eruption occurs after crown formation when mineralization is largely complete but before the roots are fully formed.

Teeth comprise a crown of insensitive enamel, surrounding sensitive dentine, and a root which has no enamel covering (Fig. 69.1). Teeth contain a vital pulp (nerve) and are supported by the periodontal ligament by which roots are attached into sockets in the alveolar process of the jaws (maxilla and mandible). The fibres of the periodontal ligament attach through cementum to the dentine surface. The alveolus is covered by the gingivae, or gums, which in health are pink, stippled and tightly bound down, and form a close-fitting cuff, with a small sulcus (gingival crevice), round the neck of each tooth.

The first or primary (deciduous or milk) dentition comprises two incisors, a canine and two molars in each of the four mouth quadrants (total 20 teeth). There are 10 deciduous (primary or milk) teeth in each jaw: all are fully erupted by the age of about 3 years (Fig. 69.2; Table 69.1). The secondary or permanent teeth begin to erupt at about the age of 6–7 years and the deciduous teeth are slowly lost by normal root resorption.

The normal permanent (adult) dentition comprises two incisors, a canine, two premolars and three molars in each quadrant (total 32 teeth). The full permanent dentition consists of 16 teeth in each jaw: normally most have erupted by about 12–14 years of age. However, some milk teeth may still be present at the age of 12–13 years. The last molars (third molars or wisdom teeth), if present, often erupt later or may impact and never appear in the mouth.

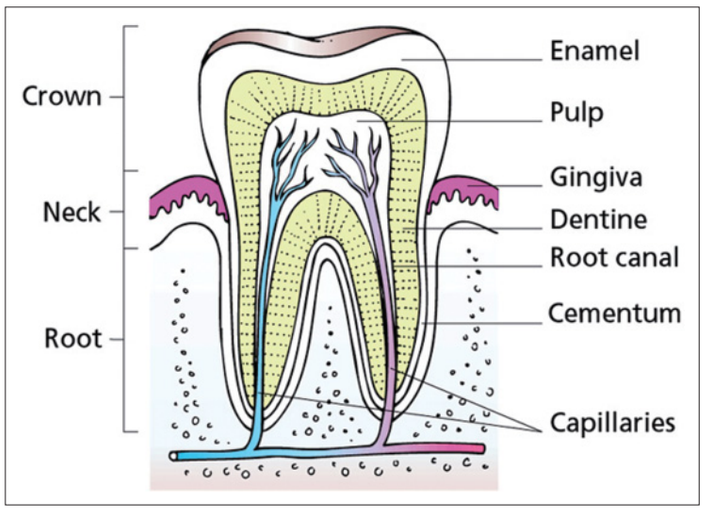


Fig. 69.1 Tooth structure.

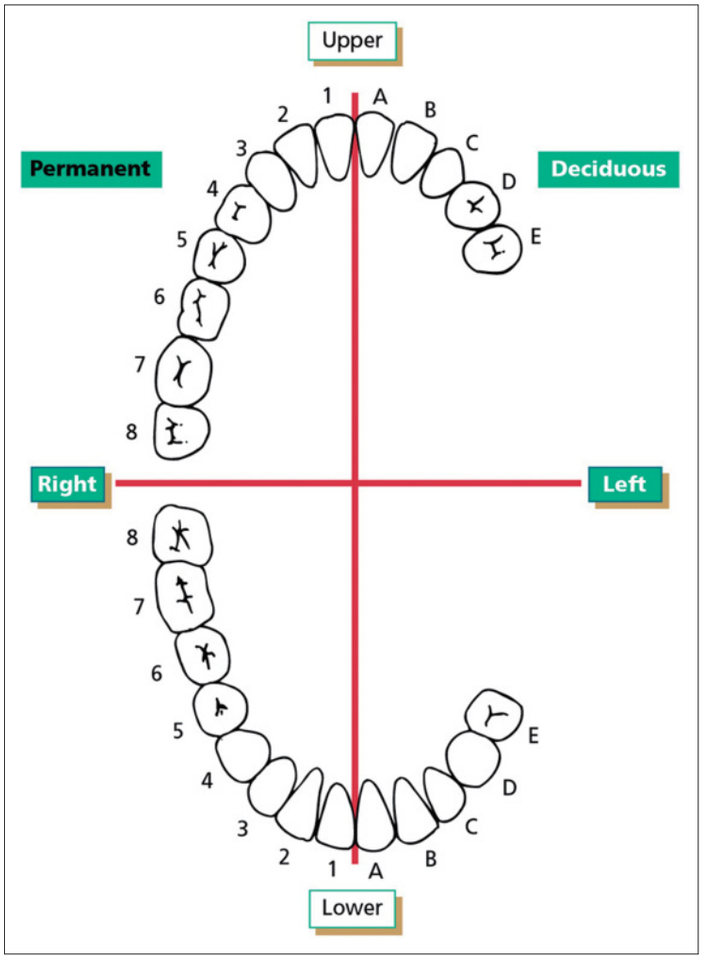


Fig. 69.2 Tooth notations.

Junction of the mucosa with the teeth

The dentogingival junction represents a unique anatomical feature concerned with the attachment of the gingival (gum) mucosa to the tooth. Non-keratinized gingival epithelium forms a cuff surrounding the tooth, and at its lowest point on the tooth is adherent to the enamel or cementum. This 'junctional' epithelium is unique in being bounded both on its tooth and lamina propria aspects by basement membranes. Above this is a shallow sulcus or crevice (up to 2 mm deep), the gingival sulcus or crevice. Neutrophils continually migrate into the gingival crevice, and there is also a slow exudate of plasma (crevicular fluid).

Immunity in the oral cavity

Movement of the soft tissues during speech and swallowing, and salivation, ensures that much foreign material is swallowed. The need for this cleaning mechanism is clearly apparent in patients with facial paralysis, or in those with xerostomia, in whom there is accumulation of oral debris and subsequent infection.

Saliva also aggregates bacteria and deters their attachment to surfaces. Salivary lysozyme, thiocyanate, peroxides and various mucins and other components may be antimicrobial and saliva is inhibitory to various microbial agents including, for example, human immunodeficiency virus (HIV).

Table 69.1 Tooth eruption timings (average timings; there is a wide range).

	Upper	Lower
Deciduous (primary) teeth		
A Central incisors	8–13 months	6–10 months
B Lateral incisors	8–13 months	10–16 months
C Canines (cuspids)	16–23 months	16–23 months
D First molars	13–19 months	13–19 months
E Second molars	25–33 months	23–31 months
Permanent teeth		
1 Central incisors	7–8 years	6–7 years
2 Lateral incisors	8–9 years	7–8 years
3 Canines (cuspids)	11–12 years	9–10 years
4 First premolars (bicuspids)	10–11 years	10–12 years
5 Second premolars (bicuspids)	10–12 years	11–12 years
6 First molars	6–7 years	6–7 years
7 Second molars	11–13 years	11–13 years
8 Third molars	17–21 years	17–21 years

Salivary tissue derives its B cells from the gut-associated lymphoid tissue (GALT) system [7]. Salivary acinar cells produce secretory component (transport piece) needed for transport of IgA into the saliva and its stability in the presence of salivary or gastric proteolytic enzymes. Although the exact contribution to oral defence made by salivary IgA antibodies is difficult to assess, some patients who have IgA deficiency suffer from oral infections, and in animals it is possible to induce protective salivary IgA antibodies to caries-producing organisms such as *Streptococcus mutans*.

Neutrophils and other leukocytes are particularly essential for oral health as shown by the fact that patients with HIV infection, neutropenia, agranulocytopenia, leukaemia or chronic granulomatous disease are predisposed to severe gingivitis and rapid periodontal breakdown, as well as mouth ulceration and infections.

References

1 Eveson JW, Scully C. *Colour Atlas of Oral Pathology*. London: Mosby, 1995.
2 Hume WJ, Potten CS. Advances in epithelial kinetics: an oral view. *J Oral Pathol* 1979; **8**: 3–22.
3 Zugerman C. The lips: anatomy and differential diagnosis. *Cutis* 1986; **38**: 116–20.
4 Meyer J, Squier CA, Gerson SJ. *The Structure and Function of Oral Mucosa*. Oxford: Pergamon Press, 1984.
5 Prime SS. Development, structure and function of oral mucosa. In: Scully C, ed. *The Mouth in Health and Disease*. Oxford: Heinemann Medical, 1989: 124–44.
6 Nanci A. *Ten Cate's. Oral Histology*, 6th edn. St Louis: Mosby, 2003.
7 Lamey PJ, Scully C. Salivary gland development, anatomy and physiology. In: Scully C, ed. *The Mouth in Health and Disease*. Oxford: Heinemann Medical, 1989: 283–8.

Examination of the mouth and perioral region

Examination includes inspection and palpation of the lymph nodes, temporomandibular joints, jaws, salivary glands and oral cavity.

Lymph nodes (Table 69.2)

Lymph from the superficial tissue of the head and neck generally drains first to groups of superficially placed lymph nodes, then to the deep cervical lymph nodes.

- Systematically, each region needs to be examined lightly with the pulps of the fingers, trying to roll the lymph nodes against harder underlying structures.
- Parotid, mastoid and occipital lymph nodes can be palpated simultaneously using both hands.
- Superficial cervical lymph nodes are examined with lighter palpation as they can only be compressed against the softer sternomastoid muscle.
- Submental lymph nodes are examined by tipping the patient's head forward and rolling the lymph nodes against the inner aspect of the mandible.
- Submandibular lymph nodes are examined in the same way with the patient's head tipped to the side being examined. Differentiation needs to be made between the submandibular salivary gland and submandibular lymph glands. Bimanual examination with one finger in the floor of the mouth may help.
- The deep cervical lymph nodes, which project anterior or posterior to the sternomastoid muscle, can be palpated. The jugulodigastric lymph node should be specifically examined, as this is the most common lymph node involved in tonsillar infections.

Table 69.2 Drainage areas of cervical lymph nodes.

Area	Draining lymph nodes
Scalp, temporal region	Superficial parotid
Scalp, posterior	Occipital
Scalp, parietal region	Mastoid
Ear, external	Superficial cervical over upper part of sternomastoid muscle
Ear, middle	Parotid
Over angle of mandible	Superficial cervical over upper part of sternomastoid muscle
Medial part of frontal region, medial eyelids, skin of nose	Submandibular
Lateral part of frontal region and lateral part of eyelids	Parotid
Cheek	Submandibular
Upper lip	Submandibular
Lower lip	Submental
Lower lip, lateral part	Submandibular
Mandibular gingivae	Submandibular
Maxillary teeth	Deep cervical
Maxillary gingivae	Deep cervical
Tongue tip	Submental; remainder drains to submandibular nodes
Tongue, anterior two-thirds	Submandibular; some midline cross-over of lymphatic drainage
Tongue, posterior third	Deep cervical
Tongue, ventrum	Deep cervical
Floor of mouth	Submandibular
Palate, hard	Deep cervical
Palate, soft	Retropharyngeal and deep cervical
Tonsil	Jugulodigastric

- The supraclavicular region should be examined at the same time as the rest of the neck; lymph nodes here may extend up into the posterior triangle of the neck on the scalene muscles, behind the sternomastoid.
- Parapharyngeal and tracheal lymph nodes can be compressed lightly against the trachea.
- Some information can be gained by the texture and nature of the lymphadenopathy.
- Tenderness and swelling should be documented. Lymph nodes that are tender may be inflammatory (lymphadenitis). Consistency should be noted. Nodes that are increasing in size and are hard or fixed to adjacent tissues may be malignant.
- Both anterior and posterior cervical nodes should be examined as well as other nodes, liver and spleen if systemic disease is a possibility.

Temporomandibular joints and muscles of mastication

Although disorders that affect the temporomandibular joint often appear to be unilateral, the joint should not be viewed in isolation but always considered together with its opposite joint, as part of the stomatognathic system. The area should be examined as follows.

Inspection

- Facial symmetry
- Evidence of enlarged masseter muscles (masseteric hypertrophy) suggestive of clenching or bruxism
- Mandibular opening and closing paths
- Mandibular opening extent:
  (i) measure the interincisal distance at maximum mouth opening
  (ii) measure the amount of lateral excursions achievable
  (iii) listen for joint noises (a stethoscope placed over the joint can help).

Palpation

- Both condyles: via the external auditory meatus to detect tenderness posteriorly, and by using a single finger placed over the joints in front of the ears to detect pain, abnormal movements or clicking within the joint.
- Masticatory muscles on both sides.

Masseters: by intraoral/extraoral compression between finger and thumb. Palpate the masseter bimanually by placing a finger of one hand intraorally and the index and middle fingers of the other hand on the cheek over the masseter over the lower mandibular ramus.

Temporalis: by direct palpation of the temporal region. Palpate the temporal origin of the temporalis muscle by asking the patient to clench the teeth. Palpate the insertion of the temporalis tendon intraorally along the anterior border of the ascending mandibular ramus.

Lateral pterygoid (lower head): by placing a little finger up behind the maxillary tuberosity (the 'pterygoid sign'). Examine

the lateral pterygoid muscle, which cannot readily be palpated, indirectly by asking the patient to open the jaw against resistance and to move the jaw to one side while a gentle resistance force is applied.

Medial pterygoid muscle: intraorally lingually to the mandibular ramus.

Some palpate using a pressure algometer to standardize the force used, and undertake range-of-movement measurements.

- Examination of the dentition and occlusion: this may require monitoring of study models on a semi-adjustable or fully adjustable articulator. Note particularly missing premolars or molars, and attrition.
- Examination of the mucosa: note particularly occlusal lines and scalloping of the tongue margins, which may indicate bruxism and tongue pressure.

Jaws

There is wide normal individual variation in morphology of the face. Most individuals have facial asymmetry but of a degree that cannot be regarded as abnormal.

- Maxillary, mandibular or zygomatic deformities or lumps may be more reliably confirmed by inspection from above (maxillae/zygomas) or behind (mandible). The jaws should be palpated to detect swelling or tenderness.
- Maxillary air sinuses can be examined by palpation for tenderness over the maxillary antrum, which may indicate sinus infection. Transillumination or endoscopy can be helpful.

Salivary glands

Inspect and palpate the major salivary glands (parotid and submandibular) for:

- symmetry
- evidence of enlarged glands
- evidence of salivary flow from salivary ducts
- appearance of saliva.

Parotid glands. Palpate by placing fingers over the pre-auricular glands, to detect pain or swelling. Early enlargement of the parotid gland is characterized by outward deflection of the lower part of the earlobe, which is best observed by looking at the patient from behind. This simple sign may allow distinction from simple obesity. Swelling of the parotid sometimes causes trismus. Swellings may affect the whole or part of a gland or tenderness may be elicited. The parotid duct (Stensen's duct) is most readily palpated with the jaws clenched firmly since the duct turns medially at the front edge of masseter, pierces the buccinator muscle and opens at a papilla on the buccal mucosa opposite the upper molars.

Submandibular glands. Bimanually palpate using fingers inside the mouth and extraorally. The submandibular gland is best palpated with a finger of one hand in the floor of the mouth lingual to the lower molar teeth, and a finger of the other hand placed over the submandibular triangle. The submandibular duct (Wharton's duct) runs anteromedially across the floor of the mouth to open at the side of the lingual fraenum.

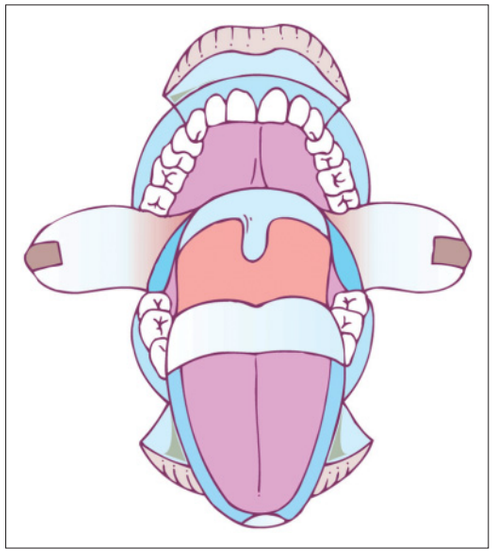


Fig. 69.3 Diagram of oral cavity.

Intraoral examination

The examination should be conducted in a systematic fashion to ensure that all areas are included. If the patient wears any removable prostheses or appliances, these should be removed in the first instance, although it may be necessary later to replace the appliance to assess fit, function and relationship to any lesion.

Complete visualization with a good source of light is essential. All mucosal surfaces should be examined, starting away from the location of any known lesions or the focus of complaint. The lips should be inspected first. The labial mucosa, buccal (cheek) mucosae, floor of mouth and ventrum of tongue, dorsal surface of the tongue, hard and soft palates, gingivae and teeth should then be examined in sequence and lesions noted on a diagram of the oral cavity (Fig. 69.3).

Lips. Features such as cyanosis are seen mainly in the lips in cardiac or respiratory disease; angular cheilitis (stomatitis) is seen mainly in oral candidosis or in iron, vitamin or immune deficiencies. Examination is facilitated if the mouth is gently closed at this stage, so that the lips can then be everted to examine the mucosa.

Labial mucosa. Normally appears moist with a fairly prominent vascular arcade. In the lower lip, the many minor salivary glands, which are often exuding mucus, are easily visible. The lips therefore feel slightly nodular and the labial arteries are readily felt. Many adults have a few yellowish, pinhead-sized papules in the vermilion border (particularly of the upper lip) and at the commissures; these are usually ectopic sebaceous glands (Fordyce spots), and may be numerous, especially as age advances.

Cheek (buccal) mucosa. This is readily inspected if the mouth is held half open. The vascular pattern and minor salivary glands so prominent in the labial mucosa are not obvious in the buccal mucosa but Fordyce spots may be conspicuous, particularly near the commissures and retromolar regions in adults. Place the surface of a dental mirror against the buccal mucosa. The mirror

should lift off easily; if it adheres to the mucosa, then xerostomia is present.

Floor of mouth and ventrum of tongue. These are best examined by asking the patient to push the tongue first into the palate then into each cheek in turn. This raises for inspection the floor of the mouth, an area where tumours may start (the 'coffin' or 'graveyard' area of the mouth). Its posterior part is the most difficult area to examine well and one where lesions are most easily missed. Lingual veins are prominent and, in the elderly, may be conspicuous (lingual varices). Bony lumps on the alveolar ridge lingual to the premolars are most often tori (torus mandibularis). During this part of the examination the quantity and consistency of saliva should be assessed. Examine for the normal pooling of saliva in the floor of the mouth; normally there is a pool of saliva in the floor of the mouth.

Dorsum of tongue. This is best inspected by protrusion, when it can be held with gauze.

This raises the floor of the mouth which aids inspection. The floor of mouth and posterolateral margin of the tongue is an area where tumours may start. The posterior aspect of the floor of the mouth is the most difficult area to examine well and one where lesions are most likely to be missed.

The anterior two-thirds of the tongue is embryologically and anatomically distinct from the posterior third, and separated by a dozen or so large circumvallate papillae. The anterior two-thirds is coated with many filiform, but relatively few fungiform, papillae. Behind the circumvallate papillae, the tongue contains several large lymphoid masses (lingual tonsil) and the foliate papillae lie on the lateral borders posteriorly. These are often mistaken for tumours. The tongue may be fissured (scrotal) but this is usually regarded as a developmental anomaly. A healthy child's tongue is rarely coated but a mild coating is not uncommon in healthy adults. The voluntary tongue movements and sense of taste should be formally tested. Abnormalities of tongue movement (neurological or muscular disease) may be obvious from dysarthria or involuntary movements and any fibrillation or wasting noted. Hypoglossal palsy may lead to deviation of the tongue towards the affected side on protrusion. Taste sensation can be tested by placing the tongue across the terminals of a pocket torch battery when a metallic taste may be obvious. Formal testing with salt, sweet, sour and bitter should be carried out by applying solutions of salt, sugar, dilute acetic acid and 5% citric acid to the tongue on a cotton swab or cotton bud.

Palate and fauces. These consist of an anterior hard and posterior soft palate, and the tonsillar area and oropharynx. The mucosa of the hard palate is firmly bound down as a mucoperiosteum (similar to the gingivae) and with no obvious vascular arcades. Rugae are present anteriorly on either side of the incisive papilla that overlies the incisive foramen. Bony lumps in the posterior centre of the vault of the hard palate are usually tori (torus palatinus). Patients may complain of lumps distal to the upper molars that they think are unerupted teeth but the pterygoid hamulus or tuberosity is usually responsible for this complaint. The soft palate and fauces may show a faint vascular arcade. In the soft palate, just posterior to the junction with the hard palate, is a conglomeration of minor salivary glands. This region is often also yellowish. The palate should be inspected and movements examined when the patient says 'Aah'. Using a mirror, this also permits inspection of the posterior tongue, tonsils, oropharynx, and can even offer a glimpse of the larynx. Glossopharyngeal palsy may lead to uvula deviation to the contralateral side.

Gingivae. In health they are firm, pale pink, with a stippled surface, and have sharp gingival papillae reaching up between the adjacent teeth to the tooth contact point. Look for gingival redness, swelling or bleeding on gently probing the gingival margin. The 'keratinized' attached gingivae (pale pink) are normally clearly demarcated from the non-keratinized alveolar mucosa (vascular) that runs into the vestibule or sulcus. Bands of tissue, which may contain muscle attachments, run centrally from the labial mucosa onto the alveolar mucosa and from the buccal mucosa in the premolar region onto the alveolar mucosa (fraena).

Teeth. The dentition should be checked to make sure that the expected complement of teeth is present for the patient's age. Extra teeth (supernumerary teeth) or deficiency of teeth (partial loss or hypodontia; oligodontia; complete loss or anodontia) can be features of many syndromes but teeth are far more frequently missing because they are unerupted, or lost as a result of caries or periodontal disease. The teeth should be fully examined for signs of disease, either malformations such as hypoplasia or abnormal shape or colour, or acquired disorders such as dental caries, erosion or abrasion, or superficial discoloration due to poor hygiene, habits, foods or drugs. The occlusion of the teeth should also be checked; it may show attrition or may be disturbed, as in some jaw fractures or dislocation of the mandibular condyles.

Anatomical variants

Patients sometimes become concerned after noticing various anatomical variants in the mouth. These include tori and exostoses [1–3], which are developmental bony lumps seen especially in Mongoloid and Negroid races. Most common is torus palatinus, a slow-growing, asymptomatic, benign, bony lump in the midline of the palate (Fig. 69.4). Tori mandibularis are bilateral, asymptomatic, benign, bony lumps lingual to the premolars.



Fig. 69.4 Torus palatinus.

The diagnosis is confirmed by radiography. Surgery is rarely indicated. These are excised or reduced only if causing severe difficulties with dentures.

References

1 Eggen S, Natvig B. Relationship between torus mandibularis and number of present teeth. *Scand J Dent Res* 1986; **94**: 233–40.
2 Rezai RF. Torus palatinus, an exostosis of unknown aetiology: review of the literature. *Compend Contin Educ Dent* 1985; **6**: 149–52.
3 Al Quran FA, Al-Dwairi ZN. Torus palatinus and torus mandibularis in edentulous patients. *J Contemp Dent Pract* 2006; **7**: 112–9.

Disorders affecting the teeth

Disorders of tooth eruption

Teething

'Teething' in infancy is a poorly understood condition and the soreness and fever is often due to infection such as herpes simplex stomatitis. Nevertheless, there may be a very minor degree of pyrexia around the time of tooth eruption [1,2].

References

1 Jaber L, Cohen IJ, Mor A. Fever associated with teething. *Arch Dis Child* 1992; **67**: 233–4.
2 Peretz B, Ram D, Hermida L, Otero MM. Systemic manifestations during eruption of primary teeth in infants. *J Dent Child (Chic)* 2003; **70**: 170–3.

Premature eruption of teeth [1–5]

Erupted teeth, particularly in the mandibular central incisor region, may be present at birth (natal teeth) or appear within the first few days or weeks of life (neonatal teeth). This rare event (about 0.1% of live births) occasionally has a familial basis or is associated with some other developmental anomaly. Such teeth occasionally cause ulceration of the infant's tongue or mother's nipple but usually they can be safely left *in situ*.

Delayed eruption of teeth

Congenital hypopituitarism, congenital hypothyroidism (cretinism), Down's syndrome, cleidocranial dysplasia, cytotoxic drugs and radiotherapy may cause delayed eruption of teeth, but most cases are of local aetiology (e.g. impactions).

Extra teeth

Extra (supernumerary or supplemental) teeth are uncommon and usually of an unknown cause. They are generally found in the premaxilla. Supernumerary teeth are common in cleidocranial dysplasia.

Missing teeth

It is important to remember that teeth may be apparently missing simply because they are unerupted but early loss or hypodontia may be responsible.

Dental aplasia

Synonyms
- Hypodontia
- Anodontia
- Oligodontia

Wisdom teeth (third molars), second premolars and upper lateral incisors are sometimes absent in otherwise normal individuals, probably because of some unidentified genetic trait. Up to 25% of white people lack a third molar. Absence of several teeth may indicate systemic disease such as cleidocranial dysplasia, incontinentia pigmenti or ectodermal dysplasia.

Hypodontia is often associated with microdontia and is often bilaterally symmetrical.

References

1 Scully C. *ABC of Oral Health*. London: BMJ Books, 2001.
2 Laskaris G, Scully C, eds. *Periodontal Manifestations of Local and Systemic Diseases*. Berlin: Springer, 2003.
3 Scully C. *Handbook of Oral Disease: Diagnosis and management*, 2nd edn. London: Martin Dunitz, 2007.
4 Scully C, Flint S, Porter SR, Moos K. *Oral and Maxillofacial Diseases*. London: Martin Dunitz, 2004.
5 Scully C, Felix D. *Oral Medicine—Update for the Dental Practitioner*. London: British Dental Association, 2006.

Loosening and early loss of teeth (Table 69.3)

Early loss of teeth is usually caused by trauma, dental caries or destructive periodontal disease, as discussed below [1–4]. Congenital disorders that may predispose to periodontal breakdown include Down's syndrome, Papillon–Lefèvre syndrome, neutropenia and other immune defects. Acquired disorders such as diabetes mellitus or immune defects also predispose to periodontal breakdown. Teeth are also lost early in other rare systemic disorders, for example eosinophilic granuloma or hypophosphatasia.

Table 69.3 Pathological causes of loosening and early loss of the teeth.

Local causes
Trauma
Periodontitis
Neoplasms
Systemic causes
Disorders with some immune deficit
Down's syndrome
Diabetes mellitus
Leukopenia or leukocyte defects
Human immunodeficiency virus disease
Juvenile periodontitis
Rapidly progressive periodontitis
Papillon–Lefèvre syndrome
Hypophosphatasia
Ehlers–Danlos syndrome (type VIII)
Others
Acrodynia
Neoplasms
Eosinophilic granuloma

Table 69.4 Causes of discoloration of teeth.

Extrinsic
Poor oral hygiene
Tobacco
Coffee, tea, other beverages/food
Drugs, e.g. iron, chlorhexidine, amoxicillin, sweetened medication
Stains, e.g. from betel chewing
Intrinsic
Trauma
Caries
Restorative materials, e.g. amalgam
Pink spot (internal resorption)
Drugs: mainly tetracyclines
Fluorosis
Dentinogenesis imperfecta
Amelogenesis imperfecta
Porphyria
Kernicterus (severe neonatal jaundice)



Fig. 69.5 A peg-shaped maxillary lateral incisor, a fairly common variant.

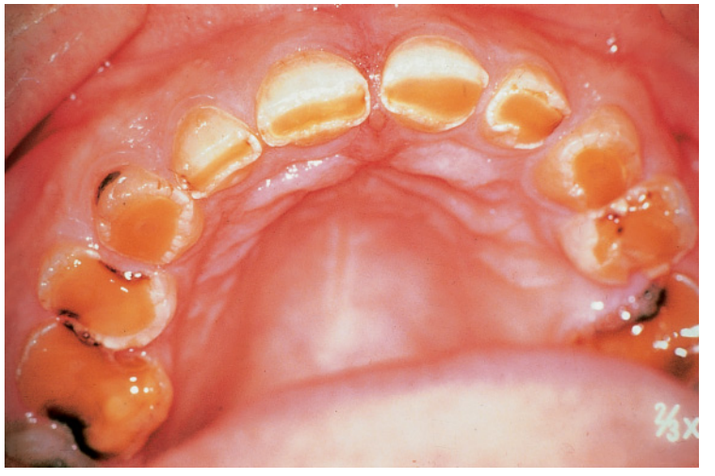


Fig. 69.6 Dentinogenesis imperfecta: staining and severe attrition.

References

1 Watanabe K. Prepubertal periodontitis: a review of diagnostic criteria, pathogenesis and differential diagnosis. *J Periodont Res* 1990; **25**: 31–48.

2 Hartsfield JK Jr. Premature exfoliation of teeth in childhood and adolescence. *Adv Pediatr* 1994; **41**: 453–70.

3 Zaromb A, Chamberlain D, Schoor R, Almas K, Blei F. Periodontitis as a manifestation of chronic benign neutropenia. *J Periodontol* 2006; **77**: 1921–6.

4 Passanezi E, Janson M, Janson G, Sant'Anna AP, de Freitas MR, Henriques JF. Interdisciplinary treatment of localized juvenile periodontitis: a new perspective to an old problem. *Am J Orthod Dentofacial Orthop* 2007; **131**: 268–76.

Malformed and discoloured teeth (Table 69.4)

There is a wide range of normal variation in tooth morphology and colour, especially between races.

Most dental discoloration is caused by lifestyle habits such as smoking, betel, foods and beverages (such as tea), medicines such as iron or chlorhexidine, or poor oral hygiene [1]. The regular use of sweetened medication at night (e.g. trimeprazine syrup in a child with eczema) can cause discoloration due to dental caries. Erosion of teeth may occur because of the repeated use of acidic drinks or sucking citrus fruits, or as a feature of gastric regurgitation in bulimia, anorexia nervosa or alcoholism.

Teeth may be malformed for genetic reasons. Peg-shaped teeth may be normal variants (Fig. 69.5) or may be found in some ectodermal dysplasias (see p. 69.10). Taurodontism (see below) can be found in a range of dermatological disorders [2]. Genetic defects that may cause tooth discoloration include dentinogenesis imperfecta (Fig. 69.6), which may be seen in some patients with osteogenesis imperfecta, and amelogenesis imperfecta [3,4].

Teeth may be damaged during their development. Local infection or trauma, or unknown factors, may cause malformation of one or more teeth. The lower premolars are usually affected because there is caries and periapical infection related to their deciduous predecessors; such hypoplastic teeth are termed *Turner's teeth*. The upper permanent incisors may be malformed if there is trauma to the deciduous incisors. Radiotherapy or cytotoxic therapy may cause hypoplasia, as may congenital rubella or cytomegalovirus infection. However, classical *Hutchinsonian* (*screwdriver-shaped*) *incisors* and *Moon's* (*or mulberry*) *molars* of congenital syphilis are extremely rare.

Hypoplasia is relatively common in apparently healthy persons [5–10] and is also seen in early-onset malabsorption syndromes, many severe childhood illnesses (Fig. 69.7) and organ transplantation [11–13] and in some forms of epidermolysis bullosa (see below). Jaundice in the neonate or infant can produce greenish teeth.

Fluoride protects against dental caries but in high water supply concentrations over 2 ppm or if administered in excess amounts may produce significant fluorosis-discoloration and even hypoplasia. Fluoride, at the concentrations present in water supplies in resource-rich countries or given prophylactically even with care, may occasionally produce inconsequential, minute white flecks. Tetracyclines given to a pregnant or lactating mother may discolour the child's teeth and, if given to a child, particularly one under the age of 12 years, may cause significant, brown, intrinsic tooth staining (Fig. 69.8).



Fig. 69.7 Hypoplasia of teeth related to severe childhood respiratory infection.



Fig. 69.8 Pronounced intrinsic tooth discoloration from use of tetracyclines in childhood.

References

1 Sulieman M. An overview of tooth discolouration: extrinsic, intrinsic and internalized stains. *Dent Update* 2005; **32**: 463–71.
2 Hill FJ, Winter GB. The teeth in dermatological diseases. In: Champion RH, ed. *Recent Advances in Dermatology*. London: Livingstone, 1986: 103–26.
3 Crawford PJ, Aldred M, Bloch-Zupan A. Amelogenesis imperfecta. *Orphanet J Rare Dis* 2007; **4**: 17.
4 Rios D, Vieira AL, Tenuta LM, Machado MA. Osteogenesis imperfecta and dentinogenesis imperfecta: associated disorders. *Quintessence Int* 2005; **36**: 695–701.
5 Scully C, Welbury R, Flaitz C, Almeida OPD. *A Color Atlas of Orofacial Health and Disease in Children and Adolescents*. London: Martin Dunitz, 2001.
6 Seow WK. Enamel hypoplasia in the primary dentition: a review. *J Dent Child* 1991; **58**: 441–52.
7 Lukacs JR, Walimbe SR, Floyd B. Epidemiology of enamel hypoplasia in deciduous teeth: explaining variation in prevalence in western India. *Am J Hum Biol* 2001; **13**: 788–807.
8 Jalevik B. Enamel hypomineralization in permanent first molars. A clinical, histomorphological and biochemical study. *Swed Dent J Suppl* 2001; **149**: 1–86.
9 Jalevik B, Klingberg G, Barregard L, Noren JG. The prevalence of demarcated opacities in permanent first molars in a group of Swedish children. *Acta Odontol Scand* 2001; **59**: 255–60.
10 Lukacs JR. Interproximal contact hypoplasia in primary teeth: a new enamel defect with anthropological and clinical relevance. *Am J Hum Biol* 1999; **11**: 718–34.

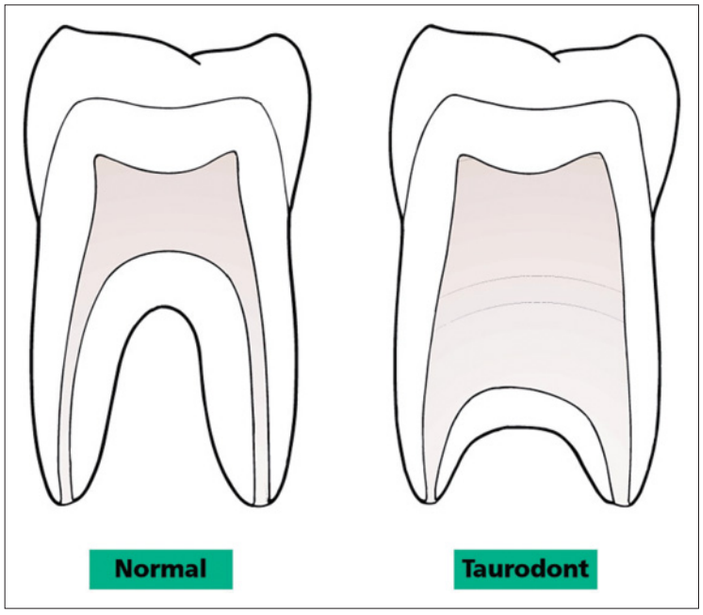


Fig. 69.9 Taurodontism.

11 Hosey MT, Gordon G, Kelly DA, Shaw L. Oral findings in children with liver transplants. *Int J Paediatr Dent* 1995; **5**: 29–34.
12 Morisaki I, Abe K, Tong LS *et al.* Dental findings of children with biliary atresia. *J Dent Child* 1990; **57**: 220–3.
13 Wondimu B, Nemeth A, Modeer T. Oral health in liver transplant children administered cyclosporin A or tacrolimus. *Int J Paediatr Dent* 2001; **11**: 424–9.

Taurodontism

Taurodont teeth have an enlarged pulp chamber and a more inferiorly placed root furcation in premolars and molars. They are not readily detectable on clinical examination and are therefore most easily diagnosed on radiographs (Fig. 69.9). However, on clinical examination, lack of constriction of the tooth at the neck may be suggestive of taurodontism. Taurodontism is generally most obvious in molars of both deciduous and permanent dentitions, and may be found in single or several teeth, with or without evidence of other disorders.

Most studies have shown an overall prevalence of the order of 2% with no sex predilection, but oriental people and some other racial groups are especially affected [1–13]. XXY and other syndromes with additional X chromosomes may be affected [4–6] as may other chromosomal anomalies [7–12]. Dermatological conditions with which taurodontism may be associated are shown in Table 69.5 [10].

References

1 Constant DA, Grine FE. A review of taurodontism with new data on indigenous southern African populations. *Arch Oral Biol* 2001; **46**: 1021–9.
2 Toure B, Kane AW, Sarr M, Wone MM, Fall F. Prevalence of taurodontism at the level of the molar in the black Senegalese population 15–19 years of age. *Odontostomatol Trop* 2000; **23**: 36–9.
3 Sarr M, Toure B, Kane AW, Fall F, Wone MM. Taurodontism and the pyramidal tooth at the level of the molar. Prevalence in the Senegalese population 15–19 years of age. *Odontostomatol Trop* 2000; **23**: 31–4.
4 Backman B, Wahlin YB. Variations in number and morphology of permanent teeth in 7-year-old Swedish children. *Int J Paediatr Dent* 2001; **11**: 11–7.

Table 69.5 Dermatological disorders in which taurodontism may occasionally be found.

Some ectodermal dysplasias
Trichodento-osseous syndrome
Tricho-onychodental syndrome
Epidermolysis bullosa
Dental oculocutaneous syndrome
Otodental dysplasia
Orofacial digital syndrome type II
Dyskeratosis congenita



Fig. 69.10 Hypodontia and malformed teeth are common in ectodermal dysplasia.

5 Varrela J, Alvesalo L. Taurodontism in 47,XXY males: an effect of the extra X chromosome on root development. *J Dent Res* 1988; **67**: 501–2.
6 Hata S, Maruyama Y, Fujita Y, Mayanagi H. The dentofacial manifestations of XXXXY syndrome: a case report. *Int J Paediatr Dent* 2001; **11**: 138–42.
7 Breen GH. Taurodontism, an unreported dental finding in Wolf–Hirschhorn (4p–) syndrome. *ASDC J Dent Child* 1998; **65**: 344–5, 356.
8 Tatakis DN, Milledge JT. Severe gingival recession in trisomy 18 primary dentition. A clinicopathologic case report of self-inflicted injury associated with mental retardation. *J Periodontol* 2000; **71**: 1181–6.
9 Rajic Z, Mestrovic SR. Taurodontism in Down's syndrome. *Coll Antropol* 1998; **22** (Suppl.): 63–7.
10 Ogden GR. Taurodontism in dermatologic disease. *Int J Dermatol* 1988; **27**: 360–4.
11 Rao A, Arathi R. Taurodontism of deciduous and permanent molars: report of two cases. *J Indian Soc Pedod Prev Dent* 2006; **24**: 42–4.
12 Schulman GS, Radford-Badwal D, Poole A, Mathieu G, Burleson J, Dauser D. Taurodontism and learning disabilities in patients with Klinefelter syndrome. *Pediatr Dent* 2005; **27**: 389–94.
13 Islam M, lurie AG, Reichenberger E. Clinical features of tricho-dento-osseous syndrome and presentation of three new cases; an addition to clinical heterogeneity. *Oral Surg Oral Med Oral Path Endod* 2005; **100**: 736–42.

Ectodermal dysplasia

Ectodermal dysplasia is typically characterized by developmental abnormalities in at least two different ectodermally derived systems [1]. Oral abnormalities are common, especially missing teeth and abnormally shaped teeth (Fig. 69.10). There are many variations, as discussed in the following sections and in Chapter 15, and current classification is based on clinical features.

X-linked hypohidrotic ectodermal dysplasia [2–4]

Hypodontia is common in X-linked hypohidrotic ectodermal dysplasia. Some anterior teeth are usually present but their crowns are typically conical or peg-shaped. The posterior teeth, when present, are smaller but otherwise normal. Overclosure of the jaws, together with maxillary hypoplasia and frontal bossing, give a characteristic facial appearance. There may be a degree of impaired salivary gland function.

Female carriers of this syndrome may have hypodontia and/or microdontia.

Autosomal recessive ectodermal dysplasia [2,5]

Dental and oral anomalies in this condition are identical to those in the X-linked form of ectodermal dysplasia, although relatives may have a normal dentition.

Hypodontia, taurodontism and sparse hair [6]

There are a few reports of a variant of ectodermal dysplasia in which there is taurodontism, and somewhat lesser hypodontia than in the more classic forms of ectodermal dysplasia.

Autosomal dominant hypodontia with nail dysgenesis [7]

Hypodontia, conical deciduous and permanent teeth, and dysplastic nails characterize this variant of ectodermal dysplasia.

Incontinentia pigmenti [8,9]

Synonym
- Bloch–Sulzberger syndrome

Hypodontia and retarded eruption affect both dentitions and the anterior teeth are small. The teeth tend also to be conical, often with accessory cusps.

Chondroectodermal dysplasia [10–14]

Synonym
- Ellis–van Creveld syndrome

This is a rare autosomal recessive condition that manifests with chondrodysplasia of tubular bones resulting in disproportionate dwarfism, polydactyly and syndactyly of hands and feet, severe dystrophic nails, bilateral partial clefts of the alveolar bone and malocclusion. Half of the cases have cardiac malformations.

The most obvious oral anomalies are the multiple fraena extending from the lips and buccal mucosae to the alveolar ridges of both jaws. Natal teeth, mild hypodontia or hyperdontia, malformed or small teeth and accessory cusps are common.

Cranioectodermal dysplasia [12]

Deciduous teeth are small and may have dysplastic enamel, although the condition is so rare that the permanent teeth have not been clearly described. There may be hypodontia or taurodontism. Dolicocephaly, hair anomalies and shortened arms, fingers and toes are associated.

Nance–Horan syndrome [13]

X-linked congenital cataracts with supernumerary teeth constitute the Nance–Horan syndrome. The incisor teeth may also be morphologically abnormal and can resemble Hutchinson's incisors of congenital syphilis.

Trichodental syndrome [14,15]

The trichodental syndrome is a rare, dominantly inherited condition in which there is fine short hair, thinning of the lateral ends of the eyebrows, hypodontia and/or conical teeth.

Trichodento-osseous syndrome [16–19]

Tight, curly hair, sclerotic cortical bone and oral anomalies (especially thin enamel) are found in this autosomal dominant condition. The hypoplasia–hypomaturation type of amelogenesis imperfecta, enamel hypoplasia, unerupted teeth and taurodontism may be associated.

Trichonychodental syndrome [20–26]

This autosomal dominant trait of fine, curly hair and thin dysplastic nails may be associated with taurodontism and enamel or dentinal developmental defects.

Curry–Hall syndrome [27]

Deciduous teeth are small and conical, and the incisors are often retained since their permanent successors may be congenitally absent. The remaining permanent teeth do erupt but are small. Other features include short limbs, polydactyly and nail dysplasia.

Otodental dysplasia [28–32]

Globe-shaped posterior teeth (globodontia) in both dentitions are the most common oral feature of this autosomal dominant condition, which is associated with sensorineural hearing loss. The incisors are not affected and the patients are otherwise well. Other oral anomalies may include taurodontism, microdontia and hypodontia.

Clouston syndrome [33] (see Chapter 15)

Palmoplantar hyperkeratosis, hair defects, nail dysplasia and oral white lesions characterize this autosomal dominant form of hidrotic ectodermal dysplasia. There may be diffuse, white lesions in the buccal mucosa, palate, tongue and elsewhere but reports of malignancy are rare.

References

1 Mehta U, Brunworth J, Fete TJ, Sindwani R. Head and neck manifestations and quality of life of patients with ectodermal dysplasia. *Otolaryngol Head Neck Surg* 2007; **136**: 843–7.
2 Levin LS. Dental and oral abnormalities in selected ectodermal dysplasia syndromes. *Birth Defects* 1988; **24**: 205–27.
3 Sofaer JA. Hypodontia and sweat pore counts in detecting carriers of X-linked hypohidrotic ectodermal dysplasia. *Br Dent J* 1981; **151**: 327–30.
4 Glavina D, Majstorovic M, Lulic-Dukic O, Juric H. Hypohidrotic ectodermal dysplasia: dental features and carriers detection. *Coll Antropol* 2001; **25**: 303–10.
5 Bartlett RC, Eversole LR, Adkins RS. Autosomal recessive hypohidrotic ectodermal dysplasia: dental manifestations. *Oral Surg* 1972; **33**: 736–42.
6 Stenvik A, Zachrisson BU, Svatum B. Taurodontism and concomitant hypodontia in siblings. *Oral Surg* 1972; **33**: 841–5.
7 Hudson CD, Witkop CJ. Autosomal dominant hypodontia with nail dysgenesis. Report of twenty-nine cases in six families. *Oral Surg* 1975; **39**: 409–23.
8 Gorlin RJ, Anderson JA. The characteristic dentition of incontinentia pigmenti: a diagnostic aid. *J Pediatr* 1960; **57**: 78–85.
9 Caputo R, Gianotti F, Innocenti M. Ultrastructural findings in Incontinentia pigmentii. *Int J Dermatol* 1975; **14**: 46–55.
10 Sarnant H, Amir E, Legum CP. Development dental anomalies in chondroectodermal dysplasia (Ellis–Van-Creveld syndrome). *J Dent Child* 1980; **47**: 28–31.
11 Hattab FN, Yassin OM, Sasa IS. Oral manifestations of Ellis–van Creveld syndrome: report of two siblings with unusual dental anomalies. *J Clin Pediatr Dent* 1998; **22**: 159–65.
12 Hunter ML, Roberts GJ. Oral and dental anomalies in Ellis van Creveld syndrome (chondroectodermal dysplasia): report of a case. *Int J Paediatr Dent* 1998; **8**: 153–7.
13 Lichiardopol C, Militaru C. Ellis van Creveld syndrome. *Rom J Morphol Embryol* 2006; **47**: 363–6.
14 Kurian K, Shanmugam S, Vardhan TH, Gupta S. Chondroectodermal dysplasia (Ellis van Creveld syndrome); a report of three cases with review of the literature. *Indian J Dent Rest* 2007; **18**: 31–4.
15 Levin LS, Perrin JCS, Ose L *et al*. A heritable syndrome of craniosynostosis, short thin hair, dental abnormalities, and short limbs: cranioectodermal dysplasia. *J Pediatr* 1977; **90**: 55–61.
16 Bixler D, Higgins M, Hartsfield J. The Nance–Horan syndrome: a rare X-linked ocular–dental trait with expression in heterozygous females. *Clin Genet* 1984; **26**: 303–35.
17 Hibbert S. A previously unreported association between Nance Horan syndrome and spontaneous dental abscesses. *Oral Surg Oral Med Oral Path Endod* 2005; **99**: 207–11.
18 Reches A, Yaron Y, Burdon K *et al*. Prenatal detection of congenital bilateral cataract leading to the diagnosis of Nance Horan Syndrome in the extended family. *Prenat Diagn* 2007; **27**: 662–4.
19 Kersey PJW. Tricho-dental syndrome: a disorder with a short hair cycle. *Br J Dermatol* 1987; **116**: 259–63.
20 Salinas CF, Spector M. Tricho-dental syndrome. In: Brown AC, Crounse RG, eds. *Hair, Trace Elements and Human Illness*. New York: Praeger, 1980: 240–56.
21 Jorgenson RJ, Warson RW. Dental abnormalities in the trichodento-osseous (TDO) syndrome. *Oral Surg* 1973; **36**: 696–700.
22 Wright JT, Roberts MW, Wilson AR, Kudhail R. Tricho-dento-osseous syndrome. *Oral Surg* 1994; **77**: 487–93.
23 Spangler GS, Hall KI, Kula K, Hart TC, Wright JT. Enamel structure and composition in the tricho-dento-osseous syndrome. *Connect Tissue Res* 1998; **39**: 165–75; discussion 187–94.
24 Price JA, Wright JT, Walker SJ, Crawford PJ, Aldred MJ, Hart TC. Tricho-dento-osseous syndrome and amelogenesis imperfecta with taurodontism are genetically distinct conditions. *Clin Genet* 1999; **56**: 35–40.
25 Koshiba H, Kimura O, Nakata M. Clinical, genetic and histologic features of the trichonychodental (TOD) syndrome. *Oral Surg* 1978; **46**: 376–85.
26 Montalvan E, Mazzone C, Tofsky N, Mupparapu M. Trichodental dysplasia: a rare syndrome with distinct dental findings. *Pediatr Dent* 2006; **28**: 345–9.
27 Shapiro SD, Jorgenson RJ, Salinas CF. Brief clinical report: Curry–Hall syndrome. *Am J Med Genet* 1984; **17**: 579–83.
28 Levin LS, Jorgenson RJ, Cook RA. Otodental dysplasia: a 'new' ectodermal dysplasia. *Clin Genet* 1975; **8**: 136–44.
29 Witkop CJ, Gudlach KH, Street WJ *et al*. Globodontia in the otodental syndrome. *Oral Surg* 1976; **41**: 472–83.
30 Sedano HO, Moreira LC, de Souza RA, Moleri AB. Otodental syndrome: a case report and genetic considerations. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001; **92**: 312–7.
31 Bloch-Zupan A, Goodman JR. Otodental syndrome. *Orphanet J Rare Dis* 2006; **21**: 1–5.
32 Van Doome L, Wackens G, De Maeseneer M, Deron P. Otodental syndrome: a case report. *Int J Oral Maxillofacial Surg* 1998; **27**: 121–4.
33 George DI, Escobar VH. Oral findings of Clouston's syndrome (hidrotic ectodermal dysplasia). *Oral Surg* 1984; **57**: 258–62.

Other rare ectodermal dysplasias [1]

Other rare ectodermal dysplasias and pachonychia congenita are discussed in Chapter 15. Others are summarized in Table 69.6.

Table 69.6 Oral features in rare ectodermal dysplasia variants [1–3].

Syndrome	Oral manifestations	Facial manifestations	Other features
GAPO (*g*rowth retardation, *a*lopecia, *p*seudoanodontia, *o*ptic atrophy)	Failure of both dentitions to erupt	Frontal bossing Midface hypoplasia	*See left-hand column*
Johanson–Blizzard	Hypodontia in both dentitions Roots of deciduous teeth are short and deformed, crowns are conical	Microcephaly Hypoplastic alae nasi	Hearing loss Pancreatic dysfunction Learning disability
Waardenburg	–	Cleft lip/palate	Deafness Hair depigmentation
LEOPARD (*l*entigines, *e*lectrocardiographic anomalies, *o*cular hypertelorism, *p*ulmonary stenosis, *a*bnormal genitalia, *r*etarded growth, *d*eafness)	No mucosal lentigines	Triangular face with hypertelorism and ptosis, cell tumour	*See left-hand column* may be granular
Congenital erythrokeratoderma with sensorineural hearing loss	Hyperkeratosis Occasional carcinoma	–	*See left-hand column*

Table 69.7 Causes of gingival bleeding.

Local
Chronic gingivitis
Chronic periodontitis
Acute necrotizing gingivitis
Systemic
Any condition causing gingival hyperaemia (e.g. pregnancy)
Leukaemia
Human immunodeficiency virus infection
Other causes of purpura
Clotting defects
Drugs, e.g. anticoagulants
Scurvy

Table 69.8 Causes of gingival swelling.

	Generalized swelling	Localized swelling
Local	Chronic gingivitis	Abscesses
	Hyperplastic gingivitis due to mouth breathing	Cysts
		Pyogenic granuloma
		Neoplasms and warts (various)
Systemic	Hereditary gingival fibromatosis and associated syndromes	Pregnancy
	Drugs (phenytoin, ciclosporin, nifedipine, diltiazem)	Sarcoidosis
	Pregnancy	Orofacial granulomatosis
	Sarcoidosis	Crohn's disease
	Crohn's disease	Wegener's granulomatosis
	Leukaemia	Amyloidosis
	Wegener's granulomatosis	Neoplasms (various)
	Scurvy	
	Amyloidosis	
	Mucopolysaccharidoses	
	Mucolipidosis	
	Lipoid proteinosis	
	Juvenile hyaline fibromatosis	
	Hypoplasminogenaemia	

Alstrom syndrome

Alstrom syndrome is a rare disorder characterized by early obesity, diabetes mellitus, loss of central vision, hearing loss and short stature. Light yellow-brown discoloured enamel bands have been observed on the anterior teeth in some patients [2,3].

References

1 Gorlin RJ. Selected ectodermal dysplasias. *Birth Defects* 1988; **24**: 123–48.

2 Koray F, Dorter C, Benderli Y *et al.* Alstrom syndrome: a case report. *J Oral Sci* 2001; **43**: 221–4.

3 Marshall TD, Bronson RT, Collin GB *et al.* New Alstrom syndrome phenotypes based on the evaluation of 182 cases. *Arch Inten Med* 2005; **165**: 675–83.

Disorders affecting the periodontium

Gingival disorders affecting the periodontium

Bleeding

Bleeding from the gingival margins is common, and is usually a consequence of inadequate oral hygiene leading to the accumulation of dental bacterial plaque and thus gingivitis (Table 69.7), which is painless and causes only some mild erythema and bleeding on brushing or eating hard foods.

Chronic gingivitis affects many, if not most, healthy adults but the tendency to gingivitis and bleeding is slightly increased in patients taking oral contraceptives and in some pregnant women (especially during the second trimester).

Gingival haemorrhage may, however, also be an early feature in some vascular or platelet disorders and is commonly a problem, for example, in leukaemic patients.

Swelling

Localized gingival swellings (epulides) may be of local aetiology or can be manifestations of pregnancy, a neoplasm or systemic disease (Table 69.8).

Gingival swelling affecting many areas is most commonly seen in chronic gingivitis, may be produced by drugs such as phenytoin, ciclosporin (cyclosporin) and calcium channel blockers (Fig. 69.11), and is occasionally hereditary. Gingival swelling is



Fig. 69.11 Gingival hyperplasia in phenytoin therapy. Concomitant folate deficiency in this patient also caused mouth ulcers, seen in the maxillary buccal vestibule.

seen with hypertrichosis in both drug-induced hyperplasias and hereditary gingival fibromatosis.

A degree of gingival swelling may also be seen in herpetic stomatitis, pregnancy, OFG, and Crohn's disease. Rare causes include leukaemia, scurvy, Wegener's granulomatosis, sarcoidosis, amyloidosis, lipoid proteinosis, hypoplasminogenaemia, mucopolysaccharidoses and other disorders.

Redness

Chronic, marginal gingivitis is the usual cause of gingival redness, and then is usually restricted to the gingival margins and interdental papillae.

More widespread erythema, particularly if associated with soreness, in children is usually caused by primary herpes simplex stomatitis. In adults the main cause is desquamative gingivitis (usually due to lichen planus or mucous membrane pemphigoid—rarely by pemphigus or other dermatoses). At any age, chemotherapy or irradiation to the head and neck, or graft-versus-host disease can cause mucositis. Erythema is also occasionally induced by allergic responses, for example plasma cell gingivitis.

Telangiectasia may be a manifestation of hereditary haemorrhagic telangiectasia, primary biliary cirrhosis or systemic sclerosis, or may follow radiotherapy. Haemangiomas are usually isolated but may occasionally extend deeply and rarely involve the ipsilateral meninges, producing a facial angioma and epilepsy, sometimes with learning disability (Sturge–Weber syndrome). Intraoral haemangiomas may be seen in Maffucci's syndrome.

Localized red areas may represent trauma, erythroplasia, carcinoma, candidosis, lichen planus or lupus erythematosus. Kaposi's sarcoma may present as a red, purple, brown or bluish macule or nodule as may epithelioid angiomatosis. Hereditary mucoepithelial dysplasia is a rare cause of oral erythema. Irradiation-induced mucositis is a further cause of a red sore mouth.

White patches (Table 69.9)

White patches may be produced by debris ('material alba') or epithelial sloughing (Fig. 69.12). Thrush (acute candidosis) produces oral white patches.

Table 69.9 Main causes of oral white lesions.

Local
Materia alba
Candidosis
Frictional keratosis
Smoker's keratosis
Idiopathic keratosis
Carcinoma
Burns (including snuff and cocaine)
Skin grafts
Systemic
Candidosis
Lichen planus
Lupus erythematosus
Papillomas (some)
Hairy leukoplakia (mainly human immunodeficiency virus disease)
Syphilitic keratosis
Chronic renal failure
Inherited lesions (e.g. white-sponge naevus)



Fig. 69.12 Gingival hyperpigmentation of racial origin. The white lesion is due to accumulated oral debris—oral hygiene is very poor.

Leukoplakia is often caused by friction or smoking, occasionally with syphilis, candidosis or chronic renal failure, but most cases are idiopathic. Lichen planus and lupus erythematosus may present as white lesions. Rarely, lichenoid lesions are associated with various drugs, liver disease or graft-versus-host disease (GVHD). Carcinoma may present as a white lesion.

Inherited causes of white patches, such as white sponge naevus and dyskeratosis congenita, are rare [1,2].

Pigmentation

Gingival pigmentation is usually seen in dark-skinned races (but may be seen even in white people) (Fig. 69.12). Other common causes include amalgam tattoo and melanotic macules.

Addison's disease, Kaposi's sarcoma and melanoma are the most important acquired causes of pigmented lesions but drugs such as hydroxychloroquine and minocycline may also cause hyperpigmentation.

Ulcers

Gingival ulcers are sometimes self-induced (artefactual) [1,2]. Herpesviruses can cause gingival ulceration, often with ulcers elsewhere in the mouth. Acute ulcerative (necrotizing) gingivitis causes ulceration of the interdental papillae and, although usually a consequence of poor oral hygiene, it or a similar disorder is a rare complication of HIV infection, neutropenia or leukaemia, and in the malnourished or some immunosuppressed patients may spread to the cheek (*noma* or *cancrum oris*). Other bacterial infections (e.g. syphilis, tuberculosis) and mycoses (deep mycoses) are uncommon causes of ulceration. Aphthae (sometimes) and other causes of mouth ulcers (rarely) involve the gingiva (Table 69.10).

Table 69.10 Main causes of mouth ulcers associated with systemic disease.

Microbial disease
Herpetic stomatitis
Chickenpox
Herpes zoster
Hand, foot and mouth disease
Herpangina
Infectious mononucleosis
Human immunodeficiency virus disease
Tuberculosis
Syphilis
Fungal infections (rare)
Malignant neoplasms
Cutaneous disease
Erosive lichen planus and chronic ulcerative stomatitis
Pemphigus
Pemphigoid
Erythema multiforme
Dermatitis herpetiformis and linear IgA disease
Epidermolysis bullosa
Other dermatoses
Blood disorders
Anaemia
Leukaemia
Neutropenia
Other white cell dyscrasias
Gastrointestinal diseases
Coeliac disease
Crohn's disease
Ulcerative colitis
Rheumatic diseases
Lupus erythematosus
Behçet's syndrome
Sweet's syndrome
Reiter's disease
Drugs
Cytotoxic, NSAIDs, nicorandil, alendronate and other agents
Acrodynia
Radiotherapy
Disorders of uncertain pathogenesis
Angina bullosa haemorrhagica
Hypereosinophilic syndrome
Eosinophilic ulcer
Necrotizing sialometaplasia

Blisters

Blisters may be seen as a result of burns or mucoceles, but the most important vesiculobullous disorders affecting the gingivae are pemphigoid (including cicatricial pemphigoid) and pemphigus and the typical presentation is of desquamative gingivitis. Vesicles may also be seen in viral infections, especially in herpes simplex stomatitis, chickenpox, herpangina and hand, foot and mouth disease [3–6].

References

1 Scully C, Porter SR. Disorders of the gums and periodontium. *Med Int* 1990; **76**: 3150–3.
2 Scully C, Porter SR. Oral medicine 1. Teeth and the periodontium. *Postgrad Dent* 1992; **2**: 93–100.
3 Scully C. *ABC of Oral Health*. London: BMJ Books, 2001.
4 Laskaris G, Scully C, eds. *Periodontal Manifestations of Local and Systemic Disease*. Berlin: Springer, 2003.
5 Scully C. *Handbook of Oral Disease: Diagnosis and Management*. London: Martin Dunitz, 1999.
6 Scully C, Flint S, Porter SR, Moos K. *Oral and Maxillofacial Diseases*. London: Martin Dunitz, 2004.

Genetic disorders affecting the periodontium

Hereditary gingival fibromatosis

Aetiology. An autosomal dominant condition due to chromosome 2 or 5 anomalies, resulting in transforming growth factor (TGF)-β1 autocrine stimulation of fibroblast proliferation with alteration in expression of matrix metalloproteinases (MMP)-1 and MMP-2. A role for increased fatty acid synthase activity has also been suggested [1–6].

Pathology. The gingival connective tissue is mainly composed of thick, interlacing collagen fibres forming a dense, almost avascular, mass in which many fibrocytes have dark, shrunken nuclei. Mucoid material and some giant cells may be found.

Clinical features. There is generalized gingival enlargement, especially obvious over the anterior maxilla and during the transition from deciduous to permanent dentitions [1,7]. If the enlargement is gross, it may move or cover the teeth and even protrude from the mouth. The changes initially involve the gingival papillae and later the attached gingiva. The affected gingiva is usually of normal colour but firm in consistency, and the surface becomes coarsely stippled. Patients may also be hirsute (as may patients with drug-induced gingival hyperplasia) [8–19]. The prognosis is good, but gingival surgery is often indicated.

Although most patients have only gingival fibromatosis, there are occasional associations with supernumerary teeth or with Zimmermann–Laband, Rutherford, Cowden and Cross syndromes [20–25].

References

1 De Angelo S, Murphy J, Claman L, Kalmar J, Leblebicioglu B. Hereditary gingival fibromatosis—a review. *Compend Contin Educ Dent* 2007; **28**: 138–43.
2 Almeida OP, Coletta RD, Silva SD, Agostini M, Vargas PA, Bozzo L, Graner E. Proliferation of fibroblasts cultured from normal gingival and hereditary gingival fibromatosis is dependent on fatty acid synthase activity. *J Periodontol* 2005; **76**: 272–8.

3 Martelli-Junior H, Cotrim P, Graner E, Sauk JJ, Coletta RD. Effect of transforming growth factor-beta1, interleukin-6, and interferon-gamma on the expression of type I collagen, heat shock protein 47, matrix metalloproteinase (MMP)-1 and MMP-2 by fibroblasts from normal gingiva and hereditary gingival fibromatosis. *J Periodontol* 2003; **74**: 296–306.
4 Tipton DA, Woodward ES 3rd, Baber MA, Dabbous MK. Role of the c-myc proto-oncogene in the proliferation of hereditary gingival fibromatosis fibroblasts. *J Periodontol* 2004; **75**: 360–9.
5 Hakkinen L, Csiszar A. Hereditary gingival fibromatosis: characteristics and novel putative pathogenic mechanisms. *J Dent Res* 2007; **86**: 25–34.
6 Haytec MC, Oxcelik O. The phenotypic overlap of syndromes associated with hereditary gingival fibromatosis: follow-up of a family for five years. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; **103**: 521–7.
7 Bozzo L, Almeida O, Scully C, Aldred M. Familial gingival fibromatosis: report of an extensive four generation pedigree. *Oral Surg* 1994; **78**: 452–4.
8 Bozzo L, Machado MA, de Almeida OP, Lopes MA, Coletta RD. Hereditary gingival fibromatosis: report of three cases. *J Clin Pediatr Dent* 2000; **25**: 41–6.
9 Hart TC, Pallos D, Bozzo L *et al.* Evidence of genetic heterogeneity for hereditary gingival fibromatosis. *J Dent Res* 2000; **79**: 1758–64.
10 de Andrade CR, Cotrin P, Graner E *et al.* Transforming growth factor-beta1 autocrine stimulation regulates fibroblast proliferation in hereditary gingival fibromatosis. *J Periodontol* 2001; **72**: 1726–33.
11 Xiao S, Bu L, Zhu L *et al.* A new locus for hereditary gingival fibromatosis (GINGF2) maps to 5q13–q22. *Genomics* 2001; **74**: 180–5.
12 Xiao S, Wang X, Qu B *et al.* Refinement of the locus for autosomal dominant hereditary gingival fibromatosis (GINGF) to a 3.8-cM region on 2p21. *Genomics* 2000; **68**: 247–52.
13 Hart TC, Pallos D, Bowden DW *et al.* Genetic linkage of hereditary gingival fibromatosis to chromosome 2p21. *Am J Hum Genet* 1998; **62**: 876–83.
14 Wright HJ, Chapple IL, Matthews JB. TGF-beta isoforms and TGF-beta receptors in drug-induced and hereditary gingival overgrowth. *J Oral Pathol Med* 2001; **30**: 281–9.
15 Coletta RD, Almeida OP, Ferreira LR, Reynolds MA, Sauk JJ. Increase in expression of Hsp47 and collagen in hereditary gingival fibromatosis is modulated by stress and terminal procollagen N-propeptides. *Connect Tissue Res* 1999; **40**: 237–49.
16 Coletta RD, Almeida OP, Reynolds MA, Sauk JJ. Alteration in expression of MMP-1 and MMP-2 but not TIMP-1 and TIMP-2 in hereditary gingival fibromatosis is mediated by TGF-beta 1 autocrine stimulation. *J Periodontal Res* 1999; **34**: 457–63.
17 Coletta RD, Almeida OP, Graner E, Page RC, Bozzo L. Differential proliferation of fibroblasts cultured from hereditary gingival fibromatosis and normal gingiva. *J Periodontal Res* 1998; **33**: 469–75.
18 Tipton DA, Dabbous MK. Autocrine transforming growth factor beta stimulation of extracellular matrix production by fibroblasts from fibrotic human gingiva. *J Periodontol* 1998; **69**: 609–19.
19 Gould AR, Escobar VH. Symmetrical gingival fibromatosis. *Oral Surg* 1981; **51**: 62–7.
20 Clark D. Gingival fibromatosis and related syndromes. *J Can Dent Assoc* 1987; **53**: 137–40.
21 Wynne SE, Aldred ME, Bartold M. Hereditary gingival fibromatosis associated with hearing loss and supernumerary teeth: a new syndrome. *J Periodontol* 1995; **66**: 75–9.
22 Katz J, Guelmann M, Barak S. Hereditary gingival fibromatosis with distinct dental, skeletal and developmental abnormalities. *Pediatr Dent* 2002; **24**: 253–6.
23 Bazoupoulou-Kyrkanidou E, Papagianoulis L, Papanicoliou S, Mavrou A. Laband syndrome: a case report. *J Oral Pathol Med* 1990; **19**: 385–7.
24 Bakaeen G, Scully C. Hereditary gingival fibromatosis and the Zimmermann–Laband syndrome. *J Oral Pathol Med* 1991; **20**: 456–9.
25 Chadwick B, Hunter B, Hunter L *et al.* Laband syndrome: report of two cases, review of the literature and identification of additional manifestations. *Oral Surg* 1994; **78**: 57–63.

Juvenile hyaline fibromatosis (see Chapter 45)

Synonym
- Murray–Puretic–Drescher syndrome

Gingival enlargement may be seen in juvenile hyaline fibromatosis. It may precede tooth eruption or may present only in the first decade. It increases with age. Histology shows dilated capillaries in a hyaline periodic acid–Schiff (PAS)-positive matrix with pseudocartilaginous cells [1–7]. Juvenile hyaline fibromatosis and infantile systemic hyalinosis overlap associated with a novel mutation in capillary morphogenesis protein-2 gene has now been reported [8].

References

1 Aldred MJ, Crawford PJM. Juvenile hyaline fibromatosis. *Oral Surg* 1987; **63**: 71–7.
2 Sciubba JJ, Nieblom T. Juvenile hyaline fibromatosis (Murray–Puretic–Drescher syndrome): oral and systemic findings in siblings. *Oral Surg* 1986; **62**: 397–409.
3 Bedford CD, Sills JA, Sommelet-Olive D *et al.* Juvenile hyaline fibromatosis: a report of two severe cases. *J Pediatr* 1991; **119**: 404–10.
4 Piattelli A, Scarano A, Di Bellucci A, Matarasso S. Juvenile hyaline fibromatosis of gingiva: a case report. *J Periodontol* 1996; **67**: 451–3.
5 Kawasaki G, Yanamoto S, Mizuno A, Fujita S. Juvenile hyaline fibromatosis complicated with oral squamous cell carcinoma: a case report. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001; **91**: 200–4.
6 Uslu H, Bal N, Guzeldemir E, Pektas ZO. Three siblings with juvenile hyaline fibromatosis. *J Oral Pathol Med* 2007; **36**: 123–5.
7 Al-Malik MI, Rehbini ZA, Eltayeb AA. Oral manifestations of juvenile hyaline fibromatosis: a case report. *J Clin Pediatr Dent* 2005; **29**: 347–51.
8 Antaya RT, Cajuba MM, Madri J, Lopez MA, Ramirez MC, Martignetti JA, Reves-Mugica M. Juvenile hyaline fibromatosis and infantile systemic hyalinosis overlap associated with a novel mutation in capillary morphogenesis protein-2 gene. *Am J Dermatopathol* 2007; **29**: 99–103.

Hypoplasminogenaemia

Chronic gingival swelling and ulceration may be seen in this disorder in which there can also be ligneous conjunctivitis. Local treatments are rarely successful; plasminogen replacement is needed [1–6].

References

1 Scully C, Gokbuget AY, Allen C *et al.* Oral manifestations indicative of plasminogen deficiency (hypoplasminogenemia). *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001; **91**: 344–7.
2 Tefs K, Tait CR, Walker ID, Pietzsch N, Ziegler M, Schuster V. A K19E missense mutation in the plasminogen gene is a common cause of familial hypoplasminogenaemia. *Blood Coagul Fibrinolysis* 2003; **14**: 411–6.
3 Silva GB, Bariani C, Mendonca EF, Batista AC. Clinical manifestations due to severe plasminogen deficiency: a case report. *J Dent Child (Chic)* 2006; **73**: 179–82.
4 Kurtulus I, Gokbuget A, Efeoglu A, Cintan S, Tefs K, Schuster V, Scully C. Hypoplasminogenemia with ligneous periodontitis: a failed local therapeutic approach. *J Periodontol* 2007; **78**: 1164–75.
5 Scully C, Gokbuget A, Kurtulus I. Hypoplasminogenaemia, gingival swelling and ulceration. *Oral Diseases* 2007; **13**: 515–8.
6 Silva GBL *et al.* Clinical manifestations due to severe plasminogen deficiency: a case report. *J Dent Child* 2006; **73**: 179–82.

Neutrophil defects (see p. 69.56)

A number of genetic disorders affecting neutrophil counts or function can lead to early-onset periodontitis, often with oral ulceration [1,2] (see p. 69.18).

References

1 Defraia E, Marinelli A. Oral manifestations of congenital neutropenia or Kostmann syndrome. *J Clin Pediatr Dent* 2001; **26**: 99–102.

2 Deas DE, Mackey SA, McDonnell, Schuster V. Systemic disease and periodontitis: manifestations of neutrophil dysfunction. *J Periodontol* 2003; **32**: 82–104.

Leukocyte adhesion deficiency

Defects in cell-surface receptors on neutrophils and other leukocytes result in a range of disorders, especially recurrent cutaneous, respiratory and middle-ear infection, as well as periodontal destruction in both dentitions.

Local efforts to preserve the dentition, using debridement together with antimicrobials, have been of little value [1–5].

References

1 Meyle J. Leukocyte adhesion deficiency and prepubertal periodontitis. *Periodontology* 1994; **6**: 26–36.
2 Waldrop TC, Anderson DC, Hallmon WW *et al.* Periodontal manifestations of the heritable Mac-1, LFA-1 deficiency syndrome. *J Periodontol* 1987; **58**: 400–16.
3 Majorana A, Notarangelo LD, Savoldi E, Gastaldi G, Lozada-Nur F. Leukocyte adhesion deficiency in a child with severe oral involvement. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1999; **87**: 691–4.
4 Roberts MW, Atkinson JC. Oral manifestations associated with leukocyte adhesion deficiency: a five-year case study. *Pediatr Dent* 1990; **12**: 107–11.
5 Waldrop TC, Hallman WW, Mealey BL. Observations of root surfaces from patients with early-onset periodontitis and leukocyte adhesion deficiency. *J Clin Periodontol* 1995; **22**: 168–78.

Papillon–Lefèvre syndrome (see Chapter 19)

This is a rare, autosomal recessive condition of palmoplantar hyperkeratosis with periodontal breakdown (periodontosis or periodontoclasia) that manifests from childhood [1–4] and is related to a defect in cathepsin C [5,6] with defective polymorphonuclear leukocyte function [7,8].

The teeth develop and erupt normally in both the deciduous and permanent dentitions but the gingiva become red, swollen and bleed easily with the formation of periodontal pockets, loss of alveolar bone, loosening and loss of the teeth. The teeth are involved roughly in the order they erupt. The deciduous teeth are often lost by the age of 5 years and the permanent teeth are almost invariably lost by the age of 16 years. There are no obvious abnormalities in either the tooth cementum or dentine.

Hyperkeratosis of the palms and particularly the soles appears at about the age of 3–5 years, concurrent with periodontal breakdown of the deciduous dentition. Similar plaques may also be seen on the lips, cheeks and eyelids. The affected skin shows diffuse hyperkeratosis, hypergranulosis and acanthosis. There may also be calcification of the dura and some patients have recurrent pyogenic infections [9,10].

Similar syndromes include Haim–Munk syndrome [11,12], late-onset Papillon–Lefèvre syndrome [13], a condition including arachnodactyly and acro-osteolysis [14], and Unna–Thost syndrome (see below).

Diagnosis is on clinical and radiographic grounds.

Retinoids may be useful in suppressing oral and cutaneous lesions and minimizing the pyogenic infections [15,16] and it is possible to retain the dentition for some years [17]. Intensive dental care is needed.

References

1 Efeoglu J, Porter SR, Mutlu S *et al.* Papillon–Lefèvre syndrome affecting two siblings. *Br J Pediatr Dent* 1990; **6**: 115–20.
2 Haneke E. The Papillon–Lefèvre syndrome: keratosis palmoplantaris with periodontopathy: report of a case and review of cases in the literature. *Hum Genet* 1979; **51**: 1–35.
3 Smith P, Rosenzweig KA. Seven cases of Papillon–Lefèvre syndrome. *Periodontics* 1967; **5**: 42–6.
4 Guildbakke KK, Millina C, Thompson TR. New lesions on the knees with palmoplantar keratoderma. *Cutis* 2007; **79**: 55–63.
5 Zhang Y, Lundgren T, Renvert *et al.* Evidence of a founder effect for four cathepsin C gene mutations in Papillon–Lefevre syndrome patients. *J Med Genet* 2001; **38**: 96–101.
6 Wani AA, Devkar N, Patole MS, Shouche YS. Description of two new cathepsin C gene mutations in patients with Papillon-Lefevre syndrome. *J Periodontol* 2006; **77**: 233–7.
7 Van Dyke TE, Taubman MA, Ebersole JL *et al.* The Papillon–Lefèvre syndrome: neutrophil dysfunction with severe periodontal disease. *Clin Immunol Immunopathol* 1984; **31**: 419–29.
8 Hattab FN, Amin WM. Papillon-Lefevre syndrome with albinism: a review of the literature and report of 2 brothers. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005; **100**: 709–16.
9 Bergman R, Friedman-Birnbaum R. Papillon–Lefèvre syndrome: a study of the long term clinical course of recurrent pyogenic infections and the effects of etretinate treatment. *Br J Dermatol* 1988; **119**: 731–6.
10 Anuradha S, Agarwal SK, Singh NP, Gupta A, Chowdhury V. An unusual presentation of the Papillon-Lefevre syndrome as recurrent liver abscesses. *J Assoc Physicians India* 2002; **50**: 974–6.
11 Hart TC, Hart PS, Michalec MD *et al.* Haim–Munk syndrome and Papillon–Lefevre syndrome are allelic mutations in cathepsin C. *J Med Genet* 2000; **37**: 88–94.
12 Cury VF, Gomez RS, Costa JE, Friedman E, Boson W, De Marco L. A homozygous cathepsin C mutation associated with Haim-Munk syndrome. *Br J Dermatol* 2005; **152**: 353–6.
13 Brown RS, Hays GL, Flaitz CM *et al.* A possible late-onset variation of Papillon–Lefèvre syndrome. *J Periodontol* 1993; **64**: 379–86.
14 Puliyel JM, Sridharanlyer KS. A syndrome of keratosis palmoplantaris congenita, pes planus, onychogryphosis, periodontosis, arachnodactyly and a peculiar acrosteolysis. *Br J Dermatol* 1986; **115**: 243–8.
15 El Darouti MA, Al Raubaie SM, Eiada MA. Papillon–Lefèvre syndrome: successful treatment with oral retinoids in three patients. *Int J Dermatol* 1988; **27**: 63–6.
16 Gelmetti C, Nazzaro V, Cerri D, Fracasso L. Long-term preservation of permanent teeth in a patient with Papillon–Lefèvre syndrome treated with etretinate. *Pediatr Dermatol* 1989; **6**: 222–5.
17 Wiebe CB, Hakkinen L, Putnins EE, Walsh P, Larjava HS. Successful periodontal maintenance of a case with Papillon–Lefevre syndrome: 12-year follow-up and review of the literature. *J Periodontol* 2001; **72**: 824–30.

Unna–Thost syndrome

Synonym
- Hereditary palmoplantar keratoderma

The Unna–Thost variety of hereditary palmoplantar keratoderma may be associated with oral keratosis and/or periodontitis [1–4].

References

1 Ergorov HA. Unna–Thost syndrome in four generations. *Vestn Dermatol Venerol* 1978; **7**: 68–71.
2 Nikolov D, Lazarevska B, Arsovski T. Hereditary palmo-plantar keratoderma Unna–Thost with periodontitis. *God Med Fak Skopje* 1976; **22**: 415–24.
3 Rode M. Soft and hard tissue changes in the oral cavity of patients with Unna–Thost syndrome. *Zobozdrav Vestn* 1986; **41**: 65–8.
4 Loh TH, Yosipovitch G, Tay YK. Palmar-plantar keratoderma of Unna Thost associated with atopic dermatitis: an underrecognized entity? *Pediatr Dermatol* 2003; **20**: 195–8.

Ehlers–Danlos syndrome [1–7]

Early-onset periodontitis is seen in Ehlers–Danlos syndrome, particularly type VIII (see Chapter 45).

References

1 Stewart RE, Hollister DW, Rimoin DL *et al.* A new variant of Ehlers–Danlos syndrome: an autosomal dominant disorder of fragile skin, abnormal scarring and generalized periodontitis. *Birth Defects* 1977; **13**: 85–93.
2 Letourneau Y, Perusse R, Buithieu H. Oral manifestations of Ehlers–Danlos syndrome. *J Can Dent Assoc* 2001; **67**: 330–4.
3 Reichert S, Riemann D, Plaschka B, Machulla HK. Early-onset periodontitis in a patient with Ehlers–Danlos syndrome type III. *Quintessence Int* 1999; **30**: 785–90.
4 Fridrich KL, Fridrich HH, Kempf KK, Moline DO. Dental implications in Ehlers–Danlos syndrome. A case report. *Oral Surg Oral Med Oral Pathol* 1990; **69**: 431–5.
5 Leung AK, Barksy RL, Lewkonia RM. Oral manifestations of Ehlers–Danlos syndrome. *J Am Dent Assoc* 1989; **119**: 696.
6 Abel MD, Carrasco LR. Ehlers-Danlos syndrome: classifications, oral manifestations, and dental considerations. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006; **102**: 582–90.
7 De Coster PJ, Martens LC, De Paepe A. Oral health in prevalent types of Ehlers-Danlos syndromes. *J Oral Pathol Med* 2005; **34**: 298–307.

Down's syndrome [1–5]

Early-onset periodontitis is common in Down's syndrome along with microdontia and hypodontia, and lip fissures may also be seen.

References

1 Saxen L, Aula S. Periodontal bone loss in patients with Down's syndrome. *J Periodontol* 1982; **53**: 158–62.
2 Amano A, Kishima T, Akiyama S *et al.* Relationship of periodontopathic bacteria with early-onset periodontitis in Down's syndrome. *J Periodontol* 2001; **72**: 368–73.
3 Lopez-Perez R, Borges-Yanes SA, Jimenez-Garcia G, Maupome G. Oral hygiene, gingivitis, and periodontitis in persons with Down syndrome. *Spec Care Dentist* 2002; **22**: 214–20.
4 Scully C, Van Bruggen W, Dios PD, Porter SR, Davison M. Down syndrome; lip lesions and *Candida albicans*. *Br J Dermatol* 2002; **147**: 37–40.
5 Zigmond M, Stabholz A, Shapira J, Bachrach G, Chaushu G, Becker A, Yefenof E, Merrick J, Chaushu S. The outcome of a preventive dental care programme on the prevalence of localized aggressive periodontitis in Down's syndrome individuals. *J Intellect Disabil Res* 2006; **50**: 492–500.

Prader–Willi syndrome [1–3]

Early-onset periodontitis has been recorded in Prader–Willi syndrome, presumably as a consequence of the diabetes.

References

1 Greenwood RE, Small ICB. Case report of the Prader–Willi syndrome. *J Clin Periodontol* 1990; **17**: 61–3.
2 Bazopoulou-Kyrkanidou E, Papagiannoulis L. Prader–Willi syndrome: report of a case with special emphasis on oral problems. *J Clin Pediatr Dent* 1992; **17**: 37–40.
3 Salako NO, Ghafouri HM. Oral findings in a child with Prader–Labhart–Willi syndrome. *Quintessence Int* 1995; **26**: 339–41.

Congenital epulis

Synonym
- Granular cell tumour or myoblastoma

Epulis is the term applied to a swelling on the gingiva. Congenital epulis is a rare, benign, pedunculated, firm pink swelling on the maxillary alveolus, seen in an infant [1,2]. It can be a prenatal ultrasonographic diagnosis [3–5]. There is an 8:1 female predominance.

It is probably a reactive mesenchymal lesion and is usually treated by excision. Histology shows large, polygonal cells with a fine granular, eosinophilic cytoplasm.

References

1 Fuhr AH, Krogh PHJ. Congenital epulis of the newborn: centennial review of the literature and case report. *J Oral Surg* 1972; **30**: 30–5.
2 Webb JD, Wescott WB, Corell RW. Firm swelling on the anterior maxillary gingiva in an infant. *J Am Dent Assoc* 1984; **109**: 307–8.
3 Lopez de Lacalle JM, Aguirre I, Irizabal JC, Nogues A. Congenital epulis: prenatal diagnosis by ultrasound. *Pediatr Radiol* 2001; **31**: 453–4.
4 Meizner I, Shalev J, Mashiach R, Vardimon D, Ben-Rafael Z. Prenatal ultrasonographic diagnosis of congenital oral granular cell myoblastoma. *J Ultrasound Med* 2000; **19**: 337–9.
5 Barbuta OI, Aprodu GS, Gavrilescu S, Mihaila D, Iliev G, Olar V, Munteanu V, Savu A. Congenital tumors with oropharyngeal localization in the newborn: problems in team diagnosis and treatment. *Rev Med Chir Soc Med Nat Iasi* 2006; **110**: 883–6.

Epstein's pearls

Synonym
- Gingival cysts of the newborn

Epstein's pearls are superficial, white, keratin-containing cysts seen on the palatal or alveolar mucosa of about 80% of neonates. They are symptomless and inconsequential, usually being shed within a few weeks, and sometimes found with cleft lip and palate [1–3].

References

1 Gilhar A, Winsterstein G, Godfried E. Gingival cysts of the newborn. *Int Dent J* 1988; **27**: 261–2.
2 Hayes PA. Hamartomas, eruption cyst, natal tooth and Epstein pearls in a newborn. *ASDC J Dent Child* 2000; **67**: 365–8.
3 Richard BM, Qiu CX, Ferguson MW. Neonatal palatal cysts and their morphology in cleft lip and palate. *Br J Plast Surg* 2000; **53**: 555–8.

Acquired disorders affecting the periodontium

Chronic gingivitis

This is an extremely common condition. Over 90% of dentate adults exhibit some degree of gingivitis. The accumulation of dental bacterial plaque because of inadequate oral hygiene produces non-specific chronic inflammation. It is painless but may manifest with bleeding from the gingival crevice. The gingival margins are red and slightly swollen [1–3]. Features may be exaggerated in pregnancy and in immune defects.

Dental advice on improved plaque control is needed. If untreated, chronic gingivitis may progress to periodontitis and tooth loss.

References

1 Page RC. Gingivitis. *J Clin Periodontol* 1986; **13**: 345–59.
2 Corbet EF. Periodontal diseases in Asians. *J Int Acad Periodontol* 2006; **8**: 136–44.
3 American Academy of Periodontal Research, Science and Therapy Committee; American Academy Pediatric Dentistry. Treatment of plaque-induced gingivitis, chronic periodontitis, and other clinical conditions. *Pediatr Dent* 2005–2006; **27**: 202–11.



Fig. 69.13 Periodontitis.

Chronic periodontitis

Chronic periodontitis (inflammation of the gingiva and periodontal membrane) may be a sequel of chronic gingivitis usually because of plaque accumulation and calculus (tartar) [1]. Smoking is a risk factor. The gingiva detaches from the tooth neck, the periodontal membrane and alveolar bone are damaged, and an abnormal gap (pocket) develops between the tooth and gum. The tooth may slowly loosen and eventually be lost (Fig. 69.13). Features may be exaggerated in immune defects.

Diagnosis. Chronic periodontitis is typically seen in adults. It is painless but may be associated with bleeding, halitosis and a foul taste. Debris and pus may be expressed from the pockets (pyorrhoea), and there may be increasing tooth mobility.

Treatment. Although periodontal disease has a bacterial component, systemic antibiotics have no place in routine treatment. Management comprises improvement in oral hygiene [2], although in this case plaque accumulates below the gumline, within periodontal pockets. Toothbrushing and mouthwashes have effect only above, or very slightly below, the gum level and are therefore ineffective alone in the treatment of periodontitis. Surgical removal of the pocket wall and removal of diseased tissue may be needed to facilitate future cleansing, or attempts to regenerate lost periodontal tissue (such as guided tissue regeneration) may be indicated. Periodontal attention is therefore required.

References

1 Page RC. Gingivitis. *J Clin Periodontol* 1986; **13**: 345–59.

2 American Academy of Periodontal Research, Science and Therapy Committee; American Academy Pediatric Dentistry. Treatment of plaque-induced gingivitis, chronic periodontitis, and other clinical conditions. *Pediatr Dent* 2005–2006; **27**: 202–11.

Early-onset periodontitis

Periodontal breakdown (periodontitis) is usually a consequence of inflammatory destruction as a result of poor oral hygiene and the subsequent accumulation of dental bacterial plaque [1] and is seen mainly in adults. The host response and periodontal microbiota can both be implicated in a heterogeneous group of causes of early-onset periodontitis [2–12]. If present in children or adolescents, it can be a manifestation of severely neglected oral hygiene, such as seen in some patients with learning disability, or may be a feature of an immunocompromised host.

That host defences are extremely important in maintaining periodontal health is demonstrated well in the periodontal breakdown that may accompany leukaemias, leukocyte defects, diabetes and HIV infection. Periodontal breakdown is also a feature of Down's syndrome, Ehlers–Danlos syndrome type VIII and Papillon–Lefèvre syndrome.

Periodontal breakdown in a child or adolescent who is capable of maintaining good oral hygiene almost invariably suggests an immune or other systemic defect.

References

1 Meyle J, Gonzales JR. Influences of systemic diseases on periodontitis in children and adolescents. *Periodontology* 2001; **26**: 92–112.

2 Mooney J, Hodge PJ, Kinane DF. Humoral immune response in early-onset periodontitis: influence of smoking. *J Periodontal Res* 2001; **36**: 227–32.

3 Seifert R, Wenzel-Seifert K. Defective Gi protein coupling in two formyl peptide receptor mutants associated with localized juvenile periodontitis. *J Biol Chem* 2001; **276**: 42043–9.

4 Shibata K, Warbington ML, Gordon BJ, Kurihara H, Van Dyke TE. Nitric oxide synthase activity in neutrophils from patients with localized aggressive periodontitis. *J Periodontol* 2001; **72**: 1052–8.

5 Haubek D, Ennibi OK, Poulsen K *et al.* Early-onset periodontitis in Morocco is associated with the highly leukotoxic clone of *Actinobacillus actinomycetemcomitans*. *J Dent Res* 2001; **80**: 1580–3.

6 Alpha CX, Guthmiller JM, Cummings HE, Schomberg LL, Noorani SM. Molecular analysis of *Peptostreptococcus micros* isolates from patients with periodontitis. *J Periodontol* 2001; **72**: 877–82.

7 Yoshihara A, Sugita N, Yamamoto K *et al.* Analysis of vitamin D and Fcgamma receptor polymorphisms in Japanese patients with generalized early-onset periodontitis. *J Dent Res* 2001; **80**: 2051–4.

8 Kubota T, Morozumi T, Shimizu K *et al.* Differential gene expression in neutrophils from patients with generalized aggressive periodontitis. *J Periodontal Res* 2001; **36**: 390–7.

9 Endo M, Tai H, Tabeta K *et al.* Analysis of single nucleotide polymorphisms in the 5'-flanking region of tumor necrosis factor-alpha gene in Japanese patients with early-onset periodontitis. *J Periodontol* 2001; **72**: 1554–9.

10 Albandar JM, DeNardin AM, Adesanya MR, Diehl SR, Winn DM. Associations between serum antibody levels to periodontal pathogens and early-onset periodontitis. *J Periodontol* 2001; **72**: 1463–9.

11 Tanner AC, Kent R Jr, Van Dyke T, Sonis ST, Murray LA. Clinical and other risk indicators for early periodontitis in adults. *J Periodontol* 2005; **76**: 573–81.

12 Kamma JJ, Nakou M, Gmur R, Baehni PC. Microbiological profile of early onset/aggressive periodontitis patients. *Oral Microbiol Immunol* 2004; **19**: 314–21.

Diabetes

Uncontrolled diabetes can lead to accelerated periodontitis [1–3].

References

1 Emingil G, Darcan S, Keskinoglu A, Kutukculer N, Atilla G. Localized aggressive periodontitis in a patient with type 1 diabetes mellitus: a case report. *J Periodontol* 2001; **72**: 1265–70.

2 Bakkshandeh S, Murtomaa H, Mofid R, Vehkalahti MM, Suomalainen K. Periodontal treatment needs of diabetic adults. *J Clin Periodontol* 2007; **34**: 53–7.

3 Pucher J, Stewart J. Periodontal disease and diabetes mellitus. *Curr Diab Rep* 2004; **4**: 46–50.



Fig. 69.14 Desquamative gingivitis.

HIV disease/AIDS

HIV disease can be complicated by necrotizing ulcerative gingivitis (see p. 69.77), periodontitis, candidosis, herpetic ulceration, Kaposi's sarcoma, lymphomas and other gingival lesions [1,2].

References

1 Laskaris G, Scully C, eds. *Periodontal Manifestations of Local and Systemic Disease*. Berlin: Springer, 2003.

2 Umadevi M, Adeyemi O, Patel M, Reichert PA, Robinson PG. Periodontal diseases and other bacterial infections. *Adv Dent Res* 2006; **19**: 139–145.

Desquamative gingivitis

In this fairly common condition, the labial gingiva are persistently glazed, red and sometimes sore but the gingival margins may be spared, differentiating desquamative gingivitis from chronic marginal gingivitis (Fig. 69.14).

Desquamative gingivitis typically affects middle-aged or elderly women and is usually a manifestation of mucous membrane pemphigoid or lichen planus [1–6]. Rarely, it may be seen in pemphigus, dermatitis herpetiformis, linear IgA disease, chronic ulcerative stomatitis with epithelial antinuclear antibodies or other dermatoses [4–6]. Allergic gingivitis has similar features.

Desquamative gingivitis tends to be chronic and recalcitrant. The underlying condition should be treated where possible [7]. Improved oral hygiene and topical corticosteroids in a nocturnally worn polythene splint may help. Dapsone or topical ciclosporin or tacrolimus may be beneficial in severe cases [8–10].

References

1 Nisengard RJ, Nieders M. Desquamative lesions of the gingiva. *J Periodontol* 1981; **52**: 500–10.

2 Nisengard RJ, Levine RA. Diagnosis and management of desquamative gingivitis. *Periodontol Insights* 1995; **2**: 4–10.

3 Rees TD. Vesiculo-ulcerative diseases and periodontal practice. *J Periodontol* 1995; **66**: 747–8.

4 Scully C, Laskaris G. Mucocutaneous disorders. In: Scully C, ed. *Oral Pathology and Medicine in Periodontics*. Copenhagen: Munksgaard, 1998: 81–94.

5 Scully C, Porter SR. The clinical spectrum of desquamative gingivitis. *Semin Cutan Med Surg* 1997; **16**: 308–13.

6 Guiglia R, Di Liberto C, Pizzo G, Picono L, Lo Muzi L, Gallo PD, Campisi G, D'Angelo M. A combined treatment regimen for desquamative gingivitis in patients with oral lichen planus. *J Oral Pathol Med* 2007; **36**: 110–6.

7 Solomon LW, Aguirre A, Neiders M, Costales-Spindler A, Jividen GJ Jr, Zwick MG, Kumar V. Chronic ulcerative stomatitis: clinical, histopathologic, and immunopathologic findings. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2003; **96**: 718–26.

8 Sanchez AR, Rogers RS 3rd, Kupp LI, Sheridan PJ. Desquamative gingivitis with IgG/IgA pemphigoid presents a challenging diagnosis and treatment: a case report. *J Periodontol* 2004; **75**: 1714–9.

9 Porter SR, Scully C, Eveson JW. The efficacy of topical cyclosporin in the management of desquamative gingivitis due to lichen planua. *Br J Dermatol* 1993; **129**: 753–5.

10 Corrocher G, Di Lorenzo G, Mansueto P, Martinelli N, Esposito-Pelleteri M, Gelio S, Lombardo G, Pacor ML. Comparison of topical tacrolimus 0.1% in pectin ointment with clobetasol 0.5% ointment in adults with moderate to severe desquamative gingivitis: a 4 week randomized, double-blind clinical trial. *Clin Ther* 2006; **28**: 1296–302.

Allergic gingivostomatitis

Synonym

- Atypical or plasma-cell gingivostomatitis

Diffusely red, swollen gingivae with or without oral ulceration may occasionally follow exposure to various allergens and other substances. Such reactions have followed the use of certain chewing gums, confectionery such as mints, and dentifrices [1–7] and dental materials [8,9], particularly 'tartar control' dentifrices containing cinnamon or cinnamaldehyde [2].

Biopsy is usually not indicated and is fairly non-specific with epithelial atrophy, oedema and a variable cellular infiltrate in the lamina propria which, in the earlier reported cases due to chewing gum, was often predominantly plasmacytic [1,3,5–7]. The lesions resolve on withdrawal of the causal agent and reappear on rechallenge. Patch testing may be of value in diagnosis.

References

1 Kerr DA, McClarchey KD, Regezi JA. Allergic gingivostomatitis (due to gum chewing). *J Periodontol* 1971; **42**: 709–12.

2 Lamey PJ, Lewis MAO, Rees TD *et al.* Sensitivity reaction to the cinnamaldehyde component of toothpaste. *Br Dent J* 1990; **168**: 115–8.

3 Lubow RM, Cooley RL, Hartman KJ *et al.* Plasma cell gingivitis: report of a case. *J Periodontol* 1984; **55**: 234–41.

4 MacLeod FI, Ellis JE. Plasma cell gingivitis related to the use of herbal toothpaste. *Br Dent J* 1989; **166**: 375–6.

5 Owings JR. An atypical gingivostomatitis: a report of four cases. *J Periodontol* 1969; **40**: 538–42.

6 Palmer RM, Eveson JW. Plasma cell gingivitis. *Oral Surg* 1981; **51**: 187–9.

7 Perry HO. Idiopathic gingivostomatitis. *Dermatol Clin* 1987; **5**: 719–22.

8 Izumi AK. Allergic contact gingivostomatitis due to gold. *Arch Dermatol Res* 1982; **272**: 387–91.

9 Martin N, Bell HK, Longman LP, King CM. Orofacial reaction to methacrylates in dental materials: a clinical report. *J Prosthet Dent* 2003; **90**: 225–7.

Idiopathic plasmacytosis (see also Plasma-cell balanitis, Chapter 71)

This term refers to red, velvety gingival lesions associated with a plasmacytic infiltrate. Most cases are restricted to the gingiva (atypical gingivostomatitis, plasmacyte gingivitis, allergic gingivostomatitis) [1,2], while a few have supraglottic laryngeal lesions [3]. Corticosteroids are the main treatment but irradiation may be required [4].

References
1 White JW, Olsen KD, Banks PM. Plasma cell orofacial mucositis. *Arch Dermatol* 1986; **122**: 1321–4.
2 Bharti O, Smith DR. Mucous membrane plasmacytosis: a case report and review of the literature. *Dermatol Online J* 2003; **9**: 15.
3 Timms M, Sloan P. Association of supraglottic and gingival idiopathic plasmacytosis. *Oral Surg* 1991; **71**: 451–3.
4 Fogarty G, Turner H, Corry J. Plasma cell infiltration of the upper aerodigestive tract treated with radiation therapy. *J Laryngol Otol* 2001; **115**: 928–30.

Fibroepithelial polyp

Synonym
- Fibrous lump

Fibrous lumps are common in the mouth and are seen mainly in adults. They appear to be purely reparative in nature. They may attain their full size (which rarely exceeds 2.5 cm diameter) quite rapidly, and then stop growing. Fibrous lumps should not be confused with the true fibroma, a benign neoplasm derived from fibroblasts, which is rare in the mouth (see below).

The variable inflammatory changes account for the different clinical presentations of fibrous lumps from red, shiny, soft lumps to those which are pale, stippled and firm [1]. Commonly, they are round pedunculated swellings arising from the marginal or papillary gingiva (epulides), sometimes adjacent to sites of irritation (e.g. a carious cavity). They are usually painless. They may reach quite a large size, but the prognosis is good.

Fibrous epulides should be removed down to the periosteum, which should be curetted thoroughly.

Fibroma [1]

The true fibroma, a benign neoplasm of fibroblastic origin, is rare in the oral cavity and many lesions in the past called fibromas were probably fibroepithelial polyps.

Histology shows marked proliferation of fibroblasts, with nuclei of uniform shape, size and staining characteristics.

The true fibroma is a continuously enlarging new growth, not necessarily arising at a site of potential trauma. It is a pedunculated growth with a smooth, non-ulcerated, pink surface.

Removal should be total, deep and wide.

Reference
1 Lee KW. The fibrous epulis and related lesions. *Periodontics* 1986; **6**: 277–99.

Pyogenic granuloma (see Chapter 56)

Pyogenic granuloma commonly affects the gingiva, the lip or the tongue [1–3] (Fig. 69.15). Features may be exaggerated in pregnancy.

In these sites, the lesion should be excised completely. It will readily recur if excision is not adequate.

References
1 Vilmann A, Vilmann P, Vilmann H. Pyogenic granuloma: evaluation of oral conditions. *Br J Oral Surg* 1986; **24**: 376–82.
2 Jafarzadeh H, Sanatkhani M, Mohtashum M. Oral pyogenic granuloma: a review. *J Oral Sci* 2006; **48**: 167–75.
3 Epivatianos A, Antoniades D, Zaraboukas T, Zaire E, Poulopoulos A, Kiziridou A. Pyogenic granuloma of the oral cavity: comparative study of its clinicopathological and immunohistochemical features. *Pathol Int* 2005; **55**: 391–7.

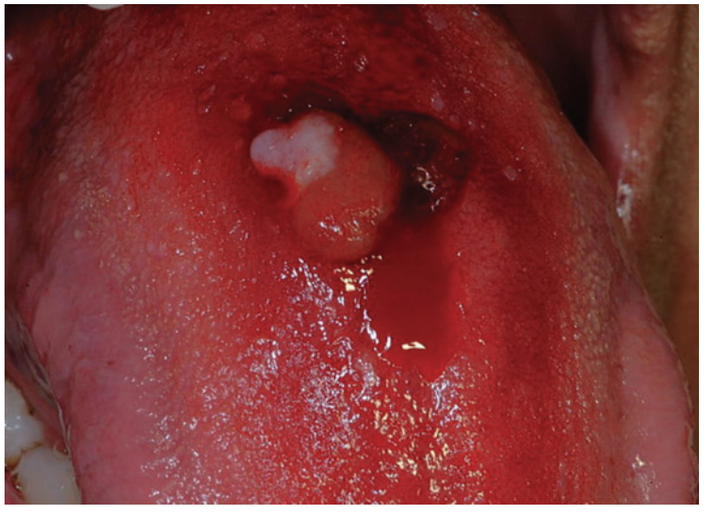


Fig. 69.15 Pyogenic granuloma of the tongue.

Giant cell epulis

Synonym
- Peripheral giant cell granuloma

The giant cell epulis probably arises because chronic irritation triggers a reactionary hyperplasia of mucoperiosteum and excessive production of granulation tissue. Giant cell granulomas are occasionally a feature of hyperparathyroidism.

The giant cell epulis characteristically arises interdentally, adjacent to permanent teeth that have had deciduous predecessors [1,2], that is not the permanent molars. Classically, the most notable feature is the deep-red colour, although older lesions tend to be paler.

This is a benign lesion which is cured by excision.

References
1 Giansanti JS, Waldron CA. Peripheral giant cell granuloma: review of 720 cases. *J Oral Surg* 1969; **27**: 787–91.
2 Chaparro-Avandano AV, Berini-Aytes L, Gay-Escoda C. Peripheral giant cell granuloma. A report of five cases and review of the literature. *Med Oral Patol Oral Cir Bucal* 2005; **10**: 53–7; 48–52.

Pregnancy gingivitis and epulis

There can be an exaggerated inflammatory reaction to dental bacterial plaque in pregnancy, and chronic gingivitis may therefore be aggravated giving rise to ‘pregnancy gingivitis’ [1,2] and, occasionally, a pyogenic granuloma (pregnancy epulis).

Pregnancy gingivitis is characterized by soft, reddish enlargements, usually of the gingival papillae, varying from small, smooth enlargements to more extensive, ragged, granular lumps resembling the surface of a strawberry. Changes of pregnancy gingivitis usually appear about the second month of pregnancy, and reach a peak at the eighth month. Poor oral hygiene predisposes to these changes. A similar appearance may occur with oral contraceptives.

Sometimes there is a localized epulis (pregnancy epulis) that, although unsightly, is usually painless. Occasionally it ulcerates

or interferes with eating. Despite the vascularity, the immaturity of the vessels may lead to superficial ischaemia and ulceration. Larger lesions are prone to trauma, which may contribute to the ulceration.

Oral hygiene should be improved. There is one unconfirmed report of a beneficial effect of folic acid on pregnancy gingivitis [3].

Most lesions tend to resolve on parturition. An epulis requires excision only if it is being traumatized or is grossly unaesthetic [4].

References

1 Amar S, Chung KM. Influence of hormonal variation on the periodontium in women. *Periodontology* 1994; **6**: 79–87.
2 Henry F, Quatrazoos P, Valverde-Lopez JC, Pierard GE. Blood vessel changes during pregnancy: a review. *Am J Clin Dermatol* 2006; **7**: 65–9.
3 Pack ARC, Thomson ME. Effect of topical and systemic folic acid supplementation on gingivitis of pregnancy. *J Clin Periodontol* 1980; **7**: 402–14.
4 Chiodo GT, Rosenstein DI. Dental treatment during pregnancy: a preventive approach. *J Am Dent Assoc* 1985; **110**: 365–8.

Drug-induced gingival swelling

Gingival swelling (sometimes termed 'hyperplasia') is a recognized adverse effect of a few medications, especially phenytoin, calcium-channel blockers and ciclosporin.

Phenytoin

Phenytoin induces gingival swelling presumably by an effect on fibroblast activity. There is no correlation between the extent of overgrowth and the dose of phenytoin, its serum level, or the age and sex of the patient. Rather, the hyperplasia is aggravated by poor oral hygiene.

Phenytoin can produce a variable degree of gingival enlargement, which characteristically affects the interdental papillae first but which may later involve the marginal and even attached gingiva. The palatal and lingual gingivae are usually involved less than the buccal and labial gingivae [1–4].

The enlargement is characteristically firm, pale and tough, with coarse stippling, although these features may take several years to develop, and earlier lesions may be softer and redder (see Fig. 69.11).

The patient's level of plaque control should be improved [5] and a 0.2% aqueous chlorhexidine mouthwash may be helpful. Excision of the enlarged tissue may be indicated but the swelling unfortunately readily recurs, although this is less likely with meticulous oral hygiene, particularly if the phenytoin can be stopped. Folic acid may improve the condition and systemic isotretinoin may be of some value [2].

Calcium-channel blockers

Nifedipine can cause gingival swelling, typically affecting the papillae in a similar fashion to phenytoin [3,6]. Several other calcium-channel blockers have a similar effect [7]. Improved oral hygiene may reduce the hyperplasia [8]. Excision of the enlarged tissue may be followed by recurrence, and patients should be warned accordingly. If possible the medication should be changed.

Ciclosporin

Ciclosporin also causes gingival hyperplasia, initially of papillae [3,9]. Only about one-third of patients are affected, more commonly children, and this change may be lessened by meticulous removal of plaque before the drug is introduced.

Amphetamines

Amphetamines may cause gingival swelling [10].

References

1 Hassell TM. *Epilepsy and the Oral Manifestations of Phenytoin Therapy*. In: Myers HM, ed. *Monographs in Oral Science*. Basel: Karger, 1981: 9–12.
2 Norris JF, Cunliffe WJ. Phenytoin-induced gum hypertrophy improved by isotretinoin. *Int J Dermatol* 1987; **26**: 602–3.
3 Slavin J, Taylor J. Cyclosporin, nifedipine and gingival hyperplasia. *Lancet* 1987; **ii**: 739.
4 Stinnett E, Rodu B, Grizzle WE. New developments in understanding phenytoin-induced gingival hyperplasia. *J Am Dent Assoc* 1987; **114**: 814–6.
5 Modeer T, Dahllof G. Development of phenytoin-induced gingival overgrowth in non-institutionalised epileptic children subjected to different plaque control programs. *Acta Odontol Scand* 1987; **45**: 81–5.
6 Shaftic AA, Widdup LL, Abate MA *et al*. Nifedipine-induced gingival hyperplasia. *Drug Intell Clin Pharm* 1986; **20**: 602–5.
7 Steele RM, Schuna AA, Schreiber RT. Calcium antagonist-induced gingival hyperplasia. *Ann Intern Med* 1994; **120**: 663–4.
8 Hancock RH, Swan RH. Nifedipine-induced gingival overgrowth: report of a case treated by controlling plaque. *J Clin Periodontol* 1992; **19**: 12–4.
9 Daley TD, Wysocki GP, Day C. Clinical and pharmacological correlations in cyclosporin-induced gingival hyperplasia. *Oral Surg* 1986; **62**: 417–21.
10 Hasan AA, Ciancio S. Relationship between amphetamine ingestion and gingival enlargement. *Pediatr Dent* 2004; **26**: 396–400.

Scurvy (see Chapter 59)

Scurvy (vitamin C deficiency) causes gingival swelling, bleeding and oral purpura, and although now rare in resource-rich countries, may still be seen [1].

Reference

1 Chaudhry SI, Newell EL, Lewis RR, Black MM. Scurvy; a forgotten disease. *Clin Exp Dermatol* 2005; **30**: 735–6.

Disorders affecting the oral mucosa or lips

Swellings

Mucosal swelling may be seen after trauma and in angio-oedema, Crohn's disease, orofacial granulomatosis, sarcoidosis, Wegener's granulomatosis, amyloidosis and other disorders. Localized swellings may be of local aetiology or can be manifestations of neoplasia or systemic disease.

Pigmentation

Mucosal pigmentation is usually seen in dark-skinned races (but may be seen even in white people) (see Fig. 69.12). Other common causes include amalgam tattoo and melanotic macules.

Addison's disease, Kaposi's sarcoma, melanoma, Laugier–Hunziker syndrome, pigmentary incontinence and other causes must be excluded. Peutz–Jeghers disease is the association of circumoral and sometimes intraoral melanosis with small-intestinal polyposis (see Chapter 62). Oral petechiae are usually caused by trauma or suction. More widespread purpura is most frequently

a manifestation of a bleeding tendency caused by thrombocytopenia and may also be seen in infectious mononucleosis, rubella, HIV infection, leukaemia or scurvy. Petechiae may also occur in amyloidosis.

Redness

Red lesions may be inflammatory, or represent erythroplasia, haemangiomas or neoplasms such as carcinoma, Wegener's granulomatosis or Kaposi's sarcoma [1,2].

Candidosis is a common cause of red lesions, which may be painful. Widespread erythema, particularly if associated with pain, is usually caused by primary herpes simplex stomatitis or a mucocutaneous disorder such as lichen planus or mucous membrane pemphigoid, rarely by pemphigus or other dermatoses and occasionally by allergic responses.

Localized red areas may represent erythema migrans, erythroplasia, carcinoma, candidosis, lichen planus, lupus erythematosus or Kaposi's sarcoma or epithelioid angiomatosis. Geographical tongue (erythema migrans) is a benign condition affecting <5% of the population and is usually asymptomatic. Kaposi's sarcoma may present as a red, purple, brown or bluish macule or nodule, as may epithelioid angiomatosis. Hereditary mucoepithelial dysplasia is a rare cause of oral erythema.

Telangiectasia may be a manifestation of hereditary haemorrhagic telangiectasia, primary biliary cirrhosis or systemic sclerosis, or may follow radiotherapy. Haemangiomas are usually isolated but may occasionally extend deeply and rarely involve the ipsilateral meninges, producing a facial angioma and epilepsy, sometimes with learning disability (Sturge–Weber syndrome). Intraoral haemangiomas may be seen in Maffucci's syndrome.

Lingual depapillation in deficiencies of iron, folate or vitamin B_{12} may produce the red tongue termed 'glossitis'. Geographical tongue may also produce red patches.

Mucositis can readily be induced by irradiation or chemotherapy.

Ulcers

Oral ulcers are often caused by trauma or recurrent aphthae (see p. 69.44). Malignant neoplasms may present as ulcers. Various infections or systemic disorders, particularly those of blood, gastrointestinal tract or skin, also produce mouth ulcers, as may drugs and irradiation (see Table 69.10).

Blisters

Blisters may be seen as a result of burns but the most important vesiculobullous disorders affecting the oral mucosa are pemphigoid (including cicatricial pemphigoid) and pemphigus (see Table 69.10). The bullae of mucous membrane pemphigoid may or may not be blood-filled and, in the former case, a bleeding tendency must be excluded. Blood-filled blisters may also be caused by localized oral purpura (angina bullosa haemorrhagica) or amyloidosis. The bullae of pemphigus are rarely seen as they break down rapidly to produce ulcers. Epidermolysis bullosa and erythema multiforme may present with oral bullae or vesicles, although ulcers are more common. Vesicles may be seen in viral infections, especially in herpes simplex stomatitis, chickenpox, herpangina and hand, foot and mouth disease.

Mucoceles, caused by extravasation of mucus from minor salivary glands, produce isolated blisters, typically in the lower labial mucosa.

White patches (see Table 69.9)

Thrush (acute candidosis) is a 'disease of the diseased' and produces oral white patches.

HIV infection causes hairy leukoplakia, a white lesion on the tongue (see p. 69.93).

Leukoplakia is often associated with friction or smoking, occasionally with syphilis, candidosis or chronic renal failure, but most cases are idiopathic. Lichen planus and lupus erythematosus may present as white lesions. Rarely, lichenoid lesions are associated with various drugs, liver disease or GVHD. Carcinoma may present as a white lesion.

Inherited causes of white patches, such as white sponge naevus and dyskeratosis congenita, are rare [1–5].

References

1 Scully C, Porter SR. Diseases of the oral mucosa. *Med Int* 1990; **76**: 3154–62.
2 Scully C, Porter SR. Oral medicine 2. Disorders affecting the oral mucosa. *Postgrad Dent* 1992; **2**: 109–13.
3 Scully C. *ABC of Oral Health*. London: BMJ Books, 2000.
4 Scully C. *Handbook of Oral Disease: Diagnosis and Management*. London: Martin Dunitz, 1999.
5 Scully C, Flint S, Porter SR, Moos K. *Oral and Maxillofacial Diseases*. London: Martin Dunitz, 2004.

Genetic disorders affecting the oral mucosa or lips

This section discusses the main congenital causes of white or whitish lesions, pigmented lesions, red lesions, vesiculoerosive lesions, lumps and swellings, and some orocutaneous disorders.

White or whitish lesions

Sebaceous glands

Fordyce spots

Synonym
- Fordyce's granules

Fordyce spots are yellowish small grains seen beneath the buccal or labial mucosa. Fordyce spots are sebaceous glands containing neutral lipids similar to those found in skin sebaceous glands [1] but are not associated with hair follicles.

Fordyce spots are extremely common: probably 80% of the population have them. They are usually seen in the buccal mucosa, particularly inside the commissures (Fig. 69.16), and sometimes in the retromolar regions and upper lip [1–5]. Fordyce spots are often not noticeable in children until after puberty (although they are present histologically), and they seem to be more obvious in males, patients with greasy skin and the elderly, and they may be increased in some rheumatic disorders [6].

Fordyce spots are totally benign, although the occasional patient or physician becomes concerned about them or misdiagnoses them as thrush or lichen planus. Occasionally they may be mistaken for leukoplakia [7].



Fig. 69.16 Fordyce spots: sebaceous glands in the buccal mucosa.

No treatment is indicated, other than reassurance. The spots may become less prominent if isotretinoin is given [8]. CO_2 laser and 5-aminolaevulinic acid-photodynamic therapy have been reported as possible effective therapies for Fordyce spots [9,10].

References

1 Nordstrom KM, McGinley KJ, Lessin SR *et al.* Neutral lipid composition of Fordyce's granules. *Br J Dermatol* 1989; **121**: 669–70.
2 Batsakis JG, el-Naggar AK. Sebaceous lesions of salivary glands and oral cavity. *Ann Otol Rhinol Laryngol* 1990; **99**: 416–8.
3 Dreher A, Grevers G. Fordyce spots. A little regarded finding in the area of lip pigmentation and mouth mucosa. *Laryngorhinootologie* 1995; **74**: 390–2.
4 Sewerein I. The sebaceous glands in the vermilion border of the lips and the oral mucosa of man. *Acta Odontol Scand* 1975; **33** (Suppl. 68): 13–226.
5 Daley TD. Pathology of intraoral sebaceous glands. *J Oral Pathol Med* 1993; **22**: 241.
6 Vilpoula AH, Vli-Kerttula UI, Terho PE *et al.* Sebaceous glands in the buccal mucosa in patients with rheumatic disorders. *Scand J Rheumatol* 1983; **12**: 337–42.
7 Sengupta P, Haldar B. Fordyce disease resembling leukoplakia. Report of a case. *Indian J Dermatol* 1982; **27**: 149–52.
8 Monk BE. Fordyce spots responding to isotretinoin therapy. *Br J Dermatol* 1994; **131**: 335.
9 Ocampo-Candiani J, Villarreal-Rodriguez A, Quinones-Fernandez AG, Herz-Ruelas ME, Ruiz-Esparza J. Treatment of Fordyce spots with CO_2 laser. *Dermatol Surg* 2003; **29**: 869–71.
10 Kim YJ, Kang HY, Lee ES, Kim YC. Treatment of Fordyce spots with 5-aminolaevulinic acid-photodynamic therapy. *Br J Dermatol* 2007; **156**: 399–400.

Sebaceous adenoma

Sebaceous adenomas are exceedingly rare in the mouth, except in association with salivary glands but have been described in the buccal mucosa [1–6].

References

1 Daley TD. Pathology of intraoral sebaceous glands. *J Oral Pathol Med* 1993; **22**: 241.
2 Batsakis JG, el-Naggar AK. Sebaceous lesions of salivary glands and oral cavity. *Ann Otol Rhinol Laryngol* 1990; **99**: 416–8.
3 Miller AS, McCrea MW. Sebaceous gland adenoma of the buccal mucosa. *J Oral Surg* 1968; **26**: 593–5.
4 Orlian AI, Salman L, Reddi T, Yamane GM, Chaudhry AP. Sebaceous adenoma of the oral mucosa. *J Oral Med* 1987; **42**: 38–9.
5 Iezzi G, Rubini C, Fioroni M, Piattelli A. Sebaceous adenoma of the cheek. *Oral Oncol* 2002; **38**: 111–3.
6 Welch KC, Papadimitriou JC, Morales R, Wolf JS. Sebaceous adenoma of the parotid gland in a 2-year-old male. *Otolaryngol Head Neck Surg* 2007; **136**: 672–3.

Nevus sebaceus of Jadassohn

Synonym
- Linear naevus syndrome

Oral manifestations may rarely occur as fibroepitheliomatous nodules in patients with a sebaceous naevus of the skin but are extremely rarely seen in isolation [1–3]. Patients have a 10 to 20% risk of development of cutaneous or adnexal neoplasia [4].

References

1 Kelley JE, Hibbard E, Giansanti J. Epidermal nevus syndrome: report of a case with unusual oral manifestations. *Oral Surg* 1972; **34**: 774–80.
2 Morency R, Labelle H. Nevus sebaceus of Jadassohn: a rare oral presentation. *Oral Surg* 1987; **64**: 460–2.
3 Reichart PA, Lubach D, Becker J. Gingival manifestation in linear nevus sebaceus syndrome. *Int J Oral Surg* 1983; **12**: 437–43.
4 Terenzi V, Indrizzi E, Buonaccorsi S, Leonardi A, Pellacchia V, Fini G. Nevus sebaceus of Jadassohn. *J Craniofac Surg* 2006; **17**: 1234–9.

Epithelium

Leukoedema

Leukoedema is not a mucosal disease but simply the name given to the faint whitish lines seen in some normal buccal mucosae, often prominent in black people. The whitish lines disappear if the mucosa is stretched—a diagnostic test [1–4]. Confusion with lichen planus should thereby be avoided.

References

1 Axell T, Henricsson V. Leukoedema: an epidemiologic study with special reference to the influence of tobacco habits. *Community Dent Oral Epidemiol* 1981; **9**: 142–6.
2 Duncan SC, Su WPD. Leukoedema of the oral mucosa (possibly an acquired white sponge naevus). *Arch Dermatol* 1980; **116**: 906–8.
3 Van Wyk CW, Ambrosio SC. Leukoedema: ultrastructural and histochemical observations. *J Oral Pathol* 1983; **12**: 29–35.
4 Canaan TJ, Meehan SC. Variations of structure and appearance of the oral mucosa. *Dent Clin North Am* 2005; **49**: 1–14.

Clouston syndrome

Palmoplantar hyperkeratosis, hair defects, nail dysplasia and oral white lesions characterize this autosomal dominant form of hidrotic ectodermal dysplasia. There may be diffuse white lesions in the buccal mucosa, palate, tongue and elsewhere but reports of malignancy are rare. See also Chapter 15.

White-sponge naevus

Synonyms
- Cannon's disease
- Pachydermia oralis
- White folded gingivostomatosis

Aetiology. A rare, familial disorder usually first seen in childhood and inherited as an autosomal dominant trait [1,2]; there appear

to be defects in keratins 4 and 13 with abnormal tonofilament aggregation [3–6].

Pathology. There is hyperplastic acanthotic epithelium in which gross oedema causes a basket-weave appearance. The superficial epithelium has a 'washed-out' appearance as it stains only very lightly.

Clinical features. The oral mucosa is almost invariably involved in white-sponge naevus. Painless, shaggy or folded white lesions typically affect the buccal mucosa bilaterally but may also involve other areas, although rarely the gingival margins. Similar lesions may also affect the upper respiratory tract, genitalia and anus [1,2].

Diagnosis. The family history and clinical examination are usually adequate to differentiate this from other more common causes of white lesions such as cheek biting, burns, lichen planus and candidosis.

Treatment. This is a benign condition with an excellent prognosis. Reassurance is all that is required, although some have suggested that tetracyclines clear the lesions [7,8].

References

1 Jorgenson RJ, Levin LS. White sponge naevus. *Arch Dermatol* 1981; **117**: 73–6.
2 Hernandez-Martin A, Fernandez-Lopez E, de Unamuno P, Armijo M. Diffuse whitening of the oral mucosa in a child. *Pediatr Dermatol* 1997; **14**: 316–20.
3 Terrinoni A, Rugg EL, Lane EB *et al.* A novel mutation in the keratin 13 gene causing oral white sponge nevus. *J Dent Res* 2001; **80**: 919–23.
4 Terrinoni A, Candi E, Oddi S *et al.* A glutamine insertion in the 1A alpha helical domain of the keratin 4 gene in a familial case of white sponge nevus. *J Invest Dermatol* 2000; **114**: 388–91.
5 Richard G, De Laurenzi V, Didona B, Bale SJ, Compton JG. Keratin 13 point mutation underlies the hereditary mucosal epithelial disorder white sponge nevus. *Nat Genet* 1995; **11**: 453–5.
6 Rugg EL, McLean WH, Allison WE *et al.* A mutation in the mucosal keratin K4 is associated with oral white sponge nevus. *Nat Genet* 1995; **11**: 450–2.
7 McDonagh AJG, Gawkrodger DJ, Walker AE. White sponge naevus successfully treated with tetracycline. *Clin Exp Dermatol* 1990; **15**: 152–3.
8 Lim J, Keting S. Oral tetracycline rinse improves symptoms of white sponge naevus. *J Am Acad Dermatol* 1992; **26**: 1003–5.

Dyskeratosis congenita (see Chapter 15)

Synonym
- Zinsser–Engman–Cole syndrome

Dyskeratosis congenita usually presents with oral lesions between the ages of 5 and 10 years, when the tongue and sometimes the buccal mucosa and palate develop diffuse white lesions with a malignant potential [1,2]. The lesions resemble leukoplakia or lichen planus and show non-specific hyperkeratosis, a prominent granular cell layer and mild acanthosis [1–5].

Other manifestations include lesions of other mucosae, skin and appendages, and bone marrow dysfunction [6,7]. Other rare oral features include taurodont or hypocalcified teeth and mucosal hyperpigmentation.

References

1 Cannell H. Dyskeratosis congenita. *Br J Oral Surg* 1971; **9**: 8–10.
2 Moretti S, Spallanzani A, Chiarugi A, Muscarella G, Battini ML. Oral carcinoma in a young man: a case of dyskeratosis congenita. *J Eur Acad Dermatol Venereol* 2000; **14**: 123–5.
3 Loh HS, Koh ML, Giam YC. Dyskeratosis congenita in two male cousins. *Br J Oral Surg* 1987; **25**: 492–9.
4 Ogden GR, Connor E, Chisholm D. Dyskeratosis congenita: report of a case and review of the literature. *Oral Surg* 1988; **65**: 586–91.
5 Brown CJ. Dyskeratosis congenita: report of a case. *Int J Paediatr Dent* 2000; **10**: 328–34.
6 Handley TP, Ogden GR. Dyskeratosis congenita: oral hyperkeratosis in association with lichenoid reaction. *J Oral Pathol Med* 2006; **35**: 508–12.
7 Vulliamy T, Vokal I. Dyskeratosis congenita. *Semin Hematol* 2006; **43**: 157–66.

Pachyonychia congenita (see Chapter 65)

Synonym
- Jadassohn–Lewandowsky syndrome

Pachyonychia congenita is a benign disorder associated with mutations in keratin 16 [1–4]. About 60% of patients have oral keratosis, 16% have natal or neonatal teeth, and 10% have angular stomatitis. Some patients also develop chronic intraoral candidosis [5–7].

The keratosis requires no treatment. Dental advice should be sought regarding natal or neonatal teeth.

References

1 Swensson O. Pachyonychia congenita. Keratin gene mutations with pleiotropic effect. *Hautarzt* 1999; **50**: 483–90.
2 Smith FJ, Fisher MP, Healy E *et al.* Novel keratin 16 mutations and protein expression studies in pachyonychia congenita type 1 and focal palmoplantar keratoderma. *Exp Dermatol* 2000; **9**: 170–7.
3 Smith FJ, Liao H, Cassidy AJ, Stewart A, Hamill KJ, Wood P, Joval I, van Steensel MA, Bjorck E, Callif-Daley F, Pals G, Collins P, Leachman SA, Munro CS, McLean WH. The genetic basis of pachyonychia congenita. *J Investig Dermatol Symp Proc* 2005; **10**: 21–30.
4 Feinstein A, Friedman J, Schewach-Millet M. Pachyonychia congenita. *J Am Acad Dermatol* 1988; **19**: 705–11.
5 Vucicevic-Boras V, Kotrulja L, Cekic-Arambasin A, Pirkic A, Vucic M. Pachyonychia congenita. Case report. *Minerva Stomatol* 2005; **54**: 691–4.
6 Lim TW, Paik JH, Kim NI. A case of pachyonychia congenita with oral leukoplakia and steatocystoma multiplex. *J Dermatol* 1999; **26**: 677–81.
7 Wimmershoff MB, Stolz W, Schiffner R, Landthaler M. Type I pachyonychia congenita (Jadassohn–Lewandowsky). *Klin Pediatr* 1999; **211**: 179–83.

Tylosis [1–5] (see Chapter 34)

Tylosis is an autosomal dominant syndrome of palmoplantar hyperkeratosis that may predispose to oesophageal carcinoma but although oral white lesions have also been described, there is little evidence that these are premalignant.

References

1 O'Mahoney MY, Ellis JP, Hellier M. Familial tylosis and carcinoma of the oesophagus. *J R Soc Med* 1984; **77**: 514–7.
2 Tyldesley WR, Osborne-Hughes R. Tylosis, leukoplakia and oesophageal carcinoma. *BMJ* 1973; **4**: 427.
3 Tyldesley WR. Oral leukoplakia associated with tylosis and esophageal carcinoma. *J Oral Pathol* 1974; **3**: 62–70.
4 Ellis A, Field JK, Field EA *et al.* Tylosis associated with carcinoma of the oesophagus and oral leukoplakia in a large Liverpool family: a review of six generations. *Oral Oncol* 1994; **30B**: 102–12.

5 Shahabi M, Noori Daloii MR, Langan JE, Rowbottom L, Jahanzad E, Khoshbin E, Taghikhani M, Field JK, Risk JM. An investigation of the tylosis with oesophageal cancer (TOC) locus in Iranian patients with oesophageal squamous cell carcinoma. *Int J Oncol* 2004; **25**: 389–95.

Focal palmoplantar and oral hyperkeratosis syndrome

Synonym
- Keratosis palmaris et plantaris

Focal hyperkeratosis at weight-bearing areas of the palms and soles, with hyperkeratosis of the attached gingiva and occasionally other sites, is an autosomal dominant trait [1–3].

References

1 Fred HL, Gieser RG, Berry WR, Eiband JM. Keratosis palmaris et plantaris. *Arch Intern Med* 1964; **113**: 866–87.
2 Laskaris G, Vareltzidis H, Augernou G. Focal palmoplantar and oral mucosa hyperkeratosis syndrome. *Oral Surg* 1980; **50**: 250.
3 Bethke G, Kolde G, Bethke G, Reichart PA. Focal palmoplantar and oral mucosa hyperkeratosis syndrome. *Mund Kiefer Gesichtschir* 2001; **5**: 202–5.

Olmsted's syndrome [1–6] (see Chapter 19)

Synonym
- Congenital palmoplantar and periorificial keratoderma with corneal epithelial dysplasia

Perioral keratoderma may be seen associated with palmoplantar keratoderma and corneal epithelial dysplasia [4]. Reported associations include haemangioma and malignant melanoma [5,6]. Retinoids may help the keratoderma [6].

References

1 Judge MR, Misch K, Wright P, Harper JI. Palmoplantar and periorificial keratoderma with corneal epithelial dysplasia: a new syndrome. *Br J Dermatol* 1991; **125**: 186–8.
2 Poulin Y, Perry HO, Muller SA. Olmsted syndrome: congenital palmoplantar and periorificial keratoderma. *J Am Acad Dermatol* 1984; **10**: 600–10.
3 Fonseca E, Pena C, Del Pozo J *et al.* Olmsted syndrome. *J Cutan Pathol* 2001; **28**: 271–5.
4 Batra P, Shah N. Olmsted syndrome—a rare syndrome with oral manifestations. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2004; **97**: 599–602.
5 Al-Mutairi N, Sharma AK, Nour-Eldin O, Al-Adawy E. Olmsted syndrome: report of a new case with unusual features. *Clin Exp Dermatol* 2005; **30**: 640–2.
6 Dessureault J, Poulin Y, Bourcier M, Gagne E. Olmsted syndrome-palmoplantar and periorificial keratodermas: association with malignant melanoma. *J Cutan Med Surg* 2003; **7**: 236–42.

Hereditary benign intraepithelial dyskeratosis [1–4]

Synonym
- Witkop–von Sallmann syndrome

Aetiology. Hereditary benign intraepithelial dyskeratosis is a rare, benign, autosomal dominant condition associated with chromosome 4 anomalies, seen mainly in some groups of mixed ethnic origin, predominantly in North Carolina, USA.

Pathology. There is pronounced epithelial acanthosis, vacuolization in the stratum spinosum and eosinophilic cells apparently engulfed by normal squamous cells ('tobacco cells').

Clinical features. Oral milky white, smooth, somewhat translucent plaques appear in childhood and become more obvious by adolescence. These lesions affect predominantly the buccal mucosae, lips and ventrum of the tongue.

Ocular lesions include conjunctivitis with gelatinous conjunctival plaques, which become evident in infancy. There may be photophobia and eventual corneal involvement.

Oral biopsy is usually indicated for diagnosis.

Treatment. No treatment is required.

References

1 Witkop CJ, Shankle CM, Graham JB. Hereditary benign intraepithelial dyskeratosis. II. Oral manifestations and hereditary transmission. *Arch Pathol* 1960; **70**: 696–711.
2 Haisley-Royster CA, Allingham RR, Klintworth GK, Prose NS. Hereditary benign intraepithelial dyskeratosis: report of two cases with prominent oral lesions. *J Am Acad Dermatol* 2001; **45**: 634–6.
3 Allingham RR, Seo B, Rampersaud E *et al.* A duplication in chromosome 4q35 is associated with hereditary benign intraepithelial dyskeratosis. *Am J Hum Genet* 2001; **68**: 491–4.
4 Jham BC, Mesquita RA, Aguiar MC, Carmo MA. Hereditary benign intraepithelial dyskeratosis: a new case? *J Oral Pathol Med* 2007; **36**: 55–7.

Darier's disease (see Chapter 39)

Oral lesions are seen in up to 50% of patients with skin lesions of Darier's disease. The oral changes are most marked in patients with the most severe skin changes and are typically flattish, coalescing, red plaques that eventually turn white and affect the keratinized mucosa of the dorsum of the tongue, palate and gingiva (Fig. 69.17) and then may resemble nicotinic stomatitis clinically [1–7].

Salivary duct anomalies, including dilatations with periodic strictures and indentations, may affect the main ducts [8,9].

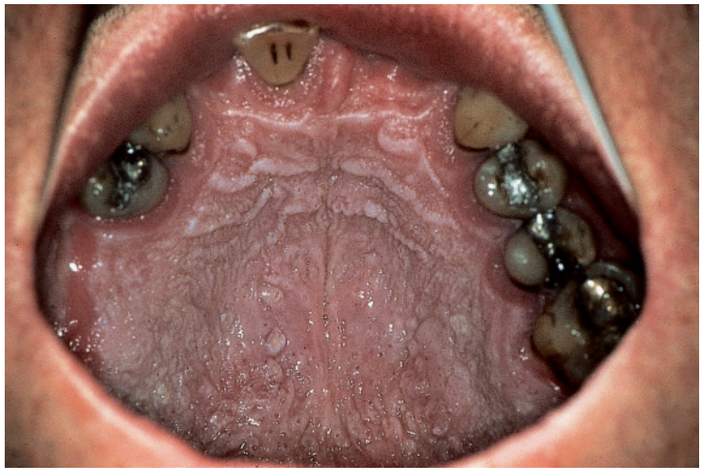


Fig. 69.17 Darier's disease: oral white lesions resemble those of nicotinic stomatitis.

References

1 Ferris T, Lamey PJ, Rennie JS. Darier's disease: oral features and genetic aspects. *Br Dent J* 1990; **168**: 71–3.
2 Macleod RI, Munro CS. The incidence and distribution of the oral lesions in patients with Darier's disease. *Br Dent J* 1991; **171**: 133–6.
3 Spouge JD, Trott JR, Chesko G. Darier–White's disease: a cause of white lesions of the oral mucosa. Report of four cases. *Oral Surg* 1966; **21**: 441–57.
4 Haught JM, Ashley JM. A 34-year-old man with Darier-White disease: a case report and review of the literature. *W V Med J* 2005; **101**: 214–6.
5 Cardoso CL, Freitas P, Taveira LA, Consalaro A. Darier disease: case report with oral manifestations. *Med Oral Patol Oral Cir Bucal* 2006; **11**: E404–6.
6 Frezzini C, Cedro M, Leao JC, Porter SR. Darier disease affecting the gingival and oral mucosal surfaces. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006; **102**: 29–33.
7 Kim C, Fangman W. Keratosis follicularis (Darier–White disease), with an unusual palmoplantar keratoderma. *Dermatol Online J* 2007; **13**: 17.
8 Tegner E, Jonsson N. Darier's disease with involvement of both submandibular glands. *Acta Derm Venereol (Stockh)* 1990; **70**: 451–2.
9 Adams AM, Macleod RI, Munro CS. Symptomatic and asymptomatic salivary duct abnormalities in Darier's disease: a sialographic study. *Dentomaxillofac Radiol* 1994; **23**: 25–8.

Warty dyskeratoma [1–4] (see Chapter 19)

Synonym
- Focal acantholytic dyskeratosis

Warty dyskeratoma, oral warty dyskeratoma or focal acantholytic dyskeratosis is rare in the oral cavity but typically presents as a nodule or papule on the gingiva, palate or alveolar ridge. The histology is similar to that of Darier's disease and transient acantholytic dermatosis, with suprabasal epithelial splits and corps ronds.

References

1 Laskaris G, Sklavounou A. Warty dyskeratoma of the oral mucosa. *Br J Oral Surg* 1985; **23**: 371–5.
2 Leider AS, Eversole LR. Focal acantholytic dyskeratosis of the oral mucosa. *Oral Surg* 1984; **58**: 64–70.
3 Chau MN, Radden BG. Oral warty dyskeratoma. *J Oral Pathol* 1984; **13**: 546–56.
4 Neville BW, Coleman PJ, Richardson MS. Verruciform xanthoma associated with an intraoral warty dyskeratoma. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1996; **81**: 3–4.

Keratitis, ichthyosis and deafness syndrome (see Chapter 19)

Synonym
- KID syndrome

Dental dysplasia, persistent oral ulceration, chronic muco-cutaneous candidosis and occasional carcinoma may be seen in the KID syndrome of keratitis, ichthyosiform dermatosis and deafness [1–3].

References

1 Baden HP, Alper JC. Ichthyosiform dermatosis, keratitis and deafness. *Arch Dermatol* 1977; **113**: 1701–4.
2 Cremers CWRJ, Philipsen VMJG, Mali JWH. Deafness, ichthyosiform erythroderma, cornea involvement, photophobia and dental dysplasia. *J Laryngol Otol* 1977; **91**: 585–7.
3 Lenane P, Cammisuli S, Chitayat D, Krafchik B. What syndrome is this? KID syndrome (keratitis, ichthyosis, deafness). *Pediatr Dermatol* 2006; **23**: 81–3.

Chronic mucocutaneous candidosis (see Chapter 36)

Chronic mucocutaneous candidosis includes a range of congenital disorders characterized by chronic candidosis involving mouth, nails and other sites. Persistent, adherent white lesions are seen in the mouth, often with angular stomatitis [1–4]; in candidosis–endocrinopathy syndrome, there may also be enamel hypoplasia [5,6] and, rarely, oral carcinoma [7,8].

References

1 Scully C, El-Kabir M, Samaranayake LP. *Candida* and oral candidiasis. *Crit Rev Oral Biol Med* 1994; **5**: 124–58.
2 Challacombe SJ. Immunologic aspects of oral candidiasis. *Oral Surg Oral Med Oral Pathol* 1994; **78**: 202–10.
3 Fotos PG, Ray TL. Oral and perioral candidiasis. *Semin Dermatol* 1994; **13**: 118–24.
4 Nielson H, Dangaard K, Schiodt M. Chronic mucocutaneous candidiasis: a review. *Tandlaegkbladet* 1985; **89**: 667–73.
5 Porter SR, Scully C. Candidiasis endocrinopathy syndrome. *Oral Surg* 1986; **61**: 573–8.
6 Porter SR, Eveson JW, Scully C. Enamel hypoplasia secondary to candidiasis endocrinopathy syndrome. *Pediatr Dent* 1995; **17**: 216–9.
7 Firth NA, O'Grady JF, Reade PC. Oral squamous cell carcinoma in a young person with candidiasis endocrinopathy syndrome: a case report. *Int J Oral Maxillofac Surg* 1997; **26**: 42–4.
8 Perheentupa J. Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. *J Clin Endocrinol Metab* 2006; **91**: 2843–50.

Pigmented lesions (Table 69.11)

Most oral hyperpigmentation is racial in origin (see Fig. 69.12). Seen mainly in blacks and Asians it can also be noted in patients of Mediterranean descent, sometimes even in some fairly light-skinned people. It is most obvious in the anterior labial gingivae and palatal mucosa and pigmentation is usually symmetrically distributed. Patches may be seen elsewhere. Pigmentation may be

Table 69.11 Causes of mucosal pigmentation.

Localized
Amalgam tattoo
Ephelis (freckle)
Naevus
Malignant melanoma
Kaposi's sarcoma
Peutz–Jegher syndrome
Laugier–Hunziker syndrome
Melanotic macules
Complex of myxomas, spotty pigmentation and endocrine overactivity
Generalized
Racial
Localized irritation, e.g. smoking
Drugs, e.g. phenothiazines, antimalarials, minocycline, contraceptives, mephenytoin
Addison's disease
Nelson's syndrome
Ectopic adrenocorticotrophic hormone (e.g. bronchogenic carcinoma)
Heavy metals
Albright's syndrome
Other rare causes, e.g. haemochromatosis, generalized neurofibromatosis, incontinentia pigmenti
Malignant acanthosis nigricans

first noted by the patient in adult life and then incorrectly assumed to be acquired rather than congenital in origin.

Melanotic macule

The melanotic macule is an acquired, small, flat, brown to brown-black, asymptomatic, benign lesion, unchanging in character [1–4]. Oral melanotic macule is similar to the ephelis and lentigo.

Melanotic macules may be seen in up to 3% of normal persons, at any age. Melanotic macules are usually solitary, discrete, pigmented brown collections of melanin-containing cells. The macules are less than 2 cm in diameter, seen especially on the vermilion of the lips, gingiva, buccal mucosa or palate. Most on the lips are seen near the midline, on the lower lip vermilion. Most are solitary and seen in white adults and their colour ranges from brown to black [1,5,6]. Occasional cases are seen in HIV infection [7].

Clinically, the melanotic macule may resemble other lesions such as early melanoma and ephelides, although the latter tend to fade in winter and darken in summer. Histopathologically, the mucosal epithelium is normal apart from increased pigmentation of the basal layer, accentuated at the tips of rete ridges. There are no naevus cells or elongated rete ridges [3]. There is melanin in the epithelial basal layer and/or upper lamina propria. Occasionally they are seen along with melanonychia striata (Laugier–Hunziker syndrome, see below).

Melanotic macules can be excised to exclude melanoma or for cosmetic reasons, or removed by laser or hidden by lipstick [8–12].

References

1 Weathers DR, Corio RL, Crawford BE. The labial melanotic macule. *Oral Surg Oral Med Oral Pathol* 1976; **42**: 192–205.
2 Wescott WB, Correll RW, Friedlander AH. Pigmented macules on the lower lip. *J Am Dent Assoc* 1983; **107**: 100–1.
3 Gupta G, Williams RE, Mackie RM. The labial melanotic macule: a review of 79 cases. *Br J Dermatol* 1997; **136**: 772–5.
4 Pais S, Hegde SK, Bhat SS. Oral melanotic macule—a case report. *J Indian Soc Pedod Prev Dent* 2004; **22**: 73–5.
5 Spann CR, Owen LG, Hodge SJ. The labial melanotic macule. *Arch Dermatol* 1987; **123**: 1029–31.
6 Ho KL, Dervan P, O'Loughlin S, Powell FC. Labial melanotic macule: a clinical, histopathologic and ultrastructural study. *J Am Acad Dermatol* 1993; **28**: 33–9.
7 Ficarra G, Shillitoe EJ, Adler-Storthz K. Oral melanotic macules in patients infected with human immunodeficiency virus. *Oral Surg Oral Med Oral Pathol* 1990; **70**: 748–55.
8 Ozawa T, Fujiwara M, Harada T, Muraoka M, Ishii M. Q-switched alexandrite laser therapy for pigmentation of the lips owing to Laugier-Hunziker syndrome. *Dermatol Surg* 2005; **31**: 709–12.
9 Ferreira MJ, Ferreira AM, Soares AP, Rodrigues JC. Laugier-Hunziker syndrome: case report and treatment with the Q-switched Nd-Yag laser. *J Eur Acad Dermatol Venereol* 1999; **12**: 171–3.
10 Benedict LM, Cohen B. Treatment of Peutz–Jeghers lentigines with the carbon dioxide laser. *J Dermatol Surg Oncol* 1991; **17**: 954–5.
11 Mafong EA, Kauvar AN, Geronemus RG. Surgical pearl: Removal of cosmetic lip-liner tattoo with the pulsed carbon dioxide laser. *J Am Acad Dermatol* 2003; **48**: 271–2.
12 Hanada K, Baba T, Sasaki C, Hashimoto I. Successful treatment of mucosal melanosis of the lip with normal pulsed ruby laser. *J Dermatol* 1996; **23**: 263–6.

Peutz–Jeghers syndrome (see Chapter 58)

Peutz–Jeghers syndrome is an autosomal dominant trait characterized by hamartomatous intestinal polyposis and mucocutaneous melanotic pigmentation, especially circumorally. Those affected have discrete, brown to bluish black macules mainly around the oral, nasal and ocular orifices. The lips, especially the lower, have pigmented macules in about 98% of patients (Fig. 69.18). Oral brown or black macules, unlike the circumoral lesions, do not fade after puberty. Mucosal and facial hyperpigmentation may also be seen in relatives [1–3].



Fig. 69.18 Peutz–Jeghers syndrome.

Intestinal polyps are found mainly in the small intestine in Peutz–Jeghers syndrome. They rarely undergo malignant change but if they produce intussusception, surgical intervention is required. There is a slightly increased risk of gastrointestinal carcinoma and carcinomas of the pancreas, breast and reproductive organs [4–9].

Ruby and argon lasers have been used to treat the pigmentation of the lips and oral mucosa [10] (see Chapter 78).

References

1 Marlette RH. Generalized melanoses and nonmelanotic pigmentations of the head and neck. *J Am Dent Assoc* 1975; **90**: 141–7.
2 Wesley RK, Delaney JR, Pensler L. Mucocutaneous melanosis and gastrointestinal polyposis (Peutz–Jeghers syndrome): clinical considerations and report of case. *J Dent Child* 1977; **44**: 131–4.
3 Wescott WB, Correll RW. Oral and perioral pigmented macules in a patient with gastric and intestinal polyposis. *J Am Dent Assoc* 1984; **108**: 385–6.
4 Burdick D, Prior JT. Peutz–Jeghers syndrome: a clinicopathological study of a large family with a 27 year follow-up. *Cancer* 1982; **50**: 2139–46.
5 Boardman LA, Pittelkow MR, Couch FJ *et al.* Association of Peutz–Jeghers-like mucocutaneous pigmentation with breast and gynecologic carcinomas in women. *Medicine (Baltimore)* 2000; **79**: 293–8.
6 Buck JL, Harned RK, Lichtenstein JE, Sobin LH. Peutz–Jeghers syndrome. *Radiographics* 1992; **12**: 365–78.
7 Gardiello FM, Welsh SB, Hamilton SR *et al.* Increased risk of cancer in the Peutz–Jeghers syndrome. *N Engl J Med* 1987; **316**: 1511–4.
8 Ohshiro T, Maruyama Y, Nakajima H, Mima M. Treatment of pigmentation of the lips and oral mucosa in Peutz–Jeghers' syndrome using ruby and argon lasers. *Br J Plast Surg* 1980; **33**: 346–9.
9 Afolabi OO. Oral melanosis: a case report of Peutz–Jegher's syndrome in Suva, Fiji. *Pac Health Dialog* 2003; **10**: 55–6.
10 Pereira CM, Coletta RD, Jorge J, Lopes MA. Peutz–Jeghers syndrome in a 14-year-old boy: case report and review of the literature. *Int J Paediatr Dent* 2005; **15**: 224–8.

Laugier–Hunziker syndrome [1–12]

Synonym
- Laugier–Hunziker–Baran syndrome

Laugier–Hunziker syndrome presents with labial, oral mucosal and nail hyperpigmentation. A possible variant of this or Peutz–Jeghers syndrome has been termed *idiopathic lenticular pigmentation* [6], in which there are oral, labial, perianal and digital hyperpigmented lenticular macules. Similar patients have been reported previously [9–11]. Treatment with the Q-switched Nd-Yag laser has been reported [12].

References

1 Haneke E. Laugier–Hunziker–Baran syndrome. *Hautarzt* 1991; **42**: 512–5.
2 Lamey PJ, Nolan A, Thomson E, Lewis MA, Rademaker M. Oral presentation of the Laugier–Hunziker syndrome. *Br Dent J* 1991; **171**: 59–60.
3 Mowad CM, Shrager J, Elenitsas R. Oral pigmentation representing Laugier–Hunziker syndrome. *Cutis* 1997; **60**: 37–9.
4 Mignogna MD, Lo Muzio L, Ruoppo E *et al.* Oral manifestations of idiopathic lenticular mucocutaneous pigmentation (Laugier–Hunziker syndrome): a clinical, histopathological and ultrastructural review of 12 cases. *Oral Dis* 1999; **5**: 80–6.
5 Ajith C, Handa S. Laugier-Hunziker pigmentation. *Indian J Dermatol Venereol Leprol* 2005; **71**: 354–6.
6 Sardana K, Mishra D, Garg V. Laugier Hunziker syndrome. *Indian Pediatr* 2006; **43**: 998–1000.
7 Gerbig AW, Hunziker T. Idiopathic lenticular mucocutaneous pigmentation or Laugier–Hunziker syndrome with atypical features. *Arch Dermatol* 1996; **132**: 844–5.
8 Siponen M, Salo T. Idiopathic lenticular mucocutaneous pigmentation (Laugier-Hunziker syndrome): a report of a case. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2003; **96**: 288–92.
9 Calnan CD. The Peutz–Jegher's syndrome. *Trans St John's Hosp Dermatol Soc* 1960; **44**: 58–64.
10 Bologa EI, Bene M, Pasztor P. Considerations sur la lentiginose eruptive de la face. *Ann Dermatol Syphiligr* 1965; **92**: 277–86.
11 Dupre A, Viraben R. Laugier's disease. *Dermatologica* 1990; **181**: 183–6.
12 Ferreira MJ, Ferreira AM, Soares AP, Rodrigues JC. Laugier–Hunziker syndrome: case report and treatment with the Q-switched Nd-Yag laser. *J Eur Acad Dermatol Venereol* 1999; **12**: 171–3.

Pseudoxanthoma elasticum
See Chapter 45.

Lentiginoses
The lentiginoses (or lentigenoses) include Peutz–Jeghers syndrome (Chapter 58) and the LEOPARD syndrome, which comprises:
- *l*entigines (multiple)
- *e*lectrocardiographic conduction abnormalities
- *o*cular hypertelorism
- *p*ulmonary stenosis
- *a*bnormalities of genitalia
- *r*etardation of growth and
- *d*eafness.

The lentiginoses also include the syndrome of arterial dissections with lentiginosis, Laugier–Hunziker syndrome, Cowden disease, Ruvalcaba–Myhre–Smith (Bannayan–Zonana) syndrome, and the centrofacial, benign patterned and segmental lentiginoses, all of which can be associated with a variety of developmental defects.

Centrofacial lentiginosis syndrome

Synonym
- Touraine's centrofacial lentiginosis

Centrofacial lentiginosis [1,2] is associated with bone abnormalities, malformations due to dysraphia, endocrine dysfunctions and neurological diseases.

References

1 Dociu I, Galaction-Nitelea O, Sirjita N, Murgu V. Centrofacial lentiginosis. A survey of 40 cases. *Br J Dermatol* 1976; **94**: 39–43.
2 Kaur TD, Kanwar AJ. Giant nevus spilus and centrofacial lentiginosis. *Pediatr Dermatol* 2004; **21**: 516–7.

Complex of myxomas, spotty pigmentation and endocrine overactivity

Synonyms
- Carney's syndrome
- Carney complex

This autosomal dominant trait causes cardiac and cutaneous myxomas, with mammary myxoid fibroadenomas, spotty cutaneous hyperpigmentation, primary pigmented nodular adrenocortical disease, testicular Sertoli cell tumours and growth hormone-secreting pituitary adenoma. It may present with oral hyperpigmentation and myxomas [1–5]. The hyperpigmentation in Carney complex is facial and occurs on the vermilion of the lips in about 35%, although about 8% have pigmented lesions on the oral mucosa and about 2% have oral myxomas, usually on the palate or tongue [2]. Carney complex differs clinically from Peutz–Jeghers syndrome in that hyperpigmentation is less common intraorally but more common on the conjunctiva, and other manifestations are also present.

Cases previously described as NAME syndrome (*n*aevi, *a*trial myxoma, *m*yxoid neurofibromas, *e*phelides) and LAMB syndrome (*l*entigines, *a*trial myxoma, *m*ucocutaneous myxoma, *b*lue naevi) may represent this complex, which also has close similarities to LEOPARD syndrome and the syndrome of arterial dissections with lentiginosis (see Chapter 58).

References

1 Carney JA, Gordon H, Carpenter PC *et al.* The complex of myxomas, spotty pigmentation and endocrine overactivity. *Medicine (Baltimore)* 1985; **64**: 270–83.
2 Cook CA, Lund BA, Carney JA. Mucocutaneous pigmented spots and oral myxomas: the oral manifestations of the complex of myxomas, spotty pigmentation and endocrine overactivity. *Oral Surg* 1987; **63**: 175–83.
3 Ohara N, Takasu N, Komiya I *et al.* Case of Carney's syndrome with primary pigment nodular adrenocortical disease (PPNAD) and pigmented spots of the lips. *Nippon Naika Gakkai Zasshi* 1993; **82**: 1718–9.
4 Stratakis CA, Carney JA, Lin J-P *et al.* Carney complex, a familial multiple neoplasia and lentiginosis syndrome. *J Clin Invest* 1996; **97**: 699–705.
5 Yoon HD, Shon HS. A typical Korean case of Carney complex. *Korean J Intern Med* 2003; **18**: 260–5.

Inherited patterned lentiginosis in black people
This autosomal dominant condition is characterized by small, discrete, hyperpigmented macules on the face, lips, extremities, buttocks and palmoplantar areas [1]. No series of patients have

been reported with oral mucosal lesions or internal organ system abnormalities.

This condition can resemble other lentiginosis syndromes, especially Peutz–Jeghers syndrome, centrofacial lentiginosis syndrome and Carney complex.

Reference

1 O'Neill JF, James WD. Inherited patterned lentiginosis in blacks. *Arch Dermatol* 1989; **125**: 1231–5.

Naevi

Pigmented naevi are much less common in the oral mucosa than in skin. Approximately half of naevi are histologically of the intradermal (intramucosal) type; one-third are blue naevi, many others are compound naevi and some are junctional naevi.

Pathology. They are formed from increased melanin-containing cells, are flat or raised, do not change rapidly in size or colour, are painless and are seen particularly on the palate. The intramucosal type of naevus is most common (about 60%), while another 25% are blue naevi. Compound and junctional naevi and combined naevi are rare in the mouth. The intramucosal naevus consists of a collection of melanocytic cells in the lamina propria without involvement of the epithelium. The blue naevus consists of spindle cells at any level in the lamina propria. The junctional naevus consists of clusters of benign naevus cells at the epitheliomesenchymal junction and the lamina propria is otherwise not involved.

Clinical features. Pigmented naevi are seen particularly on the vermilion border of the lip and on the palate or buccal mucosa [1,2]. These lesions are usually brown, macular, do not change rapidly in size or colour and are painless. The prognosis is good.

Treatment. Although there is no evidence that most pigmented naevi progress to melanoma [3], there has been concern expressed that junctional naevi may be a risk factor. Recent evidence does not support this [4].

However, pigmented naevi may resemble melanomas and if early detection of oral melanomas is to be achieved, all pigmented oral cavity lesions should be viewed with suspicion. Therefore, excision biopsy is recommended to exclude malignancy [3] and may also be performed for cosmetic reasons. This is particularly important if the lesions are raised or nodular [2,3].

References

1 Buchner A, Hansen LS. Pigmented nevi of the oral mucosa. *Oral Surg Oral Med Oral Pathol* 1980; **49**: 55–62.
2 Buchner A, Merrell PW, Carpenter WL. Relative frequency of solitary melanocytic lesions of the oral mucosa. *J Oral Pathol Med* 2004; **33**: 550–7.
3 Hansen LS, Buchner A. Changing concepts of the junctional naevus and melanoma. Review of the literature and report of a case. *J Oral Surg* 1981; **39**: 961–5.
4 Meleti M, Mooi WJ, Casparie MK, van der Waal I. Melanocytic nevi of the oral mucosa—no evidence of increased risk for oral malignant melanoma: An analysis of 119 cases. *Oral Oncol* 2007; **43**: 976–81.

Red lesions

Vascular anomalies

Hereditary haemorrhagic telangiectasia (see Chapter 48)

Synonym

- Osler–Rendu–Weber syndrome

This syndrome is characterized by multiple telangiectasia on the lips, perioral skin, oral and nasal mucosae [1,2] as well as the gastrointestinal tract. Occasionally there are colonic or hepatic complications [3–6]. Oral haemorrhage can be controlled by cryotherapy, cautery, infrared coagulation, Nd-Yag laser or intense pulsed light [7–9].

References

1 Flint SR, Keith O, Scully C. Hereditary haemorrhagic telangiectasia: family study and review. *Oral Surg* 1988; **66**: 440–4.
2 Christensen GJ. Nosebleeds may mean something much more serious: an introduction to HHT. *J Am Dent Assoc* 1998; **129**: 635–7.
3 Hisamura M, Akita K, Ide H. A case of Rendu–Osler–Weber disease associated with simultaneous, multiple advanced cancers in the colon. *Hokkaido Igaku Zasshi* 1994; **69**: 1468–75.
4 Selmaier M, Cidlinsky K, Ell C, Hahn EG. Liver hemangiomatosis in Osler's disease. *Dtsch Med Wochenschr* 1993; **118**: 1015–9.
5 Fiorella ML, Ross DA, White RI, Sabba C, Fiorella R. Hereditary haemorrhagic telangiectasia: state of the art. *Acta Otorhinolaryngol Ital* 2004; **24**: 330–6.
6 Garcia-Tsao G. Liver involvement in hereditary hemorrhagic telangiectasia (HHT). *J Hepatol* 2007; **46**: 499–507.
7 Colver GB, Davies S, Bullock J. Infra-red coagulation for bleeding mucosal telangiectasia. *J Laryngol Otol* 1992; **106**: 992–3.
8 Galletta A, Amato G. Hereditary hemorrhagic telangiectasia (Osler–Rendu–Weber disease). Management of epistaxis and oral hemorrhage by Nd-Yag laser. *Minerva Stomatol* 1998; **47**: 283–6.
9 Fernadez-Jorge B, del Pozo Losada J, Paradela S, MartinezGonzalez C. Treatment of cutaneous and mucosal telangiectases in hereditary hemorrhagic telangiectasia: Report of three cases. *J Cosmet Laser Ther* 2007; **9**: 29–33.

Haemangioma

Haemangiomas are usually deep red or blue–purple, blanch on pressure, are fluctuant to palpation, and are level with the mucosa or have a lobulated or raised surface [1,2]. Most are small and of no consequence [1,3].

Most haemangiomas are seen in isolation but a few may be multiple and/or part of a wider syndrome, such as Maffucci syndrome [4,5]. Large facial haemangiomas, which can involve the lips, may be associated with Sturge–Weber syndrome (Fig. 69.19) [4] or Dandy–Walker syndrome, or other posterior cranial fossa malformations [6,7].

Haemangiomas are at risk from trauma and prone to excessive bleeding if damaged (e.g. during tooth extraction). Occasionally, oral haemangiomas develop phlebolithiasis.

Oral lesions suspected of being haemangiomatous should not be routinely biopsied; aspiration is far safer. Kaposi's sarcoma and epithelioid angiomatosis should be excluded. After intravenous administration of contrast medium, enhancement is observed in haemangiomas in areas corresponding to those with high signal on T_2-weighted magnetic resonance imaging (MRI).

Oral haemangiomas are left alone unless causing symptoms, when they are best treated with cryosurgery or laser if small, or by ligation or embolization of feeding vessels if large.



Fig. 69.19 Haemangioma affecting the lip in Sturge–Weber syndrome.

References

1 Stal S, Hamilton S, Spira M. Haemangioma, lymphangioma and vascular malformations of the head and neck. *Otolaryngol Clin North Am* 1986; **19**: 769–96.
2 Forte V, Triglia GM, Zalzal G. Hemangioma. *Head Neck* 1998; **20**: 69–72.
3 Kaban LB, Mulliken JB. Vascular anomalies of the maxillofacial region. *J Oral Maxillofac Surg* 1986; **44**: 203–13.
4 Scully C. Orofacial manifestations of the neurodermatoses. *J Dent Child* 1980; **47**: 255–60.
5 Cohen MM Jr. Hemangiomas: their uses and abuses. *Am J Med Genet A* 2007; **143**: 235–40.
6 Reese V, Frieden IJ, Paller AS. Association of facial hemangiomas with Dandy–Walker and other posterior fossa malformations. *J Pediatr* 1993; **122**: 379–84.
7 Ghosh A, Tibrewal SR, Thapa R. PHACES syndrome with congenital hypothyroidism. *Indian Pediatr* 2007; **44**: 144–7.

Sturge–Weber–Krabbe syndrome [1–7] (see Chapter 18)

The haemangioma in the trigeminal area in Sturge–Weber syndrome is usually unilateral, may involve the mouth but fortunately rarely involves bone. It may be associated with hypertrophy of affected tissues and, if the patient is treated with phenytoin, with gingival hyperplasia [3,4].

References

1 Uram M, Zubillaga C. The cutaneous manifestations of Sturge–Weber syndrome. *J Clin Neuro Ophthalmol* 1982; **2**: 245–8.
2 Scully C. Orofacial manifestations of the neurodermatoses. *J Dent Child* 1980; **47**: 255–60.
3 Huang JS, Chen CC, Wu YM *et al.* Periodontal manifestations and treatment of Sturge–Weber syndrome: report of two cases. *Kaohsiung J Med Sci* 1997; **13**: 127–35.
4 Ahluwalia TP, Lata J, Kanwa P. Sturge Weber syndrome with intraoral manifestations. A case report. *Indian J Dent Res* 1998; **9**: 140–4.
5 Terezhalmy GT, Riley CK. Clinical images in oral medicine. Encephalotrigeminal syndrome (Sturge–Weber disease). *Quintessence Int* 2000; **31**: 62–3.
6 Dorothy A, Kamboj M, Reddy BS. Sturge Weber syndrome. *Indian J Dent Res* 2004; **15**: 152–4.
7 Lin DD, Gailloud P, McCarthy EF, Comi AM. Oromaxillofacial osseous abnormality in Sturge-Weber syndrome: case report and review of the literature. *AJNR Am J Neuroradiol* 2006; **27**: 274–7.

Klippel–Trenaunay–Weber syndrome (see Chapter 18)

Haemangiomas of the buccal mucosa and tongue, macroglossia, maxillary hyperplasia and an anterior open bite have been recorded in this syndrome [1–8]. Post-extraction bleeding can be a problem [8,9].

References

1 Sciubba JJ, Brown AM. Oral–facial manifestations of Klippel–Trenaunay–Weber syndrome. *Oral Surg* 1977; **43**: 227–32.
2 Steiner M, Gould AR, Graves SM *et al.* Klippel–Trenaunay–Weber syndrome. *Oral Surg* 1987; **63**: 208–15.
3 Hallett KB, Bankier A, Chow CW, Bateman J, Hall RK. Gingival fibromatosis and Klippel–Trenaunay–Weber syndrome. Case report. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1995; **79**: 578–82.
4 Miteva LG, Dourmishev AI, Schwartz RA, Mitev VI. Oral vascular manifestations of Klippel–Trenaunay syndrome. *Cutis* 1998; **62**: 171–4.
5 Mueller-Lessmann V, Behrendt A, Wetzel WE, Petersen K, Anders D. Orofacial findings in the Klippel–Trenaunay syndrome. *Int J Paediatr Dent* 2001; **11**: 225–9.
6 Kuhl SR, Schultze RK, Kreft A, d'Hoete B. Epulis granulomatosa as an oral manifestation of Klippel-Trenaunay syndrome. *J Oral Pathol Med* 2006; **35**: 576–8.
7 Bolan M, Ferreira MC, Almeida MC, D'Agostini DC, Ribeiro GL. Palatal expansion and the Klippel-Trenaunay-Weber syndrome. *Am J Orthod Dentofacial Orthop* 2005; **128**: 385–7.
8 Auluck A, Suhas S, Pai KM. Klippel–Trenaunay syndrome. *Oral Dis* 2005; **11**: 255–8.
9 Ita M, Okafuji M, Maruoka Y, Shinozaki F. An unusual postextraction hemorrhage associated with Klippel–Trenaunay–Weber syndrome. *J Oral Maxillofac Surg* 2001; **59**: 205–7.

Blue rubber–bleb naevus syndrome (see Chapter 18)

Synonym
- Bean's syndrome

Oral haemangiomas may be seen [1–5].

References

1 Crosher RF, Blackburn CW, Dinsdale RCW. Blue rubber-bleb naevus syndrome. *Br J Oral Surg* 1988; **26**: 160–4.
2 Sumi Y, Taguchi N, Kaneda T. Blue rubber bleb nevus syndrome with oral hemangiomas. *Oral Surg Oral Med Oral Pathol* 1991; **71**: 84–6.
3 McKinlay JR, Kaiser J, Barrett TL, Graham B. Blue rubber bleb nevus syndrome. *Cutis* 1998; **62**: 97–8.
4 Palleschi GM, Torchia D, Fabbri D. Blue rubber-bleb nevus syndrome: report of a case associated with osteoid osteomas. *J Dermatol* 2005; **32**: 589–93.
5 Starr BM, Katzenmeyer WK, Guinto F, Pou AM. The blue rubber bleb nevus syndrome: a case with prominent head and neck findings. *Am J Otolaryngol* 2005; **26**: 282–4.

Maffucci's syndrome (see Chapter 18)

Oral haemangiomas may be seen [1–5].

References

1 Laskaris G, Skouteris C. Maffucci syndrome: report of a case with oral haemangiomas. *Oral Surg* 1984; **57**: 263–6.
2 Yavuzyilmaz E, Yamalik N, Eratalay K, Atakan N. Oral–dental findings in a case of Maffucci's syndrome. *J Periodontol* 1993; **64**: 673–7.
3 Skouteris CA. More on hemangiomas in patients with Maffucci's syndrome. *J Oral Maxillofac Surg* 1994; **52**: 205.
4 Lee NH, Choi EH, Choi WK, Lee SH, Ahn SK. Maffucci's syndrome with oral and intestinal haemangioma. *Br J Dermatol* 1999; **140**: 968–9.
5 Wassef M, Vanwijck R, Clapuyt P, Boon L, Magalon G. Vascular tumours and malformations, classification, pathology and imaging. *Ann Chir Plast Esthet* 2006; **51**: 263–81.

Hereditary mucoepithelial dysplasia

Hereditary mucoepithelial dysplasia is an autosomal dominant dyskeratotic epithelial syndrome affecting oral, nasal, vaginal, urethral, anal, bladder and conjunctival mucosae, causing cataracts, follicular keratosis, non-scarring alopecia and terminal lung disease [1–5].

Pathology. The condition is probably a pan-epithelial cell defect of desmosomal and gap junction structure. Histochemically there is a lack of cornification and keratinization. Electron microscopy shows an abnormality in desmosomes and gap junctions, with a lack of keratohyalin granules, a paucity of desmosomes, intercellular accumulations, cytoplasmic vacuolization, and formation of bands and aggregates of filamentous fibres and structures in the cytoplasm resembling desmosomes and gap junctions. There is some acantholysis as well as benign dyskeratosis of individual cells [1,2]. Histologically the mucosal epithelium shows dyshesion, thinning of the epithelial layer and dyskeratosis. Mucosal Papanicolaou smears show lack of epithelial maturation, cytoplasmic vacuoles and inclusions, and individual cell dyskeratosis.

Clinical features. Red, periorificial mucosal lesions are typically noted during infancy and may persist throughout life. The oral lesions are painless, red macules or maculopapules and are seen predominantly on the palate and gingiva.

Severe photophobia, tearing and nystagmus in infancy herald the development of keratitis, corneal vascularization and lens cataracts.

In addition there may be various cardiorespiratory complications, especially potentially lethal bullous lung disease—spontaneous pneumothorax and bullous emphysema, terminating in cor pulmonale. Chronic rhinorrhoea and repeated upper respiratory infections frequently progress to bilateral pneumonia. Loss of hair, diarrhoea, melaena, enuresis, pyuria and haematuria may also be seen.

References

1 Witkop CJ, White JG, Sank JJ *et al.* Clinical, histologic, cytologic and ultrastructural characteristics of the oral lesions from hereditary mucoepithelial dysplasia. *Oral Surg* 1978; **46**: 645–57.

2 Witkop CJ Jr, White JG, King RA *et al.* Hereditary mucoepithelial dysplasia: a disease apparently of desmosome and gap junction formation. *Am J Hum Genet* 1979; **31**: 414–27.

3 Scheman AJ, Ray DJ, Witkop CJ *et al.* Hereditary mucoepithelial dysplasia. *J Am Acad Dermatol* 1989; **21**: 351–7.

4 Rogers M, Kourt G, Cameron A. Hereditary mucoepithelial dysplasia. *Pediatr Dermatol* 1994; **11**: 133–8.

5 Boralevi F, Haftek M, Vabres P, Lepreux S, Goizet C, Leaute-Labreze C, Taieb A. Hereditary mucoepithelial dysplasia: clinical, ultrastructural and genetic study of eight patients and literature review. *Br J Dermatol* 2005; **153**: 310–8.

Wiskott–Aldrich syndrome (see Chapter 17)

Oral petechiae and infections such as candidosis may occur in the Wiskott–Aldrich syndrome of thrombocytopenia, immune deficiency and eczema [1–3].

References

1 Porter SR, Sugermann PB, Scully C *et al.* Orofacial manifestations in the Wiskott–Aldrich syndrome. *J Dent Child* 1994; **61**: 404–7.

2 Boraz RA. Dental considerations in the treatment of Wiskott–Aldrich syndrome: report of case. *ASDC J Dent Child* 1989; **56**: 225–7.

3 Walcott DW, Linehan T 4th, Hilman BC, Hershfield MS, el Dahr J. Failure to thrive, diarrhea, cough, and oral candidiasis in a three-month-old boy. *Ann Allergy* 1994; **72**: 408–14.

Vesiculoerosive disorders

Acrodermatitis enteropathica

Acrodermatitis enteropathica is a rare, autosomal recessive inborn error of metabolism resulting in zinc malabsorption and severe zinc deficiency [1–7].

Clinical features. Diarrhoea, mood changes, anorexia and neurological disturbance are reported, most frequently in infancy. Growth retardation, alopecia, weight loss and recurrent infections are prevalent in affected toddlers and schoolchildren. A vesiculobullous dermatitis with perioral involvement may be seen, often sparing the vermilion [2]. Zinc deficiency during growth periods results in growth failure and lack of gonadal development in males. Other effects of zinc deficiency include skin changes, poor appetite, mental lethargy, delayed wound healing, neurosensory disorders and cell-mediated immune disorders. Skin lesions and poor wound healing are observed in severe forms and the disorder can be lethal.

Diagnosis. Assays of zinc in granulocytes and lymphocytes provide better diagnostic criteria for marginal zinc deficiency than plasma zinc assays. In cases of doubt, zinc absorption tests using radioisotopes (^{65}Zn or ^{69m}Zn) may be performed. Levels of alkaline phosphatase are reduced.

Treatment. Management includes zinc sulphate 2 mg/kg daily, at least until adult life.

References

1 Van Wouwe JP. Clinical and laboratory diagnosis of acrodermatitis enteropathica. *Eur J Pediatr* 1989; **149**: 2–8.

2 Carr PM, Wilkin JK, Rosen T. Sparing of the vermilion border in an acrodermatitis enteropathica-like syndrome. *Cutis* 1983; **31**: 82–3.

3 Goskowicz M, Eichenfield LF. Cutaneous findings of nutritional deficiencies in children. *Curr Opin Pediatr* 1993; **5**: 441–5.

4 Prasad AS. Zinc: an overview. *Nutrition* 1995; **11** (Suppl.): 93–9.

5 Jamall IS, Ally KM, Yusuf S. Acrodermatitis enteropathica: zinc therapy and possible identification of a carrier state through multiple hair zinc analyses over three decades. *Biol Trace Elem Res* 2006; **114**: 93–105.

6 Maverakis E, Fung MA, Lynch PJ, Draznin M, Michael DJ, Ruben B, Fazel N. Acrodermatitis enteropathica and an overview of zinc metabolism. *J Am Acad Dermatol* 2007; **56**: 116–24.

7 Sanchez JE, Barham KL, Sangueza OP. Acquired acrodermatitis enteropathica: case report of an atypical presentation. *J Cutan Pathol* 2007; **34**: 490–3.

Epidermolysis bullosa (see Chapter 39)

Epidermolysis bullosa is characterized by blisters, sometimes preceded by white patches, which develop rapidly, particularly where there is trauma. Blisters rupture to produce ulcers, often with eventual scarring, particularly in the recessive dystrophic types [1–9]. Oral lesions are fairly common in dystrophic and lethal forms of epidermolysis bullosa but are rare in most simplex types except the superficial type, where they are found in 70% of patients [2,10–13]. Overall, oral mucosal lesions are found in about 30% of

Table 69.12 Oral manifestations in epidermolysis bullosa (EB).

Type	EB subtype	Mucosal lesions	Dental hypoplasia
I Epidermolytic (simplex); autosomal dominant	Generalized (Koebner)	±	–
	Localized (Weber–Cockayne)	–	–
	Localized (Kallin)	–	Anodontia
	With mottled pigmentation and punctate keratoderma	+	–
	With bruising (Ogna)	–	±
	Herpetiform (Dowling–Meara)	+	–
	Superficial	+	–
II Junctional; autosomal recessive	Generalized, severe (Herlitz)	+	++
	Generalized, mild	+	+
	Localized	±	+
	Inverse	±	+
	Progressive	+	–
III Dermolytic (dystrophic)	Hyperplastic (Cockayne–Touraine)	±	–
Autosomal dominant	Albopapuloid (Pasini)	+	–
	Pretibial (Kuske–Portugal)	–	–
Autosomal recessive (Hallopeau-Siemens)	Localized	+	±
	Generalized	++	++
	Mutilating	+++	+++
	Inverse	+	–
VI Acquired type	Adult form	±	–
	Child form	+	–

–, absent; +, mild; ++, moderate; +++, severe.

patients with epidermolysis bullosa [1–5]. There is a predisposition to oral squamous cell carcinoma, mainly in the Hallopeau–Siemens type.

Dental hypoplasia and other defects and delayed tooth eruption may also be a feature, especially in junctional epidermolysis bullosa (Table 69.12) and, with the difficulty in maintaining adequate oral hygiene, there is a predisposition to caries [4,7].

Patients with recessive dystrophic epidermolysis bullosa suffer from severe growth inhibition due to reduced food intake as a result of severe oropharyngeal and oesophageal blistering or scarring, with smaller maxillae and smaller mandibles than normal [8,14–17]. Treatment has improved with modalities such as implants [17–19].

The oral manifestations in the various inherited forms of this condition are summarized in Table 69.12 and epidermolysis bullosa acquisita is discussed in Chapter 41.

References

1 Album MM, Gaisin A, Leek WT *et al.* Epidermolysis bullosa dystrophica polydysplastica. *Oral Surg* 1977; **43**: 859–72.
2 Fine JD, Johnson L, Wright T. Epidermolysis bullosa simplex superficialis. *Arch Dermatol* 1989; **125**: 633–8.
3 Sedano HO, Gorlin RJ. Epidermolysis bullosa. *Oral Surg* 1989; **67**: 555–63.
4 Wright JT, Capps J, Johnson LB *et al.* Oral and ultrastructural dental manifestations of epidermolysis bullosa. *J Dent Res* 1988; **67**: 249.
5 Wright JT, Fine JD, Johnson L. Hereditary epidermolysis bullosa: oral manifestations and dental management. *Pediatr Dent* 1993; **15**: 242–7.
6 Serrano-Martinez MC, Bagan JV, Silvestre FG, Vguer MT. Oral lesions in recessive dystrophic epidermolysis bullosa. *Oral Dis* 2003; **9**: 264–8.
7 Sadler E, Laimer M, Diem A *et al.* Dental alterations in junctional epidermolysis bullosa—report of a patient with a mutation in the LAMB3-gene. *J Dtsch Dermatol Ges* 2005; **3**: 359–63.
8 Azrak B, Kaeval K, Hoffman L, Gleissner C, Willershausen B. Dystrophic epidermolysis bullosa: oral findings and problems. *Spec Care Dentist* 2006; **26**: 111–5.
9 Sitaru C. Experimental models of epidermolysis bullosa acquisita. *Exp Dermatol* 2007; **16**: 520–31.
10 Pearson RW. Clinicopathologic types of epidermolysis bullosa and their nondermatological complications. *Arch Dermatol* 1988; **124**: 718–25.
11 Rubenstein R, Esterly NB, Fine JD. Childhood epidermolysis bullosa acquisita. *Arch Dermatol* 1987; **123**: 772–6.
12 Nowak AJ. Oropharyngeal lesions and their management in epidermolysis bullosa. *Arch Dermatol* 1988; **124**: 742–5.
13 Trigo-Guzman FX, Conti A, Aoki V *et al*. Epidermolysis bullosa acquisita in childhood. *J Dermatol* 2003; **30**: 226–9.
14 Kostara A, Roberts GJ, Gelbier M. Dental maturity in children with dystrophic epidermolysis bullosa. *Pediatr Dent* 2000; **22**: 385–8.
15 Shah H, McDonald F, Lucas V, Ashley P, Roberts G. A cephalometric analysis of patients with recessive dystrophic epidermolysis bullosa. *Angle Orthod* 2002; **72**: 55–60.
16 Harris JC, Bryan RA, Lucas VS, Roberts GJ. Dental disease and caries related microflora in children with dystrophic epidermolysis bullosa. *Pediatr Dent* 2001; **23**: 438–43.
17 Serrano Martinez C, Silvestre Donat FJ, Bagan Sebastian JV, Penarrocha Diago M, Alio Sanz JJ. Hereditary epidermolysis bullosa. Dental management of three cases. *Med Oral* 2001; **6**: 48–56.
18 Engineer L, Ahmed AR. Emerging treatment for epidermolysis bullosa acquisita. *J Am Acad Dermatol* 2001; **44**: 818–28.
19 Penarrocha-Diago M, Serrano C, Sanchis JM, Silvestre FJ, Bagan JV. Placement of endosseous implants in patients with oral epidermolysis bullosa. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2000; **90**: 587–90.

Felty's syndrome

Oral ulceration may be seen in Felty's syndrome [1–3].

References

1 Freeman NS, Plezia RA. Felty's syndrome. *Oral Surg Oral Med Oral Pathol* 1975; **40**: 409–13.

2 Holbrook WP, Turner EP, MacIver JE. Felty's syndrome. *Br J Oral Surg* 1979; **17**: 157–60.
3 Stanworth SJ, Bhavnani M, Chattopadhya C, Miller H, Swinson DR. Treatment of Felty's syndrome with the haemopoietic growth factor granulocyte colony-stimulating factor (G-CSF). *Q J Med* 1998; **91**: 49–56.

Immune defects

Mouth ulcers (and early-onset periodontitis) feature in congenital immune defects [1–8], including Chédiak–Higashi syndrome, Papillon–Lefèvre syndrome, familial neutropenia, cyclic neutropenia, Job's syndrome, chronic granulomatous disease and glycogen storage disease type 1b.

References

1 Dougherty N, Gataletto MA. Oral sequelae of chronic neutrophil defects: case report of a child with glycogen storage disease type 1b. *Pediatr Dent* 1995; **17**: 224–9.
2 Porter SR, Scully C. Orofacial manifestations in primary immunodeficiencies: polymorphonuclear leukocyte defects. *J Oral Pathol Med* 1993; **22**: 310–1.
3 Porter SR, Scully C. Orofacial manifestations in primary immunodeficiencies: T lymphocyte defects. *J Oral Pathol Med* 1993; **22**: 308–9.
4 Porter SR, Scully C. Orofacial manifestations in primary immunodeficiencies involving IgA deficiency. *J Oral Pathol Med* 1993; **22**: 117–9.
5 Scully C. Orofacial manifestations in chronic granulomatous disease of childhood. *Oral Surg* 1981; **51**: 148–51.
6 Scully C, Macfadyen E, Campbell A. Oral manifestations in cyclic neutropenia. *Br J Oral Surg* 1982; **20**: 96–101.
7 Scully C, Porter SR. Orofacial manifestations in primary immunodeficiencies: common variable immunodeficiencies. *J Oral Pathol Med* 1993; **22**: 157–8.
8 Atkinson JC, O'Connell A, Aframian D. Oral manifestations of primary immunological diseases. *J Am Dent Assoc* 2000; **131**: 345–56.

Lumps and swellings

Hereditary angio-oedema

Synonym
- C1 esterase inhibitor deficiency

Hereditary angioedema (HANE) is a rare autosomal dominant disorder caused by C1-inhibitor deficiency. HANE mimics allergic angio-oedema (see Chapter 22), although it produces a more severe reaction, with oedema affecting the lips, mouth, face and neck region, the extremities and gastrointestinal tract after minor trauma [1–5].

Blunt injury is the most consistent precipitating event. The trauma of dental treatment is a potent trigger, and some attacks even follow emotional stress. Oedema may persist for many hours and even up to 4 days. Involvement of the airway is a constant threat. The mortality may be as high as 30% in some families but the disease is compatible with prolonged survival if emergencies are avoided or effectively treated.

Diagnosis. In 85% of cases plasma C1 esterase levels are reduced (type 1 hereditary angio-oedema) but in 15% the enzyme is present but dysfunctional (type 2 hereditary angio-oedema). In both types, plasma C4 levels fall but C3 levels are normal. Rarely, similar defects are acquired.

Treatment. C1 esterase concentrates are available for treatment [3,6–10]. Plasminogen inhibitors such as tranexamic acid can be used to mitigate attacks [3,11], although more effective agents are the androgenic steroids danazol and stanozolol, which raise plasma C1 esterase inhibitor levels to normal [1–4].

References

1 Cicardi M, Agostoni A. Hereditary angioedema. *N Engl J Med* 1996; **334**: 1666–7.
2 McCarthy NR. Diagnosis and management of hereditary angioedema. *Br J Oral Maxillofac Surg* 1985; **23**: 123–7.
3 Gompels MM, Lock RJ, Abinun M *et al*. C1 inhibitor deficiency: consensus document. *Clin Exp Immunol* 2005; **139**: 379–94.
4 Sachse MM, Kachemoune A, Guldbakke KK, Kirscfink M. Hereditary angioedema. *J Drugs Dermatol* 2006; **5**: 848–52.
5 Longhurst HJ, Bork K. Hereditary angioedema: causes, manifestations and treatment. *Br J Hosp Med (Lond)* 2006; **67**: 654–7.
6 Waytes AT, Rosen FS, Frank MM. Management of hereditary angioedema with a vapor heated C1 inhibitor concentrate. *N Engl J Med* 1996; **334**: 1630–4.
7 Zuraw BL. Novel therapies for hereditary angioedema. *Immunol Allergy Clin North Am* 2006; **26**: 691–708.
8 Longhurst HJ, Carr S, Khair K. C1-inhibitor concentrate home therapy for hereditary angioedema: a viable, effective treatment option. *Clin Exp Immunol* 2007; **147**: 11–7.
9 Choi G, Soeters MR, Farkas H *et al*. Recombinant human C1-inhibitor in the treatment of acute angioedema attacks. *Transfusion* 2007; **47**: 1028–32.
10 Pedraz J, Dauden E, Garcia-Diez A. Practical management of C1 esterase deficiency *Acta Dermosfiliogr* 2007; **98**: 240–9.
11 Crosher R. Intravenous tranexamic acid in the management of hereditary angio-oedema. *Br J Oral Maxillofac Surg* 1987; **25**: 500–6.

Focal dermal hypoplasia (see Chapter 15)

Synonym
- Goltz–Gorlin syndrome

Focal dermal hypoplasia is a rare, presumably X-linked, genodermatosis [1–3] involving developmental anomalies of tissues and organs of mesoectodermal origin. Thus there are abnormalities of the eyes, skin, musculoskeletal system, central nervous system (CNS) and oral structures.

Papillomas, usually of the oral mucosae and lips, dental anomalies and occasional cleft lip and palate are the main oral features [2–6]. The dental anomalies, seen in about half of affected individuals, include hypodontia, enamel defects and taurodontism [7–10].

References

1 Greer RO, Reissner MW. Focal dermal hypoplasia: current concepts and differential diagnosis. *J Periodontol* 1989; **60**: 330–5.
2 Riyaz N, Riyaz A, Chandran R, Rakesh SV. Focal dermal hypoplasia (Goltz syndrome). *Indian J Dermatol Venereol Leprol* 2005; **71**: 279–81.
3 Malapeddi R, Chaudhry SI, Darley CR, Kurwa H. A case of focal dermal hypoplasia (Goltz) syndrome with exophytic granulation tissue treated by curettage and photodynamic therapy. *Clin Exp Dermatol* 2006; **31**: 228–31.
4 Ishibashi A, Kurihara Y. Goltz's syndrome: focal dermal dysplasia syndrome (focal dermal hypoplasia). Report of a case and its etiology and pathogenesis. *Dermatologica* 1972; **144**: 156–60.
5 Valerius NH. A case of focal dermal hypoplasia syndrome (Goltz) with bilateral cheilo-gnatho-palatoschisis. *Acta Paediatr Scand* 1984; **63**: 287–90.
6 Tejani Z, Batra P, Mason C, Atherton D. Focal dermal hypoplasia: oral and dental findings. *J Clin Pediatr Dent* 2005; **30**: 67–72.
7 Stephen LX, Behardien N, Beighton P. Focal dermal hypoplasia: management of complex dental features. *J Clin Pediatr Dent* 2001; **25**: 259–61.

8 Baxter AM, Shaw MJ, Warren K. Dental and oral lesions in two patients with focal dermal hypoplasia (Goltz syndrome). *Br Dent J* 2000; **189**: 550–3.
9 McNamara T, Trotman CA, Hahessy AM, Kavanagh P. Focal dermal hypoplasia (Goltz–Gorlin) syndrome with taurodontism. *Spec Care Dent* 1996; **16**: 26–8.
10 Balmer R, Cameron AC, Ades L, Aldred MJ. Enamel defects and Lyonization in focal dermal hypoplasia. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2004; **98**: 686–91.

Acanthosis nigricans (see Chapter 19)

Oral papilliferous lesions may be a feature of both familial [1,2] and malignant [1,3–8] acanthosis nigricans. Between 30 and 50% of patients with acanthosis nigricans secondary to neoplasia (malignant acanthosis nigricans) have oral lesions, which involve the tongue and lips predominantly.

References

1 Sedano HO, Gorlin RJ. Acanthosis nigricans. *Oral Surg* 1987; **68**: 74–9.
2 Bazopoulou E, Laskaris G, Katsabas A *et al.* Familial benign acanthosis nigricans with predominant early oral manifestations. *Clin Genet* 1991; **50**: 160.
3 Mostofi RS, Hayden NP, Soltani K. Oral malignant acanthosis nigricans. *Oral Surg* 1983; **56**: 372–4.
4 Nomachi K, Mori M, Matsuda N. Improvement of oral lesions associated with malignant acanthosis nigricans after treatment of lung cancer. *Oral Surg* 1989; **68**: 74–9.
5 Cairo F, Rubino I, Rotundo R, Prato GP, Ficarra G. Oral acanthosis nigricans as a marker of internal malignancy. A case report. *J Periodontol* 2001; **72**: 1271–5.
6 Scully C, Barrett WA, Gilkes J, Rees M, Sarner M, Southcott RJ. Oral acanthosis nigricans, the sign of Leser-Trelat and cholangiocarcinoma. *Br J Dermatol* 2001; **145**: 506–7.
7 Ramirez-Amador V, Esquival-Pedraza L, Caballero-Mendoza E *et al*. Oral manifestations as a hallmark of malignant acanthosis nigricans. *J Oral Pathol Med* 1999; **28**: 278–81.
8 Pentenero M, Carozzo M, Pagano M, Gandolfo S. Oral acanthosis nigricans, tripe palms and sign of leser-trelat in a patient with gastric adenocarcinoma. *Int J Dermatol* 2004; **43**: 530–2.

Lymphangioma (see Chapter 48)

Lymphangioma is uncommon in the mouth. At least some are hamartomas and many are of similar structure to haemangiomas and can clinically resemble them, with a 'frog-spawn' appearance, but they contain lymph rather than blood (Fig. 69.20).

Lymphangiomas are usually solitary and affect the tongue predominantly. They are occasionally associated with cystic hygroma [1–7]. One study has found blue, domed lymphangiomas on the alveolar ridges of about 4% of newborn black children [3]. These lesions, which were usually bilateral, often regressed spontaneously.

Contrast-enhanced T_1-weighted MRI can be used to differentiate between lymphangiomas and deep haemangiomas [8]. Small lymphangiomas need no treatment. Larger lesions may require excision, although cryotherapy laser therapy and sclerotherapy can be useful and, more recently, radiofrequency ablation has been described [7,9].

A number of reports describe lymphangiomas presenting on the alveolar ridges of newborn children [3,10,11].

References

1 Karmody CS, Fortson JK, Calcaterra VE. Lymphangiomas of the head and neck in adults. *Otolaryngol Head Neck Surg* 1982; **90**: 283.
2 Tanaka N, Murata A, Yamaguchi A, Kohama G. Clinical features and management of oral and maxillofacial tumors in children. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1999; **88**: 11–5.



Fig. 69.20 Lymphangioma of the tongue: a common site.

3 Levin LS, Jorgenson RJ, Jarvey BA. Lymphangiomas of the alveolar ridge in neonates. *Pediatrics* 1976; **56**: 881.
4 Flaitz CM. Oral and maxillofacial pathology case of the month. Lymphangioma. *Tex Dent J* 2000; **117**: 65, 112–3.
5 Schwab J, Baroody F. Lymphangioma circumscriptum: an unusual oral presentation. *Clin Pediatr* 1999; **38**: 619–20.
6 Stanescu L, Georgescu EF, Simionescu C, Georgescu I. Lymphangioma of the oral cavity. *Rom J Morphol Embryol* 2006; **47**: 373–7.
7 De Quieroz AM, Silva RA, Margato LC, Nelson-Filho P. Dental care management of a young patient with extensive lymphangioma of the tongue: a case report. *Spec Care Dentist* 2006; **26**: 20–4.
8 Yonetsu K, Nakayama E, Kawazu T *et al*. Value of contrast-enhanced magnetic resonance imaging in differentiation of hemangiomas from lymphangiomas in the oral and maxillofacial region. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1999; **88**: 496–500.
9 Bozkaya S, Ugar D, Karaca I *et al*. The treatment of lymphangioma in the buccal mucosa by radiofrequency ablation: a case report. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006; **102**: 28–31.
10 Wilson S, Gould AR, Wolff CC. Multiple lymphangiomas of the alveolar ridge in a neonate: case study. *Pediatr Dent* 1986; **8**: 231–4.
11 Kittle PE, Weaver RM. Lymphangiomas of the alveolar ridge in a neonate: report of case. *ASDC J Dent Child* 1987; **54**: 277–9.

Dermoid cyst (see Chapter 18)

Dermoid cyst is a hamartoma, a development lesion commonly arising in the midline of the neck, above the mylohyoid. It occasionally occurs elsewhere such as the tongue, antrum and rarely the parotid gland [1–7].

Dermoid cysts usually become clinically obvious in the second decade of life and cause elevation of the tongue. Occasionally, dermoid cysts become infected and then painful.

Treatment of dermoid cyst is by surgical excision.

References

1 Naritomi K. Oral dermoids. *Ryoikibetsu Shokogun Shirizu* 2001; **34**: 390–1.
2 Garcia Callejo FJ, Rosello Millat P, Alpera Lacruz R, Platero Zamarreno A, Jubert A. True double dermoid cyst of the tongue. *Acta Otorrinolaringol Esp* 2001; **52**: 626–32.
3 Halfpenny W, Odell EW, Robinson PD. Cystic and glial mixed hamartoma of the tongue. *J Oral Pathol Med* 2001; **30**: 368–71.
4 Torske KR, Benson GS, Warnock G. Dermoid cyst of the maxillary sinus. *Ann Diagn Pathol* 2001; **5**: 172–6.



Fig. 69.21 Lingual tonsil showing a well-demarcated midline groove. (Courtesy of Dr C.T.C. Kennedy, Bristol Royal Infirmary, Bristol, UK.)

5 Ro EY, Thomas RM, Isaacson GC. Giant dermoid cyst of the neck can mimic a cystic hygroma: using MRI to differentiate cystic neck lesions. *Int J Pediatr Otorhinolaryngol* 2007; **71**: 653–8.

6 Golden BA, Zide BF. Cutaneous cysts of the head and neck. *J Oral Maxillofac Surg* 2005; **63**: 1613–9.

7 Naujoks C, Handschel J, Braunstein S *et al*. Dermoid cyst of the parotid gland—a case report and brief review of the literature. *Int J Oral Maxillofac Surg* 2007; **36**: 861–3.

Lingual tonsil

The lingual tonsil is a mass of lymphoid tissue in the posterior third of the tongue, between the epiglottis posteriorly and the circumvallate papillae anteriorly [1,2]. It is usually divided in the midline by a ligament (Fig. 69.21). Although usually small and asymptomatic, it may become enlarged, especially in atopic individuals, in patients taking phenytoin or in some infections. It may be so prominent that it fills the vallecula and impinges against the epiglottis. If the lingual tonsil is large, it may cause a globus sensation, alteration of the voice, obstructive sleep apnoea or airways obstruction [3–8]. It tends to involute with increasing age.

Occasionally, there may be lingual tonsillitis with a red, swollen, painful tongue, fever and neutrophilia [9].

The condition must be distinguished from benign and malignant tumours of the tongue, including lingual thyroid, but the symmetry of the lingual tonsil and its midline division are helpful diagnostic pointers.

Treatment may be required if the enlarged tonsil causes symptoms. Surgery may be hazardous because of the copious blood supply to the tongue base. Electrocautery and cryotherapy are generally regarded as the safer procedures [1,10,11].

References

1 Golding-Wood DG, Whittet HB. The lingual tonsil. A neglected symptomatic structure? *J Laryngol Otol* 1989; **103**: 922–5.

2 Hellings P, Jorissen M, Ceuppens JL. The Waldeyer's ring. *Acta Otorhinolaryngol Belg* 2000; **54**: 237–41.

3 Ralph WM Jr, Huh SK, Kim H. Phenytoin-induced lingual tonsil hyperplasia causing laryngeal obstruction. *Ann Otol Rhinol Laryngol* 2001; **110**: 790–3.

4 Salvi L, Juliano G, Zucchetti M, Sisillo E. Hypertrophy of the lingual tonsil and difficulty in airway control. A clinical case. *Minerva Anestesiol* 1999; **65**: 549–53.

5 Dell RG. Upper airway obstruction secondary to a lingual tonsil. *Anaesthesia* 2000; **55**: 393.

6 Marcos Ordonez M, Benito Orejas JI, Blasco Gutierrez MJ, Morais Perez D, Ramirez Cano B. Oropharyngeal tuberculosis. Report of a case in a lingual tonsil. *Acta Otorrinolaringol Esp* 1999; **50**: 575–8.

7 Fricke BL, Donnelly LF, Schott SR *et al*. Comparison of lingual tonsil size as depicted on MR imaging between children with obstructive sleep apnea despite previous tonsillectomy and adenoidectomy and normal controls. *Pediatr Radiol* 2006; **36**: 518–23.

8 Arrica M, Crawfod MW. Complete upper airway obstruction after induction of anesthesia in a child with undiagnosed lingual tonsil hypertrophy. *Paediatr Anaesth* 2006; **16**: 584–7.

9 Joseph M, Reardon E, Goodman M. Lingual tonsillectomy: a treatment for inflammatory lesions of the lingual tonsil. *Laryngoscope* 1984; **94**: 179–84.

10 Kluszynski BA, Matt BH. Lingual tonsillectomy in a child with obstructive sleep apnea: a novel technique. *Laryngoscope* 2006; **116**: 668–9.

11 Robinson S, Ettema SL, Brusky L, Woodson BT. Lingual tonsillectomy using bipolar radiofrequency plasma excision. *Otolaryngol Head Neck Surg* 2006; **134**: 328–30.

Lingual thyroid

Ectopic thyroid tissue may rarely present in the mouth. Some 10% of cadaver tongues contain thyroid tissue, although clinical presentation is much less common. Typically, there is an asymptomatic, smooth-surfaced lump in the midline of the base of the tongue, between the sulcus terminalis and epiglottis at the site of the foramen caecum [1–5]. Occasionally, a lingual thyroid may produce dysphagia, cough, pain or, rarely, airways obstruction [1–11].

Not all lingual thyroid tissue is functional, and function tends to decline with age. Where thyroid-stimulating hormone levels are high, thyroid hormone supplements are indicated [1,12]. Malignant change is rare in lingual thyroid, although follicular carcinomas have been recorded. MRI and ^{99m}Tc pertechnate scintiscanning is important to ensure the presence of normal thyroid tissue in the neck [13–16] before considering treatment of a lingual thyroid by surgery or radioiodine [1,2,17,18].

References

1 Weider DJ, Parker W. Lingual thyroid. Review, case reports and therapeutic guidelines. *Ann Otol Rhinolaryngol* 1977; **86**: 841–5.

2 Jones JAH. Lingual thyroid. *Br J Oral Surg* 1986; **24**: 58–62.

3 Scott PM, Soo G, van Hasselt CA, Kew J. Lingual thyroid in a young woman. *Hong Kong Med J* 1997; **3**: 111.

4 Andrieux S, Douillard C, Nocaudie M *et al*. Lingual thyroid. A case report. *Ann Endocrinol* 2001; **62**: 538–41.

5 Ramzisham AR, Somasundarum S, Nasir ZM. Lingual thyroid—a lesson to learn. *Med J Malaysia* 2004; **59**: 533–4.

6 Oppenheimer R. Lingual thyroid associated with chronic cough. *Otolaryngol Head Neck Surg* 2001; **125**: 433–4.

7 Buckland RW, Pedley J. Lingual thyroid: a threat to the airway. *Anaesthesia* 2000; **55**: 1103–5.

8 Palmer JH, Ball DR. Lingual thyroid: another potential airway threat. *Anaesthesia* 2001; **56**: 386.

9 Koch CA, Picken C, Clement SC, Azumi N, Sarlis NJ. Ectopic lingual thyroid: an otolaryngologic emergency beyond childhood. *Thyroid* 2000; **10**: 511–4.

10 Gallo A, Leonetti F, Torri E *et al*. Ectopic lingual thyroid as unusual cause of severe dysphagia. *Dysphagia* 2001; **16**: 220–3.

11 Basaria S, Westra WH, Cooper DS. Ectopic lingual thyroid masquerading as thyroid cancer metastases. *J Clin Endocrinol Metab* 2001; **86**: 392–5.

12 Benhammou A, Bencheikh R, Benbouzid MA *et al*. Ectopic lingual thyroid. *B-ENT* 2006; **2**: 121–2.

13 Cappelli G, Gandossi E, Cumetti D *et al*. Ectopic lingual thyroid tissue and acquired hypothyroidism: case report. *Ann Endocrinol* 2006; **67**: 245–8.



Fig. 69.22 Multiple neuromas of the lips and tongue in a patient with multiple endocrine neoplasia syndrome (type 2). (Courtesy of Dr M. Hartog, Bristol Royal Infirmary, Bristol, UK.)

14 Aktolun C, Demir H, Berk F, Metin Kir K. Diagnosis of complete ectopic lingual thyroid with Tc-99m pertechnetate scintigraphy. *Clin Nucl Med* 2001; **26**: 933–5.
15 Takashima S, Ueda M, Shibata A *et al*. MR imaging of the lingual thyroid. Comparison to other submucosal lesions. *Acta Radiol* 2001; **42**: 376–82.
16 Uluq T, Ulubil SA, Alagol F. Dual ectopic thyroid: report of a case. *J Laryngol Otol* 2003; **117**: 574–6.
17 Danner C, Bodenner D, Breau R. Lingual thyroid: iodine 131: a viable treatment modality revisited. *Am J Otolaryngol* 2001; **22**: 276–81.
18 Park HM, Gupta S, Skierczynski P. Radioiodine-131 therapy for lingual thyroid. *Thyroid* 2003; **13**: 607.

Multiple mucosal neuroma syndrome

The syndrome of multiple endocrine neoplasia (MEN) type 2b (also called type 3) is inherited as an autosomal dominant, although new cases often arise sporadically. The gene locus is on chromosome 10.

MEN2b is characterized by medullary carcinoma of the thyroid and phaeochromocytoma, in association with multiple mucosal neuromas and an abnormal phenotype—a striking facial appearance, with thick, slightly everted lips that usually have a slightly bumpy surface due to multiple neuromas [1–3]. These are actually mucosal and submucosal hamartomatous proliferations of nerve axons, Schwann cells and ganglion cells.

Lesions may also involve the tongue and commissures but are less frequent on the buccal mucosa, gingivae, palate, pharynx or larynx (Fig. 69.22). Ganglioneuromatosis may also occur throughout the gastrointestinal tract, and this may result in constipation or megacolon [4,5]. Ocular changes include yellowish masses on the conjunctivae, thickened corneal nerves and keratitis due to decreased tear production [5,6].

Most patients have an asthenic marfanoid habitus, with high arched palate, pectus excavatum, arachnodactyly and kyphoscoliosis, but the lens subluxation and cardiovascular abnormalities of Marfan's syndrome are not present [7–11].

References

1 Brown RS, Colle F, Tashjian AH. The syndrome of multiple endocrine neoplasia and medullary thyroid carcinoma in childhood: importance of recognition of the phenotype. *J Pediatr* 1975; **86**: 77–83.
2 Casino AJ, Sciubba J, Ohri JL *et al*. Oral–facial manifestations of the multiple endocrine neoplasia syndrome. *Oral Surg* 1981; **51**: 516–23.
3 Baykal C, Buyukbabani N, Boztepe H, Barhamani N, Yazkanaglu KD. Multiple cutaneous neuromas and macular amyloidosis associated with medullary thyroid carcinoma. *J Am Acad Dermatol* 2007; **56**: S33–7.
4 Carney JA, Go VLW, Sizemore GW *et al*. Alimentary tract ganglioneuromatosis: a major component of the syndrome of multiple endocrine neoplasia. *N Engl J Med* 1976; **295**: 1287–91.
5 Schenberg ME, Zajac JD, Lim-Tio S *et al*. Multiple endocrine neoplasia syndrome-type 2b. Case report and review. *Int J Oral Maxillofac Surgery* 1992; **21**: 110–4.
6 Colombo CD, Watson AG. Ophthalmological manifestations of the multiple endocrine neoplasia type 3 syndrome. *Can J Ophthalmol* 1976; **11**: 290–4.
7 Montgomery TB, Mandelstam P, Tachman ML. Multiple endocrine neoplasia type IIB: a description of several patients and review of the literature. *J Clin Hypertens* 1987; **3**: 31–49.
8 Ohishi M, Ishii T, Shiratsychi H, Tashiro H. Mucosal endocrine neoplasia type 3: three cases with mucosal neuromata. *Br J Oral Maxillofac Surg* 1990; **28**: 317–21.
9 Rashid R, Khairi MRA, Dexter RN. Mucosal neuroma pheochromocytoma and medullary thyroid carcinoma: multiple endocrine neoplasia Type III. *Medicine* 1975; **54**: 89–112.
10 Schimke RN. Multiple endocrine adenomatosis syndromes. *Adv Intern Med* 1976; **21**: 249–65.
11 Ohta M, Tokuda Y, Suzuki Y *et al*. A case of multiple endocrine neoplasia type 2B. *Jpn J Clin Oncol* 1997; **27**: 268–73.

Other congenital anomalies

Ankyloglossia

Ankyloglossia, or tongue-tie, is an uncommon and typically isolated anomaly in which the lingual fraenum is tight and the tongue cannot be fully protruded [1,2].

There may be a family history and sometimes deviation of the epiglottis or larynx [3]. The association of cleft palate with ankyloglossia is inherited as a semi-dominant, X-linked disorder previously described in several large families of different ethnic origins and related to chromosome Xq21: the T-box transcription factor gene *TBX22* is mutated [4–6].

Speech is not usually affected in patients with ankyloglossia but the ability to suckle [7] and to cleanse the buccal sulcus with the tongue may be, and there can be effects on jaw development [8]. If necessary, surgery to the fraenum will relieve ankyloglossia [2,9,10].

References

1 Kern I. Tongue tie. *Med J Aust* 1991; **155**: 33–4.
2 Heller J, Gabbay J, O'Hara C, Heller M, Bradley JP. Improved ankyloglossia correction with four-flap Z-frenuloplasty. *Ann Plast Surg* 2005; **54**: 623–8.
3 Mukai S, Mukai C, Asaoka K. Ankyloglossia with deviation of the epiglottis and larynx. *Ann Otol Rhinol Laryngol* 1991; **100**: 3–19.
4 Braybrook C, Doudney K, Marcano AC *et al*. The T-box transcription factor gene TBX22 is mutated in X-linked cleft palate and ankyloglossia. *Nat Genet* 2001; **29**: 179–83.
5 Braybrook C, Warry G, Howell G *et al*. Physical and transcriptional mapping of the X-linked cleft palate and ankyloglossia (CPX) critical region. *Hum Genet* 2001; **108**: 537–45.
6 Chaabouni M, Smaoui N, Benneji N *et al*. Rad RMutation analysis of TBX22 reveals new mutation in Tunisian CPX family. *Clin Dysmorphol* 2005; **14**: 23–5.
7 Notestine GE. The importance of the identification of ankyloglossia (short lingual frenulum) as a cause of breast feeding problems. *J Hum Lact* 1990; **6**: 113–5.



Fig. 69.23 Fissured or scrotal tongue.

8 Defabianis P. Ankyloglossia and its influence on maxillary and mandibular development. (A seven year follow-up case report.) *Funct Orthod* 2000; **17**: 25–33.
9 Messner AH, Lalakea ML. Ankyloglossia: controversies in management. *Int J Pediatr Otorhinolaryngol* 2000; **54**: 123–31.
10 Kotlow LA. Ankyloglossia (tongue-tie): a diagnostic and treatment quandary. *Quintessence Int* 1999; **30**: 259–62.

Fissured tongue

Fissured tongue (plicated or scrotal tongue) is a common condition affecting more than 5% of the population [1,2]. The cause is unclear, but it is often accompanied by geographical tongue (Fig. 69.23).

Patients with Down's syndrome often have a fissured tongue and it is a feature of the rare Melkersson–Rosenthal syndrome comprising recurrent orofacial swelling, facial palsy and plicated tongue.

References

1 Kullaa-Mikkonen A, Sorvari T, Kotilainen R *et al*. Morphological variations on the dorsal surface of the human tongue. *Proc Finn Dent Soc* 1985; **81**: 104–10.
2 Rioboo-Crespo Mdel R, Planells-del Pozo P, Rioboo-Garcia R. Epidemiology of the most common oral mucosal diseases in children. *Med Oral Patol Oral Cir Bucal* 2005; **10**: 376–87.

Oral hair

Oral hair is a rare, innocuous anomaly [1,2], not to be confused with hairy tongue (see p. 69.93).

References

1 Baughman RA, Heidrich PD. The oral hair: an extremely rare phenomenon. *Oral Surg* 1980; **49**: 530–1.
2 Humeniuk HM, Burns RA, Shelley ED, Weaver JR. Oral mucosal hair: an ectodermal anomaly. *J Am Acad Dermatol* 1986; **15**: 1301–2.

Various orocutaneous syndromes

Cleft lip

Cleft lip and/or palate are the most common congenital craniofacial abnormalities. Cleft lip occurs in about 1 per 1000 white-skinned neonates. The prevalence is higher in oriental neonates (about 1.7 per 1000 births) and lower in black neonates (approximately 1 per 2500 births) and appears reduced if women take multivitamins containing folic acid early in pregnancy [1,2]. Clefts are often accompanied by impaired facial growth, dental anomalies, speech disorders, poor hearing and psychosocial problems [3,4]. Clefts can be seen in over 300 different syndromes [5,6].

Cleft lip is not always complete (i.e. extending into the nostril). A cleft may involve only the upper lip or may extend to involve the nostril and the hard and soft palates. In about 9% of the cases, the cleft is associated with skin bridges or Simonart's bands.

Isolated cleft lip may be unilateral or bilateral (approximately 20%). When unilateral, the cleft is more common on the left side (about 70%).

Lips are more frequently cleft bilaterally (approximately 25%) when combined with cleft palate. Cleft lip and palate is more common in men. Cleft lip and palate comprises about 50% of the cases, with cleft lip and isolated cleft palate each comprising about 25%. About 85% of bilateral cleft lips and 70% of unilateral cleft lips are associated with cleft palate. One subgroup have cleft lip and palate with median facial dysplasia and cerebrofacial malformations [7,8], others with laryngotracheal oesophageal clefts (Opitz–Firas or G syndrome) or cranial asymmetry (Opitz or B syndrome) [9,10].

Clefts in the middle of the upper lip may be true or false. True median clefts have been described in association with bifid nose and ocular hypertelorism. Other cases of true median labial cleft are associated with polydactyly or other digital anomalies, constituting an autosomal recessive trait called *orofaciodigital syndrome II*.

Pseudocleft of the middle of the upper lip may occur in *orofaciodigital syndrome I*. A somewhat similar central defect, but of mild degree, is seen in chondroectodermal dysplasia (Ellis–van Creveld syndrome). Clefts in the lower lip are rare and usually median but may involve the mandible and sometimes the tongue. Management of cleft lip is discussed elsewhere [11–14].

References

1 Shaw GM, Lammer EJ, Wasserman CR *et al.* Risks of orofacial clefts in children born to women using multivitamins containing folic acid periconceptionally. *Lancet* 1995; **346**: 393–6.
2 Wilcox AJ, Lie RT, Solvoll K *et al*. Folic acid supplements and risk of facial clefts: national population based case-control study. *BMJ* 2007; **334**: 464.
3 Habel A, Sell D, Mars M. Management of cleft lip and palate. *Arch Dis Child* 1996; **74**: 360–6.
4 Amarlal D, Muthu MS, Siva Kumar N. Root development of permanent lateral incisor in cleft lip and palate children: A radiographic study. *Indian J Dent Res* 2007; **18**: 82–6.
5 Cohen MM, Bankier A. Syndrome delineation involving orofacial clefting. *Cleft Palate J* 1991; **28**: 119–20.
6 Ghassibe M, Bayet M, Revencu N *et al*. Orofacial clefting: update on the role of genetics. *B-ENT* 2006; **2** Suppl 4: 20–4.
7 Noordhoff MS, Huang C-S, Lo L-J. Median facial dysplasia in unilateral and bilateral cleft lip and palate: a subgroup of median cerebrofacial malformations. *Plast Reconstr Surg* 1993; **91**: 966–1005.
8 Schultze BR, Tariverdian G, Komposch G, Stellzig A. Misclassification risk of patients with bilateral cleft lip and palate and manifestations of median facial dysplasia: A new variant of del(22q11.2) syndrome? *Am J Med Genet* 2001; **99**: 280–5.
9 Bershof JF, Guyuron B, Olsen MM. G syndrome: a review of the literature and a case report. *J Craniomaxillofac Surg* 1992; **20**: 24–7.

10 Bohring A, Oudeslujis GG, Grange DK, Zampino G, Thierry P. New cases of Bohring-Opitz syndrome, update, and critical review of the literature. *Am J Med Genet A* 2006; **15**: 1257–63.
11 Kaufman FL. Managing the cleft lip and palate patient. *Pediatr Clin North Am* 1991; **38**: 1127–47.
12 Melnick J. Cleft lip with or without cleft palate. *Can Dent Assoc J* 1986; **14**: 92–8.
13 Sommerlad BC. Surgery of the cleft lip and nose—the GOStA approach. *B-ENT* 2006; **2** Suppl 4: 29–31.
14 Tollefson TT, Gere RR. Presurgical cleft lip management: nasal alveolar molding. *Facial Plast Surg* 2007; **23**: 113–22.

Cowden's syndrome (see Chapter 15)

Synonym
- Multiple hamartoma syndrome

Cowden's syndrome may be associated with the *PTEN* gene [1] and multiple hamartomas [2,3]. Oral mucosal lesions may be found in the presence or absence of cutaneous stigma [3–9]. The oral lesions are typically smooth, pink or whitish benign fibromas found especially on the palatal, gingival and labial mucosae. Oral squamous carcinoma is a rare complication [10]. There may be overlap with Bannayan–Riley–Ruvalcaba syndrome [11–13].

Treatment with acitretin may lead to regression of the hypertrophic lesions of the lip and mouth [14].

References

1 Kato N, Kimura K, Sugawara H *et al*. Germline mutation of the PTEN gene in a Japanese patient with Cowden's disease. *Int J Oncol* 2001; **18**: 1017–22.
2 Cohen MM Jr. Some neoplasms and some hamartomatous syndromes: genetic considerations. *Int J Oral Maxillofac Surg* 1998; **27**: 363–9.
3 Wright DD, Whitney J. Multiple hamartoma syndrome (Cowden's syndrome): case report and literature review. *Gen Dent* 2006; **54**: 417–9.
4 Rosenberg-Gertzman CB, Clark M, Gaston B. Multiple hamartoma and neoplasia syndrome (Cowden's syndrome). *Oral Surg* 1980; **49**: 314–6.
5 Swart JGN, Lekkas C, Allard RHB. Oral manifestations in Cowden's syndrome. *Oral Surg* 1985; **59**: 264–8.
6 Porter SR, Cawson RA, Scully C, Eveson JW. Multiple hamartoma syndromes presenting with oral lesions. *Oral Surg* 1996; **82**: 295–301.
7 Almenar Beso R, Bagan Sebastian JV, Milian Masanet MA, Jimenez Soriano Y. Cowden syndrome: clinical case presentation with oral lesions. *An Med Interna* 2001; **18**: 426–8.
8 Chaudhry SI, Shirlaw PJ, Morgan PR, Challacombe SJ. Cowden's syndrome (multiple hamartoma and neoplasia syndrome): diagnostic dilemmas in three cases. *Oral Dis* 2000; **6**: 248–52.
9 Leao JC, Batista V, Guimareas PB, Belo J, Porter SR. Cowden's syndrome affecting the mouth, gastrointestinal, and central nervous system: a case report and review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005; **99**: 569–72.
10 Shapiro SD, Lambert WC, Schwartz RA. Cowden's disease: a marker for malignancy. *Int J Dermatol* 1988; **27**: 232–7.
11 Starink TM, van Der Veen JP, Arwert F. The Cowden syndrome: a clinical and genetic study in 21 patients. *Clin Genet* 1986; **29**: 222–33.
12 Perriard J, Saurat JH, Harms M. An overlap of Cowden's disease and Bannayan–Riley–Ruvalcaba syndrome in the same family. *J Am Acad Dermatol* 2000; **42**: 348–50.
13 Lachlan KL, Lucassen Am, Bunyan DJ, Temple IK. Cowden Syndrome and Bannayan-Riley-Ruvalcaba syndrome represent one condition with variable expression and age-related penetrance: a clinical study of 42 individuals with PTEN mutations. *J Med Genet* 2007; **44**: 579–85.
14 Cnudde F, Boulard F, Muller P, Chevallier J, Teron-Abou B. Cowden disease: treatment with acitretine. *Ann Dermatol Vénéréol* 1996; **123**: 739–41.

De Lange syndrome

Synonym
- Amsterdam dwarf

Classical Brachmann or Cornelia de Lange syndrome presents with a striking face, pronounced growth and learning disability, and variable limb deficiencies. Most cases are sporadic [1,2]. About 50% of patients have been found to have heterozygous mutations in the NIPBL gene with some cases being caused by mutations in the X-linked *SMC1L1* gene [3]. A long philtrum and crescent-shaped mouth with down-turned corners is typical [4–6].

The characteristic face of classical de Lange syndrome is present at birth and changes little throughout life, although there is some lengthening of the face with age and the jaw becomes squared.

References

1 Klein AD, Krantz AD, Sommer A *et al*. Cornelia de Lange syndrome: Clinical review, diagnostic and scoring systems, and anticipatory guidance. *Am J Med Genet A* 2007; **143A**: 1287–96.
2 Borck G, Zahrate M, Bonnefont JP. Incidence and clinical features of X-linked Cornelia de Lange syndrome due to SMC1L1 mutations. *Hum Mutat* 2007; **28**: 205–6.
3 Schoumans J, Wincent J, Barbaro M *et al*. Comprehensive mutational analysis of a cohort of Swedish Cornelia de Lange syndrome patients. *Eur J Hum Genet* 2007; **15**: 143–9.
4 Allanson JE, Hennekam RC, Ireland M. De Lange syndrome: subjective and objective comparison of the classical and mild phenotypes. *J Med Genet* 1997; **34**: 645–50.
5 Scully C. The de Lange syndrome. *J Oral Med* 1980; **35**: 32–4.
6 Barrett AW, Griffiths MJ, Scully C. The Cornelia de Lange syndrome in association with a bleeding tendency. *Int J Oral Maxillofac Surg* 1993; **22**: 171–2.

Double lip

Double lip is a developmental anomaly usually involving the upper lip. A fold of redundant tissue is found on the inner aspect of the involved lip [1,2]. It is reported to be common among some groups of Africans [3].

Double lip may occur alone or in association with other anomalies. The association with blepharochalasis (laxity of the upper eyelid skin) and sometimes non-toxic thyroid enlargement is known as *Ascher's syndrome* [4] (see Chapter 45).

Double lip requires no treatment except for cosmetic purposes.

References

1 Beumeir P, Weinberg A, Neuman A *et al*. Congenital double lip: report of five cases and a review of the literature. *Ann Plast Surg* 1992; **28**: 180–2.
2 Chidzonga MM, Mahomva L. Congenital double lower lip: report of a case. *Int J Paediatr Dent* 2006; **16**: 448–9.
3 Sawyer DR, Taiwo EO, Mosadomi A. Oral anomalies in Nigerian children. *Community Dent Oral Epidemiol* 1984; **12**: 269–33.
4 Halling F, Sandrock D, Merten HA *et al*. Das Ascher Syndrom. *Dtsch Z Mund Kiefer Gesichtschrift* 1991; **15**: 440–4.

Down's syndrome

The incidence of angular cheilitis is increased in people with Down's syndrome, caused by an increased level of *Staphylococcus aureus* and *Candida albicans*, possibly because of the immune defects [1–3]. Lip fissures may appear intermittently over a period of years or be intractable and long-standing (see p. 69.17).

References

1 Butterworth T, Leoni EP, Beerman H. Cheilitis of mongolism. *J Invest Dermatol* 1960; **35**: 347–52.
2 Scully C, Van Bruggen W, Dios P, Porter S, Davison MF. Down syndrome: lip lesions (angular stomatitis and fissuses) and *Candida albicans*. *Br J Dermatol* 2002; **147**: 37–40.
3 Carlstedt K, Krekmanova L, Dahllof G *et al*. Oral carriage of *Candida* species in children and adolescents with Down syndrome. *Int J Paediatr Dent* 1996; **6**: 95–100.

Erythropoietic protoporphyria

Erythropoietic protoporphyria is an autosomal dominant disorder of ferrochelatase, resulting in inhibition of the conversion of protoporphyrin to haem.

Shallow elliptical or linear scars around the lips and linear perioral furrowing (pseudorhagades) are subtle changes that are pathognomonic when observed in children [1,2].

References

1 Gross U, Frank M, Doss MO. Hepatic complications of erythropoietic protoporphyria. *Photodermatol Photoimmunol Photomed* 1998; **14**: 52–7.
2 Lim HW, Murphy GM. The porphyrias. *Clin Dermatol* 1996; **14**: 375–87.

Focal mucinosis

Oral focal mucinosis is an uncommon clinicopathological entity considered to be the oral counterpart of cutaneous focal mucinosis and/or cutaneous myxoid cyst. The nature of the lesion is unclear but may be the result of fibroblastic overproduction of hyaluronic acid. It comprises a clinically elevated mass with a histological picture of localized areas of myxomatous connective tissue. Most of the lesions affect the gingiva and alveolar mucosa [1–5].

All these diseases share distinct histological features. There is an increased number of fibroblast-like cells in early lesions, whereas these are diminished or predominantly at the margin in advanced ones. The myxomatous areas show slight to absent reticulum and elastic fibres, and collagen fibres are fragmented and replaced by variable amounts of mucin. Vimentin is consistently present and correlates with the number of fibroblast-like cells, these being negative for S-100 protein, Leu7, desmin and alpha-SMA [6].

References

1 Saito I, Ide F, Enomoto T, Kudo I. Oral focal mucinosis. *J Oral Maxillofac Surg* 1985; **43**: 372–4.
2 Buchner A, Merrell PW, Leider AS, Hansen LS. Oral focal mucinosis. *Int J Oral Maxillofac Surg* 1990; **19**: 337–40.
3 Soda G, Baiocchini A, Bosco D, Nardoni S, Melis M. Oral focal mucinosis of the tongue. *Pathol Oncol Res* 1998; **4**: 304–7.
4 Aldred MJ, Talacko AA, Rulgancich K *et al*. Oral focal mucinosis: report of 15 cases and review of the literature. *Pathology* 2003; **35**: 393–6.
5 Takemura N, Fujji N, Tanaka T. Cutaneous focal mucinosis: a case report. *J Dermatol* 2005; **32**: 1051–4.
6 Wilk M, Schmoeckel C. Cutaneous focal mucinosis: a histopathological and immunohistochemical analysis of 11 cases. *J Cutan Pathol* 1994; **21**: 446–52.

Gardner syndrome (see Chapter 15)

Multiple jaw osteomas are a feature of Gardner syndrome of familial adenomatous polyposis coli [1,2]. Some 80% of patients with familial adenomatosis polyposis coli have osteomas and 30% have dental anomalies such as supernumerary or impacted teeth, or odontomes [3–13].

References

1 Gardner EJ. Familial polyposis coli and Gardner's syndrome: is there a difference? *Prog Clin Biol Res* 1983; **115**: 39–43.
2 Perniciaro C. Gardner's syndrome. *Dermatol Clin* 1995; **13**: 51–6.
3 Sondergaard JO, Bulow S, Jarvinen H *et al.* Dental anomalies in familial adenomatous polyposis coli. *Acta Odontol Scand* 1987; **45**: 61–3.
4 Wolfe J, Jarvinen HJ, Hietanen J. Gardner's dento-maxillary stigmas in patients with familial adenomatosis coli. *Br J Oral Maxillofac Surg* 1986; **24**: 410–6.
5 Cohen MM Jr. Perspectives on craniofacial asymmetry. VI. The hamartoses. *Int J Oral Maxillofac Surg* 1995; **24**: 195–200.
6 Takeuchi T, Takenoshita Y, Kubo K, Iida M. Natural course of jaw lesions in patients with familial adenomatosis coli (Gardner's syndrome). *Int J Oral Maxillofac Surg* 1993; **22**: 226–30.
7 Lew D, DeWitt A, Hicks RJ, Cavalcanti MG. Osteomas of the condyle associated with Gardner's syndrome causing limited mandibular movement. *J Oral Maxillofac Surg* 1999; **57**: 1004–9.
8 Yuasa K, Yonetsu K, Kanda S *et al*. Computed tomography of the jaws in familial adenomatosis coli. *Oral Surg Oral Med Oral Pathol* 1993; **76**: 251–5.
9 Jones K, Korzcak P. The diagnostic significance and management of Gardner's syndrome. *Br J Oral Maxillofac Surg* 1990; **28**: 80–4.
10 Ben Lagha N, Galeazzi JM, Chapireau D, Oxeda P, Bouhnik Y, Maman L. Surgical Management of Osteoma Associated With a Familial Gardner's Syndrome. *J Oral Maxillofac Surg* 2007; **65**: 1234–40.
11 Ramaglia L, Morgese F, Filippella M, Colao A. Oral and maxillofacial manifestations of Gardner's syndrome associated with growth hormone deficiency: case report and literature review. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; **103**: e30–4.
12 Daley TD, Armstrong JE. Oral manifestations of gastrointestinal diseases. *Can J Gastroenterol* 2007; **21**: 241–4.
13 Fonseca LC, Kodama NK, Nunes FC, Maciel PH, Fonseca FA, Roitberg M, de Oliveira JX, Cavalcanti MG. Radiographic assessment of Gardner's syndrome. *Dentomaxillofac Radiol* 2007; **36**: 121–4.

Gorlin's syndrome (see Chapter 52)

Synonym
- Naevoid basal cell carcinoma syndrome

Odontogenic keratocysts (primordial cysts) of the jaws are a prominent feature of Gorlin's syndrome [1–4]. The syndrome is caused by mutations in the Sonic Hedgehog *patched* gene, a tumour-suppressor gene [5]. A single point mutation in one *patched* allele may be responsible for the various malformations found in the syndrome [5–10]. Inactivation of both *patched* alleles results in the formation of tumours and cysts (basal cell carcinomas, odontogenic keratocysts and medulloblastomas) [5].

The keratocysts should be surgically removed but have a tendency to recur. There are also occasional reports of oral neoplasms, notably fibrosarcoma, ameloblastoma and squamous carcinoma [6–12].

References

1 Gorlin RJ. Nevoid basal-cell carcinoma syndrome. *Medicine* 1987; **66**: 98–113.
2 Mirowski GW, Liu AA, Parks ET, Caldemeyer KS. Nevoid basal cell carcinoma syndrome. *J Am Acad Dermatol* 2000; **43**: 1092–3.
3 Cohen MM. Nevoid basal cell carcinoma syndrome: molecular biology and new hypotheses. *Int J Oral Maxillofac Surg* 1999; **28**: 216–23.
4 Rao S, Arulselvi S, Gupta K, Arora R, Shrivastava D Nevoid basal cell carcinoma syndrome (Gorlin's syndrome): a case report. *Indian J Pathol Microbiol* 2006; **49**: 578–80.
5 Zedan W, Robinson PA, Markham AF, High AS. Expression of the Sonic Hedgehog receptor 'PATCHED' in basal cell carcinomas and odontogenic keratocysts. *J Pathol* 2001; **194**: 473–7.

6 MacIntyre DR, Hislop SWG, Ross JW *et al.* The basal cell naevus syndrome. *Dent Update* 1985; **12**: 630–5.
7 Myoung H, Hong SP, Hong SD *et al.* Odontogenic keratocyst: review of 256 cases for recurrence and clinicopathologic parameters. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001; **91**: 328–33.
8 Lo Muzio L, Nocini PF, Savoia A *et al.* Nevoid basal cell carcinoma syndrome. Clinical findings in 37 Italian affected individuals. *Clin Genet* 1999; **55**: 34–40.
9 Moos KF, Rennie JS. Squamous cell carcinoma arising in a mandibular keratocyst in a patient with Gorlin's syndrome. *Br J Oral Surg* 1987; **25**: 280–4.
10 Lo Muzio L, Nocini P, Bucci P *et al*. Early diagnosis of nevoid basal cell carcinoma syndrome. *J Am Dent Assoc* 1999; **130**: 669–74.
11 Maroto MR, Porras JL, Saez RS, de los Rios MH, Gonzalez LB. The role of the orthodontist in the diagnosis of Gorlin's syndrome. *Am J Orthod Dentofacial Orthop* 1999; **115**: 89–98.
12 Yilmaz B, Goldberg LH, Schechter NR, Kemp BL, Ruiz H. Basal cell nevus syndrome concurrent with adenoid cystic carcinoma of salivary gland. *J Am Acad Dermatol* 2003; **48**: S64–6.

Jacob's disease

Jacob's disease is a rare condition consisting of new joint formation between the coronoid process of the mandible and the inner aspect of the zygomatic arch [1,2].

References

1 de la Torre OE, Klok EV, Roig AM, Mommaerts MY, Ayats JP. Jacob's disease: report of two cases and review of the literature. *J Craniomaxillofac Surg* 2001; **29**: 372–6.
2 Capote A, Rodriguez FJ, Blasco A, Munoz MF. Jacob's disease associated with temporomandibular joint dysfunction: a case report. *Med Oral Patol Oral Cir Bucal* 2005; **10**: 210–4.

Kindler syndrome

Kindler syndrome is characterized by bulla formation, which starts at birth on areas of the skin that receive pressure and may lead to bilateral, incomplete syndactylies involving all web spaces [1–3].

Oral lesions may include atrophy of the buccal mucosa, trismus (an inability to fully open the mouth) and a form of desquamative gingivitis [4].

Histology shows classical features of poikiloderma, namely epidermal atrophy with flattening of the rete ridges, vacuolization of basal keratinocytes, pigmentary incontinence and mild dermal perivascularization. Ultrastructural studies demonstrate reduplication of the basal lamina with branching structures within the upper dermis and cleavage between the lamina densa and the cell membrane of the keratinocytes. Antibody against type VII collagen shows extensive broad bands with intermittently discontinuous and reticular staining at the dermal–epidermal junction.

References

1 Suga Y, Tsuboi R, Hashimoto Y, Yaguchi H, Ogawa H. Japanese case of Kindler syndrome. *Int J Dermatol* 2000; **39**: 284–6.
2 Kaviarasan PK, Prasad PV, Shrada, Viswanathan P. Kindler syndrome. *Indian J Dermatol Venereol Leprol* 2005; **71**: 348–50.
3 Burch JM, Fassihi H, Jones CA *et al*. Kindler syndrome: a new mutation and new diagnostic possibilities. *Arch Dermatol* 2006; **142**: 620–4.
4 Ricketts DNJ, Morgan CL, McGregor JM, Morgan PR. Kindler syndrome: a rare cause of desquamative lesions of the gingiva. *Oral Surg Oral Med Oral Pathol* 1997; **84**: 488–91.

Lip pits and sinuses

Dimples are common at the commissures. They should be distinguished from *commissural pits*, which are distinct, definite pits ranging from 1 to 4 mm in diameter and depth [1–3] present from infancy, often showing a familial tendency and probably determined by a dominant gene (Fig. 69.24). Their incidence is 1–20% in various population groups [2,4]; for example, in one series they were found in 12% of white people and 20% of black people [5]. Commissural pits are sometimes associated with aural sinuses or pits. Rarely, they may be infected and present as recurrent or refractory angular cheilitis.

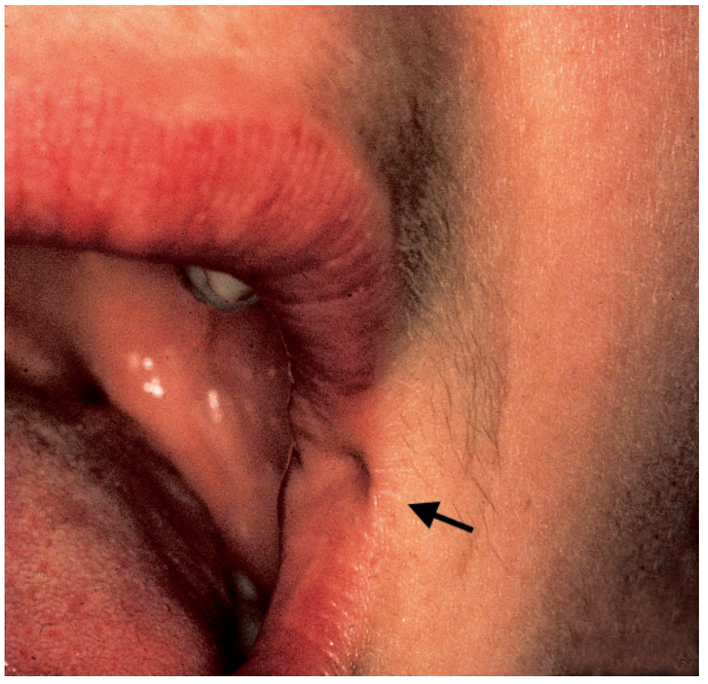


Fig. 69.24 Angular sinus (lip-pit), a congenital anomaly.

Congenital lip pits or sinuses are small, blind fistulae on the vermilion border [6]. They are usually bilateral and symmetrical, often just to one side of the philtrum. The pits may be up to 3–4 mm in diameter and up to 2 cm deep. They may communicate with underlying minor salivary glands. They may appear as isolated findings, but are often (67%) associated with cleft lip and/or palate (Van der Woude syndrome) [7–12]. This autosomal dominant syndrome [13,14] has a frequency of 1 in 75 000 to 1 in 100 000 in white populations (see Chapter 15).

Surgical removal may be indicated for cosmetic purposes.

References

1 Witkop CJ, Barros L. Oral and genetic studies of Chileans, 1960. I. Oral anomalies. *Am J Phys Anthropol* 1963; **21**: 15–24.
2 Sedano HO. Congenital oral anomalies in Argentinian children. *Community Dent Oral Epidemiol* 1975; **3**: 61–3.
3 Clementi M, Mammi I, Tenconi R. Family with branchial arch anomalies, hearing loss, ear and commissural lip pits, and rib anomalies. A new autosomal recessive condition: branchio-oto-costal syndrome? *Am J Med Genet* 1997; **68**: 91–3.
4 Everett FG, Wescott WB. Commissural lip pits. *Oral Surg Oral Med Oral Pathol* 1961; **14**: 202–9.
5 Baker B. Commissural lip pits. *Oral Surg* 1966; **21**: 56.
6 Watanabe Y, Igaku-Hakushi K, Otake K *et al.* Congenital fistulas of the lower lip. *Oral Surg Oral Med Oral Pathol* 1951; **4**: 709–22.
7 Van der Woude A. Fistula labii inferius congenita and its association with cleft lip and palate. *Am J Hum Genet* 1954; **6**: 244–56.

8 Gordon H, Davis D, Friedberg S. Congenital pits of the lower lip with cleft lip and palate. *S Afr Med J* 1969; **43**: 1275–9.
9 Rintala AE, Lahti AY, Gylling US. Congenital sinuses of the lower lip in connection with cleft lip and palate. *Cleft Palate J* 1970; **7**: 336–46.
10 Tan KL, Wong TT, Ong ES, Chiang SP. Congenital lip pits with cleft lip or palate. *J Singapore Paediatr Soc* 1971; **13**: 75–8.
11 Ziai MN, Benson AG, Djalilian HR. Congenital lip pits and van der Woude syndrome. *J Craniofac Surg* 2005; **16**: 930–2.
12 Kirzioglu Z, Erturk MS. Congenital lower lip pits (Van der Woude syndrome): report of a case. *J Contemp Dent Pract* 2006; **7**: 134–40.
13 Cervenka J, Gorlin RJ, Anderson VE. The syndrome of pits of the lower lip and cleft lip and/or palate. Genetic considerations. *Am J Hum Genet* 1967; **19**: 416–32.
14 Wang MK, Macomber WB. Congenital deformities of the lips. In: Converse MA, ed. *Reconstructive Plastic Surgery*. Philadelphia: Saunders, 1977: 1540–1.

Noonan's syndrome

Synonym
- Ullrich–Turner syndrome

Ullrich–Turner syndrome is caused by monosomy X or a structural abnormality of the second X chromosome. It is seen in females with a syndrome of short stature, sexual infantilism and a pattern of characteristic minor anomalies including pterygium colli. This syndrome was later called Noonan's syndrome, and it was shown that central giant cell lesions or cherubism of the jaws may be present [1–9]. Oral keratosis is sometimes seen [10].

References

1 Nirmal T, Muthu MS, Arranganal P. Noonan syndrome: a case report. *J Indian Soc Pedod Prev Dent* 2001; **19**: 77–9.
2 Betts NJ, Stewart JC, Fonseca RJ, Scott RF. Multiple central giant cell lesions with a Noonan-like phenotype. *Oral Surg Oral Med Oral Pathol* 1993; **76**: 601–7.
3 Addante RR, Breen GH. Cherubism in a patient with Noonan's syndrome. *J Oral Maxillofac Surg* 1996; **54**: 210–3.
4 van Damme PA, Mooren RE. Differentiation of multiple giant cell lesions, Noonan-like syndrome, and (occult) hyperparathyroidism. Case report and review of the literature. *Int J Oral Maxillofac Surg* 1994; **23**: 32–6.
5 Levine B, Skope L, Parker R. Cherubism in a patient with Noonan syndrome: report of a case. *J Oral Maxillofac Surg* 1991; **49**: 1014–8.
6 Cohen MM Jr, Gorlin RJ. Noonan-like/multiple giant cell lesion syndrome. *Am J Med Genet* 1991; **40**: 159–66.
7 Dunlap C, Neville B, Vickers RA, O'Neil D, Barker B. The Noonan syndrome/cherubism association. *Oral Surg Oral Med Oral Pathol* 1989; **67**: 698–705.
8 Jafarov T, Ferimazova N, Reichenberger E. Noonan-like syndrome mutations in PTPN11 in patients diagnosed with cherubism. *Clin Genet* 2005; **68**: 190–1.
9 Wolvius EB, de Lange J, Smeets EE *et al*. Noonan-like/multiple giant cell lesion syndrome: report of a case and review of the literature. *J Oral Maxillofac Surg* 2006; **64**: 1289–92.
10 Lucker GP, Steijlen PM. Widespread leucokeratosis in Noonan's syndrome. *Clin Exp Dermatol* 1994; **19**: 414–7.

Tuberous sclerosis (see Chapter 15)

Synonyms
- Epiloia
- Bourneville disease

Oral manifestations in tuberous sclerosis include pit-shaped enamel defects in both dentitions, and gingival fibromatosis [1–7] and rare instances of myxoma or desmoplastic fibroma [8,9].

References

1 Lygidakis NA, Lindenbaum RH. Oral fibromatosis in tuberous sclerosis. *Oral Surg* 1989; **68**: 725–8.
2 Scully C. The orofacial manifestations of tuberous sclerosis. *Oral Surg* 1977; **44**: 706–16.
3 Smith D, Porter SR, Scully C. Gingival and other oral manifestations in tuberous sclerosis. *Periodont Clin Invest* 1993; **15**: 13–8.
4 Weits-Binnerts JJ, Hoff M, van Grunsven MF. Dental pits in deciduous teeth: an early sign in tuberous sclerosis. *Lancet* 1982; **ii**: 1344–5.
5 Cutando A, Gil JA, Lopez J. Oral health management implications in patients with tuberous sclerosis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2000; **90**: 430–5.
6 Helling K, Flottmann T, Schmitt-Graff A, Scherer H. Manifestation of tuberous sclerosis in the ENT area. *HNO* 1996; **44**: 264–6.
7 Sparling JD, Hong CH, Brahim JS, Moss J, Darling MR. Oral findings in 58 adults with tuberous sclerosis complex. *J Am Acad Dermatol* 2007; **56**: 786–90.
8 Harrison MG, O'Neill ID, Chadwick BL. Odontogenic myxoma in an adolescent with tuberous sclerosis. *J Oral Pathol Med* 1997; **26**: 339–41.
9 Miyamoto Y, Satomura K, Rikimaru K, Hayashi Y. Desmoplastic fibroma of the mandible associated with tuberous sclerosis. *J Oral Pathol Med* 1995; **24**: 93–6.

Van der Woude syndrome

Van der Woude syndrome is a rare autosomal dominant syndrome [1] in which lower lip pits are associated with cleft lip and/or palate [2–7], sometimes seen with syndactyly or talipes equinovarus.

References

1 Cervenka J, Gorlin RJ, Anderson VE. The syndrome of pits of the lower lip and cleft lip and/or palate. Genetic considerations. *Am J Hum Genet* 1967; **19**: 416–32.
2 Van der Woude A. Fistula labii inferius congenita and its association with cleft lip and palate. *Am J Hum Genet* 1954; **6**: 244–56.
3 Gordon H, Davis D, Friedberg S. Congenital pits of the lower lip with cleft lip and palate. *S Afr Med J* 1969; **43**: 1275–9.
4 Rintala AE, Lahti AY, Gylling US. Congenital sinuses of the lower lip in connection with cleft lip and palate. *Cleft Palate J* 1970; **7**: 336–46.
5 Vignale R, Araujo J, Pascal G *et al*. Van der Woude syndrome: a case report. *Pediatr Dermatol* 1998; **15**: 459–63.
6 Ziai MN, Benson AG, Djalilian HR. Congenital lip pits and van der Woude syndrome. *J Craniofac Surg* 2005; **16**: 930–2.
7 Kirzioglu Z, Erturk MS. Congenital lower lip pits (Van der Woude syndrome): report of a case. *J Contemp Dent Pract* 2006; **7**: 134–40.

Von Recklinghausen's neurofibromatosis

Neurofibromatosis (NF) consists of distinct variants due to *NF* gene mutations [1]: type I (NF-I), often referred to as von Recklinghausen's disease or generalized neurofibromatosis; and type II (NF-II), a much less common disorder of bilateral acoustic schwannomas. The incidence of head and neck manifestations in patients with NF varies between 14 and 37%. Multiple neurofibromas may occur as a feature of NF; cosmetic lesions include pigmentary changes (café-au-lait spots) [2–6].

Neurofibromas may be seen mainly in NF-I. Neurofibromas may also be seen in NF-II, but bilateral acoustic neuromas are the hallmark of this disease and neurilemmomas and acoustic neuromas are the predominant neural tumours. Neurofibromas may also be part of the MEN syndrome (see Chapter 62).

Oral lesions are not uncommon in von Recklinghausen's generalized NF [7–16]. About two-thirds of patients have intraoral neurofibromas affecting predominantly the tongue, lips, buccal mucosa or palate. Neurofibroma represents a benign overgrowth

of all elements of a peripheral nerve (axon cylinder, Schwann cells and fibrous connective tissue), arranged in a variety of patterns. Enlarged fungiform papillae are found in about 50% of patients. About 60% of patients have radiographic evidence of disease, especially enlargement of the inferior alveolar canal or foramen, or branching of the canal.

Neurofibromas may occur multiply as a feature of NF but only rarely undergo sarcomatous change [17]. Other rare, malignant tumours include nerve sheath tumour [18], triton tumour [19] and Merkel cell carcinoma [20].

References

1 Buske A, Gewies A, Lehmann R *et al.* Recurrent NF1 gene mutation in a patient with oligosymptomatic neurofibromatosis type 1 (NF1). *Am J Med Genet* 1999; **86**: 328–30.
2 Scully C. Orofacial manifestations of the neurodermatoses. *J Dent Child* 1980; **47**: 255–60.
3 Keutel C, Vees B, Krimmel M, Cornelius CP, Schwenzer N. Oral, facial and cranial manifestations of von Recklinghausen neurofibromatosis (NF). *Mund Kiefer Gesichtschir* 1997; **1**: 268–71.
4 Sobol SE, Tewfik TL, Ortenberg J. Otolaryngologic manifestations of neurofibromatosis in children. *J Otolaryngol* 1997; **26**: 13–9.
5 Baart JA, van Hagen JM. Syndromes 18. Von Recklinghausen's disease. *Ned Tijdschr Tandheelkd* 2000; **107**: 57–9.
6 D'Ambroso JA, Langlais RP, Young RS. Jaw and skull changes in neurofibromatosis. *Oral Surg* 1988; **66**: 391–6.
7 Zuccoli G, Ferrozzi F, Tognini G, Troiso A. Enlarging tongue masses in neurofibromatosis type 1: MR findings of two cases. *Clin Imaging* 2001; **25**: 268–71.
8 Bekisz O, Darimont F, Rompen EH. Diffuse but unilateral gingival enlargement associated with von Recklinghausen neurofibromatosis: a case report. *J Clin Periodontol* 2000; **27**: 361–5.
9 Holtzman L. Radiographic manifestation and treatment considerations in a case of multiple neurofibromatosis. *J Endod* 1998; **24**: 442–3.
10 Allen CM, Miloro M. Gingival lesion of recent onset in a patient with neurofibromatosis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1997; **84**: 595–7.
11 Curtin JP, McCarthy SW. Perineural fibrous thickening within the dental pulp in type 1 neurofibromatosis: a case report. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1997; **84**: 400–3.
12 Van Damme PA, Freihofer HP, De Wilde PC. Neurofibroma in the articular disc of the temporomandibular joint: a case report. *J Craniomaxillofac Surg* 1996; **24**: 310–3.
13 Geist JR, Gander DL, Stefanac SJ. Oral manifestations of neurofibromatosis types I and II. *Oral Surg Oral Med Oral Pathol* 1992; **73**: 376–82.
14 Gutteridge DL Neurofibromatosis: an unusual oral manifestation. *Br Dent J* 1991; **170**: 303–4.
15 Holtzman L. Radiographic manifestation and treatment considerations in a case of multiple neurofibromatosis. *J Endod* 1998; **24**: 442–3.
16 Kunha KS, Barboza EP, Dias EP, Oliviera FM. Neurofibromatosis type I with periodontal manifestation. A case report and literature review. *Br Dent J* 2004; **196**: 457–60.
17 Neville BW, Hann J, Narang R, Garen P. Oral neurofibrosarcoma associated with neurofibromatosis type I. *Oral Surg Oral Med Oral Pathol* 1991; **72**: 456–61.
18 Muraki Y, Tateishi A, Tominaga K *et al*. Malignant peripheral nerve sheath tumour in the maxilla associated with von Recklinghausen's disease. *Oral Dis* 1999; **5**: 250–2.
19 Shotton JC, Stafford ND, Breach NJ. Malignant triton tumour of the palate: a case report. *Br J Oral Surg* 1988; **26**: 120–3.
20 Antoniades K, Giannouli T, Kaisaridou D. Merkel cell carcinoma in a patient with Recklinghausen neurofibromatosis. *Int J Oral Maxillofac Surg* 1998; **27**: 213–4.

Xeroderma pigmentosum

Squamous cell carcinoma of the lip may arise in patients with xeroderma pigmentosum [1–3] and therefore it is crucial to institute sun protection. Oral retinoids such as etretinate or isotretinoin may be of prophylactic value [4–6]. Topical 5-fluorouracil or surgery may be used to treat potentially malignant lesions (see Actinic cheilitis, p. 69.123).

References

1 Yagi KI, Prabhu S. Carcinoma of the lip in xeroderma pigmentosum. A case report. *J Oral Med* 1983; **38**: 97–8.
2 Laskaris G, Stavrou A. [Xeroderma pigmentosum with carcinoma of the lower lip.] *Hell Stomatol Chron* 1984; **28**: 107–9.
3 Chidzonga MM. Lip cancer in Zimbabwe. Report of 14 cases. *Int J Oral Maxillofac Surg* 2005; **34**: 149–51.
4 Berth-Jones J, Graham-Brown RAC. Xeroderma pigmentosum variant: response to etretinate. *Br J Dermatol* 1990; **122**: 559–61.
5 Kraemer KH, DiGiovanna JJ, Moshell AN. Prevention of skin cancer in xeroderma pigmentosum with the use of oral isotretinoin. *N Engl J Med* 1988; **318**: 1630–7.
6 Campbell RM, DiGiovanni JJ. Skin cancer chemoprevention with systemic retinoids: an adjunct in the management of selected high-risk patients. *Dermatol Ther* 2006; **19**: 306–14.

Acquired disorders of the oral mucosa or lips

This section discusses the main acquired causes of mouth ulcers, other causes of oral soreness, white, pigmented or red lesions, and lumps and swellings. Further detail is available elsewhere [1–5].

References

1 Neville BW, Damm DD, Allen CM, Bouquot JE. *Oral and Maxillofacial Pathology*. Philadelphia: Saunders, 1995.
2 Millard HD, Mason DK, eds. *Perspectives on 1998 World Workshop on Oral Medicine.* Michigan: University of Michigan, 2000.
3 Scully C. *ABC of Oral Health.* London: BMJ Books, 2001.
4 Scully C. *Handbook of Oral Disease: Diagnosis and Management*, 2nd edn. London: Martin Dunitz, 2007.
5 Scully C, Flint S, Porter SR, Moos K. *Oral and Maxillofacial Diseases*. London: Martin Dunitz, 2004.

Mouth ulcers

The causes of mouth ulcers are diverse (Tables 69.10 & 69.13), partly because lesions such as vesicles rapidly break down in the mouth as a result of trauma, moisture and infection. Ulcers are usually caused by the following.

1 Local factors
2 Recurrent aphthous stomatitis
3 Neoplasms
4 Systemic conditions
  (a) Haematological
  (b) Gastroenterological
  (c) Dermatological

Table 69.13 Causes of mouth ulcers (see also Table 69.10).

Local causes (e.g. trauma)
Recurrent aphthae (and Behçet's syndrome)
Malignant neoplasms
Ulcers associated with systemic disease
Drugs
Irradiation of the oral mucosa
Disorders of uncertain pathogenesis

(d) Infective
(e) Vasculitis
(f) Iatrogenic
(g) Uncertain causes

5 Drugs.

Mouth ulcers of local aetiology

It is surprising that oral ulceration due to local factors is not more frequent. Accidental cheek biting or facial trauma may cause ulceration in any individual; the history is usually quite clear and a single ulcer of short duration (5–10 days) is present. Ulceration due to biting an anaesthetized lower lip or tongue following a dental local analgesic injection is a fairly common problem in young children.

Orthodontic appliances or, more commonly, dentures (especially if new) are responsible for many traumatic oral ulcers. These ulcers are usually clearly related to the appliance and have been a problem in the care of cleft-palate patients [1]. Chronic trauma may cause a well-defined ulcer with a whitish, keratotic halo [2].

The possibility of some other aetiology for ulcers of apparently local cause should always be borne in mind. Riga–Fede disease consists of ulcers of the lingual frenum in neonates with natal lower incisors [3]. Child abuse may cause ulcers, especially over the upper labial fraena. Self-mutilation may be seen in some psychologically disturbed patients [4,5], patients with learning disability, individuals with sensory impairment, and in Lesch–Nyhan syndrome [6–11]. Oral purpura or ulceration may be seen on the lingual fraenum or palate due to cunnilingus or fellatio respectively [12]. Other local causes of ulceration include thermal burns, especially of the tongue and palate (e.g. 'pizza burn'—now more common with microwave oven use), chemical burns from the holding of medicaments or drugs (e.g. aspirin or cocaine) against the mucosa [13,14], and irradiation mucositis.

Prognosis. Most ulcers of local cause heal spontaneously within 7–14 days if the cause is removed.

Treatment. Maintenance of good oral hygiene and the use of hot saline mouthbaths and 0.2% aqueous chlorhexidine gluconate mouthwash aid healing. A 0.1% benzydamine mouthwash may help give relief. Occasionally, mechanical protection with a plastic guard may help [8].

Patients should be reviewed within 3 weeks to ensure healing has occurred. Any patient with a single ulcer lasting more than 2–3 weeks should be regarded with suspicion and investigated further, usually by biopsy—it may be a neoplasm or other serious disorder.

References

1 Bacher M, Goz G, Pham T *et al.* Congenital palatal ulcers in newborn infants with cleft lip and palate: diagnosis, frequency and significance. *Cleft Palate J* 1996; **33**: 37–42.
2 Reade PC, Rich AM, Steidler NE. Peripheral keratosis on oral mucosal ulcers: a clinical sign of non-neoplastic disease. *Br J Oral Surg* 1984; **22**: 372–7.
3 Baghdadi ZD. Riga–Fede disease: report of a case and review. *J Clin Pediatr Dent* 2001; **25**: 209–13.
4 Kotansky K, Goldberg M, Tenenbaum HC, Mock D. Factitious injury of the oral mucosa: a case series. *J Periodontol* 1995; **66**: 241–5.
5 Lamey PJ, McNab L, Lewis MAO, Gibb R. Oral artefactual disease. *Oral Surg* 1994; **77**: 131–4.
6 Scully C. The orofacial manifestations of the Lesch–Nyhan syndrome. *Int J Oral Surg* 1981; **10**: 380–3.
7 Stewart DJ, Kernohan DC. Self-inflicted gingival injuries: gingivitis artefacta, factitial gingivitis. *Dent Pract Dent Rec* 1972; **22**: 418–26.
8 Sugahara T, Mishima K, Mori Y. Lesch–Nyhan syndrome: successful prevention of lower lip ulceration caused by self-mutilation by use of mouth guard. *Int J Oral Maxillofac Surg* 1994; **23**: 37–8.
9 Cusumano FJ, Penna KJ, Panossian G. Prevention of self-mutilation in patients with Lesch–Nyhan syndrome: review of literature. *ASDC J Dent Child* 2001; **68**: 175–8.
10 Symons AL, Rowe PV, Romanink K. Dental aspects of child abuse. *Aust Dent J* 1987; **32**: 42–7.
11 Rashid N, Yusuf H. Oral self-mutilation by a 17-month-old child with Lesch–Nyhan syndrome. *Int J Paediatr Dent* 1997; **7**: 115–7.
12 Van Wyk CW. An oral lesion caused by fellatio. *Am J Forensic Med Pathol* 1981; **2**: 217–9.
13 Gendeh BS, Ferguson BJ, Johnson JT, Kapadia S. Progressive septal and palatal perforation secondary to intranasal cocaine abuse. *Med J Malaysia* 1998; **53**: 435–8.
14 Holmes RG, Chan GD, Singh BB. Chemical burn of the buccal mucosa. *Am J Dent* 2004; **17**: 219–20.

Eosinophilic ulcer [1–7]

Synonyms
- Traumatic eosinophilic granuloma
- Traumatic ulcerative granulomatous disease

Eosinophilic ulcer is a rare, self-limiting disease that often appears on the tongue in older adults or children. Its aetiology remains obscure and may be associated with traumatic factors. Eosinophilic ulcers are unifocal, with a benign course. Pathological features show an extensive inflammatory cell infiltration, with predominantly eosinophilic cells throughout the submucosa and histological similarities to $CD30^+$ lymphoproliferative disorders [5]. The peripheral blood eosinophil count is normal. Diagnosis and treatment is with either conservative excision or incisional biopsy.

References

1 Gao S, Wang Y, Liu N, Li S, Du J. Eosinophilic ulcer of the oral mucosa: a clinicopathological analysis. *Chin J Dent Res* 2000; **3**: 47–50.
2 El-Mofty SK, Swanson PE, Wick MR, Miller AS. Eosinophilic ulcer of the oral mucosa: report of 38 new cases with immunohistochemical observations. *Oral Surg* 1993; **75**: 716–22.
3 Elzay RP. Traumatic ulcerative granuloma with stromal eosinophilia (Riga–Fede disease and traumatic eosinophilic granuloma). *Oral Surg* 1983; **55**: 497–506.
4 Sklavounou A, Laskaris G. Eosinophilic ulcer of the oral mucosa. *Oral Surg* 1984; **58**: 431–6.
5 Segura S, Romero D, Mascaro JM Jr *et al.* Eosinophilic ulcer of the oral mucosa: another histological simulator of CD30+ lymphoproliferative disorders. *Br J Dermatol* 2006; **155**: 460–3.
6 Chawla O, Burke GA, MacBean AD. The eosinophilic ulcer revisited. *Dent Update* 2007; **34**: 56–7.
7 Pilolli GP, Luchesse A, Scivetti M, Maiorano E, Favia G. Traumatic ulcerative granuloma with stromal eosinophilia of the oral mucosa: histological and immunohistochemical analysis of three cases. *Minerva Stomatol* 2007; **56**: 73–9.

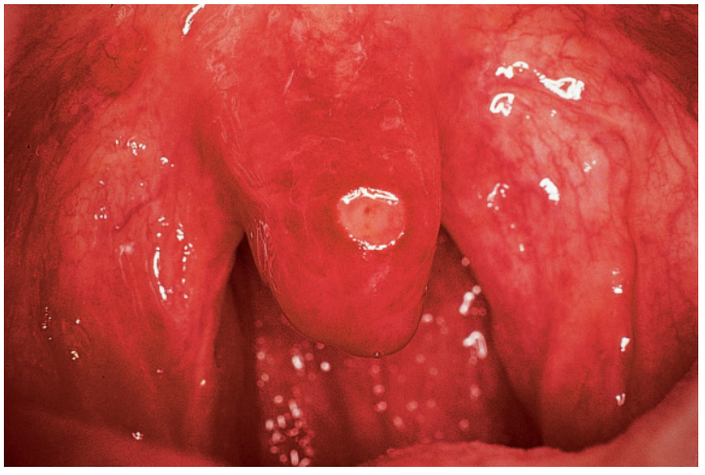


Fig. 69.25 Recurrent aphthae.

Table 69.14 Systemic and other factors that may occasionally underlie or be associated with recurrent aphthous stomatitis (RAS).

	Comments
Behçet's syndrome	Association of RAS with ocular lesions, genital ulcers and multisystem disease
Sweet's syndrome	See Chapter 50
Haematinic deficiency	In some studies, 10–20% of patients with RAS have deficiencies of iron, folic acid or vitamin B_{12}
Gastrointestinal disease	Malabsorption states (pernicious anaemia, coeliac disease and Crohn's disease) may precipitate RAS in a small minority
Endocrine factors	In some women, RAS is clearly related to a fall in progestogens in the luteal phase of the menstrual cycle; hormone therapy may be beneficial
Immunodeficiency	A few patients with RAS have an immune defect such as human immunodeficiency virus disease
Other factors	Trauma, certain foods, stress and cessation of smoking may play a part

Recurrent aphthous stomatitis

Synonyms
- Aphthae
- Canker sores

Recurrent aphthous stomatitis (RAS) is characterized by recurring episodes of ulcers, typically from childhood or adolescence, each lasting from 1 to about 4 weeks before healing. Aphthae typically are multiple round or ovoid ulcers with a circumscribed margin, erythematous halo and a yellow or grey floor (Fig. 69.25). The term 'recurrent oral ulcer' is rather imprecise and should be avoided [1–4].

Aetiology. The aetiology of RAS is not clear. A positive family history is found with about one-third of patients and there is an increased frequency of human leukocyte antigens (HLA)-A2, HLA-A11, HLA-B12 and HLA-DR2, supporting a genetic basis for susceptibility in some patients [1–4].

There are identifiable predisposing factors in some patients (Table 69.14). A minority (about 10–20%) of patients attending outpatient clinics with RAS have an underlying haematological abnormality, usually a low serum iron or ferritin, or deficiency of folate or vitamin B_{12}. A few have multiple deficiencies [5,6]. Up to 3% of RAS patients have coeliac disease but in others a gluten-free diet is of no value [7]. Patients with deficiency states often, but not always, have gastrointestinal symptoms, and their RAS is often of recent onset. Other aetiological factors in RAS can include stress, trauma and cessation of tobacco smoking. Ulcers similar to aphthae are also seen in Behçet's syndrome; Sweet's syndrome; HIV infection, cyclic neutropenia and other immunodeficiencies; and, rarely, in children in association with fever and pharyngitis (periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis; PFAPA) [8,9]. Orogenital ulceration with aphthae is probably a forme fruste of Behçet's syndrome.

There is no evidence that RAS is an autoimmune disease [1–4]. There is no known association with systemic autoimmune disorders, none of the common autoantibodies are found, and RAS tends to resolve or decrease spontaneously with increasing age. The serum immunoglobulin levels are usually normal, although IgA and IgG may be increased, and immune complexes may be found.

It now seems likely that there is a minor degree of immunological dysregulation underlying aphthae. Attempts to implicate a variety of viruses or bacteria in the aetiology of RAS have largely been unsuccessful, but there may be cross-reacting antigens between the oral mucosa and microorganisms such as *Streptococcus sanguis* or its L form, or heat-shock protein [10].

Cell-mediated immune mechanisms appear to be involved in the pathogenesis of RAS. In the lesions, helper T cells predominate early on, with some natural killer cells. Cytotoxic cells then appear and there is evidence for an antibody-dependent cellular cytotoxicity reaction [1–4].

Clinical features. RAS is a common disease that probably afflicts at least 20% of the population. There is a high prevalence in higher socio-economic classes.

There are three main clinical types of RAS. Most common are minor aphthous ulcers, which account for 80% of all RAS. Some 10% of patients with RAS have major aphthous ulcers, and a further 10% suffer from a herpetiform type of ulceration (Table 69.15).

Minor aphthous ulcers (synonym Mikulicz ulcers). Minor RAS (MiRAS) occur mainly in the 10 to 40-year age group, and often cause minimal symptoms. MiRAS are usually 2–4 mm in diameter and found mainly on the non-keratinized mobile mucosa of the lips, cheeks and floor of the mouth, sulci or ventrum of the tongue. They are uncommon on the gingiva, palate or dorsum of the tongue. Only a few ulcers (one to six) appear at a time; they heal in 7–10 days and recur at variable intervals. MiRAS are usually round or ovoid, but are often more linear when in the buccal sulcus, a common site. The ulcer floor is initially yellowish but

Table 69.15 Main features of recurrent aphthous stomatitis.

	Minor aphthae	Major aphthae	Herpetiform ulcers
Age of onset	Childhood or adolescence	Childhood or adolescence	Young adult
Ulcer size	2–4 mm	May be 10 mm or larger	Initially tiny but ulcers coalesce
Number of ulcers	Up to about 6	Up to about 6	10–100
Sites affected	Mainly vestibule, labial, buccal mucosa and floor of mouth; rarely dorsum of tongue, gingiva or palate	Any site	Any site but often on ventrum of tongue
Duration of each ulcer	Up to 10 days	Up to 1 month	Up to 1 month
Other comments	Most common type of aphthae	May heal with scarring	Affects females predominantly



Fig. 69.26 Major aphthous ulcers.

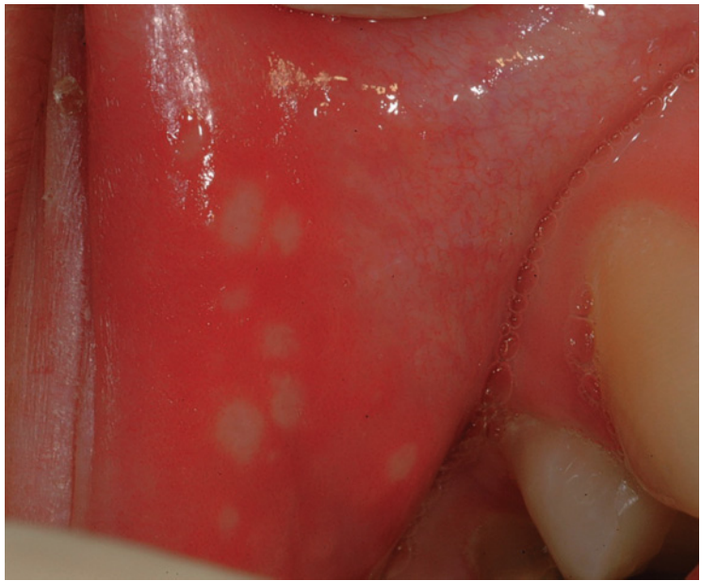


Fig. 69.27 Herpetiform ulceration

becomes greyish as epithelialization proceeds. There is an erythematous halo and some oedema but MiRAS heal with little or no evidence of scarring.

Major aphthous ulcers (synonym Sutton's ulcers). Previously known as periadenitis mucosa necrotica recurrens (PMNR), major RAS (MaRAS) are larger, recur more frequently, last longer and are more painful than MiRAS. They may reach a large size, even more than 1 cm in diameter. MaRAS are found on any area of the oral mucosa, including the dorsum of the tongue or palate. Usually only a few ulcers (one to six) occur at one time; they heal slowly over 10–40 days, and recur frequently. MaRAS are round or ovoid with an inflammatory halo, and may heal with scarring (Fig. 69.26). Occasionally, a raised erythrocyte sedimentation rate or plasma viscosity is found.

Herpetiform ulceration (Fig. 69.27). Herpetiform ulceration (HU) is found in a slightly older age group and there is a female predominance. Herpetiform ulcers are often extremely painful and recur so frequently that ulceration may be virtually continuous. HU begins with vesiculation, which passes rapidly into multiple, minute (2 mm), discrete ulcers at any oral site. The ulcers increase in size and coalesce to leave large ragged ulcers that heal in 10 days or longer. Their similarity to herpetic stomatitis gives herpetiform ulcers their name, but there is no evidence that herpes simplex virus is involved.

Prognosis. RAS in most patients resolves or abates spontaneously with age. An underlying, identifiable predisposing cause is particularly likely where RAS commences or worsens in adult life [5–10].

Diagnosis. Diagnosis is based on history and clinical features, since specific tests are unavailable. Biopsy is indicated only where some other cause of ulceration is suspected. To exclude relevant systemic predisposing factors it is often useful to perform:

- full blood count
- haemoglobin assay
- white cell count and differential
- red cell indices
- iron studies
- red cell folate level
- serum vitamin B_{12} measurements
- serum antiendomysial antibodies and IgA anti-tissue transglutaminase antibodies.

The relevance of HLA studies for differentiating RAS from Behcet's syndrome is discussed on p. 69.47.

Treatment. Few patients have spontaneous remission until after several years and thus treatment is often indicated [11–13]. Fortunately, the natural history of RAS is one of eventual remission in most cases.

Predisposing factors should be corrected. If there is an obvious relationship to certain foods, the causal food should be excluded from the diet [14]. Good oral hygiene should be maintained: chlorhexidine or triclosan mouthwashes help achieve this and may help reduce ulcer duration [1–4]. Topical minocycline and tetracycline mouthrinses may be of benefit [15].

Ulcer pain can usually be reduced, and the time to healing reduced, with hydrocortisone hemisuccinate pellets (Corlan) 2.5 mg or triamcinolone acetonide in carboxymethylcellulose paste (Adcortyl in Orabase) used four times daily; failing the success of these, a stronger topical corticosteroid (e.g. betamethasone, beclomethasone, fluticasone, mometasone, clobetasol) [16–18] or systemic corticosteroid (e.g. prednisolone) may be required.

Other therapies for RAS, such as sucralfate [19], colchicine and pentoxifylline (oxpentifylline), may have a role in individual cases but are not generally very effective or have adverse effects [3,20–23].

Thalidomide, in doses from 50 mg up to 300 mg daily, can frequently induce remission, especially in major aphthae, but its important teratogenic effects and the risk of neuropathy must be considered [22,24,25]. Topical tacrolimus may be effective but randomized trials are awaited.

There are multiple, other therapies available for RAS, including carbenoxolone, benzydamine, dapsone, cromoglicate, levamisole and many others, but generally their efficacy has not been well proven or they have unacceptable adverse effects [3].

References

1 Jurge S, Kuffer R, Scully C, Porter SR. Recurrent aphthous stomatitis. *Oral Diseases* 2006; **12**; 1–21.
2 Porter SR, Hegarty A, Kaliakatsou F, Hodgson TA, Scully C. Recurrent aphthous stomatitis. *Clin Dermatol* 2000; **18**: 569–78.
3 Porter SR, Scully C. Aphthous ulcers: recurrent. *Clin Evidence* 2001; **6**: 1037–41.
4 Porter SR, Scully C, Pedersen A. Recurrent aphthous stomatitis. *Crit Rev Oral Biol Med* 1998; **9**: 306–21.
5 Porter SR, Flint S, Scully C, Keith O. Recurrent aphthous stomatitis: the efficacy of replacement therapy in patients with underlying haematinic deficiencies. *Ann Dent* 1992; **L1**: 14–6.
6 Porter SR, Scully C, Flint SR. Haematological status in recurrent aphthous stomatitis compared with other oral disease. *Oral Surg* 1988; **66**: 41–4.
7 Hunter IP, Ferguson MM, Scully C *et al.* Effects of dietary gluten elimination in patients with recurrent minor aphthous stomatitis and no detectable gluten enteropathy. *Oral Surg* 1993; **75**: 595–8.
8 Rogers RS. Recurrent aphthous stomatitis and Behçet's syndrome. In: Safai R, Good RA, eds. *Immunodermatology*. New York: Plenum Press, 1981: 345.
9 Marshall GS, Edwards KM, Butler J *et al.* Syndrome of periodic fever, pharyngitis and aphthous stomatitis. *J Pediatr* 1987; **110**: 43–6.
10 Hasan A, Childerstone A, Pervink T *et al.* Recognition of a unique peptide epitope of the mycobacterial and human heat shock protein 65–60 antigen by T cells of patients with recurrent oral ulcers. *Clin Exp Immunol* 1995; **99**: 392–7.
11 McBride DR. Management of aphthous ulcers. *Am Fam Physician* 2000; **62**: 149–54, 160.
12 Scully C, Gorsky M, Lozada-Nur F. The diagnosis and management of recurrent aphthous stomatitis: a consensus approach. *J Am Dent Assoc* 2003; **134**: 200–7.
13 Scully C. Clinical practice. Aphthous ulceration. *N Engl J Med* 2006; **355**: 165–72.
14 Hay KD, Reade PC. The use of an elimination diet in the treatment of recurrent aphthous ulceration of the oral cavity. *Oral Surg* 1984; **57**: 504–7.
15 Gorsky M, Epstein J, Rabanstein S, Elishoov H, Yarom N. Topical minocycline and tetracycline rinses in treatment of recurrent aphthous stomatitis: a randomized cross-over study. *Dermatol Online J* 2007; **13**: 1.
16 Teixeira F, Mosqueda-Taylor A, Montano S, Dominguez-Soto L. Treatment of recurrent oral ulcers with mometasone furoate lotion. *Postgrad Med J* 1999; **75**: 574.
17 Gonzales-Mole MA, Morales P, Rodriquz-Archilla A. The treatment of oral aphthous ulceration or erosive lichen planus with topical clobetasol propionate in three preparations. A clinical study on 54 patients. *J Oral Pathol Med* 2002; **31**: 284–5.
18 Porter SR, Scully C. Aphthous ulcers (recurrent). *Clin Evid* 2005; **13**: 1687–94.
19 Rattan J, Schneider M, Arber N *et al.* Sucralfate suspension as a treatment of recurrent aphthous stomatitis. *J Intern Med* 1994; **236**: 341–3.
20 Katz J, Langevitz P, Shemer J *et al.* Prevention of recurrent aphthous stomatitis with colchicine: an open trial. *J Am Acad Dermatol* 1994; **31**: 459–61.
21 Wahba-Yahav AV. Severe idiopathic recurrent aphthous stomatitis: treatment with pentoxifylline. *Acta Derm Venereol (Stockh)* 1995; **75**: 157.
22 Letsinger JA, McCarty MA, Jorizzo JL. Complex aphthosis: a large case series with evaluation algorithm and therapeutic ladder from topicals to thalidomide. *J Am Acad Dermatol* 2005; **52**: 500–8.
23 Thornhill MH, Baccaglini L, Theaker E, Pemberton MN. A randomized, double-blind, placebo-controlled trial of pentoxifylline for the treatment of recurrent aphthous stomatitis. *Arch Dermatol* 2007; **143**: 463–70.
24 Grinspan D, Blanco GF, Aguero S. Treatment of aphthae with thalidomide. *J Am Acad Dermatol* 1989; **20**: 1060–3.
25 Samedi M, Ship JA. Refractory major aphthous stomatitis managed with systemic immunosuppressants: a case report. *Quintessence Int* 2004; **35**: 39–48.

Behçet's syndrome

Synonym
- Adamantiades syndrome

Definition. Behçet's syndrome (BS) is the association of RAS with genital ulceration and eye disease (especially iridocyclitis and retinal vasculitis) [1–6]. There may be a number of other systemic or cutaneous manifestations (Table 69.16).

Table 69.16 Behçet's syndrome.

	Features	Incidence (%)
Major criteria		
Oral	Aphthae	90–100
Genital	Ulcers	64–88
Neuro-ocular	Iridocyclitis	10–90
	Retinal vasculitis	
	Optic atrophy	
	Syndromes resembling disseminated sclerosis, pseudobulbar palsy or neurosyphilis	
	Meningoencephalitis	
	Others	
Dermatological	Pustules	48–88
	Erythema nodosum	
	Pathergy	
Minor criteria	Proteinuria and haematuria	
	Thrombophlebitis	
	Aneurysms	
	Arthralgias	

Aetiology. The aetiology of BS is uncertain but it appears to be becoming more common. There is a genetic background and, as in RAS, there are occasional familial cases and associations with HLA types, in BS particularly with HLA-B5 (Bw51 split). HLA-B51 or its B101 allele is significantly associated with BS in Japan, Korea, Turkey and France, as well as with the ocular manifestations in Britain. The MICA6 allele, a member of the polymorphic MHC class I-related gene A (MICA) family, is thought to be in linkage disequilibrium with HLA-B51 and has been shown to be significantly associated with BS in Japan and France [7,8]. HLA-DR/DQ haplotypes are more important than individual HLA-DR and HLA-DQ phenotypes for the development of mucocutaneous type of BS and for disease shift from RAS to mucocutaneous type of BS [9].

The aetiopathogenesis of BS is still unclear [6,10–12]. It does not appear to be infectious, contagious or sexually transmitted. The disease is found worldwide but is most common in the eastern Mediterranean countries and eastern Asia, along the Silk Road taken by Marco Polo. In these countries, it is a leading cause of blindness though this is not the case in resource-rich countries.

There are many immunological findings in BS:

- circulating autoantibodies against a number of components, including intermediate filaments found in mucous membranes, cardiolipin and neutrophil cytoplasm
- circulating immune complexes and changed levels of complement
- immunoglobulins and complement deposition within and around blood vessel walls
- decreased ratio of T-helper (CD4) cells to T-suppressor (CD8) cells.

These immunological changes mimic those seen in patients with RAS—various T-lymphocyte abnormalities (especially T-suppressor cell dysfunction), changes in serum complement and increased polymorphonuclear leukocyte motility. There is also evidence that mononuclear cells may initiate antibody-dependent cellular cytotoxicity to oral epithelial cells, and evidence of disturbance of natural killer cell activity.

The common denominator in all systems is vasculitis, usually leukocytoclastic vasculitis. Many of the features of BS (erythema nodosum, arthralgia, uveitis) are common to established immune complex disease and, indeed, immune complexes (usually antigen–antibody complexes) are found in the sera. The antigen responsible has not been reliably identified but may include herpes simplex virus or streptococcal antigens [13–16]. As in RAS, heat-shock proteins have been implicated.

Clinical features. BS is a chronic, multisystem disorder, most patients being male, usually in their third or fourth decade.

Because BS is rare and symptoms of the disease overlap symptoms of other diseases, it can be very difficult to diagnose. Spontaneous remission is common for patients with BS; this can add to the difficulty in diagnosis.

BS is characterized mainly by a triad of RAS [6,17,18], genital ulcers [15,16] and ocular lesions [19,20]. The CNS, heart and intestinal tract may be involved.

Table 69.17 Oculomucocutaneous syndromes.*

	Main lesions		
Disease	**Oral and genital**	**Ocular**	**Skin**
Behçet's syndrome	Aphthae	Uveitis	Erythema nodosum
Sweet's syndrome	Aphthae	Conjunctivitis, episcleritis	Inflamed papule or nodule
Erythema multiforme	Erosions	Erosions	Target lesions
Cicatricial pemphigoid	Bullae	Erosions	Occasional dome-shaped bullae
	Erosions	Scarring	
Pemphigus	Erosions	Erosions	Multiple, flaccid bullae
Reiter's syndrome	Ulcers	Conjunctivitis	Keratoderma blenorrhagica

* Ulcerative colitis, herpes simplex, syphilis, lupus erythematosus, mixed connective tissue disease and other disorders may also cause oral, cutaneous and ocular lesions.

One variant of BS (MAGIC syndrome) is associated with *m*outh *a*nd *g*enital ulcers and *i*nflamed *c*artilage [21,22]. Other oculomucocutaneous syndromes (Table 69.17) may cause similar manifestations [23,24].

Diagnosis. BS is usually diagnosed on clinical grounds, although findings of HLA-B5101 and pathergy are supportive, as are antibodies to cardiolipin and neutrophil cytoplasm. Disease activity may be assessed by serum levels of acute phase proteins or antibodies to intermediate filaments, or by erythrocyte sedimentation rate; all are raised in active BS.

Differential diagnosis is mainly from the following.

- Sweet's syndrome: aphthae, conjunctivitis, episcleritis, inflamed tender papule or nodule
- Erythema multiforme: erosions, target (iris) lesions
- Pemphigoid: bullae, erosions
- Pemphigus: erosions, multiple flaccid bullae
- Reiter's syndrome: ulcers, conjunctivitis, keratoderma blenorrhagica
- Ulcerative colitis
- Herpes simplex
- Syphilis
- Lupus erythematosus
- Mixed connective tissue disease.

The diagnosis is often made on the basis of RAS plus two or more of recurrent genital ulceration, eye lesions, skin lesions and pathergy [6,25,26].

Major criteria are:

1 RAS: in 90–100% of cases.
2 Recurrent painful genital ulcers that tend to heal with scars in 64–88% of cases. Genital ulcers are especially common in females with BS, and resemble RAS.
3 Ocular lesions: uveitis with conjunctivitis (early) and hypopyon (late), retinal vasculitis (posterior uveitis), iridocyclitis and optic atrophy. The most common ocular manifestation is relapsing iridocyclitis but uveitis, retinal vascular changes and optic atrophy may occur. Both eyes are eventually involved and blindness may result.

4 CNS lesions: meningoencephalitis, cerebral infarction, psychosis, cranial nerve palsies, cerebellar and spinal cord lesions, hemiparesis and quadriparesis.
5 Skin lesions: erythema nodosum, papulopustular lesions and acneform nodules. Venepuncture is, in some patients, followed by pustulation (pathergy).

Minor criteria are:

1 Arthralgia: large joint arthropathies that are subacute, non-migratory, self-limiting and non-deforming
2 Superficial or deep migratory thrombophlebitis, especially of lower limbs
3 Intestinal lesions: inflammatory bowel disease with discrete ulcerations
4 Lung involvement: pneumonitis
5 Haematuria and proteinuria.

However, very non-specific signs and symptoms, which may be recurrent, may precede the onset of the mucosal membrane ulceration by 6 months to 5 years. These include malaise, anorexia, weight loss, generalized weakness, headache, perspiration, decreased or elevated temperature, lymphadenopathy and pain in the substernal and temporal regions.

A history of repeated sore throats, tonsillitis, myalgias and migratory erythralgias without overt arthritis is also common.

Treatment. Unlike RAS, BS is not self-limiting. It causes morbidity (especially in terms of ocular and neurological disease) and mortality. Most patients present with oral and ocular disease but there follows a relapsing and remitting but variable course. CNS involvement, thromboses of major vessels and gastrointestinal perforation result in a poor prognosis. Few patients with BS have spontaneous remission and thus treatment is indicated [6,27,28].

Chronic morbidity is usual; the leading cause is ophthalmic involvement, which can result in blindness. The effects of the disease may be cumulative, especially with neurological, vascular and ocular involvement. Mortality is low but can occur from neurological involvement, vascular disease, bowel perforation, cardiopulmonary disease or as a complication of immunosuppressive therapy. In the face of the serious potential complications, patients with suspected BS should be referred early for specialist advice.

Topical treatment for RAS (see p. 69.46). Oral ulcers may respond to topical corticosteroids or 5-aminosalicylic acid [6,29]. Even nicotine patches may have some success [30].

Systemic treatment includes mainly colchicine 0.5–1.5 mg daily.

Other systemic treatments include corticosteroids, azathioprine, ciclosporin, chlorambucil, cyclophosphamide, dapsone, interferon-alpha, levamisole or thalidomide. Ocular lesions usually respond to ciclosporin, but tend to relapse when treatment is stopped. Thalidomide at a dose of up to 400 mg daily may be of value in recalcitrant orogenital ulceration, although it must be used with caution in view of the adverse effects of teratogenicity and neuropathy [31–34].

References

1 Ghate JV, Jorizzo JL. Behcet's disease and complex aphthosis. *J Am Acad Dermatol* 1999; **40**: 1–18.
2 Escudier M, Bagan J, Scully C. Behcets syndrome; (Adamantiades syndrome). *Oral Diseases* 2006; **12**: 78–84.
3 Sakane T, Takeno M, Suzuki N, Inaba G. Behcet's disease. *N Engl J Med* 1999; **341**: 1284–91.
4 Lee LA. Behcet disease. *Semin Cutan Med Surg* 2001; **20**: 53–7.
5 Yazici H, Yurdakul S, Hamuryudan V. Behcet's syndrome. *Curr Opin Rheumatol* 1999; **11**: 53–7.
6 Yesudian PD, Edirisinghe DN, O'Mahoney C. Behcet's disease. *Int J STD AIDS* 2007; **18**: 221–7.
7 Mizuki N, Inoko H, Ohno S. Molecular genetics (HLA) of Behcet's disease. *Yonsei Med J* 1997; **38**: 333–49.
8 Nishiyama M, Takahashi M, Manaka K *et al* Microsatellite polymorphisms of the MICA gene among Japanese patients with Behcet's disease. *Can J Ophthalmol* 2006; **41**: 210–5.
9 Sun A, Hsieh RP, Chu CT *et al*. Some specific human leukocyte antigen (HLA)-DR/DQ haplotypes are more important than individual HLA-DR and -DQ phenotypes for the development of mucocutaneous type of Behcet's disease and for disease shift from recurrent aphthous stomatitis to mucocutaneous type of Behcet's disease. *J Oral Pathol Med* 2001; **30**: 402–7.
10 Inoue C, Itoh R, Kawa Y, Mizoguchi M. Pathogenesis of mucocutaneous lesions in Behcet's disease. *J Dermatol* 1994; **21**: 474–80.
11 Sakane T, Suzuki N, Nagafuchi H. Etiopathology of Behcet's disease: immunological aspects. *Yonsei Med J* 1997; **38**: 350–8.
12 Buldanlioglu S, Turkmen S, Ayabakan HB *et al*. Nitric oxide, lipid peroxidation and antioxidant defence system in patients with active or inactive Behcet's disease. *Br J Dermatol* 2005; **153**: 526–30.
13 Narikawa S, Suzuki Y, Takahashi M *et al*. *Streptococcus oralis* previously identified as uncommon '*Streptococcus sanguis*' in Behcet's disease. *Arch Oral Biol* 1995; **40**: 685–90.
14 Lehner T, Lavery E, Smith R *et al*. Association between the 65-kilodalton heat shock protein, *Streptococcus sanguis*, and the corresponding antibodies in Behcet's syndrome. *Infect Immunol* 1991; **59**: 1434–41.
15 Pervin K, Childerston A, Shinnick T *et al*. T cell epitope expression of mycobacterial and homologous human 65-kilodalton heat shock protein peptides in short-term lines from patients with Behcet's disease. *J Immunol* 1993; **151**: 2273–82.
16 Zouboulis CC. HLA-independent antibacterial host response toward Th1 immunity mediated by IL-12: a new concept for the pathogenesis of Adamantiades-Behcet's disease. *J Invest Dermatol* 2006; **126**: 1444–7.
17 Krause I, Rosen Y, Kaplan I *et al*. Recurrent aphthous stomatitis in Behcet's disease: clinical features and correlation with systemic disease expression and severity. *J Oral Pathol Med* 1999; **28**: 193–6.
18 Verpilleux MP, Bastuji-Garin S, Revuz J. Comparative analysis of severe aphthosis and Behcet's disease: 104 cases. *Dermatology* 1999; **198**: 247–51.
19 Krause I, Uziel Y, Guedj D *et al.* Mode of presentation and multisystem involvement in Behcet's disease: the influence of sex and age of disease onset. *J Rheumatol* 1998; **25**: 1566–9.
20 Gharibdoost F, Davatchi F, Shahram F *et al.* Clinical manifestations of Behcet's disease in Iran. Analysis of 2176 cases. In: Godeau P, Wechsler B, eds. *Proceedings of the 6th International Conference on Behcet's Disease*. Amsterdam: Elsevier, 1993: 153–8.
21 Firestein GS, Gruber HC, Weisman MH *et al.* Mouth and genital ulcers with inflamed cartilage: MAGIC syndrome. *Am J Med* 1985; **79**: 65–72.
22 Caceres M, Estrera AL, Buja LM, Safi HG. Transverse aortic arch replacement associated with MAGIC syndrome: case report and literature review. *Ann Vasc Surg* 2006; **20**: 395–8.
23 Grattan CEH, Scully C. Oral ulceration: a diagnostic problem. *BMJ* 1986; **292**: 1093–4.
24 Hamza M. Orogenital ulcerations in mixed connective tissue disease. *J Rheumatol* 1985; **12**: 643–4.
25 International Study Group for Behcet's Disease. Criteria for diagnosis of Behcet's disease. *Lancet* 1990; **i**: 1078–80.
26 Lee S. Diagnostic criteria of Behcet's disease: problems and suggestions. *Yonsei Med J* 1997; **38**: 365–9.
27 Sakane T, Takeno M. Current therapy in Behcet's disease. *Skin Ther Lett* 2000; **5**: 3–5.

28 Fresko I, Yurdakul S, Hamuryudan V *et al*. The management of Behcet's syndrome. *Ann Med Interne (Paris)* 1999; **150**: 576–81.
29 Ranzi T, Campanini M, Bianchi RA. Successful treatment of genital and oral ulceration in Behçet's disease with topical 5-aminosalicylic acid. *Br J Dermatol* 1989; **120**: 471–2.
30 Scheid P, Bohadana A, Martinet Y. Nicotine patches for aphthous ulcers due to Behcet's syndrome. *N Engl J Med* 2000; **343**: 1816–7.
31 Bowers PW, Powell RJ. Effect of thalidomide on oral ulceration. *BMJ* 1983; **287**: 799–800.
32 Jenkins JS, Powell RJ, Allen BR *et al*. Thalidomide in severe orogenital ulceration. *Lancet* 1984; **ii**: 1424–6.
33 Calabrese L, Resztak K. Thalidomide revisited: pharmacology and clinical applications. *Expert Opin Investig Drugs* 1998; **7**: 2043–60.
34 Wu JJ, Huang DB, Pang KR, Hsu S, Tyring SK. Thalidomide: dermatological indications, mechanisms of action and side-effects. *Br J Dermatol* 2005; **153**: 254–73.

Sweet's syndrome (see Chapter 50)

Pustular lesions leading to aphthous-like ulcers may be found in Sweet's syndrome and there are occasional associations with BS and Sjögren's syndrome, each of which has oral manifestations. About 5% of patients in the UK with Sweet's syndrome have oral aphthous-like ulcers, although up to 30% of Japanese patients suffer these [1–5].

References

1 Driban NE, Alvarez MA. Oral manifestations of Sweet's syndrome. *Dermatologica* 1984; **169**: 102–3.
2 Mizoguchi M, Chikakane K, Goh K *et al*. Acute febrile neutrophilic dermatosis (Sweet's syndrome) in Behçet's disease. *Br J Dermatol* 1987; **116**: 727–34.
3 Femiano F, Gombos F, Scully C. Sweet's syndrome: recurrent oral ulceration, pyrexia, thrombophlebitis, and cutaneous lesions. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2003; **95**: 324–7.
4 Uysal H, Vahboglu H, Inan L, Vahaboglu G. Acute febrile neutrophilic dermatosis (Sweet's syndrome) in neuro-Behcet's disease. *Clin Neurol Neurosurg* 1993; **95**: 319–22.
5 Notani K, Kobayashi S, Kondoh K *et al*. Case of Sweet's syndrome (acute febrile neutrophilic dermatosis) with palatal ulceration. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2000; **89**: 477–9.

Malignant neoplasms

More than 90% of malignant neoplasms in the mouth are squamous cell carcinomas. Nearly 30% of all squamous cell carcinomas affect the lip; some 25% affect the tongue, the most common intraoral site [1–9]. Most intraoral cancers involve the posterolateral border of the tongue and/or the floor of the mouth (the 'graveyard' area). In betel chewing, the buccal mucosa is a common site for carcinoma [10].

Oral cancer is a significant world health problem, being overall the sixth most common malignant neoplasm. In parts of South-East Asia for example, particularly India, some 40% of all malignancy is oral cancer [11]. High levels are also seen in resource-poor countries such as Brazil, but also in parts of Europe such as areas of northern France and eastern Europe.

Oral squamous cell carcinoma

Cancer of the oral cavity is classified according to site:

- lip (International Classification of Diseases [ICD] 140)
- tongue (ICD 141)
- gum (ICD 143)
- floor of the mouth (ICD 144) and
- unspecified parts of the mouth (ICD 145).

Carcinoma of the lip

Squamous cell carcinoma is the commonest malignancy to affect the vermilion zone and, as with squamous carcinoma of the glabrous skin, it is usually due to actinic damage [1,12,13]. Like actinic cheilitis it is most common on the lower lip of fair-skinned, outdoor workers in sunny climates, and is relatively rare in pigmented skin [2–4]. Lip cancer is common in certain population groups in the UK, Romania, Hungary, Poland, Spain, Finland, Israel, Canada, the USA and Australia, but in most areas reported the incidence is falling [4–7,14–16].

Lip cancer generally occurs in men who are employed in outdoor activities such as farming and fishing [17,18]. Squamous cell carcinomas occur on the lower lip in 89%, with 3% on the upper lip and 8% at the commissures [19]. The buccal mucosa may also be involved, particularly in association with betel quid chewing [10].

Although sunlight is accepted as the major aetiological factor, some studies have shown a poor correlation between the incidence of lip cancer and the rate of annual solar radiation [20]. *Actinic radiation* may predispose to lip cancer. Facts that support such a relationship include the following.

- Lip cancer involves the more exposed lower lip, rather than the upper lip.
- There is a higher incidence of lip cancer in outdoor workers and rural populations than in office workers or urban populations.
- Fair-skinned more than dark-skinned people tend to develop lip cancer (as well as skin cancer and melanoma) in sunny climates.

Other risk factors may include low social class, tobacco smoking, syphilis, poor dentition, infection with herpes simplex virus [3,5,17,21] or human papillomaviruses [22], and immune suppression [23]; for example lip cancer is increased in immunosuppressed renal transplant recipients.

The initial features are a keratinous growth or swelling of the lip (Fig. 69.28), soreness and ulceration. Most lesions are amenable to surgical excision, with more than 70% surviving for 5 years.



Fig. 69.28 Squamous cell carcinoma of lip.

References

1 Zitsch RP. Carcinoma of the lip. *Otolaryngol Clin North Am* 1993; **26**: 265–77.
2 Keller AZ. Cellular types, survival, race, nativity, occupations, habits and associated diseases in the pathogenesis of lip cancers. *Am J Epidemiol* 1970; **91**: 486–99.
3 Picascia DD, Robinson JK. Actinic cheilitis: a review. *J Am Acad Dermatol* 1987; **17**: 255–64.
4 Szpak CA, Stone MJ, Frenkel EP. Some observations concerning the demographic and geographic incidence of carcinoma of the lip and buccal cavity. *Cancer* 1977; **40**: 343–8.
5 Keller AZ. The epidemiology of lip, oral and pharyngeal cancers, and the association with selected systemic diseases. *Am J Public Health* 1963; **53**: 1214–28.
6 Shiboski CH, Shiboski SC, Silverman S. Trends in oral cancer rates in the United States 1973–1996. *Community Dent Oral Epidemiol* 2000; **28**: 249–56.
7 Davies L, Welch HG. Epidemiology of head and neck cancer in the United States. *Otolaryngol Head Neck Surg* 2006; **135**: 451–7.
8 Conway DI, Stockton DL, Warnakulasuriya KA, Ogden G, MacPherson LM. Incidence of oral and oropharyngeal cancer in United Kingdom (1990–1999)—recent trends and regional variation. *Oral Oncol* 2006; **42**: 586–92.
9 Lam L, Logan RM, Luke C. Epidemiological analysis of tongue cancer in South Australia for the 24-year period, 1977–2001. *Aust Dent J* 2006; **51**: 16–22.
10 Su CC, Yang SF, Huang SJ, Lian IEB. Distinctive features of oral cancer in Changhua County: high incidence, buccal mucosa preponderance, and a close relation to betel quid chewing habit. *J Formos Med Assoc* 2007; **106**: 225–33.
11 Burghri Y, Burghri A, Usman A *et al*. Epidemiological review of head and neck cancers in Karachi. *Asian Pac J Cancer Prev* 2006; **7**: 195–200.
12 Markopoulous A, Arbanidou-Farmaki E, Kayavis I. Actinic cheilitis: clinical and pathologic characteristics in 65 cases. *Oral Dis* 2004; **10**: 212–6.
13 Neto Pimental DR, Michalanay N, Alchorne M *et al*. Actinic cheilitis: histopathology and p53. *J Cutan Pathol* 2006; **33**: 539–44.
14 MacFarlane GJ, Boyle P, Evstifeeva T, Scully C. Epidemiological aspects of lip cancer in Scotland. *Community Dent Oral Epidemiol* 1993; **21**: 279–82.
15 Scully C, Cawson RA. Potentially malignant oral lesions. *J Epidemiol Biostat* 1996; **1**: 3–12.
16 Tarvainnen L, Suuronen R, Lindqvist C, Malila N. Is the incidence of oral and pharyngeal cancer increasing in Finland? An epidemiological study of 17,383 cases in 1953–1999. *Oral Dis* 2004; **10**: 167–72.
17 Pukkala E, Soderholm A-L, Linqvist C. Cancers of the lip and oropharynx in different social and occupational groups in Finland. *Oral Oncol* 1994; **30B**: 209–15.
18 Ji J, Hemminki K. Occupation and upper aerodigestive tract cancers: a follow-up study in Sweden. *J Occup Environ Med* 2005; **47**: 785–95.
19 del Regato JA. Cancer of the respiratory system and upper digestive tract. In: del Regato JA, ed. *Ackerman and Del Regato's Cancer*, 6th edn. St Louis: Mosby, 1985: 248–72.
20 Lindqvist C. Risk factors of lip cancer: a critical evaluation based on epidemiological comparisons. *Am J Public Health* 1979; **69**: 256–60.
21 Blomqvist G, Hirsch JM, Alberius P. Association between development of lower lip cancer and tobacco habits. *J Oral Maxillofac Surg* 1991; **49**: 1044–7.
22 Gillison ML. Current topics in the epidemiology of oral cavity and oropharyngeal cancers. *Head Neck* 2007; **29**: 779–92.
23 King GN, Healy C, Glover MT *et al*. Increased prevalence of dysplastic and malignant lip lesions in renal transplant recipients. *N Engl J Med* 1995; **332**: 1052–7.

Intraoral carcinoma

Most intraoral carcinoma is squamous cell carcinoma [1–5]. In many countries there is evidence for an increase in oral squamous cell carcinoma (OSCC) over recent years [6–12], especially in young persons. There is marked inter-country variation in both the incidence of, and mortality from, OSCC [13]. In addition, there is also growing evidence of intra-country ethnic differences in incidence and mortality, especially in the UK and USA.

In resource-poor countries, particularly South-East Asia and Brazil, the incidence of OSCC varies widely in different areas and there are ethnic differences in incidence, often attributed to lifestyle habits.

In most resource-rich countries OSCC is uncommon. The incidence varies between countries and between different regions of the same country. For example, parts of France and Newfoundland have the highest incidence in the West, with about 10 times the incidence of oral carcinoma in the UK. Oral cancer is more than twice as common in Scotland than in England and Wales and, for example, even within Scotland there are regional differences.

Potentially malignant states. Some potentially malignant (precancerous) lesions that can progress to OSCC include especially [14,15] *erythroplasia* (erythroplakia), the most likely lesion to progress to severe dysplasia or carcinoma (see p. 69.102); and *leukoplakia* (see p. 69.89), particularly proliferative verrucous leukoplakia, sublingual leukoplakia, candidal leukoplakia and syphilitic leukoplakia.

Some other potentially malignant (precancerous) conditions include:

- lichen planus—there are also cases of dysplasia with a lichenoid appearance (lichenoid dysplasia)
- HPV infection
- discoid lupus erythematosus
- submucous fibrosis
- atypia in immunocompromised patients
- dyskeratosis congenita
- Fanconi anaemia
- Paterson–Kelly syndrome (sideropenic dysphagia, Plummer–Vinson syndrome).

One of the main features that appears to precede the onset of malignancy is epithelial dysplasia, although dysplasia can also be seen in regenerating tissue and some non-precancerous lesions such as ulcers, viral infections, candidal infections and granular cell tumours.

Dysplasia varies in severity, and it is the more severe grades that are associated with higher malignant potential.

Predisposing factors (risk factors) [1–5,10–12,14–19]. In the resource-rich countries, OSCC is seen especially in tobacco users, alcohol users, lower socio-economic groups and ethnic minority groups.

In resource-poor countries, OSCC is seen especially in tobacco users, alcohol users, 'betel quid' users (some 20% of the world's population use betel) and lower socio-economic groups. In peoples from parts of Asia, tobacco-chewing, along with a variety of ingredients in 'betel quid' (betel vine leaf, betel [areca] nut, catechu, slaked lime, together with tobacco), appears to predispose to OSCC, particularly when it is started early in life and is used frequently and for prolonged periods. Various other risky chewing habits, usually containing tobacco, are used in different cultures (e.g. khat, shammah, toombak).

Microorganisms such as *Candida* and human papillomavirus (HPV) have been detected in some potentially malignant lesions and some OSCC, where they may play a role. HPV is especially implicated in oropharyngeal and tonsillar carcinoma; HPV-16 is particularly implicated [20].

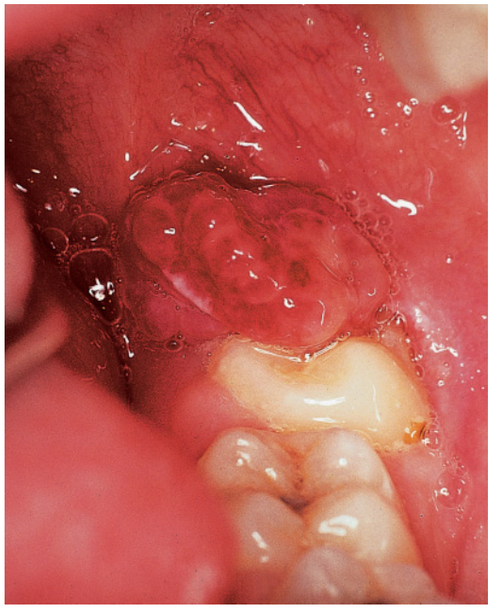


Fig. 69.29 Oral squamous cell carcinoma.

In contrast, diets rich in fresh fruits and vegetables and vitamin A may have a protective effect.

Clinical features. OSCC may present as the following [1–5] (Fig. 69.29).

- A red lesion (erythroplasia)
- A granular ulcer with fissuring or raised exophytic margins
- A white or mixed white and red lesion
- A lump sometimes with abnormal supplying blood vessels
- An indurated lump/ulcer, i.e. a firm infiltration beneath the mucosa
- A non-healing extraction socket
- A lesion fixed to deeper tissues or to overlying skin or mucosa
- Cervical lymph node enlargement, especially if there is hardness in a lymph node or fixation.

Enlarged nodes in a patient with oral carcinoma may be caused by infection, reactive hyperplasia secondary to the tumour, or metastatic disease. Occasionally, a swollen lymph node is detected in the absence of any obvious primary tumour.

In patients with OSCC for over 3 years, second primary neoplasms in the aerodigestive tract may be seen in up to 25% and in up to 40% of those who continue to smoke.

Diagnosis. Early diagnosis is important since it improves prognosis and minimizes the extent of interventions [21–25]. There should be a high index of suspicion, especially of a solitary lesion present for over 3 weeks: biopsy is invariably indicated. Clinicians should be aware that single ulcers, lumps, red patches or white patches, particularly if any of these persist for more than 3 weeks, may be manifestations of frank malignancy. Scalpel biopsy is required and toluidine blue staining may help highlight the most appropriate area for biopsy [5,26–30].

The whole oral mucosa should be examined as there may be widespread dysplastic mucosa ('field change') or even a second neoplasm and the cervical lymph nodes must be examined. Frank tumours should be inspected and palpated to determine extent of spread; for tumours in the posterior tongue, examination under general anaesthesia may facilitate this.

OSCC should be staged according to the TNM classification of the International Union against Cancer, where T represents tumour size, N nodal metastases and M distant metastases (Table 69.18), since this classification relates well to overall survival rate, that is the earlier the tumour, the better the prognosis and the less complicated the treatment.

Table 69.18 TNM classification of malignant neoplasms.*

Primary tumour size (T)	
Tx	No available information
T_0	No evidence of primary tumour
T_{is}	Only carcinoma *in situ*
T_1, T_2, T_3, T_4	Increasing size of tumour†
Regional lymph node involvement (N)	
Nx	Nodes could not be or were not assessed
N_0	No clinically positive nodes
N_1	Single clinically positive homolateral node less than 3 cm in diameter
N_2	Single clinically positive homolateral node 3–6 cm in diameter, or multiple clinically positive homolateral nodes, none more than 6 cm in diameter
N_{2a}	Single clinically positive homolateral node 3–6 cm in diameter
N_{2b}	Multiple clinically positive homolateral nodes, none more than 6 cm in diameter
N_3	Massive homolateral node(s), bilateral nodes, or contralateral node(s)
N_{3a}	Clinically positive homolateral node(s), one more than 6 cm in diameter
N_{3b}	Bilateral clinically positive nodes
N_{3c}	Contralateral clinically positive node(s)
Involvement by distant metastases (M)	
Mx	Distant metastasis was not assessed
M_0	No evidence of distant metastasis
M_1, M_2, M_3	Distant metastasis is present. Increasing degrees of metastatic involvement, including distant nodes

* Several other classifications are available, e.g. STNM (S, site).

† T_1, maximum diameter 2 cm; T_2, maximum diameter 4 cm; T_3, maximum diameter >4 cm; T_4, massive tumour >4 cm diameter, with involvement of antrum, pterygoid muscles, base of tongue or skin.

Investigations. The principles include the following.

1 Confirm the diagnosis histopathologically and determine the presence of malignant disease elsewhere.
   (a) Are bone, muscles or cervical lymph nodes involved?
   (b) Are there other primary tumours (typically in the upper aerodigestive tract—mouth, nares, pharynx, larynx, oesophagus)? There is controversy as to the need for endoscopy in all cases to detect such tumours.
   (c) Are there metastases, initially to regional lymph nodes and later to liver, bone and brain? Imaging may detect abnormalities that escape clinical examination. Sentinel lymph node biopsy may contribute to more targeted lymph node dissection strategies [34,35].

2 Ensure that the patient is as prepared as possible for the major surgery required, particularly in terms of general anaesthesia, potential blood loss and ability to metabolize drugs.
3 Address any potential dental or oral problems preoperatively, to avoid later complications such as osteoradionecrosis.

The following investigations are therefore almost invariably indicated.

- Lesional biopsy. Incisional biopsy, which is invariably required, should be sufficiently large to include enough suspect and apparently normal tissue. Red, rather than white, areas are most likely to show dysplasia, and hence should be biopsied. Attempts to highlight probable dysplastic areas before biopsy, for example by using toluidine blue dye, are unfortunately not reliable, but may be of some help in deciding which area is best to biopsy where there is widespread 'field change'. An excisional biopsy should be avoided unless the lesion is extremely small, since this is unlikely to have excised an adequately wide margin of tissue if the lesion is malignant, but will have destroyed for the surgeon or radiotherapist clinical evidence of the site and character of the lesion.
- Biopsy of equivocal neck lymph nodes.
- Jaw radiography (often rotating pantomography), although this is inadequate to exclude bone invasion.
- Chest radiography: important as a pre-anaesthetic check, especially in patients with known pulmonary or airways disease, and to demonstrate metastasis to lungs or hilar lymph nodes, ribs or vertebrae.
- MRI or computed tomography (CT) of the primary site, head and neck, and suspected sites of distant metastases, and MRI of the neck to delineate the extent of cervical node metastases. Some units routinely examine chest and abdomen. MRI is particularly useful for determining tumour spread, bone involvement and nodal metastases.
- Electrocardiography.
- Blood tests:
  — Full blood picture and haemoglobin.
  — Urea and electrolytes.
  — Liver function tests.
- Blood for grouping and cross-matching.

In selected cases, the following may also be useful.

- Bronchoscopy: if chest radiography reveals any lesions.
- Endoscopy of the upper aerodigestive tract: especially if there is a history of tobacco use.
- Gastroscopy: if a per-endoscopic gastrostomy is to be used for feeding.
- Liver ultrasound: if there is hepatomegaly or abnormal liver function.
- Doppler duplex flow studies: in planning radial free forearm flaps.
- Angiography: in planning lower limb free flaps.

Treatment. The prognosis of OSCC is around 30% survival at 5 years [5,6,31,32]. The major impact that treatment has had on the prognosis of oral cancer has been in relation to improved anaesthetic and medical care. Surgical reconstruction has also been markedly improved [32,33] and there are fewer side effects from modern radiotherapy [34].

The treatment of oral cancer involves one or a combination of radiotherapy, surgery and, very occasionally, chemotherapy. Serious consideration must be given to the complications of the various modalities [34,36,37] and the quality of life achieved [38–40].

There is now evidence that vitamin A derivatives may be of benefit in patients with premalignant lesions, and in preventing second primary neoplasms [41,42].

References

1 Silverman S. Oral cancer. *Semin Dermatol* 1994; **13**: 132–7.
2 Prince S, Bailey BM. Squamous carcinoma of the tongue: review. *Br J Oral Maxillofac Surg* 1999; **37**: 164–74.
3 Renaud-Salis JL, Blanc-Vincent MP, Brugere J *et al.* Epidermoid cancers of the oropharynx. *Br J Cancer* 2001; **84** (Suppl. 2): 37–41.
4 Gillison ML. Current topics in the epidemiology of oral cavity and oropharyngeal cancers. *Head Neck* 2007; **29**: 779–92.
5 Scully C, Bagan JV. Recent advances in oral oncology. *Oral Oncol* 2007; **43**: 107–15.
6 Boyle P, MacFarlane GJ, Zheng T *et al*. Recent advances in the epidemiology of head and neck cancer. *Curr Opin Oncol* 1992; **4**: 471–7.
7 MacFarlane GJ, Boyle P, Evstifeeva T, Robertson C, Scully C. Rising trends of oral cancer mortality in males worldwide: the return of an old public health problem. *Cancer Causes Control* 1994; **5**: 259–65.
8 MacFarlane GJ, Evstifeeva TV, Robertson C, Boyle P, Scully C. Trends of oral cancer mortality among females worldwide. *Cancer Causes Control* 1994; **5**: 255–8.
9 Mackenzie J, Ah-See K, Thakker N *et al.* Increasing incidence of oral cancer amongst young persons: what is the aetiology? *Oral Oncol* 2000; **36**: 387–9.
10 Conway DI, Stockton DL, Warnakulasuriya KA, Ogden G, MacPherson LM. Incidence of oral and oropharyngeal cancer in United Kingdom (1990–1999): recent trends and regional variation. *Oral Oncol* 2006; **42**: 586–92.
11 Lam L, Logan RM, Luke C. Epidemiological analysis of tongue cancer in South Australia for the 24-year period, 1977–2001. *Aust Dent J* 2006; **51**: 16–22.
12 Davies L, Welch HG. Epidemiology of head and neck cancer in the United States. *Otolaryngol Head Neck Surg* 2006; **135**: 451–7.
13 Scully C, Bedi R. Ethnicity and oral cancer. *Lancet Oncol* 2000; **1**: 37–42.
14 Scully C, Cawson RA. Oral potentially malignant lesions. *J Epidemiol Biostat* 1996; **1**: 3–12.
15 Mithani SK, Midlarz WK, Grumbine FL, Smith IM, Califano JA. Molecular genetics of premalignant oral lesions. *Oral Dis* 2007; **13**: 126–33.
16 Hashibe M, Mathew B, Kuruvilla B *et al.* Chewing tobacco, alcohol, and the risk of erythroplakia. *Cancer Epidemiol Biomarkers Prev* 2000; **9**: 639–45.
17 Bedi R, Jones P, eds. *Betel-quid and Tobacco Chewing Among the Bangladeshi Community in the United Kingdom: Usage and Health Issues*. London: Centre for Transcultural Oral Health, 1995.
18 Jaber MA, Porter SR, Scully C, Gilthorpe MS, Bedi R. Role of alcohol in non-smokers and tobacco in non-drinkers in the aetiology of oral epithelial dysplasia. *Int J Cancer* 1998; **77**: 333–6.
19 Jaber MA, Porter SR, Gilthorpe MS, Bedi R, Scully C. Risk factors for oral epithelial dysplasia: the role of smoking and alcohol. *Oral Oncol* 1999; **35**: 151–6.
20 Gillison M. Case–control study of human papillomavirus and oropharyngeal cancer. *N Engl J Med* 2007; **356**: 1944–56.
21 Mashberg A, Samit A. Early diagnosis of asymptomatic oral and oropharyngeal squamous cancers. *CA Cancer J Clin* 1995; **45**: 328–51.
22 Scully C, Ward-Booth P. Detection and treatment of early cancers of the oral cavity. *Crit Rev Oncol Hematol* 1995; **21**: 63–75.
23 Sciubba JJ. Oral cancer. The importance of early diagnosis and treatment. *Am J Clin Dermatol* 2001; **2**: 239–51.
24 Mehrotra R, Gupta A, Singh M, Ibrahim R. Application of cytology and molecular biology in diagnosing premalignant or malignant oral lesions. *Mol Cancer* 2006; **5**: 11.
25 Nishida AT, Tanaka S, Hirano S *et al*. Therapeutic outcomes of oral cancers at Kyoto University Hospital. *Acta Otolaryngol Suppl* 2007; **557**: 58–61.
26 Scully C. Clinical diagnostic methods for the detection of premalignant and early malignant oral lesions. *Community Dent Health* 1993; **1** (Suppl. 1): 43–52.

27 Sciubba JJ. Improving detection of precancerous and cancerous oral lesions. Computer-assisted analysis of the oral brush biopsy. U.S. Collaborative Oral CDx Study Group. *J Am Dent Assoc* 1999; **130**: 1445–57.
28 Epstein JB, Scully C, Spinelli JJ. Toluidine blue and Lugol's iodine application in the assessment of oral malignant disease and lesions at risk of malignancy. *J Oral Pathol Med* 1992; **21**: 160–3.
29 Sciubba JJ. Oral cancer and its detection. History-taking and the diagnostic phase of management. *J Am Dent Assoc* 2001; **132** (Suppl.): 12S–8S.
30 Kujan O, Glenny AM, Oliver RJ, Thakker N, Sloan P. Screening programmes for the early detection and prevention of oral cancer. *Cochrane Database Syst Rev* 2006; **3**: CD004150.
31 Chiesa F, Mauri S, Tradati N *et al.* Surfing prognostic factors in head and neck cancer at the Millennum. *Oral Oncol* 1999; **35**: 590–6.
32 Lung T, Tascau OC, Almasen HA, Muresan O. Head and neck cancer, treatment, evolution and post therapeutic survival. Part 2: A decade's results 1993–2002. *J Craniomaxillofac Surg* 2007; **35**: 126–31.
33 Langdon JD, Patel MF. *Operative Maxillofacial Surgery*. London: Chapman & Hall, 1998.
34 Mehta PS, Harrison LB. Function and organ preservation in adult cancers of the head and neck. *Expert Rev Anticancer Ther* 2007; **7**: 361–71.
35 Frerich B, Förster M, Schiefke E *et al*. Sentinel lymph node biopsy in squamous cell carcinomas of the lips and the oral cavity—a single center experience. *J Surg Oncol* 2007; **95**: 97–105.
36 de Graeff A, de Leeuw JR, Ros WJ *et al*. A prospective study on quality of life of patients with cancer of the oral cavity or oropharynx treated with surgery with or without radiotherapy. *Oral Oncol* 1999; **35**: 27–32.
37 Rogers SN, Hannah L, Lowe D, Magennis P. Quality of life 5–10 years after primary surgery for oral and oro-pharyngeal cancer. *J Craniomaxillofac Surg* 1999; **27**: 187–91.
38 Singh N, Scully C, Joyston-Bechal S. Oral complications of cancer therapies: prevention and management. *Clin Oncol* 1996; **8**: 15–24.
39 Scully C, Epstein JB. Oral health care in the cancer patient. *Oral Oncol* 1996; **32B**: 281–92.
40 Rogers SN, Miller RD, Ali K *et al*. Patients' perceived health status following primary surgery for oral and oropharyngeal cancer. *Int J Oral Maxillofac Surg* 2006; **35**: 913–9.
41 Scully C. Oral precancer: preventive and medical approaches to management. *Oral Oncol* 1995; **31B**: 16–26.
42 Scully C. Chemoprevention in oral cancer. *J Managed Care* 1997; **1**: 116–22.

Verrucous carcinoma

Verrucous carcinoma is an uncommon, warty, white neoplasm that is rarely ulcerated [1–6]. It may develop from proliferative verrucous leukoplakia (see p. 69.89). Risk factors include a possible association with HPV and some verrucous carcinomas develop as a result of the local use of snuff or tobacco. Confirmation of diagnosis by biopsy is particularly important because verrucous carcinoma responds well to excision but, if irradiated, may undergo anaplastic change, with subsequent acceleration of growth and invasiveness [7]. Methisoprinol may be of value [8].

References

1 Koch BB, Trask DK, Hoffman HT *et al*. National survey of head and neck verrucous carcinoma: patterns of presentation, care, and outcome. *Cancer* 2001; **92**: 110–20.
2 Hume WJ, Quayle AA. An unusual epithelial neoplasm of gingiva resembling the keratoacanthoma. *Br J Oral Surg* 1985; **23**: 366–70.
3 McDonald JS, Crissman JD, Gluckman JL. Verrucous carcinoma of the oral cavity. *Head Neck Surg* 1982; **5**: 22–8.
4 Firth NA. Oral lesions with a papillary surface texture: clinical and pathological correlations. *Ann R Australas Coll Dent Surg* 2000; **15**: 111–5.
5 Maraki D, Boecking A, Pomjanski N, Megahed M, Becker J. Verrucous carcinoma of the buccal mucosa: histopathological, cytological and DNA-cytometric features. *J Oral Pathol Med* 2006; **35**: 633–5.
6 Oliveira DT, de Moraes RV, Fiamengui Filho JF *et al*. Oral verrucous carcinoma: a retrospective study in Sao Paulo Region, Brazil. *Clin Oral Investig* 2006; **10**: 205–9.
7 Yoshimura Y, Mishima K, Obara S *et al*. Treatment modalities for oral verrucous carcinomas and their outcomes: contribution of radiotherapy and chemotherapy. *Int J Clin Oncol* 2001; **6**: 192–200.
8 Femiano F, Gombos F, Scully C. Oral proliferative verrucous leukoplakia: open trial of surgery compared with combined therapy using surgery and methisoprinol. *Int J Oral Maxillofac Surg* 2001; **30**: 318–22.

Florid oral papillomatosis

Florid oral papillomatosis is a rare but well-defined clinical entity of unknown pathogenesis. Risk factors include possible association with HPV, tobacco, and chronic inflammation or irritation.

Florid oral papillomatosis is essentially a verrucous carcinoma, a clinicopathological variant of squamous cell carcinoma also known by a confusing array of names such as Ackerman's tumour, Buschke–Loewenstein tumour, epithelioma cuniculatum, carcinoma cuniculatum and cutis papillomatosis carcinoides of Gottron.

Clinical features. The lesions are exuberant, warty or verrucous, and characterized by their benign appearance on histology, although this is usually associated with a marked capacity for recurrence and a tendency for carcinomatous change. Its apparent clinical benign nature may lead to lengthy periods of misdiagnosis, during which it slowly but relentlessly destroys and extends into underlying tissue but rarely metastasizes to lymph nodes [1–3].

Diagnosis. Biopsy is required, although to those unfamiliar with the diagnosis the relatively bland histological features are often more suggestive of verruca vulgaris or pseudoepitheliomatous hyperplasia than of squamous cell carcinoma. Alternatively, when it extends into underlying tissues, it may be mistaken for a benign adnexal tumour or even a cyst.

Treatment. Treatment in the early stage of the disease is usually successful. Etretinate therapy (200 mg/day) or chemotherapy with bleomycin may reduce the lesion bulk [4–6]. Surgical or laser excision is favoured. The use of radiotherapy is controversial since in numerous reported cases this has produced an anaplastic squamous cell carcinoma.

References

1 Schwartz RA. Verrucous carcinoma of the skin and mucosa. *J Am Acad Dermatol* 1995; **32**: 1–21.
2 Tyler MT, Ficarra G, Silverman S Jr, Odom RB, Regezi JA. Malignant acanthosis nigricans with florid papillary oral lesions. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1996; **81**: 445–9.
3 Cannon CR, Hayne ST. Concurrent verrucous carcinomas of the lip and buccal mucosa. *South Med J* 1993; **86**: 691–3.
4 Burg G, Sobetzko R. Florid oral papillomatosis: an indication for etretinate? *Hautarzt* 1990; **41**: 314–6.
5 Gaillard A, Hofmann B, Sapanet M, Gaillard F. Treatment of florid oral papillomatosis. Apropos of 10 cases. *Rev Stomatol Chir Maxillofac* 1983; **84**: 363–7.
6 Wienert V, Grussendorf EI. Treatment of florid oral papillomatosis with bleomycin. *Z Hautkr* 1978; **53**: 781–6.

Basal cell carcinoma

Actinic radiation is a major aetiological factor in the development of basal cell carcinoma (BCC), greater than 85% occurring on the sun-exposed areas of the head and neck [1,2]. Fair-skinned

individuals who burn and those whose occupations require excessive exposure to sunshine are at greatest risk; the tumour is rare in dark-skinned persons, and 95% occur after the age of 40 years [3].

Other significant risk factors for the development of BCC include prior burns, vaccinations, irradiation, exposure to inorganic arsenic, genetic syndromes (e.g. xeroderma pigmentosum, naevoid BCC syndrome, albinism and Bazex's syndrome) and immunosuppression [4–10].

Clinical features. On the lip these manifest as a pearly, sometimes ulcerated, nodule or papule. Unlike squamous cell carcinomas, BCCs only rarely originate on the vermilion but commonly occur periorally [11–14]. In contrast to squamous cell carcinomas, BCCs more commonly arise on the upper than the lower lip. The lesions can also arise *de novo* on the vermilion [15] or occasionally the mucosa of the lip, although spread of a tumour from an adjacent site may rarely occur.

BCC has multiple forms that can be simplistically divided as follows.

- Nodular: the most frequent type around the lips presents as a waxy translucent nodule with fine telangiectasias, often ulcerated.
- Morphoeic: an atrophic plaque resembling a scar, with an aggressive infiltrative growth pattern and high rate of recurrence after excision.
- Superficial: appears as an erythematous plaque with elevated borders and central atrophy or ulceration. It is rare around the lips.

Although the tumour rarely metastasizes, it is responsible for considerable functional and cosmetic morbidity.

Multiple lesions are commonly encountered and the various forms have overlapping clinical features. BCC can be frequently pigmented, resembling melanomas and other melanocytic lesions. BCC may, of course, be a feature of naevoid BCC syndrome (Gorlin–Goltz syndrome, see p. 69.39). Furthermore, in addition to having a significantly increased risk for new skin cancers, patients with BCC have been shown to have an increased risk of developing non-cutaneous cancers, including respiratory cancers, testicular cancer, breast cancer and non-Hodgkin's lymphoma [16–18].

Diagnosis. BCC of the lips must be differentiated from other nodules, including squamous cell carcinoma, keratoacanthoma, trichoepithelioma and sebaceous adenoma. Since lesions that arise periorally are often aggressive, early detection and confirmation by biopsy will prevent infiltration and destruction of the underlying structures.

Treatment. Various treatment modalities for BCC include scalpel, electrosurgery, cryosurgery and laser surgery, radiation, curettage and intralesional chemotherapy or alpha interferon [19–21]. Selection of the treatment modality depends on size, site and histological pattern of the tumour as well as the age of the patient.

Since lip lesions are often of the nodular or morphoeic types, Mohs' micrographic surgery, utilizing microscopically controlled excision, potentially offers the highest cure rate with the greatest preservation of tissue. The cure rate for BCC is over 90%.

References

1 Lear JT, Smith AG. Basal cell carcinoma. *Postgrad Med J* 1997; **73**: 538–42.
2 Lear W, Dahlke E, Murray CA. Basal cell carcinoma: review of epidemiology, pathogenesis, and associated risk factors. *J Cutan Med Surg* 2007; **11**: 19–30.
3 Miller SJ. Biology of basal cell carcinoma (Part 1). *J Am Acad Dermatol* 1991; **24**: 1–13.
4 Allison JR. Radiation-induced basal-cell carcinoma. *J Dermatol Surg Oncol* 1984; **10**: 200–3.
5 Di Tondo U, Berloco P, Trombetta G *et al*. Incidence of tumors in organ transplants. *Transplant Proc* 1997; **29**: 3623–4.
6 Goldberg LH. Basal cell carcinoma. *Lancet* 1996; **347**: 663–7.
7 Kimonis VE, Goldstein AM, Pastakia R *et al*. Clinical manifestations in 105 persons with naevoid basal cell carcinoma syndrome. *Am J Med Genet* 1997; **31**: 299–308.
8 Noodleman RF, Pollack SV. Trauma as a possible etiologic factor in basal cell carcinoma. *J Dermatol Surg Oncol* 1986; **12**: 841–6.
9 Schoolmaster WL, White DR. Arsenic poisoning. *South Med J* 1980; **73**: 198–207.
10 Prabhakaran VC, Gupta A, Huilgol SC, Selva D. Basal cell carcinoma of the eyelids. *Compr Ophthalmol Update* 2007; **8**: 1–14.
11 Bussani R, Grandi G, Cosatti C, Silvestri F. Basal cell epithelioma of the lip. Analysis of 42 cases. *Pathologica* 1989; **81**: 499–504.
12 Weitzner S, Heutel W. Multicentric basal cell carcinoma of the vermilion mucosa and skin of lower lip: report of a case. *Oral Surg* 1968; **26**: 269–72.
13 Weitzner S. Basal-cell carcinoma of the vermilion mucosa and skin of the lip. *Oral Surg Oral Med Oral Pathol* 1975; **39**: 634–7.
14 De Sousa J, Sanchez Yus E, Rueda M, Rojo S. Basal cell carcinoma on the vermilion border of the lip: a study of six cases. *Dermatology* 2001; **203**: 131–4.
15 Oriba HA, Sandermann S, Kircik L, Snow SN. Basal cell carcinoma of the vermilion zone of the lower lip: a report of 3 cases. *Oral Oncol* 1998; **34B**: 309–12.
16 Karagas MR, Greenberg ER, Mott LA, Baron JA, Ernster VL. Occurrence of other cancers among patients with prior basal cell and squamous cell skin cancer. *Cancer Epidemiol Biomarkers Prev* 1998; **7**: 157–61.
17 Frisch M, Hjalgrim H, Olsen JH, Melbye M. Risk for subsequent cancer after diagnosis of basal-cell carcinoma. A population-based epidemiologic study. *Ann Intern Med* 1996; **125**: 815–21.
18 Otley CC. Non-Hodgkin lymphoma and skin cancer: A dangerous combination. *Australas J Dermatol* 2006; **47**: 231–6.
19 Rowe DE, Carroll RJ, Day CL Jr. Long term recurrence rates in previously untreated (primary) basal cell carcinoma: implications for patient follow-up. *J Dermatol Surg Oncol* 1989; **15**: 315–27.
20 Bostanci C, Kocyigit P, Alp A, Erdem P, Gurgey E. Treatment of basal cell carcinoma located in the head and neck region with intralesional interferon alpha-2a: evaluation of long-term follow-up results. *Clin Drug Investig* 2005; **25**: 661–7.
21 Rodriguez-Vigil T, Vazquez-Lopez F, Perez-Oliva N. Recurrence rates of primary basal cell carcinoma in facial risk areas treated with curettage and electrodesiccation. *J Am Acad Dermatol* 2007; **56**: 91–5.

Keratoacanthoma

Keratoacanthoma is a benign, often rapidly growing lesion that probably arises from the supraseboglandular part of a sebaceous gland. Keratoacanthomas are common, self-limiting, proliferative tumours that arise most frequently in men after the sixth decade of life [1,2]. The lesions mimic squamous cell carcinoma both clinically and microscopically. Although some believe keratoacanthomas represent well-differentiated squamous cell carcinomas, significant differences between the two entities have been demonstrated [3]. A number of well-documented variants, many with generally distributed eruptive keratoacanthomas, have been described. One variant, Ferguson–Smith syndrome, is a familial trait.

Aetiology. The role of actinic damage is strongly supported by the fact that the majority of lesions occur on sun-exposed skin

(90%), with up to 10% occurring periorally or on the vermilion border of the lips. HPV has also been suggested as an aetiological agent [4], and increased numbers of keratoacanthomas have been reported in immunocompromised patients.

Clinical features. Keratoacanthomas often manifest at the vermilion border, as indurated, dome-shaped nodules displaying a characteristic central, keratin-filled, crusted and frequently darkened crater. Cutaneous lesions are asymptomatic but oral and lip lesions are frequently painful [5–7]. Intraoral keratoacanthomas are rare [8,9]. They usually appear as an ulcer with a rolled margin, clinically indistinguishable from squamous cell carcinoma, usually on the anterior or maxillary gingiva. It is unclear whether intraoral keratoacanthomas regress spontaneously, as all have been excised for diagnosis. Keratoacanthomas grow rapidly, attaining a size typically greater than 1 cm, may be locally invasive and result in significant tissue damage but, if left untreated, many undergo spontaneous involution after 1–2 months.

Diagnosis. Keratoacanthomas require differentiation from squamous cell carcinoma. When lesions develop intraorally or on the lips, they should immediately be subjected to biopsy for confirmation, since squamous cell carcinomas at these sites frequently metastasize.

Treatment. Management is often by surgical excision. Intralesional therapy with methotrexate or 5-fluorouracil can also be employed with excellent results [10,11]. Other suggested medical therapies include intralesional interferon alpha-2a and systemic isotretinoin [12,13].

References

1 Kingman J, Callen JP. Keratoacanthoma: a clinical study. *Arch Dermatol* 1984; **120**: 736–40.
2 Schwartz RA. Keratoacanthoma. *J Am Acad Dermatol* 1994; **30**: 1–19.
3 Waring AJ, Takata M, Rehman I, Rees JL. Loss of heterozygosity analysis of keratoacanthoma reveals multiple differences from cutaneous squamous cell carcinoma. *Br J Cancer* 1996; **73**: 649–53.
4 Hsi ED, Svoboda-Newman SM, Stern RA, Nickoloff BJ, Frank TS. Detection of human papillomavirus DNA in keratoacanthomas by polymerase chain reaction. *Am J Dermatopathol* 1997; **19**: 10–5.
5 Berrone S, De Gioanni PP, Gallesio C. Keratoacanthoma of the lower lip. A review of the literature and clinical case report. *Minerva Stomatol* 1992; **41**: 597–601.
6 de Visscher JGAM, van der Wal JE, Starink ThM, Tiwari RM, van der Waal I. Giant keratoacanthoma of the lower lip. Report of a case of spontaneous regression. *Oral Surg* 1996; **81**: 193–6.
7 Azaz B, Lustmann J. Keratoacanthoma of the lower lip. Review of the literature and report of a case. *Oral Surg Oral Med Oral Pathol* 1974; **38**: 918–27.
8 Eversole LR, Leider AS, Alexander G. Intraoral and labial keratoacanthomas. *Oral Surg* 1982; **54**: 663–7.
9 Whyte AM, Hansen LS, Lee C. The intraoral keratoacanthoma: a diagnostic problem. *Br J Oral Surg* 1986; **24**: 438–41.
10 De Visscher JG, van der Wal KG, Blanken R, Willemse F. Treatment of giant keratoacanthoma of the skin of the lower lip with intralesional methotrexate: a case report. *J Oral Maxillofac Surg* 2002; **60**: 93–5.
11 Melton JR, Nelson BR, Stough DB *et al*. Treatment of keraotoacanthoma with intralesional methotrexate. *J Am Acad Dermatol* 1991; **25**: 1017–23.
12 Grobb JJ, Suzini F, Richard MA *et al.* Large keratoacanthomas treated with intralesional interferon alpha-2a. *J Am Acad Dermatol* 1993; **29**: 237–41.
13 Schaller M, Korting HC, Wolff H, Schirren CG, Burgdorf W. Multiple keratoacanthomas, giant keratoacanthoma and keratoacanthoma centrifugum marginatum: development in a single patient and treatment with oral isotretinoin. *Acta Derm Venereol (Stockh)* 1996; **76**: 40–2.

Other oral malignant primary neoplasms

The following comprise up to 10% of all oral malignant tumours.

1 Salivary gland tumours
2 Malignant melanoma
3 Lymphomas: non-Hodgkin's lymphomas are increasingly seen in the fauces in HIV disease and immunocompromised persons
4 Sarcomas
5 Kaposi's sarcoma: oral Kaposi's sarcoma is typically seen in HIV disease or other immunocompromised persons and especially in the posterior palate as a brown or purple macule that becomes nodular and ulcerates
6 Some odontogenic tumours
7 Maxillary antral carcinoma (or other neoplasms)
8 Langerhans' cell histiocytosis
9 Neoplasms of bone and connective tissue
10 Other neoplasms.

Abrikossoff's tumour

Abrikossoff's tumour is a disease that develops between the second and sixth decades of life, more frequently among women and blacks. The head and neck area is affected in 45–65% of cases and, of these, 70% are located intraorally (tongue, oral mucosa, hard palate) [1,2].

The benign form shows polygonal cells with granular eosinophilic cytoplasm and small nuclei. The malignant form, however, is associated with a high mitotic index and pleomorphic cellular tissue.

The clinical feature of either is a swelling covered by mucosa of normal clinical appearance. Histological examination is required. The treatment is surgery.

References

1 Becelli R, Perugini M, Gasparini G, Cassoni A, Fabiani F. Abrikossoff's tumor. *J Craniofac Surg* 2001; **12**: 78–81.
2 Bonfils P, de Preobrajenski N, Elouraet Y *et al*. Granular cell tumours (Abrikossoff's tumour) of the parotid region. *Rev Laryngol Otol Rhinol (Bord)* 2006; **127**: 183–5.

Metastatic oral neoplasms

Metastases to the oral tissues are rare, accounting for only 1% of all oral tumours and most appear in bone, especially the mandibular premolar or molar area or condyle. Metastases may occasionally appear as an alveolar or gingival swelling or ulcer, or as described below. Most oral metastases originate from carcinomas of breast, lung, kidney, thyroid, stomach, liver, colon or prostate [1–12]. Tumour deposits arise from lymphatic or haematogenous spread.

Clinical features. Metastases usually present as a lesion arising in the jaw, sometimes only revealed coincidentally by imaging, at other times causing symptoms. In up to one-third of patients the jaw lesions are the first manifestation of the tumour.

Non-Hodgkin's lymphomas are frequently gingival or faucial in location.

Many metastases are asymptomatic but others manifest with:

- pain
- paraesthesia or hypoaesthesia
- swelling
- tooth mobility
- non-healing extraction sockets
- pathological fracture
- radiolucency or radio-opacity.

Diagnosis. Diagnosis is from history and clinical features supplemented by radiography and histopathology.

Treatment. Radiotherapy, surgery or chemotherapy.

References

1 Abdullah BH, Yahya HI, Talabani NA, Alash NI, Mirza KB. Gingival and cutaneous angiosarcoma. *J Oral Pathol Med* 2000; **29**: 410–2.
2 Alandez J, Llanes F, Herrera JI, Carasol M, Bascones A. Metastatic lung carcinoma involving the periodontium. Report of a case. *J Periodontol* 1995; **66**: 896–8.
3 Ardekian L, Rosen DJ, Peled M *et al.* Primary gingival malignant melanoma. Report of 3 cases. *J Periodontol* 2000; **71**: 117–20.
4 Bschorer R, Lingenfelser T, Kaiserling E, Schwenzer N. Malignant lymphoma of the mucosa-associated lymphoid tissue (MALT): consecutive unusual manifestation in the rectum and gingiva. *J Oral Pathol Med* 1993; **22**: 190–2.
5 Ellis GL, Jensen JL, Reingold IM, Barr RJ. Malignant neoplasms metastatic to gingivae. *Oral Surg Oral Med Oral Pathol* 1977; **44**: 238–45.
6 Horie Y, Suou T, Hirayama C *et al.* Hepatocellular carcinoma metastatic to the oral cavity including the maxilla and the mandible: report of two cases and review of the literature. *Gastroenterol Jpn* 1985; **20**: 604–10.
7 Keller EE, Gunderson LL. Bone disease metastatic to the jaw. *J Am Dent Assoc* 1987; **115**: 697–701.
8 Margiotta V, Franco V, Rizzo A *et al*. Gastric and gingival localization of mucosa-associated lymphoid tissue (MALT) lymphoma. An immunohistochemical, virological and clinical case report. *J Periodontol* 1999; **70**: 914–8.
9 Medina BR, Barba EM, Torres AV, Trujillo SM. Gingival metastases as first sign of a primary uterine angiosarcoma. *J Oral Maxillofac Surg* 2001; **59**: 467–71.
10 Nishimura Y, Yakata H, Kawasaki T *et al.* Metastatic tumours of the mouth and jaws: a review of the Japanese literature. *J Maxillofac Surg* 1982; **10**: 253–8.
11 Malhotra AK. F-18 FDG PET scan findings in a case of carcinoma of the breast with a rare site of metastases to the gingival region. *Clin Nucl Med* 2006; **31**: 820–1.
12 Nuyens M, Schüpbach J, Stauffer E, Zbären P. Metastatic disease to the parotid gland. *Otolaryngol Head Neck Surg* 2006; **135**: 844–8.

Ulcers in association with systemic disease

Aphthae (see p. 69.44) or aphthous-like ulcers are occasionally associated with systemic disease. However, a wide range of systemic diseases, especially haematological, gastrointestinal and dermatological disorders, may cause other oral lesions which, because of the moisture, trauma and infection in the mouth, tend to break down to leave ulcers or erosions. Oral ulceration is also frequently caused by infections and can be caused by iatrogenic problems such as drugs or irradiation (see Table 69.13).

Haematological diseases

Deficiency states

Low iron, folate or vitamin B_{12} levels may predispose to aphthae. A few of these patients also have anaemia, sometimes with other oral features such as glossitis or angular stomatitis, but many have a deficiency state with no established anaemia [1–3]. Occasionally, patients with deficiency of B vitamins may develop other types of oral ulcer, and sometimes epithelial dysplasia [4].



Fig. 69.30 Aphthous-like ulceration in HIV disease.

References

1 Field EA, Speechley JA, Rugman FR *et al.* Oral signs and symptoms in patients with undiagnosed vitamin B12 deficiency. *J Oral Pathol Med* 1995; **24**: 468–70.
2 Tyldesley WR. Oral signs and symptoms in anaemias. *Br Dent J* 1985; **139**: 232–6.
3 Thongprasom K, Youngnak P, Aneksuk V. Hematologic abnormalities in recurrent oral ulceration. *Southeast Asian J Trop Med Public Health* 2002; **33**: 872–7.
4 Theaker JM, Porter SR, Fleming KA. Oral epithelial dysplasia in vitamin B12 deficiency. *Oral Surg* 1989; **67**: 81–3.

Leukopenias and agranulocytosis

White cell dyscrasias and HIV infection are also often complicated by oral ulceration (Fig. 69.30). Oral ulceration may be a major symptom in patients with leukopenias, and may be the first manifestation of drug-induced agranulocytosis. Painful, deep, irregular ulcers, often with only a minimal inflammatory halo, involve the mouth and/or pharynx and tend to extend and penetrate slowly. In cyclic neutropenia, ulcers appear episodically at 21-day intervals in association with the neutropenic episodes. Severe periodontitis is often also a feature of leukocyte and other immune defects and the patients may suffer from recurrent infections elsewhere [1–5]. Methotrexate can cause oral ulceration in the absence of leukopenia.

References

1 Baehni PC, Payot P, Tsai CC *et al.* Periodontal status associated with chronic neutropenia. *J Clin Periodontol* 1983; **10**: 222–30.
2 Porter SR, Scully C, Standen G. Autoimmune neutropenia manifesting as recurrent oral ulceration. *Oral Surg* 1994; **78**: 178–80.
3 Scully C, Gilmour G. Neutropenia and dental patients. *Br Dent J* 1986; **160**: 43–6.
4 Zaromb A, Chamberlain D, Schoor R, Almas K, Blei F. Periodontitis as a manifestation of chronic benign neutropenia. *J Periodontol* 2006; **77**: 1921–6.
5 Hakki SS, Aprikyan AA, Yildirim S *et al*. Periodontal status in two siblings with severe congenital neutropenia: diagnosis and mutational analysis of the cases. *J Periodontol* 2005; **75**: 837–44.



Fig. 69.31 Herpes simplex lingual recurrence, and candidosis in leukaemia: similar lesions may be seen in HIV infection.

Leukaemias

Oral ulceration may be a prominent feature, especially in the acute leukaemias. Other oral manifestations of leukaemia include mucosal pallor, gingival haemorrhage, gingival swelling, petechiae and ecchymoses [1–7]. Oral infections with *Candida albicans* and Gram-negative bacteria including *Pseudomonas* species, *Escherichia coli*, *Proteus*, *Klebsiella* and *Serratia* species are common, especially in acute leukaemias, and may act as a portal for septicaemia [8]. Herpes simplex or zoster–varicella virus ulcers are also common (Fig. 69.31). Chemotherapy complicates the situation because it too can produce oral ulceration [1,7,9], as can bone marrow transplantation.

Other occasional findings include paraesthesia (particularly of the lower lip), facial palsy, extrusion of teeth or bone, painful swellings over the mandible and parotid swelling (Mikulicz's syndrome) [10,11].

References

1 Barrett AP. A long term prospective clinical study of oral complications during conventional chemotherapy for acute leukemia. *Oral Surg* 1987; **63**: 313–6.
2 Dreizen S, McCredie KB, Body GP *et al.* Quantitative analysis of the oral complications of anti-leukemia chemotherapy. *Oral Surg* 1986; **62**: 650–3.
3 Dreizen S, McCredie KB, Keating MJ *et al.* Malignant gingival and skin infiltrates in adult leukemia. *Oral Surg* 1983; **55**: 572–8.
4 Scully C, MacFarlane TW. Orofacial manifestations in childhood malignancy: clinical and microbiological findings during remission. *ASDC J Dent Child* 1983; **50**: 121–5.
5 Ayers AM, Colquhoun AN. Leukaemia in children. Part I: Orofacial complications and side-effects of treatment. *N Z Dent J* 2000; **96**: 60–5.
6 Dean AK, Ferguson JW, Marvan ES. Acute leukaemia presenting as oral ulceration to a dental emergency service. *Aust Dent J* 2003; **48**: 195–7.
7 Sepulveda E, Brethauer U, Rojas J, Fernandez E, Le Fort P. Oral ulcers in children under chemotherapy: clinical characteristics and their relation with Herpes Simplex Virus type 1 and Candida albicans. *Med Oral Patol Oral Cir Bucal* 2005; **10** (Suppl. 1): E1–8.
8 Dreizen S, McCredie KB, Bodey GP *et al.* Microbial mucocutaneous infections in acute adult leukaemia. *Postgrad Med* 1986; **79**: 107–18.
9 Dreizen S, McCredie KB, Keating MJ. Chemotherapy-associated oral hemorrhages in adults with acute leukemia. *Oral Surg* 1984; **57**: 494–8.
10 Filippi A, Dreyer T, Bohle RM, Pohl Y, Rosseau S. Sequestration of the alveolar bone by invasive aspergillosis in acute myeloid leukemia. *J Oral Pathol Med* 1997; **26**: 437–40.
11 Sood BR, Sharma B, Kumar S, Gupta D, Sharma A. Facial palsy as first presentation of acute myeloid leukemia. *Am J Hematol* 2003; **74**: 200–1.

Granulocytic sarcoma

Synonym
- Chloroma

Granulocytic sarcomas are rare in the oral cavity. Most present with swelling or symptoms related to skeletal involvement [1–4]. The maxilla is particularly involved [1,5–7].

References

1 Barker GR, Sloan P. Maxillary chloroma: a myeloid leukaemic deposit. *Br J Oral Surg* 1988; **26**: 124–8.
2 Ficarra G, Silverman S, Quivey JM *et al.* Granulocytic sarcoma (chloroma) of the oral cavity: a case with aleukaemic presentation. *Oral Surg* 1987; **63**: 709–14.
3 Hansen LS, Merrell PW, Bainton DF, Taylor KL. Granulocytic sarcoma: an aleukemic oral presentation. *Can Dent Assoc J* 1982; **10**: 41–6.
4 Stoopler ET, Pinto A, Alawi F *et al.* Granulocytic sarcoma: an atypical presentation in the oral cavity. *Spec Care Dentist* 2004; **24**: 65–9.
5 Castella A, Davey FR, Elbadawi A, Gordon GB. Granulocytic sarcoma of the hard palate: report of the first case. *Hum Pathol* 1984; **15**: 1190–2.
6 Amin KS, Ehsan A, McGuff HS, Albright HC. Minimally differentiated acute myelogenous leukemia (AML-M0) granulocytic sarcoma presenting in the oral cavity. *Oral Oncol* 2002; **38**: 516–9.
7 Lee SS, Kim HK, Choi SC, Lee JI. Granulocytic sarcoma occurring in the maxillary gingiva demonstrated by magnetic resonance imaging. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001; **92**: 689–93.

Myelodysplastic syndromes

Oral manifestations in myelodysplastic syndrome include particularly ulceration but also paraesthesiae, petechiae, burning mouth, gingival swelling, xerostomia and herpes labialis [1–4].

References

1 Epstein JB, Priddy RW, Sparling T *et al.* Oral manifestations in myelodysplastic syndrome. *Oral Surg* 1986; **61**: 466–70.
2 Flint SR, Sugerman P, Scully C *et al.* The myelodysplastic syndromes: case report and review. *Oral Surg* 1990; **70**: 579–83.
3 Gibson J, Lamey P-J, Watson WH *et al.* The myelodysplastic syndrome presenting with oral symptoms. *Br Dent J* 1987; **163**: 234–5.
4 Porter SR, Scully C. Gingival and oral mucosal ulceration associated with the myelodysplastic syndrome. *Oral Oncol* 1994; **30B**: 346–50.

Lymphomas

Some 2–10% of lymphomas present first in the oral cavity. Of these oral lymphomas, 80% are composed of follicular centre cells or post-follicular cells [1–6]. Lymphomas usually occur on the pharynx or palate, but occasionally on the tongue, gingivae or lips; they may appear as oral swellings, which sometimes ulcerate and may cause pain or sensory disturbance. Oral herpes zoster and herpes simplex infections are common in patients with lymphomas.

There is an increased incidence of oral lymphomas in HIV disease [7,8] including oral plasmablastic lymphomas [9–11].

Lethal midline granuloma. Lethal midline granuloma is the term sometimes used to include a spectrum of conditions including Wegener's granulomatosis, polymorphic reticulosis (lymphomatoid granulomatosis) and idiopathic midline destructive disease.

Wegener's granulomatosis. Although not a lymphoma, Wegener's granulomatosis is discussed here. Oral manifestations are common and may be the first sign of Wegener's granulomatosis [12–24]. A painless, progressive swelling of the gingiva in a previously healthy mouth, particularly associated with swollen inflamed papillae, should arouse suspicion of Wegener's granulomatosis. The gingival enlargement may have a fairly characteristic 'strawberry-like' appearance. Wegener's granulomatosis may also present with oral ulceration, failure of an extraction socket to heal or occasionally swelling of the lip or salivary gland.

Polymorphic reticulosis (synonym lymphomatoid granulomatosis). The most common oral presentation of polymorphic reticulosis is palatal ulceration but ulceration may occur elsewhere [20].

Idiopathic midline destructive disease [25–28]. Downward spread from nasal disease can lead to palatal necrosis and ulceration in idiopathic midline destructive disease. Occasionally the disease presents with delayed healing of an extraction socket.

References

1 Epstein JB, Epstein JD, Le ND, Gorsky M. Characteristics of oral and paraoral malignant lymphoma: a population-based review of 361 cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001; **92**: 519–25.
2 Baden E, Carter R. Intraoral presentation of American Burkitt's lymphoma after extraction of a mandibular left third molar. *J Oral Maxillofac Surg* 1987; **45**: 689–93.
3 Savarrio L, Gibson J, Dunlop DJ, O'Rourke N, Fitzsimons EJ. Spontaneous regression of an anaplastic large cell lymphoma in the oral cavity: first reported case and review of the literature. *Oral Oncol* 1999; **35**: 609–13.
4 Born S, Gaber G, Willgeroth K *et al*. Metastasising malignant lymphoma mimicking necrotising and hyperplastic gingivostomatitis. *Eur J Dermatol* 1999; **9**: 569–73.
5 Eisenbud L, Sciubba JJ, Mir R *et al.* Oral presentations in non-Hodgkins lymphoma: a review of thirty one cases. *Oral Surg* 1983; **56**: 151–6.
6 Cox DP, Treseler P, Dong R, Jordan RC. Rare oral cavity presentation of a B-cell lymphoblastic lymphoma. A case report and review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; **103**: 814–9.
7 Ioachim HL, Cooper MC, Hellman GC. Lymphomas in men at high risk for acquired immune deficiency syndrome (AIDS): a study of 21 cases. *Cancer* 1985; **56**: 2831–42.
8 Reichert P. US1 HIV—changing patterns in HAART era, patients' quality of life and occupational risks. *Oral Dis* 2006; **12** Suppl 1: 3.
9 Porter SR, Diz Dios P, Kumar N *et al*. Oral plasmablastic lymphoma in previously undiagnosed HIV disease. *Oral Surg Oral Med Oral Pathol* 1999; **87**: 730–4.
10 Flaitz CM, Nichols CM, Walling DM, Hicks MJ. Plasmablastic lymphoma: an HIV-associated entity with primary oral manifestations. *Oral Oncol* 2002; **38**: 96–102.
11 Toure G, Roucayrol AM, Meningaud JP, Bertrand JC. Plasmablastic lymphoma: a case report. *Quintessence Int* 2007; **38**: 161–3.
12 Lilly J, Juhlin T, Lew D, Vincent S, Lilly G. Wegener's granulomatosis presenting as oral lesions: a case report. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1998; **85**: 153–7.
13 Abraham-Inpijn L. Oral and otal manifestations as the primary symptoms in Wegener's granulomatosis. *J Head Neck Pathol* 1983; **2**: 20–2.
14 Allen CM, Canisa C, Salewski C, Weiland JE. Wegeners granulomatosis: report of three cases with oral lesions. *J Oral Maxillofac Surg* 1991; **49**: 294–8.
15 Israelson H, Binnie WH, Hurt WC. The hyperplastic gingivitis of Wegener's granulomatosis. *J Periodontol* 1981; **52**: 81–7.
16 Lutcavage GJ, Schaberg SJ, Arendt DA, Malmquist JP. Gingival mass with massive soft-tissue necrosis. *J Oral Maxillofac Surg* 1991; **49**: 1332–8.
17 Parsons E, Seymour RA, MacLeod RI *et al*. Wegener's granulomatosis: distinct gingival lesion. *J Clin Periodontol* 1992; **19**: 64–6.
18 Patten SF, Tomecki KJ. Wegeners granulomatosis: cutaneous and oral mucosal disease. *J Am Acad Dermatol* 1993; **28**: 710–8.
19 Hansen LS, Silverman S, Pons VG *et al*. Limited Wegener's granulomatosis. Report of a case with oral, renal and skin involvement. *Oral Surg* 1985; **60**: 524–30.
20 McDonald TJ, De Remee RA, Weiland LH. Wegener's granulomatosis and polymorphic reticulosis: two diseases or one? Experience with 90 patients. *Arch Otolaryngol* 1981; **107**: 141–6.
21 Fauci AS, Haynes BF, Katz P *et al*. Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years. *Ann Intern Med* 1983; **98**: 76–85.
22 Rahilly G, Rahilly M. A case of palatal Wegener's granulomatosis. *Oral Dis* 2000; **6**: 259–61.
23 Rasmussen N. Management of the ear, nose, and throat manifestations of Wegener granulomatosis: an otorhinolaryngologist's perspective. *Curr Opin Rheumatol* 2001; **13**: 3–11.
24 Stewart C, Cohen D, Bhattacharyya I *et al*. Oral manifestations of Wegener's granulomatosis: a report of three cases and a literature review. *J Am Dent Assoc* 2007; **138**: 338–48.
25 Crissman JD, Weiss MA, Gluckman J. Midline granuloma syndrome. A clinicopathologic study of 13 patients. *Am J Surg Pathol* 1982; **6**: 335–8.
26 Nelson JF, Finkelstein MW, Acevedo A *et al*. Midline 'non-healing' granuloma. *Oral Surg* 1984; **58**: 554–60.
27 Tsokos M, Fauci AS, Costa J. Idiopathic midline destructive disease (IMDD). A subgroup of patients with the midline granuloma syndrome. *Am J Clin Pathol* 1982; **77**: 162–7.
28 Rodrigo JP, Suarez C, Rinaldo A *et al*. Idiopathic midline destructive disease: fact or fiction? *Oral Oncol* 2005; **41**: 340–8.

Mycosis fungoides

Oral lesions in mycosis fungoides typically are red or white areas on the tongue but are usually late manifestations of this disease [1–6].

References

1 Barnett ML, Cole RJ. Mycosis fungoides with multiple oral mucosal lesions. *J Periodontol* 1985; **56**: 690–3.
2 Evans GE, Dalziel KL. Mycosis fungoides with oral involvement. *Int J Oral Maxillofac Surg* 1987; **16**: 634–7.
3 Patel SP, Hotterman OA. Mycosis fungoides: an overview. *J Surg Oncol* 1983; **22**: 221–6.
4 de la Fuente EG, Rodriguez-Peralto JL, Ortiz PL *et al*. Oral involvement in mycosis fungoides: report of two cases and a literature review. *Acta Derm Venereol (Stockh)* 2000; **80**: 299–301.
5 Harman M, Akdeniz S, Arslan A, Koyoglu S. Mycosis fungoides with involvement of the oral cavity. *J Eur Acad Dermatol Venereol* 1998; **10**: 253–6.
6 Hata T, Aikoh T, Hirokawa M, Hosoda M. Mycosis fungoides with involvement of the oral mucosa. *Int J Oral Maxillofac Surg* 1998; **27**: 127–8.

Pseudolymphoma

Rare tumour-like lymphoproliferative infiltrates that lack the malignant potential of lymphomas may be seen intraorally, notably in the palate [1–3].

References

1 Wright JM, Dunsworth AR. Follicular lymphoid hyperplasia of the hard palate: a benign lymphoproliferative process. *Oral Surg* 1983; **55**: 162–8.
2 Del Rio E, Sanchez Yus E, Requena L *et al*. Oral pseudolymphoma: a report of two cases. *J Cutan Pathol* 1997; **24**: 51–5.
3 Cornelio S, Rodrigues G. Benign lymphoid hyperplasia of the tongue masquerading as carcinoma: case report and literature review. *J Contemp Dent Pract* 2005; **6**: 111–9.

Histiocytoses

The histiocytoses typically produce lytic bone lesions but gingival swelling, periodontal destruction with loosening of teeth,

non-healing extraction sockets and mouth ulceration may be seen. ^{111}In-pentetreotide imaging may be useful in diagnosis of Langerhans' cell histiocytosis [1–9].

References

1 Broadbent V, Pritchard J. Histiocytosis X: current controversies. *Arch Dis Child* 1985; **60**: 605–8.
2 Favera BE, McCarthy RC, Mieran GW. Histiocytosis X. *Hum Pathol* 1983; **14**: 663–76.
3 Hartman KS. Histiocytosis X. A review of 114 cases with oral involvement. *Oral Surg* 1980; **49**: 38–54.
4 Langowska-Adamczyk H, Jedrusik-Pawlowska M. Disseminated form of Langerhans cell histiocytosis discovered in stomatological examination: a case report. *Med Sci Monit* 2000; **6**: 1174–8.
5 Shirley JC, Thornton JB. Oral manifestations of Langerhans' cell histiocytosis: review and report of case. *ASDC J Dent Child* 2000; **67**: 293–6.
6 Chen N, Peron JM. The nonhealing of the buccal mucosa after tooth extraction. Apropos a case of histiocytosis X. *Rev Stomatol Chir Maxillofac* 2000; **101**: 33–5.
7 Milian MA, Bagan JV, Jimenez Y *et al*. Langerhans' cell histiocytosis restricted to the oral mucosa. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001; **91**: 76–9.
8 Mortellaro C, Pucci A, Palmeri A *et al*. Oral manifestations of Langerhans cell histiocytosis in a pediatric population: a clinical and histological study of 8 patients. *J Craniofac Surg* 2006; **17**: 552–6.
9 Moraes Pde C, Bonecker M, Furuse C, Teixera RG, Araujo VC. Langerhans cell histiocytosis in a child: a 10-year follow-up. *Int J Paediatr Dent* 2007; **17**: 211–6.

Multicentric reticulohistiocytosis

Oral lesions are seen in up to 50% of patients with multicentric reticulohistiocytosis [1,2]. Lesions are collections of histiocytes that form nodular or granular lesions, particularly in the labial or buccal mucosa. The temporomandibular joint may also be involved as part of the polyarthropathy.

References

1 Katz RW, Anderson KF. Multicentric reticulohistiocytosis. *Oral Surg* 1988; **65**: 721–5.
2 Tajirian AL, Malik MK, Robinson-Bostam L, Lally EV. Multicentric reticulohistiocytosis. *Clin Dermatol* 2006; **24**: 486–92.

Hypereosinophilic syndrome

Oral erosions affecting buccal, gingival or labial mucosae may be a feature of the hypereosinophilic syndrome [1–6] and may herald cardiac involvement [2]. Etoposide, interferon-α and hydroxyurea (hydroxycarbamide) may be effective therapy [4,5].

References

1 Aractingi S, Janin A, Zini JM *et al*. Specific mucosal erosions in hypereosinophilic syndrome. *Arch Dermatol* 1996; **132**: 535–41.
2 Leiferman KM, O'Duffy D, Perry HO *et al*. Recurrent incapacitating mucosal ulcerations: a prodrome of the hypereosinophilic syndrome. *Am J Med* 1982; **247**: 1018–20.
3 Billon C, Gautier C, Villaret E *et al*. Isolated mucosal ulcers disclosing idiopathic hypereosinophilic syndrome. *Ann Dermatol Vénéréol* 1997; **124**: 248–50.
4 Smit AJ, van Essen LH, de Vries EG. Successful long-term control of idiopathic hypereosinophilic syndrome with etoposide. *Cancer* 1991; **67**: 2826–7.
5 Barouky R, Bencharif L, Badet F *et al*. Mucosal ulcerations revealing primitive hypereosinophilic syndrome. *Eur J Dermatol* 2003; **1**: 207–8.
6 Amano A, Sakai N, Sigashi N, Yoshizawa Y, Kawana S. A case of hypereosinophilic syndrome. *J Dermatol* 2005; **32**: 286–9.

Hypoplasminogenaemia

Gingival swelling and ulceration are features of hypoplasminogenaemia.

Gastrointestinal diseases

Aphthae in gastrointestinal diseases are discussed on p. 69.44. Other types of mouth ulcer are also sometimes found in ulcerative colitis and Crohn's disease.

Pyostomatitis vegetans

The oral lesions termed pyostomatitis vegetans are deep fissures, pustules and papillary projections. Less than 50 cases have been recorded and most patients have had inflammatory bowel disease, that is ulcerative colitis or Crohn's disease [1–14]. The course of these lesions tends to follow that of the associated bowel disease [1–5,13].

Although the oral lesions may respond at least partially to topical therapy (e.g. corticosteroids), systemic treatment is often needed [1–5,13].

References

1 Ballo FS, Camisa C, Allen CM. Pyostomatitis vegetans. *J Am Acad Dermatol* 1989; **21**: 381–7.
2 Basu MK, Asquith P. Oral manifestations of inflammatory bowel disease. *Clin Gastroenterol* 1980; **9**: 307.
3 Chan S, Scully C, Prime SS *et al*. Pyostomatitis vegetans: oral manifestation of ulcerative colitis. *Oral Surg* 1991; **27**: 689–92.
4 Neville B, Laden SA, Smith SE *et al*. Pyostomatitis vegetans. *Am J Dermatopathol* 1985; **7**: 69–77.
5 Thornhill MH, Zakrzewska JM, Gilkes JJH. Pyostomatitis vegetans: report of three cases and review of the literature. *J Oral Pathol Med* 1992; **21**: 128–33.
6 Van Hale HM, Rogers RS, Zone JJ. Pyostomatitis vegetans: a reactive mucosal marker for inflammatory disease of the gut. *Arch Dermatol* 1985; **121**: 94–8.
7 Chaudhry SI, Philpot NS, Odell EW, Challacombe SJ, Shirlaw PJ. Pyostomatitis vegetans associated with asymptomatic ulcerative colitis: a case report. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1999; **87**: 327–30.
8 Al-Rimawi HS, Hammad MM, Raweily EA, Hammad HM. Pyostomatitis vegetans in childhood. *Eur J Pediatr* 1998; **157**: 402–5.
9 Oettinger R, Gerner P, Borner N, Schopf RE. Pyostomatitis vegetans and Crohn's disease. A specific association of 2 diseases. *Dtsch Med Wochenschr* 1998; **123**: 285–8.
10 Healy CM, Farthing PM, Williams DM, Thornhill MH. Pyostomatitis vegetans and associated systemic disease. A review and two case reports. *Oral Surg Oral Med Oral Pathol* 1994; **78**: 323–8.
11 Prendiville JS, Israel DM, Wood WS, Dimmick JE. Oral pemphigus vulgaris associated with inflammatory bowel disease and herpetic gingivostomatitis in an 11-year-old girl. *Pediatr Dermatol* 1994; **11**: 145–50.
12 Calobrisi SD, Mutasim DF, McDonald JS. Pyostomatitis vegetans associated with ulcerative colitis. Temporary clearance with fluocinonide gel and complete remission after colectomy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1995; **79**: 452–4.
13 Hegarty AM, Barrett AW, Scully C. Pyostomatitis vegetans. *Clin Exp Dermatol* 2004; **29**: 1–7.
14 Ruiz-Roca JA, Berini-Aytes L, Gay-Escoda C. Pyostomatitis vegetans. Report of two cases and review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005; **99**: 447–54.

Orofacial granulomatosis (OFG)

Aetiology. Crohn's disease can affect the mouth but some patients appear to develop similar oral lesions because of an adverse reaction to various food additives, such as cinnamaldehyde or benzoates, butylated hydroxyanisole or dodecyl gallate (in margarine), or to menthol (in peppermint oil) or cobalt, although these reactions are by no means always relevant [1–16]. For example, the lesions in only one of nine patients in one study



Fig. 69.32 Orofacial granulomatosis (OFG)

had any relationship to food intake [15]. Nevertheless, cinnamon and/or benzoate-free diets may produce improvement [16]. The genetic background [17], any role of allergy [18] and diverse possible other aetiological factors such as *Mycobacterium paratuberculosis* [19] is unclear.

The term 'orofacial granulomatosis' is preferred in some centres since it is unclear where in the spectrum of Crohn's disease/sarcoidosis/allergy/infection these lesions (and related conditions such as Melkersson–Rosenthal syndrome and granulomatous cheilitis) lie [8,20–23].

Pathology. Non-caseating granulomas and lymphoedema may be seen but the granulomas tend to be sparse and deep, close to the muscle.

Clinical features. Ulcers classically involve the buccal sulcus where they appear as linear ulcers, often with granulomatous masses flanking them.

Mucosal lesions also include thickening and folding of the mucosa to produce a 'cobblestone' type of appearance and mucosal tags. Purple granulomatous enlargements may appear on the gingiva. The lips or face may swell (Fig. 69.32) and there may be splitting of the lips and angular stomatitis [24–26].

Diagnosis. The oral history is not specific, and investigation of the gastrointestinal tract is mandatory. Investigations such as chest radiography, serum angiotensin-converting enzyme and a gallium scan may be required to exclude sarcoidosis. Patch tests may be indicated to exclude reactions to various foodstuffs or additives.

Treatment. Elimination diets may be warranted in patients with OFG if allergy is suspected [11,16]. Topical or intralesional corticosteroids may effectively control the oral lesions [6]. Intralesional corticosteroid injections may also reduce the swelling. The injection of up to 10 mL triamcinolone (10 mg/L) into the lips after local analgesia may be effective [15,27–30]. The injections may have to be repeated every 4–6 months once a response plateau has been reached.

Clofazimine appears to be effective during the early stages and works by clearing granulomas. In a dose of 100 mg twice daily for 10 days, then twice weekly for 4 months, clofazimine appears to help the majority of patients [31–33].

Systemic corticosteroids are rarely indicated and in any event not all patients respond [29,31]. Metronidazole [3] or sulfasalazine [31] may be of value in some cases. Thalidomide has also been reported as beneficial [34].

References

1 Field EA, Tyldesley WR. Oral Crohn's disease revisited: a 10 year review. *Br J Oral Maxillofac Surg* 1989; **27**: 114–23.
2 Halme L, Meurman JH, Laine P *et al.* Oral findings in patients with active or inactive Crohn's disease. *Oral Surg* 1993; **76**: 175–81.
3 Kano Y, Shiohara T, Yagita A. Treatment of recalcitrant cheilitis granulomatosa with metronidazole. *J Am Acad Dermatol* 1992; **27**: 629–30.
4 Patton DW, Ferguson MM, Forsyth A *et al.* Orofacial granulomatosis: a possible allergic basis. *Br J Oral Maxillofac Surg* 1985; **23**: 235–42.
5 Ronney T. Dental caries prevalence in patients with Crohn's disease. *Oral Surg* 1984; **57**: 623–4.
6 Sakuntabhai A, MacLeod RI, Lawrence CM. Intralesional steroid injection after nerve block anesthesia in the treatment of orofacial granulomatosis. *Arch Dermatol* 1993; **129**: 477–80.
7 Scully C, Cochran KM, Russell RI *et al.* Crohn's disease of the mouth: an indication of intestinal involvement. *Gut* 1982; **23**: 198–201.
8 Scully C, Eveson JW. Orofacial granulomatosis. *Lancet* 1991; **338**: 20–1.
9 Shehade SA, Foulds IS. Granulomatous cheilitis and a positive Kveim test. *Br J Dermatol* 1986; **115**: 619–22.
10 Sundh B, Emilson CG. Salivary and microbial conditions and dental health in patients with Crohn's disease: a 3-year study. *Oral Surg* 1989; **67**: 286–90.
11 Sweatman MC, Tasker R, Warner JO *et al.* Orofacial granulomatosis. Response to elimination diet and provocation by food additives. *Clin Allergy* 1986; **16**: 331–7.
12 Pryce DW, King CM. Orofacial granulomatosis associated with delayed hypersensitivity to cobalt. *Clin Exp Dermatol* 1990; **15**: 384–96.
13 Lewis FM, Shah M, Gawkrodger DJ. Contact sensitivity to food additives can cause oral and perioral symptoms. *Contact Dermatitis* 1995; **33**: 429–30.
14 McKenna KE, Walsh MY, Burrows D. The Melkersson–Rosenthal syndrome and food additive hypersensitivity. *Br J Dermatol* 1994; **131**: 921–2.
15 Pemberton M, Yeoman CM, Clark A *et al.* Allergy to octyl gallate causing stomatitis. *Br Dent J* 1993; **175**: 106–8.
16 White A, Nunes C, Escudier M *et al.* Improvement in orofacial granulomatosis on a cinnamon- and benzoate-free diet. *Inflamm Bowel Dis* 2006; **12**: 508–14.
17 Gibson J, Wray D. Human leucocyte antigen (HLA) typing in orofacial granulomatosis. *Br J Dermatol* 2000; **143**: 1119–21.
18 Wray D, Rees S, Gibson J, Forsyth A. The role of allergy in oral mucosal diseases. *Q J Med* 2000; **93**: 507–11.
19 Riggio MP, Gibson J, Lennon A, Wray D, MacDonald DG. Search for *Mycobacterium paratuberculosis* DNA in orofacial granulomatosis and oral Crohn's disease tissue by polymerase chain reaction. *Gut* 1997; **41**: 646–50.
20 Worsaae N, Pindborg JJ. Granulomatous gingival manifestations of Melkersson–Rosenthal syndrome. *Oral Surg* 1980; **49**: 131–8.
21 Worsaae N, Christensen KO, Bondesen S *et al.* Melkersson–Rosenthal syndrome and Crohn's disease. *Br J Oral Surg* 1980; **18**: 254–8.
22 Zimmer WM, Rogers RS, Reeve CM, Sheridan PJ. Orofacial manifestations of Melkersson–Rosenthal syndrome. *Oral Surg* 1992; **74**: 610–9.
23 Goncalves DU, de Castro MM, Alvao CP *et al.* Cheilitis granulomatosa associated with Melkersson-Rosenthal syndrome. *Rev Bras Otorrinolaringol* (Engl Edn) 2007; **73**: 132–3.
24 Wiesenfield DW, Ferguson MM, Mitchell D *et al.* Orofacial granulomatosis: a clinical and pathological analysis. *Q J Med* 1985; **54**: 101–13.
25 Williams AJK, Wray D, Ferguson A. The clinical entity of orofacial Crohn's disease. *Q J Med* 1991; **79**: 451–8.
26 Sanderson J, Nunes C, Escudier M *et al.* Oro-facial granulomatosis: Crohn's disease or a new inflammatory bowel disease? *Inflamm Bowel Dis* 2005; **11**: 840–6.
27 Cermale D, Serri F. Intralesional injection of triamcinolone in the treatment of cheilitis granulomatosa. *Arch Dermatol* 1963; **72**: 695–6.

28 Williams PM, Greenberg MS. Management of cheilitis granulomatosa. *Oral Surg* 1991; **72**: 436–9.
29 Krutchkoff D, James R. Cheilitis granulomatosa: successful treatment with combined local triamcinolone injections and surgery. *Arch Dermatol* 1978; **114**: 1203–6.
30 Mignogna MD, Fedele S, Lo Russo L, Adamo D, Satriano RA. Effectiveness of small-volume, intralesional, delayed-release triamcinolone injections in orofacial granulomatosis: a pilot study. *J Am Acad Dermatol* 2004; **51**: 265–8.
31 Van der Waal RI, Schulten EA, van der Mehj EH *et al*. Cheilitis granulomatosa: overview of 13 patients with long-term follow-up—results of management. *Int J Dermatol* 2002; **41**: 225–9.
32 Neuhofer J, Fritsch P. Cheilitis granulomatosa: therapy with clofazimine. *Hautarzt* 1984; **35**: 459–63.
33 Podmore P, Burrows D. Clofazimine: an effective treatment for Melkersson–Rosenthal syndrome or Miescher's cheilitis. *Clin Exp Dermatol* 1986; **11**: 173–8.
34 Hegarty AM, Hodgson TA, Porter SR. Thalidomide for the treatment of recalcitrant oral Crohn's disease and orofacial granulomatosis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2003; **95**: 576–85.

Crohn's disease

Crohn's disease lesions are indistinguishable from OFG.

Dermatological diseases

Several dermatoses can be associated with oral ulcers or erosions; lichen planus (LP) is the most common, pemphigus the most serious and pemphgoid is intermediate.

Lichen planus (see Chapter 41)

Oral LP may affect up to 1–2% of the population and is probably about eight times more common than cutaneous LP. The oral mucosa may be involved alone or in association with lesions on skin or other mucosa, and oral lesions may precede, accompany or follow lesions elsewhere [1–7]. The association of oral LP with gingival involvement, together with vulvovaginal lesions, has been termed the *vulvovaginal–gingival syndrome*.

Aetiology. Most oral LP is idiopathic but significantly greater anxiety and depression are observed among patients with oral LP compared with controls [8,9].

Some lichenoid lesions may be related to dental materials: the prevalence of positive reactions to potential allergens in the North American Contact Dermatitis Group (NACDG) is higher in oral LP for chromate, gold and thimerosal [10]. Other lichenoid reactions may be caused by GVHD, drug use (e.g. non-steroidal anti-inflammatory agents), diabetes [11] or liver disease. Chronic liver disease, especially chronic active hepatitis and hepatitis C virus (HCV) infection, may be associated with erosive LP in persons of southern European, Japanese or some other extractions [12–14] and there may be anticardiolipin antibodies [15]. In persons of northern European extraction, oral LP is only rarely associated with liver disease or with hepatitis C, hepatitis G or transfusion-transmitted virus [16–18].

Pathology. The pathology is similar to that of cutaneous LP, although sawtooth rete ridges are rarely seen in oral biopsies, and other epithelial changes may be less distinct.

Clinical features. The common oral lesions of LP are bilateral, white lesions in the buccal and/or lingual mucosa. They may be reticular, papular or plaque-like (Figs 69.33–69.37). They are often symptomless but may cause soreness [1–6].

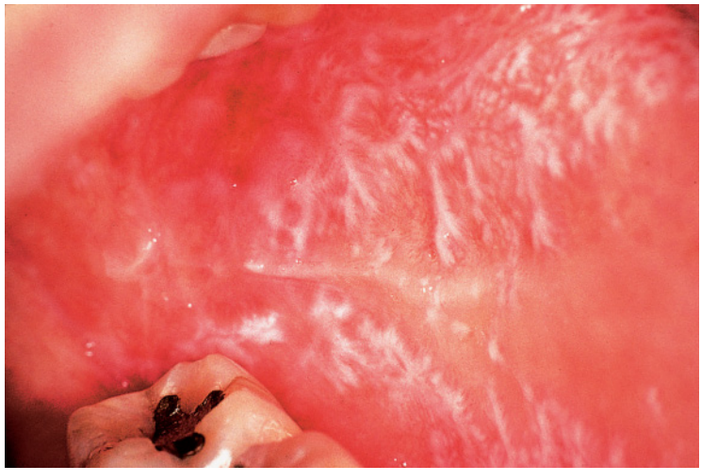


Fig. 69.33 Lichen planus: reticulopapular lesions in the common oral site, the buccal mucosa.



Fig. 69.34 Lichen planus: plaque-like lesions resemble leukoplakia.

Erosive LP, which frequently affects the dorsum and lateral borders of the tongue or the buccal mucosae on both sides, is uncommon. The erosions are often large, slightly depressed or raised with a yellow slough, and have an irregular outline (Fig. 69.34), but they are not always as painful as might be imagined. The surrounding mucosa is often erythematous and glazed in appearance, with loss of filiform papillae of the tongue, and there are often pathognomonic whitish striae. LP may also produce a desquamative gingivitis (see p. 69.106). Candidosis may complicate oral LP.

Reticular LP is the most frequent clinical presentation in both HCV-positive and HCV-negative patients. HCV-positive patients particularly have lip, tongue and gingival lesions [19].

Prognosis. There appears to be a predisposition for some oral LP, particularly the non-reticular forms, to develop carcinoma—possibly a risk of up to 5% over 10 years [1–6,20].



Fig. 69.35 Lichen planus on the tongue.



Fig. 69.36 Erosive lichen planus.



Fig. 69.37 Lichen planus on the gingivae

Diagnosis. Biopsy with immunofluorescence is often indicated to exclude keratosis, chronic ulcerative stomatitis with stratified epithelium-specific antinuclear antibodies, lichen sclerosus, lupus erythematosus, malignancy and other disorders.

Treatment. Treatment is not always necessary, unless there are symptoms. Unfortunately, although the natural history of cutaneous LP is one of remission in most cases, oral LP rarely remits, and thus treatment is indicated for symptomatic oral LP [1–6,21].

- Predisposing factors should be corrected. It may be wise to consider removal of dental amalgams if the lesions are closely related to these, or are unilateral [22], but there are no tests (e.g. patch tests) that will reliably indicate which patients will benefit from this.
- If drugs are implicated, the physician should be consulted as to possible changes in therapy. If there is diabetes or HCV infection, this should be treated by a physician.
- Improvement in oral hygiene may result in some subjective benefit. Thus good oral hygiene should be maintained. Chlorhexidine or triclosan mouthwashes may help.
- Antifungals may help, especially where there is candidal superinfection. Symptoms can be controlled with topical medication: topical corticosteroids, such as betamethasone sodium phosphate mouthwash and fluticasone propionate spray, cream or mouthwash or pastes containing fluocinonide, fluocinolone, triamcinolone, betamethasone valerate or clobetasol [23–26]. Topical tacrolimus has been used [27,28] but does not have FDA approval.
- Cessation of tobacco use is advisable and alcohol use should be minimized.

Mild LP. Topical corticosteroids are the mainstay of therapy (e.g. triamcinolone acetate, betamethasone or fluocinolone). Erosive and gingival lesions are often recalcitrant. Next, high-potency corticosteroids such as clobetasol, fluocinonide or fluticasone may be employed initially and then changed to a lower potency drug.

Moderate LP. If there is severe or extensive oral involvement, topical ciclosporin or tacrolimus may be of significant benefit, often being used with a high-potency or super-potent topical steroid such as clobetasol, fluticasone or mometasone. Topical creams or pastes can be applied in a suitable customized tray or veneer to be worn at night. This regimen is useful in the management of LP-related desquamative gingivitis recalcitrant to other therapies.

Severe LP. In severe LP in multiple sites, patients may require systemic corticosteroids, azathioprine, cyclophosphamide, hydroxychloroquine, acitretin, thalidomide or ciclosporin.

Dapsone is occasionally effective.

Other therapies for LP include retinoids, low-molecular-weight heparin [29,30] and many others, but either their efficacy has not been well proven or they have unacceptable adverse effects.

Patients with non-reticular LP should be monitored to exclude development of carcinoma; tobacco and alcohol use should be minimized.

References

1 Scully C, Beyli M, Feirrero M *et al.* Update on oral lichen planus: aetiopathogenesis and management. *Crit Rev Oral Biol Med* 1998; **9**: 86–122.
2 Wright JM. A review and update of intraoral lichen planus. *Tex Dent J* 2001; **118**: 450–4.
3 Chainani-Wu N, Silverman S Jr, Lozada-Nur F, Mayer P, Watson JJ. Oral lichen planus: patient profile, disease progression and treatment responses. *J Am Dent Assoc* 2001; **132**: 901–9.
4 Eisen D. The clinical features, malignant potential, and systemic associations of oral lichen planus: a study of 723 patients. *J Am Acad Dermatol* 2002; **46**: 207–14.
5 Torti DC, Jorizzo JL, McCarty MA. Oral lichen planus: a case series with emphasis on therapy. *Arch Dermatol* 2007; **143**: 511–5.
6 Ingafou M, Leao JC, Porter SR, Scully C, Oral lichen planus: a retrospective study of 690 British patients. *Oral Dis* 2006; **12**: 463–8.
7 Setterfield J, Neill S, Shirlaw PJ *et al*. The vulvovaginal gingival syndrome: a severe subgroup of lichen planus with characteristic clinical features and a novel association with the class II HLA DQB1*0201 allele. *J Am Acad Dermatol* 2006; **55**: 98–113.
8 Vallejo MJ, Huerta G, Cerero R, Seoane JM. Anxiety and depression as risk factors for oral lichen planus. *Dermatology* 2001; **203**: 303–7.
9 Lundqvist EN, Wahlin YB, Bergdahl M, Bergdahl J. Psychological health in patients with genital and oral erosive lichen planus. *J Eur Acad Dermatol Venereol* 2006; **20**: 661–6.
10 Scalf LA, Fowler JF Jr, Morgan KW, Looney SW. Dental metal allergy in patients with oral, cutaneous, and genital lichenoid reactions. *Am J Contact Dermatitis* 2001; **12**: 146–50.
11 Romero MA, Seoane J, Varela-Centelles P, Diz-Dios P, Garcia-Pola MJ. Prevalence of diabetes mellitus amongst oral lichen planus patients. Clinical and pathological characteristics. *Med Oral* 2002; **7**: 121–9.
12 Carrozzo M, Gandolfo S, Lodi G *et al.* Oral lichen planus patients infected or non-infected with hepatitis C virus: the role of autoimmunity. *J Oral Pathol Med* 1999; **28**: 16–9.
13 Lodi G, Scully C, Carozzo M *et a*l. Current controversies in oral lichen planus: report of an international consensus meeting. Part 1. Viral infections and etiopathogenesis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005; **100**: 40–51.
14 De MattosCamargo Grossman S, de Aguiar MC, Texeira R, do Carmo MA. Oral lichen planus and chronic hepatitis C: a controversial association. *Am J Clin Pathol* 2007; **127**: 800–4.
15 Nagao Y, Tsubone K, Kimura R *et al.* High prevalence of anticardiolipin antibodies in patients with HCV-associated oral lichen planus. *Int J Mol Med* 2002; **9**: 293–7.
16 Ingafou M, Porter SR, Scully C, Teo CG. No evidence for HCV infection or liver disease in British patients with lichen planus. *Int J Oral Maxillofac Surg* 1998; **27**: 65–6.
17 Lodi G, Carrozzo M, Harris K *et al.* Hepatitis C virus-associated oral lichen planus: no influence from hepatitis G virus co-infection. *J Oral Pathol Med* 2000; **29**: 39–42.
18 Bez C, Hallet R, Carrozzo M *et al.* Lack of association between hepatotropic transfusion transmitted virus infection and oral lichen planus in British and Italian populations. *Br J Dermatol* 2001; **145**: 990–3.
19 Romero MA, Seoane J, Varela-Centelles P, Diz-Dios P, Otero XL. Clinical and pathological characteristics of oral lichen planus in hepatitis C-positive and -negative patients. *Clin Otolaryngol* 2002; **27**: 22–6.
20 Lodi G, Scully C, Carozzo M *et al*. Current controversies in oral lichen planus: report of an international consensus meeting. Part 2. Clinical management and malignant transformation. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005; **100**: 164–78.
21 Scully C, Eisen D, Carrozzo M. Management of oral lichen planus. *Am J Clin Dermatol* 2000; **1**: 287–306.
22 Thornhill MH. Oral lichenoid lesions and amalgam fillings. *Evid Based Dent* 2006; **7**: 74–5.
23 Carbone M, Conrotto D, Carrozzo M *et al*. Topical corticosteroids in association with miconazole and chlorhexidine in the long-term management of atrophic-erosive lichen planus: a placebo-controlled and comparative study between clobetasol and fluocinonide. *Oral Dis* 1999; **5**: 44–9.
24 Muzio LL, della Valle A, Mignogna MD *et al.* The treatment of oral aphthous ulceration or erosive lichen planus with topical clobetasol propionate in three preparations: a clinical and pilot study on 54 patients. *J Oral Pathol Med* 2001; **30**: 611–7.
25 Hegarty AM, Hodgson TA, Lewsey JD, Porter SR. Fluticasone propionate spray and betamethasone sodium phosphate mouthrinse: a randomized crossover study for the treatment of symptomatic oral lichen planus. *J Am Acad Dermatol* 2002; **47**: 271–9.
26 Al-Hashimi I, Schifter M, Lockhart PB *et al*. Oral lichen planus and oral lichenoid lesions: diagnostic and therapeutic considerations. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; **103** (Suppl.): S25.e1–12.
27 Kaliakatsou F, Hodgson TA, Lewsey JD *et al*. Management of recalcitrant ulcerative oral lichen planus with topical tacrolimus. *J Am Acad Dermatol* 2002; **46**: 35–41.
28 Rozycki TW, Rogers RS 3rd, Pittelkow MR *et al.* Topical tacrolimus in the treatment of symptomatic oral lichen planus: a series of 13 patients. *J Am Acad Dermatol* 2002; **46**: 27–34.
29 Femiano F, Gombos F, Scully C. Oral erosive/ulcerative lichen planus: preliminary findings in an open trial of sulodexide compared with cyclosporine (ciclosporin) therapy. *Int J Dermatol* 2001; **42**: 308–11.
30 Femiano F, Scully C. Oral lichen planus: clinical and histological evaluation in an open trial using a low molecular weight heparinoid (sulodexide). *Int J Dermatol* 2006; **45**: 986–9.

Overlap syndromes

Lichen planus pemphigoides. Oral lesions in LP pemphigoides may be similar to those of LP or pemphigoid [1–5], clinically and histologically with direct immunofluorescence demonstrating linear deposits of immunoglobulin G and complement component C3 along the basement membrane [3].

Lichen planus/lichen sclerosus overlap syndrome. This may involve the oral and/or genital mucosa [6–8].

References

1 Allen CM, Camisa C, Grinwood R. Lichen planus pemphigoides: report of a case with oral lesions. *Oral Surg* 1987; **63**: 184–8.
2 Maceyko RF, Camisa C, Bergfeld WF, Valenzuela R. Oral and cutaneous lichen planus pemphigoides. *J Am Acad Dermatol* 1992; **27**: 889–92.
3 Solomon LW, Helm TN, Stevens C, Neiders ME, Kumar V. Clinical and immunopathologic findings in oral lichen planus pemphigoides. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; **103**: 808–13.
4 Demircay Z, Baykal C, Demirkesen C. Lichen planus pemphigoides: report of two cases. *Int J Dermatol* 2001; **40**: 757–9.
5 Harting MS, Hsu S. Lichen planus pemphigoides: a case report and review of the literature. *Dermatol Online J* 2006; **12**: 10.
6 Lessani T, Gallego H, Lynch PJ. Lichen planus and lichen sclerosus overlap. *Cutis* 1998; **61**: 103–4.
7 Yashar S, Kan KF, Haley JC. Lichen sclerosus-lichen planus overlap in a patient with hepatitis C virus infection. *Br J Dermatol* 2004; **150**: 168–9.
8 Marren P, Millard P, Chia Y, Wojnarowska F. Mucosal lichen sclerosus/lichen planus overlap syndromes. *Br J Dermatol* 1994; **131**: 118–23.

Lichen sclerosus (see Chapter 51)

Oral lichen sclerosus et atrophicus is uncommon but since it presents with whitish plaques, papules or a reticular pattern, or erosions, all features of LP [1–13], it may be underdiagnosed. Histologically, however, lichen sclerosus is characterized by epithelial atrophy with hyperkeratosis, oedema in the papillary corium but the lymphocytic infiltrate is not as closely associated to the epithelium as seen in LP.

It has been suggested that mucosal lichen sclerosus is more common than formerly thought and may even cause dysplasia [5].

References

1 MacLeod RI, Soames JV. Lichen sclerosus et atrophicus of the oral mucosa. *Br J Oral Maxillofac Surg* 1991; **89**: 64–5.
2 Ravits HG, Welsh AL. Lichen sclerosus et atrophicus of the mouth. *Arch Dermatol* 1957; **76**: 56–8.
3 De Araujo VC, Orsini SC, Marcucci G *et al.* Lichen sclerosus et atrophicus. *Oral Surg* 1985; **60**: 655–7.
4 Miller RF. Lichen sclerosus et atrophicus with oral involvement. *Arch Dermatol* 1957; **76**: 43–55.
5 Maren P, Millard P, Chia Y, Wojnarowska F. Mucosal lichen sclerosus/lichen planus overlap syndromes. *Br J Dermatol* 1994; **131**: 118–23.
6 Schulten EA, Starink TM, van der Waal I. Lichen sclerosus et atrophicus involving the oral mucosa: report of two cases. *J Oral Pathol Med* 1993; **22**: 374–7.
7 Brown AR, Dunlap CL, Bussard DA, Lask JT. Lichen sclerosus et atrophicus of the oral cavity: report of two cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1997; **84**: 165–70.
8 Buajeeb W, Kraivaphan P, Punyasingh J, Laohapand P. Oral lichen sclerosus et atrophicus. A case report. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1999; **88**: 702–6.
9 Jimenez Y, Baga JV, Milan MA, Gavalda C, Scully C. Lichen sclerosus et atrophicus manifesting with localized loss of periodontal attachment. *Oral Dis* 2002; **8**: 310–3.
10 Jensen T, Worsaae N, Melgaard B. Oral lichen sclerosus et atrophicus: a case report. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2002; **94**: 702–6.
11 Kaur S, Thami GP, Kanwar AJ, Mohan H. Linear oro-facial lichen sclerosus. *Clin Exp Dermatol* 2002; **27**: 467–70.
12 Mendonca EF, Ribeiro-Rotta RF, Silva MA, Batista AC. Lichen sclerosus et atrophicus of the oral mucosa. *J Oral Pathol Med* 2004; **33**: 637–40.
13 Kelly SC, Helm KF, Zaenglein AL. Lichen sclerosus of the lip. *Pediatr Dermatol* 2006; **23**: 500–2.

Chronic ulcerative stomatitis with epithelial antinuclear antibodies

Chronic erosive or ulcerative stomatitis (CUSP) often presents as desquamative gingivitis with or without lesions on buccal or lingual mucosa and sometimes resembles LP, and may be associated with lichenoid histology, but is associated with antinuclear antibodies directed against stratified squamous epithelia [1–4]. These autoantibodies are directed against a 70-kDa epithelial nuclear protein homologous to the p53 tumour suppressor and the p73 putative tumour suppressor, and shown to be a splicing variant of the *KET* gene [5,6].

The lesions may respond to hydroxychloroquine [1–4].

References

1 Jarenko WM, Beutner EH, Kumar V *et al.* Chronic ulcerative stomatitis associated with a specific immunologic marker. *J Am Acad Dermatol* 1990; **22**: 215–20.
2 Beutner EH, Chorzelski TP, Parodi A *et al.* Ten cases of chronic ulcerative stomatitis with stratified epithelium-specific antinuclear antibody. *J Am Acad Dermatol* 1991; **24**: 781–2.
3 Church LF, Schosser RH. Chronic ulcerative stomatitis associated with stratified epithelial specific antinuclear antibody. *Oral Surg* 1992; **73**: 579–82.
4 Solomon LW, Aguirre A, Neiders M *et al.* Chronic ulcerative stomatitis: clinical, histopathologic, and immunopathologic findings. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2003; **96**: 718–26.
5 Parodi A, Cozzani E, Cacciapuoti M, Rebora A. Chronic ulcerative stomatitis: antibodies reacting with the 70-kDa molecule react with epithelial nuclei. *Br J Dermatol* 2000; **143**: 671–2.
6 Lee LA, Walsh P, Prater CA *et al.* Characterization of an autoantigen associated with chronic ulcerative stomatitis: the CUSP autoantigen is a member of the p53 family. *J Invest Dermatol* 1999; **113**: 146–51.

Pemphigus (see Chapter 40)

Oral lesions are the rule in pemphigus vulgaris (PV) [1–9], but rare in the superficial forms of pemphigus [1].



Fig. 69.38 Pemphigus vulgaris: irregular persistent oral erosions.

Pemphigus vulgaris. The main antigen in PV is desmoglein (Dsg) 3. However, 50% of patients with PV also have autoantibodies to Dsg1 (the main antigen in pemphigus foliaceus) and the proportion of Dsg1 and Dsg3 antibodies appears to be related to clinical severity. Those cases of PV which are predominantly oral have only Dsg3 antibodies. Dsg1 autoantibodies are found in over 50% of cases of PV, and the frequency may differ with race since they are found in a significantly greater proportion of patients of Indian origin than white northern Europeans [1,10–14]; such variations may be HLA-related [5,15,16].

Typically, an individual patient develops a single variant of pemphigus, although cases have been described of transition to another variant, presumably through epitope spread, and the clinical manifestations of a single variant can change over time, possibly related to changes in the proportions of Dsg1 and Dsg3 autoantibodies.

The oral mucosa is almost invariably involved in PV and oral lesions are commonly the presenting feature (Fig. 69.38). Bullae appear on any part of the oral mucosa including the palate, but break so rapidly that they are rarely seen [1,5,9,17–23]. Usually, the patient presents with large, painful, irregular and persistent red lesions which, by the time they become secondarily infected, can be difficult to differentiate clinically from those of other erosive conditions, such as pemphigoid and other immune blistering disorders, although intact bullae are more commonly seen in these, whereas the Nikolsky sign is more often positive in pemphigus. Oral lesions of PV are typically seen in adults, rarely in childhood.

The prevalence of oral involvement varies: one multicentre study involving patients from several countries showed that Bulgarian patients with PV had oral mucous membrane lesions less frequently (66%) than Italian (83%) or Israeli (92%) patients [9]. Rarely in PV there can be an acquired macroglossia [22] or desquamative gingivitis [23–25].

Diagnosis should be confirmed by biopsy and immune studies. A biopsy of perilesional mucosa should be taken for haematoxylin and eosin stained sections and immunostaining (Table 69.19) and serum collected for autoantibody titres, which can help diagnosis

Table 69.19 Immunostaining in oral mucosal vesiculobullous disorders.

Disease	DIF	Oral mucosal deposits mainly:	Pattern of IF	IIF	Autoantibodies against:
Pemphigus	+	IgG C3	Epithelial intercellular	+	Epithelial intercellular cement
Mucous membrane pemphigoid	+	C3 IgG	Linear epithelial basement membrane	±	Epithelial basement membrane
Bullous pemphigoid	+	IgG C3	Linear epithelial basement membrane	+	Epithelial basement membrane
Dermatitis herpetiformis	+	IgA C3	Granular epithelial basement membrane	–	Reticulin
Linear IgA disease	+	IgA C3	Linear epithelial basement membrane	–	–
Erythema multiforme	±	C3 IgM	Vessel walls in lamina propria	–	-
Lichen planus*	±	Fibrin†	Globular epithelial or lamina propria and in Civatte bodies	–	–
		IgM, IgG, IgA, C3			
Discoid lupus erythematosus*	+	IgG, IgA IgM, C3	Granular epithelial basement membrane	±	None, or antinuclear
Angina bullosa haemorrhagica	–	–	–	–	–
Superficial mucoceles	–	–	–	–	–

DIF, direct immunofluorescence (biopsy); IF, immunofluorescence; IIF, indirect immunofluorescence (serology); +, present; –, absent; ±, sometimes.

* Rarely vesiculobullous.

† Non-specific deposits.

and monitoring of disease activity. Differential binding of anti-Dsg antibodies suggests that both human skin and monkey oesophagus should be used in the diagnosis of PV, since patients with predominantly oral disease may only have Dsg3 antibodies, which are not always detectable using human skin [5,26]. ELISA may help [27].

Oral cytology is of little practical diagnostic value. Treatment is largely based on systemic immunosuppression using corticosteroids, with azathioprine, dapsone, methotrexate, cyclophosphamide, gold or ciclosporin as adjuvants or alternatives; this has significantly reduced the mortality [1,8,23–30]. Adverse effects of these drugs are common, though deflazacort may have fewer adverse effects compared with prednisolone [31].

Mycophenolate mofetil offers safer immunosuppression with possibly less nephrotoxicity and hepatotoxicity [32–35].

Mucosal lesions are recalcitrant, often only healing after skin lesions have resolved when immunosuppressive therapy is given, and they may persist even though skin lesions are controlled. Topical corticosteroids may then help, or possibly prostaglandin E_2 [36,37]. Tacrolimus topically may well prove to have a place in the control of oral lesions [38–40].

Anti-CD20 monoclonal antibody, rituximab, may be an effective alternative therapy for the treatment of refractory pemphigus vulgaris [41–45].

References

1 Scully C, Challacombe SJ. Pemphigus vulgaris: update on etiopathogenesis, oral manifestations and management. *Crit Rev Oral Biol Med* 2002; **13**: 397–408.

2 Robinson NA, Yeo JF, Lee YS, Aw DC. Oral pemphigus vulgaris: a case report and literature update. *Ann Acad Med Singapore* 2004; **33**: 63–8.

3 Ben Lagha, Poulesquen V, Roujeau JC, Alantar A, Maman L. Pemphigus vulgaris: a case-based update. *J Can Dent Assoc* 2005; **71**: 667–72.

4 Bystryn JC, Rudolph JL. Pemphigus. *Lancet* 2005; **366**: 61–73.

5 Black M, Mignogna MD, Scully C. Number II. Pemphigus vulgaris. *Oral Dis* 2005; **11**: 119–30.

6 Ettlin DA. Pemphigus. *Dent Clin North Am* 2005; **49**: 107–25.

7 Da Silva K, Mandel L. Early manifestation of pemphigus vulgaris. A case report. *N Y State Dent J* 2007; **73**: 42–4.

8 Dick SE, Werth VP. Pemphigus: a treatment update. *Autoimmunity* 2006; **39**: 591–9.

9 Femiano F. Pemphigus vulgaris: recent advances in our understanding of its pathogenesis. *Minerva Stomatol* 2007; **56**: 215–23.

10 Harman KE, Gratian MJ, Seed PT *et al*. Diagnosis of pemphigus by ELISA: a critical evaluation of two ELISAs for the detection of antibodies to the major pemphigus antigens, desmoglein 1 and 3. *Clin Exp Dermatol* 2000; **25**: 236–40.

11 Harman KE, Gratian MJ, Bhogal BS, Challacombe SJ, Black MM. A study of desmoglein 1 autoantibodies in pemphigus vulgaris: racial differences in frequency and the association with a more severe phenotype. *Br J Dermatol* 2000; **143**: 343–8.

12 Harman KE, Seed PT, Gratian MJ *et al*. The severity of cutaneous and oral pemphigus is related to desmoglein 1 and 3 antibody levels. *Br J Dermatol* 2001; **144**: 775–80.

13 Kanwar AJ, Ajith AC, Narang T. Pemphigus in North India. *J Cutan Med Surg* 2006; **10**: 21–5.

14 Kumar B, Arora S, Kumaran MS, Jain R, Dogra S. Study of desmoglein 1 and 3 antibody levels in relation to disease severity in Indian patients with pemphigus. *Indian J Dermatol Venereol Leprol* 2006; **72**: 203–6.

15 Loiseau P, Lecleach L, Prost C *et al*. HLA class II polymorphism contributes to specify desmoglein derived peptides in pemphigus vulgaris and pemphigus foliaceus. *J Autoimmun* 2000; **15**: 67–73.

16 Tong JC, Tan TW, Sinha AA, Ranganathan S. Prediction of desmoglein-3 peptides reveals multiple shared T-cell epitopes in HLA DR4- and DR6-associated pemphigus vulgaris. *BMC Bioinformatics* 2006; **7** (Suppl. 5): S7.

17 Davenport S, Chen SY, Miller AS. Pemphigus vulgaris: clinicopathologic review of 33 cases in the oral cavity. *Int J Periodont Restorative Dent* 2001; **21**: 85–90.

18 Casiglia J, Woo SB, Ahmed AR. Oral involvement in autoimmune blistering diseases. *Clin Dermatol* 2001; **19**: 737–41.
19 Brenner S, Tur E, Shapiro J *et al.* Pemphigus vulgaris: environmental factors. Occupational, behavioral, medical, and qualitative food frequency questionnaire. *Int J Dermatol* 2001; **40**: 562–9.
20 Mignogna MD, Lo Muzio L, Galloro G *et al*. Oral pemphigus: clinical significance of esophageal involvement: report of eight cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1997; **84**: 179–84.
21 Scully C, Almeida OPD, Porter SR, Gilkes J. Pemphigus vulgaris: the manifestations and long-term management of 55 patients with oral lesions. *Br J Dermatol* 1999; **140**: 84–9.
22 Milgraum SS, Kanzler MH, Waldinger TP *et al.* Macroglossia: an unusual presentation of pemphigus vulgaris. *Arch Dermatol* 1985; **121**: 1328–9.
23 Stoopler ET, Sollecito TP, De Rossi SS. Desquamative gingivitis: early presenting symptom of mucocutaneous disease. *Quintessence Int* 2003; **34**: 582–6.
24 Endo H, Rees TD, Matsue M *et al*. Early detection and successful management of oral pemphigus vulgaris: a case report. *J Periodontol* 2005; **76**: 154–60.
25 Navarro CM, Sposto MR, Onofre MA, Scully C. Gingival lesions diagnosed as pemphigus vulgaris in an adolescent. *J Periodontol* 1999; **70**: 808–12.
26 Challacombe SJ, Setterfield J, Shirlaw P *et al*. Immunodiagnosis of pemphigus and mucous membrane pemphigoid. *Acta Odontol Scand* 2001; **59**: 226–34.
27 Zagorodriuk I, Weltfriend S, Shtrumginger L *et al*. A comparison of anti-desmoglein antibodies and indirect immunofluorescence in the serodiagnosis of pemphigus vulgaris. *Int J Dermatol* 2005; **44**: 541–4.
28 Lamey PJ, Rees TD, Binnie WH *et al.* Oral presentation of pemphigus vulgaris and its response to systemic steroid therapy. *Oral Surg* 1992; **74**: 54–7.
29 Yeh SW, Sami N, Ahmed RA. Treatment of pemphigus vulgaris: current and emerging options. *Am J Clin Dermatol* 2005; **6**: 327–42.
30 Olszewska M, Kolazinska-Strasz Z, Sulej J *et al*. Efficacy and safety of cyclophosphamide, azathioprine, and cyclosporine (ciclosporin) as adjuvant drugs in pemphigus vulgaris. *Am J Clin Dermatol* 2007; **8**: 85–92.
31 Mignogna MD, Lo Muzio L, Mignogna RE *et al*. Oral pemphigus: long term behaviour and clinical response to treatment with deflazacort in sixteen cases. *J Oral Pathol Med* 2000; **29**: 145–52.
32 Bredlich RO, Grundmann-Kollmann M, Behrens S, Kerscher M, Peter RU. Mycophenolate mofetil monotherapy for pemphigus vulgaris. *Br J Dermatol* 1999; **141**: 934.
33 Enk AH, Knop J. Mycophenolate is effective in the treatment of pemphigus vulgaris. *Arch Dermatol* 1999; **135**: 54–6.
34 Liu V, Mackool BT. Mycophenolate in dermatology. *J Dermatolog Treat* 2003; **14**: 203–11.
35 Beissert S, Werfel T, Frieling U *et al*. A comparison of oral methylprednisolone plus azathioprine or mycophenolate mofetil for the treatment of pemphigus. *Arch Dermatol* 2006; **142**: 1447–54.
36 Morita H, Morisaki S, Kitano Y. Clinical trial of prostaglandin E2 on the oral lesions of pemphigus vulgaris. *Br J Dermatol* 1995; **132**: 165–6.
37 Kumaran MS, Kanwar AJ. Efficacy of topical PGE2 in recalcitrant oral lesions of pemphigus vulgaris: a clinical trial. *J Eur Acad Dermatol Venereol* 2006; **20**: 898–9.
38 Wu SJ, Tanphaichitr A, Ly M. Recent advances in dermatology. *Clin Podiatr Med Surg* 2002; **19**: 65–78.
39 Hodgson TA, Malik F, Hegarty AM, Porter SR. Topical tacrolimus: a novel therapeutic intervention for recalcitrant labial pemphigus vulgaris. *Eur J Dermatol* 2003; **13**: 142–4.
40 Gach JE, Ilchyshyn A. Beneficial effects of topical tacrolimus on recalcitrant erosions of pemphigus vulgaris. *Clin Exp Dermatol* 2004; **29**: 271–2.
41 Ahmed AR, Spigelman Z, Cavacini LA, Posner MR. Treatment of pemphigus vulgaris with rituximab and intravenous immune globulin. *N Engl J Med* 2006; **355**: 1772–9.
42 El Tal AK, Posner MR, Spigelman Z, Ahmed AR. Rituximab: a monoclonal antibody to CD20 used in the treatment of pemphigus vulgaris. *J Am Acad Dermatol* 2006; **55**: 449–59.
43 Antonucci A, Negosanti M, Tabonelli M, Varotti C. Treatment of refractory pemphigus vulgaris with anti-CD20 monoclonal antibody (rituximab): Five cases. *J Dermatolog Treat* 2007; **18**: 178–83.
44 Marzano AV, Fanoni D, Venegoni L, Berti E, Caputo R. Treatment of refractory pemphigus with the anti-CD20 monoclonal antibody (rituximab). *Dermatology* 2007; **214**: 310–8.
45 Goh MS, McCormack C, Dinh HV *et al*. Rituximab in the adjuvant treatment of pemphigus vulgaris: a prospective open-label pilot study in five patients. *Br J Dermatol* 2007; **156**: 990–6.

Paraneoplastic pemphigus. Apart from PV, the other important pemphigus variant affecting the mouth is paraneoplastic pemphigus, usually associated with lymphoproliferative disease or thymoma [1–6], although one case associated with OSCC has been reported [7]. Oral lesions may be the sole manifestation [8] and have been seen in all reported cases of paraneoplastic pemphigus [4,9–13]. Oral lesions may be seen in isolation [1].

Painful extensive stomatitis, painful paronychia and lichenoid papules may be seen, and histology may show lichenoid changes, acantholytic blister formation and apoptotic keratinocytes. Direct immunofluorescence is positive for IgG both in the epidermal intercellular spaces and along the basement membrane zone. Indirect immunofluorescence is similarly positive in a PV pattern.

There is often only a partial response to intravenous corticosteroids. Recent therapeutic advances include the use of anti-CD20 monoclonal antibody (rituximab) [14–16] and mycophenolate [17–19].

References

1 Allen CM, Camisa C. Paraneoplastic pemphigus: a review of the literature. *Oral Dis* 2000; **6**: 208–14.
2 Leyn J, Degreef H. Paraneoplastic pemphigus in a patient with a thymoma. *Dermatology* 2001; **202**: 151–4.
3 Nikolskaia OV, Nousari CH, Anhalt GJ. Paraneoplastic pemphigus in association with Castleman's disease. *Br J Dermatol* 2003; **149**: 1143–51.
4 Kaplan I, Hodak E, Ackermann L *et al*. Neoplasms associated with paraneoplastic pemphigus: a review with emphasis on non-hematologic malignancy and oral mucosal manifestations. *Oral Oncol* 2004; **40**: 553–62.
5 Anhalt GJ. Paraneoplastic pemphigus. *J Invest Dermatol Symp Proc* 2004; **9**: 29–33.
6 Meneakos C, Braumann C, Hartman J, Jacobi CA. Retroperitoneal Castleman's tumor and paraneoplastic pemphigus: report of a case and review of the literature. *World J Surg Oncol* 2007; **28**: 1–5.
7 Wong KC, Ho KK. Pemphigus with pemphigoid-like presentation, associated with squamous cell carcinoma of the tongue. *Australas J Dermatol* 2000; **41**: 178–80.
8 Bialy-Golan A, Brenner S, Anhalt GJ. Paraneoplastic pemphigus: oral involvement as the sole manifestation. *Acta Derm Venereol* (*Stockh*) 1996; **76**: 253–4.
9 Anhalt GJ, Kim SC, Stanley JR *et al.* Paraneoplastic pemphigus. An autoimmune mucocutaneous disease associated with neoplasia. *N Engl J Med* 1990; **323**: 1729–35.
10 Laskaris GC, Papavasiliou SS, Bovopoulou OD, Nicolis GD. Association of oral pemphigus with chronic lymphocytic leukemia. *Oral Surg Oral Med Oral Pathol* 1980; **50**: 244–9.
11 Fullerton SH, Woodley DT, Smoller BR, Anhalt GJ. Paraneoplastic pemphigus with autoantibody deposition in bronchial epithelium after autologous bone marrow transplantation. *JAMA* 1992; **267**: 1500–2.
12 Camisa C, Helm TN, Liu YC *et al.* Paraneoplastic pemphigus: a report of three cases including one long-term survivor. *J Am Acad Dermatol* 1992; **27**: 547–53.
13 Favia GF, Di Alberti L, Piattelli A. Paraneoplastic pemphigus: a report of two cases. *Oral Oncol* 1998; **34**: 571–5.
14 Borradori L, Lombardi T, Samson J *et al*. Anti-CD20 monoclonal antibody (rituximab) for refractory erosive stomatitis secondary to CD20 follicular lymphoma-associated paraneoplastic pemphigus. *Arch Dermatol* 2001; **137**: 269–72.
15 Fatourechi MM, el-Azhary RA, Gibson LE. Rituximab: applications in dermatology. *Int J Dermatol* 2006; **45**: 1143–55.
16 Hoque SR, Black MM, Cliff S. Paraneoplastic pemphigus associated with CD20-positive follicular non-Hodgkin's lymphoma treated with rituximab: a third case resistant to rituximab therapy. *Clin Exp Dermatol* 2007; **32**: 172–5.

17 Williams JV, Marks JG Jr, Billingsley EM. Use of mycophenolate mofetil in the treatment of paraneoplastic pemphigus. *Br J Dermatol* 2000; **142**: 506–8.
18 Powell AM, Albert S, Al-Fares S *et al.* An evaluation of the usefulness of mycophenolate mofetil in pemphigus. *Br J Dermatol* 2003; **149**: 138–45.
19 Powell AM, Albert S, Oyama N *et al*. Paraneoplastic pemphigus secondary to fludarabine evolving into unusual oral pemphigus vegetans. *J Eur Acad Dermatol Venereol* 2004; **18**: 360–4.

Pemphigus vegetans. Oral lesions in pemphigus vegetans are hyperplastic masses which, on the tongue, can give a cerebriform appearance [1–3].

References

1 Ahmed AR, Blose DA. Pemphigus vegetans: Neumann type and Hallopeau type. *Int J Dermatol* 1984; **23**: 135–41.
2 Premalatha S, Jayakumar S, Yesudian P *et al*. Cerebriform tongue: a clinical sign in pemphigus vegetans. *Br J Dermatol* 1981; **104**: 587–91.
3 Markopoulos AK, Antoniades DZ, Zaraboukas T. Pemphigus vegetans of the oral cavity. *Int J Dermatol* 2006; **45**: 425–42.

Other pemphigus variants. Oral lesions may be seen in less common pemphigus variants, especially in most cases with IgA pemphigus (intraepithelial IgA pustulosis or intraepidermal neutrophilic IgA dermatosis) [1–3], and in some cases of pemphigus associated with inflammatory bowel disease [4–10].

References

1 Beutner EH, Chorzelski TP, Wilson RM *et al*. IgA pemphigus foliaceus: report of two cases and a review of the literature. *J Am Acad Dermatol* 1989; **20**: 89–97.
2 Borradori L, Saada V, Rybojad M *et al*. Oral intraepidermal IgA pustulosis and Crohn's disease. *Br J Dermatol* 1992; **126**: 383–6.
3 Teraki Y, Amagou N, Hashimoto T. Intracellular IgA dermatosis of childhood. Selective deposition of monomer IgA1 in the intercellular space of the epidermis. *Arch Dermatol* 1991; **127**: 221–4.
4 Bruckner AL, Fitzpatrick JE, Hashimoto T, Weston WL, Morelli JG. Atypical IgA/IgG pemphigus involving the skin, oral mucosa, and colon in a child: a novel variant of IgA pemphigus? *Pediatr Dermatol* 2005; **22**: 321–7.
5 Stone DD. Rectal lesions and toxic dilatation of the colon in a case of pemphigus vulgaris. *Am J Dig Dis* 1971; **16**: 163–6.
6 Lubach D, Reichart P, Wellman W. Oral manifestations during the concurrent appearance of pemphigus and ulcerative colitis. *Dtsch Z Mund Kiefer Gesichtschir* 1984; **8**: 308–12.
7 Fabbri P, Emmi L, Vignoli L *et al*. Chronic pemphigus vulgaris associated with ulcerative rectocolitis. Apropos of a clinical case. *G Ital Dermatol Venereol* 1986; **21**: 355–9.
8 Delfino M, Suppa F, Piccirillo A. Pemphigus vulgaris and ulcerative colitis. *Dermatologica* 1986; **172**: 230.
9 Schwermann M, Lechner W, Elsner C, Kirchner T. Pemphigus vulgaris involving duodenum and colon. *Z Hautkr* 1988; **63**: 101–4.
10 Prendiville JS, Israel DM, Wood WS, Dimmick JE. Oral pemphigus vulgaris associated with inflammatory bowel disease and herpetic gingivostomatitis in an 11-year old girl. *Pediatr Dermatol* 1994; **11**: 145–50.

Subepithelial immune bullous diseases

A spectrum of immune-mediated subepithelial bullous diseases can present with oral blisters and/or erosions and/or desquamative gingivitis, and with immune deposits at the epithelial basement membrane zone. Several distinct groups, and probably several overlap syndromes, are now recognized to exist.

Mucous membrane pemphigoid (see Chapter 40). Mucous membrane pemphigoid is a mucocutaneous, immune-mediated, subepithelial blistering disease characterized by autoantibodies to different molecules in the basement membrane zone [1–10]. The mouth may be involved as part of a wider disease, though in many patients only oral lesions are seen [9]. Sera of oral pemphigoid patients selectively and specifically bind to human α6 integrin, a 120-kDa protein that appears to be a target antigen in this particular variant [3,8,11].



Fig. 69.39 Pemphigoid: vesicles and desquamative gingivitis.

Mucous membrane pemphigoid involves the oral mucosa in more than one-third of cases, commonly causing gingival lesions [1–3,10]. The usual lesion, desquamative gingivitis, is characterized by erythematous, glazed, sore gingivae (Fig. 69.39). Bullae are less common, and are seen particularly on the soft palate. They rupture to form erosions [1–3,7,11–13].

The bullae in mucous membrane pemphigoid are subepithelial and tend to persist for longer than those of pemphigus. Oral lesions may scar but this is uncommon. The bullae are typically filled with serous fluid and should be distinguished from superficial mucoceles (see p. 69.84), epidermolysis bullosa acquisita, dermatitis herpetiformis and linear IgA disease. Occasionally blisters are blood-filled, and then must be differentiated from angina bullosa haemorrhagica (see p. 69.84).

A biopsy is required for diagnosis [3,7,13]. Serum autoantibodies to epithelial basement membrane may be detected in a few patients (see Table 69.19) but many have immune deposits at the epithelial and mucous gland basement membrane zone. A very small minority of patients have an associated internal malignancy which should be excluded [8].

Topical corticosteroids usually help if the lesions are restricted to the oral mucosa; azathioprine may be an alternative [1,14–17]. Systemic corticosteroids may occasionally be required but tetracyclines with or without nicotinamide may help [17–21]. Dapsone may be useful, especially in the treatment of desquamative gingivitis [2,3,21–23]. Recalcitrant MMP may respond to tacrolimus, mycophenolate mofetil [7,24–26], intravenous immunoglobulins or infliximab [27–29].

References

1 Scully C, Carrozzo M, Gandolfo S, Puiatti P, Monteil R. Update on mucous membrane pemphigoid (an immune mediated sub-epithelial blistering disease): a heterogeneous entity. *Oral Surg Oral Med Oral Pathol* 1999; **88**: 56–68.

2 Chan LS, Ahmed AR, Anhalt GJ *et al.* The first international consensus on mucous membrane pemphigoid: definition, diagnostic criteria, pathogenic factors, medical treatment, and prognostic indicators. *Arch Dermatol* 2002; **138**: 370–9.
3 Bagan J, Lo Muzio L, Scully C. Mucosal disease series. Number III. Mucous membrane pemphigoid. *Oral Dis* 2005; **11**: 197–218.
4 Endo H, Rees TD, Kuyamo K, Kono Y, Yamamoto H. Clinical and diagnostic features of mucous membrane pemphigoid. *Compend Contin Educ Dent* 2006; **27**: 512–6.
5 Darling MR, Daley T. Mucous membrane pemphigoid. *J Can Dent Assoc* 2005; **71**: 851–4.
6 Rashid KA, Gurcan HM, Ahmed AR. Antigen specificity in subsets of mucous membrane pemphigoid. *J Invest Dermatol* 2006; **126**: 2631–6.
7 Carozzo M. PL5 The diagnosis of sub-epithelial bullous diseases. *Oral Dis* 2006; **12** (Suppl. 1): 1.
8 Malik M, Gurcan HM, Christen W, Ahmed AR. Relationship between cancer and oral pemphigoid patients with antibodies to alpha6-integrin. *J Oral Pathol Med* 2007; **36**: 1–5.
9 Calabresi V, Carrozzo M, Cozzani E *et al*. Oral pemphigoid autoantibodies preferentially target BP180 ectodomain. *Clin Immunol* 2007; **122**: 207–13.
10 Bruch-Gerharz D, Hertl M, Rozika T. Mucous membrane pemphigoid: clinical aspects, immunopathological features and therapy. *Eur J Dermatol* 2007; **17**: 191–200.
11 Bhol KC, Goss L, Kumari S, Colon JE, Ahmed AR. Autoantibodies to human alpha6 integrin in patients with oral pemphigoid. *J Dent Res* 2001; **80**: 1711–5.
12 Venning VA, Frith PA, Bron AJ *et al.* Mucosal involvement in bullous and cicatricial pemphigoid. A clinical and immunopathological study. *Br J Dermatol* 1988; **118**: 7–15.
13 Challacombe SJ, Setterfield J, Shirlaw P *et al*. Immunodiagnosis of pemphigus and mucous membrane pemphigoid. *Acta Odontol Scand* 2001; **59**: 226–34.
14 Epstein JB, Gorsky M, Epstein MS, Nantel S. Topical azathioprine in the treatment of immune-mediated chronic oral inflammatory conditions: a series of cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001; **91**: 56–61.
15 Scully C. PL6 Sub-epithelial vesiculobullous disorders: treatment now and on the horizon. *Oral Dis* 2006; **12** (Suppl. 1): 2.
16 Canizares MJ, Smith DI, Connors MS, Maverick KJ, Hefferman AP. Successful treatment of mucous membrane pemphigoid with etanercept in 3 patients. *Arch Dermatol* 2006; **142**: 1457–61.
17 Salzano S, Arduino P, Zambruno G *et al*. OC9 Successful use of mycophenolate mofetil in combination with minocycline in a woman with severe predominantly oral mucous membrane pemphigoid: a case report. *Oral Dis* 2006; **12** (Suppl. 1): 11.
18 Poskitt L, Wojnarowska F. Minimizing cicatricial pemphigoid orodynia with minocycline. *Br J Dermatol* 1995; **132**: 784–9.
19 Poskitt L, Wojnarowska F. Treatment of cicatricial pemphigoid with tetracycline and nicotinamide. *Clin Exp Dermatol* 1995; **20**: 258–9.
20 Reiche L, Wojnarowska F, Mallon E. Combination therapy with nicotinamide and tetracyclines for cicatricial pemphigoid: further support for its efficacy. *Clin Exp Dermatol* 1998; **23**: 254–7.
21 Sacher C, Hunzelmann N. Cicatricial pemphigoid (mucous membrane pemphigoid): current and emerging therapeutic approaches. *Am J Clin Dermatol* 2005; **6**: 93–103.
22 Rogers RS, Seehafer JR, Perry H. Treatment of cicatricial (benign mucous membrane) pemphigoid with dapsone. *J Am Acad Dermatol* 1982; **6**: 215–23.
23 Matthews RW, Pinkney RC, Scully C. The management of desquamative gingivitis with dapsone. *Ann Dent* 1981; **48**: 41–3.
24 Letko E, Ahmed AR, Foster CS. Treatment of ocular cicatricial pemphigoid with tacrolimus (FK 506). *Graefes Arch Clin Exp Ophthalmol* 2001; **239**: 441–4.
25 Nousari HC, Sragovich A, Kimyai-Asadi A, Orlinsky D, Anhalt GJ. Mycophenolate mofetil in autoimmune and inflammatory skin disorders. *J Am Acad Dermatol* 1999; **40**: 265–8.
26 Suresh L, Martinez Calixto LE, Radfar L. Successful treatment of mucous membrane pemphigoid with tacrolimus. *Spec Care Dentist* 2006; **26**: 66–70.
27 Heffernan MP, Bentley DD. Successful treatment of mucous membrane pemphigoid with infliximab. *Arch Dermatol* 2006; **142**: 1268–70.
28 Daouid YJ, Amin KG. Comparison of cost of immune globulin intravenous therapy to conventional immunosuppressive therapy in treating patients with autoimmune mucocutaneous blistering diseases. *Int Immunopharmacol* 2006; **6**: 600–6.
29 Segura S, Iranzo P, Martinez-de Pablo I *et al*. High-dose intravenous immunoglobulins for the treatment of autoimmune mucocutaneous blistering diseases: evaluation of its use in 19 cases. *J Am Acad Dermatol* 2007; **56**: 960–7.

Vegetating cicatricial pemphigoid (synonym pemphigoid vegetans). A subset of bullous pemphigoid, although clinically indistinguishable from pemphigus vegetans and sometimes producing oral blisters and erosions, vegetating cicatricial pemphigoid shows linear deposits of IgG and C3 at the epithelial basement membrane zone on oral biopsy but no circulating basement membrane antibodies [1,2].

Palate and gingiva have been especially involved in the rare cases described [2–4].

References

1 Vincent SD, Lilly GE, Baker KA. Clinical, historic and therapeutic features of cicatricial pemphigoid. *Oral Surg* 1993; **76**: 453–9.
2 Wozniak K, Gorkiewicz A, Olszewska M, Schwartz RA, Kowolewski C. Cicatricial pemphigoid vegetans. *Int J Dermatol* 2007; **46**: 299–302.
3 Liu HN, Su WP, Rogers RS *et al.* Clinical variants of pemphigoid. *Int J Dermatol* 1986; **25**: 17–27.
4 Wolf K, Rappersberger K, Steiner A *et al.* Vegetating cicatricial pemphigoid. *Arch Dermatol Res* 1987; **279**: S30–S37.

Epidermolysis bullosa acquisita (see Chapter 40). Blisters or ulcers may be seen in the oral mucosa in epidermolysis bullosa acquisita, with antibodies directed against collagen VII [1]. Lesional biopsy shows IgG and C3 in the sublamina densa zone of the epithelial basement membrane using immunoelectron microscopy [2–5].

References

1 Sitaru C. Experimental models of epidermolysis bullosa acquisita. *Exp Dermatol* 2007; **16**: 520–31.
2 Prost C, Labeille B, Chanssade V *et al.* Immunoelectron microscopy in subepidermal autoimmune bullous diseases: a prospective study of IgG and C3 bound *in vivo* in 32 patients. *J Invest Dermatol* 1987; **89**: 567–73.
3 Rubenstein R, Sterley NB, Fine JD. Childhood epidermolysis bullosa acquisita. *Arch Dermatol* 1987; **123**: 772–6.
4 Tokuda Y, Amagai M, Yaoita H *et al.* A case of an inflammatory variant of epidermolysis bullosa acquisita: chronic bullous dermatosis associated with nonscarring mucosal blisters and circulating IgG anti-type-VII-collagen antibody. *Dermatology* 1998; **197**: 58–61.
5 Trigo-Guzaman FX, Conti A, Aoki V *et al*. Epidermolysis bullosa acquisita in childhood. *J Dermatol* 2003; **30**: 226–9.

Dermatitis herpetiformis and adult linear IgA disease. Oral lesions may occur in dermatitis herpetiformis and in most patients with linear IgA disease. Macules, papules, petechiae, vesicles, bullae and erosions or desquamative gingivitis are the usual manifestations [1–13]. These disorders must be differentiated, especially from pemphigoid, angina bullosa haemorrhagica, superficial mucoceles and LP.

Salivary IgA antigliadin antibodies may be found but this is not useful diagnostically. Dapsone and sulfapyridine are the most effective therapeutic agents along with a gluten-free diet in dermatitis herpetiformis. Mycophenolate mofetil may be of benefit in the treatment of linear IgA disease [13].

References

1 Chan LS, Regezi JA, Cooper KD. Oral manifestations of linear IgA disease. *J Am Acad Dermatol* 1990; **22**: 362–5.
2 Cowan CG, Lamey PJ, Walsh M *et al.* Linear IgA disease (LAD): immunoglobulin deposition in oral and colonic lesions. *J Oral Pathol Med* 1995; **24**: 374–8.
3 Economopoulou P, Laskaris G. Dermatitis herpetiformis: oral lesions as an early manifestation. *Oral Surg* 1986; **62**: 77–80.
4 Hall RP, Waldbauer GV. Characterisation of the mucosal immune response to dietary antigens in patients with dermatitis herpetiformis. *J Invest Dermatol* 1988; **90**: 658–63.
5 Kelly SE, Frith PA, Millard PR *et al.* A clinopathological study of mucosal involvement in linear IgA disease. *Br J Dermatol* 1988; **119**: 161–70.
6 Porter SR, Bain SE, Scully C. Linear IgA disease manifesting as recalcitrant desquamative gingivitis. *Oral Surg* 1992; **74**: 179–82.
7 Porter SR, Scully C, Midda M *et al.* Adult linear IgA disease manifesting as desquamative gingivitis. *Oral Surg* 1990; **70**: 450–3.
8 Wiesenfeld D, Martin A, Scully C *et al.* Oral manifestations in linear IgA disease. *Br Dent J* 1982; **153**: 389–9.
9 Cohen DM, Bhattacharyya I, Zunt SL, Tomich CE. Linear IgA disease histopathologically and clinically masquerading as lichen planus. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1999; **88**: 196–201.
10 Femiano F, Scully C, Gombos F. Linear IgA dermatosis induced by a new angiotensin-converting enzyme inhibitor. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2003; **95**: 169–73.
11 Procaccini M, Capisi G, Bufo P *et al*. Lack of association between celiac disease and dental enamel hypoplasia in a case–control study from an Italian central region. *Head Face Med* 2007; **3**: 25.
12 Egui del Valle A, Aguirre Urizar JM, Martinez Sahuquilo A. Oral manifestations caused by the linear IgA disease. *Med Oral* 2004; **9**: 39–44.
13 Lewis MA, Yaqoob NA, Emanuel C, Potts AJ. Successful treatment of oral linear IgA disease using mycophenolate. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; **103**: 483–6.

Chronic bullous dermatosis of childhood (see Chapter 40). Oral ulceration and desquamative gingivitis have been reported [1–6].

References

1 Wojnarowska F, Marsden RA, Bhogal B, Black MM. Chronic bullous disease of childhood, childhood cicatricial pemphigoid and linear IgA disease of adults: a comparative study demonstrating clinical and immunopathological overlap. *J Am Acad Dermatol* 1988; **19**: 792–805.
2 Casiglia J, Woo SB, Ahmed AR. Oral involvement in autoimmune blistering diseases. *Clin Dermatol* 2001; **19**: 737–41.
3 Gulati R, Bagga G. Chronic bullous dermatosis of childhood. *Indian Pediatr* 2003; **40**: 62.
4 Thappa DM, Jeevankumar B. Chronic bullous dermatosis of childhood. *Postgrad Med J* 2003; **79**: 437.
5 Hogberg L, Sokolski J, Stenhammar L. Chronic bullous dermatosis of childhood associated with coeliac disease in a 6-year-old boy. *Acta Derm Venereol* 2004; **84**: 158–9.
6 Lourenco SV, Boggio P, Agner Machado Martens RD *et al*. Childhood oral mucous membrane pemphigoid presenting as desquamative gingivitis in a 4-year-old girl. *Acta Derm Venereol* 2006; **86**: 351–4.

Erythema multiforme (see Chapter 76).

Aetiology. The aetiology of erythema multiforme (EM) is unclear in most patients, but appears to be an immunological hypersensitivity reaction with the appearance of cytotoxic effector cells (CD8 T lymphocytes) in the epithelium, inducing apoptosis of scattered keratinocytes and leading to satellite cell necrosis.

EM has been classified into a number of variants—EM minor affecting one mucosa, EM major affecting two or more mucous membranes and Stevens–Johnson syndrome (SJS) where there is extensive skin involvement and associated mortality rate 5–15%. Toxic epidermal necrolysis (TEN) may be a severe manifestation of EM [1,2].

Predisposing factors. There may be a genetic predisposition, with associations of recurrent EM with HLA-B15(B62), HLA-B35, HLA-A33, HLA-DR53 and HLA-DQB1*0301. HLA-DQ3 has been proven to be especially related to recurrent EM and may be a helpful marker for distinguishing this herpes-associated EM from other diseases with EM-like lesions. Patients with extensive mucosal involvement may have the rare HLA allele DQB1*0402 [3].

The reaction is triggered by the following.

- *Infective agents*, particularly herpes simplex virus (herpes-associated EM), which is implicated in 70% of recurrent EM. Bacteria (*Mycoplasma pneumoniae*, and many others), other viruses, fungi or parasites are less commonly implicated [1,2,4–10].
- *Drugs* such as sulphonamides (e.g. co-trimoxazole), cephalosporins, aminopenicillins, quinolones, barbiturates, oxicam non-steroidal anti-inflammatory drugs, anticonvulsants, protease inhibitors, allopurinol and many others may trigger severe EM or toxic epidermal necrolysis in particular [1,2,11,12].
- *Food additives or chemicals* such as benzoates, nitrobenzene, perfumes, terpenes.
- *Immune conditions* such as BCG or hepatitis B immunization, sarcoidosis, GVHD, inflammatory bowel disease, polyarteritis nodosa or systemic lupus erythematosus (SLE).

Clinical features. Most patients with EM (70%), of either minor or major forms, have oral lesions. The oral mucosa may be involved alone or in association with skin lesions. Mucosal lesions begin as erythematous areas that blister and break down to irregular, extensive, painful erosions with extensive surrounding erythema. The labial mucosa is often involved, and a serosanguinous exudate leads to crusting of the swollen lips [1,2,13–18].

Mucosal erosions plus typical or raised atypical targets and epidermal detachment involving less than 10% of the body surface and usually located on the extremities and/or the face characterize herpes simplex-induced EM major.

Mucosal erosions plus widespread distribution of flat atypical targets or purpuric macules and epithelial detachment involving less than 10% of body surface on the trunk, face and extremities are characteristic of drug-induced Stevens–Johnson syndrome [19].

Diagnosis. A diagnosis of EM can be difficult to readily establish, and there may be a need to differentiate from viral stomatitides, pemphigus, toxic epidermal necrolysis and the subepithelial immune blistering disorders (pemphigoid and others). There are no specific diagnostic tests.

The diagnosis is mainly clinical; the Nikolsky sign is negative. It may be helpful to undertake serology for *Mycoplasma* pneumoniae or herpes simplex virus, or other microorganisms. Biopsy of perilesional tissue with immunostaining and histological examination may help, although pathology can be variable and immunostaining is not specific.

Treatment. Spontaneous healing can be slow, up to 2–3 weeks in EM minor and up to 6 weeks in EM major. Treatment is thus

indicated but controversial. No specific treatment is available but supportive care is important; a liquid diet and intravenous fluid therapy may be necessary. Electrolytes and nutritional support should be started as soon as possible. Oral hygiene should be improved with 0.2% aqueous chlorhexidine mouthbaths.

The use of corticosteroids is controversial [1,2,20–22].

- EM minor may respond to topical corticosteroids, although systemic corticosteroids may still be required.
- EM major should be treated with systemic corticosteroids (prednisolone 0.5–1 mg/kg/day tapered over 7–10 days) and/or azathioprine or other immunomodulatory drugs [1,2]. Levamisole [22,23] and thalidomide have occasionally been used to some effect [24,25]. Plasmapheresis possibly has a place in the management of severe disease.

Antimicrobials may be indicated [1,2,26,27].

- Aciclovir in EM related to herpes simplex virus (HSV). Give a 5-day course at the first sign of lesions, or give 400 mg three times daily for 6 months for prophylaxis in EM related to HSV [10]. Continuous therapy with valaciclovir 500 mg twice a day has also been reported to be effective [1,2,10,27].
- Tetracycline is indicated in EM related to *Mycoplasma pneumoniae*.

References

1 Farthing P, Bagan JV, Scully C. Mucosal disease series. Number IV. Erythema multiforme. *Oral Dis* 2005; **11**: 261–7.
2 Al-Johani KA, Fedele S, Porter SR. Erythema multiforme and related disorders. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; **103**: 642–54.
3 Malo A, Kampgen E, Wank R. Recurrent herpes simplex virus-induced erythema multiforme: different HLA-DQB1 alleles associate with severe mucous membrane versus skin attacks. *Scand J Immunol* 1998; **47**: 408–11.
4 Aslanzadeh J, Helm KF, Espy MJ, Muller SA, Smith TF. Detection of HSV-specific DNA in biopsy tissue of patients with erythema multiforme by polymerase chain reaction. *Br J Dermatol* 1992; **126**: 19–23.
5 Weston WL, Morelli JG. Herpes simplex virus-associated erythema multiforme in prepubertal children. *Arch Pediatr Adolesc Med* 1997; **151**: 1014–6.
6 Bakis S, Zagarella S. Intermittent oral cyclosporin for recurrent herpes simplex-associated erythema multiforme. *Australas J Dermatol* 2005; **46**: 18–20.
7 Pope E, Krafchik BR. Involvement of three mucous membranes in herpes-induced recurrent erythema multiforme. *J Am Acad Dermatol* 2005; **52**: 171–2.
8 Bakis S, Zagarella S. Intermittent oral cyclosporin for recurrent herpes simplex-associated erythema multiforme. *Australas J Dermatol* 2005; **46**: 18–20.
9 Sinha A, Chander J, Natarajan S. Erythema multiforme presenting as chronic oral ulceration due to unrecognised herpes simplex virus infection. *Clin Exp Dermatol* 2006; **31**: 737–8.
10 Woo SB, Challacombe SJ. Management of recurrent oral herpes simplex infections. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; **103** (Suppl.): S12 1–18.
11 Roujeau JC, Kelly JP, Naldi L *et al.* Medication use and the risk of Stevens–Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med* 1995; **333**: 1600–7.
12 Scully C, Diz Dios P. Orofacial effects of antiretroviral therapies. *Oral Dis* 2001; **7**: 205–10.
13 Cote B, Wechsler J, Bastuji-Garin S. Clinicopathologic correlation in erythema multiforme and Stevens–Johnson syndrome. *Arch Dermatol* 1995; **131**: 1268–72.
14 Eversole LR. Immunopathology of oral mucosal ulcerative, desquamative, and bullous diseases. Selective review of the literature. *Oral Surg Oral Med Oral Pathol* 1994; **77**: 555–71.
15 Silverman S. The bullous desquamative lesions of oral mucosa. *J Calif Dent Assoc* 2000; **28**: 928–32.
16 Stewart MG, Duncan NO 3rd, Franklin DJ, Friedman EM, Sulek M. Head and neck manifestations of erythema multiforme in children. *Otolaryngol Head Neck Surg* 1994; **111**: 236–42.
17 Siegel MA, Balciunas BA. Oral presentation and management of vesiculobullous disorders. *Semin Dermatol* 1994; **13**: 78–86.
18 Farthing PM, Maragou P, Coates M *et al*. Characteristics of the oral lesions in patients with cutaneous recurrent erythema multiforme. *J Oral Pathol Med* 1995; **24**: 9–13.
19 Assier H, Bastuji-Garin S, Revuz J. Erythema multiforme with mucous membrane involvement and Stevens–Johnson syndrome are clinically different disorders with distinct causes. *Arch Dermatol* 1995; **131**: 539–43.
20 Tripathi A, Ditto AM, Grammer LC *et al.* Corticosteroid therapy in an additional 13 cases of Stevens–Johnson syndrome: a total series of 67 cases. *Allergy Asthma Proc* 2000; **21**: 101–5.
21 Eastham JH, Segal JL, Gomez MF, Cole GW. Reversal of erythema multiforme major with cyclophosphamide and prednisone. *Ann Pharmacother* 1996; **30**: 606–7.
22 Lozada-Nur F, Cram D, Gorsky M. Clinical response to levamisole in thirty-nine patients with erythema multiforme. An open prospective study. *Oral Surg Oral Med Oral Pathol* 1992; **74**: 294–8.
23 Scheinfield N, Rosenberg JD, Weinberg JM. Levamisole in dermatology: a review. *Am J Clin Dermatol* 2004; **5**: 97–104.
24 Conejo-Mir JS, del Canto S, Munoz MA *et al*. Thalidomide as elective treatment in persistent erythema multiforme; report of two cases. *J Drugs Dermatol* 2003; **2**: 40–4.
25 Wu JJ, Huang DB, Pang KR, Hsu S, Tyring SK. Thalidomide: dermatological indications, mechanisms of action and side-effects. *Br J Dermatol* 2005; **153**: 254–73.
26 Katz J, Livneh A, Shemer J, Danon YL, Peretz B. Herpes simplex-associated erythema multiforme (HAEM): a clinical therapeutic dilemma. *Pediatr Dent* 1999; **21**: 359–62.
27 Kerob D, Assier-Bonnet H, Esnault-Gelly P. Recurrent erythema multiforme unresponsive to acyclovir prophylaxis and responsive to valacyclovir continuous therapy. *Arch Dermatol* 1998; **134**: 876–7.

Toxic epidermal necrolysis (See Chapter 76)

Synonym
- Lyell's disease

Toxic epidermal necrolysis is a rare clinicopathological entity, with a high mortality, characterized by extensive detachment of full-thickness epithelium. Toxic epidermal necrolysis and Stevens–Johnson syndrome appear to be severity variants of the same disease, which differs from EM. The distinction from EM is unclear, however, but most cases of toxic epidermal necrolysis are drug-induced and the lesions are extremely widespread [1–6].

Recently, an increased number of cases in patients with HIV/acquired immune deficiency syndrome (AIDS) has been recorded [7–9].

Clinical features. Toxic epidermal necrolysis presents with cough, sore throat, burning eyes, malaise and low fever, followed after about 1–2 days by skin and mucous membrane lesions. Oral lesions can be seen in over 95% of patients with toxic epidermal necrolysis. The entire skin surface and oral mucosa may be involved, with up to 100% sloughing off. Gingival lesions are common and clinically are inflamed, with blister formation leading to painful, widespread erosions. The blisters and erosions may precede the skin lesions by a day or so and may persist [3–7,10–12].

Diagnosis. Sheet-like loss of the epithelium and a positive Nikolsky sign are characteristic. Biopsy of perilesional tissue with immunostaining and histological examination are essential to the

diagnosis. Histopathological examination is characteristic, showing necrosis of the whole epithelium detached from the lamina propria.

Treatment. Patients must be admitted to an intensive care unit as soon as possible for management [4,5,13–19]. There is no specific therapy for oral lesions but 2% lidocaine (lignocaine) and 0.2% aqueous chlorhexidine mouthbaths may provide symptomatic relief. Intravenous immunoglobulin (IVIG) has been proposed as a treatment for toxic epidermal necrolysis with varying effects reported [4,17].

References

1 Roujeau JC. Stevens–Johnson syndrome and toxic epidermal necrolysis are severity variants of the same disease which differs from erythema multiforme. *J Dermatol* 1997; **24**: 726–9.
2 Bastuji-Garin S, Rzany B, Stern RS. Clinical classification of cases of toxic epidermal necrolysis, Stevens–Johnson syndrome, and erythema multiforme. *Arch Dermatol* 1993; **129**: 92–6.
3 Parrillo SJ. Stevens–Johnson syndrome and toxic epidermal necrolysis. *Curr Allergy Asthma Rep* 2007; **7**: 243–7.
4 Mittman N, Chan BC, Knowles S, Shear SH. IVIG for the treatment of toxic epidermal necrolysis. *Skin Therapy Lett* 2007; **12**: 7–9.
5 Pereira FA, Mudgil AV, Rosmarin DM. Toxic epidermal necrolysis. *J Am Acad Dermatol* 2007; **56**: 181–200.
6 Al-Johani KA, Fedele S, Porter SR. Erythema multiforme and related disorders. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; **103**: 642–54.
7 Schmidt-Westhausen A, Grunewald T, Reichart PA, Pohle HD. Oral manifestations of toxic epidermal necrolysis (TEN) in patients with AIDS: report of five cases. *Oral Dis* 1998; **4**: 90–4.
8 Tan A, Tan HH, Lee CC, Ng S. Treatment of toxic epidermal necrolysis in AIDS with intravenous immunoglobulins. *Clin Exp Dermatol* 2003; **28**: 269–71.
9 Todd G. Adverse cutaneous drug eruptions and HIV: a clinician's global perspective. *Dermatol Clin* 2006; **24**: 459–72.
10 Marra LM, Wunderlee RC. Oral presentation of toxic epidermal necrolysis. *J Oral Maxillofac Surg* 1982; **40**: 59–61.
11 Revuz J, Penso D, Roujeau JC. Toxic epidermal necrolysis: clinical findings and prognostic factors in 87 patients. *Arch Dermatol* 1987; **123**: 1160–5.
12 Barrera JE, Meyers AD, Hartford EC. Hypopharyngeal stenosis and dysphagia complicating toxic epidermal necrolysis. *Arch Otolaryngol Head Neck Surg* 1998; **124**: 1375–6.
13 Roujeau JC. Treatment of severe drug eruptions. *J Dermatol* 1999; **26**: 718–22.
14 Baroni A, Ruocco E. Lyell's syndrome. *Skinmed* 2005; **4**: 221–5.
15 Mittman N, Chan B, Knowles S, Cosentino L, Shear N. Intravenous immunoglobulin use in patients with toxic epidermal necrolysis and Stevens–Johnson syndrome. *Am J Clin Dermatol* 2006; **7**: 359–68.
16 French LE. Toxic epidermal necrolysis and Stevens Johnson syndrome: our current understanding. *Allergol Int* 2006; **55**: 9–16.
17 Stella M, Clements A, Bollero D, Risso D, Dalmasso P. Toxic epidermal necrolysis (TEN) and Stevens–Johnson syndrome (SJS): Experience with high-dose intravenous immunoglobulins and topical conservative approach A retrospective analysis. *Burns* 2007; **33**: 452–9.
18 Khalili B, Bahna SL. Pathogenesis and recent therapeutic trends in Stevens–Johnson syndrome and toxic epidermal necrolysis. *Ann Allergy Asthma Immunol* 2006; **97**: 272–80.
19 Kocak S, Girisgen SA, Gul M, Cander B, Kaya H, Kaya E. Stevens–Johnson syndrome due to concomitant use of lamotrigine and valproic acid. *Am J Clin Dermatol* 2007; **8**: 107–11.

Lupus erythematosus (see Chapter 51)

Almost 50% of patients with systemic lupus erythematosus (SLE) suffer from oral lesions, which begin as red patches that break down to irregular slit-like ulcers which often heal with scarring [1–4]. Lesions particularly affect the palate. Sjögren's syndrome may occur in SLE. Oral petechiae and herpetic infections are also common. Rarely, dental surgery has been followed by facial swelling [5].

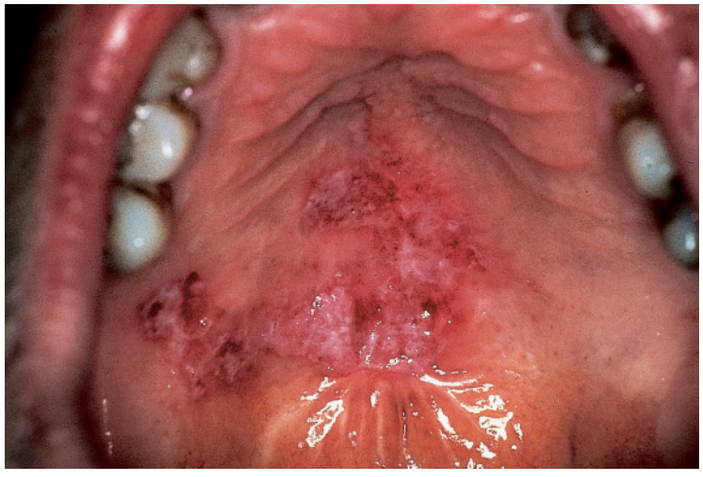


Fig. 69.40 Chronic oral lesions in discoid lupus erythematosus.

Similar erosions, with a white border, occur in discoid lupus erythematosus (DLE) (Fig. 69.40). DLE may predispose to oral carcinoma [6,7]. Oral ulceration has also been described in drug-induced lupus.

Systemic corticosteroids, often with an immunosuppressant, may be required in severe cases of SLE; topical steroids for DLE.

References

1 Schiodt M. Oral manifestations of lupus erythematosus. *Int J Oral Surg* 1984; **13**: 101–47.
2 Orteu CH, Buchanan JA, Hutchinson I, Leigh IM, Bull RH. Systemic lupus erythematosus presenting with oral mucosal lesions: easily missed? *Br J Dermatol* 2001; **144**: 1219–23.
3 Brennan MT, Valerin MA, Napenas JJ, Lockhart PB. Oral manifestations of patients with lupus erythematosus. *Dent Clin North Am* 2005; **49**: 127–41.
4 Lourenco SV, Nacagami Sotto M, Constantino Vilela MA *et al*. Lupus erythematosus: clinical and histopathological study of oral manifestations and immunohistochemical profile of epithelial maturation. *J Cutan Pathol* 2006; **33**: 657–62.
5 Loescher A, Edmondson HD. Lupus erythematosus: a case of facial swelling. *Br J Oral Surg* 1988; **26**: 129–32.
6 Handlers JP, Abrams AM, Aberle AM *et al*. Squamous cell carcinoma of the lip developing in discoid lupus erythematosus. *Oral Surg* 1985; **60**: 382–6.
7 Porter SR, Malamos D, Scully C. Mouth–skin interface: 2. Connective tissue and metabolic disorders. *Dent Update* 1986; **33**: 94–6.

Other collagen–vascular diseases

Dermatomyositis and mixed connective tissue disease may be associated with non-specific mucosal erosions [1].

Oral involvement in Reiter's syndrome may include red patches or superficial painless mucosal erosions which may resemble erythema migrans (geographical tongue) both clinically and histologically.

Reference

1 Healy CM, Tobin AM, Kirby B, Flint SR. Oral lesions as an initial manifestation of dermatomyositis with occult malignancy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006; **101**: 184–7.

Infective diseases

Oral ulceration is common worldwide in some viral infections, typically in the herpesvirus or enterovirus infections seen in childhood. It can also be seen in several bacterial diseases, notably acute necrotizing gingivitis (but also in tuberculosis and syphilis), but is rare in fungal infections in the resource-rich countries, although the deep mycoses may be responsible for infection in resource-poor countries, in travellers or in the immunocompromised.

Herpesviruses

Oral infection is common with the herpesviruses, which thereafter remain latent, are often excreted in saliva (especially in immunocompromised persons), and are sometimes implicated in clinical recurrences and malignant complications [1].

Herpes simplex stomatitis

Aetiology. HSV infection is a very common oral infection. In general, HSV-1 causes primary herpetic stomatitis (and the secondary infection of recurrent herpes labialis). There are no precise distinctions nowadays, presumably with more frequent orogenital and oroanal sexual practices, and oral infection with HSV-2 is also frequently seen [2–7].

With improving socio-economic circumstances and standards of hygiene, a larger number of children are not exposed to HSV and enter adult life without immunity. Cases of primary herpetic stomatitis are therefore now seen occasionally in adults, and the manifestations can be severe. HSV is usually transmitted in saliva and can be shed in asymptomatic individuals [8–11].

Clinical features. The incubation period is 3–7 days. Many infections with HSV occur in childhood and are subclinical and, where there is disease, it varies greatly in severity. In many it is trivial and misdiagnosed or passed off as 'teething' [4,7,12–14].

Primary herpetic stomatitis typically presents with malaise, anorexia, irritability, fever, enlarged and tender anterior cervical lymph nodes, and a diffuse, purple, boggy gingivitis (hence the alternative term *herpetic gingivostomatitis*), especially anteriorly, with multiple vesicles followed by round or ovoid ulcers 1–3 mm in diameter scattered across the oral mucosa and gingiva (Fig. 69.41) in an acute illness lasting only up to about 14 days [2,3,7,14]. In immunocompromised persons, diagnosis can be difficult since herpes may manifest with chronic ulcers [14–18].

Prognosis. Herpetic stomatitis resolves spontaneously in 7–14 days but HSV remains latent in the trigeminal ganglion. The most obvious sequel is that about one-third of patients are thereafter predisposed to recurrences [19]. HSV is shed intermittently into the saliva [8–11]. HSV is implicated in many instances of EM (see p. 69.70) and may cause chronic ulcers in the immunocompromised (see below) or occasionally ulcers following trauma to the mouth.

Diagnosis. The main differential diagnoses of herpetic stomatitis in otherwise healthy persons are chickenpox and other viral causes of mouth ulcers, and acute leukaemia. In immunocopromised persons, the differential is wider. A full blood picture, white-cell count and differential, and viral studies may therefore be required [2,3,7,14,20,21]. The latter include the following:

- Culture: this takes days to give a result.
- Electron microscopy: this is not always available.
- Polymerase chain reaction (PCR) detection of HSV DNA: this is sensitive but expensive.
- Immunodetection: detection of HSV antigens is of some value. Conventional enzyme-linked immunosorbent assays (ELISA) for serum antibodies have poor sensitivity and specificity; newer assays based on HSV glycoproteins are comparable with western blot assays. A rising titre of serum antibodies is confirmatory but only gives the diagnosis retrospectively.
- Smears for viral-damaged cells: now rarely used.



Fig. 69.41 Scattered ulcers and a furred tongue in primary herpetic stomatitis.

Treatment. Specific antiviral agents are most useful in the very early stages of disease (though most patients present later) and for immunocompromised patients who may otherwise suffer severe infection. Aciclovir or other antiviral medications may be indicated systemically [22–26].

For most, however, management is supportive with antipyretic analgesics (e.g. acetaminophen/paracetamol), sponging with tepid water and a high fluid intake. Analgesics (as elixirs or syrups for children) and, in adults, lidocaine mouthbaths help ease discomfort and 0.2% aqueous chlorhexidine mouthbaths aid resolution.

An antihistamine such as promethazine may help sedate an irritable child.

Recurrent labial HSV infection. Primary oral infection by HSV may produce perioral lesions (Fig. 69.42). However, recurrent herpes labialis involving the lip is the more common cause of blisters at the mucocutaneous junction (Fig. 69.43) [2–5,7,19]. The lesions arise at the mucocutaneous junction as itching papules which progress to vesicles, pustules and then scab. They are unsightly and occasionally become infected with *Staphylococcus* or *Streptococcus*, resulting in impetigo (Fig. 69.44). In immunocompromised persons, extensive and persistent lesions may result. In atopic persons, the lesions may spread to produce eczema herpe-



Fig. 69.42 Primary herpetic stomatitis with extraoral lesions.



Fig. 69.43 Herpes labialis.



Fig. 69.44 Impetigo.



Fig. 69.45 Eczema herpeticum.

ticum (Fig. 69.45). Aciclovir has been the standard treatment used as a 5% cream, although penciclovir 1% is reportedly more effective [27,28].

Recurrent intraoral HSV infection. Chronic oral herpetic ulcers, often with a raised white border and sometimes with a dendritic appearance, may occasionally affect apparently healthy individuals, especially at sites of trauma, for example following palatal infiltration of a local anaesthetic. Chronic indolent lesions, usually ulcerative or nodular, may be seen in patients with neutropenia or chronic leukaemia; in patients with more severe immunosuppression, such as acute leukaemia or HIV infection, more aggressive chronic ulcers may be seen [14–18,29,30]. Aciclovir or other antivirals may be indicated systemically [15,31].

References

1 Carrillo-Infante C, Abbadessa G, Bagello L, Giordano A. Viral infections as a cause of cancer. *Int J Oncol* 2007; **30**: 1521–8.

2 Whitley RJ, Roizman B. Herpes simplex virus infections. *Lancet* 2001; **357**: 1513–8.

3 Scully C. Orofacial herpes simplex virus infections: current concepts in the epidemiology, pathogenesis and treatment, and disorders in which the virus may be implicated. *Oral Surg* 1989; **68**: 701–10.

4 Glick M. Clinical aspects of recurrent oral herpes simplex virus infection. *Compend Contin Educ Dent* 2002; **23** (7 Suppl. 2): 4–8.

5 Yarom N, Buchner A, Dayan D. Herpes simplex virus infection: part I—Biology, clinical presentation and latency. *Refuat Hapeh Vehashinayim* 2005; **22**: 7–15.

6 Syrjanen S. PL7 Oral viral infections that could be transmitted oro-genitally. *Oral Dis* 2006; **12** (Suppl. 1): 2.

7 Kolokotronis A, Doumas S. Herpes simplex virus infection, with particular reference to the progression and complications of primary herpetic gingivostomatitis. *Clin Microbiol Infect* 2006; **12**: 202–11.

8 Yoshida M, Amatsu A. Asymptomatic shedding of herpes simplex virus into the oral cavity of patients with atopic dermatitis. *J Clin Virol* 2000; **16**: 65–9.
9 Knaup B, Schunemann S, Wolff MH. Subclinical reactivation of herpes simplex virus type 1 in the oral cavity. *Oral Microbiol Immunol* 2000; **15**: 281–3.
10 Da Silva LM, Guimaraes AL, Victoria JM, Gomes CC, Gomez RS. Herpes simplex virus type 1 shedding in the oral cavity of seropositive patients. *Oral Dis* 2005; **11**: 13–16.
11 Gilbert SC. Oral shedding of herpes simplex virus type 1 in immunocompetent persons. *J Oral Pathol Med* 2006; **35**: 548–53.
12 Kimberlin DW, Lin CY, Jacobs RF *et al.* Natural history of neonatal herpes simplex virus infections in the acyclovir era. *Pediatrics* 2001; **108**: 223–9.
13 Scully C. Ulcerative stomatitis gingivitis and rash: a diagnostic dilemma. *Oral Surg* 1985; **59**: 261–3.
14 Samonis G, Mantadakis E, Maraki S. Orofacial viral infections in the immunocompromised host. *Oncol Report* 2000; **7**: 1389–94.
15 Cohen SG, Greenberg MS. Chronic oral herpes simplex virus infection in immunocompromised patients. *Oral Surg* 1985; **59**: 465–71.
16 Bergmann OJ, Mogensen SC, Ellegaard J. Herpes simplex virus and intraoral ulcers in immunocompromised patients with haematologic malignancies. *Eur J Clin Microbiol Infect Dis* 1990; **9**: 184–90.
17 Greenberg MS, Cohen SG, Boosz B *et al.* Oral herpes simplex infections in patients with leukaemia. *J Am Dent Assoc* 1987; **114**: 483–6.
18 Grossman ME, Stevens AW, Cohen PR. Herpetic geometric glossitis. *N Engl J Med* 1993; **329**: 1859–60.
19 Shulman JD. Recurrent herpes labialis in US children and youth. *Community Dent Oral Epidemiol* 2004; **32**: 402–9.
20 Bezold G, Volkenandt M, Gottlober P, Peter RU. Detection of herpes simplex virus and varicella-zoster virus in clinical swabs: frequent inhibition of PCR as determined by internal controls. *Mol Diagn* 2000; **5**: 279–84.
21 Goldman BD. Herpes serology for dermatologists. *Arch Dermatol* 2000; **136**: 1158–61.
22 Birek C. Herpesvirus-induced diseases: oral manifestations and current treatment options. *J Calif Dent Assoc* 2000; **28**: 911–21.
23 Flaitz CM, Baker KA. Treatment approaches to common symptomatic oral lesions in children. *Dent Clin North Am* 2000; **44**: 671–96.
24 Spruance SI, Bodsworth N, Resnick H *et al*. Single-dose, patient-initiated famciclovir: a randomized, double-blind, placebo-controlled trial for episodic treatment of herpes labialis. *J Am Acad Dermatol* 2006; **55**: 47–53.
25 Simpson D, Lyseng-Williamson KA. Famciclovir: a review of its use in herpes zoster and genital and orolabial herpes. *Drugs* 2006; **66**: 2397–416.
26 Woo SB, Challacombe SJ. Management of recurrent oral herpes simplex infections. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; **103** Suppl: S12 1–18.
27 Femiano F, Gombos S, Scully C. Recurrent herpes labialis: efficacy of topical therapy with penciclovir compared with acyclovir (aciclovir). *Oral Dis* 2001; **7**: 31–2.
28 Raborn GW, Grace RG. Recurrent herpes simplex labialis: selected therapeutic options. *J Can Dent Assoc* 2003; **69**: 498–503.
29 Orlowski RZ, Mills SR, Hartley EE *et al*. Oral valacyclovir as prophylaxis against herpes simplex virus reactivation during high dose chemotherapy for leukemia. *Leuk Lymphoma* 2004; **45**: 2215–9.
30 Sepulveda E, Brethauer U, Rojaz J, Fernandez E, Le Fort P. Oral ulcers in children under chemotherapy: clinical characteristics and their relation with Herpes Simplex Virus type 1 and Candida albicans. *Med Oral Patol Oral Cir Bucal* 2005; **10** Suppl 1: E1–8.
31 Chilukuri S, Rosen T. Management of acyclovir-resistant herpes simplex virus. *Dermatol Clin* 2003; **21**: 311–20.

Chickenpox (see Chapter 33)

Synonym
- Varicella

Chickenpox affects children predominantly and may present with mouth ulcers that resemble those of herpetic stomatitis, but there is no gingivitis [1]. There may be a contact history. Many primary infections with varicella-zoster virus are subclinical or produce so few lesions as to pass almost unnoticed. Varicella-zoster virus remains latent in sensory ganglia and may be reactivated to produce shingles.

Herpes zoster

Synonym
- Shingles

If shingles affects the maxillary or mandibular divisions of the trigeminal nerve, mouth ulcers are usually seen [2–4].

Clinical features. The pain of trigeminal zoster may simulate toothache. Severe pain often precedes, accompanies and follows the rash, and post-herpetic neuralgia may persist for months or years.

The rash is restricted to a dermatome and is unilateral, but sometimes a few chickenpox-type lesions can be found elsewhere. Oral ulcers appear in the distribution of the involved nerve division [3]. There is ulceration of one side of the tongue, floor of mouth and lower labial and buccal mucosa if the mandibular division of the trigeminal nerve is involved. One side of the palate, the upper gingiva and buccal sulcus are involved in maxillary zoster. Rarely, mandibular or maxillary zoster may disturb the formation of developing teeth [5–7] or cause jaw necrosis [6,7].

If the geniculate ganglion of the facial nerve is affected, there may be unilateral facial palsy, with vesicles in the ipsilateral ear and ulcers in the soft palate ipsilaterally (Ramsay–Hunt syndrome) [8–14].

Occasionally there is misdiagnosis of toothache, leading to extraction, the true diagnosis becoming apparent only when the rash appears. Zoster resolves spontaneously but post-herpetic neuralgia can be distressing.

Treatment. An underlying immune defect, such as AIDS or malignancy, should be excluded in patients with zoster, although most zoster is related simply to lesser problems in advanced age.

Treatment is mainly supportive but antivirals such as aciclovir can be useful. Analgesics are indicated in zoster, although the pain may prove refractory to even potent analgesics [15,16], when antidepressants such as amitriptyline and fluphenazine may have a place [17,18]. Treatment advances include lidocaine patches, opioid analgesics and gabapentin. Early recognition and treatment of high-risk herpes zoster patients with antiviral and analgesic therapies is mandatory [18].

References

1 Kolokotronis A, Louloudiadis K, Fotiou G, Matiais A. Oral manifestations of infections due to varicella zoster virus in otherwise healthy children. *J Clin Pediatr Dent* 2001; **25**: 107–12.
2 Braverman I, Uri N, Greenberg E. Trigeminal herpes zoster/chocolate-vanilla tongue. *Otolaryngol Head Neck Surg* 2000; **122**: 463.
3 Scully C, Samaranayake LP. *Clinical Oral Virology*. Cambridge: Cambridge University Press, 1992.
4 Carbone V, Leonardi A, Pavese M, Raviola E, Giordano M. Herpes zoster of the trigeminal nerve: a case report and review of the literature. *Minerva Stomatol* 2004; **53**: 49–59.

5 Smith S, Ross JR, Scully C. An unusual oral complication of herpes zoster infection. *Oral Surg* 1984; **57**: 388–9.
6 Wright WE, Davis ML, Geffen DB *et al.* Alveolar bone necrosis and tooth loss: a rare complication associated with herpes zoster infection of the fifth cranial nerve. *Oral Surg* 1983; **56**: 39–46.
7 Siwamogstham P, Kuansuwan C, Reichert P. Herpes zoster in HIV infection with osteonecrosis of the jaw and tooth exfoliation. *Oral Dis* 2006; **12**: 500–5.
8 Sweeney CJ, Gilden DH. Ramsay Hunt syndrome. *J Neurol Neurosurg Psychiatry* 2001; **71**: 149–54.
9 Uri N, Greenberg E, Kitzes-Cohen R, Doweck I. Acyclovir in the treatment of Ramsay Hunt syndrome. *Otolaryngol Head Neck Surg* 2003; **129**: 379–81.
10 Mishriki YY. Ramsay Hunt syndrome revisited. *Skinmed* 2004; **3**: 130–1.
11 Syal R, Tyagi I, Goyal A. Bilateral Ramsay Hunt syndrome in a diabetic patient. *BMC Ear Nose Throat Disord* 2004; **4**: 3.
12 Koga C, Iwamoto O, Aoki M**.** Ramsay-Hunt syndrome with vesicular stomatitis in a 4-year-old infant. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006; **102**: 37–9.
13 T/Selasic H, Zenebe G. Ramsay hunt syndrome. *Ethiop Med J* 2006; **44**: 401–4.
14 Balatsouras DG, Rallis E, Homsioglou E, Fiska A, Korres SG. Ramsay Hunt syndrome in a 3-month-old infant. *Pediatr Dermatol* 2007; **24**: 34–7.
15 Birek C. Herpesvirus-induced diseases: oral manifestations and current treatment options. *J Calif Dent Assoc* 2000; **28**: 911–21.
16 Galluzi KE. Management strategies for herpes zoster and postherpetic neuralgia. *J Am Osteopath Assoc* 2007; **107**: S8–13.
17 Graff-Radford SB, Shaw LR, Naliboff BN. Amitriptyline and fluphenazine in the treatment of postherpetic neuralgia. *Clin J Pain* 2000; **16**: 188–92.
18 Young L. Post-herpetic neuralgia: a review of advances in treatment and prevention. *J Drugs Dermatol* 2006; **5**: 938–41.

Epstein–Barr virus infections (see Chapter 33)

Epstein–Barr virus (EBV) is responsible for infectious mononucleosis and is found in pharyngeal epithelium and appears in the saliva of patients and for several months after clinical recovery. Infection appears to be spread by close oral contact, especially kissing. It is typically a disease of the student population.

Infection is often subclinical. Infectious mononucleosis is also protean in its clinical manifestations, which include particularly lymphadenopathy, sore throat, fever, malaise and rashes. In the anginose type (sore-throat type), the throat is sore with soft-palate petechiae and a whitish exudate on oedematous tonsils [1–3]. There may be non-specific oral ulceration or pericoronitis [1]. The glandular type of infectious mononucleosis is characterized by generalized lymph node enlargement and splenomegaly; the febrile type is characterized by fever.

Similar syndromes may be caused by cytomegalovirus (CMV), human herpesvirus (HHV)-6, toxoplasmosis and HIV. Characteristic of infectious mononucleosis are large numbers of atypical mononuclear cells in the blood and a wide variety of serological changes, particularly heterophil antibodies, which are detectable by the Paul–Bunnell or Monospot tests, usually during the first or second week of illness [4]. Several other antibodies against EBV appear during the course of infectious mononucleosis, but the most frequent is the antibody to viral capsid antigen, the titre of which reaches a peak at about 4 weeks.

No specific treatment is available for infectious mononucleosis, but supportive care is important, not only because of the potential for airways obstruction but also because of the associated lassitude. Systemic corticosteroids are required if there is pharyngeal oedema severe enough to hazard the airway.

EBV is also commonly found in the mouths of immunocompromised patients [5–12] and is implicated in oral hairy leukoplakia, oral ulceration, advanced periodontal disease [13,14] and some oral lymphomas [15–18] although any relationship with other malignancies such as OSCC is controversial [19,20].

References

1 Scully C, Samaranayake LP. *Clinical Oral Virology*. Cambridge: Cambridge University Press, 1992.
2 Ebell MH. Epstein–Barr virus infectious mononucleosis. *Am Fam Physician* 2004; **70**: 1279–87.
3 Auwaerter PG. Recent advances in the understanding of infectious mononucleosis: are prospects improved for treatment or control? *Expert Rev Anti Infect Ther* 2006; **4**: 1039–49.
4 Bell AT, Fortune B, Sheeler R. Clinical inquiries. What test is the best for diagnosing infectious mononucleosis? *J Fam Pract* 2006; **55**: 799–802.
5 Ammatuna P, Campisi G, Giovannelli L *et al.* Presence of Epstein–Barr virus, cytomegalovirus and human papillomavirus in normal oral mucosa of HIV-infected and renal transplant patients. *Oral Dis* 2001; **7**: 34–40.
6 Ammatuna P, Capone F, Giambelluca D *et al*. Detection of Epstein–Barr virus (EBV) DNA and antigens in oral mucosa of renal transplant patients without clinical evidence of oral hairy leukoplakia (OHL). *J Oral Pathol Med* 1998; **27**: 420–7.
7 Triantos D, Boulter AW, Leao JC *et al*. Diversity of naturally-occurring Epstein–Barr virus revealed by nucleotide sequence polymorphism in hypervariable domains in the BamH1 K and N subgenomic regions. *J Gen Virol* 1998; **79**: 2809–17.
8 Triantos D, Leao JC, Porter SR, Scully CM, Teo CG. Tissue distribution of Epstein–Barr virus genotypes in hosts coinfected by HIV. *AIDS* 1998; **12**: 2141–6.
9 Teo CG. Viral infections in the mouth. *Oral Dis* 2002; **8**: 88–90.
10 Miller CS, Berger JR, Mootoor Y *et al*. High prevalence of multiple human herpesviruses in saliva from human immunodeficiency virus-infected persons in the era of highly active antiretroviral therapy. *J Clin Microbiol* 2006; **44**: 2409–15.
11 Webster-Cyriaque J, Duus K, Cooper C, Duncan M. Oral EBV and KSHV infection in HIV. *Adv Dent Res* 2006; **19**: 91–5.
12 Syrjanen S, Leimola-Virtanen R, Schmidt-Westhausen A, Reichart PA. Oral ulcers in AIDS patients frequently associated with cytomegalovirus (CMV) and Epstein–Barr virus (EBV) infections. *J Oral Pathol Med* 1999; **28**: 204–9.
13 Slots J, Saygun I, Sabeti M, Kubar A. Epstein–Barr virus in oral diseases. *J Periodontal Res* 2006; **41**: 235–44.
14 Slots J. Herpesviral-bacterial synergy in the pathogenesis of human periodontitis. *Curr Opin Infect Dis* 2007; **20**: 278–83.
15 Gulley 2001. Molecular diagnosis of Epstein–Barr virus-related diseases. *J Mol Diagn* 2001; **3**: 1–10.
16 Carbone A, Gloghini A. AIDS-related lymphomas: from pathogenesis to pathology. *Br J Haematol* 2005; **130**: 662–70.
17 Copur MS, Deshpande A, Mleczko K *et al*. Full clinical recovery after topical acyclovir treatment of Epstein–Barr virus associated cutaneous B-cell lymphoma in patient with mycosis fungoides. *Croat Med J* 2005; **46**: 458–62.
18 Hjalgrim H, Smedley KE, Rostgaard K *et al*. Infectious mononucleosis, childhood social environment, and risk of Hodgkin lymphoma. *Cancer Res* 2007; **67**: 2382–8.
19 Gonzalez-Moles M, Gutierrez J, Ruiz I *et al*. Epstein–Barr virus and oral squamous cell carcinoma in patients without HIV infection: viral detection by polymerase chain reaction. *Microbios* 1998; **96**: 23–31.
20 Goldenberg D, Golz A, Netzer A *et al.* Epstein–Barr virus and cancers of the head and neck. *Am J Otolaryngol* 2001; **22**: 197–205.

Cytomegalovirus infection

CMV may cause a glandular fever type of syndrome, and rarely causes oral ulceration. Indolent CMV-induced oral ulcers may be seen in immunosuppressed patients and in AIDS [1–7]. CMV has been implicated in the pathogenesis of periodontal disease [8].

References

1 Torres R, Cottrell D, Reebye UL. Ulcerative tongue lesion secondary to cytomegalovirus. *J Mass Dent Soc* 2004; **53**: 36–7.
2 Lin SS, Chou MY, Ho CC *et al*. Study of the viral infections and cytokines associated with recurrent aphthous ulceration. *Microbes Infect* 2005; **7**: 635–44.
3 Epstein JB, Scully C. Cytomegalovirus: a virus of increasing relevance to oral medicine and pathology. *J Oral Pathol Med* 1993; **22**: 348–53.
4 Kanas RJ, Jensen JL, Abrams AM *et al*. Oral mucosal cytomegalovirus as a manifestation of the acquired immune deficiency syndrome. *Oral Surg* 1987; **64**: 183–9.
5 Myerson D, Hackman RC, Nelson JA *et al*. Widespread evidence of histologically occult cytomegalovirus. *Hum Pathol* 1984; **15**: 430–9.
6 Syrjanen S, Leimola-Virtanen R, Schmidt-Westhausen A, Reichart PA. Oral ulcers in AIDS patients frequently associated with cytomegalovirus (CMV) and Epstein–Barr virus (EBV) infections. *J Oral Pathol Med* 1999; **28**: 204–9.
7 de Faria PR, Vargus PA, Saldiva PH *et al*. Tongue disease in advanced AIDS. *Oral Dis* 2005; **11**: 72–80.
8 Slots J. Update on human cytomegalovirus in destructive periodontal disease. *Oral Microbiol Immunol* 2004; **19**: 217–23.

Herpesviruses 6, 7 and 8

Oral lesions have yet to be demonstrated in infections with HHV-6 or HHV-7. However, HHV-8 is implicated in oral Kaposi's sarcoma [1–8]. Treatment with highly active antiretroviral therapy (HAART) may reduce HHV-8 infection [8,9], however, Kaposi's sarcoma-associated immune reconstitution following commencement of HAART has been reported [10–12].

References

1 Di Alberti L, Porter SR, Scully C *et al*. Genetic polymorphism of, and new diseases associated with, Kaposi's sarcoma herpes virus (KSHV). *J Oral Pathol Med* 1996; **25**: 282–6.
2 DiAlberti L, Ngui SL, Porter SR *et al*. Presence of human herpesvirus-8 variants in the oral ulcer tissues of human immunodeficiency virus-infected persons. *J Infect Dis* 1997; **175**: 703–7.
3 DiAlberti L, Porter SR, Speight P *et al*. Detection of human herpesvirus 8 DNA in oral ulcer tissues of HIV-infected individuals. *Oral Dis* 1997; **3** (Suppl. 1): S133–4.
4 Leao JC, Porter SR, Scully C. Human herpesvirus 8 and oral health care: an update. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2000; **90**: 694–704.
5 Triantos D, Horefti D, Paximadi E *et al*. Presence of human herpes virus-8 in saliva and non-lesional oral mucosa in HIV-infected and oncologic immunocompromised patients. *Oral Microbiol Immunol* 2004; **19**: 201–4.
6 Marcelin AG, Gorin I, Morand P *et al*. Quantification of Kaposi's sarcoma-associated herpesvirus in blood, oral mucosa, and saliva in patients with Kaposi's sarcoma. *AIDS Res Hum Retroviruses* 2004; **20**: 704–8.
7 Casper C. Defining a role for antiviral drugs in the treatment of persons with HHV-8 infection. *Herpes* 2006; **13**: 42–7.
8 Pica F, Volpi A. Transmission of human herpesvirus 8: an update. *Curr Opin Infect Dis* 2007; **20**: 152–6.
9 Leao JC, Kumar N, McLean KA *et al*. Effect of human immunodeficiency virus-1 protease inhibitors on the clearance of human herpesvirus 8 from blood of human immunodeficiency virus-1-infected patients. *J Med Virol* 2000; **62**: 416–20.
10 Bourboulia D, Aldam D, Lagos D *et al*. Short- and long-term effects of highly active antiretroviral therapy on Kaposi sarcoma-associated herpesvirus immune responses and viraemia. *AIDS* 2004; **18:** 485–93.
11 Connick E, Kane MA, White IE, Ryder J, Campbell TB. Immune reconstitution inflammatory syndrome associated with Kaposi sarcoma during potent antiretroviral therapy. *Clin Infect Dis* 2004; **39**: 1852–5.
12 Chan DJ. Kaposi's sarcoma-associated immune reconstitution following highly active antiretroviral treatment initiation. *Int J STD AIDS* 2006; **17**: 72.

Enteroviruses

Herpangina

Aetiology. Herpangina is caused by Coxsackieviruses mainly. The incubation period is 3–7 days and young children are predominantly affected.

Clinical features. Many infections are subclinical but features of the clinical syndrome include malaise, anorexia, irritability, low fever, slightly enlarged and tender anterior cervical lymph nodes and mouth ulcers, predominantly on the soft palate [1,2].

Diagnosis. There may be a contact history. It is possible to culture Coxsackieviruses in suckling mice if absolutely necessary. The main differential diagnosis is primary herpetic stomatitis, but in herpangina there is less fever, no acute gingivitis and ulceration is mainly restricted to the soft palate.

Treatment. The condition is self-limiting and treatment is supportive only.

References

1 Bell EJ, Williams GR, Grist NR *et al*. Enterovirus infections. *Dent Update* 1983; **26**: 967–78.
2 Fenton SJ, Unkel JS. Viral infections of the oral mucosa in children: a clinical review. *Pract Periodontics Aesthet Dent* 1997; **9**: 683–90.

Hand, foot and mouth disease (see Chapter 33)

Aetiology. Hand, foot and mouth disease is caused particularly by Coxsackie A viruses but sometimes by Coxsackie B viruses or enteroviruses [1,2].

Clinical features. The incubation period is 3–10 days and, although young children are predominantly infected, there are occasional outbreaks in adults. Many infections are subclinical but features of the clinical syndrome include the following.

- General features: malaise, anorexia, irritability and fever may be present but usually only in severe cases.
- Anterior cervical lymph nodes may occasionally be slightly enlarged and tender.
- Mouth ulcers are round or ovoid, usually sparse and may affect any site [3–8].
- Rash: painful, sometimes deep-seated vesicles may appear, usually on the hand and/or feet, particularly on digits or at the base of the phalanges.

Hand, foot and mouth disease is self-limiting and only rarely complicated by systemic illness such as encephalitis [9,10]. The condition tends to be more severe when it occurs in adults.

Diagnosis and management are as for herpangina.

References

1 Faulkner CF, Godbolt AM, De Ambrosis B, Triscott J. Hand, foot and mouth disease in an immunocompromised adult treated with aciclovir. *Australas J Dermatol* 2003; **44**: 203–6.
2 Sasidharan CK, Sugathan P, Agarawal R *et al*. Hand-foot-and-mouth disease in Calicut. *Indian J Pediatr* 2005; **72**: 17–21.

3 Conway SP. Coxsackie B2 virus causing simultaneous hand, foot and mouth disease and encephalitis. *J Infect* 1987; **15**: 191.
4 Goh KT, Doraisingham S, Tan JC *et al.* An outbreak of hand, foot and mouth disease in Singapore. *Bull WHO* 1982; **60**: 965–9.
5 Ishimaru Y, Nakano S, Yamaoka K *et al.* Outbreak of hand, foot and mouth disease caused by Enterovirus 71. *Arch Dis Child* 1980; **55**: 583–8.
6 Chan LG, Parasher UD, Lye LS *et al*. Deaths of children during an outbreak of hand, foot, and mouth disease in Sarawak, Malaysia: clinical and pathological characteristics of the disease. For the Outbreak Study Group. *Clin Infect Dis* 2000; **31**: 678–83.
7 Shah VA, Chong CY, Chan KP, Ng W, Ling AE. Clinical characteristics of an outbreak of hand, foot and mouth disease in Singapore. *Ann Acad Med Singapore* 2003; **32**: 381–7.
8 Shekhar K, Lye MS, Norlijah O *et al*. Deaths in children during an outbreak of hand, foot and mouth disease in Peninsular Malaysia—clinical and pathological characteristics. *Med J Malaysia* 2005; **60**: 297–304.
9 Chong CY, Chan KP, Shah VA *et al*. Hand, foot and mouth disease in Singapore: a comparison of fatal and non-fatal cases. *Acta Paediatr* 2003; **92**: 1163–9.
10 Chang LY, Lee CY, Kao CL *et al*. Hand, foot and mouth disease complicated with central nervous system involvement in Taiwan in 1980–1981. *J Formos Med Assoc* 2007; **106**: 173–6.



Fig. 69.47 Untreated acute necrotizing gingivitis can lead to extensive gingival ulceration and irreparable damage.

Bacterial infections

Acute necrotizing (ulcerative) gingivitis and noma

Aetiology. There is no firm evidence of communicability of acute necrotizing gingivitis, although it may occur in epidemic form, especially in institutions or in the military (trench mouth). Viral respiratory infections, overwork and fatigue, smoking or immune defects may precede the onset of disease, suggesting depression of immunity as a predisposing cause. A similar lesion may be a feature of HIV infection and related diseases [1–5].

A mixed, mostly anaerobic, flora (the fusospirochaetal complex), consisting mainly of *Fusobacterium nucleatum* (*F. fusiformis* or *Bacillus fusiformis*) and *Borrelia vincentii*, is associated with this infection [6,7,13].

Clinical features. The mouth ulceration is usually restricted to the gingiva, specifically the interdental papillae, which appear blunted (Figs 69.46 & 69.47). The history is characteristic, with an acute onset of gingival soreness, bleeding and halitosis. Acute necrotizing gingivitis occurs especially in the anterior part of the mouth where the affected gingiva are extremely tender to touch and readily bleed on minimal pressure. Occasionally the ulceration extends elsewhere on the gingiva, or onto the adjacent mucosa. There is often enlargement of the cervical lymph nodes and there may be pyrexia and malaise.



Fig. 69.46 Acute necrotizing gingivitis showing typical ulceration of interdental gingival papillae. This was in HIV infection.

Prognosis. Failure to adequately treat acute necrotizing gingivitis may predispose to recurrence and, in malnourished or immunocompromised individuals, may lead to noma (cancrum oris) [3–13]. Similar lesions of gangrenous stomatitis are increasingly reported in HIV disease.

Diagnosis. Diagnosis is mainly from gingival lesions in primary herpetic stomatitis, leukaemias and HIV disease. A bacteriological smear may be helpful.

Treatment. Gentle cleansing with a hydrogen peroxide mouthwash and a soft toothbrush is remarkably effective. Oral metronidazole 200 mg should be given three times daily for 3–7 days to limit the tissue destruction. Penicillin is equally effective. The patient should also be referred for dental advice [1].

References

1 Johnson BD, Engel D. Acute necrotising ulcerative gingivitis: a review of diagnosis, etiology and treatment. *J Periodontol* 1986; **57**: 141–50.
2 Osuji OO. Necrotizing ulcerative gingivitis and cancrum oris (noma) in Ibadan, Nigeria. *J Periodontol* 1990; **61**: 769–72.
3 Bermejo-Fenoll A, Sanchez-Perez A. Necrotising periodontal diseases. *Med Oral Patol Oral Cir Bucal* 2004; **9 (**Suppl.): 114–9.
4 Folayan MO. The epidemiology, etiology, and pathophysiology of acute necrotizing ulcerative gingivitis associated with malnutrition. *J Contemp Dent Pract* 2004; **5**: 28–41.
5 Shangase L, Feller L, Blignaut E. Necrotising ulcerative gingivitis/periodontitis as indicators of HIV-infection. *J S Afr Dent Assoc* 2004; **59**: 105–18.
6 Enwonwu CO, Falkler WA, Idigbe EO. Oro-facial gangrene (noma/cancrum oris): pathogenetic mechanisms. *Crit Rev Oral Biol Med* 2000; **11**: 159–71.
7 Salama C, Finch D, Bottone EJ. Fusospirochetosis causing necrotic oral ulcers in patients with HIV infection. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2004; **98**: 321–3.

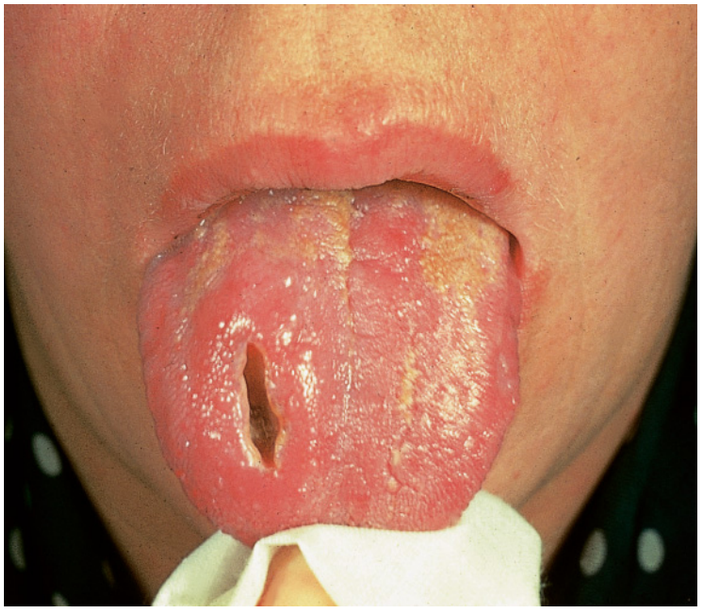


Fig. 69.48 Gumma.



Fig. 69.49 Hutchinson's maxillary central incisors.

8 Enwonwu CO. Infectious oral necrosis (cancrum oris) in Nigerian children. *Community Dent Oral Epidemiol* 1985; **13**: 190–4.
9 Madden N. An interesting case of facial gangrene (from Papua New Guinea). *Oral Surg* 1985; **59**: 279.
10 Sabiston CB. A review and proposal for the etiology of acute necrotizing gingivitis. *J Clin Periodontol* 1986; **13**: 727–34.
11 Sawyer D, Nwoku AJ. Cancrum oris (noma): past and present. *J Dent Child* 1981; **48**: 138–41.
12 Stassen LFA, Batchelor AGG, Rennie JS *et al.* Cancrum oris in an adult Caucasian female. *Br J Oral Maxillofac Surg* 1989; **27**: 417–22.
13 Jimenez LM, Duque FL, Baer PN, Jimenez SB. Necrotizing ulcerative periodontal diseases in children and young adults in Medellin, Colombia, 1965–2000. *J Int Acad Periodontol* 2005; **7**: 55–63.

Syphilis

Oral ulcers may be seen at any stage but particularly in secondary syphilis [1–9]. In primary syphilis, a primary chancre (hard or Hunterian chancre) may involve the lips, tongue or palate. A small, firm, pink macule changes to a papule which ulcerates to form a painless, round ulcer with a raised margin and indurated base [4,10]. Chancres heal spontaneously in 3–8 weeks but are highly infectious and are associated with enlarged, painless regional lymph nodes.

Secondary syphilis follows after 6–8 weeks, with oral lesions in about one-third of patients [1,3,7]. These are highly infectious and are usually fairly painless ulcers (mucous patches and snail-track ulcers).

The most characteristic oral lesion of tertiary syphilis is a localized granuloma (gumma) that varies in size from a pinhead to several centimetres, affecting particularly the palate, or the tongue. Gummas break down to form deep, chronic, punched-out ulcers that are not infectious (Fig. 69.48). However, the most common oral manifestation of tertiary syphilis is leukoplakia, which particularly affects the dorsum of the tongue and has a high potential for malignant change [9].

Congenital syphilis may, when the permanent teeth erupt, present with dental anomalies such as Hutchinson's teeth (Fig. 69.49). Oral ulcers are rare.

Exudate from a suspected oral lesion of syphilis should be examined for treponemes by dark-ground microscopy; however, since the diagnosis can be confused by oral commensal treponemes, lesions should first be thoroughly swabbed with a sterile gauze or cotton-wool and then gently scraped with a sterile spatula, the scraping being examined immediately by dark-ground microscopy. Serology is indicated. Biopsy is not usually indicated, but lesions are characterized by a dense, plasma cell infiltrate [7].

References

1 Manton SL, Eggleston SI, Alexander I *et al.* Oral presentation of secondary syphilis. *Br Dent J* 1986; **160**: 237–8.
2 Samaranayake LP, Scully C. Oral disease and sexual medicine. *Br J Sex Med* 1988; **15**: 138–43, 174–80.
3 Terezhalmy GT. Oral manifestations of sexually-related diseases. *Ear Nose Throat J* 1983; **62**: 287–96.
4 Alam F, Argiriadou AS, Hodgson TA, Kumar N, Porter SR. Primary syphilis remains a cause of oral ulceration. *Br Dent J* 2000; **189**: 352–4.
5 Lu SY, Eng HL. Secondary syphilis-related oral ulcers: report of four cases. *Chang Gung Med J* 2002; **25**: 683–8.
6 Ortega KL, Rezende NP, Watanuki F, Araujo NS, Magalhaes MH. Secondary syphilis in an HIV positive patient. *Med Oral* 2004; **9**: 33–8.
7 Little JW. Syphilis: an update. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005; **100**: 3–9.
8 Scott CM, Flint SR. Oral syphilis—re-emergence of an old disease with oral manifestations. *Int J Oral Maxillofac Surg* 2005; **34**: 58–63.
9 Leao JC, Gueiros LA, Porter SR. Oral manifestations of syphilis. *Clinics* 2006; **61**: 161–6.
10 Cousteau C, Leyder P, Laufer J. Syphilis primaire buccale: un diagnostic parfois difficile. *Rev Stomatol Chir Maxillofac* 1984; **85**: 391–8.

Gonorrhoea

Oral mucosal erythema, sometimes with oedema and ulceration, is occasionally seen in oropharyngeal gonorrhoea. Oropharyngeal asymptomatic carriage of gonococci is more common, found in around 4% of those attending clinics for sexually transmitted diseases [1–5].

References

1 Brown RT, Lossick JG, Mosure DJ *et al.* Pharyngeal gonorrhoea screening in adolescents: is it necessary? *Pediatrics* 1989; **84**: 623–5.
2 Guinta JL, Fiumara NJ. Facts about gonorrhoea and dentistry. *Oral Surg* 1986; **62**: 529.
3 Siegel MA. Syphilis and gonorrhea. *Dent Clin North Am* 1996; **40**: 369–83.
4 Bruce AJ, Rogers RS. Oral manifestations of sexually transmitted diseases. *Clin Dermatol* 2004; **22**: 520–7.
5 Laskaris G. PL10 Oral manifestations of orogenital bacterial infections. *Oral Dis* 2006; **12**: 2–3.

Tuberculosis

Oral lesions can develop in pulmonary tuberculosis but are not common. A chronic ulcer, usually of the dorsum of the tongue, is the most common oral presentation but jaw lesions or cervical lymph node involvement may be seen [1–12]. Atypical mycobacteria are not uncommonly involved.

Mycobacterial oral ulcers, particularly caused by *Mycobacterium avium–intracellulare*, have been reported as a complication of AIDS and occasionally in apparently healthy individuals [13–17]. Cervicofacial infection is occasionally caused by *M. chelonei*, usually in the form of lymph node abscesses, or occasionally as intraoral swellings [18–21].

References

1 Dimitrakopoulos I, Zouloumis L, Lazaridis N *et al.* Primary tuberculosis of the oral cavity. *Oral Surg* 1991; **72**: 712–5.
2 Haddad NM, Zaytoun GM, Hadi U. Tuberculosis of the soft palate: an unusual presentation of oral tuberculosis. *Otolaryngol Head Neck Surg* 1987; **97**: 91–9.
3 Michaud M, Blanchette G, Tomich CF. Chronic ulceration of the hard palate: first clinical sign of undiagnosed pulmonary tuberculosis. *Oral Surg* 1984; **57**: 63–7.
4 Waldman RH. Tuberculosis and the atypical mycobacteria. *Otolaryngol Clin North Am* 1982; **15**: 581–96.
5 Ito FA, de Andrade CR, Vargas PA, Jorge J, Lopes MA. Primary tuberculosis of the oral cavity. *Oral Dis* 2005; **11**: 50–3.
6 Harma CG, Pradeep AR, Karthikeyen BV. Primary tuberculosis clinically presenting as gingival enlargement: a case report. *J Contemp Dent Pract* 2006; **7**: 108–14.
7 Ajay GN, Laxmikanth C, Prashanth SK. Tuberculous ulcer of tongue with oral complications of oral antituberculosis therapy. *Indian J Dent Res* 2006; **17**: 87–90.
8 Ebenezer J, Samuel R, Matthew JC *et al*. Primary oral tuberculosis: report of two cases. *Indian J Dent Res* 2006; **17**: 41–4.
9 Kokosali K, Lloyd RE. Tuberculous cervical lymphadenitis: an unusual case. *Dent Update* 2006; **33**: 306–8.
10 Marias BJ, Wright CA, Schaaf AS *et al*. Tuberculous lymphadenitis as a cause of persistent cervical lymphadenopathy in children from a tuberculosis-endemic area. *Pediatr Infect Dis J* 2006; **25**: 142–6.
11 Sezer B, Zeytinoglu M, Tuncay U, Unal T. Oral mucosal ulceration: a manifestation of previously undiagnosed pulmonary tuberculosis. *J Am Dent Assoc* 2004; **135**: 336–40.
12 Garg RK, Singhal P. Primary tuberculosis of the tongue: a case report. *J Contemp Dent Pract* 2007; **8**: 74–80.
13 Morris CA, Grant GH, Everall PH *et al.* Tuberculoid lymphadenitis due to *Mycobacterium chelonei*. *J Clin Pathol* 1973; **26**: 422–6.
14 Ilyas SE, Chen FF, Hodgson TA, Speight PM, Lacey CJ, Porter SR. Labial tuberculosis: a unique cause of lip swelling complicating HIV infection. *HIV Med* 2002; **3**: 283–6.
15 Feller L, Anagnostopoulos C, Bouckaert M, Raubenheimer EJ. HIV/TB co-infection: literature review and report of multiple tuberculosis oral ulcers. *J S Afr Dent Assoc* 2005; **60**: 330–2.
16 Miziara ID. Tuberculosis affecting the oral cavity in Brazilian HIV-infected patients. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005; **100**: 179–82.
17 Ramirez-Amador V, Anaya-Saavedra G, Gonzalez-Ramirez I *et al*. Lingual ulcer as the only sign of recurrent mycobacterial infection in an HIV/AIDS-infected patient. *Med Oral Patol Oral Cir Bucal* 2005; **10**: 109–14.
18 Blake GC, Murray JJ, Lee KW. Cervicofacial infection with *Mycobacterium chelonei*. *Br J Oral Surg* 1976; **13**: 278–81.
19 Boyd BW. Oral infection with associated lymphadenopathy due to *Mycobacterium chelonei*. *Ala Med* 1984; **54**: 9–10.
20 Pedersen A, Reibel J. Intraoral infection with *Mycobacterium chelonei*. *Oral Surg* 1989; **67**: 262–5.
21 Volpe F, Schwimmer A, Barr C. Oral manifestations of disseminated *Mycobacterium avium-intracellulare* in a patient with AIDS. *Oral Surg* 1985; **60**: 567–70.

Epithelioid (bacillary) angiomatosis (see Chapter 30)

Oral lesions clinically and, to some extent, histologically reminiscent of Kaposi's sarcoma have been seen in HIV disease [1–4], sometimes as the first manifestation of HIV infection [3].

References

1 Glick M, Cleveland DB. Oral mucosal bacillary epithelioid angiomatosis in a patient with AIDS associated with rapid alveolar bone loss. *J Oral Pathol Med* 1993; **22**: 235–9.
2 Levell NJ, Bewley AP, Chopra S *et al.* Bacillary angiomatosis with cutaneous and oral lesions in an HIV-infected patient from the UK. *Br J Dermatol* 1995; **132**: 113–5.
3 Speight PM, Zakrzewska J, Fletcher CDM. Epithelioid angiomatosis affecting the oral cavity as the first sign of HIV infection. *Br Dent J* 1991; **171**: 367–70.
4 Lopez de Blanc S, Sambuelli R, Femopase F *et al*. Bacillary angiomatosis affecting the oral cavity. Report of two cases and review. *J Oral Pathol Med* 2000; **29**: 91–6.

Fungal infections

Oral fungal infections, apart from candidosis, rarely causes mouth ulcers in resource-rich countries, where they are usually seen only in immunocompromised or debilitated patients, including those with AIDS. However, they may be seen occasionally in otherwise healthy persons from the tropics (Table 69.20).

Aspergillosis. Rhinocerebral aspergillosis may ulcerate through to the mouth. This is a rare event, except in the severely immunocompromised [1–3]. Mandibular aspergillosis has also been reported [4].

Table 69.20 Rare orofacial fungal infections.

Infection	Oral manifestations
Aspergillosis	Aspergilloma Rhinocerebral type causes palatal necrosis Disseminated in immunocompromised patients
Blastomycosis	
North American	Oral ulcers or suppurating granulomas
South American (paracoccidioidomycosis)	Oral ulcers and lymphadenopathy
Coccidioidomycosis	Rarely oral ulcers
Cryptococcosis	Oral ulcers
Histoplasmosis	Lumps or ulcers in mouth
Phycomycosis (mucormycosis, zygomycosis)	Antral involvement with palatal ulceration in immunocompromised patients, especially diabetics
Sporotrichosis	Oral lesions rare

Occasionally, solitary aspergillosis arises as a consequence of endodontic treatment where root canal filling material enters the antrum [5–7] but this does not cause oral ulceration. Surgical debridement is usually indicated.

References

1 Schubert MM. Head and neck aspergillosis in patients undergoing bone-marrow transplantation. *Cancer* 1986; **57**: 1092–6.
2 Khatri ML, Stefanato CM, Benghazeil M *et al*. Cutaneous and paranasal aspergillosis in an immunocompetent patient. *Int J Dermatol* 2000; **39**: 853–6.
3 Karabulat AB, Kabakas F, Berkoz O, Karakaz Z, Kesim SN. Hard palate perforation due to invasive aspergillosis in a patient with acute lymphoblastic leukemia. *Int J Pediatr Otorhinolaryngol* 2005; **69**: 1395–8.
4 Lador N, Polacheck I, Gural A, Sanatski E, Garfunkel A. Trifungal infection of the mandible: case report and literature review. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006; **101**: 451–65**.**
5 Beck-Mannagetta J, Necek D, Grasserbauer M. Solitary aspergillosis of maxillary sinus, a complication of dental treatment. *Lancet* 1983; **ii**: 1260.
6 Yaltinik M, Kocak Berberoglu H, Koray M *et al*. Orbital pain and headache secondary to overfilling of a root canal. *J Endod* 2003; **29**: 771–2.
7 Khongkunthian P, Reichert PA. Aspergillosis of the maxillary sinus as a complication of overfilling root canal material into the sinus: report of two cases. *J Endod* 2001; **27**: 476–8.

Blastomycoses. Blastomycoses may produce oral lesions which are typically mulberry-like, ulcerated swellings especially seen on the gingiva and alveolus [1–3].

References

1 Almeida OP, Jacks J, Scully C *et al.* Orofacial manifestations of paracoccidioidomycosis (South American blastomycosis). *Oral Surg* 1991; **72**: 430–5.
2 Sposto MR, Scully C, Almeida OPD *et al.* Oral paracoccidioidomycosis: a study of 36 South American patients. *Oral Surg* 1993; **75**: 461–5.
3 Bicalho RN, Santo MF, de Aguiar MC, Santos VR. Oral paracoccidioidomycosis: a retrospective study of 62 Brazilian patients. *Oral Dis* 2001; **7**: 56–60.

Cryptococcosis. *Cryptococcus neoformans* may occasionally produce indolent oral ulcers in immunocompromised patients [1–4].

References

1 Glick M, Cohen SG, Cheney RT *et al*. Oral manifestations of disseminated *Cryptococcus neoformans* in a patient with acquired immunodeficiency syndrome. *Oral Surg* 1987; **64**: 454–9.
2 Lynch DP, Naftolin LZ. Oral *Cryptococcus neoformans* infection in AIDS. *Oral Surg* 1987; **64**: 449–53.
3 Piluso S, Ficarra G, Lucatorto FM *et al*. Cause of oral ulcers in HIV-infected patients: a study of 19 cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1996; **82**: 166–72.
4 Mehrabi M, Bagheri S, Leonard MK Jr, Perciacante VJ. Mucocutaneous manifestation of cryptococcal infection: report of a case and review of the literature. *J Oral Maxillofac* Surg 2005; **63**: 1543–9.

Geotrichosis. Geotrichosis is a rare, livid, sharply defined enanthema of the oral mucosa with ulcerations seen in immunocompromised persons, such as those with leukaemia or HIV infection. *Geotrichum capitatum* is responsible and there may also be pneumonic lung infiltrates [1]. Treatment includes amphotericin, 5-fluorocytosine and itraconazole.

Reference

1 Listemann H, Schonrock-Nabulsi P, Kuse R, Meigel W. Geotrichosis of oral mucosa. *Mycoses* 1996; **39**: 289–91.

Histoplasmosis. Oral lesions of histoplasmosis are uncommon. They are typically seen in chronic disseminated histoplasmosis, usually as a non-specific lump or ulcer on the tongue, palate, buccal mucosa or gingiva [1–8], sometimes in AIDS [9–15].

References

1 Adekeye EO, Edwards MB, Williams HK. Mandibular African histoplasmosis: imitation of neoplasia or giant cell granuloma. *Oral Surg* 1988; **65**: 81–4.
2 Cobb CM, Shultz RE, Brewer JH *et al.* Chronic pulmonary histoplasmosis with an oral lesion. *Oral Surg* 1989; **67**: 73–6.
3 Goodwin RA, Shapiro JL, Thurman GH *et al.* Disseminated histoplasmosis: clinical and pathologic correlations. *Medicine* 1980; **59**: 93–100.
4 Miller RL, Gould AR, Skolnick JL *et al.* Localised oral histoplasmosis. *Oral Surg* 1982; **53**: 367–74.
5 Scully C, Almeida O. Orofacial manifestations of the systemic mycoses. *J Oral Pathol Med* 1992; **21**: 289–94.
6 O'Sullivan MV, Whitby M, Chahoud C, Miller SM. Histoplasmosis in Australia: a report of a case with a review of the literature. *Aust Dent J* 2004; **49**: 94–7.
7 Valle AC, Moreira LC, Almeida-Paes R *et al*. Chronic disseminated histoplasmosis with lesions restricted to the mouth: case report. *Rev Inst Med Trop Sao Paulo* 2006; **48**: 113–6.
8 Cunha VS, Zampese MS, Aquino VR, Cestari TF, Goldani LZ. Mucocutaneous manifestations of disseminated histoplasmosis in patients with acquired immunodeficiency syndrome: particular aspects in a Latin-American population. *Clin Exp Dermatol* 2007; **32**: 250–5.
9 Filho FJS, Lopes M, Almeida OPD, Scully C. Mucocutaneous histoplasmosis in AIDS. *Br J Dermatol* 1995; **133**: 472–4.
10 Scully C, Almeida OPD, Sposto MR. Deep mycoses in HIV infection. *Oral Dis* 1997; **3** (Suppl. 1): 200–7.
11 Casariego Z, Rey Kelly G, Perez H *et al.* Disseminated histoplasmosis with orofacial involvement in HIV-1-infected patients with AIDS: manifestations and treatment. *Oral Dis* 1997; **3**: 184–7.
12 Gomes Ferreira O, Vieira Fernandes A, Sebastiao-Borges A, Simao-Ferreira M, Mota Loyola A. Orofacial manifestations of histoplasmosis in HIV-positive patients: a case report. *Med Oral* 2001; **6**: 101–5.
13 Ferreira OG, Cardosa SV, Borges AS, Ferreira MS, Loyola AM. Oral histoplasmosis in Brazil. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2002; **93**: 654–9.
14 Hernandez SL, Lopez De Blanc SA, Sambuelli RH *et al*. Oral histoplasmosis associated with HIV infection: a comparative study. *J Oral Pathol Med* 2004; **33**: 445–50.
15 Ranganthan K, Hemalatha R. Oral lesions in HIV infection in developing countries: an overview. *Adv Dent Res* 2006; **19**: 63–8.

Mucormycosis. Rhinocerebral mucormycosis typically commences in the nasal cavity or paranasal sinuses and invades the palate to produce a black necrotic ulcer, although it might occasionally commence in the palate [1–4]. Most cases are seen in diabetics or in immunocompromised patients such as those with AIDS [4,5]. Biopsy and radiography are required for diagnosis. Treatment is surgical debridement together with amphotericin intravenously and/or azoles.

References

1 Forteza G, Burgeno M, Martorell V, Sierra I. Rhinocerebral mucormycosis. *J Craniomaxillofac Surg* 1988; **16**: 80–4.
2 Hauman CHJ, Raubenheimer EJ. Orofacial mucormycosis. *Oral Surg* 1989; **68**: 624–7.
3 Jones AC, Bentsen TY, Freedman PD. Mucor in the oral cavity. *Oral Surg* 1993; **75**: 455–60.
4 Cagatay AA, Oncu SS, Calangu SS *et al*. Rhinocerebral mucormycosis treated with 32 gram liposomal amphotericin B and incomplete surgery: a case report. *BMC Infect Dis* 2001; **1**: 22.
5 Moraru RA, Grossman ME. Palatal necrosis in an AIDS patient: a case of mucormycosis. *Cutis* 2000; **66**: 15–8.

Protozoal infestations

Leishmaniasis is rare in northern Europe and the USA; it is not uncommon, however, in hotter climes and may cause ulcers in the mouth or more commonly on the lips [1–5], and is seen increasingly in HIV disease [6–10] or in other immunocompromised persons.

References

1 Abbas K, El Toumn IA, El Hassan AM. Oral leishmaniasis associated with kala-azar. *Oral Surg* 1992; **73**: 583–4.
2 Baily GG, Pitt MA, Cury A *et al.* Leishmaniasis of the tongue treated with liposomal amphotericin B. *J Infect* 1994; **28**: 327–31.
3 Kerdel-Vegas F. American leishmaniasis. *Int J Dermatol* 1982; **21**: 291–303.
4 Marsden PD, Sampaio RN, Rocha R *et al.* Mucocutaneous leishmaniasis: an unsolved clinical problem. *Trop Doct* 1977; **7**: 7–11.
5 Motta AC, Lopes MA, Ito FA *et al*. Oral leishmaniasis: a clinicopathological study of 11 cases. *Oral Dis* 2007; **13**: 335–40.
6 Imhof M, Schofer H, Milbradt R, Lutz T. Mucocutaneous leishmaniasis in a European HIV-positive patient. *Eur J Dermatol* 1995; **5**: 594–6.
7 Michiels JF, Monteil RA, Hofman P *et al*. Oral leishmaniasis and Kaposi's sarcoma in an AIDS patient. *J Oral Pathol Med* 1994; **23**: 45–6.
8 Miralles ES, Nunez M, Hilara Y *et al.* Mucocutaneous leishmaniasis and HIV. *Dermatology* 1994; **189**: 275–7.
9 Montalban C, Calleja JL, Erice A. Visceral leishmaniasis in patients infected with human immunodeficiency virus. *J Infect* 1990; **21**: 261–70.
10 Milian MA, Bagan JV, Jimenez Y, Perez A, Scully C. Oral leishmaniasis in a HIV-positive patient. Report of a case involving the palate. *Oral Dis* 2002; **8**: 59–61.

Immune defects

Human immunodeficiency virus infection [1–7] (see Chapter 35)

Oral ulceration in patients infected with HIV may be due to any of the causes of mouth ulceration (see p. 69.42), and aphthous-like ulcers are also seen. However, it is important to exclude infections, mainly herpesviruses. There are also occasional examples of mouth ulcers due to mycobacteria, *Rochalimaea*, syphilis, *Histoplasma*, *Cryptococcus*, leishmaniasis and others. Malignant disease (mainly Kaposi's sarcoma or non-Hodgkin's lymphoma) may result in lumps that can ulcerate.

Aphthous-like ulcers in HIV may respond to local treatment or, failing that, thalidomide at a dose of 200 mg a day has been shown in randomized double-blind, placebo-controlled trials to be effective in the treatment of HIV-related recurrent aphthous ulceration [8–10].

Other mouth ulcers should be treated as appropriate.

References

1 Scully C, Laskaris G, Pindborg J *et al.* Oral manifestations of HIV infection and their management. *Oral Surg* 1991; **71**: 158–71.
2 Porter SR, Scully C. HIV: the surgeon's perspective. 1: Update of pathogenesis, epidemiology, management and risk of nosocomial transmission. *Br J Oral Maxillofac Surg* 1994; **32**: 222–30.
3 Porter SR, Scully C. HIV: the surgeon's perspective. 2: Diagnosis and management of non-malignant oral manifestations. *Br J Oral Maxillofac Surg* 1994; **32**: 231–40.
4 Porter SR, Scully C. HIV: the surgeon's perspective. 3: Diagnosis and management of malignant neoplasms. *Br J Oral Maxillofac Surg* 1994; **32**: 241–7.
5 Youle M, Clarbour J, Farthing C *et al.* Treatment of resistant aphthous ulceration with thalidomide in patients positive for HIV antibody. *BMJ* 1989; **298**: 432.
6 Zakrzewska JM, Atkin PA. Oral mucosal lesions in a UK HIV/AIDS oral medicine clinic. A nine year, cross-sectional, prospective study. *Oral Health Prev Dent* 2003; **1**: 73–9.
7 Ranganathan K, Umadevi M, Saraswathi TR *et al*. Oral lesions and conditions associated with human immunodeficiency virus infection in 1000 South Indian patients. *Ann Acad Med Singapore* 2004; **33**: 37–42.
8 Pinheiro A, Marcenes W, Zakrzewska JM, Robinson PG. Dental and oral lesions in HIV infected patients: a study in Brazil. *Int Dent J* 2004; **54**: 131–7.
9 Baccaglini L, Atkinson JC, Patton LL, Glick M, Ficarra G, Petersen DE. Management of oral lesions in HIV-positive patients. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; **103**; 1–23.
10 Diz Dios P, Sopena B, Cameselle J *et al*. Thalidomide for the treatment of acquired immunodeficiency syndrome-associated refractory oral ulcers. *Arch Otolaryngol Head Neck Surg* 2000; **126**: 89–92.

Vasculitides

Periarteritis (polyarteritis) nodosa

Transient submucosal oral nodules may occur singly or in crops along the path of vessels and especially in the tongue. Other mucosal lesions include erythema, papules, haemorrhages, ulceration or necrosis [1–4].

References

1 Cowpe JG, Hislop WS. Oral presentation of polyarteritis nodosa. *Oral Surg* 1983; **56**: 597–601.
2 Standefer JA Jr, Mattox DE. Head and neck manifestations of collagen vascular diseases. *Otolaryngol Clin North Am* 1986; **19**: 181–210.
3 Ekman-Joelsson BM, Kjellman B, Hattevig G. Tongue necrosis due to vasculitis. *Acta Paediatr* 1995; **84**: 1333–6.
4 Taillandier J, Taillandier-Heriche E, Alemann M, Emile JF. Polyarteritis nodosa with temporal and oral involvement. *Rev Rhum Engl Ed* 1999; **66**: 523–4.

Giant cell arteritis

Synonym

- Horton's disease

Patients may suffer ischaemic pain during mastication, intermittent claudication of the tongue [1,2] or, rarely, facial palsy [3] or lumps [2,4,5]. Ulceration and necrosis of the tongue [6–18] or occasionally the lip [19] have also been observed [2,3].

References

1 Lamey P-J, Taylor JA, Devine J. Giant cell arteritis: a forgotten diagnosis. *Br Dent J* 1988; **164**: 48–50.
2 Liozon E, Oattara B, Portal MF *et al*. Head-and-neck swelling: an under-recognized feature of giant cell arteritis. A report of 37 patients. *Clin Exp Rheumatol* 2006; **24**: S20–5.
3 Sadzot B, Branas C. Neurovascular facial pain. *Rev Med Liege* 1995; **50**: 472–6.
4 Kannan R, Allen CM, Ockner SA, Schneider KE. Intraoral lesion in giant cell arteritis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1996; **82**: 473–4.
5 Ruiz-Masera JJ, Alamillos-Granados FJ, Dean-Ferrer A *et al.* Submandibular swelling as the first manifestation of giant cell arteritis. Report of a case. *J Craniomaxillofac Surg* 1995; **23**: 119–21.
6 Patterson A, Barnard N, Scully C *et al.* Necrosis of the tongue in a patient with intestinal infarction. *Oral Surg* 1992; **74**: 582–6.
7 Cikes A, Depairon M, Jolidon RM, Wyss P, Lang HJ. Necrosis of the tongue and unilateral blindness in temporal arteritis. *Vasa* 2001; **30**: 222–4.
8 Kleinjung T, Strutz J. Spontaneous, unilateral necrosis of the tongue. Temporal arteritis. *HNO* 1998; **46**: 274–5.
9 Crevits I, Hermans R, Wilms G, Baert AL. Tongue necrosis as a complication of temporal arteritis: CT and angiographic findings. *J Belge Radiol* 1996; **79**: 258–9.
10 Navarro M, Niembro E, Scola B, Scola E, del Pozo A. Necrosis of the tongue secondary to Horton's disease. *Acta Otorrinolaringol Esp* 1995; **46**: 227–9.
11 Llorente Pendas S, De Vicente Rodriguez JC, Gonzalez Garcia M, Junquera Gutierrez LM, Lopez Arranz JS. Tongue necrosis as a complication of temporal arteritis. *Oral Surg Oral Med Oral Pathol* 1994; **78**: 448–51.

12 McRorie ER, Chalmers J, Campbell IW. Lingual infarction in cranial arteritis. *Br J Clin Pract* 1994; **48**: 280.
13 Cikes A, Depairon M, Jolidan RM, Wyss P, Lang HJ. Necrosis of the tongue and unilateral blindness in temporal arteritis. *Vasa* 2001; **30**: 222–4.
14 Hellman DB. Temporal arteritis: a cough, toothache, and tongue infarction. *JAMA* 2002; **287**: 2996–3000.
15 Rockey JG, Anand R. Tongue necrosis secondary to temporal arteritis: a case report and literature review. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2002; **94**: 471–3.
16 Biebl MO, Hugl B, Posck L *et al*. Subtotal tongue necrosis in delayed diagnosed giant-cell arteritis: a case report. *Am J Otolaryngol* 2004; **25**: 438–41.
17 Simon RW, Fritz T, Amaan-Vesti BR *et al*. An unusual presentation of giant cell arteritis. *Vasa* 2005; **34**: 128–30.
18 Ciantar M, Adlam DM. Glossodynia and necrosis of the tongue caused by giant cell arteritis. *Br J Oral Maxillofac Surg* 2007; **46**: 231–3.
19 Scully C, Eveson JW, Barrett AW *et al*. Necrosis of the lip in giant cell arteritis. *J Oral Maxillofac Surg* 1993; **51**: 581–3.

Iatrogenic conditions

Mucositis

Aetiology. Mucositis, sometimes called *mucosal barrier injury*, is the term given to the widespread oral erythema, ulceration and soreness that is a common complication of a number of therapeutic procedures involving chemotherapy, radiotherapy or chemoradiotherapy, used largely in the treatment of cancer but also in the conditioning prior to bone marrow transplantation (i.e. haematopoietic stem cell transplantation). Mucositis appears 3–15 days after cancer treatment, earlier after chemotherapy than after radiotherapy.

Mucositis invariably follows external beam radiotherapy involving the orofacial tissues, and is also common in upper mantle head and neck radiation, and particularly in total body irradiation.

Some 40–90% of patients on chemotherapy develop mucositis. Patients on fluorouracil and cisplatin in particular develop mucositis, while etoposide and melphalan cause particularly severe mucositis. Oral mucositis is particularly severe after haemopoietic stem cell transplantation, because of radiation damage and myeloablation, and the course follows the polymorphonuclear leukocyte count.

The impaired mucosal barrier in mucositis predisposes to life-threatening septic complications; the prevalence of an oral focus in febrile neutropenia has been reported in up to 30% of cases [1–5].

Clinical features. Mucositis typically presents with pain (which can be so intense as to interfere with eating and significantly affect the quality of life), erythema, ulceration and sometimes bleeding.

Diagnosis is clinical and it is helpful to score the degree of mucositis in order to monitor progression and therapy.

Treatment. The basic strategies in management of mucositis aim at pain relief, efforts to hasten healing and prevention of infectious complications. However, prophylaxis is the goal.

Pain relief is usually achieved with opioids given by patient-controlled analgesia and benzydamine can aid relief. Oral cooling with ice chips ameliorates chemotherapy-induced mucositis [6–11].

Other treatments currently used but for which hard data for reliable efficacy are unavailable include the following.

- Medications to reduce salivation and thus exposure of the mucosa to chemotherapeutic drugs that are secreted in saliva
- Anti-inflammatory medications
- Cytokines such as interleukin (IL)-1, IL-11, TGF-beta3 and keratinocyte growth factor
- Granulocyte–macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF) [12]
- Thalidomide: an angiogenesis-inhibiting drug
- Amifostine: a cytoprotector
- Melatonin: the pineal hormone
- Protegrin antimicrobial peptides, which possess activity against Gram-positive and Gram-negative bacteria and yeasts
- Low-energy lasers
- Other agents such as sucralfate, tretinoin, glutamine, vitamin E and misoprostol [1–4,9–12].

Monitoring microbial colonization and the institution of antiviral prophylaxis and antifungal prophylaxis, to avoid colonization and superinfection, is particularly important in patients with low neutrophil counts.

Invasive fungal infections of the oral cavity can be associated with systemic fungal infection and are indications for the use of liposomal amphotericin.

References

1 Sonis ST, Clark J. Prevention and management of oral mucositis induced by antineoplastic therapy. *Oncology* 1991; **5**: 11–6.
2 Blijlevens NM, Donnelly JP, De Pauw BE. Mucosal barrier injury: biology, pathology, clinical counterparts and consequences of intensive treatment for haematological malignancy: an overview. *Bone Marrow Transplant* 2000; **25**: 1269–78.
3 Stiff P. Mucositis associated with stem cell transplantation: current status and innovative approaches to management. *Bone Marrow Transplant* 2001; **27** (Suppl. 2): S3–S11.
4 Scully C, Epstein JB. Oral healthcare for the cancer patient. *Oral Oncol* 1996; **32**: 281–92.
5 Treister N, Sonis S. Mucositis: biology and management. *Curr Opin Otolaryngol Head Neck Surg* 2007; **15**: 123–9.
6 Alterio D, Jereczek-Fossa BA, Fiore MR *et al*. Cancer treatment-induced oral mucositis. *Anticancer Res* 2007; **27**: 1105–25.
7 Silverman S Jr. Diagnosis and management of oral mucositis. *J Support Oncol* 2007; **5**: 13–21.
8 Epstein JB, Stevenson-Moore P, Jackson S, Mohammed JH, Spinelli JJ. Prevention of oral mucositis in radiation therapy: a controlled study with benzydamine hydrochloride rinse. *Int J Radiat Oncol Biol Phys* 1989; **16**: 1571–5.
9 Clarkson JE, Worthington HV, Eden OB. Prevention of oral mucositis or oral candidiasis for patients with cancer receiving chemotherapy (excluding head and neck cancer). *Cochrane Database Syst Rev* 2000; CD000978.
10 Sutherland S. Several therapies may prevent or reduce the severity of oral mucositis associated with cancer treatment. *Evid Based Dent* 2006; **7**: 104–5.
11 Clarkson J, Worthington H, Eden O. Interventions for treating oral mucositis for patients with cancer receiving treatment. *Cochrane Database Syst Rev* 2007; **2**: CD001973.
12 Scully C, Sonis S, Diz Dios P. Oral mucositis. *Oral Diseases* 2006; **12**: 229–41.

Bone marrow transplantation (haematopoietic stem cell transplantation)

Oral complications are common and can be a major cause of morbidity following bone marrow transplantation. Mucositis, infections, bleeding, xerostomia and loss of taste result from the effects of the underlying disease, chemotherapy or radiotherapy,

and GVHD. The ventrum of the tongue, buccal and labial mucosa and gingiva may be affected by ulceration or mucositis [1–8].

References

1 Barrett AP. Oral complications of bone marrow transplantation. *Aust N Z J Med* 1986; **16**: 239–40.
2 Berkowitz RJ, Strandford S, Jones P *et al.* Stomatologic complications of bone marrow transplantation in a pediatric population. *Pediatr Dent* 1987; **9**: 105–10.
3 Dahllof G, Heimdahl A, Modeer T *et al.* Oral mucous membrane lesions in children treated with bone marrow transplantation. *Scand J Dent Res* 1989; **97**: 268–77.
4 Dreizen S, McCredie KB, Dicke KA *et al.* Oral complications of bone marrow transplantation in adults with acute leukaemia. *Postgrad Med* 1979; **66**: 187–93.
5 Seto BG. Oral mucositis in patients undergoing bone-marrow transplantation. *Oral Surg* 1985; **60**: 493–7.
6 Kolbinson DA, Schubert MM, Flourney N *et al.* Early oral changes following bone marrow transplantation. *Oral Surg* 1988; **66**: 130–8.
7 Gabriel DA, Shea T, Olajida O, Serody JS, Comeau T. The effect of oral mucositis on morbidity and mortality in bone marrow transplant. *Semin Oncol* 2003; **30**: 76–83.
8 Antunes HS, de Azevedo AM, da Silva Bouzas LF *et al*. Low-power laser in the prevention of induced oral mucositis in bone marrow transplantation patients: a randomized trial. *Blood* 2007; **109**: 2250–5.

Graft-versus-host disease

The oral manifestations of acute GVHD consist of painful mucosal desquamation and ulceration, and/or cheilitis, and the presence of lichenoid plaques or striae. Small white lesions affect the buccal and lingual mucosa early on, but clear by day 14. Erythema and ulceration are most pronounced at 7–11 days, and may be associated with obvious infection. Candidosis is common, as is herpes simplex stomatitis (occasionally zoster) and oral purpura may occur, especially in adults [1–6]. Bartonella-related pseudomembranous angiomatous papillomatosis of the oral cavity has been reported secondary to bone marrow transplantation and oral chronic GVHD (CGVHD) [7].

The oral lesions in CGVHD are coincident with skin lesions, and include generalized mucosal erythema, lichenoid lesions, mainly in the buccal mucosa, and xerostomia. There may be depressed salivary IgA levels in minor gland saliva [8]. Xerostomia is most significant in the first 14 days after transplant and is a consequence of drug treatment, irradiation and/or GVHD. There may be an increased risk of developing OSCC in CGVHD patients [9,10].

Lip biopsy is useful in the diagnosis of CGVHD and should include both mucosa and underlying minor salivary glands [11]. Histology shows changes similar to those seen in Sjögren's syndrome.

References

1 Dreizen S, McCredie KB, Dicke KA *et al.* Oral complications of bone marrow transplantation in adults with acute leukaemia. *Postgrad Med* 1979; **66**: 187–93.
2 Graham-Brown RAC, Jones JAG, Shaw PV *et al.* A graft-versus-host disease-like syndrome with carcinomatosis. *Br J Dermatol* 1987; **116**: 249–52.
3 Treister NS, Woo SB, O'Holleran EW *et al*. Oral chronic graft-versus-host disease in pediatric patients after hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2005; **11**: 721–31.
4 Sato M, Tokuda N, Fukumoto T *et al*. Immunohistopathological study of the oral lichenoid lesions of chronic GVHD. *J Oral Pathol Med* 2006; **35**: 33–6.
5 de la Rosa Garcia E, Bologna Molina R, Vega Gonzalez T de J. Graft-versus-host disease, an eight case report and literature review. *Med Oral Patol Oral Cir Bucal* 2006; **11**: E486–92.
6 Pereira CM, de Almeida OP, Correa ME, Souza CA, Barjas-Castro ML. Oral involvement in chronic graft versus host disease: a prospective study of 19 Brazilian patients. *Gen Dent* 2007; **55**: 48–51.
7 Vassallo C, Ardigo M, Brazzeli V *et al*. Bartonella-related pseudomembranous angiomatous papillomatosis of the oral cavity associated with allogeneic bone marrow transplantation and oral graft-versus-host disease. *Br J Dermatol* 2007; **157**: 174–8.
8 Izutsu KT, Menard TW, Schubert MM. Graft versus host disease-related secretory immunoglobulin A deficiency in bone marrow transplant recipients: findings in labial saliva. *Lab Invest* 1985; **52**: 292–7.
9 Abdelsayed RA, Sumner T, Allen CM *et al*. Oral precancerous and malignant lesions associated with graft-versus-host disease: report of 2 cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2002; **93**: 75–80.
10 Demarosi F, Soligo D, Lodi G *et al*. Squamous cell carcinoma of the oral cavity associated with graft versus host disease: report of a case and review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005; **100**: 63–9.
11 Sale GE, Shulman HM, Schubert MM. Oral and ophthalmic pathology of graft-versus-host disease in man: predictive value of the lip biopsy. *Hum Pathol* 1981; **12**: 1022–30.

Drugs

A wide range of drugs can occasionally induce mouth ulcers, by a variety of effects [1]. Oral use of caustics or agents such as cocaine can cause erosions or ulcers [2,3]. Oral ulcers are regularly produced by cytotoxic agents [4,5] (see Mucositis above). Aphthous-like ulcers may follow the use of the potassium channel blocking cardioactive agent nicorandil [6,7].

Drugs may also cause mucocutaneous lesions; ulcers of a lichenoid type may follow exposure to non-steroidal anti-inflammatory drugs and other agents, erythema multiforme may follow the use of a range of drugs (see p. 69.69) and drug-induced ulcers may also resemble toxic epidermal necrolysis or may have features reminiscent of other dermatological disorders.

The ulcers usually resolve in 10–14 days if the offending drug can be identified and withdrawn.

References

1 Porter SR, Scully C. Adverse drug reactions in the mouth. *Clin Dermatol* 2000; **18**: 525–32.
2 Parry J, Porter SR, Scully C *et al.* Mucosal lesions due to oral cocaine use. *Br Dent J* 1996; **180**: 462–4.
3 Gandar-Rey JM, Diniz-Freitas M, Gandara-Vila P, Blanco-Carrion A, Garcia Garcia A. Lesions of the oral mucosa in cocaine users who apply the drug topically. *Med Oral* 2002; **7**: 103–7.
4 Berkowitz RJ, Jones P, Barsetti J *et al.* Stomatologic complications of bone marrow transplantation in a pediatric population. *Paediatr Dent* 1987; **9**: 105–10.
5 Pereira CM, de Almeida OP, Correa ME, Souza CA, Barjas-Castro ML. Oral involvement in chronic graft versus host disease: a prospective study of 19 Brazilian patients. *Gen Dent* 2007; **55**: 48–51.
6 Scully C, Azul A, Crighton A *et al*. Nicorandil can induce severe oral ulceration. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001; **91**: 189–93.
7 Webster K, Godbold P. Nicorandil induced oral ulceration. *Br Dent J* 2005; **198**: 619–21.

Acrodynia

Synonym
- Pink disease

Oral and perioral ulceration, hypersalivation, gingivitis and early tooth loss are features of acrodynia caused by mercury poisoning, now rarely seen [1].



Fig. 69.50 Angina bullosa haemorrhagica: a large blood blister in a typical site on the soft palate. The adjacent whitish lesions are from scarring after a previous biopsy.

Reference

1 Dinehart SM, Dillard R, Rainer SS *et al.* Cutaneous manifestations of acrodynia (Pink disease). *Arch Dermatol* 1988; **124**: 107–9.

Disorders of uncertain pathogenesis

Angina bullosa haemorrhagica

Synonym

- Localized oral purpura

This is the term given to a benign, fairly common condition of unknown aetiology that usually presents in the elderly with oral blood blisters. These subepithelial blisters are seen mainly in the soft palate and after a few hours rupture to leave ulcers (Fig. 69.50). The patients appear well otherwise, with no detectable immunological or bleeding disorder [1–5]. Occasional cases are related to the use of corticosteroid inhalers. Only symptomatic care is available.

References

1 Hopkins R, Walker DM. Oral blood blisters: angina bullosa haemorrhagica. *Br J Oral Surg* 1985; **23**: 9–16.
2 Stephenson P, Lamey P-J, Scully C *et al.* Angina bullosa haemorrhagica: clinical and laboratory features in 30 patients. *Oral Surg* 1987; **63**: 560–5.
3 Stephenson P, Scully C, Prime SS *et al.* Angina bullosa haemorrhagica: lesional immunostaining and haematological findings. *Br J Oral Surg* 1987; **25**: 488–91.
4 Giuliani M, Favia GF, Lajolo C, Miani CM. Angina bullosa haemorrhagica: presentation of eight new cases and a review of the literature. *Oral Dis* 2002; **8**: 54–8.
5 Yip HK. Angina bullosa haemorrhagica: a case report and a concise review. *Gen Dent* 2004; **52**: 162–4.

Monoclonal plasmacytic ulcerative stomatitis

Ulcerative stomatitis may occasionally appear with a lichenoid rash, related to a plasmacytic infiltrate [1,2].

References

1 Bowden JR, Scully C, Eveson JW *et al.* Multiple myeloma and bullous lichenoid lesions: an unusual association. *Oral Surg* 1990; **70**: 587–9.
2 Layton SA, Cook JN, Henry JA. Monoclonal plasmacytic ulcerative stomatitis. *Oral Surg* 1993; **75**: 483–7.

Mucocutaneous lymph node syndrome

Synonym

- Kawasaki disease (see Chapter 30)

Mucocutaneous lymph node syndrome is a disorder of uncertain, but possibly infectious, aetiology. Male children are predominantly affected. At least one oral feature should be present for the diagnosis to be made. The oral and pharyngeal mucosa become generally red and sore and the lips dry and fissured. There may be oral ulceration and a 'strawberry tongue' appearance [1–4]. Cervical lymphadenopathy, conjunctivitis and fever also occur, followed later by the characteristic desquamation of the skin of the hands and feet. Early therapy with immunoglobulin is essential to avoid cardiac complications.

References

1 Ogden GR, Kerr M. Mucocutaneous lymph node syndrome (Kawasaki disease). *Oral Surg* 1989; **67**: 569–72.
2 Terezhalmy GT. Mucocutaneous lymph node syndrome. *Oral Surg* 1979; **47**: 26–30.
3 Chen WT, Huang SR, Wang JK. Kawasaki disease presenting with hepatitis and prolonged fever: report of one case. *Acta Paediatr Taiwan* 2003; **44**: 174–6.
4 Singh S, Kasra S. Kawasaki disease. *Natl Med J India* 2005; **18**: 20–4.

Superficial mucoceles

Superficial extravasation mucoceles of the intraoral minor salivary glands in the palate, buccal mucosa or labial mucosa are not uncommon, especially associated with oral LP in middle-aged or elderly women and rarely with chronic graft versus host disease [1].

This is a benign self-limiting condition that may cause confusion with vesiculobullous disorders [2–8].

References

1 Garcia-F-Villalta MJ, Pascual Lopez M, Elices M *et al.* Superficial mucoceles and lichenoid graft versus host disease: report of three cases. *Acta Derm Venereol* 2002; **82**: 453–5.
2 Eveson JW. Superficial mucoceles: pitfall in clinical and microscopic diagnosis. *Oral Surg* 1988; **66**: 318–22.
3 Flaitz CM. Superficial mucoceles of the lower lip. *Am J Dent* 2001; **14**: 187–8.
4 Baurmash H. The etiology of superficial oral mucoceles. *J Oral Maxillofac Surg* 2002; **60**: 237–8.
5 Jinbu Y, Tsukinoki K, Kusama M, Watanabe Y. Recurrent multiple superficial mucocele on the palate: Histopathology and laser vaporization. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2003; **95**: 193–7.
6 Silva A Jr, Nikitakis NG, Balciunas BA, Meiller TF. Superficial mucocele of the labial mucosa: a case report and review of the literature. *Gen Dent* 2004; **52**: 424–7.
7 Damm DE, Fantasia JE. Vesicle of soft palate. Superficial mucocele. *Gen Dent* 2005; **53**: 447–9.
8 Inoue A, Ikeda S, Mizuno Y, Ogawa H. Superficial mucoceles of the soft palate. *Dermatology* 2005; **210**: 360–2.

Necrotizing sialometaplasia

Necrotizing sialometaplasia is an uncommon, benign, self-limiting condition seen predominantly in the posterior hard palate of young adult males, most of whom smoke tobacco [1–5]. An association with bulimia has been reported [6,7].

A painless deep ulcer persists for several weeks before spontaneously healing. Biopsy reveals necrosis and pseudoepitheliomatous changes probably resulting from squamous metaplasia following infarction of minor salivary glands. This benign lesion must be differentiated from malignancy.

References

1 Kinney RB, Burton CS, Vollmer RT. Necrotizing sialometaplasia: a sheep in wolf's clothing. *Arch Dermatol* 1986; **12**: 208–10.
2 Keogh PV, O'Regan E, Toner M, Flint SR. Necrotizing sialometaplasia: an unusual bilateral presentation associated with antecedent anaesthesia and lack of response to intralesional steroids. Case report and review of the literature. *Br Dent J* 2004; **196**: 79–81.
3 Femopase FL, Hernandez SL, Gendelman H, Crisciulo MI, Lopez-de-Blanc SA. Necrotizing sialometaplasia: report of five cases. *Med Oral* 2004; **9**: 304–8.
4 Flint SR. Necrotizing sialometaplasia: an important diagnosis—review of the literature and spectrum of clinical presentation. *J Ir Dent Assoc* 2005; **51**: 26–8.
5 Kominek P, Blasch P. Necrotizing sialometaplasia: a potential diagnostic pitfall. *Ear Nose Throat J* 2006; **85**: 604–5.
6 Scully C, Eveson J. Sialosis and necrotising sialometaplasia in bulimia; a case report. *Int J Oral Maxillofac Surg* 2004; **33**: 808–10.
7 Solomon LW, Merzianu M, Sullivan M, Rigual NR. Necrotizing sialometaplasia associated with bulimia: case report and literature review. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; **103**: 39–42.

Mucha–Haberman disease

Erythematous and ulcerative oral lesions have been reported in pityriasis lichenoides et varioliformis acuta (Mucha–Haberman disease) [1,2].

References

1 Burke DP, Adams RM, Arundell FD. Ulceronecrotic Mucha–Haberman's disease. *Arch Dermatol* 1969; **100**: 201–6.
2 McDaniel RK, White JW, Edwards PA. Mucha–Haberman's disease with oral lesions. *Oral Surg* 1982; **53**: 596–601.

Metabolic disorders

Glucagonoma

Oral ulceration can be a severe manifestation in glucagonoma [1,2].

References

1 Ditty FR, Lang PG. Cutaneous and oral changes as the only manifestations of the glucagonoma syndrome. *South Med J* 1982; **75**: 222–4.
2 Cruz-Bautista I, Lerman I, Perez-Enriquez B *et al*. Diagnostic challenge of glucagonoma: case report and literature review. *Endocr Pract* 2006; **12**: 422–6.

Oral soreness

Most oral pain is of local aetiology, usually resulting from odontogenic infections. Neurological, vascular and referred causes are less common, but must also be excluded. Psychogenic pain is all too frequent and this is discussed below.

Chronic oral soreness may be particularly caused by ulceration, or by mucosal lesions in geographical tongue, LP or deficiency states. Geographical tongue and burning mouth syndrome are the common causes of a sore tongue. LP is the most common cause of chronic soreness in the buccal mucosae. Desquamative gingivitis is the common cause of persistently sore gingivae.

Geographical tongue

See p. 69.100.



Fig. 69.51 Atrophic glossitis in vitamin B_{12} deficiency.

Lichen planus

See Chapter 41.

Deficiency glossitis

Aetiology. Deficiency glossitis may be related particularly to deficiency of iron, folate or vitamin B_{12}, and may then be associated with angular stomatitis and/or mouth ulcers. Deficiencies of other B-group vitamins occasionally cause glossitis, usually in chronic alcoholics or in those with malabsorption [1–6].

Pathology. Epithelial atrophy, rarely with some dysplasia, is seen.

Clinical features. In anaemic glossitis the tongue is red, sore and smooth (Fig. 69.51). Occasionally pernicious anaemia can also produce red areas or patterns of red lines. In many other patients the tongue can become sore but appear clinically completely normal and such patients' complaints are liable to be mislabelled as psychogenic.

Diagnosis. A full blood picture and assays of iron, folate and vitamin B_{12} are essential in management, as sore tongue can be the initial symptom of a deficiency and can precede any fall in the haemoglobin level.

Treatment. The cause of the deficiency should be sought before replacement treatment is given.

References

1 Drummond JF, White DK, Damin DD. Megaloblastic anaemia with oral lesions: a consequence of gastric bypass surgery. *Oral Surg* 1985; **59**: 149–53.
2 Greenberg MS. Clinical and histologic changes of the oral mucosa in pernicious anaemia. *Oral Surg* 1981; **52**: 38–42.
3 Ramasinghe AW, Warnakulasuriya KAAS, Tennekoon GE *et al*. Oral mucosal changes in iron deficiency anaemia in a Sri Lankan female population. *Oral Surg* 1983; **55**: 29–32.
4 Field EA, Speechley JA, Rugman FR, Varga E, Tyldesley WR. Oral signs and symptoms in patients with undiagnosed vitamin B12 deficiency. *J Oral Pathol Med* 1995; **24**: 468–70.
5 Lu SY, Wu HC. Initial diagnosis of anemia from sore mouth and improved classification of anemias by MCV and RDW in 30 patients. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2004; **98**: 679–85.
6 Lehman AS, Bruce AJ, Rogers RS. Atrophic glossitis from vitamin B12 deficiency: a case misdiagnosed as burning mouth disorder. *J Periodontol* 2006; **77**: 2090–2.

Burning mouth syndrome

Synonyms
- Oral dysaesthesia
- Glossopyrosis
- Glossodynia

Burning mouth syndrome (BMS) most frequently affects middle-aged and elderly females [1–4].

Aetiology. Several organic lesions, for example haematinic deficiency states, erythema migrans, ulcers, mucositis, LP and candidosis, can cause oral soreness or burning sensation. BMS with a tongue of normal clinical appearance may be seen in deficiency states, and with psychogenic causes, drugs (e.g. angiotensin-converting enzyme inhibitors such as captopril, enalapril, lisinopril; protease inhibitors; cytotoxic agents; clonazepam) and diabetes mellitus. A monosymptomatic hypochondriasis or an underlying anxiety about cancer or a sexually transmitted infection with perhaps excessive tongue activity appear to be the basis for the complaint of BMS in many patients (Table 69.21) [1–15]. More recently, evidence for a neuropathic basis to BMS has emerged [12,14,16].

Uncommon causes that may need to be considered include hypothyroidism, lupus erythematosus, hypersensitivity (to sodium metabisulphite, nuts, dental materials and other substances) and galvanic reactions to metals in the mouth [17–21]. However, BMS is often a medically unexplained symptom.

Table 69.21 Causes of burning mouth.

Local
Candidosis
Other infections
Geographical tongue
Lichen planus
Oral submucous fibrosis
Dentures
Systemic
Psychogenic
Cancerophobia
Depression
Anxiety states
Hypochondriasis
Deficiency states
Pernicious anaemia and other vitamin B deficiencies
Folate deficiency
Iron deficiency
Diabetes
Drugs (captopril)

Clinical features. Although the tongue is most frequently involved, the patient may also occasionally complain of burning lips, gums or palate. The burning sensation is usually bilateral and often relieved by eating and drinking [1,11,12]. In contrast, oral discomfort associated with inflammatory lesions is typically aggravated by eating.

Diagnosis. Oral examination very occasionally reveals an organic cause. Xerostomia should be excluded as this may predispose to candidosis. Laboratory screening for anaemia, diabetes, a deficiency state or candidosis should be undertaken.

Treatment. Few patients with BMS have spontaneous remission in the short term, and thus an attempt at treatment is indicated. Reassurance, treatment of any defined underlying organic abnormality and, occasionally, psychological treatment, antidepressants or psychiatric care are indicated, but active dental or oral surgical treatment, or attempts at 'hormone replacement', in the absence of any specific indication, should be avoided. However, treatment is rarely completely successful, although the condition only infrequently becomes severe. Fortunately, about 50% remit spontaneously over 6 or 7 years.

- Patients should avoid anything that aggravates symptoms, such as sparkling wines, citrus drinks and spices.
- Reassurance and attention to any factors such as dentures or haematinic deficiencies may be indicated. There are few treatments of proven benefit [12–22]. Cognitive–behavioural therapy or a specialist referral may be indicated [14,23].
- Some patients respond to medication:
  (a) effects of vitamin B are controversial [24–26]
  (b) topical benzydamine 0.01% rinse or spray [27,28]
  (c) although antidepressants must be given for at least 2–3 weeks to achieve any antidepressive effect, most patients with medically unexplained symptoms show benefit within 1 week [29–32]
  (d) topical capsaicin cream 0.025% (Zacin) or 0.075% (Axsain) [11]
  (e) clonazepam tablet sucked locally [14]
  (f) α-lipoic acid systemically [14,33].

References

1 Van der Waal I. *The Burning Mouth Syndrome*. Copenhagen: Munksgaard, 1990.
2 Marbach JJ. Medically unexplained chronic orofacial pain. Temporomandibular pain and dysfunction syndrome, orofacial phantom pain, burning mouth syndrome, and trigeminal neuralgia. *Med Clin North Am* 1999; **83**: 691–710.
3 Silvestre FJ, Serrano C. Burning mouth syndrome: concepts review and update. *Med Oral* 1997; **2**: 30–8.
4 Muzyka BC, De Rossi SS. A review of burning mouth syndrome. *Cutis* 1999; **64**: 29–35.

5 Bergdahl M, Bergdahl J. Burning mouth syndrome: prevalence and associated factors. *J Oral Pathol Med* 1999; **28**: 350–4.
6 Maresky LS, Van der Bijl P, Gird I. Burning mouth syndrome. Evaluation of multiple variables among 85 patients. *Oral Surg* 1993; **75**: 303–7.
7 Bogetto F, Maina G, Ferro G, Carbone M, Gandolfo S. Psychiatric comorbidity in patients with burning mouth syndrome. *Psychosom Med* 1998; **60**: 378–85.
8 Rojo L, Silvestre FJ, Bagan JV, de Vincente T. Psychiatric morbidity in burning mouth syndrome. Psychiatric interview versus depression and anxiety scales. *Oral Surg* 1993; **75**: 308–11.
9 Barker KE, Savage NW. Burning mouth syndrome: an update on recent findings. *Aust Dent J* 2005; **50**: 220–3.
10 Sardella A, Lodi G, Demarosi F, Uglietti D, Carassi A. Causative or precipitating aspects of burning mouth syndrome: a case–control study. *J Oral Pathol Med* 2006; **35**: 466–71.
11 Gruschka M, Ching V, Epstein J. Burning mouth syndrome. *Adv Otorhinolaryngol* 2006; **63**: 278–87.
12 Suarez P, Clark GT. Burning mouth syndrome: an update on diagnosis and treatment methods. *J Calif Dent Assoc* 2006; **34**: 611–22.
13 Zakrzewska JM. Diagnosis and management of non-dental orofacial pain. *Dent Update* 2007; **34**: 134–9.
14 Patton LL, Siegel MA, Benoliel R, De Laat A. Management of burning mouth syndrome: systematic review and management recommendations. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; **103**: S39.1–13.
15 Merigo E, Manfredi M, Zanetti MR *et al*. Burning mouth syndrome and personality profiles. *Minerva Stomatol* 2007; **56**: 159–67.
16 Forssell H, Jaskalainen S, Tenovuo O, Hinkka S. Sensory dysfunction in burning mouth syndrome. *Pain* 2002; **99**: 41–7.
17 Van Joost TH, Van Ulsen J, Van Loon LAJ. Contact allergy to denture materials in the burning mouth syndrome. *Contact Dermatitis* 1988; **18**: 97–9.
18 Wardrop RW, Hailes J, Burger H *et al*. Oral discomfort at menopause. *Oral Surg* 1989; **67**: 535–40.
19 Dutree-Meulenberg ROGM, Kozel MMA, van Joost TH. Burning mouth syndrome: a possible etiologic role for local contact hypersensitivity. *J Am Acad Dermatol* 1992; **26**: 935–40.
20 Helton J, Storrs F. The burning mouth syndrome: lack of a role for contact urticaria and contact dermatitis. *J Am Acad Dermatol* 1994; **31**: 201–5.
21 Femiano F, Gambos F, Esposito V, Nunziata M, Scully C. Burning mouth syndrome (BMS): evaluation of thyroid and taste. *Med Oral Patol Oral Cir Bucal* 2006; **11**: E22–5.
22 Buchanan J, Zakrzewska J. Burning mouth syndrome. *Clin Evidence* 2003; **9**: 1506–11.
23 Bergdahl J, Anneroth G, Perris H. Cognitive therapy in the treatment of patients with burning mouth syndrome: a controlled study. *J Oral Pathol Med* 1995; **24**: 213–5.
24 Lamey PJ, Allam BF. Vitamin status of patients with burning mouth syndrome and the response to replacement therapy. *Br Dent J* 1986; **168**: 81–4.
25 Hugoson A, Thorstensson B. Vitamin B status and response to replacement therapy in patients with burning mouth syndrome. *Acta Odontol Scand* 1991; **49**: 367–75.
26 Pinto A, Sollecito TP, De Rossi SS. Burning mouth syndrome. A retrospective analysis of clinical characteristics and treatment outcomes. *N Y State Dent J* 2003; **69**: 18–24.
27 Sardella A, Uglietti D, Demarosi F *et al*. Benzydamine hydrochloride oral rinses in management of burning mouth syndrome. A clinical trial. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1999; **88**: 683–6.
28 Zakrzewska JM, Forssell H, Glenny AM. Interventions for the treatment of burning mouth syndrome: a systematic review. *J Orofac Pain* 2003; **17**: 293–300.
29 Tammiala-Salonen T, Forssell H. Trazodone in burning mouth pain: placebo-controlled, double-blind study. *J Orofac Pain* 1999; **13**: 83–8.
30 Woda A, Navez ML, Picard P, Gremeau C, Picard-Leandri E. A possible therapeutic solution for stomatodynia (burning mouth syndrome). *J Orofac Pain* 1998; **12**: 272–8.
31 Loldrup D, Langemark M, Hansen HJ, Olesen J, Bech P. Clomipramine and mianserin in chronic idiopathic pain syndrome. A placebo controlled study. *Psychopharmacology* 1989; **99**: 1–7.
32 Demarosi F, Tarozzi M, Lodi G *et al*. The effect of levosulpiride in burning mouth syndrome. *Minerva Stomatol* 2007; **56**: 21–6.



Fig. 69.52 Materia alba.

33 Femiano F, Gombos F, Scully C, Busciolano M, Luca PD. Burning mouth syndrome (BMS): controlled open trial of the efficacy of alpha-lipoic acid (thioctic acid) on symptomatology. *Oral Dis* 2000; **6**: 274–7.

White lesions

Acquired white lesions in the mouth are usually caused by materia alba (Fig. 69.52), cheek biting or chemical burns, but keratoses, infections, dermatoses (usually LP), neoplastic disorders and other conditions must be excluded (see Table 69.9).

Congenital lesions are discussed on p. 69.22.

Cheek biting

Synonym
- Morsicatio buccarum

A horizontal white line may be seen in the buccal mucosa of healthy people (linea alba) but can be exaggerated in tense individuals. Cheek biting causes a whitish, shredded appearance usually of the buccal or lower labial mucosa at the occlusal line (adjacent to where the teeth meet) (Fig. 69.53) [1–8]. The habit is most common in tense or anxious individuals who may also show bruxism, mandibular (myofascial) pain dysfunction or other oral features of psychogenic disorders. The lesion is benign but may simulate white-sponge naevus (see p. 69.23).

References

1 Precheur I. Morsicatio buccarum: cytological study of 29 cases. *Inf Dent* 1983; **65**: 2935–9.
2 Schulten EA, Jovanovic A, van der Waal I. Prevalence study of oral mucosal lesions in 300 patients. *Ned Tijdschr Tandheelkd* 1989; **96**: 538–9.
3 Glass LF, Maize JC. Morsicatio buccarum et labiorum (excessive cheek and lip biting). *Am J Dermatopathol* 1991; **13**: 271–4.
4 Silva DR, da Fonseca MA. Self-injurious behavior as a challenge for the dental practice: a case report. *Pediatr Dent* 2003; **25**: 62–6.
5 Farsi NM. Symptoms and signs of temporomandibular disorders and oral parafunctions among Saudi children. *J Oral Rehabil* 2003; **30**: 1200–8.
6 Bessa CF, Santos CJ, Aguiar MC, do Carmo MA. Prevalence of oral mucosal alterations in children from 0 to 12 years old. *J Oral Pathol Med* 2004; **33**: 17–22.

7 Farsi N, Alamoudi N, Feteih R, El-Kateb M. Association between temporo mandibular disorders and oral parafunctions in Saudi children. *Odontostomatol Trop* 2004; **27**: 9–14.
8 Romero M, Vivente A, Bravo LA. Prevention of habitual cheek biting: a case report. *Spec Care Dentist* 2005; **25**: 214–6.

Burns

Chemical burns (due, for example, to holding mouthwashes in the mouth or drugs against the buccal mucosa) or burns caused by heat, cold or irradiation can cause white sloughing lesions of the mucosa [1–11]. Such lesions typically heal spontaneously within 1–3 weeks.

References

1 Bernstein ML. Oral mucosal white lesions associated with excessive use of Listerine mouthwash. *Oral Surg* 1978; **46**: 781.
2 Sapir S, Bimstein E. Cholinsalicylate gel induced oral lesion: report of case. *J Clin Pediatr Dent* 2000; **24**: 103–6.
3 Parry J, Porter SR, Scully C *et al*. Mucosal lesions due to oral cocaine use. *Br Dent J* 1996; **180**: 462–4.
4 Flaitz CM. Chemical burn of the labial mucosa and gingiva. *Am J Dent* 2001; **14**: 259–60.
5 Ameneiros Lago E, Marino Callejo A, Echarri Piudo A, Sesma Sanchez P. [Burns in the oral mucosa and skin erosions.] *An Med Interna* 2001; **18**: 448.

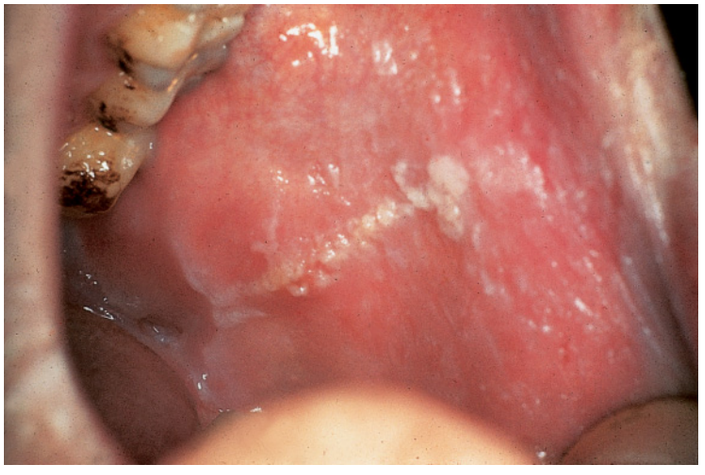


Fig. 69.53 Frictional keratosis and cheek biting (morsicatio buccarum) at the occlusal line.

6 Kerekhanjanarong V, Supiyaphun P, Saengpanich S. Upper aerodigestive tract burn: a case report of firework injury. *J Med Assoc Thai* 2001; **84**: 294–8.
7 Nahlieli O, Shapira Y, Yoffe B, Baruchin AM. An unusual iatrogenic burn from a heated dental instrument. *Burns* 2000; **26**: 676–8.
8 Shimoyama T, Kaneko T, Nasu D, Suzuki T, Horie N. A case of an electrical burn in the oral cavity of an adult. *J Oral Sci* 1999; **41**: 127–8.
9 Fantasia JE, Damm DD. White mucosa. Chemical burn. *Gen Dent* 2001; **49**: 265, 324.
10 Holmes RG, Chan DC, Singh BB. Chemical burn of the buccal mucosa. *Am J Dent* 2004; **17**: 219–20.
11 Shetty K. Hydrogen peroxide burn of the oral mucosa. *Ann Pharmacother* 2006; **40**: 351.

Lichen planus

See Chapter 41.

Candidosis

Up to 50% of the healthy population harbour *Candida albicans* as an oral commensal. Carriage is more common in cigarette smokers. *Candida* resides particularly on the posterior dorsum of the tongue [1–8].

Infection is likely to result from xerostomia, local disturbances in salivary flora such as occurs during broad-spectrum antimicrobial treatment, or depressed immune responses [1–4,9–13]. Of the several clinical presentations of oral candidosis, only thrush, candidal leukoplakia and chronic mucocutaneous candidosis present as white lesions; the other types, acute and chronic atrophic candidosis, are red (Table 69.22).

Thrush

Synonym
- Acute pseudomembranous candidosis

Aetiology. Healthy neonates, who have yet to develop immunity to *Candida* species, may develop thrush. In other patients, predisposing factors include antibiotic or corticosteroid use, xerostomia and severe T-cell immune defects associated with immunosuppression (e.g. given to prevent graft rejection in organ transplantation) or immunodeficiencies such as leukaemia or HIV disease. Thrush is a common and early feature of HIV infection and may be a portent of developing AIDS [1–4,10,12,13].

Table 69.22 Intraoral candidosis.

Type of candidosis	Usual age at onset	Predisposing factors*
Acute pseudomembranous candidosis (thrush)†	Any	Local: dry mouth, antimicrobials General: corticosteroids, leukaemia, HIV
Acute atrophic candidosis ('antibiotic mouth'; antibiotic sore mouth)	Any	Broad-spectrum antibiotics or corticosteroids
Erythematous candidosis		Any, HIV especially
Chronic atrophic candidosis (denture-related stomatitis)	Adults	Denture wearing, especially at night
Chronic hyperplastic candidosis (candidal leukoplakia)†	Usually middle-aged or elderly	Tobacco smoking, denture wearing, immune defect
Median rhomboid glossitis	Third or later decades	Tobacco smoking, denture wearing, HIV
Chronic mucocutaneous candidosis†	Usually first decade	Often immune defect; rarely endocrinopathy

HIV, human immunodeficiency virus.
* Immune defects can predispose to any form.
† White lesions.

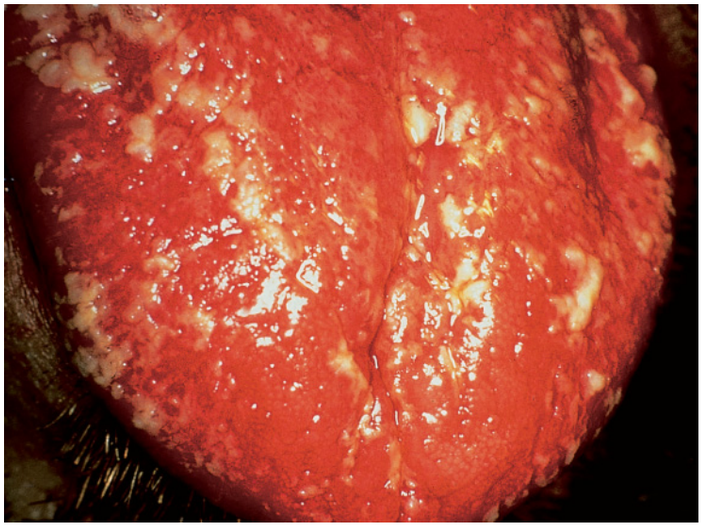


Fig. 69.54 Thrush: scattered white lesions on an erythematous background.

Clinical features. The soft creamy patches of thrush, which resemble milk curds, can be wiped off the oral mucosa with gauze, leaving an area of erythema (Fig. 69.54).

Chronic candidosis

Aetiology. The aetiology of chronic oral candidosis is unclear and in only a few patients can either a local cause or underlying immune defect be identified [1–3]. HIV/AIDS and chronic mucocutaneous candidosis syndromes are rare causes (see Chapter 36).

Clinical features. Long-standing oral candidosis may produce tough, adherent white patches (chronic hyperplastic candidosis or candidal leukoplakias) which can have a malignant potential, and may be indistinguishable from other leukoplakias except by biopsy. Candidal leukoplakias may, however, be speckled.

Diagnosis of candisosis. The diagnosis of oral thrush is usually clinical but it tends to be overdiagnosed by physicians. In contrast, erythematous candidosis is probably underdiagnosed. In immunosuppressed patients, a Gram-stained smear should be taken to distinguish thrush from the plaques produced by opportunistic bacteria. Hyphae seem to indicate that the *Candida* organisms are acting as pathogens and not simple commensals.

Suspected candidal leukoplakia should be biopsied, both to distinguish it from other non-candidal plaques and also because of possible dysplasia. Although candidal hyphae and a neutrophil infiltrate may be seen on haematoxylin and eosin staining, PAS will demonstrate the purple staining of the hyphae.

Treatment of candidosis.

Acute candidosis. Except in healthy neonates, possible predisposing causes should be looked for and treated. Topical polyenes such as nystatin or amphotericin, or imidazoles such as miconazole are often indicated but, in HIV infection, antiretroviral agents and fluconazole may be required.

Chronic hyperplastic candidosis. The oral lesions of chronic hyperplastic candidosis may respond poorly to the polyenes [6]. These cases, and some cases of chronic mucocutaneous candidosis, may respond only to flucytosine, ketoconazole, fluconazole, itraconazole, voriconazole or caspofungin [1,14–19].

References

1 Scully C, El-Kabir M, Samaranayake LP. Candida and oral candidiasis. *Crit Rev Oral Biol Med* 1994; **5**: 124–58.

2 Smith CB. Candidiasis: pathogenesis, host resistance and predisposing factors. In: Bodey GP, Feinstein V, eds. *Candidiasis*. New York: Raven Press, 1985: 53–72.

3 Epstein JB, Truelove EL, Izutzu KT. Oral candidiasis: pathogenesis and host defence. *Rev Infect Dis* 1984; **6**: 96–106.

4 Odds FC. *Candida* infections: an overview. *CRC Crit Rev Microbiol* 1987; **15**: 1–5.

5 Al-Karaawi ZM, Manfredi M, Waugh ACW *et al*. Molecular characterization of *Candida* spp. isolated from the oral cavity of patients from diverse clinical settings. *Oral Microbiol Immunol* 2002; **17**: 44–9.

6 Sitheeque MA, Samaranayake LP. Chronic hyperplastic candidosis/candidiasis (candidal leukoplakia). *Crit Rev Oral Biol Med* 2003; **14**: 253–67.

7 Yonezawa H, Takasaki K, Teraoka K *et al*. Effects of tongue and oral mucosa cleaning on oral Candida species and production of volatile sulfur compounds in the elderly in a nursing home. *J Med Dent Sci* 2003; **50**: 1–8.

8 Terai H, Shimahara M. Atrophic tongue associated with Candida. *J Oral Pathol Med* 2005; **34**: 397–400.

9 Gomes MF. Kohlmann KR, Plens G. Oral manifestations during chemotherapy for acute lymphoblastic leukemia: a case report. *Quintessence Int* 2005; **36**: 307–13.

10 Sharma G, Pai KM, Suhas S *et al*. Oral manifestations in HIV/AIDS infected patients from India. *Oral Dis* 2006; **12**: 537–42.

11 Fox RI, Liu AY. Sjogren's syndrome in dermatology. *Clin Dermatol* 2006; **24**: 393–413.

12 Ship JA, Visink A, Challacombe SJ. Use of prophylactic antifungals in the immunocompromised host. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; **103** Suppl: S6.e1–14.

13 Baccaglini L, Atkinson JC, Patton LL *et al*. Management of oral lesions in HIV-positive patients. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; **103** Suppl: S50.e1–23.

14 Hay RJ, Clayton YM. Fluconazole in the management of patients with chronic mucocutaneous candidiasis. *Br J Dermatol* 1988; **119**: 683–5.

15 Nielson H, Dangaard K, Schiodt M. Chronic mucocutaneous candidiasis: a review. *Tandlaegkbladet* 1985; **89**: 667–73.

16 Porter SR, Scully C. Candidiasis endocrinopathy syndrome. *Oral Surg* 1986; **61**: 573–8.

17 Fazlollahi MR, Farhoudi A, Movahedi M *et al*. Chronic mucocutaneous candidiasis; report of three cases with different phenotypes. *Iran J Allergy Asthma Immunol* 2005; **4**: 39–42.

18 Bhowate R, Dubey A. Chronic mucocutaneous candidiasis: a case report. *J Indian Soc Pedod Prev Dent* 2004; **22**: 21–3.

19 Jayasinghe M, Schmidt M, Walker B, Rocken M, Schaller M. Successful treatment of azole-resistant chronic mucocutaneous candidosis with caspofungin. *Acta Derm Venereol* 2006; **86**: 563–4.

Leukoplakia

The World Health Organization defines leukoplakia as a white patch or plaque on the mucosa that cannot be rubbed off and that is not recognized as a specific disease entity [1–4], which implies a diagnosis of exclusion (e.g. of LP, candidosis). The term is also used irrespective of the presence or absence of epithelial dysplasia, although there is a small malignant potential to some keratoses [1–6].

Leukoplakia is common in adults: around 1% are affected, although some populations show higher prevalences. Most cases are seen in the 50–70 age group [4,9–15].

Leukoplakia can be totally benign or sometimes can be precancerous or a marker for cancer elsewhere in the upper aerodigestive tract.

Oral keratoses

Aetiology. The cause of most keratoses is unknown (idiopathic keratoses or leukoplakia) but some are caused by chronic irritation, particular lifestyle habits or infective agents [16–31].

Tobacco-induced keratoses. Consumption of tobacco products has long been causally connected with oral cancer and is a common cause of keratosis. Tobacco use also predisposes to cancers elsewhere in the upper aerodigestive tract, bladder and other sites. Tobacco use should thus be discouraged; the drug amfebutamone or varenicline may help users break the habit.

Tobacco chewing. Tobacco is chewed in many parts of the world and may induce keratosis. In many communities from resource-poor countries, tobacco is a component of betel quid, along with areca nut and betel leaf, and sometimes slaked lime and spices. Sometimes betel is used without tobacco (pan or paan), though others use paan with tobacco. Oral carcinoma can result.

Reverse smoking (bidi). In some communities, especially in Asia, cigarettes are smoked with the lit end within the mouth. Palatal or other oral carcinoma can result.

Cigarette-induced keratoses. Mild keratosis may be seen especially on the palate, lip (occasionally nicotine-stained) and at the commissures, along with nicotine-stained teeth. Malignant change is uncommon.

Pipe smoking. Diffuse whiteness over the palate is termed 'smoker's keratosis' or 'stomatitis nicotina'. The palatal minor salivary gland orifices appear red against this white background. Malignant change is uncommon.

Cigar smoking. Cigar smokers may develop stomatitis nicotina and nicotine-stained teeth. Malignant change is uncommon.

Snuff dipper's keratosis and other smokeless tobacco lesions. Snuff may produce keratosis—white hyperkeratotic lesions caused by snuff-dipping (holding flavoured tobacco powder in the oral sulcus or vestibule), together with gingival recession at the site of use. Malignant change is rare.

Other aetiological factors

- Proliferative verrucous leukoplakia is often associated with HPV. Malignant change is uncommon.
- Candidal leukoplakias may be associated with an increased risk of malignant change, although it is uncommon.
- Syphilitic leukoplakia is rarely seen now. Malignant change is common.
- Hairy leukoplakia is caused by EBV and seen especially in HIV disease. Malignant change is not recorded.



Fig. 69.55 Homogeneous leukoplakia in the buccal mucosa.



Fig. 69.56 Speckled leukoplakia.

Clinical features. Leukoplakias vary in size: some are small and focal, others more widespread, occasionally involving very large areas of the oral mucosa; in other patients several discrete separate areas of leukoplakia can be seen. Leukoplakia has a wide range of clinical presentations, from homogeneous white plaques that can be faintly white or very thick and opaque, to nodular white lesions or lesions admixed with red lesions [1–4]. The malignant potential depends on the following.

Appearance. Homogeneous leukoplakia, the most common, presents with uniformly white plaques, common in the buccal (cheek) mucosa and usually of low premalignant potential (Fig. 69.55).

Non-homogeneous or heterogeneous leukoplakias are nodular, verrucous and speckled leukoplakias that consist of white patches or nodules in a red, often eroded, area of mucosa (Fig. 69.56). They have a high risk of malignant transformation and are therefore far more serious.

Site. High-risk sites for malignant transformation include the soft palate complex and ventrolateral tongue and floor of the mouth



Fig. 69.57 Sublingual keratosis.

(where sublingual keratosis has a particularly high risk of malignant change; Fig. 69.57). Sublingual keratosis is more common in women than men, has a typical 'ebbing-tide' appearance clinically and has a high malignant potential.

Aetiological factors.

- Proliferative verrucous leukoplakia is a diffuse white and/or papillary lesion seen in elderly patients, often associated with HPV, and shows an inexorable slow progression over one or two decades to verrucous or squamous cell carcinoma.
- Candidal leukoplakias may be associated with an increased risk of malignant change. Chronic candidal infection is common in speckled leukoplakias and *C. albicans* can cause or colonize other keratoses, particularly in smokers, and is especially likely to form speckled leukoplakias at commissures. It may be dysplastic and have higher malignant potential than some other keratoses. Candidal leukoplakias may respond to antifungals and cessation of smoking.
- Syphilitic leukoplakia, especially of the dorsum of tongue, is a feature of tertiary syphilis rarely seen now, although the malignant potential is high.
- Hairy leukoplakia is caused by EBV. It usually has a corrugated surface and mainly affects margins of the tongue almost exclusively. It is seen in the immunocompromised and is a complication of HIV infection. It is seen in all groups at risk of HIV infection. The condition appears to be benign and self-limiting. Leukoplakia in chronic renal failure causes similar symmetrical, soft keratoses, and may be caused by EBV.

Diagnosis. There are no signs or symptoms that reliably predict whether a leukoplakia will undergo malignant change, and thus histology must be used to detect dysplasia. Scalpel or punch biopsy is therefore generally indicated and is mandatory for those leukoplakias that exhibit the following characteristics:

- found in patients with previous or concurrent head and neck cancer
- are non-homogeneous, i.e. have red areas and/or are verrucous and/or are indurated
- in a high-risk site such as floor of mouth or tongue
- focal
- with symptoms
- without obvious aetiological factors.

Many would advise biopsy of all keratoses and leukoplakias.

Pathology. Keratoses show, to a varying degree, increased keratin production, change in epithelial thickness and disordered epithelial maturation. Mild dysplasia is not usually regarded as of serious significance. The presence of severe epithelial dysplasia is thought to indicate a considerable risk of malignant development [32,33]. Pagetoid dyskeratosis is considered a selective keratinocytic response in which a small part of the normal population of keratinocytes is induced to proliferate in response to friction [34]. Pagetoid dyskeratosis has been found in 42.2% of lip biopsies, more frequent in younger patients and in women. Pagetoid cells are more common in suprabasal location and in the labial mucosa. These cells show positivity for high-molecular-weight cytokeratin and negative reaction for low-molecular-weight cytokeratin, epithelial membrane antigen, carcinoembryonic antigen and HPV. The immunohistochemical profile is different from the surrounding keratinocytes, indicating premature keratinization. The morphological features of dyskeratotic pagetoid cells are distinctive and easily recognized as an incidental finding, thus preventing confusion with other important entities including an intraepidermal tumour.

The main differential diagnoses include white-sponge naevus, leukoedema, oral koilocytoses, hairy leukoplakia, pagetoid squamous cell carcinoma *in situ* and extramammary Paget's disease of the oral mucosa.

Prognosis. There is clear evidence of the malignant potential of some oral leukoplakias. Overall, around 2–5% of leukoplakias become malignant in 10 years and 5–20% of leukoplakias are dysplastic. Of leukoplakias with dysplasia, 10–35% proceed to carcinoma. Malignant change to carcinoma is most frequent in women older than 50 years and in large lesions. Interestingly, leukoplakias developing in non-smokers have a higher rather than lower risk of malignant change. However, some leukoplakias (15–30%) regress clinically, not only when supposed aetiological factors have been removed but also sometimes spontaneously.

At present, it is not possible to reliably predict which dysplastic lesions will progress to carcinoma and which will regress, and there is concern over observer and interobserver variation in diagnosis of dysplasia [35–39]. Over the recent past, much effort has gone into identifying tissue markers of malignant potential [40–43], in particular the genetic changes that underlie oral carcinoma, resulting in the identification of biomarkers such as DNA ploidy, p53, and chromosome 3 and 9 changes that might predict neoplastic change in potentially malignant lesions [42–54].

Treatment. Management can be difficult, not least because of the wide extent of some lesions, their frequent admixture with areas of erythroplasia (speckled leukoplakias), and controversy as to the prognosis and long-term benefit and effects of various therapies. Few controlled studies are available and there is no evidence of effective treatment in preventing malignant transformation of

leukoplakia [55,56]. Treatment is, therefore, empirical [55–58] but removal of known risk factors (tobacco, alcohol and trauma) is a mandatory first step following which the patient should be re-examined 3 months later. If the lesion persists, it should be removed [33,43,58–64].

Surgery (scalpel or laser excision) is an obvious option for the management of leukoplakias with a high predisposition to malignant transformation, such as leukoplakias that are:

- speckled
- verrucous
- from high-risk sites (e.g. floor of mouth/ventrum of tongue, or soft palate/fauces)
- in a patient with previous cancer of the upper aerodigestive tract
- dysplastic
- polysomic (aneuploidy or tetraploidy)
- positive for genetic markers such as mutated tumour-suppressor factor p53, or for loss of heterozygosity on chromosomes 3p or 9p—such advances in molecular biology mean that it should soon be possible to ascertain the malignant potential of leukoplakia from genetic and DNA studies.

Chemotherapy and chemoprevention are attractive possibilities [65–68]. Topical 0.5% bleomycin in dimethyl sulfoxide (dimethyl sulphoxide) has been evaluated [55,56,69,73]. Although topical or systemic vitamin A derivatives, methisoprinol and calcipotriol may induce regression of some leukoplakias and may inhibit their development, these agents have not been widely used, because of adverse effects or their uncertain long-term consequences [56,69–75] and randomized controlled trials are few.

References

1 World Health Organization Collaborating Centre for Oral Precancerous Lesions. Definitions of leucoplakia and related lesions. *Oral Surg* 1978; **45**: 518–39.

2 Scully C. Advances in oral medicine. *Prim Dent Care* 2000; **7**: 55–8.

3 Dietrich T, Reichert PA, Scheifele C. Clinical risk factors of oral leukoplakia in a representative sample of the US population. *Oral Oncol* 2004; **40**: 158–63.

4 Mishra M, Mohanty J, Sengupta S, Tripathy S. Epidemiological and clinicopathological study of oral leukoplakia. *Indian J Dermatol Venereol Leprol* 2005; **71**: 161–5.

5 Axell T, Holmstrup P, Kramer IRH *et al*. International seminar on oral leucoplakia and associated lesions related to tobacco habits. *Community Dent Oral Epidemiol* 1984; **12**: 145–54.

6 van der Waal I, Schepman KP, van der Meij EH. A modified classification and staging system for oral leukoplakia. *Oral Oncol* 2000; **36**: 264–6.

7 Huber MA. A review of premalignant oral conditions. *Tex Dent J* 2006; **123**: 502–9.

8 Mithani SK, Midlarz WK, Grumbine FL, Smith IM, Califano JA. Molecular genetics of premalignant oral lesions. *Oral Dis* 2007; **13**: 126–33.

9 Wright JM. Oral precancerous lesions and conditions. *Semin Dermatol* 1994; **13**: 125–31.

10 Sciubba JJ. Oral leukoplakia. *Crit Rev Oral Biol Med* 1995; **6**: 147–60.

11 Scully C, Cawson RA. Potentially malignant oral lesions. *J Epidemiol Biostat* 1996; **1**: 3–12.

12 Bouquot J, Weiland L, Ballard D, Kurland L. Leukoplakia of the mouth and pharynx in Rochester, MN 1935–1984: incidence, clinical features and follow-up of 463 patients from a relatively unbiased patient pool. *J Oral Pathol* 1988; **17**: 436.

13 Bouquot JE, Gorlin RJ. Leukoplakia, lichen planus and other oral keratoses in 23616 white Americans over the age of 35 years. *Oral Surg Oral Med Oral Pathol* 1986; **61**: 373–81.

14 Bouquot JE, Weiland LH, Kurland LT. Leukoplakia and carcinoma in situ synchronously associated with invasive oral/oropharyngeal carcinoma in Rochester, Minn, 1975–1984. *Oral Surg Oral Med Oral Pathol* 1988; **65**: 199–207.

15 Roosaar A, Yin L, Johannsen AL. A long-term follow-up study on the natural course of oral leukoplakia in a Swedish population-based sample. *J Oral Pathol Med* 2007; **36**: 78–82.

16 Jaber MA, Porter SR, Scully C, Gilthorpe MS, Bedi R. Role of alcohol in non-smokers and tobacco in non-drinkers in the aetiology of oral epithelial dysplasia. *Int J Cancer* 1998; **77**: 333–6.

17 Jaber MA, Porter SR, Gilthorpe MS, Bedi R, Scully C. Risk factors for oral epithelial dysplasia: the role of smoking and alcohol. *Oral Oncol* 1999; **35**: 151–6.

18 Shiu MN, Chen TH, Chang SH, Hahn LJ. Risk factors for leukoplakia and malignant transformation to oral carcinoma: a leukoplakia cohort in Taiwan. *Br J Cancer* 2000; **82**: 1871–4.

19 Hashibe M, Sankaranarayanan R, Thomas G *et al*. Alcohol drinking, body mass index and the risk of oral leukoplakia in an Indian population. *Int J Cancer* 2000; **88**: 129–34.

20 Larsson A, Axell T, Andersson G. Reversibility of snuff dippers' lesion in Swedish moist snuff users: a clinical and histologic follow-up study. *J Oral Pathol Med* 1991; **20**: 258–64.

21 Kaugars GE, Riley WT, Brandt RB *et al*. The prevalence of oral lesions in smokeless tobacco users and an evaluation of risk factors. *Cancer* 1992; **70**: 2579–85.

22 Field EA, Field JK, Martin MV. Does *Candida* have a role in oral epithelial neoplasia. *J Med Vet Mycol* 1989; **27**: 277–94.

23 Krogh P. The role of yeasts in oral cancer by means of endogenous nitrosation. *Acta Odontol Scand* 1990; **48**: 85–8.

24 Shiu MN, Chen TH. Impact of betel quid, tobacco and alcohol on three-stage disease natural history of oral leukoplakia and cancer: implication for prevention of oral cancer. *Eur J Cancer Prev* 2004; **13**: 39–45.

25 Fisher MA, Bouquet JE, Shelton BJ. Assessment of risk factors for oral leukoplakia in West Virginia. *Community Dent Oral Epidemiol* 2005; **33**: 45–52.

26 Chang CH, Yang TH, Wang TY, Shieh TY, Warnakulasuriya S. Oral precancerous disorders associated with areca quid chewing, smoking, and alcohol drinking in southern Taiwan. *J Oral Pathol Med* 2005; **34**: 460–6.

27 Majumdar M, Sikdar N, Paul RR, Roy B. Increased risk of oral leukoplakia and cancer among mixed tobacco users carrying XRCC1 variant haplotypes and cancer among smokers carrying two risk genotypes: one on each of two loci, GSTM3 and XRCC1 (Codon 280). *Cancer Epidemiol Biomarkers Prev* 2005; **14**: 2106–12.

28 Chen PC, Pan CC, Quo C, Lin CP. Risk of oral nonmalignant lesions associated with human papillomavirus infection, betel quid chewing, and cigarette smoking in Taiwan: an integrated molecular and epidemiologic study. *Arch Pathol Lab Med* 2006; **130**: 57–61.

29 Poate TW, Warnakulasuriya S. Effective management of smoking in an oral dysplasia clinic in London. *Oral Dis* 2006; **12**: 22–6.

30 Thavarajah R, Rao A, Raman U *et al*. Oral lesions of 500 habitual psychoactive substance users in Chennai, India. *Arch Oral Biol* 2006; **51**: 512–9.

31 Petti S, Scully C. Association between different alcoholic beverages and leukoplakia among non- to moderate-drinking adults: a matched case–control study. *Eur J Cancer* 2006; **42**: 521–7.

32 Lumerman H, Freedman P, Kerpel S. Oral epithelial dysplasia and the development of invasive squamous cell carcinoma. *Oral Surg Oral Med Oral Pathol* 1995; **79**: 321–9.

33 Holmstrup P, Vedtofte P, Reibel J, Stoltze K. Long-term treatment outcome of oral premalignant lesions. *Oral Oncol* 2006; **42**: 461–74.

34 Garijo MF, Val D, Val-Bernal JF. Pagetoid dyskeratosis of the lips. *Am J Dermatopathol* 2001; **23**: 329–33.

35 Abbey LM, Kaugars GE, Gunsolley JC *et al*. Interexaminer and intraexaminer reliability in the diagnosis of oral epithelial dysplasia. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1995; **80**: 188–91.

36 Karabulut A, Reibel J, Therkildsen MH *et al*. Observer variability in the histologic assessment of oral premalignant lesions. *J Oral Pathol Med* 1995; **24**: 198–200.

37 Brothwell DJ, Lewis DW, Bradley G *et al*. Observer agreement in the grading of oral epithelial dysplasia. *Community Dent Oral Epidemiol* 2003; **31**: 300–5.

38 Fischer DJ, Epsein JB, Morton TH, Schwartz SM. Interobserver reliability in the histopathologic diagnosis of oral pre-malignant and malignant lesions. *J Oral Pathol Med* 2004; **33**: 65–70.

39 Kujan O, Oliver RJ, Khattab A *et al*. Evaluation of a new binary system of grading oral epithelial dysplasia for prediction of malignant transformation. *Oral Oncol* 2006; **42**: 987–93.

40 Scully C, Burkhardt A. Tissue markers of potentially malignant oral epithelial lesions. *J Oral Pathol Med* 1993; **22**: 246–56.
41 Seoane JM, Varela-Centelles PI, Ramirez JR *et al*. Heat shock proteins (HSP70 and HSP27) as markers of epithelial dysplasia in oral leukoplakia. *Am J Dermatopathol* 2006; **28**: 417–22.
42 Takeda T, Sugihara K, Hirayama Y *et al*. Immunohistological evaluation of Ki-67, p63, CK19 and p53 expression in oral epithelial dysplasias. *J Oral Pathol Med* 2006; **35**: 369–75.
43 Brennan M, Miglatori CA, Lockhart PB *et al*. Management of oral epithelial dysplasia: a review. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; **103** (Suppl.): S19.e1–12.
44 Saito T, Yamashita T, Notani K *et al.* Flow cytometric analysis of nuclear DNA content in oral leukoplakia: relation to clinicopathologic findings. *Int J Oral Maxillofac Surg* 1995; **24**: 44–7.
45 Lee JJ, Hong WK, Hittelman WN *et al*. Predicting cancer development in oral leukoplakia: ten years of translational research. *Clin Cancer Res* 2000; **6**: 1702–10.
46 Lippman SM, Hong WK. Molecular markers of the risk of oral cancer. *N Engl J Med* 2001; **344**: 1323–6.
47 Mao L. Can molecular assessment improve classification of head and neck premalignancy? *Clin Cancer Res* 2000; **6**: 321–2.
48 Kim J, Shin DM, El-Naggar A *et al.* Chromosome polysomy and histological characteristics in oral premalignant lesions. *Cancer Epidemiol* 2001; **10**: 319–25.
49 Sudbo J, Kildal W, Risberg B *et al*. DNA content as a prognostic marker in patients with oral leukoplakia. *N Engl J Med* 2001; **344**: 1270–8.
50 Zhang L, Cheung KJ, Lam WL *et al.* Increased genetic damage in oral leukoplakia from high risk sites. *Cancer* 2001; **91**: 2148–55.
51 Poh CF, Zhang L, Lam WL *et al*. A high frequency of allelic loss in oral verrucous lesions may explain malignant risk. *Lab Invest* 2001; **81**: 629–34.
52 Jordan RC, Macabeo-Ong M, Shiboski CH *et al*. Overexpression of matrix metalloproteinase-1 and -9 mRNA is associated with progression of oral dysplasia to cancer. *Clin Cancer Res* 2004; **10**: 6460–5.
53 Bortoluzzi MC, Yurgel LS, Dekker NP, Jordan RC, Regezi JA. Assessment of p63 expression in oral squamous cell carcinomas and dysplasias. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2004; **98**: 698–704.
54 Lippman SM, Sudbo J, Hong WK. Oral cancer prevention and the evolution of molecular-targeted drug development. *J Clin Oncol* 2005; **23**: 346–56.
55 Lodi G, Sardella A, Bez C, Demarosi F, Carrassi A. Interventions for treating oral leukoplakia (Cochrane Review). In: *The Cochrane Library, Issue 1*. Oxford: Update Software, 2002.
56 Lodi G, Sardella A, Bez C, Demarosi F, Carrassi A. Interventions for treating oral leukoplakia. *Cochrane Database Syst Rev* 2006 (4): CD001829.
57 Alexander RE, Wright JM, Thiebaud S. Evaluating, documenting and following up oral pathological conditions. A suggested protocol. *J Am Dent Assoc* 2001; **132**: 329–35.
58 Tradati N, Grigolat R, Calabrese L *et al.* Oral leukoplakias: to treat or not? *Oral Oncol* 1997; **33**: 317–22.
59 Schoelch ML, Sekandari N, Regezi JA, Silverman S Jr. Laser management of oral leukoplakias: a follow-up study of 70 patients. *Laryngoscope* 1999; **109**: 949–53.
60 Gooris PJ, Roodenburg JL, Vermey A, Nauta JM. Carbon dioxide laser evaporation of leukoplakia of the lower lip: a retrospective evaluation. *Oral Oncol* 1999; **35**: 490–5.
61 Pandey M, Thomas G, Somanathan T *et al.* Evaluation of surgical excision of non-homogeneous oral leukoplakia in a screening intervention trial, Kerala, India. *Oral Oncol* 2001; **37**: 103–9.
62 Thomson PJ, Wylie J. Interventional laser surgery: an effective surgical and diagnostic tool in oral precancer management. *Int J Oral Maxillofac Surg* 2002; **31**: 145–53.
63 Ishii J, Fujita K, Munemoto S, Komori T. Management of oral leukoplakia by laser surgery: relation between recurrence and malignant transformation and clinicopathological features. *J Clin Laser Med Surg* 2004; **22**: 27–33.
64 Meltzer C. Surgical management of oral and mucosal dysplasias: The case for laser excision. *J Oral Maxillofac Surg* 2007; **65**: 293–5.
65 Lippman SM. Head and neck chemoprevention: recent advances. *Cancer Control* 1997; **4**: 128–35.
66 Sudbo J, Byrne M, Mao L *et al*. Molecular based treatment of oral cancer. *Oral Oncol* 2003; **39**: 749–58.
67 Armstrong WB, Wan XS, Kennedy AR, Taylor TH, Meyskens FL Jr. Development of the Bowman-Birk inhibitor for oral cancer chemoprevention and analysis of Neu immunohistochemical staining intensity with Bowman-Birk inhibitor concentrate treatment. *Laryngoscope* 2003; **113**: 1687–702.
68 Halder A, Raychowdhury R, Ghosh A, De M. Black tea (Camellia sinensis) as a chemopreventive agent in oral precancerous lesions. *J Environ Pathol Toxicol Oncol* 2005; **24**: 141–4.
69 Lele S. Although leukoplakia responds to some treatments relapses and adverse effects are common. *Evid Based Dent* 2005; **6**: 15–16.
70 Leunig A, Betz CS, Baumgartner R, Grevers G, Issing WJ. Initial experience in the treatment of oral leukoplakia with high-dose vitamin A and follow-up 5-aminolevulinic acid induced protoporphyrin IX fluorescence. *Eur Arch Otorhinolaryngol* 2000; **257**: 327–31.
71 Scardina GA, Carini F, Maresi A, Valenza V, Messina P. Evaluation of the clinical and histological effectiveness of isotretinoin in the therapy of oral leukoplakia: ten years of experience: is management still up to date and effective? *Methods Find Exp Clin Pharmacol* 2006; **28**: 115–9.
72 Femiano F, Gombos F, Scully C. Oral proliferative verrucous leukoplakia: open trial of surgery compared with combined therapy using surgery and methisoprinol. *Int J Oral Maxillofac Surg* 2001; **30**: 318–22.
73 Femiano F, Gombos F, Scully C *et al*. Oral leukoplakia: open trial of topical therapy with calcipotriol compared with tretinoin. *Int J Oral Maxillofac Surg* 2001; **30**: 402–6.
74 Malmstrom M, Hietanen J, Sane J *et al*. Topical treatment of oral leucoplakia with bleomycin. *Br J Oral Surg* 1988; **26**: 491–8.
75 Scully C. Oral precancer: preventive and medical approaches to management. *Oral Oncol* 1995; **31B**: 16–26.

Actinic cheilitis

See p. 69.123.

Hairy leukoplakia

Aetiology. Hairy leukoplakia (HL) is seen in severe immune defects, especially HIV/AIDS, and occasionally in the apparently immunocompetent [1–6]. HIV is not found within the genome of epithelial cells in HL and it is more likely that the features are a consequence of an opportunistic infection with EBV. It is now clear that normal human oral mucosa from HIV-negative and HIV-positive individuals may contain latent EBV [7–10]. A decreased frequency of HIV-related oral manifestations including oral hairy leukoplakia has been associated with the introduction of HAART [5].

EBV has been shown to be present in HL, especially in the upper layers of the epithelium. The oral site of predilection for HL appears to relate to the presence of EBV receptors only on the parakeratinized mucosae such as the lateral margin of the tongue. HL regresses on treatment with antivirals but fails to resolve with antifungals, despite the frequent presence of *Candida* species.

Pathology. Histological features of HL include hyperparakeratosis, hyperplasia and ballooning of prickle cells, few or absent Langerhans' cells, and only a sparse inflammatory cell infiltrate in the lamina propria.

Clinical features. HL is a white patch, usually seen on the parakeratinized mucosa of the tongue, frequently bilaterally (Fig. 69.58). The lesions are corrugated or have a shaggy or hairy appearance, are mostly symptomless and, unlike some oral keratoses, have no known premalignant potential [1,4,10,11]. The majority of the affected patients who are HIV positive appear



Fig. 69.58 Hairy leukoplakia. Found mainly in HIV infection, vertical white ridges on the lateral margin of the tongue.

eventually to develop AIDS. HL also occurs in HIV-negative persons [6,12–19].

Diagnosis. Some of the histological features typical of HL, especially the hyperparakeratosis, can be seen in oral white lesions other than HL in HIV-infected persons [20]. Not only are there oral lesions that mimic HL in HIV infection, but lesions similar to HL can be seen in other immunocompromised persons and even in some apparently healthy individuals. However, most cases can be distinguished from the HL of HIV infection by the absence of EBV DNA on histology and, of course, by presence of HIV serum antibody.

Treatment. HL really needs no treatment but in HIV/AIDS antiretroviral agents, aciclovir or ganciclovir may cause resolution.

References

1 Schiodt M, Greenspan D, Daniels TE *et al.* Clinical and histologic spectrum of oral hairy leucoplakia. *Oral Surg* 1987; **64**: 716–20.
2 Scully C, Laskaris G, Pindborg J *et al.* Oral manifestations of HIV infection and their management. *Oral Surg* 1991; **71**: 158–66, 167–71.
3 Dias EP, Israel MS, Silva Junior A *et al.* Prevalence of oral hairy leukoplakia in 120 pediatric patients infected with HIV-1. *Braz Oral Res* 2006; **20**: 103–7.
4 Sharma G, Pai KM, Suhas S. Oral manifestations in HIV/AIDS infected patients from India. *Oral Dis* 2006; **12**: 537–42.
5 Hodgson TA, Greenspan D, Greenspan JS. Oral lesions of HIV disease and HAART in industrialized countries. *Adv Dent Res* 2006; **19**: 57–62.
6 Milagres A, Dias EP, Tavares Ddos S. Prevalence of oral hairy leukoplakia and epithelial infection by Epstein–Barr virus in pregnant women and diabetes mellitus patients: cytopathologic and molecular study. *Mem Inst Oswaldo Cruz* 2007; **102**: 159–64.
7 Triantos D, Leao JR, Porter SR, Scully C, Teo CG. Tissue distribution of Epstein–Barr virus genotypes in hosts co-infected by HIV. *AIDS* 1998; **12**: 2141–6.
8 Scully C, Porter SR, Di Alberti L, Jalal M, Maitland N. Detection of Epstein–Barr virus in oral scrapes in HIV infection, in hairy leukoplakia, and in healthy non-HIV-infected people. *J Oral Pathol Med* 1998; **27**: 480–2.
9 Komatsu TL, Rivero ER, Gallotini de Magallhaes MH, Nunes FD. Epstein–Barr virus in oral hairy leukoplakia scrapes: identification by PCR. *Pesqui Odontol Bras* 2005; **19**: 317–21.
10 Walling DM, Flaitz CM, Nichols CM. Epstein–Barr virus replication in oral hairy leukoplakia: response, persistence, and resistance to treatment with valacyclovir. *J Infect Dis* 2003; **188**: 883–90.
11 Shiboski CH, Neuhaus JM, Greenspan D, Greenspan JS. Effect of receptive oral sex and smoking on the incidence of hairy leukoplakia in HIV-positive gay men. *J Acquir Immune Defic Syndr* 1999; **21**: 236–42.
12 King GN, Healy CM, Glover T *et al.* Prevalence and risk factors associated with leukoplakia, hairy leukoplakia, erythematous candidosis and gingival hyperplasia in renal transplant recipients. *Oral Surg* 1994; **78**: 718–21.
13 Euvrard S, Kanitakis J, Puteil-Nobel C *et al.* Pseudo-oral hairy leukoplakia in a renal allograft recipient. *J Am Acad Dermatol* 1994; **30**: 300–3.
14 Itin P, Rufli T, Rudlinger R *et al.* Oral hairy leukoplakia in an HIV-negative renal transplant patient: a marker for immunosuppression? *Dermatologica* 1988; **177**: 126–8.
15 Syrjanen S, Laine P, Happonen R *et al.* Oral hairy leukoplakia is not a specific sign of HIV-infection but related to immunodepression in general. *J Oral Pathol Med* 1989; **18**: 28–31.
16 Greenspan D, Greenspan JS, De Souza YG *et al.* Oral hairy leukoplakia in an HIV-negative renal transplant recipient. *J Oral Pathol Med* 1989; **18**: 32–4.
17 Kanitakis J, Euvrard S, Lefrancois N *et al.* Oral hairy leukoplakia in a HIV-negative renal graft recipient. *Br J Dermatol* 1991; **124**: 483–6.
18 Eisenberg E, Krutchkoff D, Yamase H. Incidental oral hairy leukoplakia in immunocompetent persons. *Oral Surg Oral Med Oral Pathol* 1992; **74**: 563–6.
19 De la Rossa Garcia E, Mondragon-Padilla A, Irigoyen-Camacho ME, Bustamante-Ramirez MA. Oral lesions in a group of kidney transplant patients. *Med Oral Patol Oral Cir Bucal* 2005; **10**: 196–204.
20 Green TL, Greenspan JS, Greenspan D *et al.* Oral lesions mimicking hairy leukoplakia: a diagnostic dilemma. *Oral Surg Oral Med Oral Pathol* 1989; **67**: 422–6.

Psoriasis (see Chapter 20)

The oral mucosa appears to be rarely involved in psoriasis, with less than 100 cases reported, although there are occasionally lip lesions or white oral lesions, especially in the buccal mucosa, or lesions clinically indistinguishable from geographical tongue (sometimes termed 'annulus migrans' or 'erythema circinatum'), particularly in generalized pustular psoriasis [1–15].

References

1 Heitanen J, Salo OP, Kanerva L *et al.* Study of the oral mucosa in 250 consecutive patients with psoriasis. *Scand J Dent Res* 1984; **92**: 50–4.
2 O'Keefe E, Braverman IM, Cohen T. Annulus migrans: identical lesions in pustular psoriasis, Reiter's syndrome, and geographic tongue. *Arch Dermatol* 1973; **107**: 240–4.
3 Morris LF, Phillips CM, Binnie WH *et al.* Oral lesions in patients with psoriasis: a controlled study. *Cutis* 1992; **49**: 339–44.
4 Pogrel MA, Cram D. Intraoral findings in patients with psoriasis with a special reference to ectopic geographic tongue. *Oral Surg* 1988; **66**: 184–9.
5 Wagner G, Luckasen J, Goltz R. Mucous membrane involvement in generalised pustular psoriasis. *Arch Dermatol* 1976; **112**: 1010–4.
6 White DK, Leis HJ, Miller AS. Intraoral psoriasis associated with widespread dermal psoriasis. *Oral Surg* 1976; **41**: 174–81.
7 Zhu JF, Kaminski MJ, Pulitzer DR, Hu J, Thomas HF. Psoriasis: pathophysiology and oral manifestations. *Oral Dis* 1996; **2**: 135–44.
8 Younai FS, Phelan JA. Oral mucositis with features of psoriasis: report of a case and review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1997; **84**: 61–7.
9 Kaur I, Handa S, Kumar B. Oral lesions in psoriasis. *Int J Dermatol* 1997; **36**: 78–9.
10 Brice DM, Danesh-Meyer MJ. Oral lesions in patients with psoriasis: clinical presentation and management. *J Periodontol* 2000; **71**: 1896–1903.
11 Richardson LJ, Kratochvil FJ, Zieper MB. Unusual palatal presentation of oral psoriasis. *J Can Dent Assoc* 2000; **66**: 80–2.
12 Tosti A, Misciali C, Cameli N, Vincenzi C. Guess what! Psoriasis of the lips. *Eur J Dermatol* 2001; **11**: 589–90.
13 Bruce AJ, Rogers RS 3rd. Oral psoriasis. *Dermatol Clin* 2003; **21**: 99–104.
14 Migliari DA, Penha SS, Marques MM, Matthews RW. Considerations on the diagnosis of oral psoriasis: a case report. *Med Oral* 2004; **9**: 300–3.
15 Daneshpazhooh M, Moslehi H, Akhyani M, Etesmi M. Tongue lesions in psoriasis: a controlled study. *BMC Dermatol* 2004; **4**: 16.

Koplik's spots (see Chapter 33)
White specks may be seen in the buccal mucosa in early measles.

Pigmented lesions

Congenital lesions are described on p. 69.26. The tongue is often discoloured due to superficial staining from foods, drinks or habits such as tobacco or betel use. Localized hyperpigmented lesions are usually due to pigmentary incontinence, amalgam tattoos, melanotic macule or naevi, although melanomas, Kaposi's sarcoma and epithelioid angiomatosis must be excluded. Generalized oral mucosal hyperpigmentation is usually racial in origin and only occasionally has a systemic cause, such as Addison's disease.

Furred, brown and black hairy tongue

Aetiology and pathology. Children rarely have a furred tongue in health but it may be coated with off-white debris in febrile and other illnesses.

Adults, however, not infrequently have a coating on the tongue in health, particularly if they are edentulous, are on a soft non-abrasive diet, have poor oral hygiene or are fasting. The coating appears more obvious in xerostomic and in ill patients, especially those who cannot maintain oral hygiene.

The coating in most cases consists of epithelial, food and microbial debris; indeed, the tongue is the main oral reservoir of some microorganisms, such as *Candida albicans* and viridans streptococci. The filiform papillae are excessively long and stained by the accumulation of squames and chromogenic microorganisms.

Habits such as tobacco and betel use, and various medicaments such as chlorhexidine or iron, can cause a black or brown superficial staining of the tongue (and teeth).

Occasionally, a brown hairy tongue may be caused by drugs that induce xerostomia, lansoprazole or antimicrobial therapy, when it may be related to overgrowth of microorganisms such as *Candida* species and may respond to withdrawal of the drug [1–5].

Clinical features. Black hairy tongue affects mainly the posterior part of the dorsum of the tongue, especially centrally (Fig. 69.59) [3–7].

Treatment. Patients with black hairy tongue may find the condition improves if they avoid habits or drugs that stain the tongue, increase their standard of oral hygiene, brush the tongue with a hard toothbrush, use sodium bicarbonate mouthwashes, chew gum or suck a peach stone. Topical tretinoin may be effective [8].

References

1 Heymann WR. Psychotropic agent-induced black hairy tongue. *Cutis* 2000; **66**: 25–6.
2 Scully C. Discoloured tongue: a new cause? *Br J Dermatol* 2001; **144**: 1293–4.
3 Taybos G. Oral changes associated with tobacco use. *Am J Med Sci* 2003; **326**: 179–82.
4 Yuca K, Calka O, Kiroglu AF, Akdeniz N, Cankaya H. Hairy tongue: a case report. *Acta Otorhinolaryngol Belg* 2004; **58**: 161–3.

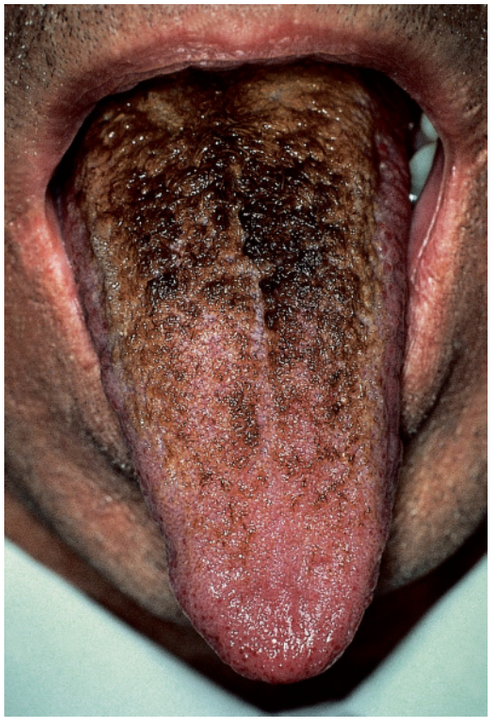


Fig. 69.59 Black hairy tongue.

5 Tamm L, Annagur BB. Black hairy tongue associated with olanzapine treatment: a case report. *Mt Sinai J Med* 2006; **73**: 891–4.
6 Winer LH. Black hairy tongue. *Arch Dermatol* 1958; **77**: 97–103.
7 Boni R. What is your diagnosis? Hairy tongue (lingua villosa nigra). *Schweiz Rundsch Med Prax* 2000; **89**: 1543–4.
8 Langtry JAA, Carr MM, Steele MC, Ive FA. Topical tretinoin: a new treatment for black hairy tongue (lingua villosa nigra). *Clin Exp Dermatol* 1992; **17**: 163–4.

Pigmentary incontinence [1,2]

Melanin pigment ingested by macrophages in the upper lamina propria (pigmentary incontinence) may give rise to hyperpigmentation in LP, especially in dark-skinned people [1].

References

1 Cawson RA, Binnie WH, Eveson JW. *Colour Atlas of Oral Disease: Clinical and Pathologic Correlations*. London: Heinemann, 1994: 1515.
2 Ayoub N, Barete S, Bouaziz JD, Le Pelletier F, Frances C. Additional conjunctival and penile pigmentation in Laugier-Hunziker syndrome: a report of two cases. *Int J Dermatol* 2004; **43**: 571–4.

Tattoos

Amalgam tattoos are common causes of blue–black pigmentation, usually seen in the mandibular gingiva or at least close to the teeth (Fig. 69.60), or in the scar of an apicectomy where there has been a retrograde root-filling with amalgam used as root-end filling material [1–6]. The amalgam associates with elastin fibres [7]. Radio-opacities may or may not be seen on radiography. Similar lesions can result if, for some reason, pencil lead or other similar foreign bodies become embedded in the oral tissues [8,9].

Radiography may help to confirm the diagnosis. Biopsy may be indicated to exclude a melanoma but otherwise these innocuous lesions require no treatment.



Fig. 69.60 Amalgam tattoo in a common site. This was presumably related to filling of the deciduous predecessor.

Deliberate tattooing is a rare cause of oral pigmentation [10,11].

References

1 Buchner A, Hansen LS. Amalgam pigmentation (amalgam tattoo) of the oral mucosa: a clinicopathological study of 268 cases. *Oral Surg* 1980; **49**: 139–47.
2 Dummett CO. Pertinent considerations in oral pigmentation. *Br Dent J* 1985; **158**: 9–12.
3 Owens BM, Johnson WW, Schuman NJ. Oral amalgam pigmentations (tattoos): a retrospective study. *Quintessence Int* 1992; **23**: 805–10.
4 Cawson RA, Binnie WH, Barrett AW, Wright JM. *Oral Disease*, 3rd edn. Mosby, 2001: 1515.
5 Shah G, Alster TS. Treatment of an amalgam tattoo with a Q-switched alexandrite (755 nm) laser. *Dermatol Surg* 2002; **28**: 1180–1.
6 Terezhalmy GT. Clinical images in oral medicine. Amalgam tattoos. *Quintessence Int* 2006; **37**: 152–3.
7 Mohr W, Gorz E. Association of silver granules with elastic fibers in amalgam reaction of mouth mucosa. *HNO* 2001; **49**: 454–7.
8 Peters E, Gardner DG. A method of distinguishing between amalgam and graphite in tissue. *Oral Surg* 1986; **62**: 73–6.
9 Phillips GE, John V. Use of a subepithelial connective tissue graft to treat an area pigmented with graphite. *J Periodontol* 2005; **76**: 1572–5.
10 Schawaf M. Gingival tattoo: an unusual gingival pigmentation. *J Oral Med* 1986; **41**: 130–3.
11 Telang GH, Ditre CM. Blue gingiva, an unusual oral pigmentation resulting from gingival tattoo. *J Am Acad Dermatol* 1994; **30**: 125–6.

Body art

Tattooing of the lower lip may occasionally be seen. A tattooed lower lip in a Sudanese woman, for example, signifies that she is married [1]. The Wodaabe people of Nigeria and Cameroon may tattoo on the skin surface at the angle of the mouth, a practice which has its basis in ritual warding-off of the 'evil eye'. Similar tattoos may be seen on Bedouin women of North Africa. The vermilion may be tattooed red in some people in the Western countries. Tattooing of the chin is seen increasingly in Maoris ('Moki') and tattooing inside the lip may now be seen in resource-rich countries. Mathur and Sahoo [2] reported an instance of fatal septicaemia following the placement of tribal tattoo marks at the angle of the mouth in a Nigerian infant.

The practice of piercing oral and facial soft tissues and then placing foreign objects in the defects on a more or less permanent basis is one which has also been largely confined, until recently, to certain tribal groups in continental Africa and isolated Amazon regions of South America, for example the Suia and Txukahameis tribes of Brazil. This practice is now not uncommon in resource-rich countries [3–6]. Complications secondary to oral and facial piercings include pain, bleeding, dental fractures and gingival damage [3].



Fig. 69.61 Betel staining of teeth.

References

1 Wilson DF, Grappin G, Miquel JL. Traditional, cultural, and ritual practices involving the teeth and orofacial soft tissues. In: Prabhu SR, Wilson DS, Daftary DK, Johnson NW, eds. *Oral Diseases in the Tropics*. Oxford: Oxford University Press, 1992: 91–124.
2 Mathur DR, Sahoo A. *Pseudomonas* septicaemia following tribal tattoo marks. *Trop Geogr Med* 1984; **36**: 301–2.
3 Lopez-Jornet P, Navarro-Guardiola C, Camacho-Alonso F, Vinvente-Ortego V, Yanez-gascon J. Oral and facial piercings: a case series and review of the literature. *Int J Dermatol* 2006; **45**: 805–9.
4 Kapferer I, Benesch T, Gregoric N, Ulm C, Hienz SA. Lip piercing: prevalence of associated gingival recession and contributing factors. A cross-sectional study. *J Periodontal Res* 2007; **42**: 177–83.
5 Maheu-Robert LF, Andrian E, Grenier D. Overview of complications secondary to tongue and lip piercings. *J Can Dent Assoc* 2007; **73**: 327–31.
6 Palacios-Sanchez B, Cerero-Lapiedro R, Esparza-Gomez G. Oral piercing: dental considerations and the legal situation in Spain. *Int Dent J* 2007; **57**: 60–4.

Food, habits, heavy metal and drug-induced hyperpigmentation

Causes (see Table 69.11) [1–4] can include:

- Foods and beverages (such as beetroot, red wine, coffee and tea).
- Confectionery (such as liquorice).
- Smoking tobacco—a fairly common cause (smoker's melanosis) and this may produce extrinsic discoloration but also intrinsic pigmentary incontinence, with pigment cells increasing and appearing in the lamina propria. This is especially likely in persons who smoke with the lighted end of the cigarette within the mouth (reverse smoking), as practised mainly in some Asian communities [5–7].
- Chewing betel may cause superficial brownish-red discoloration, mainly in the buccal mucosa (and on the teeth), with an irregular epithelial surface that has a tendency to desquamate, seen mainly in women from South and South-East Asia [8,9] (Fig.69.61). The epithelium in betel chewer's mucosa is often

hyperplastic, and brownish amorphous material from the betel quid may be seen on the epithelial surface and intracellularly and intercellularly, with ballooning of epithelial cells [8]. Betel chewer's mucosa is not known to be precancerous but betel use predisposes to submucous fibrosis and squamous cell carcinoma.

- Drugs such as chlorhexidine, iron salts, griseofulvin, crack cocaine, minocycline, bismuth subsalicylate, lansoprazole, and hormone replacement therapy. Drugs that cause intrinsic staining include the following [10–23]:
  - — Antimalarials produce a variety of colours in the mucosa, ranging from yellow with mepacrine to blue–black with amodiaquine.
  - — Minocycline may cause blackish discoloration of teeth, gingivae and bone, skin, sclera and even breast milk. Minocycline can, in a minority of patients, produce blue–grey gingival pigmentation caused by staining of the underlying bone, and some intrinsic faint bluish-grey staining, mainly near the anterior teeth.
  - — Busulphan, some other cytotoxic drugs, oral contraceptives, phenothiazines and anticonvulsants may also occasionally produce, or increase, brown pigmentation. Adrenocorticotrophic hormone (ACTH) therapy may also produce brown pigmentation, as may zidovudine and clofazimine.
  - — Gold may produce purplish gingival discoloration. Many of the heavy metals formerly implicated in producing oral hyperpigmentation (such as mercury, lead and bismuth) are not used therapeutically now, although industrial or accidental exposure is still occasionally seen [24]. Metallic sulphides deposited in the tissues were seen especially where oral hygiene was poor, with bacteria producing sulphides that resulted in pigmentation at the gingival margin (e.g. lead line).

Treatment. Some drug-induced hyperpigmentation resolves on cessation of exposure to the drug and improved oral hygiene, although resolution can take months or years.

References

1 Seoane Leston JM, Vazquez Garcia J, Aguado Santos A, Varela-Centelles PI, Romero MA. Dark oral lesions: differential diagnosis with oral melanoma. *Cutis* 1998; **61**: 279–82.
2 Lenane P, Powell FC. Oral pigmentation. *J Eur Acad Dermatol Venereol* 2000; **14**: 448–65.
3 Eisen D. Disorders of pigmentation in the oral cavity. *Clin Dermatol* 2000; **18**: 579–87.
4 Dereure O. Drug-induced skin pigmentation. Epidemiology, diagnosis and treatment. *Am J Clin Dermatol* 2001; **2**: 253–62.
5 Axell A, Hedin A. Epidemiologic study of excessive oral melanin pigmentation with special reference to the influence of tobacco habits. *Scand J Dent Res* 1982; **90**: 432–42.
6 Mercado-Ortiz G, Wilson D, Jiang DJ. Reverse smoking and palatal mucosal changes in Filipino women. Epidemiological features. *Aust Dent J* 1996; **41**: 300–3.
7 Ortiz GM, Pierce AM, Wilson DF. Palatal changes associated with reverse smoking in Filipino women. *Oral Dis* 1996; **2**: 232–7.
8 Reichart PA, Phillipsen HP. Betel chewer's mucosa: a review. *J Oral Pathol Med* 1998; **27**: 239–42.
9 Yoganathan P. Betel chewing creeps into the New World. *N Z Dent J* 2002; **98**: 40–5.
10 Birek C, Main JHP. Two cases of oral pigmentation associated with quinidine therapy. *Oral Surg* 1988; **66**: 59–61.
11 Hertz RS, Beckstead PC, Brown WJ. Epithelial melanosis possibly resulting from the use of oral contraceptives. *J Am Dent Assoc* 1980; **100**: 713–4.
12 Berger RS, Mandel EB, Hayes TJ *et al.* Minocycline staining of the oral cavity. *J Am Acad Dermatol* 1989; **21**: 1300–1.
13 Siller GM, Tod MA, Savage NW. Minocycline-induced oral pigmentation. *J Am Acad Dermatol* 1994; **30**: 350–4.
14 Patel K, Cheshire D, Vance A. Oral and systemic effects of prolonged minocycline therapy. *Br Dent J* 1998; **185**: 560–2.
15 Ozog DM, Gogstetter DS, Scott G, Gaspari AA. Minocycline-induced hyperpigmentation in patients with pemphigus and pemphigoid. *Arch Dermatol* 2000; **136**: 1133–8.
16 Cheek CC, Heymann HO. Dental and oral discolorations associated with minocycline and other tetracycline analogs. *J Esthetic Dent* 1999; **11**: 43–8.
17 Scully C. Drug induced oral mucosal hyperpigmentation. *Prim Dent Care* 1997; **4**: 35–6.
18 Scully C. Discoloured tongue: a new cause? *Br J Dermatol* 2001; **144**: 1293–4.
19 Abdollahi M, Radfar M. A review of drug-induced oral reactions. *J Contemp Dent Pract* 2003; **4**: 10–31.
20 Treister NS, Magalnick D, Woo SB. Oral mucosal pigmentation secondary to minocycline therapy: report of two cases and a review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2004; **97**: 718–25.
21 Sanchez AR, Rogers RS 3rd, Sheridan PJ. Tetracycline and other tetracycline-derivative staining of the teeth and oral cavity. *Int J Dermatol* 2004; **43**: 709–15.
22 Martin TJ, Sharp I. Oral mucosal pigmentation secondary to treatment with mepacrine, with sparing of the denture bearing area. *Br J Oral Maxillofac Surg* 2004; **42**: 351–3.
23 LaPorta VN, Nikitakis NG, Sindler AJ, Reynolds MA. Minocycline-associated intra-oral soft-tissue pigmentation: clinicopathologic correlations and review. *J Clin Periodontol* 2005; **32**: 119–22.
24 Lockhart PB. Gingival pigmentation as the sole presenting sign of chronic lead poisoning in a mentally retarded adult. *Oral Surg* 1981; **52**: 143–9.

ACTH-induced hyperpigmentation

Oral hyperpigmentation may be seen in ACTH therapy, Addison's disease, Nelson's syndrome or ectopic ACTH production (e.g. by bronchogenic carcinoma). The brown or black pigmentation is variable in distribution but is seen typically on the soft palate, buccal mucosa and at sites of trauma [1–7].

References

1 Scully C. Drug-induced oral mucosal hyperpigmentation. *Prim Dent Care* 1997; **4**: 35–6.
2 Chuong R, Goldberg MH. Case 47, part II: oral hyperpigmentation associated with Addison's disease. *J Oral Maxillofac Surg* 1983; **41**: 680–2.
3 Zain RB, Ling KC. Oral and laryngeal histoplasmosis in a patient with Addison's disease. *Ann Dent* 1988; **47**: 31–3.
4 Kim HW. Generalized oral and cutaneous hyperpigmentation in Addison's disease. *Odontostomatol Trop* 1988; **11**: 87–90.
5 Lamey PJ, Carmichael F, Scully C. Oral pigmentation, Addison's disease and results of screening. *Br Dent J* 1985; **158**: 297–305.
6 Moyer GN, Terezhalmy GT, O'Brien JT. Nelson's syndrome: another condition associated with mucocutaneous hyperpigmentation. *J Oral Med* 1982; **1**: 13–7.
7 Merchant HW, Hayes LE, Ellison LT. Soft palate pigmentation in lung disease, including cancer. *Oral Surg* 1976; **41**: 726–33.

HIV infection

Oral hyperpigmentation may be seen in HIV infection, sometimes related to adrenal hypofunction or drug use [1–5].

References

1 Porter SR, Glover S, Scully C. Oral hyperpigmentation and adrenocortical hypofunction in a patient with AIDS. *Oral Surg Oral Med Oral Pathol* 1990; **67**: 301–2.



Fig. 69.62 Melanotic macule of lower lip.

2 Granel F, Truchetet F, Grandidier M. Diffuse pigmentation (nail, mouth and skin) associated with HIV infection. *Ann Dermatol Vénéréol* 1997; **124**: 460–2.
3 Kumar SN, Sarswathi TR, Ranganthan K. Intra-oral hypermelanosis in an HIV sero-positive patient—a case report. *Indian J Dent Res* 2003; **14**: 131–4.
4 Okoje VN, Obiechina AE, Akenova YA. Orofacial lesions in 126 newly diagnosed HIV/AIDS patients seen at the University College Hospital, Ibadan. *Afr J Med Med Sci* 2006; **35**: 97–101.
5 Sharma G, Pai KM, Suhas S. Oral manifestations in HIV/AIDS infected patients from India. *Oral Dis* 2006; **12**: 537–42.

Oral mucosal melanotic macule, reactive type

Synonyms
- Melanoacanthoma
- Melanoacanthosis

Melanotic macules occasionally appear suddenly as reactive lesions following trauma [1–13]. Melanoacanthoma is a misnomer: most reported cases have been in black people as reactive lesions [4,12,14]. A hyperpigmented symptomless macule appears over a course of days or weeks (Fig.69.62). The course is benign, and some cases resolve spontaneously within 6 months.

Pigment-filled dendritic cells that appear to be melanocytes are found in the stratum malpighii but, in contrast to melanoma, basal layer melanocytes are not increased.

Excision biopsy may be indicated to exclude melanoma.

References

1 Buchner A, Hansen LS. Melanotic macule of the oral mucosa. *Oral Surg* 1979; **48**: 244–9.
2 Lamey PJ, Nolan A, Thomson E *et al.* Oral presentation of the Laugier–Hunziker syndrome. *Br Dent J* 1991; **171**: 59–60.
3 Laugier P, Hunziker N. Pigmentation melanique lenticulaire essentialle de la muquese jugale et des lèvres. *Arch Belg Dermatol Syphilol* 1970; **26**: 391–9.
4 Horlick HP, Wather RR, Zegarelli DJ *et al.* Mucosal melanotic macule, reactive type. A simulation of melanoma. *J Am Acad Dermatol* 1988; **19**: 786–91.
5 Maize JC. Mucosal melanosis. *Dermatol Clin* 1988; **6**: 283–93.
6 Zemtsov A, Bergfeld WF. Oral melanoacanthoma with prominent spongiotic intraepithelial vesicles. *J Cutan Pathol* 1989; **16**: 365–9.
7 Tomich CE, Zunt SL. Melanoacanthosis (melanoacanthoma) of the oral mucosa. *J Dermatol Surg Oncol* 1990; **16**: 231–6.
8 Eisen D, Voorhees JJ. Oral melanoma and other pigmented lesions of the oral cavity. *J Am Acad Dermatol* 1991; **24**: 527–37.
9 Heine BT, Drummond JF, Damm DD, Heine RD 2nd. Bilateral oral melanoacanthoma. *Gen Dent* 1996; **44**: 451–2.
10 Cicek Y, Ertas U. The normal and pathological pigmentation of oral mucous membrane: a review. *J Contemp Dent Pract* 2003; **4**: 76–86.
11 Pais S, Hegde SK, Bhat SS. Oral melanotic macule—a case report. *J Indian Soc Pedod Prev Dent* 2004; **22**: 73–5.
12 Buchner A, Merrell PW, Carpenter WM. Relative frequency of solitary melanocytic lesions of the oral mucosa. *J Oral Pathol Med* 2004; **33**: 550–7.
13 Kahn MA, Weathers DR, Hoffman JG. Transformation of a benign oral pigmentation to primary oral melanoma. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005; **100**: 45–9.
14 Fornatora ML, Reich RF, Haber S, Solomon F, Freedman PD. Oral melanoacanthoma: a report of 10 cases, review of the literature, and immunohistochemical analysis for HMB-45 reactivity. *Am J Dermatopathol* 2003; **25**: 12–5.

Malignant melanoma (see Chapter 54)

Oral malignant melanoma is rare. Most patients are over 50 years of age and there is a male preponderance.

Malignant melanoma may arise in apparently normal oral mucosa or in a pre-existent pigmented naevus, most commonly in the palate or maxillary alveolus [1–10]. Metastatic melanoma is rare [4]. Features suggestive of malignancy include a rapid increase in size, change in colour, ulceration, pain, bleeding, the occurrence of satellite pigmented spots, or regional lymph node enlargement. The prognosis is poor unless detected very early [2,3]. The optimal treatment is surgery [6,8].

The histology may show anaplastic spindle-shaped or squamoid cells. However, the histology is quite varied and staining with dopa or antibodies may be required to help the diagnosis. Most cases are positive for S-100, tyrosinase, and Mart-1/melana-A. Lesions suspected to be malignant melanoma should not be biopsied until the time of definitive surgical excision [11–15].

References

1 Batsakis JG, Regezi JA, Solomon AR *et al.* The pathology of head and neck tumours: mucosal melanomas. *Head Neck Surg* 1982; **4**: 404–18.
2 Eisen D, Voorhees JJ. Oral melanoma and other pigmented lesions of the oral cavity. *J Am Acad Dermatol* 1991; **24**: 527–37.
3 Hoyt DJ, Jordan T, Fisher SR. Mucosal melanoma of the head and neck. *Arch Otolaryngol Head Neck Surg* 1989; **115**: 1096–9.
4 Patton LL, Brahim JS, Baker AR. Metastatic malignant melanoma of the oral cavity. *Oral Surg* 1994; **78**: 51–6.
5 Rapini RP, Golitz LE, Greer RO *et al.* Primary malignant melanoma of the oral cavity. *Cancer* 1985; **55**: 1543–51.
6 Mendenhall WM, Amdur RJ, Hinerman RW *et al*. Head and neck mucosal melanoma. *Am J Clin Oncol* 2005; **28**: 626–30.
7 Athey EM, Sutton DN, Tekeli KM. Malignant mucosal melanoma of the right maxillary sinus: a case report. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006; **102**: e20–2.
8 Penel N, Mallett Y, Mirabel X, Van JT, LeFebvre JL. Primary mucosal melanoma of head and neck: prognostic value of clear margins. *Laryngoscope* 2006; **116**: 993–5.
9 Dass A, Virk RS, Hundal H, Mohan H. Malignant melanoma of the mucous membranes of the head and neck: three case reports. *Ear Nose Throat J* 2006; **85**: 268–70.
10 Chidzonga MM, Mahomva L, Marimo C, Makunike-Mutasa R. Primary malignant melanoma of the oral mucosa. *J Oral Maxillofac Surg* 2007; **65**: 1117–20.
11 Sooknundun M, Kacker SK, Kapila K *et al.* Oral malignant melanoma (a case report and review of the literature). *J Laryngol Otol* 1986; **100**: 371–5.
12 Tanaka N, Mimura M, Ichinose S, Odajima T. Malignant melanoma in the oral region: ultrastructural and immunohistochemical studies. *Med Electron Microsc* 2001; **34**: 198–205.
13 Owens JM, Gomez JA, Byers RM. Malignant melanoma in the palate of a 3-month-old child. *Head Neck* 2002; **24**: 91–4.

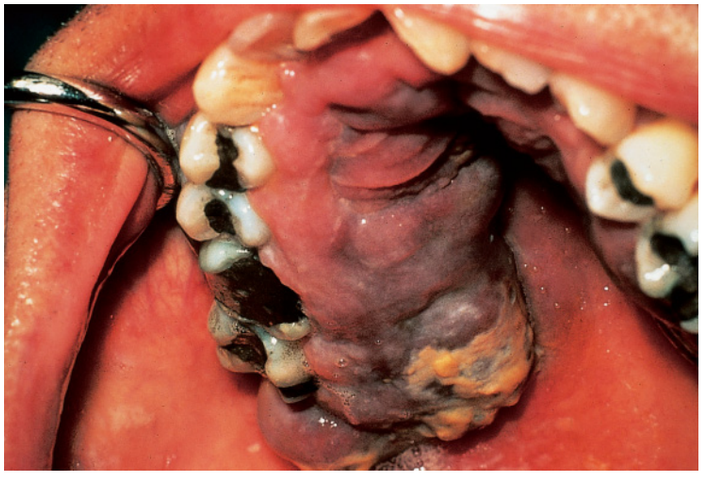


Fig. 69.63 Kaposi's sarcoma in a typical site with a characteristic purplish appearance. (Courtesy of Dr J.B. Epstein, Cancer Control Agency, Vancouver, Canada.)



Fig. 69.64 Oral purpura in thrombocytopenia.

14 Prasad ML, Jungbluth AA, Iversen K, Huvos AG, Busam KJ. Expression of melanocytic differentiation markers in malignant melanomas of the oral and sinonasal mucosa. *Am J Surg Pathol* 2001; **25**: 782–7.
15 Gorsky M, Epstein JB. Melanoma arising from the mucosal surfaces of the head and neck. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1998; **86**: 715–9.

Kaposi's sarcoma (see Chapter 56)

Kaposi's sarcoma (KS) is seen predominantly as a consequence of HIV infection, mainly in men who have sex with men. It appears to be associated with HHV-8 [1–9]. Up to 50% of male homosexual AIDS patients have developed oral KS, although it appears to be declining in frequency and is rare in other HIV-infected patients.

Oral KS is the first presentation of HIV in 20–60% of affected patients, often associated with oral candidosis. KS affects the hard-palate mucosa in particular (Fig. 69.63). Up to 95% of lesions are seen in the palate, 23% in the gingiva and others on the tongue or buccal mucosa. A red-purple macule is the early lesion, progressing to a purple nodular swelling that may be extensive and ulcerated. Multiple lesions are common [3–6]. Lesions are often asymptomatic but more than 25% are painful and about 8% bleed. Oral KS is also occasionally seen in other non-HIV-infected immunocompromised patients.

Oral KS may regress occasionally spontaneously, or with HAART, zidovudine or systemic vinca alkaloids, etoposide or interferon, but the more usual treatment is local radiotherapy, laser removal or intralesional vinblastine. The latter produces fewer adverse effects than radiotherapy [10–19].

References

1 Chang Y, Cesarman E, Pessin MS *et al.* Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. *Science* 1994; **266**: 1865–9.
2 DiAlberti L, Teo CG, Porter S *et al.* Kaposi's sarcoma herpesvirus in oral Kaposi's sarcoma. *Oral Oncol* 1996; **32B**: 68–9.
3 Sissolak G, Mayaud P. AIDS-related Kaposi's sarcoma: epidemiological, diagnostic, treatment and control aspects in sub-Saharan Africa. *Trop Med Int Health* 2005; **10**: 981–92.
4 Kostantinopoulos PA, Dezube BJ, Pantanowitz L. Morphologic and immunophenotypic evidence of in-situ Kaposi's sarcoma. *BMC Clin Pathol* 2006; **6**: 7.
5 Sullivan R, Dezube BJ, Koon HB. Signal transduction targets in Kaposi's sarcoma. *Curr Opin Oncol* 2006; **18**: 456–62.
6 Pyakurel P, Pak F, Mwakigonja AR, Kaaya E, Biberfeld P. KSHV/HHV-8 and HIV infection in Kaposi's sarcoma development. *Infect Agent Cancer* 2007; **2**: 4.
7 Kostantinopoulos PA, Sullivan RJ, Karamouzis MV, Dezube BJ. Investigational agents for treatment of AIDS-related Kaposi's sarcoma. *Expert Opin Investig Drugs* 2007; **16**: 495–504.
8 Martro E, Esteve E, Schulz TF *et al*. Risk factors for human Herpesvirus 8 infection and AIDS-associated Kaposi's sarcoma among men who have sex with men in a European multicentre study. *Int J Cancer* 2007; **120**: 1129–35.
9 Epstein JB, Scully C. HIV infection: clinical oral features and management in 33 homosexual males referred with Kaposi's sarcoma. *Oral Surg* 1991; **71**: 38–41.
10 Epstein J, Scully C. Neoplastic disease in the head and neck of patients with AIDS. *Int J Oral Maxillofac Surg* 1992; **2**: 219–26.
11 Ficarra G, Berson AM, Silverman S *et al.* Kaposi's sarcoma of the oral cavity: a study of 134 patients with a review of the pathogenesis, epidemiology, clinical aspects and treatment. *Oral Surg* 1988; **66**: 543–50.
12 Lumerman H, Freedman PD, Kerpel SM *et al.* Oral Kaposi's sarcoma: a clinicopathologic study of 23 homosexual and bisexual men from the New York metropolitan area. *Oral Surg* 1988; **65**: 711–6.
13 Kalpidis CD, Lysitsa SN, Lombardi T *et al*. Gingival involvement in a case series of patients with acquired immunodeficiency syndrome-related Kaposi sarcoma. *J Periodontol* 2006; **77**: 523–33.
14 Lager I, Altini M, Coleman H, Ali H. Oral Kaposi's sarcoma: a clinicopathologic study from South Africa. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2003; **96**: 701–10.
15 Scully C, Porter SR. An ABC of oral health care in HIV infection. *Br Dent J* 1990; **170**: 149–50.
16 Scully C, Spittle M. Malignant tumours of the oral cavity in HIV disease. In: Langdon J, Henk JM, eds. *Malignant Tumours of the Mouth, Jaws and Salivary Glands*. London: Arnold, 1995: 246–57.
17 Porter SR, Scully C, eds. *Oral Health Care for Those with HIV Infection and Other Special Needs.* Northwood: Science Reviews, 1995: 51–61.
18 Cattelan AM, Calabro ML, De Rossi A *et al*. Long-term clinical outcome of AIDS-related Kaposi's sarcoma during highly active antiretroviral therapy. *Int J Oncol* 2005; **27**: 779–85.
19 Baccaglini L, Atkinson JC, Patton LL *et al*. Management of oral lesions in HIV-positive patients. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; **103** Suppl: S50.e1–23.

Purpura

Petechiae are usually caused by trauma, often from suction, but a bleeding tendency (as in infectious mononucleosis or HIV infection) or leukaemias must be excluded [1,2] (Fig. 69.64). Petechiae may be seen in Parvovirus-related papular-purpuric 'gloves and socks' syndrome [3].

Blood-filled blisters may be seen in localized oral purpura (angina bullosa haemorrhagica) and pemphigoid, and occasionally in amyloidosis. Rarely a purpuric lesion may be seen in pigmented purpuric stomatitis [4].

References

1 Scully C, Felix DH. Oral medicine—update for the dental practitioner: red and pigmented lesions. *Br Dent J* 2005; **199**: 639–45.

2 Scully C, Porter SR. Swellings and red, white and pigmented lesions. ABC of Oral Health. *BMJ* 2000; **321**: 225–8.

3 Sklavounou-Andrikopoulou A, Iakovou M, Paikos S *et al*. Oral manifestations of papular-purpuric 'gloves and socks' syndrome due to parvovirus B19 infection: the first case presented in Greece and review of the literature. *Oral Dis* 2004; **10**: 118–22.

4 Scully C, Eveson JW. Pigmented purpuric stomatitis. *Oral Surg* 1992; **74**: 780–2.

Red lesions

Many oral red lesions are inflammatory in nature, although epithelial thinning (in geographical tongue) and desquamation (in desquamative gingivitis) are fairly common, and epithelial atrophy is an important cause, especially in deficiency glossitis and erythroplasia. Telangiectases are usually red and haemangiomas purplish in colour.

Benign migratory glossitis

Synonyms
- Lingual erythema migrans
- Geographical tongue

Definition. A benign inflammatory condition of the tongue with map-like areas of erythema which are not constant in size, shape or location. Lingual erythema migrans is unrelated to cutaneous erythema migrans.

Aetiology. Unknown, but many patients with a fissured tongue (scrotal tongue) also have lingual erythema migrans. It is a common condition, affecting about 1–2% of the population [1–4]. A positive family history may be obtainable. HLA findings have been equivocal, with reports of associations with B15 and DR7 [5].

Some patients with lingual erythema migrans have atopic allergies such as hay fever and a few relate the oral lesions to a particular food, for example cheese, or to stress. Similar oral lesions may be seen in Reiter's syndrome, generalized pustular psoriasis and acrodermatitis continua of Hallopeau [6–9]. Purported associations with diabetes [10,11] may be coincidental.

Pathology. There is epithelial thinning at the centre of the lesion with an inflammatory infiltrate mainly of polymorphonuclear leukocytes [1,2].

Clinical features. Geographical tongue may be asymptomatic or cause a sore tongue. Patients of any age may be affected but why the condition sometimes gives rise to symptoms after it has been present asymptomatically for decades is unclear [8,12–14]. Geographical tongue is characterized by map-like red areas with increased thickness of intervening filiform papillae. Alternatively, there are rounded, sometimes scalloped, reddish areas with a white margin (Figs 69.65 & 69.66). These patterns change from day to day and even within a few hours. Rarely, other sites, such as the labial or palatal mucosa, are affected. The tongue is usually, but not invariably, affected simultaneously with the other sites [15]. There are no complications.



Fig. 69.65 Classical geographical tongue (lingual erythema migrans).



Fig. 69.66 Somewhat less obvious signs of lingual erythema migrans.

Diagnosis. Clinical examination usually suffices to differentiate the condition from LP, candidosis, psoriasis, larva migrans or deficiency glossitis.

Treatment. In those with no systemic disorder, no effective treatment is available except reassurance but benzydamine hydrochloride 0.15% spray or mouthwash may provide symptomatic relief.

References

1 Drezner DA, Schaffer SR. Geographic tongue. *Otolaryngol Head Neck Surg* 1997; **117**: 291.
2 Marks R, Radden BG. Geographic tongue: a clinicopathological review. *Aust J Dermatol* 1981; **22**: 75–9.
3 Yarom N, Cantony U, Gorsky M. Prevalence of fissured tongue, geographic tongue and median rhomboid glossitis among Israeli adults of different ethnic origins. *Dermatology* 2004; **209**: 88–94.
4 Zargari O. The prevalence and significance of fissured tongue and geographical tongue in psoriatic patients. *Clin Exp Dermatol* 2006; **31**: 192–5.
5 Marks R, Tait B. HLA antigens in geographical tongue. *Tissue Antigens* 1980; **15**: 60–2.
6 Casper U, Seiffert K, Dippel E, Zouboulis CC. Exfoliatio areata linguae et mucosae oris: a mucous membrane manifestation of psoriasis pustulosa? *Hautarzt* 1998; **49**: 850–4.
7 Assimakopoulos D, Patrikakos G, Fotika G, Elisaf M. Benign migratory glossitis or geographic tongue: an enigmatic oral lesion. *Am J Med* 2002; **113**: 751–5.
8 Pass B, Brown RS, Childers EL. Geographic tongue: literature review and case reports. *Dent Today* 2005; **24**: 54, 56–7.
9 Jainkittavong A, Langlais RP. Geographic tongue: clinical characteristics of 188 cases. *J Contemp Dent Pract* 2005; **6**: 123–35.
10 Wysocki GP, Daley T. Benign migratory glossitis in patients with juvenile diabetes. *Oral Surg* 1987; **63**: 68–70.
11 Shulman JD, Carpenter WM. Prevalence and risk factors associated with geographic tongue among US adults. *Oral Dis* 2006; **12**: 381–6.
12 Brooks JK, Balciunas BA. Geographic stomatitis: review of the literature and report of five cases. *J Am Dent Assoc* 1987; **115**: 421–4.
13 Kullaa-Mikkonen A. Geographic tongue, a scanning electron microscope study. *J Cutan Pathol* 1986; **13**: 154–62.
14 Correll RW, Wescott WB, Jenson JL. Non-painful, erythematous circinate lesions of a protean nature on a fissured tongue. *J Am Dent Assoc* 1984; **109**: 90–1.
15 Luker J, Scully C. Erythema migrans affecting the palate. *Br Dent J* 1983; **155**: 385.

Larva migrans (see Chapter 37)

Cutaneous larva migrans is rarely seen in the mouth, where it presents as irregular linear lesions with an inflammatory border resembling erythema migrans [1,2].

References

1 Lopes MA, Zaia AA, Almeida OPD, Scully C. Larva migrans affecting the mouth. *Oral Surg* 1994; **77**: 362–7.
2 Thome Capuano AC, Catanhede Orsini Machado de Sousa S, Aburad De Carvalhosad A, Dos santos Pinto Junior D. Larva migrans in the oral mucosa: report of a case. *Quintessence Int* 2006; **37**: 721–3.

Glossitis

See p. 69.22.

Strawberry tongue

Prominence of the lingual papillae may be seen in scarlet fever, Kawasaki disease and Riley–Day syndrome (familial dysautonomia), giving rise to an appearance similar to a strawberry [1].

Reference

1 Singh S, Kansra S. Kawasaki disease. *Natl Med J India* 2005; **18**: 20–4.

Telangiectasia (see Chapter 47)

Oral telangiectases occur mainly in hereditary haemorrhagic telangiectasia, CREST (*c*alcinosis, *R*aynaud's, *e*sophageal, *s*clerodactyly, *t*elangiectasia) syndrome [1–3] (see Chapter 51), chronic liver disease, pregnancy [4] and after irradiation.



Fig. 69.67 Venous lake of the lip. (Courtesy of Addenbrooke's Hospital, Cambridge, UK.)

References

1 Ueda M, Abe Y, Fujiwara H *et al*. Prominent telangiectasia associated with marked bleeding in CREST syndrome. *J Dermatol* 1993; **20**: 180–4.
2 Paley M, McLaughlin P. Oral problems associated with CREST syndrome: a case report. *Br Dent J* 1993; **175**: 295–6.
3 Giordano P, Nigro A, Lenato GM *et al*. Screening for children from families with Rendu-Osler-Weber disease: from geneticist to clinician. *J Thromb Haemost* 2006; **4**: 1237–45.
4 Henry F, Quatresooz P, Valverde-Lopes JC, Pierard JE. Blood vessel changes during pregnancy: a review. *Am J Clin Dermatol* 2006; **7**: 65–9.

Venous lake

Synonyms
- Venous varix
- Senile haemangioma of lip

This is a bluish-purple soft swelling, 2–10 mm in diameter, usually seen on the lower lip of an elderly person, due to a venous dilatation (Fig. 69.67). The lesion is lined by a single layer of flattened endothelial cells with a thick wall of fibrous tissue. The lesion empties on prolonged pressure [1–4].

A venous lake may be only a trivial cosmetic problem or it can bleed severely after trauma. It can be excised, but careful cryotherapy, electrocautery, infrared coagulation or treatment with an argon laser [2–4] can also give good results.

References

1 Alcalay J, Sandbank M. The ultrastructure of cutaneous venous lakes. *Int J Dermatol* 1987; **26**: 645–6.
2 Neumann RA, Knobler RM. Venous lakes (Bean–Walsh) of the lips: treatment experience with the argon laser and 18 months follow-up. *Clin Exp Dermatol* 1990; **15**: 115–8.
3 Kuo HW, Yang CH. Venous lake of the lip treated with a sclerosing agent: report of two cases. *Dermatol Surg* 2003; **29**: 425–8.
4 Ah-Weng A, Natarajan S, Velangi S, Langtry JA. Venous lakes of the vermillion lip treated by infrared coagulation. *Br J Oral Maxillofac Surg* 2004; **42**: 251–3.

Proliferative vascular lesions

Benign, atypical vascular lesions may exhibit cytological or architectural features that simulate angiosarcoma such that

considerable caution is required in diagnosis [1]. The head and neck region is a common location, particularly for lobular capillary haemangioma (pyogenic granuloma), while the lip is an especially common site for lobular capillary haemangioma [2–5] and intravascular papillary endothelial hyperplasia (Masson's haemangioma or pseudoangiosarcoma) [5,6]. Intravascular papillary endothelial hyperplasia is a benign, non-neoplastic, vascular lesion characterized histologically by papillary fronds lined by proliferating endothelium and probably represents an organizing thrombus. Seen mainly in the lip or tongue in females, it may simulate angiosarcoma histologically [7]. Excision suffices.

Vascular lesions such as epithelioid haemangioma, epithelioid haemangioendothelioma, spindle-cell haemangioendothelioma, acquired progressive lymphangioma, or angiosarcoma and KS may also occasionally be seen.

References

1 Renshaw AA, Rosai J. Benign atypical vascular lesions of the lip. *Am J Surg Pathol* 1993; **17**: 557–65.
2 Kerr DA. Granuloma pyogenicum. *Oral Surg Oral Med Oral Pathol* 1951; **4**: 158–76.
3 Ide F, Kusama K. Endovascular papillary hemangioma of the lip. *J Oral Pathol Med* 2002; **31**: 565–6.
4 Toida M, Hasegawa T, Watanabe F *et al*. Lobular capillary hemangioma of the oral mucosa: clinicopathological study of 43 cases with a special reference to immunohistochemical characterization of the vascular elements. *Pathol Int* 2003; **53**: 1–7.
5 Kuo TT, Sayers CP, Rosai J. Masson's 'Vegetant intravascular hemangioendothelioma': a lesion often mistaken for angiosarcoma. Study of 17 cases located in the skin and soft tissues. *Cancer* 1976; **38**: 1227–36.
6 Mills SE, Cooper PH, Fechner RE. Lobular capillary hemangioma: the underlying lesion of pyogenic granuloma. A study of 73 cases from the oral and nasal mucous membranes. *Am J Surg Pathol* 1980; **4**: 471–9.
7 Tosios K, Koutlas IG, Papanicolaou SI. Intravascular papillary endothelial hyperplasia of the oral soft tissues. *J Oral Maxillofac Surg* 1994; **52**: 1263–8.

Varicosities

Bluish oral varicosities may often be seen in elderly patients, particularly in the ventrum and lateral margin of the tongue. They are benign and inconsequential.

Erythroplasia

Erythroplasia (erythroplakia) is a red velvety lesion level with, or depressed below, the surrounding mucosa. It is uncommon and affects patients of either sex in their sixth and seventh decades [1–4]. Erythroplasia usually involves the floor of the mouth, the ventrum of the tongue, or the soft palate (Fig. 69.68) [1–5]. With regard to the risk of erythroplasia, a more than additive interaction has been found between tobacco chewing and low vegetable intake, whereas a more than multiplicative interaction has been found between alcohol drinking and low vegetable intake, and between drinking and low fruit intake [6].

Some 75–90% of cases of erythroplasia prove to be carcinoma or carcinoma *in situ* or show severe dysplasia. The incidence of malignant change in erythroplasia is 17 times higher than in leukoplakia.

Areas of erythroplasia should be excised and sent for histological examination.



Fig. 69.68 Erythroplasia.

References

1 Eveson JW. Oral premalignancy. *Cancer Surv* 1983; **2**: 403–24.
2 Scully C, Cawson RA. Oral potentially malignant lesions. *J Epidemiol Biostat* 1996; **1**: 3–12.
3 Melrose RJ. Premalignant oral mucosal diseases. *J Calif Dent Assoc* 2001; **29**: 593–600.
4 Reichert PA, Philipsen HP. Oral erythroplakia—a review. *Oral Oncol* 2005; **41**: 551–61.
5 Mashberg A. Diagnosis of early oral and oropharyngeal squamous carcinoma: obstacles and their amelioration. *Oral Oncol* 2000; **36**: 253–5.
6 Hashibe M, Mathew B, Kuruvilla B *et al.* Chewing tobacco, alcohol, and the risk of erythroplakia. *Cancer Epidemiol Biomarkers Prev* 2000; **9**: 639–45.

Erythematous candidosis

Oral candidosis can cause erythema and soreness of the oral mucosa, with or without the more usual thrush.

Denture-related stomatitis

Synonym
- Denture sore mouth

This common form of mild, chronic, atrophic oral candidosis occurs only beneath a denture, usually a complete upper denture, and is not often sore despite its name [1–4]. Dentures worn throughout the night, or with a dry mouth, favour development of this infection with *Candida* species mainly. It is not caused by allergy to the denture material and it is not clear why only some denture wearers develop the condition. It is a disease mainly of the middle-aged or elderly and is more prevalent in women than men [5–8]. Patients appear otherwise healthy. In some studies of institutionalized elderly patients, as many as 70% have been found to have denture-related stomatitis but overall it is considerably less common, particularly in normal, healthy subjects.

Denture-related stomatitis consists of mild inflammation and erythema of the mucosa beneath a denture (Fig. 69.69).

Aetiopathogenesis [9–15]. Dentures can produce a number of ecological changes, including the following:



Fig. 69.69 Denture-induced stomatitis showing diffuse erythema in the denture-bearing area.

- Changes in the oral flora
- Plaque accumulation between the mucosal surface of the denture and the palate
- Saliva present between the maxillary denture and the mucosa may have a lower pH than usual
- Accumulation of microbial plaque (bacteria and/or yeasts) on and in the fitting surface of the denture and the underlying mucosa.

In some persons, the cause appears to be related to a non-specific plaque [1,2,5–7,13]. This plaque undergoes sequential development, and is colonized by *Candida* organisms mainly. Although there is no increased aspartyl proteinase production from the *Candida* involved, the decreased salivary flow and a low pH under the denture probably results in a high *Candida* enzymatic activity, which can cause inflammation.

Yeasts such as *Candida* are isolated from up to 90% of persons with denture-related stomatitis and even 66% of all denture wearers. The most frequently isolated species is *Candida albicans*. Of the *C. albicans* isolates, 75% are serotype A and 25% serotype B, a significant increase in serotype B compared with a control group of non-denture-wearing HIV-seronegative individuals with oral candidosis. Resistogram strain-C is the most predominant (24% of total isolates), while strain A-CDE is the least (1.5% of total isolates). Adherence of *C. albicans* to denture-base materials *in vitro* is related to the hydrophobicity of the organism. When *Candida* is involved in denture-related stomatitis, the more common terms '*Candida*-associated denture stomatitis', 'denture-induced candidosis' or 'chronic atrophic candidosis' are used. However, denture-related stomatitis is not exclusively associated with *Candida* and, occasionally, other factors such as bacterial infection or mechanical irritation are at play [16].

Histological examination of the soft tissue beneath dentures has shown proliferative or degenerative responses with reduced keratinization and thinner epithelium.

However, it is not clear why only some denture wearers develop denture-related stomatitis, since most patients appear otherwise healthy. There have been few studies. Patients with denture-related stomatitis have no serious, cell-mediated immune defects but they may sometimes be deficient in migration inhibition factor and may have overactive suppressor T cells or other T-lymphocyte/phagocyte defects. Mean concentrations of serum interleukin 6 and tumour necrosis factor-α are statistically significantly higher and soluble TNF receptors lower in denture wearers compared with controls but there are no differences when stomatitis is present [17].

Predisposing factors. Dental appliances (mainly maxillary dentures), especially when worn throughout the night, or with a dry mouth, are the major predisposing factor. Diabetes, immunosuppressive therapy or a high-carbohydrate diet occasionally predispose [4,15,18–21] and HIV is a rare underlying factor [22].

Factors that are usually *not* significant include allergy to the dental material (if it were, denture-related stomatitis would affect mucosae other than just that beneath the appliance), trauma (the condition is more common beneath maxillary dentures than mandibular dentures, yet trauma is more common with the latter), pharmacological agents and smoking.

Clinical features. The characteristic presenting features of denture-related stomatitis are:

- Chronic erythema and oedema of the mucosa that contacts the fitting surface of the denture (usually a complete upper denture)
- The mucosa below lower dentures is rarely involved
- Erythema is restricted to the denture-bearing area
- Usually there are no symptoms
- Uncommon complications include angular stomatitis, and papillary hyperplasia in the vault of the palate.

Diagnosis. Denture-related stomatitis is a clinical diagnosis; the lesions have been classified into three clinical types (Newton's types), increasing in severity.

- Type 1: a localized simple inflammation or a pinpoint hyperaemia
- Type 2: an erythematous or generalized simple type presenting as more diffuse erythema involving a part of, or the entire, denture-covered mucosa
- Type 3: a granular type (inflammatory papillary hyperplasia) commonly involving the central part of the hard palate and the alveolar ridge.

Treatment. Any underlying systemic disease should be treated where possible.

The denture plaque and fitting surface is infested, usually with *C. albicans*. This must be removed regularly. Therefore, to treat and prevent recurrence of denture-related stomatitis, dentures should be removed from the mouth at night, cleaned and disinfected, and stored in an antiseptic. Cleansing is crucial to therapeutic success [23–25]. Denture cleansers can be divided into groups according to their main components: alkaline peroxides, alkaline hypochlorites, acids, yeast lytic enzymes, proteolytic enzymes and disinfectants such as hypochlorite. Denture soak solution containing benzoic acid completely eradicates *C. albicans* from the denture surface as it is taken up into the acrylic resin. An oral rinse containing chlorhexidine gluconate also results in complete elimination

of *C. albicans* on the acrylic resin surface of the denture, and in reduction of palatal inflammation. A protease-containing denture soak (Alcalase) is also an effective way of removing denture plaque, especially when combined with brushing. Hypochlorite is an effective anticandidal agent but can turn chrome cobalt dentures black.

The mucosal infection is eradicated by brushing the palate and using antifungals for at least 4 weeks. Effective agents include nystatin pastilles or suspension, amphotericin lozenges, miconazole gel or fluconazole suspension or tablets, administered concurrently with an oral antiseptic such as chlorhexidine, which itself has antifungal activity. Isolates are usually sensitive to amphotericin and nystatin but less sensitive to miconazole. Fluconazole is as effective as newer agents such as itraconazole. The cyclodextrin solution and the capsule preparations of itraconazole are equally effective adjuncts in the treatment but, because of side effects, the capsules are preferred. Miconazole lacquer or fluconazole in tissue conditioners applied to the denture fitting surface are also effective [4,26–36].

Surgery may be needed to excise papillary hyperplasia [37].

References

1 Figueiral MH, Azul A, Pinto E, Fonseca PA, Branco FM, Scully C. Denture-related stomatitis: Identification and characterization of aetiological and predisposing factors—a large cohort. *J Oral Rehabil* 2007; **34**: 448–55.

2 Nikawa H, Hamada T, Yamamoto T. Denture plaque: past and recent concerns. *J Dent* 1998; **26**: 299–304.

3 Dar-Odeh NS, Shehabi AA. Oral candidosis in patients with removable dentures. *Mycoses* 2003; **46**: 187–91.

4 Scully C, Felix DH. Oral medicine—update for the dental practitioner: red and pigmented lesions. *Br Dent J* 2005; **199**: 639–45.

5 Fenlon MR, Sherriff M, Walter JD. Factors associated with the presence of denture related stomatitis in complete denture wearers: a preliminary investigation. *Eur J Prosthodont Restorative Dent* 1998; **6**: 145–7.

6 Monsenego P. Presence of microorganisms on the fitting denture complete surface: study 'in vivo'. *J Oral Rehabil* 2000; **27**: 708–13.

7 Shulman JD, Rivero Hidalgo F, Beech MM. Risk factors associated with denture stomatitis in the United States. *J Oral Pathol Med* 2005; **34**: 340–6.

8 Zissis A, Yannikakis S, Harrison A. Comparison of denture stomatitis prevalence in 2 population groups. *Int J Prosthodont* 2006; **19**: 621–5.

9 Webb BC, Thomas CJ, Willcox MD, Harty DW, Knox KW. *Candida* associated denture stomatitis. Aetiology and management: a review. Part 3. Treatment of oral candidiasis. *Aust Dent J* 1998; **43**: 244–9.

10 Webb BC, Thomas CJ, Willcox MD, Harty DW, Knox KW. *Candida* associated denture stomatitis. Aetiology and management: a review. Part 2. Oral diseases caused by *Candida* species. *Aust Dent J* 1998; **43**: 160–6.

11 Radford DR, Challacombe SJ, Walter JD. Denture plaque and adherence of *Candida albicans* to denture-base materials *in vivo* and *in vitro*. *Crit Rev Oral Biol Med* 1999; **10**: 99–116.

12 McMullan-Vogel CG, Jude HD, Ollert MW, Vogel CW. Serotype distribution and secretory acid proteinase activity of *Candida albicans* isolated from the oral mucosa of patients with denture stomatitis. *Oral Microbiol Immunol* 1999; **14**: 183–9.

13 Ramage G, Tomsett K, Wickes BL, Lopez-Ribot JL, Redding SW. Denture stomatitis: a role for Candida biofilms. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2004; **98**: 53–9.

14 Dorko E, Baranova Z, Jenca A *et al*. Diabetes mellitus and candidiases. *Folia Microbiol (Praha)* 2005; **50**: 255–61.

15 Dundar N, Ilhan Kal B. Oral mucosal conditions and risk factors among elderly in a Turkish school of dentistry. *Gerontology* 2007; **53**: 165–72.

16 Baena-Monroy T, Moreno-Moldonado V, Franco-Martinez F *et al*. Candida albicans, Staphylococcus aureus and Streptococcus mutans colonization in patients wearing dental prosthesis. *Med Oral Patol Oral Cir Bucal* 2005; **10** Suppl 1: E27–39.

17 Pietruski JK, Pietruska MD, Jablonska E *et al*. Interleukin 6, tumor necrosis factor alpha and their soluble receptors in the blood serum of patients with denture stomatitis and fungal infection. *Arch Immunol Ther Exp (Warsz)* 2000; **48**: 101–5.

18 Vitkov L, Weitgasser R, Lugstein A *et al*. Glycaemic disorders in denture stomatitis. *J Oral Pathol Med* 1999; **28**: 406–9.

19 Guggenheimer J, Moore PA, Rossie K *et al*. Insulin-dependent diabetes mellitus and oral soft tissue pathologies. II. Prevalence and characteristics of *Candida* and candidal lesions. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2000; **89**: 570–6.

20 Maruo Y, Sato T, Hara T, Shirai H. The effect of diabetes mellitus on histopathological changes in the tissues under denture base bearing masticatory pressure. *J Oral Rehabil* 1999; **26**: 345–55.

21 MacPhail LA, Komaroff E, Alves ME *et al*. Differences in risk factors among clinical types of oral candidiasis in the Women's Interagency HIV Study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2002; **93**: 45–55.

22 Golecka M, Oldakowska-Jedynak K, Mierzwinska-Nastalska E, Adamczyk-Sosinska E. Candida-associated denture stomatitis in patients after immunosuppression therapy. *Transplant Proc* 2006; **38**: 155–6.

23 Markovic D, Puskar T, Tesic D. Denture cleaning techniques in the elderly affecting the occurrence of denture-induced stomatitis. *Med Pregl* 1999; **52**: 57–61.

24 Khasawneh S, al-Wahadni A. Control of denture plaque and mucosal inflammation in denture wearers. *J Ir Dent Assoc* 2002; **48**: 132–8.

25 Dikbas I, Koksal T, Calikkocaoglu S. Investigation of the cleanliness of dentures in a university hospital. *Int J Prosthodont* 2006; **19**: 294–8.

26 Chow CK, Matear DW, Lawrence HP. Efficacy of antifungal agents in tissue conditioners in treating candidiasis. *Gerodontology* 1999; **16**: 110–8.

27 Cross LJ, Bagg J, Wray D, Aitchison T. A comparison of fluconazole and itraconazole in the management of denture stomatitis: a pilot study. *J Dent* 1998; **26**: 657–64.

28 Cross LJ, Bagg J, Aitchison TC. Efficacy of the cyclodextrin liquid preparation of itraconazole in treatment of denture stomatitis: comparison with itraconazole capsules. *Antimicrob Agents Chemother* 2000; **44**: 425–7.

29 Barnabe W, de Mendonca Neto T, Pimenta FC, Pegoraro LF, Scolara JF. Efficacy of sodium hypochlorite and coconut soap used as disinfecting agents in the reduction of denture stomatitis, *Streptococcus mutans* and *Candida albicans*. *J Oral Rehabil* 2004; **31**: 453–9.

30 Cross LJ, Williams DW, Sweeney CP, Jackson MS, Lewis MA, Bagg J. Evaluation of the recurrence of denture stomatitis and Candida colonization in a small group of patients who received itraconazole. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2004; **97**: 351–8.

31 Webb BC, Thomas CJ, Whittle T. A 2-year study of Candida-associated denture stomatitis treatment in aged care subjects. *Gerodontology* 2005; **22**: 168–76.

32 Maver-Biscanin M, Mravak-Stipetic M, Jerolimov V. Effect of low-level laser therapy on Candida albicans growth in patients with denture stomatitis. *Photomed Laser Surg* 2005; **23**: 328–32.

33 Milillo L, Lo-Muzio L, Carlino P *et al*. Candida-related denture stomatitis: a pilot study of the efficacy of an amorolfine antifungal varnish**.** *Int J Prosthodont* 2005; **18**: 55–9.

34 Koray M, Ak G, Kurklu E *et al*. Fluconazole and/or hexetidine for management of oral candidiasis associated with denture-induced stomatitis. *Oral Dis* 2005; **11**: 309–13.

35 Yoshida K, Hrai K, Ara T *et al*. Feasibility of using collagen as the base of the antifungal drug, miconazole. *J Oral Rehabil* 2006; **33**: 363–7.

36 Amanlou M, Beitollahi JM, Abdollahzadeh S, Tohidast-Ekrad Z. Miconazole gel compared with Zataria multiflora Boiss gel in the treatment of denture stomatitis. *Phytother Res* 2006; **20**: 966–9.

37 Antonelli JR, Panno FV, Witko A. Inflammatory papillary hyperplasia: supraperiosteal excision by the blade-loop technique. *Gen Dent* 1998; **46**: 390–7.

Acute candidosis

Acute oral candidosis may complicate corticosteroid or antibiotic therapy, particularly with long-term, broad-spectrum antimicrobials such as used in transplant or terminally ill patients [1–5]. There is widespread erythema and soreness of the oral mucosa, sometimes with thrush, particularly noticeable on the tongue.

References

1 Wright BA, Fenwick F. Candidiasis and atrophic tongue lesions. *Oral Surg Oral Med Oral Pathol* 1981; **51**: 55–61.
2 Sweeney MP, Bagg J, Baxter WP, Aitchison TC. Oral disease in terminally ill cancer patients with xerostomia. *Oral Oncol* 1998; **34**: 123–6.
3 Bengtsson L, Ransjo U. Acute atrophic glossitis after open-heart surgery. *Scand J Thorac Cardiovasc Surg* 1988; **22**: 143–4.
4 Appleton SS. Candidiasis: pathogenesis, clinical characteristics, and treatment. *J Calif Dent Assoc* 2000; **28**: 942–8.
5 Terai H, Shimahara M. Atrophic tongue associated with Candida. *J Oral Pathol Med* 2005; **34**: 397–400.

HIV-associated candidosis

Candida infections in and around the mouth have increased greatly, particularly as the HIV epidemic has spread, and now other species (especially *C. krusei*) and antifungal resistance are serious clinical realities [1–10]. There may be transmission of *Candida* species from HIV-infected persons [9] and new species and clades are being recognized [10,11]. The most dominant oral species, in decreasing order of frequency, are:

- *C. albicans*
- *C. tropicalis*
- *C. glabrata*
- *C. parapsilosis*
- *C. krusei*
- Other *Candida* species such as *C. dubliniensis, C. africanus* and *C. inconspicua*
- Other genera (*Rhodotorula*, *Saccharomyces*, etc.), which are rare and transient.

Erythematous or atrophic candidosis may arise as a consequence of persistent, acute pseudomembranous candidosis when the pseudomembranes are shed, may develop *de novo*, or in HIV infection may precede pseudomembranous candidosis. The clinical presentation is of erythematous areas generally on the dorsum of the tongue, palate or buccal mucosa. Lesions on the dorsum of the tongue present as depapillated areas. Red areas are often seen in the palate in HIV disease. There can be an associated angular stomatitis and/or thrush.

Thrush is a well-recognized feature of T-cell immunodeficiencies, particularly after the severe T-cell immunosuppression necessary for organ transplantation and in other secondary immunodeficiencies, such as leukaemia, diabetes or HIV/AIDS. It is a common and early feature of AIDS.

Furthermore, with increasing use of antimycotic therapy, especially in HIV disease, there is a shift towards not only resistant *C. albicans*, as well as the appearance of novel species, but also other species such as *C. glabrata* and *C. krusei*. Thrush is characterized by white patches on the surface of the oral mucosa, tongue and elsewhere. The lesions develop to form confluent plaques that resemble milk curds, and can be wiped off to reveal a raw, erythematous and sometimes bleeding base. Complications of oropharyngeal thrush may sometimes present as lesions of the adjacent mucosa, particularly in the upper respiratory tract and the oesophagus. The combination of oral and oesophageal candidosis is particularly prevalent in HIV-infected patients. Antifungal therapy is indicated [10–12]. HAART reduces the frequency of candidosis [13].

References

1 Korting HC. Clinical spectrum of oral candidosis and its role in HIV-infected patients. *Mycoses* 1989; **32** (Suppl. 2): 123–9.
2 Scully C, El-Kabir M, Samaranayake LP. *Candida* and oral candidosis. *Crit Rev Oral Biol Med* 1994; **5**: 124–58.
3 Odds FC. Mycology in oral pathology. *Acta Stomatol Belg* 1997; **94**: 75–80.
4 Campisi G, Pizzo G, Milici ME, Mancuso S, Margiotta V. Candidal carriage in the oral cavity of human immunodeficiency virus-infected subjects. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2002; **93**: 281–6.
5 Zakrzewska JM, Atkin PA. Oral mucosal lesions in a UK HIV/AIDS oral medicine clinic. A nine year, cross-sectional, prospective study. *Oral Health Prev Dent* 2003; **1**: 73–9.
6 Ranganathan K, Umadevi M, Saraswathi TR *et al*. Oral lesions and conditions associated with human immunodeficiency virus infection in 1000 South Indian patients. *Ann Acad Med Singapore* 2004; **33**: 37–42.
7 Lattif AA, Banerjee U, Prasad R *et al*. Susceptibility pattern and molecular type of species-specific Candida in oropharyngeal lesions of Indian human immunodeficiency virus-positive patients. *J Clin Microbiol* 2004; **42**: 1260–2.
8 Pinheiro A, Marcenes W, Zakrzewska JM, Robinson PG. Dental and oral lesions in HIV infected patients: a study in Brazil. *Int Dent J* 2004; **54**: 131–7.
9 Baccaglini L, Atkinson JC, Patton LL, Glick M, Ficarra G, Petersen DE. Management of oral lesions in HIV-positive patients. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; **103**: 1–23.
10 Milan EP, Kallas EG, Costa PR, da Matta DA, Lopes Colombo A. Oral colonization by *Candida* spp. among AIDS household contacts. *Mycoses* 2001; **44**: 273–7.
11 Blignaut E, Pujol C, Lockhart S, Joly S, Soll DR. Ca3 fingerprinting of *Candida albicans* isolates from human immunodeficiency virus-positive and healthy individuals reveals a new clade in South Africa. *J Clin Microbiol* 2002; **40**: 826–36.
12 Ship JA, Vissink A, Challacombe SJ. Use of prophylactic antifungals in the immunocompromised host. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; **103** Suppl: S6.e1–14.
13 Umadevi KM, Ranganthan K, Pavithra S *et al*. Oral lesions among persons with HIV disease with and without highly active antiretroviral therapy in southern India. *J Oral Pathol Med* 2007; **36**: 136–41.

Median rhomboid glossitis

Synonym
- Central papillary atrophy of the tongue

Aetiology. This red, depapillated, rhomboidal area in the midline of the dorsum of the tongue, just anterior to the sulcus terminalis, was formerly thought to be caused by persistence of the tuberculum impar. However, it is now thought to be associated with candidosis [1–6]. Multiple oral lesions may occasionally be present, especially a 'kissing' lesion in the palatal vault [7,8]. Smoking, denture wearing and, occasionally, immune defects (including HIV) and diabetes predispose to this lesion [4,9–11].

Pathology. Histology shows irregular, pseudoepitheliomatous, epithelial hyperplasia that may resemble a carcinoma but it is not a malignant condition.

Clinical features. There is typically a red central lesion of somewhat rhomboidal shape anterior to the sulcus terminalis on the dorsum of the tongue (Fig. 69.70). Occasionally, there is a nodular component. There may also sometimes be a coexistent erythematous candidosis in the palate [7,8], which some have termed 'chronic oral multifocal candidosis'.

Diagnosis. Median rhomboid glossitis is usually diagnosed on clinical grounds, although biopsy may be indicated, since some lesions are nodular and may simulate a neoplasm.



Fig. 69.70 Median rhomboid glossitis.

Treatment. Median rhomboid glossitis may respond to cessation of smoking and to the use of antifungals.

References

1 Touyz LZG, Peters E. Candidal infection of the tongue with non-specific inflammation of the palate. *Oral Surg* 1987; **63**: 304–8.
2 van der Waal I. *Candida albicans* in median rhomboid glossitis: a post-mortem study. *Int J Oral Maxillofac Surg* 1986; **15**: 322–5.
3 Barrett AW, Kingsmill VJ, Speight PM. The frequency of fungal infection in biopsies of oral mucosal lesions. *Oral Dis* 1998; **4**: 26–31.
4 Guggenheimer J, Moore PA, Rossie K *et al*. Insulin-dependent diabetes mellitus and oral soft tissue pathologies: II. Prevalence and characteristics of Candida and Candidal lesions. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2000; **89**: 570–6.
5 Lago-Mendez L, Blanco-Carrion A, Diniz-Freitas M *et al*. Rhomboid glossitis in atypical location: case report and differential diagnosis. *Med Oral Patol Oral Cir Bucal* 2005; **10**: 123–7.
6 McCullough MJ, Savage NW. Oral candidosis and the therapeutic use of antifungal agents in dentistry. *Aust Dent J* 2005; **50**: S36–9.
7 Holmstrup P, Besserman M. Clinical, therapeutic and pathogenic aspects of chronic oral multifocal candidosis. *Oral Surg* 1984; **56**: 388–95.
8 Brown RS, Krakow AM. Median rhomboid glossitis and a 'kissing' lesion of the palate. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1996; **82**: 472–3.
9 Barasch A, Safford MM, Catalanotto FA, Fine DH, Katz RV. Oral soft tissue manifestations in HIV-positive vs. HIV-negative children from an inner city population: a two-year observational study. *Pediatr Dent* 2000; **22**: 215–20.
10 Guggenheimer J, Moore PA, Rossie K *et al*. Insulin-dependent diabetes mellitus and oral soft tissue pathologies. II. Prevalence and characteristics of *Candida* and candidal lesions. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2000; **89**: 570–6.
11 Okunseri C, Badner V, Wiznia A, Rosenberg M. Prevalence of oral lesions and percent CD4+ T-lymphocytes in HIV-infected children on antiretroviral therapy. *AIDS Patient Care STDS* 2003; **17**: 5–11.

Desquamative gingivitis

This is usually caused by pemphigoid or lichen planus but is also seen in patients with pemphigus vulgaris and lupus erythematosus [1].

Reference

1 Jayakumar ND, Jaiqanesh R, Padmalatha O, Sheeja V. Systemic lupus erythematosus. *Indian J Dent Res* 2006; **17**: 91–3.

Loss of elasticity of oral tissues

Fibrosis of oral tissues can follow burns or irradiation. It may also be associated with habits such as the chewing of betel nut (areca), which predisposes to oral submucous fibrosis (see below) and may be caused by a connective tissue disorder such as scleroderma. Rarely it is occupational (polyvinylchloride workers). Epidermolysis bullosa and mucous membrane pemphigoid may cause scarring and the orofacial region is occasionally involved in multiple idiopathic fibrosis [1].

Reference

1 Lewin IG, Carter JLB, Evans N *et al*. Multiple idiopathic fibrosis presenting as facial pain and trismus. *Br J Oral Surg* 1985; **23**: 135–9.

Oral submucous fibrosis

Aetiology. Oral submucous fibrosis is a chronic disease of the oral mucosa that appears to be caused by exposure to constituents of the areca nut. It is found virtually exclusively in persons from the Indian subcontinent; most of those affected chew areca nut with tobacco, betel leaf and lime [1–11].

Pathology. There is a subepithelial chronic inflammatory reaction with fibrosis extending to the submucosa and muscle. Epithelial changes range from atrophy to keratosis and there may be dysplasia.

Clinical features. Oral submucous fibrosis develops insidiously, often initially presenting with oral dysaesthesia and a non-specific vesicular stomatitis [2,11,12]. Later there may be symmetrical fibrosis of the cheeks, lips or palate, which may be symptomless and noted only as bands running through the mucosa. This can, however, become so severe that the affected site becomes white and firm, with severely restricted opening of the mouth.

Oral submucous fibrosis appears to be restricted to the mouth, although many patients are also anaemic. Oral submucous fibrosis may predispose to the development of oral carcinoma, which occurs in 2–10% of patients over a period of 10 years [9,13–16].

The diagnosis can be confirmed by biopsy.

Treatment. Management is difficult. Intralesional corticosteroids and jaw exercises may be useful in the early stages, but surgery may be needed to relieve the fibrosis [1,6,10,17]. Pentoxyfylline and lycopene have been used with some effect [6,10].

References

1 Caniff JP. Mucosal diseases of uncertain etiology. III. Oral submucous fibrosis. In: Mackenzie IC, Squier CA, Dabelsteen E, eds. *Oral Mucosal Diseases: Biology, Etiology and Therapy*. Copenhagen: Laegeforeningen Forlag, 1987: 87–91.
2 Caniff JP, Harvey W. The aetiology of oral submucous fibrosis: the stimulation of collagen synthesis by extracts of areca nut. *Int J Oral Surg* 1981; **10**: 163–7.
3 Avon SL. Oral mucosal lesions associated with use of quid. *J Can Dent Assoc* 2004; **70**: 244–8.

4 Ranganathan K, Devi MU, Joshua E, Kirankumar A, Saraswathi TI. Oral submucous fibrosis: a case-control study in Chennai, South India. *J Oral Pathol Med* 2004; **33**: 274–7.
5 Tilacaratne WM, Klinikowski MF, Saku T, Peters TJ, Warnakulasuriya S. Oral submucous fibrosis: review on aetiology and pathogenesis. *Oral Oncol* 2006; **42**: 561–8.
6 Rajendran R, Rani V, Shaikh S. Pentoxifylline therapy: a new adjunct in the treatment of oral submucous fibrosis. *Indian J Dent Res* 2006; **17**: 190–8.
7 Porter S. Strong association between areca nut use and oral submucous fibrosis. *Evid Based Dent* 2006; **7**: 79–80.
8 Ahmad MS, Ali SA, Ali AS, Chaubey KK. Epidemiological and etiological study of oral submucous fibrosis among gutkha chewers of Patna, Bihar, India. *J Indian Soc Pedod Prev Dent* 2006; **24**: 84–9.
9 Zhang X, Reichert PA. A review of betel quid chewing, oral cancer and precancer in Mainland China. *Oral Oncol* 2007; **43**: 424–30.
10 Kumar A, Bagewadi A, Keluskar V, Singh M. Efficacy of lycopene in the management of oral submucous fibrosis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; **103**: 207–13.
11 Hazarey VK, Erlewad DM, Mundhe KA, Ughade SN. Oral submucous fibrosis: study of 1000 cases from central India. *J Oral Pathol Med* 2007; **36**: 12–17.
12 Pindborg JJ, Bhonsle RB, Murti PR *et al.* Incidence and early forms of oral submucous fibrosis. *Oral Surg* 1980; **50**: 40–4.
13 Gupta PC, Bhonsle RB, Murti PR *et al.* An epidemiologic assessment of cancer risk in oral precancerous lesions in India with special reference to nodular leukoplakia. *Cancer* 1989; **63**: 2247–52.
14 Pindborg JJ, Murti PR, Bhonsle RB *et al.* Oral submucous fibrosis as a precancerous condition. *Scand J Dent Res* 1984; **92**: 224–9.
15 Mithani SK, Mydlarz WK, Grumbine FL, Smith IM, Califano JA. Molecular genetics of premalignant oral lesions. *Oral Dis* 2007; **13**: 126–33.
16 Hsue SS, Wang WC, Chen CH, Lin CC, Chen YK, Lin LM. Malignant transformation in 1458 patients with potentially malignant oral mucosal disorders: a follow-up study based in a Taiwanese hospital. *J Oral Pathol Med* 2007; **36**: 25–9.
17 Yen DJ. Surgical treatment of submucous fibrosis. *Oral Surg* 1982; **54**: 269–72.

Systemic sclerosis (see Chapter 51)

Oral features are common in systemic sclerosis and are generally more obvious in those with diffuse than localized scleroderma. About 70% of patients have xerostomia, and there is an increase in both caries and periodontal disease. A characteristic finding is of increased width of the periodontal ligament space of all teeth on radiography [1–4]. There are mandibular erosions in the angle particularly, but also in the condyle, coronoid or digastric regions. Telangiectasia may be seen and most patients have restricted oral opening with linear wrinkles of the lips [3–6].

References

1 Alexandridis C, White SC. Periodontal ligament changes in patients with progressive systemic sclerosis. *Oral Surg* 1984; **58**: 113–8.
2 Spackman GK. Scleroderma: what the general dentist should know. *Gen Dent* 1999; **47**: 576–9.
3 Gonzales TS, Coleman GC. Periodontal manifestations of collagen vascular disorders. *Periodontol* 2000; **21**: 94–105.
4 Auluck A, Pai KM, Shetty C, Shenoi SD. Mandibular resorption in progressive systemic sclerosis: a report of three cases. *Dentomaxillofac Radiol* 2005; **34**: 384–6.
5 Masmary Y, Glais R, Pisanty S. Scleroderma: oral manifestations. *Oral Surg* 1981; **52**: 32–7.
6 Wood RE, Lee P. Analysis of the oral manifestations of systemic sclerosis (scleroderma). *Oral Surg* 1988; **65**: 172–8.

Lumps and swellings

Lumps in the mouth range from simple anatomical variants, which can cause the patient considerable concern, to lumps caused by inflammatory, cystic (Fig. 69.71), neoplastic and other disorders (Table 69.23).

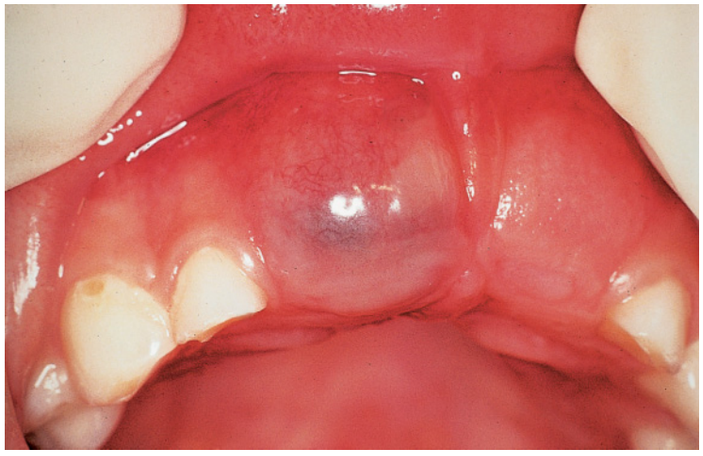


Fig. 69.71 Bluish, fluctuant swelling of an oral cyst, in this case an eruption cyst over an erupting maxillary permanent incisor. (The lesion on the maxillary canine is early dental caries.)

Foliate papillitis

The foliate lingual papillae may become inflamed and swell. Because of their location on the posterolateral tongue this may give undue concern about malignancy. The condition resolves spontaneously.

Angio-oedema

Oral swelling may be a feature of allergic angio-oedema and angio-oedema due to Cl esterase inhibitor deficiency. Allergic angio-oedema can occur secondary to antibiotic therapy, exposure to latex or ingestion of certain food substances and may be life-threatening. Angio-oedema due to C1-esterase inhibitor deficiency may be hereditary, first occurring in childhood, or acquired, with onset usually in adulthood. Type I hereditary angio-oedema exhibits low levels of functionally normal C1-esterase inhibitor while in the type II variant C1-esterase inhibitor is dysfunctional. The swelling may affect the lips, tongue or other areas and is often only mild and transient, although there is the potential for obstruction of the airway. Local anaesthetics [1] or more commonly angiotensin-converting enzyme inhibitors [2–12] may cause angio-oedema, which can occasionally be lethal [4]. It may respond to a sympathomimetic such as epinephrine or to antihistamines. Synthetic androgens have proven useful in reducing the frequency and duration of attacks [1,2].

References

1 Yaman Z, Kisnisci RS. Idiopathic swelling of the lower lip associated with topical anaesthesia. Report of three cases. *Aust Dent J* 1998; **43**: 324–7.
2 Ebo DG, Steven WJ. Angioedema of ACE inhibitors. *Allergy* 1997; **52**: 354–5.
3 Lapostolle F, Borron SW, Bekka R, Baud FJ. Lingual angioedema after perindopril use. *Am J Cardiol* 1998; **81**: 523.
4 Seymour RA, Thomason JM, Nolan A. Angiotensin converting enzyme (ACE) inhibitors and their implications for the dental surgeon. *Br Dent J* 1997; **183**: 214–8.
5 Ulmer JL, Garvey MJ. Fatal angioedema associated with lisinopril. *Ann Pharmacother* 1992; **26**: 1245–56.
6 Vleeming W, van Amstedam JG, Stricker BH, de Widt DJ. ACE inhibitor-induced angioedema. Incidence, prevention and management. *Drug Saf* 1998; **18**: 171–88.

Table 69.23 Lesions that may cause the complaint of lumps or swellings in the mouth.

Normal anatomical features
Pterygoid hamulus
Parotid papillae
Foliate or other lingual papillae
Unerupted teeth
Developmental
Haemangioma
Lymphangioma
Maxillary and mandibular tori
Hereditary gingival fibromatosis
Von Recklinghausen's neurofibromatosis
Cysts of developmental origin
Odontomes
Inflammatory
Abscess
Pyogenic granuloma
Oral Crohn's disease
Orofacial granulomatosis
Pulse granuloma
Sarcoidosis
Wegener's granuloma
Others
Traumatic
Epulis
Fibroepithelial polyp
Denture-induced granuloma
Mucocele
Herniation of buccal fat pad
Infective
Various papillomatous lesions
Cystic
Cysts of odontogenic origin (e.g. dental cysts)
Deposits
Amyloidosis
Hyalinosis
Hypoplasminogenaemia
Drug therapy (gingival swelling only)
Oral contraceptive (pill gingivitis)
Phenytoin
Calcium-channel blockers
Ciclosporin
Hormonal
Pubertal gingivitis
Pregnancy epulis/gingivitis
Blood dyscrasias
Leukaemia, lymphoma and myeloma
Benign neoplasms
Various
Malignant neoplasms
Primary and secondary
Others
Angio-oedema
Fibro-osseous diseases
Acanthosis nigricans

7 Tisch M, Lampl L, Groh A, Maier H. Angioneurotic edemas of the upper aerodigestive tract after ACE-inhibitor treatment. *Eur Arch Otorhinolaryngol* 2002; **259**: 419–21.

8 Stevenson HA, Steele JC, Field EA, Darroch CJ. Angioedema of the lips and tongue induced by angiotensin-converting enzyme inhibitor. A report of two cases. *Prim Dent Care* 2004; **11**: 17–9.

9 Peacock ME, Park DS, Swiec GD, Erley KJ. Perioral angioedema associated with angiotensin-converting enzyme inhibitor. *J Periodontol* 2005; **76**: 651–4.

10 Byrd JB, Adam A, Brown NJ. Angiotensin-converting enzyme inhibitor-associated angioedema. *Immunol Allergy Clin North Am* 2006; **26**: 725–37.

11 Malde B, Regalado J, Greenberger PA. Investigation of angioedema associated with the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. *Ann Allergy Asthma Immunol* 2007; **98**: 57–63.

12 Greaves M, Lawlor F. Angioedema: manifestations and management. *J Am Acad Dermatol* 1991; **25**: 155–61.

Oral allergy syndrome

Oral allergy syndrome is the combination of oral pruritus, irritation and swelling of the lips, tongue, palate and throat, sometimes associated with other allergic features such as rhinoconjunctivitis, asthma, urticaria–angio-oedema, and anaphylactic shock, precipitated mainly by fresh foods such as fruits and vegetables, and sometimes by pollens because of cross-reacting allergens [1–6]. Cooking often destroys the allergens.

It may respond to antihistamines or to a sympathomimetic agent such as ephedrine which can be taken by mouth.

References

1 Escribano MM, Serrano P, Munoz-Bellido FJ, De la Calle A, Coude J. Oral allergy syndrome to bird meat associated with egg intolerance. *Allergy* 1998; **53**: 903–4.

2 Liccardi G, D'Amato M, D'Amato G. Oral allergy syndrome after ingestion of salami in a subject with monosensitisation to mite allergens. *J Allergy Clin Immunol* 1996; **98**: 850–2.

3 Mari A, Ballmer-Weber BK, Vieths S. The oral allergy syndrome: improved diagnostic and treatment methods. *Curr Opin Allergy Clin Immunol* 2005; **5**: 267–73.

4 Purohith-Sheth TS, Carr WW. Oral allergy syndrome (pollen-food allergy syndrome). *Allergy Asthma Proc* 2005; **26**: 229–30.

5 Chang YC, George SJ, Hsu S. Oral allergy syndrome and contact urticaria to apples. *J Am Acad Dermatol* 2005; **53**: 736–7.

6 Nash S, Burks AW. Oral allergy syndrome. *Curr Allergy Asthma Rep* 2007; **7**: 1–2.

Osteoma mucosae

Synonym

- Osseous choristoma

There are rare cases of osteoma of the oral mucosa, usually in the tongue. Most have been in females in the third and fourth decades and have arisen as pedunculated, hard, painless lumps on the dorsum of the tongue immediately posterior to the foramen caecum [1–5]. They may arise from thyroid anlages. Simple excision suffices.

References

1 Busuttil A. An osteoma of the tongue. *J Laryngol* 1977; **91**: 259–61.

2 Markaki S, Gearty J, Markakis P. Osteoma of the tongue. *Br J Oral Surg* 1987; **25**: 79–82.

3 Sheridan SM. Osseous choristoma: a report of two cases. *Br J Oral Surg* 1984; **22**: 99–102.

4 Supiyaphun P, Sampatanukul P, Kerekhanjanaropng P, Chawakitchareon P, Sastarasadhit P. Lingual osseous choristoma: a study of eight cases and review of the literature. *Ear Nose Throat J* 1998; **77**: 316–8.



Fig. 69.72 Sinus on chin related to a dental abscess on a mandibular incisor tooth.

5 Yang SW, Chen CY, Lin CY. Lingual osteoma: case report. *Chang Gung Med J* 2000; **23**: 498–502.

Abscesses

Most intraoral abscesses are odontogenic in origin, as a final consequence of dental caries. Most abscesses discharge in the mouth on the buccal gingiva but occasionally discharge palatally, lingually, on the chin or submental region (Fig. 69.72), or elsewhere. Very occasionally abscesses follow trauma or a foreign body, or rarely are related to unusual oral infections such as actinomycosis [1–3], nocardiosis or botryomycosis [4,5].

Drainage and appropriate antimicrobials are indicated [6–10]. Dental attention is required; dental abscesses are drained by tooth extraction, incision and drainage, or through the root canal (endodontics).

References

1 Brignall ID, Gilhooly M. Actinomycosis of the tongue: a diagnostic dilemma. *Br J Oral Surg* 1989; **27**: 249–53.
2 Sakallioglu U, Acikgoz G, Kirtiloglu T, Karagoz F. Rare lesions of the oral cavity: case report of an actinomycotic lesion limited to the gingiva. *J Oral Sci* 2003; **45**: 39–42.
3 Rathnaprabu V, Rajesh R, Sunitha M. Intraoral actinomycotic lesion: a case report. *J Indian Soc Pedod Prev Dent* 2003; **21**: 144–6.
4 Small IA, Kobernick S. Botryomycosis of the tongue. *Oral Surg* 1967; **24**: 503–9.
5 Maves MD, Aguiar SW, Massanari RM, Robinson RA. Botryomycosis of the oral cavity. *Head Neck* 1989; **11**: 274–8.
6 Luker J. A case of lingual abscess. *Br Dent J* 1985; **159**: 300.
7 Kuriyama T, Absi EG, Williams DW, Lewis MA. An outcome audit of the treatment of acute dentoalveolar infection: impact of penicillin resistance. *Br Dent J* 2005; **198**: 759–63.
8 Flynn TR, Shanti RM, Levi MH *et al*. Severe odontogenic infections, part 1: prospective report. *J Oral Maxillofac Surg* 2006; **64**: 1093–103.
9 Flynn TR, Shanti RM, Hayes C. Severe odontogenic infections, part 2: prospective outcomes study. *J Oral Maxillofac Surg* 2006; **64**: 1104–13.
10 Rega AJ, Aziz SR, Ziccardi VB. Microbiology and antibiotic sensitivities of head and neck space infections of odontogenic origin. *J Oral Maxillofac Surg* 2006; **64**: 1377–80.

Sarcoidosis

Isolated nodules [1,2], gingival lesions [3], facial or labial swelling [4] and salivary gland involvement are the main oral or perioral lesions of sarcoidosis [5–11], but are uncommon. However, even where the mucosa is clinically normal, patients with sarcoidosis may have characteristic changes in palatal or labial salivary gland biopsies [9,12]. Intraosseous lesions are rare [13,14].

References

1 Mendelsohn SS, Field EA, Woolgar J. Sarcoidosis of the tongue. *Clin Exp Dermatol* 1992; **17**: 47–8.
2 Tillman HH, Taylor RG, Carchidi JE. Sarcoidosis of the tongue. *Oral Surg* 1968; **21**: 190–5.
3 Hayter JP, Robertson JM. Sarcoidosis presenting as gingivitis. *BMJ* 1988; **296**: 1504.
4 Gold RS, Sager E. Oral sarcoidosis: review of the literature. *J Oral Surg* 1976; **34**: 237–44.
5 Armstrong C, Napier S, Linden GJ. Sarcoidosis with gingival involvement: a case report. *J Periodontol* 2004; **75**: 608–12.
6 Alawi F. Granulomatous diseases of the oral tissues: differential diagnosis and update. *Dent Clin North Am* 2005; **49**: 203–21.
7 Suresh L, Radfar L. Oral sarcoidosis: a review of literature. *Oral Dis* 2005; **11**: 138–45.
8 Scully C, Felix DH. Oral medicine—update for the dental practitioner lumps and swellings. *Br Dent J* 2005; **199**: 763–70.
9 Fatahzadeh M, Rinaggio J. Diagnosis of systemic sarcoidosis prompted by orofacial manifestations: a review of the literature. *J Am Dent Assoc* 2006; **137**: 54–60.
10 Yates JM, Dichenson AJ. Sarcoidosis presenting as an isolated facial swelling—an unexpected diagnosis? *Dent Update* 2006; **33**: 112–4.
11 Kasamatsu A, Kanazawa H, Watanabe T, Matsuzaki O. Oral sarcoidosis: report of a case and review of literature. *J Oral Maxillofac Surg* 2007; **65**: 1256–9.
12 Van Maarsseveen ACMTH, Van der Waal I, Stam J *et al.* Oral involvement in sarcoidosis. *Int J Oral Surg* 1982; **11**: 21–9.
13 Grimaldi L, De Santis R, Brandi C, D'Aniello C. Mandibular intrabony lesion as first sign of sarcoidosis: case report. *Int J Oral Maxillofac Surg* 2004; **33**: 613–4.
14 Suresh L, Aguirre A, Buhite RJ, Radfar L. Intraosseous sarcoidosis of the jaws mimicking aggressive periodontitis: a case report and literature review. *J Periodontol* 2004; **75**: 478–82.

Pulse granuloma

Synonym
- Lewar's disease

Chronic mandibular periostitis caused by embedded vegetable matter of dietary origin is uncommon but typically presents as a submucosal lump over the lower alveolus. Histology shows amorphous hyaline material and a granulomatous inflammatory reaction [1–4]. Excision suffices.

References

1 Keirby FAR, Soames JV. Periostitis and osteitis associated with hyaline bodies. *Br J Oral Surg* 1985; **23**: 346–50.
2 Talacko AA, Radden BG. The pathogenesis of oral pulse granuloma: an animal model. *J Oral Pathol* 1988; **17**: 99–105.
3 Talacko AA, Radden BG. Oral pulse granuloma: clinical and histopathological features. A review of 62 cases. *Int J Oral Maxillofac Surg* 1988; **17**: 343–6.
4 Pola JG, de la Cruz A, Bustillo F, Gallas M, Leston JS. Pulse granuloma in the wall of an inflammatory radicular cyst. *Otolaryngol Head Neck Surg* 2003; **129**: 441–2.

Denture-induced hyperplasia

Synonyms
- Denture granuloma
- Epulis fissuratum



Fig. 69.73 Mucocele.

Where a denture flange is overextended and irritates the vestibular mucosa, a linear reparative process may result, eventually producing an elongated fibroepithelial enlargement known as denture-induced hyperplasia [1–4]. The pathology is that of a fibrous lump (see p. 69.20).

Firm, leaf-like, painless swellings are seen, usually in the buccal or labial vestibule.

A denture-induced granuloma should be excised and examined histologically, if modification of the denture does not induce regression [2]. Rarely, a denture granuloma arises because some other lesion develops beneath a denture and causes the mucosa to be irritated.

References

1 Budzt-Jorgensen E. Oral mucosal lesions associated with the wearing of removable dentures. *J Oral Pathol* 1981; **10**: 65–80.
2 Coelho CM, Zuculo S, Lopes RA. Denture-induced fibrous inflammatory hyperplasia: a retrospective study in a school of dentistry. *Int J Prosthodont* 2000; **13**: 148–51.
3 Esmeili T, Lozada-Nur F, Epstein J. Common benign oral soft tissue masses. *Dent Clin North Am* 2005; **49**: 223–40.
4 Macedo Firoozmand L, DiasAlmeida J, Guimaraes Cabral LA. Study of denture-induced fibrous hyperplasia cases diagnosed from 1979 to 2001. *Quintessence Int* 2005; **36**: 825–9.

Mucocele (mucous cyst)

Synonyms
- Mucous retention cyst
- Ranula
- Mucocele
- Myxoid cyst of lip

Superficial mucoceles are seen mainly in lichen planus [1,2]; palatal lesions may be seen [3]. Deeper mucoceles are more common and are usually seen in the lower labial mucosa (Fig. 69.73), usually resulting from the escape of mucus into the lamina propria from a damaged minor salivary gland duct.

Mucoceles appear as painless dome-shaped, translucent, whitish blue papules or nodules [3–10]. Care should be taken to ensure that the lesion is not a salivary gland tumour with cystic change, especially when dealing with an apparent mucous cyst in the upper lip [11]. The cysts can be excised but they also respond well to cryosurgery, using a single freeze–thaw cycle [2,12,13].

References

1 Bermejo A, Aguirre JM, Lopez P, Saez MR. Superficial mucocele: report of 4 cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1999; **88**: 469–72.
2 Campana F, Sibaud V, Chauvel A *et al*. Recurrent superficial mucoceles associated with lichenoid disorders. *J Oral Maxillofac Surg* 2006; **64**: 1830–3.
3 Jinbu Y, Tsukinoki K, Kusama M, Watanabe Y. Recurrent multiple superficial mucocele on the palate: Histopathology and laser vaporization. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2003; **95**: 193–7.
4 Lattanand A, Johnson WC. Mucous cyst (mucocele): a clinico-pathologic and histochemical study. *Arch Dermatol* 1970; **101**: 673–8.
5 Baurmash MD. Mucoceles and ranulas. *J Oral Maxillofac Surg* 2003; **61**: 369–78.
6 Rose EC, Rose C. Mucocele on the lower lip—a case report. *J Orofac Orthop* 2004; **65**: 433–5.
7 Kopp WK, St-Hilaire H. Mucosal preservation in the treatment of mucocele with CO_2 laser. *J Oral Maxillofac Surg* 2004; **62**: 1559–61.
8 Huang IY, Chen CM, Kao YH, Worthington P. Treatment of mucocele of the lower lip with carbon dioxide laser. *J Oral Maxillofac Surg* 2007; **65**: 855–8.
9 Nicolatou-Galitis O, Kitra V, Van Vliet-Constantinidou C. The oral manifestations of chronic graft-versus-host disease (cGVHD) in paediatric allogeneic bone marrow transplant recipients. *J Oral Pathol Med* 2001; **30**: 148–53.
10 Garcia F Villalta MJ, Pasqual-Lopez M, Elices M *et al*. Superficial mucoceles and lichenoid graft versus host disease: report of three cases. *Acta Derm Venereol* 2002; **82**: 453–5.
11 Mustapha IZ, Boucree SA Jr. Mucocele of the upper lip: case report of an uncommon presentation and its differential diagnosis. *J Can Dent Assoc* 2004; **70**: 318–21.
12 Bohler-Sommeregger K. Cryosurgical management of myxoid cysts. *J Dermatol Surg Oncol* 1988; **14**: 1405–8.
13 Twetman S, Isaacson S. Cryosurgical treatment of mucocele in children. *Am J Dent* 1990; **3**: 175–6.

Buccal fat-pad herniation

Trauma may rarely cause the buccal pad of fat to herniate through the buccinator muscle, producing an intraoral swelling [1–3]. This usually occurs in males under the age of 4 years. Surgery is indicated.

References

1 Fleming P. Traumatic herniation of buccal fat pad: a report of two cases. *J Oral Surg* 1986; **24**: 265–8.
2 Horie N, Shimoyamo T, Kaneko T, Ide F. Traumatic herniation of the buccal fat pad. *Pediatr Dent* 2001; **23**: 249–52.
3 Patil R, Singh S, Suba Reddy VV. Herniation of the buccal fat pad into the oral cavity: a case report. *J Indian Soc Pedod Prev Dent* 2003; **21**: 152–4.

Oral papilloma

Aetiology. These are caused by HPV [1–5].

Pathology. Histology includes acanthotic and sometimes hyperkeratotic epithelium with occasional koilocytosis.

Clinical features. Papillomas can appear anywhere in the mouth, but are most common at the junction of the hard and soft palate. The papilloma is a white or pink, cauliflower-like lesion that may resemble a wart. Papillomas of normal colour may be confused with the commoner fibroepithelial polyps, although the latter are commonest at sites of potential trauma. Papillomas are common



Fig. 69.74 Warts on the lower lip in HIV infection. (There is also a healing herpes simplex lesion on the lip.)

in HIV-infected people and have increased with the introduction of HAART [3].

Prognosis. Unlike some papillomas of the larynx or bowel, oral papillomas are generally benign although some are dysplastic [3,6].

Diagnosis. Oral papillomas should be removed and examined histologically to establish a correct diagnosis.

Treatment. Excision must be total, deep and wide enough to include any abnormal cells beyond the zone of the pedicle.

References

1 Scully C, Cox MF, Prime SS *et al.* Papillomaviruses: the current status in relation to oral disease. *Oral Surg* 1988; **65**: 526–32.
2 Paparotto Lopes SM, Meeks VI. Analysis of HPV 16 and 18 by in situ hybridization in oral papilloma of HIV+ patients. *Gen Dent* 2001; **49**: 386–9.
3 Zakrzewska JM, Atkin PA. Oral mucosal lesions in a UK HIV/AIDS oral medicine clinic. A nine year, cross-sectional, prospective study. *Oral Health Prev Dent* 2003; **1**: 73–9.
4 Bravo IM, Correnti M, Escalona L *et al.* Prevalence of oral lesions in HIV patients related to CD4 cell count and viral load in a Venezuelan population. *Med Oral Patol Oral Cir Bucal* 2006; **11**: E33–9.
5 Boj JR, Hernandez M, Espasa E, Poirier C. Laser treatment of an oral papilloma in the pediatric dental office: a case report. *Quintessence Int* 2007; **38**: 307–12.
6 Reszec J, Sulkowska M, Famulski W, Guzinska-Ustymowitz K, Sulkowski K. The expression of tumorigenesis markers in oral papilloma. *Pol J Pathol* 2002; **53**: 195–200.

Warts (see Chapter 33)

Common warts (verrucae vulgaris) and venereal warts (condyloma acuminatum) are both caused by papillomaviruses [1–8]. They are rare in the mouth (Fig. 69.74) but are more common in HIV disease. None is known to be premalignant. Most can be removed by excision, cryosurgery or laser, or podophyllum or imiquimod.

References

1 Green TL, Eversole LP, Leider AS. Oral and labial verruca vulgaris: clinical, histologic and immunohistochemical evaluation. *Oral Surg* 1986; **62**: 410–6.
2 Scully C, Cox M, Maitland N *et al.* Papillomaviruses: their current status in relation to oral disease. *Oral Surg* 1988; **65**: 526–32.
3 Scully C, Prime S, Maitland N. Papillomaviruses: their possible role in oral disease. *Oral Surg* 1985; **60**: 166–74.
4 Manganaro AM. Oral condyloma acuminatum. *Gen Dent* 2000; **48**: 62–4.
5 Flaitz CM. Condyloma acuminatum of the floor of the mouth. *Am J Dent* 2001; **14**: 115–6.
6 Aboulafia DM. Condyloma acuminatum presenting as a dorsal tongue lesion in a patient with AIDS. *AIDS Read* 2002; **12**: 165–7.
7 Kui LL, Xiu HZ, Ning LY. Condyloma acuminatum and human papilloma virus infection in the oral mucosa of children. *Pediatr Dent* 2003; **25**: 149–53.
8 Sivapathasundharam B, Shifa S. Oral verruca vulgaris: report of a rare case. *Indian J Dent Res* 2004; **15**: 32–4.

Focal epithelial hyperplasia

Synonym
- Heck's disease

Focal epithelial hyperplasia is a rare, benign, familial disorder with no sex predisposition, characterized by multiple, soft, circumscribed, sessile, nodular elevations of the oral mucosa [1–8].

Heck's disease occurs particularly in native Americans and in Inuits in Greenland but has been reported rarely from many other countries. The prevalence in Greenland and Venezuela approaches 35% [1,9,10].

Aetiology. The papillomaviruses HPV-13 and HPV-32 appear to be causal in patients with the genetic predisposition to focal epithelial hyperplasia [5–8,11–14].

Pathology. The characteristics of focal epithelial hyperplasia are local epithelial hyperplasia, acanthosis and elongated 'Bronze Age axe' rete ridges, together with a ballooning type of nuclear degeneration. Epithelial cells have a pseudomitotic appearance.

Clinical features. Among native Americans, focal epithelial hyperplasia mainly affects children and usually involves the lower lip, whereas in the Inuit and in white people the lesions are found mainly in the fourth decade and later and often affect the tongue. This is a benign asymptomatic condition, requiring only reassurance.

References

1 Axell T, Hammarstrom L, Larsson A. Focal epithelial hyperplasia in Sweden. *Acta Odontol Scand* 1981; **39**: 201–8.
2 Starink TM, Woerdeman MJ. Focal epithelial hyperplasia of the oral mucosa. *Br J Dermatol* 1977; **96**: 375–80.
3 Nartey NO, Newman MA, Nyako EA. Focal epithelial hyperplasia: report of six cases from Ghana, West Africa. *J Clin Pediatr Dent* 2002; **27**: 63–6.
4 Jayasooria PR, Abeyratne S, Ranasinghe AW, Tilakaratne WM. Focal epithelial hyperplasia (Heck's disease): report of two cases with PCR detection of human papillomavirus DNA. *Oral Dis* 2004; **10**: 240–3.
5 Gonzales LV, Gaviria AM, Sanclaments G *et al.* Clinical, histopathological and virological findings in patients with focal epithelial hyperplasia from Colombia. *Int J Dermatol* 2005; **44**: 274–9.
6 Ledesmo-Montes C, Vega-Memije E, Garces-Ortiz M, Cardiel Nieves M, Juarez-Luna C. Multifocal epithelial hyperplasia. Report of nine cases. *Med Oral Patol Oral Cir Bucal* 2005; **10**: 394–401.
7 Durso BC, Pinto JM, Jorge J Jr, de Almeida OP. Extensive focal epithelial hyperplasia: case report. *J Can Dent Assoc* 2005; **71**: 769–71.

8 Borborema-Santos CM, Castro MM, Santos PJ, Talhari S, Astolfi-Filho S. Oral focal epithelial hyperplasia: report of five cases. *Braz Dent J* 2006; **17**: 79–82.
9 Praetorius-Clausen F, Mogeltoft M, Roed-Petersen B *et al*. Focal epithelial hyperplasia of the oral mucosa in a South-West Greenlandic population. *Scand J Dent Res* 1970; **78**: 287–94.
10 Scully C, Cox M, Prime SS *et al*. Papillomaviruses: the current status in relation to oral disease. *Oral Surg* 1988; **65**: 526–32.
11 Beaudenon S, Praetorius F, Kremsdorf D *et al*. A new type of human papillomavirus associated with oral focal epithelial hyperplasia. *J Invest Dermatol* 1987; **88**: 130–5.
12 Garlick JA, Calderon S, Buchner A *et al*. Detection of human papillomavirus in focal epithelial hyperplasia. *J Oral Pathol Med* 1989; **18**: 172–7.
13 Henke RP, Guerin-Reverschon I, Milde-Langosch K *et al*. In situ detection of human papillomavirus types 13 and 32 in focal epithelial hyperplasia of the oral mucosa. *J Oral Pathol Med* 1989; **18**: 419–21.
14 Hernandes-Juaregui P, Eriksonn A, Tamayo-Perez R *et al*. Human papillomavirus type 13 DNA in focal epithelial hyperplasia among Mexicans. *Arch Virol* 1987; **93**: 131–7.

Papillary hyperplasia

Papillary hyperplasia may be seen in the vault of the palate, typically in persons with chronic denture-related stomatitis and occasionally in its absence [1–10]. It may require excision or laser removal.

References

1 O'Driscoll PM. Papillary hyperplasia of the palate. *Br Dent J* 1965; **118**: 77–80.
2 Schmitz JF. A clinical study of inflammatory papillary hyperplasia. *J Prosthet Dent* 1964; **14**: 1034–9.
3 Bergendal T, Heimdahl A, Isacsson G. Surgery in the treatment of denture-related inflammatory papillary hyperplasia of the plate. *Int J Oral Surg* 1980; **9**: 312–9.
4 Reichert PA, Althoff J. Granular type of denture stomatitis. A scanning electron microscopic study of epithelial surface patterns. *Oral Surg Oral Med Oral Pathol* 1982; **54**: 66–72.
5 Hatton ER, Gogan CM, Hatton MN. Common oral conditions in the elderly. *Am Fam Physician* 1989; **40**: 149–62.
6 Thwaites MS, Jeter TE, Ajagbe O. Inflammatory papillary hyperplasia: review of literature and case report involving a 10-year-old child. *Quintessence Int* 1990; **21**: 133–8.
7 Moskona D, Kaplan I. Oral lesions in elderly denture wearers. *Clin Prev Dent* 1992; **14**: 11–4.
8 Salonen NA, Raustia AM, Oikarinen KS. Effect of treatment of palatal inflammatory papillary hyperplasia with local and systemic antifungal agents accompanied by renewal of complete dentures. *Acta Odontol Scand* 1996; **54**: 87–91.
9 Antonelli JR, Panno FV, Witko A. Inflammatory papillary hyperplasia: supraperiosteal excision by the blade-loop technique. *Gen Dent* 1998; **46**: 390–7.
10 Infante-Cossio P, Martinez-de-Fuentes R, Torres-Caranza E, Gutierrez Perez JL. Inflammatory papillary hyperplasia of the palate: Treatment with carbon dioxide laser, followed by restoration with an implant-supported prosthesis. *Br J Oral Maxillofac Surg* 2006; **8**: 1–3.

Rhabdomyoma

Rhabdomyomas are rare but most extracardiac rhabdomyomas present in the mouth, typically as lumps in the floor of mouth, tongue or soft palate [1–5]. Most are seen in the sixth decade, predominantly in males. Surgery is effective provided total excision is achieved.

References

1 Corio RL, Lewis DM. Intraoral rhabdomyomas. *Oral Surg* 1979; **48**: 525–31.
2 Reid CO, Smith CJ. Rhabdomyoma of the floor of the mouth: a new case and review of recently reported intraoral rhabdomyomas. *Br J Oral Surg* 1985; **23**: 284–91.
3 Sclosnagle DC, Kratochvil FJ, Weathers DR, McConnell FM, Campbell WG Jr. Intraoral multifocal adult rhabdomyoma. Report of a case and review of the literature. *Arch Pathol Lab Med* 1983; **107**: 638–42.
4 Napier SS, Pagni CG, McGimpsey JG. Sublingual adult rhabdomyoma. Report of a case. *Int J Oral Maxillofac Surg* 1991; **20**: 201–3.
5 Betlach J, Nozicka Z, Spacek J. Fetal rhabdomyoma of the mucosa of the lip (case report). *Cesk Patol* 2000; **36**: 21–5.

Rhabdomyosarcoma

Some 45% of soft-tissue sarcomas in the head and neck region are rhabdomyosarcomas. The most common oral presentation is a progressively enlarging mass; some 20% have enlarged regional lymph nodes [1–8]. In advanced disease there may be pain, paraesthesia, trismus or loosening of teeth. Intraosseous lesions have been reported [5].

The prognosis is poor. Treatment includes cytotoxic chemotherapy, surgery and radiotherapy.

References

1 Bras J, Batsakis JG, Luna MA. Rhabdomyosarcoma of the oral soft tissues. *Oral Surg* 1987; **64**: 585–96.
2 Sheen JM, Lee ZF, Hsu CH, Lai MT. Congenital rhabdomyosarcoma—a case report. *Kaohsiung J Med Sci* 2000; **16**: 634–7.
3 Al-Khateeb T, Bataineh AB. Rhabdomyosarcoma of the oral and maxillofacial region in Jordanians: a retrospective analysis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2002; **93**: 580–5.
4 Chigurupati R, Alfatooni A, Myall RW, Hawkins D, Oda D. Orofacial rhabdomyosarcoma in neonates and young children: a review of literature and management of four cases. *Oral Oncol* 2002; **38**: 508–15.
5 Loducco SV, Mantesso A, de Oliveira EM, de Araujo VC. Intraosseous rhabdomyosarcoma of the mandible: a case report. *Int J Surg Pathol* 2003; **11**: 57–60.
6 Yamaguchi S, Nagasawa H, Suzuki T *et al*. Sarcomas of the oral and maxillofacial region: a review of 32 cases in 25 years. *Clin Oral Investig* 2004; **8**: 52–5.
7 Franca CM, Caran EM, Alves MT, Barreto AD, Lopes NN. Rhabdomyosarcoma of the oral tissues—two new cases and literature review. *Med Oral Patol Oral Cir Bucal* 2006; **11**: E136–40.
8 Chidzonga MM, Mahomva L. Sarcomas of the oral and maxillofacial region: a review of 88 cases in Zimbabwe. *Br J Oral Maxillofac Surg* 2007; **45**: 317–8.

Nodular fasciitis (see Chapter 56)

Nodular (pseudosarcomatous) fasciitis affects the head and neck in 20% of cases but rarely involves the mouth [1–7]. In the mouth, most cases involve the lips and buccal mucosae [7].

References

1 Davies HT, Bradley N, Bowerman JE. Oral nodular fasciitis. *Br J Oral Surg* 1989; **27**: 147–51.
2 Kawana T, Yamamoto H, Deguchi A *et al*. Nodular fasciitis of the upper labial fascia. Cytometric and ultrastructural studies. *Int J Oral Surg* 1986; **15**: 464–8.
3 Badia DM, Rossi L, Socri AR, Riminucci M. Oral nodular fasciitis. A case report. *Eur J Cancer B Oral Oncol* 1994; **30B**: 221–2.
4 Alkan A, Gunhan O, Celenk P. Oral nodular fasciitis: a case report. *J Oral Sci* 2001; **43**: 217–20.
5 Haddad AJ, Avon SL, Clokie CM, Sandor GK. Nodular fasciitis in the oral cavity. *J Can Dent Assoc* 2001; **67**: 664–7.
6 Nair P, Barrett AW, Theodossy T. Oral nodular fasciitis: case report. *Br J Oral Maxillofac Surg* 2004; **42**: 360–2.
7 Dayan D, Nasrallah V, Vered M. Clinico-pathologic correlations of myofibroblastic tumors of the oral cavity: 1. Nodular fasciitis. *J Oral Pathol Med* 2005; **34**: 426–35.

Verruciform xanthoma

Although verruciform xanthoma was originally described as a distinct oral entity, it is now also known occasionally to affect the

skin and non-oral mucosae [1,2]. The aetiology is unknown but may be a reaction to some irritant.

The lesions consist of parakeratotic verruciform epithelium, with large foamy xanthoma cells containing slightly PAS-positive granules and abundant lipid in the lamina propria between the epithelial pegs [3–10].

Verruciform xanthoma is usually a solitary symptomless lesion, typically on the gingiva, with a normal, pale, reddish or keratotic surface [1–10]. Excision is only rarely followed by recurrence.

References

1 Neville BW, Weathers DR. Verruciform xanthoma. *Oral Surg* 1980; **49**: 429–34.
2 Nowparast B, Howell FV, Rick GM. Verruciform xanthoma: a clinicopathologic review and report of fifty-four cases. *Oral Surg* 1981; **51**: 619–25.
3 Herrera-Goepfert R, Lizano Soberon M, Garcia Perales M. Verruciform xanthoma of the esophagus. *Hum Pathol* 2003; **34**: 814–5.
4 Oliveira PT, Jaeger RG, Cabral LA *et al*. Verruciform xanthoma of the oral mucosa. Report of four cases and a review of the literature. *Oral Oncol* 2001; **37**: 326–31.
5 Phillipsen HP, Reichert PA, Takata T, Igawa I. Verruciform xanthoma—biological profile of 282 oral lesions based on a literature survey with nine new cases from Japan. *Oral Oncol* 2003; **39**: 325–36.
6 Hu Ja, Li Y, Li S. Verruciform xanthoma of the oral cavity: clinicopathological study relating to pathogenesis. Report of three cases. *APMIS* 2005; **113**: 629–34.
7 Pradhan SP. Verruciform xanthoma of the oral mucosa. *JNMA J Nepal Med Assoc* 2006; **45**: 207–11.
8 Visintini E, Rizzardi C, Chiandussi S *et al*. Verruciform xanthoma of the oral mucosa. Report of a case. *Minerva Stomatol* 2006; **55**: 639–45.
9 Yu Ch, Tsai TC, Wang JT *et al*. Oral verruciform xanthoma: a clinicopathologic study of 15 cases. *J Formos Med Assoc* 2007; **106**: 141–7.
10 Rawal SY, Kalmar JR, Tatakis DN. Verruciform xanthoma: immunohistochemical characterization of xanthoma cell phenotypes. *J Periodontol* 2007; **78**: 504–9.

Lipoma (see Chapter 46)

Lipomas are uncommon in the mouth, comprising less than 5% of oral benign tumours [1–8]. They present as slow-growing, spherical, smooth and soft semi-fluctuant lumps with a characteristic yellowish colour. Most involve the buccal mucosa or floor of mouth. Occasionally, although benign, they infiltrate. Histology shows adult fat cells gathered into lobules by vascular septa of fibrous connective tissue. Surgery is rarely indicated except for infiltrating lipomas.

References

1 Batsakis JG, Regezi JA, Rice DH. The pathology of head and neck tumors: part 8. *Head Neck Surg* 1980; **3**: 145–68.
2 Lawoyin JO, Akande AO, Kolude B, Agbaje JE. Lipoma of the oral cavity: clinicopathological review of seven cases from Ibadan. *Niger J Med* 2001; **10**: 189–91.
3 Fregnani ER, Pires FR, Falzoni R, Lopes MA, Vargas PA. Lipomas of the oral cavity: clinical findings, histological classification and proliferative activity of 46 cases. *Int J Oral Maxillofac Surg* 2003; **32**: 49–53.
4 Furlong MA, Fanburg-Smith JC, Childers EL. Lipoma of the oral and maxillofacial region: Site and subclassification of 125 cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2004; **98**: 441–50.
5 Piatelli A, Perotti V, Fieroni M, Rubini C. Spindle cell lipoma of the floor of the mouth: report of a case. *Auris Nasus Larynx* 2005; **32**: 205–7.
6 Clark S, Greenwood M, Fullarton M, Russell JS. An unusual case of floor of mouth swelling: case report, differential diagnosis and a review of the literature. *Dent Update* 2005; **32**: 617–9.
7 Chidzonga MM, Mahomva L, Marimo C. Gigantic tongue lipoma: a case report. *Med Oral Patol Oral Cir Bucal* 2006; **11**: E437–9.
8 Bandeca MC, de Padua JM, Nadalin MR *et al*. Oral soft tissue lipomas: a case series. *J Can Dent Assoc* 2007; **73**: 431–4.

Myxoma

Myxomas are rare in the oral cavity [1–5]. They can arise in bone or soft tissue and, although benign, are aggressive and difficult to eradicate because of the tendency to infiltrate normal tissue.

References

1 Simon EN, Merkx MA, Vuhahula E, Ngassapa D, Stoelinga PJ. Odontogenic myxoma: a clinicopathological study of 33 cases. *Int J Oral Maxillofac Surg* 2004; **33**: 333–7.
2 Ogutcen-Toller M, Sener I, Kasap V, Cakir-Ozkan N. Maxillary myxoma: surgical treatment and reconstruction with buccal fat pad flap: a case report. *J Contemp Dent Pract* 2006; **7**: 107–16.
3 Perroti V, Rubini C, Fioroni M, Piatelli A. Soft tissue myxoma: report of an unusual case located on the gingiva. *J Clin Periodontol* 2006; **33**: 76–8.
4 Noffke CE, Raubenheimer EJ, Chabakuli NJ, Bouckaert MM. Odontogenic myxoma: review of the literature and report of 30 cases from South Africa. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; **104**: 101–9.
5 Epivatianos A, Iordanidis S, Zaraboukas T. Myxoma of the oral soft tissues: Report of a case and literature review. *J Oral Maxillofac Surg* 2007; **65**: 317–20.

Leiomyoma

This benign tumour of smooth muscle is rare in the oral cavity but if present usually affects the tongue or palate [1–5].

References

1 Lloria Benet M, Bagan JV, Lloria de Miguel E, Borja-Morant A, Alonso S. Oral leiomyoma: a case report. *Med Oral* 2003; **8**: 215–9.
2 Liang H, Frederiksen NL, Binnie WH, Cheng YS. Intraosseous oral leiomyoma: systematic review and report of one case. *Dentomaxillofac Radiol* 2003; **32**: 285–90.
3 Pitukkijronnakorn S, Leelacheikel P, Chittacharoen A. Labial leiomyoma: a case report. *J Med Assoc Thai* 2005; **88**: 118–9.
4 Luaces Rey R, Lorenzo Franco F, Gomez Oliveira G *et al*. Oral leiomyoma in retromolar trigone. A case report. *Med Oral Patol Oral Cir Bucal* 2007; **12**: E53–5.
5 Gonzalez-Sanchez MA, Colorado Bonnin M, Berrini Aytes L, Gay Escoda C. Leiomyoma of the hard palate: a case report. *Med Oral Patol Oral Cir Bucal* 2007; **12**: E221–4.

Macroglossia

The tongue may be congenitally enlarged (macroglossia) in Down's syndrome or Beckwith–Wiedemann syndrome or where there is an angioma. It may also enlarge in angio-oedema, gigantism, acromegaly or amyloidosis [1–7].

References

1 Emmanouil-Nikoloussi EN, Kerameos-Foroglu C. Developmental malformations of human tongue and associated syndromes. *Bull Group Int Rech Sci Stomatol Odontol* 1992; **35**: 5–12.
2 Guelman M, Katz J. Macroglossia combined with lymphangioma: a case report. *J Clin Pediatr Dent* 2003; **27**: 167–9.
3 Elinav E, Rabinowitz Y, Loberbaum M, Nisanewitz V. Episodic macroglossia as the sole manifestation of angiotensin-converting enzyme inhibitor-induced angioedema. *Ann Otol Rhinol Laryngol* 2004; **113**: 223–4.
4 Xavier SD, Bussoloti IF, Muller H. Macroglossia secondary to systemic amyloidosis: case report and literature review. *Ear Nose Throat J* 2005; **84**: 358–61.
5 Jeeva Rathan J, Harsha Vardhan BG, Muthu MS *et al*. Oral lymphangioma: a case report. *J Indian Soc Pedod Prev Dent* 2005; **23**: 185–9.
6 Enklaar T, Zabel BU, Prawitt D. Beckwith–Wiedemann syndrome: multiple molecular mechanisms. *Expert Rev Mol Med* 2006; **8**: 1–19.
7 Angle B. A 4-month-old girl with an enlarged tongue and limb asymmetry. Beckwith-Wiedeman syndrome. *Pediatr Ann* 2007; **36**: 261–2.

Myeloma and paraproteinaemias

Multiple myeloma very occasionally presents with an intraoral mass or oral bleeding. Bone lesions are more common. Solitary plasmacytomas may also be seen; indeed, some 80% of these rare tumours are found in the head and neck region but typically in the nasal cavity or pharynx rather than in the mouth [1–5].

References

1 Epstein JB, Boss NJS, Stevenson-Moore P. Maxillofacial manifestations of multiple myeloma. *Oral Surg* 1984; **57**: 267–71.
2 Woodruff RK, Whittle JM, Malpas JS. Solitary plasmacytoma. 1. Extra-medullary soft tissue plasmacytoma. *Cancer* 1979; **43**: 2340–3.
3 Obuekwe ON, Nwizu NN, Ojo MA, Ugbodaga PI. Extramedullary presentation of multiple myeloma in the parotid gland as first evidence of the disease—a review with case report. *Niger Postgrad Med J* 2005; **12**: 45–8.
4 Ariyaratnam S, Sweet C, Duxbury J. Low grade multiple myeloma that presented as a labial swelling—a case report. *Br Dent J* 2005; **199**: 433–5.
5 Pereira CM, Gasparetto PF, Correa ME, Vigorito AC, de Almeido OP. Primary oral and perioral amyloidosis associated with multiple myeloma. *Gen Dent* 2005; **53**: 340–1.

Waldenström's macroglobulinaemia

Oral manifestations in Waldenström's macroglobulinaemia include purpura, ulceration and occasional mental nerve anaesthesia [1–4].

References

1 Gamble JW, Driscoll EJ. Oral manifestations of macroglobulinaemia of Waldenstrom. *Oral Surg* 1960; **13**: 104–10.
2 Klokkevold PR, Miller DA, Friedlander AH. Mental nerve neuropathy: a symptom of Waldenstrom's macroglobulinaemia. *Oral Surg* 1989; **67**: 689–93.
3 Zulian M, Bellome J, DeBoom GW. Multiple linear ulcers on the dorsum of the tongue in a patient with Waldenstrom's macroglobulinaemia. *J Am Dent Assoc* 1987; **114**: 79–80.
4 Stoopler ET, Alawi F, Laudenbach JM, Sollecito TP. Bullous amyloidosis of the oral cavity: a rare clinical presentation and review. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006; **101**: 734–40.

Franklin's disease

Synonym
- Heavy-chain disease

Palatal oedema and oral ulceration have been described in a few patients with heavy-chain disease, but the former feature is not as invariable as initially described [1,2].

References

1 Kanoch T, Takigawa M, Niwa Y. Cutaneous lesions in heavy chain disease. *Arch Dermatol* 1988; **124**: 1538–40.
2 Seligmann M. Heavy chain diseases. In: Delamore IW, ed. *Multiple Myeloma and Other Paraproteinaemias*. Edinburgh: Churchill Livingstone, 1986: 263–85.

Thrombotic thrombocytopenic purpura

This may present with oral purpura and/or spontaneous gingival haemorrhage [1–3]. Gingival biopsy is a recommended investigation [4,5].

References

1 Fox P, Gordon RE, Williams AC. Thrombotic thrombocytopenic purpura: report of a case. *J Oral Surg* 1977; **35**: 921–3.



Fig. 69.75 Macroglossia and oral petechiae in amyloidosis.

2 Ridolfi R, Bell W. Thrombotic thrombocytopenic purpura: report of 25 cases and review of the literature. *Medicine* 1981; **60**: 413–28.
3 Ruggenenti P, Remuzzi G. Thrombotic thrombocytopenic purpura and related disorders. *Hematol Oncol Clin North Am* 1990; **4**: 219–41.
4 Goodman A, Ramos P, Petrelli M *et al.* Gingival biopsy in thrombotic thrombocytopenic purpura. *Ann Intern Med* 1978; **89**: 501–4.
5 Nishioka GJ, Chilcoat CC, Aufdenorte TB *et al.* The gingival biopsy in the diagnosis of thrombotic thrombocytopenic purpura. *Oral Surg* 1988; **65**: 580–5.

Amyloidosis (see Chapter 59)

In primary amyloidosis the tongue is enlarged and hard. There may also be yellowish submucosal nodules, lumps or petechiae (Fig. 69.75). Rarely, there are similar deposits elsewhere (e.g. in the soft palate), and jaw claudication, salivary gland swelling or xerostomia may occur [1–14].

Secondary amyloidoses rarely involve the mouth except in the case of multiple myeloma or haemodialysis-associated amyloid, which may occasionally produce oral nodules [9,15,16].

Some 10% of patients with oral amyloidosis have amyloid in their submandibular glands. Solitary intraoral amyloid is rare [17].

Congo red or thioflavine T staining of a biopsy usually confirms the diagnosis, although in extreme cases the deposits are seen on haematoxylin and eosin staining. Treatment is unsatisfactory but the underlying disease, where present, should be treated.

References

1 Al-Hashimi I, Drinnan AJ, Uthman AA *et al.* Oral amyloidosis: two unusual case presentations. *Oral Surg* 1987; **63**: 586–91.
2 Babejews A. Occult multiple myeloma associated with amyloid of the tongue. *Br J Oral Maxillofac Surg* 1985; **23**: 298–303.
3 Gertz MA, Kyle RA, Griffing WL *et al.* Jaw claudication in primary systemic amyloidosis. *Medicine* 1986; **65**: 173–9.
4 Salisbury PS, Jacoway JR. Oral amyloidosis: a late complication of multiple myeloma. *Oral Surg* 1983; **56**: 48–50.
5 Van der Waal I, Fehmers MCO, Kraal ER. Amyloidosis: its significance in oral surgery. *Oral Surg* 1973; **36**: 469–81.
6 Jardinet D, Westhovens R, Peeters J. Sicca syndrome as an initial symptom of amyloidosis. *Clin Rheumatol* 1998; **17**: 546–8.
7 Basak PY, Ergin S, Sezar MT, Sari A. Amyloidosis of the tongue with kappa light chain disease. *Australas J Dermatol* 2001; **42**: 55–7.
8 Gertz MA, Rajkumar SV. Primary systemic amyloidosis. *Curr Treat Options Oncol* 2002; **3:** 261–71.

Table 69.24 Endocrine disorders.

Disease	Oral manifestations
Pituitary dwarfism	Microdontia
	Retarded tooth eruption
Congenital hypothyroidism	Macroglossia
	Retarded tooth eruption
Congenital hypoparathyroidism	Dental hypoplasia
	May be chronic candidosis if associated immune defect
Gigantism/acromegaly	Spaced teeth
	Mandibular prognathism
	Macroglossia
	Megadontia (in gigantism)
Hyperparathyroidism	Bone rarefaction
	Brown tumours
Addison's disease	Mucosal hyperpigmentation
Diabetes mellitus	Periodontal disease
	Xerostomia
	Candidosis
	Sialosis
	Lichen planus
Pregnancy	Gingivitis
	Epulis
Precocious puberty	Accelerated tooth eruption (fibrous dysplasia in Albright's syndrome)

9 Koloktronis A, Chatzigiannis I, Paloukidou N. Oral involvement in a case of AA amyloidosis. *Oral Dis* 2003; **9**: 269–72.
10 Stoor P, Suuronen R, Lindqvist C, Hietanen J, Laine P. Local primary (AL) amyloidosis in the palate. A case report. *Int J Oral Maxillofac Surg* 2004; **33**: 402–3.
11 Pereira CM, Gasparetto PF, Correa ME, Vigorito AC, de Almeido OP. Primary oral and perioral amyloidosis associated with multiple myeloma. *Gen Dent* 2005; **53**: 340–1.
12 Kojima M, Sugihara S, Iijima M *et al*. Marginal zone B-cell lymphoma of minor salivary gland representing tumor-forming amyloidosis of the oral cavity. A case report. *J Oral Pathol Med* 2006; **35**: 314–6.
13 Pentenero M, Davico Bonino L, Tomasini C, Conrotto D, Gandolfo S. Localized oral amyloidosis of the palate. *Amyloid* 2006; **13**: 42–6.
14 Stoopler ET, Alawi F, Laudenbach JM, Sollecito TP. Bullous amyloidosis of the oral cavity: a rare clinical presentation and review. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006; **101**: 734–40.
15 Reinish EI, Raviv M, Srolovitz H, Gornitsky M. Tongue, primary amyloidosis, and multiple myeloma. *Oral Surg* 1994; **77**: 121–5.
16 Guccion JG, Redman RS, Winne CE. Hemodialysis-associated amyloidosis presenting as lingual nodules. *Oral Surg* 1989; **68**: 618–23.
17 Raymond AK, Sneige N, Batsakis JG. Amyloidosis in the upper aerodigestive tracts. *Ann Otol Rhinol Laryngol* 1992; **101**: 794–6.

Oral manifestations of systemic diseases

Oral manifestations can occasionally occur in many systemic diseases (Tables 69.24–69.38). Space precludes all but a brief tabular synopsis here. Further details can be found elsewhere [1–10].

References

1 Jones JH, Mason DK, eds. *Oral Manifestations of Systemic Disease*, 2nd edn. London: Baillière-Tindall, 1990.
2 Scully C, Flint S, Porter SR. *Colour Atlas of Oral Diseases*. London: Martin Dunitz, 1996.

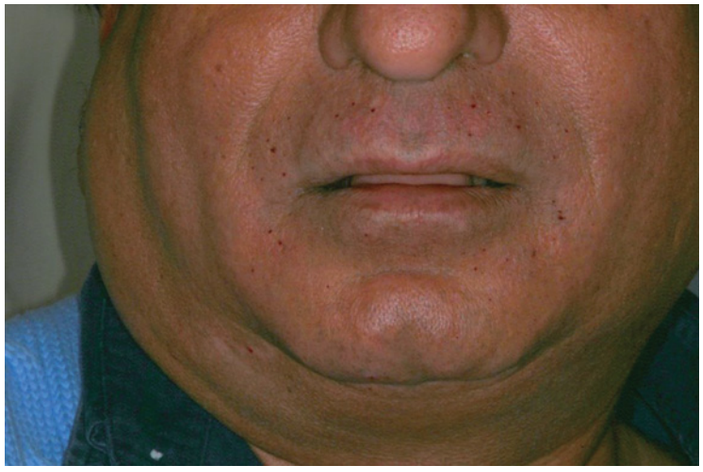


Fig. 69.76 Sialosis secondary to alcoholic cirrhosis.

Table 69.25 Liver diseases.

Disease	Oral manifestations
Most liver diseases with jaundice	Bleeding tendency
	Jaundice
Alcoholic cirrhosis	Bleeding tendency
	Sialosis (Fig. 69.76)
Chronic active hepatitis	Lichen planus
Primary biliary cirrhosis	Sjögren's syndrome
	Lichen planus
Hepatitis C	Lichen planus
	Sjögren's syndrome

Table 69.26 Psychiatric disease.

Disease	Oral manifestations
Depression, hypochondriasis and various psychoses	Various complaints such as dry mouth, discharges, pain, disturbed taste and sensation
	Drug reactions
	Often multiple complaints
	Artefactual ulcers
Anxiety states	Cheek biting
	Bruxism (teeth grinding)
Bulimia	Tooth erosion
	Palatal ulceration

3 Millard HD, Mason DK. *1998 World Workshop on Oral Medicine*. Michigan: University of Michigan, 2000.
4 Scully C, Cawson RA. Oral medicine. *Med Int* 1986; **28**: 1129–51.
5 Scully C, Cawson RA. *Medical Problems in Dentistry*, 4th edn. Oxford: Wright, 1998.
6 Scully C, Cawson RA. *Colour Aids to Oral Medicine*. Edinburgh: Churchill Livingstone, 1988.
7 Scully C, Porter SR. Oral medicine. *Med Int* 1990; **76**: 3145–74.
8 Porter SR, Scully C. HIV: the surgeon's perspective. *Br J Oral Maxillofac Surg* 1994; **32**: 222–47 (3 parts).
9 Scully C, Welbury RA, Flaitz C, Almeida ODP. *A Colour Atlas of Orofacial Diseases in Children and Adolescents*. London: Martin Dunitz, 2001.
10 Scully C, Samaranayake LP. *Clinical Virology in Oral Medicine and Dentistry*. Cambridge: Cambridge University Press, 1992.

Table 69.27 Drug effects.

Tissue	Drug effect	Drugs commonly implicated
Teeth	Discoloration	Tetracyclines
		Chlorhexidine
	Root anomalies	Phenytoin
		Cytotoxic drugs
Gingiva	Swelling	Phenytoin
		Ciclosporin
		Nifedipine
		Diltiazem
Salivary glands	Dry mouth	Tricyclic antidepressants
		Phenothiazines
		Antihypertensives
		Lithium
Taste	Disturbed	Metronidazole
		Penicillamine
Facial movements	Dyskinesias	Phenothiazines
		Metoclopramide
Mucosa	Thrush	Broad-spectrum antimicrobials
		Corticosteroids
		Cytotoxic drugs
	Ulcers	Cytotoxic drugs
		Non-steroidal anti-inflammatory agents
	Lichenoid lesions	Non-steroidal anti-inflammatory agents
	Erythema multiforme	Barbiturates
		Sulphonamides

Table 69.28 Gastrointestinal diseases.

Disease	Oral manifestations
Pernicious anaemia	Ulcers
	Glossitis
	Angular stomatitis
	Red lesions
Any cause of malabsorption	Ulcers
	Glossitis
	Angular stomatitis
Any cause of regurgitation	Tooth erosion
	Halitosis
Tylosis	Leukoplakia
Crohn's disease (and orofacial granulomatosis)	Facial swelling
	Mucosal tags
	Gingival hyperplasia
	Cobblestoning of mucosa
	Ulcers
	Glossitis
	Angular stomatitis
Coeliac disease	Ulcers
	Glossitis
	Angular stomatitis
	Dental hypoplasia
Peutz–Jegher syndrome (small intestinal polyps)	Melanosis
Chronic pancreatitis	Sialosis (rarely)
Cystic fibrosis	Salivary gland swelling
Gardner's syndrome (familial colonic polyposis)	Osteomas

Table 69.29 Renal diseases.

Disease	Oral manifestations
Chronic renal failure of any cause	Xerostomia
	Halitosis/taste disturbance
	Leukoplakia
	Dental hypoplasia in children
	Renal osteodystrophy
Post renal transplant (immunosuppressed)	Bleeding tendency (especially if anticoagulated)
	Infections, particularly herpetic and candidal
	Bleeding tendency if anticoagulated
	Gingival hyperplasia if on ciclosporin
	Kaposi's sarcoma (rarely)
	Hairy leukoplakia (rarely)
Nephrotic syndrome	Dental hypoplasia
Renal rickets (vitamin D resistant)	Delayed tooth eruption
	Dental hypoplasia (rarely)
	Enlarged pulp

Table 69.30 Haematological diseases.

Disease	Oral manifestations
Deficiency of the haematinics (iron, folic acid or vitamin B_{12})	Burning mouth sensation
	Ulcers
	Glossitis
	Angular stomatitis
Sickle-cell anaemia	Jaw deformities
	Osteomyelitis or pain
Thalassaemia major	Jaw deformities
Aplastic anaemia	Ulcers
	Bleeding tendency
Haemolytic disease of newborn	Tooth pigmentation
	Enamel defects
Any leukocyte defect	Infections, especially herpetic and candidal
	Ulcers
Any cause of purpura	Bleeding tendency
	Purpura
Leukaemia/lymphoma	Infections
	Ulcers
	Bleeding tendency and purpura (in leukaemias only)
	Gingival swelling in myelomonocytic leukaemia
Multiple myeloma	Bone pain
	Tooth mobility
	Amyloidosis
Amyloid disease	Enlarged tongue
	Purpura

Table 69.31 Cardiovascular diseases.

Disease	Oral manifestations
Any disorder causing right-to-left shunt, e.g. Fallot's tetralogy	Cyanosis
Angina pectoris	Pain referred to jaw
Hereditary haemorrhagic telangiectasia	Telangiectasis and bleeding
Giant cell arteritis (cranial or temporal arteritis)	Tongue pain or necrosis
Polyarteritis nodosa	Ulcers
Any disorder in which anticoagulants are used	Bleeding tendency
Hypertension	Dry mouth and other problems caused by some antihypertensives, e.g. gingival hyperplasia (nifedipine or diltiazem), lichenoid lesions (ACE inhibitors, methyldopa and others)

Table 69.33 Metabolic disorders.

Disease	Oral manifestations
Congenital hyperuricaemia (Lesch–Nyhan syndrome)	Self-mutilation
Mucopolysaccharidoses	Spaced teeth Retarded tooth eruption Cystic radiolucencies Temporomandibular joint anomalies Enamel defects Gingival hyperplasia
Niemann–Pick disease	Retarded tooth eruption Loosening of teeth Mucosal pigmentation
Mucolipidoses	Gingival hyperplasia
Hypophosphatasia	Loosening and loss of teeth
Erythropoietic porphyria	Reddish teeth Bullae/erosions Dental hypoplasia
Amyloidosis	Macroglossia Purpura
Vitamin B_{12} or folic acid deficiency	Ulcers Glossitis Angular stomatitis
Scurvy	Gingival swelling Purpura Ulcers
Rickets (vitamin D dependent)	Dental hypoplasia Large pulp chambers Large tooth eruption

Table 69.32 Primary and secondary immunodeficiencies.

Disease	Oral manifestations
Severe combined immunodeficiency	Candidosis Viral infections Ulcers Absent tonsils Recurrent sinusitis
Sex-linked agammaglobulinaemia	Ulcers Recurrent sinusitis Absent tonsils
Common variable immunodeficiency	Recurrent sinusitis Candidosis
Selective IgA deficiency	Tonsillar hyperplasia Ulcers Viral infections Parotitis
DiGeorge's syndrome	Abnormal facies Candidosis Viral infections Bifid uvula
Ataxia-telangiectasia	Recurrent sinusitis Ulcers Telangiectasia
Wiskott–Aldrich syndrome	Candidosis Viral infections Purpura
Hereditary angio-oedema	Swellings
Chronic benign neutropenia	Ulcers Severe periodontitis
Cyclic neutropenia	Ulcers Severe periodontitis Eczematous lesions of the face
Chronic granulomatous disease	Candidosis Enamel hypoplasia Acute gingivitis Ulcers
Myeloperoxidase deficiency	Candidosis
Chédiak–Higashi syndrome	Ulcers Periodontitis
Job's syndrome	Abnormal facies
Secondary immune defects	Ulcers Periodontitis Candidosis Viral infections Malignant neoplasms Hairy leukoplakia

Table 69.34 Collagen–vascular diseases.

Disease	Oral manifestations
Any collagen–vascular disease	Sjögren's syndrome
Rheumatoid arthritis	Temporomandibular arthritis Drug reaction (e.g. lichenoid) Ulcers in Felty's syndrome Temporomandibular ankylosis in juvenile arthritides
Lupus erythematosus	White lesions Ulcers
Systemic sclerosis	Stiffness of lips, tongue, etc. Trismus Telangiectasia Mandibular condylar resorption Periodontal ligament widened on X-ray

Table 69.35 Miscellaneous disorders.

Disease	Oral manifestations
Sarcoidosis	Xerostomia
	Salivary gland swelling
	Heerfordt's syndrome (parotid swelling, lacrimal swelling, facial palsy)
	Gingival swelling
Behçet's syndrome	Aphthous-like ulcers
Sweet's syndrome	Aphthous-like ulcers
Reiter's syndrome	Ulcers
Langerhans' cell histiocytosis	Loosening of teeth
	Jaw radiolucencies
Wegener's granulomatosis	Gingival swellings
	Ulcers
Kawasaki disease (mucocutaneous lymph node syndrome)	Sore tongue
	Cheilitis
Ellis–van Creveld syndrome (chondroectodermal dysplasia)	Multiple fraena
	Short roots
	Hypodontia
Tuberous sclerosis	Enamel defects
	Gingival fibromatosis

Table 69.36 Other infections.

Disease	Oral manifestations
Syphilis	Chancre
	Mucous patches
	Ulcers
	Gumma
	Pain from neurosyphilis
	Leukoplakia
	Lymph node enlargement
	Hutchinson's teeth and Moon molars in congenital syphilis
Gonorrhoea	Pharyngitis (occasionally)
	Gingivitis (occasionally)
	Temporomandibular arthritis (rarely)
Tuberculosis (including atypical mycobacteria)	Ulcers (rarely)
Leprosy	Cranial nerve palsies (rarely)
Lyme disease	Facial palsy
Candidosis	White lesions
	Red lesions
	Angular stomatitis
Cryptococcosis	Ulcers
Coccidioidomycosis	Ulcers
Histoplasmosis	Ulcers (especially in immune defects)
Blastomycosis	Ulcers
Paracoccidioidomycosis	Ulcers
Mucormycosis, aspergillosis	Antral infections or ulcers (especially in immune defects)

Table 69.37 Viral infections.

Disease	Oral manifestations
Herpes simplex	Ulcers in primary infection
	Gingivitis in primary infection
	Vesicles on lips in recurrence (rarely oral ulcers)
Herpes zoster–varicella	Ulcers in chickenpox, or in zoster of maxillary or mandibular divisions of the trigeminal nerve
	Pain in maxillary or mandibular zoster
Coxsackieviruses and echoviruses	Ulcers in herpangina and hand, foot and mouth disease
Epstein–Barr virus (in infectious mononucleosis)	Sore throat
	Tonsillar exudate
	Palatal petechiae
	Recurrent parotitis (possibly)
	Hairy leukoplakia
Measles	Koplik's spots
Mumps	Salivary gland swelling
Papillomaviruses	Warts
	Papillomas
	Focal epithelial hyperplasia
Human immunodeficiency virus	
Common	Candidosis
	Hairy leukoplakia
	Gingival and periodontal disease
	Herpes simplex infection
	Herpes zoster infection
	Papillomavirus infection
	Kaposi's sarcoma
	Lymphoma
	Aphthous-like ulcers
	Xerostomia
Uncommon	Infections
	Cryptococcus
	Mycobacteria
	Histoplasma
	Cytomegalovirus
	Others
	Salivary gland swelling
	Sjögren's syndrome-like disease
	Cranial neuropathies
	Fetal AIDS syndrome

Table 69.38 Neurological disorders.

Disease	Oral manifestations
Facial palsy of any cause	Palsy and poor natural cleansing of mouth on same side
Trigeminal neuralgia	Pain
Bulbar palsy	Fasciculation of tongue
Parkinsonism	Drooling
	Tremor of tongue
	Dysarthria
Neurosyphilis	Pain (rarely)
	Dysarthria
	Tremor of tongue
Cerebral palsy	Spastic tongue
	Dysarthria
	Attrition
	Periodontal disease
Choreoathetosis	Green staining of teeth in kernicterus
	Hypoplasia of deciduous dentition in congenital rubella
Epilepsy	Trauma to teeth/jaws/mucosa
	Gingival hyperplasia if taking phenytoin
Down's syndrome	Delayed tooth eruption
	Macroglossia
	Scrotal tongue
	Maxillary hypoplasia
	Anterior open bite
	Hypodontia
	Periodontal disease
	Cleft lip or palate in some

Table 69.39 Causes of cheilitis.

Chapping due to cold and wind
Eczematous cheilitis
Contact cheilitis
Drug-induced cheilitis
Infective cheilitis
Angular cheilitis
Ultraviolet irradiation
Actinic cheilitis
Actinic prurigo of the lip
Glandular cheilitis
Granulomatous cheilitis
Exfoliative (factitious) cheilitis
Plasma cell cheilitis
Nutritional cheilitis
Dermatoses
Trauma

Acquired lip lesions

Cheilitis

Synonym
- Inflammation of the lips

Cheilitis may arise as a primary disorder of the vermilion zone or the inflammation may extend from nearby skin or, less often, from the oral mucosa (Table 69.39) [1].

Table 69.40 Possible allergens in lipsticks and lipsalves.

Azo dyes	Azulene	Benzoic acid
Carmine	Castor oil	Cinnamon
Colophony	Eosin	Ester gum
Eusolex	Lanolin	Oleyl alcohol
Oxybenzone *p*-tertiary-butylphenol	Phenyl salicylate	Propolis
Propyl gallate	Ricinoleic acid	Salol
Sesame oil	Shellac	Vanilla
Wax		

Reference

1 Scully C, Bagan JV, Eisen D, Porter S, Rogers RS. *Dermatology of the Lips*. Oxford: Isis Medical Media, 2000.

'Chapping' of the lips

Chapping is a reaction to adverse environmental conditions usually caused by exposure to freezing cold or to hot dry winds. The keratin of the vermilion loses its plasticity, so that the lips become sore, cracked and scaly. The affected person tends to lick the lips, or to pick at the scales, which may aggravate the condition.

Treatment is by application of petroleum jelly and avoidance of the adverse environmental conditions.

Eczematous cheilitis

The lips are often involved secondarily to atopic dermatitis (see Chapter 24). The treatment is with emollients and topical corticosteroids. A potent steroid such as fludrocortisone may be required to bring the condition under control.

Contact cheilitis

Contact cheilitis is an inflammatory reaction provoked by the irritant or sensitizing action of chemicals. Many cases are caused by lipsticks or lipsalves but a large number of substances have been incriminated.

Lipsticks and lipsalves (Table 69.40). Lipsticks are composed of mineral oils and wax (which form the stick), castor oil as a solvent for the dyes, lanolin as an emollient, preservatives, perfumes and colours [1–7]. The dyes may include azo dyes and eosin, a bromofluorescein derivative. An eosin impurity used to be an important sensitizer [8] but is now rarely if ever used. Other ingredients occasionally incriminated include azo dyes, carmine, oleyl alcohol [9], lanolin, perfumes, azulene, propyl gallate [10], sesame oil [11], stearates [12], shellac and colophony [13,14]. Sunscreens in lipstick or lipsalve (e.g. cinnamic aldehyde) can also cause contact cheilitis [15]. Phenyl salicylate and antibiotics have also been incriminated [16,17]. Petrolatum chapsticks may cause an unusual form of acne with a single row of large open comedones along the cutaneous margin of the upper lip [18].

Mouthwashes and dentrifices [19–23]. Sensitizers used in some toothpastes include essential oils, such as peppermint, cinnamon, clove and spearmint; carvone along with imonene, pinene, phellandrene, dipentene, cineole, linalool, and esters of dihydrocuminyl alcohol and dehydrocarveol; bactericidal agents; propolis,

Table 69.41 Possible fruit and vegetable allergens.

Apple	Artichoke	Asparagus
Banana	Carrot	Celery
Cherry	Fennel	Garlic
Kiwi fruit	Lemon	Lime
Mango	Onion	Orange
Parsley	Parsnip	Peach
Pear	Pineapple	Plum
Potato	Tomato	

derived from resin collected by bees [24–26]; and tartar-control dentifrices, which contain pyrophosphate compounds [27].

Dental preparations. Mercury, eugenol, and plastics including epimine-containing materials can cause cheilitis [28–31].

Foods (Table 69.41). Peppermint, carvone, spearmint [32], citrus fruits [33], artichokes [34], nuts [35], pineapple [36], mangoes [37–39], asparagus [40], geraniol [41] and cinnamon oil [42,43] occasionally cause allergic cheilitis and perioral dermatitis. The oil on the peel of citrus fruits is irritant to the skin; in addition, some sweet oranges contain a weakly phototoxic agent that can cause a reaction in pale-skinned people [44]. Garlic may cause contact cheilitis [45].

Miscellaneous objects. Metal hair clips, metal pencils, the cobalt paint on blue pencils [46], nail varnish [47], and the metal, wooden, nickel and reed mouthpieces of musical instruments [15,48–52] may cause cheilitis.

Clinical features. Lipstick cheilitis is sometimes confined to the vermilion but more often extends beyond. There may be persistent irritation and scaling or a more acute reaction with oedema and vesiculation.

The other forms of cheilitis vary greatly in their clinical appearance. Those caused by foods commonly also involve the skin around the mouth. If a small, sucked object is responsible, the reaction may be confined to one part of the lips.

Diagnosis. If acute eczematous changes are obviously present, the diagnosis of contact cheilitis presents no difficulty. If the changes are confined to irritation and scaling, the various forms of exfoliative cheilitis must be excluded.

If an allergic reaction is suspected, patch tests should be carried out.

Treatment. Topical corticosteroids will give symptomatic relief but the offending substance must be identified and avoided.

References

1 Cronin E. *Contact Dermatitis*. Edinburgh: Churchill Livingstone, 1980: 141.
2 Shono M. Allergic contact dermatitis from isopalmityl diglyceryl sebacate in lipsticks. *Contact Dermatitis* 2003; **48**: 48–9.
3 Ha JH, Kim HO, Lee JY, Kim CW. Allergic contact cheilitis from D&C Red no 7 in lipstick. *Contact Dermatitis* 2003; **48**: 231.
4 Leow YH, Tan SH, Ng SK. Pigmented contact cheilitis from ricinoleic acid in lipsticks. *Contact Dermatitis* 2003; **49**: 48–9.
5 Strauss RM, Orton DI. Allergic contact cheilitis in the United Kingdom: a retrospective study. *Am J Contact Dermat* 2003; **14**: 75–7.
6 Ichihashi K, Soga F, Katoh N, Kishimoto S. Allergic contact cheilitis from pentaerythritol rosinate in a lipstick. *Contact Dermatitis* 2003; **49**: 213.
7 Vevsey EC, Orton DI. Photoallergic contact cheilitis due to oxybenzone found in a lip cosmetic. *Contact Dermatitis* 2006; **55**: 54.
8 Calnan CD, Sarkany I. Studies in contact dermatitis II. Lipstick cheilitis. *Trans Rep St John's Hosp Derm Soc Lond* 1957; **39**: 28–36.
9 Calnan CD, Sarkany I. Studies in contact dermatitis XII. Sensitivity to oleyl alcohol. *Trans Rep St John's Hosp Derm Soc Lond* 1960; **44**: 47–50.
10 Bonamonte D, Foti C, Angelini G. Contact allergy to ester gums in cosmetics. *Contact Dermatitis* 2001; **45**: 110–1.
11 Hayakawa R, Matsunaga K, Suzuki M *et al.* Is sesamol present in sesame oil? *Contact Dermatitis* 1987; **17**: 133–5.
12 Hayakawa R, Matsunaga K, Suzuki M *et al.* Lipstick dermatitis due to C_{18} aliphatic compounds. *Contact Dermatitis* 1987; **16**: 215–9.
13 Rademaker M, Kirby JD, White IR. Contact cheilitis to shellac, Lampol 5 and colophony. *Contact Dermatitis* 1987; **15**: 307–8.
14 Orton DI, Salim A, Shaw S. Allergic contact cheilitis due to shellac. *Contact Dermatitis* 2001; **44**: 250.
15 Freeman S, Stephens R. Cheilitis: analysis of 75 cases referred to a contact dermatitis clinic. *Am J Contact Dermat* 1999; **10**: 198–200.
16 Hindson C. Phenyl salicylate in a lip salve. *Contact Dermatitis* 1980; **6**: 216.
17 Marchand B, Barbier P, Ducombs G *et al.* Allergic contact dermatitis to various salols (phenyl salicylates). A study in man and guinea-pig. *Arch Dermatol Res* 1982; **272**: 61–6.
18 Shelley WB, Shelley ED. Chapstick acne. *Cutis* 1986; **37**: 459–60.
19 Fisher AA. *Contact Dermatitis*, 2nd edn. Philadelphia: Lea & Febiger, 1973: 320.
20 Agar N, Freeman S. Cheilitis caused by contact allergy to cocamidopropyl betaine in '2-in-1 toothpaste and mouthwash'. *Australas J Dermatol* 2005; **46**: 15–7.
21 Zoli V, Silvani S, Vincenci C, Tosti A. Allergic contact cheilitis. *Contact Dermatitis* 2006; **54**: 296–7.
22 Poon TS, Freeman S. Cheilitis caused by contact allergy to anethole in spearmint flavoured toothpaste. *Australas J Dermatol* 2006; **47**: 300–1.
23 Farina R, Andriotti C. Chronic relapsing allergic contact cheilitis from a toothpaste. A case report. *Minerva Stomatol* 2007; **56**: 145–52.
24 Trevisar G, Kokelj F. Contact dermatitis from propolis: role of gastro-intestinal absorption. *Contact Dermatitis* 1987; **16**: 48.
25 Young E. Contact dermatitis from sensitivity to propolis. *Contact Dermatitis* 1987; **16**: 49.
26 Pasolini G, Semenza D, Cappezera R *et al*. Allergic contact cheilitis induced by repeated contact with propolis-enriched honey. *Contact Dermatitis* 2004; **50**: 322–3.
27 Beacham BE, Kurgansky D, Gould WM. Circumoral dermatitis and cheilitis caused by tartar control dentifrices. *J Am Acad Dermatol* 1990; **22**: 1029–32.
28 Duxbury AJ, Turner EP, Watts DC. Hypersensitivity to epimine containing dental materials. *Br Dent J* 1979; **147**: 331–3.
29 Kulenkamp D, Hausen BM, Schulz KH. Kontakt Allergie durch neuartige, zahnartzlich verwendete Abdruckmaterialien. *Hautarzt* 1977; **28**: 353–8.
30 Maurice PD, Hopper C, Punnia-Moorthy A *et al.* Allergic contact stomatitis and cheilitis from iodoform used in a dental dressing. *Contact Dermatitis* 1988; **18**: 114–6.
31 Khamaysi Z, Bergman R, Weltfriend S. Positive patch test reactions to allergens of the dental series and the relation to the clinical presentations. *Contact Dermatitis* 2006; **55**: 216–8.
32 Hjorth N, Jervoe P. Allergies to essential oils. *Tandlaegeblader* 1967; **71**: 937.
33 Schur A. Dermatitis venenata: report of a case due to the osage orange. *Arch Dermatol Syphil* 1932; **26**: 312–3.
34 Pindborg JJ. Disorders of the oral cavity and lips. In: Rook AJ, Wilkinson DS, Ebling FJ, eds. *Textbook of Dermatology*, 2nd edn. Oxford: Blackwell Scientific Publications, 1972: 1672–721.
35 Siegal S. Local allergic oedema induced by procaine. *J Allergy* 1958; **29**: 329–35.
36 Polunin J. Pineapple dermatosis. *Br J Dermatol* 1951; **63**: 441–55.
37 Kirby-Smith JL. Mango dermatitis. *Am J Trop Med* 1938; **18**: 373–84.
38 Asai T. About mango-dermatitis. *Jpn J Dermatol Urol* 1939; **46**: 44–5.
39 Brown A, Brown FR. Mango dermatitis. *J Allergy* 1941; **12**: 310–1.
40 Halberg V. Tilfaetden af aspargedermatitis. *Hospitalstid* 1932; **75**: 1235–41.

41 Tamagawa- Mineoka R, Katoh N, Kishimoto S. Allergic contact cheilitis due to geraniol in food. *Contact Dermatitis* 2007; **56**: 242–3.
42 Leifer W. Contact dermatitis due to cinnamon. *Arch Dermatol Syphil* 1951; **64**: 52–5.
43 Miller J. Cheilitis from sensitivity to oil of cinnamon present in bubble gum. *JAMA* 1941; **116**: 131–2.
44 Volden G, Krokan H, Kavli G. Phototoxic and contact toxic reactions of the exocarp of sweet oranges: a common cause of cheilitis? *Contact Dermatitis* 1983; **9**: 201–4.
45 Ekeowa-Anderson AL, Shergill B, Goldsmith P. Allergic contact cheilitis to garlic. *Contact Dermatitis* 2007; **56**: 174–5.
46 Bruynzeel DP. A child with perioral eczema. *Contact Dermatitis* 1987; **16**: 43.
47 Cronin E. *Contact Dermatitis*. Edinburgh: Churchill Livingstone, 1980: 154.
48 Hausen BM, Bruhn G, Koenig WA. New hydroxyisoflavans as contact sensitizers in cocus wood *Brya ebenus* DC (Fabaceae). *Contact Dermatitis* 1991; **25**: 149–55.
49 Friedman SJ, Connolly SM. Clarinettists' cheilitis. *Cutis* 1986; **38**: 183–4.
50 Bischof RD. Drum and bugle corps: medical issues and problems. *Med Prob Perform Art* 1994; **9**: 131–6.
51 Holmes G, Freeman S. Cheilitis caused by contact urticaria to mint flavoured toothpaste. *Australas J Dermatol* 2001; **42**: 43–5.
52 Corazza M, Levrati A, Virgili A. Allergic contact cheilitis due to carvone in toothpastes. *Contact Dermatitis* 2002; **46**: 366–7.

Drug-induced cheilitis

Haemorrhagic crusting of the lips (Fig. 69.77) is a feature of erythema multiforme (particularly in Stevens–Johnson syndrome) (see p. 69.69), but cheilitis can also occur as an isolated feature of a drug reaction.

Aromatic retinoids such as etretinate and isotretinoin cause cheilitis, dryness and cracking of the lips in many patients [1,2].

References

1 Hanson N, Leachman S. Safety issues in isotretinoin therapy. *Semin Cutan Med Surg* 2001; **20**: 166–83.



Fig. 69.77 Haemorrhagic crusting of the lips in Stevens–Johnson syndrome.

2 Charikida A, Mouser PE, Chu AC. Safety and side effects of the acne drug, oral isotretinoin. *Expert Opin Drug Saf* 2004; **3**: 119–29.

Infective cheilitis

Viral. Lip infections with HSV are common, and VZV and HPV may also affect the lips. Rare viral infections such as orf [1–4] and vaccinia [5] can affect the lips.

Bacterial. Dental infection or occasionally a furuncle or carbuncle may cause swelling of the lip. Impetigo may mimic herpes labialis (see Chapter 33). Cancrum oris (fusospirochaetal infection) may cause labial and buccal necrosis [6–8].

The lip is the most common extragenital site for a primary syphilitic lesion. Most lip chancres in males tend to occur on the upper lip, in females on the lower lip. In secondary syphilis, moist, flat, papulonodular lesions (condylomata lata) often appear at the mucocutaneous junctions and on mucosal surfaces especially at the commissures [9,10]. The tropical treponematoses may present similarly to syphilis.

TB or leprosy may cause chronic lip swelling or ulceration [11].

Rhinoscleroma initially affects the nasal mucosa but may spread slowly to the upper lip, producing plaques or nodules with sunken centres. The extreme hardness of the infiltrations is characteristic. The lip can appear to fuse to the alveolar process but the overlying skin and mucosa remain normal.

Protozoal. Cutaneous or mucocutaneous leishmaniasis typically causes swellings on the upper lip with later enlargement and destruction of the lip [12–14], reflecting the three stages of oedema, granulomatous proliferation and then necrosis.

Fungal. Blastomycosis and paracoccidioidomycosis are uncommon causes of chronic ulceration affecting the lip, producing very similar clinical lesions to leishmaniasis [15].

Others. Red swollen lips with fissuring and exfoliation are prominent in mucocutaneous lymph node syndrome (Kawasaki disease).

References

1 Parnell AG. Ecthyma contagiosum (orf). *Br J Oral Surg* 1965; **3**: 128–35.
2 Meechan JG, MacLeod RI. Human labial orf: a case report. *Br Dent J* 1992; **173**: 343–4.
3 Bassioukas K, Orfanidou A, Stergiopoulou CH, Hatzis J. Orf. Clinical and epidemiological study. *Australas J Dermatol* 1993; **34**: 119–23.
4 Steinhart B. Orf in humans: dramatic but benign. *Can J Emerg Med Care* 2005; **7**: 417–9.
5 Scully C. Vaccinia of the lip. *Br Dent J* 1977; **143**: 57–9.
6 Enwonwu CO. Infectious oral necrosis (cancrum oris) in Nigerian children. *Community Dent Oral Epidemiol* 1985; **13**: 190–4.
7 Sawyer D, Nwoku AJ. Cancrum oris (noma): past and present. *J Dent Child* 1981; **48**: 138–41.
8 Pittet B, Jaquinet A, Montandon D. Clinical experience in the treatment of noma sequelae. *J Craniofac Surg* 2001; **12**: 273–83.
9 Manton SL, Eggleston SI, Alexander I, Scully C. Oral presentation of secondary syphilis. *Br Dent J* 1986; **160**: 237–8.
10 Vibhagool C, Raimer SS, Sanchez RL. A nodule on the lip. Nodular secondary syphilis. *Arch Dermatol* 1996; **132**: 822–3, 825–6.

11 Chimenos Kustner E, Pasquel Cruz M, Pinol Dansis C *et al*. Lepromatous leprosy: a review and case report. *Med Oral Patol Oral Cir Bucal* 2006; **11**: E474–9.
12 Asvesti C, Anastassiadis G, Kolokotronis A, Zographakis I. Oriental sore: a case report. *Oral Surg* 1992; **73**: 56–8.
13 Sangueza OP, Sangueza JM, Stiller MJ, Sangueza P. Mucocutaneous leishmaniasis: a clinicopathological classification. *J Am Acad Dermatol* 1993; **28**: 927–32.
14 Ramesh V, Mirra RS, Saxena U, Mukherjee A. Post-kala-azar dermal leishmaniasis: a clinical and therapeutic study. *Int J Dermatol* 1993; **32**: 272–5.
15 Spostos R, Scully C, Almeida OPD *et al*. Oral paracoccidioidomycosis: a study of 36 South American patients. *Oral Surg Oral Med Oral Pathol* 1993; **75**: 461–5.

Angular cheilitis

Synonym
- Angular stomatitis

Angular cheilitis is an acute or chronic inflammation of the skin and contiguous labial mucous membrane at the angles of the mouth [1–3].

Aetiology. Most cases in adults are due to mechanical and/or infective causes, but in children nutritional or immune defects are more prominent causes.

Infective agents. These are the major cause. *Candida* or staphylococci are isolated from most patients [4–7]. Permanent cure can be achieved only by eliminating the *Candida* beneath the upper denture [8,9]. Candidosis was probably responsible for some of the cases of cheilitis attributed to allergy to denture materials, since contamination of denture material by *Candida* may cause false-positive patch-test reactions [10].

Immune deficiency, such as diabetes and HIV infection, may present with angular stomatitis [11–13]. Outbreaks of acute pustular and fissured cheilitis may occur in children, particularly if they are malnourished, and in some cases streptococci or staphylococci have appeared to be causative [14].

Mechanical factors in edentulous patients who do not wear a denture or who have inadequate dentures, and also as a normal consequence of the ageing process, produce an oblique curved fold and keep the small area of skin constantly macerated. The recurrent trauma of dental flossing is a very rare cause of angular cheilitis [15].

Nutritional deficiencies, particularly deficiencies of riboflavin, folate, iron and general protein malnutrition, may produce smooth, shiny, red lips associated with angular stomatitis, a combination called *cheilosis* [1,16–18]. Crohn's disease or orofacial granulomatosis may be found in some [19].

Clinical features. Angular cheilitis presents as a roughly triangular area of erythema and oedema at one, or more commonly both, angles of the mouth (Fig. 69.78). Linear furrows or fissures radiating from the angle of the mouth (rhagades) are seen in the more severe forms, especially in denture wearers.

Diagnosis. This is usually obvious. *Candida* should be sought not only in the lesions but also beneath the denture.



Fig. 69.78 Angular cheilitis.

Treatment. Dentures should be removed from the mouth at night and stored in a candidacidal solution such as hypochlorite. Denture-related stomatitis should be treated with an antifungal. Miconazole may be preferable treatment for candidosis (cream applied locally, together with the oral gel) as it has some Gram-positive bacteriostatic action. New dentures that restore facial contour may help. The skin lesions should be swabbed and staphylococcal infection treated with fusidic acid ointment or cream at least four times daily.

References

1 Schoenfeld RJ, Schoenfeld FI. Angular cheilitis. *Cutis* 1977; **19**: 213–6.
2 Samaranyake LP. Superficial oral fungal infections. *Curr Opin Dent* 1991; **1**: 415–22.
3 Akpan A, Morgan R. Oral candidiasis. *Postgrad Med J* 2002; **78**: 455–9.
4 Ohman SC, Dahlen G, Moller A *et al*. Angular cheilitis: a clinical and microbial study. *J Oral Pathol* 1986; **15**: 213–7.
5 MacFarlane TW, Helnarska SJ. The microbiology of angular cheilitis. *Br Dent J* 1976; **140**: 403.
6 Dahlen G. A retrospective study of microbiologic samples from oral mucosal lesions. *Oral Surg* 1982; **53**: 350–4.
7 Dias AP, Samaranyake LP. Clinical, microbiological and ultrastructural features of angular cheilitis lesions in Southern Chinese. *Oral Dis* 1995; **1**: 43–8.
8 Scully C. Chronic atrophic candidiasis. *Lancet* 1986; **ii**: 437–8.
9 Ohman SC, Jontell M. Treatment of angular cheilitis. The significance of microbial analysis, antimicrobial treatment, and interfering factors. *Acta Odontol Scand* 1988; **46**: 267–72.
10 Salo OP, Hirvonen ML. Yeasts as a cause of false-positive reactions in patch-tests for allergy to dental materials. *Br J Dermatol* 1969; **81**: 338–41.
11 Taiwoo OO, Okeke EN, Jalo PH, Danfillo IS. Oral manifestation of HIV/AIDS in Plateau state indigenes, Nigeria. *West Afr J Med* 2006; **25**: 32–7.
12 Sharma G, Pai KM, Suhas S *et al*. Oral manifestations in HIV/AIDS infected patients from India. *Oral Dis* 2006; **12**: 537–42.
13 Guggenheimer J, Moore PA, Rossie K *et al*. Insulin-dependent diabetes mellitus and oral soft tissue pathologies: II. Prevalence and characteristics of Candida and Candidal lesions. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2000; **89**: 570–6.

14 MacFarlane TW, McGill JC, Samaranayake LB. Antibiotic testing and phage typing of *Staphylococcus aureus* isolated from non-hospitalized patients with angular cheilitis. *J Hosp Infect* 1984; **5**: 444–6.
15 Kahana M, Yakalom M, Yakalom R *et al*. Recurrent angular cheilitis caused by dental flossing. *J Am Acad Dermatol* 1986; **15**: 113–4.
16 Murphy NC, Bissada NF. Iron deficiency: an overlooked predisposing factor in angular cheilitis. *J Am Dent Assoc* 1979; **99**: 640–1.
17 Rose JA. Aetiology of angular cheilosis: iron metabolism. *Br Dent J* 1968; **125**: 67–72.
18 Parodi A, Priano L, Rebora A. Chronic zinc deficiency in a patient with psoriasis and alcoholic liver cirrhosis. *Int J Dermatol* 1991; **30**: 45–7.
19 Wiesenfeld D, Ferguson MM, Mitchell DN *et al*. Orofacial granulomatosis: clinical and pathological analysis. *Q J Med* 1985; **213**: 101–13.

Actinic cheilitis

Synonyms
- Actinic keratosis of lip
- Solar cheilosis

This is a premalignant keratosis of the lip caused by exposure to solar irradiation.

Aetiology. Actinic cheilitis is most common in hot dry regions, in outdoor workers and in fair-skinned people (skin types I and II). The vermilion of the lower lip receives a high dose of UV irradiation because it is almost at right angles to the rays of the midday sun and is poorly protected by keratin and melanocytes. Most actinic cheilitis is seen on the lower lip of fair-skinned men in their fourth to eighth decade of life [1].

Pathology. Histology shows a flattened or atrophic epithelium, beneath which is a band of inflammatory infiltrate in which plasma cells may predominate [2]. Nuclear atypia and abnormal mitoses may be seen in the more severe cases, and some develop into invasive squamous carcinoma [3–5]. The collagen generally shows basophilic (elastotic) degeneration [6].

Clinical features (Fig. 69.79). Actinic cheilitis tends to affect the lower lip of adults who have had prolonged exposure to sunlight [1,7]. In the early stages there may be redness and oedema, but later the lips become dry and scaly. Later still, the epithelium becomes palpably thickened with small greyish-white plaques and, eventually, warty nodules may form. Eventually these may undergo malignant change, the possibility of which must always be considered when ulceration develops or when there are other suspect features such as:
- A red and white, blotchy appearance with an indistinct vermilion border
- Generalized atrophy with focal areas of whitish thickening
- Persistent flaking and crusting [8,9].



Fig. 69.79 Chronic actinic cheilitis with leukoplakia. (Courtesy of Addenbrooke's Hospital, Cambridge, UK.)

Diagnosis. This is clinical.

Treatment. Treatment of actinic cheilitis is required to relieve symptoms and to prevent development of squamous carcinoma.
- Topical agents: 5% fluorouracil three times daily for 10 days is suitable [10,11]. Topical tretinoin [12], trichloracetic acid [13] or diclofenac gel [14] may also be effective.
- Vermilionectomy (lip shave) [15–17].
- Laser ablation [18–22].
- Photodynamic therapy [23–24].

Following treatment, prevention of recurrence by the regular use of a sunscreen lipsalve containing *p*-aminobenzoic acid probably gives the best protection [25,26]. Particular care should be taken to protect the vermilion of the lips with adequate sunscreens in patients with photosensitivity disorders such as xeroderma pigmentosum, and in those whose exposure to UVB is high, such as in farmers, fishermen, mountaineers, windsurfers and skiers.

References

1 Markopoulos A, Albanidou-Farmaki E, Kayavis I. Actinic cheilitis: clinical and pathologic characteristics in 65 cases. *Oral Dis* 2004; **10**: 212–6.
2 Koten JW. Histopathology of actinic cheilitis. *Dermatologica* 1967; **135**: 465–71.
3 Neto Pimental DR, Michalanay N, Alchome M *et al*. Actinic cheilitis: histopathology and p53. *J Cutan Pathol* 2006; **33**: 539–44.
4 Mena Simonsen Nico M, Rivitti EA, Lourenco SV. Actinic cheilitis: histologic study of the entire vermilion and comparison with previous biopsy. *J Cutan Pathol* 2007; **34**: 309–14.
5 Picascia DD, Robinson JK. Actinic cheilitis, a review of the aetiology, differential diagnosis and treatment. *J Am Acad Dermatol* 1987; **17**: 255–64.
6 Schmitt CK. Histologic evaluation of degenerative changes of the lower lip. *J Oral Surg* 1968; **26**: 51–6.
7 Cotaldo E. Solar cheilitis. *J Dermatol Surg Oncol* 1981; **7**: 289–95.
8 La Riviere W, Pickett AB. Clinical criteria in diagnosis of early squamous carcinoma of the lower lip. *J Am Dent Assoc* 1979; **99**: 972–7.
9 Birt AR, Hogg GR. The actinic cheilitis of hereditary polymorphic light eruption. *Arch Dermatol* 1979; **115**: 699–702.
10 Epstein E. Treatment of actinic cheilitis with topical fluorouracil. *Arch Dermatol* 1977; **113**: 906–8.
11 Dufresne RG Jr, Curlin MU. Actinic cheilitis. A treatment review. *Dermatol Surg* 1997; **23**: 15–21.
12 Kligman A. Topical tretinoin: indications, safety and effectiveness. *Cutis* 1987; **39**: 486–8.
13 Turk LL, Winder PR. Carcinomas of the skin and their treatment. *Semin Oncol* 1980; **7**: 376–84.
14 Ulrich C, Forschner T, Ulrich M *et al*. Management of actinic cheilitis using diclofenac 3% gel: a report of six cases. *Br J Dermatol* 2007; **156**: 43–6.
15 Birt BD. The lip-shave operation for premalignant conditions of the lower lip. *Otolaryngology* 1977; **6**: 407–11.
16 Robinson JK. Actinic cheilitis: a prospective study comparing four treatment methods. *Arch Otolaryngol Head Neck Surg* 1989; **115**: 848–52.

17 Sanchez-Conejo-Mir J, Perez-Bernal AM, Mormo-Jiminez JC *et al.* Follow-up of vermilionectomies. *J Dermatol Surg Oncol* 1986; **12**: 180–4.
18 David LM. Laser vermilion ablation for actinic cheilitis. *J Dermatol Surg Oncol* 1984; **11**: 605–8.
19 Dufresne RG, Garrett AB, Bailin PL, Ratz JL. Carbon dioxide laser treatment of chronic actinic cheilitis. *J Am Acad Dermatol* 1988; **19**: 876–8.
20 Stanley RJ. Actinic cheilitis: treatment with the carbon dioxide laser. *Mayo Clin Proc* 1988; **63**: 230–5.
21 Zelickson BD, Roenigk RK. Actinic cheilitis: treatment with the carbon dioxide laser. *Cancer* 1990; **65**: 1307–11.
22 Orenstein A, Goldan O, Weissman O, Winkler E, Haik J. A new modality in the treatment of actinic cheilitis using the Er: YAG laser. *J Cosmet Laser Ther* 2007; **9**: 23–5.
23 Hauschild A, Lischner S, Lange-Asschenfeldt B, Egberts F. Treatment of actinic cheilitis using photodynamic therapy with methyl aminolevulinate: report of three cases. *Dermatol Surg* 2005; **31**: 1344–7, discussion 1348.
24 Alexiades-Armenikas M. Aminolevulinic acid photodynamic therapy for actinic keratoses/actinic cheilitis/acne: vascular lasers. *Dermatol Clin* 2007; **25**: 25–33.
25 Lundeen RC, Langlais RP. Sunscreen protection for lip mucosa. A review and update. *J Am Dent Assoc* 1985; **11**: 617–21.
26 Payne TE. An evaluation of actinic blocking agents for the protection of lip mucosa. *J Am Dent Assoc* 1976; **92**: 409–11.

Actinic prurigo (see Chapter 29)

Actinic prurigo is a type of familial photodermatitis, seen mainly in native Americans living at high altitudes [1–6] especially in Latin America, and in China [7]. It usually presents in young women as a photosensitive facial rash with pruritic lower lip cheilitis, and it may be associated with conjunctivitis, eyebrow alopecia and pterygion.

Actinic prurigo is due to enhanced sensitivity to sunlight and is distinguished from actinic cheilitis, which is due to prolonged and excessive exposure to UV irradiation, by the relative absence of epidermal dysplasia and solar elastosis [8]. Polymorphic light eruption is almost invariably present in the actinic prurigo of native Americans [9,10].

Treatment is with sunscreens, β-carotene, psoralen and UVA (PUVA), and antihistamines. Oral thalidomide may be tried [5,11,12].

References

1 Birt AR, Davis RA. Hereditary polymorphic light eruption of American Indians. *Int J Dermatol* 1975; **14**: 105–11.
2 Scheen SR, Connolly SM, Dicken CH. Actinic prurigo. *J Am Acad Dermatol* 1981; **5**: 183–90.
3 Wiseman MC, Orr PH, MacDonald SM, Schroeder ML, Toole JW. Actinic prurigo: clinical features and HLA associations in a Canadian Inuit population. *J Am Acad Dermatol* 2001; **44**: 952–6.
4 Vega-Memije ME, Mosqueda Taylor A, Irigoyen Camacho ME *et al.* Actinic prurigo cheilitis: clinicopathologic analysis and therapeutic results in 116 cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2002; **94**: 83–91.
5 Hojyo Tomoka MT, Vega-Memije ME, Cortes Franco R, Dominguez-Soto L. Diagnosis and treatment of actinic prurigo. *Dermatol Ther* 2003; **16**: 40–4.
6 Cornelison RL Jr. Cutaneous diseases in Native Americans. *Dermatol Clin* 2003; **21**: 699–702.
7 Guogi X, Yiming H, Huibao S *et al.* Pruritic cheilitis: six cases. *Oral Surg* 1983; **55**: 359–62.
8 Herrera-Goepfert R, Magana M. Follicular cheilitis. *Am J Dermatopathol* 1995; **17**: 357–61.
9 Calnan CD, Meara RH. Actinic prurigo (Hutchinson's summer prurigo). *Clin Exp Dermatol* 1977; **2**: 365–77.
10 Mounsden T, Kratochvil T, Auclair P *et al.* Actinic prurigo of the lower lip. Review of the literature and report of 5 cases. *Oral Surg Oral Med Oral Pathol* 1988; **65**: 327–32.
11 Londono F. Thalidomide in the treatment of actinic prurigo. *Int J Dermatol* 1973; **12**: 323–8.
12 Estrada-G I, Garibay Escobar A, Nunez Vazquez A *et al.* Evidence that thalidomide modifies the immune response of patients suffering from actinic prurigo. *Int J Dermatol* 2004; **43**: 893–7.

Glandular cheilitis

Definition. Glandular cheilitis is characterized by inflammatory changes and swelling of salivary glands in the lips [1–3].

Aetiology. This is an uncommon idiopathic condition which in a few cases has apparently been familial [4]. Although it was originally thought that the condition was due to inflammation of enlarged heterotopic salivary glands, the glands are often normal in size, depth and histology [5]. It is possible that the excessive salivary secretion from minor salivary glands in this condition might be an unusual clinical response to irritation of the lip from some other cause such as actinic damage or repeated licking.

Pathology. In the milder forms there is some fibrosis surrounding the salivary glands, while in the more severe forms there may be a dense chronic inflammatory infiltrate. Only rarely do patients show genuine hyperplasia of the salivary glands or duct ectasia.

Clinical features. The onset is at any age from childhood onwards. In simple glandular cheilitis, the lower lip is slightly thickened and bears numerous pinhead-sized orifices, from which mucous saliva can readily be squeezed. The upper lip is rarely involved [6].

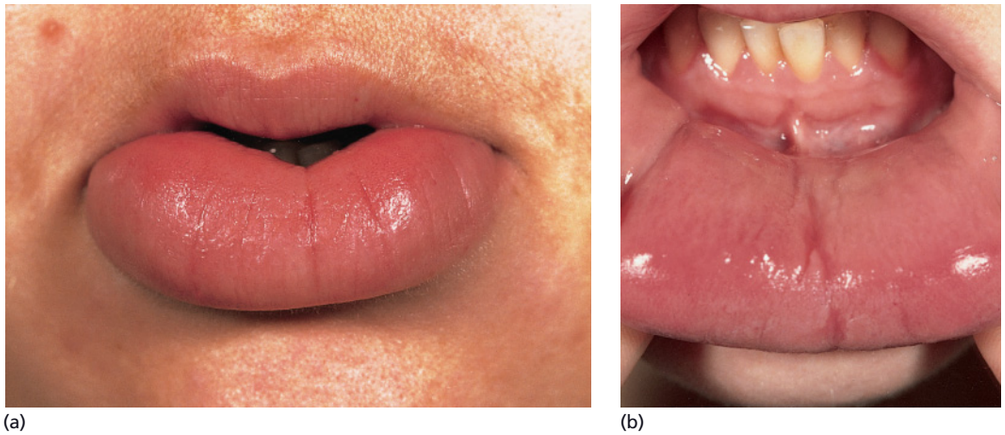
In the more severe suppurative form (*Volkmann's cheilitis*) the lip is considerably and permanently enlarged, and subject to episodes of pain, tenderness and increased enlargement. The surface is covered by crusts and scales, beneath which the salivary duct orifices may be discovered. In the most severe forms there may be deep-seated infection with abscess formation and fistulous tracts.

The condition can evidently be premalignant; in some series 20–30% of cases progress to squamous carcinoma. This does, of course, support the suggestion that in many cases glandular cheilitis is a consequence of actinic cheilitis [5].

Treatment. Actinic cheilitis, if identified, should be treated appropriately. If the lips are grossly enlarged, excision of an elongated ellipse of tissue may be required; in other cases shave vermilionectomy may be all that is necessary. Other conditions such as atopic disease or factitial cheilitis would require different treatment.

References

1 Rada DC. Cheilitis glandularis. A disorder of ductal ectasia. *J Dermatol Surg Oncol* 1985; **1**: 372–5.
2 Stuller CB, Schaberg SJ, Stokos J. Cheilitis glandularis. *Oral Surg* 1982; **53**: 602–5.
3 Thiele B, Mahrle G, Ippen H. Cheilitis glandularis simplex. *Hautarzt* 1983; **34**: 232–4.
4 Weir TW, Johnson WC. Cheilitis glandularis. *Arch Dermatol* 1971; **103**: 433–7.
5 Swerlick RA, Cooper PH. Cheilitis glandularis: a re-evaluation. *J Am Acad Dermatol* 1984; **10**: 466–72.



(a) (b)

Fig. 69.80 Granulomatous cheilitis of the lower lip. (Courtesy of Addenbrooke's Hospital, Cambridge, UK.)

6 Winchester L, Scully C, Prime SS, Eveson JW. Cheilitis glandularis: a case affecting the upper lip. *Oral Surg Oral Med Oral Pathol* 1986; **62**: 654–6.

Granulomatous cheilitis

Synonym
- Miescher's cheilitis

This is a chronic swelling of the lip due to granulomatous inflammation of unknown cause. Melkersson in 1928 [1] described labial oedema in association with recurrent facial palsy. Rosenthal in 1930 emphasized the role of genetic factors and added scrotal tongue to the syndrome. The full syndrome has since been called Melkersson–Rosenthal syndrome [2–4].

In Miescher's cheilitis the granulomatous changes are confined to the lip, and this is generally regarded as a monosymptomatic form of Melkersson–Rosenthal syndrome, although the possibility remains that these may be two separate diseases.

Aetiology. The cause is unknown, but there may be a genetic predisposition to Melkersson–Rosenthal syndrome [5]; siblings have been affected and a scrotal tongue may be present in otherwise normal relatives.

There is no convincing evidence that granulomatous cheilitis is due to an infective agent. Some cases may represent a localized form of sarcoidosis [6,7] or ectopic Crohn's disease [7–9] or orofacial granulomatosis. There is increasing evidence that some patients with granulomatous cheilitis are predisposed to Crohn's disease [9–11]. In some cases, granulomatous cheilitis is followed some years later by regional ileitis [12–16]. A few patients react to cobalt [17] or to food additives such as cinnamic aldehyde [18–21] and have no extra oral lesions, although these reactions are by no means always relevant; for example, in one study only one of nine patients had a relationship between cheilitis and food intake [22].

Pathology. Biopsy of the swollen lip or facial tissues during the early stages of the disease shows only oedema and perivascular lymphocytic infiltration. In some cases of long duration no other changes are seen, but in others the infiltrate becomes more dense and pleomorphic and small focal granulomas are formed, indistinguishable from sarcoidosis or Crohn's disease. Similar changes may be present in cervical lymph nodes [23–26]. In some cases, small granulomas occur in the lymphatic walls [27].

Clinical features. The condition affects the sexes equally. The earliest manifestations usually develop in childhood or adolescence but may be delayed until middle or old age. The earliest cutaneous manifestation is sudden diffuse or nodular swellings [10,11,28,29] involving the upper lip, the lower lip and one or both cheeks in decreasing order of frequency [8,26,30]. Labial swelling occurs in about 75% and facial swelling in 50% of patients [31]. Less commonly, the forehead, eyelids or one side of the scalp may be involved. The attacks are sometimes accompanied by fever and mild constitutional symptoms, including headache and even visual disturbance. At the first episode the oedema typically subsides completely in hours or days, but after recurrent attacks the swelling may persist, and slowly increases in degree (Fig. 69.80). It gradually becomes firmer and eventually acquires the consistency of firm rubber. After some years, the swelling may very slowly regress.

A fissured or scrotal tongue is seen in 20–40% of cases [11]. It is present from birth in some, which may indicate genetic susceptibility. There may be loss of sense of taste and decreased salivary gland secretion [26].

The regional lymph nodes are enlarged in 50% of cases [5] but not usually very greatly.

Facial palsy of the lower motor neurone type occurs in some 30% of cases. It may precede the attacks of oedema by months or years, but more commonly develops later. Although intermittent at first, the palsy may become permanent. It may be unilateral or bilateral, and partial or complete [26]. Other cranial nerves (olfactory, auditory, glossopharyngeal and hypoglossal) may occasionally be involved [32]. Involvement of the CNS has also been reported, but the significance of the resulting symptoms is easily overlooked as they are very variable, sometimes simulating disseminated sclerosis but often with a poorly defined association of psychotic and neurological features. Autonomic disturbances may occur.

Diagnosis. The essential feature of the syndrome is the granulomatous swelling of lip or face. In the early attacks clinical

Table 69.42 Macrocheilia: acute or chronic enlargement of one or both lips.

Acute	Chronic
Traumatic	Developmental
Infective	Familial idiopathic
Pyococcal	Double lip
Anthrax	Ascher's syndrome
Diphtheria	Lymphangioma
Primary syphilis	Haemangioma
Trichophytosis	Neurofibroma
Leishmaniasis	Mucopolysaccharidoses
Herpes simplex	Fucosidosis
Trichiniasis	Coffin–Siris syndrome
Angio-oedema	Acquired
Erythema multiforme	Post-traumatic
Actinic cheilitis	Post-infective on basis of developmental
Other forms of cheilitis	lymphatic defect
	Infective
	Tuberculosis
	Leprosy
	Rhinoscleroma
	Leishmaniasis
	Neoplastic
	Melkersson–Rosenthal syndrome
	Cheilitis glandularis
	Sarcoidosis
	Crohn's disease
	Orofacial granulomatosis

differentiation from angio-oedema may be impossible in the absence of either scrotal tongue or facial palsy. Persistence of the swelling between attacks should suggest the diagnosis, which can sometimes be confirmed by biopsy. However, the histological changes are not always conspicuous or specific.

In established cases, other causes of macrocheilia (Table 69.42) must be excluded. Ascher's syndrome associated with blepharochalasia is likely to cause confusion, although the swelling of the lip is caused by redundant salivary tissue and is present from childhood. Lymphoma is a rare differential diagnosis [33].

Treatment. Reactions to dietary components should be sought and possible antigens avoided. The injection of up to 10 mL triamcinolone (10 mg/L) into the lips after local analgesia may be effective [22,29,34–39]. The injections may have to be repeated every 4–6 months once a response plateau has been reached. This treatment has also been successfully combined with surgical reduction (cheiloplasty) [40–42]. The injections must be continued periodically after the surgery or there may be an exaggerated recurrence of the condition. Surgery alone is relatively unsuccessful [36,43].

Systemic corticosteroids are rarely indicated [44] since adverse effects may be a problem and not all respond [41,45]. Clofazimine appears to help the majority of patients [36,46–48], in a dose of 100 mg twice daily for 10 days, then twice weekly for 4 months. Metronidazole may also produce resolution in granulomatous cheilitis [37,49,50].

Other treatments which have occasionally been helpful include long-term penicillin, erythromycin, sulfasalazine (sulphasalazine), ketotifen or infliximab [51,52].

References

1 Melkersson E. Case of recurrent facial paralysis with angio-neurotic edema. *Hygien* 1928; **90**: 737–41.
2 Wadlington WB, Riley HD, Lowbeer I. The Melkersson–Rosenthal syndrome. *Pediatrics* 1984; **73**: 502–6.
3 McGrath DS, Doyle C, Bredin CP. The Melkersson Rosenthal syndrome—a differential diagnosis of facial sarcoidosis. *Ir J Med Sci* 1997; **166**: 253–6.
4 Hoexter DL. Melkerson Rosenthal syndrome. *N Y State Dent J* 2007; **73**: 30–2.
5 Hornstein OP. Melkersson–Rosenthal syndrome: a neuro-mucocutaneous disease of complex origin. *Curr Probl Dermatol* 1973; **5**: 117–56.
6 Shedade SA, Foulds IS. Granulomatous cheilitis and a positive Kveim test. *Br J Dermatol* 1986; **115**: 619–22.
7 Medeiros M Jr, Araujo MI, Guimaraes NS. Therapeutic response to thalidomide in Melkersson-Rosenthal syndrome: a case report. *Ann Allergy Asthma Immunol* 2002; **88**: 421–4.
8 Tatnall FM, Dodd HJ, Sarkany I. Crohn's disease with metastatic cutaneous involvement and granulomatous cheilitis. *J R Soc Med* 1987; **80**: 49–50.
9 Kano Y, Shiohara T, Yagita A, Nagashima M. Association between cheilitis granulomatosa and Crohn's disease. *J Am Acad Dermatol* 1993; **28**: 801.
10 Khouri JM, Bohane TD, Day AS. Is orofacial granulomatosis in children a feature of Crohn's disease? *Acta Paediatr* 2005; **94**: 501–4.
11 Goncalves DU, de Castro MM, Galvao CP *et al*. Cheilitis granulomatosa associated with Melkersson-Rosenthal syndrome. *Rev Bras Otorrinolaringol (Engl Ed)* 2007; **73**: 132–3.
12 Carr D. Granulomatous cheilitis in Crohn's disease. *BMJ* 1974; **iv**: 636.
13 Talbot T, Jewell L, Schloss E *et al*. Cheilitis antedating Crohn's disease. Case report and literature review. *J Clin Gastroenterol* 1984; **6**: 349–54.
14 Verbov JL. The skin in patients with Crohn's disease and ulcerative colitis. *Trans Rep St John's Hosp Derm Soc Lond* 1973; **59**: 30–8.
15 Narbutt P, Dziki A. Melkersson-Rosenthal syndrome as an early manifestation of Crohn's disease. *Colorectal Dis* 2005; **7**: 420–1.
16 Wiesenfeld D, Ferguson MM, Mitchell DN *et al*. Orofacial granulomatosis: a clinical and pathological analysis. *Q J Med* 1985; **54**: 101–13.
17 Pryce DW, King CM. Orofacial granulomatosis associated with delayed hypersensitivity to cobalt. *Clin Exp Dermatol* 1990; **15**: 384–96.
18 McKenna KE, Walsh MY, Burrows D. The Melkersson–Rosenthal syndrome and food additive hypersensitivity. *Br J Dermatol* 1994; **131**: 921–2.
19 Patton DW, Ferguson MM, Forsyth A, James J. Orofacial granulomatosis: a possible allergic basis. *Br J Oral Maxillofac Surg* 1985; **23**: 235–42.
20 Sweatman MC, Tasker R, Warner JO *et al*. Orofacial granulomatosis response to elemental diet and provocation by food additives. *Clin Allergy* 1986; **16**: 331–8.
21 White A, Nunes C, Escudier M *et al*. Improvement in orofacial granulomatosis on a cinnamon- and benzoate-free diet. *Inflamm Bowel Dis* 2006; **12**: 508–14.
22 Sakuntabhai A, MacLeod RI, Lawrence CM. Intralesional steroid injection after nerve block anaesthesia in the treatment of orofacial granulomatosis. *Arch Dermatol* 1993; **129**: 477–80.
23 Hernandez G, Hernandez F, Lucas M. Miescher's granulomatous cheilitis: literature review. *J Oral Maxillofac Surg* 1986; **44**: 474–8.
24 Kint A, De Brauwere D. Cheilitis granulomatosa und Crohnsche Krankheit. *Hautarzt* 1977; **28**: 319–21.
25 Rhodes EL, Stirling GA. Granulomatous cheilitis. *Arch Dermatol* 1965; **92**: 40–4.
26 Worsaae N, Christensen KC, Schiodt M. Melkersson–Rosenthal syndrome and cheilitis granulomatosa. *Oral Surg* 1982; **54**: 404–13.
27 Nozicka Z. Endovasal granulomatous lymphangitis as a pathogenetic factor in cheilitis granulomatosa. *J Oral Pathol* 1985; **14**: 363–5.
28 Ficarra G, Cicchi P, Amorosi A, Piluso S. Oral Crohn's disease and pyostomatitis vegetans. *Oral Surg Oral Med Oral Pathol* 1993; **75**: 220–4.
29 El-Hakim M, Chauvin P. Orofacial granulomatosis presenting as persistent lip swelling: review of 6 new cases. *J Oral Maxillofac Surg* 2004; **62**: 1114–7.
30 Mignogna MD, Fedele S, Lo Russo L, Lo Muzio L. The multiform and variable patterns of onset of orofacial granulomatosis. *J Oral Pathol Med* 2003; **32**: 200–5.
31 Zimmer WM, Rogers RS, Reeve CM, Sheridan PJ. Orofacial manifestations of Melkersson–Rosenthal syndrome. *Oral Surg* 1992; **74**: 610–9.

32 Khandpur S, Malhotra AK, Khanna N. Melkersson-Rosenthal syndrome with diffuse facial swelling and multiple cranial nerve palsies. *J Dermatol* 2006; **33**: 411–4.
33 Scully C, Eveson JW, Witherow H *et al.* Oral presentation of lymphoma: case report of T-cell lymphoma masquerading as oral Crohn's disease, and review of the literature. *Oral Oncol* 1993; **29B**: 225–30.
34 Cermale D, Serri F. Intralesional injection of triamcinolone in the treatment of cheilitis granulomatosa. *Arch Dermatol* 1963; **72**: 695–6.
35 Williams AJK, Wray D, Ferguson A. The clinical entity of orofacial Crohn's disease. *Q J Med* 1991; **79**: 451–8.
36 Van der Waal RI, Schulten EA, Van der Meij EH *et al.* Cheilitis granulomatosa: overview of 13 patients with long-term follow-up-results of management. *Int J Dermatol* 2002; **41**: 225–9.
37 Coskun B, Saral Y, Cicek D, Akpolat N. Treatment and follow-up of persistent granulomatous cheilitis with intralesional steroid and metronidazole. *J Dermatolog Treat* 2004; **15**: 333–5.
38 Kovich OI, Cohen DE. Granulomatous cheilitis. *Dermatol Online J* 2004; **10**: 10.
39 Perez-Calderon R, Gonzalo-Garijo MA, Chaves A, de Argila D. Cheilitis granulomatosa of Melkersson-Rosenthal syndrome: treatment with intralesional corticosteroid injections. *Allergol Immunopathol (Madr)* 2004; **32**: 36–8.
40 Eisenbud L, Hymowitz S, Shapiro R. Cheilitis granulomatosa. *Oral Surg Oral Med Oral Pathol* 1971; **32**: 384–9.
41 Kruse Losler B, Pressor D, Metze D, Joos U. Surgical treatment of persistent macrocheilia in patients with Melkersson-Rosenthal syndrome and cheilitis granulomatosa. *Arch Dermatol* 2005; **141**: 1085–91.
42 Krutchkoff D, James R. Cheilitis granulomatosa: successful treatment with combined local triamcinolone injections and surgery. *Arch Dermatol* 1978; **114**: 1203–6.
43 Scully C, Cochran KM, Russell RI *et al.* Oral Crohn's disease as an indicator of intestinal involvement. *Gut* 1982; **23**: 198–201.
44 Williams PM, Greenberg MS. Management of cheilitis granulomatosa. *Oral Surg* 1991; **72**: 436–9.
45 Allen CM, Camisa C, Hamzeh S, Stephens L. Cheilitis granulomatosa: report of six cases and review of the literature. *J Am Acad Dermatol* 1990; **23**: 444–50.
46 Neuhofer J, Fritsch P. Cheilitis granulomatosa: therapy with clofazimine. *Hautarzt* 1984; **35**: 459–63.
47 Podmore P, Burrows D. Clofazimine: an effective treatment for Melkersson–Rosenthal syndrome or Miescher's cheilitis. *Clin Exp Dermatol* 1986; **11**: 173–8.
48 Fdez-Freire LR, Serrano Gotteradano A, Bernabeu Wittel J *et al.* Clofazimine as elective treatment for granulomatous cheilitis. *J Drugs Dermatol* 2005; **4**: 374–7.
49 Kano Y, Shiohara T, Yagita A. Treatment of recalcitrant cheilitis granulomatosa with metronidazole. *J Am Acad Dermatol* 1992; **27**: 629–30.
50 Scully C, Eveson JW. Oral granulomatosis. *Lancet* 1991; **338**: 20–1.
51 Bender MM, Cheilitis glandularis in an African-American woman: response to antibiotic therapy. *Skinmed* 2005; **4**: 391–2.
52 Barry O, Barry J, Langan S *et al.* Treatment of granulomatous cheilitis with infliximab. *Arch Dermatol* 2005; **141**: 1080–2.

Exfoliative cheilitis

Synonyms
- Factitious cheilitis
- Le tic de lèvres

Exfoliative cheilitis is a chronic superficial inflammatory disorder of the vermilion borders of the lips characterized by persistent scaling (Figs 69.81 & 69.82). The diagnosis is now restricted to those few patients whose lesions cannot be attributed to other causes, such as contact sensitization or light (see actinic cheilitis, p. 69.123).

Aetiology. Many cases are now thought to be factitious, owing to repeated lip sucking, chewing or other manipulation of the lips [1–5]. There is no association with dermatological or systemic disease, although rare cases are seen in HIV infection. Some are infected with *Candida* species [6,7].



Fig. 69.81 Factitious cheilitis due to repeated lip sucking.



Fig. 69.82 Exfoliative cheilitis.

Clinical features. Most cases occur in girls or young women, and the majority have a personality disorder [8,9]. The process, which often starts in the middle of the lower lip and spreads to involve the whole of the lower or both lips, consists of scaling and crusting, more or less confined to the vermilion border, and persisting in varying severity for months or years. The patient often complains of irritation or burning, and can be observed frequently biting or sucking the lips. In some cases the condition appears to start with chapping or with atopic eczema, and develops into a habit tic.

In a large Russian series, almost half the cases had associated thyroid disease [10], but this observation has not been confirmed.

Diagnosis. Contact and active cheilitis must be carefully excluded. Chronic exfoliative cheilitis is readily contaminated by *Candida*. In such cases the clinical features are variable and may simulate carcinoma, LP or lupus erythematosus.

Treatment. Some cases resolve spontaneously [2,11] or with improved oral hygiene [12]. Reassurance and topical corticosteroids [1], or tacrolimus [4] may be helpful in some cases but others require psychotherapy, antidepressants or tranquillizers [3,5,11,13].

References

1 Thomas JR, Greene SL, Dicken CH. Factitious cheilitis. *J Am Acad Dermatol* 1983; **8**: 368–72.
2 Daley TD, Gupta AK. Exfoliative cheilitis. *J Oral Pathol Med* 1995; **24**: 177–9.
3 Taniguchi S, Kono T. Exfoliative cheilitis: a case report and review of the literature. *Dermatology* 1998; **196**: 253–5.
4 Connolly M, Kennedy C. Exfoliative cheilitis successfully treated with topical tacrolimus. *Br J Dermatol* 2004; **151**: 241–2.
5 Leyland L, Field EA. Case report: exfoliative cheilitis managed with antidepressant medication. *Dent Update* 2004; **31**: 524–6.
6 Reade PC, Rich AM, Hay KD, Radden BG. Cheilo-candidiasis: a possible clinical entity. *Br Dent J* 1982; **152**: 305–8.
7 Reichert PA, Weigl D, Schmidt-Westhausen A, Pohle HD. Exfoliative cheilitis (EC) in AIDS: association with Candida infection. *J Oral Pathol Med* 1997; **26**: 290–3.
8 Jeanmougin M, Civatte J, Bertail MA. Cheilites squamo-crouteuses factices. *Ann Dermatol Vénéréol* 1984; **111**: 1007–11.
9 Reade PC, Sim R. Exfoliative cheilitis: a factitious disorder? *Int J Oral Maxillofac Surg* 1986; **15**: 313–7.
10 Kutin SA. Clinical aspects and pathogenesis of exfoliative cheilitis. *Vestn Dermatol Venerol* 1970; **44**: 39–43.
11 Postlethwaite KR, Hendrickse MA. A case of exfoliative cheilitis. *Br Dent J* 1988; **165**: 23.
12 Brooke RI. Exfoliative cheilitis. *Oral Surg* 1978; **45**: 52–5.
13 Crotty CP, Dicken CH. Factitious lip crusting. *Arch Dermatol* 1981; **117**: 338–40.

Plasma cell cheilitis

Synonym
- Plasma cell orificial mucositis

Plasma cell cheilitis is an idiopathic benign inflammatory condition, characterized by dense plasma cell infiltrates in the lips and other mucosae close to body orifices [1–5]. The condition has been reported (under a wide variety of names) to affect the penis, vulva, lips, buccal mucosa, palate, gingiva, tongue, epiglottis and larynx.

Plasma cell cheilitis is the counterpart of Zoon's plasma cell balanitis (see Chapter 71). It presents as circumscribed flat or elevated patches of erythema, usually on the lower lip in an elderly person. The cause is unknown, but it responds to the application of powerful topical corticosteroids such as clobetasol, or to the intradermal injection of triamcinolone [5,6], or to systemic griseofulvin [4,7].

A similar lesion, which tends to form a tumorous mass with a hyperkeratotic surface and needs to be differentiated from extramedullary plasmacytoma [8], has been called *plasma-acanthoma* [9,10].

References

1 Baughman RD. Plasma cell cheilitis. *Arch Dermatol* 1974; **110**: 725–6.
2 Luders G. Plasmacytosis mucosae: Ein oft verkanntes neues Krankheitsbild. *Munch Med Wochenschr* 1972; **114**: 8–12.
3 White JW, Olsen KD, Banks PM. Plasma cell orificial mucositis. Report of a case and review of the literature. *Arch Dermatol* 1986; **122**: 1321–4.



Fig. 69.83 Discoid lupus erythematosus of the lower lip.

4 Rocha N, Mota F, Horta M *et al*. Plasma cell cheilitis. *J Eur Acad Dermatol Venereol* 2004; **18:** 96–8.
5 Yang JH, Lee UH, Jang SJ, Choi JC. Plasma cell cheilitis treated with intralesional injection of corticosteroids. *J Dermatol* 2005; **32**: 987–90.
6 Jones SK, Kennedy CTC. Response of plasma cell orificial mucositis to topically applied steroids. *Arch Dermatol* 1988; **124**: 1871–2.
7 Tamaki K, Osada A, Tsukamato K, Ohtake N, Furue M. Treatment of plasma cell cheilitis with griseofulvin. *J Am Acad Dermatol* 1994; **30**: 789–90.
8 Burke WA, Merritt CC, Briggaman RA. Disseminated extramedullary plasmacytomas. *J Am Acad Dermatol* 1986; **14**: 335–9.
9 Ferreira-Marques J. Beitrag zur Kenntnis der Plasmocytosis circumorificialis (Scheuermann) 'Plasmoakanthoma'. *Arch Klin Exp Dermatol* 1962; **215**: 151–64.
10 Ramos E, Silva J. Das Plasmoakanthom. *Hautarzt* 1965; **16**: 7–11.

Lupus erythematosus (see Chapter 51)

Involvement of the vermilion zone is quite common in both discoid erythematosus and SLE [1–3]. Discoid lupus can be premalignant [4–6], and should be treated vigorously with topical steroid ointments and sunscreens [7,8]. The cheilitis of SLE tends to be more severe, with erosions and haemorrhagic crusts.

Lupus erythematosus can be very difficult to distinguish from LP of the lips, both clinically and by histology (Fig. 69.83).

References

1 Coulson IH, Marsden RA. Lupus erythematosus cheilitis. *Clin Exp Dermatol* 1986; **11**: 309–13.
2 Lourenco SV, Nacagami Sotto M, Constantino Vilela M *et al*. Lupus erythematosus: clinical and histopathological study of oral manifestations and immunohistochemical profile of epithelial maturation. *J Cutan Pathol* 2006; **33**: 657–62.
3 Lourenco SV, de Carvallho FR, Boggio P *et al*. Lupus erythematosus: Clinical and histopathological study of oral manifestations and immunohistochemical profile of the inflammatory infiltrate. *J Cutan Pathol* 2007; **34**: 558–64.
4 Gupta U, Barman KD, Saify K. Squamous cell carcinoma complicating an untreated chronic discoid lupus erythematosus (CDLE) lesion in a black female. *J Dermatol* 2005; **32**: 1010–3.
5 Ee HL, Ng PP, Tan SH, Goh CL. Squamous cell carcinoma developing in two Chinese patients with chronic discoid lupus erythematosus: the need for continued surveillance. *Clin Exp Dermatol* 2006; **31**: 542–4.
6 Mulwafu WK, Fagan JJ, Jessop S. Squamous cell carcinoma in black patients with discoid lupus erythematosus. *S Afr J Surg* 2006; **44**: 144–6.
7 Martin S, Rosen T, Locker E. Metastatic squamous cancer of lips. Occurrence in Blacks with discoid lupus erythematosus. *Arch Dermatol* 1979; **115**: 1214.
8 Fotos PG, Finkelstein MW. Discoid lupus erythematosus of the lip and face. *J Oral Maxillofac Surg* 1992; **50**: 642–5.



Fig. 69.84 Lip fissure.

Sarcoidosis (see Chapter 61)

Sarcoidosis may cause chronic violaceous lesions on, or swelling of, the lips [1–5].

References

1 James DG. Lupus pernio. *Lupus* 1992; **1**: 129–31.
2 Rogers RS 3rd, Bekic M. Diseases of the lips. *Semin Cutan Med Surg* 1997 Dec; **16**: 328–36.
3 Blinder T, Yahatom R, Taicher S. Oral manifestations of sarcoidosis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1997; **83**: 458–61.
4 Sciubba JJ, Said-Al-Naief N. Orofacial granulomatosis: presentation, pathology and management of 13 cases**.** *J Oral Pathol Med* 2003; **32**: 576–85.
5 Suresh L, Radfar L. Oral sarcoidosis: a review of literature. *Oral Dis* 2005; **11**: 138–45.

Lip fissure

A lip fissure may develop when a patient, typically a child, is mouth-breathing (Fig. 69.84). Otherwise the aetiology may be obscure, though sun, wind, cold weather and smoking are thought to predispose. A hereditary predisposition for weakness in the first branchial arch fusion seems to exist.

Lip fissures are common in Down's syndrome and the lips may also crack in this way if swollen, for example in cheilitis granulomatosa [1–6].

Clinical features. Most lip fissures are seen in males, typically median in the lower lip and chronic, causing discomfort and possibly bleeding from time to time. Contrary to the clinical impression that fissures are seen only in the lower lip, there is also a high prevalence in the upper lip.

Diagnosis. The diagnosis is clinical.

Treatment. Predisposing factors should be managed. Bland creams may help the lesion heal spontaneously. Otherwise, local applications of 1–2% silver nitrate, 0.5% balsam of Peru, salicylic acid and topical antimicrobials seem less effective than excision, preferably with a Z-plasty [7–10] or cryosurgery [11].

References

1 Axell T, Skoglund A. Chronic lip fissures. *Int J Oral Surg* 1981; **10**: 354–8.
2 Ball G, Barnard D. The treatment of chronic lip fissures with cryotherapy. *Br Dent J* 1984; **157**: 64–6.
3 Dingman RO. Chronic fissure of the lower lip. *Plast Reconstr Surg* 1948; **3**: 613.
4 Ecker H. Medial clefts of the lips. *Am J Surg* 1958; **96**: 815.
5 Kluemper GT, White DK, Slevin JT. Chronic fissural cheilitis: a manifestation of anterior crowding. *Am J Orthod Dentofacial Orthop* 2001; **119**: 71–5.
6 Yenidunya MO, Emsen IM, Ozdengil E. Median lower lip fissure. *Plast Reconstr Surg* 2001; **107**: 888–9.
7 Scully C, Van Bruggen W, Dios PD, Porter SR, Davison M. Down syndrome: lip lesions and *Candida albicans*. *Br J Dermatol* 2002; **147**: 37–40.
8 Maisels DO. Chronic lip fissures. *Br J Dermatol* 1969; **81**: 621–2.
9 Rashid N, Yusuf H. Median lip fissures and their management. *Int J Oral Maxillofac Surg* 1997; **26**: 299–300.
10 Rosenquist B. Median lip fissure: etiology and suggested treatment. *Oral Surg* 1991; **72**: 10–4.
11 Rosenquist BE. Median lip fissure. *J Craniofac Surg* 1995; **6**: 390–1.

Lip ulcer due to calibre-persistent artery

A calibre-persistent artery is defined as an artery with a larger than normal diameter near a mucosal or external surface. When such arteries occur in the gut wall (Dieulafoy malformation) they may bleed, but in the lip they tend to cause chronic ulceration that can be mistaken for a squamous cancer. The ulcer is attributed to continual pulsation from the large artery running parallel to the surface, although the exact mechanism is obscure [1,2].

Ligation of the artery appears successful [3].

References

1 Mike T, Adler P, Endes P. Simulated cancer of lower lip attributed to a 'calibre-persistent artery'. *J Oral Pathol* 1980; **9**: 137–44.
2 Marshall RI, Leppard BJ. Ulceration of the lip associated with a 'calibrepersistent artery'. *Br J Dermatol* 1985; **113**: 757–60.
3 Lovas JGL, Goodday RHB. Clinical diagnosis of calibre-persistent labial artery of the lower lip. *Oral Surg* 1993; **76**: 480–3.

Reactive perforating collagenosis (see Chapter 45)

Crateriform papules of the lower lip have been reported in reactive perforating collagenosis [1].

Reference

1 Trattner A, Lueber A, Sandbank M. Mucosal involvement in reactive perforating collagenosis. *J Am Acad Dermatol* 1991; **25**: 1079–81.

CHAPTER 70
The Breast

D.A. Burns
Leicester Royal Infirmary, Leicester, UK

Supernumerary breasts or nipples; rudimentary nipples; hypomastia/amastia, 70.2
Supernumerary breasts or nipples, 70.2
Rudimentary nipples, 70.3
Hypomastia/amastia, 70.3
Breast hypertrophy, 70.3
Gigantomastia (macromastia), 70.3
Gynaecomastia, 70.3
Black galactorrhoea, 70.6
Morphoea, 70.6
Silicone breast implants and autoimmune disease, 70.7
Adnexal polyp of neonatal skin, 70.8
Inverted nipple, 70.8
The duct ectasia/periductal mastitis complex, 70.8
Hyperkeratosis of the nipple/areola, 70.8
Eczema of the nipple/areola, 70.9
'Cracked' nipples in lactation, 70.10
Jogger's and cyclist's nipples, 70.10
Guitar nipple, 70.11
Nipple piercings, 70.11
Thelalgia, 70.11
Artefactual breast disease, 70.11
Vasculitis of the breast, 70.11
Lupus panniculitis, 70.12
Sarcoidosis of the breast, 70.12
Erosive adenomatosis of the nipple, 70.12
Sebaceous hyperplasia of the areolae, 70.13
Breast telangiectasia, 70.13
Mammary duct fistula, 70.13
Breast abscess, 70.13
Breast cancer, 70.13
Breast cancer in men, 70.14
Basal cell carcinoma of the nipple/areola, 70.15
Malignant melanoma of the nipple/areola, 70.15
Hair sinus of the breast, 70.15
Seborrhoeic warts, 70.15
Mondor's disease, 70.16
Other conditions that may involve the breast, 70.17

The terms 'breasts' and 'mammary glands' are often accepted as equivalent, but they are not strictly synonymous, because the breasts contain tissues (fat, vessels, nerves, etc.) other than the glandular elements.

In the evolutionary sense, the mammary glands are believed to be related to the apocrine sweat glands. They develop from ectodermal mammary ridges ('milk lines'). The classical view, derived from comparative anatomy, that the mammary ridges extend from the base of the upper limb bud to the base of the lower limb bud, is now questioned. It is considered that the mammary ridge extends only over the axillopectoral area [1].

The skin of the breast does not differ structurally from that of the neighbouring chest wall, but the skin of the nipple and areola is very highly specialized. There are individual and racial variations in the size, shape and colour of the nipple and areola. The periphery of the areola contains hair follicles, and the development of coarse terminal hairs in this site may be a cosmetic problem for some women.

The nipple is glabrous. Lactiferous ducts and sebaceous glands open only at its tip. Sensory nerve end organs are also confined to the tip of the nipple. The areola has clusters of large sebaceous glands [2] and the so-called tubercles of Montgomery. These elevations on the areola are produced by the glands of Montgomery [3]. Each of these is a combined sebaceous unit and lactiferous gland, with the lactiferous duct opening into the sebaceous duct close to the areola or occasionally directly onto the areola [1]. The glands of Montgomery are an integral part of the lactiferous apparatus, secreting milk during lactation.

The development of the breasts at puberty requires oestrogens and progesterone, and, in a more minor role, insulin, growth hormone, corticosteroids and prolactin. The adult breast consists of several lobes, each of which is drained by a ductal system ending in a lactiferous duct that opens at the nipple. Each lobe contains up to 40 lobules, and each lobule 10–100 alveoli, the basic secretory units [1].

The breasts enlarge during pregnancy, and the veins become prominent. The areolae also enlarge and become darker. This pigmentation decreases after parturition but does not fade completely.

Although most of the more serious diseases of the breast come within the province of the surgeon, the gynaecologist or the endocrinologist, there are some diseases that affect only the breast skin and are wholly the concern of the dermatologist, and others that may involve the skin and present difficult problems in differential diagnosis.

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

References

1 Hughes LE, Mansel RE, Webster DJT. *Benign Disorders and Diseases of the Breast*. 2nd edn. London: WB Saunders, 2000.
2 Montagna W. Histology and cytochemistry of human skin XXXV. The nipple and areola. *Br J Dermatol* 1970; **83**: 2–13.
3 Montagna W, Yun JS. The glands of Montgomery. *Br J Dermatol* 1972; **86**: 126–33.

Supernumerary breasts or nipples; rudimentary nipples; hypomastia/amastia

Supernumerary breasts or nipples [1,2]

Supernumerary (accessory) breasts (polymastia) and the far more common supernumerary nipples (polythelia) usually develop along the course of the milk lines. Accessory glandular tissue most frequently occurs in the axillae [3], but rarely breast components occur in other sites [4–6].

Accessory breast tissue may consist of nipple, areola or glandular tissue singly, or in any combination (Fig. 70.1). The condition is very common in women, with an incidence of around 2–4%, although in the majority of cases the accessory nipple is insignificant, appearing as a small brown papule, usually on the chest wall, just below the breast. Much more rarely, the condition occurs in men, and in one case a fully developed breast developed on the posterior aspect of the thigh of a male [7]. A familial incidence in numerous cases suggests dominant inheritance (OMIM 163700).

Polythelia occurs as a component of a number of rare genodermatoses, and the Online Mendelian Inheritance in Man (OMIM) site is a useful reference source for these [www.ncbi.nlm.nih.gov/sites/entrez?db=OMIM].

A reported association between the presence of supernumerary nipples and urinary tract anomalies in children [8–10] prompted debate about whether to investigate the renal tract (by ultrasonography) in children with supernumerary nipples and no other obvious anomaly [11–13]. Some studies have not demonstrated an association [14,15], and specific mention has been made of the infrequency of such an association in black American infants [16,17]. However, there is evidence to indicate that the association is stronger in cases of familial polythelia, and it has been suggested that familial occurrence should prompt investigation of family members with renal ultrasonography [18,19].

The association of various mammary anomalies (supernumerary breasts; breast aplasia/hypoplasia/athelia; 'wide set' nipples) with anomalies of the kidneys/ urinary collecting system has been assessed by Urbani and Betti [20], who suggested a classification composed of four subsets: (i) pure 'mammo-renal syndromes' which occur as sporadic conditions and are characterized by the involvement of mammary tissue and kidney alone, without evidence of other developmental defects (e.g. Fleisher syndrome: 'wide set' nipples and bilateral renal hypoplasia); (ii) mammo-renal syndromes associated with chromosomal disorders (e.g. Turner phenotype: 'wide set' nipples and horseshoe kidney/bifid renal pelvis/unilateral renal hypoplasia); (iii) mammo-renal syndromes associated with dysmorphic genetic syndromes (e.g. Kallmann syndrome: breast hypoplasia and horseshoe kidney/unilateral renal agenesis); (iv) acro-mammo-renal syndromes, characterized by an additional coexistence of acral (limb) defects (e.g. Poland syndactyly: breast and nipple hypoplasia with unilateral renal hypoplasia).

An accessory nipple may be confused with a pigmented naevus. If functional breast tissue is present, enlargement at puberty or in pregnancy may be embarrassing or painful. Simple excision is advisable, as carcinoma may occur.



Fig. 70.1 Supernumerary nipple and breast tissue.

References

1 Grossl NA. Supernumerary breast tissue: historical perspectives and clinical features. *South Med J* 2000; **93**: 29–32.
2 Velanovich V. Ectopic breast tissue, supernumerary breasts, and supernumerary nipples. *South Med J* 1995; **88**: 903–6.
3 Jordan K, Laumann A, Conrad S, Medenica M. Axillary mass in a 20-year-old woman. *Arch Dermatol* 2001; **137**: 1367–72.
4 Tow SH, Shanmugaratnam K. Supernumerary mammary gland in the vulva. *BMJ* 1962; **ii**: 1234–6.
5 Shewmake SW, Izuno GT. Supernumerary areolae. *Arch Dermatol* 1977; **113**: 823–5.
6 Leung W, Heaton JPW, Morales A. An uncommon urologic presentation of a supernumerary breast. *Urology* 1997; **50**: 122–4.
7 Camisa C. Accessory breast on the posterior thigh of a man. *J Am Acad Dermatol* 1980; **3**: 467–9.
8 Varsano IB, Jaber L, Garty B-Z *et al*. Urinary tract abnormalities in children with supernumerary nipples. *Pediatrics* 1984; **73**: 103–5.
9 Méhes K, Pintér A. Minor morphological aberrations in children with isolated urinary tract malformations. *Eur J Pediatr* 1990; **149**: 339–402.
10 Meggyessy V, Méhes K. Association of supernumerary nipples with renal anomalies. *J Pediatr* 1987; **111**: 412–3.
11 Hersh J. Association of supernumerary nipples and renal anomalies. *Am J Dis Child* 1988; **142**: 591–2.
12 Mimouni F. Association of supernumerary nipples and renal anomalies. *Am J Dis Child* 1988; **142**: 591.
13 Hersh JH, Bloom AS, Cromer AO *et al*. Does a supernumerary nipple/renal field defect exist? *Am J Dis Child* 1987; **141**: 989–91.
14 Jójárt G, Seres E. Supernumerary nipples and renal anomalies. *Int Urol Nephrol* 1994; **26**: 141–4.
15 Grotto I, Browner-Elhanan K, Mimouni D *et al*. Occurrence of supernumerary nipples in children with kidney and urinary tract malformations. *Pediatr Dermatol* 2001; **18**: 291–4.
16 Kenney RD, Flippo JL, Black EB. Supernumerary nipples and renal anomalies in neonates. *Am J Dis Child* 1987; **141**: 987–8.
17 Robertson A, Sale P, Sathyanarayan. Lack of association of supernumerary nipples with renal anomalies in black infants. *J Pediatr* 1986; **109**: 502–3.

18 Leung AKC, Robson WLM. Renal anomalies in familial polythelia. *Am J Dis Child* 1990; **144**: 619–20.
19 Brown J, Schwartz RA. Supernumerary nipples and renal malformations: a family study. *J Cutan Med Surg* 2004; **8**: 170–2.
20 Urbani CE, Betti R. Mammo-renal and acro-mammo-renal syndromes. A nosologic approach, synopsis and update. *Eur J Dermatol* 1997; **7**: 251–6.

Rudimentary nipples

The association of absent or rudimentary nipples with abnormalities of the scalp and ears has been reported as an autosomal dominant trait [1–3]. Rudimentary nipples are also a feature of the ablepharon-macrostomia and Barber–Say syndromes, the other features of which include absence of the eyelids or ectropion, macrostomia, ear anomalies, redundant skin, abnormal genitalia, and hypertrichosis in the Barber–Say syndrome [4,5].

References

1 Finlay AY, Marks R. An hereditary syndrome of lumpy scalp, odd ears and rudimentary nipples. *Br J Dermatol* 1978; **99**: 423–30.
2 Le Merrer M, Renier D, Briard ML. Scalp defect, nipples absence and ears abnormalities: another case of Finlay syndrome. *Genet Couns* 1991; **2**: 233–6.
3 Edwards MJ, McDonald D, Moore P, Rae J. Scalp–ear–nipple syndrome: additional manifestations. *Am J Med Genet* 1994; **50**: 247–50.
4 Stevens CA, Sargent LA. Ablepharon-macrostomia syndrome. *Am J Med Genet* 2002; **107**: 30–7.
5 Dinulos MB, Pagon RA. Autosomal dominant inheritance of Barber–Say syndrome. *Am J Med Genet* 1999; **86**: 54–6.

Hypomastia/amastia [1]

Very small breasts are fairly common in otherwise normal women, in whom they may cause considerable psychological distress. There is some evidence of an association between hypoplastic breasts (defined as a breast size of 200 ml or less) and mitral valve prolapse [1]. Becker's naevus is occasionally associated with unilateral breast hypoplasia [2,3], possibly as a result of high androgen-receptor activity on the affected side, and with areolar hypoplasia in males [4,5]. Unilateral symbrachydactyly and ipsilateral aplasia of the sternal head of the pectoralis major muscle, aplasia of the breast and absence of axillary hair are features of the Poland syndrome (OMIM 173800). Breast hypoplasia or aplasia is a feature of the *AREDYLD* (acrorenal field defect, ectodermal dysplasia, and lipoatrophic diabetes) syndrome (OMIM 207780).

References

1 Rosenberg CA, Derman GH, Grabb WC, Buda AJ. Hypomastia and mitral-valve prolapse. *N Engl J Med* 1983; **309**: 1230–2.
2 Formigón M, Alsina MM, Mascaró JM, Rivera F. Becker's nevus and ipsilateral breast hypoplasia. Androgen-receptor study in two patients. *Arch Dermatol* 1992; **128**: 992–3.
3 Van Gerwen HJL, Koopman RJJ, Steijlen PM, Happle R. Becker's naevus with localized lipoatrophy and ipsilateral breast hypoplasia. *Br J Dermatol* 1993; **129**: 213.
4 Sharma R, Mishra A. Becker's naevus with ipsilateral areolar hypoplasia in three males. *Br J Dermatol* 1997; **136**: 471–2.
5 Crone AM, James MP. Giant Becker's naevus with ipsilateral areolar hypoplasia and limb asymmetry. *Clin Exp Dermatol* 1997; **22**: 240–1.

Breast hypertrophy

Unusually large breasts may be problematic for a number of reasons, and postural abnormalities, backache and psychological disturbance may prompt referral to a plastic surgeon for a reduction mammoplasty. A dermatologist may be consulted about associated problems such as submammary intertrigo.

Breast enlargement in the setting of HIV infection is a relatively recently described phenomenon. It may be a component of the lipodystrophy syndrome (lipomastia), or there may be true gynaecomastia (see below). Breast ultrasonography allows these two states to be differentiated [1].

References

1 Qazi NA, Morlese JF, King DM *et al*. Gynaecomastia without lipodystrophy in HIV-1-seropositive patients on efavirenz: an alternative hypothesis. *AIDS* 2002; **16**: 506–7.

Gigantomastia (macromastia)

Gigantomastia is a condition in which the female breasts enlarge rapidly until they reach an enormous size. The overlying skin may become inflamed, oedematous and tender, and there may be striae or even severe ulceration associated with breast necrosis [1]. The condition may occur at puberty [2–4] or during pregnancy [1,5,6]. The aetiology is obscure, but a suggested cause is increased sensitivity of the breast tissue to normal levels of circulating hormones. The condition is occasionally familial [7,8]. Penicillamine therapy can also cause gigantomastia [9–11]; treatment with danazol was of benefit in one such case [11]. Bromocriptine may be of benefit in patients in whom the condition occurs during pregnancy, but in many patients, and certainly in pubertal cases, reduction mammoplasty or simple mastectomy is usually required [12].

References

1 Gargan TJ, Goldwyn RM. Gigantomastia complicating pregnancy. *Plast Reconstr Surg* 1987; **80**: 121–4.
2 Hollingsworth DR, Archer R. Massive virginal breast hypertrophy at puberty. *Am J Dis Child* 1973; **125**: 293–5.
3 O'Hare PM, Frieden IJ. Virginal breast hypertrophy. *Pediatr Dermatol* 2000; **17**: 277–81.
4 Arscott GDL, Craig HR, Gabay L. Failure of bromocriptine therapy to control juvenile mammary hypertrophy. *Br J Plast Surg* 2001; **54**: 720–3.
5 Stavrides S, Hacking A, Tiltman A, Dent DM. Gigantomastia in pregnancy. *Br J Surg* 1987; **74**: 585–6.
6 Antevskil BM, Smilevski DA, Stojovski MZ *et al*. Extreme gigantomastia in pregnancy: case report and review of literature. *Arch Gynecol Obstet* 2007; **275**: 149–53.
7 Kupfer D, Dingman D, Broadbent R. Juvenile breast hypertrophy: report of a familial pattern and review of the literature. *Plast Reconstr Surg* 1992; **90**: 303–9.
8 Misirlioglu A, Akoz T. Familial severe gigantomastia and reduction with the free nipple graft vertical mammoplasty technique: report of two cases. *Aesthetic Plast Surg* 2005; **29**: 205–9.
9 Passas C, Weinstein A. Breast gigantism with penicillamine therapy. *Arthitis Rheum* 1978; **21**: 167–8.
10 Kahl LE, Medsger TA Jr, Klein I. Massive breast enlargement in a patient receiving d-penicillamine for systemic sclerosis. *J Rheumatol* 1985; **12**: 990–1.
11 Taylor PJ, Cumming DC, Corenblum B. Successful treatment of D-penicillamine-induced breast gigantism with danazol. *BMJ* 1981; **282**: 362–3.
12 Swelstad MR, Swelstad BB, Rao VK, Gutowski KA. Management of gestational gigantomastia. *Plast Reconstr Surg* 2006; **118**: 840–8.

Gynaecomastia [1–4]

Gynaecomastia, which may be defined as benign enlargement of the male breast caused by proliferation of the glandular

Table 70.1 Causes of gynaecomastia.

Physiological
Neonatal
Adolescent
Old age
Endocrine disorders
Hypogonadism, e.g. Klinefelter's
Excess oestrogen or chorionic gonadotrophin, e.g. from testicular tumour
Hyperthyroidism
Other disorders
Starvation, cachexia or refeeding
Renal disease and haemodialysis
Liver disease
Paraplegia
Erythroderma
HIV/AIDS
Idiopathic
Drugs (see Table 70.2)

components, can occur as an isolated defect or as a manifestation of a wide range of different pathological states in which it may be a valuable diagnostic sign. The multiplicity of syndromes associated with gynaecomastia reflects the complexity of the hormonal mechanisms concerned in breast enlargement. The patient complains of enlargement of the breast, which may be unilateral or bilateral, and is often tender.

Gynaecomastia can be distinguished from fatty enlargement of the breast in obesity (pseudogynaecomastia) by grasping the breast between thumb and forefinger and moving the digits up towards the nipple with the patient supine. In gynaecomastia a rubbery, mobile, disc-like mound will be felt beneath the areola.

Oestrogens stimulate and androgens inhibit development of breast tissue, and gynaecomastia occurs as a result of a disturbance of the ratio of free androgen to free oestrogen, with a relative increase in oestrogen levels. Peripheral conversion of androgens to oestrogen by aromatization contributes to oestrogen production. Local susceptibility of hormone receptors or local hormone conversion presumably play a role in unilateral gynaecomastia.

The histopathological changes [5] are related to the duration of gynaecomastia and not to its cause. At early stages, there are active proliferating ducts in a vascular fibroblastic stroma. Later, there is progressive fibrosis and hyalinization, and the number of ducts is reduced.

Gynaecomastia may be either physiological or pathological. Some of the causes are listed in Table 70.1.

Physiological gynaecomastia

There are three peaks in the age distribution of physiological gynaecomastia. It occurs in most male neonates due to transplacental passage of oestrogen from the mother. It is usually bilateral, but may be unilateral, and it regresses spontaneously. Some enlargement of the breast occurs at puberty in about 38% of normal boys [6]. The peak incidence is around the age of 14 years. It is unilateral in about 25% of cases. The degree of enlargement is usually slight, but may be sufficient to cause embarrassment and anxiety. Spontaneous regression usually takes place within a few months, but the enlargement occasionally persists for 2–3 years.

Gynaecomastia also appears to be frequent over the age of 65, increasing with age.

Gynaecomastia in endocrine disorders

Gynaecomastia occurs in a very wide range of endocrine disorders. Primary or secondary reduction of testicular androgen production is of special importance. Some tumours of the testis are associated with gynaecomastia, notably seminoma, Leydig-cell tumour, Sertoli-cell tumour and certain teratomas. Gynaecomastia occurs in most men with Klinefelter syndrome, and there is an increased risk of breast cancer in this syndrome [7,8], although other causes of gynaecomastia do not appear to be associated with an increased risk of cancer [1]. In other endocrine disorders, gynaecomastia is less common, but it may occur in association with tumours or hyperplasia of the adrenal gland, pituitary tumours and hyperthyroidism [9]. It may be an accompaniment of the use of human growth hormone as antiageing therapy [10].

Gynaecomastia in other disorders

Gynaecomastia may occur during starvation or on resumption of a more adequate diet after prolonged starvation [11]. Chronic renal failure and haemodialysis may also be associated with gynaecomastia [12–14], although the incidence of gynaecomastia in dialysis patients has decreased in recent years. Hepatic cirrhosis is usually listed as a cause of gynaecomastia, but one study found that palpable gynaecomastia was not a uniform feature in advanced cirrhosis, and that its prevalence was similar to that in a non-obese, non-cirrhotic, age-matched control population [15]. Gynaecomastia occasionally occurs in association with erythroderma [16]. Gynaecomastia in HIV-infected males is multifactorial, and contributory factors include hypogonadism, chronic hepatitis C virus coinfection and hyperprolactinaemia [17], as well as the influence of antiretroviral therapy (see below).

Drug-induced gynaecomastia [18–32]

Some of the drugs that may produce gynaecomastia are listed in Table 70.2. They produce their effect by different mechanisms, for example spironolactone and cimetidine are antiandrogens, and neuroleptic drugs produce hyperprolactinaemia. Testosterone might act by peripheral aromatization to oestrogens. Gynaecomastia is a common accompaniment of hormone therapy for prostate cancer [19] (Fig. 70.2).

True gynaecomastia, as opposed to breast hypertrophy secondary to lipodystrophy syndrome (lipomastia), can occur with all currently available classes of antiretroviral agents. The mechanism responsible is unclear, but suggestions include a direct effect of highly active antiretroviral therapy (HAART) mimicking the action of oestrogen or progesterone on breast tissue, an elevation of the oestrogen : androgen ratio, or improvement in the T-helper cytokine response after starting HAART [17,32,33]—cytokines produced during the immune restoration process have an effect on breast tissue, resulting in gynaecomastia; once immune restoration has occurred, the cytokine levels fall, and the gynaecomastia resolves spontaneously.

Table 70.2 Drugs that produce gynaecomastia.

Amiloride
Anabolic steroids
Antiandrogens, e.g. cyproterone acetate, flutamide
Amiodarone
Amphetamines
Androgens
Busulphan
Cannabis
Captopril
Chorionic gonadotrophin
Cimetidine
Cyproterone acetate
Cytotoxic agents
Diazepam
Diethylpropion
Digitalis
Domperidone
Finasteride
Highly active antiretroviral therapy (HAART)
Isoniazid
Ketoconazole
Melatonin
Methyldopa
Metoclopramide
Methotrexate
Nifedipine
Nitrosoureas
Oestrogens
Omeprazole
Penicillamine
Phenothiazines
Phenytoin
Reserpine
Spironolactone
Tricyclic antidepressants
Vincristine



Fig. 70.2 Gynaecomastia in a man taking stilboestrol for carcinoma of the prostate.

Finasteride treatment of male androgenic alopecia may be associated with gynaecomastia [34,35], and it has also been recorded in individuals who have used oestrogen-containing hair preparations [36,37] and in a men's hairdresser who had massaged the scalps of his balding customers with an oestrogen-containing lotion [38].

Gynaecomastia in three prepubertal boys was attributed to topical application of lavender and tea tree oils, both of which were shown to have oestrogenic and antiandrogenic activities [39].

Management of gynaecomastia [3,40]**.** In the majority of patients, history and examination will suggest the likely cause of the gynaecomastia. Careful examination for underlying disease and a full drug history are required, particularly if the gynaecomastia is symptomatic, progressive or of recent onset in an adult, but it should be remembered that a large proportion of otherwise normal men have some slight gynaecomastia. In unilateral disease, particularly in older men, breast cancer should be excluded. Spontaneous resolution occurs in many 'physiological' cases, or following cessation of the causative drug when it is drug related. For cases with considerable breast discomfort, or if the condition is severe enough to cause embarrassment, treatment with tamoxifen [41], clomiphene or danazol has been employed. The surgical approach of choice is excision and liposuction via a periareolar incision.

References

1 Braunstein GD. Gynaecomastia. *N Engl J Med* 1993; **328**: 490–5.
2 Sizonenko PC. Gynaecomastia. In: Grossman A, ed. *Clinical Endocrinology*, 2nd edn. Oxford: Blackwell Science, 1998: 761–8.
3 Hughes LE, Mansel RE, Webster DJT. *Benign Disorders and Diseases of the Breast*, 2nd edn. London: WB Saunders, 2000.
4 Ismail AA, Barth JH. Endocrinology of gynaecomastia. *Ann Clin Biochem* 2001; **38**: 596–607.
5 Nicolis GL, Modlinger RS, Gabrilove JL. A study of the histopathology of human gynaecomastia. *J Clin Endocrinol Metab* 1971; **32**: 173–8.
6 Nydick M, Bustos J, Dale JH Jr, Rawson RW. Gynecomastia in adolescent boys. *JAMA* 1961; **178**: 449–54.
7 Scheike O, Visfeldt J, Peterson B. Male breast cancer: breast carcinoma in association with Klinefelter syndrome. *Acta Pathol Microbiol Scand* 1973; **81**: 352–8.
8 Smyth CM, Bremner WJ. Klinefelter syndrome. *Arch Intern Med* 1998; **158**: 1309–14.
9 Tan YK, Birch CR, Valerio D. Bilateral gynaecomastia as the primary complaint in hyperthyroidism. *J R Coll Surg Edin* 2001; **46**: 176–7.
10 Liu H, Bravata DM, Olkin I *et al*. Systematic review: the safety and efficacy of growth hormone in the healthy elderly. *Ann Intern Med* 2007; **146**: 104–15.
11 Smith SR, Chhetri MK, Johanson AJ *et al*. The pituitary–gonadal axis in men with protein–calorie malnutrition. *J Clin Endocrinol Metab* 1975; **41**: 60–9.
12 Sawin CT, Longcope C, Schmitt GW, Ryan RJ. Blood levels of gonadotrophin and gonadal hormones in gynaecomastia associated with chronic haemodialysis. *J Clin Endocrinol Metab* 1973; **36**: 988–90.
13 Distiller LA, Morley JE, Sagel J *et al*. Pituitary-gonadal function in chronic renal failure: the effect of luteinizing hormone-releasing hormone and the influence of dialysis. *Metabolism* 1975; **24**: 711–20.
14 Davison AM, Cameron JS, Grünfeld J-P *et al.*, eds. *Oxford Textbook of Clinical Nephrology*, 2nd edn, Vol. 3. Oxford: Oxford University Press, 1998: 1874.
15 Cavanaugh J, Niewoehner CB, Nuttall FQ. Gynaecomastia and cirrhosis of the liver. *Arch Intern Med* 1990; **150**: 563–5.

16 Shuster S, Brown JB. Gynaecomastia and urinary oestrogens in patients with generalized skin disease. *Lancet* 1962; **ii**: 1358.
17 Gewurz BE, Dezube BJ, Pantanowitz L. HIV and the breast. *AIDS Read* 2005; **15**: 392–6; 399–402.
18 Dukes MNG, Aronson JK, eds. *Meyler's Side Effects of Drugs*. Amsterdam: Elsevier, 2000.
19 Dobs A, Darkes MJM. Incidence and management of gynaecomastia in men treated for prostate cancer. *J Urol* 2005; **174**: 1737–42.
20 Antonelli D, Luboshitzky R, Gelbendorf A. Amiodarone-induced gynecomastia. *N Engl J Med* 1986; **315**: 1553.
21 Markusse HM, Meyboom RHB. Gynaecomastia associated with captopril. *BMJ* 1988; **296**: 1262–3.
22 Clyne CAC. Unilateral gynaecomastia and nifedipine. *BMJ* 1986; **292**: 380.
23 Tanner LA, Bosco LA. Gynecomastia associated with calcium channel blocker therapy. *Arch Intern Med* 1988; **148**: 379–80.
24 Reid DM, Martynoga AG, Nuki G. Reversible gynaecomastia associated with D-penicillamine in a man with rheumatoid arthritis. *BMJ* 1982; **285**: 1083–4.
25 Monson JP, Scott DF. Gynaecomastia induced by phenytoin in men with epilepsy. *BMJ* 1987; **294**: 612.
26 Trump DL, Pavy MD, Staal S. Gynecomastia in men following antineoplastic therapy. *Arch Intern Med* 1982; **142**: 511–13.
27 Turner AR, Morrish DW, Berry J, MacDonald N. Gynecomastia after cytotoxic therapy for metastatic testicular cancer. *Arch Intern Med* 1982; **142**: 896–7.
28 Jun YY. Gynaecomastia with marked cellular atypia associated with chemotherapy. *Arch Pathol Lab Med* 2002; **126**: 613–4.
29 Del Paine DW, Leek JC, Jakle C, Robbins DL. Gynecomastia associated with low dose methotrexate therapy. *Arthritis Rheum* 1983; **26**: 691–2.
30 Thomas E, Leroux JL, Blotman F. Gynecomastia in patients with rheumatoid arthritis treated with methotrexate. *J Rheumatol* 1994; **21**: 1777–8.
31 De Bleecker JL, Lamont BH, Verstraete AG, Schelfhout VJ. Melatonin and painful gynaecomastia. *Neurology* 1999; **53**: 435–6.
32 Qazi NA, Morlese JF, King DM *et al*. Gynaecomastia without lipodystrophy in HIV-1-seropositive patients on efavirenz: an alternative hypothesis. *AIDS* 2002; **16**: 506–7.
33 Strub C, Kaufmann GR, Flepp M *et al*. Gynecomastia and potent antiretroviral therapy. *AIDS* 2004; **18**: 1347–9.
34 Wade MS, Sinclair RD. Reversible painful gynaecomastia induced by low-dose finasteride. *Australas J Dermatol* 2000; **41**: 55.
35 Ferrando J, Grimalt R, Alsina M, Manasievska E. Unilateral gynecomastia induced by treatment with 1 mg of oral finasteride. *Arch Dermatol* 2002; **138**: 543–4.
36 Edidin DV, Levitsky LL. Prepubertal gynecomastia associated with estrogen-containing hair cream. *Am J Dis Child* 1982; **136**: 587–8.
37 Gabrilove JL, Luria M. Persistent gynecomastia resulting from scalp inunction of estradiol. *Arch Dermatol* 1978; **114**: 1672–3.
38 Cimorra GA, Gonzalez-Peirona E, Ferrandez A. Percutaneous oestrogen-induced gynaecomastia: a case report. *Br J Plast Surg* 1982; **35**: 209–10.
39 Henley DV, Lipson N, Korach KS *et al*. Prepubertal gynaecomastia linked to lavender and tea tree oils. *N Engl J Med* 2007; **356**: 479–85.
40 Gikas P, Mokbel K. Management of gynaecomastia: an update. *Int J Clin Pract* 2007; **61**: 1209–15.
41 Kegg S, Lau R. Tamoxifen in antiretroviral-associated gynaecomastia. *Int J STD AIDS* 2002; **13**: 582–3.

Black galactorrhoea

Galactorrhoea is sometimes caused by drugs such as phenothiazines. In one patient taking perphenazine, the droplets of milk were stained black, due to the concomitant administration of minocycline for acne [1]. The pigment that produces the black discoloration of breast milk in women taking minocycline is thought to be due to an iron chelate of minocycline within macrophages [2].

References

1 Basler RSW, Lynch PJ. Black galactorrhea as a consequence of minocycline and phenothiazine therapy. *Arch Dermatol* 1985; **121**: 417–18.
2 Hunt MJ, Salisbury ELC, Grace J, Armati R. Black breast milk due to minocycline therapy. *Br J Dermatol* 1996; **134**: 943–4.

Morphoea [1]

If morphoea occurs on the chest wall prior to or during breast development, severe hypoplasia of the breast may result [2,3] (Fig. 70.3a,b). A feature of generalized morphoea is sparing of the nipples and areolae. Christianson *et al*. noted that the skin was pinched or squeezed like 'rising biscuits on a platter' [4] (Fig. 70.4a,b). Localized morphoea at the site of radiotherapy for breast cancer [5–10] is a well-documented entity; distant lesions have been reported in addition to involvement of the irradiated skin [11].



(a)

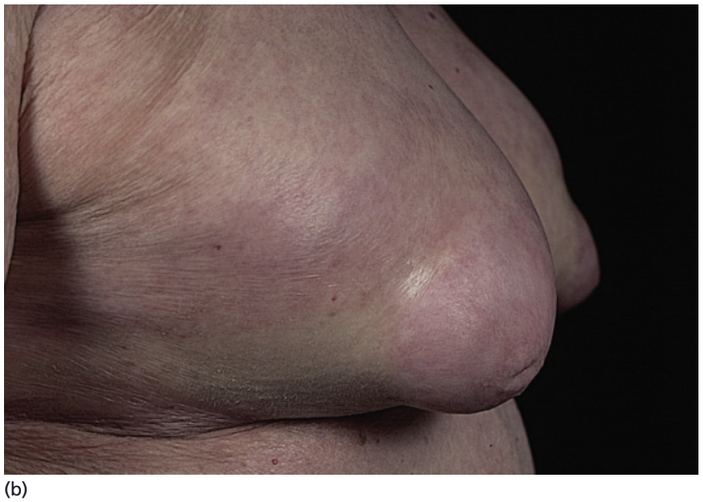


(b)

Fig. 70.3 (a and b) Breast hypoplasia associated with a plaque of morphoea which occurred during breast development.



(a)



(b)

Fig. 70.4 (a and b) A patient with generalized morphoea, showing sparing of the nipple and areola.

References

1 Whitaker-Worth DL, Carlone V, Susser WS *et al*. Dermatologic diseases of the breast and nipple. *J Am Acad Dermatol* 2000; **43**: 733–51.
2 Treiber ES, Goldberg NS, Levy H. Breast deformity produced by morphoea in a young girl. *Cutis* 1994; **54**: 267–8.
3 Slavin SA, Gupta S. Reconstruction of scleroderma of the breast. *Plast Reconstr Surg* 1997; **99**: 1736–41.
4 Christianson HB, Dorsey CS, O'Leary PA, Kierland RR. Localized scleroderma. A clinical study of two hundred thirty-five cases. *Arch Dermatol* 1956; **74**: 629–39.
5 Neill SM, Nicholl JJ, Hanham IWF, Staughton RCD. Localized morphoea at site of previous radiotherapy. *Br J Dermatol* 1988; **119**(Suppl. 33)**:** 110–1.
6 Colver GB, Rodger A, Mortimer PS *et al*. Post-irradiation morphoea. *Br J Dermatol* 1989; **120**: 831–5.
7 Verbov J. Post–irradiation morphoea. *Br J Dermatol* 1989; **121**: 819–20.
8 Trattner A, Figer A, David M *et al*. Circumscribed scleroderma induced by post-lumpectomy radiation therapy. *Cancer* 1991; **68**: 2131–3.
9 Davis DA, Cohen PR, McNeese MD, Duvic M. Localized scleroderma in breast cancer patients treated with supervoltage external beam radiation: radiation port scleroderma. *J Am Acad Dermatol* 1996; **35**: 923–7.
10 Schaffer JV, Carroll C, Dvoretsky I *et al*. Postirradiation morphea of the breast: presentation of two cases and review of the literature. *Dermatology* 2000; **200**: 67–71.
11 Ardern-Jones MR, Black MM. Widespread morphoea following radiotherapy for carcinoma of the breast. *Clin Exp Dermatol* 2003; **28**: 160–2.

Silicone breast implants and autoimmune disease

In the early 1990s, a major controversy arose about a possible relationship between silicone gel breast implants and subsequent development of connective tissue disease. Although the most common specific disease was scleroderma, many cases had a non-specific syndrome. Because of safety concerns, the US Food and Drug Administration imposed a moratorium on the use of such implants in 1992. The UK Medical Devices Directorate reviewed the scientific evidence relating to connective tissue disease and silicone gel breast implants and, in April 1992 presented a report to an independent Expert Advisory Group. The Group concluded that, on the basis of all available data, there was no evidence of an increased incidence of connective tissue disease associated with silicone gel breast implants [1]. An Independent Advisory Committee in Canada concluded that there was an absence of evidence establishing that women with silicone gel implants were more likely than those without such implants to have autoimmune disorders [2]. The issue provoked intense medicolegal activity, with approximately 400 000 women involved in a class action lawsuit against implant manufacturers in 1997, and many others elected to litigate individually [3].

Although a retrospective cohort study of 395 542 female health professionals, involving self-reported data, suggested a small increased risk of connective tissue diseases among women with breast implants [4], numerous controlled epidemiological studies did not demonstrate any statistically significant association between a recognized connective tissue disease and silicone breast implants [5], and three meta-analyses of the data failed to show an association [6–8]. However, the controversy continued [9,10]. Further studies showed no evidence of an association [11,12], and the UK Independent Review Group on Silicone Gel Breast Implants concluded that these implants were not associated with any greater health risk than other surgical implants, and if there was any risk of connective tissue disease it was too small to be quantified [13]. At about the same time as this report was issued, a settlement of the medicolegal issues was proposed [14].

A more recent, long-term study from Denmark adds to the significant body of data against any link between silicone breast implants and autoimmune disease [15]. In 2006, the US Food and Drug Administration approved the use of silicone gel-filled implants, 14 years after they were taken off the market [16].

References

1 Tinkler J, Gott D, Ludgate S. Breast implants: is there an association with connective tissue disease? *Health Trends* 1994; **26**: 25–6.
2 Independent Advisory Committee on Silicone-Gel-filled Breast Implants. Summary of the report on silicone-gel-filled breast implants. *Can Med Assoc J* 1992; **147**: 1141–6.
3 Rosenbaum JT. Lessons from litigation over silicone breast implants: a call for activism by scientists. *Science* 1997; **276**: 1524–5.
4 Hennekens CH, Lee I-M, Cook NR *et al*. Self-reported breast implants and connective-tissue diseases in female health professionals. *JAMA* 1996; **275**: 616–21.

5 Rose NR. The silicone breast implant controversy: the other courtroom. *Arthritis Rheum* 1996; **39**: 1615–18.
6 Hochberg MC, Perlmutter D. The association of augmentation mammoplasty with connective tissue disease, including systemic sclerosis (scleroderma): a meta-analysis. *Curr Top Microbiol Immunol* 1995; **210**: 411–17.
7 Perkins LL, Clark BD, Klein PJ, Cook RR. A meta-analysis of breast implants and connective tissue disease. *Ann Plast Surg* 1995; **35**: 561–70.
8 Wong O. A critical assessment of the relationship between silicone breast implants and connective tissue disease. *Regul Toxicol Pharmacol* 1996; **23**: 74–85.
9 Ault A. US Institute of Medicine panel deliberates on breast-implant safety. *Lancet* 1998; **352**: 380.
10 Cooper C, Dennison E. Do silicone breast implants cause connective tissue disease? *BMJ* 1998; **316**: 403–4.
11 Nyrén O, Yin L, Josefsson S *et al*. Risk of connective tissue disease and related disorders among women with breast implants: a nation-wide retrospective cohort study in Sweden. *BMJ* 1998; **316**: 417–22.
12 Edworthy SM, Martin L, Barr SG *et al*. A clinical study of the relationship between silicone breast implants and connective tissue disease. *J Rheumatol* 1998; **25**: 254–60.
13 McMenemy M-C. UK review group gives silicone implants all clear. *Lancet* 1998; **352**: 211.
14 Rovner J. Breast-implant settlement reached in USA. *Lancet* 1998; **352**: 211.
15 Breiting VB, Hölmich LR, Brandt B *et al*. Long-term health status of Danish women with silicone breast implants. *Plast Reconstr Surg* 2004; **114**: 217–26.
16 Tanne JH. FDA approves silicone breast implants with caveats. *BMJ* 2006; **333**: 1139.

Adnexal polyp of neonatal skin [1,2]

This small, usually solitary, tumour, occurs mainly on the areola of the neonate. The lesion is firm and pink but becomes dry and brown and falls off within a few days of birth. Histologically it contains hair follicles, eccrine glands and vestigial sebaceous glands. A survey in Tokyo showed that the condition occurred in 4% of 3257 newborn infants.

References

1 Hidano A, Kobayashi T. Adnexal polyp of neonatal skin. *Br J Dermatol* 1975; **92**: 659–62.
2 Koizumi H, Itoh E, Ohkawara A. Adnexal polyp of neonatal skin observed beyond the neonatal period. *Acta Derm Venereol (Stockh)* 1998; **78**: 391–2.

Inverted nipple

Inverted nipple is common, affecting up to 10% of adult females [1], and potentially leading to functional problems with breast-feeding and psychological distress. There are three main causes: congenital, periductal inflammation and tumour infiltration. It is also important to remember that in postmenopausal women it may result from the involutional process of periductal fibrosis. In most cases the abnormality is congenital, and the fault lies in failure of the normal eversion process [2]. The lactiferous ducts are shortened and there is a reduction in the amount of dense connective tissue that is present beneath a normal nipple [3]. The abnormality is usually bilateral, but may affect only one nipple.

Many women with inverted nipples are able to breastfeed without difficulty, probably because the nipple itself plays a relatively small part in the anatomical aspects of suckling, as the infant makes a 'teat' from the surrounding breast tissue as well as the nipple [2].

If inverted nipples pose a cosmetic problem, surgical correction may be considered. Numerous techniques have been described, suggesting that none is ideal. Procedures that involve division of the lactiferous ducts are probably more effective, but breast function is destroyed. More recent suggestions for treatment involve body-piercing devices [4–6].

References

1 Alexander JM, Campbell MJ. Prevalence of inverted and non-protractile nipples in antenatal women who intend to breast feed. *Breast* 1997; **5**: 88–9.
2 Hughes LE, Mansel RE, Webster DJT. *Benign Disorders and Diseases of the Breast*, 2nd edn. London: WB Saunders, 2000.
3 Schwager RG, Smith JW, Gray GF, Goulian D Jr. Inversion of the human female nipple, with a simple method of treatment. *Plast Reconstr Surg* 1974; **54**: 564–9.
4 Scholten E. A contemporary correction of inverted nipple. *Plast Reconstr Surg* 2001; **107**: 511–13.
5 Tal MG. Correction of inverted nipple using piercing. *Plast Reconstr Surg* 2003; **112**: 1178–9.
6 Hyakusoku H, Chin T. Usefulness of the nipple-suspension piercing device after correction of inverted nipples. *Aesthetic Plast Surg* 2006; **30**: 396–8.

The duct ectasia/periductal mastitis complex [1]

A number of pathological processes contribute to the clinical features of this complex. These features include nipple discharge, subareolar abscess, mammary duct fistula and nipple retraction. It is a rare occurrence in males, but has been described in association with HIV infection [2].

References

1 Hughes LE, Mansel RE, Webster DJT. *Benign Disorders and Diseases of the Breast*, 2nd edn. London: WB Saunders, 2000.
2 Downs AMR, Fisher M, Tomlinson D, Tanner A. Male duct ectasia associated with HIV infection. *Genitourin Med* 1996; **72**: 65–6.

Hyperkeratosis of the nipple/areola

On the basis of reported cases, hyperkeratosis of the nipple and areola is considered to be a rare condition. The classical Levy–Franckel classification includes three categories [1,2]:

1 as an extension of an epidermal naevus (in which involvement tends to be unilateral and both sexes may be affected);
2 in association with ichthyosis (in which involvement is bilateral and both sexes are affected);
3 a naevoid type, usually bilateral, and occurring predominantly in women in the second or third decade of life.

Pérez-Izquierdo *et al*. [3] suggested an alternative classification of two types:

1 idiopathic or naevoid (unilateral or bilateral);
2 secondary, divided into:
   i local (unilateral or bilateral): acanthosis nigricans, verrucous naevus, or seborrhoeic keratosis
   ii systemic (bilateral): dermatosis, ichthyosis, malignant lymphomas, Darier's disease, chronic eczemas
   iii drug related: diethylstilboestrol, spironolactone.

Another classification proposed by Mehanna *et al*. [4] includes a suggestion that the term 'naevoid' should be replaced by 'idiopathic'.

Whether described as naevoid or idiopathic, there is a distinct entity of verrucous thickening and brownish discolouration of the nipples and areolae which occurs predominantly in women in the second or third decade of life [5], in the absence of associated skin disease. It is usually bilateral, although unilateral involvement has been described [6,7], and it occasionally occurs in men [8]. Histology shows hyperkeratosis, filiform acanthosis and papillomatosis, and keratin plugging.

Hyperkeratosis of the nipples may also occur in association with ichthyosis, ichthyosiform erythroderma, acanthosis nigricans, Darier's disease (in association with other skin lesions, but also described as an isolated presenting phenomenon) [9], T-cell lymphoma [10,11], and chronic graft-versus-host disease [12]. It has also been described in men with carcinoma of the prostate treated with oestrogens [13,14].

An appearance resembling verrucous naevi around both areolae has been described as a manifestation of inadequate hygiene [15].

Suggested treatments for naevoid hyperkeratosis include topical retinoic acid [3], topical calcipotriol [16], cryotherapy [6], carbon dioxide laser [17], shave excision [18], tangential excision using a radiofrequency surgical unit [19], and removal of the areola and reconstruction with a skin graft [20]. Calcipotriol has also been effective in treating nipple hyperkeratosis associated with acanthosis nigricans [21].

References

1 Levy-Franckel A. Les hyperkératoses de l'aréole et du mamelon. *Paris Med* 1938; **28**: 63–6.
2 Whitaker-Worth DL, Carlone V, Susser WS *et al*. Dermatologic diseases of the breast and nipple. *J Am Acad Dermatol* 2000; **43**: 733–51.
3 Pérez-Izquierdo JM, Vilata JJ, Sánchez JL *et al*. Retinoic acid treatment of nipple hyperkeratosis. *Arch Dermatol* 1990; **126**: 687–8.
4 Mehanna A, Malak JA, Kibbi A-G. Hyperkeratosis of the nipple and areola. *Arch Dermatol* 2001; **137**: 1327–8.
5 Baykal C, Büyükbabani N, Kavak A, Alper M. Nevoid hyperkeratosis of the nipple and areola: a distinct entity. *J Am Acad Dermatol* 2002; **46**: 414–18.
6 Vestey JP, Bunney MH. Unilateral hyperkeratosis of the nipple: the response to cryotherapy. *Arch Dermatol* 1986; **122**: 1360–1.
7 Revert A, Bañuls J, Montesinos E *et al*. Nevoid hyperkeratosis of the areola. *Int J Dermatol* 1993; **32**: 745–6.
8 Kubota Y, Koga T, Nakayama J, Kiryu H. Naevoid hyperkeratosis of the nipple and areola in a man. *Br J Dermatol* 2000; **142**: 382–4.
9 Fitzgerald DA, Lewis-Jones MS. Darier's disease presenting as isolated hyperkeratosis of the breasts. *Br J Dermatol* 1997; **136**: 290.
10 Allegue F, Soria C, Rocamora A *et al*. Hyperkeratosis of the nipple and areola in a patient with cutaneous T-cell lymphoma. *Int J Dermatol* 1990; **29**: 519–20.
11 Ahn SK, Chung J, Lee WS *et al*. Hyperkeratosis of the nipple and areola simultaneously developing with cutaneous T-cell lymphoma. *J Am Acad Dermatol* 1995; **32**: 124–5.
12 Sanli H, Ekmekei P, Kusak F *et al*. Hyperkeratosis of the nipple associated with chronic graft versus host disease after allogeneic haematopoietic cell transplantation. *Acta Derm Venereol* 2003; **83**: 385–6.
13 Schwartz RA. Hyperkeratosis of nipple and areola. *Arch Dermatol* 1978; **114**: 1844–5.
14 Mold DE, Jegasothy BV. Estrogen-induced hyperkeratosis of the nipple. *Cutis* 1980; **26**: 95–6.
15 Ruiz-Maldonado R, Durán-McKinster C, Tamayo-Sánchez L, de la Luz Orozco-Covarrubias M. Dermatitis neglecta: dirt crusts simulating verrucous nevi. *Arch Dermatol* 1999; **135**: 728–9.
16 Bayramgürler D, Bilen N, Apaydin R, Erçin C. Nevoid hyperkeratosis of the nipple and areola: treatment of two patients with topical calcipotriol. *J Am Acad Dermatol* 2002; **46**: 131–3.
17 Busse A, Peschen M, Schöpf E, Vanscheidt W. Treatment of hyperkeratosis areolae mammae naeviformis with the carbon dioxide laser. *J Am Acad Dermatol* 1999; **41**: 274–6.
18 Swan MC, Gwilym SE, Hollowood K *et al*. Treatment of nevoid hyperkeratosis of the nipple and areolae by shave excision. *Ann Plast Surg* 2004; **53**: 510–12.
19 Ozyazgan I, Kontas O, Ferahbas A. Treatment of nevoid hyperkeratosis of the nipple and areolae using a radiofrequency surgical unit. *Dermatol Surg* 2005; **31**: 703–5.
20 Milanovic R, Martic K, Stanec S *et al*. Surgical treatment of nevoid hyperkeratosis of the areola by removal of the areola and reconstruction with a skin graft. *Ann Plast Surg* 2005; **54**: 667–9.
21 Lee H-W, Chang S-E, Lee M-W *et al*. Hyperkeratosis of the nipple associated with acanthosis nigricans: treatment with topical calcipotriol. *J Am Acad Dermatol* 2005; **52**: 529–30.

Eczema of the nipple/areola

Although eczema of the nipple and areola occurs mainly in women (Fig. 70.5a,b), it is an occasional occurrence in men (Fig. 70.6a,b); it may be unilateral or bilateral [1,2]. Often no cause can be

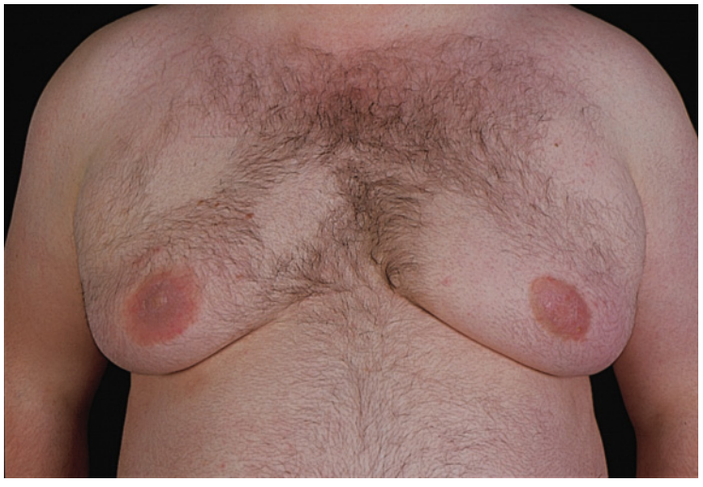


(a)



(b)

Fig. 70.5 (a and b) Severe bilateral nipple eczema in a young woman.



(a)



(b)

Fig. 70.6 (a and b) Bilateral nipple eczema in a man.

established, although there is an association with atopy [3,4] (for which it is a minor diagnostic criterion as defined by Rajka and Hanifin), and it may occur during breast feeding [5].

Contact dermatitis is a possibility, and allergic contact dermatitis of the nipples has been reported in a breastfeeding woman using a beeswax nipple protector [6], and two others applying Roman chamomile ointment [7]. Irritation from friction must also be considered (see jogger's and cyclist's nipple), and unilateral nipple dermatitis in three women with large asymmetrical breasts was attributed to friction between the larger breast and the seam of the brassière cup [8].

Treatment of nipple eczema is with mild-to-moderate potency topical steroids.

The intermittent course, more severe itching, indefinite margin and lack of distortion of the nipple help to distinguish eczema from Paget's disease (Chapter 53, Fig. 70.7). Erosive adenomatosis of the nipple (see p. 70.12) may have an eczematous appearance, and a case of clear cell acanthoma presenting as nipple eczema has been described [9]. If the diagnosis is at all doubtful, biopsy should be performed, particularly if there has been no response to topical steroids.

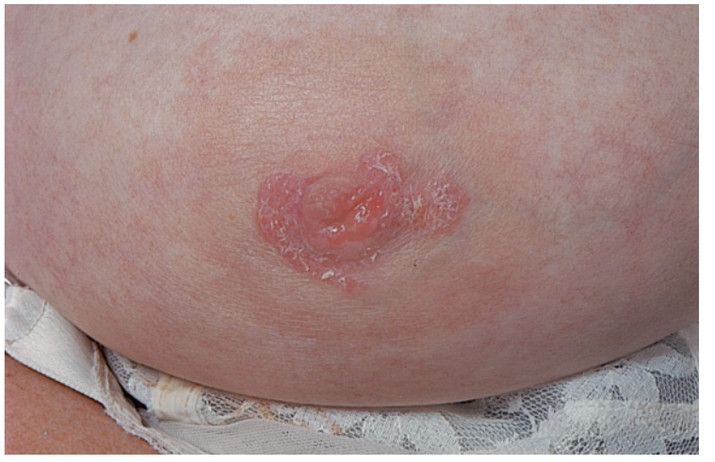


Fig. 70.7 Paget's disease of the nipple.

References

1 Graham DF. Eczema of the nipple. *Trans St John's Hosp Dermatol Soc* 1972; **58**: 98–9.

2 Topham EJ, Mortimer PS. Nipple eczema as a presenting complaint to the dermatology clinic—a 16 patient series. *Br J Dermatol* 2002; **147** (Suppl. 62): 27 (Abstr.).

3 Mevorah B, Frenk E, Wietlisbach V, Carrel CF. Minor clinical features of atopic dermatitis. Evaluation of their diagnostic significance. *Dermatologica* 1988; **177**: 360–4.

4 Amato L, Berti S, Chiarini C, Fabbri P. Atopic dermatitis exclusively localized on nipples and areolas. *Pediatr Dermatol* 2005; **22**: 64–6.

5 Barankin B, Gross MS. Nipple and areolar eczema in the breastfeeding woman. *J Cutan Med Surg* 2004; **8**: 126–30.

6 García M, del Pozo MD, Díez J *et al*. Allergic contact dermatitis from a beeswax nipple-protective. *Contact Dermatitis* 1995; **33**: 440–1.

7 McGeorge BCL, Steele MC. Allergic contact dermatitis of the nipple from Roman chamomile ointment. *Contact Dermatitis* 1991; **24**: 139–40.

8 Kapur N, Goldsmith PC. Nipple dermatitis—not all what it 'seams'. *Contact Dermatitis* 2001; **45**: 44–5.

9 Kim D-H, Kim C-W, Kang S-J, Kim T-Y. A case of clear cell acanthoma presenting as nipple eczema. *Br J Dermatol* 1999; **141**: 950–1.

'Cracked' nipples in lactation

Many women experience discomfort, irritation and fissuring of the nipples early in the puerperium when they are trying to establish breastfeeding. Anatomical features, such as relatively flat nipples, contribute to the development of this problem. Mastitis and deep abscesses may occur due to penetration of the broken skin by pyogenic bacteria. The problem is, in essence, one of friction and irritancy resulting from vigorous suckling, and can be eased considerably by the judicious use of gentle cleansing and emollients such as white soft paraffin.

Jogger's and cyclist's nipples [1,2]

Long-distance runners of either sex may suffer from irritation of the nipples caused by prolonged friction against a shirt. The problem is more pronounced in women who do not wear a brassière. The condition is self-healing and prevention includes the application of petrolatum or powder to the nipples to reduce fric-

tion, and the use of a sports brassière. Tomi *et al*. [3] reported three refractory cases who responded to treatment with topical tacrolimus.

Cyclists may suffer from cold injury to the nipple as evaporation of perspiration and wind chill combine to lower the temperature of the nipple on a cold day [4]. Pain, which may last for several days, soreness and tenderness are the result. Cycling jackets made of wind-resistant fabric offer a solution.

References

1 Levit F. Jogger's nipples. *N Engl J Med* 1977; **297**: 1127.
2 Adams BB. Dermatologic disorders of the athlete. *Sports Med* 2002; **32**: 309–21.
3 Tomi NS, Altmeyer P, Kreuter A. Tacrolimus ointment for 'jogger's nipples'. *Clin Exp Dermatol* 2006; **32**: 106–7.
4 Powell B. Bicyclist's nipples. *JAMA* 1983; **249**: 2457.

Guitar nipple

Musical instruments may be responsible for a number of dermatoses [1], and Curtis [2] described traumatic swelling at the base of the nipple in three girls, aged between 8 and 10, who were learning to play classical guitar. Pressure from the edge of the soundbox was responsible.

References

1 Gamblicher T, Boms S, Freitag M. Contact dermatitis and other skin conditions in instrumental musicians. *BMC Dermatol* 2004; **4**: http://www.biomedcentral.com/1471-5945/4/3
2 Curtis P. Guitar nipple. *BMJ* 1974; **ii**: 226.

Nipple piercings

Body piercing has been practised in some societies since antiquity, but it has usually been confined to the ears and nose. In recent years it has become 'fashionable' in Western countries, and devotees indulge not only in piercings on the face and ears, but also the genitalia and nipples [1]. Nipple piercings may cause problems due either to trauma or infection [2,3] or to the development of allergy to the metal. Lactiferous ducts may be damaged when the nipple is pierced, but this does not appear to lead to problems with breastfeeding [4].

Tassel ornaments suspended from the breasts have been popular in some cultures, particularly in the Middle East, for many generations. Some dancers have their nipples pierced to accommodate a ring from which ornaments are suspended and this can cause breast duct ectasia [5].

References

1 Stirn A. Body piercing: medical consequences and psychological motivations. *Lancet* 2003; **361**: 1205–15.
2 Ochsenfahrt C, Friedl R, Hannekum A, Schumacher BA. Endocarditis after nipple piercing in a patient with a bicuspid aortic valve. *Ann Thorac Surg* 2001; **71**: 1365–6.
3 Javaid M, Shibu M. Breast implant infection following nipple piercing. *Br J Plast Surg* 1999; **52**: 676–7.
4 Ferguson H. Body piercing. *BMJ* 1999; **319**: 1627–9.
5 Collins REC. Breast disease associated with tassel dancing. *BMJ* 1981; **283**: 1660.

Thelalgia

A patient suffering from thelalgia, which is a rare pain syndrome of the nipple–areola complex, had complete resolution of symptoms following injections of botulinum toxin [1].

Reference

1 Eigelshoven S, Kruse R, Rauch L *et al*. Thelalgia in man: successful treatment with botulinum toxin. *Arch Dermatol* 2006; **142**: 1242–3.

Artefactual breast disease

There are relatively few reports of artefactual breast disease, but the features of reported cases are as varied and bizarre as factitial lesions elsewhere on the body [1–6]. Pyoderma gangrenosum of the breast has occasionally been misdiagnosed as artefactual disease, leading to delay in introducing treatment.

References

1 Schwartz DL, So HB, Schneider KM, Becker JM. Chronic insertion of foreign bodies into the mature breast. *J Pediatr Surg* 1977; **12**: 743–4.
2 Rosenberg MW, Hughes LE. Artefactual breast disease: a report of three cases. *Br J Surg* 1985; **72**: 539–41.
3 Benson EA. Artefactual breast disease. *Br J Surg* 1986; **73**: 163.
4 Mudan SS, Ibrahim AEK, Wise M, Perry PM. Nipple discharge in a teenager. *J R Soc Med* 1998; **91**: 490–1.
5 Sampson D. An unusual self-inflicted injury of the breast. *Postgrad Med J* 1975; **51**: 116–18.
6 Whitaker-Worth DL, Carlone V, Susser WS *et al*. Dermatologic disease of the breast and nipple. *J Am Acad Dermatol* 2000; **43**: 733–51.

Vasculitis of the breast

Vasculitis affecting breast tissue is rare. It may occur as part of a systemic vasculitis, or as localized disease. There are several reported cases of polyarteritis nodosa presenting as tender breast nodules [1,2], and the simultaneous occurrence of polyarteritis nodosa and post-irradiation morphoea has been reported [3]. Breast lesions may also be a feature of Wegener's granulomatosis, sometimes as an initial manifestation [4–6].

References

1 Ng WF, Chow LTC, Lam PWY. Localized polyarteritis nodosa of breast—report of two cases and a review of the literature. *Histopathology* 1993; **23**: 535–9.
2 Trüeb RM, Scheidegger EP, Pericin M *et al*. Periarteritis nodosa presenting as a breast lesion: report of a case and review of the literature. *Br J Dermatol* 1999; **141**: 1117–21.
3 Reddy SM, Pui JC, Gold LI, Mitnick HJ. Postirradiation morphea and subcutaneous polyarteritis nodosa: case report and literature review. *Semin Arthritis Rheum* 2005; **34**: 728–34.
4 Jordan JM, Rowe WT, Allen NB. Wegener's granulomatosis involving the breast. Report of three cases and review of the literature. *Am J Med* 1987; **83**: 159–64.
5 Trüeb RM, Pericin M, Kohler E *et al*. Necrotizing granulomatosis of the breast. *Br J Dermatol* 1997; **137**: 799–803.
6 Neralic MI, Ivanovi HZ, Mazuranic I *et al*. Wegener's granulomatosis of the breast. *Wien Clin Wochenschr* 2006; **118**: 120–3.

Lupus panniculitis [1–4]

Synonyms
- Lupus erythematosus profundus
- Lupus mastitis

Lupus panniculitis can result in breast nodules which may be mistaken for carcinoma [5]. Coarse calcification may be seen on mammography [6]. Lesions are usually chronic and disfiguring. The treatment of choice is antimalarial therapy.

References

1 Whitaker-Worth DL, Carlone V, Susser WS *et al*. Dermatologic diseases of the breast and nipple. *J Am Acad Dermatol* 2000; **43**: 733–51.
2 Harris RB, Winkelmann RK. Lupus mastitis. *Arch Dermatol* 1978; **114**: 410–12.
3 Cernea SS, Kihara SM, Sotto MN, Vilela MAC. Lupus mastitis. *J Am Acad Dermatol* 1993; **29**: 343–6.
4 Holland NW, McNight K, Challa VR, Agudelo CA. Lupus panniculitis (profundus) involving the breast: report of 2 cases and review of the literature. *J Rheumatol* 1995; **22**: 344–6.
5 Carducci M, Mussi A, Lisi S *et al*. Lupus mastitis: a 2-year history of a single localization of lupus erythematosus mimicking breast carcinoma. *J Eur Acad Dermatol Venereol* 2005; **19**: 260–2.
6 Bachmeyer C, Goubin I, Berseneff H *et al*. Coarse calcifications by mammography in lupus mastitis. *Arch Dermatol* 2006; **142**: 398–9.

Sarcoidosis of the breast [1–6]

Although involvement of the breast with sarcoidosis is rare, it is important to be aware of its occurrence, as it mimics breast carcinoma. It can present as solitary or multiple, unilateral or bilateral subcutaneous masses, which may be associated with other manifestations of the disease or occur as an isolated phenomenon. Lesions may be fixed or mobile, tender or non-tender, and with or without palpable axillary lymphadenopathy.

References

1 Mingins C, Williams MR, Cox NH. Subcutaneous sarcoidosis mimicking breast carcinoma. *Br J Dermatol* 2002; **146**: 924–5.
2 Gansler TS, Wheeler JE. Mammary sarcoidosis. Two cases and literature review. *Arch Pathol Lab Med* 1984; **108**: 673–5.
3 Harris KP, Faliakou EC, Exon DJ *et al*. Isolated sarcoidosis of the breast. *J R Soc Med* 2000; **93**: 196–7.
4 Banik S, Bishop PW, Ormerod LP, O'Brien TEB. Sarcoidosis of the breast. *J Clin Pathol* 1986; **39**: 446–8.
5 Fiorucci F, Conti V, Lucantoni G *et al*. Sarcoidosis of the breast: a rare case report and a review. *Eur Rev Med Pharmacol Sci* 2006; **10**: 47–50.
6 Nicholson BT, Mill SE. Sarcoidosis of the breast: an unusual presentation of a systemic disease. *Breast J* 2007; **13**: 99–100.

Erosive adenomatosis of the nipple [1–5]

Synonyms
- Benign papillomatosis of the nipple
- Florid papillomatosis of the nipple ducts
- Papillary adenoma of the nipple
- Subareolar duct papillomatosis
- Superficial papillary adenomatosis

Definition. A complex, benign tumour arising from the lactiferous ducts of the nipple.

Incidence. This is an uncommon tumour, which occurs mainly in middle-aged women, but it can occur at any age [6], and occasionally in males [7–9]. In one case, the lesion developed 10 years after treatment for carcinoma of the prostate by bilateral orchidectomy and diethylstilbestrol [10].

Pathology [1,4,11–14]**.** The lesion consists of tubules, with an inner layer of columnar cells and an outer layer of cuboidal myoepithelial cells. A major feature is the presence of superficial keratocysts lined by both squamous and columnar epithelium, and filled with keratin flakes and an eosinophilic material, apparently secreted by the columnar cells. The cysts seem to reproduce the terminal portion of the nipple duct system. Within some of the superficial cysts or ducts, foreign-body giant cells may be seen. Some degree of intraluminal growth (intraductal papillomatosis) is present in many cases. This ranges from small papillary epithelial tufts to almost complete occlusion of the lumina by solid epithelial plugs, and there may be evidence of apocrine decapitation secretion. The overlying epidermis may show acanthosis and hyperkeratosis.

The major histopathological diagnostic pitfall is confusing erosive adenomatosis with sweat gland tumours, and as it may also be difficult to differentiate from papillary breast carcinoma immunohistological techniques are of value in demonstrating the layer of myoepithelial cells [12,13].

Clinical features. These are variable. The condition may start with a blood-stained or serous discharge, and the nipple may be enlarged, eroded, crusted or eczematous. There may be a small nodule on the nipple, and the symptoms may be worse in the premenstrual phase. The condition is commonly misdiagnosed as Paget's disease or eczema. It is usually unilateral, but bilateral involvement has been reported [15,16], and it has been described in an accessory nipple [17].

Treatment. Excision is curative—either simple local excision, or partial or complete resection of the nipple, depending on the size of the tumour [18]. There are reports of successful treatment by cryosurgery [19] and Mohs' surgery [20].

References

1 Brownstein MH, Phelps RG, Magnin PH. Papillary adenoma of the nipple: analysis of fifteen new cases. *J Am Acad Dermatol* 1985; **12**: 707–15.
2 Lewis HM, Ovitz ML, Golitz LE. Erosive adenomatosis of the nipple. *Arch Dermatol* 1976; **112**: 1427–8.
3 Bourlond J, Bourlond-Rinert L. Erosive adenomatosis of the nipple. *Dermatology* 1992; **185**: 319–24.
4 Moulin G, Darbon P, Balme B, Frappart L. Adénomatose érosive du mamelon. A propos de 10 cas avec étude histochimique. *Ann Dermatol Venereol* 1990; **117**: 537–45.
5 Montemarano AD, Sau P, James WD. Superficial papillary adenomatosis of the nipple: a case report and review of the literature. *J Am Acad Dermatol* 1995; **33**: 871–5.
6 Albers SE, Barnard M, Thorner P, Krafchick BR. Erosive adenomatosis of the nipple in an eight-year-old girl. *J Am Acad Dermatol* 1999; **40**: 834–7.

7 Miller G, Bernier L. Adénomatose érosive du mamelon. *Can J Surg* 1965; **8**: 261–6.
8 Taylor HB, Robertson AG. Adenomas of the nipple. *Cancer* 1965; **18**: 995–1002.
9 Richards AT, Jaffe A, Hunt JA. Adenoma of the nipple in a male. *S Afr Med J* 1973; **47**: 581–3.
10 Waldo ED, Sidhu GS, Hu AW. Florid papillomatosis of male nipple after diethylstilbestrol therapy. *Arch Pathol* 1975; **99**: 364–6.
11 Perzin KH, Lattes R. Papillary adenoma of the nipple (florid papillomatosis). A clinico-pathologic study. *Cancer* 1972; **29**: 996–1009.
12 Smith NP, Wilson-Jones E. Erosive adenomatosis of the nipple. *Clin Exp Dermatol* 1977; **2**: 79–84.
13 Diaz NM, Palmer JO, Wick MR. Erosive adenomatosis of the nipple: histology, immunohistology and differential diagnosis. *Mod Pathol* 1992; **5**: 179–84.
14 Moulin G. Superficial papillary adenomatosis of the nipple. *J Am Acad Dermatol* 1997; **36**: 133.
15 Handley RS, Thackray AC. Adenoma of nipple. *Br J Cancer* 1962; **16**: 187–94.
16 Bergdahl L, Bergman F, Rais O, Westling P. Bilateral adenoma of nipple. *Acta Chir Scand* 1971; **137**: 583–6.
17 Civatte J, Restout S, Delomenie DC. Adénomatose érosive sur mamelon surnuméraire. *Ann Dermatol Venereol* 1977; **104**: 777–9.
18 Vianna LL, Millis RR, Fentiman IS. Adenoma of the nipple: a diagnostic dilemma. *Br J Hosp Med* 1993; **50**: 639–42.
19 Kuflik EG. Erosive adenomatosis of the nipple treated with cryosurgery. *J Am Acad Dermatol* 1998; **38**: 270–1.
20 Van Mierlo PL, Geelen GM, Neumann HA. Mohs micrographic surgery for an erosive adenomatosis of the nipple. *Dermatol Surg* 1998; **24**: 681–3.

Sebaceous hyperplasia of the areolae

This is a rare abnormality characterized clinically by yellowish thickening of the areolae, and histologically by a large number of hyperplastic sebaceous lobules [1–3].

References

1 Hammerton MD, Shrank AB. Superficial sebaceous hyperplasia of the areolae. *Br J Dermatol* 1993; **129**: 649–50.
2 Belinchón I, Aguilar A, Tardío J, Gallego MA. Areolar sebaceous hyperplasia: a case report. *Cutis* 1996; **58**: 63–5.
3 Fariña MC, Soriano ML, Escalonilla P *et al*. Unilateral areolar sebaceous hyperplasia in a male. *Am J Dermatopathol* 1996; **18**: 417–9.

Breast telangiectasia

White and Jeffes [1] described a 77-year-old man with bilateral patches of perfectly circular, symmetrical telangiectasia of the areolae. The condition had been present for as long as he could remember, with no associated abnormalities.

Blue areolae were one feature of a familial disorder named 'hereditary acrolabial telangiectasia' [2], and Schlappner and Shelley reported a 35-year-old woman with symmetrical essential telangiectasis of the breasts, recurrent aphthous stomatitis and hypersplenism [3].

References

1 White GM, Jeffes EWB. Congenital circumareolar telangiectasia. *Arch Dermatol* 1990; **126**: 1656.
2 Millns JL, Dicken CH. Hereditary acrolabial telangiectasia. A report of familial blue lips, nails and nipples. *Arch Dermatol* 1979; **115**: 474–8.
3 Schlappner OLA, Shelley WB. Telangiectasia, aphthous stomatitis and hypersplenism. *Arch Dermatol* 1971; **104**: 668.

Mammary duct fistula [1]

Synonym
- Recurrent subareolar abscess

This condition typically occurs in a young adult woman who has a history of recurrent abscesses in a breast that has been treated by surgical drainage or has discharged spontaneously. There is typically partial inversion of the nipple and a scar or scars at the edge of the areola.

The condition is treated by passing a probe into the opening of the discharging sinus, along the track of the fistula and out of the nipple. The fistula is then laid open (fistulotomy) and left to heal by granulation, or the whole tract is excised (fistulectomy) and the wound allowed to granulate.

Reference

1 Hughes LE, Mansel RE, Webster DJT. *Benign Disorders and Diseases of the Breast*, 2nd edn. London: WB Saunders, 2000.

Breast abscess [1]

Breast abscesses may be classified as lactational (occurring in the puerperium) and non-lactational. The majority of lactational abscesses are caused by *Staphylococcus aureus*, and present as a painful, red, swollen breast, associated with fever.

Non-lactational abscesses include subareolar abscesses, which are seen mainly in women in their reproductive years in association with the duct ectasia/periductal mastitis complex, and peripheral abscesses, which occur as typical inflammatory breast abscesses in postmenopausal women. The former is associated with a mixed bacterial spectrum, and the latter with *Staph. aureus*. Lactational abscesses are now uncommon in comparison with the frequency of non-lactational lesions [2].

References

1 Hughes LE, Mansel RE, Webster DJT. *Benign Disorders and Diseases of the Breast*, 2nd edn. London: WB Saunders, 2000.
2 Schofield JH, Duncan JL, Rogers K. Review of a hospital experience of breast abscesses. *Br J Surg* 1987; **74**: 469–70.

Breast cancer (Fig. 70.8)

This common and important condition lies in the province of the surgeon rather than the dermatologist, but all physicians have a duty to detect and diagnose early breast cancer, which can sometimes be discovered on routine examination. Inspection and palpation of the breasts should be included in any full examination. The breasts should be inspected with the arms by the side, above the head, and pressing on the hips, because in some cases these manoeuvres will demonstrate a visible mass, a change in contour of the breast, or early retraction or dimpling of the skin caused by a breast cancer. The dermatologist should also remember that redness or oedema of the breast skin may be due to underlying cancer. Breast cancer can also cause flattening, broadening or inversion of the nipple. It is important that all four



Fig. 70.8 Advanced carcinoma of the breast.

quadrants of the breast, including the axillary tail and axillary lymph nodes, should be palpated.

The dermatologist should examine the breasts carefully in all patients presenting with skin disease that may be associated with systemic malignancy, for example acanthosis nigricans or dermatomyositis.

The term *peau d'orange* is applied to dimpled oedematous or indurated skin resembling the surface of an orange. The finding of peau d'orange should lead to an intensive search for underlying carcinoma. Rarely, it occurs in the absence of any clinically palpable tumour. It has also been reported as a complication of anasarca, nephrotic syndrome and cardiac failure [1].

Breast cancer frequently involves the skin, and there are several different clinicopathological types of cutaneous involvement [2]. These include Paget's disease of the nipple, inflammatory metastatic carcinoma (carcinoma erysipeloides), carcinoma en cuirasse, telangiectatic metastatic carcinoma, nodular metastatic carcinoma, alopecia neoplastica, carcinoma of the inframammary crease and metastatic mammary carcinoma of the eyelid. Carcinoma metastatic to the eyelids is a rare phenomenon, and breast carcinoma is responsible for a sizeable proportion of these cases. Involvement may be unilateral, with the right eyelids affected more frequently than the left [3], or bilateral [4–7]. In many of the reported cases the histology has shown prominent histiocytoid features [2].

Pigmented primary carcinoma of the breast is rare, and may mimic malignant melanoma clinically and histologically [8,9]. Metastatic melanoma may be responsible for inflammatory changes in breast skin [10].

Other conditions that may mimic breast carcinoma include postsurgical lymphoedema [11] and sarcoidosis [12].

Virgili *et al*. [13] described four patients with what were thought to represent cutaneous tumour-related granulomatous lesions following mastectomy for carcinoma of the breast. The lesions developed on the arm on the same side as the previous mastectomy.

Post-radiotherapy telangiectasia can be a considerable cosmetic problem, and treatment with the hyfrecator [14] or pulsed dye laser [15] may be of significant benefit.

References

1 McElligott G, Harrington MG. Heart failure and breast enlargement suggesting cancer. *BMJ* 1986; **292**: 446.
2 Schwartz RA. Cutaneous metastatic disease. *J Am Acad Dermatol* 1995; **33**: 161–82.
3 Rubio FA, Pizarro A, Robano G *et al*. Eyelid metastasis as the presenting sign of recurrent carcinoma of the breast. *Br J Dermatol* 1997; **137**: 1026–7.
4 Grinspan D, Abulafia J, Abbruzzese M. Metastatic involvement of four eyelids. *J Am Acad Dermatol* 1997; **37**: 362–4.
5 ZimmermanT, Jappe U, Hausser I *et al*. Persistent erythematous eyelid swelling due to metastatic lobular carcinoma of the breast. *Br J Dermatol* 2002; **146**: 919.
6 Tamura M, Tada T, Tsuj H *et al*. Clinical study on the metastasis to the eyes from breast cancer. *Breast Cancer* 2004; **11**: 65–8.
7 Kuchel JM, Bowling JC. Bilateral lower eyelid masses. *Arch Dermatol* 2006; **142**: 1351–6.
8 Sau P, Solis J, Lupton GP, James WD. Pigmented breast carcinoma. A clinical and histopathologic simulator of malignant melanoma. *Arch Dermatol* 1989; **125**: 536–9.
9 Saitoh K, Saga K, Okazaki M, Maeda K. Pigmented primary carcinoma of the breast: a clinical mimic of malignant melanoma. *Br J Dermatol* 1998; **139**: 287–90.
10 Tan BB, Marsden JR, Sanders DSA. Melanoma erysipeloides: inflammatory metastatic melanoma of the skin. *Br J Dermatol* 1993; **129**: 327–9.
11 King R, Duncan L, Shupp DL, Googe PB. Postsurgical dermal lymphedema clinically mimicking inflammatory breast carcinoma. *Arch Dermatol* 2001; **137**: 969–70.
12 Mingins C, Williams MR, Cox NH. Subcutaneous sarcoidosis mimicking breast carcinoma. *Br J Dermatol* 2002; **146**: 924–5.
13 Virgili A, Maranini C, Califano A. Granulomatous lesions of the homolateral limb after previous mastectomy. *Br J Dermatol* 2002; **146**: 891–4.
14 Rowland-Payne CME, Somaiah N, Neal AJ, Glees JP. The hyfrecator: a treatment for radiation-induced telangiectasia in breast cancer patients. *Br J Radiol* 2005; **78**: 143–6.
15 Lanigan SW, Joannides T. Pulsed dye laser treatment of telangiectasia after radiotherapy for carcinoma of the breast. *Br J Dermatol* 2003; **148**: 77–9.

Breast cancer in men

Breast cancer in men is relatively rare, accounting for around 0.2% of all cancers in men in the USA and less than 1% of all cases of breast cancer [1].

Risk factors include conditions associated with reduced testicular function, excess oestrogen exposure, Klinefelter's syndrome [2] and a family history of breast carcinoma. Case–control studies indicate that the disease is commoner in black men and in those who have never married [3].

The mean age of presentation is 60–65 years, and is approximately 5 years older than that for breast carcinoma in women.

As in women, the clinical features include a breast mass, which is typically subareolar, nipple inversion, and nipple discharge [4] (Fig. 70.9). Infiltrating ductal carcinoma is the predominant histological type. Paget's disease may be the presenting feature [5,6].

References

1 Donegan WL, Redlich PN. Breast cancer in men. *Surg Clin North Am* 1996; **76**: 343–63.
2 Scheike O, Visfeldt J, Peterson B. Male breast cancer: breast carcinoma in association with Klinefelter syndrome. *Acta Pathol Microbiol Scand* 1973; **81**: 352–8.
3 Sasco AJ, Lowenfels AB, Pasker de-Jong P. Epidemiology of male breast cancer. A meta-analysis of published case control studies and discussion of selected aetiological factors. *Int J Cancer* 1993; **53**: 538–49.
4 Ottuso P. The dermatologist's role in diagnosing a rare disease—male breast cancer. *Cutis* 2002; **69**: 99–102.



Fig. 70.9 Breast carcinoma in a man, showing destruction of the nipple and areola.

5 Ratón JA, Bilbao I, Gardeazábal J *et al*. Skin involvement in male breast carcinoma. *Arch Dermatol* 1998; **134**: 517–8.
6 Bodnar M, Miller F, Tyler W. Paget's disease of the male breast associated with intraductal carcinoma. *J Am Acad Dermatol* 1999; **40**: 829–31.

Basal cell carcinoma of the nipple/areola [1–6]

This is a very rare lesion. It can occur in either men or women, usually in old age. It usually presents as a red, eczema-like patch of the nipple or areola and runs a long indolent course. Biopsy is essential to differentiate it from Paget's disease.

References

1 Cain RJ, Sau P, Benson PM. Basal cell carcinoma of the nipple: report of two cases. *J Am Acad Dermatol* 1990; **22**: 207–10.
2 Benharroch D, Geffen DB, Peiser J, Rosenberg L. Basal cell carcinoma of the male nipple: case report and review of the literature. *J Dermatol Surg Oncol* 1993; **19**: 137–9.
3 Zhu YI, Ratner D. Basal cell carcinoma of the nipple: a case report and review of the literature. *Dermatol Surg* 2001; **27**: 971–4.
4 Yamamoto H, Ito Y, Hayashi T *et al*. A case of basal cell carcinoma of the nipple and areola with intraductal spread. *Breast Cancer* 2001; **8**: 229–33.
5 Betti R, Martino P, Moneghini L *et al*. Basal cell carcinoma of the areola-nipple complex: case reports and review of the literature. *J Dermatol* 2003; **30**: 822–6.
6 Rosen N, Muhn CY, Bernstein SC. A common tumor, an uncommon location: basal cell carcinoma of the nipple and areola in a 49-year-old woman. *Dermatol Surg* 2005; **31**: 480–3.

Malignant melanoma of the nipple/areola

Malignant melanoma of the nipple/areola is rare [1]. It may mimic Paget's disease [2], and a rare pigmented variety of Paget's disease mimics malignant melanoma clinically, histopathologically and dermoscopically [3].

Paget's disease, which is a marker of an underlying breast carcinoma, is discussed in Chapter 53.

References

1 Kinoshita S, Yoshimoto K, Kyoda S *et al*. Malignant melanoma originating on the female nipple: a case report. *Breast Cancer* 2007; **14**: 105–8.
2 Liu CH, Lee HS, Yu JC. Melanoma of the nipple mimicking Paget's disease. *Dermatol Online J* 2007; **13**: 18.
3 Longo C, Fantini F, Cesinaro AM *et al*. Pigmented mammary Paget disease. *Arch Dermatol* 2007; **143**: 752–4.



Fig. 70.10 Hair sinuses in a sheep-shearer. (Courtesy of Dr W. Bowers, Treliske Hospital, Truro, UK.)

Hair sinus of the breast

Hair sinus of the periareolar area of the breast has been observed in women engaged in sheep shearing (roustabout's breast) and hairdressing [1] (Fig. 70.10), and in canine beauticians whose work leaves them covered in dog hairs [2]. The lesions are similar to the interdigital pilonidal sinuses that may occur in barbers and dog groomers [3]. The histology shows a granulomatous reaction. Repeated breast abscesses in female sheep shearers may provoke concern about the ability to breastfeed or even lead to women contemplating mastectomy. This problem prompted the manufacture, in New Zealand, of a protective brassière, the Baa Bra [4].

References

1 Bowers PW. Roustabouts' and barbers' breasts. *Clin Exp Dermatol* 1982; **7**: 445–7.
2 Banerjee A. Pilonidal sinus of the nipple in a canine beautician. *BMJ* 1985; **291**: 1787.
3 Price SM, Popkin GL. Barbers' interdigital hair sinus. *Arch Dermatol* 1976; **112**: 523–4.
4 Gardiner G. Breast infections due to wool. *N Z Med J* 1994; **107**: 494.

Seborrhoeic warts

Synonym
- Basal cell papillomas (Chapter 52)

These are particularly common in the submammary creases in middle-aged or elderly women, often in association with intertrigo (Fig. 70.11). Seborrhoeic warts may also occur as sharply demarcated papules or plaques on the nipple and areola [1].

Reference

1 Baykal C, Büyükbabani N, Kavak A, Alper M. Nevoid hyperkeratosis of the nipple and areola: a distinct entity. *J Am Acad Dermatol* 2002; **46**: 414–18.



Fig. 70.11 Submammary seborrhoeic warts.

Mondor's disease (Fig. 70.12)

Synonym
- Sclerosing periphlebitis of the chest wall

Mondor's disease, a condition described in 1939 by H. Mondor [1], is usually regarded as a superficial obliterative phlebitis affecting the thoracoepigastric, lateral thoracic or superior epigastric vein. It occurs mainly between the ages of 30 and 60 years and affects women much more frequently than men [2,3]. Risk factors cited for the development of the condition include large pendulous breasts, strenuous physical activity [4], direct trauma, breast surgery [5,6] and sentinel node biopsy [7], and infection near the affected vessels. Breast cancer is an occasional cause [8] and mammography is recommended even when no mass is palpable [9–11]. Mondor's disease has characteristic mammographic and sonographic features [10,11]. It has also been described in association with metastatic axillary adenopathy 2 years after radical mastectomy for breast carcinoma [12], and in a patient with metastatic lung cancer in the breast [13]. In a case of recurrent Mondor's disease of the thoracoepigastric vein, resolution occurred after excision of a lipoma that was in close proximity to the vein [14]. It is a rare occurrence in pregnancy [15,16]. Other causes include intravenous drug abuse, following use of the breasts as injection sites [17], jellyfish stings [18], protein S deficiency [19], electrocution [20] and a lupus erythematosus-like syndrome probably induced by procainamide [21]. However, often no cause is apparent. Rarely, the condition is bilateral [21], and in one such case potential aetiological factors included breast surgery, the use of oral contraceptives, hereditary protein C deficiency and anticardiolipin antibodies [22].

There may be some tenderness or discomfort, but there are often no symptoms until the patient discovers a red linear cord running from the lateral margin of the breast, crossing the costal margin and extending to the abdominal wall. The cord is 2–3 mm in diameter and is attached to the skin but not to the deep fascia. It is usually only a few centimetres long, but may extend to 30–40 cm.



Fig. 70.12 Mondor's disease of the chest wall. (Courtesy of Professor A.Y. Finlay, University of Wales College of Medicine, Cardiff, UK.)

The symptoms subside in a few weeks and there are no known complications.

References

1 Mondor H. Tronculite sous-cutanée subaiguë de la paroi thoracique antéro-latérale. *Mem Acad Chir (Paris)* 1939; **65**: 1271–8.
2 Johnson WC, Wallrich MC, Hebwig EB. Superficial thrombophlebitis of the chest wall. *JAMA* 1962; **180**: 103–8.
3 Bejanga BI. Mondor's disease. Analysis of thirty cases. *J R Coll Surg Edin* 1992; **37**: 322–4.
4 Talhari C, Mang R, Megahed M *et al*. Mondor's disease associated with physical strain: report of 2 cases. *Arch Dermatol* 2005; **141**: 800–1.
5 Loos B, Horch RE. Mondor's disease after breast reduction surgery. *Plast Reconstr Surg* 2006; **117**: 129e–32e.
6 Jaberi M, Willey SC, Brem RF. Stereotactic vacuum-assisted breast biopsy: an unusual cause of Mondor's disease. *AJR Am J Roentgenol* 2002; **179**: 185–6.
7 Pappo I, Wasserman I, Stahl KV *et al*. Mondor's disease of the axilla: a rare complication of sentinel node biopsy. *Breast J* 2004; **10**: 253–5.
8 Levi I, Baum M. Mondor's disease as a presenting symptom of breast cancer. *Br J Surg* 1987; **74**: 700.
9 Catania S, Zurrida S, Veronesi P *et al*. Mondor's disease and breast cancer. *Cancer* 1992; **69**: 2267–70.
10 Conant EF, Wilkes AN, Mendelson EB, Feig SA. Superficial thrombophlebitis of the breast. Mammographic findings. *Am J Roentgenol* 1993; **160**: 1201–3.
11 Shetty MK, Watson AB. Mondor's disease of the breast: sonographic and mammographic findings. *Am J Roentgenol* 2001; **177**: 893–6.
12 Miller DR, Cesario TC, Slater LM. Mondor's disease associated with metastatic axillary nodes. *Cancer* 1985; **56**: 903–4.
13 Courtney SP, Polacarz S, Raftery AT. Mondor's disease associated with metastatic lung cancer in the breast. *Postgrad Med J* 1989; **65**: 779–80.
14 Rubegni P, De Aloe G, Biagioli M *et al*. Recurrent Mondor's disease resolved after exeresis of abdominal lipoma. *Dermatol Surg* 1999; **25**: 563–5.
15 Duff P. Mondor disease in pregnancy. *Obstet Gynecol* 1981; **58**: 117–20.

16 Hacker SM. Axillary string phlebitis in pregnancy: a variant of Mondor's disease. *J Am Acad Dermatol* 1994; **30**: 636–8.
17 Cooper RA. Mondor's disease secondary to intravenous drug abuse. *Arch Surg* 1990; **125**: 807–8.
18 Ingram DM, Sheiner HJ, Ginsberg A. Mondor's disease of breast resulting from jellyfish sting. *Med J Aust* 1992; **157**: 836–7.
19 de Godoy JMP, Godoy MF, Batigália F *et al*. The association of Mondor's disease with protein S deficiency: case report and review of the literature. *J Thromb Thrombolysis* 2002; **13**: 187–9.
20 Randell P. Mondor's disease and electrocution. *Australas J Dermatol* 2003; **44**: 75–6.
21 Skipworth GB, Morris JB, Goldstein N. Bilateral Mondor's disease. *Arch Dermatol* 1967; **95**: 95–7.
22 Wester JP, Kuenen BC, Meuwissen OJ, de Maat CE. Mondor's disease as first thrombotic event in hereditary protein C deficiency and anticardiolipin antibodies. *Neth J Med* 1997; **50**: 85–7.

Other conditions that may involve the breast

- *Vitiligo* sometimes shows a striking symmetrical involvement of the breasts.
- *Psoriasis* may be provoked by the trauma of suckling, and flexural psoriasis can be problematic in the submammary region.
- *Pityriasis rosea* commonly presents with a herald patch on the breast, and has been reported as a localized eruption on one breast [1].
- *Cutaneous larva migrans* may occur on the breast when women have lain 'topless' on a tropical beach in the prone position.
- *Neurofibromas* have a predilection for the nipple/areola [2] (Fig. 70.13).
- *Scabies* often produces papules around the nipple, which may persist after treatment.
- *Granular parakeratosis* may occur in the submammary regions [3,4].
- *Lichen sclerosus* confined to the areola has been reported [5].
- *Fox–Fordyce disease* (Chapter 44) may produce intensely irritable papules on the areolae.
- *Carney complex* (myxomas, spotty pigmentation and endocrine overactivity) is associated with breast myxoid fibroadenomas and ductal adenomas [6,7].
- *Cowden's syndrome* (multiple hamartoma syndrome) is an autosomal dominant disorder associated with hamartomas of various tissues and an increased risk of breast cancer, usually ductal carcinoma [8].
- *Hidradenitis suppurativa* of the breasts tends to affect the inter- and inframammary folds [9].
- *Diffuse dermal angiomatosis* (a reactive angiomatosis [10]), may involve the breasts and response to treatment with isotretinoin has been reported by McLaughlin *et al*. [11]. In another case reported by Yang *et al*. [12] the condition was associated with an occluded subclavian artery, and resolved when a stent was inserted in this.
- *Mucinosis of the areolae* has been described as a presenting feature of mycosis fungoides [13].



Fig. 70.13 Neurofibromatosis, showing the predilection of this condition for the nipple/areola.

References

1 Ahmed I, Charles-Holmes R. Localized pityriasis rosea. *Clin Exp Dermatol* 2000; **25**: 624–6.
2 Riccardi VM. Neurofibromatosis: an overview and new directions in clinical investigations. In: Riccardi VM, Mulvihill JJ, eds. *Advances in Neurology, Vol. 29, Neurofibromatosis (von Recklinhausen's Disease) Genetics, Cell Biology, and Biochemistry*. New York: Raven Press, 1981: 1–9.
3 Wohlrab J, Lüftl M, Wolter M, Marsch WCh. Submammary granular parakeratosis: an acquired punctate hyperkeratosis of exogenous origin. *J Am Acad Dermatol* 1999; **40:** 813–4.
4 Metze D, Rutten A. Granular parakeratosis—a unique acquired disorder of keratinisation. *J Cutan Pathol* 1999; **26:** 339–52.
5 Starzycki Z. Lichen sclerosus et atrophicus confined to the areolae. *Br J Dermatol* 1993; **129:** 748–9.
6 Armstrong DKB, Irvine AD, Handley JM *et al*. Carney complex: report of a kindred with predominantly cutaneous manifestations. *Br J Dermatol* 1997; **136:** 578–82.
7 Courcoutsakis NA, Chow CK, Shawker TH *et al*. Syndrome of spotty skin pigmentation, myxomas, endocrine overactivity, and Schwannomas (Carney complex): breast imaging findings. *Radiology* 1997; **205:** 221–7.
8 Schrager CA, Schneider D, Gruener AC *et al*. Clinical and pathological features of breast disease in Cowden's syndrome: an underrecognized syndrome with an increased risk of breast cancer. *Hum Pathol* 1998; **29:** 47–53.
9 Hughes LE, Mansel RE, Webster DJT. *Benign Disorders and Diseases of the Breast*, 2nd edn. London: WB Saunders, 2000: 242–4.
10 Rongioletti F, Rebora A. Cutaneous reactive angiomatoses: patterns and classification of reactive vascular proliferation. *J Am Acad Dermatol* 2003; **49:** 887–96.
11 McLaughlin ER, Morris R, Weiss SW, Arbiser JL. Diffuse dermal angiomatosis of the breast: response to isotretinoin. *J Am Acad Dermatol* 2001; **45:** 462–5.
12 Yang H, Ahmed I, Verghese M *et al*. Diffuse dermal angiomatosis of the breast. *Arch Dermatol* 2006; **142:** 343–7.
13 Vásquez-Doval FJ, Sola MA. Mucinosis of the mammary areolae and mycosis fungoides. *Clin Exp Dermatol* 1996; **21:** 374–6.

CHAPTER 71

The Genital, Perianal and Umbilical Regions

C.B. Bunker[1] *& S.M. Neill*[2]

[1]Chelsea and Westminster and Royal Marsden Hospitals, London, UK
[2]St John's Dermatology Unit, St Thomas' Hospital, London, UK

General approach to the patient and the problem, 71.1
Genitocrural dermatology, 71.4
Inflammatory dermatoses, 71.4
Infections, 71.6
Miscellaneous, 71.7
Male genital dermatology, 71.8
Structure and function of the male genitalia, 71.10
Congenital and developmental abnormalities, 71.13
Trauma and artefact, 71.14
Inflammatory dermatoses, 71.16
Non-sexually transmitted infections, 71.29
Dermatological aspects of sexually transmitted disease, 71.33
Benign tumours, 71.35
Precancerous dermatoses and carcinoma *in situ*, 71.37
Squamous carcinoma, 71.39
Other malignant neoplasms, 71.46
Miscellaneous, 71.49
Female genital dermatology, 71.52
Structure and function of the female genitalia, 71.54
Congenital and developmental abnormalities, 71.56
Trauma and artefact, 71.56
Inflammatory dermatoses, 71.58
Ulcerative and bullous disorders, 71.65
Non-sexually transmitted infections, 71.67
Dermatological aspects of sexually transmitted disease, 71.70
Benign tumours, 71.72
Precancerous dermatoses, 71.74
Squamous cell carcinoma, 71.76
Other malignant neoplasms, 71.76
Miscellaneous, 71.79
Perineal and perianal dermatology, 71.82
Structure and function, 71.83
Congenital and developmental abnormalities, 71.83
Trauma and artefact, 71.84
Inflammatory dermatoses, 71.84
Infections, 71.91
Benign tumours, 71.96
Premalignant dermatoses and frank malignancies, 71.96
Miscellaneous, 71.99
Umbilical dermatology, 71.100
Structure and function, 71.100
Congenital and developmental abnormalities, 71.100
Trauma and artefact, 71.100
Inflammatory dermatoses, 71.101
Infections, 71.101
Tumours and implantations, 71.101

Introduction

A number of common skin diseases affect the umbilical, perianal, genital and genitocrural skin only incidentally, and may present in these areas with unusual features. These will be dealt with briefly or by cross-reference to their full description elsewhere. However, those conditions that are entirely or predominantly confined to these regions are discussed in detail.

General approach to the patient and the problem

Clinical assessment begins with the history and examination. Patients with anogenital symptoms may be embarrassed and present late, or present to specialties (urology, gynaecology, general or colorectal surgery, genitourinary medicine) where training and experience are not focused on dermatological diagnosis and management.

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

Itching, rashes and tumours are the major components of general dermatology and the anogenital area is not spared. The pruritic diseases that may affect the anogenital region are listed in Tables 71.1–71.3. Itch occurring in the absence of specific diagnostic skin lesions is not usually confined to the anogenital area, but if so it should not be labelled as psychogenic until all possible causes have been excluded. The intensity with which itch can be perceived in the anogenital area may be a result of the vagaries of cortical representation afforded the region in the sensorium as well as anxiety about exposure to sexually transmitted disease and anogenital cleanliness.

The symptomatology of anogenital dermatology is more extensive than the standard symptomatic presentation of skin disease. This obliges the clinician to elicit symptoms resulting from sexual dysfunction (e.g. soreness, pain, bleeding or tearing on intercourse) and the components of sexual function (erection, lubrication, libido, ejaculation, orgasm, fertility), urinary dysfunction (frequency, discharge, dysuria) or colorectal symptomatology (pain, bleeding, discharge).

History taking must involve attention to the sexual history (orientation, marital status, last sexual activity—when; how (vaginal, oral, anal); contraception), regular partner(s), partner

Table 71.1 Common causes of anogenital pruritus. (After Bunker [1]. © 2004, with permission from Elsevier.)

Pruritus ani
Eczema/dermatitis
Exogenous
Contact
irritant
allergic
Endogenous
Atopic
Seborrhoeic
Lichen simplex
Psoriasis
Lichen sclerosus
Lichen planus
Perianal streptococcal dermatitis
Erythrasma
Herpes simplex
Candidosis
Tinea
Onchocerciasis (in developing countries)
Phthiriasis
Scabies

Table 71.2 Rare causes of anogenital pruritus. (After Bunker [1]. © 2004, with permission from Elsevier.)

Insect bites/papular urticaria
Radiodermatitis
Hirsutism
Hyperhidrosis
Fox–Fordyce disease
Urticaria and dermographism [2]
Dermatitis herpetiformis
Chlamydia
Gonorrhoea
Syphilis
Other sexually transmitted diseases
Trichosporosis
Larva currens
Cutaneous larva migrans
Onchocerciasis (in Western practice)
Bowen's disease
Extramammary Paget's disease
Langerhans' cell histiocytosis
Drugs
Foods
Senile pruritus
Dysaesthesia syndromes

Table 71.3 Causes of genital itching in the absence of fixed clinical findings. (After Bunker [1]. © 2004, with permission from Elsevier.)

Symptomatic dermographism
Contact urticaria
Non-immunological (e.g. mechanical friction of pubic hair, topical substances)
Immunological (latex, body fluids)
Contact dermatitis
Incognito disease
Psoriasis
Candidosis
Scabies
Drugs and foods
Senile pruritus
Delusions of parasitosis
Dermatological non-disease
Dysaesthesia syndromes
Psychosexual

Table 71.4 Common causes of anogenital intertrigo.

Eczema
Exogenous
irritant contact
Endogenous
seborrhoeic
Psoriasis (inverse pattern/flexural)
Erythrasma
Candidosis
Tinea
Trichosporosis (in India)
Pseudoacanthosis nigricans

symptomatology, and drug history (topical and systemic, prescribed and over-the-counter). The personal and family history of atopy, psoriasis and seborrhoeic dermatitis is often relevant. Smoking habits should be documented; smoking is a risk factor for anogenital cancer.

Complete examination is mandatory because common diagnoses will be reached with the assistance of important signs at extragenital sites. Often the patient will not have had his/her genitalia or perineum examined. The practice of anogenital dermatology demands careful inspection and often requires internal examination and urinalysis. Drawings are made and photographs obtained. Signs are described using conventional and specific terminology (e.g. posthitis, phimosis).

Intertrigo describes any dermatosis occurring in skinfolds; frictional abrasion and a degree of epithelial loss may result in erosion that renders the site especially susceptible to secondary infection (e.g. with *Candida*). Causes are listed in Tables 71.4 and 71.5.

Pigmentary change is common. Causes of anogenital hypopigmentation and leukoderma include striae, vitiligo, lichen sclerosus, viral warts, leukoplakia and post-inflammatory changes (Table 71.6). Rarer causes include *Candida*, extramammary Paget's disease, mycosis fungoides and melanoma. Common causes of anogenital hyperpigmentation include tattoos, purpura, lentigines, naevi, pseudoacanthosis nigricans and post-inflammatory changes (Table 71.7). Rarer or potential causes include Addison's disease, Nelson's syndrome, genital melanosis, Laugier–Hunziker syndrome [3], Peutz–Jeghers syndrome [4,5], LAMB syndrome (lentigines, atrial myxoma, mucocutaneous myxoma, blue naevi) [6,7], LEOPARD syndrome, Ruvalcaba–Myhre–Smith syndrome [8,9], acanthosis nigricans, eruptive melanotic macules and papules associated with internal adenocarcinoma [10], acral lentiginous melanoma, drugs and metals. Both post-inflammatory hypo- and

Table 71.5 Rare causes of anogenital intertrigo. (After Bunker [1]. © 2004, with permission from Elsevier.)

Eczema
Exogenous
allergic contact
Endogenous
atopic
Reiter's syndrome
Lichen sclerosus
Hailey–Hailey disease
Darier's disease
Streptococcal dermatitis
Gonorrhoea
Secondary syphilis
Part of a syphilide
Mucous patch
Congenital syphilis (in the infant)
Trichosporosis (in industrialized countries)
Extramammary Paget's disease
Kaposi's sarcoma
Langerhans' cell histiocytosis
Carcinoma erysipeloides

Table 71.6 Causes of anogenital post-inflammatory hypopigmentation. (After Bunker [1]. © 2004, with permission from Elsevier.)

Following cryotherapy
Electrotherapy
Chemocautery
Laser surgery
Contact dermatitis
Lichen sclerosus
Systemic sclerosis
Lichen planus
Cicatricial pemphigoid
Gonococcal dermatitis
Syphilis
Leukoderma—post-secondary syphilide
Gumma
Post-gummatous atrophic scar
Herpes simplex
Pityriasis versicolor
Onchocerciasis 'leopard skin'
Peyronie's disease
Pseudoepitheliomatous micaceous and keratotic balanitis (PEMKB)

Table 71.7 Causes of anogenital post-inflammatory hyperpigmentation. (After Bunker [1]. © 2004, with permission from Elsevier.)

Post-traumatic
Lichen planus
Herpes simplex
Fixed drug eruption

Table 71.8 Causes of white patches and plaques. (After Bunker [1]. © 2004, with permission from Elsevier.)

Post-traumatic or surgical scar
Lichen simplex
Lichen sclerosus
Vitiligo
Mucous membrane (cicatricial) pemphigoid
Peyronie's disease
Syphilis
Leukoderma—post-secondary syphilide
Gumma
Post-gummatous atrophic scar
Viral warts
Pityriasis versicolor
Pseudoepitheliomatous micaceous and keratotic balanitis (PEMKB)
Intraepithelial neoplasia
Squamous cell carcinoma

Table 71.9 Common causes of anogenital ulcers. (After Bunker [1]. © 2004, with permission from Elsevier.)

Trauma
Pressure sores
Aphthae
Pilonidal sinus
Anal fistula
Anal fissure
Erythema multiforme/Stevens–Johnson syndrome
Hidradenitis suppurativa
Crohn's disease
Chancroid
Donovanosis/granuloma inguinale
Lymphogranuloma venereum
Syphilis—primary chancre
Squamous carcinoma

hyperpigmentation are possible after acute and chronic inflammation from diverse causes; both may be more pronounced in ethnically darker skin. Lichen planus, fixed drug eruptions and recurrent herpes simplex are the common causes of post-inflammatory hyperpigmentation. Genital trauma from a zipper injury can lead to macular pseudolentiginous lesions on the glans and shaft of the penis.

A mucosal white patch or plaque is sometimes called leukoplakia (Table 71.8). This is not a diagnostic term, and it is unhelpful as it evokes connotations from oral medicine of premalignancy or even frank neoplasia.

Anogenital ulceration requires meticulous elucidation. The principal causes are benign aphthae, sexually transmitted and non-sexually transmitted infection, cancer and artefact. Tables 71.9 and 71.10 list all the causes. Several causes can co-present, especially in HIV/AIDS.

Commonly required investigations include microbiology or virology of a swab or smear, scrapings for fungal microscopy and culture, scrapings for mite identification, skin biopsy, Wood's light to demonstrate vitiligo and erythrasma, and blood tests (e.g. antistreptolysin O titre (ASOT), HLA B27, HIV). Investigations pertinent to the evaluation of sexually transmitted diseases are not

Table 71.10 Rare causes of anogenital ulcers. (After Bunker [1]. © 2004, with permission from Elsevier.)

Extrusion of testicular prosthesis
Embolization
Dermatitis artefacta
Penile necrosis
Spontaneous scrotal ulceration
Sarcoid
Autoimmune bullous diseases
Bullous pemphigoid
Cicatritial pemphigoid
Linear IgA disease
Necrobiosis lipoidica
Pyoderma gangrenosum
Erythema elevatum diutinum
Necrotizing vasculitis
Wegener's granulomatosis
Polyarteritis nodosa
Systemic lupus erythematosus
Idiopathic systemic vasculitis
Hereditary spherocytosis with vascular necrosis
Degos' malignant atrophic papulosis
Calciphylaxis
Hypereosinophilic syndrome
Pseudomonas
Ecthyma gangrenosum
Necrotizing anorectal ulcer in leukaemia
Gonorrhoea
Chancroid
Donovanosis (granuloma inguinale)
Lymphogranuloma venereum
Fournier's gangrene
Tuberculosis and tuberculides
Atypical mycobacteria e.g. *M. ulcerans*
Syphilis—snail track ulcers
Yaws
Non-syphilitic spirochaetal ulcerative balanoposthitis
Herpes simplex
Herpes zoster
HIV
Chikongunya
Deep fungal infections
Histoplasmosis
Blastomycosis
Cryptococcosis
Actinomycosis
Paracoccidioidomycosis
Leishmaniasis
Amoebiasis
Filariasis
Langerhans' cell histiocytosis
Extramammary Paget's disease
Basal cell carcinoma
Squamous carcinoma
Verrucous carcinoma
Sweat gland carcinoma
Melanoma
Kaposi's sarcoma
Leukaemia
Lymphoma
Drug reaction

discussed further, but it bears re-emphasis that if a diagnosis of a potentially sexually transmitted disease is reached (warts, molluscum contagiosum, herpes simplex, scabies, pediculosis) then the patient should be referred for a genitourinary opinion and advised to inform their partner(s) so that they may be screened also.

The opinion of another specialist may be necessary and should be sought as dictated by the urological, gynaecological, colorectal or genitourinary situation. Combined clinics are the ideal.

References

1 Bunker CB. *Male Genital Skin Disease*. London: Saunders, 2004.
2 Sherertz EF. Symptomatic dermographism as a cause of genital pruritus. *J Am Acad Dermatol* 1994; **31**: 1040–1.
3 Began D, Mirowski G. Perioral and acral lentigines in an African American man. *Arch Dermatol* 2000; **136**: 419–22.
4 Gass JDM, Glatzer RJ. Acquired pigmentation simulating Peutz–Jeghers syndrome: initial manifestation of diffuse uveal melanocytic proliferation. *Br J Ophthalmol* 1991; **75**: 693–5.
5 Eng A, Armin A, Massa M, Gradini R. Peutz-Jeghers-like melanotic macules associated with oesophageal adenocarcinoma. *Am J Dermatopathol* 1991; **13**: 152–7.
6 Voron DA, Hatfield HH, Kalkhoff RK. Multiple lentigines syndrome. *Am J Med* 1976; **60**: 447–56.
7 Rhodes AR, Silverman RA, Harrist TJ, Perez-Atayde AR. Mucocutaneous lentigines, cardiomucocutaneous myxomas, and multiple blue nevi: the 'LAMB' syndrome. *J Am Acad Dermatol* 1984; **10**: 72–82.
8 Gretzula JC, Hevia O, Schachner LS *et al*. Ruvalcaba–Myhre–Smith syndrome. *Pediatr Dermatol* 1988; **5**: 28–32.
9 Perriard J, Saurat JH, Harms M. An overlap of Cowden's disease and Bannayan–Riley–Ruvalcaba syndrome in the same family. *J Am Acad Dermatol* 2000; **42**: 348–50.
10 Busam KJ, Sachs DL, Coit DG *et al*. Eruptive melanotic macules and papules associated with adenocarcinoma. *J Cutan Pathol* 2003; **30**: 4639.

Genitocrural dermatology

Introduction

The genitocrural folds represent a region of the body that is particularly prone to intertrigo and flexural forms of common dermatoses, probably because of koebnerization. Moisture and friction also lead to maceration and fissuring, and secondary infections readily supervene. Vegetating reactions can prove resistant to treatment. Itch may be prominent in psoriasis, infections and infestations of the area. Crab louse and *Oxyuris* infestation must be excluded as primary causes of rash. Lichenification occurs readily.

Inflammatory dermatoses

Intertrigo

Intertrigo is a generic name for an inflammatory dermatosis involving the body folds, notably those of the submammary and genitocrural regions. There may be no clear distinction between constitutional and infective causes (listed in Tables 71.4 & 71.5). Physical factors such as obesity, sweating, friction, incontinence and faecal soiling may cause erythema or fissuring, and render the skin vulnerable to the effects of other agents. Initially, it is marked by soreness or slight itching, and a superficial mild erythema of the apposed surfaces. Secondary infection occurs rapidly,

and the condition is then perpetuated as an infective dermatitis. In eczematous subjects this will take on the physical characteristics of eczema; in others, the infection may progress to crusting, pustular or vegetating lesions. The organisms concerned are *Staphylococcus aureus*, rarely the haemolytic *Streptococcus*, *Escherichia coli*, *Proteus* spp. and, occasionally, *Pseudomonas aeruginosa*. In infants, diabetics and the obese, yeasts are often present. Latent diabetes should be borne in mind when the disease is refractory to treatment. Overtreatment may compound the irritation or lead to a sensitization dermatitis.

Candidosis and contact dermatitis are differentiated by the history, the appearance and microscopic examination. The diffuse macerated erythema, often with fissures at the apex of the fold and without a sharply defined edge, distinguishes non-specific intertrigo from psoriasis and dermatophytosis, although scrapings and culture should always be undertaken. Mistakes in diagnosis arise from failure to recognize that two or more aetiological factors may coexist [1]. In India, *Trichosporon* species, which normally cause white piedra trichomycosis, have been implicated in causing cutaneous lesions resembling genitocrural intertrigo [2]. Langerhans' cell histiocytosis (see Chapter 55) has a predilection for the perineum or inguinal regions [3] and is a rare cause of genitocrural intertrigo; likewise extramammary Paget's disease. Congenital syphilis may present as intertrigo in an infant.

In the early stages, the condition can be controlled by avoidance of friction and tight clothing. Driving or sitting for long periods should be avoided. In severe cases, the patient must rest in bed, preferably with groins unclothed and bedclothes lifted by a cradle, the apposed skin surfaces being kept apart with appropriate dressings. Obesity, diabetes and incontinence should receive attention. Wet dressings are often useful initially in acute cases, and may be followed by bland or mild antibacterial creams or lotions. The aniline dyes and magenta paints still have a place in therapy. In general, lotions, paints and powders are more acceptable than creams. Nystatin, hydroxyquinoline and imidazoles can be applied alone or with topical steroids for a few days.

Genitocrural dermatitis

Lichen simplex is a result and/or cause of severe and spasmodic itch; the psychological mechanisms involved are similar to those discussed in relation to pruritus vulvae and pruritus ani. The 'giant' form of lichenification described by Pautrier [4] may be extremely resistant to treatment. Local treatment with corticosteroid applications is supplemented by reassurance, rest and sedation. All factors provoking local itching must, as far as possible, be removed.

Contact dermatitis (see Chapters 25 & 26) may present suddenly with pruritus, oedema and erythema, or insidiously as a gradual intensification of a pre-existing dermatitis. Sensitization to applied medicaments, contraceptives or, in men, industrial or other contact agents transferred by hand may be responsible for allergic contact dermatitis, especially if the scrotum and thighs are also affected. Irritant contact dermatitis is common and caused by excessive or exuberant use of soap and toiletries. A good example is nappy (diaper) rash where urine, occlusion, friction and *Candida* contribute to the clinical presentation. Classically, the convex surfaces are affected and the flexures are spared, distinguishing it from psoriasis. Nappy rash has become much less common with the availability of absorbent disposable paper napkins. A severe erosive form (Jacquet's dermatitis) is still occasionally seen in children with urinary or faecal incontinence.

Constitutional eczema should be considered in the differential diagnosis of napkin erythema in an infant (see Chapter 17). In adults, the genitocrural and lower abdominal folds are likely to be involved in seborrhoeic or intertriginous dermatitis.

Miscellaneous

Psoriasis and lichen planus are recognized by their special characteristics, although the diagnosis may be difficult when they arise in an exclusively flexural distribution. In the flexures and at anogenital sites, seborrhoeic dermatitis and psoriasis may be indistinguishable. Inverse pattern psoriasis refers to the manifestation of the disease on intertriginous skin in the axillae, natal cleft, gluteal folds, groins and in the preputial sac and on the glans of the uncircumcised male; its occurrence at these sites is probably enhanced by the Koebner phenomenon. Lichen planus has a propensity to cause ovoid hyperpigmented patches in the flexures and annular lichen planus is also common at these sites [5]. Treatment of intertriginous psoriasis and lichen planus is complicated by the need to control concomitant *Candida* infection and to avoid striae from potent topical steroids; topical calcineurin inhibitors show promise [6,7]. A psoriasiform genitocrural and perineal intertrigo has been reported in hereditary mucoepithelial dysplasia [8].

Impetigo herpetiformis frequently starts in the groin with small inflammatory yellowish-green pustules, which rupture to produce scabs and crusts. Acrodermatitis enteropathica and the acquired zinc deficiency syndrome [9] may well be overlooked as causes of genitocrural dermatitis. The distinction of Jacquet's eruption from congenital syphilis and from the exuberant plaques and nodules of infantile gluteal granuloma [10,11] is important. Hidradenitis suppurativa usually involves the area widely, although localized lesions are sometimes seen.

All forms of pemphigus and pemphigoid (especially pemphigus vegetans [12] and pyodermite végétante [13]) affect this region, and juvenile pemphigoid and pemphigoid gestationis affect it selectively and sometimes exclusively. Pemphigus vegetans must be distinguished from vegetating forms of pyoderma, which are not uncommon in the groins, and from blastomycosis and other mycoses, verrucoid forms of tuberculosis and granuloma inguinale. Cicatricial pemphigoid [14] may affect the groin. Benign familial pemphigus (Hailey–Hailey disease) involved the groins or genitalia in 14 out of 21 patients in one series [15]. It can involve the groins in isolation. Secondary infection with herpes simplex has been reported after treatment with retinoids [16]. Very rarely, papular and verrucoid plaques similar in appearance to genital warts have been reported [17]. HPV 5 infection and its response to topical imiquimod has been reported [18]. Darier's disease (see Chapter 19) involving the flexures is mild in most patients but does occur in the vast majority. It can be very sore and malodorous. The intertriginous features are similar to those of Hailey–Hailey disease. There have been several reports of a genital, inguinal and perineal eruption, with clinical and histological similarity to Darier's disease and Hailey–Hailey disease, called

genitocrural papular acantholytic dermatosis. The patients had no rash elsewhere, no family history and negative immunofluorescence [19]. Subcorneal pustular dermatosis extends outwards from the inguinal folds as flaccid pustules, rapidly rupturing to form gyrate and circinate crusted lesions. Dystrophic forms of epidermolysis bullosa may cause separation of the skin during delivery or, if less severe, bullae and erosions at these sites of friction.

Clear cell papulosis is a rare condition of Asian or Hispanic children where there may be asymptomatic white papules in the pubic area and 'milk line' (i.e. axillae and on the trunk); it is not known whether it is a sequel of extramammary Paget's disease [20].

Toxic epidermal necrolysis may present as desquamation, sometimes involving the whole region. Severe erythema multiforme involves the genital or anal mucosa in half of the cases. Necrolytic migratory erythema also extends in waves from this area [21].

Inguinal (Hexsel's) hyperhidrosis is a focal type of hyperhidrosis confined to the groins. It begins in adolescence and is debilitating and difficult to treat; botulinum toxin can be effective [22].

References

1 Schlappner OLA, Rosenblum GA, Rowden G *et al.* Concomitant erythrasma and dermatophytosis of the groin. *Br J Dermatol* 1970; **100**: 147–51.

2 Kamalam A, Senthamilselvi A, Ajuthades K *et al.* Cutaneous trichosporosis. *Mycopathologia* 1988; **101**: 167–75.

3 Chu T. Langerhans' cell histiocytosis. *Australas J Dermatol* 2001; **42**: 237–42.

4 Pautrier LM. In: Darier J, ed. *Nouvelle Pratique Dermatologique*, Vol. 7. Paris: Masson, 1936: 497.

5 Reich HL, Nguyen JT, James WD. Annular lichen planus: a case series of 20 patients. *J Am Acad Dermatol* 2004; **50**: 595–9.

6 Lebwohl M, Freeman AK, Chapman MS *et al.* Tacrolimus ointment is effective for facial and intertriginous psoriasis. *J Am Acad Dermatol* 2004; **51**: 723–30.

7 Gribetz C, Ling M, Lebwohl M *et al.* Pimecrolimus cream 1% in the treatment of intertriginous psoriasis: a double-blind, randomized study. *J Am Acad Dermatol* 2004; **51**: 731–8.

8 Boralevi F, Haftek M, Vabres P *et al.* Hereditary mucoepithelial dysplasia: clinical, ultrastructural and genetic study of eight patients and literature review. *Br J Dermatol* 2005; **153**: 310–8.

9 Chew L, Chan I, McGrath JA, Atherton DJ. Infantile acquired zinc deficiency resembling acrodermatitis enteropathica. *Clin Exp Dermatol* 2005; **30**: 578–602.

10 Tappeiner J, Pfleger L. Granuloma gluteale infantum. *Hautarzt* 1971; **22**: 383–8.

11 Hamado T. Granuloma intertriginosum infantum. *Arch Dermatol* 1975; **111**: 1072–3.

12 Winkelmann RK, Su WP. Pemphigoid vegetans. *Arch Dermatol* 1979; **115**: 446–8.

13 Neuman HAM, Faber WR. Pyodermite vegetante of Hallopeau: immunofluorescence studies performed in an early disease stage. *Arch Dermatol* 1980; **116**: 1169–71.

14 Lever WF, ed. *Pemphigus and Pemphigoid*. Springfield: Thomas, 1965.

15 Raaschou-Nielsen W, Reymann F. Familial benign chronic pemphigus. *Acta Derm Venereol (Stockh)* 1959; **39**: 280–91.

16 Stallman D, Schmoeckel C. Morbus Hailey–Hailey mit dissemination und eczema herpeticum unter Etretinat therapie. *Hautartz* 1988; **39**: 454–6.

17 Langenberg A, Berger TG, Cardelli M *et al.* Genital benign chronic pemphigus (Hailey–Hailey disease) presenting as condylomas. *J Am Acad Dermatol* 1992; **26**: 951–5.

18 Chan C-C, Thyong H-Y, Chan Y-C, Liao Y-H. Human papillomavirus type 5 infection in a patient with Hailey-Hailey disease successfully treated with imiquimod. *Br J Dermatol* 2007; **156**: 579–81.

19 Wong TY, Milm MC Jr. Acantholytic dermatosis localized to genitalia and crural areas of male patients: a report of three cases. *J Cutan Pathol* 1994; **21**: 27–32.

20 Benouni S, Kos L, Ruggeri SY *et al.* Clear cell papulosis in Hispanic siblings. *Arch Dermatol* 2007; **143**: 358–60.

21 Wilkinson DS. Necrolytic migratory erythema with carcinoma of the pancreas. *Trans St John's Hosp Dermatol Soc* 1973; **59**: 244–50.

22 Hexsel DM, Dal'forno T, Hexsel CL. Inguinal, or Hexsel's hyperhidrosis. *Clin Dermatol* 2004; **22**: 53–9.

Infections

Erythrasma

Erythrasma (see Chapter 30) is a common genitocrural infection, especially of the male. It is caused by *Corynebacterium minutissimum*, an organism that is normally a commensal but which in warmer climates may become pathogenic. Tawny, slightly scaly macules are seen on the upper inner thighs. In the inguinal folds, erythrasma may present as an intertrigo and can be macerated and eroded. It is not usually very itchy, but can be slightly sore. Lesions are usually also found in the axillae or toe webs. It may coexist with *Trichophyton rubrum* [1] and candidosis. Pruritus ani has also been reported [2]. Erythrasma is a clinical diagnosis confirmed by demonstration of coral pink fluorescence under Wood's light (resulting from a porphyrin produced by the bacterium). Treatment is with topical clindamycin, erythromycin or an imidazole, or with oral erythromycin. It is prone to recur.

Candidosis

Candidosis (thrush) presents as an intertrigo. Symptoms of burning and soreness are more common than itch. Coalescent red patches or plaques involve the folds, often with superficial erosions. Pustulosis extends out onto the skin of the abdomen, buttocks or thighs from the irregularly marginated intertriginous lesions. It can be a primary infection, particularly in infants, and in pregnancy and diabetes, but *Candida* may be more often a secondary pathogen in anogenital dermatoses. Observing the signs of candidosis or demonstrating the presence of the organism does not prove that it is the cause of all the symptoms and signs. *Candida albicans* is such a ready opportunist because it is a part of the resident flora of the gastrointestinal tract and may be retrieved from intertriginous areas, including the preputial folds, in the absence of symptoms and signs. A search for an underlying dermatological or medical cause should be undertaken. The symptoms and signs of *Candida* may be more florid than the underlying predisposing cause. Obesity predisposes to candidal intertrigo but medical causes include diabetes mellitus, iatrogenic immunosuppression and systemic antibiotic treatment. Although oropharyngeal candidosis is almost invariably found in HIV infection, anogenital candidosis is not generally associated, perhaps because it is overlooked or because many patients take long-term imidazole antifungals orally.

Underlying disease should be identified and treated, and predisposing factors rectified. Treatment includes topical nystatin, clioquinol or an imidazole, often very usefully combined with hydrocortisone or a moderately potent corticosteroid. If the infection is severe, an oral imidazole may be indicated.

Tinea cruris

Tinea (see Chapter 36) is a common disease of the groins and is usually caused by *Trichophyton rubrum* [3]. It is generally rare

in women, but occurs more frequently in hot climates. Spread occurs onto the thighs, buttocks and pubis. Many patients are misdiagnosed and/or partially treated with topical corticosteroids and/or topical antifungal agents. Tinea and *Candida* may complicate other dermatoses such as psoriasis. Tinea incognito/occulta is therefore common. There is a fine peripheral scaling (eczema marginé of Hebra). Cases have been described in infants [4].

Microscopy will confirm the clinical diagnosis, and in tinea incognito/occulta there are numerous fungal elements.

Dermatophyte infection of the anogenital skin usually requires oral treatment with griseofulvin, terbinafine or itraconazole. Topical treatments often fail because the anatomical complexity of the area makes topical treatment difficult, and there may be reinfection from concomitant involvement of feet or hands, toe or fingernails.

Miscellaneous infections

Bacterial or candidal infections complicate intertrigo, eczema, napkin erythema, scabies and many tropical diseases. Vincent's organism, *Pseudomonas aeruginosa* and a wide variety of Gram-negative organisms are commonly found. The 'blue underpants' sign may point to a *Pseudomonas* crural intertrigo [5]. Bullous impetigo occurs in childhood, often secondary to scabies. Gangrenous ecthyma of infants may, very rarely, affect the inguinocrural area. Gangrene has followed operations for inguinal hernia [6]. Giant condylomata acuminata may infiltrate the groin [7]. Sacral herpes zoster may present with groin lesions and retention of urine or constipation.

Phthiriasis pubis is sometimes overlooked as a cause of pruritus in the female. In the hirsute male, the infestation may be widespread. Oxyuriasis (threadworms) can cause localized urticaria as well as pruritus. Scabies in children is diffuse, and the inguinal glands are often enlarged from secondary infection. 'Seabather's eruption' affects the bathing trunk area.

Schistosomiasis and amoebiasis cause phagedenic necrosis, fistulae and pseudoelephantiasis, and may also give rise to granulomas and condylomatous masses [8]. Onchocerciasis causes depigmentation, nodules, atrophy, lymphadenopathy and a 'hanging groin' [9]. Trichosporosis is a common cause of genitocrural intertrigo in India, with symptoms of itching or burning. Scaly papules may accompany the intertrigo. Coexisting dermatophyte, *Candida*, trichomycosis and erythrasma infection may be found. Dequalinium chloride is used topically in India [10]. Trichomycosis presents with malodour and discoloured broken hairs [11], which should be distinguished from those of trichorrhexis nodosa, caused by repeated scratching [12]. Blastomycosis, actinomycosis and other deep fungal infections (see Chapter 36) simulate tuberculosis, but are more prone to form fissures, sinuses and vegetating or exuberant granulomatous lesions. They are distinguished by histological and bacteriological examination.

Among chronic infections, tuberculosis, tertiary syphilis and leishmaniasis are diagnosed by their characteristic features, which are described elsewhere. Congenital syphilis can be overlooked as a cause of genitocrural intertrigo in an infant. In tropical countries, tuberculous inguinal lymphadenopathy may be a cause of genitocrural lymphoedema. Amoebiasis involves the groins and perineum by extension from the anus.

Sexually transmitted diseases are fully discussed in Chapter 34. Granuloma inguinale affects the genitalia in less than half of cases, causing coalescing nodules, serpiginous ulcers and fungating masses. The buboes and fistulae of lymphogranuloma venereum are characteristic. Vulval (rarely scrotal) lymphoedema and elephantiasis may occur in both diseases.

References

1 Schlappner OLA, Rosenblum GA, Rowden G *et al.* Concomitant erythrasma and dermatophytosis of the groin. *Br J Dermatol* 1979; **100**: 147–51.
2 Bowyer A, McColl I. Erythrasma and pruritus ani. *Acta Derm Venereol* 1971; **51**: 444–7.
3 Gupta AK, Chaudhry M, Elewski B. Tinea corporis, tinea cruris, tinea nigra, and piedra. *Dermatol Clin* 2003; **21**: 395–400.
4 Parry EL, Foshee WS, Hall W *et al.* Diaper dermatophytosis. *Am J Dis Child* 1982; **136**: 273–4.
5 Kaya TI, Delialioglu N, Yazici AC *et al.* Medical pearl: blue underpants sign—a diagnostic clue for *Pseudomonas aeruginosa* intertrigo of the groin. *J Am Acad Dermatol* 2005; **53**: 869–71.
6 Audebert C. La gangrene post-operatoire progressive de la peau. *Ann Dermatol Vénéréol* 1981; **108**: 451–5.
7 Eng AM, Morgan NE, Blekys I. Giant condyloma acuminatum. *Cutis* 1979; **24**: 203–6.
8 Biagi FF, Martuscelli QA. Cutaneous amebiasis in Mexico. *Dermatol Trop* 1963; **2**: 129–36.
9 Nelson GS. 'Hanging groin' and hernia, complications of onchocerciasis. *Trans R Soc Trop Med Hyg* 1958; **52**: 272–5.
10 Kamalam A, Senthamilselvi G, Ajithadas K, Thambiah AS. Cutaneous trichosporosis. *Mycopathologia* 1988; **101**: 167–75.
11 White SW, Smith J. Trichomycosis pubis. *Arch Dermatol* 1979; **115**: 444–5.
12 Chernosky ME, Owen DW. Trichorrhexis nodosa: clinical and investigative studies. *Arch Dermatol* 1966; **94**: 577–85.

Miscellaneous

In the 'short bowel syndrome', kwashiorkor-like changes include an 'enamel paint skin' [1].

Dowling–Degos disease (reticulate pigmented anomaly of the flexures) involved the flexures in eight out of 10 patients [2], but may be restricted entirely to the vulval skin [3]. It is a rare autosomal dominant disorder characterized by spotted and reticulate pigmentation of the flexures. There may be comedone-like lesions on the neck, comedones and pitted scars near the angle of the mouth, epidermoid cysts, pilonidal sinus, hidradenitis suppurativa, multiple seborrhoeic warts and squamous cell carcinomas [4].

Acanthosis nigricans almost invariably affects the groins. Pseudoacanthosis nigricans can present as a macerated intertrigo and with secondary infection. These can be distinguished from each other and from lichenification in pigmented skins by a rubber silicone impression technique [5]. Calcinosis involving the upper inner thighs may resemble pseudoxanthoma elasticum [6].

The following entities are encountered in the genitocrural area:

Angiomas, lymphangiomas and angiokeratomas—diffuse angiomas or lymphangiomas may cause irregular subcutaneous swellings; angiokeratoma corporis diffusum may be a feature of several very rare congenital diseases affecting lysosomes, with the pinhead-sized lesions of Anderson–Fabry disease (β-galactosidase deficiency) occurring around the lower limb girdle and upper thighs from the navel to the knees; a male case with no

recognizable enzyme abnormalities has been described [7]. Epidermal naevi are not uncommon. Seborrhoeic warts may be mistaken for viral warts [8] or Bowenoid papulosis, as may melanocytic naevi or acrochordons. Papilliferous (intradermal) naevi and skin tags (acrochordons) often become large and pedunculated on the inner aspect of the thighs. Inguinogenital epidermoid cysts may become infected; lesions containing molluscum contagiosum have been described [9]. Pilar cyst, including giant forms, is much rarer [10].

Pubic hair problems are relatively rare in men, whereas women may be troubled by hirsutism or pili incarnati. Alopecia areata can affect the pubic hair, but usually as part of more widespread involvement as in alopecia universalis. Loss of pubic hair occurs in secondary syphilis and has been reported in primary systemic amyloid [11]. Pubic (and axillary) hair loss occurs in the Graham Little–Piccardi–Lassueur and androgen insensitivity syndromes [12]. Trichotillomania of the pubic hair has been described [13,14].

Vitiligo is common in the groins.

Extramammary Paget's disease can involve the genitocrural folds and present as an intertrigo.

Carcinoma erysipeloides (due to anogenital cancer) [15] is probably more common in the genitocrural area than reports would suggest. Carcinoma of the cervix, bladder and prostate may be the cause [16].

References

1 Smith SR. Skin changes in short bowel syndrome. *Ann Dermatol Vénéréol* 1977; **113**: 657–9.

2 Wilson Jones E, Grice K. Reticulate pigmented anomaly of the flexures: Dowling–Degos disease, a new genodermatosis. *Arch Dermatol* 1976; **114**: 1150–7.

3 Milde P, Goerz G, Plewig G. Morbus Dowling–Degos mit ausschliesslich genitaler Manifestation. *Hautarzt* 1992; **43**: 369–72.

4 Li C-R, Xing Q-H, Li M *et al.* A gene locus responsible for reticulate pigmented anomaly of the flexures maps to chromosome 17p13.3. *J Invest Dermatol* 2006; **126**: 1297–301.

5 Sarkany I. A method of studying the microtopography of the skin. *Br J Dermatol* 1962; **74**: 254–9.

6 Cochran RJ, Wilkin JK. An unusual case of calcinosis cutis. *J Am Acad Dermatol* 1983; **8**: 103–6.

7 Kelly B, Kelly E. Angiokeratoma corporis diffusum in a patient with no recognizable enzyme abnormalities. *Arch Dermatol* 2006; **142**: 615–8.

8 Friedman SJ, Fox BJ, Albert HL. Seborrhoeic keratoses of the penis. *Urology* 1987; **29**: 204–6.

9 Park SK, Lee JY, Kim YH *et al.* Molluscum contagiosum occurring in an epidermal cyst: report of three cases. *J Dermatol* 1992; **19**: 119–21.

10 Shah SS, Varea EG, Farsaii A *et al.* Giant epidermoid cyst of the penis. *Urology* 1979; **14**: 389–91.

11 Brownstein MH, Helwig EB. The cutaneous amyloidoses. II. Systemic forms. *Arch Dermatol* 1970; **102**: 20–8.

12 Vega Gutiérrez J, Miranda-Romero A, Pérez Milán F, Martínez García G. Graham Little-Piccardi-Lassueur syndrome associated with androgen insensitivity syndrome (testicular feminization). *J Eur Acad Dermatol Venereol* 2004; **18**: 463–6.

13 Davis-Daneshfar A, Trüeb RM. Tonsur-Trichotillomanie. *Hautarzt* 1995; **46**: 804–7.

14 Cohen LJ, Stein DJ, Simeon D *et al.* Clinical profile, comorbidity, and treatment history in 123 hair pullers: a survey study. *J Clin Psychiatry* 1995; **56**: 319–26.

15 Cohen EL, Kim SW. Cutaneous manifestation of carcinoma of urinary bladder: carcinoma erysipeloides. *Urology* 1980; **16**: 410–2.

16 Ng CS. Carcinoma erysipeloides from prostate cancer presenting as cellulitis. *Cutis* 2000; **65**: 215–6.

Male genital dermatology

Introduction

Male patients with non-venereological and non-urological skin problems commonly present to genitourinary or urology clinics where the training and expertise are not orientated to adequate dermatological diagnosis and treatment [1].

Careful dermatological evaluation, including a full history and complete examination, usually allows confident clinical differential diagnosis. A biopsy and other investigations are sometimes indicated. It is important to consider the possibility of sexually transmitted disease or a urological disorder and refer accordingly; combined clinics are useful.

History taking and the primary symptomatology of anogenital dermatology are discussed on pp. 71.1–71.4. It may be necessary actively to elicit symptoms caused by sexual dysfunction (e.g. male dyspareunia), and it should be remembered that male sexual function amounts to more than erectile potency; libido, ejaculation and orgasm are the other components [2].

Complete examination is mandatory to elicit important signs at extragenital sites. The physical examination of the male at any age is incomplete without examination of the genitals and scrotum (but this is frequently not carried out in general clinical settings) and urologists teach that there are three primary reasons for careful examination of the scrotum: pain, swelling and absence of contents. The presence or absence of the prepuce, phimosis or paraphimosis should be sought and the foreskin retracted gently (if present). The gluteal and crural folds should be parted to allow adequate inspection. Sometimes it is useful to elicit dermographism of the inner thighs. Urinalysis completes the physical examination.

Findings specific to the male genitalia include phimosis, paraphimosis, balanitis and posthitis. Phimosis ('muzzling') refers to a non-retractable foreskin. The literature can be confusing; Rickwood [3] has defined it as scarring of the tip of the foreskin. There are several possible causes of phimosis (Table 71.11). In adults, phimosis is usually the consequence of disease processes. It has also been attributed to titanium formulated in proprietary topical preparations [4]. Diabetes was diagnosed in 36% of men between 17 and 59 years of age presenting with phimosis of less than 2 years' duration, with no specific preputial pathology identified histologically [5]. In boys, the histological findings may be normal in nearly half of those circumcised [6].

Table 71.11 Causes of phimosis. (After Bunker [7]. © 2004, with permission from Elsevier.)

Non-specific balanoposthitis (e.g. in diabetes)
Lichen sclerosus
Lichen planus
Hidradenitis suppurativa
Crohn's disease
Cicatricial pemphigoid
Chronic penile lymphoedema
Cutaneous lymphoma
Kaposi's sarcoma

Table 71.12 Causes of paraphimosis. (After Bunker [7]. © 2004, with permission from Elsevier.)

Acute contact urticaria
Acute allergic contact dermatitis
Lichen sclerosus

Table 71.13 Common causes of balanoposthitis. (After Bunker [7]. © 2004, with permission from Elsevier.)

Eczema
Exogenous
allergic contact
irritant contact
Endogenous
seborrhoeic
Psoriasis
Reiter's disease
Zoon's plasma cell balanitis
Lichen sclerosus
Gonorrhoea
Human papillomavirus
Herpes simplex
Candidosis

Table 71.14 Rare causes of balanoposthitis. (After Bunker [7]. © 2004, with permission from Elsevier.)

Crohn's disease
Streptococcal dermatitis
Staphylococcal cellulitis
Gonorrhoea
Syphilis
Chancre with balanitis of Follman
Mucous patch
Mycoplasma
Trichomonas vaginalis
Lymphogranuloma venereum
Non-syphilitic spirochaetal ulcerative balanoposthitis
Tinea
Amoebiasis
Myiasis
Scabies
Eccrine syringofibroadenomatosis
Erythroplasia of Queyrat
Kaposi's sarcoma
Chronic lymphatic leukaemia
Fixed drug eruption

Table 71.15 Causes of dorsal perforation of the prepuce.

Hidradenitis suppurativa
Pyoderma gangrenosum
Florid condylomata
Podophyllin
Chancroid
Herpes simplex

Paraphimosis refers to a foreskin fixed in retraction. Although some authors have used the term to describe a foreskin that is tight in retraction around the flaccid penile shaft, 'waisting' or 'constrictive posthitis' may be better terms [7]. Rickwood [8] has said that paraphimosis results from abuse not disease of the foreskin, but some medical causes can be identified (Table 71.12).

Balanitis is inflammation of the glans penis; posthitis is inflammation of the prepuce [9]. Balanoposthitis means inflammation of the glans and prepuce, and can be regarded as a special form of intertrigo (Tables 71.13 & 71.14). By definition therefore, balanoposthitis cannot occur in the circumcised male. Generally, dermatologists feel that balanitis, posthitis and balanoposthitis are probably more commonly caused by inflammatory and precancerous dermatoses than do genitourinary physicians, who teach that most cases are caused by infection, usually with *Candida* [10,11]. However, the evidence for *Candida* as a cause for balanoposthitis is not strong [12].

General aspects of anogenital ulceration are discussed on pp. 71.3–71.4 and in Tables 71.9 and 71.10. The principal causes of male genital ulceration are sexually transmitted and non-sexually transmitted infection, cancer and artefact [13]. Several causes can co-present, especially in HIV/AIDS. Dorsal perforation of the prepuce is a recently highlighted complication of several ulcerative penile diseases, sexually and non-sexually acquired, as listed in Table 71.15 [14,15]. Penile necrosis is a rare but devastating presentation with an important differential diagnosis.

Special investigations appropriate to anogenital cases are discussed on pp. 71.3–71.4. In genitourinary clinics, application of 3–5% acetic acid to the penis is used as an aid to the clinical diagnosis of viral warts and is held to reveal subclinical infection [16], but is not in routine use in dermatological practice. Human papillomavirus (HPV) polymerase chain reaction (PCR) screening suggests that the acetowhite test is not very specific [17–20]. Peniscopy is not generally practised by dermatologists. A penis biopsy can be highly informative in selected cases [21]. It is safe to use small amounts of adrenaline with the local anaesthetic. Beware of the distal ventral midline area where the urethra is very close to the skin surface. It is often not necessary to suture a punch biopsy site.

References

1 Hillman RJ, Walker MM, Harris JRW, Taylor-Robinson D. Penile dermatoses: a clinical and histopathological study. *Genitourin Med* 1992; **68**: 166–9.
2 Gasser TC, Lehmann K. Male sexual function is more than erection. *Lancet* 1995; **346**: 706.
3 Rickwood AM, Hemalatha V, Batcup G, Spitz L. Phimosis in boys. *Br J Urol* 1980; **52**: 147–50.
4 Dundas SAC, Laing RW. Titanium balanitis with phimosis. *Dermatologica* 1988; **176**: 305–7.
5 Chopra R, Fisher RD, Fencel R. Phimosis and diabetes mellitus. *J Urol* 1982; **127**: 1101–2.
6 Clemmensen OJ, Krogh J, Petri M. The histologic spectrum of prepuces from patients with phimosis. *Am J Dermatopathol* 1988; **10**: 104–8.
7 Bunker CB. *Male Genital Skin Disease*. London: Saunders, 2004.
8 Rickwood AM. Medical indications for circumcision. *BJU Int* 1999; **83** (Suppl. 1): 45–51.
9 Waugh MA. Balanitis. *Dermatol Clin* 1998; **16**: 757–62.
10 Edwards S. Balanitis and balanoposthitis: a review. *Genitourin Med* 1996; **72**: 155–9.

11 English JC III, Laws RA, Keough GC *et al.* Dermatoses of the glans penis and prepuce. *J Am Acad Dermatol* 1997; **37**: 1–24.
12 Birley HDL, Walker MM, Luzzi GA *et al.* Clinical features and management of recurrent balanitis: association with atopy and genital washing. *Genitourin Med* 1993; **69**: 400–3.
13 Rosen T, Brown TJ. Genital ulcers: evaluation and treatment. *Dermatol Clin* 1998; **16**: 673–85.
14 Gupta S, Kumar B. Dorsal perforation of prepuce: a common end point of severe ulcerative genital diseases? *Sex Transm Infect* 2000; **76**: 210–2.
15 Gupta S, Kumar B. Dorsal perforation of prepuce due to locally erosive condylomata acuminata. *Sex Transm Infect* 2001; **77**: 77–8.
16 Steinberg JL, Cibley LJ, Rice PA. Genital warts: diagnosis, treatment, and counselling for the patient. *Curr Clin Top Infect Dis* 1993; **13**: 99–122.
17 Mazzatenta C, Andreassi L, Biagioli M *et al.* Detection and typing of genital papillomaviruses in men with a single polymerase chain reaction and type specific DNA probes. *J Am Acad Dermatol* 1993; **28**: 704–10.
18 Wikström A, Hedblad MA, Johansson B *et al.* The acetic acid test in evaluation of subclinical genital papillomavirus infection: a comparative study on penoscopy, histopathology, virology and scanning electron microscopy findings. *Genitourin Med* 1992; **68**: 90–9.
19 Voog E, Ricksten A, Olofsson S *et al.* Demonstration of Epstein–Barr virus DNA and human papillomavirus DNA in acetowhite lesions of the penile skin and the oral mucosa. *Int J STD AIDS* 1997; **8**: 772–5.
20 Kumar B, Gupta S. The acetowhite test in genital human papillomavirus infection in men: what does it add? *J Eur Acad Dermatol Venereol* 2001; **15**: 27–9.
21 Mallon E, Ross JS, Hawkins DA *et al.* Biopsy of male genital dermatosis. *Genitourin Med* 1997; **73**: 421.

Structure and function of the male genitalia

The penis is the male organ of urinary elimination and sexual function for the insemination of the female. The prepuce and its secretions provide physical and immunological protective functions, and it has erogenous properties (e.g. the penile dartos muscle and the corpuscular receptor-rich ridged band), but none of these is indispensable for erogenous function in copulation [1]. The scrotum maintains the testes at the ideal temperature for spermatogenesis. The male genital structures are illustrated in Fig. 71.1. The anatomical position is that of full penile erection.

The anatomy is explained by the embryology [2]. At about the third week of fetal development, mesenchymal tissue from the primitive streak forms cloacal folds around the cloacal membrane, joined anteriorly and cranially to form the genital tubercle, posteriorly and caudally to form an annulus. The cloacal membrane is thus divided into urogenital and anal membranes craniocaudally, and lateral genital swellings appear as precursors of either the scrotum or labia majora.

Fetal and testicular androgens then induce lengthening of the genital tubercle to form first an urethral groove and then the urethral canal. The urethral epithelium of the penis is therefore derived from endoderm. Initially, it is incomplete cranially where the glans has developed from the genital tubercle. The glandular urethra and the meatus form from an invading canalizing cord of ectoderm. The scrotal swellings fuse posteriorly at about 14 weeks but are empty until birth.

The prepuce [1] is formed by a midline fusion of ectoderm, neuroectoderm and mesenchyme, resulting in a pentalaminar structure consisting of (from the inner layer outwards) squamous mucosal epithelium, lamina propria, dartos muscle, dermis and glabrous skin. The preputial fold progressively extends, but there is also an ingrowth of a cellular lamella. It then fuses with the mucosa of the glans. The female analogue is the clitoral hood.

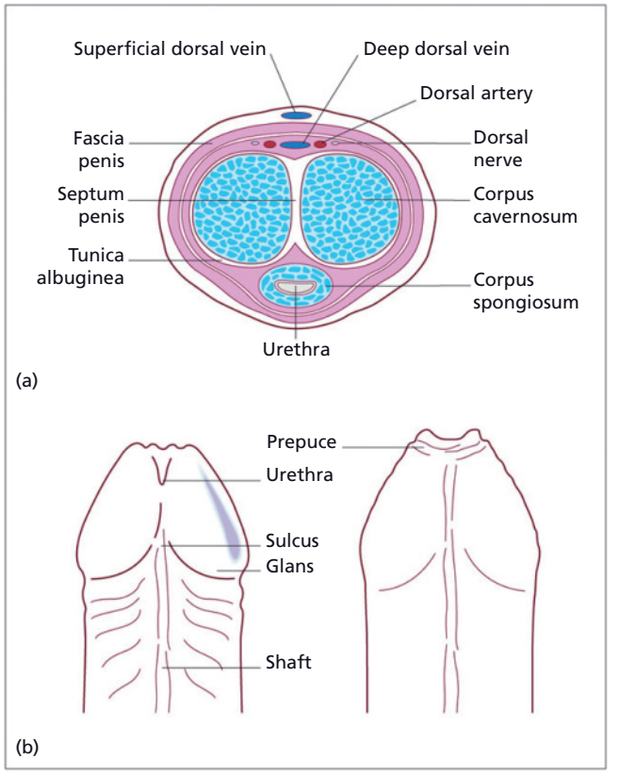


Fig. 71.1 (a) Cross-section of the body of the penis. (b) Circumcised and uncircumcised glans penis. (Adapted from *Last's Anatomy*, 9th edn. Reproduced from Bunker C.B. *Male Genital Skin Disease*, © 2004, with permission from Elsevier.)

The anogenital area is densely endowed with eccrine and apocrine sweat glands. Also in plentiful number are holocrine sebaceous glands, usually in association with hair follicles but also occurring as free glands at some sites such as the anal rim or around the coronal sulcus (Tyson's glands). These secretions exist to lubricate hair, lubricate the mucocutaneous junctions to assist in the voiding of excreta and protect the epithelia from irritation, and to lubricate the penis for sexual activity (probably mainly the retraction of the foreskin rather than the penetration of the introitus and vagina).

Pubic hair appears in puberty as vellus hair that is focally replaced by terminal hair. The pattern of pubic hair in men is different from that in women, and its distribution varies widely between men. McGregor [3] defined three patterns (Fig. 71.2). Generally, the abdominal wall, pubic mound, groins, scrotum and perineum are hairy but the natal cleft, perianal skin, distal penile shaft, prepuce and glans are hairless.

The pattern of keratinization of the epithelium is different throughout the anogenital area, particularly at the mucosal junctions, the prepuce and distal penile shaft and the glans in the circumcised male. The spectrum of differentiation of the male urogenital tract is manifest in the expression of differing epithelial cytokeratins [4].

References

1 Cold CJ, Taylor JR. The prepuce. *BJU Int* 1999; **83** (Suppl. 1): 34–44.
2 Ammini AC, Sabherwal U, Mukhopadhyay C *et al.* Morphogenesis of the human external male genitalia. *Pediatr Surg Int* 1997; **12**: 401–6.

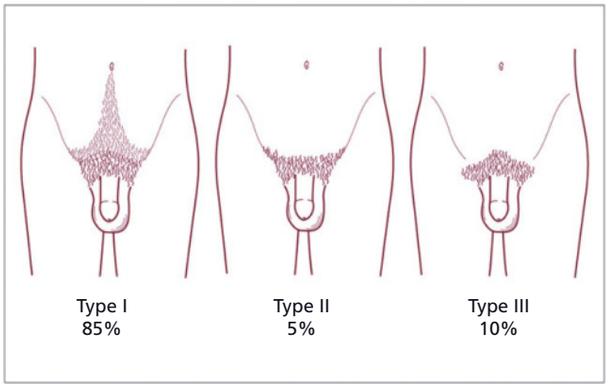


Fig. 71.2 Normal distribution of pubic hair in men. (After McGregor [3]. Reproduced from Bunker C.B. *Male Genital Skin Disease*, © 2004, with permission from Elsevier.)



Fig. 71.3 Pearly penile papules. (Courtesy of Dr D.A. Burns, Leicester, UK.)



Fig. 71.4 Prominent sebaceous glands on the penis. (Courtesy of Dr F.A. Ive, Durham, UK.)

3 McGregor D. Distribution of pubic hair in sample of fit men. *Br J Dermatol* 1961; **73**: 61–4.

4 Achtstätter T, Moll R, Moore B, Franke WW. Cytokeratin polypeptide patterns of different epithelia of the human male urogenital tract: immunofluorescence and gel electrophoretic studies. *J Histochem Cytochem* 1985; **33**: 415–26.

Normal variants

Normal male genital variants include pigmentary variation, hair variation (as above), skin tags, pearly penile papules, sebaceous prominence, melanocytic naevi, prominent veins, angiomas and angiokeratomas, common congenital abnormalities and circumcision.

Skin tags are common in the groins, especially of obese men. They may catch on clothing, bleed and become infected. Treatment is by electrocautery or scissor amputation and cautery. Fibrosed haemorrhoids result in perianal skin tags. Larger, fleshier, more oedematous skin tags should arouse the suspicion of Crohn's disease. They can predate gastrointestinal disease by several years. Sigmoidoscopy and biopsy should be considered [1].

Pearly penile papules are common; they may be found in up to 50% of men [2,3]. They present as flesh-coloured, pink, smooth, rounded, 1–3 mm papules, occurring predominantly around the coronal margin of the glans, rarely on the glans, in rows or rings (Fig. 71.3). Ectopic lesions on the penile shaft have been reported [4]. They are frequently mistaken for warts and misdiagnosed as Tyson's glands or ectopic sebaceous glands of Fordyce. The patient is often an anxious adolescent. The histology is that of angiofibroma. The lesion is analogous to other acral angiofibromas such as adenoma sebaceum, subungual and periungual fibromas, fibrous papule of the nose, acquired acral angiofibroma and oral fibroma [5]. Reassurance is usually sufficient but cryotherapy and laser treatment can be effective [6,7].

Sebaceous gland prominence, Tyson's glands, sebaceous hyperplasia and ectopic sebaceous glands of Fordyce are all virtually synonymous, common, normal variants of the skin of the scrotal sac and penile shaft, but they may cause concern to the patient (Fig. 71.4). They have been held to be very rare or their presence doubted at all [8]. Fordyce's condition also commonly affects the vermilion border of the lips. Naevoid linear lesions on the penile shaft have been seen [9–11]. The glans can be affected [12]. Reassurance is usually all that is required, but dysmorphophobia can occur.

Congenital and acquired melanocytic naevi are common. It is possible that naevi on the penis occur more frequently in patients with the atypical naevus syndrome, but this has not been formally documented. Genital epithelioid blue naevus is very rare [13]. A man who developed multiple blue naevi on the glans penis has been described [14]. Spitz naevus has been described [15]. Divided or 'kissing' naevus (analogous to the entity recognized on the eyelids) has been reported, with one component located on the



Fig. 71.5 Scrotal angiokeratoma of Fordyce. (Courtesy of Dr D.A. Burns, Leicester, UK.)

glans and the other on the distal penile shaft or prepuce, separated by uninvolved skin across the coronal sulcus [16–18]; melanoma developed in one case [19]. Large 'bathing trunk' naevi frequently involve the anogenital area and pose significant management problems, including the risk of melanoma (see Chapter 54).

Prominent veins are common, if not universal, and occasionally give rise to concern. Vascular white spots are sometimes seen on the glans, and are possibly analogous to Bier's spots seen on the palms and forearms.

Cherry Campbell de Morgan angiomas may, unusually, be confined to the genitalia. Angiokeratomas on the genitalia have also confusingly been given the Fordyce eponym (Fig. 71.5). They are multiple, rarely solitary, blue to purple, smooth, 2–5 mm papules on the scrotum, and rarely on the penile shaft [20] and glans [10,21]. The role of local venous hypertension in causation is controversial [22]. Angiomas and angiokeratomas may bleed following trauma. The differential diagnosis includes angiokeratoma corporis diffusum, acquired capillary and cavernous haemangiomas, Masson's tumour, glomus tumour, epithelioid haemangioma, bacillary angiomatosis, Kaposi's sarcoma and epithelioid haemangioendothelioma. One case of florid genital angiokeratomatosis has been associated, perhaps coincidentally, with corporeal papular xanthomatosis [23]. Hyfrecation, electrocautery or laser ablation [24] can be offered, but lesions recur. Appearing in some contexts, such as HIV infection or follow-up for genital cancer, they can cause alarm [25]. Most patients are content with reassurance, and a biopsy is not usually necessary.

References

1 Alexander-Williams J, Buchmann P. Perianal Crohn's disease. *World J Surg* 1980; **4**: 203–8.
2 Oates JK. Pearly penile papules. *Genitourin Med* 1997; **73**: 137–8.
3 Sonnex C, Dockerty WG. Pearly penile papules: a common cause of concern. *Int J STD AIDS* 1999; **10**: 726–7.
4 Neri I, Bardazzi F, Raone B *et al*. Ectopic pearly penile papules: a paediatric case. *Genitourin Med* 1997; **73**: 136.
5 Ackerman AD, Kornberg R. Pearly penile papules. *Arch Dermatol* 1973; **108**: 673–5.
6 Porter W, Bunker CB. Treatment of pearly penile papules with cryotherapy. *Br J Dermatol* 2000; **142**: 847–8.
7 McKinlay JR, Graham BS, Ross EV. The clinical superiority of continuous exposure versus short-pulsed carbon dioxide laser exposures for the treatment of pearly penile papules. *Dermatol Surg* 1999; **25**: 124–6.
8 Batistatou A, Panelos J, Zioga A, Charalabopoulos KA. Ectopic modified sebaceous glands in human penis. *Int J Surg Pathol* 2006; **14**: 355–6.
9 Kumar A, Kossard S. Band-like sebaceous hyperplasia over the penis. *Australas J Dermatol* 1999; **40**: 47–8.
10 Bunker CB. *Male Genital Skin Disease*. London: Saunders, 2004.
11 Vergara G, Belinchón I, Silvestre JF *et al*. Linear sebaceous gland hyperplasia of the penis: a case report. *J Am Acad Dermatol* 2003; **48**: 149–50.
12 Massmanian A, Valis GS, Sempere FJV. Fordyce spots on the glans penis. *Br J Dermatol* 1995; **133**: 498–9.
13 Izquierdo MJ, Pastor MA, Carrasco L *et al*. Epithelioid blue naevus of the genital mucosa: report of four cases. *Br J Dermatol* 2001; **145**: 496–501.
14 de Giorgi V, Massi D, Brunasso G *et al*. Eruptive multiple blue nevi of the penis: a clinical dermoscopic pathologic case study. *J Cutan Pathol* 2004; **31**: 185–8.
15 Aoyagi S, Sato-Matsumura KS, Akiyama M *et al*. Spitz naevus of the glans penis: an unusual location. *Acta Derm Venereol* 2004; **84**: 324–5.
16 Choi GS, Won DH, Lee SJ *et al*. Divided naevus on the penis. *Br J Dermatol* 2000; **143**: 1126–7.
17 Kono T, Nozaki M, Kikuchi Y *et al*. Divided naevus of the penis: a hypothesis on the embryological mechanism of its development. *Acta Derm Venereol* 2003; **83**: 155–6.
18 Phan PT, Francis N, Madden N, Bunker CB. Kissing naevus of the penis. *Clin Exp Dermatol* 2004; **29**: 471–2.
19 Egberts F, Egberts JH, Schwarz T, Hauschild A. Kissing melanoma or kissing nevus of the penis? *Urology* 2007; **69**: 384, e5–7.
20 Pianezza ML, Singh D, Van der Kwast T, Jarvi K. Rare case of recurrent angiokeratoma of Fordyce on penile shaft. *Urology* 2006; **68**: 891, e1–3.
21 Leis-Dosil VM, Alijo-Serrano F, Aviles-Izquierdo JA *et al*. Angiokeratoma of the glans penis: clinical, histopathological and dermatoscopic correlation. *Dermatol Online J* 2007; **13**: 19.
22 Erkek E, Basar MM, Bagci Y *et al*. Fordyce angiokeratomas as clues to local venous hypertension. *Arch Dermatol* 2005; **141**: 1325–6.
23 Caputo R, Passoni E, Cavicchini S. Papular xanthoma associated with angiokeratoma of Fordyce: considerations on the nosography of this rare non-Langerhans cell histiocytoxanthomatosis. *Dermatology* 2003; **206**: 165–8.
24 Occella C, Bleidl D, Rampini P *et al*. Argon laser treatment of cutaneous multiple angiokeratomas. *Dermatol Surg* 1995; **21**: 170–2.
25 Malalasekera AP, Goddard JC, Terry TR. Angiokeratoma of Fordyce simulating recurrent penile cancer. *Urology* 2007; **69**: 576, e13–4.

The foreskin

The prepuce has been present in primates for 65–100 million years and its function is controversial [1–4]. It is usual for it to be adherent to the glans at birth. Four per cent of boys have a retractable foreskin at birth, 15% at 6 months, 50% at 1 year and 80–90% at 3 years; the process should be complete by 17 years [5]. The foreskin varies in length and retractability: 'short' and 'long' variants are seen.

References

1 Whitfield H. Circumcision. *BJU Int* 1999; **83** (Suppl. 1): 1–113.
2 Porter WM, Bunker CB. The dysfunctional foreskin. *Int J STD AIDS* 2001; **12**: 216–20.
3 Taves DR. The intromission function of the foreskin. *Med Hypotheses* 2002; **59**: 180–2.
4 Bunker CB. *Male Genital Skin Disease*. London: Saunders, 2004.
5 Cold CJ, Taylor JR. The prepuce. *BJU Int* 1999; **83** (Suppl. 1): 34–44.

Circumcision

Circumcision has been performed for religious, cultural or medical reasons throughout history [1]. Worldwide, it has been estimated that approximately 25% of men have been circumcised [2]. Routine neonatal circumcision is controversial [3–6]. The UK General Medical Council (GMC) undertook a review of infantile circumcision in 1997, which 'demonstrated widely conflicting views in society that neither doctors nor the GMC can resolve' [7].

During infancy, circumcised boys have a higher incidence of penile problems than the uncircumcised, but after infancy the situation is significantly reversed [8,9]. Circumcision reduces the retrieval of pathogenic microorganisms from the penis [10]. Many have concluded that circumcision protects men from cancer of the penis and urinary tract, and sexually transmitted infections including HIV [11,12]. However, the incidence of penis cancer is low in countries where circumcision is uncommon [13], so other factors are important in penile carcinogenesis (see pp. 71.40–71.41). Also, the effects of circumcision on the other outcomes may be small [14] (e.g. urethritis may be more common in the circumcised, whereas ulcerative disease is more common in the uncircumcised). Circumcision protects men from inflammatory genital dermatoses including psoriasis, seborrhoeic dermatitis, lichen planus and lichen sclerosus [15]. This fact may be related to the occlusion and moisture consequent on the presence of the prepuce; O'Farrell *et al.* observed penile wetness in hardly any circumcised men, yet it is present in 40% of uncircumcised men with 'balanitis' [16].

Circumcision is important in the management of disorders of the penis and the foreskin, including dermatological disease. However, variability exists between clinicians in the indications for circumcision, especially in children. They include true phimosis, recurrent balanoposthitis, lichen sclerosus, penile lymphoedema, intraepithelial neoplasia and carcinoma.

The consensus is that circumcision has insignificant adverse effects on health, but it is not risk- or complication-free: bleeding, infection, necrosis, adhesions, bridges, fistula, keloid, concealed or buried penis, amputation, necrosis, excessive excision of penile skin, meatal stenosis, meatitis and meatal ulcer, cysts, chordee, hypospadias and epispadias, amputation neuromas, abnormal sexual behaviour, psychological distress and dysmorphophobia [17–27]. In some third world settings the complication rate can be very high [26], implying that better training is required if circumcision is going to become more commonly adopted as part of HIV-prevention strategies [12]. 'Uncircumcision' describes preputial restoration performed throughout history for various reasons [28,29].

As circumcised men age and become obese the penis may retract into the pubic mound—the 'vanishing penis syndrome'. This phenomenon can create a 'pseudoforeskin', especially if the initial circumcision was inadequate or incomplete, and this favours development of dermatoses found characteristically only in uncircumcised men, such as Zoon's balanitis and lichen sclerosus [30].

References

1 Dunsmuir WD, Gordon EM. The history of circumcision. *BJU Int* 1999; **83** (Suppl. 1): 1–12.

2 Moses S, Bailey RC, Ronald AR. Male circumcision: assessment of health benefits and risks. *Sex Transm Infect* 1998; **74**: 368–73.

3 Whitfield H. Circumcision. *BJU Int* 1999; **83** (Suppl. 1): 1–113.

4 Morris BJ. Why circumcision is a biomedical imperative for the 21st century. *BioEssays* 2007; **29**: 1147–58.

5 Malone P, Steinbrecher H. Medical aspects of male circumcision. *BMJ* 2007; **335**: 1206–9.

6 Twisselmann B. Circumcision: right or wrong? Summary of responses. *BMJ* 2008; **336**: 60.

7 Anonymous. *Guidance for Doctors who are Asked to Circumcise Male Children*. London: General Medical Council, 1997.

8 Fergusson DM, Lawton JM, Shannon FT. Neonatal circumcision and penile problems: an 8 year longitudinal study. *Pediatrics* 1988; **81**: 537–41.

9 Van Howe RS. Variability in penile appearance and penile findings: a prospective study. *Br J Urol* 1997; **80**: 776–82.

10 Günsar C, Kurutepe S, Alparslan O *et al.* The effect of circumcision status on periurethral and glandular bacterial flora. *Urol Int* 2004; **72**: 212–5.

11 O'Farrell N, Egger M. Circumcision in men and the prevention of HIV infection: a 'meta-analysis' revisited. *Int J STD AIDS* 2000; **11**: 137–42.

12 Quinn TC. Circumcision and HIV transmission. *Curr Opin Infect Dis* 2007; **20**: 33–8.

13 Frisch M, Friis S, Kjaer SK, Melbye M. Falling incidence of penis cancer in an uncircumcised population (Denmark 1943–90). *BMJ* 1995; **311**: 1471.

14 Laumann EO, Masi CM, Zuckerman EW. Circumcision in the United States: prevalence, prophylactic effects, and sexual practice. *JAMA* 1997; **277**: 1052–7.

15 Mallon E, Hawkins D, Dinneen M *et al.* Circumcision and genital dermatoses. *Arch Dermatol* 2000; **136**: 350–4.

16 O'Farrell N, Morison L, Chung C-K. Low prevalence of penile wetness among male sexually transmitted infection clinic attendees in London. *Sex Transm Dis* 2007; **34**: 408–9.

17 Williams N, Kapila L. Complications of circumcision. *Br J Surg* 1993; **80**: 1231–6.

18 Gürünlüoglu R, Bayramicli M, Dogan T, Numanoglu A. Unusual complications of circumcision. *Plast Reconstr Surg* 1999; **104**: 1938–9.

19 Esen AA, Aslan G, Kazimoglu H *et al.* Concealed penis: rare complication of circumcision. *Urol Int* 2001; **66**: 117–8.

20 Coskunfirat OK, Sayilkan S, Velidedeoglu H. Glans and penile skin amputation as a complication of circumcision. *Ann Plast Surg* 1999; **43**: 457.

21 Quintela R, Delmas V, Cannistra C, Boccon-Gibod L. Plastic surgery of the penis after circumcision. *Prog Urol* 2000; **10**: 476–8 [in French].

22 Kaplan GW. Complications of circumcision. *Urol Clin North Am* 1983; **10**: 543–9.

23 Goldman R. The psychological impact of circumcision. *BJU Int* 1999; **83** (Suppl. 1): 93–102.

24 Erdemir F. A rare complication after circumcision: keloid of the penis. *Int Urol Nephrol* 2006; **38**: 609–11.

25 Emsen IM. Catastrophic complication of the circumcision that carried out with local anaesthesia contained adrenaline. *J Trauma* 2006; **60**: 1150.

26 Okeke LI, Asinobi AA, Ikuerowo OS. Epidemiology of complications of male circumcision in Ibadan, Nigeria. *BMC Urol* 2006; **6**: 21.

27 Barnes S, Ben Chaim J, Kessler A. Postcircumcision necrosis of the glans penis: gray-scale and color Doppler sonographic findings. *J Clin Ultrasound* 2007; **35**: 105–7.

28 Schultheiss D, Truss MC, Stief CG, Jonas U. Uncircumcision: a historical review of preputial restoration. *Plast Reconstr Surg* 1998; **101**: 1990–8.

29 Brandes SB, McAninch JW. Surgical methods of restoring the prepuce: a critical review. *BJU Int* 1999; **83** (Suppl. 1): 109–13.

30 Toker SC, Baskan EB, Tunali S *et al.* Zoon's balanitis in a circumcised man. *J Am Acad Dermatol* 2007; **57**: S6–7.

Congenital and developmental abnormalities

Congenital and developmental anomalies are common, reflecting the complicated embryogenesis and subsequent sexual differentiation of the anogenital region. The dermatologist may not be called upon to make a primary diagnosis, but needs to be aware of syndromic associations as well as anatomical and functional abnormalities because these additionally predispose the area to dermatoses and infections. Naevi are discussed above. Other

common abnormalities include meatal pit, sacral pit, hypospadias, median raphe cysts, canals and sinuses, and ambiguous genitalia [1–3].

Rarer anomalies include hypospadias variants, epispadias, penile hypoplasia, mucoid or urethral cysts, dermoid cyst, juvenile xanthogranuloma, buried penis, urethral atresia, penoscrotal transposition, congenital lymphoedema, lymphangiectasia, lymphangioma, giant preputial sac, megaprepuce, accessory scrotum, haemangiomas, strawberry naevus, white sponge naevus, os penis, true aposthia and faun tail [2,4–6].

This is not the place exhaustively to catalogue all of the syndromes that may be associated with one or other of the above common or rarer anomalies; however, examples include anogenital haemangiomas in the PELVIS syndrome [7], anogenital lymphoedema in Hennekam syndrome [8], the micropenis of the MORM and Kabuki make-up syndromes [9,10], the cribriform scrotal atrophy associated with an unusual form of ectodermal dysplasia [11], and genital leukoplakia associated with dyskeratosis congenita [12].

References

1 Baskin LS, Ebbers MB. Hypospadias: anatomy, etiology and technique. *J Pediatr Surg* 2006; **41**: 463–72.
2 Bunker CB. *Male Genital Skin Disease*. London: Saunders, 2004.
3 Park CO, Chun EY, Lee JH. Median raphe cyst on the scrotum and perineum. *J Am Acad Dermatol* 2005; **55**: S114–5.
4 Browne WG, Izatt MM, Renwick JH. White sponge naevus of the mucosa: clinical and linkage data. *Ann Hum Genet* 1969; **32**: 271–81.
5 Jorgenson RJ, Levin LS. White sponge nevus. *Arch Dermatol* 1981; **117**: 73–6.
6 Shah A, Meacock L, More B, Chandran H. Lymphangioma of the penis: a rare anomaly. *Pediatr Surg Int* 2005; **21**: 329–30.
7 Girard C, Bigorre M, Guillot B, Bessis D. Pelvis syndrome. *Arch Dermatol* 2006; **142**: 884–8.
8 Musumeci ML, Nasca MR, De Pasquale R *et al.* Cutaneous manifestations and massive genital involvement in Hennekam syndrome. *Pediatr Dermatol* 2006; **23**: 239–42.
9 Hampshire DJ, Ayub M, Springell K *et al.* MORM syndrome (mental retardation, truncal obesity, retinal dystrophy and micropenis), a new autosomal recessive disorder, links to 9q34. *Eur J Hum Genet* 2006; **14**: 543–8.
10 Vaccaro M, Salpietro DC, Briuglia S *et al.* Cutis laxa in Kabuki make-up syndrome. *J Am Acad Dermatol* 2005; **53**: S247–51.
11 Hill VA, Nischal KK, Collin JRO, Harper JI. An unusual ectodermal dysplasia with unique eye defects. *Br J Dermatol* 2005; **152**: 365–7.
12 Ding Y-G, Zhu T-S, Jiang W *et al.* Identification of a novel mutation and a *de novo* mutation in DKC1 in two Chinese pedigrees with dyskeratosis congenita. *J Invest Dermatol* 2004; **123**: 470–3.

Trauma and artefact

Penile haematoma and rupture

The genitals may be readily traumatized, including by sexual activity. The penis is very vascular but haematoma formation and 'fracture' (penile rupture) are quite rare [1,2]. Pain, swelling and deformity associated with the history of a cracking noise during strenuous or contorted intercourse characterize the diagnosis. Splitting of the tunica albuginea of the corpus cavernosum can result in urethral damage, haematoma and retention. The prognosis is generally good but Peyronie's disease can occur [3]. Injection of drugs for erectile dysfunction can be complicated by haematoma.

Sclerosing lymphangitis

Non-venereal sclerosing lymphangitis/penile venereal oedema/Mondor's phlebitis/localized penile (venereal) lymphoedema/penile lymphocoele presents with a serpiginous mass in the coronal sulcus. The lesion usually arises after prolonged or frequent sexual intercourse with a passive or unenthusiastic partner; subsequent sexual activity may result in tenderness and enlargement. The circumferential scar left by circumcision may be a predisposing factor. There may be spontaneous resolution, or surgical excision may be needed [4]. It is not known whether lymphangitis or phlebitis is the cause [5]. True phlebitis of penile and scrotal veins has been reported in three patients, of whom one had been injured by a golf ball, but the other cases were idiopathic [6]. Its occurrence after taking tadalafil for erectile dysfunction has been used to argue for an anatomical variation in the distal draining subcoronal venous emissary arcade [7]. Thrombophlebitis of superficial penile and scrotal veins is analogous to Mondor's phlebitis of the chest wall (see Chapter 70), but it may be associated with polyarteritis nodosa and thromboangiitis obliterans [8]. Penile thrombophlebitis has been misdiagnosed as Peyronie's disease, and has also been the initial manifestation of a paraneoplastic migratory thrombophlebitis resulting from pancreatic cancer [9]. Given the circumstances that usually create the problem patients should be screened for underlying sexually transmitted infection, despite the appellation [10].

Strangulation of the penis

The penis may be strangulated by ring devices [11,12], including vacuum erection equipment [13], condom rings [14], rubber bands, string, rings (washers), nuts, bushes and sprockets, which are placed deliberately on the penis by the patient for masturbation or to prolong erection [15,16]. In boys, strangulation can occur following experimental use of rubber bands, string or thread to control enuresis, or can result from encoiled hair after circumcision [17]. Penile strangulation—the tourniquet syndrome—causes pain, swelling, urethral fistula, pseudoainhum, gangrene and amputation.

Foreign body

Self-instrumentation of the external genitalia may have an autoerotic, psychiatric, therapeutic (relief of itch [18]), aiding voiding, cleaning) or accidental aetiology [19]. Complications include frequency, haematuria, abscess, retention, fistulae and calculi. The diagnosis is made by palpation and radiography. Endoscopic removal is usually possible for foreign bodies below the urogenital diaphragm.

Glass beads, spheres of plastic or small round smooth stones (even pearls) may be introduced under the skin of the penis for erotic reasons, causing clinical and radiographical confusion. In the Philippines, this practice is called 'bulleetus', in Sumatra 'persimbraon', in Korea 'chagan ball' and in Thailand 'mukhsa' or 'tancho' [20–22]. Extrusion of a testicular prosthesis has been reported as a cause of scrotal ulceration [23].

If oil, petroleum jelly or silicone is used then a paraffinoma, silicone granuloma or (sclerosing) lipogranuloma can result.

Table 71.16 Anogenital signs of child abuse. (After Bunker [21].)

Overall context
Emotional disturbance
Passivity on anogenital examination
Anal relaxation/dilatation
Purpura, bruising, tearing
Signs of sexually transmitted disease

Table 71.17 Anogenital mimics of child abuse. (After Bunker [21].)

Nappy rash
Innocent skin tags and fissures
Threadworms
Eczema
Phytophotodermatitis
Lichen sclerosus
Henoch–Schönlein purpura
Acute haemorrhagic oedema of childhood
Anogenital streptococcal dermatitis
Causes of diarrhoea
Haemolytic–uraemic syndrome
Crohn's disease
Causes of constipation
Hirschsprung's disease

Lipogranuloma

Patients may take it upon themselves to inject various substances with the aim of maintaining erection or enlarging the penis. The consequences may not be desirable. Infection is an obvious risk [24]. Mineral oil, petroleum jelly and silicone introduced into the genital skin can elicit lipogranuloma or paraffinoma. Most cases are self-induced, either to increase penile size or enhance sexual pleasure, but some may be accidental [25,26]. One patient injected his penis with an industrial high-pressure pneumatic grease-gun [27]. Idiopathic cases attributed to endogenous fat liberation have been reported, predominantly from Japan [28]. The psychological consequences may be debilitating [29].

Dermatitis artefacta and mutilation

Dermatitis artefacta of the genitalia does occur. Lesions are typically geometrical, angulated and rectilinear. Sometimes they are induced by needles, knives or cigarette burns, and extraneous foreign material may be introduced into the skin (lipogranuloma and silicone granuloma are discussed above).

Psychotic patients may mutilate their genitalia, as may transvestites [30], but non-psychotic genital self-mutilation can also occur. Australian aborigines create a slit in the penis by opening the urethra ventrally, thereby creating hypospadias; this is called subincision [31,32]. Biopsy and other investigations may be necessary to exclude penile cancer. It is important also to consider pyoderma gangrenosum, which is rare but frequently omitted from the differential diagnosis of penile ulceration by non-dermatologists.

Child abuse

Physical and sexual child abuse should be considered in the differential diagnosis of cutaneous disease of the anogenital area in children (Table 71.16), but signs should be interpreted with caution and re-examination should be avoided [33–37]. Child abuse may be erroneously suspected (Table 71.17) when the anogenital area is involved by a dermatosis or a diarrhoeal illness [38].

The significance of anogenital warts in suggesting possible child sexual abuse is controversial. However, early recognition as a marker for child sexual abuse is in the child's long-term best interest [39].

Miscellaneous traumatic and arterial conditions

Sometimes the penis is bitten by another individual or an animal [40]. Purpura and ecchymoses may develop after oral sex ('love bites') or the use of vacuum erection devices [13]. Post-traumatic neuromas may be encountered and be mistaken for genital warts or pearly penile papules [41]. Degloving injuries can occur in accidents with industrial or agricultural equipment [42]. Electrical burns are rare [43]. Sex aids can result in abrasions, eczema and ulceration. Self-circumcision might be attempted, with adverse consequences [44]. Anogenital tattoos are commonplace [45].

Localized gangrene of the scrotum and penis resulting from arterial embolization with particulate matter complicating accidental femoral self-injection of heroin in an addict has been reported [46]. Scrotal gangrene from a snake bite has been described [47].

References

1 Nouri M, Koutani A, Tazi K *et al.* Fractures of the penis: apropos of 56 cases. *Prog Urol* 1998; **8**: 542–7.
2 Wessells H, Long L. Penile and genital injuries. *Urol Clin North Am* 2006; **33**: 117–26, vii.
3 Goh SH, Trapnell IE. Fracture of the penis. *Br J Surg* 1980; **67**: 680–1.
4 Kraus S, Lüdecke G, Weidner W. Mondor's disease of the penis. *Urol Int* 2000; **64**: 99–100.
5 Tanii T, Hamada T, Asai Y, Yorifuji T. Mondor's phlebitis of the penis: a study with factor VIII related antigen. *Acta Derm Venereol* 1984; **64**: 337–40.
6 Harrow BR, Sloane IA. Thrombophlebitis of superficial penile and scrotal veins. *J Urol* 1963; **89**: 841–2.
7 Guarneri C, Guarneri F. Mondor's phlebitis after using tadalafil. *Br J Dermatol* 2007; **157**: 209–10.
8 Coldiron B, Jacobson C. Common penile lesions. *Urol Clin North Am* 1988; **15**: 671–85.
9 Horn AS, Pecora A, Chiesa JC, Alloy A. Penile thrombophlebitis as a presenting manifestation of pancreatic carcinoma. *Am J Gastroenterol* 1985; **80**: 463–5.
10 Rosen T, Hwong H. Sclerosing lymphangitis of the penis. *J Am Acad Dermatol* 2003; **49**: 916–8.
11 Wasadikar PP. Incarceration of the penis by a metallic ring. *Postgrad Med J* 1997; **73**: 255.
12 Sowery RD, Beiko DT, Heaton JP. Long-term penile incarceration by a metal ring resulting in urethral erosion and chronic lymphedema. *Can J Urol* 2004; **11**: 2167–8.
13 Ganem JP, Lucey DT, Janosko EO, Carson CC. Unusual complications of the vacuum erection device. *Urology* 1998; **51**: 627–31.
14 Tash JA, Eid JF. Urethrocutaneous fistula due to a retained ring of condom. *Urology* 2000; **56**: 508.
15 Snoy FJ, Wagner SA, Woodside JR *et al.* Management of penile incarceration. *Urology* 1984; **24**: 18–20.
16 Bhat AL, Kumar A, Mathur SC, Gangwal KC. Penile strangulation. *Br J Urol* 1991; **68**: 618–21.
17 Pohlman RB. Photo quiz: a lesion that should raise suspicion. *Am Fam Physician* 2000; **62**: 2095–6.

18 Al-Durazi M, Saleem I, Mohammed AA. Urethral foreign body. *Br J Urol* 1992; **69**: 434.
19 Aliabadi H, Cass AS, Gleich P, Johnson CF. Self-inflicted foreign bodies involving the lower urinary tract and male genitals. *Urology* 1985; **26**: 12–6.
20 George WM. Papular pearly penile pearls. *J Am Acad Dermatol* 1989; **20**: 852.
21 Bunker CB. *Male Genital Skin Disease*. London: Saunders, 2004.
22 Wilcher G. Artificial penile nodules—a forensic pathosociology perspective: four case reports. *Med Sci Law* 2006; **46**: 349–56.
23 Gordon JA, Schwartz BB. Delayed extrusion of testicular prosthesis. *Urology* 1979; **14**: 59–60.
24 Al-Mutairi N, Sharma AK, Zaki A *et al.* Penile self-injections: an unusual act. *Int J Dermatol* 2004; **43**: 680–2.
25 Coldiron B, Jacobson C. Common penile lesions. *Urol Clin North Am* 1988; **15**: 671–85.
26 Santucci RA, Zehring RD, McClure D. Petroleum jelly lipogranuloma of the penis treated with excision and native skin coverage. *Urology* 2000; **56**: 331.
27 Kalsi JS, Arya M, Peters J *et al.* Grease-gun injury to the penis. *J R Soc Med* 2002; **95**: 254.
28 Matsuda T, Shichiri Y, Hida S *et al.* Eosinophilic sclerosing lipogranuloma of the male genitalia not caused by exogenous lipids. *J Urol* 1988; **140**: 1021.
29 Moon DG, Yoo JW, Bae JH *et al.* Sexual function and psychological characteristics of penile paraffinoma. *Asian J Androl* 2003; **5**: 191–4.
30 Greilsheimer H, Groves JE. Male genital self-mutilation. *Arch Gen Psychiatry* 1979; **36**: 441–6.
31 Jones IH. Subincision among Australian western desert Aborigines. *Br J Med Psychol* 1969; **42**: 183–90.
32 Pounder DJ. Ritual mutilation: subincision of the penis among Australian aborigines. *Am J Forensic Med Pathol* 1983; **4**: 227–9.
33 McCann J, Voris J. Perianal injuries resulting from sexual abuse: a longitudinal study. *Pediatrics* 1993; **91**: 390–3.
34 Clayden G. Anal appearances and child sex abuse. *Lancet* 1987; **1**: 620–1.
35 Priestley BL, Bamford FN, Miles VM *et al. Physical Signs of Sexual Abuse in Children*, 2nd edn. Report of a working party of the Royal College of Physicians. London: Royal College of Physicians, 1997.
36 Hobbs CJ, Wynne JM. Physical signs of sexual abuse in children. *J R Coll Phys Lond* 1997; **31**: 580–1.
37 Wynne JM, Hobbs CJ. Examination of children who may have been sexually abused. *Arch Dis Child* 2000; **82**: 268.
38 Vickers D, Morris K, Coulthard MG, Eastham EJ. Anal signs in haemolytic uraemic syndrome. *Lancet* 1998; **1**: 998.
39 Hobbs CJ, Wynne JM. How to manage warts. *Arch Dis Child* 1999; **81**: 460.
40 Gomes CM, Ribeiro-Filho L, Giron AM *et al.* Genital trauma due to animal bites. *J Urol* 2001; **165**: 80–3.
41 Cesinaro AM, Sighinolfi P, Monari P, Neri F. Penile condylomata? Traumatic neuromas! *J Am Acad Dermatol* 2006; **54**: S54–S55.
42 Hrbaty J, Molitor M. Traumatic skin loss from the male genitalia. *Acta Chir Plast* 2001; **43**: 17–20.
43 Xu X, Zhu W, Wu Y. Experience of the treatment of severe electric burns on special parts of the body. *Ann N Y Acad Sci* 1999; **888**: 121–30.
44 Sagar J, Sagar B, Shah DK. Penile skin necrosis—complication following selfcircumcision. *Ann R Coll Surg Engl* 2005; **87**: W5–7.
45 Goldstein N. Psychological implications of tattoos. *J Dermatol Surg Oncol* 1979; **5**: 883.
46 Somers WJ, Lowe FC. Localized gangrene of the scrotum and penis: a complication of heroin injection into the femoral vessels. *J Urol* 1986; **136**: 111–3.
47 Babata AL, Faniyi AO. A case report of scrotal gangrene from snake bite. *West Afr J Med* 2006; **25**: 159–60.

Inflammatory dermatoses

Urticaria and dermographism

These are usually generalized eruptions (see Chapter 22) but it has been proposed that they may account for some of the symptomatology in some patients with unexplained genital itching (and pruritus ani—see below). Stroking the inside of the thigh might induce a weal; indeed, stroking can cause itching without any discernible redness or wealing [1,2]. Contact urticaria is discussed below. Lisinopril has been reported to cause genital angio-oedema [3].

Eczematous dermatoses

Itching and lichenification, particularly around the scrotum, are common presenting problems. Contributory factors include preexisting dermatoses such as xerosis, atopy and psoriasis, sedentary occupations, motor car and aeroplane travel, and tight underclothing and trousers.

Irritation is a key adverse exogenous influence to which anogenital sites are vulnerable, and sweat, sebum, desquamated corneocytes, dirt, excreta, sexual secretions, clothing, detergents, toiletries, cosmetics, contraceptives and some therapeutic topical treatments are all potential irritants.

Frequently underrated are the effects of overwashing and the excessive use of soap and toiletries, especially in the presence of skin symptoms or urinary or bowel problems, and particularly if patients feel that they might have been exposed to a sexually transmitted disease.

Lichen simplex

Lichen simplex is common around the male genitalia. It is not usually a flexural condition but can be seen on the penile shaft and scrotum (Fig. 71.6). Giant forms (of Pautrier) occur, giving a pineapple appearance [4]. The skin may be broken by excoriations and become secondarily impetiginized or colonized by *Candida*.

Treatment follows the lines of management (above and below) relating to irritants, with emphasis on the relief of scratching, soap substitution and moisturization, and occlusion of the area if possible with a bland dressing—wet if the skin is fiercely eczematized. A potent topical corticosteroid ointment can be used for a few days and then tailed off. Preparations containing tar or combinations of antibacterial, anticandidal and antifungal agents are also useful. Two cases of extensive giant lichen simplex of the scrotum have been successfully treated by hemiscrotectomy [4].



Fig. 71.6 Scrotal lichen simplex. (Courtesy of Dr F.A. Ive, Durham, UK.)

Table 71.18 Anogenital irritants. (After Bunker [5]. © 2004, with permission from Elsevier.)

Sweat
Sebum
Desquamated corneocytes
Dirt
Excreta
Sexual secretions
Clothing
Soap and detergents
Toiletries
Toilet paper
Cosmetics
Contraceptives
Therapeutic
Friction
Maceration

Table 71.19 Allergens of particular relevance to anogenital contact dermatitis. (After Bunker [5]. © 2004, with permission from Elsevier.)

Euxyl K 400 (methyldibromoglutaronitrile)
Kathon CG (isothiazolinones)
Lidocaine (lignocaine) and other topical anaesthetics
Neomycin
Nystatin
Steroid moieties
Thiuramdisulphide—rubber
Latex condoms
Spermicides
Mitomycin C

Irritant contact dermatitis

Anogenital irritants are discussed above and listed in Table 71.18. Friction [6], maceration, overwashing, and concomitant anorectal or urological disease are the chief influences. There may be an association with atopy; Birley [7] diagnosed irritant dermatitis in 72% of patients presenting to a genitourinary clinic with 'balanitis' (probably meaning balanoposthitis) of whom a possible 67% had a history of atopy, but none of these patients was patch tested. An irritant scrotal dermatitis in cellists has been described [8]. Topical 5-fluorouracil used to treat keratoses at extragenital sites has caused genital irritant dermatitis [9]. Acute or chronic, sterile or superinfected (with staphylococci or *Candida*, or both), eroded or hyperkeratotic presentations are seen, depending on the scenario. A good example is nappy (diaper) rash (see Chapter 17).

Management follows lines similar to those for pruritus ani (see p. 71.86). Irritants should be identified and eliminated or reduced. Advice is given about soap substitutes, moisturizers, towels and toilet paper. Topical corticosteroid ointments, with or without antibiotic and anticandidal agents, are employed to control the dermatitis. Oral antihistamines are useful. Topical local anaesthetics should be avoided because of the risk of sensitization. Occasionally, secondary infection may be severe; a swab should be taken and oral antibiotics and oral antifungals prescribed.

A more acute picture (itch, burning or pain, swelling, erythema, vesiculation) may occur if highly irritant chemicals in high concentration are accidentally or deliberately used on the genitalia. Patients with a genital rash who are frightened that it may have been sexually acquired will sometimes self-treat with unsuitable preparations and in the process increase their morbidity and conceal an underlying sexually transmitted disease or a dermatosis. Treatment is with potassium permanganate soaks, very potent topical corticosteroid creams (sometimes systemic corticosteroids) and systemic antibiotics.

Allergic contact dermatitis

The risks of allergic contact dermatitis of the genital skin come about from: (i) direct contact with the allergen (e.g. medicaments—even coal tar allergy has been reported [10]), contraceptive usage and prosthetic limbs in amputees [11]; or, very rarely, (ii) transfer of allergen (e.g. urushiol as in poison oak, poison ivy and poison sumac dermatitis) to the genitalia [12] and possibly subsequent exposure to sunlight (e.g. psoralens from fig or citrus plants, as in phytodermatitis); and (iii) involvement in a more generalized eczematous response (e.g. to a medicament or dressing used on venous eczema or ulceration, as in the autosensitization/secondary spread/secondary generalization syndrome).

Eczematous symptomatology can appear approximately 1 week after first contact with the allergen if previously unsensitized, or within a few hours if already allergic. The patient may present with pruritus ani [13] or paraphimosis [14]. More immediate symptomatology and acute erythema and angio-oedema suggest a contact urticaria, which can occur with some of the rubber constituents of condoms and gloves [15–17].

The principles of management are the identification of the potential allergen (Table 71.19) and its likely source, and then its elimination. There may be clues to these factors at presentation but subsequent patch testing is often required. Following patch testing, Bauer *et al.* [18] made a final diagnosis of allergic contact dermatitis in 35% of patients with anogenital skin problems. Allergic contact dermatitis can persist even after withdrawal of the trigger allergen. Management is otherwise as for irritant contact dermatitis, lichen simplex and pruritus ani (see above and p. 71.86).

The most common relevant sensitivities are to rubber, contraceptives, preservatives and fragrances in toiletries and medicaments, and the active agents (antibiotics, steroids, anaesthetics) in medicaments.

Genital rubber dermatitis is not confined to young sexually active male condom users and their partners [19–22]. Incontinent men who use external urinary collection devices (Paul's tubing) are also at risk. Latex allergy may be a problem in patients with spinal cord injury using rubber products for the management of urinary difficulties; life-threatening anaphylactic reactions have occurred [21]. Condoms made from lamb caecum are available for rubber-allergic patients, but they may provide less protection against sexually transmitted disease than latex. Creating hypoallergenic condoms by washing in an ammonium solution to remove the residues of the accelerator chemicals that actually cause the hypersensitivity has proved unsuccessful [23]. Patients may become sensitized to the spermicide [19].

Celandine juice [14] and clothing dye dermatitis of the scrotum [24] have been reported.

Atopic dermatitis

Genital skin disease caused by atopic dermatis (AD) is not uncommon but rarely occurs in isolation, unlike other common chronic dermatoses such as seborrhoeic dermatitis and psoriasis. It is not known how genital AD is related to circumcision, sexual activity and sexually transmitted disease. Evidence of atopy was found in a possible 67% of a total of 72% of patients diagnosed as having irritant dermatitis from a consecutive series of men presenting to a genitourinary clinic with 'balanitis'—probably balanoposthitis [6]. AD in HIV/AIDS is discussed in Chapter 35.

Radiodermatitis

Radiodermatitis (see Chapter 79) is not usually a diagnostic challenge or a therapeutic problem in the acute stage after radiotherapy to the anogenital skin for skin disease or internal cancer. In the chronic state, there may be pruritus together with the typical poikiloderma. Radiotherapy has been used for the treatment of numerous anogenital dermatoses over the years, including Bowen's disease, erythroplasia of Queyrat, squamous carcinoma, psoriasis, Peyronie's disease and pruritus ani [25]. Radiotherapy confers a long-term increased risk of skin cancer, especially basal cell carcinoma. There is concern that radiotherapy for Bowen's disease or erythroplasia of Queyrat may increase the subsequent risk of invasive carcinoma.

Seborrhoeic dermatitis

Genital involvement is frequent with this common dermatosis. The groins and penis may be the only sites involved. A good history (including family history) and careful examination of other sites typically affected aid the diagnosis. On the scalp, the face, in the flexures and at anogenital sites seborrhoeic dermatitis and psoriasis may be indistinguishable. Seborrhoeic dermatitis in HIV/AIDS is discussed in Chapter 35.

Diagnosis is established on clinical grounds, including response to therapy, and it is not usually necessary to perform a biopsy.

No treatment may be required other than reassurance that it is not sexually transmitted or related to poor hygiene. However, treatments that diminish the *Malassezia* load and reduce irritation and eczematization can be successfully and safely used long term. These include topical antifungals (such as clioquinol, nystatin and imidazoles) as ointments, creams, lotions or shampoos, and mixtures of the same agents with mild and moderately potent topical corticosteroids used alongside emollients and soap substitutes. In severe cases, patients with concomitant seborrhoeic folliculitis, or in patients with HIV/AIDS, treatment with an oral imidazole and/or an oral tetracycline may be suitable.

Psoriasis

Approximately 2% of the population are said to have psoriasis but it is possible that many more than 2% of men may have or have had anogenital psoriasis at some time; it is certainly a common anogenital diagnosis in isolation.

Psoriasis and its clinical manifestations are discussed in Chapter 20; the relationship of psoriasis to HIV/AIDS is discussed in Chapter 35. Anogenital presentations of psoriasis may be vague in symptomatology and non-specific on examination. It is not usually itchy; significant itch should arouse suspicions of another dermatosis such as an eczematous dermatitis or tinea. Soreness occurs with superinfection, especially with *Candida*. Other typically affected sites should be examined for signs of the disease. Genital appearances may be challenging to interpret, especially in the uncircumcised patient, because a mucosal site is affected rather than keratinized skin. The diagnosis is usually easier in the circumcised male where the morphology is similar to extragenital lesions.

Inverse pattern psoriasis refers to the manifestation of the disease on intertriginous skin in the axillae, natal cleft, gluteal folds, groins and in the preputial sac and on the glans of the uncircumcised male, where its occurrence is probably brought about by the Koebner phenomenon.

Usually, the diagnosis of psoriasis is clinical, but a biopsy may be necessary (e.g. of a solitary mucosal lesion in an uncircumcised individual) to distinguish psoriasis from Zoon's balanitis, lichen planus, erythroplasia of Queyrat or Kaposi's sarcoma. Bowen's disease and extramammary Paget's disease may be misdiagnosed as psoriasis when there are single or several foci on the penile shaft and/or in the groins.

Topical treatment includes emollients, soap substitutes, corticosteroids combined with antibiotic and antifungal agents or weak tar solutions. Strong crude tar preparations should be avoided at this site given that anogenital skin has a propensity to increased absorption of topical agents and because of the risk of genital cancer; one of the first occupational diseases described was scrotal carcinoma in chimney sweeps. Dithranol is usually avoided in this region. The vitamin D analogue calcipotriol can be helpful. Topical ciclosporin (100 mg/mL in wet dressings three times daily) has been advocated [26]. Topical calcineurin inhibitors show promise [27,28]. Phototherapy is contraindicated because of the risk of anogenital cancer. Severe anogenital psoriasis can be an indication for systemic treatment.

Reiter's disease or syndrome (part of the same continuum as psoriasis in genetically predisposed individuals) is discussed in Chapter 20. Characteristic, sometimes severe, involvement of the penis (circinate balanitis) occurs. The penile lesions have the same histopathology as psoriasis [29]. Circinate balanitis responds to topical calcineurin inhibitors.

References

1 Sherertz EF. Symptomatic dermographism as a cause of genital pruritus. *J Am Acad Dermatol* 1994; **31**: 1040–1.

2 Bernhard JD. Dermographic pruritus: invisible dermographism. *J Am Acad Dermatol* 1995; **33**: 322.

3 Henson EB, Bess DT, Abraham L, Bracikowski JP. Penile angioedema possibly related to lisinopril. *Am J Health Syst Pharm* 1999; **56**: 1773–4.

4 Porter WM, Bewley A, Dinneen M *et al.* Nodular lichen simplex of the scrotum treated by surgical excision. *Br J Dermatol* 2001; **144**: 915–6.

5 Bunker CB. *Male Genital Skin Disease*. London: Saunders, 2004.

6 Ramam M, Khaitan BK, Singh MK, Gupta SD. Frictional sweat dermatitis. *Contact Dermatitis* 1998; **38**: 49.

7 Birley HDL, Walker MM, Luzzi GA *et al.* Clinical features and management of recurrent balanitis; association with atopy and genital washing. *Genitourin Med* 1993; **69**: 400–3.

8 Shapiro PE. 'Cello scrotum' questioned. *J Am Acad Dermatol* 1991; **24**: 665.

9 Shelley WB, Shelley ED. Scrotal dermatitis caused by 5-fluorouracil (Efudex). *J Am Acad Dermatol* 1988; **19**: 929–31.
10 Cusano F, Capozzi M. Photocontact dermatitis from ketoprofen with cross-reactivity to ibuproxam. *Contact Dermatitis* 1992; **27**: 50–9.
11 Lyon CC, Kulkarni J, Zimerson E *et al.* Skin disorders in amputees. *J Am Acad Dermatol* 2000; **42**: 501–7.
12 Gamulka BD. Index of suspicion. Case No 1. Diagnosis: allergic contact dermatitis. *Pediatr Rev* 2000; **21**: 421–6.
13 Harrington CI, Lewis FM, McDonagh AJ, Gawkrodger DJ. Dermatological causes of pruritus ani. *BMJ* 1992; **305**: 955.
14 Fariña LA, Alonso MV, Horjales M, Zungri ER. Contact-derived allergic balanoposthitis and paraphimosis through topical application of celandine juice. *Actas Urol Esp* 1999; **23**: 554–5.
15 Turjanmaa K, Alenius H, Makinen-Kiljunen S *et al.* Natural rubber latex allergy. *Allergy* 1996; **51**: 593–602.
16 Wakelin SH, White IR. Natural rubber latex allergy. *Clin Exp Dermatol* 1999; **24**: 245–8.
17 Wakelin SH. Contact urticaria. *Clin Exp Dermatol* 2001; **26**: 132–6.
18 Bauer A, Geier J, Elsner P. Allergic contact dermatitis in patients with anogenital complaints. *J Reprod Med* 2000; **45**: 649–54.
19 Hindson TC. Studies in contact dermatitis. *Trans St John's Hosp Dermatol Soc* 1966; **52**: 1–9.
20 Bircher AJ, Hirsbrunner P, Langauer S. Allergic contact dermatitis of the genitals from rubber additives in condoms. *Contact Dermatitis* 1993; **28**: 125–6.
21 Shenot P, Rivas DA, Kalman DD, Staas WE. Latex allergy manifested in urological surgery and care of adult spinal cord injured patients. *Arch Phys Med Rehabil* 1994; **75**: 1263–5.
22 Harmon CB, Connolly SM, Larson TR. Condom-related allergic contact dermatitis. *J Urol* 1995; **153**: 1227–8.
23 Rademaker M, Forsyth A. Allergic reactions to rubber condoms. *Genitourin Med* 1989; **65**: 194–5.
24 Lucke TW, Fleming CJ, McHenry P. Clothing dye dermatitis of the scrotum. *Contact Dermatitis* 1998; **38**: 224.
25 Wiskemann A. X-ray irradiation of dermatoses in the genital area. *Hautarzt* 1977; **28**: 219–23.
26 Jemec GBE, Baadsgaard O. Effect of cyclosporin on genital psoriasis and lichen planus. *J Am Acad Dermatol* 1993; **29**: 1048–9.
27 Lebwohl M, Freeman AK, Chapman MS *et al.* Tacrolimus ointment is effective for facial and intertriginous psoriasis. *J Am Acad Dermatol* 2004; **51**: 723–30.
28 Gribetz C, Ling M, Lebwohl M *et al.* Pimecrolimus cream 1% in the treatment of intertriginous psoriasis: a double-blind, randomized study. *J Am Acad Dermatol* 2004; **51**: 731–8.
29 Kanerva L, Kousa M, Niemi KM *et al.* Ultrahistology of balanitis circinata. *Br J Vener Dis* 1982; **58**: 188–95.

Zoon's balanitis

Aetiology. Zoon's plasma cell balanitis (ZB) is a disorder of the middle-aged and older uncircumcised male [1,2], although an analogous condition has been reported to afflict the vulva (see p. 71.61), mouth, lips [3] and epiglottis [3,4]. Since Zoon's original reports there have been many accounts in the literature, but the aetiology remains uncertain.

The evidence suggests that ZB is a chronic, reactive, principally irritant dermatosis brought about by a dysfunctional prepuce. Retention of urine and squames between two tightly apposed and infrequently and inadequately separated and/or inappropriately bathed, commensally hypercolonized, desquamative, secretory epithelial surfaces leads to a disturbed 'preputial ecology' and excessive frictional trauma (ZB is often located on the dorsal aspect of the glans and/or the adjacent prepuce, sites of maximal friction on foreskin retraction), and irritation by urine [5–8]. There is no evidence of an infectious cause, and immunohistochemical findings suggest that ZB represents a non-specific polyclonal tissue reaction [9,10], consistent with an irritant dermatosis.



Fig. 71.7 Zoon's balanitis. Symmetrical moist erythema of glans and prepuce. (Courtesy of Professor C.B. Bunker, with permission from Medical Illustration UK, Chelsea & Westminster Hospital, London, UK.)

Clinical features. The presentation is classically indolent and asymptomatic, although staining of the underclothes with blood has been reported [11]. Well-demarcated, glistening, moist, bright red or autumn brown patches involve the glans and visceral prepuce, with sparing of the keratinized penile shaft and foreskin (Fig. 71.7). The navicular fossa may be involved. Other signs include dark red stippling—'cayenne pepper spots'—and purpura with haemosiderin deposition, solitary or multiple lesions of differing sizes (guttate or nummular), characteristically symmetrical about the axis of the coronal sulcus and 'kissing'. Although vegetative and nodular presentations have been recorded, atypical or unusual morphology should be viewed with great suspicion and biopsied [7,8].

Histopathology. The classic histology is of epidermal attenuation with absent granular and horny layers, and diamond- or lozenge-shaped basal cell keratinocytes with sparse dyskeratosis and spongiosis. There is a band of dermal infiltration with plasma cells of variable density. Extravasated erythrocytes, haemosiderin and vascular proliferation are also seen. Although Zoon stressed the presence of the plasma cell infiltrate in this condition, the plasma cell numbers can be very variable [7,8,12].

Differential diagnosis. The differential diagnosis includes erosive lichen planus, psoriasis, seborrhoeic dermatitis, contact dermati-

tis, fixed drug eruption, secondary syphilis, histoplasmosis [13], erythroplasia of Queyrat [14] and Kaposi's sarcoma. A confident clinical diagnosis is not always possible or safe [6,8,15], so a biopsy is advisable, and the pathologist should be asked to look for concomitant disease. Frank cases of lichen sclerosus, lichen planus, Bowenoid papulosis and penile cancer often appear to have ZB-like changes on clinical examination and on histology [8,15]. In other words, the signs of ZB may be secondary to underlying preputial disease [8]. It is likely that some of the clinical and histological variants that have been reported [16–18], and a recent claim that ZB *per se* is a premalignant condition in a single case report [19], are a consequence of this phenomenon. ZB indicates a dysfunctional foreskin and a more sinister dermatosis may be concealed [8].

Treatment. Although ZB can improve with altered washing habits and the intermittent application of a mild or potent topical corticosteroid (with or without an antibiotic and anticandidal agent), it usually persists or relapses [7,8]. Case reports concerning the use of topical calcineurin inhibitors have appeared [20,21] but these agents should be used with circumspection in the setting of a dysfunctional foreskin and the attendant risk of penis cancer, long term. It has been claimed that Erbium : YAG or carbon dioxide laser treatment is effective [8,22–25]. Circumcision is curative [7,8]. Again, the pathologist should be asked to examine the whole specimen for signs of another underlying dermatosis.

References

1 Zoon JJ. Verenigingsverslagen. *Ned Tijdschr Geneeskd* 1950; **94**: 1528–30.
2 Zoon JJ. Balanoposthite chronique circonscrite benigne a plasmocytes. *Dermatologica* 1952; **105**: 1–7.
3 Baughman RD, Berger P, Pringle WM. Plasma cell cheilitis. *Arch Dermatol* 1974; **110**: 725–6.
4 White JW Jr, Olsen KD, Banks PM. Plasma cell orificial mucositis. *Arch Dermatol* 1986; **122**: 1321–4.
5 Yoganathan S, Bohl TG, Mason G. Plasma cell balanitis and vulvitis (of Zoon). *J Reprod Med* 1994; **39**: 939–44.
6 Altmeyer P, Kastner U, Luther H. Balanitis/balanoposthitis chronica circumscripta benigna plasmacellularis: entity or fiction? *Hautarzt* 1998; **49**: 552–5.
7 Bunker CB. Topics in penile dermatology. *Clin Exp Dermatol* 2001; **26**: 469–79.
8 Bunker CB. *Male Genital Skin Disease*. London: Saunders, 2004.
9 Nishimura M, Matsuda T, Muto M, Hori Y. Balanitis of Zoon. *Int J Dermatol* 1990; **29**: 421–3.
10 Farrell AM, Francis N, Bunker CB. Zoon's balanitis: an immunohistochemical study. *Br J Dermatol* 1996; **135** (Suppl. 47): 57.
11 Jolly BB, Krishnamurty S, Vaidyanathan S. Zoon's balanitis. *Urol Int* 1993; **50**: 182–4.
12 Souteyrand P, Wong E, MacDonald DM. Zoon's balanitis (balanitis circumscripta plasmacellularis). *Br J Dermatol* 1981; **105**: 195–9.
13 Shelley WB, Shelley ED. *Advanced Dermatologic Diagnosis*. Philadelphia: Saunders, 1992: 609.
14 Davis-Daneshfar A, Trueb RM. Bowen's disease of the glans penis (erythroplasia of Queyrat) in plasma cell balanitis. *Cutis* 2000; **65**: 395–8.
15 Weyers W, Ende Y, Schalla W, Diaz-Cascajo C. Balanitis of Zoon: a clinicopathologic study of 45 cases. *Am J Dermatopathol* 2002; **24**: 459–67.
16 Bureau Y, Barriere H, Evin Y-P. Les erythroplasies benignes a plasmocytes. *Ann Dermatol Syphiligr* 1962; **89**: 271–84.
17 Jonquières EDL. Balanitis pseudoeritroplasicas. *Arch Argentinos Dermatol* 1971; **21**: 85–95.
18 Dupré A, Schnitzler L. Plasmocytic proliferative lesions of the foreskin: a variety of Zoon's benign circumscribed balanitis. *Ann Dermatol Vénéréol* 1977; **104**: 127–31 [in French].
19 Joshi UY. Carcinoma of the penis preceded by Zoon's balanitis. *Int J STD AIDS* 1999; **10**: 823–5.
20 Moreno-Arias GA, Camps-Fresneda A, Llaberia C, Palou-Almerich J. Plasma cell balanitis treated with tacrolimus 0.1%. *Br J Dermatol* 2005; **153**: 1204–6.
21 Hernandez-Machin B, Borrego Hernando L, Báes Marrero O, Hernansez B. Plasma cell balanitis of Zoon treated successfully with topical tacrolimus. *Clin Exp Dermatol* 2005; **30**: 578–602.
22 Albertini JG, Holck DE, Farley MF. Zoon's balanitis treated with Erbium : YAG laser ablation. *Lasers Surg Med* 2002; **30**: 123–6.
23 Baldwin HF, Geronemus RG. The treatment of Zoon's balanitis with the carbon dioxide laser. *J Dermatol Surg Oncol* 1989; **15**: 491–4.
24 Aynaud O, Casanova JM, Tranbaloc P. CO_2 laser for therapeutic circumcision in adults. *Eur Urol* 1995; **28**: 74–6.
25 Retamar RA, Kien MC, Chouela EN. Zoon's balanitis: presentation of 15 patients, five treated with a carbon dioxide laser. *Int J Dernatol* 2003; **42**: 305–7.

Lichen sclerosus

Aetiology. Lichen sclerosus is discussed in Chapter 51. The aetiopathogenesis is not known. Poorly understood features are the predilection for the genitalia generally and in males, specifically the uncircumcised [1], the association with organ-specific autoimmune disease and the propensity to progress to squamous carcinoma [2–6]. HPV (types 6, 16 and 18) has been reported to be present in 70% of cases of childhood penile lichen sclerosus [7,8], and in 17.4% of adult cases (types 16, 18, 45) compared with 8.7% of normal males [9] in one study, and in 33% of adult cases (types 16, 18, 33, 51) in another [10]. Topical steroid treatment of lichen sclerosus may lead to HPV reactivation [11]. But the epidemiology and clinical tenor of lichen sclerosus is not that of an infectious or sexually transmitted disease [5,12]. There is probably a bimodal pattern of prevalence [13–15]. Anatomical abnormality and trauma seem to be contributing factors [5,16]. Specifically, lichen sclerosus has been related to hypospadias and its repair [17,18]. The presence of the histopathological features of lichen sclerosus in a percentage of acrochordons (skin tags) has led to the suggestion that occlusion of flaccid skin is a pathogenic factor [19]. The evidence points to male genital lichen sclerosus being due to chronic exposure of susceptible epithelium to urine [20]. Some men 'dribble'.

Clinical features. Lichen sclerosus of the penis may be asymptomatic, but diverse, often vague, symptomatology is usually encountered. Patients may describe itching, burning, bleeding, tearing, splitting, haemorrhagic blisters, any manner of symptoms signifying sexual dysfunction or dyspareunia, discomfort with urination and narrowing of the urinary stream, and/or they may be concerned about the changing anatomy of their genitalia [21]. Other presentations are non-retractile foreskin (phimosis) (Fig. 71.8), foreskin fixed in retraction (paraphimosis) and urinary retention, even renal failure.

Genital, like extragenital, lichen sclerosus can manifest as atrophic leukodermic patches or plaques, or lilac, slightly scaly patches with telangiectasia and sparse purpura (Fig. 71.9). Predominant purpura, bullae, erosions and ulceration may be encountered [5,22,23]. The signs may be subtle, with meatal 'pin hole' narrowing, slight tightening of the retracted prepuce because of sclerotic plaques and bands, with or without difficulty in retraction—incomplete paraphimosis or 'waisting' due to a constrictive posthitis (Fig. 71.10) or they may be florid, with severe changes caused



Fig. 71.8 Lichen sclerosus causing phimosis. (Courtesy of Dr D.A. Burns, Leicester, UK.)



Fig. 71.10 Lichen sclerosus. Sclerotic band of the prepuce causing 'waisting'. (Courtesy of Professor C.B. Bunker, with permission from Medical Illustration UK, Chelsea & Westminster Hospital, London, UK.)



Fig. 71.9 Lichen sclerosus. White plaques and haemorrhagic areas on the glans. (Courtesy of Dr D.A. Burns, Leicester, UK.)

both by the lichen sclerosus and by associated and confusing Zoon's balanoposthitis-like changes: adhesions, loss of anatomical definition and dissolution or effacement of the normally sharply defined architectural features, especially of the frenulum and the coronal sulcus. The navicule meatal fossa may be abnormal. Post-inflammatory hyper- and hypopigmentation are occasionally seen.

Whereas posthitis xerotica obliterans refers to chronic damage to the prepuce by lichen sclerosus, balanitis xerotica obliterans (BXO) properly describes involvement of the glans penis (although the term has been used imprecisely). BXO can be a consequence of other scarring dermatoses such as lichen planus and cicatricial pemphigoid [24].

Genital lichen sclerosus is more common than extragenital or oral disease, but there may (rarely) be concomitant involvement of these sites. In adults, anogenital lichen sclerosus is said to be about 10 times more common in women than men. Perianal disease is very rare in the male. The involvement of the anterior urethra can be serious; 29% of patients undergoing urethroplasty for urethral stricture had pathological evidence of lichen sclerosus [25].

The first report of genital lichen sclerosus in boys appeared only in 1977 [13]. Lichen sclerosus may be much more frequent than is generally supposed in young boys, being diagnosed histologically in 14–95% of prepuces removed for phimosis [15,18]. The development of secondary phimosis in school-age boys is highly suggestive of lichen sclerosus [14]. In the older male, persistent primary

phimosis or the secondary development of phimosis in a previously retractable foreskin may be related to lichen sclerosus [5].

Most cases of genital lichen sclerosus can be diagnosed clinically. Lichen planus and the much rarer mucous membrane pemphigoid are in the differential diagnosis. A biopsy should be performed if there is clinical doubt or if the lesion is eroded or verrucous.

Histopathology. The histology is described in Chapter 51. The occasional association of endarteritis led originally to the usage of the term 'obliterans' [26]. In two cases in boys, a dermal lymphohistiocytic and granulomatous phlebitis has been found, and one also had evidence of HPV [27]. A 'garland-like' basal lamina has been found ultrastructurally [28]. Sometimes, lichen sclerosus may be difficult to differentiate from lichen planus, and criteria to assist, in the vulva, have been proposed by Fung and LeBoit [29]. The histological features may simulate mycosis fungoides [30].

Treatment. Guidelines for the management of lichen sclerosus have been published by the British Association of Dermatologists [31]. Contact with soap and urine should be avoided. A very potent topical corticosteroid (usually clobetasol propionate) used under supervision is effective [5,32–34] and usually problem free, but herpes simplex and wart reactivation have been reported [11,31]. The plasticity of the epithelium at this site seems to allow significant remodelling, with the relief of phimosis, improvement of incomplete phimosis or 'waisting'/constrictive posthitis, improvement in the histological changes and avoidance of circumcision [5,21,33]. Topical clobetasol propionate has been shown to relieve undifferentiated 'phimosis' in many boys and so obviate the need for circumcision [34]. Secondary candidal and bacterial infection should be treated. There are reports of the efficacy of long-term systemic antibiotic therapy (penicillin and azithromycin) in cases of lichen sclerosus thought to be associated with *Borrelia* infection [35,36]. Testosterone propionate ointment, oral stanozolol, freezing with ethyl chloride, liquid nitrogen cryotherapy, carbon dioxide laser and adrenocorticotrophic hormone (ACTH) have been used but are not recommended [5].

If medical treatment is not possible or fails, then surgery may be indicated. Circumcision, frenuloplasty, meatotomy and sophisticated plastic repair, depending upon the clinical presentation, can be offered. Carbon dioxide laser circumcision has been described [37]. In boys, complete circumcision is the treatment of choice because all affected tissue is removed and any secondary involvement of the glans probably regresses or resolves [14]; it is the unproven impression that this phenomenon also occurs in most adult patients. About 40% of patients will respond to medical treatment: the majority of the remainder will be cured by surgery, usually circumcision [38]. Persistent disease requires individualised follow-up and management. Residual burnt-out disease on the glans may improve with long-term topical retinoid treatment. Lichen sclerosus can recur in donor grafts from unrelated sites [22,39].

Squamous carcinoma of the penis is the most serious potential complication of lichen sclerosus [5]. Early microinvasive disease might be difficult to diagnose clinically against a background of lichen sclerosus [40]. A risk of 2–9.5% is suggested by the literature, depending on length of follow-up; the latent period may be one to three decades [5,6,41–44]. Verrucous carcinoma (Buschke–Löwenstein tumour) has been associated with previous lichen sclerosus [45]. Carcinoma complicating lichen sclerosus constituted one-third of all cases of penile cancer seen by Campus *et al.* [46] and, of 20 patients with penile squamous cell carcinoma (SCC) studied by Powell *et al.* [47], 11 had a clinical history and/or histological evidence of lichen sclerosus. Involvement of the glans penis confers a greater risk [44].

The effect of medical and surgical treatment on the subsequent incidence of penile cancer is not known [48,49]. Liatsikos *et al.* [50] report SCC of the glans developing in one of eight patients followed-up after circumcision for lichen sclerosus. Patients should be followed-up long term, especially if circumcision has not been performed or if symptoms persist or recur after any form of treatment.

References

1 Ledwig PA, Weigand DA. Late circumcision and lichen sclerosus et atrophicus of the penis. *J Am Acad Dermatol* 1989; **20**: 211–4.
2 Ridley CM. Lichen sclerosus et atrophicus. *BMJ* 1987; **295**: 1295–6.
3 Meffert JJ, Davis BM, Grimwood RE. Lichen sclerosus. *J Am Acad Dermatol* 1995; **32**: 393–416.
4 Pugliese JM, Morey AF, Peterson AC. Lichen sclerosus: review of the literature and current recommendations for management. *J Urol* 2007; **178**: 2268–76.
5 Bunker CB. *Male Genital Skin Disease*. London: Saunders, 2004.
6 Barbagli G, Palminteri E, Mirri F *et al.* Penile carcinoma in patients with genital lichen sclerosus: a multicenter survey. *J Urol* 2006; **175**: 1359–63.
7 Ansink AC, Krul MRL, de Weger RA *et al.* Human papillomavirus, lichen sclerosus, and squamous cell carcinoma of the vulva: detection and prognostic significance. *Gynecol Oncol* 1994; **52**: 180–4.
8 Drut RM, Gómez MA, Drut R, Lojo MM. Human papillomavirus is present in some cases of childhood penile lichen sclerosus: an *in situ* hybridization and SP-PCR study. *Pediatr Dermatol* 1998; **15**: 85–90.
9 Nasca MR, Innocenzi D, Micali G. Association of penile lichen sclerosus and oncogenic human papilloma virus infection. *Int J Dermatol* 2006; **45**: 681–3.
10 Prowse DM, Ktori EN, Chandrasekaran D *et al.* Human papillomavirus-associated increase in $p16^{INK4A}$ expression in penile lichen sclerosus and squamous cell carcinoma. *Br J Dermatol* 2008; **158**: 261–5.
11 Von Krogh G, Dahlman-Ghozlan K, Syrjänen S. Potential human papillomavirus reactivation following topical corticosteroid therapy of genital lichen sclerosus and erosive lichen planus. *J Eur Acad Dermatol Venereol* 2002; **16**: 130–3.
12 Farrell AM, Millard PR, Schomberg KH, Wojnarowska F. An infective aetiology for lichen sclerosus re-addressed. *Clin Exp Dermatol* 1999; **24**: 479–83.
13 Götz H, Zabel M, Patiri C. Lichen sclerosus at atrophicus: first observation on a boy's genitalia. *Hautarzt* 1977; **28**: 235–8.
14 Meuli M, Brinker J, Hanimann B, Sacher P. Lichen sclerosus et atrophicus causing phimosis in boys: a prospective study with 5-year follow-up after complete circumcision. *J Urol* 1994; **152**: 987–9.
15 Kyriakis KP, Emmanuelides S, Terzoudi S *et al.* Gender and age prevalence distributions of morphea en plaque and anogenital lichen sclerosus. *J Eur Acad Dermatol Venereol* 2007; **21**: 825–6.
16 English JC III, King DH, Foley JP. Penile shaft hypopigmentation: lichen sclerosus occurring after the initiation of alprostadil intracavernous injections for erectile dysfunction. *J Am Acad Dermatol* 1998; **39**: 801–3.
17 Uemura S, Hutson JM, Woodward AA *et al.* Balanitis xerotica obliterans with urethral stricture after hypospadias repair. *Pediatr Surg Int* 2000; **16**: 144–5.
18 Mattioli G, Repetto P, Carlini C *et al.* Lichen sclerosus et atrophicus in children with phimosis and hypospadias. *Pediatr Surg Int* 2002; **18**: 273–5.
19 Weigand DA. Microscopic features of lichen sclerosus et atrophicus in acrochordons: a clue to the cause of lichen sclerosus et atrophicus? *J Am Acad Dermatol* 1993; **28**: 751–4.
20 Bunker CB. Male genital lichen sclerosus and topical tacrolimus. *Br J Dermatol* 2007; **157**: 1079–80.

21 Riddell L, Edwards A, Sherrard J. Clinical features of lichen sclerosus in men attending a department of genitourinary medicine. *Sex Transm Infect* 2000; **76**: 311–3.
22 Wallace HJ. Lichen sclerosus et atrophicus. *Trans St John's Hosp Dermatol Soc* 1971; **57**: 9–30.
23 Lipscombe TK, Wayte J, Wojnarowska F *et al.* A study of clinical and aetiological factors and possible associations of lichen sclerosus in males. *Australas J Dermatol* 1997; **38**: 132–6.
24 Ridley CM, Neill SM. Circumcision. *BMJ* 1993; **306**: 583–4.
25 Barbagli G, Lazzeri M, Palminteri E, Turini D. Lichen sclerosis [sic] of male genitalia involving anterior urethra. *Lancet* 1999; **354**: 429.
26 Das S, Tunuguntla HSGR. Balanitis xerotica obliterans: a review. *World J Urol* 2000; **18**: 382–7.
27 Cabaleiro P, Drut RM, Drut R. Lymphohistiocytic and granulomatous phlebitis in penile lichen sclerosus. *Am J Dermatopathol* 2000; **22**: 316–20.
28 Dupré A, Viraben R. Basal lamina with a garland-like pattern in a case of sclero-atrophic lichen: ultrastructural study. *Ann Dermatol Vénéréol* 1988; **115**: 19–26 [in French].
29 Fung MA, LeBoit PE. Light microscopic criteria for the diagnosis of early vulvar lichen sclerosus: a comparison with lichen planus. *Am J Surg Pathol* 1998; **22**: 473–8.
30 Citarella L, Massone C, Kerl H, Cerroni L. Lichen sclerosus with histopathologic features simulating early mycosis fungoides. *Am J Dermatopathol* 2003; **25**: 463–5.
31 Neill SM, Tatnall FM, Cox NH. Guidelines for the management of lichen sclerosus. *Br J Dermatol* 2002; **147**: 640–9.
32 Tremaine RDL, Miller RAW. Lichen sclerosus et atrophicus. *Int J Dermatol* 1989; **28**: 10–6.
33 Dahlman-Ghozlan K, Hedblad M-A, von Krogh G. Penile lichen sclerosus et atrophicus treated with clobetasol dipropionate 0.05% cream: a retrospective clinical and histopathologic study. *J Am Acad Dermatol* 1999; **40**: 451–7.
34 Lindhagen T. Topical clobetasol propionate compared with placebo in the treatment of unretractable foreskin. *Eur J Surg* 1996; **162**: 969–72.
35 Schempp C, Bocklage H, Lange R *et al.* Further evidence for *Borrelia burgdorferi* infection in morphoea and lichen sclerosus et atrophicus confirmed by DNA amplification. *J Invest Dermatol* 1993; **100**: 717–20.
36 Shelley WB, Shelley ED, Grunenwald MA *et al.* Long-term antibiotic therapy for balanitis xerotica obliterans. *J Am Acad Dermatol* 1999; **40**: 69–72.
37 Kartamaa M, Reitamo S. Treatment of lichen sclerosus with carbon dioxide laser vaporization. *Br J Dermatol* 1997; **136**: 356–9.
38 Hunt SJ, Francis N, Dinneen M *et al.* A retrospective study of 174 men with lichen sclerosus of the penis. *Br J Dermatol* 2003; **149** (Suppl.): 53–4.
39 Lee SJ, Phillips SMA. Recurrent lichen sclerosus et atrophicus in urethroplasties from multiple skin grafts. *Br J Urol* 1994; **74**: 802–3.
40 Nasca MR, Panetta C, Micali G, Innocenzi D. Microinvasive squamous cell carcinoma arising on lichen sclerosus of the penis. *J Eur Acad Dermatol Venereol* 2003; **17**: 337–9.
41 Simonart T, Noël JC, De Dobbeleer G, Simonart JM. Carcinoma of the glans penis arising 20 years after lichen sclerosus. *Dermatology* 1998; **196**: 337–8.
42 Bouyssou-Gauthier ML, Boulinguez S, Dumas JP *et al.* Penile lichen sclerosus: follow-up study. *Ann Dermatol Vénéréol* 1999; **126**: 804–7.
43 Nasca MR, Innocenzi D, Micali G. Penile cancer among patients with genital lichen sclerosus. *J Am Acad Dermatol* 1999; **41**: 911–4.
44 Micali G, Nasca MR, Innocenzi D. Lichen sclerosus of the glans is significantly associated with penile carcinoma. *Sex Transm Infect* 2001; **77**: 226.
45 Weber P, Rabinovitz H, Garland L. Verrucous carcinoma in penile lichen sclerosus et atrophicus. *J Dermatol Surg Oncol* 1987; **13**: 529.
46 Campus GV, Alia F, Bosincu L. Squamous cell carcinoma and lichen sclerosus et atrophicus of the prepuce. *Plast Reconstr Surg* 1992; **89**: 962–4.
47 Powell J, Robson A, Cranston D *et al.* High incidence of lichen sclerosus in patients with squamous cell carcinoma of the penis. *Br J Dermatol* 2001; **145**: 85–9.
48 Maden C, Sherman KJ, Beckmann AM *et al.* History of circumcision, medical conditions, and sexual activity and the risk of penile cancer. *J Natl Cancer Inst* 1993; **85**: 19–24.
49 Holly EA, Palefsky JM. Factors related to risk of penile cancer: new evidence from a study in the Pacific Northwest. *J Natl Cancer Inst* 1993; **85**: 2–3.
50 Liatsikos EN, Perimenis P, Dandinis K *et al.* Lichen sclerosus et atrophicus: findings after complete circumcision. *Scand J Urol Nephrol* 1997; **31**: 453–6.



Fig. 71.11 Lichen planus. Papules and annular lesions with Wickham's striae on the glans and shaft. (Courtesy of Professor C.B. Bunker, with permission from Medical Illustration UK, Chelsea & Westminster Hospital, London, UK.)

Lichen planus

Aetiology. Lichen planus is discussed in Chapter 41. It is a common inflammatory dermatosis with a particular predilection for the orogenital epithelium [1]. The aetiopathogenesis of lichen planus is not known. Drugs can cause a generalized lichenoid eruption; a case of a lichenoid drug eruption confined to the penis resulting from propranolol has been reported [2].

Clinical features. Lichen planus can present in, and remain localized to, the anogenital area, including the groins and perianal skin. Like the classical disease at other sites, it presents as itchy red–purple papules, patches, plaques and annular lesions (Fig. 71.11). It may also present as phimosis [3,4]. The male genitalia represent the commonest site for the annular subtype of lichen planus [5]. The Koebner phenomenon may partly explain the orogenital predilection [6].

Occasionally, an erosive form is encountered. There is a male equivalent of the vulvovaginal syndrome of Hewitt—the genito-gingival syndrome—with chronic erosive gingival and genital lesions [7]. In most cases, anogenital lichen planus is self-limiting, although some patients remit and relapse. Adhesions can form and contribute to phimosis. Post-inflammatory hyperpigmentation can persist for months or years. A case of paraneoplastic lichen planus with orogenital and cicatrizing conjunctival involvement in a patient with thymoma has been reported [8].

Chronic mucosal erosive lichen planus is associated with a risk of progression to squamous carcinoma, but most reports of this

concern oral lichen planus. There are rare reports of squamous carcinoma eventuating from chronic penile dermatoses thought to be lichen planus [9–11].

Lichen nitidus has an affinity for the penis. It can be difficult to diagnose because the signs may be subtle, even when the lesions are widespread.

The differential diagnosis of anogenital lichen planus includes psoriasis, Zoon's balanitis, lichen sclerosus, viral warts, Bowenoid papulosis and porokeratosis. A biopsy is frequently necessary for diagnostic purposes and in the follow-up of cases of chronic anogenital disease if erosive, ulcerative or verrucous features arouse concern about the development of squamous carcinoma.

Treatment. Potent and ultrapotent topical corticosteroids usually suffice for treatment. Patients are told to continue with the treatment until the lesions are non-itchy and flat; they are warned about post-inflammatory hyperpigmentation. Reactivation of genital warts may occur [12]. Topical and oral ciclosporin have been used [13,14], but there has been a report of squamous carcinoma arising in lichen planus of the penis treated with topical ciclosporin [15]. Topical calcineurin inhibitors should be used with caution [15–17]. Circumcision may be necessary for phimosis [18] and should be considered in refractory erosive disease [19], the rationale being that the abolition of koebnerization influences and facilitates resolution of the lichen planus. Photodynamic therapy was used inadvertently in one patient with lichen planus of the glans penis, to good effect [20].

References

1 Barnette DJ Jr, Curtin TJ, Yeager JK, Corbett DW. Asymptomatic penile lesions. *Cutis* 1993; **51**: 116–8.
2 Massa MC, Jason SM, Gradini R, Welykyj S. Lichenoid drug eruption secondary to propanolol. *Cutis* 1991; **48**: 41–3.
3 Itin PH, Hirsbrunner P, Buchner S. Lichen planus: an unusual cause of phimosis. *Acta Dermatol Venereol* 1992; **72**: 41–2.
4 Bunker CB. *Male Genital Skin Disease*. London: Saunders, 2004.
5 Reich HL, Nguyen JT, James WD. Annular lichen planus: a case series of 20 patients. *J Am Acad Dermatol* 2004; **50**: 595–9.
6 El-Gadi S. Biopsy before excision. *J Eur Acad Dermatol Venereol* 1996; **7**: 87–90.
7 Cribier B, Ndiaye I, Grosshans E. Peno-gingival syndrome: a male equivalent of vulvo-vagino-gingival syndrome. *Rev Stomatol Chir Maxillofac* 1993; **94**: 148–51.
8 Hahn JM, Meisler DM, Lowder CY *et al.* Cicatrizing conjunctivitis associated with paraneoplastic lichen planus. *Am J Ophthalmol* 2000; **129**: 98–9.
9 Worheide J, Bonsmann G, Kolde G, Hamm H. Plattenepithyelkarzinom auf dem Boden eines lichen ruber hypertrophicus an der glans penis. *Hautarzt* 1991; **42**: 112–5.
10 Bain L, Geronemus R. The association of lichen planus of the penis with squamous cell carcinoma in situ and with verrucous squamous carcinoma. *J Dermatol Surg Oncol* 1989; **15**: 413–7.
11 Leal-Khouri S, Hruza GJ. Squamous cell carcinoma developing within lichen planus of the penis: treatment with Mohs micrographic surgery. *J Dermatol Surg Oncol* 1994; **20**: 272–6.
12 Von Krogh G, Dahlman-Ghozlan K, Syrjänen S. Potential human papillomavirus reactivation following topical corticosteroid therapy of genital lichen sclerosus and erosive lichen planus. *J Eur Acad Dermatol Venereol* 2002; **16**: 130–3.
13 Jemec GBE, Baadsgaard O. Effect of cyclosporin on genital psoriasis and lichen planus. *J Am Acad Dermatol* 1993; **29**: 1048–9.
14 Schmitt EC, Pigatto PD, Boneschi V *et al.* Erosiver lichen planus der glans penis: behandlung mit cyclosporin A. *Hautarzt* 1993; **44**: 43–5.
15 Cox NH. Squamous cell carcinoma arising in lichen planus of the penis during topical cyclosporin therapy. *Clin Exp Dermatol* 1996; **21**: 323–4.
16 Langeland T, Engh V. Topical use of tacrolimus and squamous cell carcinoma of the penis. *Br J Dermatol* 2005; **152**: 183–4.
17 Bunker CB, Neill S, Staughton RCD. Topical tacrolimus, genital lichen sclerosus and risk of squamous cell carcinoma. *Arch Dermatol* 2004; **140**: 1169.
18 Aste N, Pau M, Ferreli C, Biggio P. Lichen planus in a child requiring circumcision. *Pediatr Dermatol* 1997; **14**: 129–30.
19 Porter WM, Dinneen M, Hawkins DA, Bunker CB. Erosive penile lichen planus responding to circumcision. *J Eur Acad Dermatol Venereol* 2001; **15**: 266–8.
20 Kirby B, Whitehurst C, Moore JV, Yates VM. Treatment of lichen planus of the penis with photodynamic therapy. *Br J Dermatol* 1999; **141**: 765–6.

Non-specific balanoposthitis

Clinical experience and histological evidence indicate that non-specific balanoposthitis is a real entity [1,2]. However, in practice it is a diagnosis of exclusion, sexually transmitted disease, eczematous dermatoses, psoriasis, Zoon's balanitis, lichen planus, lichen sclerosus, cicatrizing pemphigoid and penile carcinoma *in situ* having been clinically considered and eliminated by special investigations, including biopsy, and failure to respond to specific treatments. Non-specific balanoposthitis is a manifestation of a dysfunctional foreskin. Patients generally present with dyspareunia, and may have variable signs, including eczematous, lichenoid and Zoon-like inflammation, and even scarring. *Candida* and other organisms may be retrieved, but they probably represent secondary opportunistic infection. Diabetes should be excluded. Specific and non-specific interventions may be tried, such as avoidance of contact with soap and urine and other irritants, treatment for candidosis and other infections, and medical treatment for lichen sclerosus and lichen planus. Invariably these treatments fail and the patient is cured by circumcision. A prior clinical diagnosis may be overturned at this stage by foreskin histology showing lichen sclerosus, lichen planus or carcinoma *in situ*, but there will always be cases where a thorough histological examination of the excised prepuce fails to reveal more than non-specific chronic inflammatory changes.

References

1 Bunker CB. *Male Genital Skin Disease*. London: Saunders, 2004.
2 Alessi E, Coggi A, Gianotti R. Review of 120 biopsies performed on the balanopreputial sac. *Dermatol* 2004; **208**: 120–4.

Ulcerative disease and penile necrosis

The causes of genital ulceration are listed in Tables 71.9 and 71.10, and the causes of penile necrosis in Table 71.20. Many of the causes are discussed in this or other sections.

Aphthous ulceration of the penis and scrotum can occur, including in HIV/AIDS (see Chapter 35), but specific exclusion of sexually transmitted diseases and consideration of other causes of genital ulceration, especially Behçet's syndrome, is necessary. The causes are obscure and the histology is non-specific.

Five cases of spontaneous scrotal ulceration in young, previously fit men have been described [1]. Histology showed non-specific vasculitis, and spontaneous resolution occurred. This entity may be related to idiopathic scrotal panniculitis and fat necrosis. It is distinct from other causes of the acute scrotum in prepubertal boys. It presents as acute, tender, sometimes painful, swelling (classically, but not always, after swimming in cold water). Masses may be palpable in the scrotal wall. Otherwise, the boy is well, with no fever or leukocytosis. Idiopathic scrotal necrosis in a 2-month-old boy has been documented by Sarihan [2],

Table 71.20 Causes of penile necrosis. (After Bunker [20]. © 2004, with permission from Elsevier.)

Decubitus ulcer
Spider bite
Priapism
Embolism
Strangulation and tourniquet syndromes
Vacuum erection device
Systemic vasculitis [46]
Lupus erythematosus
Polyarteritis nodosa [47]
Wegener's granulomatosis
Diabetes mellitus [48,49]
Chronic renal failure [50]
Thrombocytopenia
Polycythaemia
Cryoglobulinaemia
Coagulopathy [51]
Pyoderma gangrenosum
Calciphylaxis
Ecthyma gangrenosum
Fournier's gangrene
Herpes simplex
Leukaemia
Mucormycosis (in acute myeloblastic leukaemia) [52]
Warfarin
Fixed drug eruption

where trauma, extreme cold and Fournier's gangrene were excluded. Management is expectant and conservative [3,4]. In adults, one case of idiopathic scrotal panniculitis has been reported [5] and another associated with pancreatitis [6].

Subtle or severe orogenital ulceration can occur in erythema multiforme or the Stevens–Johnson syndrome (see Chapter 76).

Adamantiades-Behçet's disease is discussed in Chapter 50. Recurrent genital ulceration is not mandatory for the diagnosis; if patients do not have genital ulceration then they must have ophthalmic and dermatological involvement or a positive pathergy test [7]. In practice, there are many patients who have an incomplete syndrome. Other anogenital manifestations include epididymitis and urethritis [8], spontaneous haematocoele from venous rupture resulting from lymphocytic venulitis [9], and erectile dysfunction [10]. The genital ulcers in men can be very painful and occur anywhere in the anogenital area, including the perianal skin. Generally, they are larger, deeper, fewer and less recurrent than those in the mouth. Patients with relapsing polychondritis and Behçet's disease have been reported, and the acronym MAGIC (mouth and genital ulcers with inflamed cartilage) syndrome has been proposed [11,12]. The histology of Behçet's disease is usually non-specific and does not enable it to be distinguished from idiopathic aphthae, although sometimes necrotizing vasculitis can be present.

Scrotal involvement can occur in Hailey–Hailey disease [13].

Degos' malignant atrophic papulosis (see Chapter 50) can cause painful penile ulceration, that may precede the development of the eruption elsewhere and be associated with fatal involvement of other organs, despite aggressive treatment [14,15].



Fig. 71.12 Pyoderma gangrenosum in a patient with severe seronegative arthropathy. (Courtesy of Dr F.A. Ive, Durham, UK.)

The hypereosinophilic syndrome involves the skin in up to 50% of cases, with orogenital ulceration, erythroderma and urticaria. It may occur in HIV infection [16].

Wegener's granulomatosis may present with glans penis ulceration and necrosis; repeated ANCA estimation may be needed and it may be some time before systemic manifestations declare themselves [17–21].

There has been one case report of a patient with erythema elevatum diutinum causing penile ulceration [22]. Three cases of necrobiosis lipoidica have been reported presenting as erythematous ulcerated lesions of the glans penis. One patient was diabetic and also had lesions on the legs [23]; the others had penile lesions only, and were treated with oral pentoxifylline [24,25].

There are a number of case reports of pyoderma gangrenosum (see Chapter 50), including the variant superficial granulomatous pyoderma [26], involving the penis and scrotum in adults and children (where the anogenital area is a site of predilection as well as the head and neck) (Fig. 71.12) [27,28]. Genital pyoderma gangrenosum may occur following local trauma such as urological surgery [29,30] or treatment for cancer [31], or complicate ulcerative colitis [32] or chronic lymphocytic leukaemia, or it may be idiopathic [33–36]. Pyoderma gangrenosum is a diagnosis made when other causes of purulent ulceration, such as infection (sexually acquired and exotic or rare, including Fournier's gangrene), malignancy and artefact have been excluded. Systemic treatment is usually required but one case has responded to topical tacrolimus [37].

Calciphylaxis (see Chapter 62) is a rare and serious complication of chronic renal failure in which extending ischaemic gangrenous necrosis affects acral tissues and sometimes the thighs, buttocks and genitals [38–43].

Ulcers in the penoscrotal region have been reported to appear 2 to 4 weeks after Chikungunya, a novel togavirus arboviral infection that causes fever, headache and arthralgia [44].

There has been one case report of primary cutaneous T-cell lymphoma of the penis presenting with a 2-year history of 'recurrent balanitis', a preputial ulcer and phimosis [45].

References

1 Devesa Mugica M, De La Torre Fraga C, Selas Perez A *et al.* Vasculitis gangrenosa juvenil del escroto. Aportacion de dos casos. *Actas Urol Esp* 1994; **18**: 237–40.
2 Sarihan H. Idiopathic scrotal necrosis. *Br J Urol* 1994; **74**: 259.
3 Koster LH, Antoon SJ. Fat necrosis in the scrotum. *J Urol* 1980; **123**: 599–600.
4 Hollander JB, Begun FP, Lee RD. Scrotal fat necrosis. *J Urol* 1985; **134**: 150–1.
5 Tsurusaki T, Maruta N, Iwasaki S *et al.* Idiopathic bilateral panniculitis of the spermatic cord in an elderly male patient. *J Urol* 2000; **164**: 1657–8.
6 Lin Y, Lin M, Huang G *et al.* Acute pancreatitis masquerading as testicular torsion. *Am J Emerg Med* 1996; **14**: 654–5.
7 International Study Group for Behçet's disease. Criteria for diagnosis of Behçet's disease. *Lancet* 1990; **335**: 1078–80.
8 Kirkali Z, Yigitbasi O, Sasmaz R. Urological aspects of Behçet's disease. *Br J Urol* 1991; **67**: 638–9.
9 Orhan I, Onur R, Ardicoglu A, Salatan Y. Behçet's disease and spontaneous haematocoele: an unusual complication. *BJU Int* 1999; **84**: 739–40.
10 Aksu K, Keser G, Gunaydin G *et al.* Erectile dysfunction in Behçet's disease without neurological involvement: two case reports. *Rheumatology (Oxford)* 2000; **39**: 1429–31.
11 Firestein GS, Gruber HE, Weisman MH *et al.* Mouth and genital ulcers and inflamed cartilage: MAGIC syndrome. *Am J Med* 1985; **79**: 65–72.
12 Orme RL, Nordlund JJ, Barich L, Brown T. The MAGIC syndrome (mouth and genital ulcers with inflamed cartilage). *Arch Dermatol* 1990; **126**: 940–4.
13 Chan C-C, Thyong H-Y, Chan Y-C, Liao Y-H. Human papillomavirus type 5 infection in a patient with Hailey-Hailey disease successfully treated with imiquimod. *Br J Dermatol* 2007; **156**: 579–81.
14 Thomson KF, Highet AS. Penile ulceration in fatal malignant atrophic papulosis (Degos' disease). *Br J Dermatol* 2000; **143**: 1320–2.
15 Aydogan K, Alkan G, Karadogan Koran S *et al.* Painful penile ulceration in a patient with malignant atrophic papulosis. *J Eur Acad Dermatol Venereol* 2005; **19**: 612–6.
16 Morgan MB, Viloria J, Morgan JD, Suarez-Hoyos J. Human immunodeficiency virus infection and hypereosinophilic syndrome. *J Florida Med Assoc* 1994; **81**: 401–2.
17 Osada T, Inoue T, Hirano A, Tanaka K. Wegener's granulomatosis with penile necrosis. *Jpn J Clin Urol* 1974; **28**: 549–55.
18 Matsuda O, Mitsukawa S, Ishii N, Shirai M. A case of Wegener's granulomatosis with necrosis of the penis. *Tohuku J Exper Med* 1976: **118**: 145–51.
19 Allen DC, Walsh MY. Malignant lymphoma of the scrotum and Wegener's granulomatosis of the penis—genital presentation of systemic disease. *Ulster Med J* 1996; **65**: 169–72.
20 Bunker CB. *Male Genital Skin Disease*. London: Saunders, 2004.
21 Bories N, Becuwe C, Marcilly MC *et al.* Glans penis ulceration revealing Wegener's granulomatosis. *Dermatology* 2007: **214**: 187–9.
22 Yoshii N, Kanekura T, Higashi Y *et al.* Erythema elevatum diutinum manifesting as a penile ulcer. *Clin Exp Dermatol* 2007; **32**: 211–3.
23 Lecroq C, Thomine E, Bouillie MC, Lauret P. Necrobiose lipoidique atypique genitale. *Ann Dermatol Vénéréol* 1984; **111**: 717–8.
24 Espana A, Sanchez-Yus E, Serna MJ *et al.* Chronic balanitis with palisading granuloma: an atypical genital localization of necrobiosis lipoidica responsive to pentoxifylline. *Dermatology* 1994; **188**: 222–5.
25 Tokura Y, Mizushima Y, Hata M, Takigawa M. Necrobiosis lipoidica of the glans penis. *J Am Acad Dermatol* 2003; **49**: 921–4.
26 Gopi SS, Evans AT, Raza A, Byrne DJ. Superficial granulomatous pyoderma gangrenosum of the penis: a case report. *Scientific World J* 2007; **7**: 2426–9.
27 Bigler LR, Flint ID, Davis LS. Painful ulcers of the scrotum. *Arch Dermatol* 1995; **31**: 609–14.
28 Çalikoglu E. Superficial granulomatous pyoderma of the scrotum: an extremely rare cause of genital ulcer. *Acta Dermatol Venereol* 2000; **80**: 311–2.
29 Farrell AM, Black MM, Bracka A, Bunker CB. Pyoderma gangrenosum of the penis. *Br J Dermatol* 1998; **138**: 337–40.
30 Gopi SS, Evans AT, Raza A, Byrne DJ. Superficial granulomatous pyoderma gangrenosum of the penis: a case report. *Scientific World J* 2007; **7**: 2426–9.
31 Kohjimoto Y, Inagaki T, Iba A *et al.* Pyoderma gangrenosum of the penis presenting as Fournier's gangrene: a case report. *Hinyokika Kiyo* 2005; **51**: 411–5.
32 Sanusi ID, Gonzalez E, Venable DD. Pyoderma gangrenosum of penile and scrotal skin. *J Urol* 1982; **127**: 547–9.
33 Harto A, Gutiérrez Sanz-Gadea C, Vives R *et al.* Pioderma gangrenoso en pene. *Acta Urol Esp* 1985; **9**: 263–6.
34 Sánchez MH, Sánchez SR, del Cerro Heredero M *et al.* Pyoderma gangrenosum of penile skin. *Int J Dermatol* 1997; **36**: 638–9.
35 Güngör E, Karakayali G, Alli N *et al.* Penile pyoderma gangrenosum. *J Eur Acad Dermatol Venereol* 1999; **12**: 59–62.
36 Park HJ, Kim YC, Cinn YW, Yoon TY. Granulomatous pyoderma gangrenosum: two unusual cases showing necrotizing granulomatous inflammation. *Clin Exp Dermatol* 2000; **25**: 617–20.
37 Lally A, Hollowood K, Bunker CB, Turner R. Penile pyoderma gangrenosum treated with topical tacrolimus. *Arch Dermatol* 2005; **141**: 1175–6.
38 Ivker RA, Woosley J, Briggaman R. Calciphylaxis in three patients with end-stage renal disease. *Arch Dermatol* 1995; **131**: 63–8.
39 Siami GA, Siami FS. Intensive tandem cryofiltration apheresis and haemodialysis to treat a patient with severe calciphylaxis, cryoglobulinemia, and end-stage renal disease. *ASAIO J* 1999; **45**: 229–33.
40 Boccaletti VP, Ricci R, Sebastio N *et al.* Penile necrosis. *Arch Dermatol* 2000; **136**: 261, 264.
41 Woods M, Pattee SF, Levine N. Penile calciphylaxis. *J Am Acad Dermatol* 2006; **54**: 736–7.
42 Ohta A, Ohomori S, Mizukami T *et al.* Penile necrosis by calciphylaxis in a diabetic patient with chronic renal failure. *Intern Med* 2007; **46**: 985–90.
43 Oikawa S, Osajima A, Tamura M *et al.* Development of proximal calciphylaxis with penile involvement after parathyroidectomy in a patient on hemodialysis. *Intern Med* 2004; **43**: 63–8.
44 Mishra K, Husain, J, Rajawat V. Ulcers in penoscrotal region, post chikungunya. *Proceedings of the Indian Association of Dermatology, Venereology and Leprology Meeting*. Gangigarh, India, 2008. P-136, P-13.
45 Thorns C, Urban H, Remmler K *et al.* Primary cutaneous T-cell lymphoma of the penis. *Histopathology* 2003; **42**: 513–4.
46 Rubio FA, Robayna G, Herranz P *et al.* Necrotizing vasculitis of the glans penis. *Br J Dermatol* 1999; **40**: 756–7.
47 Karademir K, Senkul T, Atasoyu E *et al.* Ulcerative necrosis of the glans penis resulting from polyarteritis nodosa. *J Clin Rheumatol* 2005; **11**: 167–9.
48 Bour J, Steinhardt G. Penile necrosis in diabetes mellitus and end stage renal disease. *J Urol* 1984; **132**: 560–2.
49 Frydenberg M. Penile gangrene: a separate entity from Fournier's syndrome? *Br J Urol* 1988; **61**: 532–3.
50 Lowe FC, Brendler CB. Penile gangrene: a complication of secondary hyperparathyroidism from chronic renal failure. *J Urol* 1984; **132**: 1189–91.
51 Sodal G, Ly B, Borchgrevink HH. Thrombosis of the inferior vena cava, disseminated intravascular coagulation and gangrene of the penis. *Acta Med Scand* 1978; **203**: 535–8.
52 Grossklaus DJ, Dutta SC, Shappel S, Kirchner FK. Cutaneous mucormycosis presenting as a penile lesion in a patient with acute myeloblastic leukaemia. *J Urol* 1999; **161**: 1906–7.

Pilonidal sinus

Pilonidal sinus very rarely affects the penis, but when it does it is usually in the coronal sulcus [1,2]. Some of the reported cases have been complicated by actinomycosis [1,3], and one has been associated with a dermoid cyst [4].

References

1 Val-Bernal JF, Azcarretazabal T, Garijo MF. Pilonidal sinus of the penis: a report of two cases, one of them associated with actinomycosis. *J Cutan Pathol* 1999; **26**: 155–8.
2 O'Kane HF, Duggan B, Mulholland C, Crosbie J. Pilonidal sinus of the penis. *Scientific World J* 2004; **4** (Suppl. 1): 258–9.

3 Rashid AMH, Menai Williams R, Parry D, Malone PR. Actinomycosis associated with pilonidal sinus of the penis. *J Urol* 1992; **148**: 405–6.
4 Tomasini C, Aloi F, Puiatti P, Caliendo V. Dermoid cyst of the penis. *Dermatology* 1997; **194**: 188–90.

Penile acne

There is no literature on this condition but it is occasionally encountered. Patients have comedones, papules, pustules and inflammatory nodules of the proximal shaft of the penis. The differential diagnosis should include chloracne (see Chapter 42). Patients respond to conventional treatment for acne.

Peyronie's disease

Peyronie's disease [1,2], which affects middle-aged and older men, is a localized fibrotic disorder involving tissue immediately adjacent to the erectile tissues. It presents with pain and curvature on erection, a sensation of a cord within the penis, palpation of a lump or knot, decreased erection distal to the plaque, interference with intercourse and progressive impotence. It may be subclinical in many men, given that 23% of autopsies have shown histological evidence of the condition [1]. Psychological complications and marital difficulties occur. The penis curves towards the lesion, with dorsal curvature being most common. Peyronie (a physician to Louis XIV) described nodules as 'rosary beads' but plaques vary in size. It has been associated with systemic sclerosis [3,4], and such patients may have penile Raynaud's phenomenon [5]. It has occurred as a complication of the use of a vacuum erection device [6], but in most men the cause is unknown. Some evidence has been advanced for an autoimmune pathogenesis [7]. A case complicating chronic-graft-versus host disease has been reported [8].

The differential diagnosis includes congenital curvature, fibrosis secondary to trauma or urethritis and abscess, syphilitic gumma, lymphogranuloma venereum, and infiltrative tumours (e.g. lipogranuloma). Penile thrombophlebitis as the initial presentation of a paraneoplastic migratory thrombophlebitis resulting from pancreatic cancer has been misdiagnosed as Peyronie's disease [9].

In some men there may be spontaneous regression. Treatments include intralesional corticosteroid injection [10], including delivery by Dermojet [11]. Surgery is avoided, but some specialized techniques are available [12]. Symptomatic relief has been claimed following iontophoresis of drugs such as dexamethasone, lidocaine (lignocaine) and verapamil [13].

References

1 Smith BH. Subclinical Peyronie's disease. *Am J Clin Pathol* 1969; **52**: 385–90.
2 Billig R, Baker R, Immergut M, Maxted W. Peyronie's disease. *Urology* 1975; **6**: 409–18.
3 Simeon CP, Fonollosa V, Vilardell M *et al.* Impotence and Peyronie's disease in systemic sclerosis. *Clin Exp Rheumatol* 1994; **12**: 464.
4 Aversa A, Proietti M, Bruzziches R *et al.* The penile vasculature in systemic sclerosis: a duplex ultrasound study. *J Sex Med* 2006; **3**: 554–8.
5 Mooradian AD, Viosca SP, Kaiser FE *et al.* Penile Raynaud's phenomenon: a possible cause of erectile failure. *Am J Med* 1988; **85**: 748–50.
6 Ganem JP, Lucey DT, Janosko EO, Carson CC. Unusual complications of the vacuum erection device. *Urology* 1998; **51**: 627–31.
7 Schiavino D, Sasso F, Nucera E *et al.* Immunologic findings in Peyronie's disease: a controlled study. *Urology* 1997; **50**: 764–8.
8 Grigg AP, Underhill C, Russell J, Sale G. Peyronie's disease as a complication of chronic graft versus host disease. *Hematology* 2002; **7**: 165–8.
9 Horn AS, Pecora A, Chiesa JC, Alloy A. Penile thrombophlebitis as a presenting manifestation of pancreatic carcinoma. *Am J Gastroenterol* 1985; **80**: 463–5.
10 Desanctis PN, Furey CA Jr. Steroid injection therapy for Peyronie's disease: a 10-year summary and review of 38 cases. *J Urol* 1967; **97**: 114–6.
11 Winter CC, Khanna R. Peyronie's disease: results with dermo-jet injection of dexamethasone. *J Urol* 1975; **114**: 898–900.
12 Chun JL, McGregor A, Krishnan R, Carson CC. A comparison of dermal and cadaveric pericardial grafts in the modified Horton–Devine procedure for Peyronie's disease. *J Urol* 2001; **166**: 185–8.
13 Riedl CR, Plas E, Engelhardt P *et al.* Iontophoresis for treatment of Peyronie's disease. *J Urol* 2000; **163**: 95–9.

Drug reactions

The penis is a site of predilection for fixed drug eruption (see Chapter 75). The symptoms are itch or burning. The eruption is acute, with an erythematous plaque, sometimes with central blister formation, erosion and ulceration. Cases have occurred in men after congress with sexual partners who have taken the drug to which they were known to be sensitive: co-trimoxazole, diclofenac, isosorbide and aspirin are the drugs cited [1,2]. The differential diagnosis of penile fixed drug eruption includes herpes simplex and erythema multiforme.

Ulceration has been reported following the inadvertent subcutaneous injection of papaverine for the treatment of erectile impotence [3]. Dequalinium is a topical antibacterial that was used for the treatment of impetigo and moniliasis in the 1950s and 1960s, but it caused a necrotizing balanitis with ulceration when used for the treatment of balanitis in uncircumcised men [4]. Warfarin necrosis can affect the genitalia [5]. All-*trans*-retinoic acid has been reported to induce scrotal ulceration in a patient with acute promyelocytic leukaemia [6]. Foscarnet is a recognized cause of genital ulceration in HIV-infected patients [7–9]. Nicorandil is a newly recognized cause of anogenital and peristomal ulceration [10–12]. Erosion following the use of topical steroids has been seen. Penile argyria due to chronic application of silver sulfadiazine has been reported [13].

References

1 Gruber F, Stasic A, Lenkovic M, Brajac I. Postcoital fixed drug eruption in a man sensitive to trimethoprim-sulphamethoxazole. *Clin Exp Dermatol* 1997; **22**: 144–5.
2 Zawar V, Kirloskar M, Chuh A. Fixed drug eruption—a sexually inducible reaction? *Int J STD AIDS* 2004; **15**: 560–3.
3 Borgstrom E. Penile ulcer as complication in self-induced papaverine erections. *Urology* 1988; **32**: 416–7.
4 Coles RB, Wilkinson DS. Necrosis and dequalinium. I. Balanitis. *Trans St John's Hosp Dermatol Soc* 1965; **51**: 46–8.
5 Harmanyeri Y, Taskapan O, Dogan B *et al.* A case of coumarin necrosis with penile and pedal involvement. *J Eur Acad Dermatol Venereol* 1998; **10**: 248–52.
6 Esser AC, Nossa R, Shoji T, Sapadin AN. All-*trans*-retinoic acid-induced scrotal ulcerations in a patient with acute promyelocytic leukaemia. *J Am Acad Dermatol* 2000; **43**: 316–7.
7 Evans LM, Grossman ME. Foscarnet-induced penile ulcer. *J Am Acad Dermatol* 1992; **27**: 124–6.
8 Gross AS, Dretler RH. Foscarnet-induced penile ulcer in an uncircumcised patient with AIDS. *Clin Infect Dis* 1993; **17**: 1076–7.
9 Moyle G, Gazzard BG. Opportunistic infections and tumours: cytomegalovirus infection. In: Gazzard BG, ed. *AIDS Care Handbook*. London: Mediscript, 2002.
10 Toquero L, Briggs CD, Bassuini MM, Rochester JR. Anal ulceration associated with nicorandil: case series and review of the literature. *Colorectal Dis* 2006; **8**: 717–20.
11 Birnie A, Dearing S, Littlewood S, Carlin E. Nicorandil-induced ulceration of the penis. *Clin Exp Dermatol* 2008; **33**: 215–6.



Fig. 71.13 Pemphigus of the penis. (Courtesy of Dr F.A. Ive, Durham, UK.)

12 Ogden S, Mukasa Y, Lyon CC, Coulson IH. Nicorandil-induced peristomal ulcers: is nicorandil also associated with gastrointestinal fistula formation? *Br J Dermatol* 2007; **156**: 575–612.

13 Griffiths MR, Milne JT, Porter WM. Penile argyria. *Br J Dermatol* 2006; **154**: 1074–5.

Miscellaneous inflammatory dermatoses

Bottomley and Cotterill [1] have described an acutely tender erythematous scrotum associated with zinc deficiency in a patient with Crohn's disease. Necrolytic migratory erythema can be localized to the genitalia [2]. Skin fragility and ulceration in the anogenital area are features of prolidase deficiency [3].

Autoimmune bullous diseases such as pemphigus can involve the penis (the glans is the usual site) (Fig. 71.13), but very rarely in isolation [4]. Pemphigus vegetans presenting with a 4-year history of indolent tender balanitis, where the glans penis was involved with a moist vegetative plaque with beefy red erosions separating irregular hyperkeratotic mounds, has been reported [5]. Linear immunoglobulin A (IgA) disease commonly involves the mucosae. Mucosal lesions of bullous pemphigoid are uncommon; their presence suggests another diagnosis or an underlying neoplasm. Pelvic girdle lesions are often seen, but rarely in isolation.

Cicatricial pemphigoid (or 'benign') mucous membrane pemphigoid) is a rare variant of bullous pemphigoid in which blisters affect the skin and the mucous membranes. Skin lesions are usually less widespread than in bullous pemphigoid and they may heal with scarring. Oral lesions predominantly involve the palate and gingivae, but there may be oesophageal involvement with dysphagia, and conjunctival disease can lead to blindness. Involvement of the penis may be with blisters, erosions, ulcers, transcoronal adhesions, scarring and phimosis [6–8]. Although direct immunofluorescence is usually positive, circulating antibodies to the basement membrane zone are rarely found. The disease often responds poorly to oral steroids, but dapsone or other sulpha drugs such as sulphamethoxypyridazine can be effective. Regular haematology screening is mandatory with dapsone because of the risk of agranulocytosis.

One patient with Darier's disease developed a HPV 16-associated squamous carcinoma of the scrotum during oral isotretinoin treatment; he had not previously had radiotherapy to the genitocrural area [9]. Genitocrural papular acantholytic dermatosis can involve the penis, as can granuloma annulare. Erythematous smooth, round and linear nodules are described in the latter. Most patients are uncircumcised. Extragenital granuloma annulare is uncommon in these patients.

Occasionally, patients with generalized cutaneous sarcoid present with genital lesions [10]. Tender erythematous induration of the distal shaft of the penis and several yellowish subcutaneous nodules on the glans have been described [11]. A case presenting with penile ulceration has been reported [12]. Importantly, sarcoid can masquerade as testicular malignancy [13–15].

A granulomatous lymphangitis may be found histologically in the investigation of penile lymphoedema [16]. It can be a rare feature of the Melkersson–Rosenthal syndrome. Crohn's disease can involve the penis and scrotum, presenting as penoscrotal lymphoedema or erosions and ulcers [17–23].

A soft-tissue mass in the penis associated with systemic amyloid has been reported [24]. A handful of cases of primary localized cutaneous amyloid of the penis appear in the literature [25]. Primary amyloid of the urethra is very rare indeed, but accurate diagnosis is essential, as its presentation simulates carcinoma, with dysuria, bloody discharge and tender induration of the penis [26], or as an obstructive voiding syndrome, with tender periurethral masses and irregular urethral strictures [27].

One case each of eccrine syringofibroadenomatosis with penile involvement manifesting as a balanoposthitis [28], benign mucinous metaplasia with a preputial 0.6 cm papule replacing the superficial epidermis [29], and mucinous syringometaplasia with an ulcerated papule on the shaft of the penis [30] have been reported.

Acute scrotum is a clinical syndrome defined as acute painful swelling of the scrotum or its contents, usually in boys, accompanied by local signs and general symptoms [31]. The critical differential diagnosis is torsion of the testis or spermatic cord. Other causes include idiopathic scrotal oedema, epididymitis, orchitis, hernia and haematocoele. Thromboangiitis obliterans has been found in two cases [32]. Acute scrotal swelling may be a physical sign of primary peritonitis in children and infants [33] or secondary peritonitis resulting from appendicitis, healed meconium peritonitis in the neonate, haemoperitonitis (ruptured spleen) and pseudotorsion resulting from ventriculoperitoneal shunts inserted for hydrocephalus that have migrated into the scrotum from the peritoneum. Acute idiopathic scrotal oedema usually affects children aged 4–12 years old. Allergy, infection (umbilical sepsis), trauma, insect bites, urinary extravasation and Henoch–Schönlein purpura have all been considered as causes. It is rare in adults, but cases in association with septic diabetic foot have been reported [34].

Henoch–Schönlein purpura/anaphylactoid purpura/allergic vasculitis may affect the genitalia. Ureteritis, renal pelvic haemorrhage and pain and swelling of the spermatic cord have been reported. The incidence of scrotal involvement ranges from 2 to 38%. Penile shaft involvement is less common and involvement of the glans very rare [35]. In some cases, the presentation has masqueraded as testicular torsion, resulting in unnecessary surgical exploration. Ultrasonography can help to distinguish between them [36]. However, testicular torsion can also be a real and serious complication of Henoch–Schönlein purpura [36].

Acute haemorrhagic oedema of childhood may present as tenderness, redness and swelling of the penis and scrotum with the development of more widespread haemorrhagic lesions [37]. The differential diagnosis includes acute febrile neutrophilic dermatosis, erythema multiforme, Henoch–Schönlein purpura and child abuse. The prognosis for complete recovery is excellent. Acute inflammation of the scrotum in patients with familial Mediterranean fever can occur [38]. It is manifested by pain, erythema and swelling, fever, leukocytosis and elevated erythrocyte sedimentation rate (ESR). It may occur in isolation or accompanying peritonitis. The differential diagnosis includes torsion, orchitis and epididymitis in boys.

Polyarteritis nodosa may be associated with testicular and epididymal involvement, with scrotal pain and swelling. In one case these were the sole presenting features and testicular biopsy provided the diagnosis [39–41].

There has been one patient who presented with 'inaugural' painless erythematous papules on the penis that histologically showed granulomatous vasculitis, leading to the diagnosis of Churg–Strauss syndrome [42].

References

1 Bottomley WW, Cotterill JA. Acquired zinc deficiency presenting with an acutely tender erythematous scrotum. *Br J Dermatol* 1993; **129**: 501–2.
2 Bewley AP, Ross JS, Bunker CB, Staughton RC. Successful treatment of a patient with octreotide-resistant necrolytic migratory erythema. *Br J Dermatol* 1996; **134**: 1101–4.
3 Hershkovitz T, Hassoun G, Indelman M *et al.* A homozygous missense mutation in PEPD encoding peptidase D causes prolidase deficiency associated with hyper-IgE syndrome. *Clin Exp Dermatol* 2006; **31**: 435–40.
4 Sami N, Ahmed AR. Penile pemphigus. *Arch Dermatol* 2001; **137**: 756–8.
5 Castle WN, Wentzell JM, Schwartz BK *et al.* Chronic balanitis due to pemphigus vegetans. *J Urol* 1987; **137**: 289–91.
6 Kirtschig G, Mengel R, Mittag H *et al.* Desquamative gingivitis and balanitis: linear IgA disease or cicatricial pemphigoid? *Clin Exp Dermatol* 1998; **23**: 173–7.
7 Ramlogan D, Coulsom IH, McGeorge A. Cicatricial pemphigoid: a diagnostic problem for the urologist. *J R Coll Surg Edin* 2000; **45**: 62–3.
8 Fueston JC, Adams BB, Mutasim DF. Cicatricial pemphigoid-induced phimosis. *J Am Acad Dermatol* 2001; **46**: S128–9.
9 Orihuela E, Tyring SK, Pow-Sang M *et al.* Development of human papillomavirus type 16-asssociated squamous cell carcinoma of the scrotum in a patient with Darier's disease treated with systemic isotreinoin. *J Urol* 1995; **153**: 1940–3.
10 Wei H, Friedman KA, Rudikoff D. Multiple indurated papules on penis and scrotum. *J Cutan Med Surg* 2000; **4**: 202–4.
11 Rubinstein I, Baum GL, Hiss Y. Sarcoidosis of the penis: report of a case. *J Urol* 1986; **135**: 1016–7.
12 Mahmood N, Afzal N, Joyce A. Sarcoidosis of the penis. *Br J Urol* 1997; **80**: 155.
13 Turk CO, Schacht M, Ross L. Diagnosis and management of testicular sarcoidosis. *J Urol* 1986; **135**: 380–1.
14 Sieber PR, Duggan FE. Sarcoidosis and testicular tumors. *Urology* 1988; **31**: 140–1.
15 Gross AJ, Heinzer H, Loy V, Dieckmann K-P. Unusual differential diagnosis of testis tumor: intrascrotal sarcoidosis. *J Urol* 1992; **147**: 1112–4.
16 Mor Y, Zaidi SZ, Rose DS *et al.* Granulomatous lymphangitis of the penile skin as a cause of penile swelling in children. *J Urol* 1997; **158**: 591–2.
17 Goh M, Tekchanani AH, Wojno KJ *et al.* Metastatic Crohn's disease involving penile skin. *J Urol* 1998; **159**: 506–7.
18 Corazza M, Ughi G, Spisani L, Virgili A. Metastatic ulcerative penile Crohn's disease. *J Eur Acad Dermatol Venereol* 1999; **13**: 224–6.
19 Lehrnbecher T, Kontny HU, Jeschke R. Metastatic Crohn's disease in a 9-year-old boy. *J Pediatr Gastroenterol Nutr* 1999; **28**: 321–3.
20 Acker SM, Sahn EE, Rogers HC *et al.* Genital cutaneous Crohn disease: two cases with unusual clinical and histopathologic features in young men. *Am J Dermatopathol* 2000; **22**: 443–6.
21 Slaney G, Muller S, Clay J *et al.* Crohn's disease involving the penis. *Gut* 1986; **27**: 329–33.
22 Phillips SS, Baird DB, Joshi VV *et al.* Crohn's disease of the prepuce in a 12-year-old boy: a case report and review of the literature. *Pediatr Pathol Lab Med* 1997; **17**: 497–502.
23 Tan E, David N, Kinsey W, Levell NJ. Recurrrent painful ulcers on the penis. *Clin Exp Dermatol* 2006; **31**: 317–8.
24 Leal SM, Novsam N, Kacks SI. Case report: amyloidosis presenting as a penile mass. *J Urol* 1988; **140**: 830–1.
25 Ritter M, Nawab RA, Tannenbaum M *et al.* Localized amyloidosis of the glans penis: a case report and literature review. *J Cutan Pathol* 2003; **30**: 37–40.
26 Provet JA, Rakham J, Mennen J *et al.* Primary amyloidosis of urethra. *Urology* 1989; **34**: 106–8.
27 Noone TC, Clark RL. Primary isolated urethral amyloidosis. *Abdom Imaging* 1997; **22**: 448–9.
28 Ochonisky S, Wechsler J, Marinho E, Revuz J. Eccrine syringofibroadenomatosis (Mascaro) with mucous involvement. *Arch Dermatol* 1994; **130**: 933–4.
29 Val-Bernal JF, Hernandez-Nieto E. Benign mucinous metaplasia of the penis: a lesion resembling extramammary Paget's disease. *J Cutan Pathol* 2000; **27**: 76–9.
30 Kappel TJ, Abenoza P. Mucinous syringometaplasia. *Am J Dermatopathol* 1993; **15**: 562–7.
31 Melekos MD, Asbach HW, Markou SA. Aetiology of acute scrotum in 100 boys with regard to age distribution. *J Urol* 1988; **139**: 1023.
32 Nesbit RM, Hodgson NB. Thromboangiitis obliterans of the spermatic cord. *Trans Am Assoc Genitourin Surg* 1959; **51**: 92–4.
33 Udall DA, Drake DJ, Rosenberg RS. Acute scrotal swelling: a physical sign of primary peritonitis. *J Urol* 1981; **125**: 750–1.
34 Fahal AH, Suliman SH, Sharfi AR, el Mahadi EM. Acute idiopathic scrotal oedema in association with diabetic septic foot. *Diabetes Res Clin Pract* 1993; **21**: 197–200.
35 David S, Schiff JD, Poppas DP. Henoch-Schönlein purpura involving the glans penis. *Urology* 2003; **61**: 1035.
36 Laor T, Atala A, Teele RL. Scrotal ultrasonography in Henoch–Schönlein purpura. *Pediatr Radiol* 1992; **22**: 505–6.
37 Dubin BA, Bronson DM, Eng AM. Acute hemorrhagic oedema of childhood: an unusual variant of leukocytoclastic vasculitis. *J Am Acad Dermatol* 1990; **23**: 347–50.
38 Gedalia A, Adar A, Gorodischer R. Familial Mediterranean fever in children. *J Rheumatol* 1992; **19** (Suppl. 35): 1–9.
39 Dahl EV, Baggenstoss AH, deWeerd JH. Testicular lesions of periarteritis nodosa, with special reference to diagnosis. *Am J Med* 1960; **28**: 222–8.
40 Lee LM, Moloney PJ, Wong HCG *et al.* Testicular pain: an unusual presentation of polyarteritis nodosa. *J Urol* 1983; **129**: 1243–4.
41 Wright LF, Bicknell SL. Systemic necrotizing vasculitis presenting as epididymitis. *J Urol* 1986; **136**: 1094.
42 Rivollier C, Martin L, Machet L *et al.* Genital papules revealing a Churg–Strauss syndrome. *Ann Dermatol Venereol* 2002; **129**: 1049–52.

Non-sexually transmitted infections

Staphylococcal cellulitis

Cellulitis may affect the penis. Piercing and genital jewellery predispose to infection. Cellulitis and abscess formation can

complicate cysts, sinuses and fistulae, and sexually transmitted infections. The exact relationship between episodes of acute infection and chronic penile oedema, which often is complicated by cellulitis, is uncertain.

Anogenital infection is a serious complication in patients with malignant disease, and potentially life-threatening necrotizing fasciitis and Fournier's gangrene may occur.

Streptococcal dermatitis/perianal cellulitis

This syndrome in children [1] probably also has a corollary in adults [2], but it is much more common in boys in whom, if the penis is involved, there may be dysuria, erythema and swelling of the penis and balanoposthitis. Bullous necrotic erysipelas of the penis due to *Streptococcus pyogenes* has been reported [3].

Chronic penile oedema

Chronic penile lymphoedema is a relatively rare, reactive, disfiguring condition that causes sexual dysfunction and phimosis [4]. It has been called tumorous lymphoedema or elephantiasis verrucosa nostra [5]. Evidence of streptococcal infection may be present, and this could lead to irreversible lymphatic damage. Other cases seem to be idiopathic and are perhaps brought about by primary hypoplastic lymphatics. Some patients have a coexistent penile dermatosis. Few cases of chronic penile oedema have been reported [4,6,7] and the aetiopathogenesis may have been misunderstood.

Penoscrotal oedema has also been attributed to continuous ambulatory peritoneal dialysis [8], amputation of septic limbs in diabetes [9], acute necrotizing pancreatitis [10], streptococcal infections [11], and Crohn's disease, which may be occult and asymptomatic [12]. Filariasis and pelvic mass lesions should be excluded. Penile venereal oedema has been associated with gonococcal and herpes infection, and scabies infestation, and resolves after treatment of the underlying disease [13]. Similarly, childhood penile oedema is self-limiting [14]. It is possible that some cases of chronic penile oedema are related to any of the above factors and/or temporally unrelated but repetitive sexually transmitted disease. A persistent lymphatic insult from whatever cause could result in an inflammatory process affecting genital and pelvic lymphatic vessels and nodes. Imaging of lymphatic channels is not particularly helpful [15].

Patients with chronic penile oedema present with chronic swelling of the penis, foreskin, scrotum, pubic mound, buttocks and thighs, which may be warm and red. There may be intercurrent attacks of cellulitis and/or erysipelas with systemic upset. Acute attacks require admission to hospital and treatment with systemic broad-spectrum antibiotics; a short course of prednisolone may also be helpful. Investigations should be directed at elucidating possible underlying causes (such as streptococcal infection (ASOT), Crohn's disease and sarcoid) and predisposing factors, as discussed above (see also Tables 71.25–71.27). All cases of penoscrotal oedema should be treated aggressively at first presentation, because the more chronic the genital lymphoedema the more difficult it is to treat, both medically and surgically [16]. Aims of management of chronic penile oedema must be prophylaxis against further infective episodes and aggressive treatment of relapses.

Long-term treatment with erythromycin, clarithromycin, clindamycin, trimethoprim or ciprofloxacin appears to ameliorate and stabilize the process, and improves the appearance and function of the penis. The success of this approach supports the importance of infection as a factor in the perpetuation, if not initiation, of the process. Medical control with antibiotics then allows surgical intervention in the form of circumcision. Plastic repair may be necessary after excision of affected tissue [17,18].

References

1 Peltola H. Images in clinical medicine: bacterial perianal dermatitis. *N Engl J Med* 2000; **342**: 1877.
2 Neri I, Bardazzi F, Marzaduri S, Patrizi A. Perianal streptococcal dermatitis in adults. *Br J Dermatol* 1996; **135**: 796–8.
3 Akkilic M, Weger W, Kranke B, Komericki P. Bullous necrotic lesion of the penis. *J Eur Acad Dermatol Venereol* 2006; **20**: 1024–5.
4 Porter WM, Dinneen M, Bunker C. Chronic penile lymphoedema. *Arch Dermatol* 2001; **137**: 1108–10.
5 Luelmo J, Tolosa C, Prats J *et al.* Tumorous lymphoedema of the penis: report of verrucous elephantiasis—a brief case. Preliminary note. *Actas Urol Esp* 1995; **19**: 585–7.
6 Thomas JA, Matanhelia SS, Rees RWM. Recurrent adult idiopathic penile oedema: a new clinical entity? *Hosp Update* 1993; **Dec**: 667–8.
7 Geyer H, Geyer A, Schubert J. Erysipelas and elephantiasis of the scrotum: surgical and drug therapy. *Urologe A* 1995; **34**: 59–61.
8 Abraham G, Blake PG, Mathews R *et al.* Genital swelling as a surgical complication of continuous ambulatory peritoneal dialysis. *Surg Gynecol Obstet* 1990; **170**: 306–8.
9 Fahal AH, Suliman SH, Sharfi AR, el Mahadi EM. Acute idiopathic scrotal oedema in association with diabetic septic foot. *Diabetes Res Clin Pract* 1993; **21**: 197–200.
10 Choong KK. Acute penoscrotal oedema due to acute necrotizing pancreatitis. *J Ultrasound Med* 1996; **15**: 247–8.
11 Mendelson J, Miller M. Streptococcal venereal edema of the penis. *Clin Infect Dis* 1997; **24**: 516–7.
12 Saha M, Edmonds E, Martin J, Bunker CB. Penile lymphoedema in association with asymptomatic Crohn's disease. *Clin Exp Dermatol* 2009; **34**: 88–90.
13 Wright RA, Judson FN. Penile venereal edema. *JAMA* 1979; **241**: 157–8.
14 Brandes SB, Chelsky MJ, Hanno PM. Adult acute idiopathic scrotal oedema. *Urology* 1994; **44**: 602–5.
15 Samsoen M, Deschler JM, Servelle M *et al.* Le lymphoedeme penoscrotal: two observations. *Ann Dermatol Vénéréol* 1981; **108**: 541–6.
16 Malloy TR, Wein AJ, Gross P. Scrotal and penile lymphedema: surgical considerations and management. *J Urol* 1983; **130**: 263–5.
17 Morey AF, Meng MV, McAninch JW. Skin graft reconstruction of chronic genital lymphoedema. *Urology* 1997; **50**: 423–6.
18 Muehlberger T, Homann HH, Kuhnen C *et al.* Aetiology, clinical aspects and therapy of penoscrotal lymphoedema. *Chirurg* 2001; **72**: 414–8 [in German].

Ecthyma gangrenosum

Ecthyma gangrenosum has a predilection for the acral and anogenital regions, and may affect the penis in isolation, leading to gangrene [1]. The prognosis is poor. A case has been reported that was probably caused by direct arterial septic embolization of the penis from femoral heroin injection [2].

Fournier's gangrene

Fournier's gangrene is analogous to necrotizing fasciitis and Meleney's gangrene. In 1883, the Parisian dermatologist Alfred Fournier described five cases of spontaneous genital gangrene and ulceration, but Baurienne (1764) probably first reported this condition [3]. The disease begins with urethral or appendageal polybacterial infection. Most of the organisms isolated are resident urethral

Table 71.21 Risk factors for Fournier's gangrene.

Diabetes mellitus
Alcoholism
Anogenital infection
Chemotherapy
HIV
Post-instrumentation (especially in the immunocompromised)
Postoperative (urological and colorectal)
Heroin addiction
Trauma
Unconventional sexual practices

Table 71.22 Differential diagnosis of Fournier's gangrene. (After Bunker [16]. © 2004, with permission from Elsevier.)

Trauma
Herpes simplex
Cellulitis (streptococcal, staphylococcal)
Streptococcal necrotizing fasciitis
Gonococcal balanitis and oedema
Ecthyma gangrenosum
Allergic vasculitis
Polyarteritis nodosa
Necrolytic migratory erythema
Vascular occlusion syndromes
Warfarin necrosis

or lower gastrointestinal flora, and most patients have mixed infections. In children, staphylococci and streptococci are most commonly isolated [4]. A necrotizing vasculitis, possibly exotoxin-mediated, ensues with devastating consequences for involved skin, subcutis, fascia and muscle. It is held to be the human counterpart of the local Shwartzman phenomenon [5,6]. Painful, erythematous swelling of the genitals (particularly the scrotum [7], where a dark red or a black spot may appear [8]), perianal or lower abdominal skin, no suppuration, crepitus [9], marked systemic toxicity (may be absent in children [4]), and urinary retention, describe a typical presentation. Necrosis of skin and deeper tissues can occur rapidly, and there is a very high mortality unless the diagnosis is made promptly and radical management undertaken. Plain X-rays may show soft-tissue gas [10]. Predisposing factors are listed in Table 71.21. Preceding surgery, including vasectomy and instrumentation, including genital piercing [11], especially in patients with the listed risk factors, is particularly important. The differential diagnosis is given in Table 71.22.

If a diagnosis of Fournier's gangrene is made, radical surgical debridement of all affected tissue is undertaken and broad-spectrum systemic antibiotic therapy initiated. Plastic repair can be undertaken if the patient survives [7]. Hyperbaric oxygen, high-dose systemic steroids and unprocessed honey treatment have been used [6,12–14]. In adults, the mortality is approximately 25%. Children can be treated with more conservative surgery, and their mortality rate is lower [4,15].

References

1 Rabinowitz R, Lewin EB. Gangrene of the genitalia in children with *Pseudomonas* sepsis. *J Urol* 1980; **124**: 431–2.

2 Cunningham DL, Persky L. Penile ecthyma gangrenosum. *Urology* 1989; **34**: 109–10.

3 Smith GL, Bunker CB, Dineen MD. Fournier's gangrene. *Br J Urol* 1998; **81**: 347–55.

4 Adams JR Jr, Mata JA, Venable DD *et al*. Fournier's gangrene in children. *Urology* 1990; **35**: 439–41.

5 van der Meer JB, de Jong MCJM. Recent aspects of pathogenesis and therapy of fulminant elapsing necrosis. *Neth J Med* 1992; **40**: 244–53.

6 Schultz ES, Diepgen TL, von den Driesch P, Hornstein OP. Systemic corticosteroids are important in the treatment of Fournier's gangrene: a case report. *J Dermatol* 1995; **133**: 633–5.

7 Ferreira PC, Reis JC, Amarante JM *et al*. Fournier's gangrene: a review of 43 reconstructive cases. *Plast Reconstr Surg* 2007; **119**: 175–84.

8 Bubrick MP, Hitchcock CR. Necrotizing anorectal and perineal infection. *Surgery* 1979; **86**: 655–62.

9 Chang I-J, Lee C-C, Chen S-Y. Fulminant gangrenous and crepitating scrotum. *Arch Dermatol* 2006; **142**: 797–8.

10 Fisher JR, Conway ML, Takeshita RT *et al*. Necrotizing fasciitis: importance of roentgenographic studies for soft-tissue gas. *JAMA* 1979; **241**: 803–6.

11 Ekelius L, Björkman H, Kalin M, Fohlman J. Fournier's gangrene after genital piercing. *Scand J Infect Dis* 2004; **36**: 610–2.

12 Chantarasak ND, Basu PK. Fournier's gangrene following vasectomy. *Br J Urol* 1988; **61**: 538–9.

13 van der Meer JB, van der Wal T, Bos WH *et al*. Fournier's gangrene: the human counterpart of the local Shwartzman phenomenon? *Arch Dermatol* 1990; **126**: 1376–7.

14 Tahmaz L, Erdemir F, Kibar Y *et al*. Fournier's gangrene: report of thirty-three cases and a review of the literature. *Int J Urol* 2006; **13**: 960–7.

15 Sussman SJ, Schiller RP, Shashikumar VL. Fournier's syndrome: report of three cases and a review of the literature. *Am J Dis Child* 1978; **132**: 1189–91.

16 Bunker CB. *Male Genital Skin Disease*. London: Saunders, 2004.

Trichomycosis pubis

Trichomycosis pubis causes asymptomatic yellow, red or black micronodules around hair shafts [1]. Pubic and axillary hair may be involved. The skin is normal but the sweat may be discoloured. Trichomycosis pubis is rare in Western dermatological practice but is common in the Middle East [2], and may occur concomitantly with trichosporosis in India [3]. It is caused by *Corynebacterium* spp. The differential diagnosis includes true mycoses such as white or black piedra. Treatment is with topical benzoic acid, salicylic acid, clindamycin or naftifine [1].

Tuberculosis

Tuberculosis of the penis is rare [4] but important given the resurgence of the disease. Primary penile ulceration (solitary and multiple), with or without inguinal lymphadenopathy, caused by sexual infection or contact with infected clothing may occur [5], or the ulceration may be secondary to tuberculosis elsewhere (e.g. the lung) [6]. A cold abscess (presenting as erectile impotence) has been reported [7]. Tuberculides have involved the penis, including in isolation [8].

Non-syphilitic spirochaetal ulcerative balanoposthitis

This condition is recognized in the Tropics and South Africa, presenting as large serpiginous foul-smelling ulcers in uncircumcised men, associated in some with non-tender inguinal lymphadenopathy. Treatment is with penicillin or metronidazole [9].

Yaws

An ulcerated, crusted and papillomatous lesion has been reported on the prepuce as part of disseminated early yaws (with other skin

lesions elsewhere) in a patient in an endemic region. Several family members were also infected. The genital lesion probably arose from autoinnoculation [10].

Candidosis

Genitourinary physicians maintain that *Candida* can be the cause of urethritis and balanoposthitis [11] and cause erosive disease of the glans and prepuce. The glans penis and prepuce may be eroded. *Candida* of the penis (with a prevalence of approximately 10% of that of vaginal candidosis) has attracted very little research interest [12]. However, *Candida* may be more often a secondary pathogen than a sexually acquired infection. Observing the signs of candidosis, or demonstrating the presence of the organism, does not prove that it is the cause of all the symptoms and signs. An underlying dermatological or medical cause should be excluded. The symptoms and signs of *Candida* may be more florid than the underlying predisposing cause. Medical causes include diabetes mellitus, iatrogenic immunosuppression and systemic antibiotic treatment. Although oropharyngeal candidosis is almost invariably found in HIV infection, candidal balanoposthitis is not generally associated, perhaps because it is overlooked or because many patients take long-term imidazole antifungals orally.

Candida albicans is such a ready opportunist organism because it is a part of the resident flora of the gastrointestinal tract and may be retrieved from intertriginous areas, including the preputial folds, in the absence of symptoms and signs. Candidal balanoposthitis could be a sexually transmitted disease that may have an affinity for the anatomically or physiologically abnormal penis, or in individuals predisposed by other factors or disease, and where there is chronic vaginal or anal carriage in a partner. Screening should be performed for other sexually transmitted diseases.

Diagnosis is discussed in Chapter 36. Underlying disease should be identified and treated, and predisposing factors rectified. Treatment includes topical nystatin, clioquinol or an imidazole, often very usefully combined with hydrocortisone or a moderately potent corticosteroid. In severe disease, an oral imidazole may be indicated.

Tinea

Tinea of the penis or scrotum is uncommon and when it occurs it is usually associated with crural disease. Rarely encountered is the occurrence of tinea on the glans penis as a seat of itch or pain, and producing an erythematous patch or a crop of scaly papules [13–18]. Penile tinea in India has been associated with occlusion resulting from the wearing of a langota—a T-shaped piece of cloth tied over the genitalia [15].

Deep fungal infections

Although histoplasmosis is a common cause of disseminated fungal infection in the USA, urological and anogenital disease (usually ulceration and adenopathy in an ill patient) is rare [19,20]. An otherwise well man with a small warty nodule on the glans penis has been reported [21]. One patient with a penile ulcer transmitted the disease venereally to his wife [22]. In blastomycosis, although the genitourinary tract (prostate and epididymis) is involved in 20–30% of cases [23], involvement of the genital skin is rare. However, lesions of the prepuce and perianal skin have been recorded [24,25]. Paracoccidioidomycosis can be the cause of scrotal swelling and genital nodules and erosions [26]. Zygomycosis is usually regarded as rhinocerebral infection but a diabetic with purulent lesions of the penis has been described [27].

References

1 Rosen T, Krawczynska AM, McBride ME, Ellner K. Naftifine treatment of trichomycosis pubis. *Int J Dermatol* 1991; **30**: 667–9.
2 Lestringant GG, Khalil I, Fletcher S. Is the incidence of trichomycosis of genital hair underestimated? *J Am Acad Dermatol* 1991; **24**: 297–8.
3 Kamalam A, Senthamilselvi G, Ajithadas K, Thambiah AS. Cutaneous trichosporosis. *Mycopathologia* 1988; **101**: 167–75.
4 Minkin W, Frank SB, Cohen HJ. Penile granuloma. *Arch Dermatol* 1972; **106**: 756.
5 Rossi R, Urbano F, Tortoli E *et al.* Primary tuberculosis of the penis. *J Eur Acad Dermatol Venereol* 1999; **12**: 174–6.
6 Burns DA, Sarkany I. Tuberculous ulceration of the penis. *Proc R Soc Med* 1976; **69**: 883–4.
7 Murali TR, Raja NS. Cavernosal cold abscess: a rare cause of impotence. *Br J Urol* 1998; **82**: 929–30.
8 Kashima M, Mori K, Kadono T *et al.* Tuberculide of the penis without ulceration. *Br J Dermatol* 1999; **140**: 757–9.
9 Piot P, Duncan M, van Dyck E *et al.* Ulcerative balanoposthitis associated with non-syphilitic spirochaetal infection. *Genitourin Med* 1986; **62**: 44–6.
10 Engelkens HJ, Judanarso J, van der Sluis JJ *et al.* Disseminated early yaws: report of a child with a remarkable genital lesion mimicking venereal syphilis. *Pediatr Dermatol* 1990; **7**: 60–2.
11 Wisdom A, Hawkins DA. *Diagnosis in Color. Sexually Transmitted Diseases*, 2nd edn. London: Mosby-Wolfe, 1997: 154–6.
12 Odds FC. Genital candidiasis. *Clin Exp Dermatol* 1982; **7**: 345–54.
13 Pillai KG, Singh G, Sharma BM. Trichophyton rubrum: infection of the penis. *Dermatologica* 1975; **100**: 252–4.
14 Kumar B, Talwar P, Kaur S. Penile tinea. *Mycopathologia* 1981; **75**: 169–72.
15 Pandey SS, Chandra S, Guha PK, Kaur P, Singh G. Dermatophyte infection of the penis: association with a particular undergarment. *Int J Dermatol* 1981; **20**: 112–4.
16 Dekio S, Jidio J. Tinea of the glans penis. *Dermatologica* 1989; **178**: 112–4.
17 Dekio S, Qin LM, Jidio J. Tinea of the glans penis: report of a case presenting a crop of papules. *J Dermatol* 1991; **18**: 52–5.
18 Pielop J, Rosen T. Penile dermatophytosis. *J Am Acad Dermatol* 2001; **44**: 864–7.
19 Jayalakshmi P, Goh KL. Disseminated histoplasmosis presenting as penile ulcer. *Aust NZ J Med* 1990; **20**: 175–6.
20 Preminger B, Gerard PS, Lutwick L *et al.* Histoplasmosis of the penis. *J Urol* 1993; **149**: 848–50.
21 Mankodi RC, Kanvinde MS, Mohapatra LN. Penile histoplasmosis: a case report. *Indian J Med Sci* 1970; **24**: 354–6.
22 Sills M, Schwartz A, Weg JG, Arbor A. Conjugal histoplasmosis: a consequence of progressive dissemination in the index case after steroid therapy. *Ann Intern Med* 1973; **79**: 221–4.
23 Craig MW, Davey WN, Green RA. Conjugal blastomycosis. *Am Rev Respir Dis* 1970; **102**: 86–90.
24 Eickenberg H, Amin M, Lich R. Blastomycosis of the genitourinary tract. *J Urol* 1975; **113**: 650–2.
25 English JC III, Laws RA, Keough GC *et al.* Dermatoses of the glans penis and prepuce. *J Am Acad Dermatol* 1997; **37**: 1–24; quiz 25–6.
26 Severo LC, Kauer CL, Oliveira F *et al.* Paracoccidioidomycosis of the male genital tract: report of 11 cases and a review of Brazilian literature. *Rev Inst Med Trop Sao Paulo* 2000; **42**: 37–40.
27 Cohen-Ludmann C, Kerob D, Feuilhade M *et al.* Zygomycosis of the penis due to *Rhizopus oryzae* successfully treated with surgical debridement and a combination of high dose liposomal and topical amphotericin B. *Arch Dermatol* 2006; **142**: 1657–8.

Miscellaneous infections

Bacillary angiomatosis (see Chapter 35) is important in the differential diagnosis of AIDS-related Kaposi's sarcoma. A case in which

the presenting tender red nodules affected the scrotum and groins has been published [1].

Buruli ulcer of the penis and scrotum due to *M. ulcerans* is a rare disease. Medical treatment is disappointing and lesions need excision and grafting [2].

Male genital involvement with leprosy is uncommon, but there are reports, and it may occur in isolation [3–5].

The penis is rarely affected by pityriasis versicolor and probably almost never in isolation [6,7]. However, *Malassezia* yeasts may colonize both the circumcised and uncircumcised penis [8]. Occasionally, the anterior pelvic girdle is the site involved.

One case only of superficial phaeohyphomycosis manifesting as multiple, 1–3 mm, pigmented papules, resembling seborrhoeic keratoses, on the scrotum of an HIV-positive patient has been described. Microscopy showed a mass of mycelia, and two dematiaceous fungi were cultured [9].

Genital herpes simplex may be acquired non-sexually (e.g. during contact sports such as rugby football [10]). A phenomenon of chronic erosive and verrucous herpes as part of immunoreconstitution disease has been described in HIV infection [11].

Sacral herpes zoster is discussed in Chapter 33. Lesions may be found on the scrotum and penis [12], and urinary retention and constipation can occur.

It is not unusual for the herald patch of pityriasis rosea (thought now to be due to HHV6/7) to appear on suprapubic skin or in the groin. Incomplete or limited presentations (e.g. affecting the pelvic girdle) are not rare, although careful examination may elicit another patch on the neck or in the axilla.

A distinctive sequel of Chikungunya (a novel togavirus arboviral infection that causes fever, headache and arthralgia) may be ulcers in the penoscrotal region [13]. Amoebiasis can rarely present as a painful ulcerative balanitis, with swelling, frequency, dysuria and retention [14]. Self-inoculation from concomitant intestinal infection, by heterosexual intercourse where the female partner has amoebic vaginitis, or by sodomy, are the putative mechanisms. Amoebiasis as the cause of genital ulceration should lead to the suspicion of underlying HIV infection [15].

Cutaneous leishmaniasis can affect the genitalia [16,17]. An erythematous scaly plaque on the glans [18] and a sporotrichoid distribution on the shaft of the penis [19] have been reported. Post-kala-azar dermal leishmaniasis of the penis and scrotum has been described. Rarely, genital skin lesions may lead to the diagnosis of schistosomiasis. They occur because ova shed by worms enter the perineal vessels [20]. The papules and nodules may be skin-coloured, pink or brown, scattered or grouped, affecting the penis and scrotum. They can spread onto the perineum and around the anus, and may develop into soft, warty, vegetating lesions. Ulceration is rare and, even more rarely, concomitant carcinoma has been reported [20].

The anogenital consequences of onchocerciasis are 'leopard skin' hypopigmentation (the scrotum is commonly involved), ileal crest and scrotal nodules, 'hanging groin', and scrotal enlargement [21,22]. The differential diagnosis of the scrotal enlargement includes bancroftian filariasis [23]. Other filarial infections can lead to mild hydrocoele or gross elephantiasis. Filariasis can cause secondary lymphangiectasis. Excision, grafting and genital reconstruction can be undertaken [24].

References

1 Fagan WA, Skinner SM, Ondo A *et al.* Bacillary angiomatosis of the skin and bone marrow in a patient with HIV infection. *J Am Acad Dermatol* 1995; **32**: 510–2.
2 Sica A, Dekou A, Kaba L *et al.* Genital site of Buruli ulcer (BU): clinical and therapeutic aspects. *Prog Urol* 2005; **15**: 736–8.
3 Bunker CB. *Male Genital Skin Disease*. London: Saunders, 2004.
4 Mukhopadhyay AK. Primary involvement of penile skin in lepromatous leprosy. *Indian J Lepr* 2005; **77**: 317–21.
5 Kar BR, Ebenezer G, Job CK. Penile tuberculoid leprosy in a five year old boy. *Indian J Dermatol Venereol Leprol* 2005; **71**: 125–7.
6 Avram A, Rousselet G, Benazeraf C, Grupper C. 'Pityriasis versicolor' de la verge. *Bull Soc Francaise Dermatol Syphiligr* 1973; **80**: 607–8.
7 Aljabre SHM, Sheikh YH. Penile involvement in pityriasis versicolor. *Trop Geogr Med* 1994; **46**: 184–7.
8 Aridogan IA, Ilkit M, Izol V, Ates A. *Malassezia* and *Candida* colonisation on glans penis of circumcised men. *Mycoses* 2005; **48**: 352–6.
9 Duvic M, Lowe L. Superficial phaeohyphomycosis of the scrotum in a patient with the acquired immunodeficiency syndrome. *Arch Dermatol* 1987; **123**: 1597–9.
10 Estéve E, Gironet N, Barthez JP, Maitre F. Case for diagnosis: herpes rugbiorum. *Ann Dermatol Vénéréol* 1998; **125**: 527–8.
11 Fox PA, Barton SE, Francis N *et al.* Chronic erosive herpes simplex virus infection of the penis: a possible immune reconstitution disease. *HIV Med* 1999; **1**: 10–8.
12 Spray A, Glaser DA. Herpes zoster of the penis: an unusual location for a common eruption. *J Am Acad Dermatol* 2002; **47**: S177–9.
13 Mishra K, Husain J, Rajawat V. Ulcers in penoscrotal region, post chikungunya. *Proceedings of the Indian Association of Dermatology, Venereology and Leprology Meeting*. Gangigarh, India: 2008. P-136, P-13.
14 Cooke RA, Rodriguez RB. Amoebic balanitis. *Med J Aust* 1964; **5**: 114–7.
15 Gbery IP, Dheja D, Kacou DE *et al.* Chronic genital ulcerations and HIV infection: 29 cases. *Med Trop* 1999; **59**: 279–82.
16 Cain C, Seabury-Stone M, Thieburg M, Wilson ME. Non-healing genital ulcers. *Arch Dermatol* 1994; **130**: 1311–6.
17 Schubach A, Cuzzi-Maya T, Goncalves-Costa SC *et al.* Leishmaniasis of glans penis. *J Eur Acad Dermatol Venereol* 1998; **10**: 226–8.
18 Grunwald MH, Amichai B, Trau H. Cutaneous leishmaniasis on an unusual site: the glans penis. *Br J Urol* 1998; **82**: 928.
19 Masmoudi A, Boudaya S, Bouzid L *et al.* Penile sporotrichoid cutaneous leishmaniasis. *Bull Soc Pathol Exot* 2005; **98**: 380–1.
20 Adeyemi-Doru FAB, Osoba OA, Junaid TA. Perigenital cutaneous schistosomiasis. *Br J Vener Dis* 1979; **55**: 446–9.
21 Zawahry ME. Cutaneous amoebiasis. *Indian J Dermatol* 1966; **11**: 77–8.
22 Akogun OB, Akoh JI, Hellandendu H. Non-ocular clinical onchocerciasis in relation to skin microfilaria in the Taraba River Valley, Nigeria. *J Hyg Epidemiol Microbiol Immunol* 1992; **36**: 368–83.
23 McMahon JE, Simonsen PE. Filiariases: onchocerciasis. In: Cook GC, ed. *Manson's Tropical Diseases*, 20th edn. London: Saunders, 1996: 1338–51.
24 Das S, Tuerk D, Amar AD, Sommer J. Surgery of male genital lymphedema. *J Urol* 1983; **129**: 1240–2.

Dermatological aspects of sexually transmitted disease

MRSA

MRSA presents increasing challenges in general dermatology. There is emerging evidence that community-associated MRSA can be a sexually transmitted disease [1].

Syphilis

Syphilis (see Chapter 34) is endemic throughout the world. It is enjoying a resurgence in both heterosexual and homosexual populations [2]. All manifestations of syphilis can affect the genital region [3]. In 1899, primary syphilis was reported in New York to be a complication of Mosaic circumcision rites in newborn Jewish boys where rabbis used the mouth as a means of stopping

haemorrhage [4]. Balanoposthitis can complicate and obscure penile chancre. The granulomatous gumma may affect the genital area as an ulcer, a white plaque or as an atrophic scar. Pseudochancre redux describes gummatous (tertiary stage) recurrence at the site of the primary chancre [5]; it is very rare.

Viral warts

The burden of genital infection with HPV is enormous [6]. Circumcised men are more likely to have genital warts than the uncircumcised, but when warts are present in uncircumcised men they are more likely to be distally situated [7]. The risk of acquiring genital warts is significantly reduced by using condoms [8]. Clinically inapparent disease may present as balanoposthitis [9]. Subclinical or latent genital HPV infection may be 100 times more common than classical condylomas [10]. The prevalence of HPV in the genital tract of men is similar to that in women, and is between 3% and 45% depending on the age and population [11]. The estimated lifetime risk of acquiring HPV sexually is greater than 50%, and may be 80% [10]. Only 25% of the population of the USA were thought to have no prior or current genital HPV infection in 1997 [12]. The 5% acetic acid test is not a very specific aid to the identification of warts or dysplastic lesions [13]. Accurate diagnosis of HPV infection can probably only be achieved by molecular methods [14]. Congenital and acquired immunosuppression increases the susceptibility of the anogenital region to HPV infection and reactivation and progression to dysplasia and frank malignancy [15]. Topical steroid treatment of genital dermatoses may reactivate genital warts [16].

The clinical diagnosis of HPV infection is usually certain, but condylomata lata (secondary syphilis), lichen planus, molluscum contagiosum, Bowenoid papulosis and pearly penile papules enter the differential diagnosis. Solitary lesions have a wider differential diagnosis, including giant condyloma, squamous carcinoma and transitional cell carcinoma of the distal urethra, which can present as a warty lesion at the urethral meatus [17]. Biopsy should be performed if there is diagnostic doubt. Patients with anogenital warts and their partners may require full sexually transmitted disease and sometimes colorectal assessment. Treatment can be challenging [3,6].

Molluscum contagiosum

Molluscum contagiosum is discussed in Chapter 33. Young men are commonly seen with penile and pubic lesions and it is assumed that this is a sexually transmitted infection, but this may not always be the case.

Human immunodeficiency virus infection

Ulcerative genital disease is a risk factor for HIV [18,19], but anogenital ulceration may be a consequence of HIV infection (see Chapter 35) [20]. Table 71.23 lists the main causes. Biopsy, with special stains and culture, is mandatory. Other genital problems in HIV, such as psoriasis, warts, intraepithelial neoplasia, squamous carcinoma and Kaposi's sarcoma, are discussed elsewhere.

Phthiriasis

Phthiriasis (see Chapter 38) can present with marked genital and pubic itching with few overt physical signs, or as an infected genitocrural and pubic eczema that conceals the underlying primary signs. In hirsute men, the abdomen, chest, axillae and thighs may also be involved. Screening for other sexually transmitted diseases should be offered to the patient and partner(s).

Table 71.23 Causes of penile and scrotal ulcers in HIV infection.

Pseudomonas
Syphilis
Chancroid
Herpes simplex
Penicilliosis
Amoebiasis
Fournier's gangrene
Squamous cell carcinoma
Kaposi's sarcoma
Drugs (e.g. foscarnet)



Fig. 71.14 Papules on the penis in scabies. (Courtesy of Dr C. White, University Hospital of North Durham, Durham, UK.)

Scabies

Scabies (see Chapter 38) may present with anogenital itch, 'folliculitis' (including of the buttocks) and penile, scrotal and pubic nodules (Fig. 71.14). An AIDS patient with single non-pruritic, 'crusted' lesion on the glans penis has been described [21]. Topical pimecrolimus has been used with benefit in the treatment of steroid-resistant post-scabies nodules [22].

Miscellaneous infections

Human bite injuries acquired during orogenital contact usually heal well but a penile ulcer infected with the oral flora organism *Eikenelia corrodens* has been reported [23].

References

1 Roberts JR, McCawley L, Laxton M, Trumbo H. Genital community-associated methicillin resistant *Staphylococcus aureus* infection can be a sexually transmitted disease. *Ann Emerg Med* 2007; **50**: 93–4.
2 Angus J, Langan SM, Stanway A *et al.* The many faces of secondary syphilis: a re-emergence of an old disease. *Clin Exp Dermatol* 2006; **31**: 741–5.
3 Bunker CB. *Male Genital Skin Disease*. London: Saunders, 2004.
4 Rosenbaum SN. Circumcision-syphilis. *J Cutan Genito-Urin Dis* 1899; **7**: 317.
5 Evans AL, Summerly R. Pseudo-chancre redux with negative serology: a case report. *Br J Vener Dis* 1964; **40**: 222–4.
6 Fox PA, Tung M-Y. Human papillomavirus: burden of illness and treatment cost considerations. *Am J Clin Dermatol* 2005; **6**: 365–81.
7 Cook LS, Koutsky LA, Holmes KK. Clinical presentation of genital warts among circumcised and uncircumcised heterosexual men attending an urban STD clinic. *Genitourin Med* 1993; **69**: 262–4.
8 Wen LM, Estcourt CS, Simpson JM, Mindel A. Risk factors for the acquisition of genital warts: are condoms protective? *Sex Transm Infect* 1999; **75**: 312–6.
9 Lowhagen GB, Bolmstedt A, Ryd W, Voog E. The prevalence of the 'high risk' HPV types in penile condylomata-like lesions: correlation between HPV type and morphology. *Genitourin Med* 1993; **69**: 87–90.
10 von Krogh G. Clinical relevance and evaluation of genitoanal papilloma virus infection in the male. *Semin Dermatol* 1992; **11**: 229–40.
11 Aguilar LV, Lazcano-Ponce E, Vaccarella S *et al.* Human papillomavirus in men: comparison of different genital sites. *Sex Transm Infect* 2006; **82**: 31–3.
12 Koutsky L. Epidemiology of genital human papilloma virus infection. *Am J Med* 1997; **102** (5A): 3–8.
13 Voog E, Ricksten A, Olofsson S *et al.* Demonstration of Epstein–Barr virus DNA and human papillomavirus DNA in acetowhite lesions of the penile skin and the oral mucosa. *Int J STD AIDS* 1997; **8**: 772–5.
14 De Carvalho JJ, Syrjanen KJ, Jacobino M *et al.* Prevalence of genital human papillomavirus infections established using different diagnostic techniques among males attending a urological clinic. *Scand J Urol Nephrol* 2006; **40**: 138–43.
15 Daneshpouy M, Socic G, Clavel C *et al.* Human papillomavirus infection and anogenital condyloma in bone marrow transplant recipients. *Transplantation* 2001; **71**: 167–9.
16 Von Krogh G, Dahlman-Ghozlan K, Syrjänen S. Potential human papillomavirus reactivation following topical corticosteroid therapy of genital lichen sclerosus and erosive lichen planus. *J Eur Acad Dermatol Venereol* 2002; **16**: 130–3.
17 Langlois NEI, McClinton S, Miller ID. An unusual presentation of transitional cell carcinoma of the distal urethra. *Histopathology* 1992; **21**: 482–4.
18 Stamm WE, Handsfield HH, Rompalo AM *et al.* The asssociation between genital ulcer disease and acquisition of HIV infection in homosexual men. *JAMA* 1988; **260**: 1429–33.
19 Sardana K, Sehgal VN. Genital ulcer disease and human immunodeficiency virus: a focus. *J Dermatol* 2005; **44**: 391–405.
20 Cope R, Debou JM. AIDS and anorectal pathology. *Ann Chirurg* 1995; **49**: 310–6.
21 Perna AG, Bell K, Rosen T. Localised genital Norwegian scabies in an AIDS patient. *Sex Transm Infect* 2004; **80**: 72–3.
22 De Almeida HL Jr. Treatment of steroid-resistant nodular scabies with topical pimecrolimus. *J Am Acad Dermatol* 2005; **53**: 357–8.
23 Rosen T. Penile ulcer from traumatic orogenital contact. *Dermatol Online J* 2005; **11**: 18.

Benign tumours

The following entities are all encountered in the male genital area: pearly penile papules (angiofibromas); angiomas and angiokeratomas, and angiokeratoma corporis diffusum; basal cell papillomas (may be mistaken for viral warts [1] or Bowenoid papulosis); melanocytic naevi; inguinogenital epidermoid or (much rarer) pilar (including giant forms) cysts; these may become infected, and lesions containing molluscum contagiosum have been described [2,3].



Fig. 71.15 Scrotal calcinosis. (Courtesy of Dr D.A. Burns, Leicester, UK.)

Median raphe cysts

Congenital cystic median raphe anomalies may remain unobtrusive until adulthood. Cystic or nodular and linear swellings of the ventral penis occur near the glans. In adolescence or adulthood they may become traumatized or infected with staphylococci, gonococci or *Trichomonas* and present as tender, erythematous, purulent nodules [4]. Histologically, they are either dermoid or mucoid, depending on their embryology or epithelial lining [5]. Very rarely, the basal epithelial lining of the cysts may contain melanocytes, imparting a brown-black pigment to the lesion [6].

Mucoid cysts

These are rare lesions that are present at birth or develop in childhood as small, flesh-coloured, mobile cystic papules or nodules with no punctum, commonly on the ventral glans or foreskin, rarely in the perineum. They can be asymptomatic, become infected or interfere with intercourse. The histological features suggest that they arise from ectopic urethral tissue during embryological development [7].

Scrotal calcinosis

Scrotal calcinosis is a relatively common, benign, idiopathic disorder presenting as solitary or multiple, hard, smooth, white papules or nodules on the scrotum, rarely the penis (Fig. 71.15). Interestingly, these lesions are much rarer on the vulva [8]. Occasionally, they may become secondarily inflamed or infected following trauma.

Their occurrence was first described by Hutchinson [9]. Their origin has been debated: they have been said to arise from epidermoid cysts, eccrine duct milia, eccrine epithelial cysts, dystrophy of the dartos muscle, trauma and the presence of foreign bodies [4,10–20]. Scrotal calcinosis may occur after meconium peritonitis, with leakage of meconium through the processus vaginalis, and in testicular tumours such as teratomas, gonadoblastomas and Leydig cell tumours [17]. In endemic areas of onchocerciasis, calcified scrotal cysts may be caused by the living or dead nematodes, and patients have evidence of the disease elsewhere [21,22]. Onchocercal nodules are more common on the iliac crests and the rib cage (see Chapter 37).

The unsightly and embarrassing lesions can be treated by incision and eventration under local anaesthesia.

Idiopathic calcinosis of the penis is very rare [23]. A man who presented with a dome-shaped nodule on his glans has been described; the dystrophic calcinosis here was thought to derive from syringoma [24]. Other associations are trauma, self-injection with papaverine, Peyronie's disease and cytotoxic chemotherapy [23]. Metastatic calcinosis is due to renal failure and secondary hyperparathyroidism.

Verruciform xanthoma

Verruciform xanthoma mainly affects the mouth (see Chapter 69). The genitalia are the next most frequently involved area, where it presents as a painless, yellow-brown or red, verrucous, sessile or papillary plaque. Fewer than 20 cases have been reported [25]. The histological findings are hyperkeratosis, focal parakeratosis, acanthosis and fat-filled foam cells in the papillary dermis. Verruciform xanthoma is thought to represent epidermal degeneration, with keratinocyte lipid then taken up by dermal macrophages [26] or fibroblasts to form the foam cells. HPV 6 has been implicated in one case [27] but excluded in another [28]. Treatment is by surgical excision.

Miscellaneous benign tumours

Naevus comedonicus of the glans penis, generally devoid of pilosebaceous structures, has been reported [29]. Keloid is rare, but can complicate circumcision [30–32], and other surgery and trauma [33,34]. Keloid has been simulated on the dorsum of the penis by chronic oedema caused by a condom catheter [35]. Dermoid cyst affecting the penis, presenting with pain, swelling and suppuration from abscess formation, has been reported [36].

Acanthosis nigricans almost always affects the groins. In pseudoacanthosis nigricans, the associated obesity is almost always responsible for intertrigo and skin tags.

Penile colloid degeneration has been described, presenting as a dermal plaque of the dorsal shaft [37].

Some cases of multiple syringomata localized to the penis have been described, mimicking genital warts or lichen planus [38–41].

Other benign tumours that have been reported rarely to affect the genital area include apocrine cystadenoma [42,43], syringocystadenoma papilliferum [44], mixed syringocystadenoma papilliferum and papillary eccrine adenoma occurring in a scrotal condyloma [45], composite adnexal tumour [46], dermatofibroma [47], reticulohistiocytoma [48], giant cell fibroblastoma [49], connective tissue naevi (scrotum) [50], fibrous hamartoma of infancy [51], leiomyoma [47,52], genital smooth muscle hamartoma (scrotum) [53,54], traumatic neuroma [55], neurofibroma, neurilemoma, granular cell myoblastoma [47,56–58], varicosities/venous lakes, acquired capillary and cavernous haemangioma [47] (other angiomatous lesions are very much rarer, and controversy exists as to whether they represent a true neoplasm, herniation of the corpus spongiosum or vascularization of a haematoma or thrombus [59]), Masson's vegetant intravascular haemangioendothelioma [60], angiokeratoma circumscriptum of Mibelli [61], glomus tumour [50,62], port-wine stain, strawberry naevus [63–65], haemangiomas and PELVIS syndrome [66], epithelioid haemangioma [67], epithelioid haemangioendothelioma [47,68], pyogenic granuloma [69], angiolymphoid hyperplasia with eosinophilia/Kimura's disease (penis and spermatic cord) [70–72] and lymphangioma circumscriptum [73,74].

References

1 Friedman SJ, Fox BJ, Albert HL. Seborrhoeic keratoses of the penis. *Urology* 1987; **29**: 204–6.
2 Park SK, Lee JY, Kim YH *et al.* Molluscum contagiosum occurring in an epidermal cyst: report of three cases. *J Dermatol* 1992; **19**: 119–21.
3 Shah SS, Varea EG, Farsaii A *et al.* Giant epidermoid cyst of the penis. *Urology* 1979; **14**: 389–91.
4 Bunker CB. *Male Genital Skin Disease*. London: Saunders, 2004.
5 Oshin DR, Bowles WT. Congenital cysts and canals of the scrotal and perineal raphe. *J Urol* 1962; **88**: 406–8.
6 Urahashi J, Hara H, Yamaguchi Z, Morishima T. Pigmented median raphe cysts of the penis. *Acta Derm Venereol* 2000; **80**: 297–8.
7 Cole LA, Helwig EB. Mucoid cysts of the penile skin. *J Urol* 1976; **115**: 397–400.
8 Jamaleddine FN, Salman SM, Shbaklo Z *et al.* Idiopathic vulvar calcinosis: the counterpart of idiopathic scrotal calcinosis. *Cutis* 1988; **41**: 273–5.
9 Hutchinson J. Sebaceous gland tumours in the scrotum. Plate LXVIII. *Illustrations of Clinical Surgery*, Vol 2. Philadelphia: Blakiston, 1888.
10 King DT, Brosman S, Hirose FM, Gillespie LM. Idiopathic calcinosis of scrotum. *Urology* 1979; **14**: 92–4.
11 Shapiro L, Platt N, Torres-Rodriguez VM. Idiopathic calcinosis of the scrotum. *Arch Dermatol* 1970; **102**: 199–204.
12 Veress B, Malik MAO. Idiopathic scrotal calcinosis: a report of six cases from the Sudan. *East Afr Med J* 1975; **52**: 705–10.
13 Fisher BK, Dvoretsky I. Idiopathic calcinosis of the scrotum. *Arch Dermatol* 1978; **114**: 957.
14 Takayama H, Pak K, Tomoyoshi T. Electron microscopic study of mineral deposits in idiopathic calcinosis of the scrotum. *J Urol* 1982; **127**: 915–8.
15 Dare AJ, Axelsen RA. Scrotal calcinosis: origin from dystrophic calcification of eccrine duct milia. *J Cutan Pathol* 1988; **15**: 142–9.
16 Ito A, Sakamoto F, Ito M. Dystrophic scrotal calcinosis originating from benign eccrine epithelial cysts. *Br J Dermatol* 2001; **144**: 146–50.
17 Swinehart JM, Golitz LE. Scrotal calcinosis. *Arch Dermatol* 1982; **118**: 985–8.
18 Sarma DP, Weilbaecher TG. Scrotal calcinosis: calcification of epidermal cysts. *J Surg Oncol* 1984; **27**: 76–9.
19 Song DH, Lee KH, Kang WH. Idiopathic calcinosis of the scrotum: histopathologic observations of 51 nodules. *J Am Acad Dermatol* 1988; **19**: 1095–101.
20 Wright S, Navsaria H, Leigh IM. Idiopathic scrotal calcinosis is idiopathic. *J Am Acad Dermatol* 1991; **24**: 727–30.
21 Browne SG. Calcinosis circumscripta of the scrotal wall: the aetiological role of *Onchocerca volvulus*. *Br J Dermatol* 1962; **74**: 136–40.
22 Akogun OB, Akoh JI, Hellandendu H. Non-ocular clinical onchocerciasis in relation to skin microfilaria in the Taraba River Valley, Nigeria. *J Hyg Epidemiol Microbiol Immunol* 1992; **36**: 368–83.
23 Sánchez-Merino JM, Bouso-Montero M, Fernández-Flores A, García-Alonso J. Idiopathic calcinosis cutis of the penis. *J Am Acad Dermatol* 2004; **51**: S118–9.
24 Katoh N, Okabayashi K, Wakabayashi S *et al.* Dystrophic calcinosis of the penis. *J Dermatol* 1993; **20**: 114–7.
25 Mohsin SK, Lee MW, Amin MB *et al.* Cutaneous verruciform xanthoma: a report of five cases investigating the aetiology and nature of xanthomatous cells. *Am J Surg Pathol* 1998; **22**: 479–87.
26 Orchard GE, Jones EW, Jones RR. Verruciform xanthoma: an immunocytochemical study. *Br J Biomed Sci* 1994; **51**: 28–34.
27 Khaskhely NM, Uezato H, Kamiyama T *et al.* Association of human papillomavirus type 6 with a verruciform xanthoma. *Am J Dermatopathol* 2000; **22**: 447–52.
28 Erşahin C, Szpaderska AM, Foreman K, Yong S. Verucciform xanthoma of the penis not associated with human papillomavirus infection. *Arch Pathol Lab Med* 2005; **129**: e62–4.
29 Abdel-Aal H, Abdel-Aziz AM. Naevus comedonicus: report of three cases localized on glans penis. *Acta Derm Venereol* 1975; **55**: 78–80.
30 Warwick DJ, Dickson WA. Keloid of the penis after circumcision. *Postgrad Med J* 1993; **69**: 236–7.

31 Gürünlüoglu R, Bayramicli M, Dogan T, Numanoglu A. Unusual complications of circumcision. *Plast Reconstr Surg* 1999; **104**: 1938–9.
32 Parsons RW. A case of keloid of the penis. *Plast Reconstr Surg* 1966; **37**: 431–2.
33 Kormoczy I. Enormous keloid (?) on a penis. *Br J Plast Surg* 1978; **31**: 268–9.
34 Erdemir F. A rare complication after circumcision: keloid of the penis. *Int Urol Nephrol* 2006; **38**: 609–11.
35 Bang RL. Penile oedema induced by continuous condom catheter use and mimicking keloid scar. *Scand J Urol Nephrol* 1994; **28**: 333–5.
36 Tomasini C, Aloi F, Puiatti P, Caliendo V. Dermoid cyst of the penis. *Dermatology* 1997; **194**: 188–90.
37 Preston PW, Orpin SD, Muc R, Zaki I. Penile colloid degeneration. *Clin Exp Dermatol* 2006; **31**: 674–6.
38 Lo JS, Dijkstra JW, Bergfeld WF. Syringomas on the penis. *Int J Dermatol* 1990; **29**: 309–10.
39 Sola Casas MA, de Delas JS, Bellon PR, Gutierrez EQ. Syringomas localized to the penis. *Clin Exp Dermatol* 1993; **18**: 384–5.
40 Zalla JA, Perry HO. An unusual case of syringoma. *Arch Dermatol* 1971; **103**: 215–7.
41 Lipshultz RL, Kantor GR, Vonderheid EC. Multiple penile syringomas mimicking verrucae. *Int J Dermatol* 1991; **30**: 69.
42 de Dulanto F, Armijo-Moreno M, Camacho Martinez F. Nodular hidradenoma (apocrine cystadenoma) of the penis. *Ann Dermatol Syphiligr (Paris)* 1973; **100**: 417–22.
43 Flessati P, Camoglio FN, Bianchi S *et al.* An apocrine hidrocystoma of the scrotum: a case report. *Minerva Chir* 1999; **54**: 87–9.
44 Laube S, Suarez V, Hardwick N. A cluster of papules on the buttock of a teenager. *Clin Exp Dermatol* 2005; **30**: 197–8.
45 Coyne JD, Fitzgibbon JF. Mixed syringocystadenoma papilliferum and papillary eccrine adenoma occurring in a scrotal condyloma. *J Cutan Pathol* 2000; **27**: 199–201.
46 Obaidat NA, Ghazarian DM. A proliferating composite adnexal tumour of the penis: report of the first case. *J Clin Pathol* 2007; **60**: 567–9.
47 Dehner LP, Smith BH. Soft tissue tumours of the penis. *Cancer* 1970; **25**: 1431–47.
48 Miettinen M, Fetsch JF. Reticulohistiocytoma (solitary epithelioid histiocytoma): a clinicopathologic and immunohistochemical study of 44 cases. *Am J Surg Pathol* 2006; **30**: 521–8.
49 DeSanctis DP, Maglietta R, Miranda R, Betta PG. Giant cell fibroblastoma of the scrotum: a case report. *Tumori* 1993; **79**: 367–9.
50 Fork HE, Sanchez RL, Wagner RF Jr, Raimer SS. A new type of connective tissue nevus: isolated exophytic elastoma. *J Cutan Pathol* 1991; **18**: 457–63.
51 Thami GP, Jaswal R, Kanwar AJ. Fibrous hamartoma of infancy in the scrotum. *Pediatr Dermatol* 1998; **15**: 326.
52 Ohtake N, Maeda S, Kanzaki T, Shimoinaba K. Leiomyoma of the scrotum. *Dermatology* 1997; **194**: 299–301.
53 Hsiao GH, Chen JS. Acquired genital smooth-muscle hamartoma: a case report. *Am J Dermatopathol* 1995; **17**: 67–70.
54 Oiso N, Fukai K, Ishii M *et al.* A case of acquired smooth muscle hamartoma of the scrotum. *Clin Exp Dermatol* 2005; **30**: 523–4.
55 Cesinaro AM, Sigbinolfi P, Monari P, Neri F. Penile condylomata? Traumatic neuromas! *J Am Acad Dermatol* 2006; **54**: S54–S55.
56 Chan WP, Chiang SS, Huang AH, Lin CN. Penile frenulum neurilemoma: a rare and unusual genitourinary tract tumor. *J Urol* 1990; **144**: 136–7.
57 Littlejohn JO, Belman AB, Selby D. Plexiform neurofibroma of the penis in a child. *Urology* 2000; **56**: 669.
58 Fernandez MJ, Martino A, Khan H *et al.* Giant neurilemoma: unusual scrotal mass. *Urology* 1987; **30**: 74–6.
59 Senoh K, Miyazaki T, Kikuchi I *et al.* Angiomatous lesions of the glans penis. *Urology* 1981; **17**: 194–6.
60 Paul AB, Johnston CAB, Nawroz I. Masson's tumour of the penis. *Br J Urol* 1994; **74**: 261–2.
61 Bruce DH. Angiokeratoma circumscriptum and angiokeratoma scroti. *Arch Dermatol* 1960; **81**: 388–93.
62 Macaluso JN, Sullivan JW, Tomberlin S. Glomus tumor of the glans penis. *Urology* 1985; **25**: 409–10.
63 Eastridge RR, Carrion HM, Politano VA. Hemangioma of the scrotum, perineum and buttocks. *Urology* 1979; **14**: 61–3.
64 Gotoh M, Tsai S, Sugiyama T *et al.* Giant scrotal hemangioma with azoospermia. *Urology* 1983; **22**: 637–9.
65 Achauer BM, Vander Kam VC. Ulcerated anogenital hemangioma of infancy. *Plast Reconstr Surg* 1991; **87**: 861–8.
66 Girard C, Bigorre M, Guillot B, Bessis D. Pelvis syndrome. *Arch Dermatol* 2006; **142**: 884–8.
67 Srigley JR, Ayala AG, Ordóñez NG, van Nostrand AW. Epithelioid hemangioma of the penis: a rare and distinctive vascular lesion. *Arch Pathol Lab Med* 1985; **109**: 51–4.
68 Quante M, Patel NK, Hill S *et al.* Epithelioid hemangioendothelioma presenting in the skin: a clinicopathologic study of eight cases. *Am J Dermatopathol* 1998; **20**: 541–6.
69 Eickhorst KM, Nurzia MJ, Barone JG. Pediatric pyogenic granuloma of the glans penis. *Urology* 2003; **61**: 644.
70 Rao RN, Spurlock BO, Witherington R. Angiolymphoid hyperplasia with eosinophilia: report of a case with penile lesions. *Cancer* 1981; **47**: 944–9.
71 Van Gulik TM, Jansen JW, Taat CW. Kimura's disease in the spermatic cord: an unusual site of a rare tumor. *Neth J Surg* 1986; **38**: 93–5.
72 Sezer E, Erbil H, Koseoglu D *et al.* Angiolymphoid hyperplasia with eosinophilia mimicking Bowenoid papulosis. *Clin Exp Dermatol* 2007; **32**: 281–3.
73 Osborne GE, Chinn RJ, Francis ND, Bunker CB. Magnetic resonance imaging in the investigation of penile lymphangioma circumscriptum. *Br J Dermatol* 2000; **143**: 467–8.
74 Sadikoglu B, Kuran I, Özcan H, Gözü A. Cutaneous lymphatic malformation of the penis and scrotum. *J Urol* 1999; **162**: 1445–6.

Precancerous dermatoses and carcinoma *in situ*

Squamous hyperplasia

Such lesions consist of white patches or plaques. Although it is the most common epithelial abnormality found in association with invasive squamous carcinoma of the penis, histologically there is *no* cytological atypia; acanthosis and orthokeratotic hyperkeratosis are found [1].

Penile horn

It is rare for cutaneous horn to affect the penis [2]. Multiple lesions have been described in a 70-year-old man [3]. The underlying causes include pseudoepitheliomatous micaceous and keratotic balanitis [4], verrucous carcinoma [5–8] and squamous carcinoma [9]. Chronic inflammation and recent circumcision for long-standing phimosis are said to be important predisposing factors. The lesion is premalignant or, in one-third of cases, malignant at presentation, with squamous carcinoma the underlying pathology. Treatment should be dictated by precise diagnosis achieved by adequate excision and histology of the whole lesion. Follow-up is mandatory because recurrence may occur.

Porokeratosis

Genital porokeratosis of Mibelli is rare, but classical lesions have been reported on the penis and scrotum. It may be commoner in Asian populations [10]. Pruritus and ulceration may occur [11]. Porokeratosis may be confused with psoriasis, Bowen's disease, granuloma annulare or lichen planus; biopsy differentiates these conditions [12]. Topical 5-fluorouracil and imiquimod have been used for treatment [13,14].

Pseudoepitheliomatous micaceous and keratotic balanitis

Pseudoepitheliomatous micaceous and keratotic balanitis (PEMKB) is a rare penile condition. It presents as thick, scaly, micaceous

patches (possibly a cutaneous horn) on the glans penis in older, uncircumcised men [4,15]. Perimeatal hyperkeratosis may cause multiple urinary streams on micturition—a 'watering-can penis' [16]. Histological examination shows hyperkeratosis, parakeratosis, acanthosis, prolongation of the rete ridges and mild lower epidermal dysplasia, with a non-specific dermal inflammatory infiltrate of eosinophils and lymphocytes. Some consider that PEMKB is a form of locally invasive verrucous carcinoma [17], others that it is a variant of lichen sclerosus [18]. Metastastic spread has not occurred except where there was a penile horn [19], and in one patient who developed an aggressive soft-tissue sarcoma of the penis [20]. Recurrence is common. Topical 5-fluorouracil, radiotherapy and surgery are the principal treatment choices [4].



Fig. 71.16 Bowenoid papulosis. (Courtesy of Dr D.A. Burns, Leicester, UK.)

References

1 Cubilla AL, Meijer CJLM, Young RH. Morphological features of epithelial abnormalities and precancerous lesions of the penis. *Scand J Urol Nephrol* 2000; **205** (Suppl.): 215–9.
2 Garcia Panos JM, Buendia Gonzalez E, Jimenez Leiro F *et al.* Penile cutaneous horn: report of a case and review of the literature. *Arch Esp Urol* 1999; **52**: 173–4.
3 Tewari M, Gupta SK, Kumar M. Multiple cutaneous horns of the penis: a case report. *Indian J Pathol Microbiol* 2003; **46**: 53–4.
4 Bart RS, Kopf AW. Tumor conference No. 14: on a dilemma of penile horns—pseudoepitheliomatous, hyperkeratotic and micaceous balanitis. *J Dermatol Surg Oncol* 1977; **3**: 580.
5 Willsher MK, Daley KJ, Conway JF *et al.* Penile horns. *J Urol* 1984; **132**: 1192–3.
6 Yeager JK, Findlay RF, McAleer IM. Penile verrucous carcinoma. *Arch Dermatol* 1990; **126**: 1208–10.
7 Karthikeyan K, Thappa DM, Jaisankar TJ *et al.* Cutaneous horn of glans penis. *Sex Transm Infect* 1998; **74**: 456–7.
8 Zhu J-W, Luo D, Li C-R *et al.* A case of penile verrucous carcinoma associated with cutaneous horn. *Clin Exp Dermatol* 2007; **32**: 213–4.
9 Ponce De Leon J, Algaba F, Salvador J. Cutaneous horn of the glans penis. *Br J Urol* 1994; **74**: 257–8.
10 Chen T-J, Chou Y-C, Chen C-H *et al.* Genital porokeratosis: a series of 10 patients and review of the literature. *Br J Dermatol* 2006; **155**: 325–9.
11 Watanabe T, Murakami T, Okochi H *et al.* Ulcerative porokeratosis. *Dermatology* 1998; **196**: 256–9.
12 Levell NJ, Bewley AP, Levene GM. Porokeratosis of Mibelli on the penis, scrotum and natal cleft. *Clin Exp Dermatol* 1994; **19**: 77–8.
13 Porter WM, Du P, Menagé H, Philip G, Bunker CB. Porokeratosis of the penis. *Br J Dermatol* 2001; **144**: 643–4.
14 Jain S. Successful treatment of porokeratosis of Mibelli with imiquimod 5% cream. *Clin Exp Dermatol* 2005; **31**: 281–305.
15 Ganem JP, Steele BW, Creager AJ, Carson CC. Pseudo-epitheliomatous keratotic and micaceous balanitis. *J Urol* 1999; **161**: 217–8.
16 Zawar V, Kirloskar M, Chuh A. 'Watering-can penis' in pseudoepitheliomatous, keratotic and micaceous balanitis. *Acta Derm Venereol* 2004; **84**: 329–30.
17 Beljaards RC, van Dijk E, Hausman R. Is pseudoepitheliomatous, micaceous and keratotic balanitis synonymous with verrucous carcinoma? *Br J Dermatol* 1987; **117**: 641–6.
18 Ridley CM. Lichen sclerosus et atrophicus. *BMJ* 1987; **295**: 1295–6.
19 Goldstein, HH. Cutaneous horn of penis. *J Urol* 1933; **30**: 367–74.
20 Irvine C, Anderson JR, Pye RJ. Micaceous and keratotic pseudoepitheliomatous balanitis and rapidly fatal fibrosarcoma of the penis occurring in the same patient. *Br J Urol* 1987; **116**: 719–25.

Erythroplasia of Queyrat, Bowen's disease of the penis and bowenoid papulosis

Erythroplasia of Queyrat (EQ), Bowen's disease of the penis (BDP) and bowenoid papulosis (BP) are three clinical variants of carcinoma *in situ* of the penis [1–3]. Penile intraepithelial neoplasia (PIN—corresponding to cervical, vulval and anal intraepithelial neoplasia; CIN, VIN and AIN) is the term favoured by some, and may be a convenient umbrella term, but there is no formal consensus on clinicopathological classification (particularly 'grade') and clinical utility. An alternative expression 'squamous intraepithelial lesion' (SIL) has been proposed, and qualified by the descriptor 'high-' or 'low-grade' [4]. EQ, BDP and BP all describe disorders of the penis predominantly in uncircumcised white men, although EQ has been recorded in a circumcised man [5]. CIN, VIN and AIN are terms analogous to PIN.

Although EQ and BDP are synonymous in describing carcinoma *in situ* of the penis, BD is used to refer to squamous carcinoma *in situ* at other cutaneous sites. EQ should be used to describe red shiny patches or plaques of the 'mucosal' penis (glans and prepuce of the uncircumcised). BDP should be used to describe red, sometimes slightly pigmented, scaly patches and plaques of the keratinized penis. This distinction has not always been made in the literature. BP is analogous to, but clinically different from, EQ and BDP. The term should be used to describe multiple warty lesions, which are often pigmented in keratinized sites, and more numerous and more inflamed at 'mucosal' sites (Fig. 71.16). BP lesions are less papillomatous, smoother topped, more polymorphic and more coalescent than common genital viral condylomata acuminata, and occur in younger, sexually active men, as opposed to the patches or scaly plaques of EQ and BDP, respectively, seen in older men. BP may be associated with a lesser risk of squamous carcinoma than EQ and BDP. It is associated with HPV infection (especially HPV 16) and HIV infection. Voltz *et al.* [6] found anogenital warts in 16% of all HIV-positive males, nearly half of whom showed histological signs of intraepithelial neoplasia.

The aetiology of EQ, BDP and BP is unknown. Local carcinogenic influences in uncircumcised men such as poor hygiene, smegma, trauma, friction, heat, maceration, inflammation, phimosis, dermatoses such as lichen sclerosus and smoking (tar metabolites in urine) have been proposed [7]. PIN can be found in men being screened for HPV infection [8]. HPV is particularly implicated in BP [9]. Indeed, BP is probably virus-induced epithelial dysplasia associated mainly with HPV 16, but other types have been found [10–12]. EQ has been shown to be associated with co-

infection with the rare epidermodysplasia verruciformis-associated HPV 8 and the genital high-risk HPV 16 [13]. There is a high prevalence of PIN in male sexual partners of women with CIN [14,15], but many patients with PIN have consorts with no evidence of warts or CIN.

Immunosuppression is important; 50% of HIV patients with anogenital warts had squamous carcinoma *in situ* on histology [6]. Nothing is known about the influence of immunogenotype. The evidence confirming that EQ/BDP may result in squamous carcinoma has been reviewed comprehensively [7,16]. The risk of progression of BP to invasive squamous carcinoma is not known, but is probably low in the absence of other risk factors, especially immunocompromise. The grade of the intraepithelial neoplasia and the development of invasive carcinoma are related to age [17]. *p53* mutations do not appear to be important in male genital carcinogenesis [18].

Some patients with these lesions may be quite young [19]. There may be several foci of BDP or EQ and they may occur concomitantly. The non-specificity of the clinical appearances makes for an important differential diagnosis, which includes psoriasis, lichen sclerosus, erosive lichen planus, ZB and extramammary Paget's disease. The differential diagnosis of BP includes lichen planus, common warts, seborrhoeic warts, naevi and condylomata lata. A biopsy is indicated in instances where the clinical diagnosis is uncertain. Aynaud *et al.* [20] have shown that shrewd clinical interpretation predicts which lesions will show squamous carcinoma histologically and which will contain oncogenic HPV. Occasionally, it may be necessary to perform a second biopsy if the initial histology is inconclusive. It has been suggested that, where glans and shaft are both involved, the glans may be the preferential biopsy site. On histological examination, there are the features of an intraepithelial carcinoma. Secondary amyloid deposition has been reported histologically in one case of BP [21].

Treatment. Treatment depends on many factors. Circumcision removes a major risk factor for cancer and provides extensive tissue for histology. Topical 5-fluorouracil as a 5% cream is a well-established conventional option for the treatment of BDP, EQ and BP [1–3] but there have not been any clinical trials.

Other treatments include cryosurgery, curettage and electrocautery, excisional surgery, glans resurfacing, Mohs micrographic surgery, laser and photodynamic therapy [1–3,22,23]. Radiotherapy should be avoided. Topical imiquimod may help some patients [24–26]. Patients presenting with these conditions should be counselled and screened for HPV and other sexually transmitted diseases, including HIV infection. They should stop smoking. Sexual partners should be advised to seek assessment. Follow-up should be long term [2,3,17].

References

1 Bunker CB. Topics in penile dermatology. *Clin Exp Dermatol* 2001; **26**: 469–79.
2 Porter WM, Francis N, Hawkins D *et al*. Penile intraepithelial neoplasia: clinical spectrum and treatment of 35 cases. *Br J Dermatol* 2002; **147**: 1159–65.
3 Bunker CB. *Male Genital Skin Disease*. London: Saunders, 2004.
4 Cubilla AL, Velazques EF, Reuter VE *et al.* Warty (condylomatous) squamous cell carcinoma of the penis: a report of 11 cases and proposed classification of 'verruciform' penile tumors. *Am J Surg Pathol* 2000; **24**: 505–12.
5 Milstein HG. Erythroplasia of Queyrat in a partially circumcised man. *J Am Acad Dermatol* 1982; **10**: 398.
6 Voltz JM, Drobacheff C, Derancourt C *et al.* Papillomavirus-induced anogenital lesions in 121 HIV seropositive men: clinical, histological, viral study, and evolution. *Ann Dermatol Vénéréol* 1999; **126**: 424–9.
7 Graham JH, Helwig EB. Erythroplasia of Queyrat: a clinicopathologic and histochemical study. *Cancer* 1973; **32**: 1396–414.
8 Zabbo A, Stein BS. Penile intraepithelial neoplasia in patients examined for exposure to human papilloma virus. *Urology* 1993; **41**: 24–6.
9 Griffiths TRL, Mellon JK. Human papillomavirus and urological tumours: basic science and role in penile cancer. *BJU Int* 1999; **84**: 579–86.
10 Guerin-Reverchon I, Chardonnet Y, Viac J *et al.* Human papillomavirus infection and filaggrin expression in paraffin-embedded biopsy specimens of extragenital Bowen's disease and genital bowenoid papulosis. *J Cancer Res Clin Oncol* 1990; **116**: 295–300.
11 Yoneta A, Yamashita T, Jin HY *et al.* Development of squamous cell carcinoma by two high-risk human papillomaviruses (HPVs), a novel HPV-67 and HPV-31 from bowenoid papulosis. *Br J Dermatol* 2000; **143**: 604–8.
12 Kreuter A, Brockmeyer NH, Pfister H *et al.* Increased human papillomavirus type 31 DNA load in a verrucous high-grade intraepithelial neoplasia of a human immunodeficiency virus-infected patient with extensive bowenoid papulosis. *Br J Dermatol* 2007; **156**: 596–8.
13 Wieland U, Jurk S, Weissenborn S *et al.* Erythroplasia of Queyrat: coinfection with cutaneous carcinogenic human papillomavirus type 8 and genital papillomaviruses in a carcinoma *in situ*. *J Invest Dermatol* 2000; **115**: 396–401.
14 Barrasso R, De Brux J, Croissant O, Orth G. High prevalence of papillomavirus associated penile intraepithelial neoplasia in partners of women with cervical intraepithelial neoplasia. *N Engl J Med* 1987; **317**: 916–23.
15 Kennedy L, Buntine DW, O'Connor D, Frazer IH. Human papillomavirus: a study of male sexual partners. *Med J Aust* 1988; **149**: 309–11.
16 Blau S, Hyman AB. Erythroplasia of Queyrat. *Acta Derm Venereol* 1955; **35**: 341–78.
17 Aynaud O, Asselain B, Bergeron C *et al.* Carcinomes intraépithéliaux et carcinomes invasifs de la vulve, du vagin et du pénis en Ile-de-France: enquête PETRI portant sur 423 cas. *Ann Dermatol Vénéréol* 2000; **127**: 479–83.
18 Castren K, Vähäkangas K, Heikkinen E, Ranki A. Absence of *p53* mutations in benign and pre-malignant male genital lesions with over-expressed p53 protein. *Int J Cancer* 1998; **77**: 674–8.
19 McAninch JW, Moore CA. Precancerous penile lesions in young men. *J Urol* 1970; **104**: 287–90.
20 Aynaud O, Ionesco M, Barrasso R. Penile intraepithelial neoplasia: specific clinical features correlate with histologic and virologic findings. *Cancer* 1994; **74**: 1762–7.
21 Koh BK, Oh ST, Lee JY, Cho BK. Bowenoid papulosis with amyloid deposition. *Br J Dermatol* 2002; **147**: 808–40.
22 Conejo-Mir JS, Muñoz MA, Linares M *et al*. Carbon dioxide laser treatment of erythroplasia of Queyrat: a revisited treatment to this condition. *J Eur Acad Dermatol Venereol* 2005; **19**: 643–4.
23 Hadway P, Corbishley CM, Watkin NA. Total glans resurfacing for premalignant lesions of the penis: initial outcome data. *BJU Int* 2006; **98**: 532–6.
24 Wigbels B, Luger T, Metze D. Imiquimod: a new treatment possibility in bowenoid papulosis? *Hautarzt* 2001; **52**: 128–31.
25 Pehoushek J, Smith KJ. Imiquimod and 5% fluorouracil therapy for anal and perianal squamous cell carcinoma *in situ* in an HIV-1 positive man. *Arch Dermatol* 2001; **137**: 14–6.
26 Micali G, Masca MR, De Pasquale R. Erythroplasia of Queyrat treated with imiquimod 5% cream. *J Am Acad Dermatol* 2006; **55**: 901–3.

Squamous carcinoma

Genital squamous carcinoma is sometimes called epidermoid carcinoma. The aetiology is not clearly understood but HPV is implicated [1]. Diagnosis and management can present difficulties. Squamous carcinoma should be suspected in all nodulolcerative genital disease, especially in the context of lichen sclerosus, lichen planus, hidradenitis suppurativa, intraepithelial neoplasia and immunocompromise. Genitourinary and urological

assessment should be sought. Proctoscopy and sigmoidoscopy are necessary to exclude anorectal cancer. Suspect lesions should be biopsied.

Carcinoma of the penis

Incidence and aetiology. Carcinoma of the penis accounts for less than 1% of deaths from cancer in the USA and causes 100 deaths per year in the UK (unchanged over several decades). It constitutes 10–20% of tumours seen in males in either underdeveloped countries or in areas where early circumcision is not routinely practised [2–8]. In India, the incidence of carcinoma of the penis is about five times that in the UK [9].

The earliest stages of penis cancer and precancer form a spectrum of disease [10]. Although some penile cancers arise *de novo*, others develop from premalignant states, which may be misdiagnosed or may be difficult to diagnose [11], and there are the issues of multifocality and field change [12] to acknowledge.

The precise aetiology of the types of PIN, verrucous carcinoma and frank invasive squamous carcinoma of the penis is unknown, as is their precise relationship to the various types of precursor lesion. However, Cubilla *et al.* [13] have defined several types of preceding epithelial abnormality: squamous hyperplasia and SIL (squamous, basaloid or warty, high or low grade).

Risk factors for penis cancer are listed in Table 71.24. The presence of a foreskin, HPV infection and lichen sclerosus are the most important considerations [5,8]. Neonatal circumcision protects against penile carcinoma [5,14–16]. Circumcision in later life may reduce the risk but does not abolish it, especially if the circumcision was performed for penile disease [17–19]. However, there have been very rare cases in Jews and others circumcised at birth [20–22]. The incidence of penis cancer is low in Japan and Denmark, where circumcision is rare [23,24], so other factors are important in carcinogenesis.

Table 71.24 Risk factors for squamous carcinoma of the penis.

Uncircumcised
Phimosis
Long foreskin
Poor hygiene
Chronic irritation, inflammation, scarring
Smoking
Lichen sclerosus
Lichen planus
Human papillomavirus
HIV
Squamous hyperplasia
Bowen's disease
Erythroplasia of Queyrat
Bowenoid papulosis
Giant condyloma/verrucous carcinoma
Photochemotherapy
Iatrogenic immunosuppression
Renal transplantation
Systemic lupus erythematosus
(Radiotherapy)

Phimosis and balanitis are known risk factors for penile cancer [2,5,14,25–27]. The possession of a 'long' foreskin may be important [28]. Poor personal and sexual hygiene [15] and phimosis may lead to the retention of smegma and development of balanitis. However, the carcinogenicity of human smegma has not been ascertained [29,30], and it is not widely appreciated that phimosis is a physical sign and not a diagnosis. Hence, there may be more in the carcinogenic propensity of phimosis than simply physical retention of smegma.

Lichen sclerosus is a common cause of phimosis in males and it predisposes to penile carcinoma [5,8,31–37]. Powell *et al.* [38] found that half of patients with penis cancer had a clinical history and/or histological evidence of lichen sclerosus. Chronic erosive and hypertrophic lichen planus are premalignant conditions, and lichen planus is a cause of phimosis [39,40]. Chronic irritation and inflammation or scarring are all risk factors for squamous carcinoma of the skin generally and the penis is no exception; penis cancer complicating a burn scar and a chronic sinus tract have been reported [41,42]. Quantifying the malignant potential of the precancerous dermatoses, BDP, EQ and PIN, is not possible, but they are acknowledged risks for penile cancer [43–45].

Smoking is a risk factor, independent of phimosis, for penile carcinoma [9,27], and is also a recognized risk factor for anal [46] and cervical cancer [47,48]. Smoking may cause squamoepithelial cancer, not only in parts of the body in contact with smoke but also at distant sites by dissemination of carcinogens in the circulation or in secretions. The presence of tobacco-specific nitrosamines in the preputial secretions of rats has been demonstrated [49].

Penile carcinoma is a complication of psoralen and UVA therapy (PUVA) [50–53], and possibly other treatments for psoriasis [54]. The photodye treatment of genital herpes simplex ceased in the 1970s because of the occurrence of BDP in young men who did not have other risk factors for erythroplasia [55]. However, increased UV exposure of the genitals from sunlamps and sunbeds had not led to an increase in genital skin cancer in the USA by 1986 [56].

Although penile cancer is associated with multiple sexual partners and previous sexually transmitted disease, including HIV, the epidemiological features are not those characteristic of a sexually transmitted disease [29]—unlike carcinoma of the cervix and, to a lesser extent, anal carcinoma. In cervical cancer, the evidence is that it is a sexually transmitted disease and that HPV is the aetiological agent [57–60]. Yet penile cancer puts wives and consorts at risk of cervical cancer [61] and there is a high prevalence of HPV, condylomas, SIL and PIN in sexual partners of women with CIN [62–64]. In India, the incidence of cervical cancer is lower in Muslim women compared with Hindus and Christians [65]. HPV is implicated in penis cancer [1,5,8,66,67], but its role is still uncertain, as many patients have no evidence of infection [5,8,36]. Oncogenic HPV types 16 and 18 have been incriminated [5,8,68–76]. In Brazil, Villa and Lopes [70] found HPV 18 in seven out of 18 penile squamous carcinomas and, in Argentina, Picconi *et al.* [76] found HPV DNA in 71% of 65 penis cancers, 81% of which were 'high-risk' HPV with a predominance of HPV 18. Gregoire *et al.* [77] associated HPV with higher grade, more aggressive squamous carcinomas of predominantly the glans penis, showing basaloid changes. Rubin *et al.* associated HPV positivity with a



Fig. 71.17 High-grade dysplasia and invasive squamous carcinoma. (Courtesy of Professor C.B. Bunker, with permission from Medical Illustration UK, Chelsea & Westminster Hospital, London, UK.)



Fig. 71.18 Squamous carcinoma. Severe background lichen sclerosus. (Reproduced from Bunker C.B. Skin conditions of the male genitalia. *Medicine* 2001; **29**: 9–13, by kind permission of The Medicine Publishing Company.)

subset of basaloid and warty carcinomas, at a total prevalence of 42% [78]. The overall frequency of HPV in penile squamous carcinoma suggests that a proportion of these cancers can arise from HPV-associated SIL [13,77]. As in vulval cancer [79,80], a bimodal hypothesis of HPV-related and non-HPV-related causation has evolved [13,81].

Penis cancer has been reported to complicate immunosuppression in renal transplantation [82] and HIV infection [83] (see Chapter 35: risk increased × 5–6). It has also occurred in a circumcised man with psoriasis treated with etanercept: he had previously received methotrexate, ciclosporin and hydroxyurea [84]. Topical immunosuppressive agents should be used with extreme caution for genital dermatoses, especially in the uncircumcised, because of the risk of squamous carcinoma [85–88].

Clinical features. Itch, irritation, pain, bleeding, discharge, ulceration or the discovery of a mass are the presenting symptoms of squamous carcinoma. There is often a long history of preceding problems with the penis and foreskin manifest as dyspareunia, balanoposthitis or phimosis and dysuria. Irregular nodular and ulcerative morphology is found on examination (Figs 71.17 & 71.18) and there may be background BDP, EQ and BP, lichen sclerosus or lichen planus. Undiagnosed, untreated disease is destructive and mutilating [89]. Phimosis should be regarded as a sinister situation, not least because it impedes complete inspection and palpation of the glans and coronal sulcus. The inguinal lymph glands must be palpated, although in penile cancer only 50% of enlarged glands will be found to contain tumour [3]. The concomitant presence of sexually transmitted diseases and immunocompromise should be excluded [90]. The differential diagnosis includes the manifestations of intraepithelial neoplasia (and the differential diagnosis of these), erosive or ulcerative sexually transmitted disease, basal cell carcinoma, Kaposi's sarcoma, pyoderma gangrenosum and artefact. Genitourinary and urological assessment should be sought.

Histopathology. Diagnosis is confirmed histologically by incisional or excisional biopsy. An incisional biopsy should be of adequate size and depth, and it may be necessary to sample several sites. The biopsy(ies) may need to be performed by a urologist under general anaesthesia. Patients who have negative or equivocal biopsies, but who have risk factors or in whom there is a high index of suspicion, should be followed-up closely and rebiopsied if indicated. Staging should not be based on incisional biopsies [91].

Histologically, squamous carcinoma manifests tongues of invasive atypical keratinocytes penetrating the dermis, and contains foci of aberrant and ectopic keratinization called squamous pearls [26]. Background histological signs of lichen sclerosus are commonly found in penile cancer in men, as in vulvar cancer [38]. Cubilla *et al.* [12] have identified four histological types of squamous carcinoma of the penis:

1 **Superficial spreading** (42%): a biphasic infiltrative and radially extensive carcinoma *in situ* contiguously involving several

anatomical sites or compartments (glans, coronal sulcus, foreskin, even urethra)

2 **Vertical growth** (32%): unifocal high-grade deeply invasive, unassociated with carcinoma *in situ*

3 **Verrucous** (18%): low-grade, papillary or endophytic (see below)

4 **Multicentric** (8%): two or more independent primary tumours without contiguous field change.

Verrucous carcinoma is discussed below. Sarcomatoid carcinoma and spindle cell carcinoma of the penis are rare variants [92–94].

These observations have implications for the pathogenesis of the different types, and in determining management in individual cases.

References

1 Kadish AS. Biology of anogenital neoplasia. *Cancer Treat Res* 2001; **104**: 267–86.

2 Muir CS, Nectoux J. Epidemiology of carcinoma of the testis and penis. *Natl Cancer Inst Monogr* 1979; **53**: 157–64.

3 Droller MJ. Carcinoma of the penis: an overview. *Urol Clin North Am* 1980; **7**: 783–4.

4 Micali G, Innocenzi D, Nasca MR *et al.* Squamous cell carcinoma of the penis. *J Am Acad Dermatol* 1996; **35**: 432–51.

5 Bunker CB. *Male Genital Skin Disease*. London: Saunders, 2004.

6 Soria J-C, Théodore C, Gerbaulet A. Carcinome épidermoïde de la verge (squamous cell carcinoma of the penis). *Bull Cancer* 1998; **85**: 773–84.

7 Schoeneich G, Perabo FG, Muller SC. Squamous cell carcinoma of the penis. *Andrologia* 1999; **31** (Suppl. 1): 17–20.

8 Micali G, Nasca MR, Innocenzi D, Schwartz RA. Penile cancer. *J Am Acad Dermatol* 2006; **54**: 369–91.

9 Harish K, Ravi R. The role of tobacco in penile carcinoma. *Br J Urol* 1995; **75**: 375–7.

10 Grossman HB. Premalignant and early carcinomas of the penis and scrotum. *Urol Clin North Am* 1992; **19**: 221–6.

11 von Krogh G, Horenblas S. Diagnosis and clinical presentation of premalignant lesions of the penis. *Scand J Urol Nephrol* 2000; **205** (Suppl.): 201–4.

12 Cubilla AL, Barreto J, Caballero C *et al*. Pathologic features of epidermoid carcinoma of the penis: a prospective study of 66 cases. *Am J Surg Pathol* 1993; **17**: 753–63.

13 Cubilla AL, Meijer CJLM, Young RH. Morphological features of epithelial abnormalities and precancerous lesions of the penis. *Scand J Urol Nephrol* 2000; **205** (Suppl.): 215–9.

14 Wolbarst AL. Circumcision and penile cancer. *Lancet* 1932; **1**: 150–3.

15 Schrek R, Lenowitz H. Aetiological factors in carcinoma of the penis. *Cancer Res* 1947; **7**: 180–7.

16 Schoen EJ, Oehrli M, Colby CJ, Machin G. The highly protective effect of newborn circumcision against invasive penile cancer. *Pediatrics* 2000; **105**: E36.

17 Maden C, Sherman KJ, Beckmann AM *et al.* History of circumcision, medical conditions, and sexual activity and the risk of penile cancer. *J Natl Cancer Inst* 1993; **85**: 19–24.

18 Holly EA, Palefsky JM. Factors related to risk of penile cancer: new evidence from a study in the Pacific northwest. *J Natl Cancer Inst* 1993; **85**: 2–3.

19 Rempelakos A, Bastas E, Lymperakis CH, Thanos A. Carcinoma of the penis: experience from 360 cases. *J Balkan Union Oncol* 2004; **9**: 51–5.

20 Melmed EP, Payne JR. Carcinoma of the penis in a Jew circumcised in infancy. *Br J Surg* 1967; **54**: 729–31.

21 Boczko S, Freed S. Penile carcinoma in circumcised males. *NY State J Med* 1979; **79**: 1903–4.

22 Rogus BJ. Squamous cell carcinoma in a young circumcised man. *J Urol* 1987; **138**: 861–2.

23 Williams N, Kapila L. Complications of circumcision. *Br J Surg* 1993; **80**: 1231–6.

24 Frisch M, Friis S, Krüger Kjaer S, Melbye M. Falling incidence of penis cancer in an uncircumcised population (Denmark 1943–90). *BMJ* 1995; **311**: 1471.

25 Reddy CRRM, Devendranath V, Pratap S. Carcinoma of the penis: role of phimosis. *Urology* 1984; **24**: 85–8.

26 Lucia MS, Miller GJ. Histopathology of malignant lesions of the penis. *Urol Clin North Am* 1992; **19**: 227–46.

27 Maiche AG. Epidemiological aspects of cancer of the penis in Finland. *Eur J Cancer Prev* 1992; **1**: 153–8.

28 Velazquez EG, Bock A, Soskin A *et al*. Preputial variability and preferential association of long phimotic foreskins with penile cancer. *Am J Surg Pathol* 2003; **27**: 994–8.

29 Hellberg D, Valentin J, Eklund T *et al*. Penile cancer: is there an epidemiological role for smoking and sexual behaviour? *BMJ* 1987; **295**: 1306–8.

30 Van Howe RS, Hodges FM. The carcinogenicity of smegma: debunking a myth. *J Eur Acad Dermatol Venereol* 2006; **20**: 1046–54.

31 Bingham JS. Carcinoma of the penis developing in lichen sclerosus et atrophicus. *Br J Vener Dis* 1978; **54**: 350–1.

32 Schnitzler L, Sayag J, Sayag J, Roux G. Épithélioma spino-cellulaire aigu de la verge et lichen scléro-atrophique. *Ann Dermatol Vénéréol* 1987; **114**: 979–81.

33 Pride HB, Miller OF, Tyler WB. Penile squamous cell carcinoma arising from balanitis xerotica obliterans. *J Am Acad Dermatol* 1993; **29**: 469–73.

34 Bunker CB. Topics in penile dermatology. *Clin Exp Dermatol* 2001; **26**: 469–79.

35 Nasca MR, Panetta C, Micali G, Innocenzi D. Microinvasive squamous cell carcinoma arising on lichen sclerosus of the penis. *J Eur Acad Dermatol Venereol* 2003; **17**: 337–9.

36 Perceau G, Derancourt C, Clavel C *et al*. Lichen sclerosus is frequently present in penile squamous cell carcimonas but is not always associated with oncogenic human papillomavirus. *Br J Dermatol* 2003; **148**: 934–8.

37 Barbagli G, Palminteri E, Mirri F *et al*. Penile carcinoma in patients with genital lichen sclerosus: a multicenter survey. *J Urol* 2006; **175**: 1359–63.

38 Powell J, Robson A, Cranston D *et al*. High incidence of lichen sclerosus in patients with squamous cell carcinoma of the penis. *Br J Dermatol* 2001; **145**: 85–9.

39 Worheide J, Bonsmann G, Kolde G, Hamm H. Plattenepithyelkarzinom auf dem Boden eines lichen ruber hypertrophicus an der glans penis. *Hautarzt* 1991; **42**: 112–5.

40 Itin PH, Hirsbrunner P, Buchner S. Lichen planus: an unusual cause of phimosis. *Acta Derm Venereol* 1992; **72**: 41–2.

41 Selli C, Scott CA, De Antoni P *et al.* Squamous cell carcinoma arising at the base of the penis in a burn scar. *Urology* 1999; **54**: 923.

42 Broder SR, Frierson HF Jr, Theodorescu D. Unusual case of non-exophytic invasive penile squamous cell cancer arising from a chronic sinus tract. *Scand J Urol Nephrol* 1999; **33**: 333–5.

43 Blau S, Hyman AB. Erythroplasia of Queyrat. *Acta Derm Venereol* 1955; **35**: 341–78.

44 Graham JH, Helwig EB. Erythroplasia of Queyrat: a clinicopathologic and histochemical study. *Cancer* 1973; **32**: 1396–414.

45 Gerber GS. Carcinoma *in situ* of the penis. *J Urol* 1994; **151**: 829–33.

46 Moore TO, Moore AY, Carrasco D *et al.* Human papillomavirus, smoking and cancer. *J Cutan Med Surg* 2001; **5**: 323–8.

47 Winkelstein W. Smoking and cancer of the uterine cervix: hypothesis. *Am J Epidemiol* 1977; **106**: 257–9.

48 Sasson I, Haley N, Hoffmann D, Wynder E. Cigarette smoking and neoplasia of the uterine cervix: smoke constituents in cervical mucus. *N Engl J Med* 1985; **31**: 315–6.

49 Castonguay A, Tjalve H, Hecht SS. Tissue distribution of the the tobacco specific carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and its metabolites in F344 rats. *Cancer Res* 1983; **43**: 630–8.

50 Stern RS. Genital tumours among men with psoriasis exposed to psoralens and ultraviolet A radiation (PUVA) and ultraviolet B radiation. *N Engl J Med* 1990; **322**: 1093–7.

51 Perkins W, Lamont D, MacKie RM. Cutaneous malignancy in males treated with photochemotherapy. *Lancet* 1990; **336**: 1248.

52 Brassinne de la M, Richert B. Genital squamous-cell carcinoma after PUVA therapy. *Dermatology* 1992; **185**: 316–8.

53 Park HS, Lee YS, Chun DK. Squamous cell carcinoma in vitiligo lesion after long-term PUVA therapy. *J Eur Acad Dermatol Venereol* 2003; **17**: 578–80.

54 Loughlin KR. Psoriasis: association with two rare cutaneous urological malignancies. *J Urol* 1997; **157**: 622–3.

55 Berger RS, Papa CM. Photodye herpes therapy: Cassandra confirmed? *JAMA* 1977; **238**: 133–4.

56 Goldoft MJ, Weiss NS. Incidence of male genital skin tumours: lack of increase in the United States. *Cancer Causes Control* 1992; **3**: 91–3.
57 Xavier Bosch F, Michele Manos M, Muñoz N *et al.* International Biological Study on Cervical Cancer (IBSCC) Study Group. Prevalence of human papillomavirus in cervical cancer: a worldwide perspective. *J Natl Cancer Inst* 1995; **87**: 796–802.
58 zur Hausen H. Genital papillomavirus infections. *Prog Med Virol* 1985; **32**: 15–21.
59 Keerti VS. Human papillomaviruses and anogenital cancers. *N Engl J Med* 1997; **337**: 1386–7.
60 Walboomers JMM, Meijer CJLM. Do HPV-negative cervical carcinomas exist? *J Pathol* 1997; **181**: 253–4.
61 Smith PG, Kinlen LJ, White GC *et al.* Mortality of wives of men dying with cancer of the penis. *Br J Cancer* 1980; **41**: 422–8.
62 Barrasso R, De Brux J, Croissant O, Orth G. High prevalence of papillomavirus associated penile intraepithelial neoplasia in partners of women with cervical intraepithelial neoplasia. *N Engl J Med* 1987; **317**: 916–23.
63 Kennedy L, Buntine DW, O'Connor D, Frazer IH. Human papillomavirus: a study of male sexual partners. *Med J Aust* 1988; **149**: 309–11.
64 Bleeker MC, Hogewoning CJ, Van Den Brule AJ *et al*. Penile lesions and human papillomavirus in male sexual partners of women with cervical intraepithelial neoplasia. *J Am Acad Dermatol* 2002; **47**: 351–7.
65 Gajalakshmi CK, Shanta V. Association between cervical and penile cancers in Madras, India. *Acta Oncol* 1993; **32**: 617–20.
66 Madkan VK, Cook-Norris RH, Steadman MC *et al*. The oncogenic potential of human papillomaviruses: a review on the role of host genetics and environmental cofactors. *Br J Dermatol* 2007; **157**: 228–41.
67 Nordenvall C, Chang ET, Adami HO, Ye W. Cancer risk among patients with condylomata acuminata. *Int J Cancer* 2006; **119**: 888–93.
68 Dürst M, Kleinheinz A, Hotz M, Gissmann L. The physical state of human papillomavirus type 16 DNA in benign and malignant genital tumours. *J Gen Virol* 1985; **6**: 1515–22.
69 Boshart M, Gissmann L, Ikenberg H *et al.* A new type of papillomavirus DNA, its presence in genital cancer biopsies and in cell lines derived from cervical cancer. *EMBO J* 1984; **3**: 1151–7.
70 Villa LL, Lopes A. Human papillomavirus DNA sequences in penile carcinomas in Brazil. *Int J Cancer* 1986; **37**: 853–5.
71 Löning T, Riviere A, Henke RP *et al*. Penile/anal condylomas and squamous cell cancer: a HPV DNA hybridization study. *Virchows Arch A Pathol Anat Histopathol* 1988; **413**: 491–8.
72 Strickler HD, Schiffman MH, Shah KV *et al.* A survey of human papillomavirus 16 antibodies in patients with epithelial cancers. *Eur J Cancer Prev* 1998; **7**: 305–13.
73 Cupp MR, Malek RS, Goellner JR *et al*. The detection of human papillomavirus deoxyribonucleic acid in intraepithelial, *in situ*, verrucous and invasive carcinoma of the penis. *J Urol* 1995; **154**: 1024–9.
74 Majewski S, Jablonska S. Human papillomavirus-associated tumors of the skin and mucosa. *J Am Acad Dermatol* 1997; **36**: 659–85.
75 Griffiths TRL, Mellon JK. Human papillomavirus and urological tumours: basic science and role in penile cancer. *BJU Int* 1999; **84**: 579–86.
76 Picconi MA, Eijan AM, Distefano AL *et al.* Human papillomavirus (HPV) DNA in penile carcinomas in Argentina: analysis of primary tumors and lymph nodes. *J Med Virol* 2000; **61**: 65–9.
77 Gregoire L, Cubilla AL, Reuter VE *et al*. Preferential association of human papillomavirus with high-grade histologic variants of penile-invasive squamous cell carcinoma. *J Natl Cancer Inst* 1995; **87**: 1705–9.
78 Rubin MA, Kleter B, Zhou M *et al*. Detection and typing of human papillomavirus DNA in penile carcinoma: evidence for multiple independent pathways of penile carcinogenesis. *Am J Pathol* 2001; **159**: 1211–8.
79 Leibowitch M, Neill S, Pelisse M, Moyal-Baracco M. The epithelial changes associated with squamous cell carcinoma of the vulva: a review of the clinical, histological and viral findings in 78 women. *Br J Obstet Gynaecol* 1990; **97**: 1135–9.
80 Jones RW, Baranyai J, Stables S. Trends in squamous cell carcinoma of the vulva: the influence of vulvar intraepithelial neoplasia. *Obstet Gynecol* 1997; **90**: 448–52.
81 Horenblas S, von Krogh G, Cubilla AL *et al.* Squamous cell carcinoma of the penis: premalignant lesions. *Scand J Urol Nephrol* 2000; **205** (Suppl.): 187–8.
82 Previte SR, Karian S, Cho SI, Austen G. Penile carcinoma in renal transplant recipient. *Urology* 1979; **13**: 298–9.
83 Poblet E, Alfaro L, Fernander-Segoviano P *et al*. Human papillomavirus-associated penile squamous cell carcinoma in HIV-positive patients. *Am J Surg Pathol* 1999; **23**: 1119–23.
84 Fryrear RS II, Wiggins AK, Sanguesa O, Yosipovitch G. Rapid onset of cutaneous squamous cell carcinoma of the penis in a patient with psoriasis on etanercept therapy. *J Am Acad Dermatol* 2004; **51**: 1026.
85 Cox NH. Squamous cell carcinoma arising in lichen planus of the penis during topical cyclosporin therapy. *Clin Exp Dermatol* 1996; **21**: 323–4.
86 Langeland T, Engh V. Topical use of tacrolimus and squamous cell carcinoma of the penis. *Br J Dermatol* 2005; **152**: 183–4.
87 Bunker CB, Neill S, Staughton RCD. Topical tacrolimus, genital lichen sclerosus and risk of squamous cell carcinoma. *Arch Dermatol* 2004; **140**: 1169.
88 Bunker CB. Male genital lichen sclerosus and topical tacrolimus. *Br J Dermatol* 2007; **157**: 1079–80.
89 Agarwal P, Sharma D. Autodestruction of penis due to carcinoma. *J Eur Acad Dermatol Venereol* 2005; **19**: 220–2.
90 Heyns CF, van Vollenhoven P, Steenkamp JW, Allen FJ. Cancer of the penis: a review of 50 patients. *S Afr J Surg* 1997; **35**: 120–4.
91 Velazquez EF, Barreto JE, Rodriguez I *et al*. Limitations in the interpretation of biopsies in patients with penile squamous cell carcinoma. *Int J Surg Pathol* 2004; **12**: 139–46.
92 Patel B, Hashmat A, Reddy V, Angkustsiri K. Spindle cell carcinoma of the penis. *Urology* 1982; **19**: 93–5.
93 Lont AP, Gallee MP, Snijders P, Horenblas S. Sarcomatoid squamous cell carcinoma of the penis: a clinical and pathological study of 5 cases. *J Urol* 2004; **172**: 932–5.
94 Velazquez EF, Melamed J, Barreto JE *et al.* Sarcomatoid carcinoma of the penis: a clinicopathologic study of 15 cases. *Am J Surg Pathol* 2005; **29**: 1152–8.

Carcinoma of the scrotum

Squamous carcinoma of the scrotum has been recognized in chimney sweeps (exposed to carcinogens in soot) [1], mule spinners (exposed to carcinogens in lubricating oils for the spinning jenny in the cloth industry), Persian nomads (who travelled with pots of burning charcoal between their legs) and Indian jute oil processors [2–6]. Oil-mist exposure in industry continues to be widespread and, apart from scrotal cancer, has been associated with other cutaneous problems (such as contact dermatitis and oil acne) and respiratory diseases, including cancer [7].

Other individuals at risk of scrotal squamous carcinoma include those with a history of psoriasis treated with arsenic, coal tar, UVB and PUVA [8–13], previous radiotherapy treatment [8], scrotal HPV infection, hidradenitis suppurativa, Bowen's disease and multiple cutaneous keratoses and epitheliomas [14–18]. Rarely, black men may be affected [19].

The presentation of scrotal carcinoma is similar to that of penis cancer, with itch, irritation, pain, bleeding, discharge, ulceration or the discovery of a lump, and irregular nodular and ulcerative clinical features. A pigmented squamous carcinoma of the scrotum has been reported [20]. The differential diagnosis includes the manifestations of intraepithelial neoplasia (and the differential diagnosis of these), erosive or ulcerative sexually transmitted disease, basal cell carcinoma, Kaposi's sarcoma, pyoderma gangrenosum and artefact. The diagnosis is confirmed by biopsy.

References

1 Potts P. Cancer scroti. *Chirurgical Works* 1779; **3**: 225–9.
2 Graves RC, Flo S. Carcinoma of the scrotum. *J Urol* 1940; **43**: 309–32.
3 Lowe FC. Squamous cell carcinoma of the scrotum. *J Urol* 1983; **130**: 423–7.

4 Gerber WL. Scrotal malignancies: the University of Iowa experience and a review of the literature. *Urology* 1985; **26**: 337–42.
5 Grossman HB. Premalignant and early carcinomas of the penis and scrotum. *Urol Clin North Am* 1992; **19**: 221–6.
6 Murthy KVN. Primary cutaneous carcinoma of the scrotum. *J Occup Med* 1993; **35**: 888–9.
7 Karube H, Aizawa Y, Nakamura K *et al.* Oil mist exposure in industrial health: a review. *Sangyo Eiseigaku Zasshi* 1995; **37**: 113–22.
8 Ray B, Whitmore WF Jr. Experience with carcinoma of the scrotum. *J Urol* 1977; **117**: 741–5.
9 McGarry GW, Robertson JR. Scrotal carcinoma following prolonged use of crude coal tar ointment. *Br J Urol* 1989; **63**: 211–9.
10 Stern RS. Genital tumours among men with psoriasis exposed to psoralens and ultraviolet A radiation (PUVA) and ultraviolet B radiation. *N Engl J Med* 1990; **322**: 1093–7.
11 Perkins W, Lamont D, MacKie RM. Cutaneous malignancy in males treated with photochemotherapy. *Lancet* 1990; **336**: 1248.
12 Gross DJ, Schosser RH. Squamous cell carcinoma of the scrotum. *Cutis* 1991; **47**: 402–4.
13 Loughlin KR. Psoriasis: association with two rare cutaneous urological malignancies. *J Urol* 1997; **157**: 622–3.
14 Dean AL. Epithelioma of the scrotum. *J Urol* 1948; **60**: 508–18.
15 Black SB, Woods JE. Squamous cell carcinoma complicating hidradenitis suppurativa. *J Surg Oncol* 1982; **19**: 25–6.
16 Andrews PE, Farrow GM, Oesterling JE. Squamous cell carcinoma of the scrotum: long-term follow-up of 14 patients. *J Urol* 1991; **146**: 1299–304.
17 Burmer GC, True LD, Krieger JN. Squamous cell carcinoma of the scrotum associated with human papillomaviruses. *J Urol* 1993; **149**: 374–7.
18 Ueda M, Ashida M, Kunisada M *et al.* Bowen's carcinoma of the scrotal skin associated with human papillomavirus type 82. *J Eur Acad Dermatol Venereol* 2005; **19**: 232–5.
19 Lowe FC. Squamous cell carcinoma of scrotum. *Urology* 1985; **25**: 63–5.
20 Matsumoto M, Sonobe H, Takeuchi T *et al.* Pigmented squamous cell carcinoma of the scrotum associated with a lentigo. *Br J Dermatol* 1999; **141**: 132–6.

Treatment of squamous carcinoma

The treatment of anogenital squamous carcinoma is not generally the province of the dermatologist. The overriding general principle is to offer adequate surgical excision, including circumcision, for disease of the penis. The penile surgery may need to be radical, total or partial, depending on location and extent [1–3]. To conserve tissue and minimize residual sexual dysfunction, conservative techniques are increasingly used, with narrow excisional margins [4,5] and innovative plastic repair [6], as are laser treatment [7] and Mohs micrographic surgery [8–11] for squamous carcinoma of the penis, but the concepts of field change and the implications of infection by HPV and multifocality must be considered. There is a place for sentinel node biopsy. Radiotherapy may be offered as an adjunct to surgery or as definitive alternative treatment. Combination chemotherapy has been used for palliation and proposed for adjuvant treatment of carcinoma of the penis, but remains under evaluation [12].

Lymphatic or haematogenous dissemination of genital cancer dictates individualized multidisciplinary treatment. The management of ilioinguinal lymphadenopathy is controversial [12,13].

The prognosis of penis cancer relates to the extent of inguinal lymphadenopathy [14,15] and involvement of the corpus [16]. It does not correlate with HPV status [17]. Penile cancer puts wives and consorts at risk of cervical cancer [18]. In black men who develop penile cancer there is a substantial risk (18%) of the later development of a second primary malignancy [19].

The prognosis for scrotal carcinoma is not good, despite apparently adequate primary surgical treatment: the 5-year mortality is 50–60% [20,21].

References

1 Heyns CF, van Vollenhoven P, Steenkamp JW, Allen FJ. Cancer of the penis: a review of 50 patients. *S Afr J Surg* 1997; **35**: 120–4.
2 Prosvic P, Morávek P, Stefan H, Veselsky Z. An unusual finding of penile carcinoma: case record. *Rozhl Chir* 1997; **76**: 454–7.
3 Schoeneich G, Perabo FG, Muller SC. Squamous cell carcinoma of the penis. *Andrologia* 1999; **31** (Suppl. 1): 17–20.
4 Pietrzak P, Corbishley C, Watkin N. Organ-sparing surgery for invasive penile cancer: early follow-up data. *Br J Urol* 2004; **94**: 1253–7.
5 Minhas S, Kayes O, Hegarty P *et al.* What surgical resection margins are required to achieve oncological control in men with primary penile cancer? *BJU Int* 2005; **96**: 1040–3.
6 Donnellan SM, Webb DR. Management of invasive penile cancer by synchronous penile lengthening and radical tumour excision to avoid perineal urethrostomy. *Aust NZ J Surg* 1998; **68**: 369–70.
7 Tietjen DN, Malek RS. Laser therapy of squamous cell dysplasia and carcinoma of the penis. *Urology* 1998; **52**: 559–65.
8 Mohs FE, Snow SN, Messing EM, Kuglitsch ME. Microscopically controlled surgery in the treatment of carcinoma of the penis. *J Urol* 1985; **133**: 961–6.
9 Bernstein G, Forgaard DM, Miller JE. Carcinoma of the glans penis and distal urethra. *J Dermatol Surg Oncol* 1986; **12**: 450.
10 Brown MD, Zachary CB, Grekin RC *et al.* Penile tumours: their management by Mohs micrographic surgery. *J Dermatol Surg Oncol* 1987; **13**: 1163–7.
11 Brown MD, Zachary CB, Grekin RC, Swanson NA. Genital tumours: their management by micrographic surgery. *J Am Acad Dermatol* 1988; **18**: 115–22.
12 Syed S, Eng TY, Thomas CR *et al.* Current issues in the management of advanced squamous cell carcinoma of the penis. *Urol Oncol* 2003; **21**: 431–8.
13 McDougal WS, Kirchner FR, Edwards RH, Killion LZ. Treatment of carcinoma of the penis: case for primary lymphadenectomy. *J Urol* 1986; **136**: 38–41.
14 Droller MJ. Carcinoma of the penis: an overview. *Urol Clin North Am* 1980; **7**: 783–4.
15 Srinivas V, Morse MJ, Herr HW *et al.* Penile cancer: relation of extent of nodal metastasis and survival. *J Urol* 1987; **137**: 880.
16 Soria J-C, Fizazi K, Piron D *et al.* Squamous cell carcinoma of the penis: multivariate analysis of prognostic factors and natural history in a monocentric study with a conservative policy. *Ann Oncol* 1997; **8**: 1089–98.
17 Bezerra ALR, Lopes A, Santiago GH *et al.* Human papillomavirus as a prognostic factor in carcinoma of the penis: analysis of 82 patients treated with amputation and bilateral lymphadenectomy. *Cancer* 2001; **91**: 2315–21.
18 Smith PG, Kinlen LJ, White GC *et al.* Mortality of wives of men dying with cancer of the penis. *Br J Cancer* 1980; **41**: 422–8.
19 Hubbell CR, Rabin VR, Mora RG. Cancer of the skin in blacks. V. A review of 175 black patients with squamous cell carcinoma of the penis. *J Am Acad Dermatol* 1988; **18**: 292–8.
20 Lowe FC. Squamous cell carcinoma of the scrotum. *J Urol* 1983; **130**: 423–7.
21 Gerber WL. Scrotal malignancies: the University of Iowa experience and a review of the literature. *Urology* 1985; **26**: 337–42.

Verrucous carcinoma/giant condyloma/ Buschke–Löwenstein tumour

Buschke–Löwenstein tumour and verrucous carcinoma can probably be regarded as synonymous, both terms representing verrucous, low-grade, well-differentiated squamous carcinoma. It is perhaps more accurate and more clinically useful to consider giant condyloma as a separate HPV-related entity with a better prognosis, but the matter is controversial [1–6].

Verrucous carcinoma is rare. It produces dramatic polypoid or cauliflower-like clinical lesions (Fig. 71.19). Presentation as a penile cutaneous horn has been described [7–9]. Although locally deeply invasive, the tumour is well demarcated from sur-

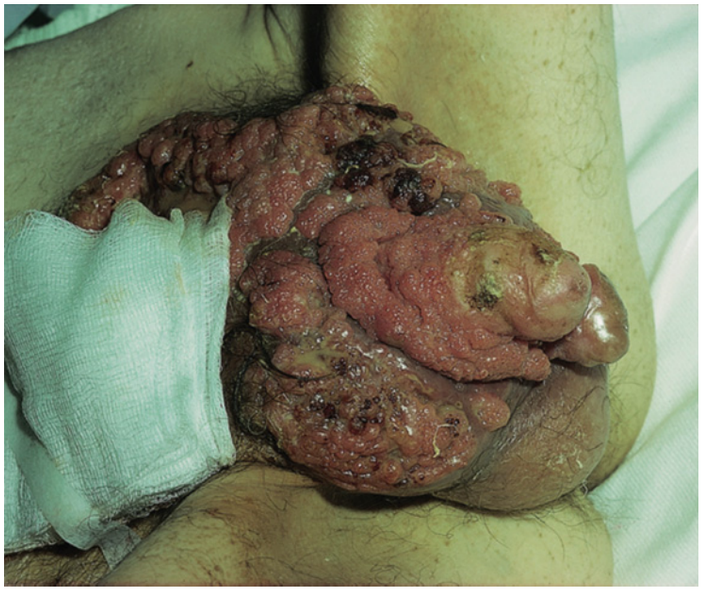


Fig. 71.19 Gross condylomas of Buschke–Löwenstein of the penis. (Courtesy of Professor R.M. MacKie, Glasgow University, Glasgow, UK.)

rounding tissue and is unlikely to metastasize. Both sexes can be affected.

A specific aetiology for verrucous carcinoma of Buschke–Löwenstein has not been unequivocally identified, but an origin from genital warts is likely. HPV types 6 and 11 are the most commonly associated [1,3,4,10–16]. A patient taking ciclosporin for psoriasis developed a verrucous carcinoma containing HPV 6 and 16 [17]. Multiple HPV types were found in a transplant patient [18]. Tumours containing several HPV types may be mixed, containing verrucous carcinoma adjacent to squamous carcinoma [19]. Tumours occurring on background lichen sclerosus, rarely chronic hidradenitis suppurativa and very rarely lichen planus, have occurred [20–23].

If verrucous carcinoma is suspected, then a deep surgical biopsy must be performed. The tumour has a different histology from squamous carcinoma, showing deep lobular invaginations of well-defined proliferative epithelium consisting of typical clear pale keratinocytes [24]. Frank squamous carcinoma [25] and foci of invasive squamous carcinoma [26] have been reported in some cases of anogenital verrucous carcinoma. Ultrastructurally, verrucous carcinoma is distinct from condyloma acuminatum but similar to SCC [27].

Clinical, histological and virological differences may distinguish verrucous carcinoma (potential for aggressive lethal behaviour) from Buschke–Löwenstein tumour, and giant condyloma (no malignant potential), and this distinction could direct treatment [2,3,11,13,16].

Surgical excision is the treatment usually recommended (e.g. glansectomy [28] or penectomy). Mohs micrographic surgery [29–31], cryotherapy [32], laser treatment [33], interferon-α [34–37], radiotherapy [38] or bleomycin [39] are alternatives.

The prognosis can be poor because the verrucous carcinoma might continue to grow and invade locally, causing death by exsanguination from femoral arterial invasion or cachexia [40]. Even with treatment, recurrence and progressive malignant transformation do occur [41,42], so follow-up is necessary.

References

1 Schwartz RA. Buschke-Loewenstein tumor: verrucous carcinoma of the penis. *J Am Acad Dermatol* 1993; **23**: 723–7.

2 Niederauer HH, Weindorf N, Schultz-Ehrenburg U. Ein fall von condyloma acuminatum giganteum. *Hautarzt* 1993; **44**: 795–9.

3 Anadolu R, Boyvat A, Calikoglu E, Gurler A. Buschke–Loewenstein tumour is not a low-grade carcinoma but a giant verruca. *Acta Dermatol Venereol* 1999; **79**: 253–4.

4 Dogan G, Oram Y, Hazneci E *et al.* Three cases of verrucous carcinoma. *J Dermatol* 1998; **39**: 251–4.

5 Codina I, Muniz C, Beyrie W *et al*. Giant condyloma of the penis. *Arch Esp Urol* 1999; **52**: 1090–2.

6 Cubilla AL, Velazques EF, Reuter VE *et al.* Warty (condylomatous) squamous cell carcinoma of the penis: a report of 11 cases and proposed classification of 'verruciform' penile tumors. *Am J Surg Pathol* 2000; **24**: 505–12.

7 Yeager JK, Findlay RF, McAleer IM. Penile verrucous carcinoma. *Arch Dermatol* 1990; **126**: 1208–10.

8 Karthikeyan K, Thappa DM, Jaisankar TJ *et al.* Cutaneous horn of glans penis. *Sex Transm Infect* 1998; **74**: 456–7.

9 Zhu J-W, Luo D, Li C-R *et al*. A case of penile verrucous carcinoma associated with cutaneous horn. *Clin Exp Dermatol* 2007; **32**: 213–4.

10 Boshart M, zur Hausen H. Human papillomaviruses in Buschke–Löwenstein tumours: physical state of the DNA and identification of a tandem duplication in the non-coding region of a human papillomavirus 6 subtype. *J Virol* 1986; **58**: 963–6.

11 Noel JC, Vandenbossche M, Peny MO *et al.* Verrucous carcinoma of the penis: importance of human papillomavirus typing for diagnosis and therapeutic decision. *Eur Urol* 1992; **22**: 83–5.

12 Grassegger A, Hopfl R, Hussl H *et al*. Buschke-Loewenstein tumour infiltrating pelvic organs. *Br J Dermatol* 1994; **130**: 221–5.

13 Gonzalez-Lopez A, Esquivias JI, Miranda-Romero A *et al.* Buschke–Löwenstein tumor and immunity. *Cutis* 1997; **59**: 119–22.

14 Dianzani C, Bucci M, Pierangeli A *et al*. Association of human papilloma virus type 11 with carcinoma of the penis. *Urology* 1998; **51**: 1046–8.

15 Yagi H, Igawa M, Shiina H *et al.* A study of growth pattern in giant condyloma acuminatum. *Urol Int* 1998; **61**: 188–91.

16 Haycox CL, Kuypers J, Krieger JN. Role of human papillomavirus typing in diagnosis and clinical decision making for a giant verrucous genital lesion. *Urology* 1999; **53**: 627–30.

17 Piepkorn M, Kumasaka B, Krieger JN, Burmer GC. Development of human papillomavirus-associated Buschke–Löwenstein penile carcinoma during cyclosporine therapy for generalized pustular psoriasis. *J Am Acad Dermatol* 1993; **29**: 321–5.

18 Soler C, Chardonnet Y, Allibert P *et al.* Detection of multiple types of human papillomavirus in a giant condyloma from a grafted patient: analysis by immunohistochemistry, *in situ* hybridization, Southern blot and polymerase reaction. *Virus Res* 1992; **23**: 193–208.

19 Noel JC, de Dobbeleer G. Development of human papillomavirus-associated Buschke–Löwenstein penile carcinoma during cyclosporine therapy for generalized pustular psoriasis. *J Am Acad Dermatol* 1994; **31**: 299–300.

20 Weber P, Rabinovitz H, Garland L. Verrucous carcinoma in penile lichen sclerosus et atrophicus. *J Dermatol Surg Oncol* 1987; **13**: 529.

21 Micali G, Nasca MR, Innocenzi D. Lichen sclerosus of the glans is significantly associated with penile carcinoma. *Sex Transm Infect* 2001; **77**: 226.

22 Cosman BC, O'Grady TC, Pekarske S. Verrucous carcinoma arising in hidradenitis suppurativa. *Int J Colorectal Dis* 2000; **15**: 342–6.

23 Bain L, Geronemus R. The association of lichen planus of the penis with squamous cell carcinoma in situ and with verrucous squamous carcinoma. *J Dermatol Surg Oncol* 1989; **15**: 413–7.

24 Lucia MS, Miller GJ. Histopathology of malignant lesions of the penis. *Urol Clin North Am* 1992; **19**: 227–46.

25 Sturm JT, Christenson CE, Vecker JH *et al.* Squamous cell carcinoma of the anus arising in a giant condyloma acuminatum. *Dis Colon Rectum* 1975; **18**: 147–51.

26 Johnson DE, Lo RK, Srigley J, Ayala AG. Verrucous carcinoma of the penis. *J Urol* 1985; **133**: 216–8.

27 Hull MT, Eble JN, Priest JB, Mulcahy JJ. Ultrastructure of Buschke–Loewenstein tumor. *J Urol* 1981; **126**: 485–9.
28 Hatzichristou DG, Apostolidis A, Tzortzis V *et al.* Glansectomy: an alternative surgical treatment for Buschke–Löwenstein tumors of the penis. *Urology* 2001; **57**: 966–9.
29 Mohs FE, Sahl WJ. Chemosurgery for verrucous carcinoma. *J Dermatol Surg Oncol* 1979; **5**: 302.
30 Brown MD, Zachary CB, Grekin RC *et al.* Penile tumours: their management by Mohs micrographic surgery. *J Dermatol Surg Oncol* 1987; **13**: 1163–7.
31 Brown MD, Zachary CB, Grekin RC, Swanson NA. Genital tumours: their management by micrographic surgery. *J Am Acad Dermatol* 1988; **18**: 115–22.
32 Hughes PSH. Cryosurgery of verrucous carcinoma of the penis (Buschke–Löwenstein tumor). *Cutis* 1979; **24**: 43–5.
33 Lenk S, Oesterwitz H, Audring H. Laser surgery in superficial penile tumours. *Int Urol Nephrol* 1991; **23**: 357–63.
34 Zachariae H, Larsen PM, Sogaard H. Recombinant interferon-α2A (Roferon-A) in a case of Buschke–Löwenstein giant condyloma. *Dermatologica* 1988; **177**: 175–9.
35 Risse L, Négrier P, Dang PM *et al.* Treatment of verrucous carcinoma with recombinant alfa-interferon. *Dermatology* 1995; **190**: 142–4.
36 Geusau A, Heinz-Peer G, Volc-Platzer B *et al*. Regression of deeply infiltrating giant condyloma (Buschke-Löwenstein tumor) following long-term intralesional interferon alfa therapy. *Arch Dermatol* 2000; **136**: 707–10.
37 Gomez De La Fuente E, Castano Suarez E, Vanaclocha Sebastian F *et al*. Verrucous carcinoma of the penis completely cured with shaving and intralesional interferon. *Dermatology* 2000; **200**: 152.
38 Sobrado CW, Mester M, Nadalin W *et al.* Radiation-induced total regression of a highly recurrent giant perianal condyloma: report of case. *Dis Colon Rectum* 2000; **43**: 257–60.
39 Puissant A, Pringuet R, Noory JY *et al.* Condylome acumine geant (syndrome de Buschke–Löwenstein): action de la bleomycine. *Bull Soc Francaise Dermatol Syphiligr* 1972; **79**: 9–12.
40 South LM, O'Sullivan JP, Gazet JC. Giant condylomata of Buschke and Löwenstein. *Clin Oncol* 1977; **3**: 107–15.
41 Tessler AN, Applebaum SM. The Buschke–Löwenstein tumor. *Urology* 1982; **20**: 36–9.
42 Creasman C, Haas PA, Fox TA Jr, Balazs M. Malignant transformation of anorectal giant condyloma acuminatum (Buschke–Loewenstein tumour). *Dis Colon Rectum* 1989; **32**: 481–7.

Other malignant neoplasms

Extramammary Paget's disease

Extramammary Paget's disease (EMPD) is discussed in Chapter 53. EMPD presents as irritating, itchy, burning, red scaly patches or plaques that may be solitary or multifocal. EMPD can occur anywhere in the anogenital area, including the glans penis [1–3]. Penile EMPD is frequently misdiagnosed as psoriasis, eczema [4], or Bowen's disease. An 'underpants' pattern of erythema has been reported in a number of patients [5]. Subclinical EMPD has been documented, where the skin looks normal macroscopically but is involved microscopically. EMPD behaves indolently, spreading by local extension and metastasis [6,7].

The concurrence of genital and extragenital EMPD is extremely rare, but overt and latent axillary EMPD can coexist and change daily in association with penile and pubic EMPD [8]. Also very rare is depigmented EMPD of the genitalia, evoking the differential diagnosis of vitiligo, hypopigmented mycosis fungoides and lichen sclerosus [9]. A focus of cutaneous squamous carcinoma has been reported complicating genital EMPD [10].

Diagnosis is by biopsy. Histological examination shows nests of large vacuolated cells with circular nuclei and foamy pale cytoplasm in the epidermis (Paget's cells). Dermal involvement signifies a poor prognosis. Pagetoid dyskeratosis can be found in a number of benign lesions such as naevi, skin tags and lentigines [11]. Pale cells resembling Paget's cells can be seen incidentally in benign papular intertriginous conditions, and in nearly 40% of prepuces sent for histological examination following circumcision for phimosis [11–13]. Anogenital Paget's disease can be accompanied by epidermal hyperplasia similar to fibroepithelioma of Pinkus [14]. Immunohistochemical and enzyme histochemical evidence points to sweat gland epithelium as the source of Paget's cells in EMPD [15]. The distribution along the 'milk line' has led to the suggestion that the 'clear cells of Toker' are the histogenic precursors of both clear cell papulosis and mammary and extramammary Paget's disease, respectively [9]. HPV is not present [16], but the c-erbB-2 oncoprotein may have a role in the pathogenesis of EMPD [17].

Mammary Paget's disease is an epidermal manifestation of an underlying breast adenocarcinoma [18]. EMPD is found in areas rich in apocrine sweat glands, such as the axillae and anogenital region and it can also be associated with an underlying malignancy [6]. In a large series, 24% of patients had a proximate cutaneous adnexal adenocarcinoma, 12% were found to have a concurrent, and another 17% to have a non-concurrent internal malignancy [19].

Although properly regarded as a type of carcinoma *in situ*, EMPD may itself become invasive and metastatic [20–22]. There may be subjacent carcinoma (e.g. in periurethral glands) [23] or distant carcinoma (e.g. prostate [24] or bladder [25]), or both (e.g. periurethral glands and bladder [26]). Pagetoid epidermal invasion of inguinal cutaneous metastatic mesothelioma of the tunica vaginalis of the testis has been reported [27].

Treatments used for EMPD include cryotherapy and topical 5-fluorouracil [28], wide excisional surgery [20], micrographic surgery [29,30], radiotherapy [7,31] and photodynamic therapy [3,7,20,28–33]. Topical imiquimod shows much promise [34]. Excision of an underlying neoplasm, if present, can cause regression of the EMPD [35].

References

1 Helwig EB, Graham JH. Anogenital (extramammary) Paget's disease: a clinicopathological study. *Cancer* 1963; **16**: 387–403.
2 Metcalf JS, Lee RE, Maize JC. Epidermotropic urothelial carcinoma involving the glans penis. *Arch Dermatol* 1985; **121**: 532–4.
3 Bunker CB. *Male Genital Skin Disease*. Saunders: London, 2004.
4 Aldeen T, Lau RK. Genital eczema in an elderly man. *Int J STD AIDS* 1999; **10**: 124–6.
5 Murata Y, Kumano K, Tani M. Underpants-pattern erythema: a previously unrecognized cutaneous manifestation of extramammary Paget's disease of the genitalia with advanced metastatic spread. *J Am Acad Dermatol* 1999; **40**: 949–56.
6 Helwig EB, Graham IH. Anogenital (extramammary) Paget's disease: a clinicopathological study. *Cancer* 1963; **16**: 387–403.
7 Gerber WL. Scrotal malignancies: the University of Iowa experience and a review of the literature. *Urology* 1985; **26**: 337–42.
8 Imakado S, Abe M, Okuno T *et al.* Two cases of genital Paget's disease with bilateral axillary involvement: mutability of axillary lesions. *Arch Dermatol* 1991; **127**: 1243.
9 Chen YH, Wong TW, Lee JY. Depigmented genital extramammary Paget's disease: a possible histogenetic link to Toker's clear cells and clear cell papulosis. *J Cutan Pathol* 2001; **28**: 105–8.
10 Tanabe H, Kishigawa T, Sayama S, Tanaka T. A case of giant extramammary Paget's disease of the genital area with squamous cell carcinoma. *Dermatology* 2001; **202**: 249–51.

11 Tschen JA, McGavran MH, Kettler AH. Pagetoid dyskeratosis: a selective keratinocytic response. *J Am Acad Dermatol* 1988; **19**: 891–4.
12 Val-Bernal JF, Garijo MF. Pagetoid dyskeratosis of the prepuce: an incidental histologic finding resembling extramammary Paget's disease. *J Cutan Pathol* 2000; **27**: 387–91.
13 Kohler S, Rouse RV, Smoller BR. The differential diagnosis of Pagetoid cells in the epidermis. *Mod Pathol* 1998; **11**: 79–92.
14 Ishida-Yamamoto A, Sato K, Wada T *et al*. Fibroepithelioma-like changes occurring in perianal Paget's disease with rectal mucinous carcinoma: case report and review of 49 cases of extramammary Paget's disease. *J Cutan Pathol* 2002; **29**: 185–9.
15 Hamm H, Vroom TM, Czarnetski BM. Extramammary Paget's cells: further evidence of sweat gland derivation. *J Am Acad Dermatol* 1986; **15**: 1275–81.
16 Snow SN, Desouky S, Lo JS, Kurtycz D. Failure to detect human papillomavirus DNA in extramammary Paget's disease. *Cancer* 1992; **69**: 249–51.
17 Wolber RA, Dupuis BA, Wick MR. Expression of C-erb-2 oncoprotein in mammary and extramammary Paget's disease. *Am J Clin Pathol* 1991; **96**: 243–7.
18 Paget J. On disease of the mammary areola preceding carcinoma of the mammary gland. *St Bart's Hosp Rep* 1874; **10**: 87–9.
19 Chanda JJ. Extramammary Paget's disease: prognosis and relationship to internal malignancy. *J Am Acad Dermatol* 1985; **13**: 1009–14.
20 Jensen SL. A randomized trial of simple excision of non-specific hypertrophied anal papillae versus expectant management in patients with chronic pruritus ani. *Ann R Coll Surg Engl* 1988; **70**: 348–9.
21 Iwamura H, Horri Y, Tokuchi H, Arai E. A case of genital Paget's disease with severe dermal invasion and early dissemination. *Acta Urol Jap* 1999; **45**: 281–4.
22 Khoubehi B, Schofield A, Leslie M *et al*. Metastatic *in situ* perianal Paget's disease. *J R Soc Med* 2001; **94**: 137–8.
23 Jenkins IL. Extra-mammary Paget's disease of the penis. *Br J Urol* 1989; **63**: 103–4.
24 Koh FBH, Nazarina AR. Paget's disease of the scrotum: report of a case with underlying carcinoma of the prostate. *Br J Dermatol* 1995; **133**: 306–7.
25 Turner AG. Pagetoid lesions associated with carcinoma of the bladder. *J Urol* 1980; **123**: 124–6.
26 Tomaszewski JE, Korat OC, LiVolsi VA *et al*. Paget's disease of the urethral meatus following transitional cell carcinoma of the bladder. *J Urol* 1986; **135**: 368–70.
27 Cartwright LE, Steinman HK. Malignant papillary mesothelioma of the tunica vaginalis testes: cutaneous metastases showing epidermal invasion. *J Am Acad Dermatol* 1987; **17**: 887–90.
28 Arensmeier M, Theuring U, Franke I *et al*. Topical therapy of extramammary Paget's disease. *Hautarzt* 1994; **45**: 780–2.
29 Mohs FE, Blanchard I. Microscopically controlled surgery for extramammary Paget's disease. *Arch Dermatol* 1979; **115**: 706–8.
30 Brown MD, Zachary CB, Grekin RC, Swanson NA. Genital tumours: their management by micrographic surgery. *J Am Acad Dermatol* 1988; **18**: 115–22.
31 Rosin RD. Paget's disease of the anus. *J R Soc Med* 1991; **84**: 112–3.
32 Petrelli NJ, Cebollero JA, Rodriguez-Bigas M, Mang T. Photodynamic therapy in the management of neoplasms of the perianal skin. *Arch Dermatol* 1992; **127**: 1436–8.
33 Zollo JD, Zeitouni NC. The Roswell Park Cancer Institute experience with extramammary Paget's disease. *Br J Dermatol* 2000; **142**: 59–65.
34 Cohen PR, Schulze KE, Tschen JA *et al*. Treatment of extramammary Paget disease with topical imiquimod cream: case report and literature review. *South Med J* 2006; **99**: 396–402.
35 Bowling JCR, Powles A, Searle A *et al*. Spontaneous regression of extramammary Paget's disease after excision of primary apocrine carcinoma in an immunosuppressed patient. *Br J Dermatol* 2005; **153**: 676–7.

Malignant melanoma

This is a very rare condition of the penis (fewer than 100 cases reported). It is estimated to account for 1–1.5% of all malignancies of the penis [1,2] and less than 0.15% of all melanomas [3]. Melanoma is even rarer on the scrotum, with only four cases appearing in the literature [4,5].

Genital melanoma presents as a pigmented macule or as a pigmented or amelanotic papule or nodule, possibly developing from a lentiginous area or pre-existing dysplastic naevus or 'kissing' naevus, that may ulcerate or bleed [1,2,6–14,15]. Multifocal melanoma of the glans penis has been reported [16]. Patients are usually middle-aged or older, although it has been reported in a boy [17]. It is exceedingly rare in Asians and has not been reported in black people (although a case of melanoma of the urethra has been seen) [18].

Sixty to 70% of lesions occur on the glans. There may be a family history of melanoma and other atypical or 'dysplastic' naevi on examination. The inguinal and other nodes, as well as the abdomen, should be palpated. Forty to 50% of patients have lymphatic or other metastatic dissemination at the time of presentation. Clinically atypical lesions should be biopsied and the histology critically reviewed [7,11]. Malignant melanoma of any histological subtype may be encountered [19].

Treatment is by primary excision. Subsequent management depends on the Breslow thickness of the lesion and complete clinical staging. Radical surgery and chemotherapy may be needed, but the prognosis is poor for all melanomas that have already metastasized [1,17,20].

References

1 Johnson DE, Ayala AG. Primary melanoma of the penis. *Urology* 1973; **2**: 174–7.
2 Stillwell TJ, Zincke H, Gaffey TA, Woods JE. Malignant melanoma of the penis. 1988; **140**: 72–5.
3 Cascinelli N. Melanoma maligno del pene. *Tumori* 1969; **55**: 313–5.
4 Gerber WL. Scrotal malignancies: the University of Iowa experience and a review of the literature. *Urology* 1985; **26**: 337–42.
5 Davis NS, Kim CA, Dever DP. Primary malignant melanoma of the scrotum: case report and literature review. *J Urol* 1991; **145**: 1056–7.
6 Bracken RB, Diokno AC. Melanoma of the penis and the urethra: two case reports and review of the literature. *J Urol* 1974; **111**: 198–200.
7 Jaeger N, Wirler H, Tschubel K. Acral lentiginous melanoma of the penis. *Eur J Urol* 1982; **8**: 182–4.
8 Jorda E, Verdeger JM, Moragon M *et al*. Desmoplastic melanoma of the penis. *J Am Acad Dermatol* 1987; **16**: 619–20.
9 Oldbring J, Mikulowski P. Malignant melanoma of the penis and male urethra: report of nine cases and review of the literature. *Cancer* 1987; **59**: 581–7.
10 Manivel JC, Fraley EE. Malignant melanoma of the penis and male urethra: four case reports and literature review. *J Urol* 1988; **139**: 813.
11 Weiss J, Elder D, Hamilton R. Melanoma of the male urethra: surgical approach and pathological analysis. *J Urol* 1982; **128**: 382–5.
12 de Bree E, Sanidas E, Tzardi M *et al*. Malignant melanoma of the penis. *Eur J Surg Oncol* 1997; **23**: 277–9.
13 Demitsu T, Nagato H, Nishimaki K *et al*. Melanoma *in situ* of the penis. *J Am Acad Dermatol* 2000; **42**: 386–8.
14 Honda S, Yamamoto O, Suenaga Y *et al*. Six cases of metastatic malignant melanoma with apparently occult primary lesions. *J Dermatol* 2001; **28**: 265–71.
15 Egberts F, Egberts JH, Schwarz T, Hauschild A. Kissing melanoma or kissing nevus of the penis? *Urology* 2007; **69**: 384.e5–7.
16 Hankins CL, Kotwal S, Majumder S *et al*. Multifocal melanoma of the glans penis. *Plast Reconstr Surg* 2006; **118**: 33e–8e.
17 Begun FP, Grossman HB, Dionko AC *et al*. Malignant melanoma of the penis and male urethra. *J Urol* 1984; **132**: 123–5.
18 Sanders TJ, Venable DD, Sanusi ID. Primary malignant melanoma of the urethra in a black man: a case report. *J Urol* 1986; **135**: 1012–4.
19 Lucia MS, Miller GJ. Histopathology of malignant lesions of the penis. *Urol Clin North Am* 1992; **19**: 227–46.
20 Bundrick WS, Culkin DJ, Mata JH *et al*. Penile malignant melanoma in association with squamous carcinoma of the penis. *J Urol* 1991; **146**: 1364–5.

Kaposi's sarcoma

Solitary Kaposi's sarcoma (KS) of the penis was very rarely seen before the HIV epidemic and cases are still occasionally seen in HIV-negative patients [1–3], but genital KS is essentially an HIV-associated problem. It presents on the penis or scrotum, perineum or perianal skin in one of its classic forms: purple, slightly scaly patches or plaques, nodules or ulcerative lesions [4]. More atypical presentations that have been seen include engorgement with hypervascularity [5], penile lymphoedema [6] and phimosis. The differential diagnosis includes cellular naevus, histiocytoma, angioma, angiokeratoma, pseudo-Kaposi's sarcoma [7], bacillary angiomatosis and melanoma.

References

1 Dehner LP, Smith BH. Soft tissue tumours of the penis. *Cancer* 1970; **25**: 1431–7.
2 Kavak A, Akman RY, Alper M, Büyükbabani N. Penile Kaposi's sarcoma in a human immunodeficiency virus-seronegative patient. *Br J Dermatol* 2001; **144**: 207–8.
3 Micali G, Nasca MR, De Pasquale R, Innocenzi D. Primary classic Kaposi's sarcoma of the penis: a report of a case and review. *J Eur Acad Dermatol Venereol* 2003; **17**: 320–3.
4 Schwartz JJ, Dias BM, Safari B. HIV-related malignancies. *Dermatol Clin* 1991; **9**: 503–15.
5 Bayne D, Wise GJ. Kaposi sarcoma of the penis and genitalia: a disease of our times. *Urology* 1988; **31**: 22–5.
6 Schwartz RA, Cohen JB, Watson RA *et al.* Penile Kaposi's sarcoma preceded by chronic penile lymphoedema. *Br J Dermatol* 2000; **142**: 153–6.
7 Kapdagli H, Gunduz K, Ozturk G, Kandiloglu G. Pseudo-Kaposi's sarcoma (Mali type). *Int J Dermatol* 1998; **37**: 223–5.

Miscellaneous malignant neoplasms

Although basal cell carcinoma is the most common type of skin cancer, it is rare in the anogenital area, although over 100 cases have been reported [1], including one case report of fibroepithelioma of Pinkus affecting the base of the penis [2]. A case of multiple erosive scrotal basal cell carcinomas with metastasis has been described [3].

Fibrosarcoma, haemangiopericytoma, leiomyosarcoma, malignant fibrous histiocytoma, epithelioid sarcoma, dermatofibrosarcoma protuberans and spindle cell sarcoma may occur, presenting as painful or painless nodules, masses or swelling with dysuria and erectile difficulties (e.g. masquerading as Peyronie's disease) [4–6]. Other rarities include Merkel cell carcinoma [7], malignant eccrine poroma [8], malignant schwannoma [4,9] and solitary reticulohistiocytic granuloma of the scrotum [10]. Scrotal angiosarcoma complicating oedema following surgery and radiotherapy for carcinoma of the rectum has been described [11].

Involvement of the penis with Langerhans' cell histiocytosis is very rare; fleshy papules on the dorsal penis, a painful nodule of the prepuce and penile ulceration have been reported [12,13].

Mycosis fungoides can be confined to or concentrated in the genital region. Localized perianal involvement [14], a solitary plaque on the penis [15] and response to treatment with imiquimod have been described [15,16].

Although lymphoma is the most frequent secondary tumour of the testis, it is rare in other parts of the male urogenital tract [4]. Penile lymphoma can present as painless subcutaneous nodules, erythematous swelling, phimosis and ulceration [17–22]. There may be no evidence of systemic lymphoma. Ulcerating scrotal lymphoma has been reported [23], as have scrotal and penile ulceration resulting from leukaemic infiltration [24,25].

Metastases to the penis are rare, but several hundred cases have been reported [26]. They are usually secondary to cancer of the urogenital tract [27] or gastrointestinal system, or other common cancers such as of the lung [28], and present with pain, swelling, priapism, urinary symptoms or haematuria. A very rare cause is secondary melanoma [26,29].

References

1 Gibson GE, Ahmed I. Perianal and genital basal cell carcinoma: a clinicopathologic review of 51 cases. *J Am Acad Dermatol* 2001; **45**: 68–71.
2 Heymann WR, Soifer I, Burk PG. Penile premalignant fibroepithelioma of Pinkus. *Cutis* 1983; **31**: 519–21.
3 Staley TE, Nieh PT, Ciesielski TE, Cieplinski W. Metastatic basal cell carcinoma of the scrotum. *J Urol* 1983; **130**: 792–4.
4 Dehner LP, Smith BH. Soft tissue tumours of the penis. *Cancer* 1970; **25**: 1431–7.
5 Moore SW, Wheeler JE, Hefter LG. Epithelioid sarcoma masquerading as Peyronie's disease. *Cancer* 1975; **35**: 1706–10.
6 Mendis D, Bott SR, Davies JH. Subcutaneous leiomyosarcoma of the frenulum. *Scientific World J* 2005; **5**: 571–5.
7 Best TJ, Metcalfe JB, Moore RB, Nguyen GK. Merkel cell carcinoma of the scrotum. *Ann Plast Surg* 1994; **33**: 83–5.
8 Werdin R, Kupczyk-Joeris D, Schumpelick V. Malignant eccrine poroma: case report of a rare tumour of the skin. *Chirurg* 1991; **62**: 350–2.
9 Marsidi PJ, Winter CC. Schwannoma of penis. *Urology* 1980; **16**: 303.
10 Anaguchi S, Sinomiya S, Kinebuchi S, Kumakiri M. Solitary reticulohistiocytic granuloma: a report of three cases and a review of the literature. *Nippon Hifuka Gakkai Zasshi* 1991; **101**: 735–42.
11 Chiu LS, Wong KH, Lam WY *et al*. Angiosarcoma of the scrotum after treatment of cancer of the rectum. *Clin Exp Dermatol* 2006; **31**: 706–7.
12 Seseke F, Kugler A, Hermanns M *et al*. Langerhans' cell histiocytosis of the penis. *Urologe A* 1999; **38**: 42–5 [in German].
13 Hagiuda J, Ueno M, Ashimine S *et al*. Langerhans cell histiocytosis on the penis: a case report. *BMC Urol* 2006; **6**: 28.
14 Hill VA, Hall-Smith P, Smith NP. Cutaneous T-cell lymphoma presenting with atypical perianal lesions. *Dermatology* 1995; **190**: 313–6.
15 Ariffin N, Khorshid M. Treatment of mycosis fungoides with imiquimod 5% cream. *Clin Exp Dermatol* 2006; **31**: 822–3.
16 Chiam LY, Chan YC. Solitary plaque mycosis fungoides on the penis responding to topical imiquimod therapy. *Br J Dermatol* 2007; **156**: 560–2.
17 Gonzalez-Campora R, Nogales FF Jr, Lerma E *et al*. Lymphoma of the penis. *J Urol* 1981; **126**: 270–1.
18 Marks D, Crosthwaite A, Varigos G *et al.* Therapy of primary diffuse large cell lymphoma of the penis with preservation of function. *J Urol* 1988; **139**: 1057.
19 Cribier B, Lipsker D, Grosshans E *et al.* Genital ulceration revealing a primary cutaneous anaplastic lymphoma. *Genitourin Med* 1997; **73**: 325.
20 Tomb RR, Stephan F, Klein-Tomb L *et al*. Recurrent primary $CD30^+$ lymphoma of the penis. *Br J Dermatol* 2003; **149**: 903–5.
21 Haque S, Noble J, Wotherspoon A *et al*. MALT lymphoma of the foreskin. *Leuk Lymphoma* 2004; **45**: 1699–701.
22 Thorns C, Urban H, Remmler K *et al*. Primary cutaneous T-cell lymphoma of the penis. *Histopathology* 2003; **42**: 513–4.
23 Doll DC, Diaz-Arias AA. Peripheral T-cell lymphoma of the scrotum. *Acta Haematologica* 1994; **91**: 77–9.
24 Gatto-Weis C, Topolsky D, Sloane B *et al.* Ulcerative balanoposthitis of the foreskin as a manifestation of chronic lymphocytic leukemia: case report and review of the literature. *Urology* 2000; **56**: 669.
25 Zax RH, Kulp-Shorten CL, Callen JP. Leukaemia cutis presenting as a scrotal ulcer. *J Am Acad Dermatol* 1989; **21**: 410–3.
26 Sagar SM, Retsas S. Metastasis of the penis from malignant melanoma: case report and review of the literature. *Clin Oncol* 1992; **4**: 130–1.
27 Kurul S, Aykan F, Tas F. Penile metastasis of cutaneous malignant melanoma: a true hematogenous spread?: case report and review of the literature. *Melanoma Res* 2006; **16**: 259–61.

28 Miyamoto T, Ikehara A, Araki M *et al*. Cutaneous metastatic carcinoma of the penis: suspected metastasis implantation from a bladder tumor. *J Urol* 2000; **163**: 1519.
29 Ortiz de Saracho J, Castrodeza Sanz R, Guzmán Dávila G. Penile metastasis and pulmonary carcinoma. *Arch Bronconeumol* 1998; **34**: 226–7 [in Spanish].

Miscellaneous

Penile melanosis

Pigmentary change is dealt with in the general introduction on pp. 71.2–71.3, and causes of anogenital hypo- and hyperpigmentation are listed in Tables 71.6 and 71.7.

Pigmented macules are not uncommon on the glans and shaft of the penis [1,2]. They are benign but, because they may be large or enlarging, with irregular edges and multifocal and variegated pigmentary patterns, they arouse concern about atypical melanocytic proliferation and acral lentiginous melanoma. Such clinical concerns should lead to biopsy [3]; it is important to decolourize slides from deeply pigmented lesions because large quantities of melanin can obscure cytological detail [2]. Post-inflammatory hyperpigmentation (e.g. lichen sclerosus, lichen planus) may be the cause in many patients. Some cases have been associated with previous treatment with anthralin, PUVA therapy for psoriasis, or diabetes [4,5]. The eruptive appearance of melanotic macules and papules in the anogenital region may be associated with advanced metastatic adenocarcinoma [6].

On histological examination there may be increased basal epidermal pigmentation, with or without benign lentiginous melanocytic hyperplasia, or an increase in basal melanocyte number. Breathnach *et al.* [7] have proposed that depigmentation is an essential element of penile melanosis and demonstrated melanocytic hyperplasia in areas of hyperpigmentation.

Penile melanosis is the term for lesions without lentiginous hyperplasia [5,8]. Revuz and Clerici [8] proposed the grouping of penile melanosis, vulvovaginal melanosis and the predominantly oral mucosal hyperpigmentation of the Laugier–Hunziker syndrome under the umbrella of essential melanotic hyperpigmentation of the mucosa. Lenane *et al.* [9] used the term genital melanotic macules.

Patients ask for treatment of penile melanosis as it is unsightly and embarrassing, but options are limited [2]. Laser treatment may help [10].

Acral lentiginous melanoma is very rare but important [11,12].

Hypopigmentation

Striae as a consequence of growth or weight surges are common around the pelvic girdle, or represent a complication of topical corticosteroid application [13]. Initially, they are often purple–red in colour. Vitiligo is a commonly observed affliction of the male genitalia, although patients may be unaware of it and clinicians might not always observe it [14]. Penile vitiligo attributed to the use of topical imiquimod for the treatment of genital warts has been described [15].

References

1 Kaporis A, Lynfield Y. Penile lentiginosis. *J Am Acad Dermatol* 1998; **38**: 781.
2 Mahto M, Woolley PD, Ashworth J. Pigmented penile macules. *Int J STD AIDS* 2004; **15**: 717–9.
3 Kopf AW, Bart RS. Tumor conference 43: penile lentigo. *J Dermatol Surg Oncol* 1982; **8**: 637–9.
4 Rhodes AR, Harrist TJ, Momtaz TK. The PUVA-induced pigmented macule: a lentiginous proliferation of large, sometimes cytologically atypical, melanocytes. *J Am Acad Dermatol* 1983; **9**: 47–58.
5 Barnhill RL, Albert LS, Sharma SK *et al*. Genital lentiginosis: a clinical and histopathologic study. *J Am Acad Dermatol* 1990; **22**: 453–60.
6 Busam KJ, Sachs DL, Coit DG *et al*. Eruptive melanotic macules and papules associated with adenocarcinoma. *J Cutan Pathol* 2003; **30**: 463–9.
7 Breathnach AS, Balus L, Amantea A. Penile lentiginosis: an ultrastructural study. *Pigment Cell Res* 1992; **5**: 404–13.
8 Revuz J, Clerici T. Penile melanosis. *J Am Acad Dermatol* 1989; **20**: 567–70.
9 Lenane P, Keane CO, Connell BO *et al*. Genital melanotic macules: clinical, histologic, immunohistochemical, and ultrastructural features. *J Am Acad Dermatol* 2000; **42**: 640–4.
10 Delaney TA, Walker NPJ. Penile melanosis successfully treated with the Q-switched ruby laser. *Br J Dermatol* 1994; **130**: 663–4.
11 Jaeger N, Wirler H, Tschubel K. Acral lentiginous melanoma of the penis. *Eur J Urol* 1982; **8**: 182–4.
12 Weiss J, Elder D, Hamilton R. Melanoma of the male urethra: surgical approach and pathological analysis. *J Urol* 1982; **128**: 382–5.
13 Stankler L. Striae of the penis. *Br J Dermatol* 1982; **107**: 371–2.
14 Moss JR, Stevenson CJ. Incidence of male genital vitiligo: report of a screening programme. *Br J Vener Dis* 1981; **57**: 145–6.
15 Stefanaki C, Nicolaidou E, Hadjivassiliou M *et al*. Imiquimod-induced vitiligo in a patient with genital warts. *J Eur Acad Dermatol Venereol* 2006; **20**: 755.

Pain and swelling

Some presentations of many entities can be painful but generally pain is an unusual presentation for a dermatosis. Swelling is more common and may be painful or not. A common factor in many but not all causes of swelling may be oedema or lymphoedema. Rigorous clinical evaluation is important [1,2]. Causes of anogenital lymphoedema and penoscrotal swelling are listed in Tables 71.25–71.27.

Iatrogenic swelling and lymphoedema

Congenital defects of the inguinal canal and other non-inguinal peritoneal leaks can lead to scrotal and penile swelling as a

Table 71.25 Causes of anogenital lymphoedema. (After Bunker [1].)

Idiopathic congenital lymphoedema (Milroy's disease)
Lipogranuloma and silicone granuloma
Strangulation of the penis
Iatrogenic
Radical abdominopelvic surgery
Radiotherapy
Granulomatous lymphangitis
Crohn's disease
Sarcoid
Post-infectious
Cellulitis and erysipelas
Chronic penile lymphoedema
Chancroid
Lymphogranuloma venereum
Tuberculosis
Leprosy
Syphilis
Filariasis/onchocerciasis
Carcinomatosis
Lymphatic involvement
Lymphatic blockage
Lymphoma

Table 71.26 Commoner causes of penoscrotal swelling. (After Bunker [1]. © 2004, with permission from Elsevier.)

Paraphimosis
Foreign body
Strangulation of the penis
Iatrogenic
Contact dermatitis
Continuous ambulatory peritoneal dialysis
Genital oedema resulting from raised right heart filling pressure in ITU
Postoperative
Post-radiotherapy
Varicocoele
Hydrocoele
Strangulated hernia
Priapism
Peyronie's disease
Epididymitis and orchitis
Cellulitis
Idiopathic chronic penile oedema
Testicular tumours

Table 71.27 Rarer causes of penoscrotal swelling. (After Bunker [1]. © 2004, with permission from Elsevier.)

Idiopathic congenital lymphoedema [6]
Lymphangiectasia (with chylous reflux) [7]
Giant haemangioma
Urethral diverticulum
Segmental urethral hypospadias
Accessory scrotum [8,9]
Herniation of scrotal contents into penile shaft
Foreign body
Haematocoele
Lipogranuloma and silicone granuloma
Aortic aneurysm [10]
Scrotal fat necrosis
Henoch–Schönlein purpura
Familial Mediterranean fever
Acute haemorrhagic oedema of childhood
Granulomatous lymphangitis
Crohn's disease
Sarcoid
Pancreatitis
Infected cyst
Abscess of corpus cavernosum [11]
Fournier's gangrene
Tuberculosis
Paracoccidioidomycosis
Amputation of septic limbs in diabetics
Giant scrotal tumours (e.g. neurilemoma)
Epithelioid haemangioma
Kaposi's sarcoma
Epithelioid haemangioendiothelioma
Lymphoma
Sarcoma
Drugs (e.g. angio-oedema caused by lisinopril)

Table 71.28 Complications of plastic surgery to the penis. (After Bunker [1] (© 2004, with permission from Elsevier) and Alter [13].)

Hypertrophic scars
Wide scars
Proximal penile hump (thick hair-bearing Y flap)
Low-hanging penis
Loss of fat
Nodules
Deformed shaft

manifestation of dialysate oedema in patients with end-stage renal failure treated by continuous ambulatory peritoneal dialysis [3]. Genital oedema is commonplace in intensive care units, because of the practice of maintaining a raised right heart filling pressure. Radical cancer surgery and/or radiotherapy to the anogenital area and the lymphatics can cause swelling because of lymphoedema, early or delayed [4]. Chronic oedema, resembling keloid, of the penis has been caused by a condom catheter for neurogenic bladder [5].

Increasingly, patients seek plastic surgery to the penis [12] for psychosexual reasons (e.g. dysmorphophobia), but surgery can result in significant complications (Table 71.28).

Idiopathic lipogranuloma

Cases of characteristic, spontaneously resolving, painless, Y-shaped swelling of the scrotum embracing the penile root, with sclerosing eosinophilic lipogranuloma on histology and electron microscopy (but no exogenous lipids) and associated with blood eosinophilia (one patient had arthralgia), have been reported from Japan [14].

References

1 Bunker CB. *Male Genital Skin Disease*. London: Saunders, 2004.
2 Weinberger LN, Zirwas MJ, English JC III. A diagnostic algorithm for male genital oedema. *J Eur Acad Dermatol Venereol* 2007; **21**: 156–62.
3 Kopecky RT, Funk MM, Kreitzer PR. Localized genital oedema in patients undergoing continuous ambulatory peritoneal dialysis. *J Eur Acad Dermatol Venereol* 2007; **21**: 156–62.
4 Horinaga M, Masuda T, Jitsukawa S. A case of scrotal elephantiasis 30 years after treatment of penile carcinoma. *Hinyokika Kiyo* 1998; **44**: 839–41.
5 Bang RL. Penile oedema induced by continuous condom catheter use and mimicking keloid scar. *Scand J Urol Nephrol* 1994; **28**: 333–5.
6 Bolt RJ, Peelen W, Nikkels PG, de Jong TP. Congenital lymphoedema of the genitalia. *Eur J Pediatr* 1998; **157**: 943–6.
7 Huang H-Y, Hu S-L. Scrotal cutaneous chylous reflux. *Br J Dermatol* 2007; **156**: 752–4.
8 Szylit J-A, Grossman ME, Luyando Y e*t al*. Becker's nevus and an accessory scrotum. *J Am Acad Dermatol* 1986; **14**: 905–7.
9 Yokokawa K, Nakano E, Takaha M. Accessory scrotum: a case report. *J Urol* 1986; **135**: 593–4.
10 Ward CS, Dundas DD, Dow J, Shearer RJ. Scrotal swelling due to perianeurysmal fibrosis. *Br J Urol* 1988; **61**: 536–8.
11 Kameda K, Hayashi N, Arima K *et al*. Abscess of corpus cavernosum: a case report. *Hinyokika Kiyo* 1998; **44**: 893–5 [in Japanese].
12 Austoni E, Guarneri A, Gatti G. Penile elongation and thickening: a myth? Is there a cosmetic or medical indication? *Andrologia* 1999; **31** (Suppl. 1): 45–51.
13 Alter GJ. Reconstruction of deformities resulting from penile enlargement surgery. *J Urol* 1997; **158**: 2153–7.
14 Matsuda T, Shichiri Y, Hida S *et al*. Eosinophilic sclerosing lipogranuloma of the male genitalia not caused by exogenous lipids. *J Urol* 1988; **140**: 1021.

Table 71.29 Causes of priapism. (After Levine *et al.* [1] and Bunker [2]. © 2004, with permission from Elsevier.)

Idiopathic
Os penis
Congenital
Acquired—ageing, trauma, metabolic disorder
Perineal trauma
Strangulation
Hypertension
Nephrotic syndrome
Neurological causes
Quadriplegia
Spinal canal stenosis
Cauda equina compression
Sickle cell disease
Coagulopathy
Protein C deficiency
Factor V Leiden
Warfarin necrosis
Peyronie's disease
Rheumatoid arthritis
Vasculitis
Tuberculosis
Pelvic tumours
Leukaemia
Lymphoma
Penile metastases
Drugs
Papaverine
Antipsychotics—chlorpromazine, trazodone
Antihypertensives—hydralazine, guanethidine, prazosin
Marijuana
Adrenal corticosteroids
Warfarin necrosis

Priapism

Priapism is defined as the prolonged, painful erection of the penis, unassociated with sexual desire and not relieved by ejaculation. Although not predominantly a dermatological concern, it has an important differential diagnosis. The principal causes [1,2] are listed in Table 71.29. It results in impotence in more than 50% of those affected [3,4] and can lead to gangrenous penile necrosis [5].

Veno-occlusive priapism can be distinguished from arterial priapism [1]. Veno-occlusive priapism results from persistent obstruction to venous outflow from the lacunar spaces. It is a potential vascular emergency because, as the corporeal bodies expand to maximal volume, an obstructed outflow causes decreased arterial inflow, with the potential for ischaemia, pain, fibrosis and hence impotence. Arterial priapism is usually secondary to trauma, such that a damaged cavernosal artery causes unregulated blood flow to the lacunar spaces; it is thus non-ischaemic [1].

References

1 Levine FJ, de Tejada IS, Payton TR, Goldstein I. Recurrent prolonged erections and priapism as a sequela of priapism: pathophysiology and management. *J Urol* 1991; **145**: 764–7.
2 Bunker CB. *Male Genital Skin Disease.* London: Saunders, 2004.
3 Nelson JH III, Winter CC. Priapism: evolution of management in 48 patients in a 22-year series. *J Urol* 1977; **117**: 455–8.
4 O'Brien WM, O'Connor KP, Lynch JH. Priapism: current concepts. *Ann Emerg Med* 1989; **18**: 980–3.
5 Khoriaty N, Schick E. Penile gangrene: an unusual complication of priapism. How to avoid it. *Urology* 1980; **16**: 280.

Dermatological non-disease, dysaesthesia and chronic pain syndromes

'Dermatological non-disease' may be the diagnosis where there is a paucity or even absence of primary dermatological signs to account for florid symptomatology. Genital symptoms include itching, excessive redness, burning and discomfort—in some cases so severe that it prevents the patient from sitting down. Dysmorphophobia, depression and psychosis may be present, and attempted suicide is a real risk in such patients [1,2].

Itching of the urethra may lead to insertion of a foreign body in an attempt to relieve the sensation [3], or this might be done for sexual gratification.

Patients with symptoms of itching, burning and pain localized to the penis or scrotum are not uncommonly encountered. The skin is usually completely normal. The situation is analogous to vulvodynia in women, and terms such as penodynia and scrotodynia have been coined to describe the syndrome in men. Doxepin, dosulepin amitriptyline and paroxetine can afford some relief.

Fisher [4] has defined the red, burning scrotum syndrome as 'persistent redness of the anterior half of the scrotum that may involve the base of the penis . . . usually accompanied by a persistent itching or burning sensation and hyperalgesia'. It is a chronic condition that is resistant to treatment and its cause is unknown [4,5]. Accompanying the erythema there may be telangiectasia. It is related to idiopathic penile and scrotal pain syndromes [6]. Prednisolone and antidepressants have given some relief to some patients.

Localized dermographism should be sought by stroking the inside of the thigh, because such patients may be helped by oral antihistamine treatment.

The possibilities of zinc deficiency and necrolytic migratory erythema should be entertained.

Chronic urogenital and rectal pain syndromes include penile pain (penodynia), scrotodynia, orchialgia, prostatodynia, coccygodynia, proctalgia fugax, perineal pain, the descending perineum syndrome and vulvodynia [7–9]. The neuroanatomy of the pelvis is complicated and the neurophysiological basis of the pathogenesis of these syndromes is poorly understood, but their clinical presentations are well recognized. The differential diagnosis is addressed above.

The *koro syndrome* is a psychiatric disorder characterized by fear of genital retraction (i.e. the penis shrinking, retracting or disappearing into the abdomen), acute anxiety and fear of death and genital pain. There is rarely real associated genital pathology. Although originally thought to be a culture-specific condition in South East Asia and China it has been observed in the West, without fear of death [10].

A diagnosis of a chronic pain syndrome implies the prospect of considerable psychological morbidity. Treatment is challenging and only empirical at best. Most agree that invasive and

irreversible procedures should be avoided if at all possible. Multidisciplinary management is recommended [6].

References

1 Cotterill JA. A dermatological non-disease: a common and potentially fatal disturbance of cutaneous body image. *Br J Dermatol* 1981; **104**: 611–9.
2 Bunker CB, Bridgett CK. Depression and the skin. In: Robertson MM, Katona CLE, eds. *Depression and Physical Illness*. London: John Wiley, 1997: 225–53.
3 Al-Durazi M, Saleem I, Mohammed AA. Urethral foreign body. *Br J Urol* 1992; **69**: 434.
4 Fisher BK. The red scrotum syndrome. *Cutis* 1997; **60**: 139–41.
5 Markos AR. The male genital skin burning syndrome (dysaesthetic peno/scrotodynia). *Int J STD AIDS* 2002; **13**: 271–2.
6 Wesselmann U, Burnett AL, Heinberg LJ. The urogenital and rectal pain syndromes. *Pain* 1997; **73**: 269–94.
7 Parks AG, Porter NH, Hardcastle J. The syndrome of descending perineum. *Proc R Soc Med* 1966; **59**: 477–82.
8 Lask B. Chronic perianal pain. *J R Soc Med* 1982; **75**: 370.
9 Neill ME, Swash M. Chronic perianal pain: an unsolved problem. *J R Soc Med* 1982; **75**: 96–101.
10 Cabellero JM, Avila A, Cardona X *et al*. Genital pain without urogenital pathology: the koro-like syndrome. *J Urol* 2000; **163**: 243.

Female genital dermatology

Introduction

Disorders of the vulval epithelium have proved confusing to the many and varied specialists who have been involved in their diagnosis and treatment. The difficulty has arisen because the majority of the problems are dermatological and the specialists—gynaecologists, urologists, paediatricians and genitourinary physicians—have had little or no training in dermatology. The problem is compounded by the fact that the normal characteristics of common diseases at this flexural site are lost or modified, making the diagnosis difficult even for an experienced dermatologist. Over the years, classifications of vulval disorders have been devised to help, but unfortunately these have only resulted in further confusion. There is no need for a separate classification for vulval disorders, as the current classifications that exist for dermatology and pathology can be used [1,2].

Dystrophy, leukoplakia and kraurosis vulvae have all now been abandoned as diagnostic terms [3]. Over the years, the term leukoplakia has unfortunately had the sinister implication that it always represented a premalignant condition [4], but now leukoplakia is used as a descriptive term only and may represent anything from a patch of lichen simplex to an SCC. Similarly, squamous cell hyperplasia is not a diagnosis but a histological description, and can be seen in many disorders including psoriasis, candidosis and hypertrophic lichen planus.

Vulval clinics have been an important step forward in the diagnosis and management of women with vulval problems [5,6]. These clinics ideally should be multidisciplinary, with input from dermatology, gynaecology, genitourinary medicine and pathology. It is important that there are links with other specialists, including paediatricians and plastic surgeons, as well as psychologists and psychosexual therapists.

The development of these clinics has been extremely important, not only for improved patient care but also for the valuable interdisciplinary education of the doctors involved.

An accurate diagnosis depends on a thorough history, examination of the affected skin and skin at extragenital sites, and pertinent investigations. The history must include the chief complaint, how long it has been present, how the problem changes in certain circumstances (e.g. variation with the menstrual cycle), what treatment has been prescribed and what were the effects of the treatment. A drug history is important, and should include direct questioning about over-the-counter oral and topical medications, oral contraceptives and hormone replacement therapy (HRT). The latter two are included in this direct questioning as patients do not always consider these as medications, particularly if the HRT is in a topical formulation. A personal and family history of autoimmune disease, atopy or psoriasis should be established, and any known skin sensitivities. The patient should also be asked about vaginal discharge, urinary symptoms and bowel function. Finally, as the vulva is important for normal sexual function, it is important to include relevant questions on problems with intercourse where appropriate.

The complaint of irritation has many meanings and it is sometimes helpful to ask the patient exactly what they mean by the term. It may be the sensation of itch, dryness, pain, burning or rawness. This point is important as a patient with itch will scratch or rub the skin, and the response will be lichen simplex or lichenification, whereas with discomfort or pain there will be no such change as the patient avoids touching the area.

Lichen simplex and lichenification. Lichen simplex and lichenification are terms used to describe the exaggerated normal rhomboidal patterning of the skin surface. Lichen simplex is used to describe the changes seen on apparently normal skin secondary to itching and rubbing, although the provoking symptom of itch may be initiated by a low-grade dermatosis such as psoriasis or seborrhoeic eczema. The term lichenification is used for similar changes arising on a background of a visible dermatosis.

The lesions of lichen simplex tend to be in one isolated area, usually on the labia majora or mons pubis. They are well defined, with a pale grey or white surface.

The histological changes of lichen simplex and lichenification are similar, except that there are the changes of the background dermatosis in the latter. There is hyperkeratosis, acanthosis, a prominent granular layer, lengthened rete ridges and a chronic inflammatory dermal infiltrate. In addition, lamellar thickening of the papillary dermis and perineural fibrosis can be seen. Twelve cases of what was termed multinucleated atypia of the vulva have been reported [7], but this is thought to be a non-specific change found in lichenified skin [8,9].

Treatment of the underlying dermatosis will usually resolve the lichenification. In cases of lichen simplex with no underlying dermatosis, the treatment is the application of a potent topical steroid to encourage a disruption of the itch–scratch cycle. A soap substitute should be introduced and possible irritants avoided. If these measures are unsuccessful, patch testing should be performed to exclude the possibility of an unsuspected allergen.

The examination is often very embarrassing for the patient, so it must be carried out sympathetically to ease any tension. It is important that there is good lighting, and a means of magnification. The skin and the mucosae in the anogenital area are exam-

ined for changes in colour, epithelial integrity and texture. If there is scarring this will be seen in loss of characteristic features (e.g. introital narrowing, loss of the labia minora or sealing of the clitoral hood). The examination must also include inspection of other flexural sites and mucosae, the scalp and nails. It is also useful to determine if the patient exhibits dermographism [10]. The vagina and cervix should be examined in patients who have dermatoses that affect mucosal surfaces and in patients with symptoms of dyspareunia, vaginal discharge or postcoital bleeding. Investigations are determined by the specific problem and include microbiological assessment. The investigation of the common bacterial or fungal problems can be easily performed by a dermatologist but if an exotic bacterial or sexually transmitted infection is high on the differential diagnosis, it is important to involve a genitourinary physician in the investigation and work-up of these patients and their partners. A biopsy is important, particularly in cases where there is no response to treatment. If a biopsy is performed, it is important to let the pathologist know what area has been biopsied, as the vulva is a mucocutaneous junction and the normal histological changes of a mucosal epithelium differ significantly from those of cornified epithelium and may be misinterpreted as pathological changes. Other investigations include those performed routinely for skin problems elsewhere (e.g. patch testing, examination with Wood's light, Tzanck smears). Some investigations are not the usual remit of the dermatologist but are necessary in patients with anogenital dermatoses, and will include a cervical smear and proctoscopy.

On occasions, the vulval changes are not caused by a primary problem of the vulval skin but are the secondary consequences of pathology at another site (e.g. an irritant vulval dermatitis resulting from a vaginal discharge because of cervical, uterine or vaginal pathology).

Diagnosis and management of vaginal discharge

The diagnosis usually falls into one of the following categories: physiological, iatrogenic, infective, inflammatory or neoplastic (Table 71.30).

Table 71.30 Causes of vaginal discharge.

Physiological
Ovulation
Iatrogenic
Medications (e.g. tamoxifen, oral contraceptive pill)
Infective
Candidosis
Bacterial vaginosis
Cervicitis
Inflammatory
Lichen planus
Mucous membrane pemphigoid
Pemphigus
Erythema multiforme
Stevens–Johnson syndrome
Vaginal adenosis
Cervical erosion
Neoplastic
Langerhans' cell histiocytosis
Vaginal, uterine or fallopian tube tumours
Foreign body

Physiological. Between 5 and 10% of women complaining of vaginal discharge do not have an infection. The discharge may be caused by an excess physiological secretion of mucus, usually resulting from cervical erosion or an increase in the amount of vaginal transudate. The discharge is thick, with a grey-white appearance, and is odourless and non-irritant. Vaginal pH is normal.

Iatrogenic. This is usually secondary to medications that have an effect on the vaginal epithelium (e.g. tamoxifen, which has oestrogenic effect on the vagina); oral contraceptive pills can cause cervical erosion and an increase in vaginal discharge. There is one report of an orange-coloured vaginal discharge due to a laxative containing the anthroquinone danthron [11].

Infective. This is the most common cause of a vaginal discharge, and a pH greater than 6 is highly predictive of an infectious cause [12]. Bacterial vaginosis is the usual diagnosis [13]. The patient complains of excessive, grey watery discharge, associated with a 'fishy' malodour, which is worsened with intercourse. Vulval irritation is slight or absent in this group, and the smell is the most distressing symptom. The condition is invariably associated with infection by a small aerobic Gram-negative rod known as *Gardnerella vaginalis*, after its discoverer Gardner [14]. It would appear that this organism alone is incapable of causing infection, and non-specific vaginitis is now regarded as a complex interrelationship between *Gardnerella* and anaerobic species of bacteria [15], two of which belong to the genus *Mobiluncus*. The fishy odour of the discharge can be accentuated by the addition of an alkali such as 10% potassium hydroxide (the Whiff test). A wet mount of a vaginal smear in saline will identify 'clue cells'. These are vaginal epithelial cells with a granular cytoplasmic appearance and indistinct cellular outlines. This indistinct border is caused by the attachment of the small Gram-negative rods to the cell. Bacterial vaginosis is not always sexually acquired—its incidence is equal in virginal and sexually active groups [16,17]. This type of abnormal bacterial colonization may be associated with preterm delivery and late miscarriage in pregnant patients [18]. Treatment is with metronidazole 400 mg twice daily for 5 days or 2 g as a single dose.

Patients with infective cervicitis will also present with an increased vaginal discharge. The four most common pathogens involved are *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Trichomonas vaginalis* and herpes virus hominis. *Chlamydia trachomatis* has been grown from the cervices of 50% of women with mucopurulent cervicitis [19]. The main symptoms are discharge, deep pelvic pain and dyspareunia.

Infestation with thread worms, *Enterobius vermicularis*, has also been recorded as a cause of a vulvovaginitis [20].

Inflammatory. Vaginal or cervical ulceration and erosion resulting from inflammatory conditions can give rise to an increased vaginal discharge. The most common inflammatory conditions are

lichen planus and pemphigus [21]. The diagnosis is often missed, particularly if these sites are affected in isolation. There is a chronic odourless discharge, which may be blood-tinged. The patient will also complain of postcoital bleeding if she is sexually active. An accurate diagnosis requires a biopsy, and immunofluorescence studies should be performed both on tissue and serum. Examination of eyes and mouth may help if the patient also has disease at these sites. Treatment requires topical steroids in the form of foams or pessaries that are currently used for inflammatory bowel disease.

Neoplastic. Tumours of the fallopian tubes, uterus, cervix and vagina may all cause an increased vaginal discharge. Rarer causes of a chronic vaginal discharge include Langerhans' cell histiocytosis.

A persistent discharge in young children should be investigated as it is often associated with a medical or social problem [22].

Management of vulval disorders depends upon the diagnosis, but general measures include the use of a soap substitute and avoidance of irritants (e.g. bubble baths, shampooing hair in the bath). If there is an incontinence problem, a barrier ointment helps to protect the skin. Weak potassium permanganate solution or Burow's solution can be used when there is erosive disease. Topical steroids are best used in an ointment formulation to avoid the irritant effect of preservatives and alcohol. Many of the patients are elderly and may have difficulty treating themselves. It is often helpful to take time in the clinic, using a mirror, to explain exactly where the treatment should be applied.

References

1 Kiryu H, Ackerman AB. A critique of current classifications of vulval disease. *Am J Dermatopathol* 1990; **12**: 377–92.

2 Wilkinson EJ, Kneale B, Lynch PJ. Report of the ISSVD terminology committee. *J Reprod Med* 1986; **31**: 973–4.

3 Ridley CM, Frankman O, Jones ISC *et al.* New nomenclature for vulval disease: report of the committee on terminology. *Am J Obstet Gynecol* 1989; **160**: 769.

4 Wallace HJ, Whimster IW. Vulval atrophy and leukoplakia. *Br J Dermatol* 1951; **63**: 241–57.

5 Weisfogel E. Aims of joint gynecologic, dermatologic and pathologic vulval clinics. *N Y State J Med* 1969; **69**: 1184–6.

6 Heller DS, Randolph P, Young A *et al.* The cutaneous–vulvar clinic revisited: a 5-year experience of the Columbia Presbyterian Medical Center cutaneous vulvar service. *Dermatology* 1997; **195**: 26–9.

7 McLachlin CM, Mutter GL, Crum CP. Multinucleated atypia of the vulva: report of a distinct entity not associated with human papillomavirus. *Am J Surg Pathol* 1994; **18**: 1233–9.

8 LeBoit PE. Multinucleated atypia. *Am J Surg Pathol* 1996; **20**: 507.

9 Tagamai H, Uehara M. Multinucleated epidermal giant cells in inflammatory skin diseases. *Arch Dermatol* 1981; **117**: 23–5.

10 Shenertz EF. Clinical pearl: symptomatic dermographism as a cause of genital pruritus. *J Am Acad Dermatol* 1994; **31**: 1040–1.

11 Greer IA. Orange periods. *BMJ (Clin Res Ed)* 1984; **289**: 323.

12 Hanna NF, Taylor-Robinson D, Kalodikki-Karamanoli M *et al.* The relation between vaginal pH and the microbiological status in vaginitis. *Br J Obstet Gynaecol* 1985; **92**: 1267–71.

13 Vontver LA, Eschenbach DA. The role of *Gardnerella vaginalis* in non-specific vaginitis. *Clin Obstet Gynecol* 1981; **24**: 439–60.

14 Gardner HL. *Haemophilus vaginalis* vaginitis after 25 years. *Am J Obstet Gynecol* 1980; **137**: 385–91.

15 Speigel CA, Amsel R, Eschenbach D *et al.* Anaerobic bacteria in non-specific vaginitis. *N Engl J Med* 1980; **303**: 601–7.

16 Holst E. Reservoir of four organisms associated with bacterial vaginosis suggests lack of sexual transmission. *J Clin Microbiol* 1990; **28**: 2033–9.

17 Bump RC, Buesching WJ. Bacterial vaginosis in virginal and sexually active adolescent females: evidence against sexual transmission. *Am J Obstet Gynecol* 1988; **158**: 935–9.

18 Hay PE, Lamont RF, Taylor-Robinson D *et al.* Abnormal bacterial colonization of the genital tract and subsequent preterm delivery and late miscarriage. *BMJ* 1994; **308**: 295–8.

19 Brunham RC, Paavonen J, Stevens CE *et al.* Mucopurulent cervicitis: the ignored counterpart in women of urethritis in men. *N Engl J Med* 1984; **311**: 1–6.

20 Kacker TP. Vulvovaginitis in an adult with threadworms in the vagina. *Br J Vener Dis* 1973; **49**: 314–5.

21 Batta K, Munday PE, Tatnall FM. Pemphigus vulgaris localized to the vagina and presenting as a chronic vaginal discharge. *Br J Dermatol* 1999; **140**: 945–7.

22 Striegel AM, Myers JB, Sorensen MD *et al.* Vaginal discharge and bleeding in girls younger than 6 years. *J Urol* 2006; **176**: 2632–5.

Structure and function of the female genitalia

The vulva is the collective term for the structures that comprise the female external genitalia. Anatomically, it is the region known as the urogenital triangle, bounded anteriorly by the symphysis pubis, the pubic rami laterally and the transverse perineal body posteriorly. The vulval structures included within this area are the mons pubis, paired labia majora and labia minora, clitoris and vulval vestibule. The epithelia that cover the vulva change from skin on the outer aspects to mucosa on the innermost region.

The mons pubis lies in front of and above the upper part of the symphysis pubis. It is softly rounded because of a thick cushion of subcutaneous fat. The epithelium is densely covered in hairs and possesses all the adnexal structures usually found in skin.

The labia majora are paired, rounded folds of skin and are the homologue of the scrotum. They extend downwards and backwards from the mons pubis and meet posteriorly in the midline to form the posterior commissure, which lies approximately 2 cm anterior to the anus. The epithelium is similar in structure to that on the mons pubis in that there is a thick layer of adipose tissue and a dense distribution of hair on the outer surfaces of the labia. Hair is absent from the inner surfaces but numerous sebaceous glands remain. The inner aspects of the labia majora fuse into the outer aspects of the labia minora laterally, forming the interlabial sulci. The labia majora enclose an elliptical fissure which is known as the pudendal cleft—this contains the vestibule with the openings of the vagina and urethra.

The labia minora are the equivalent of the prepuce, and part of the ventral portion of the penis and the floor of the spongy part of the male urethra. They are paired pendulous folds, which lie between the labia majora and the vulval vestibule. Anteriorly they split into two folds on each side, which fuse in the midline. The superior folds cover the clitoris like a hood, forming the prepuce of the clitoris, and the lower folds fuse on the inferior aspect of the clitoris, forming the clitoral frenulum. Posteriorly, the labia minora fuse to form the fourchette, and sometimes form a depression in the midline, the fossa navicularis. The labia minora possess little subcutaneous fat. Their epithelium lacks hair but there are numerous sebaceous glands and sweat glands. The epithelium is cornified but its barrier function is not as effective as skin elsewhere.

The clitoris is the homologue of the penis and contains all the vascular and muscular structures found in its male counterpart.



Fig. 71.20 Vestibular papillae.

The end of the clitoris is surmounted by a small rounded tubercle, the glans clitoris.

The vestibule is usually considered as part of the vulva, although many anatomy books refer to it as the vestibule of the vagina. It is the area that lies between the labia minora and contains the openings of the urethra and vagina. The vaginal opening is partially closed by the hymen. When the hymen is ruptured, its remnants form rounded crenulations, the hymenal caruncle. The fold between the hymenal caruncle and the vestibular floor is the nymphohymenal sulcus. Sometimes a clear line of demarcation between the labia minora and the epithelium of the vestibule can be seen, Hart's line. The vestibule is a mucosal epithelium and lacks hairs and sebaceous glands. On each side, the duct of the major vestibular gland, Bartholin's gland, can be seen sited between the hymenal ring and posterior part of the labium minus. The ducts of the minor vestibular glands, Skene's glands, open on either side of the urethral orifice. The epithelial surface is usually smooth, but occasionally tiny frond-like papillae may be seen distributed symmetrically laterally and posteriorly on the vestibule (Fig. 71.20). These vestibular papillae are a variant of normal and not related to HPV infection.

Normal flora

The skin of the perineal area has a higher pH, temperature and degree of humidity than skin elsewhere and, because of its proximity to the vagina and rectum, harbours many of the flora from these sites [1,2]. The main resident organisms are micrococci, diphtheroids and lactobacilli. Lactobacilli are probably the most common organisms, particularly on the mucosal surfaces, as the glycogenated epithelium of the vagina, under the influence of oestrogen, encourages colonization by them. The lactobacilli in turn metabolize the glycogen to lactic acid, which keeps the vaginal pH at approximately 4.5, restricting the growth of many organisms.

References

1 Aly R. Microbial flora of the vulva. In: Elsner P, Martius J, eds. *Vulvovaginitis.* New York: Marcel Dekker, 1993: 19–28.
2 Mårdh P-A. The vaginal ecosystem. *Am J Obstet Gynecol* 1991; **165**: 1163–8.

Normal variants

Angiokeratomas are small (1–4 mm) vascular papules found on the labia majora. They vary in colour from red to blue-black and are normally asymptomatic, but can become quite large and bleed if traumatized, particularly in pregnancy.

Sebaceous gland hyperplasia is seen on the inner aspects of the labia majora and labia minora where the glands do not usually have an associated hair unit. The glands open directly onto the surface, and may be very prominent and numerous. The yellow uniform papules are often best seen when the skin is stretched. Prominent and numerous glands may be associated with pruritus and sometimes they become inflamed and painful in the week prior to the menses. Occasionally, they can become very large and be mistaken for a sebaceous gland adenoma [1].

Vestibular papillomatosis is the term used to describe the occasional normal finding of myriad tiny filiform or soft frond-like projections on the vestibular epithelium and inner aspects of the labia minora. These lesions have had various names in the past, including papillomatosis labialis, hirsuties papillaris [2], hirsutoid papillomas of the vulva [3], vestibular papillae [4], pseudocondylomas, vestibular microwarts and vulval squamous papillomatosis [5]. The last two suggest that HPV is implicated but the evidence now suggests that the known HPV types are not associated with these papillae [6–8]. Clinically, vestibular papillae are unlike the lesions induced by HPV as they are symmetrically arranged and each papilla has a solitary base. Histologically, problems arise if the pathologist is unaware that the tissue is the vestibule, which has heavily glycogenated epithelial cells that become vacuolated on processing and may resemble koilocytes. The problem is also compounded by the fact that koilocyte-like lesions can be found on vulval biopsies, but these are not necessarily associated with HPV infection [9]. Currently, it is believed that this entity is a normal variant and the female equivalent of pearly penile papules.

Varicosities of the labial veins may occur unilaterally in association with limb varicosities, or appear in pregnancy. Other changes in pregnancy include a fall in the pH and increased pigmentation. At the menopause, vascularity decreases and the sebaceous glands become less active.

References

1 Rocamora A, Santonja C, Vives R *et al.* Sebaceous gland hyperplasia of the vulva: a case report. *Obstet Gynecol* 1986; **68** (Suppl.): 63–5.
2 Altmeyer P, Cliff GN, Holzmann H. Hirsutes papillaris vulvae (pseudokondylome der vulva). *Hautarzt* 1982; **33**: 281–3.
3 Khoda H, Hino Y, Fukuda H. Hirsutoid papillomas of vulva. *J Dermatol* 1986; **13**: 154–6.
4 Friedrich EG Jr. The vulvar vestibule. *J Reprod Med* 1983; **28**: 773–7.
5 Manoharon V, Somerville JM. Benign squamous papillomatosis: case report. *Genitourin Med* 1987; **63**: 393–5.

6 Bergeron C, Ferenczy A, Richart RM *et al.* Micropapillomatosis labialis appears unrelated to human papilloma virus. *Obstet Gynecol* 1990; **76**: 281–6.
7 Moyal-Barracco M, Leibowitch M, Orth G. Vestibular papillae of the vulva: lack of evidence for human papilloma virus aetiology. *Arch Dermatol* 1990; **126**: 1594–8.
8 Wilkinson EJ, Guerrero E, Daniel R *et al.* Vulvar vestibulitis is rarely associated with human papilloma virus infection types 6, 11, 16, or 18. *Int J Gynecol Pathol* 1993; **12**: 344–9.
9 Dennerstein GJ, Scurry JP, Garland SM *et al.* Human papilloma virus vulvitis: a new disease or an unfortunate mistake? *Br J Obstet Gynaecol* 1994; **101**: 992–8.

Congenital and developmental abnormalities [1]

Ambiguous external genitalia

In a newborn, the external genitalia may not be phenotypically characteristic of either male or female. It is critical that gender assignment is not made on immediate assessment of the neonate. A full work-up with a multidisciplinary team, including a paediatric endocrinologist, is essential. The initial clinical assessment includes metabolic state of neonate, size and differentiation of the phallus, position of the urethral meatus, labioscrotal folds and pigmentation, palpation for gonads in the labial folds and inguinal areas. If gonads are absent it is very likely that the infant is XX and has been virilized *in utero* due either to adrenal production by the fetus or maternal ingestion or production of androgens. If there are palpable gonads then the infant may be XY and the phenotypic changes due to under-virilization *in utero*. The underlying mechanisms are often complex, and further investigations would include ultrasound of pelvis to assess presence of uterus and ovaries, blood for karyotype, glucose, urea and electrolytes, testosterone, FSH, LH and 17-hydroxyprogesterone.

An attempt at classification of these abnormalities is based on gonadal differentiation, but the classification is still evolving. Essentially there are five main groups:

1 Female pseudohermaphrodite—two ovaries
2 True hermaphrodite—ovary and testis
3 Male pseudohermaphrodite—two testes
4 Mixed gonadal dysgenesis—testis and streak gonad
5 Pure gonadal dysgenesis—two streak gonads.

Congenital adrenal hyperplasia accounts for 60% of these intersex changes producing a female pseudohermaphrodite.

Labial problems

There may be persistence of most caudal elements of the milk line in the labia majora, and there is great variation in the size and symmetry of normal labia minora. There may be very marked hypertrophy of the labia minora, some cases of which are examples of neurofibromatosis [2].

Labial adhesions may occur as an inherited familial trait [3] or in association with abnormal sexual differentiation. In general, most occur in the neonatal period and early infancy, and usually divide spontaneously by the time the child is 6 years old. No intervention is necessary unless there is a problem with urination. Some cases of labial adhesions result from lichen sclerosus.

Accessory labioscrotal folds are well described in males, usually in association with a perineal lipoma. They are extremely rare in women and only two cases have been reported [4].

Clitoral problems

The clitoris may be absent because of a failure of the genital tubercle to fuse, remain hypoplastic [5], or be enlarged because of congenital adrenal hyperplasia. The Lawrence Seip syndrome, which is a congenital generalized lipodystrophy with the onset of insulin-resistant diabetes around the time of puberty, may also result in clitoral hypertrophy. There are clitoral tumours that may mimic genital sexual ambiguity (e.g. haemangioma, neurofibroma, lipoma [6–8]), and a pseudocyst of the clitoris caused by a build-up of keratinous debris under clitoral hood adhesions in lichen sclerosus.

Virilization of the external genitalia may also occur with maternal ingestion of testosterone or synthetic progestogens in the first trimester, and if taken later in pregnancy there may be clitoral hypertrophy alone.

An imperforate hymen is usually discovered at puberty and is caused either by failure of the epithelial cells of the hymen to degenerate or by scarring after an inflammatory reaction in the hymen at birth.

References

1 Hughes IA, Houk C, Ahmed SF, Lee PA and LWPES/ESPE Consensus Group. Consensus statement on management of intersex disorders. *Arch Dis Child* 2006; **91**: 554–63.
2 Labardini MM, Kallet HA, Cerny JC. Urogenital neurofibromatosis simulating an intersex problem. *J Urol* 1968; **98**: 627–32.
3 Klein VR, Willman SP, Carr BR. Familial posterior labial fusion. *Obstet Gynecol* 1989; **73**: 500–2.
4 Redman JF, Ick KA, North PE. Perineal lipoma and an accessory labial fold in a female neonate. *J Urol* 2001; **166**: 1450.
5 Falk HC, Hyman AB. Congenital absence of clitoris: a case report. *Obstet Gynecol* 1971; **38**: 269–71.
6 Gersell DJ, Fulling KH. Localized neurofibromatosis of the female genitourinary tract. *Am J Surg Pathol* 1989; **13**: 873–8.
7 Kauffmann-Friedman K. Hemangioma of clitoris: confused with adreno-genital syndrome—a case report. *Plast Reconstr Surg* 1978; **62**: 452–4.
8 Haddad HM, Jones WH. Clitoral enlargement simulating pseudohermaphroditism. *Am J Dis Child* 1960; **99**: 282–7.

Trauma and artefact

Factitial dermatitis

There are various causes of vulval trauma, including accidental injury, obstetrical tears, damage at the time of surgery in a nearby site and coital and sexual mutilation, both cultural and self-induced [1].

Nymphohymenal tears induced by sexual intercourse are not uncommon and may mimic the symptoms of vulval vestibulodynia (see p. 71.82).

Sclerosing lipogranuloma [2] is a granulomatous response induced artefactually.

References

1 Wise TN, Dietrich AM, Segall E. Female genital self mutilation: case reports and literature review. *J Sex Marital Therapy* 1989; **15**: 269–74.
2 Kempson, RL, Sherman AI. Sclerosing lipogranuloma of the vulva. *Am J Obstet Gynecol* 1968; **101**: 854–6.

Female genital mutilation [1,2]

Ritual and cultural female genital mutilation (FGM), although banned in most European countries, is still forced on many women

worldwide. Although it is unusual in Western society, many cases are now being seen in the UK because of the rise in immigration of women who have had previous FGM.

There are four types of operation performed, which vary according to the country and culture:

1 Clitoridectomy: removal of the clitoris and/or the clitoral hood (Sunna circumcision)
2 Excision: removal of the clitoris and part or all of the labia minora
3 Narrowing of the introitus by cutting and apposing the labia minora and/or the labia majora, with or without excision of the clitoris (infibulation), leaving a tiny opening for urination and menstruation
4 All other practices which might involve cauterization, applying corrosive material, piercing or cutting of the clitoris, surrounding skin or vagina.

FGM may be carried out at any age from the neonate to the adolescent. It is often performed without an anaesthetic in unhygienic circumstances. There may be damage to the urethra and vagina at the time of the operation, and later there may be severe damage to the urethra, bladder or anal sphincter during delivery in those who have had infibulation. Many of the women who have had FGM experience difficulties with sexual intercourse, urination and pregnancy and seek help in the clinics of their new country of residence, where unfortunately many of the health-care professionals have not encountered their specific problem. There are now a number of clinics being set up to deal specifically with these patients. The initial findings of a specialized clinic set up by a central London maternity unit found that many of the patients referred to them for problems in pregnancy were reluctant to volunteer the fact that they had been circumcised, and less than 10% refused to continue the tradition of FGM [3].

References

1 Momoh C. Female genital mutilation. *Curr Opin Obstet Gynecol* 2004; **16**: 477–80.
2 Kelly E, Hillard PJ. Female genital mutilation. *Curr Opin Obstet Gynecol* 2005; **17**: 490–4.
3 Momoh C, Ladhani S, Lochrie DP *et al.* Female genital mutilation: analysis of the first 12 months of a southeast London specialist clinic. *Br J Obstet Gynaecol* 2001; **108**: 186–91.

Dermatological manifestations of sexual abuse of children

Childhood sexual abuse is not the usual domain of the dermatologist, but occasionally it can be encountered when a dermatological opinion is sought on a genital skin problem. Lichen sclerosus and other dermatoses can be mistaken for sexual abuse [1–4], but sometimes the sexual abuse may be the initiating or exacerbating factor of the dermatological condition [5]. The possibility of sexual abuse sometimes has to be considered in a child whose lichen sclerosus, despite appropriate treatment and compliance, has not responded as expected. Sexual abuse always has to be excluded in the child who presents with a sexually transmitted disease [6,7], but conditions such as molluscum contagiosum, bacterial vaginosis [8] and genital warts are not necessarily indicative of sexual activity, and can be acquired by non-sexual means [9,10]. Genital warts in children may carry both genital and skin-type viruses [11]. If gonorrhoea or semen is found the situation is clear-cut, with the exception of neonatal infection and gonococcal eye disease [12]. Herpes simplex infection of the prepubertal genitalia is relatively uncommon and sexual transmission may be implicated in both HSV-1 and -2 infections [13]. In a review of six cases, sexual abuse was proved in four. In the two innocently acquired cases, HSV-1 infection of the oral cavity immediately preceded the genital signs [14].

There are strict protocols for the examination and assessment of a child who is suspected to be a victim of sexual abuse [15]. It is important that this evaluation is carried out by a skilled specialist, usually a paediatrician [16].

HIV has rarely been reported as being transmitted by sexual abuse of children [17,18], but direct transmission is possible, and sexual abuse may be a risk factor for HIV in later life [19–21].

References

1 Handfield Jones SE, Hinde FJR, Kennedy CTC. Lichen sclerosus et atrophicus in children misdiagnosed as sexual abuse. *BMJ* 1987; **294**: 1404–5.
2 Jenny C, Kirbu P, Furquay D. Genital lichen sclerosus mistaken for child sexual abuse. *Pediatrics* 1989; **83**: 597–9.
3 Hey F, Bucham PC, Littlewood JM, Hall RI. Differential diagnosis in child sexual abuse. *Lancet* 1986; **ii**; 792–6.
4 Levine V, Sanchez M, Nestor M. Localized vulvar pemphigoid in a child misdiagnosed as sexual abuse. *Arch Dermatol* 1992; **128**: 804–6.
5 Warrington SA, San Lazaro C. Lichen sclerosus et atrophicus and sexual abuse. *Arch Dis Child* 1996; **75**: 512–6.
6 Dattell BJ, Landers DV, Coulter K *et al.* Isolation of *Chlamydia trachomatis* from sexually abused female adolescents. *Obstet Gynecol* 1988; **72**: 240–2.
7 Herman-Giddens ME, Gutman LT, Berson N. Association of coexisting vaginal infections and multiple abusers in female children with genital warts. *Sex Transm Dis* 1988; **15**: 63–7.
8 Bump RC, Buesching WJ. Bacterial vaginosis in virginal and sexually active adolescent females: evidence against exclusive sexual transmission. *Am J Obstet Gynecol* 1988; **158**: 935–9.
9 Cohen BA, Honig P, Andophy E. Anogenital warts in children. *Arch Dermatol* 1990; **126**: 1575–80.
10 Obalek S, Misiewicz J, Jablonska S *et al*. Childhood condyloma acuminatum: association with genital and cutaneous infection with human papilloma viruses. *Pediatr Dermatol* 1993; **10**: 101–6.
11 Padel AF, Venning VA, Evans MF *et al*. Human papillomavirus in anogenital warts in children: typing by *in situ* hybridization. *BMJ* 1990; **300**: 1491–4.
12 Sgroi SM. Pediatric gonorrhoea and child sex abuse: the venereal disease connection. *Sex Transm Dis* 1982; **9**: 154–6.
13 Gardner M, Jones JG. Genital herpes acquired by sexual abuse of children. *J Pediatr* 1984; **104**: 243–4.
14 Kaplan KM, Fleischer GP, Paradise JE *et al.* Social tolerance of genital herpes simplex in children. *Am J Dis Child* 1984; **138**: 872–4.
15 Royal College of Physicians of London. *Physical Signs of Sexual Abuse in Children*, 2nd edn. London: Royal College of Physicians, 1997.
16 Makoroff KL, Brauley JL, Brandner AM *et al*. Genital examinations for alleged sexual abuse of prepubertal girls: findings by pediatric emergency medicine physicians compared with child abuse trained physicians. *Child Abuse Negl* 2002; **26**: 1235–42.
17 Liedermann BA, Grimm KT. A child with HIV infection. *JAMA* 1986; **256**: 3904.
18 Straka BF, Whitaker DL, Morrison SH *et al.* Cutaneous manifestations of acquired immunodeficiency syndrome in children. *J Am Acad Dermatol* 1988; **18**: 1089–102.
19 Lindegren ML, Hanson IC, Hammett TA *et al*. Sexual abuse of children: intersection with the HIV epidemic. *Pediatrics* 1998; **102**: 967–8.
20 Allers CT, Benjack KJ, White J, Rousey JT. HIV vulnerability and the adult survivor of childhood sexual abuse. *Child Abuse Negl* 1993; **17**: 291–8.
21 Lyon ME, Richmond D, D'Angelo LJ. Is sexual abuse in childhood or adolescence a predisposing factor for HIV infection during adolescence? *Pediatr AIDS HIV Infect* 1995; **6**: 271–5.

Inflammatory dermatoses

Eczema

Atopic eczema can involve the vulva but the eczematous dermatoses affecting the vulva in isolation are seborrhoeic eczema, irritant contact dermatitis and allergic contact dermatitis.

Seborrhoeic eczema

This condition has both eczematous and psoriasiform features, sometimes making differentiation between it and psoriasis difficult. The inguinal and genitocrural folds, labia majora, mons pubis, perineal body and perianal skin are the usual sites involved. Vulval involvement may be associated with skin changes on the scalp and changes at other flexural sites. Histological examination is not always helpful, as there may be features of both eczema and psoriasis. There is moderate acanthosis with slight spongiosis and a mild dermal inflammatory infiltrate.

Irritant contact dermatitis

The barrier function of the vulval skin is impaired, as measured by transepidermal water loss [1], and there is an increased susceptibility to irritant contact eczema [2,3]. The problem may occur because of the dampness and maceration secondary to a heavy vaginal discharge, or increased contact with urine in the incontinent patient. Contact with irritant chemicals in topical agents, particularly cleansing agents, bubble baths, disinfectants, lubricants, perfumed products, deodorants and medicaments (e.g. 5-fluorouracil, podophyllotoxin and dequalinium), may all be responsible for an irritant dermatitis.

Allergic contact dermatitis

In spite of the frequent use of topical agents in the vulval area, allergic contact dermatitis is extremely rare in clinical practice. However, high incidences of contact dermatitis in vulval dermatoses have been reported [4,5]. An explanation for these unexpected high incidences may be that the patients in the studies had perianal skin involvement as well as vulval involvement, and allergic contact dermatitis to topical medicaments is more frequently encountered in perianal skin. One study has shown a higher incidence of positive patch tests in patients with anogenital dermatoses if both the genital and perianal areas are involved, compared with dermatoses affecting the genital skin alone [6].

There are reports of allergy to vaginal preparations and an intrauterine device [7–9], sanitary wear [10] and condoms [11]. Oestradiol may rarely cause a localized allergic contact dermatitis at a transdermal patch site, or generalized contact dermatitis with oral therapy [12].

Allergic contact urticaria

The two most common causes of contact urticaria in the vulvovaginal area are latex and semen [13], and there is usually a history of atopy [14]. Seminal fluid usually induces an urticarial immediate type I reaction and rarely produces a type IV contact allergy. There are reports of mixed sensitivities; one patient was allergic to semen and latex and another to her husband's semen and sweat [15,16]. However, semen itself may not be the responsible allergen, the problem being caused by a medication or other allergen carried in the seminal fluid [17–19]. Specific immunotherapy against semen has been successfully employed on occasion [20]. A fixed eruption to seminal fluid has been reported [21], and familial allergy to semen [22].

References

1 Elsner P, Wilhelm D, Maibach HI. Physiological skin surface water loss dynamics of human vulvar and forearm skin. *Acta Derm Venereol (Stockh)* 1990; **70**: 141–4.

2 Britz MB, Maibach HI. Human cutaneous vulvar reactivity to irritants. *Contact Dermatitis* 1979; **5**: 375–7.

3 Elsner P, Wilhelm D, Maibach HI. Multiple parameter assessment of vulvar irritant contact dermatitis. *Contact Dermatitis* 1990; **23**: 20–6.

4 Marren P, Wojnarowska F, Powell S. Allergic contact dermatitis and vulvar dermatoses. *Br J Dermatol* 1992; **126**: 52–6.

5 Lewis FM, Harrington CI, Gawkrodger DJ. Contact sensitivity in pruritus vulvae: a common and manageable problem. *Contact Dermatitis* 1994; **31**: 264–5.

6 Goldsmith PC, Rycroft RJ, White IR *et al.* Contact sensitivity in women with anogenital dermatoses. *Contact Dermatitis* 1997; **36**: 174–5.

7 Robin J. Contact dermatitis to acetarsol. *Contact Dermatitis* 1978; **4**: 309–10.

8 Romaguera C, Grimalt F. Contact dermatitis from a copper-containing IUD. *Contact Dermatitis* 1981; **7**: 163–4.

9 Corazza M, Vigili A, Mantovani L. Vulval contact dermatitis to nifuratel. *Contact Dermatitis* 1992; **27**: 273–7.

10 Sterry W, Schmoll M. Contact urticaria and dermatitis from self-adhesive pads. *Contact Dermatitis* 1985; **13**: 284–8.

11 Bircher AJ, Hirsbrunner P, Langauer S. Allergic contact dermatitis of the genitals to additives in condoms. *Contact Dermatitis* 1993; **28**: 125–6.

12 Corazza M, Mantovani L, Montanari A, Virgili A. Allergic contact dermatitis from transdermal estradiol and systemic contact dermatitis from oral estradiol. *J Reprod Med* 2002; **47**: 507–9.

13 Schimkat H-G, Meynadier JM, Meynadier J. Contact urticaria. In: Elsner P, Martius J, eds. *Vulvovaginitis*. New York: Marcel Dekker, 1993: 85–110.

14 Mathias CGT, Frick OL, Caldwell TM *et al.* Immediate hypersensitivity to seminal fluid and atopic dermatitis. *Arch Dermatol* 1980; **116**: 209–12.

15 Kint B, Degreef H, Dooms-Goossens A. Combined allergy to human seminal plasma and latex: case report and review of the literature. *Contact Dermatitis* 1994; **30**: 7–11.

16 Freeman S. Woman allergic to husband's sweat and semen. *Contact Dermatitis* 1986; **14**: 110–2.

17 Green RL, Green MA. Post-coital urticaria in a penicillin-sensitive patient: possible seminal transfer of penicillin. *JAMA* 1985; **254**: 531.

18 Sell MB. Sensitization to thioridazine through sexual intercourse. *Am J Psychiatry* 1985; **142**: 271–2.

19 Paladine WJ, Cunningham TJ, Donovan MA, Dumper CW. Possible sensitivity to vinblastine in prostatic or seminal fluid [Letter]. *N Engl J Med* 1975; **292**: 52.

20 Boom BW, van Toorenenbergen AW, Nierop G *et al.* A case of seminal fluid allergy successfully treated with immunotherapy in a one day rush procedure. *J Dermatol* 1991; **18**: 206–10.

21 Best CL, Waters C, Adelman DC. Fixed cutaneous eruption to seminal plasma challenge. *Fertil Steril* 1988; **50**: 532–4.

22 Chang T. Familial allergic seminal vulvovaginitis. *Am J Obstet Gynecol* 1976; **126**: 442–4.

Psoriasis

The pattern of psoriasis affecting the anogenital skin is most frequently flexural. The areas involved include the genitocrural folds, mons pubis, outer aspects of the labia majora, the perianal skin and the natal cleft (Fig. 71.21). The characteristic silvery scaling is absent in these occluded sites and the main clinical picture is intense erythema with a well-defined margin. Rarely, there may be some scarring associated with vulval psoriasis, with loss of the labia minora and fusion of the clitoral hood.



Fig. 71.21 Fissured psoriasis in the natal cleft.



Fig. 71.22 White patches of lichen planus in the interlabial sulci.

The histology is not always typical, and there may be marked spongiosis and papillary oedema.

Reiter's disease (circinate ulcerative vulvitis)

Circinate balanitis is well recognized but the corresponding vulvitis is much rarer [1–4]. The lesions may be eroded, ulcerative or scaly. Histologically, the changes are of those seen in pustular psoriasis [5], with hyperkeratosis, parakeratosis, psoriasiform hyperplasia, an absent granular layer and collections of polymorphs in the epidermis.

References

1 Thambar IV, Dunlop R, Thin RN *et al.* Circinate vulvitis in Reiter's syndrome. *Br J Vener Dis* 1977; **53**: 260–2.

2 Daunt O'N, Kotowski KE, O'Reilly AP *et al.* Ulcerative vulvitis in Reiter's syndrome: a case report. *Br J Vener Dis* 1982; **58**: 405–7.

3 Haake N, Altmeyer P. Vulvovaginitis circinata bei morbus Reiter. *Hautarzt* 1988; **39**: 748–9.

4 Edwards L, Hansen RC. Reiter's syndrome of the vulva. *Arch Dermatol* 1992; **128**: 811–4.

5 Kanerva L, Kouse M, Niema KM *et al.* Ultrahistopathology of balanitis circinata. *Br J Vener Dis* 1982; **58**: 185–95.

Lichen planus [1–3]

Lichen planus (LP) can affect the vulva in isolation or at the same time as a generalized eruption, when approximately 20% of patients will have genital lesions. The vulval lesions are similar to those seen at other sites and may be violaceous or erythematous papules, white (Fig. 71.22) or annular plaques, and erosions with or without a lacy white border. These lesions may all ulcerate. Wickham's striae occur infrequently (Fig. 71.23). If the vulva is affected in isolation, the disease is more often erosive, with most of the lesions around the labia minora, clitoris and clitoral hood. Confluent white and red patches will also be seen in this variant.



Fig. 71.23 Delicate white striae of lichen planus, with the labia minora flattening and fusing into the surrounding skin.

A careful examination of the oral mucosae is helpful, as LP may be found on the tongue, palate, gingivae and lateral buccal mucosae.

The other clinical forms of vulval LP include the following.

1 **Pigmented flexural lichen planus** (Fig. 71.24). This variant of LP can affect the vulval area, particularly the mons pubis, the inguinal and genitocrural folds. The characteristic and striking finding is brown pigmented patches, some so deeply pigmented

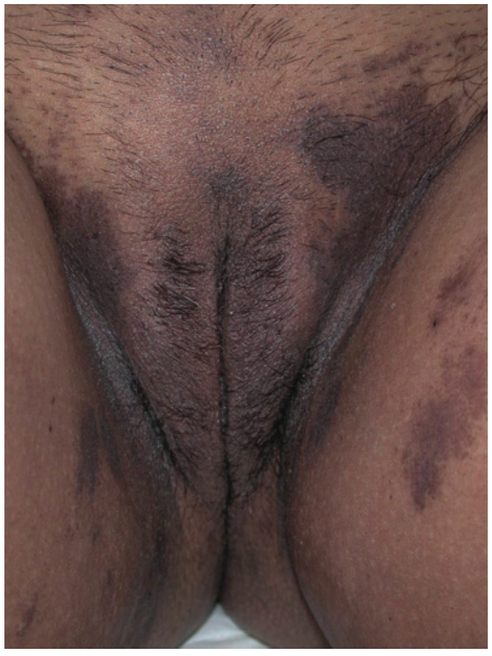


Fig. 71.24 Patches of pigmented flexural lichen planus.



Fig. 71.25 Lichen planus: vulval aspect showing glazed erythema and distortion of the architecture, with a remnant of the left labium minus and buried clitoris above it.

that they resemble melanocytic naevi. If the disease is seen in the early stages, a violaceous erythema is also observed. This form of LP is also found in the inframammary areas and axillae.

2 **Vulvovaginal–gingival lichen planus** (VVG-LP) (syndrome of Hewitt and Pelisse; desquamative vaginitis). This distinctive erosive form of LP is clinically very similar to mucous membrane pemphigoid [4,5]. In the past, many cases labelled desquamative vaginitis were probably this entity [6,7]. VVG-LP principally affects the inner aspects of the labia minora, vestibule and vagina. The condition is chronic and painful, and there is an increase in vaginal discharge, dysuria, dyspareunia and postcoital bleeding. Clinically, the epithelia are eroded and often there is a distinctive fine white lacy border. There may be marked loss of architecture (Fig. 71.25). The anal margin may also be involved. The vaginal lesions are velvety red erosions or bright red, glazed erythema, which is friable and bleeds when touched. Vaginal synechiae and adhesions develop, leading in some cases to vaginal stenosis. The cervix may also be involved [5,8,9]. Oral LP lesions can occur at any site, but the characteristic finding is an intense erythema of the gingivae, which may be asymptomatic (Fig. 71.26). Unusual extragenital lesions have been described on the conjunctiva [10], lacrimal gland canal [11], oesophagus [12–15] and the auditory canal [16]. The manifestations of this syndrome do not necessarily all occur synchronously.

3 **Lichen planopilaris.** This has been described on the vulva [17].



Fig. 71.26 Lichen planus. Intense glazed erythema of gingiva.

Histopathology. On cornified epithelium there is hyperkeratosis, irregular acanthosis with a typical saw-tooth appearance of the rete pegs, an increased granular layer, and disruption of the basal layer with a closely apposed dermal band-like lymphocytic infiltrate. The acanthosis and hyperkeratosis are marked in the hypertrophic form, and because of the chronicity of this form the characteristic band-like infiltrate is not obvious but will be found focally. Eosinophilic colloid bodies may be seen. Immunofluorescence studies reveal uneven staining of the basement membrane zone for fibrinogen and IgM, cytoid bodies and, on occasion, IgG or IgA.

Differential diagnosis. The main differential diagnosis is usually lichen sclerosus, but mucous membrane pemphigoid and

morphoea could also be included. In some cases, the differentiation between lichen sclerosus (LS) and LP can be extremely difficult, even impossible, as the two diseases share so many features in common [18,19]. If a definite diagnosis cannot be made on a combination of clinical, histological and immunofluorescence findings and response to treatment, it is perhaps best to consider the case as an overlap of the two disorders. Frequently, there are cases of LP misdiagnosed as Zoon's vulvitis.

Treatment. First-line treatment is with potent topical steroids. If the vagina is involved, a topical steroid can be introduced with a vaginal applicator, or steroid foams or suppositories that are available for inflammatory bowel conditions can be used [20]. Topical retinoids are useful for hyperkeratotic and hypertrophic LP, and recently topical tacrolimus [21] and pimecrolimus have been used [22]. Other treatments tried with variable success include oral steroids, oral and topical retinoids, methotrexate [23], ciclosporin [24] and azathioprine.

References

1 Edwards L. Vulvar lichen planus. *Arch Dermatol* 1989; **125**: 1677–80.
2 Lewis FM, Shah M, Harrington CI. Vulval involvement in lichen planus: a study of 37 women *Br J Dermatol* 1996; **135**: 89–91.
3 Ridley CM, Neill SM. Non-infective cutaneous conditions of the vulva. In: Ridley CM, Neill SM, eds. *The Vulva*. Oxford: Blackwell Science, 1999: 164–8.
4 Pelisse M, Leibowitch M, Sedel D *et al.* Un nouveau syndrome vulvovagino-gingival: lichen plan erosif plurimuqueux. *Ann Dermatol Vénéréol* 1982; **109**: 797–8.
5 Setterfield J, Neill S, Shirlaw P *et al*. The vulvovaginal gingival syndrome: a severe subgroup of lichen planus with characteristic clinical features and a novel association with the class II HLA DQB1*0201 allele. *J Am Acad Dermatol* 2006; **55**: 98–113.
6 Edwards L, Friedrich EG. Desquamative vaginitis: lichen planus in disguise. *Obstet Gynecol* 1988; **71**: 32–6.
7 Ridley CM. Chronic erosive vulval disease. *Clin Exp Dermatol* 1990; **15**: 245–52.
8 Gougerot H, Burnier R. Lichen plan du col uterin, accompagnant un lichen plan jugalet un lichen plan stomacal: lichen plurimuqueux sans lichen cutane. *Bull Soc Francaise Dermatol Syphiligr* 1937; **44**: 637–40.
9 Pelisse M. Erosive vulvar lichen planus and desquamative vaginitis. *Semin Dermatol* 1996; **15**: 47–50.
10 Moyal-Barracco M, Lautier-Frau M, Bechéral PA *et al.* Lichen plan conjunctival: une observation. *Ann Dermatol Vénéréol* 1993; **120**: 857–9.
11 McNab AA. Lacrimal gland canalicular obstruction in lichen planus. *Orbit* 1998; **17**: 201–2.
12 Keate RF, Williams JW, Connolly SM. Lichen planus esophagitis: report of 3 patients treated with oral tacrolimus or intraesophageal corticosteroid injection or both. *Dis Esophagus* 2003; **16**: 47–53.
13 Dickens CM, Hesletine D, Walton S *et al*. The oesophagus in lichen planus: an endoscopic study. *BMJ* 1990; **300**: 84.
14 Bobadilla J, van der Hulst RW, ten Kate FJ. Oesophageal lichen planus. *Gastrointest Endosc* 1999; **50**: 268–71.
15 Menges M, Hohloch K, Pueschel W, Stallmach A. Lichen planus with oesophageal involvement: a case report and review of the literature. *Digestion* 2002; **65**: 184–9.
16 Martin L, Moriniere S, Machet M-C. Bilateral conductive deafness related to erosive lichen planus. *J Laryngol Otol* 1998; **112**: 365–6.
17 Grunald MH, Zvulunov A, Halevy S. Lichen planopilaris of the vulva. *Br J Dermatol* 1998; **136**: 477–8.
18 Marren P, Millard P, Chia Y, Wojnarowska F. Mucosal lichen sclerosus/lichen planus overlap syndromes. *Br J Dermatol* 1994; **131**: 118–23.
19 Fung MA, LeBoit PE. Light microscopic criteria for the diagnosis of early vulvar lichen sclerosus: a comparison with lichen planus. *Am J Surg Pathol* 1998; **22**: 473–8.
20 Anderson M, Kutzner S, Kaufman R. Treatment of vulvovaginal lichen planus with vaginal hydrocortisone suppositories. *Obstet Gynecol* 2002; **100**: 359–62.
21 Byrd JA, Davis MD, Rogers RS 3rd. Recalcitrant symptomatic vulvar lichen planus: response to topical tacrolimus. *Arch Dermatol* 2004; **140**: 715–20.
22 Lonsdale-Eccles AA, Velangi S. Topical pimecrolimus in the treatment of genital lichen planus: a prospective case series. *Br J Dermatol* 2005; **153**: 390–4.
23 Nylander-Lunqvist E, Wahlin YB, Hofer PA. Methotrexate supplemented with steroid ointments for the treatment of severe erosive lichen ruber. *Acta Dermatol Venereol* 2002; **82**: 63–4.
24 Borrego L, Ruiz-Rodriguez R, Ortiz de Frutos J. Vulvar lichen planus treated with topical cyclosporin. *Arch Dermatol* 1993; **129**: 794.

Zoon's vulvitis

It is likely that plasma cell vulvitis (PCV; vulvitis circumscripta plasmacellularis) is not a single disease entity but represents a reaction pattern to another inflammatory condition. A plasma cell-rich infiltrate in a vestibular biopsy may be a misleading finding, because plasma cells are commonly found in inflammatory conditions of the vestibule as it is a mucosal epithelium.

Many of the cases are examples of unrecognized dermatoses such as LP, and in others the persistent change may represent a chronic post-inflammatory phenomenon.

The first descriptions of the female equivalent of ZB were by Garnier and Zoon [1–3]. The lesions described in these reports were erythematous patches with a glazed appearance, with the histological findings of a plasma cell-rich dermal infiltrate and no cytological atypia. The disorder followed a chronic but benign course. It appears to be less common in women, and in one series of 20 cases there was only one female [4].

Most of the reports of this condition in women describe the lesions in the vestibule and labia minora, whereas the typical site in men is the glans and prepuce. The glans clitoris is rarely, if ever, affected.

Histology. The criteria needed to make the diagnosis have varied in the literature, and there is some doubt whether PCV is a distinct clinicopathological entity, as many of the reports of vestibular Zoon's are probably LP [5].

The essential features are epidermal thinning, absent horny and granular layers and distinctive lozenge-shaped keratinocytes with widened intercellular spaces; in the dermis there is a dense inflammatory infiltrate composed largely of plasma cells, with dilated blood vessels and usually much haemosiderin. Russell bodies and dermal-epidermal splitting have also been described [6].

Treatment. Treatment depends on the underlying inflammatory dermatosis responsible for this histological change. In the majority of cases this is LP, and a potent topical steroid should be tried. If the inflammatory phase of disease has resolved and the patient is complaining of a sensation of rawness or burning, then topical 5% lidocaine can be effective. Finally, a barrier ointment such as Vaseline petroleum jelly may offer some relief if there is an irritant component to the problem.

Chronic vulval purpura

It is not uncommon to find patients with purpuric patches, often at the vestibule, in which haemosiderin and plasma cells are found without any specific epidermal change, and the term chronic

vulval purpura may be a more accurate description [7]. An association with lichen aureus has been suggested, as pressure factors are thought to be relevant in the extravasation of blood [8].

References

1 Garnier G. Vulvite erythemateuse circonscrite benigne a type erythroplasique. *Bull Soc Francaise Dermatol Syphilogr* 1954; **61**: 102–3.
2 Zoon JJ. Balanitis and vulvitis plasma cellularis. *Dermatologica* 1955; **111**: 157.
3 Garnier G. Benign plasma cell erythroplasia. *Br J Dermatol* 1957; **69**: 77–81.
4 Souteyrand P, Wong E, MacDonald DM. Zoon's balanitis (balanitis circumscripta plasmacellularis). *Br J Dermatol* 1981; **105**: 195–9.
5 Scurry J, Dennerstein G, Brennan J *et al*. Vulvitis circumscripta plasmacellularis: a clinicopathologic entity? *J Reprod Med* 1993; **38**: 14–8.
6 Woodruff JD, Sussman J, Shakfeh S. Vulvitis circumscripta plasmacellularis: a report of four cases. *J Reprod Med* 1989; **34**: 369–72.
7 Kato T, Kuramoto Y, Tadaki T *et al*. Chronic vulvar purpura. *Dermatologica* 1990; **180**: 174–6.
8 Li Q, Leopold K, Carlson JA. Chronic vulvar purpura: persistent pigmented purpuric dermatitis (lichen aureus) of the vulva or plasma cell (Zoon's) vulvitis? *J Cutan Pathol* 2003; **30**: 572–6.

Lichen sclerosus [1–5]

Lichen sclerosus (LS) was first described as a variant of LP with a tendency to affect the genital area. The old terms leukoplakia, leukoplakic vulvitis and kraurosis vulvae were clearly applied to examples of LS or LP, and the use of these terms led to confusion. The term vulval dystrophy was introduced in the 1960s in an attempt to overcome the problems in distinguishing and classifying vulval dermatoses characterized by pallor and scarring [6]. This terminology unfortunately proved unsuccessful in its objectives, as its use discouraged attempts to differentiate between disorders such as LS, LP and mucous membrane pemphigoid. In 1983, the Terminology Committee of the International Society for the Study of Vulvovaginal Dermatoses recommended a new classification with discontinuation of the term dystrophy [7]. The term vulval squamous cell hyperplasia was introduced with this classification (see p. 71.52).

Aetiology and pathogenesis. The aetiology is still unknown but there is mounting evidence that LS is a genetically determined autoimmune disorder. A positive family history is recognized and the disorder has been described in twins, both identical [8] and non-identical [9]. An association of LS with other autoimmune disease in females has been noted [10]. Attempts to establish a specific HLA linkage in patients with LS were initially inconclusive [11], but a later study has shown an increased incidence of DQ7 [12]. Similar findings have been reported in LS in girls [13]. The role of *Borrelia burgdorferi* as an aetiological trigger is controversial. A study in the UK showed no evidence histologically of spirochaetes but did show 'cocci' with a Fite stain, which later proved to be mast cells when stained with toluidine blue [14].

Clinical features. LS can affect females of any age, but the majority of patients are either prepubertal or menopausal. There is still uncertainty whether LS in prepubertal girls remits spontaneously at puberty. The presenting symptom is usually itching, which is often severe and distressing.

The classical lesions seen on the extragenital skin are ivory white papules and plaques with follicular delling. Anogenital disease



Fig. 71.27 Oedema and ecchymosis of lichen sclerosus.

tends to be characterized by flatter lesions of atrophic whitened epithelium, which may become confluent, extending around the vulval and perianal skin in a figure-of-eight configuration. There may also be oedema, purpura, bullae, erosions and ulceration (Fig. 71.27). The sites most commonly affected are the genitocrural folds, the inner aspects of the labia majora, labia minora, clitoris and clitoral hood. Vestibular involvement is rare and vaginal lesions do not occur, as LS seems to spare non-cornified stratified squamous epithelia (mucosal epithelium). Perianal lesions occur in approximately 30% of female patients, in contrast with men who do not seem to develop perianal involvement. Extragenital lesions occur in 10% of women with vulval disease. The extragenital areas may be truncal, at sites of pressure, upper back, wrists, buttocks and thighs. The Koebner phenomenon has also been reported at sites of radiotherapy [15], scar tissue [16], vaccination [17] and congenital haemangioma [18]. Facial [19], lip [20], scalp [21] and nail involvement [22] have been recorded.

Lesions of LS in the oral cavity are extremely rare and occur on a site in the mouth that has cornified stratified squamous epithelium, the tongue [23]. Many of the reports of oral involvement in the literature have often not been confirmed histologically [24] and may have been examples of LP. It is not uncommon for patients with vulval LS to have coexistent oral LP [25].

LS is a scarring dermatosis and the changes that can occur on the vulva include loss of the labia minora, and sealing over of the clitoral hood, burying the clitoris (Fig. 71.28). Introital narrowing resulting from anterior and posterior labial fusion sometimes results in a tiny opening into the vestibule. Milia may occur [26].

Histology. The classic histology is a thinned epidermis with flattening of the rete pegs. The underlying dermis is hyalinized and



Fig. 71.28 Lichen sclerosus. Pallor and atrophy of the vulval skin with loss of the labia minora and burying of the clitoris.



Fig. 71.29 Squamous cell carcinoma arising on a background of lichen sclerosus.

there are often extravasated red cells. Below the hyalinized area is a band-like zone of chronic inflammatory cells. There is an absence of elastic fibres in the upper dermis. There have been attempts to grade the histological appearances but there is probably little correlation between the timing of a lesion and its histological appearance [27].

In some cases the epidermis is thickened, and this is LS with squamous cell hyperplasia. It is found in approximately 30% of cases of LS in association with vulval SCC [28].

There are abnormalities of the basement membrane, but it is uncertain whether these are a primary or secondary event [29]. Immunofluorescence studies are usually negative or demonstrate non-specific fibrin deposition at the dermal–epidermal junction. There is also an alteration of the elastin and fibrillin in the affected dermis [30].

Differential diagnosis. Vitiligo, mucous membrane pemphigoid, LP and morphoea may present with a similar clinical appearance. There can be clinical and histological overlap between morphoea, LP and LS, and they may represent a spectrum of disease rather than three distinct conditions [31].

Lichen sclerosus and vulval malignancy

There is undoubtedly an association between vulval SCC and LS that was probably underestimated in the past (Fig. 71.29) [32]. The incidence of SCC developing on LS in clinical practice is of the order of 4% or less [1]. However, in retrospective reviews of pathological specimens of vulval carcinoma, histological evidence of LS is found in approximately half of the cases [33–35]. These series included patients presenting with SCC as well as those on long-term follow-up for LS. A longitudinal cohort study of 211 patients showed that the number of invasive SCCs significantly exceeded that in an age-matched group [36]. The oncogenic HPV types do not appear to be implicated in the development of SCC on LS [37,38]. It is not known whether good control of LS reduces the risk of neoplastic change.

The histological patterns associated with SCC arising on LS include epithelial hyperplasia and differentiated intraepithelial neoplasia (dysplastic changes that are confined to the basal layers).

LS has been reported in association with verrucous carcinoma [39,40], basal cell carcinoma [41] and melanoma [42–44]. However, malignant melanoma is known to be difficult to diagnose in the presence of LS [45].

Treatment. The current and recommended treatment for uncomplicated LS is the potent topical corticosteroid, clobetasol propionate. There are no randomized controlled trials providing evidence for any particular corticosteroid or treatment regimen being more effective than any other. The regimen currently recommended for a newly diagnosed case is initially clobetasol propionate once nightly for 4 weeks, then alternate nights for 4 weeks, and twice a week for a further month. A 30-g tube of clobetasol propionate should last 12 weeks, and the patient is then reviewed [46]. The clobetasol propionate is then used as and when required to control itching. Most patients seem to require 30–60 g annually. Some patients go into complete remission and do not require further treatment. Others will continue to have flares and remissions and they are advised to use clobetasol propionate as required. A soap substitute is also recommended and an information sheet on LS, including instructions for the use of the topical steroid, is provided.

Topical testosterone currently has no role in the management of LS. It is expensive and is not as effective as clobetasol propionate [47]. Recent reports have suggested the use of the calcineurin inhibitors tacrolimus [48] or pimecrolimus [49] as steroid-sparing alternatives. The use of these topical immunosuppressants should be limited to the treatment of the rare cases of LS that prove unresponsive to a potent topical steroid. The treatment should be a short course and it should not be used long term as the safety of these immunosuppressants is still unknown, particularly as the condition carries a risk of neoplastic change. Ciclosporin [50] and UVA1 [51] have also been used to treat recalcitrant disease.

Surgical excision of affected vulval skin is not necessary in the management of most cases of LS and it should be used exclusively for the management of functional problems caused by post-inflammatory scarring [52,53], premalignant lesions and malignancy.

References

1 Wallace HJ. Lichen sclerosus et atrophicus. *Trans St John's Hosp Dermatol Soc* 1971; **57**: 9–30.

2 Meffert JJ, Davis BM, Grimwood RE. Lichen sclerosus. *J Am Acad Dermatol* 1995; **32**: 393–416.

3 Ridley CM, Neill SM. Non-infective cutaneous conditions of the vulva. In: Ridley CM, Neill SM, eds. *The Vulva*. Oxford: Blackwell Science, 1999: 154–6.

4 Powell JJ, Wojnarowska F. Lichen sclerosus. *Lancet* 1999; **353**: 1777–83.

5 Ridley CM. Genital lichen sclerosus (lichen sclerosus et atrophicus) in childhood and adolescence. *J R Soc Med* 1993; **86**: 69–75.

6 Jeffcoate TNA, Woodcock AS. Premalignant conditions of the vulva, with particular reference to chronic epithelial dystrophies. *BMJ* 1961; **ii**: 127–34.

7 Wilkinson EJ, Kneale B, Lynch PJ. Report of the ISSVD terminology committee. *J Reprod Med* 1986; **31**: 973–4.

8 Meyrick-Thomas RH, Meyrick-Thomas RH, Kennedy CTC. The development of lichen sclerosus et atrophicus in monozygotic twin girls. *Br J Dermatol* 1986; **114**: 377–9.

9 Cox NH, Mitchell JNS, Morley WN. Lichen sclerosus et atrophicus in non-identical female twins. *Br J Dermatol* 1986; **115**: 743.

10 Meyrick Thomas RH, Ridley CM, McGibbon DH *et al.* Lichen sclerosus et atrophicus and autoimmunity. *Br J Dermatol* 1988; **118**: 41–6.

11 Purcell KG, Spencer LV, Simpson PM *et al.* HLA antigens in lichen sclerosus et atrophicus. *Arch Dermatol* 1990; **126**: 1043–5.

12 Marren P, Yell J, Charnock FM *et al.* The association between lichen sclerosus and antigens of the HLA system. *Br J Dermatol* 1995; **132**: 197–203.

13 Powell J, Wojnarowska F, Winsey S *et al.* Lichen sclerosus premenarche: autoimmunity and immunogenetics. *Br J Dermatol* 2000; **142**: 481–4.

14 Farrell AM, Millard PR, Schomberg KH, Wojnarowska F. An infective aetiology for vulval lichen sclerosus re-addressed. *Clin Exp Dermatol* 1999; **24**: 479–83.

15 Yates VM, King CM, Dave VK. Lichen sclerosus et atrophicus following radiation therapy. *Arch Dermatol* 1985; **121**: 1044–7.

16 Pass CJ. An unusual variant of lichen sclerosus et atrophicus: delayed appearance in a surgical scar. *Cutis* 1984; **33**: 405–8.

17 Anderton RL, Abele DC. Lichen sclerosus et atrophicus in a vaccination site. *Arch Dermatol* 1976; **112**: 1787.

18 Ostlere LS, Tildsley G, Holden CA. Lichen sclerosus over a strawberry naevus: a new example of the Koebner phenomenon? [Letter]. *Clin Exp Dermatol* 1996; **21**: 394–5.

19 Dalziel K, Reynolds AJ, Holt PJA. Lichen sclerosus et atrophicus with ocular and maxillary complications. *Br J Dermatol* 1983; **116**: 735–7.

20 Kelly SC, Helm KF, Zaenglein AL. Lichen sclerosus of the lip. *Pediatr Dermatol* 2006; **23**: 500–2.

21 Foulds IS. Lichen sclerosus et atrophicus of the scalp. *Br J Dermatol* 1980; **103**: 197–200.

22 Ramrakha-Jones VS, Paul M, McHenry P, Burden AD. Nail dystrophy due to lichen sclerosus? *Clin Exp Dermatol* 2001; **26**: 507–9.

23 Chaudhry SI, Morgan PR, Neill SM. An unusual tongue. *Clin Exp Dermatol* 2006; **31**: 831–2.

24 Brown AR, Dunlap CL, Bussard DA *et al.* Lichen sclerosus of the oral cavity: a report of two cases. *Oral Surg Oral Med Oral Pathol* 1997; **84**: 165–70.

25 Marren P, Millard P, Chia Y *et al.* Mucosal lichen sclerosus/lichen planus overlap. *Br J Dermatol* 1994; **131**: 118–23.

26 Leppard B, Sneddon IB. Milia occurring in lichen sclerosus et atrophicus. *Br J Dermatol* 1975; **92**: 711–4.

27 Marren P, Millard PR, Wojnarowska F. Vulval lichen sclerosus: lack of correlation between duration of clinical symptoms and histological appearances. *J Eur Acad Dermatol Venereol* 1997; **8**: 212–6.

28 Hart WR, Norris HJ, Helwig EB. Relation of lichen sclerosus et atrophicus of the vulva to development of squamous cell carcinoma. *Obstet Gynecol* 1975; **45**: 369–77.

29 Marren P, Dean D, Charnock M *et al.* Basement membrane zone in lichen sclerosus: an immunohistological study. *Br J Dermatol* 1997; **136**: 508–14.

30 Farrell AM, Dean D, Millard PR *et al.* Alterations in fibrillin as well as collagens I and III and elastin occur in vulval lichen sclerosus. *J Eur Acad Dermatol Venereol* 2001; **15**: 212–7.

31 Farrell AM, Marren PM, Wojnarowska F. Genital lichen sclerosus associated with morphoea or systemic sclerosis: clinical and HLA characteristics. *Br J Dermatol* 2000; **143**: 598–603.

32 Zaki I, Dalziel KL, Solomons FA *et al.* The under-reporting of skin disease in association with squamous cell carcinoma of the vulva. *Clin Exp Dermatol* 1997; **21**: 334–7.

33 Walkden V, Chia Y, Wojnarowska F. The association of squamous cell carcinoma of the vulva and lichen sclerosus: implications for management and follow-up. *J Obstet Gynecol* 1997; **17**: 551–3.

34 Leibowitch M, Neill S, Pelisse M, Moyal-Barracco M. The epithelial changes associated with squamous cell carcinoma of the vulva: a review of the clinical, histological and viral findings in 78 women. *Br J Obstet Gynaecol* 1990; **97**: 1135–9.

35 Vilmer C, Cavelier-Balloy B, Nogues C *et al.* Analysis of alterations adjacent to invasive vulvar cancer and their relationship with the associated carcinoma: a study of 67 cases. *Eur J Gynecol Oncol* 1998; **19**: 25–31.

36 Carli P, Cattaneo A, de Magnis A *et al.* Squamous cell carcinoma arising in lichen sclerosus: a longitudinal cohort study. *Eur J Cancer Prev* 1995; **4**: 491–5.

37 Carlson JA, Ambros R, Malfetano J *et al.* Vulval lichen sclerosus and squamous cell carcinoma: a cohort, case control, and investigational study with histological perspective—implications for chronic inflammation and sclerosis in the development of neoplasia. *Hum Pathol* 1998; **29**: 932–48.

38 Toki T, Kurman RJ, Park JS *et al.* Probable non-papillomavirus aetiology of squamous cell carcinoma of the vulva in older women: a clinicopathologic study using *in situ* hybridization and polymerase chain reaction. *Int J Gynecol Pathol* 1991; **10**: 107–25.

39 Brisigotti M, Moreno A, Murcia C *et al.* Verrucous carcinoma of the vulva: a clinicopathologic and immunohistochemical study of five cases. *Int J Gynecol Pathol* 1989; **8**: 1–7.

40 Derrick EK, Ridley CM, Kobza-Black A *et al.* A clinical study of 23 cases of female anogenital carcinoma. *Br J Dermatol* 2000; **143**: 1217–23.

41 Meyrick-Thomas RH, McGibbon DH, Munro DD. Basal cell carcinoma of the vulva in association with vulval lichen sclerosus et atrophicus. *J R Soc Med* 1985; **78**: 16–8.

42 Friedman RJ, Kopf AW, Jones WB. Malignant melanoma in association with lichen sclerosus on the vulva of a 14-year-old. *Am J Dermatopathol* 1984; **6** (Suppl. 1): 253–6.

43 Hassanein AM, Mrstik ME, Hardt NS *et al.* Malignant melanoma associated with lichen sclerosus in the vulva of a 10-year-old. *Pediatr Dermatol* 2004; **21**: 473–6.

44 Rosamilia LL, Schwartz JL, Lowe L *et al.* Vulvar melanoma in a 10-year-old girl in association with lichen sclerosus. *J Am Acad Dermatol* 2006; **54** (Suppl. 1): S52–3.

45 El Shabrawi-Caelen L, Soyer HP, Schaeppi HL *et al.* Genital lentigines and melanocytic nevi with superimposed lichen sclerosus: a diagnostic challenge. *J Am Acad Dermatol* 2004; **50**: 690–4.

46 Neill SM, Tatnall FM, Cox NH. Guidelines on the management of lichen sclerosus. *Br J Dermatol* 2002; **147**: 640–9.

47 Bornstein J, Heifetz S, Kellner Y *et al.* Clobetasol dipropionate 0.05% versus testosterone 2% topical application for severe vulvar lichen sclerosus. *Am J Obstet Gynecol* 1998; **178**: 80–4.

48 Virgili A, Lauriola MM, Mantovani L, Corazza M. Vulvar lichen sclerosus: 11 women treated with tacrolimus 0.1% ointment. *Acta Derm Venereol* 2007; **87**: 69–72.
49 Nissi R, Eriksen H, Risteli J, Niemimaa M. Pimecrolimus cream 1% in the treatment of lichen sclerosus. *Gynecol Obstet Invest* 2007; **63**: 151–4.
50 Bulbul Baskan E, Turan H, Tunali S *et al.* Open-label trial of cyclosporine for vulvar lichen sclerosus. *J Am Acad Dermatol* 2007; **57**: 276–8.
51 Beattie PE, Dawe RS, Ferguson J, Ibbotson SH. UVA1 phototherapy for genital lichen sclerosus. *Clin Exp Dermatol* 2006; **31**: 343–7.
52 Paniel B. Surgical procedures in benign vulval disease. In: Ridley CM, Neill SM, eds. *The Vulva*. Oxford: Blackwell Science, 1999: 288–90.
53 Rouzier R, Haddad B, Deyrolle C *et al*. Perineoplasty for the treatment of introital stenosis related to vulval lichen sclerosus. *Am J Obstet Gynecol* 2002; **186**: 49–52.

Crohn's disease

Anogenital lesions occur in approximately 30% of patients with intestinal Crohn's disease, either as a direct extension of active intestinal disease or as metastatic disease. Vulval disease may present many years before intestinal involvement, and in some cases there is vulval oedema only, with no evidence of granulomatous inflammation [1,2]. The more usual presentation is ulceration, abscess, sinus and fistula formation, with a granulomatous histology. There may be deep linear fissures (knife cut sign) along the skin creases.

A separate form of vulval granuloma akin to the orofacial lesions seen in Melkersson–Rosenthal syndrome has been described [3,4].

Treatment. If genital Crohn's disease is the presenting problem it is important to involve a gastroenterologist in management, as these patients need a full work-up to assess if there is intestinal disease as well. In ulcerative disease it is essential to exclude any fistulous tracts. In patients who have no systemic disease topical measures may be sufficient to control the cutaneous lesions, that is an ultrapotent topical steroid or topical tacrolimus [5]. Severe disease may respond to oral steroids but recalcitrant ulcerative anogenital lesions and fistulous tracts may require infliximab [6].

References

1 Urbanek M, McKee PH, Neill SM. Vulval Crohn's: difficulties in diagnosis. *Clin Exp Dermatol* 1996; **21**: 211–4.
2 Martin J, Holdstock G. Isolated vulval oedema as a feature of Crohn's disease. *J Obstet Gynecol* 1997; **17**: 92–3.
3 Hackel H, Hartmann AA, Burg G. Vulvitis granulomatosa and anoperineitis granulomatosa. *Dermatologica* 1991; **182**: 128–31.
4 Knopf B, Schaarschmidt H, Wollina U. Monosymptomatisches Melkersson–Rosenthal syndrom mit nachfolgender vulvitis und perivulvitis granulomatosa. *Hautarzt* 1992; **43**: 711–3.
5 Casson DH, Eltumi M, Tomlin S *et al*. Topical tacrolimus may be effective in the treatment of oral and perineal Crohn's disease. *Gut* 2000; **47**: 436–40.
6 Preston W, Hudson N, Lewis FM. Treatment of vulval Crohn's disease with infliximab. *Clin Exp Dermatol* 2006; **31**: 378–80.

Ulcerative and bullous disorders

Any of the blistering disorders of the skin can occur on the vulva and vagina, either as part of the generalized disease or in isolation. Diagnosis can be more difficult in the latter case.

There are many causes of vulval ulceration and some features are important in narrowing down the differential diagnosis. It is helpful to divide them into acute and chronic types.



Fig. 71.30 Solitary benign aphthous ulcer of the left labium minus.

Acute genital ulceration

Benign aphthae

Many eponymous names have been assigned to acute vulval ulcers and several of these disorders are probably examples of benign aphthae. Reiter's syndrome may be associated with an ulcerative vulvitis [1].

Benign aphthae of the vulva may or may not occur with concomitant oral lesions. The age of onset is in childhood, about the age of 6 years, and there may be a family history. The lesions are usually multiple and small, and less commonly solitary or few and larger—referred to as giant aphthae. Sometimes there are premenstrual exacerbations once the menarche is reached. The aetiology remains unknown but herpetic infection should always be excluded.

The lesions are superficial and painful, with a yellow base surrounded by a red areola. They are distributed most frequently on the labia minora, and heal quickly (Fig. 71.30).

Sutton's ulcer (periadenitis mucosa necrotica recurrens) was originally reported in the mouth [2], but vulval lesions have also been given this label. The ulcer is characterized as being solitary, painful and recurring [2]. This type of ulceration, in the light of today's knowledge, would now be regarded as an example of benign aphthosis or a manifestation of Behçet's syndrome. Lipschutz's ulcer, described 2 years after Sutton's report, encompassed three types of ulcer (ulcus vulvae acutum), two of which today would be assigned to either aphthous ulceration or Behçet's syndrome. Only one is still regarded as being a separate entity [3]. This remaining form of ulceration is sometimes associated with a systemic infection such as infectious mononucleosis [4,5], typhoid or paratyphoid fever. Epstein–Barr virus (EBV) has been isolated from the ulcers [6], and there is one case of a mistaken diagnosis of lymphoma [7]. The Lipschutz-type ulcer usually affects adoles-

cent girls and has a rapid onset. The ulcer may be very deep and large, and has a surrounding red areola and a thick adherent slough. It is most often solitary on one side of the vulva, usually the inner aspect of the labium minus, but lesions may occur bilaterally. Healing is spontaneous, but may take several weeks and leaves some scarring. Relapses may occur over 18 months but this is unusual.

Treatment includes analgesics, potassium permanganate soaks and the application of a topical steroid with or without a topical tetracycline. In very severe ulceration, a short course of oral steroids may be required.

Erythema multiforme

The pattern of recurrent acral erythema multiforme is rarely associated with genital lesions, whereas oral lesions are nearly always present. The vulva and vagina are more frequently affected in Stevens–Johnson syndrome, often with erosions. Vaginal stenosis and adenosis may be post-inflammatory complications.

Bullous fixed drug eruptions

These are less common (or less commonly recognized) on the vulva than on the penis, where the commonly implicated medications include paracetamol, fluconazole and tetracycline. It is now rare to see cases involving phenolphthalein, sulphonamides and barbiturates.

Chronic genital ulceration

Any chronic fixed ulcer of the genital mucosa must be considered malignant until proved otherwise. The differential diagnosis of chronic ulceration includes the diseases listed below, which are discussed fully in the relevant sections of this and other chapters.

1 **Genetic**. Epidermolysis bullosa, Hailey–Hailey disease and Darier's disease may all be responsible for chronic recurring ulceration. Exacerbations may follow friction, infection, irritants and herpes simplex infections.
2 **External trauma—**nymphohymenal tears, dermatitis artefacta and radiation damage. Nymphohymenal tears may occur with sexual intercourse but most heal spontaneously. They tend to occur around the nymphohymenal sulcus, usually in the inferior segment at the 5 and 7 o'clock positions (Fig. 71.31). Those that do not heal can be excised radially.
3 **Malignancy**. The two most common malignant ulcers of the vulva are squamous cell carcinoma and basal cell carcinoma. Melanoma may also present as an amelanotic ulcerating nodule. Langerhans' cell histiocytosis may present with vulval and vaginal ulceration.
4 **Infection**. Chronic infective ulcers occur in tuberculosis, actinomycosis and other deep mycoses. The late stages of lymphogranuloma venereum cause ulceration and scarring.
5 **Inflammatory**. LS, LP and lupus erythematosus can all cause chronic ulceration. Pyoderma gangrenosum may be mistaken for malignancy on the vulva [8]. Hidradenitis suppurativa and Crohn's disease can sometimes be difficult to distinguish, particularly if they occur together. Pilonidal sinuses have been recorded on the vulva and clitoris [9].



Fig. 71.31 Tear of the right inferior aspect of the nymphohymenal sulcus.



Fig. 71.32 Erosions in vulval mucous membrane pemphigoid.

Several of the autoimmune bullous diseases affect the vulva. Juvenile pemphigoid, mucous membrane pemphigoid (Fig. 71.32), pemphigus vulgaris and vegetans may all present with vulval and vaginal ulceration.

References

1 Daunt SO, Kotowski KE, O'Reilly AP, Richardson AT. Ulcerative vulvitis in Reiter's syndrome. *Br J Vener Dis* 1982; **58**: 405–7.

2 Sutton RL. Periadenitis mucosa necrotica recurrens. *J Cutan Dis* 1911; **29**: 65–71.
3 Lipschutz B. Über eine eigenartige Geschwüursform des weiblichen Genitales (ulcus vulvae acutum). *Arch Dermatol Syphilis (Berlin)* 1913; **114**: 363–96.
4 Brown ZA, Stenchever MA. Genital ulceration and infectious mononucleosis. *Am J Obstet Gynecol* 1977; **127**: 673–4.
5 Lampert A, Assier-Bonnet H, Chevallier B *et al.* Lipschutz's genital ulceration: a manifestation of Epstein–Barr virus primary infection. *Br J Dermatol* 1996; **135**: 663–5.
6 Portnoy J, Arontheim GA, Ghibu F *et al.* Recovery of Epstein–Barr virus from genital ulcers. *N Engl J Med* 1984; **311**: 966–8.
7 Eghbali H, Lacut JY, Hoernie B. Genital infectious mononucleosis mimicking high grade non-Hodgkin's lymphoma. *Med Mal Infect* 1989; **19**: 83–6.
8 McCalmont CS, Leshin B, White WL *et al*. Vulvar pyoderma gangrenosum. *Int J Gynaecol Obstet* 1991; **35**: 175–8.
9 Radman HM, Bhagavan BS. Pilonidal disease of the female genitals. *Am J Obstet Gynecol* 1972; **114**: 271–3.

Non-sexually transmitted infections

Bacterial infections

Staphylococci

Staphylococcus aureus is usually the causative agent in infective folliculitis, boils and abscesses of the vulva. It is often associated with an underlying problem (e.g. diabetes, immunosuppression). Pseudofolliculitis is a sterile folliculitis that may follow shaving or waxing and is caused by the newly regrowing hairs inducing an inflammatory reaction. It is a foreign body reaction and results in changes from mild inflammation to the formation of abscesses and sinuses. A staphylococcal folliculitis on the buttocks may occur secondary to the pruritus induced by intestinal infestation with pin worm.

Menstrual toxic shock syndrome is caused by *Staph. aureus* superantigenic toxins and is associated with fever, hypotension and macular erythema.

Histology. The impetiginous lesion shows subcorneal pustules filled with neutrophils and some spongiosis, with a moderate inflammatory response in the papillary dermis.

The acute folliculitis may be superficial, with a subcorneal pustule present at the follicular opening, or deep and associated with a perifollicular abscess, and destruction of the follicle wall and sebaceous gland. Chronic deep intrafollicular abscesses may have the additional features of fibrosis and foreign body giant cells.

Streptococcal infections

β-haemolytic Lancefield group A bacteria may be the cause of vulval cellulitis. The erythema and oedema may be extreme, and vesicles and bullae develop. There are usually associated systemic signs. The infection arises at sites of trauma where there is a wound and it is commonly seen following a vulvectomy with lymphadenectomy. If there is residual lymphoedema then further attacks of cellulitis are more common. Streptococcal dermatitis usually affects the anogenital area of children [1].

Synergistic bacterial gangrene

This severe and rapidly extending disease is caused by the synergistic effect of a microaerophilic streptococcus and *Staphylococcus aureus* (see Chapter 30).

Hidradenitis suppurativa

This chronic and debilitating condition is dealt with fully in Chapter 30, but mention is made here as staphylococcal and streptococcal infection have a secondary role. The primary problem is an abnormality of the follicular epithelium of the apocrine gland ducts, which starts with a spongiform infundibular folliculitis [2]. *Streptococcus milleri* is often found as a secondary pathogen [3].

Histology. This is characterized by distension and inflammation of apocrine ducts, with polymorphs in and around the ducts. The apocrine glands may become necrotic, with an infiltrate of lymphocytes, plasma cells and macrophages. Sinuses are lined by keratinized epithelium. Fibrosis and a foreign body reaction with granulomatous changes are common. Pseudoepitheliomatous hyperplasia may be seen, and at least nine cases of SCC have been reported—two of these were in females with buttock lesions [4].

Treatment is with long-term antibiotics, and in some cases oral isotretinoin may be helpful. The important differential diagnosis is Crohn's disease, but hidradenitis suppurativa and Crohn's disease may coexist [5,6].

Gram-negative bacilli

Pseudomonas aeruginosa is a common problem in patients with bladder problems but it is not a cause of vulvovaginitis. There has been a report of blue staining of napkins in infants with this infection [7].

Despite its name, *Trichomycosis* is caused by species of corynebacteria, which lead to red, yellow or black nodules on the shafts of the axillary and pubic hairs (see Chapter 30). Histological examination shows that these nodules consist of concretions of bacteria. The hair shafts may be damaged [8].

Diphtheria, caused by *Corynebacterium diphtheriae*, is rare in developed countries. Vulval infection takes the form of ulcers, often with a greyish membrane. It has been described in children [9,10] and in adults [11,12].

Mycobacterial infections

Vulval tuberculosis, caused by *Mycobacterium tuberculosis*, is uncommon in the UK. It may occur by means of haematogenous spread from foci outside the genital tract, by distal spread from the upper genital tract, or as a primary exogenous infection contracted from sputum or sexual intercourse. Vulval tuberculosis has been reported in a renal transplant patient [13], and three cases were described in a series of 26 patients with genital tuberculosis [14]. Genitourinary tuberculous infection is more common in HIV-positive subjects. In a primary infection the initial lesion may be inconspicuous, the main feature being a caseating lymphadenopathy. In other cases the lesions are masses or nodules that may ulcerate and lead to lymphoedema [15]. Bartholin's gland may be involved [16].

Leprosy (see Chapter 32)

The female genital tract may be involved in infection by *Mycobacterium leprae* [17], but vulval lesions are rare [18]. Pubic hair may be lost [19].

Higher bacterial infection

Higher bacteria is the name assigned to those bacteria that, like filamentous fungi, are capable of forming true branches. They include the genera *Streptomyces*, *Actinomyces* and *Nocardia.*

Actinomycosis

The Gram-positive acid-fast organisms responsible for actinomycosis are predominantly *Actinomyces israelii* and *Actinomyces gerencseriae*. They may colonize intrauterine devices and are usually asymptomatic, but invasion of the genital tract can occur [20,21]. Genital infection usually arises from bowel disease [22]. Lesions of the vulva alone have been reported [23].

Mycoplasmas

Mycoplasma hominis and *Ureaplasma urealyticum* are found in the vagina and rarely cause disease. There are rare reports of *M. hominis* being isolated from cases of Bartholin's abscess [24,25].

Abscesses of Bartholin's gland may be caused by pyococcal organisms, gonococcus and *Chlamydia trachomatis* [26]. In one study, only 21 of 109 cases were caused by staphylococci, whereas 50 were caused by *Escherichia coli* and 46 by *Streptococcus faecalis* [27]. The abscess results from distal blockage of the duct. The patient presents with fever, malaise and a tender swelling arising posterior to the origin of the labium minus. Episodes of bartholinitis may be mild and recurrent until fibrosis supervenes.

References

1 Krol AL. Perianal streptococcal dermatitis. *Pediatr Dermatol* 1990; **7**: 97–100.
2 Boer J, Weltevreden EF. Hidradenitis suppurativa or acne inversa: a clinicopathological study of early lesions. *Br J Dermatol* 1996; **135**: 721–5.
3 Highet AS, Warren RE, Staughton RCD *et al. Streptococcus milleri* causing treatable infection in perineal hidradenitis suppurativa. *Br J Dermatol* 1980; **103**: 375–82.
4 Sparks MK, Kuhlmann DS, Pietro A *et al.* Hypercalcaemia in association with cutaneous squamous cell carcinoma: occurrence as a late complication of hidradenitis suppurativa. *Arch Dermatol* 1985; **12**: 243–6.
5 Ostlere LS, Langtry JAA, Mortimer PS, Staughton RCD. Hidradenitis suppurativa in Crohn's syndrome. *Br J Dermatol* 1991; **125**: 384–6.
6 Burrows NP, Russell-Jones R. Crohn's disease in association with hidradenitis suppurativa. *Br J Dermatol* 1992; **126**: 523–9.
7 Thearle MJ, Wise R, Allen JT. Blue nappies [Letter]. *Lancet* 1973; **ii**: 499–500.
8 Orfanos CE, Schloesser E, Mahrie G. Hair destroying growth of *Corynebacterium tenuis* in the so-called trichomycosis axillaris. *Arch Dermatol* 1971; **103**: 632–6.
9 Barabe P, Delpe P, Vedy J *et al.* Primary vulvovaginal diphtheria (apropos of a case in Chad). *Med Trop* 1972; **32**: 637–9.
10 Charles V, Charles SX. A case of vulvovaginal diphtheria in a girl of 7 years. *Indian J Pediatr* 1978; **15**: 257–8.
11 Parks J. Diphtheric vaginitis in the adult. *Am J Obstet Gynecol* 1941; **41**: 714–8.
12 Machnicki S. Diphtheria of the vulva and vagina. *Z Haut Geschlechtskr* 1953; **86**: 386.
13 Tham SN, Choong HL. Primary tuberculous chancre in a renal transplant patient. *J Am Acad Dermatol* 1992; **26**: 342–4.
14 Moore D. Genito-peritoneal tuberculosis: a review of 26 cases. *S Afr Med J* 1954; **28**: 666–70.
15 Millar JW, Holt S, Gilmour HM, Robertson DHH. Vulval tuberculosis. *Tubercle* 1979; **60**: 173–6.
16 Schaefer G. Diagnosis and treatment of female genital tuberculosis. *Clin Obstet Gynecol* 1959; **2**: 530–5.
17 Bonar BE, Rabson AS. Gynaecological aspects of leprosy. *Obstet Gynecol* 1957; **9**: 33–8.
18 Grabstold H, Swan L. Genitourinary lesions in leprosy with special reference to atrophy of the testis. *JAMA* 1952; **149**: 1287–91.
19 Klostermann GF. *Handbuch der Speziellen Pathologischen Anatomie und Histologie Weibliche Geschelentsorgave*. Berlin: Springer-Verlag, 1972.
20 Purdie DW, Cartie MJ, McLeod TIF. Tubo-ovarian actinomycosis and the intrauterine contraceptive device. *BMJ* 1977; **ii**: 1392.
21 Lomax CW, Harbert GM, Thornton WN. Actinomycosis of the genital tract. *Obstet Gynecol* 1976; **48**: 341–6.
22 Wagman H. Genital actinomycosis. *Proc R Soc Med* 1975; **68**: 228–30.
23 Daniel C, Mavrodin A. L'actinomycose genitale de la femme. *Rev Francaise Gynecol Obstet* 1954; **29**: 1–11.
24 Dienes L, Edsall G. Observations on the L-organism of Kleinberger. *Proc Soc Exp Biol Med* 1937; **36**: 740–5.
25 Davies JA, Rees E, Jobson D *et al.* Isolation of *Chlamydia trachomatis* from Bartholin's ducts. *Br J Vener Dis* 1978; **54**: 409–13.
26 Mayer HGK. Pathogénie et traitement des pretendus abcés et kystes de la glande de Bartholin. *J Gynecol Obstet Biol Reprod* 1972; **1**: 71–6.
27 Lee Y-H, Rankin JS, Alpert S *et al.* Microbiological investigation of Bartholin's gland abscesses and cysts. *Am J Obstet Gynecol* 1977; **129**: 150–3.

Fungal infections

Candidal vulvovaginitis

Candida and *Torulopsis* are both yeasts that can infect the vulva and vagina. *Torulopsis* accounts for very few infections, whereas *Candida albicans* is the most frequently isolated.

Candida albicans is dimorphic, with both yeast and mycelial forms. It is a non-pathogenic commensal in the intestinal tract in 30% of the normal population. Infection in women is usually a vulvovaginitis. Changes in host factors are probably responsible for transition to pathogenicity, and are generally not directly associated with sexual contact. Factors related to cell-mediated immunity are doubtless important, but as yet are ill-understood. Pregnancy, diabetes, possibly oral antibiotics, high-dose oestrogen oral contraceptive pills and immunosuppression may all be predisposing factors. The primary infection arises in the vagina, causing inflammation and a heavy white curdy discharge, which then leads to a secondary vulvitis with well-demarcated sheets of erythema on the outer aspects of the vulva, sometimes extending on occasions into the genitocrural folds and perianally. There may be a scaly or vesiculopustular edge. Beyond this edge lie grouped or isolated superficial small pustules, which rupture rapidly, leaving a slightly scaly periphery. In all cases of candidal vulvovaginitis, but particularly in the middle-aged patient, late-onset diabetes should be considered, and appropriate tests carried out.

Diagnosis is confirmed by direct microscopy and culture.

Treatment of vulvovaginal candidiasis requires vaginal pessaries or creams and/or oral imidazoles.

In some cases of vulval eczema and psoriasis, *Candida* is cultured from skin swabs, but the candidal overgrowth is a secondary problem arising on a background of an inflamed epithelium. Treating the dermatosis alone with a topical steroid will usually resolve the problem, without the addition of anticandidal agents.

Dermatophyte fungi

Dermatophyte infections of the vulval skin are uncommon in cooler climates. The sites affected are usually the inguinal folds and perianal area. The causative agents are *Trichophyton rubrum* or *Epidermophyton floccosum*. The vulval epithelium in the adult seems to be relatively immune to dermatophyte infections. The lesions are erythematous and scaly, with a spreading raised

circinate edge. Folliculitis is also seen, particularly in the perianal area. Tinea incognito may also occur perianally following the injudicious use of a topical steroid in the presence of an unrecognized dermatophyte infection. The diagnosis is usually made by direct microscopy and culture of skin scrapings, and treatment is usually oral terbinafine or griseofulvin because the skin is hair-bearing.

Miscellaneous fungal infections

Pityriasis versicolor classically occurs on the trunk, but in severe widespread infection there may be vulval involvement [1,2].

The black and white forms of piedra (trichosporosis) are caused by *Piedraia hortai* and *Trichosporon beigelii*, respectively, the latter acting synergistically with a corynebacterium. The hair-bearing parts of the vulva can be affected with black and white nodules along the hair shafts [3]. The diagnosis is made by microscopy and culture.

Vulval phycomycosis has been described [4]. Subcutaneous infections occur in children and young adults. Histologically, the epidermis is unremarkable but subcutaneously there are deep granulomatous masses containing hyphae.

There is one case report of chromomycosis (chromoblastomycosis) affecting the vulva [5].

Cryptococcus neoformans can induce painless ulceration of the vulva in the immunosuppressed patient [6].

References

1 Bumgarner FE, Burke RC. Pityriaisis versicolor: atypical clinical and mycological variants. *Arch Dermatol* 1949; **59**: 192–4.

2 Jelliffe DB, Jacobson FW. The clinical picture of tinea versicolor in negro infants. *J Trop Med Hygiene* 1954; **57**: 290–2.

3 Kalter DC, Tschen JA, Cernoch PK. Genital white piedra: epidemiology, microbiology and therapy. *J Am Acad Dermatol* 1986; **14**: 982–93.

4 Scott RA, Gallis HA, Livengood CH. Phycomycosis of the vulva. *Am J Obstet Gynecol* 1985; **153**: 675–6.

5 Kakoti LM, Dey NC. Chronic blastomycosis in India. *J Indian Med Assoc* 1957; **28**: 351.

6 Blocher KS, Weeks JA, Noble RC. Cutaneous cryptococcal infection presenting as vulval lesion. *Genitourin Med* 1987; **63**: 341–3.

Infections with protozoa

Infection with *Trichomonas vaginalis* causes a frothy, malodorous, greyish-green, watery discharge, and a bright red vaginal mucosa studded with petechiae. The vaginal discharge may cause a secondary vulvitis, with erythema and swelling of the vestibule and labia minora. Colonization of the urethra and paraurethral glands often occurs. The diagnosis is made by microscopic examination of wet preparations and culture.

Treatment is with metronidazole 400 mg twice daily for 5 days or 2 g in a single dose.

The flagellate protozoan *Leishmania tropica* causes cutaneous, mucocutaneous and visceral forms of leishmaniasis. The vulva is mainly affected by the cutaneous form, which is endemic in areas of the eastern Mediterranean, Asia Minor and India; and to a lesser extent by the mucocutaneous form, found in Central and South America. An example of sexual transmission from post-kala-azar dermal leishmaniasis has been reported [1]. Transmission of infection is usually by sandflies. The lesions are nodular or ulcerative.

Entamoeba histolytica is found worldwide and intestinal amoebiasis may be transmitted from the bowel to other areas, including the genital tract, although such involvement is rare [2]. It appears as warty or ulcerative masses of the vulva, perineum and cervix. Live amoebae may be recovered from scrapings, or the organism seen as a small eosinophilic body in an inflammatory histological reaction.

Vulval schistosomiasis is usually caused by *Schistosoma haematobium*. The lesions are chronic, scarring and granulomatous, and may ulcerate and calcify [3–5]. Histologically, there is inflammation surrounding the organisms and their remains, with granuloma formation and many eosinophils. Ova may be found in the vagina, urine and faeces.

References

1 Symmers WS. Leishmaniasis acquired by contagion: a case of marital infection in Britain. *Lancet* 1960; **i**: 127–32.

2 Majmudar B, Chaikaen MC, Lee KU. Amoebiasis of the clitoris mimicking carcinoma. *JAMA* 1976; **236**: 1145–6.

3 McKee PH, Wright E, Hutt MSR. Vulval schistosomiasis. *Clin Exp Dermatol* 1983; **8**: 189–94.

4 Friedberg D, Berry AV, Schneider J. Schistosomiasis of the female genital tract. *S Afr Med J* 1991; **80**: 2–15.

5 Goldsmith PC, Leslie TA, Sams V *et al.* Lesions of schistosomiasis mimicking warts on the vulva. *BMJ* 1993; **307**: 556–7.

Viruses

Three groups of viruses are important causes of infection in the genital area: the poxviruses, papillomaviruses and herpesviruses. Other viruses seldom give rise to distinctive clinical pictures, although vulval lesions may occur as part of a generalized viral infection.

Genital HPV infection and herpes simplex are discussed later in the section on sexually transmitted infections (see p. 71.70).

The most common poxvirus is mollusum contagiosum virus, two types of which have been identified. There is no relationship between virus type and anatomical distribution of lesions [1]. Vulval lesions in childhood are common and usually acquired innocently, but they are more likely to be acquired sexually in adults. Lesions are often found on the mons pubis and labia majora, and if inflamed they may mimic folliculitis. The clinical diagnosis is straightforward when there are multiple pearly lesions with an umbilicated centre, but solitary large lesions can cause diagnostic problems. It is the solitary giant lesion that may miss immediate diagnosis until it is biopsied. Lesions of molluscum contagiosum can be profuse and large in immunosuppressed women, especially in those with AIDS. The condition is more fully described in Chapter 35.

Other poxvirus infections of the vulva are rare, but there are isolated reports of orf [2] and cowpox [3].

Herpes simplex (see below)

- **Varicella-zoster virus.** This may also affect the vulva if the third sacral dermatome is involved. It may be accompanied by bowel and bladder dysfunction [4].
- **Epstein–Barr virus.** This has been found rarely in genital ulcers at the time of infectious mononucleosis [5–7]. EBV may also be shed from the cervix [8] but there is no link with vulval malignancy [9].

- **Cytomegalovirus (CMV).** CMV inclusions were seen in a biopsy, and a positive culture for CMV was obtained in an infant with congenital HIV disease who presented with pustular and ulcerative lesions on the perineum [10].

References

1 Porter CD, Blake NW, Archard LC *et al.* Molluscum contagiosum: virus types in genital and non-genital lesions. *Br J Dermatol* 1989; **121**: 37–41.
2 James JRE. Orf in man. *BMJ* 1968; **iii**: 804–6.
3 Claudy AL, Gaudin OG, Granovillet R. Pox virus infection in Darier's disease. *Clin Exp Dermatol* 1982; **7**: 260–5.
4 Fugelso PD, Newman SB, Beamer JE. Herpes zoster of the anogenital area affecting urination and defaecation. *Br J Dermatol* 1973; **89**: 285–8.
5 Portnoy J, Ahronheim GA, Ghibu F *et al.* Recovery of Epstein–Barr virus from genital ulcers. *N Engl J Med* 1984; **311**: 966–8.
6 McKenna G, Edwards S, Cleland H. Genital ulceration secondary to Epstein–Barr virus infection. *Genitourin Med* 1994; **70**: 356–67.
7 Lampert A, Assier-Bonnet H, Chevalier B *et al.* Lipschutz's genital ulceration: a manifestation of Epstein–Barr virus primary infection. *Br J Dermatol* 1996; **135**: 663–5.
8 Naher H, Gissman L, Freese UK *et al.* Subclinical Epstein–Barr virus infection of both the male and female genital tracts: indication of sexual transmission. *J Invest Dermatol* 1992; **98**: 791–3.
9 Cheung ANY, Khoo VS, Kwong KY *et al.* Epstein–Barr virus in carcinoma of the vulva. *J Clin Pathol* 1993; **46**: 849–51.
10 Thiboutot DM, Beckford A, Mart CA *et al.* Cytomegalovirus diaper dermatitis. *Arch Dermatol* 1991; **127**: 396–8.

Malakoplakia of the vulva [1–4]

Malakoplakia (meaning 'soft plaque') is a granulomatous response to infection. It is not usually caused by one specific agent but the organisms involved include *Escherichia coli*, *Pseudomonas* and *Staphylococcus aureus*. Malakoplakia most often affects the urinary or gastrointestinal tract but cutaneous lesions may occur on the vagina, vulva and perineum. Involvement of Bartholin's gland has been described [5]. The lesions include persistent plaques, ulcers, nodules and sinuses. There is often underlying immunosuppression, the aetiology of which may include malignancy, dermatomyositis [6], lupus erythematosus, rheumatoid arthritis and organ transplantation [7].

Histopathology. There are confluent sheets of histiocytes with eosinophilic granular cytoplasm and small eccentric nuclei. Round, sometimes laminated structures are found with these cells and are known as Michaelis–Gutmann bodies. The histiocytic infiltrate may be mixed with neutrophils, lymphocytes and plasma cells, with associated granulation tissue. Electron microscopy of malakoplakia shows that the histiocytes contain numerous phagolysosomes within which there may be occasional intact and partly digested bacteria.

References

1 McClure J. Malakoplakia. *J Pathol* 1983; **140**: 275–330.
2 Remond B, Dompmartin A, Moreau A *et al.* Cutaneous malakoplakia. *Int J Dermatol* 1994; **33**: 538–42.
3 Sarkell B, Dannenberg M, Blaylock WK, Patterson JW. Cutaneous malakoplakia. *J Am Acad Dermatol* 1994; **30**: 834–6.
4 Lowitt MH, Kariniemi A-L, Niemi KM, Kao GF. Cutaneous malakoplakia: a report of two cases and review of the literature. *J Am Acad Dermatol* 1996; **34**: 325–32.
5 Paquin ML, Davis JR, Weiner S. Malakoplakia of Bartholin's gland. *Arch Pathol Lab Med* 1986; **110**: 757–8.
6 Singh M, Kaur S, Vijpayer BK, Banerjee AK. Cutaneous malakoplakia with dermatomyositis. *Int J Dermatol* 1987; **26**: 190–1.
7 Sian CS, McCabe RE, Lattes CG. Malakoplakia of skin and subcutaneous tissue in a renal transplant recipient. *Arch Dermatol* 1981; **117**: 654–5.

Dermatological aspects of sexually transmitted disease

A brief outline of the main sexually transmitted diseases that can affect the vulval skin is given below. Fuller descriptions of the individual diseases are given elsewhere (see Chapters 30 and 33–35).

Herpes simplex virus

Once this sexually transmitted DNA virus is acquired it lies dormant in dorsal root ganglia and can give rise to recurrent symptomatic lesions. It exists in two types: I and II. Type I usually affects non-genital sites and type II is responsible for 50–80% of genital infections. Ninety-five per cent of infections are acquired sexually and the rest are cases of autoinoculation or non-sexual contact. The lesions are typically painful vesicles or ulcers, which are often multiple in primary infection but are fewer and usually localized to one side with recurrences. There may be prodromal symptoms of tingling or tender enlarged inguinal nodes. Paraesthesiae may occur, affecting S2–4, which may lead to urinary retention. Pain and oedema may also lead to retention, particularly in primary infections. It is important to obtain a definite diagnosis with a positive culture of HSV, and it is necessary to perform the test as soon as the blisters arise, as the virus is harder to culture from older lesions. However, a negative test does not exclude an infection with HSV.

The treatment is either oral aciclovir 200 mg five times daily for 5 days, valaciclovir 500 mg twice daily for 5 days or famciclovir 250 mg three times daily for 5 days.

Suppressant therapy is sometimes required for patients with frequent recurrences (six or more in a year).

Human papillomavirus infection

HPV is a small DNA virus, and is discussed in more detail in Chapter 33. Those that most commonly infect the vulval skin are HPV 6, 11, 16 and 18. The warty lesions are known as condylomata acuminata. Extensive vegetating masses can cover the vulva and perianal area, particularly in diabetes, pregnancy and immunocompromised patients. Patients with genital warts should be screened for other sexually transmitted diseases. Secondary syphilis may also present with extensive papulosquamous lesions and has to be considered in the differential diagnosis.

Types 16 and 18 are linked with cervical and anogenital intraepithelial neoplasia and SCC.

The histology of genital warts is characterized by the koilocyte, a vacuolated squamous cell with a basophilic and pyknotic nucleus in the upper part of the epidermis; it is important not to confuse it with the heavily glycogenated clear cells of vestibular epithelium. Other histological features are elongated dermal papillae, acanthosis, a prominent granular layer often containing koilocytes, and a stratum corneum of variable thickness.

Treatment. Podophyllotoxin is the recommended initial treatment. It is applied twice daily for 3 consecutive days each week

for 4 weeks. This treatment is contraindicated in pregnancy because of the theoretical risk of teratogenicity. Diathermy, hyfrecation, topical trichloroacetic acid, cryotherapy and carbon dioxide laser have been used with variable success. These treatments are successful in patients where the lesions are few or filiform in morphology.

The new immune response modulating cream, imiquimod, is now used for resistant cases or patients with extensive lesions. This has to be used with care as it also induces an inflammatory response in patients who have a background dermatitis. It should not be used in patients who have benign vulval aphthous ulcers.

In pregnancy, only cryotherapy or destructive techniques with cautery or hyfrecation can be used safely.

Prevention. Prophylactic vaccination prior to exposure is now available for HPV types 6, 11, 16 and 18 [1]. A programme for the routine vaccination of girls aged 12–13 years against HPV 16 and 18 has been started in the UK.

Gonorrhoea

The urethra, cervix and rectum may be infected by *Neisseria gonorrhoea* and spread occurs to the endometrium and fallopian tubes. Vulval involvement is rare in adults, and infection is sited in the paraurethral and Bartholin's glands, resulting in painful abscess formation. In children, the infection is usually a result of sexual abuse, and an acute vulvitis may develop [2].

Syphilis

The causative organism is *Treponema pallidum* and vulval lesions may occur in both early and late syphilis. The primary chancre is an ulcerative lesion and is usually accompanied by unilateral or bilateral lymphadenopathy. In secondary syphilis, condylomata lata, flat-topped warty papules, affect the vulva, as may also mucous patches, which are greyish white moist-looking lesions. Gummas, which are a manifestation of tertiary syphilis, are extremely rare on the vulva, and clinically they occur as either single or multiple swellings or nodules.

Bullous, papular, papulosquamous lesions and mucous patches occur on the vulva in early congenital syphilis and condylomata lata may develop later.

The diagnosis of syphilis is made by dark ground microscopy, immunofluorescence of scrapings or serology.

Histologically, the findings are very variable but, typically, early lesions show inflammation with perivascular plasma cells and lymphocytes together with an endarteritis. There is marked epithelial hyperplasia in lesions of condylomata lata, with a prominent perivascular lymphocytic and plasma cell infiltrate.

Chancroid [3]

This sexually transmitted disease, caused by *Haemophilus ducreyi*, is rare in the UK [2] as it is normally found in tropical and semitropical countries, although the incidence is falling in Africa [3]. Single or multiple small tender ulcers appear on the labia majora, perineum and perianal area, and may also affect the vagina and cervix. The inguinal lymph glands are involved in half of cases and the adenitis is unilateral in most. Buboes develop, which are fluctuant, and rupture leaving extensive ulceration. Co-infections with *Treponema pallidum* or HSV are frequent.

Diagnosis may be confirmed by culture of scrapings from the ulcer base or aspirated pus. Microscopy of scrapings or pus will show Gram-negative coccobacilli. PCR may also be used. The histological features include epithelial hyperplasia adjacent to the ulceration, with three relatively distinct zones at the base of the ulcer. The superficial zone consists of a thin band of neutrophils, fibrin and necrotic debris; the middle zone of oedema with thin-walled, dilated and vertically orientated blood vessels; and the deep zone of a dense perivascular infiltrate of lymphocytes and plasma cells. A Giemsa or Brown–Brenn stain may reveal organisms in the superficial zone staining blue or red, respectively.

Treatment. Azithromycin, ceftriaxone, ciprofloxacin or erythromycin can be used. The recent guidelines issued by the US Centers for Disease Control and Prevention (CDC) should be consulted (http://www.cdc.gov/std). Special considerations should be given to patients with HIV infection.

Donovanosis [4]

Synonyms
- Granuloma venereum
- Granuloma inguinale

The causative organism is *Calymmatobacterium granulomatis*, formerly known as *Donovania granulomatis*. The disease is sexually transmitted and found in New Guinea, India, South Africa and Brazil. Papules or nodules break down to form ulcers with a rolled edge. Large areas are involved, and granulomatous masses may involve any part of the genitocrural area, although the lymph nodes themselves are not affected. The vagina and cervix may be involved. Scarring and lymphoedema may ensue.

Histopathology shows epithelial hyperplasia adjacent to the ulcer, sometimes with spongiosis and intraepithelial neutrophilic abscesses, and a dense dermal or submucosal infiltrate with neutrophilic abscesses surrounded by plasma cells, histiocytes and lymphocytes. The organisms occasionally are visible with silver stains, which show intracytoplasmic inclusions (Donovan bodies), seen as black oval or rod-shaped structures in the cytoplasm of histiocytes. The organisms are more reliably demonstrated on smear preparations than tissue sections.

Chlamydia (lymphogranuloma venereum)

Chlamydia trachomatis is a Gram-negative intracellular bacterium that is an obligatory parasite. The serovars L1–3 cause lymphogranuloma venereum, which occurs in tropical and subtropical countries. The incubation period varies from a few days to a few weeks. A small papule develops on the vulva, usually at the fourchette, heals quickly and is followed weeks later by striking lymphadenopathy. The nodes may form a suppurative mass that heals with scarring, leading to lymphoedema, which may be gross. Generalized chronic infection leads to abscess and fistula formation, and finally genital and anal strictures and elephantiasis [5].

Rectal lesions present as a proctocolitis with subsequent stricture formation.

The histology of the vulval ulcers is non-specific, but the affected nodes show epithelioid cells and giant cells, and later stellate abscesses develop that are surrounded by epithelioid cells, granulomatous tissue and plasma cells. Fibrosis and necrosis are seen in chronic lesions.

References

1 Adams M, Jasani B, Fiander A. Human papilloma virus (HPV) prophylactic vaccination: challenges for public health and implications for screening. *Vaccine* 2007; **25**: 3007–13.
2 Barlow D, Phillips I. Gonorrhoea in women: diagnostic, clinical and laboratory aspects. *Lancet* 1978; **i**: 761–3.
3 Lewis DA. Chancroid: clinical manifestations, diagnosis, and management. *Sex Transm Infect* 2003; **79**: 68–71.
4 O'Farrell N. Donavanosis. *Sex Transm Infect* 2002; **78**: 452–7.
5 Douglas CP. Lymphogranuloma venereum and granuloma inguinale of the vulva. *Am J Obstet Gynecol* 1962; **69**: 871–80.

Benign tumours [1,2]

Most of the tumours that arise on the anogenital skin are similar to those that occur on the skin elsewhere. Fibromas arise from deeper connective tissue structures, particularly those surrounding the introitus and perineal body. They usually occur on the labia majora, are often pedunculated or pendulous, and can attain a very large size. Fibroepitheliomatous polyps (skin tags) are usually solitary and appear as soft wrinkled polypoidal nodules. There is a fibrovascular connective tissue core covered by squamous epithelium, which may be atrophic or, more commonly, mildly acanthotic and hyperkeratotic. Cellular atypia is occasionally seen in the stromal cells. Lipomas develop from the fatty tissue of the labia majora, but there have been reports of localization to the clitoris [3], as has also been reported with haemangiomas [3,4].

Two types of lymphangioma may occur on the vulva: lymphangioma circumscriptum, which are localized thin-walled vesicles [5], and cavernous lymphangioma, which arise in childhood and present as a soft compressible mass, which, although usually located in the labia minora, can involve the whole of the vulva [6]. Acquired lymphangiectasia is discussed on p. 71.81.

Melanocytic naevi include junctional, intradermal and compound types, which generally share the same clinical and histological features as naevi at other sites of the body, with the exception that in premenopausal women vulval naevi sometimes have atypical histological features [7]. The atypia may extend into the adnexal structures, but the overall symmetry of the lesion, with cellular maturation in the deeper dermis, should help to distinguish it from a truly malignant lesion. Sometimes, differentiation from melanoma can be difficult and evaluation by an experienced dermatopathologist may be necessary.

Epidermal cysts of the vulva may develop from epithelial implants following surgical trauma, from epidermal inclusions occurring at fusion sites during embryogenesis, or from obstructed sebaceous gland ducts that have undergone squamous metaplasia. They may be single or multiple, and occur most commonly in the labia majora. Steatocystoma may present as a solitary cyst in the vulval region [8]. Calcified nodules have been recorded [9].

Syringomas

These are considered to be adenomas of the intraepidermal eccrine sweat gland ducts. They do not require treatment as they are usually asymptomatic, although there may be pruritus [10]. Vulval syringomas are multiple, bilateral and symmetrical, although a solitary lesion may occur. One case was reported that had the typical histological features of a syringoma mixed with pilosebaceous elements [11].

Papillary hidradenoma

This sweat gland adenoma with apocrine differentiation occurs almost exclusively in the anogenital region of middle-aged white women. It has been associated with anogenital glands [12]. It is a firm asymptomatic papule or nodule, which can occasionally be painful, and occurs most commonly on the labia majora, interlabial sulcus, lateral surfaces of the labia minora or perineal region [13]. Although usually single, there are occasionally multiple lesions. Curiously, when they are multiple all the lesions tend to develop on one side of the vulva. In most patients, the covering epidermis remains intact, but in a proportion the elevated epithelium may become ulcerated [14].

Malignant change within a papillary hidradenoma has been reported, producing apocrine carcinoma [15] and adenosquamous carcinoma [16].

Fox–Fordyce disease

In this condition, described in detail in Chapter 44, the apocrine ducts become blocked, with retention of sweat. Itchy skin-coloured papules appear on the mons pubis, labia majora, axillae and on the breast. They develop around the time of puberty and there are menstrual exacerbations. There is some improvement in pregnancy and after the menopause.

References

1 Fox H, Buckley CD. Neoplastic disease of the vulva and associated structures. In: Fox H, Wells M, eds. *Haines and Taylor Obstetrical and Gynaecological Pathology*, 5th edn. Edinburgh: Churchill Livingstone, 2003: 95–145.
2 Nucci MR, Fletcher CDM. Vulvovaginal soft tissue tumours: update and review. *Histopathology* 2000; **36**: 97–100.
3 Haddad HM, Jones WH. Clitoral enlargement simulating pseudohermaphroditism. *Am J Dis Child* 1960; **99**: 282–7.
4 Kaufmann-Friedman K. Hemangioma of clitoris: confused with adreno-genital syndrome—a case report. *Plast Reconstr Surg* 1978; **62**: 452–4.
5 Abu-Hamad A, Provencher D, Ganjei P *et al*. Lymphangioma circumscriptum of the vulva: case report and review of the literature. *Obstet Gynecol* 1989; **73**: 496–9.
6 Brown JV, Stenchever MA. Cavernous lymphangioma of the vulva. *Obstet Gynecol* 1989; **73**: 877–9.
7 Christensen WN, Friedman KJ, Woodruff JD, Hood AF. Histological characteristics of vulval naevocellular naevi. *J Cutan Pathol* 1987; **14**: 87–91.
8 Brownstein MH. Steatocystoma simplex. *Arch Dermatol* 1982; **118**: 409–11.
9 Jameleddine FN, Salmon SM, Shbaklo Z *et al*. Vulvar calcinosis, the counterpart of idiopathic scrotal calcinosis. *Cutis* 1988; **41**: 273–5.
10 Carter J, Elliott P. Syringoma: an unusual cause of pruritus vulvae. *Aust NZ J Obstet Gynaecol* 1990; **30**: 382–3.
11 Guindi SF, Silverberg BK, Evans TL. Multifocal mixed adenoid tumors of the vulva. *Int J Gynaecol Obstet* 1974; **12**: 138–40.
12 van der Putte SCJ. Anogenital 'sweat' glands: histology and pathology of a gland that may mimic mammary glands. *Am J Dermatopathol* 1991; **13**: 557–65.
13 Basta A, Madej JG. Hydradenoma of the vulva: incidence and clinical observations. *Eur J Gynaecol Oncol* 1990; **11**: 185–9.

14 Veraldi S, Schianchi-Veraldi R, Marini D. Hidradenoma papilliferum of the vulva: report of a case characterized by unusual clinical behaviour. *J Dermatol Surg Oncol* 1990; **16**: 674–6.
15 Pelosi G, Martignoni, G, Bonetti F. Intraductal carcinoma of mammary-type apocrine epithelium arising within a papillary hydradenoma of the vulva: report of a case and review of the literature. *Arch Pathol Lab Med* 1991; **115**: 1249–54.
16 Bannatyne P, Elliott P, Russell P. Vulvar adenosquamous carcinoma arising in a hidradenoma papilliferum with rapidly fatal outcome: a case report. *Gynecol Oncol* 1989; **35**: 395–8.

Mucinous cysts

Mucinous cysts of the vulva are not uncommon. They are usually found in the vestibule where they develop secondary to obstruction of the duct of one of the many minor vestibular mucus-secreting glands. The cysts are of urogenital sinus origin and not, as was once thought, of Müllerian origin [1,2].

References

1 Robboy SJ, Ross JS, Prat J *et al*. Urogenital sinus origin of mucinous and ciliated cysts of the vulva. *Obstet Gynecol* 1978; **51**: 347–51.
2 Oi RH, Munn R. Mucous cysts of the vulvar vestibule. *Hum Pathol* 1982; **13**: 584–6.

Bartholin's duct tumours

These are very rare and there is debate as to whether they are true neoplasms or better regarded as examples of hyperplasia or hamartoma [1,2].

References

1 Koenig C, Tavassoli FA. Nodular hyperplasia adenoma, and adenomyoma of Bartholin's gland. *Int J Dermatol* 1998; **17**: 289–94.
2 Argenta PA, Bell K, Reynolds C, Weinstein R. Bartholin's gland hyperplasia in a postmenopausal woman. *Obstet Gynecol* 1997; **90**: 695–7.

Neurofibroma and neurofibromatosis

Vulval neurofibromas may occur either as solitary lesions with no other features of neurofibromatosis, or as part of generalized neurofibromatosis. In one series, 18% had vulval lesions [1]. Vulval neurofibromas have also been described as one component of a localized neurofibromatosis of the female genitourinary tract [2,3]. Some cases have led to confusion by mimicking an intersex problem [4–7].

References

1 Schreiber MM. Vulval von Recklinghausen's disease. *Arch Dermatol* 1963; **88**: 320–1.
2 Gersell DJ, Fulling KH. Localized neurofibromatosis of the female genitourinary tract. *Am J Surg Pathol* 1989; **13**: 873–8.
3 Lewis FM, Lewis-Jones MS, Toon PG *et al*. Neurofibromatosis of the vulva. *Br J Dermatol* 1992; **127**: 540–1.
4 Kenny FM, Fetterman GH, Preeyasombat C. Neurofibromata simulating a penis and labioscrotal gonads in a girl with von Recklinghausen's disease. *Pediatrics* 1966; **37**: 956–9.
5 Labardini MM, Kallet HA, Cerny JC. Urogenital neurofibromatosis simulating an intersex problem. *J Urol* 1968; **98**: 627–32.
6 Schepel SJ, Tolhurst DE. Neurofibromata of clitoris and labium majus simulating a penis and testicle. *Br J Plast Surg* 1981; **34**: 221–3.
7 Ravikumar VR, Lakshmanan DA. Solitary neurofibroma of the clitoris masquerading as an intersex. *J Pediatr Surg* 1983; **18**: 617.

Glomus tumour

There are rare reports of this tumour on the labia minora giving rise to dyspareunia [1,2].

References

1 Kohorn EI, Merino MJ, Goldenhersh M. Vulvar pain and dyspareunia due to a glomus tumor. *Obstet Gynecol* 1986; **67**: 41–42S.
2 Katz VL, Askin FB, Bosch BD. Glomus tumor of the vulva: a case report. *Obstet Gynecol* 1986; **67**: 43–45S.

Leiomyoma

Vulval leiomyomas are uncommon [1,2], and there is no association with uterine leiomyomas. It is unclear whether these tumours originate from the smooth muscle of the vulval erectile tissue, from the muscular elements of the round ligament, or from the myoepithelial cells of Bartholin's gland.

Vulval leiomyomas occur during the reproductive years and usually present as well-circumscribed, painless, non-tender nodules or swellings in the labia. Lesions may enlarge in pregnancy. A clitoral leiomyoma can cause a mistaken diagnosis of an intersex disorder. A clitoral leiomyoma associated with a leiomyoma of the oesophagus has been reported [3].

References

1 Neri A, Peled Y, Braslavski D. Vulvar leiomyoma. *Acta Obstet Gynecol Scand* 1993; **72**: 221–2.
2 Nielsen GP, Rosenberg AE, Koerner FC *et al*. Smooth muscle tumours of the vulva: a clinicopathological study of 25 cases and a review of the literature. *Am J Surg Pathol* 1996; **20**: 779–93.
3 Stenchever MA, McDivett RW, Fisher JA. Leiomyoma of the clitoris. *J Reprod Med* 1973; **2**: 75–6.

Other benign tumours

Rarer tumours include granular cell myoblastoma [1,2], which presents as flesh-coloured, occasionally pedunculated or ulcerated lesions. Verruciform xanthomas have a predilection for the oral mucosa and the genital skin. They are rare on the vulva [3,4]. Clinically, they present as solitary plaques or warty lesions and vary in colour from yellow to grey or pink. There is acanthosis, papillomatosis and parakeratosis, and the presence of foamy macrophages in the papillary dermis and tips of the elongated rete ridges distinguishes this entity from a viral wart. Nodular fasciitis presents as a painless mass and has rarely been reported on the vulva [5].

Urethral caruncle and urethral prolapse, which are common, can sometimes be mistaken for neoplasms. A urethral caruncle occurs in postmenopausal women as a red fleshy lesion around the urethral meatus and is a chronically inflamed eversion of the urethral mucosa. It may measure from a few millimetres to a few centimetres in diameter and is usually asymptomatic; it may cause dysuria or bleeding if ulcerated. Histologically, it is essentially the same as a pyogenic granuloma, showing a highly vascular connective tissue with a heavy inflammatory infiltrate of lymphocytes and plasma cells. Enmeshed in this inflamed stroma are varying quantities of glandular structures or solid islands of urethral epithelium.

Prolapse of the urethra may occur at any age. Histologically, there is marked oedema of the underlying connective tissue, and the overlying urethral mucosa may be focally ulcerated. The underlying stroma shows marked vascular distension and engorgement, often with thrombosis. The epithelial inclusions typically seen in a urethral caruncle are not present.

References

1 Gifford RRM, Birch HW. Granular cell myoblastoma of multicentric origin involving the vulva: a case report. *Am J Obstet Gynecol* 1973; **117**: 184–7.
2 Sadler WP, Docherty MB. Malignant myoblastoma vulvae. *Am J Obstet Gynecol* 1951; **61**: 1047–55.
3 Santa Cruz DJ, Martin SA. Verruciform xanthoma of the vulva. *Am J Clin Pathol* 1979; **71**: 224–8.
4 De Rosa G, Barra E. Verruciform xanthoma of the vulva: case report. *Genitourin Med* 1989; **65**: 252–4.
5 O'Connell JX, Young RH, Nielsen GP *et al*. Nodular fasciitis of the vulva: a study of six cases and a review of the literature. *Int J Gynecol Pathol* 1997; **16**: 117–23.

Precancerous dermatoses

Vulval intraepithelial neoplasia (VIN)

This term was introduced by the International Society for the Study of Vulvovaginal Diseases (ISSVD) in 1986 to replace the previous terms—dystrophy with atypia, Bowen's disease, bowenoid papulosis, erythroplasia of Queyrat and squamous carcinoma *in situ* [1,2]. It is defined as loss of the normal orientation and architecture of the epithelium with cellular atypia. It was also graded into VIN 1–3, according to the percentage of the epithelium involved. The term 'VIN differentiated', was used for cases where there was severe atypia that was confined to the basal area but was often coincident with an SCC. The 1986 classification also included EMPD and melanoma *in situ*.

The three-tier grading of VIN is misleading as there is interobserver variation in the grading [3] and in clinical practice many cases of VIN 1 with basal atypia are not truly premalignant but reparative (e.g. LP), or proliferative as in a benign condyloma.

The VIN types that do carry a malignant potential are either those that have atypia involving two-thirds to full thickness of the epithelium (undifferentiated VIN [VIN 2 and VIN 3]), or severe atypia confined to the basal layers with fairly normal differentiation of the upper layers (differentiated VIN). In addition to the basal changes, the rete ridges may be long and forked with keratin pearls. This change on a background of LS/LP represents either very early invasive disease or heralds its imminent onset.

Therefore, in 2004, the ISSVD proposed replacing the three-tier grading system with two types of VIN, undifferentiated and differentiated. This classification eliminates the term VIN 1 and replaces the terms VIN 2 and 3 with 'undifferentiated VIN'. 'Differentiated VIN' remains as the term reserved for the severe atypia confined to the basal layers, most often seen on a background of a chronic scarring dermatosis. It was also proposed that vulval EMPD and melanoma *in situ* should not be included in the VIN classification [4,5].

Undifferentiated vulval intraepithelial neoplasia

Synonyms
- Bowen's disease
- Bowenoid papulosis
- Carcinoma *in situ*
- Carcinoma simplex

There is two-thirds to full thickness loss of cellular stratification throughout the epidermis, with large hyperchromatic cells, dyskeratosis, multinucleated cells and numerous typical and atypical mitoses. Originally, two distinct histological types of VIN were described: bowenoid, characterized by individual cell keratinization and abnormal cellular differentiation, and basaloid, with atypical parabasal cells extending throughout the full thickness of the epithelium. However, both types can sometimes be found in the same histological section so it is no longer considered helpful to distinguish the two.



Fig. 71.33 Vulval intraepithelial neoplasia. Erythematous patches with one warty plaque inferiorly on the inner aspect of the right labium minus.

Multifocal anogenital disease is strongly associated with the oncogenic papillomaviruses, particularly HPV 16 and 18 [6,7] and almost exclusively occurs in smokers. The condition is caused by a failure of the host to mount an immune response to the HPV. Patients who are immunocompromised have a higher incidence of this problem, but the majority of young women with this problem do not have an identifiable immunodeficiency. In addition to being multifocal, VIN may be associated with multicentric disease, with lesions of intraepithelial neoplasia involving the cervix, vagina and perianal skin. Up to two-thirds of patients with VIN have a current or past history of CIN [8].

Clinically, the lesions of intraepithelial neoplasia can be solitary or multiple. The morphology of the lesions is also very diverse, with lesions that resemble viral warts, plaques that may be shiny and smooth, skin-coloured, red or white, or others that are warty and pigmented and resemble seborrhoeic keratoses. Less commonly, the lesions may be large and papillomatous, particularly perianally, where they may be polypoid. The main symptom is pruritus, which can be severe and troublesome (Figs 71.33–71.35).

Vaginal involvement is uncommon. Initially, it was felt that BP could be distinguished histologically from Bowen's disease but time has proved this not to be the case.

The risk of progression to invasive disease is estimated as 10% or less in multifocal disease [9], but this risk is likely to be higher in immunocompromised patients, perianal disease and in the older woman with a solitary plaque [10].



Fig. 71.34 Vulval intraepithelial neoplasia. Solitary warty plaque.

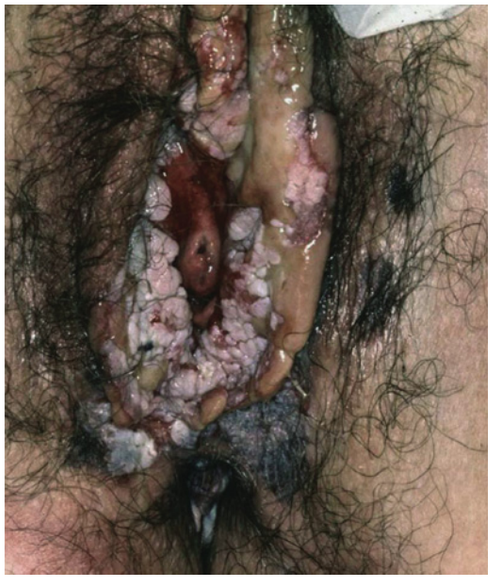


Fig. 71.35 Vulval intraepithelial neoplasia. Pigmented seborrhoeic keratosis-like lesions.

Differentiated VIN

This form of VIN is reportedly rare, but perhaps it is underdiagnosed due to the subtle histological changes that occur. The atypia is confined to the basal layers, and this type of VIN is seen most commonly on a background of lichen sclerosus where there is already a microinvasive carcinoma, or just prior to the development of invasive disease. There may or may not be epithelial hyperplasia as well. To date there has been no strong association of this type of VIN with the known oncogenic HPV viruses.

Pagetoid VIN (pagetoid Bowen's disease, pagetoid squamous cell carcinoma in situ)

A rare histological variant of VIN which resembles extramammary Paget's disease is known as pagetoid VIN or pagetoid Bowen's disease. Pagetoid Bowen's disease has been reported extragenitally and genitally in males. There is one report of vulval involvement [11]. Unexpectedly, the abnormal cells in pagetoid VIN are CK7-positive, like true Paget's cells of EMPD, but mucin stains and cam5.2 are negative [11].

Treatment. This is tailored to the individual patient's needs. In the case of a solitary lesion of differentiated or undifferentiated VIN that is amenable to simple excision, this is the treatment of choice. In the woman with extensive undifferentiated disease, surgery would be mutilating physically and distressing psychologically, and does not guarantee a cure as the risk of recurrence is significant [12]. Such patients require regular and long-term follow-up, with biopsies of suspicious areas. Thick or polypoid lesions should be excised, as early invasive changes are difficult to detect in these areas [13]. Cryotherapy is not effective, but 5-fluorouracil can be used successfully for lesions of the labia minora, vestibule and clitoral area. It is not effective on the hair-bearing parts of the vulva, probably because of the deep adnexal structures, which can all be involved. Laser vaporization has a high recurrence rate, particularly if the hair-bearing parts of the vulva are involved, and there is the additional danger that early invasive disease may be missed and therefore inappropriately treated. It is also extremely painful postoperatively.

Imiquimod has proved very effective in the treatment of multifocal undifferentiated VIN in younger patients and recurrent disease after surgical excision [14]. However, it is currently unlicensed for the treatment of VIN.

As VIN is a multicentric problem, the other sites that need to be monitored are the cervix, vagina and perianal area. If there is perianal disease, anoscopy should be performed to exclude involvement of the anal canal.

The development of HPV vaccines, which became licensed in Europe for preventative management in 2006, will hopefully have an impact on HPV-related VIN [15].

References

1 Wilkinson EJ, Kneale B, Lynch P. Report of the ISSVD Terminology Committee. *J Reprod Med* 1986; **31**: 973–4.

2 Hart WR. Vulvar intraepithelial neoplasia: historical aspects and current status. *Int J Gynecol Pathol* 2001; **20**: 16–30.

3 Preti M, Mezzetti M, Robertson C, Sideri M. Interobserver variation in histopathological diagnosis and grading of vulvar intraepithelial neoplasia: results of a European collaborative study. *Br J Obstet Gynaecol* 2000; **107**: 594–9.

4 Sideri M, Jones RW, Wilkinson EJ *et al*. Squamous vulvar intraepithelial neoplasia: 2004 modified terminology, ISSVD Vulvar Oncology Subcommittee. *J Reprod Med* 2005; **50**: 807–10.

5 Scurry J, Wilkinson EJ. Review of the terminology of vulvar squamous cell carcinoma. *J Lower Genital Tract Disease* 2006; **10**: 161–9.

6 Hillemanns P, Wang X. Integration of HPV-16 and HPV-18 DNA in vulvar intraepithelial neoplasia. *Gynecol Oncol* 2006; **100**: 276–82.

7 van Beurden M, ten Kate FW, Tjong-A-Hung SP *et al*. Papillomavirus DNA in multicentric vulvar intraepithelial neoplasia. *Int J Gynecol Pathol* 1998; **17**: 12–6.

8 Obalek S, Jablonska S, Beauderron Walcsak L, Orth G. Bowenoid papulosis of the male and female genitalia: risk of cervical neoplasia. *J Am Acad Dermatol* 1986; **14**: 433–44.

9 van Seters M, van Beurden M, de Craen AJM. Is the assumed natural history of vulvar intraepithelial neoplasia III based on enough evidence? A systematic review of 3322 published patients. *Gynecol Oncol* 2005; **97**: 645–51.

10 Belilovsky C de, Leibowitch M. Maladie de Bowen et papulose bowenoide: donnees cliniques virologiques et evolutives comparatives. *Contracept Fertil Sex* 1993; **21**: 231–6.
11 Raju, RR, Goldblum JR, Hart WR. Pagetoid squamous cell carcinoma *in situ* (pagetoid Bowen's disease) of the external genitalia. *Int J Gynecological Pathol* 2003; **22**: 127–35.
12 Shafi MI, Luesley DM, Byrne P *et al*. Vulval intraepithelial neoplasia: management and outcome. *Br J Obstet Gynaecol* 1989; **96**: 1339–44.
13 Chafe W, Richards A, Morgan L, Wilkinson E. Unrecognized invasive carcinoma in vulval intraepithelial neoplasia (VIN). *Gynecol Oncol* 1988; **31**: 154–62
14 Mathiesen O, Buus SK, Cramers M. Topical imiquimod can reverse vulvar intraepithelial neoplasia: a randomised, double-blinded study. *Gynecol Oncol* 2007; **107**: 219–22.
15 Bonnez W. Human papillomavirus vaccine—recent results and future developments. *Curr Opin Pharmacol* 2007; **7**: 470–7.

Squamous cell carcinoma

The most common vulval malignancy by far is squamous carcinoma, followed by basal cell carcinoma, adenocarcinoma, melanoma and verrucous carcinoma [1].

Aetiologically, there appear to be two types of vulval squamous cell carcinoma [2–5]. The first and largest group occurs in elderly women on a background of a chronic dermatosis such as LS or LP. The second type, which accounts for approximately 40% of cases, occurs in younger women and is associated with intraepithelial neoplasia associated with oncogenic-type HPV infection. A link with HPV has not yet been established with the first group [6].

In the 1990s, the staging of vulval cancer was replaced by a combined clinical and surgical staging [7]. One of the reasons for this change was to remove the term 'microinvasive carcinoma of the vulva', as at that time its definition was misleading. In this new classification, stage I tumours are less than 2 cm diameter and are further subdivided into Ia and Ib. Ia are lesions with less than 1 mm depth of invasion. There are some difficulties as to how this measurement should be made. The most recent recommendation is to measure from the dermal–epidermal junction of the nearest dermal papilla to the deepest point of invasion [8]. Lymph node dissection is mandatory for all lesions greater than 1 mm but can be avoided in those with stage Ia. There are three histological types of SCC: keratinizing, basaloid and warty carcinomas.

Keratinizing tumours are those seen in the older women, which are not HPV-related, and the basaloid and warty tumours are those found in younger women with HPV-related VIN.

There is also an adenoid variant of SCC with acantholysis in the centres of some of the infiltrating nests, producing cystic spaces lined by cubocolumnar nests. These pseudocysts do not contain mucin, which differentiates them from adenosquamous cell carcinoma.

There have also been reports of vulval cancer in patients with Fanconi's anaemia [9,10].

Treatment. Surgical excision is tailored to the individual, and is determined by the size and site of the tumour.

The overall 5-year survival is approximately 75%, which rises to 90% or greater in those with no nodal metastases. The main reason for failure of treatment is the inability to control lymphatic and distant metastases, lymphatic spread being the most important factor. The vulval lymphatics drain to the inguinal and femoral nodes and from there to the pelvic nodes. Central lesions (those placed near the clitoris, urethra, vagina, fourchette and perianal area) have a bilateral lymphatic drainage, and it is important in these cases that the inguinofemoral nodes on both sides are excised. Radiotherapy is used as an adjuvant in patients with positive nodes and in those with inoperable tumours. It is also sometimes used as a primary treatment in tumours of the anus and urethra, to reduce their size before surgery and to try to preserve sphincter function.

References

1 Fox H, Buckley CH. Neoplastic disease of the vulva and associated structures. In: Fox H, Wells M, eds. *Haines and Taylor Obstetrical and Gynaecological Pathology*, 5th edn. London: Churchill Livingstone, 2003: 95–145.
2 Anderson WA, Franquemont DW, Williams J *et al*. Vulval squamous cell carcinoma and papillomavirus: two separate entities? *Am J Obstet Gynecol* 1991; **165**: 329–36.
3 Crum C. Carcinoma of the vulva: epidemiology and pathogenesis. *Obstet Gynecol* 1992; **79**: 448–58.
4 Hording U, Junge J, Daugaard S *et al*. Vulval squamous cell carcinoma and papilloma viruses: indications for two different aetiologies. *Gynecol Oncol* 1994; **52**: 241–6.
5 Trimble CL, Hildesheim A, Brinton LA *et al*. Heterogeneous aetiology of squamous cell carcinoma of the vulva. *Obstet Gynecol* 1996; **87**: 59–64.
6 Toki T, Kurma RJ, Park JS *et al*. Probable non-papillomavirus etiology of squamous cell carcinoma of the vulva in older women: a clinicopathologic study using *in situ* hybridization and polymerase chain reaction. *Int J Gynecol Pathol* 1991; **10**: 107–25.
7 Shepherd JH. Staging announcement FIGO staging of gynecologic cancers: cervical and vulva. *Int J Gynecol Cancer* 1995; **5**: 319.
8 Wilkinson EJ. Superficially invasive carcinoma of the vulva. In: Wilkinson EJ, ed. *Pathology of the Vulva and Vagina*. New York: Churchill Livingstone, 1987: 103–17.
9 Kennedy AW, Hart WR. Multiple squamous cell carcinomas in Fanconi's anaemia. *Cancer* 1982; **50**: 811–4.
10 Wilkinson EJ, Morgan LS, Friedrich EG. Association of Fanconi's anaemia and squamous cell carcinoma of the lower female genital tract with condylomata acuminata: a report of two cases. *J Reprod Med* 1984; **29**: 447–53.

Other malignant neoplasms

Verrucous carcinoma

Synonym
- Giant condyloma of Buschke–Löwenstein

This tumour occurs in older women, and many arise on a background of LS [1]. Clinically, the lesions appear as a warty plaque or cauliflower-like tumour, which can ulcerate and become extremely large (Fig. 71.36). There is not a strong association with HPV [2].

The histological changes include epidermal acanthosis, with large bulbous rete ridges which compress and push down the underlying stroma. There is very little cellular atypia and the few, if any, mitoses are confined to the basal layers. The upper keratinocytes are often paler and there is a loss of the granular layer. Lymph node and distant metastases occur rarely.

Treatment is wide local excision. Radiotherapy is not used as it is associated with a worse prognosis, probably because it can induce anaplastic transformation [3]. Oral retinoids may also be helpful [4].



Fig. 71.36 Verrucous carcinoma on a background of lichen sclerosus.



Fig. 71.37 Basal cell carcinoma: lower left labium majus.

References

1 Japaze H, Dinh TV, Woodruff JD. Verrucous carcinoma of the vulva. *Obstet Gynecol* 1982; **60**: 462–6.

2 Nascimento AF, Granter SR, Cviko A *et al*. Vulvar acanthosis with altered differentiation: a precursor to verrucous carcinoma? *Am J Surg Pathol* 2004; **28**: 638–43.

3 Kraus FT, Perez-Mesa C. Verrucous carcinoma: clinical and pathologic study of 105 cases including oral cavity, larynx and genitalia. *Cancer* 1966; **19**: 26–38.

4 Mehta RK, Rytina E, Sterling JC. Treatment of verrucous carcinoma of vulva with acitretin. *Br J Dermatol* 2000; **142**: 1195–8.

Basal cell carcinoma

Vulval basal cell carcinomas are not uncommon, and present as an eroded plaque, which may be pigmented. Less commonly, the tumour may form a nodule or ulcer. They occur most frequently on the labia majora (Fig. 71.37) [1].

Histologically, the appearances are identical to BCCs seen elsewhere. Inadequate excision accounts for a high recurrence rate and metastases to regional lymph nodes [2]. Mohs surgery is often recommended to ensure adequate local excision [3,4]. Patients with vulval basal cell carcinomas frequently develop basal cell carcinomas at other sites [5].

References

1 Feakins RM, Lowe DG. Basal cell carcinoma of the vulva: a clinicopathologic study of 45 cases. *Int J Gynecol Pathol* 1997; **16**: 319–24.

2 Mizushima J, Ohara K. Basal cell carcinoma of the vulva with lymph node metastasis: report of a case and review of 20 Japanese cases. *J Dermatol* 1995; **22**: 36–42.

3 Mohs FE. Carcinoma of the vulva. In: *Chemosurgery, Microscopically Controlled Surgery of Skin Cancer*. Springfield: Charles C Thomas, 1978: 215–9.

4 Brown MD, Zachary CB, Grekin RC, Swanson N. Genital tumors: their management by micrographic surgery. *J Am Acad Dermatol* 1998; **18**: 115–22.

5 Benedet JL, Miller DM, Ehlen TG, Bertrand MA. Basal cell carcinoma of the vulva: clinical features and treatment results in 28 patients. *Obstet Gynecol* 1997; **90**: 765–8.

Adenocarcinoma

Primary adenocarcinoma unrelated to underlying glandular adnexae is exceedingly rare. The lesion usually presents as a painless subcutaneous nodule which, as it expands, becomes fixed and painful. The tumour can invade deeply into fat, muscle or bone and may be associated with a Bartholin's gland abscess. Adenocarcinoma may be associated with EMPD.

Many of the mucinous carcinomas that arise are possibly of cloacal origin [1].

There is one report of a mucinous carcinoma with neuroendocrine differentiation [2].

References

1 Willen R, Bekassy D, Carlen B *et al*. Cloacogenic adenocarcinoma of the vulva. *Gynecol Oncol* 1999; **74**: 298–301.

2 Graf AH, Su HC, Tubbs RR *et al*. Primary neuroendocrine differentiated mucinous adenocarcinoma of the vulva: case report and review of the literature. *Anticancer Res* 1998; **18**: 2041–5.

Melanoma

Vulval melanomas account for approximately 5% of vulval malignancy. Any of the variants of melanoma may occur on the vulva, and the clinical and histological features are the same as for melanomas elsewhere (Fig. 71.38). However, in one cohort of 219 patients, 27% of lesions were amelanotic [1,2]. Melanomas at this site carry the same prognosis according to the Clarke level of invasion, the Breslow thickness and the presence or absence of a vertical growth phase. Lesions occur most commonly on the inner aspects of the vulva on the labia minora and periclitoral area [3]. They may be mistakenly diagnosed as EMPD histologically.



Fig. 71.38 Melanoma of the vulva. (Courtesy of Dr F.A. Ive, Durham, UK.)



Fig. 71.39 Extramammary Paget's disease.

References

1 Ragnarsson-Olding BK, Kanter-Lewensohn LR, Lagerlöf B *et al.* Malignant melanoma of the vulva in a nationwide, 25-year study of 219 Swedish females: clinical observations and pathological features. *Cancer* 1999; **86**: 1273–84.

2 Ragnarsson-Olding BK, Nilsson BR, Kanter-Lewensohn LR *et al.* Malignant melanoma of the vulva in a nationwide, 25-year study of 219 Swedish females: predictors of survival. *Cancer* 1999; **86**: 1285–93.

3 Wechter ME, Gruber SB, Haefner HK. Vulvar melanoma: a report of 20 cases and a review of the literature. *J Am Acad Dermatol* 2004; **50**: 554–62.

Vulval extramammary Paget's disease

EMPD is discussed in Chapter 53. EMPD is a rare dermatosis, and is distinct from Paget's disease of the nipple, which is always associated with underlying breast neoplasia. The vulva is the most common site for EMPD, which is subdivided into primary and secondary disease. Primary, or cutaneous EMPD, is an intraepithelial adenocarcinoma arising in the epidermis or the epithelia of the local skin appendages. Secondary EMPD is epidermal involvement from a non-cutaneous internal neoplasm, either by direct extension or metastasis. The two most common tumours associated with secondary vulval EMPD are anorectal adenocarcinoma and urothelial carcinoma of the bladder or urethra. Other associated tumours reported include cervix, endometrium and ovary [1,2].

The differentiation between primary and secondary disease is not always straightforward clinically and sometimes relies on immunohistological investigations [3,4].

Additional changes to the vulval EMPD classification have been proposed, based on aetiology [5]. The primary and secondary categories are retained, but each is divided into three types. The primary category consists of primary intraepithelial disease, primary with invasion, and EMPD as a manifestation of an underlying primary adenocarcinoma of a vulval skin appendage or subcutaneous vulval gland. The secondary category has three groups according to the tumour from which it arises: EMPD secondary to anorectal adenocarcinoma, EMPD secondary to urothelial carcinoma and EMPD secondary to an adenocarcinoma or related tumour at other sites.

It is important to distinguish primary from secondary EMPD as management depends on the correct diagnosis.

Clinical features. Clinically, the lesion is typically a moist, red, oozing plaque, which looks like impetiginized eczema or psoriasis. The associated symptoms include pruritus and burning (Fig. 71.39).

Histopathology. There is frequently epidermal hyperplasia. The epidermis is infiltrated with pale-staining Paget's cells. The Paget's cells are PAS-positive and diastase-resistant, and stain with Alcian blue and markers for the simple keratins. In the lower epidermis, the tumour cells may compress the basal cells.

Treatment. In primary EMPD, excision of visible disease is often recommended for treatment and to exclude underlying appendageal adenocarcinoma. Sometimes in the very elderly, with extensive disease or recurrence after vulvectomy, this is not always an option that the patient wishes to accept. Patients should be regularly monitored, and topical steroids can be used if there is troublesome pruritus. Topical 5-fluorouracil, bleomycin and imiquimod have been used, as well as oral retinoids, with some success. The recurrence rates are high after carbon dioxide laser and radiotherapy.

In secondary disease, the treatment is directed predominantly at the associated carcinoma.

References

1 Parker L-P, Parker JR, Bodurka-Bevers D *et al.* Paget's disease of the vulva: pathology, pattern of involvement and prognosis. *Gynecol Oncol* 2000; **77**: 183–9.
2 Kodama S, Kaneko T, Saito M *et al.* A clinicopathologic study of 30 patients with Paget's disease of the vulva. *Gynecol Oncol* 1997; **56**: 63–70.
3 Brown HM, Wilkinson EJ. Uroplakin-III to distinguish primary vulvar Paget disease from Paget disease secondary to urothelial carcinoma. *Hum Pathol* 2002; **33**: 545–8.
4 Goldblum JR, Hart WR. Vulvar Paget's disease: a clinicopathologic and immunohistochemical study of 19 cases. *Am J Surg Pathol* 1997; **21**: 1178–87.
5 Wilkinson EJ, Brown HM. Vulvar Paget disease of urothelial origin: a report of three cases and a proposed classification of vulval Paget disease. *Hum Pathol* 2002; **33**: 549–54.

Langerhans' cell histiocytosis

The anogenital skin may be one of the sites involved in disseminated Langerhans' cell histiocytosis (LCH), but lesions may occur at this site only. Perianal ulceration is the most common presentation in adults and children [1,2], and genital involvement is more common in women [3,4]. The lesions may be plaques, nodules, erosions, ulcers or pustules. The Letterer–Siwe form consists of a seborrhoeic dermatitis-like eruption on the intertriginous zones and scalp. Some of the lesions may be purpuric.

References

1 Rivera-Luna R, Martinez-Guerra G, Altamirano-Awarez E *et al.* Langerhans' cell histiocytosis: clinical experience with 124 patients. *Pediatr Dermatol* 1988; **5**: 145–50.
2 Stein SL, Paller AS, Haut PR, Mancini AJ. Langerhans' cell histiocytosis presenting in the neonatal period: a retrospective case series. *Arch Pediatr Adolesc Med* 2001; **155**: 778–83.
3 Axiotis CA, Merino MJ, Duray PH. Langerhans' cell histiocytosis of the female genital tract. *Cancer* 1991; **67**: 1650–60.
4 Hoang MP, Owen SA, Haisley-Royster C *et al.* Papular eruption of the scalp accompanied by axillary and vulvar ulcerations. *Arch Dermatol* 2001; **137**: 1241–6.

Lymphomas

Non-Hodgkin's lymphoma of the vulva is more frequently reported [1,2] than Hodgkin's lymphoma [3]. Non-Hodgkin's lymphoma has also been reported post-transplantation [4] and in association with HIV infection [5].

References

1 Vang R, Medeiros J, Fuller GN *et al.* Non-Hodgkin's lymphoma involving the gynaecologic tract: a review of 88 cases. *Adv Anat Pathol* 2001; **8**: 200–17.
2 Vang R, Medeiros J, Malpica A *et al.* Non-Hodgkin's lymphoma involving the vulva. *Int J Gynecol Pathol* 2000; **19**: 236–42.
3 Hahn GA. Gynecologic considerations in malignant lymphoma. *Am J Obstet Gynecol* 1958; **75**: 673–83.
4 Kaplan MA, Jacobson MO, Ferry JA, Harris NL. T-cell lymphoma of the vulva in a renal allograft recipient with associated hemophagocytosis. *Am J Surg Pathol* 1993; **17**: 842–9.
5 Kaplan EG, Chadburn A, Caputo TA. HIV-related primary non-Hodgkin's lymphoma of the vulva. *Gynecol Oncol* 1996; **61**: 131–8.

Miscellaneous tumours

There are a few reports of vulval dermatofibrosarcoma protuberans on the labia majora [1], slow-growing liposarcoma [2], epithelioid sarcoma [3], Merkel cell carcinoma [4] and Bartholin's gland carcinoma [5].

References

1 Moodley M, Moodley J. Dermatofibrosarcoma protuberans of the vulva: case report and review of the literature. *Gynecol Oncol* 2000; **78**: 74–6.
2 Nucci MR, Fletcher CDM. Liposarcoma (atypical lipomatous tumors) of the vulva: a clinicopathologic study of 6 cases. *Int J Gynecol Pathol* 1998; **17**: 17–23.
3 Ulbright TM, Brokaw SA, Stehman FB *et al.* Epithelioid sarcoma of vulva. *Cancer* 1983; **52**: 1462–9.
4 Gil-Moreno A, Garcia-Jiminez A, Gonzalea-Bosquet J *et al.* Merkel cell tumour of the vulva. *Gynecol Oncol* 1997; **64**: 526–32.
5 Felix JC, Cote RJ, Kramer EE *et al.* Carcinoma of Bartholin's gland: histogenesis and the aetiological role of human papilloma virus. *Am J Pathol* 1993; **142**: 925–33.

Metastatic tumours

These are uncommon and may be from malignancies of the cervix, endometrium, vagina, ovary, urethra, kidney, breast and lung, in descending order of frequency [1].

Reference

1 Dehner IP. Metastatic and secondary tumours of the vulva. *Obstet Gynecol* 1973; **42**: 47–57.

Miscellaneous

Pigmentary disorders

Hypopigmentation

As at other sites, this can be naevoid, a post-inflammatory problem or vitiligo.

Hyperpigmentation

The increased pigmentation may be caused by haemosiderin, which results in a reddish-brown discoloration, and it is the result of extravasation of red blood cells. It is seen in capillaritis, urethral caruncle, lichen sclerosus, Zoon's vulvitis and chronic vulval purpura. However, increased pigmentation is more commonly related to melanin. There is considerable variation in the distribution and amount of melanocytes and melanin in the normal vulva, depending on site, age, ethnicity and hormonal status.

Post-inflammatory pigmentation may follow any inflammatory dermatosis, particularly if there has been a disruption of the dermal–epidermal junction and in darker skins. It is a common sequela of LP and sometimes LS, and of a fixed drug eruption. Trichomycosis and chromidrosis may cause some discoloration.

Vulval melanosis. Intense macular hyperpigmentation of vulval skin can be difficult to categorize, and a biopsy is essential for an accurate diagnosis and to exclude malignant melanoma (Fig. 71.40a) [1]. If the lesions are widespread and accompanied by oral pigmentation, they may be considered as examples of Laugier–Hunziker syndrome [2,3]. The term vulval melanosis is used for those cases where there is extensive macular pigmentation affecting the vulval skin, with the histological changes of basal hypermelanosis and a slight increase in the number of melanocytes. There may also be some pigmentary incontinence, but there is no abnormal junctional melanocytic proliferation (Fig. 71.40b) [4–8]. There have been other suggested terms: idiopathic lenticular

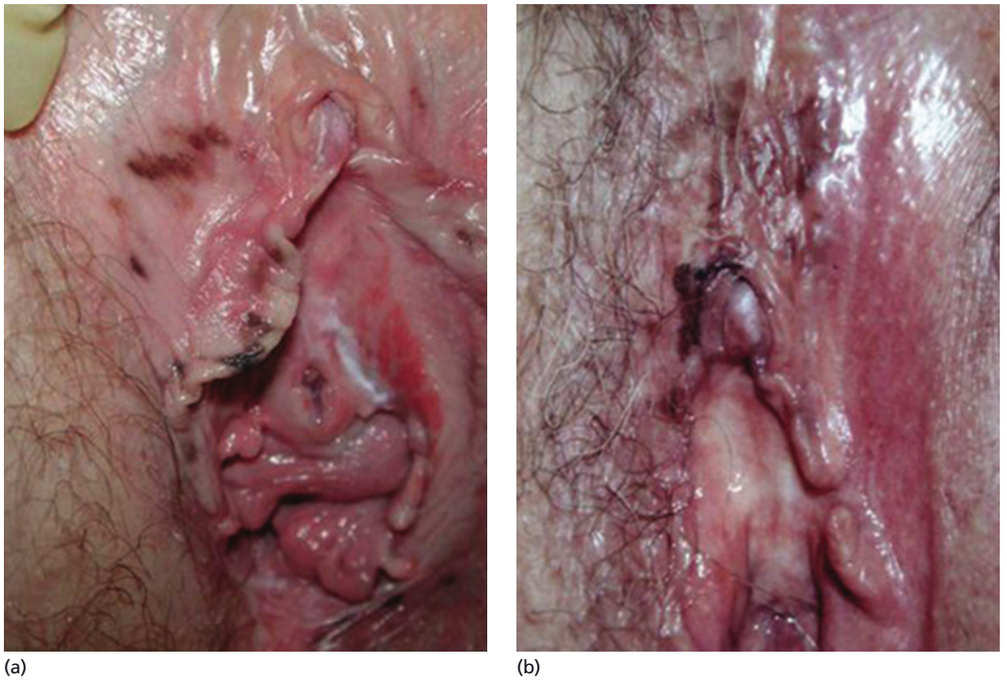

(a) (b)

Fig. 71.40 (a) *In situ* melanoma. (b) Vulval melanosis.

mucocutaneous pigmentation [9] and genital lentiginosis, particularly if there is melanocytic hyperplasia [10].

The accepted view is that vulval melanosis is a benign condition, but there are no long-term follow-up studies reported. Therefore, most clinicians advise continuing observation, using photographs or diagrams as an aid.

Lentigines. Vulval lentigines may be sporadic or part of a syndrome (e.g. LAMB syndrome) [11,12]. There is an increase in the number of basal melanocytes, with increased melanin in the epidermis and stratum corneum. Pigment-laden macrophages are found in the papillary dermis, and the rete ridges are elongated.

Acanthosis nigricans. This condition is usually associated with insulin resistance and rarely with malignancy. Initially, the appearance is of a dark and velvety thickening of the skin in the genitocrual folds and upper inner thighs, which later becomes warty. Skin tags may also occur.

Dowling–Degos disease. This rare inherited disorder presents in about the fourth decade with freckle-like lesions in flexural areas. It may be confined to the vulva [13].

References

1 Carli P, De Giorgi V, Nardini P *et al.* Vulvar melanosis mimicking melanoma: a cause for concern in patients and clinicians. *G Ital Dermatol Venereol* 1994; **129**: 143–6.

2 Laugier P, Hunziker N, Olmos L. Pigmentation melanique lenticulaire essentielle de la muqueuse jugale et des levres. *Ann Dermatol Vénéréol* 1977; **104**: 181–4.

3 Dupré A, Viraben R. Laugier's disease. *Dermatologica* 1990; **181**: 183–6.

4 Rudolph RI. Vulvar melanosis. *J Am Acad Dermatol* 1990; **23**: 982–4.

5 Sisson-Torre EQ, Ackerman AB. Melanosis of the vulva: a clinical simulator of malignant melanoma. *Am J Dermatopathol* 1985; **7**: 51–60.

6 Kanj LF, Rubeiz NG, Mrouett AM *et al.* Vulvar melanosis and lentiginosis: a case report. *J Am Acad Dermatol* 1992; **27**: 777–8.

7 Jackson R. Melanosis of the vulva. *J Dermatol Surg Oncol* 1984; **10**: 119–21.

8 Estrada R, Kaufman R. Benign vulvar melanosis. *J Reprod Med* 1993; **38**: 5–8.

9 Gerbig AW, Hunziker T. Idiopathic lenticular mucocutaneous pigmentation or Laugier–Hunziker syndrome with atypical features. *Arch Dermatol* 1996; **32**: 844–5.

10 Barnhill RL, Albert LS, Shama SK *et al.* Genital lentiginosis: a clinical and histopathologic study. *J Am Acad Dermatol* 1990; **22**: 453–60.

11 Rhodes AR, Silverman RA, Harrist TJ *et al.* Mucocutaneous lentigines, cardiomucocutaneous myxomas and multiple blue naevi: the LAMB syndrome. *J Am Acad Dermatol* 1984; **10**: 72–82.

12 Reed OM, Mellette JR, Fitzpatrick JE. Cutaneous lentiginosis with atrial myxomas. *J Am Acad Dermatol* 1986; **15**: 398–402.

13 O'Goshi K, Terui T, Tagami H. Dowling-Degos disease affecting the vulva. *Acta Derm Venereol* 2001; **81**: 148.

Necrolytic migratory erythema

This rare dermatosis occurs on the anogenital skin and lower abdomen and is characterized by extensive eroded erythema with crusting and a desquamative, serpiginous edge which spreads out centrifugally. It was initially regarded as a paraneoplastic syndrome always associated with an underlying pancreatic glucagonoma, but a similar clinical picture is seen with zinc and protein deficiency and there are now a number of reports of necrolytic migratory erythema occurring with liver diseases in the absence of a glucagonoma [1].

The histology shows a loss of the granular layer and upper epidermal necrosis.

Reference

1 Mullans EA, Cohen PR. Iatrogenic necrolytic migratory erythema: a case report and review of nonglucagonoma-associated necrolytic migratory erythema. *J Am Acad Dermatol* 1998; **38**: 866–73.

Vulval oedema, lymphoedema and lymphangiectasia

Oedema, hereditary angio-oedema [1] and dermographism [2] may all involve the vulva. Vulval oedema may be the only manifestation of Crohn's disease [3].

Lymphoedema occurs when there is impairment of the lymph drainage and it is a frequent complication following surgery and lymphadenectomy for vulval carcinoma. Lymphangiectasia is acquired dilatation of the skin lymphatics secondary to obstruction of the lymphatic vessels. It is most frequently reported following treatment of cervical carcinoma with surgery and/or radiotherapy [4–6]. Lymphangiectasia may be very profuse in Crohn's disease, and carbon dioxide laser treatment can be used in patients with troublesome lymphorrhoea [7]. Repeated episodes of cellulitis may also result in lymphangiectasia, but there may be an underlying abnormality of the lymphatics that predisposed the patient to the cellulitis initially. Lymphangiectasia may be mistaken clinically for viral warts [8].

Endometriosis

Endometriosis occasionally occurs on the vulva or in the vagina as a direct implantation. The condition may follow a previous surgical procedure [9,10], and occur in episiotomy scars after delivery [11,12]. It presents as firm bluish nodules, which become tender or bleed during menstruation. Clear cell adenocarcinoma has arisen in vulval endometriosis [13].

Genital papular acantholytic dyskeratosis

This was first described in 1984 [14], and is characterized by the presence of multiple papules or, less frequently, a single papule or plaque-like lesion on genital skin [15–18]. Cases with disseminated lesions have been described [19]. The histological changes are similar to those seen in Darier's disease or Hailey–Hailey disease, but there is no family history or evidence of these diseases at other sites. It is considered a distinct entity, although it may represent a forme fruste of Hailey–Hailey or Darier's disease. A case with positive immunofluoresence has been reported [20].

References

1 Warin RP, Champion RH. *Urticaria*. London: Saunders, 1974: 114.
2 Lambiris A, Greaves MW. Dyspareunia and vulvodynia are probably common manifestations of factitious urticaria. *Br J Dermatol* 1997; **136**: 140–1.
3 Martin J, Holdstock G. Isolated vulval oedema as a feature of Crohn's disease. *J Obstet Gynecol* 1997; **17**: 92–3.
4 LaPolla J, Foucar E, Leshin B *et al*. Vulvar lymphangioma circumscriptum: a rare complication of therapy for squamous cell carcinoma of the cervix. *Gynecol Oncol* 1985; **22**: 363–6.
5 Handfield-Jones SE, Prendeville WL, Norman S. Vulval lymphangiectasia. *Genitourin Med* 1989; **65**: 335–7.
6 Fisher I, Orkin M. Acquired lymphangioma (lymphangiectasia). *Arch Dermatol* 1970; **102**: 230–4.
7 Landthaler M, Hohenleutner U, Braun-Falco O. Acquired lymphangioma of the vulva: palliative treatment by means of laser vaporization carbon dioxide. *Arch Dermatol* 1990; **126**: 967–8.
8 Harwood CA, Mortimer PS. Acquired lymphangiomata mimicking genital warts. *Br J Dermatol* 1993; **129**: 334–6.
9 Duson CK, Zelenik JS. Vulvar endometriosis apparently produced by menstrual blood. *Obstet Gynecol* 1954; **3**: 76–9.
10 Dutta P. Vulval endometriosis. *J Indian Med Assoc* 1987; **85**: 237–8.
11 Catherwood AE, Cohen ES. Endometriosis with decidual reaction in episiotomy scar. *Am J Obstet Gynecol* 1951; **62**: 1364–6.
12 Brougher JC. Endometrial cyst in an episiotomy scar. *Am J Obstet Gynecol* 1947; **54**: 127–8.
13 Mesko JD, Gates H, McDonald TW *et al*. Clear cell (mesonephroid) adenocarcinoma of the vulva arising in endometriosis: a case report. *Gynecol Oncol* 1988; **29**: 385–91.
14 Chorzelski TP, Kudejko J, Jablonska S. Is papular acantholytic dyskeratosis of the vulva a new entity? *Am J Dermatopathol* 1984; **6**: 557–60.
15 Cooper PH. Acantholytic dermatosis localized to the vulvocrural area. *J Cutan Pathol* 1989; **16**: 81–4.
16 Lee SH, Jang JG. Papular acantholytic dyskeratosis of the genitalia. *J Dermatol* 1989; **16**: 312–4.
17 Pestereli HE, Karaveli S, Oztekin S, Zorlu G. Benign persistent acantholytic and dyskeratotic eruption of the vulva: a case report. *Int J Gynecol Pathol* 2000; **19**: 374–6.
18 Bell HK, Farrar CW, Curley RK. Papular acantholytic dyskeratosis of the vulva. *Clin Exp Dermatol* 2001; **26**: 386–8.
19 Ciupinska M, Kalbarczyk K, Jablonska S. Disseminated papular acantholytic dyskeratosis. *J Eur Acad Dermatol Venereol* 1998; **11**: 55–8.
20 GüneÉAT, Ilknur T, Pabuççuoglu U *et al*. Papular acantholytic dyskeratosis of the anogenital area with positive direct immunofluorescence results. *Clin Exp Dermatol* 2007; **32**: 301–3.

Vulval pain syndromes

Vulvodynia

The term vulvodynia was first introduced in 1983 by the ISSVD to categorize those patients who complained of a chronic sensation of burning or rawness of the vulval skin [1]. Initially, vulvodynia included several subcategories [2], but these proved unsatisfactory in the light of further experience [3]. The classification is still evolving [4].

A diagnosis of vulvodynia should be strictly reserved for those patients who have the symptoms of pain or discomfort for 3 months or more in the absence of any visible abnormality or explanation that would account for their symptoms. If any active dermatosis or dermographism is found that could account for the symptoms then that condition is the diagnosis rather than vulvodynia.

There have been many advances in our knowledge and understanding of pain in general, and the existence of complex regional pain syndromes is now well recognized. Chronic pain syndromes are rarely caused by primary psychiatric disorders as originally thought, but are the result of peripheral and/or central neuronal sensitization.

In the 1990s, it was felt that vulvodynia fulfilled many of the criteria of a complex regional pain syndrome. In clinical practice there appeared to be two major types of vulvodynia: vestibulitis and dysaesthetic vulvodynia. The main differentiation between the two was that vestibulitis was characterized by pain localized to the vulval vestibule that was precipitated by touch alone, whereas dysaesthetic vulvodynia was diffuse vulval pain that occurred spontaneously and which might or might not be aggravated by touch.

The 1999 meeting of the ISSVD recognized that there was a need for further changes in the nomenclature to fit in with the classification used for chronic pain syndromes elsewhere. It was suggested that the term dysaesthetic vulvodynia be retained for vulval pain that was diffuse, constant and spontaneous. Localized pain triggered by touch alone, previously termed vestibulitis, would be referred to by the newer and more accurate term vestibulodynia. It was also proposed that in those cases where the pain is localized

at another site this should be specified (e.g. clitorodynia if the pain is localized to the clitoris). There will probably be further changes to terminology as our knowledge about these chronic pain syndromes increases.

Vestibulodynia

Synonym
- Vestibulitis

The term vulval vestibulitis was first defined as a triad of clinical signs and symptoms that included dyspareunia, vestibular tenderness to light touch and erythema of the vestibular epithelium [5]. This syndrome was certainly recognized earlier, and terms such as focal vulvitis, hyperaesthesia of the vulva and vestibular adenitis had been used to describe the condition. It is usually a disorder of younger women, who present with the complaint of secondary dyspareunia. Most patients give a history of a precipitating event and some recall that it started during a particularly stressful time. Vestibulitis is not an inflammatory condition [6], and for this reason alone vestibulodynia is a better term. There is no evidence to support an association with chronic infection with either *Candida* or HPV. The aetiology remains unknown and it is currently best categorized as a chronic pain syndrome [7]. The majority of patients affected by vestibulodynia are psychologically normal but they do have higher anxiety and somatization scores [8,9]. Patients also seem more susceptible to irritants, not only on the vulval skin but also at other sites (e.g. hand dermatitis, poor tolerance to earrings if made of base metals). However, patch testing is usually negative [10]. It is important to assess if the patient is dermographic, as dermographism may mimic or exacerbate vulvodynia. Sometimes it is helpful to perform an examination after recent intercourse as nymphohymenal tears, fourchette or vestibular fissuring and herpes simplex infection can all be overlooked as the cause of recurrent vulval pain precipitated or exacerbated by intercourse.

Dysaesthetic vulvodynia

Dysaesthetic vulvodynia is most frequently seen in older, postmenopausal women who are often not sexually active and there is usually no precipitating event of thrush or a urinary tract infection that the patient can recall. The pain is spontaneous and often occurs independently of touch. Many of these patients are depressed, but it is difficult to establish whether this is a primary phenomenon or secondary to chronic pain. Much of the literature on the psychological profiles of patients with vulvodynia is difficult to interpret, as very often the distinction between vestibulitis (touch-provoked pain) and dysaesthetic vulvodynia (spontaneous) pain is unclear. A form of dysaesthetic vulvodynia probably more accurately labelled post-inflammatory vulval hyperaesthesia is a frequent problem following inflammatory conditions of the vulva, particularly the vestibule. It is seen most frequently following LP, when the patient still has symptoms despite the fact that the dermatitis has responded to treatment. The use of 5% lidocaine ointment usually resolves this problem.

Some of the younger patients who develop dysaesthetic vulvodynia initially had vestibulodynia.

Treatment. Management requires an unrushed and sympathetic consultation, with time spent explaining the problem of pain syndromes and the rationale for the planned treatment. Initially, topical agents are used, which include a soap substitute, avoidance of irritants and regular application of the local anaesthetic 5% lidocaine ointment. The other topical 'caine' anaesthetics should be avoided because of the risk of contact sensitivity, which is rare with lidocaine. If the patient is dermographic, an oral antihistamine should be added. If the topical measures are of no benefit or only partially effective, a tricyclic antidepressant may be used for its central action on pain. Alternative medications include pregabalin, gabapentin and carbamazepine. If there are secondary psychological or sexual issues, the input from a specialist in this field will be important. Biofeedback may improve some patients, particularly if there is associated vaginismus [11]. Finally, if there has been no improvement despite adequate doses of the medications suggested above, then advice from a Pain Clinic should be arranged. The patients may also wish to join a self-support group; in the UK this is the Vulval Pain Society.

References

1 McKay M. Burning vulva syndrome. Report of the ISSVD taskforce. *J Reprod Med* 1984; **29**: 457.
2 McKay M, Frankman O, Benson JH *et al.* Vulvar vestibulitis and vestibular papillomatosis. Report of the ISSVD Committee on Vulvodynia. *J Reprod Med* 1991; **36**: 413–5.
3 Ridley CM. Vulvodynia: evolution of classification and management. *J Eur Acad Dermatol Venereol* 1996; **7**: 129–34.
4 Moyal-Barracco M, Lynch PJ. 2003 ISSVD terminology and classification of vulvodynia: a historical perspective. *J Reprod Med* 2004; **49**: 772–7.
5 Friedrich EG. Vulvar vestibulitis syndrome. *J Reprod Med* 1987; **32**: 110–4.
6 Nylander Lundquist E, Hofer PA, Olofsson JI, Sjoberg I. Is vulvar vestibulitis an inflammatory condition? A comparison of histological findings in affected and healthy women. *Acta Derm Venereol (Stockh)* 1997; **77**: 319–22.
7 Bergeron S, Binik YM, Khalife S, Pagidas K. Vulvar vestibulitis syndrome: a critical review. *Clin J Pain* 1997; **13**: 27–42.
8 van Lankveld JJDM, Weijenborg PTM, Ter Kuile MM. Psychologic profiles of and sexual function in women with vulvar vestibulitis and their partners. *Obstetrics* 1996; **88**: 65–70.
9 Danielsson I, Sjöberg I, Wikman M. Vulvar vestibulitis: medical, psychosexual and psychosocial aspects, a case–control study. *Acta Obstet Gynecol Scand* 2000; **79**: 872–8.
10 Nunns D, Ferguson J, Beck M, Mandal D. Is patch testing necessary in vulval vestibulitis? *Contact Dermatitis* 1997; **37**: 87–9.
11 Bergeron S, Binik Y, Khalife S *et al.* A randomized comparison of group cognitive–behavioural therapy, surface electromyographic biofeedback, and vestibulectomy in the treatment of dyspareunia resulting from vulvar vestibulitis. *Pain* 2001; **91**: 297–306.

Perineal and perianal dermatology

Introduction

Dermatologists should be able to assess these areas competently and know when to involve colleagues in other disciplines. The perineum includes the perianal skin, groins and scrotum or vulva. It is important to be familiar with the anal and perianal manifestations of intestinal disease [1]. Although they are usually nonspecific, the particular skin manifestations of tuberculosis, amoebiasis, schistosomiasis and Crohn's disease may lead to diagnosis of the underlying disease by their typical histology. Clues to

internal malignancy and systemic disease may be provided by perianal skin symptoms and signs. This topic includes the differential diagnosis of pruritus ani and the presentations or complications of sexually transmitted diseases including HIV, endocrinopathies and internal and haematological malignancy: important entities and situations include perianal HPV infection, extramammary Paget's disease, pyoderma gangrenosum, Fournier's gangrene and Langerhans' cell histiocytosis. All are discussed below.

Pruritus ani is a symptom, not a diagnosis, unless qualified as constitutional or idiopathic, and, in roughly half of patients with pruritus ani, a cause will be established after dermatological evaluation [2–7]. The topic is discussed at length below (see pp. 71.85–71.87).

Inflammatory and infectious disorders of the area may be difficult to differentiate. The presence of an infective condition in this area may overlie and disguise a more important lesion of the colon or rectum [1], or signify an STD or underlying immunocompromise, whether iatrogenic or acquired.

The differential diagnosis of anogenital ulceration is addressed on p. 71.3 and in Tables 71.9 and 71.10. Many banal conditions take on a vegetating appearance in this area, especially in hot humid climates and in the presence of infection. For these, the term dermatitis vegetans can be used.

Elephantiasis forms of progressive tuberculosis [8] and syphilis are now seldom seen, but deep fungal infections must not be overlooked.

Anal and perianal symptoms and signs in homosexual males [9] have become of greater significance because of the increasing prevalence of AIDS [10–12]. Whatever the presentation of the patient, it is important to look for infective conditions and suspect the possibility of two or more concomitant diseases. Painful lesions of the anus in homosexual men are common [13], and may include traumatic lesions and herpes genitalis. Anorectal sepsis, including chronic intersphincteric abscesses, anal fistulae, fissures and ulcerated haemorrhoids were seen more frequently in a group of male homosexuals than in heterosexuals [14]. Anal intraepithelial neoplasia may be clinically subtle and invasive carcinoma is not rare. The dermatology of HIV infection is discussed generally in Chapter 35, and of the perianal and anal area below.

References

1 Grosshans E, Jenn P, Baumann R *et al.* Manifestations anales de maladies du tube digestif. *Ann Dermatol Vénéréol* 1979; **106**: 25–30.
2 Smith LE, Henrichs D, McCullah RD. Prospective studies on the aetiology and treatment of pruritus ani. *Dis Colon Rectum* 1982; **25**: 358–63.
3 Alexander-Williams J. Pruritus ani. *BMJ* 1983; **287**: 159–60.
4 Verbov J. Pruritus ani and its management: a study and reappraisal. *Clin Exp Dermatol* 1984; **9**: 46–52.
5 Hanno R, Murphy P. Pruritus ani: classification and management. *Dermatol Clin* 1987; **5**: 811–6.
6 Jones DJ. Pruritus ani. *BMJ* 1992; **305**: 575–7.
7 Rohde H. Routine anal cleansing, so-called hemorrhoids, and perianal dermatitis: cause and effect? *Dis Colon Rectum* 2000; **43**: 561–3.
8 Delacrétaz J, Christeler A. Demonstrations. *Dermatologica* 1969; **139**: 313–9.
9 Felman YM, Nikitas JA. Sexually transmitted diseases in the male homosexual. *Cutis* 1982; **30**: 706–24.
10 Penneys NS, ed. *Skin Manifestations of AIDS*. London: Martin Dunitz, 1990.
11 Cope R. Mise au point sur les lesions anoperineales et rectales observees au cours du SIDA. *Contracept Fertil Sex* 1994; **22**: 187–94.
12 Matis WL, Triana A, Shapiro R *et al.* Dermatologic findings associated with the human immunodeficiency virus. *J Am Acad Dermatol* 1987; **17**: 746–51.
13 McMillan A, Smith IW. Painful anal ulceration in homosexual men. *Br J Surg* 1984; **71**: 215–6.
14 Carr ND, Mercey D, Slack WW. Non-condylomatous perianal skin disease in homosexual men. *Br J Surg* 1989; **76**: 1064–6.

Structure and function

The anus is principally for the evacuation of faeces from the gastrointestinal tract [1], but may also be an organ of sexual utility.

The deep natal cleft, the inguinal (crural) folds and the infragluteal folds are special sites because they are areas where two layers of skin come into close apposition. Together these sites function as part of the hinge between the lower limbs and the trunk, as well as abutting the mucocutaneous junctions of anus and genitalia. The natal cleft is deep and firmly fixed to underlying fibrous and fascial tissues, and its sides are steep and closely apposed. Mucous discharges, excreta and moisture are retained easily within it. Proximity to the genital organs and anus give it a special physical and psychological importance.

The perineum is endowed with numerous eccrine sweat glands whose function is retained after lumbar and thoracolumbar sympathectomies. Sweating may be caused by an alternative parasympathetic sudomotor pathway from the fourth sacral anterior root. Apocrine glands are present but many are functionless. A variable number of sebaceous glands are present both in pilosebaceous units and as individual 'free' sebaceous glands at the transitional part of the anal canal.

The cloacal membrane is where ectodermal and endodermal tissues are in direct apposition caudally in the embryo. The separation into urogenital membrane and anal membrane with the formation of the perineum at about 7 weeks of gestation is brought about by the separation of the cloacal portion of the hindgut by the urorectal septum growing caudally between the allantois anteriorly and the hindgut posteriorly, thus partitioning the cloaca into the urogenital sinus anteriorly and the anorectal canal posteriorly. The anal membrane disintegrates at about 9 weeks to open into an ectodermal anal pit formed in the posterior cloacal folds.

Congenital and developmental abnormalities

Gross anomalies will be seen only incidentally by the dermatologist because of skin complications. Minor abnormalities such as haemangiomas, skin tags (acrochordons) and papilliferous acanthomas are common on the inner sides of the thighs and infragluteal region. Pigmented, hairy naevi may involve one or both buttocks. Involvement of the buttocks with atypical naevi is a feature of the dysplastic naevus syndrome. Dermatologist should be aware of some syndromic presentations.

Developmental cysts, fistulae, sinuses and tumours

These are not uncommon, and frequently become infected. They may be mistaken for hidradenitis suppurativa or furuncles. Dermoid cysts occur on or adjacent to the perineal raphe and scrotum. Cloacal sinuses form fistulae from the anus to the adjoining skin; others involve the urethra and perineum.

Chordoma cutis

Chordomas [2] arise from the embryonic precursor of the axial skeleton, the notochord. They can involve the skin of the perineum, sacral area and buttocks by direct extension, recurrence or metastasis. They present as single or multiple, smooth, skin-coloured, non-tender nodules. Sacrococcygeal pain of a persistent nature may precede the diagnosis for years, in a manner that may mimic the presentation of sacral cysts [3], and require scanning procedures to differentiate between them.

Miscellaneous congenital abnormalities

Congenital hypertrichosis over the midline in the lumbosacral area—faun tail—is a sign of underlying spinal dysraphism (e.g. spina bifida occulta). Pilonidal sinus is discussed on pp. 71.26 and 71.87. This is not the place to list exhaustively all the syndromes with perianal manifestations, but an example is the periorificial keratotic plaques of Olmsted syndrome [4].

References

1 Leiberman DA. Common anorectal disorders. *Ann Intern Med* 1984; **101**: 837–46.
2 Su WPD, Louback JB, Gagne EJ, Scheithauer BW. Cutaneous chordoma: a report of 19 patients with cutaneous involvement of chordoma. *J Am Acad Dermatol* 1993; **29**: 63–6.
3 Van Kleft E, Van Vyve M. Chronic perineal pain related to meningeal cysts. *Neurosurgery* 1991; **29**: 223–31.
4 Mevorah B, Goldberg I, Sprecher E *et al*. Olmsted syndrome: mutilating palmoplantar keratoderma with periorificial keratotic plaques. *J Am Acad Dermatol* 2005; **53**: S266–72.

Trauma and artefact

Anal trauma is not uncommon. The two most common causes of acute painful anal ulceration in homosexual men are trauma and herpes simplex. Primary syphilis, chancroid, lymphogranuloma venereum, granuloma inguinale and amoebiasis, in decreasing order of frequency, are much less common [1]. Foreign bodies are occasionally inserted into the rectum. Anogenital tattoos have become commonplace [2].

Pressure sore

Pressure sores (decubitus ulcers) in the sacral area are common. In elderly, debilitated or bedridden patients, a persistent patch of erythema on the sacral or ischial region is a sign of impending ulceration. Squamous carcinoma is a potential complication, as with all chronic ulceration.

Umbilical artery catheterization

Unilateral skin necrosis of the buttock has been reported following indwelling umbilical artery catheterization [3–5], probably resulting from thrombosis leading to occlusion of the inferior gluteal artery. A similar case was caused by misdirection of the tip of the arterial catheter [6].

Child sexual abuse

The significance of anogenital warts in suggesting possible child sexual abuse is controversial. However, early recognition as a marker for child sexual abuse is in the child's long-term best interest [7].

References

1 McMillan A, Smith IW. Painful anal ulceration in homosexual men. *Br J Surg* 1984; **71**: 215–6.
2 Goldstein N. Psychological implications of tattoos. *J Dermatol Surg Oncol* 1979; **5**: 883–8.
3 Bonifazi E, Meneghini C. Perianal gangrene of the buttock: an iatrogenic or spontaneous condition? *J Am Acad Dermatol* 1980; **3**: 596–8.
4 Cutler VE, Stretcher GS. Cutaneous complications of central umbilical artery catheterization. *Arch Dermatol* 1977; **113**: 61–3.
5 Mann PN. Gluteal skin necrosis after umbilical artery catheterization. *Arch Dis Child* 1980; **55**: 815–7.
6 Rudolph N, Wang HH, Dragutsky D. Gangrene of the buttock: a complication of umbilical artery catheterization. *Pediatrics* 1974; **53**: 106–9.
7 Hobbs CJ, Wynne JM. How to manage warts. *Arch Dis Child* 1999; **81**: 460.

Inflammatory dermatoses

The causes of perianal inflammation in infants are dealt with in Chapter 17. In adults, inflammation may result from the coexistence of several factors: haemorrhoids, anal discharge, proctitis, the presence of fissures or the effect of scratching. Five common conditions cause diagnostic difficulties: seborrhoeic dermatitis, psoriasis, contact dermatitis, lichen simplex and mycotic infections. *Oxyuris* infestation is sometimes postulated but seldom confirmed in adults. Phthiriasis pubis must be excluded.

The lesions of seborrhoeic dermatitis are brownish red, with branny or large, greasy scales towards the edge, extending beyond and outside the fold, and involving other areas of the body.

Psoriasis has a smooth glazed surface and a dull red hue, and is often fissured; other signs of the disease are nearly always present.

Contact dermatitis is markedly inflamed, and has an ill-defined, spreading border. Irritant dermatitis results mainly from detergents; allergic dermatitis can have many causes (Table 71.19). In 43 suspected cases, neomycin (27%) and 'caine mix' (24%) were the most frequent offenders; quinolines (7%), lanolin (7%) and ethylenediamine (5%) were less common [1]. When resulting from a medicament, the hands may be involved. Other reports concern biocide preservatives and fragrances in moistened toilet tissue [2–5], lidocaine [6,7] and tetracaine (amethocaine) hydrochloride [8] used in topical antipruritics for piles, and mitomycin C [9]. The role of food allergy in causing perianal symptoms is debatable [10]. Anoreceptive homosexual men may be susceptible to condom hypersensitivity.

Gross lichenification (lichen simplex) simulates psoriasis but is usually unilateral, except when it involves the perianal area. It may occur as a small, intensely irritable area, localized to the edge of the anus in one site, which is indicated exactly by the patient.

In all cases of perianal and perineal inflammation, the urine should be tested for glucose, and swabs and scrapings examined for organisms; tinea especially should be suspected, particularly if there has been prior use of topical corticosteroids which modify the features and thus create diagnostic confusion.

A vaginal or rectal examination is mandatory. Any irregularity of the bowels that causes straining or soiling should be corrected.

References

1 Wilkinson JD, Hambly EM, Wilkinson DS. Comparison of patch test results in two adjacent areas in England. *Acta Dermatol Venereol (Stockh)* 1980; **60**: 245–9.

2 Swinyer LJ. Connubial contact dermatitis from perfumes. *Contact Dermatitis* 1980; **6**: 226.
3 Van Ginkel CJ, Rundervoort GJ. Increasing incidence of contact allergy to the new preservative: 1,2-dibromo-2,4-dicyanobutane (methyldibromoglutaronitril). *Br J Dermatol* 1995; **132**: 918–20.
4 De Groot AC, Toon J, Baar M *et al*. Contact allergy to moist toilet paper. *Contact Dermatitis* 1991; **24**: 135–6.
5 Lucker GPH, Hulsmans R-FHJ, van der Kley AMJ, van de Staak WJBM. Evaluation of the frequency of contact allergic reactions to kathon CG in the Maastricht area, 1987–90. *Dermatology* 1992; **184**: 90–3.
6 Handfield-Jones SE, Cronin E. Contact sensitivity to lignocaine. *Clin Exp Dermatol* 1993; **18**: 342–3.
7 Hardwick N, King CM. Contact allergy to lignocaine with cross-reaction to bupivacaine. *Contact Dermatitis* 1994; **30**: 245–6.
8 Sanchez-Perez J, Cordoba S, Cortizas CF, Garcia-Diez A. Allergic contact balanitis due to tetracaine (amethocaine) hydrochloride. *Contact Dermatitis* 1998; **39**: 268.
9 Fisher AA. Allergic contact dermatitis to Mitomycin C. *Cutis* 1991; **47**: 225.
10 Sapan N. Food induced pruritus ani: a variation of allergic target organ? *Eur J Pediatr* 1993; **152**: 701–2.

Pruritus ani

The symptom complex of pruritus ani has many causes; it is not a diagnosis unless qualified as constitutional or idiopathic. Fifty per cent of patients with pruritus ani will have a cause after dermatological evaluation [1–6]. Pruritus ani is seen especially in middle-class, middle-aged, white males [7]. It occurs less frequently in females, either alone or with pruritus vulvae. It can be associated with most forms of anal disease and with skin conditions involving the perianal area. The contributory factors are complex and may complement or perpetuate each other. Anal itching occurs to a variable degree with any inflammatory or eczematous condition of the skin of that area, with anal fissures, whatever their aetiology, and with malignant tumours. Mycotic infection often causes intense pruritus, and diabetes must be excluded in all severe or persistent candidal infections. Threadworm infestation is a well-recognized cause in childhood and occasionally in adults. Idiopathic anal itching, in which there is no obvious primary dermatological cause, is discussed further here. Lichenification, excoriation and secondary bacterial and candidal infection (induced by scratching) can supervene, and a contact dermatitis can be caused by overwashing and treatment, both self-directed and physician-prescribed.

The common factor linking most cases of pruritus ani is faecal contamination [2,8]. Faeces are themselves irritant and may generate perianal itch [8,9]. The itch may be triggered by a bowel movement or wiping with toilet paper, but often occurs at night, waking the patient from sleep. Faeces also contain potential allergens and endopeptidases of bacterial origin [10,11]. In the presence of pre-existing skin disease (e.g. seborrhoeic dermatitis or flexural psoriasis), or even in the absence of visible disease, these enzymes are capable of inducing both itching and inflammation [12].

Pruritus ani may be associated with anal leakage resulting from coexisting anal disease or an exaggerated rectoanal inhibitory reflex [13] and anal sphincter dysfunction [14], or be precipitated by broad-spectrum antibiotics and diarrhoea. Hypertrophy of anal papillae is probably not relevant [15]. Many patients have a dermatosis and some will have irritant or allergic contact dermatitis [16–18].

Psychological factors often contribute to pruritus ani, particularly when the itching appears to be out of proportion to the changes observed. However, as Whitlock [19] points out in a careful review, the evidence is unsatisfactory, except perhaps in primary lichen simplex. Psychosexual connotations of suppressed homosexuality do not withstand critical assessment. It is quite understandable, however, that prolonged pruritus ani can lead to tension, irritability or depression, and the treatment of this is an important part of the management of the condition. Idiopathic pruritus ani has been attributed to stress and anxiety, and sedentary occupations.

The causes of faecal contamination are as follows (more than one factor may be operative).

- **Difficulty in cleansing the area.** This may be caused by the following factors:
  - — Simple obesity: poor ventilation and maceration have an additional role.
  - — Frequency of defaecation: patients with a colostomy never suffer from perianal itching. Patients with pruritus ani are rarely constipated, although they may sit long at stool owing to faulty training techniques, with resultant prolapse or haemorrhoids and soiling [2,14,20]. Patients frequently admit to two or more motions a day. They are often tense individuals in whom everyday problems induce a profound colonic reflex, resulting in defaecation and soiling.
  - — Anatomical factors: it is often noted that the anus is deeply placed. The association of this 'funnel anus' with marked hirsutism causes mechanical problems in the maintenance of hygiene.
- **Anal leakage.** This may result from the following factors:
  - — Local causes: such as haemorrhoids, perianal tags or fissures, which interfere with the efficient functions of the anus.
  - — Primary anal sphincter dysfunction: anal canal manometry studies have shown that leakage of infused saline occurs early [13], and in one common group of patients the sphincter relaxes in response to rectal distension in a more rapid and profound manner than in a control group [14]. The arrival of faeces or flatus in the rectum may then regularly result in reflex faecal soiling.
- **Bacterial contamination.** This is frequently a secondary cause, but rarely a primary cause alone. However, cross-infection of staphylococci may occur (e.g. between the ears and the anus).
- **Food and drink**. The role of ingested metabolites or food chemicals in inducing pruritus ani is still uncertain and virtually unexplored, but anecdotal evidence in individual cases is sometimes compelling [21].

Clinical features. Clinical features vary somewhat, with possible contributions from the effects of rubbing, secondary infection, contact dermatitis or an underlying psoriatic diathesis.

- Lichen simplex may be present in a 'pure' form, often localized to a small area at the edge of the anus or slightly away from it. The perception of itch from 'easily alerted' nerve endings is more acute in those of anxious temperament or at times of psychic trauma or fatigue.

- A more general area of maceration, lichenification and fissuring—the 'mossy bank' anus—may be present. The architecture of the anal margin may be distorted by haemorrhoids, tags, oedema and infection. There is usually a gross degree of discharge [14].
- Features of acute eczema may be caused by secondary infection of possibly minimal seborrhoeic dermatitis or psoriasis, or by contact dermatitis. The last mentioned should always be suspected when there has been any sudden change of pattern or intensity of a rash. The fingers may also be involved. One of the most common offenders is the 'caine' group of drugs [22], often self-prescribed.
- Intense erythema with no obvious features of eczema may occur. This tends to vary in intensity over short periods, and probably represents the pruritic stage of the next group.
- There may be no visible abnormality at the time of examination. These patients may have noticed erythema at times, or intense itching, and commonly give a story of an intermittent sensation of wet anal margins and slight faecal soiling. It is in this group that dyskinesia of the sphincter appears to be a primary factor.

Diagnosis. A full history is essential and a search for underlying disease must be carried out. It is important to exclude staphylococcal infection, folliculitis, erythrasma, *Candida*, tinea, warts and thread/pinworms, and to establish whether there are other underlying skin diseases such as psoriasis [23], atopic dermatitis, lichen planus, lichen sclerosus or EMPD [15]. Anal fistulae are particularly prevalent in chronic pruritus ani [24]. However, the majority of patients with piles, skin tags, fissures, warts, diarrhoea or faecal soiling do not itch [3]. Systemic diseases that have been associated with pruritus ani include lymphoma, pellagra, hypovitaminosis A and D and diabetes mellitus [4].

A rectal examination and referral for proctoscopy and sigmoidoscopy may be indicated [25]. In the young, threadworms should be sought with the Sellotape test or by stool examination for parasites. Patch testing is helpful to explore sensitivity to lanolin, medicaments, rubber, perfumed paper, etc.

Treatment. Management [2] begins with attention to the patient's washing habits. Soap is replaced with a suitable substitute and a moisturizer prescribed. A moisturizer (others recommend talcum powder) should be applied after each wash. A barrier preparation can be pre-applied to the perianal skin before the bowels are opened. Washing in a bidet after defaecation is preferable to wiping with toilet paper, if possible. Rubbing with toilet paper should be discouraged and dabbing recommended. Premoistened toilet papers should be avoided because of the potential irritancy of the moisturizing agent, which may be alcohol, and the risk of developing allergic sensitivity to fragrance or preservative components. Underwear should be loose and preferably made of cotton. Patients are best advised not to use topical anaesthetics in order to avoid sensitization to their constituents [26].

Coffee consumption might be curtailed [21]. Any other foods, such as nuts, that provoke the pruritus should be excluded from the diet, and a high-fibre diet should be encouraged if there is any history of constipation or haemorrhoids [27].

Local applications should be mild and soothing. A topical corticosteroid/antibiotic/antifungal preparation is useful for acute episodes. A wick of bandage impregnated with hydrocortisone 1% and silicone 10% inserted in the natal cleft is anti-inflammatory and lubricating. Other treatments that have been advocated include zinc paste with 1–2% phenol, St Mark's lotion, half-strength Castellani's paint, weak (0.05–0.25%) silver nitrate solution (if wet), cryotherapy, oral antihistamines, corticosteroid suppositories, intralesional triamcinolone, a 10-day tapering course of prednisolone, and intralesional methylene blue, with or without marcaine/epinephrine/xylocaine [3,4,28,29]. Caution should be exercised with topical steroid treatment because the anal skin is 'quasi-occluded' and is easily damaged by fluorinated corticosteroids.

Concomitant proctological disease (haemorrhoids, fissures, anal spasm and occult mucosal prolapse) should be treated, if found [30]. When active pathology such as fissures, haemorrhoids or anal spasm are present, surgery will be needed. Lord's stretch procedure [31] has proved helpful. The long-term results are particularly satisfactory in those patients with strong ultra-low-pressure waves [27]. However, it may not always relieve the pruritus [32]. Simple excision of anal tags is unhelpful in relieving symptoms [15].

Some authorities see a psychosexual significance in pruritus ani in men [19], and this may rarely require attention. Patients should be reassured that they do not have cancer [1].

References

1 Smith LE, Henrichs D, McCullah RD. Prospective studies on the etiology and treatment of pruritus ani. *Dis Colon Rectum* 1982; **25**: 358–63.
2 Alexander-Williams J. Pruritus ani. *BMJ* 1983; **287**: 159–60.
3 Verbov J. Pruritus ani and its management: a study and reappraisal. *Clin Exp Dermatol* 1984; **9**: 46–52.
4 Hanno R, Murphy P. Pruritus ani: classification and management. *Dermatol Clin* 1987; **5**: 811–6.
5 Jones DJ. Pruritus ani. *BMJ* 1992; **305**: 575–7.
6 Rohde H. Routine anal cleansing, so-called hemorrhoids, and perianal dermatitis: cause and effect? *Dis Colon Rectum* 2000; **43**: 561–3.
7 Leiberman DA. Common anorectal disorders. *Ann Intern Med* 1984; **101**: 837–46.
8 Kocsard E. Pruritus ani: a symptom of fecal contamination. *Cutis* 1981; **27**: 518.
9 Caplan RM. The irritant role of faeces in the genesis of perianal itch. *Gastroenterology* 1966; **50**: 19–23.
10 Keele CA. Chemical causes of pain and itch. *Proc R Soc Med* 1957; **50**: 477–84.
11 Shelley WB, Arthur RP. The neurohistology and neurophysiology of the itch sensation in man. *Arch Dermatol* 1957; **76**: 296–323.
12 Andersen PH, Bucher AP, Saeed I *et al*. Faecal enzymes: *in vivo* skin irritation. *Contact Dermatitis* 1994; **30**: 152–8.
13 Allan A, Ambrose NS, Silverman S *et al*. Physiological study of pruritus ani. *Br J Surg* 1987; **74**: 576–9.
14 Eyers AA, Thompson JPS. Pruritus ani: is anal sphincter dysfunction important in aetiology? *BMJ* 1979; **ii**: 1549–51.
15 Jensen SL. A randomized trial of simple excision of non-specific hypertrophied anal papillae versus expectant management in patients with chronic pruritus ani. *Ann R Coll Surg Engl* 1988; **70**: 348–9.
16 Harrington CI, Lewis FM, McDonagh AJ, Gawkrodger DJ. Dermatological causes of pruritus ani. *BMJ* 1992; **305**: 955.
17 Dasan S, Neill SM, Donaldson DR, Scott HJ. Treatment of persistent pruritus ani in a combined colorectal and dermatological clinic. *Br J Surg* 1999; **86**: 1337–40.
18 Bauer A, Geier J, Elsner P. Allergic contact dermatitis in patients with anogenital complaints. *J Reprod Med* 2000; **45**: 649–54.
19 Whitlock FA, ed. *Psychophysiological Aspects of Skin Disease*. London: Saunders, 1976: 118–21.

20 Kaufman HD, ed. In: *The Haemorrhoid Syndrome*. Tunbridge Wells: Abacus, 1981: 61.
21 Veien NK, Hattel T, Justesen O *et al.* Dermatoses in coffee drinkers. *Cutis* 1987; **40**: 421–2.
22 Wilkinson JD, Hambly EM, Wilkinson DS. Comparison of patch test results in two adjacent areas of England. II. Medicaments. *Acta Derm Venereol (Stockh)* 1980; **60**: 245–9.
23 Farber EM, Nall L. Perianal and intergluteal psoriasis. *Cutis* 1992; **50**: 336–8.
24 Petros JG, Rimm EB, Robillard RJ. Clinical presentation of chronic anal fissures. *Am Surg* 1993; **59**: 666–8.
25 Daniel GL, Longo WE, Vernava III AM. Pruritus ani: causes and concerns. *Dis Colon Rectum* 1994: **37**: 670–4.
26 Handfield-Jones SE, Cronin E. Contact sensitivity to lignocaine. *Clin Exp Dermatol* 1993; **18**: 342–3.
27 Hancock BD. In: Kaufman HD, ed. *The Haemorrhoid Syndrome*. Tunbridge Wells: Abacus, 1981: 93–104.
28 Minvielle L, Hernandez VL. The use of intralesional triamcinolone hexacetonide in treatment of idiopathic pruritus ani. *Dis Colon Rectum* 1969; **12**: 340–3.
29 Eusebio EB. New treatment of intractable pruritus ani. *Dis Colon Rectum* 1991; **34**: 289.
30 Pirone E, Infantin A, Masin A *et al.* Can proctological procedures resolve perianal pruritus and mycosis? *Int J Colorectal Dis* 1992; **7**: 18–20.
31 Lord PH. Diverse methods of managing haemorrhoids: dilatation. *Dis Colon Rectum* 1973; **16**: 180–92.
32 Ortiza H, Marti J, Jaurieta E *et al.* Lord's procedure: a critical study of its basic principle. *Br J Surg* 1978; **65**: 281–4.

Danthron erythema

This form of irritant contact dermatitis is caused by the use of a laxative containing danthron [1,2]. It is seen in those with Hirschsprung's disease or encopresis, and sometimes in elderly incontinent patients [2–4]. Danthron (1,8-dihydroxyanthroquinone) is reduced in the large bowel to 1,8-dihydroxyanthron, which is the active agent [2]. This is chemically identical to dithranol, and the lesions produced by faecal incontinence are equivalent to dithranol 'burns'. A bizarre livid erythema in the perianal area, groins, thighs and buttocks, with sharp outlines, corresponds to the area of contact with the faeces. Danthron erythema is easily differentiated from other causes of perianal or inguinocrural lesions.

Lichen sclerosus et atrophicus

The perianal skin is rarely involved alone in women, but is involved in up to two-thirds of the cases in which the vulva is affected [5], forming a characteristic figure-of-eight distribution. One case of carcinoma has been reported [6]. Perianal lichen sclerosus probably never occurs in males.

Anal fissure

Small erosions and fissures may occur in the sulcus beneath oedematous haemorrhoids or in any area of dermatitis. The presence of even a small fissure in an area of dermatitis maintains the pruritus and prolongs the course.

A true anal fissure is a midline linear perianal ulcer; 90% posteriorly, 10% anteriorly. Many are idiopathic; the cause is probably related to defaecation of hard stool causing pressure trauma and necrosis, or it may be a post-operative complication. Sexually transmitted diseases and Crohn's disease should be excluded. Intense pruritus, pain, bleeding, mucous discharge and constipation constitute the symptomatology. On examination there may be a 'sentinel pile' at the anal pole of the ulcer. Management is surgical: proctoscopy is mandatory if the aetiology is in doubt, and especially if the fissure extends to the anal margin or within. Benign fissures are superficial and not indurated, but when persistent they may be painful and cause bleeding, especially in the elderly. Unless they heal quickly under treatment, a biopsy should always be performed to exclude malignancy.

Small erosions and excoriations frequently heal with treatment for anogenital pruritus. If they are hidden between haemorrhoids or anal tags, protective pastes are helpful. Fissures in psoriasis and seborrhoeic dermatitis are difficult to heal, particularly in the natal cleft. If the underlying disease is satisfactorily controlled, the lesion will heal without special attention. Intralesional corticosteroids may be effective in non-infective inflammatory conditions.

Anal fistula

A perianal fistula is a communication between the anal canal and the perianal skin. Most are on the midline posteriorly, but there may be multiple openings. The origin is from infection and abscesses within the anal glands, but Crohn's disease, foreign body and tuberculosis are classic causes and hidradenitis suppurativa is an important differential diagnosis. Squamous carcinoma is a rare complication. The presentation is usually of pruritus ani related to seropurulent discharge but there may be pain resulting from abscess formation. Surrounding skin may be indurated. Management is surgical.

Pilonidal cyst/sinus

Pilonidal sinus probably derives from the perineal pilosebaceous unit and precursor pits (not the common congenital sacral pits) associated with trapped hairs [7,8]. Clinically, pilonidal sinus constitutes part of the 'follicular–occlusion tetrad' alongside hidradenitis suppurativa, acne conglobata and dissecting cellulitis of the scalp. Symptoms include itch, pain, recurrent abscess, purulent discharge and persistent nodule. Pilonidal sinus occurs in the midline. The sacrococcygeal location is the most common site but it can occur on the pubis, anterior perineum and, very rarely, the penis. It may present as a nodule or cyst, often with a pigmented or hairy surface, which ruptures and quickly becomes infected (Fig. 71.41). The sinus usually extends to the sacrum and causes sacrococcygeal fistulae with deep ramifications. This heals if the track is thoroughly cleaned. Treatment is surgical [8,9]. Squamous carcinoma can supervene [10].

References

1 Bunney MH, Noble IM. Red skin and Dorbanex. *BMJ* 1974; **ii**: 731.
2 Ippen H. Toxizität und stoffwechsel des cignolins (Wz). *Dermatologica* 1959; **119**: 211–20.
3 Barth JH, Reshad H, Darley CR *et al.* A cutaneous complication of Dorbanex therapy. *Clin Exp Dermatol* 1984; **9**: 95–6.
4 Broholm KA. A controlled trial of a new combined preparation for the treatment of constipation in geriatric patients. *Gerontol Clin (Basel)* 1973; **15**: 25–31.
5 Wallace HJ. Lichen sclerosus et atrophicus. *Trans St John's Hosp Dermatol Soc* 1971; **57**: 9–30.
6 Sloan PJM, Goepel J. Lichen sclerosus et atrophicus and perianal carcinoma. *Clin Exp Dermatol* 1981; **6**: 399–402.
7 Millar DM. Aetiology of post-anal pilonidal disease. *Proc R Soc Med* 1970; **63**: 1263–4.
8 Allen-Mersh TG. Pilonidal sinus: finding the right track for treatment. *Br J Surg* 1990; **77**: 123–32.



Fig. 71.41 Pilonidal sinus. (Courtesy of Dr D.A. Burns, Leicester, UK.)

9 Lord PH, Millar DM. Pilonidal sinus: a simple treatment. *Br J Surg* 1965; **52**: 298–300.
10 Sagi A, Rosenberg L, Grief M *et al.* Squamous cell carcinoma arising in a pilonidal sinus: a case report and review of the literature. *J Dermatol Surg Oncol* 1984; **10**: 210–2.

Hidradenitis suppurativa

Hidradenitis suppurativa ('chronic perianal pyoderma' in Japan) (see Chapter 30) can give rise to all degrees of inflammation and scarring. Friction and pressure accentuate the inflammatory changes that invade the fat and cause further granulomatous change extending widely over the buttocks and thighs. Persistent perineal sinuses are frequent, and deep lesions cause anal fistulae. In mild cases, only a few isolated lesions are present. Secondary bacterial invasion, often from the gut [1], is an important complicating factor. Seven cases have been associated with an oestrogen–progesterone contraceptive pill [2].

There is a clinical spectrum overlapping with chronic folliculitis (e.g. of the buttocks and 'penile acne'). In established hidradenitis, bridged comedones, folliculitis and furunculosis, deep burrowing discharging sinuses, nodules, cysts, fluctuant abscesses, scarring and fibrosis in the groins and axillae, the natal cleft and buttocks [3] may all be present. Some patients may also have conglobate acne, dissecting cellulitis and pilonidal sinus. Hidradenitis is more common in black and Mediterranean individuals. It affects the axillae preferentially in women and the perineum in men. A urethral–cutaneous fistula and phimosis have been reported [4]. Scarring from the disease and its treatment can be extensive. The morbidity of hidradenitis may be severe, interfering with sitting, sleeping, walking, defaecation and sexual activity, and responsible for depression. Disease that has persisted for more than 20 years carries a significant risk of progression to SCC [5–7] and rarely verrucous carcinoma [8].

Differential diagnosis. Hidradenitis is usually a clinical diagnosis. Swabs should be taken for bacteriological evaluation and to guide therapy, but the patient should be fully evaluated for sexually transmitted diseases should the presentation be in any way suspicious. An important differential diagnosis of acneiform disease presenting at any site is chloracne (see Chapter 42). A biopsy may be necessary to exclude carcinoma or Crohn's disease. Perineal Crohn's disease mimics hidradenitis, with its granulomatous inflammation, ulceration and fistula formation, but it is less painful. Also, the disease is absent from the axillae and it is rare for patients to be free of overt gastrointestinal symptoms. Very florid perianal disease can be seen in myeloma and leukaemia [9], and in homosexual men and in AIDS [10].

Mild or localized forms are frequently misdiagnosed as furunculosis or 'infected cysts', and confusion occurs with severe acne, developmental fistulae and lymphogranuloma venereum. The relatively painless recurrences in the same or other sites, and oblique sinuses that end in soft swollen inflamed nodules, are characteristic.

Treatment. This is challenging [11]. Small localized sinuses may be phenolized successfully, and early lesions may respond to intralesional corticosteroids. Recurrent or extensive lesions may require a more radical approach. Marsupialization (as with pilonidal sinuses) [12] and diathermy destruction of the affected tissue have been very successful in some cases, even those involving the scrotum. Treatment with carbon dioxide laser, can be effective [13,14]. The use of Silastic foam dressing may facilitate healing [15]. Otherwise, plastic surgery with complete excision of all the involved skin may be required [16]. Long-term antibiotic therapy (erythromycin, flucloxacillin, ciprofloxacin, metronidazole) is often given 'blind', but is seldom of lasting value, although elimination of specific secondary invaders such as *Streptococcus milleri* [1] has given good results. Oral prednisolone can be used alongside antibiotics to control intercurrent exacerbations. Isotretinoin (1 mg/kg) for 6–8 months has been used with mixed results, but is occasionally helpful in difficult cases [17,18]. Antiandrogen therapy has yet to be evaluated. Infliximab and other TNF 'biologicals' show promise [19].

References

1 Highet AS, Warren RE, Weekes AJ. Bacteriology and antibiotic treatment of perineal suppurative hidradenitis. *Arch Dermatol* 1988; **124**: 1047–51.
2 Stellon AJ, Wakeling M. Hidradenitis suppurativa associated with use of oral contraceptives. *BMJ* 1989; **298**: 28–9.
3 Coda A, Ferri F. Perianal Verneuil's disease. *Minerva Chir* 1991; **46**: 465–7.
4 Chaikin DC, Volz LR, Broderick G. An unusual presentation of hidradenitis suppurativa: case report and review of the literature. *Urology* 1994; **44**: 606–8.
5 Black SB, Woods JE. Squamous cell carcinoma complicating hidradenitis suppurativa. *J Surg Oncol* 1982; **19**: 25–6.
6 Shukla VK, Hughes LE. A case of squamous cell carcinoma complicating hidradenitis suppurativa. *Eur J Surg Oncol* 1995; **21**: 106–9.
7 Ishizawa T, Koseki S, Mitsuhashi Y, Kondo S. Squamous cell carcinoma arising in chronic perianal pyoderma: a case report and review of Japanese literature. *J Dermatol* 2000; **27**: 734–9.
8 Cosman BC, O'Grady TC, Pekarske S. Verrucous carcinoma arising in hidradenitis suppurativa. *Int J Colorectal Dis* 2000; **15**: 342–6.
9 Alexander-Williams J, Buchmann P. Perianal Crohn's disease. *World J Surg* 1980; **4**: 203–8.

Table 71.31 The cutaneous manifestations of Crohn's disease [1–6].

Erythema nodosum
Anal and perianal lesions (Table 71.32)
Spreading ulceration of perineum and buttocks after colectomy
Skin changes around ileostomies and colostomies
Genital lesions
Balanitis, posthitis, chronic penile lymphoedema and granulomatous lymphangitis
Vulval lesions
'Sarcoid' type lesions in remote sites
Pyoderma gangrenosum
Granulomatous cheilitis
Epidermolysis bullosa acquisita
Non-specific changes resulting from malabsorption

Table 71.32 Perianal features of Crohn's disease.

Pruritus ani
Maceration
Erosion
Secondary infection
Skin tags
Fissures
Anal stenosis
Fistula-*in*-*ano*
Abscess
'Metastatic' granulomatous plaques

10 Carr ND, Mercey D, Slack WW. Non-condylomatous perianal skin disease in homosexual men. *Br J Surg* 1989; **76**: 1064–6.
11 Mouly MR. A propos des suppurations périnéo-fessieres chroniques et de leur traitement chirurgical. *Bull Soc Fr Dermatol Syphiligr* 1969; **76**: 23–7.
12 Brown SCW, Kazzasi N, Lord PH. Surgical treatment of perineal hidradenitis suppurativa with special reference to recognition of the perianal form. *Br J Surg* 1986; **73**: 978–80.
13 Lapins J, Marcusson JA, Emtestam L. Surgical treatment of chronic hidradenitis suppurativa: CO_2 laser stripping—secondary intention technique. *Br J Dermatol* 1994; **131**: 551–6.
14 Finley EM, Ratz JL. Treatment of hidradenitis suppurativa with carbon dioxide laser excision and second-intention healing. *J Am Acad Dermatol* 1996; **34**: 465–9.
15 Morgan WP, Harding KG, Richardson G *et al.* The use of Silastic foam dressing in the treatment of advanced hidradenitis suppurativa. *Br J Surg* 1980; **67**: 277–80.
16 Šlauf P, Antoš F, Novák J *et al*. Perianal pyoderma. *Rozhl Chir* 1993; **72**: 331–3.
17 Brown CF, Gallup DG, Brown VM. Hidradenitis suppurativa of the ano-genital region: response to isotretinoin. *Am J Obstet Gynecol* 1988; **158**: 13–5.
18 Jones DH, Cunliffe W, King K. Hidradenitis suppurativa: lack of success with *cis*-retinoic acid. *Br J Dermatol* 1982; **107**: 252.
19 Revoz J. Hidradenitis suppurativa. *J Eur Acad Dermatol Venereol* 2009; **23**: 985–98.

Crohn's disease

Synonym
- Regional ileitis

It is a well-known aphorism that Crohn's disease can affect any part of the gut and its cutaneous borders from the mouth to the anus. The cutaneous manifestations of Crohn's disease are listed in Table 71.31. Perianal disease may occur in up to 75–90% of patients [1–8]. Table 71.32 lists the perianal features of Crohn's disease [9]; it includes those common to most chronic diarrhoeal illnesses such as pruritus ani, skin maceration, and erosions with secondary infection. Perianal manifestations of Crohn's disease in childhood are a major cause of morbidity, but only rarely progress in a destructive manner (Fig. 71.42) [9].

Clinical features. The skin tags of Crohn's disease are larger, thicker and harder than ordinary tags. Deep, undermined, angulated fissures with cyanotic edges may fuse to form 'flying buttress' skin bridges, characterized by relative lack of pain. Fistulae are less common than fissures; they may be asymptomatic even when multiple. Pain usually means that an abscess has formed because of blockage of a fistula. Multiple external openings can be encountered all over the buttock, on the scrotum and on the thigh; a distinctive sign is the cyanotic hue of the indurated skin. Anal stenosis, faecal incontinence and carcinoma are complications [10].



Fig. 71.42 Crohn's disease: perianal lesions. (Courtesy of Dr D.I. McCallum, Inverness, UK.)

Clinical diagnosis may be achieved based on symptoms, signs and investigation results (e.g. radiography and gut biopsy) consistent with Crohn's disease. Any anal lesion in a patient who is known to be suffering from Crohn's disease is likely to be perianal Crohn's [11]. Difficulty arises when the anogenital disease represents the first manifestation. Histologically positive perianal disease of all clinical types may predate frank gastrointestinal

Crohn's disease by several years [12], including in children [9]. The relative lack of pain, multiplicity of lesions, oedema of skin tags and eccentricity of fissures are important pointers [11]. Biopsy of skin lesions is helpful, and sigmoidoscopy and biopsy of intestinal mucosal lesions is mandatory. Swabs should be taken and the patient fully evaluated for sexually transmitted diseases should the presentation be in any way atypical.

Differential diagnosis. The differential diagnosis includes the causes of pruritus ani and non-specific anal fissures and fistulae. Similar, although less extensive, lesions occur, but much less commonly, in ulcerative colitis, and only very rarely in diverticulitis [2]. Hidradenitis suppurativa presents with nodules, sinuses and purulence but is more painful; other sites may be involved and severe acne is often present. Florid perianal disease can be seen in myeloma and leukaemia [11]. Proctitis, perianal ulceration, abscess, fissure and fistula are prevalent in homosexual men and those with HIV/AIDS [13]. Perineal pyoderma gangrenosum has been misdiagnosed as Crohn's disease. A solitary granulomatous nodule, with or without ulceration, creates a differential diagnosis that includes sarcoid, schistosomiasis, leishmaniasis, tuberculosis, atypical mycobacterial infection, deep fungal infection, granuloma inguinale, lymphogranuloma venereum, chancroid, amoebiasis and syphilis. Florid condylomata acuminata, anorectal carcinoma (presenting with an ischiorectal abscess) [14], and other mucocutaneous malignancies (basal cell carcinoma, Kaposi's sarcoma and amelanotic malignant melanoma) may rarely be encountered.

Treatment. The treatment of the anogenital manifestations of Crohn's disease depends on the treatment of active intestinal disease. This has been transformed by advances in immunosuppressive treatment [15,16]. Local measures include soaks with potassium permanganate and aluminium acetate, potent or very potent topical corticosteroid/antibiotic combinations and oral antibiotics (as for hidradenitis). A role has been advocated for long-term oral metronidazole (20 mg/kg/day in divided doses) [17,18]. Perianal abscess may respond to sulfasalazine and anal fissure to prednisolone and azathioprine [4]. The surgical philosophy is conservative [3,9,15]. Resection of the affected segment of bowel does not always cure the lesions or prevent their recurrence, especially at ileostomy or colostomy sites.

References

1 Markowitz J, Davim F, Aiges H *et al.* Perianal disease in children and adolescents with Crohn's disease. *Gastroenterology* 1984; **86**: 829–33.
2 Crohn NN, Yarnis H, eds. *Regional Ileitis*, 2nd edn. New York: Grune & Stratton, 1958.
3 Hibbiss JH, Schofield PF. Management of perianal Crohn's disease. *J R Soc Med* 1982; **75**: 414–7.
4 Rankin GB. National co-operative Crohn's disease study. *Gastroenterology* 1979; **77**: 914–20.
5 Smith JN, Winship DH. Complications and extraintestinal problems in inflammatory bowel disease. *Med Clin North Am* 1980; **64**: 1161–71.
6 Fielding JF. Perianal lesions in Crohn's disease. *J R Coll Surg Edin* 1972; **17**: 32–7.
7 Gruwez JA, Christiaens MR, Laquet A. La maladie de Crohn de l'anus. *Acta Endoscop* 1983; **13**: 285–92.
8 Tozer PJ, Whelan K, Phillips RK, Hart AL. Etiology of perianal Crohn's disease: role of genetic, microbiological, and immonological factors. *Inflamm Bowel Dis* 2009; **15**: 1591–8.
9 Palder SB, Shandling B, Bilik R *et al.* Perianal complications of pediatric Crohn's disease. *J Pediatr Surg* 1991; **26**: 513–5.
10 Slater G, Greenstein A, Aufses A. Anal carcinoma in patients with Crohn's disease. *Ann Surg* 1984; **199**: 348–50.
11 Alexander-Williams J, Buchmann P. Perianal Crohn's disease. *World J Surg* 1980; **4**: 203–8.
12 Baker WN, Milton-Thompson GJ. The anal lesion as the sole presenting symptom of intestinal Crohn's disease. *Gut* 1971; **12**: 865.
13 Denis BJ, May T, Bigard MA, Canton P. Anal and perianal lesions in symptomatic HIV infections: prospective study of a series of 190 patients. *Gastroenterol Clin Biol* 1992; **16**: 148–54.
14 Tait WF, Sykes PA. Unusual presentation of anorectal carcinoma. *BMJ* 1982; **285**: 1742.
15 Levy LC. Advances in inflammatory bowel diseases. *Expert Rev Gastroenterol Hepatol* 2009; **3**: 109–11.
16 van Assche G, Vermeire S, Rutgeerts P. Immunosuppression in inflammatory bowel disease: traditional, biological or both? *Curr Opin Gastroenterol* 2009; **25**: 323–8.
17 Bernstein LH, Frank MS, Brant LJ, Boley SJ. Healing of perineal Crohn's disease with metronidazole. *Gastroenterology* 1980; **79**: 357–65.
18 Brandt LJ, Bernstein LH, Boley SJ *et al.* Metronidazole therapy for perianal Crohn's disease: a follow-up study. *Gastroenterology* 1982; **83**: 383–7.

Miscellaneous inflammatory dermatoses

Radiodermatitis is occasionally encountered following previous treatment for *in situ* or frank carcinoma or, decades ago, pruritus ani. LP involving the buttocks and perianal region is extremely irritable and may become excoriated or hypertrophic; LP must be considered in the differential diagnosis of pruritus ani and perianal fissures. Solitary involvement of the perianal skin may occur (Fig. 71.43).

Behçet's disease occasionally presents with multiple shallow ulcers and fissures of the anal margin.

Calciphylaxis sometimes affects the thighs and buttocks [1–3].



Fig. 71.43 Perianal lichen planus. (Courtesy of Dr F.A. Ive, Durham, UK.)

Acrodermatitis enteropathica should be considered in the differential diagnosis of perianal eczema, psoriasis or candidosis in the paediatric setting, or in the presence of gastrointestinal disease causing malabsorption syndromes (e.g. Crohn's disease), extensive gastrointestinal surgery such as small intestinal bypass, malnutrition in alcoholism and recent prolonged parenteral nutrition where zinc supplementation may not have been optimal. A reticulate eczematous eruption may be found on the extensor aspects of the limbs in alcoholics but has also been reported to affect the perianal and scrotal skin [4,5]. Other deficiency diseases with some similarity to acrodermatitis enteropathica are pellagra, maple syrup urine disease and neonatal citrullinaemia. Hereditary mucoepithelial dysplasia is associated with perineal intertrigo [6].

Cicatricial pemphigoid [7] may affect the groin, perineum and perianal skin, and may cause anal stenosis. The drug clonidine may have been responsible in one case [8]. Pyodermite végétante can be distinguished by the histology and by immunofluorescence studies. Ulcerative colitis may be present [9]. Hailey–Hailey disease can involve the perianal skin [10].

The anus is involved in about 5% of cases of Stevens–Johnson syndrome. A connection has been recognized between epidermolysis bullosa acquisita [11] and inflammatory bowel disease, particularly Crohn's disease [12–14].

Fixed drug eruption may produce striking pigmentation. Prolonged use of potent topical corticosteroids causes a dusky erythema, atrophy or induration. Nicorandil is a newly recognized cause of anogenital and peristomal ulceration [15,16].

Eruptive perianal (and penoscrotal) melanotic macules and papules can indicate internal adenocarcinomatosis [17].

Primary systemic cutaneous anosacral amyloid has a predilection for the anogenital region, particularly the sacrum, in elderly Japanese people [18–20]. Moderately pruritic pigmented macules and glossy hyperkeratotic lesions fan out in lines from the anus. There are no systemic changes. Amyloid deposits are seen in the upper reticular dermis and around hair follicles. It is thought to represent an ageing process.

'Infantile' gluteal granuloma [21–23] (see Chapter 17), usually affecting infants of 4–6 months, may also occur in incontinent elderly patients [24].

References

1 Ivker RA, Woosley J, Briggaman R. Calciphylaxis in three patients with end-stage renal disease. *Arch Dermatol* 1995; **131**: 63–8.

2 Siami GA, Siami FS. Intensive tandem cryofiltration apheresis and hemodialysis to treat a patient with severe calciphylaxis, cryoglobulinemia, and end-stage renal disease. *ASAIO J* 1999; **45**: 229–33.

3 Boccaletti VP, Ricci R, Sebastio N *et al*. Penile necrosis. *Arch Dermatol* 2000; **136**: 261, 264.

4 Ecker RI, Schroeter AL. Acrodermatitis and acquired zinc deficiency. *Arch Dermatol* 1978; **114**: 937–9.

5 Gaveau D, Piette F, Cortot A *et al*. Cutaneous manifestations of zinc deficiency in ethylic cirrhosis. *Ann Dermatol Vénéréol* 1987; **114**: 39–53 [in French].

6 Boralevi F, Haftek M, Vabres P *et al*. Hereditary mucoepithelial dysplasia: clinical, ultrastructural and genetic study of eight patients and literature review. *Br J Dermatol* 2005; **153**: 310–8.

7 Lever WF, ed. *Pemphigus and Pemphigoid*. Springfield: Thomas, 1965.

8 Van Joost TH, Faber WR, Manuel HR. Drug-induced anogenital cicatricial pemphigoid. *Br J Dermatol* 1980; **102**: 715–8.

9 Gold S. Ulcerative colitis with pyodermite vegetante. *Proc R Soc Med* 1962; **55**: 1072–3.

10 Chan C-C, Thyong H-Y, Chan Y-C, Liao Y-H. Human papillomavirus type 5 infection in a patient with Hailey-Hailey disease successfully treated with imiquimod. *Br J Dermatol* 2007; **156**: 579–81.

11 Ray TL, Levine JB, Weiss W *et al*. Epidermolysis bullosa acquisita and inflammatory bowel disease. *J Am Acad Dermatol* 1982; **6**: 242–52.

12 Chouvet B, Guillet G, Perrot H *et al*. L'epidermolyse bulleuse acquisé: association à la maladie de Crohn. Revue generale à propos de deux observations. *Ann Dermatol Vénéréol* 1982; **109**: 53–63.

13 Livden JK, Thunold S, Schsonsby H. Epidermolysis bullosa acquisita and Crohn's disease. *Acta Derm Venereol (Stockh)* 1978; **58**: 241–4.

14 Pegum JS, Wright JT. Epidermolysis bullosa acquisita and Crohn's disease. *Proc R Soc Med* 1973; **66**: 234–5.

15 Toquero L, Briggs CD, Bassuini MM, Rochester JR. Anal ulceration associated with nicorandil: case series and review of the literature. *Colorectal Dis* 2006; **8**: 717–20.

16 Ogden S, Mukasa Y, Lyon CC, Coulson IH. Nicorandil-induced peristomal ulcers: is nicorandil also associated with gastrointestinal fistula formation? *Br J Dermatol* 2007; **156**: 575–612.

17 Busam KJ, Sachs DL, Coit DG *et al*. Eruptive melanotic macules and papules associated with adenocarcinoma. *J Cutan Pathol* 2003; **30**: 463–9.

18 Yamamoto T, Mukai H. Amyloidosis of the ano-sacral skin. *Jpn J Dermatol* 1981; **91**: 398–443.

19 Yanaghihara M, Fukishima N, Mori S. Anosacral amyloidosis. *Proceedings of 16th Congress on Dermatology*. Tokyo: Tokyo University Press, 1982: 922.

20 Mukai H, Eto H, Yamamoto T. Ano-sacral cutaneous amyloidosis. *Jpn J Dermatol* 1986; **96**: 1247–51.

21 Tappeiner J, Pfleger L. Granuloma gluteale infantum. *Hautarzt* 1971; **22**: 383–8.

22 Hamado T. Granuloma intertriginosum infantum. *Arch Dermatol* 1975; **111**: 1072–3.

23 Ortonne JP, Perrot H, Thivolet J. Granulome gluteal infantile (GGI): étude ultrastructurale. *Ann Dermatol Vénéréol* 1980; **107**: 631–4.

24 Maekawa Y, Sakazaki Y, Hayashibara T. Diaper area granuloma of the aged. *Arch Dermatol* 1978; **114**: 382–3.

Infections

Folliculitis and furunculosis

The anogenital area, particularly the buttocks and thighs of men, can be susceptible to infection with *Staphylococcus aureus*. Severe involvement with furunculosis and abscesses suggests an overlap with hidradenitis suppurativa. Although the high temperature and humidity of this area, combined with pressure [1] and friction, encourage colonization by staphylococci, primary pyococcal infections are now uncommon in countries with cultural or acquired habits of cleanliness. The perineal carriage of staphylococci [2] may not cause local lesions in the host, but is especially important in acting as a reservoir from which *S. aureus* may be disseminated to other sites or to eczematous lesions elsewhere. In adults, the carriage rate is of the order of 13–22%; in neonates it may be higher. Some persons are better 'dispersers' of staphylococci than others, and the organisms may remain (and even increase) after washing. The risk of dispersion of staphylococci from this site is of obvious importance in hospital operating theatres, where attempts have been made to minimize it by the provision of special clothing [3]. Nasal carriage, diabetes and immunodeficiency should be considered. Bacterial perianal infection is commonly seen in leukaemic patients [4].

Staphylococcal cellulitis

Cellulitis and abscess formation can complicate cysts, sinuses and fistulae. The differential diagnosis is given in Table 71.33.

Table 71.33 Differential diagnosis of anogenital cellulitis. (After Bunker [5]. © 2004, with permission from Elsevier.)

Hidradenitis suppurativa
Crohn's disease
Staphylococcal cellulitis
Streptococcal cellulitis
Gonococcal cellulitis
Fournier's gangrene and necrotizing fasciitis
Extramammary Paget's disease
Carcinoma erysipeloides (bladder and prostate)

Anorectal infection in patients with malignant disease is serious and potentially life-threatening [6]. Although some cases of anorectal cellulitis will respond to antibiotics alone, necrotizing fasciitis and Fournier's gangrene are risks. Swelling and fluctuance signifying abscess formation may develop late. It is difficult to decide on the timing of surgery. Perianal infiltration, ulceration or abscess occurs in 5% of haematological malignancies and may rarely be the presenting feature [7].

Streptococcal dermatitis/perianal cellulitis

This syndrome in children [8] probably has a corollary in adults [9]. A child may present with pruritus, painful defaecation, anal soreness and redness (without nappy/diaper rash) and satellite pustulosis of the buttocks. Examination of the anus shows a pronounced, sharply demarcated, boggy erythema and causes discomfort to the child. Rarely, there may be a systemic presentation with fever and rash [10]. It is much more common in boys, and the penis may be involved. An association with acute guttate psoriasis has been reported [11,12]. Group A β-haemolytic streptococci is the usual cause, although *S. aureus* has been retrieved from one child who also had satellite pustules on the buttocks [13]. Proctocolitis has occurred [14]. Perianal disease may be misinterpreted as sexual abuse [15]. Streptococcal infection of the upper respiratory tract in other members of the family may be found. Communal bathing has been blamed for outbreaks. Treatment is generally with systemic penicillin or topical mupirocin, or erythromycin if clinically less acute [16].

References

1 Felman YM, Kikitas JA. Non-venereal anogenital lesions. *Cutis* 1980; **26**: 347, 351, 354, 357.

2 Noble WC, Somerville DA. In: Rook AJ, ed. *Microbiology of Human Skin*, Vol. 2. *Major Problems in Dermatology*. London: Saunders, 1974.

3 Mitchell NJ, Gamble DR. Clothing design for operating room personnel. *Lancet* 1974; **ii**: 1133–6.

4 Carlson GW, Ferguson CM, Amerson JR. Perianal infections in acute leukaemia. *Am Surg* 1988; **54**: 693–5.

5 Bunker CB. *Male Genital Skin Disease*. London: Saunders, 2004.

6 Glenn J, Cotton D, Wesley R, Pizzo P. Anorectal infections in patients with malignant diseases. *Rev Infect Dis* 1988; **10**: 42–52.

7 Vanheuverzwyn R, Delannoy A, Michaux JL, Dive C. Anal lesions in haematologic disorders. *Dis Colon Rectum* 1980; **23**: 310–2.

8 Peltola H. Images in clinical medicine: bacterial perianal dermatitis. *N Engl J Med* 2000; **342**: 1877.

9 Neri I, Bardazzi F, Maraduri S, Patrizi A. Perianal streptococcal dermatitis in adults. *Br J Dermatol* 1996; **135**: 796–52.

10 Vélez A, Moreno JC. Febrile perianal streptococcal dermatitis. *Pediatr Dermatol* 1999; **16**: 23–4.

11 Rehder PA, Eliezer ET, Lane AT. Perianal cellulitis. *Arch Dermatol* 1988; **124**: 702–4.

12 Patrizi A, Costa AM, Fiorillo L *et al*. Perianal streptococcal dermatitis associated with guttate psoriasis and/or balanoposthitis: a study of five cases. *Pediatr Dermatol* 1994; **11**: 168–71.

13 Montemarano AD, James WD. *Staphylococcus aureus* as a cause of perianal dermatitis. *Pediatr Dermatol* 1993; **10**: 259–62.

14 Guss C, Larsen JG. Group A beta-hemolytic streptococcal proctocolitis. *Pediatr Infect Dis* 1984; **3**: 442.

15 Duhra P, Ilchyshyn A. Perianal streptococcal cellulitis with penile involvement. *Br J Dermatol* 1990; **123**: 793–6.

16 Paradisi M, Cianchini G, Angelo C *et al*. Efficacy of topical erythromycin in treatment of perianal streptococcal dermatitis. *Pediatr Dermatol* 1993; **10**: 297–8.

Perianal abscess

Perianal/anorectal/ischiorectal abscess presents with painful swelling and suppuration and is commonly complicated by anal fistula. The likeliest cause of perianal abscess is infection of the anal glands, but trauma (e.g. impacted fish bone), diabetes and anal cancer predispose to its development. Crohn's disease, hidradenitis, tuberculosis and *Enterobius vermicularis* (threadworm/pinworm) [1] should be considered.

Ecthyma gangrenosum

Gram-negative organisms are seldom pathogenic unless the balance of the skin flora is grossly disturbed. *Pseudomonas aeruginosa* may be found in deep ulcers and fissures. Ecthyma gangrenosum has a predilection for the anogenital (and acral) extremities. The prognosis is poor. Ill patients with leukaemia may develop a necrotizing anorectal ulcer caused by *Pseudomonas*, presenting with severe anal pain, anorectal ulceration and septicaemia. Anorectal ulceration may be the portal of entry of the infection or a consequence of it [2]. The mortality is high.

Thread/pinworms

Thread/pinworms can cause pruritus ani. Excoriations, eczematization and impetiginization may be present, but often there are few physical signs. Perianal abscess may occur very rarely [1].

Common mycoses

Candidosis causes a bright red, glazed area, often with outlying small pustules, and may spread to the groins or natal cleft. Microscopy and culture distinguish it from other fungal infections, and from psoriasis and pyococcal infections.

The well-defined, scaly, circinate edge, the spread and the chronicity of *Trichophyton rubrum* infection offer clues to diagnosis, which can be confirmed by microscopy and culture. However, prior treatment with corticosteroids may disguise the appearance. The possibility of fungal infection should therefore be considered in all unusual forms of perianal dermatitis.

Necrotizing infections

A number of overlapping, severe gangrenous and necrotizing diseases may affect the anorectal and perineal (and genital) skin and subcutaneous tissues. Although they may often be a complication of surgery or trauma, they are mentioned here because of the crucial importance of their early recognition and treatment (see also Chapter 30 and p. 71.31). These conditions are described under several names [3]:

Clostridial and non-clostridial gangrene [3–5]; streptococcal cellulitis and myositis; streptococcal toxic shock syndrome; synergistic necrotizing cellulitis; necrotizing fasciitis [6–8]; Meleney's progressive bacterial synergistic gangrene [9]; synergistic gangrene [10]; Fournier's gangrene.

Clinical features. Although middle-aged and elderly subjects are most often affected, the conditions can follow trauma in young adults, and the prognosis in the latter, given vigorous early treatment, is good [3]. They have also been described in children [11], particularly following circumcision or scalds, but sometimes after a bout of severe diarrhoea [12], or even spontaneously [13]. The problem may present as a primary perirectal abscess in the perineum (or on the scrotum or labia). Pain is generally the first symptom, and may be severe. A distinct dusky red to black spot may appear in affected tissue and is of ominous significance. Tenderness and a dusky erythema extend with extreme rapidity to involve wide areas, and all the perirectal and perineal spaces (hence the terms fasciitis and myositis). Crepitus is an important feature, as is the presence of a dark brown, turbid fluid without pus. Many patients are diabetic [3,7] or leukaemic; in these, the mortality is much higher than the overall rate of 12–25% [7]. A perianal distribution, old age and delay in treatment also greatly reduce the survival rate.

Bacteriology. Swabs should be taken from the margin of the lesion [10]. An immediate Gram stain will distinguish clostridial infections by the finding of large Gram-positive rods. *Clostridium perfringens* was the most common organism in one series [3], but other clostridia, aerobic and anaerobic streptococci, and *Pseudomonas* species [11] have all been isolated. Anaerobes may easily be missed. A wide variety of secondary organisms are commonly cultured.

Treatment. Early recognition and immediate and aggressive treatment are essential in this devastating condition. Electrolyte and fluid balance must be established, and high-dosage antibiotic therapy started without waiting for the result of culture. This will normally consist of intravenous penicillin (24–30 million units/day [3]) together with a broad-spectrum antibiotic, usually an aminoglycoside or a cephalosporin; this regimen can be modified later.

The most important single therapeutic manoeuvre is rapid and extensive debridement of all affected tissue. Other surgical procedures, such as colostomy, may also be necessary. The value of hyperbaric oxygen [14] is disputed.

References

1 Mortensen NJ, Thomson JP. Perianal abscess due to *Enterobius vermicularis*: report of a case. *Dis Colon Rectum* 1984; **27**: 677–8.

2 Givler RL. Necrotizing lesions associated with *Pseudomonas* infection in leukaemia. *Dis Colon Rectum* 1969; **12**: 438–40.

3 Bubrick MP, Hitchcock CR. Necrotizing anorectal and perineal infection. *Surgery* 1979; **86**: 655–62.

4 Bessman AN, Wagner W. Non-clostridial gas gangrene: report of 48 cases and a review of the literature. *JAMA* 1975; **233**: 958–63.

5 Skiles MS, Covert GK, Fletcher HS. Gas producing clostridial and nonclostridial infections. *Surg Gynecol Obstet* 1978; **147**: 65–7.

6 Fisher JR, Conway MJ, Takeshita RT *et al.* Necrotizing fasciitis: importance of roentgenographic studies for soft tissue gas. *JAMA* 1979; **241**: 803–6.

7 Oh C, Lee C, Jacobson JH. Necrotizing fasciitis of the perineum. *Surgery* 1982; **91**: 49–51.

8 Rosenberg PH, Shuck JM, Tempest BD *et al.* Diagnosis and therapy of necrotizing soft tissue infections of the perineum. *Ann Surg* 1978; **187**: 430–4.

9 Meleney FL. Hemolytic streptococcus gangrene. *Arch Surg* 1924; **9**: 317–64.

10 Flanigan RC, Kursh FD, McDougal WS *et al.* Synergistic gangrene of the scrotum and penis secondary to colorectal disease. *J Urol* 1978; **119**: 369–71.

11 Rabinowitz R, Lewin EB. Gangrene of the genitalia in children with *Pseudomonas* sepsis. *J Urol* 1980; **124**: 431–2.

12 Chuang JH, Wong KS. Necrotizing perianal infection in children. *J Pediatr Gastroenterol Nutr* 1990; **10**: 409–12.

13 Boisseau AM, Sarlangue J, Perel Y *et al.* Perineal ecthyma gangrenosum in infancy and early childhood: septicaemic and non-septicaemic forms. *J Am Acad Dermatol* 1992; **27**: 415–8.

14 Schweigel JF, Shim SS. A comparison of the treatment of gas gangrene with and without hyperbaric oxygen. *Surg Gynecol Obstet* 1973; **136**: 969–70.

Dermatological aspects of sexually transmitted disease

Gonorrhoea can result in anal inflammation and discharge, or an oedematous perianal dermatitis with multiple fissures and erosions.

Chancroid may cause extremely painful anal lesions instead of the classic multiple soft chancres. The initial rapidly ulcerating papule of granuloma inguinale (see Chapter 34) may occur in the perianal region in homosexual males. It is soft, painless and bleeds easily on trauma. It may be hypertrophic, sclerotic or phagedenic. There is normally no regional adenopathy, but a 'pseudobubo' may be present. In the anal canal, the lesion never extends beyond the stratified epithelium and strictures do not occur, but anal stenosis or, rarely, epitheliomatous change can supervene.

Lymphogranuloma venereum is increasing in frequency in homosexual men. It causes an ulcerative proctitis and is often misdiagnosed as ulcerative colitis or Crohn's disease [1]. If undiagnosed, lymphogranuloma venereum causes widespread vegetating and scarring lesions of the genitoperineal area. The Frei and complement fixation tests distinguish it from hidradenitis suppurativa.

Syphilis (see Chapter 34) [2] is becoming more common in homosexual men. It should never be forgotten as a possible cause of anal ulceration. Anal chancres are often mistaken for fissures; at the anal margin their significance may not be appreciated. Pain on defaecation or at night may be severe if there is secondary infection of the chancre, but is often absent. The posterior midline is the site of election. Bilateral lymphadenopathy is extremely rare with other perianal ulcers. Dark-ground examination may not be diagnostic if lubricants or ointments have been used. Discharge and bleeding, fissures (especially laterally) and fistulae should also arouse suspicion of anorectal primary syphilis. Painful syphilitic proctitis in the absence of anal lesions can occur [3,4]. Moist, flat condylomata lata (Fig. 71.44) can affect all anogenital intertriginous sites, and the differential diagnosis includes intertrigo as well as warts, lichen planus and bowenoid papulosis. The granulomatous gumma may affect the anal area as an ulcer, a white plaque or as an atrophic scar.

Perianal viral warts (condylomata acuminata) (Fig. 71.45) occasionally occur in infants and young children, but they are



Fig. 71.44 Condylomata lata. (Courtesy of Dr S.C. Gold, London, UK.)



Fig. 71.45 Perianal condylomata acuminata. (Courtesy of Dr F.A. Ive, Durham, UK.)

normally seen in young adults, and are not always sexually transmitted. They may be extraordinarily profuse, extending into the anal canal, especially in homosexuals or in immunodeficient (congenital or acquired) subjects in whom there is also a higher risk of progression to dysplasia and frank malignancy [5]. For example, anogenital warts are common in HIV-positive males, nearly half of whom show histological signs of intraepithelial neoplasia. The clinical diagnosis of HPV is usually certain but condylomata lata (secondary syphilis), LP, molluscum contagiosum and BP enter the differential diagnosis. Solitary lesions have a wider differential diagnosis, including giant condyloma and squamous carcinoma. Biopsy should be performed if there is diagnostic doubt or if dysplasia or worse is suspected. Morphology and histology cannot distinguish virus-associated from non-virus-associated lesions; molecular techniques may be preferable but are not yet routinely available [6]. Patients with anogenital warts, and their partners, may require full STD and sometimes colorecral assessment. Anogenital HPV can be very difficult to treat.

A phenomenon of chronic erosive and verrucous herpes simplex as part of immunoreconstitution disease has been described in HIV infection [7].

Table 71.34 Causes of anal ulceration in HIV infection.

Idiopathic
Haemorrhoids
Fissures
Sepsis (abscess, fistula)
Syphilis (chancre)
Herpes simplex
Cytomegalovirus
Kaposi's sarcoma
Non-Hodgkin's lymphoma
Squamous carcinoma

Human immunodeficiency virus infection

Perianal disease can be problematic in homosexual men [8]. Table 71.34 lists the main causes of anal ulceration in HIV infection. Biopsy with special stains and culture is mandatory.

Other problems in HIV infection, including psoriasis, warts, intraepithelial neoplasia, squamous carcinoma and Kaposi's sarcoma are discussed in Chapter 35.

CMV has been recorded in persistent perineal ulcers in immunosuppressed patients [9]. EBV DNA has been found in epithelial cells from the anal canals of asymptomatic HIV-positive male homosexuals, indicating possible sexual transmissibility [10]. Herpes simplex, gonorrhoea and anal warts were commonly associated in a US study on early HIV positivity [11]. Similar findings relate to a central African group with more advanced disease [12]. The importance of primary rectal syphilis has been emphasized [3]. Amoebiasis [13] may be overlooked. Dark-ground examination, and culture and microscopy for ova, should be obligatory [14]. In the absence of organisms, if pus cells are found, a rectal biopsy is indicated. Kaposi's sarcoma of the rectum can occur in HIV-positive males [15]. The relationship of KS to anoreceptive anal intercourse and HHV 8 is discussed in Chapter 35 [16,17].

References

1 Collins L, White JA, Bradbeer C. Lymphogranuloma venereum. *BMJ* 2006; **332**: 66.

2 McMillan A, Smith IW. Painful anal ulceration in homosexual men. *Br J Surg* 1984; **71**: 215–6.

3 Gluckman JB, Kleinman MS, May AG. Primary syphilis of rectum. *NY State J Med* 1974; **74**: 2210–1.

4 Akdamar K, Martin RJ, Ichinose H. Syphilitic proctitis. *Am J Dig Dis* 1977; **22**: 701.

5 Daneshpouy M, Socic G, Clavel C *et al.* Human papillomavirus infection and anogenital condyloma in bone marrow transplant recipients. *Transplantation* 2001; **71**: 167–9.
6 Strand A, Andersson S, Zehbe I, Wilander E. HPV prevalence in anal warts tested with the MY09/MY11 SHARP signal system. *Acta Dermatol Venereol* 1999; **79**: 226–9.
7 Fox PA, Barton SE, Francis N *et al.* Chronic erosive herpes simplex virus infection of the penis: a possible immune reconstitution disease. *HIV Med* 1999; **1**: 10–8.
8 Carr ND, Mercey D, Slack WW. Non-condylomatous perianal skin disease in homosexual men. *Br J Surg* 1989; **76**: 1064–6.
9 Horn TD, Hood AF. Cytomegalovirus is predictably present in perineal ulcers of immunosuppressed patients. *Arch Dermatol* 1990; **126**: 642–4.
10 Naher H, Lenhard B, Wilms J, Nickel P. Detection of Epstein–Barr virus DNA in anal scrapings from HIV-positive homosexual men. *Arch Dermatol Res* 1995; **287**: 608–11.
11 Berger RS, Stoner MF, Hobbs ER *et al.* Cutaneous manifestations of early human immunodeficiency virus exposure. *J Am Acad Dermatol* 1988; **19**: 298–303.
12 Hira SK, Wadhawam D, Kamanga J *et al.* Cutaneous manifestations of human immunodeficiency virus in Lusaka, Zambia. *J Am Acad Dermatol* 1988; **19**: 451–7.
13 Robertson DHH, McMillan A, Young H. Homosexual transmission of amoebiasis. *J R Soc Med* 1982; **75**: 564.
14 Felman YM, Nikitas JA. Sexually transmitted diseases in the male homosexual. *Cutis* 1982; **30**: 706–24.
15 Lorenz HP, Wilson W, Leigh B, Schecter WP. Kaposi's sarcoma of the rectum in patients with the acquired immune deficiency syndrome. *Am J Surg* 1990; **160**: 681–2.
16 Chang Y, Cesarman E, Pessin MS *et al.* Identification of herpes virus-like DNA sequences in AIDS-associated Kaposi's sarcoma. *Science* 1994; **266**: 1865–9.
17 Lin JC, Lin SC, Mar EC *et al.* Is Kaposi's sarcoma-associated herpes virus detectable in semen in HIV infected homosexual men? *Lancet* 1995; **346**: 1601–2.

Miscellaneous infections

Erythrasma, present also at other sites, was found in 15 of 81 patients with pruritus ani examined using Wood's light [1]; all were males. In infants, coxsackie infections can cause a transient papular or papulovesicular eruption of the perianal area and buttocks. An erythematous, desquamating, perineal eruption occurring in the first week of the disease may be the first cutaneous feature in up to two-thirds of children with Kawasaki disease [2].

Fournier's gangrene and its differential diagnosis (Table 71.22) are discussed on pp. 71.30–71.31 and 71.92–71.93. Anorectal presentation is more serious than urogenital disease because the presentation may be more cryptic and there may be a longer delay in diagnosis [3].

Perianal tuberculosis (see Chapter 31) [4] is seen where tuberculosis is common, but must always be considered, even in Western Europe [5]. A primary lesion is exceptional; the accompanying unilateral lymphadenopathy is an important feature. Indolent, irregular, painful ulcers, fistulae and abscesses may be difficult to distinguish from those accompanying Crohn's disease [6]. Lupus vulgaris and verrucous tuberculosis may spread widely over the buttocks and postanal region, or assume a fungating and vegetating appearance. Tuberculosis cutis orificialis is thought to arise from autoinoculation of organisms contained in swallowed sputum from pulmonary lesions [7]. It may occur in the immunocompromised and has been reported in association with Evans' syndrome (autoimmune haemolytic anaemia and immune thrombocytopenia) [8]. Perineal scrofuloderma (secondary skin involvement from underlying lymph node disease) may cause diagnostic confusion [9]. Pyoderma gangrenosum, Crohn's disease, hidradenitis, neoplasia, artefact, sexually transmitted diseases, amoebiasis and deep mycoses appear in the differential diagnosis [10].

Daughter yaws, initially papules but rapidly becoming ulcerated crusted plaques, have a predilection for periorificial sites on the face and around the perineum.

The giant condyloma of Buschke–Löwenstein (see pp. 71.44 and 71.76–71.77) is rare: it is probably HPV-related [11].

Non-genital herpes simplex (see Chapter 33) occurs frequently around the pelvic girdle. Vaccinia, which was usually acquired by indirect transmission [12], is now never seen. Perianal orf occurs occasionally [13]. Perianal CMV ulceration is extremely rare in the immunocompetent. It occurs in HIV infection (see below), and has been reported in a man with prior perianal HSV on immunosuppressive medication for idiopathic thrombocytopenic purpura [14].

Sacral herpes zoster [11] is rare and can be cryptic in presentation; when involving S2–S4 or, less commonly, the ileoinguinal segment of L1–L2, it may cause significant morbidity from acute cystitis or urinary or faecal retention [15–17]. Hospitalization and urological and colorectal assessment are required, and treatment should be with intravenous aciclovir. AIDS has presented as anogenital herpes zoster [18].

Trichosporosis is a common cause of genitocrural and perianal intertrigo in India. Symptoms are itching or burning. Accompanying the intertrigo may be scaly papules. Coexisting dermatophyte, *Candida*, trichomycosis and erythrasma infection may be found. Topical dequalinium chloride is used for treatment in India [19].

Amoebiasis (see Chapter 37) of the perianal skin [20] is usually associated with bowel infections but, where the disease is endemic, direct inoculation of abraded skin or operation wounds can occur. Abscesses and fistulae may at first be indolent and symptomless. Ulcers typically extend slowly, with serpiginous outlines, firm cord-like edges and a whitish slough [21]. Sometimes, however, progression is rapid and remorseless, until a phagedenic ulcer completely destroys the perianal and sacral tissues [22]. A black, foul-smelling eschar is surrounded by a violaceous edge, resembling pyoderma gangrenosum. The patient is extremely ill. Vegetating or condyloma-like lesions of intermediate severity occur less frequently. Amoebiasis should be suspected when such a lesion occurs unexpectedly in the course of 'ulcerative colitis' or in a prolonged, mild, undiagnosed colitis. Cases have been described in infants [23]. Destructive perianal and buttock ulceration may masquerade as squamous carcinoma; however, very rarely, concomitant carcinoma has been reported [24]. The diagnosis is made by finding the *Entamoeba* species in a biopsy specimen from the edge of a lesion (which is always secondarily infected) or by examination, while warm, of a fresh high sigmoidoscopy swab. Treatment with metronidazole may be dramatically effective, but in severe cases surgery may also be required.

Perineal granulomatous lesions are a rare manifestation of schistosomiasis (bilharziasis), which may present as pruritic papules in the genital, umbilical and perineal regions in countries where it is endemic [25,26]. It is usually preceded by rectal or intestinal symptoms. The papules and nodules may be skin-coloured, pink or brown, scattered or grouped, affecting the penis, scrotum and vulva. They can spread onto the perineum and around the anus, and may develop into soft warty vegetating

lesions, but remain relatively asymptomatic. Genital lesions simulating warts have been seen in travellers returning from endemic areas [27]. The unusual occurrence of anogenital lesions results from ova shed by worms that have entered the perineal vessels [25]. Viable or calcified ova are found in the dermis.

The perianal region is an extremely rare site for cutaneous leishmaniasis. One case presenting as an itchy plaque has been described. The patient frequently defaecated in the open when hunting in Sardinia and presumably thereby came to be bitten by the *Phlebotomus* vector [28].

Larva currens, caused by *Strongyloides stercoralis*, commonly occurs around the anus and on the buttocks and is therefore a cause of excoriations at these sites [29]. Likewise, cutaneous larva migrans resulting from the dog hookworm *Ancylostoma brasiliense* may occur around the pelvic girdle.

Perianal histoplasmosis and blastomycosis have also been recorded. Actinomycosis has resulted in multifocal perineal and buttock ulceration in glucose-6-phosphate dehydrogenase (G6PD) deficiency [30]. Ulcerating and vegetating lesions, often unrecognized and of long duration, have followed trauma in patients with actinomycosis [31]. Correct diagnosis depends on histological confirmation, but the yellow or red granular pus should arouse suspicion [30].

Classical lesions of scabies commonly involve the buttocks, and nodules are sometimes seen in the perineum.

References

1 Bowyer A, McColl I. Erythrasma and pruritus ani. *Acta Derm Venereol (Stockh)* 1971; **51**: 444–7.

2 Friter BS, Lucky AW. The perineal eruption of Kawasaki syndrome. *Arch Dermatol* 1988; **124**: 1805–10.

3 Enriquez JM, Moreno S, Devesa M *et al.* Fournier's syndrome of urogenital and anogenital origin: a retrospective, comparative study. *Dis Colon Rectum* 1987; **36**: 33–7.

4 Strescobich D, Donadio R, Aguilar OG *et al.* Fistulas anales de etiología poco frecuente. *Prensa Med Argent* 1969; **56**: 622–3.

5 Lé Bourgeois PC, Poynard T, Modai J *et al.* Ulceration perianale: ne pas oublier la tuberculose. *Presse Med* 1984; **13**: 2507–9.

6 Morson BC. Histopathology of Crohn's disease. *Proc R Soc Med* 1968; **61**: 79–81.

7 Leon-Mateos A, Sánchez-Aguilar D, Lado F, Toribio J. Perianal ulceration: a case of tuberculosis cutis orificialis. *J Eur Acad Dermatol Venereol* 2005; **19**: 364–6.

8 Kim SW, Choi SW, Cho BK *et al*. Tuberculosis cutis orificialis: an association with Evans' syndrome. *Acta Derm Venereol* 1995; **75**: 84–5.

9 Poláková K. Atypically localized scrofuloderma. *Bratisl Lek Listy* 1993; **94**: 536–8.

10 Betlloch I, Bañuls J, Sevila A *et al.* Perianal tuberculosis. *Int J Dermatol* 1994; **33**: 270–1.

11 Alexander RM, Kaminsky DB. Giant condyloma acuminatum (Buschke–Löwenstein tumour) of the anus. *Dis Colon Rectum* 1979; **22**: 561–5.

12 Bessiere L, Allain D, Meleville J. La vaccine ano-genitale. *Ann Dermatol Vénéréol* 1979; **105**: 339–41.

13 Kennedy CTC, Lyell A. Perianal orf. *J Am Acad Dermatol* 1984; **11**: 72–4.

14 Abe M, Sawamura D, Ito S *et al*. Perianal cytomegalovirus ulcer following herpes simplex virus in a patient with idiopathic thrombocytopenic purpura treated with immunosuppressants. *Clin Exp Dermatol* 2005; **30**: 596–7.

15 Fugelso PD, Reed WB, Newman SB, Beamer JE. Herpes zoster of the anogenital area affecting urination and defaecation. *Br J Dermatol* 1973; **89**: 285–8.

16 Waugh MA. Herpes zoster of the anogenital area affecting urination and defaecation [Letter]. *Br J Dermatol* 1974; **90**: 235.

17 Weaver SM, Keelly AP. Herpes zoster as a cause of neurogenic bladder. *Cutis* 1982; **29**: 611–2.

18 Thune P, Andersson T, Skjorten F. AIDS manifesting as anogenital herpes zoster eruption: demonstration of virus-like particles in lymphocytes. *Acta Derm Venereol (Stockh)* 1983; **63**: 540–3.

19 Kamalam A, Senthamilselvi A, Ajuthades K *et al.* Cutaneous trichosporosis. *Mycopathologia* 1988; **101**: 167–75.

20 Lord PH, Sakellariades P. Perianal skin gangrene due to amoebic infection in a diabetic. *Proc R Soc Med* 1973; **66**: 677–8.

21 Smith JN, Winship DH. Complications and extraintestinal problems in inflammatory bowel disease. *Med Clin North Am* 1980; **64**: 1161–71.

22 Venkataramaiah NR, Reinaerta HHM, Van Roalte JE *et al.* Pseudomalignant cutaneous amoebiasis. *Trop Doctor* 1982; **12**: 162–3.

23 Wynne JM. Perineal amoebiasis. *Arch Dis Child* 1980; **55**: 234–6.

24 Zawahry ME. Cutaneous amoebiasis. *Indian J Dermatol* 1966; **11**: 77–8.

25 Adeyemi-Doru FAB, Osoba OA, Junaid TA. Perigenital cutaneous schistosomiasis. *Br J Vener Dis* 1979; **55**: 446–9.

26 Cohn M, Loubiere R, Guillaume A *et al.* Les lesions cutanées de bilharziose: a propos de 14 observations. *Ann Dermatol Vénéréol* 1980; **107**: 759–67.

27 Goldsmith PC, Leslie TA, Sams V *et al.* Lesions of schistosomiasis mimicking warts on the vulva. *BMJ* 1993; **307**: 556–7.

28 Aste N, Fumo G, Pau M, Biggio P. Atypical localization of cutaneous leishmaniasis. *Acta Derm Venereol* 1997; **77**: 85–6.

29 Ho PL, Luk WK, Chan ACL, Yuen KY. Two cases of fatal strongyloidiasis in Hong Kong. *Pathology* 1997; **29**: 324–6.

30 Millet P, Sonneck J-M, Lanternier G *et al.* Actinomycose perineofessiere et deficit en G6PD. *Ann Dermatol Vénéréol* 1982; **109**: 789–90.

31 Grigoriu D, Delecretaz J. Actinomyocose peri-anale pruritive. *Ann Dermatol Vénéréol* 1981; **108**: 159–61.

Benign tumours

Many entities are encountered in the perineal/perianal area. Angiomas and angiokeratomas are common; basal cell papillomas may be mistaken for viral warts or BP, as may melanocytic naevi; inguinogenital epidermoid cysts may become infected, and lesions containing molluscum contagiosum have been described; pilar cyst, including giant forms, is much rarer. Giant congenital perineal haemangiomas can be associated with widespread anogenital abnormality involving the genitalia, lower GI tract, urinary tract and spinal cord (PELVIS syndrome) [1].

Haemorrhoids

Haemorrhoids/piles (Latin *pila*, a ball) are dilatations in the venous system draining the anus, mucosal prolapse or loose tethering of mucosa to the anal wall [2]. Symptoms are rectal bleeding, mucous discharge, pruritus ani and prolapse. The complications of piles are thrombosis, strangulation, ulceration, fibrosis, infection and abscess, which give rise to pain. Patients presenting with these symptoms should be assessed by a proctologist, and by proctoscopy and sigmoidoscopy. Signs depend on the presentation. Perianal skin tags from fibrosed piles are extremely common. The differential diagnosis includes distal bowel cancer, as well as naevi, Crohn's disease, KS and perianal metastases. Treatment is the domain of the colorectal surgeon and gastroenterologist.

Premalignant dermatoses and frank malignancies

The anogenital area is not exposed to solar radiation, the principal cutaneous carcinogen. Treatment of pruritus in the past with radiotherapy or tar preparations, and the use of radiotherapy for gynaecological malignancy, carry theoretical hazards and can occasionally be incriminated in carcinogenesis. However, they do not appear to have influenced greatly the frequency of perineal tumours. Post-granulomatous scarring is an important back-

ground to perianal malignancy in some parts of the world, and other chronic inflammatory processes, such as LS, are a potential hazard. There are cases where condylomata acuminata have preceded SCC of the anal or perianal skin [3,4] and HPV has become a major suspect in the precancerous process.

Porokeratosis

Anogenital porokeratosis of Mibelli is rare, but classic lesions have been found on the penis, scrotum and in the natal cleft. Ulceration may occur [5]. Porokeratosis may be confused with psoriasis, Bowen's disease, granuloma annulare or LP. Histopathology confirms the diagnosis [6].

Anal intraepithelial neoplasia

Anal intraepithelial neoplasia (AIN) describes full-thickness dysplasia of the anus and perianal skin [7]. It can present relatively asymptomatically as red, shiny or scaly patches like Bowen's disease, or as warty lesions like BP. AIN is frequently associated with homosexuality, anal warts, HPV and HIV, although it is not a prominent feature of other conditions involving immunosuppression. Women with anogenital Bowen's disease have an increased risk of intraepithelial neoplasia or invasive malignancy elsewhere in the genital tract [8,9], and a full gynaecological examination is thus obligatory in such cases. The risk of AIN progression to carcinoma may not be as low as originally thought [10]. Immunoreconstitution with highly active antiretroviral treatment (HAART) may not achieve regression of AIN [11]. Routine screening of the HIV-positive patient with anal cytology is advocated [11]. Treatment options are similar to those for PIN (see p. 71.39). Topical imiquimod shows promise [12]. Expert proctological advice should be sought. Relapse is common.

Carcinoma of the anus

Anogenital squamous carcinoma is sometimes called epidermoid carcinoma. Fifty-six per cent of all anal carcinomas are of the squamous variety [13]. They are slightly more common in women, but seem to be more aggressive in men [14]. In Denmark, the incidence of anal carcinoma has tripled since 1960 to 0.74 cases per 100 000 population [15].

Although associations with smoking, cervical intraepithelial dysplasia and changing sexual habits, including homosexual anal intercourse, have been postulated [15,16], and coexistent Crohn's disease has been said to be associated with a 10-fold increase in anal carcinoma [17], the aetiology is not clearly understood. HPV is implicated [18,19], especially in verrucous carcinoma (see below) [20]. Anal carcinoma is often associated with a history of anogenital warts. More than 90% of anogenital condylomata contain HPV 6 or 11, although these subtypes are not associated with cancer, and it is rare for condylomata to contain HPV 16, which has a well-documented association with anal carcinoma. Homosexual men have a higher incidence of both perianal warts and anal carcinoma (both *in situ* and invasive), and this may be related to receptive anal intercourse [16], and HPV as well as other sexually transmitted diseases such as gonorrhoea, herpes simplex and *Chlamydia trachomatis* infection [21]. These infections are also risk factors for anal carcinoma in heterosexual men and women, as is cigarette smoking [22]. A role for seminal fluid prostaglandins in homosexual anal cancer has been proposed [23]. Immunosuppression, including by HIV infection, is a risk factor for AIN and anal cancer [24] (see Chapter 35: increased risk ×50). A case of Peutz–Jeghers syndrome associated with anal squamous carcinoma has been reported [25].

Diagnosis can present difficulties. Symptoms may include bleeding, pain, presence of a mass and change in bowel habit. Examination will reveal a hard mass that may be flat, raised or polypoid [26]. Squamous carcinoma should be suspected in all noduloulcerative anal and perianal disease, especially in the context of LS, LP, hidradenitis suppurativa, intraepithelial neoplasia and immunocompromise.

Regarding the differential diagnosis [27], it must be appreciated that anal carcinoma often presents with similar symptoms to benign anal lesions such as piles and fissures (pruritus, discomfort or pain, and bleeding). The most common tumours of the anal margin are viral warts, which are distinguished by their multiplicity, their lack of induration and ulceration, and their rapid evolution. Rarely, these may give rise to anal carcinoma [28]. Syphilitic condylomas are also multiple and not indurated. A syphilitic chancre of the anal margin or canal may be more easily mistaken for carcinoma. Amoebiasis and tuberculosis must also be considered. The differential diagnosis includes the manifestations of intraepithelial neoplasia (and the differential diagnosis of these), erosive or ulcerative sexually transmitted disease, basal cell carcinoma, Kaposi's sarcoma, hidradenitis suppurativa, Crohn's disease, pyoderma gangrenosum and artefact. The differential diagnosis also includes ischiorectal or perianal abscess [29–31]. Colorectal assessment should be sought. Proctoscopy and sigmoidoscopy are necessary to exclude anorectal cancer [29–31].

An important consideration in the management of anal carcinoma is the preservation of sphincter function, and this frequently involves combined radiotherapy and chemotherapy [32,33]. Surgical excision of the tumour, and of the inguinal lymph nodes when these are involved, is the treatment of choice. For small, well-differentiated tumours, particularly adenocarcinomas, a local excision and repair is the ideal. Small squamous carcinomas may respond well to radiotherapy. Lymphatic or haematogenous dissemination of anogenital cancer dictates individualized multidisciplinary management. The prognosis for anal carcinoma is variable [33].

References

1 Girard C, Bigorre M, Guillot B, Bessis D. PELVIS syndrome. *Arch Dermatol* 2006; **142**: 884–8.

2 Nisar PJ, Scholefield JH. Clinical review: managing haemorrhoids. *BMJ* 2003; **327**: 847–51.

3 South LM, O'Sullivan JP, Gazet JC. Giant condylomata of Buschke and Löwenstein. *Clin Oncol* 1977; **3**: 107–15.

4 Sturm JT, Christenson CE, Vecker JH *et al.* Squamous cell carcinoma of the anus arising in a giant condyloma acuminatum. *Dis Colon Rectum* 1975; **18**: 147–51.

5 Watanabe T, Murakami T, Okochi H *et al*. Ulcerative porokeratosis. *Dermatology* 1998; **196**: 256–9.

6 Levell NJ, Bewley AP, Levene GM. Porokeratosis of Mibelli on the penis, scrotum and natal cleft. *Clin Exp Dermatol* 1994; **19**: 77–8.

7 Zbar AP, Fenger C, Efron J *et al*. The pathology and molecular biology of anal intraepithelial neoplasia: comparisons with cervical and vulvar intraepithelial carcinoma. *Int J Colorectal Dis* 2002; **17**: 203–15.

8 Franklin EW, Rutledge FD. Epidemiology of epidermoid carcinoma of the vulva. *Obstet Gynecol* 1972; **39**: 165–72.

9 Reynolds VH, Madden JJ, Franlin JD *et al.* Preservation of anal function after total excision of the anal mucosa for Bowen's disease. *Ann Surg* 1984; **199**: 563–8.
10 Morgan AR, Miles AJ, Wastell C. Anal warts and squamous carcinoma *in situ* of the anal canal. *J R Soc Med* 1994; **87**: 15.
11 Palefsky JM, Holly EA, Efirdc JT, Da Costa M, Jay N, Berry JM et al. Anal intraepithelial neoplasia in the highly active antiretroviral therapy era among HIV-positive men who have sex with men. *AIDS* 2005; **19**: 1407–14.
12 Wieland U, Brockmeyer NH, Weissenborn SJ *et al*. Imiquimod treatment of anal intraepithelial neoplasia in HIV-positive men. *Arch Dermatol* 2006; **142**: 1438–44.
13 Boman B, Moertel CG, O'Connell MJ. Carcinoma of the anal canal. *Cancer* 1984; **54**: 114–25.
14 Serota AI, Weil M, Williams RA. Anal cloacogenic carcinoma. *Arch Surg* 1981; **116**: 456–9.
15 Frisch M, Melbye M, Moller H. Trends in incidence of anal cancer in Denmark. *BMJ* 1993; **306**: 419–22.
16 Cantril ST, Green JP, Schall GL. Primary radiation therapy in the treatment of anal carcinoma. *Radiol Oncol Biol Physiol* 1983; **9**: 1271–8.
17 Slater G, Greenstein A, Aufses A. Anal carcinoma in patients with Crohn's disease. *Ann Surg* 1984; **199**: 348–50.
18 McDougall JK. Immortalization and transformation of human cells by human papillomavirus. *Curr Topics Microbiol Immunol* 1994; **186**: 101–19.
19 Kadish AS. Biology of anogenital neoplasia. *Cancer Treat Res* 2001; **104**: 267–86.
20 Chang F, Kosunen O, Kosma VM *et al*. Verrucous carcinoma of the anus containing human papilloma virus type 16 DNA detected by *in situ* hybridization. *Genitourin Med* 1990; **66**: 342–5.
21 Gal AA, Meyer PR, Taylor CR. Papillomavirus antigens in anorectal condyloma and carcinoma in homosexual men. *JAMA* 1987; **257**: 337–40.
22 Daling JR, Sherman KJ, Hislop TG *et al*. Cigarette smoking and the risk of anogenital cancer. *Am J Epidemiol* 1992; **135**: 180–9.
23 Kondlapoodi P. Anorectal cancer and homosexuality. *JAMA* 1982; **248**: 2114–5.
24 Hessol NA, Pipkin S, Schwarcz S, Cress RD, Bacchetti P, Scheer S. The impact of Highly Active Antiretroviral Therapy on non-AIDS-defining cancers among adults with AIDS. *Am J Epidemiol* 2007; **165**: 1143–53.
25 Mullhaupt B, Bauerfeind P, Kurrer MO, Fried M. Anal squamous cell carcinoma in a patient with Peutz–Jeghers syndrome. *Dig Dis Sci* 2001; **46**: 273–7.
26 Stearns MW, Urmacher C, Sternberg SS. Cancer of the anal canal. *Curr Probl Cancer* 1980; **4**: 1–44.
27 Fenger C. Anal neoplasia and its precursors: facts and controversies. *Semin Diagn Pathol* 1991; **8**: 190–201.
28 Goodman P, Halpert RD. Invasive squamous cell carcinoma of the anus arising in condyloma acuminatum: CT demonstration. *Gastrointest Radiol* 1991; **16**: 267–70.
29 Drumm J, Donovan IA, Clain A. Unusual presentation of anorectal carcinoma. *BMJ* 1982; **285**: 1393.
30 McConnell EM. Squamous carcinoma of the anus: a review of 96 cases. *Br J Surg* 1970; **57**: 89–92.
31 Tait WF, Sykes PA, Taylor GM *et al*. Unusual presentation of anorectal carcinoma. *BMJ* 1982; **285**: 1742.
32 Chawla AK, Willett CG. Squamous cell carcinoma of the anal canal and anal margin. *Hematol Oncol Clin North Am* 2001; **15**: 321–44.
33 Esiashvili N, Landry J, Matthews RH. Carcinoma of the anus: strategies in management. *Oncologist* 2002; **7**: 188–99.

Extramammary Paget's disease

Extramammary Paget's disease (EMPD) is discussed in Chapter 53. Perianal EMPD is a rare but important diagnosis [1]. Seventy-three per cent of cases of EMPD present as pruritus ani [2,3]. The association with an underlying malignancy is variable. Two reviews of the literature revealed only a 25% association [4,5]. Despite this, a search for a primary adenocarcinoma of underlying secretory glands should be carried out in perianal EMPD [6]. In some cases, the primary tumour is an anorectal, or even more distant, carcinoma [7,8]. The primary tumour and the Paget's cells in the epidermis are usually mucus-secreting. Paget's cells are generally believed to be derived from sweat gland epithelium [9]. Anorectal carcinomas (see below) may arise from rectal mucosa or from the intramuscular glands. In the latter case, the malignant cells may track to the buttock through the ischiorectal fossa, and the Paget's plaque may begin at a distance from the anal margin, rather like an ischiorectal abscess. Topographical studies have shown that the plaque of Paget's disease is much larger than the visible lesion [10]. Extensive surgery may be necessary, with micrographic margin control and plastic repair [11]. Photodynamic therapy and laser treatment have been used [12].

References

1 Butler JD, Hersham MJ, Wilson CA, Bryson JR. Perianal Paget's disease. *J R Soc Med* 1997; **90**: 688–9.
2 Jensen SL, Sjolin KE, Shokouh-Amiri MH. Paget's disease of the anal margin. *Br J Surg* 1988; **75**: 1089–92.
3 Redondo P, Idoate M, España A, Quintanilla E. Pruritus ani in an elderly man: extramammary Paget's disease. *Arch Dermatol* 1995; **131**: 952–3.
4 Mohs FE, Blanchard I. Microscopically controlled surgery for extramammary Paget's disease. *Arch Dermatol* 1979; **115**: 706–8.
5 Breen JL, Smith CI, Gregori CA. Extramammary Paget's disease. *Clin Obstet Gynecol* 1978; **21**: 1107–15.
6 van der Putte SCK, van Gorp LHM. Adenocarcinoma of the mammary-like glands of the vulva: a unifying concept. *J Cutan Pathol* 1994; **21**: 157–63.
7 Fetherston WC, Friedrich EG. The origin and significance of vulvar Paget's disease. *Obstet Gynecol* 1972; **39**: 735–44.
8 Helwig EB, Graham JH. Anogenital (extramammary) Paget's disease: a clinicopathological study. *Cancer* 1963; **16**: 387–403.
9 Hamm H, Vroom TM, Czarnetski BM. Extramammary Paget's cells: further evidence of sweat gland derivation. *J Am Acad Dermatol* 1986; **15**: 1275–81.
10 Gunn RA, Gallagher S. Vulvar Paget's disease: a topographic study. *Cancer* 1980; **46**: 590–4.
11 Coldiron BM, Goldsmith BA, Robinson JK. Surgical treatment of extramammary Paget's disease. *Cancer* 1991; **67**: 933–8.
12 Petrelli NJ, Cebollero JA, Rodriguez-Bigas M *et al*. Photodynamic therapy in the management of neoplasms of the perianal skin. *Arch Surg* 1992; **127**: 1436–8.

Miscellaneous malignancies

Extramucosal anorectal carcinoma may present as an inflammatory rather than a malignant condition (e.g. as a chronic fistula-*in-ano*) and so is not biopsied (or not biopsied deeply) and the diagnosis is missed or delayed; there are many cases in the literature of cancers arising from anal glands adjacent to the anorectal wall and not emergent from the mucosa [1]. The pattern of the intramuscular glands and of the wide range of tumours that arise from them resemble genitourinary rather than intestinal endothelial structures and cancers [2].

Cloacogenic carcinomas constitute only 2–3% of anorectal cancer, but may behave aggressively [3]. They derive from remnants of the cloacal membrane proximal to the pectinate line where there is an area of 'transitional mucosa' (between keratinized and non-keratinized squamous epithelium) penetrated by the anal glands. It may on occasion mimic a basal cell carcinoma both in clinical and histological appearance [4]. Most rectal cancer is adenocarcinoma (columnar epithelium).

Although basal cell carcinoma is the most common type of skin cancer, it is rare in the anogenital area, but over 100 cases have been reported [4,5]. Anorectal melanoma accounts for only 1% of all tumours of this area [6]; it may occur concomitantly with melanosis of the gastrointestinal tract [7].

Anogenital Kaposi's sarcoma is essentially an HIV-related problem.

Fibrosarcoma, haemangiopericytoma, leiomyosarcoma, malignant fibrous histiocytoma, epithelioid sarcoma, dermatofibrosarcoma protuberans and spindle cell sarcoma may occur, presenting as painful or painless nodules, masses or swellings [8]. Other rarities include Merkel cell carcinoma [9], malignant eccrine poroma [10] and malignant schwannoma [8,11].

Non-Hodgkin's lymphoma of the perianal area has been described in HIV/AIDS [12].

Perianal infiltration, ulceration or abscess occurs in 5% of haematological malignancies [13]. Chronic lymphocytic leukaemia has presented as a painless firm white mass at the anal orifice, associated with weight loss and inguinal lymphadenopathy [14]. Perianal ulceration and suppuration have been reported as the presenting manifestations of primary lymphoma of the anus [15].

Perineal/perianal metastases from transitional cell carcinoma of the distal urethra [16], from rectal carcinoma [17], and from epidermoid anal canal carcinoma [18] have occurred. Carcinoma erysipeloides has been observed in the perineum and on the thigh in carcinoma of the bladder and prostate [19].

A periorificial form of Langerhans' cell histiocytosis/eosinophilic granuloma may cause ulcerating and vegetating lesions within the anal canal and in the perianal skin [20,21].

References

1 Zimberg YH, Kay S. Anorectal carcinomas of extra-mucosal origin. *Ann Surg* 1957; **145**: 344.
2 Grenvalsky HT, Helwig EB. Carcinoma of the anorectal junction. I. Histological considerations. *Cancer* 1956; **19**: 480–8.
3 Serota Al, Weil M, Williams RA. Anal cloacogenic carcinoma. *Arch Surg* 1981; **116**: 456–9.
4 Espana A, Redondo P, Idoate MA *et al.* Perianal basal cell carcinoma. *Clin Exp Dermatol* 1992; **17**: 360–2.
5 Gibson GE, Ahmed I. Perianal and genital basal cell carcinoma: a clinicopathologic review of 51 cases. *J Am Acad Dermatol* 2001; **45**: 68–71.
6 Johnson A, Mathai G, Robinson WA. Malignant melanoma of the perineum. *J Surg Oncol* 1993; **54**: 185–9.
7 Horowitz M, Nobrega MM. Primary anal melanoma associated with melanosis of the upper gastrointestinal tract. *Endoscopy* 1998; **30**: 662–5.
8 Dehner LP, Smith BH. Soft tissue tumours of the penis. *Cancer* 1970; **25**: 1431–47.
9 Best TJ, Metcalfe JB, Moore RB, Nguyen GK. Merkel cell carcinoma of the scrotum. *Ann Plast Surg* 1994; **33**: 83–5.
10 Werdin R, Kupczyk-Joeris D, Schumpelick V. Malignant eccrine poroma: case report of a rare tumour of the skin. *Chirurg* 1991; **62**: 350–2.
11 Marsidi PJ, Winter CC. Schwannoma of penis. *Urology* 1980; **16**: 303.
12 Denis BJ, May T, Bigard MA, Canton P. Anal and perianal lesions in symptomatic HIV infections: prospective study of a series of 190 patients. *Gastroenterol Clin Biol* 1992; **16**: 148–54.
13 Vanheuverzwyn R, Delannoy A, Michaex JL, Dive C. Anal lesions in haematologic disorders. *Dis Colon Rectum* 1980; **23**: 310–2.
14 Cresson DH, Siegal GP. Chronic lymphocytic leukaemia presenting as an anal mass. *J Clin Gastroenterol* 1985; **7**: 83–7.
15 Steele RJ, Eremin O, Krajewski AS, Ritchie GL. Primary lymphoma of the anal canal presenting as perianal suppuration. *BMJ* 1985; **291**: 311.
16 Langlois NEI, McClinton S, Miller ID. An unusual presentation of transitional cell carcinoma of the distal urethra. *Histopathology* 1992; **21**: 482–4.
17 García-Armengol J, Roig JV, Alós R, Solana A. Perianal cutaneous metastasis of rectal adenocarcinoma. *Rev Esp Enferm Dig* 1995; **87**: 342–3.
18 Nazzari G, Drago F, Malatto, M, Crovato F. Epidermoid anal canal carcinoma metastatic to the skin: a clinical mimic of prostate adenocarcinoma metastases. *J Dermatol Surg Oncol* 1994; **20**: 765–6.
19 Cohen EL, Kim SW. Cutaneous manifestation of carcinoma of urinary bladder: carcinoma erysipelatodes. *Urology* 1980; **16**: 410–2.
20 Tait WF, Sykes PA. Unusual presentation of anorectal carcinoma. *BMJ* 1982; **285**: 1742.
21 Tzung T-Y, Wu J-C. Nonhealing perianal ulcers. *Arch Dermatol* 2005; **141**: 1161–6.

Miscellaneous

Effects of topical corticosteroids

The prolonged use of potent topical corticosteroids for inflammatory conditions of the groins or perianal area can produce misleading appearances. Tinea incognito [1] is well recognized, but a persistent, deep, livid erythema of the perianal skin may not be regarded as primarily infective. Striae occur readily on the upper and inner thighs. Multiple perianal comedones followed the application of a topical corticosteroid for 3 years [2].

Chronic perianal pain and the 'perineal syndrome'

A number of names have been given to sensations of pain localized to the anogenital region in the absence of evident organic cause [3,4]. Proctalgia fugax affects young adult males, and occurs chiefly at night in the form of a sudden cramp-like pain, which resolves in a few minutes. 'Coccygodynia', 'descending perineum syndrome' and 'chronic idiopathic anal pain' chiefly affect females. The pain is described as dull and throbbing. In 35 such patients, it was noted that the pain was precipitated by sitting, and that these three conditions differed from proctalgia fugax [3]. Electrophysiological studies gave variable results. There was a high incidence of previous sciatica and damage to the pelvic floor musculature. Results of treatment were disappointing. Rarely, sacral cysts and even chordoma can present with this symptomatology.

Such patients will present to surgeons or gynaecologists; however, dermatologists may be confronted by a similar problem in which a patient complains of short-lived episodes of intense burning, which may be accompanied by sweating, limited to the perineum or occasionally the scrotum. Attacks occur without warning, but may be brought about by a full rectum. In one patient, the attacks were severe enough to cause him to stop walking for some minutes. The patients tend to be stressed individuals, as are those with proctalgia fugax [4]. The skin is entirely normal.

The mechanism is unknown. Two patients appeared to have been helped by propantheline, suggesting a cholinergic mechanism [5]. However, the condition may also fall into the group of 'dermatological non-disease' [6], in which the perineum was affected in eight out of 24 patients. It has also been reported in children suffering from intrafamilial stresses [7] (see also pp. 71.51–71.52 and 71.81–71.82).

References

1 Ive FA, Marks R. Tinea incognito. *BMJ* 1968; **iii**: 149–52.
2 Oliet EJ, Estes SA. Perianal comedones associated with chronic topical fluorinated steroid use. *J Am Acad Dermatol* 1982; **7**: 405–7.
3 Neill ME, Swash M. Chronic perianal pain: an unsolved problem. *J R Soc Med* 1982; **75**: 96–101.
4 Parks AG, Porter NH, Hardcastle J. The syndrome of descending perineum. *Proc R Soc Med* 1966; **59**: 477–82.
5 Monro PAG, ed. *Sympathectomy*. Oxford: Clarendon Press, 1959: 146.

6 Cotterill JA. A dermatological non-disease: a common and potentially fatal disturbance of cutaneous body image. *Br J Dermatol* 1980; **103** (Suppl. 18): 13.
7 Lask B. Chronic perianal pain. *J R Soc Med* 1982; **75**: 370.

Umbilical dermatology

Introduction

The umbilicus is considered here for convenience. Although the umbilicus is not strictly part of the anogenital apparatus, its evolution and connections link it to the pelvic region.

Structure and function

At birth, the umbilical cord contains two arteries and a vein, the rudimentary urachus (allantois) and the vitelline (omphalomesenteric) duct, enveloped in Wharton's jelly. After separation and retraction of the stump, an umbilicus of variable depth is formed. Persistence of the urachal or vitelline ducts at this 'carrefour embryologique' may cause trouble in early or later life. A deeply retracted umbilicus may be the site of infection or foreign bodies.

Congenital and developmental abnormalities

Such abnormalities are all rare, but more common in males, and usually brought about by failure of obliteration of the omphalomesenteric duct or urachus [1]. They present as sinuses, fistulae, cysts or polypoid tumours.

Patent urachal duct

The umbilical opening is lined by skin or a pouting mucous membrane. Urine may be seen to escape from it, particularly in the elderly, when an obstruction to micturition exists.

Persistent vitelline duct and polyp

If a connection with the intestine persists, it may become inflamed or cause a faecal umbilical discharge. More commonly, the remains of the duct give rise to a polyp in later life [2]. This may be accompanied by intermittent bleeding or a more persistent mucoid discharge, sometimes profuse. A symptomless, sterile umbilical discharge should always arouse suspicion. The histopathological features are those of intestinal mucosa. It may be mistaken for a pyogenic granuloma [3].

Periumbilical 'choristia'

Under this title (meaning dysgenetic translocation of tissue), Bellone *et al.* [4] described extending, crusted, erythematous, periumbilical plaques, in which islands of intestinal mucosal cells were found in the epidermis.

Omphalocele

This form of abdominal hernia appears to be more common in African people. In 5 years in Ibadan, 33 cases were seen [5]. The minor form is caused by herniation of the umbilical cord; a major form is probably because of a fault of embryonic folding of the fetus.

References
1 Nix TE, Young CJ. Congenital umbilical anomalies. *Arch Dermatol* 1964; **90**: 160–5.
2 Hejazi N. Umbilical polyp: a report of two cases. *Dermatologica* 1975; **150**: 111–5.
3 Laradle De Luna M, Gcioni V, Herrara A *et al.* Umbilical polyps. *Pediatr Dermatol* 1987; **4**: 341–3.
4 Bellone AG, Raimondi L, Gasparini G *et al.* Choristia intestinale périumbilicale en plaques. *Ann Dermatol Vénéréol* 1978; **105**: 601–6.
5 Nivabueze I, Hekwaba F. Omphalocele: experience in the African tropics. *Postgrad Med J* 1981; **57**: 635–9.

Trauma and artefact

The umbilicus in the newborn

Haemorrhages may occur from slipped ligatures. The cord normally separates within a week of birth, and the raw surface is epithelialized by day 15. During this time, the umbilicus is prone to infection, especially in maternity hospitals and nurseries. Impetigo (pemphigus neonatorum) or, rarely, more severe bacterial infections may occur (see below). The 'absent navel' syndrome has been described as a sign of dystrophic epidermolysis bullosa [1].

Talc granuloma

This lesion, which is probably more frequent than is recognized, occurs in infants and very young children. It is distinguished histologically from a pyogenic granuloma (on which it may supervene) by the doubly refractile talc crystals [2].

Pyogenic granuloma

This is a dull-red fleshy polypoid lesion, often pedunculated. Bleeding readily takes place from trauma. If it occurs early in life, it may be confused with a capillary haemangioma.

Ileoumbilical fistula

This may follow laparotomy for Crohn's disease, or may rarely occur spontaneously [3].

Omphalith

In deeply set umbilici, an accumulation of sebum and keratin may lead to the gradual formation of a hard, stone-like mass, which may remain unnoticed for many years until discovered accidentally or revealed by secondary infection or ulceration.

'Spontaneous gangrene'

This can occur without catheterization, possibly owing to minor trauma to the umbilicus [4]. Very rarely, the bladder and kidney may also be involved.

Unilateral skin necrosis of the buttock has been reported following indwelling umbilical artery catheterization [4–6], probably caused by thrombosis leading to occlusion of the inferior gluteal artery. A similar case was caused by misdirection of the tip of the arterial catheter [7].

References
1 Paslin D. People without navels. *Br J Dermatol* 1978; **98**: 584.
2 McCallum DJ, Hall GFM. Umbilical granulomata: with particular reference to talc granuloma. *Br J Dermatol* 1970; **83**: 151–6.
3 Reutz TW Jr, Warden CS, Garcia FJ. Crohn's disease with spontaneous ileo-umbilical and ileo-vesical fistulae. *Dig Dis Sci* 1979; **24**: 316–8.

4 Bonifazi E, Meneghini C. Perianal gangrene of the buttock: an iatrogenic or spontaneous condition? *J Am Acad Dermatol* 1980; **3**: 596–8.
5 Cutler VE, Stretcher GS. Cutaneous complications of central umbilical artery catheterization. *Arch Dermatol* 1977; **113**: 61–3.
6 Mann PN. Gluteal skin necrosis after umbilical artery catheterization. *Arch Dis Child* 1980; **55**: 815–7.
7 Rudolph N, Wang HH, Dragutsky D. Gangrene of the buttock: a complication of umbilical artery catheterization. *Pediatrics* 1974; **53**: 106–9.

Inflammatory dermatoses

Eczematous conditions and psoriasis

Allergic contact dermatitis is usually brought about by medicaments. Irritant dermatitis from soap and quaternary ammonium compounds also occurs. Psoriasis commonly involves the umbilicus. A urachal sinus has presented as periumbilical dermatitis [1].

Miscellaneous inflammatory dermatoses

A pilonidal sinus may occur [2]. Granulomas [3] may present as such, or with an associated discharge, infection, bleeding or profuse sterile purulent exudate. The umbilicus is not infrequently involved in bullous and cicatricial pemphigoid; it may be the site of presentation of the latter (see Chapter 40).

Perforating pseudoxanthoma elasticum occurs in the umbilicus, and was the only site involved in six obese, multiparous, American black females [4]. It is only rarely associated with systemic problems [5,6].

Pregnancy, Addison's disease and other pigmentary disorders increase the pre-existing pigmentation. Acanthosis nigricans causes acanthotic and papillomatous lesions in the perineum. Periumbilical staining (Cullen's sign) occurs in acute pancreatitis, and occasionally in ruptured ectopic pregnancy or with duodenal ulcer perforation [7].

Umbilical haemorrhage has been described as a complication of cirrhosis following gross ulceration of the umbilical vein [8].

Infections

Infection of the umbilicus in the newborn used to carry a high mortality. It still occurs in some countries. A number of bacterial organisms may be responsible, but staphylococcal, *Pseudomonas* and clostridial species [9] are the most important. Minor forms consist of oozing, crusting and cellulitis, but a spreading oedematous erythema, progressing to necrotizing fasciitis, is of very serious import. Septicaemia and its complications may supervene [10]. At any time in later life, but usually after middle age, the umbilicus may be the seat of intertrigo or candidosis. This is more common in the obese or in those with poor personal hygiene. Genital and perianal warts can occasionally be associated with similar lesions within the umbilicus [11]. Foreign bodies, inserted by children or psychotics, may be overlooked as a cause of purulent infection in a deeply set umbilicus. The periumbilical skin is a common site of schistosomiasis when it affects the skin [12]. Disseminated strongyloidiasis has presented with subumbilical excoriations [13] and periumbilical purpura, where larvae were demonstrated in the skin biopsy [14].

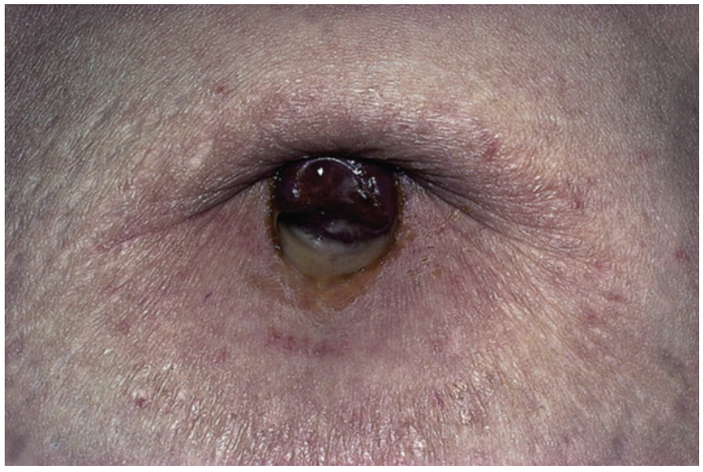


Fig. 71.46 'Sister Joseph's nodule'. (Courtesy of Dr J. Marks, Newcastle-upon-Tyne, UK.)

Tumours and implantations

The umbilicus is a site of implantation of endometriomas [15], which may clinically resemble melanomas. A unique case of postoperative endosalpingosis has also been reported [16]. Colonic mucosa was implanted in an infant, after colostomy for Hirschsprung's disease [17]. A single case of carcinoid of the umbilicus has been noted [18]. Extramammary Paget's disease has also been recorded [19,20].

Skin metastases from neoplasms of the digestive tract occurred in only 3% of 2187 cases [21], but the umbilicus is a characteristic site, especially for cancer of the stomach (Sister Joseph's nodule) (Fig. 71.46), which was the primary source in 33 out of 40 cases [22]. The ovary, uterus and colon are responsible for most of the others [23–25], but origins from pancreas [26], prostate [27], leiomyosarcoma of the small intestine [28], and malignant peritoneal mesothelioma [29] have been described. The lesions usually present as firm, irregular nodules, but can occasionally infiltrate diffusely, or ulcerate and produce a fetid discharge. Such metastases were the presenting sign in 18 out of 40 cases, and were a major diagnostic feature in 28 cases [30]. The prognosis is always poor, but not entirely hopeless [31]. Histological identification of the site of the primary tumour may be difficult, and proved possible in only 21 of 85 cases [32,33]. Fine-needle aspiration of the nodule is not particularly helpful in reaching a diagnosis [33]. CT and surgical intervention are obligatory, because it may represent the earliest and only metastasis [25].

References

1 Cox GA, Chan I, Lloyd J *et al*. Urachal sinus presenting as periumbilical dermatitis. *Br J Dermatol* 2007; **157**: 419–20.
2 Eby CS, Jetton RL. Umbilical pilonidal sinus. *Arch Dermatol* 1972; **106**: 893.
3 Laradle De Luna M, Gcioni V, Herrara A *et al*. Umbilical polyps. *Pediatr Dermatol* 1987; **4**: 341–3.
4 Hicks J, Carpenter CL, Reed RJ. Periumbilical perforating pseudoxanthoma elasticum. *Arch Dermatol* 1979; **115**: 300–3.
5 Goldstein BG, Lesher JL. Periumbilical pseudoxanthoma elasticum with systemic manifestations. *South Med J* 1991; **84**: 788–9.
6 Kim YH, Yoon JS, Lee JH *et al.* Periumbilical pseudoxanthoma elasticum. *Ann Dermatol* 1994; **6**: 49–51.

7 Evans DM. Cullen's sign in perforated duodenal ulcer. *BMJ* 1971; **i**: 154.
8 Douglas JG. Umbilical haemorrhage: an unusual complication of cirrhosis. *Postgrad Med J* 1981; **57**: 461–2.
9 Gormley D. Neonatal anaerobic (clostridial) cellulitis and omphalitis. *Arch Dermatol* 1977; **113**: 683–4.
10 Oranje AP, van Gysel D, van Praag MCG. Acquired neonatal infections. In: Harper J, Oranje A, Prose N, eds. *Textbook of Pediatric Dermatology*. Oxford: Blackwell Science, 2000: 73–7.
11 Nathan M. Umbilical warts: a new entity? *Genitourin Med* 1994; **70**: 49–50.
12 Colin M, Loubiere R, Guillaume A *et al.* Les lesions cutanées de bilharziose: a propos de 14 observations. *Ann Dermatol Vénéréol* 1980; **107**: 759–67.
13 Ho PL, Luk WK, Chan ACL, Yuen KY. Two cases of fatal strongyloidiasis in Hong Kong. *Pathology* 1997; **29**: 324–6.
14 Kalb R, Grossman ME. Periumbilical purpura in disseminated strongyloidiasis. *J Am Acad Dermatol* 1986; **256**: 1170–1.
15 Williams HE, Barsky S, Storino W. Umbilical endometrioma (silent type). *Arch Dermatol* 1976; **112**: 1435–6.
16 Dore N, Landry M, Cadotte M *et al.* Cutaneous endosalpingosis. *Arch Dermatol* 1980; **116**: 909–12.
17 Peachey RDG. Implantation of colonic mucosa in skin around colostomy. *Br J Dermatol* 1974; **90**: 108.
18 Brody HJ, Stallings WP, Fine RM *et al.* Carcinoid in an umbilical nodule. *Arch Dermatol* 1978; **114**: 570–2.
19 Ueki H, Kohda M. Multilokulärer extramammärer morbus Paget. *Hautarzt* 1979; **30**: 267–70.
20 Remond B, Aractingi S, Blanc F *et al.* Umbilical Paget's disease and prostatic carcinoma. *Br J Dermatol* 1993; **128**: 448–50.
21 Texier L, Geniaux M, Tamisier JM *et al.* Métastases cutanées des cancers digestifs. *Ann Dermatol Vénéréol* 1978; **105**: 913–9.
22 Samitz MH. Umbilical metastasis from carcinoma of the stomach. *Arch Dermatol* 1975; **111**: 1478–9.
23 Patel KS, Watkins RM. Recurrent endometrial adenocarcinoma presenting as an umbilical metastasis. *Br J Clin Pract* 1992; **46**: 69–70.
24 Brustman L, Seltzer V. Sister Joseph's nodule: seven cases of umbilical metastases from gynecologic malignancies. *Gynecol Oncol* 1984; **19**: 155–62.
25 Sharaki M, Abdel-Kader M. Umbilical deposits from internal malignancy (the Sister Joseph's nodule). *Clin Oncol* 1981; **7**: 351–5.
26 Shvili D, Halevy S, Sandbank M. Umbilical metastasis as the presenting sign of pancreatic adenocarcinoma. *Cutis* 1983; **31**: 555–8.
27 Stanko C, Grandinetti L, Baldassano M *et al*. Epidermotropic metastatic prostate carcinoma presenting as an umbilical nodule—Sister Mary Joseph nodule. *Am J Dermatopathol* 2007; **29**: 290–2.
28 Powell FC, Cooper AJ, Massa MC *et al.* Leiomyosarcoma of the small intestine: metastatic to the umbilicus. *Arch Dermatol* 1984; **120**: 402–3.
29 Chen KTK. Malignant mesothelioma presenting as a Sister Joseph's nodule. *Am J Dermatopathol* 1991; **13**: 300–3.
30 Steck WD, Helwig EB. Tumors of the umbilicus. *Cancer* 1965; **18**: 907–15.
31 Chatterjee SN, Bauer HM. Umbilical metastasis from carcinoma of the pancreas. *Arch Dermatol* 1980; **116**: 954–5.
32 Powell FC, Cooper AJ, Massa MC *et al.* Sister Mary Joseph's nodule: a clinical and histologic study. *J Am Acad Dermatol* 1984; **10**: 610–5.
33 Schneider V, Smyczek B. Sister Mary Joseph's nodule. *Acta Cytol* 1990; **34**: 555–8.

CHAPTER 72

General Aspects of Treatment

A.Y. Finlay[1] *& C.H. Smith*[2]

[1]Department of Dermatology, Cardiff University School of Medicine, Cardiff, UK
[2]St John's Institute of Dermatology, St Thomas' Hospital, London, UK

The dermatology consultation, 72.1
What do patients want?, 72.1
Risk–benefit analysis and communication of risk, 72.3
Factors influencing clinical decision taking, 72.4
Communication of bad news and realistic prognosis, 72.4
Concordance (compliance/adherence) with therapy, 72.5
Monitoring and realities of adherence, 72.5
Influences on adherence, 72.6
Quality and frequency of topical applications, 72.6
Patient attitudes and depression, 72.6
Techniques in the clinic, 72.6
Realistic information, 72.7
Strategies for improvement, 72.7
Measurement of disease, 72.8
Why measure disease?, 72.8
Measurement methods, 72.8
Objective measures, 72.11
Quality of life impairment by skin disease, 72.13
What does quality of life mean?, 72.13
Why measure quality of life?, 72.13
How do quality of life measures relate to other clinical indices?, 72.14
Methods of measuring quality of life in dermatology, 72.16
Quality of life measures used in dermatology, 72.16
General principles of therapy, 72.25
Topical and systemic treatments, 72.25
Factors that affect therapeutic outcome, 72.25
Cosmetic camouflage, 72.31
The role of complementary and alternative therapy in the context of a general consultation, 72.31
Patient self-help groups, 72.33

The dermatology consultation

What do patients want?

Over the last 60 years there has been a fundamental shift in the power balance in medical consultations. The traditional model for the doctor–patient relationship consisted of the patient in relative or total ignorance of health matters seeking both basic information about their disease and trustingly accepting whatever advice the doctor gave. Every clinician knows that there still are some consultations where this is still the model—sometimes appropriately in certain social or cultural circumstances. Many consultations today, however, are based on a relationship of mutual respect, but on the patient's side informed by prior knowledge about the disease and on the doctor's side a realization that options of management need to be discussed so that a joint agreed approach to investigation and management needs to be reached after explanation, discussion and negotiation. Growth in the understanding of the impact of skin disease on quality of life has led to the concept of 'patient-centred care' [1], with an emphasis on effective two-way communication in dermatology consultations. Trust in the doctor's knowledge and skills has to be earned from each patient rather than being taken for granted. Greater attention to, and investing greater time in meeting, patients' expectations may not only be of benefit to the patient, but help you to be a happy dermatologist [2]!

Insight into patients' attitudes and needs from the consultations may be gained from work carried out in primary care. In a survey of patients' priorities in the consultation, the most valued attributes of care in order were: a thorough physical examination; seeing a physician who knew them well; seeing a physician with a friendly manner; having a reduction in waiting time of one day; and having flexibility of appointment times [3]. High value was also placed on interest being shown in patient's ideas, enquiry about patient's social and emotional well-being and involvement of the patient in decision making. However, in an examination of the value placed by patients on shared decision taking in primary care, patients valued a 'doctor listens' attitude and easily understood information above shared treatment decisions, more information and longer consultation time [4]. A Swiss study on shared decision taking revealed that 66% of patients supported leaving decision making concerning acute respiratory tract infections to their general practitioner [5]; the nature of the decision being taken may influence the desire of the patient to be involved.

Jobling [6] stated that patients with skin disease wish for 'a sound diagnosis, clear information, and unambiguous, practical and realistic advice on what can and should be done about it, if anything, forming the basis of a joint decision'. In a survey of over 2000 patients and parents of patients with atopic eczema, expectations of the initial consultation with the dermatologist included (in order) different or better treatment, more detailed information about eczema, confirmation of the diagnosis, more detailed advice on the use of treatment, to be cured and reassurance [7]. From the doctor's perspective [8], dermatology patients would seem to need understanding, knowledgeable carers and staff who care;

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

they also need to be able to express their concerns and have their worries allayed. However, when dermatology patients were actually asked what was most important to them, the attribute of greatest importance was the expertise of the doctor, followed by thorough care and convenience [9].

From the perspective of a clinical dermatologist, the aspects of patient consultation that seem to provoke that most positive patient feedback are listening and showing evidence of listening, taking interest in specific items brought to the consultation by the patient (such as written lists of preparations used, photographs of the rash, press cuttings or Internet printouts), thoroughly examining the patient and tactfully offering to examine affected areas that the patient may have been to embarrassed to mention. Giving clear information about the diagnosis, backed up by written information, is, of course, important but sensing and addressing unspoken concerns is probably the most appreciated aspect of a successful consultation. Stating clearly that a skin problem is not cancer and does not imply any cancer risk is very reassuring, and is important to remember in situations where to the dermatologist it is obvious that there is no malignancy potential. Similarly, stating clearly that there is no risk of infection or of other members of the family 'catching' the condition may simply address the patient's main worry.

How can dermatologists encourage patients to communicate better with them? Patients often feel inhibited from asking questions—they are aware that the clinic is busy, time is limited, or the doctor does not look them in the eye or frequently interrupts [10]. Patients may be helped to get the most out of a consultation by the use of written prompts [11], but patients may not want to be labelled difficult and doctors may perceive such prompting as leading to excessive consultation time. The questions most frequently asked by patients with atopic dermatitis were identified and used to create a patient information leaflet and an interview prompt form for use by patients [12]. Such 'tailor-made' prompts may be helpful to improve patient satisfaction and communication. However, even if communication is good during a consultation, the patient may not recall later much of what was said. All patients who received a copy of the letter written by the dermatologist to the general practitioner found this useful [13]; there was an increased feeling of involvement in health care decisions and improved recall. This exercise was carried out at low cost. However, when given the opportunity to request copy letters in a trauma and orthopaedic clinic, only 0.3% of patients actively requested copies [14].

Despite a growing awareness of the importance to patients of the effects of skin disease on their lives, quality of life discussion was absent in 40% of routine general dermatology consultations monitored [15]. There was a relationship between type of decision taken at psoriasis consultations and the mean impairment of quality of life score of groups of patients in whom that decision type was taken [16]. However, there was a wide variation in scores of patients within each decision category, suggesting that in some patients inappropriate decisions may have been taken as the dermatologist was not aware of the extent of the patients' life quality impairment.

Given the central importance of patients' attitudes and the impact of skin disease on the emotional health and quality of life of dermatology patients, it is of concern that currently there is little or no formal training in communication skills or psychotherapy in the training of most dermatologists. Many dermatologists become from experience 'amateur psychodermatologists' building their insights into the patients' problems constructively into their routine consultations. However, there is a body of basic knowledge that should be incorporated into routine dermatology training [17], and some patients would benefit from seeing dermatologists with a specific extra training in this field. The psychological needs of patients with melanoma, for example, can be challenging [18], and there should be special education specifically for managing this group of patients.

It is important for dermatologists to have some insight into aspects of diseases that are not necessarily mentioned by patients, but which may influence their attitudes and compliance. About 15–20% of patients attending dermatology outpatients have used complementary and alternative medicine to treat their skin problem [19,20]. It may be helpful for dermatologists to raise this issue in consultations.

In larger teaching hospitals it is common for undergraduate or postgraduate dermatology students to be present during some outpatient consultations. The presence of students may influence the nature of the consultation. It is reassuring that 94% of patients enjoyed the interaction with a medical student and were comfortable disclosing information [21], however 22% of patients also wanted time alone with the physician; 99.5% of patients were satisfied with a trainee dermatologist participating in their care [22].

There have been attempts to understand patients' attitudes towards consultations delivered by or involving teledermatology. There is a high acceptance of real-time teledermatology consultations [23]. Key aspects of the outcome of the consultation, such as receiving a diagnosis, treatment and adequate explanation, lead to satisfaction, rather than whether or not the consultation was face to face or a teleconsultation [24]. A nurse-led store and forward teledermatology clinic was found to be convenient, but 40% of patients, and especially those with poor health-related quality of life, would have preferred to have had a face to face consultation with a dermatologist [25]. It seems, however, that for many patients being directly with a dermatologist for the consultation is not the highest priority.

In fact, for many patients with skin problems, having advice from a dermatologist in any format is not necessarily the priority. Slightly greater satisfaction has been reported by selected patients from consultations with general practitioners with a special interest in dermatology, compared to consultations with dermatologists. Aspects of the consultation such as greater accessibility and timeliness were of greater importance to the patient than the choice of who provided the advice [26].

In many dermatology practices worldwide, patients may come from a variety of cultural and linguistic backgrounds. It is obvious, but worth stating, that if the dermatologist and patient are not fluent in the same language, the quality of information flow will be inhibited. The use of translators will contribute but patient dissatisfaction, non-compliance and poorer clinical outcome may result from language problems [27].

Chren suggested a series of questions that should be addressed if we are to be able to critically assess the effectiveness of a der-

matology consultation [28]. These include 'Were the goals of the intervention defined explicitly?', 'Do the outcomes measured and evaluated reflect these goals?' and 'Was accurate and unbiased measurement of these outcomes performed?' We should indeed consider how we could better assess the effectiveness of our consultations.

References

1 Feldman S, Behnam SM, Behnam SE, Koo JY. Involving the patient: impact of inflammatory skin disease and patient-focused care. *J Am Acad Dermatol* 2005; **53**: S78–S85.

2 Poot F. How to be a happy dermatologist. *Dermatol Psychosom* 2004; **5**: 112–3.

3 Cheraghi-Sohi S, Hole AR, Mead N *et al*. What patients want from primary care consultations: a discrete choice experiment to identify patients' priorities. *Ann Fam Med* 2008; **6**: 107–15.

4 Longo MF, Cohen DR, Hood K *et al*. Involving patients in primary care consultations: assessing preferences using discrete choice experiments. *Br J Gen Pract* 2006; **56**: 35–42.

5 Briel M, Young J, Tschudi P *et al*. Shared-decision making in general practice: do patients with respiratory tract infections actually want it? *Swiss Med Wkly* 2007; **137**: 483–5.

6 Jobling R. Dermatology tomorrow—the patient's viewpoint. *Dermatol Pract* 1988; **6**: 18–21.

7 Long CC, Funnell CM, Collard R, Finlay AY. What do members of the National Eczema Society really want? *Clin Exp Dermatol* 1993; **18**: 516–22.

8 Finlay AY. Dermatology patients: what do they really need? *Clin Exp Dermatol* 2000; **25**: 444–50.

9 Coast J, Salisbury C, de Berker D *et al.* Preferences for aspects of a dermatology consultation. *Br J Dermatol* 2006; **155**: 387–92.

10 Slowie DF. Doctors should help patients to communicate better with them. *BMJ* 1999; **319**: 784.

11 Fleissig A, Glasser B, Lloyd M. Encouraging out-patients to make the most of their first hospital appointment: to what extent can a written prompt help patients get the information they want? *Patient Educ Couns* 1999; **38**: 69–79.

12 Ogawa S, Uchi H, Fukagawa S *et al*. Development of atopic dermatitis-specific communication tools: interview form and question and answer brochure. *J Dermatol* 2007; **34**: 164–71.

13 Tomkins CS, Braid JJ, Williams HC. Do dermatology outpatients value a copy of the letter sent to their general practitioner? In what way and at what cost? *Clin Exp Dermatol* 2004; **29**: 81–6.

14 Singh S, Budeda B, Housden P. Do patients want copies of their GP letters?—our experience with 7250 patients. *Int J Clin Pract* 2007; **61**: 1407–9.

15 David SE, Ahmed Z, Salek MS, Finlay AY. Does enough quality of life-related discussion occur during dermatology outpatient consultations? *Br J Dermatol* 2005; **153**: 997–1000.

16 Katugampola RP, Hongbo Y, Finlay AY. Clinical management decisions are related to the impact of psoriasis on patient-rated quality of life. *Br J Dermatol* 2005; **152**: 1256–62.

17 Poot F, Sampogna F, Onnis L. Basic knowledge in psychodermatology. *J Eur Acad Dermatol Venereol* 2007; **21**: 227–34.

18 Sollner W, Gross R, Maislinger S. Psychotherapeutic interventions in melanoma patients. *Recent Results Cancer Res* 2002; **160**: 362–9.

19 Baron SE, Goodwin RG, Nicolau N *et al*. Use of complementary medicine among outpatients with dermatologic conditions within Yorkshire and South Wales, United Kingdom. *J Am Acad Dermatol* 2005; **52**: 589–94.

20 Ernst E. The usage of complementary therapies by dermatological patients: a systematic review. *Br J Dermatol* 2000; **142**: 857–61.

21 Townsend B, Marks JG, Mauger DT, Miller JJ. Patients' attitudes toward medical student participation in a dermatology clinic. *J Am Acad Dermatol* 2003; **49**: 709–11.

22 Crawford GH, Gutman A, Kantor J, James WD. Patients' attitudes toward resident participation in dermatology outpatient clinics. *J Am Acad Dermatol* 2005; **53**: 710–2.

23 Loane MA, Bloomer SE, Corbett R *et al*. Patient satisfaction with realtime teledermatology in Northern Ireland. *J Telemed Telecare* 1998; **4**: 36–40.

24 Collins K, Walters S, Bowns I. Patient satisfaction with teledermatology: quantitative and qualitative results from a randomised controlled trial. *J Telemed Telecare* 2004; **10**: 29–33.

25 Williams TL, Esmail A, May CR *et al*. Patient satisfaction with teledermatology is related to perceived quality of life. *Br J Dermatol* 2001; **145**: 911–7.

26 Salisbury C, Noble A, Horrocks S *et al*. Evaluation of a general practitioner with special interest service for dermatology: randomised controlled trial. *BMJ* 2005; **331**: 1441–6.

27 Kanthraj GR. Role of language in dermatologist–patient relationship: 'He who speaks well, treats well!' *Indian J Dermatol Venereol Leprol* 2005; **71**: 290–1.

28 Chren MM. Dermatologic consultations—how can we know if we are effective? Initial methodologic considerations for the critical assessment of medical interventions performed by physicians. *Arch Dermatol* 1994; **130**: 1052–4.

Risk–benefit analysis and communication of risk

When a therapeutic decision is taken in dermatology, there is nearly always an assumed or overt analysis of the risk to the patient of the planned course of action compared with an assessment of the likelihood and magnitude of possible benefit. Very often the risks involved are very low and the benefits are considerable, for example the risks of developing an allergic reaction to an emollient compared to the emollient reducing the shedding of scales and embarrassment of psoriasis. However, more concerning risks are frequently encountered, such as the 'known' risks of skin cancer following UVB phototherapy; an extensive literature review counter-argued that UVB phototherapy remains a very safe treatment [1]. Dermatologists frequently face the major twin problems of having to take decisions where the absolute risks of the therapy are not known and where the likely benefit has not been quantified. In addition, methods to communicate risk to patients in an understandable and meaningful way are not well developed in dermatology. Even basic drug information provided by dermatologists is deficient when topical medications are prescribed [2].

When new drugs are developed, vast resources are used to try to demonstrate their safety. However, most of the safety data submitted at the time of registration of new therapies is based on data from within controlled clinical trials, with their strict entry criteria. It is only when drugs are used widely in the community that some side effects become apparent. This is why postmarketing surveys and side-effect reporting systems are so important. Another systematic approach to gathering information about the real risks of therapies is through creating national registries, such as that for psoriasis patients treated with the biological therapies [3]. When psoriasis patients' views were sought about the balance of risks and benefits of systemic therapies, they prioritized low risk of skin cancer and liver damage [4]. This view reflects the views of British dermatologists who considered that the risks of skin damage, followed by the risks of skin cancer, are the most important side effects of therapies for psoriasis [5].

The problems of risk–benefit analysis are not, of course, only related to drug therapy. Clinical decisions about congenital melanocytic naevi, for example, with associated costs, may be taken because of concern about malignancy risks that might in fact be low [6].

It is now possible to measure risk communication and decision making effectiveness in consultations [7], though little work has yet been carried out in dermatology [8]. Where attempts have been

made in other medical disciplines to improve risk communication through counselling, the supportive or emotional aspects of the counselling were of more benefit than the giving of information [9]. Training of doctors in risk communication in general practice did not increase doctors' confidence in risk communication. Consultation time constraints were of greater importance than lack of training in providing better risk communication with patients [10]. Before advocating the devotion of resources to try to improve risk communication in dermatology it will be important to establish that such intervention improves outcomes such as patient satisfaction with consultation; in general practice this has been difficult to establish [11].

References

1 Lee E, Koo J, Berger T. UVB phototherapy and skin cancer risk: a review of the literature. *Int J Dermatol* 2005; **44**: 355–60.
2 Storm A, Benfield E, Anderson SE, Serup J. Basic drug information given by physicians is deficient, and patients' knowledge low. *J Dermatolog Treat* 2008; **28**: 1–4.
3 Schmitt-Egenolf M. Psoriasis therapy in real life: the need for registries. *Dermatology* 2006; **213**: 327–30.
4 Seston EM, Ashcroft DM, Griffiths CEM. Balancing the benefits and risks of drug treatment: a stated-preference, discrete choice experiment with patients with psoriasis. *Arch Dermatol* 2007; **143**: 1175–9.
5 Ashcroft DM, Seston E, Griffiths CEM. Trade-offs between the benefits and risks of drug treatment for psoriasis: a discrete choice experiment with U.K. dermatologists. *Br J Dermatol* 2006; **155**: 1236–41.
6 Krengel S, Hauschild A, Schafer T. Melanoma risk in congenital melanocytic naevi: a systematic review. *Br J Dermatol* 2006; **155**: 1–8.
7 Edwards A, Elwyn G, Hood K *et al*. The development of COMRADE—a patient-based outcome measure to evaluate the effectiveness of risk communication and treatment decision making in consultations. *Patient Educ Couns* 2003; **50**: 311–22.
8 Shriner DL, Wagner RF Jr, Weedn VW *et al*. Informed consent and risk management in dermatology: to what extent do dermatologists disclose alternate diagnostic and treatment options to their patients? *J Contemp Health Law Policy* 1992; **8**: 137–62.
9 Edwards A, Gray J, Clarke A *et al*. Interventions to improve risk communication in clinical genetics: systematic review. *Patient Educ Couns* 2008; **71**: 4–25.
10 Edwards A, Elwyn G. Involving patients in decision making and communicating risk: a longitudinal evaluation of doctors' attitudes and confidence during a randomized trial. *J Eval Clin Pract* 2004; **10**: 431–7.
11 Davis RE, Dolan G, Thomas S *et al*. Exploring doctor and patient views about risk communication and shared decision-making in the consultation. *Health Expect* 2003; **6**: 198–207.

Factors influencing clinical decision taking

If decision taking in clinical dermatology were a straightforward process of applying textbook guidance about therapy or national guidelines across all patients, life would be simple. The reality is that every patient (and doctor) is different and there are many unquantifiable and unrecognized influences on daily decision taking which make the process much more complex than the narrow application of evidence-based medicine. Some of the wider influences on decision taking, listed in Table 72.1, include patient-related factors, cultural considerations, patient's family and work aspects, geographical and economic aspects, doctor-related factors, type of health care provision and pharmaceutical company activities. It is the interplay of these multiple factors that provides the daily and infinite range of clinical challenges, still best described by the concept of 'the art of medicine'.

Table 72.1 Influences on clinical decision taking.

Scientific
evidence-based information
guidelines
published standard therapies
Patient
intelligence
attitude
quality of life impairment
value judgement concerning disease importance
work
leisure activities, hobbies
travel plans
time availability for treatment
financial status
past history of therapy adherence
age
sex
Cultural aspects
patient expectations
language
religious views
Family
support from partner/close family (the 'greater patient')
impact of life quality of family
caring responsibilities of patient for family
Work/study
responsibilities at work
attitudes from employer
Geography
ability to attend for therapy
Economic aspects
whether patient has to pay
whether patient can afford to pay
Doctor
personality
interest
psychological state, e.g. tired
relationship with patient
level of experience and age
sex of doctor
attitude towards patient's cultural background
Health-care provision environment
time available for consultation
physical environment of consultation
whether students present
time patient waiting for appointment
protocols/guidelines
organization of local health care
availability of therapies
Pharmaceutical company influence
pharmaceutical representative influence
gifts, funding

Communication of bad news and realistic prognosis

In many dermatology consultations it is necessary to communicate bad news; a newly diagnosed disease may be chronic rather than curable or a lesion may malignant. The ability to successfully

communicate bad news involves many skills, including respect, tact, empathy, support and information precision [1]. Ideally, consultations where significant bad news is given should be planned for and include follow up [2]. 'Hit and run' deliveries of bad news should be avoided [3]. Physicians should sit and not stand when giving bad news; physicians who sit are perceived by patients as more compassionate [4]. The involvement of family members is of great importance when giving bad news, as the lives of partners and other close family members (the 'greater patient') are likely also to be affected by bad news for the patient. Their contribution to the subsequent caring for the patient is important, and their own needs should not be forgotten. When patients are told about a diagnosis of malignant melanoma, the subsequent psychological morbidity is related to the methods of communicating the news [5]. The following were linked to lower anxiety: preparing the patient for a possible diagnosis of cancer, having people wanted by the patient present, giving as much information as desired, providing written information, discussing the patient's questions the same day, talking about the patient's feelings and being reassuring.

Patients want to know the likely long-term outcome of their skin disease: what can they reasonably expect and what do they need to plan for? In some aspects of dermatology practice, especially concerning skin malignancies, there are good data available about overall cure rates and life expectancy. However, the prognostic data over many inflammatory skin diseases are poor, despite their high prevalence. In many situations, insufficient long-term population-based studies exist to give accurate long-term prognosis. The clinical practice of dermatologists is usually selective as of course those patients with the most severe and intractable disease are seen most frequently; 'clinical experience' as a guide to prognosis may therefore be unwittingly biased. While endeavouring to use the most accurate data available, it is important to be honest with patients about the deficiencies in knowledge about prognosis. Beware of giving specific times without cautionary explanation, as patients easily misinterpret 'average' data as being related to them individually.

References

1 Seu S, Spina M, Marongiu F *et al*. Bad news in nephrology. *G Ital Nfrol* 2008; **25**: 227–33.

2 Minichiello T, Ling D, Ucci DK. Breaking bad news: a practical approach for the hospitalist. *J Hosp Med* 2007; **2**: 415–21.

3 Helft PR, Petronio S. Communication pitfalls with cancer patients: 'hit-and-run' deliveries of bad news. *J Am Coll Surg* 2007; **205**: 807–11.

4 Bruera E, Palmer JL, Pace E *et al*. A randomized controlled trial of physician postures when breaking bad news to cancer patients. *Palliat Med* 2007; **21**: 501–5.

5 Schofield PE, Butow PN, Thompson JF *et al*. Psychological responses of patients receiving a diagnosis of cancer. *Ann Oncol* 2003; **14**: 48–56.

Concordance (compliance/adherence) with therapy

Hippocrates warned that '(the physician) should be aware . . . that patients often lie when they state they have taken their medicine'. Dermatology patients may not deliberately lie, but there may be many reasons why patients do not carry out a therapy regimen. It is essential that the clinician understands these potential difficulties and takes steps within the consultation to plan therapy which is practical and with which the patient agrees. Although it is self-evident that lack of using therapy will result in lack of effectiveness, it has been demonstrated that there is a direct relationship between better medication adherence and greater reduction in severity, at least in the topical therapy of psoriasis [1]. The terms 'concordance' or 'adherence' are now preferred over 'compliance', as the concept of compliance with treatment implies a patient passive in the treatment decision process—a situation likely to ensure inadequate or inappropriate use of therapy. Concordance issues are of relevance to practically every dermatology consultation [2]. This subject has, however, even wider implications than the issue of optimizing care for individual patients; unless compliance rates are understood, the calculation of cost–effectiveness of different therapies is likely to be inaccurate [3]. Serup *et al*. [4], Hodari *et al*. [5] and Lee and Maibach [6] have reviewed the broader dermatological and Richards *et al*. [7] and Feldman *et al*. [8] the psoriasis specific aspects of adherence. Although the consideration of concordance issues in dermatology usually focuses on topical therapies, other important therapies, such as the use of compression in the treatment of venous leg ulcers, are also often ineffective because of lack of adherence [9].

Monitoring and realities of adherence

When systemic drugs are used in an outpatient setting in cardiology and internal medicine clinics, there are widespread discrepancies in drug usage, with 76% of patients not taking the planned medication correctly [10]. The likelihood of a patient taking oral medication as planned is inversely proportional to the number of times per day that the drug should be taken [11]. There are similar problems with patients using topical preparations [12]; moreover, adherence to topical therapy may be much worse than to systemic therapy [13]. The scale of this issue was emphasized by two studies from Copenhagen which showed that 30% of patients did not collect their medication after receiving a prescription [14] and that most first-time patients with skin conditions under-dose new topical treatments, using a median of 35% of the appropriate dosages [15].

Surprisingly, adherence to prescribed topical preparations may not be 100% even in the supervised conditions of an in-patient dermatology ward [16]. Even in a controlled research setting, when a patient is asked to record the therapy used for skin disease there is poor correlation between reported treatment use and weighed ointment usage [17], with patients self-reporting almost twice the usage as that calculated from weighing used tubes [18]. Electronic monitoring of treatment containers ('the spy in the tube') has also revealed that patients over report adherence in patient logs [19]. The use of such devices allows a more precise method of adherence measurement in clinical trials [20] and has shown that even in the special circumstance of a clinical trial, where high motivation and encouragement about adherence to therapy might be expected, during a clinical trial of topical therapy adherence declined from 85% to 51% over 8 weeks. In a routine clinic setting in which electronic compliance monitoring was not revealed to the patients, there was very poor (32%) compliance in children treated for atopic dermatitis [21].

Influences on adherence

Influences on adherence include the degree of motivation of patients, the extent to which their quality of life is impaired by their disease and the attitude of the patient towards their disease and their relationship with their doctor [22]. In psoriasis, the greater the impairment of life quality of a patient, the poorer the compliance with treatment [23]. Being female, married, employed and not paying for prescriptions were all associated in psoriasis with increased medication adherence and higher life quality. Higher adherence also seems to correlate with increasing years of age [20]. In acne, young females with greatly impaired quality of life and males with little impairment of quality of life are especially prone to non-adherence [24].

A longitudinal study [25] has shown that dissatisfaction with care and psychiatric morbidity are significantly and independently associated with poor medication adherence; the physician's interpersonal skills play a major influence in medication adherence. The strongest predictor of adherence to skincare treatment in childhood atopic dermatitis is a good doctor–patient (mother) relationship [26]; the study draws attention to the crucial role of relatives in adherence. However, this role may not be confined to atopic dermatitis. A range of skin diseases may result in the quality of life of partners and families of patients (i.e. the greater patient) being severely affected [27]. As these close family members are likely to play some role in helping the patient with treatment, they need to be involved in discussions aimed at improving adherence.

Factors associated with poor adherence

There are particular cultural and age-related issues in trying to maximize the likelihood of adolescents taking medication effectively. This is of particular relevance to acne therapy [28]; the use of topical therapy that has a more rapid onset of action is likely to be an advantage in increasing its usage. It is also important to give patients a realistic idea of how quickly they are likely to experience benefit, to try to avoid patients giving up on therapy before a drug has had a chance to work. Key influences in the compliance of acne patients in attending follow-up clinic appointments were gender, race, method of payment and type of treatment [29]. Although attendance at clinics may not necessarily correlate with use of therapy [29], in another acne study being female, married, employed and not paying for prescriptions were all associated with increased medication adherence [30].

Quality and frequency of topical applications

In a study of over 1200 patients with psoriasis across Europe, the main reasons for non-compliance were that the treatment 'was too sticky', 'does not work' and 'takes too long to rub in' [31]. This study emphasized the great importance of cosmetic acceptability in the successful treatment of psoriasis. Other factors that are likely to improve adherence with therapy include patient education about how to apply topical preparations and the use of as few different preparations as possible. Realistic and simple regimens with, preferably, once-daily applications are much better than regimens with frequent applications, but a simple manoeuvre such as using a cream in the morning and an ointment at night may improve adherence [32].

Topical corticosteroids

When topical corticosteroids were introduced into clinical practice in the 1950s their great benefit to patients with inflammatory disease was immediately apparent. It is unlikely that the phobia surrounding their use, especially in children, would have been predicted. The phobia comes from a lack of understanding about the different potencies of corticosteroids available and a concern over side effects, the risk of which is minimal if they are used correctly. Lack of understanding may lead to inappropriate under use and consequent poor control, especially of atopic dermatitis [33]. Surprisingly, however, the mother's anxiety about using topical corticosteroids did not influence reported use of topical steroids in a Japanese study [26]. Fear of side effects concerning the use of topical corticosteroids is not confined to childhood atopic dermatitis and parental anxiety. Adults with atopic dermatitis apply too little topical steroids and the use of appropriate amounts results in improved Severity Scoring of Atopic Dermatitis (SCORAD) scores [34]. Adults with psoriasis also deviated from steroid treatment instructions because of safety concerns [35]. Other reasons included frustration with medication efficacy and inconvenience of use. It is important that clinicians are aware of this issue and address it in discussions of advice about their use. An approach to improving treatment compliance in occupational dermatitis has been the concept of a specialist nurse led 'eczema school' to contribute to the education of patients and carers [36].

Patient attitudes and depression

Only 33% of patients with psoriasis who were asked to apply an ointment twice daily actually did so [12]. Patients with psoriasis who report that they have not complied with treatment are more likely to believe that both psoriasis and their treatment interfered with their quality of life [37]. Self-reported non-adherer patients with psoriasis demonstrate more negative views towards all aspects of health care [38]. In both psoriasis [23,39] and in acne [30] adherence with therapy is poorer the greater the severity of the disease. There is a strong correlation between the presence of depressive symptoms in older patients and lower rates of topical medication usage for psoriasis [40]. It is possible that having severe skin disease leads to poor life quality, which in turn leads to a degree of depression and a sense of 'giving up'. This may result in poor concordance with therapy and in turn further deterioration in the disease. Strategies are needed to break this negative feedback loop. It is likely that treatment failure is much more often due to non-adherence than has been previously recognized. It is encouraging that adherence to biological therapies appears to be higher than to other psoriasis medications [41].

Techniques in the clinic

A very basic problem concerning adherence is that physicians may not have insight into the frequency and extent of adherence issues in everyday consultations. A simple technique, the 'yesterday use' question, has been suggested [42] to heighten awareness and introduce the subject in a non-threatening way into a consultation. The patient is asked whether or not they applied any medication the previous day, and if so how often. However, adherence to topical therapy may increase around the time of visits to a dermatologist and so it has been suggested that the timing of follow-

up appointments could be chosen to try to enhance compliance [43]; increasing frequency of visits might increase adherence [21].

Realistic information

The use of therapy that gives early improvement is preferable but where this is not possible the patient must understand the reality of the likelihood of speed of improvement. The patient must have the opportunity to express concerns about treatment so that unfounded fears can be allayed. For patients with psoriasis, even more important than the speed of action of a topical treatment is the opportunity to be involved in the decision taking [44]. Joint discussion and decisions between doctor and patient should be taken; this involvement by patients in the decision process is critical to adherence [45]. Patients need information about possible side effects and how to handle them: for example if a patient is warned that there may be transient stinging, the patient may continue to use a drug instead of being alarmed and stopping it. Clear instructions should be given about how long a drug should be used for; this may reduce the possibility of side effects from over use of topical corticosteroids [35]. The cost and affordability of therapy is an obvious factor in many health care settings.

Strategies for improvement

There is a major challenge for dermatologists to identify those factors that contribute to non-adherence and to develop strategies that make it more likely a patient will use medication appropriately and in their best interests. Individualized patient education, continuous treatment support with assessment of medication-taking behaviour and developing better communication skills should all be considered [45]. Specific advice for psoriasis is given by Feldman *et al*. [8]. Where educational messages about the importance for renal transplant patients of sun protection were given in a specialist dermatological setting, there was a high compliance with sunscreen use and other sun-avoidance measures [46].

Better interprofessional communication and collaboration, especially between the pharmacist and other providers, are required [47]. It has been proposed [48] that pharmacy labelling of topical corticosteroids should reflect the low risk of harm from their use and that topical corticosteroid products should include clear 'fingertip unit' [49] instructions to guide patients on how much to use.

Elwyn *et al*. [50] have proposed a series of 'concordance tasks' for clinicians: elicit the patient's views on the possibility of having to take medicine; explore those views with the patient; inform the patient of the pros and cons of taking and not taking medicine; involve the patient in the treatment decisions—over time, if necessary, and after reflection. These concepts are closely intertwined with the encouragement of patient motivation. Richards and Fortune [51] have also suggested some practical, detailed strategies for the development of a collaborative treatment approach in psoriasis to enhance adherence. These involve strategies that enhance motivation for behaviour change, for strengthening commitment and for follow-through. A series of practical suggestions to improve compliance with the treatment of children with atopic dermatitis are given in Table 72.2 [52].

Table 72.2 Solutions to improve compliance in childhood atopic dermatitis [52].

Take longer with the first consultation
Write out instructions
Keep therapy simple
Make sure the parents can afford it
Ask about side effects
Go along with a desire to have the child allergy tested
Demonstration of treatment application
Motivation of child as well as parent
Support groups
Hospitalization
Follow up your patient
Be friendly

References

1 Carroll CL, Feldman SR, Camacho FT, Balkrishnan R. Better medication adherence results in greater improvement in severity of psoriasis. *Br J Dermatol* 2004; **151**: 895–7.

2 Witkowski JA. Compliance: the dermatologic patient. *Int J Dermatol* 1988; **27**: 608–11.

3 Hughes DA, Bagust A, Haycox A, Walley T. The impact of non-compliance on the cost-effectiveness of pharmaceuticals: a review of the literature. *Health Econ* 2001; **10**: 601–15.

4 Serup J, Kettis Lindblad A, Maroti M *et al*. To follow or not to follow dermatological treatment—a review of the literature. *Acta Derm Venereol* 2006; **86**: 193–7.

5 Hodari KT, Nanton JR, Carroll CL *et al*. Adherence in dermatology: a review of the last 20 years. *J Dermatol Treat* 2006; **17**: 136–42.

6 Lee IA, Maibach HI. Pharmionics in dermatology: a review of topical medication adherence. *Am J Dermatol* 2006; **7**: 231–6.

7 Richards HL, Fortune DG, Griffiths CEM. Adherence to treatment in patients with psoriasis. *J Eur Acad Dermatol Venereol* 2006; **20**: 370–9.

8 Feldman SR, Horn EJ, Balkrishnan R *et al*. Psoriasis: improving adherence to topical therapy. *J Am Acad Dermatol* 2008; **59**: 1009–16.

9 Heinen MM, van der Vleuten C, de Rooij MJ *et al*. Physical activity and adherence to compression therapy in patients with venous leg ulcers. *Arch Dermatol* 2007; **143**: 1283–8.

10 Bedell SE, Jabbour S, Goldberg R *et al*. Discrepancies in the use of medications. *Arch Intern Med* 2000; **160**: 2129–34.

11 Nelson JD. Clinical compliance and patient tolerance. *Infect Dis Clin Prac* 1994; **3**: 158–60.

12 Van de Kerkhof PCM, Steegers-Theunissen RPM, Kuipers MV. Evaluation of topical drug treatment in psoriasis. *Dermatology* 1998; **197**: 31–6.

13 Krejci-Manwaring J, McCarty MA, Camacho F *et al*. Adherence with topical treatment is poor compared with adherence with oral agents: implications for effective clinical use of topical agents. *J Am Acad Dermatol* 2006; **54**: S235–6.

14 Storm A, Anderson SE, Benfeldt E, Serup J. One in 3 prescriptions are never redeemed: primary nonadherence in an outpatient clinic. *J Am Acad Dermatol* 2008; **59**: 27–33.

15 Storm A, Benfeldt E, Anderson SE, Serup J. A prospective study of patient adherence to topical treatments: 95% of patients underdose. *J Am Acad Dermatol* 2008; **59**: 975–80.

16 Hallai N, Finlay AY, Godfrey J *et al*. Inpatient compliance of topical applications. *Br J Dermatol* 2005; **153**: 446–8.

17 Goodwin RG, Finlay AY. Structured patient reporting of compliance is very inaccurate. *Br J Dermatol* 2002; **147** (Suppl. 62): 13–8.

18 Zaghloul SS, Goodfield M. Clinical trial patients' topical medication adherence: poor adherence or over adherence to a clinical trial regimen can adversely affect the validity of research outcomes. *J Am Acad Dermatol* 2004; **50**: P12.

19 Balkrishnan R, Carroll CL, Camacho FT, Feldman SR. Electronic monitoring of medication adherence in skin disease: results of a pilot study. *J Am Acad Dermatol* 2003; **49**: 651–4.

20 Carroll CL, Feldman SR, Camacho FT *et al*. Adherence to topical therapy decreases during the course of an 8-week psoriasis clinical trial: commonly used methods of measuring adherence to topical therapy overestimate actual use. *J Am Acad Dermatol* 2004; **51**: 212–6.
21 Krejci-Manwaring J, Tusa MG, Carroll C *et al*. Stealth monitoring of adherence to topical medication: adherence is very poor in children with atopic dermatitis. *J Am Acad Dermatol* 2007; **56**: 211–6.
22 Chren M-M. Doctor's orders: rethinking compliance in dermatology. *Arch Dermatol* 2002; **138**: 393–4.
23 Zaghloul SS, Goodfield MJD. Objective assessment of compliance with psoriasis treatment. *Arch Dermatol* 2004; **139**: 408–14.
24 Jones-Caballero M, Pedrosa E, Penas PF. Self-reported adherence to treatment and quality of life in mild to moderate acne. *Dermatology* 2008; **217**: 309–14.
25 Renzi C, Picardi A, Abeni D *et al*. Association of dissatisfaction with care and psychiatric morbidity with poor treatment compliance. *Arch Dermatol* 2002; **138**: 337–42.
26 Ohya Y, Williams H, Steptoe A *et al*. Psychosocial factors and adherence to treatment advice in childhood atopic dermatitis. *J Invest Dermatol* 2001; **117**: 852–7.
27 Basra MKA, Finlay AY. The family impact of skin diseases: the Greater Patient concept. *Br J Dermatol* 2007; **156**: 929–37.
28 Finlay AY. Better quality treatments for your patients. *J Dermatol Treat* 1998; **9** (Suppl. 2): S3–S6.
29 McEvoy B, Nydegger R, Williams G. Factors related to patient compliance in the treatment of acne vulgaris. *Int J Dermatol* 2003; **42**: 274–80.
30 Zaghloul SS, Cunliffe WJ, Goodfield MJ. Objective assessment of compliance with treatments in acne. *Br J Dermatol* 2005; **152**: 1015–21.
31 Fouéré S, Adjadj L, Pawin H. How patients experience psoriasis: results from a European survey. *J Eur Acad Dermatol Venereol* 2005; **19** (Suppl. 3): 2–6.
32 Van de Kerkhof PC, Franssen M, de la Brassine M, Kuipers M. Calcipotriol cream in the morning and in the evening: a novel regimen to improve compliance. *J Dermatol Treat* 2001; **12**: 75–9.
33 Charman CR, Morris AD, Williams HC. Topical corticosteroids phobia in patients with atopic eczema. *Br J Dermatol* 2000; **142**: 931–6.
34 Neimeier V, Kupfer J, Schill W-B, Geiler U. Atopic dermatitis—topical therapy: do patients apply much too little? *J Dermatol Treat* 2005; **16**: 95–101.
35 Brown KK, Rehmus WE, Kimball AB. Determining the relative importance of patient motivations for nonadherence to topical corticosteroid therapy in psoriasis. *J Am Acad Dermatol* 2006; **55**: 607–13.
36 Kalimo K, Kautiainen H, Niskanen T, Niemi L. 'Eczema school' to improve compliance in an occupational dermatology clinic. *Contact Dermatitis* 1999; **41**: 315–9.
37 Richards HL, Fortune DG, O'Sullivan TM *et al*. Patients with psoriasis and their compliance with medication. *J Am Acad Dermatol* 1999; **41**: 581–3.
38 Richards HL, Mason DL, Fortune DG *et al*. Adherence to treatment; does satisfaction with healthcare provision predict compliance in psoriasis? *Br J Dermatol* 2002; **147**: 1070.
39 Zaghloul S, Gonzalez M, Judodihardjo H, Finlay AY. In psoriasis, the greater the disability, the poorer the topical treatment compliance. *Br J Dermatol* 1999; **141** (Suppl. 55): 48.
40 Kulkarni AS, Balkrishnan R, Camancho FT *et al*. Medication and health care utilization related to depressive symptoms in older adults with psoriasis. *J Drugs Dermatol* 2004; **3**: 661–6.
41 Bhosle MJ, Feldman SR, Camacho FT *et al*. Medication adherence and health care costs associated with biologics in Medicaid-enrolled patients with psoriasis. *J Dermatol Treat* 2006; **17**: 294–301.
42 Belgi AS, Finlay AY. The Yesterday Use question to assess adherence with therapy in dermatology outpatients. *Br J Dermatol* 2005; **153** (Suppl. 1): 47–8.
43 Feldman SR, Camacho FT, Krejci-Manwaring J *et al*. Adherence to topical therapy increases around the time of office visits. *J Am Acad Dermatol* 2007; **57**: 81–3.
44 Van de Kerkhof PC, de Hoop D, de Korte J *et al*. Patient compliance and disease management in the treatment of psoriasis in the Netherlands. *Dermatology* 2000; **200**: 292–8.
45 Kjellgren KI, Ring L, Lindblad AK *et al*. To follow dermatological treatment regimens—patients' and providers' views. *Acta Derm Venereol* 2004; **84**: 445–50.
46 Ismail F, Mitchell L, Casabonne D *et al*. Specialist dermatology clinics for organ transplant recipients significantly improve compliance with photoprotection and levels of skin cancer awareness. *Br J Dermatol* 2006; **155**: 916–25.
47 Lindblad KA, Kjellgren K, Ring L *et al*. The role of dermatologists, nurses and pharmacists in chronic dermatological treatment: patient and provider views and experiences. *Acta Derm Venereol* 2006; **86**: 202–8.
48 Bewley A. Expert consensus: time for a change in the way we advise our patients to use topical corticosteroids. *Br J Dermatol* 2008; **158**: 917–20.
49 Long CC, Finlay AY. The finger-tip unit—a new practical measure. *Clin Exp Dermatol* 1991; **16**: 444–7.
50 Elwyn G, Edwards A, Britten N. 'Doing prescribing': how doctors can be more effective. *BMJ* 2003; **327**: 864–7.
51 Richards HL, Fortune DG. Psychological distress and adherence in patients with psoriasis. *J Eur Acad Dermatol Venereol* 2006; **20** (Suppl. 2): 33–41.
52 Fischer G. Compliance problems in paediatric atopic eczema. *Australas J Dermatol* 1996; **37**: S10–3.

Measurement of disease

Why measure disease?

Skin disease is so visible that the drive for measurement of disease for basic clinical purposes has been slow. It is helpful, however, to be able to measure skin disease for several clinical reasons. Initial assessment of the clinical severity of skin disease is likely to influence clinical decision taking. Having comparative measures may be useful in patient follow-up to assess progress with therapy. Measures may also be helpful in the doctor–patient relationship to inform discussion of management decisions. For clinical research it is essential to be able to compare disease severity between patients and before and after intervention.

Historical perspective

Measurement methods in dermatology have been described from the 19th century, but interest has accelerated over the last 40 years [1]. Multiple non-validated techniques were used in the 1970s and 1980s for the assessment of psoriasis [2]. Over the last 20 years, most researchers have gravitated to using the same method (Psoriasis Area and Severity Index, PASI) and there has been the additional use of quality of life measures [3]. The use of non-invasive methods to measure various physical properties of the skin developed from the 1970s but only recently has the instrumentation become sufficiently user-friendly, available and reliable to envisage regular clinical use.

What can be measured?

When a patient is being assessed in the clinic, the clinician takes into account a variety of facets of information. These include key aspects of the patient's history, current symptoms, clinical signs and the impact that the patient is experiencing because of the disease. All of these aspects may potentially be measured. The most widely used methods focus on recording clinical signs, using semi-objective approaches.

Measurement methods

Inflammatory disease

The Dermatology Index of Disease Severity (DIDS) has been proposed [4] for use across all inflammatory skin diseases. It consists of assessments of functional impairment and of percentage of body surface area involvement, categorizing each patient into one

Table 72.3 Methods of psoriasis measurement.

Psoriasis Area and Severity Index (PASI) [6]
Self-Administered PASI [8]
Physician's Global Assessment [12]
Lattice System Global Assessment [13]
Copenhagen Psoriasis Severity Index [15]
Salford Psoriasis Index [16]
Miscellaneous [2]
Photographs [17]
Nail Psoriasis Severity Index [18]

Table 72.4 Methods of atopic dermatitis measurement.

Rajka Langland Severity Classification [22]
Nottingham Eczema Severity Score (NESS) [23]
SCORAD [26]
Eczema Area and Severity Index (EASI) [33]
Six-Area Six Sign Atopic Dermatitis Severity Score (SASSAD) [37]
Patient Orientated Eczema Measure (POEM) [36]
Three-Item Severity Score (TIS) [39]
Objective Severity Assessment Atopic Dermatitis (OSAAD) [41]

of five stages. It has been tested in a wide range of dermatoses and shown to be responsive to change [5].

Psoriasis

A range of methods for psoriasis measurement is listed in Table 72.3. The most widely used system, the Psoriasis Area and Severity Index (PASI), was introduced as a methodology for a clinical trial of a retinoid [6] but without any supporting validation data concerning its repeatability or observer variation. It began to be widely used in the 1990s, despite evidence of its weaknesses [7]. The PASI system requires the observer to give separate scores for redness, thickness and scaling ('erythema, infiltration and desquamation' in the original description) for four body areas [6]. An estimate is made of the percentage area involvement in each of these areas and all scores placed in a formula to give an overall score from 0 to 72. The vast majority of patients with psoriasis have a score of less than 10. A self (patient) administered and validated method based on the PASI, the Self Administered PASI (SAPASI) [8], allows the possibility of measurement in large, population-based surveys [9]. There have been attempts to modify the PASI concept [10], but such suggestions have largely not been followed. The current reality is that the PASI system, although fundamentally flawed, is used so widely that it has become a way of comparing across all studies and so researchers are generally reluctant to choose alternative, though better, methods. There is considerable information about the concurrent use of the PASI, the most commonly used disease severity measure, and the Dermatology Life Quality Index (DLQI), the most commonly used quality of life outcome measure; patients in whom there is a very great improvement in PASI also show the greatest improvement in DLQI scores [11].

The simplest scoring system is the Physician's Global Assessment (PGA); this correlates reasonably well with PASI scores and may be suitable where a rapid and easy, global assessment is all that is required [12]. The Lattice System Global Assessment has been proposed [13] as an alternative and better-validated measure [14] than PASI. In the Lattice System there is an estimation of body surface area and of average plaque thickness, erythema and scale; the results are combined to reach an overall descriptor [13]. Another proposal is the Copenhagen Psoriasis Severity Index [15] in which erythema, plaque thickness and scaling are each assessed on a four-point scale at each of 10 sites, giving a score range of 0 to 90. By not involving assessment of area, the inherent inaccuracies of this are avoided.

The Salford Psoriasis Index (SPI) is an important contribution to the ongoing and as yet unresolved debate about the best way to measure psoriasis [16]. This measure acknowledges that there are three separate aspects to the assessment of a patient's psoriasis severity and it is meaningless to try to present these data as a single overall score. There are therefore three scores for clinical severity (based on the PASI), psychological impact (a simple overall score) and the history of the psoriasis, including for example history of admission for treatment. This concept of separate scores is analogous to the multiple score system used for staging some systemic malignancies. The SPI may be well suited to describing or categorizing patients. However, only the clinical severity and psychological scores are amenable to change following intervention.

Photographs may be used to record and to assess psoriasis. Where a panel of experts is used to assess photographs there is accurate and consistent global assessment [17].

There are special considerations to the measurement of psoriasis in specific sites such as the scalp or nails, or specific presentations such as pustular psoriasis of the palms or soles. The Nail Psoriasis Severity Index (NAPSI) has been used in several clinical studies [18] and there is information concerning interobserver error [19]; scoring for nail-bed features was more reliable than for nail-matrix features. A simpler variant of the NAPSI has been proposed [20,21].

Atopic dermatitis

A simple method to differentiate between mild, moderate and severe atopic dermatitis incorporated extent of disease, history and disturbance of sleep by itching [22]. This method has since been refined as the Nottingham Eczema Severity Score (NESS) and initially validated in pre-school children [23]. Although several different methods of disease measurement had been described by the 1990s, none was satisfactory [24]. A review of outcome measures of disease severity in atopic eczema identified 13 scales [25]. Only five had been tested for reliability; the most widely validated measure was the Severity Scoring of Atopic Dermatitis (SCORAD) index [26]. A more recent, systematic review identified 20 outcome measures and concluded that only SCORAD, Eczema Area and Severity Index (EASI) and the Patient-Orientated Eczema Measure (POEM) perform adequately [27] (Table 72.4).

SCORAD was created in 1993 [26] to meet the need for a validated methodology; there are further guidelines for its use [28] and experience of the practicalities of its use [29,30]. SCORAD brings together scores for clinical signs, disease extent and patient symptoms, including a question on sleep. However, subjective symptoms do not necessarily correlate well with sign measurement in atopic dermatitis [31] and the use of a modified 'objective

SCORAD' which omits pruritus and sleep is now recommended by the European Taskforce on Atopic Dermatitis [30,32].

The Eczema Area and Severity Index (EASI) can be learnt rapidly and used reliably in the clinical trial setting [33]; there is experience of its use in a large study [34]. A self-administered version of EASI has been validated [35].

The Patient-Orientated Eczema Measure (POEM) [36] is completed by patients and incorporates seven symptoms: itchiness, sleep, bleeding, weeping or oozing clear fluid, cracked skin, flaking, dry or rough. The frequency of each over the last week is recorded, giving a total score of 0 to 28. The POEM score correlates well with quality of life scores [36].

The Six Area Six Sign Atopic Dermatitis (SASSAD) severity score [37,38] has the major advantage of not incorporating any attempt to estimate area of involvement. Estimation of area in atopic dermatitis is much more difficult than for psoriasis as there is often no clear delineation between normal and abnormal skin. The six signs recorded are erythema, exudation, excoriation, dryness, cracking and lichenification. Each sign is scored at six different sites. However, a very simple Three Item Severity Score [39], measuring only excoriations, erythema and oedema/papulation may provide as much information about current severity of atopic dermatitis as more detailed measuring techniques [40].

The subjective nature of most scoring systems and the inevitable variation of scoring between observers has been a spur to develop instrument-based, objective approaches to atopic dermatitis measurement. The Objective Severity Assessment of Atopic Dermatitis (OSAAD) score incorporates measurements of stratum corneum barrier function (transepidermal water loss) and hydration (stratum corneum capacitance) with computer-assisted measurements of extent of the disease [41]. OSAAD scores correlate with the SCORAD index and also with serum levels of interleukin-16 [42].

Hand dermatitis

Some skin diseases when occurring at specific sites cannot be measured using scoring systems designed for situations when the disease affects wide areas of the body. One example is hand eczema. The Hand Eczema Severity Index (HECSI) [43] requires scoring erythema, infiltration/papulation, vesicles, fissures, scaling and oedema at five sites on the hands. The area of involvement at each location is recorded and a final score calculated. Good inter- and intraobserver reliability was demonstrated, and the HECSI has been used in a population-based study of hand eczema [44]. Similarly, the Osnabrueck Hand Eczema Severity Index (OHSI) [45] is based on scoring six clinical signs. A photographic guide has been proposed for assessing the morphological severity of hand dermatitis [46]. Four photographs are used to illustrate each of five levels of severity from clear to very severe. The Occupational contact Dermatitis Disease severity Index (ODDI) is an amalgam of assessment over the previous 2 months of disease course, treatment, clinical signs and work-related activities [47]. The validity and reliability of this instrument have been demonstrated.

Acne

There have been many methods described to measure acne, ranging from global assessments to lesion counting [48]. Several methods to try to measure acne were used in the 1960s and 1970s but the Leeds technique [49] dominated acne measurement for the following two decades. Two methods were described in this paper, the grading technique and the counting technique. The grading technique divided patients into grades from 0 to 10, with seven subgroups between 0 and 2. Photographic guides to the grades were given, but the importance of also palpating lesions was stressed. This system was based on experience from the pre-isotretinoin era, and the severity of acne in grades above 2 is now rarely seen. The counting technique involves direct counting of non-inflamed and inflamed lesions, including superficial papules and pustules, deep inflamed lesions and macules. The revised Leeds acne grading system [50] also includes numerical grading systems for the back and chest as well as for the face.

A simpler, photographic standard-based grading method, using a 0–8 scale, was used successfully in a number of clinical trials [51]. Parallel-polarized and cross-polarized photography, videomicroscopy and fluorescence photography can now all be used in acne assessment [52].

The Echelle de Cotation des Lesions d'Acne (ECLA) or 'Acne Lesion Score Scale' system has demonstrated good reliability [53]. ECLA scores do not correlate with quality of life scores and the use of both disease sign scores and quality of life scores is suggested [54].

Methods to specifically measure post-acne scarring are also needed; a global scarring grading system has been proposed with four grades of scarring described [55]. The Echelle d'Evaluation Clinique des Cicatrices d'Acne (ECCA) [56] consists of recording the number of each of six types of acne scars. The overall count is an approximation: none, a few, limited number or many. This is a relatively simple method that shows initial reliability.

Rosacea

Clinicians and patients assess rosacea differently, with patients focusing on papules and pustules and clinicians taking more note of erythema [57]. A wide variety of methods have been used to measure rosacea but there are no standard, validated methods [58,59].

Cutaneous lupus erythematosus

The Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) [60] consists of two scores, one summarizing the current activity of the disease and the other measuring the damage done. Erythema, scale/hyperkeratosis, mucous membrane damage, acute hair loss and non-scarring alopecia are all assessed at 13 anatomical sites.

Symptoms

The most dominant dermatological symptom is itch. Attempts are often made to record itch in clinical studies, usually with a single global question related to itch, either alone or as part of other standard tools such as the SCORAD or DLQI. Studies have recorded frequency of scratching as a surrogate measure of itch, either by direct observation or by the use of instruments such as the DigiTrac that detects wrist movement [61]. It has been suggested that the objective measure of wrist activity should substi-

tute for the pruritus and sleep components of SCORAD [62]. The Itch Severity Scale records the frequency of itch at different times during the day and asks the patient to choose a description of the specific sensation [63]. The site of itch is recorded on a body chart and there are questions about mood, sexual desire/function and sleep.

Objective measures

Over the last 30 years many methodologies have been developed to objectively measure various physical properties of skin; the use of ultrasound to measure skin thickness was one of the first technologies applied [64]. This method has been applied most frequently to the measurement of thickness of psoriatic plaques [65,66]. Barrier function of the skin is most effectively assessed *in vivo* by measuring transepidermal water loss (TEWL) [67]. Such measurements may be influenced by ambient temperature and humidity and so there has been some refinement of methodologies available [68]. There have been some early applications of optical coherence tomography to the skin, initially to measure epidermal thickness [69]. Serup, Jemec and Grove have produced an excellent source of information concerning all aspects of non-invasive methods of assessing the skin [70].

Several techniques have been described to try to measure skin colour, including erythema [71], and guidelines proposed for standardized procedures [72]. The problems inherent in assessment of skin colour illustrate that measurement of 'objective' properties of skin may encounter a range of variable influences as diverse as the influences on 'subjective' measures. Erythema, for example, is influenced by local light conditions, instrument-related variables and individual properties such as physical activity or menstrual cycle. Despite this, devices are now becoming available that are relatively simple to use and may have applications in aiding clinical work [73]. Skin pigmentation is primarily influenced by melanin and a variety of techniques have been used to measure pigmentation [74], including by diffuse reflectance spectroscopy [75].

Other skin properties, such as elasticity [76], hydration or surface topography, can be measured, though mostly the ability to measure has not been translated yet into use of such measurement in routine clinical work. Stratum corneum hydration is usually measured using capacitance techniques and this approach has led to a novel method of imaging the skin surface using capacitance images [77].

An accurate way to measure of the area of involvement of skin disease is needed for many clinical record and research purposes. Most subjective methods have wide variability between observers. Although it might seem that objective area methods should be relatively easy to create, following advances in image analysis, progress has been slow, partly because of the challenges of dealing with distortion caused by body contours and partly because of the difficulties in defining the margins of skin disease. Computer-aided analysis of manually outlined lesions on photographs [78] may enhance the accuracy of area estimation, but 'old-fashioned' point counting of photographs seems to be as reliable as digital planimetry in assessing the area affected by vitiligo [79].

References

1 Vazquez-Lopez F, Gotor Corrales ML, Coto Segura P *et al*. Subjective and objective measurement methods in clinical dermatology from an historical perspective: the long way from Joseph Plenck to validation. *Int J Dermatol* 2006; **45**: 1242–4.

2 Marks R, Barton SP, Shuttleworth D, Finlay AY. Assessment of disease progress in psoriasis. *Arch Dermatol* 1989; **125**: 235–40.

3 Morsy H, Kamp S, Jemec GB. Outcomes in randomized controlled trials in psoriasis: what has changed over the last 20 years? *J Dermatolog Treat* 2007; **18**: 261–7.

4 Faust HB, Gonin R, Chuang T-Y *et al*. Reliability testing of the dermatology index of disease severity (DIDS). An index for staging the severity of cutaneous inflammatory disease. *Arch Dermatol* 1997; **133**: 1443–8.

5 Hahn HB, Chuang T-Y. Using the Dermatology Index of Disease Severity (DIDS) to assess the responsiveness of dermatitis. *Clin Exp Dermatol* 2005; **31**: 19–22.

6 Fredriksson T, Pettersson U. Severe psoriasis—oral therapy with a new retinoid. *Dermatologica* 1978; **157**: 238–44.

7 Ramsay B, Lawrence CM. Measurement of involved surface area in patients with psoriasis. *Br J Dermatol* 1991; **124**: 565–70.

8 Feldman SR, Fleischer AB Jr, Reboussin DM *et al*. The self-administered psoriasis area and severity index is valid and reliable. *J Invest Dermatol* 1996; **106**: 183–6.

9 Sampogna F, Sera F, Mazzotti E *et al*. Performance of the self-administered psoriasis area and severity index in evaluating clinical and sociodemographic subgroups of patients with psoriasis. *Arch Dermatol* 2003; **139**: 353–8.

10 Jacobson CC, Kimball AB. Rethinking the Psoriasis Area and Severity Index: the impact of area should be increased. *Br J Dermatol* 2004; **151**: 381–7.

11 Revicki DA, Willian MK, Menter A *et al*. Relationship between clinical response to therapy and health-related quality of life outcomes in patients with moderate to severe plaque psoriasis. *Dermatology* 2008; **216**: 260–70.

12 Gottlieb AB, Chaudhari U, Baker DG *et al*. The National Psoriasis Foundation Psoriasis Score (NPF-PS) system versus the Psoriasis Area Severity Index (PASI) and Physician's Global Assessment (PGA): a comparison. *J Drugs Dermatol* 2003; **2**: 260–6.

13 Langley RG, Ellis CN. Evaluating psoriasis with Psoriasis Area and Severity Index, Psoriasis Global Assessment, and Lattice System Physician's Global Assessment. *J Am Acad Dermatol* 2004; **51**: 563–9.

14 Berth-Jones J, Grozinger K, Rainville C *et al*. A study examining inter- and intrarater reliability of three scales for measuring severity of psoriasis: Psoriasis Area and Severity Index, Physician's Global Assessment and Lattice System Physician's Global Assessment. *Br J Dermatol* 2006; **155**: 707–13.

15 Berth-Jones J, Thompson J, Papp K: Copenhagen Psoriasis Working Group. A study examining inter-rater and intrarater reliability of a novel instrument for assessment of psoriasis: the Copenhagen Psoriasis Severity Index. *Br J Dermatol* 2008; **159**: 407–12.

16 Kirby B, Fortune DG, Bhushan M *et al*. The Salford Psoriasis Index: an holistic measure of psoriasis severity. *Br J Dermatol* 2000; **142**: 728–32.

17 Farhi D, Falissard B, Dupuy A. Global assessment of psoriasis severity and change from photographs: a valid and consistent method. *J Invest Dermatol* 2008; **128**: 2198–203.

18 Rich P, Scher RK. Nail Psoriasis Severity Index: a useful tool for evaluation of nail psoriasis. *J Am Acad Dermatol* 2003; **49**: 206–12.

19 Aktan S, Ilknur T, Akin C, Ozkan S. Interobserver reliability of the Nail Psoriasis Severity Index. *Clin Exp Dermatol* 2007; **32**: 141–4.

20 Cannovo SP, Guarneri F, Vaccaro M *et al*. Treatment of psoriatic nails with topical cyclosporin: a prospective, randomized placebo controlled study. *Dermatology* 2003; **206**: 153–6.

21 Kacar N, Ergin S, Erdogan BS. The comparison of Nail Psoriasis Severity Index with a less time-consuming qualitative system. *J Eur Acad Dermatol Venereol* 2008; **22**: 219–22.

22 Rajka G, Langeland T. Grading of the severity of atopic dermatitis. *Acta Derm Venereol (Stockh)* 1989; **144** (Suppl.): 13–4.

23 Emerson RM, Charman CR, Williams HC. The Nottingham Eczema Severity Score: preliminary refinement of the Rajka and Langeland grading. *Br J Dermatol* 2000; **142**: 288–97.

24 Finlay AY. Measurement of disease activity and outcome in atopic dermatitis. *Br J Dermatol* 1996; **135**: 509–15.

25 Charman C, Williams H. Outcome measures of disease severity in atopic eczema. *Arch Dermatol* 2000; **136**: 763–9.

26 European Task Force. Severity scoring of atopic dermatitis: the SCORAD index. Consensus report of the European Task Force on atopic dermatitis. *Dermatology* 1993; **186**: 23–31.

27 Schmitt J, Langan S, Williams HC; European Dermato-Epidemiology Network. What are the best outcome measurements for atopic eczema? A systematic review. *J Allergy Clin Immunol* 2007; **120**: 1389–98.

28 Kunz B, Oranje AP, Labreze L *et al*. Clinical validation and guidelines for the SCORAD index: consensus report of the European Task Force on atopic dermatitis. *Dermatology* 1997; **195**: 10–9.

29 Pucci N, Novembre E, Cammarata MG *et al*. Scoring atopic dermatitis in infants and young children: distinctive features of the SCORAD index. *Allergy* 2005; **60**: 113–6.

30 Oranje AP, Glazenburg EJ, Wolkerstorfer A *et al*. Practical issues on interpretation of scoring atopic dermatitis: the SCORAD index, objective SCORAD and the three-item severity score. *Br J Dermatol* 2007; **157**: 645–8.

31 Hon KLE, Leung TF, Wong Y, Fok TF. Lesson from performing SCORADs in children with atopic dermatitis: subjective symptoms do not correlate well with disease extent or activity. *Int J Dermatol* 2006; **45**: 728–30.

32 Kunz B, Oranje AP, Labreze L *et al*. Clinical validation and guidelines for the SCORAD index: consensus report of the European Task Force on Atopic Dermatitis. *Dermatology* 1997; **195**: 10–9.

33 Hanifin JM, Thurston M, Omoto M *et al*. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. *Experimental Dermatol* 2001; **10**: 11–8.

34 Barbier N, Paul C, Luger T *et al*. Validation of the Eczema Area and Severity Index for atopic dermatitis in a cohort of 1550 patients from the pimecrolimus cream 1% randomized controlled clinical trials programme. *Br J Dermatol* 2004; **150**: 96–102.

35 Houseman TS, Patel MJ, Camacho F *et al*. Use of the Self-Administered Eczema Area and Severity index by parent caregivers: results of a validation study. *Br J Dermatol* 2002; **147**: 1192–8.

36 Charman CR, Venn AJ, Williams HC. The patient-orientated eczema measure: development and initial validation of a new tool for measuring atopic eczema from the patient's perspective. *Arch Dermatol* 2004; **140**: 1513–9.

37 Berth-Jones J. Six area, six sign atopic dermatitis (SASSAD) severity score: a simple system for monitoring disease activity in atopic dermatitis. *Br J Dermatol* 1996; **135** (Suppl. 48): 25–30.

38 Charman CR, Venn AJ, Williams HC. Reliability testing of the six area, six sign atopic dermatitis severity score. *Br J Dermatol* 2002; **146**: 1057–60.

39 Wolkerstorfer A, De Waard van der Spek FB, Glazenburg EJ *et al*. Scoring the severity of atopic dermatitis: three item severity score as a rough system for daily practice and as a pre-screening tool for studies. *Acta Derm Venereol* 1999; **79**: 356–9.

40 Charman CR, Venn AJ, Williams H, Bigby M. Measuring atopic eczema severity visually: which variables are the most important? *Arch Dermatol* 2005; **141**: 1146–51.

41 Sugarman JL, Fluhr JW, Fowler AJ *et al*. The Objective Severity Assessment Atopic Dermatitis Score. *Arch Dermatol* 2003; **139**: 1417–22.

42 Angelova-Fischer I, Bauer A, Hipler UC *et al*. The Objective Severity Assessment of Atopic Dermatitis (OSAAD) score: validity, reliability and sensitivity in adult patients with atopic dermatitis. *Br J Dermatol* 2005; **153**: 767–73.

43 Held E, Skoet R, Johansen JD, Agner T. The hand eczema severity index (HECSI): a scoring system for clinical assessment of hand eczema. A study of inter- and intraobserver reliability. *Br J Dermatol* 2005; **152**: 302–7.

44 Lerbaek A, Kyvik KO, Ravin H *et al*. Clinical characteristics and consequences of hand eczema—an 8-year follow-up study of a population-based twin cohort. *Contact Dermatitis* 2008; **58**: 210–6.

45 Skudlik C, Dulon M, Pohrt U *et al*. Osnabrueck hand eczema severity index—a study of the interobserver reliability of a scoring system assessing skin diseases of the hands. *Contact Dermatitis* 2006; **55**: 42–7.

46 Coenraads PJ, Van der Walle H, Thestrup-Pedersen K *et al*. Construction and validation of a photographic guide for assessing severity of chronic hand dermatitis. *Br J Dermatol* 2005; **152**: 296–301.

47 Curr N, Dharmage S, Keegel T *et al*. The validity and reliability of the occupational contact dermatitis disease severity index. *Contact Dermatitis* 2008; **59**: 157–64.

48 Witkowski JA, Parish LC. The assessment of acne: an evaluation of grading and lesion counting in the measurement of acne. *Clin Dermatol* 2004; **22**: 394–7.

49 Burke BM, Cunliffe WJ. The assessment of acne vulgaris—the Leeds technique. *Br J Dermatol* 1984; **111**: 83–92.

50 O'Brien SC, Lewis JB, Cunliffe WJ. The Leeds revised acne grading system. *J Dermatol Treat* 1998; **9**: 215–20.

51 Cook CH, Centner RL, Michaels SE. An acne grading method using photographic standards. *Arch Dermatol* 1979; **115**: 571–5.

52 Rizova E, Kligman A. New photographic techniques for clinical evaluation of acne. *J Eur Acad Dermatol Venereol* 2001; **15** (Suppl. 3): 13–8.

53 Dreno B, Bodokh I, Chivot M *et al*. ECLA grading: a system of acne classification for every day dermatological practice. *Ann Dermatol Venereol* 1999; **126**: 136–41.

54 Dreno B, Alirezai M, Auffret N *et al*. Clinical and psychological correlation in acne: use of the ECLA and CADI scales. *Ann Dermatol Venereol* 2007; **134**: 451–5.

55 Goodman GJ, Baron JA. Postacne scarring—a quantitative global scarring system. *J Cosmet Dermatol* 2006; **5**: 48–52.

56 Dreno B, Khammari A, Orain N *et al*. ECCA grading scale: an original validated acne scar grading scale for clinical practice in dermatology. *Dermatology* 2007; **214**: 46–51.

57 Bamford JT, Gessert CE, Renier CM. Measurement of the severity of rosacea. *J Am Acad Dermatol* 2004; **51**: 697–703.

58 Gessert CE, Bamford JT. Measuring the severity of rosacea. *Int J Dermatol* 2003; **42**: 444–8.

59 Gupta AK, Chaudhry MM. Critical review of the manner in which the efficacy of therapies for rosacea are evaluated. *Int J Dermatol* 2003; **42**: 909–16.

60 Albrecht J, Werth VP, Berlin JA *et al*. The ClASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index): an outcome instrument for cutaneous lupus erythematosus. *J Invest Dermatol* 2005; **125**: 889–94.

61 Hon KL, Lam MC, Wong KY *et al*. Pathophysiology of nocturnal scratching in childhood atopic dermatitis: the role of the brain-derived neurotrophic factor and substance P. *Br J Dermatol* 2007; **157**: 922–5.

62 Hon KL, Lam MC, Leung TF *et al*. Nocturnal wrist movements are correlated with objective clinical scores and plasma chemokine levels in children with atopic dermatitis. *Br J Dermatol* 2006; **154**: 629–35.

63 Majeski CJ, Johnson JA, Davison SN, Lauzon CJ. Itch Severity Scale: a self-report instrument for the measurement of pruritus severity. *Br J Dermatol* 2007; **156**: 667–73.

64 Tan CY, Statham B, Marks R, Payne P. Skin thickness measurement by pulsed ultrasound; its reproducibility, validation and variability. *Br J Dermatol* 1982; **106**: 657–67.

65 Vaillant L, Berson M, Machet L *et al*. Ultrasound imaging of psoriatic skin: a non-invasive technique to evaluate treatment of psoriasis. *Int J Dermatol* 1994; **33**: 786–90.

66 Ormerod AD, Dwyer CM, Weller R *et al*. A comparison of subjective and objective measures of reduction of psoriasis with the use of ultrasound, reflectance colorimetry, computerized video image analysis, and nitric oxide production. *J Am Acad Dermatol* 1997; **37**: 51–7.

67 Hon KL, Wong KY, Leung TF *et al*. Comparison of skin hydration evaluation sites and correlations among skin hydration, transepidermal water loss, SCORAD index, Nottingham Eczema Severity Score, and quality of life in patients with atopic dermatitis. *Am J Clin Dermatol* 2008; **9**: 45–50.

68 Nuutinen J, Alanen E, Autio P *et al*. A closed unventilated chamber for the measurement of transepidermal water loss. *Skin Res Technol* 2003; **9**: 85–9.

69 Mogensen M, Morsy HA, Thrane L, Jemec GBE. Morphology and epidermal thickness of normal skin imaged by optical coherence tomography. *Dermatology* 2008; **217**: 14–20.

70 Serup J, Jemec GBE, Grove GL, eds. *Handbook of Non-invasive Methods and the Skin*, 2nd edn. Boca Raton, FL: Taylor and Francis, 2006.

71 Takiwaki H. Measurement of skin color: practical application and theoretical considerations. *J Med Invest* 1998; **44**: 121–6.

72 Fullerton A, Fischer T, Lahti A *et al*. Guidelines for measurement of skin colour and erythema. *Contact Dermatitis* 1996; **35**: 1–10.

73 Pladellorens J, Pinto A, Segura J *et al*. A device for the color measurement and detection of spots on the skin. *Skin Res Technol* 2008; **14**: 65–70.

74 Stamatas GN, Zmudzka BZ, Kollias N, Beer JZ. Non-invasive measurements of skin pigmentation in situ. *Pigment Cell Research* 2004; **17**: 616–26.

75 Zonios G, Bykowski J, Kollias N. Skin melanin, hemoglobin, and light scattering properties can be quantitatively assessed in vivo using diffuse reflectance spectroscopy. *J Invest Dermatol* 2001; **117**: 1452–7.

76 Hashmi F, Malone-Lee J. Measurement of skin elasticity on the foot. *Skin Res Technol* 2007; **13**: 252–8.
77 Batisse D, Giron F, Leveque JL. Capacitance imaging of the skin surface. *Skin Res Technol* 2006; **12**: 99–104.
78 Kreft S, Kreft M, Resman A *et al*. Computer-aided measurement of psoriatic lesion area in a multicenter clinical trial—comparison to physician's estimations. *J Dermatol Sci* 2006; **44**: 21–7.
79 Aydin F, Senturk N, Sahin B *et al*. A practical method for the estimation of vitiligo surface area: a comparison between the point counting and digital planimetry techniques. *Eur J Dermatol* 2007; **17**: 30–2.

Quality of life impairment by skin disease

What does quality of life mean?

Being able to assess the impact of skin disease on patients is essential in order to understand and meet what they really need [1]. There is, however, considerable controversy about the definition of quality of life and whether it can be meaningfully assessed [2,3]. There have been several attempts to define quality of life and the closely associated concept of health-related quality of life (HRQoL) [4]. There is a need for all outcome measures used in dermatology, including quality of life measures, to be properly validated. There is too little information in the literature about the absolute meaning of different overall quality of life measurement scores or the interpretation of degrees of change in scores.

Why measure quality of life?

All clinical dermatologists are aware of the impact that skin disease may have on their patients. Attempts to develop methodology to measure the adverse impact of skin disease on quality of life started in the 1980s [5] and within two decades have become firmly established [6]. Measurement may be helpful for several reasons.

Clinical therapeutic research. When new drugs are assessed, the primary outcome measures are usually clinical measures such as the degree of scaling or the area of skin affected. Pharmaceutical companies and regulatory authorities are realizing that although these measures of disease activity are important, a patient-orientated outcome adds a meaningful extra dimension. There may be a 50% improvement in a PASI score, but if the handicap experienced by the patient is only slightly improved because visible skin remains abnormal, the intervention may not have been successful from the patient's point of view. A quality of life standard may even be better than body surface area measurement for identifying patients with severe psoriasis [7]. The addition of (not the replacement by) a HRQoL measure may be essential to make a proper assessment. In the evaluation of psoriasis, HRQoL measures are indeed now used frequently, whereas they were not used at all 20 years ago [8], and the introduction of new therapies for atopic dermatitis has also been supported by such information [9]. It has been possible to 'go back' and re-compare long-established therapies, using for the first time HRQoL outcome measures [10,11]. The impact of biological therapies for psoriasis on HRQoL has been documented in detail, for example in the assessment of the effects of etanercept [12] and adalimumab [13]. As the same measure has been used in most of such studies, it has been possible to derive some comparative data, even though no such prospective studies exist [14]. Despite these changes in attitudes to and use of HRQoL measures in clinical studies in dermatology, these instruments are usually recognized only as secondary outcome measures, partially because of the need for higher levels of validation of many measures currently used [15].

Although the main use of HRQoL assessment of therapeutic intervention has related to inflammatory skin disease, such measurement may also be used to compare surgical therapies, for example in the treatment of non-melanoma skin cancer [16].

Health service research and audit. Within some health care systems it is mandatory to produce evidence of the effectiveness of care given, and to have systems in place to monitor effectiveness and assess improvement against agreed criteria. An essential part of this process involves using patient-orientated measures and simple validated HRQoL questionnaires are well suited for this need [17,18]. The use of these measures can give additional insight into the acceptability of new methods of providing dermatology advice, such as teledermatology [19]; they have also been used to measure the effects of dermatology consultations in secondary care [20] and to compare the effectiveness of dermatology clinics between primary and secondary care [21].

Sound epidemiological data are essential for the planning of health services; HRQoL data can measure the extent of problems caused by skin disorders in a community [22] and be used to compare the HRQoL of people with specific skin diseases such as psoriasis to the general population [23]. National registries for diseases, such as that for psoriasis in Sweden, may include HRQoL data in order to assess the total burden of disease and the effectiveness of treatment [24]. A national survey of psoriasis patients in Germany has demonstrated, by gathering HRQoL data, the high percentage of psoriasis patients with a serious reduction in HRQoL [25].

Research into psychological aspects of dermatology and patient behaviour. Quality of life measures can be used to gain insight into patient attitudes; stress resulting from the anticipation of other people's reactions to their psoriasis contributed more to the variance in patients' disability than any other variable [26]. It is important that the problems relating to adherence with treatment, often not recognized by dermatologists, are better understood. Quality of life indices have been used to provide patient orientated measures in studies of compliance in psoriasis and acne.

Political/resource allocation. Patients with skin diseases are often not given priority for resource allocation in health care systems. Conditions that result in death are much more likely to find political support for service development. It is the responsibility of dermatologists to argue for appropriate resource allocation and appropriate funding of dermatology services and of the education of doctors about skin problems. One way in which the arguments for this can be strengthened is by using HRQoL data that demonstrate the devastating effects of skin disease on patients' lives [27–29]. If general HRQoL measures are used it is possible to quantify the effects of skin disease and to demonstrate the importance of skin disease in comparison to diseases of other

organs [30,31]. Similarly, the use of measures within dermatology can draw attention to the major problems experienced by some conditions to which, up to now, not enough attention may have been given. Examples include erythropoietic protoporphyria [32], hyperhidrosis [33] and hidradenitis suppurativa [34], all of which have high mean HRQoL scores indicating very major impact on quality of life.

It may be necessary to demonstrate and defend the value of dermatology clinical services whose benefit is self-evident to clinicians, for example in-patient dermatology facilities [35–37], or patch testing [38]. Dermatology-specific measures can also be used to demonstrate the value from the patients' point of view of expensive or novel therapy. A particular challenge when planning dermatology services is to understand and differentiate between need and greed when assessing the demands of patients; this may be clarified by the use of HRQoL data [39].

Estimating the burden of skin disease. Skin disease has major financial consequences; there are both direct medical costs and costs from lost productivity. In psoriasis the impact on productivity is not associated with objective clinical severity, but is associated with HRQoL [40]. The value of the additional burden on quality of life can also be expressed in financial terms, using willingness to pay methodology and HRQoL data. It is estimated that for all skin disease in the USA in 2004, the costs were: direct, $29.1 m; lost productivity, $10.2 m; and economic burden on quality of life, $56.2 m [41].

Informing clinical decisions. Most dermatologists probably consider that they have a reasonably accurate insight into the impact of skin disease on individual patients. The assumptions that are made influence clinical decisions, for example whether or not to start a patient on a systemic therapy which has risks of side effects. Unfortunately, dermatologists may not have as much insight as they think into the degree of their patients' problems [42–44]; impairment of sexual life, for example, is frequent in patients with psoriasis [45], even though the clinician may be unaware of this. Similarly, dermatologists are not good at identifying psychological distress in patients with psoriasis and, even in those patients in whom it is recognized, usually take no further action [46]. The use of a standard HRQoL measure may therefore potentially inform a clinician more accurately about their patient and allow better judgement concerning risk–benefit of therapy change. This will only become relevant on a routine basis if the absolute meaning of HRQoL scores can be more clearly understood.

It has been suggested that current severe psoriasis can be defined by using a combination of physical and quality of life descriptors [47]. The Rule of Tens for assessing psoriasis severity is:

current severe psoriasis = Body Surface Area (BSA) involved > 10% *or* PASI > 10 *or* DLQI score > 10

If this is met, the patient should be considered to have current severe psoriasis, for which active therapy should be considered [47]. The British Association of Dermatologists' subsequent guidelines [48] for the use of the biological therapies use a variation on this concept. They suggest that PASI ≥ 10 or BSA ≥ 10% *and* DLQI > 10 should be the criteria for etanercept or efalizumab to be used in the treatment of psoriasis. The National Institute for Health and Clinical Excellence (NICE) guidance is similar [49], but for the use of infliximab the criteria are PASI ≥ 20 *and* DLQI > 18 [50]. A European consensus has also suggested the use of the Rule of Tens as an indicator of moderate to severe psoriasis when decisions are taken concerning etanercept therapy for psoriasis [51]. These guidelines therefore now encourage physicians to actively investigate and take into account HRQoL information in making decisions about therapy.

How do quality of life measures relate to other clinical indices?

It seems obvious that there is likely to be a relationship between the clinical severity of skin disease and the impact of the disease on life quality. However, there are many influences on the disability experienced and individual patients show a wide variation in their responses to similar degrees of disease. There is conflicting evidence, for example in atopic dermatitis in children, where in one study the CDLQI was significantly correlated with the SCORAD [52] and in another the correlation with SCORAD and the Eczema Severity Score was poor [53]. Quality of life scores and scores from POEM correlate well; however, POEM includes a HRQoL question concerning sleep [54]. The particular body site affected is an important factor, with visible sites such as the face or the hands having much greater significance to a patient: there was only poor correlation between disease severity in hand eczema and quality of life scores [55].

The psychological attitudes of patients to their disease vary widely and these influence the degree of disability experienced [56]. Clinical scoring systems may reflect sign changes which are not of relevance to a patient's life; for example in psoriasis, the successful reduction of scaling and thickness may result in a large percentage reduction in the PASI score but if the redness persists the quality of life improvement may be much less [57]. In a cluster analysis of classical measures of clinical status of psoriasis (PASI, SAPASI) and of quality of life indices (Skindex-29, DLQI, PDI, IPSO) in over 700 patients, the instruments clustered in these two distinct groups [58]. This study stressed the need for comprehensive assessment of severity of psoriasis using both objective and patient-rated measures. There have, however, been attempts to broadly correlate these two concepts of measurement; it has been argued [59] that a 50% reduction in the PASI (PASI 50) represents a meaningful change in a patient's life and so could be considered a clinically significant endpoint when psoriasis is assessed. In patients with severe psoriasis treated with infliximab, despite a lack of correlation between absolute PASI and DLQI values, significant reductions of PASI are likely to correlate with significant improvements of HRQoL [60].

Quality of life measures should not be used instead of clinical measures as they are designed to assess a completely different, though interrelated, aspect of skin disease.

References

1 Finlay AY. Dermatology patients: what do they really need? *Clin Exp Dermatol* 2000; **25**: 444–50.

2 Koller M, Lorenz W. Quality of life: a deconstruction for clinicians. *J R Soc Med* 2002; **95**: 481–8.

3 Naldi L. Health-related quality of life: from health economics to bedside. *Dermatology* 2007; **215**: 273–6.
4 Calman KC. Quality of life in cancer patients—an hypothesis. *J Med Ethics* 1984; **10**: 124–7.
5 Finlay AY, Kelly SE. Psoriasis—an index of disability. *Clin Exper Dermatol* 1987; **12**: 8–11.
6 VanBeek M, Beach S, Braslow L *et al*. Highlights from the report of the working group on 'Core measures of the burden of skin diseases'. *J Invest Dermatol* 2007; **127**: 2701–6.
7 Krueger GG, Feldman SR, Camisa C *et al*. Two considerations for patients with psoriasis and their clinicians: what defines mild, moderate and severe psoriasis? What constitutes a clinically significant improvement when treating psoriasis? *J Am Acad Dermatol* 2000; **43**: 281–5.
8 Morsy H, Kamp S, Jemec GBE. Outcomes in randomised controlled trials in psoriasis: what has changed over the last 20 years? *J Dermatol Treat* 2007; **18**: 261–7.
9 Drake L, Prendergast M, Maher R *et al*. The impact of tacrolimus ointment on health-related quality of life of adult and pediatric patients with atopic dermatitis. *J Am Acad Dermatol* 2001; **44**: S65–S72.
10 Heydendael VM, Spuls PI, Opmeer BC *et al*. Methotrexate versus cyclosporine in moderate-to-severe chronic plaque psoriasis. *N Engl J Med* 2003; **349**: 658–65.
11 De Korte J, van der Valk PGM, Sprangers MAG *et al*. A comparison of twice-daily calcipotriol ointment with once-daily short-contact dithranol cream therapy: quality-of-life outcomes of a randomised controlled trial of supervised treatment of psoriasis in a day-care setting. *Br J Dermatol* 2008; **158**: 375–81.
12 Gordon K, Korman N, Frankel E *et al*. Efficacy of etanercept in an integrated multistudy database of patients with psoriasis. *J Am Acad Dermatol* 2006; **54**: S101–11.
13 Shikiar R, Heffernan M, Langley RG *et al*. Adalimumab treatment is associated with improvement in health-related quality of life in psoriasis: patient-reported outcomes from a phase II randomised controlled trial. *J Dermatolog Treat* 2007; **18**: 25–31.
14 Katugampola RP, Lewis VJ, Finlay AY. The Dermatology Life Quality Index: assessing the efficacy of biological therapies for psoriasis. *Br J Dermatol* 2007; **156**: 945–50.
15 Grob JJ. Why are quality of life instruments not recognised as reference measures in therapeutic trials of chronic skin disorders? *J Invest Dermatol* 2007; **127**: 2299–301.
16 Chren M-M, Sahay AP, Bertenthal DS *et al*. Quality-of-life outcomes of treatments for cutaneous basal cell carcinoma and squamous cell carcinoma. *J Invest Dermatol* 2007; **127**: 1351–7.
17 Shum KW, Lawton S, Williams HC *et al*. The British Association of Dermatologists audit of atopic eczema management in secondary care. Phase 2: audit of service process. *Br J Dermatol* 2000; **12**: 721–7.
18 Gradwell C, Thomas KS, English JSC, Williams HC. A randomised controlled trial of nurse follow-up clinics: do they help patients and do they free up consultants' time? *Br J Dermatol* 2002; **147**: 513–7.
19 Williams TL, May CR, Esmail A *et al*. Patient satisfaction with teledermatology is related to perceived quality of life. *Br J Dermatol* 2001; **145**: 911–7.
20 Baron SE, Morris PK, Dye L *et al*. The effect of dermatology consultations in secondary care on treatment outcome and quality of life in new adult patients with atopic dermatitis. *Br J Dermatol* 2006; **154**: 942–9.
21 Coast J, Noble S, Noble A *et al*. Economic evaluation of a general practitioner with special interest led dermatology service in primary care. *BMJ* 2005; **331**: 1444–8.
22 Bingefors K, Lindberg M, Isacson D. Self-reported dermatological problems and use of prescribed topical drugs correlate with decreased quality of life: an epidemiological survey. *Br J Dermatol* 2002; **147**: 285–90.
23 Wahl A, Loge JH, Wiklund I, Hanestad BR. The burden of psoriasis: a study concerning health-related quality of life among Norwegian adult patients with psoriasis compared with general population norms. *J Am Acad Dermatol* 2000; **43**: 803–8.
24 Schmitt-Egenolf M. PsoReg—the Swedish registry for systemic psoriasis treatment. *Dermatology* 2007; **214**: 112–7.
25 Augustin M, Reich K, Reich C *et al*. Quality of psoriasis care in Germany—results of the national study PsoHealth 2007. *J Dtsch Dermatol Ges* 2008; **6**: 640–5.
26 Fortune DG, Main CJ, O'Sullivan TM, Griffiths CEM. Quality of life in patients with psoriasis: the contribution of clinical variables and psoriasis-specific stress. *Br J Dermatol* 1997; **137**: 755–60.
27 All Party Parliamentary Group on Skin. *Report on the Enquiry into the Impact of Skin Disease on People's Lives*. All Party Parliamentary Group on Skin, London, 2003.
28 Katugampola RP, Finlay AY. Impact of skin diseases on quality of life. *Eur J Dermatol* 2007; 17: 102–6.
29 Katugampola RP, Finlay AY. Impact of skin diseases on quality of life. In: Fritsch P, Burgdorf W, eds. *EDF White Book: Dermatology in Europe,* 2nd edn. European Dermatology Forum. Berlin: ABW, 2005.
30 Finlay AY, Khan GK, Luscombe DK, Salek MS. Validation of sickness impact profile and psoriasis disability index in psoriasis. *Br J Dermatol* 1990; **123**: 751–6.
31 Rapp SR, Feldman SR, Exum L *et al*. Psoriasis causes as much disability as other major medical diseases. *J Am Acad Dermatol* 1999; **41**: 401–7.
32 Holme SA, Anstey AV, Finlay AY *et al*. Erythropoietic protoporphyria in the UK: clinical features and effect on quality of life. *Br J Dermatol* 2006; **155**: 574–81.
33 Bechara FG, Gambichler T, Bader A *et al*. Assessment of quality of life in patients with primary axillary hyperhidrosis before and after suction-curettage. *J Am Acad Dermatol* 2007; **57**: 207–12.
34 Wolkenstein P, Loundou A, Barrau K *et al*. Quality of life impairment in hidradenitis suppurativa: a study of 61 cases. *J Am Acad Dermatol* 2007; **56**: 621–3.
35 Ayyalaraju RS, Finlay AY, Dykes PJ *et al*. Dermatology inpatient services: a UK/USA comparative study. *J Am Acad Dermatol* 2003; **49**: 249–54.
36 Wahl AK, Mork C, Mork-Lillehol B *et al*. Changes in quality of life in persons with eczema and psoriasis after treatment in departments of dermatology. *Acta Derm Venereol* 2006; **86**: 198–201.
37 Schmitt J, Heese E, Wozel G, Meurer M. Effectiveness of inpatient treatment on quality of life and clinical disease severity in atopic dermatitis and psoriasis vulgaris – a prospective study. *Dermatology* 2007; **214**: 68–76.
38 Thompson KF, Wilkinson SM, Sommer S, Pollock B. Eczema: quality of life by body site and the effect of patch testing. *Br J Dermatol* 2002; **146**: 627–30.
39 Dalgard F, Finlay AY. Need and greed in dermatology: disease and outcome measures in dermatological healthcare planning. *Dermatology* 2006; **213**: 279–83.
40 Schmitt JM, Ford DE. Work limitations and productivity loss are associated with health-related quality of life but not with clinical severity in patients with psoriasis. *Dermatology* 2006; **213**: 102–10.
41 Bickers DB, Lim HW, Margolis D *et al*. The burden of skin diseases: 2004. *J Am Acad Dermatol* 2006; **55**: 490–500.
42 Jemec GBE, Wulf HC. Patient-physician consensus and quality of life in dermatology. *Clin Exp Dermatol* 1996; **21**: 177–9.
43 Hermansen SE, Helland CA, Finlay AY. Patients' and doctors' assessment of skin disease handicap. *Clin Exp Dermatol* 2002; **27**: 1–3.
44 Jayaprakasam A, Darvay A, Osborne G, McGibbon D. Comparison of assessments of severity and quality of life in cutaneous disease. *Clin Exp Dermatol* 2002; **27**: 306–8.
45 Sampogna F, Gisondi P, Tabolli S *et al*. Impairment of sexual life in patients with psoriasis. *Dermatology* 2007; **214**: 144–50.
46 Richards HL, Fortune DG, Weidmann A *et al*. Detection of psychological distress in patients with psoriasis: low consensus between dermatologist and patient. *Br J Dermatol* 2004; **151**: 1227–33.
47 Finlay AY. Current severe psoriasis and the Rule of Tens. *Br J Dermatol* 2005; **152**: 861–7.
48 Smith CH, Anstey AV, Barker JN *et al*. British Association of Dermatologists guidelines for the use of biological interventions in psoriasis 2005. *Br J Dermatol* 2005; **153**: 486–9.
49 National Institute for Health and Clinical Excellence. *Etanercept and Efalizumab for the Treatment of Adults with Psoriasis*. www.nice.org.uk. Accessed 7 Feb 2008.
50 National Institute for Health and Clinical Excellence. TA 134. *Infliximab for the Treatment of Psoriasis*. www.nice.org.uk. Accessed 7 Feb 2008.
51 Boehncke W-H, Brasie RA, Barker J *et al*. Recommendations for the use of etanercept in psoriasis: a European dermatology expert group consensus. *J Eur Acad Dermatol Venereol* 2006; **20**: 988–98.
52 Ben-Gashir MA, Seed PT, Hay RJ. Quality of life and disease severity are correlated in children with atopic dermatitis. *Br J Dermatol* 2004; **150**: 284–90.
53 Hon KLE, Kam WYC, Lam MCA *et al*. CDLQI, SCORAD and NESS: are they correlated? *Quality of Life Research* 2006; **15**: 1551–8.

54 Charman CR, Venn AJ, Williams H. The Patient-Orientated Eczema Measure. *Arch Dermatol* 2004; **140**: 1513–9.
55 Van Coevorden AM, van Sonderen E, Bouma J, Coenraads PJ. Assessment of severity of hand eczema: discrepancies between patient- and physician-rated scores. *Br J Dermatol* 2006; **155**: 1217–22.
56 Wittkowski A, Richards HL, Griffiths CEM, Main CJ. The impact of psychological and clinical factors on quality of life in individuals with atopic dermatitis. *J Psychosom Res* 2004; **151**: 195–200.
57 Parry EJ, Tillman DM, Long J, MacKie RM. Audit of UVB phototherapy in the treatment of psoriasis. *Br J Dermatol* 1995; **133** (Suppl. 45): 16.
58 Sampogna F, Sera F, Abeni D *et al*. Measures of clinical severity, quality of life, and psychological distress in patients with psoriasis: a cluster analysis. *J Invest Dermatol* 2004; **122**: 602–7.
59 Carlin CS, Feldman SR, Krueger JK *et al*. A 50% reduction in the Psoriasis Area and Severity Index (PASI 50) is a clinically significant endpoint in the assessment of psoriasis. *J Am Acad Dermatol* 2004; **50**: 859–66.
60 Reich K, Griffiths CEM. The relationship between quality of life and skin clearance in moderate-to-severe psoriasis: lessons learnt from clinical trials with infliximab. *Arch Dermatol Res* 2008; **300**: 537–44.

Methods of measuring quality of life in dermatology

There are several approaches to the measurement of health-related quality of life. One depends on fixed questionnaires that are scored. A second approach uses questionnaires that allow a variable response, taking into account the particular values of the patient. Another method is to assess the value that a patient of society places on the presence or absence of particular disease states—the utility approach. The US Working Group on core measures of the burden of skin diseases identified 40 health-status quality of life measurement instruments for skin disease [1]. Decisions concerning which measures are appropriate to use can be difficult; there is guidance over general principles [2,3]. A recent critical review of generic and dermatology-specific HRQoL instruments recommended for research studies the use of a combination of the SF-36 and Skindex-29 [4]; however, in the busy clinical environment a different approach is necessary, preferably using a simple, short questionnaire. There are comparisons of assessment of quality of life in cutaneous disease [5] and in psoriasis [6], and there is advice about understanding quality of life research [7] and quality of life research methodology [8]. Minimum criteria to create and establish new instruments have been suggested [9]. For example, one basic aspect of the use of a standardized questionnaire in the measurement of HRQoL is the requirement in the instrument validation process to demonstrate that it is appropriate to report grouped answers data as a single score. There are techniques to address whether or not instruments are uni-dimensional [10,11].

Some techniques are designed for use across all disease states, some for use across a range of diseases of the same organ system and some for use in patients with specific diseases. Most published questionnaires are designed for adults, but there have been techniques described for measuring HRQoL in children with skin disease and in infants with atopic dermatitis. HRQoL measures usually assess the impact of skin disease at a particular time (e.g. 'today') or over a fixed period of time (e.g. 'over the last week'). This time restricted design allows comparison of data before and after intervention. However, the long-term 'importance' or impact on a patient's life may not be captured by these indices. Patients with basal cell carcinomas at the time of presentation to dermatologists generally have little or no reduction in their current quality of life [12] but, of course, if the disease was not treated there could be major problems in the future. If HRQoL measures are used to inform priorities for resources in a health care organization, these measures should therefore not be used in isolation.

What do quality of life scores mean?

Quality of life scores are often poorly reported in published clinical studies, with insufficient information given to properly interpret the data presented [13]. One crucial aspect often not addressed is the clinical relevance of changes in score. Significant statistical differences may be proven but if the absolute magnitude of the changes is not equivalent to a noticeable change in patient experience there may be no benefit to the patient; this is true for both objective disease measures and for patient-reported measures [14].

Measuring HRQoL in the clinic is not of benefit to the clinician or patient unless the scores can be interpreted in a simple and meaningful way. Of the many questionnaires that have been described, very few have validated descriptions for the interpretation of the scores. Ideally, there should be information about the minimal important difference (MID) of score that is of relevance to patients. A complementary approach is to develop descriptive bands to interpret scores; this has been described for the DLQI [15].

Where HRQoL measures are used in international studies, validated translations should be used. However, even after the completion of an accurate translation of meaning, further work may be necessary to create a validated, culturally adapted measure. It has been suggested that psoriasis patients from different countries respond differently to items from both the DLQI and Skindex, despite having the same underlying HRQoL impairment [16]. There is a need to develop patient-reported outcome cross-cultural instruments to ultimately allow patient-reported measures to be accepted as primary outcome measures in therapeutic trials [17].

Quality of life measures used in dermatology

General health measures

General health measures are designed for use across a wide range of disease states. They are needed in order to draw comparisons between the impact of skin diseases, the impact of diseases of other systems and the general population. Examples include the SF-36 [18], the Sickness Impact Profile (SIP) [19], the Nottingham Health Profile (NHP) [20] and the EuroQol EQ-5D [21]. The WHOQOL-26 is a 26-question instrument with physical, psychological, social relations and environment domains [22]. A completely different approach is taken by the Patient Generated Index, which is an individualized quality of life measure where a subject identifies the key ways in which their life is specifically being affected, and ranks and assigns importance to each aspect [23]. This approach is excellent for gaining insight into individual patients' problems, but is cumbersome and unsuitable for large surveys.

Many of these general health measures have been used in dermatology. In many investigations both a generic measure and a

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick one box for each question.

1. Over the last week, how **itchy, sore, painful** or **stinging** has your skin been?
2. Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?
3. Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?
4. Over the last week, how much has your skin influenced the **clothes** you wear?
5. Over the last week, how much has your skin affected any **social** or **leisure** activities?
6. Over the last week, how much has your skin made it difficult for you to do any **sport**?
7. Over the last week, has your skin prevented you from **working** or **studying**?
   If "no", over the last week how much has your skin been a problem at **work** or **studying**?
8. Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?
9. Over the last week, how much has your skin caused any **sexual difficulties**?
10. Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?

Please check you have answered every question. Thank you.
© AY Finlay, GK Khan, April 1992.

Each question is answered either "Very much" (score 3), "A lot" (score 2), "A little" (score 1) or "Not at all" (score 0). Questions 3 – 10 also have the option "Not relevant" (score 0). The first part of question 7 has the choices "Yes" (score 3),"No", or "Not relevant". The second part of question 7 has the choices "A lot", "A little" or "Not at all". The maximum score (indicating highest possible impairment of quality of life) is 30 and the minimum 0. Further information: www.dermatology.org.uk.

Fig. 72.1 The Dermatology Life Quality Index (DLQI) [43].

dermatology-specific measure have been used together [24]. The UK Sickness Impact Profile has been used in psoriasis [25,26] and atopic dermatitis [27]. The SF-36 has been used in psoriasis [28,29], acne [30] and atopic dermatitis [31]. The GHQ-12 has been shown to be of value in assessing psychological distress in patients with skin disease [32], and specifically in vitiligo [33].

The EuroQol EQ-5D is of growing importance as it is being used by European drug licensing authorities as a comparative tool and as a basis for utility analysis [34]. It has been used in acne [30], psoriasis [24] and pyoderma gangrenosum [35].

The WHOQOL-26 has been used in studies of melasma [36] and urticaria [37] and in assessing the impact of tacrolimus ointment in atopic dermatitis [38]. The initial 100-question version, the WHOQOL-100, is responsive to change in psoriasis [39].

There are several separate methods used to detect or measure depression or other psychological problems in dermatology patients. One example, the General Health Questionnaire, is designed to detect psychiatric disorder and is reliable when used in dermatology patients [32]; it may be used for example to detect suicidal ideation [40]. Depression can be detected using the Mini International Neuropsychiatric Interview questionnaire as a screening method [41]. There is a strong interrelationship between psychiatric co-morbidity and quality of life impairment [42].

Dermatology-specific measures

Dermatology-specific measures are useful when comparisons need to be made between the impact of different skin diseases, or where there is a need to measure change before or after intervention in any skin disease. Having a single simple measure that can be used across all skin disease is of great practical advantage, especially in a busy clinical setting.

The two dermatology-specific measures that have been most widely used are the DLQI [43] and Skindex [44]. Other measures that have been described include the Dermatology Quality of Life Scales [45], the Dermatology-specific Quality of Life instrument [46], a German instrument, the DIELH [47], the VQ-Dermatol, developed in France [48], and a measure for use in Turkish patients [49]. The Freiberg Life Quality Assessment (FLQA) questionnaires combine a common core module relevant to all skin diseases with a disease-specific module [50].

The DLQI and Skindex mainly measure physical, psychological and social functioning. As not all aspects affected are encompassed by these measures, a broader instrument, the Impact of Chronic Skin Disease on Daily Life (ISDL), has been developed [51]. This has five categories: physical functioning, psychological functioning, stressors, illness cognitions and social support. The measure has good reliability and validity but, with over 72 items, takes 20–25 min to complete.

The Dermatology Life Quality Index

The DLQI consists of 10 questions covering a wide range of ways in which patients' lives are affected by skin disease (Fig. 72.1). Each question is answered by a simple tick-box method and scored 0–3. The DLQI takes on average only 2 min to complete [52]. Experience of the DLQI, including validation studies, has been summarized [53]; by 2007, there were 272 articles describing the use of the DLQI in a wide range of skin conditions and in 55 languages worldwide [53,54]. Validation studies have been carried out in the UK, in secondary care [43] and primary care [55], Spain [56,57], Germany [58], Denmark [59], the USA [60], Norway [61], Italy [62], Poland [63], Iran [64], Brazil [65] and Japan [66]. Its use has also been described in over 32 countries. When illustrations are added next to the text of the DLQI, the questionnaire tends to be completed more rapidly but there is an influence on the way the questionnaire is answered [52]. Descriptive score bandings for the DLQI are given in Table 72.5. In psoriasis [67] and urticaria [68] a score change of about 3 is needed for a patient to experience a minimum important change in HRQoL; preliminary work had indicated a figure of 5 in a general dermatology population [69].

Although the DLQI is copyrighted, clinicians may freely use it in routine clinical practice without seeking permission and without charge [54].

Table 72.5 Descriptive score bandings for the Dermatology Life Quality Index (DLQI) [15].

Score	Meaning
0–1	no effect on patient's life
2–5	small effect on patient's life
6–10	moderate effect on patient's life
11–20	very large effect on patient's life
21–30	extremely large effect on patient's life

Skindex

Skindex has been developed and extensively validated in four versions with 61 [44], 29 [70], 16 [71] or 17 [72] questions. Further validation studies have been carried out in Spain [73], Italy [74], Turkey [75], Saudi Arabia [76], Japan [77] and Germany [78]. There is extensive experience of the use of this measure in a wide range of languages, countries and dermatology diseases. The appropriateness of using Skindex in psoriasis along with the generic SF-29 has been emphasized [6]. Skindex-29 scores have now been categorized into four levels to aid the interpretation of scores [79].

References

1 VanBeek M, Beach S, Braslow L *et al*. Highlights from the report of the Working Group on 'Core measures of the burden of skin diseases'. *J Invest Dermatol* 2007; **127**: 2701–6.

2 Finlay AY. Quality of life measurement in dermatology: a practical guide. *Br J Dermatol* 1997; **136**: 305–14.

3 Hyland ME. A brief guide to the selection of quality of life instrument. *Health Qual Life Outcomes* 2003; **1**: 24.

4 Both H, Essink-Bot M-L, Busschbach J, Nijsten T. Critical review of generic and dermatology-specific health-related quality of life instruments. *J Invest Dermatol* 2007; **127**: 2726–39.

5 Jayaprakasam A, Darvey A, Jisborne G, McGibbon D. Comparisons of assessment of severity and quality of life in cutaneous disease. *Clin Exp Dermatol* 2002; **27**: 306–8.

6 De Korte J, Mombers FM, Sprangers MA, Bos JD. The suitability of quality-of-life questionnaires for psoriasis research: a systematic literature review. *Arch Dermatol* 2002; **138**: 1221–7.

7 Chren MM. Understanding research about quality of life and other health outcomes. *J Cut Med Surg* 1999; **3**: 312–6.

8 Finlay AY. Research methodology in quality of life assessment. In: Walker C, Papadopoulos L, eds. *Psychodermatology*. Cambridge University Press, Cambridge, 2005.

9 Chen SC. Dermatology Quality of Life instruments: sorting out the quagmire. *J Invest Dermatol* 2007; **127**: 2695–6.

10 Mazzotti E, Barbaranelli C, Picardi A *et al*. Psychometric properties of the Dermatology Life Quality Index (DLQI) in 900 Italian patients with psoriasis. *Acta Derm Venereol* 2005; **85**: 409–13.

11 Nijsten T, Meads DM, McKenna SP. Dimensionality of the Dermatology Life Quality Index (DLQI): a commentary. *Acta Derm Venereol* 2006; **86**: 284–5.

12 Blackford S, Roberts DL, Salek MS, Finlay AY. Basal cell carcinomas cause little handicap. *Quality of Life Research* 1996; **5**: 191–4.

13 Le Cleach L, Chassany O, Levy A *et al*. Poor reporting of quality of life outcomes in dermatology randomised controlled clinical trials. *Dermatology* 2008; **216**: 46–55.

14 Bhardwaj SS, Camacho F, Derrow A *et al*. Statistical significance and clinical relevance. *Arch Dermatol* 2004; **140**: 1520–3.

15 Hongbo Y, Thomas CL, Harrison MA *et al*. Translating the science of quality of life into practice: what do Dermatology Life Quality Index scores mean? *J Invest Dermatol* 2005; **125**: 659–64.

16 Nijsten T, Meads DM, de Korte J *et al*. Cross-cultural inequivalence of dermatology-specific health-related quality of life instruments in psoriasis patients. *J Invest Dermatol* 2007; **127**: 2315–22.

17 Grob JJ. Why are quality of life instruments not recognized as reference measures in therapeutic trials of chronic skin disorders? *J Invest Dermatol* 2007; **127**: 2299–301.

18 Ware JE, Sherbourne CD. The MOS 36-Item Short-Form Health Survey (SF-36). 1. Conceptual framework and item selection. *Med Care* 1992; **30**: 437–83.

19 Bergner M, Bobbit RA, Carter WB *et al*. The Sickness Impact Profile: development and final revision of a health status measure. *Med Care* 1981; **19**: 787–805.

20 Hunt SM, McEwen J, McKenna SP. Measuring health status: a new tool for clinicians and epidemiologists. *J R Coll Gen Pract* 1985; **35**: 185–8.

21 Kind P, Gudex C, Dolan P, Williams A. Practical and methodological issues in the development of the EuroQol: the York experience. *Adv Med Sociol* 1994; **5**: 219–53.

22 The WHOQOL Group. Development of the World Health Organisation WHOQOL-BREF quality of life assessment 1998. *Psychol Med* 1998; **28**: 551–8.

23 Martin F, Camfield L, Rodham K *et al*. Twelve years' experience with the Patient Generated Index (PGI) of quality of life: a graded structured review. *Qual Life Res* 2007; **16**: 705–15.

24 Shikiar R, Willian MK, Okun MM *et al*. The validity and responsiveness of three quality of life measures in the assessment of psoriasis patients: results of a phase II study. *Health Qual Life Outcomes* 2006; **4**: 71.

25 Finlay AY, Khan GK, Luscombe DK, Salek MS. Validation of Sickness Impact Profile and Psoriasis Disability Index in psoriasis. *Br J Dermatol* 1990; **123**: 751–6.

26 Prins M, Krabbe PFM, Swinkels QOJ *et al*. The effect of treatment on quality of life in psoriasis patients. *Acta Derm Venereol* 2005; **85**: 304–10.

27 Salek MS, Finlay AY, Luscombe DK *et al*. Cyclosporin greatly improves the quality of life of adults with severe atopic dermatitis. *Br J Dermatol* 1993; **129**: 422–30.

28 Sampogna F, Tabolli S, Söderfeldt B *et al*. Measuring quality of life of patients with different clinical types of psoriasis using the SF-36. *Br J Dermatol* 2006; **154**: 844–9.

29 Flytström I, Stenberg B, Svensson A, Bergbrant I-M. Methotrexate vs ciclosporin in psoriasis: effectiveness, quality of life and safety. A randomised controlled trial. *Br J Dermatol* 2008; **158**: 116–21.

30 Klassen AF, Newton JN, Mallon E. Measuring quality of life in people referred for specialist care of acne: comparing generic and disease-specific measures. *J Am Acad Dermatol* 2000; **43**: 229–33.

31 Kiebert G, Sorensen SV, Revicki D *et al*. Atopic dermatitis is associated with a decrement in health-related quality of life. *Int J Dermatol* 2002; **41**: 151–8.

32 Picardi A, Abeni D, Pasquini P. Assessing psychological distress in patients with skin diseases: reliability, validity and factor structure of the GHQ-12. *J Eur Acad Dermatol Venereol* 2001; **15**: 410–7.

33 Mattoo SK, Handa S, Kaur I *et al*. Psychiatric morbidity in vitiligo: prevalence and correlates in India. *J Eur Acad Dermatol Venereol* 2002; **16**: 573–8.

34 Szende A, Oppe M, Devlin N, eds. *EQ-5D Value Sets: Inventory, Comparative Review and User Guide*. Springer, 2007.

35 Brooklyn TN, Dunnill MGS, Shetty A *et al*. Infliximab for the treatment of pyoderma gangrenosum: a randomised, double blind, placebo controlled trial. *Gut* 2006; **55**: 505–9.

36 Cestari TF, Hexsel D, Viegas ML *et al*. Validation of a melasma quality of life questionnaire for Brazilian Portuguese language: the MelasQoL-BP study and improvement of QoL of melasma patients after triple combination therapy. *Br J Dermatol* 2007; **156** (Suppl. 1): 13–20.

37 Engin B, Uguz F, Yilmaz E *et al*. The levels of depression, anxiety and quality of life in patients with chronic idiopathic urticaria. *J Eur Acad Dermatol Venereol* 2008; **22**: 36–40.

38 Kawashima M for the QOL Research Forum. Quality of life in patients with atopic dermatitis: impact of tacrolimus ointment. *Int J Dermatol* 2006; **45**: 731–6.

39 Skevington SM, Bradshaw J, Hepplewhite A *et al*. How does psoriasis affect quality of life? Assessing an Ingram-regimen outpatient programme and validating the WHOQOL-100. *Br J Dermatol* 2006; **154**: 680–91.

40 Picardi A, Mazzotti E, Pasquini P. Prevelance and correlates of suicidal ideation among patients with skin disease. *J Am Acad Dermatol* 2006; **54**: 420–6.

41 Cohen AD, Ofek-Shlomai A, Vardy DA *et al*. Depression in dermatological patients identified by the Mini International Neuropsychiatric Interview questionnaire. *J Am Acad Dermatol* 2006; **54**: 94–9.
42 Staubach P, Eckhardt-Henn A, Dechene M *et al*. Quality of life in patients with chronic urticaria is differentially impaired by psychiatric comorbidity. *Br J Dermatol* 2006; **154**: 294–8.
43 Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI): a simple practical measure for routine clinical use. *Clin Exp Dermatol* 1994; **19**: 210–6.
44 Chren MM, Lasek RJ, Quinn LM *et al*. Skindex, a quality-of-life measure for patients with skin diseases: reliability, validity, and responsiveness. *J Invest Dermatol* 1996; **107**: 707–13.
45 Morgan M, McCreedy R, Simpson J, Hay RJ. Dermatology quality of life scales – a measure of the impact of skin diseases. *Br J Dermatol* 1997; **136**: 202–6.
46 Anderson RT, Rajagopalan R. Development and validation of a quality of life instrument for cutaneous diseases. *J Am Acad Dermatol* 1997; **37**: 41–50.
47 Schafer T, Staudt A, Ring J. German instrument for the assesment of quality of life in skin diseases (DIELH). Internal consistency, reliability, convergent and discriminant validity and responsiveness. *Hautarzt* 2001; **52**: 624–8.
48 Grob JJ, Revuz J, Ortonne JP *et al*. Comparative study of the impact of chronic urticaria, psoriasis and atopic dermatitis on the quality of life. *Br J Dermatol* 2005; **152**: 289–95.
49 Gurel MS, Yanik M, Simsek Z *et al*. Quality of life instrument for Turkish people with skin diseases. *Int J Dermatol* 2005; **44**: 933–8.
50 Augustin M, Bross F, Foldi E *et al*. Development, validation and clinical use of the FLQA-I, a disease-specific quality of life questionnaire for patients with lymphedema. *Vasa* 2005; **34**: 31–5.
51 Evers AWM, Duller P, van de Kerkhof PCM *et al*. The impact of chronic skin disease on daily life (ISDL): a generic and dermatology-specific health instrument. *Br J Dermatol* 2008; **158**: 101–8.
52 Loo WJ, Diba V, Chawla M, Finlay AY. Dermatology Life Quality Index: influence of an illustrated version. *Br J Dermatol* 2003; **148**: 279–84.
53 Basra MK, Fenech R, Gatt RM *et al*. The Dermatology Life Quality Index 1994–2007: a comprehensive review of validation data and clinical results. *Br J Dermatol* 2008; **159**: 997–1035.
54 *Dermatology Life Quality Index (DLQI)*. www.dermatology.org.uk.
55 Harlow D, Poyner T, Finlay AY, Dykes PJ. Impaired quality of life of adults with skin disease in primary care. *Br J Dermatol* 2000; **143**: 979–82.
56 De Tiedra AG, Mercadal J, Badia X *et al*. Adaptacion transcultural al Espanol del cuestionario Dermatology Life Quality Index (DLQI): el Indice de Calidad de Vida en Dermatologia. *Actas Dermo-Sifiliograficas* 1998; **89**: 692–700.
57 Badia X, Mascaro JM, Lozano R. Measuring health-related quality of life in patients with mild to moderate eczema and psoriasis: clinical validity, reliability and sensibility to change of the DLQI. *Br J Dermatol* 1999; **141**: 698–702.
58 Augustin M, Zschocke I, Lange S *et al*. Quality of life in skin diseases: methodological and practical comparison of different quality of life questionnaires in psoriasis and atopic dermatitis. *Hautarzt* 1999; **50**: 715–22.
59 Zachariae R, Zachariae C, Ibsen H *et al*. Dermatology life quality index: data from Danish inpatients and outpatients. *Acta Derm Venereol* 2000; **80**: 272–6.
60 Hahn BH, Melfi CA, Chuang TY *et al*. Use of the Dermatology Life Quality Index (DLQI) in a Midwestern US urban clinic. *J Am Acad Dermatol* 2001; **45**: 44–8.
61 Mork C, Wahl A, Moum T. The Norwegian version of the Dermatology Life Quality Index: a study of validity and reliability in psoriatics. *Acta Derm Venereol* 2002; **82**: 327–51.
62 Mazzotti E, Picardi A, Sampogna F *et al*. Sensitivity of the Dermatology Life Quality Index to clinical change in patients with psoriasis. *Br J Dermatol* 2003; **149**: 318–22.
63 Szepietowski J, Salomon J, Finlay AY *et al*. Dermatology Life Quality Index (DLQI): Polish version. *Dermatologia Kliczna* 2004; **6**: 63–70.
64 Aghaei S, Sodaifi M, Jafari P *et al*. DLQI scores in vitiligo: reliability and validity of the Persian version. *BMC Dermatology* 2004; **4**: 8.
65 Ferraz LB, Almeida FA, Vasconcellos MR *et al*. The impact of lupus erythematosus on the quality of life: the Brazilian-Portuguese version of DLQI. *Qual Life Res* 2006; **15**: 565–70.
66 Takahashi N, Suzukamo Y, Nakamura M *et al*. Japanese version of the Dermatology Life Quality Index: validity and reliability in patients with acne. *Health Qual Life Outcomes* 2006; **4**: 46.
67 Melilli L, Shikiar R, Thompson C. Minimum clinically important difference in Dermatology Life Quality Index in moderate to severe plaque psoriasis patients treated with Adalimumab. *J Am Acad Dermatol* 2005; **52** (Suppl.): AB221.
68 Shikiar R, Harding G, Leahy M, Lennox RD. Minimal important difference (MID) of the Dermatology Life Quality Index (DLQI): results from patients with chronic idiopathic urticaria. *Health Qual Life Outcomes* 2005; **3**: 36.
69 Khilji FA, Gonzalez M, Finlay AY. Clinical meaning of change in Dermatology Life Quality Index scores. *Br J Dermatol* 2002; **147** (Suppl. 62): 50.
70 Chren MM, Lasek RJ, Flocke SA, Zyzanski SJ. Improved discriminative and evaluative capability of a refined version of Skindex, a quality-of-life instrument for patients with skin diseases. *Arch Dermatol* 1997; **133**: 1433–40.
71 Chren MM, Lasek RJ, Sahay AP, Sands LP. Measurement properties of Skindex-16: a brief quality-of-life measure for patients with skin diseases. *J Cutan Med Surg* 2001; **5**: 105–10.
72 Nijsten TEC, Sampogna F, Chren M-M, Abeni DD. Testing and reducing Skindex-29 using Rasch analysis: Skindex-17. *J Invest Dermatol* 2006; **126**: 1244–50.
73 Jones-Caballero M, Penas PF, Garcia-Diaz A *et al*. The Spanish version of Skindex-29. *Int J Dermatol* 2000; **39**: 907–12.
74 Abeni D, Picardi A, Pasquini P *et al*. Further evidence of the validity and reliability of the Skindex-29: an Italian study on 2,242 dermatological outpatients. *Dermatology* 2002; **204**: 43–9.
75 Aksu AE, Urer MS, Sabuncu I *et al*. Turkish version of Skindex-29. *Int J Dermatol* 2007; **46**: 350–5.
76 AlGhamdi KM, AlShammari SA. Arabic version of Skindex-16: translation and cultural adaptation, with assessment of reliability and validity. *Int J Dermatol* 2007; **46**: 247–52.
77 Higaki Y, Kawamoto K, Kamo T *et al*. The Japanese version of Skindex-16: a brief quality-of-life measure for patients with skin disease. *J Dermatol* 2002; **29**: 693–8.
78 Augustin M, Wenninger K, Amon U *et al*. German adaptation of the Skindex-29 questionnaire on quality of life in dermatology: validation and clinical results. *Dermatology* 2004; **209**: 14–20.
79 Nijsten T, Sampogna F, Abeni D. Categorization of Skindex-29 scores using mixture analysis. *Dermatology* 2009; **218**: 151–4.

Disease-specific measures

Questions in disease-specific measures reflect as closely as possible the problems encountered by patients with that disease, and so disease-specific measures have the potential of being the most sensitive to change. They are, therefore, particularly suitable for comparative purposes within a cohort of patients with the same disease. However many skin conditions, such as widespread inflammatory skin diseases, affect patients' lives in broadly similar ways, and so dermatology-specific measures can also be used. There is, therefore, no urgent need for a disease-specific measure to be created for every skin disease.

Psoriasis

A landmark study of quality of life issues in over 17 000 patients from the USA with psoriasis [1], using a study-specific questionnaire, demonstrated the major impact that psoriasis can have on patients' lives and revealed that many patients with psoriasis do not feel that their physicians are aggressive enough with their therapy. A study of 18 000 patients from Europe [2] reached similar conclusions, with over 70% reporting only low to moderate satisfaction with the available treatment options. The greatest impact reported was on daily living activities, especially affecting clothing choice, bathing routine and sporting activities.

The Psoriasis Disability Index (PDI), originally described in 1987 [3] and revised in 1995 [4], has been extensively used [5] and is available in over 20 languages [6]. The PDI has been used in major surveys [2,7]. However, it may be suboptimal for

widespread use in patients with mild–moderate psoriasis because of insensitivity to lower levels of disability and lack of evidence to support scoring with a single score [8].

The stigmatizing effects of psoriasis can be recorded using a 33-item disease-specific questionnaire [9]. This questionnaire was used in the development of another technique for measuring stigma across all dermatology patients, the Questionnaire on Experience with Skin complaints (QES) [10]. The QES has been used to demonstrate the high stigmatization experienced by patients with psoriasis compared to patients with other skin diseases [11] and has also been applied to patients with vitiligo [12]. The stress caused by the impact of psoriasis on quality of life has been measured [13] using the final 15-item version of the Psoriasis Life Stress Inventory [14].

The Impact of Psoriasis Questionnaire (IPSO) [15] has been gradually refined and following Rasch analysis an 11-item version has been shown to have improved internal consistency [16]. Regrettably, most HRQoL studies in dermatology assess changes over a relatively short period of time [17], but the IPSO was the measure used on the longest dermatology HRQoL follow-up study, reporting changes in a cohort of psoriasis patients over 11 years [18].

The Salford Psoriasis Index (SPI) consists of three independent scores describing Signs (disease activity), Psychosocial disability, and history of Interventions [19,20]. The SPI therefore records an important aspect of psoriasis that is taken into account by clinicians in daily practice—the past history of the disease. This approach may be of great value in the recording, monitoring and classification of this chronic disease.

PSORIQoL is a 25-item questionnaire that assesses the impact of impairment and disability from psoriasis on the patient's perception of quality of life [21]; a US version has been validated [22]. Another questionnaire, the 12-item PQoL-12 [23], has been incorporated in a psoriasis severity assessment tool, the Koo-Menter Psoriasis Instrument [24].

The above and other measures used in psoriasis have been described in more detail [25] and critically reviewed [26].

Atopic dermatitis

The CDLQI and the DLQI have been used extensively in the monitoring of patients with atopic dermatitis but several disease-specific approaches have been described. In a large, managed care organization in the USA, patient-assessed severity of atopic dermatitis demonstrated a stronger correlation with the DLQI and CDLQI than did provider-assessed severity, emphasizing the importance of directly assessing the patients' attitudes [27]. Indeed, patients with atopic dermatitis are able to accurately determine their disease severity and quality of life [28]. Assessment of the burden of atopic dermatitis has been reviewed [29].

The Psychosomatic Scale for Atopic Dermatitis (PSS-AD) is a simple 12-item scale to measure the 'psychosomatic pathology' of adult atopic dermatitis [30]. The PSS-AD has been initially validated and may be useful to help identify patients who would benefit from psychological intervention. In adults there is an interrelationship between perceived stigma and atopic dermatitis severity, both of which are strong predictors of quality of life impairment [31].

A Childhood Atopic Dermatitis Impact Scale (CADIS) consisting of 45 items has been developed. This measure combines assessment of the impact on the quality of life of affected young children and on their families [32]; these are two interdependent but separate concepts. Further validation of the measure has demonstrated correlation with SCORAD scores [33].

The Parents' Index of Quality of Life in Atopic Dermatitis (PIQoL-AD) has been developed [34] to measure the parent's assessment of the impact of atopic dermatitis on the affected child (not the secondary impact on the parent, see below). Importantly, the minimum meaningful score difference has been estimated: a change of 2 to 3 points [35]. In contrast to the PIQoL, the Dermatitis Family Impact questionnaire (DFI) seeks to assess the impact of having a child with atopic dermatitis on the quality of life of the family [36].

The lives of infants with atopic dermatitis may be severely disrupted, even though the affected children may not be able to explain their distress, or have the insight to know that what they are experiencing is abnormal. The Infant's Dermatitis Quality of Life Index (IDQOL) [37,38] encapsulates and measures the impact of atopic dermatitis on infants.

Acne

The compact five-question Cardiff Acne Disability Index [39] was derived from the Acne Disability Index [40]. This simple instrument has demonstrated reliability [41] and has been validated in French [42] and Persian [43]. There is good correlation between the CADI and the CDLQI [44]. The Assessments of the Psychological and Social Effects of Acne (APSEA) questionnaire [45] has 15 questions, some of which relate to the overall impact and some to the recent past.

The Acne Quality of Life Scale (AQOL) [46] has nine questions that relate specifically to the social impact of acne. The Acne-specific Quality of Life Questionnaire (Acne-QoL) [47] has 19 questions and was designed for use in clinical trials. A four-question condensed version of this, the Acne-Q4, is likely to be more practical to use [48].

Other disease-specific measures

The number of disease-specific measures is gradually increasing. Such questionnaires include those described for ulcers [49], urticaria [50], excessive axillary sweating [51], scalp dermatitis [52], for women with androgenetic alopecia [53], for melasma [54,55], skin cancer [56], rosacea [57] and to assess bother related to hirsutism in women [58].

Site-specific measures

Nail disease, especially when the fingernails are affected, may have an impact on HRQoL that is out of proportion to the very small body surface area affected. This impact may be detected by the Skindex-29 [59], and two nail-disease-specific instruments have been developed [60,61].

References

1 Kreuger G, Koo J, Lebwohl M *et al*. The impact of psoriasis on quality of life: results of a 1998 National Psoriasis Foundation patient-membership survey. *Arch Dermatol* 2001; **58**: 280–4.

2 Dubertret L, Mrowietz U, Ranki A *et al*. European patient perspectives on the impact of psoriasis: the EUROPSO patient membership survey. *Br J Dermatol* 2006; **155**: 729–36.
3 Finlay AY, Kelly SE. Psoriasis—an index of disability. *Clin Exp Dermatol* 1987; **12**: 8–11.
4 Finlay AY, Coles EC. The effect of severe psoriasis on the quality of life of 369 patients. *Br J Dermatol* 1995; **132**: 236–44.
5 Lewis VJ, Finlay AY. Two decades experience of the Psoriasis Disability Index. *Dermatology* 2005; **210**: 261–8.
6 Dermatology Department, Cardiff University. *Psoriasis Disability Index*. www.dermatology.org.uk.
7 Garcia-Diez A, Foraster CF, Sebastian FV *et al*. What characterizes the severity of psoriasis? *Dermatology* 2008; **216**: 137–51.
8 Nijsten T, Whalley D, Gelfand J *et al*. The psychometric properties of the psoriasis disability index in United States patients. *J Invest Dermatol* 2005; **125**: 665–72.
9 Ginsberg IH, Link BG. Feelings of stigmatisation in patients with psoriasis. *J Am Acad Dermatol* 1989; **20**: 53–63.
10 Schmid-Ott G, Jaeger B, Ott R, Lamprecht F. Dimensions of stigmatisation in patients with psoriasis in a 'questionnaire on experience with skin complaints'. *Dermatology* 1996; **193**: 304–10.
11 Vardy D, Besser A, Amir M *et al*. Experiences of stigmatisation play a role in mediating the impact of disease severity on quality of life in psoriasis patients. *Br J Dermatol* 2002; **147**: 736–42.
12 Schmid-Ott G, Künsebeck H-W, Jecht E *et al*. Stigmatization experience, coping and sense of coherence in vitiligo patients. *J Eur Acad Dermatol Venereol* 2007; **21**: 456–61.
13 Zachariae R, Zachariae H, Blomqvist K *et al*. Self-reported stress reactivity and psoriasis-related stress of Nordic psoriasis sufferers. *J Eur Acad Dermatol Venereol* 2004; **18**: 27–36.
14 Gupta MA, Gupta AK. The Psoriasis Life Stress Inventory: a preliminary index of psoriasis-related stress. *Acta Dermatol Venereol (Stockh)* 1995; **75**: 240–3.
15 McKenna KE, Stern RS. The impact of psoriasis on the quality of life of patients from the 16-center PUVA follow-up cohort. *J Am Acad Dermatol* 1997; **36**: 388–94.
16 Nijsten T, Unaeze J, Stern RS. Refinement and reduction of the Impact of Psoriasis Questionnaire: classical test theory vs. Rasch analysis. *Br J Dermatol* 2006; **154**: 692–700.
17 Jobling R, Naldi L. Assessing the impact of psoriasis and the relevance of qualitative research. *J Invest Dermatol* 2006; **126**: 1438–40.
18 Unaeze J, Nijsten T, Murphy A *et al*. Impact of psoriasis on health-related quality of life decreases over time: an 11-year prospective study. *J Invest Dermatol* 2006; **126**: 1480–9.
19 Kirby B, Fortune DG, Bhushan M *et al*. The Salford Psoriasis Index: an holistic measure of psoriasis severity. *Br J Dermatol* 2000; **142**: 728–32.
20 Kirby B, Richards HL, Woo P *et al*. Physical and psychological measures are necessary to assess overall psoriasis severity. *J Am Acad Dermatol* 2001; **45**: 72–6.
21 McKenna SP, Cook SA, Whalley D *et al*. Development of the PSORIQoL, a psoriasis specific measure of quality of life designed for use in clinical practice and trials. *Br J Dermatol* 2003; **149**: 323–31.
22 McKenna SP, Lebwohl M, Kahler KN. Development of the US PSORIQoL: a psoriasis-specific measure of quality of life. *Int J Dermatol* 2005; **44**: 462–9.
23 Mease PJ, Menter MA. Quality-of-life issues in psoriasis and psoriatic arthritis outcome measures and therapies from a dermatological perspective. *J Am Acad Dermatol* 2006; **54**: 685–704.
24 Feldman SR, Koo JYM, Menter A, Bagel J. Decision points for the initiation of systemic treatment for psoriasis. *J Am Acad Dermatol* 2005; **53**: 101–7.
25 Thomas CL, Finlay AY. Measuring the effects of psoriasis on quality of life. *Expert Rev Dermatol* 2006; **1**: 723–36.
26 De Korte J, Sprangers MAG, Mombers FMC, Bos JD. Quality of life measures in psoriasis: a systematic literature review. *J Invest Dermatol Symp Proc* 2004; **9**: 140–7.
27 Fivenson D, Arnold RJG, Kaniecki DJ *et al*. The effect of atopic dermatitis on total burden of illness and quality of life on adults and children in a large managed care organisation. *J Managed Care Pharmacy* 2002; **8**: 333–42.
28 Holm EA, Wulf HC, Stegmann H, Jemec GBE. Life quality assessment among patients with atopic eczema. *Br J Dermatol* 2006; **154**: 719–25.
29 Finlay AY. The burden of atopic eczema. In: Ring J, Przybila B, Ruzicka T, eds. *Handbook of Atopic Eczema*, 2nd edn. Berlin: Springer, 2006.
30 Ando T, Hashiro M, Noda K *et al*. Development and validation of the psychosomatic scale for atopic dermatitis in adults. *J Dermatol* 2006; **33**: 439–50.
31 Wittkowski A, Richards HL, Griffiths CEM, Main CJ. The impact of psychological and clinical factors on quality of life in individuals with atopic dermatitis. *J Psychosom Res* 2004; **57**: 195–200.
32 Chamlin SL, Cella D, Frieden IJ *et al*. Development of the Childhood Atopic Dermatitis Impact Scale: initial validation of a quality-of-life measure for young children with atopic dermatitis and their families. *J Invest Dermatol* 2005; **125**: 1106–11.
33 Chamlin SL, Lai J-S, Cella D *et al*. Childhood Atopic Dermatitis Impact Scale: reliability, discriminative and concurrent validity and responsiveness. *Arch Dermatol* 2007; **143**: 768–72.
34 McKenna SP, Whalley D, Dewar AL *et al*. International development of the parents' index of quality of life in atopic dermatitis (PIQoL-AD). *Qual Life Res* 2005; **14**: 231–41.
35 Meads DM, McKenna SP, Kahler K. The quality of life of parents of children with atopic dermatitis; interpretation of PIQoL scores. *Qual Life Res* 2005; **14**: 2235–45.
36 Lawson V, Lewis-Jones MS, Finlay AY *et al*. The family impact of childhood atopic dermatitis: the Dermatitis Family Impact questionnaire. *Br J Dermatol* 1998; **138**: 107–13.
37 Lewis-Jones MS, Finlay AY, Dykes PJ. The Infant's Dermatitis Quality of Life Index. *Br J Dermatol* 2001; **144**: 104–10.
38 Beattie PE, Lewis-Jones MS. A comparative study of impairment of quality of life in children with skin disease and children with other chronic childhood diseases. *Br J Dermatol* 2006; **155**: 145–51.
39 Motley RJ, Finlay AY. Practical use of a disability index in the routine management of acne. *Clin Exp Dermatol* 1992; **17**: 1–3.
40 Motley RJ, Finlay AY. How much disability is caused by acne? *Clin Exp Dermatol* 1989; **14**: 194–8.
41 Salek MS, Khan GK, Finlay AY. Questionnaire techniques in assessing acne handicap: reliability and validity study. *Qual Life Res* 1996; **5**: 131–8.
42 Dreno B, Finlay AY, Nocera T *et al*. The Cardiff Acne Disability Index: cultural and linguistic validation in French. *Dermatology* 2004; **208**: 104–8.
43 Aghaei S, Mazharinia N, Jafari P, Abbasfard Z. The Persian version of the Cardiff Acne Disability Index. *Saudi Med J* 2006; **27**: 447–9.
44 Walker N, Lewis-Jones MS. Quality of life and acne in Scottish adolescent schoolchildren: use of the Children's Dermatology Life Quality Index (CDLQI) and the Cardiff Acne Disability Index (CADI). *J Eur Acad Dermatol Venereol* 2006; **20**: 45–50.
45 Layton AM. Psychological assessment of skin disease. *Interfaces Dermatol* 1994; **1**: 37–9.
46 Gupta MAA, Johnson AM, Gupta AK. The development of an acne quality of life scale: reliability, validity, and relation to subjective acne severity in mild to moderate acne vulgaris. *Acta Derm Venereol (Stockh)* 1998; **78**: 451–6.
47 Martin AR, Lookingbill DP, Botek A *et al*. Health-related quality of life among patients with facial acne – assessment of a new acne-specific questionnaire. *Clin Exp Dermatol* 2001; **26**: 380–5.
48 Tan J, Fung KY, Khan S. Condensation and validation of a 4-item index of the Acne-QoL. *Qual Life Res* 2006; **15**: 1203–10.
49 Hyland ME. Quality of life of leg ulcer patients: questionnaire and preliminary findings. *J Wound Care* 1994; **3**: 294–8.
50 O'Donnell BF, Lawlor F, Simpson J *et al*. The impact of chronic urticaria on the quality of life. *Br J Dermatol* 1997; **136**: 197–201.
51 Naumann MK, Hamm H, Lowe NJ. Effect of botulinum toxin type A on quality of life measures in patients with excessive axillary sweating: a randomised controlled trial. *Br J Dermatol* 2002; **147**: 1218–26.
52 Chen SC, Yeung J, Chren MM. Scalpdex: a quality of life instrument for scalp dermatitis. *Arch Dermatol* 2002; **138**: 803–7.
53 Dolte KS, Girman CJ, Hartmaier S *et al*. Development of a health-related quality of life questionnaire for women with androgenetic alopecia. *Exp Dermatol* 2000; **25**: 637–42.
54 Balkrishnan R, McMichael AJ, Camaho FT *et al*. Development and validation of a health-related quality of life instrument for women with melasma. *Br J Dermatol* 2003; **149**: 572–7.

55 Pawaskar MD, Parikh P, Markowski T *et al*. Melasma and its impact on health-related quality of life in Hispanic women. *J Dermatol Treat* 2007; **18**: 5–9.
56 Rhee JS, Matthews BA, Neuberg M *et al*. The skin cancer index: clinical responsiveness and predictors of quality of life. *Laryngoscope* 2007; **117**: 399–405.
57 Nicholson K, Abramova L, Chren MM *et al*. A pilot quality-of-life instrument for acne rosacea. *J Am Acad Dermatol* 2007; **57**: 213–21.
58 Jackson J, Caro JJ, Caro G *et al*. The effect of eflornithine 13.9% cream on the bother and discomfort due to hirsutism. *Int J Dermatol* 2007; **46**: 976–81.
59 Tabolli S, Alessandroni L, Gaido J *et al*. Health-related quality of life and nail disorders. *Acta Derm Venereol* 2007; **87**: 255–9.
60 Drake LA, Patrick DL, Fleckman P *et al*. The impact of onychomycosis on quality of life: development of an international onychomycosis-specific questionnaire to measure patient quality of life. *J Am Acad Dermatol* 1999; **41**: 189–96.
61 Warshaw EM, Foster JK, Cham PMH *et al*. NailQoL: a quality-of-life instrument for onychomycosis. *Int J Dermatol* 2007; **46**: 1279–86.

Patient-specific and utility measures

Health-related quality of life measures are, or should be, derived from information gathered from patients' experiences and not from health care professionals' concepts of what they suppose to be the impact of disease. Despite this, all fixed questionnaires suffer from the disadvantage that, for an individual patient, the impact of different aspects of life quality impairment may be different from the weighting assigned in the questionnaire or the specific issues may be missed altogether. The Patient Generated Index [1] overcomes these problems by being structured in a different way; patients are asked to identify the five ways in which their life is most affected and then assign them comparative values. This technique is effective for identifying an individual's specific problems, such as in atopic dermatitis [2].

Different approaches are used to create measures of the concept of patient preferences, for example towards attitudes to risk or to different treatments or outcomes [3]. Utility measures, for example, assess the hypothetical value placed by people on their health. There are a variety of methodologies. Standard gamble, time trade off and vertical rating scales have been proposed [4] as a way of informing decisions about methotrexate therapy for psoriasis. The willingness to pay (WTP) method is to ask patients how much they would be prepared to pay for a cure of their disease if such a cure existed. This has been used in acne [5], psoriasis [6–8] and atopic dermatitis [7,9]. WTP information showed strong test–retest reliability in an onychomycosis study [10].

Another approach is to ask patients to consider how much time they would be prepared to give up for the sake of a cure. These 'trade off' questions can be related to years of shortening of life, as in the Quality Adjusted Life Year (QALY), or be related to hours' trade off. The time trade off (TTO) method has been described in psoriasis [6,8] and in atopic dermatitis [9]. The TTO method has demonstrated that patients with atopic dermatitis and psoriasis would choose a 40% shorter life expectancy in order to avoid uncontrolled skin disease [11]. In contrast to the concept of hypothetical time that a patient would be prepared to give up, there is no correlation between the measurement of actual time spent on treatment and quality of life scores [12], though there is with SCORAD [13]. The TTO questions have been used to calculate comparative mean utilities across a range of skin diseases: the lowest mean utility was for bullous disorders [14]. These utilities can be compared with data from non-dermatological disease.

The QALY method was first applied in dermatology in acne [15]. The advent of the highly effective but also very expensive biological drugs for psoriasis resulted in considerable further attention being given to the concept [16]. The resulting QALY information has played a key role in influencing criteria for the use of these drugs. QALY calculations may use standard dermatology HRQoL information, such as DLQI data, to compare the cost effectiveness of different drug regimens [17].

There has been an attempt to bring together descriptors of a health state and the use of the standard gamble technique as a basis for the calculation of QALYs [18]. This was applied to atopic dermatitis and included information from parents of children with atopic dermatitis as well as values of the general public. Such cost–utility analyses may be undertaken to demonstrate whether or not the use of particular therapies can be justified on economic grounds. The information that is used in such analyses may include HRQoL data; an example is an analysis of the few situations where topical tacrolimus for the treatment of atopic dermatitis can be justified on economic grounds [19].

References

1 Ruta DA, Garratt AM, Leng M *et al*. A new approach to the measurement of quality of life. The patient generated index. *Med Care* 1994; **32**: 1109–26.
2 Herd RM, Tidman MJ, Ruta DA, Hunter JAA. Measurement of quality of life in atopic dermatitis: correlation and validation of two different methods. *Br J Dermatol* 1997; **136**: 502–7.
3 McCombs K, Chen SC. Patient preference quality of life measures in dermatology. *Dermatol Ther* 2007; **20**: 102–9.
4 Zug KA, Littenberg B, Baughman RD *et al*. Assessing the preferences of patients with psoriasis. *Arch Dermatol* 1995; **131**: 561–8.
5 Motley RJ, Finlay AY. How much disability is caused by acne? *Clin Exp Dermatol* 1989; **14**: 194–8.
6 Finlay AY, Coles EC. The effect of severe psoriasis on the quality of life of 369 patients. *Br J Dermatol* 1995; **132**: 236–44.
7 Lundberg L, Johanesson M, Silverdahl M *et al*. Quality of life, health state utilities and willingness to pay in patients with psoriasis and atopic eczema. *Br J Dermatol* 1999; **141**: 1067–75.
8 Schiffner R, Schiffner-Rohe JS, Gerstenhauer M *et al*. Willingness to pay and time trade-off: sensitive to changes of quality of life in psoriasis patients? *Br J Dermatol* 2003; **148**: 1153–60.
9 Finlay AY. Measures of the effect of adult severe atopic eczema on quality of life. *J Eur Acad Dermatol Venereol* 1996; **7**: 149–54.
10 Cham PMH, Chen SC, Grill JP *et al*. Reliability of self-reported willingness-to-pay and annual income in patients treated for toenail onychomycosis. *Br J Dermatol* 2007; **156**: 922–8.
11 Schmitt J, Meurer M, Klon M, Frick KD. Assessment of health state utilities of controlled and uncontrolled psoriasis and atopic eczema: a population-based study. *Br J Dermatol* 2008; **158**: 351–9.
12 Jemec GBE, Kynemund L. Time spent on treatment in dermatology—how much time do outpatients use and is it a measure of morbidity? *Acta Dermatoven APA* 2001; **10**: 17–9.
13 Holm EA, Jemec GBE. Time spent on treatment of atopic dermatitis: a new method of measuring pediatric morbidity? *Pediat Dermatol* 2004; **21**: 623–7.
14 Chen SC, Bayoumi AM, Soon SL *et al*. A catalog of dermatology utilities: a measure of the burden of skin diseases. *J Invest Dermatol Symp Proc* 2004; **9**: 160–8.
15 Simpson NB. Social and economic aspects of acne and the cost-effectiveness of isotretinoin. *J Dermatol Treat* 1993; **4** (Suppl. 2): S6–9.
16 Woolacott N, Hawkins N, Mason A *et al*. Etanercept and efalizumab for the treatment of psoriasis: a systematic review. *Health Technol Assess* 2006; **10**: 1–233.
17 Lloyd A, Reeves P, Conway P *et al*. Economic evaluation of etanercept in the management of chronic plaque psoriasis. *Br J Dermatol* 2009; **160**: 380–6.

18 Stevens KJ, Brazier JE, McKenna SP *et al*. The development of a preference-based measure of health in children with atopic dermatitis. *Br J Dermatol* 2005; **153**: 372–7.
19 Pitt M, Garside R, Stein K. A cost-utility analysis of pimecrolimus vs. topical corticosteroids and emollients for the treatment of mild and moderate atopic eczema. *Br J Dermatol* 2006; **154**: 1137–46.

Children and the greater patient family impact

Children

The assessment of quality of life impairment in children is more difficult than in adults because of issues relating to communication, rapid change in lifestyle at different ages and differing rates of maturing. The different general measures and disease-specific measures have been systematically reviewed [1]. Several atopic dermatitis specific measures for use in children have been described (see above).

The Children's Dermatology Life Quality Index (CDLQI) [2] was designed to be used by children between the ages of 4 and 15 years old. It can be completed unaided by older children but parents can help younger children as necessary. Key areas that are enquired about are given in Table 72.6. An illustrated cartoon version, using the same text, has been validated [3]. Overall, children preferred the cartoon version and completed it more rapidly than the text-only version. There are over 20 different validated language translations of the CDLQI. The CDLQI has been used in the assessment on children's lives of the effects of atopic dermatitis, the impact of admission for treatment, the impact of a nurse consultant and the effect of new topical and systemic anti-inflammatory agents. It has also been used to demonstrate a relationship between HRQoL scores and objective measures of skin function in atopic dermatitis [4]. The CDLQI was cross-validated with a generic HRQoL proxy measure for children, the Children's Life Quality Index [5]. This demonstrated that HRQoL impairment in children with chronic skin disease is at least equal to that experienced by children with many other chronic diseases of childhood.

The difficulties in measuring life quality changes in children are even greater in the very young. The Infant's Dermatitis Quality of Life Index (IDQOL) is an attempt to record the impact of atopic dermatitis on infants [6].

The Pediatric Symptom Checklist [7], which consists of 35 questions answered by the parent, has been used for psychosocial screening in paediatric dermatology clinics.

Adolescents

The lives of individuals aged from 12 to 18 years are characterized by mental and physical development, increasing independence, emerging sexuality and intimacy, and emotional changes. Skin disease may profoundly affect adolescents in a variety of specific ways, including psychological, social, lifestyle, education and employment [8]. Major, long-term life decisions, for example over which career to follow, may be influenced by having skin disease at that time. Although the CDLQI has been used in children up to the age of 15 years and the DLQI can be used in those aged 16 years or over, there are special aspects of life quality impairment experienced by adolescents that might be captured more appropriately by measures designed specifically for this age group.

Family impact—the greater patient

When a patient is affected by a skin disease, the lives of those closest to the person are usually also affected. The extent of this effect may be profound but not be realized by health care professionals. The concept of 'the greater patient' has been proposed to describe the wider family unit, including the partner or close relatives, whose lives are all affected by an individual having skin disease [9].

The impact of skin disease on the greater patient was first understood in atopic dermatitis; having a child with this condition can have a major impact on the functioning of a family, for example in causing sleep disturbance of the parents [10]. Two disease-specific methods [11,12] measure this secondary impact, and another questionnaire records both the impact on an affected child and on the parents [13]. The Dermatitis Family Impact questionnaire (DFI) [11] has been used to demonstrate the relationship of childhood dermatitis severity to family life quality [14]. In infants, the DFI and IDQOL scores correlate well; both improve following initial consultation with a dermatology team [5]. Support groups for children with atopic dermatitis and their families [15] may help to address some of these greater patient issues. The families of adults with atopic dermatitis also experience a secondary impact. The sex life of 36% of partners of adult patients with atopic dermatitis were affected by the appearance of the skin disease [16].

Following detailed qualitative interviews of partners and relatives of patients with a variety of skin diseases [9], a 10-item questionnaire, the Family Dermatology Life Quality Index, has been validated [17,18]. Key areas affected and enquired about are given in Table 72.7. This instrument allows, for example,

Table 72.6 The Children's Dermatology Life Quality Index—aspects covered in the 10 questions [2].

1	Symptoms
2	Embarrassment
3	Friendships
4	Clothes
5	Playing
6	Sports
7	School/holiday activities
8	Teasing
9	Sleep
10	Treatment

Table 72.7 The Family Dermatology Life Quality Index—aspects covered in the 10 questions [17].

1	Emotional distress
2	Physical well-being
3	Personal relationships
4	Other people's reactions
5	Social life
6	Recreation/leisure activities
7	Time assisting therapy
8	Housework
9	Work/study
10	Expenditure

comparison between the secondary impact of different skin diseases. Its use has confirmed that eczema has a greater secondary impact than acne [19].

The importance of understanding the attitudes and beliefs held by patients with psoriasis and their partners has been stressed [20]. There is a major impact on the greater patient specifically in psoriasis [21]; the Psoriasis Family Impact questionnaire has been developed to assess the psoriasis-specific issues [22]. New ways are needed to develop interventions to address these impacts on partners and family members and to critically assess outcomes [23].

Practical clinical use of measures: a vital sign?

Clinicians use a subjective view of the QoL of their patients to inform many decisions. A better understanding of this impact and the subsequent realization of the need for early and effective therapy, has led to a focus on new models for health care delivery, 'patient-centred care' [24] or 'patient-based medicine' [25]. Better communication and engagement in a dialogue of negotiation with a patient over management is at the heart of this change in emphasis.

In psoriasis there is a relationship between the type of management decision taken (for example whether or not to start on ultraviolet or systemic therapy) and patient-rated HRQoL [26]. However, there is a lack of HRQoL discussion during dermatology outpatient consultations [27]. In an observational study of inflammatory skin disease consultations, there was a greater patient reported HRQoL impact experienced by those patients in whom HRQoL issues were discussed than in those in whom these issues were not raised [28]. Where DLQI information was made available on a routine basis in a general dermatology clinic, treatment decisions were influenced in 9% of consultations, mainly in patients in whom there was high HRQoL impairment [29].

Patient-generated information about their skin disease, as assessed by HRQoL outcome measures, should be encouraged to become one of the vital signs of skin disease, essential for understanding the patient's disease and informing its appropriate management [30]. However, there remain many methodological challenges both in the appropriate capturing and use of HRQoL data; it has been stressed that QoL assessment cannot replace effective patient–physician communication [31].

References

1 Solans M, Pane S, Estrada MD *et al*. Health-related quality-of-life measurement in children and adolescents: a systematic review of generic and disease-specific instruments. *Value Health* 2007; **11**: 742–64.

2 Lewis-Jones MS, Finlay AY. The Children's Dermatology Life Quality Index (CDLQI): initial validation and practical use. *Br J Dermatol* 1995; **132**: 942–9.

3 Holme SA, Mann I, Sharpe JL *et al*. The Children's Dermatology Life Quality Index: validation of the cartoon version. *Br J Dermatol* 2003; **148**: 285–90.

4 Hon KL, Wong KY, Leung TF *et al*. Comparison of skin hydration evaluation sites and correlations among skin hydration, transepidermal water loss, SCORAD index, Nottingham Eczema Severity Score, and quality of life in patients with atopic dermatitis. *Am J Clin Dermatol* 2008; **9**: 45–50.

5 Beattie PE, Lewis-Jones MS. A comparative study of impairment of quality of life in children with skin disease and children with other chronic childhood diseases. *Br J Dermatol* 2006; **155**: 145–51.

6 Lewis-Jones MS, Finlay AY, Dykes PJ. The Infant's Dermatitis Quality of Life Index. *Br J Dermatol* 2001; **144**: 104–10.

7 Rauch PK, Jellinek MS, Murphy JM *et al*. Screening for psychosocial dysfunction in pediatric dermatology practice. *Clin Pediatr* 1991; **30**: 493–7.

8 Golics CJ, Basra MKA, Finlay AY, Salek MS. Adolescents with skin disease have specific quality of life issues. *Dermatology* 2009; **218**: 357–66.

9 Basra MKA, Finlay AY. The family impact of skin disease: the Greater Patient concept. *Br J Dermatol* 2007; **156**: 929–37.

10 Moore K, David TJ, Murray CS *et al*. Effect of childhood eczema and asthma on parental sleep and well-being: a prospective comparative study. *Br J Dermatol* 2006; **154**: 514–8.

11 Lawson V, Lewis-Jones SM, Finlay AY. The family impact of childhood atopic dermatitis: the Dermatitis Family Impact questionnaire. *Br J Dermatol* 1998; **138**: 107–13.

12 Von Reuden U, Staab D, Kehrt R, Wahn U. Development of a questionnaire to measure health-related quality of life in parents of children with atopic dermatitis. *Qual Life Res* 1998; **7**: 656–7.

13 Chamlin SL, Cella D, Frieden IJ *et al*. Development of the Childhood Atopic Dermatitis Impact Scale: initial validation of a quality-of-life measure for young children with atopic dermatitis and their families. *J Invest Dermatol* 2005; **125**: 1106–11.

14 Ben-Gashir MA, Seed PT, Hay RJ. Are quality of family life and disease severity related in childhood atopic dermatitis? *J Eur Acad Dermatol Venereol* 2002; **16**: 455–62.

15 Goh C, Lane AT, Bruckner AL. Support groups for children and their families in pediatric dermatology. *Pediatric Dermatol* 2007; **24**: 302–5.

16 Misery L, Finlay AY, Martin N *et al*. Atopic dermatitis: impact on the quality of life of patients and their partners. *Dermatology* 2007; **215**: 123–9.

17 Basra MKA, Sue-Ho R, Finlay AY. The Family Dermatology Life Quality Index: measuring the secondary impact of skin disease. *Br J Dermatol* 2007; **156**; 528–38 (Erratum *Br J Dermatol* 2007; **156**: 791).

18 Basra MKA, Edmunds O, Salek MS, Finlay AY. Measurement of family impact of skin disease: further validation of the Family Dermatology Life Quality Index (FDLQI). *J Eur Acad Dermatol Venereol* 2008; **22**: 813–21.

19 Basra M, Finlay A. Eczema has greater impact than acne on the quality of life of patients' families. *J Am Acad Dermatol* 2007; **56** (Suppl.): AB102.

20 Richards HL, Fortune DG, Chong S *et al*. Divergent beliefs about psoriasis are associated with increased psychological distress. *J Invest Dermatol* 2004; **123**: 49–56.

21 Eghlileb AM, Davies EEG, Finlay AY. Psoriasis has a major impact on the lives of family members and partners. *Br J Dermatol* 2007; **156**: 1245–50.

22 Eghlileb AM, Basra MKA, Finlay AY. The Psoriasis Family Index (PFI): preliminary results of validation of a quality of life instrument for family members of patients with psoriasis. *Dermatology* 2009; **219**: 63–70.

23 Richards HL, Fortune DG, Griffiths CEM. The Greater Patient concept. *Br J Dermatol* 2008; **158**: 176–8.

24 Feldman S, Behnam SM, Behnam SE, Koo JYM. Involving the patient: impact of inflammatory skin disease and patient-focused care. *J Am Acad Dermatol* 2005; **53**: S78–85.

25 Dubertret L. Patient-based medicine. *J Eur Acad Dermatol Venereol* 2006; **20** (Suppl. 2): 73–6.

26 Katugampola RP, Hongbo Y, Finlay AY. Clinical management decisions are related to the impact of psoriasis on patient-rated quality of life. *Br J Dermatol* 2005; **152**: 1256–62.

27 David SE, Ahmed Z, Salek MS, Finlay AY. Does enough quality-of-life related discussion occur during dermatology outpatient consultations? *Br J Dermatol* 2005; **153**: 997–1000.

28 Davies E, Patel C, Salek MS, Finlay AY. Does ad hoc quality-of-life discussion in inflammatory skin disease consultations reflect standardised patient-reported outcomes? *Clin Exp Dermatol* 2008; **33**: 16–21.

29 Salek S, Roberts A, Finlay AY. The practical reality of using a patient-reported outcome measure in a routine dermatology clinic. *Dermatology* 2007; **215**: 315–9.

30 Chren M-M. Measurement of vital signs for skin diseases. *J Invest Dermatol* 2005; **125**(4): viii–ix.

31 Naldi L. Health-related quality of life: from health economics to bedside? *Dermatology* 2007; **215**: 273–6.

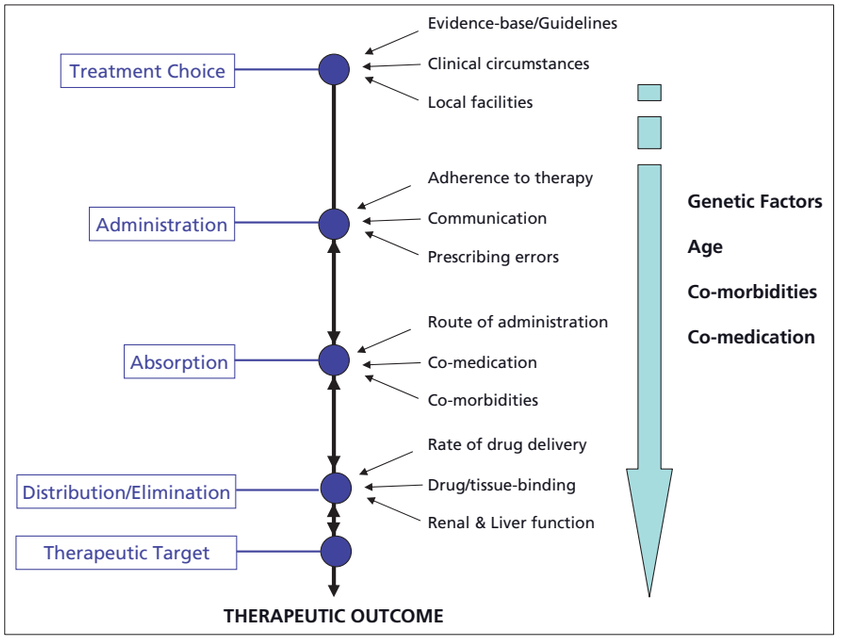


Fig. 72.2 An overview of the relationship between the dose of any particular drug and therapeutic outcome. Multiple, often interdependent, factors impact at critical points (dark blue circles) along the pharmacological pathway, some of which are relevant throughout (light blue arrow).

General principles of therapy

The term 'therapy' encompasses any intervention or approach aimed at treating or preventing disease, and within the context of traditional dermatological practice includes general measures (e.g. avoidance of irritants), conventional medicines, physical treatments (e.g. phototherapy, surgery, laser, liquid nitrogen), psychological interventions, occupational therapy and rehabilitation. Complementary and alternative medicine is also widely used by patients with dermatological disease.

An abiding principle in medicine is 'to help, or at least to do no harm' [Hippocrates]. Therapeutic interventions are at the core of disease management, but it is a sobering fact that 3–6% of hospital admissions are due to adverse drug reactions [1–3] and, of these, half could have potentially been avoided [4]. On the other hand adherence to prescribed therapy, especially for chronic conditions, is poor with the NHS spend on unused or unwanted medicines estimated at £100 million annually [5]. No drug is without risk, but every effort should be made to ensure that for any given intervention (and this includes no specific therapy), the likelihood of benefit exceeds the likelihood of harm. This requires (and is not always achievable) an accurate diagnosis, clear objectives for treatment that have been agreed between clinician and patient, a treatment choice based on sound evidence relevant to the clinical situation, an adequate therapeutic trial of the chosen intervention, and timely review of the patient to determine the outcome of treatment, adverse events and the need for ongoing therapy. Clear communication, mutual respect and understanding between clinician and patient are fundamental to successful therapeutic outcomes.

Topical and systemic treatments

Before initiating any therapeutic measures, a comprehensive assessment of the patient is essential, considering the disease that requires treatment in the context of the whole patient and shared treatment goals. Each therapeutic intervention in a patient can be considered a trial (of $n = 1$) with appropriately defined 'outcome measures' and timelines for judging success or failure. This is perhaps especially important in dermatological practice. The rarity of many skin diseases and historic lack of investment in drug development means that robust evidence to guide treatment choice and optimize drug use is often unavailable. Added to this, many drugs are unlicensed so that clear documentation of benefit (or harm) is also important. Continuing an ineffective or insufficiently effective treatment exposes patients to the ongoing risk of adverse events and expense quite apart from suboptimal management of their skin disease.

Factors that affect therapeutic outcome

Multiple factors determine the relationship between the dose of any particular drug and outcome (Fig. 72.2) and thus therapy needs to be carefully and precisely tailored to the needs and clinical circumstance of each patient. This can be a highly complex, dynamic process that requires constant re-evaluation and refinement during the course of treatment.

Patient adherence to treatment

The extent to which patients follow instructions they are given for a prescribed medication (i.e. adherence) varies enormously from missing an occasional dose to completely stopping treatment, and

therefore may or may not be relevant to treatment outcome. Non-adherence to treatment is very common but few patients will declare it to health care professionals voluntarily and assessment is best approached in a non-judgemental way. It arises for multiple and complex reasons which fall into two main overlapping categories: unintentional and intentional non-adherence. Examples of *unintentional* non-adherence include poor comprehension or recall of the details of the prescribed therapeutic regimen, difficulties applying or taking a medicine and lack of access or ability to pay for treatment. *Intentional* non-adherence, when a patient decides not to take the prescribed medicine, arises due to patients' beliefs, concerns or problems associated with their condition and/or prescribed medicine [6]. In general, patients wish to minimize the number of medicines they take and where there are multiple treatments given, may prioritize one over the other. They will evaluate for themselves the side effects and efficacy of any given treatment—and of course, the effectiveness of treatment in skin disease is manifestly obvious—and may stop therapy to see the outcome. Factors that may improve adherence include providing clear written and verbal communication about how, why and when the treatment needs to be taken, using the simplest dosing schedule possible, and employing various techniques to remind and support patients depending on the particular situation (e.g. telephone reminders, dosette boxes) [7]. Dermatology nurse specialists can play a key role in improving adherence to therapy through patient education and support, practical demonstration of where and how to apply topical treatments and, in some instances, application of treatments in formal outpatient settings. Unlicensed 'special manufacture' medicines ('specials') are widely used in topical therapy but can be associated with erratic supplies and hence poor adherence; in the UK, use of 'specials' has been rationalized and manufacture limited to fewer approved centres in order to address this issue [8].

Medication errors

Some side effects and adverse reactions to drugs are accepted risks of treatment and, whilst they can be minimized with careful prescribing and medicine use, they are unavoidable. In contrast, those arising as a consequence of errors in prescribing, dispensing and/or administration of medicines are, by definition, avoidable. The steps involved between writing a prescription and the patient receiving the medicine are multiple, and each is subject to potential error. Medication errors that lead to serious or fatal adverse events invariably occur due to a series of events, and reflect human error arising in the context of certain predisposing environmental or system factors [9]. Reasons for errors include inadequate knowledge of the patient, their clinical condition, drug history and known allergies, inadequate knowledge of the drug being prescribed, drug dose calculation errors, illegible handwriting, and confusing drug names and product labelling [10–14]. The commonest source of error is in the prescription itself [10,15]. In hospital, often the most junior member of the team with the least knowledge and experience is tasked with prescribing; this in itself is a risk, but also fails to create a culture where prescribing is perceived to be important [12]. Additional factors that predispose to errors include repeated interruptions when writing a prescription and depression in the prescriber [12,16].

Poor communication amongst clinicians, particularly where care crosses or is transferred from one clinical setting (e.g. hospital) to another (e.g. primary care), is also a significant source of error both in relation to the dose and type of medication to be used, and also, as importantly, review and monitoring of the treatment [10,11]. In this situation, a disconnect can arise between the prescriber who initiated the treatment and the clinician responsible for ongoing care, so the necessary adjustments in drug therapy and monitoring fail to occur and/or drug errors remain unchecked for prolonged periods of time, with sometimes catastrophic results. This was specifically identified as a major contributory factor in a review of 137 adverse events arising in relation to methotrexate, which included 25 deaths and 26 serious incidents requiring hospital admission in the UK and also the commonest reason in ambulatory care for adverse drug reactions leading to hospital admission [10].

Certain types of medication are subject to frequent medication errors [3,15]. Drugs with a narrow therapeutic index and/or where the therapeutic dose is close to the toxic dose (e.g. chemotherapeutic agents, anticoagulants, narcotics), drugs with an unusual dosing schedule that patients may easily confuse (e.g. once-weekly methotrexate), or drugs requiring intravenous administration where the speed of infusion or extravasation of drug into tissue can lead to problems (e.g. rapid immunoglobulin infusion and risk of thromboembolic events). Patient groups vulnerable to medication error include infants and children [17], where complex dose calculations are required using drugs that may not be licensed for use in children, and older patients due to communication difficulties, polypharmacy and presence of co-morbidities.

Whilst something is known about the cause and prevalence of medication errors, there is relatively little good evidence to indicate which interventions effectively reduce error [9,18]. Prescribing is no longer the sole remit of doctors and extends to nurses, pharmacists and physiotherapists, all of whom need to take professional responsibility for their prescribing practice. Prescribers need to be supported by appropriate training in clinical pharmacology and the practicalities of prescribing with ready access to clear guidelines and protocols on use of drugs. Clearly defined 'care pathways' can also provide clarity over where responsibility lies for prescribing and monitoring, as has been implemented as part of the UK National Patient Safety Agency alert on methotrexate [19]. However, all humans are subject to errors and lapses and so additional, multiple checks need to be in place. Pharmacists play a critical role in cross-checking scripts (although knowing that this safeguard is in place has been identified as a source of inaccurate or lazy prescription writing in hospital practice [12]). Numerous and varied information technology initiatives focusing on all aspects of the prescribing pathway have been developed, although not all are necessarily associated with a reduction in error risk. For example, electronic prescribing has been shown to reduce the incidence of illegible scripts and adverse drug reactions [20] but automated alerts about potential drug interactions and dose errors have been shown to overwhelm the prescriber so that the excessively frequent alerts are ignored. It seems likely, though, that further refinement of existing systems and new developments in this area will yield substantial benefit.

New MHRA legislation on standards for product labelling should help to reduce confusion and thus minimize dispensing errors. Perhaps most important of all, ensuring the patient is fully briefed on the treatment plan can allow patients themselves to correct mistakes.

Drug pharmacokinetics and pharmacodynamics

The amount of drug delivered to the site of therapeutic action depends on the mode of administration, pattern of drug absorption, distribution, metabolism and elimination (i.e. pharmacokinetics). Multiple variables also affect drug target responsiveness to fixed drug concentrations (i.e. pharmacodynamics). All these elements therefore need to be related to the clinical circumstances of the individual patient requiring the treatment.

Route of administration and drug delivery. The decision as to whether a topical or systemic approach is required will depend on the nature, extent, site and severity of disease, practicability, and patient choice. Topical therapy is relatively safe, and for this reason, in general, is the preferred option whenever possible. In instances where topical therapy alone is insufficiently effective, a combined topical and systemic approach may minimize the dose requirement of potentially more toxic systemic drug therapy. Oral drug administration is convenient for patients but bioavailability is highly variable and dependent on drug characteristics (e.g. lipophilicity, pH), concomitant food intake (e.g. chelation of tetracyclines by calcium in milk) and rate of gastric emptying. Drug formulation is also important [21]. Enteric coated preparations are useful for drugs that cause significant gastric irritation such as prednisolone, but may be incompletely dissolved and absorbed; similarly, controlled release preparations have relevance where the half-life of the drug is short (<4 h) but are associated with wide inter-patient variation and risk of 'dose dumping' when the dosage form fails. Parenteral administration (intravenous, intramuscular, subcutaneous) circumvents the gastrointestinal tract with consequent improved drug bioavailability, and for some drugs (e.g. biological therapy) is currently the only mode of administration. Subcutaneous administration has recently gained wide acceptance in dermatology with the advent of self-administered biological therapies in psoriasis, and also has relevance for older drugs such as methotrexate, as a substitute for intramuscular use.

Novel methods of drug delivery aim to limit systemic drug exposure (and therefore toxicity) and/or optimize bioavailability, particularly for large macromolecules (including DNA and proteins) either by facilitated access to the systemic circulation through traditional routes (skin, lung, gut) or by harnessing the specificity of the immune system to target drug action once inside the body (see Chapter 74). Advances in transdermal drug delivery systems for example, include use of chemical enhancers, iontophoresis, electroporation (where short, high-voltage pulses disrupt the lipid bilayer of the skin), cavitational ultrasound (already approved for optimizing delivery of topical lidocaine), microneedles (painless, spontaneous dissolution) and thermal ablation [22]. Inhalation also offers potential for rapid systemic delivery of small-molecule drugs and can confer better bioavailability than oral ingestion given the much lower concentrations of drug-metabolizing enzymes in the lungs compared to the gastrointestinal tract [23]. Inhalation also offers a potentially promising route for peptides and proteins, as exemplified by inhaled human insulin [24].

Distribution. Following absorption or systemic administration, a drug is distributed into interstitial and intracellular fluids. Initially, well perfused organs such as liver, kidney and brain receive most of the drug, with skin and fat levels accumulating more slowly [21]. The degree to which a drug is bound to plasma proteins and tissues determines blood–tissue partitioning, which in turn can be affected by disease states. Preferential accumulation of drugs in certain tissues may also be of clinical relevance. For example, retinoids tend to preferentially accumulate in adipose tissue so that dosing may need alteration in obese patients. Albumin is a major carrier for acidic drugs, which when reduced by liver, renal or malnutritional disease can lead to elevated levels of unbound drug and increased clearance. On the other hand, α_1-acid glycoprotein binds basic drugs and so if it is increased in acute inflammatory states, unbound drug levels may be correspondingly reduced.

Metabolism [21]. Drug metabolism is traditionally described as occurring in two phases. Phase 1 reactions, catalysed by cytochrome P450 (CYP or P450), flavin-containing mono-oxgenases (FMO) and epoxide hydrolases (mEH, sEH), lead to oxidation, reduction or hydrolysis of the drug. Usually this results in loss of drug function, but for some drugs (so-called pro-drugs), results in drug activation (e.g. mycophenolate mofetil is an ester pro-drug, which is hydrolysed to biologically active mycophenolic acid by plasma esterases). Phase II reactions lead to conjugation of the phase I product, which inactivates potentially toxic phase I metabolites, and facilitates drug elimination as a consequence of improved water solubility and increased molecular weight. Drug-metabolizing enzymes are found in most tissues in the body, including the skin, but are found in the greatest quantity in the gastrointestinal tract (liver, small and large intestine). Liver disease may impact on drug metabolism but the degree to which this occurs cannot be predicted from standard measures of liver function.

Excretion. Drugs are eliminated from the body either unchanged or as drug metabolites, with the kidney being the principle site of drug and drug metabolite elimination. Renal function is therefore a critical factor in determining drug bioavailability and potential toxicity and when reduced due to age, disease or concomitant therapy (e.g. NSAIDs, diuretics) becomes a very common source of adverse drug reactions.

Pharmacodynamics. For any given concentration of drug at the site of action, responsiveness will vary between and within individuals. Relevant contributory factors include age, concomitant medication, the disease being treated and genetic factors (see below).

Age

Age is major determinant of therapeutic outcome. Drug pharmacokinetics and pharmacodynamics are altered in the very young and in older people, although available drug-specific information

is limited largely because these groups are often excluded from clinical trials. There are also age-specific considerations that are pertinent to medical errors, adherence to treatment and co-therapy.

Children. Growth and development during childhood is associated with marked physiological change, especially during infancy and puberty, with consequent, non-linear changes in drug disposition [25]. Systemic exposure to topically applied therapies is more likely in infants and children, compared to adults. During infancy, this relates in part to the presence of a thinner stratum corneum in the preterm neonate and, during childhood, due to increased cutaneous perfusion and hydration of the epidermis compared to adults. The ratio of total body surface area to body mass in infants and young children also far exceeds that in adults. Orally administered drugs also require normalization of drug dose for either body weight or body surface area due to liver and renal developmental change. Hepatic drug metabolizing enzymes are expressed at very low levels at birth, and then undergo distinct patterns of isoform-specific developmental changes in the first year of life, with levels of activity in children exceeding those of adults. The glomerular filtration rate increases rapidly during the first 2 weeks of life and then rises steadily until adult values are reached at 8 to 12 months of age [21,25].

Older people. Ageing is associated with a number of progressive physiological changes including cutaneous atrophy, reduction in lean body mass, 40% reduction in hepatic blood flow, reduced activity of hepatic enzyme activity (especially CYP phase I) and reduced renal function. The decline in glomerular filtration rate has been estimated to be around 1 mL/min/year (or less) after middle age and is a critical determinant of disposition for many drugs. The high prevalence of co-morbidities such as hypertension, diabetes mellitus and ischaemic heart disease, together with widespread use of nephrotoxic therapies such as diuretics and NSAIDs, contribute to this decline. In completely healthy older people, renal function may not necessarily be reduced significantly. Collectively, physiological and pathological change in older people tends to increase drug bioavailability and reduce drug metabolism and elimination (for a comprehensive review see [26]), so accounting for the general advice to start drug therapy at the lowest possible dose and increase the dose slowly. Pharmacodynamic responses to drugs may also change with age—the increased effect of drugs that depress the CNS is a good example—or the pathophysiology of the disease itself may be different from younger people, as in the case of psoriasis where genetic susceptibility loci are distinct in late-onset disease.

Polypharmacy is common with 20 to 40% of older people taking five or more medications, with consequent impact on medicine adherence and risk of drug interactions. All these factors lead to increased variability in drug response with age. Adverse drug reactions are also more common, and tend to be more severe and less likely to be recognized or reported by the patient [1,3,11,27].

Conception, pregnancy and lactation

Any drug exposure prior to, during or after conception can result in an adverse fetal outcome; this risk, which is closely related to drug dose and duration, should always be considered when prescribing and the patient fully informed of the potential hazard [28]. The pre-implantation period (fertilization to implantation) is considered the 'all or nothing' period since injury will result either in embryonic loss, or, if only a small number of cells are affected, the embryo survival, as the remaining cells are not yet committed to a particular path of development and can therefore compensate for the loss. Drug exposure during the embryonic period (week 2 to week 9) carries the greatest risk of fetal malformation as this is when organogenesis occurs. Nevertheless, maternal drug exposure at any period may be associated with longer-term, functional or developmental changes that are not immediately apparent. For example, in a cohort of 31 children born to mothers exposed to isotretinoin, nearly half had evidence of developmental delay, regardless of whether the children had structural malformations at birth [29]. Drugs given just before term or during labour can have adverse effects on labour or on the neonate (e.g. sedative antihistamines), whilst ongoing maternal drug use post-pregnancy may be secreted in breast milk. In men, the effects of drugs on spermatogenesis are increasingly recognized, with those that directly interact with DNA (e.g. methotrexate, azathioprine) linked to increased incidence of congenital abnormalities [30].

Thalidomide, acitretin and isotretinoin are notable examples of drugs with specific, known risks of teratogenicity, and all of these are used in dermatology with rigorous pregnancy prevention plans attached. For the majority of drugs, however, there is insufficient evidence to properly categorize the level of risk and since very few drugs can be considered completely safe, exposure should be minimized as far as possible. Topical therapy is generally safe since systemic, and therefore fetal, exposure, is minimal.

Drug disposition can alter significantly during pregnancy [31], with most of the changes beginning during the first trimester and peaking during the second trimester [28]. Overall these physiological changes tend to increase the volume of drug distribution, reduce the amount of albumin-bound drug, and increase hepatic and renal clearance, with consequent variable effects on drug concentration depending on the drug. The impact of pregnancy on the disease being treated is also variable with, for example, both improvement and deterioration documented in psoriasis [32] and atopic eczema [33].

Drug interactions

Drug effect may be significantly altered by co-administration of another drug with consequent impact on efficacy and/or induction of toxicity. The principal mechanisms underlying most drug interactions relate to drug-metabolizing enzymes and transporters. Whilst all major drug-metabolizing enzymes have been associated with drug–drug interactions, cytochrome P40 enzymes are the major contributors to clinically relevant drug interactions with CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A, CYP2C8 and CYP2B6 38 most commonly implicated [34]. For example, ciclosporin is extensively metabolized by CYP3A isoforms. Co-therapy with erythromycin or itraconazole, both potent inhibitors of CYP3A, can therefore lead to significantly increased levels of ciclosporin, whereas phenytoin, a potent inducer of CYP3A, may reduce ciclosporin levels. Alternative remedies are also relevant

here. St John's wort contains a potent inducer of CYP3A (hyperforin), for example, and has been reported in association with reduced levels of ciclosporin, whilst echinacea variously inhibits intestinal CYP1A2 and CYP3A and induces hepatic CYP3A activities [35].

Drug–transporter interactions arise either due to a change in activity (either increased or decreased) or competition at the transporter site. For example, the activity of the efflux transporter P-glycoprotein, which normally acts to reduce gastrointestinal absorption and increase biliary excretion of drugs, is inhibited by intraconazole and ciclosporin, with resultant increase in relevant drug substrate levels (e.g. fexofenadine) [36].

Aside from these pharmacokinetic mechanisms, drugs may interact at a pharmacodynamic level. This may be used to therapeutic advantage—prednisolone is often combined with azathioprine or mycophenolate mofetil in order to achieve the same level of immunosuppressant effect, whilst reducing the toxicity of steroid monotherapy, for example, but may equally give rise to adverse events such as the synergistic nephrotoxicity seen when ciclosporin is combined with NSAIDs.

Biological therapy is one of the most rapidly developing areas of therapeutics, although relatively little is known about mechanisms underlying their disposition, and by implication, drug–drug interactions. In contrast to (small) drugs, these large molecules are cleared primarily via the reticuloendothelial system and/or through antigen-specific pathways via phagocytosis, endocytosis and renal clearance. Relatively few clinically relevant drug interactions have been reported to date, but they do occur. For example, interferons have been shown to variously inhibit and induce specific CYP isoenzymes, and concomitant administration of weekly methotrexate significantly decreases the clearance of adalimumab, an interaction that is used to therapeutic advantage [37].

Pharmacogenetics

An individual's genetic makeup is critical in determining drug response. Genes encoding drug-metabolizing enzymes, transporters and drug targets may all be subject to functionally relevant polymorphisms and are estimated to account for 15–30% of inter-individual variation in drug response.

Pharmacogenetics (the study of the relationship between individual gene variation and drug effect) offers the potential to identify those at risk of adverse drug reactions and those likely to respond (or not) to a particular treatment *prior* to drug exposure. As is the case with genetic factors in general, phenotypic–genotypic associations are strongly influenced by ethnicity, and this is especially relevant when considering the clinical applications of pharmacogenetic testing.

Inter-individual variation in drug-metabolizing enzyme activity has historically been described in terms of phenotypic variants (e.g. fast and slow acetylators, slow and fast 'metabolizers') which are now known to originate from specific genetic variants (NAT2 and CYP2D6 polymorphisms, respectively in this example) and more than half the drugs cited in adverse drug reaction studies are metabolized by at least one enzyme with a variant allele known to be associated with poor metabolism [38]. The polymorphic enzyme thiopurine methyltransferase (TPMT) which catalyses a key step in azathioprine metabolism illustrates this concept well. Three common SNPs [39,40] associated with loss of enzyme function have been identified and linked to risk of bone marrow suppression due to excess accumulation of biologically active thioguanine nucleotides. Determination of thiopurine methyltransferase (TPMT) status (either by measuring enzyme activity directly, or less commonly, by genotyping) is now accepted best practice in dermatology and meets several of the criteria necessary for a pharmacogenetic test to be clinically valuable. First, it allows identification of a small subset of people in whom a drug is absolutely contraindicated due to the risk of developing a severe adverse reaction—one in 300 individuals are homozygous for loss of function TPMT gene variants and show complete absence of TPMT enzyme activity with consequent predictable, potentially fatal, bone marrow aplasia on exposure to azathioprine. Second, it identifies a further subset of patients who may benefit from a drug but who might, without prior dose adjustment, have had to discontinue it—10% of the population carry one loss of function TPMT gene variant and although at risk of bone marrow suppression with standard dosing, tolerate azathioprine if the dose is reduced. Thirdly, TPMT testing is widely available and results are easy to interpret [41]. It therefore provides additional, clinically relevant information which directly impacts on prescribing and ultimately patient outcome. Even so, since TPMT loss of function allelic variants account for less than 30% of all adverse reactions associated with azathioprine, additional mechanisms possibly involving other polymorphic drug-metabolizing enzymes, must operate [42].

Polymorphisms in genes encoding drug transporters also influence drug response. Methotrexate toxicity, for example, is associated with specific polymorphisms in SLC19A1 (a member of the solute carrier transporter superfamily) [43] which controls influx of methotrexate into cells, whilst variants in efflux transporters ABCC1 and ABCG2 (members of the second major drug transporter superfamily, ATP binding cassette transporters) predict methotrexate efficacy [44]. Variants in the ABCB1 gene (also known as the multidrug resistance 1 gene, *MDR-1*, since it was originally identified as a factor underlying anticancer-drug-resistant tumour cell lines) can influence the pharmacokinetics of many drugs, including calcineurin inhibitors (particularly tacrolimus) since it encodes P-glycoprotein, a transporter that limits intestinal absorption and facilitates biliary excretion of lipophilic drugs [45].

Much pharmacogenetic research has focused on genetic factors underlying differences in drug pharmacokinetics which has been largely driven by prior detailed knowledge about drug metabolic pathways. Genetic variation in drug targets also plays a major role in determining drug response. One example close to use in clinical practice, is Vitamin K epoxide reductase (VKORC1), the target for warfarin, where common SNPs are associated with a lower dose requirement and shorter time to optimal International Normalized Ratio (INR) [46]. Drug targets of specific relevance to dermatology practice where SNPs have been reported to influence treatment response include vitamin D receptors and response to topical vitamin D analogues [47], intracellular metabolic pathways of folic acid, purine and pyrimidine and metabolism and response to methotrexate [43,48].

Genes may also influence drug response through involvement in the underlying disease process. Certain HLA class I alleles appear to confer drug- (and ethnic-) specific risk of severe cutaneous reactions, possibly by functioning to present specific drug or drug metabolites for HLA restricted T-cell activation. HLA-B*5701 is strongly associated with hypersensitivity reactions to abacavir which ordinarily occur in up to 7% of patients treated. Avoidance of abacavir in (white) individuals who carry the HLA-B*5701 allele reduces the risk of hypersensitivity by 50% and pre-testing is now part of routine practice [49]. Presence of HLA–B*1502 in Han Chinese (but not in Europeans) is so tightly associated with carbamazepine-triggered Stevens–Johnson syndrome and toxic epidermal necrolysis that the estimated sensitivity and specificity of pre-testing in patients approaches 100% and 97%, respectively [50]. Isolated use of HLA markers is probably only useful for predicting risk where the association is especially strong, and this is not always the case. For example, whilst HLA-B*5801 is associated with allopurinol-induced Stevens–Johnson syndrome/toxic epidermal necrolysis it is only present in around half of the affected individuals [51].

The pharmacokinetic and pharmacodynamic profile of a particular drug reflects the sum of multiple processes, each of which is potentially subject to genetic variation. Significant duplication within biological systems also means that deletion of one metabolic pathway, for example, may not necessarily result in a significant reduction in overall metabolism of the drug. Thus establishing the clinical relevance of specific polymorphisms is not straightforward. Genome-wide association studies, using response or toxicity to a particular drug as the phenotype, may better determine the major predictors of drug response. Furthermore, this genetic complexity needs to be put into the context of known clinical variables in order to properly achieve 'personalized' medicine. Promising algorithms incorporating multiple pharmacogenetic markers with important clinical factors have been developed to facilitate this for warfarin anticoagulation and methotrexate use in rheumatoid arthritis, and appear to better predict drug response than standard clinical parameters alone [48,52].

References

1 Beijer HJ, de Blaey CJ. Hospitalisations caused by adverse drug reactions (ADR): a meta-analysis of observational studies. *Pharm World Sci* 2002; **24**: 46–54.

2 Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA* 1998; **279**: 1200–5.

3 Pirmohamed M, James S, Meakin S *et al*. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ* 2004; **329**: 15–9.

4 Leendertse AJ, Egberts ACG, Stoker LJ, van den Bemt PMLA, for the HARM Study Group. Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. *Arch Intern Med* 2008; **168**: 1890–6.

5 Department of Health. *Pharmacy in England, Building on Strengths—Delivering the Future.* Department of Health, 2008.

6 National Collaborating Centre for Primary Care RCoGP. *Medicines Adherence: Involving Patients in Decisions about Prescribed Medicines and Supporting Adherence*, 2009. http://guidance.nice.org.uk/CG76/NiceGuidance/pdf/English.

7 Haynes RB, Ackloo E, Sahota N *et al*. Interventions for enhancing medication adherence. *Cochrane Database of Systematic Reviews*: 2008, Issue 2.

8 Clinical Standards Unit British Association of Dermatologists. *Preferred Unlicensed Dermatological Preparations (Specials)*, 2008.

9 Smith J. *Building a Safer NHS for Patients: Improving Medication Safety*. A report by the Chief Pharmaceutical Officer. Department of Health, 2004.

10 Thomsen LA, Winterstein AG, Sondergaard B *et al*. Systematic review of the incidence and characteristics of preventable adverse drug events in ambulatory care. *Ann Pharmacother* 2007; **41**: 1411–26.

11 Gurwitz JH, Field TS, Harrold LR *et al*. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. *JAMA* 2003; **289**: 1107–16.

12 Dean B, Schachter M, Vincent C, Barber N. Causes of prescribing errors in hospital inpatients: a prospective study. *Lancet* 2002; **359**: 1373–8.

13 Ghaleb MA, Barber N, Franklin BD *et al*. Systematic review of medication errors in pediatric patients. *Ann Pharmacoth* 2006; **40**: 1766–76.

14 Tam VC, Knowles SR, Cornish PL *et al*. Frequency, type and clinical importance of medication history errors at admission to hospital: a systematic review. *Can Med Assoc* 2005; **173**: 510–5.

15 van Doormaal JE, van den Bemt PMLA, Mol PGM *et al*. Medication errors: the impact of prescribing and transcribing errors on preventable harm in hospitalised patients. *Qual Saf Health Care* 2009; **18**: 22–7.

16 Fahrenkopf AM, Sectish TC, Barger LK *et al*. Rates of medication errors among depressed and burnt out residents: prospective cohort study. *BMJ* 2008; **336**: 488–91.

17 Wong ICK, Wong LYL, Cranswick NE. Minimising medication errors in children. *Arch Dis Child* 2009; **94**: 161–4.

18 Conroy S, Sweis D, Planner C *et al*. Interventions to reduce dosing errors in children: a systematic review of the literature. *Drug Safety* 2007; **30**: 1111–25.

19 National Patient Safety Agency. *Patient Safety Alert. Improving Compliance With Oral Methotrexate Guidelines*, 2006.

20 Ammenwerth E, Schnell-Inderst P, Machan C, Siebert U. The effect of electronic prescribing on medication errors and adverse drug events: a systematic review. *J Am Med Inform Assoc* 2008; **15**: 585–600.

21 Buxton ILO. Pharmacokinetics and pharmacodynamics. The dynamics of drug absorption, distribution, action and elimination. In: Brunton LL, Lazo JS, Parker KL, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th edn. McGraw-Hill Medical Publishing Division, 2006: 1–40.

22 Prausnitz MR, Langer R. Transdermal drug delivery. *Nature Biotech* 2008; **26**: 1261–8.

23 Patton JS, Byron PR. Inhaling medicines: delivering drugs to the body through the lungs. *Nature Rev Drug Discovery* 2007; **6**: 67–74.

24 McMahon GT, Arky RA. Inhaled insulin for diabetes mellitus. *N Engl J Med* 2007; **356**: 497–502.

25 Kearns GL, Abdel-Rahman SM, Alander SW *et al*. Developmental pharmacology—drug disposition, action, and therapy in infants and children. *N Engl J Med* 2003; **349**: 1157–67.

26 McLean AJ, Le Couteur DG. Aging biology and geriatric clinical pharmacology. *Pharmacol Rev* 2004; **56**: 163–84.

27 Zhang M, Holman CD, Price SD *et al*. Comorbidity and repeat admission to hospital for adverse drug reactions in older adults: retrospective cohort study. *BMJ* 2009; **338**: a2436.

28 Cragan JD, Friedman JM, Holmes LB *et al*. Ensuring the safe and effective use of medications during pregnancy: planning and prevention through preconception care. *Mat Child Health* 2006; **10** (Suppl. 7): 129–35.

29 Adams J, Lammer EJ. Neurobehavioural teratology of isotretinoin. *Repro Toxicol* 1993; **7**: 175–7.

30 Nørgård B, Pedersen L, Jacobsen J *et al*. The risk of congenital abnormalities in children fathered by men treated with azathioprine or mercaptopurine before conception. *Aliment Pharmacol Ther* 2004; **19**: 679–85.

31 Hodge LS, Tracy TS. Alterations in drug disposition during pregnancy: implications for drug therapy. *Exp Op Drug Metab Toxicol* 2007; **3**: 557–71.

32 Weatherhead S, Robson SC, Reynolds NJ. Management of psoriasis in pregnancy. *BMJ* 2007; **334**: 1218–20.

33 Weatherhead S, Robson SC, Reynolds NJ. Eczema in pregnancy. *BMJ* 2007; **335**: 152–4.

34 Huang SM, Strong JM, Zhang L *et al*. New era in drug interaction evaluation: US food and drug administration update on CYP enzymes, transporters, and the guidance process. *J Clin Pharmacol* 2008; **48**: 662–70.

35 Gorski JC, Huang S-M, Zaheer N. The effect of echinacea (*Echinacea purpurea* rost) on CYP3A activity *in vivo*. *Clin Pharmacol Ther* 2004; **75**: 89–100.

36 Tomonori T, Masatomo M, Toshio S, Tsukasa U. The different effects of itraconazole on the pharmacokinetics of fexofenadine enantiomers. *Br J Clin Pharmacol* 2008; **65**: 693–700.
37 Mahmood I, Green MD. Drug interaction studies of therapeutic proteins or monoclonal antibodies. *J Clin Pharmacol* 2007; **47**: 1540–54.
38 Phillips KA, Veenstra DL *et al*. Potential role of pharmacogenomics in reducing adverse drug reactions: a systematic review. *JAMA* 2001; **286**: 2270–9.
39 Tai HL, Krynetski EY, Yates CR *et al*. Thiopurine S-methyltransferase deficiency: two nucleotide transitions define the most prevalent mutant allele associated with loss of catalytic activity in Caucasians. *Am J Hu Genet* 1996; **58**: 694–702.
40 Yates CR, Krynetski EY, Loennechen T *et al*. Molecular diagnosis of thiopurine S-methyltransferase deficiency: genetic basis for azathioprine and mercaptopurine intolerance. *Ann Intern Med* 1997; **126**: 608–14.
41 Fargher EA, Tricker K, Newman W *et al*. Current use of pharmacogenetic testing: a national survey of thiopurine methyltransferase testing prior to azathioprine prescription. *J Clin Pharm Ther* 2007; **32**: 187–95.
42 Smith M, Marinaki A, Arenas M *et al*. Novel pharmacogenetic markers for treatment outcome in azathioprine-treated inflammatory bowel disease. *Alimen Pharmacol Therap* 2009; **30**: 375–84.
43 Campalani E, Arenas M, Marinaki AM *et al*. Polymorphisms in folate, pyrimidine, and purine metabolism are associated with efficacy and toxicity of methotrexate in psoriasis. *J Invest Dermatol* 2007; **127**: 1860–7.
44 Warren RB, Smith RL, Campalani E *et al*. Genetic variation in efflux transporters influences outcome to methotrexate therapy in patients with psoriasis. *J Invest Dermatol* 2008; **128**: 1925–9.
45 Hesselink DA, van Schaik RH, van der Heiden IP *et al*. Genetic polymorphisms of the CYP3A4, CYP3A5, and MDR-1 genes and pharmacokinetics of the calcineurin inhibitors cyclosporine and tacrolimus. *Clin Pharmacol Ther* 2003; **74**: 245–54.
46 Wadelius M, Chen LY, Lindh JD *et al*. The largest prospective warfarin-treated cohort supports genetic forecasting. *Blood* 2009; **113**: 784–92.
47 Halsall JA, Osborne JE, Pringle JH, Hutchinson PE. Vitamin D receptor gene polymorphisms, particularly the novel A-1012G promoter polymorphism, are associated with vitamin D3 responsiveness and non-familial susceptibility in psoriasis. *Pharmacogenet Genom* 2005; **15**: 349–55.
48 Judith A-MW, Sjoerd MM-K, Saskia LC *et al*. A clinical pharmacogenetic model to predict the efficacy of methotrexate monotherapy in recent-onset rheumatoid arthritis. *Arth Rheum* 2007; **56**: 1765–75.
49 Mallal S, Phillips E, Carosi G *et al*. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med* 2008; **358**: 568–79.
50 Chung WH, Hung SI, Hong HS *et al*. Medical genetics: a marker for Stevens-Johnson syndrome. *Nature* 2004; **428**: 486.
51 Lonou C, Borot N, Sekula P *et al*. A European study of HLA-B in Stevens-Johnson syndrome and toxic epidermal necrolysis related to five high-risk drugs. *Pharmacogene Genom* 2008; **18**: 99–107.
52 The International Warfarin Pharmacogenetics Consortium. Estimation of the warfarin dose with clinical and pharmacogenetic data. *N Engl J Med* 2009; **360**: 753–64.

Cosmetic camouflage

Cosmetic camouflage is very useful in the management of a wide range of dermatological problems ranging from scarring to vitiligo, and vascular anomalies such as port-wine stains. In the UK, the Red Cross offers a voluntary service and in some hospitals the occupational therapists and/or dermatology nurses are trained to do this work. Cosmetic camouflage has been shown to improve quality of life [1]. Cosmetic tattoos may sometimes be useful in vitiligo, reconstructive surgery and to mask scars [2].

References

1 Holme SA, Beattie PE, Fleming CJ. Cosmetic camouflage advice improves quality of life. *Br J Dermatol* 2002; **147**: 946–9.
2 DeCuyper C. Permanent makeup: indications and complications. *Clin Dermatol* 2008; **26**: 30–4.

The role of complementary and alternative therapy in the context of a general consultation

The term alternative medicine was originally introduced to refer to whole medical systems where the causes of disease, methods of diagnosis and approaches to treatment are completely different to conventional medicine. Complementary medicine (or therapies) on the other hand, refers to those methods that can be used alongside or to 'complement' conventional medicine. The distinction between alternative and complementary therapy is not absolute however, and these terms are often used interchangeably, and increasingly together, that is 'complementary and alternative medicine' (CAM). A brief outline of the commonly used approaches with information on additional resources is listed in Table 72.8.

What actually constitutes CAM, and what constitutes conventional medicine, will depend on the setting (for example, traditional Chinese medicine is part of conventional medicine in China, and yet part of CAM in the UK) and it may also change with time. Some CAM for specific indications may move into mainstream medicine; NICE has recently recommended acupuncture or spinal manipulation (osteopathy and chiropractic treatments) as first-line interventions in the early management of non-specific low back pain, for example. CAM is widely used by the general population, with prevalence figures varying from 20% in the UK [1] to around 50% in the USA [2]. These treatments are also available in the context of mainstream medicine with, for example, around half of general practitioners in the UK providing access to some CAM therapies [3] and two-thirds of Scottish general practitioners prescribing herbal or homeopathic medicines [4].

As is the case for any therapeutic intervention, benefit should outweigh the risk of potential harm. That robust evidence to indicate this is the case for CAM as applied to the spectrum of diseases in which it is used remains a contentious issue. CAM encompasses a very diverse array of different types of intervention from physical treatments involving various types of massage and manipulation through to potent herbal remedies with significant, established toxicity [5], and many of these are well-established and popular among patients. Ascertaining evidence for efficacy may be challenging in this situation, even for interventions such as herbal remedies which lend themselves to conventional methods of efficacy assessment. It is also worth noting that adverse reactions to CAM are probably under-reported [6] and so absence of known adverse effects (as is the case with conventional drugs) does not exclude the possibility of harm. 'Harm' might also include the enormous financial resource expended by health care systems collectively, and by patients individually, on treatments where benefit is not properly established. Relatively few interventions have been subject to rigorous RCT evaluation [7,8]. What published evidence there is may be difficult to access and/or interpret due to publication bias (such that negative findings on CAM are more likely to be found in mainstream journals and positive findings to be found in CAM), incomplete listing of CAM journals on mainstream databases and qualitative differences in trial design and outcome measures in CAM (reviewed in [6]).

Nevertheless, around 50% of patients seen in a dermatology outpatient setting have tried, or are using CAM specifically for

Table 72.8 Commonly available and widely used forms of complementary and alternative medicine are listed together with a brief overview of the intervention and underlying philosophy.

Therapy	Definition	Additional points
Aromatherapy	Use (by inhalation, massage and/or bathing) of essential oils extracted from flowers, leaves, twigs, bark, roots and fruits to promote and enhance the health and well-being of an individual.	The International Federation of Professional Aromatherapists maintains a register of practising members: http://www.ifparoma.org
Acupuncture	Insertion of a fine, solid needle(s) into the skin at particular points on the body, for disease prevention, therapy or maintenance of health. Based on the traditional Chinese philosophy that health is dependent on the body's motivating energy (chi or Qi) moving through a series of meridians (channels) beneath the skin. Disturbance of this flow as a consequence of physical, mental and emotional factors can be restored by inserting needles into the skin.	The British Acupuncture Council is the UK's main regulatory body for the practice of traditional acupuncture: http://www.acupuncture.org.uk/
Chiropractic	Diagnosis, treatment and prevention of mechanical disorders of the musculoskeletal system, and the effects of these disorders on the functions of the nervous system and general health. There is an emphasis on manual treatments including spinal adjustment and other joint and soft tissue manipulation.	Statutory regulation through the General Chiropractic Council (GCC): http://www.gcc-uk.org/page.cfm British Chiropractic Association: http://www.chiropractic-uk.co.uk/
Traditional Chinese herbal medicine	Chinese herbal medicines are taken, or made, from natural plants, with one or several herbs being used as the basic drug for treatment of a disease, with additional herbs used to treat various symptoms. These are combined to form a prescription, in order to boost or disperse energy (Qi).	Within Europe, registration of herbal medicines mandates adverse event reporting, but not rigorous demonstration of clinical efficacy [13]. The EMEA Committee on Herbal Medicinal Products (HMPC) approves monographs containing information on indications, restrictions on its use, drug interactions and side effects and provides a regulatory framework for licensed approval of herbal medicines.
Herbalism	Use of plant remedies native to Britain, Europe and North America with choice of herb being determined by understanding of the significance of the signs and symptoms in the individual.	
Homeopathy	Oral use of typically herbal or mineral solutions in very low concentrations ('microdose'). Successive dilution following by vigorous shaking (succession) of the Mother Tincture is used to increase the effectiveness of preparations (a process known as potentization). Homeopathy is based on the principle that 'like cures like' so that administering a substance that provokes a symptom in a healthy person, can be used to treat the same symptom in a patient with the disease (Greek derivation *homois*, similar and *pathos*, suffering).	Potential risk associated with confusion with herbal remedies.
Osteopathy	Osteopathy is a system of diagnosis and treatment using touch, manipulation, stretching and massage, with a focus on musculoskeletal problems (though a few schools claim benefits across a wider spectrum of disorders).	The General Osteopathic Council regulates the practice of osteopathy in the United Kingdom. By law osteopaths must be registered with the General Osteopathic Council in order to practise in the UK: http://www.osteopathy.org.uk

Further information is available through NHS Evidence—Complementary and Alternative Medicine [14]. The Cochrane collaboration have established the Complementary Medicine Field to facilitate the systematic review of existing randomized controlled trials (RCTs) [15] and inform areas for future research.

their skin problem, and by far the most common of these, is herbal remedies. The following broad themes are useful to consider in the context of a general consultation

Why is the patient using CAM?

CAM use in general, and also in dermatology specifically, tends to be more common in women, those under 65 years of age, and in people on higher incomes and/or professional backgrounds [9]. Most patients use CAM in the context of conventional medicine, and do so in order to optimize conventional treatments, or through dissatisfaction with standard treatments.

Evidence suggests that individuals who access CAM are more likely than non-users to prefer an active or collaborative role in treatment decisions, to believe that psychological factors have a role in the origin of the illness and in the promotion of health and to place value on an holistic approach to their management with focus on treatment of the individual rather than symptoms [10]. Most practitioners of conventional medicine would argue that these are important factors in any medical consultation, irrespective of the setting. Users also tend to perceive natural or unconventional treatments as safe and to be concerned about toxicity associated with conventional medicines [10]. Insight into why a particular patient is using or has used CAM can be enormously valuable and may reveal beliefs and perceptions about their skin disease and treatment that are highly pertinent to the overall management.

What CAM is the patient using and is there any potential for harm?

Most patients will not voluntarily declare that they are taking or using CAM, so it is crucial to make specific enquiry in a non-judgemental, open way, including use for both dermatological and other indications as both may be relevant.

Herbal remedies are by far the most commonly used CAM by dermatology patients [9,11], and some of these are already known to be associated with toxicity [5] and important interactions with pharmaceutical drugs [12]. There is sometimes confusion over terminology between herbal treatments, which are possibly hazardous, and homeopathy, which is generally safe. Contamination of preparations by additional, undeclared, products is an additional hazard. In Europe, traditional herbal remedies sit under EMEA regulation, and manufacturers are required to comply with certain standards of production and labelling. Products sourced from the Internet or locally mixed herbal remedies will not necessarily be subject to scrutiny. Herbal products are, by their very nature, subject to variation in potency and availability and prescribed treatments are often mixed or changed during a course of treatment. Collectively, these factors therefore often make it difficult to assess any potential risk of herbal therapy in the context of conventional pharmaceutical agents.

A further potential source of harm arises due to the involvement of more than one health care professional managing a disease. This is an established risk even within the mainstream health care system where the principles underlying the diagnosis and management of disease follow the same construct, so there is added complexity in CAM where this is not the case, and patients are accessing care from CAM professionals in parallel with mainstream medicine. It is therefore important to be at least familiar with the various types of CAM and possible toxicities. Depending on the type of CAM being used by the patient, communication with the patient's CAM professional may also be helpful.

References

1 Ernst E, White A. The BBC survey of complementary medicine use in the UK. *Complement Thera Med* 2000; **8**: 32–6.

2 Eisenberg DM, Davis RB, Ettner SL *et al*. Trends in alternative medicine use in the United States, 1990–1997: results of a follow-up national survey. *JAMA* 1998; **280**: 1569–75.

3 Thomas KJ, Coleman P, Nicholl JP. Trends in access to complementary or alternative medicines via primary care in England: 1995–2001. Results from a follow-up national survey. *Fam Pract* 2003; **20**: 575–7.

4 Sarah R, Colin RS, James SM. Homeopathic and herbal prescribing in general practice in Scotland. *Br J Clin Pharmacol* 2006; **62**: 647–52.

5 Nortier JL, Vanherweghem JL. For patients taking herbal therapy—lessons from aristolochic acid nephropathy. *Nephrol Dial Transplant* 2007; **22**: 1512–7.

6 Shekelle PG, Morton SC, Suttorp MJ *et al*. Challenges in systematic reviews of complementary and alternative medicine topics. *Ann Intern Med* 2005; **142**: 1042–7.

7 Ernst E, Pittler MH, Stevinson C. Complementary/alternative medicine in dermatology: evidence-assessed efficacy of two diseases and two treatments. *Am J Clin Dermatol* 2002; **3**: 341–8.

8 Zhang W, Leonard T, Bath-Hextall FJ *et al*. Chinese herbal medicine for atopic eczema. *Cochrane Database of Systematic Reviews*: Issue 4, 2004.

9 Smith N, Shin DB, Brauer JA *et al*. Use of complementary and alternative medicine among adults with skin disease: results from a national survey. *J Am Acad Dermatol* 2009; **60**: 419–25.

10 Bishop FL, Yardley L, Lewith GT. A systematic review of beliefs involved in the use of complementary and alternative medicine. *J Health Psychol* 2007; **12**: 851–67.

11 Barton SE, Goodwin RG, Nicolau N *et al*. Use of complementary medicine among outpatients with dermatologic conditions within Yorkshire and South Wales, United Kingdom. *J Am Acad Dermatol* 2005; **52**: 589–94.

12 Fugh-Berman A. Herb–drug interactions. *Lancet* 2000; **355**: 134–8.

13 De Smet PAGM. Herbal medicine in Europe—relaxing regulatory standards. *N Engl J Med* 2005; **352**: 1176–8.

14 *NHS Evidence—Complementary and Alternative Medicine*, 2009. http://www.library.nhs.uk/cam/

15 Manheimer E, Berman B. *Cochrane Complementary Medicine Field*. Cochrane Library. http://www.compmed.umm.edu/cochrane.asp

Patient self-help groups

The formation of patient self-help groups in dermatology has been stimulated by several factors. First, the quality of care and information provided to patients with skin diseases may not always have been optimal. Patients with common skin diseases may not always have access to experts in dermatology and patients with rare skin diseases may find that the knowledge of their professional carers is limited. Some patients wish to have the opportunity to meet, learn from and discuss mutual problems with others who have experienced first hand the same disease. Although the dermatologist tends to focus on the patient with skin disease, the patient's partner or close family, the 'greater patient' [1], are also affected by and concerned about the disease and may get benefit from patient self-help groups. This has been illustrated by the large number of parents of children with atopic dermatitis who gain benefit from atopic dermatitis groups [2]. Some people with skin disease develop sufficient insight into their disease and the limitations of its current management that they wish to help the advance of understanding of the disease by raising funds for research. By grouping together, patients may be able to advocate changes in the approach of health care systems to the care of their disease. The Internet has provided a massive stimulus to the effectiveness and outreach of patient self-help groups.

Dermatologists have recognized for over 20 years that patient self-help groups in dermatology may play a very helpful role in improving patient care [3]. Dermatologists are now encouraged to support and seek the help of patient self-help groups, especially to assist in education and support of patients [4].

A large number of dermatology patient self-help groups have now arisen in many countries. Links are given to over 46 dermatology patient self-help groups in the UK on the British Association of Dermatologists' website [5] and there are many more in the USA—a list is maintained by the University of Iowa [6]. In Germany, the existence of over 2000 self-help groups concerned with skin problems has been reported [7]. As the quality of the help provided by this wide range of groupings varied considerably, dermatologists were encouraged to make an effort to become well informed about the groups in their region.

There has been positive experience from the involvement of dermatology staff with self-help groups. When staff and patients jointly set up a support group to facilitate the development of positive coping strategies this contributed positively to the psychological well-being of individuals [8]. In the management of alopecia areata patient support groups are an important resource that should not be overlooked [9].

Despite ready availability of information, many patients are not aware of self-help groups concerning their disease. Dermatologists should be encouraged to make this information available to patients, by mentioning their existence to patients during consultations and by providing phone numbers and

website information. In the UK, the British Association of Dermatologists distributes to every dermatologist posters with information about the UK self-help groups for display in dermatology clinic waiting areas [5].

References

1 Basra MKA, Finlay AY. The family impact of skin disease: the Greater Patient concept. *Br J Dermatol* 2007; **156**: 929–37.

2 Goh C, Lane AT, Bruckner AL. Support groups for children and their families in pediatric dermatology. *Pediatr Dermatol* 2007; **24**: 302–5.

3 Logan RA. Self help groups for patients with chronic skin diseases. *Br J Dermatol* 1988; **118**: 505–8.

4 Rolstad T, Zimmerman G. Patient advocacy groups. A key prescription for dermatology. *Dermatol Clin* 2000; **18**: 277–85.

5 British Association of Dermatologists. www.bad.org.

6 University of Iowa College of Medicine, Department of Dermatology. *Dermatology Patient Support Groups*. http://tray.dermatology.uiowa.edu/SuprtGrps.html, accessed 5 June 2008.

7 Karches F, Kolmel KF. Self-help groups in dermatology. *Hautarzt* 1994; **45**: 4–7.

8 Burr S, Gradwell C. The psychological effects of skin diseases: need for support groups. *Br J Nurs* 1996; **5**: 1177–82.

9 Prickitt J, McMichael AJ, Gallagher L *et al*. Helping patients with chronic alopecia areata. *Dermatol Nurs* 2004; **16**: 237–41

Declaration of interest

The author (AYF) is joint copyright holder of the following questionnaires described above: ADI, CADI, CDLQI, DFI, DLQI, FDLQI, FPI, IDQOL and PDI.

CHAPTER 73
Topical Therapy

J. Berth-Jones
Department of Dermatology, University Hospitals Coventry and Warwickshire, Coventry, UK

Prescribing topical treatment, 73.1
Drug concentration, 73.1
Choice of vehicle, 73.2
Frequency of application, 73.3
Quantity to be applied, 73.3
Advice to patients, 73.4
Hazards associated with topical treatment, 73.4
Formulation of topical treatment, 73.5
Lipids, 73.5
Polyethylene glycols, 73.7
Emulsifiers, 73.7
Humectants, 73.7
Penetration enhancers, 73.7
Powders, 73.8
Preservatives, 73.8
Topical treatments used in the management of skin disease, 73.9
Antiperspirants, 73.9
Antibiotics, 73.9
Antifungal agents, 73.12
Antihistamines, 73.13
Antiparasitic agents, 73.13
Antiseptics, 73.14
Antiviral agents, 73.15
Astringents, 73.15
Corticosteroids, 73.16
Cytotoxic and antineoplastic agents, 73.23
Depigmenting agents, 73.26
Depilatories, 73.29
Dithranol, 73.29
Emollients, 73.31
Immunomodulators, 73.31
Retinoids, 73.34
Sensitizing agents, 73.39
Sunscreens, 73.40
Tars, 73.41
Vitamin D analogues (deltanoids, secosteroids), 73.43
Traditional remedies, 73.48
Miscellaneous agents, 73.49

Dermatologists have the good fortune to work on the most accessible organ of the body. This gives us numerous advantages and greatly facilitates not only the diagnosis but also the treatment of skin disease. Whilst systemic administration of drugs is often necessary in dermatology, many inflammatory and neoplastic conditions can be effectively managed using the wide range of locally applied physical or pharmacological modalities that are available. The latter are the subject of this chapter which reviews the pharmacological treatments used topically, that is by application to the surface of the skin. Some of these are time-honoured treatments which have been used for a century or more, whilst others belong to the ever expanding range of newer and increasingly potent agents constantly being developed and formulated for topical use.

Topical treatment offers the potential to achieve high concentrations of a drug in the skin with minimal exposure of other organs. This can greatly increase efficacy and also safety relative to systemic administration. When side effects do occur, they are most likely to take the form of localized reactions.

Prescribing topical treatment

Prescribing topical medication requires careful consideration of several factors if optimal results are to be achieved. When the treatment contains an active pharmaceutical agent it is necessary to specify the concentration of the drug, the vehicle and the frequency of application. The patient requires advice on the quantity to be used, precisely where it should be applied and often further explanation about precise timing of application in relation to bathing and other treatments. The prescriber needs to be aware of the hazards associated with a topical treatment, particularly the likelihood of the medication inducing irritant or allergic reactions. It is also important to understand the factors that influence systemic absorption.

Drug concentration

Conventions for defining the concentration of a drug in topical formulations can be summarized as follows:

- The concentration of a drug contained in a topical medication is usually written as a percentage representing the proportion of the formulation, by weight, which is the active constituent. A concentration of 1% indicates that 1 g of drug will be contained in 100 g of the formulation. A wide range of concentrations can be specified in this way. Thus salicylic acid may be used in concentration as high as 60% for treatment of plantar warts or corns, whereas calcitriol is used at a concentration of 0.0003% in treatment of psoriasis. A very low concentration such as this is more often written as 3 μg/g.
- A frequently used alternative, especially for liquid preparations, is to express the percentage of the drug as a proportion of the volume of the formulation, thus a 1% solution contains 1 g of drug in 100 ml of the formulation. The abbreviations w/w (weight in weight) and w/v (weight in volume) are often employed to indicate which convention is being used.
- Another convention often used to describe the concentration of a solution is in 'parts'; thus a 1 part in 1000 solution of

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

potassium permanganate contains 1 g in 1 L of solution, which could be expressed as 0.1% (w/v).

The efficacy of a topically applied drug is usually not proportionate to the concentration. Doubling or halving the concentration of a drug often has a surprisingly modest effect on the response. In the case of topical corticosteroids, for example, different concentrations of active drug often have a similar biological effect [1]. However, the effect of changing the concentration in an individual case may be much greater than the apparent effect when two concentrations are compared in a clinical trial. There may also be differences between adults and children. As discussed below, the difference in efficacy between two concentrations of tacrolimus appears to be larger in adults than in children.

Choice of vehicle

Topical medication must be applied to the skin in a suitable vehicle. This term encompasses all the constituents of the formulation apart from the active pharmaceutical agent. The properties of some types of vehicle are summarized as follows:

Ointments are semi-solid vehicles composed of lipid, for example White Soft Paraffin British Pharmacopoeia (BP) (Petrolatum). They have useful occlusive and emollient properties. Some ointments contain emulsifying agents such as polyhydric alcohols (macrogols, polyethylene glycol), or cetostearyl alcohol (e.g. emulsifying ointment BP). The latter have the advantage of being less greasy, with good solvent properties, and are easily washed off. Ointments require fewer preservatives than other vehicles since they contain no water and do not sustain growth of microorganisms.

Creams are semi-solid emulsions containing both lipid and water. Emulsions are suspensions, either of lipid droplets in water or water droplets in lipid (see emulsifiers). In the former category are aqueous or vanishing creams, for example Aqueous Cream BP. These are water-miscible, cooling and soothing, and are well absorbed into the skin. In the latter category are water-in-oil (W/O) creams, for example Oily Cream BP. These are immiscible with water and more difficult to wash off. They are emollient, lubricant and mildly occlusive (but less so than ointments).

Pastes are semi-solid preparations containing a high proportion of finely powdered material such as zinc oxide or starch. Protective (fatty) pastes are greasy and therefore messy and water insoluble. They are difficult to apply and remove, but their stiffness permits accurate localization of the paste and any constituent medication. They are occlusive, protective and hydrating. The consistency of these pastes can be 'softened' by adding oils or 'hardened' with hard paraffin. Drying pastes, also called cooling pastes, are mixtures of powder with liquid. These are non-greasy, water-miscible and easy to apply and remove. They are drying and soothing, and can be used in conjunction with dressings as paste bandages or as vehicles for active medicaments.

Lotions are liquid formulations which are usually simple suspensions or solutions of medication in water, alcohol or other liquids. Those containing alcohol often sting, especially when applied to broken skin. When left on the skin the liquid will evaporate leaving a film of medication on the surface. Aqueous suspensions of powders such as calamine which require shaking prior to each application are known as **shake lotions**.

Gels might be regarded as thickened lotions. They are semi-solid preparations containing high-molecular-weight polymers, such as carboxypolymethylene (Carbomer BP) or methylcellulose. Lotions and gels are especially suitable for treating the scalp and other hairy areas of skin. Like lotions, gels tend to dry when left on the skin. Gels can provide cosmetically acceptable formulations for use on the face.

Powders applied directly to the skin are also known as **dusting powders**. They can reduce friction (talc) or excessive moisture (starch). They are occasionally used to deliver drugs such as antifungal agents applied to the feet.

Paints are liquid preparations, either aqueous, hydroalcoholic or alcoholic (**tinctures**), which are usually applied with a brush to the skin or mucous membranes and then evaporate. Collodion preparations are also sometimes referred to as paints.

Collodions, for example Flexible Collodion BP, are liquid preparations consisting of cellulose nitrate in organic solvent. They evaporate rapidly to leave a flexible film which can hold medicaments in contact with the skin. They are most frequently used to apply salicylic and lactic acids to warts. They may also be used as protectives to seal minor cuts and abrasions. They are easy to apply and water repellent, but inflammable.

Microsponges [2] are a novel approach to formulation involving the use of porous beads, typically 10–25 μm in diameter, forming a reservoir loaded with the drug. This approach has been used for cosmetics and sunscreens as well as medications such as benzoyl peroxide and retinoids. The aim is to provide sustained release of the drug whilst reducing irritation.

Liposomes are structures comprising an aqueous phase surrounded by a lipid capsule, ranging widely in diameter from several nanometers to several microns. They may contain several lipid layers so that the structure can be likened to that of an onion. Under certain conditions liposomes can release their contents close to a target cell, fuse with the cell membrane, or be endocytosed by the cell [3]. They can be formulated into creams and gels. This technology is used in cosmetics but has so far had little impact on dermatological treatment. However, it may prove useful for reducing irritation from topical use of agents such as tretinoin, benzoyl peroxide and dithranol and reducing the staining of skin and clothes from the latter [3–5]. Liposomes do not appear to penetrate intact into the intracellular compartment of the epidermis although an *in vitro* study using reconstructed human skin has suggested that liposomal lipids can be incorporated into the intercellular lipids of the stratum corneum and cell membranes in the uppermost viable layers of the epidermis [6].

The choice of vehicle depends on the anatomical site to be treated and the condition of the skin. As a rule, acutely inflamed skin is best treated with fairly bland preparations which are least likely to irritate. Moist or exudative eruptions are conventionally treated with 'wet' medications such as lotions or creams, whilst dry skin responds well to the occlusive action of ointments. Hair-bearing skin, especially the scalp, can be treated with medicaments formulated into shampoos, lotions, gels or mousse. The cosmetic properties of the vehicle assume particular importance

when treating the face. Oily skin affected by acne is often best treated with lotions, whilst the more sensitive skin affected by rosacea may benefit from the emollient effect of a cream.

The formulation of vehicles is discussed further below.

Frequency of application

The frequency of application must be specified in order to maximize the response whilst avoiding side effects such as irritation. Excessive frequency of application may also result in unnecessary systemic exposure to the drug. Emollients should be applied frequently enough to maintain their physical effect. This may require several applications daily. Active preparations are usually applied just once or twice a day. As a general rule, twice daily application of drugs such as corticosteroids or deltanoids is only marginally more effective than once daily application, whilst requiring double the amount of medication and increasing systemic exposure to the drug. The pharmacological actions of a drug may persist long after it has left the surface of the skin. Thus the ability of a potent topical corticosteroid to inhibit flares of atopic dermatitis when applied just twice weekly [7] seems unlikely to be explained simply by persistence of a reservoir of the drug. Increasing the interval between applications can be a useful method of gradually reducing the intensity of a treatment, especially when it is difficult to do so by using a lower concentration or less potent agent.

Quantity to be applied

The total quantity to be dispensed should be specified and it is helpful to inform the patient how long the prescribed quantity is expected to last. There is a tendency, especially in the case of topical steroids, for patients to be overcautious in their interpretation of the advice to 'apply sparingly' which will be found on the package insert. Minute quantities are rarely effective. Conversely, inappropriate use of active medicaments as emollients is not only wasteful but often hazardous. The potential for systemic absorption must be taken into account when prescribing, for example, topical corticosteroids, deltanoids or salicylic acid.

Estimates of the quantity of cream or ointment required for a single total body treatment of a male adult have varied considerably. In one study a range of 12–27 g (average 18 g) was required for applications by 'trained operators' [8], whilst a range of 8–115 g (average 44 g) was required when the treatment was self-administered. In another study, in which treatment was applied by nurses, an average of 12 g of ointment was required [9]. In a more recent study, male patients treating themselves applied an average of 20 g of ointment, and females applied 17 g [10].

Based on these latter figures, the quantity required for 1 week of once-daily application to the whole body would be approximately 140 g for males and 120 g for females, whilst for twice-daily application, male and female patients require 280 and 240 g per week, respectively.

Table 73.1 provides approximate quantities required for single applications to specific anatomical regions. Table 73.2 provides a guide to total quantities required for a week of twice-daily total body treatment for children of various ages. All these guidelines can only be approximate and should be interpreted very flexibly. In addition to the obvious large differences between individuals of any age in body surface area, the condition of the skin may influence how far the medication will spread. Creams and ointments seem to cover a very similar area per unit of weight [8,9].

Simple practical guides to the quantity of a topical medication to apply are provided by the fingertip unit and the rule of hand.

Fingertip unit. An approximate but practical measure of topical medication is the fingertip unit [10]. This is the quantity of ointment, extruded from a tube with a nozzle of 5 mm diameter (note that nozzles do vary somewhat), extending from the distal crease of the forefinger to ventral aspect of the fingertip (Fig. 73.1). This unit weighs approximately 0.49 g in males and 0.43 g in females [11] and covers, on average, an area of approx 300 cm^2. The number of units required for a single treatment of each anatomical region in adults and children of various ages is given in Table 73.3.

Rule of hand. The 'rule of hand' states that an area of the size that can be covered by four adult hands (including the digits) can be treated by 1 g of ointment or two fingertip units [12].

The figures discussed above are all based on application of active medicaments. Emollients are applied for their physical properties rather than for delivery of a drug, and are generally used much more liberally. Emollient treatment of the whole body may require 100 g daily when the skin is very dry.

Table 73.1 Approximate quantities (g) required for each application of medication to different anatomical regions (adapted from [10]).

Anatomical region	Males	Females
Trunk (including buttocks)	6.6	5.8
One leg	2.9	2.5
One foot	0.9	0.7
One arm and forearm	1.7	1.3
One hand	0.6	0.5
Face, neck and ears	1.3	0.9
Whole body	20	17

Table 73.2 Quantities (g) of medication required for twice daily application to the entire body at various ages (adapted from [13]).

Requirement	Age										
	3 months	6 months	12 months	18 months	2 years	3 years	4 years	5 years	7 years	10 years	12 years
Daily (g)	8	10	12	13	14	16	19	20	25	30	37
Weekly (g)	56	67	84	93	95	112	135	140	172	210	256

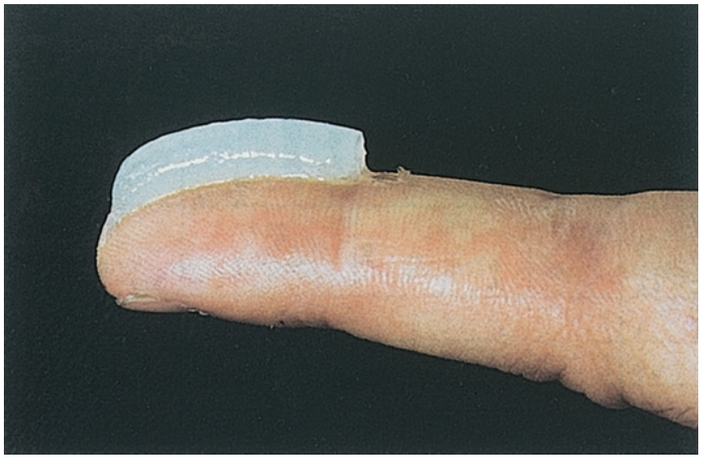


Fig. 73.1 The fingertip unit.

Table 73.3 Fingertip units required for a single treatment of various regions in children and adults adapted from [10,13]. Note that the unit is measured using an adult finger.

Age	Face and neck	One upper limb	One lower limb	Trunk	Whole body
3–6 month	1	1	1.5	2.5	8.5
1–2 years	1.5	1.5	2	5	13.5
3–5 years	1.5	2	3	6.5	18
6–10 years	2	2.5	4.5	8.5	24.5
Adult	2.5	4.5	7.6	13.5	40

Advice to patients

Detailed instructions are often required as to the timing of applications. In many cases it is most convenient to apply the medication immediately after bathing. If other topical treatments are in use it is important to explain how the applications should be timed relative to each other. For example, application of an emollient immediately after application of an active agent will inevitably dilute the active medication and probably spread it over areas of skin where it is not required. When using a medication with a tendency to induce irritation it is helpful to warn patients about this in advance and to give advice on the best course of action when this occurs.

If it is planned to use any form of occlusion, bandaging or other dressing with topically applied medication, detailed instruction is required and this should ideally take the form of a demonstration by a specially trained nurse. Occlusion will invariably increase the level of penetration of a drug into the skin. This mechanism of this effect is not fully understood but seems to be partly the result of retaining a reservoir of the medication on the surface of the skin, and partly the effect of increased hydration of the stratum corneum. The simplest method of occlusion is the use of polythene gloves on the hands or 'cling film' on the feet or limbs. Self-adhesive hydrocolloid dressings can be very useful for limited areas on the limbs or trunk. 'Wet wrap' bandaging is described in the treatment of atopic dermatitis. Various additional types of bandaging (e.g. paste bandages) can be used to increase the penetration of topical medication and have the added benefit of preventing scratching.

When self-treatment fails, the efficacy of topical therapy can almost invariably be improved if the treatment can be applied by specialist nurses in an outpatient department. Many dermatology departments are able to provide this service for patients with severe skin disease who are able to attend on a daily basis. The response to treatment is improved even further by admission to hospital for a period of rest and regular, supervised treatment.

Table 73.4 Relative levels of absorption of hydrocortisone applied at various sites (adapted from [23]).

Site	Relative levels of absorption
Forearm	1
Sole	0.1
Ankle	0.4
Palm	0.8
Back	1.7
Scalp	3.5
Axilla	3.6
Forehead	6
Scrotum	42

Hazards associated with topical treatment

The most frequent adverse effects associated with topical medication are localized irritant or allergic reactions. Irritant reactions can be minimized by applying treatment at the optimal concentration and treatment intervals and by selection of the correct vehicle. Sensitization is more difficult to anticipate and to prevent. Contact allergy can develop not only to the active medicament but also to constituents of the vehicle. Almost any component may sensitize; notable examples include ethylenediamine [14], propylene glycol [15], emulsifiers [16], sorbic acid [17,18], cetyl and stearyl alcohols [19] and fragrances [20]. Patients with chronic venous eczema or leg ulcers appear to be particularly susceptible [21,22]. Sensitivity to topical medication is often overlooked as the symptoms tend to be attributed to the disease being treated.

Systemic side effects from topically applied medication are relatively rare. Nonetheless, all topically applied drugs are absorbed to some degree and on occasions unexpected systemic toxicity occurs. Absorption varies very considerably depending on the region of skin being treated (Table 73.4) [23]. As discussed above, occlusion greatly enhances absorption [24,25]. Systemic exposure can be greater than expected in children due to their relatively high ratio of skin surface to body mass. In the elderly, penetration of drugs may be increased as a result of changes in the structure of the skin. This effect is most pronounced in drugs which are most hydrophilic [26]. Inflammation of the skin impairs barrier function and significantly increases drug absorption. This is especially significant in the erythrodermic patient [27–29].

References

1 Stoughton RB, Wullich K. The same glucocorticoid in brand-name products. Does increasing the concentration result in greater topical biologic activity? *Arch Dermatol* 1989; **125**: 1509–11.
2 Embil K, Nacht S. The Microsponge Delivery System (MDS): a topical delivery system with reduced irritancy incorporating multiple triggering mechanisms for the release of actives. *J Microencapsul* 1996; **13**: 575–88.
3 Schafer-Korting M, Korting HC, Braun-Falco O. Liposome preparations: a step forward in topical drug therapy for skin disease? A review. *J Am Acad Dermatol* 1989; **21**: 1271–5.
4 Patel VB, Misra AN, Marfatia YS. Preparation and comparative clinical evaluation of liposomal gel of benzoyl peroxide for acne. *Drug Dev Ind Pharm* 2001; **27**: 863–9.
5 Agarwal R, Saraswat A, Kaur I *et al*. A novel liposomal formulation of dithranol for psoriasis: preliminary results. *J Dermatol* 2002; **29**: 529–32.
6 Korting HC, Stolz W, Schmid MH *et al*. Interaction of liposomes with human epidermis reconstructed in vitro. *Br J Dermatol* 1995; **132**: 571–9.
7 Berth-Jones J, Damstra RJ, Golsch S *et al*. Twice weekly fluticasone propionate added to emollient maintenance treatment to reduce risk of relapse in atopic dermatitis: randomised, double blind, parallel group study. *BMJ* 2003; **326**: 1367–70.
8 Schlagel CA, Sanborn EC. The weights of topical preparations required for total and partial body inunction. *J Invest Dermatol* 1964; **42**: 253–6.
9 Maurice PDL, Saihan EG. Topical steroid requirement in inflammatory skin conditions. *Br J Clin Prac* 1991; **16**: 444–7.
10 Long CC, Finlay AY. The finger-tip unit—a new practical measure. *Clin Exp Dermatol* 1991; **16**: 444–7.
11 Finlay AY, Edwards PH, Harding KG. 'Fingertip Unit' in dermatology. *Lancet* 1989; **11**: 155.
12 Long CC, Finlay AY, Averill RW. The rule of hand: 4 hand areas = 2 FTU = 1 g. *Arch Dermatol* 1992; **128**: 1129–30.
13 Long CC, Mills CM, Finlay AY. A practical guide to topical therapy in children. *Br J Dermatol* 1998; **138**: 293–6.
14 Fisher AA. Instructions for the ethylene diamine-sensitive patient. *Cutis* 1974; **13**: 27–8.
15 Hannuksela M, Pirilä V, Salo OP. Skin reactions to propylene glycol. *Contact Dermatitis* 1975; **1**: 112–6.
16 Hannuksela M, Kousa M, Pirilä V. Contact sensitivity to emulsifiers. *Contact Dermatitis* 1976; **2**: 201–4.
17 Brown R. Another case of sorbic acid sensitivity. *Contact Dermatitis* 1979; **5**: 268.
18 Saihan EM, Harman RRM. Contact sensitivity to sorbic acid in 'Unguentum Merck'. *Br J Dermatol* 1978; **99**: 583–4.
19 Blondeel A, Oleffe J, Achten G. Contact allergy in 330 dermatological patients. *Contact Dermatitis* 1978; **4**: 270–6.
20 Larsen WG. Perfume dermatitis. A study of 20 patients. *Arch Dermatol* 1977; **113**: 623–5.
21 Breit R, Bandmann HJ. Contact dermatitis XXII—Dermatitis from lanolin. *Br J Dermatol* 1973; **88**: 414–5.
22 Wilkinson JD, Hambly EM, Wilkinson DS. Comparison of patch test results in two adjacent areas of England. II—Medicaments. *Acta Derm Venereol* 1980; **60**: 245–9.
23 Feldmann RJ, Maibach HI. Regional variation in percutaneous penetration of ^{14}C cortisol in man. *J Invest Dermatol* 1967; **48**: 181–3.
24 Sulzberger MB, Witten VH. Thin pliable plastic films in topical dermatologic therapy. *Arch Dermatol* 1961; **84**: 1027–8.
25 Bourke J, Berth-Jones J, Hutchinson PE. Occlusion enhances the efficacy of topical calcipotriol in psoriasis vulgaris. *Clin Exp Dermatol* 1993; **18**: 504–6.
26 Roskos KV, Maibach HI, Guy RH. The effect of aging on percutaneous absorption in man. *J Pharmacokinet Biopharm*; 1989; **17**: 617–30.
27 Borzyskowski M, Grant DB, Wells RS. Cushing's syndrome induced by topical steroids used for the treatment of non-bullous ichthyosiform erythroderma. *Clin Exp Dermatol* 1976; **1**: 337–42.
28 Dwyer C, Chapman R. Calcipotriol and hypercalcaemia. *Lancet* 1991; **338**: 764–5.
29 Brubacher JR, Hoffman RS. Salicylism from topical salicylates: review of the literature. *J Toxicol Clin Toxicol* 1996; **34**: 431–6.

Formulation of topical treatment

The formulation of the vehicle in which a drug is delivered topically to the skin is critical in obtaining effective and consistent results. The vehicle plays many roles. It must provide rapid delivery of the drug to the stratum corneum and into the viable layers of the skin. It must be soothing and comfortable to use and preferably also cosmetically acceptable. The vehicle must also provide a chemical environment in which the drug remains sufficiently stable prior to use to have a practical shelf-life.

Most topical treatments are now commercially formulated in vehicles which have been carefully designed for optimal results. Some caution is therefore required when adding diluents or other medicaments to such a formulation. The role of the dermatologist in formulating topical treatment has been reduced over recent years by stricter financial, legislative and safety controls, which have resulted in the increasing reluctance of pharmacists to prepare extemporaneous or personalized formulations. Nonetheless, an understanding of the roles played by the various constituents of vehicles remains important. Only the most frequently used components are reviewed here. Further information regarding many of the materials and formulations discussed in this chapter is available in the British, European and US Pharmacopoeias (BP, USP) and British Pharmaceutical Codex (BPC).

The simplest role of a vehicle is dilution of an active drug to the desired concentration. Agents such as beeswax, liquid paraffin, polyethylene glycol and powders are often added for their physical properties to adjust the thickness or texture of the medication. In addition to this, various constituents act as emollients, emulsifiers, fragrances, humectants, penetration enhancers, preservatives or solvents. Some of the constituents most often employed are listed in Table 73.5 and some are discussed further below. A single constituent often serves more than one function.

Lipids

Lipids incorporated into vehicles can act as diluents and solvents but are especially valuable as emollients, that is they have the ability to form a coating on the surface of the stratum corneum which inhibits evaporation of water, thus providing a softening and moisturizing effect. Generally speaking, the greater the proportion of lipid in the formulation, the greater will be the emollient action. Ointments are therefore more emollient than oily creams which are more so than aqueous creams, whilst most lotions have no emollient effect. Lipids from a variety of sources are incorporated into topical treatments for skin disease.

Vegetable oils

Oils can be obtained from numerous vegetable sources by pressing or by solvent extraction. Vegetable oils are largely composed of triglycerides which tend to contain large proportions of unsaturated fatty acids, such as the 18-carbon fatty acids oleic acid (monoenoic) and linoleic acid (dienoic). The presence of these unsaturated fatty acids renders vegetable oils vulnerable to oxidation. This result is rancidity which manifests as an unpleasant odour and which is a major constraint on the use of vegetable oils in medicaments.

Table 73.5 Frequently employed constituents of vehicles.

Lipids
Castor oil
Cetyl alcohol
Cocoa butter
Isopropyl myristate
Isopropyl palmitate
Lanolin
Liquid paraffin
Shea butter
Stearic acid
Stearyl alcohol
White soft paraffin (petrolatum)
Emulsifiers
Alkyl sulphates and sulphonates
Glyceryl monostearate
Lanolin and derivatives
Phosphoric acid esters
Polyethylene glycols
Polyvalent metallic soaps
Propylene glycol fatty acid esters
Quaternary ammonium cationic compounds
Sorbitan monolaurate, monopalmitate and mono-oleate
Triethanolamine oleate
Humectants
Gelatine
Glycerin
Propylene glycol
Pyrrolidone carboxylic acid
Sorbitol
Urea
Penetration enhancers
Azone
Dimethyl sulphoxide
Propylene glycol
Salicylic acid
Urea
Preservatives
Benzyl alcohol
Butylated hydroxyanisole
Butylated hydroxytoluene
Chlorocresol
Edetic acid/disodium edetate
Hydroxybenzoates (parabens)
Propylene glycol
Sodium metabisulphite
Sorbic acid/sorbates
Solvents
Acetone
Ethanol
Ether
Chloroform
Glycerin
Isopropyl alcohol
Methanol
Propylene glycol
Water

Arachis oil, derived from the ground nut or peanut, has been the subject of concern over possible contamination with allergens which could cause hypersensitivity reactions in peanut-sensitive individuals. Cocoa butter, also known as theobroma oil, is a product of the cocoa bean and consists chiefly of the triglycerides of palmitic, stearic and oleic acids. It also contains antioxidants which make it remarkably stable for a vegetable oil, and which can even help to preserve other constituents with which it is compounded. It is brittle at room temperature but melts at between 30 and 35°C. Castor oil is obtained from the castor bean *Ricinus communis* and is composed almost entirely of triglycerides of the 18-carbon long-chain fatty acid ricinoleic acid. Olive oil contains a large proportion of oleic acid. Shea butter is extracted from the fruit of the shea tree, *Vitellaria paradoxa*. This is a useful emollient containing somewhat variable proportions of palmitic, stearic, oleic and other fatty acids as well as cinnamates. The latter constituent can provide a modest degree of photoprotection.

Mineral oils and greases

Extracts of crude oil (crude petroleum) resembling those we use today have been used for treatment of skin disease since a US patent was obtained, in 1872, by Robert Chesebrough for a product he called Vaseline.

Emollient products extracted from crude oil can be produced as fluids, semi-solids or solids and include Liquid Paraffin BP, Mineral Oil USP, Yellow and White Soft Paraffin BP, Petrolatum USP etc. The extraction process involves treatments to remove elements other than hydrogen and carbon. Aromatic and unsaturated compounds are also eliminated, leaving a diverse range of hydrocarbon molecules, some straight chained, some branched and some polycyclic [1]. As a result of their fully saturated nature, these hydrocarbons are far more stable than the constituents of vegetable oils. They are remarkably inert and not vulnerable to oxidation or rancidity. For this reason, mineral oils have substantially replaced vegetable oils as the lipids used in emollients and topical treatments.

Lanolin

The use of wool extracts for cosmetic and medicinal purposes dates back at least as far as ancient Greece. Lanolin (wool fat) is extracted from wool and is essentially the product of the sheep sebaceous gland [2]. It is available in abundance and, since its natural purpose is to protect the skin and wool of the sheep, it is perhaps an obvious choice of lipid material for use as an emollient.

Lanolin comprises a complex mixture of higher fatty acids esterified with mono and dihydric alcohols, including aliphatic alcohols and cholesterol and related sterols. Its precise composition varies qualitatively and quantitatively with humidity, temperature and method of collection. It is prone to auto-oxidation and is therefore often formulated with the antioxidant butylated hydroxytoluene (BHT). Lanolin is miscible with water and is a useful emulsifying agent when mixed with other lipids.

Lanolin has gained a reputation as a frequent contact sensitizer although this remains questionable [3]. Small quantities of anionic detergent may be present in lanolin and may increase the apparent incidence of hypersensitivity [4]. It has also been suggested that

misleadingly high proportions of positive patch tests to lanolin and wool alcohols have arisen partly due to selection of groups of patients who are particularly vulnerable to irritant reactions, which are misinterpreted as allergy [3]. Sensitization to lanolin in the general population remains rare, of the order of one in a million, even though this material has so many applications that it is ubiquitous [3].

Partly because of its reputation as a sensitizer, numerous lanolin extracts and derivatives are often used instead of the natural material. These are produced by a range of processes including hydrolysis to yield the constituent acids and alcohols, acetylation, ethoxylation and solvent fractionation. Eucerin (Wool Alcohols BP) is the wool alcohol fraction of wool fat, and contains cholesterol and isocholesterol. It is mixed with liquid, soft and hard paraffin to form Ointment of Wool Alcohols BP, which, on the addition of water, produces Hydrous Ointment BP, a vehicle for many W/O creams.

Fatty acids and alcohols

Long chain fatty acids, for example palmitic and stearic acids and their alcohols, cetyl and stearyl alcohols, are very frequently used as emollients and, in creams, also serve as emulsifiers. Cetostearyl alcohol is a frequently used mixture of cetyl and stearyl alcohols. They can be obtained by hydrolysis of triglycerides from many different animal and vegetable fats and oils.

Waxes

Beeswax is secreted by worker bees to make the walls of the cells of the honeycomb and is remarkably chemically stable. It has a melting point around 60°C and is composed mainly of free cerotic acid and myricyl palmitate. It is used as a thickening agent for creams, ointments and lip salves. Occasional cases of sensitization occur due either to components of the wax or contamination with plant-derived materials such as propolis.

Emulsifying wax comprises cetostearyl alcohol, sodium lauryl sulphate and water. This is a constituent of Emulsifying Ointment BP.

Polyethylene glycols

Polyethylene glycols, also known as PEGs or macrogols, are dihydric alcohols. They are polymers of ethylene glycol linked by ether bonds with the general formula $H(O\text{-}CH_2\text{-}CH_2)_n\text{-}OH$ in which n may range from 2 to 90 000. PEGs can be designated by a number indicating the average molecular weight. At low molecular weights, up to 2000, they are hygroscopic. They variously serve as emollients, emulsifiers or thickeners and can also be used to impart a pleasant feel or texture to a formulation.

Cetomacrogols are cetylethers of polyethylene glycol, for example cetomacrogol 1000 is the monocetyl ether of polyethylene glycols with average molecular weight 1000. It is useful as a non-ionic emulsifying agent.

Emulsifiers

An emulsion is a two-phase system consisting of two immiscible components, one (the dispersed or inner phase) being suspended in the other (the continuous or outer phase) as small droplets. One phase is aqueous, the other oily. Stable emulsions remain in this form; unstable emulsions, with a large droplet size, tend to separate as cream does from milk. Production of a stable emulsion requires the presence of an emulsifier, which is a large molecule with both strongly polar (i.e. water-soluble) and non-polar (i.e. oil-soluble) groups that allow it to bridge the gap between polar and non-polar substances. A large and chemically diverse range of compounds can be used for this purpose; some examples are given in Table 73.5.

Water-in-oil (W/O) systems result from the dispersion of an aqueous phase in an oily phase, as in Oily Cream BP. Oil-in-water (O/W) systems are formed when oil is the dispersed phase and water the continuous phase, as in Aqueous Cream BP. The former constitute, in general, oily creams or 'cold creams', the latter aqueous or 'vanishing creams'. It is sometimes possible to produce both types of emulsion in the same system [5]; these are called ambiphilic creams. Emulsions can be diluted with the outer (continuous) phase only. A simple method of determining the nature of an emulsion is to interpose on a filter paper a drop of the emulsion between one of oil and one of water. In 15 minutes the continuous phase will mix with, or be dispersed by, one or other of the neighbouring drops. Alternatively, it may be tested by adding a larger quantity of water. If the emulsion separates, it is of W/O type; if not, it is of O/W type, the continuous phase being (within limits) able to expand and still retain its contained disperse phase.

The relative affinity of an emulsifier for water and for oil is quantified by a value denoting its emulsification tendency, known as the hydrophilic lipophilic balance (HLB) value [6]. Emulsifiers with an HLB value of 3–6 tend to give W/O systems and those with higher values O/W systems.

Humectants

These are compounds with a high affinity for water (hygroscopicity). They draw water into the stratum corneum and therefore have an emollient effect on dry skin. However, most of the water is drawn out from within the skin and in dry atmospheric conditions water loss from the skin surface may be increased by the presence of humectants.

Penetration enhancers

Agents that have been shown to enhance penetration of drugs through the skin include propylene glycol [7,8], azone [9], urea [10], and dimethyl sulphoxide (DMSO) and related drugs [11–14]. Mechanisms for this effect include hydration of the stratum corneum and keratolytic actions. The effect of salicylic acid as a penetration enhancing agent seems to be variable. *In vitro* studies have suggested that penetration of drugs is enhanced but this effect was not observed during *in vivo* studies of steroid penetration through normal skin [15,16]. However, in treatment of psoriasis the addition of salicylic acid does seem to improve the response to topical corticosteroids [17,18].

Dimethylsulphoxide is a highly polar, stable substance with exceptional solvent properties [19–23]. It releases histamine *in vivo* and may induce weals when applied topically. It reacts with water, liberating heat. The stratum corneum retains significant amounts of DMSO and, as most drugs are more soluble in DMSO than water, this tends to promote percutaneous absorption [22].

This quality has been shown to be of particular value in increasing the effectiveness of idoxuridine in herpes simplex [24] and zoster [25]. Toxicological considerations have precluded its more widespread use.

Powders

Inorganic powders are an important component of many dermatological treatments and include zinc oxide, titanium dioxide, talc, bentonite and calamine. Organic powders include various starches and zinc stearate. Zinc oxide is widely used as a component of many dusting powders, shake lotions and pastes. It has covering and protective properties, gives consistency to creams and pastes, and is said to have cooling and slightly astringent properties. Titanium dioxide is chemically very inert and for this reason it can be used instead of zinc oxide in pastes containing salicylic acid. Like zinc oxide, it has useful UV-reflecting properties. Talc is inert magnesium polysilicate, with a very low specific gravity. It contributes 'slip' and has a cooling effect. Calamine may be either zinc carbonate or zinc oxide, coloured with a little ferric oxide, and has bland, soothing and antipruritic properties. Starch is more absorbent than inorganic powders, but tends to deteriorate and is prone to microbiological decomposition. Some powders, for example bentonite (colloidal hydrated aluminium silicate), aluminium magnesium silicate, tragacanth, methylcellulose and carbomer are used in gels or as stabilizers in shake lotions.

Preservatives

Ointments and some creams with oil as the continuous phase do not usually require preservatives. Lotions, O/W creams and gels, however, because they contain accessible water, are easily contaminated by moulds or bacteria. Animal and vegetable oils, unless protected from oxidation, tend to become rancid. The ideal preservative should be non-toxic, non-irritant, non-sensitizing, odourless, colourless and effective even at very low concentrations and under conditions of normal usage. In addition, it must be chemically compatible with both the vehicle and the active ingredients.

The parahydroxybenzoic acid esters (parabens, hydroxybenzoates) are effective and widely used preservatives. Because, individually, they are only sparingly water-soluble, and as their effects are additive, mixtures of different esters are usually preferred. This also increases their spectrum of activity and lowers the risk of sensitization. Considering their widespread use, their sensitizing potential appears to be low [26].

Chlorocresol is a preservative used especially in the UK. It is more effective in acid than in alkaline solution. It has a low sensitizing potential. It is used in several corticosteroid creams.

Sorbic acid (2,4 hexadienoic acid) is also a good preservative, which maintains its activity in the presence of non-ionic detergents. It also has a low sensitization index. However, it can only be used in preparations with a pH of less than 6.5.

Propylene glycol can inhibit the growth of moulds and fungi, and can therefore be used as a preservative.

Organic mercurials such as thiomersal (thimerosal) are used as preservatives in many ophthalmic preparations and in some vaccines and prick test solutions and are occasionally incorporated in some topical preparations [27]. Ethylene diaminetetraacetate is a widely used preservative in ear, nose and eye drops. Gallates and other antioxidants such as butylhydroxyanisole (BHA) and butylhydroxytoluene (BHT) are used to prevent rancidity in oily and fatty preparations.

Other preservatives, including those mainly used in cosmetic products, are discussed in Chapters 25 and 26.

References

1 Morrison DS. Petrolatum: conditioning through occlusion. In: Schueller R, Romanowski P, eds. *Conditioning Agents for Hair and Skin*. New York: Marcel Dekker, Inc, 1999: 57–94.

2 Clark EW. The history and evolution of lanolin. In: Hoppe U, ed. *The Lanolin Book*. Hamberg: Beiersdorf AG, 1999: 9–50.

3 Kligman AM. The myth of lanolin allergy. Lanolin is not a contact sensitizer. In: Hoppe U, ed. *The Lanolin Book*. Hamberg: Beiersdorf AG, 1999: 161–75.

4 Clarke EW, Cronin E, Wilkinson DS. Lanolin with reduced sensitizing potential—a preliminary note. *Contact Dermatitis* 1977; **3**: 69–76.

5 Clark R. In: Hibbot HW, ed. *Handbook of Cosmetic Science*. Oxford: Pergamon Press, 1963: 175–204.

6 Griffin WC. Calculation of HLB values of non-ionic surfactant. *J Soc Cosmet Chem* 1954; **5**: 249–56.

7 Ostrenga J, Haleblan J, Poulsen B *et al*. Vehicle for a new topical steroid, flouci-nonide. *J Invest Dermatol* 1971; **56**: 392–9.

8 Polano MK, Ponec M. Dependence of corticosteroid penetration on the vehicle. *Arch Dermatol* 1976; **112**: 675–80.

9 Spruance SL, McKeough M, Sugibayashi K *et al*. Effect of azone and propylene glycol on penetration of trifluorothymidine through skin and efficacy of different topical formulations against cutaneous herpes simplex virus infections in guinea pigs. *Antimicrob Agents Chemother* 1984; **26**: 819–23.

10 Feldman RJ, Maibach HI. Percutaneous penetration of hydrocortisone with urea. *Arch Dermatol* 1974; **109**: 58–9.

11 Munro DD, Stoughton RB. Dimethylacetamide (DMAC) and dimethylformamide (DMF) effect on cutaneous absorption. *Arch Dermatol* 1965; **92**: 585–6.

12 Feldman RJ, Maibach HI. Percutaneous penetration of C^{14} hydrocortisone in man. *Arch Dermatol* 1966; **94**: 649–51.

13 Stoughton RB. Dimethylsulfoxide (DMSO) induction of a steroid reservoir in human skin. *Arch Dermatol* 1965; **91**: 657–60.

14 Stoughton RB. Hexachlorophane deposition in human stratum corneum. Enhancement by dimethylacetamide, dimethylsulfoxide and methylethylether. *Arch Dermatol* 1966; **94**: 646–8.

15 Tauber U, Weiss C, Matthes H. Does salicylic acid increase the percutaneous absorption of diflucortolone-21-valerate? *Skin Pharmacol* 1993; **6**: 276–81.

16 Wester RC, Noonan PK, Maibach HI. Effect of salicylic acid on the percutaneous absorption of hydrocortisone. In vivo studies in the rhesus monkey. *Arch Dermatol* 1978; **114**: 1162–4.

17 Koo J, Cuffie CA, Tanner DJ *et al.* Mometasone furoate 0.1%-salicylic acid 5% ointment versus mometasone furoate 0.1% ointment in the treatment of moderate-to-severe psoriasis: a multicenter study. *Clin Ther* 1998; **20**: 283–91.

18 Medansky RS, Cuffie CA, Tanner DJ. Mometasone furoate 0.1%-salicylic acid 5% ointment twice daily versus fluocinonide 0.05% ointment twice daily in the management of patients with psoriasis. *Clin Ther* 1997; **19**: 701–9.

19 Beger I, Lorenz D. Purification of analysis of dimethylsulphoxide. In: Martin D, Hauthal HG, eds. *Dimethyl Sulphoxide*. New York: Van Nostrand Reinhold, 1976: 41–8.

20 Jacob SW, Herschler R, eds. Biological actions of dimethyl sulphoxide. *Ann NY Acad Sci* 1975; **23**: 243.

21 Jacob SW, Bischel M, Herschler RJ. Dimethyl sulfoxide (DMSO): a new concept in pharmacotherapy. *Curr Ther Res* 1964; **6**: 134–5.

22 Katz M, Poulsen BJ. Absorption of drugs through the skin. In: Brodie BB, Gillette J, eds. *Handbook of Experimental Pharmacology*, Vol. 28. New York: Springer, 1971: 103–74.

23 Kligman AM. Dimethylsulfoxide—Part 2. *JAMA* 1965; **193**: 923–8.

24 MacCallum FO, Juel-Jensen BE. Herpes simplex virus skin infection in man treated with idoxuridine in dimethylsulphoxide. Results of a double-blind controlled trial. *BMJ* 1966; **ii**: 805–7.

25 Juel-Jensen BE, MacCallum FO, MacKenzie AMR. Treatment of zoster with idoxuridine in dimethylsulphoxide. Results of two double-blind controlled trials. *BMJ* 1970; **iv**: 776–80.

26 Schnuch A, Geier J, Uter W, Frosch PJ. Patch testing with preservatives, antimicrobials and industrial biocides. Results from a multicentre study. *Br J Dermatol* 1998; **138**: 467–76.
27 Wilkinson DS. Thiomersal. *Contact Dermatitis* 1978; **5**: 58–9.

Topical treatments used in the management of skin disease

Antiperspirants

Most antiperspirants marketed for cosmetic purposes contain aluminium chloride hexahydrate. In contemporary products, refined formulations of aluminium chlorohydrates (or aluminium zirconium complexes) are often used to maximize precipitation of aluminium hydroxide within the sweat duct [1]. Cosmetic antiperspirants are often combined with antimicrobial agents, which reduce axillary odour by inhibiting the action of bacterial metabolism on various components of apocrine sweat. Fragrances are often added to mask or adjust the odour in various ways [2].

In treatment of hyperhidrosis of the axillae, palms and soles, higher concentrations of aluminium chloride hexahydrate (e.g. 20–25% in ethanol) are generally used as first-line treatment. These are more effective, but more irritant, and more likely to damage clothing, than cosmetic formulations. Precipitation of aluminium chloride resulting in blockage of the sweat duct is regarded as the principal mechanism of action [1,3], although secondary degeneration of the secretory cells may develop after long-term use as a result of the increased pressure in the duct [4]. For maximal efficacy the treatment should be applied when the skin is dry and sweating is minimal. Application at night is often recommended and this also helps minimize damage to clothing. Polythene occlusion may enhance efficacy and irritancy. Irritation often limits the use of this treatment but may settle with reduced frequency of application and with use of a mild or moderately potent topical steroid.

Traditional remedies which have fallen out of favour include the aldehydes. These are believed to work by a similar mechanism to aluminium salts. Aqueous glutaraldehyde solution (up to 10%) can be applied on a swab to the soles of the feet [5,6]. The keratin stains orange–brown when higher concentrations are used. Formaldehyde solution BP (1–3%), used as a twice-daily soak, also helps mild cases. Both compounds are frequent sensitizers, and are therefore not ideal for prolonged use. Methenamine, an agent which releases formaldehyde and ammonia, seems to cause less sensitization and has been used as a 10% solution or at 5% concentration in a firm gel-stick formulation [7].

Anticholinergic agents inhibit the anomalous sympathetic (cholinergic) innervation of the sweat glands and can be applied topically to minimize the side effects associated with systemic administration. Poldine methylsulphate [8] and glycopyrronium bromide [9] can be very effective when administered by iontophoresis. Dry mouth is common and visual accommodation may be disturbed for 24–48 h following treatment. Iontophoresis with tap water is also effective, by an unknown mechanism [10,11], and avoids these side effects. Glycopyrrolate cream (2%) or lotion has been used with success in patients suffering from severe gustatory sweating following parotidectomy [12].

Surgical treatments and injection of botulinum toxin are considered in Chapters 44 and 80.

References

1 Fitzgerald JJ, Rosenberg AH. Chemistry of aluminium chlorohydrate and activated aluminium chlorohydrates. In: Laden K, ed. *Antiperspirants and Deodorants*, 2nd edn. New York: Marcel Dekker, Inc., 1999: 83–136.
2 Makin SA, Lowry MR. Deodorant ingredients. In: Laden K, ed. *Antiperspirants and Deodorants*, 2nd edn. New York: Marcel Dekker, Inc., 1999: 169–214.
3 Rosenberg AH, Fitzgerald JJ. Chemistry of aluminium-zirconium-glycine (AXG) complexes. In: Laden K, ed. *Antiperspirants and Deodorants*, 2nd edn. New York: Marcel Dekker, Inc., 1999: 137–168.
4 Holzle E, Braun-Falco O. Structural changes in axillary eccrine glands following long-term treatment with aluminium chloride hexahydrate solution. *Br J Dermatol* 1984; **110**: 399–403.
5 Juhlin L. Topical glutaraldehyde for plantar hyperhidrosis. *Arch Dermatol* 1968; **97**: 327–30.
6 Sato K, Dobson RL. Mechanism of the antiperspirant effect of topical glutaraldehyde. *Arch Dermatol* 1969; **100**: 564–9.
7 Cullen SI. Topical methenamine therapy for hyperhidrosis. *Arch Dermatol* 1975; **111**: 1158–60.
8 Hill BHR. Poldine iontophoresis in the treatment of palmar and plantar hyperhidrosis. *Aust J Dermatol* 1976; **17**: 92–3.
9 Abell E, Morgan K. The treatment of idiopathic hyperhidrosis by glycopyrrhonium bromide and tapwater iontophoresis. *Br J Dermatol* 1974; **911**: 87–91.
10 Grice K, Sattar H, Baker H. Treatment of idiopathic hyperhidrosis with iontophoresis of tap water and poldine methosulphate. *Br J Dermatol* 1972; **86**: 72–8.
11 Shrivastava SN, Singh G. Tap water iontophoresis in palmoplantar hyperhidrosis. *Br J Dermatol* 1977; **96**: 189–95.
12 May JS, McGuirt WF. Frey's syndrome: treatment with topical glycopyrrolate. *Head Neck* 1989; **11**: 85–9.

Antibiotics

Topical antibiotics are most frequently used in treatment of superficial infections such as impetigo, superficially infected surgical wounds, infected leg ulcers, and in acne vulgaris and rosacea.

When treating infected skin lesions it is important to establish the identity and antibiotic sensitivity of the organism whenever possible. Although staphylococcal infections are common, it should not be assumed that a cutaneous infection is due to this organism. Before using an antibiotic, consideration should always be given to the alternative of using an antiseptic in order to reduce the risk of promoting antibiotic resistance. Antiseptics usually have the added advantage of covering a wider spectrum of organisms.

The value of many antibiotics is limited by their tendency to sensitize when used topically, for example chloramphenicol and neomycin. Once sensitization has developed this generally precludes future systemic use of the antibiotic. It is therefore preferable, when possible, to select an antibiotic for topical application that is not related to agents used systemically.

The topical antibiotics most used in treatment of acne and rosacea are tetracyclines, erythromycin, and clindamycin. Topical metronidazole has proved useful in rosacea. In general, topical antibiotics work about as well as benzoyl peroxide or tretinoin in acne vulgaris. As in other indications, consideration should be given to alternatives to topical antibiotics, especially for long-term treatment, in order to reduce the emergence of resistant organisms. The detailed use of antibiotics in acne and rosacea is described in Chapters 42 and 43, respectively.

Bacitracin

This is an antibiotic which is too toxic for systemic use. Its antibacterial action is principally against Gram-positive organisms, so it is generally used topically in combination with other antibiotics, such as neomycin or polymyxin B. Allergic reactions of an anaphylactoid nature have been recorded [1]. In patients with leg ulcers it has been reported to be the most potent sensitizer of all the topical antibiotics that were tested [2].

Clindamycin

This is an effective topical treatment for acne vulgaris [3]. It is as effective as oral minocycline 50 mg twice daily [4], and oral tetracyline [5]. It was somewhat less effective than topical nicotinamide 4% gel in a trial involving 76 patients [6]. It was found to be as effective as 5% benzoyl peroxide gel in patients with papular or pustular acne [7]; fewer side effects were seen with topical clindamycin. In rosacea the efficacy of topical clindamycin may be comparable to that of oral tetracycline [8].

Erythromycin

Only the lipid-soluble forms, for example the base, propionate or stearate, are effective in acne vulgaris. Several authors have considered the problem of erythromycin-resistant propionibacteria [9,10]. It is equivalent in effect to topical clindamycin, is safe and well tolerated [11,12]. A topical 2% erythromycin gel has been shown to be as effective as 1% clindamycin phosphate in patients with mild to moderate acne [13], and 1.5% erythromycin and 1% clindamycin phosphate solutions were found to be equally effective [12].

Fusidic acid

Derived from *Fusidium coccineum*, this is active against staphylococcal infections and effective in erythrasma [14]. It is used as a first-line treatment for pitted keratolysis [15] although there is surprisingly little published about this indication. It is also used in combination with topical steroids in the treatment of infected eczema.

Sensitization occurs only very rarely [16,17], but bacterial resistance is not uncommon.

Gentamicin

The particular dermatological value of gentamicin lies in its broad spectrum of activity, including against *Pseudomonas aeruginosa*. Contact allergy is fairly frequent in patients with chronic otitis externa [18] and, compared with other agents, it remains a common sensitizer [19]. Cross-sensitivity can develop with other aminoglycosides [20].

Metronidazole

Metronidazole 0.75–1% has been shown to be a safe and effective treatment for rosacea [21,22]. Topical metronidazole has also been used with some success in patients with decubitus and other ulcers, eliminating malodour in 36 h [23]. In a double-blind, placebo-controlled trial, topical metronidazole was ineffective in reducing the inflammatory lesions of acne [24].

Mupirocin

This topical antibiotic is derived from *Pseudomonas fluorescens* [25]. It is chemically unrelated to other antibiotics, and its mode of action in arresting bacterial protein synthesis is novel [26]. It is active against a wide range of Gram-positive organisms and some Gram-negative organisms [27]. Naturally it is not active against pseudomonas and may allow overgrowth of this organism. It can be highly effective in cutaneous bacterial infections [28,29]. It has also proved useful in the elimination of nasal carriage of staphylococci [30], including multiply-resistant organisms, but strains resistant to mupirocin are now an increasing problem.

Neomycin and framycetin

These are aminoglycoside antibiotics with a broad spectrum of action against Gram-positive and Gram-negative organisms. Both are considered too toxic for systemic use. Many preparations containing one or other of these are marketed in the UK, and are widely used, although sensitization reactions are common, especially around leg ulcers, under occlusion and in patients with chronic otitis externa, pruritus ani/vulvae, or recurrent eye problems. Neomycin was among the commonest sensitizers reported by Wilkinson *et al*. [31]. Simultaneous contact allergy to neomycin, bacitracin, and polymyxin has been reported [32].

Retapamulin

This is a member of a novel class of antibiotics known as pleuromutilins which exert antimicrobial activity by inhibition of bacterial protein synthesis following interaction with the peptidyltransferase centre of the 50S subunit of bacterial ribosomes [33].

Retapamulin is effective *in vitro* against *Staphylococcus aureus* (including meticillin-resistant strains) and *Streptococcus pyogenes* (including macrolide-resistant strains) [34], and against a diverse range of anaerobic organisms including *Clostridium* species, anaerobic cocci and *Propionibacteria acnes* [35,36].

In clinical trials, retapamulin has shown efficacy comparable to topical fusidic acid in the treatment of impetigo and appeared effective in treating infections caused by strains of *Staph. aureus* resistant to other antibiotics [37]. Efficacy was comparable to oral cephalexin in treatment of infected wounds [38] and infected dermatitis [39].

Retapamulin is available as a 1% ointment.

Polymyxin B

This antibiotic is a cyclic peptide derived from a Gram-positive bacterium (*Bacillus polymyxa*) and has valuable activity against Gram-negative organisms including *Pseudomonas aeruginosa*. It is used in several proprietary topical formulations for application to skin, eyes and ears, usually combined with other antibiotics. The relatively low toxicity of polymyxin to keratinocytes may explain the good cosmetic results observed when it is used following dermabrasion [40].

Silver sulphadiazine

First introduced over 20 years ago [41,42], this compound has become established as a safe and convenient dressing for burns

[42]. Even when applied over wide areas, systemic absorption is minimal and the risk of renal damage is thought to be slight [43]. It is applied as a 1% cream. It appears to have a low potential for sensitization and is useful in the management of leg ulcers where it provides good prophylaxis against *Staphylococcus aureus* and some Gram-negative organisms. Some patients may become sensitive to the cetyl alcohol contained in the base of one proprietary formulation. When sulphonamide-resistant Gram-negative bacilli were present, a silver nitrate/chlorhexidine cream was found to be of value [44].

Tetracyclines

These are used alone in the topical treatment of acne [45], but are also present in several proprietary topical corticosteroid preparations. Bacterial resistance is common, especially in *Staph. aureus*. Tetracyclines tend to stain skin and clothing yellow.

References

1 Vale MA, Connolly A, Epstein A. Metal/bacitracin induced anaphylaxis. *Arch Dermatol* 1978; **114**: 800.

2 Zaki I, Shall L, Dalziel KL. Bacitracin: a significant sensitizer in leg ulcer patients? *Contact Dermatitis* 1994; **31**: 92–4.

3 Kuhlman DS, Callen JP. A comparison of clindamycin phosphate 1 percent topical lotion and placebo in the treatment of acne vulgaris. *Cutis* 1986; **38**: 203–6.

4 Sheehan-Dare RA, Papworth-Smith J, Cunliffe WJ. A double-blind comparison of topical clindamycin and oral minocycline in the treatment of acne vulgaris. *Acta Derm Venereol (Stockh)* 1990; **70**: 543–7.

5 Katsambas A, Towaky AA, Stratigos J. Topical clindamycin phosphate compared with oral tetracycline in the treatment of cane vulgaris. *Br J Dermatol* 1987; **116**: 387–91.

6 Shalita AR, Smith JG, Parish LC *et al*. Topical nicotinamide compared with clindamycin gel in the treatment of inflammatory acne vulgaris. *Int J Dermatol* 1995; **34**: 434–7.

7 Schmidt JB, Neuman R, Fanta D *et al*. 1% clindamycin phosphate solution versus 5% benzoyl peroxide gel in papular pustular acne. *Z Hautkr* 1988; **63**: 374–6.

8 Wilkin JK, De Witt S. Treatment of rosacea: topical clindamycin versus oral tetracycline. *Int J Dermatol* 1993; **32**: 65–7.

9 Bojar RA, Eady EA, Jones CE *et al*. Inhibition of erythromycin-resistant propionibacteria on the skin of acne patients by topical erythromycin with and without zinc. *Br J Dermatol* 1994; **130**: 329–36.

10 Harkaway KS, McGinley KJ, Foglia AN *et al*. Antibiotic resistance patterns in coagulase-negative staphylococci after treatment with topical erythromycin, benzoyl peroxide, and combination therapy. *Br J Dermatol* 1992; **126**: 586–90.

11 Schachner L, Pestana A, Kittles C. A clinical trial comparing the safety and efficacy of a topical erythromycin-zinc formulation with a topical clindamycin formulation. *J Am Acad Dermatol* 1990; **22**: 489–95.

12 Shalita AR, Smith EB, Bauer E. Topical erythromycin v clindamycin therapy for acne. A multicenter, double-blind comparison. *Arch Dermatol* 1984; **120**: 351–5.

13 Leyden JJ, Shalita AR, Saajian CD *et al*. Erythromycin 2% gel in comparison with clindamycin phosphate 1% solution in acne vulgaris. *J Am Acad Dermatol* 1987; **16**: 822–7.

14 MacMillan AL, Sarkany I. Specific topical therapy for erythrasma. *Br J Dermatol* 1970; **82**: 507–9.

15 Tan E, Berth-Jones J. Pitted keratolysis. In: Lebwohl M, Heymann WR, Berth-Jones J, Coulson I, eds. *Treatment of Skin Disease. Comprehensive Therapeutic Strategies*, 2nd edn. London: Mosby Harcourt, 2006: 494–5.

16 Baptista A, Barros MA. Contact dermatitis from sodium fusidate. *Contact Dermatitis* 1990; **23**: 186–7.

17 Romaguera C, Grimalt F. Contact dermatitis to sodium fusidate. *Contact Dermatitis* 1985; **12**: 176–7.

18 Holmes RC, Johns AN, Wilkinson JD *et al*. Medicament contact dermatitis in patients with chronic inflammatory ear disease. *J R Soc Med* 1982; **75**: 27–30.

19 Gollhausen R, Enders F, Przybilla B *et al*. Trends in allergic contact sensitization. *Contact Dermatitis* 1988; **18**: 147–54.

20 Forstrom L, Pirila V, Pirila L. Cross-sensitivity within the neomycin group of antibiotics. *Acta Derm Venereol Suppl (Stockh)* 1979; **59**: 67–9.

21 Aronson IK, Rumsfield JA, West EP *et al*. Evaluation of topical metronidazole gel in acne rosacea. *Drug Intell Clin Pharmacol* 1987; **21**: 346–51.

22 Erikson G, Nor CE. Impact of metronidazole on skin and colon microflora in patients with rosacea. *Infection* 1987; **15**: 8–10.

23 Witkowski JA, Parish LC. Topical metronidazole gel. The bacteriology of decubitus ulcers. *Int J Dermatol* 1991; **30**: 660–1.

24 Tong D, Peters W, Barnetson RS. Evaluation of 0.75% metronidazole gel in acne—a double-blind study. *Clin Exp Dermatol* 1994; **19**: 221–3.

25 Chain EB, Mellows C. Pseudomonic acid—Part 1. The structure of pseudomonic CID A: a novel antibiotic produced by *Pseudomonas fluorescens*. *J Chem Soc Perkin Trans* 1977; **1**: 294–309.

26 Hughes J, Mellowes C. Interaction of pseudomonic acid A with *Escherichia coli* B isoleucyl t-RNA synthetase. *Biochem J* 1980; **191**: 209–10.

27 White AR, Beale AS, Boon RJ *et al*. Antibacterial activity of mupirocin, an antibiotic produced by *Pseudomonas fluorescens*. *R Soc Med Int Congr Symp Ser* 1984; **80**: 43–55.

28 Lever R, Hadley K, Downey D, MacKie R. Staphylococcal colonisation in atopic dermatitis and the effect of topical mupirocin therapy. *Br J Dermatol* 1988; **119**: 189–98.

29 Mertz PM, Marshall DA, Eaglstein WH *et al*. Topical mupirocin treatment of impetigo is equal to oral erythromycin therapy. *Arch Dermatol* 1989; **125**: 1069–73.

30 Dacre JE, Emmerson AM, Jenner EA. Nasal carriage of gentamicin and methicillin resistant *Staphylococcus aureus* treated with topical pseudomonic acid. *Lancet* 1983; **ii**: 1036.

31 Wilkinson JD, Hambly EM, Wilkinson DS. Comparison of patch test results in two adjacent areas of England. II. Medicaments. *Acta Derm Venereol (Stockh)* 1980; **60**: 245–9.

32 Grandinetti PJ, Fowler JF Jr. Simultaneous contact allergy to neomycin, bacitracin, and polymyxin. *J Am Acad Dermatol* 1990; **23**: 646–7.

33 Yan K, Madden L, Choudhry AE *et al*. Biochemical characterization of the interactions of the novel pleuromutilin derivative retapamulin with bacterial ribosomes. *Antimicrob Agents Chemother* 2006; **50**: 3875–81.

34 Pankuch GA, Lin G, Hoellman DB *et al*. Activity of retapamulin against *Streptococcus pyogenes* and *Staphylococcus aureus* evaluated by agar dilution, microdilution, E-test, and disk diffusion methodologies. *Antimicrob Agents Chemother* 2006; **50**: 1727–30.

35 Goldstein EJ, Citron DM, Merriam CV *et al*. Comparative in vitro activities of retapamulin (SB-275833) against 141 clinical isolates of *Propionibacterium* spp., including 117 *P. acnes* isolates. *Antimicrob Agents Chemother* 2006; **50**: 379–81.

36 Odou MF, Muller C, Calvet L, Dubreuil L. In vitro activity against anaerobes of retapamulin, a new topical antibiotic for treatment of skin infections. *J Antimicrob Chemother* 2007; **59**: 646–51.

37 Oranje AP, Chosidow O, Sacchidanand S *et al*. Topical retapamulin ointment, 1%, versus sodium fusidate ointment, 2%, for impetigo: a randomized, observer-blinded, noninferiority study. *Dermatology* 2007; **215**: 331–40.

38 Free A, Roth E, Dalessandro M *et al*. Retapamulin ointment twice daily for 5 days vs oral cephalexin twice daily for 10 days for empiric treatment of secondarily infected traumatic lesions of the skin. *Skinmed* 2006; **5**: 224–32.

39 Parish LC, Jorizzo JL, Breton JJ *et al*. Topical retapamulin ointment (1%, wt/wt) twice daily for 5 days versus oral cephalexin twice daily for 10 days in the treatment of secondarily infected dermatitis: results of a randomized controlled trial. *J Am Acad Dermatol* 2006; **55**: 1003–13.

40 Berger RS, Pappert AS, Van Zile PS, Cetnarowski WE. A newly formulated topical triple-antibiotic ointment minimizes scarring. *Cutis* 2000; **65**: 401–4.

41 Fox CL. Pharmacodynamics of sulfadiazine and related topical antimicrobial agents. In: Frost P, Gomez EC, Zaias N, eds. *Recent Advances in Dermato Pharmacology*. New York: Spectrum, 1978: 441–56.

42 Fox CL. Silver sulfadiazide—a new topical therapy for *Pseudomonas* in burns. *Arch Surg* 1978; **96**: 184–8.

43 Delaveau P, Friedrich-Nove P. Absorption cutanée et l'elimination urinaire d'une combinaison sulfadiazine-argent utilisée dans le traitement de brûlures. *Therapie* 1977; **32**: 563–72.
44 Lowbury EJL, Babb JR, Bridges K. Topical chemoprophylaxis with silver sulfadiazine and silver nitrate chlorhexidine creams: emergence of sulphon-amide-resistant Gram-negative bacilli. *BMJ* 1976; **i**: 493–6.
45 Burton J. A placebo-controlled study to evaluate the efficacy of topical tetracycline and oral tetracycline in the treatment of mild to moderate acne. *J Int Med Res* 1990; **18**: 94–103.

Antifungal agents

Topical application of antifungal agents is used by dermatologists mainly for treatment of mild dermatophyte and yeast infections. Since management of specific infections is described elsewhere this chapter provides only a description of the antifungal agents available for topical application. Severe and extensive infections and infections of hair and nails are usually treated systemically (see Chapters 65 and 66). The most frequently prescribed topical antifungal agents are allylamines, imidazoles, morpholines and polyenes. Older compounds such as tolnaftate and undecylenate acid are mainly sold over the counter.

Allylamines

These inhibit fungal synthesis of ergosterol, an essential component of fungal cell membranes, by inhibiting squalene epoxidase. This also results in toxic accumulation of squalene within the organism, which is fungicidal. This class includes naftifine, butenafine (neither marketed in the UK) and terbinafine. The fungicidal nature of these compounds results in rapid response of dermatophyte infection to topical application. Naftifine and butenafine also possess anti-inflammatory activity. Terbinafine is active topically against pityriasis versicolor as well as against dermatophytes.

It is concerning that a strain of *Trichophyton rubrum* apparently resistant to squalene epoxidase inhibitors has been reported [1].

Imidazoles

This is a large group of compounds which includes bifonazole, clotrimazole, econazole, fenticonazole, ketoconazole, isoconazole, miconazole, oxiconazole, sulconazole, terconazole, tioconazole, sertaconazole and others. These have largely similar properties and act by inhibiting synthesis of ergosterol. They are fungistatic. They are active against a wide range of fungal organisms including *Candida* and *Pityrosporum* yeasts as well as dermatophytes. They also have potentially useful antibacterial properties and, at least *in vitro*, can suppress growth of *Staph. aureus* [2]. The range of formulations includes creams, powders, sprays, suspensions and nail lacquer.

There are also combined formulations available which contain imidazoles and corticosteroids. The precise role of these combined formulations is controversial. They can occasionally be useful to accelerate resolution of symptoms when infected skin is very inflamed and pruritic. However, it is also possible that they may impair the response to the antifungal agent [3], and the familiar hazards of topical corticosteroids include the potential to mask a persisting infection.

Morpholines

Amorolfine inhibits two separate stages in the synthesis of ergosterol and is fungicidal. It is marketed as a nail lacquer containing 5% amorolfine, for treatment of onychomycosis. An advantage of amorolfine in this application is that, in addition to efficacy against dermatophytes, it is also active against other filamentous fungi that cause onychomycosis, such as *Scytalidium* spp. and S*copulariopsis* spp. The water-resistant properties of the lacquer allow the convenience of once- or twice-weekly application. Twice-weekly application may be marginally more effective [4]. Cure rates are approximately 50% at 6 months. Amorolfine can act synergistically with other antifungal agents, including azoles and allylamines, with improved cure rates reported when topical amorolfine is combined with systemic itraconazole [5] or terbinafine for 3 months [6].

Polyenes

The important member of this group is nystatin—one of the earliest antifungal agents developed. It derives its name from the New York State health laboratory where it was discovered in the 1950s. Nystatin is a fungal metabolite with activity against *Candida albicans* and several other *Candida* spp. It damages the fungal cell membrane by binding irreversibly to ergosterol, an action which is fungistatic at low concentrations and fungicidal at high concentrations. It is not effective against dermatophytes. It is a safe and well-tolerated compound which is not significantly absorbed when taken orally or when used topically on skin and mucous membranes. Nystatin is available in a range of formulations including cream, ointment, oral suspension, lozenges and pessaries. There are also a range of creams and ointments containing combinations of nystatin with antiseptics, antibiotics and various potencies of corticosteroids.

Ciclopirox olamine [7]

This hydroxypyridone compound has a different mode of action to most other antifungal agents and does not directly inhibit sterol synthesis. It binds with high affinity to trivalent cations, such as Fe^{3+}, which are essential for the function of numerous enzymes, including cytochromes. Several metabolic pathways are likely to be disrupted by this process, including mitochondrial electron transport. It demonstrates activity against a broad spectrum of dermatophytes, yeasts and moulds including *Scytalidium* spp. and S*copulariopsis* spp. and is also effective against Gram-positive and Gram-negative bacteria including meticillin resistant *Staph. aureus*. Ciclopirox is commercially formulated in a variety of creams, lotions, shampoo, powder and as a nail lacquer, but most of these are not currently marketed in the UK.

Tolnaftate

This compound is available in a variety of formulations (creams, lotions, powder), generally sold over the counter for topical treatment of dermatophyte infections. It is a thiocarbamate derivative, chemically unrelated to other antifungal drugs, and is an inhibitor of squalene epoxidase. It is considered less effective than more recently developed agents but is superior to placebo [8].

Undecylenic acid

Undecylenic acid, a monounsaturated fatty acid, is largely used as an over-the-counter topical treatment for dermatophyte infection. In addition to its fungistatic activity, it has antiseptic and antiviral properties. Various formulations are produced including cream, ointment, paint, spray and powder. It is probably less effective than newer agents although it has proved superior to placebo and equivalent to tolnaftate in controlled trials [8,9]. Occasional cases of sensitization are reported.

Other topical antifungal agents

Whitfield's ointment, a combination of 6% benzoic acid and 3% salicylic acid, is effective in treatment of superficial dermatophyte infections. Studies in the tropics suggest that cure rates are quite acceptable when very low cost is a priority [10]. However this formulation is not very cosmetically acceptable.

The antiseptic properties of benzoyl peroxide have been put to use in treatment of dermatophyte infection and pityriasis versicolor, although this compound is irritant and bleaches clothing so some caution is required [11].

Zinc pyrithione 1% and selenium disulphide 2.5% are used in shampoos to treat dandruff and seborrhoeic dermatitis. Both compounds have also been shown in placebo-controlled trials to be effective in treatment of tinea versicolor in the same concentrations. Zinc pyrithione shampoo can be lathered over the affected skin for 5 min, then rinsed off, every day for 2 weeks [12]. Selenium sulphide has been shown to be effective used in the same way but applied for 10 min daily for 7 days [13]. Some irritation may develop.

Resorcinol (1,3 dihydroxybenzene) is an antiseptic agent and preservative which is also added to some shampoos to suppress dandruff by inhibition of pityrosporum yeasts.

Azelaic acid demonstrates antifungal properties and is discussed under the heading of depigmenting agents.

References

1 Mukherjee PK, Leidich SD, Isham N *et al*. Clinical *Trichophyton rubrum* strain exhibiting primary resistance to terbinafine. *Antimicrob Agents Chemother* 2003; **47**: 82–6.

2 Jones BM, Geary I, Lee ME, Duerden BI. Comparison of the in vitro activities of fenticonazole, other imidazoles, metronidazole, and tetracycline against organisms associated with bacterial vaginosis and skin infections. *Antimicrob Agents Chemother* 1989; **33**: 970–2.

3 Alston SJ, Cohen BA, Braun M. Persistent and recurrent tinea corporis in children treated with combination antifungal/corticosteroid agents. *Pediatrics* 2003; **111**: 201–3.

4 Reinel D, Clarke C. Comparative efficacy and safety of amorolfine nail lacquer 5% in onychomycosis, once-weekly versus twice-weekly. *Clin Exp Dermatol* 1992; **17** (Suppl. 1): 44–9.

5 Lecha M. Amorolfine and itraconazole combination for severe toenail onychomycosis; results of an open randomized trial in Spain. *Br J Dermatol* 2001; **145** (suppl 60): 21–6.

6 Baran R. Topical amorolfine for 15 months combined with 12 weeks of oral terbinafine, a cost-effective treatment for onychomycosis. *Br J Dermatol* 2001; **145** (suppl 60): 15–9.

7 Bohn M, Kraemer KT. Dermatopharmacology of ciclopirox nail lacquer topical solution 8% in the treatment of onychomycosis. *J Am Acad Dermatol* 2000; **43**: S55–69.

8 Battistini F, Cordero C, Urcuyo FG *et al*. The treatment of dermatophytoses of the glabrous skin: a comparison of undecylenic acid and its salt versus tolnaftate. *Int J Dermatol* 1983; **22**: 388–9.

9 Fuerst JF, Cox GF, Weaver SM, Duncan WC. Comparison between undecylenic acid and tolnaftate in the treatment of tinea pedis. *Cutis* 1980; **25**: 544–6, 549.

10 Gooskens V, Ponnighaus JM, Clayton Y *et al*. Treatment of superficial mycoses in the tropics: Whitfield's ointment versus clotrimazole. *Int J Dermatol* 1994; **33**: 738–42.

11 Kligman AM, Leyden JJ, Stewart R. New uses for benzoyl peroxide: a broad-spectrum antimicrobial agent. *Int J Dermatol* 1977; **16**: 413–7.

12 Fredriksson T, Faergemann J. Double-blind comparison of zinc-pyrithione shampoo and its shampoo base, in the treatment of tinea versicolor. *Cutis* 1981; **31**: 436–7.

13 Sanchez JL, Torres VM. Double-blind efficacy study of selenium sulfide in tinea versicolor. *J Am Acad Dermatol* 1984; **11**: 235–8.

Antihistamines

Topical antihistamines (e.g. diphenhydramine, mepyramine maleate, promethazine) are widely employed in non-prescription preparations as antipruritic agents. The efficacy of such preparations is questionable. Limited efficacy, combined with the marked potential for many antihistamines to sensitize when applied topically, has tended to deter dermatologists from using them.

Topical application of doxepin, a potent H_1 and H_2 receptor antagonist and anticholinergic agent, reduced the pruritus associated with atopic dermatitis [1] and other eczematous dermatoses such as lichen simplex [2] in placebo-controlled trials. Like other topical antihistamines, this compound may sensitize [3]. Systemic absorption may be significant, especially in children, and may give rise to sedation [1,2,4].

References

1 Drake LA, Fallon JD, Sober A. Doxepin Study Group. Relief of pruritus in patients with atopic dermatitis after treatment with topical doxepin cream. *J Am Acad Dermatol* 1994; **31**: 613–6.

2 Drake LA, Millikan LE. Doxepin Study Group. The antipruritic effect of 5% doxepin cream in patients with eczematous dermatitis. *Arch Dermatol* 1995; **131**: 1403–8.

3 Bonnel RA, La Grenade L, Karwoski CB, Beitz JG. Allergic contact dermatitis from topical doxepin: Food and Drug Administration's postmarketing surveillance experience. *J Am Acad Dermatol* 2003; **48**: 294–6.

4 Zell-Kanter M, Toerne TS, Spiegel K, Negrusz A. Doxepin toxicity in a child following topical administration. *Ann Pharmacother* 2000; **34**: 328–9.

Antiparasitic agents

The principles of treatment of lice infestations and scabies are discussed in Chapter 38. Insecticide resistance has emerged as a significant problem in the treatment of head lice [1] and may necessitate treatment with a second agent or by using non-pharmacological approaches.

Pyrethroids

Pyrethroids are highly effective [2,3] and are now probably the most widely used agents. These are insecticides which are neurotoxic to parasites. Permethrin 5% cream is a first-line treatment for scabies. It should be applied from the neck down for 12 h. The 5% 'dermal cream' for treatment of scabies should not be confused with the 1% 'creme rinse' marketed for treatment of head lice. This has caused treatment failure in scabies [4]. The creme rinse is applied to the scalp for 10 min to treat head lice. For pubic lice the 5% cream should be used as for scabies.

Phenothrin is another pyrethroid used for head and pubic lice. For head lice, formulations available include in an aqueous 0.5%

lotion (washed off after 12 h), an alcoholic 0.2% lotion (washed off after 2 h) and a 0.5% concentration in a mousse (washed off after 30 min). For pubic lice the aqueous lotion should be applied to the whole body for 12 h.

Whether treating head lice, pubic lice or scabies, two treatments at an interval of 1 week are generally recommended for both these agents.

Malathion

Malathion is an organophosphorus cholinesterase inhibitor which paralyses parasites. In treatment of scabies, a 0.5% aqueous lotion is applied to the skin for 24 h and repeated after a week. For head lice, 0.5% aqueous or alcoholic lotions can be applied for 12 h on three occasions at 3-day intervals. For crab lice, the aqueous preparation should be applied all over the body for 12 h and this should be repeated after 7 days.

Dimeticone

Dimeticone is a recently introduced agent for treatment of head lice, available as a 4% solution [5]. Two applications a week apart are recommended. Dimeticone is silicone-based and coats lice, possibly killing them by preventing them from excreting excess water. It has little activity against the eggs (nits), hence the need for a second treatment. However, it is not an insecticidal chemical and there should not be problems with resistance, which limits the use of conventional treatments for lice.

Other antiparasitic agents

Benzyl benzoate is also believed to be neurotoxic to parasites. It can be used as a scabicide in a 25% emulsion applied daily for 3 days. It is somewhat irritant. Carbaryl is another organophosphorus insecticide which can be used for head and pubic lice. It is available as 1% aqueous and 0.5% alcoholic lotions which are usually left on the skin for 12 h. A single application may be effective but is often repeated after 7 days. Gamma benzene hexachloride (lindane), used as a 1% lotion, is an effective scabicide although it has been withdrawn in the UK as a result of concern over systemic absorption and possible neurotoxicity [6]. It is applied for 12 h and this is sometimes repeated after a week. The risks seem small but are relatively greater in infants and young children and when multiple applications are used. Both topical and oral ivermectin have been successfully used for both scabies and head lice [7–9]. A 1% solution in propylene glycol applied twice with a 1-week interval has proved highly effective in scabies [10]. Crotamiton has weak scabicidal activity and is an antipruritic. It is often used as a follow-up treatment to other therapies.

References

1 Downs AM, Stafford KA, Hunt LP *et al*. Widespread insecticide resistance in head lice to the over-the-counter pediculocides in England, and the emergence of carbaryl resistance. *Br J Dermatol* 2002; **146**: 88–93.

2 Taplin D, Meinking TL. Permethrin. Sexually transmitted diseases. Advances in diagnosis and treatment. *Curr Probl Dermatol* 1996; **24**: 255–60.

3 Taplin D, Meinking TL, Porcelain SL *et al*. Permethrin 5% dermal cream: a new treatment for scabies. *J Am Acad Dermatol* 1986; **15**: 995–1001.

4 Cox NH. Permethrin for scabies: importance of the correct formulation. *BMJ* 2000; **320**: 37–8.

5 Burgess IF, Brown CM, Lee PN. Treatment of head louse infestation with 4% dimeticone lotion: randomised controlled equivalence trial. *BMJ* 2005; **330**: 1423.

6 Franz TJ, Lehman PA, Franz SF *et al*. Comparative percutaneous absorption of lindane and permethrin. *Arch Dermatol* 1996; **132**: 901–5.

7 Youssef MY, Sadaka HA, Eissa MM *et al*. Topical application of ivermectin for human ectoparasites. *Am J Trop Med Hyg* 1995; **53**: 652–3.

8 Glaziou P, Cartel JL, Alzeiu P *et al*. Comparison of ivermectin and benzyl benzoate for treatment of scabies. *Trop Med Parasitol* 1993; **44**: 331–2.

9 Glaziou P, Nyguyen LN, Moulia-Pelat JP *et al*. Efficacy of ivermectin for the treatment of head lice (Pediculosis capitis). *Trop Med Parasitol* 1994; **45**: 253–4.

10 Victoria J, Trujillo R. Topical ivermectin: a new successful treatment for scabies. *Pediatr Dermatol* 2001; **18**: 63–5.

Antiseptics

This term is used for a very wide variety of agents used topically for skin cleansing and treatment of infection. Some of these are described under other headings (see, for example, astringents). Antiseptics are distinguished from disinfectants, which are used to clean and sterilize inanimate materials, surfaces, instruments, etc. Antiseptics, by their nature, exhibit broad-spectrum antimicrobial efficacy but some organisms tend to be more sensitive than others. Gram-positive bacteria such as *Staph. aureus* tend to be more sensitive than Gram-negative bacteria. *Pseudomonas aeruginosa* is among the most resistant Gram-negative organisms. Bacterial spores (e.g. those of *Clostridium difficile*) are relatively protected. Viruses, fungi and mycobacteria often require higher concentrations and prions are extremely resistant to antiseptics.

Alcohols (especially **isopropyl alcohol**, **ethanol** and ***n*-propanol**) are widely used for skin cleansing. These are rapidly acting agents with a broad spectrum of antimicrobial activity which denature cell membranes and proteins.

Aldehydes (formaldehyde, glutaraldehyde) are also broad-spectrum antimicrobials. These compounds are used more often for sterilizing equipment than for treatment of the skin as they have marked potential to sensitize. Formaldehyde-releasing agents such as Quaternium 15 are widely used as preservatives in cosmetics and shampoos.

Cetrimide, like **benzalkonium chloride**, is a quaternary ammonium, cationic surfactant. It has a wide spectrum of activity against bacteria and fungi. It has many applications including use in proprietary antiseptic creams and as a constituent of shampoos for treating seborrhoeic dermatitis.

Chlorhexidine is one of the most frequently used antiseptics, especially in hand cleansing products and as a skin cleanser prior to surgery. The ability of chlorhexidine to persist and remain active in the skin makes it especially useful for these purposes. It is most active at neutral or alkaline pH. It exhibits a wide spectrum of antibacterial activity, by multiple mechanisms including disruption of membrane structure and function. Activity against mycobacteria and viruses is rather limited.

Chloroxylenol (4-chloro-3,5-dimethylphenol) is a bactericidal compound that has been used as a domestic antiseptic and disinfectant for many years. It is not effective against *Pseudomonas aeruginosa*.

Hydrogen peroxide (H_2O_2) has long been used as an antiseptic. It is a colourless liquid available in various concentrations and also in cream formulations. H_2O_2 demonstrates broad-spectrum

efficacy against bacteria, viruses and yeasts, with somewhat greater activity against Gram-positive than Gram-negative bacteria. H_2O_2 acts as an oxidant by producing hydroxyl free radicals ($^{\bullet}OH$) which damage various cell components, including lipids, proteins, and DNA.

Iodine and iodine releasing agents are rapidly acting, broad-spectrum antimicrobial agents demonstrating cidal activity against Gram-positive and Gram-negative bacteria, mycobacteria, viruses, fungi and yeasts. Multiple mechanisms of action include inactivation of numerous proteins, nucleotides and lipids. Iodine is available in a range of aqueous, and alcoholic solutions (tinctures) which generally contain sodium and/or potassium iodide in addition to iodine. Free molecular iodine (I_2) is the most potent and rapidly acting microbicide. To reduce the irritancy, staining and risk of toxicity, formulations containing 'iodine releasing' compounds (iodophores) have been developed and are now more widely used than simple solutions. Examples of these include povidone iodine, cadexomer iodine and poloxamer iodine. Iodophores are less potent as antimicrobials than iodine solutions.

Iodine toxicity seems to be unusual when iodine-releasing compounds are used but both hypothyroidism and hyperthyroidism, as well as renal failure and metabolic acidosis, are among the manifestations of systemic toxicity that have occasionally been reported with use of povidone iodine [1]. Systemic exposure is related to the area treated, so patients with extensive burns are at particular risk. Iodine is excreted largely by the kidneys and the risk of accumulation is higher in the presence of pre-existing renal impairment. Prolonged treatment is not recommended for patients with thyroid dysfunction, including endemic goitre. Hypersensitivity reactions can also occur. Chlorine-releasing agents such as sodium hypochlorite have a similarly broad spectrum of action but are used mainly as disinfectants.

Triclosan, triclocarban and **hexachlorophene** (hexachlorophane) are bisphenol compounds which are most active against Gram-positive bacteria. They probably act mainly by impairing the cytoplasmic membrane.

Reference

1 Dela Cruz F, Harper Brown D. Iodine absorption after topical administration. *West J Med* 1987; **146**: 43–5.

Antiviral agents

There are few topical agents available with specific antiviral activity although many antiseptics, especially povidone iodine [1,2], are known to inactivate viruses. The use of imiquimod, 5-fluorouracil and podophyllin in treatment of viral warts is discussed elsewhere in this chapter. Aciclovir, penciclovir and idoxuridine are used topically in management of herpes simplex and the latter is also used for herpes zoster.

Aciclovir and penciclovir

Topical aciclovir is used in the treatment of primary and recurrent herpes simplex type I and II [3]. The drug is a nucleoside analogue and is phosphorylated by a viral thymidine kinase to an active form which inhibits effective replication of viral DNA. A recommended regimen is application of 5% aciclovir cream at 4-hourly intervals for 5 days. Both labial and genital lesions can respond. Severe episodes are best treated systemically. Some protective effect may be obtained by regular prophylactic application of aciclovir cream [4]. Penciclovir has a similar mechanism of action. This is applied as a 1% cream 2-hourly for 4 days. Both of these agents should be applied as early as possible in the course of the episode.

Idoxuridine

Idoxuridine was the first agent to become available for topical treatment of herpes infections. It is a thymidine analogue which inhibits viral DNA replication. It is effective in reducing symptoms in treatment of herpes simplex [5] and zoster infections [6] applied topically at concentrations of 5–15%. A 5% solution in dimethylsulphoxide can be applied to affected areas of skin with a brush four times daily for 4 days. At lower concentrations, idoxuridine appears effective in treatment of genital warts [7]. Topical use of idoxuridine can occasionally sensitize [8].

References

1 Kawana R, Kitamura T, Nakagomi O, Inactivation of human viruses by povidone-iodine in comparison with other antiseptics. *Dermatology* 1997; **195** (Suppl. 2): 29–35.

2 Simmons A. An open-label study conducted to evaluate the efficacy of Betadine cold sore paint. *Dermatology* 1997; **195** (Suppl. 2): 85–8.

3 Wagstaff AJ, Faulds D, Goa KL. Aciclovir. A reappraisal of its antiviral activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1994; **47**: 153–205.

4 Gibson JR, Klaber MR, Harvey SG *et al*. Prophylaxis against herpes labialis with acyclovir cream—a placebo-controlled study. *Dermatologica* 1986; **172**: 104–7.

5 Spruance SL, Stewart JC, Freeman DJ *et al*. Early application of topical 15% idoxuridine in dimethyl sulfoxide shortens the course of herpes simplex labialis: a multicenter placebo-controlled trial. *J Infect Dis* 1990; **161**: 191–7.

6 Burton WJ, Gould PW, Hursthouse MW *et al*. A multicentre trial of Zostrum (5 percent idoxuridine in dimethyl sulphoxide) in herpes zoster. *N Z Med J* 1981; **94**: 384–6.

7 Happonen HP, Lassus A, Santalahti J *et al*. Topical idoxuridine for treatment of genital warts in males. A double-blind comparative study of 0.25% and 0.5% cream. *Genitourin Med* 1990; **66**: 254–6.

8 Thormann J, Wildenhoff KE. Contact allergy to idoxuridine. Sensitization following treatment of herpes zoster. *Contact Dermatitis* 1980; **6**: 170–1.

Astringents

Astringents are compounds used to reduce exudation by precipitation of protein. Those most frequently employed are aqueous solutions of potassium permanganate, aluminium acetate and silver nitrate.

Potassium permanganate

This is an oxidizing agent with antiseptic and fungicidal activity. It is used at concentrations of 1:4000 to 1:25000. It can be applied as a rinse or soak or as a bath. A bath containing 1:25000 $KMnO_4$ can be prepared by adding 2 g to each 50 L of water. The astringent and antiseptic properties of this solution are invaluable in treatment of very acute exudative eczematous dermatoses. It is messy however, and stains the skin and other materials.

Aluminium acetate

Also known as Burow's solution, this astringent is also mildly antiseptic and has the advantage of not causing the staining asso-

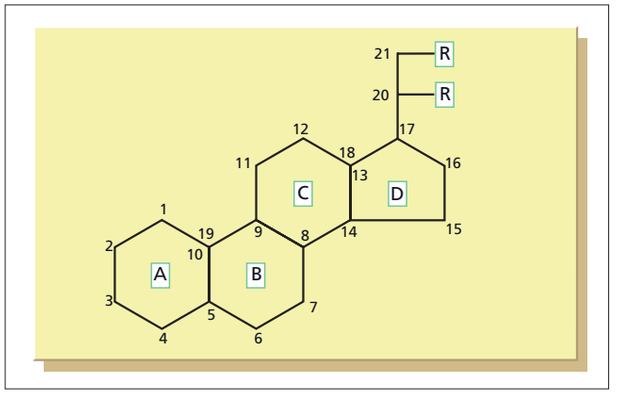


Fig. 73.2 The configuration of the basic corticosteroid structure.

ciated with potassium permanganate. The solution is prepared using aluminium sulphate, acetic acid, tartaric acid and calcium carbonate. The solution contains 5% aluminium acetate and is diluted 1:10 to 1:40 with water for use in soaks, rinses or wet dressings.

Silver nitrate

In concentrations 0.1–0.5% silver nitrate is an effective astringent and antiseptic often used in management of leg ulcers and burns. Higher concentrations may cause pain. Silver nitrate causes staining of skin and most other materials.

Corticosteroids

Topical corticosteroids have now been in use for treating skin disease for over half a century, since the introduction of 'compound F' or hydrocortisone (cortisol) in 1952 [1]. Their impact has been immense. In addition to becoming the mainstay of treatment in eczematous dermatoses, they are used, either regularly or occasionally, in the management of most inflammatory skin diseases.

During the decades since hydrocortisone was introduced, numerous analogues have been developed from this molecule. The basic structure of the steroid moiety is shown in Fig. 73.2. Modifications to both the ring structure and the side chains have increased specificity of action, increased penetration, dramatically increased potency and, to some degree, reduced side effects.

Hydrocortisone has considerable mineralocorticoid activity, which can be reduced by methylation or hydroxylation at position 16. Esterification at positions 16, 17 and 21 increases lipid solubility, promoting greater penetration of the stratum corneum barrier. This strategy leads to the development of highly lipophilic compounds such as betamethasone dipropionate and triamcinolone acetonide. Fluorination of the 9α position, the introduction of an unsaturated bond between the first two carbon atoms and changes in the nature of the side chains, particularly in the 21 position, brought about enhanced glucocortioid activity [2]. Fluticasone propionate has a fluoride thioester carbothiate at C21, a propionate ester at C17 and a methyl group at C16; this molecule is inactivated rapidly on first passage through the liver, conferring greater systemic safety. Similar properties are demonstrated by methylprednisolone aceponate and mometasone furoate, whilst systemic exposure to prednicarbate is minimized by metabolism within the skin.

In view of the great differences in potency between different corticosteroids it is essential for the dermatologist to be able to rank or classify them by potency in order to predict the response and possible adverse effects. This classification ideally needs to take account not only of the relative potency of the molecules, but also factors such as the concentration and the nature of the vehicle which can significantly alter penetration.

Perhaps the ideal approach would be a large series of clinical trials to compare clinical efficacy of all the available corticosteroids. However, even if this were possible, it is by no means certain that the same ranking would be obtained in two different diseases. Many different approaches have therefore been developed to compare potencies of topical corticosteroids. Some of these employ various animal models of inflammation such as the implantation of a pellet of cotton into a subcutaneous pocket in rats. The potency of the antimitotic action of steroids can be assayed by applying the compound to the skin of hairless mice and measuring the level of suppression of the mitotic index after tape stripping [3]. However, the most widely used approach has been the vasoconstrictor assay; this depends upon the vasoconstricting property of glucocorticosteroids, apparent and measurable as pallor of the skin. This assay has the advantage of using human subjects and evaluates not only the intrinsic potency of the molecule but also its ability to penetrate the stratum corneum from a specific vehicle, and even takes into account certain aspects of the removal and metabolism of the drug [4,5]. The degree of pallor produced following application of a compound to the skin seems to correlate fairly well with clinical potency and with the potential for side effects such as atrophogenicity. Typically, pallor reaches a peak at around 9–12 h after application and then falls, initially fairly rapidly over the next 10 h, then more slowly [6]. The total duration of action varies considerably between different compounds.

The various classifications adopted to provide a guide to the relative potencies of different compounds are substantially based on the vasoconstrictor assay but also take into account other evidence such as comparative clinical trials. The British National Formulary employs a four-point scale: mild, moderate, potent and very potent. In the US, topical corticosteroids are ranked using a scale ranging from class 1 (super potent) to class 7 (mild).

Mechanism of action

Corticosteroids diffuse through the stratum corneum barrier and through cell membranes to reach the cytoplasm of keratinocytes and other cells present in the epidermis and dermis. Diffusion through the stratum corneum is generally considered to be the rate-limiting step in delivery of the drug. In the cytoplasm they bind to a specific receptor, the glucocorticoid receptor alpha (GRα). Clinical potency of corticosteroids seems to be strongly related to receptor binding affinity, which is very sensitive to certain structural changes in the steroid. Thus, the introduction of a double-bond in the A ring, esterification in the 17α position, and fluorination at position 9α increase binding affinity, whereas

esterification in the 21 position reduces binding affinity (Fig. 73.2).

The glucocorticoid receptor GRα is a protein of molecular weight 330 kD, and is a member of the same receptor superfamily as receptors for other classes of steroid, thyroid hormone, calcitriol, etc. When not associated with a steroid ligand, this receptor is found in the cytoplasm as a component of a heterotetrameric structure containing two molecules of the 90-kD heat shock protein hsp90, and a 59-kD protein p59. Interestingly, p59 seems to belong to the family of immunophilins that interact with other immunosuppressant drugs. The binding of the receptor to its ligand results in activation of the receptor which dissociates from the other components of the tetrameric complex [7]. The ligand-bound receptor then enters the nuclear compartment and interacts with specific response elements on the genome, glucocorticoid response elements (GREs). This modulates transcription of numerous genes. In addition the ligand-bound receptor can inhibit, directly or indirectly, the activity of other transcription factors including NFκB, AP-1 and NFAT [8]. These interactions lead to changes in the expression of a wide range of genes, resulting in diverse cellular effects which include suppression of the production of inflammatory cytokines, inhibition of T-cell activation, changes in the function of endothelial cells, granulocytes, mast cells and fibroblasts, and inhibition of proliferation. Part of the anti-inflammatory activity of corticosteroids may be explained by their ability to induce synthesis of lipocortin [9,10], a family of glycoproteins which regulate the activity of phospholipase A_2. This enzyme affects the production of arachidonic acid, the precursor for leukotrienes and prostaglandins.

The transcriptional activity of the steroid receptor seems likely to be regulated by an alternative isoform of the receptor known as glucocorticoid receptor β (GRβ), formed by alternative splicing. GRβ is an endogenous inhibitor of glucocorticoid action which does not bind steroid ligands but competes with ligand bound receptor for binding to GREs [11]. Staphylococcal superantigen can upregulate expression of GRβ [12], providing a potential mechanism by which these bacteria might induce corticosteroid resistance.

Side effects of topical corticosteroids

The potential side effects of topical corticosteroids are significant but must be kept in proportion. When these compounds are prescribed appropriately they can be of enormous benefit and clinically significant side effects are rare, especially in the short term (over a few days or weeks). Dermatologists have been very successful in making pharmacists, general practitioners and the public aware of the hazards. Patients are now frequently encountered whose dermatosis requires potent corticosteroids but who are denied effective treatment by the inappropriate prescription of hydrocortisone or simple emollients. Others apply the medication so 'sparingly' that it is completely ineffective. At times the fear of using topical corticosteroids can be quite out of proportion to the likelihood of side effects developing. This situation is often termed 'steroid phobia'.

With the exception of structural changes introduced to minimize systemic exposure to topical corticosteroids, it has proved difficult to separate the various unwanted actions of these compounds from those which are so desirable. The side effects of topical steroids are directly related to their potencies. It is often appropriate to use more than one compound simultaneously so that mild or moderate steroids are used on areas where they are often effective, such as the face, whilst the more potent preparations are used only where they are required.

Local effects

The most common side effects are localized to application sites. The most worrying is cutaneous atrophy since this may become permanent. Other problems include the development of contact allergy and the risk of promoting infection. When treating the face there is the additional risk of inducing acneiform eruptions. There are also potential risks from absorption and systemic exposure to the steroid.

Atrophic changes affect both the epidermis and the dermis. The epidermis becomes thinned. This is initially due to a reduction in the size of epidermal cells, which reflects a reduction in metabolic activity [13]. After intense or prolonged steroid exposure the number of cell layers is reduced, the stratum granulosum disappears and the stratum corneum is thinned [14–16]. There is suppression of many aspects of cell metabolism, including the synthesis of stratum corneum lipids, synthesis of keratohyalin granules and the formation of corneodesmosomes required for structural integrity of the stratum corneum [17]. Inhibition of melanocyte function may develop, giving rise to localized hypopigmentation. This complication is most likely to occur with steroids applied under occlusion or with intracutaneous steroid injections [18,19].

In the dermis, topical corticosteroids induce resorption of mucopolysaccharide ground substance. This is likely to explain the rapid development of thinning which reaches approximately 15% reduction in skin thickness after 3 weeks of treatment under occlusion with 0.1% betamethasone valerate [20]. Collagen synthesis is suppressed within 3 days of treatment with this compound [21]. Even mild corticosteroids, such as hydrocortisone, have been shown to inhibit collagen synthesis [22,23]. In a study in which betamethasone valerate was applied for 3 days there was still significant inhibition of collagen synthesis 2 weeks after treatment was discontinued [24]. When steroid exposure persists, thinning becomes clinically evident and fragility and striae may develop. The loss of connective tissue support for the dermal vasculature results in erythema, telangiectasia and purpura. With long-term use of potent preparations these atrophic changes can become irreversible (Figs. 73.3 and 73.4). The areas most vulnerable to developing atrophy are those where the skin is already relatively thin, including the flexures and especially the face. In general, potent steroids should be used on the face only when treating severe dermatoses such as chronic discoid lupus erythematosus.

Contact allergy may develop to corticosteroids as well as to preservatives and other components of the vehicle. Contact sensitivity to hydrocortisone was first reported in 1959 but was initially considered a rare problem [25]. It is now clear that this is, in fact, a common event. In a large series of patients who were patch tested, 4.9% yielded positive results to one or more corticosteroids



Fig. 73.3 Atrophy and striae induced by topical steroids.



Fig. 73.4 Permanent atrophy induced by topical steroids.

[26]. Tixocortol pivalate, considered the best patch test reagent for screening, was positive in just over 90% of these. The most frequent sensitizers in this series were hydrocortisone, budesonide and hydrocortisone butyrate. Sensitivity to more than one topical corticosteroid is common and four groups have been identified within which cross-reactivity is most likely to occur (Table 73.6) [27]. Reactivation of contact dermatitis after inhalation of a corticosteroid may also be under-recognized [28].

Caution is required when applying topical corticosteroids in the presence of infection as there is a risk of exacerbation. Clinically unequivocal bacterial superinfection of eczema is usually treated prior to use of topical corticosteroids. However, there is evidence that colonization with *Staph. aureus* can be reduced by improving the condition of the skin with potent or very potent topical corticosteroid treatment [29,30]. It is advisable to avoid the use of topical corticosteroids, whenever possible, in the presence of active viral infection including lesions of herpes simplex, viral warts or molluscum contagiosum. When dermatophyte infections are inadvertently treated with corticosteroid the symptoms and signs may transiently improve, giving rise to the situation known as tinea incognito (Fig. 73.5). Scabies presents a similar trap, as the pruritus can be improved by topical corticosteroids whilst the infestation persists unless a scabicidal treatment is also applied. However, topical corticosteroids are invaluable for treating the eczema associated with scabies. Infantile gluteal granuloma (Chapter 17) is found only in infants who wear napkins (diapers) and is often associated with the use of topical corticosteroids. Impairment of the immune response to *Candida* by the steroids has been suggested as the cause [31].

Table 73.6 Groups of topical corticosteroids within which cross-sensitization is most likely to occur [27].

Group A	**Group C**
Cloprednol	Betamethasone
Cortisone	Betamethasone sodium phosphate
Cortisone acetate	Dexamethasone
Fludrocortisone	Dexamethasone sodium phosphate
Hydrocortisone	Fluocortolone
Hydrocortisone acetate	
Methylprednisolone acetate	**Group D**
Prednisolone	Alclometasone dipropionate
Prednisolone acetate	Betamethasone dipropionate
Prednisone	Betamethasone valerate
Tixocortol pivalate	Clobetasol-17-propionate
	Clobetasone-17-butyrate
Group B	Flucortolone caproate
Amcinonide	Flucortolone pivalate
Budesonide	Fluprednidene acetate
Desonide	Hydrocortisone-17-butyrate
Fluocinolone acetonide	Hydrocortisone-17-valerate
Fluocinonide	
Halcinonide	
Triamcinolone acetonide	
Triamcinolone alcohol	



Fig. 73.5 Tinea incognito. Signs of dermatophyte infection are partly suppressed by treatment with a potent topical steroid.

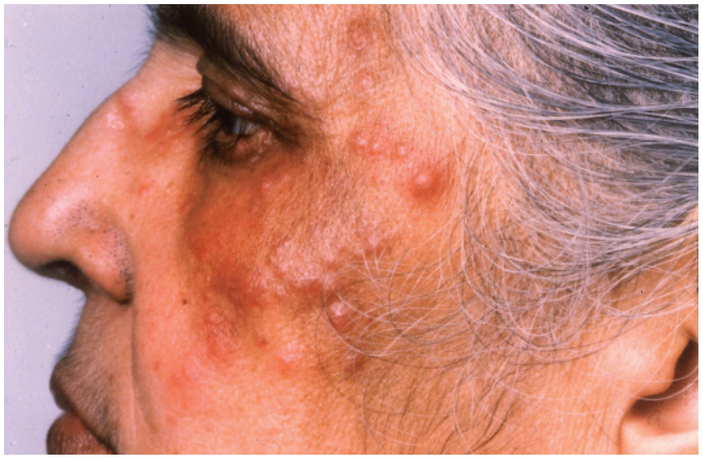


Fig. 73.6 Steroid rosacea.



Fig. 73.7 Perioral dermatitis induced by a potent topical steroid.

The use of topical corticosteroids on the face can result in eruptions resembling rosacea (Fig. 73.6) and perioral dermatitis (Fig. 73.7) (see Chapter 43). Eruptions of inflammatory papules may also develop around the eyes and have been termed periocular dermatitis [32]. On other occasions, an eruption more closely resembling acne vulgaris, comprising inflammatory papules and pustules as well as comedones, may develop in treated areas of skin, usually on the face or upper trunk. Comedones have also been induced in perianal skin by the application of potent steroids [33]. The mechanisms involved in these eruptions are not well understood.

It is possible that the use of topical corticosteroids on the eyelids and periorbital skin can result in some exposure of the eye to the steroid. The use of corticosteroid eye drops is known to raise intraocular pressure, increase risk of cataract formation and aggravate infections, especially herpes simplex. There have been only occasional reports of such ocular complications arising from the use of topical steroids applied around the eyes to treat skin disease [34–36]. Glaucoma has also been reported in a patient regularly treating hand eczema with betamethasone valerate at night, presumably resulting from inadvertent contamination of the eyes with the steroid [37]. These scant reports should be offset against the benefit of treating periocular skin disease, especially atopic dermatitis which is associated with keratoconus, probably as a result of frequent rubbing around the eyes [38].

Locally applied corticosteroids have been demonstrated to impair wound healing and re-epithelialization in a variety of animal and human models [39–41].

The question of whether tachyphylaxis develops during continued treatment with corticosterods remains controversial. It is certainly common for patients to report that a topical corticosteroid which was highly effective during the first few days of application has subsequently lost efficacy. On occasions, withdrawal of corticosteroids is followed by a flare of disease. The hypothesis that these phenomena are due to tachyphylaxis is supported by data from vasoconstrictor assays showing that successive applications of topical corticosteroids are associated with a decreasing response [42]. Furthermore, inhibitory effects on epidermal cell proliferation decreased during repeated administration of topical corticosteroids to hairless mice [43].

However, tachyphylaxis has not been shown to occur in clinical trials of corticosteroids in treatment of atopic dermatitis or psoriasis. It has therefore been proposed that patients report that the effect of the corticosteroid is diminishing when the underlying disease activity is increasing. Physicians observing patients intermittently may mistake stable disease activity for a failure to improve, even when there has been improvement from baseline, and may interpret this as tachyphylaxis. In a survey of dermatologists with 70 respondents, 57% believed that tachyphylaxis occurred within 8 weeks of initiating treatment of chronic plaque psoriasis with a potent corticosteroid. When this was put to the test in a clinical trial of 12 weeks' treatment duration, tachyphylaxis was not observed [44].

Rebound phenomena when topical corticosteroids are withdrawn have principally been of concern in the management of psoriasis. In several cases, withdrawal of treatment with potent or very potent corticosteroids has been followed by the eruption of severe generalized pustular psoriasis. This seems to have been especially likely to happen after potent or very potent corticosteroids have been used in large quantities or applied under occlusion [45]. In these cases it is likely that significant systemic exposure to the steroid was occurring and this was consequently withdrawn at the same time. The risk of this happening when unoccluded treatment with topical corticosteroids is used for chronic plaque psoriasis of moderate severity and disease extent is clearly very small as this treatment has been so widely used, especially in the US, and generalized pustular psoriasis remains rare. Nonetheless, this phenomenon has resulted in a general reluctance of dermatologists in the UK to rely on topical steroids in the treatment of psoriasis vulgaris and this approach has the undoubted benefit of sparing patients other side effects such as cutaneous atrophy.

Vascular effects of corticosteroids include prompt vasoconstriction of the superficial small vessels, followed by a phase of rebound vasodilatation. After prolonged treatment the vasodilatation may

become fixed and more conspicuous as a result of dermal and epidermal atrophy [46].

Systemic effects

Inhibition of the pituitary–adrenal axis by excessive application of moderately potent topical steroids or by relatively modest use of stronger steroids is well documented [47]. Temporary reversible suppression was seen after using 49 g of superpotent steroids per week for 2 weeks [48] in eight out of 40 patients, and similar results were seen in two further studies [49,50]. Significant suppression was reported in three patients using less than 50 g/week [51]. Recommended weekly dosage is less than 50 g of superpotent steroids or 100 g of potent steroids. In addition, prolonged usage at this level is best avoided. Children and babies have a high ratio of surface area to body volume and are more vulnerable to pituitary–adrenal suppression as a result of systemic absorption. Even hydrocortisone applied topically may suppress the adrenocortical response in some children [52]. Cushingoid features may be seen in infants inappropriately treated [53]. Severe medical problems are fortunately rare, despite alarmingly abnormal biochemical parameters.

Vehicles and formulations

There are a large range of topical formulations of corticosteroids on the market. At first glance this may seem more than necessary but it is undoubtedly helpful to have a range of compounds available in a range of formulations. It is clearly important to be able to adjust the potency of the steroid being used so that the least potent compound which is effective can be employed at each site and at each stage in the progression of the dermatosis. It is necessary to be able to avoid corticosteroids to which patients are known or suspected to be sensitized. It is also helpful to have a range of formulations for each compound. Thus, ointments are helpful when eczema is dry, whilst creams are more effective if the eruption is moist or exudative. Lotions, gels, or a mousse formulation are useful for the scalp. When the distribution is limited, as is often the case in lichen simplex chronicus or prurigo, the use of a steroid impregnated tape will simultaneously prevent scratching and increase drug penetration by effective occlusion [54].

Several antimicrobial agents are commercially formulated in combination with topical steroids including clioquinol, clotrimazole, fusidic acid, miconazole, neomycin and nystatin. These compound formulations are the subject of some controversy. They can be helpful when there is a clear indication for each constituent but are probably used more often when the diagnosis is unclear in the hope of 'covering all the possibilities'. The latter approach is not recommended. Disadvantages include the risks of obscuring the diagnosis, promoting development of microbial resistance to antibiotics and sensitization of patients to antimicrobial agents which may then be impossible to use topically or systemically in the future. The aminoglycosides, including neomycin, carry a particularly high risk of sensitization [55].

The case for use of these combinations is much stronger in the treatment of eczemas with evidence of secondary infection, although many dermatologists still prefer to give an antibiotic systemically. It seems very likely that some cases of atopic dermatitis are exacerbated by the presence of *Staph. aureus* on the skin. Superantigen production by these bacteria may play a role in this exacerbation of the disease [56] and may also have the effect of reducing sensitivity to corticosteroids [12].

There is also a special case for combining clioquinol with topical steroids in treatment of nickel dermatitis. This antiseptic is a potent chelating agent which can effectively inactivate nickel [57].

There are also commercially developed formulations combining corticosteroids with other active constituents. Mixtures containing tar, salicylic acid or calcipotriol can be useful in treatment of psoriasis. As in the case of antimicrobial agents, it is important that these compounds should only be used when there is a clear indication for each constituent and potent corticosteroids should only be used when they are really necessary.

Many dermatologists have found it useful to create their own formulations by dilution of proprietary products or addition of other medicaments such as tar and salicylic acid. There are some disadvantages to these practices. The stability of the steroid in a different formulation is unpredictable [58]. Changes in the vehicle may also alter levels of steroid penetration into the skin and systemic absorption [59]. In the UK, many of these mixtures and unlicensed topical agents (chosen according to their perceived need by dermatologists) are made in specific manufacturing units, under the auspices of the NHS Medicines Manufacturing Board; they are therefore made to commercial standards, and issues of stability and shelf-life are being investigated [60].

Occlusion and topical steroids

The penetration of a topical corticosteroid can be greatly increased by occlusion using polythene film or gloves, or by using hydrocolloid dressings [61]. Polythene gloves are most easily used overnight, although they are uncomfortable, especially in warm weather. A similar occlusive effect is obtained when a steroid is covered by paste bandages and by the use of wet wrap bandaging in treatment of atopic dermatitis. Using corticosteroids in this way will undoubtedly increase adverse as well as beneficial effects. However, judicious use of occlusion can be an invaluable strategy in the management of pompholyx, a refractory plaque of psoriasis on the leg, or a patch of lichen simplex. The incorporation of a corticosteroid such as fludroxycortide (flurandrenolone) into the adhesive of a plastic tape provides another effective method of using occlusion.

Whole-body occlusion of corticosteroids was formerly used, but adverse effects were common so this has fallen out of favour.

Intralesional steroids

Recalcitrant dermatoses (e.g. alopecia areata, keloid scars, lichen simplex, nodular prurigo) may respond to injection of steroid into the lesions. Triamcinolone is often used, but dermal atrophy and leukoderma may occur.

Indications for topical corticosteroids

The anti-inflammatory, immunosuppressant and antiproliferative properties of corticosteroids find numerous applications in dermatology, which are considered in more detail in the relevant

Table 73.7 Indications for topical corticosteroids, potency of preparations generally employed (M = mild, Mod = moderate, P = potent, VP = very potent) and level of evidence [62] available for efficacy (A = double-blind trial, B = clinical trial, C = small trial or >20 cases reported, D at least 5 cases reported to respond, E < 5 cases reported). Ocl (occlusion) and I/L (intralesional injection) indicate that these approaches have been reported to be useful in selected cases.

Indication	Potency	Evidence grade	Occlusion and intralesional use
Actinic prurigo	P, VP	C	
Alopecia areata	P, VP	B	Ocl, I/L
Aphthous stomatitis	P	A	
Atopic eczema	M, Mod, P	A	
Bullous pemphigoid	P, VP	B	
Chronic actinic dermatitis	Mod, P	C	
Contact allergic dermatitis	Mod, P	B	
Contact irritant dermatitis	M, Mod, P, VP	C	
Cutaneous T-cell lymphoma	Mod, P	B	
Discoid eczema	P, VP	C	
Discoid lupus	P, VP	B	I/L
Geographical tongue	P	C	
Granuloma annulare	P, VP	E	Ocl, I/L
Granuloma faciale	Mod, P	E	Ocl, I/L
Grover's disease	P	D	
Hailey–Hailey disease	M, Mod, P	C	
Juvenile plantar dermatosis	Mod, P	C	
Lichen nitidus	P	E	
Lichen planopilaris	P, VP	D	I/L
Lichen planus	P, VP	C	Ocl, I/L
Lichen sclerosus	P, VP	A	
Lichen simplex	P, VP	A	Ocl, I/L
Lymphocytoma cutis	P	E	I/L
Lymphomatoid papulosis	P, VP	E	
Morphoea	P	E	I/L
Necrobiosis lipoidica	P	D	Ocl, I/L
Pemphigoid gestationis	P, VP	C	
Pityriasis rosea	Mod, P	E	
Polymorphic eruption of pregnancy	P	B	
Pompholyx	P, VP	A	Ocl
Pretibial myxoedema	P	C	Ocl
Prurigo nodularis	P, VP	E	Ocl, IL
Pruritus ani	M, Mod	B	I/L
Pruritus vulvae	Mod, P	B	
Psoriasis	M, Mod, P, VP	A	Ocl
Pyoderma gangrenosum	P, VP	D	
Sarcoidosis	P, VP	C	Ocl, I/L
Scleromyxoedema	P	D	Ocl, I/L
Seborrhoeic eczema	M, Mod	A	
Strawberry haemangioma	VP	D	
Subacute cutaneous lupus	Mod, P	E	
Subcorneal pustular dermatosis	Mod, P	D	
Sweet's syndrome	P	C	I/L
Urticaria pigmentosa	P, VP	C	Ocl
Vitiligo	P, VP	A	

sections of this text. Table 73.7 lists some of these applications, together with the potencies of compounds which are most often used and the level of evidence available to support their efficacy [62].

References

1 Sulzberger MB, Witten VH. The effect of topically applied compound F in selected dermatoses. *J Invest Dermatol* 1952; **19**: 101–2.

2 Carson-Jurica MA, Schrader WT, O'Malley BW. Steroid receptor family: structure and functions. *Endocr Rev* 1990; **11**: 201–20.

3 Marks R, Pongsehirun D, Saylan T. A method for the assay of topical corticosteroids. *Br J Dermatol* 1973; **88**: 69–74.

4 McKenzie AW, Stoughton RB. Method for comparing percutaneous absorption of steroids. *Arch Dermatol* 1962; **86**: 608–10.

5 Barry BW, Woodford R. Activity and bioavailability of topical steroids. In vivo/in vitro correlations for the vasoconstrictor test. *J Clin Pharm* 1978; **3**: 43–65.

6 Barry BW, Woodford R. Comparative bio-availability and activity of proprietary topical corticosteroid preparations: vasoconstrictor assays on thirty-one ointments. *Br J Dermatol* 1975; **93**: 563–71.
7 Gehring U. The structure of glucocorticoid receptors. *J Steroid Biochem Molec Biol* 1993; **45**: 183–90.
8 Almawi WY, Melemedjian OK. Molecular mechanisms of glucocorticoid antiproliferative effects: antagonism of transcription factor activity by glucocorticoid receptor. *J Leukoc Biol* 2002; **71**: 9–15.
9 Blackwell GJ, Canuccio R, Di Rosa M *et al*. Macrocortin: a polypeptide causing the anti-phospholipase effect of glucocorticoids. *Nature* 1980; **287**: 147–9.
10 Hammarstrom S, Hamberg M, Duell EA *et al*. Glucocorticoid in inflammatory proliferative skin disease reduces arachidonic and hydroxyeicosatetraenoic acids. *Science* 1977; **197**: 994–5.
11 Bamberger CM, Bamberger AM, de Castro M, Chrousos GP. Glucocorticoid receptor beta, a potential endogenous inhibitor of glucocorticoid action in humans. *J Clin Invest* 1995; **95**: 2435–41.
12 Hauk PJ, Hamid QA, Chrousos GP, Leung DY. Induction of corticosteroid insensitivity in human PBMCs by microbial superantigens. *J Allergy Clin Immunol* 2000; **105**: 782–7.
13 Delforno C, Holt PJ, Marks R. Corticosteroid effect on epidermal cell size. *Br J Dermatol* 1978; **98**: 619–23.
14 Lehmann P, Zheng P, Lavker RM, Kligman AM. Corticosteroid atrophy in human skin. A study by light, scanning, and transmission electron microscopy. *J Invest Dermatol* 1983; **81**: 69–76.
15 Sheu HM, Chang CH. Alterations in water content of the stratum corneum following long-term topical corticosteroids. *J Formos Med Assoc* 1991; **90**: 664–9.
16 Sheu HM, Lee JY, Chai CY, Kuo KW. Depletion of stratum corneum intercellular lipid lamellae and barrier function abnormalities after long-term topical corticosteroids. *Br J Dermatol* 1997; **136**: 884–90.
17 Kao JS, Fluhr JW, Man MQ *et al*. Short-term glucocorticoid treatment compromises both permeability barrier homeostasis and stratum corneum integrity: inhibition of epidermal lipid synthesis accounts for functional abnormalities. *J Invest Dermatol* 2003; **120**: 456–64.
18 Arnold J, Anthonioz P, Marchand JP. Depigmenting action of corticosteroids. *Dermatologica* 1975; **151**: 274–80.
19 McCormack PG, Ledesma CN, Vaillant JC. Linear hypopigmentation after intraarticular corticosteroid injection. *Arch Dermatol* 1984; **120**: 708–9.
20 Lubach D, Bensmann A, Bornemann U. Steroid-induced dermal atrophy. Investigations on discontinuous application. *Dermatologica* 1989; **179**: 67–72.
21 Oikarinen A, Haapasaari KM, Sutinen M, Tasanen K. The molecular basis of glucocorticoid-induced skin atrophy: topical glucocorticoid apparently decreases both collagen synthesis and the corresponding collagen mRNA level in human skin in vivo. *Br J Dermatol* 1998; **139**: 1106–10.
22 Haapasaari KM, Risteli J, Karvonen J, Oikarinen A. Effect of hydrocortisone, methylprednisolone aceponate and momethasone furoate on collagen synthesis in human skin in vivo. *Skin Pharmacol* 1997; **10**: 261–4.
23 Nuutinen P, Riekki R, Parikka M, Salo T *et al*. Modulation of collagen synthesis and mRNA by continuous and intermittent use of topical hydrocortisone in human skin. *Br J Dermatol* 2003; **148**: 39–45.
24 Haapasaari KM, Risteli J, Oikarinen A. Recovery of human skin collagen synthesis after short-term topical corticosteroid treatment and comparison between young and old subjects. *Br J Dermatol* 1996; **135**: 65–9.
25 Burckhardt W. Kontaktekzem durch Hydrocortison. *Hautarzt* 1959; **10**: 42–3.
26 Burden AD, Beck MH. Contact hypersensitivity to topical corticosteroids. *Br J Dermatol* 1992; **127**: 497–500.
27 Coopman S, Degreef H, Dooms-Goossens A. Identification of cross-reaction patterns in allergic contact dermatitis from topical corticosteroids. *Br J Dermatol* 1989; **121**: 27–34.
28 Isaksson M, Bruze M. Allergic contact dermatitis in response to budesonide reactivated by inhalation of the allergen. *J Am Acad Dermatol* 2002; **46**: 880–5.
29 Nilsson E, Henning C, Hjorleifsson ML. Density of the microflora in hand eczema before and after topical treatment with a potent corticosteroid. *J Am Acad Dermatol* 1986; **15**: 192–7.
30 Nilsson EJ, Henning CG, Magnusson J. Topical corticosteroids and *Staphylococcus aureus* in atopic dermatitis. *J Am Acad Dermatol* 1992; **27**: 29–34.
31 Bonifazi E, Garofalo L, Lospalluti M. Granuloma gluteale infantum with atrophic scars: clinical and histological observations in eleven cases. *Clin Exp Dermatol* 1981; **6**: 23–9.
32 Velangi SS, Humphreys F, Beveridge GW. Periocular dermatitis associated with prolonged use of a steroid eye ointment. *Clin Exp Dermatol* 1998; **23**: 297–8.
33 Oliet EJ, Estes SA. Perianal comedones associated with chronic topical fluorinated steroid use. *J Am Acad Dermatol* 1982; **7**: 407.
34 Cubey RB. Glaucoma following the application of corticosteroid to the skin of the eyelids. *Br J Dermatol* 1976; **95**: 207–8.
35 Zugerman C, Saunders D, Levit F. Glaucoma from topically applied steroids. *Arch Dermatol* 1976; **112**: 1326.
36 Nielsen NW, Sorensen PN. Glaucoma induced by application of corticosteroids to the periorbital region. *Arch Dermatol* 1978; **114**: 953–4.
37 Schwartzenberg GW, Buys YM. Glaucoma secondary to topical use of steroid cream. *Can J Ophthalmol* 1999; **34**: 222–5.
38 Bawazeer AM, Hodge WG, Lorimer B. Atopy and keratoconus: a multivariate analysis. *Br J Ophthalmol* 2000; **84**: 834–6.
39 Marks JG Jr, Cano C, Leitzel K, Lipton A. Inhibition of wound healing by topical steroids. *J Dermatol Surg Oncol* 1983; **9**: 819–21.
40 Levy JJ, von Rosen J, Gassmuller J *et al*. Validation of an in vivo wound healing model for the quantification of pharmacological effects on epidermal regeneration. *Dermatology* 1995; **190**: 136–41.
41 Eaglstein WH, Mertz PM. New methods for assessing epidermal wound healing: the effects of triamcinolone acetonide and polyethelene film occlusion. *J Invest Dermatol* 1978; **71**: 382–4.
42 du Vivier A, Stoughton RB. Tachyphylaxis to the action of topically applied corticosteroids. *Arch Dermatol* 1975; **111**: 581–3.
43 du Vivier A. Tachyphylaxis to topically applied steroids. *Arch Dermatol* 1976; **112**: 1245–8.
44 Miller JJ, Roling D, Margolis D, Guzzo C. Failure to demonstrate therapeutic tachyphylaxis to topically applied steroids in patients with psoriasis. *J Am Acad Dermatol* 1999; **41**: 546–9.
45 Baker H. Corticosteroids and pustular psoriasis. *Br J Dermatol* 1976; **94** (Suppl. 12): 83–8.
46 Smith JG, Wehr RF, Chalker DK. Corticosteroid induced cutaneous atrophy and telangiectasia. *Arch Dermatol* 1976; **112**: 1115–7.
47 Cornell RC, Stoughton RB. Six month controlled study of effect of desoximetasone and betamethasone-17-valerate on the pituitary–adrenal axis. *Br J Dermatol* 1981; **105**: 91–5.
48 Katz HI, Hien NT, Prawer SE *et al*. Superpotent topical steroid treatment of psoriasis vulgaris—clinical efficacy and adrenal function. *J Am Acad Dermatol* 1987; **16**: 804–11.
49 Walsh P, Aeling JL, Huff L *et al*. Hypothalamus-pituitary-adrenal axis suppression by superpotent topical steroids. *J Am Acad Dermatol* 1993; **29**: 501–3.
50 Weston WL, Fennessey PV, Morelli J *et al*. Comparison of hypothalamus-pituitary-adrenal axis suppression from superpotent topical steroids by standard endocrine function testing and gas chromatographic mass spectrometry. *J Invest Dermatol* 1988; **90**: 532–5.
51 Ohman EM, Rogers S, Meenan FO *et al*. Adrenal suppression following low-dose topical clobetasol propionate. *J R Soc Med* 1987; **80**: 422–4.
52 Turpeinen M. Adrenocortical response to adrenocorticotrophic hormone in relation to duration of topical therapy and percutaneous absorption of hydrocortisone in children with dermatitis. *Eur J Paediatr* 1989; **148**: 729–31.
53 Borzvkowski M, Grant DB, Wells RS. Cushing's syndrome induced by topical steroids used for the treatment of non-bullous ichthyosiform erythroderma. *Clin Exp Dermatol* 1976; **1**: 337–42.
54 Cattaneo M, Betti R, Lodi A. Evaluation of efficacy and tolerability of K-SA fluocinolone acetonide tape. *Ind J Clin Pharmacol Res* 1987; **7**: 279–82.
55 Morris SD, Rycroft RJ, White IR *et al*. Occlusion and topical corticosteroids: comparative frequency of patch test reactions to topical antibiotics. *Br J Dermatol* 2002; **146**: 1047–51.
56 Skov L, Baadsgaard O. Bacterial superantigens and inflammatory skin diseases. *Clin Exp Dermatol* 2000; **25**: 57–61.
57 Memon AA, Molokhia MM, Friedmann PS. The inhibitory effects of topical chelating agents and antioxidants on nickel-induced hypersensitivity reactions. *J Am Acad Dermatol* 1994; **30**: 560–5.
58 Ryatt KS, Feather JW, Mehta A *et al*. The stability and blanching efficacy of betamethasone-17-valerate in emulsifying ointment. *Br J Dermatol* 1982; **107**: 71–6.

59 Harding SM, Sohail S, Busse MJ. Percutaneous absorption of clobetasol propionate from novel ointment and cream foundations. *Clin Exp Dermatol* 1985; **10**: 13–21.
60 Cox NH, Farrell J. Modernising NHS Medicines Manufacturing. *Br Assoc Dermatol Newsletter* 2003; **6**: 30–1.
61 David M, Lowe NJ. Psoriasis therapy: comparative studies with a hydrocolloid dressing, plastic film occlusion and triamcinolone cream. *J Am Acad Dermatol* 1989; **21**: 511–4.
62 Lebwohl M, Heymann WR, Berth-Jones J, Coulson I, eds. *Treatment of Skin Disease. Comprehensive Therapeutic Strategies*, 2nd edn. London: Mosby, 2006.

Cytotoxic and antineoplastic agents

Bleomycin

Bleomycin is a cytotoxic agent with antitumour, antibacterial and antiviral activity. It binds to DNA, causing strand scission and elimination of pyrimidine and purine bases.

A number of reports have appeared on the successful treatment of recalcitrant viral warts with intralesional injections of 0.1% bleomycin [1–3]. Two large, double-blind, placebo-controlled trials gave similar results [2,3]. Seventy-five to ninety-five per cent of warts on the hands and 60% of plantar warts cleared following one to three injections. Local pain is significant, but tolerated by patients who had previously received many unsuccessful treatments. The mechanism of action in warts is not yet known. The small volumes used do not cause systemic toxicity. Treatment of a periungual wart resulted in a permanent nail dystrophy [4]. The compound must be handled with care.

Bleomycin has also been used in treatment of oral leukoplakia. A 1% solution in dimethyl sulphoxide administered for 5 min over 14 consecutive days reduced the size of lesions and histological dysplasia in a trial with 22 patients [5].

5-Fluorouracil (5-FU)

This pyrimidine analogue is an antimetabolite which inhibits pyrimidine metabolism and DNA synthesis.

In the form of a 5% cream, 5-FU is a very effective treatment for multiple solar keratoses. Lesions on the scalp and face respond more readily than lesions on the limbs. A commonly used regimen comprises twice daily application for 2 weeks but there are many variations on this which are used to improve tolerability. Once-daily application is sometimes adequate. Some dermatologists suggest a 1 week on, 1 week off regimen, or use the treatment for 1 week each month, or use it continuously but omit treatment at the weekend, etc. Some patients require longer periods of treatment, and others are cleared only by occlusion of the agent with polyethylene film. A brisk inflammatory response should occur within the keratoses, otherwise clearing is incomplete. Severe ulcerative reactions occur in a few patients. Combination with a fluorinated steroid has been shown to limit the intensity of the inflammatory response without reducing the efficacy of the 5-FU [6]. Combination of topical 5-FU applied twice daily with oral isotretinoin 20 mg daily for a median treatment duration of 21 days proved highly effective in a series of cases with disseminated actinic keratoses [7]. Actinic cheilitis and keratosis of the lip can be improved although the treatment may cause some transient discomfort, and dysplastic changes can persist histologically after apparently satisfactory clinical response [8].

5-FU can be effective in Bowen's disease with 24 out of 26 lesions being cured in a series with 10-year follow-up [9]. However, a recent comparison with photodynamic therapy indicated that the latter was more effective [10]. Bowenoid papulosis can be treated with 5-FU and erythroplasia of Queyrat can also respond [11].

In treatment of basal cell carcinoma, topical 5-FU is considered most useful for low-risk lesions on the trunk and lower limbs [12]. It has proved successful in reducing the number of lesions appearing in the basal cell naevus syndrome [13]. Intralesional 5-FU has also been used with success in this indication [14].

Fluorouracil, applied daily under adhesive plasters, proved effective in a placebo-controlled trial for the treatment of common viral warts [15]. Applied once or twice a week it has also been shown to be effective and well tolerated in curing resistant vaginal condylomas [16]. A proprietary combination of 5-FU and salicylic acid, applied on a daily basis, resulted in complete healing of genital warts in an average of 12 days [17].

5-FU can also be effective in extramammary Paget's disease [18]. It has been used with variable results in naevoid keratotic conditions including Darier's disease [19], and in superficial actinic porokeratosis [20].

T4 endonuclease V

This is a bacterial DNA repair enzyme which excises damaged sections of DNA. This is the initial step in repair of a DNA strand which has sustained photodamage. Remarkably, in a placebo-controlled study of 1 year duration, a liposomal formulation containing this enzyme has been demonstrated to reduce the occurrence of new neoplasms in patients with xeroderma pigmentosum [21]. This has implications not only for patients with this rare group of diseases. If one enzyme can be delivered into cells simply by application to the skin within liposomes, then it is possible that many other enzyme treatments might be delivered in similar vehicles.

Methotrexate

There are several published studies investigating the use of topical methotrexate in psoriasis. Results have generally been superior to placebo [22–25] although not entirely consistent. The treatment has been well tolerated. The development of a suitable vehicle may result in a safer approach to the use of methotrexate in this disease relative to the more familiar systemic administration (Chapters 20 and 74).

Mechlorethamine

Mechlorethamine (mustine, nitrogen mustard) is a cytotoxic drug which is highly active when applied topically. It is an alkylating agent and acts by binding covalently to DNA and thus inhibiting replication. Its use is often constrained by its marked tendency to induce contact allergic dermatitis. Immediate hypersensitivity reactions can also occur but are less common. It is also potentially carcinogenic although the precise level of risk is difficult to establish as many groups of treated patients have received additional carcinogenic treatments. Mechlorethamine has a number of dermatological applications.

The most frequent use is probably in treatment of cutaneous T-cell lymphoma. Concentrations used most frequently are 0.01–

0.02% and the treatment is applied once daily [26]. Aqueous solutions and also ointment formulations are highly effective. The latter seem to carry a lower risk of sensitization although irritant reactions still occur. In a large series, 137 patients with stage T1 or T2 disease were treated with topical mechlorethamine alone for a median period of 5 years. Complete remission was achieved in the majority and only four progressed to a more advanced stage [26]. Topical carmustine is also used in some centres.

Topical mechlorethamine 0.02% can be highly effective and seems to be well tolerated in children with Langerhans' cell histiocytosis [27]. In this series, treatment was initially applied daily to affected areas of skin and the children were bathed to remove excess medication 10 min after the application was completed. The frequency of application was later reduced to every second or third day as the skin improved. Only two out of 20 children treated developed an irritant dermatitis [28].

Topical mechlorethamine has been recognized as effective in treatment of psoriasis since a placebo-controlled trial was published in 1970 [29]. A solution containing 0.05% was effective after weekly application for 4–20 weeks but most patients eventually became sensitized and this has proved a major disadvantage. Some patients have successfully maintained long-term control of the disease using a concentration of 0.02% [30]. The risk of sensitization can be reduced by concurrent use of UVB [31] or PUVA [32].

An encouraging report of alopecia areata and totalis responding to topical mechlorethamine 0.02% has not yet been followed up by further reports of success [33]. In a subsequent report, no response was obtained in seven patients with alopecia totalis although the treatment was well tolerated [34]. However, a study on a mouse model of alopecia areata did yield a positive response [35].

In single cases, pyoderma gangrenosum [36] and ulcerating lesions of chronic granulocytic leukaemia [37] have been reported to respond to topical mechlorethamine.

Imiquimod

This interesting compound belongs to a group known as imidazoquinolones. The actions of these compounds seem likely to be mediated by Toll-like receptor 7 (TLR-7) [38]. This is a cell surface receptor found on cells of monocyte lineage. The naturally occurring ligands for Toll-like receptors are highly conserved microbial products essential for microbial survival, which are responsible for stimulating the relatively primitive innate immune response. Interaction of TLR-7 with ligands activates a signalling pathway, leading to release of large amounts of interferon-α, IL-12, TNF-α and other potent cytokines. In addition to stimulating the innate response, these cytokines promote the development of antigen-specific, cell-mediated immune responses.

The first clinical application in which imiquimod proved useful was for treatment of genital warts. In large, placebo-controlled [39] and open-label [40] trials imiquimod 5% cream applied three times weekly for 16 weeks produced complete clearance in 48–50% of patients. Relapse rates in those who had cleared (recurrence of at least one visible wart) were 13% at 3 months [39] and 23% at 6 months [40] post-treatment. Common warts may also respond; 30% of patients were cleared in a series of 50 treated with 5% imiquimod cream on 5 days each week for up to 16 weeks [41]. Sixteen of eighteen children with warts of 2–7 years' duration were cleared of lesions after applying 5% imiquimod cream twice daily for 2–11 months [42]. Facial planar warts responded convincingly in a report of a single case [43]. In one case stucco keratoses responded to imiquimod [44]. Interestingly, human papillomavirus was detected in the lesions. Molluscum contagiosum has also been reported to respond, in an uncontrolled study [41].

Imiquimod would seem to have potential in many additional applications including treatment of *in situ* malignancy. Actinic keratoses have been shown to respond in a placebo-controlled trial; 84% of patients were cleared after using imiquimod three times weekly for up to 12 weeks [45]. There was no response to the vehicle control. Fourteen of 15 patients with Bowen's disease had no residual lesion after daily application for up to 16 weeks [46]. Local skin reactions were common but these are thought to reflect the immune response to the tumour. In a series of similar size, actinic cheilitis responded well to imiquimod applied three times weekly for up to 6 weeks [47]. Partial and complete responses have been observed in treatment of cervical, vaginal and vulvar intraepithelial neoplasia and Bowenoid papulosis although results have not been consistent [48–50]. Extramammary Paget's disease resolved in response to imiquimod in two cases treated daily or on alternate days, as tolerated, for 7.5 and 16 weeks [51]. Both of these patients experienced systemic symptoms (flu-like illness and nausea). Complete resolution was reported in a case of porokeratosis [52].

Trials on basal cell carcinoma (BCC) have demonstrated unequivocal efficacy in dose-ranging and placebo-controlled studies. In superficial BCC, resolution occurred in 81–88% of lesions treated daily, or on 5 days per week, for 6 or 12 weeks [53,54]. Treatment for 6 weeks appeared as effective as 12 weeks. Applying imiquimod on 3 days weekly for 6 weeks produced cure rates of 76%, or 87% when occluded [55]. In nodular BCC, daily treatment has yielded somewhat lower cure rates at 71% or 76% after 6 weeks or 12 weeks, respectively [56]. Treatment on 3 days weekly cured 50%, and 65% with use of occlusion [55].

Imiquimod may find at least a palliative role in treatment of lentigo maligna and melanoma. In treatment of lentigo maligna, apparently complete clinical resolution has been reported in three cases [57–59], and was confirmed histologically in two. In another report, lentigo maligna also resolved following treatment with imiquimod but the course of the resolution was complicated by the development of a nodular melanoma and microsatellites which were excised with the patient remaining disease-free after 17 months of follow-up [60]. Complete clinical and histological resolution has been reported in two cases of cutaneous metastatic melanoma [61], whilst marked improvement has been observed in additional cases [62,63]. In a further case, the cutaneous metastases resolved but lymph node metastasis developed [64].

Imiquimod may prove effective in suppressing the recurrence of keloids following excision. In an uncontrolled study with 12 subjects, the cream was applied nightly for 8 weeks, starting immediately after excision [65]. No recurrences were seen at 6 months.

Diclofenac

This compound is a non-steroidal anti-inflammatory drug which appears to be effective in topical treatment of actinic keratoses. A gel formulation containing 3% diclofenac and 2.5% hyaluronic acid has been developed specifically for this purpose. The mechanism of action remains uncertain. It has been proposed that excessive arachidonic acid metabolism due to overactivation of cyclo-oxygenase enzymes is carcinogenic [66]. If so, diclofenac may help suppress actinic keratoses by inhibition of cyclo-oxygenase.

In an open-label study this formulation was applied twice daily until patients were clear, or for up to 180 days. Twenty-two (81%) of 27 patients who completed the study and were assessed 30 days after treatment was discontinued, had a complete response and another four (15%) showed marked improvement [67]. These results have been supported by double-blind trials in which 3% diclofenac gel has been applied twice daily for 30–90 days and proved superior to vehicle in clearing solar keratoses [66,68,69]. Consistently, the largest and most statistically significant difference between diclofenac and vehicle has been observed at follow-up 30 days after treatment has been discontinued. This has occurred even when the difference has not been significant at the end of treatment [69]. As assessed at this follow-up visit, the proportions of patients completely cleared have been approx 16% when treatment duration was 30 days [56], 31% when this was 60 days [56], 38% for 12 weeks [69] and 47% when the duration was 90 days [68]. It would therefore seem that the clearance rate continues to increase with increasing treatment duration.

The treatment seems to be well tolerated although pruritus has not been uncommon and dermatitis, confined to the treated site, has developed occasionally.

Podophyllin and podophyllotoxin

Podophyllin (podophyllum) is a plant extract traditionally used to treat genital warts. Podophyllotoxin is the most active constituent. This is now available in standardized formulations free of the unwanted constituents of podophyllin. Podophyllotoxin is an antimitotic agent which arrests cells in metaphase by binding to tubulin. Podophyllin is known to be highly mutagenic and although podophyllotoxin may be less hazardous, both of these treatments should be avoided in pregnancy. Irritant reactions are common with these agents, and severe necrosis occurs rarely.

Podophyllin 0.5% in ethanol may be applied on three consecutive days each week to treat penile warts [70]. Podophyllin 10–25% in tincture of benzoin compound may be applied once or twice a week to genital or perianal warts (washed off after 6–12 h). Podophyllotoxin can be used at a 0.5% concentration in ethanol as a once-daily application. It will clear 60–70% of genital warts within 3–5 days [71]. A cream formulation containing 0.15% podophyllotoxin is also available and can be applied twice daily for 3 days each week.

References

1 Cordero AA, Guglielmi HA, Woscoff A. The common wart: intra-lesional treatment with bleomycin sulfate. *Cutis* 1980; **26**: 319–20.

2 Bunney HH, Nolan MW, Buxton PK *et al*. The treatment of resistant warts with intralesional bleomycin: a controlled clinical trial. *Br J Dermatol* 1984; **110**: 197–207.

3 Shumer SM, O'Keefe EJ. Bleomycin in the treatment of recalcitrant warts. *J Am Acad Dermatol* 1983; **9**: 91–6.

4 Miller RAW. Nail dystrophy following intralesional injections of bleomycin for periungual wart. *Arch Dermatol* 1984; **120**: 963–4.

5 Epstein JB, Wong FL, Millner A *et al*. Topical bleomycin treatment of oral leukoplakia: a randomized double-blind clinical trial. *Head Neck* 1994; **16**: 539–44.

6 Breza T, Taylor R, Eaglestein WH. Non-inflammatory destruction of actinic keratoses by fluorouracil. *Arch Dermatol* 1977; **112**: 1256–8.

7 Sander CA, Pfeiffer C, Kligman AM, Plewig G. Chemotherapy for disseminated actinic keratoses with 5-fluorouracil and isotretinoin. *J Am Acad Dermatol* 1997; **36**: 236–8.

8 Warnock GR, Fuller RP Jr, Pelleu GB Jr. Evaluation of 5-fluorouracil in the treatment of actinic keratosis of the lip. *Oral Surg Oral Med Oral Pathol* 1981; **52**: 501–5.

9 Bargman H, Hochman J. Topical treatment of Bowen's disease with 5-fluorouracil. *J Cutan Med Surg* 2003; **7**: 101–5.

10 Salim A, Leman JA, McColl JH *et al*. Randomized comparison of photodynamic therapy with topical 5-fluorouracil in Bowen's disease. *Br J Dermatol* 2003; **148**: 539–43.

11 Goette DK, Carson TE. Erythroplasia of Queyrat: treatment with topical 5-fluorouracil. *Cancer* 1976; **38**: 1498–502.

12 Telfer NR, Colver GB, Bowers PW. Guidelines for the management of basal cell carcinoma. *Br J Dermatol* 1999; **141**: 415–23.

13 Strange PR, Lang PG Jr. Long-term management of basal cell nevus syndrome with topical tretinoin and 5-fluorouracil. *J Am Acad Dermatol* 1992; **27**: 842–5.

14 Miller BH, Shavin JS, Cognetta A *et al*. Nonsurgical treatment of basal cell carcinomas with intralesional 5-fluorouracil/epinephrine injectable gel. *J Am Acad Dermatol* 1997; **36**: 72–7.

15 Hursthouse MW. A controlled trial on the use of topical 5-fluorouracil on viral warts. *Br J Dermatol* 1975; **92**: 93–6.

16 Krebs HB. Treatment of vaginal condylomata acuminata by weekly topical application of 5-fluorouracil. *Obstet Gynecol* 1987; **70**: 68–71.

17 Djawari D. Fluorouracil treatment on condyloma accuminata. *Z Hautkr* 1986; **61**: 463–9.

18 Bewley AP, Bracka A, Staughton RC *et al*. Extramammary Paget's disease of the scrotum: treatment with topical 5-fluorouracil and plastic surgery. *Br J Dermatol* 1994; **131**: 445–6.

19 Knulst AC, De La Faille HB, Van Vloten WA. Topical 5-fluorouracil in the treatment of Darier's disease. *Br J Dermatol* 1995; **133**: 463–6.

20 Shelley WB, Shelley ED. Disseminated superficial porokeratosis: rapid therapeutic response to 5-fluorouracil. *Cutis* 1983; **32**: 139–40.

21 Yarosh D, Klein J, O'Connor A *et al*. Effect of topically applied T4 endonuclease V in liposomes on skin cancer in xeroderma pigmentosum: a randomised study. *Lancet* 2001; **357**: 926–9.

22 Weinstein GD, McCullough JL, Olsen E. Topical methotrexate therapy for psoriasis. *Arch Dermatol* 1989; **125**: 227–30.

23 Syed TA, Hadi SM, Qureshi ZA *et al*. Management of psoriasis vulgaris with methotrexate 0.25% in a hydrophilic gel: a placebo-controlled, double-blind study. *J Cutan Med Surg* 2001; **5**: 299–302.

24 Eskicirak B, Zemheri E, Cerkezoglu A. The treatment of psoriasis vulgaris: 1% topical methotrexate gel. *Int J Dermatol* 2006; **45**: 965–9.

25 Bjerring P, Beck HI, Zachariae H, Søgaard H. Topical treatment of psoriatic skin with methotrexate cream: a clinical, pharmacokinetic, and histological study. *Acta Derm Venereol* 1986; **66**: 515–9.

26 Kim YH, Martinez G, Varghese A, Hoppe RT. Topical nitrogen mustard in the treatment of mycosis fungoides. *Arch Dermatol* 2003; **139**: 165–73.

27 Sheehan MP, Atherton DJ, Broadbent V, Pritchard J. Topical nitrogen mustard: an effective treatment for cutaneous Langerhans cell histiocytosis. *J Pediatr* 1991; **119**: 317–21.

28 Hoeger PH, Nanduri VR, Harper JI *et al*. Long term follow up of topical mustine treatment for cutaneous Langerhans cell histiocytosis. *Arch Dis Child* 2000; **82**: 483–7.

29 Epstein E, Ugel AR. Effects of topical mechlorethamine on skin lesions of psoriasis. *Arch Dermatol* 1970; **102**: 504–6.

30 Taylor JR, Halprin K. Topical use of mechlorethamine in the treatment of psoriasis. *Arch Dermatol* 1972; **106**: 362–4.

31 Nusbaum BP, Edwards EK, Horwitz SN, Frost P. Psoriasis therapy. The effect of UV radiation on sensitization to mechlorethamine. *Arch Dermatol* 1983; **119**: 117–21.

32 Maduit G, Silvestre O, Thivolet J. PUVA therapy prevents sensitization to mechlorethamine in patients with psoriasis. *Br J Dermatol* 1985; **113**: 515–21.

33 Arrazola JM, Sendagota E, Harto A, Ledo A. Treatment of alopecia areata with topical nitrogen mustard. *Int J Dermatol* 1985; **24**: 608–10.

34 Harrison PV, Latona J, Jovanovic M. Alopecia totalis and topical mustine. *Arch Dermatol* 1993; **129**: 514.

35 Tang L, Cao L, Bernardo O *et al*. Topical mechlorethamine restores autoimmune-arrested follicular activity in mice with an alopecia areata-like disease by targeting infiltrated lymphocytes. *J Invest Dermatol* 2003; **120**: 400–6.

36 Tsele E, Yu RCH, Chu AC. Pyoderma gangrenosum—response to topical nitrogen mustard. *Clin Exp Dermatol* 1992; **17**: 437–40.

37 Murphy WG, Fotheringham GH, Busuttil A *et al*. Skin lesions in chronic granulocytic leukemia. Treatment of a patient with topical nitrogen mustard. *Cancer* 1985; **55**: 2630–3.

38 Stanley MA. Imiquimod and the imidazoquinolones: mechanism of action and therapeutic potential. *Clin Exp Dermatol* 2002; **27**: 571–7.

39 Edwards L, Ferenczy A, Eron L *et al*. Self-administered topical 5% imiquimod cream for external anogenital warts. *Arch Dermatol* 1998; **134**: 25–30.

40 Garland SM, Sellors JW, Wikstrom A *et al*. Imiquimod 5% cream is a safe and effective self-applied treatment for anogenital warts—results of an open-label, multicentre Phase IIIB trial. *Int J STD AIDS* 2001; **12**: 722–9.

41 Hengge U, Esser S, Schultewolter T *et al*. Self-administered topical 5% imiquimod for the treatment of common warts and molluscum contagiosum. *Br J Dermatol* 2000; **143**: 1026–31.

42 Grussendorf-Conen E-I, Jacobs S. Efficacy of imiquimod 5% cream in the treatment of recalcitrant warts in children. *Pediatr Dermatol* 2002; **19**: 263–6.

43 Khan Durani B, Jappe U. Successful treatment of facial plane warts with imiquimod. *Br J Dermatol* 2002; **147**: 1018.

44 Stockfleth E, Rowert J, Arndt R *et al*. Detection of human papillomavirus and response to topical imiquimod in a case of stucco keratosis. *Br J Dermatol* 2000; **143**: 846–50.

45 Stockfleth E, Meyer T, Benninghoff B *et al*. A randomized, double-blind, vehicle-controlled study to assess 5% imiquimod cream for the treatment of multiple actinic keratoses. *Arch Dermatol* 2002; **138**: 1498–502.

46 MacKenzie-Wood A, Kossard S, de Launey J. Imiquimod 5% cream in the treatment of Bowen's disease. *J Am Acad Dermatol* 2001; **44**: 462–70.

47 Smith KJ, Germain M, Yeager J, Skelton H. Topical 5% imiquimod for the therapy of actinic cheilitis. *J Am Acad Dermatol* 2002; **47**: 497–501.

48 Diaz-Arrastia C, Arany I, Robazetti SC *et al*. Clinical and molecular responses in high grade intraepithelial neoplasia treated with topical imiquimod 5%. *Clin Cancer Res* 2001; **7**: 3031–3.

49 Todd R, Etherington I, Luesley D. The effects of 5% imiquimod cream on high-grade vulval intraepithelial neoplasia. *Gynecologic Oncology* 2002; **85**: 67–70.

50 Porter WM, Francis N, Hawkins D *et al*. Penile intraepithelial neoplasia: clinical spectrum and treatment of 35 cases. *Br J Dermatol* 2002; **147**: 1159–65.

51 Zampogna JC, Flowers FP, Roth WI, Hassenein AM. Treatment of primary limited cutaneous extramammary Paget's disease with topical imiquimod monotherapy: two case reports. *J Am Acad Dermatol* 2002; **47**: S229–35.

52 Agarwal S, Berth-Jones J. Porokeratosis of Mibelli: successful treatment with 5% imiquimod cream. *Br J Dermatol* 2002; **146**: 338–9.

53 Marks R, Gebauer K, Shumack S *et al*. Imiquimod 5% cream in the treatment of superficial basal cell carcinoma: results of a multicentre 6 week dose-response trial. *J Am Acad Dermatol* 2001; **44**: 807–13.

54 Geisse J, Rich P, Pandya A *et al*. Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: a double-blind randomized vehicle-controlled study. *J Am Acad Dermatol* 2002; **47**: 390–8.

55 Sterry W, Ruzicka T, Herrera E *et al*. Imiquimod 5% cream for the treatment of superficial and nodular basal cell carcinoma: randomized studies comparing low-frequency dosing with and without occlusion. *Br J Dermatol* 2002; **147**: 1227–36.

56 Shumack S, Robinson J, Kossard S *et al*. Efficacy of topical 5% imiquimod cream for the treatment of nodular basal cell carcinoma. *Arch Dermatol* 2002; **138**: 1165–71.

57 Ahmed I, Berth-Jones J. Imiquimod: a novel treatment for lentigo maligna. *Br J Dermatol* 2000; **143**: 843–5.

58 Chapman MS, Spencer SK, Brennick JB. Histologic resolution of melanoma in situ (lentigo maligna) with 5% imiquimod cream. *Arch Dermatol* 2003; **139**: 943–4.

59 Epstein E. Extensive lentigo maligna clearing with topical imiquimod. *Arch Dermatol* 2003; **139**: 944–5.

60 Fisher GH, Lang PG. Treatment of melanoma in situ on sun-damaged skin with topical 5% imiquimod cream complicated by the development of invasive disease. *Arch Dermatol* 2003; **139**: 945–7.

61 Wolf IH, Smolle J, Binder B *et al*. Topical imiquimod in the treatment of metastatic melanoma to skin. *Arch Dermatol* 2003; **139**: 273–6.

62 Steinmann A, Funk JO, Schuler G, von den Driesch P. Topical imiquimod treatment of a cutaneous melanoma metastasis. *J Am Acad Dermatol* 2000; **43**: 555–6.

63 Bong AB, Bonnekoh B, Franke I *et al*. Imiquimod, a topical immune response modifier, in the treatment of cutaneous metastases of malignant melanoma. *Dermatology* 2002; **205**: 135–8.

64 Ugurel S, Wagner A, Pfohler C *et al*. Topical imiquimod eradicates skin metastases of malignant melanoma but fails to prevent rapid lymphogenous metastatic spread. *Br J Dermatol* 2002; **147**: 621–4.

65 Berman B. Pilot study of the effect of postoperative imiquimod 5% cream on the recurrence rate of excised keloids. *J Am Acad Dermatol* 2002; **47**: S209–11.

66 Rivers JK, Arlette J, Shear N *et al*. Topical treatment of actinic keratoses with 3.0% diclofenac in 2.5% hyaluronan gel. *Br J Dermatol* 2002; **146**: 94–100.

67 Rivers JK, McLean DI. An open study to assess the efficacy and safety of topical 3% diclofenac in a 2.5% hyaluronic acid gel for the treatment of actinic keratoses. *Arch Dermatol* 1997; **133**: 1239–42.

68 Wolf JE Jr, Taylor JR, Tschen E, Kang S. Topical 3.0% diclofenac in 2.5% hyaluronan gel in the treatment of actinic keratoses. *Int J Dermatol* 2001; **40**: 709–13.

69 Gebauer K, Brown P, Varigos G. Topical diclofenac in hyaluronan gel for the treatment of solar keratoses. *Australas J Dermatol* 2003; **44**: 40–3.

70 Maiti H, Hayl KR. Treatment of condyloma accuminata with podophyllin resin. *Practitioner* 1985; **229**: 37–9.

71 Von Krogh G. Topical self-treatment of penile warts with a 0.5% podophyllotoxin in ethanol for 4–5 days. *Sex Transm Dis* 1987; **14**: 135–40.

Depigmenting agents

Depigmenting agents are most frequently used by dermatologists in treatment of melasma. Hydroquinone, used alone in concentrations usually ranging from 2–5%, or in combination with retinoic acid in 0.025–0.1%, is currently the most widely used treatment for this indication.

Post-inflammatory hyperpigmentation is another commonly encountered problem and is particularly difficult to treat as much of the pigment is often contained in dermal melanophages. Nonetheless, depigmenting compounds such as tretinoin, hydroquinone or azelaic acid are sometimes prescribed.

In severe cases of vitiligo when depigmentation is already extensive, depigmenting agents can improve the appearance of the skin by removing residual patches of normal pigmentation.

Solar lentiginosis is another indication for which depigmenting agents can prove useful. Retinoid acid has the best evidence base in this indication.

There is also a demand among populations with pigmented skin for agents to reduce the intensity of pigmentation for purely cosmetic purposes. In parts of Africa, treatments abused for this purpose include very potent topical corticosteroids, mercury compounds and high concentrations of hydroquinone [1–3].

Hydroquinone

Hydroquinone (1,4 dihydroxybenzene) is widely used as a depigmenting agent both in clinical and cosmetic contexts.

The efficacy of 4% hydroquinone cream in treatment of melasma was demonstrated in a placebo-controlled trial in which treatment

was applied nightly for 3 months [4]. Higher concentrations are sometimes used in extemporaneous formulations for severe or resistant cases of chloasma or post-inflammatory hyperpigmentation. The efficacy of hydroquinone in post-inflammatory hyperpigmentation is likely to be highly variable as this is a very heterogeneous entity. Hydroquinone is used at 5% concentration as a constituent of Kligman cream (see below) [5]. It can cause both irritant and allergic reactions. The addition of a weak topical steroid reduces the irritant effect. It is unstable and tends to darken due to auto-oxidation. Hydroquinone probably reduces pigmentation at least partly as a result of inhibition of melanin synthesis, since it is known to inhibit tyrosinase. However, the mechanism is not fully understood. It has also been proposed that its action may be partly mediated by release of free radicals. In animal models, the effect of the drug is potentiated by the use of buthionine sulphoxime or cystamine to inhibit synthesis of the protective free radical scavenger glutathione [6].

Epidemiological studies indicate that a very large proportion of the African population (perhaps the majority of women) have used hydroquinone cosmetically as a skin lightening agent [1–3]. This practice has been strongly associated with the development, in these black-skinned individuals, of exogenous ochronosis [1–3,7,8]. This disease, like endogenous ochronosis (alkaptonuria), derives its name from the colour of the cutaneous pigment deposits which characterize these conditions (Gk. ochro, yellow). When these are examined histologically they appear yellow or brown, although clinically the pigment appears dark brown or black. Endogenous ochronosis is an inborn error of metabolism in which deficiency of homogentisic acid oxidase results in accumulation of homogentisic acid, a metabolite of tyrosine and phenylalanine. Oxidation products of homogentisic acid are thought to constitute the pigment deposited in the skin, cartilage and elsewhere.

The pigment in exogenous ochronosis strongly resembles that in the endogenous form and may result from inhibition of homogentisic acid oxidase by hydroquinone. Milder cases show only macular sooty pigmentation whilst more advanced cases develop irregular stippling, papulation and pigmented colloid milia [8,9]. These features tend to be most prominent over the areas of skin most intensely exposed to the sun. Histologically, deposits of pigment are observed in the papillary and reticular dermis and probably represent accumulations of the pigment in association with degenerated collagen [9,10]. In many countries, the concentration of hydroquinone in cosmetic products has been legally restricted to 2% with the aim of reducing the risk of causing ochronosis. However, it is not established that this risk is dependent on the concentration [11].

In striking contrast to Africa, exogenous ochronosis seems to be rare in the USA, even though hydroquinone-containing compounds are widely used there [12,13]. Possible explanations put forward for this paradox include under-reporting, combined use with other compounds in Africa, the need for intense solar irradiation as a synergistic factor, the use of different formulations (especially hydro-alcoholic solutions) in Africa, or that the use of these compounds in the USA may be relatively cautious.

Exogenous ochronosis occurs almost entirely in black skin. It does not seem to be a hazard in white skin although occasional cases have occurred in Hispanics. The relatively high levels of enzyme activity associated with melanin synthesis in black skin and additional stimulation of these pathways by intense sun exposure seem to be required for ochronosis to develop.

Monobenzylether of hydroquinone

Skin bleaching with 20% monobenzyl ether of hydroquinone (monobenzone) is generally reserved for treatment of carefully selected cases of vitiligo. The resulting depigmentation may be permanent so this treatment is only suitable for those with extensive disease in whom the appearance of the skin would be improved by removing the residual pigment. Patients should be warned that results are unpredictable. Treatment may need to be prolonged and is not always successful [14]. Depigmentation may be permanent and may occur at sites other than those being treated. Conversely, spontaneous repigmentation may occur unexpectedly after cessation of the treatment, slowly or rapidly, at both treated and untreated sites [15]. Contact dermatitis can develop [14,16]. It has also been reported that this treatment may cause corneal and conjunctival pigmentation [17].

The addition of monobenzone to cosmetic skin lightening preparations caused an epidemic of leukomelanoderma in South Africa during the early 1970s [9].

Additional phenol derivatives

Mequinol (4-hydroxyanisole, 4-methoxyphenol) is another phenol derivative with depigmenting properties. It is a constituent of a commercially formulated solution containing 2% mequinol and 0.01% retinoic acid, marketed for treatment of solar lentiginosis. In trials with a treatment duration of 24 weeks, this combination appeared to be more effective than either of the constituents used alone, or than placebo [18]. Mequinol 20% cream has been successfully used to remove residual pigmentation in severe vitiligo with efficacy considered comparable to monobenzone [19].

N-acetyl-4-*S*-cysteaminylphenol (*N*-Ac-4-*S*-CAP) produces reversible depigmentation in the Yucatan pig model [20,21]. In one report of its use in melasma, 8% of patients showed complete depigmentation, 66% marked improvement, and 25% moderate improvement [22].

Retinoic acid

Retinoic acid (tretinoin) has been successfully used to reduce pigmentation in a variety of disorders including melasma [23], solar lentiginosis [24,25] and post-inflammatory hyperpigmentation [26]. In most trials, tretinoin 0.1% cream has been used for 40 weeks. Retinoid dermatitis is a common side effect and may result in post-inflammatory hyperpigmentation. Some mild reduction of pigment may occur in normal skin surrounding the treated areas. The mechanism of action is not fully understood but may be at least partly explained by reduction in melanogenesis consequent upon reduction of tyrosinase activity [27].

Attempts have been made to use other retinoids for this purpose with variable results; 10% all-*trans* retinol gel proved effective, although irritant, in a Japanese study [28]. A study on the use of topical 0.05% isotretinoin in melasma showed no difference from placebo after 40 weeks [29].

Kligman cream

This formulation comprises 5% hydroquinone, 0.1% tretinoin and 0.1% dexamethasone in hydrophilic ointment [5]. It has been widely used as a depigmenting treatment, especially for melasma. The combined formulation is considered more effective than any of the individual constituents.

Azelaic acid

This dicarboxylic acid is a relatively safe, though mildly irritant, agent with several roles to play in dermatology.

As a depigmenting agent, azelaic acid is moderately effective in treatment of melasma. The proposed mechanism is direct or indirect inhibition of tyrosinase [30]. Azelaic acid 20% cream proved more effective than 2% hydroquinone cream after 24 weeks of treatment [31]. In two other studies with the same treatment duration, 20% azelaic acid proved equivalent in efficacy to 4% hydroquinone cream [32,33]. Another study on facial hyperpigmentation in darker skinned individuals compared a combination of azelaic acid 20% cream and glycolic acid 15% or 20% lotion, with 4% hydroquinone cream; similar efficacy was observed from the two regimens [34]. The addition of tretinoin enhances the depigmenting effect [1,2]. Azelaic acid has also proved effective in treatment of Kitamura's reticulate acropigmentation [35].

Azelaic acid also has antineoplastic properties, inhibiting mitochondrial function and DNA synthesis [36], and has been used as a palliative treatment for lentigo maligna and malignant melanoma [37–39]. However, since some cases of lentigo maligna have progressed to invasive melanoma whilst using this treatment it must be regarded as purely palliative in these indications [37].

Azelaic acid 20% cream is effective in treatment of acne vulgaris [40]. This is likely to be due to a combination of antimicrobial and anti-inflammatory properties. It can inhibit growth of *Propionibacterium acnes* and *Staph. epidermidis*, and inhibits production of free radicals by polymorphs [41]. The latter property may also explain why it is effective in rosacea [42,43].

It may also prove to have a role as an antimycotic, inhibiting growth of dermatophytes [44,45], and as a topical antimicrobial agent with activity against antibiotic resistant *Staph. aureus* [46].

Kojic acid

This is a fungal metabolite known to inhibit tyrosinase [47]. It is a constituent of over-the-counter depigmenting creams sold mainly in Japan. In treatment of melasma, 1% kojic acid proved equally effective in comparison with 2% hydroquinone when each was used in combination with glycolic acid [48].

Liquiritin

This compound, which can be extracted from liquorice (*Glycyrrhiza glabra*) and other herbal sources, has been reported to effectively reduce the pigmentation of melasma in a double-blind trial [49].

References

1 Adebajo SB. An epidemiological survey of the use of cosmetic skin lightening cosmetics among traders in Lagos, Nigeria. *West Afr J Med* 2002; **21**: 51–5.

2 Del Giudice P, Yves P. The widespread use of skin lightening creams in Senegal: a persistent public health problem in West Africa. *Int J Dermatol* 2002; **41**: 69–72.

3 Mahe A, Ly F, Aymard G, Dangou JM. Skin diseases associated with the cosmetic use of bleaching products in women from Dakar, Senegal. *Br J Dermatol* 2003; **148**: 493–500.

4 Haddad AL, Matos LF, Brunstein F *et al*. A clinical, prospective, randomized, double-blind trial comparing skin whitening complex with hydroquinone vs. placebo in the treatment of melasma. *Int J Dermatol* 2003; **42**: 153–6.

5 Kligman AM, Willis I. A new formula for depigmenting human skin. *Arch Dermatol* 1975; **111**: 40–8.

6 Bolognia JL, Sodi SA, Osber MP *et al*. Enhancement of the depigmenting effect of hydroquinone by cystamine and buthionine sulfoximine. *Br J Dermatol* 1995; **133**: 349–57.

7 Bentley-Phillips B, Bayles MA. Cutaneous reactions to topical application of hydroquinone. Results of a 6-year investigation. *S Afr Med J* 1975; **49**: 1391–5.

8 Hardwick N, van Celder LW, van der Merwe CA *et al*. Exogenous ochronosis: an epidemiological study. *Br J Dermatol* 1989; **120**: 229–38.

9 Findlay CH, Morrison JCL, Simson IW. Exogenous ochronosis and pigmented colloid milium from hydroquinone bleaching creams. *Br J Dermatol* 1975; **93**: 613–22.

10 Snider RL, Thiers BH. Exogenous ochronosis. *J Am Acad Dermatol* 1993; **28**: 662–4.

11 Williams H. Skin lightening creams containing hydroquinone. The case for a temporary ban. *BMJ* 1992; **305**: 903–4.

12 Grimes P. Melasma. Etiologic and therapeutic considerations. *Arch Dermatol* 1995; **131**: 1453–7.

13 Burke PA, Maibach HI. Exogenous ochronosis: an overview. *J Dermatol Treat* 1997; **8**: 21–6.

14 Mosher DB, Parrish JA, Fitzpatrick TB. Monobenzylether of hydroquinone. A retrospective study of treatment of 18 vitiligo patients and a review of the literature. *Br J Dermatol* 1977; **97**: 669–79.

15 Oakley AM. Rapid repigmentation after depigmentation therapy: vitiligo treated with monobenzyl ether of hydroquinone. *Australas J Dermatol* 1996; **37**: 96–8.

16 Lyon CC, Beck MH. Contact hypersensitivity to monobenzyl ether of hydroquinone used to treat vitiligo. *Contact Dermatitis* 1998; **39**: 132–3.

17 Hedges TR 3rd, Kenyon KR, Hanninen LA, Mosher DB. Corneal and conjunctival effects of monobenzone in patients with vitiligo. *Arch Ophthalmol* 1983; **101**: 64–8.

18 Fleischer AB Jr, Schwartzel EH, Colby SI, Altman DJ. The combination of 2% 4-hydroxyanisole (Mequinol) and 0.01% tretinoin is effective in improving the appearance of solar lentigines and related hyperpigmented lesions in two double-blind multicenter clinical studies. *J Am Acad Dermatol* 2000; **42**: 459–67.

19 Njoo MD, Vodegel RM, Westerhof W. Depigmentation therapy in vitiligo universalis with topical 4-methoxyphenol and the Q-switched ruby laser. *J Am Acad Dermatol* 2000; **42**: 760–9.

20 Jimbow M, Marusyk H, Jimbow K. The *in vivo* melanocytotoxicity and depigmenting potency of *N*-2,4-acetoxyphenyl thioethyl acetamide in the skin and hair. *Br J Dermatol* 1995; **133**: 526–36.

21 Alena F, Dixon W, Thomas P *et al*. Glutathione plays a key role in the depigmenting and melanocytotoxic action of *N*-acetyl-4-*S*-cysteaminylphenol in black and yellow hair follicles. *J Invest Dermatol* 1995; **104**: 792–7.

22 Jimbow K. *N*-acetyl-4-*S*-cysteaminylphenol as a new type of depigmenting agent for the melanoderma of patients with melasma. *Arch Dermatol* 1991; **127**: 1528–34.

23 Griffiths CEM, Finkel LJ, Ditre CM *et al*.Topical tretinoin (retinoic acid) improves melasma. A vehicle-controlled, clinical trial. *Br J Dermatol* 1993; **129**: 415–21.

24 Rafal ES, Griffiths CE, Ditre CM *et al*. Topical tretinoin (retinoic acid) treatment for liver spots associated with photodamage. *N Engl J Med* 1992; **326**: 368–74.

25 Griffiths CE, Goldfarb MT, Finkel LJ *et al*. Topical tretinoin (retinoic acid) treatment of hyperpigmented lesions associated with photoaging in Chinese and Japanese patients: a vehicle-controlled trial. *J Am Acad Dermatol* 1994; **30**: 76–84.

26 Bulengo-Ransby SM, Griffiths CE, Kimbrough-Green CK *et al*. Topical tretinoin (retinoic acid) therapy for hyperpigmented lesions caused by inflammation of the skin in black patients. *N Engl J Med* 1993; **328**: 1438–43.

27 Romero C, Aberdam E, Larnier C, Ortonne JP. Retinoic acid as modulator of UVB-induced melanocyte differentiation. Involvement of the melanogenic enzymes expression. *J Cell Sci* 1994; **107**: 1095–103.

28 Yoshimura K, Momosawa A, Aiba E *et al*. Clinical trial of bleaching treatment with 10% all-trans retinol gel. *Dermatol Surg* 2003; **29**: 155–60.

29 Leenutaphong V, Nettakul A, Rattanasuwon P. Topical isotretinoin for melasma in Thai patients: a vehicle-controlled clinical trial. *J Med Assoc Thai* 1999; **82**: 868–75.
30 Schallreuter KU, Wood JW. A possible mechanism of action for azelaic acid in the human epidermis. *Arch Dermatol Res* 1990; **282**: 168–71.
31 Verallo-Rowell VM, Verallo V, Graupe K *et al*. Double-blind comparison of azelaic acid and hydroquinone in the treatment of melasma. *Acta Derm Venereol* 1989; **143** (Suppl.): 58–61.
32 Piquero Martin J, Rothe de Arocha J, Beniamini Loker D. Double-blind clinical study of the treatment of melasma with azelaic acid versus hydroquinone. *Med Cutan Ibero Lat Am* 1988; **16**: 511–4.
33 Baliña LM, Graupe K. The treatment of melasma. 20% azelaic acid versus 4% hydroquinone cream. *Int J Dermatol* 1991; **30**: 893–5.
34 Kakita LS, Lowe NJ. Azelaic acid and glycolic acid combination therapy for facial hyperpigmentation in darker-skinned patients: a clinical comparison with hydroquinone. *Clin Ther* 1998; **20**: 960–70.
35 Kameyama K, Morita M, Sugaya K *et al*. Treatment of reticulate acropigmentation of Kitamura with azelaic acid. An immunohistochemical and electron microscopic study. *J Am Acad Dermato*l 1992; **26**: 817–20.
36 Breathnach AS. Azelaic acid: potential as a general antitumoural agent. *Med Hypotheses* 1999; **52**: 221–6.
37 McLean DI, Peter KK. Apparent progression of lentigo maligna to invasive melanoma during treatment with topical azelaic acid. *Br J Dermatol* 1986; **114**: 685–9.
38 Sowden J, Paramsothy Y, Smith AG. Malignant melanoma arising in the scar of lupus vulgaris and response to treatment with topical azelaic acid. *Clin Exp Dermatol* 1988; **13**: 353–6.
39 Vereecken P, Heenen M. Recurrent lentigo maligna melanoma: regression associated with local azelaic acid 20%. *Int J Clin Pract* 2002; **56**: 68–9.
40 Graupe K, Cunliffe WJ, Gollnick HP *et al*. Efficacy and safety of topical azelaic acid (20% cream): an overview of results from European clinical trials and experimental reports. *Cutis* 1996; **57** (Suppl. 1): 20–35.
41 Fitton A, Goa KL. Azelaic acid. A review of its pharmacological properties and therapeutic efficacy in acne and hyperpigmentary skin disorders. *Drugs* 1991; **41**: 780–98.
42 Carmichael AJ, Marks R, Graupe KA, Zaumseil RP. Topical azelaic acid in the treatment of rosacea. *J Derm Treat* 1993; **4** (Suppl. 1): 19–22.
43 Maddin S. A comparison of topical azelaic acid 20% cream and topical metronidazole 0.75% cream in the treatment of patients with papulopustular rosacea. *J Am Acad Dermatol* 1999; **40**: 961–5.
44 Brasch J, Friege B. Dicarboxylic acids affect the growth of dermatophytes *in vitro. Acta Derm Venereol (Stockh)* 1994; **74**: 347–50.
45 Brasch J, Christophers E. Azelaic acid has antimycotic properties *in vitro. Dermatology* 1993; **186**: 55–8.
46 Maple PA, Hamilton-Miller JM, Brumfitt W. Comparison of the *in-vitro* activities of the topical antimicrobials azelaic acid, nitrofurazone, silver sulphadiazine and mupirocin against methicillin-resistant *Staphylococcus aureus. J Antimicrob Chemother* 1992; **29**: 661–8.
47 Kahn V. Effect of kojic acid on the oxidation of DL-DOPA, norepinephrine, and dopamine by mushroom tyrosinase. *Pigment Cell Res* 1995; **8**: 234–40.
48 Garcia A, Fulton JE Jr. The combination of glycolic acid and hydroquinone or kojic acid for the treatment of melasma and related conditions. *Dermatol Surg* 1996; **22**: 443–7.
49 Amer M, Metwalli M.Topical liquiritin improves melasma. *Int J Dermatol* 2000; **39**: 299–301.

Depilatories

Depilation can be defined as temporary removal of hair, whilst epilation denotes permanent destruction of the follicle. Epilation therefore requires physical methods of destruction of the follicle such as electrolysis, lasers and intense pulsed light. Depilation can be achieved by shaving, waxing, plucking, threading and by use of topical depilatory creams. Systemic androgen antagonists have a role to play in some cases. All these techniques are described further in Chapter 66. Only topical treatments are discussed here.

Traditional depilatory creams depend upon breaking the disulphide bonds in hair. Three main classes are currently used. The oldest are various sulphides, which have a powerful effect but may irritate, and in the presence of water generate hydrogen sulphide which has an unpleasant odour. Strontium or barium sulphide 20% are widely used. They are effective on the terminal hair in the axillae. Thioglycollates are being used more frequently, but they are slower to work than sulphides. Concentrations of 2.5–4% produce an effect in 5–15 min. Substituted mercaptans (thioalcohols) are most widely used. They work slowly, but are suitable for use on the face.

Eflornithine hydrochloride is an irreversible inhibitor of ornithine decarboxylase, an enzyme required for hair growth. This is marketed as an 11.5% cream which can slow the growth of facial hair. A response takes 4–8 weeks to develop and the effect wears off over a similar period when the treatment is discontinued. The benefit seems to be rather modest in many cases, with only 32% of patients reporting marked improvement [1,2]. Some irritation may occur.

References

1 Shapiro J, Lui H. Vaniqa—eflornithine 13.9% cream. *Skin Therapy Lett* 2001; **6**: 1–3, 5.
2 Balfour JA, McClellan K. Topical eflornithine. *Am J Clin Dermatol* 2001; **2**: 197–201.

Dithranol

Dithranol (anthralin, dihydroxyanthranol; Fig. 73.8) [1] is a time-honoured topical treatment for psoriasis similar in its irritating and staining properties to chrysarobin, which it supplanted in the early 20th century, but more effective. It is used in ointments, pastes, creams and as a pomade for use on the scalp.

The mechanism of action of dithranol is still uncertain. It inhibits its glycolytic enzymes *in vitro* [2]. Reactive oxygen species are generated during auto-oxidation of dithranol [3] and these may inhibit mitochondrial function [4]. It has been suggested that enzyme inactivation may result from lipid peroxidation leading to cross-linkage of enzyme proteins [5]. *In vitro* studies with human skin showed decreased oxygen consumption and inhibition of the pentose phosphate shunt [6]. The level of cyclic guanosine monophosphate is known to be increased in psoriasis. Dithranol has been shown to restore cyclic nucleosides in skin to normal levels [7]. Dithranol induces a marked antiproliferative effect [8,9].

The use of dithranol has proved remarkably safe. Staining of the skin and other materials is certainly inconvenient although, as a result, the appearance of the skin provides a reliable guide to

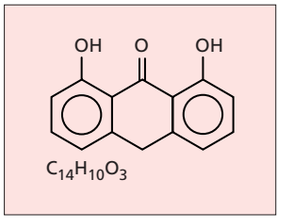


Fig. 73.8 Dithranol.

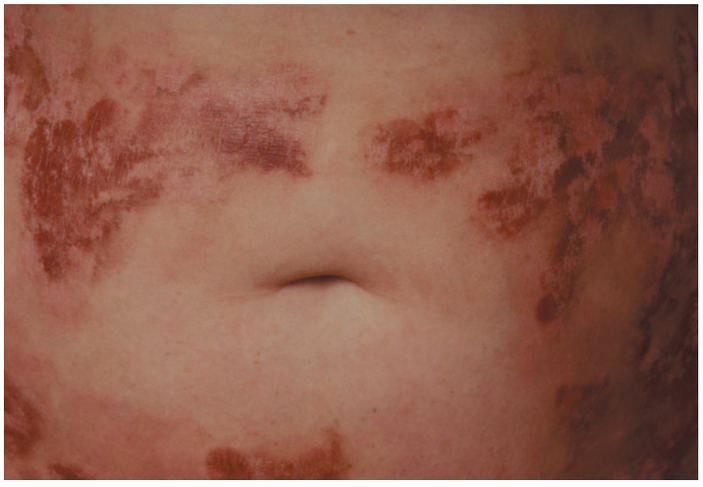


Fig. 73.9 Staining of the skin due to dithranol treatment.



Fig. 73.10 An irritant reaction following accidental contamination of normal skin with dithranol.

compliance (Fig. 73.9). Local reactions are common and irritation of normal skin accidentally contaminated with dithranol can be severe (Fig. 73.10). However, there is no evidence of systemic toxicity and it is not considered to be carcinogenic.

Dithranol, especially when incorporated in zinc oxide, is slowly oxidized by alkaline impurities to an inactive pink anthrone [10]. The effect of salicylic acid in preventing this has been known for a long time [11–13]. Salicylic acid neutralizes hydroxyl ions in an alkaline medium, and perhaps reacts with free zinc ions to form an inactive zinc–dithranol complex. It has been found that zinc ions and salicylic acid, like dithranol itself, inhibit glucose-6-phosphate dehydrogenase, thus further justifying the time-honoured combination of these three agents [6]. The combination of tar with dithranol is said to reduce dithranol irritancy without inhibiting therapeutic effect [14]. The use of a water-soluble antioxidant, ascorbic acid, has allowed the production of stable dithranol cream preparations [10]. These are not as therapeutically potent as equivalent strengths of pastes or ointments but show much greater patient acceptability for home usage [15]. The development of a lipid encapsulated cream formulation also seems likely to increase acceptability by further reducing staining and irritation [16,17].

Short-contact applications of strong dithranol pastes or creams are known to be almost as effective as prolonged contact and facilitate treatment on an outpatient basis and self-treatment at home [18–20].

Dithranol has also been used to stimulate an inflammatory response and regrowth of hair in patients with alopecia areata [21], and for the treatment of warts [22].

References

1 Shroot B, Schaefer J, Juhlin L. Editorial: anthralin—the challenge. *Br J Dermatol* 1981; **105** (Suppl. 20): 3–5.

2 Rassner G. Enzymaktivitätshemmung in vitro durch Dithranol (Cignolin). *Arch Dermatol Res* 1972; **243**: 47–51.

3 Muller K. Antipsoriatic anthrones: aspects of oxygen radical formation, challenges and prospects. *Gen Pharmacol* 1996; **27**: 1325–35.

4 Fuchs J, Zimmer G, Wolbling RH, Milbradt R. On the interaction between anthralin and mitochondria: a revision. *Arch Dermatol Res* 1986; **279**: 59–65.

5 Diezel W, Mefferth H, Sonnichsen N. Untersuchungen zum Wirkungsmechanisms von Dithranol: Erhöhte Lipidperoxidation und Enzymhemmung. *Dermatologica* 1975; **150**: 154–62.

6 Raab WP. Dithranol (anthralin) versus triacetoxyanthracene. *Br J Dermatol* 1976; **95**: 193–6.

7 Saihan EM, Albano J, Burton JL. The effect of steroid and dithranol therapy on cyclic nucleotides in psoriasis epidermis. *Br J Dermatol* 1980; **102**: 565–9.

8 Swinkels OQ, Prins M, Gerritsen MJ *et al*. An immunohistochemical assessment of the response of the psoriatic lesion to single and repeated applications of high-dose dithranol cream. *Skin Pharmacol Appl Skin Physiol* 2002; **15**: 393–400.

9 Fisher LB, Maibach HI. The effect of anthralin and its derivatives on epidermal cell kinetics. *J Invest Dermatol* 1975; **64**: 338–41.

10 Whitefield M. Pharmaceutical formulations of anthralin. *Br J Dermatol* 1981; **105** (Suppl 20): 28–32.

11 Luckacs S, Braun-Falco O. Uber das Verhalten von Dithranol (Cignolin) in Pasten und Lösungen und seine Beeingflussbarkeit durch Salicylsäure. *Hautarzt* 1973; **24**: 304–9.

12 Ponec-Waelsh M, Hulsebotsch HJ. Further studies on the interaction between anthralin, salicylic acid and zinc oxide in pastes. *Arch Dermatol Res* 1974; **249**: 141–52.

13 Raab WP, Gmeiner B. The inhibition of glucose-6-phosphate dehydrogenase activity by dithranol (anthralin), zinc ions/or salicylic acid. *Arch Dermatol Res* 1974; **251**: 87–94.

14 Schulz HJ, Schander S, Mahrle G *et al*. Combined tar-anthralin versus anthralin treatment lowers irritancy with unchanged antipsoriatic efficacy. *J Am Acad Dermatol* 1987; **17**: 19–24.

15 Wilson PD, Ive FA. Dithrocream in psoriasis. *Br J Dermatol* 1980; **103**: 105–6.

16 Thune P, Brolund L. Short- and long-contact therapy using a new dithranol formulation in individually adjusted dosages in the management of psoriasis. *Acta Derm Venereol Suppl* 1992; **172**: 28–9.

17 Agarwal R, Saraswat A, Kaur I *et al*. A novel liposomal formulation of dithranol for psoriasis: preliminary results. *J Dermatol* 2002; **29**: 529–32.

18 Runne V, Kunze J. Short duration ('minutes') therapy with dithranol for psoriasis: a new out-patient regimen. *Br J Dermatol* 1982; **106**: 135–9.

19 Runne V, Kunze J. Minute therapy of psoriasis with dithranol and its modifications. A critical evaluation based on 315 patients. *Hautarzt* 1985; **36**: 40–6.

20 Ryatt KS, Statham BN, Rowell NR. Short-contact modification of the Ingram regime. *Br J Dermatol* 1984; **111**: 455–9.
21 Fiedler-Weiss VC, Buys CM. Evaluation of anthralin in the treatment of alopecia areata. *Arch Dermatol* 1987; **123**: 1491–3.
22 Flindt-Hansen H, Tikjob G, Brandrup F. Wart treatment with anthralin. *Acta Derm Venereol (Stockh)* 1984; **64**: 177–9.

Emollients

The word emollient is derived from the Latin verb *mollire*, to soften. The term is used by dermatologists to denote materials which soften and moisturize the surface of the skin. Most of the formulations used as emollients are creams, ointments, bath oils or soap substitutes. Emollient creams and ointments are formulated using the various materials described earlier in this chapter as constituents of vehicles and are essentially vehicles without a drug to deliver. They are applied to the skin purely to take advantage of their physical properties, that is protecting, lubricating and moisturizing effects. The efficacy of an emollient is not related to the cost, although this may have some impact on cosmetic acceptability. The most effective emollient is probably white soft paraffin (petrolatum).

The value of bath oils is not well established although these are widely used in the UK. Most contain lipids such as liquid paraffin which probably help reduce the drying effect of bathing by protecting the stratum corneum with a layer of lipid. Some also contain antiseptics and antipruritic compounds which can be of additional value. The use of bath oils is best avoided for elderly patients as they tend to make the bath slippery.

The use of soaps on inflamed skin, especially in atopic dermatitis, is generally considered harmful and likely to exacerbate damage to the stratum corneum [1,2]. Compounds used as soap substitutes are lipid materials containing emulsifiers such as Aqueous Cream BP, and Emulsifying Ointment BP. Most emollient creams can be used in this way. These can effectively remove lipid-soluble dirt and contamination from the skin surface, whilst preventing the damage done to the stratum corneum by irritant surfactants. Patients with dry skin conditions do report that soap substitutes improve the condition of the skin [3]. Paradoxically, the introduction of washing with common toilet soap was accompanied by improvement in atopic dermatitis in one study [4], possibly reflecting increased compliance with other aspects of treatment.

References

1 Van der Valk PGM, Nater JP, Bleumink E. Vulnerability of the skin to surfactants in different groups of eczema patients and controls as measured by water vapour loss. *Clin Exp Dermatol* 1985; **10**: 98–103.
2 White MI, McEwan Jenkinson D, Lloyd DH. The effect of washing on the thickness of the stratum corneum in normal and atopic individuals. *Br J Dermatol* 1987; **116**: 525–30.
3 Berth-Jones J, Graham-Brown RAC. How useful are soap substitutes ? *J Dermatol Treat* 1992; **3**: 9–11.
4 Uehara M, Takada K. Use of soap in the management of atopic dermatitis. *Clin Exp Dermatol* 1985; **10**: 419–25.

Immunomodulators

Synonym
- Calcineurin inhibitors

These compounds have been developed for topical treatment of atopic dermatitis but seem likely to find numerous additional applications. There are currently two agents, tacrolimus and pimecrolimus, available in this class and others are likely to follow. The mechanism of action is similar to ciclosporin. Lymphocyte activation is suppressed by inhibition of calcineurin, a calcium and calmodulin dependent serine/threonine phosphatase. This cytoplasmic enzyme activates the nuclear factor of activated T-cells (NFAT), a transcription factor regulating numerous lymphokines in both Th1 and Th2 lymphocyte subsets, and constitutes an important link in signal transduction from the T-cell receptor to the nucleus [1]. Similar mechanisms operating in other cell types, including mast cells [2,3], antigen-presenting cells [4] and keratinocytes [5], may provide additional targets for these drugs. In contrast to ciclosporin, these molecules have a sufficiently low molecular weight to penetrate the stratum corneum, at least when barrier function is impaired as is the case in atopic dermatitis. They are therefore active when applied topically. Both compounds have been under investigation in clinical trials for several years now. A notable advantage of these agents is that they do not induce cutaneous atrophy [6,7], even with long-term regular application [8–10], and it is therefore possible to apply them to facial and flexural areas where prolonged use of topical corticosteroids causes concern. Theoretically the local immunosuppression related to these compounds could increase the risks of infections and neoplasia. In the numerous trials on atopic dermatitis infections have not been more frequent than expected. The risk of neoplasia also remains theoretical.

Tacrolimus

Tacrolimus (FK-506) is a macrolide lactam antibiotic (macrolactam) discovered in Japan, where it was first isolated from a soil fungus *Streptomyces tsukubaensis*. It has been used systemically in transplantation for over 15 years and is known to be effective, used systemically, in treatment of psoriasis [11]. It has a molecular weight of 822 Da and a complex structure (Fig. 73.11). The efficacy of tacrolimus in atopic dermatitis has been demonstrated in several placebo-controlled trials in both adults [12,13] and children [14,15]. In comparative trials, tacrolimus ointment 0.1% applied twice daily is comparable in efficacy to potent topical corticosteroids such as hydrocortisone butyrate 0.1% [16] and betamethasone valerate 0.12% ointment [17]. It is been more effective than hydrocortisone acetate 1% ointment in children [15] and was more effective than the moderately potent alclometasone dipropionate 0.1% ointment in treatment of eczema on the face and neck in adults [18]. In children, a lower concentration of 0.03% tacrolimus has proved nearly as effective as 0.1% [14,15], whilst in adults there is a more marked difference between these concentrations and 0.1% is clearly more effective [16,19]. The most frequently encountered side effect is a burning sensation lasting for a few minutes after application. This tends to resolve after a few days and is very rarely of sufficient severity to require withdrawal of the treatment. Systemic exposure is low and drug levels in blood are usually too low to measure [14,20,21]. Using data obtained from application of 0.3% tacrolimus ointment, systemic bioavailability has been estimated at 0.5% of that obtained by intravenous administration [21]. It is therefore unlikely that topical application of tacrolimus

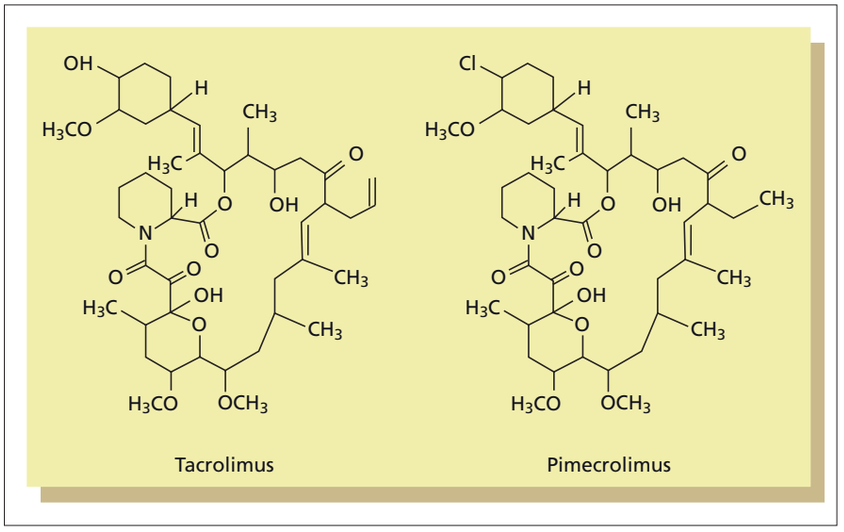


Fig. 73.11 The structures of tacrolimus and pimecrolimus.

will exhibit systemic activity. Furthermore, systemic exposure tends to fall as the eczema improves, indicating that penetration of the drug is reduced as barrier function is restored [22].

Additional applications for topical tacrolimus have currently been less formally investigated and it should be noted, in particular, that extensive safety data relating to systemic exposure are available only for atopic dermatitis. The use of topical tacrolimus in Netherton's syndrome (ichthyosis linearis circumflexa) can result in clinically significant systemic exposure to the drug [23], indicating that some care is required.

Reports indicate that topical tacrolimus is effective in treatment of several other varieties of eczema including chronic actinic dermatitis [24], endogenous hand eczema [25] and eyelid dermatitis [26]. In a guinea pig model, irritant and allergic contact dermatitis have been suppressed [27]. Treatment of psoriasis has so far proved less successful [28] although the author has treated facial and flexural psoriasis with unequivocal improvement and similar reasonably successful results have been reported by others [29]. This relatively modest response in psoriasis is somewhat surprising given that systemic use of calcineurin inhibitors (ciclosporin and tacrolimus) is highly effective and a good response has also been observed when tacrolimus was applied under occlusion in a microplaque assay [30]. It would seem, however, that penetration of the drug through the plaques of psoriasis vulgaris is not adequate. Sadly, the efficacy of topical tacrolimus in the Dundee experimental bald rat model of alopecia areata [31] has not so far been reproduced in the treatment of human cases of this disease. Development of a more appropriate formulation might improve results in psoriasis and alopecia areata.

There are more encouraging reports of efficacy of topical tacrolimus in a variety of other dermatoses including oral and genital erosive lichen planus [32–36], pyoderma gangrenosum [37–39], cutaneous graft-versus-host disease [40], rheumatoid leg ulceration [41], cutaneous sarcoidosis [42], steroid-induced rosacea [43], uraemic pruritus [44], vitiligo [45,46], discoid lupus erythematosus [47], eosinophilic pustular folliculitis [48] and epidermolysis bullosa [49]. Oral and perineal lesions of Crohn's disease have responded [50] and topical tacrolimus has been effective in suppression of skin allograft rejection [51]. Improvement has been observed in Netherton's syndrome [23,52], although, as discussed above, significant systemic absorption may occur in this disease. Three cases of erosive pustular dermatosis of the legs responded to topical tacrolimus [53].

Pimecrolimus

Pimecrolimus (SDZ ASM 981) is another macrolactam with a structure similar, though not identical, to tacrolimus, with a molecular weight of 810 Da (Fig. 73.11). The relatively small differences in structure compared to tacrolimus confer greater lipophilicity but reduce potency. Most of the clinical research on this compound has so far been in atopic dermatitis. Placebo-controlled trials have demonstrated efficacy and safety of pimecrolimus 1% cream in adults [54–56], and in children from age 3 months upward [57,58]. In a comparative study, this treatment was less effective than betamethasone valerate 0.1% cream [55]. Used in long-term studies, pimecrolimus has effectively inhibited flares of the disease and reduced the requirement for topical corticosteroids [56,58]. Systemic exposure to pimecrolimus has been low and usually undetectable [59,60]. Topical pimecrolimus has been safe and well tolerated; although a burning sensation is sometimes reported in the treated areas this usually resolves after a few days. Infections have not been increased and there has been no evidence of increased neoplasia.

Experience with pimecrolimus in other skin diseases has been very limited so far. In animal models, pimecrolimus inhibits induction of contact allergic dermatitis [61]. An initial report suggests that it may suppress established nickel dermatitis [62]. Used systemically [63] and also applied topically under occlusion, it can be effective in psoriasis [64]. A response has also been reported in a case of seborrhoeic dermatitis [65].

Ciclosporin (cyclosporin)

Despite the best endeavours of many investigators over the years to develop topical uses for ciclosporin this has failed to find any

consistently useful role. Ciclosporin has a high molecular weight of 1202 Da and this is probably the reason why it does not penetrate through the skin in sufficient concentration to be effective. Early reports of efficacy in oral erosive lichen planus may have been the result of significant systemic absorption. A controlled study using triamcinolone as comparator found no difference between the treatments and the improvement observed was only modest [66].

References

1 Ruzicka T, Assmann T, Homey B. Tacrolimus. The drug for the turn of the millenium? *Arch Dermatol* 1999; **135**: 574–80.

2 De Paulis A, Stellato C, Cirillo R *et al*. Antiinflammatory effect of FK-506 on human skin mast cells. *J Invest Dermatol* 1992; **99**: 723–8.

3 Zuberbier T, Chong S-U, Grunow K *et al*. The ascomycin macrolactam pimecrolimus (Elidel, SDZ ASM 981) is a potent inhibitor of mediator release from human dermal mast cells and peripheral blood basophils. *J Allergy Clin Immunol* 2001; **108**: 275–80.

4 Wollenberg A, Sharma S, von Bubnoff D *et al*. Topical tacrolimus (FK506) leads to profound phenotypic and functional alterations of epidermal antigen-presenting dendritic cells in atopic dermatitis. *J Allergy Clin Immunol* 2001; **107**: 519–25.

5 Al-Daraji WI, Grant KR, Ryan K *et al*. Localization of calcineurin/NFAT in human skin and psoriasis and inhibition of calcineurin/NFAT activation in human keratinocytes by cyclosporin A. *J Invest Dermatol* 2002; **118**: 779–88.

6 Reitamo S, Rissanen J, Remitz A *et al*. Tacrolimus ointment does not affect collagen synthesis: results of a single-centre randomized trial. *J Invest Dermatol* 1998; **111**: 396–8.

7 Queille-Roussel C, Paul C, Duteil L *et al*. The new topical ascomycin derivative SDZ ASM 981 does not induce skin atrophy when applied to normal skin for 4 weeks: a randomized, double-blind controlled study. *Br J Dermatol* 2001; **144**: 507–13.

8 Kapp A, Papp K, Bingham A *et al*. Long-term management of atopic dermatitis in infants with topical pimecrolimus, a nonsteroid anti-inflammatory drug. Flare reduction in eczema with Elidel (infants) multicenter investigator study group. *J Allergy Clin Immunol* 2002; **110**: 277–84.

9 Wahn U, Bos JD, Goodfield M *et al*. Efficacy and safety of pimecrolimus cream in the long-term management of atopic dermatitis in children. *Pediatrics* 2002; **110**: e2.

10 Kang S, Lucky AW, Pariser D *et al*. Long-term safety and efficacy of tacrolimus ointment for the treatment of atopic dermatitis in children. *J Am Acad Dermatol* 2001; **44**: S58–64.

11 Rappersberger K, Meingassner JG, Fialla R *et al*. Clearing of psoriasis by a novel immunosuppressive macrolide. *J Invest Dermatol* 1996; **106**: 701–10.

12 Nakagawa H, Etoh T, Ishibashi Y *et al*. Tacrolimus ointment for atopic dermatitis. *Lancet* 1994; **344**: 883.

13 Ruzicka T, Bieber T, Schopf E *et al*. A short-term trial of tacrolimus ointment for atopic dermatitis. *New Engl J Med* 1997; **337**: 816–21.

14 Paller A, Eichenfield LF, Leung DY *et al*. A 12-week study of tacrolimus ointment for the treatment of atopic dermatitis in pediatric patients. *J Am Acad Dermatol* 2001; **44** (1 Suppl.): S47–57.

15 Reitamo S, Van Leent EJ, Ho V *et al*. Efficacy and safety of tacrolimus ointment compared with that of hydrocortisone acetate ointment in children with atopic dermatitis. *J Allergy Clin Immunol* 2002; **109**: 539–46.

16 Reitamo S, Rustin M, Ruzicka T *et al*. Efficacy and safety of tacrolimus ointment compared with hydrocortisone butyrate ointment in adult patients with atopic dermatitis. *J Allergy Clin Immunol* 2002; **109**: 547–55.

17 FK506 ointment study group. Phase III comparative study of FK506 ointment versus betamethasone valerate ointment in atopic dermatitis of the trunk and extremities. *Nishinihon J Dermatol* 1997; **59**: 870–9.

18 FK506 ointment study group. Phase III comparative study of FK506 ointment versus alclometasone dipropionate ointment in atopic dermatitis of the face and neck. *Hifuka Kiyo* 1997; **92**: 277–88.

19 Hanifin JM, Ling MR, Langley R *et al*. Tacrolimus ointment for the treatment of atopic dermatitis in adult patients: part I, efficacy. *J Am Acad Dermatol* 2001; **44** (1 Suppl.): S28–38.

20 Bekersky I, Fitzsimmons W, Tanase A *et al*. Nonclinical and early clinical development of tacrolimus ointment for the treatment of atopic dermatitis. *J Am Acad Dermatol* 2001; **44**: S17–27.

21 Soter NA, Fleischer AB, Webster GF *et al*. Tacrolimus ointment for the treatment of atopic dermatitis in adult patients: Part II, safety. *J Am Acad Dermatol* 2001; **44**: S39–46.

22 Alaiti S, Kang S, Fiedler VC *et al*. Tacrolimus (FK506) ointment for atopic dermatitis: a phase I study in adults and children. *J Am Acad Dermatol* 1998; **38**: 69–76.

23 Allen A, Siegfried E, Silverman R *et al*. Significant absorption of topical tacrolimus in 3 patients with Netherton syndrome. *Arch Dermatol* 2001; **137**: 747–50.

24 Suga Y, Hashimoto Y, Matsuba S *et al*. Topical tacrolimus for chronic actinic dermatitis. *J Am Acad Dermatol* 2002; **46**: 321–3.

25 Schnopp C, Remling R, Mohrenschlager M *et al*. Topical tacrolimus (FK506) and mometasone furoate in treatment of dyshidrotic palmar eczema: a randomized, observer-blinded trial. *J Am Acad Dermatol* 2002; **46**: 73–7.

26 Krupnick A, Clarke J, Fadness D *et al*. Tacrolimus 0.1% ointment in the treatment of eyelid dermatitis. *J Invest Dermatol* 2001; **117**: 533.

27 Lauerma AI, Stein BD, Homey B *et al*. Topical FK506: suppression of allergic and irritant contact dermatitis in the guinea pig. *Arch Dermatol Res* 1994; **286**: 337–40.

28 Zonneveld IM, Rubins A, Jablonska S *et al*. Topical tacrolimus is not effective in chronic plaque psoriasis. A pilot study. *Arch Dermatol* 1998; **134**: 1101–2.

29 Yamamoto T, Nishioka K. Topical tacrolimus is effective for facial lesions of psoriasis. *Acta Derm Venereol* 2000; **80**: 451.

30 Remitz A, Reitamo S, Erkko P *et al*. Tacrolimus ointment improves psoriasis in a microplaque assay. *Br J Dermatol* 1999; **141**: 103–7.

31 Mc Elwee KJ, Rushton DH, Trachy R, Oliver RF. Topical FK506: a potent immunotherapy for alopecia areata? Studies using the Dundee experimental bald rat model. *Br J Dermatol* 1997; **137**: 491–7.

32 Vente C, Reich K, Rupprecht R, Neumann C. Erosive mucosal lichen planus: response to topical treatment with tacrolimus. *Br J Dermatol* 1999; **140**: 338–42.

33 Lener EV, Brieva J, Schachter M *et al*. Successful treatment of erosive lichen planus with topical tacrolimus. *Arch Dermatol* 2001; **137**: 419–22.

34 Rozycki TW, Rogers RS 3rd, Pittelkow MR *et al*.Topical tacrolimus in the treatment of symptomatic oral lichen planus: a series of 13 patients. *J Am Acad Dermatol* 2002; **46**: 27–34.

35 Kaliakatsou F, Hodgson TA, Lewsey JD. Management of recalcitrant ulcerative oral lichen planus with topical tacrolimus. *J Am Acad Dermatol* 2002; **46**: 35–41.

36 Kirtschig G, Van Der Meulen AJ, Ion Lipan JW, Stoof TJ. Successful treatment of erosive vulvovaginal lichen planus with topical tacrolimus. *Br J Dermatol* 2002; **147**: 625–6.

37 Reich K, Vente C, Neumann C. Topical tacrolimus for pyoderma gangrenosum. *Br J Dermatol* 1998; **139**: 755–7.

38 Jolles S, Niclasse S, Benson E. Combination oral and topical tacrolimus in therapy-resistant pyoderma gangrenosum. *Br J Dermatology* 1999; **140**: 564–5.

39 Lyon CC, Stapleton M, Smith AJ *et al*. Topical tacrolimus in the management of peristomal pyoderma gangrenosum. *J Dermatol Treat* 2001; **12**: 13–7.

40 Choi CJ, Nghiem P. Tacrolimus ointment in the treatment of chronic cutaneous graft-vs-host disease: a case series of 18 patients. *Arch Dermatol* 2001; **137**: 1202–6.

41 Schuppe H, Richter-Hintz D, Stierle HE *et al*. Topical tacrolimus for recalcitrant leg ulcer in rheumatoid arthritis. *Rheumatology (Oxford)* 2000; **39**: 105–6.

42 Katoh N, Mihara H, Yasuno H. Cutaneous sarcoidosis successfully treated with topical tacrolimus. *Br J Dermatol* 2002; **147**: 154–6.

43 Goldman D. Tacrolimus ointment for the treatment of steroid-induced rosacea: a preliminary report. *J Am Acad Dermatol* 2001; **44**: 995–8.

44 Pauli-Magnus C, Klumpp S, Alscher DM *et al*. Short-term efficacy of tacrolimus ointment in severe uremic pruritus. *Perit Dial Int* 2000; **20**: 802–3.

45 Grimes PE, Soriano T, Dytoc MT. Topical tacrolimus for repigmentation of vitiligo. *J Am Acad Dermatol* 2002; **47**: 789–91.

46 Smith DA, Tofte SJ, Hanifin JM. Repigmentation of vitiligo with topical tacrolimus. *Dermatology* 2002; **205**: 301–3.

47 Walker SL, Kirby B, Chalmers RJ. The effect of topical tacrolimus on severe recalcitrant chronic discoid lupus erythematosus. *Br J Dermatol* 2002; **147**: 405–6.

48 Dale S, Shaw J. Clinical picture: eosinophilic pustular folliculitis. *Lancet* 2000; **356**: 1235.

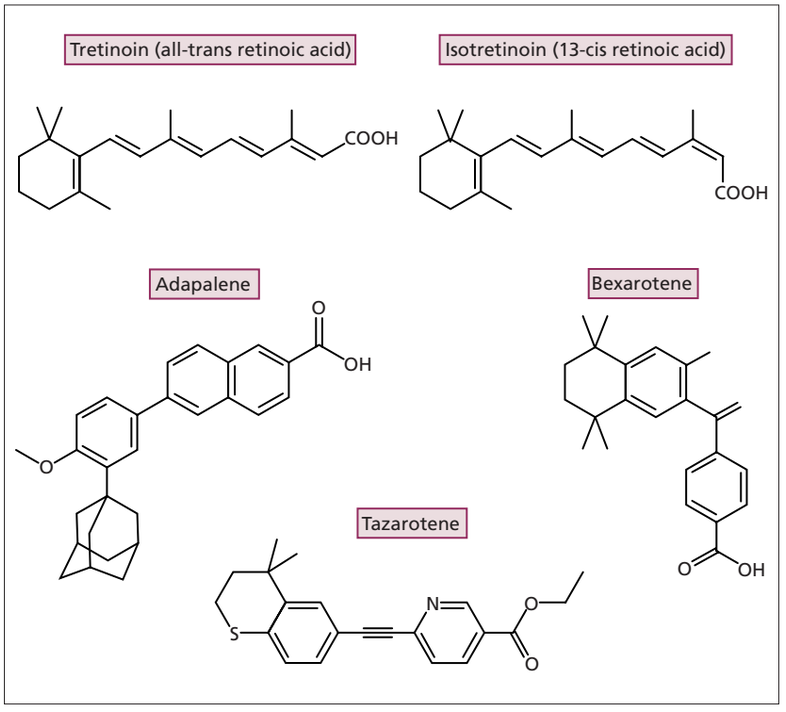


Fig. 73.12 Retinoid molecules used topically.

49 Carroll PB, Rilo HL, Abu Elmagd K *et al*. Effect of tacrolimus (FK506) in dystrophic epidermolysis bullosa: rationale and preliminary results. *Arch Dermatol* 1994; **130**: 1457–8.

50 Casson DH, Eltumi M, Tomlin S *et al*. Topical tacrolimus may be effective in the treatment of oral and perineal Crohn's disease. *Gut* 2000; **47**: 436–40.

51 Yuzawa K, Taniguchi H, Seino K *et al*. Topical immunosuppression in skin grafting with FK506 ointment. *Transplant Proc* 1996; **28**: 137–9.

52 Suga Y, Tsuboi R, Hashimoto Y *et al*. A case of ichthyosis linearis circumflexa successfully treated with topical tacrolimus. *Arch Dermatol* 2000; **42**: 520–2.

53 Brouard MC, Prins C, Chavaz P *et al*. Erosive pustular dermatosis of the leg: report of three cases. *Br J Dermatol* 2002; **147**: 765–9.

54 Van Leent EJM, Graber M, Thurston M *et al*. Effectiveness of the ascomycin macrolactam SDZ ASM 981 in the topical treatment of atopic dermatitis. *Archives of Dermatology* 1998; **134**: 805–9.

55 Luger T, Van Leent EJ, Graeber M *et al*. SDZ ASM 981: an emerging safe and effective treatment for atopic dermatitis. *Br J Dermatol* 2001; **144**: 788–94.

56 Meurer M, Folster-Holst R, Wozel G *et al*. Pimecrolimus cream in the long-term management of atopic dermatitis in adults: a six-month study. D*ermatology* 2002; **205**: 271–7.

57 Eichenfield LF, Lucky AW, Boguniewicz M *et al*. Safety and efficacy of pimecrolimus (ASM 981) cream 1% in the treatment of mild and moderate atopic dermatitis in children and adolescents. *J Am Acad Dermatol* 2002; **46**: 495–504.

58 Kapp A, Papp K, Bingham A *et al*. Long-term management of atopic dermatitis in infants with topical pimecrolimus, a nonsteroid anti-inflammatory drug. *J Allergy Clin Immunol* 2002; **110**: 277–84.

59 Harper J, Green A, Scott G *et al* First experience of topical SDZ ASM 981 in children with atopic dermatitis. *Br J Dermatol* 2001; **144**: 781–7.

60 Van Leent EJM, Ebelin M-E, Burtin P *et al*. Low systemic exposure after repeated topical application of pimecrolimus (Elidel(R), SDZ ASM 981) in patients with atopic dermatitis. *Dermatology* 2002; **204**: 63–8.

61 Meingassner JG, Grassberger M, Fahrngruber H *et al*. A novel anti-inflammatory drug, SDZ ASM 981, for the topical and oral treatment of skin diseases: in vivo pharmacology. *Br J Dermatol* 1997; **137**: 568–76.

62 Queille-Roussel C, Graeber M, Thurston M *et al*. SDZ ASM 981 is the first non-steroid that suppresses established nickel contact dermatitis elicited by allergen challenge. *Contact Dermatitis* 2000; **42**: 349–50.

63 Rappersberger K, Komar M, Ebelin ME *et al*. Pimecrolimus identifies a common genomic anti-inflammatory profile, is clinically highly effective in psoriasis and is well tolerated. *J Invest Dermatol* 2002; **119**: 876–87.

64 Mrowietz U, Graeber M, Brautigam M *et al*. The novel ascomycin derivative SDZ ASM 981 is effective for psoriasis when used topically under occlusion. *Br J Dermatol* 1998; **139**: 992–6.

65 Crutchfield CE 3rd. Pimecrolimus: a new treatment for seborrheic dermatitis. *Cutis* 2002; **70**: 207–8.

66 Sieg P, Von Domarus H, Von Zitzewitz V *et al*. Topical cyclosporin in oral lichen planus: a controlled, randomized, prospective trial. *Br J Dermatol* 1995; **132**: 790–4.

Retinoids

The retinoids can be defined either as compounds related structurally to vitamin A (retinol) or as compounds that are able to interact with retinoid receptors. The latter definition has become more useful as an increasing number of synthetic 'retinoids' are developed with diverse structures. Formulae of natural and synthetic retinoids used topically are shown in Fig. 73.12. Topical retinoic acid has been used in treatment of acne vulgaris for over three decades. During this period much has been learned about the fundamental role played by endogenous retinoids in the regulation of cell differentiation and proliferation and about the mechanisms involved. Retinoids are now used for many indications, including psoriasis, photoageing and numerous disorders of keratinization as well as for suppression of dysplasia and malignancy.

The activity of endogenous retinoids within the cell is regulated by binding proteins known as cellular retinol binding proteins (CRBP-I and -II) and cellular retinoic acid binding proteins (CRABP-I and -II). These proteins are widely distributed throughout the body in many cell types. CRABP-II predominates in skin, and is found in keratinocytes and fibroblasts [1]. This protein is upregulated by retinoic acid [2] and other compounds demon-

strating retinoid activity, and is believed to play a role in regulating the availability of free retinoic acid within the cell.

Within the nucleus, retinoids bind to specific receptors, retinoic acid receptors (RAR α, β and γ) and retinoid X receptors (RXR α, β and γ). Alternative splicing of each of these receptors generates further diversity (the subtypes being known as RAR-α1, RAR-α2 etc.) [3]. All-*trans* retinoic acid is the endogenous ligand for the RARs whilst 9-*cis* retinoic acid is the endogenous ligand for the RXRs. The receptors most abundantly expressed in the epidermis are RAR-γ and RXR-α, while RAR-α and RXR-β are present at relatively low levels. These receptors bind to specific elements of DNA, known as response elements, within the regulatory regions of numerous genes; this interaction may increase or decrease transcription of the gene. There are usually several such response elements involved in regulating the transcription of any single gene. The retinoid receptors are mainly active as heterodimers of RXR and RAR. RXRs can also dimerize with several other similar receptors, such as the vitamin D receptor, the thyroid receptor and orphan receptors (which have no established endogenous ligand). This range of different receptors and their dimers, the various possible states of binding with different ligands and the wide range of different response elements, allows for the highly diverse and complex signalling required to regulate cellular metabolism. The end result of these processes acting on numerous different genes is that retinoids demonstrate a tendency to normalize keratinocyte differentiation in diverse circumstances where this is disturbed.

Metabolism of retinoids takes place within keratinocytes. The initial step is usually 4-hydroxylation by cytochrome-P450 enzyme systems, such as CYP2S1 and CYP26, which can be induced by their substrate and which may show considerable inter-individual variation [4]. This variation may explain some of the variability between individuals in responses to topical retinoids.

Systemic retinoids are known to be highly teratogenic when administered in doses sufficient to induce the mucocutaneous symptoms associated with hypervitaminosis A. This has led to some concern about the potential for the topical application of retinoids to exert teratogenic effects. Fortunately this risk is entirely hypothetical. Systemic exposure to retinoids applied topically seems to be minimal [5,6]. Nonetheless, it is generally recommended that even the topical use of retinoids should be avoided during pregnancy.

The naturally occurring 'endogenous' retinoids include vitamin A (retinol), which is metabolized within most cells, including keratinocytes, to retinoic acid. This process seems to be regulated by a variety of mechanisms so that the level of free retinoic acid is tightly controlled. Retinoic acid can isomerize to 13-*cis* and 9-*cis* retinoic acid, a process which occurs readily in the presence of visible light. The synthetic retinoids currently used in the topical treatment of skin disease are adapalene, bexarotene and tazarotene. All these compounds are effectively absorbed into the epidermis when applied topically.

Retinol

Synonym
- Vitamin A

Vitamin A is used widely in cosmetic products and tends to be regarded as a vitamin supplement rather than a medicament in this context. However, it is clear that retinol applied topically to the skin is absorbed into the epidermis and exhibits many of the pharmacological properties of retinoic acid. Topical application of retinol increases levels of retinyl esters within the epidermis [7]. These esters of retinol with long chain fatty acids constitute an intracellular reservoir of inactive vitamin A. Esterification of retinol is induced by retinoic acid and this probably represents an autoregulatory mechanism which inhibits excess synthesis of retinoic acid [8]. In addition, topically applied retinol induces 4-hydroxylase activity, and thus increases metabolism and inactivation of retinoic acid [9]. Levels of cellular retinoid binding proteins CRABP-II and CRBP are also induced by topical application of retinol [7].

Retinol increases epidermal thickness in a manner similar to retinoic acid but causes much less irritation [7,10]. Retinol 10% gel has been used as a component of a depigmenting regimen with results considered comparable to those obtained from retinoic acid. However, this high concentration was irritant [11].

Retinoic acid

Synonyms
- Tretinoin
- All-*trans*-retinoic acid
- Vitamin A acid

Retinoic acid is well absorbed into the skin when applied topically and exerts potent local effects on cellular metabolism. This is the endogenous ligand for the retinoic acid (RAR) receptors. Isomerization of retinoic acid results in formation of 13-*cis* and 9-*cis* retinoic acid [12], the latter being the naturally occurring ligand for the RXR receptors. These isomerizations are accelerated in visible light.

Retinoic acid is most frequently used in treatment of acne vulgaris. It is normally applied once or twice daily at a concentration of 0.01%–0.025% in a lotion, cream or gel. Higher concentrations (e.g. 0.1%) have often been used in the past. It is particularly effective in reducing comedones [13,14] and is therefore often used in cases where these non-inflammatory lesions are prominent. It may cause some initial exacerbation of the symptoms for the first 6 weeks of treatment. During this period comedones are expelled and then prevented from reforming if use of retinoic acid is continued. Inflammatory lesions of acne are also reduced, possibly as a secondary event following the reduction in comedones. Irritant reactions are common and may even accelerate the response. However, neither erythema nor peeling is essential for response to be achieved [15]. The irritation can be managed by reducing the concentration or frequency of application. Topical retinoic acid is also effective for treatment of comedonal acne induced by systemic corticosteroids [16].

Topical retinoic acid improves several features of photoageing, including fine and coarse wrinkling, and dyspigmentation [17]. The clinical improvement is accompanied by reversal of epidermal atrophy and dysplasia, and increased collagen synthesis in the papillary dermis [18]. Similar effects can also be induced in

intrinsically aged skin [19]. Treatment may need to be applied daily for 4 months or more to achieve these effects. A formulation containing 0.05% retinoic acid in an emollient cream base is marketed specifically for treatment of photoageing. Lower concentrations can also be effective [20].

Tretinoin has both a therapeutic and prophylactic effect on chemically-induced skin tumours, and may be both a promoter and inhibitor of UVB carcinogenesis. Clinically, it exhibits an antineoplastic effect, and may be used to treat small solar keratoses either alone [21], or in combination with 5% 5-fluorouracil cream [22]. It also has a 'normalizing' effect on the histological appearance of dysplastic naevi [23].

Despite theoretical mechanisms and early claims that it could be effective, topical application of retinoic acid has not found a role in the treatment of psoriasis.

Retinoic acid can be effective in reducing various forms of hyperpigmentation (see 'Depigmenting agents', above).

Another interesting property of tretinoin is its ability to accelerate wound healing [24]. It needs to be applied before wounding, preferably for several weeks. Results of application after wounding have not been consistent, probably due to the irritant effect. The ability of retinoic acid to promote healing has been used to improve results from procedures such as chemical peeling [25] and dermabrasion [26].

A number of other conditions have been treated with topical retinoic acid with varying success. It is of value in the treatment of senile comedones [27]. Comedo and warty naevi may show some response, as may plane warts and reactive perforating collagenosis. Some cases of Darier's disease respond, especially if mild or localized [28]. Keratosis pilaris was reported to respond by eight of 49 respondents in a patient survey [29]. Of the ichthyoses, the lamellar variety appears to be helped most, although ichthyosis vulgaris was also responsive in a four-centre trial [30], as was erythrokeratoderma variabilis [31]. It can be useful in oral lichen planus [32], and in geographic tongue [33]. Fox–Fordyce disease (apocrine miliaria) has been effectively treated with a 0.1% solution [34]. Hydrocortisone cream (1%) has been recommended to control the associated axillary discomfort [35]. Hypertrophic scars and keloids have been reported to respond to a daily application of a 0.05% solution [36,37].

Although sensitization to retinoic acid has been reported this seems to be a rare event [38].

Isotretinoin

Synonym
- 13-*cis* retinoic acid

Isotretinoin is readily isomerized to tretinoin and *vice versa*. It therefore exhibits a similar receptor specificity to tretinoin, interacting with RARs. Isotretinoin is used both topically and systemically for treatment of acne vulgaris. When used topically it is considered somewhat less irritant than tretinoin but may be more so than adapalene [39]. The efficacy of isotretinoin 0.05% gel in acne vulgaris has been confirmed in comparison with placebo [40], and seems similar to that of retinoic acid [41]. In a trial comparing topical isotretinoin with benzoyl peroxide, the latter treatment improved inflammatory lesions more rapidly although both comedones and inflammatory lesions eventually responded to a similar degree [42]. Topical isotretinoin is believed to work mainly by inhibiting comedogenesis, although it is also known to penetrate into sebaceous glands [43] and may reduce sebum secretion [44].

Isotretinoin cream does not appear effective in treatment of chronic plaque psoriasis [45]. However, it shares with tretinoin the ability to reduce features of photoageing [46,47]. It also demonstrates antineoplastic properties. A limited degree of response is seen in treatment of actinic keratoses when applied twice at a concentration of 0.1% for up to 24 weeks [48], and a degree of efficacy was shown in a trial on topical treatment of basal cell carcinoma although complete regression was only observed in four out of 50 cases treated [49].

In isolated reports, topical isotretinoin has proved helpful in treatment of perifolliculitis capitis abscedens et suffodiens [50], oral [51] and vulval [52] leukoplakia, oral lichen planus [53], hyperkeratosis of the nipple [54] and actinic granuloma [55]. It has not proved effective in melasma [56]. In treatment of Darier's disease isotretinoin can prove helpful in treatment of small areas of hyperkeratosis but is also irritant [57,58].

Alitretinoin

Synonym
- 9-*cis* retinoic acid

Alitretinoin has recently been introduced as a systemic agent for treatment of hand dermatitis, but has also been used as a 0.1% gel applied twice daily for treatment of skin lesions of Kaposi's sarcoma. It may cause local rash or discomfort, and is a weak photosensitizer.

Adapalene

Adapalene is a synthetic retinoid which has been developed for treatment of acne vulgaris. In randomized comparative trials adapalene gel 0.1% has proved equally effective and better tolerated than retinoic acid gel 0.025% [39]. In comparison with topical isotretinoin, adapalene was slightly more effective and less irritant [59,60]. Adapalene appears to retain comedolytic activity whilst showing less potential for irritancy that retinoic acid. It exhibits specificity for RAR-β and γ receptors with low affinity for RAR-α relative to retinoic acid [61]. It is highly lipophilic, a property likely to enhance efficacy by increasing penetration of the hair follicle. In addition, adapalene has anti-inflammatory properties which may improve both efficacy and tolerability [61]. Formulations available are cream, aqueous gel, lotion and single-use pledgets, all containing 0.1% adapalene.

Bexarotene

Bexarotene is a novel synthetic retinoid with specificity for RXR receptors. Compounds with this pattern of receptor specificity are sometimes called rexinoids. It has proved helpful in the treatment of cutaneous T-cell lymphoma and can be used orally as well as topically in this indication. In a study on early (plaque stage) cutaneous T-cell lymphoma, topical treatment with bexarotene gel

in concentrations ranging up to 1% applied up to four times daily achieved complete clinical clearance in 21% of cases and partial response in a further 42% [62]. The median time to response was 20 weeks. Topical bexarotene is produced as a 1% gel formulation. Treatment is usually commenced cautiously with applications on alternate days, gradually increased up to four times daily [63].

Tazarotene

Tazarotene is a synthetic retinoid. It is a pro-drug which is rapidly hydrolysed to its active form, tazarotenic acid. The molecule has a rigid structure in contrast to that of retinoic acid which can undergo conformational changes. Tazarotene exhibits a degree of receptor specificity, interacting with RARs α, β and γ. The latter receptor is likely to be most important in the epidermis. Tazarotene does not bind to RXRs and, unlike retinoic acid, it is not susceptible to isomerization into a conformation which might do so [64].

It has been developed mainly for treatment of psoriasis and acne vulgaris. It is also known to be effective in treatment of psoriasis when administered orally.

The efficacy of topical tazarotene in psoriasis has been established in placebo-controlled trials, around 65% of patients showing 50% or greater improvement after 12 weeks of treatment with 0.1% tazarotene gel once daily [65]. In more recent studies investigating a cream formulation, 39–51% of patients were reported to experience clinical success after application of 0.1% tazarotene cream once daily for 12 weeks [66]. In a comparative study, the global improvement on 0.1% tazarotene gel applied once daily was slightly less than that obtained from 0.05% fluocinonide cream applied twice daily. In all of these trials, and in contrast to fluocinonide, the response to tazarotene was notably well maintained during the 12 weeks after treatment was stopped [67]. Psoriatic onycholysis and nail pitting were improved by tazarotene in a small controlled trial [68]. Irritant reactions at the application site are common, so tazarotene is sometimes used in conjunction with a topical corticosteroid. It has also been used with phototherapy. There are isolated reports of severe genital ulceration [69] and of pyogenic granuloma developing during topical treatment of psoriasis with tazarotene. The latter is a well recognized side effect associated with systemic retinoids [70].

Tazarotene 0.1% gel has been shown to be effective in acne vulgaris in a placebo-controlled trial, even when applied once daily for short contact periods of 30 s to 5 min [71]. In comparison with tretinoin in a 0.1% microsponge gel, tazarotene 0.1% gel proved more effective. The tolerability of the two treatments was considered comparable [72]. In a comparative study using once-daily applications, tazarotene 0.1% gel proved more effective than adapalene 0.1% gel although it was also slightly more irritant [73].

Tazarotene seems to share with retinoic acid the ability to improve photoageing. In a trial of 1-year treatment duration, 0.1% tazarotene cream applied once daily significantly improved several features of photoaged skin [74].

In small trials, tazarotene 0.1% gel was effective in management of oral lichen planus [75], and an oil in water emulsion containing 0.01% tazarotene applied each night for up to 8 weeks proved helpful in keratosis pilaris [76]. In single cases or small series, useful responses to topical application of tazarotene have been reported in lamellar ichthyosis [77–80], X-linked ichthyosis and ichthyosis vulgaris [79], confluent and reticulate papillomatosis [81], elastosis perforans serpiginosa [82], Darier's disease [83,84] and warty dyskeratoma [85], pseudoacanthosis nigricans [86], spiny keratoderma [87], keratoderma blenorrhagica [88] and discoid lupus erythematosus [89].

Tazarotene is produced in gel and cream formulations at concentrations of 0.1 and 0.05%. The higher concentration appears more effective in psoriasis but also more irritant. In treatment of acne the higher concentration is used most frequently.

References

1 Astrom A, Tavakkol A, Pettersson U *et al*. Molecular cloning of two human cellular retinoic acid-binding proteins (CRABP). Retinoic acid-induced expression of CRABP-II but not CRABP-I in adult human skin in vivo and in skin fibroblasts in vitro. *J Biol Chem* 1991; **266**: 17662–6.

2 Elder JT, Cromie MA, Griffiths CE *et al*. Molecular cloning of two human cellular retinoic acid-binding proteins. Stimulus-selective induction of CRABP-II mRNA: a marker for retinoic acid action in human skin. *J Invest Dermatol* 1993; **100**: 356–9.

3 Craven NM, Griffiths CEM. Topical retinoids and cutaneous biology. *Clin Exp Dermatol* 1996; **21**: 1–10.

4 Smith G, Wolf CR, Deeni YY *et al*. Cutaneous expression of cytochrome P450 CYP2S1: individuality in regulation by therapeutic agents for psoriasis and other skin diseases. *Lancet* 2003; **361**: 1336–43.

5 Chen C, Jensen BK, Mistry G *et al*. Negligible systemic absorption of topical isotretinoin cream: implications for teratogenicity. *J Clin Pharmacol* 1997; **37**: 279–84.

6 Johnson EM. A risk assessment of topical tretinoin as a potential human developmental toxin based on animal and comparative human data. *J Am Acad Dermatol* 1997; **36**: S86–90.

7 Kang S, Duell EA, Fisher GJ *et al*. Application of retinol to human skin in vivo induces epidermal hyperplasia and cellular retinoid binding proteins characteristic of retinoic acid but without measurable retinoic acid levels or irritation. *J Invest Dermatol* 1995; **105**: 549–56.

8 Kurlandsky SB, Duell EA, Kang S *et al*. Auto-regulation of retinoic acid biosynthesis through regulation of retinol esterification in human keratinocytes. *J Biol Chem* 1996; **271**: 15346–52.

9 Duell EA, Kang S, Voorhees JJ. Retinoic acid isomers applied to human skin in vivo each induce a 4-hydroxylase that inactivates only trans retinoic acid. *J Invest Dermatol* 1996; **106**: 316–20.

10 Duell EA, Kang S, Voorhees JJ. Unoccluded retinol penetrates human skin in vivo more effectively than unoccluded retinyl palmitate or retinoic acid. *J Invest Dermatol* 1997; **109**: 301–5.

11 Yoshimura K, Momosawa A, Aiba E *et al*. Clinical trial of bleaching treatment with 10% all-trans retinol gel. *Dermatol Surg* 2003; **29**: 155–60.

12 MacKenzie RM, Hellwege DM, McGregor ML *et al*. Separation and identification of geometric isomers of retinoic acid and methyl retinoate. *J Chromatogr* 1978; **155**: 379–87.

13 Kligman AM, Fulton JE Jr, Plewig G. Topical vitamin A acid in acne vulgaris. *Arch Dermatol* 1969; **99**: 469–76.

14 Pedace FJ, Stoughton R. Topical retinoic acid in acne vulgaris. *Br J Dermatol* 1971; **84**: 465–9.

15 Gunther S. Vitamin-A acid in acne vulgaris: association between peeling effect and improvement. *Dermatol Wochenschr* 1974; **160**: 215–8.

16 Mills OH, Leyden JJ, Kligman AM. Tretinoin treatment of steroid acne. *Arch Dermatol* 1973; **108**: 381–4.

17 Leyden JJ, Grove GL, Grove MJ *et al*. Treatment of photodamaged facial skin with topical tretinoin. *J Am Acad Dermatol* 1989; **21**: 638–44.

18 Kligman AM, Grove GL, Hirose RL *et al*. Topical tretinoin for photodamaged skin. *J Am Acad Dermatol* 1986; **15**: 836–59.

19 Kligman AM, Dogadkina D, Lavker RM. Effects of topical tretinoin on non-sun-exposed protected skin of the elderly. *J Am Acad Dermatol* 1993; **29**: 25–33.

20 Nyirady J, Bergfeld W, Ellis C *et al*. Tretinoin cream 0.02% for the treatment of photodamaged facial skin: a review of 2 double-blind clinical studies. *Cutis* 2001; **68**: 135–42.

21 Epstein JH. All-*trans*-retinoic acid and cutaneous cancers. *J Am Acad Dermatol* 1986; **15**: 772–8.
22 Robinson TA, Kligman AM. Treatment of solar keratoses of the extremities with retinoic acid and 5-fluorouracil. *Br J Dermatol* 1975; **92**: 703–6
23 Meyskens FL Jr, Edwards L, Levine MS. Role of topical tretinoin in melanoma and dysplastic naevi. *J Am Acad Dermatol* 1986; **15**: 822–5.
24 Popp C, Kligman AM, Stoudemayer TJ. Pretreatment of photoaged forearm skin with topical tretinoin accelerates healing of full-thickness wounds. *Br J Dermatol* 1995; **132**: 46–53.
25 Hevia O, Nemeth AJ, Taylor JR. Tretinoin accelerates healing after trichloroacetic acid chemical peel. *Arch Dermatol* 1991; **127**: 678–82.
26 Mandy SH. Tretinoin in the preoperative and postoperative management of dermabrasion. *J Am Acad Dermatol* 1986; **15**: 878–9, 888–9.
27 Kligman AM, Plewig G, Mills OH Jr. Topically applied tretinoin for senile (solar) comedones. *Arch Dermatol* 1971; **104**: 420–1.
28 O'Malley MP, Haake A, Goldsmith L, Berg D. Localized Darier disease. Implications for genetic studies. *Arch Dermatol* 1997; **133**: 1134–8.
29 Poskitt L, Wilkinson JD. Natural history of keratosis pilaris. *Br J Dermatol* 1994; **130**: 711–3.
30 Muller SA, Belcher RW, Esterley NB. Keratinizing dermatoses. *Arch Dermatol* 1977; **113**: 1052–4.
31 Van der Wateren AR, Cormane RH. Oral retinoic acid as therapy for erythrokeratoderma variabilis. *Br J Dermatol* 1977; **97**: 83–5.
32 Gunther S. Vitamin A acid in treatment of oral lichen planus. *Arch Dermatol* 1973; **107**: 277.
33 Helfman RJ. The treatment of geographic tongue with topical Retin-A solution. *Cutis* 1979; **24**: 179–80.
34 Tkach JR. Tretinoin treatment for Fox–Fordyce disease. *Arch Dermatol* 1979; **115**: 1285.
35 Giacobetti R, Caro WA, Roenigk JR. Fox–Fordyce disease—control with tretinoin cream. *Arch Dermatol* 1979; **115**: 1365–6.
36 Janssen De Limpens AMP. The local treatment of hypertrophic scars and keloids with topical retinoic acid. *Br J Dermatol* 1980; **103**: 319–23.
37 Panagerie-Castaings H. Retinoic acid in the treatment of keloids. *J Dermatol Surg Oncol* 1988; **14**: 1275–6.
38 Lindgren S, Groth O, Molin L. Allergic contact response to vitamin A acid. *Contact Dermatitis* 1976; **2**: 212–7.
39 Cunliffe WJ, Poncet M, Loesche C, Verschoore M. A comparison of the efficacy and tolerability of adapalene 0.1% gel versus tretinoin 0.025% gel in patients with acne vulgaris: a meta-analysis of five randomized trials. *Br J Dermatol* 1998; **139** (Suppl. 52): 48–56.
40 Chalker DK, Lesher JL Jr, Smith JG Jr *et al*. Efficacy of topical isotretinoin 0.05% gel in acne vulgaris: results of a multicenter, double-blind investigation. *J Am Acad Dermatol* 1987; **17**: 251–4.
41 Elbaum DJ. Comparison of the stability of topical isotretinoin and topical tretinoin and their efficacy in acne. *J Am Acad Dermatol* 1988; **19**: 486–91.
42 Hughes BR, Norris JF, Cunliffe WJ. A double-blind evaluation of topical isotretinoin 0.05%, benzoyl peroxide gel 5% and placebo in patients with acne. *Clin Exp Dermatol* 1992; **17**: 165–8.
43 Tschan T, Steffen H, Supersaxo A. Sebaceous-gland deposition of isotretinoin after topical application: an in vitro study using human facial skin. *Skin Pharmacol* 1997; **10**: 126–34.
44 Plewig G, Ruhfus A, Klovekorn W. Sebum suppression after topical application of retinoids (arotenoid and isotretinoin). *J Invest Dermatol* 1983; **80**: 357.
45 Bischoff R, De Jong EM, Rulo HF *et al*. Topical application of 13-cis-retinoic acid in the treatment of chronic plaque psoriasis. *Clin Exp Dermatol* 1992; **17**: 9–12.
46 Sendagorta E, Lesiewicz J, Armstrong RB. Topical isotretinoin for photodamaged skin. *J Am Acad Dermatol* 1992; **27**: S15–8.
47 Maddin S, Lauharanta J, Agache P *et al*. Isotretinoin improves the appearance of photodamaged skin: results of a 36-week, multicenter, double-blind, placebo-controlled trial. *J Am Acad Dermatol* 2000; **42**: 56–63.
48 Alirezai M, Dupuy P, Amblard P *et al*. Clinical evaluation of topical isotretinoin in the treatment of actinic keratoses. *J Am Acad Dermatol* 1994; **30**: 447–51.
49 Sankowski A, Janik P, Jeziorska M *et al*. The results of topical application of 13-cis-retinoic acid on basal cell carcinoma. A correlation of the clinical effect with histopathological examination and serum retinol level. *Neoplasma* 1987; **34**: 485–9.
50 Karpouzis A, Giatromanolaki A, Sivridis E, Kouskoukis C. Perifolliculitis capitis abscedens et suffodiens successfully controlled with topical isotretinoin. *Eur J Dermatol* 2003; **13**: 192–5.
51 Piattelli A, Fioroni M, Santinelli A, Rubini C. bcl-2 expression and apoptotic bodies in 13-cis-retinoic acid (isotretinoin)-topically treated oral leukoplakia: a pilot study. *Oral Oncol* 1999; **35**: 314–20.
52 Markowska J, Janik P, Wiese E, Ostrowski J. Leukoplakia of the vulva locally treated by 13-cis-retinoic acid. *Neoplasma* 1987; **34**: 33–6.
53 Giustina TA, Stewart JC, Ellis CN *et al*. Topical application of isotretinoin gel improves oral lichen planus. A double-blind study. *Arch Dermatol* 1986; **122**: 534–6.
54 Toros P, Onder M, Gurer MA. Bilateral nipple hyperkeratosis treated successfully with topical isotretinoin. *Australas J Dermatol* 1999; **40**: 220–2.
55 Ratnavel RC, Grant JW, Handfield-Jones SE, Norris PG. O'Brien's actinic granuloma: response to isotretinoin. *J R Soc Med* 1995; **88**: 528P–529P.
56 Leenutaphong V, Nettakul A, Rattanasuwon P. Topical isotretinoin for melasma in Thai patients: a vehicle-controlled clinical trial. *J Med Assoc Thai* 1999; **82**: 868–75.
57 Burge SM, Buxton PK. Topical isotretinoin in Darier's disease. *Br J Dermatol* 1995; **133**: 924–8.
58 McKenna KE, Walsh MY, Burrows D. Treatment of unilateral Darier's disease with topical isotretinoin. *Clin Exp Dermatol* 1999; **24**: 425–7.
59 Griffiths CEM, Elder JT, Bernard BA *et al.* Comparison of CD271 (adapalene) and all-*trans* retinoic acid in human skin: dissociation of epidermal effects and CRABP II m-RNA expression. *J Invest Dermatol* 1993; **101**: 325–8.
60 Ioannides D, Rigopoulos D, Katsambas A. Topical adapalene gel 0.1% vs. isotretinoin gel 0.05% in the treatment of acne vulgaris: a randomized open-label clinical trial. *Br J Dermatol* 2002; **147**: 523–7.
61 Michel S, Jomard A, Demarchez M. Pharmacology of adapalene. *Br J Dermatol* 1998; **139** (Suppl. 52): 3–7.
62 Breneman D, Duvic M, Kuzel T *et al*. Phase 1 and 2 trial of bexarotene gel for skin-directed treatment of patients with cutaneous T-cell lymphoma. *Arch Dermatol* 2002; **138**: 325–32.
63 Liu HL. Bexarotene gel. A Food and Drug Administration-approved skin-directed therapy for early stage cutaneous T-cell lymphoma. *Arch Dermatol* 2002; **138**: 398–9.
64 Chandraratna RA. Tazarotene—first of a new generation of receptor-selective retinoids. *Br J Dermatol* 1996; **135** (Suppl. 49): 18–25.
65 Weinstein GD, Krueger GG, Lowe NJ *et al*. Tazarotene gel, a new retinoid, for topical therapy of psoriasis: vehicle-controlled study of safety, efficacy, and duration of therapeutic effect. *J Am Acad Dermatol* 1997; **37**: 85–92.
66 Weinstein GD, Koo JY, Krueger GG *et al.* Tazarotene cream in the treatment of psoriasis: two multicenter, double-blind, randomized, vehicle-controlled studies of the safety and efficacy of tazarotene creams 0.05% and 0.1% applied once daily for 12 weeks. *J Am Acad Dermatol* 2003; **48**: 760–7.
67 Lebwohl M, Ast E, Callen JP *et al*. Once-daily tazarotene gel versus twice-daily fluocinonide cream in the treatment of plaque psoriasis. *J Am Acad Dermatol* 1998; **38**: 705–11.
68 Scher RK, Stiller M, Zhu YI. Tazarotene 0.1% gel in the treatment of fingernail psoriasis: a double-blind, randomized, vehicle-controlled study. *Cutis* 2001; **68**: 355–8.
69 Wollina U. Genital ulcers in a psoriasis patient using topical tazarotene. *Br J Dermatol* 1998; **138**: 713–4.
70 Dawkins MA, Clark AR, Feldman SR. Pyogenic granuloma-like lesion associated with topical tazarotene therapy. *J Am Acad Dermatol* 2000; **43**: 154–5.
71 Bershad S, Kranjac Singer G *et al*. Successful treatment of acne vulgaris using a new method: results of a randomized vehicle-controlled trial of short-contact therapy with 0.1% tazarotene gel. *Arch Dermatol* 2002; **138**: 481–9.
72 Leyden JJ, Tanghetti EA, Miller B *et al*. Once-daily tazarotene 0.1% gel versus once-daily tretinoin 0.1% microsponge gel for the treatment of facial acne vulgaris: a double-blind randomized trial. *Cutis* 2002; **69** (Suppl.): 12–9.
73 Webster GF, Guenther L, Poulin YP *et al*. A multicenter, double-blind, randomized comparison study of the efficacy and tolerability of once-daily tazarotene 0.1% gel and adapalene 0.1% gel for the treatment of facial acne vulgaris. *Cutis* 2002; **69** (Suppl.): 4–11.
74 Phillips TJ, Gottlieb AB, Leyden JJ *et al*. Efficacy of 0.1% tazarotene cream for the treatment of photodamage: a 12-month multicenter, randomized trial. *Arch Dermatol* 2002; **138**: 1486–93.

75 Petruzzi M, De Benedittis M, Grassi R *et al*. Oral lichen planus: a preliminary clinical study on treatment with tazarotene. *Oral Dis* 2002; **8**: 291–5.
76 Gerbig AW. Treating keratosis pilaris. *J Am Acad Dermatol* 2002; **47**: 457.
77 Stege H, Hofmann B, Ruzicka T, Lehmann P. Topical application of tazarotene in the treatment of nonerythrodermic lamellar ichthyosis. *Arch Dermatol* 1998; **134**: 640.
78 Marulli GC, Campione E, Chimenti MS *et al*. Type I lamellar ichthyosis improved by tazarotene 0.1% gel. *Clin Exp Dermatol* 2003; **28**: 391–3.
79 Marulli GC, Campione E, Chimenti MS *et al*. Type I lamellar ichthyosis improved by tazarotene 0.1% gel. *Clin Exp Dermatol* 2003; **28**: 391–3.
80 Hofmann B, Stege H, Ruzicka T, Lehmann P. Effect of topical tazarotene in the treatment of congenital ichthyoses. *Br J Dermatol* 1999; **141**: 642–6.
81 Bowman PH, Davis LS. Confluent and reticulated papillomatosis: response to tazarotene. *J Am Acad Dermatol* 2003; **48** (Suppl.): S80–1.
82 Outland JD, Brown TS, Callen JP. Tazarotene is an effective therapy for elastosis perforans serpiginosa. *Arch Dermatol* 2002; **138**: 169–71.
83 Oster-Schmidt C, Stucker M, Altmeyer P. Follicular dyskeratosis: successful treatment with local retinoid. *Hautarzt* 2000; **51**: 196–9.
84 Burkhart CG, Burkhart CN. Tazarotene gel for Darier's disease. *J Am Acad Dermatol* 1998; **38**: 1001–2.
85 Abramovits W, Abdelmalek N. Treatment of warty dyskeratoma with tazarotenic acid. *J Am Acad Dermatol* 2002; **46** (2 Suppl. Case Reports): S4.
86 Weisshaar E, Bonnekoh B, Franke I, Gollnick H. Successful symptomatic tazarotene treatment of juvenile acanthosis nigricans of the familial obesity-associated type in insulin resistance. *Hautarzt* 2001; **52**: 499–503.
87 Helm TN, Lee J, Helm KF. Spiny keratoderma. *Cutis* 2000; **66**: 191–2.
88 Lewis A, Nigro M, Rosen T. Treatment of keratoderma blennorrhagicum with tazarotene gel 0.1%. *J Am Acad Dermatol* 2000; **43**: 400–2.
89 Edwards KR, Burke WA. Treatment of localized discoid lupus erythematosus with tazarotene. *J Am Acad Dermatol* 1999; **41**: 1049–50.

Sensitizing agents

Sensitizing agents such as dinitrochlorobenzene, squaric acid and diphencyprone are known as universal sensitizers. Almost every individual will develop allergic dermatitis after repeated contact with these substances on the skin. Animals are also readily sensitized. For many years dermatologists have tried to use the induction of contact sensitization, using these and other allergens, to manipulate immune responses to advantage in a wide variety of benign and malignant skin disease [1]. Numerous attempts have been made, with some reported success, to use sensitizers to stimulate an immune response to malignancies, including melanoma [1,2]. Currently, topical sensitizers have found two main roles in dermatology, for the treatment of alopecia areata and viral warts [1]. The sensitizers that have been most intensively investigated are dinitrochlorobenzene (DNCB), squaric acid dibutylester (SADE) and diphencyprone (diphenylcyclopropenone, DCP). The earliest of these to be used was DNCB which was found to be mutagenic. The use of SADE or of diphencyprone avoids this hazard, and diphencyprone has the advantage of a practical shelf-life. The latter has therefore become the most widely used sensitizer for treatment of alopecia areata and warts. Diphencyprone does not cross-sensitize patients to any other household or medicinal substances. An additional advantage of this compound is that it is photochemically unstable and degrades in the presence of visible light. Accidental spills will therefore not indefinitely contaminate the environment. It also follows that diphencyprone must be stored in the dark.

The precise mechanisms by which induction of contact allergy can induce hair regrowth in alopecia areata have not been established. It seems likely that regulatory mechanisms activated to modulate the contact allergic reaction also downregulate the autoimmune reaction responsible for the alopecia. Increased production of IL-10 may explain this effect [3]. There is no doubt that these agents can stimulate regrowth of hair. Dinitrochlorobenzene [4], SADE [5] and diphencyprone [6] have all been shown to stimulate hair regrowth on treated areas of the scalp in studies using untreated areas as a control. The same effect has been achieved, in sensitized individuals, by use of *Primula* leaves [7] and by nickel patch test reagent [8]. The demonstration of hair regrowth on one side of the scalp which has been treated with allergen, whilst there is none on the other side, constitutes a well-controlled experiment which has been repeated regularly by the author. Sensitization can usually be achieved by application of 2% or higher concentration of diphencyprone to a small area of the scalp once weekly until a reaction is seen. Subsequent treatment can begin with a 0.01% solution and usually continues on a weekly basis adjusting the concentration as required to maintain mild dermatitis. Attempts have been made to achieve the same effect by use of a simple inflammatory response induced by contact irritants. Phenolics, cantharides, camphor and other irritants have been used for many years, mostly without controlled trials [9]. Trials using croton oil and retinoic acid have not confirmed a response to these irritants [8,10]. With the possible exception of dithranol [11], it has proved difficult to establish the efficacy of irritants.

The efficacy of topical sensitizers in treatment of warts is still not so clearly established. Published controlled trials have been small and inconclusive [1,12]. Uncontrolled data are fairly convincing but inconsistent, perhaps because treatment regimens have also been variable [1]. The best results with diphencyprone have been obtained by first sensitizing patients at a site remote from the warts and then applying diphencyprone 0.01–6% to the lesions at intervals of 1–4 weeks. Complete clearance was reported in 70% of patients with this method [13]. Again, the mechanism of action has not been fully clarified but it is likely that the induction of an inflammatory reaction within the wart induces an influx of immunocompetent cells which can then promote an appropriate immune response to the infecting human papilloma virus.

References

1 Buckley DA, Du Vivier AWP. The therapeutic use of topical contact sensitizers in benign dermatoses. *Br J Dermatol* 2001; **145**: 385–405.
2 Wack C, Kirst A, Becker JC *et al*. Chemoimmunotherapy for melanoma with dacarbazine and 2,4-dinitrochlorobenzene elicits a specific T cell-dependent immune response. *Cancer Immunol Immunother* 2002; **51**: 431–9.
3 Hoffmann R, Wenzel E, Huth A *et al*. Cytokine mRNA levels in alopecia areata before and after treatment with the contact allergen diphenylcyclopropenone. *J Invest Dermatol* 1994; **103**: 530–3.
4 Daman LA, Rosenberg EW, Drake L. Treatment of alopecia areata with dinitrochlorobenzene. *Arch Dermatol* 1978; **114**: 1036–8.
5 Chua SH. Topical squaric acid dibutylester therapy for alopecia areata: a double-sided patient-controlled study. *Ann Acad Med Singapore* 1996; **25**: 842–7.
6 Happle R, Hausen BM, Wiesner-Menzel L. Diphencyprone in the treatment of alopecia areata. *Acta Derm Venereol* 1983; **63**: 49–52.
7 Rhodes EL, Dolman W, Kennedy C *et al*. Alopecia areata regrowth induced by *Primula obconica*. *Br J Dermatol* 1981; **104**: 339–40.
8 Suarez Martin E. Treatment of alopecia areata profiting from 'natural' allergy to nickel. *Arch Dermatol* 1984; **120**: 1138–9.
9 Swanson NA, Mitchell AJ, Leahy MS *et al*. Topical treatment of alopecia areata. *Arch Dermatol* 1981; **117**: 384–7.
10 Ashworth J, Tuyp E, MacKie RM. Allergic and irritant dermatitis compared in the treatment of alopecia totalis and universalis. A comparison of the value of topical diphencyprone and tretinoin gel. *Br J Dermatol* 1989; **120**: 397–401.

11 Schmoeckel C, Weissmann I, Plewig G, Braun-Falco O. Treatment of alopecia areata by anthralin-induce dermatitis. *Arch Dermatol* 1979; **115**: 1254–5.
12 Gibbs S. Topical immunotherapy with contact sensitizers for viral warts. *Br J Dermatol* 2002; **146**: 705.
13 Buckley DA, Keane FM, Munn SE *et al*. Recalcitrant viral warts treated by diphencyprone immunotherapy. *Br J Dermatol* 1999; **141**: 292–6.

Sunscreens

It is likely that in the early evolution of *Homo sapiens*, pigmentation of the skin developed primarily as protection from the risk of sunburn. Subsequent migration away from our equatorial origins reduced the risk of sunburn and skin pigmentation was lost in order to facilitate adequate penetration of ultraviolet (UV) radiation into the skin for photochemical synthesis of vitamin D. The adverse consequences of this loss of endogenous sunscreen may not have impaired reproductive potential since they tend to occur mainly in later life. However, individuals with white skin are clearly at greater risk from malignant melanoma, non-melanoma skin cancer, pre-malignant skin disorders, and the premature ageing effects of UV irradiation. The, sadly, fashionable trend over recent decades to purposely expose the skin to solar irradiation in order to obtain a sun tan has undoubtedly increased the frequency of these diseases.

It seems a logical approach to attempt to replace the pigment with an exogenous sunscreen applied to the skin surface and a large number of formulations are marketed for this purpose. Used properly, these compounds can reduce UV exposure and probably also the risks associated with photodamage, notably neoplasia. Regrettably, sunscreens may be misused by individuals with pale skin, who could not normally withstand any significant sun exposure without burning, to enable them to be able to lie in the sun for hours on end. Such 'abuse' of sunscreens seems likely to be harmful since it can result in significantly greater cumulative UV irradiation than would otherwise be possible. This is especially likely to happen if sunscreens with low sun protection factor ratings (see below) are used.

The ideal sunscreen should completely block the transmission of both UVB (280–315 nm) and UVA (315–400 nm) whilst at the same time being cosmetically acceptable and pleasant to use. Additional important properties are durability on the surface of the skin and water resistance. The latter is especially important if the sunscreen is to be used when swimming. Sunscreens are generally more effective in blocking UVB than UVA but effective filtration of UVA is important because these wavelengths contribute to photoageing [1], cutaneous immunosuppression [2,3] and carcinogenesis [4], and can play a central role in photodermatoses such as polymorphic light eruption [5]. No single compound can achieve all the desired aims, so most commercial formulations contain a mixture of active constituents. These fall into two broad categories—physical sunscreens, which act by reflecting and scattering UV light, and chemical agents, which absorb UV light [6–8]. Frequently used compounds are listed in Table 73.8.

Physical agents such as titanium dioxide and zinc oxide can block a broad spectrum of UVB, UVA and visible light (the latter can be useful in some photodermatoses). However, their efficacy against UVA and visible light depends on particle size. Larger particle size results in superior efficacy but reduced cosmetic acceptability due to the increased whitening of the skin (which is, of course, reflection of visible light). There has been some concern over the potential for the interaction of both zinc and titanium oxides with UV light to release free radicals [9] but, fortunately, the harmful effects of these seem likely to be very limited as the oxide particles do not seem to penetrate below the surface layers of the stratum corneum into viable skin [10].

Table 73.8 Compounds used as active constituents of sunscreens.

Physical agents	Zinc oxide	UVA, UVB
	Titanium dioxide	UVA, UVB
	Ferrous oxide	UVA, UVB
Chemical agents	Para-aminobenzoic acid (PABA) and derivatives	UVB
	Anthranilates	UVA
	Cinnamates	UVB
	Salicylates	UVB
	Octocrylene	UVB
	Benzotriazoles	UVA, UVB
	Dibenzoylmethanes	UVA
	Benzophenones	UVA, UVB
	Bis-ethylhexyloxyphenol methoxyphenol triazine	UVA, UVB
	Camphor derivatives	UVA

Chemical agents are each effective against a different range of wavelengths of UV light. Some absorb UVB and others UVA. Relatively few absorb long-wave UVA approaching the visible range, exceptions being butyl methoxydibenzoylmethane which has an absorption spectrum of 320–400 nm, and terephthalylidene dicamphor sulphonic acid, with an absorption spectrum of 290–400 nm. Chemical sunscreens can occasionally cause dermatitis. Irritant, allergic, phototoxic or photoallergic reactions may occur, and may be caused not only by the active constituents but also by the base or by additives such as fragrances and stabilizers. Benzophenones are probably the commonest sensitizers, whilst dibenzoylmethanes, para-amino benzoic acid (PABA) and cinnamates may cause photoallergic dermatitis [11,12].

The concept of sun protection factors (SPF) was introduced to help consumers evaluate the level of protection from UVB and the risk of sunburn. Unfortunately, different systems of assay are used in different countries, making direct comparisons very misleading. However, all depend on deriving a ratio of the time or the amount of energy to reach a given end point, such as minimal erythema, when using the sunscreen compared to that required to reach the same end point when not using the sunscreen.

$$\text{SPF} = \frac{\text{Dose of UVB radiation producing minimal erythema with sunscreen}}{\text{Dose of UVB radiation producing minimal erythema without sunscreen}}$$

It should be noted that the SPF is based on application of an adequate quantity of the sunscreen, usually 2 mg/cm^2 of skin. This is probably more than is routinely applied by most users, so the protection achieved in actual use may be less than that anticipated. As a guide, SPFs of up to 10 can be regarded as mild, 10–15 as medium, and over 15 as strong protectors. International agree-

ment is needed to standardize end points, light sources and conditions of testing. As a result, the classification of sunscreens into the broad categories listed above is helpful but comparisons between one product and another are not as accurate as they might appear. This is especially true of comparisons between products with high SPF values (above 15). There is currently even less standardization of the assessment of protection against UVA. Measurement of resistance to water has also not been standardized but can be assessed by several methods [13,14].

Whilst it would seem likely that correct use of sunscreens will reduce the risk of malignancy this has not been easy to confirm, especially in retrospective studies. Part of the difficulty is the likely association between use of a sunblock and sun exposure.

Suncreens have been shown to reduce UV-induced immunosuppression which is considered to play a role in cutaneous carcinogenesis. Both the sensitization [15] and elicitation [2] phases of immune responses can be preserved by sunscreens.

In a placebo-controlled trial on a high-risk population, appropriate strength sunscreens have been shown to be effective in reducing the incidence of actinic keratoses [16]. In an Australian prospective controlled study, regular use of sunscreen reduced the total number of squamous cell carcinomas (SCCs) but not of BCCs [17]. A study of BCCs indicated that there were fewer p53 mutations in those which developed in patients who had used sunscreen. This might be indicative of effective protection against UV-induced DNA mutation by the sunscreen [18], whilst some BCCs develop due to other causes.

The prevention of melanoma by the use of sunscreens is a further controversial topic, since two case–control studies have linked sunscreen usage to a higher incidence of melanoma [19,20]. This may be related in part to the likelihood that the subjects studied had previously used sunscreens that provided protection against UVB radiation alone, and had exposed themselves to higher doses of solar radiation than those who did not use sunscreen. Other studies have examined the development of naevi as a marker for risk of melanoma. A retrospective epidemiological study from Israel found that use of sunscreen was associated with a higher number of naevi [21]. Conversely, a prospective controlled trial from Vancouver demonstrated a reduced rate of development of naevi over a 3-year period in children provided with sunblock and instructed on its use. The effect was especially evident in those children who were freckled [22].

In addition to the protection of healthy skin, sunscreens have an important role in the management of patients with photodermatoses. The commonest of these, polymorphic light eruption, often seems to show rather limited benefit from sunscreens but may respond well to formulations which block a broad spectrum of UVA, including longer wavelengths [5]. Sunscreens effective in blocking the offending wavelengths of UV light can also be helpful in management of less common photodermatoses including actinic prurigo, chronic actinic dermatitis, hydroa vacciniforme, lupus erythematosus, porphyrias and solar urticaria.

Whether sunscreens are applied to prevent solar damage to healthy skin or to alleviate a photodermatosis, it is important that these should not be regarded as the only means of limiting sun exposure. Staying indoors during the hours of peak sunlight intensity and, when outdoors, covering the skin with suitable clothing and headwear constitute more effective strategies than using sunscreens.

References

1 Seite S, Moyal D, Richard S *et al*. Effects of repeated suberythemal doses of UVA in human skin. *Eur J Dermatol* 1997; **7**: 204–9.

2 Moyal DD, Fourtanier AM. Efficacy of broad-spectrum sunscreens against the suppression of elicitation of delayed-type hypersensitivity responses in humans depends on the level of ultraviolet A protection. *Exp Dermatol* 2003; **12**: 153–9.

3 Seite S, Zucchi H, Moyal D *et al*. Alterations in human epidermal Langerhans cells by ultraviolet radiation: quantitative and morphological study. *Br J Dermatol* 2003; **148**: 291–9.

4 Wang SQ, Setlow R, Berwick M *et al*. Ultraviolet A and melanoma: a review. *J Am Acad Dermatol* 2001; **44**: 837–46.

5 Allas S, Lui H, Moyal D, Bissonnette R. Comparison of the ability of two sunscreens to protect against polymorphous light eruption induced by a UV-A/UV-B metal halide lamp. *Arch Dermatol* 1999; **135**: 1421–2.

6 Shaath NA. The chemistry of sunscreens. In: Lowe NJ, Shaath NA, eds. *Sunscreens: Development, Evaluation and Regulatory Aspects*. New York: Marcel Dekker, 1990: 211–33.

7 Kaidbey KH, Kligman AM. An appraisal of the efficacy and substantivity of the new high-protection sunscreens. *J Am Acad Dermatol* 1981; **4**: 566–70.

8 Klein K. Formulating suncreen products. In: Lowe NJ, Shaath NA, eds. *Sunscreens: Development, Evaluation and Regulatory Aspects*. New York: Marcel Dekker, 1990: 235–66.

9 Yamamoto Y, Imai N, Mashima R *et al*. Singlet oxygen from irradiated titanium dioxide and zinc. *Methods Enzymol* 2000; **319**: 29–37.

10 Lademann J, Weigmann H, Rickmeyer C *et al*. Penetration of titanium dioxide microparticles in a sunscreen formulation into the horny layer and the follicular orifice. *Skin Pharmacol Appl Skin Physiol* 1999; **12**: 247–56.

11 English JS, White IR, Cronin E. Sensitivity to sunscreens. *Contact Dermatitis* 1987; **17**: 159–62.

12 Bilsland D, Ferguson J. Contact allergy to sunscreen chemicals in photosensitivity dermatitis/actinic reticuloid syndrome (PD/AR) and polymorphic light eruption (PLE). *Contact Dermatitis* 1993; **29**: 70–3.

13 Antoniou C, Kosmadaki MG, Stratigos AJ, Katsambas AD. Sunscreens—what's important to know. *J Eur Acad Derm Venereol* 2008; **22**: 1110–4.

14 Stokes RP, Diffey BL, Dawson LC, Barton SP. A novel in vitro technique for measuring the water resistance of sunscreens. *Int J Cosmet Sci* 1998; **20**: 235–40.

15 Whitmore SE, Morison WL. Prevention of UVB-induced immunosuppression in humans by a high sun protection factor sunscreen. *Arch Dermatol* 1995; **131**: 1128–33.

16 Naylor MF, Boyd A, Smith DW *et al*. High sun protection factor sunscreens in the suppression of actinic neoplasia. *Arch Dermatol* 1995; **131**: 170–5.

17 Green A, Williams G, Neale R *et al*. Daily sunscreen application and betacarotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomised controlled trial. *Lancet* 1999; **354**: 723–9.

18 Rosenstein BS, Phelps RG, Weinstock MA *et al*. P53 mutations in basal cell carcinomas arising in routine users of sunscreens. *Photochem Photobiol* 1999; **70**: 798–806.

19 Westerdahl J, Olsson H, Masback A *et al*. Is the use of sunscreens a risk factor for malignant melanoma? *Melanoma Res* 1995; **5**: 59–65.

20 Autier P, Dore JF, Schifflers E *et al*. Melanoma and use of sunscreens: an EORTC case-control study in Germany, Belgium and France. *Int J Cancer* 1995; **61**: 749–55.

21 Azizi E, Iscovich J, Pavlotsky F *et al*. Use of sunscreen is linked with elevated naevi counts in Israeli school children and adolescents. *Melanoma Res* 2000; **10**: 491–8.

22 Gallagher RP, Rivers JK, Lee TK *et al*. Broad-spectrum sunscreen use and the development of new nevi in white children: a randomized controlled trial. *JAMA* 2000; **283**: 2955–60.

Tars

Tars are distillation products of organic material. There are three main sources of therapeutic tars: wood, shale and coal.

Wood tars

Oils of Cade (juniper), beech, birch and pine are widely used, particularly in Scandinavian countries. Wood tars lack certain basic chemical structures characteristic of coal tars, such as pyridine, quinoline and quinaline rings [1]. They may sensitize but do not photosensitize.

Wood tars are used for treating eczema and psoriasis in some countries. Oil of Cade is particularly used in scalp preparations (Chapter 20) or when tar preparations are needed on the face. They are normally applied in 1–10% strength in ointments or pastes, or as a paint in 95% alcohol.

Shale tars

Oils were extracted from shale (sedimentary rock containing fossilized fish) for centuries before crude oil became available. Various extracts and distillates have long been used for medicinal purposes. Ichthammol (ichthyol) is a shale tar (bituminous tar). It contains a very high proportion of sulphur (about 10%), as compounds of thiopen. Shale tars have antiseptic and anti-inflammatory properties but are generally less effective than coal tars and may have a different mode of action. They are not photosensitizers. Ichthammol is often used in paste bandages for treating atopic eczema.

Coal tar

Coal tar [2–4] is a black, viscous fluid with a characteristic smell. Attempts to remove the colour, odour, photosensitizing property and carcinogenicity have not been entirely successful [5], and variations in this natural product have made the assessment of active ingredients particularly difficult [3,4]. Of some 10 000 different constituents believed to make up coal tar, only 400 have been identified. These constitute 55% of the whole.

All coal tars are products of different distillates of heated coal. The content of the tar depends on the type used and the temperature of the distillation. 'Low-temperature' tar was found to contain a greater number of components but to be less effective in producing orthokeratosis in mouse-tail skin than 'high-temperature' tar [3,4]. It was also more irritating. However, a comparison of high- and low-temperature tars showed no eventual difference in effect in the treatment of psoriasis itself, although crude (high-temperature) coal tar gave quicker results [6]. This suggests that the reversal of parakeratosis is only one factor in the control of psoriasis. The authors of this study point out that dithranol was not very effective in the mouse-tail test [7].

The hydrocarbons, which constitute about half the composition of tar, include benzol, naphthalene and anthracene. The high-boiling-point tar acids (phenolics) include isomers of substituted polyhydroxyphenols, and it seems likely that it is such phenols which may be responsible for the therapeutic effect of tar [3,4,8]. However, the exact mechanism by which tar exerts its effect remains unknown. These high-temperature fractions may have a direct effect on the granular layer by release of lysosomes followed by mitotic stimulation. Low-temperature extracts appear to cause epidermal thickening without restitution of the granular layer [3,4], and may be the reason for the indifferent action of some synthetic and proprietary tar preparations [3,4,9].

Until a more suitable preparation is available, many dermatologists will continue to believe that crude tar remains therapeutically superior [9,10].

The combination of tar with UV light (the Goeckerman regimen) has long been known to be helpful in psoriasis.

In recent years, attempts have been made to identify the critical wavelengths of radiation involved [11,12]. Generally, UVB radiation has been found to be more effective than UVA [13,14]. Refined tars are less phototoxic than the crude product, but phototoxicity is directly related to therapeutic efficacy. UVA [15] did not appear to be a useful adjunct to tar and UVB, in the treatment of psoriasis in one study.

Laboratory studies have shown that tar plus UV light reduces epidermal DNA synthesis [12,16]. This may be related to the formation of cross-links between opposite strands on the DNA double helix [17].

A cytostatic effect of crude coal tar has also been postulated [18] following the finding that prolonged application to normal skin produces epidermal thinning associated with retention hyperkeratosis. More studies are still required, particularly to identify the more active fractions of tar distillates.

The well-established carcinogenicity of pitch and heavy tar fractions has aroused renewed interest in the current climate of therapeutic conservatism, concerns about the oncogenic potential of polycyclic hydrocarbons, and consumer protection [19–21], fuelled perhaps by reports which showed urine from psoriatic subjects using crude coal tar to be mutagenic to certain bacterial strains [5]. Reports of malignant tumours in humans in relation to tar therapy are rare. Rook *et al*. reported five cases [22] and Greither *et al*. 13 [23]. Most had genital or groin involvement, but these are nowadays unlikely sites for tar application. Several large, long-term follow-up studies, reassuringly, have shown no increased incidence of skin tumours [14,24–27].

Coal tar is now mainly used in treatment of psoriasis and is the basis of the Goeckerman regimen (Chapter 20). Prior to the advent of topical corticosteroids coal tar was widely used in treatment of eczematous dermatoses and it can still prove useful as a steroid sparing agent and antipruritic. Coal tar can be added to paste bandages although ichthammol is often preferred.

References

1 Obermeyer ME, Becker SA. A study of crude coal tar and allied substances. *Arch Dermatol Syphilol* 1935; **31**: 796–810.

2 Muller SA, Kierland RR. Crude coal tar in dermatologic therapy. *Mayo Clin Proc* 1964; **39**: 275–80.

3 Wrench R, Britten AZ. Evaluation of coal tar fractions for use in psoriasiform diseases using the mouse tail test (i). High and low temperature tars and their constituents. *Br J Dermatol* 1975; **92**: 569–74.

4 Wrench R, Britten AZ. Evaluation of coal tar fractions for use in psoriasiform diseases using the mouse tail test (ii). Tar oil, acids. *Br J Dermatol* 1975; **92**: 575–9.

5 Wheeler LA, Soperstein MD, Lowe NJ *et al*. Mutagenicity of urine from psoriatic patients undergoing treatment with coal tar and ultraviolet light. *J Invest Dermatol* 1981; **77**: 181–5.

6 Chapman RS, Finn OR. An assessment of high and low temperature tars in psoriasis. *Br J Dermatol* 1976; **94**: 71–4.

7 Wrench R, Britten AZ. Evaluation of dithranol and a 'synthetic tar' as antipsoriatic treatments using the mouse tail test. *Br J Dermatol* 1975; **93**: 75–8.

8 Hellier FF, Whitefield M. The treatment of psoriasis with triacetoxyanthracene. *Br J Dermatol* 1967; **79**: 491–6.

9 Young E. An external treatment of psoriasis. A controlled investigation of the effects of coal tar. *Br J Dermatol* 1970; **82**: 510–5.
10 Champion RH. Treatment of psoriasis. *BMJ* 1966; **ii**: 993–5.
11 Fischer T. Comparative treatment of psoriasis with UV-light, trioxsalen plus UV-light and coal tar plus UV-light. *Acta Derm Venereol (Stockh)* 1971; **57**: 345–50.
12 Stoughton RB, Dequoy P, Walters JF. Crude coal tar plus near ultraviolet light suppresses DNA synthesis in epidermis. *Arch Dermatol* 1978; **114**: 43–5.
13 Parrish JA, Morison WL, Gonzalez E. Therapy of psoriasis by tar sensitization. *J Invest Dermatol* 1978; **70**: 111–2.
14 Petrozzi JK, Barton JO, Kaidbey KK. Updating of the Goeckerman regime for psoriasis. *Br J Dermatol* 1978; **98**: 437–44.
15 Diette KM, Momtaz K, Stern RS *et al*. Role of ultraviolet A in phototherapy for psoriasis. *J Am Acad Dermatol* 1984; **11**: 441–7.
16 Walter JF, Stoughton RB, Dequoy PR. Suppression of epidermal proliferation by ultraviolet light, coal tar and anthralin. *Br J Dermatol* 1978; **99**: 89–96.
17 Pathak MA, Biswas RK. Skin photosensitization and DNA cross linking ability of photochemotherapeutic agents. *J Invest Dermatol* 1977; **68**: 236.
18 Lavker RM, Grove GL, Kligman AM. The atrophogenic effect of crude coal tar on human epidermis. *Br J Dermatol* 1981; **105**: 77–82.
19 Zackheim HS. Should therapeutic coal tar preparations be available over-the-counter? *Arch Dermatol* 1978; **14**: 125–6.
20 Gilman AG, Rall TW, Nies AS *et al*., eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 8th edn. New York: Pergamon, 1990.
21 Stern RS, Laird N. Carcinogenic risk of treatments for severe psoriasis. *Cancer* 1994; **73**: 2760–3.
22 Rook AJ, Gresham GA, Davis RA. Epithelioma possibly induced by therapeutic application of tar. *Br J Cancer* 1967; **10**: 17–23.
23 Greither A, Gisbertz C, Ippen H. Teerbehandlung und Krebs. *Zeitschr Haut Geschlkr* 1967; **42**: 631–5.
24 Jones SK, Mackie RM, Holt DJ *et al*. Further evidence of the safety of tar in the management of psoriasis. *Br J Dermatol* 1985; **113**: 97–101.
25 Pittelkow MR, Perry HO, Muller SA *et al*. Psoriasis treated with coal tar—25-year follow-up study. *Arch Dermatol* 1981; **117**: 465–8.
26 Maughan WZ, Muller SA, Perry HO *et al*. Incidence of skin cancers in patients with atopic dermatitis treated with coal tar. *J Am Acad Dermatol* 1980; **3**: 612–5.
27 Schmid MH, Korting HC. Coal tar, pine tar and sulphonated shale oil preparations: comparative activity, efficacy and safety. *Dermatology* 1996; **193**: 1–5.

Vitamin D analogues (deltanoids, secosteroids)

The therapeutic potential of vitamin D in psoriasis has been recognized for many years. Systemic use of these compounds can be highly effective but requires monitoring to avoid causing disturbance of calcium homeostasis. Used topically, considerable efficacy can be maintained with a wide safety margin. The advent of calcipotriol in the early 1990s has greatly increased the use of this modality. Tacalcitol and calcitriol, which were known to be effective even earlier, have only more recently become widely available for treatment of psoriasis. The novel analogue maxacalcitol is also known to be effective.

Vitamin D is not strictly a vitamin because an exogenous source is not essential. Photochemical cleavage of 7-dehydrocholesterol to form vitamin D (cholecalciferol) takes place in the skin and requires fairly minimal exposure to UVB to generate physiological quantities of the product. It is this break in the steroid nucleus that characterizes vitamin D and its analogues and gives rise to the term secosteroids. Cholecalciferol requires two hydroxylations for activation. The first is 25-hydroxylation, which takes place mainly in the liver and is not a tightly controlled step [1]. 25-hydroxycholecalciferol is the main storage form of vitamin D within the body. This is finally 'activated' mainly in the kidney, by a very tightly regulated hydroxylation to 1α-25 dihydroxycholecalciferol [2,3]. Since the latter has three hydroxyl groups it is also known as calcitriol (Fig. 73.13). Calcitriol is a potent hormone, first characterized by its ability to increase calcium absorption from the gut. It has subsequently become recognized that the receptor for this potent hormone is expressed in virtually all types of cell. Calcitriol is of fundamental importance in the regulation of differentiation and proliferation.

The vitamin D receptor is a phosphopeptide with molecular weight around 60 kD, able to move freely between the cytoplasm and the nucleus. It is a member of the steroid receptor superfamily, being similar in structure to the retinoid receptors, the thyroid hormone (T_3) receptor and receptors for other classes of steroid hormone. It is active mainly as a heterodimer in combination with the RXR receptor [4]. The vitamin D receptor complex regulates transcription of numerous genes by binding to regulatory regions of DNA, termed vitamin D response elements. These are specific but heterogeneous regions of DNA, generally situated upstream of regulated genes [4].

The therapeutic actions of vitamin D appear to result from a potent antiproliferative effect [5–8], the ability to promote differentiation [9–12], and perhaps also from immunosuppressive activity. *In vitro*, secosteroids inhibit interleukin (IL)-2 release, lymphocyte activation [13,14], and release of IL-8 [15]. They also upregulate expression of the receptor for the anti-inflammatory cytokine, IL-10 [16]. They inhibit monocyte differentiation into dendritic cells, possibly by promoting expression of colony-stimulating factor-1 [17]. They inhibit keratinocyte synthesis of RANTES and IL-8 [18]. *In vivo*, they have been shown to inhibit expression of IL-8 [19], IL-6 [20] and other cytokines. During treatment of psoriasis they have been reported to reduce infiltration with lymphocytes and neutrophils [8,21,22] and to reduce expression of IL-8 and adhesion molecules (ICAM-1, ELAM-1, LFA-1, VLA-3 and VLA-6) [23,24].

Vitamin D, especially in activated (1α-hydroxylated) forms, increases calcium absorption from the bowel. At a low level this can be compensated by increased calcium excretion in urine but at higher levels of exposure the serum calcium will rise. All the analogues currently used in treatment of psoriasis are 1α-hydroxylated compounds which effectively bypass the regulatory step of 1α-hydroxylation. They can potentially cause hypercalcaemia in overdose. This 'calciotropic activity' of vitamin D analogues constitutes the main constraint on the safe use of these compounds. The goal of secosteroid research, to develop an analogue which would normalize proliferation and differentiation without influencing calcium metabolism, has yet to be effectively realized.

In comparison to traditional treatments for psoriasis, vitamin D analogues have the advantage that they are more pleasant to use than tar or dithranol. They also have the advantage over topical corticosteroids that they are not atrophogenic. However, they can all cause irritant reactions which are concentration dependent [25]. Sensitization can also occur but seems to be rare [26]. A characteristic pattern of circumlesional scaling appears around psoriatic lesions treated with vitamin D analogues (Fig. 73.14), which gives a guide to compliance almost as reliable as the staining produced by dithranol [27]. It is not clear whether this is a manifestation of irritancy or a pharmacological effect.

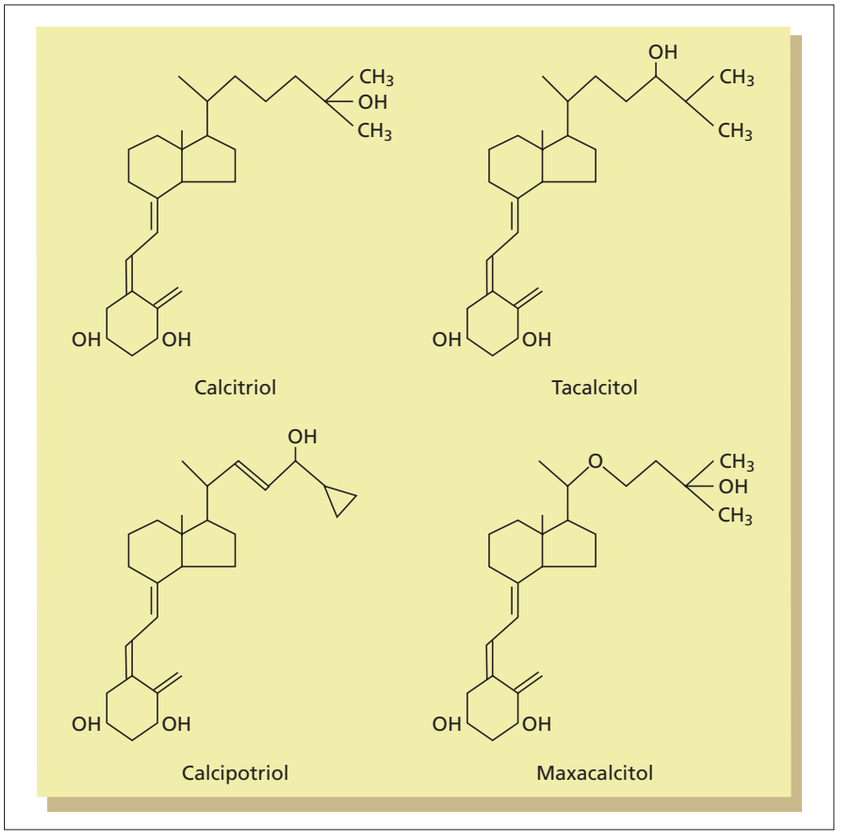


Fig. 73.13 Formulae of calcitriol, tacalcitol, calcipotriol and maxacalcitol.



Fig. 73.14 Circumslesional scaling characteristic of psoriasis lesions treated with vitamin D analogues.

Tacalcitol (1,24 dihydroxycholecalciferol)

This analogue has been used for topical treatment of psoriasis for many years in Japan where the concentrations employed have ranged from 1 to 20 μg/g [28,29]. In Europe, tacalcitol is often used once daily at a concentration of 4 μg/g. Efficacy of this regimen has been demonstrated in placebo-controlled and dose-ranging studies [30,31]. Tacalcitol 4 μg/g applied once daily is less effective than calcipotriol 50 μg/g applied twice daily [32]. However, the lower concentration of tacalcitol results in a low irritant potential and it can therefore be safely used for treating facial or flexural psoriasis [33]. A long-term trial has indicated that, in patients who have responded well, the benefit can be maintained for up to 18 months, although only 64 out of 299 subjects completed the full duration of this trial [34]. Tacalcitol has been used in conjunction with both UVB [35] and PUVA [36] and accelerates the response to these treatments, potentially reducing the UV exposure required.

Currently, the recommended maximum dose of tacalcitol 4 μg/g is 10 g daily. However, no significant increase in serum or urine calcium was observed with daily doses of 15–20 g for up to 26 days [37]. It also appears safe to use tacalcitol at the higher concentration of 20 μg/g [29]. Hypercalcaemia has not yet been reported in association with topical application of this analogue. Sensitization may rarely occur [38].

Other conditions in which topical tacalcitol has been employed with reported success include Nekam's disease [39], confluent and reticulate papillomatosis [40], Grover's disease [41], subcorneal

pustular dermatosis [42], Hailey–Hailey disease [43], disseminated superficial actinic porokeratosis [44] and prurigo [45].

Calcitriol (1,25 dihydroxycholecalciferol)

As discussed above, calcitriol is the naturally occurring form of activated vitamin D. This is known to be active both topically and systemically in treatment of psoriasis [46,47]. Like other analogues it is rarely used systemically because of the need to monitor calcium homeostasis, although the hazards are probably not out of proportion to the potential benefit.

Calcitriol has been used topically at various concentrations ranging from 0.3 to 15 μg/g [48,49]. At the higher end of this range changes are seen in urine and/or serum calcium levels, especially when large areas of skin are treated. At the lower end, efficacy is very limited. When applied twice daily at a concentration of 3 μg/g, controlled trials have demonstrated that a degree of efficacy can be maintained with minimal risk of effects on calcium homeostasis [50]. The efficacy of this regimen was comparable to that of short-contact dithranol therapy in an 8-week trial with 114 subjects although the overall improvement was not very impressive in either group, suggesting that the dithranol regimen may not have been optimal [50]. Calcitriol 3 μg/g is less effective than calcipotriol 50 μg/g [51]. In a long-term study it was disappointing that only 75 out of 253 subjects continued to use the treatment for a year. Lack of efficacy was given as the main reason for withdrawal by 108 of the subjects. Twice-daily treatment with calcitriol has shown a dose-sparing effect on UVB exposure when used in conjunction with broad-band phototherapy [52]. Calcitriol ointment 3 μg/g seems to have very little potential for irritancy or sensitization [53].

Calcipotriol (calcipotriene, MC903)

Although developed relatively recently, calcipotriol has now been more intensively investigated than any other secosteroid for the treatment of psoriasis. The molecule has a cyclopropane group at the end of the side chain which facilitates rapid metabolism (Fig. 73.13). It is therefore ideal for topical administration and can be safely used in higher concentration than calcitriol or tacalcitol [54]. Placebo-controlled and dose-ranging trials demonstrated maximal response at the concentration of 50 μg/g [55,56]. Virtually all subsequent research has investigated the use of calcipotriol at this concentration.

Efficacy and safety of calcipotriol in childhood psoriasis has been confirmed in trials on children from age 2 years upwards [57,58]. It has also proved useful in an infant [59].

Reports indicate that topical calcipotriol can be useful in generalized pustular psoriasis [60,61] and erythrodermic psoriasis [62,63]. However, absorption of the drug can be significantly higher in these circumstances and careful monitoring is required. In one case, generalized pustular psoriasis was thought to have been precipitated by calcipotriol [64]. Acrodermatitis continua [65] and nail psoriasis [66,67] may respond, although the results are not consistent.

In comparative studies, calcipotriol 50 μg/g generally compares well to other topical treatments for psoriasis [68]. It has shown efficacy similar to potent topical corticosteroids such as betamethasone-17-valerate [69] and superior to tacalcitol 4 μg/g [31], calcitriol 3 μg/g [50], and to self-treatment with dithranol [70]. The response has been relatively well sustained over time in long-term trials [71,72]. It is notable, however, that only 26% of the patients on this treatment are able to discontinue the vitamin D analogue altogether (the rest requiring continuous treatment).

The use of calcipotriol has also been investigated in a wide range of combinations with other antipsoriatic medication. Combinations with topical corticosteroids can be particularly useful to increase efficacy and reduce irritation. When each medication is applied once daily, the combination with moderately potent or potent steroid reduces irritation and a potent steroid increases efficacy relative to twice daily application of calcipotriol alone [73]. A combined formulation (Dovobet®, Daivobet®), containing betamethasone diproponate 0.05% and calcipotriol 50 μg/g, has proved more effective applied once daily than twice-daily application of calcipotriol alone. The combined formulation was also less irritant [74]. A regimen combining short contact dithranol with twice-daily application of calcipotriol proved more effective than dithranol alone [75].

Topical calcipotriol can also be used concomitantly with second-line therapies and exerts a useful dose-sparing effect when combined with UVB [76,77], PUVA [78–80], ciclosporin [81], retinoids [82] or fumaric acid esters [83].

Occlusion with polythene or hydrocolloid dressings can be used to augment the efficacy of calcipotriol [84]. This technique can be particularly useful for refractory plaques of psoriasis on the shins. Systemic absorption is also likely to be increased.

Calcipotriol not uncommonly induces irritant reactions, especially when applied to the face. Sensitization can also occur to calcipotriol although this seems to be rare [85–87]. In one case, propylene glycol in the base was responsible for the reaction [88].

The maximum recommended rate of usage is 100 g of ointment weekly. Exceeding this dose can induce hypercalcaemia, although the safety margin seems reasonable and the use of higher doses can improve efficacy [89]. It is advisable to monitor urine and serum calcium in situations where there is a risk of inducing hypervitaminosis, for example when the recommended dose is exceeded or when calcipotriol is used for indications other than psoriasis vulgaris, especially if large areas of skin are treated. Monitoring of serum calcium presents little difficulty but measurement of urine calcium excretion depends on obtaining accurate 24-h urine collections.

There are now a wide range of dermatoses in addition to psoriasis which have been reported to respond to calcipotriol, although the evidence is largely anecdotal in nature. These include confluent and reticulate papillomatosis [90], disseminated superficial actinic porokeratosis [91], erythema annulare centrifugum [92], extragenital lichen sclerosus [93], Flegel's disease [94], Grover's disease [95,96], inflammatory linear verrucous epidermal naevus [97], keratosis lichenoides chronica [98], lichen amyloidosus [99], lichen planus [100], nodular prurigo [101], naevoid hyperkeratosis of the nipple [102], morphoea [91], pityriasis rubra pilaris [91], Reiter's syndrome [91], ichthyoses [103,104], vitiligo [105] and Vorner's syndrome (epidermolytic palmoplantar keratoderma) [106].

Calcipotriol has not proved beneficial in trials on actinic keratosis [107], alopecia totalis [108], Darier's disease [103], hereditary

palmoplantar keratoderma [103], keratosis pilaris [103] or seborrhoeic dermatitis [109].

Maxacalcitol (22-oxa-calcitriol)

This is an analogue currently not marketed in the UK with efficacy similar to calcipotriol [110].

References

1 Ponchon G, Kennan AL, DeLuca HF. 'Activation' of vitamin D by the liver. *J Clin Invest* 1969; **48**: 2032–7.
2 Fraser DR, Kodicek E. Unique biosynthesis by kidney of a biological active vitamin D metabolite. *Nature* 1970; **228**: 764–6.
3 Boyle IT, Gray RW, DeLuca HF. Regulation by calcium of in vivo synthesis of 1,25-dihydroxycholecalciferol and 21,25-dihydroxycholecalciferol. *Proc Natl Acad Sci* 1971; **68**: 2131–4.
4 Carlberg C. Mechanisms of nuclear signaling by vitamin D3: interplay with retinoid and thyroid hormone signaling. *Eur J Biochem* 1995; **231**: 517–27.
5 Smith EL, Walworth NC, Holick MF. Effect of 1 alpha, 25-dihydroxyvitamin D3 on the morphologic and biochemical differentiation of cultured human epidermal keratinocytes grown in serum-free conditions. *J Invest Dermatol* 1986; **86**: 709–14.
6 Ohta T, Mimura H, Kiyoki M. Effect of 1,24-dihydroxyvitamin D-3 on proliferation stimulated by epidermal growth factor in cultured mouse epidermal keratinocytes. *Arch Dermatol Res* 1996; **288**: 415–7.
7 De Mare S, De Jong EGJM, Van de Kerkhof PCM. DNA content and KS8.12 binding of the psoriatic lesion during treatment with the vitamin D3 analogue MC903 and betamethasone. *Br J Dermatol* 1990; **123**: 291–5.
8 Berth-Jones J, Fletcher A, Hutchinson PE. Epidermal cytokeratin and immunocyte responses during treatment of psoriasis with calcipotriol and betamethasone valerate. *Br J Dermatol* 1992; **126**: 356–61.
9 Hosomi J, Hosoi J, Suda T, Kuroki T. Regulation of terminal differentiation of cultured mouse epidermal cells by 1 alpha, 25-dihydroxyvitamin D3. *Endocrinology* 1983; **113**: 1950–7.
10 Glade CP, Van Erp PEJ, Van Hooijdonk CAEM *et al*. Topical treatment of psoriatic plaques with 1 alpha, 24 dihydroxyvitamin D-3: a multiparameter flow cytometrical analysis of epidermal growth, differentiation and inflammation. *Acta Derm Venereol* 1995; **75**: 381–5.
11 Gerritsen MJP, Rulo HFC, Van Vlijmen-Willems I *et al*. Topical treatment of psoriatic plaques with 1,25-dihydroxyvitamin D3: a cell biological study. *Br J Dermatol* 1993; **128**: 666–73.
12 Gerritsen MJP, Van Erp PEJ, Van de Kerkhof PCM. Transglutaminase-positive cells in psoriatic epidermis during treatment with calcitriol (1 alpha, 25 dihydroxy vitamin D-3) and tacalcitol (1 alpha, 24 dihydroxy vitamin D-3). *Br J Dermatol* 1995; **133**: 656–9.
13 Binderup L, Latini S, Binderup E *et al*. 20-Epi-vitamin D3 analogues: a novel class of potent regulators of cell growth and immune responses. *Biochem Pharmacol* 1991; **42**: 1569–75.
14 Rigby WFC, Stacy T, Fanger MW. Inhibition of T lymphocyte mitogenesis by 1,25-dihydroxyvitamin D3 (calcitriol). *J Clin Invest* 1984; **74**: 1451–5.
15 Zhang JZ, Maruyama K, Ono T, Iwatsuki K, Kaneko F. Regulatory effects of 1,25-dihydroxyvitamin D3 and a novel vitamin D-3 analogue MC903 on secretion of interleukin-1 alpha (IL-1 alpha) and IL8 by normal human keratinocytes and a human squamous cell carcinoma cell line (HSC-1). *J Dermatol Sci* 1994; **7**: 24–31.
16 Michel G, Gailis A, Jarzebska-Deussen B *et al*. 1,25-(OH)2-vitamin D3 and calcipotriol induce IL-10 receptor gene expression in human epidermal cells. *Inflammation Research* 1997; **46**: 32–4.
17 Zhu K, Glaser R, Mrowietz U. Vitamin D(3) and analogues modulate the expression of CSF-1 and its receptor in human dendritic cells. *Biochem Biophys Res Commun* 2002; **297**: 1211.
18 Fukuoka M, Ogino Y, Sato H *et al*. RANTES expression in psoriatic skin, and regulation of RANTES and IL-8 production in cultured epidermal keratinocytes by active vitamin D3 (tacalcitol). *Br J Dermatol* 1998; **138**: 63–70.
19 Reichrath J, Perez A, Muller SM *et al*. Topical calcitriol (1,25-dihydroxyvitamin D3) treatment of psoriasis: an immunohistological evaluation. *Acta Dermato-Venereologica* 1997; **77**: 268–72.
20 Oxholm A, Oxholm P, Staberg B, Bendtzen K. Expression of interleukin-6-like molecules and tumour necrosis factor after topical treatment of psoriasis with a new vitamin D analogue (MC903). *Acta Derm Venereol* 1989; **69**: 385–90.
21 De Jong EMGJ, van de Kerkhof PCM. Simultaneous assessment of inflammation and epidermal proliferation in psoriatic plaques during long-term treatment with vitamin D3 analogue MC 903: modulations and interrelations. *Br J Dermatol* 1991; **124**: 221–9.
22 Gerritsen MJP, Boezeman JBM, van Vlijmen-Willems IMJJ *et al*. The effect of tacalcitol (1,24(OH2)D3) on cutaneous inflammation, epidermal proliferation and keratinization in psoriasis: a placebo-controlled, double-blind study. *Br J Dermatol* 1994; **131**: 57–63.
23 Mozzanica N, Cattaneo A, Schmitt E *et al*. Topical calcipotriol for psoriasis—an immunohistochemical study. *Acta Derm Venereol* 1994; **186** (Suppl.): 171–2.
24 Cagnoni ML, Ghersetich I, Lotti T *et al*. Treatment of psoriasis vulgaris with topical calcipotriol: is the clinical improvement of lesional skin related to down-regulation of some adhesion molecules? *Acta Derm Venereol* 1994; **186** (Suppl.): 55–7.
25 Fullerton A, Serup J. Topical D-vitamins: multiparametric comparison of the irritant potential of calcipotriol, tacalcitol and calcitriol in a hairless guinea pig model. *Contact Dermatitis* 1997; **36**: 184–90.
26 Kimura K, Katayama I, Nishioka K. Allergic contact dermatitis from tacalcitol. *Contact Dermatitis* 1995; **33**: 441–2.
27 Berth-Jones J. Circumlesional scaling induced by vitamin D—a guide to compliance. *Br J Dermatol* 2000; **143**: 206–7.
28 Kato T, Rokugo M, Terui T, Tagami H. Successful treatment of psoriasis with topical application of active vitamin D3 analogue, 1alpha,24-dihydroxycholecalciferol. *Br J Dermatol* 1986; **115**: 431–3.
29 Miyachi Y, Ohkawara A, Ohkido M *et al*. Long-term safety and efficacy of high-concentration (20 μg/g) tacalcitol ointment in psoriasis vulgaris. *Eur J Dermatol* 2002; **12**: 463–8.
30 Van de Kerkhof PC, Werfel T, Haustein UF *et al*. Tacalcitol ointment in the treatment of psoriasis vulgaris: a multicentre, placebo-controlled, double-blind study on efficacy and safety. *Br J Dermatol* 1996; **135**: 758–65.
31 Baadsgaard O, Traulsen J, Roed-Petersen J, Jakobsen HB. Optimal concentration of tacalcitol in once-daily treatment of psoriasis. *J Dermatol Treatment* 1995; **6**: 145–50.
32 Veien NK, Bjerke JR, Rossmann-Ringdahl I, Jakobsen HB. Once daily treatment of psoriasis with tacalcitol compared with twice daily treatment with calcipotriol. A double-blind trial. *Br J Dermatol* 1997; **137**: 581–6.
33 Schlotmann K, Ortland C, Neumann NJ *et al*. Placebo-controlled evaluation of the irritant potential of tacalcitol (1a,24-dihydroxyvitamin D3) in healthy volunteers. *Contact Dermatitis* 2000; **42**: 260–3.
34 Van de Kerkhof PC, Berth-Jones J, Griffiths CE *et al*. Long-term efficacy and safety of tacalcitol ointment in patients with chronic plaque psoriasis. *Br J Dermatol* 2002; **146**: 414–22.
35 Messer G, Degitz K, Plewig G, Rocken M. Pretreatment of psoriasis with the vitamin D_3 derivative tacalcitol increases the responsiveness to 311-nm ultraviolet B: results of a controlled right/left study. *Br J Dermatol* 2001; **144**: 628–9.
36 Tzaneva S, Honigsmann H, Tanew A. A comparison of psoralen plus ultraviolet A (PUVA) monotherapy, tacalcitol plus PUVA and tazarotene plus PUVA in patients with chronic plaque-type psoriasis. *Br J Dermatol* 2002; **147**: 748–53.
37 Ahmed I, Berth-Jones J. High dose tacalcitol in the treatment of extensive psoriasis. *J Eur Acad Dermatol Venereol* 2000; **14** (Suppl. 1): 258–9.
38 Kimura K, Katayama I, Nishioka K. Allergic contact dermatitis from tacalcitol. *Contact Dermatitis* 1995; **33**: 441–2.
39 Nijsten T, Mentens G, Lambert J. Vascular variant of keratosis lichenoides chronica associated with hypothyroidism and response to tacalcitol and acitretin. *Acta Derm Venereol* 2002; **82**: 128–30.
40 Ginarte M, Fabeiro JM, Toribio J. Confluent and reticulated papillomatosis (Gougerot-Carteaud) successfully treated with tacalcitol. *J Dermatol Treat* 2002; **13**: 27–30.
41 Hayashi H. Treatment of Grover's disease with tacalcitol. *Clin Exp Dermatol* 2002; **27**: 160–1.
42 Kawaguchi M, Mitsuhashi Y, Kondo S. A case of subcorneal pustular dermatosis treated with tacalcitol (1alpha,24-dihydroxyvitamin D3). *J Dermatol* 2000; **27**: 669–72.

43 Aoki T, Hashimoto H, Koseki S *et al*. 1alpha,24-dihydroxyvitamin D3 (tacalcitol) is effective against Hailey-Hailey disease both in vivo and in vitro. *Br J Dermatol* 1998; **139**: 897–901.

44 Bohm M, Luger TA, Bonsmann G. Disseminated superficial actinic porokeratosis: treatment with topical tacalcitol. *J Am Acad Dermatol* 1999; **40**: 479–80.

45 Katayama I, Miyazaki Y, Nishioka K. Topical vitamin D3 (tacalcitol) for steroid-resistant prurigo. *Br J Dermatol* 1996; **135**: 237–40.

46 Smith EL, Pincus SH, Donovan L, Holick MF. A novel approach for the evaluation and treatment of psoriasis. *J Am Acad Dermatol* 1988; **19**: 516–28.

47 Morimoto S, Yoshikawa K, Kozuka T *et al*. An open study of vitamin D_3 treatment in psoriasis vulgaris. *Br J Dermatol* 1986; **115**: 421–9.

48 Rizova E, Corroller M. Topical calcitriol—studies on local tolerance and systemic safety. *Br J Dermatol* 2001; **144** (Suppl. 58): 3–10.

49 Langner A, Stapor W, Ambroziak M. Efficacy and tolerance of topical calcitriol 3 μg g^{-1} in psoriasis treatment: a review of our experience in Poland. *Br J Dermatol* 2001; **144** (Suppl. 58): 11–6.

50 Hutchinson PE, Marks R, White J. The efficacy, safety and tolerance of calcitriol 3 μg/g ointment in the treatment of plaque psoriasis: a comparison with short-contact dithranol. *Dermatology* 2000; **201**: 139–45.

51 Bourke JF, Featherstone S, Iqbal SJ, Hutchinson PE. A double-blind comparison of topical calcitriol (3 μg/g) and calcipotriol (50 μg/g) in the treatment of chronic plaque psoriasis vulgaris. *Br J Dermatol* 1995; **133** (Suppl. 45): 17.

52 Ring J, Kowalzick L, Christophers E *et al*. Calcitriol 3 microg g-1 ointment in combination with ultraviolet B phototherapy for the treatment of plaque psoriasis: results of a comparative study. *Br J Dermatol* 2001; **144**: 495–9.

53 Queille-Roussel C, Duteil L, Parneix-Spake A *et al*. The safety of calcitriol 3 μg/g ointment. Evaluation of cutaneous contact sensitization, cumulative irritancy, photoallergic contact sensitization and phototoxicity. *Eur J Dermatol* 2001; **11**: 219–24.

54 Mortensen JT, Lichtenberg J, Binderup L. Toxicity of 1,25-dihydroxyvitamin D3, tacalcitol, and calcipotriol after topical treatment in rats. *J Investig Dermatol Symp Proc* 1996; **1**: 60–3.

55 Kragballe K, Beck HI, Sogaard H. Improvement of psoriasis by a topical vitamin D3 analogue (MC903) in a double-blind study. *Br J Dermatol* 1988; **119**: 223–30.

56 Kragballe K. Treatment of psoriasis by the topical application of the novel cholecalciferol analogue calcipotriol (MC903). *Arch Dermatol* 1989; **125**: 1647–52.

57 Darley CR, Cunliffe WJ, Green CM *et al*. Safety and efficacy of calcipotriol ointment (Dovonex®) in treating children with psoriasis vulgaris. *Br J Dermatol* 1996; **135**: 390–3.

58 Oranje AP, Marcoux D, Svensson A *et al*. Topical calcipotriol in childhood psoriasis. *J Am Acad Dermatol* 1997; **36**: 203–8.

59 Travis LB, Silverberg NB. Psoriasis in infancy: therapy with calcipotriene ointment. *Cutis* 2001; **68**: 341–4.

60 Berth-Jones J, Bourke JF, Bailey K *et al*. Generalised pustular psoriasis responds to topical calcipotriol. *BMJ* 1992; **305**: 868–9.

61 Matsubara K, Kanauchi H, Imamura S. Successful treatment of generalized pustular psoriasis with tacalcitol [1 alpha,24(R)-(OH)-2D-3] ointment. *Acta Dermatol Kyoto* 1995; **90**: 447–52.

62 Dwyer C, Chapman RS. Calcipotriol and hypercalcaemia. *Lancet* 1991; **338**: 764–5.

63 Russell S, Young MJ. Hypercalcaemia during treatment of psoriasis with calcipotriol (letter). *Br J Dermatol* 1994; **130**: 795–6.

64 Georgala S. Generalised pustular psoriasis precipitated by topical calcipotriol cream. *Int J Dermatol* 1994; **33**: 515–6.

65 Emtestam L, Weden U. Successful treatment for acrodermatitis continua of Hallopeau using topical calcipotriol. *Br J Dermatol* 1996; **135**: 644–6.

66 Kokelj F, Lavaroni G, Piraccini BM, Tosti-A. Nail psoriasis treated with calcipotriol (MC 903): an open study. *J Dermatol Treat* 1994; **5**: 149–50.

67 Petrow W. Treatment of a nail psoriasis with topical calcipotriol. *Aktuelle Dermatologie* 1995; **21**: 396–400.

68 Ashcroft DM, Po AL, Williams HC, Griffiths CE. Systematic review of comparative efficacy and tolerability of calcipotriol in treating chronic plaque psoriasis. *BMJ* 2000; **320**: 963–7.

69 Cunliffe WJ, Berth-Jones J, Claudy A *et al*. Comparative study of calcipotriol (MC903) ointment and betamethasone 17-valerate ointment in patients with psoriasis vulgaris. *J Am Acad Dermatol* 1993; **26**: 736–43.

70 Berth-Jones J, Chu AC, Dodd WAH *et al*. A multicentre, parallel-group comparison of calcipotriol ointment and short-contact dithranol therapy in chronic plaque psoriasis. *Br J Dermatol* 1992; **127**: 266–71.

71 Ramsay CA, Berth-Jones J, Brundin G *et al*. Long-term use of topical calcipotriol in chronic plaque psoriasis. *Dermatology* 1994; **189**: 260–4.

72 Poyner T, Hughes IW, Dass BK *et al*. Long-term treatment of chronic plaque psoriasis with calcipotriol. *J Dermatol Treat* 1993; **4**: 173–7.

73 Kragballe K, Barnes L, Hamberg KJ *et al*. Calcipotriol cream with or without concurrent topical corticosteroid in psoriasis: tolerability and efficacy. *Br J Dermatol* 1998; **139**: 649–54.

74 Guenther L, Van de Kerkhof PC, Snellman E *et al*. Efficacy and safety of a new combination of calcipotriol and betamethasone dipropionate (once or twice daily) compared to calcipotriol (twice daily) in the treatment of psoriasis vulgaris: a randomized, double-blind, vehicle-controlled clinical trial. *Br J Dermatol* 2002; **147**: 316–23.

75 Monastirli A, Georgiou S, Pasmatzi E *et al*. Calcipotriol plus short-contact dithranol: a novel topical combination therapy for chronic plaque psoriasis. *Skin Pharmacol Appl Skin Physiol* 2002; **15**: 246–51.

76 Kerscher M, Volkenandt M, Plewig G, Lehmann P. Combination of phototherapy of psoriasis with calcipotriol and narrow-band UVB. *Lancet* 1993; **342**: 923.

77 Kokelj F, Plozzer C, Guadagnini A. Topical tacalcitol reduces the total UVB dosage in the treatment of psoriasis vulgaris. *J Dermatol Treat* 1996; **7**: 265–6.

78 Frappaz A, Thivolet J. Calcipotriol in combination with PUVA: a randomized double-blind placebo study in severe psoriasis. *Eur J Dermatol* 1993; **3**: 351–4.

79 Speight EL, Farr PM. Calcipotriol improves the response of psoriasis to PUVA. *Br J Dermatol* 1994; **130**: 79–82.

80 Kiriyama T, Danno K, Uehara M. Combination of topical tacalcitol and PUVA for psoriasis vulgaris. *J Dermatol Treat* 1997; **8**: 62–4.

81 Grossman RM, Thivolet J, Claudy A *et al*. A novel therapeutic approach to psoriasis with combination calcipotriol ointment and very low dose cyclosporine: results of a multicentre placebo-controlled study. *J Am Acad Dermatol* 1994; **31**: 68–74.

82 Van de Kerkhof PCM, Hutchinson PE. Topical use of calcipotriol improves outcome in acitretin treated patients with severe psoriasis vulgaris. *Br J Dermatol* 1996; **135** (Suppl. 47): 30.

83 Gollnick H, Altmeyer P, Kaufmann R *et al*. Topical calcipotriol plus oral fumaric acid is more effective and faster acting than oral fumaric acid monotherapy in the treatment of severe chronic plaque psoriasis vulgaris. *Dermatology* 2002; **205**: 46–53.

84 Bourke J, Berth-Jones J, Hutchinson PE. Occlusion enhances the efficacy of topical calcipotriol in psoriasis vulgaris. *Clin Exp Dermatol* 1993; **18**: 504–6.

85 Frosch PJ, Rustemeyer T. Contact allergy to calcipotriol does exist. Report of an unequivocal case and review of the literature. *Contact Dermatitis* 1999; **40**: 66–71.

86 Yip J, Goodfield M. Contact dermatitis from MC903, a topical vitamin D3 analogue. *Contact Dermatitis* 1991; **25**: 139–40.

87 Bruynzeel DP, Hol CW, Nieboer C. Allergic contact dermatitis to calcipotriol. *Br J Dermatol* 1992; **127**: 66.

88 Fisher DA. Allergic contact dermatitis to propylene glycol in calcipotriene ointment. *Cutis* 1997; **60**: 43–4.

89 Bourke JF, Berth-Jones J, Hutchinson PE. High-dose topical calcipotriol in the treatment of extensive psoriasis vulgaris. *Br J Dermatol* 1993; **129**: 74–6.

90 Kurkcuoglu N, Celebi CR. Confluent and reticulated papilomatosis: response to topical calcipotriol. *Dermatology* 1995; **191**: 341–2.

91 Thiers BH. The use of topical calcipotriene/calcipotriol in conditions other than plaque-type psoriasis. *J Am Acad Dermatol* 1997; **37**: S69–71.

92 Gniadecki R. Calcipotriol for erythema annulare centrifugum. *Br J Dermatol* 2002; **146**: 317–9.

93 Kreuter A, Gambichler T, Sauermann K *et al*. Extragenital lichen sclerosus successfully treated with topical calcipotriol: evaluation by in vivo confocal laser scanning microscopy. *Br J Dermatol* 2002; **146**: 332–3.

94 Bayramgurler D, Apaydin R, Dokmeci S, Ustun M. Flegel's disease: treatment with topical calcipotriol. *Clin Exp Dermatol* 2002; **27**: 161–2.

95 Keohane SG, Cork MJ. Treatment of Grover's disease with calcipotriol (Dovonex®). *Br J Dermatol* 1995; **132**: 832–3.

96 Mota AV, Correia TM, Lopes JM, Guimaraes JM. Successful treatment of Grover's disease with calcipotriol. *Eur J Dermatol* 1998; **8**: 33–5.

97 Gatti S, Carrozzo AM, Orlandi A, Nini G. Treatment of inflammatory linear verrucous epidermal naevus with calcipotriol. *Br J Dermatol* 1995; **132**: 837–9.
98 Chang SE, Jung EC, Hong SM *et al*. Keratosis lichenoides chronica: marked response to calcipotriol ointment. *J Dermatol* 2000; **27**: 123–6.
99 Khoo BP, Tay YK, Goh CL. Calcipotriol ointment vs. betamethasone 17-valerate ointment in the treatment of lichen amyloidosis. *Int J Dermatol* 1999; **38**: 539–41.
100 Bayramgurler D, Apaydin R, Bilen N. Limited benefit of topical calcipotriol in lichen planus treatment: a preliminary study. *J Dermatolog Treat* 2002; **13**: 129–32.
101 Wong SS, Goh CL. Double-blind, right/left comparison calcipotriol ointment and betamethasone ointment in the treatment of prurigo nodularis. *Arch Dermatol* 2000; **136**: 807–8.
102 Bayramgürler D, Bilen N, Apaydin R, Erçin C. Nevoid hyperkeratosis of the nipple and areola: treatment of two patients with topical calcipotriol. *J Am Acad Dermatol* 2002; **46**: 131–3.
103 Delfino M, Fabbrocini G, Sammarco E *et al*. Efficacy of calcipotriol versus lactic acid cream in the treatment of lamellar ichthyosis and X-linked ichthyosis. *J Dermatolog Treat* 1994; **5**: 151–2.
104 Kragballe K, Steijlen PM, Ibsen HH *et al*. Efficacy, tolerability and safety of calcipotriol ointment in disorders of keratinization. *Arch Dermatol* 1995; **131**: 556–60.
105 Parsad D, Saini R, Verma N. Combination of PUVAsol and topical calcipotriol in vitiligo. *Dermatology* 1998; **197**: 167–70.
106 Lucker GPH, van de Kerkhof PCM, Steijlen PM. Topical calcipotriol in the treatment of epidermolytic palmoplantar keratoderma of Vorner. *Br J Dermatol* 1994; **130**: 543–5.
107 Smit JV, Cox S, Blokx WA *et al*. Actinic keratoses in renal transplant recipients do not improve with calcipotriol cream and all-trans retinoic acid cream as monotherapies or in combination during a 6-week treatment period. *Br J Dermatol* 2002; **147**: 816–8.
108 Berth-Jones J, Hutchinson PE. Alopecia totalis does not respond to the vitamin D analogue calcipotriol. *J Dermatolog Treat* 1991; **1**: 293–4.
109 Berth-Jones J, Adnitt PI. Topical calcipotriol is not effective in facial seborrhoeic dermatitis. *J Dermatolog Treat* 2001; **12**: 179.
110 Barker JNWN, Ashton REA, Marks R *et al*. Topical maxacalcitol for the treatment of psoriasis vulgaris: a placebo-controlled, double-blind, dose finding study with active comparator. *Br J Dermatol* 1999; **141**: 274–8.

Traditional remedies

Camphor

Camphor is an extract from the camphor laurel *Cinnamonum camphora*, best known as a moth repellent. It is sometimes added to lotions for its antipruritic and cooling effects. It is widely used in proprietary chilblain preparations.

Dyes

Gentian (crystal) violet is a triphenylmethane dye, which has antiseptic properties against bacteria and yeasts. Employed for many years as a topical treatment for bacterial and fungal skin infections, its use was drastically curtailed after experimental studies demonstrated that it interacted with DNA of living cells [1] and was linked to malignancies in mice [2]. No reports of human malignancy attributed to the use of gentian violet on the skin have been found in the recent literature. It is now licensed for topical application, as a 0.5% aqueous solution, to unbroken skin, and is not recommended for application to mucous membranes or open wounds. It has the advantages of being cheap, chemically stable and easy to prepare.

Brilliant green is also a triphenylmethane dye and has properties similar to gentian violet. It was often used in combination with the latter but does not seem to increase the spectrum of activity [3]. It has suffered similar restrictions in usage, as have other members of the group, such as malachite green.

Magenta, or basic fuchsin, is a major component of Castellani's paint. It is known to have activity against Gram-positive bacteria and fungi, but is no longer used because of potential carcinogenicity. Colourless Castellani's paint, the same formula without the magenta (boric acid, resorcinol, phenol), has been used to reduce secondary bacterial contamination in onycholysis and in chronic paronychia.

Eosin is a red dye that has astringent and antiseptic properties. It is used in aqueous solution, typically at 2% concentration.

References

1 Rosenkranz HS, Carr HS. Possible hazard in use of gentian violet. *BMJ* 1971; **3**: 702–3.
2 Food Advisory Committee. *Final Report on the Review of the Colouring Matter in Food Regulations 1973*:Fd AC\REP\4. London, HM Stationery Office, 1987.
3 Bakker P, Van Doorne H, Booskens V *et al*. Activity of gentian violet and brilliant green against some microorganisms associated with skin infections. *Int J Dermatol* 1992; **31**: 210–3.

Honey

Among the various traditional medicinal applications for honey, has been its use, since ancient times, for dressing wounds. This remains quite fashionable and potential indications include decubitus ulcers, venous ulcers and surgical wounds among others. Honey can inhibit bacterial growth—a useful property in treatment of wounds. A range of commercially formulated products are available. Manuka honey, made from nectar collected from the manuka bush, a native shrub of New Zealand, has been popular recently. Honey can be a well-tolerated treatment which seems highly acceptable to patients [1]. Superior wound healing relative to other methods of wound dressing may not be established [2] but published results (e.g. in treatment of venous ulcers) appear to be satisfactory [3].

References

1 Dunford CE, Hanano R. Acceptability to patients of a honey dressing for non-healing venous leg ulcers. *J Wound Care* 2004; **13**: 193–7.
2 Jull AB, Rodgers A, Walker N. Honey as a topical treatment for wounds. *Cochrane Database Syst Rev* 2008; (4): CD005083.
3 Gethin G, Cowman S. Manuka honey vs. hydrogel—a prospective, open label, multicentre, randomised controlled trial to compare desloughing efficacy and healing outcomes in venous ulcers. *J Clin Nurs* 2009; **18**: 466–74.

Menthol

Menthol is still mainly extracted from the Japanese mint (*Mentha arvensis*) although synthetic sources are now available. It is added to calamine and other lotions and creams to induce a cooling sensation and relieve pruritus; in the UK it is usually used at 1% concentration in Aqueous Cream.

Thymol

This compound is found in plants of the genus *Thymus* and contributes much of the characteristic flavour to thyme (*Thymus vulgaris*). It is a traditional and potent antibacterial and antifungal agent. It has limited solubility in water and is therefore most often used as a solution in chloroform or absolute alcohol. A traditional formulation is 4% thymol in chloroform. This has been used for

paronychia and fungal nail infections and should be applied two or three times daily.

Miscellaneous agents

Caffeine

Caffeine is a relatively small molecule with the potential for adequate penetration when applied topically. A cream containing 30% caffeine has been used for treatment of atopic dermatitis [1], and is claimed to have a marked antipruritic effect.

In a study on mice, caffeine has been shown to enhance UVB-induced apoptosis and to inhibit UVB-induced carcinogenesis [2].

In a study using *ex vivo* cultured human hair follicles caffeine increased the rate of hair growth [3]. In the same model testosterone reduced the rate of hair growth and this effect was counteracted by caffeine. Shampoos and hair tonics have been developed incorporating caffeine as a potential method of retarding androgenic alopecia.

References

1 Kaplan RJ, Daman L, Rosenberg EW. Treatment of atopic dermatitis with topically applied caffeine—a folllow-up report. *Arch Dermatol* 1977; **113**: 107.

2 Lu YP, Lou YR, Liao J *et al*. Administration of green tea or caffeine enhances the disappearance of UVB-induced patches of mutant p53 positive epidermal cells in SKH-1 mice. *Carcinogenesis* 2005; **26**: 1465–72.

3 Fischer TW, Hipler UC, Elsner P. Effect of caffeine and testosterone on the proliferation of human hair follicles *in vitro*. *Int J Dermatol* 2007; **46**: 27–35.

Capsaicin

Capsaicin is a remarkably potent compound extracted from hot peppers and responsible for the gustatory discomfort they induce. It is a very stable alkaloid probably produced by these plants to prevent the seeds being eaten by animals. Capsaicin stimulates release of substance P which is subsequently depleted in sensory neurons [1]. It is also a potent ligand of the vanilloid receptor (VR1), which is expressed on sensory neurones [2]. Stimulation of this receptor by capsaicin can result in a refractory state in the neurone, probably explaining the hypoalgesia which can be induced by capsaicin.

The first application to be established for this drug was in treatment of post-herpetic neuralgia [3]. The increasing range of conditions for which capsaicin has been reported to be useful include diabetic neuropathy [4], glossodynia [5], nodular prurigo [6], notalgia paraesthetica [7], pruritus ani [8], pruritus caused by pityriais rubra pilaris [9], psoriasis [10,11], PUVA itch [12] and uraemic pruritus [13].

References

1 Buck SH, Burks TF. The neuropharmacology of capsaicin: review of some recent observations. *Pharmacol Rev* 1986; **38**: 179–226.

2 Szallasi A. Vanilloid (capsaicin) receptors in health and disease. *Am J Clin Pathol* 2002; **118**: 110–21.

3 Watson CP, Evans RJ, Watt VR. Post-herpetic neuralgia and topical capsaicin. *Pain* 1988; **33**: 333–40.

4 Forst T, Pohlmann T, Kunt T *et al*. The influence of local capsaicin treatment on small nerve fibre function and neurovascular control in symptomatic diabetic neuropathy. *Acta Diabetol* 2002; **39**: 1–6.

5 Epstein JB, Marcoe JH. Topical application of capsaicin for treatment of oral neuropathic pain and trigeminal neuralgia. *Oral Surg Oral Path* 1994; **77**: 135–40.

6 Stander S, Luger T, Metze D. Treatment of prurigo nodularis with topical capsaicin. *J Am Acad Dermatol* 2001; **44**: 471–8.

7 Wallengren J, Klinker M. Successful treatment of notalgia paresthetica with topical capsaicin: vehicle-controlled, double-blind, crossover study. *J Am Acad Dermatol* 1995; **32**: 287–9.

8 Lysy J, Sistiery-Ittah M, Israelit Y *et al*. Topical capsaicin—a novel and effective treatment for idiopathic intractable pruritus ani: a randomised, placebo controlled, crossover study. *Gut* 2003; **52**: 1323–6.

9 Neess CM, Hinrichs R, Dissemond J. Treatment of pruritus by capsaicin in a patient with pityriasis rubra pilaris receiving RE-PUVA therapy. *Clin Exp Dermatol* 2000; **25**: 209–11.

10 Bernstein JE, Parish LC, Rapaport M *et al*. Effects of topically applied capsaicin on moderate and severe psoriasis vulgaris. *J Am Acad Dermatol* 1986; **15**: 504–7.

11 Ellis CN, Berberian B, Sulica VI *et al*. A double-blind evaluation of topical capsaicin in pruritic psoriasis. *J Am Acad Dermatol* 1993; **29**: 438–42.

12 Kirby B, Rogers S. Treatment of PUVA itch with capsaicin. *Br J Dermatol* 1997; **137**: 152.

13 Cho YL, Liu HN, Huang TP, Tarng DC. Uremic pruritus: roles of parathyroid hormone and substance P. *J Am Acad Dermatol* 1997; **36**: 538–43.

Dihydroxyacetone

Dihydroxyacetone (DHA) reacts with amino acids in the stratum corneum to form a brown pigment. This reaction is the basis of a large industry that revolves around 'false tanning'. DHA is a constituent of a vast array of proprietary cosmetic products (creams, lotions and sprays) used to mimic a sun tan. It is also incorporated into sunscreen products, but the 'false tan' itself offers little photoprotection. DHA seems remarkably safe, although the resemblance to natural tanning is somewhat variable depending on the product used and the skill with which it is applied. Some sufferers from vitiligo find the use of DHA helpful as a cosmetic camouflage.

Glycyrrhetinic acid

Glycyrrhetinic acid is extracted from the root of the liquorice plant *Glycyrrhiza glabra*. This compound has anti-inflammatory properties, which may be partly related to inhibition of cortisol metabolism by 11-β-hydroxysteroid hydrogenase. It has been incorporated into topical preparations for treatment of atopic dermatitis, being more effective than its vehicle in controlled trials [1,2].

References

1 Boguniewicz M, Zeichner JA, Eichenfield LF *et al*. MAS063DP is effective monotherapy for mild to moderate atopic dermatitis in infants and children: a multicenter, randomized, vehicle-controlled study. *J Pediatr* 2008; **152**: 854–9.

2 Abramovits W, Boguniewicz M. A multicenter, randomized, vehicle-controlled clinical study to examine the efficacy and safety of MAS063DP (Atopiclair) in the management of mild to moderate atopic dermatitis in adults. *J Drugs Dermatol* 2006; **5**: 236–44.

Minoxidil

This vasodilating agent was initially introduced as a systemic treatment for hypertension and was found to cause hypertrichosis. Subsequently, lotions containing minoxidil have been employed in various forms of alopecia. Formulations containing 2% and 5% solutions of minoxidil are currently available commercially. The most established indication is androgenetic alopecia, although results are usually modest. Minoxidil can also accelerate hair

regrowth after chemotherapy and there is possibly some modest benefit in patients with alopecia areata.

Topical application of minoxidil has proved remarkably safe. One potential hazard arising from long-term use is sensitization to the minoxidil or to components of the vehicle. A more common problem is hypertrichosis, usually on the face but sometimes more generalized [1]. This seems most likely to result from contamination of facial skin with minoxidil but systemic absorption has also been proposed to explain the most generalized cases. It is more problematic in female patients and is more likely to occur when the higher concentration is used.

The mechanism by which minoxidil stimulates hair growth remains to be established. It may exert direct effects on keratinocyte differentiation and proliferation within the hair follicle [2], it may alter the pattern of androgen metabolism in the dermal papilla [3] and it may improve vascularization of the papilla [4].

Androgenetic alopecia shows a positive though modest response to topical minoxidil in males and females. In a double-blind multicentre trial of 2% minoxidil in the USA, 256 females with androgenetic alopecia were treated for 32 weeks. Terminal (non-vellus) hairs increased from 140 to 163/cm^2 compared with a rise from 139 to 149/cm^2 in the placebo group. At the end of the study no dense regrowth was observed. Investigators reported moderate regrowth in 13% of the patients on active treatment and minimal regrowth in 50%, whereas the patients' assessments were more optimistic at 20% and 40%, respectively. The patients receiving placebo reported moderate and minimal regrowth in 7% and 33% respectively [5]. In a similar European trial involving 294 female subjects, there was an increase in non-vellus hair of 33/cm^2 in the active group and 19/cm^2 in the placebo group [6]. In an Australian trial on males with early-pattern alopecia only 12% had moderate regrowth after 48 weeks [7]. Response to the 5% lotion is somewhat better. In a recent study of 48 weeks' treatment duration completed by 351 male subjects, 5% solution was superior to 2% lotion and placebo from 8 weeks onward. At 48 weeks the mean terminal hair count had risen from 151 to 170/cm^2 in the 5% group, from 144 to 156 in the 2% group and from 152 to 156 in the placebo group [8]. In male patients, topical minoxidil is sometimes combined with oral finasteride [9].

Alopecia areata is sometimes treated with topical minoxidil although cosmetically useful responses have not been documented in most studies. The best results were reported by Fenton and Wilkinson [10] who conducted a double-blind, crossover trial in which 30 subjects applied 1% minoxidil (lotion or ointment) and placebo twice daily, each for 3 months. By the end of the study 16 patients had grown cosmetically acceptable terminal hair, only one of them whilst on placebo. In a subsequent trial of very similar design on 23 patients, 13 subjects demonstrated some degree of regrowth on the active medication whilst none did so with placebo; however, the result was cosmetically satisfactory in only one case [11]. In another study using 1% lotion on 48 subjects with severe disease no difference was detected from placebo [12]. Similarly, no difference was observed between placebo and 3% minoxidil lotion after 3 months in a trial on 30 subjects with extensive disease [13]. In a study comparing 1% and 5% solutions a total of 66 patients applied treatments twice daily [14]. Patients with extensive (75% or greater) scalp hair loss showed a response, defined as terminal hair growth, in 38% of cases with 1% minoxidil versus 81% with 5% minoxidil. However, even in this high-dose group, only 6% showed a cosmetically acceptable response. A slightly higher rate of cosmetic response, 11%, was observed in an uncontrolled study in which 45 patients with severe disease applied 5% minoxidil twice daily and 0.5% dithranol (anthralin) cream once daily for 6 months [15]. Application of 2% minoxidil three times daily appeared to prolong the response to a 6-week tapering course of prednisolone in a double-blind study, although the numbers were too small to achieve statistical significance relative to placebo [16].

Other applications for topical minoxidil have included reduction in the duration of alopecia caused by chemotherapy. In a controlled trial on patients undergoing chemotherapy for breast carcinoma, the duration of baldness was 87 days in patients applying 2% minoxidil solution twice daily versus 137 days in those applying placebo [17]. Additional applications have included stimulation of growth in hair transplants [18] and prevention of hair loss which may occur as a complication of cosmetic surgery [19].

References

1 Peluso AM, Misciali C, Vincenzi C, Tosti A. Diffuse hypertrichosis during treatment with 5% topical minoxidil. *Br J Dermatol* 1997; **136**: 118–20.

2 Boyera N, Galey I, Bernard BA. Biphasic effects of minoxidil on the proliferation and differentiation of normal human keratinocytes. *Skin Pharmacol* 1997; **10**: 206–20.

3 Sato T, Tadokoro T, Sonoda T *et al*. Minoxidil increases 17 beta-hydroxysteroid dehydrogenase and 5 alpha-reductase activity of cultured human dermal papilla cells from balding scalp. *J Dermatol Sci* 1999; **19**: 123–5.

4 Lachgar S, Charveron M, Gall Y, Bonafe JL. Minoxidil upregulates the expression of vascular endothelial growth factor in human hair dermal papilla cells. *Br J Dermatol* 1998; **138**: 407–11.

5 DeVillez RL, Jacobs JP, Szpunar CA, Warner ML. Androgenetic alopecia in the female. Treatment with 2% minoxidil solution. *Arch Dermatol* 1994; **130**: 303–7.

6 Jacobs JP, Szpunar CA, Warner ML. Use of topical minoxidil therapy for androgenetic alopecia in women. *Int J Dermatol* 1993; **32**: 758–62.

7 Connors TJ, Cooke DE, De Launey WE *et al*. Australasian trial of topical minoxidil and placebo in early male pattern baldness. *Australas J Dermatol* 1990; **31**: 17–25.

8 Olsen EA, Dunlap FE, Funicella T *et al*. A randomized clinical trial of 5% topical minoxidil versus 2% topical minoxidil and placebo in the treatment of androgenetic alopecia in men. *J Am Acad Dermatol* 2002; **47**: 377–85.

9 Khandpur S, Suman M, Reddy BS. Comparative efficacy of various treatment regimens for androgenetic alopecia in men. *J Dermatol* 2002; **29**: 489–98.

10 Fenton DA, Wilkinson JD. Alopecia areata treated with topical minoxidil. *BMJ* 1983; **287**: 1015–7.

11 Frentz G. Topical minoxidil for extended areate alopecia. *Acta Derm Venereol* 1985; **65**: 172–5.

12 Vesty JP, Savin JA. A trial of 1% minoxidil used topically for severe alopecia areata. *Acta Derm Venereol* 1986; **66**: 179–80.

13 Price V. Topical minoxidil (3%) in extensive alopecia areata, including long term efficacy. *J Am Acad Dermatol* 1987; **16**: 737–44.

14 Fiedler-Weiss VC. Topical minoxidil solution (1% and 5%) in the treatment of alopecia areata. *J Am Acad Dermatol* 1987; **16**: 745–8.

15 Fiedler VC, Wendrow A, Szpunar GJ *et al*. Treatment-resistant alopecia areata: response to combination therapy with minoxidil plus anthralin. *Arch Dermatol* 1990; **126**: 756–9.

16 Olsen EA, Carson SC, Turney EA. Systemic steroids with or without 2% topical minoxidil in the treatment of alopecia areata. *Arch Dermatol* 1992; **128**: 1467–73.

17 Duvic M, Lemak NA, Valero V *et al*. A randomized trial of minoxidil in chemotherapy-induced alopecia. *J Am Acad Dermatol* 1996; **35**: 74–8.

18 Avram MR. The potential role of minoxidil in the hair transplantation setting. *Dermatol Surg* 2002; **28**: 894–900.

19 Eremia S, Umar SH, Li CY. Prevention of temporal alopecia following rhytidectomy: the prophylactic use of minoxidil. A study of 60 patients. *Dermatol Surg* 2002; **28**: 66–74.

Nicotinamide and nicotinic acid [1]

The marked anti-inflammatory properties of nicotinamide, the amide derivative of vitamin B_3 (niacin, nicotinic acid), have been used in topical treatment of acne vulgaris. A 4% alcoholic gel is available. It is not yet certain by what mechanism the preparation exerts its anti-inflammatory effect. In a multicentre trial, it gave a global reduction in acne of 82% compared with 68% for 1% clindamycin gel over an 8-week period. An advantage of nicotinamide is that it avoids the problem of antibiotic resistance.

Topical application of nicotinic acid is used for its ability to induce vasodilatation, a property not shared with the amide derivative. The effect seems likely to be mediated through prostaglandin synthesis and specifically the prostaglandin D_2 receptor 1 (DP1) [2]. This action can provide a warming and soothing remedy for soft tissue injuries and has also been used to increase the diameter of cutaneous capillaries to facilitate treatment of flushing and telangiectasia with lasers or intense pulsed light [3].

References

1 Shalita AR, Smith JG, Parish LC *et al.* Topical nicotinamide compared with clindamycin gel in the treatment of inflammatory acne vulgaris. *Int J Dermatol* 1995; **34**: 434–7.
2 Cheng K, Wu TJ, Wu KK *et al*. Antagonism of the prostaglandin D2 receptor 1 suppresses nicotinic acid-induced vasodilation in mice and humans. *Proc Natl Acad Sci U S A* 2006; **103**: 6682–7.
3 Cho SB, Lee S J, Kang JM *et al*. Treatment of facial flushing by topical application of niacin cream followed by 595-nm pulsed-dye laser treatment. *Clin Exp Dermatol* 2009; in press.

Nitrite, nitric oxide (NO)

Nitric oxide (NO) is a short lived gaseous free radical. Synthesis of NO by endothelial cells has been known since the 1980s to play a pivotal physiological role in regulation of vascular smooth muscle contraction. This compound was previously known as endothelium derived relaxing factor (EDRF). In addition, NO is known to be synthesized by macrophages and neutrophils and exerts potent antimicrobial activity against a wide range of organisms.

Since NO is a gaseous compound, topical delivery requires some ingenuity. The difficulties seem to be substantially overcome by application of acidified nitrite–sodium nitrite, applied to the skin with ascorbic or acetic acid. The mixture generates NO at the site of application. NO generated in this way is capable of permeating not only the stratum corneum, but also nails.

Vasodilatation induced by application of acidified nitrite may prove beneficial in promoting survival of surgical flaps [1].

The antimicrobial properties of NO generated from acidified nitrite have been exploited to treat dermatophyte infections of skin and nails [2] and also molluscum contagiosum [3].

References

1 Gribbe O, Gustafsson LE, Wiklund NP. Transdermally administered nitric oxide by application of acidified nitrite increases blood flow in rat epigastric island skin flaps. *Eur J Pharmacol* 2008; **578**: 51–6.
2 Finnen MJ, Hennessy A, McLean S *et al*. Topical application of acidified nitrite to the nail renders it antifungal and causes nitrosation of cysteine groups in the nail plate. *Br J Dermatol* 2007; **157**: 494–500.
3 Ormerod AD, White MI, Shah SA, Benjamin N. Molluscum contagiosum effectively treated with a topical acidified nitrite, nitric oxide liberating cream. *Br J Dermatol* 1999; **141**: 1051–3.

Silicone

A range of silicone gels and sheet dressings are marketed for the prevention and treatment of hypertrophic and keloid scars. Good quality controlled trials to establish the efficacy of these treatments are lacking [1], but there seems to be agreement that these dressings are safe and well tolerated. Published trials, anecdotal reports and some evidence from animal models suggest efficacy [2–4]. The most likely mechanism is the effect of occlusion on keratinocyte hydration which could alter epidermal cytokine signalling directed to dermal fibroblasts [3,4].

References

1 O'Brien L, Pandit A. Silicon gel sheeting for preventing and treating hypertrophic and keloid scars. *Cochrane Database Syst Rev* 2006; **25**: CD003826.
2 Mustoe TA. Scars and keloids. Several treatments are used, but the evidence base is lacking. *BMJ* 2004; **328**: 1329–30.
3 Tandara AA, Mustoe TA. The role of the epidermis in the control of scarring: evidence for mechanism of action for silicone gel. *J Plast Reconstr Aesthet Surg* 2008; **61**: 1219–25.
4 Kloeters O, Schierle C, Tandara A, Mustoe TA. The use of a semiocclusive dressing reduces epidermal inflammatory cytokine expression and mitigates dermal proliferation and inflammation in a rat incisional model. *Wound Repair Regen* 2008; **16**: 568–75.

Sodium cromoglycate

Sodium cromoglycate is a member of the chromone group of drugs which also contains nedcromil sodium. These compounds inhibit release of inflammatory mediators from mast cells and may also inhibit sensory nerve activation in response to histamine [1]. These compounds are used topically in treatment of asthma, rhinitis and conjunctivitis, and orally for treatment of food allergy. Systemic absorption is minimal.

Sodium cromoglycate has been the subject of several trials for topical treatment of atopic dermatitis with seemingly conflicting results. In 1977, Haider reported a controlled trial showing significant benefit from a 10% suspension in white soft paraffin [2] but these results were not confirmed by other investigators [3]. Encouraging results from investigations using a 4% oil in water cream formulation [4] were also not confirmed [5]. Further positive results have been reported from Japan [6], using a 1% aqueous solution occluded with white soft paraffin, and more recently from the UK [7] using a novel 4% lotion, suggesting that it may yet be possible to develop a useful formulation. In view of the familiarity of sodium cromoglycate in other applications and its good record of safety and tolerability, further investigation is warranted to determine whether this drug has a potential role as a topical anti-inflammatory or antipruritic agent.

References

1 Willis EF, Clough GF, Church MK. Investigation into the mechanisms by which nedocromil sodium, frusemide and bumetanide inhibit the histamine-induced itch and flare response in human skin in vivo. *Clin Exp Allergy* 2004; **34**: 450–5.

2 Haider SA. Treatment of atopic eczema in children: clinical trial of 10% sodium cromoglycate ointment. *BMJ* 1977; **1**: 1570–2.
3 Thirumoorthy T, Greaves MW. Disodium cromoglycate ointment in atopic eczema. *BMJ* 1978; **2**: 500–1.
4 Ariyanayagam M, Barlow TJ, Graham P *et al*. Topical sodium cromoglycate in the management of atopic eczema—a controlled trial. *Br J Dermatol* 1985; **112**: 343–8.
5 Kjellman NIM, Gustaffson MIE. Topical sodium cromoglycate in atopic dermatitis. *Allergy* 1986; **41**: 423–8.
6 Kimata H, Igarashi M. Topical cromolyn (disodium cromoglycate) solution in the treatment of young children with atopic dermatitis. *Clin Exp Allerg* 1990; **20**: 281–3.
7 Stainer R, Matthews S, Arshad SH *et al*. Efficacy and acceptability of a new topical skin lotion of sodium cromoglicate (Altoderm) in atopic dermatitis in children aged 2–12 years: a double-blind, randomized, placebo-controlled trial. *Br J Dermatol* 2005; **152**: 334–41.

CHAPTER 74
Systemic Therapy

S.M. Breathnach[1], *C.H. Smith*[1], *R.J.G. Chalmers*[2] *& R.J. Hay*[3]

[1]St John's Institute of Dermatology, St Thomas' Hospital, London, UK
[2]Dermatology Centre, University of Manchester, Salford Royal Hospital, Manchester, UK
[3]Dermatology Department, Kings College Hospital, London, UK

Systemic anti-inflammatory agents, 74.2
Systemic corticosteroid therapy, 74.2
Biological therapies (protein therapeutics), 74.4
Non-specific immunosuppressive agents, 74.14
Immunomodulating agents, 74.25
Systemic antiallergic agents including antihistamines and leukotriene antagonists, 74.31
Sex hormones and related compounds, 74.32
Androgens, 74.32
Anabolic steroids, 74.32
Antiandrogens, 74.32
Oestrogens, 74.32
Antioestrogens, 74.33
Retinoids, 74.33
Isotretinoin (13-*cis*-retinoic acid), 74.34
Acitretin, 74.35
Alitretinoin (9-cis-retinoic acid), 74.36
Bexarotene, 74.36
Retinoic acid metabolism blocking agents, 74.37
Antimicrobial and antiparasitic agents, 74.38
Antibiotics and antibacterial agents, 74.38
Antifungal drugs, 74.46
Antiviral drugs, 74.48
Antiparasitic agents, 74.50
Miscellaneous systemic agents, 74.51
Drugs to improve the peripheral circulation, 74.51
Traditional Chinese herbal medicine, 74.52

Introduction

Topical therapy is generally preferable for skin diseases because it minimizes the risk of systemic toxicity. However, there are quite a number of drugs that are only effective when administered systemically. This chapter gives a brief survey of some of the more important systemic agents used by dermatologists. The reader is also directed to additional information on drug therapy for specific conditions dispersed amongst other chapters in these volumes.

Where more information on a drug is required there are now many Internet-based resources to consult. Some of these require an institutional login such as is provided by many universities and hospitals.

The important subjects of drug reactions and interactions are referred to in Chapters 75 and 76. The particular problems of prescribing for special groups, such as children, pregnant and lactating women and elderly people, are dealt with in some detail in the *British National Formulary* [1] (and other national formularies), as are the difficulties in prescribing for patients with liver failure, renal failure and diseases affecting other organs. Where there is any doubt, the advice of a clinical pharmacologist, a pharmacist or the drug manufacturer should be sought, or information obtained from such reference works as *Martindale* [2] and *Goodman and Gilman* [3]. The *ABPI Data Sheet Compendium* [4] is also valuable. The dosage for children is often calculated roughly on the basis of age, but should more accurately be based on body weight or, even better, body surface area [1].

In the tables, relevant licensed indications (UK) are given in bold. Other entries include either more precise disease specification than is given in the licence or unlicensed use of the product. Where appropriate, levels of evidence of efficacy are labelled using the following schema (based on [5]):

A RCTs with no important limitations or overwhelming evidence from observational studies
B RCTs with important limitations (inconsistent results; methodological flaws; indirect or imprecise) or exceptionally strong evidence from observational studies
C Observational studies or case series
D >10 case reports with consistent findings
E Small numbers of case reports

References

1 *British National Formulary*, No 56. London: British Medical Association and the Pharmaceutical Society of Great Britain, 2008.
2 Reynolds JEF. *Martindale: The Extra Pharmacopoeia*, 30th edn. London: Pharmaceutical Trade Press, 1993.
3 Gilman AG, Goodman LS, Rall TW. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 8th edn. New York: Pergamon, 1990.
4 Association of British Pharmaceutical Industry (ABPI). *ABPI Data Sheet Compendium*. London: Datapharm, 1996–7.
5 Guyatt G, Gutterman D, Baumann MH *et al*. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American College of Chest Physicians task force. *Chest* 2006; **129**: 179–81.

Information resources

The *Skin Disorders Specialist Collection* (http://www.library.nhs.uk/skin) is one of a set of specialty-specific health information resources available from *NHS Evidence* (http://www.evidence.nhs.uk) and contains links to guidelines, evidence-based reviews

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

and patient information on skin disease. General advice about prescribing can be obtained from the *British National Formulary* (BNF: http://www.bnf.org/bnf) and the *BNF for Children* (BNFC; http://bnfc.org/bnfc). More detailed information about individual drugs can be found in the *electronic Medicines Compendium* (eMC: http://www.emc.medicines.org) which gives ready access to the Summaries of Product Characteristics (SPCs) and Patient Information Leaflets (PILs) of preparations licensed in the United Kingdom. The US National Library of Medicine provides similar information about drugs marketed in the US at *DailyMed* (http://dailymed.nlm.nih.gov/dailymed/about.cfm) and *Medline Plus* (http://www.nlm.nih.gov/medlineplus/druginformation.html). *Medicines Complete* (http://www.medicinescomplete.com/mc/) is a web portal published by the Royal Pharmaceutical Society of Great Britain and gives access not only to the *BNF* and *BNF for Children* but also to more specialized reference sources such as *Martindale's Complete Drug Reference*, its American equivalent *AHFS Drug Information* and *Stockley's Drug Interactions*.

Systemic anti-inflammatory agents

Systemic corticosteroid therapy

Corticosteroids were first introduced into dermatology by Marion Sulzberger [1]. Most of their effects are mediated by the intracellular glucocorticoid receptor via activation or repression of gene expression [2,3]. Activation requires DNA binding of the receptor, while repression is mediated by protein–protein interactions with other transcription factors. The immunosuppressive and anti-inflammatory effects are exerted mainly by an interaction of the glucocorticoid receptor with the activating protein 1 (AP-1) and nuclear factor κB (NF-κB) families of transcription factors without DNA binding. Cytokines such as tumour necrosis factor-α (TNF-α) and interleukin 1 (IL-1) activate the hypothalamus–pituitary–adrenal (HPA) axis; glucocorticoids inhibit IL-1 and TNF-α, forming a cytokine–HPA axis feedback circuit. In addition, glucocorticoids induce apoptosis of inflammatory cells of the haematopoietic system, such as monocytes, macrophages and T lymphocytes, while protecting resident tissue cells [4]. Corticosteroids, by evoking formation of a cell-membrane protein termed lipocortin, also inhibit phospholipase A_2 (PLA_2), a membrane enzyme that generates a variety of pro-inflammatory lipids from membrane phospholipids, including the prostaglandins, the leukotrienes and platelet-activating factor [5]. Other proposed mechanisms of corticosteroids include a cytostatic action, a 'stabilizing' action on lysosomal membranes and suppression of cytokine expression. Glucocorticoid effects on bone result from inhibition of bone formation because of a decrease in the number and function of osteoblasts, and increased bone resorption resulting from osteoclastogenesis (with increased expression of RANK ligand and decreased expression of its decoy receptor, osteoprotegerin), as well as stimulated expression of collagenase 3 [6]. Corticosteroids inhibit dendritic cell function [7].

Indications

Systemic corticosteroid treatment, rather than topical corticosteroid therapy, is indicated in special circumstances only. These include the following:

1. Acute self-limited steroid-sensitive disorders (e.g. acute contact allergic dermatitis), where the offending allergen is evident. In these circumstances a 1-week course of oral prednisone in reducing dosage may be sufficient.
2. Acute anaphylactic reactions (e.g. following a bee or wasp sting or a drug to which the patient is sensitized). Hydrocortisone should be given intravenously in a dose of 100 mg, after prior administration of epinephrine (adrenaline) 0.5 mg intramuscularly, and chlorphenamine (chlorpheniramine) 4 mg intramuscularly (adult doses).
3. Acute autoimmune connective tissue diseases and generalized immunological vascular disorders (e.g. systemic lupus erythematosus, dermatomyositis, polyarteritis nodosa, giant cell arteritis, Wegener's granulomatosis).
4. Chronic disabling immunological bullous diseases (e.g. pemphigus vulgaris, pemphigoid).
5. Acute generalized exfoliative dermatitis (e.g. resulting from a severe drug reaction).
6. A number of miscellaneous disorders including severe lichen planus, pyoderma gangrenosum and sarcoidosis, in which there is evidence of cardiac, renal, ocular or extensive pulmonary or cutaneous involvement.
7. Although systemic steroids are often used, the value of such treatment is unproven in erythema multiforme, Stevens–Johnson syndrome, toxic epidermal necrolysis, chronic urticaria and cutaneous T-cell lymphoma.

Pharmacological considerations

Corticosteroids are anti-inflammatory, immunosuppressive, antiproliferative and vasoconstrictive.

Prednisone and prednisolone

Like cortisone and hydrocortisone, prednisone and prednisolone differ chemically only in the presence of a hydroxy group instead of a keto group at C11. The biological properties are similar, but prednisone has to be metabolically transformed in the liver to the 11β-hydroxy derivative to acquire biological potency, and hence prednisone should not be given to patients with liver disease. Both drugs possess four times the glucocorticoid potency and relatively less mineralocorticoid (salt-retaining) activity than hydrocortisone and cortisone.

Route of administration

Intramuscular

The intramuscular route, especially for triamcinolone, is popular in the USA for systemic steroid administration for short-term (less than 4 weeks) treatment. Triamcinolone does not differ significantly from prednisolone in its actions on a short-term basis, although in the long term it possesses greater mineralocorticoid activity. In the longer term, intramuscular steroids, especially in depot formulation, can cause marked HPA suppression and severe local atrophic changes, although the latter partially remit after a year or more. In the event of untoward steroid-induced complications, the drugs cannot be withdrawn promptly.

Intravenous

The intravenous route is useful in emergency treatment of acute anaphylaxis and in the pre- and postoperative cover of patients

who have previously been receiving systemic steroid treatment for 4 weeks or more. A suitable regimen is 25 mg hydrocortisone preoperatively at the time of induction of anaesthesia, 100 mg during the operation and 100 mg on the first postoperative day—all doses being intravenous.

Thereafter the patient can be maintained on oral therapy as required. In fact, hypotensive crises attributable to adrenal insufficiency are extremely rare in patients withdrawn from glucocorticoid therapy and subsequently undergoing surgery without supplemental corticosteroid cover.

Pulsed steroid therapy

This is usually administered as doses of 1 g of methylprednisolone given intravenously over several hours using an intravenous line. The dose can be repeated daily for up to 5 days. It may be indicated in patients with severe bullous dermatoses, especially pemphigus vulgaris. It is a potentially hazardous procedure, and thromboembolism, cardiac arrest and steroid psychosis are occasional complications [8].

Oral steroids

Oral steroids may be taken in a single daily dose or using an alternate-day regimen.

Single daily dose. Short-term systemic steroid therapy is best given as a single daily dose. Prednisone and prednisolone have minimal mineralocorticoid activity and have a sufficiently prolonged action to ensure the sustained effectiveness of a single daily dose. The single dose should be given first thing in the morning. This is because the maximum rate of adrenocortical cortisol secretion occurs early in the morning and therefore less pituitary–adrenal suppression occurs at this time, while therapeutic efficacy is maintained [9].

Alternate-day dosage. Prolonged therapy may be instituted using an alternate-day regimen (twice the daily dose on alternate days with no steroid treatment on the other days) [10]. Conversion from a daily to an alternate-day regimen should be carried out gradually rather than abruptly (e.g. by progressive diminution of the dose on even-numbered days while building up the dose on odd-numbered days). In order to prevent alternate-day relapses, it may be necessary to maintain a small dose on the even-numbered day. Institution of an alternate-day systemic steroid regimen reduces but does not prevent steroid toxicity. Posterior subcapsular cataracts and osteoporosis may remain problems [11–13]. Alternate-day systemic steroid therapy is not always as effective as daily treatment when given in equivalent dosage.

Systemic steroid toxicity

A comprehensive account of the range of unwanted side effects consequent upon systemic steroid therapy is beyond the scope of this text, and is addressed in Chapter 75. Betamethasone and deflazacort may be used in emergencies in patients with adverse immunoglobulin E (IgE)-mediated allergic reactions to hydrocortisone and methylprednisolone [14].

The approximate physiological daily cortisol secretion by the adrenal cortex is 20 mg/day for an average adult (prednisone equivalent 5 mg/day). Short courses of prednisolone (e.g. up to 30 mg/day for less than 2 weeks), although suppressing pituitary–adrenal function, do not require tapering because recovery is rapid. However, for patients with a longer history of oral steroid treatment, gradual reduction of dosage prior to discontinuation is important, because abrupt reduction may lead to the 'steroid-withdrawal' syndrome, which resembles the clinical features of adrenocortical insufficiency. Random plasma-cortisol determination may be within normal limits and stimulation tests of pituitary and adrenal function may also be normal [15].

One of the major problems with prolonged systemic corticosteroid therapy is osteoporosis. Patients receiving the equivalent of prednisolone 7.5 mg/day or more for over 3 months should receive prophylactic therapy to prevent bone resorption, such as calcium, bisphosphonates (alendronate, etidronate or risedronate), calcitriol or gonadal steroids (hormone replacement therapy in women, testosterone in men) [16–21]. Corticosteroid-induced lipodystrophy may also be a problem [22]. Common mood disturbances include hypomania and euphoria, and less common ones are depression, psychosis or delirium. They usually occur within the first 2 weeks of corticosteroid therapy and seem to be dose related; the elderly are particularly at risk [23–25].

Tests of pituitary–adrenal function

Baseline plasma-cortisol levels and study of diurnal variation of plasma cortisol are crude estimates of HPA integrity. The adrenocorticotrophic hormone (ACTH) stimulation test measures adrenal but not hypothalamo-pituitary integrity. The metyrapone test is based upon inhibition of an enzyme involved in synthesis of a cortisol precursor (2-deoxycortisol) resulting in reduction in cortisol levels and a consequent increase in ACTH. The cortisol precursors are measured in the urine and the resultant values give an indication of HPA integrity. Stress tests including insulin-induced hypoglycaemia measure the integrity of the whole HPA system, and are best carried out with the assistance of a specialized unit.

Systemic corticosteroids and pregnancy

There is little concrete evidence that systemic corticosteroids are harmful in pregnancy. Although the literature contains sporadic reports of stillbirth, spontaneous abortion and cleft palate associated with systemic corticosteroids [26], a recent review concluded that they are not teratogenic. Very little corticosteroid ingested by a mother enters her breast milk [27]. Children exposed to courses of antenatal corticosteroids do not differ significantly in physical or neurocognitive measures from their peers at 2 years of age [28,29].

Systemic corticosteroids and cataracts

Posterior subcapsular cataracts are a recognized complication of systemic corticosteroid therapy. Screening by slit-lamp examination for patients in whom prolonged treatment with systemic corticosteroids is contemplated may help to obviate medicolegal consequences [11].

ACTH and tetracosactide

Although these agents are not corticosteroids, they provoke increased secretion of endogenous adrenal corticoids. There is little or no evidence to support the use of ACTH or tetracosactide (tetracosactrin) in place of systemic steroids. Their

anti-inflammatory actions depend entirely upon increased hydrocortisone production by the adrenal cortex. They also suffer from the disadvantage that they stimulate adrenal androgen as well as hydrocortisone production, and therefore cause more salt and water retention than prednisolone [30]. Maximum response of adult adrenals is no more than 100 mg/day cortisol. ACTH and tetracosactide have to be given by injection and can cause severe anaphylactic reactions. There is no sound evidence for the often asserted view that these drugs are associated with less growth retardation in children than with oral corticosteroids. The only arguable advantage of ACTH or tetracosactide therapy is a reduced likelihood of pituitary–adrenal suppression, and this view has been challenged [30]. Certainly, overall, and dose for dose, manifestations of steroid toxicity are at least as frequent as in oral corticosteroid treatment.

References

1 Sulzberger MB, Witten VH. The effect of topically applied compound E in selected dermatoses. *J Invest Dermatol* 1952; **19**: 101–2.
2 Schaaf MJ, Cidlowski JA. Molecular mechanisms of glucocorticoid action and resistance. *J Steroid Biochem Mol Biol* 2002; **83**: 37–48.
3 Neeck G, Renkawitz R, Eggert M. Molecular aspects of glucocorticoid hormone action in rheumatoid arthritis. *Cytokines Cell Mol Ther* 2002; **7**: 61–9.
4 Amsterdam A, Sasson R. The anti-inflammatory action of glucocorticoids is mediated by cell type specific regulation of apoptosis. *Mol Cell Endocrinol* 2002; **189**: 1–9.
5 Flower RJ. Background and discovery of lipocortins. *Agents Actions* 1986; **17**: 255–62.
6 Canalis E, Delany AM. Mechanisms of glucocorticoid action in bone. *Ann N Y Acad Sci* 2002; **966**: 73–81.
7 Suda T, Chida K, Matsuda H, Hashizume H *et al.* High-dose intravenous glucocorticoid therapy abrogates circulating dendritic cells. *J Allergy Clin Immunol* 2003; **112**: 1237–9.
8 White KP, Driscoll MS, Rothe MJ, Grant-Kels JM. Severe adverse cadiovascular effects of pulse steroid therapy: is continuous cardiac monitoring necessary? *J Am Acad Dermatol* 1994; **30**: 768–73.
9 Nugent CA, Ward J, MacDiamid WD *et al.* Glucocorticoid toxicity: single versus divided daily doses of prednisolone. *J Chron Dis* 1965; **18**: 323–32.
10 Reichling GH, Kligman AM. Alternate-day corticosteroid therapy. *Arch Dermatol* 1961; **83**: 980–3.
11 Castrow FF. Atopic cataracts versus steroid cataracts. *J Am Acad Dermatol* 1981; **5**: 64–6.
12 MacGregor RR, Sheagren JN, Lipsett MB *et al.* Alternate-day prednisone therapy: evaluation of delayed hypersensitivity responses, control of disease and steroid side-effects. *N Engl J Med* 1969; **280**: 1427–31.
13 Gallant C, Kenny P. Oral glucocorticoids and their complications: a review. *J Am Acad Dermatol* 1986; **14**: 161–77.
14 Ventura MT, Calogiuri GF, Matino MG *et al.* Alternative glucocorticoids for use in cases of adverse reaction to systemic glucocorticoids: a study on 10 patients. *Br J Dermatol* 2003; **148**: 139–41.
15 Amatruda TT, Hollingsworth DR, D'Esopo G *et al.* A study of the mechanism of the steroid withdrawal syndrome: evidence for integrity of the hypothalamic–pituitary–adrenal system. *J Clin Endocrinol* 1960; **20**: 339–54.
16 Summey BT, Yosipovitch G. Glucocorticoid-induced bone loss in dermatologic patients: an update. *Arch Dermatol* 2006; **142**: 82–90.
17 Canalis E, Mazziotti G, Giustina A, Bilezikian JP. Glucocorticoid-induced osteoporosis: pathophysiology and therapy. *Osteoporos Int* 2007; **18**: 1319–28.
18 Leonard MB. Glucocorticoid-induced osteoporosis in children: impact of the underlying disease. *Pediatrics* 2007; **119** (Suppl. 2): S166–74.
19 Gourlay M, Franceschini N, Sheyn Y. Prevention and treatment strategies for glucocorticoid-induced osteoporotic fractures. *Clin Rheumatol* 2007; **26**: 44–53.
20 Curtis JR, Saag KG. Prevention and treatment of glucocorticoid-induced osteoporosis. *Curr Osteoporos Rep* 2007; **5**: 14–21.
21 De Nijs RN. Glucocorticoid-induced osteoporosis: a review on pathophysiology and treatment options. *Minerva Med* 2008; **99**: 23–43.
22 Fardet L, Cabane J, Lebbé C *et al.* Incidence and risk factors for corticosteroid-induced lipodystrophy: a prospective study. *J Am Acad Dermatol* 2007; **57**: 604–9.
23 Brown ES, Khan DA, Nejtek VA. The psychiatric side effects of corticosteroids. *Ann Allergy Asthma Immunol* 1999; **83**: 495–503.
24 Warrington TP, Bostwick JM. Psychiatric adverse effects of corticosteroids. *Mayo Clin Proc* 2006; **81**: 361–7.
25 Cerullo MA. Expect psychiatric side effects from corticosteroid use in the elderly. *Geriatrics* 2008; **63**: 15–8.
26 Reinisch JM, Simon NG, Karow WG *et al.* Prenatal exposure to prednisolone in humans and animals retards uterine growth. *Science* 1978; **202**: 436–8.
27 Lockshin MD, Sammaritano LR. Corticosteroids during pregnancy. *Scand J Rheumatol* 1998; **107** (Suppl.): 136–8.
28 Crowther CA, Doyle LW, Haslam RR *et al.* Outcomes at 2 years of age after repeat doses of antenatal corticosteroids. *N Engl J Med* 2007; **357**: 1179–89.
29 Wapner RJ, Sorokin Y, Mele L *et al.* Long-term outcomes after repeat doses of antenatal corticosteroids. *N Engl J Med* 2007; **357**: 1190–8.
30 Hirschmann JV. Some principles of systemic glucocorticoid therapy. *Clin Exp Dermatol* 1986; **11**: 27–33.

Biological therapies (protein therapeutics)

Introduction

Biological therapy (also known as protein therapeutics) is a term that encompasses, in its broadest sense, a group of pharmacologically active protein (or peptide)-based molecules produced by living organisms that are designed to alleviate disease by inhibiting or imitating naturally occurring proteins in the body. Insulin could be considered the very first 'biological' therapy, purified from bovine and porcine pancreas in 1922 to treat diabetes mellitus, while pooled immunoglobulins (IVIg), introduced in the 1980s, remain an important intervention for a number of dermatological diseases. However, the advent of recombinant DNA technology, which allows the large-scale production of recombinant proteins with highly specific structure and function, together with better understanding of the complex role of endogenous proteins in health and disease (e.g. enzymes, receptors, channels in membranes, molecule 'transporters'), has led to an exponential increase in drug development in the field of biological therapy. Biological therapies include those that are identical to an endogenous protein, and function to either replenish or enhance an endogenous supply (e.g. interferons, pooled immunoglobulins) and those that target a specific pathway, using the specificity of the antigen-recognition site of immunoglobulins (monoclonal antibodies) or the receptor-binding domains of native protein ligands (immunoadhesins) to guide the immune system to destroy the relevant molecule or cell. Their structure can be inferred, in part, by nomenclature (Fig. 74.1).

This field of therapeutics confers many potential advantages over small molecule pharmacology; a high degree of functional specificity and extra-cellular binding should result in fewer 'off target' actions compared to small molecules which often have direct intracellular effects with consequent hepatoxicity and other toxic effects. However, this does not necessarily translate to safer drugs, since the complexities of biological systems are such that interruption of a particular pathway may, nevertheless, result in undesired pharmacodynamic effects. Reactivation of latent tuberculosis with TNF-antagonist therapy for psoriasis is one such example as was the catastrophic trial of the CD28 agonist which invoked 'cytokine storm' in the six volunteers involved [1]. Further,

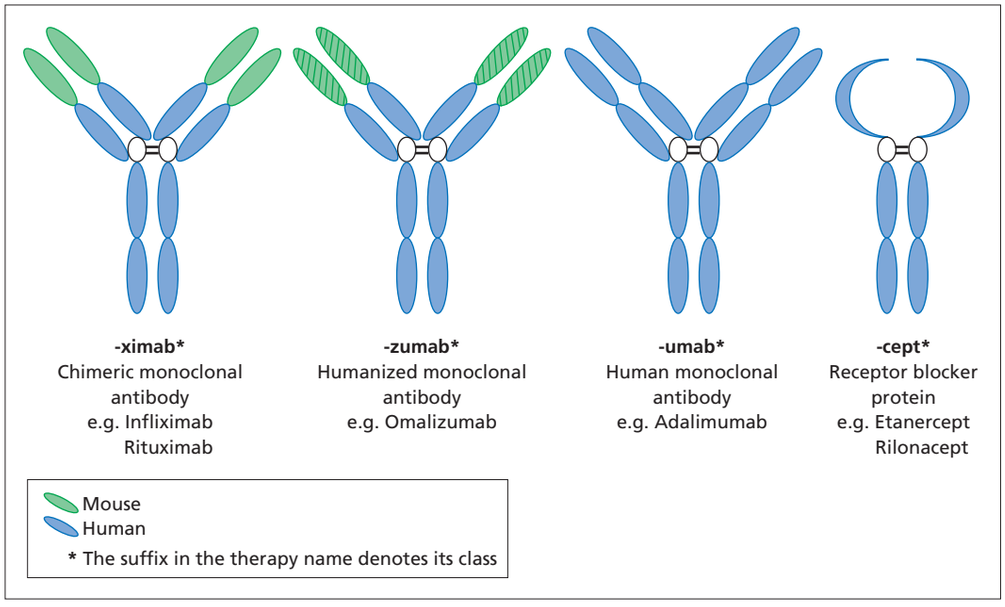


Fig. 74.1 Biological therapies: naming conventions.

since these drugs are proteins, all those currently available for dermatological conditions (and, at present, mostly also for other indications) have to be given parenterally, and immunogenicity remains a significant problem, even in the context of 'fully human' monoclonal antibodies such as adalimumab.

Biological therapies targeting tumour necrosis factor

Tumour necrosis factor (TNF) is a pro-inflammatory cytokine produced by a wide variety of cell types including keratinocytes. It plays a complex role in innate immunity and host defence, particularly against mycobacterial infection, and can both enhance and suppress adaptive immunity. Over the last 10 years, it has been shown to play a central role in the pathogenesis of a number of chronic inflammatory disease states, evidenced in large part, by the striking clinical efficacy of TNF antagonists in diseases such as psoriasis, rheumatoid arthritis and Crohn's disease. TNF is released from cells as a soluble cytokine (sTNF) following cleavage from its cell surface-bound precursor (tmTNF). Both sTNF and tmTNF are biologically active, and bind to either of two distinct receptors: TNF receptor 1 (TNFR1, p55) and TNF receptor 2 (TNFR2, p75). This leads to NF-κB activation (which promotes inflammation) and/or cell apoptosis. In addition, tmTNF can itself act as a ligand (via a process of reverse signalling) to induce cell activation, cytokine suppression or apoptosis of the tmTNF-bearing cell. Soluble forms of the TNF receptors also exist and, by binding and neutralizing sTNF, may act as natural TNF antagonists.

There are currently two types of biological agents that target TNF: anti-TNF monoclonal antibodies (adalimumab, golimumab, infliximab) and soluble TNF receptors (etanercept). Infliximab is a chimeric human–murine monoclonal antibody (~25% mouse-derived protein) whereas golimumab and adalimumab are fully human. Etanercept is a genetically engineered fusion protein composed of a dimer of the extracellular portions of human TNFR2 (p75) fused to the Fc domain of human IgG1. All these agents specifically bind both soluble and transmembrane forms of TNF and act by: (i) blocking TNFR-mediated mechanisms; and (ii) inducing tmTNF (reverse-signalling) events. Etanercept also binds members of the lymphotoxin family (LTα3 [also known as TNF-β] and LTα2β1) although the biological significance of this is unclear. Aside from the latter, there are important differences between the various TNF-antagonists with respect to pharmacokinetics, immunogenicity and structure-based mechanisms of action (only some of which are completely understood) [2]. A further anti-TNF agent of potential relevance to dermatological disease is certolizumab pegol, which is a humanized anti-TNF Fab' fragment conjugated to a polyethylene glycol to prolong the plasma half life, and thus allow once-monthly dosing [3].

Adalimumab, etanercept and infliximab have all been shown to be very effective in psoriasis, and also psoriatic arthritis, in large-scale, randomized, controlled trials (RCTs). These interventions now form a standard part of the treatment approach for severe psoriasis (and also psoriatic arthritis). Ongoing studies with golimumab and certolizumab should establish the role of these two newer TNF agents in psoriasis [4]. Loss of efficacy over time is seen in some patients due, in part, to the development of antidrug antibodies. Accumulating, largely observational, data also indicate a potential role for TNF antagonists in hidradenitis suppurativa, pyoderma gangrenosum and Behçet's disease. The role of infliximab in sarcoidosis is unclear as although initial reports were favourable, subsequent RCT data in pulmonary disease has shown only limited efficacy perhaps due to case selection. Etanercept appears not to be effective. Notably, in Wegener's granulomatosis, infliximab whilst effective was associated with an unacceptably high incidence of infection, and etanercept has been shown not to be effective. There are little data on adalimumab as it has only recently been widely available. Sporadic case reports of positive treatment responses to TNF antagonists (mainly infliximab) in an

Table 74.1 TNF or T-cell-directed biological therapy.

Drug name and indications	Usual dose range	Evidence level	References
TNF-α antagonists			
Etanercept			
Psoriasis CPP	25 mg or 50 mg biweekly	A	[90]
Generalized PP	50 mg biweekly	D	
Erythrodermic psoriasis	50 mg biweekly	D	
Infliximab			
Psoriasis CPP	5 mg/kg at 0, 2 & 6 weeks then every 8 weeks	A	[102]
Generalized PP	As above	D	
Erythrodermic psoriasis	As above	D	
Pityriasis rubra pilaris	5 mg/kg every 8 weeks	D	[22]
Pyoderma gangrenosum	5 mg/kg at weeks 0, 2 & 6 then every 8 weeks if maintenance required	B	[23,112]
Hidradenitis suppurativa	As above	C	[40,42,53]
Sarcoidosis	As above	B	[46]
Behçet disease	As above	C	[46]
ANCA +ve vasculitides	As above	C	[46]
Adalimumab			
Psoriasis CPP	40 mg every other week or weekly	A	[18,19]
T-cell inhibitor			
Alefacept			
Psoriasis CPP	15 mg weekly for 12 weeks	A	[90]

even wider spectrum of diseases are in the literature (reviewed in [5]) but require further study. Proper assessment of the risk/benefit ratio in all these 'off label' indications is hampered by a lack of controlled trial data, poorly defined treatment outcomes and limited follow-up.

TNF antagonists are generally well tolerated. Principal side effects include injection site reactions, infusion reactions (infliximab) and infection. Reactivation of tuberculosis is a particular risk, given the role of TNF in host defence against mycobacterial infection and granuloma formation. Heart failure (both new onset and worsening of pre-existing heart disease) and demyelinating disorders have also been reported. Paradoxically, new-onset psoriasis and sarcoidosis have developed in patients on TNF antagonists for, mainly, rheumatological indications, illustrating that the impact of TNF blockade on what is a highly complex cytokine network is not always predictable. Ongoing concern exists about whether or not TNF-antagonists confer an increased risk of malignancy, particularly in relation to lymphoma and skin cancer. So far, information accrued is reassuring, but largely relates to relatively short-term use in psoriasis (i.e. less than 3 years) and data from non-dermatological indications such as rheumatoid arthritis. Risks in patients with psoriasis and other inflammatory skin diseases may be different, and data currently being collected in a number of registries in the UK, Europe and the US will be important to properly answer the question of risk of malignancy in the pertinent population.

Clinical indications (Table 74.1)

Psoriasis

Etanercept. This has been shown to be effective in chronic plaque psoriasis in three large RCTs [6–8]. The onset of action is slower than that seen with infliximab and adalimumab. Efficacy is dose-related with 34% (25 mg biweekly) and 48% (50 mg biweekly) of patients achieving Psoriasis Area and Severity Index (PASI) 75 by 12 weeks. Continuous therapy provides better disease control than intermittent therapy; disease relapses slowly over several weeks on stopping treatment. The combination of etanercept and methotrexate has been shown to be more effective in rheumatoid arthritis than either agent alone and limited data suggest that the addition of methotrexate may also confer improved etanercept efficacy in psoriasis [9,10].

Infliximab. Two RCTs [11,12] indicate that infliximab therapy is highly effective in psoriasis and also associated nail disease. Onset of improvement occurs within the first 2 weeks of treatment and reaches maximum benefit by week 10, with 79% achieving a PASI 75 (and a 10-point drop in Dermatology Life Quality Index, DLQI [13]) at 10 weeks; this response is largely maintained over time with 74% and 53% achieving PASI 75 at 6 and 12 months, respectively. Loss of efficacy correlates with development of antibodies to infliximab [11]. Intermittent therapy should be avoided as it can be associated with an increased incidence of infusion reactions on re-treatment. In both rheumatoid and psoriatic arthritis, co-therapy with methotrexate is a licensed recommendation, and response rates (with and without methotrexate) are at least comparable in these disease indications. Higher serum levels of infliximab have been reported with methotrexate co-administration which may in part explain reports of improved efficacy. Methotrexate (low dose, 7.5 mg weekly) also reduces the incidence of antibodies to infliximab [14–16].

Adalimumab. Three large RCTs demonstrate that adalimumab is a highly effective treatment for chronic plaque psoriasis [17–19]. Onset of action is rapid, and response dose related with 68% of

patients achieving PASI 75 at week 12 with adalimumab 40 mg every other week (i.e. the licensed dose for psoriasis) and 80% achieving PASI 75 with adalimumab 40 mg weekly [17,18,20,21]. Interrupted therapy may result in loss of treatment response. Anti-adalimumab antibodies develop in 8.4% of patients and are associated with increased clearance and reduced efficacy of adalimumab (but not specific adverse events). The addition of methotrexate in rheumatoid arthritis results in reduced immunogenicity (i.e. a lower rate of antiadalimumab antibody formation) and increased effectiveness (in part due to reduced clearance of adalimumab) with no increase in adverse events. No prospective studies have investigated the potential benefit of adalimumab in combination with methotrexate in psoriasis. In the ADEPT study, a *post hoc* analysis comparing those patients who were on a stable dose of methotrexate at initiation of adalimumab, and those who were not, suggests that for both skin and joint disease, the combination of adalimumab and methotrexate is more effective than adalimumab alone, although the differences were only significant between the groups for the percentage achieving PASI 50 [20,21].

Not surprisingly, there are no head-to-head studies looking at the comparative efficacy of the three currently available TNF blockers. Data on long-term use of these agents are limited to 1–2 years, but there is evidence to indicate that in a significant minority of patients, efficacy diminishes over time, which can only partly be explained by the development of antidrug antibodies. Small case series and case reports suggest that failure to respond to, or loss of response to, one TNF antagonist does not preclude response to another.

Pityriasis rubra pilaris

At least 10 case reports attest to efficacy of TNF antagonists in adult-onset pityriasis rubra pilaris [5,22], the majority with infliximab. This is perhaps not surprising given the clinical overlap with psoriasis in some of the cases.

Neutrophilic dermatoses

TNF-antagonists can be extremely effective in inflammatory bowel disease and rheumatoid arthritis, and since both these conditions can be associated with pyoderma gangrenosum, investigators have assessed the efficacy of TNF antagonists in this condition. The largest body of information available is in relation to infliximab, although even this is limited. A small (n = 30), short-term (6 weeks) RCT [23] assessed the effectiveness of infliximab (monotherapy) in pyoderma gangrenosum. Following an initial infusion (infliximab or placebo), response was assessed at 2 weeks, with those who had failed to respond receiving open-label infliximab. Overall, 29 out of the 30 patients received infliximab, and 69% of these demonstrated some beneficial effect; complete remission was observed in 21%, and no response in 31% by week 6. Further case series [24] and case reports (reviewed in [25]) also report efficacy of infliximab, both to induce remission and/or as maintenance therapy, and with and without concomitant immunosuppressants. Onset of action may occur within 2 weeks of the first infusion, although recalcitrant disease may take longer. Presence or absence of concomitant inflammatory bowel disease does not seem to influence treatment outcome. Case reports also describe disease response to etanercept [26] and adalimumab [27–29].

Other neutrophilic dermatoses that reportedly respond dramatically to infliximab include Sweet's syndrome [30–34] and subcorneal pustular dermatosis [35,36].

Hidradenitis suppurativa

The beneficial effects of infliximab in hidradenitis suppuritiva (HS) were first observed in patients with Crohn's disease who also had the condition. Since then, more than 70 case reports and small case series describe use of all three of the available TNF antagonists in HS but outcomes are variable.

Three prospective, open-label studies have assessed the use of etanercept in a total of 31 patients [37–39]. In the short term, at least 50% of patients derived modest benefit in terms of reduced pain, improved quality of life and a reduction in disease severity scores by 3 months, but *clinically significant* change (>50% improvement) occurred in only a minority of patients [37,38]. Off therapy, patients relapse within 4–6 weeks [38], but with ongoing therapy, continued benefit is reported up to 40 weeks of treatment [39]. Most of the patients have been treated with low-dose etanercept (i.e. 50 mg once weekly), and it may be that high-dose etanercept may improve the response rates, particularly given the high BMI in this group of patients [37].

Three prospective, open-label studies have evaluated infliximab in a total of 24 patients [40–42]. In the short term, as with etanercept, some benefit was seen in most patients, with a minority reporting clinically significant reductions in pain and disease severity scores, and marked improvements in quality of life. In one study, remission up to 1 year was observed in two out of 12 patients treated with a standard induction course of infliximab (week 0, 2 and 6), with the remaining patients relapsing off therapy after a mean of 8.5 months. However, even in patients where treatment is continued, benefit is short lived, with a loss of efficacy occurring in the majority of patients treated for longer than a year, despite use of low-dose methotrexate [41].

Overall, perhaps predictably, patients with prominent inflammatory disease appear to respond more favourably than those with established sinuses, fistulae and scarring, where many of the changes are irreversible. Most patients relapse off therapy, although there may be a subset of patients who gain long-lasting remissions. Treatment is generally well tolerated, although the side effects typically associated with TNF antagonists have been reported. Extension or dissemination of soft tissue infection is a theoretical concern in this group of patients but has not been reported to date. The place of TNF antagonists in the treatment of HS is currently unclear; large RCTs are required to establish whether early intervention with TNF antagonists alters the overall prognosis in HS.

Sarcoidosis

Whilst TNF appears to be important in the development of granulomatous inflammation in sarcoidosis, the role of TNF-antagonists in disease management is currently unclear. Infliximab has been shown to produce only minimal benefit in pulmonary sarcoidosis in two, early phase II RCTs [43,44]. However, further analysis of patients in one of these studies [45] suggested that those with extra

pulmonary involvement (including skin) and/or those requiring corticosteroids (i.e. severe, refractory disease) may be more likely to benefit. This is supported by data in a number of uncontrolled series and case reports, involving more than 60 patients, showing a favourable treatment response to infliximab in sarcoidosis, including those with extensive skin involvement, and lupus pernio [46]. Etanercept, on the other hand, does not appear to be effective as evidenced by a small RCT in ocular sarcoid [47], and less than 30% response rate overall in case reports.

Paradoxically, a variety of granulomatous reactions, particularly involving the lung and including some indistinguishable from sarcoid, have been described in patients on anti-TNF therapy for rheumatological indications. These reactions resolve on cessation of therapy and/or with concomitant steroids, and may be more common with etanercept [48]. A possible mechanism involves enhanced Th1 reactivity in a subset of patients.

Vasculitides

Evidence suggests that TNF plays an important role in the pathogenesis of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, especially in the granuloma formation associated with Wegener's disease. Infliximab appears to show promise for both induction and maintenance of remission in patients not adequately managed with standard treatment approaches. A number of uncontrolled trials (and case reports) in heterogeneous cohorts of patients report treatment responses in the majority of patients [46,49,50] with associated reduction in concomitant corticosteroids and improved disease control. However, treatment was complicated by serious infections in a number of patients, probably because of the use of significant associated immunosuppressive drug therapy in the cohorts treated [49,51] and the results of a number of ongoing RCTs will be important to properly establish the balance of risk/benefit with infliximab [52].

Anecdotal reports also suggest infliximab may be of benefit in other severe, treatment-recalcitrant vasculitides (see [53]) but a small RCT appeared to show no benefit in maintaining remission in patients with giant cell arteritis [54].

Etanercept, in contrast to infliximab, does not appear to be effective in Wegener's granulomatosis. In a large RCT, patients were randomly assigned to receive either etanercept or placebo in addition to standard therapy (corticosteroids plus cyclophosphamide for patients with severe disease and corticosteroids plus methotrexate for patients with limited disease) [55]. No differences were found in remission rates with the addition of etanercept or placebo to methotrexate and corticosteroids. Of note, six patients in the etanercept group, and none in the placebo group, developed solid cancers, although all patients were treated with cyclophosphamide. It is possible that the combination of TNF-inhibitors and cyclophosphamide increases the risk of cancer beyond that observed with cyclophosphamide alone [56].

Paradoxically, TNF-antagonists have been associated with the development of small vessel vasculitis which, in approximately 75% of patients, is confined to the skin. However, the majority of patients affected were on treatment for rheumatoid arthritis which itself is associated with vasculitis; therefore it is unclear whether this was specifically due to the drug, or simply a reflection of disease-associated risk [57].

Behçet disease

Etanercept (25 mg biweekly) has been evaluated in a small RCT with 40 male patients randomized 1:1 to receive either etanercept or placebo [58]. At 4 weeks, mucocutaneous disease significantly reduced (oral ulcers, nodular and papulopustular lesions) with 45% of patients achieving complete remission (compared to 5% on placebo) but with no significant change in genital ulceration; at 4-week follow-up, most patients had relapsed. The role of etanercept is further supported by a number of case reports [5,46]. Infliximab has been shown to be dramatically effective in a number of open-label studies and case reports involving more than 150 patients, mainly with refractory eye involvement [46,59–62], but also including those with recalcitrant mucocutaneous disease. Complete remission of papulopustular lesions, oral and genital ulceration occurs during the induction phase of infliximab [5,63–66], with ongoing infusions at 6 to 8 weeks intervals required to maintain remission in most patients.

Systemic lupus erythematosus

The role of TNF antagonists in the treatment of systemic lupus erythematosus (SLE) is controversial. Experimental data suggest that TNF may be variously both pathogenic and protective [67], whilst TNF antagonist therapy has been associated with induction of ANA and anti-dsDNA, and less commonly, lupus-like clinical syndromes [57]. Nevertheless, in a small open-label study involving six patients with refractory SLE, joint symptoms (three patients) resolved, and associated nephritis (four patients) improved or resolved, despite increases in levels of autoantibodies with infliximab therapy [68].

Miscellaneous

There are sporadic case reports of use of TNF antagonists in toxic epidermal necrolysis, scleroderma, necrobiosis lipoidica and granuloma annulare [53].

Biological T-cell inhibitors

Alefacept. This is a fully human, dimeric fusion protein that comprises the extracellular CD2-binding portion of the human leukocyte function antigen-3 (LFA-3) linked to the Fc (hinge, CH2 and CH3 domains) portion of human IgG1. CD2 is preferentially expressed on memory-effector T cells and thus alefacept works by inhibition of T-cell activation and proliferation through blocking the CD2/LFA-3 co-stimulatory pathway, and also by reducing the number of memory-effector T cells in the circulation, skin and probably other tissues via Fc-receptor-mediated apoptosis.

Alefacept was specifically developed for the treatment of psoriasis, given the known pivotal role of T cells in the disease, and was the first biological therapy to be approved for this indication (FDA, 2003); in Europe, however, it is available only in Switzerland. An initial course, given as 12 weekly 15 mg doses, either i.m. or s.c. has been shown to be moderately effective in chronic plaque psoriasis with around 25% of patients achieving a PASI 75 by 12 weeks [69–71]; onset of action is slow with maximal benefit evident 2–6 weeks after course completion. Extending treatment beyond 12 weeks may further improve response rates and efficacy; it is also interesting to note that a subset of patients, albeit a minority, achieve prolonged remissions of 6 months or more when treat-

ment is stopped [69,72]. Combination therapy with narrow-band UVB may result in better response rates [72,73]. Alefacept has also been shown to be moderately effective in psoriatic arthritis when combined with methotrexate [74]. Small case series suggest limited benefit of alefacept in pyoderma gangrenosum [75] and atopic dermatitis [76,77].

The principal adverse effect is reduction in the total lymphocyte count ($CD4^+$ T cells) which may require temporary cessation of treatment in approximately 10% of patients. No serious infections, tuberculosis or opportunistic infections have been reported to date.

Abatacept. This is a fusion protein comprising the extracellular domain of human CTLA-4, expressed on activated T cells linked to Fc region of IgG1 and functions in an analogous way to alefacept, but inhibits a different co-stimulatory pathway through binding to CD80 and CD86 on antigen-presenting cells, thereby inhibiting T cell activation. It has recently been licensed for rheumatoid arthritis with trials ongoing in psoriasis [78].

Efalizumab. This is a recombinant humanized IgG1 monoclonal antibody that binds specifically to the CD11a subunit of lymphocyte function-associated antigen-1(LFA-1) and was specifically developed for psoriasis. LFA-1 is a cell surface protein that binds to intracellular adhesion molecules 1–3 (ICAM-1, -2, -3) and plays a key role in T lymphocyte recirculation, trafficking to sites of inflammation, antigen presentation by dendritic cells and other activated cells including keratinocytes, and T-cell co-stimulation; by interfering with LFA-1/ICAM binding, efalizumab inhibits several key steps important in the pathogenesis of psoriasis and potentially other T-cell mediated diseases [53] including T-cell migration into the skin and T-cell activation [79]. Despite moderate efficacy in psoriasis, the drug has recently been withdrawn due to the development of at least three confirmed cases of progressive, multi-focal leukoencephalopathy in patients on prolonged (>3 years) monotherapy, and highlights the potential for any new drug to result in delayed but important, unexpected, serious adverse events.

B-cell directed biological therapies

Rituximab. This is a potent B-cell depleting chimeric IgG1 anti-CD 20 antibody. It has been successfully used for the treatment of a wide range of B-cell malignancies (including cutaneous B-cell lymphoma) for the last 10 years. More recently, it has been used to treat a wide spectrum of autoimmune and chronic inflammatory disease (off-label), and is licensed for use in rheumatoid arthritis that has failed anti-TNF therapy [46,53].

CD20 is a four trans-membrane phosphoprotein that is specifically expressed on the cell surface of B cells and is regulated by differentiation. It is expressed during the transition from pre-B to immature cell in the bone marrow, and on naïve, activated and memory B cells in the circulation and tissue, but is lost on differentiation into plasma cells. Rituximab does not therefore affect long-lived plasma cells present in bone marrow, which are the major source of serum antibody production. Following binding of the rituximab Fab fragment to CD20, B cell lysis occurs, primarily via antibody-dependent cellular cytotoxicity mediated by one or more of the Fcγ receptors on the surface of granulocytes, macrophages and natural killer cells, although other mechanisms have also been implicated. Naïve B cells disappear rapidly from peripheral blood circulation and, also, to a more variable extent, from tissues, depending on the pathology and setting. Circulating B-cell populations recover to normal over the ensuing 3 to 6 months.

In diseases where autoantibodies are of direct pathogenic significance, as in the case of pemphigus for example, therapy directed at reducing antibody production via B-cell targeted agents such as rituximab might be expected to work. However, the therapeutic application of rituximab has extended into disease areas where associated autoantibodies are not necessarily considered to be major contributors to pathogenesis (although they may be of diagnostic and or prognostic significance). Examples include SLE, rheumatoid arthritis, dermatomyositis and systemic sclerosis. The clinical efficacy of rituximab in these indications probably relates to interruption of recently recognized antibody-*independent* functions of B cells which include regulation of T-cell activation and expansion (through antigen presentation and expression of co-stimulatory signals) and release of pro-inflammatory cytokines and chemokines [80].

Rituximab is given as an intravenous infusion, and although the dosing schedules have varied in different clinical trials, and according to the disease being treated, in clinical practice, for most dermatological conditions, a single cycle of treatment is given (usually 375 mg/m^2 or 1 g total dose, weekly for 2–4 weeks) in the context of concomitant immunosuppressant agents such as corticosteroids. Subsequent cycles may be given on disease relapse if necessary, but not usually until 6 months has elapsed. Adverse effects include infusion reactions, serious infection (rate of clinically significant infection in rheumatoid arthritis trials 0.05 per patient year), and rare cases of progressive multifocal leukoencephalopathy. At present, the cohort of patients receiving rituximab tend to have severe, recalcitrant disease, and have therefore necessarily received significant, often very long term immunosuppression prior to treatment, which probably further increases the risks of infection. Human antichimeric antibodies develop in about 25% of patients treated, and can be associated with worsening of infusion or allergic reactions and failure to deplete B cells, although not predictably so.

Clinical indications (Table 74.2)

Autoimmune blistering disease

Rituximab has been reported to be highly effective in four, uncontrolled open-label studies involving 55 patients with severe pemphigus (46 with pemphigus vulgaris and nine with pemphigus foliaceus) [81–84], with additional case reports reporting similar findings [52,85–87]. In the first of these studies [81], patients received an induction cycle of rituximab (375 mg/m^2) weekly for 3 weeks with adjuvant IVIg (2 g/kg body weight) on week 4, followed by monthly infusions of rituximab and IVIg for the ensuing 4 months, whereas in subsequent studies, patients received a single induction course of rituximab (i.e. 375 mg/m^2 weekly for 3–4 weeks) as adjuvant treatment to corticosteroids and azathioprine or other immunosuppressants. Despite the differing treatment schedules, significant improvements were observed within 1–2 months of starting therapy, and complete remission achieved

Table 74.2 B-cell directed biological therapy.

Drug name and indications	Usual dose range	Evidence level	References
Rituximab			
Pemphigus	375 mg/m^2 or 1 g total dose, weekly for 2–4 weeks*	B	[81,82,84]
SLE	Variable	C	[46]
Dermatomyositis	Variable	C	[46]
ANCA +ve vasculitides	Variable	C	[46]

* Usually with adjuvant corticosteroids/immunosuppressants.

Table 74.3 Anticytokine-directed biological therapy.

Drug name and indications	Usual dose range	Evidence level	References
Ustekinumab			
Psoriasis CPP	45 mg or 90 mg every 12 weeks following induction course	A	[100,101]
Rilonacept			
Cryopyrin-associated autoinflammatory syndromes	160 mg/week	A	[106]

in the majority by 3 months. Sustained disease remissions for 1–3 years, with associated reduction or complete cessation of concomitant corticosteroid therapy occurred in at least 80% of patients, with relapses subsequently responding to further cycles of rituximab. Generally the treatment appears to be well tolerated, although a number of serious infections, some of which occurred many months after treatment, have been reported. Skin healing and remission from further blistering appears to largely correlate with titres of pathogenic antibodies (antidesmoglein 1 and 3), although evidence indicates that the efficacy of rituximab extends beyond simple elimination of autoantibody production [88]. Treatment outcomes in paraneoplastic pemphigus are less predictable, in some cases due to the nature of the underlying disease [89]. Efficacy in epidermolysis bullosa acquisita, mucous membrane pemphigoid and bullous pemphigoid is also anecdotally reported (summarized in [90]).

Other indications

Rituximab has been consistently reported to induce partial or complete remission in SLE, ANCA-associated vasculitides (including Wegener's granulomatosis, Churg–Strauss syndrome, microscopic angiitis and mixed cryoglobulinaemia) and primary Sjögren syndrome [46,90,91]. All data to date come from uncontrolled trials and case reports, using a variety of dosing schedules, usually in association with concomitant immunosuppression.

Efficacy in dermatomyositis is variable [91–95] with some patients achieving complete remission from both skin and muscle disease whilst others have only modest improvement in myositis and little or no change in skin disease. Case selection (particularly stage in disease history) and possibly dosing regimen may account for these differing treatment responses.

Other B-cell-directed biological therapies. A number of other biological therapies are currently in clinical development, principally for the treatment of SLE but with potential applications in skin disease, particularly autoimmune blistering disease. These include epratuzumab, which binds to another B-cell specific antigen, CD22, and belimumab, which binds to BAFF (B-cell activation factor) [90].

Biological therapies directed against cytokines (Table 74.3)

Anti-IL12/23. IL-12 and IL-23 are heterodimeric cytokines secreted by activated antigen presenting cells, and share a common protein subunit, p40. Of relevance to psoriasis, IL-12 activates CD4 and natural killer cells to induce expression of type 1 cytokines (TNF and interferon-γ) whilst IL-23 stimulates survival and proliferation of a subset of T cells that produce IL-17 (Th17 cells). Recent immunological [96] and genetic studies indicate a central role for IL-23 in the pathogenesis of psoriasis [97]. Two fully human monoclonal antibodies that bind specifically to the p40 protein subunit thereby preventing IL-12 and IL-23 from binding to their IL-12Rβ1 receptor protein expressed on the surface of T cells, NK cells and antigen-presenting cells have been developed for use in psoriasis: ABT-874 and ustekinumab. Both have been shown to be effective in psoriasis. ABT-874 is at an earlier stage of clinical development, although phase III studies are ongoing, and a phase II, dose-finding study involving 180 patients has shown marked efficacy in chronic plaque psoriasis [98]. Ustekinumab is now licensed for use in moderate to severe psoriasis where standard systemic therapy cannot be used. It is given as a 45 mg dose (or 90 mg for patients over 100 kg) at week 0, 4 and 12, and then 3 monthly thereafter. Three large RCTs [99–101] demonstrate that both the 45 mg and 90 mg dose of ustekinumab are highly effective; onset of action is evident within 2 weeks, with 67% and 72% of patients achieving PASI 75 by week 12 for the 45 mg and 90 mg doses respectively, and maximal efficacy evident between week 20 and week 24. Disease responses are maintained with continued therapy for up to 1.5 years. On cessation of therapy, median time to relapse (i.e. loss of PASI 50) is 15 weeks, with no reports of rebound psoriasis. Similar response rates are achieved on re-treatment. Whilst there is clearly a relationship between dose (serum drug levels) and response, this is not linear, since the 90 mg dose appears to be only slightly more effective than the 45 mg dose. Furthermore, in partial responders, increasing the frequency of dosing to every 8 weeks (as compared to every 12 weeks) whilst increasing serum drug levels, significantly improves response rates only in those on 90 mg regimen—approximately two-thirds of partial responders (defined as >PASI 50, <PASI 75 at week 28) converted to responders (PASI 75) by week 52 with

intensification of the 90 mg dose to 8 weekly. Factors aside from the lower dose that are predictive of poorer response include higher body weight, previous poor response to at least one biological therapy, longer duration of psoriasis and a history of psoriatic arthritis. Perhaps surprisingly in light of the latter finding, an early study has suggested that ustekinumab may also be moderately effective in psoriatic arthritis [102].

IL-1 antagonists. Interleukin-1 plays a central role in a wide range of inflammatory conditions, and a number of novel biological agents that target IL-1 are of potential relevance to dermatology. Anakinra is a recombinant IL-1 receptor antagonist which functions as a competitive inhibitor for receptor binding of IL-1 [103]. Rilonacept (IL-1 trap) is a dimeric fusion protein that contains in a single chain the extracellular domains of IL-receptor type 1 and IL-1 receptor accessory protein fused to the human Fc portion of IgG, which functions to 'trap' IL-1 [104]. Both anakinra [105] and rilonacept [106] have been demonstrated to be extremely effective in the rare cryopyrin-associated autoinflammatory syndromes such as familial cold urticaria and Muckle–Wells syndrome, and have the potential for much broader applications [107].

Miscellaneous biological therapies

Omalizumab. This is recombinant, humanized monoclonal antibody that selectively binds to human immunoglobulin E (IgE) and thus inhibits binding of IgE to the high-affinity FCεRI receptor present on mast cells and basophils, and reduces the number of FCεRI receptors present in atopic patients. It has been approved for use in severe asthma as adjuvant therapy, with dosing based on total serum IgE and body weight, and may also have application in allergic rhinitis, and in allergen desensitization [108] to both reduce risk of anaphylaxis and optimize efficacy. Early pilot data in very limited numbers of patients report variable efficacy (i.e. marked improvement to no effect or worsening disease) in both chronic urticaria [109] (with and without anti-IgE receptor antibodies) and atopic dermatitis [5].

Human immunoglobulin (known as IV immunoglobulin, IVIg). This has been used in the treatment of a wide range of autoimmune and immunological conditions, including a number relevant to dermatology, since the 1980s, although the mechanism of action is still unclear for many indications [110]. A number of different products are commercially available, all of which comprise purified Ig from the plasma of between 1000 and 15000 donors, and contain mainly immunoglobulin G, with the distribution of Ig subclasses closely proportional to that in native human plasma. Treatment is usually given as an infusion over 2–3 days, and is generally well tolerated. Rarely, severe hypersensitivity reactions may occur in those who are IgA deficient with anti-IgA antibodies and also thromboembolic events and acute tubular necrosis, especially in patients with relevant pre-existing risk factors who are given high-dose IVIg with rapid infusion rates. Modern viral inactivation techniques and careful screening of donors have largely eliminated the risk of transmitting known infectious agents, but unfortunately do not guard against the transmission of unknown or novel viruses. Given this risk, the limited supply of IVIg and increasing availability of alternative immunomodulatory agents, use tends to be reserved for the acute management of very severe and/or life threatening disease. There is a reasonable body of evidence to support the use of IVIg in toxic epidermal necrolysis, immunobullous disease (especially pemphigus) and in selected cases of dermatomyositis. IVIg is also reported to be of variable efficacy in a variety of other diseases including chronic urticaria [111], pyoderma gangrenosum [112], SLE and ANCA-associated vasculitides [113]. Efficacy in atopic dermatitis is limited, and mostly reported in combination with other immunosuppressants [114,115]. Studies to date are mainly uncontrolled, and reporting bias is potentially a major confounder.

Table 74.4 Miscellaneous biological therapies.

Drug name and indications	Usual dose range	Evidence level	References
Omalizumab			
Chronic urticaria	Variable (weight/IgE dose adjusted)	D	[109]
Human immunoglobulin (IVIg)			
TEN	2 g/kg	C	[116,117]
Pemphigus (vulgaris and foliaceus)	2 g/kg	C	[119–121]
Bullous pemphigoid	2 g/kg	D	[122]
Dermatomyositis	2 g/kg	B	[5,123]

Clinical indications (Table 74.4)

Toxic epidermal necrolysis

Fas is a cell-surface death receptor which triggers apoptosis following interaction with its respective Fas ligand (FasL). A series of experiments by Viard *et al*. [116] suggest that up-regulation of keratinocyte FasL is the critical trigger for the widespread keratinocyte necrosis that characterizes toxic epidermal necrolysis (TEN), that *in vitro*, antibodies present in IVIg can block Fas-mediate keratinocyte death. In the same report, IVIg therapy given to a series of 10 consecutive patients with TEN coincided with a rapid interruption of skin necrosis, accompanied by skin healing and no significant adverse events [117]. Since then a number of multi-centre, prospective and retrospective case series have been published, involving more than 200 patients. In the majority of these, IVIg is reported to be associated with positive outcomes and reduced mortality (compared to either historical cohorts or SCORTEN based prognosis) [115,117], although at least two studies show minimal or no impact on outcome [118]. One of many suggested reasons for the discrepancies between the studies in terms of response relates to whether or not the pooled immunoglobulin used contains antibodies to FasL. Despite the lack of controlled data, IVIg has become a widely used intervention in TEN in some countries.

Autoimmune blistering disease

Open label, uncontrolled studies and case reports in pemphigus (vulgaris and foliaceus) [119–121], bullous pemphigoid [122] and chronic mucous membrane pemphigoid report induction of remission in patients who have failed conventional immunosuppression in the majority of patients treated, coincident with a slow fall in circulating pathogenic antibodies. Maintenance therapy has also been reported to allow discontinuation of concomitant immunosuppressive treatments. There are also case reports citing benefit in linear IgA disease, epidermolysis bullosa and pemphigoid gestationis (reviewed in [115]).

Dermatomyositis

One small RCT (total number treated 12, IVIg versus placebo, cross-over design) [123], and several uncontrolled trials [115] suggest that IVIg is of therapeutic benefit in dermatomyositis. The focus of the reports is invariably on the improvement of myositis, but associated improvement in skin disease is reported in some of these studies.

Summary

The field of protein therapeutics using novel biological molecules is changing rapidly. Many new entities are under development and one drug (efalizumab) has already had to be withdrawn because of unanticipated serious adverse events. Regular reevaluation of efficacy and safety is essential if these agents are to be used to the maximum benefit of patients [124].

References

1 Suntharalingam G, Perry MR, Ward S *et al*. Cytokine storm in a phase 1 trial of the anti-CD28 monoclonal antibody TGN1412. *N Engl J Med* 2006; **355**: 1018–28.

2 Tracey D, Lareskog L, Sasso E *et al*. Tumour necrosis factor antagonist mechanisms of action: a comprehensive review. *Pharmacol Ther* 2008; **117**: 244–79.

3 Melmed GY, Targan SR, Yasothan U *et al*. Certolizumab pegol. *Nat Rev Drug Discov* 2008; **7**: 641–2.

4 Kavanaugh A, McInnes I, Mease P *et al*. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. *Arthritis Rheum* 2009; **60**: 976–86.

5 Graves JE, Nunley K, Heffernan MP. Off-label uses of biologics in dermatology: rituximab, omalizumab, infliximab, etanercept, adalimumab, efalizumab, and alefacept (Part 2 of 2). *J Am Acad Dermatol* 2007; **56**: e55–e79.

6 Leonardi CL, Powers JL, Matheson RT *et al*. Etanercept as monotherapy in patients with psoriasis. *N Eng J Med* 2003; **349**: 2014–22.

7 Papp KA, Tyring S, Lahfa M *et al*. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. *Br J Dermatol* 2005; **152**: 1304–12.

8 Tyring S, Gordon KB, Poulin Y *et al*. Long-term safety and efficacy of 50 mg of etanercept twice weekly in patients with psoriasis. *Arch Dermatol* 2007; **143**: 719–26.

9 Zachariae C, Mork NJ, Reunala T *et al*. The combination of etanercept and methotrexate increases the effectiveness of treatment in active psoriasis despite inadequate effect of methotrexate therapy. *Acta Dermatovenereol* 2008; **88**: 495–501.

10 Driessen RJB, van de Kerkhof PCM, De Jong EMGJ. Etanercept combined with methotrexate for high-need psoriasis. *Br J Dermatol* 2008; **159**: 460–3.

11 Reich K, Nestle FO, Papp K *et al.* Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. *Lancet* 2005; **366** (9494): 1367–74.

12 Gottlieb AB, Evans R, Li S *et al*. Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomized, double-blind, placebo-controlled trial. *J Am Acad Dermat* 2004; **51**: 534–42.

13 Reich K, Nestle FO, Papp K *et al*. Improvement in quality of life with infliximab induction and maintenance therapy in patients with moderate-to-severe psoriasis: a randomized controlled trial. *Br J Dermatol* 2006; **154**: 1161–8.

14 Maini RN, Breedveld FC, Kalden JR *et al*. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum* 1998; **41**: 1552–63.

15 Baert F, Noman M, Vermeire S *et al*. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *N Eng J Med* 2003; **348**: 601–8.

16 Kapetanovic MC, Larsson L, Truedsson L *et al*. Predictors of infusion reactions during infliximab treatment in patients with arthritis. *Arthritis Res Ther* 2006; **8**: R131.

17 Gordon KB, Langley RG, Leonardi C *et al*. Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: double-blind, randomized controlled trial and open-label extension study. *J Am Acad Dermatol* 2006; **55**: 598–606.

18 Menter A, Tyring SK, Gordon K *et al*. Adalimumab therapy for moderate to severe psoriasis: a randomized, controlled phase III trial. *J Am Acad Dermatol* 2008; **58**: 106–15.

19 Saurat JH, Stingl G, Dubertret L *et al*. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). *Br J Dermatol* 2008; **158**: 556–66.

20 Mease PJ, Gladman DD, Ritchlin CT *et al*. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum* 2005; **52**: 3279–89.

21 Gladman DD, Mease PJ, Ritchlin CT *et al*. Adalimumab for long-term treatment of psoriatic arthritis: forty-eight week data from the adalimumab effectiveness in psoriatic arthritis trial. *Arthritis Rheum* 2007; **56**: 476–88.

22 Muller H, Gattringer C, Zelger B *et al*. Infliximab monotherapy as first-line treatment for adult-onset pityriasis rubra pilaris: case report and review of the literature on biologic therapy. *J Am Acad Dermatol* 2008; **59** (5 Suppl.): S65–S70.

23 Brooklyn TN, Dunnill MGS, Shetty A *et al*. Infliximab for the treatment of pyoderma gangrenosum: a randomised, double blind, placebo controlled trial. *Gut* 2006; **55**: 505–9.

24 Regueiro M, Valentine J, Plevy S *et al*. Infliximab for treatment of pyoderma gangrenosum associated with inflammatory bowel disease. *Am J Gastroenterol* 2003; **98**: 1821–6.

25 Juillerat P, Christen-Zach S, Troillet F-X *et al*. Infliximab for the treatment of disseminated pyoderma gangrenosum associated with ulcerative colitis: case report and literature review. *Dermatology* 2007; **215**: 245–51.

26 Roy DB, Conte ET, Cohen DJ. The treatment of pyoderma gangrenosum using etanercept. *J Am Acad Dermatol* 2006; **54** (3 Suppl. 2): S128–S134.

27 Heffernan MP, Anadkat MJ, Smith DI. Adalimumab treatment for pyoderma gangrenosum. *Arch Dermatol* 2007; **143**: 306–8.

28 Hubbard VG, Friedmann AC, Goldsmith P. Systemic pyoderma gangrenosum responding to infliximab and adalimumab. *Br J Dermatol* 2005; **152**: 1059–61.

29 Pomerantz RG, Husni ME, Mody E, Qureshi AA. Adalimumab for treatment of pyoderma gangrenosum. *Br J Dermatol* 2007; **157**: 1274–5.

30 Foster EN, Nguyen KK, Sheikh RA, Prindiville TP. Crohn's disease associated with Sweet's syndrome and Sjøgren's syndrome treated with infliximab. *Clin Develop Immunol* 2005; **12**: 145–9.

31 Karamlou K, Gorn AH. Refractory Sweet syndrome with autoimmune organizing pneumonia treated with monoclonal antibodies to tumor necrosis factor. *J Clin Rheumatol* 2004; **10**: 331–5.

32 Rahier JF, Lion L, Dewit O, Lambert M. Regression of Sweet's syndrome associated with Crohn's disease after anti-tumour necrosis factor therapy. *Acta Gastroenterol Belgica* 2005; **68**: 376–9.

33 Vanbiervliet G, Anty R, Schneider S *et al*. Sweet's syndrome and erythema nodosum associated with Crohn's disease treated by infliximab. *Gastroenterologie Clinique Biologique* 2002; **26**: 295–7.

34 Yamauchi PS, Turner L, Lowe NJ *et al*. Treatment of recurrent Sweet's syndrome with coexisting rheumatoid arthritis with the tumor necrosis factor antagonist etanercept. *J Am Acad Dermatol* 2006; **54** (3 Suppl. 2): S122–S126.

35 Bonifati C, Trento E, Cordiali FP *et al*. Early but not lasting improvement of recalcitrant subcorneal pustular dermatosis (Sneddon-Wilkinson disease) after infliximab therapy: relationships with variations in cytokine levels in suction blister fluids. *Clin Exp Dermatol* 2005; **30**: 662–5.

36 Voigtlander C, Luftl M, Schuler G, Hertl M. Infliximab (anti-tumor necrosis factor alpha antibody): a novel, highly effective treatment of recalcitrant subcorneal pustular dermatosis (Sneddon-Wilkinson disease). *Arch Dermatol* 2001; **137**: 1571–4.

37 Lee RA, Dommasch E, Treat J *et al*. A prospective clinical trial of open-label etanercept for the treatment of hidradenitis suppurativa. *J Am Acad Dermatol* 2009; **60**: 565–73.

38 Giamarellos-Bourboulis EJ, Pelekanou E, Antonopoulou A *et al*. An open-label phase II study of the safety and efficacy of etanercept for the therapy of hidradenitis suppurativa. *Br J Dermatol* 2008; **158**: 567–72.

39 Cusack C, Buckley C. Etanercept: effective in the management of hidradenitis suppurativa. *Br J Dermatol* 2006; **154**: 726–9.

40 Fardet L, Dupuy A, Kerob D *et al*. Infliximab for severe hidradenitis suppurativa: transient clinical efficacy in 7 consecutive patients. *J Am Acad Dermatol* 2007; **56**: 624–8.

41 Brunasso AM, Delfino C, Massone C. Hidradenitis suppurativa: are tumour necrosis factor-alpha blockers the ultimate alternative? *Br J Dermatol* 2008; **159**: 761–3.

42 Mekkes JR, Bos JD. Long-term efficacy of a single course of infliximab in hidradenitis suppurativa. *Br J Dermatol* 2008; **158**: 370–4.

43 Rossman MD, Newman LS, Baughman RP *et al*. A double-blinded, randomized, placebo-controlled trial of infliximab in subjects with active pulmonary sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2006; **23**: 201–8.

44 Baughman RP, Drent M, Kavuru M *et al*. Infliximab therapy in patients with chronic sarcoidosis and pulmonary involvement. *Am J Respir Critical Care Med* 2006; **174**: 795–802.

45 Judson MA, Baughman RP, Costabel U *et al*. Efficacy of infliximab in extrapulmonary sarcoidosis: results from a randomised trial. *Eur Respir J* 2008; **31**: 1189–96.

46 Ramos-Casals M, Brito-Zeron P, Munoz S, Soto MJ, BIOGEAS Study Group. A systematic review of the off-label use of biological therapies in systemic autoimmune diseases. *Medicine* 2008; **87**: 345–64.

47 Baughman RP, Lower EE, Raymond LA, Kaufman A. Etanercept for refractory ocular sarcoidosis: results of a double-blind randomized trial. *Chest* 2005; **128**: 1062–47.

48 Massara A, Cavazzini L, La Corte R, Trotta F. Sarcoidosis appearing during anti-tumor necrosis factor alpha therapy: a new 'Class Effect' paradoxical phenomenon. Two case reports and literature review. *Semin Arthritis Rheum* 2009, in press.

49 Booth A, Harper L, Hammad T. Prospective study of TNFalpha blockade with infliximab in anti-neutrophil cytoplasmic antibody-associated systemic vasculitis. *J Amer Soc Nephrol* 2004; **15**: 717–21.

50 Josselin L, Mahr A, Cohen P *et al*. Infliximab efficacy and safety against refractory systemic necrotising vasculitides: long-term follow-up of 15 patients. *Ann Rheum Dis* 2008; **67**: 1343–6.

51 Sangle SR, Hughes GR, D'Cruz DP. Infliximab in patients with systemic vasculitis that is difficult to treat: poor outcome and significant adverse effects. *Ann Rheum Dis* 2007; **66**: 564–5.

52 Mukhtyar C, Guillevin L, Cid MC *et al*. EULAR recommendations for the management of primary small and medium vessel vasculitis. *Ann Rheum Dis* 2009; **68**: 310–7.

53 Alexis AF, Strober BE. Off-label dermatologic uses of anti-TNF-a therapies. *J Cutan Med Surg* 2005; **9**: 296–302.

54 Hoffman GS, Cid MC, Rendt-Zagar KE *et al*. Infliximab for maintenance of glucocorticosteroid-induced remission of giant cell arteritis: a randomized trial. *Ann Int Medicine* 2007; **146**: 621–30.

55 Wegener's Granulomatosis Etanercept Trial (WGET) Research Group. Etanercept plus standard therapy for Wegener's granulomatosis. *N Eng J Med* 2005; **352**: 351–61.

56 Stone JH, Holbrook JT, Marriott MA *et al*. Solid malignancies among patients in the Wegener's Granulomatosis Etanercept Trial. *Arthritis Rheum* 2006; **54**: 1608–18.

57 Ramos-Casals M, Brito-Zeron P, Munoz S *et al*. Autoimmune diseases induced by TNF-targeted therapies: analysis of 233 cases. *Medicine* 2007; **86**: 242–51.

58 Melikoglu M, Fresko I, Mat C *et al*. Short-term trial of etanercept in Behçet's disease: a double blind, placebo controlled study. *J Rheumatol* 2005; **32**: 98–105.

59 Hatemi G, Silman A, Bang D *et al*. EULAR recommendations for the management of Behçet disease. *Ann Rheum Dis* 2008; **67**: 1656–62.

60 Munoz-Fernandez S, Hidalgo V, Fernandez-Melon J *et al*. Effect of infliximab on threatening panuveitis in Behçet's disease. *Lancet* 2001; **358** (9293): 1644.

61 Niccoli L, Nannini C, Benucci M *et al*. Long-term efficacy of infliximab in refractory posterior uveitis of Behçet's disease: a 24-month follow-up study. *Rheumatology* 2007; **46**: 1161–4.

62 Tabbara KF, Al-Hemidan AI. Infliximab effects compared to conventional therapy in the management of retinal vasculitis in Behçet disease. *Am J Ophthalmol* 2008; **146**: 845–50.

63 Almoznino G, Ben-Chetrit E. Infliximab for the treatment of resistant oral ulcers in Behçet's disease: a case report and review of the literature. *Clin Exp Rheumatol* 2007; **25** (4 Suppl. 45): S99–102.

64 Connolly M, Armstrong JS, Buckley DA. Infliximab treatment for severe orogenital ulceration in Behçet's disease. *Br J Dermatol* 2005; **153**: 1073–5.

65 Haugeberg G, Velken M, Johnsen V. Successful treatment of genital ulcers with infliximab in Behçet's disease. *Ann Rheum Dis* 2004; **63**: 744–5.

66 O'Neill ID. Off-label use of biologicals in the management of inflammatory oral mucosal disease. *J Oral Pathol Med* 2008; **37**: 575–81.

67 Rahman A, Isenberg DA. Systemic lupus erythematosus. *N Eng J Med* 2008; **358**: 929–39.

68 Aringer M, Smolen JS. Efficacy and safety of TNF-blocker therapy in systemic lupus erythematosus. *Expert Opin Drug Saf* 2008; **7**: 411–9.

69 Krueger GG, Papp KA, Stough DB *et al*. A randomized, double-blind, placebo-controlled phase III study evaluating efficacy and tolerability of 2 courses of alefacept in patients with chronic plaque psoriasis. *J Am Acad Dermatol* 2002; **47**: 821–33.

70 Lebwohl M, Christophers E, Langley R *et al*. An international, randomized, double-blind, placebo-controlled phase 3 trial of intramuscular alefacept in patients with chronic plaque psoriasis. *Arch Dermatol* 2003; **139**: 719–27.

71 Ellis CN, Krueger GG. Treatment of chronic plaque psoriasis by selective targeting of memory effector T lymphocytes. *N Eng J Med* 2001; **345**: 248–55.

72 Perlmutter A, Cather J, Franks B *et al*. Alefacept revisited: our 3-year clinical experience in 200 patients with chronic plaque psoriasis. *J Am Acad Dermatol* 2008; **58**: 116–24.

73 Legat FJ, Hofer A, Wackernagel A *et al*. Narrowband UV-B phototherapy, alefacept, and clearance of psoriasis. *Arch Dermatol* 2007; **143**: 1016–22.

74 Mease PJ, Reich K. Alefacept with methotrexate for treatment of psoriatic arthritis: open-label extension of a randomized, double-blind, placebo-controlled study. *J Am Acad Dermatol* 2009; **60**: 402–11.

75 Foss CE, Clark AR, Inabinet R *et al*. An open-label pilot study of alefacept for the treatment of pyoderma gangrenosum. *J Eur Acad Dermatol Venereol* 2008; **22**: 943–9.

76 Moul DK, Routhouska SB, Robinson MR, Korman NJ. Alefacept for moderate to severe atopic dermatitis: a pilot study in adults. *J Am Acad Dermatol* 2008; **58**: 984–9.

77 Simon D, Wittwer J, Kostylina G *et al*. Alefacept (lymphocyte function-associated molecule 3/IgG fusion protein) treatment for atopic eczema. *J All Clin Immunol* 2008; **122**: 423–4.

78 Korhonen R, Moilanen E. Abatacept, a novel CD80/86-CD28 T cell co-stimulation modulator, in the treatment of rheumatoid arthritis. *Basic Clinical Pharmacol Toxicol* 2009; **104**: 276–84.

79 Joshi A, Bauer R, Kuebler P *et al*. An overview of the pharmacokinetics and pharmacodynamics of efalizumab: a monoclonal antibody approved for use in psoriasis. *J Clin Pharmacol* 2006; **46**: 10–20.

80 Nagel A, Hertl M, Eming R. B-cell-directed therapy for inflammatory skin diseases. *J Invest Dermatol* 2009; **129**: 289–301.

81 Ahmed AR, Spigelman Z, Cavacini LA, Posner MR. Treatment of pemphigus vulgaris with rituximab and intravenous immune globulin. *N Eng J Med* 2006; **355**: 1772–9.

82 Cianchini G, Corona R, Frezzolini A *et al*. Treatment of severe pemphigus with rituximab: report of 12 cases and a review of the literature. *Arch Dermatol* 2007; **143**: 1033–8.

83 Eming R, Nagel A, Wolff-Franke S *et al*. Rituximab exerts a dual effect in pemphigus vulgaris. *J Invest Dermatol* 2008; **128**: 2850–8.

84 Joly P, Mouquet H, Roujeau J-C *et al*. A single cycle of rituximab for the treatment of severe pemphigus. *N Eng J Med* 2007; **357**: 545–52.
85 El Tal AK, Posner MR, Spigelman Z, Ahmed AR. Rituximab: A monoclonal antibody to CD20 used in the treatment of pemphigus vulgaris. *J Am Acad Dermatol* 2006; **55**: 449–59.
86 Faurschou A, Gniadecki R. Two courses of rituximab (anti-CD20 monoclonal antibody) for recalcitrant pemphigus vulgaris. *Int J Dermatol* 2008; **47**: 292–4.
87 Goh MSY, McCormack C, Dinh HV *et al*. Rituximab in the adjuvant treatment of pemphigus vulgaris: a prospective open-label pilot study in five patients. *Br J Dermatol* 2007; **156**: 990–6.
88 Zambruno G, Borradori L. Rituximab immunotherapy in pemphigus: therapeutic effects beyond B-cell depletion. *J Invest Dermatol* 2008; **128**: 2745–7.
89 Vezzoli P, Berti E, Marzano AV. Rationale and efficacy for the use of rituximab in paraneoplastic pemphigus. *Exp Rev Clin Immunol* 2008; **4**: 351–63.
90 Brimhall AK, King LN, Licciardone JC *et al*. Safety and efficacy of alefacept, efalizumab, etanercept and infliximab in treating moderate to severe plaque psoriasis: a meta-analysis of randomized controlled trials. *Br J Dermatol* 2008; **159**: 274–85.
91 Furst DE, Keystone EC, Kirkham B *et al*. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2008. *Ann Rheum Dis* 2008; **67** (Suppl. 3): iii2–iii25.
92 Chung L, Genovese MC, Fiorentino DF. A pilot trial of rituximab in the treatment of patients with dermatomyositis. *Arch Dermatol* 2007; **143**: 763–7.
93 Cooper MA, Willingham DL, Brown DE *et al*. Rituximab for the treatment of juvenile dermatomyositis: a report of four pediatric patients. *Arthritis Rheum* 2007; **56**: 3107–11.
94 Dinh HV, McCormack C, Hall S, Prince HM. Rituximab for the treatment of the skin manifestations of dermatomyositis: a report of 3 cases. *J Am Acad Dermatol* 2007; **56**: 148–53.
95 Levine TD. Rituximab in the treatment of dermatomyositis: an open-label pilot study. *Arthritis Rheum* 2005; **52**: 601–7.
96 Wilson NJ, Boniface K, Chan JR *et al*. Development, cytokine profile and function of human interleukin 17-producing helper T cells. *Nature Immunol* 2007; **8**: 950–7.
97 Blauvelt A. T-helper 17 cells in psoriatic plaques and additional genetic links between IL-23 and psoriasis. *J Invest Dermatol* 2008; **128**: 1064–7.
98 Kimball AB, Gordon KB, Langley R *et al*. Safety and efficacy of ABT-874, a fully human interleukin 12/23 monoclonal antibody, in the treatment of moderate to severe chronic plaque psoriasis: results of a randomized, placebo-controlled, phase 2 trial. *Arch Dermatol* 2008; **144**: 200–7.
99 Krueger GG, Langley RG, Leonardi C *et al*. A human interleukin-12/23 monoclonal antibody for the treatment of psoriasis. *N Eng J Med* 2007; **356**: 580–92.
100 Leonardi CL, Kimball AB, Papp K *et al*. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet* 2008; **371**: 1665–74.
101 Papp K, Langley RG, Lebwohl M *et al*. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet* 2008; **371**: 1675–84.
102 Gottlieb A, Menter A, Mendelsohn A *et al.* Ustekinumab, a human interleukin 12/23 monoclonal antibody, for psoriatic arthritis: randomised, double-blind, placebo-controlled, crossover trial. Lancet 2009; **373**: 633–40.
103 Kary S, Burmester GR. Anakinra: The first interleukin-1 inhibitor in the treatment of rheumatoid arthritis. *Int J Clin Practice* 2003; **57**: 231–4.
104 Hoffman HM, Yasothan U, Kirkpatrick P. Rilonacept. *Nat Rev Drug Discovery* 2008; **7**: 385–6.
105 Hawkins PN, Lachmann HJ, Aganna E, McDermott MF. Spectrum of clinical features in Muckle-Wells syndrome and response to anakinra. *Arthritis Rheum* 2004; **50**: 607–12.
106 Hoffman HM, Throne ML, Amar NJ *et al*. Efficacy and safety of rilonacept (Interleukin-1 Trap) in patients with cryopyrin-associated periodic syndromes: results from two sequential placebo-controlled studies. *Arthritis Rheum* 2008; **58**: 2443–52.
107 Shinkai K, McCalmont TH, Leslie KS. Cryopyrin-associated periodic syndromes and autoinflammation. *Clin Exp Dermatol* 2008; **33**: 1–9.
108 Casale TB, Busse WW, Kline JN *et al*. Omalizumab pretreatment decreases acute reactions after rush immunotherapy for ragweed-induced seasonal allergic rhinitis. *J Allergy Clin Immunol* 2006; **117**: 134–40.
109 Kaplan AP, Joseph K, Maykut RJ *et al*. Treatment of chronic autoimmune urticaria with omalizumab. *J Allergy Clin Immunol* 2008; **122**: 569–73.
110 Negi V-S, Elluru S, Siberil S *et al*. Intravenous immunoglobulin: an update on the clinical use and mechanisms of action. *J Clin Immunol* 2007; **27**: 233–45.
111 O'Donnell BF, Barr RM, Kobza BA *et al*. Intravenous immunoglobulin in autoimmune chronic urticaria. *Br J Dermatol* 1998; **138**: 101–6.
112 Reichrath J, Bens G, Bonowitz A, Tilgen W. Treatment recommendations for pyoderma gangrenosum: an evidence-based review of the literature based on more than 350 patients. *J Am Acad Dermatol* 2005; **53**: 273–83.
113 Bosch X, Guilabert A, Espinosa G, Mirapeix E. Treatment of antineutrophil cytoplasmic antibody associated vasculitis: a systematic review. *JAMA* 2007; **298**: 655–69.
114 Paul C, Lahfa M, Bachelez H *et al*. A randomized controlled evaluator-blinded trial of intravenous immunoglobulin in adults with severe atopic dermatitis. *Br J Dermatol* 2002; **147**: 518–22.
115 Smith DI, Swamy PM, Heffernan MP. Off-label uses of biologics in dermatology: interferon and intravenous immunoglobulin (Part 1 of 2). *J Am Acad Dermatol* 2007; **56**: e1–e54.
116 Viard I, Wehrli P, Bullani R *et al*. Inhibition of toxic epidermal necrolysis by blockade of CD95 with human intravenous immunoglobulin. *Science* 1998; **282**: 490–3.
117 Trent J, Halem M, French LE, Kerdel F. Toxic epidermal necrolysis and intravenous immunoglobulin: a review. *Semin Cutan Med Surg* 2006; **25**: 91–3.
118 Schneck J, Fagot J-P, Sekula P *et al*. Effects of treatments on the mortality of Stevens-Johnson syndrome and toxic epidermal necrolysis: a retrospective study on patients included in the prospective EuroSCAR Study. *J Am Acad Dermatol* 2008; **58**: 33–40.
119 Ahmed AR, Sami N. Intravenous immunoglobulin therapy for patients with pemphigus foliaceus unresponsive to conventional therapy. *J Am Acad Dermatol* 2002; **46**: 42–9.
120 Ahmed AR. Intravenous immunoglobulin therapy in the treatment of patients with pemphigus vulgaris unresponsive to conventional immunosuppressive treatment. *J Am Acad Dermatol* 2001; **45**: 679–90.
121 Martin LK, Agero AL, Werth V *et al*. Interventions for pemphigus vulgaris and pemphigus foliaceus. *Cochrane Database Syst Rev* 2009, Issue 1. Art. No.: CD006263. DOI: 10.1002/14651858.CD006263.pub2.
122 Ahmed AR. Intravenous immunoglobulin therapy for patients with bullous pemphigoid unresponsive to conventional immunosuppressive treatment. *J Am Acad Dermatol* 2001; **45**: 825–35.
123 Dalakas MC, Illa I, Dambrosia JM *et al*. A controlled trial of high-dose intravenous immune globulin infusions as treatment for dermatomyositis. *N Engl J Med* 1993; **329**: 1993–2000.
124 Smith CH, Anstey AV, Barker JNWN *et al*. British Association of Dermatologists' guidelines for biologic interventions for psoriasis 2009. *Br J Dermatol* 2009; **161**: 987–1019.

Non-specific immunosuppressive agents

Azathioprine

Azathioprine is one of many immunosuppressive drugs used in dermatology, following original use in organ transplant recipients. It is converted non-enzymatically in the body to 6-mercaptopurine (6-MP) and then processed by one of three metabolic pathways, of which two involve breakdown to inactive metabolites by either thiopurine methyltransferase (TPMT) or xanthine oxidase (XO); the third pathway involves the conversion of 6-MP by hypoxanthine guanine phosphoribosyl transferase (HGPRT) to 6-thioguanine nucleotides. Their immunosuppressive activity results from disruption of normal DNA and RNA synthesis. Additionally, an imidazole metabolite appears to have powerful anti-inflammatory properties. Failure of either of the two catabolic

Table 74.5 Azathioprine.

Drug name and indications	Usual dose range	Evidence level	References
Azathioprine			
Dermatomyositis	1–3 mg/kg daily*	B	[5]
Systemic lupus erythematosus	As above	B	[6]
Pemphigus vulgaris	As above	C	[7]
Bullous pemphigoid	As above	C	[8–10]
Atopic dermatitis	As above	A	[4,11]
Chronic actinic dermatitis	As above	B	[12]
Behçet disease	As above	B	[13]
Wegener granulomatosis	As above	E	[14]
Other vasculitides	As above	E	[6]
Pyoderma gangrenosum	As above	E	[15]
Psoriasis	As above	D	[16]
Pityriasis rubra pilaris	As above	E	[17]

* Contraindicated in patients with very low TPMT; if used in patients with low TPMT, use at dose of 0.5–1.0 mg/kg daily.

pathways increases the proportion of 6-MP converted to active metabolites and can result in toxicity.

The TPMT pathway functions normally in approximately 90% of Caucasian populations but various allelic polymorphisms can result in low enzyme activity [1]. Homozygotes for a low activity allele (0.33% of the population) are known to be at high risk for myelosuppression [1–3]. It is recommended that all patients should have blood TPMT levels measured before starting azathioprine so that the real dangers of giving the drug to a patient who is TPMT deficient can be avoided [3,4]. The drug should be avoided in patients taking allopurinol because the latter interferes with the other principal metabolic pathway for azathioprine, XO, and can thereby result in dangerous myelosuppression [3].

Clinical indications (Table 74.5)

The licensed indications for azathioprine are dermatomyositis [5], systemic lupus erythematosus (it may also be considered for severe cutaneous disease [6]) and pemphigus vulgaris [7,8]. Other dermatological conditions in which it may be of value include bullous pemphigoid [9,10], intractable atopic dermatitis [4,11], chronic actinic dermatitis [12], Behçet disease [13], Wegener's granulomatosis [14] and other vasculitides [6], pyoderma gangrenosum [15], psoriasis [16] and possibly pityriasis rubra pilaris in adults [17]. It appears to be inferior to methotrexate in the treatment of psoriasis but may be useful for psoriatic arthritis.

Management of the patient. Azathioprine should not be introduced until the patient's TPMT status is known. The one in 300 of the population with profound TPMT deficiency is at serious risk of fatal myelosuppression if exposed to the drug. The usual azathioprine regimen is 1–3 mg/kg/day in patients with normal TPMT activity but in the 10% of the population with subnormal TPMT activity the dose should be limited to 0.5–1 mg/kg/day [3]. It is also generally advised that lower doses are used in the elderly.

Azathioprine is usually employed as a steroid-sparing agent, but has been used as monotherapy, especially in atopic dermatitis. It takes several weeks to reach a steady state; dose titration may be required. Weekly blood monitoring is advocated for the first 4 weeks of therapy or when the dose is increased. Once the dose is stable the frequency of monitoring may be gradually extended to once every 3 months [3].

Contraindications include very low or absent TPMT activity, pregnancy or risk of pregnancy, hypersensitivity, concurrent malignancy and concurrent allopurinol therapy (because of risk of marrow toxicity). Other drugs that may interact with azathioprine include sulfsalazine, warfarin, angiotensin-converting enzyme inhibitors and any drug that suppresses bone marrow function.

Complications of treatment. Myelosuppression can develop very quickly despite regular blood monitoring and can be severe. It is more common at the start of treatment, especially if TPMT deficiency is not recognized, but it may also occur in those with normal TPMT activity.

Nausea is common. Hypersensitivity reactions present with various combinations of fever, hypotension, hepatitis, oliguria and respiratory distress and are sometimes accompanied by a morbilliform rash [18,19].

References

1 Zhou S. Clinical pharmacogenomics of thiopurine S-methyltransferase. *Curr Clin Pharmacol* 2006; **1**: 119–28.
2 Snow JL, Gibson LE. The role of genetic variation in thiopurine methyltransferase activity and the efficacy and/or side-effects of azathioprine therapy in dermatologic patients. *Arch Dermatol* 1995; **131**: 193–7.
3 Anstey A, Wakelin S, Reynolds NJ. Guidelines for prescribing azathioprine in dermatology. *Br J Dermatol* 2004; **151**: 1123–32.
4 Meggitt SJ, Reynolds NJ. Azathioprine for atopic dermatitis. *Clin Exp Dermatol* 2001; **26**: 369–75.
5 Fam AG. Recent advances in the management of adult myositis. *Expert Opin Investig Drugs* 2001; **10**: 1265–77.
6 Callen JP, Spencer LV, Burruss JB *et al.* Azathioprine: an effective, corticosteroid-sparing therapy for patients with recalcitrant cutaneous lupus erythematosus or with recalcitrant cutaneous leukocytoclastic vasculitis. *Arch Dermatol* 1991; **127**: 515–22.
7 Aberer W, Wolff-Schreiner EC, Stingl G, Wolff K. Azathioprine in the treatment of pemphigus vulgaris. *J Am Acad Dermatol* 1987; **16**: 527–33.
8 Harman KE, Albert S, Black MM. Guidelines for the management of pemphigus vulgaris. *Br J Dermatol* 2003; **149**: 926–37.
9 Burton JL, Harman RMM, Peachey RDG, Warin RP. A controlled trial of azathioprine in the treatment of pemphigoid. *BMJ* 1978; **2**: 1190–1.
10 Wojnarowska F, Kirtschig G, Highet AS *et al.* Guidelines for the management of bullous pemphigoid. *Br J Dermatol* 2003; **147**: 214–21.
11 Berth-Jones J, Takwale A, Tan E *et al.* Azathioprine in severe adult atopic dermatitis: a double-blind, placebo-controlled, crossover trial. *Br J Dermatol* 2002; **147**: 324–30.
12 Murphy GM, Maurice PM, Norris PG *et al.* Azathioprine in the treatment of chronic actinic dermatitis: a double-blind controlled trial with monitoring of exposure to ultraviolet radiation. *Br J Dermatol* 1989; **121**: 639–46.
13 Yazici H, Pazarli H, Barnes CG *et al.* A controlled trial of azathioprine in Behçet's syndrome. *N Engl J Med* 1990; **322**: 281–5.
14 Wisehart JM. Wegener's granulomatosis: controlled by azathioprine and corticosteroids. *Br J Dermatol* 1975; **92**: 461–7.
15 Chow RKP, Ho VC. Treatment of pyoderma gangrenosum. *J Am Acad Dermatol* 1996; **34**: 1047–60.
16 du Vivier A, Munro DD, Verbov J. Treatment of psoriasis with azathioprine. *BMJ* 1974; **1**: 49–51.

Table 74.6 Calcineurin inhibitors.

Drug name and indications	Usual dose range	Evidence level	References
Ciclosporin			
Atopic dermatitis	3–5 mg/kg/day	A	[6]
Chronic plaque psoriasis	3–5 mg/kg/day	A	[1]
Palmoplantar pustulosis	1–3 mg/kg/day	A	[4]
Pyoderma gangrenosum	5 mg/kg/day	C	[1,9]
Chronic urticaria	3–5 mg/kg/day	A	[7,8]
Tacrolimus			
Psoriasis		A	[11]
Pimecrolimus			
Psoriasis	40–60 mg/day	B	[15]
Atopic dermatitis	40–60 mg/day	B	[14]

17 Hunter GA, Forbes IJ. Treatment of pityriasis rubra pilaris with azathioprine. *Br J Dermatol* 1972; **87**: 42–5.

18 Knowles SR, Gupta AK, Shear NH, Sauder D. Azathioprine hypersensitivity-like reactions—a case report and a review of the literature. *Clin Exp Dermatol* 1995; **20**: 353–6.

19 Jones JJ, Ashworth J. Azathioprine-induced shock in dermatology patients. *J Am Acad Dermatol* 1993; **29**: 795–6.

Calcineurin inhibitors (Table 74.6)

Ciclosporin. First isolated from a soil fungus *Tolypocladium inflatum* Gams, it is a potent inhibitor of T-cell function, and has remained of central importance in the management of severe inflammatory skin disease—especially psoriasis—since the early 1990s. Ciclosporin is a pro-drug that becomes active only after forming a complex with an intracytoplasmic immunophilin (protein) known as cycliphilin. This ciclosporin–cycliphilin complex inhibits calcineurin phosphatase—an enzyme catalysing dephosphorylation of the cytoplasmic protein nuclear factor of activated T cells (NF-ATc). Ordinarily, dephosphorylation of NF-ATc allows it to translocate to the nucleus where it enables transcription of a number of pro-inflammatory cytokines including IL-2, IL-4, interferon-γ (IFN-γ), transforming growth factor-β and up-regulation of receptors such as IL-2R (CD25). Ciclosporin thus acts by inhibiting calcineurin phosphatase to suppress production of IL-2 and IL-2 receptor expression, key regulators of T-cell activation. Additional actions of therapeutic relevance include reduced histamine release and down-regulation of high-affinity IgE receptors on mast cells and basophils [1,2].

It is given orally, dose range 3–5 mg/kg, usually as a divided dose, and is widely distributed in tissues. Metabolism takes place in the liver and since this is heavily dependent on the cytochrome P450 enzyme complex, a number of important drug interactions can potentially arise. Generally, patients experience few symptomatic side effects but important complications of therapy include hypertension, nephrotoxicity and an increased risk of malignancy (primarily skin cancer). In the short-term, acute, dose-related nephrotoxicity (and related hypertension) is due to increased arterial resistance resulting in vasoconstriction of the afferent, and also to a lesser extent, efferent, renal arterioles. This responds to dose reduction and is reversible. Chronic nephrotoxicity on the other hand, is largely irreversible, and is characterized histologically by interstitial fibrosis, tubular atrophy and glomerulosclerosis. It occurs to some degree in all patients on continuous therapy for more than 2 years; it is more likely to occur in patients over 50 years of age, particularly in the presence of hypertension and/or pre-existing renal insufficiency. Careful monitoring of renal function, active management of hypertension, dose adjustment or discontinuation when necessary, and avoidance of continuous therapy beyond a year, should avoid significant irreversible renal impairment in most patients. The increased risk of cutaneous squamous cell carcinoma seems particularly to be related to use of ciclosporin following excess photochemotherapy (i.e. >1000 J/cm^2) and this combination should therefore be avoided. Additional side effects include hyperlipidaemia (affecting both triglycerides and cholesterol), neurological symptoms such as paraesthesiae and tremor, hypertrichosis and gingival hypertrophy.

Clinical indications

Psoriasis

Ciclosporin has been licensed for use in chronic plaque disease since 1992, and is widely used to treat moderate to severe disease requiring systemic therapy [2,3]. It also has some limited benefit in psoriatic arthropathy. Most patients with plaque psoriasis respond to therapy within 4–8 weeks with more than 50% achieving PASI 75 by week 8. For long-term disease control, intermittent short courses of 6 to 12 months are used in preference to long-term, continuous therapy in order to minimize risks of nephrotoxicity. Whilst no drug is completely 'safe' for use in pregnancy, ciclosporin is considered a permissible option, as it is neither teratogenic nor mutagenic, and has been used extensively in transplant medicine. Ciclosporin may improve but rarely clears palmoplantar pustulosis [4].

Atopic dermatitis

Ciclosporin is licensed for use in atopic dermatitis unresponsive to topical corticosteroids and produces a reduction in overall disease severity of approximately 50%, and marked relief of itch [5]; onset of action occurs within 2 weeks, with higher dosing (4–5 mg/kg) achieving remission more predictably. Whilst efficacy is sustained on maintenance therapy, disease relapse occurs rapidly on discontinuation of treatment; 50% of patients by 2 weeks and 80% by 2 months [6].

Chronic urticaria

Two RCTs [7,8] and a number of uncontrolled trials indicate that around two-thirds of patients with chronic autoimmune urticaria respond to ciclosporin. In those with associated autoantibodies, treatment success correlates roughly with *in vitro* basophil histamine release, but the absence of functional autoantibodies does not necessarily preclude successful treatment outcomes either. Case series suggest that ciclosporin may induce long-lasting remission in a subset of patients, but further studies are required to properly establish whether indeed this is the case, particularly given the relapsing and remitting nature of urticaria.

Pyoderma gangrenosum

A number of uncontrolled, open-label studies and case reports involving more than 50 patients [9] describe marked and rapid efficacy of ciclosporin both alone and in combination with corticosteroids.

Other indications

Anecdotal reports suggest ciclosporin may also have a role in the treatment of Behçet disease, lichen planus, prurigo nodularis, chronic actinic dermatitis and toxic epidermal necrolysis [1,10].

Tacrolimus. The macrolide antibiotic tacrolimus (FK506) was discovered as a naturally occurring metabolite of the fungus *Streptomyces tsukubaensis*. Although structurally different from ciclosporin, both molecules share a similar mechanism of action; tacrolimus also binds to cytoplasmic immunophilins (known as tacrolimus-binding proteins) to form complexes that inhibit calcineurin phosphatase, so preventing NF-AT mediated transcription of cytokines critical for T-cell activation. In contrast to ciclosporin however, tacrolimus is pharmacologically active topically (due to its smaller size) and its place in dermatology is thus primarily as a topical agent, especially in atopic dermatitis. Use of the oral formulation is limited, despite proven efficacy in psoriasis for example [11], largely due to its side-effect profile being comparable to ciclosporin, with no evidence that the risk of nephrotoxicity (in particular) or infection is any less. In organ transplantation medicine, the main advantage of tacrolimus over ciclosporin is increased potency (with improved graft survival), and a lower incidence of hypertension, but at the expense of more post-transplant diabetes, and gastrointestinal and neurological side effects [12,13].

Pimecrolimus. This is a semi-synthetic derivative of ascomycin (a macrolactam isolated from *Streptomyces hygroscopicus var. ascomyceticus*) and is, like ciclosporin and tacrolimus, a calcineurin inhibitor. It binds to the cytosolic immunophilin macrophilin-12, which then prevents dephosphorylation of the cytosolic form of the nuclear factor of activated T cells, and thus production and release of inflammatory cytokines and activation of T cells. It also inhibits production and release of pro-inflammatory mediators and cytokines from mast cells. It is a widely used agent topically for atopic dermatitis, but is also active orally. Two, 12-week-long, phase II studies have demonstrated marked, dose related efficacy in both atopic dermatitis [14] and chronic plaque psoriasis [15], with no significant adverse events, although the drug development programme for these indications was on hold at the time of writing.

References

1 Madan V, Griffiths CEM. Systemic ciclosporin and tacrolimus in dermatology. *Dermatologic Therapy* 2007; **20**: 239–50.

2 Berth-Jones J. The use of ciclosporin in psoriasis. *J Dermatol Treatment* 2005; **16**: 258–77.

3 Griffiths CEM, Clark CM, Chalmers RJG *et al*. A systematic review of treatments for severe psoriasis. *Health Technol Assess* 2000; **4**: 13–23.

4 Marsland AM, Chalmers RJG, Hollis S *et al*. Interventions for chronic palmoplantar pustulosis. *Cochrane Database Syst Rev* 2006, Issue 1. Art. No.: CD001433. DOI: 10.1002/14651858.CD001433.pub2.

5 Schmitt J, Schmitt N, Meurer M. Cyclosporin in the treatment of patients with atopic eczema—a systematic review and meta-analysis. *J Eur Acad Dermatol Venereol* 2007; **21**: 606–19.

6 Schmitt J, Schakel K, Schmitt N, Meurer M. Systemic treatment of severe atopic eczema: a systematic review. *Acta Dermatovenereol* 2007; **87**: 100–11.

7 Grattan CEH, O'Donnell BF, Francis DM *et al*. Randomized double-blind study of cyclosporin in chronic 'idiopathic' urticaria. *Br J Dermatol* 2000; **143**: 365–72.

8 Vena GA, Cassano N, Colombo D *et al.*, Neo-1-30 Study Group. Cyclosporine in chronic idiopathic urticaria: a double-blind, randomized, placebo-controlled trial. *J Amer Acad Dermatol* 2006; **55**: 705–9.

9 Reichrath J, Bens G, Bonowitz A, Tilgen W. Treatment recommendations for pyoderma gangrenosum: an evidence-based review of the literature based on more than 350 patients. *J Amer Acad Dermatol* 2005; **53**: 273–83.

10 Arevalo JM, Lorente JA, Gonzalez-Herrada C, Jimenez-Reyes J. Treatment of toxic epidermal necrolysis with cyclosporin A. *J Trauma* 2000; **48**: 473–8.

11 The European FK 506 Multicentre Psoriasis Study Group. Systemic tacrolimus (FK 506) is effective for the treatment of psoriasis in a double-blind, placebo-controlled study. *Arch Dermatol* 1996; **13**: 19–23.

12 Webster AC, Woodroffe RC, Taylor RS *et al*. Tacrolimus versus ciclosporin as primary immunosuppression for kidney transplant recipients: meta-analysis and meta-regression of randomised trial data. *BMJ* 2005; **331**: 810–4.

13 Xiao L, Fu H, Ni Z-J *et al*. A meta-analysis of therapeutic effect of cyclosporine microemulsion and tacrolimus for patients undergoing liver transplantation. *Acad J Second Military Med University* 2008; **29**: 663–70.

14 Wolff K, Fleming C, Hanifin J *et al*. Efficacy and tolerability of three different doses of oral pimecrolimus in the treatment of moderate to severe atopic dermatitis: a randomized controlled trial. *Br J Dermatol* 2005; **152**: 1296–303.

15 Gottlieb AB, Griffiths CEM, Ho VC *et al*. Oral pimecrolimus in the treatment of moderate to severe chronic plaque-type psoriasis: A double-blind, multicentre, randomized, dose-finding trial. *Br J Dermatol* 2005; **152**: 1219–27.

Cyclophosphamide

Cyclophosphamide is a DNA alkylating agent whose potential therapeutic value beyond cancer was first demonstrated in the 1970s, when daily administration of cyclophosphamide (1–2 mg/kg) in combination with prednisolone (1 mg/kg) was found to be highly effective at induction of remission in, what was then, usually fatal Wegener's granulomatosis. It has subsequently been shown to be effective in the management of a variety of severe autoimmune disorders (Table 74.7), especially when complicated by extensive disease or major organ involvement including ANCA-associated vasculitides [1], pemphigus (vulgaris and foliaceus) [2] and SLE [3,4], usually in combination with corticosteroids and other immunosuppressant agents. Cyclophosphamide is a pro-drug which is actively transported into cells following metabolism in the liver by multiple cytochrome P450 enzymes to hydroxycyclophosphamide; once inside cells, released nitrogen mustards covalently cross-link DNA to inhibit DNA replication and ultimately, induce cell apoptosis. Additional effects on humoral and cellular aspects of immunity have been demonstrated in both inflammatory and mitotic conditions [5]. Therapy is associated with a spectrum of highly significant adverse effects including bone marrow suppression, infections (particularly

Table 74.7 Cyclophosphamide.

Drug name and indications	Usual dose range	Evidence level	References
Cyclophosphamide			
ANCA +ve vasculitides	Variable	A	[1]
SLE	Variable	A	
Pemphigus (vulgaris/foliaceus)	Variable	B	[2,7]

Pneumocystis jiroveci [formerly *P. carinii*]) [6], infertility, haemorrhagic cystitis (due to direct urothelial toxicity of acrolein, a cyclophosphamide metabolite), and in the long term, an increased incidence of myelodysplasia and bladder cancer. Modern dosing regimens are geared around minimizing cumulative drug exposure, and therefore adverse effects. For example, in ANCA-associated vasculitides, pulsed intravenous cyclophosphamide (usually 0.6 to 0.7 g/m^2 or 15 mg/kg, maximal dose 1 g/m^2) every 3 weeks for 6 months) with prednisolone (1 mg/kg) is as effective as continuous oral therapy at induction of remission, and is associated with a significant reduction in neutropenic sepsis; maintenance cyclophosphamide therapy is avoided whenever possible, with azathioprine or methotrexate being preferred, safer, options [1]. Additional measures that reduce toxicity are use of mesna (which protects the urothelium), and careful dose adjustment in the elderly and/or those with concomitant renal impairment.

References

1 Bosch X, Guilabert A, Espinosa G, Mirapeix E. Treatment of antineutrophil cytoplasmic antibody associated vasculitis: a systematic review. *JAMA* 2007; **298**: 655–69.

2 Martin LK, Agero AL, Werth V *et al*. Interventions for pemphigus vulgaris and pemphigus foliaceus. *Cochrane Database Syst Rev* 2009, Issue 1. Art. No.: CD006263. DOI: 10.1002/14651858.CD006263.pub2.

3 Flanc RS, Roberts MA, Strippoli GFM *et al*. Treatment for lupus nephritis. *Cochrane Database Syst Rev* 2004; Issue 1. Art. No.: CD002922. DOI: 10.1002/14651858.CD002922.pub2

4 Trevisani VFM, Castro AA, Neves Neto JF, Atallah AN. Cyclophosphamide versus methylprednisolone for treating neuropsychiatric involvement in systemic lupus erythematosus. *Cochrane Database Syst Rev* 2006, Issue 2. Art. No.: CD002265. DOI: 10.1002/14651858.CD002265.pub2.

5 Zhang J, Tian Q, Zhu Q, Zhou SF. Clinical pharmacology of cyclophosphamide and ifosfamide. *Curr Drug Therapy* 2006; **1**: 55–84.

6 Gupta DM, Zachariah AM, Roppelt HM *et al*. Prophylactic antibiotic usage for Pneumocystis jirovecii pneumonia in patients with systemic lupus erythematosus on cyclophosphamide: a survey of US rheumatologists and the review of literature. *J Clin Rheumatol* 2008; **14**: 267–72.

7 Chams-Davatchi C, Esmaili N, Daneshpazhooh M *et al*. Randomized controlled open-label trial of four treatment regimens for pemphigus vulgaris. *J Am Acad Dermatol* 2007; **57**: 622–8.

Hydroxycarbamide

Hydroxycarbamide (formerly hydroxyurea) is an antimetabolite that selectively inhibits DNA synthesis in proliferating cells. It has been used to treat psoriasis since the late 1960s (Table 74.8), and several small studies and retrospective case series describing use in a total of about 300 patients, report satisfactory response rates in 45 to 80% of patients [1]. No RCT data exist however, and most of the studies lack clear descriptions as to the degree of improvement. It has no effect on psoriatic arthritis. Hydroxyurea is easy to administer, relatively inexpensive and has few contraindications or side effects. Dose-related bone marrow toxicity is the principal concern: macrocytosis is universal, and some degree of leukopenia common; thrombocytopenia and anaemia may also occur. Overall, temporary cessation of therapy and/or dose reduction is required in up to a third of patients on long-term therapy due to haematological abnormalities, and careful, frequent monitoring throughout the duration of therapy is essential [2]. A number of cutaneous adverse effects may occur including hyperpigmentation of the skin and nails, dermatomyositis-like rash, and particularly with long-term therapy, persistent leg ulceration. Concern over an increased risk of malignancy is not substantiated but cannot be excluded. In contrast with many other second-line agents however, co-existing renal and liver disease do not necessarily preclude treatment and there are few drug interactions likely to be of clinical relevance in dermatology. It therefore has a useful place in the management of patients with significant comorbidities where perhaps standard systemic therapy cannot be used.

Table 74.8 Hydroxycarbamide.

Drug name and indications	Usual dose range	Evidence level	References
Hydroxycarbamide			
Psoriasis	0.5–1.5 g/day	C	[1]

References

1 Griffiths CEM, Clark CM, Chalmers RJG *et al*. A systematic review of treatments for severe psoriasis. *Health Technol Assess* 2000; **4**: 75–7.

2 Smith CH. Use of hydroxyurea in psoriasis. *Clin Exp Dermatol* 1999; **24**: 2–6.

Methotrexate

Methotrexate has been used for the treatment of severe psoriasis and psoriatic arthritis since the 1950s [1–6] and remains an important agent for psoriasis despite the advent of biological agents for psoriasis [7]. It is a structural analogue of folic acid and is a potent competitive inhibitor of dihydrofolate reductase, which converts dietary folic acid via dihydrofolate to tetrahydrofolate. These steps are essential in the generation of 1-carbon fragments needed for the synthesis of nucleic acids. Methotrexate is converted to methotrexate polyglutamates, which have prolonged intracellular storage. They block not only dihydrofolate reductase but also other essential enzymes involved in nucleotide synthesis including thymidylate synthase and AICAR (5-aminoimidazole-4-carboxamide ribonucleotide) transformylase [7,8]. The latter is involved in purine biosynthesis and indirectly inhibits the metabolism of intracellular adenosine, which is known to be toxic to T lymphocytes and is potently anti-inflammatory. Indirect evidence of adenosine accumulation has been shown in psoriasis patients, whose adenosine excretion was found to be double that of controls following each methotrexate dose; greater increases were seen in those showing clinical improvement than in those without [9]. Although originally hypothesized that the effects of methotrexate in psoriasis were brought about by a direct interference in epidermal cell division [10,11], it is now recognized that it significantly inhibits proliferating lymphoid cells but has little effect on epidermal cells at therapeutic doses [12]. Inhibition of epidermal proliferation, on the other hand, is probably relevant in the context of acute methotrexate toxicity.

References

1 Zachariae H. Methotrexate. In: van de Kerkhof PCM, ed. *Textbook of Psoriasis*. Oxford: Blackwell Science, 1999: 196–232.

2 Gubner R, August S, Ginsberg V. Therapeutic suppression of tissue reactivity: effect of aminopterin in rheumatoid arthritis and psoriasis. *Am J Med Sci* 1951; **221**: 176–82.
3 Gubner R. Effect of 'aminopterin' on epithelial tissues. *Arch Dermatol* 1983; **119**: 513–24.
4 Weinstein GD. Commentary: three decades of folic acid antagonists in dermatology. *Arch Dermatol* 1983; **119**: 525–7.
5 Jones G, Crotty M, Brooks P. Interventions for treating psoriatic arthritis. *Cochrane Database Syst Rev* 2000; Issue 3. Art. No.: CD000212. DOI: 10.1002/14651858.CD000212.
6 Kalb RE, Strober B, Weinstein G, Lebwohl M. Methotrexate and psoriasis: 2009 National Psoriasis Foundation Consensus Conference. *J Am Acad Dermatol* 2009: **60**: 824–37.
7 Warren RB, Chalmers RJG, Griffiths CEM, Menter A. Methotrexate for psoriasis in the era of biological therapy. *Clin Exp Dermatol* 2008; **33**: 551–4.
8 Cronstein BN. The mechanism of action of methotrexate. *Rheum Dis Clin North Am* 1997; **23**: 739–55.
9 Baggott JE, Morgan SL, Sams WM, Linden J. Urinary adenosine and aminoimidazolecarboxamide excretion in methotrexate-treated patients with psoriasis. *Arch Dermatol* 1999; **135**: 813–7.
10 Bleyer WA. The clinical pharmacology of methotrexate: new applications of an old drug. *Cancer* 1978; **41**: 36–51.
11 Olsen EA. The pharmacology of methotrexate. *J Am Acad Dermatol* 1991; **25**: 306–18.
12 Jeffes EW III, McCullough JL, Pittelkow MR *et al.* Methotrexate therapy of psoriasis: differential sensitivity of proliferating lymphoid and epithelial cells to the cytotoxic and growth-inhibitory effects of methotrexate. *J Invest Dermatol* 1995; **104**: 183–8.

Therapeutic indications and efficacy (Table 74.9)

Psoriasis and psoriatic arthritis

Methotrexate is of particular value in the management of acute generalized pustular psoriasis and psoriatic erythroderma [1–3], but has been most widely employed for inducing and then maintaining control of psoriasis in patients with extensive chronic plaque disease, especially in those who also have psoriatic arthritis [4]. Published studies suggest that methotrexate can produce a reduction in disease severity of at least 50% in more than three-quarters of patients treated [5–10]. It has been shown to have at least comparable efficacy to ciclosporin in two small short-term, randomized trials [11,12]. For more details of the place of methotrexate for psoriasis see Chapter 20.

Table 74.9 Methotrexate.

Drug name and indications	Usual dose range	Evidence level	References
Psoriasis	5–25 mg once weekly	A	[1–12]
Atopic dermatitis	As above	C	[13,14]
Bullous pemphigoid	As above	C	[15–17]
Dermatomyositis	As above	B	[18–20]
Cutaneous lupus erythematosus	As above	C	[21–26]
Childhood morphoea	0.3–0.5 mg/kg/wk	C	[29–31]
Cutaneous sarcoidosis	5–25 mg weekly	D	[32,33]
Polyarteritis nodosa		E	[34,35]
Behçet disease	As above	E	[35]
Cutaneous small vessel vasculitis	As above	E	[36]
Antiphospholipid syndrome	As above	E	[37]
Pyoderma gangrenosum	As above	E	[38]
Pityriasis lichenoides	As above	D	[39–41]
Pemphigus	As above	E	[42]
Multicentric reticulohistiocytosis	As above	E	[43]
Scleromyxoedema	As above	E	[44]
Langerhans' cell histiocytosis	Variable	C	[45,46]
Oral lichen planus	2.5–12.5 mg weekly	C	[47]

Atopic dermatitis

Two small studies of weekly oral methotrexate for severe atopic dermatitis in adults, one prospective, open-label, 24-week study in 12 patients [13] and one retrospective review of 20 patients followed for up to 30 months [14], support claims of benefit reported in earlier case reports. Between half and three-quarters of treated patients gained worthwhile benefit. Improvement, if it occurred, was generally apparent by 12 weeks. Controlled studies are required to define more precisely the role of methotrexate in the management of this disabling disease.

Bullous pemphigoid

In a retrospective review from Sweden, 103 of 138 patients presenting to one institution with bullous pemphigoid (BP) had been treated with methotrexate [15]. Methotrexate had to be withdrawn in five patients because of mild or moderate adverse events. Of the remaining 98, 61 required methotrexate alone and 19 could be successfully weaned off oral corticosteroid therapy commenced before the diagnosis of BP had been confirmed and then controlled with methotrexate alone; only 18 required periodic additional oral corticosteroids to control flares of disease activity. The median weekly dose of methotrexate administered was 5 mg and only three were given doses above 10 mg weekly. The authors commented, however, that they would now tend to increase the methotrexate dose rather than resort to supplemental oral corticosteroid therapy. Their finding that remission in patients treated with methotrexate alone occurred after a median interval of 11 months is in accord with the findings of two smaller case series from France involving a total of 34 patients [16,17]. They concluded that methotrexate is an effective and safe treatment option for patients with BP.

Dermatomyositis

Methotrexate is increasingly advocated for cutaneous lesions. Eight of 13 patients given weekly low-dose oral methotrexate (2.5–30 mg) for skin disease inadequately controlled either by topical and systemic corticosteroids or by antimalarials, were considered to have had a good or excellent response and in all 13 it was possible to reduce or discontinue corticosteroid therapy [18]. Early introduction of methotrexate in children with juvenile dermatomyositis has been claimed to hasten recovery and allow a more rapid reduction in corticosteroid dosage [19,20].

Cutaneous lupus erythematosus (LE)

Small studies suggest benefit from methotrexate for cutaneous lesions of LE [21–24]. In a larger prospective, randomized, controlled trial of patients with mild systemic LE only three of 18 patients receiving low-dose methotrexate (15–20 mg/week) had residual cutaneous disease after 6 months of therapy compared to

16 of 19 patients given placebo [25]. Although there is less evidence in chronic discoid LE [26], there is thus reasonable evidence to suggest that methotrexate may enable corticosteroid dosage to be reduced in patients with systemic lupus and that it is worth considering for patients with cutaneous LE unresponsive to more standard therapies.

Systemic sclerosis and morphoea

In one randomized, double-blind study of 29 patients with active systemic sclerosis allocated to weekly injections of either methotrexate 15 mg or placebo for 24 weeks, a predefined favourable response was seen in a significantly greater proportion of patients in the methotrexate group (8 of 17; 47%) than in the placebo group (1 of 12; 8%) [27]. However, a larger double-blind, controlled trial of 71 patients with early diffuse systemic sclerosis randomized to the same interventions failed to demonstrate significant benefit after 12 months' treatment [28], although even this study was insufficiently powered. However, both studies showed improvement in skin scores.

A treatment regimen which has been widely used for localized morphoea in children consists of an initial combination of methotrexate and high-dose systemic corticosteroids followed by methotrexate monotherapy for maintenance. Two retrospective case series reporting on a total of 73 children have supported the use of this regimen. In the first, progression of disease was arrested in 32 of 34 children and morphoea was considered to be completely inactive in 14 of 19 (74%) children reviewed at 2 years [29]. The authors noted, however, that relapse occurred quite frequently and methotrexate had to be reintroduced in seven of 16 whose methotrexate had been discontinued. Similar observations were reported in the second study of a total of 39 children where all three children who received less than 6 months' treatment relapsed and required further methotrexate [30]. Three children with progressive hemifacial atrophy failed to respond but otherwise 35 of 36 children improved. The mean overall duration of treatment required was 19.9 months. A small uncontrolled study of methotrexate 15 mg/week for 24 weeks claimed some benefit in nine patients with widespread morphoea but these claims must be treated with caution in a disease where spontaneous improvement is not uncommon [31].

Cutaneous sarcoidosis

Small open studies have demonstrated improvement in skin lesions of various morphologies [32,33]. However, methotrexate was less effective in pulmonary sarcoidosis where improvement in lung function was seen in only one-third of patients [33], and it is important to be aware that improvement in skin lesions is often slow. The side-effect profile appears to be similar to that seen in psoriasis patients, although the significance of liver biopsy abnormalities may be more difficult to assess because many patients with sarcoidosis will show granulomatous infiltration in the liver [33].

Other dermatoses

Benefit from weekly low-dose methotrexate has been claimed in individual case reports or small series for polyarteritis nodosa [34,35], Behçet's disease [35], cutaneous small vessel vasculitis [36], antiphospholipid syndrome [37], pyoderma gangrenosum [38], pityriasis lichenoides [39–41], pemphigus [42], multicentric reticulohistiocytosis [43], scleromyxoedema [44], Langerhans' cell histiocytosis [45,46] and refractory oral lichen planus [47].

References

1 Ryan TJ, Baker H. Systemic corticosteroids and folic acid antagonists in the treatment of generalized pustular psoriasis: evaluation and prognosis based on the study of 104 cases. *Br J Dermatol* 1969; **81**: 134–45.

2 Ozawa A, Ohkido M, Haruki Y *et al*. Treatments of generalized pustular psoriasis: a multicenter study in Japan. *J Dermatol* 1999; **26**: 141–9.

3 Collins P, Rogers S. The efficacy of methotrexate in psoriasis: a review of 40 cases. *Clin Exp Dermatol* 1992; **17**: 257–60.

4 Jones G, Crotty M, Brooks P. Interventions for treating psoriatic arthritis. *Cochrane Database Syst Rev* 2000; Issue 3. Art. No.: CD000212. DOI: 10.1002/14651858.CD000212.

5 Griffiths CEM, Clark CM, Chalmers RJ *et al*. A systematic review of treatments for severe psoriasis. *Health Technol Assess* 2000; **4**: 1–125.

6 Weinstein GD, Frost P. Methotrexate for psoriasis: a new therapeutic schedule. *Arch Dermatol* 1971; **103**: 33–8.

7 Van Scott E, Auerbach R, Weinstein GD. Parenteral methotrexate in psoriasis. *Arch Dermatol* 1964; **89**: 550–6.

8 Nyfors A, Brodthagen H. Methotrexate for psoriasis in weekly oral doses without any adjunctive therapy. *Dermatologica* 1970; **140**: 345–55.

9 Jeffes E, Weinstein GD. Methotrexate and other chemotherapeutic agents used to treat psoriasis. *Dermatol Clin* 1995; **13**: 875–90.

10 Nyfors A. Benefits and adverse drug experiences during long-term methotrexate treatment of 248 psoriatics. *Dan Med Bull* 1978; **25**: 208–11.

11 Heydendael VMR, Spuls PI, Opmeer BC *et al*. Methotrexate versus cyclosporine in moderate-to-severe chronic plaque psoriasis. *N Engl J Med* 2003; **349**: 658–65.

12 Sandhu K, Kaur I, Kumar B, Saraswat A. Efficacy and safety of cyclosporine versus methotrexate in severe psoriasis: a study from north India. *J Dermatol (Japan)* 2003; **30**: 458–63.

13 Weatherhead SC, Wahie S, Reynolds NJ, Meggitt SJ. An open-label, dose-ranging study of methotrexate for moderate-to-severe adult atopic eczema. *Br J Dermatol* 2007; **156**: 346–51.

14 Goujon C, Berard F, Dahel K *et al*. Methotrexate for the treatment of adult atopic dermatitis. *Eur J Dermatol* 2006; **16**: 155–8.

15 Kjellman P, Eriksson H, Berg P. A retrospective analysis of patients with bullous pemphigoid treated with methotrexate. *Arch Dermatol* 2008; **144**: 612–6.

16 Dereure O, Bessis D, Guillot B, Guilhou JJ. Treatment of bullous pemphigoid by low-dose methotrexate associated with short-term potent topical steroids: an open prospective study of 18 cases. *Arch Dermatol* 2002; **138**: 1255–6.

17 Bara C, Maillard H. Methotrexate for bullous pemphigoid: preliminary study. *Arch Dermatol* 2003; **139**: 1506–7.

18 Kasteler JS, Callen JP. Low-dose methotrexate administered weekly is an effective corticosteroid-sparing agent for the treatment of the cutaneous manifestations of dermatomyositis. *J Am Acad Dermatol* 1997; **36**: 67–71.

19 Fischer TJ, Rachelefsky GS, Klein RB *et al*. Childhood dermatomyositis and polymyositis: treatment with methotrexate and prednisone. *Am J Dis Child* 1979; **133**: 386–9.

20 Reed AM, Lopez M. Juvenile dermatomyositis: recognition and treatment. *Paediatr Drugs* 2002; **4**: 315–21.

21 Miescher PA, Reithmuller D. Diagnosis and treatment of systemic lupus erythematosus. *Semin Hematol* 1965; **2**: 1–28.

22 Rothenberg RJ, Graziano FM, Grandone JT *et al*. The use of methotrexate in steroid-resistant lupus erythematosus. *Arthritis Rheum* 1988; **31**: 612–5.

23 Bottomley WW, Goodfield M. Methotrexate for the treatment of severe mucocutaneous lupus erythematosus. *Br J Dermatol* 1995; **133**: 311–4.

24 Boehm IB, Boehm GA, Bauer R. Management of cutaneous lupus erythematosus with low-dose methotrexate: indication for modulation of inflammatory mechanisms. *Rheumatol Int* 1998; **18**: 59–62.

25 Carneiro J, Sato E. Double blind, randomized, placebo controlled clinical trial of methotrexate in systemic lupus erythematosus. *J Rheumatol* 1999; **26**: 1275–9.

26 Bottomley WW, Goodfield M. Methotrexate for the treatment of discoid lupus erythematosus. *Br J Dermatol* 1995; **133**: 655–6.

27 van den Hoogen FH, Boerbooms AM, Swaak AJ *et al.* Comparison of methotrexate with placebo in the treatment of systemic sclerosis: a 24-week randomized double-blind trial, followed by a 24-week observational trial. *Br J Rheumatol* 1996; **35**: 364–72.
28 Pope JE, Bellamy N, Seibold JR *et al.* A randomized, controlled trial of methotrexate versus placebo in early diffuse scleroderma. *Arthritis Rheum* 2001; **44**: 1351–8.
29 Weibel L, Sampaio MC, Visentin MT *et al*. Evaluation of methotrexate and corticosteroids for the treatment of localized scleroderma (morphea) in children. *Br J Dermatol* 2006; **155**: 1013–20.
30 Christen-Zaech S, Hakim MD, Afsar S, Paller AS. Pediatric morphea (localized scleroderma): review of 136 patients. *J Am Acad Dermatol* 2008; **59**: 385–96.
31 Seyger MM, van den Hoogen FH, de Boo T, de Jong EM. Low-dose methotrexate in the treatment of widespread morphoea. *J Am Acad Dermatol* 1998; **39**: 220–5.
32 Veien NK, Brodthagen H. Cutaneous sarcoidosis treated with methotrexate. *Br J Dermatol* 1977; **97**: 213–6.
33 Lower EE, Baughman RP. Prolonged use of methotrexate for sarcoidosis. *Arch Intern Med* 1995; **155**: 846–51.
34 Brody M, Bohm I, Biwer E, Bauer R. Erfolgreiche Behandlung einer Panerteritis nodosa mit Methotrexat Low-dose-therapie. *Hautarzt* 1994; **45**: 476–9.
35 Jorizzo JL, White WL, Wise CM *et al*. Low-dose weekly methotrexate for unusual neutrophilic vascular reactions: cutaneous polyarteritis nodosa and Behçet's disease. *J Am Acad Dermatol* 1991; **24**: 973–8.
36 Lotti T, Ghersetich I, Comacchi C, Jorizzo JL. Cutaneous small-vessel vasculitis. *J Am Acad Dermatol* 1998; **39**: 667–87.
37 Bauer R, Brody M, Boehm I. Methotrexat-low-dose-Therapie zur Behandlung inflammatorischer and autoaggressiver Dermatosen. In: Tebbe B, Goerdt S, Orfanos CE, eds. *Dermatologie—Heutiger Stand: Ergebnisse und Berichte der 38.* Tagung der Deutschen Dermatologischen Gesellschaft in Berlin vom 29, April bis 3, Mai 1995. Stuttgart: Thieme, 1995: 318–20.
38 Teitel AD. Treatment of pyoderma gangrenosum with methotrexate. *Cutis* 1996; **57**: 326–8.
39 Lynch PJ, Saied NK. Methotrexate treatment of pityriasis lichenoides and lymphomatoid papulosis. *Cutis* 1979; **23**: 634–6.
40 Fink-Puches R, Soyer HP, Kerl H. Febrile ulceronecrotic pityriasis lichenoides et varioliformis acuta. *J Am Acad Dermatol* 1994; **30**: 261–3.
41 Tsianakas A, Hoeger PA. Transition of pityriasis lichenoides et varioliformis acuta to febrile ulceronecrotic Mucha–Habermann disease is associated with elevated serum tumour necrosis factor-α. *Br J Dermatol* 2005; **152**: 794–9.
42 Schaumburg-Lever G. Die Therapie des Pemphigus und Pemphigoid. *Z Hautkr* 1986; **61**: 811–2.
43 Franck N, Amor B, Ayral X *et al.* Multicentric reticulohistiocytosis and methotrexate. *J Am Acad Dermatol* 1995; **33**: 524–5.
44 McAdam LP, Pearson CM, Pitts WH *et al*. Papular mucinosis with myopathy, arthritis, and eosinophilia: a histopathologic study. *Arthritis Rheum* 1977; **20**: 989–96.
45 Steen AE, Steen KH, Bauer R, Bieber T. Successful treatment of cutaneous Langerhans' cell histiocytosis with low-dose methotrexate. *Br J Dermatol* 2001; **145**: 137–40.
46 Womer RB, Anunciato KR, Chehrenama M. Oral methotrexate and alternate-day prednisone for low-risk Langerhans cell histiocytosis. *Med Pediatr Oncol* 1995; **25**: 70–3.
47 Torti DC, Jorizzo JL, McCarty MA. Oral lichen planus: a case series with emphasis on therapy. *Arch Dermatol* 2007; **143**: 511–5.

Safety precautions and side effects

Haematological or renal abnormality. Myelosuppression is the most important cause of methotrexate-associated death. Methotrexate should be avoided in patients with significant haematological abnormalities or renal impairment. Because methotrexate is eliminated largely via the kidneys, toxic levels may build up rapidly in patients with renal impairment, and even low doses of the drug may then produce acute myelosuppression [1]. This is particularly liable to occur in the elderly when concomitant drug administration or illness such as fever or diarrhoea may result in sudden deterioration of renal function; elderly patients especially should be warned to omit methotrexate doses whenever they are at risk of acute dehydration. Patients on renal dialysis are at particular risk of catastrophic bone marrow failure [2].

Drug interactions. Certain drugs may increase toxicity of methotrexate by increased antifolate effect (e.g. sulphonamides, trimethoprim, phenytoin) or by decreasing renal elimination (e.g. aspirin and NSAIDs, probenecid, ciclosporin) [3]. As life-threatening myelosuppression may result from interactions between methotrexate and such drugs, patients and all their medical attendants should be made aware of these risks.

Liver disease, alcohol and diabetes. Methotrexate should not be administered to patients with significant current or previous liver disease, especially if caused by viral hepatitis or alcohol. Any patient suspected of alcohol abuse is unsuitable for methotrexate, although many dermatologists allow patients receiving methotrexate to continue taking small amounts of alcohol (e.g. 4–6 units of alcohol weekly). There is an increased incidence of obesity and type 2 diabetes amongst patients with severe psoriasis. These conditions predispose to non-alcoholic steatohepatitis (NASH) and increase the risk of liver fibrosis from methotrexate [4].

Fertility. Because methotrexate is both arbortifacient and teratogenic [5–8], it is strictly contraindicated in pregnancy. Adequate contraceptive measures must be taken by women of child-bearing potential during methotrexate therapy and for at least three menstrual cycles after stopping the drug [9]. It should also be avoided during lactation. Although low-dose methotrexate has not been found to be mutagenic in sperm [10] and normal children have been born where the father was taking methotrexate at the time of conception [11], the drug may depress spermatogenesis [12]. It is customary to advise men to avoid fathering children during therapy and for at least 3 months thereafter.

Miscellaneous precautions. Other important contraindications to the use of low-dose methotrexate include active peptic ulceration, hepatitis virus infection, active infectious disease such as tuberculosis, immunodeficiency states and unreliability of the patient.

Management of the patient

The risks and benefits of therapy should be clearly explained to the patient both verbally and in writing. Adequate contraceptive measures must be commenced where appropriate and baseline blood tests obtained.

Methotrexate is usually given orally and is given as a single weekly dose, as it is well-established that the toxicity for a given total dose is considerably increased when it is administered daily [13]. Unambiguous instructions, including which day of the week the tablets are to be taken, should be given to the patient and specified on the prescription. Deaths have occurred where prescribers, dispensers or patients have confused 10-mg for 2.5-mg tablets. It is thus good practice always to specify 2.5-mg tablets for inflammatory diseases. The rationale proposed for giving methotrexate in three divided doses once weekly [14] is now recognized to be invalid [15] and this regimen may have a higher risk of hepatic fibrosis [16].

Most serious problems and the rare deaths associated with low-dose methotrexate arise because of an absolute or relative overdosage. A small initial test dose, usually 5–7.5 mg, is advisable in order to detect those patients who may be unduly sensitive to the drug [17]. If the full blood count is stable at 7 days then subsequent doses may be gradually increased (usually in 2.5 to 5-mg steps) according to clinical response and any accompanying toxicity. The aim of therapy should not be to induce complete clearance of psoriasis but to achieve sufficient control that it may readily be managed with topical therapy. Most patients are adequately controlled on doses of 7.5–15 mg weekly and few patients require more than 20 mg. Even lower doses may suffice, particularly in the elderly.

Folic acid supplementation. There is little evidence that folate supplementation has a significant effect on methotrexate efficacy [18,19] though one study from the United Kingdom suggested that slightly higher doses of methotrexate might be required in patients receiving supplemental folic acid [20]. It is clear, however, that methotrexate toxicity is enhanced by folate depletion. Recent studies in both rheumatoid arthritis and psoriasis patients have shown that low-dose methotrexate increases circulating concentrations of homocysteine and that this rise can be reversed by folic acid administration [21,22]; elevated homocysteine levels are associated with increased risk of cardiovascular disease. People with severe psoriasis tend to have reduced folate and elevated homocysteine levels even before commencing systemic therapy [23]. Given that folic acid also has protective effects on the bone marrow and liver [24], it seems appropriate to recommend that all patients treated with methotrexate should receive supplemental folic acid. There is as yet insufficient information to determine the most appropriate dosage but 1–5 mg/day appears to be adequate to correct these problems without significantly affecting clinical response to therapy [18,19,24].

Monitoring schedule. Initially, patients should be assessed weekly by clinical examination and laboratory measurement of full blood count, plasma urea, electrolytes and creatinine, and liver enzyme tests. Once therapy has been stabilized, assessments should be performed every 2–3 months. Results should be carefully monitored; recording of results such as haemoglobin or platelets in a table or graph makes it easier to detect abnormal trends. In any individual, the dosage of methotrexate required to maintain adequate control of psoriasis will vary from time to time and should be adjusted accordingly.

As alcohol abuse greatly increases the risks of liver damage in patients receiving methotrexate, they should be reminded regularly of the need to restrict alcohol intake. Liver damage cannot be reliably detected by standard liver enzyme tests or imaging techniques and regular liver biopsy for all patients receiving low-dose methotrexate for psoriasis is still advocated by several authorities [9,25]. However, several studies suggest that the risk of serious liver damage in carefully monitored patients receiving once-weekly low-dose methotrexate is small [26–28] and that the cost and morbidity of repeated biopsy may be difficult to justify when compared with the low yield of significant liver pathology. If there are concerns about pre-existing liver damage then it may be appropriate to obtain a liver biopsy as a baseline soon after successful methotrexate therapy has been established.

It can reasonably be argued that liver biopsy need no longer be performed routinely in all patients receiving long-term methotrexate [29] but, to provide greater reassurance that significant damage is not overlooked, several investigators have recommended the use of a serological marker of fibrosis, the aminoterminal peptide of type III procollagen (PIIINP). They have concluded that patients whose PIIINP levels are consistently normal are very unlikely to have significant liver damage [30–32]. If PIIINP assay is available it should be performed 3-monthly and liver biopsy may be restricted to the small minority in whom PIIINP levels are repeatedly elevated.

Management of problems

Inadequate response. A small minority of patients are unable to absorb methotrexate adequately but may respond satisfactorily if it is given parenterally. Although there is rather little data in psoriasis patients [33], subcutaneous administration has been shown in a randomized, controlled trial to have greater efficacy than oral methotrexate in the treatment of rheumatoid arthritis [34]. Prefilled syringes for self-injection are available in Europe. Patients with psoriasis who relapse while receiving methotrexate may frequently be brought satisfactorily under control by a course of intensive topical therapy and/or UVB phototherapy [35]; in contrast to the combination of methotrexate and PUVA, which should be avoided, a major increased risk of skin cancer from combining UVB with methotrexate has not been demonstrated [36].

Nausea. This occurs in 25%, usually appears within 12 h of methotrexate ingestion, and may last up to 3 days. It is usually mild but may limit therapy [37]. Folic acid 5 mg/day has been found to be more helpful than antiemetics, taking methotrexate with the evening meal or dividing the dose, although any of these manoeuvres may help some patients. Ondansetron 8 mg orally 2 h before and, if necessary, 12 and 24 h after the weekly methotrexate dose, can be dramatically effective [38]. Change to subcutaneous or intramuscular administration does not reliably abolish nausea.

Liver inflammation and fibrosis. An acute rise in liver enzymes to greater than three times the upper limit of normal is usually an indication to discontinue methotrexate. If PIIINP levels are repeatedly abnormal over a 12-month period then liver biopsy should be considered. The decision to discontinue methotrexate depends not only on the results of liver biopsy but also on the ease with which an individual patient's psoriasis may be managed by other means. In general, severe fibrosis and cirrhosis are considered contraindications to further methotrexate therapy. Nevertheless, some dermatologists have continued treatment in patients with documented cirrhosis without encountering significant deterioration of liver disease [39]. In patients with hepatic inflammation or mild to moderate fibrosis without cirrhosis, continuation of methotrexate therapy is probably still safe so long as alcohol is strictly avoided and patients are closely monitored. If PIIINP remains elevated then a further liver biopsy should be considered after 12 months to 2 years of continued therapy.

Respiratory disease. Methotrexate-induced pneumonitis is rare in psoriasis. It is characterized by acute onset with fever, cough and dyspnoea. Chest X-ray shows pulmonary infiltration. It resolves rapidly with withdrawal of methotrexate and systemic corticosteroids [36]. Pulmonary fibrosis is a rare complication.

Haematological abnormalities. A rise in mean corpuscular volume (MCV) is common in patients receiving long-term methotrexate and usually indicates relative folate deficiency although it is important to exclude other causes of macrocytosis. If MCV rises above 106 fl despite folate replacement then further methotrexate therapy is probably contraindicated [40]. Falls in haemoglobin, white cell or platelet counts should prompt a reduction in dose or, if severe, withdrawal of methotrexate.

Acute toxicity and overdosage. Absolute or relative overdosage of methotrexate can result in acute toxicity, manifested clinically by myelosuppression, mucosal ulceration and, rarely, cutaneous necrolysis. Early treatment may be life-saving. The metabolic effects of methotrexate can be bypassed by administration of folinic acid. As soon as overdose is suspected, serum should be collected for measurement of methotrexate levels and folinic acid should be administered intravenously. The dose of folinic acid should be at least as high as the total dose of methotrexate thought to be responsible for the overdose and should in any event not be less than 20 mg. Subsequent doses (which may be taken orally if no more than 20 mg) should be given at 6-hourly intervals until the serum methotrexate is less than 0.01 µmol/L. The dose of folinic acid required will vary according to the serum methotrexate concentration. A dose of 20 mg suffices where the methotrexate concentration is 0.5 µmol/L or less, but at higher concentrations the dose can be calculated at 100 mg for every 1 µmol/L of measured serum methotrexate concentration [41].

References

1 Shupack JL, Webster GF. Pancytopenia following low-dose oral methotrexate therapy for psoriasis. *JAMA* 1988; **259**: 3594–6.
2 Cheung KK, Chow KM, Szeto CC *et al*. Fatal pancytopenia in a hemodialysis patient after treatment with low-dose methotrexate. *J Clin Rheumatol* 2009; **15**: 177–80.
3 Evans WE, Christensen ML. Drug interactions with methotrexate. *J Rheumatol* 1985; **12**: 15–20.
4 Rosenberg P, Urwitz H, Johannesson A *et al*. Psoriasis patients with diabetes type 2 are at high risk of developing liver fibrosis during methotrexate treatment. *J Hepatol* 2007; **46**: 1111–8.
5 Kozlowski RD, Steinbrunner JV, MacKenzie AH *et al*. Outcome of first-trimester exposure to low-dose methotrexate in eight patients with rheumatic disease. *Am J Med* 1990; **88**: 589–92.
6 Milunsky A, Graef JW, Gaynor MF. Methotrexate-induced congenital malformations. *J Pediatr* 1968; **72**: 790–5.
7 Nguyen C, Duhl AJ, Escallon CS, Blakemore KJ. Multiple anomalies in a fetus exposed to low-dose methotrexate in the first trimester. *Obstet Gynecol* 2002; **99**: 599–602.
8 Powell HR, Ekert H. Methotrexate-induced congenital malformations. *Med J Aust* 1971; **2**: 1076–7.
9 Weatherhead S, Robson C, Reynolds NJ. Management of psoriasis in pregnancy. *BMJ* 2007; **334**: 1218–20.
10 Estop AM. Sperm chromosome studies in patients taking low-dose methotrexate. *Am J Hum Genet* 1992; **51** (Suppl. 4): A314.
11 Perry WH. Methotrexate and teratogenesis. *Arch Dermatol* 1983; **119**: 874.
12 Sussman A, Leonard JM. Psoriasis, methotrexate, and oligospermia. *Arch Dermatol* 1980; **116**: 215–7.
13 Dahl MG, Gregory MM, Scheuer PJ. Methotrexate hepatotoxicity in psoriasis: comparison of different dose regimens. *BMJ* 1972; **1**: 654–6.
14 Weinstein GD, Frost P. Methotrexate for psoriasis: a new therapeutic schedule. *Arch Dermatol* 1971; **103**: 33–8.
15 Zanolli MD, Sherertz EF, Hedberg AE. Methotrexate: anti-inflammatory or antiproliferative? *J Am Acad Dermatol* 1990; **22**: 523–4.
16 Roenigk HH, Auerbach R, Bergfeld WF *et al*. A cooperative prospective study of the effects of psoriasis on liver biopsies. In: Farber EM, Cox AJ, eds. *Psoriasis: Proceedings of the Second International Symposium*. New York: Yorke Medical, 1977: 243–8.
17 Jih DM, Werth VP. Thrombocytopenia after a single test dose of methotrexate. *J Am Acad Dermatol* 1998; **39**: 349–51.
18 Kirby B, Lyon CC, Griffiths CE, Chalmers RJ. The use of folic acid supplementation in psoriasis patients receiving methotrexate: a survey in the United Kingdom. *Clin Exp Dermatol* 2000; **25**: 265–8.
19 Ortiz Z, Shea B, Suarez-Almazor ME *et al*. Folic acid and folinic acid for reducing side effects in patients receiving methotrexate for rheumatoid arthritis. *Cochrane Database Syst Rev* 1999, Issue 4. Art. No.: CD000951. DOI: 10.1002/14651858.CD000951.
20 Salim A, Tan E, Ilchyshyn A *et al*. Folic acid supplementation during treatment of psoriasis with methotrexate: a randomized, double-blind, placebo-controlled trial. *Br J Dermatol* 2006; **154**: 1169–74.
21 van Ede AE, Laan RFJM, Blom HJ *et al*. Homocysteine and folate status in methotrexate-treated patients with rheumatoid arthritis. *Rheumatology* 2002; **41**: 658–65.
22 Hanrahan E, Barnes L. Elevated serum homocysteine levels in patients with psoriasis receiving long-term, low-dose methotrexate therapy. *Br J Dermatol* 2001; **145** (Suppl. 59): 43.
23 Malerba M, Gisondi P, Radaeli A *et al*. Plasma homocysteine and folate levels in patients with chronic plaque psoriasis. *Br J Dermatol* 2006; **155**: 1165–9.
24 Prey S, Paul C. Effect of folic or folinic acid supplementation on methotrexate-associated safety and efficacy in inflammatory disease: a systematic review. *Br J Dermatol* 2009; **160**: 622–8.
25 Kuijpers AL, van de Kerkhof PC. Risk–benefit assessment of methotrexate in the treatment of severe psoriasis. *Am J Clin Dermatol* 2000; **1**: 27–39.
26 Boffa MJ, Chalmers RJ, Haboubi NY *et al*. Sequential liver biopsies during long-term methotrexate treatment for psoriasis: a reappraisal. *Br J Dermatol* 1995; **133**: 774–8.
27 Lanse SB, Arnold GL, Gowans JD, Kaplan MM. Low incidence of hepatotoxicity associated with long-term, low-dose oral methotrexate in treatment of refractory psoriasis, psoriatic arthritis, and rheumatoid arthritis: an acceptable risk–benefit ratio. *Dig Dis Sci* 1985; **30**: 104–9.
28 Aithal GP, Haugk B, Das S *et al*. Monitoring methotrexate induced hepatic fibrosis in patients with psoriasis: are serial biopsies justified? *Aliment Pharmacol Ther* 2004; **19**: 391–9.
29 Kalb RE, Strober B, Weinstein G, Lebwohl M. Methotrexate and psoriasis: 2009 National Psoriasis Foundation Consensus Conference. *J Am Acad Dermatol* 2009; **60**: 824–37.
30 Boffa MJ, Smith A, Chalmers RJ *et al*. Serum type III procollagen aminopeptide for assessing liver damage in methotrexate-treated psoriatic patients. *Br J Dermatol* 1996; **135**: 538–44.
31 Zachariae H, Heickendorff L, Sogaard H. The value of amino-terminal propeptide of type III procollagen in routine screening for methotrexate-induced liver fibrosis: a 10-year follow-up. *Br J Dermatol* 2001; **144**: 100–3.
32 Chalmers RJG, Kirby B, Smith A *et al*. Replacement of routine liver biopsy by procollagen III aminopeptide for monitoring patients with psoriasis receiving long-term methotrexate: a multicentre audit and health economic analysis. *Br J Dermatol* 2005; **152**: 444–50.
33 Zackheim HS. Subcutaneous administration of methotrexate. *J Am Acad Dermatol* 1992; **26**: 1008.
34 Braun J, Kastner P, Flaxenberg P *et al*. Comparison of the clinical efficacy and safety of subcutaneous versus oral administration of methotrexate in patients with active rheumatoid arthritis: results of a six-month, multicenter, randomized, double-blind, controlled, phase IV trial. *Arthritis Rheum* 2008; **58**: 73–81.
35 Roenigk HH, Maibach HI. Methotrexate. In: Roenigk HH, Maibach HI, eds. *Psoriasis*, 3rd edn. New York: Marcel Dekker, 1998: 609–29.

36 Zachariae H. Methotrexate. In: van de Kerkhof PCM, ed. *Textbook of Psoriasis*. Oxford: Blackwell Science, 1999: 196–232.
37 Duhra P. Treatment of gastrointestinal symptoms associated with methotrexate therapy for psoriasis. *J Am Acad Dermatol* 1993; **28**: 466–9.
38 Walker SL, Kirby B, Griffiths CEM *et al*. The use of oral ondansetron for severe methotrexate-induced nausea in psoriasis. *Br J Dermatol* 2002; **147** (Suppl. 62): 38.
39 Zachariae H, Sogaard H, Heickendorff L. Methotrexate-induced liver cirrhosis: clinical, histological and serological studies—a further 10-year follow-up. *Dermatology* 1996; **192**: 343–6.
40 Dodd HJ, Kirby JD, Munro DD. Megaloblastic anaemia in psoriatic patients treated with methotrexate. *Br J Dermatol* 1985; **112**: 630–1.
41 Chalmers RJG, Boffa MJ. Current management of psoriasis: methotrexate. *J Dermatol Treat* 1997; **8**: 41–4.

Table 74.10 Mycophenolate mofetil.

Drug name and indications	Usual dose range	Evidence level	References
Mycophenolate mofetil			
Atopic dermatitis	1–2 g daily	C	[8]
Psoriasis	2 g daily	C	[5–7]
Pemphigus	2 g daily*	A	[1,2]
Bullous pemphigoid	2 g daily*	A	[4]

* With corticosteroids.

Mycophenolic acid

Mycophenolic acid (mycophenolate mofetil; mycophenolate sodium; MPA) is a potent, lymphocyte selective immunosuppressant widely used in transplant medicine. The two currently available forms of the drug—mycophenolate mofetil (MMF) and mycophenolate sodium—have been developed to circumvent the problematic gastrointestinal side effects that are associated with the active moiety (MPA) itself. Mycophenolate mofetil is an ester pro-drug, which is hydrolysed to MPA by plasma esterases. The more recently available enteric coated mycophenolate sodium enters the small intestine having bypassed the stomach (due to low solubility in acid) where MPA is released and absorbed. MPA is metabolized primarily in the liver by glucuronlyl transferase to form the pharmacologically inactive metabolite phenolic glucuronide of MPA (MPAG), which is then renally excreted. Circulating MPAG can be converted back into active MPA via enterohepatic recirculation, and this can, in the context of renal impairment and reduced MPAG excretion, lead to increased potency (and toxicity). MPA is a specific, and non-competitive, inhibitor of the enzyme inosine monophosphate dehydrogenase (IMPDH), a key enzyme in *de novo* purine synthesis. The lymphocyte-specific effects of MPA arise for two, related, reasons. Firstly, T and B lymphocytes are solely dependent on the *de novo* pathway for purine synthesis, whereas the majority of cell types can generate purines via two routes—the *de novo* and salvage pathways. Secondly, MPA is particularly effective in blocking the type II isoform of IMPDH which is preferentially expressed in activated lymphocytes. Consequent depletion of guanosine nucleotides results in inhibition of DNA replication, transcription and protein translation, cell cycle arrest, and cell death. Overall, this results in inhibition of T- and B-cell activation and proliferation and reduced B-cell antibody production. Additional effects include impaired glycoprotein production and therefore reduced expression of adhesion molecules.

Clinical indications (Table 74.10)

Most clinical studies of relevance to dermatology relate to MMF since mycophenolate sodium has only recently been available. MMF is of proven benefit in autoimmune bullous diseases, particularly bullous pemphigoid and pemphigus, where it is used to induce remission, commonly with corticosteroids and, subsequently, to maintain disease control [1]. In pemphigus, MMF appears to be more effective as adjuvant therapy to methylprednisolone than azathioprine in inducing disease control [2] but may have inferior steroid-sparing effect compared to azathioprine [3]. In bullous pemphigoid, MMF has been shown to be of comparable efficacy to azathioprine [4]. In psoriasis, open-label studies suggest MMF monotherapy is moderately effective [5,6], and it has been used in severe recalcitrant disease in combination with ciclosporin [7]. However, the advent of TNF-antagonists has largely superseded this approach. Uncontrolled, open-label studies collectively involving more than 50 patients with severe atopic dermatitis, report an improvement in disease severity of between 40 and 50% with MMF 1 g twice daily [8,9]; efficacy has also been demonstrated with mycophenolate sodium in a single series of 10 patients [10]. However, in the latter study, despite a moderate reduction in objective disease severity scores, there was no change in topical steroid use suggesting that the efficacy is not dramatic and at least one case series has shown no benefit with MMF [11]. Prospective, controlled studies are therefore required to properly determine the role of MMF in atopic dermatitis.

Anecdotal reports and small case series indicate potential benefit of MMF monotherapy in chronic urticaria [12], chronic actinic dermatitis [13], pyoderma gangrenosum [14], lichen planus [15] and MMF as a steroid sparing agent in ANCA-associated vasculitides [16] and dermatomyositis [17]. Data in lupus is conflicting [18], although benefit in recalcitrant skin disease associated with SLE, and also DLE and subacute cutaneous LE has been anecdotally reported (reviewed in [15]).

Adverse effects include gastrointestinal upset (diarrhoea, nausea, abdominal cramps) and genitourinary symptoms (dysuria, sterile pyuria), both of which tend to improve with continued therapy. Bone marrow suppression (typically leukopenia) and bacterial, viral (particularly herpes zoster, simplex and CMV infection) and mycobacterial infection may also complicate therapy. Generally though, treatment is well tolerated with minimal hepatic or renal toxicity. Notably, clinical trial data from use in organ transplantation, whilst not necessarily generalizable to dermatological disease, has failed to show any major differences between MMF and azathioprine in terms of short-term tolerability although in patients who are unable to tolerate azathioprine, a switch to MMF may be beneficial. Mycophenolate mofetil lacks the direct mutagenic effects of azathioprine (i.e. accumulation of 6-thioguanine in patients' DNA, and known mutagenic synergy between 6-thioguanine and UVA [19]), and may therefore confer advantages in terms of reducing potential immunosuppression-related long-term risks of malignancy [20].

References

1 Martin LK, Agero AL, Werth V *et al*. Interventions for pemphigus vulgaris and pemphigus foliaceus. *Cochrane Database Syst Rev* 2009, Issue 1. Art. No.: CD006263. DOI: 10.1002/14651858.CD006263.pub2.

2 Beissert S, Werfel T, Frieling U *et al*. A comparison of oral methylprednisolone plus azathioprine or mycophenolate mofetil for the treatment of pemphigus. *Arch Dermatol* 2006; **142**: 1447–54.
3 Chams-Davatchi C, Esmaili N, Daneshpazhooh M *et al*. Randomized controlled open-label trial of four treatment regimens for pemphigus vulgaris. *J Am Acad Dermatol* 2007; **57**: 622–8.
4 Beissert S, Werfel T, Frieling U *et al*. A comparison of oral methylprednisolone plus azathioprine or mycophenolate mofetil for the treatment of bullous pemphigoid. *Arch Dermatol* 2007; **143**: 1536–42.
5 Geilen CC, Arnold M, Orfanos CE. Mycophenolate mofetil as a systemic antipsoriatic agent: positive experience in 11 patients. *Br J Dermatol* 2001; **144**: 583–6.
6 Zhou Y, Rosenthal D, Dutz J, Ho V. Mycophenolate mofetil (CellCept) for psoriasis: a two-center, prospective, open-label clinical trial. *J Cutan Med Surg* 2003; **7**: 193–7.
7 Ameen M, Smith HR, Barker JN. Combined mycophenolate mofetil and cyclosporin therapy for severe recalcitrant psoriasis. *Clin Exp Dermatol* 2001; **26**: 480–3.
8 Schmitt J, Schakel K, Schmitt N, Meurer M. Systemic treatment of severe atopic eczema: a systematic review. *Acta Dermatovenereol* 2007; **87**: 100–11.
9 Murray ML, Cohen JB. Mycophenolate mofetil therapy for moderate to severe atopic dermatitis. *Clin Exp Dermatol* 2007; **32**: 23–7.
10 van Velsen SG, Haeck IM, Brunijnzeel-Koomen CA, de Bruin-Weller MS. First experience with enteric-coated mycophenolate sodium (Myfortic) in severe recalcitrant adult atopic dermatitis: an open label study. *Br J Dermatol* 2009; **160**: 687–91.
11 Hansen ER, Buus S, Deleuran M, Andersen KE. Treatment of atopic dermatitis with mycophenolate mofetil. *Br J Dermatol* 2000; **143**: 1324–6.
12 Shahar E, Bergman R, Guttman-Yassky E, Pollack S. Treatment of severe chronic idiopathic urticaria with oral mycophenolate mofetil in patients not responding to antihistamines and/or corticosteroids. *Int J Dermatol* 2006; **45**: 1224–7.
13 Thomson MA, Stewart DG, Lewis HM. Chronic actinic dermatitis treated with mycophenolate mofetil. *Br J Dermatol* 2005; **152**: 784–6.
14 Reichrath J, Bens G, Bonowitz A, Tilgen W. Treatment recommendations for pyoderma gangrenosum: an evidence-based review of the literature based on more than 350 patients. *J Am Acad Dermatol* 2005; **53**: 273–83.
15 Orvis AK, Wesson SK, Breza J *et al*. Mycophenolate mofetil in dermatology. *J Am Acad Dermatol* 2009; **60**: 183–99.
16 Stassen PM, Cohen Tervaert JW, Stegeman CA. Induction of remission in active anti-neutrophil cytoplasmic antibody-associated vasculitis with mycophenolate mofetil in patients who cannot be treated with cyclophosphamide. *Ann Rheum Dis* 2007; **66**: 798–802.
17 Edge JC, Outland JD, Dempsey JR, Callen JP. Mycophenolate mofetil as an effective corticosteroid-sparing therapy for recalcitrant dermatomyositis. *Arch Dermatol* 2006; **142**: 65–9.
18 Mok CC. Mycophenolate mofetil for non-renal manifestations of systemic lupus erythematosus: a systematic review. *Scand J Rheumatol* 2007; **36**: 329–37.
19 O'Donovan P, Perrett CM, Zhang X *et al*. Azathioprine and UVA light generate mutagenic oxidative DNA damage. *Science* 2005; **309**: 1871–4.
20 Domhan S, Zeier M, Abdollahi A. Immunosuppressive therapy and post-transplant malignancy. *Nephrol Dial Transplant* 2009; **24**: 1097–103.

Sirolimus

Sirolimus (also known as rapamycin) is a macrolide antibiotic compound with potent immunosuppressive and antiproliferative properties. It is structurally related to tacrolimus, and similarly binds to the cytoplasmic immunophilin, FK binding protein but has a distinct mechanism of action, in that it inhibits activation of the mammalian target of rapamycin (mTOR), a critical regulatory kinase for cell cycle progression and cell growth. Sirolimus was originally developed for use in organ transplantation as a potential replacement for calcineurin inhibitors, since early studies suggested that it lacked intrinsic nephrotoxicity whilst also being a potent suppressor of interleukin-2 driven T- and B-cell activation and proliferation. However, subsequent studies have now shown that the risks of nephrotoxicity appear to be similar for both drugs. Myelotoxicity, dyslipidaemia and post-transplant diabetes occur much more frequently with sirolimus than ciclosporin and around a third of patients discontinue therapy due to side effects [1].

Sirolimus and other mTOR inhibitors (everolimus, temsirolimus) may, however, confer advantages over other immunosuppressants in terms of long-term risks of malignancy. In renal transplant patients for example, maintenance of immunosuppression with sirolimus and everolimus alone or even in combination with calcineurin inhibitors showed a significantly reduced risk of developing any post-transplant malignancy, including skin malignancy, compared to therapy with calcineurin-inhibitors alone [2]. Also, again in renal transplant recipients, dramatic regression of Kaposi's sarcoma has been reported on switching therapy from ciclosporin (and mycophenolate mofetil) to sirolimus [3].

More recently, attention has focused on the marked antiproliferative properties of sirolimus, notably in tuberous sclerosis where activation of mTOR pathway results from tuberin gene mutations, and sirolimus treatment was associated with a 50% reduction in angiomyolipoma tumour volume [4].

Currently, sirolimus itself has a limited role in dermatology, but new, less toxic mTOR inhibitors are likely to have wider applications given the central importance of mTOR in cancer and in metabolic and inflammatory disease.

References

1 Webster AC, Lee VWS, Chapman JR, Craig JC. Target of rapamycin inhibitors (sirolimus and everolimus) for primary immunosuppression of kidney transplant recipients: a systematic review and meta-analysis of randomized trials. *Transplantation* 2006; **81**: 1234–48.
2 Kauffman HM, Cherikh WS, Cheng Y *et al*. Maintenance immunosuppression with target-of-rapamycin inhibitors is associated with a reduced incidence of de novo malignancies. *Transplantation* 2005; **80**: 883–9.
3 Barozzi P, Bonini C, Potenza L *et al*. Changes in the immune responses against human herpesvirus-8 in the disease course of posttransplant Kaposi sarcoma. *Transplantation* 2008; **86**: 738–44.
4 Bissler JJ, McCormack FX, Young LR *et al*. Sirolimus for angiomyolipoma in tuberous sclerosis complex or lymphangioleiomyomatosis. *N Engl J Med* 2008; **358**: 140–51.

Immunomodulating agents

Antimalarials

The quinine-related drugs, chloroquine, hydroxychloroquine and mepacrine (quinacrine in the US), have antimalarial properties but have been used in dermatology and rheumatology for many years because of their anti-inflammatory effects (Table 74.11) [1]. Antimalarials interfere with many biological processes. Which of these is most important for their clinical activity is not well understood. They are highly concentrated within intracellular lysosomes where they inhibit acidic proteases. This may be particularly important in antigen-presenting cells where they interfere with the digestion and subsequent presentation of antigens to T cells. They have been shown experimentally to inhibit a number of inflammatory pathways, including secretion of macrophage and monocyte-derived cytokines and Toll-like receptor signalling in response to DNA-associated autoantigens. These effects are reviewed in [1].

Antimalarials are of particular value in cutaneous lupus erythematosus and lupus panniculitis but also have a place in managing

Table 74.11 Antimalarials.

Drug name and indications	Usual dose range	Evidence level	References
Hydroxychloroquine	≤6.5 mg/kg/day		
Chloroquine	≤3.0 mg/kg/day		
Mepacrine	100–200 mg/day		
Cutaneous lupus erythematosus	as above	B	[1,4,5]
Porphyria cutanea tarda	*	B	[1,6]
Polymorphic light eruption	as above	C	[1,7]
Solar urticaria	as above	E	[1,8]
Cutaneous sarcoidosis	as above	D	[1,9]
Granuloma annulare	as above	E	[1,10]
Dermatomyositis	as above	E	[11]
Oral lichen planus	as above	E	[12]
Reticular erythematous mucinosis	as above	E	[13]

* Hydroxychloroquine 100 mg × 2 weekly.

non-cutaneous aspects of systemic lupus erythematosus [1,2]. They have been advocated as second-line agents in porphyria cutanea tarda, polymorphic light eruption, solar urticaria, cutaneous sarcoidosis, granuloma annulare, the cutaneous manifestations of dermatomyositis, oral lichen planus and reticular erythematous mucinosis [1]. If response to any one of the antimalarials is inadequate then switching to an alternative or using a combination of two drugs may result in improved efficacy.

High doses of chloroquine and hydroxychloroquine may cause retinopathy; doses of up to 3 mg/kg/day and 6.5 mg/kg/day, respectively, are, however, thought to be safe [3]. Patients receiving chloroquine also commonly develop corneal deposits which, although usually asymptomatic, are not found with hydroxychloroquine. Mepacrine lacks ocular toxicity which may make it more acceptable for patients who have concerns about their eyesight. In effective dosage (200 mg/day) mepacrine usually causes the skin to turn yellow. Long-term use of antimalarials may produce marked blue-black pigmentation of the skin which slowly diminishes after discontinuation of treatment. Haemolytic anaemia may be precipitated in patients with glucose-6-phosphatase deficiency. This possibility should be considered before starting therapy in patients from populations where this deficiency is prevalent. Agranulocytosis and aplastic anaemia are rare but blood counts should be performed monthly for 3 months then periodically thereafter.

References

1 Kalia S, Dutz JP. New concepts in antimalarial use and mode of action in dermatology. *Dermatol Ther* 2007; **20**: 160–74.

2 The Canadian Hydroxychloroquine Study Group. A randomized study of the effect of withdrawing hydroxychloroquine sulfate in systemic lupus erythematosus. *N Engl J Med* 1991; **324**: 150–4.

3 Marmor MF, Carr RE, Easterbrook M *et al*. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy. A report by the American Academy of Ophthalmology. *Ophthalmology* 2002; **109**: 1377–82.

4 Kraak JH, Van Ketel W, Prakken JR, Van Zwet W. The value of hydroxychloroquine (plaquenil) for the treatment of chronic discoid lupus erythematosus: a double blind trial. *Dermatologica* 1965; **130**: 293–305.

5 Callen JP. Chronic cutaneous lupus erythematosus. Clinical, laboratory, therapeutic, and prognostic examination of 62 patients. *Arch Dermatol* 1982; **118**: 412–6.

6 Ashton RE, Hawk JL, Magnus IA. Low-dose oral chloroquine in the treatment of porphyria cutanea tarda. *Br J Dermatol* 1984; **111**: 609–13.

7 Murphy GM, Hawk JL, Magnus IA. Hydroxychloroquine in polymorphic light eruption: a controlled trial with drug and visual sensitivity monitoring. *Br J Dermatol* 1987; **116**: 379–86.

8 Wolf R, Wolf D, Ruocco V. Antimalarials: unapproved uses or indications. *Clin Dermatol* 2000; **18**: 17–35.

9 Jones E, Callen JP. Hydroxychloroquine is effective therapy for control of cutaneous sarcoidal granulomas. *J Am Acad Dermatol* 1990; **23**: 487–9.

10 Cannistraci C, Lesnoni La Parola I *et al*. Treatment of generalized granuloma annulare with hydroxychloroquine. *Dermatology* 2005; **211**: 167–8.

11 Quain RD, Werth VP. Management of cutaneous dermatomyositis: current therapeutic options. *Am J Clin Dermatol* 2006; **7**: 341–51.

12 Eisen D. Hydroxychloroquine sulfate (plaquenil) improves oral lichen planus: an open trial. *J Am Acad Dermatol* 1993; **28**: 609–12.

13 Cernea SS, Rivitti EA. Successful treatment of mucinosis with chloroquine. *J Dermatol Treat* 1990; **1**: 163–5.

Clofazimine

Clofazimine is a synthetic tricyclic phenazine licensed for treatment of multibacillary leprosy [1]. It has long been known to have anti-inflammatory as well as antibacterial activity and has recently been shown to have potent inhibitory effects, similar to those of ciclosporin and tacrolimus, on the intracellular T-cell receptor-mediated signal transduction pathway involved in the promotion of interleukin-2 synthesis [2]. Its anti-inflammatory effect has been utilized both in the prevention and treatment of erythema nodosum leprosum [3].

Its clinical use in dermatology has been reviewed [4]. Clofazimine has a long elimination half-life (70 days). The main side effect is an orange-red to deep umber discoloration of skin, conjunctivae and body fluids such as urine and tears. It may cause ichthyosis [5] but is otherwise generally well tolerated. In addition to its use in leprosy it has been used in a number of other infectious disorders including atypical mycobacterial infections [4] and rhinoscleroma [6]. Its anti-inflammatory properties have been advocated for a variety of skin disorders (Table 74.12) [4].

References

1 World Health Organization. *Leprosy Elimination: WHO Recommended MDT Regimens*. Available at http://www.who.int/lep/mdt/regimens/en/index.html.

Table 74.12 Clofazimine.

Drug name and indications	Usual dose range	Evidence level	References
Clofazimine			
Multibacillary leprosy	300 mg/month + 50 mg/day	A	[1]
Erythema nodosum leprosum	300 mg/day + systemic steroids	A	[3]
Atypical mycobacteria	Variable	D	[4]
Rhinoscleroma	Variable	D	[6]
Pyoderma gangrenosum	300–400 mg/day	D	[4]
Discoid lupus	100–300 mg/day	D	[4,7]

2 Ren YR, Pan F, Parvez S *et al.* Clofazimine inhibits human Kv1.3 potassium channel by perturbing calcium oscillation in T lymphocytes. *PLoS ONE* 2008; **3**: e4009.
3 World Health Organization. *WHO Guidelines for the Management of Severe Erythema Nodosum Leprosum (ENL) Reactions*. Available at: http://www.who.int/lep/research/WHOenlguide.pdf.
4 Arbiser J, Moschella S. Clofazimine: a review of its medical uses and mechanisms of action. *J Am Acad Dermatol* 1995; **32**: 241–7.
5 Caver CV. Clofazimine-induced ichthyosis and its treatment. *Cutis* 1982; **29**: 341–3.
6 Shehata MA, Salama AM. Clofazimine in the treatment of scleroma. *J Laryngol Otol* 1989; **103**: 856–60.
7 Lo JS, Berg RE, Tomecki KJ. Treatment of discoid lupus erythematosus. *Int J Dermatol* 1989; **28**: 497–507.

Colchicine

Colchicine is an alkaloid extracted from the seeds of the autumn crocus, *Colchicum autumnale* (meadow saffron). It has been used medicinally for at least 1500 years and has maintained its position as treatment of choice for acute gouty crisis from the middle of the 18th century until the present day [1]. It is also important in the management of familial Mediterranean fever. Colchicine interrupts cellular mitosis in metaphase by blocking the polymerization of tubulin dimers into microtubules, an essential component of the cellular cytoskeleton. Its cytotoxic effects are greatest on cells with a high turnover such as polymorphonuclear leukocytes. Further actions include interference with polymorph chemotaxis and with various intercellular adhesion molecules involved in the activation of T cells [1,2]. In therapeutic doses colchicine may cause nausea, vomiting and abdominal pain but in the low doses (0.5–2.0 mg/day) employed in dermatology it is usually well tolerated. A reassuringly low incidence of side effects was found in a review of studies involving over 1200 children and adolescents treated for a total of nearly 30 000 months for familial Mediterranean fever [3]. In overdose, however, it can be highly toxic with the ability to cause profuse diarrhoea and gastrointestinal haemorrhage, renal failure, severe liver damage and myelosuppression. A severe reaction mimicking toxic epidermal necrolysis has been reported in a patient who died from overdose of colchicine [4]. Colchicine should be avoided in pregnancy.

There are a number of diseases in which polymorphs are presumed to play an important role where colchicine has been advocated (Table 74.13). In dapsone-responsive diseases such as dermatitis herpetiformis or linear IgA disease colchicine may be a valuable alternative where dapsone is either contraindicated or not tolerated. There are few controlled studies of its use in dermatological diseases. Despite the paucity of formal evidence of efficacy, it does, however, retain a valuable position in the management of a number of uncommon skin diseases.

Table 74.13 Colchicine.

Drug name and indications	Usual dose range	Evidence level	References
Colchicine			
Familial Mediterranean fever	0.5–2.0 mg/day	B	[3]
Behçet disease	1.0–2.0 mg/day	C	[5,6]
Sweet disease	as above	D	[7–9]
Dermatitis herpetiformis	as above	E	[1,10]
Adult linear IgA disease	as above	E	[1]
Childhood linear IgA disease	0.5–1.0 mg/day	D	[11,12]
Relapsing polychondritis	1.0–2.0 mg/day	E	[13,14]
Urticarial vasculitis	as above	E	[15]
Epidermolysis bullosa acquisita	as above	D	[16,17]
Generalized pustular psoriasis	as above	E	[18]
Palmoplantar pustulosis*	as above	D	[1,19]

* Response appears to be largely limited to suppression of pustules.

References

1 Bibas R, Gaspar NK, Ramos-e-Silva M. Colchicine for dermatologic diseases. *J Drugs Dermatol* 2005; **4**: 196–204.
2 Sullivan TP, King LE Jr, Boyd AS. Colchicine in dermatology. *J Am Acad Dermatol* 1998; **39**: 993–9.
3 Kallinich T, Haffner D, Niehues T *et al.* Colchicine use in children and adolescents with familial Mediterranean fever: literature review and consensus statement. *Pediatrics* 2007; **119**: 474–83.
4 Arroyo MP, Sanders S, Yee H *et al*. Toxic epidermal necrolysis-like reaction secondary to colchicine overdose. *Br J Dermatol* 2004; **150**: 581–8.
5 Ghayad E, Tohme A. Behçet's disease in Lebanon: report of 100 cases. *Lebanese Med J* 1995; **43**: 2–7.
6 Roux H, Richard P, Arrighi A, Bergaoui N. La maladie de Behçet autochtone. A propos de 73 cas. *Rev Rhumatisme Maladies Osteo-Articulaires* 1989; **56**: 383–8.
7 Török L, Seres K. Akute febrile Neutrophilen-Dermatose (AFN) (Sweet-Syndrome). *Z Hautkr* 1988; **63**: 63–5.
8 Suehisa S, Tagami H, Inoue F *et al*. Colchicine in the treatment of acute febrile neutrophilic dermatosis (Sweet's syndrome). *Br J Dermatol* 1983; **108**: 99–101.
9 Ritter S, George R, Serwatka LM, Elston DM. Long-term suppression of chronic Sweet's syndrome with colchicine. *J Am Acad Dermatol* 2002; **47**: 323–4.
10 Silvers D, Juhlin EA, Berczeller PH, McSorley J. Treatment of dermatitis herpetiformis with colchicine. *Arch Dermatol* 1980; **116**: 1373–4.
11 Banodkar DD, al-Suwaid AR. Colchicine as a novel therapeutic agent in chronic bullous dermatosis of childhood. *Int J Dermatol* 1997; **36**: 213–6.
12 Zeharia A, Hodak E, Mukamel M *et al*. Successful treatment of chronic bullous dermatosis of childhood with colchicine. *J Am Acad Dermatol* 1994; **30**: 660–1.
13 Askari AD. Colchicine for treatment of relapsing polychrondritis. *J Am Acad Dermatol* 1984; **10**: 506–10.
14 Mark KA, Franks AG. Colchicine and indomethacin for the treatment of relapsing polychondritis. *J Am Acad Dermatol* 2002; **46**: S22–4.
15 Asherson RA, Buchanan N, Kenwright S *et al.* The normocomplementemic urticarial vasculitis syndrome: report of a case and response to colchicine. *Clin Exp Dermatol* 1991; **16**: 424–7.
16 Cunningham BB, Kirchmann TT, Woodley D. Colchicine for epidermolysis bullosa acquisita. *J Am Acad Dermatol* 1996; **34**: 781–4.
17 Megahed M, Scharffetter-Kochanek K. Epidermolysis bullosa acquisita: successful treatment with colchicine. *Arch Dermatol Res* 1994; **286**: 35–46.
18 Zachariae H, Kragballe K, Herlin T. Colchicine in generalized pustular psoriasis: clinical response and antibody-dependent cytotoxicity by monocytes and neutrophils. *Arch Dermatol Res* 1982; **274**: 327–33.
19 Chalmers R, Hollis S, Leonardi-Bee J *et al*. Interventions for chronic palmoplantar pustulosis. *Cochr Database System Rev* 2006, Issue 1. Art. No.: CD001433. DOI: 10.1002/14651858.CD001433.pub2.

Dapsone, sulfapyridine and sulfamethoxypyridazine (Table 74.14) [1–5]

Dapsone (DDS) has been the mainstay of the treatment of leprosy for many years. It also has some action against malaria and other

Table 74.14 Sulfones.

Drug name and indications	Usual dose range	Evidence level	References		
			Dap	Spdn	Smpdz
Dapsone	100–150 mg/day				
Sulfapyridine	1.5–4.5 g/day				
Sulfamethoxypyridazine	0.25–1.5 g/day				
Dermatitis herpetiformis		C	[1–3,8]	[3]	[6]
Linear IgA disease & chronic bullous dermatosis of childhood		C	[1,6,7]	[2]	[6]
IgA pemphigus		D	[1,2,9]		
Subcorneal pustular dermatosis		E	[1,2,10]		
Cicatricial (mucous membrane) pemphigoid		C	[2,11]	[12]	[6]
Pyoderma gangrenosum		E	[1,2]		
Behçet disease		E	[2]		
Erythema elevatum diutinum		E	[1,2]		
Relapsing polychondritis		D	[1,2,13]		
Granuloma annulare		E	[1,14]		
Granuloma faciale		E	[1,15]		
Acne fulminans		E	[1,2,16]		

parasites, and has also proved a very valuable drug in the management of a wide range of mainly uncommon dermatoses. Its mode of action is not fully understood. Although many of the diseases found empirically to respond to this drug have in common the involvement of either polymorphs or immune complexes, the metabolic action of dapsone cannot be explained simply in these terms [1–4]. Dermatoses for which dapsone has been found to be particularly effective are dermatitis herpetiformis, linear IgA disease and chronic bullous dermatosis of childhood, cicatricial (mucous membrane) pemphigoid, Sneddon–Wilkinson disease, IgA pemphigus and erythema elevatum diutinum [2]. Other diseases for which dapsone has been advocated include Behçet disease, pyoderma gangrenosum, relapsing polychondritis, acne fulminans, and granuloma faciale (Table 74.14) [1–4].

Toxicity is a considerable problem with dapsone but overall the drug has probably fewer long-term side effects than do corticosteroids or sulfapyridine [1–4]. The main toxic side effect is haemolysis, which is not usually dependent on glucose-6-phosphate dehydrogenase deficiency, although that enzyme defect may compound the problem. Some haemolysis is almost invariably found on therapeutic dosage. Methaemoglobinaemia is also common and is responsible for the bluish lips commonly seen in patients on this drug. A level of 3% methaemoglobinaemia is often unnoticed, 12% may be acceptable, but 20% is usually not. Regular blood checks of haemoglobin and reticulocytes, but also including white cells and platelets, should therefore be undertaken in all patients for the first few months after starting dapsone. Dapsone has several other but less common side effects, including agranulocytosis, peripheral neuropathy, drug rashes, renal damage, hypoalbuminaemia, cholestasis, psychoses and reversible male infertility. A dosage of 100 mg/day is often used as a starting dose. Many patients with dermatitis herpetiformis can be controlled on very much less. Some diseases can only be controlled by larger doses, but the incidence of side effects then rises very sharply and most dermatologists prefer not to exceed a dosage of 100–150 mg/day. It is possible to reduce dapsone-dependent methaemoglobinaemia by the concomitant administration of cimetidine (400 mg three times daily) [5].

Other drugs that share some of the useful assets of dapsone and may in some patients be better tolerated than dapsone include sulfapyridine [1,3,4] and sulfamethoxypyridazine [6]. Sulfapyridine is in general less effective than dapsone and, in doses that are effective, tends to cause more side effects, especially marrow suppression, although not haemolysis. The usual dose is 0.5 g twice or three times daily.

References

1 Zhu YI, Stiller MJ. Dapsone and sulfones in dermatology: overview and update. *J Am Acad Dermatol* 2001; **45**: 420–34.

2 Wolf R, Matz H, Orion E *et al*. Dapsone. *Dermatol Online J* 2002; **8**: 2.

3 Paniker U, Levine N. Dapsone and sulfapyridine. *Dermatol Clin* 2001; **19**: 79–86, viii.

4 Pfeiffer C, Wozel G. Dapsone and sulfones in dermatology: overview and update. *J Am Acad Dermatol* 2003; **48**: 308–9.

5 Coleman MD, Scott AK, Breckenridge AM *et al*. The use of cimetidine as a selective inhibitor of dapsone *N*-hydroxylation in man. *Br J Clin Pharmacol* 1990; **30**: 761–7.

6 McFadden JP, Leonard JN, Powles AV *et al*. Sulphamethoxypyridazine for dermatitis herpetiformis, linear IgA disease and cicatricial pemphigoid. *Br J Dermatol* 1989; **121**: 759–62.

7 Kulthanan K, Akaraphanth R, Piamphongsant T, Kullavanijaya P. Linear IgA bullous dermatosis of childhood: a long-term study. *J Med Assoc Thai* 1999; **82**: 707–12.

8 Egan CA, O'Loughlin S, Gormally S, Powell FC. Dermatitis herpetiformis: a review of fifty-four patients. *Ir J Med Sci* 1997; **166**: 241–4.

9 Yasuda H, Kobayashi H, Hashimoto T *et al*. Subcorneal pustular dermatosis type of IgA pemphigus: demonstration of autoantibodies to desmocollin-1 and clinical review. *Br J Dermatol* 2000; **143**: 144–8.

10 Sneddon I, Wilkinson D. Subcorneal pustular dermatosis. *Br J Dermatol* 1956; **68**: 385–94.

11 Rogers RS, Mehregan DA. Dapsone therapy of cicatricial pemphigoid. *Semin Dermatol* 1988; **7**: 201–5.

12 Elder MJ, Leonard J, Dart JKG. Sulphapyridine—a new agent for the treatment of ocular cicatricial pemphigoid. *Br J Ophth* 1996; **80**: 549–52.
13 White JW Jr. Relapsing polychondritis. *South Med J* 1985; **78**: 448–51.
14 Czarnecki DB, Gin D. The response of generalized granuloma annulare to dapsone. *Acta Derm Venereol* 1986; **66**: 82–4.
15 van de Kerkhof PC. On the efficacy of dapsone in granuloma faciale. *Acta Derm Venereol* 1994; **74**: 61–2.
16 Kaminsky C, Kaminsky A, Schicci C *et al*. Acne: treatment with diaminodiphenylsulfone. *Cutis* 1974; **13**: 869–71.

Fumaric acid esters

Common fumitory (*Fumaria officinalis*) is a plant rich in fumaric acid that is known to have been in use for treatment of skin complaints, including leprosy, as early as the 17th century when Nicholas Culpeper claimed it to be 'very effectual for. . . . clarifying the blood from saltish, choleric humours which cause leprosy, scabs, tetters, and itches, and such like breakings-out of the skin' [1]. Its use at this time may represent an early example of systemic therapy for psoriasis, as it was not until the 19th century that psoriasis was clearly differentiated from leprosy.

The beneficial properties of fumaric acid in psoriasis were first reported by Schweckendiek in 1959. Both a chemist and a psoriasis sufferer, he found through self-experimentation a combination of esters of fumaric acid (FAEs) which he was able to tolerate and which improved his psoriasis (Table 74.15) [2]. A commercial preparation (Fumaderm®) containing a defined mixture of dimethylfumarate (DMF) along with the calcium, magnesium and zinc salts of monoethylfumarate has been available in Germany since 1994. More recently, it has become clear that DMF is the only important component of this mixture and that DMF must first be hydrolysed in the gut to monomethylfumarate (MMF) to become pharmacodynamically active [3]. The precise mechanisms involved in suppressing psoriasis are poorly understood though MMF interferes with maturation of dendritic cells and interferes with cell–cell signalling [3].

There is marked interindividual variation in tolerance of FAEs. Flushing and gastrointestinal hypermotility, with symptoms similar to the irritable bowel syndrome, are common. In order to minimize these, FAE therapy is introduced at a low dose and only gradually increased to therapeutic levels over a period of 6–9 weeks. Although these symptoms often improve with time, up to a quarter of patients may stop treatment because of them [4]. We have found that mebeverine 135 mg taken half an hour before each FAE dose can enable many patients who might have otherwise abandoned treatment to continue therapy with greatly reduced gastrointestinal side effects. A degree of lymphopenia is common though serious side effects appear to be rare [5] and were not seen in 41 patients who had received therapy for between 1 and 14 years [6].

A systematic review has found firm RCT evidence of its efficacy in severe psoriasis [5] and it has become a mainstay of systemic therapy for psoriasis in that country. It is available elsewhere, including the United Kingdom [4], as an unlicensed medication. It is now recognized that DMF is its therapeutically active constituent [4]. A large phase III RCT of DMF monotherapy in psoriasis has confirmed this [7], though further commercial development of DMF monotherapy has been put on hold.

There is limited evidence that FAEs may have a therapeutic effect in a variety of granulomatous skin disorders including disseminated granuloma annulare and sarcoidosis [8]. More evidence is required before they can be recommended for these indications.

Table 74.15 Fumaric acid esters.

Drug name and indications	Usual dose range	Evidence level	References
Fumaric acid esters[§]			
Chronic plaque psoriasis	*30 mg DMF# daily increased in weekly stages to maximum of 240 mg DMF t.d.s.	A	[5]
Dimethylfumarate			
Chronic plaque psoriasis	¶720 mg daily	A	[7]

§ As Fumaderm.
* Licensed in Germany.
¶ Not licensed nor commercially available.
# DMF = principal ingredient.

References

1 Culpeper N. *The Complete Herbal*. London, 1653.
2 Schweckendiek W. Heilung von psoriasis [Treatment of psoriasis vulgaris]. *Med Monatschr* 1959; **13**: 103–4.
3 Yazdi MR, Mrowietz U. Fumaric acid esters. *Clinics Dermatol* 2008; **26**: 522–6.
4 Harries MJ, Chalmers RJG, Griffiths CEM. Fumaric acid esters for severe psoriasis: a retrospective review of 58 cases. *Br J Dermatol* 2005; **153**: 549–51.
5 Griffiths CEM, Clark CM, Chalmers RJG *et al*. A systematic review of treatments for severe psoriasis. *Health Technol Assess* 2000; **4**: 76–80.
6 Hoefnagel JJ, Thio HB, Willemze R *et al*. Longterm safety aspects of systemic therapy with fumaric acid esters in severe psoriasis. *Br J Dermatol* 2003; **149**: 363–9.
7 Mrowietz U, Reich K, Spellman MC. Efficacy, safety, and quality of life effects of a novel oral formulation of dimethyl fumarate in patients with moderate to severe plaque psoriasis: results of a phase 3 study. *J Am Acad Derm* 2006; **54** (Suppl. 3): AB202, P2816.
8 Breuer K, Gutzmer R, Volker B *et al*. Therapy of noninfectious granulomatous skin diseases with fumaric acid esters. *Br J Dermatol* 2005; **152**: 1290–5.

Gold

Gold, as sodium aurothiomalate, was one of the mainstays of therapy for rheumatoid arthritis in the 20th century. It exerts a range of anti-inflammatory effects, although it is still not clear which are the most relevant clinically. It is taken up by macrophages and stored in lysosomes where it has an inhibitory effect on processing of sulphur-containing peptide antigens rich in amino acids such as cysteine and methionine; by suppressing NF-κ B binding activity, it inhibits production of pro-inflammatory cytokines including TNF-α, IL-1 and IL-6; it also upregulates IL-4 production, resulting in a shift of the T-cell population towards a Th2 phenotype [1].

The use of gold has declined as more satisfactory alternatives have become available. It has the potential to cause serious cutaneous side effects including lichenoid eruptions and exfoliative dermatitis; prolonged use may result in skin dyspigmentation from deposits of the metal in dermal macrophages (chrysiasis) [2].

Table 74.16 Gold.

Drug name and indications	Usual dose range	Evidence level	References
Sodium aurothiomalate			
Pemphigus vulgaris	10 mg (day 1) & 25 mg (day 8) test doses; then 50 mg weekly until response and every 2–3 weeks for maintenance	B	[2–4]
Auranofin			
Discoid lupus erythematosus	3–6 mg/day, increasing to 9 mg at 3 months if required	D	[5]

Table 74.17 Tetracycline and nicotinamide.

Drug name and indications	Usual dose range	Evidence level	References
Minocycline			
Pyoderma gangrenosum	100–200 mg/day	D	[3]
Tetracycline			
Palmoplantar pustulosis	250 mg b.d.	E	[4]
Tetracycline and nicotinamide			
Bullous pemphigoid	T 500 mg q.d.s. + N 400–500 mg t.d.s.	C	[6–9]

Proteinuria is found in up to 10% of patients and it rarely may cause leukopenia, thrombocytopenia or aplastic anaemia.

In dermatology it has been used successfully as a steroid-sparing agent in the management of pemphigus vulgaris, where it may still have a role in resistant cases (Table 74.16) [3,4]. Auranofin is an oral preparation of gold which may be less toxic but is also less potent than sodium aurothiomalate. It has been advocated for resistant cases of discoid lupus erythematosus [5].

References

1 Burmester GR. Molecular mechanisms of action of gold treatment in rheumatoid arthritis—an update. *Z Rheumatologie* 2001; **60**: 167–73.
2 Thomas I. Gold therapy and its indications in dermatology. *J Am Acad Dermatol* 1987; **16**: 845–54.
3 Penneys NS, Eaglstein WH, Frost P. Management of pemphigus with gold compounds. *Arch Dermatol* 1976; **112**: 185–7.
4 Iranzo P, Alsina MM, Martinez-De Pablo I *et al*. Gold: An old drug still working in refractory pemphigus. *J Eur Acad Dermatol Venereol* 2007; **21**: 902–7.
5 Dalziel K, Going S, Cartwright PH *et al*. Treatment of chronic discoid lupus erythematosus with an oral gold compound (auranofin). *Br J Dermatol* 1986; **115**: 211–6.

Tetracycline and nicotinamide

Tetracyclines have long been recognized to have anti-inflammatory as well as antibacterial activity and have been proposed as treatment for a range of inflammatory dermatological diseases including pyoderma gangrenosum and palmoplantar pustulosis (Table 74.17) [1–4]. They have complex pharmacological actions including inhibition of neutrophil and eosinophil chemotaxis, prostaglandin synthesis and nitric oxide production [1,2].

Nicotinamide also has anti-inflammatory properties [5]. The combination of tetracycline with nicotinamide for the treatment of bullous pemphigoid was first proposed by Berk and Lorincz in 1986 [6]. Since that time this combination has been widely advocated as being effective, particularly if combined with potent topical corticosteroids, and safer than alternatives such as systemic corticosteroids and azathioprine [7,8].

References

1 Tsankov N, Broshtilova V, Kazandjieva J. Tetracyclines in dermatology. *Clin Dermatol* 2003; **21**: 33–9.
2 Sapadin AN, Fleischmajer R. Tetracyclines: nonantibiotic properties and their clinical implications. *J Am Acad Dermatol* 2006; **54**: 258–65.
3 Berth-Jones J, Tan SV, Graham-Brown RAC, Pembroke AC. The successful use of minocycline in pyoderma gangrenosum—a report of seven cases and review of the literature. *J Dermatol Treatment* 1989; **1**: 23–5.
4 Chalmers R, Hollis S, Leonardi-Bee J *et al*. Interventions for chronic palmoplantar pustulosis. *Cochr Database System Rev* 2006, Issue 1. Art. No.: CD001433. DOI: 10.1002/14651858.CD001433.pub2.
5 Niren NM. Pharmacologic doses of nicotinamide in the treatment of inflammatory skin conditions: a review. *Cutis* 2006; **77** (Suppl. 1): 11–6.
6 Berk MA, Lorincz AL. The treatment of bullous pemphigoid with tetracycline and niacinamide: a preliminary report. *Arch Dermatol* 1986; **122**: 670–4.
7 Fivenson DP, Breneman DL, Rosen GB *et al*. Nicotinamide and tetracycline therapy of bullous pemphigoid. *Arch Dermatol* 1994; **130**: 753–8.
8 Hornschuh B, Hamm H, Wever S *et al*. Treatment of 16 patients with bullous pemphigoid with oral tetracycline and niacinamide and topical clobetasol. *J Am Acad Dermatol* 1997; **36**: 101–3.
9 Khumalo N, Kirtschig G, Middleton P *et al*. Interventions for bullous pemphigoid. *Cochrane Database Syst Rev* 2005 Jul 20; (3): CD002292.

Thalidomide

Although thalidomide achieved a bad press in the 1960s as a result of its widespread use in pregnant women who subsequently gave birth to children with severe limb deformities, it still retains an important place in the management of selected patients with inflammatory skin disease [1,2]. In view of its potent teratogenicity there are strict controls on its use. Otherwise its main drawback is that it may cause irreversible peripheral neuropathy [1,2].

Thalidomide has been shown to have a range of biological actions, though which is most important for its therapeutic effects is not known. It inhibits lymphocyte and neutrophil chemotaxis and suppresses phagocytosis by neutrophils and macrophages. Perhaps more importantly it also markedly decreases TNF-α and IFN-γ levels [1].

It is licensed for the management of severe erythema nodosum leprosum but may also be useful in a range of inflammatory dermatological conditions including cutaneous lupus erythematosus, nodular prurigo and Behçet disease (Table 74.18).

References

1 Perry AJ, Hsu S. A review of thalidomide's history and current dermatological applications. *Dermatol Online J* 2003; **9**: 5.
2 Wu JJ, Huang DB, Pang KR *et al*. Thalidomide: dermatological indications, mechanisms of action and side-effects. *Br J Dermatol* 2005; **153**: 254–73.

Table 74.18 Thalidomide.

Drug name and indications	Usual dose range	Evidence level	References
Thalidomide			
Erythema nodosum leprosum	100–400 mg/day	A	[1,3]
Cutaneous lupus erythematosus	100–200 mg/day	B	[4,5]
Jessner's lymphocytic infiltration	100 mg daily	B	[6]
Behçet disease in adults	100–300 mg/day	A	[7,8]
Behçet disease in children	1 mg/kg/week to 1 mg/kg/day	D	[9]
Aphthous stomatitis	100–200 mg/day	A	[10,11]
Nodular prurigo	100–300 mg/day	D	[12,13]
Langerhans' cell histiocytosis	100–300 mg/day	E	[14,15]

3 Iyer, CG, Languillon J, Ramanujam K *et al*. WHO co-ordinated short-term double-blind trial with thalidomide in the treatment of acute lepra reactions in male lepromatous patients. *Bull World Health Organ* 1971; **45**: 719–32.
4 Knop J, Bonsmann G, Happle R *et al*. Thalidomide in the treatment of 60 cases of chronic discoid lupus erythematosus. *Br J Dermatol* 1983; **108**: 461–6.
5 Housman TS, Jorizzo JL, McCarty MA *et al*. Low-dose thalidomide therapy for refractory cutaneous lesions of lupus erythematosus. *Arch Dermatol* 2003; **139**: 50–4.
6 Guillaume JC, Moulin G, Dieng MT *et al*. Crossover study of thalidomide vs placebo in Jessner's lymphocytic infiltration of the skin. *Arch Dermatol* 1995; **131**: 1032–5.
7 Hamuryudan V, Mat C, Saip S *et al*. Thalidomide in the treatment of the mucocutaneous lesions of Behçet syndrome: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1998; **128**: 443–50.
8 Hamza MH. Treatment of Behçet's disease with thalidomide. *Clin Rheumatol* 1986; **5**: 365–71.
9 Kari JA, Shah V, Dillon MJ. Behçet's disease in UK children: clinical features and treatment including thalidomide. *Rheumatology* 2001; **40**: 933–8.
10 Revuz J, Guillaume JC, Janier M *et al*. Crossover study of thalidomide vs placebo in severe recurrent aphthous stomatitis. *Arch Dermatol* 1990; **126**: 923–7.
11 Jacobson JM, Greenspan JS, Spritzler J *et al*. Thalidomide for the treatment of oral aphthous ulcers in patients with human immunodeficiency virus infection. *N Eng J Med* 1997; **336**: 1487–93.
12 Winkelmann RK, Connolly SM, Doyle JA, Padilha-Goncalves A. Thalidomide treatment of prurigo nodularis. *Acta Dermatovenereol* 1984; **64**: 412–7.
13 Johnke H, Zachariae H. Thalidomide treatment of prurigo nodularis [in Danish]. *Ugeskr Laeger* 1993; **155**: 3028–30.
14 Thomas L, Ducros B, Secchi T *et al*. Sussessful treatment of adult Langerhans' cell histiocytosis with thalidomide. *Arch Dermatol* 1993; **129**: 1261.
15 McClain KL, Kozinetz CA. A phase II trial using thalidomide for Langerhans cell histiocytosis. *Pediatr Blood Cancer* 2007; **48**: 44–9.

Systemic antiallergic agents including antihistamines and leukotriene antagonists

H_1 antihistamines are inverse agonists of H_1 receptors. When treating skin symptoms, their main action is by decreasing activity of the histamine receptors on the sensory cutaneous nerves and on the endothelial cells of post-capillary venules. They also stabilize mast cell and basophil cell membranes and may thus decrease the release of histamine and other mediators from these cells. The first-generation antihistamines cross the blood–brain barrier and have sedating effects which may be desirable but should be used with care as they interfere with REM sleep and may impair cognitive functioning. They are valuable in alleviating itch in pruritic dermatoses such as eczema and lichen planus. Chlorphenamine given by subcutaneous, intramuscular or slow intravenous injection is used in conjunction with epinephrine and hydrocortisone in the management of acute angio-oedema and/or anaphylaxis.

Table 74.19 Antihistamines and leukotriene antagonists.

Drug Name	Indications	Evidence level	References
Antihistamines			
Non-sedating	**Chronic idiopathic/ordinary (spontaneous) urticaria**	A	[1,2]
Cetirizine		A	
Desloratadine	Angio-oedema	A	[1,2]
Fexofenadine	Dermographism	D	
Levocetirizine	Solar urticaria	E	
Loratadine	Other forms of urticaria	A	
Mizolastine			
Rupatadine	Mastocytosis		[4]
Sedating			
Alimemazine			
Chlorphenamine			
Clemastil	Pruritus, e.g. atopic eczema	C	
Cyproheptadine			
Hydroxyzine			
Promethazine			
Intravenous	**Acute angio-oedema**	A	
Chlorphenamine	**Anaphylaxis**	A	
Leukotriene antagonists			
Montelukast	Aspirin-associated urticaria	D	[5]
	Delayed pressure urticaria	D	[5]
	Cold urticaria	D	[5]
	Symptomatic dermographism	D	[5]

Second-generation H_1 antihistamines are the mainstay of treatment for mast-cell mediated disorders such as urticaria and angio-oedema (Table 74.19). Daily use may be more effective than 'rescue' use [1]. Large doses may be required to achieve adequate control in urticaria; up to four times licensed doses have been advocated for refractory cases in recent European guidelines [2]. Combinations of more than one antihistamine are sometimes used and have recently been reported to be successful in management of solar urticaria [3]. Rupatadine, a non-sedating H_1 antihistamine available in mainland Europe, has been shown to have potent anti-PAF effects *in vitro*, but whether this will prove to be of clinical relevance remains to be determined [4].

Preference of non-sedating (second-generation) antihistamines tends to be based on claims of efficacy, onset of action, duration of action, risk of sedation and inhibition of liver enzymes. The older second-generation antihistamines terfenadine and astemizole occasionally caused dangerous arrhythmias due to interaction with hERG1 potassium channels. The newer H_1 antihistamines are not believed to be cardiotoxic at licensed dosage and are

considered to be very safe drugs. H_2 antihistamines (e.g. cimetidine) have little place in the management of skin disease. Doxepin, a tricyclic antidepressant with both H_1 and H_2 antihistamine action, has been used orally for chronic urticarias and topically for eczema and lichen simplex reactions. Like first-generation antihistamines it may cause unwanted side effects including drowsiness and anticholinergic effects.

There is some evidence that the leukotriene antagonist, montelukast, may be efficacious in the treatment of urticaria when combined with H_1 antihistamines. Studies have suggested they may be more effective in certain subgroups including autoimmune urticaria and patients with aspirin intolerance [5].

References

1 Grob J-J, Auquier P, Dreyfus I, Ortonne J-P. How to prescribe antihistamines for chronic idiopathic urticaria: desloratadine daily vs PRN and quality of life. *Eur J Allergy Clin Immunol* 2009; **64**: 605–12.

2 Zuberbier T, Bindslev-Jensen C, Canonica W *et al*. EAACI/GA2LEN/EDF guideline: management of urticaria. *Eur J Allergy Clin Immunol* 2006; **61**: 321–31.

3 Grundmann SA, Ständer S, Luger TA, Beissert S. Antihistamine combination treatment for solar urticaria. *Br J Dermatol* 2008; **158**: 1384–6.

4 Gimenez-Arnau A, Pujol RM, Ianosi S *et al*. Rupatadine in the treatment of chronic idiopathic urticaria: a double-blind, randomized, placebo-controlled multicentre study. *Eur J Allergy Clin Immunol* 2007; **62**: 539–46.

5 Di Lorenzo G, Pacor ML, Mansueto P *et al*. Is there a role for antileukotrienes in urticaria? *Clin Exp Dermatol* 2006; **31**: 327–34.

Sex hormones and related compounds

Androgens

Testosterone is the most potent androgen and is currently only used for replacement therapy. Although many derivatives of testosterone have been developed with a pronounced anabolic action (the 'anabolic steroids'), they nevertheless retain significant and often troublesome virilizing activity.

Anabolic steroids

Danazol (100–600 mg/day). Danazol is a synthetic steroid derived from ethisterone. It has a high affinity for androgen receptors, and although itself a weak androgen, it has marked antiandrogenic activity. It also inhibits gonadal steroid production and reduces secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) by the pituitary. It increases the hepatic synthesis of a number of proteins including complement C1-esterase inhibitor and antitrypsin [1,2], and is of great value in hereditary angio-oedema because of C1-esterase inhibitor deficiency [3]. It causes enhanced production by the liver of functional C1-esterase inhibitor, but its beneficial effect is probably a result of more complex actions [4]. It can also be used to treat more severely affected patients with cholinergic urticaria who are unresponsive to antihistamines [5], probably because of its ability to enhance hepatic synthesis of antitrypsin, and can be used to inhibit ovulation in autoimmune progesterone dermatitis. Apart from its troublesome virilizing actions, it may cause hepatotoxicity; liver function tests should be carried out before and at monthly intervals during treatment.

Stanozolol (2.5–10 mg/day). Stanozolol is also a potent anabolic steroid with mild virilizing activity. It is just as effective as danazol in hereditary angio-oedema and with similar side effects, but considerably cheaper. Additionally, it has marked fibrinolytic properties, and has been advocated in the management of lipodermatosclerosis [6]. Its side effects are similar to those of danazol.

Antiandrogens

Pregnancy must be avoided during therapy with antiandrogens because of the possible risk of abnormal development of a male fetus. Antiandrogens may be useful in the management of androgen excess causing acne or hirsutism in women [7–10]; combined low-dose pioglitazone, flutamide and metformin has been advocated for androgen excess [11], and spironolactone or finasteride in combination with contraceptives, or flutamide with metformin, for hirsutism [12].

Cyproterone acetate. Cyproterone is a potent antiandrogen that competes with androgens at receptor sites and inhibits gonadotrophin secretion. In low doses (2 mg/day), usually in combination with ethinylestradiol in a reverse sequential regimen, it can be used for treatment of acne in females. It can also be used to treat hirsutism [13] and other signs of virilization in females (at 12.5–50 mg/day in a reverse sequential regimen). Liver toxicity is an occasional problem and the drug is contraindicated in pregnancy.

Spironolactone [10]. Spironolactone blocks androgen receptors, but at low dosage it is less effective than other antiandrogens; higher dosage (100–200 mg/day) is more effective at the cost of several adverse effects (particularly dysfunctional uterine bleeding). The concomitant use of a combined oral contraceptive may prevent these. It may be used in the management of hirsutism or acne [14].

Flutamide. This also blocks androgen receptors, and at 250–500 mg/day for 6 months may be effective at treating hirsutism [15]. Dry skin is very frequent, and hepatotoxicity is possible with high dosage.

Finasteride. Finasteride, a 5α-reductase type 2 inhibitor that blocks conversion of testosterone to dihydrotestosterone in the skin, is the least effective antiandrogen, but a dosage of 5 mg/day may decrease hirsutism without adverse effects. At a dosage of 1 mg/day, the drug produced clinical improvement in up to 66% of men with androgenetic alopecia treated for 2 years [16,17]; sexual function appears to be largely unimpaired [18,19].

Oestrogens

Oestrogens prevent skin ageing [20], and may be useful in the management of autoimmune progesterone dermatitis [21].

Ethinylestradiol (10–35 μg/day). Ethinylestradiol (ethinyl oestradiol) is valuable replacement therapy in the treatment of post-

menopausal symptoms including hot flushes, vaginitis and vaginal atrophy [22]. Plasma levels of FSH and LH, which are elevated in postmenopausal females, are useful guides to dosage. Ethinylestradiol should be avoided in patients with a history of breast cancer, liver or thromboembolic disease.

Antioestrogens

Tamoxifen (20 mg/day). Tamoxifen is an antioestrogenic drug that acts at receptor sites to block oestrogen binding. It therefore inhibits ovulation in fertile women. It may be useful in the treatment of progesterone-induced dermatitis or erythema multiforme [23]. Side effects are those associated with the menopause, together with abnormal vaginal bleeding. Bone density may be affected in the course of long-term treatment.

References

1 Gadek JE, Fulmer JD, Gelfand JA *et al.* Danazol-induced augmentation of serum α-antitrypsin levels in individuals with marked deficiency of this antiprotease. *J Clin Invest* 1980; **66**: 82–7.

2 Gelfand JA, Sherins RJ, Alling DW, Frank MM. Treatment of hereditary angioedema with danazol: reversal of clinical and biochemical abnormalities. *N Engl J Med* 1976; **295**: 1444–8.

3 Nzeako UC, Frigas E, Tremaine WJ. Hereditary angioedema: a broad review for clinicians. *Arch Intern Med* 2001; **161**: 2417–29.

4 Warin AP, Greaves MW, Gatecliff M *et al.* Treatment of hereditary angioedema by low dose attenuated androgens: disassociation of clinical response from levels of C1-esterase inhibitor and C4. *Br J Dermatol* 1980; **103**: 405–9.

5 Wong E, Eftekhari N, Greaves MW, Milford Ward A. Beneficial effects of danazol on symptoms and laboratory changes in cholinergic urticaria. *Br J Dermatol* 1987; **116**: 553–6.

6 Burnand K, Clemenson G, Morland M *et al.* Venous lipodermatosclerosis: treatment by fibrinolytic enhancement and elastic compression. *BMJ* 1980; **280**: 7–11.

7 Thiboutot D, Chen W. Update and future of hormonal therapy in acne. *Dermatology* 2003; **206**: 57–67.

8 Azziz R. The evaluation and management of hirsutism. *Obstet Gynecol* 2003; **101**: 995–1007.

9 Falsetti L, Gambera A, Platto C, Legrenzi L. Management of hirsutism. *Am J Clin Dermatol* 2000; **1**: 89–99.

10 Farquhar C, Lee O, Toomath R, Jepson R. Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne. *Cochrane Database Syst Rev* 2001; **4**: CD000194.

11 Ibáñez L, López-Bermejo A, del Rio L *et al.* Combined low-dose pioglitazone, flutamide, and metformin for women with androgen excess. *J Clin Endocrinol Metab* 2007; **92**: 1710–4.

12 Swiglo BA, Cosma M, Flynn DN *et al.* Clinical review: antiandrogens for the treatment of hirsutism: a systematic review and metaanalyses of randomized controlled trials. *J Clin Endocrinol Metab* 2008; **93**: 1153–60.

13 Van der Spuy ZM, le Roux PA. Cyproterone acetate for hirsutism. *Cochrane Database Syst Rev* 2003; (**4**): CD001125.

14 Farquhar C, Lee O, Toomath R, Jepson R. Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne. *Cochrane Database Syst Rev* 2003; (**4**): CD000194.

15 Calaf J, López E, Millet A *et al.* Long-term efficacy and tolerability of flutamide combined with oral contraception in moderate to severe hirsutism: a 12-month, double-blind, parallel clinical trial. *J Clin Endocrinol Metab* 2007; **92**: 3446–52.

16 Wolff H, Kunte C. Current management of androgenetic alopecia in men. *Eur J Dermatol* 1999; **9**: 606–9.

17 Tosti A, Camacho-Martinez F, Dawber R. Management of androgenetic alopecia. *J Eur Acad Dermatol Venereol* 1999; **12**: 205–14.

18 Tosti A, Pazzaglia M, Soli M *et al.* Evaluation of sexual function with an international index of erectile function in subjects taking finasteride for androgenetic alopecia. *Arch Dermatol* 2004; **140**: 857–8.

19 Stough D, Stenn K, Haber R *et al.* Psychological effect, pathophysiology, and management of androgenetic alopecia in men. *Mayo Clin Proc* 2005; **80**: 1316–22.

20 Shah MG, Maibach HI. Estrogen and skin: an overview. *Am J Clin Dermatol* 2001; **2**: 143–50.

21 Oskay T, Kutluay L, Kaptanoglu A, Karabacak O. Autoimmune progesterone dermatitis. *Eur J Dermatol* 2002; **12**: 589–91.

22 Tzingouris VA, Aksu MF, Greenblatt RB. Estriol in the management of the menopause. *JAMA* 1978; **239**: 1638–41.

23 Wojnarowska F, Greaves MW, Peachey RDG *et al.* Progesterone-induced erythema multiforme. *J R Soc Med* 1985; **78**: 407–8.

Retinoids

Retinoids are molecules capable of binding to and activating retinoic acid receptors, members of the nuclear hormone receptor superfamily. Vitamin A (retinol), its provitamin (β-carotene) and its aldehyde (retinal) and acid (all-*trans*-retinoic acid) forms are all natural retinoids and are involved in a wide variety of essential biological processes, such as vertebrate embryonic morphogenesis and organogenesis, cell growth arrest, cell differentiation, apoptosis and immune regulation. The activity of retinoids is mediated through specific receptors including retinoic acid (RAR) and retinoid X receptors (RXR), all of which belong to the family of steroid–thyroid–vitamin D receptors [1,2].

Effects on cell differentiation. It has been known for many years that vitamin A deficiency results in epithelial squamous metaplasia and that vitamin A supplements reverse this effect. Retinoids have now been shown to induce differentiation in a number of cell types (e.g. mouse teratocarcinoma and human myeloid leukaemia cells), and to cause regression of bronchial metaplasia in heavy smokers [3]. Epidermis undergoes profound changes and shows hypergranulosis and hyperplasia with decreased numbers of tonofilaments and desmosomes and widening of intercellular spaces [4]. The effect on desmosomes appears to contribute to the keratolytic effect of retinoids in hyperkeratotic disorders.

Effects on cancer suppression. Retinoids can prevent epithelial cell tumorigenesis by directing cells to cease proliferating and undergo either differentiation or apoptosis, thus preventing or reversing neoplasia (reviewed in [5] and [6]).

Immunostimulation. In animal models, retinoids may act as an adjuvant and stimulate antibody formation to antigens that were previously not immunogenic [7,8]. In addition, retinoids may stimulate cell-mediated cytotoxicity.

Neutrophil migration. The migration of neutrophils is reduced by retinoids, both in experimental models of inflammation [9,10] and in patients with acne [11].

Skin flora. Retinoids do not seem to have an appreciable direct action on the skin flora.

Ageing and photoageing. The effects of retinoids on the ageing process are complex but their ability to remodel damaged dermal

connective tissue has resulted in their introduction for the topical treatment of photodamaged skin.

References

1 Germain P, Chambon P, Eichele G *et al.* International Union of Pharmacology. LX. Retinoic Acid Receptors. *Pharmacol Rev* 2006; **58**: 712–25.
2 Davidovici BB, Tüzün Y, Wolf R. Retinoid receptors. *Dermatol Clin* 2007; **25**: 525–30.
3 Gouveia J, Mathé G, Hercent T *et al.* Degree of bronchial metaplasia in heavy smokers and its regression after treatment with a retinoid. *Lancet* 1982; **i**: 710–2.
4 Elias PM, Williams ML. Retinoids, cancer, and the skin. *Arch Dermatol* 1981; **117**: 160–80.
5 Fields AL, Soprano DR, Soprano KJ. Retinoids in biological control and cancer. *J Cell Biochem* 2007; **102**: 886–98.
6 Garattini E, Gianni M, Terao M. Retinoids as differentiating agents in oncology: a network of interactions with intracellular pathways as the basis for rational therapeutic combinations. *Curr Pharm Des* 2007; **13**: 1375–400.
7 Dennert G. Immunostimulation by retinoic acid. *Ciba Found Symp* 1985; **113**: 117–31.
8 Sporn MB, Roberts AB, Goodman DS, eds. *The Retinoids*, Vols 1 and 2. Orlando: Academic Press, 1984.
9 Dubertret L, Lebreton C, Touraine R. Inhibition of neutrophil migration by etretinate and its main metabolite. *Br J Dermatol* 1982; **107**: 681–5.
10 Orfanos CE, Bauer R. Evidence for anti-inflammatory activities of oral synthetic retinoids: experimental findings and clinical experience. *Br J Dermatol* 1983; **109** (Suppl. 25): 55–60.
11 Norris DA, Tonnesen MG, Lee LA *et al.* 13-*cis*-retinoic acid has major anti-inflammatory activity *in vivo* [Abstract]. *Clin Res* 1983; **31**: 593.

Isotretinoin (13-*cis*-retinoic acid)

Isotretinoin is an RAR agonist which has found a particular place in the treatment of severe acne. In addition to acne, isotretinoin has been advocated for the treatment of seborrhoea, Gram-negative folliculitis and severe rosacea. It is also an alternative to acitretin for many disorders of keratinization.

Clinical indications (Table 74.20)

Table 74.20 Isotretinoin.

Drug name and indications	Usual dose range	Evidence level	References
Isotretinoin			
Severe acne	0.5–1.0 mg/kg	A	[1,2]
Rosacea	0.5 mg/kg	C	[3]
Seborrhoea	5 mg/day or less	E	[4]
Gram-negative folliculitis	0.5–1.0 mg/kg	D	[6]
Dissecting cellulitis of the scalp	0.75–1.0 mg/kg	E	[7,8]
Transient acantholytic dermatosis (Grover)	40 mg daily reducing to 10 mg daily	E	[9]
Cutaneous sarcoidosis	0.5–1.0 mg/kg	E	[10]

Acne

Oral isotretinoin is licensed in Europe for 'severe forms of acne (such as nodular or conglobate acne or acne at risk of permanent scarring) resistant to adequate courses of standard therapy with systemic antibacterials and topical therapy'. The most effective dose commensurate with side effects is 1 mg/kg bw/day for 4 months [1,2]. It is now usual, however, to commence more cautiously with 0.5 mg/kg bw for the first month and then to increase as tolerated up to 1.0 mg/kg bw for a further 12–16 weeks. Long-term remission and relapse rates are more closely related to the total dose administered than to either duration of treatment or daily dose. It has been shown that no substantial additional benefit is to be expected beyond a cumulative treatment dose of 120–150 mg/kg body weight. This produces prolonged remission in the majority of patients.

In a long-term follow-up study of patients who received a 4-month course of isotretinoin, 85% clinical improvement was observed at the end of treatment and 69% of patients were still free of acne at review up to 10 years (mean 9 years) later. Twenty-three per cent required a second course, the relapse occurring within 3 years in 96% of patients [1]. The need for a second course of isotretinoin is more likely if low-dose regimens are used (0.1 and 0.5 mg/kg) [2]. The major therapeutic effect seems to be a profound reduction in sebaceous gland size and activity. There are reductions in bacterial flora, but it is likely that these changes are secondary to the reduction in sebum secretion. The anti-inflammatory and desquamating effects of retinoids may also have a beneficial role.

Rosacea and seborrhoea

Isotretinoin may be of value for selected patients with rosacea. In an open study of 92 patients given isotretinoin at a dose of 0.5 mg/kg bw/day for 20 weeks, not only papules and pustules but also seborrhoea, rhinophyma, oedema and erythema were claimed to have improved considerably [3]. Severe seborrhoea can itself be a distressing condition. In a small pilot study very low dose isotretinoin (5 mg/day or less) was reported to be effective in controlling seborrhoea with few subjective side effects; mean sebaceous gland size and sebum production were both reduced 50% or more [4].

Gram-negative folliculitis

Isotretinoin is the treatment of choice for Gram-negative folliculitis [5,6].

Dissecting cellulitis of the scalp

Success has been claimed in treating this refractory inflammatory scalp dermatosis with isotretinoin alone [7] and in combination with rifampicin [8].

Disorders of keratinization

A wide range of disorders of keratinization has been found to be responsive to isotretinoin. In Europe, however, this group of disorders is now usually treated with acitretin. In women who may be contemplating future pregnancy, isotretinoin offers the advantage that it is cleared from the body much more quickly than acitretin and thus pregnancy need not be delayed for 2 to 3 years after discontinuing treatment (see below).

References

1 Layton AM, Knaggs H, Taylor J *et al.* Isotretinoin for acne vulgaris: 10 years later—safe and effective treatment. *Br J Dermatol* 1993; **129**: 292–6.

2 Stainforth JM, Layton AM, Taylor JP *et al*. Isotretinoin for the treatment of acne vulgaris: which factors may predict the need for more than one course? *Br J Dermatol* 1993; **129**: 297–301.
3 Hoting E, Paul E, Plewig G. Treatment of rosacea with isotretinoin. *Int J Dermatol* 1986; **25**: 660–3.
4 Geissler SE, Michelsen S, Plewig G. Very low dose isotretinoin is effective in controlling seborrhea. *J Dtsch Dermatol Ges* 2003; **1**: 952–8.
5 James WD, Leyden JJ. Treatment of Gram-negative folliculitis with isotretinoin: positive clinical and microbiologic response. *J Am Acad Dermatol* 1985; **12**: 319–24.
6 Böni R, Nehrhoff B. Treatment of Gram-negative folliculitis in patients with acne. *Am J Clin Dermatol* 2003; **4**: 273–6.
7 Scerri L, Williams HC, Allen BR. Dissecting cellulitis of the scalp: response to isotretinoin. *Br J Dermatol* 1996; **134**: 1105–8.
8 Georgala S, Korfitis C, Ioannidou D *et al*. Dissecting cellulitis of the scalp treated with rifampicin and isotretinoin. *Cutis* 2008; **82**: 195–8.
9 Helfman RJ. Grover's disease treated with isotretinoin: report of four cases. *J Am Acad Dermatol* 1985; **12**: 981–4.
10 Doherty CB, Rosen T. Evidence-based therapy for cutaneous sarcoidosis. *Drugs* 2008; **68**: 1361–83.

Acitretin

The principal uses of acitretin are for psoriasis and for inherited disorders of keratinization. Its activity is very similar to etretinate, which was the first synthetic retinoid to be developed for clinical use and was used for the majority of clinical studies in these disorders [1].

Acitretin, the hydrolysis product and active metabolite of etretinate, is an RAR agonist. Etretinate is 50 times more lipophilic than acitretin and, with an elimination half-life of more than 100 days (cf. 2 days for acitretin), can remain stored in body fat for up to 2 years after discontinuation of treatment. Because of the teratogenicity of retinoids this was a major disadvantage. Acitretin was developed in the hope that female patients would require to delay consideration of pregnancy for only a matter of weeks rather than years after completing a course of treatment. However, it has been shown in some patients that there is reverse metabolism to etretinate (particularly in the presence of alcohol) and therefore it is advised that there should be a gap of at least 2 years (3 years in the US) between the end of a course and pregnancy [2].

Clinical indications (Table 74.21)

Chronic plaque psoriasis

Mucocutaneous side effects limit the dose which is tolerated and indeed there is some evidence to suggest that treatment success in psoriasis at 6 months is as high with low-dose (25 mg daily) as with high-dose (≥50 mg) therapy, presumably because of a lower rate of discontinuation from side effects with the lower dose [3]. As monotherapy it has been shown to be less effective than ciclosporin but in combination with phototherapy, topical corticosteroids or topical vitamin D analogues it retains an important place in the management of chronic plaque psoriasis [1].

Generalized pustular psoriasis

Response to retinoids in generalized pustular psoriasis (von Zumbusch) (GPP) is much more rapid than in chronic plaque psoriasis. It is likely that inhibition of neutrophil migration plays a key role here. In a large retrospective study from Japan retinoid treatment was effective in 84.1% of 385 patients with GPP compared with 76.2% for methotrexate and 71.2% for ciclosporin [4]. Acitretin has been advocated for treating erythrodermic psoriasis but there is little information on how it compares with other options.

Table 74.21 Acitretin.

Drug name and indications	Usual dose range	Evidence level	References
Acitretin			
Severe extensive psoriasis	25–75 mg/day	A	[1,2]
Generalized pustular psoriasis	as above	A	[1,2]
Palmoplantar pustulosis		A	[6]
Acropustulosis of Hallopeau		D	[7]
Pityriasis rubra pilaris		D	[8]
Severe Darier's disease	10–50 mg/day	B	[10]
Severe congenital ichthyosis	as above		[9]
Bullous ichyosiform erythroderma		C	[9]
Non-bullous ichthyosiform erythroderma		C	[9]
Harlequin ichthyosis		E	[9,12]
Lamellar ichthyosis		C	[9]
Erythrokeratoderma variabilis		C	[11]
Lichen planus	30 mg/day	B	[13]
Discoid lupus erythematosus	10–75 mg/day	C	[14,15]
Cancer chemoprophylaxis in patients on long-term immunosuppressive therapy	as above	C	[16,17]
Epidermodysplasia verruciformis	25–75 mg/day	E	[18]
Porokeratosis of Mibelli	as above	E	[19]
Multiple keratoacanthomata		E	[20]
Vulval lichen sclerosus	20–30 mg/day	C	[21]
Subcorneal pustular dermatosis	25–75 mg/day	E	[22]

Psoriatic nail dystrophy

In a prospective open study of 36 patients with psoriatic nail disease, improvements observed after acitretin 0.2–0.3 mg/kg bw/day for 6 months were comparable to those reported in studies of infliximab and adalimumab with complete or almost complete clearing of the nail lesions in a quarter of patients and moderate improvement in a further quarter [5].

Palmoplantar pustulosis and acropustulosis of Hallopeau

Retinoids are amongst the few agents that are beneficial for palmoplantar pustulosis (PPP) though side effects limit their usefulness for long-term management. Response to a combination of psoralen photochemotherapy and oral retinoids is greater than to either intervention alone [6]. Retinoids may be helpful in acropustulosis of Hallopeau [7] and, unpredictably, in pityriasis rubra pilaris [8].

Disorders of keratinization

A variety of disorders of keratinization may respond to retinoids [9]. Although a reduction in keratin thickness can be achieved in palmoplantar keratodermas, the usefulness of retinoids is here limited by side effects, in particular increased tenderness on

walking or performing manual tasks. Acitretin can, however, dramatically ameliorate a number of generalized keratinizing disorders including severe Darier's disease (keratosis follicularis) [10], erythrokeratoderma variabilis [11], lamellar ichthyosis and harlequin ichthyosis [12]. It is also useful for bullous ichthyosiform erythroderma (epidermolytic hyperkeratosis) but may increase the tendency to blistering. The side effects often outweigh the benefits in milder forms of ichthyosis and in limited Darier's disease.

Miscellaneous inflammatory dermatoses

There is evidence of benefit from acitretin for cutaneous [13] and, less convincingly, for erosive oral lichen planus [13]. Both chronic and subacute forms of cutaneous lupus may respond to retinoid therapy. Both acitretin [14] and isotretinoin [15] appear to be beneficial.

Skin cancer chemoprophylaxis

Etretinate and acitretin have been used to reduce the rate of tumour formation in patients at high risk of development of skin cancer including xeroderma pigmentosum, naevoid basal cell carcinoma syndrome and organ transplant recipients requiring long-term immunosuppression [16]. In a retrospective study of organ transplant recipients who had had at least one histologically proven squamous cell carcinoma (SCC), continuous treatment with acitretin 0.2–0.4 mg/kg bw daily significantly reduced the rate of new SCC development for at least the first 3 years and probably for at least 8 years after starting retinoid therapy; when treatment was discontinued the rate of SCC development increased significantly again [17].

References

1 Griffiths CEM, Clark CM, Chalmers RJG *et al*. A systematic review of treatments for severe psoriasis. *Health Technol Assess* 2000; **4**: 25–49.
2 Lee CS, Koo J. A review of acitretin, a systemic retinoid for the treatment of psoriasis. *Expert Opin Pharmacother* 2005; **6**: 1725–34.
3 Pearce DJ, Klinger S, Ziel KK *et al*. Low-dose acitretin is associated with fewer adverse events than high-dose acitretin in the treatment of psoriasis. *Arch Dermatol* 2006; **142**: 1000–4.
4 Ozawa A, Ohkido M, Haruki Y *et al*. Treatments of generalized pustular psoriasis: a multicenter study in Japan. *J Dermatol* 1999; **26**: 141–9.
5 Tosti A, Ricotti C, Romanelli P *et al*. Evaluation of the efficacy of acitretin therapy for nail psoriasis. *Arch Dermatol* 2009; **145**: 269–71.
6 Marsland AM, Chalmers RJG, Hollis S *et al*. Interventions for chronic palmoplantar pustulosis. *Cochrane Database Syst Rev* 2006, Issue 1. Art. No.: CD001433. DOI: 10.1002/14651858.CD001433.pub2.
7 Van Dooren-Greebe RJ, Van De Kerkhof PCM, Chang A, Happle R. Acitretin monotherapy in acrodermatitis continua Hallopeau. *Acta Dermatovenereol* 1989; **69**: 344–6.
8 Clayton BD, Jorizzo JL, Hitchcock MG *et al*. Adult pityriasis rubra pilaris: a 10-year case series. *J Am Acad Dermatol* 1997; **36**: 959–64.
9 Brecher AR, Orlow SJ. Oral retinoid therapy for dermatologic conditions in children and adolescents. *J Am Acad Dermatol* 2003; **49**: 171–82.
10 Burge SM, Wilkinson JD. Darier-White disease: a review of the clinical features in 163 patients. *J Am Acad Dermatol* 1992; **27**: 40–50.
11 Common JEA, O'Toole EA, Leigh IM *et al*. Clinical and genetic heterogeneity of erythrokeratoderma variabilis. *J Invest Dermatol* 2005; **125**: 920–7.
12 Lawlor F, Peiris S. Harlequin fetus successfully treated with etretinate. *Br J Dermatol* 1985; **112**: 585–90.
13 Cribier B, Frances C, Chosidow O. Treatment of lichen planus: an evidence-based medicine analysis of efficacy. *Arch Dermatol* 1998; **134**: 1521–30.
14 Ruzicka T, Meurer M, Bieber T. Efficiency of acitretin in the treatment of cutaneous lupus erythematosus. *Arch Dermatol* 1988; **124**: 897–902.
15 Vena GA, Coviello C, Angelini G. Use of oral isotretinoin in the treatment of cutaneous lupus erythematosus. *G Ital Dermatol Venereol* 1989; **124**: 311–5.
16 Campbell RM, DiGiovanna JJ. Skin cancer chemoprevention with systemic retinoids: an adjunct in the management of selected high-risk patients. *Dermatol Ther* 2006; **19**: 306–14.
17 Harward CA, Leedham-Green M, Leigh I, Proby CM. Low-dose retinoids in the prevention of cutaneous squamous cell carcinomas in organ transplant recipients: a 16-year retrospective study. *Arch Dermatol* 2005; **141**: 456–64.
18 Anadolu R, Oskay T, Erden C *et al*. Treatment of epidermodysplasia verruciformis with a combination of acitretin and interferon alfa-2a. *J Am Acad Dermatol* 2001; **45**: 296–9.
19 Hacham-Zadeh S, Holubar K. Etretinate in the treatment of disseminated porokeratosis of Mibelli. *Int J Dermatol* 1985; **24**: 258–60.
20 Aydin F, Senturk N, Sabanciler E *et al*. A case of Ferguson-Smith type multiple keratoacanthomas associated with keratoacanthoma centrifugum marginatum: response to oral acitretin. *Clin Exp Dermatol* 2007; **32**: 683–6.
21 Bousema MT, Romppanen U, Geiger JM *et al*. Acitretin in the treatment of severe lichen sclerosus et atrophicus of the vulva: a double-blind, placebo-controlled study. *J Am Acad Dermatol* 1994; **30**: 225–31.
22 Marlière V, Beylot-Barry M, Beylot C, Doutre M-S. Successful treatment of subcorneal pustular dermatosis (Sneddon-Wilkinson disease) by acitretin: report of a case. *Dermatology* 1999; **199**: 153–5.

Alitretinoin (9-cis-retinoic acid)

This retinoid, unlike isotretinoin and acitretin, acts on both RAR and RXR receptors.

Clinical indications

Chronic hand eczema

Alitretinoin has been studied in recalcitrant severe chronic hand eczema unresponsive to potent topical corticosteroids (Table 74.22). Nearly half (48%) of 409 patients who received 30 mg/day for 6 months were clear or almost clear at 6 months compared with 17% of 205 who received placebo [1].

Reference

1 Ruzicka T, Lynde CW, Jemec GB *et al*. Efficacy and safety of oral alitretinoin (9-cis retinoic acid) in patients with severe chronic hand eczema refractory to topical corticosteroids: results of a randomized, double-blind, placebo-controlled, multicentre trial. *Br J Dermatol* 2008; **158**: 808–17.

Bexarotene

A number of studies carried out in the 1980s showed some beneficial effect of RAR retinoids including etretinate and isotretinoin in cutaneous T-cell lymphoma (CTCL). Small numbers of treated patients and a lack of standardization in assessing response have

Table 74.22 Alitretinoin.

Drug name and indications	Usual dose range	Evidence level	References
Alitretinoin			
Severe chronic hand eczema	30 mg daily	A	[1]

Table 74.23 Bexarotene.

Drug name and indications	Usual dose range	Evidence level	References
Bexarotene			
Refractory advanced CTCL	300 mg/m² daily	B	[1]

CTCL, cutaneous T-cell lymphoma

made it difficult to draw firm conclusions from these. Acitretin plus PUVA has, however, been shown to be inferior to interferon-α plus PUVA in achieving complete remission in early stage CTCL. More recent research has focused on producing receptor-specific retinoids with greater antitumour activity. Bexarotene is an RXR-selective retinoid (rexinoid) which is licensed for the treatment of advanced CTCL. It has been shown to induce apoptosis in T-cell lines from patients with CTCL. The main side effects are hypertriglyceridaemia (79%) and central hypothyroidism (reviewed in [1]).

Clinical indications

Cutaneous T-cell lymphoma

Bexarotene is licensed for 'treatment of the skin manifestations of advanced stage cutaneous T-cell lymphoma refractory to at least one systemic treatment' (Table 74.23). In a study of 94 such patients approximately half showed at least a partial response to bexarotene monotherapy though this took a median time of 6 months to achieve [2]. Although there is some evidence to suggest benefit from combination therapies with PUVA or interferon, their value cannot be assessed until the results of controlled trials are known [1].

References

1 Gniadecki R, Assaf C, Bagot M *et al.* The optimal use of bexarotene in cutaneous T-cell lymphoma. *Br J Dermatol* 2007; **157**: 433–40.

2 Duvic M, Hymes K, Heald P *et al.* Bexarotene is effective and safe for treatment of refractory, advanced-stage cutaneous T-cell lymphoma: multinational phase II–III trial results. *J Clin Oncol* 2001; **19**: 2456–71.

Retinoic acid metabolism blocking agents

Retinoic acid metabolism blocking agents (RAMBAs), though structurally unrelated to retinoids, have similar clinical actions in that they inhibit the intracellular catabolism of all-*trans*-retinoic acid, resulting in its intracellular accumulation. Two RAMBAs have been investigated in dermatology, liarozole and talarozole (Table 74.24) [1]. Both drugs are rapidly eliminated upon withdrawal, with reversal of increased retinoic acid levels to normal within 24 h. They thus have theoretical advantages over retinoids such as acitretin in that their teratogenic risk can be reversed much more rapidly than is the case with acitretin. They have shown promise in psoriasis [1], palmoplantar pustulosis [2] and a variety of ichthyoses [3] though their risks and benefits have yet to be adequately evaluated. Liarozole has been given orphan drug status for treatment of ichthyosis both in Europe and in the United States [1].

Table 74.24 Liarozole.

Drug name and indications	Usual dose range	Evidence level	References
Liarozole			
Chronic plaque psoriasis	75–150 mg/day	B	[1]
Palmoplantar pustulosis	150 mg/day	D	[2]
Congenital ichthyosis	150 mg/day	B	[3]

References

1 Verfaille CJ, Borgers M, van Steensel MAM. Retinoic acid metabolism blocking agents (RAMBAs): a new paradigm in the treatment of hyperkeratotic disorders. *J Dtsch Dermatol Ges* 2008; **6**: 355–64.

2 Bhushan M, Burden AD, McElhone K *et al.* Oral liarozole in the treatment of palmoplantar pustular psoriasis: a randomized, double-blind, placebo-controlled study. *Br J Dermatol* 2001; **145**: 546–53.

3 Verfaille CJ, Vanhoutte FP, Blanchet-Bardon C *et al.* Oral liarozole vs. acitretin in the treatment of ichthyosis: a phase II/III multicentre, double-blind, randomized, active-controlled study. *Br J Dermatol* 2007; **156**: 965–73.

Safety precautions and side effects of retinoids

A number of side effects are common to all the retinoids. These appear to be dose related and are largely cutaneous. They include cheilitis, conjunctivitis, epistaxis, dryness of mucous membranes, xerosis and skin peeling, palmoplantar desquamation, pruritus, alopecia, myalgia, arthralgia and lethargy [1]. Patients receiving synthetic retinoids should be advised to avoid supplementary therapy with vitamin A. Intracranial hypertension may occur and is a reason not to combine isotretinoin with tetracyclines. There is reasonable circumstantial evidence that some patients may experience mood change including depression, aggressiveness and suicidal ideation whilst receiving isotretinoin [2,3]. Indeed it is the only non-psychotropic drug in the FDA's top 10 list of drugs reported to be associated with depression. Nevertheless, this problem appears to be rare and a causal relationship has not as yet been conclusively demonstrated [3,4].

Patients may develop abnormal liver enzyme levels during therapy with retinoids; not all values have returned to normal on cessation of the drug [3,4]. Retinoids may increase the hepatotoxicity of methotrexate.

Increase in very-low-density lipoprotein (VLDL) cholesterol and reduction in high-density lipoprotein (HDL) cholesterol have been reported with retinoid therapy. Many patients receiving isotretinoin have been reported with elevated serum VLDL triglyceride in the absence of a preceding hyperlipoproteinaemia. These levels have returned to normal on cessation of treatment, but all patients should be screened for hyperlipoproteinaemia prior to treatment with any retinoid. The effect on lipids is greatest with bexarotene; 80% of patients develop hyperlipidaemia [5].

An ossification disorder resembling idiopathic skeletal hyperostosis has been reported in patients receiving long-term retinoids. These drugs should only be given to younger children when there are sound indications [1,6,7].

Teratogenicity. Retinoids are known to be teratogenic. Maternal ingestion of retinoids early in pregnancy can lead to severe fetal abnormalities [6,8–10]. It is important that women are not pregnant prior to starting treatment. Effective contraception is mandatory during and after a course of treatment; 'pregnancy prevention programmes' have been introduced in many countries for women receiving isotretinoin for acne. Isotretinoin has a short half-life and therefore contraceptive measures need to be taken for only 1 month after cessation of treatment. Because of the small risk of esterification of acitretin to etretinate (which has a very long half-life) it is recommended that attempts to conceive should be delayed for at least 2 years (3 years in US) after cessation of acitretin therapy. Males can safely father children even when they are taking the drug.

References

1 Gollnick H, Cunliffe W, Berson D *et al*. Management of acne: a report from a global alliance to improve outcomes in acne. *J Am Acad Dermatol* 2003; **49**: S1–S38.
2 Jick SS, Kremers HM, Vasilakis-Scaramozza C. Isotretinoin use and risk of depression, psychotic symptoms, suicide, and attempted suicide. *Arch Dermatol* 2000; **136**: 1231–6.
3 Kontaxakis VP, Skourides D, Ferentinos P *et al*. Isotretinoin and psychopathology: a review. *Ann Gen Psych* 2009; **8**: 2–9.
4 Marqueling AL, Zane LT. Depression and suicidal behavior in acne patients treated with isotretinoin: a systematic review. *Semin Cutan Med Surg* 2005; **24**: 92–102.
5 Gniadecki R, Assaf C, Bagot M *et al.* The optimal use of bexarotene in cutaneous T-cell lymphoma. *Br J Dermatol* 2007; **157**: 433–40.
6 Katz HI, Waalen J, Leach EE. Acitretin in psoriasis: an overview of adverse effects. *J Am Acad Dermatol* 1999; **41**: S7–S12.
7 Carey BM, Parker GJS, Cunliffe WJ *et al.* Skeletal toxicity with isotretinoin therapy; a clinico-radiological evaluation. *Br J Dermatol* 1988; **119**: 609–14.
8 Rosa FW. Teratogenicity of isotretinoin. *Lancet* 1983; **ii** (8348): 513.
9 Benke EP. The isotretinoin teratogen syndrome. *JAMA* 1984; **251**: 3267–9.
10 de la Cruz E, Sun S, Van Guanichyakorn K *et al.* Multiple congenital malformations associated with maternal isotretinoin therapy. *Pediatrics* 1984; **74**: 428–30.

Antimicrobial and antiparasitic agents

Antibiotics and antibacterial agents

Antibiotics were originally substances synthesized by microorganisms that were toxic to other microorganisms at high dilution. The term is now more widely applied to any drug with therapeutic activity against living organisms, particularly bacteria. Antifungals and antivirals are drugs with activity against fungi and viruses, respectively.

Most modern antibiotics are synthetic or semi-synthetic. They are usually divided into bacteriostatic and bactericidal groups, although the distinction is not complete; erythromycin, for example, may be either bactericidal or bacteriostatic depending on the nature of the infecting organism and the drug concentration achieved.

In clinical use, antibiotics are divided into those with a narrow spectrum of activity and those broad-spectrum drugs that act against Gram-positive and Gram-negative organisms. In the laboratory, antibiotics can be further divided into five main groups:

1 Antibiotics that interfere with bacterial cell wall synthesis (e.g. the penicillins, cephalosporins and glycopeptide antimicrobials such as vancomycin and teicoplanin)
2 Antibiotics affecting bacterial cell-membrane permeability (e.g. the polymyxins)
3 Antibiotics that inhibit bacterial protein biosynthesis (e.g. the tetracyclines, aminoglycosides, macrolides, lincosamides and chloramphenicol)
4 Antibiotics that affect bacterial nucleic acid metabolism (e.g. the rifamycins and quinolones)
5 *Para*-aminobenzoic acid (PABA) antagonists (e.g. the sulphonamides).

Drug resistance

Bacterial resistance can emerge in three ways. When all sensitive bacteria have been eradicated, any remaining inherently resistant bacteria are free to multiply; this is the most common form of resistance. Less frequently, bacteria may acquire resistance, by mutation, to a drug to which they were initially sensitive. The third form, which is cause for concern, is transferable drug resistance. Here, genetic information affecting the expression of resistance contained in a plasmid or a transposable section of chromosomal DNA can be transferred from one bacterium to another different, but previously susceptible, bacterium. This often takes place in the bowel or skin and may involve a variety of different organisms. Multiple drug resistance can be transferred with a single plasmid.

The mechanisms of drug resistance are variable and include changes in permeability of the cell membrane or antibiotic efflux, alterations in ribosomes, altered cell-wall precursors or target enzymes and the emergence of auxotrophs that have different growth substrates.

Sulphonamides

These antibacterial drugs were introduced into clinical practice in the 1930s, but the frequency of resistance combined with adverse events have limited their use. The combination of a sulphonamide (sulfamethoxazole) with trimethoprim, known as co-trimoxazole, however, is still used in dermatology although less frequently than previously. Resistance is widespread.

Sulphonamides are derivatives of *para*-amino-benzenesulphonamide. They act by inhibiting the bacterial enzyme dihydrofolic acid synthetase, which converts PABA to dihydrofolic acid. Mammalian cells and resistant bacteria do not synthesize folic acid and are unaffected.

Sulphonamides are bacteriostatic and most are well absorbed orally. They are distributed through all body tissues, metabolized in the liver and excreted mainly by the kidneys.

Adverse effects. Although the frequency of serious adverse events is low, sulphonamides can cause a number of serious problems. Besides crystalluria, a risk if there is inadequate fluid intake, they may rarely cause blood dyscrasias such as acute haemolytic anaemia (particularly in patients with glucose-6-phosphate dehydrogenase deficiency), fever, serum sickness and a large variety of skin reactions including erythema nodosum and erythema multiforme. Potentially fatal cases of erythema multiforme major and

toxic epidermal necrolysis have followed the use of sulphonamides [1].

Uses. There are now very few situations where they are drugs of first choice. They have been used in lymphogranuloma venereum, chancroid, nocardiosis and toxoplasmosis (combined with pyrimethamine). Sulfapyridine is now used only as an alternative to dapsone in dermatitis herpetiformis and allied conditions.

Sulfapyridine

Dose: 0.5–1.5 g/day as an alternative to dapsone in dermatitis herpetiformis.

Silver sulfadiazine

This has a role as a topical non-absorbable topical antimicrobial with a broad spectrum.

Reference

1 Wolkenstein P, Charue D, Laurent P *et al*. Metabolic predisposition to cutaneous adverse drug reactions. Role in toxic epidermal necrolysios caused by sulphonamides and anticonvulsants. *Arch Dermatol* 1995; **131**: 544–51.

Trimethoprim [1]

Trimethoprim is a synthetic antimicrobial agent in its own right. It is a potent inhibitor of bacterial dihydrofolic acid reductase, which converts dihydrofolic acid to tetra-hydrofolic acid, but has many thousand times less effect on the comparable mammalian enzyme. Trimethoprim is very well absorbed orally, distributed widely through most body tissues and is excreted almost completely by the kidney. Although available as a separate drug, it is often used in combination with sulfamethoxazole in the proportions 1 to 5 as co-trimoxazole. This is a logical mix as these drugs inhibit successive stages in bacterial folate metabolism and it is not surprising that their combined effect is synergistic. Both drugs used singly are bacteriostatic but co-trimoxazole appears to be bactericidal.

Co-trimoxazole tablets BP

There are two strengths containing sulfamethoxazole 400 or 800 mg and trimethoprim 80 or 160 mg, respectively. The dose is two tablets twice daily. The combination is effective against a wide range of Gram-positive and Gram-negative bacteria as well as *Nocardia* and actinomycetoma agents and *Pneumocystis* and is in general well tolerated. However, it is best avoided in pregnancy and in infants under 6 weeks and therefore in lactating mothers feeding young babies. Adverse reactions are similar to those seen with sulphonamides. Typical skin reactions may occur in up to 8% of patients and this has limited its use for relatively benign conditions such as acne. Impairment of red cell folate utilization may occur, particularly in the elderly, and supplements of folinic acid may be necessary [1]. Rarer side effects include renal impairment and hepatic reactions.

Co-trimoxazole may be used for urinary tract and respiratory infections but, in infections affecting the skin, is of value in chancroid, *Mycobacterium marinum* infections [2] and mycetoma. Co-trimoxazole is also used in the treatment of *Pneumocystis* infections, particularly in AIDS patients in whom, unfortunately, there is a high frequency of adverse reactions. Resistance rates in some settings may exceed 10% [3].

References

1 Kucers A, Crowe SM, Grayson ML, Hoy JF. *The Use of Antibiotics*, 5th edn. Oxford: Butterworth Heinemann, 1997.
2 Barrow GI, Hewitt M. Skin infection with *Mycobacterium marinum* from a tropical fish tank. *BMJ* 1971; **ii**: 505–6.
3 Gupta K, Hooton TM, Stamm WE. Increasing antimicrobial resistance and the management of uncomplicated community acquired urinary tract infections. *Ann Intern Med* 2001; **135**: 1165–9.

Penicillins

The basic structure of a penicillin consists of a thiazolidine ring, a β-lactam ring and a variable side-chain. The starting point for the semi-synthetic penicillins, of which there are now many, is 6-aminopenicillamic acid. It is convenient to divide the penicillins into five main groups according to their antibacterial properties and consequent clinical usage [1]:

1 Penicillinase-sensitive penicillins (natural penicillins; e.g. benzyl penicillin, penicillin G; and phenoxymethyl penicillin; penicillin V)
2 Penicillinase-resistant penicillins (e.g. methicillin, flucloxacillin)
3 Amino penicillins, which are broad-spectrum penicillins (vulnerable to penicillinase) (e.g. ampicillin, amoxicillin); by combining clavulanic acid, a potent β-lactamase inhibitor, with amoxicillin (Augmentin®), the spectrum of activity has been broadened to cover penicillin-resistant staphylococci
4 Carboxy penicillins (e.g. carbenicillin)
5 Other penicillins, which include extended-spectrum penicillins (e.g. piperacillin), aminopenicillins and penicillins that are stable against Gram-negative lactamases (e.g. temocillin).

Toxicity. The main problems with their use are hypersensitivity reactions, which are not uncommon. An incidence between 1 and 10% is usually accepted [2], and it appears that administration of these drugs by the oral route is associated with a lower frequency of adverse reactions than the intravenous route [3]. These reactions range from urticaria and vasculitis to anaphylaxis. Cross-reactivity in this allergy is usual. Rare side effects include interstitial nephritis, haemolytic anaemia and pancytopenia.

Penicillinase-sensitive penicillins (penicillin)

Penicillin is the drug of choice against *Streptococcus pyogenes* group A, *Treponema pallidum* and meningococcal septicaemia as well as in yaws, actinomycosis and diphtheria. Because of the emergence of resistant strains of the organism, its use in the treatment of gonorrhoea has largely been superseded. In most serious infections, penicillin is given by injection as benzyl penicillin but treatment may be continued with oral penicillin V and this drug also has a role in prophylaxis against streptococcal cellulitis in patients with lymphoedema.

Benzyl penicillin injection BP (penicillin G). Dose: 300 mg (0.5 mega-units) four times daily up to 1.8 g (3 mega-units) daily. Long-acting, injectable preparations are available.

Phenoxymethyl penicillin (penicillin V). Dose: 250–500 mg orally every 6 h.

Penicillinase-resistant penicillins

These are intended for use against methicillin-sensitive organism, but for practical purposes in dermatology this means cloxacillin or flucloxacillin, which are resistant to staphylococcal β-lactamase and are drugs of choice against penicillin-resistant staphylococci [4]. Flucloxacillin is somewhat less effective against other Gram-positive infections. Adequate levels are achieved by the oral route but parenteral administration is preferred in serious infections.

Flucloxacillin. Dose: 250–500 mg every 6 h and at least 30 min before food.

Amino penicillins

Ampicillin is commonly used, having a spectrum of activity against Gram-positive and Gram-negative bacteria. It is acid stable and therefore absorbed orally, but is not resistant to penicillinase. It is little used in dermatology but is important as a cause of cutaneous adverse drug reactions. These occur in about 5–10% of all patients treated but in a majority of those with infectious mononucleosis, cytomegalovirus infections or lymphatic leukaemia [2]. The typical morbilliform rash is thought to be toxic in nature and unrelated to true penicillin hypersensitivity. Amoxicillin is almost identical, is twice as well absorbed as ampicillin but is more expensive. It should probably only replace ampicillin in the patient known to be susceptible to antibiotic-induced diarrhoea [5]. Where an even broader spectrum is needed, perhaps in the treatment of heavily infected leg ulcers with surrounding cellulitis, amoxicillin with clavulanic acid (Augmentin) is worth consideration [6,7]. However, its role in dermatology is a limited one.

Ampicillin. Dose: 250 mg to 1 g every 6 h and at least 30 min before a meal.

Amoxicillin capsules. Dose: 250–500 mg every 8 h.

Amoxicillin 250 mg and clavulanic acid (Augmentin) tablets. Dose: 1–2 tablets every 8 h.

Other penicillins

Carbenicillin, piperacillin, ticarcillin and azlocillin must all be given by injection or infusion and have little place in dermatology.

Methicillin resistance

Penicillinase-producing bacteria such as *Staph. aureus* were originally susceptible to methicillin and analogues such as cloxacillin or flucloxacillin. However, increasingly, strains of *Staph. aureus*, initially from hospital [8] but more recently from community sources, are methicillin resistant [9]. In the case of hospital-acquired methicillin resistant *Staph. aureus* (HA-MRSA) strains also usually show multiple drug resistance. Community-acquired methicillin resistant *Staph. aureus* strains may only show resistance to methicillin and the penicillins [9]. The spread of both forms of MRSA is a worrying trend as it is endemic in many hospitals and as a result standard and specific antibiotic regimens are ineffective. Control of spread of these strains both as pathogens or as skin or mucosal commensals is difficult but much can be achieved by rigorous application of simple anticross-infection measures including correct hand washing procedures, attention to ward hygiene and cleanliness, surveillance and the implementation of well designed antibiotic use policies. Dermatologists are involved in all aspects of this development as many patients with skin disease are densely colonized with *Staph. aureus*. In addition, community-acquired methicillin-resistant strains are particularly associated with skin or soft tissue infection and therefore may present in patients with skin or subcutaneous lesions such as abscesses. Community-acquired MRSA (CA-MRSA) is also associated with a higher morbidity including death which is largely due to the fact that these organisms usually express a virulence determinant called the Pontin Valentin leucocidin. Transmission of this gene can occur between different strains of *Staph. aureus* which thereby acquire enhanced virulence. Outbreaks with CA-MRSA are being reported with increasing frequency.

Imipenem

Imipenem is a carbapenem, a bi-cyclic β-lactam compound with a broad spectrum [10]. It shows considerable activity against many Gram-positive bacteria, as well as *Neisseria* spp. and is also used in *Nocardia* infections. Imipenem is seldom used in dermatology and is given intravenously.

References

1 Sutherland R. B Lactams: penicillins. In: O'Grady F, Lambert H, Finch RG *et al.*, eds. *Antibiotics and Chemotherapy*, 7th edn. Edinburgh: Churchill Livingstone, 1997: 256–305.

2 Beeley L. Allergy to penicillin. *BMJ* 1984; **228**: 511–2.

3 Saxon A. Immediate hypersensitivity reactions to β-lactam antibiotics. *Rev Infect Dis* 1983; **5** (Suppl. 2): 368–73.

4 Neu HC. Antistaphylococcal penicillins. *Med Clin North Am* 1982; **66**: 51–66.

5 Malik ZA, Litman N. Ampicillin and amoxicillin. *Pediatr Rev* 2006; **27**: 434–6.

6 Anonymous. Augmentin—nice idea, but more trials please. *Drug Ther Bull* 1982; **20**: 21–4.

7 Sader HS, Jacobs MR, Fritsche TR. Review of the spectrum and potency of orally administered cephalosporins and amoxicillin/clavulanate. *Diagn Microbiol Infect Dis*. 2007; **57** (3 Suppl.): 5S–12S.

8 Martins A, Cunha M de L. Methicillin resistance in *Staphylococcus aureus* and coagulase-negative staphylococci: epidemiological and molecular aspects. *Microbiol Immunol* 2007; **51**: 787–95.

9 Tristan A, Bes M, Meugnier H *et al*. Global distribution of Panton-Valentine leukocidin–positive methicillin-resistant *Staphylococcus aureus*, 2006. *Emerg Infect Dis* 2007; **13**: 594–600.

10 Zhanel GG, Wiebe R, Dilay L *et al*. Comparative review of the carbapenems. *Drugs* 2007; **67**: 1027–52.

Cephalosporins [1–3]

The cephalosporins are derivatives of 7-amino-cephalosporamic acid and are similar in structure and properties to the penicillins containing a β-lactam ring. They are bactericidal, acting on peptidoglycans in bacterial cell walls, and have wide spectra of activity encompassing Gram-negative organisms and staphylococci. Penicillin-resistant staphylococci are generally susceptible but the degree of effectiveness varies between cephalosporins. Many

cephalosporins are given parenterally but some orally effective ones are available (e.g. cefalexin, cefaclor). They are excreted by the kidney but unlike penicillin may cause tubular damage. Their main role is perhaps as an alternative therapy in penicillin hypersensitivity, but this is not without risk as some 8–10% of all penicillin-allergic patients react to cephalosporins [3]. Apart from this they have little dermatological use but may be given in *Neisseria* infections and in unusual infections such as those caused by *Pasteurella multocida* following animal bites.

References

1 Sader HS, Jacobs MR, Fritsche TR. Review of the spectrum and potency of orally administered cephalosporins and amoxicillin/clavulanate. *Diagn Microbiol Infect Dis* 2007; **57** (3 Suppl.): 5S–12S.

2 Hedrick J. Cephalosporins for uncomplicated skin and skin structure infections in emerging community-acquired MRSA. *Expert Opin Pharmacother* 2006; **7**: 2019–24.

3 Antúnez C, Martín E, Cornejo-García JA *et al*. Immediate hypersensitivity reactions to penicillins and other betalactams. *Curr Pharm Des* 2006; **12**: 3327–33.

Quinolones [1,2]

The chief quinolone antibiotics are more correctly classified as fluoroquinolones or 4-quinolones. Their mode of action is via inhibition of DNA synthesis and spectrum of activity is broad, generally including both Gram-positive and Gram-negative bacteria. The principal quinolone in wide use is ciprofloxacin; others include norfloxacin and ofloxacin. This can be given orally in doses of 750 mg twice daily for soft-tissue infections [3]. Ciprofloxacin is active *in vitro* against a wide range of bacteria from *Escherichia coli* to *Bacillus anthracis* and *Yersinia enterocolitica*. It is also active against staphylococci and streptococci as well as *Mycobacterium tuberculosis*, although atypical mycobacteria are generally less sensitive. In dermatology, ciprofloxacin is best reserved for severe infections such as those occurring in the immunocompromised patient, but other indications include Gram-negative folliculitis, rhinoscleroma and cutaneous anthrax. It is an alternative treatment for chancroid and genital chlamydial infections.

References

1 Andriole VT. The quinolones: past, present, and future. *Clin Infect Dis* 2005; **41** Suppl 2: S113–9

2 Wispelwey B. Clinical implications of pharmacokinetics and pharmacodynamics of fluoroquinolones. *Clin Infect Dis* 2005; **41** (Suppl. 2): S127–35.

3 Gentry LO. Review of quinolones in treatment of infections of the skin and skin structure. *J Antimicro Chemother* 1991; **28** (Suppl. C): 97–110.

Tetracyclines

These are orally effective broad-spectrum antibiotics with relatively low toxicity [1]. The original three tetracyclines were chlortetracycline, oxytetracycline and tetracycline. Later derivatives include demethylchlortetracycline, methacycline, doxycycline and minocycline (the last three being synthetic). They act by inhibition of protein synthesis through ribosomal binding. With the exception of minocycline they all have similar spectra of activity; differing, however, in their absorption, distribution and excretion.

Both streptococci and staphylococci may be resistant to tetracyclines, although the incidence of staphylococcal resistance is less than previously and some such strains are sensitive to minocycline [1]. However, as much more effective agents are available for these organisms, the tetracyclines are generally not used in these infections.

The tetracyclines are bacteriostatic against many Gram-positive and Gram-negative bacteria and are also active against rickettsiae, *Mycoplasma*, *Chlamydia*, which cause lymphogranuloma venerum, psittacosis and trachoma, as well as amoebae.

Absorption of some tetracyclines is impaired by simultaneously taking milk, aluminium, calcium or magnesium salts or iron preparations, because of chelation. However, food does not interfere with the absorption of doxycycline or minocycline. All tetracyclines are concentrated in the liver and excreted into the bile, whence they enter an enterohepatic circulation. Urinary excretion is significant and renal failure may be exacerbated by all except doxycycline [2].

Side effects [3–5]. A variety of tetracycline related rashes has been described (see Chapter 78), including phototoxicity, especially shown by demethylchlortetracycline and analogues [6]. Glossitis, cheilitis and persistent pruritus ani may occur. Gastrointestinal disturbances are dose dependent [7] and are much more common with doses of 2 g/day or more, which are rarely used in dermatology. Nausea and vomiting are direct irritant effects; diarrhoea may be the result of superinfection, resistant staphylococci being especially dangerous. Minocycline can cause vertigo and hyperpigmentation. The latter is usually slate-grey and can affect the skin, nails and sclerae [8]. Tetracyclines are deposited in growing teeth and bones [9] and their use should be avoided in pregnancy, during lactation and in childhood. Rarely, there may be diffuse fatty degeneration of the liver. An uncommon dermatological problem is the development of Gram-negative folliculitis after tetracycline therapy of acne [10,11].

Dermatological uses. Apart from the infections mentioned above, tetracyclines are rarely drugs of choice. The exception, of course, is the treatment of acne vulgaris (see Chapter 42) [12,13] and rosacea (see Chapter 43).

Tetracycline, chlortetracycline, oxytetracycline

Dose: daily doses range from 500 mg (for acne) up to 3 g.

Doxycycline, minocycline

Dose: 100–200 mg/day. Doxycycline is the ordinary tetracycline of choice in patients with renal impairment. It is used in acne although not as a first-line treatment [13] (50 mg twice daily). Preparations are also available as syrups, and injections for intramuscular, intravenous or intralesional use. Tetracycline resistance has been reported in *Propionibacterium acnes* and caution should be exercised over the use of repeated courses of these antibiotics. Resistance may also be passed to other bacteria [14].

References

1 Roberts MC. Tetracycline therapy. Update. *Clin Infect Dis* 2003; **36**: 462–7

2 Ribush N, Morgan T. Tetracyclines and renal failure. *Med J Aust* 1972; **i**: 53–5.

3 Ad Hoc Committee Report. Systemic antibiotics for treatment of acne vulgaris. *Arch Dermatol* 1975; **111**: 1630–6.

4 Clendenning WE. Complications of tetracycline therapy. *Arch Dermatol* 1965; **91**: 628–32.
5 Kunin CM. The tetracyclines. *Pediatr Clin North Am* 1968; **15**: 43–55.
6 Falk MS. Light sensitivity due to demethylchlortetracycline: report of four cases. *JAMA* 1960; **172**: 1156–7.
7 Alestig K. Tetracyclines and chloramphenicol. In: Cohen J, Powderly WG, eds. *Infectious Diseases*. London: Mosby, 2004: 1843–7.
8 Angeloni VL, Salasche SJ, Ortiz R. Nail, skin and scleral pigmentation induced by minocycline. *Cutis* 1987; **40**: 229–33.
9 Macaulay JC, Leistyna JA. Preliminary observations on the prenatal administration of demethylchlortetracycline. *Pediatrics* 1964; **34**: 423–4.
10 Fulton JE, McGinley K, Leyden J *et al*. Gram-negative folliculitis in acne vulgaris. *Arch Dermatol* 1968; **98**: 349–53.
11 Leyden JL, Marples RR, Mills OH *et al*. Gram-negative folliculitis: complication of antibiotic therapy in acne vulgaris. *Br J Dermatol* 1973; **88**: 533–8.
12 Fry L, Ramsay CA. Tetracycline in acne vulgaris: clinical evaluation and sebum production. *Br J Dermatol* 1966; **78**: 653–60.
13 Garner SE, Eady EA, Popescu C *et al*. Minocycline for acne vulgaris: efficacy and safety. *Cochrane Database Syst Rev* 2003; CD002086
14 Moller JM, Leth Bak A, Stenderup A *et al*. Changing patterns of plasmid-mediated drug resistance during tetracycline therapy. *Antimicrob Agents Chemother* 1977; **11**: 388–94.

Macrolides

The main macrolide antibiotics are erythromycin and its derivatives azithromycin and clarithromycin. They work by binding to ribosomes and inhibiting protein synthesis.

Erythromycin [1]

Dose: 1–2 g/day in divided doses. This is the most widely used member of the macrolide group of antibiotics. It is active mainly against Gram-positive organisms such as staphylococci and streptococci. Staphylococci may rapidly develop resistance, especially in hospital, where in some studies as many as 50% of strains may be resistant; streptococci are also occasionally resistant.

Side effects include an allergic cholestatic hepatitis that occurs only with erythromycin estolate. Otherwise gastrointestinal problems such as dyspepsia and diarrhoea are not uncommon. Erythromycin is an extremely useful drug for the outpatient treatment of staphylococcal or streptococcal pyodermas, especially in the penicillin-allergic patient. However, the increasing frequency of drug resistance limits its usefulness [2]. It may also be used for atypical mycobacterial infections. Particular dermatological uses are for erythrasma and acne; it may safely be used in renal failure as less than 5% of the drug is excreted in the urine.

Azithromycin and clarithromycin [3]

These are newer macrolide agents with a somewhat different spectrum of activity than erythromycin and longer half-life. At present they are little used in dermatology, although they show promise for the treatment of atypical mycobacterial infections, particularly those caused by the *Mycobacterium avium* complex, but *M. marinum* is also responsive [4].

References

1 Washington JA, Wilson WR. Erythromycin: a microbial and clinical perspective after 30 years of clinical use. *Mayo Clin Proc* 1984; **60**: 189–203.
2 Leclerq R, Courvaluin P. Resistance to macrolides and related antibiotics. I Streptococcus pneumoniae. *Antimicrob Ag Chemother* 2002; **46**: 2727–34.
3 Zuckerman JM. Macrolides and ketolides: azithromycin, clarithromycin, telithromycin. *Infect Dis Clin North Am* 2004; **18**: 621–49.
4 Bonnet E, Debat-Zoguerch D, Petit N *et al*. Clarithromycin: a potent agent against infections due to *Mycobacterium marinum*. *Clin Infect Dis* 1994; **18**: 664–9.

Aminoglycosides

This group includes streptomycin (see below), neomycin, gentamicin, amikacin and tobramycin. Aminoglycosides are little used in dermatological practice, their chief use being against Gram-negative infections. They inhibit protein synthesis; bacteria may rapidly become resistant, and cross-resistance occurs within the group. Normally there is almost no absorption by mouth. They are ototoxic and, to a lesser degree, nephrotoxic.

Dermatological uses. These are few. Streptomycin is still used in some countries for tuberculosis, is effective in tularaemia and some forms of actinomycetoma and can be used as an alternative to tetracyclines in granuloma venereum. The topical use of neomycin is discussed in Chapter 73.

Gentamicin and amikacin [1,2]

Amikacin is now more widely used than gentamicin [2]. Its use is mainly restricted to the treatment of serious Gram-negative infections, especially those caused by *Pseudomonas aeruginosa* [3,4] and to *Nocardia* infections [5]. Gentamicin has a synergistic effect with carbenicillin against *Pseudomonas* and other Gram-negative organisms and is used in combination with penicillin for some forms of endocarditis. Aminoglycosides should not be used in pregnancy and dosing should be controlled by measurements of plasma concentration.

References

1 Silva JG, Carvalho I. New insights into aminoglycoside antibiotics and derivatives. *Curr Med Chem* 2007; **14**: 1101–19.
2 Gilbert DN. Aminoglycosides. In: Mandell GL, Bennett JE, Dolin R, eds. *Principles and Practice of Infectious Diseases*, 6th edn. Philadelphia: Elsevier Churchill Livingstone, 2005: 328–56.
3 Bulger RJ, Sidell S, Kirby WMM. Laboratory and clinical studies of gentamicin: a new broad-spectrum antibiotic. *Ann Intern Med* 1963; **59**: 593–604.
4 Jao RL, Jackson GG. Gentamicin sulfate: new antibiotic against Gramnegative bacilli. *JAMA* 1964; **189**: 817–22.
5 Gombert ME, Berkowitz LB, Aulicino TM *et al*. Therapy of pulmonary nocardiosis in immunocompromised mice. *Antimicrob Agents Chemother* 1990; **34**: 1766–70.

Spectinomycin

This is an aminocyclitol antibiotic derived from a streptomycete species and is related to the aminoglycosides. Its use in dermatology is limited but it is effective in the management of gonorrhoea as a single intramuscular injection [1].

Reference

1 Holloway WJ. Spectinomycin. *Med Clin North Am* 1982; **66**: 169–84.

Lincosamides

Lincomycin and its derivative clindamycin (which ought to be used in preference to lincomycin) act against Gram-positive cocci including some penicillin-resistant staphylococci. They are highly active against *Bacteroides* infections and penetrate into bone.

Side effects. Diarrhoea may occur in up to 20% of cases; *Clostridium difficile* colitis may supervene and may last for weeks after

the drug has been withdrawn [1,2]. There have been a number of deaths from this complication; one severe case has been reported in a patient treated for acne.

Clindamycin

This is an effective alternative drug for the treatment of acne [3]; however, in view of its known toxicity, it is seldom if ever used systemically for this condition. It is useful in a 1% formulation for the topical treatment of mild to moderate acne. It has been used, with varying success, in patients with folliculitis decalvans and hidradenitis suppurativa or orally as an alternative to rifampicin to eradicate carriage of *Staph. aureus.*

References

1 Tedesco FJ, Barton RW, Alpers DH. Clindamycin associated colitis: a prospective study. *Ann Intern Med* 1974; **81**: 429–33.

2 Bartlett JG. *Clostridium difficile*: history of its role as an enteric pathogen and the current state of knowledge about the organism. *Clin Infect Dis* 1994; **18** (Suppl. 4): 265–9.

3 Christian GL, Krueger GG. Clindamycin vs placebo as adjunctive therapy in moderately severe acne. *Arch Dermatol* 1975; **111**: 997–1000.

Chloramphenicol

This would be a useful drug for a number of infections were it not for bone marrow aplasia, which occurs in 1 in 40 000 courses of treatment [1]. This has been known for 25 years, and yet a survey of 576 cases of blood dyscrasia caused by chloramphenicol concluded that in most cases there had been no indication to justify its use. Nevertheless, it remains an alternative treatment for typhoid fever and *Haemophilus influenzae* meningitis.

Reference

1 Polak BCP, Wesseling H, Schut D *et al.* Blood dyscrasias attributed to chloramphenicol: a review of 576 published and unpublished cases. *Acta Med Scand* 1972; **192**: 409–14.

Rifamycins

See p. 74.44.

Polymyxins

Polymyxin B and polymyxin E (colistin) are relatively toxic drugs that are not absorbed from the gastrointestinal tract. Their use for Gram-negative infections has been largely superseded by gentamicin and ciprofloxacin. Polymyxin B is used topically.

Glycopeptide antibiotics

The two main examples of this group are vancomycin and teicoplanin. They act by inhibition of peptidoglycan polymer formation in bacterial cell walls. Vancomycin is chiefly used for the treatment of serious staphylococcal infections such as septicaemia as well as other life-threatening conditions such as *C. difficile* colitis. It has no obvious use in skin disease [1].

Reference

1 Deresinski S. Vancomycin: does it still have a role as an antistaphylococcal agent? *Expert Rev Anti Infect Ther* 2007; **5**: 393–401.

Fusidic acid [1]

This is produced by a strain of *Fusidium coccineum* and has the basic structure of a steroid, although it shows little in the way of metabolic effects. It is a very safe drug, primarily used for staphylococcal infections, although it is also active against other Gram-positive bacteria and the Gram-negative cocci. Nearly all strains of staphylococci are outstandingly sensitive to fusidic acid [2] but there have been increasing reports of resistant mutants, which can multiply rapidly. However, concomitant administration of penicillin can be used to kill any resistant mutants as they emerge. It is available for oral use, as an injection and for topical application. Fusidic acid is a useful drug for staphylococcal osteomyelitis in particular, and its indiscriminate prescription for minor infections should be discouraged for fear of encouraging the resistant strains that are now emerging.

References

1 Verbist L. The antimicrobial activity of fusidic acid. *J Antimicrob Chemother* 1990; **25** (Suppl. B): 1–5.

2 Drugeon HB, Caillon J, Juvin ME. *In vitro* antibacterial activity of fusidic acid alone and in combination with other antibiotics against methicillin sensitive and resistant *Staphylococcus aureus*. *J Antimicrob Chemother* 1994; **34**: 899–903.

Metronidazole [1,2]

Metronidazole is a synthetic agent active against protozoa and anaerobic bacteria. It is particularly useful in trichomoniasis, bacterial vaginosis [2], amoebiasis and giardiasis, and has proved extremely valuable against *Bacteroides* and *Helicobacter* species [3]. For the dermatologist it has a limited role in the treatment of tetracycline-failed rosacea [4]. Metronidazole is well absorbed by the oral or rectal route and it may be applied topically. It may also be given intravenously. It is available as 200 and 400-mg tablets, the usual adult oral dosage being 200 mg twice daily for rosacea, 200 mg every 8 h for *Trichomonas* infections, 400 mg every 8 h for anaerobic bacterial infections and 800 mg every 8 h for amoebiasis. Suppositories of metronidazole contain 500 mg, and in anaerobic infections are prescribed in the adult dosage of 1 g every 8 h at first, dropping to 1 g every 12 h. Topical formulations are available for the treatment of rosacea.

The fate and mode of excretion of metronidazole are not fully understood [5]; it is generally regarded as safe in hepatic and renal disease. There is no evidence that it is a human teratogen, and it may be given to lactating mothers, although it causes darkening of milk and may give it a bitter taste. In normal doses and for short periods it is generally a remarkably safe drug but minor gastrointestinal side effects such as nausea and an unpleasant taste in the mouth are not uncommon. Vomiting, abdominal pain and diarrhoea may follow. Darkening of urine, headache and drowsiness also occur, and leukopenia may be noted. Much less common adverse reactions are peripheral neuropathy, particularly associated with prolonged treatment, and central nervous system effects (dizziness, ataxia and seizures) from high dosage. The only important interaction is with alcohol, which produces a disulfiram-like reaction in some patients.

References

1 Boyanova L, Kolarov R, Mitov I. Antimicrobial resistance and the management of anaerobic infections. *Expert Rev Anti Infect Ther* 2007; **5**: 685–701.

2 Centers for Disease Control (CDC). Sexually transmitted diseases: treatment guidelines. *MMWR* 42 (No RR-14).

3 Rosenblatt JE, Edson RS. Metronidazole. *Mayo Clin Proc* 1983; **53**: 154–62.

4 Saihan EM, Burton JL. A double-blind trial of metronidazole versus oxytetracycline therapy for rosacea. *Br J Dermatol* 1980; **102**: 443–5.
5 Somogyi AA, Kong CE, Gurr FW *et al.* Metronidazole pharmacokinetics in patients with acute renal failure. *J Antimicrob Chemother* 1984; **13**: 183–9.

Antituberculous drugs (see Chapter 31)

The important first-line drugs for the treatment of *Mycobacterium tuberculosis* infections are isoniazid, rifampicin, ethambutol and, in some cases, streptomycin [1,2]. In the initial period of treatment, usually 60 days or until sensitivities are available, three of these drugs are used concurrently. For the continuation phase of therapy, two drugs to which the organism is sensitive are sufficient for cure without the occurrence of resistant strains (for details see Chapter 31).

Second-line drugs such as pyrazinamide, ethionamide, cycloserine, PABA or thiacetazone may be required where drug resistance or adverse reactions preclude the use of more than one of the four first-line agents.

The emergence of multidrug-resistant strains of *Mycobacterium tuberculosis* (MDR-TB) is a major potential threat [3], particularly as they may affect AIDS patients who expectorate large numbers of bacilli.

Isoniazid

This is a synthetic, orally absorbed bactericidal agent usually given in a dosage of 300 mg/day to adults (5–10 mg/kg every 24 h). It is excreted mainly by the kidney after acetylation and further metabolism. It can be used in pregnancy [4] but during lactation should be supplemented with pyridoxine because of the theoretical risk of toxic side effects (see below). In severe renal failure, the adult dosage should be reduced to 200 mg/day. Adverse reactions may be divided into toxic and allergic. Toxic reactions are more common in slow acetylators and include, most commonly, peripheral neuropathy but also convulsions, mental disturbances and a pellagra-like rash [5]. They are usually reversible on cessation of therapy. Pyridoxine 10 mg/day given prophylactically will reduce the incidence of these problems where high doses are used. The main allergic reactions are rashes, agranulocytosis and hepatitis, this last being apparently more common in patients with pre-existing liver disease [6].

Rifampicin

This is a synthetically modified antibiotic of the rifamycin group. It is bactericidal and very effective against *M. tuberculosis*, many atypical myobacteria and Gram-positive cocci. It is also useful in leprosy. To counter the emergence of resistant strains, it is always used in combination with other antimicrobials.

Rifampicin is well absorbed orally and is available as 150 mg capsules and a 100 mg/5 mL mixture. In adults it is usual to prescribe 450–600 mg/day as a single dose before breakfast (10 mg/kg/day). Excretion is predominantly in the bile and so hepatic impairment is an indication for avoidance or at least lower dosage. In pregnancy, rifampicin is best avoided but where it has been used the incidence of abnormalities noted at birth has not been excessively high—4.3% compared with 1.8% in tuberculous controls [7]. If used in late pregnancy it may cause haemorrhagic problems in neonates. Rifampicin is generally regarded as a relatively non-toxic antituberculous drug but many different adverse reactions have been described: mild gastrointestinal disturbances and rashes—particularly flushing [8,9]. Transient impairment of liver function, as revealed by elevation of transaminase levels, is common but need not usually interrupt therapy. Orange or red discoloration of urine, saliva and sweat may be noticed. Thrombocytopenia, however, is an uncommon side effect that must not be ignored. Three other serious adverse reactions are a flu-like illness, a syndrome of dyspnoea, wheezing and hypotension, and the occurrence of renal failure, all of which are characteristically associated with intermittent or irregular medication [10]. Drug interactions occur with warfarin (diminished anticoagulant effect), oral contraceptives (possibly) and corticosteroids (diminished steroid effect).

Other rifamycins

Rifabutin has particular activity against *M. avium–intracellulare* in addition to *M. tuberculosis*. It is used, for instance, as prophylaxis in patients with low CD4 counts. It may also be useful in areas where there is a high risk of rifampicin resistance. Rifapentine is also a useful compound with excellent activity against intracellular organisms.

Streptomycin

This is an aminoglycoside antibiotic used mainly in the treatment of tuberculosis, although not commonly in current practice. It must be administered parenterally and is commonly given in a dosage of 500–1000 mg/day by intramuscular injection. Lower dosage is preferred in patients over 40 years of age [11]. Excretion is by the kidney so that dosage should be reduced in renal impairment. Dosage reduction is also important in the premature infant. Of the important side effects, the most common is vertigo, which is especially troublesome in elderly people. Deafness may also develop and both these eighth-nerve effects are dose related [12]. These two adverse reactions provide a strong contraindication to the use of streptomycin in pregnancy and lactation as the infant may be affected, and in patients with pre-existing vestibular or auditory impairment. Allergic reactions include skin eruptions from the trivial to exfoliative dermatitis, eosinophilia and drug fever. Contact sensitization to streptomycin is a well-recognized hazard among nurses, justifying precautions to avoid skin contamination (e.g. by wearing gloves). Because streptomycin is a neuromuscular-blocking agent, it may increase the effects of suxamethonium and other similar drugs, and should be used only with extreme caution in myasthenia gravis.

Ethambutol

This is a synthetic agent effective only against *M. tuberculosis* and some atypical mycobacteria. It is orally absorbed and is available on its own as 100 and 400-mg tablets and in combination with isoniazid in a variety of strengths. The usual initial dosage is 15 mg/kg/day in adults and 25 mg/kg/day in children, reducing later in that age group to 15 mg/kg/day. It may also be used as intermittent treatment in a dosage of 45–50 mg/kg twice weekly. Excretion is mainly via the kidney, necessitating reduction of dosage in renal impairment. Optic (retrobulbar) neuritis with diminished visual acuity and red–green colour blindness, slowly

reversible on cessation of therapy, was a relatively common side effect of higher dosage regimens but should be rare with currently recommended levels [13,14]. It seems to be more effective to train patients to check their own vision regularly when on this drug than to rely on periodic ophthalmic examinations. Ethambutol may also, although rarely, cause peripheral neuropathy and renal damage, and may precipitate attacks of gout. It appears not to be a teratogen in humans and is not contraindicated during lactation.

Para-aminosalicylic acid

This drug is much less active than the aforementioned drugs, but has a role in preventing the emergence of resistant strains of *M. tuberculosis*. It is given in the high dosage of 10–20 g/day and unfortunately is associated with a high incidence of minor but unpleasant side effects [15]—gastrointestinal symptoms occur in nearly all patients. Allergic reactions with rashes and fever are common and there seems to be either cross-hypersensitivity with streptomycin or potentiation of streptomycin allergy. Although once a valued drug in triple therapy, its use is now largely restricted to poorer countries where its low cost is a major consideration.

Other antituberculous drugs [2]

A number of other antituberculous drugs are available and may be required if resistance or hypersensitivity reactions preclude the use of standard treatment. They include pyrazinamide, capreomycin, ethionamide and cycloserine. Pyrazinamide is bactericidal and low-priced [16]. There is a growing list of alternative agents which are of potential values in the management of mycobacterial infections [17].

References

1 Grange J. Antimycobacterial agents. In: Finch RG, Greenwood D, Norrby SR, Whitley RJ, eds. *Antibiotics and Chemotherapy*, 8th edn. Edinburgh: Churchill Livingstone, 2003: 507–32.

2 Inderlied CB. Mycobacteria. In: Cohen J, Powderly WG, eds. *Infectious Diseases*. London: Mosby, 2004: 2285–308.

3 Frieden TR, Sterling T, Pablos-Mendez A *et al.* The emergence of drug-resistant tuberculosis in New York City. *N Engl J Med* 1993; **328**: 521–6.

4 Ludford J, Doster B, Woolpert SF. Effect of isoniazid on reproduction. *Am Rev Respir Dis* 1973; **108**: 1170–4.

5 Horne NW. Side-effects of isoniazid. *Practitioner* 1972; **208**: 263–4.

6 Girling DJ. The hepatic toxicity of antituberculosis regimens containing isoniazid, rifampicin and pyrazinamide. *Tubercle* 1978; **59**: 13–32.

7 Steen JSM, Stainton-Ellis DM. Rifampicin in pregnancy. *Lancet* 1977; **ii**: 604–5.

8 Girling DJ. Adverse reactions to rifampicin in antituberculous regimens. *J Antimicrob Chemother* 1977; **3**: 115–32.

9 Girling DJ, Hitze KL. Adverse reactions to rifampicin. *Bull WHO* 1979; **57**: 45–9.

10 Flynn CT, Rainford DJ, Hope E. Acute renal failure and rifampicin: danger of unsuspected intermittent dosage. *BMJ* 1974; **ii**: 482.

11 Line DH, Poole GW, Waterworth PM. Serum streptomycin levels and dizziness. *Tubercle* 1970; **51**: 76–81.

12 Ballantyne J. Iatrogenic deafness. *J Laryngol Otol* 1970; **84**: 967–1000.

13 Clarke GEM, Cuthbert J, Cuthbert RJ *et al.* Isoniazid plus ethambutol in the initial treatment of pulmonary tuberculosis. *Br J Dis Chest* 1972; **66**: 272–5.

14 Lees AW, Allan GW, Smith J *et al.* Toxicity for rifampicin plus isoniazid and rifampicin plus ethambutol therapy. *Tubercle* 1971; **52**: 182–90.

15 Russouw JE, Saunders SJ. Hepatic complications of antituberculous chemotherapy. *QJM* 1975; **44**: 1–16.

16 Heifets LB, Lindholm-Levy PJ. Is pyrazinamide bactericidal against *Mycobacterium tuberculosis*? *Am Rev Respir Dis* 1990; **141**: 250–3.

17 Spigelman MK. New tuberculosis therapeutics: a growing pipeline. *J Infect Dis* 2007; **196** (Suppl. 1): S28–34.

Antileprosy agents

Sulphones

The sulphones were the first effective compounds used for the treatment of leprosy. The principal agent is 4,4-diaminodiphenyl sulphone (dapsone). The sulphones are related to the sulphonamides, and probably act in the same way. *Mycobacterium leprae* is usually extremely sensitive [1] but may become resistant. The sulphones are bacteriostatic, not bactericidal.

Dapsone. This drug is orally absorbed and is available in the form of 50 and 100-mg tablets. The usual adult dosage in leprosy is 50–100 mg/day. It is excreted mainly in the urine [2]. Some degree of haemolysis is an extremely common adverse reaction [3,4]. In pregnancy and lactation there is clearly a risk of haemolysis and methaemoglobinaemia in the baby, but the presence of dapsone in breast milk may have prophylactic value against leprosy [5]. Resistance to dapsone is known to occur in approximately 20% of patients who receive the drug for the treatment of leprosy as a single agent. With the use of multiple-drug regimens, this complication is thought to be much rarer. Leprosy apart, dapsone is a well-established means of suppressing the cutaneous lesions of dermatitis herpetiformis [6] and several other diseases. Most dermatologists are more familiar with the use of the drug in this way and further details are described in Chapter 40.

Clofazimine (Lamprene®) [7,8]

This oral synthetic drug is a phenazine dye. The usual dosage is 100 mg three times a week or 100 mg/day in combination with rifampicin if sulphone resistance has occurred [9]. It has an anti-inflammatory effect that may prevent erythema nodosum from developing. For lepra reactions, 300 mg/day is recommended. Clofazimine has a very long half-life: 70 days or more. It accumulates in the tissues and is slowly excreted in urine, sweat, sebum and milk.

The main side effect is the emergence of red-brown to black discoloration of skin and conjunctivae, but urine and sputum become red too and breast milk may be discoloured. Mild gastrointestinal reactions may occur and ichthyosiform rashes [10]. In general, clofazimine is a well-tolerated drug that may be prescribed in pregnancy and during lactation. In renal and hepatic impairment, biochemical tests of function are recommended from time to time but the drug may be used. Clofazimine may be valuable in treating pyoderma gangrenosum [11] and perhaps also in discoid lupus erythematosus.

Rifampicin

This drug has been discussed previously (under Antituberculosis Drugs). It seems to be bactericidal for *M. leprae* in very low dosage and acts much more rapidly than dapsone, rendering the patient non-contagious in a few days or weeks [12]. It does not shorten the total duration of treatment, which should be continued with dapsone.

Thiambutosine

This is a diphenylthiourea, useful as a second-line drug when dapsone cannot be used. Resistance may develop, especially after 1 year of treatment.

References

1 Shepard CC, Levy L, Fasal P. The sensitivity to dapsone (DDS) of *Mycobacterium leprae* from patients with and without previous treatment. *Am J Trop Med Hyg* 1969; **18**: 258–63.
2 Alexander JO'D, Young E, McFadyen T *et al.* Absorption and excretion of 35S dapsone in dermatitis herpetiformis. *Br J Dermatol* 1970; **83**: 620–31.
3 Anonymous. Adverse reactions to dapsone. *Lancet* 1981; **ii**: 184–5.
4 Cream JJ, Scott GL. Anaemia in dermatitis herpetiformis: the role of dapsone-induced haemolysis and malabsorption. *Br J Dermatol* 1970; **82**: 333–42.
5 Forrest JM. Drugs in pregnancy and lactation. *Med J Aust* 1976; **ii**: 138–41.
6 Fry L, Walkden V, Wojnarowska F *et al.* A comparison of IgA-positive and IgA-negative dapsone responsive dermatoses. *Br J Dermatol* 1980; **102**: 371–82.
7 Levy L. Pharmacological studies of clofazimine. *Am J Trop Med Hyg* 1974; **23**: 1097–109.
8 Rodriguez JN, Albalos RM, Reich CV *et al.* Effects of the administration of B663 (Lamprene®, clofazimine) on three groups of lepromatous and borderline cases of leprosy. *Int J Leprosy* 1974; **42**: 276–88.
9 Yawalker SJ, Vischer W. Lamprene (clofazimine) in leprosy. *Leprosy Rev* 1979; **50**: 135–44.
10 Michaelsson G, Molin L, Ohman S *et al.* Clofazimine: a new agent for the treatment of pyoderma gangrenosum. *Arch Dermatol* 1976; **112**: 344–9.
11 Kark EC, Davis BR, Pomeranz JR. Pyoderma gangrenosum treated with clofazimine: report of three cases. *J Am Acad Dermatol* 1981; **4**: 152–9.
12 Walker SL, Lockwood DN. Leprosy. *Clin Dermatol* 2007; **25**: 165–72.

Antifungal drugs [1–3]

The drugs available for systemic use against fungal diseases are few in number. There are three main families of antifungals: polyenes (amphotericin B); azoles, which include imidazoles (e.g. ketoconazole, miconazole); triazoles (fluconazole and itraconazole); allylamines. There is also a miscellaneous group of drugs such as griseofulvin, tolnaftate and flucytosine. Most antifungals work through damage to or inhibition of the fungal cell membrane. The main exceptions are the pyrimidine analogue, flucytosine, which affects RNA and DNA synthesis, and potassium iodide which probably affects phagocytic function.

Polyenes [4]

Nystatin [4]

Nystatin was the first polyene antibiotic discovered and is still valuable today as a topical anti-*Candida* agent. It is not absorbed from the gut in significant amounts.

Amphotericin B [1,4]

This is a polyene antibiotic derived from *Streptomyces nodosus*. It has a very wide range of activity against *Candida* spp. and almost all deep fungal pathogens. Resistance is rare. Absorption from the gut is negligible and so, as with nystatin, tablets and lozenges are for practical purposes topical therapy for the mouth or prophylaxis. For systemic use, amphotericin B must be given by slow intravenous infusion in 5% dextrose. This solution is unstable; it should be used promptly and other drugs should not be added, except heparin or hydrocortisone. The definitive adult dosage range is normally in the range of 0.4–1 mg/kg/day but toxicity is minimized if there is a build-up from a very low dose (1 mg) on the first day, to full dosage by days 3–5. In the seriously ill patient, a more rapid build-up to full dosage over 24–48 h is necessary.

The fate of amphotericin in the body is not fully understood [5]. Only small amounts appear in urine; much is probably bound to sterol-containing membranes. Adverse reactions are common: initially, fever, rigors, hypotension, nausea, vomiting, tinnitus and bronchospasm. Phlebitis at the site of infusion is also frequent. Hypokalaemia and hypochromic anaemia may occur and, rarely, liver function abnormalities. Nephrotoxicity is of great importance; renal clearance may be decreased and tubular damage may develop. These are particularly problems of extended treatment but are potentially reversible. If renal impairment is severe, therapy must be interrupted and should be restarted at a lower dosage.

Amphotericin B is used principally for systemic mycoses such as candidosis, aspergillosis, mucormycosis and cryptococcosis as well as the endemic respiratory infections such as histoplasmosis.

Lipid-associated amphotericins

Three formulations of lipid-associated amphotericin B have been developed: a liposomal formulation (AmBisome), a colloidal dispersion (Amphocil®) and a lipid complex (Abelcet®). They can be used at much higher dosage (usually 3 mg/day) without nephrotoxicity [6].

Flucytosine [7]

This is a synthetic cytosine analogue that is converted to 5-fluorouracil in the body. It is effective against yeasts, including *Candida* spp., *Cryptococcus neoformans* and many of the fungi involved in chromoblastomycosis. It is orally absorbed but may be given intravenously too. The tablets contain 500 mg, the usual adult dosage being 150 mg/kg/day. Lower doses are necessary in renal failure. It is important to monitor serum levels, aiming to achieve 40–60 mg/L and to avoid toxic levels—above 120 mg/L. Because resistance, both primary and secondary, is well recognized, sensitivity testing initially and at intervals is strongly recommended. It is rarely used on its own. In cryptococcal meningitis in the non-AIDS patient, flucytosine and amphotericin B are given in combination. They appear to be more effective as a combination than amphotericin B on its own and the daily dosage of the latter can be reduced to 0.4–0.6 mg/kg.

The main side effects are nausea, vomiting, diarrhoea and rashes, but thrombocytopenia and neutropenia may also occur.

Azoles

Miconazole

This is a commonly used topical imidazole, poorly absorbed by the oral route. It may be administered intravenously by slow infusion three times in 24 h, the usual adult dosage being 1.8–3 g/day. Side effects are not particularly common. They include pruritus, rashes, fever, faintness and venous thrombosis at the infusion site. Anorexia, nausea, vomiting and diarrhoea occur and anaphylaxis is a rare but genuine problem. It is seldom used now except in infections caused by *Scedosporium apiospermum* [8].

Ketoconazole [9,10]
Ketoconazole is a broad-spectrum imidazole, which is available in different topical formulations from cream to shampoo or as an oral agent. The drug is well absorbed after oral administration, although lower levels are seen in patients who are neutropenic. It is effective in a range of infections from chronic mucocutaneous candidosis to pityriasis versicolor and mycetoma infections caused by *Madurella mycetomatis* but not in sporotrichosis. Certain systemic mycoses such as paracoccidioidomycosis and those with soft-tissue lesions are the most sensitive [10].

Adverse events are uncommon but include headache, vomiting and giddiness as well as nausea. It also leads to blockade of androgen biosynthesis by interference with cytochrome P-450 at high dosage [11]. This results in symptoms such as gynaecomastia in men and menstrual irregularities in women. In addition, it causes asymptomatic changes in liver function and overt hepatitis on occasions [12]. The true frequency of the latter is estimated to be about 1 in 10 000 but it may be more common in patients receiving treatment for nail disease. It is more common also in those with a prior history of liver disease. While this is a comparatively uncommon complaint, it is sufficient to limit the use of the drug in superficial fungal disease. Also, much of its function has been assumed by the development of triazole antifungals (see below). Drug resistance is also seen rarely [13].

Itraconazole [14]
Itraconazole is a triazole antifungal drug that is avidly bound in tissue, including skin. Its serum levels are generally low after a 100–200-mg dose. It is given orally and has a broad spectrum of action against the main fungal pathogens. It is effective in dermatophytosis, candidosis and *Malassezia* infections. Originally used in a dosage of 100 mg/day, it is now often given at 200 or 400 mg. At higher doses it is possible to use shorter courses such as 400 mg/day for 1 week in tinea corporis. Because it is retained for very long periods in the nail, itraconazole is used in pulses of 400 mg/day for 1 week per month for 3–4 months [15].

In vaginal candidosis itraconazole is given as a single treatment of 600 mg/day and produces responses in oropharyngeal candidiasis in doses of 100–200 mg/day. For recalcitrant pityriasis versicolor, a total dose of 1000 mg is necessary. Other infections responding to itraconazole include sporotrichosis, chromomycosis, paracoccidioidomycosis and histoplasmosis [14]. It has also been reported to be effective in cryptococcal meningitis, particularly as a long-term suppressive therapy of HIV-positive patients. Itraconazole is unusual amongst azoles in producing responses against aspergillosis.

Although itraconazole may occasionally cause nausea and headache, more serious adverse reactions, such as hepatic reactions and anaphylaxis, are extremely rare.

A new formulation of itraconazole in cyclodextrin, as well as an intravenous form, are also available. This oral solution is much better absorbed in AIDS patients than the conventional formulation.

Fluconazole [16]
Fluconazole is a triazole antifungal that is well absorbed after oral administration. It may also be given intravenously. Unusually for an azole, it is mainly excreted via the kidney. It is active against a range of fungal pathogens.

The principal uses of fluconazole in dermatology are in the treatment of oropharyngeal and vaginal candidosis [17]. In the latter disease, it is effective in a single dose of 150 mg; with oropharyngeal infections, treatment responses are rapid, often within 3 days of starting therapy with 50–100 mg/day [18]. For dermatophytosis, it has been found that weekly doses of 150 mg may be effective after 2–3 weeks and a similar weekly pulse has been used for onychomycosis. In systemic mycoses it is used in the management of cryptococcosis, either as primary therapy or long-term suppression, and in systemic candidosis [19].

Few adverse effects apart from nausea and dyspepsia have been attributed to fluconazole. The dosage of the drug has to be reduced in patients with renal impairment.

Certain fungi such as *Candida krusei*, *C. glabrata* and some strains of *C. albicans* are primarily resistant to fluconazole and secondary resistance may develop in immunocompromised patients [16].

Other azoles
Two new orally active triazoles, voriconazole [20] and posaconazole [21], have not been evaluated in superficial fungal disease. They show promise in the management of a range of systemic infections and in severe oropharyngeal candidosis as well as *Candida* oesophagitis. Voriconazole is particularly effective against *Aspergillus* infections.

Allylamines

Terbinafine [22]
Terbinafine is a fungicidal allylamine antifungal, similar to naftifine. It works by the inhibition of squalene epoxidation in the synthesis of the ergosterol in the fungal cell membrane [23]. The accumulation of squalene in the cell is thought to contribute to its *in vitro* fungicidal activity. Terbinafine may be given orally or topically in a dosage of 125 mg twice daily. Its chief use is in dermatophytosis, where it is highly effective even in patients with chronic infections of the hands and feet. In onychomycosis it is given in a regimen of 250 mg/day for 6 weeks for fingernails and 12 weeks for toenails [24]. It is less active when given orally in superficial candidosis and pityriasis versicolor. In dermatophytosis there is a particularly low relapse rate with this drug. Recently, it has been shown to be active in a range of other deep fungal infections, from sporotrichosis to chromoblastomycosis.

There are few side effects apart from the occasional episode of gastrointestinal discomfort. Loss of taste may occur but is reversible. It may rarely, however, cause Stevens–Johnson syndrome or toxic epidermal necrolysis. Hepatic reactions are extremely rare.

Griseofulvin [25]
Griseofulvin, derived from a number of *Penicillium* species, is a fungistatic drug whose principal activity is directed against dermatophytes. Its mode of action is via the inhibition of the formation of intracellular microtubules.

The usual human dosage is 10 mg/kg/day in tablet or, in children, solution form. Treatment duration varies between 2 and 4 weeks for tinea corporis to over 1 year for onychomycosis. The

success rate even after 1 year of treatment for toenail infections is less than 30–40%.

Drug interaction with phenobarbital and coumarin anticoagulants occur. Side effects include headaches and nausea, but serious reactions are extremely rare. There are a few reports of apparent precipitation or exacerbation of systemic lupus erythematosus and porphyrias by griseofulvin.

Potassium iodide [2]

In the form of a saturated aqueous solution (100 g in 100 mL water), this is the preferred treatment for lymphocutaneous sporotrichosis and subcutaneous zygomycosis (basidiobolomycosis). It is administered orally, starting with 0.6 mL three times daily and gradually increasing until a level of four or five times the dose is attained in an adult. The mode of action is obscure. Progress must be expected to be slow and treatment should be continued until 4 weeks after apparent cure. Iodides are best avoided in pregnancy because of the risk of goitre and hypothyroidism in the infant. Adverse reactions include iododerma, salivary and lacrimal gland swelling and hypersecretion, and gastrointestinal disturbances, as well as anxiety, depression and hypothyroidism.

Cell wall antagonists

A number of new antifungals are in development that have a different site of action namely the inhibition of the formation of the cell wall. Caspofungin and anidulomycin are echinocandins that block glucan synthase [26]. They are available as intravenous drugs for use in the treatment of aspergillosis or candidosis, particularly caused by resistant *Candida* species.

References

1 Bennett JE. Chemotherapy of systemic mycoses. *N Engl J Med* 1974; **290**: 30–2.
2 Roberts DT. The current status of systemic antifungal agents. *Br J Dermatol* 1982; **106**: 597–602.
3 Speller DCE, ed. *Antifungal Chemotherapy*. Chichester: John Wiley, 1980.
4 Medoff G, Kobayashi GA. The polyenes. In: Speller DCE, ed. *Antifungal Chemotherapy*. Chichester: John Wiley, 1980: 3–33.
5 Atkinson AJ, Bennett JE. Amphotericin B pharmacokinetics in humans. *Antimicrob Agents Chemother* 1978; **13**: 271–6.
6 Hay RJ. Lipid amphotericin B combinations: 'la crème de la crème'? *J Infect* 1999; **38**: 16–20.
7 Bennett JE. Flucytosine. *Ann Intern Med* 1977; **86**: 319–22.
8 Lutwick LI, Rytel MW, Yanez JP *et al.* Deep infections of *Petriellidium boydii* treated with miconazole. *JAMA* 1979; **241**: 272–3.
9 Cox FW, Stiller RL, South DA *et al.* Oral ketoconazole for dermatophyte infections. *J Am Acad Dermatol* 1982; **6**: 455–62.
10 Jones HE. *Ketoconazole Today*. Manchester: Adis, 1987.
11 Stern RS. Ketoconazole: assessing the risks. *J Am Acad Dermatol* 1982; **6**: 544.
12 Heidberg JK, Svejgaard E. Toxic hepatitis during ketoconazole treatment. *BMJ* 1981; **283**: 825–6.
13 Ryley JF, Wilson RG, Barrett-Bee KJ. Azole resistance in *Candida albicans*. *Sabouraudia* 1984; **22**: 53–63.
14 Grant SM, Clissold SP. Itraconazole. *Drugs* 1989; **37**: 310–44.
15 Hay RJ, ed. *Itraconazole*. Manchester: Adis, 1994.
16 Powderly WB, Van't Wout JW, eds. *Fluconazole*. York: Marius, 1992.
17 Brammer KW. Treatment of vaginal candidiasis with a single oral dose of fluconazole. *Eur J Clin Microbiol Infect Dis* 1988; **7**: 364–7.
18 Dupont B, Drouhet E. Fluconazole in the management of oropharyngeal candidosis in a predominantly HIV antibody positive group of patients. *J Med Vet Mycol* 1988; **26**: 67–71.
19 Stern JJ, Hartman BJ, Sharkey P *et al.* Oral fluconazole therapy for patients with acquired immunodeficiency syndrome and cryptococcosis: experience with 22 patients. *Am J Med* 1988; **85**: 477–80.
20 Maschmeyer G, Haas A. Voriconazole: a broad spectrum triazole for the treatment of serious and invasive fungal infections. *Future Microbiol* 2006; **1**: 365–85.
21 Schiller DS, Fung HB. Posaconazole: an extended-spectrum triazole antifungal agent. *Clin Ther* 2007; **29**: 1862–86.
22 Jones TC, Villars VV. Terbinafine. In: Ryley J, ed. *Chemotherapy of Fungal Diseases*. Berlin: Springer, 1990: 455–82.
23 Ryder NS, Meith H. Allylamine antifungal drugs. In: Borgers M, Hay R, Rinaldi MG, eds. *Current Topics in Medical Mycology*, Vol. 4. New York: Springer, 1992: 158–88.
24 Crawford F. Young P. Godfrey C *et al.* Oral treatments for toenail onychomycosis: a systematic review. *Arch Dermatol* 2002; **138**: 811–6.
25 Davies RR. Griseofulvin. In: Speller DCE, ed. *Antifungal Chemotherapy*. Chichester: John Wiley, 1980: 149–82.
26 Cappelletty D, Eiselstein-McKitrick K. The echinocandins. *Pharmacotherapy*. 2007; **27**: 369–88.

Antiviral drugs

With the spread of HIV infection and other viruses with the capacity to cause human pandemics, considerable efforts have now been expended in searching for new antiviral drugs. Despite this there are still few effective antiviral agents [1] and the primary targets of the newer agents are retroviruses and respiratory pathogens. Because there are fewer steps involved in the assembly of viruses, and these are inextricably associated with human metabolic and other cellular functions, the ratio between antiviral activity and host toxicity is often a narrow one. Many agents employed in the treatment of viral infections of the skin have one of three viral targets: inhibition of viral polymerase (e.g. aciclovir), inhibition of reverse transcriptase (e.g. zidovudine) or protease inhibition (e.g. indinavir). The two latter groups are mainly used for the treatment of retroviral infections.

Other approaches to treatment have involved the use of interferons, which have proved to be of limited value in most viral infections apart from some genital papillomavirus infections, and many of the available preparations are associated with dose-limiting side effects when given intravenously. Imiquimod is used as a topical agent against human papilloma viruses but is an immunomodulator.

Drug resistance will occur with antivirals but often it involves a modification of the viral genome that may, in turn, affect viral pathogenetic mechanisms. This alteration in viruses may affect their capacity to cause disease except in severely immunocompromised patients such as those with AIDS.

Vidarabine (adenosine arabinoside, ARA-A)

This purine nucleoside acts by inhibiting viral DNA synthesis. It has effects mainly against the herpes group of viruses and appears to be effective in early cases of herpes simplex encephalitis and in varicella-zoster infections of immunocompromised subjects. However, its use has largely been superseded by aciclovir. At a dosage of 10 mg/kg/day intravenously it causes mainly mild gastrointestinal side effects, and rashes in 5% of subjects. Central nervous system and haematological side effects have also been reported [2]. A 3% ointment has an established place in the topical treatment of herpes simplex keratoconjunctivitis.

Idoxuridine

This synthetic nucleoside is effective against DNA viruses, particularly the herpes group. Its use is now restricted to topical application because of severe bone marrow and hepatic toxicity when given intravenously. It has been used in 5–40% concentrations in dimethyl sulphoxide (DMSO) to shorten the duration of clinical symptoms in herpes zoster infections. It can also be used in herpes keratitis but is less effective in genital herpes simplex infections [3].

Aciclovir [4–7]

This antiviral agent works by inhibition of DNA synthesis. Its mode of action involves activation by thymidine kinase and subsequent inhibition of viral DNA polymerase. Resistance to aciclovir is well recognized, following alterations to, or deficiency of, thymidine kinase or altered DNA polymerase. This has been associated with lack of response to therapy [8,9]. Prevalence of resistance amongst human herpes virus types 1 and 2 varies from 0.1% in normal subjects to as high as 14% in immunocompromised patients.

Aciclovir is active against human herpes viruses. In serious infections it has been used intravenously but it is also available as 200-mg tablets, as an ophthalmic ointment and as a cream [5]. Unfortunately, it has no effect on the latent phase of either herpes simplex or zoster and is apparently ineffective in clinical practice against other viruses. The intravenous dosage for serious systemic herpes simplex infections is 5 mg/kg every 8 h by slow infusion (over 1 h). In herpes zoster, 10 mg/kg every 8 h is advised. Orally, 200 mg every 4 h (five times daily) is effective and a remarkably safe treatment for severe vulvovaginal herpes simplex [10], for example.

Studies with aciclovir have shown that it is possible to suppress recurrences of herpes simplex by intermittent administration over a long period. This has given rise to concerns over the risk of drug resistance and this approach is really only indicated in a few patients with incapacitating recurrent attacks of infection [11].

Aciclovir is less effective against herpes zoster unless given in higher dosage (e.g. 10 mg/kg intravenously 8 hourly) [12]. It is therefore mainly used for treatment of varicella-zoster infection in immunocompromised patients.

The main route of excretion is renal [13]. Side effects include elevation of blood urea and creatinine, which may rarely progress to acute renal failure. In patients with established renal impairment, lower doses are indicated. Although animal and human evidence shows no teratogenic activity, aciclovir is best avoided in pregnancy. Levels are reported to be higher in human milk than in serum when given during lactation.

Drugs related to aciclovir

These include famciclovir, penciclovir, ganciclovir and valaciclovir [14].

Famciclovir [15]. This is well absorbed after oral administration, and used at a dosage of 250–500 mg up to three times daily. At these dosages it appears to be as effective as the higher-dose regimen of intravenous aciclovir and is well-tolerated. There is also a lower frequency of post-herpetic neuralgia after its use.

Penciclovir [14]. This is a promising treatment for severe herpes simplex infections and, because of its pharmacokinetic properties, is given less frequently than aciclovir.

Ganciclovir [14]. This is another deoxyguanosine analogue, which can be used in the treatment or prophylaxis of cytomegalovirus (CMV) infections. It is also active against other herpesviruses. Its use is generally reserved for CMV infections in severely immunocompromised patients when it is given in a starting dosage of 5 mg/kg/12 h intravenously. Ganciclovir can also be used as long-term suppressive therapy to prevent relapse. However, there is a high frequency of nephrotoxicity as well as metabolic disturbances such as hypokalaemia or hypocalcaemia.

Valaciclovir [16]. This has a similar antiviral spectrum to aciclovir. It is mainly used for the treatment of herpes zoster infections (1000 mg for 7–14 days). It is also used for shorter periods (5 days) for herpes simplex infections [16].

Zidovudine (AZT, Retrovir®) [17,18]

AZT has been developed for the treatment of human retrovirus infections. Its principal site of action is the inhibition of virus-RNA-dependent DNA polymerase (reverse transcriptase) [17,18]. AZT is given by the oral route and the normal dosage is 250–500 mg/day; variations to this regimen and drug combinations are under assessment. The use of AZT in patients with AIDS or symptomatic HIV infections results in higher levels of circulating CD4 lymphocytes and, in some studies, a decrease in mortality over the short-term. Treated patients are still infectious and AZT does not cure the infection. It is currently used to treat HIV patients with CD4 counts lower than 500/mm^3 [19]. There are suggestions that AZT may benefit some skin complications of AIDS such as psoriasis. Administration of AZT to infected women in the second and third trimesters of pregnancy significantly reduces the risk of neonatal infection [20].

The main toxic side effects of zidovudine are neutropenia and anaemia, which occur in the majority of patients, particularly at higher doses. This is a particular problem in advanced disease. Other side effects include headache, myalgia and nausea. Progressive nail pigmentation has been described in black patients [21]. Resistance to AZT occurs regularly with long-term use [22].

Other antiretroviral agents [18,22]

There have been a large number of new antiretroviral drugs, with nucleoside or reverse transcriptase inhibition, licensed in recent years. These include zalcitabine (DDC), didanosine, zalcitabine, lamivudine, abacavir, tenofovir, emtrictabine and stavudine, which is a thymidine analogue. These have been used for the treatment of patients with very low CD4 counts or where there is AZT resistance or in primary combination therapy. Zalcitabine causes a painful neuropathy and pancreatitis, rashes, ulceration and hepatitis have been described. Stavudine also causes a painful neuropathy.

Non-nucleoside reverse transcriptase inhibitors

These agents are all non-competitive inhibitors of reverse transcriptase and act at sites that differ from the nucleoside binding

region. Nevirapin, delavirdine and efavirenz are all examples of this group of drugs. In the case of the first two there is a high frequency of rash associated with administration. With nevirapine this is often a generalized maculopapular erythematous reaction which is generalized usually sparing the palms and soles [23].

Protease inhibitors [24,25]

In order to circumvent the rising problem of drug resistance with antiretrovirals, a new family of drugs whose main focus of action is on the inhibition of aspartic proteases encoded by retroviruses has been developed. These cleave the Gag and Gag-Pol proteins into smaller moieties needed for maturation. The main compounds are saquinavir, indinavir, ritonavir and nelfinavir, amprenavir, lopinavir and atazanavir but there are others in development [25]. Most work by mimicking the transitional state that occurs during peptide bond cleavage by aspartic proteases. Generally they are used in combination, usually with AZT or other reverse transcriptase inhibitors and/or further protease inhibitors, to prevent viral replication and increase CD4 counts. These compounds differ in structure and in the specific sites inhibited [24–26]. Treatment using combinations of these drugs is known as highly active antiretroviral therapy (HAART), and successful maintenance therapy can be given for HIV-infected individuals. There is both primary and secondary resistance to protease inhibitors [26]. Primary resistance which arises in a specific drug through selection and primary mutation within the protease there may not be cross resistance to other protease inhibitors; whereas secondary resistance is through natural mutation and cross resistance is common.

Retroviral entry inhibitors

A new strategy has been to develop drugs that disrupt/prevent the process of binding of viral particles to the CD4 receptor site on target lymphocytes. Enfuvirtide is an example of this newer group of drugs; it is a synthetic peptide that inhibits the change in the viral envelope conformation necessary for entry [27].

Foscarnet phosphonoformate [28]

Foscarnet is a pyrophosphate analogue that inhibits herpesvirus polymerase. It is active against most herpesviruses including CMV. It also inhibits reverse transcriptase and has activity *in vitro* against HIV, particularly in combination with AZT. It is given intravenously in severe treatment resistant herpes simplex and CMV infections, or topically. It is an alternative drug for severe aciclovir-resistant herpes simplex infections and for this indication the usual initial treatment is 40 mg/kg every 8 h. Adverse effects include renal tubular damage, malaise, nausea and headache. Tremor and hallucination may occur at high dosage.

References

1 Hirsch MS, Swartz MN. Antiviral agents. *N Engl J Med* 1980; **302**: 903–7, 949–53.

2 Whitley RJ, Spruance S, Hayden F. Vidarabine therapy of mucocutaneous herpes simplex virus infection in the immunocompromised host. *J Infect Dis* 1984; **149**: 1–8.

3 Silvestri DL, Corey L, Holmes KK. Ineffectiveness of topical idoxuridine in dimethyl sulfoxide for therapy of genital herpes. *JAMA* 1982; **248**: 953–9.

4 Elion GB. The biochemistry and mechanisms of action of acyclovir. *J Antimicrob Chemother* 1983; **12** (Suppl. B): 9–17.

5 Fiddian AP, Yeo JM, Clark AE. Treatment of herpes labialis. *J Infect* 1983; **6** (Suppl. 1): 41–7.

6 King DH, Galasso G, eds. Symposium on acyclovir. *Am J Med* 1982; **73** (Suppl. 1).

7 Field HJ, Phillips I, eds. Acyclovir. Based on the Second International Acyclovir Symposium. *J Antimicrob Chemother* 1983; **12** (Suppl. B): 1–11.

8 Field HJ, Larder BA, Darby G. Isolation and characterization of acyclovir resistant strains of herpes simplex virus. *Am J Med* 1982; **73** (Suppl. 1): 369–71.

9 Bacon TH, Levin MJ, Leary JJ *et al*. Herpes simplex virus resistance to acyclovir and penciclovir after two decades of antiviral therapy. *Clin Microbiol Rev* 2003; **16**: 114–28.

10 Bryson YJ. Current status and prospects for oral acyclovir treatment of first episode and recurrent genital herpes simplex virus. *J Antimicrob Chemother* 1983; **12** (Suppl. B): 61–9.

11 Thomas RHM, Dodd HJ, Yeo JM *et al.* Oral acyclovir in the suppression of recurrent non-genital herpes simplex virus infection. *Br J Dermatol* 1985; **113**: 731–5.

12 Huff JC, Bean B, Balfour HH *et al.* Therapy of herpes zoster with oral acyclovir. *Am J Med* 1988; **85** (Suppl. 2A): 84–9.

13 De Miranda P, Blum MR. Pharmacokinetics of acyclovir after intravenous and oral administration. *J Antimicrob Chemother* 1983; **12** (Suppl. B): 27–37.

14 Kleymann G. Agents and strategies in development for improved management of herpes simplex virus infection and disease. *Expert Opin Investig Drugs* 2005; **14**: 135–61.

15 Simpson D, Lyseng-Williamson KA. Famciclovir: a review of its use in herpes zoster and genital and orolabial herpes. *Drugs* 2006; **66**: 2397–416.

16 Brantley JS, Hicks L, Sra K, Tyring SK. Valacyclovir for the treatment of genital herpes. *Expert Rev Anti Infect Ther* 2006; **4**: 367–76.

17 Hirsch MS. AIDS commentary: azidothymidine. *J Infect Dis* 1988; **157**: 427–31.

18 Warnke D, Barreto J, Temesgen Z. Antiretroviral drugs. *J Clin Pharmacol* 2007; **47**: 1570–9.

19 McLeod GX, Hammer SM. Zidovudine: five years later. *Ann Intern Med* 1992; **117**: 487–501.

20 Graham NMH, Zeger SL, Park LP *et al.* The effects on survival of early treatment of human immunodeficiency virus infection. *N Engl J Med* 1992; **326**: 1037–42.

21 Furth PA, Kazakis AM. Nail pigmentation changes associated with azidothymidine (zidovudine). *Ann Intern Med* 1988; **107**: 350.

22 Samuel R, Bettiker R, Suh B. Antiretroviral therapy 2006: pharmacology, applications, and special situations. *Arch Pharm Res* 2006; **29**: 431–58.

23 Manosuthi W, Sungkanuparph S, Tansuphaswadikul S *et al.* Incidence and risk factors of nevirapine-associated skin rashes among HIV-infected patients with CD4 cell counts <250 cells/muL. *Int J STD AIDS* 2007; **18**: 782–6.

24 Barreiro P, Soriano V, Casas E *et al.* Different degree of immune recovery using antiretroviral regimens with protease inhibitors or non-nucleosides. *AIDS* 2002; **16**: 245–9.

25 Mastrolorenzo A, Rusconi S, Scozzafava A *et al.* Inhibitors of HIV-1 protease: current state of the art 10 years after their introduction. From antiretroviral drugs to antifungal, antibacterial and antitumor agents based on aspartic protease inhibitors. *Curr Med Chem* 2007; **14**: 2734–48.

26 Garriga C, Pérez-Elías MJ, Delgado R *et al.* Mutational patterns and correlated amino acid substitutions in the HIV-1 protease after virological failure to nelfinavir- and lopinavir/ritonavir-based treatments. *J Med Virol* 2007; **79**: 1617–28.

27 Moyle G. Stopping HIV fusion with enfivirtide: the first step to extracellular HAART. *J Antimicrob Ag Chemother* 2003; **51**: 213–7.

28 Oleg B, Behrmetz S, Eriksson B. Clinical use of foscarnet (phosphonoformate). In: De Clerq E, ed. *Clinical Use of Antiviral Drugs*. Amsterdam: Martinus Nijhoff, 1991: 223–40.

Antiparasitic agents

Drugs that are used to treat parasitic infections which affect the skin include antibacterial agents such as metronidazole and cotrimoxazole as well as those with specific activity against parasites. This section is largely concerned with the latter group.

Drugs used to treat roundworms

Benzimidazoles. Mebendazole and albendazole are the best known of these compounds. Mebendazole (methyl 5-

benzoylbenzimidazole-2 carbamate) is a synthetic drug that is active against diverse species such as *Ascaris*, *Enterobius* and *Trichuris* [1]. It is also active against the adult forms of *Trichinella spiralis* and some filariae such as *Loa loa*. Mebendazole works through blocking the assembly of microtubules; it is poorly absorbed from the gastrointestinal tract. Adverse events are not uncommon and are mainly seen at high dosage. The more common but trivial side effects are abdominal pain and diarrhoea.

Albendazole (methyl 5-*N*-propoxythio-2-benzimidazole carbamate) has broad-spectrum activity for parasites from *Ascaris* to *Trichuris* [2,3]. Albendazole is absorbed after oral administration but this is enhanced in the presence of a fatty meal. Once again it is well tolerated and abdominal pain and diarrhoea are the main side effects. Liver and bone marrow toxicity occur only at high dosage. It is also used in combination with ivermectin in filarial infections, mainly lymphatic filariasis [4].

Thiabendazole is less used than previously. It is well absorbed and is active against a range of nematodes as well as some fungi. However, side effects such as nausea and vomiting are common.

Diethylcarbamazine

Diethylcarbamazine (DEC), discussed in Chapter 37, is a piperazine derivative used in the treatment of microfilariae [5]. It rapidly kills these microorganisms, an event that leads to considerable inflammation, which can cause damage in the eye and skin. DEC acts by affecting microfilarial muscle activity and affects their membranes, leading to increased host killing capacity. In onchocerciasis it can cause severe itching, oedema, erythema and hypotension—the DEC reaction. The dosage is usually built up from an initial 50-mg dose, depending on the infection.

Ivermectin

This is a macrocyclic lactone derived from avermectin B1, which is used for intestinal parasites in animals and for the management of onchocerciasis, lymphatic filariasis and other nematode infections, including cutaneous larva migrans [6–9]. Ivermectin blocks the transmission of signals from interneurones to excitatory motor neurones. It is also effective against *Sarcoptes scabiei*. Its advantage in onchocerciasis is that it is microfilaricidal but does not lead to severe inflammatory responses. Ivermectin is well absorbed after oral administration. Side effects are uncommon but include fever, itching and headache. A mild DEC-like reaction may occur in some patients. Its usual dose is 150 μg/kg orally, repeated when necessary every 6–12 months.

Pentavalent antimony

The main variants of pentavalent antimony used for the treatment of leishmaniasis are sodium stibogluconate and meglumine antimoniate. Neither variant is orally active and both have to be given parenterally (intramuscularly or intravenously) [10]. There is a slow elimination phase, which may give rise to toxicity at high dosage. Common adverse events include abdominal pain, nausea and headache [11]. Other effects are renal impairment, pancreatitis and alterations in electrocardiogram (ECG) and cardiac arrhythmias. In particular the Q–T interval may be prolonged.

Milfetosine

Milfetosine is a compound [12] that has been used to treat both visceral and cutaneous leishmaniasis. Originally an antineoplastic drug it is thought to interfere with protein kinase C and cell signalling in the parasite. It can be given orally.

References

1 Keystone JS, Murdoch JK. Mebendazole. *Ann Intern Med* 1979; **91**: 582–6.
2 Jones SK, Reynolds NJ, Oliwiecki S *et al.* Oral albendazole for the treatment of cutaneous larva migrans. *Br J Dermatol* 1990; **122**: 99–101.
3 Pugh RNH, Teesdale CH, Burnham GM. Albendazole in children with hookworm infection. *Ann Trop Med Parasitol* 1986; **80**: 565–7.
4 Olsen A. Efficacy and safety of drug combinations in the treatment of schistosomiasis, soil-transmitted helminthiasis, lymphatic filariasis and onchocerciasis. *Trans R Soc Trop Med Hyg* 2007; **101**: 747–58.
5 Hawking F. Diethyl carbamazine and new compounds for the treatment of filariasis. *Adv Pharmacol Chemother* 1979; **16**: 129–94.
6 Grover JK, Vats V, Uppal G *et al.* Antihelmintics: a review. *Trop Gastroenterol* 2001; **22**: 180–9.
7 Collins RC, Gonzalez-Peralta C, Castro J *et al.* Ivermectin: reduction in prevalence and infection intensity of *Onchocerca volvulus* following biannual treatments in five Guatemalan communities. *Am J Trop Med Hyg* 1992; **47**: 156–69.
8 Pacque M, Greene BM, Munoz B *et al.* Ivermectin therapy: a 5-year follow-up. *J Infect Dis* 1991; **164**: 1035–6.
9 Fox LM. Ivermectin: uses and impact 20 years on. *Curr Opin Infect Dis* 2006; **19**: 588–93.
10 Navin TR, Arana BA, Arana FA *et al.* Placebo-controlled clinical trial of sodium stibogluconate (pentostam) versus ketoconazole for treating cutaneous leishmaniasis in Guatemala. *J Infect Dis* 1992; **165**: 528–34.
11 Ballou WR, McClain JB, Gordon DM *et al.* Safety and efficacy of high dose stibogluconate therapy for American cutaneous leishmaniasis. *Lancet* 1987; **2**: 13–6.
12 Pearson RD. The development of milfetosine for the treatment of visceral and cutaneous leishmaniasis. *Curr Infect Dis Rep* 2003; **5**: 41–2.

Miscellaneous systemic agents

Drugs to improve the peripheral circulation

Raynaud's phenomenon and perniosis are the principal dermatological indications for systemic vasodilator therapy. Raynaud's phenomenon occurs in a primary, usually mild, form unassociated with systemic disease, or secondary to various underlying causes. The most common of these is connective tissue diseases; others include hyperviscosity disorders, cervical rib, drugs with a vasoconstrictor action and, rarely, occupational causes (see Chapter 27). The management of Raynaud's phenomenon has been extensively reviewed [1–6], and includes the use of calcium-channel blockers [7,8], angiotensin II receptor antagonists such as losartan [9], phosphodiesterase inhibitors including sildenafil [10,11], prostacyclin analogues, serotonin antagonists, calcitonin gene-related peptides and newer agents such as endothelin-1 receptor antagonists [12,13] and nitric oxide donors.

Calcium-channel blocking agents are of moderate benefit, and of these nifedipine is the treatment of choice [14]. It acts by inhibiting contraction of smooth muscle cells by reducing the cellular uptake of calcium, a process fundamental to vasospasm; it also reduces platelet aggregability. Modified release nifedipine 20–60 mg/day is usually effective. Diltiazem is also useful, but verapamil less so. Side effects include flushing, headaches and peripheral oedema. The response of primary Raynaud's

phenomenon is usually more impressive than that secondary to connective tissue disease. Use of calcium-channel antagonists can occasionally precipitate erythromelalgia [15].

Severe Raynaud's phenomenon (see Chapter 28), especially that secondary to systemic sclerosis and other connective tissue diseases, is more difficult to treat and may be poorly responsive to nifedipine. For these patients, intravenous prostacyclin or one of its stable analogues such as iloprost may be necessary [16–21]. Prostacyclin inhibits platelet adhesion and aggregation, and vascular smooth muscle proliferation, increases red cell deformability, and decreases blood viscosity. For reasons that are poorly understood, it causes sustained clinical benefit, a single low-dose infusion (0.5 ng/kg/min) often causing clinical remission for several weeks. Side effects include flushing, headaches and hypotension.

The serotonin antagonist ketanserin is not clinically beneficial [22], but fluoxetine, a selective serotonin reuptake inhibitor, has been reported to be effective [23], as has dazoxiben, a thromboxane synthetase inhibitor [24]. α-Adrenergic-blocking agents [25,26] (e.g. thymoxamine, a non-selective α-adrenoceptor blocker) 40 mg three times daily, or prazosin [25], a selective α-adrenergic-blocking agent, 0.5–1.0 mg three times daily, may suffice in mild cases. The use of intravenous calcitonin gene-related peptide (CGRP) has been recommended for severe Raynaud's phenomenon [27]. CGRP, which was given in a dosage of 0.6 µg/min for 3 h/day on 5 consecutive days, causes flushing, diarrhoea, headache and hypotension.

Perniosis also responds well to calcium-channel antagonists. A double-blind cross-over placebo-controlled study of nifedipine in 10 patients [28] showed a convincing response in the nifedipine phase of the trial. Other drugs reported anecdotally to improve the peripheral circulation include oxpentifylline (pentoxifylline), fibrinolytic agents including stanozolol, and low-molecular-weight dextran infusion.

References

1 Block JA, Sequeira W. Raynaud's phenomenon. *Lancet* 2001; **357**: 2042–8.
2 Herrick AL. Treatment of Raynaud's phenomenon: new insights and developments. *Curr Rheumatol Rep* 2003; **5**: 168–74.
3 Generini S, Del Rosso A, Pignone A, Matucci Cerinic M. Current treatment options in Raynaud's phenomenon. *Curr Treat Options Cardiovasc Med* 2003; **5**: 147–61.
4 Hummers LK, Wigley FM. Management of Raynaud's phenomenon and digital ischaemic lesions in scleroderma. *Rheum Dis Clin North Am* 2003; **29**: 293–313.
5 Riemekasten G, Sunderkötter C. Vasoactive therapies in systemic sclerosis. *Rheumatology (Oxford)* 2006; **45** (Suppl. 3): iii, 49–51.
6 Henness S, Wigley FM. Current drug therapy for scleroderma and secondary Raynaud's phenomenon: evidence-based review. *Curr Opin Rheumatol* 2007; **19**: 611–8.
7 Thompson AE, Shea B, Welch V *et al.* Calcium-channel blockers for Raynaud's phenomenon in systemic sclerosis. *Arthritis Rheum* 2001; **44**: 1841–7.
8 Thompson AE, Pope JE. Calcium channel blockers for primary Raynaud's phenomenon: a meta-analysis. *Rheumatology (Oxford)* 2005; **44**: 145–50.
9 Dziadzio M, Denton CP, Smith R *et al.* Losartan therapy for Raynaud's phenomenon and scleroderma: clinical and biochemical findings in a 15-week, randomized, parallel-group, controlled trial. *Arthritis Rheum* 1999; **42**: 2646–55.
10 Fries R, Shariat K, von Wilmowsky H, Böhm M. Sildenafil in the treatment of Raynaud's phenomenon resistant to vasodilatory therapy. *Circulation* 2005; **112**: 2980–5.
11 Levien TL. Phosphodiesterase inhibitors in Raynaud's phenomenon. *Ann Pharmacother* 2006; **40**: 388–93.
12 Ramos-Casals M, Brito-Zerón P, Nardi N *et al.* Successful treatment of severe Raynaud's phenomenon with bosentan in four patients with systemic sclerosis. *Rheumatology (Oxford)* 2004; **43**: 1454–6.
13 Selenko-Gebauer N, Duschek N, Minimair G *et al.* Successful treatment of patients with severe secondary Raynaud's phenomenon with the endothelin receptor antagonist bosentan. *Rheumatology (Oxford)* 2006; **45** (Suppl. 3): iii, 45–8.
14 Smith CD, McKendry RJR. Controlled trial of nifedipine in the treatment of Raynaud's phenomenon. *Lancet* 1982; **ii**: 1299–301.
15 Drenth JPH, Michiels JJ, Van Joost T, Vuzeuski VD. Verapamil-induced secondary erythermalgia. *Br J Dermatol* 1992; **127**: 292–4.
16 Fink AN, Frishman WH, Azizad M, Agarwal Y. Use of prostacyclin and its analogues in the treatment of cardiovascular disease. *Heart Dis* 1999; **1**: 29–40.
17 Pope J, Fenlon D, Thompson A *et al.* Iloprost and cisaprost for Raynaud's phenomenon in progressive systemic sclerosis. *Cochrane Database Syst Rev* 2000; CD000953.
18 Stratton R, Shiwen X, Martini G *et al.* Iloprost suppresses connective tissue growth factor production in fibroblasts and in the skin of scleroderma patients. *J Clin Invest* 2001; **108**: 241–50.
19 Scorza R, Caronni M, Mascagni B *et al.* Effects of long-term cyclic iloprost therapy in systemic sclerosis with Raynaud's phenomenon: a randomized, controlled study. *Clin Exp Rheumatol* 2001; **19**: 503–8.
20 Mittag M, Beckheinrich P, Haustein UF. Systemic sclerosis-related Raynaud's phenomenon: effects of iloprost infusion therapy on serum cytokine, growth factor and soluble adhesion molecule levels. *Acta Derm Venereol (Stockh)* 2001; **81**: 294–7.
21 Bettoni L, Geri A, Airo P *et al.* Systemic sclerosis therapy with iloprost: a prospective observational study of 30 patients treated for a median of 3 years. *Clin Rheumatol* 2002; **21**: 244–50.
22 Pope J, Fenlon D, Thompson A *et al.* Ketanserin for Raynaud's phenomenon in progressive systemic sclerosis. *Cochrane Database Syst Rev* 2000; CD000954.
23 Coleiro B, Marshall SE, Denton CP *et al.* Treatment of Raynaud's phenomenon with the selective serotonin reuptake inhibitor fluoxetine. *Rheumatology (Oxford)* 2001; **40**: 1038–43.
24 Tindell H, Tooke JE, Menys VC *et al.* Effect of dazoxiben, a thromboxane synthetase inhibitor on skin blood flow following cold challenge in patients with Raynaud's phenomenon. *Eur J Clin Invest* 1985; **15**: 20–3.
25 Pope J, Fenlon D, Thompson A *et al.* Prazosin for Raynaud's phenomenon in progressive systemic sclerosis. *Cochrane Database Syst Rev* 2000; CD000956.
26 Wise RA, Wigley FM, White B *et al.* Efficacy and tolerability of a selective alpha(2C)-adrenergic receptor blocker in recovery from cold-induced vasospasm in scleroderma patients: a single-center, double-blind, placebo-controlled, randomized crossover study. *Arthritis Rheum* 2004; **50**: 3994–4001.
27 Bunker CB, Reavley C, O'Shaungmessy DJ, Dowd PM. Calcitonin gene related peptide in treatment of severe peripheral vascular insufficiency in Raynaud's phenomenon. *Lancet* 1993; **342**: 80–3.
28 Dowd PM, Rustin MHA, Lanigan S. Nifedipine in the treatment of chilblains. *BMJ* 1986; **293**: 923–4.

Traditional Chinese herbal medicine

The treatment involves taking a 'tea' prepared from a decoction of plant materials. Usually 10 or so plant materials are included. Trials have also been performed using a tablet form of treatment (Zemaphyte®) and showed a beneficial response in children [1] and adults [2] with atopic eczema. Even when treatment is effective and continued, the benefit often wears off after 6–12 months. Relapses occur once treatment is stopped. Of concern are the reports of hepatotoxicity [3–6] and renal toxicity [7] potentially associated with Chinese herbal remedies. While Chinese herbs cannot yet be recommended for the routine treatment of children with atopic eczema, they did help approximately half of the children who took part in the Great Ormond Street Hospital Trial [8]. Further adequate randomized controlled trials are necessary [9]. Chinese herbs have also been advocated for psoriasis [10]. Side effects of Chinese herbal medicine are discussed in Chapter 75.

References

1 Sheehan MP, Atherton DJ. A controlled trial of traditional Chinese medical plants in widespread non-exudative atopic eczema. *Br J Dermatol* 1992; **126**: 179–84.

2 Sheehan MP, Rustin MHA, Atherton DJ *et al.* Efficacy of traditional Chinese herbal therapy in adult atopic dermatitis. *Lancet* 1992; **340**: 13–7.

3 Davies EG, Pollock I, Steele HM. Chinese herbs for eczema. *Lancet* 1990; **336**: 177.

4 Graham-Brown R. Toxicity of Chinese herbal remedies. *Lancet* 1992; **340**: 673.

5 Perharic-Walton L, Murray V. Toxicity of Chinese herbal remedies. *Lancet* 1992; **340**: 674.

6 Mostefa-Cara N, Pauwels A, Pinus E *et al.* Fatal hepatitis after herbal tea. *Lancet* 1992; **340**: 674.

7 Lord GM, Tagore R, Cook T *et al.* Nephropathy caused by Chinese herbs in the UK. *Lancet* 1999; **354**: 481–2.

8 Sheehan MP, Atherton DJ. One year follow-up of children treated with Chinese medicinal herbs for atopic eczema. *Br J Dermatol* 1994; **130**: 488–93.

9 Armstrong NC, Ernst E. The treatment of eczema with Chinese herbs: a systematic review of randomized clinical trials. *Br J Clin Pharmacol* 1999; **48**: 262–4.

10 Tse TW. Use of common Chinese herbs in the treatment of psoriasis. *Clin Exp Dermatol* 2003; **28**: 469–75.

CHAPTER 75
Drug Reactions

S.M. Breathnach
St John's Institute of Dermatology, St Thomas' Hospital, London, UK

Incidence of drug reactions, 75.3
Classification and mechanisms of drug reactions, 75.9
Histopathology of drug reactions, 75.21
Types of clinical reaction, 75.22
Exanthematic (maculopapular) reactions, 75.22
Purpura, 75.23
Annular erythema, 75.23
Pityriasis rosea-like reactions, 75.24
Psoriasiform eruptions, 75.24
Exfoliative dermatitis, 75.24
Anaphylaxis and anaphylactoid reactions, 75.25
Urticaria, 75.26
Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, 75.26
Erythema multiforme, Stevens–Johnson syndrome and toxic epidermal necrolysis, 75.27
Serum sickness, 75.27
Fixed eruptions, 75.28
Lichenoid eruptions, 75.30
Photosensitivity, 75.30
Pigmentation reactions, 75.32
Acneiform and pustular eruptions, 75.34
Acute generalized exanthematous pustulosis (toxic pustuloderma), 75.34
Eczematous eruptions, 75.35
Bullous eruptions, 75.37
Vasculitis, 75.40
Lupus erythematosus-like syndrome, 75.41
Dermatomyositis reactions, 75.42
Scleroderma-like reactions, 75.42
Erythema nodosum, 75.43
Pseudolymphomatous drug hypersensitivity syndrome, 75.44
Acanthosis nigricans-like and ichthyosiform eruptions, 75.44
Erythromelalgia, 75.44
Hair changes, 75.45
Nail changes, 75.46
Oral conditions, 75.46
Important or widely prescribed drugs, 75.47
Antibacterial agents, 75.47
Antileprotic drugs, 75.62
Antifungal drugs, 75.64
Antiviral agents, 75.66
Antimalarials, 75.69
Anthelmintics, 75.71
Drugs for *Pneumocystis*, 75.72
Non-steroidal anti-inflammatory drugs, 75.72
Drugs acting on the central nervous system, 75.78
Drugs acting on the cardiovascular system, 75.89
Drugs acting on the respiratory system, 75.98
Drugs acting on the renal system, 75.99
Drugs acting on the skeletal system, 75.99
Drugs for erectile dysfunction, 75.99
Metals and metal antagonists, 75.99
Anticoagulants, fibrinolytic agents and antiplatelet drugs, 75.104
Vitamins including retinoids, 75.108
Hormones and related compounds, 75.114
Chemotherapeutic (cytotoxic) agents, 75.121
Drugs affecting the immune response, 75.136
Injections, infusions and procedures, 75.150
Drugs affecting metabolism or gastrointestinal function, 75.156
Miscellaneous drugs, 75.158
Herbal remedies, homeopathy and naturopathy (alternative therapy), 75.160
Industrial and other exposure to chemicals, 75.162
Local and systemic effects of topical applications, 75.163
Management of drug reactions, 75.167
Diagnosis, 75.167
Treatment, 75.175

Introduction [1–4]

A drug may be defined as a chemical substance, or combination of substances, administered for the investigation, prevention or treatment of diseases or symptoms, real or imagined. The distinction between drugs and 'other chemicals' is not always easily made, as chemicals of very diverse structure are increasingly added to foods and beverages as dyes, flavours or preservatives. Such chemicals may cause harmful side effects. Moreover, chemicals used in agriculture or in veterinary medicine may contaminate human food. In addition, with the advent of therapeutic agents that may be useful for improving the appearance, as with minoxidil for androgenetic alopecia and tretinoin for photo-aged skin, the distinction between drugs and cosmetics has become blurred [5].

An adverse drug reaction (ADR) may be defined as an undesirable clinical manifestation resulting from administration of a particular drug; this includes reactions due to overdose, predictable side effects and unanticipated adverse manifestations. Another definition is that of 'an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product' [6]. It has been proposed that therapeutic ineffectiveness should also be regarded as an ADR [7]. ADRs may be said to be the inevitable price we pay for the benefits of modern drug therapy [8]. They are costly

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

both in terms of the human illness caused and in economic terms, and can undermine the doctor–patient relationship.

Sometimes, ADRs result from human error [9]. In one study, 0.9% of 530 medication errors resulted in ADRs [10]; these usually involved errors at the ordering stage, but also occurred at the administration stage [11]. In hospitals, medication errors occur at a rate of about one per patient per day; dispensing errors made by pharmacy staff range from 0.87 to 2.9% [12]. ADRs are underreported and are an underestimated cause of morbidity and mortality; it has been estimated that ADRs represent the fourth to the sixth leading cause of death [13]. The actual frequency of fatal adverse drug events is unknown; estimates in the USA are as high as 140 000/year, although this number is heavily disputed [14]. In one study, 68% of fatal ADRs were judged to have been preventable; of these, a pharmacist could have prevented 57% [15]. Approximately 1 in 2000 of all deaths for which there were records of coroners' inquests in one district were related to drugs; of these, 20% were due to errors [16]. During 1995, 206 deaths were attributed to ADRs on death certificates in the USA, but the spontaneous post-marketing surveillance system (MedWatch) of the Food and Drug Administration (FDA) tabulated 6894 fatalities. The numbers of deaths in these datasets varied 34-fold and were up to several 100-fold less than values based on extrapolations of surveillance programmes [17]. Confusion may occur between drugs with similar spelling of their brand names [18,19]. It has been proposed that licensing authorities should exercise more control over the naming of new proprietary formulations, that non-proprietary and new proprietary names should be internationalized, and that doctors should issue printed prescriptions if possible [20].

The average extra length of stay for patients with an adverse drug event in one study in the USA was 1.9 days, and the average extra cost of hospitalization was $1939 [21]. In another study, at a university-affiliated hospital, the mean cost of an ADR or medication error varied from $95 for additional laboratory tests to $2640 for intensive care; the estimated total cost for the medication-related problems reported in 1994 was almost $1.5 million [22]. In a European study, ADRs occurred at 10.1 per 1000 patient-days, and the cost of ADRs leading to hospitalization was estimated at €11 357 per hospital bed per year [23]. Litigation was reported for 14% of fatal ADR cases at one centre; judgements and settlements averaged $1.1 million [15]. Drug reactions, principally to corticosteroids and methotrexate, accounted for 32% of claims and 26% of dollar losses in dermatology malpractice suits in the USA from 1963 to 1973 inclusive [24]. Medication side effects, most frequently to corticosteroids, antibiotics and chemotherapeutic agents, represented 26% of lawsuits in a study of dermatology residency programmes in the USA between 1964 and 1988 [25]. If legal consequences are to be avoided, consistent care is needed at every stage from drug manufacture to administration [26].

It is in everyone's interests to minimize the chances of ADR occurrence, and to this end government regulatory bodies and the pharmaceutical industry collaborate to ensure adequate screening of new products. In addition to extensive *in vitro* and animal testing, prolonged and strictly controlled clinical trials are essential. Even so, hazards cannot be completely eliminated, because a serious reaction of low incidence may not be suspected until a very large number of patients have been treated with a new drug. Pre-marketing clinical trials conducted before a new drug is licensed may have involved less than 5000 patients, with exclusion of women of childbearing potential, the elderly and children, and those with coexistent disease and using a number of common drug treatments [27]. They will not identify adverse reactions occurring in less than 0.1–1% of patients, or those occurring only after prolonged administration, or with a long latency period, or only in susceptible patients, or when the drug is combined with some other factor, such as another drug [28,29]. Participation in post-marketing pharmacosurveillance by clinicians is generally voluntary, and underreporting is widespread [27].

Another problem is that only a very small fraction of all adverse reactions are ever reported to monitoring agencies, and first warning is still often given by anecdotal reports published in medical journals [30,31]. Many of these reports are subsequently validated, but a substantial proportion of poorly documented reports are not [31,32]. In an analysis of 5737 articles from 80 countries between 1972 and 1979, only half the reports contained enough information for the calculation of the frequency of a particular reaction [32]. The usefulness of anecdotal case reports has been called into question, as suspicions are seldom subjected to confirmatory investigation, and such alerts are not systematically incorporated into drug reference sources [33,34]. As incorrect reports may have serious legal and other consequences, a heavy responsibility rests with medical editors; a chance association or coincidental reaction should not be allowed to enter the literature. Criteria for assessment of potential drug reactions have been promulgated, and include: recurrence on challenge; existence of a pharmacological basis for the reactions; the occurrence of immediate acute or local reactions at the time of administration, of previously known reactions with a new route of administration, or of repeated rare reactions; and the presence of immunological abnormalities [31,35]. In the assessment of an unrecorded new reaction, the existence of similar but unpublished reports to the manufacturer or to surveillance bodies is of particular importance.

References

1 Bork K. *Cutaneous Side Effects of Drugs*. Philadelphia: Saunders, 1988.
2 Breathnach SM, Hintner H. *Adverse Drug Reactions and the Skin*. Oxford: Blackwell Scientific Publications, 1992.
3 Zürcher L, Krebs A. *Cutaneous Drug Reactions*. Basel: Karger, 1992.
4 Litt JZ, Pawlak WA Jr. *Drug Eruption Reference Manual*. New York: Parthenon, 1997.
5 Lavrijsen APM, Vermeer BJ. Cosmetics and drugs. Is there a need for a third group: cosmeceutics? *Br J Dermatol* 1991; **124**: 503–4.
6 Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *Lancet* 2000; **356**: 1255–9.
7 Meyboom RH, Lindquist M, Flygare AK *et al*. The value of reporting therapeutic ineffectiveness as an adverse drug reaction. *Drug Saf* 2000; **23**: 95–9.
8 Nolan L, O'Malley K. Adverse drug reactions in the elderly. *Br J Hosp Med* 1989; **41**: 446–57.
9 Wright D, Mackenzie SJ, Buchan I *et al*. Critical events in the intensive therapy unit. *Lancet* 1991; **338**: 676–8.
10 Bates DW, Boyle DL, Vander Vliet MB *et al*. Relationship between medication errors and adverse drug events. *J Gen Intern Med* 1995; **10**: 199–205.
11 Bates DW, Cullen DJ, Laird N *et al*. Incidence of adverse drug events and potential adverse drug events. Implications for prevention. ADE Prevention Study Group. *JAMA* 1995; **274**: 29–34.
12 Allan EL, Barker KN. Fundamentals of medication error research. *Am J Hosp Pharm* 1990; **47**: 555–71.

13 Brown SD Jr, Landry FJ. Recognizing, reporting, and reducing adverse drug reactions. *South Med J* 2001; **94**: 370–3.
14 Kelly WN. Can the frequency and risks of fatal adverse drug events be determined? *Pharmacotherapy* 2001; **21**: 521–7.
15 Kelly WN. Potential risks and prevention. Part 1: fatal adverse drug events. *Am J Health Syst Pharm* 2001; **58**: 1317–24.
16 Ferner RE, Whittington RM. Coroner's cases of death due to errors in prescribing or giving medicines or to adverse drug reactions: Birmingham 1986–1991. *J R Soc Med* 1994; **87**: 145–8.
17 Chyka PA. How many deaths occur annually from adverse drug reactions in the United States? *Am J Med* 2000; **109**: 122–30.
18 Fine SN, Eisdorfer RM, Miskovitz PF, Jacobson IM. Losec or Lasix? *N Engl J Med* 1990; **322**: 1674.
19 Faber J, Azzugnuni M, Di Romana S, Vanhaeverbeek M. Fatal confusion between 'Losec' and 'Lasix'. *Lancet* 1991; **337**: 1286–7.
20 Aronson JK. Confusion over similar drug names. Problems and solutions. *Drug Saf* 1995; **12**: 55–60.
21 Evans RS, Classen DC, Stevens LE *et al*. Using a hospital information system to assess the effects of adverse drug events. In: *Proceedings of the Ann Symp Comp Appl Medical Care*. 1993: 161–5.
22 Schneider PJ, Gift MG, Lee YP *et al*. Cost of medication-related problems at a university hospital. *Am J Health System Pharm* 1995; **52**: 2415–8.
23 Lagnaoui R, Moore N, Fach J *et al*. Adverse drug reactions in a department of systemic diseases-oriented internal medicine: prevalence, incidence, direct costs and avoidability. *Eur J Clin Pharmacol* 2000; **56**: 181–6.
24 Altman J. Survey of malpractice claims in dermatology. *Arch Dermatol* 1975; **111**: 641–4.
25 Hollabaugh ES, Wagner RF Jr, Weedon VW, Smith EB. Patient personal injury litigation against dermatology residency programs in the United States 1964–1988. *Arch Dermatol* 1990; **126**: 618–22.
26 Day AT. Adverse drug reactions and medical negligence. *Adverse Drug React Bull* 1995; **172**: 651–4.
27 Gough S. Post-marketing surveillance: a UK/European perspective. *Curr Med Res Opin* 2005; **21**: 565–70.
28 Bruinsma W. Drug monitoring in dermatology. *Int J Dermatol* 1986; **25**: 166–7.
29 Committee of Management Prescribers' Journal. Adverse drug reactions. *Prescribers J* 1991; **31**: 1–3.
30 Anonymous. Crying wolf on drug safety. *BMJ* 1982; **284**: 219–20.
31 Venning GR. Validity of anecdotal reports of suspected adverse drug reactions: the problem of false alarms. *BMJ* 1982; **284**: 249–52.
32 Venulet J, Blattner R, von Bülow J, Berneker GC. How good are articles on adverse drug reactions? *BMJ* 1982; **284**: 252–4.
33 Stern RS, Chan H-L. Usefulness of case report literature in determining drugs responsible for toxic epidermal necrolysis. *J Am Acad Dermatol* 1989; **21**: 317–22.
34 Loke YK, Price D, Derry S, Aronson JK. Case reports of suspected adverse drug reactions—systematic literature survey of follow-up. *BMJ* 2006; **332**: 335–9.
35 Stern RS, Wintroub BU. Adverse drug reactions: reporting and evaluating cutaneous reactions. *Adv Dermatol* 1987; **2**: 3–18.

Incidence of drug reactions [1,2]

Data collection

It is difficult to obtain reliable information on the incidence of drug reactions, despite attempts at monitoring by government and the pharmaceutical industry. One problem is the lack of standardized coding for drug reactions [3]. Moreover, the information that is available must be interpreted with considerable care, because data will be biased, depending on the method of collection [1,2]. Thus, data on medical in-patients, especially from acute care facilities, may indicate a relatively high incidence, because these patients are generally sicker and receive more intensive drug treatment. In contrast, spontaneous reporting may underestimate the true incidence [4–7]. National schemes for collating reported ADRs exist in many countries, and the World Health Organization's Adverse Reaction Collaborating Centre, in Uppsala, provides a very large database [2], as does the Adverse Event Reporting System of the US Food and Drug Administration [6–8]. For the 33-year period from 1969 to 2002, about 2.3 million case reports of adverse events for the cumulative number of approximately 6000 marketed drugs were entered in the FDA database [8]. During this period, numerous drug reactions were identified, over 75 drugs/drug products were removed from the market, and 11 drugs were restricted; drugs withdrawn or restricted represent about 1% of marketed drugs. The UK's 'yellow card' reporting scheme solicits ADR reports from doctors, dentists, coroners and drug manufacturers; the wide availability of reporting forms is important in encouraging reporting [2]. The scheme has recently encouraged reporting by nursing staff, midwives and health visitors [9]. Yellow reporting cards may be obtained electronically on http://yellowcard.mhra.gov.uk/. Pharmacists also play an important role in reporting ADRs [10]. The advisability of direct reporting of ADRs by patients is becoming an increasingly important topic for discussion in the world of pharmacovigilance [11–13]. Patient reports identified possible new ADRs not previously reported by health professionals [12], and were judged to contribute significantly to pharmacovigilance [13]. However, 94% of claimed ADRs in children were not confirmed following complete evaluation [14]. 'Pharmacovigilence' in France, which involves reporting to regional centres, along with most other national schemes, also relies entirely on spontaneous reporting [15,16]. Institution of an ADR reporting project in Rhode Island in the USA increased the rate of reporting of such reactions more than 17-fold over a 2-year period [17]. The quality of ADR reporting to the FDA improved following introduction of the MedWatch scheme [18]. Specialty-based systems for spontaneous reporting of ADRs (e.g. the Adverse Drug Reaction Reporting System of the American Academy of Dermatology [19] and the Gruppo Italiano Studi Epidemiologici in Dermatologia [20]) have been introduced. In the UK, in contrast, the specialty-based Cutaneous Reactions Database established at the Institute of Dermatology in 1988 was unfortunately closed in 1990 because of a meagre response [21].

Reporting of ADRs in clinical trials is neglected, compared with efficacy outcomes; of 192 randomized trials analysed, only 46% specified reasons for withdrawals due to toxicity, and only 39% of clinical adverse effects and 29% of laboratory-determined toxicity were adequately documented [22]. Inherent difficulties with spontaneous reporting are that reactions associated with newly marketed drugs, those of unusual morphology and reactions starting soon after initiation of therapy are more likely to be notified; at best only a crude estimate of true incidence is provided [23–25]. Thus, drugs with a high potential for eliciting clinically significant ADRs are usually detected and either withdrawn from the market or placed on restricted use within the first year or two of marketing [26]. In contrast, spontaneous reports do not reliably detect ADRs widely separated in time from the original use of the drug, or that occur more commonly in populations not usually exposed to the drug [27]. They are an unreliable measure of risk, and may simply provide evidence of the relative awareness among physicians of specific toxic effects [28], or of variation in prescribing practice [29].

All national spontaneous reporting systems are compromised by underreporting [2,4,5]; in the UK, past surveys suggested that only around 10% of serious reactions were notified to the Committee on Safety of Medicines [30,31]. A survey of 44 000 patients receiving one or other of seven new drugs suggested that underreporting by the spontaneous system may be as high as 98% when compared with information collected by the more objective 'event monitoring' system [15]. A recent report emphasizes that most UK doctors do not report adverse drug reactions [32]. This is a worldwide phenomenon. The Global Advisory Committee on Vaccine Safety of the WHO Adverse Reactions Database determined that, in 2005, three countries contributed 82% of vaccine-related reports, the mean time lag being 2.4 years [33]; concern was expressed that many member countries did not forward all or even any reports of adverse events, and that poor timeliness and regularity of reporting jeopardized timely generation of safety signals. Heavy prescribing by a minority of doctors immediately following licensing may place patients at unnecessary risk, and affects safety monitoring of new drugs; the 10% of doctors who prescribed most heavily accounted for 42% of total prescribing in a survey of 28 402 general practitioners asked to supply post-marketing data on 27 new drugs dispensed in England between September 1984 and June 1991, but returned proportionately far fewer questionnaires [34]. Reasons for underreporting include lack of time, lack of report forms and the misconception that absolute confidence in the diagnosis of an adverse reaction was important [35]; workload may affect reporting [36]. Another factor is the perceived deterrent to reporting ADRs caused by fear of involvement in litigation [37]; reporting of errors should be free of recrimination [38]. The offer of a small fee increased the rate of reporting in one hospital study almost 50-fold [39].

Pharmacoepidemiology, the epidemiological assessment of adverse drug effects, and pharmacovigilance, the process of identifying and responding to safety issues about marketed drugs, necessitate making use of information from clinical trials, spontaneous reporting systems, speciality-based reporting systems, case reports, prescription monitoring, case series, cohort studies, case–control studies, population-based registries using computerized material, and special surveillance programmes (e.g. Boston Collaborative Drug Surveillance Program in the USA) [40–42]. Crude inspection of lists of spontaneously reported drug-event combinations can be supplemented by quantitative and automated numerator-based methods such as Bayesian data mining; pharmacovigilance specialists should not be intimidated by the mathematics [43]. Computerized detection of adverse events may soon be practical on a widespread basis [44]. This is just as well, as it has been estimated that the top 20 drug companies will each need to launch four to six times the number of drugs they currently produce merely to maintain shareholder returns, with more trials, and more safety reports for evaluation [45].

References

1 Breathnach SM, Hintner H. *Adverse Drug Reactions and the Skin*. Oxford: Blackwell Scientific Publications, 1992.

2 Rawlins MD, Breckenridge AM, Wood SM. National adverse drug reaction reporting: a silver jubilee. *Adverse Drug React Bull* 1989; **138**: 516–9.

3 Bonnetblanc JM, Roujeau JC, Benichou C. Standardized coding is needed for reports of adverse drug reactions. *BMJ* 1996; **312**: 776–7.

4 Edwards IR. The management of adverse drug reactions: from diagnosis to signal. *Therapie* 2001; **56**: 727–33.

5 Hazell L, Shakir SA. Under-reporting of adverse drug reactions: a systematic review. *Drug Saf* 2006; **29**: 385–96.

6 Rodriguez EM, Staffa JA, Graham DJ. The role of databases in drug postmarketing surveillance. *Pharmacoepidemiol Drug Saf* 2001; **10**: 407–10.

7 Ahmad SR. Adverse drug event monitoring at the Food and Drug Administration. *J Gen Intern Med* 2003; **18**: 57–60.

8 Wysowski DK, Swartz L. Adverse drug event surveillance and drug withdrawals in the United States, 1969–2002: the importance of reporting suspected reactions. *Arch Intern Med* 2005; **165**: 1363–9.

9 Morrison-Griffiths S, Walley TJ, Park BK *et al.* Reporting of adverse drug reactions by nurses. *Lancet* 2003; **361**: 1347–8.

10 van Grootheest AC, van Puijenbroek EP, de Jong-van den Berg LT. Contribution of pharmacists to the reporting of adverse drug reactions. *Pharmacoepidemiol Drug Saf* 2002; **11**: 205–10.

11 van Grootheest K, de Graaf L, de Jong-van den Berg LT. Consumer adverse drug reaction reporting: a new step in pharmacovigilance? *Drug Saf* 2003; **26**: 211–7.

12 Blenkinsopp A, Wilkie P, Wang M, Routledge PA. Patient reporting of suspected adverse drug reactions: a review of published literature and international experience. *Br J Clin Pharmacol* 2007; **63**: 148–56.

13 de Langen J, van Hunsel F, Passier A *et al.* Adverse drug reaction reporting by patients in the Netherlands: three years of experience. *Drug Saf* 2008; **3**: 515–24.

14 Rebelo Gomes E, Fonseca J, Araujo L, Demoly P. Drug allergy claims in children: from self-reporting to confirmed diagnosis. *Clin Exp Allergy* 2008; **38**: 191–8.

15 Fletcher AP. Spontaneous adverse drug reaction reporting vs event monitoring: a comparison. *J R Soc Med* 1991; **84**: 341–4.

16 Moore N, Paux G, Begaud B *et al.* Adverse drug reaction monitoring: doing it the French way. *Lancet* 1985; **ii**: 1056–8.

17 Scott HD, Thacher-Renshaw A, Rosenbaum SE *et al.* Physician reporting of adverse drug reactions. Results of the Rhode Island Adverse Drug Reaction Reporting Project. *JAMA* 1990; **263**: 1785–8.

18 Piazza-Hepp TD, Kennedy DL. Reporting of adverse events to MedWatch. *Am J Health Syst Pharm* 1995; **52**: 1436–9.

19 Stern RS, Bigby M. An expanded profile of cutaneous reactions to nonsteroid anti-inflammatory drugs. Reports to a specialty-based system for spontaneous reporting of adverse reactions to drugs. *JAMA* 1984; **252**: 1433–7.

20 Gruppo Italiano Studi Epidemiologici in Dermatologia. Spontaneous monitoring of adverse reactions to drugs by Italian dermatologists: a pilot study. *Dermatologica* 1991; **182**: 12–7.

21 Kobza Black A, Greaves MM. Cutaneous reactions database closure. *Br J Dermatol* 1990; **123**: 277.

22 Ioannidis JP, Lau J. Improving safety reporting from randomised trials. *Drug Saf* 2002; **25**: 77–84.

23 Griffin JP, Weber JCP. Voluntary systems of adverse reaction reporting: Part I. *Adverse Drug React Acute Poisoning Rev* 1985; **4**: 213–30.

24 Griffin JP, Weber JCP. Voluntary systems of adverse reaction reporting: Part II. *Adverse Drug React Acute Poisoning Rev* 1986; **5**: 23–55.

25 Griffin JP, Weber JCP. Voluntary systems of adverse reaction reporting: Part III. *Adverse Drug React Acute Poisoning Rev* 1989; **8**: 203–15.

26 Ajayi FO, Sun H, Perry J. Adverse drug reactions: a review of relevant factors. *J Clin Pharmacol* 2000; **40**: 1093–101.

27 Brewer T, Colditz GA. Postmarketing surveillance and adverse drug reactions: current perspectives and future needs. *JAMA* 1999; **281**: 824–9.

28 Miwa LJ, Jones JK, Pathiyal A, Hatoum H. Value of epidemiologic studies in determining the true incidence of adverse events. The nonsteroidal anti-inflammatory drug story. *Arch Intern Med* 1997; **157**: 2129–36.

29 Clark RC, Maxwell SR, Kerr S *et al.* The influence of primary care prescribing rates for new drugs on spontaneous reporting of adverse drug reactions. *Drug Saf* 2007; **30**: 357–66.

30 Rawlins MD. Spontaneous reporting of adverse drug reactions I: the data. *Br J Clin Pharmacol* 1988; **26**: 1–5.

31 Bem JL, Mann RD, Rawlins MD. Review of yellow cards 1986 and 1987. *BMJ* 1988; **296**: 1319.

32 Hitchen L. Most doctors still don't report adverse reactions to drugs. *BMJ* 2008; **336**: 299.

33 Letourneau M, Wells G, Walop W, Duclos P. Improving global monitoring of vaccine safety: a quantitative analysis of adverse event reports in the WHO Adverse Reactions Database. *Vaccine* 2008; **26**: 1185–94.
34 Inman W, Pearce G. Prescriber profile and post-marketing surveillance. *Lancet* 1993; **342**: 658–61.
35 Belton KJ, Lewis SC, Payne S *et al.* Attitudinal survey of adverse drug reaction reporting by medical practitioners in the United Kingdom. *Br J Clin Pharmacol* 1995; **39**: 223–6.
36 Bateman DN, Sanders GL, Rawlins MD. Attitudes to adverse drug reaction reporting in the Northern Region. *Br J Clin Pharmacol* 1992; **34**: 421–6.
37 Kaufman MB, Stoukides CA, Campbell NA. Physicians' liability for adverse drug reactions. *South Med J* 1994; **87**: 780–4.
38 Upton DR, Cousins DH. Avoiding drug errors. Reporting of errors should be free of recrimination. *BMJ* 1995; **311**: 1367.
39 Feely J, Moriarty S, O'Connor P. Stimulating reporting of adverse drug reactions by using a fee. *BMJ* 1990; **300**: 22–3.
40 Stern RS, Wintroub BU. Adverse drug reactions: reporting and evaluating cutaneous reactions. *Adv Dermatol* 1987; **2**: 3–18.
41 Stern RS. Epidemiologic assessment of adverse drug effects. *Semin Dermatol* 1989; **8**: 136–40.
42 Rawlins MD. Pharmacovigilance: paradise lost, regained or postponed? *J R Coll Physicians Lond* 1995; **29**: 41–5.
43 Hauben M, Zhou X. Quantitative methods in pharmacovigilance: focus on signal detection. *Drug Saf* 2003; **26**: 159–86.
44 Bates DW, Evans RS, Murff H *et al.* Detecting adverse events using information technology. *J Am Med Inform Assoc* 2003; **10**: 115–28.
45 Peachey J. From pharmacovigilance to pharmacoperformance. *Drug Saf* 2002; **25**: 399–405.

General incidence of adverse drug reactions

The incidence of ADRs varies from 6% [1] to 30% [2], with an estimated at least 90 million courses of drug treatment given yearly in the USA, as recorded in 1984 [3]. A report in 2006 estimated that adverse drug reactions resulted in 250 000 UK admissions a year [4]. The reported percentage of patients who develop an ADR during hospitalization varies markedly in different studies from 1.4 to 44%, although in most studies the incidence is about 10–20% [5–7], of which about one-third are allergic or pseudoallergic [7]. In one study, 0.23% of a total of 90 910 admissions had drug allergy; antimicrobials and antiepileptic drugs comprised 75% of the drug allergies reported [8]. The incidence of drug allergy in hospitalized patients was 4.2 per 1000; drug allergy developed during in-patient treatment in 2.07 per 1000 hospitalizations [8]. About 3–8% of hospital admissions are a consequence of ADRs [9–11]. A survey of 30 195 randomly selected hospital records in 51 hospitals in the state of New York found that 19% of adverse events caused by medical treatment were the result of drug complications; the most frequently implicated classes of drugs were antibiotics, antitumour agents and anticoagulants [12]. Negligence accounted for 18% of ADRs, and allergic/cutaneous complications constituted 14% of all drug-related complications.

Less information is available about the incidence among outpatients. It has been estimated that about 1 in 40 consultations in general practice are the result of ADRs [13], and eventually 41% of patients develop a reaction [14]. In one multicentre general practice study in the UK, the percentage of consultations involving an ADR increased from 0.6% for patients aged 0–20 years to 2.7% for patients aged over 50 years [15]; in another study, 2.5% of consultations were the result of iatrogenic illness [16]. It was estimated that more than 1 in 9 emergency department visits were due to drug-related adverse events, a potentially preventable problem [17].

Fatal reactions to drugs are more common than is generally realized. It was previously estimated that penicillin caused 300 deaths each year in the USA alone [18]. Anaphylactic reactions to penicillin were reported, in 1968, to occur in about 0.015%, and fatal reactions in up to 0.002% (i.e. 1 per 50 000), of treatment courses [19]. These figures may be somewhat lower today, with use of newer beta-lactam antibiotics. The risk of fatal aplastic anaemia with chloramphenicol therapy was reported as at least 1 in 60 000 [20], and the risk of a fatal outcome from treatment with monoamine oxidase inhibitors may be of the same order. It has been estimated that the incidence of fatality as a result of a drug reaction among in-patients is between 0.1 and 0.3% [6,21,22]; fatality due to allergy occurs at a rate of 0.09 per 1000 cases [8].

References

1 Deswarte RD. Drug allergy: problems and strategies. *J Allergy Clin Immunol* 1984; **74**: 209–21.
2 Jick H. Adverse drug reactions: the magnitude of the problem. *J Allergy Clin Immunol* 1984; **74**: 555–7.
3 Goldstein RA. Foreword. Symposium proceedings on drug allergy: prevention, diagnosis, treatment. *J Allergy Clin Immunol* 1984; **74**: 549–50.
4 Hitchen L. Adverse drug reactions result in 250,000 UK admissions a year. *BMJ* 2006; **332**: 1109.
5 Breathnach SM, Hintner H. *Adverse Drug Reactions and the Skin*. Oxford: Blackwell Scientific Publications, 1992.
6 Gruchalla R. Understanding drug allergies. *J Allergy Clin Immunol* 2000; **105**: S637–44.
7 Demoly P, Bousquet J. Epidemiology of drug allergy. *Curr Opin Allergy Clin Immunol* 2001; **1**: 305–10.
8 Thong BY, Leong KP, Tang CY, Chung HH. Drug allergy in a general hospital: results of a novel prospective inpatient reporting system. *Ann Allergy Asthma Immunol* 2003; **90**: 342–7.
9 McKenney JM, Harrison WL. Drug-related hospital admissions. *Am J Hosp Pharm* 1976; **33**: 792–5.
10 Levy M, Kewitz H, Altwein W *et al.* Hospital admissions due to adverse drug reactions: a comparative study from Jerusalem and Berlin. *Eur J Clin Pharmacol* 1980; **17**: 25–31.
11 Black AJ, Somers K. Drug-related illness resulting in hospital admission. *J R Coll Physicians Lond* 1984; **18**: 40–1.
12 Leape LL, Brennan TA, Laird N *et al.* The nature of adverse events in hospitalized patients. Results of the Harvard Medical Practice Study II. *N Engl J Med* 1991; **324**: 377–84.
13 Kellaway GSM, McCrae E. Intensive monitoring of adverse drug effects in patients discharged from acute medical wards. *NZ Med J* 1973; **78**: 525–8.
14 Martys CR. Adverse reactions to drugs in general practice. *BMJ* 1979; **ii**: 1194–7.
15 Lumley LE, Walker SR, Hall CG *et al.* The under-reporting of adverse drug reactions seen in general practice. *Pharm Med* 1986; **1**: 205–12.
16 Mulroy R. Iatrogenic disease in general practice: its incidence and effects. *BMJ* 1973; **ii**: 407–10.
17 Zed PJ, Abu-Laban RB, Balen RM *et al.* Incidence, severity and preventability of medication-related visits to the emergency department: a prospective study. *Can Med Assoc J* 2008; **178**: 1563–9.
18 Parker CW. Allergic reactions in man. *Pharmacol Rev* 1983; **34**: 85–104.
19 Idsøe O, Guthe T, Willcox RR, De Weck AL. Nature and extent of penicillin side reactions, with particular reference to fatalities from anaphylactic shock. *Bull WHO* 1968; **38**: 159–88.
20 Witts LJ. Adverse reactions to drugs. *BMJ* 1965; **ii**: 1081–6.
21 Davies DM, ed. *Textbook of Adverse Drug Reactions*, 3rd edn. Oxford: Oxford University Press, 1985: 1–11.
22 Caranasos GJ, May FE, Stewart RB, Cluff LE. Drug-associated deaths of medical inpatients. *Arch Intern Med* 1976; **136**: 872–5.

Risk of adverse drug reactions among different patient groups

Certain patient groups are at increased risk of developing an ADR. Women are more likely than men to develop ADRs [1]. The incidence of such reactions increases with the number of drugs taken in both hospital in-patients [2–4] and out-patients [5,6]. Although data are somewhat conflicting [7], the burden of evidence suggests that the incidence of adverse reactions increases with patient age [1,8,9]. Although those over 65 years of age comprise only 12% of the population in the USA, 33% of all drugs are prescribed for this age group, and the elderly have a significantly higher incidence of ADRs, related to decreased organ reserve capacity, altered pharmacokinetics and pharmacodynamics, and polypharmacy [10]. Similarly, in the UK, the elderly are dispensed twice as many prescriptions as the national average [11]. Potential adverse drug interactions are more common in elderly patients because of the higher number of concurrent medications, rather than age-based factors [12].

ADRs contribute to the need for hospitalization in 6–17% of elderly in-patients [13–16]. Inappropriate medication is a major cause of ADRs in elderly patients [16,17]; 27% of elderly patients on medication who were admitted to a teaching hospital experienced ADRs, of which almost 50% were due to drugs with absolute contraindications and/or that were unnecessary [18]. ADRs occur in 6–17% of children admitted to specialist paediatric hospitals [19].

Immunosuppressed patients are most frequently affected, such as those with connective tissue diseases, including systemic lupus erythematosus (SLE) (relative risk 4.68 higher) and autoimmune hepatitis, AIDS patients (relative risk 8.68), and non-Hodgkin's lymphoma [20,21]. Patients with Sjögren's syndrome (SS) have also been reported to have a high frequency of drug allergy. In different series, drug allergy has been reported in 43% of SS patients compared with 9% of patients with SLE without SS [22], in 62% of SS patients [23], and in 41% of rheumatoid arthritis patients with SS compared with 17% of those without SS [24]. Antibiotic allergy is increased in SLE [25].

References

1 Davies DM, ed. *Textbook of Adverse Drug Reactions*, 3rd edn. Oxford: Oxford University Press, 1985: 1–11.

2 Vakil BJ, Kulkarni RD, Chabria NL *et al.* Intense surveillance of adverse drug reactions. An analysis of 338 patients. *J Clin Pharmacol* 1975; **15**: 435–41.

3 May FE, Stewart RB, Cluff LE. Drug interactions and multiple drug administration. *Clin Pharmacol Ther* 1977; **22**: 322–8.

4 Steel K, Gertman PM, Crescenzi C, Anderson J. Iatrogenic illness on a general medical service at a university hospital. *N Engl J Med* 1981; **304**: 638–42.

5 Kellaway GSM, McCrae E. Intensive monitoring of adverse drug effects in patients discharged from acute medical wards. *NZ Med J* 1973; **78**: 525–8.

6 Hutchinson TA, Flegel KM, Kramer MS *et al.* Frequency, severity, and risk factors for adverse reactions in adult outpatients: a prospective study. *J Chron Dis* 1986; **39**: 533–42.

7 Gurwitz JH, Avorn J. The ambiguous relation between aging and adverse drug reactions. *Ann Intern Med* 1991; **114**: 956–66.

8 Nolan L, O'Malley K. Adverse drug reactions in the elderly. *Br J Hosp Med* 1989; **41**: 446–57.

9 Sullivan JR, Shear NH. Drug eruptions and other adverse drug effects in aged skin. *Clin Geriatr Med* 2002; **18**: 21–42.

10 Sloan RW. Principles of drug therapy in geriatric patients. *Am Fam Physician* 1992; **45**: 2709–18.

11 Black D, Denham MJ, Acheson RM *et al.* Medication for the elderly. A report of the Royal College of Physicians. *J R Coll Physicians Lond* 1984; **18**: 7–17.

12 Heininger-Rothbucher D, Bischinger S, Ulmer H *et al.* Incidence and risk of potential adverse drug interactions in the emergency room. *Resuscitation* 2001; **49**: 283–8.

13 Col N, Fanale JE, Kronholm P. The role of medication noncompliance and adverse drug reactions in hospitalizations of the elderly. *Arch Intern Med* 1990; **150**: 841–5.

14 Levy M, Kewitz H, Altwein W *et al.* Hospital admissions due to adverse drug reactions: a comparative study from Jerusalem and Berlin. *Eur J Clin Pharmacol* 1980; **17**: 25–31.

15 Williamson J, Chopin JM. Adverse reactions to prescribed drugs in the elderly: a multicentre investigation. *Age Ageing* 1980; **9**: 73–80.

16 Franceschi M, Scarcelli C, Niro V *et al.* Prevalence, clinical features and avoidability of adverse drug reactions as cause of admission to a geriatric unit: a prospective study of 1756 patients. *Drug Saf* 2008; **31**: 545–56.

17 Passarelli MC, Jacob-Filho W, Figueras A. Adverse drug reactions in an elderly hospitalised population: inappropriate prescription is a leading cause. *Drugs Aging* 2005; **22**: 767–77.

18 Lindley CM, Tully MP, Paramsothy V, Tallis RC. Inappropriate medication is a major cause of adverse drug reactions in elderly patients. *Age Ageing* 1992; **21**: 294–300.

19 Rylance G, Armstron D. Adverse drug events in children. *Adverse Drug React Bull* 1997; **184**: 689–702.

20 Hernández-Salazar A, Rosales SP, Rangel-Frausto S *et al.* Epidemiology of adverse cutaneous drug reactions. A prospective study in hospitalized patients. *Arch Med Res* 2006; **37**: 899–902.

21 Fiszenson-Albala F, Auzerie V, Mahe E *et al.* A 6-month prospective survey of cutaneous drug reactions in a hospital setting. *Br J Dermatol* 2003; **149**: 1018–22.

22 Katz J, Marmary Y, Livneh A, Danon Y. Drug allergy in Sjögren's syndrome. *Lancet* 1991; **337**: 239.

23 Bloch KJ, Buchanan WW, Wohl MJ, Bunim JJ. Sjögrens's syndrome: a clinical, pathological and serological study of 62 cases. *Medicine (Baltimore)* 1965; **44**: 187–231.

24 Williams BO, Onge RAST, Young A *et al.* Penicillin allergy in rheumatoid arthritis with special reference to Sjögren's syndrome. *Ann Rheum Dis* 1969; **28**: 607–11.

25 Petri M, Allbritton J. Antibiotic allergy in systemic lupus erythematosus: a case–control study. *J Rheumatol* 1992; **19**: 265–9.

Acquired immune deficiency syndrome

Patients with acquired immune deficiency syndrome (AIDS) appear to be at increased risk for ADRs [1–7], up to 100-fold by some estimates [6,7]. The reasons are likely to be multifactorial, and include changes in drug metabolism, oxidative stress, cytokine profiles and immune hyperactivation. Human immunodeficiency virus (HIV)-positive individuals have been postulated to have a systemic glutathione deficiency, resulting in a decreased capacity to scavenge reactive hydroxylamine derivatives of sulphonamides, although this has been disputed (see section on pharmacogenetic mechanisms, p. 75.12). In the past, drugs especially implicated included sulphonamides such as co-trimoxazole (trimethoprim–sulfamethoxazole) [8–14], other sulphur congeners, for example dapsone [15], pentamidine, antituberculosis regimens containing thioacetazone (thiacetazone) [16,17] or isoniazid and rifampicin, amoxicillin–clavulanate [18,19], clindamycin, pyrimethamine [20] and thalidomide. Patients with AIDS are more likely to have particularly severe reactions, ranging from erythema multiforme to toxic epidermal necrolysis (TEN) (especially with sulphonamides, clindamycin, phenobarbital (phenobarbitone) and chlormezanone) [21,22], and to demonstrate multiple cutaneous drug reactions [2] (see Chapter 76). Drugs that are implicated in hypersensitivity have changed since the advent of highly active

antiretroviral therapy, including abacavir, non-nucleoside reverse transcriptase inhibitors such as nevirapine, and protease inhibitors such as amprenavir [6]. There has been a decrease in the use of antimicrobials such as co-trimoxazole, and in Europe nevirapine has replaced sulphonamides as the leading cause of Stevens–Johnson syndrome and TEN related to AIDS [23] (see also Chapter 76).

References

1 Bayard PJ, Berger TG, Jacobson MA. Drug hypersensitivity reactions and human immunodeficiency virus disease. *J Acquir Immune Defic Syndr* 1992; **5**: 1237–57.
2 Carr A, Tindall B, Penny R, Cooper DA. Patterns of multiple-drug hypersensitivities in HIV-infected patients. *AIDS* 1993; **7**: 1532–3.
3 Sadick NS, McNutt NS. Cutaneous hypersensitivity reactions in patients with AIDS. *Int J Dermatol* 1993; **32**: 621–7.
4 Coopman SA, Johnson RA, Platt R, Stern RS. Cutaneous disease and drug reactions in HIV infection. *N Engl J Med* 1993; **328**: 1670–4.
5 Heller HM. Adverse cutaneous drug reactions in patients with human immunodeficiency virus-1 infection. *Clin Dermatol* 2000; **18**: 485–9.
6 Pirmohamed M, Park BK. HIV and drug allergy. *Curr Opin Allergy Clin Immunol* 2001; **1**: 311–6.
7 Phillips E, Mallal S. Drug hypersensitivity in HIV. *Curr Opin Allergy Clin Immunol* 2007; **7**: 324–30.
8 Kletzel M, Beck S, Elser J *et al.* Trimethoprim–sulfamethoxazole oral desensitization in hemophiliacs infected with human immunodeficiency virus with a history of hypersensitivity reactions. *Am J Dis Child* 1991; **145**: 1428–9.
9 Carr A, Swanson C, Penny R, Cooper DA. Clinical and laboratory markers of hypersensitivity to trimethoprim–sulfamethoxazole in patients with *Pneumocystis carinii* pneumonia and AIDS. *J Infect Dis* 1993; **167**: 180–5.
10 Mathelier-Fusade P, Leynadier F. Intolerance aux sulfamides chez les sujets infectés par le VIH. Origine toxique et allergique. *Presse Med* 1993; **22**: 1363–5.
11 Chanock SJ, Luginbuhl LM, McIntosh K, Lipshultz SE. Life-threatening reaction to trimethoprim/sulfamethoxazole in pediatric human immunodeficiency virus infection. *Pediatrics* 1994; **93**: 519–21.
12 Roudier C, Caumes E, Rogeaux O *et al.* Adverse cutaneous reactions to trimethoprim–sulfamethoxazole in patients with the acquired immunodeficiency syndrome and *Pneumocystis carinii* pneumonia. *Arch Dermatol* 1994; **130**: 1383–6.
13 Rabaud C, Charreau I, Izard S *et al.* Adverse reactions to cotrimoxazole in HIV-infected patients: predictive factors and subsequent HIV disease progression. *Scand J Infect Dis* 2001; **33**: 759–64.
14 Eliaszewicz M, Flahault A, Roujeau JC *et al.* Prospective evaluation of risk factors of cutaneous drug reactions to sulfonamides in patients with AIDS. *J Am Acad Dermatol* 2002; **47**: 40–6.
15 Jorde UP, Horowitz HW, Wormser GP. Utility of dapsone for prophylaxis of *Pneumocystis carinii* pneumonia in trimethoprim–sulfamethoxazole-intolerant, HIV-infected individuals. *AIDS* 1993; **7**: 355–9.
16 Nunn P, Kibuga D, Gathua S *et al.* Cutaneous hypersensitivity reactions due to thiacetazone in HIV-1 seropositive patients treated for tuberculosis. *Lancet* 1991; **337**: 627–30.
17 Pozniak AL, MacLeod GA, Mahari M *et al.* The influence of HIV status on single and multiple drug reactions to antituberculous therapy in Africa. *AIDS* 1992; **6**: 809–14.
18 Battegay M, Opravil M, Wütrich B, Lüthy R. Rash with amoxycillin–clavulanate therapy in HIV-infected patients. *Lancet* 1989; **ii**: 1100.
19 Paparello SF, Davis CE, Malone JL. Cutaneous reactions to amoxicillin–clavulanate among Haitians. *AIDS* 1994; **8**: 276–7.
20 Piketty C, Weiss L, Picard-Dahan C *et al.* Toxidermies à la pyrimethamine chez les patients infectés par le virus de l'immunodeficience acquise. *Presse Med* 1995; **24**: 1710.
21 Porteous DM, Berger TG. Severe cutaneous drug reactions (Stevens–Johnson syndrome and toxic epidermal necrolysis) in human immunodeficiency virus infection. *Arch Dermatol* 1991; **127**: 740–1.
22 Saiag P, Caumes E, Chosidow O *et al.* Drug-induced toxic epidermal necrolysis (Lyell syndrome) in patients infected with the human immunodeficiency virus. *J Am Acad Dermatol* 1992; **26**: 567–74.
23 Fagot JP, Mockenhaupt M, Bouwes-Bavinck JN *et al.* Nevirapine and the risk of Stevens–Johnson syndrome or toxic epidermal necrolysis. *AIDS* 2001; **15**: 1843–8.

Drug reaction frequency in relation to types of medication

The incidence of reactions to a particular drug must obviously be related to the quantity prescribed [1]. Nearly one in every 10 prescriptions in the USA in 1981 contained either hydrochlorothiazide or codeine [2]. One in every five prescriptions was for a diuretic or other cardiovascular drug; analgesics and antiarthritics constituted 13%, anti-infectives 13%, and sedatives and other psychotropics 11% of prescriptions. Of the 10 drugs most frequently reported by the yellow-card system to the UK Committee on Safety of Medicines in the first 6 months of 1986, seven were non-steroidal anti-inflammatory drugs (NSAIDs) (accounting for 74% of serious adverse reactions); the remaining drugs were the angiotensin-converting enzyme (ACE) inhibitors enalapril and captopril (accounting for 19% of serious reactions) and co-trimoxazole (accounting for 7% of serious adverse reactions) [3]. In another study, anti-inflammatory agents were the drugs responsible for almost 50% of the reactions necessitating admission to a general medical ward; most of the drug-related admissions to the hospital as a whole were caused by digoxin, phenytoin, tranquillizers, antihypertensives, cardiac depressants and antineoplastic agents [4]. ADRs accounted for 8% of 1999 consecutive admissions to medical wards in yet another study [5]; the drugs most frequently involved were antirheumatics and analgesics (27%), cardiovascular drugs (23%), psychotropic drugs (14%), antidiabetics (12%), antibiotics (7%) and corticosteroids (5%). Nitrofurantoin and insulin were associated with admission rates of 617 and 182 per million daily doses, compared with 10 for diuretics and seven for benzodiazepines. ADRs were responsible for the admission of 2% of 5227 consecutive patients to the University Hospital Centre in Zagreb [6]; drugs incriminated included acetylsalicylic acid (aspirin) (38%), other NSAIDs (23%), cardiovascular agents (20%) and antimicrobials (3%).

References

1 Committee on Safety of Medicines. CSM update: non-steroidal anti-inflammatory drugs and serious gastrointestinal reactions-2. *BMJ* 1986; **292**: 1190–1.
2 Baum C, Kennedy DL, Forbes MB, Jones JK. Drug use in the United States in 1981. *JAMA* 1984; **251**: 1293–7.
3 Mann RD. The yellow card data: the nature and scale of the adverse drug reactions problem. In: Mann RD, ed. *Adverse Drug Reactions*. Carnforth: Parthenon, 1987: 5–66.
4 Black AJ, Somers K. Drug-related illness resulting in hospital admission. *J R Coll Physicians Lond* 1984; **18**: 40–1.
5 Hallas J, Gram LF, Grodum E *et al.* Drug related admissions to medical wards: a population based survey. *Br J Clin Pharmacol* 1992; **33**: 61–8.
6 Huic M, Mucolic V, Vrhovac B *et al.* Adverse drug reactions resulting in hospital admission. *Int J Clin Pharmacol Ther* 1994; **32**: 675–82.

Incidence of drug eruptions (adverse cutaneous drug reactions (ACDRs))

Drug eruptions are probably the most frequent of all manifestations of drug sensitivity—24% of all ADRs in one study [1] and 29% in another [2]—although their incidence is difficult to determine. Even where the eruption is apparently the only

manifestation, death can result from exfoliative dermatitis, erythema multiforme or TEN. For information on the incidence of drug-induced erythema multiforme, Stevens–Johnson syndrome and TEN, the reader is referred to Chapter 76. Epidemiological data suggest that a relatively small number of drugs are most frequently responsible for the most serious reactions [3]. Cutaneous reactions to common drugs such as digoxin, antacids, paracetamol (acetaminophen), glyceryl trinitrate, spironolactone, meperidine, aminophylline, propranolol, prednisone, salbutamol and diazepam are very rare.

The baseline rate of rash development, reflecting a variety of different causes, was similar for 36 marketed drugs in the UK, at around 1 per 1000 patients per month from the second to the sixth month of one study; however, the rate for rash in the first month after prescription varied substantially from 0.9 to 6.4 per 1000 patients per month, and was highest for diltiazem [4]. Most estimates of the incidence of drug eruptions are inaccurate, because many mild and transitory eruptions are not recorded, and because skin disorders are sometimes falsely attributed to drugs. There have been several studies of the incidence of drug eruptions [4–15]. The reaction rate has been reported as about 2% [7,10], or 5.5 adverse skin reactions per 100 000 of the population in four Italian regions [11]. The prevalence of drug reactions in 4785 hospitalized patients was 0.7% in another series, the most commonly seen dermatoses being a morbilliform rash (51.2%), urticaria (12.2%) and erythema multiforme (4.9%), and drugs most frequently associated with ACDRs were amoxicillin clavulanate, amphotericin B and metamizole [16]. In yet another series of hospitalized patients, cutaneous drug reactions occurred at a prevalence of 3.6/1000, were principally exanthematous (56%), and were severe in 34% of cases and life-threatening in 2%; imputable drugs were mainly antibiotics, especially penicillins [17]. There is reportedly a relatively low incidence of severe ACDRs in China; antibiotics, anticonvulsants and traditional Chinese medicines are the most common causative drugs [18].

A survey [8] of ACDRs among in-patients found that one-third were fixed drug reactions, one-third were exanthematous and 20% were urticaria or angio-oedema; the high frequency of fixed drug reactions in this series reflects the fact that patients under study had been admitted to hospital. Antimicrobial agents were most frequently incriminated (42%), then antipyretic/anti-inflammatory analgesics (27%), with drugs acting on the central nervous system accounting for 10% of reactions. A few drugs gave specific reactions (e.g. phenazone salicylate caused a fixed eruption, and penicillin and salicylates caused urticaria); however, most were capable of causing several types of eruption. Morbilliform exanthematous eruptions, urticaria and generalized pruritus were the commonest reactions in other large series [10,15]. The average patient had received eight different medications, which contributed considerably to the difficulties in identifying the causative drugs [10]. Antibiotics, blood products and inhaled mucolytics together caused 75% of the eruptions; amoxicillin (51 cases/1000 exposed), trimethoprim–sulfamethoxazole (33 cases/1000 exposed) and ampicillin (33 cases/1000 exposed) caused the most reactions. Reaction rates varied in the range of 1–8% for several classes of antibiotic [15]. In a study of ACDRs among children and adolescents in northern India, antibiotics were responsible for most eruptions, followed by antiepileptics; co-trimoxazole was the commonest antibacterial culprit, followed by penicillin and its semi-synthetic derivatives, and then sulphonamides, with antiepileptics being the most frequently incriminated drugs in erythema multiforme, Stevens–Johnson syndrome and TEN [12]. More recent studies from India found that the drugs most often incriminated included antimicrobials (especially sulphonamides, including co-trimoxazole), anticonvulsants and NSAIDs (especially ibuprofen) [13,14]. Antimicrobials, NSAIDs, analgesics and radiological contrast media were the most frequent culprits in a study from Italy [11], and the most common drug classes involved in yet another study were cardiovascular agents (36%), contrast media (20%), drugs affecting blood clotting (13%) and anti-infectives (14%) [1].

Desensitizing vaccines, muscle relaxants, intravenous anaesthetics and radiological contrast media were the most frequent causes of anaphylaxis or anaphylactoid reactions reported to the UK Committee on Safety of Medicines in 1986/1987 [19]. The chairman of the Committee accordingly advised, in 1986, that desensitizing vaccines only be given where full cardiorespiratory resuscitation facilities are available. Quinidine, cimetidine, phenylbutazone, hydrochlorothiazide (especially in combination with amiloride) and furosemide (frusemide) have also been frequently implicated in drug eruptions [20,21]. In the USA and the UK, antibiotics, hypnotics and tranquillizers are the most frequent offenders; on a reaction per dose basis, penicillin, warfarin and imipramine are the three drugs most frequently incriminated [22]. The prevalence of a history of penicillin allergy in the US population has been estimated to be between 5 and 10% [23]. An international study of 1790 patients from 11 countries documented the frequency of allergic reactions to long-term benzathine benzylpenicillin (benzathine penicillin) prophylaxis for rheumatic fever at 3.2%; anaphylaxis occurred in 0.2% (1.2/10 000 injections) and the fatality rate was 0.05% (0.31/10 000 injections) [24]. Reactions to sulphonamides may affect up to 5% of those treated [25]. Rashes occurred in 7.3% of children given commonly used oral antibiotics [26]. Based on the number of patients treated, the frequency of rash with cefaclor was 12.3%, with penicillins 7.4%, with sulphonamides 8.5%, and with other cephalosporins 2.6%.

References

1 Bordet R, Gautier S, Le Louet H *et al.* Analysis of the direct cost of adverse drug reactions in hospitalised patients. *Eur J Clin Pharmacol* 2001; **56**: 935–41.

2 Thiessard F, Roux E, Miremont-Salamé G *et al.* Trends in spontaneous adverse drug reaction reports to the French pharmacovigilance system (1986–2001). *Drug Saf* 2005; **28**: 731–40.

3 Stern RS, Steinberg LA. Epidemiology of adverse cutaneous reactions to drugs. *Dermatol Clin* 1995; **13**: 681–8.

4 Kubota K, Kubota N, Pearce GL *et al.* Signalling drug-induced rash with 36 drugs recently marketed in the United Kingdom and studied by Prescription-Event Monitoring. *Int J Clin Pharmacol Ther* 1995; **33**: 219–25.

5 Kaplan AP. Drug-induced skin disease. *J Allergy Clin Immunol* 1984; **74**: 573–9.

6 Kauppinen K. Cutaneous reactions to drugs. With special reference to severe mucocutaneous bullous eruptions and sulphonamides. *Acta Derm Venereol Suppl (Stockh)* 1972; **68**: 1–89.

7 Arndt KA, Jick H. Rates of cutaneous reactions to drugs. A report from the Boston Collaborative Drug Surveillance Program. *JAMA* 1976; **235**: 918–22.

8 Kauppinen K, Stubb S. Drug eruptions: causative agents and clinical types. A series of inpatients during a 10-year period. *Acta Derm Venereol (Stockh)* 1984; **64**: 320–4.
9 Alanko K, Stubb S, Kauppinen K. Cutaneous drug reactions: clinical types and causative agents. A five year survey of in-patients (1981–1985). *Acta Derm Venereol (Stockh)* 1989; **69**: 223–6.
10 Bigby M, Jick S, Jick H, Arndt K. Drug-induced cutaneous reactions. A report from the Boston Collaborative Drug Surveillance Program on 15438 consecutive inpatients, 1975 to 1982. *JAMA* 1986; **256**: 3358–63.
11 Naldi L, Conforti A, Venegoni M *et al*. Cutaneous reactions to drugs. An analysis of spontaneous reports in four Italian regions. *Br J Clin Pharmacol* 1999; **48**: 839–46.
12 Sharma VK, Dhar S. Clinical pattern of cutaneous drug eruption among children and adolescents in north India. *Pediatr Dermatol* 1995; **12**: 178–83.
13 Sharma VK, Sethuraman G, Kumar B. Cutaneous adverse drug reactions: clinical pattern and causative agents. A 6 year series from Chandigarh, India. *J Postgrad Med* 2001; **47**: 95–9.
14 Raksha MP, Marfatia YS. Clinical study of cutaneous drug eruptions in 200 patients. *Indian J Dermatol Venereol Leprol* 2008; **74**: 80.
15 Bigby M. Rates of cutaneous reactions to drugs. *Arch Dermatol* 2001; **137**: 765–70.
16 Hernández-Salazar A, Rosales SP, Rangel-Frausto S *et al*. Epidemiology of adverse cutaneous drug reactions. A prospective study in hospitalized patients. *Arch Med Res* 2006; **37**: 899–902.
17 Fiszenson-Albala F, Auzerie V, Mahe E *et al*. A 6-month prospective survey of cutaneous drug reactions in a hospital setting. *Br J Dermatol* 2003; **149**: 1018–22.
18 Li LF, Ma C. Epidemiological study of severe cutaneous adverse drug reactions in a city district of China. *Clin Exp Dermatol* 2006; **31**: 642–7.
19 Bem JL, Mann RD, Rawlins MD. Review of yellow cards 1986 and 1987. *BMJ* 1988; **296**: 1319.
20 Kalish RS. Drug eruptions: a review of clinical and immunological features. *Adv Dermatol* 1991; **6**: 221–37.
21 Thestrup-Pedersen K. Adverse reactions in the skin from antihypertensive drugs. *Dan Med Bull* 1987; **34**: 3–5.
22 Davies DM, ed. *Textbook of Adverse Drug Reactions*, 3rd edn. Oxford: Oxford University Press, 1985: 1–11.
23 Green CR, Rosenblum A. Report of the Penicillin Study Group: American Academy of Allergy. *J Allergy Clin Immunol* 1971; **48**: 331–43.
24 International Rheumatic Fever Study Group. Allergic reactions to long-term benzathine penicillin prophylaxis for rheumatic fever. *Lancet* 1991; **337**: 1308–10.
25 Anonymous. Hypersensitivity to sulphonamides: a clue? *Lancet* 1986; **ii**: 958–9.
26 Ibia EO, Schwartz RH, Wiedermann BL. Antibiotic rashes in children: a survey in a private practice setting. *Arch Dermatol* 2000; **136**: 849–54.

Classification and mechanisms of drug reactions [1–11]

Drug reactions may arise as a result of immunological allergy directed against the drug itself, a reactive metabolite or some contaminant of the drug or, more commonly, by non-immunological mechanisms, such as pseudoallergic reactions caused by non-immune-mediated degranulation of mast cells and basophils. Autoimmune reactions, in which the drug elicits an immune reaction to autologous structures, may also occur. Drug reactions may be predictable (type A) or unpredictable (type B) (Table 75.1). About 80% of drug reactions are predictable, usually dose-related, are a function of the known pharmacological actions of the drug and occur in otherwise normal individuals. Side effects are unavoidable at the regular prescribed dose. Unpredictable reactions are dose-independent, are not related to the pharmacological action of the drug, and may have a basis in pharmacogenetic variation in drug bioactivation and drug or metabolite detoxification or clearance. Intolerance refers to an expected drug reaction occurring at a lower dose, and idiosyncratic and hypersensitivity reactions are qualitatively abnormal, unexpected responses. Type C reactions include those associated with prolonged therapy (e.g. analgesic nephropathy), and type D reactions consist of delayed reactions (e.g. carcinogenesis and teratogenicity). The skin has a limited repertoire of morphological reaction patterns in response to a wide variety of stimuli, and it is therefore often impossible to identify an offending drug, or the pathological mechanism involved, on the basis of clinical appearances alone. We therefore remain relatively ignorant about the mechanisms underlying many clinical drug eruptions.

Table 75.1 Classification of adverse drug reactions.

Non-immunological
Predictable
Overdosage
Side effects
Cumulation
Delayed toxicity
Facultative effects
Drug interactions
Metabolic alterations
Teratogenicity
Non-immunological activation of effector pathways
Exacerbation of disease
Drug-induced chromosomal damage
Unpredictable
Intolerance
Idiosyncrasy
Immunological (unpredictable)
IgE-dependent drug reactions
Immune complex-dependent drug reactions
Cytotoxic drug-induced reactions
Cell-mediated reactions
Miscellaneous
Jarisch–Herxheimer reactions
Infectious mononucleosis–ampicillin reaction

References

1 Rawlins MD, Thompson JW. Mechanisms of adverse drug reactions. In: Davies DM, ed. *Textbook of Adverse Drug Reactions*, 3rd edn. Oxford: Oxford University Press, 1985: 12–38.
2 Wintroub BU, Stern R. Cutaneous drug reactions: pathogenesis and clinical classification. *J Am Acad Dermatol* 1985; **13**: 833–45.
3 Stern RS, Wintroub BU, Arndt KA. Drug reactions. *J Am Acad Dermatol* 1986; **15**: 1282–8.
4 Breathnach SM, Hintner H. *Adverse Drug Reactions and the Skin*. Oxford: Blackwell Scientific Publications, 1992.
5 Weiss ME. Drug allergy. *Med Clin North Am* 1992; **76**: 857–82.
6 Gibaldi M. Adverse drug effect-reactive metabolites and idiosyncratic drug reactions: Part I. *Ann Pharmacother* 1992; **26**: 416–21.
7 Anderson JA. Allergic reactions to drugs and biological agents. *JAMA* 1992; **268**: 2844–57.
8 Pichler WJ. Medikamentenallergien. *Ther Umsch* 1994; **51**: 55–60.
9 Rieder MJ. Mechanisms of unpredictable adverse drug reactions. *Drug Saf* 1994; **11**: 196–212.
10 Breathnach SM. Mechanisms of drug eruptions: Part I. *Australas J Dermatol* 1995; **36**: 121–7.
11 Bonnetblanc JM, Vaillant L, Wolkenstein P. Facteurs predisposants des reactions cutanées aux medicaments. *Ann Dermatol Vénéréol* 1995; **122**: 484–6.

Non-immunological drug reactions

Overdosage

The manifestations are a predictable exaggeration of the desired pharmacological actions of the drug, and are directly related to the total amount of drug in the body. Overdosage may be absolute, as a result of a prescribing or dispensing error or due to deliberate excess intake by the patient. It may also occur despite standard dosage, due to varying individual rates of absorption, metabolism or excretion (see below). An inappropriately large dose may be given to an infant or very old person or to one with renal impairment. Drug interaction (see below) may also cause drug overdosage.

Side effects

These include unwanted or toxic effects, which are not separable from the desired pharmacological action of the drug. Examples are: the drowsiness induced by antihistamines; the atropine-like anticholinergic properties of some phenothiazines, many antihistamines, and tricyclic antidepressants; and the anagen alopecia caused by cytotoxic drugs.

Cumulative toxicity

Prolonged exposure may lead to cumulative toxicity. Accumulation of drugs in the skin may lead to colour disturbance, as a result of either deposition within phagocytic cells or mucous membranes (e.g. prolonged administration of gold, silver, bismuth or mercury) or binding of the drug or a metabolite to a skin component (e.g. high-dose chlorpromazine therapy).

Delayed toxicity

Examples are the keratoses and skin tumours that appear many years after inorganic arsenic, and the delayed hepatotoxicity associated with methotrexate therapy.

Facultative effects

These include the consequences of drug-induced alterations in skin or mucous membrane flora. Antibiotics that destroy Gram-positive bacteria may allow the multiplication of resistant Gram-negative species. Broad-spectrum antibiotics, corticosteroids and immunosuppressive drugs may promote multiplication of *Candida albicans* and favour its transition from saprophytism to pathogenicity. Corticosteroids promote the spread of tinea and erythrasma. Antibiotics such as clindamycin and tetracycline may be associated with pseudomembranous enterocolitis following bowel superinfection with *Clostridium difficile*.

Drug interactions

Interactions between two or more drugs administered simultaneously may occur before entry into the body (in an intravenous drip), in the intestine, in the blood and/or at tissue receptor sites; interaction may also occur indirectly as a result of acceleration or slowing in the rate of drug metabolism or excretion. It should be remembered that the adverse consequences of drug interactions may occur not only on introduction of a drug but also on removal of a drug that causes acceleration of drug metabolism, as this may result in effective overdosage of the remaining drug. The subject of drug interactions has been extensively reviewed [1,2]. Combinations of drugs with potential adverse interactions continue to be prescribed [3].

Intestinal drug interactions. Examples include inhibition of griseofulvin absorption by phenobarbital [1], inhibition of tetracycline absorption by antacids [4] and decreased absorption of the oral contraceptive by tetracycline [5]. Whether the last-mentioned is of real significance is a matter of debate [6].

Displacement from carrier or receptor sites. Most drugs are reversibly bound to carrier proteins in plasma or extracellular fluid; bound drug acts as a reservoir, preventing excessive fluctuation in the level of the active, unbound fraction. Displacement from a carrier protein augments drug activity, whereas displacement from a receptor site diminishes it. Many acidic drugs such as salicylates, coumarins, sulphonamides and phenylbutazone are bound to plasma albumin, and compete for binding sites. Thus, a sulphonamide may displace tolbutamide from albumin, leading to hypoglycaemia; or aspirin, sulphonamides, clofibrate or phenylbutazone may displace warfarin from albumin, causing bleeding and ecchymoses. Similarly, sulphonamides and aspirin may increase methotrexate toxicity. Ciprofloxacin increases plasma levels of theophylline.

Enzyme stimulation or inhibition [2]. A drug may either stimulate or inhibit metabolic enzymes important to its own degradation or that of another agent, with significant clinical consequences. Thus, some drugs induce synthesis of drug-metabolizing enzymes in liver microsomes. The liver microsomal hydroxylating system (which mediates metabolism of phenytoin and debrisoquine) is based on cytochrome P-450, and appears to be a family of enzymes capable of acting on different substrates including barbiturates, fatty acids and endogenous steroids. The cytochrome P-450-dependent system also catalyses deamination (e.g. amfetamine (amphetamine)), dealkylation (e.g. morphine, azathioprine), sulphoxidation (e.g. chlorpromazine, phenylbutazone), desulphuration (thiopental (thiopentone)) and dehalogenation (e.g. halogenated anaesthetics). This lack of specificity accounts for the ability of an inducing agent to stimulate metabolism of many other drugs, and of one drug to inhibit metabolism of a structurally unrelated drug. Antibiotics, if administered over a period of time (e.g. rifampicin for tuberculosis), can be enzyme inducers. Barbiturates stimulate metabolism of griseofulvin, phenytoin and coumarin anticoagulants, and griseofulvin induces increased metabolism of coumarins. Similarly, rifampicin, phenytoin and carbamazepine increase the metabolism of ciclosporin [7]. Drugs causing enzyme inhibition include chloramphenicol, cimetidine, monoamine oxidase inhibitors, *p*-aminosalicylic acid, pethidine and morphine. Dicoumarol, chloramphenicol and phenylbutazone inhibit metabolic inactivation of tolbutamide. Allopurinol inhibits metabolism of azathioprine and mercaptopurine by xanthine oxidase. Cimetidine inhibits liver enzymes and decreases hepatic blood flow, thereby potentiating the action of some β-blockers (propranolol) and benzodiazepines, carbamazepine, warfarin, morphine, phenytoin and theophylline. Ketoconazole may potentiate oral anticoagulants [8] and erythromycin may potentiate carbamazepine [9]; both may potentiate ciclosporin. Nifedipine and ciclosporin

are both metabolized by the same cytochrome P-450 enzyme, P-450cpn; ciclosporin potentiates the action of nifedipine, phenytoin and to a lesser extent valproate, by decreasing P-450cpn availability by competitive inhibition [10].

Altered drug excretion. Examples include the well-known probenecid-induced reduction in the renal excretion of penicillin, and aspirin-induced reduction in renal clearance of methotrexate.

References

1 Griffin JP, D'Arcy PF, Speirs CJ. *A Manual of Adverse Drug Interactions*, 4th edn. London: Wright (Butterworth), 1988.
2 Shapiro LE, Shear NH. Drug interactions: proteins, pumps, and P-450s. *J Am Acad Dermatol* 2002; **47**: 467–84.
3 Beers MH, Storrie MS, Lee G. Potential adverse drug interactions in the emergency room. An issue in the quality of care. *Ann Intern Med* 1990; **112**: 61–4.
4 Garty M, Hurwitz A. Effect of cimetidine and antacids on gastrointestinal absorption of tetracycline. *Clin Pharmacol Ther* 1980; **28**: 203–7.
5 Bacon JF, Shenfield GM. Pregnancy attributable to interaction between tetracycline and oral contraceptives. *BMJ* 1980; **280**: 293.
6 Fleischer AB, Resnick SD. The effect of antibiotics on the efficacy of oral contraceptives. *Arch Dermatol* 1989; **125**: 1562–4.
7 Schofield OMV, Camp RDR, Levene GM. Cyclosporin A in psoriasis: interaction with carbamazepine. *Br J Dermatol* 1990; **122**: 425–6.
8 Smith AG. Potentiation of oral anticoagulants by ketoconazole. *BMJ* 1984; **288**: 188–9.
9 Wroblewski BA, Singer WD, Whyte J. Carbamazepine–erythromycin interaction: case studies and clinical significance. *JAMA* 1986; **255**: 1165–7.
10 McFadden JP, Pontin JE, Powles AV *et al*. Cyclosporin decreases nifedipine metabolism. *BMJ* 1989; **299**: 1224.

Metabolic changes

Drugs may induce cutaneous changes by their effects on nutritional or metabolic status. Thus, drugs such as phenytoin that interfere with folate absorption or metabolism increase the risk of aphthous stomatitis, and isotretinoin may cause xanthomas by elevation of very low-density lipoproteins [1].

Reference

1 Dicken CH. Eruptive xanthomas associated with isotretinoin (13-*cis*-retinoic acid). *Arch Dermatol* 1980; **116**: 951–2.

Teratogenicity and other effects on the fetus [1–6]

The advent of isotretinoin has focused the attention of dermatologists considerably on the problem of teratogenicity in general [5]. The fetus is particularly at risk from drug-induced developmental malformations during the period of organogenesis, which lasts from about the third to the tenth week of gestation. Thalidomide, retinoids and cytotoxic drugs are proven teratogens. Heavy alcohol intake (which produces fetal alcohol syndrome), smoking, anticonvulsants (especially phenytoin and trimethadione (troxidone)), warfarin and antiplatelet drugs, inhalational anaesthetics, lithium, quinine, ACE inhibitors, misoprostol, certain antimicrobials (e.g. trimethoprim, aminoglycosides, 4-quinolones and itraconazole) and cocaine are probably teratogenic. High-dose corticosteroids have been linked to cleft palate. A major correlation has been found between the incidence of glucocorticoid-induced cleft palate and the chromosome 8 segment identified by *N*-acetyltransferase in mice [7]. 6-Aminonicotinamide-induced cleft palate and phenytoin-induced cleft lip with or without cleft palate are also influenced by this genetic region, but not as strongly. Sex hormones, psychotropic drugs, benzodiazepines, tetracycline, rifampicin, penicillamine and the folate antagonist pyrimethamine are possibly teratogenic and should be avoided in the first trimester of pregnancy. Chlorpheniramine appears safe to use. The potential adverse effects on the fetus and on the breastfed infant of a number of drugs not infrequently used by the dermatologist have been reviewed [4].

Drugs may also cause fetal damage later in pregnancy. Warfarin may cause haemorrhage, and phenytoin near to term produces a coagulation defect in the neonate, which is correctable by vitamin K. Antithyroid drugs and iodides may cause neonatal goitre and hypothyroidism. Fetal adrenal atrophy may follow high-dose maternal corticosteroid therapy. NSAIDs have various ill effects, although aspirin has been advocated in pregnancy for the prevention of fetal growth retardation. Tetracyclines are deposited in developing bones and cause discoloration and enamel hypoplasia of teeth [8]. Aminoglycoside antibiotics are ototoxic, and chloroquine has caused a neonatal chorioretinitis. Androgens and progestogens may virilize the fetus. Diethylstilbestrol (stilboestrol) administered from early pregnancy for several months has been associated with female and male genital tract abnormalities, and carcinoma of the vagina 20 years later in the offspring.

References

1 Ellis C, Fidler J. Drugs in pregnancy: adverse reactions. *Br J Hosp Med* 1982; **28**: 575–84.
2 Kalter H, Warkany J. Congenital malformations: etiologic factors and their role in prevention. *N Engl J Med* 1983; **308**: 424–31, 491–7.
3 Ashton CH. Disorders of the fetus and infant. In: Davis DM, ed. *Textbook of Adverse Drug Reactions*, 3rd edn. Oxford: Oxford University Press, 1985: 77–127.
4 Stockton DL, Paller AS. Drug administration to the pregnant or lactating woman: a reference guide for dermatologists. *J Am Acad Dermatol* 1990; **23**: 87–103.
5 Mitchell AA. Teratogens and the dermatologist. New knowledge, responsibilities, and opportunities. *Arch Dermatol* 1991; **127**: 399–401.
6 Ferner RE. Teratogenic drugs: an update. *Adverse Drug React Bull* 1993; **161**: 607–10.
7 Karolyi J, Erickson RP, Liu S, Killewald L. Major effects on teratogen-induced facial clefting in mice determined by a single genetic region. *Genetics* 1990; **126**: 201–5.
8 Witkop CJ, Wolf RO. Hypoplasia and intrinsic staining of enamel following tetracycline therapy. *JAMA* 1963; **185**: 1008–11.

Effects on spermatogenesis

Most chemotherapeutic agents potentially damage sperm; conception should also be avoided for 3 months after griseofulvin. A number of drugs cause oligospermia [1], which may come to light only as a result of infertility investigations; oestrogens, androgens, cyproterone acetate, cytotoxic drugs, including methotrexate given for psoriasis [2], colchicine, most monoamine oxidase inhibitors, ketoconazole and sulfasalazine (sulphasalazine) have all been incriminated. The synthetic retinoids isotretinoin and etretinate do not seem to affect the numbers of sperm [3,4].

References

1 Drife JO. Drugs and sperm. *BMJ* 1982; **284**: 844–5.
2 Sussman A, Leonard J. Psoriasis, methotrexate, and oligospermia. *Arch Dermatol* 1980; **116**: 215–7.
3 Schill W-B, Wagner A, Nikolowski JM, Plewig G. Aromatic retinoid and 13-*cis*-retinoic acid: spermatological investigations. In: Orfanos CE, Braun-Falco O,

Farber EM *et al.*, eds. *Retinoids, Advances in Basic Research and Therapy*. Berlin: Springer, 1981: 389–95.
4 Töröck L, Kása M. Spermatological and endocrinological examinations connected with isotretinoin treatment. In: Saurat JH, ed. *Retinoids: New Trends in Research and Therapy*. Basel: Karger, 1985: 407–10.

Non-immunological activation of effector pathways (anaphylactoid reactions)

Certain drugs, such as opiates, codeine, amfetamine, polymyxin B, D-tubocurarine, atropine, hydralazine, pentamidine, quinine and radiocontrast media, may release mast cell mediators directly to produce urticaria or angio-oedema [1–7]. Some drugs, such as radiocontrast media, may activate complement by an antibody-independent method [8]. Anaphylaxis-like responses to cyclo-oxygenase inhibitors such as aspirin and other NSAIDs may lead to amplified mast cell degranulation and enhanced biosynthesis of lipoxygenase products of arachidonic acid, which cause vasodilatation and oedema [9,10]. ACE inhibitors, which cause or exacerbate angio-oedema, may potentiate bradykinin activity; they have been reported to enhance bradykinin-induced cutaneous weals in normal individuals [11,12].

References

1 Schoenfeld MR. Acute allergic reactions to morphine, codeine, meperidine hydrochloride and opium alkaloids. *NY State J Med* 1960; **60**: 2591–3.
2 Comroe JH, Dripps RD. Histamine-like action of curare and tubocurarine injected intracutaneously and intra-arterially in man. *Anesthesiology* 1946; **7**: 260–2.
3 Greenberger PA. Contrast media reactions. *J Allergy Clin Immunol* 1984; **74**: 600–5.
4 Assem ESK, Bray K, Dawson P. The release of histamine from human basophils by radiological contrast agents. *Br J Radiol* 1983; **56**: 647–52.
5 Rice MC, Lieberman P, Siegle RL, Mason J. *In vitro* histamine release induced by radiocontrast media and various chemical analogs in reactor and control subjects. *J Allergy Clin Immunol* 1983; **72**: 180–6.
6 Watkins J. Markers and mechanisms of anaphylactoid reactions. *Monogr Allergy* 1992; **30**: 108–29.
7 Bircher AJ. Drug-induced urticaria and angioedema caused by non-IgE mediated pathomechanisms. *Eur J Dermatol* 1999; **9**: 657–63.
8 Arroyave CM, Bhatt KN, Crown NR. Activation of the alternative pathway of the complement system by radiographic contrast media. *J Immunol* 1976; **117**: 1866–9.
9 Stevenson DD, Lewis RA. Proposed mechanisms of aspirin sensitivity reactions. *J Allergy Clin Immunol* 1987; **80**: 788–90.
10 Morassut P, Yang W, Karsh J. Aspirin intolerance. *Semin Arthritis Rheum* 1989; **19**: 22–30.
11 Wood SM, Mann RD, Rawlins MD. Angio-oedema and urticaria associated with angiotensin converting enzyme inhibitors. *BMJ* 1987; **294**: 91–2.
12 Ferner RE. Effects of intradermal bradykinin after inhibition of angiotensin converting enzyme. *BMJ* 1987; **294**: 1119–20.

Exacerbation of disease

Examples of adverse drug effects on pre-existing skin conditions include lithium exacerbation of acne and psoriasis, β-blocker induction of a psoriasiform dermatitis [1] and corticosteroid withdrawal resulting in exacerbation of psoriasis; cimetidine, penicillin or sulphonamide exacerbation of lupus erythematosus (LE); and vasodilator exacerbation of rosacea. Sometimes, a drug may unmask a latent condition, as when barbiturates precipitate symptoms of porphyria.

Reference

1 Abel EA, Dicicco LM, Orenberg EK *et al.* Drugs in exacerbation of psoriasis. *J Am Acad Dermatol* 1986; **15**: 1007–22.

Intolerance

The characteristic effects of the drug are produced to an exaggerated extent by an abnormally small dose. This may simply represent an extreme within normal biological variation. Alternatively, the intolerance may be contributed to by delayed metabolism or excretion due to impaired hepatic or renal function, or by genetic variation in the rate of drug metabolism (see below).

Idiosyncrasy

This describes an uncharacteristic response, not predictable from animal experiments, and not mediated by an immunological mechanism. The cause is often unknown, but genetic variation in metabolic pathways may be involved. Such genetic abnormalities include glucose-6-phosphate dehydrogenase deficiency, hereditary methaemoglobinaemia, porphyria, glucocorticoid glaucoma and malignant hyperthermia of anaesthesia, all of which are characterized by unusual pharmacological responses to various drugs.

Pharmacogenetic mechanisms and genetic influences underlying intolerance and idiosyncratic reactions [1–5]

The pharmacokinetics of drugs, including their absorption, plasma protein binding, distribution, transportation and metabolism, and elimination, may be influenced by genetic factors. Oxidation, hydrolysis and acetylation are the three metabolic pathways most subject to genetic influence. Variation in the regulation and expression of the human cytochrome P-450 enzyme system may play a key role in both interindividual variation in sensitivity to drug toxicity and tissue-specific damage [4]. Polymorphisms in drug-metabolizing enzymes, including: cytochrome P450 (CYP) 2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5; dihydropyrimidine dehydrogenase; uridine diphosphate glucuronosyltransferase (UGT) 1A1; glutathione S-transferase, sulfotransferase 1A1; *N*-acetyltransferase, and thiopurine methyltransferase (TPMT), and in drug transporters including: P-glycoprotein (multidrug resistance 1), multidrug resistance protein 2 (MRP2), and breast cancer resistance protein (BCRP), may influence efficacy and toxicity of chemotherapy agents [5]. Thus, polymorphisms in UGT1A1*28 are associated with an increase in toxicity with irinotecan [5]. Other polymorphisms are associated with docetaxel-induced leukopenia [6]. Genetic variation in thiopurine methyltransferase activity may be linked to the side effects of azathioprine therapy, as homozygotes for the low-activity allele are at risk of myelosuppression, whereas homozygotes for high activity are inadequately immunosuppressed with conventional doses of azathioprine [5,7]. Genetic factors also influence pharmacodynamics, that is tissue or organ responsiveness. Thus, genetic variations in all these areas may underlie both intolerance and idiosyncrasy. Pharmacogenetic variability probably underlies reactions such as TEN (see Influence of human leukocyte antigen (HLA) types, below, p. 75.14). It has been proposed that most patients who have a severe ACDR have an abnormal metabolism of the offending drug [8].

Examples of genetically-mediated intolerance include pupil size responses to phenylephrine and parasympatholytics, and the very rare, dominantly-inherited, familial resistance to coumarin anticoagulants, the result of mutation in the receptor for vitamin K and anticoagulants. Low levels of red cell glucose-6-phosphate dehydrogenase, inherited as a sex-linked dominant trait, are common in black people, certain Levantine peoples and Filipinos, and result in a chronic deficit of reduced glutathione sulphydryl (SH) groups. Affected individuals are at risk of acute haemolysis on exposure to antimalarials, sulphonamides, dapsone, nitrofurantoin, phenacetin, aspirin and chloramphenicol, all of which may oxidize the few reduced SH groups in older red cells. Increased susceptibility to aminoglycoside-induced deafness in two Japanese pedigrees was associated with a particular mitochondrial DNA polymorphism [9].

References

1 Shear NH, Bhimji S. Pharmacogenetics and cutaneous drug reactions. *Semin Dermatol* 1989; **8**: 219–26.
2 Lennard MS, Tucker GT, Woods HF. Inborn 'errors' of drug metabolism. Pharmacokinetic and clinical implications. *Clin Pharmacokinet* 1990; **19**: 257–63.
3 Knowles SR, Uetrecht J, Shear NH. Idiosyncratic drug reactions: the reactive metabolite syndromes. *Lancet* 2000; **356**: 1587–91.
4 Park BK, Pirmohamed M, Kitteringham NR. The role of cytochrome P450 enzymes in hepatic and extrahepatic human drug toxicity. *Pharmacol Ther* 1995; **68**: 385–424.
5 Bosch TM, Meijerman I, Beijnen JH, Schellens JH. Genetic polymorphisms of drug-metabolising enzymes and drug transporters in the chemotherapeutic treatment of cancer. *Clin Pharmacokinet* 2006; **45**: 253–85.
6 Kiyotani K, Mushiroda T, Kubo M *et al.* Association of genetic polymorphisms in SLCO1B3 and ABCC2 with docetaxel-induced leukopenia. *Cancer Sci* 2008; **99**: 967–72.
7 Snow JL, Gibson LE. The role of genetic variation in thiopurine methyltransferase activity and the efficacy and/or side effects of azathioprine therapy in dermatologic patients. *Arch Dermatol* 1995; **131**: 193–7.
8 Chosidow O, Bourgault L, Roujeau JC. Drug rashes. What are the targets of cell-mediated cytotoxicity? *Arch Dermatol* 1994; **130**: 627–9.
9 Hutchin T, Haworth I, Higashi K *et al.* A molecular basis for human hypersensitivity to aminoglycoside antibiotics. *Nucleic Acids Res* 1993; **21**: 4174–9.

Oxidation. Anticonvulsants, many hypnotics, tricyclic antidepressants, anticoagulants and various anti-inflammatory and anxiolytic agents are eliminated by oxidation. For many drugs, oxidation rates vary as a continuous spectrum within the population. Genetic differences in metabolism of sulphonamides may underlie idiosyncratic toxicity [1–6]. Oxidative metabolism of sulphonamides by cytochrome P-450 enzymes and *N*-acetylation yields a reactive hydroxylamine intermediate [7], which is inactivated by glutathione conjugation. The hydroxylamine metabolite is toxic to lymphocytes, and the lymphocyte toxicity is markedly increased in patients with a history of hypersensitivity or with glutathione synthetase deficiency. HIV-positive individuals have been reported in some studies to have a systemic glutathione deficiency, resulting in a decreased capacity to scavenge hydroxylamine derivatives of sulphonamides, which may partially explain the increased frequency of sulphonamide reactions [8–10]. However, other studies have not been able to confirm intracellular glutathione deficiency in peripheral blood cells of HIV-infected patients [11,12].

Phenytoin, phenobarbital and carbamazepine are oxidized by the cytochrome P-450 enzyme system into potentially reactive arene oxide intermediates; liver microsomal epoxide hydrolase converts such reactive intermediates to non-toxic dihydrodiols [13–17]. Phenytoin hypersensitivity syndrome appears to be associated with an inherited deficiency of epoxide hydrolase, which is primarily responsible for detoxifying the toxic arene-oxide intermediate [13–16]. Activated phenytoin has been shown to be toxic to lymphocytes from patients with phenytoin reactions and, to a lesser degree, to lymphocytes from their parents [15]. However, in another study a genetic defect altering the structure and function of the microsomal epoxide hydrolase protein was thought unlikely to be responsible for predisposing patients to anticonvulsant adverse reactions [17].

Culprit drug-reactive metabolites, generated by a microsomal oxidation system, had increased toxic effects on lymphoid cells from patients with TEN (13 each with sulphonamide and anticonvulsant reactions) and on those from first-degree relatives, whereas oxygen free radical and/or aldehyde detoxification pathways were normal [18].

Impaired metabolism of phenacetin and phenformin, inherited as a result of genetic polymorphism in liver microsomal oxidation, may result in adverse reactions [19,20]. The induction of liver enzymes responsible for drug oxidation may itself be under genetic control [21]. There is a fourfold increase in toxicity to penicillamine in patients with rheumatoid arthritis with a genetically determined poor capacity to sulphoxidate the structurally related mucolytic agent, carbocysteine [22].

References

1 Shear NH, Spielberg SP. *In vitro* evaluation of a toxic metabolite of sulfadiazide. *Can J Physiol Pharmacol* 1985; **63**: 1370–2.
2 Shear NH, Spielberg SP. An *in vitro* lymphocytotoxicity assay for studying adverse reactions to sulphonamides. *Br J Dermatol* 1985; **113**: 112–3.
3 Shear N, Spielberg S, Grant D *et al.* Differences in metabolism of sulfonamides predisposing to idiosyncratic toxicity. *Ann Intern Med* 1986; **105**: 179–84.
4 Anonymous. Hypersensitivity to sulphonamides: a clue? *Lancet* 1986; **ii**: 958–9.
5 Rieder MJ, Uetrecht J, Shear NH *et al.* Synthesis and *in vitro* toxicity of hydroxylamine metabolites of sulphonamides. *J Pharmacol Exp Ther* 1988; **244**: 724–8.
6 Rieder MJ, Uetrecht J, Shear NH *et al.* Diagnosis of sulfonamide hypersensitivity reactions by *in-vitro* 'rechallenge' with hydroxylamine metabolites. *Ann Intern Med* 1989; **110**: 286–9.
7 Meekins CV, Sullivan TJ, Gruchalla RS. Immunochemical analysis of sulfonamide drug allergy: identification of sulfamethoxazole-substituted human serum proteins. *J Allergy Clin Immunol* 1994; **94**: 1017–24.
8 Buhl R, Jaffe HA, Holroyd KJ *et al.* Systemic glutathione deficiency in symptom-free HIV-seropositive individuals. *Lancet* 1989; **334**: 1294–8.
9 van der Ven AJAM, Koopmans PP, Vree TB, van der Meer JWM. Adverse reactions to co-trimoxazole in HIV infection. *Lancet* 1991; **338**: 431–3.
10 Koopmans PP, van der Ven AJ, Vree TB, van der Meer JWM. Pathogenesis of hypersensitivity reactions to drugs in patients with HIV infection: allergic or toxic? *AIDS* 1995; **9**: 217–22.
11 Aukrust P, Svardal AM, Muller F *et al.* Increased levels of oxidized glutathione in $CD4^+$ lymphocytes associated with disturbed intracellular redox balance in human immunodeficiency type 1 infection. *Blood* 1995; **86**: 258–67.
12 Pirmohamed M, Williams D, Tingle MD *et al.* Intracellular glutathione in the peripheral blood cells of HIV-infected patients: failure to show a deficiency. *AIDS* 1996; **10**: 501–7.
13 Shear NH, Spielberg SP. Anticonvulsant hypersensitivity syndrome. *In vitro* assessment of risk. *J Clin Invest* 1988; **82**: 1826–32.
14 Spielberg SP, Gordon GB, Blake DA *et al.* Predisposition to phenytoin hepatotoxicity assessed *in vitro*. *N Engl J Med* 1981; **305**: 722–7.

15 Spielberg SP. *In vitro* assessment of pharmacogenetic susceptibility to toxic drug metabolites in humans. *Fed Proc* 1984; **43**: 2308–13.
16 Yoo JH, Kang DS, Chun WH *et al.* Anticonvulsant hypersensitivity syndrome with an epoxide hydrolase defect. *Br J Dermatol* 1999; **140**: 181–3.
17 Gaedigk A, Spielberg SP, Grant DM. Characterization of the microsomal epoxide hydrolase gene in patients with anticonvulsant adverse drug reactions. *Pharmacogenetics* 1994; **4**: 142–53.
18 Wolkenstein P, Charue D, Laurent P *et al.* Metabolic predisposition to cutaneous adverse drug reactions. Role in toxic epidermal necrolysis caused by sulfonamides and anticonvulsants. *Arch Dermatol* 1995; **131**: 544–51.
19 Shahidi NT. Acetophenetidin sensitivity. *Am J Dis Child* 1967; **113**: 81–2.
20 Eichelbaum M. Defective oxidation of drugs: pharmacokinetic and therapeutic implications. *Clin Pharmacokinet* 1982; **7**: 1–22.
21 Vessell ES, Passananti T, Greene FE, Page JG. Genetic control of drug levels and of the induction of drug-metabolizing enzymes in man: individual variability in the extent of allopurinol and nortriptyline inhibition of drug metabolism. *Ann NY Acad Sci* 1971; **179**: 752–3.
22 Dasgupta B. Adverse reactions profile: 2. Penicillamine. *Prescribers J* 1991; **31**: 72–7.

Hydrolysis. Genetic influence on drug hydrolysis is well illustrated in the case of suxamethonium, which normally results in only very brief neuromuscular blockade due to rapid hydrolysis by plasma pseudocholinesterase. Genetically determined atypical cholinesterases cannot hydrolyse the drug, leading to prolonged apnoea in affected individuals; conversely, dominantly inherited resistance to suxamethonium, mediated by a highly active cholinesterase, has been reported.

Acetylation. Isoniazid, many sulphonamides, hydralazine, dapsone, procainamide, etc. are inactivated by conversion to acetyl conjugates. Acetylation rates vary greatly, with a bimodal frequency distribution, and there is marked ethnic variation. Rapid inactivation is dominantly inherited, and is commonest among Eskimos and Japanese and least common among certain Mediterranean Jews. The LE-like syndrome due to procainamide may occur more in fast acetylators, implying that a conjugate and not the parent compound is responsible [1]. Slow acetylators, in whom higher and more persistent drug levels occur, are more liable to develop adverse reactions to isoniazid (pellagra-like syndrome and peripheral neuritis), dapsone (haemolysis) [2] and hydralazine (LE-like syndrome) [3,4]. A slow acetylation phenotype is a risk factor for hypersensitivity to trimethoprim–sulfamethoxazole in HIV-infected subjects [5,6], and for sulphonamide-induced TEN and Stevens–Johnson syndrome independent of HIV infection [7,8].

References

1 Davies DM, Beedie MA, Rawlins MD. Antinuclear antibodies during procainamide treatment and drug acetylation. *BMJ* 1975; **iii**: 682–4.
2 Ellard GA, Gammon PT, Savin LA, Tan RSH. Dapsone acetylation in dermatitis herpetiformis. *Br J Dermatol* 1974; **90**: 441–4.
3 Perry HM Jr, Sakamoto A, Tan EM. Relationship of acetylating enzyme to hydralazine toxicity. *J Lab Clin Med* 1967; **70**: 1020–1.
4 Russell GI, Bing RF, Jones JA *et al.* Hydralazine sensitivity: clinical features, autoantibody changes and HLA-DR phenotype. *QJM* 1987; **65**: 845–52.
5 Carr A, Gross AS, Hoskins JM *et al.* Acetylation phenotype and cutaneous hypersensitivity to trimethoprim–sulphamethoxazole in HIV-infected patients. *AIDS* 1994; **8**: 333–7.
6 Delomenie C, Grant DM, Mathelier-Fusade P *et al. N*-Acetylation genotype and risk of severe reactions to sulphonamides in AIDS patients. *Br J Clin Pharmacol* 1994; **38**: 581–2.
7 Wolkenstein P, Carriere V, Charue D *et al.* A slow acetylator genotype is a risk factor for sulphonamide-induced toxic epidermal necrolysis and Stevens–Johnson syndrome. *Pharmacogenetics* 1995; **5**: 255–8.
8 Dietrich A, Kawakubo Y, Rzany B *et al.* Low *N*-acetylating capacity in patients with Stevens–Johnson syndrome and toxic epidermal necrolysis. *Exp Dermatol* 1995; **4**: 313–6.

Influence of human leukocyte antigen (HLA) types. An association between HLA types and susceptibility to drug eruptions has been previously reported [1], particularly in relation to gold (HLA-DRw3, HLA-DR5 and HLA-B8) and penicillamine toxicity [2–7]. Penicillamine toxicity is associated with HLA phenotypes as follows [2]: HLA-DR3 and HLA-B8 with renal toxicity; HLA-DR3, HLA-B7 and HLA-DR2 with haematological toxicity; HLA-A1 and HLA-DR4 with thrombocytopenia; and HLA-DRw6 with cutaneous adverse reactions. DR1/DR4 heterozygosity, or the DR5 subtypes DRB1*1102 or DRB1*1201, have been found in 61% of patients with intolerance to tiopronin given for rheumatoid arthritis [8].

A positive association with HLA-Aw33 and HLA-B17/Bw58 haplotypes, and a negative association with the HLA-A2 haplotype, was reported some time ago in southern Chinese patients with drug eruptions after exposure to allopurinol [9]. Several more recent studies have reported strong genetic associations between HLA alleles and susceptibility to drug hypersensitivity [10–15]. The genetic associations can be drug specific. HLA-B*5701 has been linked with abacavir hypersensitivity, such that prospective HLA typing has dramatically reduced the risk of abacavir hypersensitivity [10–13]. Significant predisposition to nevirapine hypersensitivity has been reported in Caucasian Australians with HLA-DRB1*0101 and high $CD4^+$ T-cell counts, and Sardinians and Japanese with HLA-Cw8 [13]. Most Han Chinese individuals with allopurinol-induced severe cutaneous adverse reactions are positive for HLA-B*5801 [13,14]. HLA-B*1502 is associated with carbamazepine-induced Stevens–Johnson syndrome and toxic epidermal necrolysis (SJS/TEN), but not with carbamazepine-induced maculopapular eruption or carbamazepine hypersensitivity syndrome; thus, a genetic association can be phenotype specific [12]. Moreover, a genetic association can also be ethnicity specific, as carbamazepine-SJS/TEN associated with B*1502 is seen in Han Chinese from Taiwan and other Asian countries but not in whites, which may be explained by the different allele frequencies [12,13,15]. Even when HLA-B alleles behave as strong risk factors, they are neither sufficient nor necessary to explain the disease. The high sensitivity/specificity of some markers provides a basis for developing tests to identify individuals at risk for drug hypersensitivity, and allows personalized treatment [13]. As with HLA-B*5701 and abacavir hypersensitivity, HLA-B*1502 genotyping as a screening tool before prescribing carbamazepine could be valuable in preventing carbamazepine-induced SJS/TEN in southeast Asian countries.

Aspirin-sensitive asthma is associated with HLA-DQw2 [16]. HLA-linkage associations with certain bullous disorders have been reported [17,18]. Hydralazine-induced LE is commonest in female patients with the HLA-DRw4 haplotype [19,20]. Fixed drug eruptions to feprazone and trimethoprim–sulfamethoxazole are linked, respectively, to HLA-B22 and HLA-A30 B13 Cw6 [21,22].

References

1 Ingelman-Sundberg M. Pharmacogenomic biomarkers for prediction of severe adverse drug reactions. *N Engl J Med* 2008; **358**: 637–9.
2 Dasgupta B. Adverse reactions profile: 2. Penicillamine. *Prescribers J* 1991; **31**: 72–7.
3 Wooley PH, Griffin J, Payani GS *et al.* HLA-DR antigens and toxic reaction to sodium aurothiomalate and D-penicillamine in patients with rheumatoid arthritis. *N Engl J Med* 1980; **303**: 300–2.
4 Latts JR, Antel JP, Levinson DJ *et al.* Histocompatibility antigens and gold toxicity: a preliminary report. *J Clin Pharmacol* 1980; **20**: 206–9.
5 Bardin T, Dryll A, Debeyre N *et al.* HLA system and side effects of gold salts and D-penicillamine treatment of rheumatoid arthritis. *Ann Rheum Dis* 1982; **41**: 599–601.
6 Emery P, Panayi GS, Huston G *et al.* D-penicillamine induced toxicity in rheumatoid arthritis: the role of sulphoxidation status and HLA-DR3. *J Rheumatol* 1984; **11**: 626–32.
7 Rodriguez-Perez M, Gonzalez-Dominguez J, Mataran L *et al.* Association of HLA-DR5 with mucocutaneous lesions in patients with rheumatoid arthritis receiving gold sodium thiomalate. *J Rheumatol* 1994; **21**: 41–3.
8 Ju LY, Paolozzi L, Delecoeuillerie G *et al.* A possible linkage of HLA-DRB haplotypes with tiopronin intolerance in rheumatoid arthritis. *Clin Exp Rheumatol* 1994; **12**: 249–54.
9 Chan SH, Tan T. HLA and allopurinol drug eruption. *Dermatologica* 1989; **179**: 32–3.
10 Waters LJ, Mandalia S, Gazzard B, Nelson M. Prospective HLA-B*5701 screening and abacavir hypersensitivity: a single centre experience. *AIDS* 2007; **21**: 2533–4.
11 Phillips E, Mallal S. Drug hypersensitivity in HIV. *Curr Opin Allergy Clin Immunol* 2007; **7**: 324–30.
12 Chung WH, Hung SI, Chen YT. Human leukocyte antigens and drug hypersensitivity. *Curr Opin Allergy Clin Immunol* 2007; **7**: 317–23.
13 Gatanaga H, Honda H, Oka S. Pharmacogenetic information derived from analysis of HLA alleles. *Pharmacogenomics* 2008; **9**: 207–14.
14 Lonjou C, Borot N, Sekula P *et al.* A European study of HLA-B in Stevens–Johnson syndrome and toxic epidermal necrolysis related to five high-risk drugs. *Pharmacogenet Genomics* 2008; **18**: 99–107.
15 Lonjou C, Thomas L, Borot N *et al.* A marker for Stevens–Johnson syndrome: ethnicity matters. *Pharmacogenomics J* 2006; **6**: 265–8.
16 Mullarkey MF, Thomas PS, Hansen JA *et al.* Association of aspirin-sensitive asthma with HLA-DQw2. *Am Rev Respir Dis* 1986; **133**: 261–3.
17 Roujeau J-C, Bracq C, Huyn NT *et al.* HLA phenotypes and bullous cutaneous reactions to drugs. *Tissue Antigens* 1986; **28**: 251–4.
18 Mobini N, Ahmed AR. Immunogenetics of drug-induced bullous diseases. *Clin Dermatol* 1993; **11**: 449–60.
19 Batchelor JR, Welsh KI, Mansilla Tinoco R *et al.* Hydralazine-induced systemic lupus erythematosus: influence of HLA-DR and sex on susceptibility. *Lancet* 1980; **i**: 1107–9.
20 Russell GI, Bing RF, Jones JA *et al.* Hydralazine sensitivity: clinical features, autoantibody changes and HLA-DR phenotype. *QJM* 1987; **65**: 845–52.
21 Pellicano R, Lomuto M, Ciavarella G *et al.* Fixed drug eruptions with feprazone are linked to HLA-B22. *J Am Acad Dermatol* 1997; **36**: 782–4.
22 Özkaya-Bayazit E, Akar U. Fixed drug eruption induced by trimethoprim–sulfamethoxazole: evidence for a link to HLA-A30 B13 Cw6 haplotype. *J Am Acad Dermatol* 2001; **45**: 712–7.

Drug-induced chromosomal damage [1–3]

This may be studied by examining the chromosomes of patients or animals exposed to drugs, or *in vitro* by the addition of drugs to cell cultures; substances capable of inducing chromosomal damage are termed clastogens. Effects may be dose related, but *in vitro* results may not be representative of the *in vivo* situation. Antimitotic and antibiotic agents have been the most studied, although psychotropics, anticonvulsants, hallucinogens, immunosuppressants and oral contraceptives have also been investigated and shown to cause, in varying degree, chromosomal damage. Damage ranges from staining variations through 'gaps' in staining, chromosome breaks, gross aberrations (such as deletions, fragments, translocations and inversions) to polyploidy. Such damage may be stable and retained over a succession of cell divisions, or transient.

References

1 Shaw MW. Human chromosome damage by chemical agents. *Annu Rev Med* 1970; **21**: 409–32.
2 Bender MA, Griggs HG, Bedford JS. Mechanisms of chromosomal aberration production. III. Chemicals and ionizing radiation. *Mutat Res* 1974; **23**: 197–212.
3 Rawlins MD, Thompson JW. Mechanisms of adverse drug reactions. In: Davies DM, ed. *Textbook of Adverse Drug Reactions*, 3rd edn. Oxford: Oxford University Press, 1985: 12–38.

Miscellaneous

Jarisch–Herxheimer reaction. This is the focal exacerbation of lesions of infective origin when potent antimicrobial therapy is initiated, and is classically observed in the treatment of early syphilis with penicillin; it may also occur 3 days after starting griseofulvin therapy, during therapy with diethylcarbamazine for onchocerciasis and tiabendazole (thiabendazole) for strongyloidiasis, and with penicillin or minocycline for erythema chronicum migrans due to *Borrelia burgdorferi* infection [1]. The reaction has been attributed to sudden release of pharmacologically and/or immunologically active substances from killed microorganisms or damaged tissues. However, there is little evidence that it is an allergic reaction [2]. Clinically, there may be fever, rigors, lymphadenopathy, arthralgia and transient macular urticarial eruptions; a vesicular eruption has also been described [3].

References

1 Weber K. Jarisch–Herxheimer-Reaktion bei Erythema-migrans-Krankheit. *Hautarzt* 1984; **35**: 588–90.
2 Skog E, Gudjónsson H. On the allergic origin of the Jarisch–Herxheimer reaction. *Acta Derm Venereol (Stockh)* 1966; **46**: 136–43.
3 Rosen T, Rubin H, Ellner K *et al.* Vesicular Jarisch–Herxheimer reaction. *Arch Dermatol* 1989; **125**: 77–81.

Infectious mononucleosis–ampicillin reaction. Ampicillin almost always causes a severe morbilliform eruption when given to a patient with infectious mononucleosis or lymphatic leukaemia (see later). The reaction occurs much less frequently with amoxicillin. The exact mechanism is not known, although one report suggests that real sensitization to ampicillin and amoxicillin occurs, and is detectable *in vivo* and *in vitro* by skin tests and the lymphocyte transformation test [1].

Reference

1 Renn CN, Straff W, Dorfmüller A *et al.* Amoxicillin-induced exanthema in young adults with infectious mononucleosis: demonstration of drug-specific lymphocyte reactivity. *Br J Dermatol* 2003; **147**: 1166–7.

Immunological drug reactions

Allergic hypersensitivity reactions are usually caused by immunological sensitization to a drug, as a result of previous exposure to that drug or to a chemically related cross-reacting substance [1–5]. It has been estimated that only about 6–10% of ADRs are immunologically mediated [6]. Although drugs frequently elicit an immune response, clinically evident hypersensitivity reactions

are manifest only in a small proportion of exposed individuals. Thus, using highly sensitive passive haemagglutination assays, IgM class antibodies to the penicilloyl group (the major hapten determinant derived from penicillin) are detectable in almost 100% of normal individuals, even in the absence of a history of penicillin therapy; 40% of patients receiving more than 2 g of penicillin for more than 10 days develop IgG class antibodies [7]. Macromolecular drugs such as protein or peptide hormones, insulin or dextran are antigenic in their own right. In contrast, most drugs are small organic molecules with a molecular mass of less than 1 kDa. In the past, it had been understood, according to the classical 'hapten hypothesis', that conjugation of free drug, reactive drug metabolites, or minor contaminants such as haptens with a macromolecular self protein, was required to initiate an immune response [8], and that, fortunately, many drugs have only a limited capacity to form covalent bonds with tissue proteins. This historical view is being challenged by new findings that drug-specific clones are stimulated by the parent drug much more often than by reactive metabolites [9]. Instead, it seems that medications usually stimulate specific T-cells after non-covalent binding to major histocompatibility (MHC) molecules on antigen-presenting cells. Drugs may be immunogenic not only because of their chemical reactivity, but also because they bind in a labile way to available T-cell receptors and possibly MHC molecules. In some patients with drug hypersensitivity this occurs within hours, even upon first exposure to the drug. The T-cell reaction to the drug might thus not be due to a classical primary response, but to peptide-specific T-cells which happen to be stimulated by the drug [10].

Clinical features distinguishing allergic from non-allergic drug reactions. Prior exposure before sensitization should have been without adverse effect. If there has been no previous exposure, there should usually be a latent period of several days of uneventful therapy before the reaction supervenes, during which primary sensitization occurs. Thereafter, reactions may develop within minutes (or even seconds) and certainly within 24 h. However, as stated above, occasionally reactions can occur without prior exposure. Allergic reactions do not resemble the pharmacological action of the drug, may follow exposure to doses far below the therapeutic level, and are reproducible on readministration (if judged safe).

Factors concerned in the development of hypersensitivity. The route of administration of a drug may affect its immunogenicity and the nature of any allergy. Topical drug exposure is more likely to result in sensitization than oral administration, and favours development of contact dermatitis; thus, poison ivy is a potent contact sensitizer but oral ingestion may promote tolerance. Anaphylaxis is more likely to be associated with intravenous drug administration. However, anaphylaxis may sometimes occur as quickly after oral penicillin administration [11]. Whether allergy develops may also depend on the antigenic load in terms of degree of drug exposure, and individual genetic variation in drug absorption and metabolism. Thus, an LE-like syndrome with antinuclear antibody formation following hydralazine therapy occurs more frequently in slow acetylators of the drug [12]. Hydralazine-related SLE is 10 times more frequent in HLA-DR4-positive patients than in the population at large, and is commoner in females. Allergic drug reactions are less common in childhood and possibly in the aged; in the latter, this may be related to impaired immunological responsiveness. Immunosuppression may increase the risk by inhibiting the regulatory function of suppressor T cells [13]. Environmental factors may also affect susceptibility to drug hypersensitivity, as for example the well-recognized increase in ampicillin-induced morbilliform eruptions associated with infectious mononucleosis, and photoallergic reactions to drugs such as thiazide diuretics or phenothiazines.

Duration of hypersensitivity. The duration of allergic sensitivity is unpredictable. Although there is a general tendency for immunological responses to a drug to fall off with time, provided the patient is not re-exposed to the drug or a related substance, this can never be relied on; where necessary, safe confirmatory procedures (if available) should be carried out. Drug-reactive peripheral blood T cells were detectable at a significant level as long as 12 years later in a patient, even after strict drug avoidance [14].

References

1 Wintroub BU, Stern R. Cutaneous drug reactions: pathogenesis and clinical classification. *J Am Acad Dermatol* 1985; **13**: 833–45.
2 De Swarte RD. Drug allergy: an overview. *Clin Rev Allergy* 1986; **4**: 143–69.
3 Stern RS, Wintroub BU, Arndt KA. Drug reactions. *J Am Acad Dermatol* 1986; **15**: 1282–8.
4 Blaiss MS, de Shazo RD. Drug allergy. *Pediatr Clin North Am* 1988; **35**: 1131–47.
5 Kalish RS. Drug eruptions: a review of clinical and immunological features. *Adv Dermatol* 1991; **6**: 221–37.
6 Gruchalla RS. Drug allergy. *J Allergy Clin Immunol* 2003; **111** (Suppl. 2): S548–59.
7 Weiss ME, Adkinson NF. Immediate hypersensitivity reactions to penicillin and related antibiotics. *Clin Allergy* 1988; **18**: 515–40.
8 Park BK, Naisbitt DJ, Gordon SF *et al.* Metabolic activation in drug allergies. *Toxicology* 2001; **158**: 11–23.
9 Roujeau JC. Immune mechanisms in drug allergy. *Allergol Int* 2006; **55**: 27–33.
10 Posadas SJ, Pichler WJ. Delayed drug hypersensitivity reactions—new concepts. *Clin Exp Allergy* 2007; **37**: 989–99.
11 Simmonds J, Hodges S, Nicol F, Barnett D. Anaphylaxis after oral penicillin. *BMJ* 1978; **ii**: 1404.
12 Perry HM Jr, Sakamoto A, Tan EM. Relationship of acetylating enzyme to hydralazine toxicity. *J Lab Clin Med* 1967; **70**: 1020–1.
13 Lakin JD, Grace WR, Sell KW. IgE antipolymyxin B antibody formation in a T-cell depleted bone marrow transplant patient. *J Allergy Clin Immunol* 1975; **56**: 94–103.
14 Beeler A, Engler O, Gerber BO, Pichler WJ. Long-lasting reactivity and high frequency of drug-specific T cells after severe systemic drug hypersensitivity reactions. *J Allergy Clin Immunol* 2006; **117**: 455–62.

Drug eruptions may occur as a result of a variety of different immunological mechanisms as described below.

IgE-dependent (type I) drug reactions: urticaria and anaphylaxis [1]

In vivo cross-linkage by polyvalent drug–protein conjugates of two or more specific IgE molecules, fixed to sensitized tissue mast cells or circulating basophil leukocytes, triggers the cell to release a variety of chemical mediators, including histamine, peptides such as eosinophil chemotactic factor of anaphylaxis, lipids such as leukotriene C_4 or prostaglandin D_2, and a variety of pro-

inflammatory cytokines [2]. Interleukin-5 (IL-5) and eotaxin play a role in activating and recruiting eosinophils in drug-induced cutaneous eruptions [3]. Such cytokines in turn have effects on a variety of target tissues including skin, respiratory, gastrointestinal and/or cardiovascular systems. Eosinophil degranulation may also result in release of pro-inflammatory mediators [4]. Dilatation and increased permeability of small blood vessels with resultant oedema and hypotension, contraction of bronchiolar smooth muscle and excessive mucus secretion, and chemotaxis of inflammatory cells, including polymorphs and eosinophils, occurs. Clinically, this may produce pruritus, urticaria, bronchospasm and laryngeal oedema, and in severe cases anaphylactic shock with hypotension and possibly death. Immediate reactions occur within minutes of drug administration; accelerated reactions may occur within hours or days, and are generally urticarial but may involve laryngeal oedema. Penicillins are the commonest cause of IgE-dependent drug eruptions.

References

1 Champion RH, Greaves MW, Kobza Black A, eds. *The Urticarias*. Edinburgh: Churchill Livingstone, 1985.
2 Schwartz LB. Mast cells and their role in urticaria. *J Am Acad Dermatol* 1991; **25**: 190–204.
3 Yawalkar N, Shrikhande M, Hari Y *et al.* Evidence for a role for IL-5 and eotaxin in activating and recruiting eosinophils in drug-induced cutaneous eruptions. *J Allergy Clin Immunol* 2000; **106**: 1171–6.
4 Leiferman KM. A current perspective on the role of eosinophils in dermatologic diseases. *J Am Acad Dermatol* 1991; **24**: 1101–12.

Antibody-mediated (type II) drug reactions

Binding of antibody to cells may lead to cell damage following complement-mediated cytolysis. The classical example of immune complex formation between a drug (as hapten) bound to the surface of a cell (in this case, platelets) and IgG-class antibody, with subsequent complement fixation, was the purpura caused by apronalide (Sedormid). A further example is the thrombocytopenic purpura that may result from antibodies to quinidine–platelet conjugates [1,2]. A number of drugs, including penicillin, quinine and sulphonamides, may rarely produce a haemolytic anaemia via this mechanism. Methyldopa very occasionally induces a haemolytic anaemia mediated by autoantibodies directed against red cell antigens.

References

1 Christie DJ, Weber RW, Mullen PC *et al.* Structural features of the quinidine and quinine molecules necessary for binding of drug-induced antibodies to human platelets. *J Lab Clin Med* 1984; **104**: 730–40.
2 Garty M, Ilfeld D, Kelton JG. Correlation of a quinidine-induced platelet-specific antibody with development of thrombocytopenia. *Am J Med* 1985; **79**: 253–5.

Immune complex-dependent (type III) drug reactions

Urticaria and anaphylaxis. Immune complexes may activate the complement cascade, with resultant formation of anaphylatoxins such as the complement protein fragments C3a and C5a, which trigger release of mediators from mast cells and basophils directly, resulting in urticaria or anaphylaxis.

Serum sickness. Serum sickness-like reactions and other immune complex-mediated conditions necessitate persistence of a drug antigen in the circulation for long enough to enable antibody, largely of IgG or IgM class, to be synthesized and to combine with it to form circulating antibody–antigen immune complexes. They therefore develop about 6 days or more after drug administration. Serum sickness occurs when antibody combines with antigen in antigen excess, leading to slow removal of persistent complexes by the mononuclear phagocyte system. It was usually seen in the context of serum therapy with large doses of heterologous antibody, as with horse antiserum for the treatment of diphtheria. It has been reported more recently with antilymphocyte globulin therapy [1]. Clinical manifestations of serum sickness include fever, arthritis, nephritis, neuritis, oedema, and an urticarial or papular rash.

Vasculitis [2–4]. Drug-induced immune complexes play a part in the pathogenesis of cutaneous necrotizing vasculitis. Deposition of immune complexes on vascular endothelium results in activation of the complement cascade, with generation of the anaphylatoxins C3a and C5a, which have chemotactic properties. Vasoactive amines and pro-inflammatory cytokines are released from basophils and mast cells, with resultant increased vascular permeability and attraction of polymorphonuclear neutrophil cells. Immune complex interaction with platelets via their Fc receptors causes platelet aggregation and microthrombus formation. Release of lysosomal enzymes by neutrophils contributes further to local inflammation. These events lead to the histological appearance of leukocytoclastic vasculitis. Deposition of immunoglobulins and complement in and around blood vessel walls is detectable by direct immunofluorescence staining of skin biopsies. Hydralazine and the hydroxylamine metabolite of procainamide bind to complement component C4 and inhibit its function; this may impair clearance of immune complexes, and predispose to development of an LE syndrome [4].

Arthus reaction. The Arthus reaction is a localized form of immune complex vasculitis. Intradermal or subcutaneous injection of antigen such as a vaccine into a sensitized individual with circulating precipitating antibodies, usually of IgG1 class, leads to local immune complex formation and the cascade of events described above. Clinically, there is erythema and oedema, haemorrhage and occasionally necrosis at the injection site, which reaches a peak at 4–10 h, and then gradually wanes.

References

1 Lawley TJ, Bielory L, Gascon P *et al.* A prospective clinical and immunologic analysis of patients with serum sickness. *N Engl J Med* 1984; **311**: 1407–13.
2 Mackel SE, Jordon RE. Leukocytoclastic vasculitis. A cutaneous expression of immune complex disease. *Arch Dermatol* 1983; **118**: 296–301.
3 Sams WM. Hypersensitivity angiitis. *J Invest Dermatol* 1989; **93**: 78S–81S.
4 Sim E. Drug-induced immune complex disease. *Complement Inflamm* 1989; **6**: 119–26.

Cell-mediated (type IV) reactions

The role of delayed-type cell-mediated immune reactions in contact drug hypersensitivity, as with penicillin [1], is well established, but the importance of such mechanisms involving specific effector lymphocytes in other varieties of cutaneous drug allergy has only recently been elucidated [2–7]. A number of ACDRs,

including some morbilliform and bullous ACDRs, fixed drug reactions, lichenoid reactions, LE-like reactions, DRESS syndrome and erythema multiforme, Stevens–Johnson syndrome and TEN, involve T-lymphocyte responses to altered self. The involvement of the skin immune system in cell-mediated drug eruptions, and graft-versus-host disease as a model for cutaneous drug eruptions, have been reviewed [2,8,9]. Patients with acute drug allergy to carbamazepine, phenytoin, sulfamethoxazole, allopurinol or paracetamol had activated drug-specific $CD4^+$ or $CD8^+$ T cells in the circulation [10]. Sulfamethoxazole-reactive lymphocytes were detected in peripheral blood of patients with drug-induced eruptions, at a frequency of 1/172 000, within the frequency range of urushiol-reactive T cells in patients with urushiol (poison ivy) dermatitis [11]. In another study, about 1 : 250 to 1 : 10 000 of all the T cells in patients following a severe systemic drug hypersensitivity reaction were reactive to the relevant drugs, a frequency of drug-reactive T cells higher than the frequency of T cells able to recognize recall antigens such as tetanus toxoid in the same subjects [12]. Moreover, drug-reactive T cells were detectable at a significant level for as long as 12 years later in one patient, despite strict drug avoidance. In one study, predominant $CD8^+$ T-cell activation was associated with more severe (bullous) skin lesions or liver involvement, whereas predominant activation of $CD4^+$ cells elicited mainly maculopapular reactions [13]. Drug-specific T-cell clones from drug-induced exanthems contained heterogeneous T-cell subsets with distinct phenotypes ($CD4^+ > CD8^+$ perforin and granzyme B positive) and cell functions (strong IL-5 production, moderate interferon-γ (IFN-γ) production and cytotoxic potential) [14,15]. Perivascular predominantly $CD4^+$ T cells, with 30% $CD8^+$ cells, basal keratinocyte HLA-DR and intercellular adhesion molecule (ICAM)-1 expression, and E selectin expression by endothelial cells, were seen in maculopapular or exfoliative antibiotic-induced ACDRs [16,17]. However, in other studies, $CD8^+$ T cells predominated in the epidermis in drug-induced maculopapular and bullous eruptions and patch-test reactions to beta-lactam antibiotics [18,19]. β-lactam-specific peripheral and epidermal T lymphocytes from bullous exanthems were predominantly $CD8^+CD4^-$, displayed a Th1-like cytokine pattern, proliferated in an antigen- and major histocompatibility complex (MHC)-specific manner, and were cytotoxic against epidermal keratinocytes in lectin-induced cytotoxicity assays. In contrast, T-cell lines from patients with penicillin-induced urticarial exanthems were predominantly $CD4^+CD8^-$, with a Th2-like cytokine pattern. Drug-specific T-cell clones and cell lines from a phenobarbital-induced eruption were heterogeneous with regard to CD4/CD8 phenotype, T-cell receptor Vβ repertoire, antigen recognition pattern and cytokine production [20]. Epicutaneous test reactions to antibiotics contained a heterogeneous population of drug-specific T cells [21]; it has been proposed that T cells producing IL-5 might contribute to eosinophilia, whereas cytotoxic $CD4^+$ T cells might account for tissue damage [21–23]. Drug-specific T cells also contribute to the neutrophil infiltration in drug-induced acute generalized exanthematous pustulosis, by secreting the chemokine IL-8 [24–26].

Proliferation of $CD8^+$ dermal T cells, from a sulfamethoxazole-induced bullous exanthem, to sulfamethoxazole was significantly increased in the presence of liver microsomes, suggesting that microsomal enzymes, such as the cytochrome P-450 system, generate highly reactive metabolites, which are the nominal antigens for T-cell activation [27,28]. The expression of ICAM-1 by target keratinocytes plays an important role in the cytotoxicity of epidermal T cells in bullous drug eruptions [29]. Penicilloyl-modified MHC-associated peptides may act as T-cell epitopes; T cells may have specificity for both the backbone and the side-chain of penicillin [30]. Penicillin G may also stimulate T cells directly by binding to MHC molecules on the cell surface. Alternatively, it may bind to soluble proteins such as human serum albumin, which require processing for presentation in an immunogenic form. These different modes of presentation, which elicit a variety of immunological reactivities, may explain the heterogeneity of clinical pictures seen in penicillin allergy [31]. Morbilliform drug hypersensitivity reactions in HIV-infected subjects showed spongiosis, hydropic generation of the basal layer, Civatte bodies, an epidermal lymphocytic infiltrate, and perivascular lymphocytes and macrophages [32]. Immunohistochemistry demonstrated $CD8^+$ HLA-DR-positive T lymphocytes, marked depletion of epidermal Langerhans' cells and strong keratinocyte IL-6, tumour necrosis factor-α (TNF-α) and, to a lesser degree, IFN-γ expression.

The above data have established the importance of T-cell-mediated immunity in delayed-type hypersensitivity-mediated drug eruptions. In delayed reactions, drug-specific $CD4^+$ and $CD8^{(+)}$ T cells recognize drugs through their T-cell receptors (TCRs) in an MHC-dependent way. MHC restriction could explain the key role of HLA genes as factors predisposing to severe drug reactions (see section on Pharmacogenetic mechanisms and genetic influences, pp. 75.12–15). Immunohistochemical and functional studies of drug-reactive T cells in patients with distinct forms of exanthems revealed that distinct T cell functions lead to different clinical phenotypes. Thus, delayed hypersensitivity reactions (type IV) may be subclassified according to which cytokines and chemokines are released [4,7]. Maculopapular exanthema may be either Th1 or Th2 in nature, depending on whether they are interferon-γ/tumour necrosis factor-α or interleukin-4, 5 and 13 driven. Bullous reactions to drugs (i.e. Stevens–Johnson syndrome or toxic epidermal necrolysis) are characterized by widespread keratinocyte apoptosis, a consequence of high $CD8^+$ T-cell involvement and the molecular cytotoxicity of Fas, perforin and granzyme B. Pustular exanthematic reactions to medications are stimulated via the T-cell release of IL-8 and granulocyte–monocyte colony-stimulating factor (GM-CSF). Delayed-type IV hypersensitivity reactions have therefore been re-classified into four main subtypes: IVa (Th1/monocyte directed), IVb (Th2/eosinophil directed), IVc ($CD8^+$/Fas/perforin/granzyme B directed) and IVd (IL-8/GM-CSF/neutrophil directed). In practice, delayed hypersensitivity eruptions are often an overlap of cytokine pathways, with one preferential reaction dominating the final picture.

An intercurrent infectious disease (especially respiratory tract and urinary tract infections in the case of maculopapular eruptions) was documented in 58.5% of patients with ACDRs, compared with 7.5% of a control group [33]. It has been proposed that viruses may non-specifically stimulate cytotoxicity in general, which spills over to affect target cells altered by drug antigen [34]. Viruses incriminated, especially in the DRESS (drug hypersensitiv-

ity) syndrome, include human herpesvirus 6 and 7, Epstein–Barr virus, cytomegalovirus and hepatitis C virus [35–43]. The sequential reactivation of these viruses may be responsible for the delayed onset, paradoxical worsening of clinical symptoms after discontinuation of the causative drugs, and a step-wise development of several organ system failures, including encephalitis and type 1 diabetes mellitus, long after discontinuation of the causative drug [37,40,43]. In conclusion, DRESS is a complex disease composed of drug allergy and viral reactivation, with similarities to graft-versus-host disease.

References

1 Stejskal VDM, Forsbeck M, Olin R. Side chain-specific lymphocyte responses in workers with occupational allergy induced by penicillins. *Int Arch Allergy Appl Immunol* 1987; **82**: 461–4.

2 Roujeau JC. Immune mechanisms in drug allergy. *Allergol Int* 2006; **55**: 27–33.

3 Schmid DA, Depta JP, Pichler WJ. T cell-mediated hypersensitivity to quinolones: mechanisms and cross-reactivity. *Clin Exp Allergy* 2006; **36**: 59–69.

4 Meth MJ, Sperber KE. Phenotypic diversity in delayed drug hypersensitivity: an immunologic explanation. *Mt Sinai J Med* 2006; **73**: 769–76.

5 Rodriguez-Pena R, Lopez S, Mayorga C *et al.* Potential involvement of dendritic cells in delayed-type hypersensitivity reactions to beta-lactams. *J Allergy Clin Immunol* 2006; **118**: 949–56.

6 Nishio D, Izu K, Kabashima K, Tokura Y. T cell populations propagating in the peripheral blood of patients with drug eruptions. *J Dermatol Sci* 2007; **48**: 25–33.

7 Posadas SJ, Pichler WJ. Delayed drug hypersensitivity reactions—new concepts. *Clin Exp Allergy* 2007; **37**: 989–99.

8 Breathnach SM, Hintner H. *Adverse Drug Reactions and the Skin*. Oxford: Blackwell Scientific Publications, 1992.

9 Breathnach SM. Mechanisms of drug eruptions: Part I. *Australas J Dermatol* 1995; **36**: 121–7.

10 Mauri-Hellweg D, Bettens F, Mauri D. Activation of drug-specific $CD4^+$ and $CD8^+$ T cells in individuals allergic to sulfonamides, phenytoin, and carbamazepine. *J Immunol* 1995; **155**: 462–72.

11 Kalish RS, Laporte A, Wood JA, Johnson KL. Sulfonamide-reactive lymphocytes detected at very low frequency in the peripheral blood of patients with drug-induced eruptions. *J Allergy Clin Immunol* 1994; **94**: 465–72.

12 Beeler A, Engler O, Gerber BO, Pichler WJ. Long-lasting reactivity and high frequency of drug-specific T cells after severe systemic drug hypersensitivity reactions. *J Allergy Clin Immunol* 2006; **117**: 455–62.

13 Hari Y, Frutig-Schnyder K, Hurni M *et al.* T cell involvement in cutaneous drug eruptions. *Clin Exp Allergy* 2001; **31**: 1398–408.

14 Yawalkar N, Egli F, Hari Y *et al.* Infiltration of cytotoxic T cells in drug-induced cutaneous eruptions. *Clin Exp Allergy* 2000; **30**: 847–55.

15 Yawalkar N, Pichler WJ. Pathogenesis of drug-induced exanthema. *Int Arch Allergy Immunol* 2001; **124**: 336–8.

16 Barbaud AM, Béné M-C, Schmutz J-L *et al.* Role of delayed cellular hypersensitivity and adhesion molecules in amoxicillin-induced morbilliform rashes. *Arch Dermatol* 1997; **133**: 481–6.

17 Barbaud AM, Béné MC, Reichert-Penetrat S *et al.* Immunocompetent cells and adhesion molecules in 14 cases of cutaneous drug reactions induced with antibiotics. *Arch Dermatol* 1998; **134**: 1040–1.

18 Hertl M, Geisel J, Boecker C, Merk HF. Selective generation of $CD8^+$ T-cell clones from the peripheral blood of patients with cutaneous reactions to beta-lactam antibiotics. *Br J Dermatol* 1993; **128**: 619–26.

19 Hertl M, Bohlen H, Jugert F *et al.* Predominance of epidermal $CD8^+$ T lymphocytes in bullous cutaneous reactions caused by β-lactam antibiotics. *J Invest Dermatol* 1993; **101**: 794–9.

20 Hashizume H, Takigawa M, Tokura Y. Characterization of drug-specific T cells in phenobarbital-induced eruption. *J Immunol* 2002; **168**: 5359–68.

21 Yawalkar N, Hari Y, Frutig K *et al.* T cells isolated from positive epicutaneous test reactions to amoxicillin and ceftriaxone are drug specific and cytotoxic. *J Invest Dermatol* 2000; **115**: 647–52.

22 Choquet-Kastylevsky G, Intrator L, Chenal C *et al.* Increased levels of interleukin 5 are associated with the generation of eosinophilia in drug-induced hypersensitivity syndrome. *Br J Dermatol* 1998; **139**: 1026–32.

23 Mikami C, Ochiai K, Umemiya K *et al.* Eosinophil activation and *in situ* interleukin-5 production by mononuclear cells in skin lesions of patients with drug hypersensitivity. *J Dermatol* 1999; **26**: 633–9.

24 Britschgi M, Steiner UC, Schmid S *et al.* T-cell involvement in drug-induced acute generalized exanthematous pustulosis. *J Clin Invest* 2001; **107**: 1433–41.

25 Schmid S, Kuechler PC, Britschgi M *et al.* Acute generalized exanthematous pustulosis: role of cytotoxic T cells in pustule formation. *Am J Pathol* 2002; **161**: 2079–86.

26 Britschgi M, Pichler WJ. Acute generalized exanthematous pustulosis, a clue to neutrophil-mediated inflammatory processes orchestrated by T cells. *Curr Opin Allergy Clin Immunol* 2002; **2**: 325–31.

27 Hertl M, Merk HF. Lymphocyte activation in cutaneous drug reactions. *J Invest Dermatol* 1995; **105** (Suppl.): S95–8.

28 Hertl M, Jugert F, Merk HF. $CD8^+$ dermal T cells from a sulphamethoxazole-induced bullous exanthem proliferate in response to drug-modified liver microsomes. *Br J Dermatol* 1995; **132**: 215–20.

29 Hertl M, Rönnau A, Bohlen H *et al.* The cytotoxicity of epidermal T lymphocytes in bullous drug reactions is strongly but not completely abrogated by inhibition of ICAM-1 on target cells (abstract). *Arch Dermatol Res* 1993; **285**: 63.

30 Weltzien HU, Padovan E. Molecular features of penicillin allergy. *J Invest Dermatol* 1998; **110**: 203–6.

31 Brander C, Mauri-Hellweg D, Bettens F *et al.* Heterogeneous T cell responses to beta-lactam-modified self-structures are observed in penicillin-allergic individuals. *J Immunol* 1995; **155**: 2670–8.

32 Carr A, Vasak E, Munro V *et al.* Immunohistological assessment of cutaneous drug hypersensitivity in patients with HIV infection. *Clin Exp Immunol* 1994; **97**: 260–5.

33 Cohen AD, Friger M, Sarov B, Halevy S. Which intercurrent infections are associated with maculopapular cutaneous drug reactions? A case–control study. *Int J Dermatol* 2001; **40**: 41–4.

34 Chosidow O, Bourgault L, Roujeau JC. Drug rashes. What are the targets of cell-mediated cytotoxicity? *Arch Dermatol* 1994; **130**: 627–9.

35 Mizukawa Y, Shiohara T. Virus-induced immune dysregulation as a triggering factor for the development of drug rashes and autoimmune diseases: with emphasis on EB virus, human herpesvirus 6 and hepatitis C virus. *J Dermatol Sci* 2000; **22**: 169–80.

36 Aihara M, Sugita Y, Takahashi S *et al.* Anticonvulsant hypersensitivity syndrome associated with reactivation of cytomegalovirus. *Br J Dermatol* 2001; **144**: 1231–4.

37 Hashimoto K, Yasukawa M, Tohyama M. Human herpesvirus 6 and drug allergy. *Curr Opin Allergy Clin Immunol* 2003; **3**: 255–60.

38 Kano Y, Inaoka M, Sakuma K, Shiohara T. Virus reactivation and intravenous immunoglobulin (IVIG) therapy of drug-induced hypersensitivity syndrome. *Toxicology* 2005; **209**: 165–7.

39 Seishima M, Yamanaka S, Fujisawa T *et al.* Reactivation of human herpesvirus (HHV) family members other than HHV-6 in drug-induced hypersensitivity syndrome. *Br J Dermatol* 2006; **155**: 344–9.

40 Kano Y, Hiraharas K, Sakuma K, Shiohara T. Several herpesviruses can reactivate in a severe drug-induced multiorgan reaction in the same sequential order as in graft-versus-host disease. *Br J Dermatol* 2006; **155**: 301–6.

41 Shiohara T, Inaoka M, Kano Y. Drug-induced hypersensitivity syndrome (DIHS): a reaction induced by a complex interplay among herpesviruses and antiviral and antidrug immune responses. *Allergol Int* 2006; **55**: 1–8.

42 Tohyama M, Hashimoto K, Yasukawa M *et al.* Association of human herpesvirus 6 reactivation with the flaring and severity of drug-induced hypersensitivity syndrome. *Br J Dermatol* 2007; **157**: 934–40.

43 Shiohara T, Kano Y. A complex interaction between drug allergy and viral infection. *Clin Rev Allergy Immunol* 2007; **33**: 124–33.

Erythema multiforme, Stevens–Johnson syndrome and TEN. The reader is referred to Chapter 76.

Lichenoid drug eruptions. The mechanisms underlying lichenoid drug eruptions are essentially unknown, but they may develop as

a result of autoreactive cytotoxic T-cell clones directed against a drug–class II MHC antigen complex, such that keratinocytes and Langerhans' cells are viewed by the immune system as 'non-self'. Cloned murine autoreactive T cells produce a lichenoid reaction in recipient animals following injection [1]. The presence of epidermotropic T cells correlates with that of class II MHC (HLA-DR)-expressing keratinocytes and Langerhans' cells in lichenoid eruptions [2].

References

1 Shiohara T. The lichenoid tissue reaction. An immunological perspective. *Am J Dermatopathol* 1988; **10**: 252–6.

2 Shiohara T, Moriya N, Tanaka Y *et al.* Immunopathological study of lichenoid skin diseases: correlation between HLA-DR-positive keratinocytes or Langerhans cells and epidermotropic T cells. *J Am Acad Dermatol* 1988; **18**: 67–74.

LE-like syndrome induced by drugs. Drug-induced LE, with production of antihistone antibodies, may result from interaction between the drug and nuclear material to produce a drug–nucleoprotein complex that is immunogenic. Alternatively, drugs may alter immunoregulation in such a way that autoantibody production is favoured; procainamide and hydralazine modulate lymphocyte function directly and induce autoreactivity. Thus, drugs may cause an SLE-like condition by a mechanism analogous to that in immunostimulatory graft-versus-host disease [1]. Hydralazine, isoniazid and the hydroxylamine metabolites of procainamide and practolol may also predispose to the development of an LE-like syndrome by inhibiting binding of C4 and in turn of C3 to immune complexes, thus preventing complement-mediated clearance of immune complexes by solubilization and opsonization [2].

References

1 Gleichman E, Pals ST, Rolinck AG *et al.* Graft-versus-host reactions: clues to the etiopathogenesis of a spectrum of immunological diseases. *Immunol Today* 1984; **5**: 324–32.

2 Sim E. Drug-induced immune complex disease. *Complement Inflamm* 1989; **6**: 119–26.

Drug-induced pemphigus. Immunoprecipitation studies have shown that patients with drug-induced pemphigus foliaceus and pemphigus vulgaris often have circulating autoantibodies with the same antigenic specificity at a molecular level as autoantibodies from patients with idiopathic pemphigus [1]. Binding of an active thiol group in a drug to the pemphigus antigen complex might result in autoantibody production, or culprit drugs may result in immune dysregulation. In addition, drugs with thiol groups in their molecule, such as penicillamine, captopril and thiopronine, and piroxicam can cause acantholysis directly *in vitro* in the absence of autoantibody [2].

References

1 Korman NJ, Eyre RW, Stanley JR. Drug-induced pemphigus: autoantibodies directed against the pemphigus antigen complexes are present in penicillamine and captopril-induced pemphigus. *J Invest Dermatol* 1991; **96**: 273–6.

2 Ruocco V, Pisani M, de Angelis E, Lombardi ML. Biochemical acantholysis provoked by thiol drugs. *Arch Dermatol* 1990; **126**: 965–6.

Fixed drug eruptions. Graft autotransplantation investigations carried out in the 1930s demonstrated cutaneous memory in involved skin in fixed drug eruption [1]. Serum factors from patients with fixed drug eruption have been reported to cause inflammation on injection into a previously involved site, but not when injected into normal skin [2], and to induce lymphocyte blast transformation [3,4]. However, cell-mediated rather than humoral immunity is thought to play the major role in the development of lesions in this condition.

Lesional skin contains increased numbers of both helper and suppressor T lymphocytes [5–8], and T suppressor/cytotoxic T cells may be seen adjacent to necrotic keratinocytes in the epidermis in the acute phase [6]. $CD8^+$ cytotoxic T cells persist within lesional skin and contribute to immunological memory [5,7,9]. Intraepidermal $CD8^+$ memory T cells phenotypically resembling effector memory T cells are greatly enriched in resting lesional skin of fixed drug eruption; upon activation, they can rapidly produce large amounts of IFN-γ, transiently acquire a natural killer-like phenotype, and express cytotoxic granules, followed by localized epidermal injury [10,11]. T cells from lesional epidermis in two patients with fixed drug eruption utilized a very limited range of Vα and Vβ genes compared with peripheral blood T cells, indicating expansion of T cells recognizing a restricted set of antigens [12]. Interleukin-15 derived from lesional epidermis could maintain the survival of the intraepidermal $CD8^+$ T cells, even in the absence of antigenic stimulus, over a prolonged period of time [13]. The influx into the epidermis of IL-10-producing $CD4^+$ T cells and $CD8^+$ T cells, including $Foxp3^+$ regulatory T cells, during the evolution of an acute attack serves to ameliorate epidermal damage induced by activation of the intraepidermal $CD8^+$ T cells and promotes resolution [13,14]. Successful desensitization to allopurinol-induced fixed drug eruption was associated with a significant increase in $CD25^+CD4^+$ T cells in lesional epidermis [15].

Keratinocytes in lesional skin express ICAM-1 [16], which is involved in interaction between keratinocytes and lymphocytes, HLA-DR [6] and the chemotactic protein IP-10 [8], findings that suggest a role for cytokines in the evolution of the histological changes [8,17]. ICAM-1 was noted to be induced on endothelium and keratinocytes 1.5 h after drug challenge, and there was increased reactivity in lesional skin *in vitro* to TNF-α and IFN-γ, as well as to the causative drug [17]; drug-induced, TNF-α-dependent keratinocyte ICAM-1 expression in lesional skin may provide a localized initiating stimulus for epidermal T-cell activation. Early release of histamine from mast cells or basophils has been reported in fixed drug eruption, based on suction blister fluid levels [18]. Significantly higher frequencies of HLA-B22 and HLA-Cw1 antigens were found in 36 patients with fixed drug eruption, and familial cases occur, suggesting a genetic predisposition [19].

References

1 Korkij W, Soltani K. Fixed drug eruption. A brief review. *Arch Dermatol* 1984; **120**: 520–4.

2 Wyatt E, Greaves M, Søndergaard J. Fixed drug eruption (phenolphthalein). *Arch Dermatol* 1972; **106**: 671–3.

3 Gimenez-Camarasa JM, Garcia-Calderon P, De Moragas JM. Lymphocyte transformation test in fixed drug eruption. *N Engl J Med* 1975; **292**: 819–21.

4 Suzuki S, Asai Y, Toshio H *et al.* Drug-induced lymphocyte transformation in peripheral lymphocytes from patients with drug eruption. *Dermatologica* 1978; **157**: 146–53.
5 Hindsén M, Christensen OB, Gruic V, Löfberg H. Fixed drug eruption: an immunohistochemical investigation of the acute and healing phase. *Br J Dermatol* 1987; **116**: 351–6.
6 Murphy GF, Guillén FJ, Flynn TC. Cytotoxic T lymphocytes and phenotypically abnormal epidermal dendritic cells in fixed cutaneous eruption. *Hum Pathol* 1985; **16**: 1264–71.
7 Visa K, Käyhkö K, Stubb S, Reitamo S. Immunocompetent cells of fixed drug eruption. *Acta Derm Venereol (Stockh)* 1987; **67**: 30–5.
8 Smoller BR, Luster AD, Krane JF *et al.* Fixed drug eruptions: evidence for a cytokine-mediated process. *J Cutan Pathol* 1991; **18**: 13–9.
9 Scheper RJ, Von Blomberg M, Boerrigter GH *et al.* Induction of immunological memory in the skin. Role of local T cell retention. *Clin Exp Immunol* 1983; **51**: 141–8.
10 Shiohara T, Mizukawa Y, Teraki Y. Pathophysiology of fixed drug eruption: the role of skin-resident T cells. *Curr Opin Allergy Clin Immunol* 2002; **2**: 317–23.
11 Teraki Y, Shiohara T. IFN-gamma-producing effector $CD8^+$ T cells and IL-10-producing regulatory $CD4^+$ T cells in fixed drug eruption. *J Allergy Clin Immunol* 2003; **112**: 609–15.
12 Komatsu T, Moriya N, Shiohara T. T cell receptor (TCR) repertoire and function of human epidermal T cells: restricted TCR V alpha-V beta genes are utilized by T cells residing in the lesional epidermis in fixed drug eruption. *Clin Exp Immunol* 1996; **104**: 343–50.
13 Mizukawa Y, Yamazaki Y, Shiohara T. *In vivo* dynamics of intraepidermal $CD8^+$ T cells and CD4+ T cells during the evolution of fixed drug eruption. *Br J Dermatol* 2008; **158**: 1230–8.
14 Teraki Y, Kokaji T, Shiohara T. Expansion of IL-10-producing $CD4^+$ and $CD8^+$ T cells in fixed drug eruption. *Dermatology* 2006; **213**: 83–7.
15 Teraki Y, Shiohara T. Successful desensitization to fixed drug eruption: the presence of $CD25^+CD4^+$ T cells in the epidermis of fixed drug eruption lesions may be involved in the induction of desensitization. *Dermatology* 2004; **209**: 29–32.
16 Shiohara T, Nickoloff BJ, Sagawa Y *et al.* Fixed drug eruption. Expression of epidermal keratinocyte intercellular adhesion molecule-1 (ICAM-1). *Arch Dermatol* 1989; **125**: 1371–6.
17 Teraki Y, Moriya N, Shiohara T. Drug-induced expression of intercellular adhesion molecule-1 on lesional keratinocytes in fixed drug eruption. *Am J Pathol* 1994; **145**: 550–60.
18 Alanko K, Stubb S, Salo OP, Reitamo S. Suction blister fluid histamine in fixed drug eruption. *Acta Derm Venereol (Stockh)* 1992; **72**: 89–91.
19 Pellicano R, Ciavarella G, Lomuto M, Di Giorgio G. Genetic susceptibility to fixed drug eruption: evidence for a link with HLA-B22. *J Am Acad Dermatol* 1994; **30**: 52–4.

Histopathology of drug reactions [1]

In most patterns of reaction to drugs, the histological changes are no more distinctive than are the clinical features. For example, urticaria, erythema multiforme, TEN and exfoliative dermatitis provoked by drugs cannot be differentiated from the same reactions resulting from other causes. Graft-versus-host disease-type drug eruptions in the acute phase show a predominance of epidermal $CD8^+$ T cells, reduced epidermal OKT6-positive Langerhans' cells, and increased keratinocyte expression of HLA-DR and ICAM-1 [2]. In contrast, in one study [3], Langerhans' cells from lesional maculopapular drug eruptions reportedly increased in number by 66% and displayed more intense staining and more prominent dendrites. No single or combined histological feature, including tissue eosinophilia, is useful in differentiating graft-versus-host disease from drug eruptions in bone marrow recipients; the cause of a new-onset, blanchable, erythematous rash in a bone marrow transplant recipient is most accurately determined by close clinical examination and follow-up [4].

The histological changes in the vegetating iododermas and bromodermas, certain lichenoid eruptions and fixed drug eruptions are not pathognomonic, but are sufficiently characteristic to be of importance in differential diagnosis. The histology of a number of other drug eruptions has been reviewed [5]. Amiodarone-induced hyperpigmentation shows a lymphocytic dermatitis and yellowish-brown granules within several cell types; the drug or a metabolite forms at least a portion of the deposits. Clofazimine-induced hyperpigmentation involves accumulation of a ceroid lipofuscin within lipid-laden macrophages. The cutaneous eruption of lymphocyte recovery after chemotherapeutic agents is a maculopapular eruption with a non-specific, superficial perivascular dermatitis. Chemotherapy-induced acral erythema reveals a non-specific interface dermatitis. Specific reactions occur with etoposide (starburst cells) and busulfan (busulphan) (large atypical keratinocytes), and other chemotherapeutic agents may involve sweat glands: neutrophilic eccrine hidradenitis is characterized by neutrophil infiltration and by necrosis; syringosquamous metaplasia involves squamous metaplasia of the sweat duct. Drug-induced, generalized, pustular toxic erythema is characterized by subcorneal pustules and occasional eosinophils. Cephalosporins may produce a syndrome clinically and histologically like pemphigus, and naproxen produces one like porphyria cutanea tarda. The photosensitive dermatitis associated with quinine and piroxicam is histologically a non-specific spongiotic dermatitis. A lichenoid giant cell dermatitis may be caused by methyldopa or chlorothiazide, and phenytoin and carbamazepine dermatitis histologically imitates mycosis fungoides.

Bromodermas and iododermas

In bromoderma, verrucous pseudoepitheliomatous hyperplasia is associated with abscesses containing neutrophils and eosinophils in the epidermis, and a dense dermal infiltrate initially consisting mainly of neutrophils and eosinophils and later containing many lymphocytes, plasma cells and histiocytes. The abundant dilated blood vessels may show endothelial proliferation. In iododermas, ulceration is more marked, but there is usually less epithelial hyperplasia. Both conditions must be differentiated from blastomycosis and coccidioidomycosis, and from pemphigus vegetans.

Fixed eruptions

In the acute stage, the epidermal changes may be indistinguishable from erythema multiforme, with loss of cell outlines and necrosis of the lower epidermis. In less acute lesions, the epidermis may show little abnormality, but the dermis is oedematous and there is a conspicuous perivascular lymphocytic infiltrate. Later, there is increased melanin in the epidermis and within melanophages in the dermis.

Lichenoid eruptions

The changes may be non-specific or may resemble idiopathic lichen planus, although the cellular infiltrate tends to be more pleomorphic and less dense, and the presence of focal parakeratosis, focal interruption of the granular layer, and cytoid bodies in the cornified and granular layers suggest a drug cause [6]. Later, there may be scarring, with destruction of the sweat glands.

References

1 Elder D, Elenitsas R, Jaworsky C, Johnson B Jr, eds. *Lever's Histopathology of the Skin*, 8th edn. Philadelphia: Lippincott, 1997.
2 Osawa J, Kitamura K, Saito S *et al.* Immunohistochemical study of graft-versus-host reaction (GVHR)-type drug eruptions. *J Dermatol* 1994; **21**: 25–30.
3 Dascalu DI, Kletter Y, Baratz M, Brenner S. Langerhans' cell distribution in drug eruption. *Acta Derm Venereol (Stockh)* 1992; **72**: 175–7.
4 Marra DE, McKee PH, Nghiem P. Tissue eosinophils and the perils of using skin biopsy specimens to distinguish between drug hypersensitivity and cutaneous graft-versus-host disease. *J Am Acad Dermatol* 2004; **51**: 543–6.
5 Fitzpatrick JE. New histopathologic findings in drug eruptions. *Dermatol Clin* 1992; **10**: 19–36.
6 Van den Haute V, Antoine JL, Lachapelle JM. Histopathological discriminant criteria between lichenoid drug eruption and idiopathic lichen planus: retrospective study on selected samples. *Dermatologica* 1989; **179**: 10–3.

Types of clinical reaction [1–13]

The mucocutaneous reactions that may result from ADRs have been the subject of extensive reviews, to which the reader is referred for further information. The following section details a number of different drug-induced reaction patterns; see also the discussion of adverse effects of individual drugs later. The clinical presentation of drug eruptions is highly variable, in part explicable by involvement of a variety of cytokines, inflammatory cells and regulatory mechanisms, and ranges from common transient and benign erythema occurring 6–9 days after the introduction of a new drug in up to 3% of users, to the most severe forms which affect fewer than 1/10 000 users. It is important for clinicians to recognize these severe cutaneous adverse reactions: anaphylaxis; drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome (previously termed drug hypersensitivity syndrome) (mortality 10%); acute generalized exanthematous pustulosis (AGEP) (mortality 5%); bullous fixed drug eruptions; serum sickness syndrome; vasculitis; Stevens–Johnson syndrome and toxic epidermal necrolysis (TEN) (mortality 25 to 30%). It is clearly critical to realize as rapidly as possible that an unusual, acute eruption with high fever and severe constitutional symptoms is caused by a medication and not by an infection, and to look for relevant internal involvement. Chronic-onset drug-induced disorders may mimic dermatological diseases; these include pigmentary changes, drug-induced autoimmune bullous diseases, lichenoid eruptions, lupus erythematosus, pseudolymphoma and acneiform eruptions. It is unfortunate that although certain drugs are commonly associated with a specific reaction pattern (e.g. pristinamycin, hydroxychloroquine, and diltiazem for AGEP; minocycline for DRESS; anti-infectious sulfonamides and allopurinol for TEN), most drugs are capable of causing several different types of eruption.

References

1 Stern RS, Wintroub BU. Adverse drug reactions: reporting and evaluating cutaneous reactions. *Adv Dermatol* 1987; **2**: 3–18.
2 Bork K. *Cutaneous Side Effects of Drugs*. Philadelphia: Saunders, 1988.
3 Alanko K, Stubbs S, Kauppinen K. Cutaneous drug reactions: clinical types and causative agents. A five year survey of in-patients (1981–1985). *Acta Derm Venereol (Stockh)* 1989; **69**: 223–6.
4 Shear NH, ed. Adverse reactions to drugs. *Semin Dermatol* 1989; **8**: 135–226.
5 Kalish RS. Drug eruptions: a review of clinical and immunological features. *Adv Dermatol* 1991; **6**: 221–37.



Fig. 75.1 Maculopapular erythema caused by ampicillin.

6 Breathnach SM, Hintner H. *Adverse Drug Reactions and the Skin*. Oxford: Blackwell Scientific Publications, 1992.
7 Zürcher L, Krebs A. *Cutaneous Drug Reactions*. Basel: Karger, 1992.
8 Bruinsma WA. *A Guide to Drug Eruptions: File of Side Effects in Dermatology*, 6th edn. Oosthuizen, The Netherlands: File of Medicines, 1996.
9 Litt JZ, Pawlak WA Jr. *Drug Eruption Reference Manual*. New York: Parthenon, 1997.
10 Wolf R, Orion E, Marcos B, Matz H. Life-threatening acute adverse cutaneous drug reactions. *Clin Dermatol* 2005; **23**: 171–81.
11 Roujeau JC. Clinical heterogeneity of drug hypersensitivity. *Toxicology* 2005; **209**: 123–9.
12 Valeyrie-Allanore L, Sassolas B, Roujeau JC. Drug-induced skin, nail and hair disorders. *Drug Saf* 2007; **30**: 1011–30.
13 Segal AR, Doherty KM, Leggott J, Zlotoff B. Cutaneous reactions to drugs in children. *Pediatrics* 2007; **120**: e1082–96.

Exanthematic (maculopapular) reactions [1]

These are the most frequent of all cutaneous reactions to drugs, and can occur after almost any drug at any time up to 3 (but usually 2) weeks after administration; they may be accompanied by fever, pruritus and eosinophilia. It is not possible to identify the offending drug by the nature of the eruption. The clinical features are variable; the lesions may be scarlatiniform, rubelliform or morbilliform, or may consist of a profuse eruption of small papules showing no close resemblance to any infective exanthem (Fig. 75.1). Less common are eruptions with large macules, polycylic and gyrate erythema, reticular eruptions and sheet-like erythema. The distribution is also variable but is generally symmetrical. The trunk and extremities are usually involved, and not uncommonly intertriginous areas may be favoured, but the face may be spared. Palmar and plantar lesions may occur, and sometimes the eruption is generalized. Purpuric lesions, especially on the legs,

Table 75.2 Drugs causing exanthematic reactions.

Most common	Less common
Ampicillin and penicillin	Cephalosporins
Phenylbutazone and other pyrazolones	Barbiturates
Sulphonamides	Thiazides
Phenytoin	Naproxen
Carbamazepine	Isoniazid
Gold	Phenothiazines
Gentamicin	Quinidine
	Meprobamate
	Atropine

and erosive stomatitis may develop. There may be relative sparing of pressure areas. If the administration of the drug is continued, an exfoliative dermatitis may develop, although occasionally the eruption subsides despite continuation of the medication.

Morbilliform drug eruptions usually, but not always, recur on rechallenge. The main differential diagnosis is from viral rashes. In a recent series of atypical exanthems, morphology and laboratory investigations led to an aetiological diagnosis in about 70% of cases [2]. It is useful, in differentiating exanthematic drug eruptions from viral exanthems, to remember that viral rashes may start on the face and progress to involve the trunk, and are more often accompanied by conjunctivitis, lymphadenopathy and fever. Maculopapular drug eruptions usually fade with desquamation, sometimes with post-inflammatory hyperpigmentation. Commoner causes are listed in Table 75.2.

References

1 Yawalkar N. Drug-induced exanthems. *Toxicology* 2005; **209**: 131–4.
2 Drago F, Rampini PR, Rampini E, Rebora A. Atypical exanthems: morphology and laboratory investigations may lead to an aetiological diagnosis in about 70% of cases. *Br J Dermatol* 2002; **147**: 255–60.

Purpura

A purpuric element to a drug eruption is not uncommon, but primarily purpuric drug-induced rashes also occur. Many drugs may interfere with platelet aggregation [1] but, with the exception of aspirin, this does not usually result in bleeding. A number of drugs have been implicated in the development of drug-induced purpura [2–4]. Several mechanisms may be involved. These include altered coagulation after anticoagulants or some cephalosporins, allergic and non-allergic thrombocytopenia, altered platelet function (as after valproic acid) or vascular causes, including steroid-induced fragility and loss of support. Cytotoxic drug therapy may result in non-allergic purpura due to bone marrow depression, with a platelet count of less than $30\,000/mm^3$. Bleomycin may induce thrombocytopenia by causing endothelial damage and consequent platelet aggregation [5]. A large number of drugs have been reported to cause allergic thrombocytopenia [2–4]. Heparin may cause purpura with overdosage or due to an allergic thrombocytopenia [6]. The classical example of complement-mediated destruction of platelets, following immune complex formation between a drug (as hapten) bound to the platelet surface and IgG class antibody, was the purpura caused by apronalide (Sedormid). Quinine, quinidine [7,8] and chlorothiazide may also cause allergic purpura. Tissue plasminogen activator (alteplase) has been associated with painful purpura [9]. A purpuric vasculitis-like rash followed secondary spread of a contact dermatitis to balsam of Peru [10].

Capillaritis (pigmented purpuric eruption) may be due to aspirin, carbromal or more rarely to thiamine or meprobamate [11], carbamazepine, phenacetin, as well as glipizide, pefloxacin, lorazepam, aspirin, paracetamol (acetuminophen), polyvinyl pyrrolidone plasma expander, ciclosporin and griseofulvin [12–16]; it may be due to formation of antibody to a drug–capillary endothelial cell complex [12]. Chronic pigmented purpura is recorded with thiamine propyldisulphide and chlordiazepoxide [13], and aminoglutethimide [17]. NSAIDs, diuretics, meprobamate and ampicillin were the commonest drug cause of pigmented purpuric eruptions in one study [18].

References

1 George JN, Shattil SJ. The clinical importance of acquired abnormalities of platelet function. *N Engl J Med* 1991; **324**: 27–39.
2 Miescher PA, Graf J. Drug-induced thrombocytopenia. *Clin Haematol* 1980; **9**: 505–19.
3 Moss RA. Drug-induced immune thrombocytopenia. *Am J Hematol* 1980; **9**: 439–46.
4 Bork K. *Cutaneous Side Effects of Drugs*. Philadelphia: Saunders, 1988.
5 Hilgard P, Hossfeld DK. Transient bleomycin-induced thrombocytopenia. A clinical study. *Eur J Cancer* 1978; **14**: 1261–4.
6 Babcock RB, Dumper CW, Scharfman WB. Heparin-induced thrombocytopenia. *N Engl J Med* 1976; **295**: 237–41.
7 Christie DJ, Weber RW, Mullen PC *et al.* Structural features of the quinidine and quinine molecules necessary for binding of drug-induced antibodies to human platelets. *J Lab Clin Med* 1984; **104**: 730–40.
8 Gary M, Ilfeld D, Kelton JG. Correlation of a quinidine-induced platelet-specific antibody with development of thrombocytopenia. *Am J Med* 1985; **79**: 253–5.
9 Detrana C, Hurwitz RM. Painful purpura: an adverse effect to a thrombolysin. *Arch Dermatol* 1990; **126**: 690–1.
10 Bruynzeel DP, van den Hoogenband HM, Koedijk F. Purpuric vasculitis-like eruption in a patient sensitive to balsam of Peru. *Contact Dermatitis* 1984; **11**: 207–9.
11 Peterson WC, Manick KP. Purpuric eruptions associated with use of carbromal and meprobamate. *Arch Dermatol* 1967; **95**: 40–2.
12 Carmel WJ, Dannenberg T. Nonthrombocytopenic purpura due to Miltown (2-methyl-2-*n*-propyl-1,3-propanediol dicarbamate). *N Engl J Med* 1956; **255**: 7701.
13 Nishioka K, Katayama I, Masuzawa M *et al.* Drug-induced chronic pigmented purpura. *J Dermatol* 1989; **16**: 220–2.
14 Abeck D, Gross GE, Kuwert C *et al.* Acetaminophen-induced progressive pigmentary purpura (Schamberg's disease). *J Am Acad Dermatol* 1992; **27**: 123–4.
15 Tsao H, Lerner LH. Pigmented purpuric eruption associated with injection medroxyprogesterone acetate. *J Am Acad Dermatol* 2000; **43**: 308–10.
16 Adams BB, Gadenne AS. Glipizide-induced pigmented purpuric dermatosis. *J Am Acad Dermatol* 1999; **41**: 827–9.
17 Stratakis CA, Chrousos GP. Capillaritis (purpura simplex) associated with use of aminoglutethimide in Cushing's syndrome. *Am J Hosp Pharm* 1994; **51**: 2589–91.
18 Pang BK, Su D, Ratnam KV. Drug-induced purpura simplex: clinical and histological characteristics. *Ann Acad Med Singapore* 1993; **22**: 870–2.

Annular erythema

Erythema annulare centrifugum has been reported in association with chloroquine and hydroxychloroquine [1], oestrogens, cimetidine [2], penicillin, salicylates and piroxicam, as well as with hydrochlorothiazide [3], spironolactone [4], thioacetazone [5], the phenothiazine levomepromazine [6], etizolam [7] and finasteride [8]. Annular erythema has occurred with vitamin K [9].

Table 75.3 Drugs causing pityriasis rosea-like reactions.

Acetylsalicylic acid	Griseofulvin
Allopurinol	Hydrochlorothiazide
Arsenicals	Isotretinoin
Bismuth	Methoxypromazine
Barbiturates	Metronidazole
β-Blockers	Nimesulide
Clonidine	Omeprazole
Captopril	Pyribenzamine
Gold	

References

1 Ashurst PJ. Erythema annulare centrifugum due to hydroxychloroquine sulfate and chloroquine sulfate. *Arch Dermatol* 1967; **95**: 37–9.
2 Merrett AC, Marks R, Dudley FJ. Cimetidine-induced erythema annulare centrifugum: no cross-sensitivity with ranitidine. *BMJ* 1981; **283**: 698.
3 Goette DK, Beatrice E. Erythema annulare centrifugum caused by hydrochlorothiazide-induced interstitial nephritis. *Int J Dermatol* 1988; **27**: 129–30.
4 Carsuzaa F, Pierre C, Dubegny M. Érytheme annulaire centrifuge a l'aldactone. *Ann Dermatol Vénéréol* 1987; **114**: 375–6.
5 Ramesh V. Eruption resembling erythema annulare centrifugum. *Australas J Dermatol* 1987; **28**: 44.
6 Blazejak T, Hölzle E. Phenothiazin-induziertes Pseudolymphom. *Hautarzt* 1990; **41**: 161–3.
7 Kuroda K, Yabunami H, Hisanaga Y. Etizolam-induced superficial erythema annulare centrifugum. *Clin Exp Dermatol* 2002; **27**: 34–6.
8 Al Hammadi A, Asai Y, Patt ML, Sasseville D. Erythema annulare centrifugum secondary to treatment with finasteride. *J Drugs Dermatol* 2007; **6**: 460–3.
9 Kay MH, Duvic M. Reactive annular erythema after intramuscular vitamin K. *Cutis* 1986; **37**: 445–8.

Pityriasis rosea-like reactions

The best-known drug cause of a pityriasiform rash is gold therapy [1], but several other drugs have been implicated, including metronidazole [2], captopril [3], isotretinoin [4] and omeprazole [5] (Table 75.3). An Italian series reported cases linked to: angiotensin-converting enzyme inhibitors, alone or in combination with hydrochlorothiazide, followed by one case each for hydrochlorothiazide plus sartan, allopurinol, nimesulide, and acetylsalicylic acid [6].

References

1 Wile UJ, Courville CJ. Pityriasis rosea-like dermatitis following gold therapy: report of two cases. *Arch Dermatol* 1940; **42**: 1105–12.
2 Maize JC, Tomecki J. Pityriasis rosea-like drug eruption secondary to metronidazole. *Arch Dermatol* 1977; **113**: 1457–8.
3 Wilkin JK, Kirkendall WM. Pityriasis rosea-like rash from captopril. *Arch Dermatol* 1982; **118**: 186–7.
4 Helfman RJ, Brickman M, Fahey J. Isotretinoin dermatitis simulating acute pityriasis rosea. *Cutis* 1984; **33**: 297–300.
5 Buckley C. Pityriasis rosea-like eruption in a patient receiving omeprazole. *Br J Dermatol* 1996; **135**: 660–1.
6 Atzori L, Pinna AL, Ferreli C, Aste N. Pityriasis rosea-like adverse reaction: review of the literature and experience of an Italian drug-surveillance center. *Dermatol Online J* 2006; **12**: 1.

Psoriasiform eruptions

See Chapter 20 and Table 75.4.

Table 75.4 Drugs reported to exacerbate psoriasis.

Antimalarials
β-Blockers
Lithium salts
Non-steroidal anti-inflammatory drugs
Ibuprofen
Indometacin (indomethacin) (disputed)
Meclofenamate sodium
Pyrazolone derivatives (phenylbutazone, oxyphenbutazone)
Miscellaneous
Captopril
Chlortalidone (chlorthalidone)
Cimetidine
Clonidine
Gemfibrozil
Interferon
Methlydopa
Penicillamine
Penicillin
Terfenadine
Trazodone

Table 75.5 Drugs causing erythroderma and exfoliative dermatitis.

Allopurinol	Hydantoins
p-Aminosalicylic acid	Isoniazid
Ampicillin	Lithium
Barbiturates	Nitrofurantoin
Captopril	Penicillamine
Carbamazepine	Penicillin
Cefoxitin	Phenylbutazone
Chloroquine	Quinidine
Chlorpromazine	Streptomycin
Cimetidine	Sulphonamides
Diltiazem	Sulphonylureas
Gold	Thioacetazone (thiacetazone)
Griseofulvin	

Exfoliative dermatitis

Exfoliative dermatitis is one of the most dangerous patterns of cutaneous reaction to drugs [1–5]. It may follow exanthematic eruptions or may develop, as in some reactions to arsenicals and the heavy metals, as erythema and exudation in the flexures, rapidly generalizing. The eruption may start several weeks after initiation of the therapy. A dermatitis in patients previously sensitized by contact may also become universal.

The main drugs implicated are listed in Table 75.5. In one large series, sulphonamides, antimalarials and penicillin were most frequently implicated [1]. In another series from India [3], the commonest associated drugs were isoniazid (20%), thioacetazone (15%), topical tar (15%) and a variety of homeopathic medicines (20%), with phenylbutazone, streptomycin and sulfadiazine (sulphadiazine) each accounting for 5% of cases. Phenytoin is a well-recognized cause [6]. Recently incriminated drugs have included captopril, cefoxitin, cimetidine and ampicillin.

References

1 Nicolis GD, Helwig EB. Exfoliative dermatitis. A clinicopathologic study of 135 cases. *Arch Dermatol* 1973; **108**: 788–97.
2 Hasan T, Jansén DT. Erythroderma: a follow-up of fifty cases. *J Am Acad Dermatol* 1983; **8**: 836–40.
3 Sehgal VN, Srivastava G. Exfoliative dermatitis. A prospective study of 80 patients. *Dermatologica* 1986; **173**: 278–84.
4 Sage T, Faure M. Conduite à tenir devant les érythrodermies de l'adulte. *Ann Dermatol Vénéréol* 1989; **116**: 747–52.
5 Irvine C. 'Skin failure'—a real entity: discussion paper. *J R Soc Med* 1991; **84**: 412–3.
6 Danno K, Kume M, Ohta M *et al.* Erythroderma with generalized lymphadenopathy induced by phenytoin. *J Dermatol* 1989; **16**: 392–6.

Anaphylaxis and anaphylactoid reactions

This systemic reaction, which usually develops within minutes to hours (the vast majority within the first hour), is often severe and may be fatal [1–3]. Fatal drug-induced anaphylactic shock was estimated at 0.3 cases per million inhabitants per year, based on notifications to the Danish Committee on Adverse Drug Reactions and to the Central Death Register during the period 1968–90 [3]. The most frequent causes were contrast media for X-ray examinations, antibiotics and extracts of allergens. In less severe cases, there may be premonitory dizziness or faintness, skin tingling and reddening of the bulbar conjunctiva, followed by urticaria, angio-oedema, bronchospasm, abdominal pain and vasomotor collapse. It usually develops on second exposure to a drug, but may develop during the first treatment if this lasts sufficiently long for sensitization to occur. Anaphylaxis is unlikely to occur with a drug taken continuously for several months; in contrast, intermittent administration may predispose to anaphylaxis [1]. It is commoner after parenteral than oral drug administration. The β-blockers enhance anaphylactic reactions caused by other allergens, and may make resuscitation more difficult [4].

The principal drug causes are shown in Table 75.6. Antibiotics (especially penicillin) and radiocontrast media are the most common known causes of anaphylactic events [2]; the incidence of such reactions for each is about 1 in 5000 exposures [5,6], of which less than 10% are fatal [2]. The risk for recurrent anaphylactic reactions is 10–20% for penicillins [5] and 20–40% for radiocontrast media [7]. Anaphylaxis to paracetamol-containing tablets has occurred, although it was the additive polyvinyl pyrrolidone that was responsible [8]. Anaphylaxis does occur after non-mucosal topical drug administration, especially to skin wounds or to skin with impaired barrier function, but TEN or SJS following non-mucosal topical drug application seems to be extremely rare [9].

Anaphylactoid reactions are those that clinically resemble an immediate immune response but in which the mechanism is undetermined. Some drugs and agents, such as mannitol and radiographic contrast media, can stimulate mediator release by an as yet unknown direct mechanism independent of IgE or complement. Anaphylactoid reactions may be produced by non-steroidal analgesics and anti-inflammatory agents (NSAIDs) [10,11], including aspirin and other salicylates, indometacin (indomethacin), phenylbutazone, propyphenazone, metamizole and tolmetin [12], as well as by radiographic contrast media, *d*-tubocurarine, benzoic acid preservatives [13], tartrazine dyes, sulphite preservatives [14] and ciprofloxacin [15]. The HLA-DRB1*11 allele showed a positive association with NSAID-induced anaphylactoid systemic reactions but not with purely cutaneous reactions [16].

Table 75.6 Drugs causing urticaria or anaphylaxis.

Animal sera	Dextrans
Vaccines containing egg protein	Mannitol
Desensitizing agents including pollen vaccines	Sorbitol complexes
Antibiotics	Enzymes
Penicillins	Trypsin
Cephalosporins	Streptokinase
Aminoglycosides	Chymopapain
Tetracyclines	Steroids
Sulphonamides	Progesterone
Antifungal agents	Hydrocortisone
Fluconazole	Polypeptide hormones
Ketoconazole	Insulin
Blood products	Corticotrophin
Angiotensin-converting enzyme inhibitors	Vasopressin
Radiographic contrast media	Food and drug additives
Non-steroidal anti-inflammatory drugs (NSAIDs)	Benzoates
Salicylates	Sulphites
Other NSAIDs (e.g. phenylbutazone, aminopyrine, propyphenazone, metamizole, tolmetin)	Tartrazine dyes
	Hydantoins
Narcotic analgesics	Hydralazine
Anaesthetic agents: local and general	Quinidine
Muscle relaxants	Anticancer drugs
Suxamethonium	Vitamins
Curare	Protamine

References

1 Sussman GL, Dolovich J. Prevention of anaphylaxis. *Semin Dermatol* 1989; **8**: 158–65.
2 Bochner BS, Lichtenstein LM. Anaphylaxis. *N Engl J Med* 1991; **324**: 1785–90.
3 Lenler-Petersen P, Hansen D, Andersen M *et al.* Drug-related fatal anaphylactic shock in Denmark 1968–1990. A study based on notifications to the Committee on Adverse Drug Reactions. *J Clin Epidemiol* 1995; **48**: 1185–8.
4 Toogood JH. Risk of anaphylaxis in patients receiving beta-blocker drugs. *J Allergy Clin Immunol* 1988; **81**: 1–5.
5 Weiss ME, Adkinson NF. Immediate hypersensitivity reactions to penicillin and related antibiotics. *Clin Allergy* 1988; **18**: 515–40.
6 Ansell G, Tweedie MCK, West DR *et al.* The current status of reactions to intravenous contrast media. *Invest Radiol* 1980; **15** (Suppl. 6): S32–S39.
7 Greenberger P, Patterson R, Kelly J *et al.* Administration of radiographic contrast media in high-risk patients. *Invest Radiol* 1980; **15** (Suppl. 6): S40–S43.
8 Rönnau AC, Wulferink M, Gleichmann E *et al.* Anaphylaxis to polyvinylpyrrolidone in an analgesic preparation. *Br J Dermatol* 2000; **143**: 1055–8.
9 Sachs B, Fischer-Barth W, Erdmann S *et al.* Anaphylaxis and toxic epidermal necrolysis or Stevens–Johnson syndrome after nonmucosal topical drug application: fact or fiction? *Allergy* 2007; **62**: 877–83.
10 Antépara I, Martín-Gil D, Dominguez MA, Oehling A. Adverse drug reactions produced by analgesic drugs. *Allergol Immunopathol* 1981; **9**: 545–54.
11 Stevenson DD. Diagnosis, prevention and treatment of adverse reactions to aspirin (ASA) and nonsteroidal anti-inflammatory drugs (NSAID). *J Allergy Clin Immunol* 1984; **74**: 617–22.
12 Rossi AC, Knapp DE. Tolmetin-induced anaphylactoid reactions. *N Engl J Med* 1982; **307**: 499–500.
13 Michils A, Vandermoten G, Duchateau J, Yernault J-C. Anaphylaxis with sodium benzoate. *Lancet* 1991; **337**: 1424–5.
14 Twarog FJ, Leung DYM. Anaphylaxis to a component of isoetharine (sodium bisulfite). *JAMA* 1982; **248**: 2030–1.
15 Davis H, McGoodwin E, Reed TG. Anaphylactoid reactions reported after treatment with ciprofloxin. *Ann Intern Med* 1989; **111**: 1041–3.



Fig. 75.2 Urticaria induced by acetylsalicylic acid. (Courtesy of St John's Institute of Dermatology, King's College London, UK.)

16 Quiralte J, Sanchez-Garcia F, Torres MJ *et al.* Association of HLA-DR11 with the anaphylactoid reaction caused by nonsteroidal anti-inflammatory drugs. *J Allergy Clin Immunol* 1999; **103**: 685–9.

Urticaria

Urticaria (see Chapter 22) is, after an exanthematous eruption, the second most common type of ACDR [1,2] (Fig. 75.2). Drug-induced urticaria is seen in 0.16% of medical in-patients and accounts for 9% of chronic urticaria or angio-oedema seen in dermatology outpatient departments [1]. Occurring within 24–36 h of drug ingestion, it is most commonly caused by penicillins, sulphonamides and NSAIDs. Drug-induced urticaria is seen in association with anaphylaxis, angio-oedema and serum sickness. On rechallenge, lesions may develop within minutes. Angio-oedema, involving oedema of the deep dermis or subcutaneous and submucosal areas, is more rarely seen than urticaria as an ACDR, and occurs in less than 1% of patients receiving the particular drug.

The commoner drug causes of urticaria/angio-oedema are listed in Table 75.6. The frequency of urticaria/angio-oedema or anaphylactic responses to aspirin and other NSAIDs is about 1% in an outpatient population and is familial [3]. Aspirin (salicylates) may also aggravate chronic urticaria [4,5]. In addition, an unsuspected agent, for example the yellow dye tartrazine, may really be responsible for an urticaria attributed to aspirin or another drug. The analgesic codeine is also a cause of urticaria [6]. Penicillin is a very well-documented cause of acute urticaria, but the role of this drug in chronic urticaria is controversial [7]. Urticaria develops in about 1% of patients receiving blood transfusions [8]. There have been numerous papers on the potential role of food and drug additives [9–17], including preservatives such as benzoic acid, butylated hydroxyanisole, butylated hydroxytoluene, sulphites and rarely aspartame, as well as tartrazine dyes, in the development of chronic urticaria. However, one study suggested that common food additives are seldom, if ever, of significance in urticaria [10]. Urticaria may follow alcohol consumption [18], intra-articular methylprednisolone [19] and even cetirizine [20].

Certain drugs, such as opiates, codeine, amfetamine, polymyxin B, *d*-tubocurarine, atropine, hydralazine, pentamidine, quinine and radiocontrast media, may release mast cell mediators directly. Cyclo-oxygenase inhibitors, such as aspirin and indometacin, and ACE inhibitors, such as captopril and enalapril, may cause urticaria or angio-oedema by pharmacological mechanisms. ACE inhibitors may cause increased frequency, intensity and duration of bouts of idiopathic angio-oedema during long-term use [21,22].

References

1 Shipley D, Ormerod AD. Drug-induced urticaria. Recognition and treatment. *Am J Clin Dermatol* 2001; **2**: 151–8.
2 Mathelier-Fusade P. Drug-induced urticarias. *Clin Rev Allergy Immunol* 2006; **30**: 19–23.
3 Settipane GA, Pudupakkam RK. Aspirin intolerance. III. Subtypes, familial occurrence and cross reactivity with tartrazine. *J Allergy Clin Immunol* 1975; **56**: 215–21.
4 Settipane RA, Constantine HP, Settipane GA. Aspirin intolerance and recurrent urticaria in normal adults and children. Epidemiology and review. *Allergy* 1980; **35**: 149–54.
5 Grattan CEH. Aspirin sensitivity and urticaria. *Clin Exp Dermatol* 2003; **28**: 123–7.
6 De Groot AC, Conemans J. Allergic urticarial rash from oral codeine. *Contact Dermatitis* 1986; **14**: 209–14.
7 Boonk WJ, Van Ketel WG. The role of penicillin in the pathogenesis of chronic urticaria. *Br J Dermatol* 1982; **106**: 183–90.
8 Shulman IA. Adverse reactions to blood transfusion. *Texas Med* 1990; **85**: 35–42.
9 Simon RA. Adverse reactions to drug additives. *J Allergy Clin Immunol* 1984; **74**: 623–30.
10 Hannuksela M, Lahti A. Peroral challenge tests with food additives in urticaria and atopic dermatitis. *Int J Dermatol* 1986; **25**: 178–80.
11 Supramaniam G, Warner JO. Artificial food additives intolerance in patients with angioedema and urticaria. *Lancet* 1986; **ii**: 907–9.
12 Juhlin L. Additives and chronic urticaria. *Ann Allergy* 1987; **59**: 119–23.
13 Goodman DL, McDonnell JT, Nelson HS *et al.* Chronic urticaria exacerbated by the antioxidant food preservatives, butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT). *J Allergy Clin Immunol* 1990; **86**: 570–5.
14 Settipane GA. Adverse reactions to sulfites in drugs and foods. *J Am Acad Dermatol* 1984; **10**: 1077–80.
15 Kulczycki A Jr. Aspartame-induced urticaria. *Ann Intern Med* 1986; **104**: 207–8.
16 Neuman I, Elian R, Nahum H *et al.* The danger of 'yellow dyes' (tartrazine) to allergic subjects. *J Allergy* 1972; **50**: 92–8.
17 Miller K. Sensitivity to tartrazine. *BMJ* 1982; **285**: 1597–8.
18 Ormerod AD, Holt PJA. Acute urticaria due to alcohol. *Br J Dermatol* 1983; **108**: 723–4.
19 Pollock B, Wilkinson SM, MacDonald Hull SP. Chronic urticaria associated with intra-articular methylprednisolone. *Br J Dermatol* 2001; **144**: 1228–30.
20 Calista D, Schianchi S, Morri M. Urticaria induced by cetirizine. *Br J Dermatol* 2001; **144**: 196.
21 Chin HL. Severe angioedema after long-term use of an angiotensin converting enzyme inhibitor. *Ann Intern Med* 1990; **112**: 312.
22 Kozel MMA, Mekkes JR, Bos JD. Increased frequency and severity of angio-oedema related to long-term therapy with angiotensin-converting enzyme inhibitor in two patients. *Clin Exp Dermatol* 1995; **20**: 60–1.

Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome

Synonyms
- Drug hypersensitivity syndrome
- Anticonvulsant hypersensitivity syndrome

The drug hypersensitivity syndrome [1–3], also known as *d*rug *r*ash with *e*osinophilia and *s*ystemic *s*ymptoms (DRESS) syndrome

[2] or as *d*rug-*i*nduced *d*elayed *m*ulti*o*rgan *h*ypersensitivity syndrome (DIDMOHS) [4], has been reported with the anticonvulsants phenytoin, carbamazepine, phenobarbital and lamotrigine (anticonvulsant hypersensitivity syndrome; see also section on anticonvulsants, pp. 75.83–86), and with trimethoprim–sulfamethoxazole, minocycline, procarbazine, allopurinol, terbinafine, dapsone, abacavir and nevirapine. This syndrome should be distinguished from drug-induced pseudolymphoma syndrome, also caused especially by anticonvulsants, which has a more insidious beginning with nodules and infiltrated plaques appearing several weeks after starting the drug, without constitutional symptoms (see p. 75.44). Cross-reactivity occurs between different anticonvulsants [5–7]; even valproate has been incriminated [7]. Superimposed, or reactivation of, viral infection may have a role in the aetiology [8] (see also Classification and mechanisms of drug reactions, Cell-mediated (type IV) reactions, pp. 75.17–19).

The syndrome comprises fever, facial oedema with infiltrated papules, generalized papulopustular or exanthematous rash which may extend to exfoliative dermatitis, lymphadenopathy, haematological abnormalities (hypereosinophilia in 90% of cases, atypical lymphocytes/mononucleosis in 40% of cases), and organ involvement such as hepatitis, possible nephritis, pneumonitis, myocarditis and hypothyroidism, and encephalitis, occurring after 3–6 weeks of drug therapy. The cutaneous histological pattern shows a lymphocytic infiltrate, sometimes mimicking a cutaneous lymphoma. The mortality is of the order of 10%; the syndrome may proceed to Stevens–Johnson syndrome or TEN [9] (see Chapter 76). There has been some controversy as to whether the constellation of various symptoms and signs occurring in multiorgan drug-induced reactions should be classified as a single, clearly defined, unified entity [10,11], but the concept of DRESS is generally accepted [12].

Management is usually with systemic corticosteroids. A combination of systemic steroids and intravenous immunoglobulin was successful in four patients with anticonvulsant hypersensitivity [13].

References

1 Sullivan JR, Shear NH. The drug hypersensitivity syndrome: what is the pathogenesis? *Arch Dermatol* 2001; **137**: 357–64.
2 Bocquet H, Bagot M, Roujeau JC. Drug-induced pseudolymphoma and drug hypersensitivity syndrome (drug rash with eosinophilia and systemic symptoms: DRESS). *Semin Cutan Med Surg* 1996; **15**: 250–7.
3 Carroll MC, Yueng-Yue KA, Esterly NB, Drolet BA. Drug-induced hypersensitivity syndrome in pediatric patients. *Pediatrics* 2001; **108**: 485–92.
4 Sontheimer RD, Houpt KR. DIDMOHS: a proposed consensus nomenclature for the drug-induced delayed multiorgan hypersensitivity syndrome. *Arch Dermatol* 1998; **134**: 874–5.
5 Allam JP, Paus T, Reichel C *et al*. DRESS syndrome associated with carbamazepine and phenytoin. *Eur J Dermatol* 2004; **14**: 339–42.
6 Mendiratta V, Bhushan P. Phenytoin-induced DRESS with cross-reactivity to carbamazepine in a 10-year-old Indian child. *Clin Exp Dermatol* 2006; **31**: 720–1.
7 Yun SJ, Lee JB, Kim EJ *et al*. Drug rash with eosinophilia and systemic symptoms induced by valproate and carbamazepine: formation of circulating auto-antibody against 190-kDa antigen. *Acta Derm Venereol* 2006; **86**: 241–4.
8 Aihara Y, Ito S-I, Kobayashi Y *et al.* Carbamazepine-induced hypersensitivity syndrome associated with transient hypogammaglobulinaemia and reactivation of human herpesvirus 6 infection demonstrated by real-time quantitative polymerase chain reaction. *Br J Dermatol* 2003; **149**: 165–9.
9 Wolf R, Matz H, Marcos B, Orion E. Drug rash with eosinophilia and systemic symptoms vs toxic epidermal necrolysis: the dilemma of classification. *Clin Dermatol* 2005; **23**: 311–4.
10 Peyrière H, Dereure O, Breton H *et al*. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? *Br J Dermatol* 2006; **155**: 422–8.
11 Kardaun SH, Sidoroff A, Valeyrie-Allanore L *et al*. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? *Br J Dermatol* 2007; **156**: 609–11.
12 Shiohara T, Iijima M, Ikezawa Z, Hashimoto K. The diagnosis of a DRESS syndrome has been sufficiently established on the basis of typical clinical features and viral reactivations. *Br J Dermatol* 2007; **156**: 1083–4.
13 Prais D, Straussberg R, Amir J *et al*. Treatment of anticonvulsant hypersensitivity syndrome with intravenous immunoglobulins and corticosteroids. *J Child Neurol* 2006; **21**: 380–4.

Erythema multiforme, Stevens–Johnson syndrome and toxic epidermal necrolysis

See Chapter 76.

Serum sickness

Serum sickness, a type III immune complex-mediated reaction, may occur between 5 days and 3 weeks after initial exposure [1–5], and in its complete form combines fever, urticaria, angio-oedema, joint pain and swelling, lymphadenopathy, and occasionally nephritis or endocarditis, with eosinophilia. In minor forms of serum sickness, fever, urticaria and transitory joint tenderness may be the only manifestations.

Drugs implicated include heterologous serum [1,2], immune globulin (as treatment for Kawasaki disease) [6], aspirin, antibiotics [7,8] such as penicillin [3,7,9], amoxicillin [7], flucloxacillin [7], cefaclor [10–14], cefprozil [15], piperacillin [16], ciprofloxacin [17], cefatrizine [18], cotrimoxazole [7], troleandomycin (triacetyloleandomycin) [7], streptomycin, sulphonamides and sulfasalazine [19], thiouracils, intravenous streptokinase [20,21], *N*-acetylcysteine [22], staphylococcal protein A immunomodulation [23] and amfebutamone (bupropion) [24]. Of 32 women in an *in vitro* fertilization programme, 15% developed serum sickness 8–12 days after oocyte retrieval by echographic puncture, when a medium containing bovine serum was employed for rinsing follicles [25]. Patients had specific IgG antibodies against, and positive intradermal skin testing to, bovine serum albumin. A characteristic serpiginous, erythematous and purpuric eruption developed on the hands and feet at the borders of palmar and plantar skin in a series of patients treated with intravenous infusions of horse antithymocyte globulin for bone marrow failure [1,2]. Circulating immune complexes, low serum C4 and C3 levels, and elevated plasma C3a anaphylatoxin levels were found. Direct immunofluorescence revealed the presence of immunoreactants including IgM, C3, IgE and IgA in the walls of dermal blood vessels.

References

1 Lawley TJ, Bielory L, Gascon P *et al.* A prospective clinical and immunologic analysis of patients with serum sickness. *N Engl J Med* 1984; **311**: 1407–13.
2 Bielory L, Yancey KB, Young NS *et al.* Cutaneous manifestations of serum sickness in patients receiving antithymocyte globulin. *J Am Acad Dermatol* 1985; **13**: 411–7.
3 Erffmeyer JE. Serum sickness. *Ann Allergy* 1986; **56**: 105–9.
4 Lin RY. Serum sickness syndrome. *Am Fam Physician* 1986; **33**: 157–62.
5 Virella G. Hypersensitivity reactions. *Immunol Ser* 1993; **58**: 329–41.

6 Comenzo RL, Malachowski ME, Meissner HC *et al.* Immune hemolysis, disseminated intravascular coagulation, and serum sickness after large doses of immune globulin given intravenously for Kawasaki disease. *J Pediatr* 1992; **120**: 926–8.
7 Martin J, Abbott G. Serum sickness-like illness and antimicrobials in children. *NZ Med J* 1995; **108**: 123–4.
8 Smith JM. Serum sickness-like reactions with antibiotics. *NZ Med J* 1995; **108**: 258.
9 Tatum AJ, Ditto AM, Patterson R. Severe serum sickness-like reaction to oral penicillin drugs: three case reports. *Ann Allergy Asthma Immunol* 2001; **86**: 330–4.
10 Vial T, Pont J, Pham E *et al.* Cefaclor-associated serum sickness-like disease: eight cases and review of the literature. *Ann Pharmacother* 1992; **26**: 910–4.
11 Parra FM, Igea JM, Martin JA *et al.* Serum sickness-like syndrome associated with cefaclor therapy. *Allergy* 1992; **47**: 439–40.
12 Kearns GL, Wheeler JG, Childress SH, Letzig LG. Serum sickness-like reactions to cefaclor: role of hepatic metabolism and individual susceptibility. *J Pediatr* 1994; **125**: 805–11.
13 Grammer LC. Cefaclor serum sickness. *JAMA* 1996; **275**: 1152–3.
14 Isaacs D. Serum sickness-like reaction to cefaclor. *J Paediatr Child Health* 2001; **37**: 298–9.
15 Lowery N, Kearns GL, Young RA, Wheeler JG. Serum sickness-like reactions associated with cefprozil therapy. *J Pediatr* 1994; **125**: 325–8.
16 Rye PJ, Roberts G, Staugas RE, Martin AJ. Coagulopathy with piperacillin administration in cystic fibrosis: two case reports. *J Paediatr Child Health* 1994; **30**: 278–9.
17 Guharoy SR. Serum sickness secondary to ciprofloxacin use. *Vet Hum Toxicol* 1994; **36**: 540–1.
18 Plantin P, Milochau P, Dubois D. Maladie serique medicamenteuse apres prise de cefatrizine. Premier cas reporté. *Presse Med* 1992; **21**: 1915.
19 Brooks H, Taylor HG, Nichol FE. The three week sulphasalazine syndrome. *Clin Rheumatol* 1992; **11**: 566–8.
20 Patel A, Prussick R, Buchanan WW, Sauder DN. Serum sickness-like illness and leukocytoclastic vasculitis after intravenous streptokinase. *J Am Acad Dermatol* 1991; **24**: 652–3.
21 Clesham GJ, Terry HJ, Jalihal S, Toghill PJ. Serum sickness and purpura following intravenous streptokinase. *J R Soc Med* 1992; **85**: 638–9.
22 Mohammed S, Jamal AZ, Robison LR. Serum sickness-like illness associated with *N*-acetylcysteine therapy. *Ann Pharmacother* 1994; **28**: 285.
23 Smith RE, Gottschall JL, Pisciotta AV. Life-threatening reaction to staphylococcal protein A immunomodulation. *J Clin Apheresis* 1992; **7**: 4–5.
24 Davis JS, Boyle MJ, Hannaford R, Watson A. Bupropion and serum sickness-like reaction. *Med J Aust* 2001; **174**: 479–80.
25 Morales C, Braso JV, Pellicer A *et al.* Serum sickness due to bovine serum albumin sensitization during in vitro fertilization. *J Invest Allergol Clin Immunol* 1994; **4**: 246–9.

Fixed eruptions [1–9]

A fixed drug eruption characteristically recurs in the same site or sites each time the drug is administered; with each exposure, however, the number of involved sites may increase. Usually, just one drug is involved, although independent lesions from more than one drug have been described [10]. Cross-sensitivity to related drugs may occur, such as between phenylbutazone and oxyphenbutazone, between tetracycline-type drugs, and between anticonvulsants [11]. There may be a refractory period after the occurrence of a fixed eruption.

Acute lesions usually develop 30 min to 8 h after drug administration as sharply marginated, round or oval itchy plaques of erythema and oedema becoming dusky violaceous or brown, and sometimes vesicular or bullous (Fig. 75.3). The eruption may initially be morbilliform, scarlatiniform or erythema multiforme-like; urticarial, nodular or eczematous lesions are less common. Lesions are sometimes solitary at first, but with repeated attacks new lesions usually appear and existing lesions may increase in size. A multifocal bullous fixed drug eruption due to mefenamic acid resembled erythema multiforme [12]. Occasionally, involvement is so extensive as to mimic TEN [13,14].



Fig. 75.3 Bullous fixed drug eruption with hyperpigmentation. (Courtesy of St John's Institute of Dermatology, London, UK.)

Lesions are commoner on the limbs than on the trunk; the hands and feet, genitalia and perianal areas are favoured sites. Perioral and periorbital lesions may occur. Genital [15] and oral mucous membranes [16] may be involved in association with skin lesions, or alone. In the case of isolated male genital fixed drug eruption (often affecting only the glans penis), the drugs most commonly implicated in one series were co-trimoxazole (trimethoprim–sulfamethoxazole), tetracycline and ampicillin [15]. With oral fixed drug eruption, co-trimoxazole, oxyphenbutazone and tetracycline were the most common causative drugs [16]. Pigmentation of the tongue may occur as a form of fixed drug eruption in heroin addicts [17]. As healing occurs, crusting and scaling are followed by pigmentation, which may be very persistent and occasionally extensive, especially in pigmented individuals; pigmentation may be all that is visible between attacks. Non-pigmenting fixed reactions have been reported in association with the sympathomimetic agents pseudoephedrine [18,19] and tetryzoline (tetrahydrozoline) hydrochloride, diflunisal, thiopental (thiopentone), piroxicam, the radiopaque contrast medium iothalamate, arsphenamine [20], paracetamol [21], intra-articular triamcinolone acetonide [22] and eperisone hydrochloride [23].

The number of drugs capable of producing fixed drug eruption is very large. However, most fixed drug eruptions are due to one or other of the substances listed in Table 75.7. Earlier series incriminated particularly analgesics, sulphonamides and tetracyclines. In a report from Finland, phenazones caused most eruptions, with barbiturates, sulphonamides, tetracyclines and carbamazepine causing fewer reactions [24]. A series from India reported that

Table 75.7 Drugs causing fixed eruptions.

Antibacterial substances	*Non-steroidal anti-inflammatory drugs*
Sulphonamides (co-trimoxazole)	Aspirin (acetylsalicylic acid)
Tetracyclines	Oxyphenbutazone
Penicillin	Phenazone (antipyrine)
Ampicillin	Metamizole
Amoxicillin	Paracetamol (acetaminophen)
Erythromycin	Ibuprofen
Trimethoprim	Various non-proprietary analgesic combinations
Nystatin	*Phenolphthalein and related compounds*
Griseofulvin	*Miscellaneous*
Dapsone	Codeine
Arsenicals	Hydralazine
Mercury salts	Oleoresins
p-Aminosalicylic acid	Sympathomimetics
Thioacetazone (thiacetazone)	Sympatholytics
Quinine	Parasympatholytics: hyoscine butylbromide
Metronidazole	Magnesium hydroxide
Clioquinol	Magnesium trisilicate
Barbiturates and other tranquillizers	Anthralin
Barbiturate derivatives	Chlorthiazone
Opium alkaloids	Chlorphenesin carbamate
Chloral hydrate	Food substitutes and flavours
Benzodiazepines: chlordiazepoxide	
Anticonvulsants	
Dextromethorphan	

acetylsalicylic acid was the drug most commonly implicated in children [25]; a more recent study found that co-trimoxazole was the usual culprit in children [26]. Co-trimoxazole has been implicated as the most frequent cause in many studies [6,8,27]. A fixed drug eruption apparently caused by co-trimoxazole was reported in a man following intercourse with his wife, who was taking the drug [28]. Trimethoprim has caused a linear fixed drug eruption [29]. A report in 1991 showed that co-trimoxazole caused the maximum incidence (36.3%), followed by tetracycline (15.9%), pyrazolones (14.2%), sulfadiazine (12.4%), dipyrine (9.3%), paracetamol (7.9%), aspirin (1.7%), thioacetazone (0.88%) and levamisole (0.88%) [27]. Co-trimoxazole was also the most common cause of fixed drug eruption (75%), followed by naproxen sodium (12.5%), dipyrone (9.5%), dimenhydrinate (1.5%) and paracetamol (1.5%) in a study in 2000 [8]. However, a survey of current causes of fixed drug eruption in the UK listed NSAIDs including aspirin, paracetamol, antibacterial agents, systemic antifungal agents, psychotropic drugs, proton pump inhibitors, calcium channel blockers, ACE inhibitors and hormonal preparations [9], reflecting the decreased use of co-trimoxazole.

A drug-specific clinical pattern in fixed drug eruptions based on a study of 113 patients has been reported [8,27]. Sulphonamides, including co-trimoxazole, induced lesions on the lips, trunk and limbs, with only minimal involvement of mucosae. Naproxen predominantly affected the lips and face. Tetracycline and co-trimoxazole caused lesions mainly on the glans penis. Pyrazolones affected mainly the lips and mucosae, with a few lesions of the trunk and limbs. Dipyrine, aspirin and paracetamol caused lesions of the trunk and limbs, sparing the lips, genitalia and mucosae. Levamisole caused associated constitutional disturbances with extensive skin lesions, as did thioacetazone [27]. Paracetamol (acetaminophen) is a rare cause of fixed drug eruption [30–33]; other drugs implicated have included codeine [34], naproxen [35], rofecoxib [36], ciprofloxacin [37], clarithromycin [38], rifampicin [39], metronidazole [40], terbinafine [41], fluconazole [42], lamotrigine [43], dimenhydrinate [44], cetirizine [45], loratadine [46], ticlopidine [47], phenylpropanolamine hydrochloride [48], and lactulose in an injected botulinum toxin preparation [49]. Familial fixed drug eruption has occurred occasionally [50,51].

References

1 Korkij W, Soltani K. Fixed drug eruption. A brief review. *Arch Dermatol* 1984; **120**: 520–4.
2 Kauppinen K, Stubb S. Fixed eruptions: causative drugs and challenge tests. *Br J Dermatol* 1985; **112**: 575–8.
3 Sehgal VN, Gangwani OP. Fixed drug eruption. Current concepts. *Int J Dermatol* 1987; **26**: 67–74.
4 Kanwar AJ, Bharija SC, Singh M, Belhaj MS. Ninety-eight fixed drug eruptions with provocation tests. *Dermatologica* 1988; **177**: 274–9.
5 Sehgal VN, Gangwani OP. Fixed drug eruptions. A study of epidemiological, clinical and diagnostic aspects of 89 cases from India. *J Dermatol* 1988; **15**: 50–4.
6 Mahboob A, Haroon TS. Drugs causing fixed eruptions: a study of 450 cases. *Int J Dermatol* 1998; **37**: 833–8.
7 Lee A-Y. Topical provocation in 31 cases of fixed drug eruption: change of causative drugs in 10 years. *Contact Dermatitis* 1998; **38**: 258–60.
8 Özkaya-Bayazit E, Bayazit H, Ozarmagan G. Drug related clinical pattern in fixed drug eruption. *Eur J Dermatol* 2000; **10**: 288–91.
9 Savin JA. Current causes of fixed drug eruption in the UK. *Br J Dermatol* 2001; **145**: 667–8.
10 Kivity S. Fixed drug eruption to multiple drugs: clinical and laboratory investigation. *Int J Dermatol* 1991; **30**: 149–51.
11 Chan HL, Tan KC. Fixed drug eruption to three anticonvulsant drugs: an unusual case of polysensitivity. *J Am Acad Dermatol* 1997; **36**: 259.
12 Sowden JM, Smith AG. Multifocal fixed drug eruption mimicking erythema multiforme. *Clin Exp Dermatol* 1990; **15**: 387–8.
13 Saiag P, Cordoliani F, Roujeau JC *et al.* Érytheme pigmenté fixe bulleux disséminé simulant un syndrome de Lyell. *Ann Dermatol Vénéréol* 1987; **114**: 1440–2.
14 Baird BJ, De Villez RL. Widespread bullous fixed drug eruption mimicking toxic epidermal necrolysis. *Int J Dermatol* 1988; **27**: 170–4.
15 Gaffoor PMA, George WM. Fixed drug eruptions occurring on the male genitals. *Cutis* 1990; **45**: 242–4.
16 Jain VK, Dixit VB, Archana. Fixed drug eruption of the oral mucous membrane. *Ann Dent* 1991; **50**: 9–11.
17 Westerhof W, Wolters EC, Brookbakker JTW *et al.* Pigmented lesions of the tongue in heroin addicts: fixed drug eruption. *Br J Dermatol* 1983; **109**: 605–10.
18 Vidal C, Prieto A, Perez-Carral C, Armisen M. Nonpigmenting fixed drug eruption due to pseudoephedrine. *Ann Allergy Asthma Immunol* 1998; **80**: 309–10.
19 Hindioglu U, Sahin S. Nonpigmenting solitary fixed drug eruption caused by pseudoephedrine hydrochloride. *J Am Acad Dermatol* 1998; **38**: 499–500.
20 Krivda SJ, Benson PM. Nonpigmenting fixed drug eruption. *J Am Acad Dermatol* 1994; **31**: 291–2.
21 Galindo PA, Borja J, Feo F *et al.* Nonpigmented fixed drug eruption caused by paracetamol. *J Invest Allergol Clin Immunol* 1999; **9**: 399–400.
22 Sener O, Caliskaner Z, Yazicioglu K *et al.* Nonpigmenting solitary fixed drug eruption after skin testing and intra-articular injection of triamcinolone acetonide. *Ann Allergy Asthma Immunol* 2001; **86**: 335–6.
23 Choonhakarn C. Non-pigmenting fixed drug eruption: a new case due to eperisone hydrochloride. *Br J Dermatol* 2001; **144**: 1288–9.
24 Stubb S, Alanko K, Reitamo S. Fixed drug eruptions: 77 cases from 1981 to 1985. *Br J Dermatol* 1989; **120**: 583.

25 Kanwar AJ, Bharija SC, Belhaj MS. Fixed drug eruptions in children: a series of 23 cases with provocative tests. *Dermatologica* 1986; **172**: 315–8.
26 Morelli JG, Tay YK, Rogers M *et al.* Fixed drug eruptions in children. *J Pediatr* 1999; **134**: 365–7.
27 Thankappan TP, Zachariah J. Drug-specific clinical pattern in fixed drug eruptions. *Int J Dermatol* 1991; **30**: 867–70.
28 Gruber F, Stasic A, Lenkovic M, Brajac I. Postcoital fixed drug eruption in a man sensitive to trimethoprim–sulphamethoxazole. *Clin Exp Dermatol* 1997; **22**: 144–5.
29 Özkaya-Bayazit E, Baykal C. Trimethoprim-induced linear fixed drug eruption. *Br J Dermatol* 1997; **137**: 1028–9.
30 Zemtsov A, Yanase DJ, Boyd AS, Shehata B. Fixed drug eruption to Tylenol: report of two cases and review of the literature. *Cutis* 1992; **50**: 281–2.
31 Hern S, Harman K, Clement M, Black MM. Bullous fixed drug eruption due to paracetamol with an unusual immunofluorescence pattern. *Br J Dermatol* 1998; **139**: 1129–31.
32 Silva A, Proenca E, Carvalho C *et al.* Fixed drug eruption induced by paracetamol. *Pediatr Dermatol* 2001; **18**: 163–4.
33 Hayashi H, Shimizu T, Shimizu H. Multiple fixed drug eruption caused by acetaminophen. *Clin Exp Dermatol* 2003; **28**: 455–6.
34 Gonzalo-Garijo MA, Revenga-Arranz F. Fixed drug eruption due to codeine. *Br J Dermatol* 1996; **135**: 498–9.
35 Gonzalo MA, Alvarado MI, Fernandez L *et al.* Fixed drug eruption due to naproxen: lack of cross-reactivity with other propionic acid derivatives. *Br J Dermatol* 2001; **144**: 1291–2.
36 Kaur C, Sarkar R, Kanwar AJ. Fixed drug eruption to rofecoxib with cross-reactivity to sulfonamides. *Dermatology* 2001; **203**: 351.
37 Dhar S, Sharma VK. Fixed drug eruption due to ciprofloxacin. *Br J Dermatol* 1996; **134**: 56–8.
38 Hamamoto Y, Ohmura A, Kinoshita E, Muto M. Fixed drug eruption due to clarithromycin. *Clin Exp Dermatol* 2001; **26**: 48–9.
39 Goel A, Balachandran C. Bullous necrotizing fixed drug eruption with hepatitis due to rifampicin. *Ind J Leprosy* 2001; **73**: 159–62.
40 Vila JB, Bernier MA, Gutierrez JV *et al.* Fixed drug eruption caused by metronidazole. *Contact Dermatitis* 2002; **46**: 122.
41 Munn SE, Russell Jones R. Terbinafine and fixed drug eruption. *Br J Dermatol* 1995; **133**: 815–6.
42 Ghislain PD, Ghislain E. Fixed drug eruption due to fluconazole: a third case. *J Am Acad Dermatol* 2002; **46**: 467.
43 Hsiao CJ, Lee JY, Wong TW, Sheu HM. Extensive fixed drug eruption due to lamotrigine. *Br J Dermatol* 2001; **144**: 1289–91.
44 Smola H, Kruppa A, Hunzelmann N *et al.* Identification of dimenhydrinate as the causative agent in fixed drug eruption using patch-testing in previously affected skin. *Br J Dermatol* 1998; **138**: 920–1.
45 Kranke B, Kern T. Multilocalized fixed drug eruption to the antihistamine cetirizine. *J Allergy Clin Immunol* 2000; **106**: 988.
46 Ruiz-Genao DP, Hernandez-Nunez A, Sanchez-Perez J, Garcia-Diez A. Fixed drug eruption due to loratadine. *Br J Dermatol* 2002; **146**: 528–9.
47 Garcia CM, Carmena R, Garcia R *et al.* Fixed drug eruption from ticlopidine, with positive lesional patch test. *Contact Dermatitis* 2001; **44**: 40–1.
48 Heikkilä H, Kariniemi A-L, Stubb S. Fixed drug eruption due to phenylpropanolamine hydrochloride. *Br J Dermatol* 2000; **142**: 845–7.
49 Cox NH, Duffey P, Royle J. Fixed drug eruption caused by lactulose in an injected botulinum toxin preparation. *J Am Acad Dermatol* 1999; **40**: 263–4.
50 Pellicano R, Silvestris A, Iannantuono M *et al.* Familial occurrence of fixed drug eruptions. *Acta Derm Venereol (Stockh)* 1992; **72**: 292–3.
51 Hatzis J, Noutsis K, Hatzidakis E *et al.* Fixed drug eruption in a mother and her son. *Cutis* 1992; **50**: 50–2.

Lichenoid eruptions

Lichenoid drug eruptions and lichen planus are discussed in Chapter 41. Some of the drugs that induce this pattern of reaction are listed in Table 75.8. Photodistributed lichenoid lesions may occur with a number of drugs, including thiazide diuretics (Fig. 75.4).

Table 75.8 Drugs causing lichenoid eruptions.

Gold salts	Antitubercular drugs
Antimalarials	Ethambutol
Mepacrine (quinacrine, atabrine)	Isoniazid
Chloroquine	*p*-Aminosalicylic acid
Quinine	Streptomycin
Quinidine	Cycloserine
Pyrimethamine	Antifungal drugs: ketoconazole
Penicillamine	Chemotherapeutic agents
Diuretics	Hydroxyurea
Thiazides	5-Fluorouracil
Furosemide (frusemide)	Heavy metals
Spironolactone	Mercurials
Diazoxide	Arsenicals
Antihypertensive agents	Bismuth
β-Blockers	Miscellaneous
Angiotensin-converting enzyme inhibitors: captopril, enalapril	Tetracyclines
	Carbamazepine
Methyldopa	Phenytoin
Calcium channel blockers	Procainamide
Nifedipine	Allopurinol
Phenothiazine derivatives	Iodides and radiocontrast media
Metopromazine	Tiopronin
Levomepromazine	Pyritinol
Chlorpromazine	Cyanamide
Sulphonylurea hypoglycaemic agents	Dapsone
Chlorpropamide	Amiphenazole
Tolazamide	Levamisole
Non-steroidal anti-inflammatory drugs: phenylbutazone	Nandrolone furylpropionate
	Cinnarizine
Sulfasalazine (sulphasalazine) and mesalazine	Flunarizine



Fig. 75.4 Lichenoid photosensitivity eruption caused by thiazide diuretic. (Courtesy of Dr A. Ive, Durham, UK.)

Photosensitivity

Drug–light reactions, which cause eruptions on exposed areas, with sparing of upper eyelids, submental and retroauricular areas, may be phototoxic or photoallergic; these cannot always be dis-

Table 75.9 Drugs causing photosensitivity.

Frequent	*Less frequent: systemic*
Amiodarone	Ampicillin
Phenothiazines	Antidepressants (tricyclic)
Chlorpromazine	Imipramine
Promethazine	Protriptyline
Psoralens	Antidepressants (monoamine oxidase inhibitors): phenelzine
Sulphonamides: co-trimoxazole	Antifungal agents
Tetracyclines: demeclocycline	Griseofulvin
Thiazides	Ketoconazole
Non-steroidal anti-inflammatory drugs	β-Blockers
Azapropazone	Carbamazepine
Piroxicam	Cimetidine
Carprofen	Cytotoxic agents
Tiaprofenic acid	Dacarbazine
Benoxaprofen (withdrawn)	Fluorouracil
Nalidixic acid	Mitomycin
Coal tar	Vinblastine
Less frequent: topical	Diazepam
Antihistamines	Furosemide (frusemide)
Local anaesthetics	Methyldopa
Benzydamine	Oral contraceptives
Hydrocortisone	Quinine
Sunscreens	Quinidine
p-Aminobenzoic acid	Sulphonylureas
Benzophenone	Chlorpropamide
Halogenated salicylanilides	Tolbutamide
	Retinoids
	Isotretinoin
	Etretinate
	Triamterene

tinguished clinically, and some drugs may produce cutaneous involvement by both mechanisms [1–6]. The main drugs implicated in photosensitivity reactions are listed in Table 75.9.

References

1 Johnson BE, Ferguson J. Drug and chemical photosensitivity. *Semin Dermatol* 1990; **9**: 39–46.
2 Elmets CA. Cutaneous phototoxicity. In: Lim HW, Soter NA, eds. *Clinical Photomedicine*. New York: Marcel Dekker, 1993: 207–26.
3 Deleo VA. Photoallergy. In: Lim HW, Soter NA, eds. *Clinical Photomedicine*. New York: Marcel Dekker, 1993: 227–39.
4 Gould JW, Mercurion MG, Elmets CA. Cutaneous photosensitivity diseases induced by exogenous agents. *J Am Acad Dermatol* 1995; **33**: 551–73.
5 González E, González S. Drug photosensitivity, idiopathic photodermatoses, and sunscreens. *J Am Acad Dermatol* 1996; **35**: 871–5.
6 Stein KR, Scheinfeld NS. Drug-induced photoallergic and phototoxic reactions. *Expert Opin Drug Saf* 2007; **6**: 431–43.

Phototoxic reactions

Phototoxic reactions are commoner than photoallergic reactions, and can be produced in almost all individuals given a high enough dose of drug and sufficient light irradiation. They occur within 5–20 h of the first exposure, and resemble exaggerated sunburn. Erythema, oedema, blistering, weeping, desquamation and residual hyperpigmentation occur on exposed areas; there may be photo-onycholysis. The following are well-recognized causes of phototoxicity:

- Tetracyclines [1–4], especially demeclocycline, less frequently doxycycline, oxytetracycline and tetracycline, and rarely minocycline and methacycline
- Other antibacterials including sulphonamides and fluoroquinolones [4]
- Phenothiazines, especially chlorpromazine, promethazine and, less commonly, thioridazine
- Furosemide [5] and nalidixic acid [4,6], both of which produce a pseudoporphyria syndrome, with blistering of the exposed areas
- NSAIDs, including ibuprofen [7], piroxicam [8–11], carprofen and tiaprofenic acid [12]
- Psoralens
- Amiodarone (which causes photosensitivity in over 50% of cases) [13]
- Certain anticancer drugs [14], including dacarbazine [14,15], 5-fluorouracil, mitomycin and vinblastine
- Coal tar and its derivatives
- Fibric acid derivatives, including bezafibrate and fenofibrate [16,17]
- The non-steroid antiandrogen flutamide given for prostatic carcinoma [18,19].

References

1 Cullen SI, Catalano PM, Helfmann RS. Tetracycline sun sensitivity. *Arch Dermatol* 1966; **93**: 77.
2 Frost P, Weinstein GP, Gomez EC. Phototoxic potential of minocycline and doxycycline. *Arch Dermatol* 1972; **105**: 681–3.
3 Layton AM, Cunliffe WJ. Phototoxic eruptions due to doxycycline: a dose-related phenomenon. *Clin Exp Dermatol* 1993; **18**: 425–7.
4 Wainwright NJ, Collins P, Ferguson J. Photosensitivity associated with antibacterial agents. *Drug Saf* 1993; **9**: 437–40.
5 Burry JN, Lawrence JR. Phototoxic blisters from high frusemide dosage. *Br J Dermatol* 1976; **94**: 495–9.
6 Ramsay CA, Obreshkova E. Photosensitivity from nalidixic acid. *Br J Dermatol* 1974; **91**: 523–8.
7 Bergner T, Przybilla B. Photosensitisation caused by ibuprofen. *J Am Acad Dermatol* 1992; **26**: 114–6.
8 Stern RS. Phototoxic reactions to piroxicam and other nonsteroidal antiinflammatory agents. *N Engl J Med* 1983; **309**: 186–7.
9 Serrano G, Bonillo J, Aliaga A *et al.* Piroxicam-induced photosensitivity. *In vivo* and *in vitro* studies of its photosensitizing potential. *J Am Acad Dermatol* 1984; **11**: 113–20.
10 Figueiredo A, Fontes Ribeiro CA, Conçalo S *et al.* Piroxicam-induced photosensitivity. *Contact Dermatitis* 1987; **17**: 73–9.
11 Serrano G, Fortea JM, Latasa JM. Oxicam-induced photosensitivity. Patch and photopatch testing studies with tenoxicam and piroxicam photoproducts in normal subjects and in piroxicam–droxicam photosensitive patients. *J Am Acad Dermatol* 1992; **26**: 545–8.
12 Przybilla B, Ring J, Galosi A, Dorn M. Photopatch test reactions to tiaprofenic acid. *Contact Dermatitis* 1984; **1**: 55–6.
13 Ferguson J, Addo HA, Jones S *et al.* A study of cutaneous photosensitivity induced by amiodarone. *Br J Dermatol* 1985; **113**: 537–49.
14 Kerker BJ, Hood AF. Chemotherapy-induced cutaneous reactions. *Semin Dermatol* 1989; **8**: 173–81.
15 Bonifazi E, Angelini G, Meneghini CL. Adverse photoreaction to dacarbazine (DITC). *Contact Dermatitis* 1981; **7**: 161.
16 Leenutaphong V, Manuskiatti W. Fenofibrate-induced photosensitivity. *J Am Acad Dermatol* 1996; **35**: 775–7.

17 Serrano G, Fortea JM, Latasa JM *et al.* Photosensitivity induced by fibric acid derivatives and its relation to photocontact dermatitis to ketoprofen. *J Am Acad Dermatol* 1992; **27**: 204–8.
18 Fujimoto M, Kikuchi K, Imakado S, Furue M. Photosensitive dermatitis induced by flutamide. *Br J Dermatol* 1996; **135**: 496–7.
19 Kaur C, Thami GP. Flutamide-induced photosensitivity: is it a forme fruste of lupus? *Br J Dermatol* 2003; **148**: 603–4.

Photoallergic reactions

Photoallergic reactions require a latent period during which sensitization occurs, and usually appear within 24 h of re-exposure to drug and light in a sensitized individual; unlike phototoxic reactions, they may spread beyond irradiated areas. Most systemic drugs causing photoallergy also cause phototoxicity. There may be cross-reactivity with chemically related substances.

Photoallergic reactions may occur as a result of local photocontact dermatitis to a topical photoallergen. Photocontact dermatitis is a relatively common cause of photosensitivity, accounting for 9% of cases in a multicentre study [1]. Topical photoallergens include antihistamines, chlorpromazine, local anaesthetics, benzydamine, hydrocortisone, desoximetasone (desoxymethasone) and sunscreens containing *p*-aminobenzoic acid (PABA) and its derivatives. Contact allergy and photoallergy to benzophenones in PABA-free sunscreens may be commoner than is realized [2]. Halogenated salicylanilides, previously used as a disinfectant in soaps, and related compounds also cause photocontact dermatitis.

Photoallergic reactions may also occur as a result of systemically administered drugs [3], such as phenothiazines (chlorpromazine, promethazine), sulphonamides, aromatic sulphonamides such as thiazide diuretics [4,5] and oral hypoglycaemic agents (chlorpropamide and tolbutamide), griseofulvin [6] and quinidine [7,8]. Quinidine-induced photoeruptions may be either eczematous or lichenoid; a persistent livedo reticularis-like eruption may be seen in severe cases of quinidine photosensitivity. Enalapril has caused a photosensitive lichenoid eruption [9]. Tricyclic antidepressants may cause allergy as well as photosensitivity [10]. NSAIDs, disinfectants, sunscreens, phenothiazines and fragrances caused photoallergic reactions most often in a 5-year survey by the German, Austrian and Swiss photopatch test group [11].

References

1 Wennersten G, Thune P, Brodthagen H *et al.* The Scandinavian multicenter photopatch study. Preliminary results. *Contact Dermatitis* 1984; **10**: 305–9.
2 Knobler E, Almeida L, Ruxkowski AM *et al.* Photoallergy to benzophenone. *Arch Dermatol* 1989; **125**: 801–4.
3 Giudici PA, Maguire HC. Experimental photoallergy to systemic drugs. *J Invest Dermatol* 1985; **85**: 207–11.
4 Robinson HN, Morison WL, Hood AF. Thiazide diuretic therapy and chronic photosensitivity. *Arch Dermatol* 1985; **121**: 522–4.
5 Addo HA, Ferguson J, Frain-Bell W. Thiazide-induced photosensitivity: a study of 33 subjects. *Br J Dermatol* 1987; **116**: 749–60.
6 Kojima T, Hasegawa T, Ishida H *et al.* Griseofulvin-induced photodermatitis. Report of six cases. *J Dermatol* 1988; **15**: 76–82.
7 Bruce S, Wolf JE Jr. Quinidine-induced photosensitive livedo reticularis-like eruption. *J Am Acad Dermatol* 1985; **12**: 332–6.
8 Schurer NY, Holzle E, Plewig G, Lehmann P. Photosensitivity induced by quinidine sulfate: experimental reproduction of skin lesions. *Photodermatol Photoimmunol Photomed* 1992; **9**: 78–82.
9 Kanwar AJ, Dhar S, Ghosh S. Photosensitive lichenoid eruption due to enalapril. *Dermatology* 1993; **187**: 80.
10 Ljunggren B, Bojs G. A case of photosensitivity and contact allergy to systemic tricyclic drugs, with unusual features. *Contact Dermatitis* 1991; **24**: 259–65.
11 Hölzle E, Neumann N, Hausen B *et al.* Photopatch testing: the 5-year experience of the German, Austrian and Swiss photopatch test group. *J Am Acad Dermatol* 1991; **25**: 59–68.

Porphyria and pseudoporphyria

A number of drugs may precipitate porphyria cutanea tarda with resultant photosensitivity, or cause a pseudoporphyria syndrome with bulla formation. The reader is referred to Chapter 59.

Photorecall reactions

A curious photorecall-like eruption, restricted to an area of sunburn sustained 1 month previously, occurred in a patient treated with cefazolin (cephazolin) and gentamicin [1]. An ultraviolet recall-like eruption has been reported with piperacillin, tobramycin and ciprofloxacin [2]. A recurrent cutaneous reaction localized to the site of pelvic radiotherapy for adenocarcinoma of the prostate followed sun exposure in one patient [3]. Methotrexate is associated with severe reactivation of sunburn [4,5].

References

1 Flax SH, Uhle P. Photo recall-like phenomenon following the use of cefazolin and gentamicin sulfate. *Cutis* 1990; **46**: 59–61.
2 Krishnan RS, Lewis AT, Kass JS, Hsu S. Ultraviolet recall-like phenomenon occurring after piperacillin, tobramycin, and ciprofloxacin therapy. *J Am Acad Dermatol* 2001; **44**: 1045–7.
3 Del Guidice SM, Gerstley JK. Sunlight-induced radiation recall. *Int J Dermatol* 1988; **27**: 415–6.
4 Mallory SB, Berry DH. Severe reactivation of sunburn following methotrexate use. *Pediatrics* 1986; **78**: 514–5.
5 Westwick TJ, Sherertz EF, McCarley D, Flowers FP. Delayed reactivation of sunburn by methotrexate: sparing of chronically sun-exposed skin. *Cutis* 1987; **39**: 49–51.

Photo-onycholysis

Photo-onycholysis may be caused by tetracycline, psoralens and UVA (PUVA) therapy, and the fluoroquinolone antibiotics pefloxacin and ofloxacin.

Pigmentation reactions

Hyperpigmentation (Table 75.10)

Drug-induced alteration in skin colour [1–3] may result from increased (or more rarely decreased) melanin synthesis, increased

Table 75.10 Drugs causing pigmentation.

Oral contraceptives	Chemotherapeutic agents
Minocycline	Miscellaneous
Antimalarials	Amiodarone
Chloroquine	Carotene
Hydroxychloroquine	Clofazimine
Mepacrine	Pefloxacin
Antidepressants	Sulfasalazine (sulphasalazine)
Chlorpromazine	
Imipramine	
Heavy metals	
Gold	
Lead	
Silver	

lipofuscin synthesis, cutaneous deposition of drug-related material, or most commonly as a result of post-inflammatory hyperpigmentation (e.g. fixed drug eruption). Oral contraceptives may induce chloasma [4]. Other drugs implicated in cutaneous hyperpigmentation include minocycline [5,6], antimalarials [7,8], chlorpromazine [9,10], imipramine (photodistributed) [11–13] and desimipramine [14], amiodarone [15], carotene and heavy metals. Long-term (more than 4 months) antimalarial therapy may result in brownish or blue-black pigmentation, especially on the shin, face and hard palate or subungually. Yellowish discoloration may occur with mepacrine (quinacrine) or amodiaquine. Long-term, high-dose phenothiazine (especially chlorpromazine) therapy results in a blue-grey or brownish pigmentation of sun-exposed areas, the result of a phototoxic reaction, with pigment deposits in the lens and cornea [10]. The cancer chemotherapeutic agents may be associated with pigmentation as follows [16]: skin pigmentation may be caused by bleomycin, busulfan, topical carmustine, cyclophosphamide, daunorubicin, fluorouracil, hydroxyurea, topical mechlorethamine, methotrexate, mithramycin, mitomycin and thiotepa. Busulfan and doxorubicin cause mucous membrane pigmentation. Nail pigmentation may result from bleomycin, cyclophosphamide, daunorubicin, doxorubicin and fluorouracil. Methotrexate may induce pigmentation of the hair, and cyclophosphamide of teeth. Sulfasalazine has caused reversible hyperpigmentation [17], and pefloxacin blue-black pigmentation of the legs [18].

Gold may cause blue-grey pigmentation in light-exposed areas (*chrysiasis*) [19,20] and silver may cause a similar discoloration (*argyria*) [21]. Lead poisoning can cause a blue-black line at the gingival margin and grey discoloration of the skin. Clofazimine produces red-brown discoloration of exposed skin and the conjunctivae, together with red sweat, urine and faeces [22]. Slate-grey to blue-black pigmentation may occur after long-term topical application of hydroquinone, causing ochronosis [23].

References

1 Levantine A, Almeyda J. Drug reactions: XXII. Drug induced changes in pigmentation. *Br J Dermatol* 1973; **89**: 105–12.
2 Granstein RD, Sober AJ. Drug- and heavy metal-induced hyperpigmentation. *J Am Acad Dermatol* 1981; **5**: 1–18.
3 Ferguson J, Frain-Bell W. Pigmentary disorders and systemic drug therapy. *Clin Dermatol* 1989; **7**: 44–54.
4 Smith AG, Shuster S, Thody AJ *et al.* Chloasma, oral contraceptives, and plasma immunoreactive beta-melanocyte-stimulating hormone. *J Invest Dermatol* 1977; **68**: 169–70.
5 Dwyer CM, Cuddihy AM, Kerr RE *et al.* Skin pigmentation due to minocycline treatment of facial dermatoses. *Br J Dermatol* 1993; **129**: 158–62.
6 Pepine M, Flowers FP, Ramos-Caro FA. Extensive cutaneous hyperpigmentation caused by minocycline. *J Am Acad Dermatol* 1993; **28**: 292–5.
7 Tuffanelli D, Abraham RK, Dubois EJ. Pigmentation from antimalarial therapy. Its possible relationship to the ocular lesions. *Arch Dermatol* 1963; **88**: 419–26.
8 Leigh IM, Kennedy CTC, Ramsey JD, Henderson WJ. Mepacrine pigmentation in systemic lupus erythematosus. New data from an ultrastructural, biochemical and analytical electron microscope investigation. *Br J Dermatol* 1979; **101**: 147–53.
9 Benning TL, McCormack KM, Ingram P *et al.* Microprobe analysis of chlorpromazine pigmentation. *Arch Dermatol* 1988; **124**: 1541–4.
10 Wolf ME, Richer S, Berk MA, Mosnaim AD. Cutaneous and ocular changes associated with the use of chlorpromazine. *Int J Clin Pharmacol Ther Toxicol* 1993; **31**: 365–7.
11 Hashimoto K, Joselow SA, Tye MJ. Imipramine hyperpigmentation: a slate-gray discoloration caused by long-term imipramine administration. *J Am Acad Dermatol* 1991; **25**: 357–61.
12 Ming ME, Bhawan J, Stefanato CM *et al.* Imipramine-induced hyperpigmentation: four cases and a review of the literature. *J Am Acad Dermatol* 1999; **40**: 159–66.
13 Sicari MC, Lebwohl M, Baral J *et al.* Photoinduced dermal pigmentation in patients taking tricyclic antidepressants: histology, electron microscopy, and energy dispersive spectroscopy. *J Am Acad Dermatol* 1999; **40**: 290–3.
14 Steele TE, Ashby J. Desipramine-related slate-gray skin pigmentation. *J Clin Psychopharmacol* 1993; **13**: 76–7.
15 Zachary CB, Slater DN, Holt DW *et al.* The pathogenesis of amiodarone-induced pigmentation and photosensitivity. *Br J Dermatol* 1984; **110**: 451–6.
16 Kerber BJ, Hood AF. Chemotherapy-induced cutaneous reactions. *Semin Dermatol* 1989; **8**: 173–81.
17 Gabazza EC, Taguchi O, Yamakami T *et al.* Pulmonary infiltrates and skin pigmentation associated with sulfasalazine. *Am J Gastroenterol* 1992; **87**: 1654–7.
18 Le Cleach L, Chosidow O, Peytavin G *et al.* Blue-black pigmentation of the legs associated with pefloxacin therapy. *Arch Dermatol* 1995; **131**: 856–7.
19 Leonard PA, Moatamed F, Ward JR *et al.* Chrysiasis: the role of sun exposure in dermal hyperpigmentation secondary to gold therapy. *J Rheumatol* 1986; **13**: 58–64.
20 Smith RW, Leppard B, Barnett NL *et al.* Chrysiasis revisited: a clinical and pathological study. *Br J Dermatol* 1995; **133**: 671–8.
21 Gherardi R, Brochard P, Chamak B *et al.* Human generalized argyria. *Arch Pathol Lab Med* 1984; **108**: 181–2.
22 Thomsen K, Rothenborg HW. Clofazimine in the treatment of pyoderma gangrenosum. *Arch Dermatol* 1979; **115**: 851–2.
23 Williams H. Skin lightening creams containing hydroquinone. The case for a temporary ban. *BMJ* 1992; **305**: 903–4.

Hypopigmentation

Topical thiotepa has produced periorbital leukoderma [1]. Hypopigmentation has occurred as a result of occupational exposure to monobenzyl ether of hydroquinone, *p*-tertiary-butylcatechol, *p*-tertiary-butylphenol, *p*-tertiary-amylphenol, monomethyl ether of hydroquinone and hydroquinone [2]. In addition, hypopigmentation may result from phenolic detergent germicides [3], and following use of diphencyprone for alopecia areata [4,5]. Depigmentation of the skin and hair occurred after a phenobarbital-induced eruption [6]. Photoleukomelanodermatitis occurred due to afloqualone for cervical spondylosis; photopatch and oral challenge tests were positive [7]. Generalized cutaneous depigmentation followed a sulphamide-induced ADR [8].

References

1 Harben DJ, Cooper PH, Rodman OG. Thiotepa-induced leukoderma. *Arch Dermatol* 1979; **115**: 973–4.
2 Stevenson CJ. Occupational vitiligo: clinical and epidemiological aspects. *Br J Dermatol* 1981; **105** (Suppl. 21): 51–6.
3 Kahn G. Depigmentation caused by phenolic detergent germicides. *Arch Dermatol* 1970; **102**: 177–87.
4 Hatzis J, Gourgiotou K, Tosca A *et al.* Vitiligo as a reaction to topical treatment with diphencyprone. *Dermatologica* 1988; **177**: 146–8.
5 Henderson CA, Ilchyshyn A. Vitiligo complicating diphencyprone sensitization therapy for alopecia universalis. *Br J Dermatol* 1995; **133**: 496–7.
6 Mion N, Fusade T, Mathelier-Fusade P *et al.* Depigmentation cutaneo-phanerienne consecutive à une toxidermie au phenobarbital. *Ann Dermatol Vénéréol* 1992; **119**: 927–9.
7 Ishikawa T, Kamide R, Niimura M. Photoleukomelanodermatitis (Kobori) induced by afloqualone. *J Dermatol* 1994; **21**: 430–3.
8 Martinez-Ruiz E, Ortega C, Calduch L *et al.* Generalized cutaneous depigmentation following sulfamide-induced drug eruption. *Dermatology* 2000; **201**: 252–4.

Acneiform and pustular eruptions

The term 'acneiform' is applied to eruptions that resemble acne vulgaris [1,2] (see Chapter 42). Lesions are papulopustular but comedones are usually absent. Adrenocorticotrophic hormone (ACTH), corticosteroids [3], dexamethasone in neurosurgical patients, anabolic steroids for body-building [4], androgens (in females), oral contraceptives, iodides and bromides may produce acneiform eruptions. Isoniazid may induce acne, especially in slow inactivators of the drug [5]. Other drugs implicated in the production of acneiform rashes include dantrolene [6], danazol [7], quinidine [8], lithium [9,10] and azathioprine [11]. Acne rosacea was temporally associated with daily high-dose vitamin B supplement therapy in one patient [12], and eosinophilic pustular folliculitis (Ofuji's disease) developed in association with use of the cerebral activator indeloxazine hydrochloride [13].

References

1 Hitch JM. Acneform eruptions induced by drugs and chemicals. *JAMA* 1967; **200**: 879–80.
2 Bedane C, Souyri N. Les acnés induites. *Ann Dermatol Vénéréol* 1990; **117**: 53–8.
3 Hurwitz RM. Steroid acne. *J Am Acad Dermatol* 1989; **21**: 1179–81.
4 Merkle T, Landthaler M, Braun-Falco O. Acne-conglobata-artige Exazerbation einer Acne vulgaris nach Einnahme von Anabolika und Vitamin-B-Komplex-haltigen Präparaten. *Hautarzt* 1990; **41**: 280–2.
5 Cohen LK, George W, Smith R. Isoniazid-induced acne and pellagra. Occurrence in slow inactivators of isoniazid. *Arch Dermatol* 1974; **109**: 377–81.
6 Pembroke AC, Saxena SR, Kataria M, Zilkha KD. Acne induced by dantrolene. *Br J Dermatol* 1981; **104**: 465–8.
7 Greenberg RD. Acne vulgaris associated with antigonadotrophic (danazol) therapy. *Cutis* 1979; **24**: 431–2.
8 Burkhart CG. Quinidine-induced acne. *Arch Dermatol* 1981; **117**: 603–4.
9 Heng MCY. Cutaneous manifestations of lithium toxicity. *Br J Dermatol* 1982; **106**: 107–9.
10 Kanzaki T. Acneiform eruption induced by lithium carbonate. *J Dermatol* 1991; **18**: 481–3.
11 Schmoeckel C, von Liebe V. Akneiformes Exanthem durch Azathioprin. *Hautarzt* 1983; **34**: 413–5.
12 Sherertz EF. Acneiform eruption due to 'megadose' vitamins B6 and B12. *Cutis* 1991; **48**: 119–20.
13 Kimura K, Ezoe K, Yokozeki H *et al.* A case of eosinophilic pustular folliculitis (Ofuji's disease) induced by patch and challenge tests with indeloxazine hydrochloride. *J Dermatol* 1996; **23**: 479–83.

Acute generalized exanthematous pustulosis (toxic pustuloderma)

Pustular reactions (toxic pustuloderma, acute generalized exanthematous pustulosis, AGEP) have been reported in association with a number of drugs [1]. The main differential diagnosis of a generalized pustular drug eruption is pustular psoriasis [2]. Two histological patterns may be seen: (i) a toxic pustuloderma with spongiform intraepidermal pustules, papillary oedema and a mixed upper dermal perivascular inflammatory infiltrate; or (ii) a leukocytoclastic vasculitis with neutrophil collections both below and within the epidermis, suggesting passive neutrophil elimination via the overlying epidermis [3,4]. The presence of eosinophils in the inflammatory infiltrate is a helpful pointer to a drug cause [2]. A responsible drug was found in 87% of a series of 63 patients with acute generalized exanthematous pustulosis; antibiotics were implicated as the causative agent in 80% of individuals [4]. The latter included particularly ampicillin, amoxicillin, spiramycin, erythromycin and cyclins. Hypersensitivity to mercury was also recorded as a precipitating cause. Pustulosis developed within 24 h of drug administration. It often started on the face or in flexural areas, rapidly became disseminated, with fever, and settled spontaneously with desquamation. Facial oedema, purpura, vesicles, blisters and erythema multiforme-like lesions were also seen; transient renal failure was noted in 32% of cases. Occasionally, TEN may be mimicked [5].

Acute generalized exanthematic pustulosis is usually due to penicillins or macrolides, especially ampicillin/amoxicillin ± clavulanic acid, pristinamycin, quinolones, (hydroxy)chloroquine, anti-infective sulphonamides, terbinafine, diltiazem, carbamazepine and spiramycin ± metronidazole [6–10]. There may be positive patch test reactions to the suspected drug [9,11]. Fatalities are recorded [8].

There have been individual reports of pustular drug reactions with ampicillin (which may be localized [12]), amoxicillin (with or without clavulanic acid) [13], propicillin [14], imipenem [15], the cephalosporins cefalexin (cephalexin) and cefradine (cephradine) [16,17], co-trimoxazole [18], doxycycline [19], chloramphenicol [20], ciprofloxacin [21], norfloxacin [22], ofloxacin [23], teicoplanin [24], streptomycin [25], isoniazid, metronidazole [26], terbinafine [27–29], fluconazole [30], itraconazole [31], nystatin [32], salazosulfapyridine/salazopyrine [33], mesalazine [34], diltiazem [35], captopril [36] and enalapril [37], furosemide [38], hydrochlorothiazide [39], azathioprine [40], cytarabine [41], high-dose chemotherapy [42], sertraline [43], chlorpromazine [44], nitrazepam, morphine [45], acetylsalicylic acid [46], naproxen [47], allopurinol [48], hydroxychloroquine [49], pyrimethamine, piperazine ethionamate, the mucolytic agent eprazinone [50], pseudoephedrine [51], dextropropoxyphene [52], icodextrin [53], mexiletine [54], dalteparin [55] and intravenous non-ionic contrast media [56]. Cases of generalized pustulation in association with the anticonvulsant hypersensitivity syndrome caused by phenytoin [57] and carbamazepine [58] have been recorded.

References

1 Webster GF. Pustular drug reactions. *Clin Dermatol* 1993; **11**: 541–3.
2 Spencer JM, Silvers DN, Grossman ME. Pustular eruption after drug exposure: is it pustular psoriasis or a pustular drug eruption? *Br J Dermatol* 1994; **130**: 514–9.
3 Burrows NP, Russell Jones RR. Pustular drug eruptions: a histopathological spectrum. *Histopathology* 1993; **22**: 569–73.
4 Roujeau J-C, Bioulac-Sage P, Bourseau C *et al.* Acute generalized exanthematous pustulosis. Analysis of 63 cases. *Arch Dermatol* 1991; **127**: 1333–8.
5 Cohen AD, Cagnano E, Halevy S. Acute generalized exanthematous pustulosis mimicking toxic epidermal necrolysis. *Int J Dermatol* 2001; **40**: 458–61.
6 Manders SM, Heymann WR. Acute generalized exanthemic pustulosis. *Cutis* 1994; **54**: 194–6.
7 Trevisi P, Patrizi A, Neri I, Farina P. Toxic pustuloderma associated with azithromycin. *Clin Exp Dermatol* 1994; **19**: 280–1.
8 Saissi EH, Beau-Salinas F, Jonville-Béra AP *et al*. Drugs associated with acute generalized exanthematic pustulosis. *Ann Dermatol Venereol* 2003; **130**: 612–8.
9 Gensch K, Hodzic-Avdagic N, Megahed M *et al*. Acute generalized exanthematous pustulosis with confirmed type IV allergy. Report of 3 cases. *Hautarzt* 2007; **58**: 250–2, 254–5.
10 Sidoroff A, Dunant A, Viboud C *et al*. Risk factors for acute generalized exanthematous pustulosis (AGEP)—results of a multinational case-control study (EuroSCAR). *Br J Dermatol* 2007; **157**: 989–96.
11 Moreau A, Dompmartin A, Castel B *et al*. Drug-induced acute generalized exanthematous pustulosis with positive patch tests. *Int J Dermatol* 1995; **34**: 263–6.

12 Jay S, Kang J, Watcher MA *et al.* Localized pustular skin eruption. Localized pustular drug eruption secondary to ampicillin. *Arch Dermatol* 1994; **130**: 787, 790.
13 Armster H, Schwarz T. Arzneimittelreaktion auf Amoxicillin unter dem Bild eines toxischen Pustuloderms. *Hautarzt* 1991; **42**: 713–6.
14 Gebhardt M, Lustig A, Bocker T, Wollina U. Acute generalized exanthematous pustulosis (AGEP): manifestation of drug allergy to propicillin. *Contact Dermatitis* 1995; **33**: 204–5.
15 Escallier F, Dalac S, Foucher JL *et al.* Pustulose exanthématique aiguë généralisée imputabilité a l'imipéneme (Tienam®). *Ann Dermatol Vénéréol* 1989; **116**: 407–9.
16 Kalb RE, Grossman ME. Pustular eruption following administration of cephradine. *Cutis* 1986; **38**: 58–60.
17 Jackson H, Vion B, Levy PM. Generalized eruptive pustular drug rash due to cephalexin. *Dermatologica* 1988; **177**: 292–4.
18 MacDonald KJS, Green CM, Kenicer KJA. Pustular dermatosis induced by cotrimoxazole. *BMJ* 1986; **293**: 1279–80.
19 Trueb RM, Burg G. Acute generalized exanthematous pustulosis due to doxycycline. *Dermatology* 1993; **186**: 75–8.
20 Lee AY, Yoo SH. Chloramphenicol induced acute generalized exanthematous pustulosis proved by patch test and systemic provocation. *Acta Derm Venereol (Stockh)* 1999; **79**: 412–3.
21 Hausermann P, Scherer K, Weber M, Bircher AJ. Ciprofloxacin-induced acute generalized exanthematous pustulosis mimicking bullous drug eruption confirmed by a positive patch test. *Dermatology* 2005; **211**: 277–80.
22 Shelley ED, Shelley WB. The subcorneal pustular eruption: an example induced by norfloxacin. *Cutis* 1988; **42**: 24–7.
23 Tsuda S, Kato K, Karashima T *et al.* Toxic pustuloderma induced by ofloxacin. *Acta Derm Venereol (Stockh)* 1993; **73**: 382–4.
24 Chu CY, Wu J, Jean SS, Sun CC. Acute generalized exanthematous pustulosis due to teicoplanin. *Dermatology* 2001; **202**: 141–2.
25 Kushimoto H, Aoki T. Toxic erythema with generalized follicular pustules caused by streptomycin. *Arch Dermatol* 1981; **117**: 444–5.
26 Watsky KL. Acute generalised exanthematous pustulosis induced by metronidazole: the role of patch testing. *Arch Dermatol* 1999; **135**: 93–4.
27 Kempinaire A, De Raeve L, Merckx M *et al.* Terbinafine-induced acute generalized exanthematous pustulosis confirmed by positive patch-test result. *J Am Acad Dermatol* 1997; **37**: 653–5.
28 Condon CA, Downs AMR, Archer CB. Terbinafine-induced acute generalized exanthematous pustulosis. *Br J Dermatol* 1998; **138**: 709–10.
29 Bennett ML, Jorizzo JL, White WL. Generalized pustular eruptions associated with oral terbinafine. *Int J Dermatol* 1999; **38**: 596–600.
30 Alsadhan A, Taher M, Krol A. Acute generalized exanthematous pustulosis induced by oral fluconazole. *J Cutan Med Surg* 2002; **6**: 122–4.
31 Heymann WR, Manders SM. Itraconazole-induced acute generalised exanthematic pustulosis. *J Am Acad Dermatol* 1996; **33**: 130–1.
32 Kuchler A, Hamm H, Weidenthaler-Barth B *et al.* Acute generalized exanthematous pustulosis following oral nystatin therapy: a report of three cases. *Br J Dermatol* 1997; **137**: 808–11.
33 Kawaguchi M, Mitsuhashi Y, Kondo S. Acute generalized exanthematous pustulosis induced by salazosulfapyridine in a patient with ulcerative colitis. *J Dermatol* 1999; **26**: 359–62.
34 Gibbon KL, Bewley AP, Thomas K. Mesalazine-induced pustular drug eruption. *J Am Acad Dermatol* 2001; **45**: S220–S221.
35 Vincente-Calleja JM, Aguirre A, Landa N *et al.* Acute generalized exanthematous pustulosis due to diltiazem: confirmation by patch testing. *Br J Dermatol* 1997; **137**: 837–9.
36 Carroll J, Thaler M, Grossman E *et al.* Generalized pustular eruption associated with converting enzyme inhibitor therapy. *Cutis* 1995; **56**: 276–8.
37 Ferguson JE, Chalmers RJ. Enalapril-induced toxic pustuloderma. *Clin Exp Dermatol* 1996; **21**: 54–5.
38 Noce R, Paredes BE, Pichler WJ, Krahenbuhl S. Acute generalized exanthematic pustulosis (AGEP) in a patient treated with furosemide. *Am J Med Sci* 2000; **320**: 331–3.
39 Petavy-Catala C, Martin L, Fontes V *et al.* Hydrochlorothiazide-induced acute generalized exanthematous pustulosis. *Acta Derm Venereol (Stockh)* 2001; **81**: 209.
40 Elston GE, Johnston GA, Mortimer NJ, Harman KE. Acute generalized exanthematous pustulosis associated with azathioprine hypersensitivity. *Clin Exp Dermatol* 2007; **32**: 52–3.
41 Chiu A, Kohler S, McGuire J, Kimball AB. Cytarabine-induced acute generalised exanthematous pustulosis. *J Am Acad Dermatol* 2002; **45**: 633–5.
42 Valks R, Fraga J, Munoz E *et al.* Acute generalized exanthematous pustulosis in patients receiving high-dose chemotherapy. *Arch Dermatol* 1999; **135**: 1418–20.
43 Thedenat B, Loche F, Albes B *et al.* Acute generalized exanthematous pustulosis with photodistribution pattern induced by sertraline. *Dermatology* 2001; **203**: 87–8.
44 Burrows NP, Ratnavel RC, Norris PG. Pustular eruptions after chlorpromazine. *BMJ* 1994; **309**: 97.
45 Kardaun SH, de Monchy JG. Acute generalized exanthematous pustulosis caused by morphine, confirmed by positive patch test and lymphocyte transformation test. *J Am Acad Dermatol* 2006; **55** (Suppl. 2): S21–3.
46 Ballmer-Weber BK, Widmer M, Burg G. Acetylsalicylsaure-induzierte generalisierte Pustulose. *Schweiz Med Wochenschr* 1993; **123**: 542–6.
47 Grattan CEH. Generalized pustular drug rash due to naproxen. *Dermatologica* 1989; **179**: 57–8.
48 Boffa MJ, Chalmers RJ. Allopurinol-induced toxic pustuloderma. *Br J Dermatol* 1994; **131**: 447.
49 Paradisi A, Bugatti L, Sisto T *et al.* Acute generalized exanthematous pustulosis induced by hydroxychloroquine: three cases and a review of the literature. *Clin Ther* 2008; **30**: 930–40.
50 Faber M, Maucher OM, Stengel R, Goerttler E. Epraxinonenexanthem mit subkornealer Pustelbildung. *Hautarzt* 1984; **35**: 200–3.
51 Padial MA, Alvarez-Ferreira J, Tapia B *et al.* Acute generalized exanthematous pustulosis associated with pseudoephedrine. *Br J Dermatol* 2004; **150**: 139–42.
52 Machet L, Martin L, Machet MC *et al.* Acute generalized exanthematous pustulosis induced by dextropropoxyphene and confirmed by patch testing. *Acta Derm Venereol (Stockh)* 2000; **80**: 224–5.
53 Al-Hoqail IA, Crawford RI. Acute generalized exanthematous pustulosis induced by icodextrin. *Br J Dermatol* 2001; **145**: 1026–7.
54 Sasaki K, Yamamoto T, Kishi M *et al.* Acute exanthematous pustular drug eruption induced by mexiletine. *Eur J Dermatol* 2001; **11**: 469–71.
55 Komericki P, Grims R, Kränke B, Aberer W. Acute generalized exanthematous pustulosis from dalteparin. *J Am Acad Dermatol* 2007; **57**: 718–21.
56 Peterson A, Katzberg RW, Fung MA *et al.* Acute generalized exanthematous pustulosis as a delayed dermatotoxic reaction to IV-administered nonionic contrast media. *AJR Am J Roentgenol* 2006; **187**: W198–201.
57 Kleier RS, Breneman DL, Boiko S. Generalized pustulation as a manifestation of the anticonvulsant hypersensitivity syndrome. *Arch Dermatol* 1991; **127**: 1361–4.
58 Commens CA, Fischer GO. Toxic pustuloderma following carbamazepine therapy. *Arch Dermatol* 1988; **124**: 178–9.

Eczematous eruptions

Allergic contact dermatitis is discussed in Chapter 26. This section concerns the entity termed 'systemic contact-type dermatitis medicamentosa' [1–5] (Table 75.11). A patient initially sensitized to a drug by way of allergic contact dermatitis may develop an eczematous reaction when the same, or a chemically related, substance is subsequently administered systemically. The eruption tends to be symmetrical, and may involve first, or most severely, the site(s) of the original dermatitis, before becoming generalized. Patients with a contact allergy to ethylenediamine may develop urticaria or systemic eczema following injection of aminophylline preparations containing ethylenediamine as a solubilizer for theophylline [6,7]. Patients with contact allergy to parabens may develop systemic eczema on medication with a drug containing parabens as a preservative [8]. Similarly, sensitized patients may develop eczema following oral ingestion of neomycin or hydroxyquinolines [9]. Diabetic patients sensitized by topical preparations containing *p*-amino compounds, such as *p*-phenylenediamine hair dyes, PABA sunscreens and certain local anaesthetic agents (e.g. benzocaine), may develop a systemic contact dermatitis

Table 75.11 Systemic drugs that can reactivate allergic contact eczema to chemically related topical medicaments. (From Fisher [1].)

Systemic drug	Topical medicament
Ethylenediamine antihistamines	Aminophylline suppositories and ethylenediamine hydrochloride
Aminophylline	
Piperazine	
Organic and inorganic mercury compounds	Ammoniated mercury
Tincture of benzoin inhalation	Balsam of Peru
Procaine	Benzocaine (*p*-amino compound) and glyceryl
Acetohexamide	*p*-aminobenzoic acid sunscreens
p-Aminosalicylic acid	
Azo dyes in foods and drugs	
Chlorothiazide	
Chlorpropamide	
Tolbutamide	
Chloral hydrate	Chlorobutanol
Iodochlorhydroxyquinoline	Halogenated hydroxyquinoline creams (Vioform)
Iodides, iodinated organic compounds, radiographic contrast media	Iodine
Streptomycin, kanamycin, paromycin, gentamicin	Neomycin sulphate
Glyceryl trinitrate tablets	Glyceryl trinitrate ointment
Disulfiram (Antabuse)	Thiuram (rubber chemical)

with the hypoglycaemic agents tolbutamide or chlorpropamide. Sulphonylureas may also induce eczematous eruptions in sulphanilamide-sensitive patients as a result of cross reactivity. Phenothiazines can produce allergic contact dermatitis, photoallergic reactions and eczematous contact-type dermatitis, and may cross-react with certain antihistamines. Tetraethylthiuram disulphide (disulfiram, Antabuse) for the management of alcoholism can cause eczematous reactions in patients sensitized to thiurams via rubber gloves. 'Systemic contact-type dermatitis' reactions have also been described with [4] acetylsalicylic acid, codeine [10], phenobarbital, pseudoephedrine hydrochloride and norephedrine hydrochloride [11], ephedrine [12], erythromycin [13], isoniazid [14], dimethylsulfoxide, hydroxyquinone, nystatin, subcutaneous hydromorphone given for cancer pain [15], amlexanox [16], enoxolone [17], vitamin B_1, vitamin C, parabens, butylated hydroxyanisole, hydroxytoluene and tea-tree oil [18]. Allergic eczematous reactions to endogenous or exogenous systemic corticosteroids, including hydrocortisone and methylprednisolone, have been documented in patients who are patch-test positive to topical corticosteroids [19,20].

The term 'baboon syndrome' denotes a characteristic pattern of systemic allergic contact dermatitis [21–23], in which there is diffuse erythema of the buttocks, upper inner thighs and axillae, provoked by penicillin [24], ampicillin, amoxicillin [25], nickel, heparin, mercury (including that found in a homeopathic medicine [26]), terbinafine [27] and hydroxyurea [28]. Patch tests are commonly positive and usually vesicular, although histology of the eruption itself may show leukocytoclastic vasculitis; oral challenge with the suspected antigen may be required to substantiate the diagnosis. Disulfiram therapy of a nickel-sensitive alcoholic patient may induce this syndrome, as the drug leads to an initial acute increase in blood nickel concentration [21]. Cases have been described from Japan under the name 'mercury exanthem' following inhalation of mercury vapour from crushed thermometers in patients with a history of mercury allergy.

The term 'endogenic contact eczema' [29] refers to the occurrence of an eczematous contact drug reaction following primary sensitization by oral therapy, as in the case of a patient with a drug-related exanthem who later develops localized dermatitis due to topical therapy. Thus, eczematous eruptions may develop following therapy with penicillin [30], methyldopa, allopurinol, indometacin, sulphonamides, gold, quinine, chloramphenicol, clonidine or bleomycin [31]. The alkylating agent mitomycin C administered intravesically for carcinoma of the bladder has been associated with an eczematous eruption, particularly on the face, palms and soles in some patients; these may have positive patch tests to the drug [32,33].

Some of the more important causes of eczematous drug reactions are listed in Table 75.11. Sensitivity to the suspected drug may be confirmed by subsequent patch testing, when the skin reaction has settled.

References

1 Fisher AA. *Contact Dermatitis*. Philadelphia: Lea & Febiger, 1986.
2 Rycroft RJG, Menné T, Frosch PJ, Benezra CM, eds. *Textbook of Contact Dermatitis*. Berlin: Springer, 1992.
3 Cronin E. Contact dermatitis XVII. Reactions to contact allergens given orally or systemically. *Br J Dermatol* 1972; **86**: 104–7.
4 Menné T, Veien NK, Maibach HI. Systemic contact-type dermatitis due to drugs. *Semin Dermatol* 1989; **8**: 144–8.
5 Aquilina C, Sayag J. Eczéma par réactogenes internes. *Ann Dermatol Vénéréol* 1989; **116**: 753–65.
6 Berman BA, Ross RN. Ethylenediamine: systemic eczematous contact-type dermatitis. *Cutis* 1983; **31**: 594–8.
7 Hardy C, Schofield O, George CF. Allergy to aminophylline. *BMJ* 1983; **286**: 2051–2.
8 Aeling JL, Nuss DD. Systemic eczematous 'contact-type' dermatitis medicamentosa caused by parabens. *Arch Dermatol* 1974; **110**: 640.
9 Ekelund E-G, Möller H. Oral provocation in eczematous contact allergy to neomycin and hydroxy-quinolines. *Acta Derm Venereol (Stockh)* 1969; **49**: 422–6.
10 Estrada JL, Puebla MJ, de Urbina JJ *et al.* Generalized eczema due to codeine. *Contact Dermatitis* 2001; **44**: 185.
11 Tomb RR, Lepoittevin JP, Espinassouze F *et al.* Systemic contact dermatitis from pseudoephedrine. *Contact Dermatitis* 1991; **24**: 86–8.
12 Villas Martinez F, Badas AJ, Garmendia Goitia JF, Aguirre I. Generalized dermatitis due to oral ephedrine. *Contact Dermatitis* 1993; **29**: 215–6.
13 Fernandez Redondo V, Casas L, Taboada M, Toribio J. Systemic contact dermatitis from erythromycin. *Contact Dermatitis* 1994; **30**: 311.
14 Meseguer J, Sastre A, Malek T, Salvador MD. Systemic contact dermatitis from isoniazid. *Contact Dermatitis* 1993; **28**: 110–1.
15 de Cuyper C, Goeteyn M. Systemic contact dermatitis from subcutaneous hydromorphone. *Contact Dermatitis* 1992; **27**: 220–3.
16 Hayakawa R, Ogino Y, Aris K, Matsunaga K. Systemic contact dermatitis due to amlexanox. *Contact Dermatitis* 1992; **27**: 122–3.
17 Villas Martinez F, Joral Badas A, Garmendia Goitia JF, Aguirre I. Sensitization to oral enoxolone. *Contact Dermatitis* 1994; **30**: 124.
18 de Groot AC, Weyland JW. Systemic contact dermatitis from tea tree oil. *Contact Dermatitis* 1992; **27**: 279–80.
19 Lauerma AI, Reitamo S, Maibach HI. Systemic hydrocortisone/cortisol induces allergic skin reactions in presensitized subjects. *J Am Acad Dermatol* 1991; **24**: 182–5.

20 Murata Y, Kumano K, Ueda T *et al.* Systemic contact dermatitis caused by systemic corticosteroid use. *Arch Dermatol* 1997; **133**: 1053–4.
21 Andersen KE, Hjorth N, Menné T. The baboon syndrome: systemically-induced allergic contact dermatitis. *Contact Dermatitis* 1984; **10**: 97–100.
22 Herfs H, Schirren CG, Przybilla B, Plewig G. Das 'Baboon-Syndrom'. Eine besondere Manifestation einer hamatogenen Kontaktreaktion. *Hautarzt* 1993; **44**: 466–9.
23 Duve S, Worret W, Hofmann H. The baboon syndrome: a manifestation of haematogenous contact-type dermatitis. *Acta Derm Venereol (Stockh)* 1994; **74**: 480–1.
24 Panhans-Gross A, Gall H, Peter RU. Baboon syndrome after oral penicillin. *Contact Dermatitis* 1999; **41**: 352–3.
25 Kick G, Przybilla B. Delayed prick test reaction identifies amoxicillin as elicitor of baboon syndrome. *Contact Dermatitis* 2000; **43**: 366–7.
26 Audicana M, Bernedo N, Gonzalez I *et al.* An unusual case of baboon syndrome due to mercury present in a homeopathic medicine. *Contact Dermatitis* 2001; **45**: 185.
27 Weiss JM, Mockenhaupt M, Schopf E, Simon JC. Reproducible drug exanthema to terbinafine with characteristic distribution of baboon syndrome. *Hautarzt* 2001; **52**: 1104–6.
28 Chowdhury MM, Patel GK, Inaloz HS, Holt PJ. Hydroxyurea-induced skin disease mimicking the baboon syndrome. *Clin Exp Dermatol* 1999; **24**: 336–7.
29 Pirilä V. Endogenic contact eczema. *Allerg Asthma* 1970; **16**: 15–9.
30 Girard JP. Recurrent angioneurotic oedema and contact dermatitis due to penicillin. *Contact Dermatitis* 1978; **4**: 309.
31 Lincke-Plewig H. Bleomycin-Exantheme. *Hautarzt* 1980; **31**: 616–8.
32 Colver GB, Inglis JA, McVittie E *et al.* Dermatitis due to intravesical mitomycin C: a delayed-type hypersensitivity reaction? *Br J Dermatol* 1990; **122**: 217–24.
33 De Groot AC, Conemans JMH. Systemic allergic contact dermatitis from intravesical instillation of the antitumor antibiotic mitomycin C. *Contact Dermatitis* 1991; **24**: 201–9.

Bullous eruptions

Bullous drug eruptions encompass many different clinical reactions and pathomechanisms [1,2]. Isolated blisters, often located preferentially on the extremities, may be caused by a wide variety of chemically distinct drugs. Fixed drug eruptions and drug-induced vasculitis may have a bullous component; these are reviewed elsewhere in this chapter. Erythema multiforme, Stevens–Johnson syndrome and drug-induced TEN are discussed in Chapter 76. The specific drug-induced entities of porphyria and pseudoporphyria, bullous pemphigoid, pemphigus and linear IgA disease are discussed here.

Bullous eruption in drug overdosage

Bullae, often at pressure areas, may be seen in patients comatose after overdosage with barbiturates (Fig. 75.5), methadone, meprobamate, imipramine, nitrazepam or glutethimide [1–5].

References

1 Bork K. *Cutaneous Side Effects of Drugs*. Philadelphia: Saunders, 1988.
2 Breathnach SM, Hintner H. *Adverse Drug Reactions and the Skin*. Oxford: Blackwell Scientific Publications, 1992.
3 Brehmer-Andersson E, Pedersen NB. Sweat gland necrosis and bullous skin changes in acute drug intoxication. *Acta Derm Venereol (Stockh)* 1969; **49**: 157–62.
4 Mandy S, Ackerman AB. Characteristic traumatic skin lesions in drug-induced coma. *JAMA* 1970; **213**: 253–6.
5 Herschtal D, Robinson MJ. Blisters of the skin in coma induced by amitriptyline and chlorazepate dipotassium. Report of a case with underlying sweat gland necrosis. *Arch Dermatol* 1979; **115**: 499.

Drug-induced porphyria

Porphyria is discussed in Chapter 59. Drugs reported to exacerbate the acute hepatic porphyrias are listed in Table 75.12; these either cause excess destruction of haem or inhibit haem synthesis [1–3].



Fig. 75.5 Bullous eruption in barbiturate overdose. (Courtesy of Charing Cross Hospital, London, UK.)

Table 75.12 Drugs that are unsafe to use in patients with acute intermittent porphyria, porphyria cutanea tarda or variegate porphyria.

Aminoglutethimide	Meprobamate
Barbiturates	Novobiocin
Carbamazepine	Oestrogens
Carbromal	Primidone
Chlorpropamide	Progestogens
Danazol	Pyrazolone derivatives
Diclofenac	Rifampicin
Diphenylhydantoin (phenytoin)	Sulphonamides
Ergot preparations	Tolbutamide
Glutethimide	Trimethadione
Griseofulvin	Valproic acid

Pseudoporphyria

Pseudoporphyria, in which porphyria-like blistering of exposed areas on the extremities occurs in the absence of abnormal porphyrin metabolism, may be caused by high-dose furosemide [4], naproxen [5,6] and other NSAIDs [7–9], combined carisoprodol and aspirin [10], nalidixic acid [11], tetracyclines [12] and sulphonylureas. Phototoxic mechanisms have been implicated in some cases. A similar syndrome has been reported in a patient taking very large doses of pyridoxine (vitamin B_6) [13].

References

1 Targovnick SE, Targovnik JH. Cutaneous drug reactions in porphyrias. *Clin Dermatol* 1986; **4**: 111–7.
2 Köstler E, Seebacher C, Riedel H, Kemmer C. Therapeutische und pathogenetische Aspekte der Porphyria cutanea tarda. *Hautarzt* 1986; **37**: 210–6.
3 Ayala F, Santoianni P. Drug-induced cutaneous porphyria. *Clin Dermatol* 1993; **11**: 535–9.
4 Burry JN, Lawrence JR. Phototoxic blisters from high frusemide dosage. *Br J Dermatol* 1976; **94**: 495–9.
5 Judd LE, Henderson DW, Hill DC. Naproxen-induced pseudoporphyria: a clinical and ultrastructural study. *Arch Dermatol* 1986; **122**: 451–4.

6 Lang BA, Finlayson LA. Naproxen-induced pseudoporphyria in patients with juvenile rheumatoid arthritis. *J Pediatr* 1994; **124**: 639–42.
7 Stern RS. Phototoxic reactions to piroxicam and other nonsteroidal anti-inflammatory agents. *N Engl J Med* 1983; **309**: 186–7.
8 Taylor BJ, Duffill MB. Pseudoporphyria from nonsteroidal anti-inflammatory drugs. *NZ Med J* 1987; **100**: 322–3.
9 Meggitt SJ, Farr PM. Pseudoporphyria and propionic acid non-steroidal anti-inflammatory drugs. *Br J Dermatol* 1999; **141**: 591–2.
10 Hazen PG. Pseudoporphyria in a patient receiving carisoprodol/aspirin therapy. *J Am Acad Dermatol* 1994; **31**: 500.
11 Keane JT, Pearson RW, Malkinson FD. Nalidixic acid-induced photosensitivity in mice: a model for pseudoporphyria. *J Invest Dermatol* 1984; **82**: 210–3.
12 Hawk JLM. Skin changes resembling hepatic cutaneous porphyria induced by oxytetracycline photosensitization. *Clin Exp Dermatol* 1980; **5**: 321–5.
13 Baer R, Stilman RA. Cutaneous skin changes probably due to pyridoxine abuse. *J Am Acad Dermatol* 1984; **10**: 527–8.

Drug-induced bullous pemphigoid

Idiopathic bullous pemphigoid is discussed in Chapter 40. In drug-induced bullous pemphigoid, patients tend to be younger; tissue-bound and circulating anti-basement-membrane zone IgG antibodies may be absent, or additional antibodies such as intercellular or antiepidermal cytoplasmic antibodies may be detected. Some cases of drug-induced bullous or cicatricial pemphigoid have been reported with a number of medications [1–5], especially furosemide [6,7], but also bumetanide [8], spironolactone [9,10], penicillamine [11,12], the penicillamine analogue tiobutarit [13], penicillin [14] and its derivatives [15], ciprofloxacin [16], sulfasalazine, salicylazosulfapyridine, phenacetin [17], enalapril [18], fluoxetine [19], novoscabin, topical fluorouracil, and PUVA therapy [20]. In the case of enalapril-induced bullous pemphigoid, the IgG antibody was directed against the 230-kDa bullous pemphigoid antigen [18]. Cicatricial pemphigoid has been described in association with penicillamine [12] and clonidine [21]. An association with vaccination for influenza and with tetanus toxoid and induction of bullous pemphigoid has been noted rarely [22–25].

References

1 Ahmed AR, Newcomer VD. Drug-induced bullous pemphigoid. *Clin Dermatol* 1987; **5**: 8–10.
2 Ruocco V, Sacerdoti G. Pemphigus and bullous pemphigoid due to drugs. *Int J Dermatol* 1991; **30**: 307–12.
3 Fellner MJ. Drug-induced bullous pemphigoid. *Clin Dermatol* 1993; **11**: 515–20.
4 Van Joost T, Van't Veen AJ. Drug-induced cicatricial pemphigoid and acquired epidermolysis bullosa. *Clin Dermatol* 1993; **11**: 521–7.
5 Vassileva S. Drug-induced pemphigoid: bullous and cicatricial. *Clin Dermatol* 1998; **16**: 379–87.
6 Fellner MJ, Katz JM. Occurrence of bullous pemphigoid after furosemide therapy. *Arch Dermatol* 1976; **112**: 75–7.
7 Castel T, Gratacos R, Castro J *et al*. Bullous pemphigoid induced by furosemide. *Clin Exp Dermatol* 1981; **6**: 635–8.
8 Boulinguez S, Bernard P, Bedane C *et al.* Bullous pemphigoid induced by bumetanide. *Br J Dermatol* 1998; **138**: 548–9.
9 Bastuji-Garan S, Joly P, Picard-Dahan C *et al.* Drugs associated with bullous pemphigoid. *Arch Dermatol* 1996; **132**: 272–6.
10 Grange F, Koessler A, Scrivener Y *et al.* Pemphigoide bulleuse induite par la spironolactone. *Ann Dermatol Venereol* 1996; **123**: S110–S111.
11 Rasmussen HB, Jepsen LV, Brandrup F. Penicillamine-induced bullous pemphigoid with pemphigus-like antibodies. *J Cutan Pathol* 1989; **16**: 154–7.
12 Bialy-Golan A, Brenner S. Penicillamine-induced bullous dermatoses. *J Am Acad Dermatol* 1996; **35**: 732–42.
13 Yamaguchi R, Oryu F, Hidano A. A case of bullous pemphigoid induced by tiobutarit (D-penicillamine analogue). *J Dermatol* 1989; **16**: 308–11.
14 Alcalay J, David M, Ingber A *et al.* Bullous pemphigoid mimicking bullous erythema multiforme: an untoward side effect of penicillins. *J Am Acad Dermatol* 1988; **18**: 345–9.
15 Hodak E, Ben-Shetrit A, Ingber A, Sandbank M. Bullous pemphigoid: an adverse effect of ampicillin. *Clin Exp Dermatol* 1990; **15**: 50–2.
16 Kimyai-Asadi A, Usman A, Nousari HC. Ciprofloxacin-induced bullous pemphigoid. *J Am Acad Dermatol* 2000; **42**: 847.
17 Kashihara M, Danno K, Miyachi Y *et al.* Bullous pemphigoid-like lesions induced by phenacetin: report of a case and an immunopathologic study. *Arch Dermatol* 1984; **120**: 1196–9.
18 Pazderka Smith E, Taylor TB, Meyer LJ, Zone JJ. Antigen identification in drug-induced bullous pemphigoid. *J Am Acad Dermatol* 1993; **29**: 879–82.
19 Rault S, Grosieux-Dauger C, Verraes S *et al.* Bullous pemphigoid induced by fluoxetine. *Br J Dermatol* 1998; **139**: 1092–6.
20 Abel EA, Bennett A. Bullous pemphigoid. Occurrence in psoriasis treated with psoralens plus long-wave ultraviolet radiation. *Arch Dermatol* 1979; **115**: 988–9.
21 Van Joost T, Faber WR, Manuel HR. Drug-induced anogenital cicatricial pemphigoid. *Br J Dermatol* 1980; **102**: 715–8.
22 Bodokh I, Lacour JP, Bourdet JF *et al.* Réactivation de pemphigoïde bulleuse apres vaccination antigrippale. *Thérapie* 1994; **49**: 154.
23 Venning VA, Wojnarowska F. Induced bullous pemphigoid. *Br J Dermatol* 1995; **132**: 831–2.
24 Fournier B, Descamps V, Bouscarat F *et al*. Bullous pemphigoid induced by vaccination. *Br J Dermatol* 1996; **135**: 153–4.
25 Downs AMR, Lear JT, Bower CPR, Kennedy CTC. Does influenza vaccination induce bullous pemphigoid? A report of four cases. *Br J Dermatol* 1998; **138**: 363.

Drug-induced pemphigus

The variants of idiopathic pemphigus are discussed in Chapter 40. A number of drugs have been implicated in drug-induced pemphigus (Table 75.13) [1,2], usually of foliaceus type, although the erythematosus, herpetiformis and urticaria-like forms also occur; drug-induced pemphigus vulgaris is rare. Most patients with drug-induced pemphigus have tissue-bound and/or low-titre circulating autoantibodies with the same antigenic specificity at a molecular level as autoantibodies from patients with the corresponding subtype of idiopathic pemphigus [3,4]; however, in the case of penicillamine-induced pemphigus, 10% do not have tissue-bound, and more than 30% do not have circulating, autoantibodies. About 80% of cases are caused by drugs associated with a thiol group in the molecule, especially penicillamine [5–11], but also the structurally related ACE inhibitors captopril [3,12–14] and ramipril [15], gold sodium thiomalate, drugs with disulphide bonds such as pyritinol [16], *S*-thiopyridoxine, tiopronin (mercaptopropionylglycine, which is chemically related to penicillamine and used as an alternative therapy in penicillamine intolerance) [4,17,18], and bucillamine [19], as well as those with a sulphur-containing ring that may undergo metabolic change to the thiol form, such as piroxicam [20]. Penicillin [21–23], and its derivatives ampicillin [22], procaine penicillin and amoxicillin, may also cause pemphigus. Other drugs that cause pemphigus may contain an active amide group [24].

Rifampicin [25], cefalexin [26], cefadroxil, ceftazidime [27], pyrazolone derivatives [28] including dipyrone [29], propranolol, propranolol–meprobamate [30], optalidon, pentachlorophenol, phenobarbital [31], nifedipine [32], phosphamide, hydantoin, combinations of indometacin and aspirin [33], glibenclamide [34], as well as heroin [35], have all been established as rare causes of

Table 75.13 Drugs implicated in the development of pemphigus.

Thiol drugs
Penicillamine
Captopril, ramipril
Gold sodium thiomalate
Pyritinol
Thiamazole (methimazole)
Tiopronin (mercaptopropionylglycine)
Non-thiol drugs
Antibiotics
Penicillin and derivatives
Rifampicin
Cefalexin (cephalexin)
Cefadroxil
Ceftazidine
Pyrazolone derivatives
Aminophenazone
Aminopyrine
Azapropazone
Oxyphenbutazone
Phenylbutazone
Miscellaneous
Glibenclamide
Hydantoin
Levodopa
Lysine acetylsalicylate
Nifedipine
Phenobarbital (phenobarbitone)
Piroxicam
Progesterone
Propranolol
Interferon-β and interleukin-2
Heroin

a pemphigus-like reaction. Fatal pemphigus vulgaris has been recorded after IFN-β and IL-2 therapy for lymphoma [36]. Fludarabine has been implicated in the development of paraneoplastic pemphigus [37,38].

References

1 Brenner S, Wolf R, Ruocco V. Drug-induced pemphigus. I. A survey. *Clin Dermatol* 1993; **11**: 501–5.
2 Ruocco V, De Angelis E, Lombardi ML. Drug-induced pemphigus. II. Pathomechanisms and experimental investigations. *Clin Dermatol* 1993; **11**: 507–13.
3 Korman NJ, Eyre RW, Stanley JR. Drug-induced pemphigus: autoantibodies directed against the pemphigus antigen complexes are present in penicillamine and captopril-induced pemphigus. *J Invest Dermatol* 1991; **96**: 273–6.
4 Verdier-Sevrain S, Joly P, Thomine E *et al.* Thiopronine-induced herpetiform pemphigus: report of a case studied by immunoelectron microscopy and immunoblot analysis. *Br J Dermatol* 1994; **130**: 238–40.
5 Goldberg I, Kashman Y, Brenner S. The induction of pemphigus by phenol drugs. *Int J Dermatol* 1999; **38**: 888–92.
6 Kishimoto K, Iwatsuki K, Akiba H *et al.* Subcorneal pustular dermatosis-type IgA pemphigus induced by thiol drugs. *Eur J Dermatol* 2001; **11**: 41–4.
7 Zillikens D, Zentner A, Burger M *et al.* Pemphigus foliaceus durch Penicillamin. *Hautarzt* 1993; **44**: 167–71.
8 Jones E, Sobkowski WW, Murray SJ, Walsh NMG. Concurrent pemphigus and myasthenia gravis as manifestations of penicillamine toxicity. *J Am Acad Dermatol* 1993; **28**: 655–6.
9 Bialy-Golan A, Brenner S. Penicillamine-induced bullous dermatoses. *J Am Acad Dermatol* 1996; **35**: 732–42.
10 Peñas PF, Buezo GF, Carvajal I *et al.* D-Penicillamine-induced pemphigus foliaceus with autoantibodies to desmoglein-1 in a patient with mixed connective tissue disease. *J Am Acad Dermatol* 1997; **37**: 121–3.
11 Toth GG, Jonkman MF. Successful treatment of recalcitrant penicillamine-induced pemphigus foliaceus by low-dose intravenous immunoglobulins. *Br J Dermatol* 1999; **141**: 583–5.
12 Clement M. Captopril-induced eruptions. *Arch Dermatol* 1981; **117**: 525–6.
13 Katz RA, Hood AF, Anhalt GJ. Pemphigus-like eruption from captopril. *Arch Dermatol* 1987; **123**: 20–1.
14 Kaplan RP, Potter TS, Fox JN. Drug-induced pemphigus related to angiotensin-converting enzyme inhibitors. *J Am Acad Dermatol* 1992; **26**: 364–6.
15 Vignes S, Paul C, Flageul B, Dubertret L. Ramipril-induced superficial pemphigus. *Br J Dermatol* 1996; **135**: 657–8.
16 Civatte J, Duterque M, Blanchet P *et al.* Deux cas de pemphigus superficiel induit par le pyritinol. *Ann Dermatol Vénéréol* 1978; **105**: 573–7.
17 Alinovi A, Benoldi D, Manganelli P. Pemphigus erythematosus induced by thiopronin. *Acta Derm Venereol (Stockh)* 1982; **62**: 452–4.
18 Lucky PA, Skovby F, Thier SO. Pemphigus foliacaeus and proteinuria induced by α-mercaptopropionylglycine. *J Am Acad Dermatol* 1983; **8**: 667–72.
19 Ogata K, Nakajima H, Ikeda M *et al.* Drug-induced pemphigus foliaceus with features of pemphigus vulgaris. *Br J Dermatol* 2001; **144**: 421–2.
20 Martin RL, McSweeny GW, Schneider J. Fatal pemphigus vulgaris in a patient taking piroxicam. *N Engl J Med* 1983; **309**: 795–6.
21 Duhra PL, Foulds IS. Penicillin-induced pemphigus vulgaris. *Br J Dermatol* 1988; **118**: 307.
22 Fellner MJ, Mark AS. Penicillin- and ampicillin-induced pemphigus vulgaris. *Int J Dermatol* 1980; **19**: 392–3.
23 Heymann AD, Chodick G, Kramer E *et al*. Pemphigus variant associated with penicillin use. *Arch Dermatol* 2007; **143**: 704–7.
24 Wolf R, Brenner S. An active amide group in the molecule of drugs that induce pemphigus: a casual or causal relationship? *Dermatology* 1994; **189**: 1–4.
25 Lee CW, Lim JH, Kang HJ. Pemphigus foliaceus induced by rifampicin. *Br J Dermatol* 1984; **111**: 619–22.
26 Wolf R, Dechner E, Ophir J, Brenner S. Cephalexin. A nonthiol drug that may induce pemphigus vulgaris. *Int J Dermatol* 1991; **30**: 213–5.
27 Pellicano R, Iannantuono M, Lomuto M. Pemphigus erythematosus induced by ceftazidime. *Int J Dermatol* 1993; **32**: 675–6.
28 Chorzelski TP, Jablonska S, Blaszczyk M. Autoantibodies in pemphigus. *Acta Derm Venereol (Stockh)* 1966; **46**: 26.
29 Brenner S, Bialy-Golan A, Crost N. Dipyrone in the induction of pemphigus. *J Am Acad Dermatol* 1997; **36**: 488–90.
30 Goddard W, Lambert D, Gavanou J, Chapius JL. Pemphigus acquit après traitement par l'association propranolol–meprobamate. *Ann Dermatol Vénéréol* 1980; **107**: 1213–6.
31 Dourmishev AL, Rahman MA. Phenobarbital-induced pemphigus vulgaris. *Dermatologica* 1986; **173**: 256–8.
32 Kim SC, Won JH, Ahn SK. Pemphigus foliaceus induced by nifedipine. *Acta Derm Venereol (Stockh)* 1993; **73**: 210–1.
33 Demento FJ, Grover RW. Acantholytic herpetiform dermatitis. *Arch Dermatol* 1973; **107**: 883–7.
34 Paterson AJ, Lamey PJ, Lewis MA *et al.* Pemphigus vulgaris precipitated by glibenclamide therapy. *J Oral Pathol Med* 1993; **22**: 92–5.
35 Fellner MJ, Winiger J. Pemphigus erythematosus and heroin addiction. *Int J Dermatol* 1978; **17**: 308–11.
36 Ramseur WL, Richards F, Duggan DB. A case of fatal pemphigus vulgaris in association with beta interferon and interleukin-2 therapy. *Cancer* 1989; **63**: 2005–7.
37 Anhalt GJ. Paraneoplastic pemphigus: the role of tumours and drugs. *Br J Dermatol* 2001; **144**: 1102–4.
38 Gooptu C, Littlewood TJ, Frith P *et al.* Paraneoplastic pemphigus: an association with fludarabine? *Br J Dermatol* 2001; **144**: 1255–61.

Linear IgA disease

Idiopathic linear IgA disease is discussed in Chapter 40. The drugs implicated as a cause of this condition have been reviewed [1–3],

and include vancomycin especially [1–9], but also amiodarone, ampicillin, atorvastatin [10], captopril [11], carbamazepine [12], cefamandole (cephamandole), diclofenac, furosemide [13], glibenclamide, IFN-γ, iodine, lithium, penicillin [14,15], phenytoin [16] and somatostatin, as well as tea-tree oil [17]. Most patients lack circulating antibodies to the basement membrane; resolution of the rash follows discontinuation of medication.

References

1 Collier PM, Wojnarowska F. Drug-induced linear immunoglobulin A disease. *Clin Dermatol* 1993; **11**: 529–33.
2 Kuechle ML, Stegemeir E, Maynard B *et al.* Drug-induced linear IgA bullous dermatosis: report of six cases and review of the literature. *J Am Acad Dermatol* 1994; **30**: 187–92.
3 Geissmann C, Beylot-Barry M, Doutre MS, Beylot C. Drug-induced linear IgA bullous dermatosis. *J Am Acad Dermatol* 1995; **32**: 296.
4 Carpenter S, Berg D, Sidhu-Malik N *et al.* Vancomycin-associated linear IgA dermatosis. A report of three cases. *J Am Acad Dermatol* 1992; **26**: 45–8.
5 Piketty C, Meeus F, Nochy D *et al.* Linear IgA dermatosis related to vancomycin. *Br J Dermatol* 1994; **130**: 130–1.
6 Whitworth JM, Thomas I, Peltz S *et al.* Vancomycin-induced linear IgA bullous dermatosis (LABD). *J Am Acad Dermatol* 1996; **34**: 890–1.
7 Palmer RA, Ogg G, Allen J *et al.* Vancomycin-induced linear IgA disease with autoantibodies to BP180 and LAD285. *Br J Dermatol* 2001; **145**: 816–20.
8 Ahkami R, Thomas I. Linear IgA bullous dermatosis associated with vancomycin and disseminated varicella-zoster infection. *Cutis* 2001; **67**: 423–6.
9 Dellavalle RP, Burch HM, Tyal S *et al.* Vancomycin-associated linear IgA bullous dermatosis mimicking toxic epidermal necrolysis. *J Am Acad Dermatol* 2003; **48**: S56–S57.
10 Konig C, Eickert A, Scharfetter-Kochanek K *et al.* Linear IgA bullous dermatosis induced by atorvastatin. *J Am Acad Dermatol* 2001; **44**: 689–92.
11 Friedman IS, Rudikoff D, Phelps RG, Sapadin AN. Captopril-triggered linear IgA bullous dermatosis. *Int J Dermatol* 1998; **37**: 608–12.
12 Cohen LM, Ugent RB. Linear IgA bullous dermatosis occurring after carbamazepine. *J Am Acad Dermatol* 2002; **46**: S32–S33.
13 Cerottini J-P, Ricci C, Guggisberg D, Panizzon RG. Drug-induced linear IgA bullous dermatosis probably induced by furosemide. *J Am Acad Dermatol* 1999; **41**: 103–5.
14 Combemale P, Gavaud C, Cozzani E *et al.* Dermatose a IgA lineaire (DIAL) induite par penicilline G. *Ann Dermatol Vénéréol* 1993; **120**: 847–8.
15 Wakelin S, Allen J, Zhou S, Wojnorowska F. Drug-induced linear IgA disease with antibodies to collagen VII. *Br J Dermatol* 1998; **138**: 310–4.
16 Acostamadiedo JM, Perniciaro C, Rogers RS III. Phenytoin-induced linear IgA bullous disease. *J Am Acad Dermatol* 1998; **38**: 352–6.
17 Perett CM, Evans AV, Russell-Jones R. Tea tree oil dermatitis associated with linear IgA disease. *Clin Exp Dermatol* 2003; **28**: 167–70.

Drug-induced epidermolysis bullosa acquisita

This entity has been linked to antibiotics, including vancomycin [1].

Reference

1 Delbaldo C, Chen M, Friedli A *et al.* Drug-induced epidermolysis bullosa acquisita with antibodies to type VII collagen. *J Am Acad Dermatol* 2002; **46**: S161–S164.

Vasculitis

Drug-induced cutaneous necrotizing vasculitis [1–3] may also involve internal organs, including the heart, liver and kidneys, with fatal results. The patterns of polyarteritis nodosa, Henoch–Schönlein vasculitis and hypocomplementaemic vasculitis are not seen commonly with drugs. Drugs that have been implicated are listed in Table 75.14. These include ampicillin, sulphonamides, furosemide [4], thiazide diuretics, phenylbutazone and other NSAIDs, quinidine, amiodarone [5], hydralazine [6], enalapril [7], propylthiouracil [8,9], mefloquine [10], cimetidine [11], coumadin [12,13], anticonvulsants including phenytoin and in isolated cases carbamazepine and trimethadione [14,15], zidovudine (azidothymidine) [16], indinavir [17], fluoxetine [18], didanosine [19], piperazine [20], centrally acting appetite suppressants [21], hyposensitization therapy [22,23], bacille Calmette–Guérin (BCG) vaccination (which may cause a papulonecrotic type of vasculitis) [24], radiographic contrast media [25], food and drug additives including dye excipients such as tartrazine (FD&C yellow no. 5), ponceau, sodium benzoate, 4-hydroxybenzoic acid [26,27], vitamin B_6 [28] and the use of a nicotine patch [29]. Leukocytoclastic vasculitis and necrotizing angiitis have also been documented in drug abusers [30–32].

Table 75.14 Drugs recorded as inducing vasculitis.

Additives	Levamisole
Allopurinol	Maprotiline
Aminosalicylic acid	Mefloquine
Amfetamine (amphetamine)	Methotrexate
Amiodarone	Penicillin
Ampicillin	Phenacetin
Arsenic	Phenothiazines
Aspirin	Phenylbutazone
Captopril	Phenytoin
Carbamazepine	Piperazine
Cimetidine	Procainamide
Coumadin	Propylthiouracil
Didanosine	Quinidine
Enalapril	Radiocontrast media
Erythromycin	Streptomycin
Etacrynic acid (ethacrynic acid)	Sulphonamides
Fluoroquinolone antibiotics	Tetracycline
Fluoxetine	Thiazides
Furosemide (frusemide)	Trazodone
Griseofulvin	Trimethadione
Guanethidine	Vaccines
Hydralazine	Zidovudine
Iodides	

References

1 Mullick FG, McAllister HA Jr, Wagner BM, Fenoglio JJ Jr. Drug-related vasculitis. Clinicopathologic correlations in 30 patients. *Hum Pathol* 1979; **10**: 313–25.
2 Mackel SE, Jordon RE. Leukocytoclastic vasculitis. A cutaneous expression of immune complex disease. *Arch Dermatol* 1983; **118**: 296–301.
3 Sanchez NP, Van Hale HM, Su WPD. Clinical and histopathologic spectrum of necrotizing vasculitis. Report of findings in 101 cases. *Arch Dermatol* 1985; **121**: 220–4.
4 Hendricks WM, Ader RS. Furosemide-induced cutaneous necrotizing vasculitis. *Arch Dermatol* 1977; **113**: 375–6.
5 Staubli M, Zimmerman A, Bircher J. Amiodarone-induced vasculitis and polyserositis. *Postgrad Med J* 1985; **61**: 245–7.
6 Peacock A, Weatherall D. Hydralazine-induced necrotizing vasculitis. *BMJ* 1981; **282**: 1121–2.
7 Carrington PR, Sanusi ID, Zahradka S, Winder PR. Enalapril-associated erythema and vasculitis. *Cutis* 1993; **51**: 121–3.
8 Vasily DB, Tyler WB. Propylthiouracil-induced cutaneous vasculitis. Case presentation and review of literature. *JAMA* 1980; **243**: 458–61.

9 Gammeltoft M, Kristensen JK. Propylthio-uracil-induced cutaneous vasculitis. *Acta Derm Venereol (Stockh)* 1982; **62**: 171–3.
10 Scerri L, Pace JL. Mefloquine-associated cutaneous vasculitis. *Int J Dermatol* 1993; **32**: 517–8.
11 Mitchell GG, Magnusson AR, Weiler JM. Cimetidine-induced cutaneous vasculitis. *Am J Med* 1983; **75**: 875–6.
12 Tanay A, Yust I, Brenner S *et al.* Dermal vasculitis due to coumadin hypersensitivity. *Dermatologica* 1982; **165**: 178–85.
13 Tamir A, Wolf R, Brenner S. Leukocytoclastic vasculitis: another coumarin-induced hemorrhagic reaction. *Acta Derm Venereol (Stockh)* 1994; **74**: 138–9.
14 Drory VE, Korczyn AD. Hypersensitivity vasculitis and systemic lupus erythematosus induced by anticonvulsants. *Clin Neuropharmacol* 1993; **16**: 19–29.
15 Kaneko K, Igarashi J, Suzuki Y *et al.* Carbamazepine-induced thrombocytopenia and leucopenia complicated by Henoch–Schonlein purpura symptoms. *Eur J Pediatr* 1993; **152**: 769–70.
16 Torres RA, Lin RY, Lee M, Barr MR. Zidovudine-induced leukocytoclastic vasculitis. *Arch Intern Med* 1992; **152**: 850–1.
17 Rachline A, Lariven S, Descamps V *et al.* Leucocytoclastic vasculitis and indinavir. *Br J Dermatol* 2000; **143**: 1112–3.
18 Roger D, Rolle F, Mausset J *et al.* Urticarial vasculitis induced by fluoxetine. *Dermatology* 1995; **191**: 164.
19 Herranz P, Fernandez-Diaz ML, de Lucas R *et al.* Cutaneous vasculitis associated with didanosine. *Lancet* 1994; **344**: 680.
20 Balzan M, Cacciottolo JM. Hypersensitivity vasculitis associated with piperazine therapy. *Br J Dermatol* 1994; **131**: 133–4.
21 Papadavid E, Yu RC, Tay A, Chu AC. Urticarial vasculitis induced by centrally acting appetite suppressants. *Br J Dermatol* 1996; **134**: 990–1.
22 Phanuphak P, Kohler PF. Onset of polyarteritis nodosa during allergic hyposensitisation treatment. *Am J Med* 1980; **68**: 479–85.
23 Merk H, Kober ML. Vasculitis nach spezifischer Hyposensibilisierung. *Z Hautkr* 1982; **57**: 1682–5.
24 Lübbe D. Vasculitis allergica vom papulonekrotischen Typ nach BCG-Impfung. *Dermatol Monatsschr* 1982; **168**: 186–92.
25 Kerdel FA, Fraker DL, Haynes HA. Necrotizing vasculitis from radiographic contrast media. *J Am Acad Dermatol* 1984; **10**: 25–9.
26 Michäelsson G, Petterson L, Juhlin L. Purpura caused by food and drug additives. *Arch Dermatol* 1974; **109**: 49–52.
27 Lowry MD, Hudson CF, Callen FP. Leukocytoclastic vasculitis caused by drug additives. *J Am Acad Dermatol* 1994; **30**: 854–5.
28 Ruzicka T, Ring J, Braun-Falco O. Vasculitis allergica durch vitamin B_6. *Hautarzt* 1984; **35**: 197–9.
29 Van der Klauw MM, Van Hillo B, Van den Berg WH *et al.* Vasculitis attributed to the nicotine patch (Nicotinell). *Br J Dermatol* 1996; **34**: 361–4.
30 Citron BP, Halpen M, McCarron M *et al.* Necrotizing angiitis associated with drug abuse. *N Engl J Med* 1970; **283**: 1003–11.
31 Lignelli GJ, Bucheit WA. Angiitis in drug abusers. *N Engl J Med* 1971; **284**: 112–3.
32 Gendelman H, Linzer M, Barland P *et al.* Leukocytoclastic vasculitis in an intravenous heroin abuser. *NY State J Med* 1983; **83**: 984–6.

Lupus erythematosus-like syndrome

A reaction resembling idiopathic LE has been reported in association with a large variety of drugs [1–46], although only about 5% of cases of SLE are drug induced. Cutaneous manifestations are in general rare: 18% and 26%, respectively, of patients with procainamide- and hydralazine-induced LE had skin changes in one series [6]. Photosensitivity may be prominent; some patients develop discoid LE lesions; urticarial or erythema multiforme-like lesions may also be seen. Constitutional symptoms may be present, and there may be evidence of Raynaud's disease, arthritis or polyserositis. Renal involvement is rare, as is central nervous system involvement. The condition usually, but not always, resolves after discontinuation of the drug. Abnormal laboratory findings include the presence of LE cells, and of antinuclear antibodies directed against ribonucleoprotein, single-stranded DNA and especially histones [11,12]. Antibodies against native double-stranded DNA are rarely found in drug-induced LE, and complement levels are normal; deposition of immunoreactants in uninvolved skin is rare. Patients with drug-induced LE may have the lupus anticoagulant [13,14].

Table 75.15 Drugs inducing lupus erythematosus-like syndromes.

Allopurinol	Lithium
Aminoglutethimide	Methyldopa
p-Aminosalicylic acid	Methysergide
Angiotensin-converting enzyme inhibitors (captopril)	Nitrofurantoin
	Oral contraceptives
Anticonvulsants	Penicillamine
Carbamazepine	Penicillin
Hydantoins	Phenothiazines (chlorpromazine)
Primidone	Phenylbutazone
Trimethadione	Procainamide
Valproate	Quinidine
β-Blockers	Streptomycin
Calcium channel blockers	Sulfasalazine co-trimoxazole (sulphasalazine)
Clonidine	Sulphonamides
Ethosuximide	Terbinafine
Gold salts	Tetracycline
Griseofulvin	Thiazide diuretics
Hydralazine	Thionamide
Ibuprofen	Thiouracils
Isoniazid	

A partial list of drugs reported to induce an SLE-like syndrome or exacerbate idiopathic LE is given in Table 75.15. Drugs most commonly implicated in inducing LE include especially hydralazine [15,16] and procainamide [17,18], and less commonly β-blockers, methyldopa [19,20], isoniazid, most anticonvulsants in clinical use including phenytoin, carbamazepine, ethosuximide, trimethadione, primidone and valproate (but not phenobarbital or benzodiazepines) [21], and quinidine [22,23]. LE following penicillamine therapy [24,25], 2-mercaptopropionylglycine [26], rifampicin [27], etanercept [28] and the tetracycline derivative COL-3 used in antiangiogenesis [29] has also been documented. Minocycline may induce an autoimmune syndrome of which LE may form part [30–32].

Subacute LE with positive Ro/SSA antibodies has been reported in association with a number of drugs [9], including phenytoin [33], thiazide diuretics such as hydrochlorothiazide [34–37], ACE inhibitors [38,39], calcium channel blockers [40], terbinafine [41–43], griseofulvin [44], piroxicam, oxprenolol, interferons and statins. The oral contraceptive induced LE lesions on the palms and feet of a patient [45]. In addition, a number of drugs may exacerbate pre-existing SLE, such as griseofulvin, β-blockers, sulphonamides [46], testosterone and oestrogens.

References

1 Reidenberg MM. The chemical induction of systemic lupus erythematosus and lupus-like illnesses. *Arthritis Rheum* 1981; **24**: 1004–9.
2 Harmon CE, Portnova JP. Drug-induced lupus: clinical and serological studies. *Clin Rheum Dis* 1982; **8**: 121–35.
3 Stratton MA. Drug-induced systemic lupus erythematosus. *Clin Pharm* 1985; **4**: 657–63.

4 Totoritis MC, Rubin RL. Drug-induced lupus. Genetic, clinical, and laboratory features. *Postgrad Med* 1985; **78**: 149–52.
5 Moureaux P. Les formes cutanées du lupus. *Allerg Immunol* 1995; **27**: 196–9.
6 Dubois EL. Serologic abnormalities in spontaneous and drug-induced systemic lupus erythematosus. *J Rheumatol* 1975; **2**: 204–14.
7 Callen JP. Drug-induced cutaneous lupus erythematosus, a distinct syndrome that is frequently unrecognised. *J Am Acad Dermatol* 2001; **45**: 315–6.
8 Callen JP. How frequently are drugs associated with the development or exacerbation of subacute cutaneous lupus? *Arch Dermatol* 2003; **139**: 89–90.
9 Srivastava M, Rencic A, Diglio G *et al.* Drug-induced, Ro/SSA-positive cutaneous lupus erythematosus. *Arch Dermatol* 2003; **139**: 45–9.
10 Rubin RL. Drug-induced lupus. *Toxicology* 2005; **209**: 135–47.
11 Hobbs RN, Clayton AL, Bernstein RM. Antibodies to the five histones and poly(adenosine diphosphateribose) in drug-induced lupus: implications for pathogenesis. *Ann Rheum Dis* 1987; **46**: 408–16.
12 Totoritis MC, Tan EM, McNally EM *et al.* Association of antibody to histone complex H2A-H2B with symptomatic procainamide-induced lupus. *N Engl J Med* 1988; **318**: 1431–6.
13 Bell WR, Boss GR, Wolfson JS. Circulating anticoagulant in the procainamide-induced lupus syndrome. *Arch Intern Med* 1977; **137**: 1471–3.
14 Canoso RT, Sise HS. Chlorpromazine-induced lupus anticoagulant and associated immunologic abnormalities. *Am J Hematol* 1982; **13**: 121–9.
15 Mansilla Tinoco R, Harland SJ, Ryan PJ *et al.* Hydralazine, antinuclear antibodies, and the lupus syndrome. *BMJ* 1982; **284**: 936–9.
16 Russell GI, Bing RF, Jones JA *et al.* Hydralazine sensitivity: clinical features, autoantibody changes and HLA-DR phenotype. *QJM* 1987; **65**: 845–52.
17 Dubois EL. Procainamide induction of a systemic lupus erythematosus-like syndrome. Presentation of six cases, review of the literature, and analysis and follow up of reported cases. *Medicine (Baltimore)* 1969; **48**: 217–28.
18 Blomgren SE, Condemi JJ, Vaughan JH. Procainamide-induced lupus erythematosus. Clinical and laboratory observations. *Am J Med* 1972; **52**: 338–48.
19 Harrington TM, Davis DE. Systemic lupus-like syndrome induced by methyldopa therapy. *Chest* 1981; **79**: 696–7.
20 Dupont A, Six R. Lupus-like syndrome induced by methyldopa. *BMJ* 1982; **285**: 693–4.
21 Drory VE, Korczyn AD. Hypersensitivity vasculitis and systemic lupus erythematosus induced by anticonvulsants. *Clin Neuropharmacol* 1993; **16**: 19–29.
22 McCormack GD, Barth WF. Quinidine induced lupus syndrome. *Semin Arthritis Rheum* 1985; **15**: 73–9.
23 Cohen MG, Kevat S, Prowse MV *et al.* Two distinct quinidine-induced rheumatic syndromes. *Ann Intern Med* 1988; **108**: 369–71.
24 Chalmers A, Thompson D, Stein HE *et al.* Systemic lupus erythematosus during penicillamine therapy for rheumatoid arthritis. *Ann Intern Med* 1982; **97**: 659–63.
25 Condon C, Phelan M, Lyons JF. Penicillamine-induced type II bullous systemic lupus erythematosus. *Br J Dermatol* 1997; **136**: 474–5.
26 Katayama I, Nishioka K. Lupus like syndrome induced by 2-mercaptopropionylglycine. *J Dermatol* 1986; **13**: 151–3.
27 Patel GK, Anstey AV. Rifampicin-induced lupus erythematosus. *Clin Exp Dermatol* 2001; **26**: 260–2.
28 Shakoor N, Michalska M, Harris CA, Block JA. Drug-induced systemic lupus erythematosus associated with etanercept therapy. *Lancet* 2002; **359**: 45–9.
29 Ghate JV, Turner ML, Rudek MA *et al.* Drug-induced lupus associated with COL-3. Report of 3 cases. *Arch Dermatol* 2001; **137**: 471–4.
30 Crosson J, Stillman MT. Minocycline-related lupus erythematosus with associated liver disease. *J Am Acad Dermatol* 1997; **36**: 867–8.
31 Elkayam O, Yaron M, Caspi D. Minocycline-induced autoimmune syndromes: an overview. *Semin Arthritis Rheum* 1999; **28**: 392–7.
32 Dunphy J, Oliver M, Rands AL *et al.* Antineutrophil cytoplasmic antibodies and HLA class II alleles in minocycline-induced lupus-like syndrome. *Br J Dermatol* 2000; **142**: 461–7.
33 Ross S, Dywer C, Ormerod AD *et al.* Subacute cutaneous lupus erythematosus associated with phenytoin. *Clin Exp Dermatol* 2002; **27**: 474–6.
34 Darken M, McBurney EI. Subacute cutaneous lupus erythematosus-like drug eruption due to combination diuretic hydrochlorothiazide and triamterene. *J Am Acad Dermatol* 1988; **18**: 38–42.
35 Wollenberg A, Meurer M. Thiazid-Diuretika-induzierter subakut-kutaner Lupus erythematodes. *Hautarzt* 1991; **42**: 709–12.
36 Goodrich AL, Kohn SR. Hydrochlorothiazide-induced lupus erythematosus: a new variant? *J Am Acad Dermatol* 1993; **28**: 1001–2.
37 Brown CW Jr, Deng JS. Thiazide diuretics induce cutaneous lupus-like adverse reaction. *J Toxicol Clin Toxicol* 1995; **33**: 729–33.
38 Callen JP, Fernandez-Diaz MC, Herranz P *et al.* Subacute cutaneous lupus erythematosus associated with cilazapril. *J Am Acad Dermatol* 1997; **37**: 781.
39 Patri P, Nigro A, Rebora A. Lupus erythematosus-like eruption from captopril. *Acta Derm Venereol (Stockh)* 1985; **65**: 447–8.
40 Crowson AN, Magro CM. Subacute cutaneous lupus erythematosus arising in the setting of calcium channel blocker therapy. *Hum Pathol* 1997; **28**: 67–73.
41 Brooke R, Coulson IH, Al-Dawoud A. Terbinafine-induced subacute cutaneous lupus erythematosus. *Br J Dermatol* 1998; **139**: 1132–3.
42 Bonsmann G, Schiller M, Luger TA. Terbinafine-induced subacute cutaneous lupus erythematosus. *J Am Acad Dermatol* 2001; **44**: 925–31.
43 Callen JP, Hughes AP, Kulp-Shorten CL. Terbinafine-exacerbated/induced subacute cutaneous lupus erythematosus: a report of 5 patients. *Arch Dermatol* 2001; **137**: 1196–8.
44 Miyagawa S, Okuchi T, Shiomo Y *et al.* Subacute cutaneous lupus erythematosus lesions precipitated by griseofulvin. *J Am Acad Dermatol* 1989; **21**: 343–6.
45 Furukawa F, Tachibana T, Imamura S, Tamura T. Oral contraceptive-induced lupus erythematosus in a Japanese woman. *J Dermatol* 1991; **18**: 56–8.
46 Petri M, Allbritton J. Antibiotic allergy in systemic lupus erythematosus: a case–control study. *J Rheumatol* 1992; **19**: 265–9.

Dermatomyositis reactions

Dermatomyositis has been reported to be precipitated by a variety of drugs, including penicillamine [1–3], NSAIDs (niflumic acid and diclofenac) [4], carbamazepine [5] and vaccination, as with BCG [6]. Acral skin lesions simulating chronic dermatomyositis have been reported during long-term hydroxyurea therapy [7]. Allergy to benzalkonium chloride has caused a dermatomyositis-like reaction [8].

References

1 Simpson NB, Golding JR. Dermatomyositis induced by penicillamine. *Acta Derm Venereol (Stockh)* 1979; **59**: 543–4.
2 Wojnorowska F. Dermatomyositis induced by penicillamine. *J R Soc Med* 1980; **73**: 884–6.
3 Carroll GC, Will RK, Peter JB *et al.* Penicillamine induced polymyositis and dermatomyositis. *J Rheumatol* 1987; **14**: 995–1001.
4 Grob JJ, Collet AM, Bonerandi JJ. Dermatomyositis-like syndrome induced by nonsteroidal anti-inflammatory agents. *Dermatologica* 1989; **178**: 58–9.
5 Simpson JR. 'Collagen disease' due to carbamazepine (Tegretol). *BMJ* 1966; **ii**: 1434.
6 Kass E, Staume S, Mellbye OJ *et al.* Dermatomyositis associated with BCG vaccination. *Scand J Rheumatol* 1979; **8**: 187–91.
7 Richard M, Truchetet F, Friedel J *et al.* Skin lesions simulating chronic dermatomyositis during long-term hydroxyurea therapy. *J Am Acad Dermatol* 1989; **21**: 797–9.
8 Cox NH. Allergy to benzalkonium chloride simulating dermatomyositis. *Contact Dermatitis* 1994; **31**: 50.

Scleroderma-like reactions

Penicillamine [1,2], bleomycin [3,4], bromocriptine [5], vitamin K (phytomenadione) [6,7], sodium valproate [8] and 5-hydroxytryptophan combined with carbidopa [9,10] (see also the eosinophilia–myalgia syndrome below) have all been implicated in either localized or generalized morphoea-like, or systemic sclerosis-like, reactions. Eosinophilic fasciitis has been associated with tryptophan ingestion in some cases [11], as well as with phenytoin [12].

References

1 Bernstein RM, Hall MA, Gostelow BE. Morphea-like reaction to D-penicillamine therapy. *Ann Rheum Dis* 1981; **40**: 42–4.

2 Miyagawa S, Yoshioka A, Hatoko M *et al.* Systemic sclerosis-like lesions during long-term penicillamine therapy for Wilson's disease. *Br J Dermatol* 1987; **116**: 95–100.
3 Finch WR, Rodnan GP, Buckingham RB *et al.* Bleomycin-induced scleroderma. *J Rheumatol* 1980; **7**: 651–9.
4 Snauwaert J, Degreef H. Bleomycin-induced Raynaud's phenomenon and acral sclerosis. *Dermatologica* 1984; **169**: 172–4.
5 Leshin B, Piette WW, Caplin RM. Morphea after bromocriptine therapy. *Int J Dermatol* 1989; **28**: 177–9.
6 Brunskill NJ, Berth-Jones J, Graham-Brown RAC. Pseudosclerodermatous reaction to phytomenadione injection (Texier's syndrome). *Clin Exp Dermatol* 1988; **13**: 276–8.
7 Pujol RM, Puig L, Moreno A *et al.* Pseudoscleroderma secondary to phytonadione (vitamin K1) injections. *Cutis* 1989; **43**: 365–8.
8 Goihman-Yahr M, Leal G, Essenfeld-Yahr E. Generalized morphea: a side effect of valproate sodium? *Arch Dermatol* 1980; **116**: 621.
9 Chamson A, Périer C, Frey J. Syndrome sclérodermiforme et poïkilodermique observé au cours d'un traitement par carbidopa et 5-hydroxytryptophanne. Culture de fibroblastes avec analyse biochimique du métabolisme du collagene. *Ann Dermatol Vénéréol* 1986; **113**: 71.
10 Joly P, Lampert A, Thomine E, Lauret P. Development of pseudo-bullous morphea and scleroderma-like illness during therapy with L-5-hydroxytryptophan and carbidopa. *J Am Acad Dermatol* 1991; **25**: 332–3.
11 Gordon ML, Lebwohl MG, Phelps RG *et al.* Eosinophilic fasciitis associated with tryptophan ingestion. A manifestation of eosinophilia–myalgia syndrome. *Arch Dermatol* 1991; **127**: 217–20.
12 Buchanan RR, Gordon DA, Muckle TJ *et al.* The eosinophilic fasciitis syndrome after phenytoin (Dilantin) therapy. *J Rheumatol* 1980; **7**: 733–6.

Chemical and industrial causes of scleroderma-like reactions [1]

Scleroderma-like changes formed part of the clinical spectrum of the Spanish toxic oil syndrome, which resulted from contamination of rapeseed cooking oil with acetanilide [2]. Scleroderma-like changes have been induced by industrial exposure to vinyl chloride [3], epoxy resins [1,4], organic solvents [5] including perchlorethylene [6], trichlorethylene and trichlorethane [7], and in coalminers due to silica exposure [8,9].

References

1 Ishikawa O, Warita S, Tamura A, Miyachi Y. Occupational scleroderma. A 17-year follow-up study. *Br J Dermatol* 1995; **133**: 786–9.
2 Rush PJ, Bell MJ, Fam AG. Toxic oil syndrome (Spanish oil disease) and chemically induced scleroderma-like conditions. *J Rheumatol* 1984; **11**: 262–4.
3 Harris DK, Adams WGF. Acroosteolysis occurring in men engaged in the polymerisation of vinyl chloride. *BMJ* 1967; **3**: 712–24.
4 Yamakage A, Ishikawa H, Saito Y, Hattori A. Occupational scleroderma-like disorders occurring in men engaged in the polymerization of epoxy resins. *Dermatologica* 1980; **161**: 33–44.
5 Yamakage A, Ishikawa H. Generalized morphea-like scleroderma occurring in people exposed to organic solvents. *Dermatologica* 1982; **165**: 186–93.
6 Sparrow GP. A connective tissue disease similar to vinyl chloride disease in a patient exposed to perchlorethylene. *Clin Exp Dermatol* 1977; **2**: 17–22.
7 Flindt-Hansen H, Isager H. Scleroderma after occupational exposure to trichlorethylene and trichlorethane. *Acta Derm Venereol (Stockh)* 1987; **67**: 263–4.
8 Rodnan GP, Benedek TG, Medsger TA Jr, Cammarata RJ. The association of progressive systemic sclerosis (scleroderma) with coalminers' pneumoconiosis and other forms of silicosis. *Ann Intern Med* 1967; **66**: 323–4.
9 Rustin MHA, Bull HA, Ziegler V *et al.* Silica-associated systemic sclerosis is clinically, serologically and immunologically indistinguishable from idiopathic systemic sclerosis. *Br J Dermatol* 1990; **123**: 725–34.

Eosinophilia–myalgia syndrome

Ingestion of tryptophan, taken as a mild antidepressant, a 'natural hypnotic', or by athletes to increase pain tolerance, was associated with eosinophilia–myalgia syndrome [1–4], characterized by eosinophilia, myalgia, arthralgia, limb swelling, fever, weakness and fatigue, respiratory complaints, pulmonary hypertension, arrhythmias, ascending polyneuropathy and a variety of cutaneous manifestations. The latter included diffuse morbilliform erythema, urticaria, angio-oedema, dermatographism, livedo reticularis, alopecia and papular mucinosis. Some patients developed chronic muscle weakness, with diffuse scleroderma-like or fasciitis-like skin changes. The eosinophilia–myalgia syndrome is now thought to have been caused by a contaminant of L-tryptophan following a change in the manufacturing process between October 1988 and June 1989 [5,6].

References

1 Kaufman LD, Seidman RJ, Phillips ME, Gruber BL. Cutaneous manifestations of the L-tryptophan-associated eosinophilia–myalgia syndrome: a spectrum of sclerodermatous skin disease. *J Am Acad Dermatol* 1990; **23**: 1063–9.
2 Reinauer S, Plewig G. Das Eosinophilie-Myalgie Syndrom. *Hautarzt* 1991; **42**: 137–9.
3 Gordon ML, Lebwohl MG, Phelps RG *et al.* Eosinophilic fasciitis associated with tryptophan ingestion. A manifestation of eosinophilia–myalgia syndrome. *Arch Dermatol* 1991; **127**: 217–20.
4 Connolly SM, Quimby SR, Griffing WL, Winkelmann RK. Scleroderma and L-tryptophan: a possible explanation of the eosinophilia–myalgia syndrome. *J Am Acad Dermatol* 1991; **23**: 451–7.
5 Slutsker L, Hoesly FC, Miller LM *et al.* Eosinophilia–myalgia syndrome associated with exposure to tryptophan from a single manufacturer. *JAMA* 1990; **264**: 213–7.
6 Mayeno AN, Lin F, Foote CS *et al.* Characterization of 'peak E', a novel amino acid associated with eosinophilia–myalgia syndrome. *Science* 1990; **250**: 1707–8.

Erythema nodosum [1]

Sulphonamides, other antibiotics [2], a variety of analgesics, antipyretics and anti-infectious agents, as well as the contraceptive pill [2–5], oestrogen replacement therapy [6], treatment of haematological disorders with granulocyte colony-stimulating factor [7], all-*trans*-retinoic acid [8] and *Echinacea* herbal therapy [9] have all been implicated in the aetiology of erythema nodosum. Erythema nodosum leprosum was induced by prolonged treatment with recombinant IFN-γ (in 60% of patients within 7 months) [10] and by co-trimoxazole [11].

References

1 Bork K. *Cutaneous Side Effects of Drugs*. Philadelphia: Saunders, 1988.
2 Puavilai S, Sakuntabhai A, Sriprachaya-Anunt S *et al.* Etiology of erythema nodosum. *J Med Assoc Thailand* 1995; **78**: 72–5.
3 Posternal F, Orusco MMM, Laugier P. Eythème noueux et contraceptifs oraux. *Bull Dermatol* 1974; **81**: 642–5.
4 Bombardieri S, Di Munno O, Di Punzio C, Pasero G. Erythema nodosum associated with pregnancy and oral contraceptives. *BMJ* 1977; **i**: 1509–10.
5 Muller-Ladner U, Kaufmann R, Adler G, Scherbaum WA. Rezidivierendes Erythema nodosum nach Einnahme eines niedrig dosierten oralen Antikonzeptivums. *Med Klin* 1994; **89**: 100–2.
6 Yang SG, Han KH, Cho KH, Lee AY. Development of erythema nodosum in the course of oestrogen replacement therapy. *Br J Dermatol* 1997; **137**: 319–20.
7 Nomiyama J, Shinohara K, Inoue H. Erythema nodosum caused by the administration of granulocyte colony-stimulating factor in a patient with refractory anemia. *Am J Hematol* 1994; **47**: 333.
8 Hakimian D, Tallman MS, Zugerman C, Caro WA. Erythema nodosum associated with all-*trans*-retinoic acid in the treatment of acute promyelocytic leukemia. *Leukemia* 1993; **7**: 758–9.
9 Soon SL, Crawford RI. Recurrent erythema nodosum associated with *Echinacea* herbal therapy. *J Am Acad Dermatol* 2001; **44**: 298–9.

10 Sampaio EP, Moreira AL, Sarno EN *et al.* Prolonged treatment with recombinant interferon-gamma induces erythema nodosum leprosum in lepromatous leprosy patients. *J Exp Med* 1992; **175**: 1729–37.
11 Nishioka SA, Goulart IM, Burgarelli MK *et al.* Necrotizing erythema nodosum leprosum triggered by cotrimoxazole? *Int J Lepr Other Mycobact Dis* 1994; **62**: 296–7.

Pseudolymphomatous drug hypersensitivity syndrome

This syndrome should be differentiated from DRESS (the drug hypersensitivity syndrome, anticonvulsant hypersensitivity syndrome), which has a more acute onset (see pp. 75.26–27). Skin involvement may consist of erythematous plaques, multiple infiltrative papules or solitary nodules; there may be facial oedema. Pseudolymphomatous syndrome develops between 2 weeks and 5 years after starting drug therapy, but usually within 7 weeks. Histopathologically, there is epidermotropism of atypical lymphocytes, often with Pautrier's microabscess-like structures; pseudolymphomatous syndrome differs from mycosis fungoides in that there may be moderate to marked spongiosis, necrotic keratinocytes, epidermal eosinophils, papillary dermal oedema and extravasated erythrocytes, and a mixed dermal inflammatory infiltrate including neutrophils. Misdiagnosis of pseudolymphomatous syndrome as malignant lymphoma may lead to patients being treated unnecessarily with chemotherapy.

A number of drugs may produce a reaction pattern that simulates a lymphoma [1–6]. Phenytoin especially, but also phenobarbital and carbamazepine, mephenytoin, trimethadione and sodium valproate have been implicated [7–12]. Cutaneous lesions in patients with reactions to phenytoin or carbamazepine may show histological features of mycosis fungoides; cutaneous lesions resembling those of mycosis fungoides in the absence of fever have been reported with phenytoin and carbamazepine. Phenobarbital has produced a hypersensitivity syndrome resembling Langerhans' cell histiocytosis [13].

Other drugs have been associated with mycosis fungoides-like drug eruptions, including allopurinol, antidepressants (e.g. fluoxetine [14,15] and amitriptyline [15]), phenothiazines [16], thioridazine, benzodiazepines, methylphenidate hydrochloride [17], antihistamines [4], β-blockers (e.g. atenolol [18]), ACE inhibitors [19], calcium channel blockers, salazosulfapyridine [20], lipid-lowering agents, mexiletine, ciclosporin [21], penicillamine, amiloride hydrochloride with hydrochlorothiazide, bromocriptine [22] and gemcitabine [23]. A generalized cutaneous B-cell pseudolymphoma was induced by neuroleptics [24]. Cutaneous T-cell lymphoma and Sézary syndrome have been reported in association with silicone breast implants [25,26].

Pseudolymphomatous syndrome usually responds to drug withdrawal, although not for many months in some cases [5]. Occasionally, a true lymphoma may develop.

References

1 Kardaun SH, Scheffer E, Vermeer BJ. Drug-induced pseudolymphomatous skin reactions. *Br J Dermatol* 1988; **118**: 545–52.
2 Sigal M, Pulik M. Pseudolymphomes medicamenteux a expression cutanée predominante. *Ann Dermatol Vénéréol* 1993; **120**: 175–80.
3 Handfield-Jones SE, Jenkins RE, Whittaker SJ *et al.* The anticonvulsant hypersensitivity syndrome. *Br J Dermatol* 1993; **129**: 175–7.
4 Magro CM, Crowson AN. Drugs with antihistaminic properties as a cause of atypical cutaneous lymphoid hyperplasia. *J Am Acad Dermatol* 1995; **32**: 419–28.
5 Magro CM, Crowson AN. Drug-induced immune dysregulation as a cause of atypical cutaneous lymphoid infiltrates: a hypothesis. *Hum Pathol* 1996; **27**: 125–32.
6 Choi TS, Doh KS, Kim SH *et al.* Clinicopathological and genotypic aspects of anticonvulsant-induced pseudolymphoma syndrome. *Br J Dermatol* 2003; **148**: 730–6.
7 Wolf R, Kahane E, Sandbank M. Mycosis fungoides-like lesions associated with phenytoin therapy. *Arch Dermatol* 1985; **121**: 1181–2.
8 Rijlaarsdam U, Scheffer E, Meijer CJLM *et al.* Mycosis fungoides-like lesions associated with phenytoin and carbamazepine therapy. *J Am Acad Dermatol* 1991; **24**: 216–20.
9 Shuttleworth D, Graham-Brown RAC, Williams AJ *et al.* Pseudo-lymphoma associated with carbamazepine. *Clin Exp Dermatol* 1984; **9**: 421–3.
10 Welykyj S, Gradini R, Nakao J, Massa M. Carbamazepine-induced eruption histologically mimicking mycosis fungoides. *J Cutan Pathol* 1990; **17**: 111–6.
11 Nathan DL, Belsito DV. Carbamazepine-induced pseudolymphoma with CD-30 positive cells. *J Am Acad Dermatol* 1998; **38**: 806–9.
12 Cogrel O, Beylot-Barry M, Vergier B *et al.* Sodium valproate-induced cutaneous pseudolymphoma followed by recurrence with carbamazepine. *Br J Dermatol* 2001; **144**: 1235–8.
13 Nagata T, Kawamura N, Motoyama T *et al.* A case of hypersensitivity syndrome resembling Langerhans cell histiocytosis during phenobarbital prophylaxis for convulsion. *Jpn J Clin Oncol* 1992; **22**: 421–7.
14 Gordon KB, Guitart J, Kuzel T *et al.* Pseudomycosis fungoides in a patient taking clonazepam and fluoxetine. *J Am Acad Dermatol* 1996; **34**: 304–6.
15 Crowson AN, Magro CM. Antidepressant therapy. A possible cause of atypical cutaneous lymphoid hyperplasia. *Arch Dermatol* 1995; **131**: 925–9.
16 Blazejak T, Hölzle E. Phenothiazin-induziertes Pseudolymphom. *Hautarzt* 1990; **41**: 161–3.
17 Welsh JP, Ko C, Hsu WT. Lymphomatoid drug reaction secondary to methylphenidate hydrochloride. *Cutis* 2008; **81**: 61–4.
18 Henderson CA, Shamy HK. Atenolol-induced pseudolymphoma. *Clin Exp Dermatol* 1990; **15**: 119–20.
19 Furness PN, Goodfield MJ, MacLennan KA *et al.* Severe cutaneous reactions to captopril and enalapril: histological study and comparison with early mycosis fungoides. *J Clin Pathol* 1986; **39**: 902–7.
20 Gallais V, Grange F, De Bandt M *et al.* Toxidermie a la salazosulfapyridine. Erythrodermie pustuleuse et syndrome pseudolymphomateux: 2 observations. *Ann Dermatol Vénéréol* 1994; **121**: 11–4.
21 Harman KE, Morris SD, Higgins EM. Persistent anticonvulsant hypersensitivity syndrome responding to ciclosporin. *Clin Exp Dermatol* 2003; **28**: 364–5.
22 Wiesli P, Joos L, Galeazzi RL, Dummer R. Cutaneous pseudolymphoma associated with bromocriptine therapy. *Clin Endocrinol* 2000; **53**: 656–7.
23 Marucci G, Sgarbanti E, Maestri A *et al.* Gemcitabine-associated $CD8^+$ $CD30^+$ pseudolymphoma. *Br J Dermatol* 2001; **145**: 650–2.
24 Luelmo Aguilar J, Mieras Barcelo C, Martin-Urda MT *et al.* Generalized cutaneous B-cell pseudolymphoma induced by neuroleptics. *Arch Dermatol* 1992; **128**: 121–3.
25 Duvic M, Moore D, Menter A, Vonderheid EC. Cutaneous T-cell lymphoma in association with silicone breast implants. *J Am Acad Dermatol* 1995; **32**: 939–42.
26 Sena E, Ledo A. Sézary syndrome in association with silicone breast implant. *J Am Acad Dermatol* 1995; **33**: 1060–1.

Acanthosis nigricans-like and ichthyosiform eruptions

See Chapter 19.

Erythromelalgia [1]

Drugs implicated include iodide contrast media, vaccines (influenza and hepatitis), nifedipine, felodipine, nicardipine, bromocriptine, norephedrine, pergolide and ticlopidine.

Table 75.16 Drugs causing alopecia.

Anticoagulants	Retinoids
Coumarins	Acitretin
Dextran	Etretinate
Heparin	Isotretinoin
Heparinoids	Miscellaneous
Anticonvulsants	Albendazole
Carbamazepine	Allopurinol
Valproic acid	Amfetamine (amphetamine)
Cytotoxic agents	Antithyroid drugs
Drugs acting on the central nervous system	Bromocriptine
Amitriptyline	Captopril
Doxepin	Cholestyramine
Haloperidol	Cimetidine
Lithium	Dixyrazine
Hypocholesterolaemic agents	Gentamicin
Clofibrate	Gold
Nicotinic acid	Ibuprofen
Triparanol	Levodopa
Antithyroid drugs	Metoprolol
Carbimazole	Oral contraceptives
Thiouracils	Propranolol
	Trimethadione

Table 75.17 Drugs causing hypertrichosis.

Androgens	Penicillamine
Corticosteroids	Phenytoin
Ciclosporin	Psoralens
Diazoxide	Streptomycin
Minoxidil	

Reference

1 Cohen JS. Erythromelalgia: new theories and new therapies. *J Am Acad Dermatol* 2000; **43**: 841–7.

Hair changes (see also Chapter 66)

Drug-induced alopecia

A considerable number of drugs have been reported to cause hair loss [1–5]; the most important causes are listed in Table 75.16. Cytotoxic drugs may cause alopecia by either anagen or telogen effluvium. Chemotherapeutic agents implicated in the production of alopecia include amsacrine, bleomycin, cyclophosphamide, cytarabine, dactinomycin, daunorubicin, doxorubicin, etoposide, fluorouracil, methotrexate and the nitrosoureas [2]. Telogen alopecia has been caused by anticoagulants (heparins and coumarins), antithyroid drugs (carbimazole and thiouracils), levodopa, propranolol, albendazole and oral contraceptives. Retinoids cause alopecia by disrupting keratinization. Hydantoins may cause scalp alopecia and hypertrichosis elsewhere, and clofibrate may cause alopecia by interfering with keratinization. Temporary hair loss has been described after 5-aminosalicylic acid enemas [6] and bromocriptine [7], and danazol has induced generalized alopecia [8]. Certain β-blockers have caused increased hair loss [9–11], as have dixyrazine [12] and ibuprofen [13].

Drug-induced hirsutism and hypertrichosis

The hirsutism induced in women by corticosteroids, androgens and certain progestogens is well recognized. Other drugs that may cause hypertrichosis are listed in Table 75.17 [3,4]. Up to 50% of children treated with diazoxide, and up to 40% of patients on ciclosporin, develop hypertrichosis. Zidovudine has caused excessive growth of eyelashes [14].

References

1 Brodin MB. Drug-related alopecia. *Dermatol Clin* 1987; **5**: 571–9.
2 Kerber BJ, Hood AF. Chemotherapy-induced cutaneous reactions. *Semin Dermatol* 1989; **8**: 173–81.
3 Rook A, Dawber R. *Diseases of the Hair and Scalp*, 2nd edn. Oxford: Blackwell Scientific Publications, 1990.
4 Merk HF. Drugs affecting hair growth. In: Orfanos CE, Happle R, eds. *Hair and Hair Diseases*. Berlin: Springer, 1990: 601–9.
5 Pillans PI, Woods DJ. Drug-associated alopecia. *Int J Dermatol* 1995; **34**: 149–58.
6 Kutty PK, Raman KRK, Hawken K, Barrowman JA. Hair loss and 5-aminosalicylic acid enemas. *Ann Intern Med* 1982; **97**: 785–6.
7 Blum I, Leiba S. Increased hair loss as a side effect of bromocriptine treatment. *N Engl J Med* 1980; **303**: 1418.
8 Duff P, Mayer AR. Generalized alopecia: an unusual complication of danazol therapy. *Am J Obstet Gynecol* 1981; **141**: 349–50.
9 England JR, England JD. Alopecia and propranolol therapy. *Aust Fam Physician* 1982; **11**: 225–6.
10 Graeber CW, Lapkin RA. Metoprolol and alopecia. *Cutis* 1981; **28**: 633–4.
11 Fraunfelder FT, Meyer SM, Menacker SJ. Alopecia possibly secondary to topical ophthalmic β-blockers. *JAMA* 1990; **263**: 1493–4.
12 Poulsen J. Hair loss, depigmentation of hair, ichthyosis, and blepharoconjunctivitis produced by dixyrazine. *Acta Derm Venereol (Stockh)* 1981; **61**: 85–8.
13 Meyer HC. Alopecia associated with ibuprofen. *JAMA* 1979; **242**: 142.
14 Klutman NE, Hinthorn DR. Excessive growth of eyelashes in a patient with AIDS being treated with zidovudine. *N Engl J Med* 1991; **324**: 1896.

Drug-induced hair discoloration (see Chapter 66)

Drug-induced change in hair colour, usually occurring 3–12 months after the onset of treatment, is a rare but well-recognized phenomenon [1,2]. Darkening of hair has occurred during treatment with verapamil [3], tamoxifen [4], carbidopa [5] and PABA. Etretinate has caused darkening as well as lightening, curling and kinking of hair [6]. Greying of hair has been reported with chloroquine and mephenesin [7]. Chloroquine depigmentation is reversible and occurs only in red- or blonde-haired individuals; both IFN-α [8] and chloroquine are capable of arresting phaeomelanin synthesis.

References

1 Rook A. Some chemical influences on hair growth and pigmentation. *Br J Dermatol* 1965; **77**: 115–29.
2 Bublin JG, Thompson DF. Drug-induced hair colour changes. *Clin Pharmacol Ther* 1992; **17**: 297–302.
3 Read GM. Verapamil and hair colour change. *Lancet* 1991; **338**: 1520.
4 Hampson JP, Donnelly A, Lewisones MS, Pye JK. Tamoxifen induced hair colour change. *Br J Dermatol* 1995; **132**: 483–4.
5 Reynolds NJ, Crossley J, Ferguson I, Peachey RDG. Darkening of white hair in Parkinson's disease. *Clin Exp Dermatol* 1989; **14**: 317–8.
6 Vesper JL, Fenske A. Hair darkening and new growth associated with etretinate therapy. *J Am Acad Dermatol* 1996; **34**: 860.
7 Spillane JD. Brunette to blonde. Depigmentation of hair during treatment with oral mephenesin. *BMJ* 1963; **i**: 997–8.
8 Fleming CJ, MacKie RM. Alpha interferon-induced hair discolouration. *Br J Dermatol* 1996; **135**: 337–8.

Table 75.18 Drugs causing onycholysis.

Antibiotics	*Miscellaneous*
Cefaloridine (cephaloridine)	Acridine
Chloramphenicol	Captopril
Chlortetracycline	Norethindrone and mestranol
Cloxacillin	Phenothiazines
Demethylchlortetracycline	Practolol (discontinued)
Doxycycline	Psoralens
Fluoroquinolones	Retinoids
Minocycline	Sulpha-related drugs
Tetracycline hydrochloride	Thiazides
Chemotherapeutic agents	*Photo-onycholysis*
Adriamycin	Fluoroquinolones
Bleomycin	Oral contraceptives
5-Fluorouracil	Psoralens
Mitoxantrone	Tetracyclines

Nail changes

Drug-induced nail abnormalities have been the subject of several reviews [1–7] (see Chapter 65). Heavy metals may induce the following changes: arsenic causes transverse, broad, white lines (Mee's lines); silver causes blue discoloration of the lunulae; gold results in thin and brittle nails with longitudinal streaking, yellow-brown discoloration and onycholysis; and lead produces partial leukonychia. Penicillamine therapy is associated with the yellow nail syndrome and nail dystrophy. Cytotoxic agents may produce transverse or longitudinal pigmentation, splinter haemorrhages, Beau's lines, leukonychia, Mee's lines, onycholysis, shortening of lunulae, pallor, atrophy, nail shedding and slow growth; acute paronychia has occurred with methotrexate. The β-blockers may induce a psoriasiform nail dystrophy, with onycholysis and subungual hyperkeratosis. Thiazide diuretics may result in onycholysis. Discoloration or pigmentation occurs with antimalarials (blue-brown discoloration), lithium (golden discoloration), phenolphthalein (dark-blue discoloration), phenothiazines (blue-black or purple pigmentation), phenytoin (pigmentation), psoralens and tetracyclines (yellow pigmentation). Oral contraceptives may induce photo-onycholysis and onycholysis, and are associated with an increased growth rate and reduced splitting and fragility. In contrast, heparin reduces nail growth and causes transverse banding and subungual haematomas. Retinoids cause thinning and increased fragility, onychoschizia, onycholysis, temporary nail shedding, onychomadesis, ingrowing nails, periungual granulation tissue and paronychia.

Onycholysis

Drugs causing onycholysis [6,7] and photo-onycholysis are listed in Table 75.18.

References

1 Daniel CR III, Scher RK. Nail changes secondary to systemic drugs or ingestants. *J Am Acad Dermatol* 1984; **10**: 250–8.

2 Fenton DA. Nail changes due to drugs. In: Samman PD, Fenton DA, eds. *The Nails in Disease*, 4th edn. London: Heinemann, 1986: 121–5.

3 Fenton DA, Wilkinson JD. The nail in systemic diseases and drug-induced changes. In: Baran R, Dawber RPR, eds. *Diseases of the Nails and Their Management*. Oxford: Blackwell Scientific Publications, 1984: 205–65.

Table 75.19 Drugs associated with xerostomia.

Antidepressants (tricyclic)	Minor tranquillizers
Amitriptyline	Chlordiazepoxide
Doxepin	Diazepam
Imipramine	Hydroxyzine
Antidepressants (monoamine oxidase inhibitors)	Antiparkinsonian drugs
Isocarboxazid	Antihypertensives (ganglion blockers)
Phenelzine	Gastrointestinal antispasmodics
Psychotropic agents	Atropine
Chlorpromazine	Phenobarbital (phenobarbitone)
Haloperidol	Propantheline bromide
Prochlorperazine	
Thioridazine	

4 Daniel CR III, Scher RK. Nail changes secondary to systemic drugs or ingestants. In: Scher RK, Daniel CR III, eds. *Nails: Therapy, Diagnosis, Surgery*. Philadelphia: Saunders, 1990: 192–201.

5 Zaias N. *The Nail in Health and Disease*, 2nd edn. East Norwalk, CT: Appleton Lange, 1990.

6 Baran R, Juhlin L. Drug-induced photo-onycholysis. Three subtypes identified in a study of 15 cases. *J Am Acad Dermatol* 1987; **17**: 1012–6.

7 Daniel CR. Onycholysis: an overview. *Semin Dermatol* 1991; **10**: 34–40.

Oral conditions (see also Chapter 69)

ADRs affecting the mouth have been extensively reviewed [1–6]. Disturbance of taste has been reported with a wide variety of drugs [3,4], including captopril, griseofulvin, metronidazole and protease inhibitor antiretrovirals. Orofacial effects of antiretroviral therapies have been reviewed [4]. These include mouth ulcers due to bone marrow suppression, erythema multiforme (e.g. with didanosine), lichenoid reactions with zidovudine, xerostomia (seen in up to one-third of patients taking didanosine), oral and perioral paraesthesiae (especially with ritonavir), and cheilitis with indinavir.

Xerostomia

Dryness of the mouth (xerostomia) may result from anticholinergic side effects of drugs. Xerostomia has been recorded in association with antidepressants, tranquillizers, antiparkinsonian drugs, antihypertensives and gastrointestinal antispasmodics (Table 75.19). Parotitis with salivary sialadenitis has been reported in up to 15% of patients taking phenylbutazone, and may be associated with fever and a rash [7]. A similar syndrome may occur with repeated administration of iodinated contrast media [8] and with nitrofurantoin [9].

References

1 Porter SR, Scully C. Adverse drug reactions in the mouth. *Clin Dermatol* 2000; **18**: 525–32.

2 Torpet LA, Kragelund C, Reibel J, Nauntofte B. Oral adverse drug reactions to cardiovascular drugs. *Crit Rev Oral Biol Med* 2004; **15**: 28–46.

3 Griffin JP. Drug-induced disorders of taste. *Adverse Drug React Toxicol Rev* 1992; **11**: 229–39.

4 Scully C, Diz Dios P. Orofacial effects of antiretroviral therapies. *Oral Dis* 2001; **7**: 205–10.

5 Abdollahi M, Rahimi R, Radfar M. Current opinion on drug-induced oral reactions: a comprehensive review. *J Contemp Dent Pract* 2008; **9**: 1–15.

6 Femiano F, Lanza A, Buonaiuto C *et al*. Oral manifestations of adverse drug reactions: guidelines. *J Eur Acad Dermatol Venereol* 2008; **22**: 681–91.

Table 75.20 Drugs causing stomatitis or buccal ulceration.

Chemotherapeutic agents	Antihypertensive agents
Antirheumatic drugs	Captopril
Gold	Hydralazine
Indometacin (indomethacin)	Methyldopa (rare)
Naproxen	Miscellaneous
Penicillamine	Chlorpromazine
Zomepirac	Valproic acid
Antidepressants	
Amitriptyline	
Doxepin	
Imipramine	

7 Speed BR, Spelman DW. Sialadenitis and systemic reactions associated with phenylbutazone. *Aust NZ J Med* 1982; **12**: 261–4.
8 Chohen JC, Roxe DM, Said R *et al.* Iodide mumps after repeated exposure to iodinated contrast media. *Lancet* 1980; **i**: 762–3.
9 Meyboom RH, van Gent A, Zinkstok DJ. Nitrofurantoin-induced parotitis. *BMJ* 1982; **285**: 1049.

Stomatitis

Type I immediate hypersensitivity and type IV delayed hypersensitivity reactions may be involved in allergic stomatitis [1]. The allergic stomatitides may present with clinical appearances that mimic classic oral vesiculobullous and ulcerative lesions. Stomatitis may form a part of drug-induced lichenoid reactions, fixed drug reactions or erythema multiforme, but may also arise separately from these conditions as a side effect of a number of drugs (Table 75.20). Chemotherapeutic agents causing stomatitis or buccal ulceration include [2] actinomycin D, adriamycin, amsacrine, bleomycin, busulfan, chlorambucil, cyclophosphamide, dactinomycin, daunorubicin, doxorubicin, fluorouracil, IL-2, mercaptopurine, methotrexate, mithramycin, mitomycin, nitrosoureas, procarbazine and vincristine. Penicillamine may induce stomatitis or ulceration as part of drug-induced pemphigus [3] or a lichenoid drug eruption. Gold therapy is another well-recognized cause of stomatitis [4–6]. Allergic reactions to dental materials and therapy may cause stomatitis. Positive patch tests to mercuric chloride were seen in 42%, and to copper sulphate in 16%, of patients with oral mucosal lesions associated with amalgam restorations, compared with 9% of controls, in one series [7]. It has been postulated that mercury released from dental amalgams can cause hypersensitivity / toxic reactions resulting in lichen planus lesions, and may play a major role in the pathogenesis of gingivitis, periodontitis and periodontal disease [8]. Mercuric chloride caused statistically significant increased IFN-γ release, but not proliferation, in lymphocyte cultures from patients with hypersensitivity to amalgam restorations [9]. β-Blockers have been implicated in aphthous ulcers [10].

References

1 Jainkittivong A, Langlais RP. Allergic stomatitis. *Semin Dermatol* 1994; **13**: 91–101.
2 Kerker BJ, Hood AF. Chemotherapy-induced cutaneous reactions. *Semin Dermatol* 1989; **8**: 173–81.
3 Hay KD, Muller HK, Rade PC. D-Penicillamine-induced mucocutaneous lesions with features of pemphigus. *Oral Surg* 1978; **45**: 385–95.
4 Glenert U. Drug stomatitis due to gold therapy. *Oral Surg* 1984; **58**: 52–6.
5 Gall H. Allergien auf zahnärztliche Werkstoffe und Dentalpharmaka. *Hautarzt* 1983; **34**: 326–31.
6 Wiesenfeld D, Ferguson MM, Forsyth A *et al.* Allergy to dental gold. *Oral Surg* 1984; **57**: 158–60.
7 Nordlind K, Liden S. Patch test reactions to metal salts in patients with oral mucosal lesions associated with amalgam restorations. *Contact Dermatitis* 1992; **27**: 157–60.
8 Swartzendruber DE. The possible relationship between mercury from dental amalgam and diseases. I. Effects within the oral cavity. *Med Hypotheses* 1993; **41**: 31–4.
9 Nordlind K, Liden S. *In vitro* lymphocyte reactivity to heavy metal salts in the diagnosis of oral mucosal hypersensitivity to amalgam restorations. *Br J Dermatol* 1993; **128**: 38–41.
10 Boulinguez S, Reix S, Bedane C *et al.* Role of drug exposure in aphthous ulcers: a case–control study. *Br J Dermatol* 2000; **143**: 1261–5.

Hyperpigmentation

Hyperpigmentation of the buccal mucosa may occur with chemotherapeutic agents [1]. Oestrogen is associated with gingival hypermelanosis [2]. Amalgam tattoos with localized hyperpigmentation of the buccal mucosa result from implantation of amalgam in soft tissues, especially of the gingival or alveolar mucosa [3].

Reactions caused by antibacterial, antifungal and immunosuppressive therapy

Systemic antibiotics or immunosuppressive medication [4], and corticosteroids administered by aerosol [5], may lead to the development of candidiasis of the buccal mucosa. Black hairy tongue may be associated with broad-spectrum antibiotic therapy and with griseofulvin treatment.

Gingival hyperplasia

Gingival hyperplasia may be caused by phenytoin [6], nifedipine [7], diltiazem [8], felodipine, verapamil and ciclosporin [9].

References

1 Krutchik AN, Buzdar AU. Pigmentation of the tongue and mucous membranes associated with cancer chemotherapy. *South Med J* 1979; **72**: 1615–6.
2 Hertz RS, Beckstead PC, Brown WJ. Epithelial melanosis of the gingiva possibly resulting from the use of oral contraceptives. *J Am Dent Assoc* 1980; **100**: 713–4.
3 Buchner A, Hansen LS. Amalgam pigmentation (amalgam tattoo) of the oral mucosa: a clinicopathologic study of 268 cases. *Oral Surg* 1980; **49**: 139–47.
4 Torack RM. Fungus infections associated with antibiotic and steroid therapy. *Am J Med* 1957; **22**: 872–82.
5 Chervinsky P, Petraco AJ. Incidence of oral candidiasis during therapy with triamcinolone acetonide aerosol. *Ann Allergy* 1979; **43**: 80–3.
6 Hassell TM, Page RC, Narayanan AS, Cooper CG. Diphenylhydantoin (Dilantin) gingival hyperplasia: drug induced abnormality of connective tissue. *Proc Natl Acad Sci USA* 1976; **73**: 2909–12.
7 Benini PL, Crosti C, Sala F *et al.* Gingival hyperplasia by nifedipine. Report of a case. *Acta Derm Venereol (Stockh)* 1985; **65**: 362–5.
8 Giustiniani S, Robustelli della Cuna F, Marieni M. Hyperplastic gingivitis during diltiazem therapy. *Int J Cardiol* 1987; **15**: 247–9.
9 Frosch PJ, Ruder H, Stiefel A *et al.* Gingivahyperplasie und Seropapeln unter Cyclosporinbehandlung. *Hautarzt* 1988; **39**: 611–6.

Important or widely prescribed drugs

Antibacterial agents

Antibiotic-induced drug reactions have been reviewed [1–4].

References

1 Eschenauer GA, Regal RE, DePestel DD. Antibiotic allergy. *N Engl J Med* 2006; **354**: 2293–4.
2 Iannini P, Mandell L, Felmingham J *et al*. Adverse cutaneous reactions and drugs: a focus on antimicrobials. *J Chemother* 2006; **18**: 127–39.
3 Miller DD, Warshaw EM. Adverse cutaneous reactions to antimicrobials in patients with human immunodeficiency virus infection. *Dermatitis* 2007; **18**: 8–25.
4 Baldo BA, Zhao Z, Pham NH. Antibiotic allergy: immunochemical and clinical considerations. *Curr Allergy Asthma Rep* 2008; **8**: 49–55.

Beta-lactam antibiotics

Inaccurate histories of allergy to antibiotics are frequently documented in medical records by hospital doctors [1]. Reactions to beta-lactam antibiotics may be immediate, accelerated or delayed [2–7]. Of 210 patients with a proven hypersensitivity reaction, 36.7% had urticaria occurring at any time as a single symptom; anaphylaxis without or with shock occurred in 19.1% and 17.6% respectively within 1 h after drug administration, and 19.1% had a maculopapular exanthem occurring after 24 h [6]. Non-immediate reactions to beta-lactams include several clinical entities, from maculopapular rash to severe reactions such as Stevens–Johnson syndrome and toxic epidermal necrolysis [7]. Non-immediate reactions to penicillins are a reproducible phenomenon, suggesting that a specific mechanism is responsible [8]. In one study, 39% of 74 subjects with a cutaneous reaction to a penicillin derivative had a non-immediate reaction, in 93% to an aminopenicillin (10.3% ampicillin, 82.7% amoxicillin). There was a positive delayed direct challenge and a delayed skin-test response in 65% of cases, and a lymphomonocytic infiltrate on skin biopsy [8]. Cross-reactivity exists between several members of this group of antibiotics, but restricted sensitivity to a single penicillin derivative also occurs [9]. As a group, penicillins had a higher frequency of allergic reactions than cephalosporins in a study of patients with cystic fibrosis treated with parenteral beta-lactam antibiotics [10]. Serum sickness reactions occur [11]. (See also acute generalized exanthematous pustulosis (AGEP), p. 75.34.)

References

1 Absy M, Glatt AE. Antibiotic allergy: inaccurate history taking in a teaching hospital. *South Med J* 1994; **87**: 805–7.
2 Vega JM, Blanca M, Garcia JJ *et al*. Immediate allergic reactions to amoxicillin. *Allergy* 1994; **49**: 317–22.
3 Warrington RJ, Silviu-Dan F, Magro C. Accelerated cell-mediated immune reactions in penicillin allergy. *J Allergy Clin Immunol* 1993; **92**: 626–8.
4 Ortiz-Frutos FJ, Quintana I, Soto T *et al*. Delayed hypersensitivity to penicillin. *Allergy* 1996; **51**: 134–5.
5 Lopez Serrano C, Villas F, Cabanas R, Contreras J. Delayed hypersensitivity to beta-lactams. *J Invest Allergol Clin Immunol* 1994; **4**: 315–9.
6 Bousquet PJ, Kvedariene V, Co-Minh HB *et al*. Clinical presentation and time course in hypersensitivity reactions to beta-lactams. *Allergy* 2007; **62**: 872–6.
7 Lopez S, Blanca-Lopez N, Cornejo-Garcia JA *et al*. Nonimmediate reactions to betalactams. *Curr Opin Allergy Clin Immunol* 2007; **7**: 310–6.
8 Terrados S, Blanca M, Garcia J *et al*. Nonimmediate reactions to betalactams: prevalence and role of the different penicillins. *Allergy* 1995; **50**: 563–7.
9 Blanca M, Vega JM, Garcia J *et al*. New aspects of allergic reactions to betalactams: crossreactions and unique specificities. *Clin Exp Allergy* 1994; **24**: 407–15.
10 Pleasants RA, Walker TR, Samuelson WM. Allergic reactions to parenteral beta-lactam antibiotics in patients with cystic fibrosis. *Chest* 1994; **106**: 1124–8.
11 Tatum AJ, Ditto AM, Patterson R. Severe serum sickness-like reaction to oral penicillin drugs: three case reports. *Ann Allergy Asthma Immunol* 2001; **86**: 330–4.

Penicillin

Toxic reactions to penicillin are extremely rare and usually only follow massive doses, but can occur with normal doses in patients with renal impairment; encephalopathy with epilepsy may result from binding of the beta-lactam ring to γ-aminobutyric acid receptors [1]. In contrast, immunological reactions are common [2–4]; allergy to penicillin has been reported in up to 10% of patients treated [5]. All forms of penicillin, including the semi-synthetic penicillins, are potentially cross-allergenic; in general, allergic reactions to semi-synthetic compounds are commoner than to natural penicillins. All four types of immunological reaction may occur: urticaria and anaphylactic shock (type I), haemolytic anaemia or agranulocytosis (type II), allergic vasculitis or serum sickness-like reaction (type III) and allergic contact dermatitis [6] (type IV). Immediate reactions occur within 1 h, and take the form of urticaria, laryngeal oedema, bronchospasm and/or anaphylactic shock. So-called accelerated reactions with the same clinical features develop 1–72 h later. Reactions occurring more than 72 h after exposure are termed late reactions; these include maculopapular rashes with scarlatiniform and morbilliform exanthems, urticaria, serum sickness, erythema multiforme, haemolytic anaemia, thrombocytopenia and neutropenia. Fever is the commonest reaction.

The antigenic structures responsible for penicillin allergy include a 'major determinant', the penicilloyl group formed by spontaneous hydrolysis of penicillin (penicilloyl polylysine is used for skin testing), and additional antigenic compounds to which benzylpenicillin is metabolized, termed 'minor determinants' [3]. Most immediate-type anaphylactic hypersensitivity reactions are mediated by IgE antibodies to minor antigenic determinants, whereas accelerated reactions are usually the result of IgE antibodies directed against the major antigenic determinant [3,7]. For information on skin testing for penicillin, see the diagnosis section at the end of the chapter (p. 75.170).

Anaphylactic reactions to penicillin reportedly occur in about 0.015% of treatment courses; fatal reactions occur in 0.0015–0.002% (i.e. 1 in 50 000 to 1 in 100 000) of treatment courses [8]. Young and middle-aged adults aged 20–49 years are at most risk [9]. Atopy does not augment the risk of a reaction to beta-lactam antibiotics, but may increase the risk of any reaction being severe [3]. Anaphylaxis is commoner after parenteral administration, and is very rare, but has been recorded, after oral ingestion [9]. Maculopapular reactions occur in about 2% of treatment courses [3]; where there is a history of a prior penicillin reaction, the risk of a subsequent reaction increases to about 10% [10]. A fair proportion (33% in one study) of children may lose their skin-test reactivity within a year [11]. In practice, when penicillin is given to children said to be allergic to penicillin, very few experience an adverse reaction [7]. In adults, the rate of disappearance of penicillin-specific IgE is highly variable, from 10 days to indefinite persistence [3]. For a group of penicillin-allergic patients, the time lapsed since a previous reaction is inversely related to the risk of a further IgE-mediated reaction [10]. In one study, 80–90% of patients were skin-test positive 2 months after an acute allergic reaction, but less than 20% were skin-test positive 10 years later [12]. Nevertheless, patients with a prior history of an IgE-dependent reaction remain at risk of recurrence, even though IgE antibodies

become undetectable by skin testing [13]. Most serious and fatal allergic reactions to beta-lactam antibiotics occur in individuals who have never had a prior allergic reaction; a negative history should therefore not induce a false sense of security [3]. Continuous prophylactic treatment is associated with a very low incidence of reactions [14].

Activation of allergy in a sensitized individual may require only minute amounts of the drug, as from contaminated syringes, dental root-canal fillings, viral vaccines, contaminated milk or meat products, and contamination of transfused blood [15]. Urticaria and wheezing occurred in the penicillin-sensitive spouse of a man receiving parenteral mezlocillin, and was postulated to have arisen as a result of seminal fluid transmission of penicillin [16]. Hypersensitivity reactions have occurred after intrauterine placement, in penicillin-sensitive patients, of spermatozoa or embryos exposed to penicillin *in vitro* [17].

Penicillin has been reported to cause erythema multiforme [18], vesicular and bullous eruptions, exfoliative dermatitis [19], vascular purpura or fixed eruptions, serum sickness [20], post-inflammatory elastolysis (cutis laxa), which was generalized and eventually fatal in one case [21], and a very few cases of pemphigus vulgaris [22,23], pemphigoid [24] and pustular psoriasis [25]. It has been proposed that penicillin may have a role in chronic 'idiopathic' urticaria [26].

Cloxacillin and flucloxacillin

Cloxacillins cross-react with penicillins, but unlike ampicillin do not produce distinctive eruptions. Flucloxacillin rarely elicits primary penicillin hypersensitivity. In one case report, parenteral cloxacillin was tolerated but oral administration caused progressive generalized erythema with pruritus, facial angio-oedema and tachycardia [27]. Flucloxacillin has been implicated as a cause of cholestatic jaundice; this complication is rare, and the risk is greater in elderly patients and those receiving therapy for more than 2 weeks [28].

References

1 Barrons RW, Murray KM, Richey RM. Populations at risk for penicillin-induced seizures. *Ann Pharmacother* 1992; **26**: 26–9.
2 Erffmeyer JE. Penicillin allergy. *Clin Rev Allergy* 1986; **4**: 171–88.
3 Weiss ME, Adkinson NF. Immediate hypersensitivity reactions to penicillin and related antibiotics. *Clin Allergy* 1988; **18**: 515–40.
4 Weber EA, Knight A. Testing for allergy to antibiotics. *Semin Dermatol* 1989; **8**: 204–12.
5 Van Arsdael PP. The risk of penicillin reactions. *Ann Intern Med* 1968; **69**: 1071.
6 Stejskal VDM, Forsbeck M, Olin R. Side chain-specific lymphocyte responses in workers with occupational allergy induced by penicillins. *Int Arch Allergy Appl Immunol* 1987; **82**: 461–4.
7 Anonymous. Penicillin allergy in childhood. *Lancet* 1989; **i**: 420.
8 Idsøe O, Guthe T, Willcox RR, de Weck AL. Nature and extent of penicillin side reactions, with particular reference to fatalities from anaphylactic shock. *Bull WHO* 1968; **38**: 159–88.
9 Simmonds J, Hodges S, Nicol F, Barnett D. Anaphylaxis after oral penicillin. *BMJ* 1978; **ii**: 1404.
10 Sogn DD. Penicillin allergy. *J Allergy Clin Immunol* 1984; **74**: 589–93.
11 Chandra RK, Joglekar SA, Tomas E. Penicillin allergy: anti-penicillin IgE antibodies and immediate hypersensitivity skin reactions employing major and minor determinants of penicillin. *Arch Dis Child* 1980; **55**: 857–60.
12 Sullivan TJ, Wedner JH, Shatz GS *et al.* Skin testing to detect penicillin allergy. *J Allergy Clin Immunol* 1981; **68**: 171–80.
13 Adkinson NF Jr. Risk factors for drug allergy. *J Allergy Clin Immunol* 1984; **74**: 567–72.
14 Wood HF, Simpson R, Feinstein AR *et al.* Rheumatic fever in children and adolescents. A long-term epidemiologic study of subsequent prophylaxis, streptococcal infections, and clinical sequelae. I. Description of the investigative techniques and the population studied. *Ann Intern Med* 1964; **60** (Suppl. 5): 6–17.
15 Michel J, Sharon R. Non-haemolytic adverse reaction after transfusion of a blood unit containing penicillin. *BMJ* 1980; **i**: 152–3.
16 Burks JH, Fliegalman R, Sokalski SJ. An unforeseen complication of home parenteral antibiotic therapy. *Arch Intern Med* 1989; **149**: 1603–4.
17 Smith YR, Hurd WW, Menge AC *et al.* Allergic reactions to penicillin during in vitro fertilization and intrauterine insemination. *Fertil Steril* 1992; **58**: 847–9.
18 Staretz LR, Deboom GW. Multiple oral and skin lesions occurring after treatment with penicillin. *J Am Dent Assoc* 1990; **121**: 436–7.
19 Levine BB. Skin rashes with penicillin therapy: current management. *N Engl J Med* 1972; **286**: 42–3.
20 Clark BM, Kotti GH, Shah AD, Conger NG. Severe serum sickness reaction to oral and intramuscular penicillin. *Pharmacotherapy* 2006; **26**: 705–8.
21 Kerl H, Burg G, Hashimoto K. Fatal, penicillin-induced, generalized, postinflammatory elastolysis (cutis laxa). *Am J Dermatopathol* 1983; **5**: 267–76.
22 Duhra PL, Foulds IS. Penicillin-induced pemphigus vulgaris. *Br J Dermatol* 1988; **118**: 307.
23 Fellner MJ, Mark AS. Penicillin- and ampicillin-induced pemphigus vulgaris. *Int J Dermatol* 1980; **19**: 392–3.
24 Alcalay J, David M, Ingber A *et al.* Bullous pemphigoid mimicking bullous erythema multiforme: an untoward side effect of penicillins. *J Am Acad Dermatol* 1988; **18**: 345–9.
25 Katz M, Seidenbaum M, Weinrauch L. Penicillin-induced generalized pustular psoriasis. *J Am Acad Dermatol* 1988; **17**: 918–20.
26 Boonk WJ, Van Ketel WG. The role of penicillin in the pathogenesis of chronic urticaria. *Br J Dermatol* 1982; **106**: 183–90.
27 Torres MJ, Blanca M, Fernandez J *et al.* Selective allergic reaction to oral cloxacillin. *Clin Exp Allergy* 1996; **26**: 108–11.
28 Fairley CK, McNeil JJ, Desmond P *et al.* Risk factors for development of flucloxacillin-associated jaundice. *BMJ* 1993; **306**: 233–5.

Ampicillin

A morbilliform rash, with onset on the extremities and becoming generalized, occurs in 5–10% of patients treated with ampicillin, and usually develops 7–12 days after onset of therapy. This time interval suggests an allergic mechanism, although the rash disappears spontaneously even if ampicillin is continued, and may not develop on re-exposure [1]. Skin tests are generally negative. An urticarial reaction, present in about 1.5% of patients, indicates the presence of type I IgE-mediated general penicillin allergy [2,3]. Administration of ampicillin when a patient has infectious mononucleosis leads to florid morbilliform and sometimes purpuric eruptions in up to 100% of patients [4–6]. Cutaneous reactions to ampicillin are increased in cytomegalovirus infection [7], chronic lymphatic leukaemia [8], renal insufficiency or when allopurinol is administered concomitantly [9]. Ampicillin has been reported to cause a fixed drug eruption [10], erythema multiforme and Stevens–Johnson syndrome [11,12], TEN [13], Henoch–Schönlein purpura [14], serum sickness [15] and pemphigus vulgaris [16] in individual cases. Administration of ampicillin to a patient with a history of psoriasis resulted in erythroderma on two separate occasions [17]. A recurrent, localized, pustular skin eruption developed on the cheeks with ampicillin in one case [18].

Delayed intradermal skin tests and patch tests, indicating delayed hypersensitivity, were positive in about half of 60 subjects with maculopapular reactions to the aminopenicillins ampicillin and amoxicillin [19]; in another study, hypersensitivity to an

antigenic determinant in the side-chain structure was suggested, as intradermal and patch tests were positive to ampicillin but there was good tolerance to benzylpenicillin [20]. Re-exposure of patients to ampicillins and other penicillins is contraindicated after urticarial reactions; anaphylactic reactions to ampicillin have been recorded. The risk is far less after morbilliform rashes but is not negligible.

References

1 Adcock BB, Rodman DP. Ampicillin-specific rashes. *Arch Fam Med* 1996; **5**: 301–4.
2 Bass JW, Crowley DM, Steele RW *et al.* Adverse effects of orally administered ampicillin. *J Pediatr* 1973; **83**: 106–8.
3 Anonymous. Ampicillin rashes. *BMJ* 1975; **ii**: 708–9.
4 Weiss ME, Adkinson NF. Immediate hypersensitivity reactions to penicillin and related antibiotics. *Clin Allergy* 1988; **18**: 515–40.
5 Pullen H, Wright N, Murdoch JMcC. Hypersensitivity reactions to antibacterial drugs in infectious mononucleosis. *Lancet* 1967; **ii**: 1176–8.
6 Renn CN, Straff W, Dorfmüller A *et al.* Amoxicillin-induced exanthema in young adults with infectious mononucleosis: demonstration of drug-specific lymphocyte reactivity. *Br J Dermatol* 2003; **147**: 1166–7.
7 Klemola E. Hypersensitivity reactions to ampicillin in cytomegalovirus mononucleosis. *Scand J Infect Dis* 1970; **2**: 29.
8 Cameron SJ, Richmond J. Ampicillin hypersensitivity in lymphatic leukaemia. *Scott Med J* 1972; **16**: 425–7.
9 Jick H, Slone D, Shapiro S *et al.* Excess of ampicillin rashes associated with allopurinol or hyperuricemia. A report from the Boston Collaborative Drug Surveillance Program, Boston University Medical Center. *N Engl J Med* 1972; **286**: 505–7.
10 Arndt KA, Parrish J. Ampicillin rashes. *Arch Dermatol* 1973; **107**: 74.
11 Gupta HL, Dheman R. Ampicillin-induced Stevens–Johnson syndrome. *J Indian Med Assoc* 1979; **72**: 188–9.
12 Garty BZ, Offer I, Livni E, Danon YL. Erythema multiforme and hypersensitivity myocarditis caused by ampicillin. *Ann Pharmacother* 1994; **28**: 730–1.
13 Tagami H, Tatsuta K, Iwatski K, Yamada M. Delayed hypersensitivity in ampicillin-induced toxic epidermal necrolysis. *Arch Dermatol* 1983; **119**: 910–3.
14 Beeching NJ, Gruer LD, Findlay CD, Geddes AM. A case of Henoch–Schönlein purpura syndrome following oral ampicillin. *J Antimicrob Chemother* 1982; **10**: 479–82.
15 Caldwell JR, Cliff LE. Adverse reactions to antimicrobial agents. *JAMA* 1974; **230**: 77–80.
16 Fellner MJ, Mark AS. Penicillin- and ampicillin-induced pemphigus vulgaris. *Int J Dermatol* 1980; **19**: 392–3.
17 Saito S, Ikezawa Z. Psoriasiform intradermal test reaction to ABPC in a patient with psoriasis and ABPC allergy. *J Dermatol* 1990; **17**: 677–83.
18 Lim JT, Ng SK. An unusual drug eruption to ampicillin. *Cutis* 1995; **56**: 163–4.
19 Romano A, Di Fonso M, Papa G *et al.* Evaluation of adverse cutaneous reactions to aminopenicillins with emphasis on those manifested by maculopapular rashes. *Allergy* 1995; **50**: 113–8.
20 Lopez Serrano C, Villas F, Cabanas R, Contreras J. Delayed hypersensitivity to beta-lactams. *J Invest Allergol Clin Immunol* 1994; **4**: 315–9.

Amoxicillin

Cutaneous eruptions including urticaria, morbilliform or maculopapular rashes occur in 1–2% of treatment courses with amoxicillin [1–3]. Immediate allergy (anaphylaxis or urticaria/angio-oedema) to amoxicillin has occurred in patients with good tolerance of benzylpenicillin, aztreonam and ceftazidime [4,5]. However, amoxicillin has been reported to cross-react with penicillin on first exposure [6]. Amoxicillin caused an unusual intertriginous eruption in two patients [7]. Serum sickness has been reported with amoxicillin in children [8]. Amoxicillin has caused a fixed eruption [9], and a curious, recurrent, localized, pustular eruption [10]. This drug has also been implicated in the development of an acute generalized exanthematous pustulosis [11]. There may be an increased frequency of rash with amoxicillin and clavulanate therapy in HIV-positive patients [12]. Amoxicillin, like clavulanic acid and flucloxacillin, may cause a cholestatic hepatitis [13]. This occurs at a frequency of 1 in 6000 adults when the drug is combined with clavulanic acid (co-amoxiclav) [14]. Amoxicillin has also been implicated in the baboon syndrome [15], palmar exfoliative exanthem [16] and localized peri-buccal pustulosis [17].

Methicillin

Methicillin caused reappearance of a recently faded ampicillin rash in a patient with glandular fever [18].

References

1 Wise PJ, Neu HC. Experience with amoxicillin: an overall summary of clinical trials in the United States. *J Infect Dis* 1974; **129** (Suppl.): S266–S267.
2 Levine LR. Quantitative comparison of adverse reactions to cefaclor versus amoxicillin in a surveillance study. *Pediatr Infect Dis* 1985; **4**: 358–61.
3 Bigby M, Jick S, Jick H, Arndt K. Drug-induced cutaneous reactions. A report from the Boston Collaborative Drug Surveillance Program on 15438 consecutive inpatients, 1975 to 1982. *JAMA* 1986; **256**: 3358–63.
4 Vega JM, Blanca M, Garcia JJ *et al.* Immediate allergic reactions to amoxicillin. *Allergy* 1994; **49**: 317–22.
5 Martin JA, Igea JM, Fraj J *et al.* Allergy to amoxicillin in patients who tolerated benzylpenicillin, aztreonam, and ceftazidime. *Clin Infect Dis* 1992; **14**: 592–3.
6 Fellner MJ. Amoxicillin cross reacts with penicillin on first exposure. *Int J Dermatol* 1993; **32**: 308–9.
7 Wolf R, Brenner S, Krakowski A. Intertriginous drug eruption. *Acta Derm Venereol (Stockh)* 1992; **72**: 441–2.
8 Chopra R, Roberts J, Warrington RJ. Severe delayed-onset hypersensitivity reactions to amoxicillin in children. *Can Med Assoc J* 1989; **140**: 921–3.
9 Chowdhury FH. Fixed genital drug eruption. *Pract Med* 1982; **226**: 1450.
10 Shuttleworth D. A localized, recurrent pustular eruption following amoxycillin administration. *Clin Exp Dermatol* 1989; **14**: 367–8.
11 Roujeau J-C, Bioulac-Sage P, Bourseau C *et al.* Acute generalized exanthematous pustulosis. Analysis of 63 cases. *Arch Dermatol* 1991; **127**: 1333–8.
12 Battegay M, Opravil M, Wütrich B, Lüthy R. Rash with amoxycillin–clavulanate therapy in HIV-infected patients. *Lancet* 1989; **ii**: 1100.
13 Anonymous. Drug-induced cholestatic hepatitis from common antibiotics. *Med J Aust* 1992; **157**: 531.
14 Anonymous. Revised indications for co-amoxiclav (Augmentin). *Curr Prob Pharmacovig* 1997; **23**: 8.
15 Kick G, Przybilla B. Delayed prick test reaction identifies amoxicillin as elicitor of baboon syndrome. *Contact Dermatitis* 2000; **43**: 366–7.
16 Gastaminza G, Audicana MT, Fernandez E *et al.* Palmar exfoliative exanthema to amoxicillin. *Allergy* 2000; **55**: 510–1.
17 Novalbos A, Bombin C, Figueredo E *et al.* Localized pustulosis induced by betalactams. *J Invest Allergol Clin Immunol* 2000; **10**: 178–9.
18 Fields DA. Methicillin rash in infectious mononucleosis. *West J Med* 1981; **133**: 521.

Cephalosporins [1]

In general, cephalosporins are fairly well tolerated [1–3], adverse reactions ranging from 1 to 10% [1]; parenteral administration may cause minor adverse reactions, including thrombophlebitis and pain. The most common adverse effects are allergic reactions, occurring in 1–3% of patients [2]; haematological toxicity occurs in less than 1% of patients. Anaphylaxis is rare (less than 0.02%) [1]. Other reactions include localized gastrointestinal disturbances, hepatotoxicity, nephrotoxicity and mild central nervous system effects. The incidence of cephalosporin reactions in patients with histories of penicillin allergy has been reported as minimally, if at

all, increased [1]. Post-marketing studies of second- and third-generation cephalosporins showed no increase in allergic reactions in patients with a history of penicillin allergy. Cephalosporin antibiotics have been judged safe in penicillin-allergic patients and penicillin skin tests do not identify potential reactors [1]. In contrast with this, a more recent study reported a markedly increased risk of events after subsequent cephalosporins [4]. However, the risk of anaphylaxis was very low [4]. The R1 side chain, rather than the beta-lactam structure shared by penicillins and cephalosporins, seems to play a dominant role in determining the specificity of immunological reactions to cephalosporins [5]. Thus, penicillin can be administered safely to patients allergic to cephalosporins, with a negative skin test to penicillin determinants. Conversely, a negative result in skin testing to penicillin and cephalosporins with different side chains seems to be a good predictor of tolerance to a cephalosporin [6]. Isolated independent hypersensitivity to individual cephalosporins, such as cefazolin [7,8], cefonicid [9] and cefuroxime [10], with good tolerance to other beta-lactam antibiotics, has been described.

Hypersensitivity reactions include various exanthems and contact urticaria [11]; cases of anaphylaxis to cefaclor [12] and of fatal anaphylactic shock related to cefalotin (cephalothin) [13] have been reported. Vulvovaginitis and pruritus ani are not uncommon. Delayed reactions have been reported with cefonicid [9] and cefuroxime [14]. Serum sickness reactions occur [15–18], especially with cefaclor; the last-mentioned drug may also cause urticaria and erythema multiforme [18]. Exfoliative dermatitis has been attributed to cefoxitin [19]. Disulfiram-like reactions to alcohol have been described with newer members of this group. Pustular reactions have been documented with cefradine, cefalexin and cefazolin [20–22]. Ceftazidime has been implicated in the development of erythema multiforme [23]. Cephalosporins [24], including cefalexin [25], have been reported to cause TEN, and cefalexin has precipitated pemphigus vulgaris [26]. Cefazolin has caused an unusual fixed drug eruption [27]. A curious photorecall-like phenomenon followed the use of cefazolin and gentamicin sulphate, in that the eruption was restricted to an area of sunburn sustained 1 month previously [28]. Cefotaxime has caused a photodistributed phototoxic telangiectasia [29].

References

1 Anne S, Reisman RE. Risk of administering cephalosporin antibiotics to patients with histories of penicillin allergy. *Ann Allergy Asthma Immunol* 1995; **74**: 167–70.

2 Thompson JW, Jacobs RF. Adverse effects of newer cephalosporins. An update. *Drug Saf* 1993; **9**: 132–42.

3 Matsuno K, Kunihiro E, Yamatoya O *et al.* Surveillance of adverse reactions due to ciprofloxacin in Japan. *Drugs* 1995; **49** (Suppl. 2): 495–6.

4 Apter AJ, Kinman JL, Bilker WB *et al*. Is there cross-reactivity between penicillins and cephalosporins? *Am J Med* 2006; **119**: 354.e11–9.

5 Antunez C, Blanca-Lopez N, Torres MJ *et al*. Immediate allergic reactions to cephalosporins: evaluation of cross-reactivity with a panel of penicillins and cephalosporins. *J Allergy Clin Immunol* 2006; **117**: 404–10.

6 Moreno E, Macías E, Dávila I *et al*. Hypersensitivity reactions to cephalosporins. *Expert Opin Drug Saf* 2008; **7**: 295–304.

7 Igea JM, Fraj J, Davila I *et al.* Allergy to cefazolin: study of *in vivo* cross reactivity with other betalactams. *Ann Allergy* 1992; **68**: 515–9.

8 Warrington RJ, McPhillips S. Independent anaphylaxis to cefazolin without allergy to other beta-lactam antibiotics. *J Allergy Clin Immunol* 1996; **98**: 460–2.

9 Martin JA, Alonso MD, Lazaro M *et al.* Delayed allergic reaction to cefonicid. *Ann Allergy* 1994; **72**: 341–2.

10 Marcos Bravo C, Luna Ortiz I, Gonzalez Vazquez R. Hypersensitivity to cefuroxime with good tolerance to other betalactams. *Allergy* 1995; **50**: 359–61.

11 Tuft L. Contact urticaria from cephalosporins. *Arch Dermatol* 1975; **111**: 1609.

12 Nishioka K, Katayama I, Kobayashi Y, Takijiri C. Anaphylaxis due to cefaclor hypersensitivity. *J Dermatol* 1986; **13**: 226–7.

13 Spruell FG, Minette LJ, Sturner WQ. Two surgical deaths associated with cephalothin. *JAMA* 1974; **229**: 440–1.

14 Romano A, Pietrantonio F, Di Fonso M, Venuti A. Delayed hypersensitivity to cefuroxime. *Contact Dermatitis* 1992; **27**: 270–1.

15 Kearns GL, Wheeler JG, Childress SH, Letzig LG. Serum sickness-like reactions to cefaclor: role of hepatic metabolism and individual susceptibility. *J Pediatr* 1994; **125**: 805–11.

16 Grammer LC. Cefaclor serum sickness. *JAMA* 1996; **275**: 1152–3.

17 Isaacs D. Serum sickness-like reaction to cefaclor. *J Paediatr Child Health* 2001; **37**: 298–9.

18 Joubert GI, Hadad K, Matsui D *et al*. Selection of treatment of cefaclor-associated urticarial, serum sickness-like reactions and erythema multiforme by emergency pediatricians: lack of a uniform standard of care. *Can J Clin Pharmacol* 1999; **6**: 197–201.

19 Kannangara DW, Smith B, Cohen K. Exfoliative dermatitis during cefoxitin therapy. *Arch Intern Med* 1982; **142**: 1031–2.

20 Kalb R, Grossman ME. Pustular eruption following administration of cephradine. *Cutis* 1986; **38**: 58–60.

21 Jackson H, Vion B, Levy PM. Generalized eruptive pustular drug rash due to cephalexin. *Dermatologica* 1988; **177**: 292–4.

22 Fayol J, Bernard P, Bonnetblanc JM. Pustular eruption following the administration of cefazolin: a second case report. *J Am Acad Dermatol* 1988; **19**: 571.

23 Pierce TH, Vig SJ, Ingram PM. Ceftazidime in the treatment of lower respiratory tract infection. *J Antimicrob Chemother* 1983; **12** (Suppl. A): 21–5.

24 Nichter LS, Harman DM, Bryant CA *et al.* Cephalosporin-induced toxic epidermal necrolysis. *J Burn Care Rehabil* 1983; **4**: 358–60.

25 Hogan DJ, Rooney ME. Toxic epidermal necrolysis due to cephalexin. *J Am Acad Dermatol* 1987; **17**: 852.

26 Wolf R, Dechner E, Ophir J, Brenner S. Cephalexin. A non-thiol drug that may induce pemphigus vulgaris. *Int J Dermatol* 1991; **30**: 213–5.

27 Sigal-Nahum M, Konqui A, Gauliet A, Sigal S. Linear fixed drug eruption. *Br J Dermatol* 1988; **118**: 849–51.

28 Flax SH, Uhle P. Photo recall-like phenomenon following the use of cefazolin and gentamicin sulfate. *Cutis* 1990; **46**: 59–61.

29 Borgia F, Vaccaro M, Guarneri F, Cannavo SP. Photodistributed telangiectasia following use of cefotaxime. *Br J Dermatol* 2000; **143**: 674–8.

Monobactams

Monobactams (e.g. aztreonam) show weak and rare cross-reactivity with IgE antibodies to penicillin [1–3], although immediate hypersensitivity on first exposure to aztreonam in penicillin-allergic patients has been recorded [4,5]. In general, aztreonam is well tolerated in high-risk patients allergic to other beta-lactam antibiotics, but there is a 20% sensitization rate following exposure [6]. However, aztreonam and the monobactams can be safely given to penicillin-allergic patients [7]. Generalized urticaria to aztreonam but good tolerance of the other beta-lactams has been recorded [8].

Carbapenems

Cross-reactivity and allergic reactions to imipenem occur in patients known to be allergic to penicillin [9]. Carbapenems should be avoided in patients with penicillin allergy [7]. Imipenem combined with cilastatin, a non-antibiotic enzyme inhibitor that prevents breakdown of imipenem to nephrotoxic metabolites, may cause phlebitis or pain at the site of infusion [10]. Imipenem has been associated with a pustular eruption [11], and imipenem–

cilastatin with palmoplantar pruritus during infusion in a child with AIDS [12].

References

1 Adkinson NF, Saxon A, Spence MR, Swabb EA. Cross-allergenicity and immunogenicity of aztreonam. *Rev Infect Dis* 1985; **7** (Suppl. 4): S613–S621.
2 Saxon A, Hassner A, Swabb EA *et al.* Lack of cross-reactivity between aztreonam, a monobactam antibiotic, and penicillin-allergic subjects. *J Infect Dis* 1984; **149**: 16.
3 Adkinson NF Jr. Beta-lactam crossreactivity. *Clin Exp Allergy* 1998; **28** (Suppl. 4): 37–40.
4 Hantson P, de Coninck B, Horn JL, Mahieu P. Immediate hypersensitivity to aztreonam and imipenem. *BMJ* 1991; **302**: 294–5.
5 Alvarez JS, Del Castillo JAS, Garcia IS, Ortiz MJA. Immediate hypersensitivity to aztreonam. *Lancet* 1990; **335**: 1094.
6 Moss RB. Sensitization to aztreonam and cross-reactivity with other beta-lactam antibiotics in high-risk patients with cystic fibrosis. *J Allergy Clin Immunol* 1991; **87**: 78–88.
7 Kishiyama JL, Adelman DC. The cross-reactivity and immunology of beta-lactam antibiotics. *Drug Saf* 1994; **10**: 318–27.
8 de la Fuente Prieto R, Armentia Medina A, Sanchez Palla P *et al.* Urticaria caused by sensitization to aztreonam. *Allergy* 1993; **48**: 634–6.
9 Saxon A, Adelman DC, Patel A *et al.* Imipenem cross-reactivity with penicillin in humans. *J Allergy Clin Immunol* 1988; **82**: 213–7.
10 Anonymous. Imipenem cilastatin: a new type of antibiotic. *Drug Ther Bull* 1991; **29**: 43–4.
11 Escallier F, Dalac S, Foucher JL *et al.* Pustulose exanthématique aiguë généralisée: imputabilité a l'imipéneme (Tienam®). *Ann Dermatol Vénéréol* 1989; **116**: 407–9.
12 Machado ARL, Silva CLO, Galvão NAM. Unusual reaction to imipenem–cilastatin in a child with the acquired immunodeficiency syndrome. *J Allergy Clin Immunol* 1991; **87**: 754.

Tetracyclines

Many of the side effects are common to all drugs within the group, and cross-sensitivity occurs [1]. Nausea, vomiting and diarrhoea are well-recognized dose-related effects. Oral or vaginal candidiasis may occur as a result of overgrowth of commensals. Resumption of therapy does not necessarily lead to recurrence of the vaginitis [2].

Photosensitivity

All tetracyclines, but especially demethylchlortetracycline, may cause phototosensitive eruptions [1,3–6], which clinically resemble exaggerated sunburn, sometimes with blistering. Phototoxicity is thought to be involved, in that high serum levels predispose to its occurrence. Reactions to both UVA and UVB have been reported. High concentrations of tetracycline are found in sun-damaged skin [3]. Symptoms may persist for months [1]. Photo-onycholysis may develop in fingernails and (if exposed) toenails; the thumb (normally less exposed) may be spared [7,8]. Tetracycline therapy is best avoided if there is a prospect of considerable sun exposure. Porphyria cutanea tarda-like changes may develop after chronic sun exposure [6,9]. A photosensitive lichenoid rash has been attributed to demethylchlortetracycline [10].

References

1 Wright AL, Colver GB. Tetracyclines: how safe are they? *Clin Exp Dermatol* 1988; **13**: 57–61.
2 Hall JH, Lupton ES. Tetracycline therapy for acne: incidence of vaginitis. *Cutis* 1977; **20**: 97–8.
3 Blank H, Cullen SI, Catalano PM. Photosensitivity studies with demethylchlortetracycline and doxycycline. *Arch Dermatol* 1968; **97**: 1–2.
4 Frost P, Weinstein GP, Gomez EC. Phototoxic potential of minocycline and doxycycline. *Arch Dermatol* 1972; **105**: 681–3.
5 Kaidbey KH, Kligman AM. Identification of systemic phototoxic drugs by human intradermal assay. *J Invest Dermatol* 1978; **70**: 272–4.
6 Hawk JLM. Skin changes resembling hepatic cutaneous porphyria induced by oxytetracycline photosensitization. *Clin Exp Dermatol* 1980; **5**: 321–5.
7 Baker H. Photo-onycholysis caused by tetracyclines. *BMJ* 1977; **ii**: 519–20.
8 Kestel JL Jr. Photo-onycholysis from minocycline. Side effects of minocycline therapy. *Cutis* 1981; **28**: 53–4.
9 Epstein JH, Tuffanelli DL, Seibert JS, Epstein WL. Porphyria-like cutaneous changes induced by tetracycline hydrochloride photosensitization. *Arch Dermatol* 1976; **112**: 661–6.
10 Jones HE, Lewis CW, Reisner JE. Photosensitive lichenoid eruption associated with demeclocycline. *Arch Dermatol* 1972; **106**: 58–63.

Pigmentation

Methacycline is a rare cause [1]. Long-term minocycline therapy for acne may result in pigmentation. Although this is generally held to be a rare event, it may occur in about 1.4% of patients [2–5]. The average time for the development of pigmentary changes was 5 months, and onset of this complication did not seem to be related to cumulative dosage of the drug [3]. Facial hyperpigmentation was reported in two sisters on long-term minocycline therapy, who were also being treated with Dianette (cyproterone acetate and ethinylestradiol); it was suggested that pigmentation occurred either as a result of a genetic alteration in the metabolic handling of the drug or because of accentuation by the concomitant therapy [6]. Other drugs, including amitriptyline [2], phenothiazines and 13-*cis*-retinoic acid, have been implicated in the accentuation of minocycline-related hyperpigmentation.

Three types of pigmentation are described with minocycline and may occur in combination or isolation [3]. A focal type with well-demarcated blue-black macules is seen in areas of previous inflammation or scarring, especially in relation to acne scars. Minocycline has been associated with post-inflammatory hyperpigmentation in women who have undergone sclerotherapy [7]. Macular or more diffuse hyperpigmentation may appear distant from acne sites, especially on the extensor surface of the lower legs and forearms and on sun-exposed areas. These two types resolve on cessation of therapy, with a mean time to resolution of 12 months [3]. A more persistent diffuse brown-grey change may develop, especially in sun-exposed areas [5]. Minocycline pigmentation may respond well to laser therapy [8–11].

The oral cavity and lips may be involved [12,13]. Conjunctival pigmentation may occur with tetracyclines [14,15] and scleral pigmentation with minocycline [16,17]. Minocycline can cause nail pigmentation and longitudinal melanonychia [5,18,19], and tetracycline may produce yellow discoloration of the nail [20]. Cutaneous osteomas presenting as blue skin nodules that fluoresce yellow under UV light may rarely develop in patients being treated with tetracycline [21] or minocycline [22] for acne. Black galactorrhoea occurred in a patient taking both minocycline and phenothiazines [23].

Pigmentation may also involve bones, teeth, thyroid, aorta and endocardium [19,24]. Histological and electron microscopic studies have demonstrated increased melanin, haemosiderin and either minocycline or a metabolite in the skin [25–27]; pigment may be seen in dermal histiocytes and eccrine myoepithelial cells [26].

Minocycline is metabolized to form a brown-black degradation product [28].

References

1 Möller H, Rausing A. Methacycline pigmentation: a five-year follow-up. *Acta Derm Venereol (Stockh)* 1980; **60**: 495–501.
2 Basler RSW, Goetz CS. Synergism of minocycline and amitriptyline in cutaneous hyperpigmentation. *J Am Acad Dermatol* 1985; **12**: 577.
3 Layton AM, Cunliffe WJ. Minocycline induced pigmentation in the treatment of acne: a review and personal observations. *J Dermatol Treat* 1989; **1**: 9–12.
4 Dwyer CM, Cuddihy AM, Kerr RE *et al.* Skin pigmentation due to minocycline treatment of facial dermatoses. *Br J Dermatol* 1993; **129**: 158–62.
5 Pepine M, Flower FP, Ramos-Caro FA. Extensive cutaneous hyperpigmentation caused by minocycline. *J Am Acad Dermatol* 1993; **28**: 292–5.
6 Eedy DJ, Burrows D. Minocycline-induced pigmentation occurring in two sisters. *Clin Exp Dermatol* 1991; **16**: 55–7.
7 Leffell DJ. Minocycline hydrochloride hyperpigmentation complicating treatment of venous ectasia of the extremities. *J Am Acad Dermatol* 1991; **24**: 501–2.
8 Collins P, Cotterill JA. Minocycline-induced pigmentation resolves after treatment with the Q-switched ruby laser. *Br J Dermatol* 1996; **135**: 317–9.
9 Wilde JL, English JC III, Finley EM. Minocycline-induced hyperpigmentation. Treatment with the neodymium:Yag laser. *Arch Dermatol* 1997; **133**: 1344–6.
10 Wood B, Munro CS, Bilsland D. Treatment of minocycline-induced pigmentation with the neodymium-Yag laser. *Br J Dermatol* 1998; **139**: 562.
11 Green D, Friedman KJ. Treatment of minocycline-induced cutaneous pigmentation with the Q-switched Alexandrite laser and a review of the literature. *J Am Acad Dermatol* 2001; **44**: 342–7.
12 Siller GM, Tod MA, Savage NW. Minocycline-induced oral pigmentation. *J Am Acad Dermatol* 1994; **30**: 350–4.
13 Chu PSL, Yen TS, Berger TG. Minocycline hyperpigmentation localized to the lips: an unusual fixed drug reaction? *J Am Acad Dermatol* 1994; **30**: 802–3.
14 Brothers DM, Hidayat AA. Conjunctival pigmentation associated with tetracycline medication. *Ophthalmology* 1981; **88**: 1212–5.
15 Messmer E, Font RL, Sheldon G, Murphy D. Pigmented conjunctival cysts following tetracycline/minocycline therapy. Histochemical and electron microscopic observations. *Ophthalmology* 1983; **90**: 1462–8.
16 Angeloni VL, Salasche SJ, Ortiz R. Nail, skin, and scleral pigmentation induced by minocycline. *Cutis* 1988; **42**: 229–33.
17 Sabroe RA, Archer CB, Harlow D *et al.* Minocycline-induced discolouration of the sclerae. *Br J Dermatol* 1996; **135**: 314–6.
18 Mallon E, Dawber RPR. Longitudinal melanonychia induced by minocycline. *Br J Dermatol* 1995; **130**: 794–5.
19 Wolfe ID, Reichmister J. Minocycline hyperpigmentation: skin, tooth, nail, and bone involvement. *Cutis* 1984; **33**: 475–8.
20 Hendricks AA. Yellow lunulae with fluorescence after tetracycline therapy. *Arch Dermatol* 1980; **116**: 438–40.
21 Walter JF, Macknet KD. Pigmentation of osteoma cutis caused by tetracycline. *Arch Dermatol* 1979; **115**: 1087–8.
22 Moritz DL, Elewski B. Pigmented postacne osteoma cutis in a patient treated with minocycline: report and review of the literature. *J Am Acad Dermatol* 1991; **24**: 851–3.
23 Basler RSW, Lynch PJ. Black galactorrhea as a complication of minocycline and phenothiazine therapy. *Arch Dermatol* 1985; **121**: 417–8.
24 Butler JM, Marks R, Sutherland R. Cutaneous and cardiac valvular pigmentation with minocycline. *Clin Exp Dermatol* 1985; **10**: 432–7.
25 Sato S, Murphy GF, Bernard JD *et al.* Ultrastructural and x-ray microanalytical observations on minocycline-related hyperpigmentation of the skin. *J Invest Dermatol* 1981; **77**: 264–71.
26 Argenyi ZB, Finelli L, Bergfeld WF *et al.* Minocycline-related cutaneous hyperpigmentation as demonstrated by light microscopy, electron microscopy and x-ray energy spectroscopy. *J Cutan Pathol* 1987; **14**: 176–80.
27 Okada N, Moriya K, Nishida K *et al.* Skin pigmentation associated with minocycline therapy. *Br J Dermatol* 1989; **121**: 247–54.
28 Nelis HJCF, DeLeenheer AP. Metabolism of minocycline in humans. *Drug Metab Dispos* 1982; **10**: 142–6.

Other cutaneous side effects

Allergic reactions are far less common than with penicillin. Morbilliform, urticarial, erythema multiforme-like and bullous eruptions [1,2], exfoliative dermatitis and erythema nodosum [3] have been reported, as well as a recurrent follicular acneiform eruption in one patient [4]. Minocycline has caused eosinophilic cellulitis and pustular folliculitis with eosinophilia [5]. Gram-negative folliculitis of the face is uncommon but well recognized; *Proteus* may be responsible, and the condition responds to ampicillin [6]. Tetracyclines are a well-known cause of fixed drug eruptions [7–9], and minocycline [10] and doxycycline [11] have caused Stevens–Johnson syndrome. TEN has been recorded [12]. Doxycycline caused a severe drug hypersensitivity reaction [13]. It has been suggested that tetracyclines may exacerbate psoriasis [14,15]. An eruption resembling Sweet's syndrome has occurred with minocycline, tetracycline and doxycycline [16–18]. Pruritus at the site of active acne has been recorded within 2–6 weeks of starting oral tetracyclines (oxytetracycline, doxycycline or minocycline) [19].

References

1 Shelley WB, Heaton CL. Minocycline sensitivity. *JAMA* 1973; **224**: 125–6.
2 Fawcett IW, Pepys J. Allergy to a tetracycline preparation: a case report. *Clin Allergy* 1976; **6**: 301–4.
3 Bridges AJ, Graziano FM, Calhoun W, Reizner GT. Hyperpigmentation, neutrophilic alveolitis, and erythema nodosum resulting from minocycline. *J Am Acad Dermatol* 1990; **22**: 959–62.
4 Bean SF. Acneiform eruption from tetracycline. *Br J Dermatol* 1971; **85**: 585–6.
5 Kaufmann D, Pichler W, Beer JH. Severe episode of high fever with rash, lymphadenopathy, neutropenia, and eosinophilia after minocycline therapy for acne. *Arch Intern Med* 1994; **154**: 1983–4.
6 Leyden JJ, Marples RR, Mills OH Jr, Kligman AM. Gram-negative folliculitis: a complication of antibiotic therapy in acne vulgaris. *Br J Dermatol* 1973; **88**: 533–8.
7 Jolly HW, Sherman IJ Jr, Carpenter CL *et al.* Fixed drug eruptions to tetracyclines. *Arch Dermatol* 1978; **114**: 1484–5.
8 Fiumara NJ, Yaqub M. Pigmented penile lesions (fixed drug eruptions) associated with tetracycline therapy for sexually transmitted diseases. *Sex Transm Dis* 1980; **8**: 23–5.
9 Chan HL, Wong SN, Lo FL. Tetracycline-induced fixed drug eruptions: influence of dose and structure of tetracyclines. *J Am Acad Dermatol* 1985; **13**: 302–3.
10 Shoji A, Someda Y, Hamada T. Stevens–Johnson syndrome due to minocycline therapy. *Arch Dermatol* 1987; **123**: 18–20.
11 Curley RK, Verbov JL. Stevens–Johnson syndrome due to tetracyclines: a case report (doxycycline) and review of the literature. *Clin Exp Dermatol* 1987; **12**: 124–5.
12 Tatnall FM, Dodd HJ, Sarkany I. Elevated serum amylase in a case of toxic epidermal necrolysis. *Br J Dermatol* 1985; **113**: 629–30.
13 Robles DT, Leonard JL, Compton N *et al*. Severe drug hypersensitivity reaction in a young woman treated with doxycycline. *Dermatology* 2008; **217**: 23–6.
14 Tsankov M, Botev-Zlatkov M, Lazarova AZ *et al.* Psoriasis and drugs: influence of tetracyclines on the course of psoriasis. *J Am Acad Dermatol* 1988; **19**: 629–32.
15 Bergner T, Przybilla B. Psoriasis and tetracyclines. *J Am Acad Dermatol* 1990; **23**: 770.
16 Mensing H, Kowalzick L. Acute febrile neutrophilic dermatosis (Sweet's syndrome) caused by minocycline. *Dermatologica* 1991; **182**: 43–6.
17 Thibault MJ, Billick RC, Srolovitz H. Minocycline-induced Sweet's syndrome. *J Am Acad Dermatol* 1992; **27**: 801–4.
18 Khan Durani B, Jappe U. Drug-induced Sweet's syndrome in acne caused by different tetracyclines: case report and review of the literature. *Br J Dermatol* 2002; **147**: 558–62.
19 Yee KC, Cunliffe WJ. Itching in acne: an unusual complication of therapy. *Dermatology* 1994; **189**: 117–9.

Gastrointestinal absorption and drug interactions

Absorption of tetracyclines is reduced when taken with meals, especially those containing calcium or iron such as milk, or with drugs such as iron or antacids [1]. The decrease in serum levels following a test meal has been reported as follows: oxytetracycline 50% [1], minocycline 13% [1] and doxycycline 20% [2]. Oxytetracycline may have a hypoglycaemic effect in insulin-dependent diabetics [3]. Tetracyclines can potentiate the action of warfarin by depressing prothrombin activity, and elevate serum levels of lithium given simultaneously [4].

References

1 Leyden JJ. Absorption of minocycline HCl and tetracycline hydrochloride. Effect of food, milk and iron. *J Am Acad Dermatol* 1985; **12**: 308–12.
2 Welling PG, Koch PA, Lau CC, Craig WA. Bioavailability of tetracycline and doxycycline in fasted and nonfasted subjects. *Antimicrob Agents Chemother* 1977; **11**: 462–9.
3 Miller JB. Hypoglycaemic effect of oxytetracycline. *BMJ* 1966; **2**: 1007.
4 McGennis AJ. Lithium carbonate and tetracycline interaction. *BMJ* 1978; **i**: 1183.

Systemic side effects of tetracyclines

Long-term use of tetracycline for acne may rarely result in benign intracranial hypertension [1,2]. As retinoids may potentiate this effect, it is safest not to use them in combination with tetracycline therapy for acne. Oesophageal ulceration has been described in a number of patients [3]. With the exception of doxycycline and minocycline, tetracyclines may exacerbate renal failure. Combination therapy with tetracyclines and nephrotoxic drugs such as gentamicin or diuretics should be avoided [4]. Deteriorated tetracyclines have caused nephropathy accompanied by an exanthematic eruption. Patients should be warned not to use outdated or poorly stored tetracycline, because degraded tetracycline can cause a Fanconi-type syndrome comprising renal tubular acidosis and proteinuria [5,6] and lactic acidosis [7]. Dose-related vestibular disturbance has been reported with minocycline [8]. Reversible pulmonary infiltration with eosinophilic or neutrophilic alveolitis has been rarely described in association with tetracycline [9] and especially minocycline [10–12] therapy. There have been isolated case reports linking tetracycline with SLE [13].

Minocycline has been reported to cause other serious, albeit rare, adverse events. Serum sickness-like reactions occur at about 15 days [14,15]. A hypersensitivity syndrome may develop at about 23–35 days, with a severe self-limiting eruption, sometimes exfoliative dermatitis, associated with eosinophilia and acute hepatic failure, occasionally fatal [16–20]. A drug-induced autoimmune syndrome with hepatitis or vasculitis and some features of SLE occurs rarely with minocycline, on average 1–2 years after the start of therapy, and is commoner in women [20–25]. Hepatitis, sometimes with the histological features of chronic active hepatitis, may be associated with polyarthralgia and positive antinuclear antibodies but negative or only weakly positive anti-DNA antibodies, and is only rarely fatal; patients usually recover within 3 months of drug cessation. Perinuclear antineutrophilic cytoplasmic antibody (p-ANCA) may be a marker for development of minocycline-induced autoimmunity [26–28]; in one study, all such patients were p-ANCA positive and had the haplotype HLA-DR4 or HLA-DR2, and all had the HLA-DQB1 allele, suggesting genetic susceptibility [28]. Systemic reactions to minocycline are certainly more frequent than those to oxytetracycline or doxycycline [29], and it has therefore been suggested that the use of minocycline in acne should be restricted to patients unresponsive to other tetracyclines [30].

References

1 Walters BNJ, Gubbay SS. Tetracycline and benign intracranial hypertension: report of five cases. *BMJ* 1979; **282**: 19–20.
2 Pearson MG, Littlewood SM, Bowden AN. Tetracycline and benign intracranial hypertension. *BMJ* 1981; **282**: 568–9.
3 Channer KS, Hollanders D. Tetracycline-induced oesophageal ulceration. *BMJ* 1981; **282**: 1359–60.
4 Wright AL, Colver GB. Tetracyclines: how safe are they? *Clin Exp Dermatol* 1988; **13**: 57–61.
5 Moser RH. Bibliographies on diseases: medical progress. Reactions to tetracyclines. *Clin Pharmacol Ther* 1966; **7**: 117–31.
6 Frimpter GW, Timpanelli AE, Eisenmenger WJ *et al.* Reversible 'Fanconi syndrome' caused by degraded tetracycline. *JAMA* 1963; **184**: 111–3.
7 Montoliu J, Carrera M, Darnell A *et al.* Lactic acidosis and Fanconi's syndrome due to degraded tetracycline. *BMJ* 1981; **281**: 1576–7.
8 Allen JC. Minocycline. *Ann Intern Med* 1976; **85**: 482–7.
9 Ho D, Tashkin DP, Bein ME, Sharma O. Pulmonary infiltrates with eosinophilia associated with tetracycline. *Chest* 1979; **76**: 33–5.
10 Bando T, Fujimura M, Noda Y *et al.* Minocycline-induced pneumonitis with bilateral hilar lymphadenopathy and pleural effusion. *J Intern Med* 1994; **33**: 177–9.
11 Sitbon O, Bidel N, Dussopt C *et al.* Minocycline and pulmonary eosinophilia. A report on eight patients. *Arch Intern Med* 1994; **154**: 1633–40.
12 Dykhuizen RS, Zaidi AM, Godden DJ *et al.* Minocycline and pulmonary eosinophilia. *BMJ* 1995; **310**: 1520–1.
13 Domz CA, Minamara DH, Hozapfel HF. Tetracycline provocation in lupus erythematosus. *Ann Intern Med* 1959; **50**: 1217.
14 Landau M, Shachar E, Brenner S. Minocycline-induced serum sickness-like reaction. *J Eur Acad Dermatol Venereol* 2000; **14**: 67–8.
15 Malakar S, Dhar S, Shah Malakar R. Is serum sickness an uncommon adverse effect of minocycline treatment? *Arch Dermatol* 2001; **137**: 100–1.
16 Davies MG, Kersey PJW. Acute hepatitis and exfoliative dermatitis associated with minocycline. *BMJ* 1989; **298**: 1523–4.
17 Kaufmann D, Pichler W, Beer JH. Severe episode of high fever with rash, lymphadenopathy, neutropenia, and eosinophilia after minocycline therapy for acne. *Arch Intern Med* 1994; **154**: 1983–4.
18 Knowles SR, Shapiro L, Shear NH. Serious adverse reactions induced by minocycline. Report of 13 patients and review of the literature. *Arch Dermatol* 1996; **132**: 934–9.
19 MacNeil M, Haase DA, Tremaine R, Marrie TJ. Fever, lymphadenopathy, eosinophilia, lymphocytosis, hepatitis, and dermatitis: a severe adverse reaction to minocycline. *J Am Acad Dermatol* 1997; **36**: 347–50.
20 Lawrenson RA, Seaman HE, Sundstrom A *et al.* Liver damage associated with minocycline use in acne: a systematic review of the published literature and pharmacovigilance data. *Drug Saf* 2000; **23**: 333–49.
21 Elkayam O, Yaron M, Caspi D. Minocycline-induced autoimmune syndromes: an overview. *Semin Arthritis Rheum* 1999; **28**: 392–7.
22 Byrne PAC, Williams BD, Pritchard MH. Minocycline-related lupus. *Br J Rheumatol* 1994; **33**: 674–6.
23 Gordon PM, White MI, Herriot R *et al.* Minocyline-associated lupus erythematosus. *Br J Dermatol* 1995; **132**: 120–1.
24 Gough A, Chapman S, Wagstaff K *et al.* Minocycline-induced autoimmune hepatitis and systemic lupus erythematosus-like syndrome. *BMJ* 1996; **312**: 169–72.
25 Crosson J, Stillman MT. Minocycline-related lupus erythematosus with associated liver disease. *J Am Acad Dermatol* 1997; **36**: 867–8.
26 Shapiro LE, Uetrecht J, Shear NH. Minocycline, perinuclear antineutrophilic cytoplasmic antibody, and pigment: the biochemical basis. *J Am Acad Dermatol* 2001; **45**: 787–9.
27 Schaffer JV, Davidson DM, McNiff JM, Bolognia JL. Perinuclear antineutrophilic cytoplasmic antibody-positive cutaneous polyarteritis nodosa associated with minocycline therapy for acne vulgaris. *J Am Acad Dermatol* 2001; **44**: 198–206.

28 Dunphy J, Oliver M, Rands AL *et al.* Antineutrophil cytoplasmic antibodies and HLA class II alleles in minocycline-induced lupus-like syndrome. *Br J Dermatol* 2000; **142**: 461–7.
29 Shapiro LE, Knowles SR, Shear NH. Comparative safety of tetracycline, minocycline, and doxycycline. *Arch Dermatol* 1997; **133**: 1224–30.
30 Ferner RE, Moss C. Minocycline for acne. First line antibacterial treatment of acne should be with tetracycline or oxytetracycline. *BMJ* 1996; **312**: 138.

Effects on the fetus and on teeth

There is little evidence that tetracycline is teratogenic [1]. There is an isolated case report of congenital abnormalities in a child whose mother took clomocycline for acne [2]. Yellow discoloration of the teeth due to tetracycline exposure during mineralization of the deciduous or permanent teeth is well known [3–5]. A yellow-brown fluorescent discoloration is formed as a result of a complex with calcium orthophosphate. Tetracyclines should not be given to pregnant women or children under the age of 12 years. Tetracyclines are excreted in breast milk, but chelation with calcium decreases their absorption so that tooth discoloration is probably prevented [1].

Tetracycline may be deposited up to late adolescence in calcifying teeth such as the molars, but as these are not normally visible this is not a problem [5]. Minocycline may rarely stain the teeth of adults [6–8].

References

1 Wright AL, Colver GB. Tetracyclines: how safe are they? *Clin Exp Dermatol* 1988; **13**: 57–61.
2 Corcoran R, Castles JM. Tetracycline for acne vulgaris and possible teratogenesis. *BMJ* 1977; **ii**: 807–8.
3 Conchie JM, Munroe JD, Anderson DO. The incidence of staining of permanent teeth by the tetracyclines. *Can Med Assoc J* 1970; **103**: 351–6.
4 Moffitt JM, Cooley RO, Olsen NH, Hefferren JJ. Prediction of tetracycline-induced tooth discolouration. *J Am Dent Assoc* 1974; **88**: 547–52.
5 Grossman ER. Tetracycline and staining of the teeth. *JAMA* 1986; **225**: 2442.
6 Poliak SC, DiGiovanna JJ, Gross EG *et al.* Minocycline-associated tooth discoloration in young adults. *JAMA* 1985; **254**: 2930–2.
7 Rosen T, Hoffmann TJ. Minocycline-induced discoloration of the permanent teeth. *J Am Acad Dermatol* 1989; **21**: 569.
8 Berger RS, Mandel EN, Hayes TJ, Grimwood RR. Minocycline staining of the oral cavity. *J Am Acad Dermatol* 1989; **21**: 1300–1.

Tetracyclines and the contraceptive pill

Tetracyclines have been reported to interfere with the action of the contraceptive pill [1,2], and it is standard practice to inform female patients of this and to suggest use of an additional or alternative method of contraception while on medication. However, there is controversy as to whether there is really a significant risk of interaction [3–6]. It has been argued that there is a baseline pill failure rate of at least 1% per year, and that antibiotics commonly used in dermatology do not increase the risk of pregnancy [6].

References

1 Bacon JF, Shenfield GM. Pregnancy attributable to interaction between tetracycline and oral contraceptives. *BMJ* 1980; **280**: 293.
2 Hughes BR, Cunliffe WJ. Interactions between the oral contraceptive pill and antibiotics. *Br J Dermatol* 1990; **122**: 717–8.
3 Fleischer AB Jr, Resnick SD. The effect of antibiotics on the efficacy of oral contraceptives. *Arch Dermatol* 1989; **125**: 1562–4.
4 Orme ML'E, Back DJ. Interactions between oral contraceptive steroids and broad-spectrum antibiotics. *Clin Exp Dermatol* 1986; **11**: 327–31.
5 De Groot AC, Eshuis H, Stricker BHC. Oral contraceptives and antibiotics in acne. *Br J Dermatol* 1991; **124**: 212.
6 Helms SE, Bredle DL, Zajic J *et al.* Oral contraceptive failure rates and oral antibiotics. *J Am Acad Dermatol* 1997; **36**: 705–10.

Sulphonamides and trimethoprim

Reactions occur in 1–5% of those exposed [1–6]. They are commoner in patients with AIDS [7–9], and slow acetylators are at greater risk [10]. Type I reactions (urticaria and anaphylaxis) are rare but recorded. Phototoxic and photoallergic eruptions occur [11,12]. Morbilliform and rubelliform rashes are seen, and erythema multiforme, Stevens–Johnson syndrome and TEN [13–18], erythema nodosum [1], generalized exfoliative dermatitis [1,19,20] and fixed eruptions [21] are all well known. In addition, an LE-like syndrome and allergic vasculitis [22] are documented. Agranulocytosis or haemolytic anaemia is occasionally precipitated.

References

1 Koch-Weser J, Sidel VW, Dexter M *et al.* Adverse reactions to sulfisoxazole, sulfamethoxazole, and nitrofurantoin. Manifestations and specific reaction rates during 2,118 courses of therapy. *Arch Intern Med* 1971; **128**: 399–404.
2 Kauppinen K, Stubb S. Drug eruptions: causative agents and clinical types. A series of inpatients during a 10-year period. *Acta Derm Venereol (Stockh)* 1984; **64**: 320–4.
3 Bigby M, Jick S, Jick H, Arndt K. Drug-induced cutaneous reactions. A report from the Boston Collaborative Drug Surveillance Program on 15438 consecutive inpatients, 1975 to 1982. *JAMA* 1986; **256**: 3358–63.
4 Anonymous. Hypersensitivity to sulphonamides: a clue? *Lancet* 1986; **ii**: 958–9.
5 Rieder MJ, Uetrecht J, Shear NH *et al.* Diagnosis of sulfonamide hypersensitivity reactions by *in-vitro* 'rechallenge' with hydroxylamine metabolites. *Ann Intern Med* 1989; **110**: 286–9.
6 Dibbern DA Jr, Montanaro A. Allergies to sulfonamide antibiotics and sulfur-containing drugs. *Ann Allergy Asthma Immunol* 2008; **100**: 91–100.
7 De Raeve L, Song M, Van Maldergem L. Adverse cutaneous drug reactions in AIDS. *Br J Dermatol* 1988; **119**: 521–3.
8 van der Ven AJAM, Koopmans PP, Vree TB, van der Meer JWM. Adverse reactions to co-trimoxazole in HIV infection. *Lancet* 1991; **338**: 431–3.
9 Roudier C, Caumes E, Rogeaux O *et al.* Adverse cutaneous reactions to trimethoprim–sulfamethoxazole in patients with the acquired immunodeficiency syndrome and *Pneumocystis carinii* pneumonia. *Arch Dermatol* 1994; **130**: 1383–6.
10 Carr A, Gross AS, Hoskins JM *et al.* Acetylation phenotype and cutaneous hypersensitivity to trimethoprim–sulphamethoxazole in HIV-infected patients. *AIDS* 1994; **8**: 333–7.
11 Epstein JH. Photoallergy. A review. *Arch Dermatol* 1972; **106**: 741–8.
12 Hawk JLM. Photosensitizing agents used in the United Kingdom. *Clin Exp Dermatol* 1984; **9**: 300–2.
13 Kauppinen K. Cutaneous reactions to drugs. With special reference to severe mucocutaneous bullous eruptions and sulphonamides. *Acta Derm Venereol Suppl (Stockh)* 1972; **68**: 1–89.
14 Jick H, Derby LE. A large population-based follow-up study of trimethoprim–sulfamethoxazole, trimethoprim, and cephalexin for uncommon serious drug toxicity. *Pharmacotherapeutica* 1995; **15**: 428–32.
15 Carrol OM, Bryan PA, Robinson RJ. Stevens–Johnson syndrome associated with long-acting sulfonamides. *JAMA* 1966; **195**: 691–3.
16 Aberer W, Stingl G, Wolff K. Stevens–Johnson-Syndrom und toxische epidermale Nekrolyse nach Sulfonamideinahme. *Hautarzt* 1982; **33**: 484–90.
17 Chan H-L, Stern RS, Arndt KA *et al.* The incidence of erythema multiforme, Stevens–Johnson syndrome, and toxic epidermal necrolysis. A population-based study with particular reference to reactions caused by drugs among outpatients. *Arch Dermatol* 1990; **126**: 43–7.
18 Schöpf E, Stühmer A, Rzany B *et al.* Toxic epidermal necrolysis and Stevens–Johnson syndrome. An epidemiologic study from West Germany. *Arch Dermatol* 1991; **127**: 839–42.

19 Nicolis GD, Helwig EB. Exfoliative dermatitis. A clinicopathologic study of 135 cases. *Arch Dermatol* 1973; **108**: 788–97.
20 Sehgal VN, Srivastava G. Exfoliative dermatitis. A prospective study of 80 patients. *Dermatologica* 1986; **173**: 278–84.
21 Sehgal VN, Gangwani OP. Fixed drug eruption. Current concepts. *Int J Dermatol* 1987; **26**: 67–74.
22 Lehr D. Sulfonamide vasculitis. *J Clin Pharmacol* 1972; **2**: 181–9.

Sulfasalazine

Rashes occur in 1–5% of patients, and may be widespread as part of a hypersensitivity syndrome with hepatitis and encephalopathy [1–5], but desensitization is possible [6]. Blood disorders attributable to sulfasalazine occur at a rate of 3 per 1000 users [7]. An autoimmune syndrome has been described [8]. Photosensitivity [9] and a fixed eruption [10] have been documented. TEN, erythroid hypoplasia and agranulocytosis have been reported [11]. Bronchiolitis obliterans and alveolitis are well-recognized complications, and acute hypersensitivity pneumonia is recorded. LE, including cerebral LE, may be induced [12]. Reversible oligospermia may occur [13], and reversible hair loss has been attributed to use of this drug in enemas [14]. Many of the above adverse effects are attributable to the carrier molecule, sulfapyridine, which delivers 5-aminosalicylic acid, the component of sulfasalazine active in ulcerative colitis, to its site of action in the colon; patients who are slow acetylators may be especially prone to side effects [15]. Urticaria, and possibly the renal toxicity, are due to the 5-aminosalicylic acid component [16].

Mesalazine (5-aminosalicylic acid)

Fever, erythematous skin eruption and lung involvement [17], and fever, diarrhoea, exfoliative dermatitis, marked atypical lymphocytosis and severe hepatotoxicity [18] have been described in patients with a previous history of sulfasalazine hypersensitivity. Additional cutaneous hypersensitivity reactions including vasculitis [19], a Kawasaki-like syndrome [20] and an LE-like syndrome [21] have been documented. This drug may cause renal damage, and is associated with blood dyscrasia [22], including fatal bone marrow suppression and thrombocytopenia [23]. A pustular reaction is recorded [24].

Olsalazine

This drug, which consists of a dimer of two molecules of 5-aminosalicylic acid linked by an azo bond, dispenses with the unwanted effects of sulfapyridine. Nonetheless, up to one in five patients experience diarrhoea, rash, nausea and abdominal pain severe enough to stop treatment with the drug [16].

Sulfamethoxypyridazine

Obliterative bronchiolitis and alveolitis have been documented in a patient with linear IgA disease of adults [25].

References

1 Leroux JL, Ghezail M, Chertok P, Blotman F. Hypersensitivity reaction to sulfasalazine: skin rash, fever, hepatitis and activated lymphocytes. *Clin Exp Rheumatol* 1992; **10**: 427.
2 Gran JT, Myklebust G. Toxicity of sulphasalazine in rheumatoid arthritis. Possible protective effect of rheumatoid factors and corticosteroids. *Scand J Rheumatol* 1993; **22**: 229–32.
3 Gabay C, De Bandt M, Palazzo E. Sulphasalazine-related life-threatening side effects: is *N*-acetylcysteine of therapeutic value? *Clin Exp Rheumatol* 1993; **11**: 417–20.
4 Schoonjans R, Mast A, Van Den Abeele G *et al.* Sulfasalazine-associated encephalopathy in a patient with Crohn's disease. *Am J Gastroenterol* 1993; **88**: 1416–20.
5 Rubin R. Sulfasalazine-induced fulminant hepatic failure and necrotizing pancreatitis. *Am J Gastroenterol* 1994; **89**: 789–91.
6 Koski JM. Desensitization to sulphasalazine in patients with arthritis. *Clin Exp Rheumatol* 1993; **11**: 169–70.
7 Jick H, Myers MW, Dean AD. The risk of sulfasalazine- and mesalazine-associated blood disorders. *Pharmacotherapeutica* 1995; **15**: 176–81.
8 Vyse T, So AK. Sulphasalazine-induced autoimmune syndrome. *Br J Rheumatol* 1992; **31**: 115–6.
9 Watkinson G. Sulfasalazine: a review of 40 years' experience. *Drugs* 1986; **32**: 1–11.
10 Kanwar AJ, Singh M, Yunus M, Belhaj MS. Fixed eruption to sulphasalazine. *Dermatologica* 1987; **174**: 104.
11 Maddocks JL, Slater DN. Toxic epidermal necrolysis, agranulocytosis and erythroid hypoplasia associated with sulphasalazine. *J R Soc Med* 1980; **73**: 587–8.
12 Rafferty P, Young AC, Haeny MR. Sulphasalazine-induced cerebral lupus erythematosus. *Postgrad Med J* 1982; **58**: 98–9.
13 Drife JO. Drugs and sperm. *BMJ* 1982; **284**: 844–5.
14 Kutty PK, Raman KRK, Hawken K, Barrowman JA. Hair loss and 5-aminosalicylic acid enemas. *Ann Intern Med* 1982; **97**: 785–6.
15 Das KM, Eastwood MA, McManus JPA, Sircus W. Adverse reactions during salicylazosulfapyridine therapy and the relation with drug metabolism and acetylator phenotype. *N Engl J Med* 1973; **289**: 491–5.
16 Anonymous. Olsalazine: a further choice in ulcerative colitis. *Drug Ther Bull* 1990; **28**: 57–8.
17 Hautekeete ML, Bourgeois N, Potvin P *et al.* Hypersensitivity with hepatotoxicity to mesalazine after hypersensitivity to sulfasalazine. *Gastroenterology* 1992; **103**: 1925–7.
18 Aparicio J, Carnicer F, Girona E, Gomez A. Cutaneous hypersensitivity reaction to mesalazine. *Am J Gastroenterol* 1996; **91**: 620–1.
19 Lim AG, Hine KR. Fever, vasculitic rash, arthritis, pericarditis, and pericardial effusion after mesalazine. *BMJ* 1994; **308**: 113.
20 Waanders H, Thompson J. Kawasaki-like syndrome after treatment with mesalazine. *Am J Gastroenterol* 1991; **86**: 219–21.
21 Dent MT, Ganatpathy S, Holdworth CD, Channer KC. Mesalazine-induced lupus-like syndrome. *BMJ* 1992; **305**: 159.
22 Anonymous. Blood dyscrasias and mesalazine. *Curr Prob Pharmacovig* 1995; **21**: 5.
23 Daneshmend TK. Mesalazine-associated thrombocytopenia. *Lancet* 1991; **337**: 1297–8.
24 Gibbon KL, Bewley AP, Thomas K. Mesalazine-induced pustular drug eruption. *J Am Acad Dermatol* 2002; **46**: S220–S221.
25 Godfrey KM, Wojnarowska F, Friedland JS. Obliterative bronchiolitis and alveolitis associated with sulphamethoxypyridazine (Lederkyn) therapy for linear IgA disease of adults. *Br J Dermatol* 1990; **123**: 125–31.

Sulfadoxine

This sulphonamide is used in malaria prophylaxis in combination with pyrimethamine. The risk of reactions seems to be very low, but drug fever, TEN and photodermatitis have been recorded [1]. Stevens–Johnson syndrome may occur with Fansidar (pyrimethamine and sulfadoxine) for malaria prophylaxis [1–4] or with sulfadoxine alone [5]. TEN has occurred with Fansidar in an AIDS patient [6].

References

1 Koch-Weser J, Hodel C, Leimer R, Styk S. Adverse reactions to pyrimethamine/sulfadoxine. *Lancet* 1982; **ii**: 1459.
2 Hornstein OP, Ruprecht KW. Fansidar-induced Stevens–Johnson syndrome. *N Engl J Med* 1982; **307**: 1529–30.
3 Miller KD, Lobel HO, Satriale RF *et al.* Severe cutaneous reactions among

American travelers using pyrimethamine–sulfadoxine (Fansidar) for malaria prophylaxis. *Am J Trop Med Hyg* 1986; **35**: 451–8.
4 Ortel B, Sivayathorn A, Hönigsmann H. An unusual combination of phototoxicity and Stevens–Johnson syndrome due to antimalarial therapy. *Dermatologica* 1989; **178**: 39–42.
5 Hernborg A. Stevens–Johnson syndrome after mass prophylaxis with sulfadoxine for cholera in Mozambique. *Lancet* 1985; **i**: 1072–3.
6 Raviglione MC, Dinan WA, Pablos-Mendez A *et al.* Fatal toxic epidermal necrolysis during prophylaxis with pyrimethamine and sulfadoxine in a human immunodeficiency virus-infected person. *Arch Intern Med* 1988; **148**: 2863–5.

Trimethoprim–sulfamethoxazole (co-trimoxazole)

The general incidence and patterns of reactions to this mixture of sulfamethoxazole and trimethoprim are about the same as for sulphonamides in general; cutaneous reactions are seen in 3.3% of patients [1–3]. Severe cutaneous reactions of all types occur in about 1 per 100 000 users of the drug [2,3]. In view of these severe reactions, the drug is now indicated primarily for *Pneumocystis carinii* pneumonia, and for acute exacerbations of chronic bronchitis and urinary tract infections, and otitis media in children, only where there is good reason to prefer this combination [4]. There is a greatly increased incidence of reactions in patients with AIDS [5–13]. In one study, 18 of 38 patients with AIDS and *P. carinii* pneumonia treated with trimethoprim–sulfamethoxazole developed cutaneous reactions within a median of 11 days. It is sometimes possible to continue treatment through a hypersensitivity reaction, as reported for 67% of cases in the above study [14]. Adjuvant corticosteroids reduce the incidence of adverse cutaneous reactions to co-trimoxazole in patients with AIDS who are treated for hypoxaemic *P. carinii* pneumonia, but the incidence of mucocutaneous herpes simplex virus infection is higher [15]. If it is deemed essential to continue the drug, desensitization can be attempted [16,17].

Fixed eruptions occur [18–22], and may be due to the sulphonamide or trimethoprim components; a widespread fixed eruption mimicking TEN has been documented in one case [23]. Pustular reactions [24] and Sweet's syndrome [25] have been documented. Severe reactions have included erythema multiforme or Stevens–Johnson syndrome [26,27] that has been fatal [27], TEN in AIDS patients [5,11,12], cutaneous vasculitis [28] and fatal agranulocytosis [29]. One patient developed a rapidly progressive, subepidermal bullous eruption within hours of intravenous trimethoprim–sulfamethoxazole [30].

References

1 Jick J. Adverse reactions to trimethoprim–sulphamethoxazole in hospitalized patients. *Rev Infect Dis* 1982; **4**: 426–8.
2 Lawson DH, Paice BJ. Adverse reactions to trimethoprim–sulfamethoxasole. *Rev Infect Dis* 1982; **4**: 429–33.
3 Huisman MV, Buller HR, TenCate JW. Co-trimoxasole toxicity. *Lancet* 1984; **ii**: 1152.
4 Anonymous. Revised indications for co-trimoxazole (Septrin, Bactrim, various generic preparations). *Curr Probl Pharmacovig* 1995; **21**: 5.
5 Coopman SA, Johnson RA, Platt R, Stern RS. Cutaneous disease and drug reactions in HIV infection. *N Engl J Med* 1993; **328**: 1670–4.
6 Mitsuyasu R, Groopman J, Volberding P. Cutaneous reaction to trimethoprim–sulfamethoxazole in patients with AIDS and Kaposi's sarcoma. *N Engl J Med* 1983; **308**: 1535–6.
7 Gordin FM, Simon GL, Wofsy CB *et al.* Adverse reactions to trimethoprim sulfamethoxazole in patients with the acquired immune deficiency syndrome. *Ann Intern Med* 1984; **100**: 495–9.
8 Cohn DL, Penley KA, Judson FN *et al.* The acquired immunodeficiency syndrome and a trimethoprim–sulfamethoxazole-adverse reaction. *Ann Intern Med* 1984; **100**: 311.
9 Kovacs JA, Hiemenz JW, Macher AM *et al. Pneumocystis carinii* pneumonia: a comparison between patients with the acquired immunodeficiency syndrome and patients with other immunodeficiencies. *Ann Intern Med* 1984; **100**: 663–71.
10 De Raeve L, Song M, Van Maldergem L. Adverse cutaneous drug reactions in AIDS. *Br J Dermatol* 1988; **119**: 521–3.
11 Arnold P, Guglielmo J, Hollander H. Severe hypersensitivity reaction upon rechallenge with trimethoprim–sulfamethoxazole in a patient with AIDS. *Drug Intel Clin Phar* 1988; **22**: 43–4.
12 Coopman SA, Stern RS. Cutaneous drug reactions in human immunodeficiency virus infection. *Arch Dermatol* 1991; **127**: 714–7.
13 Chanock SJ, Luginbuhl LM, McIntosh K, Lipshultz SE. Life-threatening reaction to trimethoprim/sulfamethoxazole in pediatric human immuno-deficiency virus infection. *Pediatrics* 1994; **93**: 519–21.
14 Roudier C, Caumes E, Rogeaux O *et al.* Adverse cutaneous reactions to trimethoprim–sulfamethoxazole in patients with the acquired immuno-deficiency syndrome and *Pneumocystis carinii* pneumonia. *Arch Dermatol* 1994; **130**: 1383–6.
15 Caumes E, Roudier C, Rogeaux O *et al.* Effect of corticosteroids on the incidence of adverse cutaneous reactions to trimethoprim–sulfamethoxazole during treatment of AIDS-associated *Pneumocystis carinii* pneumonia. *Clin Infect Dis* 1994; **18**: 319–23.
16 Kletzel M, Beck S, Elser J *et al.* Trimethoprim–sulfamethoxazole oral desensitization in hemophiliacs infected with human immunodeficiency virus with a history of hypersensitivity reactions. *Am J Dis Child* 1991; **145**: 1428–9.
17 Carr A, Penny R, Cooper DA. Efficacy and safety of rechallenge with low-dose trimethoprim–sulphamethoxazole in previously hypersensitive HIV-infected patients. *AIDS* 1993; **7**: 65–71.
18 Talbot MD. Fixed genital drug reaction. *Practitioner* 1980; **224**: 823–4.
19 Varsano I, Amir Y. Fixed drug eruption due to co-trimoxazole. *Dermatologica* 1989; **178**: 232.
20 Van Voorhees A, Stenn KS. Histological phases of Bactrim-induced fixed drug eruption. The report of one case. *Am J Dermatopathol* 1987; **9**: 528–32.
21 Bharija SC, Belhaj MS. Fixed drug eruption due to cotrimoxazole. *Australas J Dermatol* 1989; **30**: 43–4.
22 Lim JT, Chan HL. Fixed drug eruptions due to co-trimoxazole. *Ann Acad Med Singapore* 1992; **21**: 408–10.
23 Baird BJ, De Villez RL. Widespread bullous fixed drug eruption mimicking toxic epidermal necrolysis. *Int J Dermatol* 1988; **27**: 170–4.
24 MacDonald KJS, Green CM, Kenicer KJA. Pustular dermatosis induced by co-trimoxazole. *BMJ* 1986; **293**: 1279–80.
25 Walker DC, Cohen PR. Trimethoprim–sulfamethoxazole-associated acute febrile neutrophilic dermatosis: case report and review of drug-induced Sweet's syndrome. *J Am Acad Dermatol* 1996; **34**: 918–23.
26 Azinge NO, Garrick GA. Stevens–Johnson syndrome (erythema multiforme) following ingestion of trimethoprim–sulfamethoxazole on two separate occasions in the same person. A case report. *J Allergy Clin Immunol* 1978; **62**: 125–6.
27 Beck MH, Portnoy B. Severe erythema multiforme complicated by fatal gastrointestinal involvement following co-trimoxasole therapy. *Clin Exp Dermatol* 1979; **4**: 201–4.
28 Wåhlin A, Rosman N. Skin manifestations with vasculitis due to cotrimoxazole. *Lancet* 1976; **ii**: 1415.
29 Lawson DH, Henry DA, Jick H. Fatal agranulocytosis attributed to cotrimoxazole therapy. *BMJ* 1976; **ii**: 316.
30 Roholt NS, Lapiere JC, Traczyk T *et al.* A nonscarring sublamina densa bullous drug eruption. *J Am Acad Dermatol* 1995; **32**: 367–71.

Trimethoprim

Used alone, this substance causes fewer reactions than sulphonamides; fixed eruption has been proven [1–3] and was linear in one case [4]. Two patients experienced life-threatening immediate reactions and one patient developed generalized urticaria following oral trimethoprim–sulfamethoxazole; prick tests and

oral challenge tests were positive with trimethoprim but not sulfamethoxazole [5].

References

1 Kanwar AJ, Bharija SC, Singh M, Belhaj MS. Fixed drug eruption to trimethoprim. *Dermatologica* 1986; **172**: 230–1.
2 Hughes BR, Holt PJA, Marks R. Trimethoprim associated fixed drug eruption. *Br J Dermatol* 1987; **116**: 241–2.
3 Lim JT, Chan HL. Fixed drug eruptions due to co-trimoxazole. *Ann Acad Med Singapore* 1992; **21**: 408–10.
4 Özkaya-Bayazit E, Baykal C. Trimethoprim-induced linear fixed drug eruption. *Br J Dermatol* 1997; **137**: 1028–9.
5 Alonso MD, Marcos C, Davila I *et al.* Hypersensitivity to trimethoprim. *Allergy* 1992; **47**: 340–2.

Aminoglycosides

Gentamicin, tobramycin, streptomycin and kanamycin cross-react and are all potentially ototoxic and nephrotoxic. Exanthematic eruptions are common with streptomycin, developing in 5% or more of patients. Continued treatment may lead to generalized exfoliative dermatitis in a minority [1], but in a proportion of patients the rash subsides and treatment can be continued. Fever and eosinophilia may be associated with the reactions. Urticaria [2], maculopapular rashes, fever and eosinophilia are well recognized with this group of drugs. Skin necrosis following subcutaneous injection of aminoglycoside antibiotics (gentamicin, sisomicin and netilmicin) has been reported in elderly females with a history of thrombosis being treated with heparin anticoagulant therapy [3–5]. The reaction has also occurred following intramuscular sisomicin in a patient with defective fibrinolysis and abnormal neutrophil function [6]. A toxic erythema with generalized follicular pustulosis has been documented with streptomycin [7]. Deafness has rarely followed topical therapy with neomycin, including administration of aerosol preparations in the treatment of extensive burns. An anaphylactic reaction due to streptomycin occurred during *in vitro* fertilization immediately after embryo transfer [8].

References

1 Karp S, Bakris G, Cooney A *et al.* Exfoliative dermatitis secondary to tobramycin sulfate. *Cutis* 1991; **47**: 331–2.
2 Schretlen-Doherty JS, Troutman WG. Tobramycin-induced hypersensitivity reaction. *Ann Pharmacother* 1995; **29**: 704–6.
3 Taillandier J, Manigaud G, Fixy P, Dumont D. Nécroses cutanées induites par la gentamicine sous-cutanée. *Presse Med* 1984; **13**: 1574–5.
4 Duterque M, Hubert Asso AM, Corrard A. Lésions nécrotiques par injections sous cutanées de gentamicine et de sisomicine. *Ann Dermatol Vénéréol* 1985; **112**: 707–8.
5 Bernard P, Paris M, Cantanzano G, Bonnetblanc JM. Vascularite cutanée localisée induite par la Nétilmicine. *Presse Med* 1987; **16**: 915–6.
6 Grob JJ, Mege JL, Follano J *et al.* Skin necrosis after injection of aminoglycosides. Arthus reaction, local toxicity, thrombotic process or pathergy? *Dermatologica* 1990; **181**: 258–62.
7 Kushimoto H, Aoki T. Toxic erythema with generalized follicular pustules caused by streptomycin. *Arch Dermatol* 1981; **117**: 444–5.
8 Abeck D, Kuwert C, Segnini-Torres M *et al.* Streptomycin-induced anaphylactic reaction during in vitro fertilization (IVF). *Allergy* 1994; **49**: 388–9.

Macrolide antibiotics

Macrolides account for 10–15% of the worldwide oral antibiotic market, with severe adverse reactions being rare [1]. Gastrointestinal reactions occur in 15–20% of patients on erythromycins and in 5% or fewer patients treated with some recently developed macrolide derivatives that seldom or never induce endogenous release of motilin, such as roxithromycin, clarithromycin, dirithromycin, azithromycin and rikamycin. Except for troleandomycin and some erythromycins administered at high dose and for long periods of time, the hepatotoxic potential of macrolides is low. Transient deafness and allergic reactions to macrolide antibacterials are highly unusual and are more common with the erythromycins than with the recently developed 14-, 15- and 16-membered macrolides.

Azithromycin

This drug has caused toxic pustuloderma [2].

Clarithromycin

Fixed drug eruption is recorded [3].

Erythromycin

This is one of the most innocuous antibiotics in current use. Cholestasis caused by the estolate ester is the only potentially serious side effect. Hypersensitivity skin reactions are rare but when they occur skin tests may be positive [4,5]. Erythema multiforme, Stevens–Johnson syndrome, toxic pustuloderma [6], systemic contact dermatitis [7] and vasculitis have all been recorded.

Spiramycin

Rashes, usually transient erythema, may occur in up to 1% of cases. Spiramycin, given for toxoplasmosis in pregnancy, was associated in one case with an erythematous maculopapular pruritic eruption with eosinophilia and raised γ-glutamyl transpeptidase [8]. The drug has caused an allergic vasculitis [9].

References

1 Periti P, Mazzei T, Mini E, Novelli A. Adverse effects of macrolide antibacterials. *Drug Saf* 1993; **9**: 346–64.
2 Trevisi P, Patrizi A, Neri I, Farina P. Toxic pustuloderma associated with azithromycin. *Clin Exp Dermatol* 1994; **19**: 280–1.
3 Rosina P, Chieregato C, Schena D. Fixed drug eruption from clarithromycin. *Contact Dermatitis* 1998; **38**: 105.
4 Van Ketel WG. Immediate and delayed-type allergy to erythromycin. *Contact Dermatitis* 1976; **2**: 363–4.
5 Shirin H, Schapiro JM, Arber N *et al.* Erythromycin base-induced rash and liver function disturbances. *Ann Pharmacother* 1992; **26**: 1522–3.
6 Roujeau J-C, Bioulac-Sage P, Bourseau C *et al.* Acute generalized exanthematous pustulosis. Analysis of 63 cases. *Arch Dermatol* 1991; **127**: 1333–8.
7 Fernandez Redondo V, Casas L, Taboada M, Toribio J. Systemic contact dermatitis from erythromycin. *Contact Dermatitis* 1994; **30**: 311.
8 Ostlere LS, Langtry JAA, Staughton RCD. Allergy to spiramycin during prophylactic treatment of fetal toxoplasmosis. *BMJ* 1991; **302**: 970.
9 Galland MC, Rodor F, Jouglard J. Spiramycin allergic vasculitis: first report. *Therapie* 1987; **42**: 227–9.

Clindamycin and lincomycin

These antibiotics have become particularly associated with a potentially lethal pseudomembranous colitis due to superinfection with *Clostridium difficile* [1–3]. Vancomycin or metronidazole is the treatment of choice for this complication. Hypersensitivity skin reactions are rare with lincomycin but common with clinda-

mycin, occurring in up to 10% of patients [4]. Erythema multiforme and anaphylaxis are very rare [5].

References

1 Dantzig PI. The safety of long-term clindamycin therapy for acne. *Arch Dermatol* 1976; **112**: 53–4.
2 Tan SG, Cunliffe WJ. The unwanted effects of clindamycin in acne. *Br J Dermatol* 1976; **94**: 313–5.
3 Anonymous. Antibiotic-associated colitis: a progress report. *BMJ* 1978; **i**: 669–71.
4 Lammintausta K, Tokola R, Kalimo K. Cutaneous adverse reactions to clindamycin: results of skin tests and oral exposure. *Br J Dermatol* 2002; **146**: 643–8.
5 Lochmann O, Kohout P, Vymola F. Anaphylactic shock following the administration of clindamycin. *J Hyg Epid Microb Immunol* 1977; **21**: 441–7.

Miscellaneous antibiotics

Chloramphenicol

Although contact dermatitis from topical application is common, hypersensitivity skin reactions to oral therapy are rare. Macular, papular and urticarial eruptions are reported [1], as is acute generalized exanthematous pustulosis [2]. Pruritus may be prominent. Erythema multiforme and TEN [3] occur rarely. There is a risk of aplastic anaemia [4] and death has exceptionally followed the use of eye drops [5].

References

1 Unsdek HE, Curtiss WP, Neill EJ. Skin eruption due to chloramphenicol (Chloromycetin®). *Arch Dermatol Syphilol* 1951; **64**: 217.
2 Lee AY, Yoo SH. Chloramphenicol induced acute generalized exanthematous pustulosis proved by patch test and systemic provocation. *Acta Derm Venereol (Stockh)* 1999; **79**: 412–3.
3 Mathe P, Aubert L, Labouche F *et al.* Syndrome de Lyell. Etiologie médicamenteuse: rôle probable de chloramphénicol. *J Méd Bordeaux* 1965; **42**: 1367–76.
4 Hargraves MM, Mills SD, Heck FJ. Aplastic anemia associated with the administration of chloramphenicol. *JAMA* 1952; **149**: 1293–300.
5 Fraunfelder FT, Bagby GC. Ocular chloramphenicol and aplastic anemia. *N Engl J Med* 1983; **308**: 1536.

Fusidic acid

Topical use can lead to contact dermatitis but hypersensitivity reactions to oral or parenteral use are very rare; jaundice has accompanied intravenous use. Acanthosis nigricans-like lesions have been reported after local application [1].

Reference

1 Teknetzis A, Lefaki I, Joannides D, Minas A. Acanthosis nigricans-like lesions after local application of fusidic acid. *J Am Acad Dermatol* 1993; **28**: 501–2.

Metronidazole and tinidazole

Metronidazole. Pruritus, fixed eruptions and generalized erythema [1–4] are rare. A pityriasis rosea-like eruption has been described [5]. A reversible peripheral neuropathy may complicate prolonged therapy.

Tinidazole. A fixed eruption with cross-reactivity with metronidazole has been reported [6,7].

References

1 Naik RPC, Singh G. Fixed drug eruption due to metronidazole. *Dermatologica* 1977; **155**: 59–60.
2 Shelley WB, Shelley ED. Fixed drug eruption due to metronidazole. *Cutis* 1987; **39**: 393–4.
3 Gastaminza G, Anda M, Audicana MT *et al.* Fixed-drug eruption due to metronidazole with positive topical provocation. *Contact Dermatitis* 2001; **44**: 36.
4 Knowles S, Choudhury T, Shear NH. Metronidazole hypersensitivity. *Ann Pharmacother* 1994; **28**: 325–6.
5 Maize JC, Tomecki KJ. Pityriasis rosea-like drug eruption secondary to metronidazole. *Arch Dermatol* 1977; **113**: 1457–8.
6 Kanwar AJ, Sharma R, Rajagopalan M, Kaur S. Fixed drug eruption due to tinidazole with cross-reactivity with metronidazole. *Dermatologica* 1990; **181**: 277.
7 Mishra D, Mobashir M, Zaheer MS. Fixed drug eruption and cross-reactivity between tinidazole and metronidazole. *Int J Dermatol* 1990; **29**: 740.

Nitrofurantoin

Pruritus, morbilliform rashes and urticaria may be seen occasionally. Erythema multiforme, erythema nodosum [1], exfoliative dermatitis and an LE-like syndrome [2] are documented. Acute or chronic pulmonary reactions may accompany these skin manifestations, and may lead to pulmonary fibrosis [3]. Polyneuritis is a dose-dependent toxic reaction. Hepatitis, cholestatic jaundice and marrow suppression may occur rarely. Abnormal immunoelectrophoretic patterns may be induced [4].

References

1 Chisholm JC, Hepner M. Nitrofurantoin induced erythema nodosum. *J Natl Med Assoc* 1981; **73**: 59–61.
2 Selross O, Edgren J. Lupus-like syndrome associated with pulmonary reaction to nitrofurantoin. *Acta Med Scand* 1975; **197**: 125–9.
3 Rantala H, Kirvelä O, Anttolainen I. Nitrofurantoin lung in a child. *Lancet* 1979; **ii**: 799–80.
4 Teppo AM, Haltia K, Wager O. Immunoelectrophoretic 'tailing' of albumin line due to albumin–IgG antibody complexes: a side effect of nitrofurantoin treatment? *Scand J Immunol* 1976; **5**: 249–61.

Quinolones

These compounds are related to nalidixic acid; central nervous system toxicity, upper gastrointestinal tract reactions and phototoxicity have been recorded [1–7]. Cross-reactivity occurs [8]. Gastrointestinal side effects occur in up to 6% of patients. Hypersensitivity reactions involving the skin have been reported in 0.5–2% of patients, and in up to 2.4% of patients receiving cinoxacin; they most frequently manifest themselves as rash or pruritus. Delayed hypersensitivity reactions are recorded with ciprofloxacin, norfloxacin and moxifloxacin [9]. Fever, urticaria, angio-oedema and anaphylactoid reactions are rare. Anaphylactic or anaphylactoid reactions have been documented with cinoxacin [10], ciprofloxacin (1.2 per 100 000 prescriptions) [11,12] and pipemidic acid [13]. Fixed drug eruption due to pipemidic acid is recorded [14]. Norfloxacin [15] and ofloxacin [16] have caused a pustular eruption, and ciprofloxacin acute generalized exanthematous pustulosis [17]. Ciprofloxacin [18–20], pefloxacin, fleroxacin [21] and enoxacin [22] have been associated with photosensitivity. Photolocalized purpura has occurred with ciprofloxacin [20]. Pefloxacin and ofloxacin have caused photo-onycholysis [23], and sparfloxacin has been implicated in photosensitivity and a lichenoid tissue reaction [24]. Levofloxacin has caused a radiation recall reaction [25]. Hypersensitivity leukocytoclastic vasculitis has been reported with both ofloxacin and ciprofloxacin [26,27], and serum sickness with ciprofloxacin [28]. Intravenous administration of ciprofloxacin through small veins on the dorsa of the hands may

be associated with local reactions at the site of infusion [29]. Stevens–Johnson syndrome or TEN has been described with quinolones [30], including ciprofloxacin [31]. Ciprofloxacin has caused bullous pemphigoid [32].

Nalidixic acid. Cutaneous reactions are common, occurring in up to 5% of patients; various hypersensitivity reactions are seen, including exfoliative dermatitis. Phototoxicity is now well recognized [33–37]. A bullous photodermatitis may occur, usually on the hands or feet; chronic scarring and increased skin fragility may mimic porphyria cutanea tarda. Long-wave UV light is responsible [37]. An LE-like syndrome has been reported [38], as well as transient alopecia.

References

1 Christ W, Lehnert T, Ulbrich B. Specific toxicologic aspects of the quinolones. *Rev Infect Dis* 1988; **10** (Suppl. 1): S141–S146.
2 Wolfson JS, Hooper DC. Fluoroquinolone antimicrobial agents. *Clin Microbiol Rev* 1989; **2**: 378–424.
3 Hooper DC, Wolfson JS. Fluoroquinolone antimicrobial agents. *N Engl J Med* 1991; **324**: 384–94.
4 Sisca TS, Heel RC, Romankiewicz JA. Cinoxacin: a review of its pharmacological properties and therapeutic efficacy in the treatment of urinary tract infections. *Drugs* 1983; **25**: 544–69.
5 Campoli-Richards DM, Monck JP, Price A *et al.* Ciprofloxacin. A review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1988; **35**: 373–447.
6 Norrby SR, Lietman PS. Safety and tolerability of fluoroquinolones. *Drugs* 1993; **45** (Suppl. 3): 59–64.
7 Matsuno K, Kunihiro E, Yamatoya O *et al.* Surveillance of adverse reactions due to ciprofloxacin in Japan. *Drugs* 1995; **49** (Suppl. 2): 495–6.
8 Davila I, Diez ML, Quirce S *et al.* Cross-reactivity between quinolones. Report of three cases. *Allergy* 1993; **48**: 388–90.
9 Schmid DA, Depta JP, Pichler WJ. T cell-mediated hypersensitivity to quinolones: mechanisms and cross-reactivity. *Clin Exp Allergy* 2006; **36**: 59–69.
10 Stricker BHC, Slagboom G, Demaeseneer R *et al.* Anaphylactic reactions to cinoxacin. *BMJ* 1988; **297**: 1434–5.
11 Davis H, McGoodwin E, Reed TG. Anaphylactoid reactions reported after treatment with ciprofloxacin. *Ann Intern Med* 1989; **111**: 1041–3.
12 Deamer RL, Prichard JG, Loman GJ. Hypersensitivity and anaphylactoid reactions to ciprofloxacin. *Ann Pharmacother* 1992; **26**: 1081–4.
13 Gerber D. Anaphylaxis caused by pipemidic acid. *S Afr Med J* 1985; **67**: 999.
14 Miyagawa S, Yamashina Y, Hirota S, Shirai T. Fixed drug eruption due to pipemidic acid. *J Dermatol* 1991; **18**: 59–60.
15 Shelley ED, Shelley WB. The subcorneal pustular drug eruption: an example induced by norfloxacin. *Cutis* 1988; **42**: 24–7.
16 Tsuda S, Kato K, Karashima T *et al.* Toxic pustuloderma induced by ofloxacin. *Ann Dermatol Vénéréol* 1993; **73**: 382–4.
17 Hausermann P, Scherer K, Weber M, Bircher AJ. Ciprofloxacin-induced acute generalized exanthematous pustulosis mimicking bullous drug eruption confirmed by a positive patch test. *Dermatology* 2005; **211**: 277–80.
18 Nederost ST, Dijkstra JWE, Handel DW. Drug-induced photosensitivity reaction. *Arch Dermatol* 1989; **125**: 433–4.
19 Ferguson J, Johnson BE. Ciprofloxacin-induced photosensitivity: *in vitro* and *in vivo* studies. *Br J Dermatol* 1990; **123**: 9–20.
20 Urbina F, Barrios M, Sudy E. Photolocalized purpura during ciprofloxacin therapy. *Photodermatol Photo* 2006; **22**: 111–2.
21 Bowie WR, Willetts V, Jewesson PJ. Adverse reactions in a dose-ranging study with a new long-acting fluoroquinolone, fleroxacin. *Antimicrob Agents Chemother* 1989; **33**: 1778–82.
22 Izu R, Gardeazabal J, Gonzalez M *et al.* Enoxacin-induced photosensitivity: study of two cases. *Photodermatol Photoimmunol Photomed* 1992; **9**: 86–8.
23 Baran R, Brun P. Photo-onycholysis induced by the fluoroquinolones pefloxacine and ofloxacine. Report on 2 cases. *Dermatologica* 1986; **173**: 185–8.
24 Hamanaka H, Mizutani H, Shimizu M. Sparfloxacin-induced photosensitivity and the occurrence of a lichenoid tissue reaction after prolonged exposure. *J Am Acad Dermatol* 1998; **38**: 945–9.
25 Cho S, Breedlove JJ, Gunning ST. Radiation recall reaction induced by levofloxacin. *J Drugs Dermatol* 2008; **7**: 64–7.
26 Huminer C, Cohen JD, Majafla R, Dux S. Hypersensitivity vasculitis due to ofloxacin. *BMJ* 1989; **299**: 303.
27 Choc U, Rothschield BM, Laitman L. Ciprofloxacin-induced vasculitis. *N Engl J Med* 1989; **320**: 257–8.
28 Guharoy SR. Serum sickness secondary to ciprofloxacin use. *Vet Hum Toxicol* 1994; **36**: 540–1.
29 Thorsteinsson SB, Bergan T, Johannesson G *et al.* Tolerance of ciprofloxacin at injection site, systemic safety and effect on electroencephalogram. *Chemotherapy* 1987; **33**: 448–51.
30 Roujeau JC, Kelly JP, Naldi L *et al.* Medication use and the risk of Stevens–Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med* 1995; **333**: 1600–7.
31 Tham TCK, Allen G, Hayes D *et al.* Possible association between toxic epidermal necrolysis and ciprofloxacin. *Lancet* 1991; **338**: 522.
32 Kimyai-Asadi A, Usman A, Nousari HC. Ciprofloxacin-induced bullous pemphigoid. *J Am Acad Dermatol* 2000; **42**: 847.
33 Baes H. Photosensitivity caused by nalidixic acid. *Dermatologica* 1968; **136**: 61–4.
34 Birkett DA, Garretts M, Stevenson CJ. Phototoxic bullous eruptions due to nalidixic acid. *Br J Dermatol* 1969; **81**: 342–4.
35 Ramsay CA, Obreshkova E. Photosensitivity from nalidixic acid. *Br J Dermatol* 1974; **91**: 523–8.
36 Rosén K, Swanbeck G. Phototoxic reactions from some common drugs provoked by a high-intensity UVA lamp. *Acta Derm Venereol (Stockh)* 1982; **62**: 246–8.
37 Nederost ST, Dijkstra JWE, Handel DW. Drug-induced photosensitivity reaction. *Arch Dermatol* 1989; **125**: 433–4.
38 Rubinstein A. LE-like disease caused by nalidixic acid. *N Engl J Med* 1979; **301**: 1288.

Synergistins

An eczema-like drug eruption is recorded after oral antibiotic synergistins, pristinamycin and virginiamycin, following contact sensitization with topical virginiamycin [1]. Pristinamycin is associated with acute generalized exanthematous pustulosis (AGEP) [2,3].

References

1 Michel M, Dompmartin A, Szczurko C *et al.* Eczematous-like drug eruption induced by synergistins. *Contact Dermatitis* 1996; **34**: 86–7.
2 Saissi EH, Beau-Salinas F, Jonville-Béra AP *et al.* Drugs associated with acute generalized exanthematic pustulosis. *Ann Dermatol Venereol* 2003; **130**: 612–8.
3 Sidoroff A, Dunant A, Viboud C *et al.* Risk factors for acute generalized exanthematous pustulosis (AGEP) – results of a multinational case-control study (EuroSCAR). *Br J Dermatol* 2007; **157**: 989–96.

Vancomycin

Allergic skin reactions are not uncommon, occurring in up to 5% of patients. Rapid intravenous infusion of vancomycin can cause a histamine-induced anaphylactoid reaction characterized by flushing, a maculopapular eruption of the neck, face, trunk and extremities (so-called 'red man syndrome'), prolonged hypotension and, in rare cases, cardiac arrest [1–3]. Desensitization has been successfully achieved in patients with vancomycin hypersensitivity [4–6]. TEN has occurred [7]. Vancomycin has been reported to have induced linear IgA bullous dermatosis [8–12], which may mimic TEN [13].

References
1 Pau AK, Khakoo R. Red-neck syndrome with slow infusion of vancomycin. *N Engl J Med* 1985; **313**: 756–7.
2 Valero R, Gomar C, Fita G *et al.* Adverse reactions to vancomycin prophylaxis in cardiac surgery. *J Cardiothor Vasc Anesth* 1991; **5**: 574–6.
3 Killian AD, Sahai JV, Memish ZA. Red man syndrome after oral vancomycin. *Ann Intern Med* 1991; **115**: 410–31.
4 Lin RY. Desensitization in the management of vancomycin hypersensitivity. *Arch Intern Med* 1990; **150**: 2197–8.
5 Anne S, Middleton E Jr, Reisman RE. Vancomycin anaphylaxis and successful desensitization. *Ann Allergy* 1994; **73**: 402–4.
6 Wong JT, Ripple RE, MacLean JA *et al.* Vancomycin hypersensitivity: synergism with narcotics and 'desensitization' by a rapid continuous intravenous protocol. *J Allergy Clin Immunol* 1994; **94**: 189–94.
7 Vidal C, Gonzalez Quintela A, Fuente R. Toxic epidermal necrolysis due to vancomycin. *Ann Allergy* 1992; **68**: 345–7.
8 Baden LA, Apovian C, Imber MJ, Dover JS. Vancomycin-induced linear IgA bullous dermatosis. *Arch Dermatol* 1988; **124**: 1186–8.
9 Carpenter S, Berg D, Sidhu-Malik N *et al.* Vancomycin-associated linear IgA dermatosis. A report of three cases. *J Am Acad Dermatol* 1992; **26**: 45–8.
10 Piketty C, Meeus F, Nochy D *et al.* Linear IgA dermatosis related to vancomycin. *Br J Dermatol* 1994; **130**: 130–1.
11 Whitworth JM, Thomas I, Peltz S *et al.* Vancomycin-induced linear IgA bullous dermatosis (LABD). *J Am Acad Dermatol* 1996; **34**: 890–1.
12 Palmer RA, Ogg G, Allen J *et al.* Vancomycin-induced linear IgA disease with autoantibodies to BP180 and LAD285. *Br J Dermatol* 2001; **145**: 816–20.
13 Dellavalle RP, Burch HM, Tyal S *et al.* Vancomycin-associated linear IgA bullous dermatosis mimicking toxic epidermal necrolysis. *J Am Acad Dermatol* 2003; **48**: S56–S57.

Topical antibiotics

The side effects of topical antibiotics have been reviewed [1]. Allergic contact dermatitis is rare with topical clindamycin, erythromycin and tetracycline, polymyxin B, gentamicin and mupirocin, but is more frequent with neomycin.

Bacitracin

Anaphylaxis due to bacitracin allergy has followed topical application of this antibiotic [2–5]. The patients had had multiple prior exposures and previous local reactions of pruritus, urticaria or possible allergic contact dermatitis. Two patients with anaphylactic reactions to Polyfax ointment, containing polymyxin B and bacitracin, have been reported; one had previously documented positive patch tests to Polyfax, and the other had clinical intolerance to the preparation [5]. Another patient developed anaphylaxis to a similar proprietary mixture (Polysporin) [6]. Intracutaneous injection of bacitracin in sensitive individuals induces histamine release with large weal-and-flare reactions [7].

Chloramphenicol

Urticaria and angio-oedema have been described with topical use [8]. Fatal aplastic anaemia has followed the use of eye drops containing this antibiotic [9].

Sulphonamides

Erythema multiforme and Stevens–Johnson syndrome have been reported from topical preparations [10,11].

References
1 Hirschmann JV. Topical antibiotics in dermatology. *Arch Dermatol* 1988; **124**: 1691–700.
2 Roupe G, Strannegård Ö. Anaphylactic shock elicited by topical administration of bacitracin. *Arch Dermatol* 1969; **100**: 450–2.
3 Shechter JF, Wilkinson RD, Del Carpio J. Anaphylaxis following the use of bacitracin ointment: report of a case and review of the literature. *Arch Dermatol* 1984; **120**: 909–11.
4 Katz BE, Fisher AA. Bacitracin: a unique topical antibiotic sensitiser. *J Am Acad Dermatol* 1987; **17**: 1016–24.
5 Eedy DJ, McMillan JC, Bingham EA. Anaphylactic reactions to topical antibiotic combinations. *Postgrad Med J* 1990; **66**: 858–9.
6 Knowles SR, Shear NH. Anaphylaxis from bacitracin and polymyxin B (Polysporin) ointment. *Int J Dermatol* 1995; **34**: 572–3.
7 Bjorkner B, Moller H. Bacitracin: a cutaneous allergen and histamine releaser. *Acta Derm Venereol (Stockh)* 1973; **53**: 487–91.
8 Schewach-Millet M, Shapiro D. Urticaria and angioedema due to topically applied chloramphenicol ointment. *Arch Dermatol* 1985; **121**: 587.
9 Fraunfelder FT, Bagby GC. Ocular chloramphenicol and aplastic anemia. *N Engl J Med* 1983; **308**: 1536.
10 Genvert GI, Cohen EJ, Donnenfeld ED, Blecher MH. Erythema multiforme after use of topical sulfacetamide. *Am J Ophthalmol* 1985; **99**: 465–8.
11 Gottschalk HR, Stone OJ. Stevens–Johnson syndrome from ophthalmic sulphonamide. *Arch Dermatol* 1976; **112**: 513–4.

Antituberculous drugs

Side effects from first-line antituberculous medications (isoniazid, rifampin, pyrazinamide, ethambutol and streptomycin) are common, and include hepatitis, cutaneous reactions, gastrointestinal intolerance, haematological reactions and renal failure [1]. Severe cutaneous reactions (such as Stevens–Johnson syndrome and TEN) and multiple drug reactions to antituberculous drugs (including thioacetazone, streptomycin and isoniazid) occur more often in HIV-positive patients [2–6]. The World Health Organization has advised against the use of thioacetazone in tuberculosis patients with known, or suspected, HIV infection in view of the severe cutaneous hypersensitivity [4–6]. The following drugs are reported to cause contact dermatitis: isoniazid, rifampicin, ethambutol, *p*-aminosalicylic acid, streptomycin and kanamycin [7]. The incidence of other reactions to individual drugs is difficult to assess because several drugs are usually used in combination.

Cycloserine

A lichenoid drug eruption with positive patch tests and resolution 4 months after withdrawal has been reported [8].

Ethambutol

Hypersensitivity reactions are very rare. Side effects are largely confined to visual disturbances, with loss of acuity, colour blindness and restricted visual fields; these are usually reversible if the drug is stopped promptly. Patients should have ophthalmic assessments prior to and during therapy. Lichenoid reactions occur and may be restricted to light-exposed sites [9,10].

Ethionamide

Eczema chiefly affecting the forehead, acneiform eruptions, butterfly eruptions on the face, stomatitis, alopecia and purpura have been reported.

Isoniazid

Allergic skin reactions occur in fewer than 1% of patients. An acneiform eruption, usually occurring in slow inactivators of the drug, is well recognized [11,12]. Urticaria, purpura and an LE-like

syndrome [13,14] have been reported, as have photosensitive lichenoid eruptions [15]. Rarely, a pellagra-like syndrome has been induced in malnourished patients, due to metabolic antagonism of nicotinic acid with resultant pyridoxine deficiency [11,16]. Exfoliative dermatitis [17] and Stevens–Johnson syndrome [3] have been reported.

Pyrazinamide

Hepatitis, arthralgia, flushing, photosensitivity, lichenoid photodermatitis, maculopapular rashes, urticaria and pellagra are recorded [18].

Rifampicin

Cutaneous hypersensitivity reactions are very uncommon but are recorded [19]. There have been isolated reports of LE [20], erythema nodosum leprosum-like eruption in borderline lepromatous leprosy [21], exacerbation of bullous erythema multiforme, TEN [22] and pemphigus [23,24]; existing pemphigus may also be exacerbated [25]. Altered liver function, usually transient, and thrombocytopenic purpura may occur. Rifampicin has precipitated porphyria cutanea tarda [26]. It induces liver enzymes and may thus reduce the effectiveness of a number of drugs, including oral contraceptives.

Streptomycin

See Aminoglycosides section on p. 75.58.

Thioacetazone

Severe cutaneous hypersensitivity reactions have been reported, including maculopapular rashes (which progress to mucosal involvement with constitutional symptoms), Stevens–Johnson syndrome and TEN, especially in HIV-seropositive patients [3,4,6,27,28]. Cutaneous hypersensitivity reactions have been reported in 20% of HIV-seropositive patients compared with 1% of HIV-seronegative patients who receive the drug as part of treatment for tuberculosis [26]. Figurate erythematous eruptions resembling erythema annulare centrifugum may occur [29].

References

1 Forget EJ, Menzies D. Adverse reactions to first-line antituberculosis drugs. *Expert Opin Drug Saf* 2006; **5**: 231–49.
2 Pozniak AL, MacLeod GA, Mahari M *et al.* The influence of HIV status on single and multiple drug reactions to antituberculous therapy in Africa. *AIDS* 1992; **6**: 809–14.
3 Dukes CS, Sugarman J, Cegielski JP *et al.* Severe cutaneous hypersensitivity reactions during treatment of tuberculosis in patients with HIV infection in Tanzania. *Trop Geogr Med* 1992; **44**: 308–11.
4 Chintu C, Luo C, Bhat G *et al.* Cutaneous hypersensitivity reactions due to thiacetazone in the treatment of tuberculosis in Zambian children infected with HIV-I. *Arch Dis Child* 1993; **68**: 665–8.
5 Nunn P, Porter J, Winstanley P. Thiacetazone: avoid like poison or use with care? *Trans R Soc Trop Med Hyg* 1993; **87**: 578–82.
6 Kelly P, Buve A, Foster SD *et al.* Cutaneous reactions to thiacetazone in Zambia: implications for tuberculosis treatment strategies. *Trans R Soc Trop Med Hyg* 1994; **88**: 113–5.
7 Holdiness MR. Contact dermatitis to antituberculous drugs. *Contact Dermatitis* 1986; **15**: 282–8.
8 Shim JH, Kim TY, Kim HO, Kim CW. Cycloserine-induced lichenoid drug eruption. *Dermatology* 1995; **191**: 142–4.
9 Frentz G, Wadskov S, Kssis V. Ethambutol-induced lichenoid eruption. *Acta Derm Venereol (Stockh)* 1981; **61**: 89–91.
10 Grossman ME, Warren K, Mady A, Satra KH. Lichenoid eruption associated with ethambutol. *J Am Acad Dermatol* 1995; **33**: 675–6.
11 Cohen LK, George W, Smith R. Isoniazid-induced acne and pellagra. Occurrence in slow acetylators of isoniazid. *Arch Dermatol* 1974; **109**: 377–81.
12 Oliwiecki S, Burton JL. Severe acne due to isoniazid. *Clin Exp Dermatol* 1988; **13**: 283–4.
13 Grunwald M, David M, Feuerman EJ. Appearance of lupus erythematosus in a patient with lichen planus treated by isoniazid. *Dermatologica* 1982; **165**: 172–7.
14 Sim E, Gill EW, Sim RB. Drugs that induce systemic lupus erythematosus inhibit complement C4. *Lancet* 1984; **ii**: 422–4.
15 Lee AY, Jung SY. Two patients with isoniazid-induced photosensitive lichenoid eruptions confirmed by photopatch test. *Photodermatol Photoimmunol Photomed* 1998; **14**: 77–8.
16 Schmutz JL, Cuny JF, Trechot P *et al.* Les érythemes pellagroïdes médicamenteux. Une observation d'érytheme pellagroïde secondaire a l'isoniazide. *Ann Dermatol Vénéréol* 1987; **114**: 569–76.
17 Rosin MA, King LE Jr. Isoniazid-induced exfoliative dermatitis. *South Med J* 1982; **75**: 81.
18 Choonhakarn C, Janma J. Pyrazinamide-induced lichenoid photodermatitis. *J Am Acad Dermatol* 1999; **40**: 645–6.
19 Buergin S, Scherer K, Häusermann P, Bircher AJ. Immediate hypersensitivity to rifampicin in 3 patients: diagnostic procedures and induction of clinical tolerance. *Int Arch Allergy Immunol* 2006; **140**: 20–6.
20 Patel GK, Anstey AV. Rifampicin-induced lupus erythematosus. *Clin Exp Dermatol* 2001; **26**: 260–2.
21 Karthikeyan K, Thappa DM, Kadhiravan T. Rifampicin-induced erythema nodosum leprosum-like eruption in borderline lepromatous leprosy. *Ind J Leprosy* 2001; **73**: 167–9.
22 Okano M, Kitano Y, Igarashi T. Toxic epidermal necrolysis due to rifampicin. *J Am Acad Dermatol* 1987; **17**: 303–4.
23 Gange RW, Rhodes EL, Edwards CO, Powell MEA. Pemphigus induced by rifampicin. *Br J Dermatol* 1976; **95**: 445–8.
24 Lee CW, Lim JH, Kang HJ. Pemphigus foliaceus induced by rifampicin. *Br J Dermatol* 1984; **111**: 619–22.
25 Miyagawa S, Yamanashi Y, Okuchi T *et al.* Exacerbation of pemphigus by rifampicin. *Br J Dermatol* 1986; **114**: 729–32.
26 Millar JW. Rifampicin-induced porphyria cutanea tarda. *Br J Dis Chest* 1980; **74**: 405–8.
27 Fegan D, Glennon J. Cutaneous sensitivity to thiacetazone. *Lancet* 1991; **337**: 1036.
28 Nunn P, Kibuga D, Gathua S *et al.* Cutaneous hypersensitivity reactions due to thiacetazone in HIV-1 seropositive patients treated for tuberculosis. *Lancet* 1991; **337**: 627–30.
29 Ramesh V. Eruption resembling erythema annulare centrifugum. *Australas J Dermatol* 1987; **28**: 44.

Antileprotic drugs

Clofazimine

This drug regularly causes a reversible, dose-dependent, brown-orange pigmentation of the skin [1–3]. Biopsy specimens from two lepromatous leprosy patients on long-term clofazimine therapy revealed ceroid-lipofuscin pigment as well as clofazimine inside macrophage phagolysosomes [3]. Reddish-blue pigmentation occurred in scarred areas of LE in one patient [4]. Xeroderma, pruritus, phototoxicity, acne and non-specific rashes are described [2]. Gastrointestinal symptoms may occur early due to direct irritation of the gut and are quickly reversible; ulcerative enteritis may occur after 9–14 months of treatment. After prolonged high-dose therapy, persistent diarrhoea, abdominal pain and weight loss, associated with deposition of crystalline clofazimine in the small intestinal submucosa and mesenteric lymph nodes, may occur [5,6]. Splenic infarction has been associated with this syndrome [7,8].

References

1 Thomsen K, Rothenborg HW. Clofazimine in the treatment of pyoderma gangrenosum. *Arch Dermatol* 1979; **115**: 851–2.
2 Yawalker SJ, Vischer W. Lamprene (clofazimine) in leprosy. Basic information. *Lepr Rev* 1979; **50**: 135–44.
3 Job CK, Yoder L, Jacobson RR, Hastings RC. Skin pigmentation from clofazimine therapy in leprosy patients: a reappraisal. *J Am Acad Dermatol* 1990; **23**: 236–41.
4 Kossard S, Doherty E, McColl I, Ryman W. Autofluorescence of clofazimine in discoid lupus erythematosus. *J Am Acad Dermatol* 1987; **17**: 867–71.
5 Harvey RF, Harman RRM, Black C *et al.* Abdominal pain and malabsorption due to tissue deposition of clofazimine (Lamprene) crystals. *Br J Dermatol* 1977; **97** (Suppl. 15): 19.
6 Venencie PY, Cortez A, Orieux G *et al.* Clofazimine enteropathy. *J Am Acad Dermatol* 1986; **15**: 290–1.
7 Jopling WAH. Complications of treatment with clofazimine (Lamprene: B.663). *Lepr Rev* 1976; **47**: 1–3.
8 McDougal AC, Horsfall WR, Hede JE, Chaplin AJ. Splenic infarction and tissue accumulation of crystals associated with the use of clofazimine (Lamprene: B.663) in the treatment of pyoderma gangrenosum. *Br J Dermatol* 1980; **102**: 227–30.

Dapsone

Reactions have been reviewed [1]. Fixed eruptions occur in 3% of West Africans being treated for leprosy. Erythema multiforme [2] and exfoliative dermatitis [3] have been described during leprosy treatment. Another uncommon side effect is a hypersensitivity reaction (dapsone or sulphone syndrome) within 2 to 7 weeks (mean 29 days), with fever, a widespread erythematous eruption studded with pustules, exfoliative dermatitis, hepatitis, lymphadenopathy and anaemia; it may progress to Stevens–Johnson syndrome [4–11]. In Vanuatu, 24% of 37 patients treated over 4 years with daily dapsone 100 mg, clofazimine, and monthly rifampicin and clofazimine for leprosy developed the dapsone syndrome, with a fatality rate of 11% [12]. The increase in reactions may have related to a high starting dose of dapsone, possibly enhanced by the combination with clofazimine and rifampicin and by a genetic susceptibility of the Melanesian population.

Red cell life is always shortened, but clinical haemolytic anaemia is uncommon; patients with low red cell glucose-6-phosphate dehydrogenase levels [13] and those who are slow acetylators [14] are at a special risk of developing this complication. Methaemoglobinaemia and Heinz body formation are seen [15]. Agranulocytosis is rare but well recognized and may occur in the first weeks of therapy [16–19]. For patients receiving the drug for dermatitis herpetiformis, this side effect occurred at a median dosage of 100 mg/day and a median duration of therapy of 7 weeks [17]. The total risk was one case per 3000 patient-years of exposure to the drug; however, agranulocytosis was estimated to occur in 1 in 240 to 1 in 425 new patients receiving dapsone for dermatitis herpetiformis [17]. Agranulocytosis occurred in approximately 1 in 10 000 to 1 in 20 000 US soldiers receiving dapsone for malarial prophylaxis [19]. Elderly patients do not tolerate dapsone well, and sulfapyridine or sulfamethoxypyridazine (the latter obtainable on a named-patient basis from Lederle Laboratories) is to be preferred for IgA-related diseases. A fatal haematological reaction developed in a Burmese boy during induction of treatment for lepromatous leprosy [20].

Severe but usually reversible hypoalbuminaemia due to failure of albumin production [21,22] or an atypical nephrotic syndrome may occur. Rarely, dapsone causes a peripheral neuropathy, usually purely motor or mixed sensorimotor and usually recovering within a year [23–26], and optic atrophy [26]. Permanent retinal damage has followed overdosage [27]. Headaches [28], and occasionally a psychosis [29], may be precipitated.

References

1 Zhu YI, Stiller MJ. Dapsone and sulfones in dermatology. Overview and update. *J Am Acad Dermatol* 2001; **45**: 420–34.
2 Dutta RK. Erythema multiforme bullosum due to dapsone. *Lepr India* 1980; **52**: 306–9.
3 Browne SG. Antileprosy drugs. *BMJ* 1971; **iv**: 558–9.
4 Tomecki KJ, Catalano CJ. Dapsone hypersensitivity: the sulfone syndrome revisited. *Arch Dermatol* 1981; **117**: 38–9.
5 Mohle-Boetani J, Akula SK, Holodniy M *et al.* The sulfone syndrome in a patient receiving dapsone prophylaxis for *Pneumocystis carinii* pneumonia. *West J Med* 1992; **156**: 303–6.
6 Barnard GF, Scharf MJ, Dagher RK. Sulfone syndrome in a patient receiving steroids for pemphigus. *Am J Gastroenterol* 1994; **89**: 2057–9.
7 Saito S, Ikezawa Z, Miyamoto H, Kim S. A case of the 'dapsone syndrome'. *Clin Exp Dermatol* 1994; **19**: 152–6.
8 Chalasani P, Baffoe-Bonnie H, Jurado RL. Dapsone therapy causing sulfone syndrome and lethal hepatic failure in an HIV-infected patient. *South Med J* 1994; **87**: 145–6.
9 Bocquet H, Bourgault-Villada I, Delfau-Larue MH *et al.* Syndrome d'hypersensibilité à la dapsone. Clone T circulant transitoire. *Ann Dermatol Vénéréol* 1995; **122**: 514–6.
10 Prussick R, Shear NH. Dapsone hypersensitivity syndrome. *J Am Acad Dermatol* 1996; **35**: 346–9.
11 Agrawal S, Agarwalla A. Dapsone hypersensitivity syndrome: a clinico-epidemiological review. *J Dermatol* 2005; **32**: 883–9.
12 Reeve PA, Ala J, Hall JJ. Dapsone syndrome in Vanuatu: a high incidence during multidrug treatment (MDT) of leprosy. *J Trop Med Hyg* 1992; **95**: 266–70.
13 Beutler E. Glucose-6-phosphate dehydrogenase deficiency. *Lancet* 1991; **324**: 169–74.
14 Ellard GA, Gammon PT, Savin LA, Tan RSH. Dapsone acetylation in dermatitis herpetiformis. *Br J Dermatol* 1974; **90**: 441–4.
15 Wagner A, Marosi C, Binder M *et al.* Fatal poisoning due to dapsone in a patient with grossly elevated methaemoglobin levels. *Br J Dermatol* 1995; **133**: 816–7.
16 Potter MN, Yates P, Slade R, Kennedy CTC. Agranulocytosis caused by dapsone therapy for granuloma annulare. *J Am Acad Dermatol* 1989; **20**: 87–8.
17 Hörnstein P, Keisu M, Wiholm B-E. The incidence of agranulocytosis during treatment of dermatitis herpetiformis with dapsone as reported in Sweden, 1972 through 1988. *Arch Dermatol* 1990; **126**: 919–22.
18 Cockburn EM, Wood SM, Waller PC, Bleehen SS. Dapsone-induced agranulocytosis: spontaneous reporting data. *Br J Dermatol* 1993; **128**: 702–3.
19 Ognibene AJ. Agranulocytosis due to dapsone. *Ann Intern Med* 1970; **75**: 521–4.
20 Frey HM, Gershon AA, Borkowsky W, Bullock WE. Fatal reaction to dapsone during treatment of leprosy. *Ann Intern Med* 1981; **94**: 777–9.
21 Kingham JG, Swain P, Swarbrick ET *et al.* Dapsone and severe hypoalbuminaemia: a report of two cases. *Lancet* 1979; **ii**: 662–4.
22 Cowan RE, Wright JT. Dapsone and severe hypoalbuminaemia in dermatitis herpetiformis. *Br J Dermatol* 1981; **104**: 201–4.
23 Waldinger TP, Siegle RJ, Weber W *et al.* Dapsone-induced peripheral neuropathy. Case report and review. *Arch Dermatol* 1984; **120**: 356–9.
24 Ahrens EM, Meckler RJ, Callen JP. Dapsone-induced peripheral neuropathy. *Int J Dermatol* 1986; **25**: 314–6.
25 Rhodes LE, Coleman MD, Lewis-Jones MS. Dapsone-induced motor peripheral neuropathy in pemphigus foliaceus. *Clin Exp Dermatol* 1995; **20**: 155–6.
26 Homeida M, Babikr A, Daneshmend TK. Dapsone-induced optic atrophy and motor neuropathy. *BMJ* 1980; **281**: 1180.
27 Kenner DJ, Holt K, Agnello R, Chester GH. Permanent retinal damage following massive dapsone overdose. *Br J Ophthalmol* 1980; **64**: 741–4.
28 Guillet G, Krausz I, Guillet MH, Carlhant D. Survenue de cephalées en cours de traitement par dapsone. *Ann Dermatol Vénéréol* 1992; **119**: 46.
29 Fine J-D, Katz SI, Donahue MJ, Hendricks AA. Psychiatric reaction to dapsone and sulfapyridine. *J Am Acad Dermatol* 1983; **9**: 274–5.

Thalidomide

Teratogenicity (phocomelia), gastric intolerance, drowsiness, neuropsychiatric upset and a sensory peripheral neuropathy developing after several months have been reported [1]. Minor to moderate skin eruptions occur in up to 46% of patients taking thalidomide, including morbilliform, seborrhoeic, maculopapular and non-specific rashes; severe skin reactions such as exfoliative erythroderma, erythema multiforme and TEN are rare [2]. A dermatitis associated with eosinophilia develops in a few cases of erythema nodosum leprosum treated with thalidomide over several years [3]. Hypersensitivity reactions characterized by fever, tachycardia and an extensive erythematous macular eruption developed on rechallenge in a number of patients with HIV infection treated with thalidomide for severe aphthous oropharyngeal ulceration [4]. In addition, brittle fingernails, exfoliative erythroderma [5], toxic pustuloderma [6], face or limb oedema, pruritus, red palms and xerostomia have been described [7]. Deep vein thrombosis is documented [8].

References

1 Revuz J. Actualité du thalidomide. *Ann Dermatol Vénéréol* 1990; **117**: 313–21.
2 Hall VC, El-Azhary RA, Bouwhuis S, Rajkumar SV. Dermatologic side effects of thalidomide in patients with multiple myeloma. *J Am Acad Dermatol* 2003; **48**: 548–52.
3 Waters MFR. An internally controlled double blind trial of thalidomide in severe erythema nodosum leprosum. *Lepr Rev* 1971; **42**: 26–42.
4 Williams I, Weller IVD, Malin A *et al.* Thalidomide hypersensitivity in AIDS. *Lancet* 1991; **337**: 436–7.
5 Bielsa I, Teixido J, Ribera M, Ferrandiz C. Erythroderma due to thalidomide: report of two cases. *Dermatology* 1994; **189**: 179–81.
6 Darvay A, Basarab T, Russell-Jones R. Thalidomide-induced toxic pustuloderma. *Clin Exp Dermatol* 1997; **22**: 297–9.
7 Tseng S, Pak G, Washenik K *et al.* Rediscovering thalidomide: a review of its mechanism of action, side effects, and potential uses. *J Am Acad Dermatol* 1996; **35**: 969–79.
8 Sharma NL, Sharma VC, Mahajan VK *et al*. Thalidomide: an experience in therapeutic outcome and adverse reactions. *J Dermatolog Treat* 2007; **18**: 335–40.

Antifungal drugs

Dermatological aspects of antifungal drugs have been reviewed [1–3]. Rashes occur as follows.

- Itraconazole: in 1.1% of cases, with pruritus in 0.7%; the drug is teratogenic.
- Fluconazole: in 1.8% of cases; exfoliative dermatitis is recorded.
- Terbinafine: in 2.7% of cases, including erythema, urticaria, eczema, pruritus, and isolated Stevens–Johnson syndrome and TEN [3].

Relevant interactions between itraconazole, fluconazole and terbinafine have been discussed [4].

References

1 Lesher JL, Smith JG Jr. Antifungal agents in dermatology. *J Am Acad Dermatol* 1987; **17**: 383–94.
2 Gupta AK, Sauder DN, Shear NH. Antifungal agents: an overview. Part I. *J Am Acad Dermatol* 1994; **30**: 677–98.
3 Gupta AK, Sauder DN, Shear NH. Antifungal agents: an overview. Part II. *J Am Acad Dermatol* 1994; **30**: 911–33.
4 Gupta AK, Katz HI, Shear NH. Drug interactions with itraconazole, fluconazole, and terbinafine and their management. *J Am Acad Dermatol* 1999; **41**: 237–49.

Amphotericin

Skin reactions are rare. The 'grey syndrome', characterized by ashen colour, acral cyanosis and prostration, may occur as an immediate reaction to infusion. Allergic reactions occur to liposomal amphotericin [1,2].

Fluconazole

Angio-oedema has occurred [3], as has fixed drug eruption [4]. An anaphylactic reaction developed in a patient who had previously received ketoconazole and metronidazole, suggesting cross-sensitization [5], and Stevens–Johnson syndrome has been reported in a patient with AIDS [6]. Thrombocytopenia is described [7].

Flucytosine

Transitory macular and urticarial rashes have been seen. A toxic erythema occurred in a patient [8]. Anaphylaxis has been reported in a patient with AIDS [9]. Bone marrow depression can occur.

Itraconazole

Fixed drug eruption [10], serum sickness [11], and acute generalized exanthematous pustulosis [12] are recorded.

References

1 Tollemar J, Ringden O, Andersson S *et al.* Randomized double-blind study of liposomal amphotericin B (AmBisome) prophylaxis of invasive fungal infections in bone marrow transplant recipients. *Bone Marrow Transplant* 1993; **12**: 577–82.
2 Ringden O, Andstrom E, Remberger M *et al.* Allergic reactions and other rare side-effects of liposomal amphotericin. *Lancet* 1994; **344**: 1156–7.
3 Abbott M, Hughes DL, Patel R, Kinghorn GR. Angio-oedema after fluconazole. *Lancet* 1991; **338**: 633.
4 Heikkila H, Timonen K, Stubb S. Fixed drug eruption due to fluconazole. *J Am Acad Dermatol* 2000; **42**: 883–4.
5 Neuhaus G, Pavic N, Pletscher M. Anaphylactic reaction after oral fluconazole. *BMJ* 1991; **302**: 1341.
6 Gussenhoven MJE, Haak A, Peereboom-Wynia JDR, van't Wout JW. Stevens–Johnson syndrome after fluconazole. *Lancet* 1991; **338**: 120.
7 Mercurio MG, Elewski BE. Thrombocytopenia caused by fluconazole therapy. *J Am Acad Dermatol* 1996; **32**: 525–6.
8 Thyss A, Viens P, Ticchioni M *et al.* Toxicodermie au cours d'un traitement par 5 fluorocytosine. *Ann Dermatol Vénéréol* 1987; **114**: 1131–2.
9 Kotani S, Hirose S, Niiya K *et al.* Anaphylaxis to flucytosine in a patient with AIDS. *JAMA* 1988; **260**: 3275–6.
10 Gupta R, Thami GP. Fixed drug eruption caused by itraconazole: reactivity and cross reactivity. *J Am Acad Dermatol* 2008; **58**: 521–2.
11 Park H, Knowles S, Shear NH. Serum sickness-like reaction to itraconazole. *Ann Pharmacother* 1998; **32**: 1249.
12 Park YM, Kim JW, Kim CW. Acute generalised exanthematous pustulosis induced by itraconazole. *J Am Acad Dermatol* 1997; **36**: 794–7.

Griseofulvin

Reactions to griseofulvin are uncommon and usually mild; headaches and gastrointestinal disturbances are the most frequent. Morbilliform, erythematous or, rarely, haemorrhagic eruptions are occasionally seen [1,2]. Photodermatitis [3,4] with sensitivity to wavelengths above 320 nm is by no means rare; clinically, the features are mainly eczematous, although pellagra-like changes may be seen [4]. The reaction is thought to be photoallergic and photopatch tests are positive in some cases; there may be photo cross-reactivity with penicillin [4]. Histology may be non-specific; direct immunofluorescence showed immunoglobulin and

complement at the dermal–epidermal junction and around papillary blood vessels in one series [4]. Urticaria and a fixed drug eruption [5,6], cold urticaria [7], severe angio-oedema [8], erythema multiforme [9,10], serum sickness [11], exfoliative dermatitis [12] and TEN [13,14] are recorded. Exacerbation of LE has been reported [15–19], with fatality in one case [18]. Patients with anti-SSA/Ro and SSB/La antibodies may be at increased risk of developing a drug eruption [19,20]. Temporary granulocytopenia has been reported, and proteinuria may occur. Hepatitis and a morbilliform eruption are recorded [21]. Griseofulvin may interfere with the action of anticoagulants and the contraceptive pill [22], and should be avoided in pregnancy as potentially teratogenic; men should avoid conception for 6 months after taking the drug.

References

1 Faergemann J, Maibach H. Griseofulvin and ketoconazole in dermatology. *Semin Dermatol* 1983; **2**: 262–9.
2 Von Pöhler H, Michalski H. Allergisches Exanthem nach Griseofulvin. *Dermatol Monatsschr* 1972; **58**: 383–90.
3 Jarratt M. Drug photosensitization. *Int J Dermatol* 1976; **15**: 317–23.
4 Kojima T, Hasegawa T, Ishida H *et al*. Griseofulvin-induced photodermatitis. Report of six cases. *J Dermatol* 1988; **15**: 76–82.
5 Feinstein A, Sofer E, Trau H, Schewach-Millet M. Urticaria and fixed drug eruption in a patient treated with griseofulvin. *J Am Acad Dermatol* 1984; **10**: 915–7.
6 Savage J. Fixed drug eruption to griseofulvin. *Br J Dermatol* 1977; **97**: 107–8.
7 Chang T. Cold urticaria and photosensitivity due to griseofulvin. *JAMA* 1965; **193**: 848–50.
8 Goldblatt S. Severe reaction to griseofulvin: sensitivity investigation. *Arch Dermatol* 1961; **83**: 936–7.
9 Rustin NHA, Bunker CB, Dowd P, Robinson TWE. Erythema multiforme due to griseofulvin. *Br J Dermatol* 1989; **120**: 455–8.
10 Thami GP, Kaur S, Kanwar AJ. Erythema multiforme due to griseofulvin with positive re-exposure test. *Dermatology* 2001; **203**: 84–5.
11 Colton RL, Amir J, Mimouni M, Zeharia A. Serum sickness-like reaction associated with griseofulvin. *Ann Pharmacother* 2004; **38**: 609–11.
12 Reaves LE III. Exfoliative dermatitis occurring in a patient treated with griseofulvin. *J Am Geriatr Soc* 1964; **12**: 889–92.
13 Taylor B, Duffill M. Toxic epidermal necrolysis from griseofulvin. *J Am Acad Dermatol* 1988; **19**: 565–7.
14 Mion G, Verdon G, Le Gulluche Y *et al*. Fatal toxic epidermal necrolysis after griseofulvin. *Lancet* 1989; **ii**: 1331.
15 Alexander S. Lupus erythematosus in two patients after griseofulvin treatment of *Trichophyton rubrum* infection. *Br J Dermatol* 1962; **74**: 72–4.
16 Anderson WA, Torre D. Griseofulvin and lupus erythematosus. *J Med Soc NJ* 1966; **63**: 161–2.
17 Watsky MS, Linfield YL. Lupus erythematosus exacerbated by griseofulvin. *Cutis* 1976; **17**: 361–3.
18 Madhok R, Zoma A, Capell H. Fatal exacerbation of systemic lupus erythematosus after treatment with griseofulvin. *BMJ* 1985; **291**: 249–50.
19 Miyagawa S, Okuchi T, Shiomi Y, Sakamoto K. Subacute cutaneous lupus erythematosus lesions precipitated by griseofulvin. *J Am Acad Dermatol* 1989; **21**: 343–6.
20 Miyagawa S, Sakamoto K. Adverse reactions to griseofulvin in patients with circulating anti-SSA/Ro and SSB/La autoantibodies. *Am J Med* 1989; **87**: 100–2.
21 Gaudin JL, Bancel B, Vial T, Bel A. Hepatite aigue cytolytique et eruption morbiliforme imputables à la prise de griseofulvin. *Gastroenterol Clin Biol* 1993; **17**: 145–6.
22 Coté J. Interaction of griseofulvin and oral contraceptives. *J Am Acad Dermatol* 1990; **22**: 124–5.

Ketoconazole

Pruritus and gastrointestinal upset are the most frequent side effects [1]. Urticaria and angio-oedema are recorded [2]. Severe anaphylaxis has been observed in two patients, one of whom had previously reacted to topical miconazole [3]. Other adverse reactions include exfoliative erythroderma [4]. The drug may block testosterone synthesis, causing dose-dependent lowering of serum testosterone and resultant oligospermia, impotence, decreased libido and gynaecomastia in some men [5–7]. It also blocks the cortisol response to ACTH, and may lead to adrenal insufficiency [7–9]. Hypothyroidism has been documented [10]. The most serious side effect is idiosyncratic hepatitis, which occurs in about 1 in 10 000 patients, and which may lead to fulminant and potentially fatal hepatic necrosis [11–17]. Trichoptilosis has resulted from misuse of ketoconazole 2% shampoo [18].

References

1 Faergemann J, Maibach H. Griseofulvin and ketoconazole in dermatology. *Semin Dermatol* 1983; **2**: 262–9.
2 Gonzalez-Delgado P, Florido-Lopez F, Saenz de San Pedro B *et al*. Hypersensitivity to ketoconazole. *Ann Allergy* 1994; **73**: 326–8.
3 Van Dijke CPH, Veerman FR, Haverkamp HC. Anaphylactic reactions to ketoconazole. *BMJ* 1983; **287**: 1673.
4 Rand R, Sober AJ, Olmstead PM. Ketoconazole therapy and exfoliative erythroderma. *Arch Dermatol* 1983; **119**: 97–8.
5 Graybill JR, Drutz DJ. Ketoconazole: a major innovation for treatment of fungal disease. *Ann Intern Med* 1980; **93**: 921–3.
6 Moncada B, Baranda L. Ketoconazole and gynecomastia. *J Am Acad Dermatol* 1982; **7**: 557–8.
7 Pont A, Graybill JR, Craven PC *et al*. High-dose ketoconazole therapy and adrenal and testicular function in humans. *Arch Intern Med* 1984; **144**: 2150–3.
8 Pont A, Williams P, Loose D *et al*. Ketoconazole blocks adrenal steroid synthesis. *Ann Intern Med* 1982; **97**: 370–2.
9 Sonino N. The use of ketoconazole as an inhibitor of steroid production. *N Engl J Med* 1987; **317**: 812–8.
10 Kitching NH. Hypothyroidism after treatment with ketoconazole. *BMJ* 1986; **293**: 993–4.
11 Horsburgh CR Jr, Kirkpatrick CJ, Teutsch CB. Ketoconazole and the liver. *Lancet* 1982; **i**: 860.
12 Stern RS. Ketoconazole: assessing its risks. *J Am Acad Dermatol* 1982; **6**: 544.
13 Rollman O, Lööf L. Hepatic toxicity of ketoconazole. *Br J Dermatol* 1983; **108**: 376–8.
14 Duarte PA, Chow CC, Simmons F, Ruskin J. Fatal hepatitis associated with ketoconazole therapy. *Arch Intern Med* 1984; **144**: 1069–70.
15 Lewis J, Zimmerman HJ, Benson GD, Ishak KG. Hepatic injury associated with ketoconazole therapy: analysis of 33 cases. *Gastroenterology* 1984; **86**: 503–13.
16 Lake-Bakaar G, Scheuer PJ, Sherlock S. Hepatic reactions associated with ketoconazole in the United Kingdom. *BMJ* 1987; **294**: 419–22.
17 Knight TE, Shikuma CY, Knight J. Ketoconazole-induced fulminant hepatitis necessitating liver transplantation. *J Am Acad Dermatol* 1991; **25**: 398–400.
18 Aljabre SH. Trichoptilosis caused by misuse of ketoconazole 2% shampoo. *Int J Dermatol* 1993; **32**: 150–1.

Nystatin

A fixed drug eruption has been reported [1], as has Stevens–Johnson syndrome in an isolated case [2].

References

1 Pareek SS. Nystatin-induced fixed eruption. *Br J Dermatol* 1980; **103**: 679–80.
2 Garty B-Z. Stevens–Johnson syndrome associated with nystatin treatment. *Arch Dermatol* 1991; **127**: 741–2.

Terbinafine

This drug is well tolerated with relatively few side effects [1]. Idiosyncratic hepatitis has been reported [2], with serious hepatobiliary dysfunction occurring in 1 in 54 000 [3]. Neutropenia,

pancytopenia and thrombocytopenia are recorded [4–8]. Cutaneous adverse effects occur in 3% of patients [3,9]; these include severe urticaria, pityriasiform rashes, erythroderma, erythema multiforme [10,11] and TEN [12], serum sickness-like reactions, acute generalized exanthematous pustulosis [13–17], LE-like rashes [18–20], induction or exacerbation of psoriasis which may be pustular [21–24], baboon syndrome [25], fixed drug eruption [26] and alopecia [27], and bullous pemphigoid [28].

Voriconazole

This novel, second-generation triazole for treatment of severe fungal infections has been recorded as producing mucocutaneous retinoid-effects and facial erythema [29], pseudoporphyria [30], cheilitis, erythema, discoid lupus erythematosus, Stevens–Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, and photosensitivity reactions [31].

References

1 Villars V, Jones TC. Present status of the efficacy and tolerability of terbinafine (Lamisil) used systemically in the treatment of dermatomycoses of skin and nails. *J Dermatol Treat* 1990; **1** (Suppl. 2): 33–8.
2 Lowe G, Green C, Jennings P. Hepatitis associated with terbinafine treatment. *BMJ* 1993; **306**: 248.
3 Gupta AK, Kopstein JB, Shear NH. Hypersensitivity reaction to terbinafine. *J Am Acad Dermatol* 1997; **36**: 1018–9.
4 Kovacs MJ, Alshammari S, Guenther L, Bourcier M. Neutropenia and pancytopenia associated with oral terbinafine. *J Am Acad Dermatol* 1994; **31**: 806.
5 Gupta AK, Soori G, Del Rosso JQ *et al.* Severe neutropenia associated with oral terbinafine therapy. *J Am Acad Dermatol* 1998; **38**: 765–7.
6 Ornstein DL, Ely P. Reversible agranulocytosis associated with oral terbinafine for onychomycosis. *J Am Acad Dermatol* 1998; **39**: 1023–4.
7 Shapiro M, Li L-J, Miller J. Terbinafine-induced neutropenia. *Br J Dermatol* 1999; **140**: 1196–7.
8 Tsai H-H, Lee W-R, Hu C-H. Isolated thrombocytopenia associated with oral terbinafine. *Br J Dermatol* 2002; **147**: 627–8.
9 Gupta AK, Lynde CW, Lauzon GJ *et al.* Cutaneous adverse effects associated with terbinafine therapy: 10 case reports and a review of the literature. *Br J Dermatol* 1998; **138**: 529–32.
10 McGregor JM, Rustin MHA. Terbinafine and erythema multiforme. *Br J Dermatol* 1994; **131**: 587–8.
11 Todd P, Halpern S, Munro DD. Oral terbinafine and erythema multiforme. *Clin Exp Dermatol* 1995; **20**: 247–8.
12 White SI, Bowen-Jones D. Toxic epidermal necrolysis induced by terbinafine in a patient on long-term anti-epileptics. *Br J Dermatol* 1996; **134**: 188–9.
13 Kempinaire A, De Raeve L, Merckx M *et al.* Terbinafine-induced acute generalized exanthematous pustulosis confirmed by positive patch-test result. *J Am Acad Dermatol* 1997; **37**: 653–5.
14 Bennett ML, Jorizzo JL, White WL. Generalized pustular eruptions associated with oral terbinafine. *Int J Dermatol* 1999; **38**: 596–600.
15 Hall AP, Tate B. Acute generalized exanthematous pustulosis associated with oral terbinafine. *Australas J Dermatol* 2000; **41**: 42–5.
16 Lombardo M, Cerati M, Pazzaglia A. Acute generalized exanthematous pustulosis induced by terbinafine. *J Am Acad Dermatol* 2003; **49**: 158–9.
17 Beltraminelli HS, Lerch M, Arnold A *et al.* Acute generalized exanthematous pustulosis induced by the antifungal terbinafine: case report and review of the literature. *Br J Dermatol* 2005; **152**: 780–3.
18 Brooke R, Coulson IH, Al-Dawoud A. Terbinafine-induced subacute cutaneous lupus erythematosus. *Br J Dermatol* 1998; **139**: 1132–3.
19 Holmes S, Kemmett D. Exacerbation of systemic lupus erythematosus induced by terbinafine. *Br J Dermatol* 1998; **139**: 1133.
20 Murphy M, Barnes L. Terbinafine-induced lupus erythematosus. *Br J Dermatol* 1998; **138**: 708–9.
21 Wach F, Stolz W, Hein R, Landthaler M. Severe erythema anulare centrifugum-like psoriatic drug eruption induced by terbinafine. *Arch Dermatol* 1995; **131**: 960–1.
22 Gupta AK, Sibbald RG, Knowles SR *et al.* Terbinafine therapy may be associated with the development of psoriasis de novo or its exacerbation: four case reports and a review of drug-induced psoriasis. *J Am Acad Dermatol* 1997; **36**: 858–62.
23 Papa CA, Miller OF. Pustular psoriasiform eruption with leukocytosis associated with terbinafine. *J Am Acad Dermatol* 1998; **39**: 115–7.
24 Wilson NJE, Evans S. Severe pustular psoriasis provoked by oral terbinafine. *Br J Dermatol* 1998; **139**: 168.
25 Weiss JM, Mockenhaupt M, Schopf E, Simon JC. Reproducible drug exanthema to terbinafine with characteristic distribution of baboon syndrome. *Hautarzt* 2001; **52**: 1104–6.
26 Munn SE, Russell Jones R. Terbinafine and fixed drug eruption. *Br J Dermatol* 1995; **133**: 815–6.
27 Richert B, Uhoda I, de la Brassinne M. Hair loss after terbinafine treatment. *Br J Dermatol* 2001; **145**: 842.
28 Aksakal BA, Ozsoy E, Arnavut O, Ali Gürer M. Oral terbinafine-induced bullous pemphigoid. *Ann Pharmacother* 2003; **37**: 1625–7.
29 Denning DW, Griffiths CE. Muco-cutaneous retinoid-effects and facial erythema related to the novel triazole antifungal agent voriconazole. *Clin Exp Dermatol* 2001; **26**: 648–53.
30 Dolan CK, Hall MA, Blazes DL, Norwood CW. Pseudoporphyria as a result of voriconazole use: a case report. *Int J Dermatol* 2004; **43**: 768–71.
31 Racette AJ, Roenigk HH Jr, Hansen R *et al.* Photoaging and phototoxicity from long-term voriconazole treatment in a 15-year-old girl. *J Am Acad Dermatol* 2005; **52** (5 Suppl. 1): S81–5.

Antiviral agents

Aciclovir (acyclovir)

In general, there are very few side effects [1]. Vesicular reactions, palm and sole dermatitis, peripheral oedema, erythema nodosum, exanthems, hyperhidrosis, acne, lichenoid eruption, pruritus, urticaria, vasculitis, alopecia and fixed drug eruption are recorded [2–4]. Intravenous use may cause inflammation and phlebitis. A nephropathy may develop with intravenous use, especially in patients with renal failure, due to renal precipitation of the drug; the dose should be reduced in patients with impaired renal function. An encephalopathy may occur. Peripheral oedema has been reported very rarely [5,6].

References

1 Arndt KA. Adverse reactions to acyclovir: topical, oral, and intravenous. *J Am Acad Dermatol* 1988; **18**: 188–90.
2 Buck ML, Vittone SB, Zaglul HF. Vesicular eruptions following acyclovir administration. *Ann Pharmacother* 1993; **27**: 1458–9.
3 Carrasco L, Pastor MA, Izquierdo MJ *et al.* Drug eruption secondary to aciclovir with recall phenomenon in a dermatome previously affected by herpes zoster. *Clin Exp Dermatol* 2002; **27**: 132–4.
4 Montoro J, Basomba A. Fixed drug eruption due to acyclovir. *Contact Dermatitis* 1997; **36**: 225.
5 Hisler BM, Daneshvar SA, Aronson PJ, Hashimoto K. Peripheral edema and oral acyclovir. *J Am Acad Dermatol* 1988; **18**: 1142–3.
6 Medina S, Torrelo A, España A, Ledo A. Edema and oral acyclovir. *Int J Dermatol* 1991; **30**: 305–6.

Idoxuridine

This drug is used only topically for herpes simplex and herpes zoster, in view of its toxicity on systemic administration. Severe alopecia and loss of nails followed parenteral use [1].

Reference

1 Nolan DC, Carruthers MM, Lerner AM. Herpesvirus hominis encephalitis in Michigan: report of thirteen cases, including six treated with idoxuridine. *N Engl J Med* 1970; **282**: 10–3.

Foscarnet

This drug is used for cytomegalovirus retinitis in AIDS, and for mucocutaneous herpes simplex virus unresponsive to aciclovir in immunocompromised patients. A generalized cutaneous rash has been reported with use of this drug in AIDS [1]. Genital ulceration, both of the penis [2,3] and vulva [4], is documented. In one study [2], 15% of 60 patients treated with intravenous foscarnet developed penile ulceration [2]. Eosinophilic folliculitis has been reported [5].

References

1 Green ST, Nathwani D, Goldberg DJ *et al*. Generalised cutaneous rash associated with foscarnet usage in AIDS. *J Infect* 1990; **21**: 227–8.
2 Katlama C, Dohin E, Caumes E *et al*. Foscarnet induction therapy for cytomegalovirus retinitis in AIDS: comparison of twice-daily and three-times-daily regimens. *J Acquir Immune Defic Syndr* 1992; **5** (Suppl. 1): S18–S24.
3 Evans LM, Grossman ME. Foscarnet-induced penile ulcer. *J Am Acad Dermatol* 1992; **27**: 124–6.
4 Caumes E, Gatineau M, Bricaire F *et al*. Foscarnet-induced vulvar erosion. *J Am Acad Dermatol* 1993; **28**: 799.
5 Roos TC, Albrecht H. Foscarnet-associated eosinophilic folliculitis in a patient with AIDS. *J Am Acad Dermatol* 2001; **44**: 546–7.

Ribavirin (tribavirin)

This synthetic guanosine analogue used in the treatment of relapsing chronic hepatitis C infection has been implicated in the development of Grover's disease [1].

Reference

1 Antunes I, Azevedo F, Mesquita-Guimaraes J *et al*. Grover's disease secondary to ribavirin. *Br J Dermatol* 2000; **142**: 1257–8.

Antiretroviral drugs

Cutaneous side effects of antiretroviral agents have been reviewed [1–9]. There are three categories of agent: nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors and protease inhibitors. Nucleoside reverse transcriptase inhibitors have resulted in alterations of the nails, nail and mucocutaneous pigmentation, hair changes, vasculitis and morbilliform eruptions. Drug hypersensitivity varying from a mild morbilliform rash to Stevens–Johnson syndrome, with drug-induced hepatitis, anaemia and lactic acidosis, is associated with the non-nucleoside reverse transcriptase inhibitors nevirapine, delavirdine and efavirenz, as well as the nucleoside reverse transcriptase inhibitor abacavir and the protease inhibitor amprenavir [2,7]. Recurrent reactions occurred in 12.6% of 239 reported patients with rash switched from nevirapine to efavirenz, compared with 50% of 16 patients switched from efavirenz to nevirapine. Thus, substituting efavirenz for nevirapine following hepatotoxicity or cutaneous hypersensitivity appears to be reasonable, providing that the adverse reaction to nevirapine was not life-threatening [10]. Protease inhibitors have been associated with lipodystrophy syndrome (lipoatrophy with or without lipohypertrophy), hypersensitivity reactions, urticaria, morbilliform eruptions and a large number of drug interactions. Potential management of lipoatrophy includes switching antiretrovirals and surgical treatment with facial fillers. The fusion inhibitor enfuvirtide causes injection-site reactions in the overwhelming majority of patients, although a new method of delivery has decreased their rate and severity [7].

Highly active antiretroviral treatment (HAART) may elicit skin manifestations of the immune reconstitution inflammatory syndrome, including herpes zoster and warts. Long-term side effects, apart from the lipodystrophy syndrome, include dyslipidaemia, cardiovascular disease and diabetes. HLA-B*5701 has been linked with abacavir hypersensitivity, and HLA-DRB1*0101 in Caucasian Australians, and HLA-Cw8 in Sardinians and Japanese, with nevirapine hypersensitivity (see section Pharmacogenetic mechanisms and genetic influences, p. 75.12).

References

1 Carr A, Cooper DA. Adverse effects of antiretroviral therapy. *Lancet* 2000; **356**: 1423–30.
2 Ward HA, Russo GG, Shrum J. Cutaneous manifestations of antiretroviral therapy. *J Am Acad Dermatol* 2002; **46**: 284–93.
3 Rotunda A, Hirsch RJ, Scheinfeld N, Weinberg JM. Severe cutaneous reactions associated with the use of human immunodeficiency virus medications. *Acta Derm Venereol (Stockh)* 2003; **83**: 1–9.
4 Phillips EJ, Knowles SR, Shear N. Cutaneous manifestations of antiviral therapy. *J Am Acad Dermatol* 2003; **48**: 985–6.
5 Kong HH, Myers SA. Cutaneous effects of highly active antiretroviral therapy in HIV-infected patients. *Dermatol Ther* 2005; **18**: 58–66.
6 Martins CR. Cutaneous drug reactions associated with newer antiretroviral agents. *J Drugs Dermatol* 2006; **5**: 976–82.
7 Luther J, Glesby MJ. Dermatologic adverse effects of antiretroviral therapy: recognition and management. *Am J Clin Dermatol* 2007; **8**: 221–33.
8 Tymchuk CN, Currier JS. The safety of antiretroviral drugs. *Expert Opin Drug Saf* 2008; **7**: 1–4.
9 Stankov MV, Behrens GM. HIV-therapy associated lipodystrophy: experimental and clinical evidence for the pathogenesis and treatment. *Endocr Metab Immune Disord Drug Targets* 2007; **7**: 237–49.
10 Mehta U, Maartens G. Is it safe to switch between efavirenz and nevirapine in the event of toxicity? *Lancet Infect Dis* 2007; **7**: 733–8.

Nucleoside reverse transcriptase inhibitors

Abacavir. This drug is associated with a hypersensitivity syndrome in 4% of cases [1]. Stevens–Johnson syndrome is recorded [2].

Dideoxycytidine. A maculopapular reaction with oral ulceration developed in 70% of patients treated with this anti-AIDS agent, but resolved spontaneously in those who continued on therapy [3].

Lamivudine. Paronychia is recorded [4].

Tenofovir (disoproxil fumarate). Hypersensitivity consisting mainly of a maculopapular rash on the face, extremities and trunk is recorded [5].

Zidovudine. This drug may cause gastrointestinal upset and marrow suppression (with serious anaemia in 32% and leukopenia in 37%), myalgia, headache and insomnia [6–9]. Such side effects have been reported in healthcare workers treated with zidovudine for attempted prophylaxis of HIV infection following accidental needlestick injury [10,11]. Zidovudine-related thrombocytopenia resulted in ecchymoses around Kaposi's sarcoma lesions in a patient with AIDS, simulating rapid intracutaneous spread of neoplasm [12]. Vaginal tumours have been documented in rodents. Diffuse pigmentation, as well as isolated hyperpigmented spots

on the palms, soles and fingers, and pigmentation of the fingernails and toenails (usually starting at 4–8 weeks into therapy, but up to 1 year), and buccal mucosa, have been described [13–18]. Postural hypotension has been recorded [19]. Hypertrichosis of the eyelids has occurred [20]. A possible link with neutrophilic eccrine hidradenitis has been postulated in HIV-infected patients [21]. Hypersensitivity reactions, from rash to anaphylaxis, have been documented [22,23]. Other reported cutaneous reactions include acne, pruritus, urticaria and leukocytoclastic vasculitis [24].

References

1 Phillips EJ, Knowles SR, Shear N. Cutaneous manifestations of antiviral therapy. *J Am Acad Dermatol* 2003; **48**: 985–6.
2 Bossi P, Roujeau JC, Bricaire F, Caumes E. Stevens–Johnson syndrome associated with abacavir therapy. *Clin Infect Dis* 2002; **35**: 902.
3 McNeely MC, Yarchoan R, Broder S, Lawley TJ. Dermatologic complications associated with administration of 2′,3′-dideoxycytidine in patients with human immunodeficiency virus infection. *J Am Acad Dermatol* 1989; **21**: 1213–7.
4 Tosti A, Piraccini BM, D'Antuono A *et al*. Paronychia associated with antiretroviral therapy. *Br J Dermatol* 1999; **140**: 1165–8.
5 Lockhart SM, Rathbun RC, Stephens JR *et al*. Cutaneous reactions with tenofovir disoproxil fumarate: a report of nine cases. *AIDS* 2007; **21**: 1370–3.
6 Gill PS, Rarick M, Brynes RK *et al.* Azidothymidine associated with bone marrow failure in AIDS. *Ann Intern Med* 1987; **107**: 502–5.
7 Richman DD, Fiscal MA, Grieco MH *et al*. The toxicity of azidothymidine (AZT) in the treatment of patients with AIDS or AIDS-related complex: a double blind, placebo-controlled trial. *N Engl J Med* 1987; **317**: 192–7.
8 Gelmon K, Montaner JS, Fanning M *et al.* Nature, time course and dose dependence of zidovudine-related side-effects: results from the Multicenter Canadian Azidothymidine Trial. *AIDS* 1989; **3**: 555–61.
9 Moore RD, Creagh-Kirk T, Keruly J *et al.* Long-term safety and efficacy of zidovudine in patients with advanced human immunodeficiency virus infection. *Arch Intern Med* 1991; **151**: 981–6.
10 Centers for Disease Control. Public health service statement on management of occupational exposure to human immunodeficiency virus, including considerations regarding zidovudine post-exposure use. *MMWR* 1990; **39**: 1–14.
11 Jeffries DJ. Zidovudine after occupational exposure to HIV. Hospitals should be able to give it within an hour. *BMJ* 1991; **302**: 1349–51.
12 Barnett JH, Gilson E. Zidovudine-related thrombocytopenia simulating rapid growth of Kaposi's sarcoma. *Arch Dermatol* 1991; **127**: 1068–9.
13 Azon-Masoliver A, Mallolas J, Gatell J, Castel T. Zidovudine-induced nail pigmentation. *Arch Dermatol* 1988; **124**: 1570–1.
14 Fisher CA, McPoland PR. Azidothymidine-induced nail pigmentation. *Cutis* 1989; **43**: 552–4.
15 Bendick C, Rasokat H, Steigleder GK. Azidothymidine-induced hyperpigmentation of skin and nails. *Arch Dermatol* 1989; **125**: 1285–6.
16 Greenberg RG, Berger TG. Nail and mucocutaneous hyperpigmentation with azidothymidine therapy. *J Am Acad Dermatol* 1990; **22**: 327–30.
17 Grau-Massanes M, Millan F, Febrer MI *et al.* Pigmented nail bands and mucocutaneous pigmentation in HIV-positive patients treated with zidovudine. *J Am Acad Dermatol* 1990; **22**: 687–8.
18 Tadini G, D'Orso M, Cusini M *et al.* Oral mucosa pigmentation: a new side effect of azidothymidine therapy in patients with acquired immunodeficiency syndrome. *Arch Dermatol* 1991; **127**: 267–8.
19 Loke RHT, Murray-Lyon IM, Carter GD. Postural hypotension related to zidovudine in a patient infected with HIV. *BMJ* 1990; **300**: 163–4.
20 Klutman NE, Hinthorn DR. Excessive growth of eyelashes in a patient with AIDS being treated with zidovudine. *N Engl J Med* 1991; **324**: 1896.
21 Smith KJ, Skelton HG III, James WD *et al.* Neutrophilic eccrine hidradenitis in HIV-infected patients. *J Am Acad Dermatol* 1990; **23**: 945–7.
22 Carr A, Penny R, Cooper DA. Allergy and desensitization to zidovudine in patients with acquired immunodeficiency syndrome (AIDS). *J Allergy Clin Immunol* 1993; **91**: 683–5.
23 Wassef M, Keiser P. Hypersensitivity of zidovudine: report of a case of anaphylaxis and review of the literature. *Clin Infect Dis* 1995; **20**: 1387–9.
24 Torres RA, Lin RY, Lee M, Barr MR. Zidovudine-induced leukocytoclastic vasculitis. *Arch Intern Med* 1992; **152**: 850–1.

Non-nucleoside reverse transcriptase inhibitors

Delavirdine. Various rashes occur in 18–50% of cases.

Efavirenz. Mild rashes are recorded within the first 2 weeks of therapy [1]. A hypersensitivity reaction manifesting in a rash and hepatitis has been documented [2].

Nevirapine. Severe rashes have been observed in 3% of patients taking nevirapine in clinical trials, 85% of whom were men [3,4]. A hypersensitivity syndrome is well recorded [5–7]. The drug is the leading cause of Stevens–Johnson syndrome and TEN related to AIDS in Europe [8–12].

References

1 Phillips EJ, Knowles SR, Shear N. Cutaneous manifestations of antiviral therapy. *J Am Acad Dermatol* 2003; **48**: 985–6.
2 Leung JM, O'Brien JG, Wong HK, Winslow DL. Efavirenz-induced hypersensitivity reaction manifesting in rash and hepatitis in a Latino male. *Ann Pharmacother* 2008; **42**: 425–9.
3 Bersoff-Matcha SJ, Miller WC, Aberg JA *et al.* Sex differences in nevirapine rash. *Clin Infect Dis* 2001; **32**: 124–9.
4 Anonymous. From the Centers for Disease Control and Prevention. Serious adverse events attributed to nevirapine regimens for postexposure prophylaxis after HIV exposures: worldwide, 1997–2000. *JAMA* 2001; **285**: 402–3.
5 Claudio GA, Martin AF, de Dios Perrino S, Velasco AA. DRESS syndrome associated with nevirapine therapy. *Arch Intern Med* 2001; **161**: 2501–2.
6 Lanzafame M, Rovere P, De Checchi G *et al.* Hypersensitivity syndrome (DRESS) and meningoencephalitis associated with nevirapine therapy. *Scand J Infect Dis* 2001; **33**: 475–6.
7 Wit FW, Kesselring AM, Gras L *et al*. Discontinuation of nevirapine because of hypersensitivity reactions in patients with prior treatment experience, compared with treatment-naive patients: the ATHENA cohort study. *Clin Infect Dis* 2008; **46**: 933–40.
8 Wetterwald E, Le Cleach L, Michel C *et al.* Nevirapine-induced overlap Stevens–Johnson syndrome/toxic epidermal necrolysis. *Br J Dermatol* 1999; **140**: 980–2.
9 Metry DW, Lahart CJ, Farmer KL, Hebert AA. Stevens–Johnson syndrome caused by the antiretroviral drug nevirapine. *J Am Acad Dermatol* 2001; **44** (Suppl. 2): 354–7.
10 Fagot JP, Mockenhaupt M, Bouwes-Bavinck JN *et al.* Nevirapine and the risk of Stevens–Johnson syndrome or toxic epidermal necrolysis. *AIDS* 2001; **15**: 1843–8.
11 Dodi F, Alessandrini A, Camera M *et al.* Stevens–Johnson syndrome in HIV patients treated with nevirapine: two case reports. *AIDS* 2002; **16**: 1197–8.
12 Mason AR, Cortes GY, Pollack RB. Nevirapine-induced Stevens–Johnson syndrome in a pediatric patient. *Pediatr Dermatol* 2008; **25**: 128–9.

Protease inhibitors

Saquinivir causes rashes, and indinavir causes taste disturbance and dry skin [1]. Indinavir has been associated with retinoid-like manifestations such as the development of cheilitis in 40% of cases, paronychia, scalp hair loss in 12%, ingrown toe-nails, curling of straight hair, diffuse cutaneous dryness and pruritus in 12%, and asteatotic dermatitis on the trunk, arms and thighs [2,3]. Multiple pyogenic granulomas were observed in the toenails in 6% and softening of the nail plate in 5% of subjects. Multiple subcutaneous lipomas are associated with protease inhibitors [4]. Paronychia is a recognized complication [5,6]. Angiolipomas shortly after initiation of therapy [7] and leukocytoclastic vasculitis [8] have been documented with indinavir. A peripheral lipodystro-

phy syndrome has been linked to therapy with protease inhibitors [9–13] and was noted in 14% of patients on indinavir [2]. It comprises peripheral lipoatrophy, relative central adiposity, sometimes with a 'buffalo hump', insulin resistance and serum lipid abnormalities. The mix of features is variable in individual patients.

References

1 Anonymous. Safety issues with anti-HIV drugs. *Curr Prob Pharmacovig* 1997; **23**: 5.
2 Calista D, Boschini A. Cutaneous side effects induced by indinavir. *Eur J Dermatol* 2000; **10**: 292–6.
3 Luther J, Glesby MJ. Dermatologic adverse effects of antiretroviral therapy: recognition and management. *Am J Clin Dermatol* 2007; **8**: 221–33.
4 Bornhovd E, Sakrauski AK, Bruhl H *et al.* Multiple circumscribed subcutaneous lipomas associated with use of human immunodeficiency virus protease inhibitors? *Br J Dermatol* 2000; **143**: 1113–4.
5 Tosti A, Piraccini BM, D'Antuono A *et al.* Paronychia associated with antiretroviral therapy. *Br J Dermatol* 1999; **140**: 1165–8.
6 Daudén E, Pascual-López M, Martínez-Garcia C, García-Díez A. Paronychia and excess granulation tissue of the toes and finger in a patient treated with indinavir. *Br J Dermatol* 2000; **142**: 1063–4.
7 Dank JP, Colven R. Protease inhibitor-associated angiolipomatosis. *J Am Acad Dermatol* 2000; **42**: 129–31.
8 Rachline A, Lariven S, Descamps V *et al.* Leucocytoclastic vasculitis and indinavir. *Br J Dermatol* 2000; **143**: 1112–3.
9 Ward HA, Russo GG, Shrum J. Cutaneous manifestations of antiretroviral therapy. *J Am Acad Dermatol* 2002; **46**: 284–93.
10 Williamson K, Reboli AC, Manders SM. Protease-inhibitor-induced lipodystrophy. *J Am Acad Dermatol* 1999; **40**: 635–6.
11 Panse I, Vasseur E, Raffin-Sanson ML *et al.* Lipodystrophy associated with protease inhibitors. *Br J Dermatol* 2000; **142**: 496–500.
12 Pujol RM, Domingo P, Guiu X-M *et al.* HIV-1 protease inhibitor-associated partial lipodystrophy: clinicopathologic review of 14 cases. *J Am Acad Dermatol* 2000; **42**: 193–8.
13 Mallon PW, Cooper DA, Carr A. HIV-associated lipodystrophy. *HIV Med* 2001; **2**: 166–73.

Antimalarials [1–4]

Pruritus, lichenoid eruptions [5], exfoliative dermatitis, pigment changes, bleaching of hair, alopecia, photosensitivity with exacerbation of psoriasis and porphyria cutanea tarda, retinopathy and corneal opacities have all been reported.

References

1 Ribrioux A. Antipaludéens de synthese et peau. *Ann Dermatol Vénéréol* 1990; **117**: 975–90.
2 Ochsendorf FR, Runne U. Chloroquin und Hydroxychloroquin: Nebenwirkungsprofil wichtiger Therapeutika. *Hautarzt* 1991; **42**: 140–6.
3 Ziering CL, Rabinowitz LG, Esterly NB. Antimalarials for children. Indications, toxicities, and guidelines. *J Am Acad Dermatol* 1993; **28**: 764–70.
4 Sowunmi A, Falade AG, Adedeji AA, Falade CO. Comparative clinical characteristics and responses to oral 4-aminoquinoline therapy of malarious children who did and did not develop 4-aminoquinoline-induced pruritus. *Ann Trop Med Parasitol* 2001; **95**: 645–53.
5 Geraminejad P, Stone MS, Sontheimer RD. Antimalarial lichenoid tissue reactions in patients with pre-existing lupus erythematosus. *Lupus* 2004; **13**: 473–7.

Chloroquine and hydroxychloroquine

Adverse cutaneous reactions to hydroxychloroquine are commoner in patients with dermatomyositis than in those with cutaneous LE [1]. Pruritus is common in Africans on acute or prolonged treatment, but rare in Europeans [2–5]. Pigmentary changes develop in about 25% of patients receiving any of the antimalarials for more than 4 months [6–9]; chloroquine binds to melanin [9]. Blackish-purple patches on the shins are often seen, and brown-grey pigmentation may appear in light-exposed skin [8]. The nail beds may be pigmented diffusely or in transverse bands, and the hard palate is diffusely pigmented. In contrast, red-blonde (but not dark) hair may be bleached [10]. Chloroquine has been associated with vitiligo-like depigmentation [11].

Photosensitivity may be seen [12]; in addition, certain types of porphyria may be provoked [13]. Effects on psoriasis are unpredictable, but precipitation of severe psoriasis has long been recognized [14–19], including erythroderma [19]. However, 88% of a series of 50 psoriatics who were treated with standard doses of chloroquine noted no change in their psoriasis [20]. Lichenoid eruptions are uncommon, and erythema annulare centrifugum is rare [21]. A pustular eruption with hydroxychloroquine has been reported [22]. Acute generalized exanthematous pustulosis is recorded [23]. TEN with oral involvement has been documented. Toxic psychosis has been described with hydroxychloroquine [24]. All antimalarials are potentially teratogenic.

Chloroquine and hydroxychloroquine may cause serious ophthalmic side effects [25,26]. Corneal deposits occur in 95% of patients on long-term therapy, but of these 95% are asymptomatic [27]. A potentially irreversible retinopathy leading to blindness may develop in 0.5–2% of cases [28,29]. The retinal changes may progress after the drug is stopped. Use of less than 250 mg (or 4 mg/kg) daily of chloroquine, with pretreatment and 6-monthly ophthalmological assessment using an Amsler grid, is recommended. Malaria prophylaxis with two tablets weekly is said not to carry an appreciable risk. Ocular toxicity with hydroxychloroquine is rare below 6.5 mg/kg; guidelines for screening include baseline renal and liver function tests, assessment of near visual acuity and yearly visual acuity [30].

References

1 Pelle MT, Callen JP. Adverse cutaneous reactions to hydroxychloroquine are more common in patients with dermatomyositis than in patients with cutaneous lupus erythematosus. *Arch Dermatol* 2002; **138**: 1231–3.
2 Spencer HC, Poulter NR, Lury JD, Poulter CJ. Chloroquine-associated pruritus in a European. *BMJ* 1982; **285**: 1703–4.
3 Salako LA. Toxicity and side-effects of antimalarials in Africa: a critical review. *Bull WHO* 1984; **62** (Suppl.): 63–8.
4 Mnyika KS, Kihamia CM. Chloroquine-induced pruritus: its impact on chloroquine utilization in malaria control in Dar es Salaam. *J Trop Med Hyg* 1991; **94**: 27–31.
5 Ezeamuzie IC, Igbigbi PS, Ambakederemo AW *et al.* Halofantrine-induced pruritus amongst subjects who itch to chloroquine. *J Trop Med Hyg* 1991; **94**: 184–8.
6 Dall JLC, Keane JA. Disturbances of pigmentation with chloroquine. *BMJ* 1959; **i**: 1387–9.
7 Tuffanelli D, Abraham RK, Dubois EJ. Pigmentation from antimalarial therapy: its possible relationship to the ocular lesions. *Arch Dermatol* 1963; **88**: 419–26.
8 Levy H. Chloroquine-induced pigmentation. Case reports. *S Afr Med J* 1982; **2**: 735–7.
9 Sams WM, Epstein JH. The affinity of melanin for chloroquine. *J Invest Dermatol* 1965; **45**: 482–8.
10 Dupré A, Ortonne J-P, Viraben R, Arfeux F. Chloroquine-induced hypopigmentation of hair and freckles. Association with congenital renal failure. *Arch Dermatol* 1985; **121**: 1164–6.
11 Martín-García RF, Camacho N del R, Sánchez JL. Chloroquine-induced, vitiligo-like depigmentation. *J Am Acad Dermatol* 2003; **48**: 981–3.

12 Van Weelden H, Boling HH, Baart de la Faille H, Van Der Leun JC. Photosensitivity caused by chloroquine. *Arch Dermatol* 1982; **118**: 290.
13 Davis MJ, Vander Ploeg DE. Acute porphyria and coproporphyrinuria following chloroquine therapy: a report of two cases. *Arch Dermatol* 1957; **75**: 796–800.
14 O'Quinn SE, Kennedy CB, Naylor LZ. Psoriasis, ultraviolet light and chloroquine. *Arch Dermatol* 1964; **90**: 211–6.
15 Baker H. The influence of chloroquine and related drugs on psoriasis and keratoderma blenorrhagicum. *Br J Dermatol* 1966; **78**: 161–6.
16 Abel EA, Dicicco LM, Orenberg EK *et al.* Drugs in exacerbation of psoriasis. *J Am Acad Dermatol* 1986; **15**: 1007–22.
17 Nicolas J-F, Mauduit G, Haond J *et al.* Psoriasis grave induit par la chloroquine (nivaquine). *Ann Dermatol Vénéréol* 1988; **115**: 289–93.
18 Luzar MJ. Hydroxychloroquine in psoriatic arthropathy: exacerbation of psoriatic skin lesions. *J Rheumatol* 1982; **9**: 462–4.
19 Slagel GA, James WD. Plaquenil-induced erythroderma. *J Am Acad Dermatol* 1985; **12**: 857–62.
20 Katugampola G, Katugampola S. Chloroquine and psoriasis. *Int J Dermatol* 1990; **29**: 153–4.
21 Ashurst PJ. Erythema annulare centrifugum. Due to hydroxychloroquine sulfate and chloroquine sulfate. *Arch Dermatol* 1967; **95**: 37–9.
22 Lotem M, Ingber A, Segal R, Sandbank M. Generalized pustular drug rash induced by hydroxychloroquine. *Acta Derm Venereol (Stockh)* 1990; **70**: 250–1.
23 Paradisi A, Bugatti L, Sisto T *et al*. Acute generalized exanthematous pustulosis induced by hydroxychloroquine: three cases and a review of the literature. *Clin Ther* 2008; **30**: 930–40.
24 Ward WQ, Walter-Ryan WG, Shehi GM. Toxic psychosis: a complication of antimalarial therapy. *J Am Acad Dermatol* 1985; **12**: 863–5.
25 Olansky AJ. Antimalarials and ophthalmologic safety. *J Am Acad Dermatol* 1982; **6**: 19–23.
26 Portnoy JZ, Callen JP. Ophthalmologic aspects of chloroquine and hydroxychloroquine safety. *Int J Dermatol* 1983; **22**: 273–8.
27 Easterbrook M. Ocular side effects and safety of antimalarial agents. *Am J Med* 1988; **85**: 23–9.
28 Marks JS. Chloroquine retinopathy: is there a safe daily dose? *Ann Rheum Dis* 1982; **41**: 52–8.
29 Easterbrook M. Dose relationships in patients with early chloroquine retinopathy. *J Rheumatol* 1987; **14**: 472–5.
30 Jones SK. Ocular toxicity and hydroxychloroquine: guidelines for screening. *Br J Dermatol* 1999; **140**: 3–7.

Mefloquine

Dizziness, nausea, erythema and neurological disturbance are documented. Pruritus occurs in 4–10% and maculopapular rash in up to 30% of cases; urticaria, facial lesions, cutaneous vasculitis, Stevens–Johnson syndrome and TEN [1,2], and exfoliative dermatitis [3] have been recorded.

References

1 Van Den Enden E, Van Gompel A, Colebunders R, Van Den Ende J. Mefloquine-induced Stevens–Johnson syndrome. *Lancet* 1991; **337**: 683.
2 Smith HR, Croft AM, Black MM. Dermatological adverse effects with the antimalarial drug mefloquine: a review of 74 published case reports. *Clin Exp Dermatol* 1999; **24**: 249–54.
3 Martin GJ, Malone JL, Ross EV. Exfoliative dermatitis during malarial prophylaxis with mefloquine. *Clin Infect Dis* 1993; **16**: 341–2.

Mepacrine (atabrine, quinacrine)

This drug constantly causes yellow staining of the skin, which may involve the conjunctiva and may mimic jaundice [1]. Lichenoid eruptions are well known. Large numbers of military personnel given mepacrine for malaria prophylaxis in the Second World War developed a tropical lichenoid dermatitis, which was quickly followed by anhidrosis, cutaneous atrophy, alopecia, nail changes, altered pigmentation and keratoderma [2,3]. A few patients developed localized, bluish-black hyperpigmentation confined to the palate, face, pretibial area and nail beds after prolonged administration of more than a year. Years later, lichenoid nodules, scaly red plaques, atrophic lesions on the soles, erosions and leukoplakia of the tongue, and fungating warty growths appeared [3,4]. Progression to squamous cell carcinoma, especially on the palm, has occurred. Ocular toxicity is much less than with chloroquine.

References

1 Leigh JM, Kennedy CTC, Ramsey JD, Henderson WJ. Mepacrine pigmentation in systemic lupus erythematosus. *Br J Dermatol* 1979; **101**: 147–53.
2 Bauer F. Late sequelae of atabrine dermatitis: a new premalignant entity. *Aust J Dermatol* 1978; **19**: 9–12.
3 Bauer F. Quinacrine hydrochloride drug eruption (tropical lichenoid dermatitis). Its early and late sequelae and its malignant potential. A review. *J Am Acad Dermatol* 1981; **4**: 239–48.
4 Callaway JL. Late sequelae of quinacrine dermatitis, a new premalignant entity. *J Am Acad Dermatol* 1979; **1**: 456.

Pyrimethamine

This folate antagonist can cause agranulocytosis even in very low dosage, especially when combined with dapsone [1]. A lichenoid eruption has been reported [2], as has photosensitivity. The reported rate for all serious reactions to pyrimethamine–sulfadoxine (Fansidar) in one study was 1 in 2100 prescriptions and for cutaneous reactions including Stevens–Johnson syndrome 1 in 4900, with a fatality rate of 1 in 11 100 [3]. In another study [4], severe cutaneous adverse reactions to Fansidar, including erythema multiforme, Stevens–Johnson syndrome and TEN, were estimated at 1.1 (0.9–1.3) per million. Similar rates for severe reactions to pyrimethamine–dapsone (Maloprim) were 1 in 9100 prescriptions and for blood dyscrasias 1 in 20 000, with a fatality rate of 1 in 75 000. For developing countries with mainly single-dose use, the risk was estimated at 0.1 per million, compared with mainly prophylactic use in Europe and North America at a risk of 10 and 36 per million, respectively. Prophylactic use thus had a 40 times higher risk than single-dose therapeutic use [4]. Reactions to pyrimethamine are more common in patients with HIV infection [5]. Epidermal necrolysis, angio-oedema, bullous disorders and serious hepatic disorders also occurred. Because few serious reactions have been recorded with chloroquine and proguanil, it has been recommended that use of compound antimalarials should be restricted [3].

References

1 Friman G, Nyström-Rosander C, Jonsell G *et al.* Agranulocytosis associated with malaria prophylaxis with Maloprim. *BMJ* 1983; **286**: 1244–5.
2 Cutler TP. Lichen planus caused by pyrimethamine. *Clin Exp Dermatol* 1980; **5**: 253–6.
3 Phillips-Howard PA, West LJ. Serious adverse drug reactions to pyrimethamine–sulphadoxine, pyrimethamine–dapsone and to amodiaquine in Britain. *J R Soc Med* 1990; **83**: 82–5.
4 Sturchler D, Mittelholzer ML, Kerr L. How frequent are notified severe cutaneous adverse reactions to Fansidar? *Drug Saf* 1993; **8**: 160–8.
5 Piketty C, Weiss L, Picard-Dahan C *et al.* Toxidermies a la pyrimethamine chez les patients infectés par le virus de l'immunodeficience acquise. *Presse Med* 1995; **24**: 1710.

Quinine
Purpura due to quinine may or may not be thrombocytopenic [1,2]. Erythematous, urticarial, photoallergic [3–5], bullous and fixed eruptions are recorded. Lichenoid eruptions are rare. If contact allergic sensitivity is already present, eczematous reactions may occur, as in 'systemic contact-type eczema' [6]. Splinter haemorrhages, and a maculopapular and a photosensitive papulonecrotic eruption, due to a lymphocytic vasculitis, have been recorded in one case [7].

References

1 Belkin GA. Cocktail purpura. An unusual case of quinine sensitivity. *Ann Intern Med* 1967; **66**: 583–6.
2 Helmly RB, Bergin JJ, Shulman NR. Quinine-induced purpura: observation on antibody titers. *Arch Intern Med* 1967; **20**: 59–62.
3 Ljunggren B, Sjövall P. Systemic quinine photosensitivity. *Arch Dermatol* 1986; **122**: 909–11.
4 Ferguson J, Addo HA, Johnson BE *et al.* Quinine induced photosensitivity: clinical and experimental studies. *Br J Dermatol* 1987; **117**: 631–40.
5 Diffey BL, Farr PM, Adams SJ. The action spectrum in quinine photosensitivity. *Br J Dermatol* 1988; **118**: 679–85.
6 Calnan CD, Caron GA. Quinine sensitivity. *BMJ* 1961; **ii**: 1750–2.
7 Harland CC, Millard LG. Another quirk of quinine. *BMJ* 1991; **302**: 295.

Anthelmintics

Amocarzine (CGP 6140)
This macrofilaricidal and microfilaricidal drug used for the therapy of onchocerciasis may be associated with dizziness and pruritus with or without a rash [1].

Benzimidazole compounds
These are used for the therapy of both intestinal helminthiasis and hydatid disease; fever, gastrointestinal upset, reversible neutropenia and transient abnormalities in liver function are reported. Telogen effluvium has been documented with both albendazole [2,3] and mebendazole.

Ivermectin
Fever, rash, pruritus, local swelling and tender regional lymphadenopathy are documented [4]. The incidence of moderate adverse reactions, including pruritus, localized rash and fever, was 4% in a study of patients with onchocerciasis from Ecuador [5], and increased itching and/or rash occurred in 8% of cases in another study [6]. Patients with reactive onchodermatitis (sowda) may have severe pruritus and limb swelling with ivermectin [7]. A 3-year, placebo-controlled, double-blind trial involving 7148 patients given ivermectin annually for onchocerciasis by mass distribution identified musculosketetal pains, oedema of the face or extremities, itching and papular rash as adverse reactions; bullous skin lesions that did not recur developed in five persons [8].

Levamisole
Prolonged use at high dosage as an immunostimulant is associated with type I reactions, with itching, pruritus and urticaria. Lichenoid [9] and non-specific [10] rashes, leukocytoclastic vasculitis with a reticular livedo pattern due to circulating immune complexes [11], and cutaneous necrotizing vasculitis [12], have been reported. A distinctive purpuric eruption of the ears is recorded [13].

Niridazole
Urticaria and a pellagra-like dermatitis have been described.

Piperazine
Occupational dermatitis has been caused [14]. Previous contact sensitization induced by ethylenediamine has led to severe cross-reactions on subsequent oral administration of piperazine, including generalized exfoliative dermatitis [15].

Tetrachlorethylene
This drug has caused TEN.

Tiabendazole
An unusual body odour is well known after the administration of this drug. Skin reactions, consisting of urticaria or maculopapular rashes, are infrequent and usually mild and transient. Erythema multiforme [16] and TEN [17] have been reported.

References

1 Poltera AA, Zea-Flores G, Guderian R *et al.* Onchocercacidal effects of amocarzine (CGP 6140) in Latin America. *Lancet* 1991; **337**: 583–4.
2 Karawifa MA, Yasawi MI, Mohamed AE. Hair loss as a complication of albendazole therapy. *Saudi Med J* 1988; **9**: 530.
3 Garcia-Muret MP, Sitjas D, Tuneu L, de Moragas JM. Telogen effluvium associated with albendazole therapy. *Int J Dermatol* 1990; **29**: 669–70.
4 Bryan RT, Stokes SL, Spencer HC. Expatriates treated with ivermectin. *Lancet* 1991; **337**: 304.
5 Guderian RH, Beck BJ, Proano S Jr, Mackenzie CD. Onchocerciasis in Ecuador, 1980–86: epidemiological evaluation of the disease in the Esmerldas province. *Eur J Epidemiol* 1989; **5**: 294–302.
6 Whitworth JAG, Maude GH, Luty AJF. Expatriates treated with ivermectin. *Lancet* 1991; **337**: 625–6.
7 Guderian RH, Anselmi M, Sempertegui R, Cooper PJ. Adverse reactions to ivermectin in reactive onchodermatitis. *Lancet* 1991; **337**: 188.
8 Burnham GM. Adverse reactions to ivermectin treatment for onchocerciasis. Results of a placebo-controlled, double-blind trial in Malawi. *Trans R Soc Trop Med Hyg* 1993; **87**: 313–7.
9 Kirby JD, Black MM, McGibbon D. Levamisole-induced lichenoid eruptions. *J R Soc Med* 1980; **73**: 208–11.
10 Parkinson DR, Cano PO, Jerry LM *et al.* Complications of cancer immunotherapy with levamisole. *Lancet* 1977; **ii**: 1129–32.
11 Macfarlane DG, Bacon PA. Levamisole-induced vasculitis due to circulating immune complexes. *BMJ* 1978; **i**: 407–8.
12 Scheinberg MA, Bezera JBG, Almeida LA, Silveira LA. Cutaneous necrotising vasculitis induced by levamisole. *BMJ* 1978; **i**: 408.
13 Rongioletti F, Ghio L, Ginevri F *et al.* Purpura of the ears: a distinctive vasculopathy with circulating autoantibodies complicating long-term treatment with levamisole in children. *Br J Dermatol* 1999; **140**: 948–51.
14 Calnan CD. Occupational piperazine dermatitis. *Contact Dermatitis* 1975; **1**: 126.
15 Burry JN. Ethylenediamine sensitivity with a systemic reaction to piperazine treatment. *Contact Dermatitis* 1978; **4**: 380.
16 Humphreys F, Cox NH. Thiabendazole-induced erythema multiforme with lesions around melanocytic naevi. *Br J Dermatol* 1988; **118**: 855–6.
17 Robinson HM, Samorodin CS. Thiabendazole-induced toxic epidermal necrolysis. *Arch Dermatol* 1976; **112**: 1757–60.

Drugs for *Pneumocystis*

Pentamidine

This drug is increasingly being used in the treatment and prophylaxis of *Pneumocystis carinii* pneumonia in patients with AIDS. Urticaria, including contact urticaria [1], or maculopapular eruption proceeding to erythroderma have been reported with nebulized therapy [2,3]. TEN may occur with systemic therapy [4,5].

References

1 Belsito DV. Contact urticaria from pentamidine isethionate. *Contact Dermatitis* 1993; **29**: 158–9.
2 Leen CLS, Mandal BK. Rash due to nebulised pentamidine. *Lancet* 1988; **ii**: 1250–1.
3 Berger TG, Tappero JW, Leoung GS, Jacobson MA. Aerosolized pentamidine and cutaneous eruptions. *Ann Intern Med* 1989; **110**: 1035–6.
4 Wang JJ, Freeman AI, Gaeta JF, Sinks LF. Unusual complications of pentamidine in the treatment of *Pneumocystis carinii* pneumonia. *J Pediatr* 1970; **77**: 311–4.
5 Walzer PD, Perl DP, Krogstadt DJ *et al. Pneumocystis carinii* pneumonia in the United States: epidemiologic, diagnostic and clinical features. *Ann Intern Med* 1974; **80**: 83–93.

Non-steroidal anti-inflammatory drugs

Acetylsalicylic acid and related compounds

Aspirin

Reactions to aspirin [1–4] occur in 0.3% of normal subjects [2,4]. These are usually sporadic, but occasionally more than one family member may be affected, and an HLA linkage has been reported [5]. Urticaria or angio-oedema is the commonest reaction [1]. Two types of specific IgE antibody were found in sera from aspirin-sensitive patients with salicyloyl and *O*-methylsalicyloyl discs using radioallergosorbent tests, favouring an IgE-dependent mechanism [6]. Chronic idiopathic urticaria is often aggravated by aspirin [7,8]; this exacerbation probably has a non-allergic basis. It has been estimated that patients with chronic urticaria or angio-oedema have a risk of up to 30% of developing a flare in the condition following administration of aspirin or an NSAID [3]. The reaction is dose dependent and is greater when the urticaria is in an active phase. Aspirin may render the skin of such patients more reactive to histamine [5]. The syndrome of nasal polyposis, bronchial asthma and aspirin intolerance is well known [4,9]; up to 40% of patients with nasal polyps, and 4% of patients with asthma, may develop bronchoconstriction on exposure to aspirin, but only 2% develop urticaria [4]. Anaphylactoid responses may occur [3]; these may involve abnormalities of platelet function [10]. Cross-sensitivity between aspirin and tartrazine is now thought to be rare [3]. Oral desensitization is feasible if essential, and may be maintained by daily aspirin intake [3].

Other reported reactions include purpura, scarlatiniform erythema, erythema multiforme, fixed eruption and a lichenoid eruption (which recurred on challenge) [11], but all are rare [1]. Neonatal petechiae may result from aspirin therapy of the mother [12]. Aspirin has been reported to provoke generalized pustular psoriasis [13]. Oral ulceration may follow prolonged chewing of aspirin [14], and at the site of an insoluble aspirin tablet placed at the side of an aching tooth.

Nephropathy, marrow depression and gastric haemorrhage are well-recognized hazards. The elderly are at increased risk of developing such complications [15]. The drug may interfere with renal clearance, for example of methotrexate. Aspirin is safe to administer to patients with glucose-6-phosphate dehydrogenase deficiency [16].

References

1 Baker H, Moore-Robinson M. Drug reactions. IX. Cutaneous responses to aspirin and its derivatives. *Br J Dermatol* 1970; **82**: 319–21.
2 Settipane RA, Constantine HP, Settipane GA. Aspirin intolerance and recurrent urticaria in normal adults and children. *Epidemiol Rev Allergy* 1980; **35**: 149–54.
3 Stevenson DD. Diagnosis, prevention and treatment of adverse reactions to aspirin and nonsteroidal anti-inflammatory drugs. *J Allergy Clin Immunol* 1984; **74**: 617–22.
4 Morassut P, Yang W, Karsh J. Aspirin intolerance. *Semin Arthritis Rheum* 1989; **19**: 22–30.
5 Mullarkey MF, Thomas PS, Hansen JA *et al.* Association of aspirin-sensitive asthma with HLA-DQw2. *Am Rev Respir Dis* 1986; **133**: 261–3.
6 Daxun Z, Becker WM, Schulz KH, Schlaak M. Sensitivity to aspirin: a new serological diagnostic method. *J Invest Allergol Clin Immunol* 1993; **3**: 72–8.
7 Champion RH, Roberts SOB, Carpenter RG, Roger JH. Urticaria and angio-oedema. A review of 554 patients. *Br J Dermatol* 1969; **81**: 588–97.
8 Doeglas HMG. Reactions to aspirin and food additives in patients with chronic urticaria, including the physical urticarias. *Br J Dermatol* 1975; **93**: 135–44.
9 Samter M, Beers RF. Intolerance to aspirin. Clinical studies and consideration of its pathogenesis. *Ann Intern Med* 1968; **68**: 975–83.
10 Wüthrich B. Azetylsalizylsäure-Pseudoallergie. Eine Anomalie der Thrombozyten-Funktion? *Hautarzt* 1988; **39**: 631–4.
11 Bharija SC, Belhaj MS. Acetylsalicylic acid may induce a lichenoid eruption. *Dermatologica* 1988; **177**: 19.
12 Stuart MJ, Gross SJ, Elrad H, Graeber JE. Effects of acetylsalicylic-acid ingestion on maternal and neonatal hemostasis. *N Engl J Med* 1982; **307**: 909–12.
13 Shelley WB. Birch pollen and aspirin psoriasis. *JAMA* 1964; **189**: 985–8.
14 Claman HN. Mouth ulcers associated with prolonged chewing of gum containing aspirin. *JAMA* 1967; **202**: 651–2.
15 Karsh J. Adverse reactions and interactions with aspirin. Considerations in the treatment of the elderly patient. *Drug Saf* 1990; **5**: 317–27.
16 Beutler E. Glucose-6-phosphate dehydrogenase deficiency. *Lancet* 1991; **324**: 169–74.

Diflunisal

Various cutaneous reactions have been reported in up to 5% of patients, including pruritus, urticaria, exanthems, Stevens–Johnson syndrome, erythroderma [1] and a lichenoid photoreactive rash [2]. A non-pigmenting fixed drug eruption has been documented [3].

References

1 Chan L, Winearls C, Oliver D *et al.* Acute interstitial nephritis and erythroderma associated with diflunisal. *BMJ* 1980; **280**: 84–5.
2 Street ML, Winkelmann RK. Lichenoid photoreactive epidermal necrosis with diflunisal. *J Am Acad Dermatol* 1989; **20**: 850–1.
3 Roetzheim RG, Herold AH, Van Durme DJ. Nonpigmenting fixed drug eruption caused by diflunisal. *J Am Acad Dermatol* 1991; **24**: 1021–2.

Paracetamol (acetaminophen)

This drug is a major metabolite of phenacetin, and has largely replaced it. Allergic reactions are very rare, considering that it has been estimated that more than 1.4 billion tablets are sold per annum in the UK [1,2]. Urticaria [3], anaphylaxis, a widespread maculopapular eruption, a fixed eruption [2,4–8] that may be non-pigmenting [8], exfoliative dermatitis [9], delayed hypersensitivity reactions [10], linear IgA bullous dermatosis [11] and figurate purpura [12] have been seen.

References
1 Stricker BHC, Meyboom RHB, Lindquist M. Acute hypersensitivity reactions to paracetamol. *BMJ* 1985; **291**: 938–9.
2 Thomas RH, Munro DD. Fixed drug eruption due to paracetamol. *Br J Dermatol* 1986; **115**: 357–9.
3 Cole FOA. Urticaria from paracetamol. *Clin Exp Dermatol* 1985; **10**: 404.
4 Guin JD, Haynie LS, Jackson D, Baker GF. Wandering fixed drug eruption: a mucocutaneous reaction to acetaminophen. *J Am Acad Dermatol* 1987; **3**: 399–402.
5 Guin JD, Baker GF. Chronic fixed drug eruption caused by acetaminophen. *Cutis* 1988; **41**: 106–8.
6 Valsecchi R. Fixed drug eruption to paracetamol. *Dermatologica* 1989; **179**: 51–8.
7 Duhra P, Porter DI. Paracetamol-induced fixed drug eruption with positive immunofluorescence findings. *Clin Exp Dermatol* 1990; **15**: 293–5.
8 Galindo PA, Borja J, Feo F *et al.* Nonpigmented fixed drug eruption caused by paracetamol. *J Invest Allergol Clin Immunol* 1999; **9**: 399–400.
9 Girdhar A, Bagga AK, Girdhar BF. Exfoliative dermatitis due to paracetamol. *Indian J Dermatol Venereol Lepr* 1984; **50**: 162–3.
10 Ibanez MD, Alonso E, Munoz MC *et al.* Delayed hypersensitivity reaction to paracetamol (acetaminophen). *Allergy* 1996; **51**: 121–3.
11 Avci O, Õkmen M, Cetiner S. Acetaminophen-induced linear IgA bullous dermatosis. *J Am Acad Dermatol* 2003; **48**: 299–301.
12 Kwon SJ, Lee CW. Figurate purpuric eruptions on the trunk: acetaminophen-induced rashes. *J Dermatol* 1998; **25**: 756–8.

Phenacetin

Capillaritis, vasculitis and a bullous pemphigoid-like eruption [1] have been documented.

Salicylamide

Use of teething jellies containing this substance has resulted in severe urticaria in infants [2].

References
1 Kashihara M, Danno K, Miyachi Y *et al.* Bullous pemphigoid-like lesions induced by phenacetin. Report of a case and an immunopathologic study. *Arch Dermatol* 1984; **120**: 1196–9.
2 Bentley-Phillips B. Infantile urticaria caused by salicylamide teething powder. *Br J Dermatol* 1968; **80**: 341.

Other NSAIDs

Dermatological aspects of the NSAIDs have been extensively reviewed [1–13]. All these drugs inhibit the enzyme cyclo-oxygenase, and decrease the production of prostaglandins and thromboxanes [6]. NSAIDs represent about 5% of all prescriptions in the UK [5] and USA [2]; nearly one in seven Americans were treated with an NSAID in 1984, and in 1986 100 million prescriptions for these drugs were written in the USA [14]. NSAIDs accounted for 25% of all suspected ADRs reported to the UK Committee on Safety of Medicines in 1986 [5,15]. Reactions to NSAIDs occur in about 1 in 50 000 administrations; NSAIDs should be avoided in patients known to be intolerant of aspirin [6]. In a large series, allergic or pseudoallergic reactions were observed in 0.2% of patients exposed to minor analgesics (including aspirin and pyrazolones, mainly metamizole, propyphenazone) and in 0.8% of patients exposed to NSAIDs (including the pyrazolone oxyphenbutazone); most reactions were cutaneous, mainly maculopapular exanthems, urticaria and angio-oedema [10]. Piroxicam, meclofenamate sodium, sulindac and zomepirac sodium had the highest reaction rates relative to the number of new prescriptions in the USA [1,2]. In contrast, naproxen, fenoprofen, ibuprofen and indometacin all had low rates of reaction; ibuprofen is available as a non-prescription drug in the USA and the UK. In another study of 2747 patients with rheumatoid arthritis, toxicity index scores computed from symptoms, laboratory abnormalities and hospitalizations attributed to NSAID therapy indicated that indometacin, tolmetin sodium and meclofenamate sodium were the most toxic, and buffered aspirin, salsalate and ibuprofen the least toxic [16].

Cutaneous adverse reactions to NSAIDs were, in order of frequency in one study [11], urticaria/angio-oedema, fixed eruptions, exanthems, erythema multiforme and Stevens–Johnson syndrome. Drug exanthems and urticaria occur in 0.2–9% of patients treated with NSAIDs [2,6]. Drug exanthems develop in 1% of patients on phenylbutazone and 0.3% of patients on indometacin [6]; they are most frequently associated with diflunisal, sulindac, meclofenamate sodium, piroxicam and phenylbutazone. All the NSAIDs, but particularly aspirin and tolmetin, may cause urticaria and anaphylactoid reactions, especially in a patient with a history of aspirin-induced urticaria. Pyrazolone NSAIDs, feprazone, nimesulide, piroxicam and flurbiprofen cause fixed drug eruptions. Although all NSAIDs may precipitate exfoliative erythroderma, this is commonest with phenylbutazone [6]. All the NSAIDs, but particularly phenylbutazone, piroxicam, fenbufen and sulindac, may cause Stevens–Johnson syndrome or TEN [6]. Oral lichenoid lesions have also been recorded with NSAIDs [17]. Psoriasis has been reported anecdotally to be exacerbated by indometacin and meclofenamate sodium, but there is no definitive evidence that NSAIDs consistently exacerbate psoriasis [5]. Contact dermatitis induced by topical NSAIDs is rare but increasing; ketoprofen and bufexamac are major contact allergens [13]. Children on NSAIDs were 2.4 times as likely to have shallow facial scars, as described in drug-induced pseudoporphyria, in one study; this relative risk was increased to 6 with naproxen [18].

Most of the NSAIDs causing photosensitivity are phenylpropionic acid derivatives: carprofen, ketoprofen, tiaprofenic acid, naproxen and nabumetone [19–24]. NSAIDs that cause photosensitivity absorb UV radiation at wavelengths longer than 310 nm, resulting in the generation of singlet oxygen molecules, which damage cell membranes [12]. The cutaneous photosensitivity appears to be elicited by a phototoxic mechanism [19–21,24]. The phototoxic reactions with NSAIDs are immediate, consisting of itching, burning, erythema and at higher fluences wealing; this contrasts with the delayed reactions associated with psoralens and tetracyclines, which produce abnormal delayed erythema or exaggerated sunburn. Propionic acid derivatives may also precipitate photourticaria by mast cell degranulation [23]. Piroxicam, an enolic acid derivative structurally unrelated to phenylpropionic acid, is the most frequently cited non-phenylpropionic acid NSAID to cause photosensitivity [20,21,25]; phototoxicity to the parent drug has not been elicited in volunteers or experimental animals, although a phototoxic metabolite has been identified *in vitro*. Indometacin, sulindac [26], meclofenamate sodium and phenylbutazone have all been associated with photosensitivity [2]. NSAIDs may cause pseudoporphyria changes [27].

Apart from the cutaneous complications, NSAIDs may cause a variety of adverse effects [14,28–30], including gastrointestinal bleeding, intestinal perforations and acute deterioration in renal function with interstitial nephritis [28]; the elderly and patients

with impaired renal function or receiving concomitant diuretic therapy are most at risk. NSAIDs may inhibit platelet aggregation and increase bleeding times [29]. Aplastic anaemia is a recognized complication, and has occurred in the same individual with two different NSAIDs (sulindac and fenbufen) [31]. Hepatic syndromes [30], pneumonitis (naproxen, ibuprofen, fenoprofen and sulindac can elicit pulmonary infiltrates with eosinophilia [32]), and neurological problems, such as headache, aseptic meningitis and dizziness, are recorded [14]. Niflumic acid and diclofenac both precipitated a dermatomyositis-like syndrome in a patient [33]. The potential for adverse interactions between NSAIDs and other drugs is considerable [14].

References

1 Stern RS, Bigby M. An expanded profile of cutaneous reactions to nonsteroid anti-inflammatory drugs. Reports to a specialty-based system for spontaneous reporting of adverse reactions to drugs. *JAMA* 1984; **252**: 1433–7.
2 Bigby M, Stern R. Cutaneous reactions to non-steroidal anti-inflammatory drugs. A review. *J Am Acad Dermatol* 1985; **12**: 866–76.
3 O'Brien WM, Bagby GF. Rare reactions to nonsteroidal anti-inflammatory drugs. *J Rheumatol* 1985; **12**: 13–20.
4 Roujeau JC. Clinical aspects of skin reactions to NSAIDs. *Scand J Rheumatol* 1987; **65** (Suppl.): 131–4.
5 Greaves MW. Pharmacology and significance of nonsteroidal antiinflammatory drugs in the treatment of skin diseases. *J Am Acad Dermatol* 1987; **16**: 751–64.
6 Bigby M. Nonsteroidal anti-inflammatory drug reactions. *Semin Dermatol* 1989; **8**: 182–6.
7 Arnaud A. Allergy and intolerance to nonsteroidal anti-inflammatory agents. *Clin Rev Allergy Immunol* 1995; **13**: 245–51.
8 Van Arsdel PP Jr. Pseudoallergic reactions to nonsteroidal anti-inflammatory drugs. *JAMA* 1991; **266**: 3343–4.
9 Bottoni A, Criscuolo D. Cutaneous adverse reactions following the administration of nonsteroidal antiinflammatory drugs and antibiotics: an Italian survey. *Int J Clin Pharmacol Ther Toxicol* 1992; **30**: 257–9.
10 Oberholzer B, Hoigne R, Hartmann K *et al.* Die Haufigkeit von unerwunschten Arzneimittelwirkungen nach Symptomen und Syndrome. Aus den Erfahrungen des CHDM und der SANZ. Als Beispiel: die allergischen und pseudoallergischen Reaktionen unter leichten Analgetika und NSAIDs. *Ther Umsch* 1993; **50**: 13–9.
11 Anonymous. Cutaneous reactions to analgesic-antipyretics and nonsteroidal anti-inflammatory drugs. Analysis of reports to the spontaneous reporting system of the Gruppo Italiano Studi Epidemiologici in Dermatologia. *Dermatology* 1993; **186**: 164–9.
12 Figueras A, Capella D, Castel JM, Laorte JR. Spontaneous reporting of adverse drug reactions to non-steroidal anti-inflammatory drugs. A report from the Spanish System of Pharmacovigilance, including an early analysis of topical and enteric-coated formulations. *Eur J Clin Pharmacol* 1994; **47**: 297–303.
13 Gebhardt M, Wollina U. Kutane Nebenwirkungen nichtsteroidaler Antiphlogistika (NSAID). *Z Rheumatol* 1995; **54**: 405–12.
14 Brooks PM, Day RO. Nonsteroidal antiinflammatory drugs: differences and similarities. *N Engl J Med* 1991; **324**: 1716–25.
15 Committee on Safety of Medicines. Nonsteroidal anti-inflammatory drugs and serious gastrointestinal adverse reaction: 1. *BMJ* 1986; **292**: 614.
16 Fries JF, Williams CA, Bloch DA. The relative toxicity of nonsteroidal antiinflammatory drugs. *Arthritis Rheum* 1991; **34**: 1353–60.
17 Hamburger J, Potts AJC. Non-steroidal anti-inflammatory drugs and oral lichenoid reactions. *BMJ* 1983; **287**: 1258.
18 Wallace CA, Farrow D, Sherry DD. Increased risk of facial scars in children taking nonsteroidal antiinflammatory drugs. *J Pediatr* 1994; **125**: 819–22.
19 Ljunggren B. Propionic acid-derived nonsteroidal anti-inflammatory drugs are phototoxic in vitro. *Photodermatology* 1985; **2**: 3–9.
20 Stern RS. Phototoxic reactions to piroxicam and other nonsteroidal antiinflammatory agents. *N Engl J Med* 1983; **309**: 186–7.
21 Diffey BL, Daymond TJ, Fairgreaves H. Phototoxic reactions to piroxicam, naproxen and tiaprofenic acid. *Br J Rheumatol* 1983; **22**: 239–42.
22 Przybilla B, Ring J, Schwab U *et al.* Photosensibilisierende Eigenschaften nichtsteroidaler Antirheumatika im Photopatch-Test. *Hautarzt* 1987; **38**: 18–25.
23 Kaidbey KH, Mitchell FN. Photosensitizing potential of certain nonsteroidal anti-inflammatory agents. *Arch Dermatol* 1989; **125**: 783–6.
24 Kochevar IE. Phototoxicity of nonsteroidal inflammatory drugs. Coincidence or specific mechanism? *Arch Dermatol* 1989; **125**: 824–6.
25 Serrano G, Bonillo J, Aliaga A *et al.* Piroxicam-induced photosensitivity and contact sensitivity to thiosalicylic acid. *J Am Acad Dermatol* 1990; **23**: 479–83.
26 Jeanmougin M, Manciet J-R, Duterque M *et al.* Photosensibilisation au sulindac. *Ann Dermatol Vénéréol* 1987; **114**: 1400–1.
27 Taylor BJ, Duffill MB. Pseudoporphyria from nonsteroidal anti-inflammatory drugs. *NZ Med J* 1987; **100**: 322–3.
28 Clive DM, Stoff JS. Renal syndromes associated with nonsteroidal anti-inflammatory drugs. *N Engl J Med* 1984; **310**: 563–72.
29 Ekenny GN. Potential renal, haematological and allergic adverse effects associated with nonsteroidal anti-inflammatory drugs. *Drugs* 1992; **44** (Suppl. 5): 31–7.
30 Carson JL, Willett LR. Toxicity of nonsteroidal anti-inflammatory drugs. An overview of the epidemiological evidence. *Drugs* 1993; **46** (Suppl. 1): 243–8.
31 Andrews R, Russell N. Aplastic anaemia associated with a non-steroidal anti-inflammatory drug: relapse after exposure to another such drug. *BMJ* 1990; **301**: 38.
32 Goodwin SD, Glenny RW. Nonsteroidal anti-inflammatory drug-associated pulmonary infiltrates with eosinophilia. Review of the literature and Food and Drug Administration Adverse Drug Reaction reports. *Arch Intern Med* 1992; **152**: 1521–4.
33 Grob JJ, Collet AM, Bonerandi JJ. Dermatomyositis-like syndrome induced by nonsteroidal anti-inflammatory agents. *Dermatologica* 1989; **178**: 58–9.

Propionic acid derivatives

Carprofen. This drug causes photosensitivity [1].

Fenbufen. Morbilliform and erythematous rashes, erythema multiforme [2], Stevens–Johnson syndrome and allergic vasculitis have been recorded rarely. Fenbufen has caused exfoliative dermatitis, haemolytic anaemia and hepatitis [3], and was the drug implicated most commonly in adverse reactions reported to the UK Committee on Safety of Medicines in 1986 and 1987. A florid erythematous rash with pulmonary eosinophilia has been described in four cases [4].

Fenoprofen. This drug has caused pruritus, urticaria, vesicobullous eruption, thrombocytopenic purpura and TEN [5].

Ibuprofen. Pruritus is the only common cutaneous reaction. When used in rheumatoid arthritis, rashes are rare, although patients with SLE are liable to develop a generalized rash with fever and abdominal symptoms [6]. Angio-oedema/urticaria [7,8], anaphylaxis [9,10], fixed eruptions [8], a linear eruption [11], vesicobullous rashes, erythema multiforme, vasculitis [12] and alopecia [13] occur. Psoriasis has been reported to be exacerbated [14]. This drug is available over the counter in the UK.

Ketoprofen. Topical application has caused photoallergic contact dermatitis [15] and systemic ketoprofen has caused pseudoporphyria.

Naproxen. The incidence of side effects is low given the widespread and long-term use of naproxen. Rashes occur in about 5% of patients; pruritus is the commonest symptom. Naproxen is associated with a photosensitivity dermatitis [16] and pseudopor-

phyria [17–21]; most photourticarial reactions are evoked by the UVA band. Urticaria/angio-oedema, anaphylaxis [22], purpura and thrombocytopenia [23], hyperhidrosis, acneiform problems in women [24], vasculitis [25,26], vesicobullous and fixed drug eruptions [27], erythema multiforme, a pustular reaction [28] and lichen planus-like reaction [29] have all been reported, as has recurrent allergic sialadenitis [30].

Tiaprofenic acid. This drug may cause photosensitivity [31].

References

1 Merot Y, Harms M, Saurat JH. Photosensibilisation au carprofén (imadyl), un nouvel anti-inflammatoire non stéroidien. *Dermatologica* 1983; **166**: 301–7.
2 Peacock A, Ledingham J. Fenbufen-induced erythema multiforme. *BMJ* 1981; **283**: 582.
3 Muthiah MM. Severe hypersensitivity reaction to fenbufen. *BMJ* 1988; **297**: 1614.
4 Burton GH. Rash and pulmonary eosinophilia associated with fenbufen. *BMJ* 1990; **300**: 82–3.
5 Stotts JS, Fang ML, Dannaker CJ, Steinman HK. Fenoprofen-induced toxic epidermal necrolysis. *J Am Acad Dermatol* 1988; **18**: 755–7.
6 Shoenfeld Y, Livni E, Shaklai M, Pinkhas J. Sensitization to ibuprofen in SLE. *JAMA* 1980; **244**: 547–8.
7 Shelley ED, Shelley WB. Ibuprofen urticaria. *J Am Acad Dermatol* 1987; **17**: 1057–8.
8 Diaz Jara M, Perez Montero A, Gracia Bara MT *et al*. Allergic reactions due to ibuprofen in children. *Pediatr Dermatol* 2001; **18**: 66–7.
9 Takahama H, Kubota Y, Mizoguchi M. A case of anaphylaxis due to ibuprofen. *J Dermatol* 2000; **27**: 337–40.
10 Kang LW, Kidon MI, Chin CW *et al*. Severe anaphylactic reaction to ibuprofen in a child with recurrent urticaria. *Pediatrics* 2007; **120**: e742–4.
11 Alfonso R, Belinchon I. Linear drug eruption. *Eur J Dermatol* 2001; **11**: 122–3.
12 Davidson KA, Ringpfeil F, Lee JB. Ibuprofen-induced bullous leukocytoclastic vasculitis. *Cutis* 2001; **67**: 303–7.
13 Meyer HC. Alopecia associated with ibuprofen. *JAMA* 1979; **242**: 142.
14 Ben-Chetrit E, Rubinow A. Exacerbation of psoriasis by ibuprofen. *Cutis* 1986; **38**: 45.
15 Alomar A. Ketoprofen photodermatitis. *Contact Dermatitis* 1985; **12**: 112–3.
16 Shelley WB, Elpern DJ, Shelley ED. Naproxen photosensitization demonstrated by challenge. *Cutis* 1986; **38**: 169–70.
17 Farr PM, Diffey BL. Pseudoporphyria due to naproxen. *Lancet* 1985; **i**: 1166–7.
18 Judd LE, Henderson DW, Hill DC. Naproxen-induced pseudoporphyria: a clinical and ultrastructural study. *Arch Dermatol* 1986; **122**: 451–4.
19 Mayou S, Black MM. Pseudoporphyria due to naproxen. *Br J Dermatol* 1986; **114**: 519–20.
20 Burns DA. Naproxen pseudoporphyria in a patient with vitiligo. *Clin Exp Dermatol* 1987; **12**: 296–7.
21 Levy ML, Barron KS, Eichenfield A, Honig PJ. Naproxen-induced pseudoporphyria: a distinctive photodermatitis. *J Pediatr* 1990; **117**: 660–4.
22 Cistero A, Urias S, Guindo J *et al*. Coronary artery spasm and acute myocardial infarction in naproxen-associated anaphylactic reaction. *Allergy* 1992; **47**: 576–8.
23 Hunt PJ, Gibbons SS. Naproxen induced thrombocytopenia: a case report. *NZ Med J* 1995; **108**: 483–4.
24 Hamman CO. Severe primary dysmenorrhea treated with naproxen. A prospective, double-blind crossover investigation. *Prostaglandins* 1980; **19**: 651–7.
25 Grennan DM, Jolly J, Holloway LJ, Palmer DG. Vasculitis in a patient receiving naproxen. *NZ Med J* 1979; **89**: 48–9.
26 Singhal PC, Faulkner M, Venkatesham J, Molho L. Hypersensitivity angiitis associated with naproxen. *Ann Allergy* 1989; **63**: 107–9.
27 Habbema L, Bruynzeel DP. Fixed drug eruption due to naproxen. *Dermatologica* 1987; **174**: 184–5.
28 Grattan CEH. Generalized pustular drug rash due to naproxen. *Dermatologica* 1989; **179**: 57–8.
29 Heymann WR, Lerman JS, Luftschein S. Naproxen-induced lichen planus. *J Am Acad Dermatol* 1984; **10**: 299–301.
30 Knulst AC, Stengs CJ, Baart de la Faille H *et al*. Salivary gland swelling following naproxen therapy. *Br J Dermatol* 1995; **133**: 647–9.
31 Neumann RA, Knobler RM, Lindemayr H. Tiaprofenic acid-induced photosensitivity. *Contact Dermatitis* 1989; **20**: 270–3.

Phenylacetic acids

Diclofenac. A variety of cutaneous adverse effects [1,2], including pruritus, urticaria, various exanthems, papulovesicular eruptions [3], delayed allergy [4], vasculitis [5], a bullous eruption associated with linear basement membrane deposition of IgA [6] and fatal erythema multiforme [1] have been recorded.

References

1 Ciucci AG. A review of spontaneously reported adverse drug reactions with diclofenac sodium (Voltarol). *Rheum Rehabil* 1979; Suppl. **2**: 116–21.
2 O'Brien WM. Adverse reactions to nonsteroidal antiinflammatory drugs. Diclofenac compared with other nonsteroidal antiinflammatory drugs. *Am J Med* 1986; **80**: 70–80.
3 Seigneuric C, Nougué J, Plantavid M. Érythème polymorphe avec atteinte muqueuse: responsabilité du diclofénac? *Ann Dermatol Vénéréol* 1982; **109**: 287.
4 Schiavino D, Papa G, Nucera E *et al*. Delayed allergy to diclofenac. *Contact Dermatitis* 1992; **26**: 357–8.
5 Bonafé J-L, Mazières B, Bouteiller G. Trisymptôme de Gougerot induit par les anti-inflammatoires. Rôle du diclofénac? *Ann Dermatol Vénéréol* 1982; **109**: 283–4.
6 Gabrielson TØ, Staerfelt F, Thune PO. Drug induced bullous dermatosis with linear IgA deposits along the basement membrane. *Acta Derm Venereol (Stockh)* 1981; **61**: 439–41.

Oxicams

Piroxicam. This drug may cause adverse cutaneous reactions in 2–3% of patients [1,2]. More than two-thirds of affected patients have photosensitivity; lesions may be vesicobullous or eczematous, and occur within 3 days of starting therapy in 50% of cases [3–10]. Photosensitivity may result from phototoxic metabolites [7]. Photocontact dermatitis developed in three patients after the application of a gel containing 0.5% piroxicam. Patch tests were positive to thiomersal and thiosalicylic acid, and photopatch tests with piroxicam were positive. Patch tests in patients with systemic photosensitivity to piroxicam were also positive for thiomersal and thiosalicylic acid. Contact allergic sensitivity to the latter is a marker for patients with a high risk of developing photosensitivity reactions to piroxicam [10,11].

Other eruptions include urticaria, maculopapular [12] or lichenoid rashes, alopecia, erythema multiforme [13] and vasculitis [14]. Piroxicam was well tolerated in patients with an urticarial reaction to a single NSAID, but provoked urticaria in 27% of patients with allergy to at least two different NSAIDs, indicating that mechanisms other than interference with prostaglandin synthesis and release of inflammatory mediators participate in allergic reactions to NSAIDs [15]. Classical fixed drug eruption [16,17] and a non-pigmenting fixed drug reaction [18], with cross-sensitivity among piroxicam, tenoxicam and droxicam in one case [19], have also been reported. Contact sensitivity to piroxicam is recorded [20]. Piroxicam was thought to have triggered subacute LE in a patient with Sjögren's syndrome and seronegative arthritis [21]. Isolated case reports of linear IgA bullous dermatosis [22], fatal pemphigus vulgaris [23] and fatal TEN [24] have appeared. The drug has caused peripheral neuropathy and erythroderma [25]. Blood dyscrasias have been reported.

References

1 Pitts N. Efficacy and safety of piroxicam. *Am J Med* 1982; **72** (Suppl. 2A): 77–87.
2 Gerber D. Adverse reactions of piroxicam. *Drug Intel Clin Phar* 1987; **21**: 707–10.
3 Stern RS. Phototoxic reactions to piroxicam and other nonsteroidal antiinflammatory agents. *N Engl J Med* 1983; **309**: 186–7.
4 Diffey BL, Daymond TJ, Fairgreaves H. Phototoxic reactions to piroxicam, naproxen and tiaprofenic acid. *Br J Rheumatol* 1983; **22**: 239–42.
5 Serrano G, Bonillo J, Aliaga A *et al.* Piroxicam-induced photosensitivity. *J Am Acad Dermatol* 1984; **11**: 113–20.
6 McKerrow KJ, Greig DE. Piroxicam-induced photosensitive dermatitis. *J Am Acad Dermatol* 1986; **15**: 1237–41.
7 Kocheva IE, Morison WL, Lamm JL *et al.* Possible mechanism of piroxicam-induced photosensitivity. *Arch Dermatol* 1986; **122**: 1283–7.
8 Kaidbey KH, Mitchell FN. Photosensitizing potential of certain nonsteroidal anti-inflammatory agents. *Arch Dermatol* 1989; **125**: 783–6.
9 Kocheva IE. Phototoxicity of nonsteroidal inflammatory drugs. Coincidence or specific mechanism? *Arch Dermatol* 1989; **125**: 824–6.
10 Serrano G, Bonillo J, Aliaga AET *et al.* Piroxicam-induced photosensitivity and contact sensitivity to thiosalicylic acid. *J Am Acad Dermatol* 1990; **23**: 479–83.
11 Trujillo MJ, de Barrio M, Rodriguez A *et al.* Piroxicam-induced photodermatitis. Cross-reactivity among oxicams. A case report. *Allergol Immunopathol* 2001; **29**: 133–6.
12 Faure M, Goujon C, Perrot H *et al.* Accidents cutanés provoqués par le piroxicam. A propos de trois observations. *Ann Dermatol Vénéréol* 1982; **109**: 255–8.
13 Bertail M-A, Cavelier B, Civatte J. Réaction au piroxicam (Feldène®). A type d'ectoderme érosive pluri-orificielle. *Ann Dermatol Vénéréol* 1982; **109**: 261–2.
14 Goebel KN, Mueller-Brodman W. Reversible overt nephropathy with Henoch–Schönlein purpura due to piroxicam. *BMJ* 1982; **284**: 311–2.
15 Carmona MJ, Blanca M, Garcia A *et al.* Intolerance to piroxicam in patients with adverse reactions to nonsteroidal antiinflammatory drugs. *J Allergy Clin Immunol* 1992; **90**: 873–9.
16 Stubb S, Reitamo S. Fixed drug eruption caused by piroxicam. *J Am Acad Dermatol* 1990; **22**: 1111–2.
17 de la Hoz B, Soria C, Fraj J *et al.* Fixed drug eruption due to piroxicam. *Int J Dermatol* 1990; **29**: 672–3.
18 Valsecchi R, Cainelli T. Nonpigmenting fixed drug reaction to piroxicam. *J Am Acad Dermatol* 1989; **21**: 1300.
19 Ordoqui E, De Barrio M, Rodriguez VM *et al.* Cross-sensitivity among oxicams in piroxicam-caused fixed drug eruption: two case reports. *Allergy* 1995; **50**: 741–4.
20 Valsecchi R, Pansera B, di Landro A, Cainelli T. Contact sensitivity to piroxicam. *Contact Dermatitis* 1993; **29**: 167.
21 Roura M, Lopez-Gil F, Umbert P. Systemic lupus erythematosus exacerbated by piroxicam. *Dermatologica* 1991; **182**: 56–8.
22 Camilleri M, Pace JL. Linear IgA bullous dermatosis induced by piroxicam. *J Eur Acad Dermatol Venereol* 1998; **10**: 70–2.
23 Martin RL, McSweeny GW, Schneider J. Fatal pemphigus vulgaris in a patient taking piroxicam. *N Engl J Med* 1983; **309**: 795–6.
24 Roujeau JC, Revuz I, Touraine R *et al.* Syndrome de Lyell au cours d'un traitement par un nouvel antiinflammatoire. *Nouv Presse Med* 1981; **10**: 3407–8.
25 Sangla I, Blin O, Jouglard J *et al.* Neuropathic axonale et toxidermie iatrogene par le piroxicam. Manifestations d'hypersensibilite? *Rev Neurol* 1993; **149**: 217–8.

Anthranilic acids

Meclofenamate sodium. Rashes occur in up to 9% of patients. More than two-thirds of reactions have been exanthematous, with prominent pruritus; vasculitic, purpuric or petechial reactions are also noted, as well as occasional urticaria, fixed drug eruption, erythema multiforme [1], exfoliative erythroderma and a vesicobullous reaction. It has been reported to exacerbate psoriasis [2]. Selective adverse reactions to glafenine and meclofenamate occurred in a patient tolerating aspirin and other cyclo-oxygenase inhibitors [3].

Mefenamic acid. Urticaria, a morbilliform eruption, fixed drug eruption [4,5], pseudoporphyria [6] and generalized exfoliative dermatitis are documented. Acute renal failure, severe thrombocytopenia and jaundice developed after a small dose of mefenamic acid in one patient with drug-dependent antibodies reacting against platelets [7].

References

1 Harrington T, Davis D. Erythema multiforme induced by meclofenamate sodium. *J Rheumatol* 1983; **10**: 169–70.
2 Meyerhoff JO. Exacerbation of psoriasis with meclofenamate. *N Engl J Med* 1983; **309**: 496.
3 Fernandez-Rivas M, de la Hoz B, Cuevas M *et al.* Hypersensitivity reactions to anthranilic acid derivatives. *Ann Allergy* 1993; **71**: 515–8.
4 Wilson DL, Otter A. Fixed drug eruption associated with mefenamic acid. *BMJ* 1986; **293**: 1243.
5 Watson A, Watt G. Fixed drug eruption to mefenamic acid. *Australas J Dermatol* 1986; **27**: 6–7.
6 O'Hagan AH, Irvine AD, Allen GE, Walsh M. Pseudoporphyria induced by mefenamic acid. *Br J Dermatol* 1998; **139**: 1131–2.
7 Schwartz D, Gremmel F, Kurz R *et al.* Case report: acute renal failure, thrombocytopenia and nonhemolytic icterus probably caused by mefenamic acid (Parkemed)-dependent antibodies. *Beitr Infusionsther* 1992; **30**: 413–5.

Heterocyclic acetic acids

Indometacin (indomethacin). Allergic reactions are very uncommon, but pruritus, urticaria, purpura and morbilliform eruptions are documented. Stomatitis [1] and thrombocytopenia occur rarely, as well as a generalized exfoliative dermatitis and TEN [2]. Vasculitis has been documented [3]. There have been rare reports of exacerbation of psoriasis [4,5]; however, indometacin in a standard dose of 75 mg/day had no significant harmful effect on psoriasis in a series of patients treated with the Ingram regimen of coal-tar bath, suberythemal UVB phototherapy and dithranol in Lassar's paste [6]. Exacerbation of dermatitis herpetiformis has been recorded [7].

References

1 Guggenheimer J, Ismail YH. Oral ulcerations associated with indomethacin therapy: report of three cases. *J Am Dent Assoc* 1975; **90**: 632–4.
2 O'Sullivan M, Hanly JG, Molloy M. A case of toxic epidermal necrolysis secondary to indomethacin. *Br J Rheumatol* 1983; **22**: 47–9.
3 Marsh FP, Almeyda JR, Levy IS. Non-thrombocytopenic purpura and acute glomerulonephritis after indomethacin therapy. *Ann Rheum Dis* 1971; **30**: 501–5.
4 Katayama H, Kawada A. Exacerbation of psoriasis induced by indomethacin. *J Dermatol* 1981; **8**: 323–7.
5 Powles AV, Griffiths CEM, Seifert MH, Fry L. Exacerbation of psoriasis by indomethacin. *Br J Dermatol* 1987; **117**: 799–800.
6 Sheehan-Dare RA, Goodfield MJD, Rowell NR. The effect of oral indomethacin on psoriasis treated with the Ingram regime. *Br J Dermatol* 1991; **125**: 253–5.
7 Griffiths CEM, Leonard JN, Fry L. Dermatitis herpetiformis exacerbated by indomethacin. *Br J Dermatol* 1985; **112**: 443–5.

Sulindac. Rashes occur in up to 9% of patients. The drug has caused anaphylaxis [1] and anaphylactoid reactions [2], photosensitivity [3], facial and oral erythema, a pernio-like reaction [4] and fixed drug eruption [5]. Stevens–Johnson syndrome [6–8], TEN [6,9], serum sickness and exfoliative erythroderma are documented. Blood dyscrasias, toxic hepatitis, pancreatitis and aseptic meningitis in patients with SLE are recorded.

Tolmetin. Anaphylactoid reactions are well recognized [10]. TEN has been recorded.

References

1 Smith F, Lindberg P. Life-threatening hypersensitivity to sulindac. *JAMA* 1980; **244**: 269–70.
2 Hyson CP, Kazakoff MA. A severe multisystem reaction to sulindac. *Arch Intern Med* 1991; **151**: 387–8.
3 Jeanmougin M, Manciet J-R, Duterque M *et al.* Photosensibilisation au sulindac. *Ann Dermatol Vénéréol* 1987; **114**: 1400–1.
4 Reinertsen J. Unusual pernio-like reaction to sulindac. *Arthritis Rheum* 1981; **24**: 1215.
5 Aram HA. Fixed drug eruption due to sulindac. *Int J Dermatol* 1984; **23**: 421.
6 Levitt L, Pearson RW. Sulindac-induced Stevens–Johnson toxic epidermal necrolysis syndrome. *JAMA* 1980; **243**: 1262–3.
7 Husain Z, Runge LA, Jabbs JM, Hyla JA. Sulindac-induced Stevens–Johnson syndrome: report of 3 cases. *J Rheumatol* 1981; **8**: 176–9.
8 Maguire FW. Stevens–Johnson syndrome due to sulindac: a case report and review of the literature. *Del Med J* 1981; **53**: 193–7.
9 Chevrant Breton J, Pibouin M, Allain H *et al.* Toxic epidermal necrolysis induced by sulindac. *Thérapie* 1985; **40**: 67–9.
10 Rossi A, Knapp D. Tolmetin-induced anaphylactoid reactions. *N Engl J Med* 1982; **307**: 499–500.

Pyrazolones

Amidopyrine (aminophenazone). This is the most dangerous of all analgesics and has caused hundreds of deaths due to blood dyscrasias. It has been withdrawn from western Europe and North America but is still available in certain parts of the world. TEN, exfoliative dermatitis and erythema multiforme are all well known.

Azapropazone. Photosensitivity is recognized [1]. A multifocal, bullous fixed drug eruption resembling erythema multiforme has been reported [2]. A bullous eruption on the face and extremities, with histological features suggestive of pemphigoid but negative immunofluorescence, has been reported [3]. The drug is contraindicated in patients receiving warfarin, as the latter medication is potentiated [4].

References

1 Olsson S, Biriell C, Boman G. Photosensitivity during treatment with azapropazone. *BMJ* 1985; **291**: 939.
2 Sowden JM, Smith AG. Multifocal fixed drug eruption mimicking erythema multiforme. *Clin Exp Dermatol* 1990; **15**: 387–8.
3 Barker DJ, Cotterill JA. Skin eruptions due to azapropazone. *Lancet* 1977; **i**: 90.
4 Win N, Mitchell DC. Azapropazone and warfarin. *BMJ* 1991; **302**: 969–70.

Phenylbutazone and oxyphenbutazone. Reactions have been frequent and often fatal [1,2]. Therefore, in the UK oxyphenbutazone has been withdrawn and phenylbutazone is restricted to hospital use for ankylosing spondylitis. Pruritus, morbilliform eruptions, urticaria and buccal ulceration are most common; erythema multiforme, fixed eruptions (especially with oxyphenbutazone), generalized exfoliative dermatitis and TEN [3] are all well-documented hazards. Drug exanthems or erythroderma may occur in up to 4% of patients treated with phenylbutazone. Occasional reports of exacerbation of psoriasis have occurred [4]. Rarer reactions have included generalized lymphadenopathy, a Sjögren-like syndrome, non-thrombocytopenic purpura, allergic vasculitis [5] and polyarteritis nodosa. Provocation of temporal arteritis has been reported. A haemorrhagic bullous eruption of the hands was observed in three patients [6]. Cutaneous necrosis has been seen after intramuscular injection. Phenylbutazone causes fluid retention, gastrointestinal bleeding and bone marrow depression [2]; the hazards of the latter are greatly increased if the dose exceeds 200 mg/day.

References

1 Van Joost T, Asghar SS, Cormane RH. Skin reactions caused by phenylbutazone. Immunologic studies. *Arch Dermatol* 1974; **110**: 929–33.
2 Inman WHW. Study of fatal bone marrow depression with special reference to phenylbutazone and oxyphenbutazone. *BMJ* 1977; **i**: 1500–5.
3 Montgomery PR. Toxic epidermal necrolysis due to phenylbutazone. *Br J Dermatol* 1970; **83**: 220.
4 Reshad H, Hargreaves GK, Vickers CFH. Generalized pustular psoriasis precipitated by phenylbutazone and oxyphenbutazone. *Br J Dermatol* 1983; **109**: 111–3.
5 Von Paschoud J-M. Vasculitis allergica cutis durch phenylbutazon. *Dermatologica* 1966; **133**: 76–86.
6 Millard LG. A haemorrhagic bullous eruption of the hands caused by phenylbutazone: a report of 3 cases. *Acta Derm Venereol (Stockh)* 1977; **57**: 83–6.

Cyclo-oxygenase-2 inhibitors

Erythema multiforme, Stevens–Johnson syndrome and toxic epidermal necrolysis (TEN) have rarely been reported with the cyclo-oxygenase (COX)-2 selective inhibitors celecoxib, rofecoxib, etoricoxib and valdecoxib [1,2].

Celecoxib. Angio-oedema [3], fixed drug eruption [4] and Sweet's syndrome [5] are documented.

Nabumetone. A severe, immediate reaction with pruritus, erythema, palm erythema, a morbilliform eruption and a sensation of a swollen tongue has been documented [6].

Nimesulide. A fixed eruption is recorded [7].

Valdecoxib. Erythematous, target-like skin eruptions with facial oedema and dyspnoea occur [8].

References

1 Layton D, Marshall V, Boshier A *et al*. Serious skin reactions and selective COX-2 inhibitors: a case series from prescription-event monitoring in England. *Drug Saf* 2006; **29**: 687–96.
2 La Grenade L, Lee L, Weaver J *et al*. Comparison of reporting of Stevens–Johnson syndrome and toxic epidermal necrolysis in association with selective COX-2 inhibitors. *Drug Saf* 2005; **28**: 917–24.
3 Liccardi G, Cazzola M, De Giglio C *et al*. Safety of celecoxib in patients with adverse skin reactions to acetaminophen (paracetamol) and other non-steroidal anti-inflammatory drugs. *J Investig Allergol Clin Immunol* 2005; **15**: 249–53.
4 Bandyopadhyay D. Celecoxib-induced fixed drug eruption. *Clin Exp Dermatol* 2003; **28**: 452.
5 Fye KH, Crowley E, Berger TG *et al.* Celecoxib-induced Sweet's syndrome. *J Am Acad Dermatol* 2001; **45**: 300–2.
6 Gonzalo-Garijo MA, Cordobés-Duran C, Lamilla-Yerga AM, Moreno-Gastón I. Severe immediate reaction to nabumetone. *J Investig Allergol Clin Immunol* 2007; **17**: 274–6.
7 Malheiro D, Cadinha S, Rodrigues J *et al*. Nimesulide-induced fixed drug eruption. *Allergol Immunopathol (Madr)* 2005; **33**: 285–7.
8 Ziemer M, Wiesend CL, Vetter R *et al*. Cutaneous adverse reactions to valdecoxib distinct from Stevens–Johnson syndrome and toxic epidermal necrolysis. *Arch Dermatol* 2007; **143**: 711–6.

Miscellaneous anti-inflammatory agents

Benzydamine

Photoallergy has been described to both topical and systemic administration of this drug [1].

Reference

1 Frosch PJ, Weickel R. Photokontakallergie durch Benzydamin (Tantum). *Hautarzt* 1989; **40**: 771–3.

Allopurinol

Dermatological complications occur in up to 10% of cases [1–7]. Acute sensitivity reactions are well known, including scarlatiniform erythema, morbilliform rashes, urticaria or generalized exfoliative dermatitis, which may be associated with fever, eosinophilia, hepatic abnormalities and a nephropathy. Vasculitis (perhaps triggered by oxypurinol, the principal metabolite of allopurinol, which has a long half-life and accumulates in renal failure [5]), erythema multiforme [7], Stevens–Johnson syndrome and TEN [5,8,9] have been reported. Cell-mediated immunity directed towards allopurinol, and more importantly to its oxypurinol metabolite, is thought to be involved in the pathogenesis of allopurinol-induced hypersensitivity [10]. Hypersensitivity reactions occur on average within 2–6 weeks of starting the drug, although the interval may be much longer. Eruptions are commoner in the setting of impaired renal function [11] and with concomitant thiazide therapy [12], and may first appear up to 3 weeks after the drug has been discontinued [13]. The mortality is about 20% [5]. Other allopurinol-induced cutaneous changes include alopecia and ichthyosis [14]. Allopurinol potentiates the risk of a reaction to ampicillin [15] and increases blood ciclosporin levels [16]. Desensitization may be successful in cases with minor rashes induced by allopurinol [17–19].

References

1 Lupton GP. The allopurinol hypersensitivity syndrome. *J Am Acad Dermatol* 1979; **1**: 365–74.
2 McInnes GT, Lawson DH, Jick H. Acute adverse reactions attributed to allopurinol in hospitalised patients. *Ann Rheum Dis* 1981; **40**: 245–9.
3 Singer JZ, Wallace SL. The allopurinol hypersensitivity syndrome. Unnecessary morbidity and mortality. *Arthritis Rheum* 1986; **29**: 82–7.
4 Foucault V, Pibouin M, Lehry D *et al.* Accidents médicamenteux sévères et allopurinol. *Ann Dermatol Vénéréol* 1988; **115**: 1169–72.
5 Arellano F, Sacristan JA. Allopurinol hypersensitivity syndrome: a review. *Ann Pharmacother* 1993; **27**: 337–43.
6 Elasy T, Kaminsky D, Tracy M, Mehler PS. Allopurinol hypersensitivity syndrome revisited. *West J Med* 1995; **162**: 360–1.
7 Kumar A, Edward N, White MI *et al.* Allopurinol, erythema multiforme, and renal insufficiency. *BMJ* 1996; **312**: 173–4.
8 Bennett TO, Sugar J, Sahgal S. Ocular manifestations of toxic epidermal necrolysis associated with allopurinol use. *Arch Ophthalmol* 1977; **95**: 1362–4.
9 Dan M, Jedwab M, Peled M *et al.* Allopurinol-induced toxic epidermal necrolysis. *Int J Dermatol* 1984; **23**: 142–4.
10 Braden GL, Warzynski MJ, Golightly M, Ballow M. Cell-mediated immunity in allopurinol-induced hypersensitivity. *Clin Immunol Immunopathol* 1994; **70**: 145–51.
11 Handke KR, Noone RM, Stone WJ. Severe allopurinol toxicity. Description and guidelines for prevention in patients with renal insufficiency. *Am J Med* 1984; **76**: 47–56.
12 Handke KR. Evaluation of a thiazide allopurinol drug interaction. *Am J Med Sci* 1986; **292**: 213–6.
13 Bigby M, Jick S, Jick H, Arndt K. Drug-induced cutaneous reactions. A report from the Boston Collaborative Drug Surveillance Program on 15438 consecutive inpatients, 1975 to 1982. *JAMA* 1986; **256**: 3358–63.
14 Auerbach R, Orentreich N. Alopecia and ichthyosis secondary to allopurinol. *Arch Dermatol* 1968; **98**: 104.
15 Jick H, Slone D, Shapiro S *et al.* Excess of ampicillin rashes associated with allopurinol or hyperuricemia. A report from the Boston Collaborative Drug Surveillance Program, Boston University Medical Center. *N Engl J Med* 1972; **286**: 505–7.
16 Gorrie M, Beaman M, Nicholls A, Backwell A. Allopurinol interaction with cyclosporin. *BMJ* 1994; **308**: 113.
17 Fam AG, Lewtas J, Stein J, Paton TW. Desensitization to allopurinol in patients with gout and cutaneous reactions. *Am J Med* 1992; **93**: 299–302.
18 Kelso JM, Keating RM. Successful desensitization for treatment of a fixed drug eruption to allopurinol. *J Allergy Clin Immunol* 1996; **97**: 1171–2.
19 Walz-LeBlanc BA, Reynolds WJ, MacFadden DK. Allopurinol sensitivity in a patient with chronic tophaceous gout: success of intravenous desensitization after failure of oral desensitization. *Arthritis Rheum* 1991; **34**: 1329–31.

Drugs acting on the central nervous system

Psychotropic medication

The adverse effects of psychotropic medication have been reviewed [1–4]; the prevalence of skin reactions to psychotropic medications is about 5% [2].

References

1 Gupta MA, Gupta AK, Haberman HF. Psychotropic drugs in dermatology. A review and guidelines for use. *J Am Acad Dermatol* 1986; **14**: 633–45.
2 Srebrnik A, Hes JP, Brenner S. Adverse cutaneous reactions to psychotropic drugs. *Acta Derm Venereol Suppl (Stockh)* 1991; **158**: 1–12.
3 Kimyai-Asadi A, Harris JC, Nousari HC. Critical overview: adverse cutaneous reactions to psychotropic medications. *J Clin Psychiatry* 1999; **60**: 714–25.
4 Warnock JK, Morris DW. Adverse cutaneous reactions to mood stabilizers. *Am J Clin Dermatol* 2003; **4**: 21–30.

Antidepressants

Tricyclics and related compounds

Antidepressants are associated with a range of idiosyncratic reactions affecting the liver, skin, haematological and central nervous systems; reactions are mediated by chemically reactive metabolites formed by the cytochrome P-450 enzyme system either directly or indirectly via an immune mechanism. Individual susceptibility is determined by genetic and environmental factors, which result in inadequate detoxification of the chemically reactive metabolite [1]. Sedative, cardiovascular, anticholinergic and gastrointestinal side effects are well known [2,3]. Agranulocytosis may occur occasionally. Cutaneous reactions are rare [2] but include maculopapular rashes, photosensitivity (protriptyline and imipramine), urticaria, pruritus, hyperhidrosis, vasculitis or acne (maprotiline), and TEN (amoxapine).

Amineptine. Severe acne [4,5] and rosacea [6] have been reported.

Amitriptyline. A bullous reaction in a patient with overdosage of amitriptyline and clorazepate dipotassium has been reported [7]. Alopecia is documented.

Clomipramine. A photoallergic eruption [8] and a hypersensitivity reaction associated with human herpesvirus-6 reactivation [9] have been documented.

Imipramine. This drug has caused urticarial or exanthematic eruptions occasionally [10] and agranulocytosis has occurred. Oedema of the feet is seen in older people. Glossitis and stomatitis are rare, as are transient erythema of the face, photosensitivity and exfoliative dermatitis. Slate-grey pigmentation of exposed skin may develop; golden-yellow granules, which ultrastructurally are electron-dense inclusion bodies in phagocytes, fibroblasts and dendrocytes, are seen in the papillary dermis [11–13]. Q-switched alexandrite and ruby lasers may be helpful in treating the pigmentation [14]. Cutaneous vasculitis is well documented. Atypical cutaneous lymphoid hyperplasia has been documented [15].

Maprotiline. Acne [16] and vasculitis [17] are recorded.

Mianserin. Erythema multiforme has recently been reported [18], as has a severe allergic reaction [19].

Trazodone. This drug has caused leukonychia [20], erythema multiforme [21] and vasculitis [22], and has been implicated in causing a psoriasiform eruption. Skin swelling is recorded [23].

References

1 Pirmohamed M, Kitteringham NR, Park BK. Idiosyncratic reactions to antidepressants: a review of the possible mechanisms and predisposing factors. *Pharmacol Ther* 1992; **53**: 105–25.
2 Gupta MA, Gupta AK, Haberman HF. Psychotropic drugs in dermatology. A review and guidelines for use. *J Am Acad Dermatol* 1986; **14**: 633–45.
3 Gupta MA, Gupta AK, Ellis CN. Antidepressant drugs in dermatology. An update. *Arch Dermatol* 1987; **123**: 647–52.
4 Thioly-Bensoussan D, Edelson Y, Cardinne A, Grupper C. Acné monstrueuse iatrogène provoquée par le Survector®: première observation mondiale à propos de deux cas. *Nouv Dermatol* 1987; **6**: 535–7.
5 De Galvez Aranda MV, Sanchez PS, Alonso Corral MJ *et al.* Acneiform eruption caused by amineptine. A case report and review of the literature. *J Eur Acad Dermatol Venereol* 2001; **15**: 337–9.
6 Jeanmougin M, Civatte J, Cavelier-Balloy B. Toxiderme rosaceiforme a l'amineptine (Survector). *Ann Dermatol Vénéréol* 1988; **115**: 1185–6.
7 Herschtal D, Robinson MJ. Blisters of the skin in coma induced by amitriptyline and clorazepate dipotassium. Report of a case with underlying sweat gland necrosis. *Arch Dermatol* 1979; **115**: 499.
8 Ljunggren B, Bojs G. A case of photosensitivity and contact allergy to systemic tricyclic drugs, with unusual features. *Contact Dermatitis* 1991; **24**: 259–65.
9 Nishimura Y, Kitoh A, Yoshida Y, Tanaka T. Clomipramine-induced hypersensitivity syndrome with unusual clinical features. *J Am Acad Dermatol* 2005; **53** (5 Suppl. 1): S231–3.
10 Almeyda J. Drug reactions XIII. Cutaneous reactions to imipramine and chlordiazepoxide. *Br J Dermatol* 1971; **84**: 298–9.
11 Hashimoto K, Joselow SA, Tye MJ. Imipramine hyperpigmentation: a slate-gray discoloration caused by long-term imipramine administration. *J Am Acad Dermatol* 1991; **25**: 357–61.
12 Ming ME, Bhawan J, Stefanato CM *et al.* Imipramine-induced hyperpigmentation: four cases and a review of the literature. *J Am Acad Dermatol* 1999; **40**: 159–66.
13 Sicari MC, Lebwohl M, Baral J *et al.* Photoinduced dermal pigmentation in patients taking tricyclic antidepressants: histology, electron microscopy, and energy dispersive spectroscopy. *J Am Acad Dermatol* 1999; **40**: 290–3.
14 Atkin DH, Fitzpatrick RE. Laser treatment of imipramin-induced hyperpigmentation. *J Am Acad Dermatol* 2000; **43**: 77–80.
15 Crowson AN, Magro CM. Antidepressant therapy. A possible cause of atypical cutaneous lymphoid hyperplasia. *Arch Dermatol* 1995; **131**: 925–9.
16 Ponte CD. Maprotiline-induced acne. *Am J Psychiatry* 1982; **139**: 141.
17 Oakley AM, Hodge L. Cutaneous vasculitis from maprotiline. *Aust NZ J Med* 1985; **15**: 256–7.
18 Quraishy E. Erythema multiforme during treatment with mianserin. *Br J Dermatol* 1981; **104**: 481.
19 Bazin N, Beaufils B, Feline A. A severe allergic reaction to mianserin. *Am J Psychiatry* 1991; **148**: 1088–9.
20 Longstreth GF, Hershman J. Trazodone-induced hepatotoxicity and leukonychia. *J Am Acad Dermatol* 1985; **13**: 149–50.
21 Ford HE, Jenike MA. Erythema multiforme associated with trazodone therapy. *J Clin Psychiatry* 1985; **46**: 294–5.
22 Mann SC, Walker MM, Messenger GG *et al.* Leukocytoclastic vasculitis secondary to trazodone treatment. *J Am Acad Dermatol* 1984; **10**: 669–70.
23 Fisher S, Bryant SG, Kent TA. Postmarketing surveillance by patient self-monitoring: trazodone versus fluoxetine. *J Clin Psychopharmacol* 1993; **13**: 235–42.

Monoamine oxidase inhibitors

Iproniazid. Vasculitis and peripheral neuritis are documented.

Phenelzine. Hypersensitivity skin reactions are rare.

Selective serotonin reuptake inhibitors

Fluoxetine. This drug has caused urticaria [1], urticarial vasculitis [2], hypersensitivity [3], and serum sickness [4]; familial cases are documented [5]. Atypical cutaneous lymphoid hyperplasia [6], including pseudomycosis fungoides [6–8], is recorded.

Paroxetine. Exanthematous hypersensitivity [9] and vasculitis [10,11] have been reported.

Miscellaneous selective serotonin reuptake inhibitors

The 5-HT_3 receptor antagonists granisetron, ondansetron and tropisetron are antiemetic medications used during chemotherapy. Effects include headache and gastrointestinal symptoms, and rarely hypersensitivity reactions [12]. There were no cross-over reactions to citalopram or paroxetine among patients hypersensitive to zimeldine [13]. Alopecia has been caused rarely with sertraline and citalopram [14].

Mirtazapine

This presynaptic alpha$_2$ adrenoreceptor antagonist has caused increased liver enzymes, cutaneous oedema and collapse [15].

References

1 Leznoff A, Binkley KE, Joffee RT *et al.* Adverse cutaneous reactions associated with fluoxetine strategy for reintroduction of this drug in selected patients. *J Clin Psychopharmacol* 1992; **12**: 355–7.
2 Roger D, Rolle F, Mausset J *et al.* Urticarial vasculitis induced by fluoxetine. *Dermatology* 1995; **191**: 164.
3 Beer K, Albertini J, Medenica M, Busbey S. Fluoxetine-induced hypersensitivity. *Arch Dermatol* 1994; **130**: 803–4.
4 Shapiro LE, Knowles SR, Shear NH. Fluoxetine-induced serum sickness-like reaction. *Ann Pharmacother* 1997; **31**: 927.
5 Olfson M, Wilner MT. A family case history of fluoxetine-induced skin reactions. *J Nerv Ment Dis* 1991; **179**: 504–5.
6 Crowson AN, Magro CM. Antidepressant therapy. A possible cause of atypical cutaneous lymphoid hyperplasia. *Arch Dermatol* 1995; **131**: 925–9.
7 Gordon KB, Guitart J, Kuzel T *et al.* Pseudomycosis fungoides in a patient taking clonazepam and fluoxetine. *J Am Acad Dermatol* 1996; **34**: 304–6.
8 Vermeer MH, Willemze R. Is mycosis fungoides exacerbated by fluoxetine? *J Am Acad Dermatol* 1996; **35**: 635–6.
9 Mera MT, Pérez BV, Fernández RO, Iglesias JF. Hypersensitivity to paroxetine. *Allergol Immunopathol (Madr)* 2006; **34**: 125–6.
10 Margolese HC, Chouinard G, Beauclair L, Rubino M. Cutaneous vasculitis induced by paroxetine. *Am J Psychiatry* 2001; **158**: 497.

11 Welsh JP, Cusack CA, Ko C. Urticarial vasculitis secondary to paroxetine. *J Drugs Dermatol* 2006; **5**: 1012–4.
12 Kataja V, de Bruijn KM. Hypersensitivity reactions associated with 5-hydroxytryptamine(3)-receptor antagonists: a class effect? *Lancet* 1996; **347**: 584–5.
13 Bengtsson BO, Lundmark J, Walinder J. No crossover reactions to citalopram or paroxetine among patients hypersensitive to zimeldine. *Br J Psychiatry* 1991; **158**: 853–5.
14 Hedenmalm K, Sundström A, Spigset O. Alopecia associated with treatment with selective serotonin reuptake inhibitors (SSRIs). *Pharmacoepidemiol Drug Saf* 2006; **15**: 719–25.
15 Degner D, Grohmann R, Kropp S. Severe adverse drug reactions of antidepressants: results of the German multicenter drug surveillance program AMSP. *Pharmacopsychiatry* 2004; **37** (Suppl. 1): S39–45.

Lithium

Skin reactions [1–5] are relatively uncommon. Pustular and psoriasiform lesions induced by this drug have received particular attention [6]. The pustular propensities of lithium have been attributed to lysosomal enzyme release and increased neutrophil chemotaxis [2]. Tetracycline should be avoided in treating these pustular eruptions as it may precipitate serious lithium toxicity. The acneiform 'erysipelas' eruption consists of monomorphic pustules on an erythematous base, tends to affect mainly the arms and legs, is not associated with comedones or cystic lesions, and may be very persistent. Various patterns of folliculitis may occur. Lithium can aggravate pre-existing psoriasis, making it more difficult to control [6–10], and may precipitate a palmoplantar pustular reaction [11] or even generalized pustular psoriasis [12]. Psychiatrists should avoid the use of lithium in psoriatics if possible. Darier's disease may also be exacerbated or initiated [13,14].

Additional reactions described include morbilliform rashes, erythema multiforme [15], a dermatitis herpetiformis-like rash [16], linear IgA bullous dermatosis [17] and a generalized exfoliative eruption [18]. An LE-like syndrome [19] with increased prevalence of antinuclear antibodies [20], toenail dystrophy [21] and hair loss [22,23] have been reported. Keratoderma has been documented [24], as has hidradenitis suppurativa [25]. None of these effects is related to excessive blood levels of lithium or other evidence of toxicity.

References

1 Callaway CL, Hendrie HC, Luby ED. Cutaneous conditions observed in patients during treatment with lithium. *Am J Psychiatry* 1968; **124**: 1124–5.
2 Heng MCY. Cutaneous manifestations of lithium toxicity. *Br J Dermatol* 1982; **106**: 107–9.
3 Deandrea D, Walker N, Mehlmauer M, White K. Dermatological reactions to lithium: a review. *J Clin Psychopharmacol* 1982; **2**: 199–204.
4 Sarantidis D, Waters B. A review and controlled study of cutaneous conditions associated with lithium carbonate. *Br J Psychiatry* 1983; **143**: 42–50.
5 Albrecht G. Unerwünschte Wirkungen von Lithium an der Haut. *Hautarzt* 1985; **36**: 77–82.
6 Chan HH, Wing Y, Su R *et al.* A control study of the cutaneous side effects of chronic lithium therapy. *J Affective Disord* 2000; **57**: 107–13.
7 Lazarus GS, Gilgor RS. Psoriasis, polymorphonuclear leukocytes, and lithium carbonate. An important clue. *Arch Dermatol* 1979; **115**: 1183–4.
8 Skoven I, Thormann J. Lithium compound treatment and psoriasis. *Arch Dermatol* 1979; **115**: 1185–7.
9 Abel EA, Dicicco LM, Orenberg EK *et al.* Drugs in exacerbation of psoriasis. *J Am Acad Dermatol* 1986; **15**: 1007–22.
10 Sasaki T, Saito S, Aihara M *et al.* Exacerbation of psoriasis during lithium treatment. *J Dermatol* 1989; **16**: 59–63.
11 White SW. Palmoplantar pustular psoriasis provoked by lithium therapy. *J Am Acad Dermatol* 1982; **7**: 660–2.
12 Lowe NJ, Ridgway HB. Generalized pustular psoriasis precipitated by lithium. *Arch Dermatol* 1978; **114**: 1788–9.
13 Milton GP, Peck GL, Fu J-J *et al.* Exacerbation of Darier's disease by lithium carbonate. *J Am Acad Dermatol* 1990; **23**: 926–8.
14 Rubin MB. Lithium-induced Darier's disease. *J Am Acad Dermatol* 1996; **32**: 674–5.
15 Balldin J, Berggren U, Heijer A, Mobacken H. Erythema multiforme caused by lithium. *J Am Acad Dermatol* 1991; **24**: 1015–6.
16 Meinhold JM, West DP, Gurwich E *et al.* Cutaneous reaction to lithium carbonate: a case report. *J Clin Psychiatry* 1980; **41**: 395–6.
17 McWhirter JD, Hashimoto K, Fayne S *et al.* Linear IgA bullous dermatosis related to lithium carbonate. *Arch Dermatol* 1987; **123**: 1120–2.
18 Kuhnley EJ, Granoff AL. Exfoliative dermatitis during lithium treatment. *Am J Psychiatry* 1979; **136**: 1340–1.
19 Shukla VR, Borison RL. Lithium and lupus-like syndrome. *JAMA* 1982; **248**: 921–2.
20 Presley AP, Kahn A, Williamson N. Antinuclear antibodies in patients on lithium carbonate. *BMJ* 1976; **ii**: 280–1.
21 Hooper JF. Lithium carbonate and toenails. *Am J Psychiatry* 1981; **138**: 1519.
22 Dawber R, Mortimer P. Hair loss during lithium treatment. *Br J Dermatol* 1982; **107**: 124–5.
23 Orwin A. Hair loss following lithium therapy. *Br J Dermatol* 1983; **108**: 503–4.
24 Labelle A, Lapierre YD. Keratodermia: side effects of lithium. *J Clin Psychopharmacol* 1991; **11**: 149–50.
25 Gupta AK, Knowles SR, Gupta MA *et al.* Lithium therapy associated with hidradenitis suppurativa: case report and a review of the dermatologic side effects of lithium. *J Am Acad Dermatol* 1995; **32**: 382–6.

Hypnotics, sedatives and anxiolytics

Barbiturates

A toxic bullous eruption may appear at pressure points in comatose patients after overdosage [1–4]. In one series, 8% of patients admitted with drug-induced coma had such bullae [3] (see Fig. 75.5). The bullae are few, large and may lead to ulceration [2]. Necrotic lesions are seen in 4% of patients recovering from, and in 40% of fatalities related to, barbiturate-induced coma [4]. Allergic reactions are very uncommon and may be scarlatiniform or morbilliform. Exfoliative dermatitis has proved fatal [5], as has erythema multiforme. Urticaria and serum sickness are very rare, as is purpuric capillaritis. Fixed eruptions are well known [6] and particularly occur on the glans penis. TEN, LE-like syndrome, purpura and photosensitivity are recorded [7]. Phenobarbital is one cause of the anticonvulsant hypersensitivity syndrome (see p. 75.44) [8,9]. In one case, a syndrome resembling Langerhans' cell histiocytosis was produced [10]. Hypopigmentation may follow a severe reaction [11]. Exfoliative dermatitis is recorded [12].

References

1 Beveridge GW, Lawson AAH. Occurrence of bullous lesions in acute barbiturate intoxication. *BMJ* 1965; **i**: 835–7.
2 Gröschel D, Gerstein AR, Rosenbaum JM. Skin lesions as a diagnostic aid in barbiturate poisoning. *N Engl J Med* 1970; **283**: 409–10.
3 Pinkus NB. Skin eruptions in drug-induced coma. *Med J Aust* 1971; **2**: 886–8.
4 Almeyda J, Levantine A. Drug reactions XVII. Cutaneous reactions to barbiturates, chloralhydrate and its derivatives. *Br J Dermatol* 1972; **86**: 313–6.
5 Sneddon IB, Leishman AWD. Severe and fatal phenobarbitone eruptions. *BMJ* 1952; **i**: 1276–8.
6 Korkij W, Soltani K. Fixed drug eruption. A brief review. *Arch Dermatol* 1984; **120**: 520–4.
7 Gupta MA, Gupta AK, Haberman HF. Psychotropic drugs in dermatology. A review and guidelines for use. *J Am Acad Dermatol* 1986; **14**: 633–45.

8 Vittorio CC, Muglia JJ. Anticonvulsant hypersensitivity syndrome. *Arch Intern Med* 1995; **155**: 2285–90.
9 De Vriese AS, Philippe J, Van Renterghem DM *et al.* Carbamazepine hypersensitivity syndrome: report of 4 cases and review of the literature. *Medicine (Baltimore)* 1995; **74**: 144–51.
10 Nagata T, Kawamura N, Motoyama T *et al.* A case of hypersensitivity syndrome resembling Langerhans cell histiocytosis during phenobarbital prophylaxis for convulsion. *Jpn J Clin Oncol* 1992; **22**: 421–7.
11 Mion N, Fusade T, Mathelier-Fusade P *et al.* Depigmentation cutaneo-phanerienne consecutive a une toxidermie au phenobarbital. *Ann Dermatol Vénéréol* 1992; **119**: 927–9.
12 Sawaishi Y, Komatsu K, Takeda O *et al.* A case of tubulo-interstitial nephritis with exfoliative dermatitis and hepatitis due to phenobarbital hypersensitivity. *Eur J Pediatr* 1992; **151**: 69–72.

Benzodiazepines

Allergic reactions are very rare [1].

Alprazolam. Photosensitivity has been recorded with this newer benzodiazepine [2].

Chlordiazepoxide. Morbilliform erythema, urticaria [3], fixed eruption [4], photoallergic eczema [5] and exacerbation of porphyria have been recorded. Erythema multiforme and chronic pigmented purpuric eruption occur rarely [6].

Clobazam. A generalized erythematous pruritic eruption [7] and TEN confined to light-exposed areas [8] have been reported. There has been a report of coma-induced bullae and sweat gland necrosis associated with the drug [9].

Diazepam and nitrazepam. Bullae similar to those seen after barbiturates may occur in comatose patients after overdosage [10,11]. Thrombophlebitis may follow intravenous injection of diazepam [12]. Hyperpigmentation in previously dermabraded scars has been attributed to diazepam [13]. Vasculitis is documented [14]. An eruption comprising oedema, moon face and generalized erythema, with erosions of cheeks, axillae and the genitocrural area was attributed to nitrazepam; a provocation test was positive [15].

Lormetazepam. A fixed drug eruption has been reported [16].

Temazepam. An extensive fixed drug eruption has been reported [17]. Extravasation following attempted femoral vein injection of a suspension of the contents of capsules in tap water, by an addict, resulted in extensive necrosis of genital and pubic skin [18].

References

1 Edwards JG. Adverse effects of antianxiety drugs. *Drugs* 1981; **22**: 495–514.
2 Kanwar AJ, Gupta R, Das Mehta S, Kaur S. Photosensitivity to alprazolam. *Dermatologica* 1990; **181**: 75.
3 Almeyda J. Drug reactions XIII. Cutaneous reactions to imipramine and chlordiazepoxide. *Br J Dermatol* 1971; **84**: 298–9.
4 Blair HM III. Fixed drug eruption from chlordiazepoxide: report of a case. *Arch Dermatol* 1974; **109**: 914.
5 Luton EF, Finchum RN. Photosensitivity reaction to chlordiazepoxide. *Arch Dermatol* 1965; **91**: 362–3.
6 Nishioka K, Katayama I, Masuzawa M *et al.* Drug-induced chronic pigmented purpura. *J Dermatol* 1989; **16**: 220–2.
7 Machet L, Vaillant L, Dardaine V, Lorette G. Patch testing with clobazam: relapse of generalised drug eruption. *Contact Dermatitis* 1992; **26**: 347–8.
8 Redondo P, Vicente J, España A *et al.* Photo-induced toxic epidermal necrolysis caused by clobazam. *Br J Dermatol* 1996; **135**: 999–1002.
9 Setterfield JF, Robinson R, MacDonald D, Calonje E. Coma-induced bullae and sweat gland necrosis following clobazam. *Clin Exp Dermatol* 2000; **25**: 215–8.
10 Ridley CM. Bullous lesions in nitrazepam-overdosage. *BMJ* 1971; **iii**: 28.
11 Varma AJ, Fisher BK, Sarin MK. Diazepam-induced coma with bullae and eccrine sweat gland necrosis. *Arch Intern Med* 1977; **137**: 1207–10.
12 Langdon DE, Harlan JR, Bailey RL. Thrombophlebitis with diazepam used intravenously. *JAMA* 1973; **223**: 184–5.
13 Fereira JA. The role of diazepam in skin hyperpigmentation. *Aesthetic Plast Surg* 1980; **4**: 343–8.
14 Olcina GM, Simonart T. Severe vasculitis after therapy with diazepam. *Am J Psychiatry* 1999; **156**: 972–3.
15 Shoji A, Kitajima J, Hamada T. Drug eruption caused by nitrazepam in a patient with severe pustular psoriasis successfully treated with methotrexate and etretinate. *J Dermatol* 1987; **14**: 274–8.
16 Jafferany M, Haroon TS. Fixed drug eruption with lormetazepam (Noctamid). *Dermatologica* 1988; **177**: 386.
17 Archer CB, English JSC. Extensive fixed drug eruption induced by temazepam. *Clin Exp Dermatol* 1988; **13**: 336–8.
18 Meshikhes AN, Duthie JS. Untitled report. *BMJ* 1991; **303**: 478.

Miscellaneous hypnotics, sedatives and anxiolytics

Carbromal

This drug, now rarely used, commonly produced a characteristic capillaritis with punctate purpura and haemosiderin giving a golden-brown discoloration of the skin, especially on the legs [1].

Chloral hydrate

Hypersensitivity reactions are very rare. Chloral is now virtually only given in tablet form as dichloralphenazone, in which the phenazone may cause a fixed eruption [2].

Ethchlorvynol

Overdose has caused bullous lesions [3].

Glutethimide

Dermographism with subsequent erythema, and vesicles that lasted several days, were reported in one comatose patient [4] and bullae in another patient [5] following overdosage. Fixed eruptions are recorded [6].

Meprobamate

Anorexia, drowsiness, dizziness, flushing and gastrointestinal symptoms may occur, especially with high doses. Fixed eruptions may occur [7]. The most characteristic cutaneous reaction, preceded by itching, malaise and fever, is an erythema starting in the limb flexures that rapidly gives way to a fierce non-thrombocytopenic purpura [8]. A widespread toxic erythema was associated with an anaphylactoid reaction in a patient in whom patch testing proved useful in diagnosis [9].

References

1 Peterson WC Jr, Manick KP. Purpuric eruptions associated with use of carbromal and meprobamate. *Arch Dermatol* 1967; **95**: 40–2.
2 McCulloch H, Zeligman I. Fixed drug eruption and epididymitis due to antipyrine. *Arch Dermatol Syphilol* 1951; **64**: 198–9.

3 Brodin MD, Redmon WJ. Bullous eruptions due to ethchlorvynol. *J Cutan Pathol* 1980; **7**: 326–9.
4 Leavell UW Jr, Coyer JR, Taylor RJ. Dermographism and erythematous lines in glutethimide overdose. *Arch Dermatol* 1972; **106**: 724–5.
5 Burdon JGW, Cade JF. 'Barbiturate burns' caused by glutethimide. *Med J Aust* 1979; **1**: 101–2.
6 Fisher M, Lerman JS. Fixed eruption due to glutethimide. *Arch Dermatol* 1971; **104**: 87–9.
7 Gore HC Jr. Fixed drug eruption cross reaction of meprobamate and carisoprodol. *Arch Dermatol* 1965; **91**: 627.
8 Levan NE. Meprobamate reaction. *Arch Dermatol* 1957; **75**: 437–8.
9 Felix RH, Comaish JS. The value of patch and other skin tests in drug eruptions. *Lancet* 1974; **i**: 1017–9.

Antipsychotics

The most important clinical side effects include those on the central nervous and cardiovascular systems and the ocular effects [1,2]. Drugs with high potency, such as haloperidol and pimozide, tend to have fewer cardiovascular and anticholinergic effects and are less sedating, but have more neurological effects. Long-term use of antipsychotic agents results in tardive dyskinesia.

Phenothiazines

The side effects of this group of drugs have been reviewed [1–4].

Chlorpromazine. This drug is still widely used, although many related compounds are now available. Pigmentation of the skin in light-exposed areas after chronic use may be a problem, especially in women and black people [5–11]. Rarely, a purplish or slate-grey pigmentation develops [6]. There may be brown discoloration of cornea and lens [5], and bulbar conjunctiva [7]. Chlorpromazine has an affinity for melanin *in vitro* [8]. Electron microscopy shows many melanosome complexes within lysosomes of dermal macrophages, and electron-dense 'chlorpromazine bodies' in macrophages, endothelial cells and Schwann cells [9,10]; energy-dispersive X-ray microanalysis has revealed the abundant presence of sulphur in these granules, which is a constituent of the chlorpromazine molecule [10]. Similar pigmentary deposits are found in internal organs [11] and in blood neutrophils and monocytes.

Chlorpromazine has caused lichenoid eruptions [12], exfoliative dermatitis, erythema multiforme, an LE-like illness [13] with positive antinuclear factor [14] and the lupus anticoagulant [15], and Henoch–Schönlein vasculitis [16]. Phototoxicity is well known [17–19] and phenothiazine-derived antihistamines may cause photosensitivity in atopics and subsequent development of actinic reticuloid [19]. Photocontact urticaria has been documented [20]. A pustular reaction is recorded [21]. Cholestatic jaundice is an important hazard.

Fluspirilene. Subcutaneous nodules may develop at injection sites after long-term high doses of this depot preparation [22].

Thioridazine. Vasculitis is documented [23].

Thiothixene. A sensitivity reaction has been recorded [24].

Trifluoperazine. A fixed eruption has been recorded [25].

Loxapine. Dermatitis, pruritus and seborrhoea have been recorded, and photosensitivity eruptions may occur occasionally [26].

Levomepromazin. An erythema annulare centrifugum-like pseudolymphomatous eruption has been reported [27].

References

1 Simpson GM, Pi EH, Sramek JJ Jr. Adverse effects of antipsychotic agents. *Drugs* 1981; **21**: 138–51.
2 Gupta MA, Gupta AK, Haberman HF. Psychotropic drugs in dermatology. A review and guidelines for use. *J Am Acad Dermatol* 1986; **14**: 633–45.
3 Hägermark Ö, Wennersten G, Almeyda J. Drug reactions XIV. Cutaneous side effects of phenothiazines. *Br J Dermatol* 1971; **84**: 605–7.
4 Bond WS, Yee GC. Ocular and cutaneous effects of chronic phenothiazine therapy. *Am J Hosp Pharm* 1980; **37**: 74–8.
5 Greiner AC, Berry K. Skin pigmentation and corneal and lens opacities with prolonged chlorpromazine therapy. *Can Med Assoc J* 1964; **90**: 663–5.
6 Hays GB, Lyle CB Jr, Wheeler CE Jr. Slate-grey color in patients receiving chlorpromazine. *Arch Dermatol* 1964; **90**: 471–6.
7 Satanove A. Pigmentation due to phenothiazines in high and prolonged dosage. *JAMA* 1965; **191**: 263–8.
8 Blois MS Jr. On chlorpromazine binding *in vivo*. *J Invest Dermatol* 1965; **45**: 475–81.
9 Hashimoto K, Wiener W, Albert J, Nelson RG. An electron microscopic study of chlorpromazine pigmentation. *J Invest Dermatol* 1966; **47**: 296–306.
10 Benning TL, McCormack KM, Ingram P *et al.* Microprobe analysis of chlorpromazine pigmentation. *Arch Dermatol* 1988; **124**: 1541–4.
11 Greiner AC, Nicolson GA. Pigment deposition in viscera associated with prolonged chlorpromazine therapy. *Can Med Assoc J* 1964; **90**: 627–35.
12 Matsuo I, Ozawa A, Niizuma K, Ohkido M. Lichenoid dermatitis due to chlorpromazine phototoxicity. *Dermatologica* 1979; **159**: 46–9.
13 Pavlidakey GP, Hashimoto K, Heller GL, Daneshvar S. Chlorpromazine-induced lupuslike disease: case report and review of the literature. *J Am Acad Dermatol* 1985; **13**: 109–15.
14 Zarrabi MH, Zucker S, Miller F *et al.* Immunologic and coagulation disorders in chlorpromazine-treated patients. *Ann Intern Med* 1979; **91**: 194–9.
15 Canoso RT, Sise HS. Chlorpromazine-induced lupus anticoagulant and associated immunologic abnormalities. *Am J Hematol* 1982; **13**: 121–9.
16 Aram H. Henoch–Schönlein purpura induced by chlorpromazine. *J Am Acad Dermatol* 1987; **17**: 139–40.
17 Johnson BE. Cellular mechanisms of chlorpromazine photosensitivity. *Proc R Soc Med* 1974; **67**: 871–3.
18 Ljunggren B. Phenothiazine phototoxicity: toxic chlorpromazine photoproducts. *J Invest Dermatol* 1977; **69**: 383–6.
19 Amblard P, Beani J-C, Reymond J-L. Photo-allergie rémanente aux phénothiazines chez l'atopique. *Ann Dermatol Vénéréol* 1982; **109**: 225–8.
20 Lovell CR, Cronin E, Rhodes EL. Photocontact urticaria from chlorpromazine. *Contact Dermatitis* 1986; **14**: 290–1.
21 Burrows NP, Ratnavel RC, Norris PG. Pustular eruptions after chlorpromazine. *BMJ* 1994; **309**: 97.
22 UK Committee on Safety of Medicines. *Current Problems* 1981; **7**.
23 Greenfield JR, McGrath M, Kossard S *et al.* ANCA-positive vasculitis induced by thioridazine: confirmed by rechallenge. *Br J Dermatol* 2003; **147**: 1265–7.
24 Matsuoka LY. Thiothixene drug sensitivity. *J Am Acad Dermatol* 1982; **7**: 405–6.
25 Kanwar AJ, Singh M, El-Sheriff AK, Belhaj MS. Fixed eruption due to trifluoperazine hydrochloride. *Br J Dermatol* 1987; **117**: 798–9.
26 Anonymous. Cloxapine and loxapine for schizophrenia. *Drug Ther Bull* 1991; **29**: 41–2.
27 Blazejak T, Hölzle E. Phenothiazin-induziertes Pseudolymphom. *Hautarzt* 1990; **41**: 161–3.

Miscellaneous antipsychotic agents

Clozapine. An acute severe adverse reaction resembling SLE is recorded [1].

Haloperidol. This drug causes reactions at injection sites [2,3].

Olanzapine. A pustular reaction [4] and vasculitis [5] are documented.

Quetiapine. Erythema multiforme minor has been reported [6].

Methylphenidate hydrochloride (Risperidone). This ubiquitously prescribed medication for attention deficit hyperactivity disorder has produced erythema multiforme minor [7] and pseudolymphoma [8].

References

1 Reinke M, Wiesert KN. High incidence of haloperidol decanoate injection site reactions (letter). *J Clin Psychiatry* 1992; **53**: 415–6.
2 Maharaj K, Guttmacher LB, Moeller R. Haloperidol decanoate: injection site reactions. *J Clin Psychiatry* 1995; **56**: 172–3.
3 Wickert WA, Campbell NR, Martin L. Acute severe adverse clozapine reaction resembling systemic lupus erythematosus. *Postgrad Med J* 1994; **70**: 940–1.
4 Adams BB, Mutasim DF. Pustular eruption induced by olanzapine, a novel antipsychotic agent. *J Am Acad Dermatol* 1999; **41**: 851–3.
5 Duggal MK, Singh A, Arunabh *et al*. Olanzapine-induced vasculitis. *Am J Geriatr Pharmacother* 2005; **3**: 21–4.
6 Lin GL, Chiu CH, Lin SK. Quetiapine-induced erythema multiforme minor: a case report. *J Clin Psychopharmacol* 2006; **26**: 668–9.
7 Desarkar P, Nizamie SH. Risperidone-induced erythema multiforme minor. *Br J Clin Pharmacol* 2006; **62**: 504–5.
8 Welsh JP, Ko C, Hsu WT. Lymphomatoid drug reaction secondary to methylphenidate hydrochloride. *Cutis* 2008; **81**: 61–4.

Anticonvulsants

In a recent study of 1890 outpatients, the average rate of antiepileptic drug-related rashes was 2.8% [1]. Rash rates were highest with phenytoin (5%), lamotrigine (4.8%), and carbamazepine (3.7%), and lowest (<1%) with clobazam, felbamate, gabapentin, levetiracetam, oxcarbazepine, phenobarbital, primidone, tiagabine, topiramate, vigabatrin, valproate and zonisamide. In another study of 663 patients with 2567 exposures to 15 different antiepileptic drugs [2], reactions were found in 14% of patients and in 5% of exposures; 97% of reactions were to either carbamazepine (11%), phenytoin (8%), lamotrigine (8%), oxcarbazepine (8%) or phenobarbital (2%), and reactions were commoner in females. Reaction rates are approximately five times greater in patients with a history of a reaction to another antiepileptic drug [1]. Carbamazepine and oxcarbazepine caused rashes in the range of 27–35%, and lamotrigine in 17%, of patients with a history of another antiepileptic drug-related rash [3]. There may be 40–80% cross-reactivity in terms of clinical reactions to the aromatic anticonvulsants (phenytoin, phenobarbital, carbamazepine, primidone and clonazepam), as well as to tricyclic antidepressant agents [4,5]. Allergic rashes to antiepileptic drugs are usually mild, taking the form of urticarial or morbilliform eruptions. However, all of the aromatic anticonvulsants may cause DRESS (drug hypersensitivity syndrome, anticonvulsant hypersensitivity syndrome) (see pp. 75.26–27), which reportedly occurs at a rate of 1 in 1000 to 1 in 10 000 exposures [4,5]. Clinical features of the syndrome include fever, mucocutaneous eruptions, lymphadenopathy and hepatitis, 1 week to 3 months into therapy; there may be multiorgan involvement with renal and pulmonary lesions [6–14]. The reaction may develop into TEN. These drugs are oxidized by the cytochrome P-450 enzyme system into potentially reactive toxic arene oxide intermediates; the anticonvulsant hypersensitivity syndrome is associated with an inherited deficiency of liver microsomal epoxide hydrolase, which converts such reactive intermediates to non-toxic dihydrodiols (see section on Pharmacogenetic mechanisms, pp. 75.12–13). There may be associated reactivation of herpes-type viruses [14], and/or ethnic predisposition with certain HLA subtypes [5]. The occurrence of a severe reaction indicates that the drug should be ceased, and this can be done abruptly with minimal risk of status epilepticus [15,16]. Patients with a history of antiepileptic drug hypersensitivity should avoid further use of any aromatic anticonvulsant drug. In addition, family members should be instructed that they may be at increased risk for developing severe reactions to aromatic anticonvulsant drugs. Anticonvulsant drugs that are generally considered safe in these circumstances are valproic acid, benzodiazepines, and other non-aromatic anticonvulsant drugs.

Generalized pustulation may be a manifestation of anticonvulsant hypersensitivity [17]. A severe form of hypersensitivity vasculitis, with extensive visceral involvement and poor prognosis, is seen very rarely with phenytoin and in isolated cases with carbamazepine and trimethadione [18]. Drug-induced SLE is much more frequent, and has been described with most anticonvulsants in clinical use (phenytoin, carbamazepine, ethosuximide, trimethadione, primidone and valproate) [18]. Of the newer anticonvulsant drugs, vigabatrin is usually well tolerated, but lamotrigine is associated with rashes [19,20]. Anticonvulsants may be associated with pseudolymphoma syndrome (see p. 75.44).

References

1 Arif H, Buchsbaum R, Weintraub D *et al*. Comparison and predictors of rash associated with 15 antiepileptic drugs. *Neurology* 2007; **68**: 1701–9.
2 Alvestad S, Lydersen S, Brodtkorb E. Rash from antiepileptic drugs: influence by gender, age, and learning disability. *Epilepsia* 2007; **48**: 1360–5.
3 Alvestad S, Lydersen S, Brodtkorb E. Cross-reactivity pattern of rash from current aromatic antiepileptic drugs. *Epilepsy Res* 2008; **80**: 194–200.
4 Seitz CS, Pfeuffer P, Raith P *et al*. Anticonvulsant hypersensitivity syndrome: cross-reactivity with tricyclic antidepressant agents. *Ann Allergy Asthma Immunol* 2006; **97**: 698–702.
5 Bohan KH, Mansuri TF, Wilson NM. Anticonvulsant hypersensitivity syndrome: implications for pharmaceutical care. *Pharmacotherapy* 2007; **27**: 1425–39.
6 Chang DK, Shear NH. Cutaneous reactions to anticonvulsants. *Semin Neurol* 1992; **12**: 329–37.
7 Handfield-Jones SE, Jenkins RE, Whittaker SJ *et al*. The anticonvulsant hypersensitivity syndrome. *Br J Dermatol* 1993; **129**: 175–7.
8 Richens A, Davidson DL, Cartlidge NE, Easter DJ. A multicentre comparative trial of sodium valproate and carbamazepine in adult onset epilepsy. Adult EPITEG Collaborative Group. *J Neurol Neurosurg Psychiatry* 1994; **57**: 682–7.
9 Vittorio CC, Muglia JJ. Anticonvulsant hypersensitivity syndrome. *Arch Intern Med* 1995; **155**: 2285–90.
10 Licata AL, Louis ED. Anticonvulsant hypersensitivity syndrome. *Compr Ther* 1996; **22**: 152–5.
11 Allam JP, Paus T, Reichel C *et al*. DRESS syndrome associated with carbamazepine and phenytoin. *Eur J Dermatol* 2004; **14**: 339–42.
12 Mendiratta V, Bhushan P. Phenytoin-induced DRESS with cross-reactivity to carbamazepine in a 10-year-old Indian child. *Clin Exp Dermatol* 2006; **31**: 720–1.
13 Yun SJ, Lee JB, Kim EJ *et al*. Drug rash with eosinophilia and systemic symptoms induced by valproate and carbamazepine: formation of circulating autoantibody against 190-kDa antigen. *Acta Derm Venereol* 2006; **86**: 241–4.

14 Aihara Y, Ito S-I, Kobayashi Y *et al.* Carbamazepine-induced hypersensitivity syndrome associated with transient hypogammaglobulinaemia and reactivation of human herpesvirus 6 infection demonstrated by real-time quantitative polymerase chain reaction. *Br J Dermatol* 2003; **149**: 165–9.
15 Hebert AA, Ralston JP. Cutaneous reactions to anticonvulsant medications. *J Clin Psychiatry* 2001; **62** (Suppl. 14): 22–6.
16 Pelekanos J, Camfield P, Camfield C, Gordon K. Allergic rash due to antiepileptic drugs: clinical features and management. *Epilepsia* 1991; **32**: 554–9.
17 Kleier RS, Breneman DL, Boiko S. Generalized pustulation as a manifestation of the anticonvulsant hypersensitivity syndrome. *Arch Dermatol* 1991; **127**: 1361–4.
18 Drory VE, Korczyn AD. Hypersensitivity vasculitis and systemic lupus erythematosus induced by anticonvulsants. *Clin Neuropharmacol* 1993; **16**: 19–29.
19 Schmidt D, Kramer G. The new anticonvulsant drugs. Implications for avoidance of adverse effects. *Drug Saf* 1994; **11**: 422–31.
20 Brodie MJ. Lamotrigine versus other antiepileptic drugs: a star rating system is born. *Epilepsia* 1994; **35** (Suppl. 5): S41–S46.

Carbamazepine [1]

Eruptions occur in 3% [2–5] to 12% [6–8] of patients and include diffuse erythema, miliary exanthem, maculopapular or speckled morbilliform reddish rash, urticaria, purpuric petechiae or a mucocutaneous syndrome, any of which may occur from day 8 to 60. The drug hypersensitivity syndrome [9–11], erythroderma and exfoliative dermatitis, erythema multiforme and TEN [3,4,12] are well recognized. Eczema and photosensitivity [13], an LE-like syndrome and dermatomyositis [14], as well as a pustular [15–17] and a lichenoid [3,18] reaction, are very rare. Lesions with clinical and histological features suggestive of mycosis fungoides (pseudolymphoma) have been reported [18–21]. Patch testing has been advocated for the diagnosis of carbamazepine eruptions [9,10,22,23], but has resulted in reinduction of exfoliative dermatitis [24]. A psoriasiform eruption has been reported [25], as has thrombocytopenia and leukopenia complicated by Henoch–Schönlein purpura [26]. Cross-reactivity may occur with oxcarbazepine [27,28]. Other adverse effects include nausea, vomiting, ataxia, vertigo and drowsiness. Abnormal liver function [29] and bone marrow suppression with occasional deaths due to aplastic anaemia have been recorded [3]. Development of a rash may act as an early warning of marrow toxicity. Carbamazepine therapy during pregnancy carries a 1% risk of development of spina bifida in the offspring [30].

Oral steroid therapy enabled 16 of 20 patients successfully to continue on carbamazepine after development of a rash shortly after introduction of the drug [31]. Desensitization has been achieved by induction of tolerance in patients in whom there was no suitable alternative therapy [32,33].

References

1 Pasmans SG, Bruijnzeel-Koomen CA, van Reijsen FC. Skin reactions to carbamazepine. *Allergy* 1999; **54**: 649–50.
2 Harman PRM. Carbamazepine (Tegretol) drug eruptions. *Br J Dermatol* 1967; **79**: 500–1.
3 Roberts DL, Marks R. Skin reactions to carbamazepine. *Arch Dermatol* 1981; **117**: 273–5.
4 Breathnach SM, McGibbon DH, Ive FA *et al.* Carbamazepine ('Tegretol') and toxic epidermal necrolysis: report of three cases with histopathological observations. *Clin Exp Dermatol* 1982; **7**: 585–91.
5 Chadwick D, Shan M, Foy P *et al.* Serum anticonvulsant concentrations and the risk of drug-induced skin eruptions. *J Neurol Neurosurg Psychiatry* 1984; **47**: 642–4.
6 Richens A, Davidson DL, Cartlidge NE, Easter DJ. A multicentre comparative trial of sodium valproate and carbamazepine in adult onset epilepsy. Adult EPITEG Collaborative Group. *J Neurol Neurosurg Psychiatry* 1994; **57**: 682–7.
7 Kramlinger KG, Phillips KA, Post RM. Rash complicating carbamazepine treatment. *J Clin Psychopharmacol* 1994; **14**: 408–13.
8 Konishi T, Naganuma Y, Hongo K *et al.* Carbamazepine-induced skin rash in children with epilepsy. *Eur J Pediatr* 1993; **152**: 605–8.
9 Scerri L, Shall L, Zaki I. Carbamazepine-induced anticonvulsant hypersensitivity syndrome: pathogenic and diagnostic considerations. *Clin Exp Dermatol* 1993; **18**: 540–2.
10 De Vriese AS, Philippe J, Van Renterghem DM *et al.* Carbamazepine hypersensitivity syndrome: report of 4 cases and review of the literature. *Medicine (Baltimore)* 1995; **74**: 144–51.
11 Okuyama R, Ichinohasama R, Tagami H. Carbamazepine induced erythroderma with systemic lymphadenopathy. *J Dermatol* 1996; **23**: 489–94.
12 Reed MD, Bertino JA, Blumer JL. Carbamazepine-associated exfoliative dermatitis. *Clin Pharmacol* 1982; **1**: 78–9.
13 Terui T, Tagami H. Eczematous drug eruption from carbamazepine: coexistence of contact and photocontact sensitivity. *Contact Dermatitis* 1989; **20**: 260–4.
14 Simpson JR. 'Collagen disease' due to carbamazepine (Tegretol). *BMJ* 1966; **ii**: 1434.
15 Staughton RCD, Harper JI, Rowland Payne CME *et al.* Toxic pustuloderma: a new entity? *J R Soc Med* 1984; **77**: 6–8.
16 Commens CA, Fischer GO. Toxic pustuloderma following carbamazepine therapy. *Arch Dermatol* 1988; **124**: 178–9.
17 Mizoguchi S, Setoyama M, Higashi Y *et al.* Eosinophilic pustular folliculitis induced by carbamazepine. *J Am Acad Dermatol* 1998; **38**: 641–3.
18 Atkin SL, McKenzie TMM, Stevenson CJ. Carbamazepine-induced lichenoid eruption. *Clin Exp Dermatol* 1990; **15**: 382–3.
19 Welykyj S, Gradini R, Nakao J, Massa M. Carbamazepine-induced eruption histologically mimicking mycosis fungoides. *J Cutan Pathol* 1990; **17**: 111–6.
20 Rijlaarsdam U, Scheffer E, Meijer CJLM *et al.* Mycosis fungoides-like lesions associated with phenytoin and carbamazepine therapy. *J Am Acad Dermatol* 1991; **24**: 216–20.
21 Nathan DL, Belsito DV. Carbamazepine-induced pseudolymphoma with CD-30 positive cells. *J Am Acad Dermatol* 1998; **38**: 806–9.
22 Houwerzijl J, De Gast GC, Nater JP *et al.* Lymphocyte-stimulation tests and patch tests in carbamazepine hypersensitivity. *Clin Exp Immunol* 1977; **29**: 272–7.
23 Silva R, Machado A, Brandao M, Gonçalo S. Patch test diagnosis in carbamazepine erythroderma. *Contact Dermatitis* 1986; **15**: 254–5.
24 Vaillant L, Camenen I, Lorette G. Patch testing with carbamazepine: reinduction of an exfoliative dermatitis. *Arch Dermatol* 1989; **125**: 299.
25 Brenner S, Wolf R, Landau M, Politi Y. Psoriasiform eruption induced by anticonvulsants. *Isr J Med Sci* 1994; **30**: 283–6.
26 Kaneko K, Igarashi J, Suzuki Y *et al.* Carbamazepine-induced thrombocytopenia and leucopenia complicated by Henoch–Schönlein purpura symptoms. *Eur J Pediatr* 1993; **152**: 769–70.
27 Beran RG. Cross-reactive skin eruption with both carbamazepine and oxcarbazepine. *Epilepsia* 1993; **34**: 163–5.
28 Dam M. Practical aspects of oxcarbazepine treatment. *Epilepsia* 1994; **35** (Suppl. 3): S23–S25.
29 Ramsey ID. Carbamazepine-induced jaundice. *BMJ* 1967; **4**: 155.
30 Rosa FW. Spina bifida in infants of women treated with carbamazepine during pregnancy. *N Engl J Med* 1991; **324**: 674–7.
31 Murphy JM, Mashman J, Miller JD, Bell JB. Suppression of carbamazepine-induced rash with prednisone. *Neurology* 1991; **41**: 144–5.
32 Eames P. Adverse reaction to carbamazepine managed by desensitization. *Lancet* 1989; **i**: 509–10.
33 Boyle N, Lawlor BA. Desensitization to carbamazepine-induced skin rash. *Am J Psychiatry* 1996; **153**: 1234.

Diphenylhydantoin (phenytoin, Dilantin)

Cutaneous manifestations related to phenytoin have been reviewed [1–7]. The various diverse presentations share certain histopathological findings: adhesion of the infiltrated cells to the basal layer of the epidermis, cell infiltration into the epidermis, vacuolation of the basal cells, and dyskeratotic cells in the epidermis and

epidermal necrosis, with $CD8^+$ T cells predominant in the epidermis [5].

About 5% of children develop a mild, transient maculopapular rash within 3 weeks of starting treatment. This is more likely to occur if high loading doses are given initially [3,4]. In other series, between 8.5% [8] and 19% [9] of patients receiving phenytoin developed exanthematic rashes [10]. A phenytoin-induced hypersensitivity state, with generalized lymphadenopathy, hepatosplenomegaly, fever, arthralgia and eosinophilia, occurs in about 1% of patients, and may be accompanied by hepatitis, nephritis and haematological abnormalities [7,11–13]. Skin involvement may lead to a suspicion of lymphoma, the phenytoin-induced pseudolymphoma syndrome [14–19]. Cutaneous lesions may be restricted to a few erythematous plaques [18], or cutaneous nodules [15], or consist of a generalized erythematous maculopapular rash [14], generalized exfoliative dermatitis [16,20] or TEN [21,22]. Generalized pustulation has been recorded as a manifestation of the anticonvulsant drug hypersensitivity syndrome [23]. Universal depigmentation has resulted from TEN [24]. Cutaneous histopathology in the pseudolymphoma syndrome is often indistinguishable from that of mycosis fungoides, with infiltrating cells having cerebriform nuclei and forming Pautrier microabscesses [17,19]. The rash resolves after cessation of the drug; systemic corticosteroids may aid resolution [25]. However, there is a threefold risk of true lymphoma on long-term therapy [26–28], and T-cell lymphoma has been reported in an adult [29].

Long-term treatment causes fibroblast proliferation, and may result in dose-dependent gingival hyperplasia [30,31] or coarsening of the features [32]; hypertrophic retroauricular folds were reported in an isolated case [33]. Hypertrichosis may be seen. Other reactions have included fixed eruptions [34], including a widespread fixed drug eruption mimicking TEN [35], erythema multiforme [1,3], TEN with cholestasis [36], cutaneous vasculitis [37], an LE-like syndrome [38,39] and eosinophilic fasciitis [40]. Linear IgA bullous dermatosis has been provoked [41]. Localized reactions to intravenous phenytoin have included delayed bluish discoloration, erythema and oedema, sometimes with bullae, distal to the site of injection; immediate burning pain and swelling, and a delayed erythematous eruption with superficial sloughing, partial epidermal necrosis and frequent multinucleate keratinocytes on histology have also been reported [42,43].

Treatment during pregnancy may lead to a characteristic 'fetal hydantoin syndrome', with general underdevelopment and hypoplasia of phalanges and nails [44]; neonatal acne may be associated [45]. However, recent controlled observations suggest that acne is neither caused nor worsened by hydantoins [46], despite reports to the contrary [47].

References

1 Silverman AK, Fairley J, Wong RC. Cutaneous and immunologic reactions to phenytoin. *J Am Acad Dermatol* 1988; **18**: 721–41.
2 Levantine A, Almeyda J. Drug reactions XX. Cutaneous reactions to anticonvulsants. *Br J Dermatol* 1972; **87**: 646–9.
3 Pollack MA, Burk PG, Nathanson G. Mucocutaneous eruptions due to antiepileptic drug therapy in children. *Ann Neurol* 1979; **5**: 262–7.
4 Wilson JT, Höjer B, Tomson G *et al.* High incidence of a concentration-dependent skin reaction in children treated with phenytoin. *BMJ* 1978; **i**: 1583–6.
5 Tone T, Nishioka K, Kameyama K *et al.* Common histopathological processes of phenytoin drug eruption. *J Dermatol* 1992; **19**: 27–34.
6 Potter T, DiGregorio F, Stiff M, Hashimoto K. Dilantin hypersensitivity syndrome imitating staphylococcal toxic shock. *Arch Dermatol* 1994; **130**: 856–8.
7 Conger LA Jr, Grabski WJ. Dilantin hypersensitivity reaction. *Cutis* 1996; **57**: 223–6.
8 Leppik IE, Lapora A, Loewenson R. Seasonal incidence of phenytoin allergy unrelated to plasma levels. *Arch Neurol* 1985; **42**: 120–2.
9 Rapp RP, Norton JA, Young B, Tibbs PA. Cutaneous reactions in head-injured patients receiving phenytoin for seizure prophylaxis. *Neurosurgery* 1983; **13**: 272–5.
10 Robinson HM, Stone JH. Exanthem due to diphenylhydantoin therapy. *Arch Dermatol* 1970; **101**: 462–5.
11 Stanley J, Fallon-Pellici V. Phenytoin hypersensitivity reaction. *Arch Dermatol* 1978; **114**: 1350–3.
12 Brown M, Schubert T. Phenytoin hypersensitivity hepatitis and mononucleosis syndrome. *J Clin Gastroenterol* 1986; **8**: 469–77.
13 Shear N, Spielberg S. Anticonvulsant hypersensitivity syndrome. *In vitro* assessment of risk. *J Clin Invest* 1989; **82**: 1826–32.
14 Charlesworth EN. Phenytoin-induced pseudolymphoma syndrome. An immunologic study. *Arch Dermatol* 1977; **113**: 477–80.
15 Adams JD. Localized cutaneous pseudolymphoma associated with phenytoin therapy: a case report. *Australas J Dermatol* 1981; **22**: 28–9.
16 Rosenthal CJ, Noguera CA, Coppola A, Kapelner SN. Pseudolymphoma with mycosis fungoides manifestations, hyperresponsiveness to diphenyl-hydantoin, and lymphocyte disregulation. *Cancer* 1982; **49**: 2305–14.
17 Kardaun SH, Scheffer E, Vermeer BJ. Drug-induced pseudolymphomatous skin reactions. *Br J Dermatol* 1988; **118**: 545–52.
18 Wolf R, Kahane E, Sandbank M. Mycosis fungoides-like lesions associated with phenytoin therapy. *Arch Dermatol* 1985; **121**: 1181–2.
19 Rijlaarsdam U, Scheffer E, Meijer CJLM *et al.* Mycosis fungoides-like lesions associated with phenytoin and carbamazepine therapy. *J Am Acad Dermatol* 1991; **24**: 216–20.
20 Danno K, Kume M, Ohta M *et al.* Erythroderma with generalized lymphadenopathy induced by phenytoin. *J Dermatol* 1989; **16**: 392–6.
21 Sherertz EF, Jegasothy BV, Lazarus GS. Phenytoin hypersensitivity reaction presenting with toxic epidermal necrolysis and severe hepatitis: report of a patient treated with corticosteroid 'pulse therapy'. *J Am Acad Dermatol* 1985; **12**: 178–81.
22 Schmidt D, Kluge W. Fatal toxic epidermal necrolysis following reexposure to phenytoin. A case report. *Epilepsia* 1983; **24**: 440–3.
23 Kleier RS, Breneman DL, Boiko S. Generalized pustulation as a manifestation of the anticonvulsant hypersensitivity syndrome. *Arch Dermatol* 1991; **127**: 1361–4.
24 Smith DA, Burgdorf WHC. Universal cutaneous depigmentation following phenytoin-induced toxic epidermal necrolysis. *J Am Acad Dermatol* 1984; **10**: 106–9.
25 Chopra S, Levell NJ, Cowley G, Gilkes JJ. Systemic corticosteroids in the phenytoin hypersensitivity syndrome. *Br J Dermatol* 1996; **134**: 1109–12.
26 Tashima CK, De Los Santos R. Lymphoma and anticonvulsant therapy. *JAMA* 1974; **228**: 287–8.
27 Bichel J. Hydantoin derivatives and malignancies of the haemopoietic system. *Acta Med Scand* 1975; **198**: 327–8.
28 Li FP, Willard DR, Goodman R *et al.* Malignant lymphoma after diphenylhydantoin (Dilantin) therapy. *Cancer* 1975; **36**: 1359–62.
29 Isobe T, Horimatsu T, Fujita T *et al.* Adult T cell lymphoma following diphenylhydantoin therapy. *Acta Haematol Jpn* 1980; **43**: 711–4.
30 Angelopoulos AP, Goaz PW. Incidence of diphenylhydantoin gingival hyperplasia. *Oral Surg* 1972; **34**: 898–906.
31 Hassell TM, Page RC, Narayanan AS, Cooper CG. Diphenylhydantoin (Dilantin) gingival hyperplasia: drug induced abnormality of connective tissue. *Proc Natl Acad Sci USA* 1976; **73**: 2909–12.
32 Lefebvre EB, Haining RG, Labbé RF. Coarse facies, calvarial thickening and hyperphosphatasia associated with long-term anticonvulsant therapy. *N Engl J Med* 1972; **286**: 1301–2.
33 Trunnell TN, Waisman M. Hypertrophic retroauricular folds attributable to diphenylhydantoin. *Cutis* 1982; **30**: 207–9.
34 Sweet RD. Fixed skin eruption due to phenytoin sodium. *Lancet* 1950; **i**: 68.

35 Baird BJ, De Villez RL. Widespread bullous fixed drug eruption mimicking toxic epidermal necrolysis. *Int J Dermatol* 1988; **27**: 170–4.
36 Spechler SJ, Sperber H, Doos WG, Koff RS. Cholestasis and toxic epidermal necrolysis associated with phenytoin sodium ingestion: the role of bile duct injury. *Ann Intern Med* 1981; **95**: 455–6.
37 Yermakov VM, Hitti IF, Sutton AL. Necrotizing vasculitis associated with diphenylhydantoin: two fatal cases. *Hum Pathol* 1983; **14**: 182–4.
38 Gleichman H. Systemic lupus erythematosus triggered by diphenylhydantoin. *Arthritis Rheum* 1982; **25**: 1387–8.
39 Ross S, Dywer C, Ormerod AD *et al.* Subacute cutaneous lupus erythematosus associated with phenytoin. *Clin Exp Dermatol* 2002; **27**: 474–6.
40 Buchanan RR, Gordon DA, Muckle TJ *et al.* The eosinophilic fasciitis syndrome after phenytoin (Dilantin) therapy. *J Rheumatol* 1980; **7**: 733–6.
41 Acostamadiedo JM, Perniciaro C, Rogers RS III. Phenytoin-induced linear IgA bullous disease. *J Am Acad Dermatol* 1998; **38**: 352–6.
42 Hunt SJ. Cutaneous necrosis and multinucleate epidermal cells associated with intravenous phenytoin. *Am J Dermatopathol* 1995; **17**: 399–402.
43 Kilarski DJ, Buchanan C, Von Behren L. Soft tissue damage associated with intravenous phenytoin. *N Engl J Med* 1984; **311**: 1186–7.
44 Nagy R. Fetal hydantoin syndrome. *Arch Dermatol* 1981; **117**: 593–5.
45 Stankler L, Campbell AGM. Neonatal acne vulgaris: a possible feature of the fetal hydantoin syndrome. *Br J Dermatol* 1980; **103**: 453–5.
46 Greenwood R, Fenwick PBC, Cunliffe WJ. Acne and anticonvulsants. *BMJ* 1983; **287**: 1669–70.
47 Jenkins RB, Ratner AC. Diphenylhydantoin and acne. *N Engl J Med* 1972; **287**: 148.

Gabapentin

This drug given for postherpetic neuralgia has caused leukocytoclastic vasculitis [1].

Reference

1 Sahin S, Comert A, Akin O *et al.* Cutaneous drug eruptions by current antiepileptics: case reports and alternative treatment options. *Clin Neuropharmacol* 2008; **31**: 93–6.

Lamotrigine

Dosage-related allergic rashes occur in about 5–10% of patients, usually in the first 8 weeks, leading to a withdrawal rate of 2% of patient exposures [1–4]. In one study, six of eight patients with a prior lamotrigine-related rash had no recurrence on rechallenge, and two other patients had only mild rashes [5]. Rashes leading to hospitalization, including hypersensitivity syndrome [6], Stevens–Johnson syndrome and TEN [7,8], occurred in 1 in 100 to 1 in 300 individuals in clinical trials, and appeared to be increased with over-rapid titration when starting therapy and with concurrent valproate medication [3,9].

References

1 Richens A. Safety of lamotrigine. *Epilepsia* 1994; **35** (Suppl. 5): S37–S40.
2 Calabrese JR, Sullivan JR, Bowden CL *et al.* Rash in multicenter trials of lamotrigine in mood disorders: clinical relevance and management. *J Clin Psychiatry* 2002; **63**: 1012–9.
3 Guberman AH, Besag FM, Brodie MJ *et al.* Lamotrigine-associated rash: risk/benefit considerations in adults and children. *Epilepsia* 1999; **40**: 985–91.
4 Messenheimer JA. Lamotrigine. *Epilepsia* 1995; **36** (Suppl. 2): S87–S94.
5 Tavernor SJ, Wong IC, Newton R, Brown SW. Rechallenge with lamotrigine after initial rash. *Seizure* 1995; **4**: 67–71.
6 Jones D, Chhiap V, Resor S *et al.* Phenytoin-like hypersensitivity associated with lamotrigine. *J Am Acad Dermatol* 1997; **36**: 1016–8.
7 Sterker M, Berrouschot J, Schneider D. Fatal course of toxic epidermal necrolysis under treatment with lamotrigine. *Int J Clin Pharmacol Ther* 1995; **33**: 595–7.
8 Sahin S, Comert A, Akin O *et al.* Cutaneous drug eruptions by current antiepileptics: case reports and alternative treatment options. *Clin Neuropharmacol* 2008; **31**: 93–6.
9 Anonymous. Lamotrigine (Lamictal): increased risk of serious skin reactions in children. *Curr Probl Pharmacovig* 1997; **23**: 8.

Sodium valproate

Occasional transient rashes and stomatitis are documented. Temporary hair loss may be followed by increasing curliness of the regrowing hair [1]. Alteration in hair colour has been noted [2]. One case of generalized morphoea [3] and two cases of cutaneous leukocytoclastic vasculitis recurring on challenge [4] have been reported. An extrapyramidal syndrome may be induced [5], and the drug may be teratogenic [6]. Yellow nail pigmentation is recorded [7].

References

1 Jeavons PM, Clark JE, Harding GFA. Valproate and curly hair. *Lancet* 1977; **i**: 359.
2 Herranz JL, Arteaga R, Armijo JA. Change in hair colour induced by valproic acid. *Dev Med Child Neurol* 1981; **23**: 386–7.
3 Goihman-Yahr M, Leal H, Essenfeld-Yahr E. Generalized morphea: a side effect of valproate sodium? *Arch Dermatol* 1980; **116**: 621.
4 Kamper AM, Valentijn RM, Stricker BHC, Purcell PM. Cutaneous vasculitis induced by sodium valproate. *Lancet* 1991; **337**: 497–8.
5 Lautin A, Stanley M, Angrist B, Gershon S. Extrapyramidal syndrome with sodium valproate. *BMJ* 1979; **ii**: 1035–6.
6 Gomez MR. Possible teratogenicity of valproic acid. *J Pediatr* 1981; **98**: 508–9.
7 Buka R, Hille R, McCormack P. Yellow nail pigmentation following Depakote therapy. *J Drugs Dermatol* 2003; **2**: 545–7.

Trimethadione

Serious hypersensitivity reactions may occur, including erythema multiforme, urticaria and generalized exfoliative dermatitis.

Vigabatrin

An allergic vasculitis developed in one patient 6 months after commencement of this drug [1].

Zonisamide

Toxic epidermal necrolysis associated with reactivation of human herpesvirus 6 is recorded [2].

References

1 Dieterle L, Becker EW, Berg PA *et al.* Allergische Vaskulitis durch Vigabatrin. *Nervenarzt* 1994; **65**: 122–4.
2 Teraki Y, Murota H, Izaki S. Toxic epidermal necrolysis due to zonisamide associated with reactivation of human herpesvirus 6. *Arch Dermatol* 2008; **144**: 232–5.

Opioid analgesics and amfetamine (amphetamine)

Cutaneous side effects common to drug abuse, most frequently cocaine, heroin and pentazocine, following parenteral injection include [1,2] infections, abscesses, septic phlebitis, subcutaneous and deep dermal cellulitis, necrosis, tetanus, widespread urticaria, cutaneous manifestations of primary and secondary syphilis; HIV infection and endocarditis occur. Starch and talc granulomas, lymphangitis and lymphadenitis in draining lymph nodes, pigmentary abnormalities including hyperpigmentation over the injected veins, accidental 'soot' tattoos (caused by needles sterilized over an open flame), scarring, ulceration, necrotizing angiitis and leukocytoclastic vasculitis may supervene. Skin popping refers to injection of drugs beneath the skin without concern for vascular access; this may result in delayed development of ulcers [3]. Injection drug use may lead to venous disease [4].

References

1 Rosen VJ. Cutaneous manifestations of drug abuse by parenteral injections. *Am J Dermatopathol* 1985; **7**: 79–83.
2 Smith DJ, Busito MJ, Velanovich V *et al.* Drug injection injuries of the upper extremity. *Ann Plastic Surg* 1989; **22**: 19–24.
3 Pardes JB, Falanga V, Kerdel FA. Delayed cutaneous ulcerations arising at sites of prior parenteral drug abuse. *J Am Acad Dermatol* 1993; **29**: 1052–4.
4 Pieper B, Kirsner RS, Templin TN, Birk TJ. Injection drug use. An understudied cause of venous disease. *Arch Dermatol* 2007; **143**: 1305–9.

Methylamfetamine

A link with necrotizing angiitis has been recorded when this drug is used alone or with heroin or d-lysergic acid diethylamide [1].

Reference

1 Citron BP, Halpern M, McCarron M *et al.* Necrotizing angiitis associated with drug abuse. *N Engl J Med* 1970; **283**: 1003–11.

Buprenorphine

An addict accidentally injected a suspension of crushed tablets into the superficial pudendal artery instead of the femoral vein, and developed pain, oedema and mottling of the penis [1]. Hypersensitivity reactions, and local or systemic infection have been reported [2].

References

1 Naylor AR, Gordon M, Jenkins AMcL. Untitled report. *BMJ* 1991; **303**: 478.
2 Del Giudice P. Cutaneous complications of intravenous drug abuse. *Br J Dermatol* 2004; **150**: 1–10.

Codeine

This drug has been associated with pruritus, urticaria (usually due to non-immunological release of histamine) [1,2], angio-oedema, macular and maculopapular eruptions, scarlatiniform rashes [1,3,4], fixed eruption, bullous eruption, generalized eczema [5], erythema multiforme and erythema nodosum, and a hypersensitivity reaction [6].

References

1 Hunskaar S, Dragsund S. Scarlatiniform rash and urticaria due to codeine. *Ann Allergy* 1985; **54**: 240–1.
2 De Groot AC, Conemans J. Allergic urticarial rash from oral codeine. *Contact Dermatitis* 1986; **14**: 209–14.
3 Voohost R, Sparreboom S. Four cases of recurrent pseudo-scarlet fever caused by phenanthrene alkaloids with a 6-hydroxy group (codeine and morphine). *Ann Allergy* 1980; **44**: 116–20.
4 Mohrenschlager M, Glockner A, Jessberger B *et al.* Codeine caused pruritic scarlatiniform exanthemata: patch test negative but positive to oral provocation test. *Br J Dermatol* 2000; **143**: 663–4.
5 Estrada JL, Puebla MJ, de Urbina JJ *et al.* Generalized eczema due to codeine. *Contact Dermatitis* 2001; **44**: 185.
6 Enomoto M, Ochi M, Teramae K *et al.* Codeine phosphate-induced hypersensitivity syndrome. *Ann Pharmacother* 2004; **38**: 799–802.

Heroin

Use of the dorsal vein of the penis for administration of the drug has produced ulceration [1]. Systemic infections, such as candidiasis, may supervene [2]. Leukocytoclastic vasculitis and necrotizing angiitis have been reported in drug abusers [3–5]. Pigmentation of the tongue may occur as a form of fixed drug eruption in heroin addicts [6]. A possible association with development of pemphigus erythematosus has been suggested [7].

References

1 White WB, Barrett S. Penile ulcer in heroin abuse: a case report. *Cutis* 1982; **29**: 62–3.
2 Bielsa I, Miro JM, Herrero C *et al.* Systemic candidiasis in heroin abusers. *Int J Dermatol* 1987; **26**: 314–9.
3 Citron BP, Halpern M, McCarron M *et al.* Necrotizing angiitis associated with drug abuse. *N Engl J Med* 1970; **283**: 1003–11.
4 Lignelli GJ, Bucheit WA. Angiitis in drug abusers. *N Engl J Med* 1971; **284**: 112–3.
5 Gendelman H, Linzer M, Barland P *et al.* Leukocytoclastic vasculitis in an intravenous heroin abuser. *NY State J Med* 1983; **83**: 984–6.
6 Westerhof W, Wolters EC, Brookbakker JTW *et al.* Pigmented lesions of the tongue in heroin addicts: fixed drug eruption. *Br J Dermatol* 1983; **109**: 605–10.
7 Fellner MJ, Winiger J. Pemphigus erythematosus and heroin addiction. *Int J Dermatol* 1978; **17**: 308–11.

Morphine

Morphine is a potent histamine releaser and may cause pruritus and urticaria [1]. Profuse sweating is a common effect. Morphine provokes facial flushing blocked by naloxone [2]. Local skin irritation during subcutaneous morphine infusion is recorded [3]. Acute generalized exanthematous pustulosis, pseudoallergic anaphylactoid reactions and blisters are reported [4].

Nefopam

Reactions to this analgesic include pruritus, erythema, urticaria, angio-oedema and anaphylactic shock [5].

References

1 McLelland J. The mechanism of morphine-induced urticaria. *Arch Dermatol* 1986; **122**: 138–9.
2 Cohen RA, Coffman JD. Naloxone reversal of morphine-induced peripheral vasodilatation. *Clin Pharmacol Ther* 1980; **28**: 541–4.
3 Shvartzman P, Bonneh D. Local skin irritation in the course of subcutaneous morphine infusion: a challenge. *J Palliat Care* 1994; **10**: 44–5.
4 Kardaun SH, de Monchy JG. Acute generalized exanthematous pustulosis caused by morphine, confirmed by positive patch test and lymphocyte transformation test. *J Am Acad Dermatol* 2006; **55** (Suppl. 2): S21–3.
5 Durrieu G, Olivier P, Bagheri H *et al.* Overview of adverse reactions to nefopam: an analysis of the French Pharmacovigilance database. *Fundam Clin Pharmacol* 2007; **21**: 555–8.

Pentazocine

Woody induration of the skin and subcutaneous tissues at injection sites, perhaps with central ulceration and peripheral pigmentation, and a granulomatous histology, is well recognized [1–8]. Pigmentation, ulceration and a chronic panniculitis have supervened after many years of use. Phlebitis, cellulitis, fibrous myopathy [9] and limb contractures can complicate these changes. Generalized eruptions are rare [10]. There is an isolated report of TEN [11].

References

1 Parks DL, Perry HO, Muller SA. Cutaneous complications of pentazocine injections. *Arch Dermatol* 1971; **104**: 231–5.
2 Schlicher JE, Zuehlke RL, Lynch PJ. Local changes at the site of pentazocine injection. *Arch Dermatol* 1971; **104**: 90–1.
3 Swanson DW, Weddige RL, Morse RM. Hospitalised pentazocine abusers. *Mayo Clin Proc* 1973; **48**: 85–93.
4 Schiff BL, Kern AB. Unusual cutaneous manifestations of pentazocine addiction. *JAMA* 1977; **238**: 1542–3.
5 Padilla RS, Becker LE, Hoffman H, Long G. Cutaneous and venous complications of pentazocine abuse. *Arch Dermatol* 1979; **115**: 975–7.

6 Palestine RF, Millns JL, Spigel GT *et al.* Skin manifestations of pentazocine abuse. *J Am Acad Dermatol* 1980; **2**: 47–55.
7 Mann RJ, Gostelow BE, Meacock DJ, Kennedy CTC. Pentazocine ulcers. *J R Soc Med* 1982; **75**: 903–5.
8 Jain A, Bhattacharya SN, Singal A *et al.* Pentazocine induced widespread cutaneous and myo-fibrosis. *J Dermatol* 1999; **26**: 368–70.
9 Johnson KR, Hsueh WA, Glusman SM, Arnett FC. Fibrous myopathy: a rheumatic complication of drug abuse. *Arthritis Rheum* 1976; **19**: 923–6.
10 Pedragosa R, Vidal J, Fuentes R, Huguet P. Tricotropism by pentazocine. *Arch Dermatol* 1987; **123**: 297–8.
11 Hunter JAA, Davison AM. Toxic epidermal necrolysis associated with pentazocine therapy and severe reversible renal failure. *Br J Dermatol* 1973; **88**: 287–90.

Antiparkinsonian drugs

Amantadine

Reversible livedo reticularis has occurred in a high percentage of patients receiving amantadine, a tricyclic amine used in the treatment of Parkinson's disease [1,2].

Apomorphine

Panniculitis, ranging from mild pruritic erythema to painful nodules, has been observed [3].

Bromocriptine

Transient livedo reticularis [4], erythromelalgia [5], acrocyanosis with Raynaud's phenomenon [6,7], morphoea [8] and swelling of the legs with a sclerodermatous histology [9] have been reported rarely, as have alopecia [10], pseudolymphoma [11] and psychosis.

Carbidopa

Scleroderma-like reactions have occurred when this drug has been given in conjunction with tryptophan [12,13].

Levodopa

There have been several isolated reports of the occurrence of malignant melanoma [14–16], in certain instances involving multiple primaries, but the association may be by chance alone.

References

1 Shealy CN, Weeth JB, Mercier D. Livedo reticularis in patients with parkinsonism receiving amantadine. *JAMA* 1970; **212**: 1522–3.
2 Hayes BB, Cook-Norris RH, Miller JL *et al.* Amantadine-induced livedo reticularis: a report of two cases. *J Drugs Dermatol* 2006; **5**: 288–9.
3 Acland KM, Churchyard A, Fletcher CL *et al.* Panniculitis in association with apomorphine infusion. *Br J Dermatol* 1998; **138**: 480–2.
4 Calne DB, Plotkin C, Neophytides A *et al.* Long-term treatment of Parkinsonism with bromocriptine. *Lancet* 1978; **i**: 735–7.
5 Eisler T, Hall RP, Kalavar KAR, Calne DB. Erythromelalgia-like eruption in parkinsonian patients treated with bromocriptine. *Neurology* 1981; **37**: 1368–70.
6 Duvoisin RC. Digital vasospasm with bromocriptine. *Lancet* 1976; **ii**: 204.
7 Pearce I, Pearce JMS. Bromocriptine in Parkinsonism. *BMJ* 1978; **i**: 1402–4.
8 Leshin B, Piette WW, Caplin RM. Morphea after bromocriptine therapy. *Int J Dermatol* 1989; **28**: 177–9.
9 Dupont E, Olivarius B, Strong MJ. Bromocriptine-induced collagenosis-like symptomatology in Parkinson's disease. *Lancet* 1982; **i**: 850–1.
10 Blum I, Leiba S. Increased hair loss as a side effect of bromocriptine treatment. *N Engl J Med* 1980; **303**: 1418.
11 Wiesli P, Joos L, Galeazzi RL, Dummer R. Cutaneous pseudolymphoma associated with bromocriptine therapy. *Clin Endocrinol* 2000; **53**: 656–7.
12 Sternberg EM, Van Woert MH, Young SN *et al.* Development of a scleroderma-like illness during therapy with l-5-hydroxytryptophan and carbidopa. *N Engl J Med* 1980; **303**: 782–7.
13 Chamson A, Périer C, Frey J. Syndrome sclérodermiforme et poïkilodermique observé au cours d'un traitement par carbidopa et 5-hydroxytryptophane. Culture de fibroblastes avec analyse biochimique du métabolisme du collagene. *Ann Dermatol Vénéréol* 1986; **113**: 71.
14 Sober AJ, Wick MM. Levodopa therapy and malignant melanoma. *JAMA* 1978; **240**: 554–5.
15 Bernstein JE, Medenica M, Soltani K *et al.* Levodopa administration and multiple primary cutaneous melanomas. *Arch Dermatol* 1980; **116**: 1041–4.
16 Rosin MA, Braun M III. Malignant melanoma and levodopa. *Cutis* 1984; **33**: 572–4.

Antivertigo drugs and cerebrovascular dilators

Cinnarizine

This drug [1], and its derivative flunarizine [2], have been implicated in the precipitation of lichenoid eruptions. In the case of cinnarizine, clinical and immunofluorescence features of lichen planus were combined with the presence of a circulating anti-basement-membrane zone IgG antibody [2]. Other side effects include drowsiness, depression and parkinsonism.

References

1 Miyagawa W, Ohi H, Muramatsu T *et al.* Lichen planus pemphigoides-like lesions induced by cinnarizine. *Br J Dermatol* 1985; **112**: 607–13.
2 Suys E, De Coninck A, De Pauw I, Roseeuw D. Lichen planus induced by flunarizine. *Dermatologica* 1990; **181**: 71–2.

Miscellaneous nervous system drugs

Drugs for alcoholism

Cyanamide. This inhibitor of alcohol dehydrogenase, used in the treatment of alcoholism in some countries, has been implicated in the development of a lichen planus-like eruption with oesophageal involvement [1,2], as well as exfoliative dermatitis [2].

Disulfiram. This drug causes vasomotor flushing, morbilliform rash and urticaria, as well as eczema in patients sensitized to rubber; it cross-reacts with rubber [3–5]. A toxic pustular eruption is recorded [6].

References

1 Torrelo A, Soria C, Rocamora A *et al.* Lichen planus-like eruption with esophageal involvement as a result of cyanamide. *J Am Acad Dermatol* 1990; **23**: 1168–9.
2 Kawana S. Drug eruption induced by cyanamide (carbimide): a clinical and histopathologic study of 7 patients. *Dermatology* 1997; **195**: 30–4.
3 Webb PK, Gibbs SC, Mathias CT *et al.* Disulfiram hypersensitivity and rubber contact dermatitis. *JAMA* 1979; **241**: 2061.
4 Fischer AA. Dermatologic aspects of disulfiram use. *Cutis* 1982; **30**: 461–524.
5 Minet A, Frankart M, Eggers S *et al.* Réactions allergiques aux implants de disulfirame. *Ann Dermatol Vénéréol* 1989; **116**: 543–5.
6 Larbre B, Larbre JP, Nicolas JF *et al.* Toxicodermie pustuleuse aus disulfirame. A propos d'un cas. *Ann Dermatol Vénéréol* 1990; **117**: 721–2.

Drugs to aid smoking cessation

Amfebutamone. This antidepressant drug, structurally related to the phenylethylamines (amfetamines) and used in aiding smoking cessation, has been implicated in causing liver dysfunction, pruritus and urticaria [1], serum sickness [2,3], and generalized pustular and erythrodermic psoriasis [4].

References

1 Fays S, Tréchot P, Schmutz JL *et al.* Bupropion and generalised acute urticaria: eight cases. *Br J Dermatol* 2003; **148**: 177–8.

2 McCollom RA, Elbe DH, Ritchie AH. Bupropion-induced serum sickness-like reaction. *Ann Pharmacother* 2000; **34**: 471–3.
3 Davis JS, Boyle MJ, Hannaford R, Watson A. Bupropion and serum sickness-like reaction. *Med J Aust* 2001; **174**: 479–80.
4 Cox NH, Gordon PM, Dodd H. Generalized pustular and erythrodermic psoriasis associated with bupropion treatment. *Br J Dermatol* 2002; **146**: 1061–3.

Appetite suppressants and stimulants

Centrally acting appetite suppressants may induce urticarial vasculitis [1]. Megestrol, a synthetic orally active progesterone derivative used to stimulate appetite and weight gain in cachectic patients, caused a generalized morbilliform rash in a man; skin testing with progesterone acetate was positive [2]. Sibutramine, a centrally acting drug used in weight management, caused an erythema multiforme-like reaction [3].

Pyritinol

This drug, given for cerebral concussion, caused an unusual erythema multiforme-like eruption and severe headache after 10 days' treatment [4].

References

1 Papadavid E, Yu RC, Tay A, Chu AC. Urticarial vasculitis induced by centrally acting appetite suppressants. *Br J Dermatol* 1996; **134**: 990–1.
2 Fisher DA. Drug-induced progesterone dermatitis. *J Am Acad Dermatol* 1996; **34**: 863–4.
3 Goh BK, Ng PPL, Giam YC. Severe bullous drug eruption due to sibutramine (Reductil©). *Br J Dermatol* 2003; **149**: 215–6.
4 Nachbar F, Korting HC, Vogl T. Erythema multiforme-like eruption in association with severe headache following pyritinol. *Dermatology* 1993; **187**: 42–6.

Drugs acting on the cardiovascular system

Adverse cutaneous reactions due to cardiovascular and antiarrhythmic drug therapy have been reviewed [1–3].

References

1 Reiner DM, Frishman WH, Luftschein S, Grossman M. Adverse cutaneous reactions from cardiovascular drug therapy. *NY State J Med* 1992; **92**: 137–47.
2 Sun DK, Reiner D, Frishman W *et al.* Adverse dermatologic reactions from antiarrhythmic drug therapy. *J Clin Pharmacol* 1994; **34**: 953–66.
3 Torpet LA, Kragelund C, Reibel J, Nauntofte B. Oral adverse drug reactions to cardiovascular drugs. *Crit Rev Oral Biol Med* 2004; **15**: 28–46.

Cardiac antiarrhythmic drugs

Amiodarone

This iodinated antiarrhythmic drug causes photosensitivity in around 40% of patients [1–13]. Symptoms develop within 2 h of sun exposure as a burning sensation followed by erythema; the action spectrum is UVA, extending to a degree into visible light wavebands above 400 nm [4]. Light sensitivity may persist for up to 4 months after the drug is stopped [1,2]. Blue or grey pigmentation of the face and other sun-exposed areas, resembling that in argyria, is a much less common late effect, occurring in 2–5% of cases; areas not exposed to the sun may also be involved [3,6–12]. It is induced by a phototoxic reaction involving both UVB and UVA [3,6], and is related to both duration and dosage of the drug [11]. However, although cutaneous side effects are more likely with increasing duration of treatment and cumulative dosage, neither the serum amiodarone level nor the serum metabolite level have any predictive power [13]. Amiodarone-pigmented skin contains the drug and its metabolities in higher concentrations than non-pigmented skin [3]. Iodine-rich amiodarone and its metabolites have been detected bound to lipofuscin within secondary lysosomes in perivascular dermal macrophages [7–10]. Electron-dense granules and myelin-like bodies are also found in peripheral blood leukocytes [12]. The cutaneous pigmentation slowly fades after discontinuation of therapy, but may persist for months to years [8].

Iododerma has occurred with long-term therapy. Vasculitis [14] and linear IgA disease [15] have been recorded. A fatal case of TEN has been reported [16]. The most severe adverse effect seen with amiodarone is pulmonary fibrosis, which occurs in 5–10% of exposed patients and which has a 10% mortality rate. Other problems have been cardiac dysrhythmias, thyroid dysfunction, peripheral neuropathy and reversible corneal deposits [17].

References

1 Marcus FI, Fontaine GH, Frank R, Grosgogeat Y. Clinical pharmacology and therapeutic applications of the antiarrhythmic agent amiodarone. *Am Heart J* 1981; **101**: 480–93.
2 Chalmers RJ, Muston HL, Srinivas V, Bennett DH. High incidence of amiodarone-induced photosensitivity in North-west England. *BMJ* 1982; **285**: 341.
3 Zachary CB, Slater DN, Holt DW *et al.* The pathogenesis of amiodarone-induced pigmentation and photosensitivity. *Br J Dermatol* 1984; **110**: 451–6.
4 Ferguson J, Addo HA, Jones S *et al.* A study of cutaneous photosensitivity induced by amiodarone. *Br J Dermatol* 1985; **113**: 537–49.
5 Roupe G, Larkö O, Olsson SB *et al.* Amiodarone photoreactions. *Acta Derm Venereol (Stockh)* 1987; **67**: 76–9.
6 Waitzer S, Butany J, From L *et al.* Cutaneous ultrastructural changes and photosensitivity associated with amiodarone therapy. *J Am Acad Dermatol* 1987; **16**: 779–87.
7 McGovern B, Garan H, Kelly E, Ruskin JN. Adverse reactions during treatment with amiodarone hydrochloride. *BMJ* 1983; **287**: 175–9.
8 Miller RAW, McDonald ATJ. Dermal lipofuscinosis associated with amiodarone therapy. Report of a case. *Arch Dermatol* 1984; **120**: 646–9.
9 Holt DW, Adams PC, Campbell RWF *et al.* Amiodarone and its desethyl-metabolite: tissue distribution and ultrastructural changes in amiodarone treated patients. *Br J Clin Pharmacol* 1984; **17**: 195–6.
10 Török L, Szekeres L, Lakatos A, Szücs M. Amiodaronebedingte Hyperpigmentierung. *Hautarzt* 1986; **37**: 507–10.
11 Heger JJ, Prystowsky EN, Zipes DP. Relationships between amiodarone dosage, drug concentrations, and adverse side effects. *Am Heart J* 1983; **106**: 931–5.
12 Rappersberger K, Konrad K, Wieser E *et al.* Morphological changes in peripheral blood cells and skin in amiodarone-treated patients. *Br J Dermatol* 1986; **114**: 189–96.
13 Shukla R, Jowett NI, Thompson DR, Pohl JE. Side effects with amiodarone therapy. *Postgrad Med J* 1994; **70**: 492–8.
14 Staubli M, Zimmerman A, Bircher J. Amiodarone-induced vasculitis and polyserositis. *Postgrad Med J* 1985; **61**: 245–7.
15 Primka EJ III, Liranzo MO, Bergfeld W *et al.* Amiodarone-induced linear IgA disease. *J Am Acad Dermatol* 1996; **31**: 809–11.
16 Bencini PL, Crosti C, Sala F *et al.* Toxic epidermal necrolysis and amiodarone. *Arch Dermatol* 1985; **121**: 838.
17 Morgan DJR. Adverse reactions profile: 3. Amiodarone. *Drug Ther Bull* 1991; **31**: 104–11.

Digoxin

Allergic reactions are very rare [1], but exanthematic erythema, urticaria, bullous eruptions and thrombocytopenic purpura are documented. In one patient, a psoriasiform rash occurred, confirmed by later re-exposure [2].

References

1 Martin SJ, Shah D. Cutaneous hypersensitivity reaction to digoxin. *JAMA* 1994; **271**: 1905.
2 David M, Livni E, Stern E *et al.* Psoriasiform eruption induced by digoxin: confirmed by reexposure. *J Am Acad Dermatol* 1981; **5**: 702–3.

Procainamide

This drug is well known for precipitating an LE-like syndrome [1–6], perhaps partly as a result of binding of the hydroxylamine metabolite of procainamide to complement component C4, with resultant impaired complement-mediated clearance of immune complexes [5,6]. A lichenoid eruption followed the occurrence of drug-induced LE in one case [7]. Urticarial vasculitis has been reported [8].

References

1 Dubois EL. Procainamide induction of a systemic lupus erythematosus-like syndrome. Presentation of six cases, review of the literature, and analysis and follow-up of reported cases. *Medicine (Baltimore)* 1969; **48**: 217–8.
2 Blomgren SE, Condemi JJ, Vaughan JH. Procainamide-induced lupus erythematosus. Clinical and laboratory observations. *Am J Med* 1972; **52**: 338–48.
3 Whittle TS Jr, Ainsworth SK. Procainamide-induced systemic lupus erythematosus. Renal involvement with deposition of immune complexes. *Arch Pathol Lab Med* 1976; **100**: 469–74.
4 Tan EM, Rubin RL. Autoallergic reactions induced by procainamide. *J Allergy Clin Immunol* 1984; **74**: 631–4.
5 Sim E, Stanley L, Gill EW, Jones A. Metabolites of procainamide and practolol inhibit complement components C3 and C4. *Biochem J* 1988; **251**: 323–6.
6 Sim E. Drug-induced immune complex disease. *Complement Inflamm* 1989; **6**: 119–26.
7 Sherertz EF. Lichen planus following procainamide-induced lupus erythematosus. *Cutis* 1988; **42**: 51–3.
8 Knox JP, Welykyj SE, Gradini R, Massa MC. Procainamide-induced urticarial vasculitis. *Cutis* 1988; **42**: 469–72.

Quinidine

An eczematous photosensitivity is well described [1–5]; fever is common. Thrombocytopenic purpura may be induced, resulting from antibodies to drug–platelet conjugates [6,7]. Urticarial, scarlatiniform and morbilliform eruptions occur; the latter may proceed to generalized exfoliative dermatitis if the drug is continued. Fixed and lichenoid eruptions [8–14], often induced by light, are recorded, as well as an acneiform rash [15]. Livedo reticularis has been documented; the mechanism is unknown, although recent exposure to sunlight was a feature common to all cases [16–18]. Drug-induced LE [19–21] and Henoch–Schönlein vasculitis [22,23] have been seen. Psoriasis may be exacerbated [24,25]. Localized blue-grey pigmentation of the shins, hard palate, nails, nose, ears and forearms has been recorded [26].

References

1 Berger TG, Sesody SJ. Quinidine-induced lichenoid photodermatitis. *Cutis* 1982; **29**: 595–8.
2 Marx JL, Eisenstat BA, Gladstein AH. Quinidine photosensitivity. *Arch Dermatol* 1983; **119**: 39–43.
3 Armstrong RB, Leach EE, Whitman G *et al.* Quinidine photosensitivity. *Arch Dermatol* 1985; **121**: 525–8.
4 Jeanmougin M, Sigal M, Djian B *et al.* Photo-allergie à la quinidine. *Ann Dermatol Vénéréol* 1986; **113**: 985–7.
5 Schürer NY, Lehmann P, Plewig G. Chinidininduzierte Photoallergie. Eine klinische und experimentelle Studie. *Hautarzt* 1991; **42**: 158–61.
6 Christie DJ, Weber RW, Mullen PC *et al.* Structural features of the quinidine and quinine molecules necessary for binding of drug-induced antibodies to human platelets. *J Lab Clin Med* 1984; **104**: 730–40.
7 Gary M, Ilfeld D, Kelton JG. Correlation of a quinidine-induced platelet-specific antibody with development of thrombocytopenia. *Am J Med* 1985; **79**: 253–5.
8 Anderson TE. Lichen planus following quinidine therapy. *Br J Dermatol* 1967; **79**: 500.
9 Pegum JS. Lichenoid quinidine eruption. *Br J Dermatol* 1968; **80**: 343.
10 Maltz BL, Becker LE. Quinidine-induced lichen planus. *Int J Dermatol* 1980; **19**: 96–7.
11 Bonnetblanc J-M, Bernard P, Catanzano G, Souyri N. Eruptions lichénoides photinduites aux quinidiniques. *Ann Dermatol Vénéréol* 1987; **114**: 957–61.
12 Wolf R, Dorfman B, Krakowski A. Quinidine induced lichenoid and eczematous photodermatitis. *Dermatologica* 1987; **174**: 285–9.
13 De Larrard G, Jeanmougin M, Moulonguet I *et al.* Toxidermie lichénoïde alopéciante à la quinidine. *Ann Dermatol Vénéréol* 1988; **115**: 1172–4.
14 Jeanmougin M, Elkara-Marrak H, Pons A *et al.* Éruption lichénoïde photo-induite a l'hydroxyquinidine. *Ann Dermatol Vénéréol* 1987; **114**: 1397–9.
15 Burckhart CG. Quinidine-induced acne. *Arch Dermatol* 1987; **117**: 603–4.
16 Marion DF, Terrien CM. Photosensitive livedo reticularis. *Arch Dermatol* 1973; **108**: 100–1.
17 De Groot WP, Wuite J. Livedo racemosa-like photosensitivity reaction during quinidine durettes medication. *Dermatologica* 1974; **148**: 371–6.
18 Bruce S, Wolf JE Jr. Quinidine-induced photosensitive livedo reticularis-like eruption. *J Am Acad Dermatol* 1985; **12**: 332–6.
19 Lavie CJ, Biundo J, Quinet RJ, Waxman J. Systemic lupus erythematosus (SLE) induced by quinidine. *Arch Intern Med* 1985; **145**: 446–8.
20 McCormack GD, Barth WF. Quinidine induced lupus syndrome. *Semin Arthritis Rheum* 1985; **15**: 73–9.
21 Cohen MG, Kevat S, Prowse MV *et al.* Two distinct quinidine-induced rheumatic syndromes. *Ann Intern Med* 1988; **108**: 369–71.
22 Aviram A. Henoch–Schönlein syndrome associated with quinidine. *JAMA* 1980; **243**: 432–4.
23 Zax RH, Hodge SJ, Callen JP. Cutaneous leukocytoclastic vasculitis. Serial histopathologic evaluation demonstrates the dynamic nature of the infiltrate. *Arch Dermatol* 1990; **126**: 69–72.
24 Baker H. The influence of chloroquine and related drugs on psoriasis and keratoderma blenorrhagicum. *Br J Dermatol* 1966; **78**: 161–6.
25 Brenner S, Cabili S, Wolf R. Widespread erythematous scaly plaques in an adult. Psoriasiform eruption induced by quinidine. *Arch Dermatol* 1993; **129**: 1331–2, 1334–5.
26 Mahler R, Sissons W, Watters K. Pigmentation induced by quinidine therapy. *Arch Dermatol* 1986; **122**: 1062–4.

β-Adrenoceptor-blocking agents

This group of drugs shares certain potential side effects in common [1,2]. Peripheral ischaemia may be aggravated, and cold extremities and Raynaud's phenomenon [3] may present as new symptoms. Peripheral gangrene and peripheral skin necrosis have been reported [4,5]. An LE-like syndrome [6,7], and eczematous or lichenoid eruptions [1,2] may be induced rarely. Psoriasis vulgaris is occasionally aggravated or precipitated by a number of β-blockers including atenolol, oxprenolol and propranolol [8–14]. Cross-sensitivity is not usual [15], but cross-reactivity between atenolol, oxprenolol and propranolol has been reported [16]. Peyronie's disease (induratio penis plastica) has been attributed to labetalol, metoprolol and propranolol [17,18]. Aphthous ulcers have been linked to β-blockers [19], and vasculitis occurred with sotalol [20]. β-Blockers may enhance anaphylactic reactions caused by other allergens, and may make resuscitation more difficult [21–23]. Vitiligo may be exacerbated [24]. Topical ophthalmic β-blockers, especially timolol, have been implicated in pruritus [25], alopecia [26], chronic erythroderma [27] and LE [28].

References

1 Felix RH, Ive FA, Dahl MGC. Skin reactions to beta-blockers. *BMJ* 1975; **i**: 626.
2 Hödl S. Nebenwirkungen der Betarezeptorenblocker an der Haut. Übersicht und eigene Beobachtungen. *Hautarzt* 1985; **36**: 549–57.
3 Marshall AJ, Roberts CJC, Barritt DW. Raynaud's phenomenon as a side effect of beta-blockers in hypertension. *BMJ* 1976; **i**: 1498–9.
4 Gokal R, Dornan TL, Ledingham JGG. Peripheral skin necrosis complicating beta-blockade. *BMJ* 1979; **i**: 721–2.
5 Hoffbrand BI. Peripheral skin necrosis complicating beta-blockade. *BMJ* 1979; **i**: 1082.
6 Hughes GRV. Hypotensive agents, beta-blockers, and drug-induced lupus. *BMJ* 1982; **284**: 1358–9.
7 McGuinness M, Frye RA, Deng J-S. Atenolol-induced lupus erythematosus. *J Am Acad Dermatol* 1997; **37**: 298–9.
8 Arntzen N, Kavli G, Volden G. Psoriasis provoked by β-blocking agents. *Acta Derm Venereol (Stockh)* 1984; **64**: 346–8.
9 Abel EA, Dicicco LM, Orenberg EK *et al.* Drugs in exacerbation of psoriasis. *J Am Acad Dermatol* 1986; **15**: 1007–22.
10 Heng MCY, Heng MK. Beta-adrenoceptor antagonist-induced psoriasiform eruption. Clinical and pathogenetic aspects. *Int J Dermatol* 1988; **27**: 619–27.
11 Gold MH, Holy AK, Roenigk HH Jr. Beta-blocking drugs and psoriasis. A review of cutaneous side effects and retrospective analysis of their effects on psoriasis. *J Am Acad Dermatol* 1988; **19**: 837–41.
12 Halevy S, Livni E. Psoriasis and psoriasiform eruptions associated with propranolol: the role of an immunologic mechanism. *Arch Dermatol Res* 1990; **283**: 472–3.
13 Steinkraus V, Steinfath M, Mensing H. Beta-adrenergic blocking drugs and psoriasis. *J Am Acad Dermatol* 1992; **27**: 266–7.
14 Halevy S, Livni E. Beta-adrenergic blocking drugs and psoriasis: the role of an immunologic mechanism. *J Am Acad Dermatol* 1993; **29**: 504–5.
15 Furhoff A-K, Norlander M, Peterson C. Cross-sensitivity between practolol and other beta-blockers? *BMJ* 1976; **i**: 831.
16 Van Joost T, Smitt JHS. Skin reactions to propranolol and cross sensitivity to β-adrenoreceptor blocking agents. *Arch Dermatol* 1981; **117**: 600–1.
17 Yudkin JS. Peyronie's disease in association with metoprolol. *Lancet* 1977; **ii**: 1355.
18 Jones HA, Castleden WM. Peyronie's disease. *Med J Aust* 1981; **ii**: 514–5.
19 Boulinguez S, Reix S, Bedane C *et al.* Role of drug exposure in aphthous ulcers: a case–control study. *Br J Dermatol* 2000; **143**: 1261–5.
20 Rustmann WC, Carpenter MT, Harmon C, Botti CF. Leukocytoclastic vasculitis associated with sotalol therapy. *J Am Acad Dermatol* 1998; **38**: 111–2.
21 Hannaway PJ, Hopper GDK. Severe anaphylaxis and drug-induced beta-blockade. *N Engl J Med* 1983; **308**: 1536.
22 Toogood JH. Risk of anaphylaxis in patients receiving beta-blocker drugs. *J Allergy Clin Immunol* 1988; **81**: 1–5.
23 Hepner MJ, Ownby DR, Anderson JA *et al.* Risk of systemic reactions in patients taking beta-blocker drugs receiving allergen immunotherapy injections. *J Allergy Clin Immunol* 1990; **86**: 407–11.
24 Schallreuter KU. Beta-adrenergic blocking drugs may exacerbate vitiligo. *Br J Dermatol* 1995; **132**: 168–9.
25 Lazarov A, Amicha B. Skin reactions due to eye drops: report of two cases. *Cutis* 1996; **58**: 363–4.
26 Fraunfelder FT, Meyer SM, Menacker SJ. Alopecia possibly secondary to topical ophthalmic β-blockers. *JAMA* 1990; **263**: 1493–4.
27 Shelley WB, Shelley ED. Chronic erythroderma induced by β-blocker (timolol maleate). *J Am Acad Dermatol* 1997; **37**: 799–800.
28 Zamber RW, Starkebaum G, Rubin RL *et al.* Drug induced systemic lupus erythematosus due to ophthalmic timolol. *J Rheumatol* 1992; **19**: 977–9.

Acebutolol

Rashes with mixed lichenoid and LE-like features have been reported [1]. The LE syndrome may have pleuropulmonary features [2].

Atenolol

Conjunctivitis and a periocular dermatitis [3], as well as a psoriasiform rash [4], pseudolymphomatous reaction [5] and vasculitis [6], are recorded.

Cetamolol

A psoriasiform eruption has been documented [7].

Labetalol

Mixed eruptions with psoriasiform and pityriasis rubra pilaris-like changes [8], a bullous lichenoid eruption [9] and an SLE-like syndrome [10] are documented.

Metoprolol

Various psoriasiform or eczematous rashes may follow long-term therapy [11,12]. Conjunctivitis and periocular dermatitis have occurred [3]. Peyronie's disease appears to be a rare but confirmed side effect and may be reversible. Telogen effluvium has been noted [13].

Oxprenolol

This drug, like practolol, has caused an oculocutaneous syndrome [14]. An eruption combining well-defined, eroded or scaly red rings with a lichenoid histology [15,16] is recognized. Acute psoriasis with arthropathy has been described [17]. Peripheral skin necrosis associated with Raynaud's phenomenon, an LE syndrome, various patterns of dermatitis [3] and generalized pigmentation [18] are all documented.

Practolol

This drug has been withdrawn, but is discussed in view of its important side-effect profile. It caused an oculocutaneous syndrome comprising dry eyes and scarring, fibrosis and metaplasia of the conjunctiva; a psoriasiform, lichenoid or mixed eruption with a characteristic histology; pleural and pericardial reactions; fibrinous peritonitis; and serous otitis media [19,20]. Subsequent treatment with another β-blocker did not elicit cross-sensitivity reactivation of the syndrome [21]. Ocular cicatricial pemphigoid was seen [22], and exacerbation of psoriasis was recorded [23].

Pindolol

Psoriasiform [24] and lichenoid rashes with pemphigus-like antibodies demonstrated by immunofluorescence have been seen, as well as an SLE syndrome [25].

Propranolol

This is probably the most widely used β-blocker, and many adverse cutaneous reactions have been reported [26–29]. Rashes may be lichenoid [30], psoriasiform [29] or generalized and exfoliative. Other miscellaneous reported reactions include alopecia [31], erythema multiforme [32] and a cheilostomatitis with ulceration of the lips. Peyronie's disease has developed. Generalized pustular psoriasis [33] and pemphigus [34] have occurred.

References

1 Taylor AEM, Hindson C, Wacks H. A drug eruption due to acebutolol with combined lichenoid and lupus erythematosus features. *Clin Exp Dermatol* 1982; **7**: 219–21.
2 Record NB. Acebutolol-induced pleuropulmonary lupus syndrome. *Ann Intern Med* 1981; **95**: 326–7.
3 Van Joost T, Middelkamp Hup H, Ros FE. Dermatitis as a side-effect of long-term topical treatment with certain beta-blocking agents. *Br J Dermatol* 1979; **101**: 171–6.

4 Gawkrodger DJ, Beveridge GW. Psoriasiform reaction to atenolol. *Clin Exp Dermatol* 1984; **9**: 92–4.
5 Henderson CA, Shamy HK. Atenolol-induced pseudolymphoma. *Clin Exp Dermatol* 1990; **15**: 119–20.
6 Wolf R, Ophir J, Elman M, Krakowski A. Atenolol-induced cutaneous vasculitis. *Cutis* 1989; **43**: 231–3.
7 White WB, Schulman P, McCabe EJ. Psoriasiform cutaneous eruptions induced by cetamolol hydrochloride. *Arch Dermatol* 1986; **122**: 857–8.
8 Finlay AY, Waddington E, Savage RL *et al.* Cutaneous reactions to labetalol. *BMJ* 1978; **i**: 987.
9 Gange RW, Wilson Jones E. Bullous lichen planus caused by labetalol. *BMJ* 1978; **i**: 816–7.
10 Brown RC, Cooke M, Losowsky MS. SLE syndrome, probably induced by labetalol. *Postgrad Med J* 1981; **57**: 189–90.
11 Neumann HAM, van Joost T, Westerhof W. Dermatitis as a side-effect of long-term metoprolol. *Lancet* 1979; **ii**: 745.
12 Neumann HAM, van Joost T. Adverse reactions of the skin to metoprolol and other beta-adrenergic-blocking agents. *Dermatologica* 1981; **162**: 330–5.
13 Graeber CW, Lapkin RA. Metoprolol and alopecia. *Cutis* 1981; **28**: 633–4.
14 Holt PJA, Waddington E. Oculocutaneous reaction to oxprenolol. *BMJ* 1975; **ii**: 539–40.
15 Levene GM, Gange RW. Eruption during treatment with oxprenolol. *BMJ* 1978; **i**: 784.
16 Gange RW, Levene GM. A distinctive eruption in patients receiving oxprenolol. *Clin Exp Dermatol* 1979; **4**: 87–97.
17 MacFarlane DG, Settas L. Acute psoriatic arthropathy precipitated by oxprenolol. *Ann Rheum Dis* 1984; **43**: 102–4.
18 Harrower ADB, Strong JA. Hyperpigmentation associated with oxprenolol administration. *BMJ* 1977; **ii**: 296.
19 Felix RH, Ive FA, Dahl MGC. Cutaneous and ocular reactions to practolol. *BMJ* 1974; **iv**: 321–4.
20 Wright P. Untoward effects associated with practolol administration: oculomucocutaneous syndrome. *BMJ* 1975; **i**: 595–8.
21 Furhoff A-K, Norlander M, Peterson C. Cross-sensitivity between practolol and other beta-blockers? *BMJ* 1976; **i**: 831.
22 Van Joost T, Crone RA, Overdijk AD. Ocular cicatricial pemphigoid associated with practolol therapy. *Br J Dermatol* 1976; **94**: 447–50.
23 Søndergaard J, Wadskov S, Ærenlund-Jensen H, Mikkelsen HI. Aggravation of psoriasis and occurrence of psoriasiform cutaneous eruptions induced by practolol (Eraldin®). *Acta Derm Venereol (Stockh)* 1976; **56**: 239–43.
24 Bonerandi J-J, Follana J, Privat Y. Apparition d'un psoriasis au cours d'un traitement par bêta-bloquants (Pindolol). *Ann Dermatol Syphiligr* 1976; **103**: 604–6.
25 Bensaid J, Aldigier J-C, Gualde N. Systemic lupus erythematosus syndrome induced by pindolol. *BMJ* 1979; **i**: 1603–4.
26 Ærenlund-Jensen H, Mikkelsen HI, Wadskov S, Søndergaard J. Cutaneous reactions to propranolol (Inderal®). *Acta Med Scand* 1976; **199**: 363–7.
27 Cochran REI, Thomson J, McQueen A, Beevers DG. Skin reactions associated with propranolol. *Arch Dermatol* 1976; **112**: 1173–4.
28 Scribner MD. Propranolol therapy. *Arch Dermatol* 1977; **113**: 1303.
29 Faure M, Hermier C, Perrot H. Accidents cutanés provoqués par le propranolol. *Ann Dermatol Vénéréol* 1979; **106**: 161–5.
30 Hawk JLM. Lichenoid drug eruption induced by propranolol. *Clin Exp Dermatol* 1980; **5**: 93–6.
31 Hilder RJ. Propranolol and alopecia. *Cutis* 1979; **24**: 63–4.
32 Pimstone B, Joffe B, Pimstone N *et al.* Clinical response to long-term propranolol therapy in hyperthyroidism. *S Afr Med J* 1969; **43**: 1203–5.
33 Hu C-H, Miller AC, Peppercorn R, Farber EM. Generalized pustular psoriasis provoked by propranolol. *Arch Dermatol* 1985; **121**: 1326–7.
34 Godard W, Lambert D, Gavanou J, Chapuis J-L. Pemphigus induit après traitement par l'association propranolol–méprobamate. *Ann Dermatol Vénéréol* 1980; **107**: 1213–6.

Antihypertensive drugs and vasodilators

The dermatological side effects of antihypertensive agents have been reviewed [1].

Reference

1 Thestrup-Pedersen K. Adverse reactions in the skin from antihypertensive drugs. *Dan Med Bull* 1987; **34**: 3–5.

ACE inhibitors

In addition to dermatological problems, these drugs may be nephrotoxic, cause cough and electrolyte disturbances, and are teratogenic [1,2]. The overall incidence of adverse effects from ACE inhibitors is estimated at 28%, of which about 50% occur in the skin. Cutaneous reactions comprise life-threatening angio-oedema, pruritus, bullous eruptions, urticaria, other generalized rashes, photosensitivity and hair loss [3]. Angio-oedema has been reported with captopril, enalapril maleate and lisinopril [4–11]. The cumulative incidence of angio-oedema, almost always on the head and neck, has been estimated at 0.1–0.7% of cases treated; it usually occurs in the first week of treatment [5,9], although onset more than 6 weeks after starting treatment occurs in 20% of patients [6]. In addition, increased frequency, intensity and duration of bouts of angio-oedema have been recorded during long-term use of ACE inhibitors [7–9]. There may be cross-reactivity between drugs; angio-oedema has developed after substituting lisinopril for captopril [10]. Fatal angio-oedema occurred in a patient on captopril for 2 years [11]. Anaphylactoid reactions have been reported during haemodialysis with AN69 membranes in patients receiving ACE inhibitors; the role of bacterial contamination of dialysate is controversial [12–14]. Anaphylactoid reactions have also occurred with LDL apheresis with dextran sulphate [15].

ACE inhibitors have been implicated in both the exacerbation and induction of psoriasis [16–19]. ACE inhibitors most commonly produce a dose-related pruritic maculopapular eruption on the upper trunk and arms, especially with captopril (2.4–7%) and less with enalapril (1.5%), which is often transitory and rarely requires discontinuation of the drug. Urticaria, a pemphigoid-like reaction, a pityriasis rosea-like reaction, a lichenoid eruption, erythroderma, alopecia and Stevens–Johnson syndrome have been reported [20]. Captopril and enalapril may produce eruptions with histological similarities to mycosis fungoides [21]. An interstitial granulomatous drug reaction characterized by violaceous plaques with a predilection for skinfold areas and by histology resembling the diffuse interstitial phase of granuloma annulare without complete collagen necrobiosis has been documented with ACE inhibitors [22].

References

1 Ferner RE. Adverse effects of angiotensin-converting-enzyme inhibitors. *Adverse Drug React Bull* 1990; **141**: 528–31.
2 Parish RC, Miller LJ. Adverse effects of angiotensin converting enzyme inhibitors: an update. *Drug Saf* 1992; **7**: 14–31.
3 Steckelings UM, Artuc M, Wollschlager T *et al.* Angiotensin-converting enzyme inhibitors as inducers of adverse cutaneous reactions. *Acta Derm Venereol (Stockh)* 2001; **81**: 321–5.
4 Orfan N, Patterson R, Dykewicz MS. Severe angioedema related to ACE inhibitors in patients with a history of idiopathic angioedema. *JAMA* 1990; **264**: 1287–9.
5 Slater EE, Merill DD, Guess HA *et al.* Clinical profile of angioedema associated with angiotensin converting-enzyme inhibition. *JAMA* 1988; **260**: 967–70.
6 Hedner T, Samuelsson O, Lindholm L *et al.* Angio-oedema in relation to treatment with angiotensin converting enzyme inhibitors. *BMJ* 1992; **304**: 941–6.

7 Chin HL. Severe angioedema after long-term use of an angiotensin converting enzyme inhibitor. *Ann Intern Med* 1990; **112**: 312.
8 Kozel MMA, Mekkes JR, Bos JD. Increased frequency and severity of angio-oedema related to long-term therapy with angiotensin-converting enzyme inhibitor in two patients. *Clin Exp Dermatol* 1995; **20**: 60–1.
9 Sabroe RA, Kobza Black A. Angiotensin-converting enzyme (ACE) inhibitors and angio-oedema. *Br J Dermatol* 1997; **136**: 153–8.
10 McElligott S, Perlroth M, Raish L. Angioedema after substituting lisinopril for captopril. *Ann Intern Med* 1992; **116**: 426–7.
11 Jason DR. Fatal angioedema associated with captopril. *J Forensic Sci* 1992; **37**: 1418–21.
12 Verresen L, Waer M, Vanrenterghem Y, Michielsen P. Angiotensin-converting-enzyme inhibitors and anaphylactoid reactions to high-flux membrane dialysis. *Lancet* 1990; **336**: 1360–2.
13 Tielemans C, Madhoun P, Lenears M *et al.* Anaphylactoid reactions during hemodialysis on AN69 membranes in patients receiving ACE inhibitors. *Kidney Int* 1990; **38**: 982–4.
14 Verresen L, Waer M, Vanrenterghem Y, Michielsen P. Anaphylactoid reactions, haemodialysis, and ACE inhibitors. *Lancet* 1991; **337**: 1294.
15 Keller C, Grutzmacher P, Bahr F *et al.* LDL-apheresis with dextran sulphate and anaphylactoid reactions to ACE inhibitors. *Lancet* 1993; **341**: 60–1.
16 Wolf R, Tamir A, Brenner S. Psoriasis related to angiotensin-converting enzyme inhibitors. *Dermatologica* 1990; **181**: 51–3.
17 Coulter DM, Pillans PI. Angiotensin-converting enzyme inhibitors and psoriasis. *NZ Med J* 1993; **106**: 392–3.
18 Tamir A, Wolf R, Brenner S. Exacerbation and induction of psoriasis by angiotensin-converting enzyme inhibitors. *J Am Acad Dermatol* 1994; **30**: 1045.
19 Ikai K. Exacerbation and induction of psoriasis by angiotensin-converting enzyme inhibitors. *J Am Acad Dermatol* 1996; **32**: 819.
20 Vollenweider Roten S, Mainetti C, Donath R, Saurat J-H. Enalapril-induced lichen planus-like eruption. *J Am Acad Dermatol* 1995; **32**: 293–5.
21 Furness PN, Goodfield MJ, MacLennan KA *et al.* Severe cutaneous reactions to captopril and enalapril: histological study and comparison with early mycosis fungoides. *J Clin Pathol* 1986; **39**: 902–7.
22 Perrin C, Lacour JP, Castanet J, Michiels JF. Interstitial granulomatous drug reaction with a histological pattern of interstitial granulomatous dermatitis. *Am J Dermatopathol* 2001; **23**: 295–8.

Captopril. Dermatological complications occur in 4% [1] to 12% [2] of patients treated with captopril, and less commonly with other ACE inhibitors; side effects are more likely with renal impairment. Loss of sense of taste (ageusia), or a metallic taste, ulceration of the tongue and aphthous stomatitis [3] are reported. Early changes within the first months [4–6] include pruritus, urticaria [7] and angio-oedema, which occurs in about 1 in 1000 patients and may occasionally be fatal [8], and pityriasis rosea-like [9] and morbilliform rashes. These are dose dependent and have a good prognosis. Late changes [4–6] consist of pemphigus-like [10–12] and lichenoid [13–17] eruptions. SLE-like eruptions have been recorded [18,19]. Antinuclear antibodies may develop [20,21]. Oral changes may be due to a leukocytoclastic vasculitis [22], and a serum sickness-like syndrome has been induced [23]. Psoriasis has been reported to be exacerbated or triggered [24,25].

Severe reactions [26,27] have included exfoliative dermatitis [28–30], and marrow depression with neutropenia or agranulocytosis [31]. Lymphadenopathy may be induced [32]. Alopecia [33] and an acquired IgA deficiency [34] have been reported. The merits of skin testing in the prediction of captopril reactions have been discussed [35]. It has been postulated that some toxic effects are related to the presence of a sulphydryl group, as enalapril (another ACE inhibitor lacking this group) has been safely substituted in certain cases of captopril hypersensitivity [36].

Cilazapril. Cilazapril had more neurological (mainly headache) but fewer skin reactions than the other ACE inhibitors, lisinopril, enalapril and captopril [37].

Enalapril. Enalapril produces rashes in approximately 1.4% of patients, requiring discontinuation in about 0.4% [38]. Toxic pustuloderma is recorded [38]. A single report of pemphigus foliaceus has appeared; part of the structure of this drug is identical to that of captopril, although it does not contain a sulphydryl group [39]. Bullous eruptions [40] and lichenoid eruptions [41] occur.

Lisinopril [42]. Vasculitis has been recorded [43], as has pallor, flushing and oedema [44].

Ramipril. Superficial pemphigus [45] and Stevens–Johnson syndrome [46] are recorded.

References

1 Williams GH. Converting-enzyme inhibitors in the treatment of hypertension. *N Engl J Med* 1988; **319**: 1517–25.
2 Wilkin JK, Hammond JJ, Kirkendall WM. The captopril-induced eruption. A possible mechanism: cutaneous kinin potentiation. *Arch Dermatol* 1980; **116**: 902–5.
3 Seedat YK. Aphthous ulcers of mouth from captopril. *Lancet* 1979; **ii**: 1297–8.
4 Clement M. Captopril-induced eruptions. *Arch Dermatol* 1981; **117**: 525–6.
5 Luderer JR, Lookingbill DP, Schneck DW *et al.* Captopril-induced skin eruptions. *J Clin Pharmacol* 1982; **22**: 151–9.
6 Daniel F, Foix C, Barbet M *et al.* Captopril-induced eruptions: occurrence over a three-year period. *Ann Dermatol Vénéréol* 1983; **110**: 441–6.
7 Wood SM, Mann RD, Rawlins MD. Angio-oedema and urticaria associated with angiotensin converting enzyme inhibitors. *BMJ* 1987; **294**: 91–2.
8 Slater EE, Merrill DD, Guess HA *et al.* Clinical profile of angioedema associated with angiotensin converting-enzyme inhibition. *JAMA* 1988; **260**: 967–70.
9 Wilkin JK, Kirkendall WM. Pityriasis rosea-like rash from captopril. *Arch Dermatol* 1982; **118**: 186–7.
10 Parfrey PS, Clement M, Vandenburg MJ, Wright P. Captopril-induced pemphigus. *BMJ* 1980; **281**: 194.
11 Katz RA, Hood AF, Anhalt GJ. Pemphigus-like eruption from captopril. *Arch Dermatol* 1987; **123**: 20–1.
12 Korman NJ, Eyre RW, Stanley JR. Drug-induced pemphigus: autoantibodies directed against the pemphigus antigen complexes are present in penicillamine and captopril-induced pemphigus. *J Invest Dermatol* 1991; **96**: 273–6.
13 Reinhardt LA, Wilkin JK, Kirkendall WM. Lichenoid eruption produced by captopril. *Cutis* 1983; **31**: 98–9.
14 Bravard P, Barbet M, Eich D *et al.* Éruption lichénoïde au captopril. *Ann Dermatol Vénéréol* 1983; **110**: 433–8.
15 Flageul B, Foldes C, Wallach D *et al.* Captopril-induced lichen planus pemphigoides with pemphigus-like features. A case report. *Dermatologica* 1986; **173**: 248–55.
16 Bretin N, Dreno B, Bureau B, Litoux P. Immunohistological study of captopril-induced late cutaneous reactions. *Dermatologica* 1988; **177**: 11–5.
17 Rotstein E, Rotstein H. Drug eruptions with lichenoid histology produced by captopril. *Australas J Dermatol* 1989; **30**: 9–14.
18 Patri P, Nigro A, Rebora A. Lupus erythematosus-like eruption from captopril. *Acta Derm Venereol (Stockh)* 1985; **65**: 447–8.
19 Sieber C, Grimm E, Follath F. Captopril and systemic lupus erythematosus syndrome. *BMJ* 1990; **301**: 669.
20 Reidenberg MM, Case DB, Drayer DE *et al.* Development of antinuclear antibodies in patients treated with high doses of captopril. *Arthritis Rheum* 1984; **27**: 579–81.
21 Kallenberg CGM. Autoantibodies during captopril treatment. *Arthritis Rheum* 1985; **28**: 597–8.
22 Viraben R, Adoue D, Dupre A, Touron P. Erosions and ulcers of the mouth. *Arch Dermatol* 1982; **118**: 959.

23 Hoorntje SJ, Weening JJ, Kallenberg GGM *et al.* Serum-sickness-like syndrome with membranous glomerulopathy in a patient on captopril. *Lancet* 1979; **ii**: 1297.
24 Hauschild TT, Bauer R, Kreysel HW. Erstmanifestation einer eruptivexanthematischen Psoriasis vulgaris unter Captoprilmedikation. *Hautarzt* 1986; **37**: 274–7.
25 Wolf R, Dorfman B, Krakowski A. Psoriasiform eruption induced by captopril and chlorthalidone. *Cutis* 1987; **40**: 162–4.
26 Goodfield MJ, Millard LG. Severe cutaneous reactions to captopril. *BMJ* 1985; **290**: 1111.
27 Furness PN, Goodfield MJ, MacLennan KA *et al.* Severe cutaneous reactions to captopril and enalapril: histological study and comparison with early mycosis fungoides. *J Clin Pathol* 1986; **39**: 902–7.
28 Solinger AM. Exfoliative dermatitis from captopril. *Cutis* 1982; **29**: 473–4.
29 O'Neill PG, Rajan N, Charlat ML, Bolli R. Captopril-related exfoliative dermatitis. *Texas Med* 1989; **85**: 40–1.
30 Daniel F, Foix C, Barbet M *et al.* Toxidermies au captopril: incidences au cours d'un traitement de 1321 mois/patients. *Ann Dermatol Vénéréol* 1983; **110**: 441–6.
31 Edwards CRW, Drury P, Penketh A, Damluji SA. Successful reintroduction of captopril following neutropenia. *Lancet* 1981; **i**: 723.
32 Åberg H, Mörlin C, Frithz G. Captopril-associated lymphadenopathy. *BMJ* 1981; **283**: 1297–8.
33 Motel PJ. Captopril and alopecia: a case report and review of known cutaneous reactions in captopril use. *J Am Acad Dermatol* 1990; **23**: 124–5.
34 Hammarström L, Smith CIE, Berg U. Captopril-induced IgA deficiency. *Lancet* 1991; **337**: 436.
35 Smit AJ, van der Laan S, De Monchy J *et al.* Cutaneous reactions to captopril. Predictive values of skin tests. *Clin Allergy* 1984; **14**: 413–9.
36 Gavras I, Gavras H. Captopril and enalapril. *Ann Intern Med* 1983; **98**: 556–7.
37 Coulter DM. Short term safety assessment of cilazapril. *NZ Med J* 1993; **106**: 497–9.
38 Ferguson JE, Chalmers RJ. Enalapril-induced toxic pustuloderma. *Clin Exp Dermatol* 1996; **21**: 54–5.
39 Shelto RM. Pemphigus foliaceus associated with enalapril. *J Am Acad Dermatol* 1991; **24**: 503–4.
40 Mullins PD, Choudhury SL. Enalapril and bullous eruptions. *BMJ* 1994; **309**: 1411.
41 Vollenweider Roten S, Mainetti C, Donath R, Saurat J-H. Enalapril-induced lichen planus-like eruption. *J Am Acad Dermatol* 1995; **32**: 293–5.
42 Horiuchi Y, Matsuda M. Eruptions induced by the ACE inhibitor, lisinopril. *J Dermatol* 1999; **26**: 128–30.
43 Barlow RJ, Schulz EJ. Lisinopril-induced vasculitis. *Clin Exp Dermatol* 1988; **13**: 117–20.
44 Fallowfield JM, Blenkinsopp J, Raza A *et al.* Post-marketing surveillance of lisinopril in general practice in the UK. *Br J Clin Pract* 1993; **47**: 296–304.
45 Vignes S, Paul C, Flageul B, Dubertret L. Ramipril-induced superficial pemphigus. *Br J Dermatol* 1996; **135**: 657–8.
46 Oskay T, Ozçelik T, Kutluay L. Stevens–Johnson syndrome associated with ramipril. *Int J Dermatol* 2003; **42**: 580–1.

Angiotensin II receptor antagonists

Sartans, angiotensin II receptor antagonists, have been implicated in the induction of psoriasis [1] and of Henoch–Schönlein purpura [2]. Candersartan has been implicated in erythema multiforme [3].

References

1 Marquart-Elbaz C, Grosshans E, Alt M, Lipsker D. Sartans, angiotensin II receptor antagonists, can induce psoriasis. *Br J Dermatol* 2002; **147**: 617–8.
2 Brouard M, Piguet V, Chavaz P, Borradori L. Schönlein–Henoch purpura associated with losartan treatment and presence of antineutrophil cytoplasmic antibodies of x specificity. *Br J Dermatol* 2001; **145**: 362–3.
3 Ejaz AA, Walsh JS, Wasiluk A. Erythema multiforme associated with candesartan cilexetil. *South Med J* 2004; **97**: 614–5.

Calcium-channel blockers

Calcium-channel blockers are commonly used as antihypertensive medications. Cutaneous reactions are comparatively rare and have been reported in six per million prescriptions of nifedipine, 17 per million prescriptions of verapamil, and six per million prescriptions of diltiazem [1,2]. In one study, reactions to the dihydropyridine drugs (including nicardipine, nifedipine and nisoldipine), verapamil and diltiazem occurred after an average of 95 days (range 7 days to 10 years) [3]. These drugs have been associated with cutaneous reactions ranging from exanthems to severe adverse events [4]. The most common are ankle or pedal oedema (up to 30%), gingival hyperplasia (up to 21%) and flushing (up to 10%). Less common are facial or truncal telangiectasia, photosensitivity reactions, new-onset psoriasis (as well as exacerbation of it) [3], purpuric exanthems, pemphigoid manifestations, subacute cutaneous lupus erythematosus, gynaecomastia, erythromelalgia and oral ulcers [4].

Pruritus, maculopapular rashes, and urticaria/angio-oedema, alopecia and a hypersensitivity syndrome have been described with all these drugs, as have Stevens–Johnson syndrome and erythema multiforme; TEN has occurred with diltiazem. There is a suggestion that the more severe reactions are commoner with diltiazem. Peripheral oedema as a side effect is common with the dihydropyridine calcium antagonists, including nifedipine, nicardipine, isradipine and amlodipine; it is usually mild [5]. Amlodipine has caused pruritus [6], a lichenoid eruption [7] and photosensitivity presenting as telangiectasia [8]. Felodipine has also been associated with photodistributed telangiectasia [9].

References

1 Stern R, Khalsa JH. Cutaneous adverse reactions associated with calcium channel blockers. *Arch Intern Med* 1989; **149**: 829–32.
2 Sadick NS, Katz AS, Schreiber TL. Angioedema from calcium channel blockers. *J Am Acad Dermatol* 1989; **21**: 132–3.
3 Kitamura K, Kanasashi M, Suga C *et al.* Cutaneous reactions induced by calcium channel blockers: high frequency of psoriasiform eruptions. *J Dermatol* 1993; **20**: 279–86.
4 Ioulios P, Charalampos M, Efrossini T. The spectrum of cutaneous reactions associated with calcium antagonists: a review of the literature and the possible etiopathogenic mechanisms. *Dermatol Online J* 2003; **9**: 6.
5 Maclean D, MacConnachie AM. Selected side-effects: 1. Peripheral oedema with dihydropyridine calcium antagonists. *Prescribers J* 1991; **31**: 4–6.
6 Orme S, da Costa D. Generalised pruritus associated with amlodipine. *BMJ* 1997; **315**: 463.
7 Swale VJ, McGregor JM. Amlodipine-associated lichen planus. *Br J Dermatol* 2001; **144**: 920–1.
8 Grabczynska SA, Cowley N. Amlodipine-induced photosensitivity presenting as telangiectasia. *Br J Dermatol* 2000; **142**: 1255–6.
9 Silvestre JF, Albares P, Carnero L, Botella R. Photodistributed felodipine-induced facial telangiectasia. *J Am Acad Dermatol* 2001; **45**: 323–4.

Diltiazem. Cutaneous reactions to diltiazem have been reviewed [1–3]. They include pruritic macular exanthem, toxic erythema with fever and occasionally facial angio-oedema [4–6], generalized cutaneous reactions [7], erythema multiforme [8], subcorneal pustular dermatosis, a generalized pustular dermatitis [9,10], a lichenoid photodistributed eruption with pigmentary incontinence [11], photodistributed hyperpigmentation [12,13], a photosensitive erythroderma [14], psoriasiform eruptions [2], exfoliative dermatitis in a patient with psoriasis [15], a subacute cutaneous LE-like syndrome [16], vasculitis [17] and vasculitic leg ulcers [18], recurrent nail dystrophy, hyperplastic gingivitis [19], and proptosis and periorbital oedema [20]. Generalized lymphadenopathy has

occurred [21]. Patch tests may be positive in diltiazem reactions [5,6,10]. Dermatological cross-sensitivity between diltiazem and amlodipine is reported [22].

References

1 Kitamura K, Kanasashi M, Suga C *et al.* Cutaneous reactions induced by calcium channel blocker: high frequency of psoriasiform eruptions. *J Dermatol* 1993; **20**: 279–86.
2 Knowles S, Gupta AK, Shear NH. The spectrum of cutaneous reactions associated with diltiazem: three cases and a review of the literature. *J Am Acad Dermatol* 1998; **38**: 201–6.
3 Gonzalo Garijo MA, Pérez Calderón R, de Argila Fernández-Durán D, Rangel Mayoral JF. Cutaneous reactions due to diltiazem and cross reactivity with other calcium channel blockers. *Allergol Immunopathol (Madr)* 2005; **33**: 238–40.
4 Wakeel RA, Gavin MP, Keefe M. Severe toxic erythema caused by diltiazem. *BMJ* 1988; **296**: 1071.
5 Hammentgen R, Lutz G, Köhler U, Nitsch J. Makulopapulöses Exanthem bei Diltiazem-Therapie. *Dtsch Med Wochenschr* 1988; **113**: 1283–5.
6 Romano A, Pietrantonio F, Garcovich A *et al.* Delayed hypersensitivity to diltiazem in two patients. *Ann Allergy* 1992; **69**: 31–2.
7 Sousa-Basto A, Azenha A, Duarte ML, Pardal-Oliveira F. Generalized cutaneous reaction to diltiazem. *Contact Dermatitis* 1993; **29**: 44–5.
8 Berbis P, Alfonso MJ, Levy JL, Privat Y. Diltiazem associated erythema multiforme. *Dermatologica* 1990; **179**: 90.
9 Lambert DG, Dalac S, Beer F *et al.* Acute generalized exanthematous pustular dermatitis induced by diltiazem. *Br J Dermatol* 1988; **118**: 308–9.
10 January V, Machet L, Gironet N *et al.* Acute generalized exanthematous pustulosis induced by diltiazem: value of patch testing. *Dermatology* 1998; **197**: 274–5.
11 Scherschun L, Lee MW, Lim HW. Diltiazem-associated photodistributed hyperpigmentation: a review of 4 cases. *Arch Dermatol* 2001; **137**: 179–82.
12 Boyer M, Katta R, Markus R. Diltiazem-induced photodistributed hyperpigmentation. *Dermatol Online J* 2003; **9**: 10.
13 Kuykendall-Ivy T, Collier SL, Johnson SM. Diltiazem-induced hyperpigmentation. *Cutis* 2004; **73**: 239–40.
14 Hashimoto M, Tanaka S, Horio T. Photosensibility due to diltiazem hydrochloride. *Acta Dermatol* 1979; **74**: 181–4.
15 Larvijsen APM, Van Dijke C, Vermeer B-J. Diltiazem-associated exfoliative dermatitis in a patient with psoriasis. *Acta Derm Venereol (Stockh)* 1986; **66**: 536–8.
16 Crowson AN, Magro CM. Diltiazem and subacute cutaneous lupus erythematosus-like lesions. *N Engl J Med* 1995; **333**: 1429.
17 Sheehan-Dare RA, Goodfield MJ. Severe cutaneous vasculitis induced by diltiazem. *Br J Dermatol* 1988; **119**: 134.
18 Carmichael AJ, Paul CJ. Vasculitic leg ulcers associated with diltiazem. *BMJ* 1988; **297**: 562.
19 Giustiniani S, Robustelli della Cuna F, Marieni M. Hyperplastic gingivitis during diltiazem therapy. *Int J Cardiol* 1987; **15**: 247–9.
20 Friedland S, Kaplan S, Lahav M, Shapiro A. Proptosis and periorbital edema due to diltiazem treatment. *Arch Ophthalmol* 1993; **111**: 1027–8.
21 Scolnick B, Brinberg D. Diltiazem and generalized lymphadenopathy. *Ann Intern Med* 1985; **102**: 558.
22 Baker BA, Cacchione JG. Dermatologic cross-sensitivity between diltiazem and amlodipine. *Ann Pharmacother* 1994; **28**: 118–9.

Nicardipine. Erythromelalgia is recorded [1].

Nicorandil. Oral, anal and parastomal ulceration are documented [2–7].

Nifedipine. Headache, tachycardia and flushing are common side effects. Gingival hyperplasia is well recognized [8]. Burning sensations, erythema, painful oedema and erythromelalgia have been described [9–12]. There have been isolated reports of a truncal morbilliform rash [13], fixed drug eruption [14], a generalized bullous eruption, vasculitis [15], purpura, photosensitivity [16] in one case confirmed by rechallenge [17], gynaecomastia [18], erysipelas-like lesions on the shins with erythematous plaques on the trunk [19], exfoliative dermatitis [20,21] and pemphigoid nodularis [22].

Verapamil. Erythema multiforme has been reported [23], as have gingival hyperplasia, gynaecomastia [24], alopecia, maculopapular eruptions, ecchymosis, vasculitis, urticaria and hyperkeratosis.

References

1 Levesque H, Moore N, Wolfe LM, Courtoid H. Erythromelalgia induced by nicardipine (inverse Raynaud's phenomenon?). *BMJ* 1989; **298**: 1252–3.
2 Cribier B, Marquart-Elbaz C, Lipsker D *et al.* Chronic buccal ulceration induced by nicorandil. *Br J Dermatol* 1998; **138**: 372–3.
3 Desruelles R, Bahadoran P, Lacour J-P *et al.* Giant oral aphthous ulcers induced by nicorandil. *Br J Dermatol* 1998; **138**: 712–3.
4 Baker RP, Al-Kubati W, Atuf M *et al*. Nicorandil-induced severe perianal ulceration. *Tech Coloproctol* 2007; **11**: 343–5.
5 Akbar F, Maw A, Bhowmick A. Anal ulceration induced by nicorandil. *BMJ* 2007; **335**: 936–7.
6 Williams C, Tamuno P, Smith AJ *et al*. Perianal ulcerations and other cutaneous ulcerations complicating nicorandil therapy. *J Am Acad Dermatol* 2007; **56** (Suppl. 5): S116–7.
7 Egred M. Nicorandil-associated ulcerations. *Eur J Gastroenterol Hepatol* 2007; **19**: 395–8.
8 Benini PL, Crosti C, Sala F *et al.* Gingival hyperplasia by nifedipine. Report of a case. *Acta Derm Venereol (Stockh)* 1985; **65**: 362–5.
9 Bridgman JF. Erythematous edema of the legs due to nifedipine. *BMJ* 1978; **i**: 578.
10 Fisher JR, Padnick MB, Olstein S. Nifedipine and erythromelalgia. *Ann Intern Med* 1983; **98**: 671–2.
11 Brodmerkel GJ Jr. Nifedipine and erythromelalgia. *Ann Intern Med* 1983; **99**: 415.
12 Alcalay J, David M, Sandbank M. Cutaneous reactions to nifedipine. *Dermatologica* 1987; **175**: 191–3.
13 Parish LC, Witkowski JA. Truncal morbilliform eruption due to nifedipine. *Cutis* 1992; **49**: 113–4.
14 Alcalay J, David M. Generalized fixed drug eruptions associated with nifedipine. *BMJ* 1986; **292**: 450.
15 Brenner S, Brau S. Vasculitis following nifedipine. *Harefuah* 1985; **108**: 139–40.
16 Thomas SE, Wood ML. Photosensitivity reactions associated with nifedipine. *BMJ* 1986; **292**: 992.
17 Zenarola P, Gatti S, Lomuto M. Photodermatitis due to nifedipine: report of 2 cases. *Dermatologica* 1991; **182**: 196–8.
18 Clyne CAC. Unilateral gynaecomastia and nifedipine. *BMJ* 1986; **292**: 380.
19 Leibovici V, Zlotogorski A, Heyman A *et al.* Polymorphous drug eruption due to nifedipine. *Cutis* 1988; **41**: 367.
20 Reynolds NJ, Jones SK, Crossley J, Harman RRM. Exfoliative dermatitis due to nifedipine. *Br J Dermatol* 1989; **121**: 401–4.
21 Mohammed KN. Nifedipine-induced exfoliative dermatitis and pedal edema. *Ann Pharmacother* 1994; **28**: 967.
22 Ameen M, Harman KE, Black MM. Pemphigoid nodularis associated with nifedipine. *Br J Dermatol* 2000; **142**: 575–7.
23 Kürkçüoglu N, Alaybeyi F. Erythema multiforme after verapamil treatment. *J Am Acad Dermatol* 1991; **24**: 511–2.
24 Rodriguez LaG, Jick H. Risk of gynaecomastia associated with cimetidine, omeprazole, and other antiulcer drugs. *BMJ* 1994; **308**: 503–6.

Centrally acting antihypertensive drugs

Clonidine. Hypersensitivity rashes occur in up to 5% of patients. A pityriasis rosea-like and LE-like syndrome, exacerbation of psoriasis [1] and an isolated instance of anogenital cicatricial pemphigoid [2] have been documented. Transdermally administered clonidine has caused allergic contact dermatitis, but also erythema,

scaling, vesiculation, excoriation, induration and dyspigmentation [3].

References

1 Wilkin JK. Exacerbation of psoriasis during clonidine therapy. *Arch Dermatol* 1981; **117**: 4.
2 Van Joost T, Faber WR, Manuel HR. Drug-induced anogenital cicatricial pemphigoid. *Br J Dermatol* 1980; **102**: 715–8.
3 Prisant LM. Transdermal clonidine skin reactions. *J Clin Hypertens* 2002; **4**: 136–8.

Methyldopa. An eczematous eruption of discoid or seborrhoeic pattern is characteristic, is more likely to occur in previously eczematous subjects and persists until the drug is stopped [1]. Eczema of the palms and soles has also been described and may become widespread. The reaction is probably allergic as it may be dose related. Purpuric, erythematous and lichenoid rashes occur, sometimes in association with fever and other allergic symptoms [2,3]. Lichenoid eruptions may be ulcerated [4,5] and persistent ulceration of the tongue has been described. Fixed eruptions are very rare. An LE-like syndrome is documented [6,7] and an autoimmune haemolytic anaemia is well known [5]. Psoriasis may be precipitated. An extensive erythematous skin eruption, fever, lymphadenopathy and eosinophilia due to methyldopa, recurrent on re-exposure, has been recorded [8].

References

1 Church R. Eczema provoked by methyldopa. *Br J Dermatol* 1974; **91**: 373–8.
2 Stevenson CJ. Lichenoid eruptions due to methyldopa. *Br J Dermatol* 1971; **85**: 600.
3 Burry JN, Kirk J. Lichenoid drug reaction from methyldopa. *Br J Dermatol* 1974; **91**: 475–6.
4 Burry JN. Ulcerative lichenoid eruption from methyldopa. *Arch Dermatol* 1976; **112**: 880.
5 Furhoff A-K. Adverse reactions with methyldopa: a decade's reports. *Acta Med Scand* 1978; **203**: 425–8.
6 Harrington TM, Davis DE. Systemic lupus-like syndrome induced by methyldopa therapy. *Chest* 1981; **79**: 696–7.
7 Dupont A, Six R. Lupus-like syndrome induced by methyldopa. *BMJ* 1982; **285**: 693–4.
8 Wolf R, Tamir A, Werbin N, Brenner S. Methyldopa hypersensitivity syndrome. *Ann Allergy* 1993; **71**: 166–8.

Adrenergic neurone-blocking agents

Guanethidine. Hypersensitivity eruptions are very rare but polyarteritis nodosa has been attributed to this drug [1].

Reference

1 Dewar HA, Peaston MJT. Three cases resembling polyarteritis nodosa arising during treatment with guanethidine. *BMJ* 1964; **ii**: 609–11.

Vasodilator antihypertensive drugs

Diazoxide. Transient flushing is common. During long-term treatment, up to half the patients develop hypertrichosis without other signs of virilization [1]. A clinical picture resembling hypertrichosis lanuginosa may develop [2,3]. Oedema occurs in at least 10% of patients; photosensitivity is very uncommon but well recognized. Lichenoid [3,4] and other rashes occur rarely.

References

1 Burton JL, Schutt WH, Caldwell JW. Hypertrichosis due to diazoxide. *Br J Dermatol* 1975; **93**: 707–11.
2 Koblenzer PJ, Baker J. Hypertrichosis lanuginosa associated with diazoxide therapy in prepubertal children: a clinicopathologic study. *Ann NY Acad Sci* 1968; **150**: 373–82.
3 Menter MA. Hypertrichosis lanuginosa and a lichenoid eruption due to diazoxide therapy. *Proc R Soc Med* 1973; **66**: 326–7.
4 Okun R, Russell RP, Wilson WR. Use of diazoxide with trichlormethiazide for hypertension. *Arch Intern Med* 1963; **112**: 882–6.

Hydralazine. The LE-like syndrome due to this drug is well known [1–7]. Hydralazine binds to complement component C4 and inhibits its function; this may impair clearance of immune complexes, and predispose to development of an LE syndrome [6,7].

Orogenital ulceration may be part of the picture [8], and the syndrome has presented as a leg ulcer [9]. Cutaneous vasculitis may be severe and necrotizing [10,11]. An association between hydralazine-induced LE syndrome and the development of Sweet's syndrome has been noted rarely [12]. Fixed drug eruption has been reported [13]. Characteristic lung changes are attributed to the drug [14].

References

1 Alarcon-Segovia D, Wakin KG, Worthington JW *et al.* Clinical and experimental studies on the hydralazine syndrome and its relationship to systemic lupus erythematosus. *Medicine (Baltimore)* 1967; **46**: 1–33.
2 Batchelor JR, Welsh KI, Mansilla Tinoco R *et al.* Hydralazine-induced systemic lupus erythematosus: influence of HLA-DR and sex upon susceptibility. *Lancet* 1980; **i**: 1107–9.
3 Dubroff LM, Reid R Jr, Papalian M. Molecular models for hydralazine-related systemic lupus erythematosus. *Arthritis Rheum* 1981; **24**: 1082–5.
4 Perry HM Jr. Possible mechanisms of the hydralazine-related lupus-like syndrome. *Arthritis Rheum* 1981; **24**: 1093–105.
5 Mansilla Tinoco R, Harland SJ, Ryan P *et al.* Hydralazine, antinuclear antibodies, and the lupus syndrome. *BMJ* 1982; **284**: 936–9.
6 Sim E, Law S-KA. Hydralazine binds covalently to complement component C4. Different reactivity of C4A and C4B gene products. *FEBS Lett* 1985; **184**: 323–7.
7 Sim E. Drug-induced immune complex disease. *Complement Inflamm* 1989; **6**: 119–26.
8 Neville E, Graham PY, Brewis RA. Orogenital ulcers, SLE and hydralazine. *Postgrad Med J* 1981; **57**: 378–9.
9 Kissin MW, Williamson RCN. Hydrallazine-induced SLE-like syndrome presenting as a leg ulcer. *BMJ* 1979; **ii**: 1330.
10 Bernstein RM, Egerton-Vernon J, Webster J. Hydrallazine-induced cutaneous vasculitis. *BMJ* 1980; **280**: 156–7.
11 Peacock A, Weatherall D. Hydralazine-induced necrotising vasculitis. *BMJ* 1981; **282**: 1121–2.
12 Servitje O, Ribera M, Juanola X, Rodriguez-Moreno J. Acute neutrophilic dermatosis associated with hydralazine-induced lupus. *Arch Dermatol* 1988; **123**: 1435–6.
13 Sehgal VN, Gangwani OP. Hydralazine-induced fixed drug eruption. *Int J Dermatol* 1986; **25**: 394.
14 Bass BH. Hydralazine lung. *Thorax* 1981; **36**: 695–6.

Minoxidil. This arterial vasodilator causes hypertrichosis, especially of the arms and face, which may be unacceptable to women [1,2]; the hair disappears slowly after the drug is withdrawn. Fluid retention may require diuretic therapy to control it. Thrombocytopenia [3], bullous eruptions [4], erythema multiforme or Stevens–Johnson syndrome [5] and pseudoacromegaly [6] have been described.

References

1 Burton JL, Marshall A. Hypertrichosis due to minoxidil. *Br J Dermatol* 1979; **101**: 593–5.

2 Ryckmanns F. Hypertrichose durch Minoxidil. *Hautarzt* 1980; **31**: 205–6.
3 Peitzmann SJ, Martin C. Thrombocytopenia and minoxidil. *Ann Intern Med* 1980; **92**: 874.
4 Rosenthal T, Teicher A, Swartz J, Boichis H. Minoxidil-induced bullous eruption. *Arch Intern Med* 1978; **138**: 1856–7.
5 DiSantis DJ, Flanagan J. Minoxidil-induced Stevens–Johnson syndrome. *Arch Intern Med* 1981; **141**: 1515.
6 Nguyen KH, Marks JG Jr. Pseudoacromegaly induced by the long-term use of minoxidil. *J Am Acad Dermatol* 2003; **48**: 962–5.

Nitrate vasodilators

Glyceryl and pentaerythritol tetranitrate. Reactions to nitrate vasodilators are rare, but erythroderma with cross-reactivity to glyceryl trinitrate has been caused by this drug [1].

Reference

1 Ryan FP. Erythroderma due to peritrate and glyceryl trinitrate. *Br J Dermatol* 1972; **87**: 498–500.

Diuretics

Carbonic anhydrase inhibitor

Acetazolamide. This drug has caused hirsutism in a child [1]. Hypersensitivity reactions are rare.

Reference

1 Weiss IS. Hirsutism after chronic administration of acetazolamide. *Am J Ophthalmol* 1974; **78**: 327–8.

Loop diuretics

Bumetanide. Occasional hypersensitivity rashes occur. Pseudoporphyria has been reported with this sulphonamide-derived drug [1].

Etacrynic acid (ethacrynic acid). A Henoch–Schönlein type of vasculitis has been documented.

Furosemide (frusemide). Reactions are rare: only two patients of 3830 receiving this medication in one study developed cutaneous complications [2]. Phototoxic blistering has followed very high dosage (2.0 g/day) in chronic renal failure [3] but erythema multiforme [4,5], bullous pemphigoid [6,7], other bullous haemorrhagic eruptions [8] and an acquired blistering disorder with skin fragility [9] have apparently been precipitated by conventional dosage. The skin changes may mimic those of porphyria. Several cases of generalized exfoliative dermatitis have been documented. Anaphylaxis [10], a necrotizing vasculitis [11] and an eruption resembling Sweet's syndrome [12] have been reported. Cross-reactivity between furosemide, hydrochlorothiazide and sulphonamides is recorded, but the use of one of these drugs in a patient known to have allergy to another involves only low risk [13].

References

1 Leitao EA, Person JR. Bumetanide-induced pseudoporphyria. *J Am Acad Dermatol* 1990; **23**: 129–30.
2 Bigby M, Jick S, Jick H, Arndt K. Drug-induced cutaneous reactions. A report from the Boston Collaborative Drug Surveillance Program on 15438 consecutive inpatients, 1975 to 1982. *JAMA* 1986; **256**: 3358–63.
3 Burry JN, Lawrence JR. Phototoxic blisters from high frusemide dosage. *Br J Dermatol* 1976; **94**: 493–9.
4 Gibson TP, Blue P. Erythema multiforme and furosemide therapy. *JAMA* 1970; **212**: 1709.
5 Zugerman C, La Voo EJ. Erythema multiforme caused by oral furosemide. *Arch Dermatol* 1980; **116**: 518–9.
6 Fellner MI, Katz JM. Occurrence of bullous pemphigoid after furosemide therapy. *Arch Dermatol* 1976; **112**: 75–7.
7 Castel T, Gratacos R, Castro J *et al.* Bullous pemphigoid induced by frusemide. *Clin Exp Dermatol* 1981; **6**: 635–8.
8 Ebringer A, Adam WR, Parkin JD. Bullous haemorrhagic eruption associated with frusemide. *Med J Aust* 1969; **1**: 768–71.
9 Kennedy AC, Lyell A. Acquired epidermolysis bullosa due to high dose frusemide. *BMJ* 1976; **i**: 1509–10.
10 Hansbrough JR, Wedner HJ, Chaplin DD. Anaphylaxis to intravenous furosemide. *J Allergy Clin Immunol* 1987; **80**: 538–41.
11 Hendricks WM, Ader RS. Furosemide-induced cutaneous necrotizing vasculitis. *Arch Dermatol* 1977; **113**: 375.
12 Cobb MW. Furosemide-induced eruption simulating Sweet's syndrome. *J Am Acad Dermatol* 1989; **21**: 339–43.
13 Sullivan TJ. Cross-reactions among furosemide, hydrochlorothiazide, and sulfonamides. *JAMA* 1991; **265**: 120–1.

Potassium-sparing diuretics

Spironolactone. This drug, which is also used for the treatment of acne vulgaris and hirsutism [1], may cause gynaecomastia [2–4], gastrointestinal upset, hyperkalaemia and rarely agranulocytosis [1]. Spironolactone has an antiandrogenic effect [4] and may result in loss of libido and impotence or menstrual irregularities. A maculopapular eruption [5], LE-like syndrome [6], annular LE [7], erythema annulare centrifugum [8] and a lichenoid eruption [9] have been seen.

References

1 Shaw JC. Spironolactone in dermatologic therapy. *J Am Acad Dermatol* 1991; **24**: 236–43.
2 Clarke E. Spironolactone therapy and gynecomastia. *JAMA* 1965; **193**: 157–8.
3 Loriaux DL, Meuard R, Taylor A *et al.* Spironolactone and endocrine dysfunction. *Ann Intern Med* 1976; **85**: 630–6.
4 Rose LI, Underwood RH, Newmark SR *et al.* Pathophysiology of spironolactone-induced gynecomastia. *Ann Intern Med* 1977; **87**: 398–403.
5 Gupta AK, Knowles SR, Shear NH. Spironolactone-associated cutaneous effects: a case report and a review of the literature. *Dermatology* 1994; **189**: 402–5.
6 Uddin MS, Lynfield YL, Grosberg SJ, Stiefler R. Cutaneous reaction to spironolactone resembling lupus erythematosus. *Cutis* 1979; **24**: 198–200.
7 Leroy D, Dompmartin A, Le Jean S *et al.* Toxidermie a l'aldactone® à type d'érytheme annulaire centrifuge lupique. *Ann Dermatol Vénéréol* 1987; **114**: 1237–40.
8 Carsuzaa F, Pierre C, Dubegny M. Erytheme annulaire centrifuge à l'aldactone. *Ann Dermatol Vénéréol* 1987; **114**: 375–6.
9 Downham TF III. Spironolactone-induced lichen planus. *JAMA* 1978; **240**: 1138.

Thiazides and related diuretics

Photosensitivity is uncommon, occurring in 1 in 1000 to 1 in 100 000 prescriptions [1–7]. Hydrochlorothiazide causes considerably more reactions than bendroflumethiazide (bendrofluazide). The mechanism is unknown, and both phototoxic [1,4,7] and photoallergic [2,3] mechanisms have been proposed. The commonest reaction is lichenoid [8], but petechial and erythematous eruptions may occur in exposed skin. Xerostomia has been reported, as has a vasculitis [9]. An eruption resembling subacute cutaneous LE has been described in patients taking a combination of hydrochlorothiazide and triamterene [10,11] and with hydrochlorothiazide alone [12]. Other side effects include hypokalaemia, short-term

elevation of LDL cholesterol, impotence, a diabetogenic effect and exacerbation of gout [13].

Chlortalidone (chlorthalidone). Pseudoporphyria has been documented with this thiazide-related diuretic [14]. Psoriasis has been triggered in a patient also receiving captopril [15].

References

1 Diffey BL, Langtry J. Phototoxic potential of thiazide diuretics in normal subjects. *Arch Dermatol* 1989; **125**: 1355–8.
2 Harber LC, Lashinsky AM, Baer RL. Photosensitivity to chlorothiazide and hydrochlorothiazide. *N Engl J Med* 1959; **261**: 1378–81.
3 Torinuki W. Photosensitivity due to hydrochlorothiazide. *J Dermatol* 1980; **7**: 293–6.
4 Rosén K, Swanbeck G. Phototoxic reactions from some common drugs provoked by a high-intensity UVA lamp. *Acta Derm Venereol (Stockh)* 1982; **62**: 246–8.
5 Hawk JLM. Photosensitizing agents used in the United Kingdom. *Clin Exp Dermatol* 1984; **9**: 300–2.
6 Robinson HN, Morison WL, Hood AF. Thiazide diuretic therapy and chronic photosensitivity. *Arch Dermatol* 1985; **121**: 522–4.
7 Addo HA, Ferguson J, Frain-Bell W. Thiazide-induced photosensitivity: a study of 33 subjects. *Br J Dermatol* 1987; **116**: 749–60.
8 Johnston GA. Thiazide-induced lichenoid photosensitivity. *Clin Exp Dermatol* 2002; **27**: 670–2.
9 Björnberg A, Gisslén H. Thiazides: a cause of necrotising vasculitis? *Lancet* 1965; **ii**: 982–3.
10 Berbis P, Vernay-Vaisse C, Privat Y. Lupus cutané subaigu observé au cours d'un traitement par diurétiques thiazidiques. *Ann Dermatol Vénéréol* 1986; **113**: 1245–8.
11 Darken M, McBurney EI. Subacute cutaneous lupus erythematosus-like drug eruption due to combination diuretic hydrochlorothiazide and triamterene. *J Am Acad Dermatol* 1988; **18**: 38–42.
12 Reed BR, Huff JC, Jones SK *et al*. Subacute cutaneous lupus erythematosus associated with hydrochlorothiazide therapy. *Ann Intern Med* 1985; **103**: 49–51.
13 Orme M. Thiazides in the 1990s. The risk : benefit ratio still favours the drug. *BMJ* 1990; **300**: 1168–9.
14 Baker EJ, Reed KD, Dixon SL. Chlorthalidone-induced pseudoporphyria: clinical and microscopic findings of a case. *J Am Acad Dermatol* 1989; **21**: 1026–9.
15 Wolf R, Dorfman B, Krakowski A. Psoriasiform eruption induced by captopril and chlorthalidone. *Cutis* 1987; **40**: 162–4.

Miscellaneous cardiovascular drugs

Dobutamine

Two patients with local dermal hypersensitivity at the site of dobutamine hydrochloride injection, consisting of erythema, pruritus and phlebitis with or without bullae, have been described [1]. Dermal cellulitis has also been reported [2].

Dopamine

This positive inotropic agent has caused local skin necrosis, due to extravasation at the site of an intravenous cannula [3], and acral gangrene secondary to distal vasoconstriction [4,5]. Localized piloerection and vasoconstriction proximal to the site of infusion have been documented [6]. Allergic reactions may occur [7].

Phenylephrine

A microvascular occlusion syndrome in a patient with a heterozygous factor V Leiden mutation has been recorded [8].

References

1 Wu CC, Chen WJ, Cheng J. Local dermal hypersensitivity from dobutamine hydrochloride (Dobutrex solution) injection. *Chest* 1991; **99**: 1547–8.
2 Cernek PK. Dermal cellulitis: a hypersensitivity reaction from dobutamine hydrochloride. *Ann Pharmacother* 1994; **28**: 964.
3 Green SI, Smith JW. Dopamine gangrene. *N Engl J Med* 1976; **294**: 114.
4 Boltax RS, Dineen JP, Scarpa FJ. Gangrene resulting from infiltrated dopamine solution. *N Engl J Med* 1977; **296**: 823.
5 Park JY, Kanzler M, Swetter SM. Dopamine-associated symmetric peripheral gangrene. *Arch Dermatol* 1997; **133**: 247–8.
6 Ross M. Dopamine-induced localized cutaneous vasoconstriction and piloerection. *Arch Dermatol* 1991; **127**: 586–7.
7 Merola B, Sarnacchiaro F, Colao A *et al*. Allergy to ergot-derived dopamine agonists. *Lancet* 1992; **339**: 620.
8 Kalajian AH, Turpen KB, Donovan KO *et al*. Phenylephrine-induced microvascular occlusion syndrome in a patient with a heterozygous factor V Leiden mutation. *Arch Dermatol* 2007; **143**: 1314–7.

Vasopressin

This drug, when used intravenously for control of bleeding oesophageal varices or as a local vasoconstrictor agent, has caused cutaneous necrosis at sites of extravasation, and occasionally at distant sites, a bullous eruption [1]. Mottling, cyanosis, ecchymoses, bullae, ulcers and gangrene are often preceded by coolness and paraesthesiae [2].

References

1 Korenberg RJ, Landau-Price D, Penneys NS. Vasopressin-induced bullous disease and cutaneous necrosis. *J Am Acad Dermatol* 1986; **15**: 393–8.
2 Maceyko RF, Vidimos AT, Steck WD. Vasopressin-associated cutaneous infarcts, alopecia, and neuropathy. *J Am Acad Dermatol* 1994; **31**: 111–3.

Rutosides (Paroven)

This mixture of oxerutins, used for relief of symptoms of oedema related to chronic venous insufficiency and for reduction of lymphoedema, has been associated with transient urticaria [1].

Reference

1 Anonymous. Paroven: not much effect in trials. *Drug Ther Bull* 1992; **30**: 7–8.

Drugs acting on the respiratory system

β-Agonists

Albuterol

Patchy erythema of the hands developed in a pregnant patient following infusion [1].

Salbutamol

LE-like acral erythema developed after infusion in three pregnant patients with premature labour [2].

Salmeterol

An urticarial reaction that recurred on challenge was attributed to this drug administered from a metered dose inhaler [3].

References

1 Morin Leport LRM, Loisel JC, Feuilly C. Hand erythema due to infusion of sympathomimetics. *Br J Dermatol* 1990; **122**: 116–7.
2 Reygagne P, Lacour JP, Ortonne J-P. Palmar and plantar erythema due to infusion of sympathomimetics in pregnant women. *Br J Dermatol* 1991; **124**: 210.
3 Hatton MQF, Allen MB, Mellor EJ, Cooke NJ. Salmeterol rash. *Lancet* 1991; **337**: 1169–70.

Aminophylline

This drug is a mixture of theophylline and ethylenediamine. Urticaria, generalized erythema and exfoliative dermatitis have followed systemic administration, probably as a result of reactions to the ethylenediamine component rather than to theophylline itself [1]. Cross-reactions may occur with ethylenediamine in antihistamines and topical preparations [1,2]. Patch tests may or may not be positive [3].

References

1 Gibb W, Thompson PJ. Allergy to aminophylline. *BMJ* 1983; **287**: 501.
2 Elias JA, Levinson AI. Hypersensitivity reactions to ethylenediamine in aminophylline. *Am Rev Respir Dis* 1981; **123**: 550–2.
3 Kradjan WA, Lakshminarayan S. Allergy to aminophylline: lack of predictability by skin testing. *Am J Hosp Pharm* 1981; **38**: 1031–3.

Miscellaneous respiratory system drugs

Sodium cromoglicate (sodium cromoglycate)

Hypersensitivity reactions are rare, but urticaria, angio-oedema and anaphylactic shock are recorded [1].

Reference

1 Scheffer AL, Rocklin RE, Goetzl EJ. Immunologic components of hypersensitivity reactions to cromolyn sodium. *N Engl J Med* 1975; **293**: 1220–4.

Pseudoephedrine

This drug is present in nasal decongestants and has caused a fixed drug eruption [1–3], recurrent pseudoscarlatina [4,5], allergic reactions [6], systemic contact dermatitis [7] and a reaction simulating recurrent toxic shock syndrome [8].

References

1 Shelley WB, Shelley ED. Nonpigmenting fixed drug reaction pattern: examples caused by sensitivity to pseudoephedrine hydrochloride and tetra-hydrozoline. *J Am Acad Dermatol* 1987; **17**: 403–7.
2 Hauken M. Fixed drug eruption and pseudoephedrine. *Ann Intern Med* 1994; **120**: 442.
3 Quan MB, Chow WC. Nonpigmenting fixed drug eruption after pseudoephedrine. *Int J Dermatol* 1996; **35**: 367–70.
4 Taylor BJ, Duffill MB. Recurrent pseudo-scarlatina and allergy to pseudoephedrine hydrochloride. *Br J Dermatol* 1988; **118**: 827–9.
5 Rochina A, Burches E, Morales C *et al.* Adverse reaction to pseudoephedrine. *J Invest Allergol Clin Immunol* 1995; **5**: 235–6.
6 Heydon J, Pillans P. Allergic reaction to pseudoephedrine. *NZ Med J* 1995; **108**: 112–3.
7 Tomb RR, Lepoittevin JP, Espinassouze F *et al.* Systemic contact dermatitis from pseudoephedrine. *Contact Dermatitis* 1991; **24**: 86–8.
8 Cavanah DK, Ballas ZK. Pseudoephedrine reaction presenting as recurrent toxic shock syndrome. *Ann Intern Med* 1993; **119**: 302–3.

Drugs acting on the renal system

Icodextrin

This osmotic agent used in peritoneal dialysis has caused a variety of allergic reactions [1,2], a psoriasiform eruption limited to the palms and soles [3], and acute generalized exanthematous pustulosis [4].

References

1 Goldsmith D, Jayawardene S, Sabharawal N, Cooney K. Allergic reactions to the polymeric glucose-based peritoneal dialysis fluid icodextrin in patients with renal failure. *Lancet* 2000; **355**: 897.
2 Divino Filho JC. Allergic reactions to icodextrin in patients with renal failure. *Lancet* 2000; **355**: 1364–5.
3 Valance A, Lebrun-Vignes B, Descamps V. Icodextrin cutaneous hypersensitivity: report of 3 psoriasiform cases. *Arch Dermatol* 2001; **137**: 309–10.
4 Al-Hoqail IA, Crawford RI. Acute generalized exanthematous pustulosis induced by icodextrin. *Br J Dermatol* 2001; **145**: 1026–7.

Drugs acting on the skeletal system

Alendronate

This drug for osteoporosis has caused urticaria [1] and a gyrate erythema [2].

Other bisphosphonates

Symptoms of influenza-like illness have been associated with both oral and intravenous bisphosphonates. Osteonecrosis of the jaw has also been associated with intravenous bisphosphonate treatment, as for metastatic bone disease [3,4]. Earlier generation intravenous bisphosphonates (e.g. etidronate) were associated with acute renal failure, but late-generation intravenous bisphosphonates (i.e. ibandronate) have a better safety profile.

References

1 Kontoleon P, Ilias I, Stavropoulos PG, Papapetrou PD. Urticaria after administration of alendronate. *Acta Derm Venereol (Stockh)* 2000; **80**: 398.
2 High WA, Cohen JB, Wetherington W, Cockerell CJ. Superficial gyrate erythema as a cutaneous reaction to alendronate for osteoporosis. *J Am Acad Dermatol* 2003; **48**: 945–6.
3 Strampel W, Emkey R, Civitelli R. Safety considerations with bisphosphonates for the treatment of osteoporosis. *Drug Saf* 2007; **30**: 755–63.
4 Diel IJ, Bergner R, Grötz KA. Adverse effects of bisphosphonates: current issues. *J Support Oncol* 2007; **5**: 475–82.

Drugs for erectile dysfunction

Sildenafil (Viagra)

A lichenoid reaction is reported [1].

Reference

1 Goldman BD. Lichenoid drug reaction due to sildenafil. *Cutis* 2000; **65**: 282–3.

Metals and metal antagonists

Metals

Arsenic

Features of acute [1] and chronic [2] arsenic poisoning have been reviewed. Bullous eruptions, photosensitivity, exfoliative dermatitis, erythroderma with pustulation, and alopecia may be acute manifestations of arsenic toxicity. Occupational exposure may occur, especially in agriculture. Inorganic arsenic is sometimes present in Chinese proprietary medicines [2]. Fowler's solution (containing 1% potassium arsenite) and sodium arsenate were used in the past for psoriasis; as little as 0.19 g has been carcinogenic and the interval between exposure and tumour induction may be as long as 47 years [3]. Subjects with an abnormally high retention of ingested arsenic may be at particular risk [4]. The cutaneous manifestations of arsenic exposure, including macular pigmentation, palmoplantar punctate keratoses, basal cell and squamous cell carcinomas, are well known [2–11]. Keratoses and

tumours may be present without pigmentation. In one series of patients, there was a dose-related development of palmar and plantar keratoses in 40%, and carcinomas of the skin in 8%, of patients who received arsenic in the form of Fowler's solution for 6–26 years; the minimum latent period before development of keratoses was 2.5 years, and the average was 6 years [5]. In another series, Bowen's disease occurred within 10 years and invasive carcinomas within 20 years [9]. The lag times for development of keratoses, Bowen's disease and squamous cell cancer were, respectively, 28, 39 and 41 years in another series [2]. Arsenic contamination of well water in Taiwan resulted in numerous affected individuals with arsenical keratoses and cutaneous carcinomas [7]. Carcinomas may arise in the arsenical keratoses [7]. Groundwater contamination leads to an endemic problem [12,13]. Cutaneous electron microscopic changes are said to be characteristic [10]. The diagnostic significance of the skin arsenic content is disputed. A 42-year-old man who took arsenic for 35 years for psoriasis developed melanoderma, keratoses, muscular dystrophies, hyperlipidaemia, testicular atrophy, gynaecomastia, skin tumours and an obliterating angiitis of leg vessels, which led to amputation [6]. The role of arsenic in causing internal malignancy is the subject of controversy [9,14,15].

References

1 Bartolomé B, Córdoba S, Nieto S *et al.* Acute arsenic poisoning: clinical and histopathological features. *Br J Dermatol* 1999; **141**: 1106–9.
2 Wong SS, Tan KC, Goh CL. Cutaneous manifestations of chronic arsenicism: review of seventeen cases. *J Am Acad Dermatol* 1998; **38**: 179–85.
3 Evans S. Arsenic and cancer. *Br J Dermatol* 1977; **97** (Suppl. 15): 13–4.
4 Bettley FR, O'Shea JA. The absorption of arsenic and its relation to carcinoma. *Br J Dermatol* 1975; **92**: 563–8.
5 Fierz U. Katamnestische Untersuchungen über die Nebenwirkungen der Therapie mit anorganischem Arsen bei Hautkrankheiten. *Dermatologica* 1965; **131**: 41–58.
6 Meyhofer W, Knoth W. Über die Auswirkung einer langjährigen antipsoriatischen Arsentherapie auf mehrere Organe unter besonderer Berücksichtigung andrologischer Befunde. *Hautarzt* 1966; **117**: 309–13.
7 Yeh S. Skin cancer in chronic arsenicism. *Hum Pathol* 1973; **4**: 469–85.
8 Weiss J, Jänner M. Multiple Basaliome und Menigiom nach mehrjähriger Arsentherapie. *Hautarzt* 1980; **31**: 654–6.
9 Miki Y, Kawatsu T, Matsuda K *et al.* Cutaneous and pulmonary cancers associated with Bowen's disease. *J Am Acad Dermatol* 1982; **6**: 26–31.
10 Ohyama K, Sonoda K, Kuwahara H. Electron microscopic observations of arsenical keratoses and Bowen's disease associated with chronic arsenicism. *Dermatologica* 1982; **64**: 161–6.
11 Ratnam KV, Espy MJ, Muller SA *et al.* Clinicopathologic study of arsenic-induced skin lesions: no definite association with human papillomavirus. *J Am Acad Dermatol* 1992; **27**: 120–2.
12 Woollons A, Russell-Jones R. Chronic endemic hydroarsenicism. *Br J Dermatol* 1998; **139**: 1092–6.
13 Kurokawa M, Ogata K, Idemori M *et al.* Investigation of skin manifestations of arsenicism due to intake of arsenic-contaminated groundwater in residents of Samta, Jessore, Bangladesh. *Arch Dermatol* 2001; **137**: 102–3.
14 Reymann F, Møller R, Nielsen A. Relationship between arsenic intake and internal malignant neoplasms. *Arch Dermatol* 1978; **114**: 378–81.
15 Callen JP, Headington J. Bowen's and non-Bowen's squamous intraepidermal neoplasia of the skin. Relationship to internal malignancy. *Arch Dermatol* 1980; **116**: 422–6.

Gold

The use of gold in rheumatoid arthritis is associated with a 23–30% incidence of reactions [1–3]; most of these are minor, but about 15% may be severe or even fatal [4]. Possession of the HLA-DR3 and HLA-B8 phenotypes reportedly predisposes to thrombocytopenia, leukopenia and nephrotoxicity, HLA-DR4 is linked to leukopenia, and HLA-B7 is associated with cutaneous adverse reactions [2]. In another study, HLA-DR5 was significantly associated with mucocutaneous lesions, whereas HLA-B8 and HLA-DR3 antigens were associated with proteinuria in rheumatoid arthritis patients after gold therapy; HLA-DR7 was negatively associated with reactions and may confer protection, and HLA-B27 was associated with chrysiasis due to gold therapy [5]. A further study showed that gold dermatitis in patients with rheumatoid arthritis was associated with HLA-B35 and disease duration [6]. Antibodies to the Ro 52-kDa antigen are associated with skin eruptions in rheumatoid arthritis patients treated with gold [7].

Rashes and mouth ulcers are common [1,2,8–13], representing about 50% of all complications with parenteral gold and 35% of those with oral gold. Localized or generalized pruritus is an important warning sign of potential toxicity. Gold reactions may simulate exanthematic eruptions [14], erythema annulare centrifugum [15], seborrhoeic dermatitis or lichen planus [16,17]; a mixture of these patterns, sometimes with discoid eczematoid lesions, is characteristic. Lichen planus is often of the hypertrophic variety, especially on the scalp, and severe and irreversible alopecia may follow [18]. There may be striking and persistent post-inflammatory hyperpigmentation. Permanent nail dystrophy has followed onycholysis [19]. Yellow nails have been described [20].

In one study, eczematous or lichenoid rashes persisted up to 11 months after cessation of therapy [21]. Histology was characterized by a sparse dermal perivascular infiltrate, predominantly of $CD4^+$ HLA-DR-positive helper T lymphocytes, an increase in the number of dermal Langerhans' cells and epidermal macrophage-like cells, and Langerhans' cell apposition to mononuclear cells. A patient with a lichenoid and seborrhoeic dermatitis-like rash on gold sodium thiomalate therapy had a positive intradermal test to gold thiomalate; patch tests were positive to thiomalate (the thiol carrier of gold thiomalate) but negative to gold itself [22]. Interestingly, the same patient subsequently developed a seborrhoeic dermatitis-like eruption, but not a lichenoid eruption, while on auranofin; this time, patch tests were positive to both auranofin and gold. A previous contact dermatitis from gold jewellery may be reactivated [23].

Other reactions documented include erythema nodosum [24], severe hypersensitivity reactions [25], vasculitis [26], polyarteritis, an SLE-like syndrome, generalized exfoliative dermatitis and TEN. Psoriasis was reported to be exacerbated in a patient with arthritis treated with gold [27].

Prolonged administration of gold may cause a distinct grey, blue or purple pigmentation of exposed skin (chrysiasis), which is a dose-dependent reaction that occurs above a threshold of 20 mg/kg; gold granules are seen within dermal endothelial cells and macrophages [28–32]. Even in the absence of pigmentation, gold can be detected histochemically in the skin up to 20 years after therapy. Localized argyria with chrysiasis has been caused by implanted acupuncture needles [33]. An unusual late cutaneous reaction involved the appearance of widespread keloid-like angiofibromatoid lesions [34].

A benign vasodilatory 'nitritoid' reaction, consisting of flushing, light-headedness and transient hypotension, may occur immediately after the first injection of gold [2,35]. It occurs in roughly 5% of patients taking gold sodium thiomalate. Non-vasomotor effects, including arthralgia, myalgia and constitutional symptoms within the first 24 h, are recognized. Mucous membrane symptoms include loss of taste, metallic taste, stomatitis, glossitis and diarrhoea. Punctate stomatitis may occur with or without skin lesions. Gold is also deposited in the cornea and may cause a keratitis with ulceration. A polyneuropathy is recorded. In general, auranofin is less toxic than intramuscular gold [2]. Eosinophilia is common and may sometimes herald another complication; serum IgE may be raised [36]. Other immunological reactions are rare, although pulmonary fibrosis is recorded [37]. Blood dyscrasias, especially thrombocytopenic purpura, and occasionally fatal neutropenia or aplastic anaemia occur in a small proportion of cases and usually present within the first 6 months of therapy. Jaundice occurs in about 3% of cases, and may result from idiosyncratic intrahepatic cholestasis [38]. Proteinuria and renal damage are well known.

References

1 Thomas I. Gold therapy and its indications in dermatology. A review. *J Am Acad Dermatol* 1987; **16**: 845–54.
2 Pullar T. Adverse reactions profile: 1. Gold. *Prescribers J* 1991; **31**: 22–6.
3 Lemmel EM. Comparison of pyritinol and auranofin in the treatment of rheumatoid arthritis. The European Multicentre Study Group. *Br J Rheumatol* 1993; **32**: 375–82.
4 Girdwood RH. Death after taking medicaments. *BMJ* 1974; **i**: 501–4.
5 Rodriguez-Perez M, Gonzalez-Dominguez J, Mataran L *et al.* Association of HLA-DR5 with mucocutaneous lesions in patients with rheumatoid arthritis receiving gold sodium thiomalate. *J Rheumatol* 1994; **21**: 41–3.
6 van Gestel A, Koopman R, Wijnands M *et al.* Mucocutaneous reactions to gold: a prospective study of 74 patients with rheumatoid arthritis. *J Rheumatol* 1994; **21**: 1814–9.
7 Tishler M, Nyman J, Wahren M, Yaron M. Anti-Ro (SSA) antibodies in rheumatoid arthritis patients with gold-induced side effects. *Rheumatol Int* 1997; **17**: 133–5.
8 Almeyda J, Baker H. Drug reactions XII. Cutaneous reactions to anti-rheumatic drugs. *Br J Dermatol* 1970; **83**: 707–11.
9 Penneys NS, Ackerman AB, Gottlieb NL. Gold dermatitis: a clinical and histopathological study. *Arch Dermatol* 1974; **109**: 372–6.
10 Penneys NS. Gold therapy: dermatologic uses and toxicities. *J Am Acad Dermatol* 1979; **1**: 315–20.
11 Webster CG, Burnett JW. Gold dermatitis. *Cutis* 1994; **54**: 25–8.
12 Lizeaux-Parmeix V, Bedane C, Lavignac C *et al.* Reactions cutanées aux sels d'or. *Ann Dermatol Vénéréol* 1994; **121**: 793–7.
13 Laeijendecker R, van Joost T. Oral manifestations of gold allergy. *J Am Acad Dermatol* 1994; **30**: 205–9.
14 Möller H, Björkner B, Bruze M. Clinical reactions to systemic provocation with gold sodium thiomalate in patients with contact allergy to gold. *Br J Dermatol* 1996; **135**: 423–7.
15 Tsuji T, Nishimura M, Kimura S. Erythema annulare centrifugum associated with gold sodium thiomalate therapy. *J Am Acad Dermatol* 1992; **27**: 284–7.
16 Lasarowa AZ, Tsankov NK, Stoimenov AP. Lichenoide Eruptionen nach Goldtherapie. Bericht uber zwei Falle. *Hautarzt* 1992; **43**: 514–6.
17 Russell MA, King LE Jr, Boyd AS. Lichen planus after consumption of a gold-containing liquor. *N Engl J Med* 1996; **334**: 603.
18 Burrows NP, Grant JW, Crisp AJ, Roberts SO. Scarring alopecia following gold therapy. *Acta Derm Venereol (Stockh)* 1994; **74**: 486.
19 Voigt K, Holzegel K. Bleibende nagelveränderungen nach Goldtherapie. *Hautarzt* 1977; **28**: 421–3.
20 Roest MAB, Ratnavel R. Yellow nails associated with gold therapy for rheumatoid arthritis. *Br J Dermatol* 2001; **145**: 855–6.
21 Ranki A, Niemi K-M, Kanerva L. Clinical, immunohistochemical, and electron-microscopic findings in gold dermatitis. *Am J Dermatopathol* 1989; **11**: 22–8.
22 Ikezawa Z, Kitamura K, Nakajima H. Gold sodium thiomalate (GTM) induces hypersensitivity to thiomalate, the thiol carrier of GTM. *J Dermatol* 1990; **17**: 550–4.
23 Rennie T. Local gold toxicity. *BMJ* 1976; **ii**: 1294.
24 Stone RL, Claflin A, Penneys NS. Erythema nodosum following gold sodium thiomalate therapy. *Arch Dermatol* 1973; **107**: 603–4.
25 Walzer RA, Feinstein R, Shapiro L, Einbinder J. Severe hypersensitivity reaction to gold. Positive lymphocyte transformation test. *Arch Dermatol* 1972; **106**: 231–4.
26 Roenigk HR, Handel D. Gold vasculitis. *Arch Dermatol* 1974; **109**: 253–5.
27 Smith DL, Wernick R. Exacerbation of psoriasis by chrysotherapy. *Arch Dermatol* 1991; **127**: 268–70.
28 Beckett VL, Doyle JA, Hadley GA *et al.* Chrysiasis resulting from gold therapy in rheumatoid arthritis: identification of gold by X-ray microanalysis. *Mayo Clin Proc* 1982; **57**: 773–5.
29 Pelachyk IM, Bergfeld WF, McMahon JT. Chrysiasis following gold therapy for rheumatoid arthritis. *J Cutan Pathol* 1984; **11**: 491–4.
30 Smith RW, Leppard B, Barnett NL *et al.* Chrysiasis revisited: a clinical and pathological study. *Br J Dermatol* 1995; **133**: 671–8.
31 Fleming CJ, Salisbury ELC, Kirwan P *et al.* Chrysiasis after low-dose gold and UV light exposure. *J Am Acad Dermatol* 1996; **34**: 349–51.
32 Keen CE, Brady K, Kirkham N, Levison DA. Gold in the dermis following chrysotherapy: histopathology and microanalysis. *Histopathology* 1993; **23**: 355–60.
33 Suzuki H, Baba S, Uchigasaki S, Murase M. Localized argyria with chrysiasis caused by implanted acupuncture needles. Distribution and chemical forms of silver and gold in cutaneous tissue by electron microscopy and X-ray microanalysis. *J Am Acad Dermatol* 1993; **29**: 833–7.
34 Herbst WM, Hornstein OP, Grießmeyer G. Ungewöhnliche kutane Angiofibromatose nach Goldtherapie einer primär chronischen Polyarthritis. *Hautarzt* 1989; **40**: 568–72.
35 Arthur AB, Klinkhoff A, Teufel A. Nitritoid reactions: case reports, review, and recommendations for management. *J Rheumatol* 2001; **28**: 2209–12.
36 Davis P, Ezeoke A, Munro J *et al.* Immunological studies on the mechanism of gold hypersensitivity reactions. *BMJ* 1973; **iii**: 676–8.
37 Morley TF, Komansky HJ, Adelizzi RA *et al.* Pulmonary gold toxicity. *Eur J Respir Dis* 1984; **65**: 627–32.
38 Favreau M, Tannebaum H, Lough J. Hepatic toxicity associated with gold therapy. *Ann Intern Med* 1977; **87**: 717–9.

Iron

Iron-induced brownish discoloration has been noted at the site of local injection (local siderosis) [1].

Reference

1 Bork K. Lokalisierte kutane Siderose nach intramuskulären Eiseninjekition. *Hautarzt* 1984; **35**: 598–9.

Mercury

Skin manifestations of mercury exposure have been reviewed [1,2]. Mercury-containing teething powders have long been banned, but occasional occupational or environmental exposure can occur. Mercury amalgam in dental fillings has caused buccal pigmentation. Stomatitis may occur as a toxic reaction. Allergic reactions may be scarlatiniform or morbilliform, and can progress to generalized exfoliative dermatitis. Eczema is recorded [3]. Pink disease or acrodynia, a distinctive pattern of reaction to chronic exposure to mercury in young infants and children, is now very rare [4]. Painful extremities, pinkish acral discoloration, peeling of the palms and soles, gingivitis and various systemic complications may occur. Acrodynia developed in a child following inhalation of mercury-containing vapours from phenyl-mercuric acetate

contained in latex paint [5]. A mercury-containing drug given for 3 weeks to a patient with long-standing pustular psoriasis of the palms was associated with development of generalized pustular psoriasis [6]. (See also exogenous ochronosis from topical mercury-containing preparations, p. 75.165.) Cutaneous granulomas are recorded [1], and a nodular reaction occurred after intake of a duck soup that contained metallic mercury for a neck abscess 18 years previously [7].

References

1 Boyd AS, Seger D, Vannucci S *et al.* Mercury exposure and cutaneous disease. *J Am Acad Dermatol* 2000; **43**: 81–90.
2 Chan MHM, Cheung RCK, Chan IHS, Lam CWK. An unusual case of mercury intoxication. *Br J Dermatol* 2001; **144**: 192–4.
3 Adachi A, Horikawa T, Takashima T, Ichihashi M. Mercury-induced nummular eczema. *J Am Acad Dermatol* 2000; **43**: 383–5.
4 Dinehart SM, Dillard R, Raimer SS *et al.* Cutaneous manifestations of acrodynia (pink disease). *Arch Dermatol* 1988; **124**: 107–9.
5 Anonymous. From the MMWR. Mercury exposure from interior latex paint: Michigan. *Arch Dermatol* 1990; **126**: 577.
6 Wehner-Caroli J, Scherwitz C, Schweinsberg F, Fierlbeck G. Exazerbation einer Psoriasis pustulosa bei Quecksilber-Intoxikation. *Hautarzt* 1994; **45**: 708–10.
7 June JB, Min PK, Kim DW *et al.* Cutaneous nodular reaction to oral mercury. *J Am Acad Dermatol* 1997; **37**: 131–3.

Silver

Ingestion of silver or topical application of silver preparations to the oral mucosa or upper respiratory tract can produce slate-blue discoloration, especially of exposed skin, including oral and conjunctival mucosae [1–8]. Argyria localized to the left hand occurred in an antique restorer due to polishing silver [9]. Scar-localized argyria is recorded following application of topical silver sulfadiazine cream [10]. Topical application may also cause systemic argyria, in which visceral organs are also discoloured [11]. Localized argyria can result when the backs of earrings become embedded [12]. In some patients, the nail beds of the fingers but not the toes may show bluish discoloration [13]. Silver granules are found free within the dermis; melanin may be increased in the epidermis or within melanophages [14–16].

References

1 Pariser RJ. Generalized argyria. Clinicopathologic features and histochemical studies. *Arch Dermatol* 1978; **114**: 373–7.
2 Reynold J-L, Stoebner P, Amblard P. Argyrie cutanée. Étude en microscopie electronique et en microanalyse X de 4 cas. *Ann Dermatol Vénéréol* 1980; **107**: 251–5.
3 Johansson EA, Kanerva L, Niemi K-M *et al.* Generalized argyria with low ceruloplasmin and copper levels in the serum. A case report with clinical and microscopical findings and a trial of penicillamine treatment. *Clin Exp Dermatol* 1982; **7**: 169–76.
4 Pezzarossa E, Alinovi A, Ferrari C. Generalized argyria. *J Cutan Pathol* 1983; **10**: 361–3.
5 Gherardi R, Brochard P, Chamak B *et al.* Human generalized argyria. *Arch Pathol Lab Med* 1984; **108**: 181–2.
6 Jurecka W. Generalisierte Argyrose. *Hautarzt* 1986; **37**: 628–31.
7 Mittag H, Knecht J, Arnold R *et al.* Zur Frage der Argyrie. Ein klinische, analytisch-chemische und mikromorphologische Untersuchung. *Hautarzt* 1987; **38**: 670–7.
8 Tanner LS, Gross DJ. Generalized argyria. *Cutis* 1990; **45**: 237–9.
9 Kapur N, Landon G, Yu RC. Localized argyria in an antique restorer. *Br J Dermatol* 2001; **144**: 191–2.
10 Fisher NM, Marsh E, Lazova R. Scar-localized argyria secondary to silver sulfadiazine cream. *J Am Acad Dermatol* 2003; **49**: 730–2.
11 Marshall IP, Schneider RP. Systemic argyria secondary to topical silver nitrate. *Arch Dermatol* 1977; **113**: 1077–9.
12 van den Nieuwenhijsen IJ, Calame JJ, Bruynzeel DP. Localized argyria caused by silver earrings. *Dermatologica* 1988; **177**: 189–91.
13 Plewig G, Lincke H, Wolff HH. Silver-blue nails. *Acta Derm Venereol (Stockh)* 1977; **57**: 413–9.
14 Hönigsmann H, Konrad K, Wolff K. Argyrose (Histologie und Ultrastruktur). *Hautarzt* 1973; **24**: 24–30.
15 Shelley WB, Shelley ED, Burmeister V. Argyria: the intradermal 'photograph', a manifestation of passive photosensitivity. *J Am Acad Dermatol* 1987; **16**: 211–7.
16 Sato S, Sueki H, Nishijima A. Two unusual cases of argyria: the application of an improved tissue processing method for X-ray microanalysis of selenium and sulphur in silver-laden granules. *Br J Dermatol* 1999; **140**: 158–63.

Metal antagonists

Deferoxamine (desferrioxamine)

Itching, erythema and urticaria are occasionally seen [1]. An indurated erythema with oedema lasting 2 weeks has been reported following infusion of this drug [2].

References

1 Bousquet J, Navarra M, Robert G *et al.* Rapid desensitisation for desferrioxamine anaphylactoid reactions. *Lancet* 1983; **ii**: 859–60.
2 Venencie P-Y, Rain B, Blanc A, Tertian G. Toxidermie a la déféroxamine (Desféral). *Ann Derm Vénéréol* 1988; **115**: 1174.

Penicillamine

There is a fourfold increase in toxicity with this drug in patients with rheumatoid arthritis who have a genetically determined poor capacity to sulphoxidate the structurally related mucolytic agent carbocysteine [1,2]. In addition, penicillamine toxicity is independently associated with HLA phenotype [1–3]. HLA-DR3 and HLA-B8 are associated with renal toxicity, HLA-DR3, HLA-B7 and HLA-DR2 with haematological toxicity, and HLA-A1 and HLA-DR4 with thrombocytopenia. Cutaneous adverse reactions are linked to HLA-DRw6. Anti-Ro(SSA)-positive patients with rheumatoid arthritis more often developed rashes and acute febrile reactions [4].

The cutaneous side effects of this chelating agent comprise three distinct types: (i) acute hypersensitivity reactions occurring early during treatment; (ii) late reactions including disturbances of autoimmune mechanisms leading to pemphigus foliaceus or erythematosus and cicatricial pemphigoid; and (iii) lathyrogenic effects on connective tissue [2,5–9]. Hypersensitivity reactions are common and consist of urticarial or morbilliform rashes appearing within the first few weeks; the eruption clears on drug withdrawal and does not always recur on re-exposure. It is possible to desensitize patients to penicillamine [10].

Autoimmune syndromes caused by penicillamine are well documented. The development of pemphigus during the treatment of both Wilson's disease and rheumatoid arthritis with penicillamine was first noted in the French literature [11,12]. Since then, there have been numerous case reports [13–25]; about 7% of patients receiving penicillamine for more than 6 months develop drug-induced pemphigus [13]. The reader is referred to the section on drug-induced pemphigus (pp. 75.38–39). Findings with direct immunofluorescence mimic the idiopathic disorder, with epidermal intercellular deposition of immunoreactants [16]. Most patients develop pemphigus foliaceus, although there have been

isolated reports of pemphigus vulgaris [14] and of pemphigus erythematosus with both epidermal intercellular and subepidermal deposition of IgG [15,17]. In some patients, clinical appearances may resemble dermatitis herpetiformis [21,22]. Oral lesions may be indistinguishable from those seen in idiopathic pemphigus, with cheilosis, glossitis and stomatitis [23]. Painful erosive vulvovaginitis may lead to scarring. Penicillamine-induced pemphigus usually subsides rapidly after cessation of the drug; occasionally it may be more persistent [13] and fatalities have occurred [24,25]. A curious bullous dermatosis without the features of pemphigus has been described recently [26]. Other autoimmune manifestations include a bullous pemphigoid-like reaction [27], cicatricial pemphigoid [28,29], both discoid and systemic LE [30–33], dermatomyositis [34–37], and both morphoea and systemic sclerosis [38,39]. Pre-existing lichen planus [40] may be exacerbated, and lichenoid eruptions develop *de novo* [41,42]. Alopecia, facial dryness and scaling, nail changes and hypertrichosis are recorded. The yellow nail syndrome has been reported frequently in association with penicillamine [43].

Prolonged high-dose therapy for more than a year, as for Wilson's disease, has effects on collagen and elastin [44,45], resulting from inhibition of the condensation of soluble tropocollagen to insoluble collagen. There is anisodiametricity of connective tissue fibres, resulting in the 'lumpy-bumpy' elastic fibre [46–48]. The skin becomes wrinkled and thin, aged looking and abnormally fragile; asymptomatic, violaceous, friable, haemorrhagic macules, papules and plaques develop on pressure sites, and minor trauma causes ecchymoses [49]. There may be light-blue anetoderma-like lesions [50], and small white papules at venepuncture sites. Lymphangiectasis may develop [49]. Blisters may occur, with a picture resembling epidermolysis bullosa with scarring and milia formation (Fig. 75.6) [51]. Cutis laxa and elastosis perforans serpiginosa [52–58], which may be verruciform [52,53], are described. Lesions resembling pseudoxanthoma elasticum have been documented rarely [59–62].

Penicillamine may induce impaired taste sensation in up to 25% of patients, but other gastrointestinal effects are usually minor. Important non-dermatological complications [2,8] include: marrow suppression; various renal problems, such as reversible proteinuria, in up to 30% of patients on therapy for more than 6 months; established nephrotic syndrome; and Goodpasture's syndrome. Thrombocytopenia occurs in up to 3% of patients, and may be either of gradual or precipitous onset. Immunological abnormalities include acquired IgA deficiency [63] and development of myasthenia gravis [64]. The bones may be involved in the connective tissue disorder. A chronic bronchoalveolitis is recognized [65]. Breast enlargement and breast gigantism [66] are documented.



Fig. 75.6 Penicillamine dermopathy with milia. (Courtesy of St John's Institute of Dermatology, King's College London, UK.)

References

1 Emery P, Panayi GS, Huston G *et al.* D-Penicillamine-induced toxicity in rheumatoid arthritis: the role of sulphoxidation status and HLA-DR3. *J Rheumatol* 1984; **11**: 626–32.

2 Dasgupta B. Adverse reactions profile: 2. Penicillamine. *Prescribers J* 1991; **31**: 72–7.

3 Wooley PH, Griffin J, Panayi GS *et al.* HLA-DR antigens and toxic reaction to sodium aurothiomalate and D-penicillamine in patients with rheumatoid arthritis. *N Engl J Med* 1980; **303**: 300–2.

4 Vlachoyiannopoulos PG, Zerva LV, Skopouli FN *et al.* D-Penicillamine toxicity in Greek patients with rheumatoid arthritis: anti-Ro(SSA) antibodies and cryoglobulinemia are predictive factors. *J Rheumatol* 1991; **18**: 44–9.

5 Katz R. Penicillamine-induced skin lesions. Occurrence in a patient with hepatolenticular degeneration (Wilson's disease). *Arch Dermatol* 1967; **95**: 196–8.

6 Greer KE, Askew FC, Richardson DR. Skin lesions induced by penicillamine. *Arch Dermatol* 1976; **112**: 1267–9.

7 Sternlieb I, Fisher M, Scheinberg IH. Penicillamine-induced skin lesions. *J Rheumatol* 1981; **8** (Suppl. 7): 149–54.

8 Levy RS, Fisher M, Alter JN. Penicillamine: review and cutaneous manifestations. *J Am Acad Dermatol* 1983; **8**: 548–58.

9 Bialy-Golan A, Brenner S. Penicillamine-induced bullous dermatoses. *J Am Acad Dermatol* 1996; **35**: 732–42.

10 Chan CY, Baker AL. Penicillamine hypersensitivity: successful desensitization of a patient with severe hepatic Wilson's disease. *Am J Gastroenterol* 1994; **89**: 442–3.

11 Degos R, Touraine R, Belaïch S *et al.* Pemphigus chez un malade traité par pénicillamine pour maladie de Wilson. *Bull Soc Fr Dermatol Syphiligr* 1969; **76**: 751–3.

12 Benveniste M, Crouzet J, Homberg JC *et al.* Pemphigus induit par la D-pénicillamine dans la polyarthrite rhumatoïde. *Nouv Presse Med* 1975; **4**: 3125–8.

13 Marsden RA, Ryan TJ, Vanhegan RI *et al.* Pemphigus foliaceus induced by penicillamine. *BMJ* 1976; **ii**: 1423–4.

14 From E, Frederiksen P. Pemphigus vulgaris following D-penicillamine. *Dermatologica* 1976; **152**: 358–62.

15 Thorvaldsen J. Two cases of penicillamine-induced pemphigus erythematosus. *Dermatologica* 1979; **159**: 167–70.

16 Santa Cruz DJ, Prioleau PG, Marcus MD, Uitto J. Pemphigus-like lesions induced by D-penicillamine. Analysis of clinical, histopathological, and immunofluorescence features in 34 cases. *Am J Dermatopathol* 1981; **3**: 85–92.

17 Yung CW, Hambrick GW Jr. D-Penicillamine-induced pemphigus syndrome. *J Am Acad Dermatol* 1982; **6**: 317–24.

18 Bahmer FA, Bambauer R, Stenger D. Penicillamine-induced pemphigus foliaceus-like dermatosis. A case with unusual features, successfully treated by plasmapheresis. *Arch Dermatol* 1985; **121**: 665–8.

19 Kind P, Goerz G, Gleichmann E, Plewig G. Penicillamininduzierter Pemphigus. *Hautarzt* 1987; **38**: 548–52.

20 Civatte J. Durch Medikamente induzierte Pemphigus-Erkrankungen. *Dermatol Monatsschr* 1989; **175**: 1–7.
21 Marsden RA, Dawber RPR, Millard PR, Mowat AG. Herpetiform pemphigus induced by penicillamine. *Br J Dermatol* 1977; **97**: 451–2.
22 Weltfriend S, Ingber A, David M, Sandbank M. Pemphigus herpetiformis nach D-Penicillamin bei einem Patienten mit HLA B8. *Hautarzt* 1988; **39**: 587–8.
23 Eisenberg E, Ballow M, Wolfe SH *et al.* Pemphigus-like mucosal lesions: a side effect of penicillamine therapy. *Oral Surg* 1981; **51**: 409–14.
24 Sparrow GP. Penicillamine pemphigus and the nephrotic syndrome occurring simultaneously. *Br J Dermatol* 1978; **98**: 103–5.
25 Matkaluk RM, Bailin PL. Penicillamine-induced pemphigus foliaceus. A fatal outcome. *Arch Dermatol* 1981; **117**: 156–7.
26 Fulton RA, Thomson J. Penicillamine-induced bullous dermatosis. *Br J Dermatol* 1982; **107** (Suppl. 22): 95–6.
27 Brown MD, Dubin HV. Penicillamine-induced bullous pemphigoid-like eruption. *Arch Dermatol* 1987; **123**: 1119–20.
28 Pegum JS, Pembroke AC. Benign mucous membrane pemphigoid associated with penicillamine treatment. *BMJ* 1977; **i**: 1473.
29 Shuttleworth D, Graham-Brown RAC, Hutchinson PE, Jolliffe DS. Cicatricial pemphigoid in D-penicillamine treated patients with rheumatoid arthritis: a report of three cases. *Clin Exp Dermatol* 1985; **10**: 392–7.
30 Burns DA, Sarkany I. Penicillamine induced discoid lupus erythematosus. *Clin Exp Dermatol* 1979; **4**: 389–92.
31 Walshe JM. Penicillamine and the SLE syndrome. *J Rheumatol* 1981; **8** (Suppl. 7): 155–60.
32 Chalmers A, Thompson D, Stein HE *et al.* Systemic lupus erythematosus during penicillamine therapy for rheumatoid arthritis. *Ann Intern Med* 1982; **97**: 659–63.
33 Tsankov NK, Lazarov AZ, Vasileva S, Obreshkova EV. Lupus erythematosus-like eruption due to D-penicillamine in progressive systemic sclerosis. *Int J Dermatol* 1990; **29**: 571–4.
34 Simpson NB, Golding JR. Dermatomyositis induced by penicillamine. *Acta Derm Venereol (Stockh)* 1979; **59**: 543–4.
35 Wojnarowska F. Dermatomyositis induced by penicillamine. *J R Soc Med* 1980; **73**: 884–6.
36 Carroll GC, Will RK, Peter JB *et al.* Penicillamine induced polymyositis and dermatomyositis. *J Rheumatol* 1987; **14**: 995–1001.
37 Wilson CL, Bradlow A, Wojnarowska F. Cutaneous problems with drug therapy in rheumatoid arthritis. *Int J Dermatol* 1991; **30**: 148–9.
38 Bernstein RM, Hall MA, Gostelow BE. Morphea-like reaction to D-penicillamine therapy. *Ann Rheum Dis* 1981; **40**: 42–4.
39 Miyagawa S, Yoshioka A, Hatoko M *et al.* Systemic sclerosis-like lesions during long-term penicillamine therapy for Wilson's disease. *Br J Dermatol* 1987; **116**: 95–100.
40 Powell FC, Rogers RS III, Dickson ER. Lichen planus, primary biliary cirrhosis and penicillamine. *Br J Dermatol* 1982; **107**: 616.
41 Seehafer JR, Rogers RS III, Fleming R, Dickson ER. Lichen planus-like lesions caused by penicillamine in primary biliary cirrhosis. *Arch Dermatol* 1981; **117**: 140–2.
42 Van Hecke E, Kint A, Temmerman L. A lichenoid eruption induced by penicillamine. *Arch Dermatol* 1981; **117**: 676–7.
43 Ilchyshyn A, Vickers CFH. Yellow nail syndrome associated with penicillamine therapy. *Acta Derm Venereol (Stockh)* 1983; **63**: 554–5.
44 Poon E, Mason GH, Oh C. Clinical and histological spectrum of elastotic changes induced by penicillamine. *Australas J Dermatol* 2002; **43**: 147–50.
45 Iozumi K, Nakagawa H, Tamaki K. Penicillamine-induced degenerative dermatoses: report of a case and brief review of such dermatoses. *J Dermatol* 1997; **24**: 458–65.
46 Bardach H, Gebhart W, Niebauer G. 'Lumpy-bumpy' elastic fibers in the skin and lungs of a patient with a penicillamine-induced elastosis perforans serpiginosa. *J Cutan Pathol* 1979; **6**: 243–52.
47 Gebhart W, Bardach H. The 'lumpy-bumpy' elastic fiber. A marker for long-term administration of penicillamine. *Am J Dermatopathol* 1981; **3**: 33–9.
48 Hashimoto K, McEvoy B, Belcher R. Ultrastructure of penicillamine-induced skin lesions. *J Am Acad Dermatol* 1981; **4**: 300–15.
49 Goldstein JB, McNutt S, Hambrick GW. Penicillamine dermatopathy with lymphangiectases. A clinical, immunohistologic, and ultrastructural study. *Arch Dermatol* 1989; **125**: 92–7.
50 Davis W. Wilson's disease and penicillamine-induced anetoderma. *Arch Dermatol* 1977; **113**: 976.
51 Beer WE, Cooke KB. Epidermolysis bullosa induced by penicillamine. *Br J Dermatol* 1967; **79**: 123–5.
52 Guilane J, Benhamou JP, Molas G. Élastome perforant verruciforme chez un malade traité par pénicillamine pour maladie de Wilson. *Bull Soc Fr Derm Syph* 1972; **79**: 450–3.
53 Sfar Z, Lakhua M, Kamoun MR *et al.* Deux cas d'élastomes verruciforme après administration prolongée de D-pénicillamine. *Ann Dermatol Vénéréol* 1982; **109**: 813–4.
54 Reymond JL, Stoebner P, Zambelli P *et al.* Penicillamine induced elastosis perforans serpiginosa: an ultrastructural study of two cases. *J Cutan Pathol* 1982; **9**: 352–7.
55 Price RG, Prentice RSA. Penicillamine-induced elastosis perforans serpiginosa. Tip of the iceberg? *Am J Dermatopathol* 1986; **8**: 314–20.
56 Sahn EE, Maize JC, Garen PD *et al.* D-Penicillamine-induced elastosis perforans serpiginosa in a child with juvenile rheumatoid arthritis. Report of a case and review of the literature. *J Am Acad Dermatol* 1989; **20**: 979–88.
57 Wilhelm K, Wolff HH. Penicillamin-induzierte Elastosis perforans serpiginosa. *Hautarzt* 1994; **45**: 45–7.
58 Hill VA, Seymour CA, Mortimer PS. Penicillamine-induced elastosis perforans serpiginosa and cutis laxa in Wilson's disease. *Br J Dermatol* 2000; **142**: 560–1.
59 Meyrick-Thomas RH, Light N, Stephens AD *et al.* Pseudoxanthoma elasticum-like skin changes induced by penicillamine. *J R Soc Med* 1984; **77**: 794–8.
60 Meyrick-Thomas RH, Kirby JDT. Elastosis perforans serpiginosa and pseudoxanthoma elasticum-like skin change due to D-penicillamine. *Clin Exp Dermatol* 1985; **10**: 386–91.
61 Light N, Meyrick Thomas RH, Stephens A *et al.* Collagen and elastin changes in D-penicillamine-induced pseudoxanthoma elasticum. *Br J Dermatol* 1986; **114**: 381–8.
62 Burge S, Ryan T. Penicillamine-induced pseudo-pseudoxanthoma elasticum in a patient with rheumatoid arthritis. *Clin Exp Dermatol* 1988; **13**: 255–8.
63 Hjalmarson O, Hanson L-Å. IgA deficiency during D-penicillamine treatment. *BMJ* 1977; **i**: 549.
64 Garlepp MJ, Dawkins RL, Christiansen FT. HLA antigens and acetylcholine receptor antibodies in penicillamine induced myasthenia gravis. *BMJ* 1983; **286**: 338–40.
65 Murphy KC, Atkins CJ, Offer RC *et al.* Obliterative bronchiolitis in two rheumatoid arthritis patients treated with penicillamine. *Arthritis Rheum* 1981; **24**: 557–60.
66 Passas C, Weinstein A. Breast gigantism with penicillamine therapy. *Arthritis Rheum* 1978; **21**: 167–8.

Tiopronin (N-(2-mercaptopropionyl) glycine)

This drug, used in Japan for the treatment of liver disease, mercury intoxication, cataracts and allergic dermatoses, dissociates disulphide bonds, like penicillamine. Morbilliform, urticarial and lichenoid eruptions, bullous in one case, have occurred [1].

Reference

1 Hsiao L, Yoshinaga A, Ono T. Drug-induced bullous lichen planus in a patient with diabetes mellitus and liver disease. *J Am Acad Dermatol* 1986; **15**: 103–5.

Anticoagulants, fibrinolytic agents and antiplatelet drugs

Oral anticoagulants

Adverse reactions to oral anticoagulant drugs have been reviewed [1–3].

References

1 Baker H, Levene GM. Drug reactions V. Cutaneous reactions to anticoagulants. *Br J Dermatol* 1969; **81**: 236–8.
2 Hirsh J. Oral anticoagulant drugs. *N Engl J Med* 1991; **324**: 1865–75.

3 Gallerani M, Manfredini R, Moratelli S. Non-haemorrhagic adverse reactions of oral anticoagulant therapy. *Int J Cardiol* 1995; **49**: 1–7.

Coumarins

There may be cross-sensitivity across the group comprising acenocoumarol (nicoumalone), phenprocoumon and warfarin [1].

Phenprocoumon. A patient on long-term anticoagulation developed repeated episodes of skin and subcutaneous fat necrosis related to episodes of excessive anticoagulation with acquired functional deficiency of protein C, thought to be due to hepatic dysfunction resulting from congestive cardiac failure [2].

Warfarin. Haemorrhage is the commonest adverse reaction. Maculopapular rashes occur [1], and may be seen after a single dose of warfarin [3]. Rarely, an oral loading dose may lead to one or more areas of painful erythema and ecchymosis, which rapidly progress to central blistering and massive cutaneous and subcutaneous necrosis (Fig. 75.7) [4–12]; if extensive, the condition may be fatal [3]. The lesions usually start after 2–14 days of treatment (most often 3–5 days), tend to be symmetrical, and occur over fatty areas, for example the breasts, buttocks, thighs, calves and abdomen. Most patients have been women, but lesions of the penis may occur [6]. Warfarin necrosis has been associated with the heterozygous state for deficiency of protein C, a vitamin K-dependent serine protease [8–10]. Activated protein C is a potent anticoagulant that selectively inactivates co-factors Va and VIIIa, and inhibits platelet coagulant activity by inactivation of platelet factor Va. Continued coumarin therapy does not aggravate the condition, but resumption of therapy with loading doses may lead to new lesions [7]. The condition is preventable by vitamin K_1 injections. Other side effects are rare, and include urticaria [13], dermatitis, gastrointestinal upset, purple erythema of the dependent parts (purple toe syndrome) [14–16], acral purpura [17] and alopecia [18].

Oral anticoagulants and quinidine act synergistically to depress vitamin K-sensitive hepatic clotting synthesis [19]. Their combined use can precipitate serious hypoprothrombinaemic haemorrhage. Azapropazone displaces warfarin from protein-binding sites and also alters renal clearance of *R* and *S* isomers of warfarin; this may lead to effective warfarin overdosage [20]. Itraconazole may potentiate the action of warfarin [21].



Fig. 75.7 Warfarin necrosis. (Courtesy of Dr A. Ive, Durham, UK.)

References

1 Kruis-de Vries MH, Stricker BHC, Coenraads PJ, Nater JP. Maculopapular rash due to coumarin derivatives. *Dermatologica* 1989; **178**: 109–11.
2 Teepe RGC, Broekmans AW, Vermeer BJ *et al*. Recurrent coumarin-induced skin necrosis in a patient with an acquired functional protein C deficiency. *Arch Dermatol* 1986; **122**: 1408–12.
3 Antony SJ, Krick SK, Mehta PM. Unusual cutaneous adverse reaction to warfarin therapy. *South Med J* 1993; **86**: 1413–4.
4 Lacy JP, Goodin RR. Warfarin-induced necrosis of skin. *Ann Intern Med* 1975; **82**: 381–2.
5 Schleicher SM, Fricker MP. Coumarin necrosis. *Arch Dermatol* 1980; **116**: 444–5.
6 Weinberg AC, Lieskovsky G, McGehee WG, Skinner DG. Warfarin necrosis of the skin and subcutaneous tissue of the male external genitalia. *J Urol* 1983; **130**: 352–4.
7 Slutzki S, Bogokowsky H, Gilboa Y, Halpern Z. Coumadin-induced skin necrosis. *Int J Dermatol* 1984; **23**: 117–9.
8 Kazmier FJ. Thromboembolism, coumarin necrosis, and protein C. *Mayo Clin Proc* 1985; **60**: 673–4.
9 Gladson CL, Groncy P, Griffin JH. Coumarin necrosis, neonatal purpura fulminans, and protein C deficiency. *Arch Dermatol* 1988; **123**: 1701a–1706a.
10 Auletta MJ, Headington JT. Purpura fulminans. A cutaneous manifestation of severe protein C deficiency. *Arch Dermatol* 1988; **124**: 1387–91.
11 Sharafuddin MJ, Sanaknaki BA, Kibbi AG. Erythematous, hemorrhagic, and necrotic plaques in an elderly man. Coumarin-induced skin necrosis. *Arch Dermatol* 1992; **128**: 105, 108.
12 Comp PC. Coumarin-induced skin necrosis. Incidence, mechanisms, management and avoidance. *Drug Saf* 1993; **8**: 128–35.
13 Sheps ES, Gifford RW. Urticaria after administration of warfarin sodium. *Am J Cardiol* 1959; **3**: 118–20.
14 Feder W, Auerbach R. 'Purple toes': an uncommon sequela of oral coumarin drug therapy. *Ann Intern Med* 1961; **55**: 911–7.
15 Akle CA, Joiner CL. Purple toe syndrome. *J R Soc Med* 1981; **74**: 219.
16 Lebsack CS, Weibert RT. Purple toes syndrome. *Postgrad Med* 1982; **71**: 81–4.
17 Stone MS, Rosen T. Acral purpura: an unusual sign of coumarin necrosis. *J Am Acad Dermatol* 1986; **14**: 797–802.
18 Umlas J, Harken DE. Warfarin-induced alopecia. *Cutis* 1988; **42**: 63–4.
19 Koch-Weser J. Quinidine-induced hypoprothrombinemic hemorrhage in patients on chronic warfarin therapy. *Ann Intern Med* 1968; **68**: 511–7.
20 Win N, Mitchell DC. Azapropazone and warfarin. *BMJ* 1991; **302**: 969–70.
21 Yeh J, Soo SC, Summerton C, Richardson C. Potentiation of action of warfarin by itraconazole. *BMJ* 1990; **301**: 669.

Indandiones

Hypersensitivity reactions occur in up to 0.3% of patients within 3 months of onset of treatment with phenindione. Scarlatiniform, eczematous, erythema multiforme-like or generalized exfoliative eruptions are seen [1,2]. Alopecia and stomatitis may accompany the rash. Brownish-yellow or orange discoloration of the palmar or finger skin on handling the tablets develops after contact with soap alkali [3]. Cutaneous necrosis occurs rarely.

References

1 Hollman A, Wong HO. Phenindione sensitivity. *BMJ* 1964; **ii**: 730–2.
2 Copeman PWM. Phenindione toxicity. *BMJ* 1965; **ii**: 305.
3 Silverton NH. Skin pigmentation by phenindione. *BMJ* 1966; **i**: 675.

Heparin: parenteral anticoagulant

The most frequent side effect is haemorrhage [1,2]. Other common side effects include osteoporosis and (temporary) telogen

effluvium 6–16 weeks after administration. Hypoaldosteronism may occur. Hypersensitivity reactions including urticaria and anaphylactic shock are well documented but very uncommon [3]. Rapid desensitization was achieved in a patient with heparin urticarial hypersensitivity who required cardiac surgery [4]. Hypereosinophilia is recorded [5]. Vasospastic reactions, including pain, cyanosis and severe itching or burning plantar sensations, are described.

Erythematous infiltrated plaques developing 3–21 days after commencement of heparin therapy [6–14] may closely mimic contact dermatitis both clinically and histologically, and patch tests may be positive [8,9]. Delayed-type hypersensitivity reactions in patients receiving heparin may occur with both unfractionated and low-molecular-weight heparins. Delayed-type hypersensitivity to heparins is characterized by considerable cross-reactivity between low-molecular-weight heparins, unfractionated heparins and danaparoid [13]. Unfractionated heparins may be tolerated even if low-molecular-weight heparins are not. Subcutaneous provocation testing with a panel of heparins, danaparoid and desirudin (hirudin) is recommended for determining acceptable treatment options for patients allergic to specific heparins. Low-molecular-weight heparin analogues may be satisfactorily substituted in some patients with this reaction [6,15], but are not always tolerated [7,16,17]; a panel of different low-molecular-weight heparin preparations should be checked by subcutaneous provocation tests before reinstitution of heparin therapy. Chlorocresol may be responsible for some reactions attributed to heparin [7,18], including anaphylactoid reactions.

Skin necrosis occurring 6–8 days after onset of subcutaneous heparin is rare, but may occur at injection sites and occasionally at distal sites elsewhere [19–27]. Diabetic women on high-dose antibiotics are predisposed to this complication. A scleroderma-like evolution has been recorded [22]. Clinically, the skin necrosis resembles that of coumarin necrosis [25]. It may occur with use of low-molecular-weight heparin [23,26].

Heparin may cause an allergic thrombocytopenia [28–35]. Thrombocytopenia is usually asymptomatic, but may be associated with arterial or venous thrombosis in about 0.4% of cases [29,33,34]; thromboembolism may occasionally be lethal [30]. Thrombocytopenia usually begins 3–15 days after initiation of therapy, but may occur within hours in previously exposed patients, and is thought to be caused by an IgG–heparin immune complex involving both the Fab and Fc portions of the IgG molecule [29]. Heparin-induced antiendothelial cell antibodies, which recognize heparin-like glycans on the cell surface of platelets and endothelial cells, may lead to platelet aggregation and endothelial cell expression of procoagulant tissue factor, with resultant thrombocytopenia and thrombosis [21]. Thrombocytopenia may occur with both unfractionated and low-molecular-weight heparins [20]. Clinical cross-reactivity between heparin and the polysulphated chondroitin-like substance Arteparon, used in the treatment of degenerative joint disease, has been described [32].

References

1 Tuneu A, Moreno A, de Moragas JM. Cutaneous reactions secondary to heparin injections. *J Am Acad Dermatol* 1985; **12**: 1072–7.

2 Hirsh J. Heparin. *N Engl J Med* 1991; **324**: 1565–74.

3 Curry N, Bandana EJ, Pirofsky B. Heparin sensitivity: report of a case. *Arch Intern Med* 1973; **132**: 744–5.

4 Patriarca G, Rossi M, Schiavino D *et al.* Rush desensitization in heparin hypersensitivity: a case report. *Allergy* 1994; **49**: 292–4.

5 Bircher AJ, Itin PH, Buchner SA. Skin lesions, hypereosinophilia, and subcutaneous heparin. *Lancet* 1994; **343**: 861.

6 Zimmermann R, Harenberg J, Weber E *et al.* Behandlung bei heparin-induzierter kutaner Reaktion mit einem niedermolekularen Heparin-Analog. *Dtsch Med Wochenschr* 1984; **109**: 1326–8.

7 Klein GF, Kofler H, Wol H, Fritsch PO. Eczema-like, erythematous, infiltrated plaques: a common side-effect of subcutaneous heparin therapy. *J Am Acad Dermatol* 1989; **21**: 703–7.

8 Guillet G, Delaire P, Plantin P, Guillet MH. Eczema as a complication of heparin therapy. *J Am Acad Dermatol* 1989; **21**: 1130.

9 Bircher AJ, Flückiger R, Buchner SA. Eczematous infiltrated plaques to subcutaneous heparin: a type IV allergic reaction. *Br J Dermatol* 1990; **123**: 507–14.

10 Koch P, Hindi S, Landwehr D. Delayed allergic skin reactions due to subcutaneous heparin-calcium, enoxaparin-sodium, pentosan polysulfate and acute skin lesions from systemic sodium-heparin. *Contact Dermatitis* 1996; **34**: 156–8.

11 Koch P, Münßinger T, Rupp-John C, Uhl K. Delayed-type hypersensitivity skin reactions caused by subcutaneous unfractionated and low-molecular-weight heparins: tolerance of a new recombinant hirudin. *J Am Acad Dermatol* 2000; **42**: 612–9.

12 Szolar-Platzer C, Aberer W, Kranke B. Delayed-type skin reaction to the heparin-alternative danaparoid. *J Am Acad Dermatol* 2000; **43**: 920–2.

13 Grassegger A, Fritsch P, Reider N. Delayed-type hypersensitivity and cross-reactivity to heparins and danaparoid: a prospective study. *Dermatol Surg* 2001; **27**: 47–52.

14 Wutschert R, Piletta P, Bounameaux H. Adverse skin reactions to low molecular weight heparins: frequency, management and prevention. *Drug Saf* 1999; **20**: 515–25.

15 Koch P, Bahmer FA, Schafer H. Tolerance of intravenous low-molecular-weight heparin after eczematous reaction to subcutaneous heparin. *Contact Dermatitis* 1991; **25**: 205–6.

16 Bosch A, Las Heras G, Martin E, Oller G. Skin reaction with low molecular weight heparins. *Br J Haematol* 1993; **85**: 637.

17 Phillips JK, Majumdar G, Hunt BJ, Savidge GF. Heparin-induced skin reaction due to two different preparations of low molecular weight heparin (LMWH). *Br J Haematol* 1993; **84**: 349–50.

18 Ainley EJ, Mackie IG, MacArthur D. Adverse reaction to chlorocresol preserved heparin. *Lancet* 1977; **i**: 705.

19 Shelley WB, Säyen JJ. Heparin necrosis: an anticoagulant-induced cutaneous infarct. *J Am Acad Dermatol* 1982; **7**: 674–7.

20 Levine LE, Bernstein JE, Soltani K *et al.* Heparin-induced skin necrosis unrelated to injection sites: a sign of potentially lethal complications. *Arch Dermatol* 1983; **119**: 400–3.

21 Mathieu A, Avril MF, Schlumberger M *et al.* Un cas de nécrose cutanée induite par l'héparine. *Ann Dermatol Vénéréol* 1984; **111**: 733–4.

22 Barthelemy H, Hermier C, Perrot H. Nécrose cutanée avec évolution sclérodermiforme après l'injection souscutanée d'heparinate de calcium. *Ann Dermatol Vénéréol* 1985; **112**: 245–7.

23 Cordoliani F, Saiag P, Guillaume J-C *et al.* Nécrose cutanés étendues induites par la fraxiparine. *Ann Dermatol Vénéréol* 1987; **114**: 1366–8.

24 Rongioletti F, Pisani S, Ciaccio M, Rebora A. Skin necrosis due to intravenous heparin. *Dermatologica* 1989; **178**: 47–50.

25 Gold JA, Watters AK, O'Brien E. Coumadin versus heparin necrosis. *J Am Acad Dermatol* 1987; **16**: 148–50.

26 Ojeda E, Perez MC, Mataix R *et al.* Skin necrosis with a low molecular weight heparin. *Br J Haematol* 1992; **82**: 620.

27 Yates P, Jones S. Heparin skin necrosis: an important indicator of potentially fatal heparin hypersensitivity. *Clin Exp Dermatol* 1993; **18**: 138–41.

28 Cine DB, Tomaski A, Tannenbaum S. Immune endothelial cell injury in heparin-associated thrombocytopenia. *N Engl J Med* 1987; **316**: 581–9.

29 Warkentin TE, Kelton JG. Heparin-induced thrombocytopenia. *Annu Rev Med* 1989; **40**: 31–44.

30 Jaffray B, Welch GH, Cooke TG. Fatal venous thrombosis after heparin therapy. *Lancet* 1991; **337**: 561.

31 Eichinger S, Kyrle PA, Brenner B *et al.* Thrombocytopenia associated with low-molecular-weight heparin. *Lancet* 1991; **337**: 1425–6.
32 Greinacher A, Michels I, Schafer M *et al.* Heparin-associated thrombocytopenia in a patient treated with polysulphated chondroitin sulphate: evidence for immunological crossreactivity between heparin and polysulphated glycosaminoglycan. *Br J Haematol* 1992; **81**: 252–4.
33 Gross AS, Thompson FL, Arzubiaga MC *et al.* Heparin-associated thrombocytopenia and thrombosis (HATT) presenting with livedo reticularis. *Int J Dermatol* 1993; **32**: 276–9.
34 O'Bryan-Tear G. Heparin induced thrombosis. Datasheet warns of risk. *BMJ* 1993; **307**: 561.
35 Ouellette D, Menkis AH. Heparin-induced thrombocytopenia. *Ann Thorac Surg* 1993; **55**: 809.

Protamine: heparin antagonist

This low-molecular-weight protein, derived from salmon sperm and/or testes, is used for neutralization of heparin anticoagulation after cardiac surgery. Adverse reactions have been reviewed [1]. Idiosyncratic responses or those related to complement generation of anaphylatoxins are recorded [2]. IgE-dependent anaphylaxis [3], as well as delayed reactions causing skin nodules [4–6], which may be granulomatous [6], may occur in diabetics treated with protamine-containing insulin.

References

1 Cormack JG, Levy JH. Adverse reactions to protamine. *Coron Artery Dis* 1993; **4**: 420–5.
2 Sussman GL, Dolovich J. Prevention of anaphylaxis. *Semin Dermatol* 1989; **8**: 158–65.
3 Kim R. Anaphylaxis to protamine masquerading as an insulin allergy. *Del Med J* 1993; **65**: 17–23.
4 Sarche MB, Paolillo M, Chacon RS *et al.* Protamine as a cause of generalized allergic reactions to NPH insulin. *Lancet* 1982; **i**: 1243.
5 Kollner A, Senff H, Engelmann L *et al.* Protaminallergie vom Spattyp und Insulinallergie vom Soforttyp. *Dtsch Med Wochenschr* 1991; **116**: 1234–8.
6 Hulshof MM, Faber WR, Kniestedt WF *et al.* Granulomatous hypersensitivity to protamine as a complication of insulin therapy. *Br J Dermatol* 1992; **127**: 286–8.

Fibrinolytic drugs

Haemorrhage is the most common untoward effect from use of thrombolysins [1]. Allergic complications are rare, particularly with alteplase or urokinase. These agents should be used electively in all patients previously exposed to streptokinase or anistreplase [2].

Alteplase (tissue-type plasminogen activator)

Painful purpura occurring within hours of administration has been recorded [3].

Aminocaproic acid

A maculopapular eruption occurring 12–72 h after administration of ε-aminocaproic acid, with positive patch tests to the drug, has been described [4]. A transient, non-inflammatory, subepidermal, bullous eruption on the legs, with fibrin thrombi in papillary dermal vessels, has also been recorded [5].

Anistreplase (anisoylated plasminogen streptokinase activator complex)

Anistreplase given for acute myocardial infarction was associated with leukocytoclastic vasculitis [6]. Maculopapular rashes and urticaria are described; patients with maculopapular rashes had significantly higher rises in serum IgM, IgG, IgA and IgE antistreptokinase level [7].

References

1 Chesebro JH, Knatterud G, Roberts R *et al.* Thrombolysis in myocardial infarction (TIMI) trial, phase I: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase. *Circulation* 1987; **76**: 142–54.
2 de Bono DP. Complications of thrombolysis and their clinical management. *Z Kardiol* 1993; **82** (Suppl. 2): 147–51.
3 DeTrana C, Hurwitz RM. Painful purpura: an adverse effect to a thrombolysin. *Arch Dermatol* 1990; **126**: 690–1.
4 Gonzalez Gutierrez ML, Esteban Lopez MI, Ruiz Ruiz MD. Positivity of patch tests in cutaneous reaction to aminocaproic acid: two case reports. *Allergy* 1995; **50**: 745–6.
5 Brooke CP, Spiers EM, Omura EF. Noninflammatory bullae associated with epsilon-aminocaproic acid infusion. *J Am Acad Dermatol* 1992; **27**: 880–2.
6 Burrows N, Russell Jones R. Vasculitis occurring after intravenous anistreplase. *J Am Acad Dermatol* 1992; **26**: 508.
7 Dykewicz MS, McMorrow NK, Davison R *et al.* Drug eruptions and isotypic antibody responses to streptokinase after infusions of anisoylated plasminogen–streptokinase complex (APSAC, anistreplase). *J Allergy Clin Immunol* 1995; **95**: 1020–8.

Streptokinase

Allergic reactions have been reported in up to 6% of patients [1–3], ranging from minor rashes to angio-oedema or anaphylaxis (which may be fatal [4–6]), bleeding, strokes and a syndrome resembling adult respiratory distress syndrome [3]. Patients who develop reactions to streptokinase cannot be predicted on the basis of antistreptokinase IgG antibody titres at presentation; minor reactions to streptokinase would not appear to be antibody mediated [7]. However, streptokinase-related thrombolytic agents should be avoided in reinfarction thrombolysis therapy in patients with raised antistreptokinase antibody titres, as hypersensitivity reactions including serum sickness may occur [8–10]. This drug has been reported in association with a hypersensitivity vasculitis [11,12], serum sickness with leukocytoclastic vasculitis [13,14] and a lymphocytic angiitis [15]. Skin necrosis is recorded [16].

Urokinase

Haemorrhagic bullae occurred as a complication of urokinase therapy for haemodialysis catheter thrombosis [17].

References

1 Dykewicz MS, McGratt KG, Davison R *et al.* Identification of patients at risk for anaphylaxis due to streptokinase. *Arch Intern Med* 1986; **146**: 305–7.
2 ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988; **ii**: 349–60.
3 Siebert WJ, Ayres RW, Bulling MT *et al.* Streptokinase morbidity: more common than previously recognised. *Aust NZ J Med* 1992; **22**: 129–33.
4 Allpress SM, Cluroe AD, Vuletic JC, Kolemeyer TD. Death after streptokinase. *NZ Med J* 1993; **106**: 295.
5 Hohage H, Schulte B, Pfeiff B, Pullmann H. Anaphylaktische Reaktion unter Streptokinase-Therapie. *Wien Klin Wochenschr* 1993; **105**: 176–8.
6 Cooper JP, Quarry DP, Beale DJ, Chappell AG. Life-threatening, localized angio-oedema associated with streptokinase. *Postgrad Med J* 1994; **70**: 592–3.
7 Lynch M, Pentecost BL, Littler WA, Stockley RA. Why do patients develop reactions to streptokinase? *Clin Exp Immunol* 1993; **94**: 279–85.
8 Lee HS, Yule S, McKenzie A *et al.* Hypersensitivity reactions to streptokinase in patients with high pretreatment antistreptokinase antibody and neutralisation titres. *Eur Heart J* 1993; **14**: 1640–3.

9 Cross DB. Should streptokinase be readministered? Insights from recent studies of antistreptokinase antibodies. *Med J Aust* 1994; **161**: 100–1.
10 Jennings K. Antibodies to streptokinase. *BMJ* 1996; **312**: 393–4.
11 Ong ACM, Handler CE, Walker JM. Hypersensitivity vasculitis complicating intravenous streptokinase therapy in acute myocardial infarction. *Int J Cardiol* 1988; **21**: 71–3.
12 Thompson RF, Stratton MA, Heffron WA. Hypersensitivity vasculitis associated with streptokinase. *Clin Pharmacol* 1985; **4**: 383–8.
13 Patel IA, Prussick R, Buchanan WW, Sauder DN. Serum sickness-like illness and leukocytoclastic vasculitis after intravenous streptokinase. *J Am Acad Dermatol* 1991; **24**: 652–3.
14 Totto WG, Romano T, Benian GM *et al.* Serum sickness following streptokinase therapy. *Am J Rheumatol* 1982; **138**: 143–4.
15 Sorber WA, Herbst V. Lymphocytic angiitis following streptokinase therapy. *Cutis* 1988; **42**: 57–8.
16 Penswick J, Wright AL. Skin necrosis induced by streptokinase. *BMJ* 1994; **309**: 378.
17 Ejaz AA, Aijaz M, Nawab ZM *et al.* Hemorrhagic bullae as a complication of urokinase therapy for hemodialysis catheter thrombosis. *Am J Nephrol* 1995; **15**: 178–9.

Antiplatelet drugs

Clopidogrel

This drug, a novel thienopyridine derivative chemically related to ticlopidine and used in patients at risk of thromboembolic disorders, has caused a photosensitive lichenoid eruption [1] and a hypersensitivity disorder [2]. The USA Food and Drug Administration reported 50 hypersensitivity reactions after coronary stent placement but later concluded these were in fact due to concomitantly prescribed medications such as clopidogrel [3].

Ticlopidine

This antiplatelet drug, indicated for coronary artery disease, cerebrovascular disease, peripheral vascular disease and diabetic retinopathy, is also a thienopyridine derivative [4,5]. Gastrointestinal symptoms, thrombocytopenia with minor bleeding including bruising, neutropenia, rashes in 10–15% of patients, and hepatic dysfunction in 4% of cases have been reported. Thrombotic thrombocytopenic purpura has also been documented [6]. Cutaneous reactions, including urticaria, pruritus, maculopapular and fixed drug eruptions, erythromelalgia and erythema multiforme, are recorded in up to 11.8% of patients [7]. Acute generalized exanthematous pustulosis has been documented [8].

References

1 Dogra S, Kanwar AJ. Clopidogrel bisulphate-induced photosensitive lichenoid eruption: first report. *Br J Dermatol* 2003; **148**: 593–611.
2 Doogue MP, Begg EJ, Bridgman P. Clopidogrel hypersensitivity syndrome with rash, fever, and neutropenia. *Mayo Clin Proc* 2005; **80**: 1368–70.
3 Nebeker JR, Virmani R, Bennett CL *et al.* Hypersensitivity cases associated with drug-eluting coronary stents: a review of available cases from the Research on Adverse Drug Events and Reports (RADAR) project. *J Am Coll Cardiol* 2006; **47**: 175–81.
4 McTavish D, Faulds D, Goa KL. Ticlopidine. An updated review of its pharmacology and therapeutic use in platelet-dependent disorders. *Drugs* 1990; **40**: 238–59.
5 Anonymous. Ticlopidine. *Lancet* 1991; **337**: 459–60.
6 Page Y, Tardy B, Zeni F *et al.* Thrombotic thrombocytopenic purpura related to ticlopidine. *Lancet* 1991; **337**: 774–6.
7 Yosipovitch G, Rechavia E, Feinmesser M, David M. Adverse cutaneous reactions to ticlopidine in patients with coronary stents. *J Am Acad Dermatol* 1999; **41**: 473–6.
8 Cannavò SP, Borgia F, Guarneri F, Vaccaro M. Acute generalized exanthematous pustulosis following use of ticlopidine. *Br J Dermatol* 2000; **142**: 577–8.

Vitamins including retinoids

Vitamin A

Generalized peeling may be a delayed manifestation of acute intoxication [1]. Chronic intoxication produces the following epithelial problems: pruritus, erythema, hyperkeratosis, dryness of mouth, nose and eyes, epistaxis, fissuring, dryness and scaling of the lips, peeling of the palms and soles, and alopecia. A yellow-orange skin discoloration, photosensitivity and nail changes have also been observed [2–5]. Headache, pseudotumour cerebri, anaemia, hepatomegaly and skeletal pain may be present. Cortical hyperostoses and periosteal reaction of tubular bone [6], and more rarely premature epiphyseal closure and change in the contour of long bones [7], are seen.

References

1 Nater P, Doeglas HMG. Halibut liver poisoning in 11 fishermen. *Acta Derm Venereol (Stockh)* 1970; **50**: 109–13.
2 Oliver TK. Chronic vitamin A intoxication. Report of a case in an older child and a review of the literature. *Am J Dis Child* 1959; **95**: 57–67.
3 Muenter MD, Perry HO, Ludwig J. Chronic vitamin A intoxication in adults. Hepatic, neurologic and dermatologic complications. *Am J Med* 1971; **50**: 129–36.
4 Teo ST, Newth J, Pascoe BJ. Chronic vitamin A intoxication. *Med J Aust* 1973; **2**: 324–6.
5 Bobb R, Kieraldo JH. Cirrhosis due to hypervitaminosis A. *West J Med* 1978; **128**: 244–6.
6 Frame B, Jackson CE, Reynolds WA, Umphrey JE. Hypercalcemia and skeletal effects in chronic hypervitaminosis A. *Ann Intern Med* 1974; **80**: 44–8.
7 Ruby LK, Mital MA. Skeletal deformities following chronic hypervitaminosis A. *J Bone Joint Surg* 1974; **56**: 1283–7.

Retinoids

The cutaneous and systemic side effects of these synthetic vitamin A-related compounds resemble those of hypervitaminosis A, and have been extensively reviewed [1–12].

References

1 Orfanos CE, Braun-Falco O, Farber EM *et al.*, eds. *Retinoids. Advances in Basic Research and Therapy*. Berlin: Springer, 1981.
2 Foged E, Jacobsen F. Side-effects due to Ro 10-3959 (Tigason). *Dermatologica* 1982; **164**: 395–403.
3 Windhorst DB, Nigra T. General clinical toxicology of oral retinoids. *J Am Acad Dermatol* 1982; **4**: 675–82.
4 Cunliffe WJ, Miller AJ, eds. *Retinoid Therapy. A Review of Clinical and Laboratory Research*. Lancaster: MTP Press, 1984.
5 Saurat JH, ed. *Retinoids: New Trends in Research and Therapy*. Basel: Karger, 1985.
6 Yob EH, Pochi PE. Side effects and long-term toxicity of synthetic retinoids. *Arch Dermatol* 1987; **123**: 1375–8.
7 Bigby M, Stern RS. Adverse reactions to isotretinoin. A report from the Adverse Drug Reaction Reporting System. *J Am Acad Dermatol* 1988; **18**: 543–52.
8 Saurat J-H. Side effects of systemic retinoids and their clinical management. *J Am Acad Dermatol* 1992; **27**: S23–S28.
9 Vahlquist A. Long-term safety of retinoid therapy. *J Am Acad Dermatol* 1992; **27**: S29–S33.
10 Gollnick HPM. Oral retinoids: efficacy and toxicity in psoriasis. *Br J Dermatol* 1996; **135** (Suppl. 49): 6–17.
11 Mørk N-J, Kolbenstvedt A, Austad J. Skeletal side-effects of 5 years' acitretin treatment. *Br J Dermatol* 1996; **134**: 1156–7.
12 Hermann G, Jungblut RM, Goerz G. Skeletal changes after long-term therapy with synthetic retinoids. *Br J Dermatol* 1997; **136**: 469–70.

Acitretin

The side effects of this principal metabolite of etretinate, which it has replaced are similar to those of the parent compound [1–6], comprising cheilitis, alopecia, conjunctivitis, peeling of the palms and soles, xerosis, myalgia and pancreatitis; elevated levels of serum triglyceride, cholesterol and liver transaminase are seen. There has been no biopsy-proven hepatotoxicity [7]. Alopecia is particularly frequent [4], and scaling of the palms and soles appears more prominent than with etretinate [5]. There is a higher occurrence of vulvovaginal candidiasis during acitretin exposure [8]. Multiple milia have occurred [9]. Skeletal effects may be significant, but are not an absolute contraindication to therapy [10]. Acitretin does not seem to cause osteoporosis [11].

Persistent levels of etretinate have been detected in plasma following a change to acitretin therapy. Detectable plasma etretinate was present in 45% of current acitretin users and 18% of those who had stopped acitretin, whereas detectable subcutaneous tissue etretinate was present in 83% of current acitretin users and 86% of those who had discontinued the drug [12]. Inability to detect plasma etretinate is therefore a poor predictor of the absence of etretinate in fat. Acitretin and/or etretinate were detectable in fat, and in some cases plasma, from women who had ceased acitretin therapy for up to 29 months [12]. It has been proposed that subcutaneous tissue levels of acitretin and etretinate should be monitored when plasma measurements are negative, and that the recommended contraception period of 2 years after cessation of acitretin therapy should be reconsidered to avoid the risk of teratogenicity [13]. It has been suggested that acitretin is only converted to etretinate following alcohol intake [14].

References

1 Geiger J-M, Czarnetzki BM. Acitretin (Ro 10-1670, Etretin): overall evaluation of clinical studies. *Dermatologica* 1988; **176**: 182–90.

2 Gupta AK, Goldfarb MT, Ellis CN, Voorhees JJ. Side-effect profile of acitretin therapy in psoriasis. *J Am Acad Dermatol* 1989; **21**: 1088–93.

3 Ruzicka T, Sommerburg C, Braun-Falco O *et al.* Efficiency of acitretin in combination with UV-B in the treatment of severe psoriasis. *Arch Dermatol* 1990; **126**: 482–6.

4 Murray HE, Anhalt AW, Lessard R *et al.* A 12-month treatment of severe psoriasis with acitretin: results of a Canadian open multicenter study. *J Am Acad Dermatol* 1991; **24**: 598–602.

5 Blanchet-Bardon C, Nazzaro V, Rognin C *et al.* Acitretin in the treatment of severe disorders of keratinization. Results of an open study. *J Am Acad Dermatol* 1991; **24**: 982–6.

6 Katz HI, Waalen J, Leach EE. Acitretin in psoriasis: an overview of adverse effects. *J Am Acad Dermatol* 1999; **41**: S7–S12.

7 Roenigk HH Jr, Callen JP, Guzzo CA *et al.* Effects of acitretin on the liver. *J Am Acad Dermatol* 1999; **41**: 584–8.

8 Sturkenboom MC, Middelbeek A, de Jong van den Berg LT *et al.* Vulvo-vaginal candidiasis associated with acitretin. *J Clin Epidemiol* 1995; **48**: 991–7.

9 Chang A, Kuligowski ME, van de Kerkhof PC. Multiple milia during treatment with acitretin for mycosis fungoides. *Acta Derm Venereol (Stockh)* 1993; **73**: 235.

10 Mørk N-J, Kolbenstvedt A, Austad J. Skeletal side-effects of 5 years' acitretin treatment. *Br J Dermatol* 1996; **134**: 1156–7.

11 McMullen EA, McCarron P, Irvine D *et al.* Association between long-term acitretin therapy and osteoporosis: no evidence of increased risk. *Clin Exp Dermatol* 2003; **28**: 307–9.

12 Lambert WE, De Leenheer AP, De Bersaques JP, Kint A. Persistent etretinate levels in plasma after changing the therapy to acitretin. *Arch Dermatol Res* 1990; **282**: 343–4.

13 Sturkenboom MC, de Jong van den Berg LT, van Voorst Vader PC *et al.* Inability to detect plasma etretinate and acitretin is a poor predictor of the absence of these teratogens in tissue after stopping acitretin treatment. *Br J Clin Pharmacol* 1994; **38**: 229–35.

14 Grønhøy Larsen F, Steinkjer B, Jakobsen P *et al.* Acitretin is converted to etretinate only during concomitant alcohol intake. *Br J Dermatol* 2000; **143**: 1164–9.

Etretinate

This drug is discussed because of its relationship to acitretin. The dermatological side effects are dose dependent, and resemble those associated with isotretinoin therapy [1–3]. With dosage over 0.5 mg/kg, cheilitis with dryness, scaling and fissuring of the lips is almost universal. There may be pruritus, a dry mouth, dry nose, epistaxis, meatitis, desquamation including the face, hands and feet, and reduced tolerance of sunlight [4] and therapeutic products such as tar or dithranol. Pseudoporphyria has been reported in a renal transplant recipient treated with etretinate to suppress cutaneous neoplasia [5]. A 'retinoid dermatitis' resembling asteatotic eczema may develop in up to 50% of patients [6]. Increased stickiness of the palms and soles, possibly due to increased quantities of carcinoembryonic antigen and other glycoproteins in eccrine sweat [7,8], has been reported. Mucosal erosions, conjunctivitis, paronychia, alopecia [9] and curling, kinking or darkening of hair [10] are all well documented. Intertriginous erosions have also been described [11]. Oedema [12], excess granulation tissue [13] and multiple pyogenic granulomas [14] develop rarely. Erythroderma has been reported [15].

Prolonged therapy may lead to skin fragility [16,17]; blistering, erosions and scarring have been reported in one patient [18]. Softening of the nails is seen [19], and chronic paronychia, onycholysis, onychomadesis, nail shedding, onychoschizia and fragility may occur [20,21]. Parakeratotic digitate keratoses appearing after treatment of disseminated superficial actinic porokeratosis may arise as a result of etretinate-resistant regions in the ring of the cornoid lamella [22]. There has been a single case of generalization of palmoplantar pustulosis following cessation of etretinate therapy [23].

Systemic side effects of etretinate include benign intracranial hypertension [24]. Minor disturbances in tests of liver function are not uncommon, and may not always be reversible; liver changes range from non-specific reactive hepatitis to acute hepatitis, chronic active hepatitis and severe fibrosis or cirrhosis [25–28]. Fatal liver necrosis occurred in a patient with ichthyosiform erythroderma [29], but other factors may have been relevant. However, several studies involving liver biopsies have indicated good tolerance of etretinate without significant hepatotoxic side effects [30–32]; in one study, patients were followed for 3 years [32]. Etretinate, like isotretinoin, can cause increase in triglycerides and cholesterol [33–36] but to a lesser extent [36]. There have been isolated reports of possible etretinate-related thrombocytopenia [37]. Retinal toxicity has been postulated [38], although a recent report has not confirmed this [39]. Erectile dysfunction has been documented occasionally [40].

Skeletal abnormalities, such as periosteal thickening, vertebral hyperostosis, disc degeneration, osteoporosis and calcification of spinal ligaments, occur in a significant number of adults receiving long-term therapy for disorders of keratinization, but the severity of the changes is minor [41,42]. Radiological evidence of thinning of long bones may be seen in children [43], and premature epiphyseal closure has been recorded [44].

Etretinate, like isotretinoin, is grossly teratogenic, and because of its deposition in body fat stores is excreted only very slowly, especially in the obese [45]. Detectable serum levels have been found in some patients more than 2 years after discontinuation of therapy. It is therefore recommended that female patients of childbearing years should be advised to prevent pregnancy not only during the course of treatment but also for at least 2 years after stopping therapy; if pregnancy is contemplated after this period of time, an estimation of circulating levels of retinoid metabolites should be obtained.

References

1 Foged E, Jacobsen F. Side-effects due to Ro 10-3959 (Tigason). *Dermatologica* 1982; **164**: 395–403.
2 Ellis CN, Voorhees JJ. Etretinate therapy. *J Am Acad Dermatol* 1987; **16**: 267–91.
3 Halioua B, Saurat J-H. Risk: benefit ratio in the treatment of psoriasis with systemic retinoids. *Br J Dermatol* 1990; **122** (Suppl. 36): 135–50.
4 Collins MRL, James WD, Rodman OG. Etretinate photosensitivity. *J Am Acad Dermatol* 1986; **14**: 274.
5 McDonagh AJG, Harrington CI. Pseudoporphyria complicating etretinate therapy. *Clin Exp Dermatol* 1989; **14**: 437–8.
6 Taieb A, Maleville J. Retinoid dermatitis mimicking 'eczéma craquelé'. *Acta Derm Venereol (Stockh)* 1985; **65**: 570.
7 Pennys NS, Hernandez D. A sticky problem with etretinate. *N Engl J Med* 1991; **325**: 521.
8 Higgins EM, Pembroke AC. Sticky palms: an unusual side-effect of etretinate therapy. *Clin Exp Dermatol* 1993; **18**: 389–90.
9 Berth-Jones J, Shuttleworth D, Hutchinson PE. A study of etretinate alopecia. *Br J Dermatol* 1990; **122**: 751–5.
10 Vesper JL, Fenske A. Hair darkening and new growth associated with etretinate therapy. *J Am Acad Dermatol* 1996; **34**: 860.
11 Shelley ED, Shelley WB. Inframammary, intertriginous, and decubital erosion due to etretinate. *Cutis* 1991; **47**: 111–3.
12 Allan S, Christmas T. Severe edema associated with etretinate. *J Am Acad Dermatol* 1988; **19**: 140.
13 Hodak E, David M, Feuerman EJ. Excess granulation tissue during etretinate therapy. *J Am Acad Dermatol* 1984; **11**: 1166–7.
14 Williamson DM, Greenwood R. Multiple pyogenic granulomata occurring during etretinate therapy. *Br J Dermatol* 1983; **109**: 615–7.
15 Levin J, Almeyda J. Erythroderma due to etretinate. *Br J Dermatol* 1985; **112**: 373.
16 Williams ML, Elias PM. Nature of skin fragility in patients receiving retinoids for systemic effect. *Arch Dermatol* 1981; **117**: 611–9.
17 Neild VS, Moss RF, Marsden RA *et al.* Retinoid-induced skin fragility in a patient with hepatic disease. *Clin Exp Dermatol* 1985; **10**: 459–65.
18 Ramsay B, Bloxham C, Eldred A *et al.* Blistering, erosions and scarring in a patient on etretinate. *Br J Dermatol* 1989; **121**: 397–400.
19 Lindskov R. Soft nails after treatment with aromatic retinoids. *Arch Dermatol* 1982; **118**: 535–6.
20 Baran R. Action thérapeutique et complications du rétinoïde aromatique sur l'appareil unguéal. *Ann Dermatol Vénéréol* 1982; **109**: 367–71.
21 Baran R. Etretinate and the nails (study of 130 cases): possible mechanisms of some side-effects. *Clin Exp Dermatol* 1986; **11**: 148–52.
22 Carmichael AJ, Tan CY. Digitate keratoses: a complication of etretinate used in the treatment of disseminated superficial actinic porokeratosis. *Clin Exp Dermatol* 1990; **15**: 370–1.
23 Miyagawa S, Muramatsu T, Shirai T. Generalization of palmoplantar pustulosis after withdrawal of etretinate. *J Am Acad Dermatol* 1991; **24**: 305–6.
24 Viraben R, Mathieu C. Benign intracranial hypertension during etretinate therapy for mycosis fungoides. *J Am Acad Dermatol* 1985; **13**: 515–7.
25 Schmidt H, Foged E. Some hepatotoxic side effects observed in patients treated with aromatic retinoid (Ro 10-9359). In: Orfanos CE, Braun-Falco O, Farber EM *et al.*, eds. *Retinoids. Advances in Basic Research and Therapy.* Berlin: Springer, 1981: 359–62.
26 Van Voorst Vader P, Houthoff H, Eggink H, Gips C. Etretinate (Tigason) hepatitis in two patients. *Dermatologica* 1984; **168**: 41–6.
27 Kano Y, Fukuda M, Shiohara T, Nagashima M. Cholestatic hepatitis occurring shortly after etretinate therapy. *J Am Acad Dermatol* 1994; **31**: 133–4.
28 Sanchez MR, Ross B, Rotterdam H *et al.* Retinoid hepatitis. *J Am Acad Dermatol* 1993; **28**: 853–8.
29 Thune P, Mørk NJ. A case of centrolobular necrosis of the liver due to aromatic retinoid: Tigason (Ro-10-9359). *Dermatologica* 1980; **160**: 405–8.
30 Foged E, Bjerring P, Kragballe K *et al.* Histologic changes in the liver during etretinate treatment. *J Am Acad Dermatol* 1984; **11**: 580–3.
31 Zachariae H, Foged E, Bjerring P *et al.* Liver biopsy during etretinate (Tigason®) treatment. In: Saurat JH, ed. *Retinoids: New Trends in Research and Therapy.* Basel: Karger, 1985: 494–7.
32 Roenigk HH Jr. Retinoids: effect on the liver. In: Saurat JH, ed. *Retinoids: New Trends in Research and Therapy.* Basel: Karger, 1985: 476–88.
33 Ellis CN, Swanson NA, Grekin RC *et al.* Etretinate therapy causes increases in lipid levels in patients with psoriasis. *Arch Dermatol* 1982; **118**: 559–62.
34 Michaëlsson G, Bergquist A, Vahlquist A, Vessby B. The influence of 'Tigason' (R 10-9359) on the serum lipoproteins in man. *Br J Dermatol* 1981; **105**: 201–5.
35 Vahlquist C, Michaëlsson G, Vahlquist A, Vessby B. A sequential comparison of etretinate (Tigason®) and isotretinoin (Roaccutane®) with special regard to their effects on serum lipoproteins. *Br J Dermatol* 1985; **112**: 69–76.
36 Marsden J. Hyperlipidaemia due to isotretinoin and etretinate: possible mechanisms and consequences. *Br J Dermatol* 1986; **114**: 401–7.
37 Naldi L, Rozzoni M, Finazzi G *et al.* Etretinate therapy and thrombocytopenia. *Br J Dermatol* 1991; **124**: 395.
38 Weber U, Melink B, Goerz G, Michaelis L. Abnormal retinal function associated with long-term etretinate? *Lancet* 1988; **i**: 235–6.
39 Pitts JF, MacKie RM, Dutton GN *et al.* Etretinate and visual function: a 1-year follow-up study. *Br J Dermatol* 1991; **125**: 53–5.
40 Reynolds OD. Erectile dysfunction in etretinate treatment. *Arch Dermatol* 1991; **127**: 425–6.
41 DiGiovanna JJ, Gerber LH, Helfgott RK *et al.* Extraspinal tendon and ligament calcification associated with long-term therapy with etretinate. *N Engl J Med* 1986; **315**: 1177–82.
42 Halkier-Sørensen L, Andresen J. A retrospective study of bone changes in adults treated with etretinate. *J Am Acad Dermatol* 1989; **20**: 83–7.
43 Halkier-Sørensen L, Laurberg G, Andresen J. Bone changes in children on long-term treatment with etretinate. *J Am Acad Dermatol* 1987; **16**: 999–1006.
44 Prendiville J, Bingham EA, Burrows D. Premature epiphyseal closure: a complication of etretinate therapy in children. *J Am Acad Dermatol* 1986; **15**: 1259–62.
45 DiGiovanna JJ, Zech LA, Ruddel ME *et al.* Etretinate: persistent serum levels after long-term therapy. *Arch Dermatol* 1989; **125**: 246–51.

Isotretinoin (13-cis-retinoic acid)

Dermatological complications have been reviewed [1,2]; erythema and scaling of the face, generalized xerosis, skin fragility, pruritus, epistaxis, dry nose and dry mouth may be seen in up to 80% of cystic acne patients; hoarseness is documented. A dose-related cheilitis occurs in over 90% and conjunctivitis in about 40% of patients. Transient exacerbation of acne may occur, especially in the early stages of therapy. Exuberant granulation tissue, or pyogenic granulomas at the site of healing acne lesions, has been reported frequently [3–7].

Rashes, including erythema, and thinning of the hair (in rare cases persistent) occur in fewer than 10% of patients. Both isotretinoin and etretinate have caused curliness or kinking of hair [8]. Nasolabial follicular sebaceous casts have been reported [9]. The following have occurred in approximately 5% of cases: peeling of the palms and soles, skin infections and possible increased susceptibility to sunburn. Phototesting confirmed photosensitivity in some patients in one study [10] but not another [11]. A photoaggravated allergic reaction has been documented in which the patient had positive patch tests to isotretinoin [12]. Reversible melasma is recorded [13], as is facial cellulitis [14]. Angio-oedema and urticaria [15], facial oedema [16], and pyoderma gangrenosum

[17] are recorded. Scarring, which may be keloidal, may occur after dermabrasion or laser therapy within a year of isotretinoin therapy; such procedures are best postponed during this period [18–20].

References

1 Yob EH, Pochi PE. Side effects and long-term toxicity of synthetic retinoids. *Arch Dermatol* 1987; **123**: 1375–8.
2 Bigby M, Stern RS. Adverse reactions to isotretinoin. A report from the Adverse Drug Reaction Reporting System. *J Am Acad Dermatol* 1988; **18**: 543–52.
3 Campbell JP, Grekin RC, Ellis CN *et al*. Retinoid therapy is associated with excess granulation tissue responses. *J Am Acad Dermatol* 1983; **9**: 708–13.
4 Exner JH, Dahod S, Pochi PE. Pyogenic granuloma-like acne lesions during isotretinoin therapy. *Arch Dermatol* 1983; **119**: 808–11.
5 Valentic JP, Barr RJ, Weinstein GD. Inflammatory neovascular nodules associated with oral isotretinoin treatment of severe acne. *Arch Dermatol* 1983; **119**: 871–2.
6 Stary A. Acne conglobata: Ungewöhnlicher Verlauf unter 13-*cis*-Retinsäuretherapie. *Hautarzt* 1986; **37**: 28–30.
7 Blanc D, Zultak M, Wendling P, Lonchampt F. Eruptive pyogenic granulomas and acne fulminans in two siblings treated with isotretinoin. A possible common pathogenesis. *Dermatologica* 1988; **177**: 16–8.
8 Bunker CB, Maurice PDL, Dowd PM. Isotretinoin and curly hair. *Clin Exp Dermatol* 1990; **15**: 143–5.
9 Plewig G. Nasolabial follicular sebaceous casts: a novel complication of isotretinoin therapy. *Br J Dermatol* 2001; **144**: 919.
10 Ferguson J, Johnson BE. Photosensitivity due to retinoids: clinical and laboratory studies. *Br J Dermatol* 1986; **115**: 275–83.
11 Wong RC, Gilber M, Woo TY *et al*. Photosensitivity and isotretinoin therapy. *J Am Acad Dermatol* 1986; **15**: 1095–6.
12 Auffret N, Bruley C, Brunetiere RA *et al*. Photoaggravated allergic reaction to isotretinoin. *J Am Acad Dermatol* 1990; **23**: 321–2.
13 Burke H, Carmichael AJ. Reversible melasma associated with isotretinoin. *Br J Dermatol* 1996; **135**: 862.
14 Boffa MJ, Dave VK. Facial cellulitis during oral isotretinoin treatment for acne. *J Am Acad Dermatol* 1994; **31**: 800–2.
15 Saray Y, Seçkin D. Angioedema and urticaria due to isotretinoin therapy. *J Eur Acad Dermatol Venereol* 2006; **20**: 118–20.
16 Scheinfeld N, Bangalore S. Facial edema induced by isotretinoin use: a case and a review of the side effects of isotretinoin. *J Drugs Dermatol* 2006; **5**: 467–8.
17 Freiman A, Brassard A. Pyoderma gangrenosum associated with isotretinoin therapy. *J Am Acad Dermatol* 2006; **55** (Suppl. 5): S107–8.
18 Rubenstein R, Roenigk HH Jr, Stegman SJ *et al*. Atypical keloids after dermabrasion of patients taking isotretinoin. *J Am Acad Dermatol* 1986; **15**: 280–5.
19 Zachariae H. Delayed wound healing and keloid formation following argon laser treatment or dermabrasion during isotretinoin treatment. *Br J Dermatol* 1988; **118**: 703–6.
20 Katz BE, MacFarlane DF. Atypical facial scarring after isotretinoin therapy in a patient with previous dermabrasion. *J Am Acad Dermatol* 1994; **30**: 852–3.

Systemic side effects. These include headache, which is not uncommon; anorexia, nausea and vomiting are much more common than with etretinate, as are lethargy, irritability and fatigue [1]. Isotretinoin therapy has been associated with benign intracranial hypertension [2]; in some cases, there was concomitant use of tetracyclines, so this combination should be avoided. A variety of central nervous system reactions have been reported, but may bear no relationship to therapy.

Patients treated for disorders of keratinization have developed corneal opacities, which improved when the drug was withdrawn [3]. Blepharoconjunctivitis, dry eyes with decreased tolerance of contact lenses and blurred vision due to myopia may occur [4]. Decreased night vision has been documented rarely, as have cataracts and other visual disturbances [5,6]; decreased night vision after isotretinoin therapy may be more permanent than generally suspected [7,8], and many asymptomatic patients have abnormal electroretinograms [6]. Loss of sense of taste is recorded [9].

Transient chest pain is uncommon. Non-specific urogenital findings and non-specific gastrointestinal symptoms have occurred in approximately 5% of cases. Isotretinoin therapy has been associated with onset of inflammatory bowel disease [10,11] and with impairment of pulmonary function in patients with systemic sclerosis [12,13]. Proteinuria is recorded.

Approximately 16% of patients develop musculoskeletal symptoms, including arthralgia, of mild to moderate degree; cases of acute knee aseptic arthritis have been documented [14]. High-dose prolonged therapy in a child for epidermolytic hyperkeratosis was associated with premature closure of epiphyses [15]. A high prevalence of skeletal hyperostosis has been noted in patients on prolonged (1 year or more), relatively high-dose (2 mg/kg daily) isotretinoin therapy for disorders of keratinization [16–20]. The syndrome of *d*iffuse *i*diopathic *s*keletal *h*yperostosis (DISH) includes ossification of ligaments and accretion of bone onto vertebral bodies, especially of the cervical spine. Mild osteoporosis has also been seen. X-ray changes have been minimal in prospective studies of patients with cystic acne treated with a single course of isotretinoin at recommended doses [21–23]. Nasal bone osteophytosis has been described with short-term therapy for acne [24].

Mild to moderate elevation of liver enzymes occurs in about 15% of cases; in some patients these return to normal despite continued administration of the drug. A single case of fatty liver developing in a patient (with low to normal levels of α_1-antitrypsin) on low-dose isotretinoin has been reported [25]. Elevated sedimentation rates occur in about 40% of patients. Between 10 and 20% of patients show decreased red blood cell parameters and white blood cell counts, elevated platelet counts and pyuria. Thrombocytopenia may occur [26].

Isotretinoin induces reversible changes in serum lipids in a significant number of treated subjects [27–32]. A dose-related increase in triglycerides occurs in about 25% of individuals according to the Roche data sheet; five of 135 cystic acne patients, and 32 of 298 patients treated for all diagnoses, showed triglyceride levels above 500 mg/dL. In another study, 17% of patients taking isotretinoin for 20 weeks exhibited hypertriglyceridaemia, but in 15% this was of only mild to moderate degree [30]. About 15% showed a mild to moderate decrease in serum high density lipoprotein levels, and 7% experienced minimal elevations of serum cholesterol during therapy; some patients had increases in LDL cholesterol [30]. Lipid abnormalities peaked within 4 weeks in men, but not until 12 weeks in women. If sustained over a long period, these alterations in lipoproteins might be risk factors for coronary artery disease. Patients with an increased tendency to develop hypertriglyceridaemia include those with diabetes mellitus, obesity, increased alcohol intake or a familial history. Some patients have been able to reverse triglyceride elevation by reduction in weight, restriction of dietary fat and alcohol, and reduction in dose while continuing the drug. An obese male patient with Darier's disease developed elevated triglycerides and subsequent eruptive xanthomas [33].

References

1 Windhorst DB, Nigra T. General clinical toxicology of oral retinoids. *J Am Acad Dermatol* 1982; **4**: 675–82.

2 Anonymous. Adverse effects with isotretinoin. *J Am Acad Dermatol* 1984; **10**: 519–20.
3 Cunningham WJ. Use of isotretinoin in the ichthyoses. In: Cunliffe WJ, Miller AJ, eds. *Retinoid Therapy. A Review of Clinical and Laboratory Research.* Lancaster: MTP Press, 1984: 321–5.
4 Fraunfelder FT, La Braico JM, Meyer SM. Adverse ocular reactions possibly associated with isotretinoin. *Am J Ophthalmol* 1985; **100**: 534–7.
5 Brown RD, Grattan CEH. Visual toxicity of synthetic retinoids. *Br J Ophthalmol* 1989; **73**: 286–8.
6 Gold JA, Shupack JL, Nemec MA. Ocular side effects of the retinoids. *Int J Dermatol* 1989; **28**: 218–25.
7 Denman ST, Welebar RG, Hanifin JM *et al.* Abnormal night vision and altered dark adaptometry in patients treated with isotretinoin for acne. *J Am Acad Dermatol* 1986; **14**: 692–3.
8 Maclean H, Wright M, Choie D, Tidman MJ. Abnormal night vision with isotretinoin therapy for acne. *Clin Exp Dermatol* 1995; **20**: 86.
9 Halpern SM, Todd PM, Kirby JD. Loss of taste associated with isotretinoin. *Br J Dermatol* 1996; **134**: 378.
10 Gold MH, Roenigk HH. The retinoids and inflammatory bowel disease. *Arch Dermatol* 1988; **124**: 325–6.
11 Passier JL, Srivastava N, van Puijenbroek EP. Isotretinoin-induced inflammatory bowel disease. *Neth J Med* 2006; **64**: 52–4.
12 Bunker CB, Sheron N, Maurice PDL *et al.* Isotretinoin and eosinophilic pleural effusion. *Lancet* 1989; **i**: 435–6.
13 Bunker CB, Maurice PDL, Little S *et al.* Isotretinoin and lung function in systemic sclerosis. *Clin Exp Dermatol* 1991; **16**: 11–3.
14 Matsuoka LY, Wortsman J, Pepper JJ. Acute arthritis during isotretinoin treatment for acne. *Arch Intern Med* 1984; **144**: 1870–1.
15 Milstone LM, McGuire J, Ablow RC. Premature epiphyseal closure in a child receiving oral 13-*cis*-retinoic acid. *J Am Acad Dermatol* 1982; **7**: 663–6.
16 Pittsley R, Yoder K. Retinoid hyperostosis. Skeletal toxicity associated with long-term administration of 13 *cis*-retinoic acid for refractory ichthyosis. *N Engl J Med* 1983; **308**: 1012–4.
17 Ellis CN, Madison KC, Pennes DR *et al.* Isotretinoin is associated with early skeletal radiographic changes. *J Am Acad Dermatol* 1984; **10**: 1024–9.
18 Gerber L, Helfgott R, Gross E *et al.* Vertebral abnormalities associated with synthetic retinoid use. *J Am Acad Dermatol* 1984; **10**: 817–23.
19 Pennes D, Ellis C, Madison K *et al.* Early skeletal hyperostosis secondary to 13-*cis*-retinoic acid. *Am J Roentgenol* 1984; **142**: 979–83.
20 McGuire J, Milstone L, Lawson J. Isotretinoin administration alters juvenile and adult bone. In: Saurat JH, ed. *Retinoids: New Trends in Research and Therapy.* Basel: Karger, 1985: 419–39.
21 Ellis CN, Pennes DR, Madison KC *et al.* Skeletal radiographic changes during retinoid therapy. In: Saurat JH, ed. *Retinoids: New Trends in Research and Therapy*. Basel: Karger, 1985: 440–4.
22 Kilcoyne RF, Cope R, Cunningham W *et al.* Minimal spinal hyperostosis with low-dose isotretinoin therapy. *Invest Radiol* 1986; **21**: 41–4.
23 Carey BM, Parkin GJS, Cunliffe WJ, Pritlove J. Skeletal toxicity with isotretinoin therapy: a clinico-radiological evaluation. *Br J Dermatol* 1988; **119**: 609–14.
24 Novick NL, Lawson W, Schwartz IS. Bilateral nasal bone osteophytosis associated with short-term oral isotretinoin therapy for cystic acne vulgaris. *Am J Med* 1984; **77**: 736–9.
25 Taylor AEM, Mitchison H. Fatty liver following isotretinoin. *Br J Dermatol* 1991; **124**: 505–6.
26 Johnson TM, Rainin R. Isotretinoin-induced thrombocytopenia. *J Am Acad Dermatol* 1987; **17**: 838–9.
27 Nigra TP, Katz RA, Jorgensen H. Elevation of serum triglyceride levels from oral 13-*cis*-retinoic acid. In: Orfanos CE, Braun-Falco O, Farber EM *et al.*, eds. *Retinoids. Advances in Basic Research and Therapy*. Berlin: Springer, 1981: 363–9.
28 Lyons F, Laker MF, Marsden JR *et al.* Effect of oral 13-*cis*-retinoic acid on serum lipids. *Br J Dermatol* 1982; **107**: 591–5.
29 Zech LA, Gross EG, Peck GL, Brewer HB. Changes in plasma cholesterol and triglyceride levels after treatment with oral isotretinoin. A prospective study. *Arch Dermatol* 1983; **119**: 987–93.
30 Bershad S, Rubinstein A, Paterniti JR Jr *et al.* Changes in plasma lipids and lipoproteins during isotretinoin therapy for acne. *N Engl J Med* 1985; **313**: 981–5.
31 Gollnick H, Schwartzkopff W, Pröschle W *et al.* Retinoids and blood lipids: an update and review. In: Saurat JH, ed. *Retinoids: New Trends in Research and Therapy*. Basel: Karger, 1985: 445–60.
32 Marsden J. Hyperlipidaemia due to isotretinoin and etretinate: possible mechanisms and consequences. *Br J Dermatol* 1986; **114**: 401–7.
33 Dicken CH, Connolly SM. Eruptive xanthomas associated with isotretinoin (13-*cis*-retinoic acid). *Arch Dermatol* 1980; **16**: 951–2.

Effects on mood. The issue of whether isotretinoin may be associated with initiation or exacerbation of depression is a particular matter of controversy [1,2]. Anecdotal reports suggested this possibility; resolution usually, but not always [3], occurs within a few weeks of cessation of therapy. Psychiatric symptoms occurred in seven of 700 patients in one study, with recurrence of depression following rechallenge in some cases [4]. Of 5 million individuals exposed to isotretinoin in the USA between 1982 and 2000, 37 patients committed suicide, 100 were hospitalized for treatment of depression and 284 were managed as out-patients [5]. This incidence of suicide is less than that predicted for a group of comparable age and sex distribution. A large study comparing 7195 patients treated with isotretinoin with 13 700 patients treated with antibiotics, drawn from Canadian and UK databases, concluded that there was no increase in depression or suicide in the isotretinoin-treated group [6]. However, the study has been criticized as flawed with regard to the UK data, because it was provided by general practitioners who were not responsible for prescribing the drug, and there may have been selection bias in the ascertainment of mental disorders. A study of 2821 patients found no evidence to support an association between use of isotretinoin and onset of depression [7]. The field is complicated by the fact that there may be a confounding effect of acne on the development of psychological or psychiatric effects [8,9]. In addition, there is an increased frequency of pretreatment anxiety in patients and their families [5]. Conversely, isotretinoin therapy may lead to an improvement in mental state in some patients [8–11]. The majority of recent surveys have failed to show any increase in depression in isotretinoin-treated patients [10–13]. However, a single report has documented a slight increase in the risk of depression [14].

References

1 Ellis CN, Krach KJ. Uses and complications of isotretinoin therapy. *J Am Acad Dermatol* 2001; **45** (Suppl.): S150–S157.
2 O'Connell KA, Wilkin JK, Pitts M. Isotretinoin (Accutane) and serious psychiatric adverse events. *J Am Acad Dermatol* 2003; **48**: 306–8.
3 Gatti S, Serri F. Acute depression from isotretinoin. *J Am Acad Dermatol* 1991; **25**: 132.
4 Scheinman PL, Peck GL, Rubinow DR *et al.* Acute depression from isotretinoin. *J Am Acad Dermatol* 1990; **23**: 1112–4.
5 Wysowski DK, Pitts M, Beitz J. An analysis of reports of depression and suicide in patients treated with isotretinoin. *J Am Acad Dermatol* 2001; **45**: 515–9.
6 Jick SS, Kremers HM, Vasilakis-Scaramozza C. Isotretinoin use and risk of depression, psychotic symptoms, suicide and attempted suicide. *Arch Dermatol* 2000; **136**: 1231–6.
7 Hersom K, Neary MP, Levaux HP *et al.* Isotretinoin and antidepressant pharmacotherapy: a prescription sequence symmetry analysis. *J Am Acad Dermatol* 2003; **49**: 424–32.
8 Rubinow DR, Peck GL, Sqillace KM, Gantt GG. Reduced anxiety and depression in cystic acne patients after successful treatment with oral isotretinoin. *J Am Acad Dermatol* 1987; **17**: 25–32.
9 Kellett SC, Gawkrodger DJ. The psychological and emotional impact of acne and the effect of treatment with isotretinoin. *Br J Dermatol* 1999; **140**: 273–82.

10 Chia CY, Lane W, Chibnall J *et al*. Isotretinoin therapy and mood changes in adolescents with moderate to severe acne: a cohort study. *Arch Dermatol* 2005; **141**: 557–60.
11 Marqueling AL, Zane LT. Depression and suicidal behavior in acne patients treated with isotretinoin: a systematic review. *Semin Cutan Med Surg* 2007; **26**: 210–20.
12 Kaymak Y, Kalay M, Ilter N, Taner E. Incidence of depression related to isotretinoin treatment in 100 acne vulgaris patients. *Psychol Rep* 2006; **99**: 897–906.
13 Cohen J, Adams S, Patten S. No association found between patients receiving isotretinoin for acne and the development of depression in a Canadian prospective cohort. *Can J Clin Pharmacol* 2007; **14**: e227–33.
14 Azoulay L, Blais L, Koren G *et al*. Isotretinoin and the risk of depression in patients with acne vulgaris: a case-crossover study. *J Clin Psychiatry* 2008; **69**: 526–32.

Effects on pregnancy. Major human fetal abnormalities related to isotretinoin therapy during pregnancy have been documented [1–4]. The most frequently reported abnormalities involve the central nervous system (microcephaly or hydrocephalus and cerebellar malformation) and cardiovascular system (anomalies of the great vessels). Microtia or absence of external ears, microphthalmia, facial dysmorphia and thymus gland abnormalities have also been reported. There is an increased risk of spontaneous abortion. Women of child-bearing potential should sign a consent form and be instructed that they should not be pregnant when isotretinoin therapy is started (preferably on the second or third day of the next normal menstrual period) and should use effective contraception (two methods, one of which should be a barrier method) during, and for 1 month after stopping, therapy. The guidelines state that women of child-bearing age should be monitored monthly with screening pregnancy tests whilst on treatment and a month after stopping the drug. Isotretinoin has a much shorter half-life than etretinate, so that pregnancy is permissible 1 month after stopping therapy. Unfortunately, despite the guidelines, women continue to become pregnant whilst on the drug [5,6]. In one recent series, of 53 pregnant women exposed to isotretinoin, only 41% reported using any birth control, and only one patient used two methods; 45% of exposed pregnancies were terminated before delivery, and 22% delivered a healthy child; two babies were born with malformations [6]. Analysis of data voluntarily reported to Hoffmann La Roche Inc. in the USA enabled prospective study of 88 patients who had completed or discontinued isotretinoin therapy prior to becoming pregnant; 90% of all pregnancies occurred within 2 months after cessation of therapy, and 64% within 1 month [7]. There were no significant increases in the rates of spontaneous abortion or of congenital malformations among the live births. There appears to be no adverse effect of isotretinoin on male reproductive function [8,9].

References

1 Ellis Hill RM. Isotretinoin teratogenicity. *Lancet* 1984; **i**: 1465.
2 Stern RS, Rosa F, Baum C. Isotretinoin and pregnancy. *J Am Acad Dermatol* 1984; **10**: 851–4.
3 Chen DT. Human pregnancy experience with the retinoids. In: Saurat JH, ed. *Retinoids: New Trends in Research and Therapy.* Basel: Karger, 1985: 398–406.
4 Rosa FW, Wilk AL, Kelsey FO. Teratogen update: vitamin A cogeners, the outcome of pregnancies in patients who had taken isotretinoin. *Teratology* 1986; **33**: 355–64.
5 Robertson J, Polifka JE, Avner M *et al.* A survey of pregnant women using isotretinoin. *Birth Defects Res A Clin Mol Teratol* 2005; **73**: 881–7.
6 Garcia-Bournissen F, Tsur L, Goldstein LH *et al*. Fetal exposure to isotretinoin—an international problem. *Reprod Toxicol* 2008; **25**: 124–8.
7 Dai WS, Hsu M-A, Itri L. Safety of pregnancy after discontinuation of isotretinoin. *Arch Dermatol* 1989; **125**: 362–5.
8 Schill W-B, Wagner A, Nikolowski J, Plewig G. Aromatic retinoid and 13-*cis*-retinoic acid: spermatological investigations. In: Orfanos CE, Braun-Falco O, Farber EM *et al*., eds. *Retinoids. Advances in Basic Research and Therapy.* Berlin: Springer, 1981: 389–95.
9 Töröck L, Kása M. Spermatological and endocrinological examinations connected with isotretinoin treatment. In: Saurat JH, ed. *Retinoids: New Trends in Research and Therapy.* Basel: Karger, 1985: 407–10.

Tazarotene

Pyogenic granuloma-like lesions have been associated with the use of this topical retinoid in the treatment of psoriasis [1,2].

Tretinoin

Oral tretinoin administered as differentiation therapy of acute promyelocytic leukaemia was associated with mild rashes, the nature of which was unspecified [3]. An acute neutrophilic dermatosis with a myeloblastic infiltrate occurred in a leukaemic patient receiving all-*trans*-retinoic acid therapy [4].

References

1 Dawkins MA, Clark AR, Feldman SR. Pyogenic granuloma-like lesion associated with topical tazarotene therapy. *J Am Acad Dermatol* 2000; **43**: 154–5.
2 Pierson JC, Owens NM. Pyogenic granuloma-like lesions associated with topical retinoid therapy. *J Am Acad Dermatol* 2001; **45**: 967–8.
3 Warrell RP, Frankel SR, Miller WH *et al.* Differentiation therapy of acute promyelocytic leukemia with tretinoin (all-*trans*-retinoic acid). *N Engl J Med* 1991; **324**: 1385–93.
4 Piette WW, Trapp JF, O'Donnell MJ *et al.* Acute neutrophilic dermatosis with myeloblastic infiltrate in a leukemia patient receiving all-*trans*-retinoic acid therapy. *J Am Acad Dermatol* 1994; **30**: 293–7.

Vitamin B

Vitamin B_1

Anaphylaxis following intravenous administration has occurred [1].

Vitamin B_6 (pyridoxine)

Vasculitis is recorded [2], as is a pseudoporphyria syndrome with megadosage [3]. A photosensitive eruption [4] and rosacea fulminans (with concommitant vitamin B12 therapy) are documented [5].

Nicotinic acid

Flushing is common; other transient rashes, urticaria, pruritus, scaling, hyperpigmentation and an acanthosis nigricans-like eruption [6,7] are all documented. Persistent rashes and hair loss have rarely occurred.

References

1 Kolz R, Lonsdorf G, Burg G. Unverträglichkeitsreaktionen nach parenteraler Gabe von Vitamin B_1. *Hautarzt* 1980; **31**: 657–9.
2 Ruzicka T, Ring J, Braun-Falco O. Vasculitis allergica durch Vitamin B_6. *Hautarzt* 1984; **35**: 197–9.
3 Baer R, Stilman MA. Cutaneous skin changes probably due to pyridoxine abuse. *J Am Acad Dermatol* 1984; **10**: 527–8.
4 Murata Y, Kumano K, Ueda T *et al.* Photosensitive dermatitis caused by pyridoxine hydrochloride. *J Am Acad Dermatol* 1998; **39**: 314–7.
5 Jansen T, Romiti R, Kreuter A, Altmeyer P. Rosacea fulminans triggered by high-dose vitamins B6 and B12. *J Eur Acad Dermatol Venereol* 2001; **15**: 484–5.

6 Tromovitch TA, Jacobs PH, Kern S. Acanthosis nigricans-like lesions from nicotinic acid. *Arch Dermatol* 1964; **89**: 222–3.
7 Elgart ML. Acanthosis nigricans and nicotinic acid. *J Am Acad Dermatol* 1981; **5**: 709–10.

Vitamin C (ascorbic acid)

Patients with cutaneous and respiratory allergy have been described.

Vitamin E (α-tocopherol)

White hair developed at injection sites in infants given intramuscular vitamin E for epidermolysis bullosa, probably due to quinones formed during vitamin E degradation [1].

Reference

1 Sehgal VN. Vitamin E: a melanotoxic agent. A preliminary report. *Dermatologica* 1972; **145**: 56–9.

Vitamin K

Skin reactions with vitamin K have been reviewed [1–11]. Three distinct types of cutaneous reaction are seen: (i) localized eczematous at the injection site (onset 4–16 days, dose range 10–410 mg); (ii) localized morphoea-form (average onset 8.5 months, range 5 weeks to 1.5 years, dose range 30–2080 mg); and (iii) very rarely, a diffuse maculopapular eruption [10,11]. The pruritic, erythematous, macular lesions or plaques may last for up to 6 months, whereas the prognosis for resolution of the morphoea-form changes is very poor. Patch and intradermal skin tests may be positive, suggesting an immunological basis. Most, but not all [3,6,8], cases have occurred in patients with liver disease. In addition, a proportion of these reactions progress to produce scleroderma-like changes [9,12–16]. An annular erythema has been documented [17].

References

1 Barnes HM, Sarkany I. Adverse skin reactions from vitamin K_1. *Br J Dermatol* 1976; **95**: 653–6.
2 Bullen AW, Miller JP, Cunliffe WJ, Losowsky MS. Skin reactions caused by vitamin K in patients with liver disease. *Br J Dermatol* 1978; **98**: 561–5.
3 Sanders MN, Winkelmann RK. Cutaneous reactions to vitamin K. *J Am Acad Dermatol* 1988; **19**: 699–704.
4 Mosser C, Janin-Mercier A, Souteyrand P. Les réactions cutanées apres administration parentérale de vitamine K. *Ann Dermatol Vénéréol* 1987; **114**: 243–51.
5 Finkelstein H, Champion MC, Adam JE. Cutaneous hypersensitivity to vitamin K_1 injection. *J Am Acad Dermatol* 1987; **16**: 540–5.
6 Joyce JP, Hood AF, Weiss MM. Persistent cutaneous reaction to intramuscular vitamin K injection. *Arch Dermatol* 1988; **124**: 27–8.
7 Tuppal R, Tremaine R. Cutaneous eruption from vitamin K_1 injection. *J Am Acad Dermatol* 1992; **27**: 105–6.
8 Lee MM, Gellis S, Dover JS. Eczematous plaques in a patient with liver failure. Fat-soluble vitamin K hypersensitivity. *Arch Dermatol* 1992; **128**: 257, 260.
9 Lemlich G, Green M, Phelps R *et al.* Cutaneous reactions to vitamin K_1 injections. *J Am Acad Dermatol* 1993; **28**: 345–7.
10 Wong DA, Freeman S. Cutaneous allergic reaction to intramuscular vitamin K1. *Australas J Dermatol* 1999; **40**: 147–52.
11 Wilkins K, DeKoven J, Assaad D. Cutaneous reactions associated with vitamin K1. *J Cutan Med Surg* 2000; **4**: 164–8.
12 Texier L, Gendre PH, Gauthier O *et al.* Hypodermites sclérodermiformes lombofessières induites par des injections médicamenteuses intramusculaires associées a la vitamine K_1. *Ann Dermatol Syphiligr* 1972; **99**: 363–71.
13 Janin-Mercier A, Mosser C, Souteyrand P, Bourges M. Subcutaneous sclerosis with fasciitis and eosinophilia after phytonadione injections. *Arch Dermatol* 1985; **121**: 1421–3.
14 Brunskill NJ, Berth-Jones J, Graham-Brown RAC. Pseudosclerodermatous reaction to phytomenadione injection (Texier's syndrome). *Clin Exp Dermatol* 1988; **13**: 276–8.
15 Pujol RM, Puig L, Moreno A *et al.* Pseudoscleroderma secondary to phytonadione (vitamin K1) injections. *Cutis* 1989; **43**: 365–8.
16 Guidetti MS, Vincenzi C, Papi M, Tosti A. Sclerodermatous skin reaction after vitamin K1 injections. *Contact Dermatitis* 1994; **31**: 45–6.
17 Kay MH, Duvic M. Reactive annular erythema after intramuscular vitamin K. *Cutis* 1986; **37**: 445–8.

Hormones and related compounds

ACTH and systemic corticosteroids

The side effects of these agents have been reviewed [1–13]. Well-known side effects include acne, cutaneous thinning and atrophy, telangiectasia, striae distensae, purpura and ecchymoses, hypertrichosis, impaired wound healing, pigmentary changes, cushingoid (moon) facies, truncal adiposity [14] and buffalo hump of the upper back. Acne occurred in one of 51 patients treated with intravenous corticosteroids in one study [15]. Other systemic side effects include fluid and electrolyte abnormalities, weight gain, oedema, hypertension, cardiac failure, peptic ulcer disease, pancreatitis, diabetes, muscular weakness, myopathy, tendon rupture, glaucoma, posterior subcapsular cataracts, mental changes including psychosis, osteoporosis, vertebral collapse, necrosis of the femoral head, growth suppression in children, opportunistic infection, masking of infection or reactivation of a dormant infection (e.g. tuberculosis), polycythaemia and suppression of the hypothalamic–pituitary axis. Pulse steroid therapy with systemic methylprednisolone has resulted in sudden death due to anaphylaxis, arrhythmia or ischaemic heart disease, but not particularly in dermatological patients [16].

Adrenocorticotrophic hormone

Allergic reactions to ACTH are recorded but are uncommon. Urticaria and dizziness, nausea and weakness are the most frequent, but severe anaphylactic shock has occurred. Synthetic ACTH is usually tolerated by patients sensitive to animal ACTH [17]. Depot preparations containing tetracosactide (tetracosactrin) adsorbed on a zinc phosphate complex have produced reactions [18] and may induce melanoderma [19].

References

1 Lucky AW. Principles of the use of glucocorticosteroids in the growing child. *Pediatr Dermatol* 1984; **1**: 226–35.
2 Fritz KA, Weston WL. Systemic glucocorticosteroid therapy of skin disease in children. *Pediatr Dermatol* 1984; **1**: 236–45.
3 Davis GF. Adverse effects of corticosteroids. II. Systemic. *Clin Dermatol* 1986; **4**: 161–9.
4 Gallant C, Kenny P. Oral glucocorticoids and their complications. A review. *J Am Acad Dermatol* 1986; **14**: 161–77.
5 Seale PS, Compton MR. Side-effects of corticosteroid agents. *Med J Aust* 1986; **144**: 139–42.
6 Chosidow O, Étienne SD, Herson S, Puech AJ. Pharmacologie des corticoides. Notions classiques et nouvelles. *Ann Dermatol Vénéréol* 1989; **116**: 147–66.
7 Fine R. Glucocorticoids (1989). *Int J Dermatol* 1990; **29**: 377–9.
8 Kyle V, Hazleman BL. Treatment of polymyalgia rheumatica and giant cell arteritis. II. Relation between steroid dose and steroid associated side effects. *Ann Rheum Dis* 1989; **48**: 662–6.
9 Truhan AP, Ahmed AR. Corticosteroids: a review with emphasis on complications of prolonged systemic therapy. *Ann Allergy* 1989; **62**: 375–90.

10 Weiss MM. Corticosteroids in rheumatoid arthritis. *Semin Arthritis Rheum* 1989; **19**: 9–21.
11 Rasanen L, Hasan T. Allergy to systemic and intralesional corticosteroids. *Br J Dermatol* 1993; **128**: 407–11.
12 Dooms-Goossens A. Sensitisation to corticosteroids. Consequences for anti-inflammatory therapy. *Drug Saf* 1995; **13**: 123–9.
13 Imam AP, Halpern GM. Uses, adverse effects of abuse of corticosteroids. Part II. *Allergol Immunopathol* 1995; **23**: 2–15.
14 Horber HH, Xurcher RM, Herren H *et al*. Altered body fat distribution in patients with glucocorticoid treatment and in patients on long-term dialysis. *Am J Clin Nutr* 1986; **43**: 758–69.
15 Fung MA, Berger TG. A prospective study of acute-onset steroid acne associated with administration of intravenous corticosteroids. *Dermatology* 2000; **200**: 43–4.
16 White KP, Driscoll MS, Rothe MJ, Grant-Kels JM. Severe adverse cardiovascular effects of pulse steroid therapy: is continuous cardiac monitoring necessary? *J Am Acad Dermatol* 1994; **30**: 768–73.
17 Patriarca G. Allergy to tetracosactrin-depot. *Lancet* 1971; **i**: 138.
18 Clee MD, Ferguson J, Browning MCK *et al*. Glucocorticoid hypersensitivity in an asthmatic patient: presentation and treatment. *Thorax* 1985; **40**: 477–8.
19 Khan SA. Melanoderma caused by depot tetracosactrin. *Trans St John's Hosp Dermatol Soc* 1970; **56**: 168–71.

Systemic corticosteroids

In addition to those listed above, the cutaneous side effects of systemic corticosteroids include allergic and immediate reactions [1,2]. In one study, seven of 25 patients with cutaneous delayed-type hypersensitivity to hydrocortisone had an immediate reaction following intradermal injection of hydrocortisone sodium succinate, and had significantly increased levels of IgG antibodies to hydrocortisone. These patients are at risk of developing type III and possibly type I reactions following systemic hydrocortisone [3].

Protein binding of hydrocortisone or a degradation product may be important in the development of corticosteroid allergy [4]. Urticarial reactions have followed the intra-arterial injection of prednisone, prednisolone, hydrocortisone [5] or methylprednisolone [6], but are rare. Anaphylaxis occurred after intradermal injection of triamcinolone for alopecia areata [7]. Anaphylactoid reactions have been reported to topical and parenteral hydrocortisone, but may represent pseudoallergic reactions rather than IgE-mediated immediate hypersensitivity [8,9].

Generalized skin reactions, including urticaria and maculopapular eruptions, developed in patients after therapy with oral triamcinolone acetonide [10], prednisone [11], or dexamethasone and betamethasone [12]; the patients were subsequently shown to be patch-test positive to these corticosteroids. In another study, five patients reacted with diffuse erythema principally on the trunk or on the face, appearing within a few hours to 24 h and fading in 1–3 days, on treatment with systemic or intralesional hydrocortisone, methylprednisolone, prednisolone or betamethasone [2]. On patch testing, one patient reacted to prednisolone and methylprednisolone and two patients were positive to pivalone. Patients sensitive to hydrocortisone or methylprednisolone reacted to these corticosteroids in intradermal tests. A combination of intradermal and patch tests is recommended when allergy to systemic or intralesional corticosteroids is suspected [2].

Other cases of generalized, delayed systemic corticosteroid reactions, including eczematous or exanthematous eruptions and erythroderma, with or without bullae or purpura, often with positive patch or intradermal testing, have been recorded [13–18]. Systemic administration of hydrocortisone, and provocation of endogenous cortisol secretion by injection of the ACTH analogue tetracosactide, provoked dose-dependent allergic skin reactions at sites of previous allergic reactions to topical steroids in two patients with proven topical corticosteroid sensitivity (i.e. systemic allergic contact-type dermatitis); in one case, this was at a positive patch-test site to hydrocortisone 17-butyrate [19]. Thus, it has been postulated that high stress levels, which cause increased secretion of endogenous adrenocortical hormones, could be implicated in exacerbations of eczema in corticosteroid-sensitive patients, and a persistent autoimmune skin reaction to cortisol might occur following topical sensitization to topical hydrocortisone [19]. The fact that, in steroid-sensitive patients, systemic provocation testing with hydrocortisone results in a reaction confined to the skin may be partly explained by the observation *in vitro* that only enriched Langerhans' cells, and not peripheral blood mononuclear antigen-presenting cells, are capable of presenting corticosteroid to T cells of corticosteroid-sensitive subjects [20].

Perioral dermatitis has been recorded in renal transplant recipients on corticosteroids and immunosuppressive therapy [21]. Panniculitis following short-term high-dose steroid therapy in children manifests as subcutaneous nodules on the cheeks, arms and trunk [22]. Reversible panniculitis occurred in a child treated with steroids for hepatic encephalopathy [23]. Juxta-articular adiposis dolorosa developed in a patient treated with high doses of prednisone for the L-tryptophan-induced eosinophilia myalgia syndrome [24]. Acanthosis nigricans may occur with corticosteroid therapy [25]. Immunosuppression with corticosteroids has been associated with the development of Kaposi's sarcoma during the treatment of temporal arteritis [26].

Inhaled corticosteroids have been associated with purpura and dermal thinning [27] as well as acne [28,29], perioral dermatitis and tongue hypertrophy [30], allergic reactions [31], an eczematous dermatitis [32] and adrenal suppression [29]. Nasal corticosteroids may cause nasal congestion, pruritus, burning and perforation of the septum, urticaria and eczema of the face [33]. Intralesional corticosteroid injection may also lead to allergic reactions [34], including a disseminated morbilliform and persistent urticarial dermatitis following intra-articular triamcinolone acetonide [35], erythroderma following intradermal budesonide [36] and erythema multiforme after intradural injection of prednisolone acetate [37]. Facial flushing and/or generalized erythema has followed epidural steroid injection [38]. Anaphylactic shock has been recorded after intra-articular injections of corticosteroids containing carboxymethylcellulose, benzylic acid, polysorbate 80 and merthiolate; skin tests to carboxymethylcellulose were positive [39].

References

1 Preuss L. Allergic reactions to systemic glucocorticoids: a review. *Ann Allergy* 1985; **55**: 772–5.
2 Rasanen L, Hasan T. Allergy to systemic and intralesional corticosteroids. *Br J Dermatol* 1993; **128**: 407–11.
3 Wilkinson SM, Mattey DL, Beck MH. IgG antibodies and early intradermal reactions to hydrocortisone in patients with cutaneous delayed-type hypersensitivity to hydrocortisone. *Br J Dermatol* 1994; **131**: 495–8.
4 Wilkinson SM, English JS, Mattey DL. *In vitro* evidence of delayed-type hypersensitivity to hydrocortisone. *Contact Dermatitis* 1993; **29**: 241–5.

5 Ashford RF, Bailey A. Angioneurotic oedema and urticaria following hydrocortisone: a further case. *Postgrad Med J* 1980; **56**: 437.
6 Pollock B, Wilkinson SM, MacDonald Hull SP. Chronic urticaria associated with intra-articular methylprednisolone. *Br J Dermatol* 2001; **144**: 1228–30.
7 Downs AMR, Lear JT, Kennedy CTC. Anaphylaxis to intradermal triamcinolone acetonide. *Arch Dermatol* 1998; **134**: 1163–4.
8 King RA. A severe anaphylactoid reaction to hydrocortisone. *Lancet* 1960; **ii**: 1093–4.
9 Peller JS, Bardana EL Jr. Anaphylactoid reaction to corticosteroid: case report and review of the literature. *Ann Allergy* 1985; **54**: 302–5.
10 Brambilla L, Boneschi V, Chiappino G *et al.* Allergic reactions to topical desoxymethasone and oral triamcinolone. *Contact Dermatitis* 1989; **21**: 272–3.
11 De Corres LF, Bernaola G, Urrutia I *et al.* Allergic dermatitis from systemic treatment with corticosteroids. *Contact Dermatitis* 1990; **22**: 104–5.
12 Maucher O, Faber M, Knipper H *et al.* Kortikoidallergie. *Hautarzt* 1987; **38**: 577–82.
13 Whitmore SE. Delayed systemic allergic reactions to corticosteroids. *Contact Dermatitis* 1995; **32**: 193–8.
14 Torres V, Tavares-Bello R, Melo H, Soares AP. Systemic contact dermatitis from hydrocortisone. *Contact Dermatitis* 1993; **29**: 106.
15 Vidal C, Tome S, Fernandex-Redondo V, Tato F. Systemic allergic reaction to corticosteroids. *Contact Dermatitis* 1994; **31**: 273–4.
16 Whitmore SE. Dexamethasone injection-induced generalised dermatitis. *Br J Dermatol* 1994; **131**: 296–7.
17 Fernandez de Corres L, Urrutia I, Audicana M *et al.* Erythroderma after intravenous injection of methylprednisolone. *Contact Dermatitis* 1991; **25**: 68–70.
18 Yawalkar N, Hari Y, Helbling A *et al.* Elevated serum levels of interleukins 5, 6, and 10 in a patient with drug-induced exanthem caused by systemic corticosteroids. *J Am Acad Dermatol* 1998; **39**: 790–3.
19 Lauerma AI, Reitamo S, Maibach HI. Systemic hydrocortisone/cortisol induces allergic skin reactions in presensitized subjects. *J Am Acad Dermatol* 1991; **24**: 182–5.
20 Lauerma AI, Räsänen L, Reunala T, Reitamo S. Langerhans cells but not monocytes are capable of antigen presentation *in vitro* in corticosteroid contact hypersensitivity. *Br J Dermatol* 1991; **123**: 699–705.
21 Adams SJ, Davison AM, Cunliffe WJ, Giles GR. Perioral dermatitis in renal transplant recipients maintained on corticosteroids and immunosuppressive therapy. *Br J Dermatol* 1982; **106**: 589–92.
22 Roenigk HH, Haserick JR, Arundell FD. Poststeroid panniculitis. *Arch Dermatol* 1964; **90**: 387–91.
23 Saxena AK, Nigam PK. Panniculitis following steroid therapy. *Cutis* 1988; **42**: 341–2.
24 Greenbaum SS, Varga J. Corticosteroid-induced juxta-articular adiposis dolorosa. *Arch Dermatol* 1991; **127**: 231–3.
25 Brown J, Winkelmann RK. Acanthosis nigricans: a study of 90 cases. *Medicine (Baltimore)* 1968; **47**: 33–51.
26 Leung F, Fam AG, Osoba D. Kaposi's sarcoma complicating corticosteroid therapy for temporal arteritis. *Am J Med* 1981; **71**: 320–2.
27 Capewell S, Reynolds S, Shuttleworth D *et al.* Purpura and dermal thinning associated with high-dose inhaled corticosteroids. *BMJ* 1990; **300**: 1548–51.
28 Monk B, Cunliffe WJ, Layton AM, Rhodes DJ. Acne induced by inhaled corticosteroids. *Clin Exp Dermatol* 1993; **18**: 148–50.
29 Bong JL, Connell JM, Lever R. Intranasal betamethasone induced acne and adrenal suppression. *Br J Dermatol* 2000; **142**: 579–80.
30 Dubus JC, Marguet C, Deschildre A *et al.* Local side-effects of inhaled corticosteroids in asthmatic children: influence of drug, dose, age, and device. *Allergy* 2001; **56**: 944–8.
31 Lauerma AH, Kiistala R, Makinen-Kiljunen S *et al.* Allergic skin reaction after inhalation of budesonide. *Clin Exp Allergy* 1993; **23**: 232–3.
32 Holmes P, Cowen P. Spongiotic (eczematous-type) dermatitis after inhaled budesonide. *Aust NZ J Med* 1992; **22**: 511.
33 Isaksson M. Skin reactions to inhaled corticosteroids. *Drug Saf* 2001; **24**: 369–73.
34 Saff DM, Taylor JS, Vidimos AT. Allergic reaction to intralesional triamcinolone acetonide: a case report. *Arch Dermatol* 1995; **131**: 742–3.
35 Ijsselmuiden OE, Knegt-Junk KJ, van Wijk RG, van Joost T. Cutaneous adverse reactions after intra-articular injection of triamcinolone acetonide. *Acta Derm Venereol (Stockh)* 1995; **75**: 57–8.
36 Wilkinson SM, Smith AG, English JS. Erythroderma following the intradermal injection of the corticosteroid budesonide. *Contact Dermatitis* 1992; **27**: 121–2.
37 Lavabre C, Chevalier X, Larget-Piet B. Erythema multiforme after intradural injection of prednisolone acetate. *Br J Rheumatol* 1992; **31**: 717–8.
38 DeSio JM, Kahn CH, Warfield CA. Facial flushing and/or generalized erythema after epidural steroid injection. *Anesth Analg* 1995; **80**: 617–9.
39 Beaudouin E, Kanny G, Gueant JL, Moneret-Vautrin DA. Anaphylaxie à la carboxymethylcellulose: à propos de deux cas de chocs à des corticoides injectables. *Allerg Immunol* 1992; **24**: 333–5.

Topical corticosteroids

The dermatological complications of topical corticosteroids have been reviewed [1–5]. Concerns have been expressed about the illegal availability of potent topical steroids in the UK, and their consequent unregulated use [6]. Many of the adverse reactions are related to the potency of the preparation; thus, in general, fluorinated steroids are associated with more significant side effects. Topical steroids cause decreased epidermal kinetic activity [7], decreased synthesis of dermal collagen types I and III and ground substance, and thinning of the dermis and epidermis [8–12]. Initial vasoconstriction of the superficial small vessels is followed by rebound vasodilatation, which becomes permanent in later stages. There are resultant striae, easy bruising, purpura, hypertrichosis and telangiectasia; stellate pseudoscars or ulcerated areas may be seen. Reversible hypopigmentation may develop. Local injection of a potent steroid may result in atrophy with telangiectasia, and localized lipoatrophy may occur. Perilymphatic atrophy is recorded following intradermal steroid injection. Long-term daily use of a potent steroid, especially under plastic occlusion as for fingertip eczema, may result in acroatrophy of terminal phalanges of the fingers [13,14].

Topical steroids may exacerbate acne, or lead to acne rosacea, with papules, pustules and telangiectasia, or perioral dermatitis, characterized by erythema, papules and pustules in the perioral area [15–17]. They decrease the number and antigen-presenting capacity of epidermal Langerhans' cells [18], and mask or potentiate skin infections, including fungal (tinea incognito) and bacterial infections and verruca vulgaris. They may delay wound healing. Their withdrawal may provoke conversion of plaque- to pustular-type psoriasis [19]. Topical steroid therapy around the eye has been associated with development of glaucoma.

Topical corticosteroids may induce allergic contact dermatitis [20–25]. The prevalence of positive patch tests to corticosteroids in contact dermatitis clinics ranges from 2 to 5%. The allergen may be the steroid itself, or a preservative or stabilizer such as ethylenediamine. There may be cross-reactivity between different steroids [20–22]. Cross-reactivity is more likely between steroids with similar substitutions at C-6 and C-9 positions. Intradermal tests may be a more sensitive means of detecting corticosteroid hypersensitivity than patch testing [23].

Systemic side effects of topical corticosteroids occur particularly from the use of large amounts of high-potency topical corticosteroids, especially under plastic occlusion [26,27]. Oedema due to sodium retention occurs more frequently with halogenated corticosteroids [27]. Hypothalamic–pituitary axis suppression may occur [28,29]; a single application of 25 g of 0.05% clobetasol propionate ointment suppressed plasma cortisol for 96 h [30]. Cushing's syndrome [31,32] may result, and growth retardation in

children is a hazard [33]. Glycosuria and hyperglycaemia may rarely occur [34].

References

1 Miller JA, Munro DD. Topical corticosteroids: clinical pharmacology and therapeutic use. *Drugs* 1980; **19**: 119–34.
2 Behrendt H, Korting HC. Klinische Prüfung von erwünschten und unerwünschten Wirkungen topisch applizierbarer Glukokortikosteroide am Menschen. *Hautarzt* 1990; **41**: 2–8.
3 Coskey RJ. Adverse effects of corticosteroids. I. Topical and intralesional. *Clin Dermatol* 1986; **4**: 155–60.
4 Kligman AM. Adverse effects of topical corticosteroids. In: Christophers E, Schöpf E, Kligman AM, Stoughton RB, eds. *Topical Corticosteroid Therapy: a Novel Approach to Safer Drugs*. New York: Raven Press, 1988: 181–7.
5 Hengge UR, Ruzicka T, Schwartz RA, Cork MJ. Adverse effects of topical glucocorticosteroids. *J Am Acad Dermatol* 2006; **54**: 1–15.
6 Keane FM, Munn SE, Taylor NF, du Vivier AW. Unregulated use of clobetasol propionate. *Br J Dermatol* 2001; **144**: 1095–6.
7 Marshall RC, Du Vivier RA. The effects on epidermal DNA synthesis of the butyrate esters of clobetasone and clobetasol, and the propionate ester of clobetasol. *Br J Dermatol* 1978; **98**: 355–9.
8 Smith JG, Wehr RF, Chalker DK. Corticosteroid-induced cutaneous atrophy and telangiectasia. *Arch Dermatol* 1976; **112**: 1115–7.
9 Winter GD, Burton JL. Experimentally induced steroid atrophy in the domestic pig and man. *Br J Dermatol* 1976; **94**: 107–9.
10 Lehmann P, Zheng P, Lacker RM, Kligman AM. Corticosteroid atrophy in human skin: a study by light, scanning and transmission electron microscopy. *J Invest Dermatol* 1983; **81**: 169–76.
11 Oikarinen A, Haapasaari KM, Sutinen M, Tasanen K. The molecular basis of glucocorticoid-induced skin atrophy: topical glucocorticoid apparently decreases both collagen synthesis and the corresponding collagen mRNA level in human skin *in vivo*. *Br J Dermatol* 1998; **139**: 1106–10.
12 Oishi Y, Fu ZW, Ohnuki Y *et al.* Molecular basis of the alteration in skin collagen metabolism in response to *in vivo* dexamethasone treatment: effects on the synthesis of collagen type I and III, collagenase, and tissue inhibitors of metalloproteinases. *Br J Dermatol* 2002; **147**: 859–68.
13 Requena L, Zamora E, Martin L. Acroatrophy secondary to long-standing applications of topical steroids. *Arch Dermatol* 1990; **126**: 1013–4.
14 Wolf R, Tur E, Brenner S. Corticosteroid-induced 'disappearing digit'. *J Am Acad Dermatol* 1990; **23**: 755–6.
15 Sneddon I. Perioral dermatitis. *Br J Dermatol* 1972; **87**: 430–2.
16 Cotterill JA. Perioral dermatitis. *Br J Dermatol* 1979; **101**: 259–62.
17 Edwards EK Jr, Edwards ED Sr. Perioral dermatitis secondary to the use of a corticosteroid ointment as moustache wax. *Int J Dermatol* 1987; **26**: 649.
18 Ashworth J, Booker J, Breathnach SM. Effect of topical corticosteroid therapy on Langerhans cell function in human skin. *Br J Dermatol* 1988; **118**: 457–69.
19 Boxley JD, Dawber RPR, Summerly R. Generalised pustular psoriasis on withdrawal of clobetasol propionate ointment. *BMJ* 1975; **2**: 225–6.
20 Lepoittevin JP, Drieghe J, Dooms-Goossens A. Studies in patients with corticosteroid contact allergy. Understanding cross-reactivity among different steroids. *Arch Dermatol* 1995; **131**: 31–7.
21 Wilkinson SM, Hollis S, Beck MH. Cross-reaction patterns in patients with allergic contact dermatitis from hydrocortisone. *Br J Dermatol* 1995; **132**: 766–71.
22 Wilkinson M, Hollis S, Beck M. Reactions to other corticosteroids in patients with positive patch test reactions to budesonide. *J Am Acad Dermatol* 1995; **33**: 963–8.
23 Wilkinson SM, Heagerty AHM, English JSC. A prospective study into the value of patch and intradermal tests in identifying topical corticosteroid allergy. *Br J Dermatol* 1992; **127**: 22–5.
24 Sommer S, Wilkinson SM, English JSC *et al.* Type-IV hypersensitivity to betamethasone valerate and clobetasol propionate: results of a multicentre study. *Br J Dermatol* 2002; **147**: 266–9.
25 Scheuer E, Warshaw E. Allergy to corticosteroids: update and review of epidemiology, clinical characteristics, and structural cross-reactivity. *Am J Contact Dermat* 2003; **14**: 179–87.
26 Vickers CFH, Fritsch WC. A hazard of plastic film therapy. *Arch Dermatol* 1963; **87**: 633–5.
27 Fitzpatrick TB, Griswold MC, Hicks JH. Sodium retention and edema from percutaneous absorption of fluorcortisone acetate. *JAMA* 1955; **158**: 1149–52.
28 Carruthers JA, August PJ, Staughton RCD. Observations on the systemic effect of topical clobetasol propionate (Dermovate). *BMJ* 1975; **4**: 203–4.
29 Weston WL, Fennessey PV, Morelli J *et al.* Comparison of hypothalamus–pituitary–adrenal axis suppression from superpotent topical steroids by standard endocrine function testing and gas chromatographic mass spectrometry. *J Invest Dermatol* 1988; **90**: 532–5.
30 Hehir M, du Vivier A, Eilon L *et al.* Investigation of the pharmacokinetics of clobetasol propionate and clobetasone butyrate after a single application of ointment. *Clin Exp Dermatol* 1983; **8**: 143–51.
31 May P, Stein ES, Ryler RJ *et al.* Cushing syndrome from percutaneous absorption of triamcinolone cream. *Arch Intern Med* 1976; **136**: 612–3.
32 Himathongkam T, Dasanabhairochana P, Pitchayayothin N, Sriphrapradang A. Florid Cushing's syndrome and hirsutism induced by desoximetasone. *JAMA* 1978; **239**: 430–1.
33 Bode HH. Dwarfism following long-term topical corticosteroid therapy. *JAMA* 1980; **244**: 813–4.
34 Gomez EC, Frost P. Induction of glycosuria and hyperglycemia by topical corticosteroid therapy. *Arch Dermatol* 1976; **112**: 1559–62.

Sex hormones

Gonadotrophins

These drugs may cause allergic reactions [1]. Menotrophin (Pergonal) has been associated with localized keratosis follicularis (Darier's disease) [2]. Intracutaneous administration of two human menopausal gonadotrophin preparations (Organon and Pergonal) caused local induration and erythema [3].

References

1 Dore PC, Rice C, Killick S. Human gonadotrophin preparations may cause allergic reaction. *BMJ* 1994; **308**: 1509.
2 Telang GH, Atillasoy E, Stierstorfer M. Localized keratosis follicularis associated with menotropin treatment and pregnancy. *J Am Acad Dermatol* 1994; **30**: 271–2.
3 Odink J, Zuiderwijk PB, Schoen ED, Gan RA. A prospective, double-blind, split-subject study on local skin reactions after administration of human menopausal gonadotrophin preparations to healthy female volunteers. *Hum Reprod* 1995; **10**: 1045–7.

Gonadorelin analogues

Buserelin. A pigmented roseola-like eruption has been documented [1].

Leuprorelin. This drug, given for precocious puberty, has caused anaphylaxis [2], rashes [3] and local reactions [4].

References

1 Kono T, Ishii M, Taniguchi S. Intranasal buserelin acetate-induced pigmented roseola-like eruption. *Br J Dermatol* 2000; **143**: 658–9.
2 Taylor JD. Anaphylactic reaction to LHRH analogue, leuprorelin. *Med J Aust* 1994; **161**: 455.
3 Carel JC, Lahlou N, Guazzarotti L *et al.* Treatment of central precocious puberty with depot leuprorelin. French Leuprorelin Trial Group. *Eur J Endocrinol* 1995; **132**: 699–704.
4 Manasco PK, Pescovitz OH, Blizzard RM. Local reactions to depot leuprolide therapy for central precocious puberty. *J Pediatr* 1993; **123**: 334–5.

Oestrogens and related compounds

Oestrogens. Spider naevi and melanocytic naevi may develop under oestrogen therapy, as may chloasma. Severe premenstrual exacerbation of papulovesicular eruptions, urticaria, eczema or generalized pruritus occurred in seven women; several had a positive delayed tuberculin-type skin test to oestrogen [1]. Patients

with generalized chronic urticaria had an urticarial reaction to intradermal oestrogens. Elimination of oral oestrogen therapy or antioestrogen therapy with tamoxifen proved effective. In another patient, a premenstrual urticarial reaction was exacerbated by oestrogen; oophorectomy cured the eruption [2]. A bullous autoimmune oestrogen dermatitis has been delineated [3].

Diethylstilbestrol therapy of pregnant women has been associated with female and male genital tract abnormalities in the offspring. Diethylstilbestrol is a transplacental carcinogen and has caused adenocarcinoma of the vagina 20 years later in young women whose mothers took the drug in the first 18 weeks of pregnancy [4–6]. Acanthosis nigricans has resulted from use of diethylstilbestrol [7]. Hyperkeratosis of the nipples developed in a man treated for adenocarcinoma of the prostate with diethylstilbestrol [8]. Porphyria cutanea tarda may also be precipitated [9,10].

References

1 Shelley WB, Shelley ED, Talanin NY, Santoso-Pham J. Estrogen dermatitis. *J Am Acad Dermatol* 1995; **32**: 25–31.
2 Mayou SC, Charles-Holmes R, Kenney A *et al*. A premenstrual urticarial eruption treated with bilateral oophorectomy and hysterectomy. *Clin Exp Dermatol* 1988; **13**: 114–6.
3 Mutasim DF, Baumbach JL. Bullous autoimmune estrogen dermatitis. *J Am Acad Dermatol* 2003; **49**: 130–1.
4 Monaghan JM, Sirisena LAW. Stilboestrol and vaginal clear-cell adenocarcinoma syndrome. *BMJ* 1978; **i**: 1588–90.
5 Wingfield M. The daughters of stilboestrol. Grown up now but still at risk. *BMJ* 1991; **302**: 1414–5.
6 Anonymous. Diethylstilboestrol: effects of exposure *in utero*. *Drug Ther Bull* 1991; **29**: 49–50.
7 Banuchi SR, Cohen L, Lorincz AL, Morgan J. Acanthosis nigricans following diethylstilbestrol therapy. *Arch Dermatol* 1974; **109**: 544–6.
8 Mold DE, Jegasothy BV. Estrogen-induced hyperkeratosis of the nipple. *Cutis* 1980; **26**: 95–6.
9 Becker FT. Porphyria cutanea tarda induced by estrogens. *Arch Dermatol* 1965; **92**: 252–6.
10 Roenigk HH, Gottlob ME. Estrogen-induced porphyria cutanea tarda. *Arch Dermatol* 1970; **102**: 260–6.

Oral contraceptives. Cutaneous complications of oral contraceptives have been reviewed [1–4]. These drugs combine an oestrogen with a progestogen. Candidiasis is common; the sexual partner may suffer penile irritation after coitus without physical signs of frank candidal balanoposthitis. Genital warts may increase. Facial hyperpigmentation (chloasma) is well recognized [5,6], as are hirsutism and acne. Gingival epithelial melanosis has been recorded [7]. Alopecia related to contraceptive therapy may be of either androgenic or postpartum telogen pattern following withdrawal of the drug. Erythema nodosum is a well-recognized but rare complication [8,9].

The relapse of herpes gestationis is well documented [10]. Rare lichenoid, eczematous and fixed eruptions have been described, as have a lymphocytic cutaneous vasculitis and an eruption resembling Sweet's syndrome [11]. Oral contraceptives have been implicated in both the provocation [12] and induction of remission of pityriasis lichenoides. An SLE-like reaction has also been reported [13]. An oral contraceptive-induced LE-like eruption, with erythematous lesions on the palms and feet in association with a weakly positive antinuclear factor and C1q deposition at the dermal–epidermal junction on direct immunofluorescence, developed in a patient. It resolved on cessation of medication [14].

The jaundice rarely induced by these drugs resembles cholestatic jaundice of pregnancy. The hepatotoxic effects may result in provocation of variegate porphyria, porphyria cutanea tarda [15,16] and hereditary coproporphyria [17]; onycholysis may occur [16]. Photosensitivity unrelated to porphyrin disturbances has also been reported [18,19]. Benign hepatomas may also be a hazard [20].

Other hormonal contraceptives. Keloid formation has followed levonorgestrel implantion [21]. Vaginal erythematous areas were associated with use of a levonorgestrel-releasing contraceptive ring in 48 of 139 subjects [22]. Rosacea has been associated with a progesterone-releasing intrauterine contraceptive device [23].

Hormone replacement therapy. Melasma of the arms is recorded [24–26].

References

1 Baker H. Drug reactions VIII. Adverse cutaneous reaction to oral contraceptives. *Br J Dermatol* 1969; **81**: 946–9.
2 Jelinek JE. Cutaneous complications of oral contraceptives. *Arch Dermatol* 1970; **101**: 181–6.
3 Coskey RJ. Eruptions due to oral contraceptives. *Arch Dermatol* 1977; **113**: 333–4.
4 Girard M. Évaluation des risques cutanés de la pilule. *Ann Dermatol Vénéréol* 1990; **117**: 436–40.
5 Resnik S. Melasma induced by oral contraceptive drugs. *JAMA* 1967; **199**: 601.
6 Smith AG, Shuster S, Thody AJ *et al*. Chloasma, oral contraceptives, and plasma immunoreactive beta melanocyte-stimulating hormone. *J Invest Dermatol* 1977; **68**: 169–70.
7 Hertz RS, Beckstead PC, Brown WJ. Epithelial melanosis of the gingiva possibly resulting from the use of oral contraceptives. *J Am Dent Assoc* 1980; **100**: 713–4.
8 Posternal F, Orusco MMM, Laugier P. Eythème noueux et contraceptifs oraux. *Bull Dermatol* 1974; **81**: 642–5.
9 Bombardieri S, Di Munno O, Di Punzio C, Pasero G. Erythema nodosum associated with pregnancy and oral contraceptives. *BMJ* 1977; **i**: 1509–10.
10 Morgan JK. Herpes gestationis influenced by an oral contraceptive. *Br J Dermatol* 1968; **80**: 456–8.
11 Tefany FJ, Georgouras K. A neutrophilic reaction of Sweet's syndrome type associated with the oral contraceptive. *Australas J Dermatol* 1991; **32**: 55–9.
12 Hollander A, Grotts IA. Mucha–Habermann disease following estrogen–progesterone therapy. *Arch Dermatol* 1973; **107**: 465.
13 Garrovich M, Agudelo C, Pisko E. Oral contraceptives and systemic lupus erythematosus. *Arthritis Rheum* 1980; **23**: 1396–8.
14 Furukawa F, Tachibana T, Imamura S, Tamura T. Oral contraceptive-induced lupus erythematosus in a Japanese woman. *J Dermatol* 1991; **18**: 56–8.
15 Degos R, Touraine R, Kalis B *et al*. Porphyrie cutanée tardive après prise prolongé de contraceptifs oraux. *Ann Dermatol Syphiligr* 1969; **96**: 5–14.
16 Byrne JPH, Boss JM, Dawber RPR. Contraceptive pill-induced porphyria cutanea tarda presenting with onycholysis of the finger nails. *Postgrad Med J* 1976; **52**: 535–8.
17 Roberts DT, Brodie MJ, Moore MR *et al*. Hereditary coproporphyria presenting with photosensitivity induced by the contraceptive pill. *Br J Dermatol* 1977; **96**: 549–54.
18 Erickson LR, Peterka ES. Sunlight sensitivity from oral contraceptives. *JAMA* 1968; **203**: 980–1.
19 Cooper SM, George S. Photosensitivity reaction associated with use of the combined oral contraceptive. *Br J Dermatol* 2001; **144**: 641–2.
20 Baum JK, Holtz F, Bookstein JJ, Klein EW. Possible association between benign hepatomas and oral contraceptives. *Lancet* 1973; **ii**: 926–8.

21 Nuovo J, Sweha A. Keloid formation from levonorgestrel implant (Norplant System) insertion. *J Am Board Family Pract* 1994; **7**: 152–4.
22 Bounds W, Szarewski A, Lowe D, Guillebaud J. Preliminary report of unexpected local reactions to a progestogen-releasing contraceptive vaginal ring. *Eur J Obstet Gynecol Reprod Biol* 1993; **48**: 123–5.
23 Choudry K, Humphreys F, Menage J. Rosacea in association with the progesterone-releasing intrauterine contraceptive device. *Clin Exp Dermatol* 2001; **26**: 102.
24 Johnston GA, Sviland L, McLelland J. Melasma of the arms associated with hormone replacement therapy. *Br J Dermatol* 1998; **139**: 932.
25 Varma S, Roberts DL. Melasma of the arms associated with hormone replacement therapy. *Br J Dermatol* 1999; **141**: 592.
26 O'Brien TJ, Dyall-Smith D, Hall AP. Melasma of the arms associated with hormone replacement therapy. *Br J Dermatol* 1999; **141**: 592–3.

Antioestrogens

Clomifene (clomiphene). Hot flushes [1] and recurrent petechiae and palpable purpura of the legs with neutrophilic infiltration in a woman treated for infertility with multiple courses of clomifene [2] have been reported.

References

1 Derman SG, Adashi EY. Adverse effects of fertility drugs. *Drug Saf* 1994; **11**: 408–21.
2 Coots NV, McCoy CE, Gehlbach DL, Becker LE. A neutrophilic drug reaction to Clomid. *Cutis* 1996; **57**: 91–3.

Tamoxifen. This oestrogen receptor antagonist used in the therapy of breast cancer in women has caused hirsutism, hair loss, dry skin and a variety of rashes [1].

Reference

1 Descamps V, Bouscarat F, Boui M *et al.* Delayed appearance of maculopapular eruptions induced by tamoxifen. *Ann Dermatol Vénéreol* 1999; **126**: 716–7.

Progesterone and progestogens

Autoimmune progesterone dermatitis. A number of eruptions, including urticaria, eczema, pompholyx, erythema annulare centrifugum and erythema multiforme, have been reported to recur cyclically in the second (luteal) phase of the menstrual cycle, with a peak in severity immediately before menstruation [1–8]. Oral and perineal lesions may occur. It has been proposed that they result from sensitization to endogenous progesterone. There is frequently, but not always, a history of prior exposure to synthetic progesterones [1,3]. Confirmation is with a positive intradermal test with progesterone, preferably in an aqueous or aqueous alcohol solution, and/or existence of circulating antibody to progesterone, and by suppression of symptoms with agents that inhibit ovulation and result in decreased serum progesterone [7]. Two patients with recurrent premenstrual erythema multiforme and autoreactivity to 17α-hydroxyprogesterone have been described [5,6]; in one case, the eruption spread in pregnancy, cleared after abortion and was associated with a high-affinity binding factor to 17α-hydroxyprogesterone in the serum [6]. In another case with recurrent erythema multiforme, cured by oophorectomy, progesterone sensitivity was confirmed by challenge with medroxyprogesterone acetate [9].

Medroxyprogesterone acetate. A pigmented purpura [10] and skin necrosis following intramuscular Depo-Provera [11] are recorded.

Megestrol. A generalized morbilliform rash developed in a cachectic man treated with this synthetic, orally active progesterone derivative to stimulate appetite and weight gain; skin testing with progesterone acetate was positive [12].

References

1 Hart R. Autoimmune progesterone dermatitis. *Arch Dermatol* 1977; **113**: 426–30.
2 Wojnarowska F, Greaves MW, Peachey RDG *et al.* Progesterone-induced erythema multiforme. *J R Soc Med* 1985; **78**: 407–8.
3 Stephens CJM, Black MM. Perimenstrual eruptions: autoimmune progesterone dermatitis. *Semin Dermatol* 1989; **8**: 26–9.
4 Yee KC, Cunliffe WJ. Progesterone-induced urticaria: response to buserelin. *Br J Dermatol* 1994; **130**: 121–3.
5 Cheesman KL, Gaynor LV, Chatterton RT Jr *et al.* Identification of a 17α-hydroxyprogesterone-binding immunoglobulin in the serum of a woman with periodic rashes. *J Clin Endocrinol Metab* 1982; **55**: 597–9.
6 Pinta JS, Sobrinho L, da Silva MB *et al.* Erythema multiforme associated with autoreactivity to 17α-hydroxyprogesterone. *Dermatologica* 1990; **180**: 146–50.
7 Herzberg AJ, Strohmeyer CR, Cirillo-Hyland VA. Autoimmune progesterone dermatitis. *J Am Acad Dermatol* 1995; **32**: 333–8.
8 Halevy S, Cohen AD, Lunenfeld E, Grossman N. Autoimmune progesterone dermatitis manifested as erythema annulare centrifigum: confirmation of progesterone sensitivity by *in vitro* interferon-γ release. *J Am Acad Dermatol* 2002; **47**: 311–3.
9 Ródenas JM, Herranz MT, Tercedor J. Autoimmune progesterone dermatitis: treatment with oophorectomy. *Br J Dermatol* 1998; **139**: 508–11.
10 Tsao H, Lerner LH. Pigmented purpuric eruption associated with injection medroxyprogesterone acetate. *J Am Acad Dermatol* 2000; **43**: 308–10.
11 Clark SM, Lanigan SW. Acute necrotic skin reaction to intramuscular Depo-Provera®. *Br J Dermatol* 2000; **143**: 1356–7.
12 Fisher DA. Drug-induced progesterone dermatitis. *J Am Acad Dermatol* 1996; **34**: 863–4.

Androgens

Anabolic steroids. Exacerbation of acne vulgaris with development of acne conglobata has been reported [1]. Both the size of sebaceous glands and the rate of sebum secretion are increased [2,3]. A lichenoid eruption was reported in a patient with aplastic anaemia treated with nandrolone furylpropionate (Cemelon) [4].

Danazol. This 17-ethinyltestosterone derivative, which is an inhibitor of pituitary gonadotrophin, is a very weak androgen. Of 530 recipients of danazol, 29% reported at least one adverse event within 45 days after receiving the drug, but there were no known long-term sequelae [5]. Acne, hirsutism, seborrhoea, rash and generalized alopecia are documented [6–8]. Exacerbation of LE-like eruptions has been reported in patients receiving this drug for non-C1-esterase inhibitor-dependent angio-oedema [9] or for hereditary angio-oedema [10].

Gestrinone. This derivative of 19-nortestosterone, like danazol, may cause weight gain, hirsutism, acne, voice change or irregular menstrual bleeding [11].

Testosterone. Severe acne or acne fulminans has followed therapy with testosterone, with [2,12] or without [13] anabolic steroids.

Yohimbine. Yohimbine is an indole alkaloid obtained from the yohimbe tree in West Africa and is used in the treatment of male impotence. A case of generalized erythrodermic skin eruption, progressive renal failure and LE-like syndrome is recorded [14].

References

1 Merkle T, Landthaler M, Braun-Falco O. Acne-conglobata-artige Exazerbation einer Acne vulgaris nach Einnahme von Anabolika und Vitamin-B-Komplex-haltigen Präparaten. *Hautarzt* 1990; **41**: 280–2.
2 Király CL, Collan Y, Alén M. Effect of testosterone and anabolic steroids on the size of sebaceous glands in power athletes. *Am J Dermatopathol* 1987; **9**: 515–9.
3 Király CL, Alén M, Rahkila P, Horsmanheimo M. Effect of androgenic and anabolic steroids on the sebaceous gland in power athletes. *Acta Derm Venereol (Stockh)* 1987; **67**: 36–40.
4 Aihara M, Kitamura K, Ikezawa Z. Lichenoid drug eruption due to nandrolone furylpropionate (Cemelon). *J Dermatol* 1989; **16**: 330–4.
5 Jick SS, Myers MW. A study of danazol's safety. *Pharmacotherapy* 1995; **15**: 40–1.
6 Spooner JB. Classification of side-effects to danazol therapy. *J Int Med Res* 1977; **5** (Suppl. 3): 15–7.
7 Greenberg RD. Acne vulgaris associated with antigonadotrophic (Danazol) therapy. *Cutis* 1979; **24**: 431–2.
8 Duff P, Mayer AR. Generalized alopecia: an unusual complication of danazol therapy. *Am J Obstet Gynecol* 1981; **141**: 349–50.
9 Fretwell MD, Altman LC. Exacerbation of a lupus-erythematosus-like syndrome during treatment of non-C1-esterase-inhibitor dependent angioedema with danazol. *J Allergy Clin Immunol* 1982; **69**: 306–10.
10 Sassolas B, Guillet G. Lupus, hereditary angioneurotic oedema and the risks of danazol treatment. *Br J Dermatol* 1991; **125**: 190–1.
11 Anonymous. Gestrinone (Dimetriose): another option in endometriosis. *Drug Ther Bull* 1991; **29**: 45.
12 Heydenreich G. Testosterone and anabolic steroids and acne fulminans. *Arch Dermatol* 1989; **125**: 571–2.
13 Traupe H, von Mühlendahl KE, Brämswig J, Happle R. Acne of the fulminans type following testosterone therapy in three excessively tall boys. *Arch Dermatol* 1988; **124**: 414–7.
14 Sandler B, Aronson P. Yohimbine-induced cutaneous drug eruption, progressive renal failure, and lupus-like syndrome. *Urology* 1993; **41**: 343–5.

Antiandrogens

Cyproterone acetate. Fixed drug eruption is recorded [1].

Finasteride. Erythema annulare centrifugum has been reported [2].

References

1 Galindo PA, Borja J, Feo F *et al.* Fixed drug eruption caused by cyproterone acetate. *Allergy* 1998; **53**: 813.
2 Al Hammadi A, Asai Y, Patt ML, Sasseville D. Erythema annulare centrifugum secondary to treatment with finasteride. *J Drugs Dermatol* 2007; **6**: 460–3.

Insulin

Adverse reactions to insulin [1–5] used to be relatively common, with bovine insulin having the most potential for production of allergic reactions, followed by porcine and human insulin. Insulin allergy and other local cutaneous reactions are rarely seen with highly purified and biosynthetic preparations [2,3], although local symptoms still occur in approximately 5% of patients [2]. Lipoatrophy, which was reported in 10–55% of patients treated with non-purified bovine/porcine insulin preparations, has almost disappeared since the advent of exclusive human insulin treatment. Allergic symptoms to human insulin are found in less than 1% of *de novo*-treated patients, but still occur when human insulin is used in the insulin-allergic patient [3]. Anaphylaxis may occur with recombinant human insulin [6]. Local allergic reactions are often of immediate hypersensitivity type; they are more common in the first few months, and usually subside with continued therapy. Generalized pruritus and urticaria occur rarely. Typically, more severe anaphylactoid reactions follow reintroduction of insulin in patients who have previously received long-term therapy. Delayed reactions may also occur, and take the form of pruritic erythema and induration, sometimes with papulation, within 24 h of injection [7]. Biphasic responses may be seen in the same individual, with initial immediate urticaria and a delayed reaction after 4–6 h. Allergy may develop to the insulin itself (i.e. bovine or porcine protein), to preservatives such as parabens and zinc [8,9], protamine (Surfen) present in depot preparations [10–14], or to cresol [15,16]. Sterile furunculoid lesions at injection sites, which heal with scars and which have a granulomatous histology, may result. Lipoatrophy at injection sites, or more rarely distally, occurred especially with longer-acting preparations; affected patients had lesional immunoglobulin deposits and circulating anti-insulin antibodies [17]. Exceptionally, hypertrophic lipodystrophy [18], or hyperkeratotic verrucous plaques at the site of repeated injections [19], may develop.

References

1 De Shazo RD, Mather P, Grant W *et al.* Evaluation of patients with local reactions to insulin with skin tests and *in vitro* techniques. *Diabetes Care* 1987; **10**: 330–6.
2 Schernthaner G. Immunogenicity and allergenic potential of animal and human insulins. *Diabetes Care* 1993; **16** (Suppl. 3): 155–65.
3 Patrick AW, Williams G. Adverse effects of exogenous insulin. Clinical features, management and prevention. *Drug Saf* 1993; **8**: 427–44.
4 Barbaud A, Got I, Trechot P *et al.* Allergies cutanées et insulinotherapie. Aspects recents, conduite a tenir. *Ann Dermatol Vénéréol* 1996; **123**: 214–8.
5 Hoffman AG, Schram SE, Ercan-Fang NG, Warshaw EM. Type I allergy to insulin: case report and review of localized and systemic reactions to insulin. *Dermatitis* 2008; **19**: 52–8.
6 Fineberg SE, Galloway JA, Fineberg NS *et al.* Immunogenicity of recombinant human insulin. *Diabetologica* 1983; **25**: 465–9.
7 White WN, DeMartino SA, Yoshida T. Severe delayed inflammatory reactions from injected insulin. *Am J Med* 1983; **74**: 909–13.
8 Feinglos MN, Jegasothy BV. 'Insulin' allergy due to zinc. *Lancet* 1979; **i**: 122–4.
9 Jordaan HF, Sandler M. Zinc-induced granuloma: a unique complication of insulin therapy. *Clin Exp Dermatol* 1989; **14**: 227–9.
10 Kim R. Anaphylaxis to protamine masquerading as an insulin allergy. *Del Med J* 1993; **65**: 17–23.
11 Kollner A, Senff H, Engelmann L *et al.* Protaminallergie vom Spattyp und Insulinallergie vom Soforttyp. *Dtsch Med Wochenschr* 1991; **116**: 1234–8.
12 Hulshof MM, Faber WR, Kniestedt WF *et al.* Granulomatous hypersensitivity to protamine as a complication of insulin therapy. *Br J Dermatol* 1992; **127**: 286–8.
13 Lee AY, Chey WY, Choi J, Jeon JS. Insulin-induced drug eruptions and reliability of skin tests. *Acta Derm Venereol (Stockh)* 2002; **82**: 114–7.
14 Bodtger U, Wittrup M. A rational clinical approach to suspected insulin allergy: status after five years and 22 cases. *Diabet Med* 2005; **22**: 102–6.
15 Rajpar SF, Foulds IS, Abdullah A, Maheshwari M. Severe adverse cutaneous reaction to insulin due to cresol sensitivity. *Contact Dermatitis* 2006; **55**: 119–20.
16 Kim D, Baraniuk J. Delayed-type hypersensitivity reaction to the meta-cresol component of insulin. *Ann Allergy Asthma Immunol* 2007; **99**: 194–5.
17 Reeves WG, Allen BR, Tattersal RB. Insulin-induced lipoatrophy: evidence for an immune pathogenesis. *BMJ* 1980; **280**: 1500–3.
18 Johnson DA, Parlette HL. Insulin-induced hypertrophic lipodystrophy. *Cutis* 1983; **32**: 273–4.
19 Fleming MG, Simon SI. Cutaneous insulin reaction resembling acanthosis nigricans. *Arch Dermatol* 1986; **122**: 1054–6.

Thyroxine

Chronic urticaria and angio-oedema was reported in a patient, associated with exogenous thyrotoxicosis, related to thyroid replacement therapy [1].

Reference

1 Pandya AG, Beaudoing DL. Chronic urticaria associated with exogenous thyroid use. *Arch Dermatol* 1990; **126**: 1238–9.

Antithyroid drugs

Thiouracils

Hypersensitivity reactions include drug fever, pruritus, urticaria, angio-oedema, exanthems, acneiform rashes, depigmentation of hair and LE-like syndromes. Propylthiouracil has caused allergic vasculitis [1–3], and methylthiouracil has resulted in erythema multiforme. Thiouracils may cause excessive hair loss. These drugs may cause marrow failure [4].

References

1 Vasily DB, Tyler WB. Propylthiouracil-induced cutaneous vasculitis. *JAMA* 1980; **243**: 458–60.

2 Gammeltoft M, Kristensen JK. Propylthiouracil-induced cutaneous vasculitis. *Acta Derm Venereol (Stockh)* 1982; **62**: 171–3.

3 Otsuka S, Kinebuchi A, Tabata H *et al*. Myeloperoxidase-antineutrophil cytoplasmic antibody-associated vasculitis following propylthiouracil therapy. *Br J Dermatol* 2000; **142**: 828–30.

4 International Agranulocytosis and Aplastic Anemia Study. Risk of agranulocytosis and aplastic anemia in relation to use of antithyroid drugs. *BMJ* 1988; **287**: 262–5.

Chemotherapeutic (cytotoxic) agents

General side effects

There have been a number of excellent reviews of the dermatological complications of these compounds [1–13], including histopathological reactions [14,15]. Women experience greater toxicity from certain chemotherapeutic drugs than men [16]. In attributing a given reaction to a chemotherapeutic agent, one should always consider the possibility that a different drug might be the responsible agent [17]. Bone marrow depression, with aplastic anaemia, agranulocytosis or thrombocytopenia, and gastrointestinal intolerance may occur with any of these drugs. Mucocutaneous surfaces are especially vulnerable to the toxic effects of this group of drugs on rapidly dividing cells. Common side effects therefore include alopecia (see p. 75.45) and stomatitis [18]. Cytotoxic drugs may cause alopecia by either anagen or telogen effluvium. Severe alopecia of anagen type within 2 weeks of administration of the drug is frequently seen with cyclophosphamide, doxorubicin and the nitrosoureas; it is usually reversible with cessation of therapy. Other chemotherapeutic agents implicated in the production of alopecia include amsacrine, bleomycin, cyclophosphamide, cytarabine, dactinomycin, daunorubicin, etoposide, fluorouracil and methotrexate. Stomatitis occurs most frequently with acridinyl anisidide, dactinomycin, daunorubicin, doxorubicin, fluorouracil and methotrexate; it may respond to reduced dosage. Similarly, a number of drugs may cause pigmentation of the buccal mucosa [19] or of the nails [20–22]. Onycholysis may be induced [23].

Hypersensitivity or allergic reactions such as urticaria and angio-oedema [24,25] occur with all cancer chemotherapeutic agents except altretamine, the nitrosoureas and dactinomycin. With L-asparaginase and mitomycin (administered intravesically) they occur in about 10% of patients, and are relatively frequent with cisplatin; they are very rare with methotrexate. Type I reactions are commonest, but all four types of reactions are represented.

Many of these agents have distinctive cutaneous side effects, ranging from localized or diffuse hyperpigmentation to less usual ones, including radiation enhancement and recall phenomena, photosensitivity and hypersensitivity reactions, and phlebitis or chemical cellulitis. Confluent erythematous and hyperpigmented patches, with focal basal layer vacuolar degeneration, occurred within flexural areas during the first month after autologous peripheral stem cell transplantation [26]. Photosensitivity reactions occur with dacarbazine, fluorouracil, mitomycin and vinblastine. Radiation recall effects involve reactivation of an inflammatory response in areas irradiated months or years previously. Clinically, these range from erythema to vesiculation, with erosions and subsequent hyperpigmentation. They have most often been reported in association with dactinomycin and doxorubicin therapy [27], but also with edatrexate [28] and gemcitabine [29]; melphalan, etoposide, vinblastine, bleomycin, fluorouracil, hydroxyurea, methotrexate and gatifloxacin [30] may also cause radiation enhancement. An unusual radiation recall reaction in the form of lipodermatosclerosis of the buttocks occurred 3 months after irradiation for carcinoma of the anus, on subsequent chemotherapy with 5-fluorouracil and cisplatin [31]. UV recall is recorded with mitomycin and the combination of etoposide and cyclophosphamide [32]. Rare complications such as diffuse sclerosis of the hands and feet, Raynaud's phenomenon [33], sterile folliculitis and flushing reactions may also occur. Multiple drug regimens may pose special problems in trying to elucidate the cause of a specific reaction, such as white-banded nails [34] or multiple Beau's lines [35]. A pityriasis lichenoides-like eruption occurred during therapy for myelogenous leukaemia with vincristine and mercaptopurine, antibiotics and aciclovir [36]. Fingertip necrosis occurred during chemotherapy with bleomycin, vincristine and methotrexate for HIV-related Kaposi's sarcoma [37].

Most cytotoxic drugs are teratogenic and are contraindicated during pregnancy, especially during the first trimester. Alkylating drugs usually cause sterility in males, and may shorten reproductive life in women.

References

1 Weiss RB. Hypersensitivity reactions to cancer chemotherapy. *Semin Oncol* 1982; **9**: 5–13.

2 Bronner AK, Hood AF. Cutaneous complications of chemotherapeutic agents. *J Am Acad Dermatol* 1983; **9**: 645–63.

3 McDonald CJ. Cytotoxic agents for use in dermatology. I. *J Am Acad Dermatol* 1985; **12**: 753–5.

4 McDonald CJ. Use of cytotoxic drugs in dermatologic diseases. II. *J Am Acad Dermatol* 1985; **12**: 965–75.

5 Hood AF. Cutaneous side effects of cancer chemotherapy. *Med Clin North Am* 1986; **70**: 187–209.

6 Delaunay M. Effets cutanés indésirables de la chimiothérapie antitumorale. *Ann Dermatol Vénéréol* 1989; **116**: 347–61.

7 Kerker BJ, Hood AF. Chemotherapy-induced cutaneous reactions. *Semin Dermatol* 1989; **8**: 173–81.

8 Rapini RP. Cytotoxic drugs in the treatment of skin disease. *Int J Dermatol* 1991; **30**: 313–22.

9 Mansouri S, Dubertret L, Bastuji-Garin S *et al*. Role of drugs in cutaneous eruptions after chemotherapy for acute myelogenous leukemia. *Arch Dermatol* 1998; **134**: 881–2.

10 Susser WS, Whitaker-Worth DL, Grant-Kels JM. Mucocutaneous reactions to chemotherapy. *J Am Acad Dermatol* 1999; **40**: 367–98.
11 Payne AS, James WD, Weiss RB. Dermatologic toxicity of chemotherapeutic agents. *Semin Oncol* 2006; **33**: 86–97.
12 Sanborn RE, Sauer DA. Cutaneous reactions to chemotherapy: commonly seen, less described, little understood. *Dermatol Clin* 2008; **26**: 103–19, ix.
13 Heidary N, Naik H, Burgin S. Chemotherapeutic agents and the skin: An update. *J Am Acad Dermatol* 2008; **58**: 545–70.
14 Fitzpatrick JE, Hood AF. Histopathologic reactions to chemotherapeutic agents. *Adv Dermatol* 1988; **3**: 161–84.
15 Fitzpatrick JE. The cutaneous histopathology of chemotherapeutic reactions. *J Cutan Pathol* 1993; **20**: 1–14.
16 Wang J, Huang Y. Pharmacogenomics of sex difference in chemotherapeutic toxicity. *Curr Drug Discov Technol* 2007; **4**: 59–68.
17 Bursztejn AC, Tréchot P, Cuny JF *et al*. Cutaneous adverse drug reactions during chemotherapy: consider non-antineoplastic drugs. *Contact Dermatitis* 2008; **58**: 365–8.
18 Bottomley WK, Perlin E, Ross GR. Antineoplastic agents and their oral manifestations. *Oral Surg* 1977; **44**: 527–34.
19 Krutchik AN, Buzdar AU. Pigmentation of the tongue and mucous membranes associated with cancer chemotherapy. *South Med J* 1979; **72**: 1615–6.
20 Sulis E, Floris C. Nail pigmentation following cancer chemotherapy: a new genetic entity? *Eur J Cancer* 1980; **16**: 1517–9.
21 Daniel CR III, Scher RK. Nail changes secondary to systemic drugs or ingestants. *J Am Acad Dermatol* 1984; **10**: 250–8.
22 Daniel CR III, Scher PK. Nail changes secondary to systemic drugs or ingestants. In: Scher RK, Daniel CR III, eds. *Nails: Therapy, Diagnosis, Surgery*. Philadelphia: Saunders, 1990: 192–201.
23 Makris A, Mortimer P, Powles TJ. Chemotherapy-induced onycholysis. *Eur J Cancer* 1996; **32A**: 374–5.
24 Weiss RB. Hypersensitivity reactions. *Semin Oncol* 1992; **19**: 458–77.
25 O'Brien ME, Souberbielle BE. Allergic reactions to cytotoxic drugs: an update. *Ann Oncol* 1992; **3**: 605–10.
26 Brazzelli V, Ardigo M, Chiesa MG *et al*. Flexural erythematous eruption following autologous peripheral blood stem cell transplantation: a study of four cases. *Br J Dermatol* 2001; **145**: 490–5.
27 Solberg LA Jr, Wick MR, Bruckman JE. Doxorubicin-enhanced skin reaction after whole-body electron beam irradiation for leukemia cutis. *Mayo Clin Proc* 1980; **55**: 711–5.
28 Perez EA, Campbell DL, Ryu JK. Radiation recall dermatitis induced by edatrexate in a patient with breast cancer. *Cancer Invest* 1995; **13**: 604–7.
29 Jeter MD, Janne PA, Brooks S *et al*. Gemcitabine-induced radiation recall. *Int J Radiat Oncol Biol Phys* 2002; **53**: 394–400.
30 Jain S, Agarwal J, Laskar S *et al*. Radiation recall dermatitis with gatifloxacin: a review of literature. *J Med Imaging Radiat Oncol* 2008; **52**: 191–3.
31 Sroa N, Bartholomew DA, Magro CM. Lipodermatosclerosis as a form of vascular compromise-associated radiation recall dermatitis: case report and a review of literature. *J Cutan Pathol* 2006; **33** (Suppl. 2): 55–9.
32 Williams BJ, Roth DJ, Callen JP. Ultraviolet recall associated with etoposide and cyclophosphamide therapy. *Clin Exp Dermatol* 1993; **18**: 452–3.
33 Vogelzang NJ, Bosl GJ, Johnson D *et al*. Raynaud's phenomenon: a common toxicity after combination chemotherapy for testicular cancer. *Ann Intern Med* 1981; **95**: 288–92.
34 James WD, Odom RB. Chemotherapy-induced transverse white lines in the fingernails. *Arch Dermatol* 1983; **119**: 334–5.
35 Singh M, Kaur S. Chemotherapy-induced multiple Beau's lines. *Int J Dermatol* 1986; **25**: 590–1.
36 Isoda M. Pityriasis lichenoides-like eruption occurring during therapy for myelogenous leukemia. *J Dermatol* 1989; **16**: 73–5.
37 Pechère M, Zulian GB, Vogel J-J *et al*. Fingertip necrosis during chemotherapy with bleomycin, vincristine and methotrexate for HIV-related Kaposi's sarcoma. *Br J Dermatol* 1996; **134**: 378–9.

Extravasation

Extravasation, leading to skin necrosis with ulceration, occurs with several agents [1–5]. Phlebitis and chemical cellulitis have been recorded with most antimitotic agents. Residual drug should be aspirated and the limb elevated; plastic surgical advice should be sought as soon as possible. High dermal concentrations of doxorubicin have been documented as late as 28 days after accidental extravasation [6]. Histological examination of doxorubicin-related extravasation lesions demonstrated exaggerated interface-type dermatitis with thrombosis of venous tributaries [7].

References

1 Ignoffo RJ, Friedman MA. Therapy of local toxicities caused by extravasation of cancer chemotherapeutic drugs. *Cancer Treat Rev* 1980; **7**: 17–27.
2 Harwood KV, Aisner J. Treatment of chemotherapy extravasation: current status. *Cancer Treat Rep* 1984; **68**: 939–45.
3 Banerjee A, Brotherston TM, Lamberty BGH *et al*. Cancer chemotherapy agent-induced perivenous extravasation injury. *J Postgrad Med* 1987; **63**: 5–9.
4 Rudolph R, Larson DL. Etiology and treatment of chemotherapeutic agent extravasation injuries: a review. *J Clin Oncol* 1987; **5**: 1116–26.
5 Dufresne RG Jr. Skin necrosis from intravenously infused materials. *Cutis* 1989; **39**: 197–8.
6 Sonneveld P, Wassenaar HA, Nooter K. Long persistence of doxorubicin in human skin after extravasation. *Cancer Treat Rep* 1984; **68**: 895–6.
7 Bhawan J, Petry J, Rybak ME. Histologic changes induced in skin by extravasation of doxorubicin (adriamycin). *J Cutan Pathol* 1989; **16**: 158–63.

Acral erythema

Several cytotoxic drugs (especially cytosine arabinoside, fluorouracil, docetaxel and doxorubicin, and rarely cyclophosphamide, hydroxyurea, mercaptopurine, methotrexate and mitotane) can cause dose-dependent acral erythema, often preceded by paraesthesiae, either alone or in combination [1–17]. Bulla formation, desquamation and subsequent re-epithelialization may occur. Reactions may occur sooner (from 24 h to 3 weeks) and more severely with bolus or short-term chemotherapy than with low-dose continuous infusion, and are usually reproducible on challenge. Intravenous ciclosporin, given in bone marrow transplant patients, reportedly worsens the pain of acral erythema [12]. The condition should be distinguished from graft-versus-host disease in patients who receive chemotherapy followed by bone marrow transplantation, and from chemotherapy-induced Raynaud's phenomenon. This may not be easy, as histological changes may suggest graft-versus-host disease [18].

References

1 Doyle LA, Berg C, Bottino G, Chabner E. Erythema and desquamation after high-dose methotrexate. *Ann Intern Med* 1983; **98**: 611–2.
2 Feldman LD, Jaffer A. Fluorouracil-associated palmar-plantar erythro-dysesthesia syndrome. *JAMA* 1985; **254**: 3479.
3 Crider MK, Jansen J, Norins AL, McHale MS. Chemotherapy-induced acral erythema in patients receiving bone marrow transplantation. *Arch Dermatol* 1986; **122**: 1023–7.
4 Cox GJ, Robertson DB. Toxic erythema of palms and soles associated with high-dose mercaptopurine chemotherapy. *Arch Dermatol* 1986; **122**: 1413–4.
5 Guillaume J-C, Carp E, Rougier P *et al*. Effets secondaires cutanéo-muqueux des perfusions continues de 5-fluorouracile: 12 observations. *Ann Dermatol Vénéréol* 1988; **115**: 1167–9.
6 Horwitz LJ, Dreizen S. Acral erythemas induced by chemotherapy and graft-versus-host disease in adults with hematogenous malignancies. *Cutis* 1990; **46**: 397–404.
7 Baack BR, Burgdorf WHC. Chemotherapy-induced acral erythema. *J Am Acad Dermatol* 1991; **24**: 457–61.
8 Reynaert H, De Coninck A, Neven AM *et al*. Chemotherapy-induced acral erythema and acute graft-versus-host disease after allogeneic bone marrow transplantation. *Bone Marrow Transplant* 1992; **10**: 185–7.

9 Cohen PR. Acral erythema: a clinical review. *Cutis* 1993; **51**: 175–9.
10 Pirisi M, Soardo G. Images in clinical medicine. Chemotherapy-induced acral erythema. *N Engl J Med* 1994; **330**: 1279.
11 Komamura H, Higashiyama M, Hashimoto K *et al.* Three cases of chemotherapy-induced acral erythema. *J Dermatol* 1995; **22**: 116–21.
12 Kampmann KK, Graves T, Rogers SD. Acral erythema secondary to high-dose cytosine arabinoside with pain worsened by cyclosporin infusions. *Cancer* 1989; **63**: 2482–5.
13 Revenga Arranz F, Fernandez-Duran DA, Grande C *et al.* Acute and painful erythema of the hands and feet. Acral erythema induced by chemotherapy. *Arch Dermatol* 1997; **133**: 499–500, 502–3.
14 Nagore E, Insa A, Sanmartin O. Antineoplastic therapy-induced palmar plantar erythrodysesthesia ('hand–foot') syndrome. Incidence, recognition and management. *Am J Clin Dermatol* 2000; **1**: 225–34.
15 Tsuruta D, Mochida K, Hamada T *et al.* Chemotherapy-induced acral erythema: report of a case and immunohistochemical findings. *Clin Exp Dermatol* 2000; **25**: 386–8.
16 Soker M, Akdeniz S, Devecioglu C, Haspolat K. Chemotherapy-induced bullous acral erythema in a subject with B-cell lymphoma. *J Eur Acad Dermatol Venereol* 2001; **15**: 490–1.
17 de Bono JS, Stephenson J Jr, Baker SD *et al.* Troxacitabine, an L-stereoisomeric nucleoside analog, on a five-times-daily schedule: a phase I and pharmacokinetic study in patients with advanced solid malignancies. *J Clin Oncol* 2002; **20**: 96–109.
18 Beard JS, Smith KJ, Skelton HG. Combination chemotherapy with 5-fluorouracil, folinic acid, and α-interferon producing histologic features of graft-versus-host disease. *J Am Acad Dermatol* 1993; **29**: 325–30.

Neutrophilic eccrine hidradenitis

Neutrophilic eccrine hidradenitis may represent a reaction pattern to a variety of chemotherapeutic agents [1–8], but particularly cytarabine and bleomycin. It has been induced by granulocyte–macrophage colony stimulating factor [9]. Clinically, erythematous papules or plaques or nodules are most frequent, although hyperpigmented plaques, pustules, purpura and urticaria have been described. Lesions resolve spontaneously over several days. The histology is characterized by infiltration of eccrine coils with neutrophils and necrosis of the secretory epithelium. The condition has also been described in a patient receiving haemodialysis without chemotherapy [10] and in a patient without a malignancy who was taking paracetamol [11].

References

1 Fitzpatrick JE, Bennion SD, Reed OM *et al.* Neutrophilic eccrine hidradenitis associated with induction chemotherapy. *J Cutan Pathol* 1987; **14**: 272–8.
2 Scallan PJ, Kettler AH, Levy ML *et al.* Neutrophilic eccrine hidradenitis. *Cancer* 1988; **62**: 2532–6.
3 Fernández Cogolludo E, Ambrojo Antunez P, Aguilar Martínez A *et al.* Neutrophil eccrine hidradenitis: a report of two additional cases. *Clin Exp Dermatol* 1989; **14**: 341–6.
4 Burg G, Bieber T, Langecker P. Lokalisierte neutrophile ekkrien Hidraden-itis unter Mitoxantron: eine typische Zytostatikanebenwirkung. *Hautarzt* 1988; **39**: 233–6.
5 Allegue F, Soria C, Rocamora A *et al.* Neutrophilic eccrine hidradenitis in two neutropenic patients. *J Am Acad Dermatol* 1990; **23**: 1110–3.
6 Margolis DJ, Gross PR. Neutrophilic eccrine hidradenitis: a case report and review of the literature. *Cutis* 1991; **48**: 198–200.
7 Thorisdottir K, Tomecki KJ, Bergfeld WF *et al.* Neutrophilic eccrine hidradenitis. *J Am Acad Dermatol* 1993; **28**: 775–7.
8 Kanzki H, Takashi O, Makino E *et al.* Neutrophilic eccrine hidradenitis: report of two cases. *J Dermatol* 1995; **22**: 137–42.
9 Bachmeyer C, Chaibi P, Aractingi S. Neutrophilic eccrine hidradenitis induced by granulocyte-stimulating factor. *Br J Dermatol* 1998; **139**: 354–5.
10 Moreno A, Barnadas MA, Ravella A, Moragas JM. Infectious eccrine hidradenitis in a patient undergoing hemodialysis. *Arch Dermatol* 1985; **121**: 1106–7.
11 Kuttner BJ, Kurban RS. Neutrophilic eccrine hidradenitis in the absence of an underlying malignancy. *Cutis* 1988; **41**: 403–5.

Syringosquamous metaplasia

A related but distinct entity termed 'syringosquamous metaplasia', which may be confused with well-differentiated squamous cell carcinoma histologically, has been described in patients receiving chemotherapy for leukaemia and other cancers [1–3]. Clinically, this may appear as an erythematous, blanching, papular crusted eruption, or as erythematous oedematous plaques or confluent erythematous macular areas, in the axillae or groins, with painful erythema and oedema on the palms and soles [4].

References

1 Bhawan J, Malhotra R. Syringosquamous metaplasia. A distinctive eruption in patients receiving chemotherapy. *Am J Dermatopathol* 1990; **12**: 1–6.
2 Hurt MA, Halvorson RD, Petr FC Jr *et al.* Eccrine squamous syringometaplasia. A cutaneous sweat gland reaction in the histologic spectrum of 'chemotherapy-associated eccrine hidradenitis' and 'neutrophilic eccrine hidradenitis'. *Arch Dermatol* 1990; **126**: 73–7.
3 Valks R, Buezo GF, Dauden E *et al.* Eccrine squamous syringometaplasia in intertriginous areas. *Br J Dermatol* 1996; **134**: 984–6.
4 Valks R, Fraga J, Porras-Luque J *et al.* Chemotherapy-induced eccrine squamous syringometaplasia. A distinctive eruption in patients receiving hematopoietic progenitor cells. *Arch Dermatol* 1997; **133**: 873–8.

Side effects related to immunosuppression

The cutaneous manifestations of immunosuppression have been reviewed [1–4]. Immunosuppressive therapy, such as azathioprine and prednisone for renal transplant patients, may encourage skin infections of various types, for example warts, herpes simplex and herpes zoster [5], pityriasis versicolor and fungal infections [6]. Development of disseminated superficial actinic porokeratosis [7–9], porokeratosis of Mibelli [10–13] and increased numbers of benign [14,15] or eruptive dysplastic [16] melanocytic naevi may be promoted. Eruptive keratoacanthomas occurred in a patient with SLE on prednisolone and cyclophosphamide [17].

References

1 Cohen EB, Komorowski RA, Clowry LJ. Cutaneous complications in renal transplant recipients. *Am J Clin Pathol* 1987; **88**: 32–7.
2 Abel EA. Cutaneous manifestations of immunosuppression in organ transplant recipients. *J Am Acad Dermatol* 1989; **21**: 167–79.
3 Boitard C, Nach J-F. Long-term complications of conventional immuno-suppressive treatment. *Adv Nephrol* 1989; **18**: 335–54.
4 Paller AS, Mallory SB. Acquired forms of immunosuppression. *J Am Acad Dermatol* 1991; **24**: 482–8.
5 Spencer ES, Anderson HK. Viral infections in renal allograft recipients treated with long-term immunosuppression. *BMJ* 1979; **2**: 829–30.
6 Shelley WB. Induction of tinea cruris by topical nitrogen mustard and systemic chemotherapy. *Acta Derm Venereol (Stockh)* 1981; **61**: 164–5.
7 Bencini PL, Crosti C, Sala F. Porokeratosis: immunosuppression and exposure to sunlight. *Br J Dermatol* 1987; **116**: 113–6.
8 Neumann RA, Knobler RM, Metze D, Jurecka W. Disseminated superficial porokeratosis and immunosuppression. *Br J Dermatol* 1988; **119**: 375–80.
9 Lederman JS, Sober AJ, Lederman GS. Immunosuppression: a cause of porokeratosis? *J Am Acad Dermatol* 1985; **13**: 75–9.
10 Grattan CEH, Christopher AP. Porokeratosis and immunosuppression. *J R Soc Med* 1987; **80**: 597–8.
11 Tatnall FM, Sarkany I. Porokeratosis of Mibelli in an immunosuppressed patient. *J R Soc Med* 1987; **80**: 180–1.
12 Wilkinson SM, Cartwright PH, English JSC. Porokeratosis of Mibelli and immunosuppression. *Clin Exp Dermatol* 1991; **16**: 61–2.

13 Herranz P, Pizarro A, De Lucas R *et al.* High incidence of porokeratosis in renal transplant recipients. *Br J Dermatol* 1997; **136**: 176–9.
14 McGregor JM, Barker JNWN, MacDonald DM. The development of excess numbers of melanocytic naevi in an immunosuppressed identical twin. *Clin Exp Dermatol* 1991; **16**: 131–2.
15 Hughes BR, Cunliffe WJ, Bailey CC. Excess benign melanocytic naevi after chemotherapy for malignancy in childhood. *BMJ* 1989; **299**: 88–91.
16 Barker JNWN, MacDonald DM. Eruptive dysplastic naevi following renal transplantation. *Clin Exp Dermatol* 1988; **13**: 123–5.
17 Dessoukey MW, Omar MF, Abdel-Dayem H. Eruptive keratoacanthomas associated with immunosuppressive therapy in a patient with systemic lupus erythematosus. *J Am Acad Dermatol* 1997; **37**: 478–80.

Internal malignancy

The frequency of internal cancers common in the general population is not increased in transplant patients. However, that of a variety of otherwise uncommon malignancies is increased [1–3], including: non-Hodgkin's lymphoma (mostly B-cell, with 14% of T-cell, and less than 1% of null-cell, origin), which accounts for 21% of cancers in transplant recipients; Kaposi's sarcoma; other sarcomas; carcinoma of the vulva and perineum; carcinoma of the kidney; and hepatobiliary tumours. Non-Hodgkin's lymphoma appears commoner and develops earlier where potent immunosuppressive agents such as ciclosporin and/or the monoclonal antibody OKT3 have been used; however, although cancer develops in 6% of all transplant recipients, only 1% of patients die from this complication [3]. Leukaemia may develop following chemotherapy [4], and bladder cancer has been associated with cyclophosphamide therapy [5].

Skin cancers

Actinic keratoses, squamous cell and basal cell cancer of the lip and skin [6–12], and malignant melanoma [13] have been reported to be more common, especially in immunosuppressed renal transplant patients. The majority of these patients have received azathioprine and corticosteroids. Interestingly, the immunosuppressed renal transplant recipients have been reported to be at high risk for skin cancer unless they express the HLA class I allele A11 [14]. Furthermore, patients with long-standing renal grafts mismatched for HLA-B have a significantly higher incidence of squamous cell cancers than other mismatches, and patients who are homozygous for HLA-DR are at increased risk for actinic keratoses and skin cancer [15]. These findings imply that MHC gene products participate in the pathogenesis of skin cancer in immunosuppressed patients, probably via influences on T-cell recognition of neoantigens [16]. There was no difference from control levels in the number of $CD1^+$ $HLA\text{-}DR^+$ antigen-presenting Langerhans' cells in the epidermis of immunosuppressed renal transplant recipients treated with either azathioprine/prednisone or ciclosporin/prednisone [17].

References

1 Penn I. Depressed immunity and the development of cancer. *Clin Exp Immunol* 1981; **146**: 459–74.
2 Penn I. Tumors of the immunocompromised patient. *Annu Rev Med* 1988; **39**: 63–73.
3 Penn I. Cancers complicating organ transplantation. *N Engl J Med* 1990; **323**: 1767–9.
4 Williams CJ. Leukaemia and cancer chemotherapy. The risk is acceptably small but may be reducible further. *BMJ* 1990; **301**: 73–4.
5 Elliot RW, Essenhigh DM, Morley AR. Cyclophosphamide treatment of systemic lupus erythematosus: risk of bladder cancer exceeds benefit. *Blood* 1970; **35**: 543–8.
6 Walder BK, Robertson MR, Jeremy D. Skin cancer and immunosuppression. *Lancet* 1971; **ii**: 1282–3.
7 Lowney ED. Antimitotic drugs and aggressive squamous cell tumors. *Arch Dermatol* 1972; **105**: 924.
8 Kinlen LJ, Sheil AGR, Peto J, Doll R. Collaborative United Kingdom–Australasian study of cancer in patients treated with immunosuppressive drugs. *BMJ* 1979; **ii**: 1461–6.
9 Boyle J, Briggs JD, MacKie RM *et al.* Cancer, warts and sunshine in renal transplant patients. *Lancet* 1984; **i**: 702–5.
10 McLelland J, Rees A, Williams G *et al.* The incidence of immunosuppression-related skin disease in long-term transplant patients. *Transplantation* 1988; **46**: 871–4.
11 Gupta AK, Cardella CJ, Haberman HF. Cutaneous malignant neoplasms in patients with renal transplants. *Arch Dermatol* 1986; **122**: 1288–93.
12 Hintner H, Fritsch P. Skin neoplasia in the immunodeficient host. *Curr Probl Dermatol* 1989; **18**: 210–7.
13 Greene MH, Young TI. Malignant melanoma in renal transplant recipients. *Lancet* 1981; **i**: 1196–9.
14 Bouwes Bavinck JN, Koottee AMM, van der Woude FJ *et al.* HLA-A11 associated resistance to skin cancer in renal-transplant recipients. *N Engl J Med* 1990; **323**: 1350.
15 Bouwes Bavinck JM, Vermeer BJ, vans der Woude FJ *et al.* Relation between skin cancer and HLA antigens in renal-transplant recipients. *N Engl J Med* 1991; **325**: 843–8.
16 Streilein JW. Immunogenetic factors in skin cancer. *N Engl J Med* 1991; **325**: 884–7.
17 Scheibner KG, Murray A, Sheil R *et al.* T6 and HLA-DR cell numbers in epidermis of immunosuppressed renal transplant recipients. *J Cutan Pathol* 1987; **14**: 202–6.

Alkylating agents

These drugs interfere with cell replication by damaging DNA. Gametogenesis is often severely affected, and their use is associated with a marked increase in non-lymphocytic leukaemia, especially when used in conjunction with radiotherapy.

Alkyl sulphonates

Busulfan. Reactions are rare, but have included urticaria, bullous erythema multiforme [1], Addisonian-like pigmentation [2,3] due to increased epidermal and dermal melanin, and drug-induced porphyria cutanea tarda [4]. Vasculitis has been reported. Keratinocyte nuclear abnormalities with abundant pale cytoplasm have been described [5]. Progressive pulmonary fibrosis may occur.

References

1 Dosik H, Hurewitz DJ, Rosner F, Schwartz JM. Bullous eruptions and elevated leukocyte alkaline phosphatase in the course of busulphan-treated chronic granulocytic leukaemia. *Blood* 1970; **35**: 543–8.
2 Harrold BP. Syndrome resembling Addison's disease following prolonged treatment with busulphan. *BMJ* 1966; **1**: 463–4.
3 Burns WA, McFarland W, Matthews MJ. Toxic manifestations of busulfan therapy. *Med Ann DC* 1971; **40**: 567–9.
4 Kyle RA, Dameshek W. Porphyria cutanea tarda associated with chronic granulocytic leukemia treated with busulfan. *Blood* 1964; **23**: 776–85.
5 Hymes SR, Simonton SC, Farmer ER *et al.* Cutaneous busulfan effect in patients receiving bone marrow transplanation. *J Cutan Pathol* 1985; **12**: 125–9.

Nitrogen mustard derivatives

Chlorambucil. Morbilliform rashes occur; urticarial plaques and periorbital oedema have been described rarely [1–4]. A delayed allergic reaction on the third cycle of chemotherapy, with general-

ized erythroderma with exfoliation and oedema of the face and arms, as well as immune haemolytic anaemia and TEN, have been described [5]. Alopecia is uncommon. Sterility with azoospermia and amenorrhoea is documented.

References

1 Knisely RE, Settipane GA, Albala MM. Unusual reaction to chlorambucil in a patient with chronic lymphocytic leukemia. *Arch Dermatol* 1971; **104**: 77–9.
2 Millard LG, Rajah SM. Cutaneous reaction to chlorambucil. *Arch Dermatol* 1977; **113**: 1298.
3 Peterman A, Braunstein B. Cutaneous reaction to chlorambucil therapy. *Arch Dermatol* 1986; **122**: 1358–60.
4 Zervas J, Karkantaris C, Kapiri E *et al.* Allergic reaction to chlorambucil in chronic lymphocytic leukaemia: case report. *Leuk Res* 1992; **16**: 329–30.
5 Torricelli R, Kurer SB, Kroner T, Wuthrich B. Allergie vom Spattyp auf Chlorambucil (Leukeran). Fallbeschreibung und Literaturubersicht. *Schweiz Med Wochenschr* 1995; **125**: 1870–3.

Cyclophosphamide and mesna. Alopecia is common and occurs in 5–30% of cases [1]. Pigmentation, which may be widespread or localized to the palms, soles or nails, is well documented and usually reversible [2,3]. Nail dystrophy may be seen. Allergic exanthems are rare, but anaphylactic and urticarial reactions less so [4–7]. Type I hypersensitivity with a markedly delayed onset (from 8 to 16 h up to 10 days), associated with immediate skin-test results to cyclophosphamide metabolites but not the parent drug, has been documented [7]. There may be cross-sensitivity to other alkylating agents, especially mechlorethamine and chlorambucil [8]. Sterility may supervene.

Haemorrhagic cystitis, the result of toxicity of the metabolite acrolein, is a complication in up to 40% of cases if cyclophosphamide is used alone. Introduction of the thiol compound mesna (2-mercaptoethane sulphonate) has virtually eliminated this complication. There have been recent reports of urticaria, angio-oedema, allergic maculopapular pruritic rashes, generalized fixed drug eruption, and occasional more severe reactions with flushing, widespread erythema and ulceration or blistering of mucous membranes related to mesna; patch tests may be positive [9–13].

References

1 Ahmed AR, Hombal SM. Cyclophosphamide (Cytoxan). *J Am Acad Dermatol* 1984; **11**: 1115–26.
2 Harrison BM, Wood CBS. Cyclophosphamide and pigmentation. *BMJ* 1972; **1**: 352.
3 Shah PC, Rao KRP, Patel AR. Cyclophosphamide induced nail pigmentation. *Br J Dermatol* 1978; **98**: 675–80.
4 Murti L, Horsman LR. Acute hypersensitivity reaction to cyclophosphamide. *J Pediatr* 1979; **94**: 844–5.
5 Lakin JD, Cahill RA. Generalized urticaria to cyclophosphamide: type I hypersensitivity to an immunosuppressive agent. *J Allergy Clin Immunol* 1976; **58**: 160–71.
6 Knysak DJ, McLean JA, Solomon WR *et al.* Immediate hypersensitivity reaction to cyclophosphamide. *Arthritis Rheum* 1994; **37**: 1101–4.
7 Popescu NA, Sheehan MG, Kouides PA *et al.* Allergic reactions to cyclophosphamide: delayed clinical expression associated with positive immediate skin tests to drug metabolites in five patients. *J Allergy Clin Immunol* 1996; **97**: 26–33.
8 Kritharides L, Lawrie K, Varigos GA. Cyclophosphamide hypersensitivity and cross-reactivity with chlorambucil. *Cancer Treat Rep* 1987; **71**: 1323–4.
9 Pratt CB, Sandlund JT, Meyer WH, Cain AM. Mesna-induced urticaria. *Drug Intel Clin Phar* 1988; **22**: 914.
10 Seidel A, Andrassy K, Ritz E *et al.* Allergic reactions to mesna. *Lancet* 1991; **338**: 381.
11 Gross WL, Mohr J, Christophers E. Allergic reactions to mesna. *Lancet* 1991; **338**: 381.
12 D'Cruz D, Haga H-J, Hughes GRV. Allergic reactions to mesna. *Lancet* 1991; **338**: 705–6.
13 Zonzits E, Aberer W, Tappeiner G. Drug eruptions from mesna. After cyclophosphamide treatment of patients with systemic lupus erythematosus and dermatomyositis. *Arch Dermatol* 1992; **128**: 80–2.

Lomustine. Flushing has been reported.

Mechlorethamine. Angio-oedema and pruritus have been recorded [1]; however, in view of the large number of patients receiving this drug as part of the MOPP (mechlorethamine, Oncovin (vincristine), procarbazine, prednisone) regimen for lymphoma, these side effects must be exceedingly rare. Topical mechlorethamine [2] used to treat psoriasis or mycosis fungoides may cause hyperpigmentation of involved and uninvolved skin [3], contact sensitization [4,5] and rarely immediate-type hypersensitivity with urticaria or anaphylactoid reactions [6].

References

1 Wilson KS, Alexander S. Hypersensitivity to mechlorethamine. *Ann Intern Med* 1981; **94**: 823.
2 Price NM, Deneau DG, Hoppe RT. The treatment of mycosis fungoides with ointment-based mechlorethamine. *Arch Dermatol* 1982; **118**: 234–7.
3 Flaxman BA, Sosis AC, Van Scott EJ. Changes in melanosome distribution in Caucasoid skin following topical application of nitrogen mustard. *J Invest Dermatol* 1973; **60**: 321–6.
4 Van Scott EJ, Winters PL. Responses of mycosis fungoides to intensive external treatment with nitrogen mustard. *Arch Dermatol* 1970; **102**: 507–14.
5 Ramsay DL, Halperin PS, Zeleniuch-Jacquotte A. Topical mechlorethamine therapy for early stage mycosis fungoides. *J Am Acad Dermatol* 1988; **19**: 684–91.
6 Daughters D, Zackheim H, Maibach H. Urticaria and anaphylactoid reactions after topical application of mechlorethamine. *Arch Dermatol* 1973; **107**: 429–30.

Melphalan. Trivial morbilliform rashes are relatively common [1]. Severe anaphylactic reactions may occur after intravenous use, especially in patients with IgA κ myeloma [2]. Urticaria or angio-oedema after oral use is very rare [3]. Vasculitis has been documented, and melanonychia striata has been recorded [4]. Scleroderma has supervened after isolated limb perfusion [5]. Radiation recall is uncommon [6]. Sterility with azoospermia and amenorrhoea are recorded.

References

1 Costa GG, Engle RL Jr, Schilling A *et al.* Melphalan and prednisone: an effective combination for the treatment of multiple myeloma. *Am J Med* 1973; **54**: 589–99.
2 Cornwell GG, Pajak TF, McIntyre OR. Hypersensitivity reactions to i.v. melphalan during the treatment of multiple myeloma: cancer and leukemia group B experience. *Cancer Treat Rep* 1979; **63**: 399–403.
3 Lawrence BV, Harvey HA, Lipton A. Anaphylaxis due to oral melphalan. *Cancer Treat Rep* 1980; **64**: 731–2.
4 Malacarne P, Zavagli G. Melphalan-induced melanonychia striata. *Arch Dermatol Res* 1977; **258**: 81–3.
5 Landau M, Brenner S, Gat A *et al.* Reticulate scleroderma after isolated limb perfusion with melphalan. *J Am Acad Dermatol* 1998; **39**: 1011–2.
6 Kellie SJ, Plowman PN, Malpas JS. Radiation recall and radio-sensitization with alkylating agents. *Lancet* 1987; **i**: 1149–50.

Ethylenemine derivatives

Thiotepa (triethylenethiophosphoramide)

Intravesical installation caused pruritus, urticaria or angio-oedema in five of 164 patients with bladder carcinoma [1]. Intravenous

administration resulted in patterned hyperpigmentation confined to skin occluded by adhesive bandages or electrocardiograph pads, probably due to secretion of the drug in sweat [2]. Diffuse erythema with progression to desquamation and hyperpigmentation, originating in intertriginous and occluded areas, occurred in nearly 80% of paediatric patients receiving high-dose chemotherapy with autologous stem cell transplantation [3]. Topical thiotepa has produced periorbital leukoderma [4].

References

1 Veenema RJ, Dean AL, Uson AC *et al.* Thiotepa bladder installations: therapy and prophylaxis for superficial bladder tumors. *J Urol* 1969; **101**: 711–5.
2 Horn TD, Beveridge RA, Egorine MJ *et al.* Observations and proposed mechanism of *N*,*N*′,*N*′-triethylenethiophosphoramide (thiotepa)-induced hyperpigmentation. *Arch Dermatol* 1989; **125**: 524–7.
3 Rosman IS, Lloyd BM, Hayashi RJ, Bayliss SJ. Cutaneous effects of thiotepa in pediatric patients receiving high-dose chemotherapy with autologous stem cell transplantation. *J Am Acad Dermatol* 2008; **58**: 575–8.
4 Harben DJ, Cooper PH, Rodman OG. Thiotepa-induced leukoderma. *Arch Dermatol* 1979; **115**: 973–4.

Nitrosoureas

Carmustine

Topical carmustine (BCNU) used for the treatment of cutaneous T-cell lymphoma may result in erythema, skin tenderness and telangiectasia. Contact sensitization may develop [1]. Mild bone marrow suppression has been recorded.

Reference

1 Zackheim HS, Epstein EH Jr, Crain WR. Topical carmustine (BCNU) for cutaneous T cell lymphoma: a 15-year experience in 143 patients. *J Am Acad Dermatol* 1990; **22**: 802–10.

Dacarbazine (DTIC)

Photosensitivity [1,2] and a fixed eruption-like rash [3] have been reported. A patient with malignant melanoma treated with DTIC developed sudden hepatic vein thrombosis (Budd–Chiari syndrome) following intravenous administration [4]. Increasing blood eosinophilia appears to be a sign of the imminent development of this complication. Chemical cellulitis occurs following extravasation.

References

1 Bolling R, Meyer-Hamme S, Schauder S. Lichtsensibilisierung unter DTIC-Therapie beim metastasierenden malignen Melanom. *Hautarzt* 1980; **31**: 602–5.
2 Yung CW, Winston EM, Lorincz AL. Dacarbazine-induced photosensitivity reaction. *J Am Acad Dermatol* 1981; **4**: 451–3.
3 Koehn GG, Balizet LR. Unusual local cutaneous reaction to dacarbazine. *Arch Dermatol* 1982; **118**: 1018–9.
4 Swensson-Beck H, Trettel WH. Budd–Chiari-Syndrom bei DTIC-Therapie. *Hautarzt* 1981; **33**: 30–1.

Procarbazine

Type I reactions are rare; recurrent angio-oedema, urticaria and arthralgia with decreased serum complement have been reported [1,2]. Hypersensitivity to procarbazine in patients treated with mechlorethamine, vincristine and procarbazine (MOP) for high-grade glioma manifested as a maculopapular rash, fever, reversible abnormal liver function and interstitial pneumonitis [3].

References

1 Glovsky MM, Braunwald J, Opelz G, Alenty A. Hypersensitivity to procarbazine associated with angio-edema, urticaria and low serum complement activity. *J Allergy Clin Immunol* 1976; **57**: 134–40.
2 Andersen E, Videbaeck A. Procarbazine-induced skin reactions in Hodgkin's disease and other malignant lymphomas. *Scand J Haematol* 1980; **24**: 149–51.
3 Coyle T, Bushunow P, Winfield J *et al.* Hypersensitivity reactions to procarbazine with mechlorethamine, vincristine, and procarbazine chemotherapy in the treatment of glioma. *Cancer* 1992; **69**: 2532–40.

Cytotoxic antibiotics

Bleomycin

The principal problem of systemic therapy is progressive pulmonary fibrosis. Alopecia, glossitis and buccal ulceration occur, and drug fever is common, usually 1–4 h after injection. Distinctive, localized, erythematous, tender macules, nodules or infiltrated plaques on the hands, elbows, knees and buttocks have been documented [1–3]. Their causation is uncertain, and the rash may resolve despite continued therapy [4]. Raynaud's phenomenon with or without ischaemic ulcerations, and systemic sclerosis-like changes in men, have been described [5–7]. Capillary microscopy has been advocated for the investigation of bleomycin acral vascular toxicity [8]. In normal human skin, intradermal bleomycin induced a localized time- and dose-dependent inflammatory reaction and persistent post-inflammatory hyperpigmentation; histology showed neutrophilic eccrine hidradenitis, with keratinocyte necrosis, HLA-DR and ICAM-1 expression, and endothelial cell ICAM-1 up-regulation and E-selectin induction [9]. Intralesional bleomycin therapy for warts induced keratinocyte apoptosis and complete epidermal necrosis with diffuse neutrophil accumulation and microabscess formation at the granular layer [10]. Clinically, intralesional therapy may cause persistent Raynaud's phenomenon [11,12] and loss of nails [13].

Cutaneous erythema or hyperpigmentation, which may be diffuse [14], patchy or linear, and prominent over pressure areas, especially the elbows or in striae distensae [15], is seen in approximately 30% of patients [16]. 'Flagellate' streaked erythema or pigmentation [17–25] on the trunk and proximal extremities is common (Fig. 75.8); it recurs in previously involved sites, and develops in new sites, within 24 h of rechallenge [21]. It has been proposed that trauma from scratching induces localized vasodilatation, with increased concentration of cutaneous bleomycin; hyperpigmentation has been documented in a patient treated with bleomycin where a heating pad had been applied [26]. There may be darkening of the nail cuticle and palmar creases.

References

1 Lincke-Plewig H. Bleomycin-Exanthem. *Hautarzt* 1980; **31**: 616–8.
2 Cohen IS, Mosher MB, O'Keefe EJ. Cutaneous toxicity of bleomycin therapy. *Arch Dermatol* 1973; **107**: 553–5.
3 Haerslev T, Avnstorp C, Joergensen M. Sudden onset of adverse effects due to low-dosage bleomycin indicates an idiosyncratic reaction. *Cutis* 1993; **52**: 45–6.
4 Bennett JP, Burns CP. Absence of progression of recurrent bleomycin skin toxicity without postponement or attenuation of therapy. *Am J Med* 1988; **85**: 585–6.
5 Finch WR, Rodnan GP, Buckingham RB *et al.* Bleomycin-induced scleroderma. *J Rheumatol* 1980; **7**: 651–9.
6 Bork K, Korting GW. Symptomatische Sklerodermie durch Bleomyzin. *Hautarzt* 1983; **34**: 10–2.
7 Snauwaert J, Degreef H. Bleomycin-induced Raynaud's phenomenon and acral sclerosis. *Dermatologica* 1984; **169**: 172–4.



Fig. 75.8 Flagellate pigmentation caused by bleomycin. (Courtesy of Dr A. Ilchyshyn, Coventry and Warwickshire Hospital, Coventry, UK.)

8 Bellmunt J, Navarro M, Morales S *et al.* Capillary microscopy is a potentially useful method for detecting bleomycin vascular toxicity. *Cancer* 1990; **65**: 303–9.

9 Templeton SF, Solomon AR, Swerlick RA. Intradermal bleomycin injections into normal human skin. A histopathologic and immunopathologic study. *Arch Dermatol* 1994; **130**: 577–83.

10 James MP, Collier PM, Aherne W *et al.* Histologic, pharmacologic, and immunocytochemical effects of injection of bleomycin into viral warts. *J Am Acad Dermatol* 1993; **28**: 933–7.

11 Epstein E, O'Keefe EJ, Hayes M, Bovenmyer DA. Persisting Raynaud's phenomenon following intralesional bleomycin treatment of finger warts. *J Am Acad Dermatol* 1985; **13**: 468–71.

12 Epstein E. Intralesional bleomycin and Raynaud's phenomenon. *J Am Acad Dermatol* 1991; **24**: 785–6.

13 Gonzalez FU, Gil MCC, Martinez AA *et al.* Cutaneous toxicity of intralesional bleomycin in the treatment of periungual warts. *Arch Dermatol* 1986; **122**: 974–5.

14 Wright AL, Bleehen SS, Champion AE. Reticulate pigmentation due to bleomycin: light- and electron-microscopic studies. *Dermatologica* 1990; **181**: 255–7.

15 Tsuji T, Sawabe M. Hyperpigmentation in striae distensae after bleomycin treatment. *J Am Acad Dermatol* 1993; **28**: 503–5.

16 Ohnuma T, Selawry OS, Holland JF *et al.* Clinical study with bleomycin: tolerance to twice weekly dosage. *Cancer* 1972; **30**: 914–22.

17 Cortina P, Garrido JA, Tomas JF *et al.* 'Flagellate' erythema from bleomycin, with histopathological findings suggestive of inflammatory oncotaxis. *Dermatologica* 1990; **180**: 106–9.

18 Fernandez-Obregon AC, Hogan KP, Bibro MK. Flagellate pigmentation from intrapleural bleomycin. A light and electron microscopic study. *J Am Acad Dermatol* 1985; **13**: 464–8.

19 Polla BS, Saurat JG, Merot Y, Slosman D. Flagellate pigmentation from bleomycin. *J Am Acad Dermatol* 1986; **14**: 690.

20 Rademaker M, Meyrick Thomas RH, Lowe DG, Munro DD. Linear streaking due to bleomycin. *Clin Exp Dermatol* 1987; **12**: 457–9.

21 Mowad CM, Nguyen TV, Elenitsas R, Leyden JJ. Bleomycin-induced flagellate dermatitis: a clinical and histopathological review. *Br J Dermatol* 1994; **131**: 700–2.

22 Nigro MG, Hsu S. Bleomycin-induced flagellate pigmentation. *Cutis* 2001; **68**: 285–6.

23 von Hilsheimer GE, Norton SA. Delayed bleomycin-induced hyperpigmentation and pressure on the skin. *J Am Acad Dermatol* 2002; **46**: 642–3.

24 Abess A, Keel DM, Graham BS. Flagellate hyperpigmentation following intralesional bleomycin treatment of verruca plantaris. *Arch Dermatol* 2003; **139**: 337–9.

25 Arseculeratne G, Berroeta L, Meiklejohn D *et al.* Bleomycin-induced 'flagellelate dermatitis'. *Arch Dermatol* 2007; **143**: 1461–2.

26 Kukla LJ, McGuire WP. Heat-induced recall of bleomycin skin changes. *Cancer* 1982; **50**: 2283–4.

Dactinomycin (actinomycin D)

A papulopustular acneiform sterile folliculitis, spreading from the face to the trunk and buttocks, and which may mimic septic cutaneous emboli, is common [1]. Dactinomycin-related lesions with the histology of an interface dermatitis with syringometaplasia developed in the axillae, groins and central line exit site of two children [2]. Radiation recall occurs [3]. Persistent serpentine supravenous hyperpigmentation was recorded in combination dactinomycin and vincristine therapy [4].

References

1 Epstein EH, Lutzner MA. Folliculitis induced by actinomycin D. *N Engl J Med* 1969; **281**: 1094–6.

2 Kanwar VS, Gajjar A, Ribeiro RC *et al.* Unusual cutaneous toxicity following treatment with dactinomycin: a report of two cases. *Med Pediatr Oncol* 1995; **24**: 329–33.

3 Coppes MJ, Jorgenson K, Arlette JP. Cutaneous toxicity following the administration of dactinomycin. *Med Pediatr Oncol* 1997; **29**: 226–7.

4 Marcoux D, Anex R, Russo P. Persistent serpentine supravenous hyperpigmented eruption as an adverse reaction to chemotherapy combining actinomycin and vincristine. *J Am Acad Dermatol* 2000; **43**: 540–6.

Daunorubicin

Angio-oedema with generalized urticaria [1], and hyperpigmentation of the oral mucosa, skin and nails [2–4] have been described.

References

1 Freeman AI. Clinical note. Allergic reaction to daunomycin (NSC-82151). *Cancer Chemother Rep* 1970; **54**: 475–6.

2 Kelly TM, Fishman LM, Lessner HE. Hyperpigmentation with daunorubicin therapy. *Arch Dermatol* 1984; **120**: 262–3.

3 Anderson LL, Thomas ED, Berger TG *et al.* Cutaneous pigmentation after daunorubicin chemotherapy. *J Am Acad Dermatol* 1992; **26**: 255–6.

4 Kroumpouzos G, Travers R, Allan A. Generalised hyperpigmentation with daunorubicin chemotherapy. *J Am Acad Dermatol* 2002; **46**: S1–S3.

Doxorubicin (Adriamycin)

Short-lived, localized erythema or urticaria with pruritus along the vein proximal to the injection site may occur in up to 3% of patients [1]. Angio-oedema, generalized urticaria with or without anaphylaxis and chronic urticaria have been reported rarely [2]. Cutaneous and nail pigmentation are well recognized [3,4]. Erythema and desquamation of palmar and plantar skin, with or without onycholysis, occurs frequently in patients receiving doxorubicin [5–7]. Liposomal doxorubicin is associated with a dose-limiting hand–foot syndrome with palmar–plantar erythro-

dysesthesia, stomatitis [8,9], psoriasiform pustular reactions [10], diffuse follicular rash, intertrigo-like eruption, morbilliform eruptions, and new formation of melanotic macules [11–13]. Pyridoxine has been advocated as prophylactic therapy for the palmar–plantar erythrodysesthesia [14]. Allergic cross-reaction occurs with daunorubicin. Toxic epidermal injury after intra-arterial injection [15], phlebitis and chemical cellulitis with extensive tissue necrosis and ulceration following extravasation [16] are well documented.

References

1 Vogelzang NJ. 'Adriamycin flare': a skin reaction resembling extravasation. *Cancer Treat Rep* 1979; **63**: 2067–9.
2 Hatfield AK, Harder L, Abderhalden RT. Chronic urticarial reactions caused by doxorubicin-containing regimens. *Cancer Chemother Rep* 1981; **65**: 353–4.
3 Giacobetti R, Esterly NB, Morgan ER. Nail hyperpigmentation secondary to therapy with doxorubicin. *Am J Dis Child* 1981; **135**: 317–8.
4 Curran CF. Doxorubicin-associated hyperpigmentation. *NZ Med J* 1990; **103**: 517.
5 Vogelzang NJ, Ratain MJ. Cancer chemotherapy and skin changes. *Ann Intern Med* 1985; **103**: 303–4.
6 Jones AP, Crawford SM. Anthracycline-induced toxicity affecting palmar and plantar skin. *Br J Cancer* 1989; **59**: 814.
7 Curran CF. Onycholysis in doxorubicin-treated patients. *Arch Dermatol* 1990; **126**: 1244.
8 Uziely B, Jeffers S, Isacson R *et al.* Liposomal doxorubicin: antitumor activity and unique toxicities during two complementary phase I studies. *J Clin Oncol* 1995; **13**: 1777–85.
9 Gordon KB, Tajuddin A, Guitart J *et al.* Hand–foot syndrome associated with liposome-encapsulated doxorubicin therapy. *Cancer* 1995; **75**: 2169–73.
10 Kreuter A, Gambichler T, Schlottmann R *et al.* Psoriasiform pustular eruptions from pegylated-liposomal doxorubicin in AIDS-related Kaposi's sarcoma. *Acta Derm Venereol (Stockh)* 2001; **81**: 224.
11 Lotem M, Hubert A, Lyass O *et al.* Skin toxic effects of polyethylene glycol-coated liposomal doxorubicin. *Arch Dermatol* 2000; **136**: 1475–80.
12 Campanelli A, Kerl K, Lübbe J. Severe palmoplantar erythrodysesthesia and intertrigolike eruption induced by polyethylene glycol-coated liposomal doxorubicin. *J Eur Acad Dermatol Venereol* 2006; **20**: 1022–4.
13 Cady FM, Kneuper-Hall R, Metcalf JS. Histologic patterns of polyethylene glycol-liposomal doxorubicin-related cutaneous eruptions. *Am J Dermatopathol* 2006; **28**: 168–72.
14 Rossi D, Catalano G. Pyridoxine as prophylactic therapy for palmar-plantar erythrodysesthesia associated with administration of pegylated liposomal doxorubicin (caelyx): a single-center experience. *Oncology* 2007; **73**: 277–8.
15 Von Eyben FE, Bruze M, Eksborg S *et al.* Toxic epidermal injury following intra-arterial adriamycin treatment. *Cancer* 1981; **48**: 1535–8.
16 Reilly JJ, Neifeld JP, Rosenberg SA. Clinical course and management of accidental adriamycin extravasation. *Cancer* 1977; **40**: 2053–6.

Mitomycin

Urticaria and dermatitis [1–3], particularly on the face, palms and soles, or genitals and sometimes more generalized, have been reported after intravesical therapy. Sunlight-induced recall of ulceration following extravasation has been recorded [4].

References

1 Colver GB, Inglis JA, McVittie E *et al.* Dermatitis due to intravesical mitomycin C: a delayed-type hypersensitivity reaction? *Br J Dermatol* 1990; **122**: 217–24.
2 De Groot AC, Conemans JMH. Systemic allergic contact dermatitis from intravesical instillation of the antitumor antibiotic mitomycin C. *Contact Dermatitis* 1991; **24**: 201–9.
3 Arregui MA, Aguirre A, Gil N *et al.* Dermatitis due to mitomycin C bladder instillations: study of 2 cases. *Contact Dermatitis* 1991; **24**: 368–70.
4 Fuller B, Lind M, Bonomi P. Mitomycin C extravasation exacerbated by sunlight. *Ann Intern Med* 1981; **94**: 542.

Antimetabolites

Aminoglutethimide

This inhibitor of adrenal steroid synthesis has been reported to induce SLE [1].

Reference

1 McCraken M, Benson EA, Hickling P. Systemic lupus erythematosus induced by aminoglutethimide. *BMJ* 1980; **281**: 1254.

Azathioprine

The dermatological aspects of this derivative of the antimetabolite mercaptopurine have been reviewed [1–3]. Bone marrow suppression is the main problem; blood counts should be performed weekly for the first month, then monthly thereafter. Homozygotes for the low-activity allele for thiopurine methyltransferase are at risk of myelosuppression [4–7]. It is therefore recommended that thiopurine methyltransferase levels should be measured before commencing patients on azathioprine [6]. Gastrointestinal upset is common and may necessitate discontinuation of therapy. Hypersensitivity reactions [8–10], including fever [11], maculopapular rashes, urticaria, vasculitis, erythema multiforme or erythema nodosum [12], cholestatic jaundice, hepatitis, liver necrosis, interstitial pneumonitis, polyneuropathy, pancreatitis, shock [13] with hypotension, nephritis and oliguria are well recognized.

An acneiform exanthem has been described, confirmed on challenge [14]. An eruption comprising tiny superficial blisters and peeling in the flexures is described [15]. Acute generalized exanthematous pustulosis is recorded [16]. Multiple large resistant warts are common on the hands of renal transplant recipients maintained on long-term azathioprine and prednisolone therapy; herpes simplex and herpes zoster infection may occur [17], and Norwegian scabies may be promoted [18]. Disseminated superficial actinic porokeratosis [19] and porokeratosis of Mibelli [20] have been documented. Keratoacanthomas and squamous cell carcinomas may develop [21]. Long-term therapy may predispose to the development of malignancy, especially non-Hodgkin's lymphoma [22]. Azathioprine crosses the placenta, although there is little evidence that it is teratogenic in humans, and detailed analysis of successful pregnancies notified to the European Dialysis and Transplant Association did not suggest an excessive rate of congenital abnormality [23]. However, depressed fetal haemopoiesis and resultant neonatal thrombocytopenia and leukopenia have been documented [24]. Pregnancy may be best avoided in patients receiving this drug [25]. Allopurinol may potentiate the effect of azathioprine by inhibiting its metabolism; the dose of azathioprine should therefore be reduced to one-quarter of the regular dose.

References

1 Speerstra F, Boerbooms AM, van de Putte LB *et al.* Side effects of azathioprine treatment in rheumatoid arthritis: analysis of ten years of experience. *Ann Rheum Dis* 1982; **41**: 37–9.
2 Gendler E. Azathioprine for use in dermatology. *J Dermatol Surg Oncol* 1984; **10**: 462–4.
3 Younger IR, Harris DWS, Colver GB. Azathioprine in dermatology. *J Am Acad Dermatol* 1991; **25**: 281–6.
4 Snow JL, Gibson LE. The role of genetic variation in thiopurine methyltransferase activity and the efficacy and/or side effects of azathioprine therapy in dermatologic patients. *Arch Dermatol* 1995; **131**: 193–7.

5 Snow JL, Gibson LE. A pharmacogenetic basis for the safe and effective use of azathioprine and other thiopurine drugs in dermatologic patients. *J Am Acad Dermatol* 1995; **32**: 114–6.
6 Jackson AP, Hall AG, McLelland J. Thiopurine methyltransferase levels should be measured before commencing patients on azathioprine. *Br J Dermatol* 1997; **136**: 133–4.
7 Tavadia SMB, Mydlarski PR, Reis MD *et al.* Screening for azathioprine toxicity: a pharmacoeconomic analysis based on a target case. *J Am Acad Dermatol* 2000; **42**: 628–32.
8 Stetter M, Schmidl M, Krapf R. Azathioprine hypersensitivity mimicking Goodpasture's syndrome. *Am J Kidney Dis* 1994; **23**: 874–7.
9 Knowles SR, Gupta AK, Shear NH, Sauder D. Azathioprine hypersensitivity-like reactions: a case report and a review of the literature. *Clin Exp Dermatol* 1995; **20**: 353–6.
10 Parnham AP, Dittmer I, Mathieson PW *et al.* Acute allergic reactions associated with azathioprine. *Lancet* 1996; **348**: 542–3.
11 Smak Gregoor PJ, van Saase JL, Weimar W, Kramer P. Fever and rigors as sole symptoms of azathioprine hypersensitivity. *Neth J Med* 1995; **47**: 288–90.
12 de Fonclare A-L, Khosrotehrani K, Aractingi S *et al.* Erythema nodosum-like eruption as a manifestation of azathioprine hypersensitivity in patients with inflammatory bowel disease. *Arch Dermatol* 2007; **143**: 744–8.
13 Jones JJ, Ashworth J. Azathioprine-induced shock in dermatology patients. *J Am Acad Dermatol* 1993; **29**: 795–6.
14 Schmoeckel C, von Liebe V. Akneiformes Exanthem durch Azathioprin. *Hautarzt* 1983; **34**: 413–5.
15 Hermanns-Le T, Pierard GE. Azathioprine-induced skin peeling syndrome. *Dermatology* 1997; **194**: 175–6.
16 Elston GE, Johnston GA, Mortimer NJ, Harman KE. Acute generalized exanthematous pustulosis associated with azathioprine hypersensitivity. *Clin Exp Dermatol* 2007; **32**: 52–3.
17 Spencer ES, Anderson HK. Viral infections in renal allograft recipients treated with long-term immunosuppression. *BMJ* 1979; **2**: 829–30.
18 Paterson WD, Allen BR, Beveridge GW. Norwegian scabies during immunosuppressive therapy. *BMJ* 1983; **4**: 211–2.
19 Neumann RA, Knobler RM, Metze D *et al.* Disseminated superficial porokeratosis and immunosuppression. *Br J Dermatol* 1988; **119**: 375–80.
20 Tatnell FM, Sarkany I. Porokeratosis of Mibelli in an immunosuppressed patient. *J R Soc Med* 1987; **80**: 180–1.
21 McLelland J, Rees A, Williams G *et al.* The incidence of immunosuppression-related skin disease in long-term transplant patients. *Transplantation* 1988; **46**: 871–4.
22 Phillips LT, Salisbury J, Leigh I, Baker H. Non-Hodgkin's lymphoma associated with long-term azathioprine therapy. *Clin Exp Dermatol* 1987; **12**: 444–5.
23 Registration Committee of the European Dialysis and Transplant Association. Successful pregnancies in women treated by dialysis and kidney transplantation. *Br J Obstet Gynaecol* 1980; **87**: 839–45.
24 Davison JM, Dellagrammatikas H, Parkin JM. Maternal azathioprine therapy and depressed haemopoiesis in the babies of renal allograft patients. *Br J Obstet Gynaecol* 1985; **92**: 233–9.
25 Gebhart DOE. Azathioprine teratogenicity: review of the literature and case report. *Obstet Gynecol* 1983; **61**: 270.

Cytarabine (cytosine arabinoside)

This drug interferes with pyrimidine synthesis. A self-limited palmoplantar erythema, occasionally with bullae, may occur [1–4]. Neutrophilic eccrine hidradenitis has been reported [5]. A syndrome with fever, malaise, arthralgia, conjunctivitis and diffuse erythematous maculopapular rash is documented [6]. The overall incidence of cutaneous reactions, including morbilliform eruptions, acral erythema, swelling and generalized urticaria, was almost 53% in one series [7].

References

1 Walker IR, Wilson WEB, Sauder DN *et al.* Cytarabine-induced palmar–plantar erythema. *Arch Dermatol* 1985; **121**: 1240–1.
2 Shall L, Lucas GS, Whittaker JA, Holt PJA. Painful red hands: a side-effect of leukaemia therapy. *Br J Dermatol* 1988; **119**: 249–53.
3 Brown J, Burck K, Black D, Collins C. Treatment of cytarabine acral erythema with corticosteroids. *J Am Acad Dermatol* 1991; **24**: 1023–5.
4 Richards C, Wujcik D. Cutaneous toxicity associated with high-dose cytosine arabinoside. *Oncol Nurs Forum* 1992; **19**: 1191–5.
5 Flynn TC, Harrist TJ, Murphy GF *et al.* Neutrophilic eccrine hidradenitis: a distinctive type of neutrophilic dermatosis associated with cytarabine therapy and acute leukemia. *J Am Acad Dermatol* 1984; **11**: 584–90.
6 Shah SS, Rybak ME, Griffin TW. The cytarabine syndrome in an adult. *Cancer Treat Rep* 1983; **67**: 405–6.
7 Cetkovska P, Pizinger K, Cetkovsky P. High-dose cytosine arabinoside-induced cutaneous reactions. *J Eur Acad Dermatol Venereol* 2002; **16**: 481–5.

Fluorouracil

Anaphylaxis is rare; alopecia and recall phenomena [1] may be seen. Erythema followed by hyperpigmentation of sun-exposed areas occurs in up to 5% of patients [2]. Hyperpigmentation may be reticulate [3]. Photosensitivity is recorded; pellagra may be caused by direct inhibition of the transformation of tryptophan into nicotinamide. Rarely, hyperpigmented streaks (serpentine supravenous hyperpigmentation) develop over arm veins used for injection [2,4–6]. Continuous infusion may be followed by the development of erythema, oedema and desquamation of the hands [7–11]. Pyridoxine may decrease the intensity and pain of fluorouracil-induced acral erythema [9]. Oral administration resulted in painful erythema multiforme-like erosions and blisters on the soles and arms in one case [10]. Systemic fluorouracil may result in marked inflammation of metastatic skin lesions [12] and of solar keratoses [13]. Topical application may lead to hyperpigmentation with or without a preceding irritant or allergic contact dermatitis [14].

Capecitabine

Capecitabine is a fluoropyrimidine carbamate that is metabolized to fluorouracil, and has been recorded as causing hand–foot syndrome in 50% of patients, and rarely leopard-like vitiligo, onycholysis and periungual pyogenic granulomas [15].

Gemcitabine

This drug has caused radiation recall [16].

References

1 Prussick R, Thibault A, Turner ML. Recall of cutaneous toxicity from fluorouracil. *Arch Dermatol* 1993; **129**: 644–5.
2 Hrushesky WJ. Unusual pigmentary changes associated with 5-fluorouracil therapy. *Cutis* 1980; **26**: 181–2.
3 Jogi R, Garman M, Pielop J *et al.* Reticulate hyperpigmentation secondary to 5-fluorouracil and idarubicin. *J Drugs Dermatol* 2005; **4**: 652–6.
4 Hrushesky WJ. Serpentine supravenous 5-fluorouracil (NSC-19893) hyperpigmentation. *Cancer Treat Rep* 1976; **60**: 639.
5 Vukelja SJ, Bonner MW, McCollough M *et al.* Unusual serpentine hyperpigmentation associated with 5-fluorouracil. Case report and review of cutaneous manifestations associated with systemic 5-fluorouracil. *J Am Acad Dermatol* 1991; **25**: 905–8.
6 Pujol RM, Rocamora V, Lopez-Pousa A *et al.* Persistent supravenous erythematous eruption: a rare local complication of intravenous 5-fluorouracil therapy. *J Am Acad Dermatol* 1998; **39**: 839–42.
7 Feldman LD, Jaffer A. Fluorouracil-associated palmar–plantar erythrodysesthesia syndrome. *JAMA* 1985; **254**: 3479.
8 Guillaume J-C, Carp E, Rougier P *et al.* Effects secondaires cutanéo-muqueux des perfusions continues de 5-fluorouracile: 12 observations. *Ann Dermatol Vénéréol* 1988; **115**: 1167–9.

9 Vukelja SJ, Lombardo RA, James WD *et al.* Pyridoxine for the palmar–plantar erythrodysesthesia syndrome. *Ann Intern Med* 1989; **111**: 688–9.
10 Ueki H, Namba M. Arzneimittelexanthem durch ein neues 5-Fluorourazilderivat. *Hautarzt* 1980; **31**: 207–8.
11 Chiara S, Nobile MT, Barzacchi C *et al.* Hand–foot syndrome induced by high-dose, short-term, continuous 5-fluorouracil infusion. *Eur J Cancer* 1997; **33**: 967–9.
12 Schlang HA. Inflammation of malignant skin involvement with fluorouracil. *JAMA* 1977; **238**: 1722.
13 Bataille V, Cunningham D, Mansi J, Mortimer P. Inflammation of solar keratoses following systemic 5-fluorouracil. *Br J Dermatol* 1996; **135**: 478–80.
14 Goette DK, Odom RB. Allergic contact dermatitis to topical fluorouracil. *Arch Dermatol* 1977; **113**: 1058–61.
15 Piguet V, Borradori L. Pyogenic granuloma-like lesions during capecitabine therapy. *Br J Dermatol* 2002; **147**: 1270–2.
16 Jeter MD, Janne PA, Brooks S *et al.* Gemcitabine-induced radiation recall. *Int J Radiat Oncol Biol Phys* 2002; **53**: 394–400.

Methotrexate

Dermatological aspects. These have been reviewed [1–3]. Methotrexate is a folic acid analogue and antagonist that inactivates dihydrofolate reductase. There is marked individual variation in absorption from the gastrointestinal tract, and hence in expression of toxic effects. Alopecia occurs in 6% of patients receiving low-dose therapy for psoriasis and in 8% of patients on high-dose regimens for malignancy, and is usually the result of telogen effluvium. Intermittent high dosage has resulted in horizontal pigmented banding of hair (the 'flag sign' of chemotherapy) [4]. Urticaria develops in about 4% of patients on low-dose oral or parenteral therapy for psoriasis [5]. Exacerbation of urticarial vasculitis has been documented [6]. Photosensitivity occurs in up to 5% of cases. Methotrexate use has been associated with severe reactivation of sunburn [7,8]; in one case, there was sparing of chronically sun-exposed skin [8]. Chronic viral wart and molluscum infections may result from immunosuppression. Cutaneous toxicity with local epidermal necrosis may occasionally occur [9,10]. A macular erythema occurring in 15% of patients, and biopsy-proven capillaritis, have been reported with high-dose therapy [3]. An eruption of erythematous indurated papules on the proximal parts of the limbs has been documented in patients with collagen vascular disease [11]. Anaphylactic reactions [12] and pain, burning, erythema and desquamation of the palms and soles [13–15] are seen with high-dose intravenous methotrexate, but are extremely rare. Vasculitis has been very rarely documented with both intermediate dosage therapy for leukaemia [16] and high-dose therapy [17]. TEN is recorded [18,19], and occurred after a single injection of 25 mg for pustular psoriasis [19].

References

1 Plantin P, Saraux A, Guillet G. Méthotrexate en dermatologie: aspects actuels. *Ann Dermatol Vénéréol* 1989; **116**: 109–15.
2 Zachariae H. Methotrexate side-effects. *Br J Dermatol* 1990; **122** (Suppl. 36): 127–33.
3 Olsen EA. The pharmacology of methotrexate. *J Am Acad Dermatol* 1991; **25**: 306–18.
4 Wheeland RG, Burgdorf WH, Humphrey GB. The flag sign of chemotherapy. *Cancer* 1983; **51**: 1356–8.
5 Weinstein GD, Frost P. Methotrexate for psoriasis. A new therapeutic schedule. *Arch Dermatol* 1971; **103**: 33–8.
6 Borcea A, Greaves MW. Methotrexate-induced exacerbation of urticarial vasculitis: an unusual adverse reaction. *Br J Dermatol* 2000; **143**: 203–4.
7 Mallory SB, Berry DH. Severe reactivation of sunburn following methotrexate use. *Pediatrics* 1986; **78**: 514–5.
8 Westwick TJ, Sherertz EF, McCarley D, Flowers FP. Delayed reactivation of sunburn by methotrexate: sparing of chronically sun-exposed skin. *Cutis* 1987; **39**: 49–51.
9 Harrison PV. Methotrexate-induced epidermal necrosis. *Br J Dermatol* 1987; **116**: 867–9.
10 Kaplan DL, Olsen EA. Erosion of psoriatic plaques after chronic methotrexate administration. *Int J Dermatol* 1988; **27**: 59–62.
11 Goerttler E, Kutzner H, Peter HH, Requena L. Methotrexate-induced papular eruption in patients with rheumatic diseases: a distinctive adverse cutaneous reaction produced by methotrexate in patients with collagen vascular diseases. *J Am Acad Dermatol* 1999; **40**: 702–7.
12 Klimo P, Ibrahim E. Anaphylactic reaction to methotrexate used in high doses as an adjuvant treatment of osteogenic sarcoma. *Cancer Treat Rep* 1981; **65**: 725.
13 Doyle LA, Berg C, Bottino G *et al.* Erythema and desquamation after high-dose methotrexate. *Ann Intern Med* 1983; **98**: 611–2.
14 Martins da Cunha AC, Rappersberger K, Gadner H. Toxic skin reaction restricted to palms and soles after high-dose methotrexate. *Pediatr Hematol Oncol* 1991; **8**: 277–80.
15 Aractingi S, Briant E, Marolleau J *et al.* Décollements cutanés induits par le methotrexate. *Presse Med* 1992; **21**: 1668–70.
16 Fondevila CG, Milone GA, Pavlovsky S. Cutaneous vasculitis after intermediate dose of methotrexate (IDMTX). *Br J Haematol* 1989; **72**: 591–2.
17 Navarro M, Pedragosa R, Lafuerza A *et al.* Leukocytoclastic vasculitis after high-dose methotrexate. *Ann Intern Med* 1986; **105**: 471–2.
18 Collins P, Rogers S. The efficacy of methotrexate in psoriasis: a review of 40 cases. *Clin Exp Dermatol* 1992; **17**: 257–60.
19 Primka EJ III, Camisa C. Methotrexate-induced toxic epidermal necrolysis in a patient with psoriasis. *J Am Acad Dermatol* 1997; **36**: 815–8.

Systemic complications. Because folic acid is an essential cofactor for DNA synthesis and cell division, bone marrow suppression may occur even on low-dose therapy [1–4]. Thrombocytopenia may develop after a single test dose [5]. Severe bone marrow suppression [6] with the dosage used in the therapy of psoriasis is fortunately not common. Stomatitis may be a warning sign of overdosage. The risk of myelosuppression is much greater in the presence of renal impairment. Gastrointestinal upset is common. Abnormalities of taste sensation occur rarely [7].

The main hazard is hepatotoxicity with long-term use [8]. The risk of developing severe hepatotoxicity is related to the daily dose, the dose frequency and the cumulative dose [9]. Alcohol consumption, underlying liver disease and obesity, especially in the presence of diabetes, are aggravating factors. Previous monitoring recommendations included obtaining baseline haematological, renal and hepatic function tests and a liver biopsy before or within 4 months of starting therapy, and repeating after every 1.5 g [10]. Liver function tests may be unreliable indicators of fibrosis or cirrhosis. These guidelines appeared prudent but have never been rigorously tested, and are variously applied in clinical practice [10,11]. There seems to be a discrepancy between the degree of hepatotoxicity in rheumatoid arthritis and that in psoriasis, and many rheumatologists do not routinely carry out liver biopsy [11]. The requirement for liver biopsies in psoriasis patients on long-term, low-dose, once-weekly oral methotrexate has been questioned [12]. Radionuclide liver scans are thought to be of little value in the detection of methotrexate-induced liver disease, but liver ultrasound may be of some assistance [13]. Abnormal liver biopsy may improve after cessation of therapy [14]. Assay of serum levels of the aminopropeptide of type III procollagen is

increasingly used to screen for patients in whom liver biopsy is really mandatory [15–17].

Acute renal failure may follow high-dose methotrexate therapy, although renal damage is rare in patients treated for psoriasis. Pulmonary complications, such as pneumonitis or fibrosis, are rare [18,19]. Hepatotoxicity with methotrexate is more common in psoriatic arthritis, and pulmonary toxicity in rheumatoid arthritis [20]. There do not appear to be adverse effects on humoral or cellular immunity from low weekly doses as given for rheumatoid arthritis or psoriasis [21]. A survey of systemic complications of methotrexate therapy in rheumatoid arthritis patients over the period between 1986 and 1999 found that 10.7% of all patients stopped because of inefficacy or patient choice, 5.5% stopped due to abnormal haematology (usually low neutrophils), and 5.5% stopped due to abnormalities in liver function tests. Life-threatening side-effects were identified in 1.8%, including cytopenias, pneumonitis and disseminated varicella zoster, and were fatal in 0.3% of cases [22].

Methotrexate is a known teratogen, and may cause oligospermia [23,24]. It is recommended that patients avoid pregnancy or impregnation during, and for at least 12 weeks after cessation of, methotrexate therapy [25].

Care must be taken with regard to potential drug interactions with methotrexate [26,27]. Drugs that also interfere with folate metabolism, such as trimethoprim–sulfamethoxazole [28–30], may cause pancytopenia; both trimethoprim and sulfamethoxazole bind to dihydrofolate reductase. Drugs that displace methotrexate from plasma protein-binding sites, such as salicylates, sulphonamides and diphenylhydantoin, as well as drugs that impair the renal clearance of methotrexate, such as NSAIDs and sulphonamides, may also cause pancytopenia. A toxic reaction occurred in a patient treated with penicillin and furosemide [31].

References

1 MacKinnon SK, Starkebaum G, Wilkens RF. Pancytopenia associated with low-dose pulse methotrexate in the treatment of rheumatoid arthritis. *Semin Arthitis Rheum* 1985; **15**: 119–26.

2 Shupack JL, Webster GF. Pancytopenia following low-dose oral methotrexate therapy for psoriasis. *JAMA* 1988; **259**: 3594–6.

3 Abel EA, Farber EM. Pancytopenia following low-dose methotrexate therapy. *JAMA* 1988; **259**: 3612.

4 Copur S, Dahut W, Chu E, Allegra CJ. Bone marrow aplasia and severe skin rash after a single low dose of methotrexate. *Anticancer Drugs* 1995; **6**: 154–7.

5 Jih DM, Werth VP. Thrombocytopenia after a single test dose of methotrexate. *J Am Acad Dermatol* 1998; **39**: 349–51.

6 Takami M, Kuniyoshi Y, Oomukai T *et al*. Severe complications after high-dose methotrexate treatment. *Acta Oncol* 1995; **34**: 611–2.

7 Duhra P, Foulds IS. Methotrexate-induced impairment of taste acuity. *Clin Exp Dermatol* 1988; **13**: 126–7.

8 Zachariae H, Kragballe K, Søgaard H. Methotrexate induced liver cirrhosis: studies including serial liver biopsies during continued treatment. *Br J Dermatol* 1980; **102**: 407–12.

9 Lewis JH, Schiff E. ACG Committee on FDA-Related Matters. Methotrexate-induced chronic liver injury: guidelines for detection and prevention. *Am J Gastroenterol* 1988; **88**: 1337–45.

10 Roenigk HH Jr, Auerbach R, Maibach HI, Weinstein GD. Methotrexate in psoriasis: revised guidelines. *J Am Acad Dermatol* 1988; **19**: 145–56.

11 Petrazzuoli M, Rothe MJ, Grin-Jorgensen C *et al.* Monitoring patients taking methotrexate for hepatotoxicity. Does the standard of care match published guidelines? *J Am Acad Dermatol* 1994; **31**: 969–77.

12 Boffa MJ, Chalmers RJG, Haboubi NY *et al*. Sequential liver biopsies during long-term methotrexate treatment for psoriasis: a reappraisal. *Br J Dermatol* 1995; **133**: 774–8.

13 Coulson IH, McKenzie J, Neild VS *et al.* A comparison of liver ultrasound with liver biopsy histology in psoriatics receiving long-term methotrexate therapy. *Br J Dermatol* 1987; **116**: 491–5.

14 Newman M, Auerbach R, Feiner H *et al.* The role of liver biopsies in psoriatic patients receiving long-term methotrexate treatment. Improvement in liver abnormalities after cessation of therapy. *Arch Dermatol* 1989; **125**: 1218–24.

15 Zachariae H, Søgaard H, Heickendorff L. Serum aminoterminal propeptide of type III procollagen. *Acta Derm Venereol (Stockh)* 1989; **69**: 241–4.

16 Boffa MJ, Smith A, Chalmer RJG *et al.* Serum type III procollagen aminopeptide for assessing liver damage in methotrexate-treated psoriatic patients. *Br J Dermatol* 1996; **135**: 538–44.

17 Zachariae H, Heickendorff L, Søgaard H. The value of amino-terminal propeptide of type III procollagen in routine screening for methotrexate-induced liver fibrosis: a 10 year follow up. *Br J Dermatol* 2001; **144**: 100–3.

18 Phillips TJ, Jones DH, Baker H. Pulmonary complications following methotrexate therapy. *J Am Acad Dermatol* 1987; **16**: 373–5.

19 Carson CW, Cannon GW, Egger MJ *et al*. Pulmonary disease during the treatment of rheumatoid arthritis with low dose pulse methotrexate. *Semin Arthritis Rheum* 1987; **16**: 186–95.

20 Helliwell PS, Taylor WJ; CASPAR Study Group. Treatment of psoriatic arthritis and rheumatoid arthritis with disease modifying drugs—comparison of drugs and adverse reactions. *J Rheumatol* 2008; **35**: 472–6.

21 Andersen PA, West SG, O'Dell JR *et al*. Weekly pulse methotrexate in rheumatoid arthritis: clinical and immunologic effects in a randomized, double-blind study. *Ann Intern Med* 1985; **103**: 489–96.

22 Kinder AJ, Hassell AB, Brand J *et al*. The treatment of inflammatory arthritis with methotrexate in clinical practice: treatment duration and incidence of adverse drug reactions. *Rheumatology (Oxford)* 2005; **44**: 61–6.

23 Sussman A, Leonard JM. Psoriasis, methotrexate, and oligospermia. *Arch Dermatol* 1980; **116**: 215–7.

24 Shamberger RC, Rosenberg SA, Seipp CA *et al*. Effects of high-dose methotrexate and vincristine on ovarian and testicular functions in patients undergoing postoperative adjuvant treatment of osteosarcoma. *Cancer Treat Rep* 1981; **65**: 739–46.

25 Morris LF, Harrod MJ, Menter MA, Silverman AK. Methotrexate and reproduction in men: case report and recommendations. *J Am Acad Dermatol* 1993; **29**: 913–6.

26 Evans WE, Christensen ML. Drug interactions with methotrexate. *J Rheumatol* 1985; **12** (Suppl. 12): 15–20.

27 Liddle BJ, Marsden JR. Drug interactions with methotrexate. *Br J Dermatol* 1989; **120**: 582–3.

28 Thomas DR, Dover JS, Camp RDR. Pancytopenia induced by the interaction between methotrexate and trimethoprim–sulfamethoxazole. *J Am Acad Dermatol* 1987; **17**: 1055–6.

29 Ferrazzini G, Klein J, Sulh H *et al.* Interaction between trimethoprim–sulfamethoxazole and methotrexate in children with leukemia. *J Pediatr* 1990; **117**: 823–6.

30 Groenendal H, Rampen FHJ. Methotrexate and trimethoprim–sulphamethoxazole: a potentially hazardous combination. *Clin Exp Dermatol* 1990; **15**: 358–60.

31 Nierenberg DW, Mamelok RD. Toxic reaction to methotrexate in a patient receiving penicillin and furosemide. *Arch Dermatol* 1983; **119**: 449–50.

Vinca alkaloids and etoposide

These drugs cause metaphase arrest by interfering with microtubule assembly.

Etoposide (VP-16)

This semi-synthetic podophyllotoxin derivative causes bone marrow suppression, alopecia and gastrointestinal symptoms. It has caused Stevens–Johnson syndrome and radiation recall. Four cases of a diffuse, erythematous, maculopapular rash occurring 5–9 days after initiation of therapy, with spontaneous resolution within 3 weeks, have been reported [1]. On histology, scattered,

markedly enlarged individual keratinocytes with a 'starburst' nuclear chromatin pattern were seen. Hypersensitivity reactions are generally held to be rare [2–4], but 51% of patients with newly diagnosed Hodgkin's disease had one or more acute hypersensitivity reactions to etoposide administration, including flushing, respiratory problems, changes in blood pressure and abdominal pain [5].

Vincristine

Peripheral neuropathy is well recognized with long-term therapy [6].

Vinblastine

Photosensitivity is common [7]. Acute alopecia and radiation recall are documented. Erythema multiforme-like reactions are described following intravenous injection [8].

References

1 Yokel BK, Friedman KJ, Farmer ER, Hood AF. Cutaneous pathology following etoposide therapy. *J Cutan Pathol* 1987; **14**: 326–30.
2 Kasperek C, Black CD. Two cases of suspected immunologic-based hypersensitivity reactions to etoposide therapy. *Ann Pharmacother* 1992; **26**: 1227–30.
3 de Souza P, Friedlander M, Wilde C *et al*. Hypersensitivity reactions to etoposide. A report of three cases and review of the literature. *Am J Clin Oncol* 1994; **17**: 387–9.
4 Hoetelmans RM, Schornagel JH, ten Bokkel Huinink WW, Beijnen JH. Hypersensitivity reactions to etoposide. *Ann Pharmacother* 1996; **30**: 367–71.
5 Hudson MM, Weinstein HJ, Donaldson SS *et al*. Acute hypersensitivity reactions to etoposide in a VEPA regimen for Hodgkin's disease. *J Clin Oncol* 1993; **11**: 1080–4.
6 Watkins SM, Griffin JP. High incidence of vincristine-induced neuropathy in lymphomas. *BMJ* 1978; **i**: 610–2.
7 Breza TS, Halprin KM, Taylor JR. Photosensitivity reaction to vinblastine. *Arch Dermatol* 1975; **111**: 1168–70.
8 Arias D, Requena L, Hasson A *et al*. Localized epidermal necrolysis (erythema multiforme-like reactions) following intravenous injection of vinblastine. *J Cutan Pathol* 1991; **18**: 344–6.

Enzymes

L-Asparaginase (crisantaspase)

Dose-dependent IgE-mediated hypersensitivity reactions, including urticaria and anaphylaxis, are frequent, especially when the drug is used alone [1]. Allergic reactions to intramuscular L-asparaginase include local painful erythema, and urticaria or a general exanthem; continuous infusion is better tolerated [2].

References

1 Ertel IJ, Nesbit ME, Hammond D *et al*. Effective dose of L-asparaginase for induction of remission in previously treated children with acute lymphocytic leukemia: a report from Children's Cancer Study Group. *Cancer Res* 1979; **39**: 3893–6.
2 Rodriguez T, Baumgarten E, Fengler R *et al*. Langzeitinfusion von L-Asparaginase: eine Alternative zur intramuskularen Injektion? *Klin Pediatr* 1995; **207**: 207–10.

Inhibitors of epidermal growth factor receptor (anti-EGFR therapy)

Anti-EGFR (epidermal growth factor receptor) therapies are active against certain solid tumours, including colorectal, head and neck, pancreatic and lung cancers; they include tyrosine kinase inhibitors and monoclonal antibodies which act via different mechanisms. Monoclonal antibodies bind to the extracellular domain of EGFR, preventing ligand binding and interrupting the signalling cascade, whereas tyrosine kinase inhibitors bind to the intracellular domain of EGFR and inhibit the downstream effects of EGFR ligand binding [1]. Adverse effects of these agents have been extensively reviewed [2–10]. Several studies have reported a link between the antitumour efficacy of EGFR inhibitors and cutaneous side effects [3,7]. Cutaneous adverse reactions to monoclonal antibodies may be limited to infusion reactions, local inflammation at injection sites and ill-defined transient eruptions; however, their use in gastrointestinal and head and neck cancer has been frequently associated with significant skin reactions [6]. Key cutaneous manifestations include papulopustular follicular acneiform eruptions, superinfection with *Staphylococcus aureus*, hair and nail disorders including paronychia, pruritus, hyperpigmentation, mucositis, xerosis, eczema and desquamation [2,4,5,8–10].

Cetuximab [8–16]. The most common toxicities are rash, diarrhoea, fever, headache, nausea, hypomagnesaemia and hypersensitivity reactions. Paronychia and aphthous ulcers, follicular papulopustules, and a facial acneiform follicular eruption are recorded with this chimeric antiepidermal growth factor receptor antibody. Adverse cutaneous reactions appear to be a marker for response.

Erlotinib. Acneiform reactions occur [17].

Imatinib [18,19]. This protein tyrosine kinase inhibitor, used in the therapy of chronic myeloid leukaemia, commonly causes maculopapular exanthematous eruptions, oedema, and periorbital oedema; reactions are usually self-limited despite continuation of the drug. Rarer side effects include: hypopigmentation, lichenoid reactions [20,21], pityriasiform eruptions, pityriasis rosea, psoriasis, exfoliative dermatoses, acute generalized exanthematous pustulosis, purpuric vasculitis, erythema nodosum, reactivation or induction of porphyria cutanea tarda, neutrophilic eccrine hidradenitis, Sweet's syndrome [22], EBV-positive cutaneous B-cell lymphoproliferative disease [23], follicular mucinosis, pseudolymphoma-type drug eruptions, lymphomatoid granulomatosis [24], eosinophilia, fasciitis, and a mycosis fungoides-like reaction with antinuclear autoantibodies [25], Stevens–Johnson syndrome [26], and toxic epidermal necrolysis.

Sorafenib. A hand–foot skin reaction is a distinctive cutaneous side effect of this antineoplastic tyrosine kinase inhibitor for metastatic cancer. Well-demarcated, tender, erythematous papules and plaques with greyish blisters, or hyperkeratotic, callus-like formations on palmoplantar surfaces and distal phalanges occur. Other skin toxicities encompassed angular cheilitis, seborrhoeic dermatitis and perianal dermatitis. Histopathological findings include keratinocyte vacuolar degeneration, presence of intracytoplasmic eosinophilic bodies, and intraepidermal blisters [27].

References

1 Vokes EE, Chu E. Anti-EGFR therapies: clinical experience in colorectal, lung, and head and neck cancers. *Oncology (Williston Park)* 2006; **20** (5 Suppl. 2): 15–25.
2 Fox LP. Pathology and management of dermatologic toxicities associated with anti-EGFR therapy. *Oncology (Williston Park)* 2006; **20** (5 Suppl. 2): 26–34.

3 Robert C, Soria JC, Spatz A *et al.* Cutaneous side-effects of kinase inhibitors and blocking antibodies. *Lancet Oncol* 2005; **6**: 491–500.
4 Boone SL, Rademaker A, Liu D *et al.* Impact and management of skin toxicity associated with anti-epidermal growth factor receptor therapy: survey results. *Oncology* 2007; **72**: 152–9.
5 Galimont-Collen AF, Vos LE, Lavrijsen AP *et al.* Classification and management of skin, hair, nail and mucosal side-effects of epidermal growth factor receptor (EGFR) inhibitors. *Eur J Cancer* 2007; **43**: 845–51.
6 Myskowski PL, Halpern AC. Cutaneous adverse reactions to therapeutic monoclonal antibodies for cancer. *Curr Allergy Asthma Rep* 2008; **8**: 63–8.
7 Hammond-Thelin LA. Cutaneous reactions related to systemic immunomodulators and targeted therapeutics. *Dermatol Clin* 2008; **26**: 121–59, ix.
8 Mitchell EP, Perez-Soler R, Van Cutsem E, Lacouture ME. Clinical presentation and pathophysiology of EGFRI dermatologic toxicities. *Oncology (Williston Park)* 2007; **21** (11 Suppl. 5): 4–9.
9 Yamazaki N, Muro K. Clinical management of EGFRI dermatologic toxicities: the Japanese perspective. *Oncology (Williston Park)* 2007; **21** (11 Suppl. 5): 27–8.
10 Segaert S, Van Cutsem E. Clinical management of EGFRI dermatologic toxicities: the European perspective. *Oncology (Williston Park)* 2007; **21** (11 Suppl. 5): 22–6.
11 Busam KJ, Capodieci P, Motzer R *et al.* Cutaneous side-effects in cancer patients treated with the antiepidermal growth factor receptor antibody C225. *Br J Dermatol* 2001; **144**: 1169–76.
12 Boucher KW, Davidson K, Mirakhur B *et al.* Paronychia induced by cetuximab, an antiepidermal growth factor receptor antibody. *J Am Acad Dermatol* 2002; **45**: 632–3.
13 Kimyai-Asadi A, Jih MH. Follicular toxic effects of chimeric anti-epidermal growth factor receptor antibody cetuximab used to treat human solid tumors. *Arch Dermatol* 2002; **138**: 129–31.
14 Wong SF. Cetuximab: an epidermal growth factor receptor monoclonal antibody for the treatment of colorectal cancer. *Clin Ther* 2005; **27**: 684–94.
15 Blick SK, Scott LJ. Cetuximab: a review of its use in squamous cell carcinoma of the head and neck and metastatic colorectal cancer. *Drugs* 2007; **67**: 2585–607.
16 Saif MW, Kim R. Incidence and management of cutaneous toxicities associated with cetuximab. *Expert Opin Drug Saf* 2007; **6**: 175–82.
17 Schalock PC, Zug KA. Acneiform reaction to erlotinib. *Dermatitis* 2007; **18**: 230–1.
18 Valeyrie L, Bastuji-Garin S, Revuz J *et al.* Adverse cutaneous reactions to imatinib (ST1571) in Philadelphia chromosome-positive leukemias: a prospective study of 54 patients. *J Am Acad Dermatol* 2003; **48**: 201–6.
19 Scheinfeld N. Imatinib mesylate and dermatology part 2: a review of the cutaneous side effects of imatinib mesylate. *J Drugs Dermatol* 2006; **5**: 228–31.
20 Ena P, Chiarolini F, Siddi GM, Cossu A. Oral lichenoid eruption secondary to imatinib (Glivec). *J Dermatolog Treat* 2004; **15**: 253–5.
21 Pascual JC, Matarredona J, Miralles J *et al.* Oral and cutaneous lichenoid reaction secondary to imatinib: report of two cases. *Int J Dermatol* 2006; **45**: 1471–3.
22 Ayirookuzhi SJ, Ma L, Ramshesh P, Mills G. Imatinib-induced Sweet syndrome in a patient with chronic myeloid leukemia. *Arch Dermatol* 2005; **141**: 368–70.
23 Bekkenk MW, Vermeer MH, Meijer CJ *et al.* EBV-positive cutaneous B-cell lymphoproliferative disease after imatinib mesylate. *Blood* 2003: **102**: 4243.
24 Yazdi AS, Metzler G, Weyrauch SI *et al.* Lymphomatoid granulomatosis induced by imatinib-treatment. *Arch Dermatol* 2007; **143**: 1222–3.
25 Jardin F, Courville P, Lenain P *et al.* Concomitant eosinophilia, fasciitis, and mycosis fungoides-like reaction with antinuclear autoantibodies in chronic myeloid leukaemia: role of a T-cell clone induced by imatinib. *Lancet Oncol* 2005; **6**: 728–9.
26 Mahapatra M, Mishra P, Kumar R. Imatinib-induced Stevens–Johnson syndrome: recurrence after re-challenge with a lower dose. *Ann Hematol* 2007; **86**: 537–8.
27 Yang CH, Lin WC, Chuang CK *et al.* Hand-foot skin reaction in patients treated with sorafenib: a clinicopathological study of cutaneous manifestations due to multitargeted kinase inhibitor therapy. *Br J Dermatol* 2008; **158**: 592–6.

Miscellaneous chemotherapeutic agents

Acridinyl anisidide (AMSA)

Skin reactions are rare, but widespread erythema has been reported [1].

Reference

1 Rosenfelt FP, Rosenbloom BE, Weinstein IM. Allergic reaction following administration of AMSA. *Cancer Treat Rep* 1982; **66**: 549–50.

Bortezomib

Skin reactions to this proteasome inhibitor used in the treatment of multiple myeloma have been reviewed [1–4]. These include sharply-demarcated erythematous plaques or nodules on the trunk, generalized morbilliform erythema with ulcerations and fever, and a neutrophilic dermatitis. The time between the first bortezomib dose and occurrence of the cutaneous eruptions was at least 30 days; eruptions usually resolved within a few days. Histological findings ranged from perivascular dermatitis to interstitial and interface dermatitis [2].

References

1 Agterof MJ, Biesma DH. Images in clinical medicine. Bortezomib-induced skin lesions. *N Engl J Med* 2005; **352**: 2534.
2 Wu KL, Heule F, Lam K, Sonneveld P. Pleomorphic presentation of cutaneous lesions associated with the proteasome inhibitor bortezomib in patients with multiple myeloma. *J Am Acad Dermatol* 2006; **55**: 897–900.
3 Paiva CM, Kurtis B, Mekki M *et al.* Neutrophilic dermatitis associated with bortezomib in a patient with multiple myeloma. *Ann Oncol* 2007; **18**: 1744–5.
4 Sanchez-Politta S, Favet L, Kerl K *et al.* Bortezomib-induced skin eruption. *Dermatology* 2008; **216**: 156–8.

Bromodeoxyuridine

A distinctive eruption comprising linear supravenous papules and erythroderma has been described with bromodeoxyuridine given in combination with radiotherapy for central nervous system tumours [1]. Ipsilateral facial dermatitis with epilation of eyebrows and eyelashes, ocular irritation, bilateral nail dystrophy, oral ulceration, exanthem or erythema multiforme have also been described [2].

References

1 Fine J-D, Breathnach SM. Distinctive eruption characterized by linear supravenous papules and erythroderma following broxuridine (bromodeoxyuridine) therapy and radiotherapy. *Arch Dermatol* 1986; **122**: 199–200.
2 McCuaig CM, Ellis CN, Greenberg HS *et al.* Mucocutaneous complications of intra-arterial 5-bromodeoxyuridine and radiation. *J Am Acad Dermatol* 1989; **21**: 1235–40.

Carboplatin

Hypersensitivity reactions occur in 1–30% of patients [1–6]; acute allergic reactions include urticaria, bronchospasm, hypotension, facial erythema and facial swelling. Desensitization can be successful [7]. A pruritic maculopapular rash occurred in 10 of 40 patients treated with carboplatin, etoposide and ifosfamide plus mesna followed by autologous stem cell reinfusion; the rash was distributed at the extremities or was confluent on the trunk and face, with facial oedema and painful swelling of hands and feet, and resolved spontaneously with hyperpigmentation in all patients [6].

References

1 Hendrick AM, Simmons D, Cantwell BM. Allergic reactions to carboplatin. *Ann Oncol* 1992; **3**: 239–40.
2 Tonkin KS, Rubin P, Levin L. Carboplatin hypersensitivity: case reports and review of the literature. *Eur J Cancer* 1993; **29A**: 1356–7.

3 Weidmann B, Mulleneisen N, Bojko P, Niederle N. Hypersensitivity reactions to carboplatin. Report of two patients, review of the literature, and discussion of diagnostic procedures and management. *Cancer* 1994; **73**: 2218–22.
4 Chang SM, Fryberger S, Crouse V *et al.* Carboplatin hypersensitivity in children. A report of five patients with brain tumors. *Cancer* 1995; **75**: 1171–5.
5 Broome CB, Schiff RI, Friedman HS. Successful desensitization to carboplatin in patients with systemic hypersensitivity reactions. *Med Pediatr Oncol* 1996; **26**: 105–10.
6 Zorzou MP, Efstathiou E, Galani E *et al.* Carboplatin hypersensitivity reactions: a single institution experience. *J Chemother* 2005; **17**: 104–10.
7 Beyer J, Grabbe J, Lenz K *et al.* Cutaneous toxicity of high-dose carboplatin, etoposide and ifosfamide followed by autologous stem cell reinfusion. *Bone Marrow Transplant* 1992; **10**: 491–4.

Cisplatin

Periungual hyperpigmentation [1] and acral erythema [2] or digital necrosis [3] have been documented. Severe hypersensitivity reactions, including flushing, erythema, maculopapular eruptions, urticaria and anaphylaxis, occur in about 5% of cases when this drug is used as a single agent, and in up to 20% when given with other chemotherapeutic agents [4,5]. Cross-reactivity with carboplatin may occur [5]. Atopic subjects are especially at risk. Local reactions follow extravasation [6]. Severe allergic exfoliative dermatitis with ischaemia and necrosis of the hands developed in a patient who had received multiple doses of cisplatin [7].

Oxaliplatin

Hypersensitivity reactions are recorded [8].

References

1 Kim KJ, Chang SE, Choi JH *et al.* Periungal hyperpigmentation induced by cisplatin. *Clin Exp Dermatol* 2002; **27**: 118–9.
2 Vakalis D, Ioannides D, Lazaridou E *et al.* Acral erythema induced by chemotherapy with cisplatin. *Br J Dermatol* 1998; **139**: 750–1.
3 Marie I, Levesque H, Plissonier D *et al.* Digital necrosis related to cisplatin in systemic sclerosis. *Br J Dermatol* 2000; **142**: 833–4.
4 Vogl SE, Zaravinos T, Kaplan BH. Toxicity of cis-diaminedichloro-platinum II given in a two-hour outpatient regimen of diuresis and hydration. *Cancer* 1980; **45**: 11–5.
5 Shlebak AA, Clark PI, Green JA. Hypersensitivity and cross-reactivity to cisplatin and analogues. *Cancer Chemother Pharmacol* 1995; **35**: 349–51.
6 Fields S, Koeller J, Topper RL *et al.* Local soft tissue toxicity following cisplatin extravasation. *J Natl Cancer Inst* 1990; **82**: 1649–50.
7 Lee TC, Hook CC, Long HJ. Severe exfoliative dermatitis associated with hand ischemia during cisplatin therapy. *Mayo Clin Proc* 1994; **69**: 80–2.
8 Siu SW, Chan RT, Au GK. Hypersensitivity reactions to oxaliplatin: experience in a single institute. *Ann Oncol* 2006; **17**: 259–61.

Colchicine

Alopecia is recorded [1].

Reference

1 Haarms M. Haarausfall und Haarveränderungen nach Kolchizintherapie. *Hautarzt* 1980; **31**: 161–3.

Flutamide

A photosensitive dermatitis [1,2] and pseudoporphyria [3] have been reported with this non-steroid antiandrogen used in the treatment of prostatic carcinoma.

References

1 Fujimoto M, Kikuchi K, Imakado S, Furue M. Photosensitive dermatitis induced by flutamide. *Br J Dermatol* 1996; **135**: 496–7.
2 Yokote R, Tokura Y, Igarashi N *et al.* Photosensitive drug eruption induced by flutamide. *Eur J Dermatol* 1998; **8**: 427–9.
3 Borroni G, Brazzelli V, Baldini F *et al.* Flutamide-induced pseudoporphyria. *Br J Dermatol* 1998; **138**: 711–2.

Hydroxycarbamide (hydroxyurea)

Dermatological aspects of this drug have been reviewed [1–6]. Impaired renal function has been reported in some, but not all, studies [3]. A modest fall in haemoglobin and development of macrocytosis is almost constant. Stomatitis occurs especially with high-dose therapy and has been accompanied by soreness, violet erythema, and oedema of the palms and soles with subsequent intense universal hyperpigmentation [7], but alopecia is rare. Morbilliform erythema occurs, and hyperpigmentation, generalized or localized to pressure areas, was recorded in up to 5% of cases [2]. A more recent survey reported mucocutaneous adverse reactions after a mean duration of 6.4 weeks of treatment in up to 65% of patients, with pigmentation of nails, skin or mucosa seen in 58.6% [6]. Other less common findings were xerosis, diffuse alopecia, oedema of the legs, oral ulcers and actinic psoriasis; scleral pigmentation and acquired ichthyosis were also noted. Nail changes including pigmentation [8], multiple pigmented nail bands [9], nail ridging, partial leukonychia, and longitudinal melanonychia [10], or onycholysis with nail dystrophy, occur. Fixed drug eruption has been reported [3], as has baboon syndrome [11]. Dermatomyositis-like acral erythema, scaling, and atrophy especially on the dorsum of the hands, with lesser involvement of the feet [1,4,12–15], and palmar and plantar keratoderma have been rarely described with long-term therapy for chronic myeloid leukaemia. Photosensitivity is documented, and LE [16] and vasculitis have been reported. An ulcerative lichen planus-like dermatitis has been recorded [17]. Lichenoid eruptions similar to graft-versus-host disease are documented [18,19]. Several reports have recorded an association with leg ulcers [13,14,20–24]. Treatment of these with a protease-modulating matrix has been described [25]. Accelerated development of skin malignancies occurs, and eruptive squamous and basal cell cancers on light-exposed areas may be seen [26]. Radiation recall occurs [27].

References

1 Kennedy BJ, Smith LR, Goltz RW. Skin changes secondary to hydroxyurea therapy. *Arch Dermatol* 1975; **111**: 183–7.
2 Layton AM, Sheehan-Dare RA, Goodfield MJD, Cotterill JA. Hydroxyurea in the management of therapy resistant psoriasis. *Br J Dermatol* 1989; **121**: 647–53.
3 Boyd AS, Neldner KH. Hydroxyurea therapy. *J Am Acad Dermatol* 1991; **25**: 518–24.
4 Kelly RI, Bull RH, Marsden A. Cutaneous manifestations of long-term hydroxyurea therapy. *Australas J Dermatol* 1994; **35**: 61–4.
5 Chaine B, Neonato M-G, Girot R, Aractingi S. Cutaneous adverse reactions to hydroxyurea in patients with sickle cell disease. *Arch Dermatol* 2001; **137**: 467–70.
6 Kumar B, Saraswat A, Kaur I. Mucocutaneous adverse effects of hydroxyurea: a prospective study of 30 psoriasis patients. *Clin Exp Dermatol* 2002; **27**: 8–13.
7 Brincker H, Christensen BE. Acute mucocutaneous toxicity following high-dose hydroxyurea. *Cancer Chemother Pharmacol* 1993; **32**: 496–7.
8 Aste N, Gumo G, Contu F *et al.* Nail pigmentation caused by hydroxyurea: report of 9 cases. *J Am Acad Dermatol* 2002; **47**: 146–7.
9 Vomvouras S, Pakula AS, Shaw JM. Multiple pigmented nail bands during hydroxyurea therapy: an uncommon finding. *J Am Acad Dermatol* 1991; **24**: 1016–7.

10 Zargari O, Kimyai-Asadi A, Jafroodi M. Cutaneous adverse reactions to hydroxyurea in patients with intermediate thalassemia. *Pediatr Dermatol* 2004; **21**: 633–5.
11 Chowdhury MM, Patel GK, Inaloz HS, Holt PJ. Hydroxyurea-induced skin disease mimicking the baboon syndrome. *Clin Exp Dermatol* 1999; **24**: 336–7.
12 Richard M, Truchetet F, Friedel J *et al.* Skin lesions simulating chronic dermatomyositis during long-term hydroxyurea therapy. *J Am Acad Dermatol* 1989; **21**: 797–9.
13 Suehiro M, Kishimoto S, Wakabayashi T *et al.* Hydroxyurea dermopathy with a dermatomyositis-like eruption and a large leg ulcer. *Br J Dermatol* 1998; **139**: 748–9.
14 Varma S, Lanigan SW. Dermatomyositis-like eruption and leg ulceration caused by hydroxyurea in a patient with psoriasis. *Clin Exp Dermatol* 1999; **24**: 164–6.
15 Dacey MJ, Callen JP. Hydroxyurea-induced dermatomyositis-like eruption. *J Am Acad Dermatol* 2003; **48**: 439–41.
16 Layton AM, Cotterill JA, Tomlinson IW. Hydroxyurea-induced lupus erythematosus. *Br J Dermatol* 1994; **130**: 687–8.
17 Renfro L, Kamino H, Raphael B *et al.* Ulcerative lichen planus-like dermatitis associated with hydroxyurea. *J Am Acad Dermatol* 1991; **24**: 143–5.
18 Daoud MS, Gibson LE, Pittelkow MR. Hydroxyurea dermopathy: a unique lichenoid eruption complicating long-term therapy with hydroxyurea. *J Am Acad Dermatol* 1997; **36**: 178–82.
19 Eming SA, Peters T, Hartmann K *et al.* Lichenoid chronic graft-versus-host disease-like acrodermatitis induced by hydroxyurea. *J Am Acad Dermatol* 2001; **45**: 321–3.
20 Weinlich G, Schuler G, Greil R *et al.* Leg ulcers associated with long-term hydroxyurea therapy. *J Am Acad Dermatol* 1998; **39**: 372–4.
21 Kido M, Tago O, Fujiwara H *et al.* Leg ulcer associated with hydroxyurea treatment in a patient with chronic myelogenous leukaemia: successful treatment with prostaglandin E_1 and pentoxifylline. *Br J Dermatol* 1998; **139**: 1124–6.
22 Sirieix ME, Debure C, Baudot N *et al.* Leg ulcers and hydroxyurea: forty-one cases. *Arch Dermatol* 1999; **135**: 818–20.
23 Weinlich G, Fritsch P. Leg ulcers in patients treated with hydroxyurea for myeloproliferative disorders: what is the trigger? *Br J Dermatol* 1999; **141**: 171–2.
24 Aragane Y, Ikamoto T, Yajima A *et al.* Hydroxyurea-induced foot ulcer successfully treated with a topical basic fibroblast growth factor product. *Br J Dermatol* 2003; **148**: 599–600.
25 Romanelli M, Dini V, Romanelli P. Hydroxyurea-induced leg ulcers treated with a protease-modulating matrix. *Arch Dermatol* 2007; **143**: 1310–3.
26 Papi M, Didona B, DePita O *et al.* Multiple skin tumors on light-exposed areas during long-term treatment with hydroxyurea. *J Am Acad Dermatol* 1993; **28**: 485–6.
27 Sears ME. Erythema in areas of previous irradiation in patients treated with hydroxyurea (NSC-32065). *Cancer Chemother Rep* 1964; **40**: 31–2.

Suramin

Suramin sodium, a polysulphonated naphthylurea used in the treatment of metastatic prostatic and other cancers, has caused generalized, erythematous, maculopapular eruptions within the first 24 h of therapy (which were self-limited despite continued drug infusion), keratoacanthoma and disseminated superficial actinic porokeratosis [1–3]. Distinctive findings include scaling erythematous papules (suramin keratoses) and a predilection for previously sun-exposed areas (UV recall). Severe cutaneous reactions occur in 10% of cases [3]. Histopathological findings have included hyperkeratosis, parakeratosis, spongiosis, acanthosis, exocytosis, apoptosis, a perivascular lymphohistiocytic infiltrate, upper dermal oedema and increased dermal mucin [3]. Erythema multiforme [4] and TEN [5,6] are recorded.

References

1 O'Donnell BP, Dawson NA, Weiss RB *et al.* Suramin-induced skin reactions. *Arch Dermatol* 1992; **128**: 75–9.
2 Wichterich K, Tebbe B, Handke A *et al.* Kutane Arzneimittelreaktion durch Suramin bei 4 Patienten mit metastasierendem Prostata-Karzinom. *Hautarzt* 1994; **45**: 84–7.
3 Lowitt MH, Eisenberger M, Sina B, Kao GF. Cutaneous eruptions from suramin. A clinical and histopathologic study of 60 patients. *Arch Dermatol* 1995; **131**: 1147–53.
4 Katz SK, Medenica MM, Kobayashi K *et al.* Erythema multiforme induced by suramin. *J Am Acad Dermatol* 1995; **32**: 292–3.
5 May E, Allolio B. Fatal toxic epidermal necrolysis during suramin therapy. *Eur J Cancer* 1991; **28A**: 1294.
6 Falkson G, Rapoport BL. Lethal toxic epidermal necrolysis during suramin therapy. *Eur J Cancer* 1992; **27**: 1338.

Taxanes

Docetaxel. Docetaxel, a semi-synthetic analogue of paclitaxel from the needles of the European yew *Taxus baccata*, and used in the treatment of advanced and/or metastatic cancer, caused neutropenia, skin reactions (81%) and nail changes (41%), neurosensory toxicity (59%), fluid retention with oedema and hypersensitivity reactions (16–55%) [1–3]. The commonest skin reaction is characterized by discrete erythematous to violaceous patches or oedematous plaques similar to acral erythema [4]. Nail changes recorded [5,6] include horizontal banding [7], dyschromia [8] and subungual abscess [9]. Squamous syringometaplasia [10] and supravenous discoloration of the skin are documented [11].

References

1 ten Bokkel Huinink WW, Prove AM, Piccard M *et al.* A phase II trial with docetaxel (Taxotere) in second line treatment with chemotherapy for advanced breast cancer. A study of the EORTC Early Clinical Trials Group. *Ann Oncol* 1994; **5**: 527–32.
2 Pazdur R, Lassere Y, Soh LT *et al.* Phase II trial of docetaxel (Taxotere) in metastatic colorectal carcinoma. *Ann Oncol* 1994; **5**: 468–70.
3 Mertens WC, Eisenhauer EA, Jolivet J *et al.* Docetaxel in advanced renal carcinoma. A phase II trial of the National Cancer Institute of Canada Clinical Trials Group. *Ann Oncol* 1994; **5**: 185–7.
4 Zimmerman GC, Keeling JH, Burris HA *et al.* Acute cutaneous reactions to docetaxel, a new chemotherapeutic agent. *Arch Dermatol* 1995; **131**: 202–6.
5 Valero V, Holmes FA, Walters RS *et al.* Phase II trial of docetaxel: a new, highly effective antineoplastic agent in the management of patients with anthracycline-resistant metastatic breast cancer. *J Clin Oncol* 1995; **13**: 2886–94.
6 Pavithran K, Doval DC. Nail changes due to docetaxel. *Br J Dermatol* 2002; **146**: 709–10.
7 Llombart-Cussac A, Pivot X. Docetaxel chemotherapy induces transverse superficial loss of the nail plate. *Arch Dermatol* 1997; **133**: 1466–7.
8 Jacob CI, Frunza Patten S. Nail bed dyschromia secondary to docetaxel therapy. *Arch Dermatol* 1998; **134**: 1167–8.
9 Vanhooteghem O, Richert B, Vindevoghel A *et al.* Subungual abscess: a new ungual side-effect related to docetaxel therapy. *Br J Dermatol* 2000; **143**: 462–4.
10 Karam A, Metges JP, Labat JP *et al.* Squamous syringometaplasia associated with docetaxel. *Br J Dermatol* 2002; **146**: 524–5.
11 Schrijvers D, van den Brande J, Vermorken JB. Supravenous discoloration of the skin due to docetaxel treatment. *Br J Dermatol* 2000; **142**: 1069–70.

Paclitaxel. Paclitaxel, a diterpenoid taxane derivative found in the bark and needles of the western yew *Taxus brevifolia*, interrupts mitosis by promoting and stabilizing microtubule formation, and shows substantial activity against advanced refractory cancer. Neutropenia is the major dose-limiting toxic effect; other adverse effects include severe hypersensitivity reactions including anaphylaxis, cardiac toxicity, neurotoxicity, arthralgia or myalgia, mucositis, nausea and vomiting, and alopecia [1–6]. Local necrosis has followed accidental subcutaneous extravasation of paclitaxel

[7], and administration via a central vein has produced a recall reaction at a site of prior extravasation [8]. Bullous fixed drug eruption is recorded [9], as is a scleroderma-like reaction [10,11]. Desensitization is possible [12].

References

1 Onetto N, Canetta R, Winograd B *et al.* Overview of Taxol safety. *Monogr Natl Cancer Inst* 1993; **15**: 131–9.
2 Schiller JH, Storer B, Tutsch K *et al.* A phase I trial of 3-hour infusions of paclitaxel (Taxol) with or without granulocyte colony-stimulating factor. *Semin Oncol* 1994; **21** (Suppl. 8): 9–14.
3 Gelmon K. The taxoids: paclitaxel and docetaxel. *Lancet* 1994; **344**: 1267–72.
4 van Herpen CM, van Hoesel QG, Punt CJ. Paclitaxel-induced severe hypersensitivity reaction occurring as a late toxicity. *Ann Oncol* 1995; **6**: 852.
5 Berghmans T, Klastersky J. Paclitaxel-induced cutaneous toxicity. *Support Care Cancer* 1995; **3**: 203–4.
6 Payne JY, Holmes F, Cohen P *et al.* Paclitaxel: severe mucocutaneous toxicity in a patient with hyperbilirubinemia. *South Med J* 1996; **89**: 542–5.
7 Raymond E, Cartier S, Canuel C *et al.* Extravasation de paclitaxel (Taxol). *Rev Med Int* 1995; **16**: 141–2.
8 Meehan JL, Sporn JR. Case report of Taxol administration via central vein producing a recall reaction at a site of prior Taxol extravasation. *J Natl Cancer Inst* 1994; **86**: 1250–1.
9 Young PC, Montemarano AD, Lee N *et al.* Hypersensitivity to paclitaxel manifested as a bullous fixed drug eruption. *J Am Acad Dermatol* 1996; **34**: 313–4.
10 Läuchli S, Trüeb RM, Fehr M, Hafner J. Scleroderma-like drug reaction to paclitaxel (Taxol®). *Br J Dermatol* 2002; **147**: 619–21.
11 Kupfer I, Balguerie X, Courville P *et al.* Scleroderma-like cutaneous lesions induced by paclitaxel: a case study. *J Am Acad Dermatol* 2003; **48**: 279–81.
12 Essayan DM, Kagey-Sobotka A, Colarusso PJ *et al.* Successful parenteral desensitization to paclitaxel. *J Allergy Clin Immunol* 1996; **97**: 42–6.

Triazinate

Acanthosis nigricans-like hyperpigmentation has been recorded [1].

Reference

1 Greenspan AH, Shupack JL, Foo S-H. Acanthosis nigricans-like hyperpigmentation secondary to triazinate therapy. *Arch Dermatol* 1985; **121**: 232–5.

Topical nitrogen mustard

Urticaria, anaphylactoid reactions and a local bullous reaction have been recorded [1,2]. Contact dermatitis is well recognized.

References

1 Daughters D, Zackheim H, Maibach H. Urticaria and anaphylactoid reactions after topical application of mechlorethamine. *Arch Dermatol* 1973; **107**: 429–30.
2 Goday JJ, Aguirre A, Raton JA *et al.* Local bullous reaction to topical mechlorethamine (mustine). *Contact Dermatitis* 1990; **22**: 306–7.

Drugs affecting the immune response

Ciclosporin

Ciclosporin is a ligand for the immunophilin, cyclophilin A, and is thought to block early events in T-cell gene activation by interfering with the intracellular translocation of a substance known as nuclear factor of activated T cells [1,2]. It selectively inhibits antigen-induced activation of, and IL-2 production by, $CD4^+$ helper T lymphocytes, thereby blocking T-cell proliferation [3,4]. It inhibits transcription of genes encoding for IL-2 and IFN-γ [5], and blocks expression of IL-2 receptors. Ciclosporin also inhibits Langerhans' cell antigen-presenting function [6–8] and suppresses ICAM-1 expression by papillary endothelium in inflamed skin, thus reducing T-cell recruitment [9]. Much of the information on side effects was derived from patients who underwent organ transplants, and in diseases such as rheumatoid arthritis [10]. The drug is now used by dermatologists [11–18], especially in the management of difficult psoriasis [13–16], refractory atopic eczema [17] and a number of other conditions [16].

Dermatological complications. Hypertrichosis develops in a high proportion of patients; it affects especially the face and eyebrows, the upper back along the spinal column and the lateral upper arms [18–23]. The hypertrichosis is reversible, and children and adolescents seem to be at greater risk of developing this complication [23]. Other cutaneous complications include gingival hyperplasia [21,24], angio-oedema [25] and hyperplastic pseudofolliculitis barbae [26]. Acne keloidalis is recorded [27]. Anaphylaxis may occur in response to intravenous ciclosporin [11], probably due to the solvent. A mild capillary leak syndrome has resulted in purpuric lesions in the flexures and at pressure points [28], and cutaneous vasculitis is recorded [29].

There have been isolated reports of the development of benign lymphocytic infiltrates in patients with psoriasis or alopecia areata [30,31], of pseudolymphoma after therapy of actinic reticuloid [32] and of an aggressive T-cell lymphoma after ciclosporin therapy for Sézary syndrome [33]. Squamous cell skin cancer may develop [34,35] and could potentially be predisposed to by previous PUVA [36]. A study showed no difference in the incidence of cutaneous malignancy in renal allograft recipients treated with either ciclosporin or azathioprine [34]. Kaposi's sarcoma may occur; a renal transplant patient treated with ciclosporin and methylprednisolone developed a Kaposi's sarcoma, which completely regressed on reducing the dosage of both drugs [37]. There have been isolated reports of development of malignant melanoma in ciclosporin-treated patients, but the incidence of this complication does not seem to be increased above the risk in the general population [38,39].

Systemic side effects. Headache and rarely seizures [40], gastrointestinal and musculoskeletal symptoms are well recognized. There is an increased risk of nephrotoxicity [41,42], which appears to be caused by arteriolar vasoconstriction due to local thromboxane A_2 release [43], and consequent hypertension [44]. Impaired renal function may develop after short- as well as long-term treatment for psoriasis [45]. Both renal dysfunction and hypertension are reversible, and lymphoma development unlikely, in patients on short-term low-dose (less than 5 mg/kg) therapy. Adverse effects on renal function and systolic blood pressure appear greater in psoriasis patients receiving higher doses [15]. Some degree of renal impairment is inevitable with longer-term therapy [46]. Rarely, a serious capillary leak syndrome occurs, with marked fluid retention and periorbital oedema, and may be fatal; there may be associated gastrointestinal bleeding, pneumonitis, uraemia and urinary sodium loss followed by hypertension and convulsions [21].

Hepatotoxicity is a complication [47] and hypercholesterolaemia is recorded [48]. Ciclosporin may be associated with myopathy without rhabdomyolysis or with rhabdomyolysis; the latter

occurs in the setting of concomitant lovastatin or colchicine therapy [49]. Lymphoma and other cancers have developed on high dosage, as used for organ grafting [19,50]. Transplant patients treated with ciclosporin have not been shown to have a higher incidence of neoplasms than those receiving other immunosuppressive agents.

Successful pregnancies have occurred in patients receiving ciclosporin for psoriasis [51,52]. There is no evidence of a teratogenic effect in humans, based on the experience of 107 transplant recipients [53].

Interactions of ciclosporin and other drugs have been reviewed [54]. Ciclosporin blood levels may be increased by concomitant therapy with erythromycin or ketoconazole, as a result of inhibition of the hepatic microsomal cytochrome P-450 enzyme system [55], as well as with danazol, oral contraceptives and calcium channel antagonists. Decreased blood levels may be caused by drugs that induce hepatic enzymes, including phenytoin, phenobarbital and tuberculostatic therapy with rifampicin and isoniazid. Aminoglycoside antibiotics, melphalan, amphotericin and trimethoprim (alone or in combination with sulfamethoxazole) interact with ciclosporin by altering renal function. Patients should avoid grapefruit juice taken within 1 h of oral ciclosporin as it contains a psoralen that inhibits the CYP 3A subfamily of cytochrome P-450 and reduces metabolism of ciclosporin [56].

References

1 Gallagher RB, Cambier JC. Signal transmission pathways and lymphocyte function. *Immunol Today* 1990; **11**: 187–9.

2 Anonymous. Unmasking immunosuppression. *Lancet* 1991; **338**: 789.

3 Ryffel B. Pharmacology of cyclosporine. 6. Cellular activation: regulation of intracellular events by cyclosporine. *Pharmacol Rev* 1989; **41**: 407–22.

4 Borel JF. Pharmacology of cyclosporin (Sandimmune). 4. Pharmacological properties *in vivo*. *Pharmacol Rev* 1989; **41**: 259–371.

5 Granelli-Piperno A. Lymphokine gene expression *in vivo* is inhibited by cyclosporin A. *J Exp Med* 1990; **171**: 533–44.

6 Furue M, Katz SI. The effects of cyclosporin on epidermal cells. I. Cyclosporin inhibits accessory cell functions of epidermal Langerhans cells *in vitro*. *J Immunol* 1988; **140**: 4139–43.

7 Demidem A, Taylor JR, Grammer SF, Streilein JW. Comparison of effects of transforming growth factor-beta and cyclosporin A on antigen-presenting cells of blood and epidermis. *J Invest Dermatol* 1991; **96**: 401–7.

8 Dupuy P, Bagot M, Michel L *et al.* Cyclosporin A inhibits the antigen-presenting functions of freshly isolated human Langerhans cells *in vitro*. *J Invest Dermatol* 1991; **96**: 408–13.

9 Petzelbauer P, Stingl G, Wolff K, Volc-Platzer B. Cyclosporin A suppresses ICAM-1 expression by papillary endothelium in healing psoriatic plaques. *J Invest Dermatol* 1991; **96**: 362–9.

10 Dougados M, Awada H, Amor B. Cyclosporin in rheumatoid arthritis: a double blind placebo controlled study in 52 patients. *Ann Rheum Dis* 1988; **47**: 127–33.

11 Gupta AK, Brown MD, Ellis CN *et al.* Cyclosporine in dermatology. *J Am Acad Dermatol* 1989; **21**: 1245–56.

12 Fradin MS, Ellis CN, Voorhees JJ. Management of patients and side effects during cyclosporine therapy for cutaneous disorders. *J Am Acad Dermatol* 1990; **23**: 1265–74.

13 De Rie MA, Meinardi MMHM, Bos JD. Analysis of side-effects of medium- and low-dose cyclosporin maintenance therapy in psoriasis. *Br J Dermatol* 1990; **123**: 347–53.

14 Mihatsch MJ, Wolff K, eds. Risk/benefit ratio of cyclosporin A (Sandimmun®) in psoriasis. *Br J Dermatol* 1990; **122** (Suppl. 36): 1–115.

15 Ellis CN, Fradin MS, Messana JM *et al.* Cyclosporine for plaque-type psoriasis. Results of a multidose, double-blind trial. *N Engl J Med* 1991; **324**: 277–84.

16 Ellis CN, ed. Cyclosporine in dermatology. Proceedings of a symposium. *J Am Acad Dermatol* 1991; **23**: 1231–4.

17 Sowden JM, Berth-Jones J, Ross JS *et al.* Double-blind, controlled, crossover study of cyclosporin in adults with severe refractory atopic dermatitis. *Lancet* 1991; **338**: 137–40.

18 Fradin MS, Ellis CN, Voorhees JJ. Management of patients and side effects during cyclosporine therapy for cutaneous disorders. *J Am Acad Dermatol* 1990; **23**: 1265–75.

19 European Multicentre Trial. Cyclosporin A as sole immunosuppressive agent in recipients of kidney allografts from cadaver donors. Preliminary results. *Lancet* 1982; **ii**: 57–60.

20 Mortimer PS, Thompson JF, Dawber RP *et al.* Hypertrichosis and multiple cutaneous squamous cell carcinomas in association with cyclosporin A therapy. *J R Soc Med* 1983; **76**: 786–7.

21 Harper JI, Kendra JR, Desai S *et al.* Dermatological aspects of the use of cyclosporin A for prophylaxis of graft-versus-host disease. *Br J Dermatol* 1984; **110**: 469–74.

22 Bencini PL, Montagnino G, Sala F *et al.* Cutaneous lesions in 67 cyclosporin-treated renal transplant recipients. *Dermatologica* 1986; **172**: 24–30.

23 Wysocki GP, Daley TD. Hypertrichosis in patients receiving cyclosporine therapy. *Clin Exp Dermatol* 1987; **12**: 191–6.

24 Bennett JA, Christian JM. Cyclosporin-induced gingival hyperplasia: case report and literature review. *J Am Dent Assoc* 1985; **3**: 272–3.

25 Isenberg DA, Snaith ML, Al-Khader AA *et al.* Cyclosporin relieves arthralgia, causes angioedema. *N Engl J Med* 1980; **303**: 754.

26 Lear J, Bourke JF, Burns DA. Hyperplastic pseudofolliculitis barbae associated with cyclosporin. *Br J Dermatol* 1997; **136**: 132–3.

27 Azurdia RM, Graham RM, Weismann K *et al.* Acne keloidalis in Caucasian patients on cyclosporin following organ transplantation. *Br J Dermatol* 2000; **143**: 465–7.

28 Ramon D, Bettloch E, Jimenez A *et al.* Remission of Sézary's syndrome with cyclosporin A. Mild capillary leak syndrome as an unusual side effect. *Acta Derm Venereol (Stockh)* 1986; **66**: 80–2.

29 Gupta MN, Sturrock RD, Gupta G. Cutaneous leucocytoclastic vasculitis caused by cyclosporin A. *Ann Rheum Dis* 2000; **59**: 319.

30 Brown MD, Ellis CN, Billings J *et al.* Rapid occurrence of nodular cutaneous T-lymphocyte infiltrates with cyclosporine therapy. *Arch Dermatol* 1988; **124**: 1097–100.

31 Gupta AK, Cooper KD, Ellis CN *et al.* Lymphocytic infiltrates of the skin in association with cyclosporine therapy. *J Am Acad Dermatol* 1990; **23**: 1137–41.

32 Thestrup-Pedersen K, Zachariae C, Kaltoft K *et al.* Development of cutaneous pseudolymphoma following ciclosporin therapy of actinic reticuloid. *Dermatologica* 1988; **177**: 376–81.

33 Catterall MD, Addis BJ, Smith JL, Coode PE. Sézary syndrome: transformation to a high grade T-cell lymphoma after treatment with cyclosporin A. *Clin Exp Dermatol* 1983; **8**: 159–69.

34 Bunney MH, Benton EC, Barr BB *et al.* The prevalence of skin disorders in renal allograft recipients receiving cyclosporin A compared with those receiving azathioprine. *Nephrol Dial Transplant* 1990; **5**: 379–82.

35 Paul C, Ho VC, McGeown C *et al.* Risk of malignancies in psoriasis patients treated with cyclosporine: a 5 year cohort study. *J Invest Dermatol* 2003; **120**: 211–6.

36 Stern RS. Risk assessment of PUVA and cyclosporine. Lessons from the past: challenges for the future. *Arch Dermatol* 1989; **125**: 545–7.

37 Pilgrim M. Spontane Manifestation und Regression eines Kaposi-Sarkoms unter Cyclosporin A. *Hautarzt* 1988; **39**: 368–70.

38 Mérot Y, Miescher PA, Balsiger F *et al.* Cutaneous malignant melanomas occurring under cyclosporin A therapy: a report of two cases. *Br J Dermatol* 1990; **123**: 237–9.

39 Arellano F, Krupp PF. Cutaneous malignant melanoma occurring after cyclosporin A therapy. *Br J Dermatol* 1991; **124**: 611.

40 Humphreys TR, Leyden JJ. Acute reversible central nervous system toxicity associated with low-dose oral cyclosporin therapy. *J Am Acad Dermatol* 1993; **29**: 490–2.

41 Myers BD, Ross J, Newton L *et al.* Cyclosporine-associated chronic nephropathy. *N Engl J Med* 1984; **311**: 699–705.

42 Myers BD, Sibley R, Newton L *et al.* The long-term course of cyclosporine-associated chronic nephropathy. *Kidney Int* 1988; **33**: 590–600.

43 Coffman TM, Carr DR, Yarger WE, Klotman PE. Evidence that renal prostaglandin and thromboxane production is stimulated in chronic cyclosporine nephrotoxicity. *Transplantation* 1987; **43**: 282–5.
44 Porter GAM, Bennett WM, Sheps SG. Cyclosporine-associated hypertension. *Arch Intern Med* 1990; **150**: 280–3.
45 Powles AV, Carmichael D, Julme B *et al.* Renal function after long-term low-dose cyclosporin for psoriasis. *Br J Dermatol* 1990; **122**: 665–9.
46 Markham T, Watson A, Rogers S. Adverse effects with long-term cyclosporin for severe psoriasis. *Clin Exp Dermatol* 2002; **27**: 111–4.
47 Lorber MI, Van Buren CT, Flechner SM *et al.* Hepatobiliary and pancreatic complications of cyclosporine therapy in 466 renal transplant recipients. *Transplantation* 1987; **43**: 35–40.
48 Ballantyne CM, Podet EJ, Patsch WP *et al.* Effects of cyclosporine therapy on plasma lipoprotein levels. *JAMA* 1989; **262**: 53–6.
49 Arellano F, Krupp P. Muscular disorders associated with cyclosporin. *Lancet* 1991; **337**: 915.
50 Penn I, First MR. Development and incidence of cancer following cyclosporin therapy. *Transplant Proc* 1986; **18** (Suppl. 1): 210–3.
51 Wright S, Glover M, Baker H. Psoriasis, cyclosporine, and pregnancy. *Arch Dermatol* 1991; **127**: 426.
52 Imal N, Tatanabe R, Fujiwara H *et al.* Successful treatment of impetigo herpetiformis with oral cyclosporine during pregnancy. *Arch Dermatol* 2002; **138**: 128–9.
53 Cockburn I, Krupp P, Monka C. Present experience of Sandimmune in pregnancy. *Transplant Proc* 1989; **21**: 3730–2.
54 Yee GC, McGuire TR. Pharmacokinetic drug interactions with cyclosporin (Part I). *Clin Pharmacokinet* 1990; **19**: 319–32.
55 Abel EA. Isotretinoin treatment of severe cystic acne in a heart transplant patient receiving cyclosporine: consideration of drug interactions. *J Am Acad Dermatol* 1991; **24**: 511.
56 Anonymous. Drug interactions with grapefruit. *Curr Probl Pharmacovig* 1997; **23**: 2.

Leflunomide

This immunomodulating agent, recently introduced to treat rheumatoid and psoriatic arthritis, is reported to cause a drug hypersensitivity syndrome comprising fever, widespread and long lasting rash, generalized weakness and internal organ involvement [1]. A blistering eruption in SLE patients [2], an erythema multiforme-like drug eruption [3], and a photodistributed lichenoid drug eruption with rhabdomyolysis [4] have all been recorded.

References

1 Shastri V, Betkerur J, Kushalappa PA *et al.* Severe cutaneous adverse drug reaction to leflunomide: a report of five cases. *Indian J Dermatol Venereol Leprol* 2006; **72**: 286–9.
2 Jian X, Guo G, Ruan Y *et al.* Severe cutaneous adverse drug reaction to leflunomide: a report of two cases. *Cutan Ocul Toxicol* 2008; **27**: 5–9.
3 Fischer TW, Bauer HI, Graefe T *et al.* Erythema multiforme-like drug eruption with oral involvement after intake of leflunomide. *Dermatology* 2003; **207**: 386–9.
4 Rivarola de Gutierrez E, Abaca H. Photodistributed lichenoid drug eruption with rhabdomyolysis occurring during leflunomide therapy. *Dermatology* 2004; **208**: 232–3.

Sirolimus

This macrolide immunosuppressant, which impairs lymphocyte activation by IL-2, IL-4 and IL-12, has caused a capillary leak syndrome [1].

Reference

1 Kaplan MJ, Ellis CN, Bata-Csorgo Z *et al.* Systemic toxicity following administration of sirolimus (formerly rapamycin) for psoriasis. Association of capillary leak syndrome with apoptosis of lesional lymphocytes. *Arch Dermatol* 1999; **135**: 553–7.

PUVA therapy

See Chapter 74.

Immunotherapy

Sera

Animal immune sera can produce any type of early or late hypersensitivity reactions, from urticaria, asthma or fatal anaphylaxis to serum sickness. Clinical manifestations of serum sickness include fever, arthritis, nephritis, neuritis, myocarditis, uveitis, oedema and an urticarial or papular rash. A characteristic serpiginous, erythematous and purpuric eruption developed on the hands and feet, at the borders of palmar and plantar skin, in patients treated with equine antithymocyte globulin [1,2]. Low serum C4 and C3 levels, elevated plasma C3a anaphylatoxin levels, and circulating immune complexes were found. Immunoreactants, including IgM, C3, IgE and IgA, were deposited in the walls of dermal blood vessels on direct immunofluorescence [1,2]. Patients with autoimmune disease may have a particular liability to react to antilymphocyte globulin.

Intravenous immunoglobulin

Human intravenous immunoglobulin (IVIG) preparations are used to treat a number of autoimmune and inflammatory disorders [1]. Common and mild side effects include headache, malaise, nausea, low-grade fever, urticaria [2], arthralgias, and myalgia; these typically resolve within a few days. Rare, serious and potentially fatal side effects include anaphylactic reactions, aseptic meningitis, acute renal failure, stroke, myocardial infarction and other thrombotic complications [3]. Angio-oedema-like hypersensitivity eruptions and eczematous, purpuric, petechial/purpuric, lichenoid and vasculitic reactions are recorded [4–6]. A severe, extensive eczematous reaction characterized by dyshidrotic lesions on the palms, rapidly followed by pruriginous maculopapular lesions involving the whole body, occurred 10 days after high-dose IVIG infusion [7].

References

1 Prins C, Gelfand EW, French LE. Intravenous immunoglobulin: properties, mode of action and practical use in dermatology. *Acta Derm Venereol* 2007; **87**: 206–18.
2 Gürcan HM, Ahmed AR. Frequency of adverse events associated with intravenous immunoglobulin therapy in patients with pemphigus or pemphigoid. *Ann Pharmacother* 2007; **41**: 1604–10.
3 Hamrock DJ. Adverse events associated with intravenous immunoglobulin therapy. *Int Immunopharmacol* 2006; **6**: 535–42.
4 Lawley TJ, Bielory L, Gascon P *et al.* A prospective clinical and immunologic analysis of patients with serum sickness. *N Engl J Med* 1984; **311**: 1407–13.
5 Bielory L, Yancey KB, Young NS *et al.* Cutaneous manifestations of serum sickness in patients receiving antithymocyte globulin. *J Am Acad Dermatol* 1985; **13**: 411–7.
6 Smith KJ, Dutka AL, Skelton HG. Lichenoid/interface cutaneous eruptions to IVIg with the primary infusion may be related to the re-regulation of anti-idiotype network. *J Cutan Med Surg* 1998; **3**: 96–101.
7 Vecchietti G, Kerl K, Prins C *et al.* Severe eczematous skin reaction after high-dose intravenous immunoglobulin infusion: report of 4 cases and review of the literature. *Arch Dermatol* 2006; **142**: 213–7.

Vaccines

Overall, the incidence of significant side effects is very low [1]. In Canada during 1990, from more than 12 million doses of vaccines there were 2832 reports of adverse events associated with immu-

nizing agents received by the Childhood Immunization Division of the Laboratory Centre for Disease Control [2]. Hepatitis B and bacille Calmette-Guérin vaccines are the most frequently incriminated products, whereas cutaneous adverse effects are less frequent following vaccination against varicella, diphtheria/tetanus/pertussis (primary and booster doses), measles, poliomyelitis, rubella, pneumococcus, tick-borne encephalitis, smallpox, *Meningococcus* and influenza [3]. Adverse effects may occur at the site of injection or at a distance, and involve predominantly non-specific lymphoid or granulomatous reactions. Local allergic reactions may develop to the vaccine strain, egg, gelatine, antibiotics such as neomycin, adjuvants, preservatives or other components including aluminium, thimerosal (merthiolate), 2-phenoxyethanol and formaldehyde [1,3,4]; needle gauge and length may affect the incidence of local reactions [5]. Systemic reactions may involve immediate-type or immune complex-related allergic reactions to toxoid-, ovalbumin-, gelatine- or pneumococcal-containing vaccines, and are sometimes related to a specific vaccine strain. Erythema multiforme minor is a recognized complication [6].

Local reactions include erythema, swelling and tenderness, which may result from an Arthus reaction [7–9]. Keloid scarring may develop. Local inflammatory reactions, fever, lymphadenopathy, urticaria and lichenoid rashes have been observed following vaccination in patients sensitive to the preservative merthiolate; patch testing and intradermal testing may be positive [10,11]. Inflammatory nodular reactions may occur as a result of aluminium sensitization, as with hepatitis B, diphtheria and tetanus vaccination [12–14]; patch testing to aluminium may be positive [12]. Itching, eczema and circumscribed hypertrichosis developed over nodules following immunization with vaccines adsorbed on aluminium hydroxide in three children [13]. Vaccination may result in development of an autoimmune state; dermatomyositis has been provoked. Fatalities have rarely occurred following vaccination as a result of anaphylaxis [15,16].

Urticaria and systemic symptoms including malaise and fever, or Stevens–Johnson syndrome may follow tetanus toxoid vaccination [17,18]. Urticaria, angio-oedema or anaphylaxis may occur in patients allergic to egg protein who are vaccinated with live measles vaccine. However, in a series of children with egg allergy and a positive skin-prick test to egg white, 0.98% developed a mild reaction not requiring therapy following immunization with a full dose of vaccine [19]. Measles and measles–mumps–rubella vaccine, hepatitis B vaccine, and diphtheria and tetanus toxoids have been statistically associated with anaphylaxis [20], and measles–mumps–rubella vaccine with thrombocytopenia and purpura [20,21], erythema multiforme [22], and Gianotti–Crosti syndrome [23]. Only 39 of 43 618 Alaskan natives who received 101 360 doses of hepatitis B plasma-derived vaccine developed side effects, including myalgia/arthralgia lasting longer than 3 days, rashes (eight patients) and dizziness [24]. A variety of other reactions have been documented following hepatitis B vaccination [25], including urticaria/angio-oedema [26], erythema multiforme [27], erythema nodosum [28], polyarteritis nodosa and pityriasis rosea [29], lichenoid eruptions [30–32] and granuloma annulare [32]. Influenza vaccination in the elderly was reported to cause no more systemic side effects than placebo [33]. In contrast, another study found local reactions in 17.5% of patients, including swelling, itching and pain [34]. Leukocytoclastic vasculitis has been reported with influenza vaccination [35]. An association with vaccination for influenza and with tetanus toxoid and induction of bullous pemphigoid has been noted rarely [36–38]. Erythema multiforme has been recorded with meningitis vaccine [39]. Transient subcutaneous nodule formation at the injection site, and increased regional adenopathy, have been rarely noted in patients with HIV infection treated with gp160 vaccination [40]. Of 98 patients with a history of previous inoculations with human diploid cell rabies vaccine, 3% developed generalized urticaria or wheezing within 1 day, and a further 3% developed urticaria within 6–14 days, after booster vaccination [41]. Hypersensitivity to smallpox vaccine provoked exanthematous, urticarial and erythema multiforme-like reactions [42,43]. Vaccination against Japanese encephalitis caused serious adverse reactions, including urticaria, angio-oedema, hypotension and collapse [44].

References

1 Georgitis JW, Fasano MB. Allergenic components of vaccines and avoidance of vaccination-related adverse events. *Curr Allergy Rep* 2001; **1**: 11–7.
2 Duclos P, Pless R, Koch J, Hardy M. Adverse events temporally associated with immunizing agents. *Can Fam Physician* 1993; **39**: 1907–13.
3 Nikkels AF, Nikkels-Tassoudji N, Piérard GE. Cutaneous adverse reactions following anti-infective vaccinations. *Am J Clin Dermatol* 2005; **6**: 79–87.
4 Heidary N, Cohen DE. Hypersensitivity reactions to vaccine components. *Dermatitis* 2005; **16**: 115–20.
5 Watson M. Needle length and incidence of local reactions to immunization. Needle gauge is more important than needle length. *BMJ* 2001; **322**: 492.
6 Frederiksen MS, Brenøe E, Trier J. Erythema multiforme minor following vaccination with paediatric vaccines. *Scand J Infect Dis* 2004; **36**: 154–5.
7 Jacobs RL, Lowe RS, Lanier BQ. Adverse reactions to tetanus toxoid. *JAMA* 1982; **247**: 40–2.
8 Sutter RW. Adverse reactions to tetanus toxoid. *JAMA* 1994; **271**: 1629.
9 Marrinan LM, Andrews G, Alsop-Shields L, Dugdale AE. Side effects of rubella immunisation in teenage girls. *Med J Aust* 1990; **153**: 631–2.
10 Noel I, Galloway A, Ive FA. Hypersensitivity to thiomersal in hepatitis B vaccine. *Lancet* 1991; **338**: 705.
11 Rueff F. Nebenwirkungen durch Thiomersal und Huhnereiweiss bei Impfungen. *Hautarzt* 1994; **45**: 879–81.
12 Cosnes A, Flechet M-L, Revuz J. Inflammatory nodular reactions after hepatitis B vaccination due to aluminium sensitization. *Contact Dermatitis* 1990; **23**: 65–7.
13 Pembroke AC, Marten RH. Unusual cutaneous reactions following diphtheria and tetanus immunization. *Clin Exp Dermatol* 1979; **4**: 345–8.
14 Bergfors E, Björkelund C, Trollfors B. Nineteen cases of persistent pruritic nodules and contact allergy to aluminium after injection of commonly used aluminium-adsorbed vaccines. *Eur J Pediatr* 2005; **164**: 691–7.
15 Boston Collaborative Drug Surveillance Program. Drug-induced anaphylaxis. A cooperative study. *JAMA* 1973; **224**: 613–5.
16 Lockey RF, Benedict LM, Turkeltaub PC, Bukantz SC. Fatalities from immunotherapy (IT) and skin testing (ST). *J Allergy Clin Immunol* 1987; **79**: 660–77.
17 Kuhlwein A, Bleyl A. Tetanusantitoxintiter und Reaktionen nach Tetanusimpfungen. *Hautarzt* 1985; **36**: 462–4.
18 Weisse ME, Bass JW. Tetanus toxoid allergy. *JAMA* 1990; **264**: 2448.
19 Aickin R, Hill D, Kemp A. Measles immunisation in children with allergy to egg. *BMJ* 1994; **309**: 223–5.
20 Stratton KR, Howe CJ, Johnson RB Jr. Adverse events associated with childhood vaccines other than pertussis and rubella. Summary of a report from the Institute of Medicine. *JAMA* 1994; **271**: 1602–5.
21 Farrington P, Pugh S, Colville A *et al.* A new method for active surveillance of adverse events from diphtheria/tetanus/pertussis and measles/mumps/rubella vaccines. *Lancet* 1995; **345**: 567–9.
22 Bernardini ML, D'Angelo G, Oggiano N *et al.* Erythema multiforme following live attenuated trivalent measles-mumps-rubella vaccine. *Acta Derm Venereol* 2006; **86**: 359–60.

23 Velangi SS, Tidman MJ. Gianotti–Crosti syndrome after measles, mumps and rubella vaccination. *Br J Dermatol* 1998; **139**: 1122–3.
24 McMahon BJ, Helminiak C, Wainwright RB *et al.* Frequency of adverse reactions to hepatitis B vaccine in 43,618 persons. *Am J Med* 1992; **92**: 254–6.
25 Drago F, Rebora A. Cutaneous immunologic reactions to hepatitis B virus vaccine. *Ann Intern Med* 2002; **136**: 780.
26 Barbaud A, Trechot P, Reichert-Pénétrat S *et al.* Allergic mechanisms and urticaria/angioedema after hepatitis B immunization. *Br J Dermatol* 1998; **139**: 925–6.
27 Loche F, Schwarze HP, Thedenat B *et al.* Erythema multiforme associated with hepatitis B immunization. *Clin Exp Dermatol* 2002; **25**: 167–8.
28 Rogerson S, Nye F. Hepatitis B vaccine associated with erythema nodosum and polyarthritis. *BMJ* 1990; **301**: 345.
29 De Heyser F, Naeyaert JM, Hindryckz P *et al.* Immune-mediated pathology following hepatitis B vaccination. Two cases of polyarteritis nodosa and one case of pityriasis-rosea-like drug eruption. *Clin Exp Rheumatol* 2000; **18**: 81–5.
30 Saywell CA, Wittal RA, Kossard S. Lichenoid reaction to hepatitis B vaccination. *Australas J Dermatol* 1997; **38**: 152–4.
31 Ferrando MF, Doutre MS, Beylot-Barry M *et al.* Lichen planus following hepatitis B vaccination. *Br J Dermatol* 1998; **139**: 350.
32 Criado PR, de Oliveira Ramos R, Vasconcellos C *et al.* Two case reports of cutaneous adverse reactions following hepatitis B vaccine: lichen planus and granuloma annulare. *J Eur Acad Dermatol Venereol* 2004; **18**: 603–6.
33 Margolis KL, Nichol KL, Poland GA, Pluhar RE. Frequency of adverse reactions to influenza vaccine in the elderly. A randomized, placebo-controlled trial. *JAMA* 1990; **264**: 1139–41.
34 Govaert TME, Dinant GJ, Aretz K *et al.* Adverse reactions to influenza vaccine in elderly people: randomised double blind placebo controlled trial. *BMJ* 1993; **307**: 988–90.
35 Tavadia S, Drummond A, Evans CD, Wainwright NJ. Leucocytoclastic vasculitis and influenza vaccination. *Clin Exp Dermatol* 2003; **28**: 154–6.
36 Bodokh I, Lacour JP, Bourdet JF *et al.* Réactivation de pemphigoïde bulleuse apres vaccination antigrippale. *Thérapie* 1994; **49**: 154.
37 Venning VA, Wojnarowska F. Induced bullous pemphigoid. *Br J Dermatol* 1995; **132**: 831–2.
38 Fournier B, Descamps V, Bouscarat F *et al.* Bullous pemphigoid induced by vaccination. *Br J Dermatol* 1996; **135**: 153–4.
39 Studdiford J, Oppenheim L, McCann E, Altshuler M. Erythema multiforme after meningitis vaccine: patient safety concerns with repeat immunization. *Pharmacotherapy* 2006; **26**: 1658–61.
40 Redfield RR, Birx DL, Ketter N *et al.* A phase I evaluation of the safety and immunogenicity of vaccination with recombinant gp160 in patients with early human immunodeficiency virus infection. *N Engl J Med* 1991; **324**: 1677–84.
41 Fishbein DB, Yenne KM, Dreesen DW *et al.* Risk factors for systemic hypersensitivity reactions after booster vaccinations with human diploid cell rabies vaccine: a nationwide prospective study. *Vaccine* 1993; **11**: 1390–4.
42 Greenberg RN, Schosser RH, Plummer EA *et al.* Urticaria, exanthems, and other benign dermatologic reactions to smallpox vaccination in adults. *Clin Infect Dis* 2004; **38**: 958–65.
43 Bessinger GT, Smith SB, Olivere JW, James BL. Benign hypersensitivity reactions to smallpox vaccine. *Int J Dermatol* 2007; **46**: 460–5.
44 Ruff TA, Eisen D, Fuller A, Kass R. Adverse reactions to Japanese encephalitis vaccine. *Lancet* 1991; **338**: 881–2.

Hyposensitization immunotherapy

Hyposensitization immunotherapy is a standard treatment for recalcitrant hay fever and bee or wasp stings in many countries in the world, including the USA, Scandinavia and the continent of Europe [1]. However, in the UK, allergen-injection immunotherapy for IgE-mediated diseases has been largely discontinued, following the recommendations of the Committee on Safety of Medicines in 1986 [2], because of concern about deaths related to bronchospasm and anaphylaxis. The Committee recommended that immunotherapy be given only where full facilities for cardiopulmonary resuscitation are available and that patients be kept under medical observation for at least 2 h. The necessity for the latter recommendation has been questioned, as serious reactions occur within minutes [1]. The British Society for Allergy and Clinical Immunology Working Party concluded that specific allergen immunotherapy for summer hay fever uncontrolled by conventional medication and for wasp and bee venom hypersensitivity has an acceptable risk/benefit ratio, provided that treatment is given by experienced practitioners in a clinic where full resuscitative facilities are immediately available; a symptom-free observation period of 60 min after injection is sufficient [3,4]. Rush immunotherapy (rapid desensitization) of 893 patients to multiple aeroallergens using a modified schedule involving premedication with corticosteroids and antihistamines resulted in 2.0% experiencing a mild systemic reaction, responding to subcutaneous epinephrine and/or nebulized albuterol, with only one patient (0.1%) experiencing true anaphylaxis [5]. Patients with asthma should be excluded, however, in view of an increased frequency of reactions [4,6]. Fatalities from allergen immunotherapy are extremely rare [7]. In one series, β-blocker drugs did not increase the frequency of systemic reactions in patients receiving allergen immunotherapy, but patients developed more severe systemic reactions that were more refractory to therapy [8].

In contrast, local urticarial reactions are common [1]. Desensitization injections for hay fever have resulted in occasional tender nodules lasting for several months or years [9,10]; these are thought to develop as a result of allergy to aluminium, as it is present in the lesions and patch tests may be positive [10,11]. Inflammatory nodules at injection sites, first developing several years later, have also been described [12]. Injections of mixtures of grass pollens, cereal pollens and dust-mite allergens have resulted in multiple cutaneous B-cell pseudolymphomas [13]. Polyarteritis nodosa [14], vasculitis [15,16] and serum sickness [17,18] have been described following hyposensitization therapy for allergy to pollen, house-dust mite and wasp venom. Cold urticaria developed during the course of hyposensitization to wasp venom [19].

References

1 Varney VA, Gaga M, Frew AJ *et al.* Usefulness of immunotherapy in patients with severe summer hay fever uncontrolled by antiallergic drugs. *BMJ* 1991; **302**: 265–9.
2 Anonymous. CSM update. Desensitising vaccines. *BMJ* 1986; **293**: 948.
3 Anonymous. Position paper on allergen immunotherapy. Report of a BSACI working party, January–October 1992. *Clin Exp Allergy* 1993; **23** (Suppl. 3): 1–44.
4 British Society for Allergy and Clinical Immunology Working Party. Injection immunotherapy. *BMJ* 1993; **307**: 919–23.
5 Smits WL, Giese JK, Letz KL *et al.* Safety of rush immunotherapy using a modified schedule: a cumulative experience of 893 patients receiving multiple aeroallergens. *Allergy Asthma Proc* 2007; **28**: 305–12.
6 Bousquet J, Michel FB. Safety considerations in assessing the role of immunotherapy in allergic disorders. *Drug Saf* 1994; **10**: 5–17.
7 Lockey RF, Benedict LM, Turkeltaub PC, Bukantz SC. Fatalities from immunotherapy and skin testing. *J Allergy Clin Immunol* 1987; **79**: 660–77.
8 Hepner MJ, Ownby DR, Anderson JA *et al.* Risk of systemic reactions in patients taking beta-blocker drugs receiving allergen immunotherapy injections. *J Allergy Clin Immunol* 1990; **86**: 407–11.
9 Osterballe O. Side effects during immunotherapy with purified grass pollen extracts. *Allergy* 1982; **37**: 553–62.
10 Frost L, Johansen S, Pedersen S *et al.* Persistent subcutaneous nodules in children hyposensitised with aluminium-containing allergen extracts. *Allergy* 1985; **40**: 368–72.

11 Nagore E, Martinez-Escribano JA, Tato A *et al.* Subcutaneous nodules following treatment with aluminium-containing allergen extracts. *Eur J Dermatol* 2001; **11**: 138–40.
12 Jones SK, Lovell CR, Peachey RDG. Delayed onset of inflammatory nodules following hay fever desensitization injections. *Clin Exp Dermatol* 1988; **13**: 376–8.
13 Goerdt S, Spieker T, Wölffer L-U *et al.* Multiple cutaneous B-cell pseudolymphomas after allergen injections. *J Am Acad Dermatol* 1996; **35**: 1072–4.
14 Phanuphak P, Kohler PF. Onset of polyarteritis nodosa during allergic hyposensitisation treatment. *Am J Med* 1980; **68**: 479–85.
15 Merk H, Kober ML. Vasculitis nach spezifischer Hyposensibilisierung. *Z Hautkr* 1982; **57**: 1682–5.
16 Berbis P, Carena MC, Auffranc JC, Privat Y. Vascularite nécrosante cutanéo-systémique survenue en cours de désensibilisation. *Ann Dermatol Vénéréol* 1986; **113**: 805–9.
17 Umetsu DT, Hahn JS, Perez-Atayde AR, Geha RS. Serum sickness triggered by anaphylaxis: a complication of immunotherapy. *J Allergy Clin Immunol* 1985; **76**: 713–6.
18 De Bandt M, Atassi-Dumont M, Kahn MF, Herman D. Serum sickness after wasp venom immunotherapy: clinical and biological study. *J Rheumatol* 1997; **24**: 1195–7.
19 Anfosso-Capra F, Philip-Joet F, Reynaud-Gaubert M, Arnaud A. Occurrence of cold urticaria during venom desensitization. *Dermatologica* 1990; **181**: 276–7.

Bacille Calmette-Guérin (BCG) vaccination

Vaccination with BCG causes a benign self-limiting lesion consisting of a small papule, pustule or ulcer, which heals to leave a small scar within weeks. Axillary lymphadenitis and abscesses occurred after vaccination of rural Haitian children [1], and disseminated BCG infection in children born to HIV-1-infected women [2]. Occasionally, local abscess formation may follow vaccination of strongly tuberculin-positive individuals, administration of too much vaccine, or injection of vaccine too deeply [3–5]. BCG abscesses may also rarely arise following needlestick injury in health-care professionals [6]. In Austria, where the Ministry of Health's recommendation is for all neonates to be vaccinated, the normal complication rate is 0.3–0.6%, with suppurative lymphadenitis, generalized lymphadenopathy and osteitis [7]. Following a change to a more virulent vaccine strain, this rate temporarily increased substantially, with 5% of 659 children vaccinated at the University Hospital, Innsbruck requiring surgical excision of suppurating lymph nodes [7]. Anaphylactoid reactions to BCG vaccine, probably as a result of immune complex reactions mediated by antibodies to dextran in the vaccine, have been reported [8]. A papulonecrotic type of vasculitis has been documented [9]. Dermatomyositis may occasionally be a complication [10].

BCG immunotherapy for malignant melanoma [11] has been associated with local ulceration [11,12], local recurrent erysipelas, keloid formation, influenza-like symptoms, lymphadenopathy, urticaria and angio-oedema, granulomatous hepatitis, arthritis [13] and reactivation of pulmonary tuberculosis. Widespread miliary granulomas were present in a patient with fatal disseminated infection following intralesional immunotherapy of cutaneous malignant melanoma [14]. Cryoglobulinaemic vasculitis has followed intravesical instillation of bacille Calmette-Guérin [15].

References

1 Bonnlander H, Rossignol AM. Complications of BCG vaccinations in rural Haiti. *Am J Public Health* 1993; **83**: 583–5.
2 O'Brien KL, Andrae JR, Marie AL *et al.* Bacillus Calmette-Guérin complications in children born to HIV-1-infected women, with a review of literature. *Pediatrics* 1995; **95**: 414–7.
3 Lotte A, Wasz-Hockert O, Poisson N *et al.* BCG complications. *Adv Tuberculosis Res* 1984; **21**: 107–93, 194–245.
4 de Souza GRM, Sant'anna CC, Lapa e Silva JR *et al.* Intradermal BCG complications: analysis of 51 cases. *Tubercle* 1983; **64**: 23–7.
5 Puliyel JM, Hughes A, Chiswick ML, Mughal MZ. Adverse local reactions from accidental BCG overdose in infants. *BMJ* 1996; **313**: 528–9.
6 Warren JP, Nairn DS, Robertson MH. Cold abscess after accidental BCG inoculation. *Lancet* 1984; **ii**: 289.
7 Hengster P, Fille M, Menardi G. Suppurative lymphadenitis in newborn babies after change of BCG vaccine. *Lancet* 1991; **337**: 1168–9.
8 Rudin C, Amacher A, Berglund A. Anaphylactoid reactions to BCG vaccination. *Lancet* 1991; **337**: 377.
9 Lübbe D. Vasculitis allergica vom papulonekrotischen Typ nach BCG-Impfung. *Dermatol Monatsschr* 1982; **168**: 186–92.
10 Kass E, Staume S, Mellbye OJ *et al.* Dermatomyositis associated with BCG vaccination. *Scand J Rheumatol* 1979; **8**: 187–91.
11 Schult C. Nebenwirkungen der BCG-Immuntherapie bei 511 Patienten mit malignen Melanom. *Hautarzt* 1984; **35**: 78–83.
12 Korting HC, Strasser S, Konz B. Multiple BCG-Ulzera nach subkutaner Impfstoffapplikation im Rahmen der Immunochemotherapie des malignen Melanoms. *Hautarzt* 1988; **39**: 170–3.
13 Torisu M, Miyahara T, Shinohara A *et al.* A new side effect of BCG immunotherapy: BCG-induced arthritis in man. *Cancer Immunol Immunother* 1978; **5**: 77–83.
14 de la Monte SM, Hutchins GM. Fatal disseminated bacillus Calmette-Guérin infection and arrested growth of cutaneous malignant melanoma following intralesional immunotherapy. *Am J Dermatopathol* 1986; **8**: 331–5.
15 Granel B, Serratrice J, Morange PE *et al*. Cryoglobulinemia vasculitis following intravesical instillations of bacillus Calmette-Guerin. *Clin Exp Rheumatol* 2004; **22**: 481–2.

Cytokines

Cytokines are being increasingly used in the management of neoplastic and haematological disorders and AIDS, and in addition are starting to be used for the therapy of specific dermatological disorders; side effects have been reviewed [1]. Reactions range from minor injection-site reactions, pruritus and flushing to life-threatening autoimmune disorders, severe erythroderma or bullous skin reactions [2].

References

1 Luger TA, Schwarz T. Therapeutic use of cytokines in dermatology. *J Am Acad Dermatol* 1991; **24**: 915–26.
2 Asnis LA, Gaspari AA. Cutaneous reactions to recombinant cytokine therapy. *J Am Acad Dermatol* 1995; **33**: 393–410.

Colony-stimulating factors

Recombinant haematopoietic colony-stimulating factors used in the treatment of haematological disorders are usually well tolerated, but may induce itching and erythema or lichenoid reactions [1] at the site of injection, thrombophlebitis with intravenous infusion, facial flushing and a transient maculopapular eruption, fever, chills, myalgias, arthralgia and bone pain, transient leukopenia, decreased appetite, nausea and mild elevation of transaminase levels [2]. Neutrophilic dermatoses have been recorded in children [3]. Two types of recombinant human granulocyte colony-stimulating factor are in use for neutropenia: one is a glycosylated natural product from mammalian cells, and the other a non-glycosylated form from *Escherichia coli*. A drug eruption may occur with either type without detectable antibodies; intradermal tests may be useful and there may not be cross-reactivity [4]. Both local reactions at the site of injection and diffuse maculopapular eruptions may be seen [4–7]. Local pustular reactions [8] or subcorneal

pustular dermatosis [9] are documented. Intravenous recombinant granulocyte–macrophage colony-stimulating factor (GM-CSF) therapy for leukaemia resulted in a widespread, confluent maculopapular eruption in three patients, associated with a dermal lymphocyte, macrophage and granulocyte infiltration, exocytosis, and keratinocyte ICAM-1 expression [10]. Of 23 patients with advanced malignancy treated with GM-CSF, nine had a cutaneous eruption characterized by local erythema and pruritus at the injection site, recall erythema at previous injection sites or a generalized maculopapular rash [11]. Other studies have reported widespread rashes [12,13], in one series manifested as annular erythematous papules and plaques on the extremities, becoming generalized and clearing with fine desquamation [13]. Recurrent exacerbation of acne [14], widespread folliculitis [15], toxic folliculitis [16] and a Sweet's syndrome-like rash [17–19] have been recorded. A capillary leak syndrome with pleural and pericardial effusions, ascites and large-vessel thrombosis has been noted only with high-dose GM-CSF therapy [20]. Necrotizing vasculitis developed at GM-CSF injection sites in one patient with white cell aplasia, but not in over 150 other neutropenic patients who received the drug [21]. However, vasculitis was reported in a large series [22]. Thrombotic and necrotizing panniculitis has been documented [23]. Psoriasis [24], and arthritis in Felty's syndrome with rheumatoid arthritis [25], have been reported to deteriorate.

References

1 Viallard AM, Lavenue A, Balme B *et al.* Lichenoid cutaneous drug reaction at injection sites of granulocyte colony-stimulating factor (Filgrastim). *Dermatology* 1999; **198**: 301–3.

2 Wakefield PE, James WD, Samlaska CP, Meltzer MS. Colony-stimulating factors. *J Am Acad Dermatol* 1990; **23**: 903–12.

3 Prendiville J, Thiessen P, Mallory SB. Neutrophilic dermatoses in two children with idiopathic neutropenia: association with granulocyte colony-stimulating factor (G-CSF) therapy. *Pediatr Dermatol* 2001; **18**: 417–21.

4 Sasaki O, Yokoyama A, Uemura S *et al.* Drug eruption caused by recombinant human G-CSF. *Intern Med* 1994; **33**: 641–3.

5 Schiro JA, Kupper TS. Cutaneous eruptions during GM-CSF infusion. Clues for cytokine biology. *Arch Dermatol* 1991; **127**: 110–2.

6 Samlaska CP, Noyes DK. Localized cutaneous reactions to granulocyte colony-stimulating factor. *Arch Dermatol* 1993; **129**: 645–6.

7 Scott GA. Report of three cases of cutaneous reactions to granulocyte–macrophage colony-stimulating factor and a review of the literature. *Am J Dermatopathol* 1995; **17**: 107–14.

8 Passweg J, Buser U, Tichelli A *et al.* Pustular eruption at the site of subcutaneous injection of recombinant human granulocyte–macrophage colony-stimulating factor. *Ann Hematol* 1991; **63**: 326–7.

9 Lautenschlager S, Itin PH, Hirsbrunner P, Büchner SA. Subcorneal pustular dermatosis at the injection site of recombinant human granulocyte–macrophage colony-stimulating factor in a patient with IgA myeloma. *J Am Acad Dermatol* 1994; **30**: 783–9.

10 Horn TD, Burke PJ, Karp JE, Hood AF. Intravenous administration of recombinant human granulocyte–macrophage colony-stimulating factor causes a cutaneous eruption. *Arch Dermatol* 1991; **127**: 49–52.

11 Lieschke GJ, Maher D, Cebon J *et al.* Effects of bacterially synthesized recombinant human granulocyte–macrophage colony-stimulating factor in patients with advanced malignancy. *Ann Intern Med* 1989; **110**: 357–64.

12 Yamashita N, Natsuaki M, Morita H *et al.* Cutaneous eruptions induced by granulocyte colony-stimulating factor in two cases of acute myelogenous leukemia. *J Dermatol* 1993; **20**: 473–7.

13 Glass LF, Fotopoulos T, Messina JL. A generalized cutaneous reaction induced by granulocyte colony-stimulating factor. *J Am Acad Dermatol* 1996; **34**: 455–9.

14 Lee PK, Dover JS. Recurrent exacerbation of acne by granulocyte colony-stimulating factor administration. *J Am Acad Dermatol* 1996; **34**: 855–6.

15 Ostlere LS, Harris D, Prentice HG, Rustin MH. Widespread folliculitis induced by human granulocyte-colony-stimulating factor therapy. *Br J Dermatol* 1992; **127**: 193–4.

16 Paul C, Giachetti S, Pinquier L *et al.* Cutaneous effects of granuloycte colony-stimulating factor in healthy volunteers. *Arch Dermatol* 1998; **134**: 111–2.

17 Karp DL. The Sweet syndrome or G-CSF reaction? *Ann Intern Med* 1992; **117**: 875–6.

18 Richard MA, Grob JJ, Laurans R *et al.* Sweet's syndrome induced by granulocyte colony-stimulating factor in a woman with congenital neutropenia. *J Am Acad Dermatol* 1996; **35**: 629–31.

19 Prevost-Blank PL, Shwayder AT. Sweet's syndrome secondary to granulocyte colony-stimulating factor. *J Am Acad Dermatol* 1996; **35**: 995–7.

20 Antman KS, Griffin JD, Elias A *et al.* Effect of recombinant human granulocyte–macrophage colony-stimulating factor on chemotherapy-induced myelosuppression. *N Engl J Med* 1988; **319**: 593–8.

21 Farmer KL, Kurzrock R, Duvic M. Necrotizing vasculitis at granulocyte–macrophage-colony-stimulating factor injection sites. *Arch Dermatol* 1990; **126**: 1243–4.

22 Jain KK. Cutaneous vasculitis associated with granulocyte colony-stimulating factor. *J Am Acad Dermatol* 1994; **31**: 213–5.

23 Dereure O, Bessis D, Lavabre-Bertrand T *et al.* Thrombotic and necrotizing panniculitis associated with recombinant human granulocyte colony stimulating factor treatment. *Br J Dermatol* 2000; **142**: 834–6.

24 Kelly RI, Marsden RA. Granulocyte–macrophage colony-stimulating factor and psoriasis. *J Am Acad Dermatol* 1994; **30**: 144.

25 McMullin MF, Finch MB. Felty's syndrome treated with rhG-CSF associated with flare of arthritis and skin rash. *Clin Rheumatol* 1995; **14**: 204–8.

Interferon

Cutaneous reactions to recombinant IFN [1–12] given to patients with chronic hepatitis C, cancer or AIDS are frequent (5–10%) but usually of moderate degree. No adverse cutaneous side effects resulted from intralesional injection of IFN-γ in 10 patients treated for keloid scarring [13]. Most patients experience influenza-like symptoms following systemic therapy; reversible leukopenia and thrombocytopenia are recorded with higher dosage. Local reactions [14,15] consist of erythema, eczema, epilation, or induration at injection sites or urticaria. Pegylated IFN-α-2b plus ribavirin combination therapy for chronic hepatitis C virus infection was associated with vesicular erythematous eruptions at injection sites, and pruritic papular erythematous eruptions on the face, neck, distal limbs, dorsa of the hands, trunk and buttocks away from the injection sites, in one case [15]. More serious reactions include vesiculobullous reactions, vasculitis, necrosis, ulceration, alopecia and exacerbation of psoriasis. Skin ulceration or necrosis may be a serious problem with both IFN-α and IFN-β [7–12,16]. Raynaud's phenomenon and digital necrosis induced by IFN-α is recorded [17].

Of 63 patients treated with IFN-γ for prophylaxis of infection in chronic granulomatous disease, one had a severe cutaneous reaction (unspecified), and rashes or injection-site erythema or tenderness occurred in 17% and 14% of cases, respectively [1]. Diffuse inflammatory lesions have occurred with IFN-α and ribavirin therapy for hepatitis C [18]. Transient, localized or disseminated oedematous, erythematous and/or papular changes, vesicles or petechiae were seen in six patients during intravenous IFN-α for chronic active hepatitis C, 5–14 days after starting therapy [2]. Eruptions disappeared in 10–14 days despite continuation of IFN-α; histology revealed upper dermal perivascular $CD4^+$ lymphoid infiltration and oedema, with endothelial cell but not keratinocyte ICAM-1 and E-selectin expression, suggesting a non-allergic mechanism.

Capillaritis is recorded with IFN-α [19], as is lichen planus [3,20]. Reactivation of oral herpes simplex and enhanced radiation toxicity have been recorded. IFN-α-2a for the treatment of cutaneous T-cell lymphoma has induced temporary alopecia [21]. In contrast, IFN-α therapy has caused increased eyelash and eyebrow growth [22], as well as straight hair [23]. Severe urticaria has been documented with IFN-α-1a [24] and mucinoses with IFN-α-1b [25]. Both IFN-α and IFN-α-1b have been associated with granulomatous or sarcoidal reactions [26–29]. IFN-α has caused hypertriglyceridaemia [30] and IFN-β has been related to squamous cell cancer following ulceration [31].

IFN-α used in the treatment of disseminated carcinoma [32,33] or intralesionally for viral warts [34], and IFN-β therapy for multiple sclerosis [11,35], have been reported to exacerbate or trigger onset of psoriasis; psoriatic arthritis has also been triggered by IFN-α [36] and IFN-γ [37], and Reiter's syndrome by IFN-α [38]. Psoriasis appeared at the site of subcutaneous injection of recombinant IFN-γ in patients with psoriatic arthritis [39], and at the site of intralesional injection in a patient receiving recombinant IFN-β for a basal cell carcinoma [40]. Exacerbation of underlying autoimmune disease is documented with IFN-α [41]. Neutralizing antibodies to recombinant IFN-α may be produced [42]. Systemic sclerosis has been associated with IFN-α [43]. Systemic LE has been recorded following IFN therapy of myelogenous leukaemia [44], and pemphigus vulgaris after IFN-β and IL-2 therapy for lymphoma [45].

References

1 International Chronic Granulomatous Disease Cooperative Study Group. A controlled trial of interferon gamma to prevent infection in chronic granulomatous disease. *N Engl J Med* 1991; **324**: 509–16.

2 Toyofuku K, Imayama S, Yasumoto S *et al.* Clinical and immunohistochemical studies of skin eruptions: relationship to administration of interferon-alpha. *J Dermatol* 1994; **21**: 732–7.

3 Papini M, Bruni PL. Cutaneous reactions to recombinant cytokine therapy. *J Am Acad Dermatol* 1996; **35**: 1021.

4 Elgart GW, Sheremata W, Ahn YS. Cutaneous reactions to recombinant human interferon beta-1b: the clinical and histologic spectrum. *J Am Acad Dermatol* 1997; **37**: 553–8.

5 Paquet P, Pierard-Franchimont C, Arrese JE, Pierard GE. Cutaneous side effects of interferons. *Rev Med Liege* 2001; **56**: 699–702.

6 Manjon-Haces JA, Vazquez-Lopez F, Gomez-Diez S *et al.* Adverse cutaneous reactions to interferon alfa-2b plus ribavirin therapy in patients with chronic hepatitis C virus. *Acta Derm Venereol (Stockh)* 2001; **81**: 223.

7 Charron A, Bessis D, Dereure O *et al.* Local cutaneous side effects of interferons. *Presse Med* 2001; **30**: 1555–60.

8 Garcia-F-Villalta M, Dauden E, Sanchez J *et al.* Local reactions associated with subcutaneous injections of both beta-interferon 1a and 1b. *Acta Derm Venereol (Stockh)* 2001; **81**: 152.

9 Weinberg JM. Cutaneous necrosis associated with recombinant interferon injection. *J Am Acad Dermatol* 1998; **39**: 807.

10 Sheremata WA, Taylor JR, Elgart GW. Severe necrotizing cutaneous lesions complicating treatment with interferon beta-1b. *N Engl J Med* 1995; **332**: 1584.

11 Webster GF, Knobler RL, Lublin FD *et al.* Cutaneous ulcerations and pustular psoriasis flare caused by recombinant interferon beta injections in patients with multiple sclerosis. *J Am Acad Dermatol* 1996; **34**: 365–7.

12 Levesque H, Cailleux N, Moore N *et al.* Autoimmune phenomena associated with cutaneous aseptic necrosis during interferon-alpha treatment for chronic myelogenous leukaemia. *Br J Rheumatol* 1995; **34**: 582–3.

13 Granstein RD, Rook A, Flotte RJ *et al.* A controlled trial of intralesional recombinant interferon-γ in the treatment of keloidal scarring. *Arch Dermatol* 1990; **126**: 1295–302.

14 Samuel L, Lowenstein EJ. Recurrent injection site reactions from interferon beta 1-b. *J Drugs Dermatol* 2006; **5**: 366–7.

15 Hashimoto Y, Kanto H, Itoh M. Adverse skin reactions due to pegylated interferon alpha 2b plus ribavirin combination therapy in a patient with chronic hepatitis C virus. *J Dermatol* 2007; **34**: 577–82.

16 Ozden MG, Erel A, Erdem O, Oztas MO. Dermal fibrosis and cutaneous necrosis after recombinant interferon-beta1a injection in a multiple sclerosis patient. *J Eur Acad Dermatol Venereol* 2005; **19**: 112–3.

17 Bachmeyer C, Farge D, Gluckman E *et al.* Raynaud's phenomenon and digital necrosis induced by interferon-alpha. *Br J Dermatol* 1996; **135**: 481–3.

18 Dereure O, Faison-Peyron N, Larrey D *et al.* Diffuse inflammatory lesions in patients treated with interferon alfa and ribavirin for hepatitis C: a series of 20 patients. *Br J Dermatol* 2003; **147**: 1142–6.

19 Gupta G, Holmes SC, Spence E, Mills PR. Capillaritis associated with interferon-alfa treatment of chronic hepatitis C infection. *J Am Acad Dermatol* 2000; **43**: 937–8.

20 Schlesinger TE, Camisa C, Gay D, Bergfeld WF. Oral erosive lichen planus with epidermolytic hyperkeratosis during interferon alfa-2b therapy for chronic hepatitis C virus infection. *J Am Acad Dermatol* 1997; **36**: 1023–5.

21 Olsen EA, Rosen ST, Vollmer RT *et al.* Inteferon alfa-2a in the treatment of cutaneous T cell lymphoma. *J Am Acad Dermatol* 1989; **20**: 395–407.

22 Foon KA, Dougher G. Increased growth of eyelashes in a patient given leukocyte A interferon. *N Engl J Med* 1984; **311**: 1259.

23 Bessis D, Luong MS, Blanc P *et al.* Straight hair associated with inteferon-alfa plus ribavirin in hepatitis C infection. *Br J Dermatol* 2002; **147**: 392–3.

24 Mazzeo L, Ricciardi L, Fazio MC *et al.* Severe urticaria due to recombinant interferon beta-1a. *Br J Dermatol* 2003; **148**: 172–3.

25 Benito-Leon J, Borbujo J, Cortes L. Cutaneous mucinoses complicating interferon beta-1b therapy. *Eur Neurol* 2002; **47**: 123–4.

26 Sanders S, Busam K, Tahan SR *et al.* Granulomatous and suppurative dermatitis at interferon alfa injection sites: report of 2 cases. *J Am Acad Dermatol* 2002; **46**: 611–6.

27 Cogrel O, Doutre MS, Marliere V *et al.* Cutaneous sarcoidosis during interferon alfa and ribavirin treatment of hepatitis C virus infection: two cases. *Br J Dermatol* 2002; **146**: 320–4.

28 Mehta CL, Tyler RJ, Cripps DJ. Granulomatous dermatitis with focal sarcoidal features associated with recombinant interferon β-1b injections. *J Am Acad Dermatol* 1998; **39**: 1024–8.

29 Pelletier F, Manzoni P, Jacoulet P *et al.* Pulmonary and cutaneous sarcoidosis associated with interferon therapy for melanoma. *Cutis* 2007; **80**: 441–5.

30 Junghans V, Rünger TM. Hypertriglyceridaemia following adjuvant inteferon-α treatment in two patients with malignant melanoma. *Br J Dermatol* 1999; **140**: 183–4.

31 Fruland JE, Sandermann S, Snow SN *et al.* Skin necrosis with subsequent formation of squamous cell carcinoma after subcutaneous interferon beta injection. *J Am Acad Dermatol* 1997; **37**: 488–9.

32 Quesada JR, Gutterman JU. Psoriasis and alpha-interferon. *Lancet* 1986; **i**: 1466–8.

33 Hartmann F, von Wussow P, Deicher H. Psoriasis: exacerbation bei therapie mit alpha-Interferon. *Dtsch Med Wochenschr* 1989; **114**: 96–8.

34 Shiohara T, Kobayashi M, Abe K, Nagashima M. Psoriasis occurring predominantly on warts. Possible involvement of interferon alpha. *Arch Dermatol* 1988; **124**: 1816–21.

35 Kowalzick L. Psoriasis flare caused by recombinant interferon beta injections. *J Am Acad Dermatol* 1997; **36**: 501.

36 Jucgla A, Marcoval J, Curco N, Servitje O. Psoriasis with articular involvement induced by interferon alfa. *Arch Dermatol* 1991; **127**: 910–1.

37 O'Connell PG, Gerber LH, Digiovanna JJ, Peck GL. Arthritis in patients with psoriasis treated with gamma-interferon. *J Rheumatol* 1992; **19**: 80–2.

38 Cleveland MG, Mallory SB. Incomplete Reiter's syndrome induced by systemic interferon alpha treatment. *J Am Acad Dermatol* 1993; **29**: 788–9.

39 Fierlbeck G, Rassner G, Müller C. Psoriasis induced at the injection site of recombinant interferon gamma. *Arch Dermatol* 1990; **126**: 351–5.

40 Kowalzick L, Weyer U. Psoriasis induced at the injection site of recombinant interferons. *Arch Dermatol* 1990; **126**: 1515–6.

41 Conlon KC, Urba WJ, Smith JW II *et al.* Exacerbation of symptoms of autoimmune disease in patients receiving alpha-interferon therapy. *Cancer* 1990; **65**: 2237–42.

42 Steis RG, Smith JW, Urba WJ. Resistance to recombinant interferon alfa-2a in hairy-cell leukemia associated with neutralizing anti-interferon antibodies. *N Engl J Med* 1988; **318**: 1409–13.
43 Beretta L, Caronni M, Vanoli M, Scorza R. Systemic sclerosis after interferon-alfa therapy for myeloproliferative disorders. *Br J Dermatol* 2002; **147**: 385–6.
44 Shilling PJ, Kurzrock P, Kantarijian H *et al.* Development of systemic lupus erythematosus after interferon therapy for chronic myelogenous leukemia. *Cancer* 1991; **68**: 1536–7.
45 Ramseur WL, Richards F, Duggan DB. A case of fatal pemphigus vulgaris in association with beta interferon and interleukin-2 therapy. *Cancer* 1989; **63**: 2005–7.

Interleukins

IL-1. Mucositis and an erythematous eruption with erosions in intertriginous areas and under occlusive tape have been documented [1].

IL-2. Immunotherapy with IL-2, either alone or in conjunction with lymphokine-activated killer cells, is used in the treatment of metastatic cancer; mild, influenza-like symptoms are common. Cutaneous complications [2–8] include mucositis, macular erythema (principally restricted to the head, neck and upper chest), burning and pruritus (which resolves with mild desquamation), erythroderma and petechiae. Transient urticaria, necrotic lesions and blisters may be seen [8]. Type I hypersensitivity reactions, ranging from pruritus, erythema and oedema to hypotension, within hours of chemotherapy in patients previously treated with high-dose IL-2, have occurred [9]. A generalized capillary leak syndrome, with non-pitting oedema and diffuse pulmonary infiltrate on chest X-ray, is recorded [6], and is also documented with denileukin diftitox, formed from the fusion of human IL-2 with diphtheria toxin [10]. Exacerbation of psoriasis (including erythroderma) has been described [2–6]. IL-2 treatment predisposes to acute hypersensitivity reactions to iodine-containing contrast media [6]. Glossitis, telogen effluvium, punctate superficial ulcers and erosions in scars may be seen. Erythema nodosum has been documented [11]. Local inflammatory painful nodules with a central multiloculated vesicle have occurred at the site of subcutaneous injections of IL-2 and IFN-α [12]. Linear IgA bullous dermatosis has been associated with IL-2 therapy [13]. TEN is a rare complication [14]. It is of interest that lymphocytes activated by IL-2 can non-specifically destroy keratinocytes *in vitro* [15].

Other side effects include hypothyroidism (antithyroid antibodies are present in 50% of patients), neurological and psychiatric disturbances, musculoskeletal disorders, impaired renal function, cardiovascular injuries, cholestasis, pancreatitis, anaemia, thrombocytopenia, lymphocytopenia and eosinophilia [6].

IL-3. Erythema and purpura at the site of injection, and urticaria [16] may be induced.

IL-4. Transient acantholytic dermatosis is recorded [17].

IL-6. Coalescent, erythematous, scaling macules and papules occurred [18].

References

1 Prussick R, Horn TD, Wilson WH, Turner MC. A characteristic eruption associated with ifosfamide, carboplatin, and etoposide chemotherapy after pretreatment with recombinant interleukin-1α. *J Am Acad Dermatol* 1996; **35**: 705–9.
2 Rosenberg SA, Lotze MT, Muul LM *et al.* Clinical experience with the treatment of 157 patients with advanced cancer using lymphokine-activated killer cells and interleukin-2 or high dose interleukin 2 alone. *N Engl J Med* 1987; **316**: 889–97.
3 Gaspari A, Lotze MT, Rosenberg SA *et al.* Dermatologic changes associated with interleukin-2 administration. *JAMA* 1987; **258**: 1624–9.
4 Rosenberg SA. Immunotherapy of cancer using interleukin 2: current status and future prospects. *Immunol Today* 1988; **9**: 58–62.
5 Lee RE, Gaspari AA, Lotze MT *et al.* Interleukin 2 and psoriasis. *Arch Dermatol* 1988; **124**: 1811–5.
6 Vial T, Descotes J. Clinical toxicity of interleukin-2. *Drug Saf* 1992; **7**: 417–33.
7 Larbre B, Nicolas JF, Sarret Y *et al.* Immunotherapie par interleukine 2 et manifestations cutanées. *Ann Dermatol Vénéréol* 1993; **120**: 528–33.
8 Wolkenstein P, Chosidow O, Wechster J *et al.* Cutaneous side effects associated with interleukin 2 administration for metastatic melanoma. *J Am Acad Dermatol* 1993; **28**: 66–70.
9 Heywood GR, Rosenberg SA, Weber JS. Hypersensitivity reactions to chemotherapy agents in patients receiving chemoimmunotherapy with high-dose interleukin 2. *J Natl Cancer Inst* 1995; **87**: 915–22.
10 Railan D, Fivenson DP, Wittenberg G. Capillary leak syndrome in a patient treated with interleukin 2 fusion toxin for cutaneous T-cell lymphoma. *J Am Acad Dermatol* 2000; **43**: 323–4.
11 Weinstein A, Bujak D, Mittelman A *et al.* Erythema nodosum in a patient with renal cell carcinoma treated with interleukin 2 and lymphokine activated killer cells. *JAMA* 1987; **258**: 3120–1.
12 Klapholz L, Ackerstein A, Goldenhersh MA *et al.* Local cutaneous reaction induced by subcutaneous interleukin-2 and interferon alpha-2a immunotherapy following ABMT. *Bone Marrow Transplant* 1993; **11**: 443–6.
13 Tranvan A, Pezen DS, Medenica M *et al.* Interleukin-2 associated linear IgA bullous dermatosis. *J Am Acad Dermatol* 1996; **35**: 865–7.
14 Wiener JS, Tucker JA Jr, Walther PJ. Interleukin-2-induced dermatotoxicity resembling toxic epidermal necrolysis. *South Med J* 1992; **82**: 656–9.
15 Kalish RS. Non-specifically activated human peripheral blood mononuclear cells are cytotoxic for human keratinocytes in vitro. *J Immunol* 1989; **142**: 74–80.
16 Bridges AG, Helm TN, Bergfeld WF *et al.* Interleukin-3-induced urticaria-like eruption. *J Am Acad Dermatol* 1996; **34**: 1076–8.
17 Mahler SJ, De Villez RL, Pulitzer DR. Transient acantholytic dermatosis induced by recombinant human interleukin 4. *J Am Acad Dermatol* 1993; **29**: 206–9.
18 Fleming TE, Mirando WS, Soohoo LF *et al.* An inflammatory eruption associated with recombinant human IL-6. *Br J Dermatol* 1994; **130**: 534–6.

Stem cell factor

Human recombinant stem cell factor, a cytokine that acts on haematopoietic progenitor cells and which is used for human anaemic disorders and for speeding haematological recovery after chemotherapy, causes reversible hyperpigmentation at sites of injection; there are increases in melanocyte numbers, dendrite extension and melanin [1].

Reference

1 Grichnik JM, Crawford J, Jimenez F *et al.* Human recombinant stem-cell factor induces melanocytic hyperplasia in susceptible patients. *J Am Acad Dermatol* 1995; **33**: 577–83.

Tumour necrosis factor

Subcutaneous or intramuscular administration of TNF for advanced malignancy was limited by local pain, erythema and swelling or frank ulceration, and intravenous infusion may cause hypotension [1].

Reference

1 Wakefield PE, James WD, Samlaska CP, Meltzer MS. Tumor necrosis factor. *J Am Acad Dermatol* 1991; **24**: 675–85.

Inhibitors of tumour necrosis factor (Anti-TNF-α therapy)

These include adalimumab (a recombinant human IgG1 anti-TNF-α monoclonal antibody), etanercept (a recombinant human fusion protein, comprising the extracellular ligand-binding domain of the 75-kDa receptor for TNF-α (TNFR-2) and the Fc fragment of the constant domain of human IgG1), and infliximab (a mouse/human chimeric anti-TNF-α antibody comprising the constant domain of human IgG1 and a murine variable region). They are indicated in the treatment of rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, Crohn's disease and ulcerative colitis [1,2]. Adverse reactions associated with these drugs have been extensively reviewed. There is evidence of an increased risk of serious infections [2–6], especially in the skin and soft tissues, and including with *Mycobacterium tuberculosis*, *Mycobacterium avium intracellulare*, *Listeria monocytogenes*, and histoplasmosis [7]; there is also concern about a possible increased risk of malignancies [2], particularly lymphoma. Use of anti-TNF agents has been associated with an increase in autoimmune disease, principally lupus-like syndrome with positive antinuclear factor, SLE and interstitial lung disease [8–10]. Cutaneous vasculitis is well recognized [11–13]. Caution is recommended in the use of etanercept in patients with a current or past history of demyelinating disease, and in patients with heart failure [4,14], because of several reports indicating a worsening or *de novo* occurrence of congestive heart failure [15,16].

Injection site reactions are the commonest cutaneous manifestation [4,14,17–22]. Cutaneous infections caused by viral, bacterial and fungal agents may be seen, and chronic inflammatory skin diseases such as psoriasis and eczema-like manifestations also occur [6,23]. The appearance of psoriasis, either palmoplantar pustulosis, guttate or plaque type, as a potential side effect of a drug usually used to treat the condition is paradoxical [24] yet widely reported [25–32]. The mean time to appearance of this cutaneous adverse effect for all TNF-α inhibitors was 9.5 months [32]. There is controversy as to whether the psoriatic eruption is 'true' or not [33]. Annular plaques on the trunk and extremities with diffuse interstitial granulomatous infiltrates on histology have been associated separately with lenalidomide, infliximab, etanercept and adalimumab [34].

Adalimumab. Urticaria and angio-oedema-like skin reactions were recorded in one patient [35].

Etanercept. This drug has in addition been associated with follicular hyperkeratosis at distant sites and necrotic and purpuric reactions [20], urticaria [36], recall injection-site reactions [37], an eosinophilic cellulitis-like reaction [38], and onset of cutaneous squamous cell cancer [39].

Infliximab. Various other dermatological complications are recorded, including an eczematid-like purpura [40], erythema multiforme and lichenoid reactions [41], necrotizing fasciitis and sepsis [42], and serum sickness [43]. In the main, the drug is well tolerated, although thrombocytopenia and hepatitis [44] and occasional infusion reactions [45] are recorded.

References

1 Woolacott N, Hawkins N, Mason A *et al*. Etanercept and efalizumab for the treatment of psoriasis: a systematic review. *Health Technol Assess* 2006; **10**: 1–233, i–iv.

2 Bongartz T, Sutton AJ, Sweeting MJ *et al*. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA* 2006; **295**: 2275–85.

3 Dixon WG, Watson K, Lunt M *et al*. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. *Arthritis Rheum* 2006; **54**: 2368–76.

4 Sánchez Carazo JL, Mahiques Santos L, Oliver Martinez V. Safety of etanercept in psoriasis: a critical review. *Drug Saf* 2006; **29**: 675–85.

5 Curtis JR, Patkar N, Xie A *et al*. Risk of serious bacterial infections among rheumatoid arthritis patients exposed to tumor necrosis factor alpha antagonists. *Arthritis Rheum* 2007; **56**: 1125–33.

6 Lee HH, Song IH, Friedrich M *et al*. Cutaneous side-effects in patients with rheumatic diseases during application of tumour necrosis factor-alpha antagonists. *Br J Dermatol* 2007; **156**: 486–91.

7 Lee JH, Slifman NR, Gershon SK *et al*. Life-threatening histoplasmosis complicating immunotherapy with tumor necrosis factor alpha antagonists infliximab and etanercept. *Arthritis Rheum* 2002; **46**: 2565–70.

8 Brion PH, Mittal-Henkle A, Kalunian KC. Autoimmune skin rashes associated with etanercept for rheumatoid arthritis. *Ann Intern Med* 1999; **131**: 634.

9 Ramos-Casals M, Brito-Zerón P, Muñoz S *et al*. Autoimmune diseases induced by TNF-targeted therapies: analysis of 233 cases. *Medicine (Baltimore)* 2007; **86**: 242–51.

10 Poulalhon N, Begon E, Lebbé C *et al*. A follow-up study in 28 patients treated with infliximab for severe recalcitrant psoriasis: evidence for efficacy and high incidence of biological autoimmunity. *Br J Dermatol* 2007; **156**: 329–36.

11 Galaria NA, Werth VP, Schumacher HR. Leukocytoclastic vasculitis due to etanercept. *J Rheumatol* 2000; **27**: 2041–4.

12 Mohan N, Edwards ET, Cupps TR *et al*. Leukocytoclastic vasculitis associated with tumor necrosis factor-alpha blocking agents. *J Rheumatol* 2004; **31**: 1955–8.

13 Saint Marcoux B, De Bandt M; CRI (Club Rhumatismes et Inflammation). Vasculitides induced by TNF alpha antagonists: a study in 39 patients in France. *Joint Bone Spine* 2006; **73**: 710–3.

14 Romero-Maté A, García-Donoso C, Córdoba-Guijarro S. Efficacy and safety of etanercept in psoriasis/psoriatic arthritis: an updated review. *Am J Clin Dermatol* 2007; **8**: 143–55.

15 Curtis JR, Kramer JM, Martin C *et al*. Heart failure among younger rheumatoid arthritis and Crohn's patients exposed to TNF-alpha antagonists. *Rheumatology (Oxford)* 2007; **46**: 1688–93.

16 Listing J, Strangfeld A, Kekow J *et al*. Does tumor necrosis factor alpha inhibition promote or prevent heart failure in patients with rheumatoid arthritis? *Arthritis Rheum* 2008; **58**: 667–77.

17 Zeltser R, Valle L, Tanck C *et al*. Clinical, histological, and immunophenotypic characteristics of injection site reactions associated with etanercept: a recombinant tumor necrosis factor alpha receptor: Fc fusion protein. *Arch Dermatol* 2001; **137**: 893–9.

18 Werth VP, Levinson AI. Etanercept-induced injection site reactions: mechanistic insights from clinical findings and immunohistochemistry. *Arch Dermatol* 2001; **137**: 953–5.

19 Zeltser R, Valle L, Tanck C *et al*. Clinical, histological, and immunophenotypic characteristics of injection site reactions associated with etanercept. *Arch Dermatol* 2001; **137**: 893–9.

20 Misery L, Perrot JL, Gentil-Perret A *et al*. Dermatological complications of etanercept therapy for rheumatoid arthritis. *Br J Dermatol* 2002; **146**: 334–5.

21 Scheinfeld N. The medical uses and side effects of etanercept with a focus on cutaneous disease. *J Drugs Dermatol* 2004; **3**: 653–9.

22 Davis JC Jr, van der Heijde DM, Braun J *et al*. Efficacy and safety of up to 192 weeks of etanercept therapy in patients with ankylosing spondylitis. *Ann Rheum Dis* 2008; **67**: 346–52.

23 Wright RC. Atopic dermatitis-like eruption precipitated by infliximab. *J Am Acad Dermatol* 2003; **49**: 160–1.

24 Aslanidis S, Pyrpasopoulou A, Douma S, Triantafyllou A. Tumor necrosis factor-α antagonist-induced psoriasis: yet another paradox in medicine. *Clin Rheumatol* 2008; **27**: 377–80.
25 Verea MM, Del Pozo J, Yebra-Pimentel MT *et al*. Psoriasiform eruption induced by infliximab. *Ann Pharmacother* 2004; **38**: 54–7.
26 Pirard D, Arco D, Debrouckere V, Heenen M. Anti-tumor necrosis factor alpha-induced psoriasiform eruptions: three further cases and current overview. *Dermatology* 2006; **213**: 182–6.
27 de Gannes GC, Ghoreishi M, Pope J *et al*. Psoriasis and pustular dermatitis triggered by TNF-α inhibitors in patients with rheumatologic conditions. *Arch Dermatol* 2007; **14**: 223–31.
28 Cohen JD, Bournerias I, Buffard V *et al*. Psoriasis induced by tumor necrosis factor-alpha antagonist therapy: a case series. *J Rheumatol* 2007; **34**: 380–5.
29 Ubriani R, Van Voorhees AS. Onset of psoriasis during treatment with TNF-α antagonists: a report of 3 cases. *Arch Dermatol* 2007; **143**: 270–1.
30 Severs GA, Lawlor TH, Purcell SM *et al*. Cutaneous adverse reaction to infliximab: report of psoriasis developing in 3 patients. *Cutis* 2007; **80**: 231–7.
31 Roux CH, Brocq O, Leccia N *et al*. New-onset psoriatic palmoplantaris pustulosis following infliximab therapy: a class effect? *J Rheumatol* 2007; **34**: 434–7.
32 Wollina U, Hansel G, Koch A *et al*. Tumor necrosis factor-alpha inhibitor-induced psoriasis or psoriasiform exanthemata: first 120 cases from the literature including a series of six new patients. *Am J Clin Dermatol* 2008; **9**: 1–14.
33 Seneschal J, Lepreux S, Bouyssou-Gauthier ML *et al*. Psoriasiform drug eruptions under anti-TNF treatment of arthritis are not true psoriasis. *Acta Derm Venereol* 2007; **87**: 77–80.
34 Deng A, Harvey V, Sina B *et al*. Interstitial granulomatous dermatitis associated with the use of tumor necrosis factor alpha inhibitors. *Arch Dermatol* 2006; **142**: 198–202.
35 Nikas SN, Voulgari PV, Drosos AA. Urticaria and angioedema-like skin reactions in a patient treated with adalimumab. *Clin Rheumatol* 2007; **26**: 787–8.
36 Skytta E, Pohjankoski H, Savolainen A. Etanercept and urticaria in patients with juvenile idiopathic arthritis. *Clin Exp Rheumatol* 2001; **18**: 533–4.
37 González-López MA, Martínez-Taboada VM, González-Vela MC *et al*. Recall injection-site reactions associated with etanercept therapy: report of two new cases with immunohistochemical analysis. *Clin Exp Dermatol* 2007; **32**: 672–4.
38 Winfield H, Lain E, Horn T, Hoskyn J. Eosinophilic cellulitis like reaction to subcutaneous etanercept injection. *Arch Dermatol* 2006; **142**: 218–20.
39 Smith KJ, Skelton HG. Rapid onset of cutaneous squamous cell carcinoma in patients with rheumatoid arthritis after starting tumor necrosis factor α receptor IgG1-Fc fusion complex therapy. *J Am Acad Dermatol* 2002; **45**: 953–6.
40 Wang LC, Medenica MM, Shea CR, Busbey S. Infliximab-induced eczematid-like purpura of Doucas and Kapetenakis. *J Am Acad Dermatol* 2003; **49**: 157–8.
41 Vegara G, Sivestre JF, Betlloch I *et al*. Cutaneous drug eruption to infliximab: report of 4 cases with an interface dermatitis pattern. *Arch Dermatol* 2002; **138**: 1258–9.
42 Chan AT, Cleeve V, Daymond TJ. Necrotising fasciitis in a patient receiving infliximab for rheumatoid arthritis. *Postgrad Med J* 2002; **78**: 47–8.
43 Gamarra RM, McGraw SD, Drelichman VS, Maas LC. Serum sickness-like reactions in patients receiving intravenous infliximab. *J Emerg Med* 2006; **30**: 41–4.
44 Smith CH, Jackson K, Bashir SJ *et al*. Infliximab for severe, treatment-resistant psoriasis: a prospective, open-label study. *Br J Dermatol* 2006; **155**: 160–9.
45 Vultaggio A, Matucci A, Parronchi P *et al*. Safety and tolerability of infliximab therapy: suggestions and criticisms based on wide clinical experience. *Int J Immunopathol Pharmacol* 2008; **21**: 367–74.

Monoclonal antibodies—miscellaneous

Anakinra. This recombinant human IL-1 receptor antagonist used in the treatment of rheumatoid arthritis, familial Mediterranean fever and the Muckle Wells syndrome, caused erythema and oedema at injection sites within the first month of treatment, with marked dermal oedema and a lichenoid dermal infiltrate [1].

Basiliximab. This IL-2 receptor monoclonal antibody has caused myalgia [2].

Efalizumab [3]. This recombinant humanized IgG1 kappa isotype monoclonal antibody against the CD11a molecule was used as a weekly injection in the treatment of moderate to severe psoriasis. Headache, chills, fever, nausea and myalgia followed the first two injections within 2 days. Arthralgia, asthenia, peripheral oedema and psoriasis occured in up to 2%, and a rebound flare reaction on cessation of therapy in approximately 5%, of patients [3,4]. Immune-mediated thrombocytopenia and haemolytic anaemia were recorded. Severe arthritis events, including psoriatic arthritis events, were reported in clinical trials and post-marketing surveillance. However, the incidence of arthropathy adverse events in efalizumab-treated patients was more recently judged similar to placebo [5]. The drug has recently been withdrawn due to associated onset of multifocal leukoencephalopathy [6].

OKT3. Orthoclone OKT3, a murine monoclonal antibody directed against the CD3 subset of T lymphocytes, has been used as an immunosuppressive agent in renal transplant recipients, and was anecdotally associated with anaphylaxis [7].

Omalizumab. Therapy for asthma was associated with anaphylactoid reactions; polysorbate, an excipient in omalizumab, may have been responsible [8].

Rituximab. This murine–human chimeric anti-CD20 antibody for patients with CD20-expressing B-cell lymphoma, currently under investigation for other indications including autoimmune diseases, in particular rheumatoid arthritis, is usually well tolerated [9], but has caused vasculitis and serum sickness [10,11].

References

1 Vila AT, Puig L, Fernández-Figueras MT *et al*. Adverse cutaneous reactions to anakinra in patients with rheumatoid arthritis: clinicopathological study of five patients. *Br J Dermatol* 2005; **153**: 417–23.
2 Bell HK, Parslew RAG. Use of basiliximab as a cyclosporin-sparing agent in palmopustular psoriasis with myalgia as an adverse effect. *Br J Dermatol* 2002; **147**: 606–7.
3 Scheinfeld N. Efalizumab: a review of events reported during clinical trials and side effects. *Expert Opin Drug Saf* 2006; **5**: 197–209.
4 Hassan AS, Simon D, Sumon H-U *et al*. Efalizumab-associated papular psoriasis. *Arch Dermatol* 2007; **143**: 900–6.
5 Pincelli C, Henninger E, Casset-Semanaz F. The incidence of arthropathy adverse events in efalizumab-treated patients is low and similar to placebo and does not increase with long-term treatment: pooled analysis of data from Phase III clinical trials of efalizumab. *Arch Dermatol Res* 2006; **298**: 329–38.
6 Korman BD, Tyler KL, Korman NJ. Progressive multifocal leukoencephalopathy, efalizumab and immunosuppression: a cautionary tale for dermatologists. *Arch Dermatol* 2009; **145**: 937–42.
7 Werier J, Cheung AHS, Matas AJ. Anaphylactic hypersensitivity reaction after repeat OKT3 treatment. *Lancet* 1991; **337**: 1351.
8 Price KS, Hamilton RG. Anaphylactoid reactions in two patients after omalizumab administration after successful long-term therapy. *Allergy Asthma Proc* 2007; **28**: 313–9.
9 Kimby E. Tolerability and safety of rituximab (MabThera). *Cancer Treat Rev* 2005; **31**: 456–73.
10 Dereure O, Navarro R, Rossi JF, Guilhou JJ. Rituximab-induced vasculitis. *Dermatology* 2001; **203**: 83–4.
11 D'Arcy CA, Mannik M. Serum sickness secondary to treatment with the murine–human chimeric antibody IDEC-C2B8 (rituximab). *Arthritis Rheum* 2001; **44**: 1717–8.

Miscellaneous drugs affecting the immune response

Topical calcineurin inhibitors

Both pimecrolimus [1–9] and tacrolimus [9–14] are well tolerated. Transient application site reactions, including burning or pruritus, are related to disease severity, and decrease over time; skin infections, flu-like symptoms and headache occur, but no more frequently than with placebo. Focal hypertrichosis [15] and acne [16] are recorded with tacrolimus, and rosacea with both tacrolimus and pimecrolimus [17,18].

References

1 Shah Meurer M, Fölster-Holst R, Wozel G *et al*. Pimecrolimus cream in the long-term management of atopic dermatitis in adults: a six-month study. *Dermatology* 2002; **205**: 271–7.

2 Kapp A, Papp K, Bingham A *et al*. Long-term management of atopic dermatitis in infants with topical pimecrolimus, a nonsteroid anti-inflammatory drug. *J Allergy Clin Immunol* 2002; **110**: 277–84.

3 Wahn U, Bos JD, Goodfield M *et al*. Efficacy and safety of pimecrolimus cream in the long-term management of atopic dermatitis in children. *Pediatrics* 2002; **110**: e2.

4 Meurer M, Fartasch M, Albrecht G *et al*. Long-term efficacy and safety of pimecrolimus cream 1% in adults with moderate atopic dermatitis. *Dermatology* 2004; **208**: 365–72.

5 Hebert AA. Review of pimecrolimus cream 1% for the treatment of mild to moderate atopic dermatitis. *Clin Ther* 2006; **28**: 1972–82.

6 Langley RG, Luger TA, Cork MJ *et al*. An update on the safety and tolerability of pimecrolimus cream 1%: evidence from clinical trials and post-marketing surveillance. *Dermatology* 2007; **215** (Suppl. 1): 27–44.

7 Gollnick H, Kaufmann R, Stough D *et al*. Pimecrolimus cream 1% in the long-term management of adult atopic dermatitis: prevention of flare progression. A randomized controlled trial. *Br J Dermatol* 2008; **158**: 1083–93.

8 Zuberbier T, Bräutigam M. Long-term management of facial atopic eczema with pimecrolimus cream 1% in paediatric patients with mild to moderate disease. *J Eur Acad Dermatol Venereol* 2008; **22**: 718–21.

9 Draelos ZD. Use of topical corticosteroids and topical calcineurin inhibitors for the treatment of atopic dermatitis in thin and sensitive skin areas. *Curr Med Res Opin* 2008; **24**: 985–94.

10 Won CH, Seo PG, Park YM *et al*. A multicenter trial of the efficacy and safety of 0.03% tacrolimus ointment for atopic dermatitis in Korea. *J Dermatolog Treat* 2004; **15**: 30–4.

11 Schachner LA, Lamerson C, Sheehan MP *et al*. Tacrolimus ointment 0.03% is safe and effective for the treatment of mild to moderate atopic dermatitis in pediatric patients: results from a randomized, double-blind, vehicle-controlled study. *Pediatrics* 2005; **116**: e334–42.

12 Paller AS, Lebwohl M, Fleischer AB Jr *et al*. Tacrolimus ointment is more effective than pimecrolimus cream with a similar safety profile in the treatment of atopic dermatitis: results from 3 randomized, comparative studies. *J Am Acad Dermatol* 2005; **52**: 810–22.

13 Remitz A, Harper J, Rustin M *et al*. Long-term safety and efficacy of tacrolimus ointment for the treatment of atopic dermatitis in children. *Acta Derm Venereol* 2007; **87**: 54–61.

14 Rustin MH. The safety of tacrolimus ointment for the treatment of atopic dermatitis: a review. *Br J Dermatol* 2007; **157**: 861–73.

15 Prats Caelles I, Pinto PH, Casado ELA, Laguna RL. Focal hypertrichosis during topical tacrolimus therapy for childhood vitiligo. *Pediatr Dermatol* 2005; **22**: 86–7.

16 Bakos L, Marchiori Bakos R. Focal acne during topical tacrolimus therapy for vitiligo. *Arch Dermatol* 2007; **143**: 123–4.

17 Antille C, Saurat JH, Lübbe J. Induction of rosaceiform dermatitis during treatment of facial inflammatory dermatoses with tacrolimus ointment. *Arch Dermatol* 2004; **140**: 457–60.

18 El Sayed F, Ammoury A, Dhaybi R *et al*. Rosaceiform eruption to pimecrolimus. *J Am Acad Dermatol* 2006; **54**: 548–9.

Diphencyprone

Diphencyprone [1] used for alopecia areata has resulted in urticaria [2,3] and erythema multiforme [4], and has been linked to the development of vitiligo [5–7]. Severe contact dermatitis reactions may be induced.

References

1 Shah M, Lewis FM, Messenger AG. Hazards in the use of diphencyprone. *Br J Dermatol* 1996; **134**: 1153.

2 van der Steen PHM, van Baar HMJ, Perret CM, Happle R. Treatment of alopecia areata with diphenylcyclopropenone. *J Am Acad Dermatol* 1991; **24**: 253–7.

3 Alam M, Gross EA, Savin RC. Severe urticarial reaction to diphenylcyclopropenone therapy for alopecia areata. *J Am Acad Dermatol* 1999; **40**: 110–2.

4 Perret CM, Steijlen PM, Zaun H, Happle R. Erythema multiforme-like eruptions: a rare side effect of topical immunotherapy with diphenylcyclopropenone. *Dermatologica* 1990; **180**: 5–7.

5 Hatzis J, Gourgiotou K, Tosca A *et al*. Vitiligo as a reaction to topical treatment with diphencyprone. *Dermatologica* 1988; **177**: 146–8.

6 Duhra P, Foulds IS. Persistent vitiligo induced by diphencyprone. *Br J Dermatol* 1990; **123**: 415–6.

7 Henderson CA, Ilchyshyn A. Vitiligo complicating diphencyprone sensitization therapy for alopecia universalis. *Br J Dermatol* 1995; **133**: 496–7.

Erythropoietin

This drug has caused a generalized eczematous reaction [1].

Reference

1 Hardwick N, King CM. Generalized eczematous reaction to erythropoietin. *Contact Dermatitis* 1993; **28**: 123.

Topical imiquimod

This topical imidazoquinoline immunodulator drug, a toll-like receptor agonist, which induces cytokine production and stimulates the innate and cellular immune responses, is currently used in the management of anogenital warts, actinic keratoses, basal cell carcinoma and other skin lesions, including lentigo maligna [1]. It is broadly well tolerated; local application-site reactions, including pruritus, erythema, oedema and bleeding are common, usually mild, and do not necessitate discontinuation of therapy [2–9]. Inflammatory papules in the surrounding skin have been recorded [10]. There is evidence that the more severe the local reaction, the higher the clearance rate [3], without compromising the eventual cosmetic result [9]. Imiquimod appears safe to use in transplant patients [11]. Rarely, headache, influenza-like symptoms, myalgia, angio-oedema [12], Stevens–Johnson syndrome, and cutaneous lupus erythematosus-like reactions are seen.

Erosive cheilitis [13] and aphthous ulceration [14], localized multiple comedones and epidermoid cysts [15,16], multiple keratoacanthomas [17], lymphocytic vasculitis [18], and chronic neuropathic pain [19] are documented. There are a number of published reports on vitiligo-like hypopigmentation [20–25], permanent on the face [25], and occasionally hyperpigmentation. Severe exacerbation of eczema [26], triggering of local or generalized psoriasis [27–30], or pemphigus [31–33] may occur rarely. Concerns about the possible risks of immunostimulation have been expressed [34]; exacerbation of HLA-B27 spondyloarthropathy [34] and exacerbation of myasthenia gravis [35] are recorded.

References

1 Hardwick Wagstaff AJ, Perry CM. Topical imiquimod: a review of its use in the management of anogenital warts, actinic keratoses, basal cell carcinoma and other skin lesions. *Drugs* 2007; **67**: 2187–210.

2 Micali G, De Pasquale R, Caltabiano R *et al*. Topical imiquimod treatment of superficial and nodular basal cell carcinomas in patients affected by basal cell nevus syndrome: a preliminary report. *J Dermatolog Treat* 2002; **13**: 123–7.
3 Geisse J, Caro I, Lindholm J *et al*. Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: results from two phase III, randomized, vehicle-controlled studies. *J Am Acad Dermatol* 2004; **50**: 722–33.
4 Lebwohl M, Dinehart S, Whiting D *et al*. Imiquimod 5% cream for the treatment of actinic keratosis: results from two phase III, randomized, double-blind, parallel group, vehicle-controlled trials. *J Am Acad Dermatol* 2004; **50**: 714–21.
5 Schulze HJ, Cribier B, Requena L *et al*. Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: results from a randomized vehicle-controlled phase III study in Europe. *Br J Dermatol* 2005; **152**: 939–47.
6 Ferrándiz C. Update on actinic keratosis in clinical trial experience with imiquimod. *Br J Dermatol* 2007; **157** (Suppl. 2): 32–3.
7 Rivers JK, Rosoph L, Provost N, Bissonnette R. Open-label study to assess the safety and efficacy of imiquimod 5% cream applied once daily three times per week in cycles for treatment of actinic keratoses on the head. *J Cutan Med Surg* 2008; **12**: 97–101.
8 Jacobs AA, Snavely N, Markus J, Rosen T. Vasodilatory adverse events associated with topical imiquimod 5 percent cream. *Dermatol Online J* 2008; **14**: 4.
9 Greenberg HL, Cohen JL, Rosen T, Orengo I. Severe reaction to 5% imiquimod cream with excellent clinical and cosmetic outcomes. *J Drugs Dermatol* 2007; **6**: 452–8.
10 Stinco G, Frattasio A, Forcione M *et al*. The appearance of inflammatory papules in the skin surrounding areas treated with imiquimod cream for basal cell carcinoma. *Br J Dermatol* 2008; **158**: 408–9.
11 Ulrich C, Bichel J, Euvrard S *et al*. Topical immunomodulation under systemic immunosuppression: results of a multicentre, randomized, placebo-controlled safety and efficacy study of imiquimod 5% cream for the treatment of actinic keratoses in kidney, heart, and liver transplant patients. *Br J Dermatol* 2007; **157** (Suppl. 2): 25–31.
12 Barton JC. Angioedema associated with imiquimod. *J Am Acad Dermatol* 2004; **51**: 477–8.
13 Campanelli A, Lübbe J. Erosive cheilitis after facial application of imiquimod 5% cream. *J Eur Acad Dermatol Venereol* 2007; **21**: 1429–30.
14 Chakrabarty AK, Mraz S, Geisse JK, Anderson NJ. Aphthous ulcers associated with imiquimod and the treatment of actinic cheilitis. *J Am Acad Dermatol* 2005; **52** (2 Suppl. 1): 35–7.
15 Marty CL, Randle HW, Walsh JS. Eruptive epidermoid cysts resulting from treatment with imiquimod. *Dermatol Surg* 2005; **31**: 780–2.
16 Nasca MR, De Pasquale R, Micali G. Multiple and clustered eruptive epidermoid cysts following treatment with topical imiquimod. *Dermatology* 2007; **215**: 352–3.
17 D'Addario S, Carrington PR. Multiple keratoacanthomas as an untoward response to imiquimod therapy for actinic keratoses. *Acta Derm Venereol* 2006; **86**: 366–7.
18 Treviño J, Prieto VG, Hearne R *et al*. Atypical lymphocytic reaction with epidermotropism and lymphocytic vasculopathic reaction (lymphocytic vasculitis) after treatment with imiquimod. *J Am Acad Dermatol* 2006; **55** (5 Suppl.): S123–5.
19 Yi BA, Nirenberg MJ, Goldstein SM, Berger TG. Chronic neuropathic pain associated with imiquimod: report of 2 cases. *J Am Acad Dermatol* 2005; **52** (2 Suppl. 1): 57–8.
20 Brown T, Zirvi M, Cotsarelis G, Gelfand JM. Vitiligo-like hypopigmentation associated with imiquimod treatment of genital warts. *J Am Acad Dermatol* 2005; **52**: 715–6.
21 Stefanaki C, Nicolaidou E, Hadjivassiliou M *et al*. Imiquimod-induced vitiligo in a patient with genital warts. *J Eur Acad Dermatol Venereol* 2006; **20**: 755–6.
22 Serrão VV, Páris FR, Feio AB. Genital vitiligo-like depigmentation following use of imiquimod 5% cream. *Eur J Dermatol* 2008; **18**: 342–3.
23 Mashiah J, Brenner S. Possible mechanisms in the induction of vitiligo-like hypopigmentation by topical imiquimod. *Clin Exp Dermatol* 2008; **33**: 74–6.
24 Jacob SE, Blyumin M. Vitiligo-like hypopigmentation with poliosis following treatment of superficial basal cell carcinoma with imiquimod. *Dermatol Surg* 2008; **34**: 844–5.
25 Mendonça CO, Yates VM. Permanent facial hypopigmentation following treatment with imiquimod cream. *Clin Exp Dermatol* 2006; **31**: 721–2.
26 Taylor CL, Maslen M, Kapembwa M. A case of severe eczema following use of imiquimod 5% cream. *Sex Transm Infect* 2006; **82**: 227–8.
27 Gilliet M, Conrad C, Geiges M *et al*. Psoriasis triggered by toll-like receptor 7 agonist imiquimod in the presence of dermal plasmacytoid dendritic cell precursors. *Arch Dermatol* 2004; **140**: 1490–5.
28 Wu JK, Siller G, Strutton G. Psoriasis induced by topical imiquimod. *Australas J Dermatol* 2004; **45**: 47–50.
29 Fanti PA, Dika E, Vaccari S *et al*. Generalized psoriasis induced by topical treatment of actinic keratosis with imiquimod. *Int J Dermatol* 2006; **45**: 1464–5.
30 Rajan N, Langtry JA. Generalized exacerbation of psoriasis associated with imiquimod cream treatment of superficial basal cell carcinomas. *Clin Exp Dermatol* 2006; **31**: 140–1.
31 Lin R, Ladd DJ Jr, Powell DJ, Way BV. Localized pemphigus foliaceus induced by topical imiquimod treatment. *Arch Dermatol* 2004; **140**: 889–90.
32 Ruocco E, Baroni A, Rossiello L, Ruocco V. Imiquimod contact pemphigus: a comment. *Eur J Obstet Gynecol Reprod Biol* 2004; **115**: 242–3.
33 Mashiah J, Brenner S. Possible mechanisms in the induction of pemphigus foliaceus by topical imiquimod treatment. *Arch Dermatol* 2005; **141**: 908–9.
34 Benson E. Imiquimod: potential risk of an immunostimulant. *Australas J Dermatol* 2004; **45**: 123–4.
35 Wolfe CM, Tafuri N, Hatfield K. Exacerbation of myasthenia gravis during imiquimod treatment. *J Drugs Dermatol* 2007; **6**: 745–6.

Roquinimex

The incidence of graft-versus-host reactions is enhanced in patients treated with the cytokine inducer carboxamide–quinoline immunotherapeutic agent roquinimex (Linomide), used for post-transplantation immunotherapy in autologous bone marrow transplantation for acute and chronic myelogenous leukaemia [1,2]. Cutaneous graft-versus-host reactions were associated with eccrine sweat gland necrosis.

References

1 Gaspari AA, Cheng SF, DiPersio JF, Rowe JM. Roquinimex-induced graft-versus-host reaction after autologous bone marrow transplantation. *J Am Acad Dermatol* 1995; **33**: 711–7.
2 Ohsuga Y, Rowe JM, Liesveld J *et al*. Dermatologic changes associated with roquinimex immunotherapy after autologous bone marrow transplant. *J Am Acad Dermatol* 2000; **43**: 437–41.

Antihistamines

H_1 antihistamines

All traditional H_1 antagonists cause side effects [1–4], especially sedation, most marked with the aminoalkylether and phenothiazine groups. Dizziness, poor coordination, blurred vision and diplopia, as well as nervousness, insomnia and tremor may occur. In addition, atropine-like anticholinergic effects, including dryness of mucous membranes, urinary retention, palpitations, agitation, increased intraocular pressure and gastrointestinal upset are seen. Phenothiazine-derived drugs may cause photosensitivity or cholestatic jaundice. The effects of nervous system depressants, such as alcohol, hypnotics, sedatives, analgesics and anxiolytics, may be potentiated. Decreased efficacy of drugs metabolized by the liver microsomal enzyme system, including oral anticoagulants, phenytoin and griseofulvin, may occur as a result of liver-enzyme induction by antihistamines. The newer antihistamines (e.g. terfenadine, astemizole, loratadine, cetirizine) are much less likely to cause sedation [1–4].

Terfenadine and astemizole rarely cause QT interval prolongation and torsade de pointes. Arrhythmias occur when metabolism of terfenadine is impaired, as with inhibition of the cytochrome P-450 isoform CYP 3A4 by ketoconazole, itraconazole and related imidazole antifungals, erythromycin, clarithromycin and related

macrolide antibiotics, grapefruit juice, or liver disease [5–7]. Patients on terfenadine or astemizole should be instructed accordingly. The UK Committee on Safety of Medicines withdrew terfenadine from over-the-counter sale, as did the US FDA. However, in one study, there was no increased risk of life-threatening ventricular arrhythmic events or cardiac arrest with terfenadine compared with over-the-counter antihistamines, ibuprofen or clemastine [8].

True hypersensitivity reactions are rare. Fixed eruptions have been caused by thonzylamine and cyclizine [9], cetirizine [10,11], levocetirizine [12], hydroxyzine [13] and loratadine [14]. Skin eruptions have been documented with terfenadine [15,16], including possible exacerbation of psoriasis [17]; alopecia has been reported rarely [18]. Cetirizine has been linked to maculopapular morbilliform eruptions, with cross-reactivity to other piperazine (ethylenediamine) derivatives hydroxyzine and azelastine, and precipitation of urticaria [19–23]. Mizolastine has been reported to cause immediate hypersensitivity [24]. Lichenoid and subacute LE-like dermatoses are recorded with antihistamine therapy [25]. Hydroxyzine caused a systemic contact dermatitis in one case [26]. A pityriasis lichenoides et varioliformis acuta-like drug exanthem was reportedly caused by astemizole, with a positive challenge test [27]. Antihistamines are associated with atypical lymphoid hyperplasia, presenting as solitary or multiple nodules and plaques, or multiple papules, in some patients [28]. Urticaria was induced by different families of antihistamines—piperazines and piperidines—in one patient [29].

References

1 Woodward JK. Pharmacology and toxicology of nonclassical antihistamines. *Cutis* 1988; **42**: 5–9.
2 Lichtenstein LM, Simons FER, eds. Advancements in antiallergic therapy: beyond conventional antihistamines. *J Allergy Clin Immunol* 1990; **86** (Suppl.): 995–1046.
3 Kennard CD, Ellis CN. Pharmacologic therapy for urticaria. *J Am Acad Dermatol* 1991; **25**: 176–89.
4 Soter NA. Treatment of urticaria and angioedema: low-sedating H1-type antihistamines. *J Am Acad Dermatol* 1991; **24**: 1084–7.
5 Thomas SHL. Drugs, QT interval abnormalities and ventricular arrhythmias. *Adverse Drug React Acute Toxicol Rev* 1994; **13**: 77–102.
6 Woosley RL. Cardiac actions of antihistamines. *Annu Rev Pharmacol Toxicol* 1996; **36**: 233–52.
7 Thomas SHL. Drugs and the QT interval. *Adverse Drug React Bull* 1997; **182**: 691–4.
8 Pratt CM, Hertz RP, Ellis BE *et al.* Risk of developing life-threatening ventricular arrhythmia associated with terfenadine in comparison with over-the-counter antihistamines, ibuprofen and clemastine. *Am J Cardiol* 1994; **73**: 346–52.
9 Griffiths WAD, Peachey RDG. Fixed drug eruption due to cyclizine. *Br J Dermatol* 1970; **82**: 616–7.
10 Inamadar AC, Palit A, Athanikar SB *et al.* Multiple fixed drug eruptions due to cetirizine. *Br J Dermatol* 2002; **147**: 1025–6.
11 Cravo M, Gonçalo M, Figueiredo A. Fixed drug eruption to cetirizine with positive lesional patch tests to the three piperazine derivatives. *Int J Dermatol* 2007; **46**: 760–2.
12 Mahajan VK, Sharma NL, Sharma VC. Fixed drug eruption: a novel side-effect of levocetirizine. *Int J Dermatol* 2005; **44**: 796–8.
13 Cohen HA, Barzilai A, Matalon A, Harel L, Gross S. Fixed drug eruption of the penis due to hydroxyzine hydrochloride. *Ann Pharmacother* 1997; **31**: 327–9.
14 Ruiz-Genao DP, Hernández-Nünez A, Sánchez-Pérez J, García-Díez A. Fixed drug eruption due to loratadine. *Br J Dermatol* 2002; **146**: 528–9.
15 Stricker BHCH, Van Dijke CHP, Isaacs AJ, Lindquist M. Skin reactions to terfenadine. *BMJ* 1986; **293**: 536.
16 McClintock AD, Ching DW, Hutchinson C. Skin reactions and terfenadine. *NZ Med J* 1995; **108**: 208.
17 Harrison PV, Stones RN. Severe exacerbation of psoriasis due to terfenadine. *Clin Exp Dermatol* 1988; **13**: 275.
18 Jones S, Morley W. Terfenadine causing hair loss (unreviewed report). *BMJ* 1985; **291**: 940.
19 Stingeni L, Caraffini S, Agostinelli D *et al.* Maculopapular and urticarial eruption from cetirizine. *Contact Dermatitis* 1997; **37**: 249–50.
20 Lew BL, Haw CR, Lee MH. Cutaneous drug eruption from cetirizine and hydroxyzine. *J Am Acad Dermatol* 2004; **50**: 953–6.
21 Karamfilov T, Wilmer A, Hipler UC, Wollina U. Cetirizine-induced urticarial reaction. *Br J Dermatol* 1999; **140**: 979–80.
22 Calista D, Schianchi S, Morri M. Urticaria induced by cetirizine. *Br J Dermatol* 2001; **144**: 196.
23 Schröter S, Damveld B, Marsch WC. Urticarial intolerance reaction to cetirizine. *Clin Exp Dermatol* 2002; **27**: 185–7.
24 Gonzalo-Garijo MA, Jiménez-Ferrera G, Bobadilla-González P, Cordobés-Durán C. Hypersensitivity reaction to mizolastine: study of cross reactions. *J Investig Allergol Clin Immunol* 2006; **16**: 391–3.
25 Crowson AN, Magro CM. Lichenoid and subacute cutaneous lupus erythematosus-like dermatitis associated with antihistamine therapy. *J Cutan Pathol* 1999; **26**: 95–9.
26 Menne T. Systemic contact dermatitis to hydroxyzine. *Am J Contact Dermatitis* 1997; **8**: 2–5.
27 Stosiek N, Peters KP, von den Driesch P. Pityriasis-lichenoides-et-varioliformis-acuta-ähnliches Arzneiexanthem durch Astemizol. *Hautarzt* 1993; **44**: 235–7.
28 Magro CM, Crowson AN. Drugs with antihistaminic properties as a cause of atypical cutaneous lymphoid hyperplasia. *J Am Acad Dermatol* 1995; **32**: 419–28.
29 González de Olano D, Roán Roán J, de la Hoz Caballer B *et al*. Urticaria induced by antihistamines. *J Investig Allergol Clin Immunol* 2006; **16**: 144–6.

H_2 antihistamines

Severe adverse reactions are rare with cimetidine, ranitidine, nizatidine and famotidine [1]. Gastrointestinal upset, headache, drowsiness, fatigue or muscular pain occur in fewer than 3% of patients. Confusion, dizziness, somnolence, gynaecomastia or galactorrhoea with increased prolactin levels (cimetidine and ranitidine only), impotence and loss of libido (with cimetidine), bone marrow depression, hepatitis, abnormal renal function or nephritis, arthralgia, myalgia, cardiac abnormalities, and minor or severe skin reactions occur in fewer than 1% of patients.

Cimetidine. Mucocutaneous reactions are rare in relation to the enormous, worldwide use of this drug. Reported reactions include a seborrhoeic dermatitis-like rash [2] and asteatotic dermatitis [3], erythema annulare centrifugum [4], erythrosis [5], giant urticaria [6], transitory alopecia [7], erythema multiforme [8] and exfoliative dermatitis [9]. Other effects have included thrombocytopenia [10] and leukocytoclastic vasculitis [11]. Exacerbation of cutaneous LE [12] and SLE with granulocytopenia [13] are documented. Cimetidine binds to androgen receptors, thereby blocking the binding of dihydrotestosterone, and gynaecomastia and hypogonadism are now well-known side effects [14]. The drug augments cell-mediated immunity *in vitro* by blockade of H_2 receptors on T lymphocytes [15].

References

1 Feldman M, Burton ME. Histamine$_2$-receptor antagonists. Standard therapy for acid-peptic diseases. *N Engl J Med* 1990; **323**: 1672–80.
2 Kanwar A, Majid A, Garg MP, Singh G. Seborrheic dermatitis-like eruption caused by cimetidine. *Arch Dermatol* 1981; **117**: 65–6.

3 Greist MC, Epinette WW. Cimetidine-induced xerosis and asteatotic dermatitis. *Arch Dermatol* 1982; **118**: 253–4.
4 Merrett AC, Marks R, Dudley FJ. Cimetidine-induced erythema annulare centrifugum: no cross-sensitivity with ranitidine. *BMJ* 1981; **283**: 698.
5 Angelini G, Bovo P, Vaona B, Cavallini G. Cimetidine and erythrosis-like lesions. *BMJ* 1979; **i**: 1147–8.
6 Hadfield WA Jr. Cimetidine and giant urticaria. *Ann Intern Med* 1979; **91**: 128–9.
7 Vircburger MI, Prelevic GM, Brkic S *et al*. Transitory alopecia and hypergonadotrophic hypogonadism during cimetidine treatment. *Lancet* 1981; **i**: 1160–1.
8 Ahmed AH, McLarly DG, Sharma SK, Masawe AEJ. Stevens–Johnson syndrome during treatment with cimetidine. *Lancet* 1979; **ii**: 433.
9 Yantis PL, Bridges ME, Pittman FE. Cimetidine-induced exfoliative dermatitis. *Dig Dis Sci* 1980; **25**: 73–4.
10 Rate R, Bonnell M, Chervenak C, Pavinich G. Cimetidine and hematologic effects. *Ann Intern Med* 1979; **91**: 795.
11 Dernbach WK, Taylor G. Leukocytoclastic vasculitis from cimetidine. *JAMA* 1981; **246**: 331.
12 Davidson BL, Gilliam JN, Lipsky PE. Cimetidine-associated exacerbation of cutaneous lupus erythematosus. *Arch Intern Med* 1982; **142**: 166–7.
13 Littlejohn GO, Urowitz MB. Cimetidine, lupus erythematosus, and granulocytopenia. *Ann Intern Med* 1979; **91**: 317–8.
14 Jensen RT, Collen MJ, Pandol SJ *et al*. Cimetidine-induced impotence and breast changes in patients with gastric hypersecretory states. *N Engl J Med* 1983; **308**: 883–7.
15 Mavligit GM. Immunologic effects of cimetidine: potential uses. *Pharmacotherapy* 1987; **7** (Suppl. 2): S120–S124.

Famotidine. This drug has been associated with the development of symptomatic dermographism [1], pruritic exanthem [2–4], contact eczema [4], leukocytoclastic vasculitis [5] and TEN.

References

1 McCarley Warner D, Ramos-Caro FA, Flowers FP. Famotidine (Pepcid)-induced symptomatic dermatographism. *J Am Acad Dermatol* 1994; **31**: 677–8.
2 Reynolds JC. Famotidine in the management of duodenal ulcer: an analysis of multicenter findings worldwide. *Clin Ther* 1988; **10**: 436–49.
3 Dragosics B, Weiss W, Okulski G. Zur Therapie peptischer Ulzera mit Famotidin. Erfahrungsbericht einer offenen klinischen Studie. *Wien Med Wochenschr* 1992; **142**: 408–13.
4 Monteseirin J, Conde J. Contact eczema from famotidine. *Contact Dermatitis* 1990; **22**: 290.
5 Andreo JA, Vivancos F, Lopez VM *et al*. Vasculitis leucocitoclastica y famotidina. *Med Clin (Barc)* 1990; **95**: 234–5.

Ranitidine. Urticaria [1] and anaphylaxis [2] are recorded, as are allergic dermatitis and allergic contact dermatitis [3,4]. Immune complex-mediated rashes [5], lichenoid eruptions [6] and photosensitivity with UVA sensitivity on monochromator light testing [7] have been documented, as has cholestatic hepatitis [8]. This drug has a less marked effect on androgen receptors than cimetidine, but gynaecomastia has occurred [9].

References

1 Picardo M, Santucci B. Urticaria from ranitidine. *Contact Dermatitis* 1983; **9**: 327.
2 Lazaro M, Compaired JA, De La Hoz B *et al*. Anaphylactic reaction to ranitidine. *Allergy* 1993; **48**: 385–7.
3 Juste S, Blanco J, Garces M, Rodriguez G. Allergic dermatitis due to oral ranitidine. *Contact Dermatitis* 1992; **27**: 339–40.
4 Alomar A, Puig L, Vilaltella I. Allergic contact dermatitis due to ranitidine. *Contact Dermatitis* 1987; **17**: 54–5.
5 Haboub N. Rash mediated by immune complexes associated with ranitidine treatment. *BMJ* 1988; **296**: 897.
6 Horiuchi Y, Katagiri T. Lichenoid eruptions due to the H2-receptor antagonists roxatidine and ranitidine. *J Dermatol* 1996; **23**: 510–2.
7 Todd P, Norris P, Hawk JLM, du Vivier AWP. Ranitidine-induced photosensitivity. *Clin Exp Dermatol* 1995; **20**: 146–8.
8 Devuyst O, Lefebvre C, Geubel A, Coche E. Acute cholestatic hepatitis with rash and hypereosinophilia associated with ranitidine treatment. *Acta Clin Belg* 1993; **48**: 109–14.
9 Tosti S, Cagnoli M. Painful gynaecomastia with ranitidine. *Lancet* 1982; **ii**: 160.

Leukotriene receptor antagonists

Montelukast. This drug for asthma, occasionally used in urticaria, has been associated with urticaria [1] and cutaneous lesions of Churg–Strauss syndrome [2].

References

1 Minciullo PL, Saija A, Bonanno D *et al*. Montelukast-induced generalized urticaria. *Ann Pharmacother* 2004; **38**: 999–1001.
2 Gal AA, Morris RJ, Pine JR, Spraker MK. Cutaneous lesions of Churg–Strauss syndrome associated with montelukast therapy. *Br J Dermatol* 2002; **147**: 618–9.

Injections, infusions and procedures

Radiographic contrast media and radiopharmaceuticals

Radiographic contrast media

Reactions to radiographic contrast media were previously reported to occur in about 4–8% of cases; severe reactions occurred in 1 in 1000 administrations, and occasionally fatal anaphylactoid reactions developed (1 in 3000 for intravenous cholangiograms and between 1 in 10 000 and 1 in 100 000 for intravenous urography) [1–3]. Although IgE-mediated mechanisms may be involved [4], the vast majority of contrast reactions are not due to iodine allergy but rather to non-immunological release of mast cell mediators or to direct complement activation [5,6]. The risk of severe reactions is increased in atopics, asthmatics, those taking β-blockers, and with higher doses of contrast media; up to 40% of patients with a previous reaction may develop a recurrence [7,8].

Newer, low-osmolality radiocontrast media are associated with fewer reactions [8–14]. For example, administration of iohexol in 50 660 patients undergoing excretory urography resulted in a frequency of adverse reactions of any type of 2.1% [9]. In another series, there was a 7.0% incidence of mild adverse reactions to low-osmolar iodine contrast medium in 4550 radiological procedures, including computed tomography (CT), intravenous urography, arteriography, venography and myelography [10]. There were only two cases of severe anaphylactoid reactions during 783 consecutive cases undergoing voiding cystourethrography or retrograde pyelography [11]. The incidence of contrast media complications in the catheterization laboratory is 0.23%, with one death per 55 000 [12]. Non-serious and transient acute adverse events occurred in 0.9% of 49 975 patients undergoing intravenous urography using the intravenous contrast medium iobitridol; only one patient developed anaphylactic shock [13]. In another series involving iobitridol, 0.96% of 52 057 patients had an adverse event, and 0.044% of all patients (and 0.057% of at-risk patients) had a serious adverse event [14].

Low-osmolality radiocontrast media (e.g. iohexol or iopamidol) should be the contrast media of choice for patients with a prior immediate generalized reaction to conventional contrast media. In

addition, patients should receive H_1 antihistamines and corticosteroid prophylaxis [8,11,15], although a large number of patients need to receive premedication to prevent one potentially serious reaction [16]. However, although in one study the relative risk for all adverse drug reactions was three to six times higher for ionic versus non-ionic contrast media [17], in another study mortality was not lower with the newer, low-osmolar media than with the older high-osmolar media [18]. In this latter large study, the overall mortality was 13 per million intravenous injections of radiocontrast media, rising to 35 per million in those over 65 years of age. A further study in the USA found that in a clinical trial comparing the safety of low- versus high-osmolality radiologic contrast media in patients who underwent either cardiac angiography or contrast-enhanced body CT, 19% of 1004 patients had at least one adverse reaction [19]. The mean cost per patient of treating adverse reactions was $459 (range $0–39 057).

Allergic reactions to intravenous gadolinium-based magnetic resonance imaging (MRI) contrast agents may occur despite premedication with corticosteroids and antihistamines [20]. In addition to immediate reactions, widespread erythema and oedema at 6 h, reaching a maximum at 9–12 h, followed intravenous injection of a CT contrast medium (iotrolan) [21]. Mild to moderate, delayed allergy-like reactions to contrast media of the maculopapular exanthematous and urticarial/angio-oedematous types were reported in 0.5–2% of recipients [22]. In more recent series, late adverse reactions to iodinated contrast media, including generalized maculopapular eruptions with fever, DRESS syndrome, late-onset urticaria with loss of consciousness, and facial oedema and respiratory distress, occurred in 2% to 5% of patients [23,24]. Fixed drug eruptions have been recorded with iopamidol and iomeprol [25,26]. Isolated cases of reticulate purpura [27], bullous lichen planus [28], iododerma [29], vasculitis [30] and erythrodermic psoriasis [31] have been documented. There has been a single case report of fatal TEN following second exposure to diatrizoate solution for excretory pyelography [32].

Nephrogenic systemic fibrosis

Nephrogenic systemic fibrosis (NSF), previously known as nephrogenic fibrosing dermopathy, a fibromucinous scleromyxoedema-like disorder associated with renal dysfunction, has been linked to administration of gadolinium-based MRI contrast agents, including gadodiamide [33–39]. Symptom onset is from 3 weeks to 18 months after gadolinium exposure [36]. Skin involvement may take the form of papules and plaques with peau d'orange surface changes, especially on the legs and trunk. In other patients, it presents as grossly thickened, indurated, tight skin that is woody hard on palpation. In one case the fibrosis involved the breasts, clinically mimicking inflammatory breast carcinoma [34]. Histologically, the dermis contains thickened collagen bundles, numerous plump fibroblast-like cells and elevated hyaluronan expression [36]. Patient fibroblasts appear activated to synthesize elevated levels of hyaluronic acid and collagen in response to a serum factor [35,37]. Gadolinium has been detected in patients' skin biopsies [36,38] and may be mobilized over time from bone stores, explaining the variably delayed onset and increasing skin concentration over time in patients with NSF. Gadodiamide stimulates control fibroblast growth, matrix synthesis and differentiation into myofibroblasts, suggesting a possible role for the agent in the pathophysiology of NSF [38]. Photophoresis has been advocated for the treatment of fibrosis [39].

References

1 Lieberman P, Siegle RL, Treadwell G. Radiocontrast reactions. *Clin Rev Allergy* 1986; **4**: 229–45.
2 Grammer LC, Patterson R. Adverse reactions to radiographic contrast material. *Clin Dermatol* 1986; **4**: 149–54.
3 Katayama H, Tanaka T. Clinical survey of adverse reactions to contrast media. *Invest Radiol* 1988; **23** (Suppl.): S88–S89.
4 Kanny G, Maria Y, Mentre B, Moneret-Vautrin DA. Case report: recurrent anaphylactic shock to radiographic contrast media. Evidence supporting an exceptional IgE-mediated reaction. *Allerg Immunol* 1993; **25**: 425–30.
5 Arroyave CM, Bhatt KN, Crown NR. Activation of the alternative pathway of the complement system by radiocontrast media. *J Immunol* 1976; **117**: 1866–9.
6 Rice MC, Lieberman P, Siegle RL, Mason J. *In vitro* histamine release induced by radiocontrast media and various chemical analogs in reactor and control subjects. *J Allergy Clin Immunol* 1983; **72**: 180–6.
7 Enright T, Chua-Lim A, Duda E, Lim DT. The role of a documented allergic profile as a risk factor for radiographic contrast media reaction. *Ann Allergy* 1989; **62**: 302–5.
8 Porri F, Vervloet D. Les reactions aux produits de contraste iodes. *Allerg Immunol* 1994; **26**: 374–6.
9 Schrott KM, Behrends B, Clauss W *et al.* Iohexol in excretory urography: results of the drug monitoring programs. *Fortschr Med* 1986; **104**: 153–6.
10 Kuwatsuru R, Katayama H, Tomita T *et al.* Adverse reactions to low osmolar iodine contrast media (second report) (in Japanese). *Nippon Acta Radiologica* 1992; **52**: 1233–46.
11 Weese DL, Greenberg HM, Zimmern PE. Contrast media reactions during voiding cystourethrography or retrograde pyelography. *Urology* 1993; **41**: 81–4.
12 Guéant-Rodriguez RM, Romano A, Barbaud A *et al*. Hypersensitivity reactions to iodinated contrast media. *Curr Pharm Des* 2006; **12**: 3359–72.
13 Wendt-Nordahl G, Rotert H, Trojan L *et al*. Intravenous contrast media in uroradiology: evaluation of safety and tolerability in almost 50,000 patients. *Med Princ Pract* 2006; **15**: 358–61.
14 Vogl TJ, Honold E, Wolf M *et al*. Safety of iobitridol in the general population and at-risk patients. *Eur Radiol* 2006; **16**: 1288–97.
15 Goss JE, Chambers CE, Heupler FA Jr. Systemic anaphylactoid reactions to iodinated contrast media during cardiac catheterization procedures: guidelines for prevention, diagnosis, and treatment. Laboratory Performance Standards Committee of the Society for Cardiac Angiography and Interventions. *Cathet Cardiovasc Diagn* 1995; **34**: 99–105.
16 Tramèr MR, von Elm E, Loubeyre P, Hauser C. Pharmacological prevention of serious anaphylactic reactions due to iodinated contrast media: systematic review. *BMJ* 2006; **333**: 675.
17 Andrew E, Haider T. Incidence of roentgen contrast medium reactions after intravenous injection in pre-registration trials and post-marketing surveillances. *Acta Radiol* 1993; **34**: 210–3.
18 Cashman JD, McCredie J, Henry DA. Intravenous contrast media: use and associated mortality. *Med J Aust* 1991; **155**: 618–23.
19 Powe NR, Moore RD, Steinberg EP. Adverse reactions to contrast media: factors that determine the cost of treatment. *Am J Roentgenol* 1993; **161**: 1089–95.
20 Dillman JR, Ellis JH, Cohan RH *et al*. Allergic-like breakthrough reactions to gadolinium contrast agents after corticosteroid and antihistamine premedication. *Am J Roentgenol* 2008; **190**: 187–90.
21 Kanzaki T, Sakagami H. Late phase allergic reaction to a CT contrast medium (iotrolan). *J Dermatol* 1991; **18**: 528–31.
22 Christiansen C, Pichler WJ, Skotland T. Delayed allergy-like reactions to X-ray contrast media: mechanistic considerations. *Eur Radiol* 2000; **10**: 1965–75.
23 Kanny G, Pichler W, Morisset M *et al*. T cell-mediated reactions to iodinated contrast media: evaluation by skin and lymphocyte activation tests. *J Allergy Clin Immunol* 2005; **115**: 179–85.
24 Torres MJ, Mayorga C, Cornejo-Garcia JA *et al*. Monitoring non-immediate allergic reactions to iodine contrast media. *Clin Exp Immunol* 2008; **152**: 233–8.
25 Yamauchi R, Morita A, Tsuji T. Fixed drug eruption caused by iopamidol, a contrast medium. *J Dermatol* 1997; **24**: 243–5.

26 Watanabe H, Sueki H, Nakada T *et al*. Multiple fixed drug eruption caused by iomeprol (Iomeron), a nonionic contrast medium. *Dermatology* 1999; **198**: 291–4.
27 Rinker MH, Sangueza OP, Davis LS. Reticulated purpura occurring with contrast medium after hysterosalpingography. *Br J Dermatol* 1998; **138**: 919–20.
28 Grunwald MH, Halevy S, Livni E, Feuerman EJ. Bullous lichen planus after intravenous pyelography. *J Am Acad Dermatol* 1985; **13**: 512–3.
29 Chang MW, Miner JE, Moiin A, Hashimoto K. Iododerma after computed tomographic scan with intravenous radiopaque contrast media. *J Am Acad Dermatol* 1997; **36**: 1014–6.
30 Kerdel FA, Fraker DL, Haynes HA. Necrotizing vasculitis from radiographic contrast media. *J Am Acad Dermatol* 1984; **10**: 25–9.
31 Evans AV, Parker JC, Russell-Jones R. Erythrodermic psoriasis precipitated by radiologic contrast media. *J Am Acad Dermatol* 2002; **46**: 960–1.
32 Kaftori JK, Abraham Z, Gilhar A. Toxic epidermal necrolysis after excretory pyelography. Immunologic-mediated contrast medium reaction? *Int J Dermatol* 1988; **27**: 346–7.
33 Khurana A, Runge VM, Narayanan M *et al*. Nephrogenic systemic fibrosis: a review of 6 cases temporally related to gadodiamide injection (omniscan). *Invest Radiol* 2007; **42**: 139–45.
34 Solomon GJ, Wu E, Rosen PP. Nephrogenic systemic fibrosis mimicking inflammatory breast carcinoma. *Arch Pathol Lab Med* 2007; **131**: 145–8.
35 Edward M, Fitzgerald L, Thind C *et al*. Cutaneous mucinosis associated with dermatomyositis and nephrogenic fibrosing dermopathy: fibroblast hyaluronan synthesis and the effect of patient serum. *Br J Dermatol* 2007; **156**: 473–9.
36 Wiginton CD, Kelly B, Oto A *et al*. Gadolinium-based contrast exposure, nephrogenic systemic fibrosis, and gadolinium detection in tissue. *Am J Roentgenol* 2008; **190**: 1060–8.
37 Edward M, Quinn JA, Mukherjee S *et al*. Gadodiamide contrast agent 'activates' fibroblasts: a possible cause of nephrogenic systemic fibrosis. *J Pathol* 2008; **214**: 584–93.
38 Abraham JL, Thakral C, Skov L *et al*. Dermal inorganic gadolinium concentrations: evidence for *in vivo* transmetallation and long-term persistence in nephrogenic systemic fibrosis. *Br J Dermatol* 2008; **158**: 273–80.
39 Richmond H, Zwerner J, Kim Y, Fiorentino D. Nephrogenic systemic fibrosis. Relationship to gadolinium and response to photophoresis. *Arch Dermatol* 2007; **143**: 1025–30.

Radiopharmaceuticals

The reported incidence of reactions to agents used in nuclear medicine is low; these usually take the form of immediate urticaria or angio-oedema [1–3]. Urticarial or anaphylactic reactions to technetium (^{99m}Tc) sulphur colloid and ^{99m}Tc human albumin microspheres together accounted for 50% of reported reactions [2]. The bone-scanning agent ^{99m}Tc methylene diphosphonate produces a delayed-onset erythematous pruritic eruption within 4–24 h [4].

References

1 Rhodes BA, Cordova MA. Adverse reactions to radio-pharmaceuticals: incidence in 1978, and associated symptoms. *J Nucl Med* 1980; **2**: 1107.
2 Cordova MA, Hladik WB III, Rhodes BA. Validation and characterization of adverse reactions to radiopharmaceuticals. *Noninvasive Med Imaging* 1984; **1**: 17–24.
3 Keeling D, Sampson CB. Adverse reactions to radiopharmaceuticals: incidence, reporting, symptoms, treatment. *Nuklearmedizin* 1986; **23** (Suppl.): 478–82.
4 Collins MRL, James WD, Rodman OG. Adverse cutaneous reaction to technetium Tc 99m methylene diphosphonate. *Arch Dermatol* 1988; **124**: 180–1.

Halides

Bromides

Bromides have a long half-life and are excreted slowly by the kidney; bromism may develop in patients with impaired renal function, and eruptions may not develop until as much as 2 months after the drug has been discontinued. Acneiform and vegetating lesions occur more often, and bullae less frequently, than with iodism [1,2]. Vegetating bromoderma presents as single or multiple papillomatous nodules or plaques, studded with small pustules, on the face or limbs. Bromoderma tuberosum has been caused by anticonvulsive treatment with potassium bromide [3]. Bromism is also characterized by weakness, restlessness, headache, ataxia and personality changes [2].

Iodides

Serious and even fatal reactions of anaphylactic type have been caused by radiographic contrast media containing organic iodine [4]. Iodism, nasal congestion and conjunctivitis, often accompanied by an exanthematic eruption, may be associated with a wide variety of systemic symptoms [5,6]. Prolonged administration of small doses of iodide, as in many cough mixtures, may provoke eruptions with or without mucosal or systemic symptoms. Lesions may first develop some days after the drug is discontinued. The following may occur: urticaria, an acneiform rash, papulopustular lesions, nodules, anthracoid or carbuncular lesions, or clear or haemorrhagic bullae on the face, forearms, neck and flexures or on the buccal mucosa [6]. If the iodine is continued, the bullae may be replaced by vegetating masses, which simulate pemphigus vegetans or a granulomatous infection [7]. Iododerma has developed after administration of oral [8] and intravenous [9,10] radiographic contrast media, and during thyroid protection treatment [11]. Iododerma seems more frequent in patients with renal failure, and may be accompanied by leukocytoclastic vasculitis [2]. The eruption recurs within days of readministration in a sensitized individual [12]. Cell-mediated [5] and 'hyperinflammatory' [13] mechanisms have been postulated. Vegetating iododerma may be an idiosyncratic response that is commoner in patients with polyarteritis nodosa or paraproteinaemia [14]. Fixed eruptions occur rarely [15]. Generalized pustular psoriasis has been reportedly provoked by potassium iodide [16].

Histology of bromoderma and iododerma

In bromoderma, verrucous pseudoepitheliomatous hyperplasia is associated with abscesses containing neutrophils and eosinophils in the epidermis, and with a dense dermal infiltrate initially consisting mainly of neutrophils and eosinophils and later containing many lymphocytes, plasma cells and histiocytes. The abundant dilated blood vessels may show endothelial proliferation. In iododermas, ulceration is more marked, but there is usually less epithelial hyperplasia. Both conditions must be differentiated from blastomycosis and coccidioidomycosis, and from pemphigus vegetans [17].

References

1 Blasik LG, Spencer SK. Fluoroderma. *Arch Dermatol* 1979; **115**: 1334–5.
2 Carney MWP. Five cases of bromism. *Lancet* 1971; **ii**: 523–4.
3 Pfeifle J, Grieben U, Bork K. Bromoderma tuberosum durch antikonvulsive Behandlung mit Kaliumbromid. *Hautarzt* 1992; **43**: 792–4.
4 Vaillant L, Pengloan J, Blanchier D *et al*. Iododerma and acute respiratory distress with leucocytoclastic vasculitis following the intravenous injection of contrast medium. *Clin Exp Dermatol* 1990; **15**: 232–3.
5 Kincaid MC, Green WR, Hoover RE, Farmer ER. Iododerma of the conjunctiva and skin. *Ophthalmology* 1981; **88**: 1216–20.
6 O'Brien TJ. Iodic eruptions. *Australas J Dermatol* 1987; **28**: 119–22.
7 Rosenberg FR, Einbinder J, Walzer RA, Nelson CT. Vegetating iododerma. An immunologic mechanism. *Arch Dermatol* 1972; **105**: 900–5.

8 Boudoulas O, Siegle RJ, Grinwood RE. Iododerma occurring after orally administered iopanoic acid. *Arch Dermatol* 1987; **123**: 387–8.
9 Heydenreich G, Larsen PO. Iododerma after high dose urography in an oliguric patient. *Br J Dermatol* 1977; **97**: 567–9.
10 Lauret P, Godin M, Bravard P. Vegetating iodides after an intravenous pyelogram. *Dermatologica* 1985; **71**: 463–8.
11 Wilkin JK, Strobel D. Iododerma during thyroid protection treatment. *Cutis* 1985; **36**: 335–7.
12 Jones LE, Pariser H, Murray PF. Recurrent iododerma. *Arch Dermatol* 1958; **28**: 353–8.
13 Stone OJ. Proliferative iododerma: a possible mechanism. *Int J Dermatol* 1985; **24**: 565–6.
14 Soria C, Allegue F, España A *et al.* Vegetating iododerma with underlying systemic diseases: report of three cases. *J Am Acad Dermatol* 1990; **22**: 418–22.
15 Baker H. Fixed drug eruption due to iodide and antipyrine. *Br J Dermatol* 1962; **74**: 310–6.
16 Shelley WB. Generalized pustular psoriasis induced by potassium iodide. *JAMA* 1967; **201**: 1009–14.
17 Elder D, Elenitsas R, Jaworsky C, Johnson B Jr, *et al.* eds. *Lever's Histopathology of the Skin*, 10th edn. Philadelphia: Lippincott, 2009.

Agents used in general anaesthesia

Neuromuscular blocking agents, skeletal muscle relaxants and general anaesthetics

The incidence of life-threatening anaphylactic or anaphylactoid reactions during anaesthesia has been variously reported to occur in 1 in 1000 to 1 in 20 000, and minor reactions probably occur in more than 1% of cases; neuromuscular blocking agents are the triggering agents in 50–69% of these reactions, with latex being less frequently incriminated (about 12%) [1–10]. The mortality rate in anaphylactic reactions to drugs used in general anaesthesia is between 4 and 6% [8]. Reactions were most likely with suxamethonium and gallamine, then D-tubocurarine and alcuronium, and least likely with pancuronium and vecuronium [3,6,9]; in another study, succinylcholine and rocuronium were most frequently incriminated [10]. Mucocutaneous manifestations including erythema, urticaria and angio-oedema are reported in up to 80% of reactions, but may only be recognized after the acute phase has passed. Reactions are more frequent in women and in atopic patients. Proposed mechanisms for anaphylactic reactions include type I (IgE antibody-mediated) hypersensitivity [9,11–13], with antibodies persisting for up to 29 years [12], and direct histamine release. Only one reaction in three is likely to be IgE-mediated (type I) anaphylaxis, but non-immune reactions are no less hazardous than type I reactions [9]. Cross-reactivity is widespread with most of the drugs but is least with pancuronium. It has been suggested that pancuronium should be used where muscle relaxation during anaesthesia is essential but sensitivity to another relaxant exists [3], although others have questioned the safety of this procedure [7]. IgE-dependent sensitivity to thiopental may result in anaphylactic reactions [5].

References

1 Fisher MMcD. Intradermal testing in the diagnosis of acute anaphylaxis during anaesthesia: results of five years experience. *Anaesth Intensive Care* 1979; **7**: 58–61.
2 Fisher MMcD. The diagnosis of acute anaphylactoid reactions to neuromuscular blocking agents: a commonly undiagnosed condition. *Anaesth Intensive Care* 1981; **9**: 235–41.
3 Galletly DC, Treuren BC. Anaphylactoid reactions during anaesthesia. Seven years' experience of intradermal testing. *Anaesthesia* 1985; **40**: 329–33.
4 Leynadier F, Sansarricq M, Didier JM, Dry J. Prick tests in the diagnosis of anaphylaxis to general anaesthetics. *Br J Anaesth* 1987; **59**: 683–9.
5 Cheema AL, Sussman GL, Jancelewicz Z *et al.* Update: pentothal-induced anaphylaxis. *J Allergy Clin Immunol* 1988; **81**: 220.
6 Fisher MM, Baldo BA. The incidence and clinical features of anaphylactic reactions during anesthesia in Australia. *Ann Fr Anesth Reanim* 1993; **12**: 97–104.
7 Moneret-Vautrin DA, Laxenaire MC. Anaphylaxis to muscle relaxants: predictive tests. *Anaesthesia* 1990; **45**: 246–7.
8 Moscicki RA, Sockin SM, Corsello BF *et al.* Anaphylaxis during induction of general anesthesia: subsequent evaluation and management. *J Allergy Clin Immunol* 1990; **86**: 325–32.
9 Watkins J. Adverse reaction to neuromuscular blockers: frequency, investigation, and epidemiology. *Acta Anaesthesiol Scand* 1994; **102** (Suppl.): 6–10.
10 Laxenaire MC, Mertes PM, Groupe d'Etudes des Reactions Anaphylactoides Peranesthesiques. Anaphylaxis during anaesthesia. Results of a two-year survey in France. *Br J Anaesth* 2001; **87**: 549–58.
11 Baldo BA, Fisher MM. Mechanisms in IgE-dependent anaphylaxis to anesthetic drugs. *Ann Fr Anesth Reanim* 1993; **12**: 131–40.
12 Fisher MM, Baldo BA. Persistence of allergy to anaesthetic drugs. *Anaesth Intensive Care* 1992; **20**: 143–6.
13 Assem ES. Anaphylactoid reactions to neuromuscular blockers: major role of IgE antibodies and possible contribution of IgE-independent mechanisms. *Monogr Allergy* 1992; **30**: 24–53.

Local anaesthetic agents

Local anaesthetics may cause both immediate anaphylactic reactions and contact dermatitis [1–10]. In a large series of 236 patients with suspected allergy to local anaesthetics, allergic reactions were not reproduced during prick and intradermal skin testing or challenge with preparations that contained preservatives or preservatives with adrenaline [11]. True allergic reactions caused by local anaesthetics are extremely rare [9,12]; more often, the allergic response is caused by a metabolite, preservative or unrelated substance. Acute anaphylactic reactions are uncommon, but are probably less likely to occur when amide linkage agents are used [4,5]. Necrosis of the fingertip has followed local injection for nail extraction [13]. Dizziness and confusion due to systemic absorption followed repeated application of topical lidocaine (lignocaine) [14]. Severe lidocaine intoxication with progressive neurological and psychiatric abnormalities and cardiorespiratory arrest occurred following topical application to painful ulcerated areas in a patient with cutaneous T-cell lymphoma [15].

Amethocaine (tetracaine). Tetracaine in the form of a self-adhesive patch caused slight or moderate erythema at the site of application in 26% of patients, and slight oedema in 5% [16].

Bupivacaine (Marcain). A delayed hypersensitivity rash may occur after injection of arthroscopy portals with bupivacaine [17].

Prilocaine/lidocaine (EMLA). A eutectic mixture of prilocaine and lidocaine in a cream base (EMLA cream) has been associated with methaemoglobinaemia [18–20]; two metabolites of prilocaine, namely 4-hydroxy-2-methylaniline and 2-methylaniline (*o*-toluidine), have been incriminated. A 3-month-old infant became cyanosed after application of 5 g, but concomitant sulphonamide therapy may have made a contribution [18]. Small but significant increases in methaemoglobin levels have been reported in children aged 1–6 years following routine administration of 5 g before surgery, and these may persist for at least 24 h [19], so it is recommended that the minimum effective dose be used in children requiring daily application. Blanching following application of EMLA cream is common [21]. Hyperpigmentation is recorded

[22]. Contact dermatitis can arise to both lidocaine and prilocaine [23–25].

References

1 Schatz M. Skin testing and incremental challenge in the evaluation of adverse reactions of local anesthetics. *J Allergy Clin Immunol* 1984; **74**: 606–16.
2 Fisher MMcD, Graham R. Adverse responses to local anaesthetics. *Anaesth Intensive Care* 1984; **12**: 325–7.
3 Ruzicka T, Gerstmeier M, Przybilla B, Ring J. Allergy to local anesthetics: comparison of patch test with prick and intradermal test results. *J Am Acad Dermatol* 1987; **16**: 1202–8.
4 Christie JL. Fatal consequences of local anesthesia: report of five cases and a review of the literature. *J Forensic Sci* 1975; **21**: 671–9.
5 Haugen RN, Brown CW. Case reports: type I hypersensitivity to lidocaine. *J Drugs Dermatol* 2007; **6**: 1222–3.
6 Glinert RJ, Zachary CB. Local anesthetic allergy. Its recognition and avoidance. *J Dermatol Surg Oncol* 1991; **17**: 491–6.
7 Grognard C. Complications des anesthesiques locaux. *Ann Dermatol Vénéréol* 1993; **120**: 172–4.
8 Skidmore RA, Patterson JD, Tomsick RS. Local anesthetics. *Dermatol Surg* 1996; **22**: 511–22.
9 Gall H, Kaufmann R, Kalveram CM. Adverse reactions to local anesthetics: analysis of 197 cases. *J Allergy Clin Immunol* 1996; **97**: 933–7.
10 Kajimoto Y, Rosenberg ME, Kytta J *et al.* Anaphylactoid skin reactions after intravenous regional anaesthesia using 0.5% prilocaine with or without preservative: a double-blind study. *Acta Anaesthesiol Scand* 1995; **39**: 782–4.
11 Berkun Y, Ben-Zvi A, Levy Y *et al*. Evaluation of adverse reactions to local anesthetics: experience with 236 patients. *Ann Allergy Asthma Immunol* 2003; **91**: 342–5.
12 Jackson D, Chen AH, Bennett CR. Identifying true lidocaine allergy. *J Am Dent Assoc* 1994; **125**: 1362–6.
13 Roser-Maass E. Nekrosen an Fingerendgliedern nach Lokalanästhesie bei Nagelextraktion. *Hautarzt* 1981; **32**: 39–41.
14 Goodwin DP, McMeekin TO. A case of lidocaine absorption from topical administration of 40% lidocaine cream. *J Am Acad Dermatol* 1999; **41**: 280–1.
15 Lie RL, Vermeer BJ, Edelbroek PM. Severe lidocaine intoxication by cutaneous absorption. *J Am Acad Dermatol* 1990; **23**: 1026–8.
16 Doyle E, Freeman J, Im NT, Morton NS. An evaluation of a new selfadhesive patch preparation of amethocaine for topical anaesthesia prior to venous cannulation in children. *Anaesthesia* 1993; **48**: 1050–2.
17 Magsamen BF. Delayed hypersensitivity rash to the knee after injection of arthroscopy portals with bupivacaine (Marcain). *Arthroscopy* 1995; **11**: 512–3.
18 Jakobson B, Nilsson A. Methaemoglobinaemia associated with a prilocaine–lidocaine cream and trimethoprim–sulphamethoxazole. A case report. *Acta Anaesthesiol Scand* 1985; **29**: 453–5.
19 Frayling IM, Addison GM, Chattergee K, Meakin G. Methaemoglobinaemia in children treated with prilocaine–lignocaine cream. *BMJ* 1990; **301**: 153–4.
20 Nilsson A, Engberg G, Henneberg S *et al.* Inverse relationship between age-dependent erythrocyte activity of methaemoglobin reductase and prilocaine-induced methaemoglobinaemia during infancy. *Br J Anaesth* 1990; **64**: 72–6.
21 Villada G, Zetlaoui J, Revuz J. Local blanching after epicutaneous application of EMLA cream. *Dermatologica* 1990; **181**: 38–40.
22 Godwin Y, Brotherston M. Hyperpigmentation following the use of EMLA cream. *Br J Plast Surg* 2001; **54**: 82–3.
23 Duggan M, Burns D, Henry M, Mitchell T. Reaction to topical lignocaine in a patient with contact dermatitis. *Contact Dermatitis* 1993; **28**: 190–1.
24 van den Hove J, Decroix J, Tennstedt D, Lachapelle JM. Allergic contact dermatitis from prilocaine, one of the local anaesthetics in EMLA cream. *Contact Dermatitis* 1994; **30**: 239.
25 Thakur BK, Murali MR. EMLA cream-induced allergic contact dermatitis: a role for prilocaine as an immunogen. *J Allergy Clin Immunol* 1995; **95**: 776–8.

Infusions and injections

Intravenous infusion

Pain, oedema, induration and thrombophlebitis are well-recognized complications [1–4]. Localized bullous eruptions following infusion of commonly used non-vesicant fluids, such as saline, have been described [5]. Extravasation was reported to occur in 11% of 16 380 administrations to children monitored over a 6-month period [6]. Skin necrosis following intravenous infusion of chemotherapeutic agents occurs in up to 6% of patients [1,3,5–9].

References

1 Barton A. Adverse reactions to intravenous catheters and other devices. *Lancet* 1993; **342**: 683.
2 Dufresne RG. Skin necrosis from intravenously infused materials. *Cutis* 1987; **39**: 197–8.
3 MacCara E. Extravasation: a hazard of intravenous therapy. *Drug Intel Clin Phar* 1987; **17**: 713–7.
4 Rudolph R, Larson DL. Etiology and treatment of chemotherapeutic agent extravasation injuries. A review. *J Clin Oncol* 1987; **5**: 1116–26.
5 Robijns BJL, de Wit WM, Bosma NJ, van Vloten WA. Localized bullous eruptions caused by extravasation of commonly used intravenous infusion fluids. *Dermatologica* 1991; **182**: 39–42.
6 Brown AS, Hoelzer DJ, Piercy SA. Skin necrosis from extravasation of intravenous fluids in children. *Plast Reconstr Surg* 1979; **64**: 145–50.
7 Ignoffo RJ, Friedman MA. Therapy of local toxicities caused by extravasation of cancer chemotherapeutic drugs. *Cancer Treat Rev* 1980; **7**: 17–27.
8 Harwood KV, Aisner J. Treatment of chemotherapeutic extravasation: current status. *Cancer Treat Rep* 1984; **68**: 939–45.
9 Banerjee A, Brotherston TM, Lamberty BGH *et al*. Cancer chemotherapy agent-induced perivenous extravasation injury. *J Postgrad Med* 1987; **63**: 5–9.

Blood transfusion

Urticaria occurs in about 1% of transfusions [1], and may be the result of allergy to soluble proteins in donor plasma. Post-transfusion purpura may rarely occur as a result of profound thrombocytopenia about 1 week after transfusion, and is associated with antiplatelet alloantibodies. Other potential side effects include transmission of infectious diseases, including syphilis, hepatitis B and HIV-related syndromes (AIDS).

Graft-versus-host disease may develop following transfusion of unirradiated blood in immunosuppressed patients [2–8], including those with malignancies [2], and infants with severe congenital immunodeficiency [3]. Isolated reports of fatal transfusion-associated graft-versus-host disease in presumed immunocompetent hosts receiving fresh unirradiated blood have been reported [9–11]. This paradoxical situation may be partly explained by situations in which recipients heterozygous for a given MHC haplotype receive a transfusion from a donor homozygous for this haplotype, as the recipient would not react to the donor haplotype but the donor lymphocytes would react to the non-identical recipient haplotype [8]. Thus, some recipients of non-irradiated blood from their offspring may be at risk of developing graft-versus-host disease. An acute fatal illness, characterized by fever, diffuse erythematous rash and progressive leukopenia, has been described in Japanese patients 10 days after surgical operation and has been termed 'postoperative erythroderma' [12]. Histologically, scattered single cell epidermal cell eosinophilic necrosis, satellite cell necrosis, basal cell liquefaction degeneration and a scanty dermal infiltrate may be seen; the reaction is compatible with an acute graft-versus-host reaction following blood transfusion [12].

References

1 Shulman IA. Adverse reactions to blood transfusion. *Texas Med* 1990; **85**: 35–42.

2 Decoste SD, Boudreaux C, Dover JS. Transfusion-associated graft-vs-host disease in patients with malignancies. Report of two cases and review of the literature. *Arch Dermatol* 1990; **126**: 1324–9.
3 Hathaway WE, Githens JH, Blackburn WR *et al.* Aplastic anemia, histiocytosis and erythrodermia in immunologically deficient children. *N Engl J Med* 1965; **273**: 953–8.
4 Brubaker DB. Human posttransfusion graft-versus-host disease. *Vox Sang* 1983; **45**: 401–20.
5 Leitman SF, Holland PV. Irradiation of blood products: indications and guidelines. *Transfusion* 1985; **25**: 292–300.
6 Anderson KC, Weinstein HJ. Transfusion-associated graft-versus-host disease. *N Engl J Med* 1990; **323**: 315–21.
7 Ray TL. Blood transfusions and graft-vs-host disease. *Arch Dermatol* 1990; **126**: 1347–50.
8 Ferrara JLM, Deeg HJ. Graft-versus-host disease. *N Engl J Med* 1991; **324**: 667–74.
9 Arsura EL, Bertelle A, Minkowitz S *et al.* Transfusion-associated graft-vs-host disease in a presumed immunocompetent patient. *Arch Intern Med* 1988; **148**: 1941–4.
10 Capond SM, DePond WD, Tyan DB *et al.* Transfusion-associated graft-versus-host disease in an immunocompetent patient. *Ann Intern Med* 1991; **114**: 1025–6.
11 Juji T, Takahashi K, Shibata Y *et al.* Post-transfusion graft-versus-host disease in immunocompetent patients after cardiac surgery in Japan. *N Engl J Med* 1989; **321**: 56.
12 Hidano A, Yamashita N, Mizuguchi M, Toyoda H. Clinical, histological, and immunohistological studies of postoperative erythroderma. *J Dermatol* 1989; **16**: 20–30.

Hydroxyethyl starch

Hydroxyethyl starch (hetastarch) is used as a plasma expander for hypovolaemia, to prime cardiopulmonary bypass machines, as a sedimenting agent to increase the yield of granulocytes during leukapheresis and to improve microcirculation as in the treatment of sudden deafness. It has been implicated in the development of lichen planus [1], and severe generalized pruritus in up to 32% of recipients, beginning 2 weeks after exposure and taking up to 2 years to settle [2–6].

References

1 Bode U, Deisseroth AB. Donor toxicity in granulocyte collections: association of lichen planus with the use of hydroxyethyl starch leukapheresis. *Transfusion* 1981; **21**: 83–5.
2 Parker NE, Porter JB, Williams HJM, Leftley N. Pruritus after administration of hetastarch. *BMJ* 1982; **284**: 385–6.
3 Gall H, Kaufmann R, von Ehr M *et al.* Persistierender Pruritus nach Hydroxyathylstarke-Infusionen. Retrospektive Langzeitstudie an 266 Fallen. *Hautarzt* 1993; **44**: 713–6.
4 Cox NH, Popple AW. Persistent erythema and pruritus, with a confluent histiocytic skin infiltrate, following the use of a hydroxyethylstarch plasma expander. *Br J Dermatol* 1996; **134**: 353–7.
5 Speight EL, MacSween RM, Stevens A. Persistent itching due to etherified starch plasma expander. *BMJ* 1997; **314**: 1466–7.
6 Murphy M, Carmichael AJ, Lawler PG *et al.* The incidence of hydroxyethyl starch-associated pruritus. *Br J Dermatol* 2001; **144**: 973–6.

Fluorescein

A psoriasiform eruption followed parenteral administration for fluorescein angiography [1].

Reference

1 Mayama M, Hirayama K, Nakano H *et al.* Psoriasiform drug eruption induced by fluorescein sodium used for fluorescein angiography. *Br J Dermatol* 1999; **140**: 982–4.

Renal dialysis

Dermatological complications of renal dialysis have been reviewed [1,2]. These include marked premature ageing, hyperpigmentation, xeroderma, decreased sebaceous and sweat gland secretion, Raynaud's syndrome, generalized pruritus and carpal tunnel syndrome due to amyloid β deposition [1]. Extravasation, phlebitis and bacterial infection of the cannula, with resulting septicaemia, may occur and are related to the site of insertion of the cannula into the arteriovenous fistula. A bullous dermatosis of haemodialysis has been described [2,3]. This resembles porphyria clinically and histologically, and porphyrins may be elevated [3], although cases with pseudoporphyria in which there are no abnormalities of porphyrin metabolism have also been documented [2]. Two-thirds of patients with dialysis-associated anaphylaxis have IgE antibodies to ethylene oxide/human serum albumin [4]. Allergic contact dermatitis due to rubber chemicals in the haemodialysis equipment may be seen around the arteriovenous shunt [5]. Porokeratosis localized to the access region for haemodialysis has also been reported [6].

References

1 Altmeyer P, Kachel H-G, Jünger M *et al.* Hautveränderungen bei Langzeitdialysepatienten. *Hautarzt* 1982; **33**: 303–9.
2 Gupta AK, Gupta MA, Cardella CJ, Haberman HF. Cutaneous complications of chronic renal failure and dialysis. *Int J Dermatol* 1986; **25**: 498–504.
3 Poh-Fitzpatrick MB, Bellet N, DeLeo VA *et al.* Porphyria cutanea tarda in two patients treated with hemodialysis for chronic renal failure. *N Engl J Med* 1978; **299**: 292–4.
4 Grammer LC, Roberts M, Wiggins CA *et al.* A comparison of cutaneous testing and ELISA testing for assessing reactivity to ethylene oxide–human serum albumin in hemodialysis patients with anaphylactic reactions. *J Allergy Clin Immunol* 1991; **87**: 674–6.
5 Kruis-De Vries M, Coenraads P, Nater J. Allergic contact dermatitis due to rubber chemicals in haemodialysis equipment. *Contact Dermatitis* 1987; **17**: 303–5.
6 Nakazawa A, Matsuo I, Ohkido M. Porokeratosis localized to the access region for hemodialysis. *J Am Acad Dermatol* 1991; **25**: 338–40.

Necrosis from intramuscular injections

Severe painful local necrosis at the site of an injected medicament (embolia cutis medicamentosa; also known as Nicolau's syndrome) may follow intramuscular therapeutic injections and was originally described with bismuth. It occurs particularly with preparations containing corticosteroids, local anaesthetics, antirheumatic drugs and antihistamines; more rarely, chlorpromazine, penicillin, phenobarbital and sulphonamides have been implicated [1,2]. The condition has also followed sclerotherapy [3]. Clinically, stellate erythema and infiltration are followed by central deep necrosis that heals with scarring.

References

1 Bork K. *Cutaneous Side Effects of Drugs*. Philadelphia: Saunders, 1988.
2 Faucher L, Marcoux D. What syndrome is this? Nicolau syndrome. *Pediatr Dermatol* 1995; **12**: 187–90.
3 Geukens J, Rabe E, Bieber T. Embolia cutis medicamentosa of the foot after sclerotherapy. *Eur J Dermatol* 1999; **9**: 132–3.

Glatiramer acetate

This drug administered for the treatment of relapsing-remitting multiple sclerosis caused lobular panniculitis at the site of injection [1].

Polidocanol

The sclerosing solution polidocanol is said to cause allergic reactions in up to 0.06% of cases; systemic allergic reactions may be more common than previously recognized [2].

References

1 Ball NJ, Cowan BJ, Moore GR, Hashimoto SA. Lobular panniculitis at the site of glatiramer acetate injections for the treatment of relapsing-remitting multiple sclerosis. A report of two cases. *J Cutan Pathol* 2008; **35**: 407–10.
2 Feied CF, Jackson JJ, Bren TS *et al.* Allergic reactions to polidocanol for vein sclerosis. Two case reports. *J Dermatol Surg Oncol* 1994; **20**: 466–8.

Soft tissue fillers

Continuing pain, erythema, swelling, nodules, pigmentation and abscess formation have been reported [1]. Cutaneous reactions may occur at sites distant from injected sites, due to secondary migration of the filler substance. A lapse of months to years may occur prior to the development of a cutaneous reaction [2]. Granulomatous reactions to injectable hyaluronic acid gel have been documented [3].

References

1 Zielke H, Wölber L, Wiest L, Rzany B. Risk profiles of different injectable fillers: results from the Injectable Filler Safety Study (IFS Study). *Dermatol Surg* 2008; **34**: 326–35.
2 Dadzie OE, Mahalingam M, Parada M *et al*. Adverse cutaneous reactions to soft tissue fillers—a review of the histological features. *J Cutan Pathol* 2008; **35**: 536–48.
3 Ghislanzoni M, Bianchi F, Barbareschi M, Alessi E. Cutaneous granulomatous reaction to injectable hyaluronic acid gel. *Br J Dermatol* 2006; **154**: 755–8.

Drugs affecting metabolism or gastrointestinal function

Hypoglycaemic drugs

Dermatological aspects of the oral hypoglycaemic drugs have been reviewed [1–4].

Biguanides

Rashes are much less frequent with metformin and phenformin than with sulphonylureas. Transient erythemas, pruritus and urticaria have been noted.

Sulphonylureas

Chlorpropamide and tolbutamide are most often prescribed, and both can give rise to toxic or allergic reactions. Angio-oedema with glibornuride, urticaria with glibenclamide and a bullous dermatitis with carbutamide have been described [5]; there was no cross-reactivity between first- and second-generation sulphonylureas.

Chlorpropamide. Eruptions occur in 2–3% of patients on chlorpropamide [2]. These include maculopapular rashes, photosensitivity [6], erythema annulare, Stevens–Johnson syndrome [7], erythema nodosum [1], lichenoid eruptions [8,9], purpura and exfoliative dermatitis [10]. Porphyria has been provoked [11]. A disulfiram-like effect, with flushing of the face, headache and palpitations after taking alcohol, occurs in up to 30% of patients [12,13]. The fact that the flush is blocked by naloxone suggests that opioids may be involved in the response.

Glibenclamide. Bullae and cholestasis have occurred together [14].

Glipizide. Pigmented purpuric eruption is documented [15].

Glyburide. A generalized lichenoid dermatitis has been reported [16].

References

1 Beurey J, Jeandidier P, Bermont A. Les complications dermatologiques des traitements antidiabétiques. *Ann Dermatol Syphiligr* 1966; **93**: 13–42.
2 Almeyda J, Baker H. Drug reactions. X. Adverse cutaneous reactions to hypoglycaemic agents. *Br J Dermatol* 1970; **82**: 634–6.
3 Harris EL. Adverse reactions to oral antidiabetic agents. *BMJ* 1971; **3**: 29–30.
4 Perez MI, Kohn SR. Cutaneous manifestations of diabetes mellitus. *J Am Acad Dermatol* 1994; **30**: 519–31.
5 Chichmanian RM, Papasseudi G, Hieronimus S *et al.* Allergies aux sulfonylurees hypoglycemiantes. Les reactions croisées existent-elles? *Thérapie* 1991; **46**: 163–7.
6 Hitselberger JF, Fosnaugh RP. Photosensitivity due to chlorpropamide. *JAMA* 1962; **180**: 62–3.
7 Yaffee HS. Stevens–Johnson syndrome caused by chlorpropamide: report of a case. *Arch Dermatol* 1960; **82**: 636–7.
8 Dinsdale RCW, Ormerod TP, Walker AE. Lichenoid eruption due to chlorpropamide. *BMJ* 1968; **i**: 100.
9 Barnett JH, Barnett SM. Lichenoid drug reactions to chlorpropamide and tolazamide. *Cutis* 1984; **34**: 542–4.
10 Rothfeld EL, Goldman J, Goldberg HH, Einhorn S. Severe chlorpropamide toxicity. *JAMA* 1960; **172**: 54–6.
11 Zarowitz H, Newhouse S. Coproporphyrinuria with a cutaneous reaction induced by chlorpropamide. *NY State J Med* 1965; **65**: 2385–7.
12 Stakosch CR, Jefferys DB, Keen H. Blockade of chlorpropamide alcohol flush by aspirin. *Lancet* 1980; **i**: 394–6.
13 Medback S, Wass JAH, Clement-Jones V *et al.* Chlorpropamide alcohol flush and circulating met-enkephalin: a positive link. *BMJ* 1981; **283**: 937–9.
14 Wongpaitoon V, Mills PR, Russell RI, Patrick RS. Intra-hepatic cholestasis and cutaneous bullae associated with glibenclamide therapy. *Postgrad Med J* 1981; **57**: 244–6.
15 Adams BB, Gadenne AS. Glipizide-induced pigmented purpuric dermatosis. *J Am Acad Dermatol* 1999; **41**: 827–9.
16 Fox GN, Harrell CC, Mehregan DR. Extensive lichenoid drug eruption due to glyburide: a case report and review of the literature. *Cutis* 2005; **76**: 41–5.

Lipid-lowering drugs

Acipimox

This nicotinic acid analogue causes less prostaglandin-mediated flushing and itching than nicotinic acid [1].

Clofibrate

Erythema multiforme and a variety of other erythematous rashes have been described [2].

Gemfibrozil

This lipid-lowering drug, which mainly lowers triglycerides, has been associated with exacerbation of psoriasis [3,4].

Statins

The lipid-lowering drugs lovastatin, simvastatin and pravastatin can cause eczema [4,5]; these drugs block an early step in cholesterol biosynthesis by inhibiting the activity of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. Simvastatin has caused a lichenoid eruption with skin and mucosal involvement

[6,7], and chronic actinic dermatitis [8]. Pravastatin has also been associated with a lichenoid rash [9]. Atorvastatin has caused linear IgA bullous dermatosis [10] and TEN [11]. A recent review documented 28 cases of autoimmune disease linked to therapy with statins [12]; systemic lupus erythematosus in 10 cases, subacute cutaneous lupus erythematosus in three cases, dermatomyositis and polymyositis in 14 cases and one case of lichen planus pemphigoides. The mean time of exposure before disease onset was 12.8 ± 18 months; range 1 month–6 years. The majority of cases required systemic immunosuppressive therapy; there were nonetheless two fatalities. Antinuclear antibodies were still positive many months after clinical recovery in some patients.

Triparanol and diazacholesterol

These drugs inhibit a late step in cholesterol biosynthesis (Δ^{24} sterol reductase) and can induce ichthyosis or palmoplantar hyperkeratosis [4].

References

1 Anonymous. Acipimox: a nicotinic acid analogue for hyperlipidaemia. *Drug Ther Bull* 1991; **29**: 57–9.
2 Murata Y, Tani M, Amano M. Erythema multiforme due to clofibrate. *J Am Acad Dermatol* 1988; **18**: 381–2.
3 Fisher DA, Elias PM, LeBoit PL. Exacerbation of psoriasis by the hypolipidemic agent, gemfibrozil. *Arch Dermatol* 1988; **124**: 854–5.
4 Proksch E. Lipidsenker-induzierte Nebenwirkungen an der Haut. *Hautarzt* 1995; **46**: 76–80.
5 Krasovec M, Elsner P, Burg G. Generalized eczematous skin rash possibly due to HMG-CoA reductase inhibitors. *Dermatology* 1993; **186**: 248–52.
6 Feldmann R, Mainetti C, Saurat JH. Skin lesions due to treatment with simvastatin (Zocor). *Dermatology* 1993; **186**: 272.
7 Roger D, Rolle F, Labrousse F *et al*. Simvastatin-induced lichenoid drug eruption. *Clin Exp Dermatol* 1994; **19**: 88–9.
8 Granados MT, de la Torre C, Cruces MJ, Pineiro G. Chronic actinic dermatitis due to simvastatin. *Contact Dermatitis* 1998; **38**: 294–5.
9 Keough GC, Richardson TT, Grabski WJ. Pravastatin-induced lichenoid drug eruption. *Cutis* 1998; **61**: 98–100.
10 Konig C, Eickert A, Scharfetter-Kochanek K *et al.* Linear IgA bullous dermatosis induced by atorvastatin. *J Am Acad Dermatol* 2001; **44**: 689–92.
11 Pfeiffer CM, Kazenoff S, Rothberg HD. Toxic epidermal necrolysis from atorvastatin. *JAMA* 1998; **279**: 1613–4.
12 Noël B. Lupus erythematosus and other autoimmune diseases related to statin therapy: a systematic review. *J Eur Acad Dermatol Venereol* 2007; **21**: 17–24.

Drugs for gastrointestinal ulceration

Proton pump inhibitors

Esomeprazole. DRESS syndrome is recorded [1].

Lansoprazole. Anaphylactic reactions have been documented [2].

Omeprazole. This proton pump inhibitor, a substituted benzimidazole, has gained widespread use in the treatment of gastric and duodenal ulceration and reflux oesophagitis. Adverse events with the drug are rare and involve mainly the gastrointestinal and central nervous systems, with diarrhoea, headache and dizziness, and confusion in the elderly, moderate elevation of aminotransferases and possible leukopenia [1,3,4]. The prevalence of cutaneous reactions to omeprazole is approximately 0.5–1.5% [3–6]. A variety of eruptions are recorded, including angio-oedema and urticaria [6,7], anaphylaxis [8,9], maculopapular rashes, hyperpigmentation mimicking ashy dermatosis [10], lichen planus [11,12], pityriasiform eruption [13], erythema multiforme and erythroderma [14], exfoliative dermatitis [15,16], bullous eruption [17], vasculitis [18] and photosensitivity. Gynaecomastia is recorded [19].

Tripotassium dicitratobismuthate (De-Nol)

The Netherlands Centre for Monitoring of Adverse Reactions to Drugs has received several reports of skin reactions, on average 2 days after starting treatment, including maculopapular exanthema, angio-oedema and erythema [20].

Bismuth subsalicylate (PeptoBismol)

Black granules at follicular orifices have been reported [21]. Blue linear pigmentation of the soft palate, oral mucosa and vagina, ulcerative stomatitis, generalized pigmentation, dermatitis and erythroderma are recorded.

References

1 Caboni S, Gunera-Saad N, Ktiouet-Abassi S *et al*. Esomeprazole-induced DRESS syndrome. Studies of cross-reactivity among proton-pump inhibitor drugs. *Allergy* 2007; **62**: 1342–3.
2 Demirkan K, Bozkurt B, Karakaya G, Kalyoncu AF. Anaphylactic reaction to drugs commonly used for gastrointestinal system diseases: 3 case reports and review of the literature. *J Investig Allergol Clin Immunol* 2006; **16**: 203–9.
3 McTavish D, Buckley MM, Heel RC. Omeprazole: an update review of its pharmacology and therapeutic use in acid related disorders. *Drugs* 1991; **42**: 138–70.
4 Castot A, Bidault I, Dahan R, Efthymiou ML. Bilan des effects inattendus et toxiques de l'omeprazole (Mopral) rapportés aux centres regionaux de pharmacovigilance, au cours des 22 premiers mois de commercialisation. *Thérapie* 1993; **48**: 469–74.
5 Yeomans ND. Omeprazole: short- and long-term safety. *Adverse Drug React Acute Toxicol Rev* 1994; **13**: 145–56.
6 Bowlby HA, Dickens GR. Angioedema and urticaria associated with omeprazole confirmed by drug rechallenge. *Pharmacotherapy* 1994; **14**: 119–22.
7 Haeney MR. Angio-oedema and urticaria associated with omeprazole. *BMJ* 1992; **305**: 870.
8 Ottervanger JP, Phaff RA, Vermeulen EG, Stricker BH. Anaphylaxis to omeprazole. *J Allergy Clin Immunol* 1996; **97**: 1413–4.
9 González P, Soriano V, López P, Niveiro E. Anaphylaxis to proton pump inhibitors. *Allergol Immunopathol (Madr)* 2002; **30**: 342–3.
10 Ramírez-Hernández M, Martínez-Escribano JA, Martínez-Barba E *et al*. Cutaneous hyperpigmentation induced by omeprazole mimicking ashy dermatosis. *J Eur Acad Dermatol Venereol* 2006; **20**: 584–7.
11 Sharma BK, Walt RP, Pounder RE *et al.* Optimal dose of oral omeprazole for maximal 24 hour decrease of intragastric acidity. *Gut* 1984; **25**: 957–64.
12 Bong JL, Lucke TW, Douglas WS. Lichenoid drug eruption with proton pump inhibitors. *BMJ* 2000; **320**: 283.
13 Buckley C. Pityriasis rosea-like eruption in a patient receiving omeprazole. *Br J Dermatol* 1996; **135**: 660–1.
14 Cockayne SE, Glet RJ, Gawkrodger DJ, McDonagh AJ. Severe erythrodermic reactions to the proton pump inhibitors omeprazole and lansoprazole. *Br J Dermatol* 1999; **141**: 173–5.
15 Epelde Gonzalo FD, Boada Montagut L, Thomas Vecina S. Exfoliative dermatitis related to omeprazole. *Ann Pharmacother* 1995; **29**: 82–3.
16 Borrás-Blasco J, Navarro-Ruiz A, Navarro-Blasco F *et al*. Erythrodermia induced by omeprazole. *Int J Clin Pharmacol Ther* 2001; **39**: 219–23.
17 Stenier C, Fiasse R, Bourlond J *et al.* Bullous skin reaction induced by omeprazole. *Br J Dermatol* 1995; **133**: 343–4.
18 Odeh M, Lurie M, Oliven A. Cutaneous leucocytoclastic vasculitis associated with omeprazole. *Postgrad Med J* 2002; **78**: 114–5.
19 Lindquist M, Edwards IR. Endocrine effects of omeprazole. *BMJ* 1992; **305**: 451–2.

20 Ottervanger JP, Stricker BH. Huidafwijkingen door bismutoxide (De-Nol). *Ned Tijdschr Geneeskd* 1994; **138**: 152–3.
21 Ruiz-Maldonado R, Contreras-Ruiz J, Sierra-Santoyo A *et al.* Black granules on the skin after bismuth subsalicylate ingestion. *J Am Acad Dermatol* 1997; **37**: 489–90.

Laxatives

Side effects of laxatives have been reviewed [1].

Dantron (danthron)

A highly characteristic irritant erythema of the buttocks and thighs has been observed in patients who are partially incontinent. The erythema results from skin soiling by faecal matter containing an anthralin (dithranol)-like breakdown product [2].

Phenolphthalein

Fixed eruptions are well known [3–5]. Bullous erythema multiforme and an LE-like reaction are documented.

References

1 Ruoff H-J. Unerwünschte Wirkungen und Wechselwirkungen von Abführmitteln. *Med Klin* 1980; **75**: 214–8.
2 Barth JH, Reshad H, Darley CR, Gibson JRA. A cutaneous complication of Dorbanex therapy. *Clin Exp Dermatol* 1984; **9**: 95–6.
3 Shelley WB, Schlappner OL, Heiss HB. Demonstration of intercellular immunofluorescence and epidermal hysteresis in bullous fixed drug eruption due to phenolphthalein. *Br J Dermatol* 1972; **6**: 118–25.
4 Wyatt E, Greaves M, Sondergaard J. Fixed drug eruption (phenolphthalein). Evidence for a blood-borne mediator. *Arch Dermatol* 1972; **106**: 671–3.
5 Zanolli MD, McAlvany J, Krowchuk DP. Phenolphthalein-induced fixed drug eruption: a cutaneous complication of laxative use in a child. *Pediatrics* 1993; **91**: 1199–201.

Miscellaneous drugs

Food and drug additives

Dermatological complications of food and drug additives have been reviewed [1–14]. These substances have been implicated in the causation of urticaria [4–7], anaphylaxis, purpura and vasculitis [8–12]. However, one study suggested that common food additives are seldom if ever of significance in urticaria [11]. In another study, only 0.63% of food additive provocation tests resulted in exacerbation in 1110 patients with urticaria; tests were again not positive on re-provocation [13]. The prevalence of adverse reactions to food additives is estimated to be 0.03–0.23% [15]. The necessity for double-blind, placebo-controlled testing to substantiate alleged food additive allergy has been emphasized [16]. Information about excipients ('inert ingredients') has been reported in a study that examined the sweeteners, flavourings, dyes and preservatives present in chewable and liquid preparations of 102 over-the-counter and prescription brands of antidiarrhoeal, cough and cold, antihistamine/decongestant, analgesic/antipyretic and liquid theophylline medications [17]. An average preparation contained two sweeteners, primarily saccharin and sucrose, followed by sorbitol, glucose, fructose and others. The type of flavouring was not specified in 36 of the 102 preparations; cherry was the most common flavouring, followed by vanilla and lemon. Twenty-one different dyes and colouring agents were used; red dye no. 40 was the most common, followed by yellow no. 6. Sodium benzoate and methylparabens were the commonest of eight preservatives used. Mandatory labelling of excipients in all pharmaceutical preparations is the only way that physicians and patients can be fully informed [17]. It is important to appreciate that peanut oil, to which patients may be strongly allergic, is found in certain medications [18]. Caffeine in coffee and cola beverages caused urticaria in a 10-year-old child, confirmed by prick test and oral challenge test with caffeine [19].

References

1 Levantine AJ, Almeyda J. Cutaneous reactions to food and drug additives. *Br J Dermatol* 1977; **91**: 359–62.
2 Simon RA. Adverse reactions to drug additives. *J Allergy Clin Immunol* 1984; **74**: 623–30.
3 Ruzicka T. Diagnostik von Nahrungsmittelallergien. *Hautarzt* 1987; **38**: 10–5.
4 Juhlin LG, Michäelsson G, Zetterström O. Urticaria and asthma induced by food-and-drug additives in patients with aspirin hypersensitivity. *J Allergy* 1972; **50**: 92–8.
5 Doeglas HMG. Reactions to aspirin and food additives in patients with chronic urticaria, including the physical urticarias. *Br J Dermatol* 1975; **93**: 135–44.
6 Supramaniam G, Warner JO. Artificial food additive intolerance in patients with angio-oedema and urticaria. *Lancet* 1986; **ii**: 907–9.
7 Juhlin L. Additives and chronic urticaria. *Ann Allergy* 1987; **59**: 119–23.
8 Michäelsson G, Petterson L, Juhlin L. Purpura caused by food and drug additives. *Arch Dermatol* 1974; **109**: 49–52.
9 Kubba R, Champion RI. Anaphylactoid purpura caused by tartrazine and benzoates. *Br J Dermatol* 1975; **93** (Suppl. 2): 61–2.
10 Eisenmann A, Ring J, von der Helm D *et al.* Vasculitis allergica durch Nahrungsmittelallergie. *Hautarzt* 1988; **39**: 319–21.
11 Veien NK, Krogdahl A. Cutaneous vasculitis induced by food additives. *Acta Derm Venereol (Stockh)* 1991; **71**: 73–4.
12 Lowry MD, Hudson CF, Callen FP. Leukocytoclastic vasculitis caused by drug additives. *J Am Acad Dermatol* 1994; **30**: 854–5.
13 Hernandez Garcia J, Garcia Selles J, Negro Alvarez JM *et al.* Incidencias de reacciones adversas con aditivos. Nuestra experiencia de 10 anos. *Allergol Immunopathol* 1994; **22**: 233–42.
14 Barbaud A. Place of excipients in drug-related allergy. *Clin Rev Allergy Immunol* 1995; **13**: 253–63.
15 Wuthrich B. Adverse reactions to food additives. *Ann Allergy* 1993; **71**: 379–84.
16 Goodman DL, McDonnell JT, Nelson HS *et al.* Chronic urticaria exacerbated by the antioxidant food preservatives, butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT). *J Allergy Clin Immunol* 1990; **86**: 570–5.
17 Kumar A, Rawlings RD, Beaman DC. The mystery ingredients: sweeteners, flavorings, dyes, and preservatives in analgesic/antipyretic, antihistamine/decongestant, cough and cold, antidiarrheal, and liquid theophylline preparations. *Pediatrics* 1993; **91**: 927–33.
18 Weeks R. Peanut oil in medications. *Lancet* 1996; **348**: 759–60.
19 Caballero T, Garcia-Ara C, Pascual C *et al.* Urticaria induced by caffeine. *J Invest Allergol Clin Immunol* 1993; **3**: 160–2.

Colouring agents

Colourings in food and medications (including some antihistamines), such as tartrazine, sunset yellow and other azo dyes, have been reported to cause adverse reactions [1,2], including urticaria [3,4] or vasculitis [5,6].

References

1 Vandelle C, Belegaud D, Bidault I, Castol A. Allergie aux colorants des medicaments. Confrontation des cas publiés et de l'experience du Centre Regional de Pharmacovigilance. *Thérapie* 1993; **48**: 484–5.
2 Gracey-Whitman L, Ell S. Artificial colourings and adverse reactions. *BMJ* 1995; **311**: 1204.
3 Neuman I, Elian R, Nahum H *et al.* The danger of 'yellow dyes' (tartrazine) to allergic subjects. *J Allergy* 1972; **50**: 92–8.

4 Miller K. Sensitivity to tartrazine. *BMJ* 1982; **285**: 1597–8.
5 Lowry MD, Hudson CF, Callen FP. Leukocytoclastic vasculitis caused by drug additives. *J Am Acad Dermatol* 1994; **30**: 854–5.
6 Wuthrich B. Adverse reactions to food additives. *Ann Allergy* 1993; **71**: 379–84.

Flavouring agents

Aspartame. Aspartame, a synthetic dipeptide composed of aspartic acid and the methyl ester of phenylalanine and used under the trade name of NutraSweet (G.D. Searle & Co., Skokie, Illinois, USA) as a low-calorie artificial sweetener, has been associated with relatively few adverse side effects despite its widespread use [1]. Cutaneous side effects reported include urticaria, angio-oedema and other non-descript 'rashes' [2], granulomatous septal panniculitis [3] and lobular panniculitis [4]. However, in a recent study of patients with a history of aspartame sensitivity, it was not possible to identify any subject with a clearly reproducible adverse reaction [5]. Similarly, a multicentre, placebo-controlled, challenge study showed that aspartame and its conversion products are no more likely than placebo to cause urticaria and/or angio-oedema reactions in subjects with a history consistent with hypersensitivity to aspartame [6].

Cyclamates. Cyclamates, used as sweeteners in soft drinks, have caused photosensitivity [7].

Quinine. Quinine in tonic water and other bitter drinks may cause fixed eruptions [8].

References

1 US Food and Drug Administration. Food additives permitted for direct addition to food for human consumption: aspartame. *Federal Register* 1983; **48**: 31376–82.
2 Kulczycki A Jr. Aspartame-induced urticaria. *Ann Intern Med* 1986; **104**: 207–8.
3 Novick NL. Aspartame-induced granulomatous panniculitis. *Ann Intern Med* 1985; **102**: 206–7.
4 McCauliffe DP, Poitras K. Aspartame-induced lobular panniculitis. *J Am Acad Dermatol* 1991; **24**: 298–300.
5 Garriga MM, Berkebile C, Metcalfe DD. A combined single-blind, double-blind, placebo-controlled study to determine the reproducibility of hypersensitivity reactions to aspartame. *J Allergy Clin Immunol* 1991; **87**: 821–7.
6 Geha R, Buckley CE, Greenberger P *et al.* Aspartame is no more likely than placebo to cause urticaria/angioedema: results of a multicenter, randomized, double-blind, placebo-controlled, crossover study. *J Allergy Clin Immunol* 1993; **92**: 513–20.
7 Lambert SI. A new photosensitizer. The artificial sweetener cyclamate. *JAMA* 1967; **201**: 747–50.
8 Commens C. Fixed drug eruption. *Aust J Dermatol* 1983; **24**: 1–8.

Preservatives

The antioxidant food preservatives butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) have been reported to exacerbate chronic urticaria [1]. Sodium benzoate has been associated with urticaria, angio-oedema, asthma and, rarely, anaphylaxis [2]. Parabens used as preservatives may also cause urticaria [3].

Sulphiting agents are commonly used in parenteral emergency drugs, including epinephrine (adrenaline), dexamethasone, dobutamine, dopamine, norepinephrine (noradrenaline), phenylephrine, procainamide and physostigmine [4]. Published anaphylactic or asthmatic reactions have been associated with sulphited local anaesthetics, gentamicin, metoclopramide, doxycycline and vitamin B complex. The reactions have a rapid onset and do not always coincide with a positive oral challenge, although patients with a history of positive oral challenge to 5–10 mg of sulphite may be at increased risk of developing a reaction to parenteral sulphites. Sulphites added as antioxidant preservatives may provoke urticaria, asthma, anaphylaxis and shock [4–10], as well as urticarial vasculitis [11]. Intolerance due to metabisulphite as an antioxidant in a dental anaesthetic has led to angio-oedema; patch tests were positive [12]. Basophil activation induced by sulphites may be IgE dependent [13]. It has been claimed that there is a high specificity of patch testing in the diagnosis of patients with sulphite sensitivity [14].

References

1 Goodman DL, McDonnell JT, Nelson HS *et al.* Chronic urticaria exacerbated by the antioxidant food preservatives, butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT). *J Allergy Clin Immunol* 1990; **86**: 570–5.
2 Michils A, Vandermoten G, Duchateau J, Yernault J-C. Anaphylaxis with sodium benzoate. *Lancet* 1991; **337**: 1424–5.
3 Nagel JE, Fuscaldo JT, Fireman P. Paraben allergy. *JAMA* 1977; **237**: 1594–5.
4 Smolinske SC. Review of parenteral sulfite reactions. *J Toxicol Clin Toxicol* 1992; **30**: 597–606.
5 Habenicht HA, Preuss L, Lovell RG. Sensitivity to ingested metabisulfites: cause of bronchospasm and urticaria. *Immunol Allergy Pract* 1983; **5**: 243–5.
6 Settipane GA. Adverse reactions to sulfites in drugs and foods. *J Am Acad Dermatol* 1984; **10**: 1077–80.
7 Belchi-Hernandez J, Florido-Lopez JF, Estrada-Rodriguez JL *et al.* Sulfite-induced urticaria. *Ann Allergy* 1993; **71**: 230–2.
8 Twarog FJ, Leung DYM. Anaphylaxis to a component of isoetharine (sodium bisulfite). *JAMA* 1982; **248**: 2030–1.
9 Przybilla B, Ring J. Sulfit-Überempfindlichkeit. *Hautarzt* 1987; **38**: 445–8.
10 Hassoun S, Bonneau JC, Drouet M, Sabbah A. Enquete sur pathologies induites par les sulfites en allergologie. *Allerg Immunol* 1994; **26**: 184, 187–8.
11 Wuthrich B. Adverse reactions to food additives. *Ann Allergy* 1993; **71**: 379–84.
12 Dooms-Goosens A, Gidi de Alan A, Degreef H, Kochuyt A. Local anaesthetic intolerance due to metabisulfite. *Contact Dermatitis* 1989; **20**: 124–6.
13 Sainte-Laudy J, Vallon C, Guerin JC. Mise en evidence des IgE specifiques du groupe des sulfites chez les intolerants à ces conservateurs. *Allerg Immunol* 1994; **26**: 132–4, 137–8.
14 Gay G, Sabbah A, Drouet M. Valeur diagnostique de l'epidermotest aux sulfites. *Allerg Immunol* 1994; **26**: 139–40.

Miscellaneous food additives

Agricultural or veterinary chemicals may leave residues in animals and plants used as human food, for example penicillin in milk or meat, with resultant urticaria [1,2]. The exposure of a rural Turkish population to flour contaminated with hexachlorobenzene induced an outbreak of cutaneous porphyria [3]. Contaminated rapeseed cooking oil containing acetanilide resulted in the Spanish 'toxic oil syndrome'; the central feature of the illness was a toxic pneumonitis, but fixed rashes and scleroderma-like changes in survivors were seen [4–6]. Outbreaks of atypical erythema multiforme and other exanthems in the Netherlands were attributed to an additive in margarine [7,8]. The high arsenic content of a rural water supply in Taiwan caused arsenicism [9]. Chemicals added to tobacco, for example menthol in cigarettes, have caused urticaria [10]. *N*-Nitroso compounds, which are known to be carcinogenic in animals, occur in food products and certain alcoholic drinks, but there is no direct proof as yet of a causal role in human disease [11].

References

1 Boonk WJ, Van Ketel WG. The role of penicillin in the pathogenesis of chronic urticaria. *Br J Dermatol* 1982; **106**: 183–90.
2 Kanny G, Puygrenier J, Beaudoin E, Moneret-Vautrin DA. Choc anaphylactique alimentaire: implication des residus de penicilline. *Allerg Immunol* 1994; **26**: 181–3.
3 Peters HA, Gocmen A, Cripps DJ *et al.* Epidemiology of hexachlorobenzene-induced porphyria in Turkey. *Arch Neurol* 1982; **39**: 744–9.
4 Martinez-Tello FJ, Navas-Palacios JJ, Ricoy JR *et al.* Pathology of a new toxic syndrome caused by ingestion of adulterated oil in Spain. *Virchows Arch A* 1982; **397**: 261–85.
5 Anonymous. Toxic oil syndrome. *Lancet* 1983; **i**: 1257–8.
6 Rush PJ, Bell MJ, Fam AG. Toxic oil syndrome (Spanish oil disease) and chemically induced scleroderma-like conditions. *J Rheumatol* 1984; **11**: 262–4.
7 Sternberg TH, Bierman SM. Unique syndromes involving the skin induced by drugs, food additives, and environmental contaminants. *Arch Dermatol* 1963; **88**: 779–88.
8 Mali JW, Malten KE. The epidemic of polymorphic toxic erythema in the Netherlands in 1960. The so-called margarine disease. *Acta Derm Venereol (Stockh)* 1966; **46**: 123–35.
9 Yeh S. Skin cancer in chronic arsenicism. *Hum Pathol* 1973; **4**: 469–85.
10 McGowan EM. Menthol urticaria. *Arch Dermatol* 1966; **94**: 62–3.
11 Tannenbaum SR. N-nitroso compounds: a perspective on human exposure. *Lancet* 1983; **i**: 628–30.

Herbal remedies, homeopathy and naturopathy (alternative therapy)

Adverse cutaneous effects of herbal drugs have been reviewed [1–5]. Virtually all alternative remedies may cause allergic or hypersensitivity reactions; the most frequently involved are tea tree oil, members of the Compositae family, propolis, oils used in aromatherapy, substances responsible for photosensitization and metal-containing compounds [5]. Skin manifestations range from contact dermatitis (the most common) to urticaria–angio-oedema, anaphylaxis, maculopapular eruptions, photosensitivity reactions and the Stevens–Johnson syndrome. Some herbal medicines, particularly Ayurvedic remedies, contain arsenic or mercury that may produce typical skin lesions. Other popular remedies that can cause dermatological side effects include St John's wort (*Hypericum perforatum*), kava, aloe vera, eucalyptus, camphor, henna and yohimbine. St John's wort may interact with certain drugs, resulting in a decrease in the concentration or effect of the drug, due to induction of cytochrome P-450s and the key drug transporter P-glycoprotein [6]. In addition, pharmacodynamic interactions of St John's wort with some drugs (e.g. selective serotonin re-uptake inhibitors) have been identified, which are associated with an increased risk of adverse reactions.

Some herbal treatments used specifically for dermatological conditions, for example Chinese oral herbal remedies for atopic eczema, have been reported to cause systemic adverse effects. There is concern that some agents, notably Chinese herbal creams, have been shown repeatedly to be adulterated with corticosteroids [7,8].

References

1 Monk B. Severe cutaneous reactions to alternative remedies. *BMJ* 1986; **293**: 665–6.
2 Ernst E. Adverse effects of herbal drugs in dermatology. *Br J Dermatol* 2000; **143**: 923–9.
3 Ernst E. The usage of complementary therapies by dermatological patients: a systematic review. *Br J Dermatol* 2000; **143**: 857–61.
4 Bedi MK, Shenefelt PD. Herbal therapy in dermatology. *Arch Dermatol* 2002; **138**: 232–42.
5 Ventura MT, Viola M, Calogiuri G *et al.* Hypersensitivity reactions to complementary and alternative medicine products. *Curr Pharm Des* 2006; **12**: 3393–9.
6 Zhou SF, Lai X. An update on clinical drug interactions with the herbal antidepressant St. John's wort. *Curr Drug Metab* 2008; **9**: 394–409.
7 But PPH. Herbal poisoning caused by adulterants or erroneous substitutes. *J Trop Med Hyg* 1994; **97**: 371–4.
8 Bircher AJ, Hauri U, Niederer M *et al.* Stealth triamcinolone acetonide in a phytocosmetic cream. *Br J Dermatol* 2002; **146**: 531–2.

Chinese herbal medicine

Adverse effects of Chinese herbal medicines, including life-threatening 'dazao'-induced angio-oedema and liquorice-induced hypokalaemic periodic paralysis, accounted for 0.2% of medical admissions to a hospital in Hong Kong over an 8-month period [1]. Herbal poisoning in Hong Kong, Taipei and Kuala Lumpur has occurred as a result of addition of adulterants (*Podophyllum emodi*) or erroneous substitutes (*Datura metel*) [2]. A fatality due to total liver necrosis associated with ingestion of Chinese herbal medicines is believed to have occurred because the patient prepared a decoction from a herbal mixture containing *Eurysolen gracilis* Prain (Labiatae), a herb not used in Chinese medicine [3]. A multisystem illness developed in a patient after ingestion of Chinese herbal medicines containing the potentially toxic compounds benzaldehyde, cinnamoyl alcohol and ephedrine [4]. Toxic epidermal necrolysis from traditional Chinese medicine, acute generalized exanthematous pustulosis from piroxicam and salicylate-contaminated traditional Chinese medicine, and DRESS from traditional Chinese medicine and from phenylbutazone-adulterated traditional Chinese medicine have been recorded [5]. Some Chinese patent medicines contain mercurial ingredients—cinnabar (red mercuric sulphide) and calomel (mercurous chloride) [6]. Alopecia and sensory polyneuropathy from thallium in a Chinese herbal medication has been reported [7]. Cutaneous aspects of thallium poisoning include palmar and plantar scaling, acneiform lesions on the face and diffuse alopecia, accompanied by acute nervous system and gastrointestinal symptoms [8]. Chinese herbal medicine may contain camouflaged prescription anti-inflammatory drugs, corticosteroids and lead [9], and some practitioners of Chinese medicine supply 'herbal creams' that actually contain potent topical steroid ointments [10,11]. Fixed drug eruption has been documented with use of a Chinese traditional herbal medicine containing mainly pseudoephedrine and ephedrine [12].

There are major concerns about hepatotoxicity [13–17] and nephrotoxicity [18–24] with Chinese herbal medicine. In one case, hepatotoxicity was associated with ingestion of the Chinese herbal product jin bu huan anodyne tablets (*Lycopodium serratum*) [15]. A rapidly progressive fibrosing interstitial nephritis developed in young women who followed the same slimming regimen containing two Chinese herbs (*Stephania tetrandra* and *Magnolia officinalis*) [18–20]. The known carcinogen, aristolochic acid, has been suspected in some cases of nephropathy [21,22]. Urothelial malignancy has supervened [23]. Acquired Fanconi's syndrome was induced by a mixture of Chinese crude drugs [24].

The need for correct identification of herbs in herbal poisoning [25], and for monitoring of the safety of herbal medicines [26], has been emphasized. Greater awareness of their toxicity is required

[27,28]. Special licensing of herbal remedies exists in Germany, France and Australia, and has been advocated in the UK [29].

Analgesic and anti-inflammatory Chinese medicinal materials, especially those containing fragrance, may cause contact sensitization and can cause systemic contact dermatitis [29,30]. Erythema multiforme [31,32], exanthem [33] and erythroderma [34] are described. Fever with oedematous erythema was caused by a decoction of the crude drug Boi of Kampo (Sino-Japanese traditional) medicine for the alleviation of arthralgia; oral ingestion tests incriminated the constituent sinomenine [35].

A 'tea' prepared from a decoction of herbs has been reported to be of benefit in eczema [36,37]. The decoction contains paenol (2'-hydroxy-4'-methoxyacetophenone), which is known to have platelet antiaggregatory, analgesic and antipyretic properties [38]. Hepatotoxicity was described in a 9-year-old girl who consumed a Chinese herbal tea for 6 months [39], and was reported in a further patient [40]. Reversible abnormal liver function tests have been reported in two children receiving Chinese herbal therapy (Zemaphyte) [41]. Toxicology screening in a group of adults on Zemaphyte for 1 year revealed no abnormalities in haematological or biochemical parameters; transient nausea and abdominal distension, with a mild laxative effect, was noted in about one-third of patients [42]. Dilated cardiomyopathy followed therapy of atopic eczema with Chinese herbal medicine [43].

References

1 Chan TY, Chan AY, Critchley JA. Hospital admissions due to adverse reactions to Chinese herbal medicines. *J Trop Med Hyg* 1992; **95**: 296–8.
2 But PP. Herbal poisoning caused by adulterants or erroneous substitutes. *J Trop Med Hyg* 1994; **947**: 371–4.
3 Perharic-Walton L, Murray V. Toxicity of Chinese herbal remedies. *Lancet* 1992; **340**: 674.
4 Gorey JD, Wahlqvist ML, Boyce NW. Adverse reaction to a Chinese herbal remedy. *Med J Aust* 1992; **157**: 484–6.
5 Lim YL, Thirumoorthy T. Serious cutaneous adverse reactions to traditional Chinese medicines. *Singapore Med J* 2005; **46**: 714–7.
6 Kang-Yum E, Oransky SH. Chinese patent medicine as a potential source of mercury poisoning. *Vet Hum Toxicol* 1992; **34**: 235–8.
7 Schaumburg HH, Berger A. Alopecia and sensory polyneuropathy from thallium in a Chinese herbal medication. *JAMA* 1992; **268**: 3430–1.
8 Tromme I, Van Neste D, Dobbelaere F *et al.* Skin signs in the diagnosis of thallium poisoning. *Br J Dermatol* 1998; **138**: 321–5.
9 Goldman JA, Myerson G. Chinese herbal medicine: camouflaged prescription anti-inflammatory drugs, corticosteroids, and lead. *Arthritis Rheum* 1991; **34**: 1207.
10 Allen BR, Parkinson R. Chinese herbs for eczema. *Lancet* 1990; **336**: 177.
11 O'Driscoll J, Burden AD, Kingston TP. Potent topical steroid obtained from a Chinese herbalist. *Br J Dermatol* 1992; **127**: 543–4.
12 Matsumoto K, Mikoshiba H, Saida T. Nonpigmenting solitary fixed drug eruption caused by a Chinese traditional herbal medicine, ma huang (*Ephedra hebra*), mainly containing pseudoephedrine and ephedrine. *J Am Acad Dermatol* 2003; **48**: 628–30.
13 Mostefa-Kara N, Pauwels A, Pinus E *et al.* Fatal hepatitis after herbal tea. *Lancet* 1992; **340**: 674.
14 Graham-Brown R. Toxicity of Chinese herbal remedies. *Lancet* 1992; **340**: 673.
15 Woolf GM, Petrovic LM, Rojter SE *et al.* Acute hepatitis associated with the Chinese herbal product jin bu huan. *Ann Intern Med* 1994; **121**: 729–35.
16 Pillans PI. Toxicity of herbal products. *NZ Med J* 1995; **108**: 469–71.
17 Larrey D, Pageaux GP. Hepatotoxicity of herbal remedies and mushrooms. *Semin Liver Dis* 1995; **15**: 183–8.
18 Vanherweghem JL, Depierreux M, Tielemans C *et al.* Rapidly progressive interstitial renal fibrosis in young women: association with slimming regimen including Chinese herbs. *Lancet* 1993; **341**: 387–91.
19 Depierreux M, Van Damme B, Vanden Houte K, Vanherweghem JL. Pathologic aspects of a newly described nephropathy related to the prolonged use of Chinese herbs. *Am J Kidney Dis* 1994; **24**: 172–80.
20 Cosyns JP, Jadoul M, Squifflet JP *et al.* Chinese herbs nephropathy: a clue to Balkan endemic nephropathy? *Kidney Int* 1994; **45**: 1680–8.
21 Vanhaelen M, Vanhaelen-Fastre R, But P, Vanherweghem JL. Identification of aristolochic acid in Chinese herbs. *Lancet* 1994; **343**: 174.
22 Diamond JR, Pallone TL. Acute interstitial nephritis following use of tung shueh pills. *Am J Kidney Dis* 1994; **24**: 219–21.
23 Cosyns JP, Jadoul M, Squifflet JP *et al.* Urothelial malignancy in nephropathy due to Chinese herbs. *Lancet* 1994; **344**: 188.
24 Izumotani T, Ishimura E, Tsumura K *et al.* An adult case of Fanconi syndrome due to a mixture of Chinese crude drugs. *Nephron* 1993; **65**: 137–40.
25 But PP. Need for correct identification of herbs in herbal poisoning. *Lancet* 1993; **341**: 637.
26 Mills SY. Monitoring the safety of herbal remedies. European pilot studies are under way. *BMJ* 1995; **311**: 1570.
27 Atherton DJ. Towards the safer use of traditional remedies. Greater awareness of toxicity is needed. *BMJ* 1994; **308**: 673–4.
28 Harper J. Traditional Chinese medicine for eczema. Seemingly effective, but caution must prevail. *BMJ* 1994; **308**: 489–90.
29 De Smet PAGM. Should herbal medicine-like products be licensed as medicines? Special licensing seems the best way forward. *BMJ* 1995; **310**: 1023–4.
30 Li LF. A clinical and patch test study of contact dermatitis from traditional Chinese medicinal materials. *Contact Dermatitis* 1995; **33**: 392–5.
31 Mateo MP, Velasco M, Miquel FJ, de la Cuadra J. Erythema-multiforme-like eruption following allergic contact dermatitis from sesquiterpene lactones in herbal medicine. *Contact Dermatitis* 1995; **33**: 449–50.
32 Tan WP, Goh BK, Tan SH. Extensive erythema multiforme-like eruption due to traditional Chinese herbal drug 'Dong Ling Hou Tong Pian'. *Clin Exp Dermatol* 2006; **31**: 291–3.
33 Li LF, Zhao J, Li SY. Exanthematous drug eruption due to Chinese herbal medicines sanjieling capsule and huoxuexiaoyan pill. *Contact Dermatitis* 1994; **30**: 252–3.
34 Catlin DH, Sekera M, Adelman DC. Erythroderma associated with ingestion of an herbal product. *West J Med* 1993; **159**: 491–3.
35 Okuda T, Umezawa Y, Ichikawa M *et al.* A case of drug eruption caused by the crude drug Boi (*Sinomenium* stem/Sinomeni caulis et Rhizoma). *J Dermatol* 1995; **22**: 795–800.
36 Atherton D, Sheehan M, Rustin MHA *et al.* Chinese herbs for eczema. *Lancet* 1990; **336**: 1254.
37 Sheehan MP, Atherton DJ, Luo HD. Controlled trial of traditional Chinese medicinal plants in widespread non-exudative atopic eczema (abstract). *Br J Dermatol* 1991; **125** (Suppl. 38): 17.
38 Galloway JH, Marsh ID, Bittiner SB *et al.* Chinese herbs for eczema, the active compound? *Lancet* 1991; **337**: 566.
39 Davies EG, Pollock I, Steel HM. Chinese herbs for eczema. *Lancet* 1990; **336**: 177.
40 Carlsson C. Herbs and hepatitis. *Lancet* 1990; **336**: 1068.
41 Sheehan MP, Atherton DJ. One year follow-up of children with atopic eczema treated with traditional Chinese medicinal plants. *Br J Dermatol* 1992; **127** (Suppl. 40): 13.
42 Sheehan MP, Stevens H, Ostlere LS *et al.* Follow-up of adult patients with atopic eczema treated with Chinese herbal therapy for 1 year. *Clin Exp Dermatol* 1995; **20**: 136–40.
43 Ferguson JE, Chalmers RJG, Rowlands DJ. Reversible dilated cardiomyopathy following treatment of atopic eczema with Chinese herbal medicine. *Br J Dermatol* 1997; **136**: 592–3.

Kava dermopathy

The kava plant, a member of the black-pepper family, is used ceremonially by many traditional societies of the southern Pacific in the form of an intoxicant beverage prepared from roots to induce relaxation and sociability and promote sleep. Herbal drugs containing kava have been used for insomnia, nervousness and depression. A reversible ichthyosiform kava dermopathy resulted

from excessive use of kava [1,2]. Systemic contact-type dermatitis occurred after oral administration of kava extract [2].

References

1 Norton SA, Ruze P. Kava dermopathy. *J Am Acad Dermatol* 1994; **31**: 89–97.
2 Suss R, Lehmann P. Hamatogenes Kontaktekzem durch pflanzliche Medikamente am Beispiel des Kavawurzel-extraktes. *Hautarzt* 1996; **47**: 459–61.

Homeopathic drugs

Cases of erythroderma, confluent urticaria and anaphylaxis have been reported following homeopathic medication [1]. Treatment of a diaper dermatitis and mild respiratory and enteral infections with the homeopathic mercurial medicine Mercurius 6a (cinnabar dilute $1 \times 10(6)$) was followed by dissemination of the dermatitis, irritability and albuminuria [2]. Baboon syndrome was associated with use of a homeopathic medicine containing mercury [3].

References

1 Aberer W, Strohal R. Homeopathic preparations: severe adverse effects, unproven benefits. *Dermatologica* 1991; **182**: 253.
2 Montoya-Cabrera MA, Rubio-Rodriguez S, Velazquez-Gonzalez E, Avila Montoya S. Intoxicacion mercurial causada por un medicamento homeopatico. *Gaceta Med Mex* 1991; **127**: 267–70.
3 Audicana M, Bernedo N, Gonzalez I *et al.* An unusual case of baboon syndrome due to mercury present in a homeopathic medicine. *Contact Dermatitis* 2001; **45**: 185.

Naturopathy

Bizarre and unpredictable cutaneous reactions may follow topical application or ingestion of naturally occurring substances. A curious gyrate erythematous eruption was seen in a patient following local application of onion rings as a home remedy for arthralgia [1]. Substantial amounts of psoralen may be absorbed from vegetables; a patient who consumed a large quantity of celery root (*Apium graveolens*) 1 h before a visit to a suntan parlour developed a severe generalized phototoxic reaction [2]. A bullous phototoxic reaction developed after exposure to aerosolized bergamot aromatherapy oil in a sauna and subsequent UVA radiation in a tanning salon [3]. Phytophotodermatitis followed application of *Citrus hystrix* as a mosquito repellent [4]. Phototoxicity has been reported from herbal remedies for vitiligo incorporating powdered seeds of *Psoralea corylifolia*, which contains psoralen, isopsoralen and psoralidin [5].

Contact sensitization has been caused by alternative topical medicaments containing plant extracts [6–10], including tea-tree oil, the extracted oil of *Melaleuca alternifolia* [7–9]. Tea-tree oil has also caused systemic contact dermatitis [7], linear immunoglobulin A disease [11], erythema multiforme-like id reactions, and systemic hypersensitivity reactions [9]. Allergic airborne contact dermatitis has been caused by benzaldehyde, eucalyptus oil, laurel oil, pomerance flower oil, lavender oil, rosewood oil and jasmine oil used for aromatherapy [12]. Application of henna as a decoration may cause allergic contact eczema [13]. A diffuse morbilliform eruption and other skin reactions occurred with a *Gingko biloba* supplement [14,15], recurrent erythema nodosum, other rashes and gastrointestinal upset with *Echinacea* therapy [16,17], and erythroderma with intake of St John's wort (*Hypericum perforatum*) [18].

References

1 Breathnach SM, Hintner H. *Adverse Drug Reactions and the Skin*. Oxford: Blackwell Scientific Publications, 1992.
2 Ljunggren B. Severe phototoxic burn following celery ingestion. *Arch Dermatol* 1990; **126**: 1334–6.
3 Kaddu S, Kerl H, Wolf P. Accidental bullous phototoxic reactions to bergamot aromatherapy oil. *J Am Acad Dermatol* 2001; **45**: 458–61.
4 Koh D, Ong C-N. Phytophotodermatitis due to the application of *Citrus hystrix* as a folk remedy. *Br J Dermatol* 1999; **140**: 737–8.
5 Maurice PDL, Cream JJ. The dangers of herbalism. *BMJ* 1989; **299**: 1204.
6 Bruynzeel DP, van Ketel WG, Young E *et al.* Contact sensitization by alternative topical medicaments containing plant extracts. The Dutch Contact Dermatoses Group. *Contact Dermatitis* 1992; **27**: 278–9.
7 de Groot AC, Weyland JW. Systemic contact dermatitis from tea tree oil. *Contact Dermatitis* 1992; **27**: 279–80.
8 Knight TE, Hausen BM. *Melaleuca* oil (tea tree oil) dermatitis. *J Am Acad Dermatol* 1994; **30**: 423–7.
9 Crawford GH, Sciacca JR, James WD. Tea tree oil: cutaneous effects of the extracted oil of *Melaleuca alternifolia*. *Dermatitis* 2004; **15**: 59–66.
10 Hong SJ, Chang CH. Erythema multiforme-like generalized allergic contact dermatitis caused by *Alpinia galanga*. *Contact Dermatitis* 2006; **54**: 118–20.
11 Perett CM, Evans AV, Russell-Jones R. Tea tree oil dermatitis associated with linear IgA disease. *Clin Exp Dermatol* 2003; **28**: 167–70.
12 Schaller M, Korting HC. Allergic airborne contact dermatitis from essential oils used in aromatherapy. *Clin Exp Dermatol* 1995; **20**: 143–5.
13 Lestringant GG, Bener A, Frossard PM. Cutaneous reactions to henna and associated additives. *Br J Dermatol* 1999; **141**: 598–600.
14 Chiu AE, Lane AT, Kimball AB. Diffuse morbilliform eruption after consumption of *Ginkgo biloba* supplement. *J Am Acad Dermatol* 2002; **46**: 145–6.
15 Mahadevan S, Park Y. Multifaceted therapeutic benefits of *Ginkgo biloba* L.: chemistry, efficacy, safety, and uses. *J Food Sci* 2008; **73**: R14–9.
16 Soon SL, Crawford RI. Recurrent erythema nodosum associated with *Echinacea* herbal therapy. *J Am Acad Dermatol* 2001; **44**: 298–9.
17 Huntley AL, Thompson Coon J, Ernst E. The safety of herbal medicinal products derived from *Echinacea* species: a systematic review. *Drug Saf* 2005; **28**: 387–400.
18 Holme SA, Roberts DL. Erythroderma associated with St John's wort. *Br J Dermatol* 2000; **143**: 1127–8.

Miscellaneous

Canthaxanthin, a synthetic non-provitamin A carotenoid deposited in epidermis and subcutaneous fat, caused fatal aplastic anaemia when ingested to promote tanning [1].

Reference

1 Bluhm R, Branch R, Johnston P, Stein R. Aplastic anemia associated with canthaxanthin ingested for 'tanning' purposes. *JAMA* 1990; **264**: 1141–2.

Industrial and other exposure to chemicals

For a discussion of sclerodermatous reactions to environmental agents, see p. 75.43. A form of fluoride toxicity occurred due to industrial poisoning in the Italian town of Chizzolo, resulting in pinkish brown, round or oval macules seen in hundreds of the local population [1]. Similar small outbreaks have occurred in North America [2]. Exfoliative dermatitis has been recorded with trichloroethylene [3]. Occupational exposure to trichloroethylene has also caused Stevens–Johnson syndrome [4].

Patients exposed to dioxin after an industrial accident at Seveso, Italy developed early irritative lesions, comprising erythema and oedema of exposed areas, vesicobullous and necrotic lesions of the palms and fingertips, and papulonodular lesions; later lesions were those of chloracne [5]. Contamination of rice-bran cooking oil with polychlorinated biphenyls in Taiwan resulted in chloracne, and congenital abnormalities in offspring [6].

Pruritus, urticaria, and discoid and diffuse eczema may occur following the use of brominated disinfectant compounds such as 1-bromo-3-chlor-5,5-dimethylhydantoin (Di-halo, Aquabrome) in public swimming pools [7]. Accidental occupational exposure to high concentrations of methyl bromide during a fumigation procedure resulted in erythema with multiple vesicles and large bullae, with predilection for moist flexures and pressure areas [8]. Idiopathic thrombocytopenic purpura has been associated with industrial exposure to wood preservatives [9], turpentine [10], and to insecticides such as chlordane and heptachlor [11]. Reversible alopecia occurred with occupational exposure to borax-containing solutions [12].

References

1 Waldbott GC, Cecilioni VA. 'Chizzolo' maculae. *Cutis* 1970; **6**: 331–4.
2 Tabuenca JM. Toxic–allergic syndrome caused by ingestion of rapeseed oil denatured with aniline. *Lancet* 1981; **ii**: 567–8.
3 Nakayama H, Kobayashi M, Takahashi M *et al.* Generalized eruption with severe liver dysfunction associated with occupational exposure to trichloroethylene. *Contact Dermatitis* 1988; **19**: 48–51.
4 Phoon WH, Chan MOY, Rahan VS *et al.* Stevens–Johnson syndrome associated with occupational exposure to trichloroethylene. *Contact Dermatitis* 1984; **10**: 270–6.
5 Caputo R, Monti M, Ermacora E *et al.* Cutaneous manifestations of tetrachlorodibenzo-*p*-dioxin in children and adolescents. *J Am Acad Dermatol* 1988; **19**: 812–9.
6 Gladen BC, Taylor JS, Wu Y-C *et al.* Dermatological findings in children exposed transplacentally to heat-degraded polychlorinated biphenyls in Taiwan. *Br J Dermatol* 1990; **122**: 799–808.
7 Rycroft RJG, Penny PT. Dermatoses associated with brominated swimming pools. *BMJ* 1983; **28**: 462.
8 Hezemans-Boer M, Toonstra J, Meulenbelt J *et al.* Skin lesions due to exposure to methyl bromide. *Arch Dermatol* 1988; **124**: 917–21.
9 Hay A, Singer CRJ. Wood preservatives, solvents, and thrombocytopenic purpura. *Lancet* 1991; **338**: 766.
10 Wahlberg P, Nyman D. Turpentine and thrombocytopenic purpura. *Lancet* 1969; **ii**: 215–6.
11 Epstein SS, Ozonoff D. Leukemias and blood dyscrasias following exposure to chloradone and heptachlor. *Carcinogen Mutagen Teratogen* 1987; **7**: 527–40.
12 Beckett WS, Oskvig R, Gaynor ME, Goldgeier MH. Association of reversible alopecia with occupational topical exposure to common borax-containing solutions. *J Am Acad Dermatol* 2001; **44**: 599–602.

Local and systemic effects of topical applications

Many topical therapeutic agents may cause serious or even dangerous systemic side effects if absorbed in sufficient quantity; such absorption may be facilitated through diseased skin, and with use of newer vehicles or occlusive polythene dressings. The risk of serious systemic effects is greatest in infancy and in the old and frail. The quantity absorbed in relation to body weight is greatest in infancy, when the surface area is relatively greater; moreover, neonatal skin is more permeable. Most dangerous or fatal reactions have occurred because either the physician was unaware of the potential hazard or the patient continued self-treatment without medical supervision.

Topical therapy

Anthralin (dithranol)

Topical anthralin, used in the therapy of stable plaque psoriasis, is well known for causing erythema, irritation and a sensation of burning in normal skin; it stains the skin and clothing [1]. Application of 10% triethanolamine following short-contact anthralin treatment has been reported to inhibit anthralin-induced inflammation without preventing the therapeutic effect [2]. Allergic contact dermatitis to anthralin is very rare. The natural and synthetic anthranols have toxic effects on liver, intestines and the central nervous system, but systemic toxicity in humans under therapeutic conditions has not been established [3].

References

1 Paramsothy Y, Lawrence CM. Time course and intensity of anthralin inflammation on involved and uninvolved psoriatic skin. *Br J Dermatol* 1987; **116**: 517–9.
2 Ramsay B, Lawrence CM, Bruce JM, Shuster S. The effect of triethanolamine application on anthralin-induced inflammation and therapeutic effect in psoriasis. *J Am Acad Dermatol* 1990; **23**: 73–6.
3 Ippen H. Basic questions on toxicology and pharmacology of anthralin. *Br J Dermatol* 1981; **105** (Suppl. 20): 72–6.

Boric acid

Poisoning has usually occurred in infants treated for napkin eruptions. Almost all cases have been caused by the use of boric ointments or lotions. However, use of borated talc proved fatal in one infant [1]. Wet boric dressings caused the death of an adult woman [2].

References

1 Brooke C, Boggs T. Boric-acid poisoning: report of a case and review of the literature. *Am J Dis Child* 1951; **82**: 465–72.
2 Jordan JW, Crissey JT. Boric acid poisoning: report of fatal adult case from cutaneous use. A critical evaluation of this drug in dermatologic practice. *Arch Dermatol* 1957; **75**: 720–8.

Calcineurin inhibitors (pimecrolimus and tacrolimus)

(see pp. 75.146–147)

Calcipotriol

This vitamin D_3 analogue has been reported to cause transient local irritation, and facial or perioral dermatitis [1]. Contact allergy is recorded [2]. Topical application of calcipotriol for 5 weeks to a mean of 16% of the body surface of psoriatic patients did not result in detectable systemic alteration of calcium metabolism [3]. The manufacturer's data sheet (Leo Laboratories) states that increased serum calcium may occur with application in daily doses of 50–100 g of the 50 μg/g ointment. Severe symptomatic hypercalcaemia developed after application of about 200 g of the ointment over 1 week to exfoliative psoriasis covering 40% of the body surface [4]. It is recommended that treatment be confined to stable mild to moderate psoriasis, and that the recommended dose of 100 g/week should not be exceeded. Hyperpigmentation occurred at the site of topical calcipotriol application in two patients receiving photochemotherapy [5].

References

1 Kragballe K, Gjertsen BT, De Hoop D *et al.* Double-blind, right/left comparison of calcipotriol and betamethasone valerate in treatment of psoriasis vulgaris. *Lancet* 1991; **337**: 193–6.
2 de Groot AC. Contact allergy to calcipotriol. *Contact Dermatitis* 1994; **30**: 242–3.
3 Saurat J-H, Gumowski Sunek D, Rizzoli R. Topical calcipotriol and hypercalcaemia. *Lancet* 1991; **337**: 1287.
4 Dwyer C, Chapman RS. Calcipotriol and hypercalcaemia. *Lancet* 1991; **338**: 764–5.
5 Gläser R, Röwert J, Mrowietz U. Hyperpigmentation due to topical calcipotriol and photochemotherapy in two psoriatic patients. *Br J Dermatol* 1998; **139**: 148–51.

Coal tar

Coal tar vapour inhalation precipitated severe symptomatic bronchoconstriction in an atopic asthmatic subject following application of coal-tar bandages for treatment of eczema, confirmed by challenge [1].

Reference

1 Ibbotson SH, Stenton SC, Simpson NB. Acute severe bronchoconstriction precipitated by coal tar bandages. *Clin Exp Dermatol* 1995; **20**: 58–9.

Chlorhexidine gluconate (Hibitane)

Urticaria, dyspnoea and anaphylactic shock have occurred following topical application as a disinfectant [1,2], as have contact urticaria, photosensitive dermatitis [3] and deafness.

References

1 Okano M, Nomura M, Hata S *et al.* Anaphylactic symptoms due to chlorhexidine gluconate. *Arch Dermatol* 1989; **125**: 50–2.
2 Snellman E, Rantanen T. Severe anaphylaxis after a chlorhexidine bath. *J Am Acad Dermatol* 1999; **40**: 771–2.
3 Wahlberg JE, Wennersten G. Hypersensitivity and photosensitivity to chlorhexidine. *Dermatologica* 1971; **143**: 376–9.

Dequalinium chloride

Necrotic lesions have occurred following its use in the treatment of balanitis [1].

Reference

1 Coles RB, Simpson WT, Wilkinson DS. Dequalinium: a possible complication of its use in balanitis. *Lancet* 1964; **ii**: 531.

Dimethylsulfoxide

Topical application can cause erythema, pruritus and urticaria, but systemic reactions are very rare; a generalized contact dermatitis-like reaction followed intravesical instillation in a sensitized individual [1].

Reference

1 Nishimura M, Takano Y, Toshitani Y. Systemic contact dermatitis medicamentosa occurring after intravesical dimethyl sulfoxide treatment for interstitial cystitis. *Arch Dermatol* 1988; **124**: 182–3.

Diphencyprone (see p. 75.147)

Doxepin

Doxepin cream causes allergic contact dermatitis and systemic contact dermatitis [1,2].

References

1 Taylor JS, Praditsuwan P, Handel D, Kuffner G. Allergic contact dermatitis from doxepin cream. One-year patch test clinic experience. *Arch Dermatol* 1996; **132**: 515–8.
2 Shelley W, Shelley ED, Talanin NY. Self-potentiating allergic contact dermatitis caused by doxepin hydrochloride cream. *J Am Acad Dermatol* 1996; **34**: 143–4.

EMLA cream (see pp. 75.153–154)

5-Fluorouracil (see p. 75.129)

Formaldehyde

Industrial exposure is recognized to be a health hazard, and a threshold limit of 2 ppm is allowed in the UK and the USA [1]. Irritant or allergic dermatitis is common in exposed workers [2]. Systemic symptoms including breathlessness, headache and drowsiness have been attributed to prolonged exposure to very low levels in the home [3].

References

1 Anonymous. The health hazards of formaldehyde. *Lancet* 1981; **i**: 926–7.
2 Glass WI. An outbreak of formaldehyde dermatitis. *NZ Med J* 1961; **60**: 423.
3 Harris JC, Rumack BH, Aldrich FD. Toxicology of urea formaldehyde and polyurethane foam insulation. *JAMA* 1981; **245**: 243–6.

Lindane (gamma benzene hexachloride)

Lindane therapy for scabies has potential toxicity, which includes neurotoxicity with convulsions, especially in children [1–7]. Most reports have occurred with overexposure or misuse, although side effects have followed single applications, particularly when the epidermal barrier has been compromised. Whether this constitutes a significant problem in normal individuals is doubtful [6]. Nevertheless, it has been suggested that permethrin may be a safer and less toxic alternative [8].

References

1 Lee B, Groth P. Scabies: transcutaneous poisoning during treatment. *Arch Dermatol* 1979; **115**: 124–5.
2 Pramanik AK, Hansen RC. Transcutaneous gamma benzene hexachloride absorption and toxicity in infants and children. *Arch Dermatol* 1979; **115**: 124–5.
3 Matsuoka LY. Convulsions following application of gamma benzene hexachloride. *J Am Acad Dermatol* 1981; **5**: 98–9.
4 Rasmussen JE. The problem of lindane. *J Am Acad Dermatol* 1981; **5**: 507–16.
5 Davies JE, Dehdia HV, Morgade C *et al.* Lindane poisonings. *Arch Dermatol* 1983; **119**: 142–4.
6 Rasmussen J. Lindane: a prudent approach. *Arch Dermatol* 1987; **123**: 1008–10.
7 Friedman SJ. Lindane neurotoxic reaction in nonbullous ichthyosiform erythroderma. *Arch Dermatol* 1987; **123**: 1056–8.
8 Schultz MW, Gomez M, Hansen RC *et al.* Comparative study of 5% permethrin cream and 1% lindane lotion for the treatment of scabies. *Arch Dermatol* 1990; **126**: 167–70.

Hexachlorophene (hexachlorophane)

This substance has potential neurotoxicity. Exposure of babies to a talc containing 6.3% hexachlorophene due to a manufacturing error resulted in deaths, with ulceration, skin lesions and a characteristic demyelinating encephalopathy [1]. A 3% emulsion has produced milder neurological changes, but a 0.33% concentration in talc is apparently safe. Encephalopathy has occurred in burns patients [2].

References

1 Martin-Bouyer G, Lebreton R, Toga M *et al.* Outbreak of accidental hexachlorophene poisoning in France. *Lancet* 1982; **i**: 91–5.
2 Larson DL. Studies show hexachlorophene causes burn syndrome. *J Am Hosp Assoc* 1968; **42**: 63–4.

Hydroquinone

Depigmenting creams containing 6–8% hydroquinone, used especially by black South African women, have caused rebound hyperpigmentation and coarsening of the skin, with ochronotic changes in the dermis, colloid degeneration and colloid milium [1–6]. Collagen degeneration may be seen histologically [2]. Similar changes have been seen in black women in the USA [3] and in a Mexican-American woman [4]. Interestingly, ochronosis does not develop in areas of vitiligo [7]. The Q-switched ruby laser may be helpful in treating exogenous ochronosis [8]. The nails may be pigmented [9].

References

1 Findlay GH, Morrison JGL, Simson IW. Exogenous ochronosis and pigmented colloid milium from hydroquinone bleaching creams. *Br J Dermatol* 1975; **93**: 613–22.
2 Phillips JI, Isaacson C, Carman H. Ochronosis in Black South Africans who used skin lighteners. *Am J Dermatopathol* 1986; **8**: 14–21.
3 Lawrence N, Bligard CA, Reed R, Perret WJ. Exogenous ochronosis in the United States. *J Am Acad Dermatol* 1988; **18**: 1207–11.
4 Howard KL, Furner BB. Exogenous ochronosis in a Mexican-American woman. *Cutis* 1990; **45**: 180–2.
5 Camarasa JG, Serra-Baldrich E. Exogenous ochronosis with allergic contact dermatitis from hydroquinone. *Contact Dermatitis* 1994; **31**: 57–8.
6 Snider RL, Thiers BH. Exogenous ochronosis. *J Am Acad Dermatol* 1993; **28**: 662–4.
7 Hull PR, Procter PR. The melanocyte: an essential link in hydroquinone-induced ochronosis. *J Am Acad Dermatol* 1990; **22**: 529–31.
8 Kramer KE, Lopez A, Stefanato CM, Phillips TJ. Exogenous ochronosis. *J Am Acad Dermatol* 2000; **42**: 869–71.
9 Garcia RL, White JW, Willis WF. Hydroquinone nail pigmentation. *Arch Dermatol* 1978; **114**: 1402–3.

Imiquimod (see pp. 75.147–148)

Iodine

Povidone-iodine scrub for acne (Betadine) induced hyperthyroidism [1].

Reference

1 Smit E, Whiting DA, Feld S. Iodine-induced hyperthyroidism caused by acne treatment. *J Am Acad Dermatol* 1994; **31**: 115–7.

Latanoprost

Topical latanoprost for glaucoma may induce eyelash hypertrichosis [1].

Reference

1 Demitsu T, Manabe M, Harima N *et al.* Hypertrichosis induced by latanoprost. *J Am Acad Dermatol* 2001; **44**: 721–3.

Lead lotions

The continued use of wet dressings of lead subacetate in the treatment of exfoliative dermatitis caused lead poisoning, with punctate basophilia and an elevated urinary lead level [1].

Reference

1 Kennedy CC, Lynas HA. Lead poisoning by cutaneous absorption from lead dressings. *Lancet* 1949; **i**: 650–2.

Mercury

Poisoning is now fortunately rare, but was seen from continued application of large amounts of a topical application, as for psoriasis [1,2]. Idiosyncratic poisoning after much smaller doses is also recognized [3]. Intoxication has followed the use of a mercury dusting powder [4] and poisoning of a suckling infant has followed the use of perchloride of mercury lotion for cracked nipples [5]. Fever, a generalized morbilliform rash and oedema of the extremities have been the usual clinical features. Exfoliative dermatitis and encephalopathy have developed; permanent damage to the renal tubules is manifest as persistent albuminuria or frank nephrotic syndrome [6]. Rarely, gross symptoms, such as loose teeth [7], swollen bleeding gums and weight loss, may be observed.

Application of a mercury-containing cream to the face over many years can produce slate-grey pigmentation, especially on the eyelids, nasolabial folds and neck folds (exogenous ochronosis) [8–10]; mercury granules lie free in the dermis or within macrophages [11]. Mercury is a moderate sensitizer and leads to contact sensitivity.

References

1 Inman PM, Gordon B, Trinder P. Mercury absorption and psoriasis. *BMJ* 1956; **ii**: 1202–6.
2 Young E. Ammoniated mercury poisoning. *Br J Dermatol* 1960; **72**: 449–55.
3 Williams BH, Beach WC. Idiosyncrasy to ammoniated mercury: treatment with 2,3-dimercapto-propanol (BAL). *JAMA* 1950; **142**: 1286–8.
4 MacGregor ME, Rayner PHW. Pink disease and primary renal tubular acidosis: a common cause. *Lancet* 1964; **ii**: 1083–5.
5 Hunt GM. Mercury poisoning in infancy. *BMJ* 1966; **i**: 1482.
6 Silverberg DS, McCall JT, Hunt JC. Nephrotic syndrome with use of ammoniated mercury. *Arch Intern Med* 1967; **20**: 581–6.
7 Bourgeois M, Dooms-Goossens A, Knockaert D *et al.* Mercury intoxication after topical application of a metallic mercury ointment. *Dermatologica* 1986; **172**: 48–51.
8 Lamar LM, Bliss BO. Localized pigmentation of the skin due to topical mercury. *Arch Dermatol* 1966; **93**: 450–3.
9 Prigent F, Cohen J, Civatte J. Pigmentation des paupieres probablement secondaire l'application prolongée d'une pomade ophtalmologique contenant du mercure. *Ann Dermatol Vénéréol* 1986; **113**: 357–8.
10 Aberer W. Topical mercury should be banned: dangerous, outmoded but still popular. *J Am Acad Dermatol* 1991; **24**: 150–1.
11 Burge KM, Winkelmann RK. Mercury pigmentation. An electron microscopic study. *Arch Dermatol* 1970; **102**: 51–61.

Methyl salicylate (oil of wintergreen)

Topical application of methyl salicylate and menthol as a rubefacient, with use of a heating pad, resulted in local skin necrosis and interstitial nephritis [1].

Reference

1 Heng MCY. Local necrosis and interstitial nephritis due to topical methyl salicylate and menthol. *Cutis* 1987; **39**: 442–4.

Mexiletine

Mexiletine hydrochloride induced contact urticaria in a patient receiving iontophoresis [1]. A generalized drug eruption followed topical provocation on previously involved skin [2].

References

1 Yamazaki S, Katayama I, Kurumaji Y *et al.* Contact urticaria induced by mexiletine hydrochloride in a patient receiving iontophoresis. *Br J Dermatol* 1994; **130**: 538–40.
2 Kikuchi K, Tsunoda T, Tagami H. Generalized drug eruption due to mexiletine hydrochloride: topical provocation on previously involved skin. *Contact Dermatitis* 1991; **25**: 70–2.

Minoxidil

Topical minoxidil, as used for androgenetic alopecia, is associated with cutaneous problems in up to 10% of patients, with allergic contact dermatitis occurring in 4% of individuals [1]. The contact allergen is often propylene glycol [2]. Diffuse hypertrichosis occurred during treatment with 5% topical minoxidil in female patients [3]. Acute non-allergic eruptions of the scalp resulted from combined use of minoxidil and retinoic acid [4].

References
1 Wilson C, Walkden V, Powell S *et al*. Contact dermatitis in reaction to 2% topical minoxidil solution. *J Am Acad Dermatol* 1991; **24**: 661–2.
2 Friedman ES, Friedman PM, Cohen DE, Washenik K. Allergic contact dermatitis to topical minoxidil solution: etiology and treatment. *J Am Acad Dermatol* 2002; **46**: 309–12.
3 Peluso AM, Misciali C, Vincenzi C, Tosti A. Diffuse hypertrichosis during treatment with 5% topical minoxidil. *Br J Dermatol* 1997; **136**: 118–20.
4 Fisher AA. Unusual acute, nonallergic eruptions of the scalp from combined use of minoxidil and retinoic acid. *Cutis* 1993; **51**: 17–8.

Non-steroidal anti-inflammatory drugs

Allergic and photoallergic contact dermatitis and phototoxicity have resulted from topical NSAIDs [1–3]. An erythema multiforme-like reaction followed acute contact dermatitis from two different bufexamac-containing topical preparations [4].

References
1 Ophaswongse S, Maibach H. Topical nonsteroidal antiinflammatory drugs: allergic and photoallergic contact dermatitis and phototoxicity. *Contact Dermatitis* 1993; **29**: 57–64.
2 Oh VM. Ketoprofen gel and delayed hypersensitivity dermatitis. *BMJ* 1994; **309**: 512.
3 Valsecchi R, Pansera B, Leghissa P, Reseghetti A. Allergic contact dermatitis of the eyelids and conjunctivitis from diclofenac. *Contact Dermatitis* 1996; **34**: 150–1.
4 Koch P, Bahmer FA. Erythema-multiforme-like, urticarial papular and plaque eruptions from bufexamac: report of 4 cases. *Contact Dermatitis* 1994; **31**: 97–101.

Phenol

Severe systemic reactions, such as abdominal pain, dizziness, haemoglobinuria, cyanosis and sometimes fatal coma, have followed the application of phenol to extensive wounds. Accidental application of pure phenol to a small area of skin in an infant has proved fatal. The prolonged use of phenol as a dressing for a large ulcer may give rise to exogenous ochronosis, with darkening of the cornea and of the skin of face and hands.

Podophyllin

Excessive application may lead to severe local irritation or ulceration [1]. There have been occasional reports of confusional states, coma, peripheral neuropathy, vomiting and even death following the application of this resin to large areas of genital warts, especially in pregnancy [2,3]. However, careful review of the reports suggests that in the majority the effects could not be attributed with certainty to podophyllin [2]. Animal experiments suggest teratogenicity; although teratogenicity is controversial in humans, the drug is best avoided in pregnancy.

References
1 Higgins SP, Stedman YF, Chandiok P. Severe genital ulceration in two females following self-treatment with podophyllin solutions. *Genitourin Med* 1994; **70**: 146–7.
2 Bargman H. Is podophyllin a safe drug to use and can it be used in pregnancy? *Arch Dermatol* 1988; **124**: 1718–20.
3 Sundharam JA, Bargman H. Is podophyllin safe for use in pregnancy? *Arch Dermatol* 1989; **125**: 1000–1.

Resorcinol

Acute resorcinol poisoning is very rare, but an ointment containing 12.5% resorcinol applied to the napkin area produced dusky cyanosis, a maculopapular eruption, haemolytic anaemia and haemoglobinuria in an infant [1]. The continued application to large leg ulcers of ointments containing resorcinol has caused myxoedema and widespread blue-grey pigmentation mimicking ochronosis [2]. Application for warts caused generalized urticaria with angio-oedema, pompholyx of palms and soles, or papulovesicular eczema with pompholyx [3].

References
1 Cunningham AA. Resorcin poisoning. *Arch Dis Child* 1956; **31**: 173–6.
2 Thomas AE, Gisburn MA. Exogenous ochronosis and myxoedema from resorcinol. *Br J Dermatol* 1961; **73**: 378–81.
3 Barbaud A, Modiano P, Cocciale M *et al*. The topical application of resorcinol can provoke a systemic allergic reaction. *Br J Dermatol* 1996; **135**: 1014–5.

Salicylic acid and salicylates

The frequent application of salicylic acid ointments to extensive lesions will produce symptoms of salicylism even in adults [1–7]. Most cases of poisoning have occurred in children with psoriasis or ichthyosis [1,2]; fatal cases have been recorded [4]. Drowsiness and delusions are followed by acidosis, coma and death from respiratory failure.

References
1 Young CJ. Salicylate intoxication from cutaneous absorption of salicylate acid: review of the literature and report of a case. *South Med J* 1952; **45**: 1075–7.
2 Cawley EP, Peterson NT, Wheeler CE. Salicylic acid poisoning in dermatological therapy. *JAMA* 1953; **151**: 372–4.
3 Von Weiss JF, Lever WF. Percutaneous salicylic acid intoxication in psoriasis. *Arch Dermatol* 1964; **90**: 614–9.
4 Lindsey LP. Two cases of fatal salicylate poisoning after topical application of an anti-fungal solution. *Med J Aust* 1969; **1**: 353–4.
5 Davies MG, Vella Briffa D, Greaves MW. Systemic toxicity from topically applied salicylic acid. *BMJ* 1979; **i**: 661.
6 Anderson JAR, Ead RD. Percutaneous salicylate poisoning. *Clin Exp Dermatol* 1979; **4**: 349–51.
7 Pec J, Strmenova M, Palencarova E *et al*. Salicylate intoxication after use of topical salicylic acid ointment by a patient with psoriasis. *Cutis* 1992; **50**: 307–9.

Silver sulfadiazine

Topical application has caused hyperpigmentation [1], contact sensitivity [2], dermatitis [3] and scar-localized argyria [4].

References
1 Dupuis LL, Shear NH, Zucker RM. Hyperpigmentation due to topical application of silver sulfadiazine cream. *J Am Acad Dermatol* 1985; **12**: 1112–4.
2 Fraser-Moodie A. Sensitivity to silver in a patient treated with silver sulphadiazine (Flamazine). *Burns* 1992; **18**: 74–5.
3 McKenna SR, Latenser BA, Jones LM *et al*. Serious silver sulphadiazine and mafenide acetate dermatitis. *Burns* 1995; **21**: 310–2.
4 Fisher NM, Marsh E, Lazova R. Scar-localized argyria secondary to silver sulfadiazine cream. *J Am Acad Dermatol* 2003; **49**: 730–2.

Tretinoin

Topical tretinoin, used for the management of photo-aged skin, may cause erythema, peeling, burning and itching of the skin within days [1,2]. Pink discoloration without other signs may also develop, as may inflammation in solar keratoses.

References
1 Weiss JS, Ellis CN, Headington JT *et al*. Topical tretinoin improves photoaged skin: a double-blind, vehicle-controlled study. *JAMA* 1988; **259**: 527–32.
2 Weinstein GD, Nigra TP, Pochi PE *et al*. Topical tretinoin for treatment of photodamaged skin. *Arch Dermatol* 1991; **127**: 659–65.

Vitamin E

Vitamin E in deodorants has caused contact dermatitis [1].

Reference

1 Minkin W, Cohen HJ, Frank SB. Contact dermatitis from deodorants. *Arch Dermatol* 1973; **107**: 774–5.

Warfarin

An epidemic of haemorrhagic disease with fatalities occurred due to warfarin-contaminated talcs [1]. Poisoning has also been attributed to preparation of rodent baits [2].

References

1 Martin-Bouyer G, Linh PD, Tuan LC *et al.* Epidemic of haemorrhagic disease in Vietnamese infants caused by warfarin-contaminated talcs. *Lancet* 1983; **i**: 230–2.
2 Fristedt B, Sterner N. Warfarin intoxication from percutaneous absorption. *Arch Environ Health* 1965; **11**: 205–8.

Transdermal drug-delivery systems

Cutaneous reactions to transdermal therapeutic systems have been reviewed [1]. Transdermal delivery systems are available for clonidine, estradiol (oestradiol), glyceryl trinitrate, scopolamine, nicotine, and methylphenidate, and systems for other drugs are being developed. Erythema, irritancy, scaling, vesiculation, excoriation, induration, pigmentary changes and contact sensitization are not uncommon; the occlusive element may lead to miliaria rubra [2–14]. Systemic reactions may occur. Allergic skin reactions occur in up to 50% of patients with clonidine, but with glyceryl trinitrate, scopolamine, estradiol and testosterone [3] and methylphenidate [15] they are much less frequent. Reactivation of an area of contact dermatitis may develop via oral medication rarely [3]. Transdermal compared with oral metoprolol had comparable efficacy, and systemic side effects were comparable; 69% of patients had local side effects at the patch site (erythema, papular exanthem, pruritus, localized urticarial exanthem) [5]. Allergic contact dermatitis is recorded with nicotine [9–12], glyceryl trinitrate and estradiol [13], and methylphenidate [15]. Use of transdermal oestrogen patches resulted in systemic sensitization to ethanol [16]. Transdermal fentanyl patches have been associated with a diffuse rash [17].

References

1 Musel AL, Warshaw EM. Cutaneous reactions to transdermal therapeutic systems. *Dermatitis* 2006; **17**: 109–22.
2 Hogan DJ, Maibach HI. Adverse dermatologic reactions to transdermal drug delivery systems. *J Am Acad Dermatol* 1990; **22**: 811–4.
3 Holdiness MR. A review of contact dermatitis associated with transdermal therapeutic systems. *Contact Dermatitis* 1989; **20**: 3–9.
4 Berti JJ, Lipsky JJ. Transcutaneous drug delivery: a practical review. *Mayo Clin Proc* 1995; **70**: 581–6.
5 Jeck T, Edmonds D, Mengden T *et al.* Betablocking drugs in essential hypertension: transdermal bupranolol compared with oral metoprolol. *Int J Clin Pharmacol Res* 1992; **12**: 139–48.
6 Kolloch RE, Mehlburger L, Schumacher H, Gobel BO. Efficacy and safety of two different galenic formulations of a transdermal clonidine system in the treatment of hypertension. *Clin Auton Res* 1993; **3**: 373–8.
7 Antihypertensive Patch Italian Study (APIS) Investigators. One year efficacy and tolerability of clonidine administered by the transdermal route in patients with mild to moderate essential hypertension: a multicentre open label study. *Clin Auton Res* 1993; **3**: 379–83.
8 Breidthardt J, Schumacher H, Mehlburger L. Long-term (5 year) experience with transdermal clonidine in the treatment of mild to moderate hypertension. *Clin Auton Res* 1993; **3**: 385–90.
9 Bircher AJ, Howard H, Rufli T. Adverse skin reactions to nicotine in a transdermal therapeutic system. *Contact Dermatitis* 1991; **25**: 230–6.
10 Farm G. Contact allergy to nicotine from a nicotine patch. *Contact Dermatitis* 1993; **29**: 214–5.
11 Dwyer CM, Forsyth A. Allergic contact dermatitis from methacrylates in a nicotine transdermal patch. *Contact Dermatitis* 1994; **30**: 309–10.
12 Sudan BJ. Nicotine skin patch treatment and adverse reactions: skin irritation, skin sensitization, and nicotine as a hapten. *J Clin Psychopharmacol* 1995; **15**: 145–6.
13 Torres V, Lopes JC, Leite L. Allergic contact dermatitis from nitroglycerin and estradiol transdermal therapeutic systems. *Contact Dermatitis* 1992; **26**: 53–4.
14 Prisant LM. Transdermal clonidine skin reactions. *J Clin Hypertens* 2002; **4**: 136–8.
15 Warshaw EM, Paller AS, Fowler JF, Zirwas MJ. Practical management of cutaneous reactions to the methylphenidate transdermal system: recommendations from a dermatology expert panel consensus meeting. *Clin Ther* 2008; **30**: 326–37.
16 Grebe SK, Adams JD, Feek CM. Systemic sensitization to ethanol by transdermal estrogen patches. *Arch Dermatol* 1993; **129**: 379–80.
17 Stoukides CA, Stegman M. Diffuse rash associated with transdermal fentanyl. *Clin Pharm* 1992; **11**: 222.

Management of drug reactions

Diagnosis

Drug reactions, apart from fixed drug eruption, have non-specific clinical features, and it is often impossible to identify the offending chemical with certainty, especially when a patient with a suspected reaction is receiving many drugs simultaneously. Drug reactions may be mistaken for naturally occurring conditions and may therefore be overlooked. By the same token, it may on occasion be very difficult to state that a given eruption is drug induced. Experience with the type of reaction most commonly caused by particular drugs may enable the range of suspects to be narrowed, but familiar drugs may occasionally produce unfamiliar reactions and new drugs may mimic the reactions of the familiar. The assessment of a potential adverse drug reaction always necessitates taking a careful history, and may involve a trial of drug elimination, skin tests, *in vitro* tests and challenge by re-exposure [1–8].

A drug reaction may first become evident after the offending medication has been stopped, and depot injections may have delayed effects. Interpretation of elimination tests should be tempered by the knowledge that drug reactions may take weeks to settle. *In vivo* and *in vitro* tests are only applicable to truly allergic reactions. The success of drug skin testing, including prick and intradermal testing and patch testing, varies with the drug tested, with a high percentage of positive results on delayed readings of intradermal tests with beta-lactam antibiotics and heparins, or on patch testing with beta-lactam antibiotics, pristinamycin, carbamazepine and tetrazepam. The results of skin tests also depend on the clinical features of the adverse drug reaction. Regrettably, drug skin tests are as yet unreliable overall, even when apparently appropriate antigens are used; they may be hazardous [9–11]. *In vitro* tests are not widely available and are essentially research tools.

All too frequently, therefore, the diagnosis is no more than an assessment of probability. The fact that major disagreements

occurred between clinical pharmacologists asked to assess the likelihood of adverse drug reaction in two series confirms that identification of a responsible drug is often a subjective judgement [12,13]. An algorithm has been reported that provides detailed criteria for ranking the probability of whether a given drug is responsible for a reaction, based on (i) previous experience, (ii) the alternative aetiological candidates, (iii) timing of events, (iv) drug level and (v) the results of drug withdrawal and rechallenge [14,15]. A number of other algorithms have been developed to assist in the diagnosis of which, if any, drug is the cause of a given eruption [16–19]. In a recent review, 34 different methods for causality assessment of adverse drug reactions were identified, falling into three broad categories: expert judgement based on experience alone, algorithms for calculating the likelihood of a cause–effect relationship, and probabilistic methods (Bayesian approaches) using epidemiological information modified by the specific findings in a case to achieve a mathematical estimate of likely causation [20]. As a result of problems of reproducibility and validity, and because assessment methods are inevitably not entirely devoid of individual judgements, inter-rater reliability can be low. In conclusion, there is still no method universally accepted for causality assessment of ADRs [21].

References

1 Ring J. Diagnostik von Arzneimittel-bedingten Unverträglichkeitsreaktionz. *Hautarzt* 1987; **38**: S16–S22.
2 Shear NH. Diagnosing cutaneous adverse reactions to drugs. *Arch Dermatol* 1990; **126**: 94–7.
3 Nigen S, Knowles SR, Shear NH. Drug eruptions: approaching the diagnosis of drug-induced skin diseases. *J Drugs Dermatol* 2003; **2**: 278–99.
4 Romano A, Demoly P. Recent advances in the diagnosis of drug allergy. *Curr Opin Allergy Clin Immunol* 2007; **7**: 299–303.
5 Cotliar J. Approach to the patient with a suspected drug eruption. *Semin Cutan Med Surg* 2007; **26**: 147–54.
6 Knowles SR, Shear NH. Recognition and management of severe cutaneous drug reactions. *Dermatol Clin* 2007; **25**: 245–53, viii.
7 Sachs B, Al Masaoudi T, Merk HF, Erdmann S. Combined *in vivo* and *in vitro* approach for the characterization of penicillin-specific polyclonal lymphocyte reactivity: tolerance tests with safe penicillins instead of challenge with culprit drugs. *Br J Dermatol* 2004; **151**: 809–16.
8 Bousquet PJ, Kvedariene V, Co-Minh HB *et al*. Clinical presentation and time course in hypersensitivity reactions to beta-lactams. *Allergy* 2007; **62**: 872–6.
9 Bruynzeel D, van Ketel W. Skin tests in the diagnosis of maculopapular drug eruptions. *Semin Dermatol* 1987; **6**: 119–24.
10 Vaillant L, Camenen I, Lorette G. Patch testing with carbamazepine: reinduction of an exfoliative dermatitis. *Arch Dermatol* 1989; **125**: 299.
11 Machet L, Vaillant L, Dardaine V, Lorette G. Patch testing with clobazam: relapse of generalized drug eruption. *Contact Dermatitis* 1992; **26**: 347–8.
12 Karch FE, Smith CL, Kerzner B *et al*. Adverse drug reactions: a matter of opinion. *Clin Pharmacol Ther* 1976; **19**: 489–92.
13 Koch-Weser J, Sellers EM, Zacest R. The ambiguity of adverse drug reactions. *Eur J Clin Pharmacol* 1977; **11**: 75–8.
14 Kramer MS, Leventhal JM, Hutchinson TA, Feinstein AR. An algorithm for the operational assessment of adverse drug reactions. I. Background, description, and instructions for use. *JAMA* 1979; **242**: 623–32.
15 Leventhal JM, Hutchinson TA, Kramer MS, Feinstein AR. An algorithm for the operational assessment of adverse drug reactions. III. Results of tests among clinicians. *JAMA* 1979; **242**: 1991–4.
16 Naranjo CA, Busto U, Sellers EM *et al*. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981; **27**: 239–45.
17 Louick C, Lacouture P, Mitchell A *et al*. A study of adverse reaction algorithms in a drug surveillance program. *Clin Pharmacol Ther* 1985; **38**: 183–7.
18 Pere J, Begaud B, Harramburu F, Albin H. Computerized comparison of six adverse drug reaction assessment procedures. *Clin Pharmacol Ther* 1986; **40**: 451–61.
19 Ghajar BM, Lanctôt KL, Shear NH, Naranjo CA. Bayesian differential diagnosis of a cutaneous reaction associated with the administration of sulfonamides. *Semin Dermatol* 1989; **8**: 213–8.
20 Agbabiaka TB, Savović J, Ernst E. Methods for causality assessment of adverse drug reactions: a systematic review. *Drug Saf* 2008; **31**: 21–37.
21 Macedo AF, Marques FB, Ribeiro CF. Can decisional algorithms replace global introspection in the individual causality assessment of spontaneously reported ADRs? *Drug Saf* 2006; **29**: 697–702.

Drug history

Patients should be specifically questioned about laxatives, oral contraceptives, vaccines, homeopathic medicines, etc. as these may not be volunteered as medications. The case of a patient who developed DRESS after taking a dietary supplement containing phenobarbital purchased over the Internet illustrates this point [1]. They should be asked when they last took a tablet for any reason. The history should include information on when each drug was first taken relative to the onset of the reaction, whether the same or a related drug has been administered previously, and whether there is a prior history of drug sensitivity or contact dermatitis. Allergic drug reactions do not usually develop for at least 4 days, more commonly 7–10 days, after initial drug administration in a previously unsensitized individual. However, this time relationship cannot be relied on to differentiate between allergic and non-allergic reactions, as a previous sensitizing exposure may not have produced a clinically evident reaction.

Drug elimination

Resolution of a reaction on withdrawal of a drug is supportive incriminatory evidence but not diagnostic. Failure of a rash to subside on drug withdrawal does not necessarily exonerate it, as traces of the drug may persist for long periods and some reactions, once initiated, continue for many days without re-exposure to the drug. The unwitting substitution of a drug that is chemically closely related may perpetuate a reaction, as when an antihistamine of phenothiazine structure is prescribed to alleviate the symptoms of a reaction caused by another phenothiazine. Elimination diets have been advocated for diagnosis of food additive intolerance leading to urticaria [2,3].

References

1 Kubota Y, Yoneda K, Nakai K *et al*. DRESS in a patient taking a dietary supplement containing phenobarbital purchased over the internet. *Eur J Dermatol* 2008; **18**: 209–10.
2 Rudzki E, Czubalski K, Grzywa Z. Detection of urticaria with food additives intolerance by means of diet. *Dermatologica* 1980; **161**: 57–62.
3 Metcalfe DD, Sampson HA, eds. Workshop on experimental methodology for clinical studies of adverse reactions to foods and food additives. *J Allergy Clin Immunol* 1990; **86** (Suppl.): 421–42.

Skin testing

Skin testing has been extensively reviewed [1–16]. Drug skin tests are of three types: prick tests for immediate hypersensitivity, patch tests for delayed cellular hypersensitivity, and intradermal tests for both immediate and delayed hypersensitivity. Drug skin tests should be performed 6 weeks to 6 months after complete resolution of the reaction, as it is unknown whether positive results will

persist. Appropriate controls are essential to avoid false-positive results. Drug prick tests are performed on the volar forearm skin with the commercialized form of the drug, but with sequential dilutions in cases of urticaria. Intradermal tests are performed with sequential dilutions (10^{-4}, 10^{-3}, 10^{-2}, 10^{-1}) of 0.04 mL of a pure sterile or injectable form of the drug. Prick tests and intradermal tests should be read at 20 min and at 24 h. For patch tests, the commercial form of the drug should be tested diluted at 30% in petrolatum and/or water; the pure drug should be tested diluted at 10%. Lower concentrations should be used in severe drug reactions such as DRESS. It is useful to carry out the test on the site most affected in the initial reaction [17]. Patch tests are read at day 2 and day 4 and preferably also at 1 week. The quick patch test (application under a Finn chamber for 30 min) can be used in patients with severe hypersensitivity [18].

Prick tests and intradermal tests performed with sequential dilutions may be useful in the identification of patients who present with immediate IgE-related hypersensitivity reactions to certain drugs, such as penicillin and other beta-lactam antibiotics, agents used in general anaesthesia, tetanus toxoid, streptokinase, chymopapain, heterologous sera or insulin, and may thus aid in the prevention of anaphylaxis [8] (see also following sections). Older series suggested that positive patch tests were found in about 15% of patients with drug eruptions [2,3] and 25% of patients with penicillin allergy [1–3]. More recent reviews have indicated that drug patch tests are positive in 32–50% of patients with a drug eruption, being of potential value in generalized eczema, systemic contact dermatitis, photosensitivity (photopatch testing), maculopapular rashes, acute generalized exanthematous pustulosis (AGEP), and fixed drug eruption [12,13]. Significantly higher numbers of positive patch tests are seen in maculopapular than in urticarial reactions [11]. Drug skin tests are of occasional value in investigating Stevens–Johnson syndrome or TEN; relevant positive patch tests were seen in only 9% of 22 patients with Stevens–Johnson syndrome/TEN compared with 50% of 14 patients with AGEP [19]. Vasculitis related to circulating immune complexes is not amenable to investigation by skin testing.

Unfortunately, the usefulness of skin testing is limited by the fact that the significant antigenic determinants are unknown for most drugs. False-negative skin testing may occur because of poor absorption through the skin, because a metabolite rather than the substance administered in the test is the sensitizing antigen, or because testing is performed either too soon after a reaction, in a refractory period, or too late, so that the patient no longer demonstrates skin-test reactivity. False-positive reactions may also occur in drug allergy skin testing. Sodium lauryl sulphate in the commercial form of some drugs can induce irritation when they are patch tested as such, and positive patch tests to drugs can be related to an excipient [11,20], such as the surfactant polysorbate or the emulsion stabilizer carboxymethylcellulose, or even to sensitization to petrolatum [21] rather than the drug itself.

Moreover, intradermal testing is not always safe. A patch test with a solution of the drug will sometimes induce a generalized petechial reaction in patients with purpura caused by drug sensitivity, for example in carbromal or apronalide (Sedormid) purpura. Anaphylactoid responses may occur even in response to the small amounts of drug absorbed from a patch test. Re-elicitation of an exfoliative dermatitis [19,22] and relapse of a generalized drug eruption [23] have followed patch testing.

The results of skin-test reactions, including intradermal testing and patch testing, were evaluated in 242 patients with delayed-type (non-immediate) drug eruptions [14]. Intradermal testing was positive in 89.7% of patients, and patch tests were positive in 31.5% of cases; overall, 62% of patients had either a positive intradermal or patch test. Intradermal testing was more frequently positive in maculopapular rashes, erythema multiforme and erythrodermic rashes than in eczematous reactions, whereas positive patch tests were comparatively frequent in erythroderma, eczematous reactions and anticonvulsant-induced reactions. It was concluded that a combination of patch testing and intradermal testing is useful in the demonstration of causative agents in delayed-type drug eruptions. Skin tests, including patch tests and skin prick tests, were examined in 947 patients with a history of suspected cutaneous adverse drug reaction [16]. Positive patch test reactions to one or more drugs were seen in 10.8%, most often to beta-lactams, clindamycin and trimethoprim, whereas positive prick test reactions were seen in only 1.1% of patients. Eighty-one per cent of patch test-positive patients who underwent drug challenge developed exanthema, whereas only 9.6% of challenges in skin test-negative individuals resulted in a drug eruption, either exanthema, fixed drug eruption or urticaria. It was again concluded that skin testing, especially patch testing, was a useful screening method to find a cause of exanthematous adverse drug reactions.

References

1 Bruynzeel DP, von Blomberg-van der Flier M, Scheper RJ *et al.* Allergy for penicillin and the relevance of epicutaneous tests. *Dermatologica* 1985; **171**: 429–34.

2 Bruynzeel DP, van Ketel WG. Skin tests in the diagnosis of maculo-papular drug eruptions. *Semin Dermatol* 1987; **6**: 119–24.

3 Bruynzeel DP, van Ketel WG. Patch testing in drug eruptions. *Semin Dermatol* 1989; **8**: 196–203.

4 Calkin JM, Maibach HI. Delayed hypersensitivity drug reactions diagnosed by patch testing. *Contact Dermatitis* 1993; **29**: 223–33.

5 Alanko K, Stubb S, Reitamo S. Topical provocation of fixed drug eruption. *Br J Dermatol* 1987; **116**: 561–7.

6 Alanko K. Topical provocation of fixed drug eruption. A study of 30 patients. *Contact Dermatitis* 1994; **31**: 25–7.

7 Lee A-Y. Topical provocation in 31 cases of fixed drug eruption: change of causative drugs in 10 years. *Contact Dermatitis* 1998; **38**: 258–60.

8 Sussman GL, Dolovich J. Prevention of anaphylaxis. *Semin Dermatol* 1989; **8**: 158–65.

9 Deleo VA. Skin testing in systemic cutaneous drug reactions. *Lancet* 1998; **352**: 1488–90.

10 Barbaud A, Goncalo M, Bruynzeel D, Bircher A. Guidelines for performing skin tests with drugs in the investigation of cutaneous adverse drug reactions. *Contact Dermatitis* 2001; **45**: 321–8.

11 Barbaud A, Trechot P, Reichert-Penetrat S *et al.* Relevance of skin tests with drugs in investigating cutaneous adverse drug reactions. *Contact Dermatitis* 2001; **45**: 265–8.

12 Barbaud A. The use of skin testing in the investigation of toxidermia: from pathophysiology to the results of skin testing. *Therapie* 2002; **57**: 258–62.

13 Barbaud A. Drug patch testing in systemic cutaneous drug allergy. *Toxicology* 2005; **209**: 209–16.

14 Osawa J, Naito S, Aihara M *et al.* Evaluation of skin test reactions in patients with non-immediate type drug eruptions. *J Dermatol* 1990; **17**: 235–9.

15 Bruynzeel DP, Maibach HI. Patch testing in systemic drug eruptions. *Clin Dermatol* 1997; **15**: 479–84.

16 Lammintausta K, Kortekangas-Savolainen O. The usefulness of skin tests to prove drug hypersensitivity. *Br J Dermatol* 2005; **152**: 968–74.
17 Barbaud A, Trechot P, Reichert-Penetrat S *et al.* The usefulness of patch testing on the previously most severely affected site in a cutaneous adverse drug reaction to tetrazepam. *Contact Dermatitis* 2001; **44**: 259–60.
18 Oi M, Satoh T, Yokozeki H, Nishioka K. Detection of immediate-type reaction to the epitope of β-lactam antibiotics by the quick patch test. *Br J Dermatol* 2003; **148**: 182–3.
19 Wolkenstein P, Chosidow O, Fléchet ML *et al.* Patch testing in severe cutaneous adverse drug reactions including Stevens–Johnson syndrome and toxic epidermal necrolysis. *Contact Dermatitis* 1996; **35**: 234–6.
20 Grims RH, Kränke B, Aberer W. Pitfalls in drug allergy skin testing: false-positive reactions due to (hidden) additives. *Contact Dermatitis* 2006; **54**: 290–4.
21 Ulrich G, Schmutz JL, Trechot P *et al.* Sensitization to petrolatum: an unusual cause of false-positive drug patch-tests. *Allergy* 2004; **59**: 1006–9.
22 Vaillant L, Camenen I, Lorette G. Patch testing with carbamazepine: reinduction of an exfoliative dermatitis. *Arch Dermatol* 1989; **125**: 299.
23 Machet L, Vaillant L, Dardaine V, Lorette G. Patch testing with clobazam: relapse of generalized drug eruption. *Contact Dermatitis* 1992; **26**: 347–8.

Patch testing

Patch testing in a previously involved site, but not in normal skin, yielded a positive response in a proportion of cases of fixed drug eruption, especially with phenazone (pyrazolone) derivatives (e.g. phenylbutazone), but also with a sulphonamide, doxycycline, trimethoprim, chlormezanone, a barbiturate and carbamazepine [1]. In a series of 30 patients [2], positive reactions were always seen with phenazone salicylate and carbamazepine, and in one case with chlormezanone. Both positive and negative reactions were seen with trimethoprim, doxycycline and sulfadiazine. The vehicle used as a diluent for the drug may be important in determining whether a reaction is seen; use of dimethylsulfoxide as the vehicle may increase the number of positive patch tests [1,3,4]. Topical provocation of fixed drug eruption has also been reported with sulfamethoxazole [5], dimenhydrinate [6] and metronidazole [7]. However, other reports in the literature do not suggest that patch testing is helpful in fixed drug eruption [8].

Patch testing has supported a diagnosis of allergy, in the absence of topical sensitization, to diazepam, meprobamate and practolol [9], anticonvulsants including hydantoin derivatives and carbamazepine [10–12] (but only in patients with exfoliative dermatitis and maculopapular exanthem and not with fixed drug eruption, erythema multiforme or urticaria [11]), tartrazine dyes [13], chloramphenicol [14], diclofenac-induced maculopapular eruption [15], and in TEN induced by ampicillin [16]. Antibiotics (especially penicillin, ampicillin and other beta-lactam antibiotics [17,18], cephalosporins [19] and aminoglycosides), NSAIDs (pyrazolone derivatives and occasionally aspirin), neuroleptics (phenothiazines, barbiturates, meprobamate, benzodiazepines), β-blockers, gold salts, carbimazole, amantadine, corticosteroids, mitomycin, heparin and amide anaesthetics have all been associated with positive drug patch tests in allergic subjects. Positive patch tests to the following drugs have been found in patients with acute generalized exanthematous pustulosis: diltiazem [20,21], metronidazole [22], nystatin [23] and terbinafine [24].

References

1 Alanko K, Stubb S, Reitamo S. Topical provocation of fixed drug eruption. *Br J Dermatol* 1987; **116**: 561–7.
2 Alanko K. Topical provocation of fixed drug eruption. A study of 30 patients. *Contact Dermatitis* 1994; **31**: 25–7.
3 Özkaya-Bayazit E, Güngör H. Trimethoprim-induced fixed drug eruption: positive topical provocation on previously involved and uninvolved skin. *Contact Dermatitis* 1997; **39**: 87–8.
4 Özkaya-Bayazit H, Ozarmagan G. Topical provocation in 27 cases of cotrimoxazole-induced fixed drug eruption. *Contact Dermatitis* 1999; **41**: 185–9.
5 Oleaga JM, Aguirre A, Gonzalez M, Diaz-Perez JL. Topical provocation of fixed drug eruption due to sulphamethoxazole. *Contact Dermatitis* 1993; **29**: 155.
6 Smola H, Kruppa A, Hunzelmann N *et al.* Identification of dimenhydrinate as the causative agent in fixed drug eruption using patch-testing in previously affected skin. *Br J Dermatol* 1998; **138**: 920–1.
7 Short KA, Salisbury JR, Fuller LC. Fixed drug eruption following metronidazole therapy and the use of topical provocation testing in diagnosis. *Clin Exp Dermatol* 2002; **27**: 464–6.
8 Sehgal VN, Gangwani OP. Fixed drug eruption. Current concepts. *Int J Dermatol* 1987; **26**: 67–74.
9 Felix RE, Comaish JS. The value of patch and other skin tests in drug eruptions. *Lancet* 1984; **i**: 1017–9.
10 Houwerzijl J, de Gast GC, Nater JP. Patch test in drug eruptions. *Contact Dermatitis* 1982; **8**: 155–8.
11 Alanko K. Patch testing in cutaneous reactions caused by carbamazepine. *Contact Dermatitis* 1993; **29**: 254–7.
12 Jones M, Fernandez-Herrera J, Dorado JM *et al.* Epicutaneous test in carbamazepine cutaneous reactions. *Dermatology* 1994; **188**: 18–20.
13 Roeleveld CG, Van Ketel WG. Positive patch tests to the azo dye tartrazine. *Contact Dermatitis* 1976; **2**: 180.
14 Rudzki E, Grzywa Z, Maciejowska E. Drug reaction with positive patch tests to chloramphenicol. *Contact Dermatitis* 1976; **2**: 181.
15 Romano A, Pietrantonio F, Di Fonso M *et al.* Positivity of patch tests in cutaneous reaction to diclofenac. Two case reports. *Allergy* 1994; **49**: 57–9.
16 Tagami H, Tatsuda K, Iwatski K, Yamada M. Delayed hypersensitivity in ampicillin-induced toxic epidermal necrolysis. *Arch Dermatol* 1983; **119**: 910–3.
17 Galindo Bonilla PA, Garcia Rodriguez R, Feo Brito F *et al.* Patch testing for allergy to beta-lactam antibiotics. *Contact Dermatitis* 1994; **31**: 319–20.
18 Romano A, Di Fonso M, Pietrantonio F *et al.* Repeated patch testing in delayed hypersensitivity to beta-lactam antibiotics. *Contact Dermatitis* 1993; **28**: 190.
19 Gonzalo-Garijo MA, Rodríguez-Nevado I, de Argila D. Patch tests for diagnosis of delayed hypersensitivity to cephalosporins. *Allergol Immunopathol (Madr)* 2006; **34**: 39–41.
20 Vincente-Calleja JM, Aguirre A, Landa N *et al.* Acute generalized exanthematous pustulosis due to diltiazem: confirmation by patch testing. *Br J Dermatol* 1997; **137**: 837–9.
21 January V, Machet L, Gironet N *et al.* Acute generalized exanthematous pustulosis induced by diltiazem: value of patch testing. *Dermatology* 1998; **197**: 274–5.
22 Watsky KL. Acute generalised exanthematous pustulosis induced by metronidazole: the role of patch testing. *Arch Dermatol* 1999; **135**: 93–4.
23 Kuchler A, Hamm H, Weidenthaler-Barth B *et al.* Acute generalized exanthematous pustulosis following oral nystatin therapy: a report of three cases. *Br J Dermatol* 1997; **137**: 808–11.
24 Kempinaire A, De Raeve L, Merckx M *et al.* Terbinafine-induced acute generalized exanthematous pustulosis confirmed by positive patch-test result. *J Am Acad Dermatol* 1997; **37**: 653–5.

Penicillin

It is clearly important to exclude from treatment with penicillin those patients truly at risk of developing hypotensive episodes or fatal anaphylaxis. The role of skin testing in this situation has been reviewed [1–11]. Skin tests should be carried out using major-determinant antigens (benzylpenicilloyl polylysine, PPL) and minor-determinant mixture (benzylpenicillin, benzylpenicilloate and benzylpenilloate) antigens [12]. Allergopharma and Hollister-Stier stopped production of penicillin reagents around 2005, but new reagents from Diater (DAP) are a safe alternative [13,14]. Procedures have been published, and the reader is referred to the

original articles for details about methodology [12,15,16]. Epicutaneous testing should precede intradermal testing, and positive (histamine or opiate) and negative (diluent) controls should be included. False-negative results may be found after a systemic allergic reaction, as a result of a refractory period or temporary desensitization, so that skin testing should be postponed for at least 4–6 weeks [12].

There is a high incidence of wrongly diagnosed penicillin allergy on the basis of history, and a considerable proportion of patients who have had proven allergic reactions to penicillins eventually stop producing the IgE antibody responsible. A recent study in fact reported that even positive penicillin skin test results for patients with a remote history of non-life-threatening allergic reaction to penicillin were not associated with a greater prevalence of adverse reactions to oral challenge with penicillin than negative results [17]. In a large study, only 1% of 566 patients with a history of penicillin allergy, and negative skin tests to major determinant (PPL) and minor-determinant mixture and its components (potassium benzylpenicillin, benzylpenicilloate and benzylpenicilloyl-*N*-propylamine), had possibly IgE-mediated reactions [3]. Similarly, only 1.7% of 290 patients with a history of beta-lactam allergy and negative penicillin skin test results had urticarial adverse reactions [18]. In another study [6], 7.1% of 776 individuals with a previous history of penicillin allergy, and 1.7% of 4287 subjects negative by history, had positive skin tests to major determinant (PPL) and/or a minor-determinant mixture. Positive skin tests were seen in 17% and 12% of patients with a history of anaphylaxis or urticaria, respectively, but in only 4% with a history of an exanthem. Mild adverse reactions to skin tests occurred in 1% of patients positive by history and 9% of those with positive skin tests. In patients with negative skin tests who received benzylpenicillin or ampicillin, mild acute allergic reactions occurred in 0.5% of subjects negative by history and 2.9% of subjects positive by history. Thus, routine penicillin skin testing can facilitate the safe use of penicillin in 90% of individuals with a previous history of allergy [6]. Positive skin tests, an average of 5 years later, to major and minor determinants of benzylpenicillin and/or minor-determinant mixtures of ampicillin, amoxicillin or cloxacillin were found in 19% of 112 patients with a history of urticaria and angio-oedema or exanthem to penicillins and other semi-synthetic penicillins (most frequently ampicillin and amoxicillin) [7]. Skin-test reactivity was limited in about half to the semi-synthetic penicillin reagents derived from ampicillin, amoxicillin or cloxacillin. The existence of isolated skin-test positivity to reagents specific for ampicillin or amoxicillin, with good tolerance of major and minor penicillin determinants, has been confirmed in other reports [8,19,20], emphasizing the necessity for using reagents specific for the side-chains of these aminopenicillin drugs to exclude possible immediate hypersensitivity in patients who reacted to these antibiotics clinically [7–10,19,20]. Thus, 7% of 288 patients with a history of penicillin allergy reacted only to skin testing with amoxicillin and not to benzylpenicillin or phenoxymethylpenicillin diagnostic reagent determinants [21]; these would have been missed if the latter agents had been used alone.

Patients treated with penicillin after a negative skin test to PPL and to minor-determinant mixture develop IgE-mediated reactions only very rarely, and these are almost always mild and self-limited [1,3,6]. Thus, when adequately performed, negative skin tests indicate that the risk of a life-threatening reaction is almost negligible, and that any beta-lactam antibiotic may be safely given. In contrast, the risk of an acute allergic reaction, including respiratory obstruction or hypotension, with a positive history and positive skin test is 50–70%; the risk in a patient with a negative history but a positive skin test is about 10% [1,12,21]. Both patch testing and intradermal testing appeared valuable for the diagnosis of non-immediate reactions to aminopenicillins, but intradermal testing diagnosed more patients than patch testing [22].

Intradermal skin testing is generally safe, with few reactions, and although skin testing may rarely cause sensitization [23], it does not usually do so [12]. However, there is a risk, albeit very small, of fatality from skin testing [24]. A more major problem with skin testing is that use of the major determinant (PPL) alone misses about 10–25% of all positive subjects, and that even addition of benzylpenicillin G as the sole minor-determinant antigen misses 5–10% of positive subjects [25,26]. This is significant because patients with reactivity to minor antigenic determinants are thought to be at a higher risk for anaphylaxis [12,27]. In addition, as detailed above, reagents for detecting sensitivity to aminopenicillins (ampicillin and amoxicillin) should be used [16]. Comprehensive skin testing is therefore only practicable in specialized centres. Skin tests can give both false-positive and false-negative reactions [21]. Thus, it has been argued that a positive or negative result in an individual patient cannot be used to entirely reliably predict outcome [28].

Further difficulties are that skin prick tests have no predictive value in non-IgE-mediated reactions such as serum sickness, haemolytic anaemia, drug fever, interstitial nephritis, contact dermatitis, maculopapular exanthems or exfoliative dermatitis. Accelerated or late IgE-mediated reactions may occur despite a negative pretreatment skin test [1,12]. Positive intradermal skin-test reactions occurred in only 87% of patients with a history of delayed-type rashes induced by penicillins and cephalosporins, and who had positive oral provocation tests [29]. Oral challenge was positive in 18 of 33 patients with positive delayed skin testing and patch testing to ampicillin or amoxicillin, but also in 16 of 27 patients with negative allergy tests [30]. Skin testing is contraindicated where there is a history of exfoliative dermatitis, Stevens–Johnson syndrome or TEN.

There is clearly individual variation in the approach to the diagnosis and management of beta-lactam allergy [11], based on a survey of 3500 physician members and fellows of the American Academy of Allergy and Immunology and of allergy training programme directors in the USA. PPL and fresh penicillin G were used for skin testing by more than 86% of both respondent groups, whereas minor-determinant mixtures were used by only 40%. Epicutaneous followed by intradermal injection was the skin-test technique used by 86% of these allergists.

References

1 Weiss ME, Adkinson NF. Immediate hypersensitivity reactions to penicillin and related antibiotics. *Clin Allergy* 1988; **18**: 515–40.

2 Shepherd G, Mendelson L. The role of skin testing for penicillin allergy. *Arch Intern Med* 1992; **152**: 2505.

3 Sogn DD, Evans R III, Shepherd GM *et al.* Results of the National Institute of Allergy and Infectious Diseases Collaborative Clinical Trial to test the predictive

value of skin testing with major and minor penicillin derivatives in hospitalized adults. *Arch Intern Med* 1992; **152**: 1025–32.
4 Lin RY. A perspective on penicillin allergy. *Arch Intern Med* 1992; **152**: 930–7.
5 Weiss ME. Evaluation and treatment of patients with prior reactions to beta-lactam antibiotics. *Curr Clin Top Infect Dis* 1993; **3**: 131–45.
6 Gadde J, Spence M, Wheeler B, Adkinson NF Jr. Clinical experience with penicillin skin testing in a large inner-city STD clinic. *JAMA* 1993; **270**: 2456–63.
7 Silviu-Dan F, McPhillips S, Warrington RJ. The frequency of skin test reactions to side-chain penicillin determinants. *J Allergy Clin Immunol* 1993; **91**: 694–701.
8 Audicana M, Bernaola G, Urrutia I *et al.* Allergic reactions to betalactams: studies in a group of patients allergic to penicillin and evaluation of cross-reactivity with cephalosporin. *Allergy* 1994; **49**: 108–13.
9 Blanca M. The contribution of the side chain of penicillins in the induction of allergic reactions. *J Allergy Clin Immunol* 1994; **94**: 562–3.
10 Warrington RJ. The contribution of the side chain of penicillins in the induction of allergic reactions. *J Allergy Clin Immunol* 1995; **95**: 640.
11 Wickern GM, Nish WA, Bitner AS, Freeman TM. Allergy to beta-lactams: a survey of current practices. *J Allergy Clin Immunol* 1994; **94**: 725–31.
12 Weber EA, Knight A. Testing for allergy to antibiotics. *Semin Dermatol* 1989; **8**: 204–12.
13 Romano A, Viola M, Bousquet PJ *et al*. A comparison of the performance of two penicillin reagent kits in the diagnosis of beta-lactam hypersensitivity. *Allergy* 2007; **62**: 53–8.
14 Matheu V, Pérez E, González R *et al*. Assessment of a new brand of determinants for skin testing in a large group of patients with suspected beta-lactam allergy. *J Investig Allergol Clin Immunol* 2007; **17**: 257–60.
15 Adkinson NF Jr. Tests for immunoglobulin drug reactions. In: Rose NF, Friedman H, eds. *Manual of Clinical Immunology.* Washington, DC: American Society for Microbiology, 1986: 692–7.
16 Lisi P, Lapomarda V, Stingeni L *et al.* Skin tests in the diagnosis of eruptions caused by betalactams. *Contact Dermatitis* 1997; **37**: 151–4.
17 Goldberg A, Confino-Cohen R. Skin testing and oral penicillin challenge in patients with a history of remote penicillin allergy. *Ann Allergy Asthma Immunol* 2008; **100**: 37–43.
18 del Real GA, Rose ME, Ramirez-Atamoros MT *et al*. Penicillin skin testing in patients with a history of beta-lactam allergy. *Ann Allergy Asthma Immunol* 2007; **98**: 355–9.
19 Blanca M, Vega JM, Garcia J *et al.* Allergy to penicillin with good tolerance to other penicillins: study of the incidence in subjects allergic to betalactams. *Clin Exp Allergy* 1990; **20**: 475–81.
20 Vega JM, Blanca M, Garcia JJ *et al.* Immediate allergic reactions to amoxicillin. *Allergy* 1994; **49**: 317–22.
21 Green GR, Rosenblum AH, Sweet LC. Evaluation of penicillin hypersensitivity: value of clinical history and skin testing with penicilloyl-polylysine and penicillin G. A cooperative prospective study of the penicillin Study Group of the American Academy of Allergy. *J Allergy Clin Immunol* 1977; **60**: 339–45.
22 Torres MJ, Sánchez-Sabaté E, Alvarez J *et al*. Skin test evaluation in nonimmediate allergic reactions to penicillins. *Allergy* 2004; **59**: 219–24.
23 Nugent JS, Quinn JM, McGrath CM *et al.* Determination of the incidence of sensitization after penicillin skin testing. *Ann Allergy Asthma Immunol* 2003; **90**: 398–403.
24 Dogliotti M. An instance of fatal reaction to the penicillin scratch test. *Dermatologica* 1968; **136**: 489–96.
25 Gorevic PD, Levine BB. Desensitization of anaphylactic hypersensitivity specific for the penicilloate minor determinant of penicillin and carbenicillin. *J Allergy Clin Immunol* 1981; **68**: 267–72.
26 Sogn DD. Penicillin allergy. *J Allergy Clin Immunol* 1984; **74**: 589–93.
27 Adkinson NF Jr. Risk factors for drug allergy. *J Allergy Clin Immunol* 1984; **74**: 567–72.
28 Ewan P. Allergy to penicillin. *BMJ* 1991; **302**: 1462.
29 Aihara M, Ikezawa Z. Evaluation of the skin test reactions in patients with delayed type rash induced by penicillins and cephalosporins. *J Dermatol* 1987; **14**: 440–8.
30 Romano A, Di Fonso M, Papa G *et al.* Evaluation of adverse cutaneous reactions to aminopenicillins with emphasis on those manifested by maculopapular rashes. *Allergy* 1995; **50**: 113–8.

Iodinated contrast media

Diagnostic measures have been reviewed [1].

Reference

1 Kvedariene V, Martins P, Rouanet L, Demoly P. Diagnosis of iodinated contrast media hypersensitivity: results of a 6-year period. *Clin Exp Allergy* 2006; **36**: 1072–7.

Agents used in general anaesthesia

Intradermal [1–4] or prick [5,6] testing may be helpful in identifying the causative drug [7], and is essential in confirming lack of sensitivity to pancuronium before use in cases of documented sensitivity to other relaxants [3]. In one series of patients with a history of anaphylaxis during induction of general anaesthesia, skin testing was performed by the prick and intracutaneous methods with dilutions of thiobarbiturates, muscle relaxants or beta-lactam antibiotics [8]. No patient experienced a recurrence of anaphylaxis during subsequent general anaesthesia when agents producing positive skin tests were avoided, provided a premedication regimen of prednisone and diphenhydramine was given [8]. However, there is controversy over the diagnostic value of intradermal tests for the diagnosis of anaphylaxis during anaesthesia with the newer aminosteroidal neuromuscular blocking agents pancuronium, vecuronium and rocuronium and the benzylisoquinoline cisatracurium, as these all may induce nonspecific skin reactivity [9]. Strategies for prevention of reactions have been recently reviewed [10].

References

1 Fisher MMcD. Intradermal testing in the diagnosis of acute anaphylaxis during anaesthesia: results of five years experience. *Anaesth Intensive Care* 1979; **7**: 58–61.
2 Fisher MMcD. The diagnosis of acute anaphylactoid reactions to neuromuscular blocking agents: a commonly undiagnosed condition. *Anaesth Intensive Care* 1981; **9**: 235–41.
3 Galletly DC, Treuren BC. Anaphylactoid reactions during anaesthesia. Seven years' experience of intradermal testing. *Anaesthesia* 1985; **40**: 329–33.
4 Soetens FM, Smolders FJ, Meeuwis HC *et al.* Intradermal skin testing in the investigation of suspected anaphylactic reactions during anaesthesia: a retrospective survey. *Acta Anaesthesiol Belg* 2003; **54**: 59–63.
5 Leynadier F, Sansarricq M, Didier JM, Dry J. Prick tests in the diagnosis of anaphylaxis to general anaesthetics. *Br J Anaesth* 1987; **59**: 683–9.
6 Moneret-Vautrin DA, Laxenaire MC. Anaphylaxis to muscle relaxants: predictive tests. *Anaesthesia* 1990; **45**: 246–7.
7 Moneret-Vautrin DA, Laxenaire MC. Skin tests in diagnosis of allergy to muscle relaxants and other anesthetic drugs. *Monogr Allergy* 1992; **30**: 145–55.
8 Moscicki RA, Sockin SM, Corsello BF *et al.* Anaphylaxis during induction of general anesthesia: subsequent evaluation and management. *J Allergy Clin Immunol* 1990; **86**: 325–32.
9 Mertes PM, Moneret-Vautrin DA, Leynadier F, Laxenaire MC. Skin reactions to intradermal neuromuscular blocking agent injections: a randomized multicenter trial in healthy volunteers. *Anesthesiology* 2007; **107**: 245–52.
10 Liccardi G, Lobefalo G, Di Florio E *et al*. Strategies for the prevention of asthmatic, anaphylactic and anaphylactoid reactions during the administration of anesthetics and/or contrast media. *J Investig Allergol Clin Immunol* 2008; **18**: 1–11.

Local anaesthetics

Avoidance of local anaesthetics on the basis of a vague or equivocal history of a prior adverse reaction may result in substantial increased pain and risk. True allergic reactions probably constitute no more than 1% of all adverse reactions to these drugs, some, but

not the majority, of which are due to preservatives, especially parabens. Skin testing and/or incremental challenge beginning with diluted drug is a safe and effective method for identifying a drug that a patient with a history of an adverse reaction can tolerate [1–8]. Patients with positive patch tests to local anaesthetics and a negative history of anaphylactoid reactions rarely have positive intradermal skin tests. The risk of anaphylactic reactions with amide local anaesthetics (except butanilicaine) is therefore low in such patients [3]. Conversely, patients with anaphylactic reactions to local anaesthetics are usually patch-test negative [3]. Skin testing may produce systemic adverse reactions, especially with undiluted drug. False-positive reactions occur, but false-negative reactions have not been reported, and most skin-tested patients who tolerate a local anaesthetic are skin-test negative to the drug. The choice of a drug for use in skin testing and incremental challenge may be facilitated by current concepts of non-cross-reacting groups of local anaesthetics. Thus, benzoic acid esters, both those with and without *p*-aminobenzoyl groups, do not cross-react with amide local anaesthetic agents.

References

1 Schatz M. Skin testing and incremental challenge in the evaluation of adverse reactions of local anesthetics. *J Allergy Clin Immunol* 1984; **74**: 606–16.
2 Fisher MMcD, Graham R. Adverse responses to local anaesthetics. *Anaesth Intensive Care* 1984; **12**: 325–7.
3 Ruzicka T, Gerstmeier M, Przybilla B, Ring J. Allergy to local anesthetics: comparison of patch test with prick and intradermal test results. *J Am Acad Dermatol* 1987; **16**: 1202–8.
4 Glinert RJ, Zachary CB. Local anesthetic allergy. Its recognition and avoidance. *J Dermatol Surg Oncol* 1991; **17**: 491–6.
5 Hodgson TA, Shirlaw PJ, Challacombe SJ. Skin testing after anaphylactoid reactions to dental local anesthetics. A comparison with controls. *Oral Surg Oral Med Oral Pathol* 1993; **75**: 706–11.
6 Wasserfallen JB, Frei PC. Long-term evaluation of usefulness of skin and incremental challenge tests in patients with history of adverse reaction to local anesthetics. *Allergy* 1995; **50**: 162–5.
7 Gall H, Kaufmann R, Kalveram CM. Adverse reactions to local anesthetics: analysis of 197 cases. *J Allergy Clin Immunol* 1996; **97**: 933–7.
8 Phillips JF, Yates AB, Deshazo RD. Approach to patients with suspected hypersensitivity to local anesthetics. *Am J Med Sci* 2007; **334**: 190–6.

Analgesics and NSAIDs

Prick tests were positive in only 13% of 117 patients with a history suggestive of anaphylactoid reactions to a variety of mild analgesics, including NSAIDs [1]. Delayed-reading intradermal tests were more sensitive than patch tests in the diagnosis of non-immediate reactions to pyrazolones [2].

References

1 Przybilla B, Ring J, Harle R, Galosi A. Hauttestung mit Schmerzmittelinhaltsstoffen bei Patienten mit anaphylaktoiden Unverträgli-chkeitsreaktionen auf 'leichte' Analgetika. *Hautarzt* 1985; **36**: 682–7.
2 Macías E, Ruiz A, Moreno E *et al*. Usefulness of intradermal test and patch test in the diagnosis of nonimmediate reactions to metamizol. *Allergy* 2007; **62**: 1462–4.

Heparin

Provocation testing may be a useful diagnostic measure [1–7]. Low-molecular-weight heparin analogues may be satisfactorily substituted in some patients with this reaction, but are not always tolerated [2]. Subcutaneous testing of a panel of heparins, danaparoid and desirudin (hirudin) is recommended for determining acceptable treatment options for patients allergic to specific heparins [3,6]. In type I reactions, or in the presence of skin necrosis with or without heparin-induced thrombocytopenia, a low-molecular-weight heparin should be replaced by danaparoid sodium or hirudin. In the presence of a negative subcutaneous provocation test, the compound can be used with little risk. If all types of low-molecular-weight heparin and danaparoid sodium show positive skin tests, oral anticoagulants should be used, and intravenous injections of any kind of heparin should be avoided because of the potential for anaphylactic shock.

References

1 Zimmermann R, Harenberg J, Weber E *et al*. Behandlung bei heparin-induzierter kutaner Reaktion mit einem niedermolekularen Heparin-Analog. *Dtsch Med Wochenschr* 1984; **109**: 1326–8.
2 Klein GF, Kofler H, Wol H, Fritsch PO. Eczema-like, erythematous, infiltrated plaques: a common side effect of subcutaneous heparin therapy. *J Am Acad Dermatol* 1989; **21**: 703–7.
3 Wutschert R, Piletta P, Bounameaux H. Adverse skin reactions to low molecular weight heparins: frequency, management and prevention. *Drug Saf* 1999; **20**: 515–25.
4 Koch P, Münßinger T, Rupp-John C, Uhl K. Delayed-type hypersensitivity skin reactions caused by subcutaneous unfractionated and low-molecular-weight heparins: tolerance of a new recombinant hirudin. *J Am Acad Dermatol* 2000; **42**: 612–9.
5 Szolar-Platzer C, Aberer W, Kranke B. Delayed-type skin reaction to the heparin-alternative danaparoid. *J Am Acad Dermatol* 2000; **43**: 920–2.
6 Grassegger A, Fritsch P, Reider N. Delayed-type hypersensitivity and cross-reactivity to heparins and danaparoid: a prospective study. *Dermatol Surg* 2001; **27**: 47–52.
7 Ludwig RJ, Schindewolf M, Utikal J *et al*. Management of cutaneous type IV hypersensitivity reactions induced by heparin. *Thromb Haemost* 2006; **96**: 611–7.

Skin testing in urticaria

Skin tests have been advocated as useful in the investigation of chronic urticaria [1,2]. Patch testing with a series of penicillins was positive in 6.9% of patients in one study [1], and there were positive intracutaneous tests to cilligen and/or penicillin G in 21.5% of patients. Avoidance of dietary dairy produce, which potentially might have contained penicillin, alleviated the urticaria in 50% of the penicillin-allergic patients. The reported prevalence of positive intracutaneous tests to penicillin was much higher in this study than in other reported series in the literature.

References

1 Boonk WJ, van Ketel WG. Skin testing in chronic urticaria. *Dermatologica* 1981; **163**: 151–9.
2 Antony SJ, Fisher RH. Association of penicillin allergy with idiopathic anaphylaxis. *J Fam Pract* 1993; **37**: 499–502.

In vitro tests

Tests for IgE antibody

The detection of drug-specific circulating antibodies does not prove an allergy. It is important to record when a blood test is taken in relation to the evolution of a drug reaction, as the antibody response to a drug has a finite duration. For example, antipenicillin IgE antibodies begin to disappear within 10–30 days. Radioallergosorbent tests (RASTs) for drug-specific IgE class antibody are available for penicillin, insulin and ACTH. RAST detects specific IgE antibody to the penicilloyl determinant, and is positive in 60–90% of patients with a positive skin test to PPL [1,2];

however, there is no *in vitro* test for minor-determinant antigens, and therefore in practice this test is of very limited use [2,3]. The specificity of beta-lactam-specific IgE measurement is good but sensitivity is low [4]. Investigation of cross-reactivity of antibodies to penicillin in 123 patients with a history of penicillin allergy, using enzyme-linked immunosorbent assay, detected IgE antibodies specific to amoxicillin, ampicillin or flucloxacillin, respectively, in three patients [5]. These antibodies did not cross-react with other penicillin antigens, and would have been missed had testing involved only the use of benzylpenicillin. Thus, allergy to semisynthetic penicillins can occur without allergy to benzylpenicillin, negative tests specific for benzylpenicillin or phenoxymethylpenicillin cannot be generalized to other penicillins, and exclusive reliance on benzylpenicilloyl RAST to detect allergy to semisynthetic penicillins could lead to serious adverse consequences [6]. The Pharmacia CAP System RAST FEIA amoxicilloyl and benzylpenicilloyl test is beneficial for evaluating patients allergic to beta-lactams [7]. IgE antibodies specific for 1-phenyl-2,3-dimethyl-3-pyrazoline-5-one were found in 17 of 19 serum samples from individuals sensitive to pyrazoline drugs with 4-aminoantipyrine discs by RAST [8].

References

1 Wide L, Juhlin L. Detection of penicillin allergy of the immediate type by radioimmunoassay of reagins (IgE) to penicilloyl conjugates. *Clin Allergy* 1971; **1**: 171–7.
2 Weiss ME, Adkinson NF. Immediate hypersensitivity reactions to penicillin and related antibiotics. *Clin Allergy* 1988; **18**: 515–40.
3 Ewan P. Allergy to penicillin. *BMJ* 1991; **302**: 1462.
4 Fontaine C, Mayorga C, Bousquet PJ *et al*. Relevance of the determination of serum-specific IgE antibodies in the diagnosis of immediate beta-lactam allergy. *Allergy* 2007; **62**: 47–52.
5 Christie G, Coleman J, Newby S *et al*. A survey of the prevalence of penicillin specific IgG, IgM and IgE antibodies detected by ELISA and defined by hapten inhibition in patients with suspected penicillin allergy and in healthy volunteers. *Br J Clin Pharmacol* 1988; **25**: 381–6.
6 Walley T, Coleman J. Allergy to penicillin. *BMJ* 1991; **302**: 1462–3.
7 Blanca M, Mayorga C, Torres MJ *et al*. Clinical evaluation of Pharmacia CAP System RAST FEIA amoxicilloyl and benzylpenicilloyl in patients with penicillin allergy. *Allergy* 2001; **56**: 862–70.
8 Zhu D, Becker WM, Schulz KH *et al*. Detection of IgE antibodies specific for 1-phenyl-2,3-dimethyl-3-pyrazoline-5-one by RAST: a serological diagnostic method for sensitivity to pyrazoline drugs. *Asian Pac J Allergy Immunol* 1992; **10**: 95–101.

Miscellaneous in vitro tests

The histamine-release test [1], basophil degranulation test [2–6] and passive haemagglutination test [7] are of limited use. A positive basophil degranulation assay, which involves binding of drug to specific IgE on the basophil surface, has been reported with penicillin, erythromycin, sulphonamides, non-steroidals and aspirin, but false-negative results are common. The leukocyte and macrophage migration inhibition tests [8–11], platelet-activating factor release from white blood cells after antigenic challenge as tested by platelet aggregation [12], and the lymphocyte toxicity assay [13–16] have essentially been research tools.

A number of drugs have been reported to induce lymphocyte proliferation, as determined by incorporation of ^{3}H-thymidine, in patients with drug eruptions, including penicillin, carbamazepine, phenytoin, furosemide, sulfamethoxazole and hydrochlorothiazide [17–22]. Positive lymphocyte transformation test reactions were obtained when the test was performed at the acute stage (within 1 week after the onset of the rash) but not the recovery stage in maculopapular eruptions and SJS/TEN, and in the recovery stage (5–8 weeks after the rash) but not the acute stage in DRESS [23]. However, in general, only low levels of stimulation are observed, perhaps because the antigen responsible for the reaction is a drug metabolite rather than the parent compound, and the significance of the test is difficult to interpret. Addition of human liver microsomes containing cytochrome P-450 enzymes to the reaction medium of the lymphocyte transformation test, in order to aid generation of potentially reactive drug metabolites, may increase the sensitivity of *in vitro* detection of T-cell reactivity [24,25]. Upregulation of CD69 expression on T cells after 48 h of drug-stimulation [26] and *in vitro* drug-induced IFN-γ release from peripheral blood lymphocytes [27] have been claimed to be promising diagnostic tools in cutaneous adverse drug reactions.

References

1 Perelmutter L, Eisen AH. Studies on histamine release from leukocytes of penicillin-sensitive individuals. *Int Arch Allergy* 1970; **38**: 104–12.
2 Shelley WB. Indirect basophil degranulation test for allergy to penicillin and other drugs. *JAMA* 1963; **184**: 171–8.
3 Sastre Dominguez J, Sastre Castillo A. Human basophil degranulation test in drug allergy. *Allergol Immunopathol* 1986; **14**: 221–8.
4 Harrabi S, Loiseau P, Dehenry J. A technic for human basophil degranulation. *Allerg Immunol* 1987; **19**: 287–9.
5 Sanz ML, Gamboa PM, Antépara I *et al*. Flow cytometric basophil activation test by detection of CD63 expression in patients with immediate-type reactions to betalactam antibiotics. *Clin Exp Allergy* 2002; **32**: 277–86.
6 Rodríguez-Trabado A, Cámara-Hijón C, Ramos-Cantariño A *et al*. Basophil activation test for the *in vitro* diagnosis of nonsteroidal anti-inflammatory drug hypersensitivity. *Allergy Asthma Proc* 2008; **29**: 241–9.
7 Thiel JA, Mitchell S, Parker CW. The specificity of hemagglutination reactions in human and experimental penicillin hypersensitivity. *J Allergy* 1964; **35**: 399–424.
8 David JR, al-Askari S, Lawrence HS, Thomas L. Delayed hypersensitivity *in vitro*. I. The specificity of inhibition of cell migration by antigens. *J Immunol* 1964; **93**: 264–73.
9 Halevy S, Grunwald MH, Sandbank M *et al*. Macrophage migration inhibition factor (MIF) in drug eruption. *Arch Dermatol* 1990; **126**: 48–51.
10 Lazarov A, Livni E, Halevy S. Generalised pustular drug eruptions: confirmation by *in vitro* tests. *J Eur Acad Dermatol Venereol* 1998; **10**: 36–41.
11 Kivity S. Fixed drug eruption to multiple drugs: clinical and laboratory investigation. *Int J Dermatol* 1991; **30**: 149–51.
12 Dunoyer-Geindre S, Ludi F *et al*. PAF acether release on antigenic challenge. A method for the investigation of drug allergic reactions. *Allergy* 1992; **47**: 50–4.
13 Shear N, Spielberg S, Grant D *et al*. Differences in metabolism of sulfonamides predisposing to idiosyncratic toxicity. *Ann Intern Med* 1986; **105**: 179–84.
14 Shear N, Spielberg S. Anticonvulsant hypersensitivity syndrome. *In vitro* assessment of risk. *J Clin Invest* 1989; **82**: 1826–32.
15 Rieder MJ, Uetrecht J, Shear NH *et al*. Diagnosis of sulfonamide hypersensitivity reactions by in-vitro 'rechallenge' with hydroxylamine metabolites. *Ann Intern Med* 1989; **110**: 286–9.
16 Shear NH. Diagnosing cutaneous adverse reactions to drugs. *Arch Dermatol* 1990; **126**: 94–7.
17 Rocklin RE, David JR. Detection *in vitro* of cellular hypersensitivity to drugs. *J Allergy Clin Immunol* 1971; **48**: 276–82.
18 Gimenez-Camarasa JM, Garcia-Calderon P, de Moragas JM. Lymphocyte transformation test in fixed drug eruption. *N Engl J Med* 1975; **292**: 819–21.
19 Dobozy A, Hunyadi J, Kenderessy AS, Simon N. Lymphocyte transformation test in detection of drug hypersensitivity. *Clin Exp Dermatol* 1981; **6**: 367–72.
20 Sarkany I. Role of lymphocyte transformation in drug allergy. *Int J Dermatol* 1981; **8**: 544–5.
21 Roujeau JC, Albengres E, Moritz S *et al*. Lymphocyte transformation test in drug-induced toxic epidermal necrolysis. *Int Arch Allergy Appl Immunol* 1985; **78**: 22–4.

22 Zakrzewska JM, Ivanyi L. *In vitro* lymphocyte proliferation by carbamazepine, carbamazepine-10,11-epoxide, and oxcarbazepine in the diagnosis of drug-induced hypersensitivity. *J Allergy Clin Immunol* 1988; **82**: 1826–32.
23 Kano Y, Hirahara K, Mitsuyama Y *et al*. Utility of the lymphocyte transformation test in the diagnosis of drug sensitivity: dependence on its timing and the type of drug eruption. *Allergy* 2007; **62**: 1439–44.
24 Merk HF, Baron J, Kawadubo Y *et al.* Metabolites and allergic drug reactions. *Clin Exp Allergy* 1998; **28** (Suppl. 4): 21–4.
25 Sachs B, Erdmann S, Al-Masaoudi T, Merk HF. *In vitro* drug allergy detection system incorporating human liver microsomes in chlorazepate-induced skin rash: drug-specific proliferation associated with interleukin-5 secretion. *Br J Dermatol* 2001; **144**: 316–20.
26 Beeler A, Zaccaria L, Kawabata T. CD69 upregulation on T cells as an *in vitro* marker for delayed-type drug hypersensitivity. *Allergy* 2008; **63**: 181–8.
27 Halevy S, Cohen AD, Grossman N. Clinical implications of *in vitro* drug-induced interferon gamma release from peripheral blood lymphocytes in cutaneous adverse drug reactions. *J Am Acad Dermatol* 2005; **52**: 254–61.

Challenge tests

A drug suspected of causing a drug eruption may be reliably incriminated by the reaction in response to a test dose administered after recovery. However, fatal reactions have occurred to test doses, for example penicillin and quinine, and provocation tests should only be performed in exceptional circumstances [1–6]. A history of Stevens–Johnson syndrome or TEN constitutes an absolute contraindication to drug challenge, and test dosing in reactions of anaphylactic type, blood dyscrasia or SLE-like reaction is seldom advisable. Sensitization to two antibiotics without shared chemical structures can occur during the same episode of a cutaneous adverse drug reaction; thus, reintroduction of any drug suspected should be performed under hospital surveillance, even if skin tests with other drugs taken simultaneously were positive [7]. Challenge tests are open to misinterpretation [6], because a very small challenge dose may fail to elicit a reaction that a therapeutic dose would provoke, because of false positives, and because false negatives may occur as a result of a refractory period following a reaction [8]. Of 1001 challenges in 784 patients carried out from 1975 to 2000, 13% of patients developed a positive challenge reaction; antimicrobial drugs were most commonly suspected, accounting for 67% of challenges and 66% of the positive reactions, and exanthema was the most common skin reaction (72%), followed by fixed drug eruption (16%) and urticaria (12%), with a single serious challenge reaction to salazosulfapyridine [9].

Test dosing in patients with drug reactions such as fixed drug eruption, which are not potentially fatal, may be helpful [5]. Topical challenge in the form of patch testing in a previously involved site may yield a positive response in a high proportion of such cases [10]. Oral provocation tests using tartrazine, and other food additives such as sodium benzoate, have been advocated for the investigation of chronic urticaria or food intolerance [11–14]. Protocols for the analysis of adverse reactions to foods and food additives have been published [15].

References

1 Kauppinen K. Cutaneous reactions to drugs. With special reference to severe mucocutaneous bullous eruptions and sulphonamides. *Acta Derm Venereol Suppl (Stockh)* 1972; **68**: 1–89.
2 Kauppinen K. Rational performance of drug challenge in cutaneous hypersensitivity. *Semin Dermatol* 1983; **2**: 117–230.
3 Kauppinen K, Stubb S. Drug eruptions. Causative agents and clinical types. *Acta Derm Venereol (Stockh)* 1984; **64**: 320–4.
4 Girard M. Conclusiveness of rechallenge in the interpretation of adverse drug reactions. *Br J Clin Pharmacol* 1987; **23**: 73–9.
5 Kauppinen K, Alanko K. Oral provocation: uses. *Semin Dermatol* 1989; **8**: 187–91.
6 Girard M. Oral provocation: limitations. *Semin Dermatol* 1989; **8**: 192–5.
7 Dellestable P, Weber-Muller F, Tréchot P *et al*. Co-sensitization to drugs belonging to different chemical classes during the same episode of cutaneous adverse drug reaction: two cases. *Ann Dermatol Venereol* 2007; **134**: 655–8.
8 Stevenson DD, Simon RA, Mathison DA. Aspirin-sensitive asthma: tolerance to aspirin after positive oral aspirin challenges. *J Allergy Clin Immunol* 1980; **66**: 82–8.
9 Lammintausta K, Kortekangas-Savolainen O. Oral challenge in patients with suspected cutaneous adverse drug reactions: findings in 784 patients during a 25-year-period. *Acta Derm Venereol* 2005; **85**: 491–6.
10 Alanko K, Stubb S, Reitamo S. Topical provocation of fixed drug eruption. *Br J Dermatol* 1987; **116**: 561–7.
11 Warin RP, Smith RJ. Challenge test battery in chronic urticaria. *Br J Dermatol* 1976; **94**: 401–6.
12 Supramaniam G, Warner JO. Artificial food additive intolerance in patients with angio-oedema and urticaria. *Lancet* 1986; **ii**: 907–9.
13 Wilson N, Scott A. A double blind assessment of additive intolerance in children using a 12 day challenge period at home. *Clin Exp Allergy* 1989; **19**: 267–72.
14 Michils A, Vandermoten G, Duchateau J, Yemault J-C. Anaphylaxis with sodium benzoate. *Lancet* 1991; **337**: 1424–5.
15 Metcalfe DD, Sampson HA, eds. Workshop on experimental methodology for clinical studies of adverse reactions to foods and food additives. *J Allergy Clin Immunol* 1990; **86** (Suppl.): 421–42.

Treatment

Clearly, prevention is better than cure [1,2]. Drugs implicated in a previous reaction should be avoided; the patient should be asked about allergies, and hypersensitivity records in the notes and on prescription charts should be checked. In the case of suspected penicillin allergy, an alternative antibiotic, preferably with a non-beta-lactam structure such as erythromycin, should be substituted; use of griseofulvin should be avoided as it has a 5–10% cross-reactivity based on non-structural mechanisms [2]. However, lack of a positive history does not eliminate the possibility of an allergic reaction, as in the case of penicillin hypersensitivity [3]. Where it is essential to readminister one of a group of drugs to a patient with a previous history of an adverse reaction to a related medication, as with radiographic contrast media and agents used in general anaesthesia, then if possible preliminary skin testing should be carried out to enable identification of safe alternative therapy. In addition, the procedure should be covered by premedication with oral corticosteroids and antihistamines, with or without epinephrine, in order to obtund the onset of an anaphylactic reaction. In the situation where there is no acceptable alternative for an essential drug, then rapid desensitization therapy should be considered.

The approach to treatment of an established presumed drug eruption obviously depends on the severity of the reaction. For many minor conditions, withdrawal of the suspected drug, and symptomatic therapy with emollients, mild to moderately potent topical corticosteroids and systemic antihistamines where indicated, is all that is necessary. When a patient is receiving multiple drugs, it is wise to withdraw all but the essential medications, and to consider substituting alternative, non-cross-reacting drugs for the remainder. Because of the wide variety of patterns of drug reaction, it is only possible to summarize the therapy of individual

reactions here. The reader is referred to the discussion of the more serious conditions in this book and elsewhere [1–9].

References

1 Sheffer AL, Pennoyer MD. Management of adverse drug reactions. *J Allergy Clin Immunol* 1984; **74**: 580–8.
2 Fellner MJ, Ledesma GN. Current comments on cutaneous allergy. Management of antibiotic allergies. *Int J Dermatol* 1991; **30**: 184–5.
3 Weber EA, Knight A. Testing for allergy to antibiotics. *Semin Dermatol* 1989; **8**: 204–12.
4 Braun-Falco O, Plewig G, Wolff HH, Winkelmann RK. *Dermatology*. Berlin: Springer, 1991.
5 Breathnach SM, Hintner H. *Adverse Drug Reactions and the Skin*. Oxford: Blackwell Scientific Publications, 1992.
6 Breathnach SM. Management of drug eruptions. Part II. Diagnosis and treatment. *Australas J Dermatol* 1995; **36**: 187–91.
7 Drake LA, Dinehart SM, Farmer ER *et al.* Guidelines of care for cutaneous adverse drug reactions. American Academy of Dermatology. *J Am Acad Dermatol* 1996; **35**: 458–61.
8 Ellis AK, Day JH. Diagnosis and management of anaphylaxis. *Can Med Assoc J* 2003; **169**: 307–11.
9 Bahna SL, Khalili B. New concepts in the management of adverse drug reactions. *Allergy Asthma Proc* 2007; **28**: 517–24.

Anaphylaxis

The management of severe acute urticaria and anaphylaxis is detailed in Table 75.21.

Exfoliative dermatitis/erythroderma

The complications of this potentially serious drug-induced condition include hypothermia, fluid and electrolyte loss, infection, high-output cardiac failure, stress ulceration and gastrointestinal haemorrhage, malabsorption and venous thrombosis. The management [1,2] includes maintenance of body temperature and fluid and electrolyte balance, treatment of cardiac failure by use of digitalization and diuretics (avoiding vasodilator drugs), and administration of intravenous albumin for hypoalbuminaemia. If the patient does not respond rapidly to potent topical corticosteroids, prednisolone 40–60 mg/day should be given. This approach also applies to the anticonvulsant hypersensitivity syndrome (DRESS); oral corticosteroid therapy has been helpful [3,4].

Table 75.21 Management of anaphlyaxis.

Stop drug administration
Give 0.5–1 mL epinephrine (adrenaline) 1 in 1000 i.m. immediately
Check airway and give oxygen
Antihistamines
Chlorpheniramine maleate 10–20 mg i.v. *or*
Hydroxyzine 25–50 mg i.m. and four times daily orally *or*
H_1 and H_2 antagonists *or*
Cimetidine 300 mg i.v. 6 hourly
Corticosteroids
Hydrocortisone 250 mg i.v. and 100 mg 6 hourly
Prednisolone 40 mg/day for 3 days
Give i.v. 0.9% NaCl or 5% glucose
Monitor blood pressure and pulse
For bronchospasm
Aminophylline 250 mg i.v. over 5 min and 250 mg in 500 mL 0.9% NaCl over 6 h *or*
Nebulized terbutaline, salbutamol or metaproterenol

References

1 Marks J. Erythroderma and its management. *Clin Exp Dermatol* 1982; **7**: 415–22.
2 Roujeau JC, Revuz J. Intensive care in dermatology. In: Champion RH, Pye RJ, eds. *Recent Advances in Dermatology*, Vol. 8. Edinburgh: Churchill Livingstone, 1990: 85–99.
3 Murphy JM, Mashman J, Miller JD, Bell JB. Suppression of carbamazepine-induced rash with prednisone. *Neurology* 1991; **41**: 144–5.
4 Chopra S, Levell NJ, Cowley G, Gilkes JJ. Systemic corticosteroids in the phenytoin hypersensitivity syndrome. *Br J Dermatol* 1996; **134**: 1109–12.

Toxic epidermal necrolysis

See Chapter 76.

Desensitization

It is possible to induce a state of antigen-specific mast cell unresponsiveness, in patients with type I IgE-mediated reactions, if a drug is essential for a patient's well-being and no alternative is available. Desensitization markedly diminishes the risk of anaphylactic reactions but not of non-IgE-mediated reactions; it should only be carried out in an intensive care setting. Mechanisms proposed to explain the development of tolerance following desensitization procedures include mediator depletion, tachyphylaxis, production of blocking antibodies, or change in the level of specific IgE antibodies.

Desensitization is most frequently carried out for patients with penicillin allergy, with increasing doses of penicillin being administered over 3–5 h [1–4]. The drug is usually given orally; increasing doses are given, starting with a very weak concentration (e.g. one millionth of the therapeutic dose) and working up to a full dose. There have been no severe allergic reactions recorded in patients who completed oral desensitization to penicillin; about 35% experience minor cutaneous reactions including pruritus or urticaria. Although the protection is usually short-lived, tolerance can be maintained by long-term administration of low doses of oral penicillin. Patients with sensitivity to vancomycin [5], 5-aminosalicylic acid [6] and allopurinol [7] have been successfully desensitized. Intravenous and oral rapid desensitization protocols are available for taxenes, platinums, doxorubicin and monoclonal antibodies [8].

Patients with HIV infection with previous cutaneous reactions to sulphonamides [9–13] or antituberculous medication [14] have also been desensitized. A 10-day oral desensitization regimen was described for trimethoprim–sulfamethoxazole in 28 HIV-infected patients [10]; 82% were successfully desensitized, and four of the 28 patients had relatively severe rashes (three maculopapular, one erythroderma) during the desensitization phase. Four patients subsequently had rashes 12–33 weeks after desensitization [10].

References

1 Wendel GD, Stark BJ, Jamison RB *et al.* Penicillin allergy and desensitization in serious infections during pregnancy. *N Engl J Med* 1985; **312**: 1229–32.
2 Stark BJ, Earl HS, Gross GN *et al.* Acute and chronic desensitization of pencillin-allergic patients using oral penicillin. *J Allergy Clin Immunol* 1987; **79**: 523–32.
3 Weiss ME, Adkinson NF. Immediate hypersensitivity reactions to penicillin and related antibiotics. *Clin Allergy* 1988; **18**: 515–40.
4 Castells M. Desensitization for drug allergy. *Curr Opin Allergy Clin Immunol* 2006; **6**: 476–81.

5 Wong JT, Ripple RE, MacLean JA *et al.* Vancomycin hypersensitivity: synergism with narcotics and 'desensitization' by a rapid continuous intravenous protocol. *J Allergy Clin Immunol* 1994; **94**: 189–94.
6 Stelzle RC, Squire EN. Oral desensitization to 5-aminosalicylic acid medications. *Ann Allergy Asthma Immunol* 1999; **83**: 23–4.
7 Fam AG, Dunne SM, Iazzetta J, Paton TW. Efficacy and safety of desensitization to allopurinol following cutaneous reactions. *Arthritis Rheum* 2001; **44**: 231–8.
8 Castells M. Rapid desensitization for hypersensitivity reactions to chemotherapy agents. *Curr Opin Allergy Clin Immunol* 2006; **6**: 271–7.
9 Torgovnick J. Desensitization to sulfonamides in patients with HIV infection. *Am J Med* 1990; **88**: 548–9.
10 Absar N, Daneshvar H, Beall G. Desensitization to trimethoprim/sulfamethoxazole in HIV-infected patients. *J Allergy Clin Immunol* 1994; **93**: 1001–5.
11 Belchi-Hernandez J, Espinosa-Parra FJ. Management of adverse reactions to prophylactic trimethoprim–sulfamethoxazole in patients with human immunodeficiency virus infection. *Ann Allergy Asthma Immunol* 1996; **76**: 355–8.
12 Douglas R, Spelman D, Czarny D, O'Hehir RE. Successful desensitization of two patients who previously developed Stevens–Johnson syndrome while receiving trimethoprim-sulfamethoxazole. *Clin Infect Dis* 1997; **25**: 1480.
13 Caumes E, Guermonprez G, Lecomte C *et al.* Efficacy and safety of desensitization with sulfamethoxazole and trimethoprim in 48 previously hypersensitive patients infected with human immunodeficiency virus. *Arch Dermatol* 1997; **133**: 465–9.
14 Kura MM, Hira SK. Reintroducing antituberculosis therapy after Stevens–Johnson syndrome in human immunodeficiency virus-infected patients with tuberculosis: role of desensitization. *Int J Dermatol* 2001; **40**: 481–4.

CHAPTER 76

Erythema Multiforme, Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis

S.M. Breathnach

St John's Institute of Dermatology, St Thomas' Hospital, London, UK

Definition and terminology, 76.1
Erythema multiforme, 76.2
Aetiology, 76.2
Pathology, 76.5
Clinical features, 76.6
Differential diagnosis, 76.7
Treatment, 76.7
Stevens–Johnson syndrome and toxic epidermal necrolysis, 76.8
Incidence of reactions, 76.8
Aetiology, 76.9
Pathology, 76.15
Clinical features, 76.16
Prognosis, 76.18
Diagnosis, 76.19
Treatment, 76.20
Prevention and future use of drugs, 76.22

Definition and terminology

Clinically, erythema multiforme involves macular, papular or urticarial lesions, as well as the classical iris or 'target lesions', distributed preferentially on the distal extremities. Lesions may involve the palms or trunk, as well as the oral and genital mucous membranes with erosions. Stevens–Johnson syndrome (SJS), first described in 1922, comprises extensive erythema multiforme of the trunk and mucous membranes, accompanied by fever, malaise, myalgia and arthralgia [1,2]. Toxic epidermal necrolysis (TEN; Lyell's syndrome), first described in 1956 [3], is characterized by extensive, sheet-like skin erosions with widespread purpuric macules or flat atypical target lesions, accompanied by severe involvement of conjunctival, corneal, irideal, buccal, labial and genital mucous membranes [4,5]. Historically, the three presentations were considered to form a spectrum from mild to fulminatingly severe cases. More recently, there has been a re-evaluation of this concept and a tendency to consider erythema multiforme minor and major as part of one spectrum, often related to infections (especially herpesvirus) and perhaps on occasion to drug reactions. On this basis SJS and TEN are separable from erythema multiforme and are more closely linked to drug sensitivities, and may be regarded as severe variants of a single disease [6–10].

Erythema multiforme major occurs in younger males, frequently recurs, has less fever and milder mucosal lesions, and lacks association with collagen vascular diseases, human immunodeficiency virus (HIV) infection or cancer; herpes simplex is associated with SJS in up to 10% of cases [10]. SJS, with occasional skin blisters and erosions covering less than 10% of the body's surface area, is differentiated from TEN, in which typically sheet-like erosions involve more than 30% of the body surface. However, there are a number of cases (10–20% in adults, and a higher percentage in children) that even experienced clinicians and histopathologists are unable to classify, as they seem to have features of both groups.

There are significant differences between countries in the clinical classification of severe cutaneous reactions, indicating the need for precise definitions [11]. The term 'acute disseminated epidermal necrosis (ADEN)' was proposed [12], with ADEN type 1 corresponding to SJS, type 2 to transitional SJS/TEN with epidermal detachment between 10 and 29% and type 3 to full-blown TEN, and Lyell advocated that the term 'exanthematic necrolysis' should replace TEN [13]. These suggestions have not been taken up.

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

References

1 Stevens AH, Johnson FC. A new eruptive fever associated with stomatitis and ophthalmia: report of two cases in children. *Am J Dis Child* 1922; **24**: 526–7.
2 Côté B, Wechsler J, Bastuji-Garin S *et al*. Clinicopathologic correlation in erythema multiforme and Stevens–Johnson syndrome. *Arch Dermatol* 1995; **131**: 1268–72.
3 Lyell A. Toxic epidermal necrolysis: an eruption resembling scalding of the skin. *Br J Dermatol* 1956; **68**: 355–61.
4 Revuz JE, Roujeau JC. Advances in toxic epidermal necrolysis. *Semin Cutan Med Surg* 1996; **15**: 258–66.
5 Wolkenstein P, Revuz J. Toxic epidermal necrolysis. *Dermatol Clin* 2000; **18**: 485–95, ix.
6 Bastuji-Garin S, Rzany B, Stern RS *et al*. A clinical classification of cases of toxic epidermal necrolysis, Stevens–Johnson syndrome, and erythema multiforme. *Arch Dermatol* 1993; **129**: 92–6.
7 Roujeau JC. The spectrum of Stevens–Johnson syndrome and toxic epidermal necrolysis: a clinical classification. *J Invest Dermatol* 1994; **102**: 28S–30S.
8 Assier H, Bastuji-Garin S, Revuz J, Roujeau JC. Erythema multiforme with mucous membrane involvement and Stevens–Johnson syndrome are clinically different disorders with distinct causes. *Arch Dermatol* 1995; **131**: 539–43.

9 Roujeau JC. Stevens–Johnson syndrome and toxic epidermal necrolysis are severity variants of the same disease which differs from erythema multiforme. *J Dermatol* 1997; **24**: 726–9.
10 Auquier-Dunant A, Mockenhaupt M, Naldi L *et al*. Correlations between clinical patterns and causes of erythema multiforme majus, Stevens–Johnson syndrome, and toxic epidermal necrolysis: results of an international prospective study. *Arch Dermatol* 2002; **138**: 1019–24.
11 Stern RS, Albengres E, Carlson J *et al*. An international comparison of case definition of severe adverse cutaneous reactions to medicines. *Drug Saf* 1993; **8**: 69–77.
12 Ruiz-Maldonado R. Acute disseminated epidermal necrosis types 1, 2, and 3: study of 60 cases. *J Am Acad Dermatol* 1985; **13**: 623–35.
13 Lyell A. Requiem for toxic epidermal necrolysis. *Br J Dermatol* 1990; **122**: 837–8.

Erythema multiforme

Aetiology

Immunology

The clinical picture would seem to be a reaction pattern to many different triggering factors; it appears to have an immunological basis. Human leukocyte antigen (HLA) studies have shown an association with HLA-B62 (B15), HLA-B35 and HLA-DR53 in recurrent cases [1–3]. Immune complexes, both in the skin and circulation [4,5], autoantibodies against epithelial cells [6], and autoantibodies against desmosomal plaque proteins desmoplakin I and II, with suprabasal acantholysis, have been demonstrated [7,8]. However, these findings are probably simply epiphenomena. The histology suggests delayed hypersensitivity; CD4 lymphocytes have been found in the dermis and CD8 cells in the epidermis. Herpesvirus-infected peripheral blood mononuclear cells induced up-regulation of CD54 and major histocompatibility complex class I molecules in adjacent non-infected human dermal microvascular endothelial cells *in vitro*, and consequent increased endothelial binding of peripheral blood mononuclear cells [9]. Herpes simplex virus (HSV) DNA can be identified in lesions of herpes-induced erythema multiforme [10,11]. It has been proposed that peripheral blood mononuclear cells (macrophages or Langerhans' cells) pick up HSV DNA and transport fragments to distant skin sites, leading to viral protein Pol-mediated activation of SP1, interferon-γ (IFN-γ) potentiated upregulation of SP1 target genes (notably TGF-β) involved in localized inflammation, and recruitment of HSV-specific CD4 Th1 cells that produce further IFN-γ [12–14]. This initiates an inflammatory cascade that includes expression of IFN-γ induced genes, increased sequestration of circulating leukocytes, monocytes and natural killer (NK) cells, and recruitment of autoreactive T cells. By extrapolation, drug hapten-specific T cells could be involved in the pathogenesis of drug-induced erythema multiforme. Peripheral blood mononuclear cells obtained from a patient with carbamazepine-induced erythema multiforme at the time of disease showed increased binding to intercellular adhesion molecule-1 (ICAM-1) positive heterologous keratinocytes, and to autologous keratinocytes *in vitro*, which could be inhibited completely by antibodies to lymphocyte function-associated antigen-1 (LFA-1), the ligand for ICAM-1 [15]. Perforin-positive cells may mediate apoptotic cell death in erythema multiforme and SJS [16]. MCP-1, RANTES, macrophage IFN-γ inducible gene (Mig) and IFN-γ inducible protein 10 (IP 10) were expressed by basal keratinocytes above, and mononuclear cells within, inflammatory foci. These cytokines contribute to the cell-specific and spatially restricted recruitment of mononuclear cells in the acute inflammation of erythema multiforme [17].

References

1 Duvic M, Reisner EG, Dawson DV *et al*. HLA-B15 associates with erythema multiforme. *J Am Acad Dermatol* 1983; **8**: 493–6.
2 Kämpgen E, Burg G, Wank R. Association of herpes simplex virus-induced erythema multiforme with the human leucocyte antigen Dqw3. *Arch Dermatol* 1988; **124**: 1372–5.
3 Schofield JK, Tatnall FM, Brown J *et al*. Recurrent erythema multiforme: tissue typing in a large series of patients. *Br J Dermatol* 1994; **131**: 532–5.
4 Bushkell LL, Mackel SE, Jordan RE. Erythema multiforme: direct immunofluorescence studies and detection of circulating immune complexes. *J Invest Dermatol* 1980; **74**: 372–4.
5 Kazmierowski JA, Wuepper KD. Erythema multiforme: clinical spectrum and immunopathogenesis. *Springer Semin Immunopathol* 1981; **4**: 45–53.
6 Matsuoka LY, Wortsmann J, Stanley JR. Epidermal autoantibodies in erythema multiforme. *J Am Acad Dermatol* 1989; **21**: 677–80.
7 Foedinger D, Stericzky B, Elbe A *et al*. Autoantibodies against desmoplakin I and II define a subset of patients with erythema multiforme major. *J Invest Dermatol* 1996; **106**: 1012–6.
8 Fukiwake N, Moroi Y, Urabe K *et al*. Detection of autoantibodies to desmoplakin in a patient with oral erythema multiforme. *Eur J Dermatol* 2007; **17**: 238–41.
9 Larcher C, Gasser A, Hattmannstorfer R *et al*. Interaction of HSV-1 infected peripheral blood mononuclear cells with cultured dermal microvascular endothelial cells: a potential model for the pathogenesis of HSV-1 induced erythema multiforme. *J Invest Dermatol* 2001; **116**: 150–6.
10 Brice S, Krzemien D, Weston W *et al*. Detection of herpes simplex virus DNA in cutaneous lesions of erythema multiforme. *J Invest Dermatol* 1989; **93**: 183–7.
11 Aslanzadeh J, Helm KF, Espy MJ *et al*. Detection of HSV-specific DNA in biopsy of patients with erythema multiforme by polymerase chain reaction. *Br J Dermatol* 1992; **126**: 19–23.
12 Aurelian L, Ono F, Burnett J. Herpes simplex virus (HSV)-associated erythema multiforme (HAEM): a viral disease with an autoimmune component. *Dermatol Online J* 2003; **9**: 1.
13 Ono F, Sharma BK, Smith CC *et al*. CD34+ cells in the peripheral blood transport herpes simplex virus DNA fragments to the skin of patients with erythema multiforme (HAEM). *J Invest Dermatol* 2005; **124**: 1215–24.
14 Gober MD, Laing JM, Burnett JW, Aurelian L. The Herpes simplex virus gene Pol expressed in herpes-associated erythema multiforme lesions upregulates/activates SP1 and inflammatory cytokines. *Dermatology* 2007; **215**: 97–106.
15 Bruynzeel L, Van der Raaij EMH, Boorsma DM *et al*. Increased adherence to keratinocytes of peripheral blood mononuclear leucocytes of a patient with drug-induced erythema multiforme. *Br J Dermatol* 1992; **129**: 45–9.
16 Inachi S, Mizutani H, Shimizu M. Epidermal apoptotic cell death in erythema multiforme and Stevens–Johnson syndrome: contribution of perforin-positive cell infiltration. *Arch Dermatol* 1997; **133**: 845–9.
17 Spandau U, Brocker EB, Kampgen E, Gillitzer R. CC and CXC chemokines are differentially expressed in erythema multiforme *in vivo*. *Arch Dermatol* 2002; **138**: 1027–33.

Triggering factors

Potential triggering factors are listed in Table 76.1 [1–24]. In up to 50% of cases, there is no known provoking factor. The most common association is with a preceding herpes simplex infection (facial or genital) [1–3], or with a *Mycoplasma* infection [4,5]; other viral or bacterial infections have also been incriminated.

References

1 Anderson JA, Bolin V, Sutow WW *et al*. Virus as possible aetiologic agent of erythema multiforme exudativum, bullous type. *Arch Dermatol Syphilol* 1949; **59**: 251–62.
2 Editorial. Recurrent erythema multiforme and herpes simplex virus. *Lancet* 1989; **ii**: 1311–2.

Table 76.1 Some causes of erythema multiforme.

Herpes simplex virus [2,3]	Bacterial infections
Mycoplasma infections [4,5]	A wide range has been recorded
Other viral infections [1]	Rickettsiae [14]
Acquired immune deficiency syndrome	Fungal infections [15,16]
Adenovirus [6]	Histoplasmosis [17,18]
Cytomegalovirus [7,8]	Drug reactions including vaccination (see below)
Hepatitis B [9]	Contact reactions
Infectious mononucleosis [10,11]	Miscellaneous
Lymphogranuloma inguinale	Carcinoma, lymphoma, leukaemia
Milker's nodules	Lupus erythematosus (Rowell's syndrome)
Mumps	Polyarteritis nodosa
Orf [12]	Pregnancy, premenstrual, 'autoimmune progesterone dermatitis' [19]
Poliomyelitis	Sarcoidosis [20]
Psittacosis	Wegener's granulomatosis
Variola	X-ray therapy [21–23]
Vaccinia	Polymorphic light eruption [24]
Varicella [13]	

3 Schofield JK, Tatnall FM, Leigh IM. Recurrent erythema multiforme: clinical features and treatment in a large series of patients. *Br J Dermatol* 1992; **128**: 542–5.

4 Sontheimer RD, Garibaldi RA, Kruegger GG. Stevens–Johnson syndrome associated with *Mycoplasma pneumoniae* infections. *Arch Dermatol* 1978; **114**: 241–4.

5 Grosber M, Alexandre M, Poszepczynska-Guigné E *et al*. Recurrent erythema multiforme in association with recurrent *Mycoplasma pneumoniae* infections. *J Am Acad Dermatol* 2007; **56** (5 Suppl.): S118–9.

6 Strom J. Febrile mucocutaneous syndromes (ectodermosis erosiva pleuriorificialis, Stevens–Johnson syndrome, etc.) in adenovirus infections. *Acta Derm Venereol (Stockh)* 1967; **47**: 281.

7 Seishima M, Oyama Z, Yamamura M. Erythema multiforme associated with cytomegalovirus infection in non-immunosuppressed patients. *Dermatology* 2001; **203**: 299–302.

8 Wanner M, Pol-Rodriguez M, Hinds G *et al*. Persistent erythema multiforme and CMV infection. *J Drugs Dermatol* 2007; **6**: 333–6.

9 Olut AI, Erkek E, Ozunlu H, Ozsakarya F. Erythema multiforme associated with acute hepatitis B virus infection. *Clin Exp Dermatol* 2006; **31**: 137–8.

10 Williamson DM. Erythema multiforme in infectious mononucleosis. *Br J Dermatol* 1974; **91**: 345–6.

11 Hughes T, Burrows NP. Infectious mononucleosis presenting as erythema multiforme. *Clin Exp Dermatol* 1993; **18**: 373–4.

12 Schmidt E, Weissbrich B, Bröcker EB *et al*. Orf followed by erythema multiforme. *J Eur Acad Dermatol Venereol* 2006; **20**: 612–3.

13 Prais D, Grisuru-Soen G, Barzilai A, Amir J. Varicella zoster virus infection associated with erythema multiforme in children. *Infection* 2001; **29**: 37–9.

14 Lang MH, Wehrenberg O. Erythema exsudativum multiforme bei Rickettsiose. *Hautarzt* 1987; **38**: 432–4.

15 Salim A, Young E. Erythema multiforme associated with *Trichophyton mentagrophytes* infection. *J Eur Acad Dermatol Venereol* 2002; **16**: 645–6.

16 Gilaberte Y, Coscojuela C, García-Prats MD, Mairal MP. Erythema multiforme associated with inflammatory ringworm on the hand. *Br J Dermatol* 2003; **149**: 1078–9.

17 Leznoff A, Frank H, Telner P *et al*. Histoplasmosis in Montreal during the fall of 1963, with observations on erythema multiforme. *Can Med Assoc J* 1963; **91**: 1154–60.

18 Sellers TF, Price WN, Newberry WM. An epidemic of erythema multiforme and erythema nodosum caused by histoplasmosis. *Ann Intern Med* 1965; **62**: 1244–62.

19 Warin AP. Case 2: diagnosis—erythema multiforme as a presentation of autoimmune progesterone dermatitis. *Clin Exp Dermatol* 2001; **26**: 107–8.

20 Carswell WA. A case of sarcoidosis presenting with erythema multiforme. *Am Rev Respir Dis* 1972; **106**: 462–4.

21 Davis J, Pack GT. Erythema multiforme following deep X-ray therapy. *Arch Dermatol Syphilol* 1952; **66**: 41–8.

22 Nawalkjha PL, Mathur NK, Malhotra YK *et al*. Severe erythema multiforme (Stevens–Johnson syndrome) following telecobalt therapy. *Br J Radiol* 1972; **45**: 768–9.

23 Yoshitake T, Nakamura K, Shioyama Y *et al*. Erythema multiforme and Stevens–Johnson syndrome following radiotherapy. *Radiat Med* 2007; **25**: 27–30.

24 Fraser-Andrews EA, Morris-Jones R, Novakovic L, Hawk JL. Erythema multiforme following polymorphic light eruption: a report of two cases. *Clin Exp Dermatol* 2005; **30**: 232–4.

Drug induced

Erythema multiforme has been regarded as a well-recognized pattern of adverse cutaneous drug reaction [1–7], although in a prospective study of cases of erythema multiforme only 10% were drug related [2]. In another study, antecedent medication use, especially cephalosporins, was recorded in 59% of erythema multiforme patients and 68% of SJS patients [4]. Perhaps all too frequently, drugs are blamed on inadequate evidence and this is a controversial area; description of some reactions as 'erythema multiforme-like' does not help in this regard. Confirmation of drug sensitivity really necessitates re-exposure to the drug, which may carry an unacceptable risk and is not usually carried out.

Some of the drugs implicated (Table 76.2), often on anecdotal evidence, include: sulphonamides and co-trimoxazole, sulphones, penicillins, rifampicin, barbiturates, hydantoin derivatives, carbamazepine, phenothiazines, pyrazolone derivatives (phenylbutazone), phenolphthalein, chlorpropamide, and thiazide diuretics. Individual reports have incriminated phenazone, acetaminophen [8], fenbufen, sulindac, celecoxib [9], rofecoxib [10], etoricoxib [11], piroxicam [12], allopurinol [13,14], mianserin, quetiapine [15], risperidone [16], lithium [17], trazodone [18], indapamide and sertraline [19], bupropion (amfebutamone) [20], minoxidil, candesartan [21], metformin [22], sulfaguanidine [23], methaqualone, hydroxyzine [24], the H_2-blocker roxatidine [25], ampicillin [26], amoxicillin [13], vancomycin [27], ofloxacin [28], ceftazidime [29], griseofulvin [30], terbinafine [31,32], suramin [33], atovaquone and proguanil hydrochloride [34], antiretroviral agents including didanosine [35,36], progesterone [37,38], danazol [39], intradural prednisolone acetate [40], fenoterol [41], thalidomide [42], capecitabine [43], sorafenib [44], methotrexate [45], granulocyte macrophage stimulating factor [46], the traditional Chinese herbal drug 'Dong Ling Hou Tong Pian' [47], and porfirin sodium as part of photodynamic therapy [48]. Erythema multiforme may follow vaccination [49–55].

References

1 Kauppinen K. Cutaneous reactions to drugs: with special reference to severe mucocutaneous bullous eruptions and sulphonamides. *Acta Derm Venereol (Stockh)* 1972; **52** (Suppl. 68): 1–89.

2 Huff JC, Weston WL, Tonnesen MG. Erythema multiforme. a critical review of characteristics, diagnostic criteria, and causes. *J Am Acad Dermatol* 1983; **8**: 763–75.

3 Stewart MG, Duncan NO III, Franklin DJ *et al*. Head and neck manifestations of erythema multiforme in children. *Otolaryngol Head Neck Surg* 1994; **111**: 236–42.

4 Gebel K, Hornstein OP. Drug-induced oral erythema multiforme: results of a long-term retrospective study. *Dermatologica* 1984; **168**: 35–40.

5 Nethercott JR, Choi BC. Erythema multiforme (Stevens–Johnson syndrome): chart review of 123 hospitalized patients. *Dermatologica* 1985; **171**: 383–96.

6 Fabbri P, Panconesi E. Erythema multiforme ('minus' and 'maius') and drug intake. *Clin Dermatol* 1993; **11**: 479–89.

Table 76.2 Drugs reported as causing erythema multiforme or Stevens–Johnson syndrome.

Antibiotics	*Anticonvulsants*
Sulphonamides	Barbiturates
Co-trimoxazolene	Carbamazepine
Sulfadoxine–pyrimethamine	Hydantoin derivatives
Sulphones	Lamotrigine
Penicillins and ampicillin	Trimethadione
Cephalosporins	Cephalosporins
Ceftazidimes	*Antihypertensives*
Quinolones	Frusemide (furosemide)
Rifampicin	Hydralazine
Tetracyclines	Minoxidil
Erythromycin	Thiazide diuretics
Thiacetazone	
Antifungal or antiyeast preparations	*Drugs acting on the central nervous system*
Terbinafine	Lithium
Griseofulvin	Mianserin
Nystatin	Phenothiazines
Antiretroviral drugs	Trazodone
Abacavir	
Nevirapine	
Non-steroidal anti-inflammatory drugs	*Miscellaneous*
Salicylates	Allopurinol
Fenbufen	Chlorpropamide
Ibuprofen	Codeine
Sulindac	Cyclophosphamide
Paracetamol (acetaminophen)	Danazol
Pyrazolone derivatives	Methaqualone
Antipyrine	Nitrogen mustard
Phenylbutazone	Pentazocine
Phenazone	Phenolphthalein
Metals	Progesterone
Arsenic	Topical agents (see text)
Mercury	Vaccination
Gold	
Bromides	
Iodides	

7 Rzany B, Hering O, Mockenhaupt M *et al*. Histopathological and epidemiological characteristics of patients with erythema exudativum multiforme major, Stevens–Johnson syndrome and toxic epidermal necrolysis. *Br J Dermatol* 1996; **135**: 6–11.

8 Oh SW, Lew W. Erythema multiforme induced by acetaminophen: a recurrence at distant sites following patch testing. *Contact Dermatitis* 2005; **53**: 56–7.

9 Ernst EJ, Egge JA. Celecoxib-induced erythema multiforme with glyburide cross-reactivity. *Pharmacotherapy* 2002; **22**: 637–40.

10 Sarkar R, Kaur C, Kanwar AJ. Erythema multiforme due to rofecoxib. *Dermatology* 2002; **204**: 304–5.

11 Thirion L, Nikkels AF, Piérard GE. Etoricoxib-induced erythema-multiforme-like eruption. *Dermatology* 2008; **216**: 227–8.

12 Prieto A, De Barrio M, Pérez C. Piroxicam-induced erythema multiforme. *Contact Dermatitis* 2004; **50**: 263.

13 Perez A, Cabrerizo S, de Barrio M *et al*. Erythema-multiforme-like eruption from amoxycillin and allopurinol. *Contact Dermatitis* 2001; **44**: 113–4.

14 Kumar A, Edward N, White MI *et al*. Allopurinol, erythema multiforme, and renal insufficiency. *BMJ* 1996; **312**: 173–4.

15 Lin GL, Chiu CH, Lin SK. Quetiapine-induced erythema multiforme minor: a case report. *J Clin Psychopharmacol* 2006; **26**: 668–9.

16 Desarkar P, Nizamie SH. Risperidone-induced erythema multiforme minor. *Br J Clin Pharmacol* 2006; **62**: 504–5.

17 Balldin J, Berggren U, Heijer A, Mobacken H. Erythema multiforme caused by lithium. *J Am Acad Dermatol* 1991; **24**: 1015–6.

18 Ford HE, Jenike MA. Erythema multiforme associated with trazadone therapy. *J Clin Psychiatry* 1985; **46**: 294–5.

19 Gales BJ, Gales MA. Erythema multiforme and angioedema with indapamide and sertraline (Letter). *Am J Hosp Pharm* 1994; **51**: 118–9.

20 Lineberry TW, Peters GE Jr, Bostwick JM. Bupropion-induced erythema multiforme. *Mayo Clin Proc* 2001; **76**: 664–6.

21 Ejaz AA, Walsh JS, Wasiluk A. Erythema multiforme associated with candesartan cilexetil. *South Med J* 2004; **97**: 614–5.

22 Burger DE, Goyal S. Erythema multiforme from metformin. *Ann Pharmacother* 2004; **38**: 1537.

23 de Frutos C, de Barrio M, Tornero P *et al*. Erythema multiforme from sulfaguanidine. *Contact Dermatitis* 2002; **46**: 186–7.

24 Peña AL, Henriquezsantana A, Gonzalez-Seco E *et al*. Exudative erythema multiforme induced by hydroxyzine. *Eur J Dermatol* 2008; **18**: 194–5.

25 Horiuchi Y. Erythema multiforme caused by the H_2-blocker, roxatidine. *J Dermatol* 2000; **27**: 352–3.

26 Garty BZ, Offer I, Livni E, Danon YL. Erythema multiforme and hypersensitivity myocarditis caused by ampicillin. *Ann Pharmacother* 1994; **28**: 730–1

27 Padial MA, Barranco P, Lopez-Serrano C. Erythema multiforme to vancomycin. *Allergy* 2000; **55**: 1201.

28 Nettis E, Giordano D, Pierluigi T *et al*. Erythema multiforme-like rash in a patient sensitive to ofloxacin. *Acta Derm Venereol (Stockh)* 2002; **82**: 395–6.

29 Pierce TH, Vig SJ, Ingram PM. Ceftazidime in the treatment of lower respiratory tract infection. *J Antimicrob Chemother* 1983; **12** (Suppl. A): 21–5.

30 Thami GP, Kaur S, Kanwar AJ. Erythema multiforme due to griseofulvin with positive re-exposure test. *Dermatology* 2001; **203**: 84–5.

31 Todd P, Halpern S, Munro DD. Oral terbinafine and erythema multiforme. *Clin Exp Dermatol* 1995; **20**: 247–8.

32 Gupta AK, Kopstein JB, Shear NH. Hypersensitivity reaction to terbinafine. *J Am Acad Dermatol* 1997; **36**: 1018–9.

33 Katz SK, Medenica MM, Kobayashi K *et al*. Erythema multiforme induced by suramin. *J Am Acad Dermatol* 1995; **32**: 292–3.

34 Remich SA, Otieno W, Polhemus ME *et al*. Bullous erythema multiforme after treatment with Malarone, a combination antimalarial composed of atovaquone and proguanil hydrochloride. *Trop Doct* 2008; **38**: 190–1.

35 Scully C, Diz Dios P. Orofacial effects of antiretroviral therapies. *Oral Dis* 2001; **7**: 205–10.

36 Borrás-Blasco J, Navarro-Ruiz A, Borrás C, Casterá E. Adverse cutaneous reactions associated with the newest antiretroviral drugs in patients with human immunodeficiency virus infection. *J Antimicrob Chemother* 2008; **62**: 879–88.

37 Wojnarowska F, Greaves MW, Peachey RDG *et al*. Progesterone-induced erythema multiforme. *J R Soc Med* 1985; **78**: 407–8.

38 Suzuki R, Matsumura Y, Kambe N *et al*. Erythema multiforme due to progesterone in a low-dose oral contraceptive pill. *Br J Dermatol* 2005; **152**: 370–1.

39 Reynolds NJ, Sansom JE. Erythema multiforme during danazol therapy. *Clin Exp Dermatol* 1992; **17**: 140.

40 Lavabre C, Chevalier X, Larget-Piet B. Erythema multiforme after intradural injection of prednisolone acetate. *Br J Rheumatol* 1992; **31**: 717–8.

41 Sachs B, Renn C, al Masaoudi T, Merk HF. Fenoterol-induced erythema exudativum multiforme-like exanthem: demonstration of drug-specific lymphocyte reactivity *in vivo* and *in vitro*. *Acta Derm Venereol* 2001; **81**: 368–9.

42 Hall VC, El-Azhary RA, Bouwhuis S, Rajkumar SV. Dermatologic side effects of thalidomide in patients with multiple myeloma. *J Am Acad Dermatol* 2003; **48**: 548–52.

43 Sendur MA, Kilickap S. Stevens–Johnson syndrome after treatment with capecitabine. *Clin Oncol (R Coll Radiol)* 2008; **20**: 202–3.

44 MacGregor JL, Silvers DN, Grossman ME, Sherman WH. Sorafenib-induced erythema multiforme. *J Am Acad Dermatol* 2007; **56**: 527–8.

45 Blanes M, Silvestre JF, Albares MP *et al*. Erythema multiforme due to methotrexate reproduced with patch test. *Contact Dermatitis* 2005; **52**: 164–5.

46 Mori T, Sato N, Watanabe R, *et al*. Erythema exsudativum multiforme induced by granulocyte colony-stimulating factor in an allogeneic peripheral blood stem cell donor. *Bone Marrow Transplant* 2000; **26**: 239–40.

47 Tan WP, Goh BK, Tan SH. Extensive erythema multiforme-like eruption due to traditional Chinese herbal drug 'Dong Ling Hou Tong Pian'. *Clin Exp Dermatol* 2006; **31**: 291–3

48 Wolfsen HC, Ng CS. Cutaneous consequences of photodynamic therapy. *Cutis* 2002; **69**: 140–2.
49 Frederiksen MS, Brenøe E, Trier J. Erythema multiforme minor following vaccination with paediatric vaccines. *Scand J Infect Dis* 2004; **36**: 154–5.
50 Bernardini ML, D'Angelo G, Oggiano N *et al*. Erythema multiforme following live attenuated trivalent measles-mumps-rubella vaccine. *Acta Derm Venereol* 2006; **86**: 359–60.
51 Karincaoğlu Y, Aki T, Erguvan-Onal R, Seyhan M. Erythema multiforme due to diphtheria-pertussis-tetanus vaccine. *Pediatr Dermatol* 2007; **24**: 334–5.
52 Studdiford J, Oppenheim L, McCann E, Altshuler M. Erythema multiforme after meningitis vaccine: patient safety concerns with repeat immunization. *Pharmacotherapy* 2006; **26**: 1658–61.
53 Loche F, Schwarze HP, Thedenat B *et al.* Erythema multiforme associated with hepatitis B immunization. *Clin Exp Dermatol* 2000; **25**: 167–8.
54 Frey SE, Couch RB, Tacket CO *et al*. Clinical responses to undiluted and diluted smallpox vaccine. *N Engl J Med* 2002; **346**: 1265–74.
55 Karakaya G, Sahin S, Fuat Kalyoncu A. Erythema multiforme: as a complication of allergen-specific immunotherapy. *Allergol Immunopathol (Madr)* 2001; **29**: 276–8.

Topical agents and erythema multiforme-like reactions

Topical sensitivities reportedly also provoke erythema multiforme [1]. The substances involved are usually potent sensitizers such as *Primula obconica* [2,3], poison ivy [4], a variety of weeds [5], laurel oil [6], *Alpinia galanga* (spicy edible Thai ginger) [7], diphenylcyclopropenone and bromofluorene [8–10]. A large number of topical medications can induce erythema multiforme-like eruptions, including balsam of Peru, chloramphenicol, econazole, ethylenediamine, furazolidone, mafenide acetate cream used to treat burns, the muscle relaxant mephenesin, neomycin, nifuroxime, promethazine, scopolamine, sulphonamides, ophthalmic anticholinergic preparations (scopolamine hydrobromide and tropicamide drops), vitamin E, the antimycotic agent pyrrolnitrin, as well as proflavine, topical steroids [11,12], topical nitrogen mustard [13], sesquiterpene lactones in herbal medicine [14], bufexamac [15] and phenylbutazone [16], nitroglycerin patch [17], tea tree oil [18] and para-phenylenediamine, including in a henna tattoo [19–21]. A topical ketoprofen-containing tape provoked a photocontact dermatitis and subsequent erythema multiforme [22].

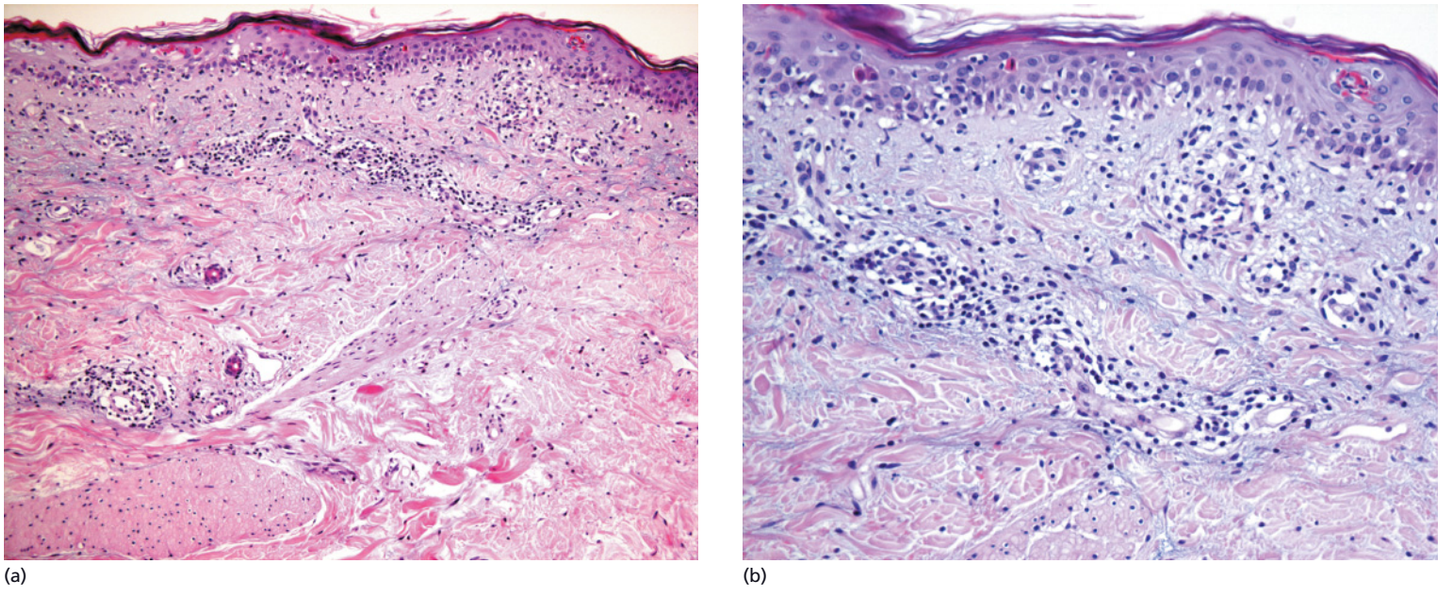
Erythema multiforme has also been associated with use of rubber gloves [23] and with blister beetle dermatitis [24]. In addition, contact with a number of environmental substances may induce erythema multiforme-like reactions [25], including nickel, formaldehyde, trichloroethylene, phenyl sulphone derivative, the insecticide methyl parathion, a glyphosate pesticide [26], epoxy compounds, trinitrotoluene, cutting oil [27] and bisphenol A [28].

References

1 Wiedemeyer K, Enk A, Jappe U. Erythema multiforme following allergic contact dermatitis: case report and literature review. *Acta Derm Venereol* 2007; **87**: 559–61.
2 Lengrand F, Tellart AS, Segard M *et al*. Erythema multiforme-like eruption: an unusual presentation of primula contact allergy. *Contact Dermatitis* 2001; **44**: 35.
3 Bonamonte D, Filotico R, Mastrandrea V *et al*. Erythema multiforme-like contact dermatitis from primin. *Contact Dermatitis* 2008; **59**: 174–6.
4 Werchniak AE, Schwarzenberger K. Poison ivy: an underreported cause of erythema multiforme. *J Am Acad Dermatol* 2004; **51** (5 Suppl.): S159–60.
5 Jovanovic M, Mimica-Dukic N, Poljacki M, Boza P. Erythema multiforme due to contact with weeds: a recurrence after patch testing. *Contact Dermatitis* 2003; **48**: 17–25.
6 Athanasiadis GI, Pfab F, Klein A *et al*. Erythema multiforme due to contact with laurel oil. *Contact Dermatitis* 2007; **57**: 116–8.
7 Hong SJ, Chang CH. Erythema multiforme-like generalized allergic contact dermatitis caused by *Alpinia galanga*. *Contact Dermatitis* 2006; **54**: 118–20.
8 Agrup G, Cronin E. Contact dermatitis X. *Br J Dermatol* 1970; **82**: 428–33.
9 Fisher AA. Erythema multiforme-like eruptions due to topical medications. II. *Cutis* 1986; **37**: 158–61.
10 Perret CM, Steijlen PM, Zaun H, Happle R. Erythema multiforme-like lesions: a rare side effect of topical immunotherapy with diphenylcyclopropenone. *Dermatologica* 1990; **180**: 5–7.
11 Stingeni L, Caraffini S, Assalve D *et al*. Erythema multiforme-like contact dermatitis from budesonide. *Contact Dermatitis* 1996; **34**: 154–5.
12 Calista D, Schianchi S. Erythema multiforme-like eruption induced by contact dermatitis caused by topical corticosteroids. *G Ital Dermatol Venereol* 2008; **143**: 227–8.
13 Newman JM, Rindler JM, Bergfeld WF. Stevens–Johnson syndrome associated with topical nitrogen mustard therapy. *J Am Acad Dermatol* 1997; **36**: 112–4.
14 Mateo MP, Velasco M, Miquel FJ, de la Cuadra J. Erythema multiforme-like eruption following allergic contact dermatitis from sesquiterpene lactones in herbal medicine. *Contact Dermatitis* 1995; **33**: 449–50.
15 Koch P, Bahmer FA. Erythema multiforme-like, urticarial papular and plaque eruptions from bufexamac: report of four cases. *Contact Dermatitis* 1994; **31**: 97–101.
16 Kerre S, Busschots A, Dooms-Goossens A. Erythema multiforme-like contact dermatitis due to phenylbutazone. *Contact Dermatitis* 1995; **33**: 213–4.
17 Silvestre JF, Betlloch I, Guijarro J *et al*. Erythema multiforme-like eruption on the application site of a nitroglycerin patch, followed by widespread erythema multiforme. *Contact Dermatitis* 2001; **45**: 299–300.
18 Khanna M, Qasem K, Sasseville D. Allergic contact dermatitis to tea tree oil with erythema multiforme-like id reaction. *Am J Contact Dermat* 2000; **11**: 238–42.
19 Balato A, Patruno C, Balato N *et al*. Erythema multiforme-like eruption because of para-phenylenediamine. *Contact Dermatitis* 2008; **58**: 65–6.
20 Jappe U, Hausen BM, Petzoldt D. Erythema-multiforme-like eruption and depigmentation following allergic contact dermatitis from a paint-on henna tattoo, due to para-phenylenediamine contact hypersensitivity. *Contact Dermatitis* 2001; **45**: 249–50.
21 Sidwell RU, Francis ND, Basarab T, Morar N. Vesicular erythema multiforme-like reaction to para-phenylenediamine in a henna tattoo. *Pediatr Dermatol* 2008; **25**: 201–4.
22 Izu K, Hino R, Isoda H *et al*. Photocontact dermatitis to ketoprofen presenting with erythema multiforme. *Eur J Dermatol* 2008; **18**: 710–3.
23 Lu CY, Sun CC. Localized erythema-multiforme-like contact dermatitis from rubber gloves. *Contact Dermatitis* 2001; **45**: 311–2.
24 Inanir I. Erythema multiforme associated with blister beetle dermatitis. *Contact Dermatitis* 2002; **46**: 175.
25 Fisher AA. Erythema multiforme-like eruptions due to topical miscellaneous compounds. III. *Cutis* 1986; **37**: 262–4.
26 Heras-Mendaza F, Casado-Fariñas I, Paredes-Gascón M, Conde-Salazar L. Erythema multiforme-like eruption due to an irritant contact dermatitis from a glyphosate pesticide. *Contact Dermatitis* 2008; **59**: 54–6.
27 Hata M, Tokura Y, Takigawa M. Erythema multiforme-like eruption associated with contact dermatitis to cutting oil. *Eur J Dermatol* 2001; **11**: 247–8.
28 Akita H, Washimi Y, Akamatsu H *et al*. Erythema multiforme-like occupational contact dermatitis due to bisphenol A. *Contact Dermatitis* 2001; **45**: 305.

Pathology [1–4]

The most important changes are in the upper dermis and lower epidermis. Some cases have prominent dermal inflammatory changes, with a lymphohistiocytic infiltrate rich in T lymphocytes around blood vessels, oedema and vasodilatation, but little epidermal change. There may also be vacuolar degeneration of the lower epidermis or individually necrotic epidermal cells (Fig. 76.1). Such changes occur especially in classical erythema multiforme with target lesions. In more severe bullous cases, there is more dramatic necrosis of the whole epidermis. Electron microscopy demonstrates the damaged basement membrane in the floor of the bulla, with a few ragged islands of epidermal cells showing



(a) (b)

Fig. 76.1 (a,b) Histopathology of erythema multiforme. Note upper dermal perivascular lymphocytic infiltration, epidermal vaculoar degeneration and scattered individual necrotic keratinocytes (H&E). (Courtesy of Dr E. Calonje, St John's Institute of Dermatology, King's College London, UK.)

some evidence of regeneration. The histology of the oral lesions is similar to that in the skin, and there may be very marked degenerative changes in the epithelium [5].

References

1 Ackerman AB. Dermal and epidermal types of erythema multiforme. *Arch Dermatol* 1975; **111**: 795.

2 Bedi TR, Pinkus H. Histopathological spectrum of erythema multiforme. *Br J Dermatol* 1976; **95**: 243–50.

3 Rzany B, Hering O, Mockenhaupt M *et al*. Histopathological and epidemiological characteristics of patients with erythema exudativum multiforme major, Stevens–Johnson syndrome and toxic epidermal necrolysis. *Br J Dermatol* 1996; **135**: 6–11.

4 Paquet P, Pierard GE. Erythema multiforme and toxic epidermal necrolysis: a comparative study. *Am J Dermatopathol* 1997; **19**: 127–32.

5 Lozada-Nur F, Gorsky M, Silverman S. Oral erythema multiforme: clinical observation and treatment of 95 patients. *Oral Surg Oral Med Oral Pathol* 1989; **67**: 36–40.

Clinical features [1–4]

Erythema multiforme can occur at any age, including neonates [5,6] or young children [7]. In general, the course is that of an eruption developing over a few days and resolving in 2–3 weeks. Repeated attacks associated with recurrent herpes simplex are frequent.

Erythema multiforme minor; papular or simplex form. This accounts for approximately 80% of cases. Clinically, macular, papular or urticarial lesions, as well as the classical iris or 'target lesions' (Fig. 76.2), are distributed preferentially on the distal extremities. Lesions may involve the palms or trunk, as well as the oral (Fig. 76.3) and genital mucous membranes. The lesions are dull red, flat or slightly raised maculopapules, which may remain small or may increase in size to reach a diameter of 1–3 cm in 48 h. Typical cases show at least some target (or iris) lesions. Target lesions are less than 3 cm in diameter, rounded and have three zones: a central area of dusky erythema or purpura, a middle paler zone of oedema and an outer ring of erythema with a well-defined edge. Atypical target lesions have only two of the zones. The lesions appear in successive crops for a few days and fade in 1–2 weeks, sometimes leaving dusky discoloration. There may be a few lesions, or they may be very profuse.



Fig. 76.2 Erythema multiforme. Typical target lesions over knuckles.



Fig. 76.3 Erythema multiforme. Mucosal lesions.

Classically, the backs of the hands, palms, wrists, feet and extensor aspects of the elbows and knees are affected; less commonly the face. Often the hands are selectively involved. Thus, the typical distribution is acral. The Koebner phenomenon is not uncommon, and accounts for some bizarre distributions. There may be occasional erythematous lesions, erosions or bullae on the mucous membranes. Photoaggravation of erythema multiforme is well recognized [8].

Localized vesiculobullous form. This form is intermediate in severity. The skin lesions present as erythematous macules or plaques, often with a central bulla and a marginal ring of vesicles (herpes iris of Bateman). Mucous membranes are quite often involved. In this type, the skin lesions tend to occur in the classical acral distribution, but may be few in number.

Erythema multiforme major. This is a severe illness associated with more extensive target lesions and mucous membrane involvement. The onset is usually sudden, although there may be a prodromal systemic illness of 1–13 days before the eruption appears.

Atypical cases. Because the diagnosis of erythema multiforme depends on the clinical and pathological appearance, criteria for the diagnosis of atypical cases are difficult to apply. However, there are cases where the clinical picture is atypical but the histology nevertheless shows the characteristic changes. Erythema multiforme-like lesions have been reported in the setting of acute generalized exanthematous pustulosis [9]. Lesions many centimetres across may remain stationary or slowly enlarge over several weeks or months (persistent erythema multiforme) [10,11]. On rare occasions, cases with otherwise typical morphology and histology may develop lesions almost continuously rather than episodically [10]. Erythema multiforme along Blaschko's lines has been reported [12], as has disseminated granuloma annulare following erythema multiforme minor [13].

Rowell's syndrome. This syndrome comprises lupus erythematosus associated with erythema multiforme-like lesions, and immunological findings of speckled antinuclear antibodies, anti-La or anti-Ro antibodies, and a positive test for rheumatoid factor [14–19]. However, the existence of the syndrome as a defined entity has been questioned [19].

Differential diagnosis

Drug eruptions, such as vancomyin-induced linear IgA disease [20] and lupus erythematosus, must be excluded, along with pemphigoid and other autoimmune bullous conditions, and toxic erythemas of unknown cause. Stem cell transplantation erythematous eruptions may be difficult to differentiate from erythema multiforme [21]. The distinction between atypical erythema multiforme and urticarial vasculitis can be difficult. Kawasaki disease (see Chapter 30) may resemble erythema multiforme, but the characteristic red lips, strawberry tongue, red and swollen palms and soles, and the lymphadenopathy should permit a clinical diagnosis. Differential diagnosis of mouth lesions is considered in Chapter 69.

Treatment [7,22]

Symptomatic treatment only is necessary in the papular and localized bullous forms. Ocular involvement requires the early help of an ophthalmologist. In the more severe cases, good nursing is of paramount importance; such cases may require the sort of attention used for TEN (see below), in a dermatological intensive care unit or burns unit. The value of systemic corticosteroids is still debated [7,22–24], but relief of systemic symptoms such as fever is achieved. For more severe cases, prednisolone at an initial dosage of 30–60 mg/day, decreasing over a period of 1–4 weeks, may be given.

Antiviral therapy with agents such as aciclovir for erythema multiforme following overt herpes simplex infections tends to be disappointing once the eruption has appeared; this is so for recurrent cases, even when given at the very first sign of recurrent herpes. However, long-term prophylactic use may be quite helpful [25–27]. A dosage of 200 mg three times daily may be appropriate, but smaller or larger doses may be needed. Relapses tend to occur when the drug is omitted. It is of interest that some patients who suffer from recurrent erythema multiforme without overt herpes infection are helped by prophylactic aciclovir, implying that recurrent herpes infection may nevertheless be responsible. Aciclovir prevented recurrent polyarthritis associated with erythema multiforme [28].

Thalidomide has been used in a few cases to prevent relapses of recurrent erythema multiforme [29–31]. Other drugs used have included dapsone [11,32], azathioprine [11], mycophenolate mofetil [33] and ciclosporin [34].

References

1 Huff JC, Weston WL. Recurrent erythema multiforme. *Medicine* 1989; **68**: 133–40.

2 Huff JC, Weston WL, Tonnesen MG. Erythema multiforme: a critical review of characteristics, diagnostic criteria and causes. *J Am Acad Dermatol* 1983; **8**: 763–75.

3 Bastuji-Garin S, Rzany B, Stern RS *et al*. A clinical classification of cases of toxic epidermal necrolysis, Stevens–Johnson syndrome, and erythema multiforme. *Arch Dermatol* 1993; **129**: 92–6.

4 Auquier-Dunant A, Mockenhaupt M, Naldi L *et al*. Correlations between clinical patterns and causes of erythema multiforme majus, Stevens–Johnson syndrome,

and toxic epidermal necrolysis: results of an international prospective study. *Arch Dermatol* 2002; **138**: 1019–24.
5 Johnston GA, Ghura HS, Carter E, Graham-Brown RA. Neonatal erythema multiforme major. *Clin Exp Dermatol* 2002; **27**: 661–4.
6 Torrelo A, Moreno M, De Prada I *et al*. Erythema multiforme in a neonate. *J Am Acad Dermatol* 2003; **48** (Suppl. 5): 78–9.
7 Rasmussen JE. Erythema multiforme in children. *Br J Dermatol* 1976; **95**: 181–6.
8 Murphy GM. Diseases associated with photosensitivity. *J Photochem Photobiol B* 2001; **64**: 93–8.
9 Lin JH, Sheu HM, Lee JY. Acute generalized exanthematous pustulosis with erythema multiforme-like lesions. *Eur J Dermatol* 2002; **12**: 475–8.
10 Drago F, Parodi A, Rebora A. Persistent erythema multiforme: report of new cases and review of the literature. *J Am Acad Dermatol* 1995; **33**: 366–9.
11 Pavlovic MD, Karadaglic DM, Kandolf LO, Mijuskovic ZP. Persistent erythema multiforme: a report of three cases. *J Eur Acad Dermatol Venereol* 2001; **15**: 54–8.
12 Micalizzi C, Farris A. Erythema multiforme along Blaschko's lines. *J Eur Acad Dermatol Venereol* 2000; **14**: 203–4.
13 Abraham Z, Feuerman EJ, Schafer I, Feinmesser M. Disseminated granuloma annulare following erythema multiforme minor. *Australas J Dermatol* 2000; **41**: 238–41.
14 Rowell NR, Beck JS, Anderson JR. Lupus erythematosus and erythema multiforme-like lesions. *Arch Dermatol* 1963; **88**: 176–80.
15 Zeitouni NC, Funaro D, Cloutier RA *et al*. Redefining Rowell's syndrome. *Br J Dermatol* 2000; **142**: 343–6.
16 Shteyngarts AR, Warner MR, Camisa C. Lupus erythematosus associated with erythema multiforme: does Rowell's syndrome exist? *J Am Acad Dermatol* 1999; **40**: 773–7.
17 Aydogan K, Karadogan S, Balaban Adim S, Tunali S. Lupus erythematosus associated with erythema multiforme: report of two cases and review of the literature. *J Eur Acad Dermatol Venereol* 2005; **19**: 621–7.
18 Shadid NH, Thissen CA, van Marion AM *et al*. Lupus erythematosus associated with erythema multiforme: Rowell's syndrome. *Int J Dermatol* 2007; **46** (Suppl. 3): 30–2.
19 Duarte AF, Mota A, Pereira M *et al*. Rowell syndrome—case report and review of the literature. *Dermatol Online J* 2008; **14**: 15.
20 Armstrong AW, Fazeli A, Yeh SW *et al*. Vancomycin-induced linear IgA disease manifesting as bullous erythema multiforme. *J Cutan Pathol* 2004; **31**: 393–7.
21 Burnett JW, Laing JM, Aurelian L. Acute skin eruptions that are positive for herpes simplex virus DNA polymerase in patients with stem cell transplantation: a new manifestation within the erythema multiforme reactive dermatoses. *Arch Dermatol* 2008; **144**: 902–7.
22 Rasmussen JE. Erythema multiforme: a practical approach to recent advances. *Pediatr Dermatol* 2002; **19**: 82–4.
23 Renfro L, Grant-Kels JM, Feder HH *et al*. Are systemic steroids indicated in the treatment of erythema multiforme? *Pediatr Dermatol* 1989; **6**: 43–50.
24 Martinez AE, Atherton DJ. High-dose systemic corticosteroids can arrest recurrences of severe mucocutaneous erythema multiforme. *Pediatr Dermatol* 2000; **17**: 87–90.
25 Huff JC. Therapy and prevention of erythema multiforme with acyclovir. *Semin Dermatol* 1988; **7**: 212–7.
26 Lemak MA, Duvic M, Bean SF. Oral acyclovir for the prevention of herpes-associated erythema multiforme. *J Am Acad Dermatol* 1986; **15**: 50–4.
27 Tatnall FM, Schofield JK, Leigh I. A double-blind placebo controlled trial of continuous acyclovir therapy in recurrent erythema multiforme. *Br J Dermatol* 1995; **132**: 267–70.
28 Molnar I, Matulis M. Arthritis associated with recurrent erythema multiforme responding to oral acyclovir. *Clin Rheumatol* 2002; **21**: 415–7.
29 Moisson YF, Janier M, Civatte J. Thalidomide for recurrent erythema multiforme. *Br J Dermatol* 1992; **126**: 92–3.
30 Conejo-Mir JS, del Canto S, Muñoz MA *et al.* Thalidomide as elective treatment in persistent erythema multiforme; report of two cases. *J Drugs Dermatol* 2003; **2**: 40–4.
31 Chen CW, Tsai TF, Chen YF, Hung CM. Persistent erythema multiforme treated with thalidomide. *Am J Clin Dermatol* 2008; **9**: 123–7.
32 Mahendran R, Grant JW, Norris PG. Dapsone-responsive persistent erythema multiforme. *Dermatology* 2000; **200**: 281–2.
33 Davis MD, Rogers RS III, Pittelkow MR. Recurrent erythema multiforme/Stevens–Johnson syndrome: response to mycophenolate mofetil. *Arch Dermatol* 2002; **138**: 1547–50.
34 Bakis S, Zagarella S. Intermittent oral cyclosporin for recurrent herpes simplex-associated erythema multiforme. *Australas J Dermatol* 2005; **46**: 18–20.

Stevens–Johnson syndrome and toxic epidermal necrolysis

Incidence of reactions

The incidence of TEN has been estimated at 1.2 cases per million per year in France, based on nationwide surveillance between 1981 and 1985 inclusive [1]. Another study, based on data of the Group Health Cooperative of Puget Sound, Seattle, Washington (which covers about 260 000 individuals), investigated hospitalized patients from 1972 to 1986 inclusive. The incidence of erythema multiforme, SJS and TEN was estimated at 1.8 cases per million person-years for patients aged between 20 and 64 years; the incidence for patients aged less than 20 years, and 65 years or more, increased to 7 and 9 cases per million person-years, respectively [2]. The incidence of TEN was estimated at 0.5 per million per year. Reaction rates per 100 000 exposed individuals were as follows: phenobarbital 20, nitrofurantoin 7, co-trimoxazole and ampicillin 3, and amoxicillin 2. An Italian study estimated the incidence of TEN at about 1.2 cases per million per year [3]. A study based on computerized Medicaid billing data for 1980–84 from the states of Michigan, Minnesota and Florida reported an incidence of SJS of 7.1, 2.6 and 6.8 per million per year, respectively; penicillins, especially aminopenicillins, were most frequently implicated [4]. In West Germany, the overall annual risk of TEN and of SJS was estimated over the years 1981–85 as 0.93 and 1.1 per million, respectively; drugs most frequently implicated were antibiotics (sulphonamides and beta-lactam agents), and analgesics and non-steroidal anti-inflammatory agents (NSAIDs) [5]. In this study, it was possible to attribute the cause of the TEN to a drug in 88% of cases. Another study estimated the incidence for West Germany and Berlin for SJS and TEN as up to 1.89 per million inhabitants per year [6]. An ongoing international case–control study of TEN and SJS in relation to the use of drugs is based on data collection in France, Italy, Germany and Portugal [7]. A recent report from the United States found that there were about 5000 hospitalizations each year with a primary diagnosis of erythema multiforme, SJS or TEN, of which 35% were specifically ascribed to drugs [8]. There are more than 100 000 outpatient visits annually for these diagnoses, and about two million visits for immediate hypersensitivity reactions that may be due to drugs. Outpatient visits for drug eruptions and drug allergies that include a skin component exceed 500 000 annually [8]. The incidence of SJS/TEN with long-acting sulphonamides, sulphones, antibiotics, anticonvulsants, NSAIDs or allopurinol is fortunately rare, occurring only once per 10 000–100 000 courses of drug given [9,10]. The incidence of TEN (cases/million/year) has been reported to be 2.7 times higher, and the fatality twice as high (51% compared with 25%), in the elderly compared with younger adults; the same drugs (NSAIDs, antibacterials and anticonvulsants) are incriminated in both groups [11]. Patients with AIDS have a dramatically

increased incidence of TEN [12]; 14 of 80 consecutive cases of TEN patients were HIV infected, and 15 cases of AIDS-associated TEN occurred in the Paris area over a study period, compared with the expected 0.04 cases [13]. Sulphonamides (sulfadiazine, co-trimoxazole, sulfadoxine), clindamycin, phenobarbital and chlormezanone were implicated [13], as were sulfadiazine and pyrimethamine/clindamycin [14]. Patients with AIDS are more likely to demonstrate multiple cutaneous drug reactions [15].

References

1 Roujeau J-C, Guillaume J-C, Fabre J-D *et al*. Toxic epidermal necrolysis (Lyell syndrome): incidence and drug aetiology in France, 1981–85. *Arch Dermatol* 1990; **126**: 37–42.

2 Chan H-L, Stern RS, Arndt KA *et al*. The incidence of erythema multiforme, Stevens–Johnson syndrome, and toxic epidermal necrolysis: a population based study with particular reference to reactions caused by drugs among outpatients. *Arch Dermatol* 1990; **126**: 43–7.

3 Naldi L, Locati F, Marchesi L, Cainelli T. Incidence of toxic epidermal necrolysis in Italy. *Arch Dermatol* 1990; **126**: 1103–4.

4 Strom BL, Carson JL, Halpern AC *et al*. A population based study of Stevens–Johnson syndrome: incidence and antecedent drug exposures. *Arch Dermatol* 1991; **127**: 831–8.

5 Schöpf E, Stühmer A, Rzany B *et al*. Toxic epidermal necrolysis and Stevens–Johnson syndrome: an epidemiologic study from West Germany. *Arch Dermatol* 1991; **127**: 839–42.

6 Rzany B, Mockenhaupt M, Baur S *et al*. Epidemiology of erythema exudativum multiforme majus, Stevens–Johnson syndrome, and toxic epidermal necrolysis in Germany (1990–92): structure and results of a population based registry. *J Clin Epidemiol* 1996; **49**: 769–73.

7 Kaufman DW. Epidemiologic approaches to the study of toxic epidermal necrolysis. *J Invest Dermatol* 1994; **102**: 31S–33S.

8 Stern RS. Utilization of hospital and outpatient care for adverse cutaneous reactions to medications. *Pharmacoepidemiol Drug Saf* 2005; **14**: 677–84.

9 Leenutaphong V, Sivayathorn A, Suthipinittharm P, Sunthopalin P. Stevens–Johnson syndrome and toxic epidermal necrolysis in Thailand. *Int J Dermatol* 1993; **32**: 428–31.

10 Roujeau JC, Kelly JP, Naldi L *et al*. Medication use and the risk of Stevens–Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med* 1995; **333**: 1600–7.

11 Bastuji-Garin S, Zahedi M, Guillaume JC, Roujeau JC. Toxic epidermal necrolysis (Lyell syndrome) in 77 elderly patients. *Age Ageing* 1993; **22**: 450–6.

12 Porteous DM, Berger TG. Severe cutaneous drug reactions (Stevens–Johnson syndrome and toxic epidermal necrolysis) in human immunodeficiency virus infection. *Arch Dermatol* 1991; **127**: 740–1.

13 Saiag P, Caumes E, Chosidow O *et al*. Drug-induced toxic epidermal necrolysis (Lyell syndrome) in patients infected with the human immunodeficiency virus. *J Am Acad Dermatol* 1992; **26**: 567–74.

14 Caumes E, Bocquet H, Guermonprez G *et al*. Adverse cutaneous reactions to pyrimethamine/sulfadiazine and pyrimethamine/clindamycin in patients with AIDS and toxoplasmic encephalitis. *Clin Infect Dis* 1995; **21**: 656–8.

15 Carr A, Tindall B, Penny R, Cooper DA. Patterns of multiple-drug hypersensitivities in HIV-infected patients. *AIDS* 1993; **7**: 1532–3.

Aetiology

Immunology

SJS and TEN, like erythema multiforme, would seem to have an immunological pathogenesis. In general, CD4 T cells predominate in the upper dermis, while epidermal CD8 T cells and macrophages are variable and Langerhans' cells virtually disappear. Keratinocytes express HLA-DR and ICAM-1, and there is endothelial cell ICAM-1, vascular cell adhesion molecule 1 (VCAM-1) and E-selectin expression [1–7]. CD3 activated T cells expressing the skin-homing receptor (cutaneous leukocyte antigen; CLA) in both skin and peripheral blood parallel the severity of the disease, and tumour necrosis factor-α (TNF-α), IFN-γ and interleukin-2 (IL-2) are overexpressed in peripheral blood mononuclear cells, suggesting an important role for T cells in TEN [7]. Prominent involvement of the monocyte–macrophage lineage, including factor XIIIa$^+$ HLA-DR$^+$ dendrocytes and CD68$^+$ Mac387$^+$ macrophages, before, during and especially after epidermal necrosis has been reported [6], with dense labelling of the epidermis for TNF-α. Factor-XIIIa dendrocytes appear activated in the skin, and depleted from lymph nodes [8]. Expression of the CD40/CD40 ligand system in lesional skin reinforces the importance of interaction between activated T lymphocytes and macrophages in the pathogenesis of SJS/TEN [9]. There is a predominantly Th1 cytokine profile in erythema multiforme, while SJS/TEN lesions show a mixed Th1/Th2 cytokine pattern [10,11]. Serum IL-13 levels are increased in patients with SJS/TEN but not in those with erythema multiforme [12].

TNF-α is strongly expressed in SJS/TEN lesions and may therefore be involved in the characteristic epidermal necrosis [6,10]. Soluble TNF-α (sTNF-α), sTNF-R1 and sTNF-R2 levels were significantly higher in TEN blisters than in burns [13]. sTNF-R1 and sTNF-R2 were significantly more abundant in TEN blisters than serum, indicating that TNF-α processing was mainly a local event in TEN skin [13]. Significantly higher levels of sIL-2R and lower levels of IL-1α were present in blister fluid, but not serum, of patients with TEN compared with patients with burns [14].

Mechanisms mediating keratinocyte death. Keratinocytes from TEN patients have been reported to undergo extensive apoptosis [15]. Cytokines released by activated lymphocytes and/or from keratinocytes may contribute to local cell death in TEN. Activated lymphocytes may induce apoptosis via an interaction between *Fas*-ligand (FasL), expressed on the surface of and secreted by lymphocytes, and *Fas* antigen (CD95), expressed by keratinocytes after exposure to IFN-γ [16–21]. There is keratinocyte overexpression of Fas antigen in drug-induced erythema multiforme, SJS and TEN [19]. Sera from TEN and SJS patients contain high concentrations of soluble FasL (sFasL) [11,17], and induced abundant keratinocyte apoptosis *in vitro*, compared with sera from patients with an erythema multiforme-type drug eruption [17]. Moreover, peripheral blood mononuclear cells from TEN and SJS patients secreted high levels of sFasL on stimulation with the causal drug [17]. Increased sFasL levels precede skin detachment in patients with SJS and TEN [22]. Bcl-2, a protein known to block apoptosis, is strongly expressed along the basal layer and in the dermal infiltrate both in erythema multiforme and SJS/TEN; thus Fas-mediated cell death may be partially suppressed by Bcl-2 protein [19].

Keratinocyte necrosis may, in addition, be mediated by drug-specific CD8 cytotoxic T cells via the perforin–granzyme route [23]. The key role of drug-specific T lymphocytes in the mechanisms of most drug reactions has been confirmed by *in vitro* studies of many clones of T lymphocytes [24]. CD3$^+$, CD8$^+$, CD28$^-$, KIR/KAR (killer inhibitory receptor), CLA-positive cytotoxic T cells (CTL) with NK-like cytotoxicity predominated in early TEN blister fluid [25]. In a case of co-trimoxazole-induced TEN, CD8$^+$, DR$^+$, CLA$^+$, CD56 perforin-positive CTL predominated in blister fluid [26]; cytotoxicity *in vitro* was expressed only in the presence of

either co-trimoxazole, sulfamethoxazole or the nitroso metabolite of sulfamethoxazole, but not with the hydroxylamine metabolite of sulfamethoxazole. In a patient with carbamazepine-induced TEN, lymphocytes were more susceptible to cytotoxic killing by liver microsome-induced carbamazepine intermediates than by the parent drug [27].

Inducible nitric acid synthase is demonstrable in skin in TEN/SJS, which might indicate that nitric oxide contributes to apoptosis and necrosis [28]. The matrix metalloproteinase MMP2 has a significant role in epidermal detachment, inflammation and re-epithelialization. Increased levels of the activated forms of MMP2 were higher in TEN blister fluid compared with bullous pemphigoid, second-degree burns or suction blisters, indicating a potential role for MMP2 in the inflammatory reaction and repair process in TEN skin [29].

References

1 Merot Y, Gravallese E, Guillén FJ, Murphy GF. Lymphocyte subsets and Langerhans' cells in toxic epidermal necrolysis: report of a case. *Arch Dermatol* 1986; **122**: 455–8.

2 Villada G, Roujeau J-C, Cordonnier C *et al*. Toxic epidermal necrolysis after bone marrow transplantation: study of nine cases. *J Am Acad Dermatol* 1990; **23**: 870–5.

3 Miyauchi H, Hosokawa H, Akaeda T *et al*. T-cell subsets in drug-induced toxic epidermal necrolysis: possible pathogenic mechanism induced by CD8 T cells. *Arch Dermatol* 1991; **127**: 851–5.

4 Villada G, Roujeau JC, Clerici T *et al*. Immunopathology of toxic epidermal necrolysis: keratinocytes, HLA-DR expression, Langerhans' cells, and mononuclear cells: an immunopathologic study of five cases. *Arch Dermatol* 1992; **128**: 50–3.

5 Correia O, Delgado L, Ramos JP *et al*. Cutaneous T-cell recruitment in toxic epidermal necrolysis: further evidence of CD8 lymphocyte involvement. *Arch Dermatol* 1993; **129**: 466–8.

6 Paquet P, Nikkels A, Arrese JE *et al*. Macrophages and tumor necrosis factor-α in toxic epidermal necrolysis. *Arch Dermatol* 1994; **130**: 605–8.

7 Leyva L, Torres MJ, Posadas S *et al*. Anticonvulsant-induced toxic epidermal necrolysis: monitoring the immunologic response. *J Allergy Clin Immunol* 2000; **105**: 157–65.

8 Paquet P, Quatresooz P, Pierard GE. Factor-XIIIa dendrocytes in drug-induced toxic epidermal necrolysis (Lyell's syndrome): paradoxical activation in skin and rarefaction in lymph nodes. *Dermatology* 2003; **206**: 374–8.

9 Caproni M, Torchia D, Schincaglia E *et al*. The CD40/CD40 ligand system is expressed in the cutaneous lesions of erythema multiforme and Stevens–Johnson syndrome/toxic epidermal necrolysis spectrum. *Br J Dermatol* 2006; **154**: 319–24.

10 Caproni M, Torchia D, Schincaglia E *et al*. Expression of cytokines and chemokine receptors in the cutaneous lesions of erythema multiforme and Stevens–Johnson syndrome/toxic epidermal necrolysis. *Br J Dermatol* 2006; **155**: 722–8.

11 Quaglino P, Caproni M, Antiga E *et al*. Serum levels of the Th1 promoter IL-12 and the Th2 chemokine TARC are elevated in erythema multiforme and Stevens–Johnson syndrome/toxic epidermal necrolysis and correlate with soluble Fas ligand expression. An immunoenzymatic study from the Italian Group of Immunopathology. *Dermatology* 2007; **214**: 296–304.

12 Quaglino P, Caproni M, Osella-Abate S *et al*. Serum interleukin-13 levels are increased in patients with Stevens–Johnson syndrome/toxic epidermal necrolysis but not in those with erythema multiforme. *Br J Dermatol* 2008; **158**: 184–6.

13 Paquet P, Pierard GE. Soluble fractions of tumor necrosis factor-α, interleukin-6 and of their receptors in toxic epidermal necrolysis: a comparison with second-degree burns. *Int J Mol Med* 1998; **1**: 459–62.

14 Correia O, Delgado L, Roujeau JC *et al*. Soluble interleukin-2 receptor and interleukin-1α in toxic epidermal necrolysis: a comparative analysis of serum and blister fluid samples. *Arch Dermatol* 2002; **138**: 29–32.

15 Paul C, Wolkenstein P, Adle H *et al*. Apoptosis as a mechanism of keratinocyte death in toxic epidermal necrolysis. *Br J Dermatol* 1996; **134**: 710–4.

16 Sayama K, Yonehara S, Watanabe Y, Miki Y. Expression of *Fas* antigen on keratinocytes *in vivo* and induction of apoptosis in cultured keratinocytes. *J Invest Dermatol* 1994; **103**: 330–4.

17 Abe R, Shimizu T, Shibaki A *et al*. Toxic epidermal necrolysis and Stevens–Johnson syndrome are induced by soluble *fas* ligand. *Am J Pathol* 2003; **162**: 1515–20.

18 Murata J, Abe R. Soluble Fas ligand: is it a critical mediator of toxic epidermal necrolysis and Stevens–Johnson syndrome? *J Invest Dermatol* 2007; **127**: 744–5.

19 Marzano AV, Frezzolini A, Caproni M *et al*. Immunohistochemical expression of apoptotic markers in drug-induced erythema multiforme, Stevens–Johnson syndrome and toxic epidermal necrolysis. *Int J Immunopathol Pharmacol* 2007; **20**: 557–66.

20 Abe R. Toxic epidermal necrolysis and Stevens–Johnson syndrome: soluble Fas ligand involvement in the pathomechanisms of these diseases. *J Dermatol Sci* 2008; **52**: 151–9.

21 Borchers AT, Lee JL, Naguwa SM *et al*. Stevens–Johnson syndrome and toxic epidermal necrolysis. *Autoimmun Rev* 2008; **7**: 598–605.

22 Murata J, Abe R, Shimizu H. Increased soluble Fas ligand levels in patients with Stevens–Johnson syndrome and toxic epidermal necrolysis preceding skin detachment. *J Allergy Clin Immunol* 2008; **122**: 992–1000.

23 Borchers AT, Lee JL, Naguwa SM *et al*. Stevens–Johnson syndrome and toxic epidermal necrolysis. *Autoimmun Rev* 2008; **7**: 598–605.

24 Schnyder B, Burkhart C, Schnyder-Frutig K *et al*. Recognition of sulfamethoxazole and its reactive metabolites by drug-specific CD4 T cells from allergic individuals. *J Immunol* 2000; **164**: 6647–54.

25 Le Cleach L, Delaire S, Boumsell L *et al*. Blister fluid T lymphocytes during toxic epidermal necrolysis are functional cytotoxic cells which express human natural killer (NK) inhibitory receptors. *Clin Exp Immunol* 2000; **119**: 225–30.

26 Nassif A, Bensussan A, Dorothee G *et al*. Drug specific cytotoxic T-cells in the skin lesions of a patient with toxic epidermal necrolysis. *J Invest Dermatol* 2002; **118**: 728–33.

27 Friedmann PS, Strickland I, Pirmohamed M, Park BK. Investigation of mechanisms in toxic epidermal necrolysis induced by carbamazepine. *Arch Dermatol* 1994; **130**: 598–604.

28 Lerner LH, Qureshi AA, Reddy BV, Lerner EA. Nitric acid synthase in toxic epidermal necrolysis and Stevens–Johnson syndrome. *J Invest Dermatol* 2000; **114**: 196–9.

29 Paquet P, Nusgens BV, Pierard GE, Lapiere CM. Gelatinases in drug-induced toxic epidermal necrolysis. *Eur J Clin Invest* 1998; **28**: 528–32.

Pharmacogenetics

The reason why some individuals develop such marked immune reactions against medications has until very recently been obscure. A widely accepted hypothesis has been that patients suffering from severe drug reactions are exposed to increased amounts of reactive (oxidative) metabolites because of a lowered ability to detoxify reactive metabolites, either on a genetic basis, or on a functional basis (e.g. enzyme dysfunction in AIDS or other diseases) (see Chapter 75). Thus, genetic differences in metabolism of sulphonamides may underlie idiosyncratic toxicity [1] and phenytoin hypersensitivity syndrome appears to be associated with an inherited deficiency of epoxide hydrolase [2]. Over the last few years, it has become apparent that pharmacogenetic influences underlie a great number of drug reactions (see Chapter 75). Thus, in relation to SJS, associated polymorphisms have been described in the Fas ligand gene [3], the IL-13/IL-4R signalling pathway gene [4,5], and the Toll-like receptor 3 gene [6]. Several recent studies have reported strong genetic associations between particular HLA alleles and susceptibility to drug hypersensitivity [7–9]. The genetic associations can be drug specific, such as HLA-B*1502 being associated with SJS and TEN induced by carbamazepine [10–12] as well as phenytoin [11,12] and lamotrigine [11], HLA-B*5801 with allopurinol-induced severe cutaneous adverse reac-

tions [13], and HLA-B*5701 with abacavir hypersensitivity [14,15]; nevirapine hypersensitivity has been reported in Caucasian Australians with HLA-DRB1*0101 and high $CD4^+$ T-cell counts, and Sardinians and Japanese with HLA-Cw8 [8]. The genetic association can also be ethnicity specific; as HLA-B*1502 is seen in almost all cases of carbamazepine-SJS/TEN occurring in Han Chinese from Taiwan and other Asian countries including Thailand [11,12,16], but this is not true for Caucasians [16,17]. There was a correlation for SJS with HLA-B*44, DRB1*07 and with the MHC ancestral 57.1 haplotype (and its constituents) in Caucasians [18], whilst HLA-A*0206 is strongly associated with SJS/TEN with ocular complications in Japanese subjects [19,20]. Finally, a genetic association can be phenotype-specific, as the association with HLA-B*1502 in Asians is with carbamazepine- or phenytoin-induced SJS/TEN, and not with maculopapular drug eruptions or with the drug hypersensitivity syndrome [7,10,11]. Carbamazepine maculopapular eruptions were by contrast associated with single nucleotide polymorphisms (SNPs) in the HLA-E region and a nearby allele, HLA-A*3101, and drug hypersensitivity with SNPs in the motilin gene located terminal to the MHC class II genes [10]. Cutaneous adverse reactions to carbamazepine were not associated with SNPs in genes involved in metabolism of the drug [10]. Whilst the association of HLA-B*5801 and antiepileptic drug-related SJS/TEN is almost absolute in Asians, HLA-B*5801 was present in only 55% of allopurinol-induced SJS/TEN patients of European ancestry [13]; thus the HLA-B alleles behave as strong risk factors, but are neither sufficient nor necessary to explain the disease.

References

1 Shear NH, Spielberg SP, Grant DM *et al*. Differences in metabolism of sulfonamides predisposing to idiosyncratic toxicity. *Ann Intern Med* 1986; **105**: 179–84.

2 Yoo JH, Kang DS, Chun WH *et al.* Anticonvulsant hypersensitivity syndrome with an epoxide hydrolase defect. *Br J Dermatol* 1999; **140**: 181–3.

3 Ueta M, Sotozono C, Inatomi T *et al*. Association of Fas ligand gene polymorphism with Stevens–Johnson syndrome. *Br J Ophthalmol* 2008; **92**: 989–91.

4 Ueta M, Sotozono C, Inatomi T *et al*. Association of IL4R polymorphisms with Stevens–Johnson syndrome. *J Allergy Clin Immunol* 2007; **120**: 1457–9.

5 Ueta M, Sotozono C, Inatomi T *et al*. Association of combined IL-13/IL-4R signaling pathway gene polymorphism with Stevens–Johnson syndrome accompanied by ocular surface complications. *Invest Ophthalmol Vis Sci* 2008; **49**: 1809–13.

6 Ueta M, Sotozono C, Inatomi T *et al*. Toll-like receptor 3 gene polymorphisms in Japanese patients with Stevens–Johnson syndrome. *Br J Ophthalmol* 2007; **91**: 962–5.

7 Chung WH, Hung SI, Chen YT. Human leukocyte antigens and drug hypersensitivity. *Curr Opin Allergy Clin Immunol* 2007; **7**: 317–23.

8 Gatanaga H, Honda H, Oka S. Pharmacogenetic information derived from analysis of HLA alleles. *Pharmacogenomics* 2008; **9**: 207–14.

9 Chessman D, Kostenko L, Lethborg T *et al*. Human leukocyte antigen class I-restricted activation of CD8+ T cells provides the immunogenetic basis of a systemic drug hypersensitivity. *Immunity* 2008; **28**: 822–32.

10 Hung SI, Chung WH, Jee SH *et al*. Genetic susceptibility to carbamazepine-induced cutaneous adverse drug reactions. *Pharmacogenet Genomics* 2006; **16**: 297–306.

11 Man CB, Kwan P, Baum L *et al*. Association between HLA-B*1502 allele and antiepileptic drug-induced cutaneous reactions in Han Chinese. *Epilepsia* 2007; **48**: 1015–8.

12 Locharernkul C, Loplumlert J, Limotai C *et al.* Carbamazepine and phenytoin induced Stevens–Johnson syndrome is associated with HLA-B*1502 allele in Thai population. *Epilepsia* 2008; **49**: 2087–91.

13 Lonjou C, Borot N, Sekula P *et al*. A European study of HLA-B in Stevens–Johnson syndrome and toxic epidermal necrolysis related to five high-risk drugs. *Pharmacogenet Genomics* 2008; **18**: 99–107.

14 Mallal S, Nolan D, Witt C *et al*. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. *Lancet* 2002; **359**: 727–32.

15 Sun HY, Hung CC, Lin PH *et al*. Incidence of abacavir hypersensitivity and its relationship with HLA-B*5701 in HIV-infected patients in Taiwan. *J Antimicrob Chemother* 2007; **60**: 599–604.

16 Lonjou C, Thomas L, Borot N *et al*. A marker for Stevens–Johnson syndrome: ethnicity matters. *Pharmacogenomics J* 2006; **6**: 265–8.

17 Alfirevic A, Jorgensen AL, Williamson PR *et al*. HLA-B locus in Caucasian patients with carbamazepine hypersensitivity. *Pharmacogenomics* 2006; **7**: 813–8.

18 Pirmohamed M, Arbuckle JB, Bowman CE *et al*. Investigation into the multidimensional genetic basis of drug-induced Stevens–Johnson syndrome and toxic epidermal necrolysis. *Pharmacogenomics* 2007; **8**: 1661–91.

19 Ueta M, Sotozono C, Tokunaga K *et al*. Strong association between HLA-A*0206 and Stevens–Johnson syndrome in the Japanese. *Am J Ophthalmol* 2007; **143**: 367–8.

20 Ueta M, Tokunaga K, Sotozono C *et al.* HLA class I and II gene polymorphisms in Stevens–Johnson syndrome with ocular complications in Japanese. *Mol Vis* 2008; **14**: 550–5.

Drugs implicated in Stevens–Johnson syndrome

Drugs potentially causing SJS are listed in Table 76.2 [1–8]. A retrospective study from Malaysia reported that the most common causes of SJS were sulphonamides, tetracycline and the penicillin derivatives [8]. In the USA, NSAIDs were reported to be an important cause [9]. Severe SJS-like reactions have been described resulting from sulphonamides with or without trimethoprim [10–12] and following malaria prophylaxis with Fansidar (pyrimethamine and sulfadoxine) [13,14]. Patients with AIDS are at an increased risk of developing severe SJS reactions to co-trimoxazole and thiacetazone [15–17]. The culprit drugs in a study from Thailand included the following: antibiotics (penicillin, sulphonamides, tetracycline, erythromycin); anticonvulsants (phenytoin, carbamazepine, barbiturates); antitubercular drugs (thiacetazone); analgesics (acetylsalicylic acid, fenbufen); sulphonylurea; and allopurinol. The total mortality rate was 14%: 5% for SJS and 40% for TEN [7]. Data from surveillance networks in France, Germany, Italy and Portugal on 245 people hospitalized because of SJS or TEN [18] indicated that for drugs usually used for short periods, relative risks were increased as follows: co-trimoxazole and other sulphonamide antibiotics 172, chlormezanone 62, aminopenicillins 6.7, quinolones 10 and cephalosporins 14, and for paracetamol (acetaminophen) 0.6 in France but 9.3 in the other countries. For drugs used for months or years, the increased risk was largely in the first 2 months, and was as follows: carbamazepine 90, phenobarbital 45, phenytoin 53, valproic acid 25, oxicam NSAIDs 72, allopurinol 52 and corticosteroids 54. For many drugs, including thiazide diuretics and oral hypoglycaemic agents, there was no significant increase in risk. The excess risk did not exceed five cases per million users per week for any of the drugs. Acetylsalicylic acid and other salicylates are not associated with a measurable increase in the risk of SJS or TEN [19].

Other drugs implicated in SJS include: the antiretroviral drugs nevirapine [20–23] and abacavir [24], lamotrigine [25,26], terbinafine [27], nystatin [28], ciprofloxacin [29], the antimalarials mefloquine [30] and hydroxychloroquine [31], cyclophosphamide [32], methotrexate [33], rituximab [34], the tyrosine kinase inhibitor

imatinib used in leukaemia therapy [35], propylthiouracil [36], ranitidine [37], mebendazole and metronidazole [38], bezafibrate [39], diltiazem, nifedipine and verapamil [40], ramipril [41], sertraline [42], fluoxetine and fluvoxamine [43] and tetrazepam [44]. SJS has followed vaccination [45], ingestion of a health drink (Eberu) containing ophiopogonis tuber [46] and use of cocaine [47].

References

1 Bianchine JR, Macaraeg PVJ, Lasagna L *et al*. Drugs as aetiologic factors in the Stevens–Johnson syndrome. *Am J Med* 1968; **44**: 390–405.
2 Kauppinen K. Cutaneous reactions to drugs: with special reference to severe mucocutaneous bullous eruptions and sulphonamides. *Acta Derm Venereol (Stockh)* 1972; **52** (Suppl. 68): 1–89.
3 Böttiger LE, Strandberg I, Westerholm B. Drug-induced febrile mucocutaneous syndrome: with a survey of the literature. *Acta Med Scand* 1975; **198**: 229–33.
4 Ruiz-Maldonado R. Acute disseminated epidermal necrosis types 1, 2, and 3: study of 60 cases. *J Am Acad Dermatol* 1985; **13**: 623–35.
5 Nethercott JR, Choi BC. Erythema multiforme (Stevens–Johnson syndrome): chart review of 123 hospitalized patients. *Dermatologica* 1985; **171**: 383–96.
6 Ting HC, Adam BA. Stevens–Johnson syndrome: a review of 34 cases. *Int J Dermatol* 1985; **24**: 587–91.
7 Leenutaphong V, Sivayathorn A, Suthipinittharm P, Sunthonpalin P. Stevens–Johnson syndrome and toxic epidermal necrolysis in Thailand. *Int J Dermatol* 1993; **32**: 428–31.
8 Gebel K, Hornstein OP. Drug-induced oral erythema multiforme: results of a long-term retrospective study. *Dermatologica* 1984; **168**: 35–40.
9 Stern R, Bigby M. An expanded profile of cutaneous reactions to non-steroidal anti-inflammatory drugs. *JAMA* 1984; **252**: 1433–7.
10 Carrol OM, Bryan PA, Robinson RJ. Stevens–Johnson syndrome associated with long-acting sulfonamides. *JAMA* 1966; **195**: 691–3.
11 Azinge NO, Garrick GA. Stevens–Johnson syndrome (erythema multiforme) following ingestion of trimethoprim–sulfamethoxazole on two separate occasions in the same person: a case report. *J Allergy Clin Immunol* 1978; **62**: 125–6.
12 Aberer W, Stingl G, Wolff K. Stevens–Johnson-Syndrom und toxische epidermale Nekrolyse nach Sulfonamideinahme. *Hautarzt* 1982; **33**: 484–90.
13 Hornstein OP, Ruprecht KW. Fansidar-induced Stevens–Johnson syndrome. *N Engl J Med* 1982; **307**: 1529–30.
14 Miller KD, Lobel HO, Satriale RF *et al*. Severe cutaneous reactions among American travelers using pyrimethamine–sulfadoxine (Fansidar) for malaria prophylaxis. *Am J Trop Med Hyg* 1986; **35**: 451–8.
15 De Raeve L, Song M, Van Maldergem L. Adverse cutaneous drug reactions in AIDS. *Br J Dermatol* 1988; **119**: 521–3.
16 Porteous DM, Berger TG. Severe cutaneous drug reactions (Stevens–Johnson syndrome and toxic epidermal necrolysis) in human immunodeficiency virus infection. *Arch Dermatol* 1991; **127**: 740–1.
17 van der Ven AJAM, Koopmans PP, Vree TB, van der Meer JWM. Adverse reactions to co-trimoxazole in HIV infection. *Lancet* 1991; **338**: 431–3.
18 Roujeau JC, Kelly JP, Naldi L *et al*. Medication use and the risk of Stevens–Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med* 1995; **333**: 1600–7.
19 Kaufman DW, Kelly JP. Acetylsalicylic acid and other salicylates in relation to Stevens–Johnson syndrome and toxic epidermal necrolysis. *Br J Clin Pharmacol* 2001; **51**: 174–6.
20 Wetterwald E, Le Cleach L, Michel C *et al*. Nevirapine-induced overlap Stevens–Johnson syndrome/toxic epidermal necrolysis. *Br J Dermatol* 1999; **140**: 980–2.
21 Metry DW, Lahart CJ, Farmer KL, Hebert AA. Stevens–Johnson syndrome caused by the antiretroviral drug nevirapine. *J Am Acad Dermatol* 2001; **44** (2 Suppl.): 354–7.
22 Fagot JP, Mockenhaupt M, Bouwes-Bavinck JN *et al*. Nevirapine and the risk of Stevens–Johnson syndrome or toxic epidermal necrolysis. *AIDS* 2001; **15**: 1843–8.
23 Dodi F, Alessandrini A, Camera M *et al*. Stevens–Johnson syndrome in HIV patients treated with nevirapine: two case reports. *AIDS* 2002; **16**: 1197–8.
24 Bossi P, Roujeau JC, Bricaire F, Caumes E. Stevens–Johnson syndrome associated with abacavir therapy. *Clin Infect Dis* 2002; **35**: 902.
25 Guberman AH, Besag FM, Brodie MJ *et al*. Lamotrigine-associated rash: risk–benefit considerations in adults and children. *Epilepsia* 1999; **40**: 985–91.
26 Hilas O, Charneski L. Lamotrigine-induced Stevens–Johnson syndrome. *Am J Health Syst Pharm* 2007; **64**: 273–5.
27 Rzany B, Mockenhaupt M, Gehring W, Schöpf E. Stevens–Johnson syndrome after terbinafine therapy. *J Am Acad Dermatol* 1994; **30**: 509.
28 Garty B-Z. Stevens–Johnson syndrome associated with nystatin treatment. *Arch Dermatol* 1991; **127**: 741–2.
29 Bhatia RS. Stevens Johnson syndrome following a single dose of ciprofloxacin. *J Assoc Physicians India* 1994; **42**: 344.
30 Smith HR, Croft AM, Black MM. Dermatological adverse effects with the antimalarial drug mefloquine: a review of 74 published case reports. *Clin Exp Dermatol* 1999; **24**: 249–54.
31 Leckie MJ, Rees RG. Stevens–Johnson syndrome in association with hydroxychloroquine treatment for rheumatoid arthritis. *Rheumatology (Oxford)* 2002; **41**: 473–4.
32 Assier-Bonnet HJ, Aractingi S, Cadranel J *et al*. Stevens–Johnson syndrome induced by cyclophosphamide: report of two cases. *Br J Dermatol* 1996; **135**: 864–5.
33 Hani N, Casper C, Groth W *et al*. Stevens–Johnson syndrome-like exanthema secondary to methotrexate histologically simulating acute graft-versus-host disease. *Eur J Dermatol* 2000; **10**: 548–50.
34 Lowndes S, Darby A, Mead G, Lister A. Stevens–Johnson syndrome after treatment with rituximab. *Ann Oncol* 2002; **13**: 1948–50.
35 Mahapatra M, Mishra P, Kumar R. Imatinib-induced Stevens–Johnson syndrome: recurrence after re-challenge with a lower dose. *Ann Hematol* 2007; **86**: 537–8.
36 Dysseleer A, Buysschaert M, Fonck C *et al*. Acute interstitial nephritis and fatal Stevens–Johnson syndrome after propylthiouracil therapy. *Thyroid* 2000; **10**: 713–6.
37 Lin CC, Wu JC, Huang DF *et al*. Ranitidine-related Stevens–Johnson syndrome in patients with severe liver diseases: a report of two cases. *J Gastroenterol Hepatol* 2001; **16**: 481–3.
38 Chen KT, Twu SJ, Chang HJ, Lin RS. Outbreak of Stevens–Johnson syndrome/toxic epidermal necrolysis associated with mebendazole and metronidazole use among Filipino laborers in Taiwan. *Am J Public Health* 2003; **93**: 489–92.
39 Sawamura D, Umeki K. Stevens–Johnson syndrome associated with bezafibrate. *Acta Derm Venereol (Stockh)* 2000; **80**: 457.
40 Knowles S, Gupta AK, Shear NH. The spectrum of cutaneous reactions associated with diltiazem: three cases and a review of the literature. *J Am Acad Dermatol* 1998; **38**: 201–6.
41 Oskay T, Ozçelik T, Kutluay L. Stevens–Johnson Syndrome associated with ramipril. *Int J Dermatol* 2003; **42**: 580–1.
42 January V, Toledano C, Machet L *et al*. Stevens–Johnson syndrome after sertraline. *Acta Derm Venereol (Stockh)* 1999; **79**: 401.
43 Richard MA, Fiszenson F, Jreissati M *et al*. Cutaneous adverse effects during selective serotonin reuptake inhibitors therapy: two cases. *Ann Dermatol Vénéréol* 2001; **128**: 759–61.
44 Sanchez I, Garcia-Abujeta JL, Fernandez L *et al*. Stevens–Johnson syndrome from tetrazepam. *Allergol Immunopathol (Madr)* 1998; **26**: 55–7.
45 Ball R, Ball LK, Wise RP *et al*. Stevens–Johnson syndrome and toxic epidermal necrolysis after vaccination: reports to the vaccine adverse event reporting system. *Pediatr Infect Dis J* 2001; **20**: 219–23.
46 Mochitomi Y, Inoue A, Kawabata H *et al*. Stevens–Johnson syndrome caused by a health drink (Eberu) containing ophiopogonis tuber. *J Dermatol* 1998; **25**: 662–5.
47 Hofbauer GF, Burg G, Nestle FO. Cocaine-related Stevens–Johnson syndrome. *Dermatology* 2000; **201**: 258–60.

Drugs implicated in toxic epidermal necrolysis

There is a degree of overlap between SJS and TEN; SJS may evolve into TEN, and thus several drugs have been recorded as producing both entities (Tables 76.2 & 76.3) [1–18].

A large number of different drugs have been implicated anecdotally, but in the past the most common triggers (Table 76.3) have included: antiepileptic drugs (phenytoin, barbiturates, carbam-

Table 76.3 Drugs causing toxic epidermal necrolysis.

Antibiotics	*Anticonvulsants*
Sulphonamides	Barbiturates
Co-trimoxazole*	Phenobarbital*
Sulfadoxine	Carbamazepine*
Sulfadiazine	Lamotrigine*
Sulfasalazine	Phenytoin*
Penicillins	Valproic acid†
Amoxicillin†	*Antiretroviral drugs*
Ampicillin†	Abacavir
Cephalosporins†	Nevirapine*
Ethambutol	*Antifungal agents*
Fluoroquinolones†	Terbinafine
Isoniazid	Griseofulvin
Streptomycin	
Tetracycline	
Thiacetazone*	
Non-steroidal anti-inflammatory drugs	*Gastrointestinal drugs*
Phenylbutazone*	Famotidine
Oxyphenabutazone	Omeprazole
Oxicam-derivatives	Ranitidine
Meloxicam*	*Miscellaneous*
Piroxicam*	Allopurinol*
Tenoxicam*	Chlorpromazine
Isoxicam	Dapsone
Diclofenac†	Gold
Fenbufen	Nitrofurantoin
Salicylates	Pentamidine
Naproxen	Tolbutamide
Pyrazolon derivatives	Vaccination
COX-2 inhibitors	
Celecoxib	
Valdecoxib*	

* Definite high risk.

† Probable low-risk association.

azepine and lamotrigine [19–23]); sulphonamides and trimethoprim [24]; ampicillin and other beta-lactam antibiotics [25]; allopurinol [26–28], NSAIDs (especially pyrazolon derivatives, e.g. phenylbutazone and oxicam derivatives) [26] and sulphonamide COX-2 inhibitors (particularly valdecoxib, less commonly celecoxib) [29–31]); terbinafine [32–34]; antiretrovirals including nevirapine [35,36] and abacavir [37,38]; and pentamidine. A high proportion of adult cases of SJS or TEN related to anticonvulsants reportedly occur in patients receiving radiotherapy for brain tumour, and it has been suspected that cancer and/or radiotherapy increases the risk. The absolute incidence of phenytoin-induced TEN recorded in 1991 was very low, with nine cases reported in the USA over a decade, compared with 2 million Americans who took phenytoin [11]. The incidence of erythema multiforme, SJS and TEN with the following drugs was reported in a US series from 1990 as follows: phenobarbital 20, nitrofurantoin 7, co-trimoxazole and ampicillin each 3, and amoxicillin 2, per 100 000 exposed patients [7]. A more recent study in 2005 documented risk estimates for new users of carbamazepine, lamotrigine, phenytoin and phenobarbitone as varying between 1 and 10 per 10 000, with a consistently lower risk for valproic acid [23]. The risk of SJS/TEN is highest in the first 8 weeks of therapy with phenytoin, phenobarbital, carbamazepine and lamotrigine [19]. A study from 1995 found that 4 of 232 390 patients on co-trimoxazole developed erythema multiforme or SJS, while only 1 in 196 397 prescribed cephalexin developed TEN [24].

In France, a survey from 1981 to 1985 showed drugs most often responsible as: antibacterial agents (especially sulphonamides); NSAIDs including oxyphenabutazone and fenbufen; and phenytoin [39]. Review of the English language literature from 1966 to 1987 suggested that allopurinol, NSAIDs, phenytoin and the sulphonamide antibiotics were most frequently responsible [40]. A study from the USA in 1991 reported that penicillins, especially aminopenicillins, were most frequently implicated [9]. In West Germany, drugs most frequently implicated in 1991 were antibiotics (sulphonamides and beta-lactam agents) and analgesics and NSAIDs [10]. In India, one-third of cases reported in 1991 were the result of drugs used for the treatment of tuberculosis, especially thiacetazone and isoniazid [41].

A more recent study documented strong associations for nevirapine and lamotrigine, and weaker associations for sertraline, pantoprazole, and tramadol, and confirmed those for anti-infective sulphonamides, allopurinol, carbamazepine, phenobarbital, phenytoin, and oxicam-NSAIDs [42]. Nevirapine was reported to have replaced sulphonamides as the leading cause of SJS and TEN related to AIDS in Europe in 2001 [36]. Allopurinol is reportedly the most common cause of SJS and TEN in Europe and Israel [28]. By contrast, the following medications are not associated with a moderate or high risk of causing TEN: contraceptive pills, benzodiazepines, thiazide diuretics, sulphonylurea antidiabetics, angiotensin-converting enzyme inhibitors, β-blockers, acetyl salicylic acid and fibrate cholesterol-lowering agents [17].

Over 100 different medications have been reported as having caused TEN, and the number keeps on increasing, but case reports are of limited significance because publications are biased toward 'original' and new associations. Nonetheless, other antibiotics, antifungals and antiprotozoal drugs incriminated include ciprofloxacin [43,44], vancomycin [45,46], ofloxacin [47], telithromycin [48], thiacetazone [49], fluconazole [50], griseofulvin [51,52], Fansidar [53] and foscarnet [54], as well as the antimalarials mefloquine [55] and hydroxychloroquine [56,57]. Miscellaneous causes include fluoxetine and fluvoxamine [58–60], paroxetine [61], tetrazepam [62], the antiepileptic zonisamide [63], diltiazem, nifedipine and verapamil [64], sildenafil [65], pseudophedrine [66], omeprazole [67], lansoprazole [68], ranitidine [69], famotidine [70] and cimetidine [71], atorvastatin [72], leflunomide [73], thalidomide [74], etretinate [75], methotrexate [76,77], cytosine arabinoside [78], IL-2 [79], cetuximab [80], and amifostine [81]. Even acetaminophen (paracetamol) has rarely been recorded as causing TEN [82].

Immunization with diphtheria–pertussis–tetanus (DPT), measles, poliomyelitis, smallpox and influenza vaccines has been recorded as a cause of TEN [11,83,84]. Single cases of TEN have followed use of the radiological contrast media diatrizoate solution for excretory pyelography [85] and iopamidol for cardiac catherization [86], use of a terconazole vaginal suppository [87], application of eye drops [88] and contact with a toxic fumigant, acrylonitrile [89]. TEN or SJS following non-mucosal topical drug

application seems to be extremely rare [90]. TEN has been described in association with graft-versus-host reactions [91,92] and with lupus erythematosus [93].

References

1 Heng MCY. Drug-induced toxic epidermal necrolysis. *Br J Dermatol* 1985; **113**: 597–60.
2 Fabrizio PJ, McCloshey WW, Jeffrey LP. Drugs causing toxic epidermal necrolysis. *Drug Intell Clin Pharmacol* 1985; **19**: 733–5.
3 Guillaume J-C, Roujeau J-C, Penso D *et al*. The culprit drugs in 87 cases of toxic epidermal necrolysis (Lyell's syndrome). *Arch Dermatol* 1987; **123**: 1166–70.
4 Ruiz-Maldonado R. Acute disseminated epidermal necrosis types 1, 2 and 3: study of 60 cases. *J Am Acad Dermatol* 1985; **13**: 623–35.
5 Roujeau J-C, Chosidow O, Saiag P, Guillaume J-C. Toxic epidermal necrolysis (Lyell syndrome). *J Am Acad Dermatol* 1990; **23**: 1039–58.
6 Roujeau J-C, Guillaume J-C, Fabre J-D *et al*. Toxic epidermal necrolysis (Lyell syndrome): incidence and drug aetiology in France, 1981–85. *Arch Dermatol* 1990; **126**: 37–42.
7 Chan H-L, Stern RS, Arndt KA *et al*. The incidence of erythema multiforme, Stevens–Johnson syndrome, and toxic epidermal necrolysis: a population based study with particular reference to reactions caused by drugs among outpatients. *Arch Dermatol* 1990; **126**: 43–7.
8 Naldi L, Locati F, Marchesi L, Cainelli T. Incidence of toxic epidermal necrolysis in Italy. *Arch Dermatol* 1990; **126**: 1103–4.
9 Strom BL, Carson JL, Halpern AC *et al*. A population based study of Stevens–Johnson syndrome: incidence and antecedent drug exposures. *Arch Dermatol* 1991; **127**: 831–8.
10 Schöpf E, Stühmer A, Rzany B *et al*. Toxic epidermal necrolysis and Stevens–Johnson syndrome: an epidemiologic study from West Germany. *Arch Dermatol* 1991; **127**: 839–42.
11 Avakian R, Flowers FP, Araujo OE, Ramos-Caro FA. Toxic epidermal necrolysis: a review. *J Am Acad Dermatol* 1991; **25**: 69–79.
12 Parsons JM. Toxic epidermal necrolysis. *Int J Dermatol* 1992; **31**: 749–68.
13 Paquet P. Les medicaments responsables de necrolyse epidermique toxique (syndrome de Lyell). *Thérapie* 1993; **48**: 133–9.
14 Lyell A. Drug-induced toxic epidermal necrolysis. I. An overview. *Clin Dermatol* 1993; **11**: 491–2.
15 Roujeau JC. Drug-induced toxic epidermal necrolysis. II. Current aspects. *Clin Dermatol* 1993; **11**: 493–500.
16 Leenutaphong V, Sivayathorn A, Suthipinittharm P, Sunthopalin P. Stevens–Johnson syndrome and toxic epidermal necrolysis in Thailand. *Int J Dermatol* 1993; **32**: 428–31.
17 Roujeau JC, Kelly JP, Naldi L *et al*. Medication use and the risk of Stevens–Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med* 1995; **333**: 1600–7.
18 Sharma VK, Sethuraman G, Minz A. Stevens Johnson syndrome, toxic epidermal necrolysis and SJS-TEN overlap: a retrospective study of causative drugs and clinical outcome. *Indian J Dermatol Venereol Leprol* 2008; **74**: 238–40.
19 Rzany B, Correia O, Kelly JP *et al*. Risk of Stevens–Johnson syndrome and toxic epidermal necrolysis during first weeks of antiepileptic therapy: a case-control study. Study Group of the International Case Control Study on Severe Cutaneous Adverse Reactions. *Lancet* 1999; **354**: 1033–4.
20 Creamer JD, Whittaker SJ, Kerr-Muir M, Smith NP. Phenytoin-induced toxic epidermal necrolysis: a case report. *Clin Exp Dermatol* 1996; **21**: 116–20.
21 Sterker M, Berrouschot J, Schneider D. Fatal course of toxic epidermal necrolysis under treatment with lamotrigine. *Int J Clin Pharmacol Ther* 1995; **33**: 595–7.
22 Bhushan M, Brooke R, Hewitt-Symonds M *et al*. Prolonged toxic epidermal necrolysis due to lamotrigine. *Clin Exp Dermatol* 2000; **25**: 349–51.
23 Mockenhaupt M, Messenheimer J, Tennis P, Schlingmann J. Risk of Stevens–Johnson syndrome and toxic epidermal necrolysis in new users of antiepileptics. *Neurology* 2005; **64**: 1134–8.
24 Jick H, Derby LE. A large population based follow-up study of trimethoprim-sulfamethoxazole, trimethoprim, and cephalexin for uncommon serious drug toxicity. *Pharmacotherapy* 1995; **15**: 428–32.
25 Romano A, Di Fonso M, Pocobelli D *et al*. Two cases of toxic epidermal necrolysis caused by delayed hypersensitivity to beta-lactam antibiotics. *J Invest Allergol Clin Immunol* 1993; **3**: 53–5.
26 Stratigos JD, Bartsokas SK, Capetanakis J. Further experiences of toxic epidermal necrolysis incriminating allopurinol, pyrazolone, and derivatives. *Br J Dermatol* 1972; **86**: 564–7.
27 Lee HY, Pang SM, Thamotharampillai T. Allopurinol-induced Stevens–Johnson syndrome and toxic epidermal necrolysis. *J Am Acad Dermatol* 2008; **59**: 352–3.
28 Halevy S, Ghislain PD, Mockenhaupt M *et al*. Allopurinol is the most common cause of Stevens–Johnson syndrome and toxic epidermal necrolysis in Europe and Israel. *J Am Acad Dermatol* 2008; **58**: 25–32.
29 La Grenade L, Lee L, Weaver J *et al*. Comparison of reporting of Stevens–Johnson syndrome and toxic epidermal necrolysis in association with selective COX-2 inhibitors. *Drug Saf* 2005; **28**: 917–24.
30 Glasser DL, Burroughs SH. Valdecoxib-induced toxic epidermal necrolysis in a patient allergic to sulfa drugs. *Pharmacotherapy* 2003; **23**: 551–3.
31 Giglio P. Toxic epidermal necrolysis due to administration of celecoxib (Celebrex). *South Med J* 2003; **96**: 320–1.
32 Carstens J, Wendelboe P, Sogaard H, Thestrup-Pedersen K. Toxic epidermal necrolysis and erythema multiforme following therapy with terbinafine. *Acta Derm Venereol (Stockh)* 1994; **74**: 391–2.
33 White SI, Bowen-Jones D. Toxic epidermal necrolysis induced by terbinafine in a patient on long-term antiepileptics. *Br J Dermatol* 1996; **134**: 188–9.
34 Gupta AK, Kopstein JB, Shear NH. Hypersensitivity reaction to terbinafine. *J Am Acad Dermatol* 1997; **36**: 1018–9.
35 Wetterwald E, Le Cleach L, Michel C *et al*. Nevirapine-induced overlap Stevens–Johnson syndrome/toxic epidermal necrolysis. *Br J Dermatol* 1999; **140**: 980–2.
36 Fagot JP, Mockenhaupt M, Bouwes-Bavinck JN *et al*. Nevirapine and the risk of Stevens–Johnson syndrome or toxic epidermal necrolysis. *AIDS* 2001; **15**: 1843–8.
37 Mallal S, Nolan D, Witt C *et al*. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. *Lancet* 2002; **359**: 727–32.
38 Mallal S, Phillips E, Carosi G *et al*. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med* 2008; **358**: 568–79.
39 Roujeau J-C, Guillaume J-C, Fabre J-D *et al*. Toxic epidermal necrolysis (Lyell syndrome): incidence and drug aetiology in France, 1981–85. *Arch Dermatol* 1990; **126**: 37–42.
40 Stern RS, Chan H-L. Usefulness of case report literature in determining drugs responsible for toxic epidermal necrolysis. *J Am Acad Dermatol* 1989; **21**: 317–22.
41 Nanda A, Kaur S. Drug-induced toxic epidermal necrolysis in developing countries. *Arch Dermatol* 1990; **126**: 125.
42 Mockenhaupt M, Viboud C, Dunant A *et al*. Stevens–Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR-study. *J Invest Dermatol* 2008; **128**: 35–44.
43 Tham TCK, Allen G, Hayes D *et al*. Possible association between toxic epidermal necrolysis and ciprofloxacin. *Lancet* 1991; **338**: 522.
44 Moshfeghi M, Mandler HD. Ciprofloxacin-induced toxic epidermal necrolysis. *Ann Pharmacother* 1993; **27**: 467–9.
45 Vidal C, Gonzalez Quintela A, Fuente R. Toxic epidermal necrolysis due to vancomycin. *Ann Allergy* 1992; **68**: 345–7.
46 Hsu SI. Biopsy-proved acute tubulointerstitial nephritis and toxic epidermal necrolysis associated with vancomycin. *Pharmacotherapy* 2001; **21**: 1233–9.
47 Melde SL. Ofloxacin: a probable cause of toxic epidermal necrolysis. *Ann Pharmacother* 2001; **35**: 1388–90.
48 Bédard M-S, Gilbert M. Telithromycin-induced TEN: report of a case. *Arch Dermatol* 2007; **143**: 427–8.
49 Ipuge YA, Rieder HL, Enarson DA. Adverse cutaneous reactions to thiacetazone for tuberculosis treatment in Tanzania. *Lancet* 1995; **346**: 657–60.
50 Azon-Masoliver A, Vilaplana J. Fluconazole-induced toxic epidermal necrolysis in a patient with human immunodeficiency virus infection. *Dermatology* 1993; **187**: 268–9.
51 Taylor B, Duffill M. Toxic epidermal necrolysis from griseofulvin. *J Am Acad Dermatol* 1988; **19**: 565–7.
52 Mion G, Verdon G, Le Gulluche Y *et al*. Fatal toxic epidermal necrolysis after griseofulvin. *Lancet* 1989; **2**: 1331.
53 Sturchler D, Mittelholzer ML, Kerr L. How frequent are notified severe cutaneous adverse reactions to Fansidar? *Drug Saf* 1993; **8**: 60–8.

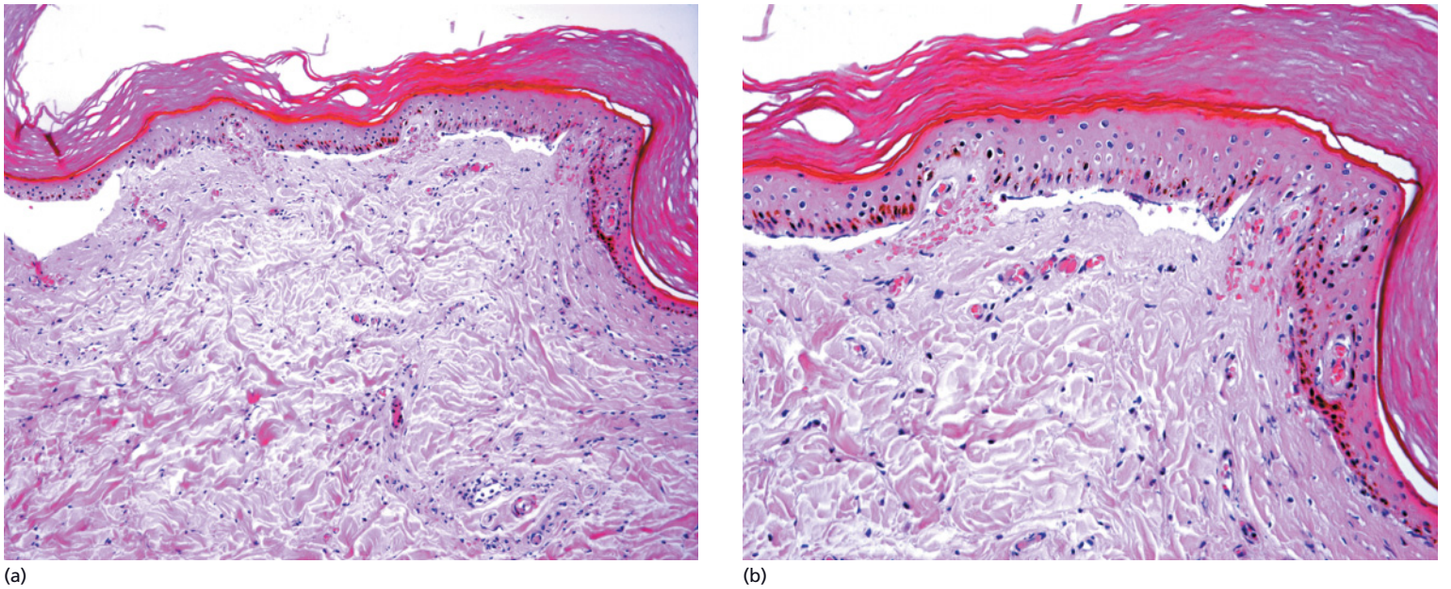
54 Wharton JR, Laughlin C, Cockerell CJ. Toxic epidermal necrolysis occurring as a consequence of treatment with foscarnet. *Cutis* 1999; **63**: 333–5.
55 Smith HR, Croft AM, Black MM. Dermatological adverse effects with the antimalarial drug mefloquine: a review of 74 published case reports. *Clin Exp Dermatol* 1999; **24**: 249–54.
56 Murphy M, Carmichael AJ. Fatal toxic epidermal necrolysis associated with hydroxychloroquine. *Clin Exp Dermatol* 2001; **26**: 457–8.
57 Callaly EL, FitzGerald O, Rogers S. Hydroxychloroquine-associated, photo-induced toxic epidermal necrolysis. *Clin Exp Dermatol* 2008; **33**: 572–4.
58 Bodokh I, Lacour JP, Rosenthal E *et al*. Syndrome de Lyell ou necrolyse epidermique toxique et syndrome de Stevens–Johnson après traitement par fluoxetine. *Thérapie* 1992; **47**: 441.
59 Jonsson GW, Moosa MY, Jeenah FY. Toxic epidermal necrolysis and fluoxetine: a case report. *J Clin Psychopharmacol* 2008; **28**: 93–5.
60 Richard MA, Fiszenson F, Jreissati M *et al*. Cutaneous adverse effects during selective serotonin reuptake inhibitors therapy: two cases. *Ann Dermatol Vénéréol* 2001; **128**: 759–61.
61 Ahmed R, Eagleton C. Toxic epidermal necrolysis after paroxetine treatment. *N Z Med J* 2008; **121**: 86–9.
62 Lagnaoui R, Ramanampamonjy R, Julliac B *et al*. Fatal toxic epidermal necrolysis associated with tetrazepam. *Therapie* 2001; **56**: 187–8.
63 Teraki Y, Murota H, Izaki S. Toxic epidermal necrolysis due to zonisamide associated with reactivation of human herpesvirus 6. *Arch Dermatol* 2008; **144**: 232–5.
64 Knowles S, Gupta AK, Shear NH. The spectrum of cutaneous reactions associated with diltiazem: three cases and a review of the literature. *J Am Acad Dermatol* 1998; **38**: 201–6.
65 Al-Shouli S, Abouchala N, Bogusz MJ *et al*. Toxic epidermal necrolysis associated with high intake of sildenafil and its response to infliximab. *Acta Derm Venereol* 2005; **85**: 534–5.
66 Nagge JJ, Knowles SR, Juurlink DN, Shear NH. Pseudoephedrine-induced toxic epidermal necrolysis. *Arch Dermatol* 2005; **141**: 907–8.
67 Cox NH. Acute disseminated epidermal necrosis due to omeprazole. *Lancet* 1992; **340**: 857.
68 Heaton NR, Edmonds EV, Francis ND *et al*. Fatal toxic epidermal necrolysis due to lansoprazole. *Clin Exp Dermatol* 2004; **29**: 612–3.
69 Miralles ES, Nunez M, del Olmo N, Ledo A. Ranitidine-related toxic epidermal necrolysis in a patient with idiopathic thrombocytopenic purpura. *J Am Acad Dermatol* 1995; **32**: 133–4.
70 Brunner M, Vardarman E, Goldermann R *et al*. Toxic epidermal necrolysis (Lyell syndrome) following famotidine administration. *Br J Dermatol* 1995; **133**: 814–5.
71 Tidwell BH, Paterson TM, Burford B. Cimetidine-induced toxic epidermal necrolysis. *Am J Health Syst Pharm* 1998; **55**: 163–4.
72 Pfeiffer CM, Kazenoff S, Rothberg HD. Toxic epidermal necrolysis from atorvastatin. *JAMA* 1998; **279**: 1613–4.
73 Hassikou H, El Haouri M, Tabache F *et al*. Leflunomide-induced toxic epidermal necrolysis in a patient with rheumatoid arthritis. *Joint Bone Spine* 2008; **75**: 597–9.
74 Hall VC, El-Azhary RA, Bouwhuis S, Rajkumar SV. Dermatologic side effects of thalidomide in patients with multiple myeloma. *J Am Acad Dermatol* 2003; **48**: 548–52.
75 McIvor A. Fatal toxic epidermal necrolysis associated with etretinate (Letter). *BMJ* 1992; **304**: 548.
76 Collins P, Rogers S. The efficacy of methotrexate in psoriasis: a review of 40 cases. *Clin Exp Dermatol* 1992; **17**: 257–60.
77 Primka EJ III, Camisa C. Methotrexate-induced toxic epidermal necrolysis in a patient with psoriasis. *J Am Acad Dermatol* 1997; **36**: 815–8.
78 Ozkan A, Apak H, Celkan T *et al*. Toxic epidermal necrolysis after the use of high-dose cytosine arabinoside. *Pediatr Dermatol* 2001; **18**: 38–40.
79 Wiener JS, Tucker JA Jr, Walther PJ. Interleukin-2-induced dermatotoxicity resembling toxic epidermal necrolysis. *South Med J* 1992; **85**: 656–9.
80 Lin WL, Lin WC, Yang JY *et al*. Fatal toxic epidermal necrolysis associated with cetuximab in a patient with colon cancer. *J Clin Oncol* 2008; **26**: 2779–80.
81 Valeyrie-Allanore L, Poulalhon N, Fagot JP *et al*. Stevens–Johnson syndrome and toxic epidermal necrolysis induced by amifostine during head and neck radiotherapy. *Radiother Oncol* 2008; **87**: 300–3.
82 Halevi A, Ben-Amitai D, Garty BZ. Toxic epidermal necrolysis associated with acetaminophen ingestion. *Ann Pharmacother* 2000; **34**: 32–4.
83 Shoss RG, Rayhanzadeh S. Toxic epidermal necrolysis following measles vaccination. *Arch Dermatol* 1974; **110**: 766–70.
84 Ball R, Ball LK, Wise RP *et al*. Stevens–Johnson syndrome and toxic epidermal necrolysis after vaccination: reports to the vaccine adverse event reporting system. *Pediatr Infect Dis J* 2001; **20**: 219–23.
85 Kaftori JK, Abraham Z, Gilhar A. Toxic epidermal necrolysis after excretory pyelography: immunologic-mediated contrast medium reaction? *Int J Dermatol* 1988; **27**: 346–7.
86 Lee ML, Chiu IS. Toxic epidermal necrolysis incriminating iopamidol in a child after cardiac catheterization. *Intl J Cardiol* 2002; **82**: 95–7.
87 Searles GE, Tredget EE, Lin AN. Fatal toxic epidermal necrolysis associated with use of terconazole vaginal suppository. *J Cutan Med Surg* 1998; **3**: 85–7.
88 Flórez A, Rosón E, Conde A *et al*. Toxic epidermal necrolysis secondary to timolol, dorzolamide, and latanoprost eyedrops. *J Am Acad Dermatol* 2005; **53**: 909–11.
89 Radimer GF, Davis J II, Ackerman AB. Fumigant-induced toxic epidermal necrolysis. *Arch Dermatol* 1974; **110**: 103–4.
90 Sachs B, Fischer-Barth W, Erdmann S *et al*. Anaphylaxis and toxic epidermal necrolysis or Stevens–Johnson syndrome after nonmucosal topical drug application: fact or fiction? *Allergy* 2007; **62**: 877–83.
91 Peck GL, Herzig GP, Elias PM. Toxic epidermal necrolysis in a patient with graft-vs-host reaction. *Arch Dermatol* 1972; **105**: 561–9.
92 Villada G, Roujeau J-C, Cordonnier C *et al*. Toxic epidermal necrolysis after bone marrow transplantation: study of nine cases. *J Am Acad Dermatol* 1990; **23**: 870–5.
93 Mandelcorn R, Shear NH. Lupus-associated toxic epidermal necrolysis: a novel manifestation of lupus? *J Am Acad Dermatol* 2003; **48**: 525–9.

Pathology

The histology of early lesions is characterized by moderate perivascular mononuclear cell infiltration in the papillary dermis, with epidermal spongiosis and exocytosis. Satellite cell necrosis, with close apposition of mononuclear cells to necrotic keratinocytes, may be seen. In established TEN (Fig. 76.4), there is full-thickness necrosis of the whole epidermis with blister formation. The necrotic process involves the epithelial lining of sweat ducts, while hair follicles are much less affected. There is little in the way of any dermal abnormality. Macrophages and dendrocytes with a strong immunoreactivity for TNF-α predominate in a cell-poor infiltrate [1]. TEN may be rapidly differentiated from the staphylococcal scalded skin syndrome (SSSS), in which blister formation results from intraepidermal subcorneal splitting caused by a toxin produced by *Staphylococcus aureus* group II, phage type 71, by examination of frozen sections of blister roof material [2,3]. The level of splitting is subcorneal in SSSS, while in TEN it is much lower, because the full thickness of the necrotic epidermis forms the roof of the blister. Differentiation from graft-versus-host disease may be difficult [4]. Direct immunofluorescence is negative, with the exception of a possible 'lupus band test' in cases associated with SLE.

References

1 Paquet P, Pierard GE. Erythema multiforme and toxic epidermal necrolysis: a comparative study. *Am J Dermatopathol* 1997; **19**: 127–32.
2 Amon RB, Dimond RL. Toxic epidermal necrolysis: rapid differentiation between staphylococcal- and drug-induced disease. *Arch Dermatol* 1975; **111**: 1433–7.
3 Ochsendorf FR, Schöfer H, Milbradt R. Diagnostik des 'Lyell-Syndroms': SSSS oder TEN? *Dtschr Med Wochenschr* 1988; **113**: 860–3.
4 Paquet P, Arrese JE, Beguin Y, Pierard GE. Clinicopathological differential diagnosis of drug-induced toxic epidermal necrolysis (Lyell's syndrome) and acute graft-versus-host reaction. *Curr Top Pathol* 2001; **94**: 49–63.



(a) (b)

Fig. 76.4 (a,b) Histopathology of toxic epidermal necrolysis. Note full-thickness necrosis of epidermis, dermal–epidermal separation, and paucity of upper dermal cellular infiltration (H&E). (Courtesy of Dr E. Calonje, St John's Institute of Dermatology, King's College London, UK.)

Clinical features

Stevens–Johnson syndrome [1–8]

SJS is a severe illness of usually sudden onset, associated with marked constitutional symptoms of high fever, malaise, myalgia, arthralgia and extensive erythema multiforme of the trunk, with occasional skin blisters and erosions covering less than 10% of the body's surface area. A prodromal systemic illness lasting 1–13 days before the eruption may occur. The skin lesions are variable in extent, and consist of typical maculopapular lesions of erythema multiforme, bullous or, rarely, pustular lesions. New crops of lesions develop over a period of 10 days, or sometimes 3–4 weeks. There is significant involvement of mucous membranes: the frequency in one review of 81 cases was oral mucosa 100%, eyes 91%, male genitalia 57% and anal mucous membrane 5%, while bronchitis and pneumonitis occurred in 6% and 23% of cases, respectively [6].

The oral mucous membrane shows extensive bulla formation followed by erosions and a greyish white membrane, so that the mouth and lips show characteristic haemorrhagic crusting (Fig. 76.5) [7]. The most common change in the eyes is a severe catarrhal or purulent conjunctivitis, but bulla formation may occur. Corneal ulceration is frequent, and anterior uveitis or panophthalmitis may occur. The eye changes often regress completely, but synechiae, corneal opacities and rarely blindness are possible sequelae. Genital lesions are frequent; retention of urine may occur, as may involvement of the bladder. Respiratory symptoms may occur, and often the radiological changes within the lungs are far greater than the symptoms. Abnormalities of liver function may be present. Renal involvement with haematuria or even renal tubular necrosis has been reported and may lead to progressive renal failure. Less common symptoms include diarrhoea, paronychia, shedding of nails, polyarthritis and otitis media. Untreated, this disease used to have a mortality of 5–15% from infection, toxaemia or renal damage, but the mortality rate is now lower. The eruption usually heals without sequelae, although the eyes may be permanently damaged. Eruptive melanocytic naevi are reported as developing after SJS [9].

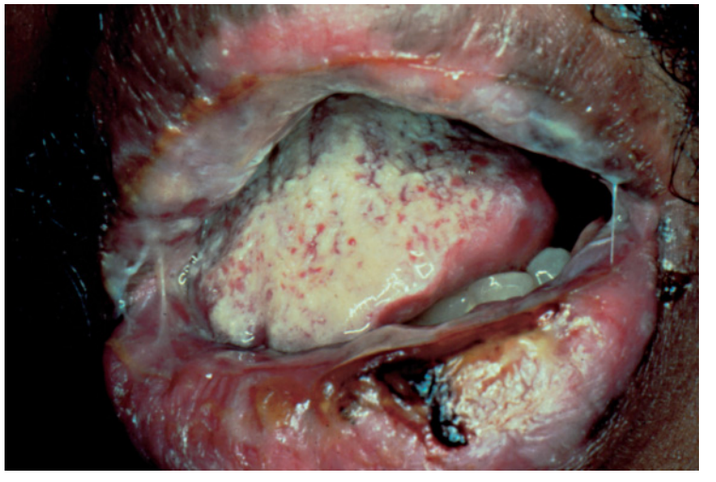


Fig. 76.5 Stevens–Johnson syndrome. Severe erosions at the lips.

References

1 Kauppinen K. Cutaneous reactions to drugs: with special reference to severe mucocutaneous bullous eruptions and sulphonamides. *Acta Derm Venereol (Stockh)* 1972; **52** (Suppl. 68): 1–89.

2 Böttiger LE, Strandberg I, Westerholm B. Drug-induced febrile mucocutaneous syndrome: with a survey of the literature. *Acta Med Scand* 1975; **198**: 229–33.

3 Ruiz-Maldonado R. Acute disseminated epidermal necrosis types 1, 2, and 3: study of 60 cases. *J Am Acad Dermatol* 1985; **13**: 623–35.

4 Nethercott JR, Choi BC. Erythema multiforme (Stevens–Johnson syndrome): chart review of 123 hospitalized patients. *Dermatologica* 1985; **171**: 383–96.

5 Ting HC, Adam BA. Stevens–Johnson syndrome: a review of 34 cases. *Int J Dermatol* 1985; **24**: 587–91.
6 Ashby DW, Lazar T. Erythema multiforme exudativum major (Stevens–Johnson syndrome). *Lancet* 1951; **i**: 1091–5.
7 Rzany B, Hering O, Mockenhaupt M *et al*. Histopathological and epidemiological characteristics of patients with erythema exudativum multiforme major, Stevens–Johnson syndrome and toxic epidermal necrolysis. *Br J Dermatol* 1996; **135**: 6–11.
8 Hazin R, Ibrahimi OA, Hazin MI, Kimyai-Asadi A. Stevens–Johnson syndrome: pathogenesis, diagnosis, and management. *Ann Med* 2008; **40**: 129–38.
9 Gelfer A, Rivers JK. Long-term follow-up of a patient with eruptive melanocytic nevi after Stevens–Johnson syndrome. *Arch Dermatol* 2007; **143**: 1555–7.

Toxic epidermal necrolysis [1–10]

SJS should be differentiated from TEN, in which typically sheet-like erosions involve more than 30% of the body surface with widespread purpuric macules or flat atypical target lesions, and in which there is severe involvement of conjunctival, corneal, irideal, buccal, labial and genital mucous membranes [1–3]. SJS may, however, evolve into TEN.

Clinically, TEN presents with a prodromal period with flu-like symptoms (malaise, fever, rhinitis and conjunctivitis), sometimes accompanied by difficulty in urination, which usually lasts 2–3 days; however, it may last from 1 day to 3 weeks before signs of skin involvement develop. The acute phase of TEN is characterized by persistent fever, severe mucous membrane involvement and generalized epidermal sloughing to leave large, raw, painful areas, and lasts from 8 to 12 days. There may be an initial 'burning' maculopapular, urticarial or erythema multiforme-like eruption. This may start on the face and on the upper part of the body and rapidly extends. Most frequently, the initial individual skin lesions form poorly defined macules with darker purpuric or blistering centres, progressively merging on the chin, upper parts of chest and back. Less frequently, the initial manifestation may be a more confluent erythema. Sometimes the lesions are predominantly in photoexposed areas.

There is rapid progression to areas of confluent erythema, often starting in the axillae and groins, followed by blistering and sloughing of large areas of skin (Fig. 76.6). Nikolsky's sign, the ability to extend the area of superficial sloughing by gentle lateral pressure on the surface of the skin at an apparently unaffected site, may be positive. Detachment of the full thickness of the epidermis at sites of pressure or trauma, such as the back, shoulders or buttocks, leaves a dark red oozing dermis. In other areas, the pale necrotic epidermis remains *in situ*, with a wrinkled appearance. Blisters on the palms and soles may remain intact. However, the entire skin surface may be involved, with up to 100% of the epidermis sloughing off. Only the hairy portion of the scalp is never affected. The process tends to occur in waves, over a 3- to 5-day period (sometimes a week), but involvement of the whole of the body surface occurs within 24 h in approximately 10% of cases.



Fig. 76.6 Toxic epidermal necrolysis showing dusky erythema and stripping off of necrotic epidermis.

Mucous membranes (particularly the buccal, and less commonly the conjunctival, genital, perianal, nasal, tracheal, bronchial, pharyngeal and oesophageal membranes) are involved in nearly all patients (85–95%). Widespread painful erosions cause crusted lips and increased salivation, and redness and soreness of the eyes is conspicuous, with photophobia. Mucous membrane lesions may precede the skin lesions by up to 3 days in one-third of cases [3]. Urethritis develops in up to two-thirds of patients, and may lead to urinary retention. Stomatitis and mucositis lead to impaired oral intake with consequent malnutrition and dehydration. Intestinal involvement has been documented [5]. Healing occurs by re-epithelialization; this may occur within a few days on the anterior thorax, but is slower on the back and at intertriginous areas. Most patients' skin lesions are completely healed in about 3–4 weeks, but mucosal lesions take longer and the glans penis may take up to 2 months to heal over.

Investigations. Approximately 50% of patients have a slight increase in serum aminotransferases, and approximately 10% have overt hepatitis. A rise in serum amylase is often present during the first few days, probably secondary to involvement of salivary glands. Anaemia is constant after a few days, and lymphopenia is usual, with a selective and transient depletion of $CD4^+$ T lymphocytes. Neutropenia is observed in approximately 30% of patients, and thrombocytopenia in 15%; eosinophilia is very unusual. Hypophosphataemia is nearly constant, and hyperglycaemia is frequent, as are increased urea and creatinine levels. Subclinical interstitial oedema is often noted on early chest X-rays.

Complications (Table 76.4). Acute complications are similar to those of extensive burns. The total daily fluid loss averages 3–4 L in adult patients with TEN affecting 50% of body surface area. It induces a reduction of intravascular volume and functional renal failure. If not corrected, hypovolaemia may lead to haemodynamic alterations and organic renal failure. Pneumonia or pneumonitis occurs in up to 30% of patients, contributed to by sloughing of the tracheobronchial tree [11]. Adult respiratory distress syndrome (ARDS) is one of the main complications. Anaemia or leukopenia, caused by selective depletion of $CD4^+$ helper T cells, is moderately common [9]. Oesophageal and intestinal erosions, with an endoscopic appearance reminiscent of ulcerative or pseudomembranous colitis, are recorded [12]; strictures may result. Disseminated intravascular coagulation is documented. Septicaemia, primarily the result of *Staphylococcus aureus* or *Pseudomonas* but on occasion caused by Gram-negative organisms or *Candida*, may result from infection of the skin, lungs, urinary tract catheters

Table 76.4 Complications of toxic epidermal necrolysis.

Acute	Chronic
Similar to burns: depends on extent	*Ocular complications* (up to 35%)
Massive fluid and electrolyte loss (3–4 L/day)	Conjunctivitis, ectropion or entropion, corneal scarring
Prerenal renal failure	Symblepharon, Sjögren-like sicca syndrome
Bacterial infection and septicaemia	*Other mucous membrane involvement*
Hypercatabolism: insulin resistance	Oesophageal stricture
Diffuse interstitial pneumonitis	Phimosis
Mucous membrane involvement	Vaginal synechiae
	Orogenital ulcers
	Miscellaneous
	Wound infection
	Pigmentary changes
	Nail dystrophy
	Hypohidrosis
	Scarring alopecia
	Contractures
	Development of melanocytic naevi

and intravenous (especially central) lines. Patients are usually febrile and shivering, even in the absence of infection. Hypothermia is infrequent and usually a marker of severe infection and irreversible septic shock. Protein loss, from skin lesions and increased catabolism, may reach 150–200 g/day. Inhibition of insulin secretion and/or insulin resistance in peripheral tissues is frequent, resulting in elevated plasma glucose levels and glycosuria.

Mucocutaneous complications of TEN [13,14] include wound infections, pigmentary changes (either hyper- or hypopigmentation) which may or may not resolve with time, nail shedding or dystrophy, hypohidrosis or hyperhidrosis, scarring alopecia and hypertrophic scarring which may lead to contractures. Development of melanocytic naevi has been reported [15]. Mucosal involvement may lead to chronic xerostomia, oesophageal strictures, phimosis, and chronic orogenital erosions or vulvovaginal stenosis [16]. Appearances may resemble scarring from cicatricial pemphigoid or lichen planus.

Ocular complications occur in 40–50% of survivors [9], and include conjunctivitis, watery eyes because of tear duct obstruction, pseudomembrane formation, photophobia, ectropion, entropion with trichiasis, symblepharon and corneal vascularization, corneal opacities, and corneal ulceration and scarring [12]. Blindness may result. Lacrimal duct destruction may result in xerophthalmia. A Sjögren-like sicca syndrome may be seen [17]. A 'post-SJS/TEN' ocular syndrome with punctuate keratitis and formation of a corneal pannus may result in photophobia, burning eyes and visual impairment. Ankylosymblepharon (fusion of eyelids to each other and to the globe) may follow secondary infection.

References

1 Bastuji-Garin S, Rzany B, Stern RS *et al*. A clinical classification of cases of toxic epidermal necrolysis, Stevens–Johnson syndrome, and erythema multiforme. *Arch Dermatol* 1993; **129**: 92–6.

2 Roujeau JC. The spectrum of Stevens–Johnson syndrome and toxic epidermal necrolysis: a clinical classification. *J Invest Dermatol* 1994; **102**: 28S–30S.

3 Roujeau JC. Stevens–Johnson syndrome and toxic epidermal necrolysis are severity variants of the same disease which differs from erythema multiforme. *J Dermatol* 1997; **24**: 726–9.

4 Lyell A. Toxic epidermal necrolysis (the scalded skin syndrome): a reappraisal. *Br J Dermatol* 1979; **100**: 69–86.

5 Rasmussen JE. Toxic epidermal necrolysis. *Med Clin North Am* 1980; **64**: 901–20.

6 Chan HL. Observations on drug-induced toxic epidermal necrolysis in Singapore. *J Am Acad Dermatol* 1984; **10**: 973–8.

7 Heng MCY. Drug-induced toxic epidermal necrolysis. *Br J Dermatol* 1985; **113**: 597–60.

8 Revuz J, Penso D, Roujeau J-C *et al*. Toxic epidermal necrolysis: clinical findings and prognosis factors in 87 patients. *Arch Dermatol* 1987; **123**: 1160–5.

9 Roujeau J-C, Chosidow O, Saiag P, Guillaume J-C. Toxic epidermal necrolysis (Lyell syndrome). *J Am Acad Dermatol* 1990; **23**: 1039–58.

10 Avakian R, Flowers FP, Araujo OE, Ramos-Caro FA. Toxic epidermal necrolysis: a review. *J Am Acad Dermatol* 1991; **25**: 69–79.

11 Lebargy F, Wolkenstein P, Gisselbrecht M *et al*. Pulmonary complications in toxic epidermal necrolysis: a prospective clinical study. *Intensive Care Med* 1997; **23**: 1237–44.

12 Chosidow O, Delchier J-C, Chaumette M-T *et al*. Intestinal involvement in drug-induced toxic epidermal necrolysis. *Lancet* 1991; **337**: 928.

13 De Felice GP, Caroli R, Auteliano A. Long-term complications of toxic epidermal necrolysis (Lyell's disease): clinical and histopathologic study. *Ophthalmologica* 1987; **195**: 1–6.

14 Sheridan RL, Schulz JT, Ryan CM *et al*. Long-term consequences of toxic epidermal necrolysis in children. *Pediatrics* 2002; **109**: 74–8.

15 Burns DA, Sarkany I. Junctional naevi following toxic epidermal necrolysis. *Clin Exp Dermatol* 1978; **3**: 323–6.

16 Meneux E, Wolkenstein P, Haddad B *et al*. Vulvovaginal involvement in toxic epidermal necrolysis: a retrospective study of 40 cases. *Obstet Gynecol* 1998; **91**: 283–7.

17 Roujeau J-C, Phlippoteau C, Koso M *et al*. Sjögren-like syndrome after drug-induced toxic epidermal necrolysis. *Lancet* 1985; **i**: 609–11.

Prognosis

There is an appreciable mortality as a result of TEN, increasing from 5% in SJS, to 10–15% in transitional SJS–TEN and 30–40% in TEN. ARDS and multiple organ failure are the usual causes of death [1]. They are often precipitated by sepsis with septicaemia, mainly resulting from *Staphylococcus aureus* and *Pseudomonas aeruginosa* [2]. Other causes of death are pulmonary embolism and gastrointestinal bleeding. A recent study of 64 patients with TEN recorded that 28% did not survive the acute episode, and another 23% died following discharge from hospital; the remaining longer-term survivors continued to suffer from ocular (54%), skin (81%) and renal (23%) problems. Of the patients with ocular involvement in the acute phase of TEN 79% had long-term ocular complications, and 73% of patients with mucosal involvement had persistent mucosal lesions [3].

Early withdrawal of the causative drug improves the prognosis, and drugs with a long half-life are associated with an increased risk of death [4,5]. Increased age in most [6] but not all [1] studies, extensive TEN, delay (more than 3–4 days) in referral to a regional centre [7], early thrombocytopenia and early empirical antibiotic treatment elsewhere are associated with a worse prognosis. It has been claimed that severe granulocytopenia is a poor prognostic indicator [8], although this has been disputed on the basis that lymphopenia is more usually found in severe TEN [9]. A specific severity-of illness score to determine prognosis for cases of TEN (SCORTEN) based on seven independent risk factors for death as

Table 76.5 SCORTEN prognosis score [10].

*Parameter**
Age > 40 years
Presence of a malignancy
Epidermal detachment > 30%
Heart rate > 120/min
Bicarbonate < 20 mmol/L
Urea > 10 mmol/L
Glycaemia > 14 mmol/L

1 point awarded for each parameter; SCORTEN derived by totalling scores

SCORTEN	Probability of death (%)
0–1	3
2	12
3	35
4	58
≥5	90

* Worst recorded value in the 24 h after admission.

assessed on the first day of hospitalization has been judged helpful (Table 76.5) [10–12]; others have pointed out that it does not take account of respiratory involvement in TEN, which may portend a poor prognosis [13].

References

1 Schulz JT, Sheridan RL, Ryan CM *et al*. A 10-year experience with toxic epidermal necrolysis. *J Burn Care Rehabil* 2000; **21**: 199–204.
2 Roujeau J-C, Chosidow O, Saiag P, Guillaume J-C. Toxic epidermal necrolysis (Lyell syndrome). *J Am Acad Dermatol* 1990; **23**: 1039–58.
3 Oplatek A, Brown K, Sen S *et al*. Long-term follow-up of patients treated for toxic epidermal necrolysis. *J Burn Care Res* 2006; **27**: 26–33.
4 Garcia-Doval I, LeCleach L, Bocquet H *et al*. Toxic epidermal necrolysis and Stevens–Johnson syndrome: does early withdrawal of causative drugs decrease the risk of death? *Arch Dermatol* 2000; **136**: 323–7.
5 Stern RS. Improving the outcome of patients with toxic epidermal necrolysis and Stevens–Johnson syndrome. *Arch Dermatol* 2000; **136**: 410–1.
6 Honari S, Gibran NS, Heimbach DM *et al*. Toxic epidermal necrolysis (TEN) in elderly patients. *J Burn Care Rehabil* 2001; **22**: 132–5.
7 McGee T, Munster A. Toxic epidermal necrolysis syndrome: mortality rate reduced with early referral to regional burn center. *Plast Reconstr Surg* 1998; **102**: 1018–22.
8 Westly ED, Wechsler HL. Toxic epidermal necrolysis: granulocytic leukopenia as a prognostic indicator. *Arch Dermatol* 1984; **120**: 721–6.
9 Roujeau JC, Guillaume JC, Revuz J *et al*. Granulocytes, lymphocytes and toxic epidermal necrolysis. *Arch Dermatol* 1985; **121**: 305.
10 Bastuji-Garin S, Fouchard N, Bertocchi M *et al*. SCORTEN: a severity-of illness score for toxic epidermal necrolysis. *J Invest Dermatol* 2000; **115**: 149–53.
11 Guégan S, Bastuji-Garin S, Poszepczynska-Guigné E *et al*. Performance of the SCORTEN during the first five days of hospitalization to predict the prognosis of epidermal necrolysis. *J Invest Dermatol* 2006; **126**: 272–6.
12 Cartotto R, Mayich M, Nickerson D, Gomez M. SCORTEN accurately predicts mortality among toxic epidermal necrolysis patients treated in a burn center. *J Burn Care Res* 2008; **29**: 141–6.
13 Hague JS, Goulding JM, Long TM, Gee BC. Respiratory involvement in toxic epidermal necrolysis portends a poor prognosis that may not be reflected in SCORTEN. *Br J Dermatol* 2007; **157**: 1294–6.

Diagnosis

Toxic shock syndrome, which usually occurs in menstruating women, may cause widespread erythema and desquamation, but skin tenderness and bullae are absent. Similarly, SSSS can generally be differentiated on clinical appearances and on the basis of histology. Linear IgA bullous dermatosis, whether idiopathic or drug-induced (e.g. vancomycin), may mimic SJS or TEN clinically [1–3], as may a widespread bullous fixed drug eruption [4,5]. The subcorneal aseptic pustules of acute generalized exanthematous pustulosis (AGEP) or acute pustular psoriasis (von Zumbusch) are usually distinctive but may coalesce to produce extensive superficial detachment mimicking TEN. Paraneoplastic pemphigus may closely resemble SJS, but direct immunofluorescence is positive.

Identification of the responsible drug is often difficult, because patients frequently take more than one medication [6,7] (an average of 4.4 in one series). A helpful guideline is that most drugs that cause TEN have been given first between 1 and 3 weeks previously [8–10]; another very suggestive guide is that of recurrence within 48 h on administration of a drug previously recorded as having caused a similar reaction. A given drug is unlikely to be responsible for TEN if it was first given 24 h previously, or if the duration of treatment exceeds 3 weeks [6,9]. In case–control analyses, the risk of SJS/TEN with drugs normally used on a long-term basis, such as phenytoin, phenobarbital, carbamazepine and lamotrigine, was largely restricted to the first 8 weeks, that is the risk is with short-term rather than in the long-term therapy [10,11]. In another study, more than 90% of SJS and TEN cases related to introduction of antiepileptic drugs occurred in the first 63 days [12]. Phenytoin-induced TEN may occur any time between 2 and 8 weeks after initiation of therapy, and may progress despite discontinuation of phenytoin days or weeks earlier [13].

Skin testing is unfortunately unreliable. Relevant positive patch tests were found in only 9% of 22 patients with SJS/TEN, compared with 50% of 14 patients with AGEP [14]. The *in vitro* lymphocyte transformation test is of no great value [15]. In summary, there is no reliable test to confirm the aetiological role of a given drug in an individual case [8]. Re-exposure to drugs suspected of causing a reaction has resulted in fatality, and should not be carried out for diagnostic purposes [16].

References

1 Cummings JE, Snyder RR, Kelly EB, Raimer SS. Drug-induced linear immunoglobulin A bullous dermatosis mimicking Stevens–Johnson syndrome: a case report. *Cutis* 2007; **79**: 203–7.
2 Dellavalle RP, Burch JM, Tayal S *et al*. Vancomycin-associated linear IgA bullous dermatosis mimicking toxic epidermal necrolysis. *J Am Acad Dermatol* 2003; **48**: S56–7.
3 Waldman MA, Black DR, Callen JP. Vancomycin-induced linear IgA bullous disease presenting as toxic epidermal necrolysis. *Clin Exp Dermatol* 2004; **29**: 633–6.
4 Saiag P, Cordoliani F, Roujeau JC *et al*. Érytheme pigmenté fixe bulleux disséminé simulant un syndrome de Lyell. *Ann Dermatol Vénéréol* 1987; **114**: 1440–2.
5 Baird BJ, De Villez RL. Widespread bullous fixed drug eruption mimicking toxic epidermal necrolysis. *Int J Dermatol* 1988; **27**: 170–4.
6 Guillaume J-C, Roujeau J-C, Penso D *et al*. The culprit drugs in 87 cases of toxic epidermal necrolysis (Lyell's syndrome). *Arch Dermatol* 1987; **123**: 1166–70.
7 Prendiville JS, Hebert AA, Greenwald MJ *et al*. Management of Stevens–Johnson syndrome and toxic epidermal necrolysis in children. *J Pediatr* 1989; **115**: 881–7.
8 Roujeau J-C, Chosidow O, Saiag P, Guillaume J-C. Toxic epidermal necrolysis (Lyell syndrome). *J Am Acad Dermatol* 1990; **23**: 1039–58.
9 Avakian R, Flowers FP, Araujo OE, Ramos-Caro FA. Toxic epidermal necrolysis: a review. *J Am Acad Dermatol* 1991; **25**: 69–79.
10 Roujeau JC, Kelly JP, Naldi L *et al*. Medication use and the risk of Stevens–Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med* 1995; **333**: 1600–7.

11 Rzany B, Correia O, Kelly JP *et al*. Risk of Stevens–Johnson syndrome and toxic epidermal necrolysis during first weeks of antiepileptic therapy: a case–control study. Study Group of the International Case Control Study on Severe Cutaneous Adverse Reactions. *Lancet* 1999; **354**: 1033–4.
12 Mockenhaupt M, Messenheimer J, Tennis P, Schlingmann J. Risk of Stevens–Johnson syndrome and toxic epidermal necrolysis in new users of antiepileptics. *Neurology* 2005; **64**: 1134–8.
13 Kelly DF, Hope DG. Fatal phenytoin-related toxic epidermal necrolysis: case report. *Neurosurgery* 1989; **25**: 976–8.
14 Wolkenstein P, Chosidow O, Fléchet ML *et al*. Patch testing in severe cutaneous adverse drug reactions including Stevens–Johnson syndrome and toxic epidermal necrolysis. *Contact Dermatitis* 1996; **35**: 234–6.
15 Roujeau J-C, Albengres E, Moritz SI. Lymphocyte transformation test in drug-induced toxic epidermal necrolysis. *Int Arch Allergy Appl Immunol* 1985; **78**: 22–4.
16 Bianchine JR, Macaraeg PVJ, Lasagna L *et al*. Drugs as aetiologic factors in the Stevens–Johnson syndrome. *Am J Med* 1968; **44**: 390–405.

Treatment [1–10]

The management of TEN is summarized in Table 76.6, and is perhaps best carried out on a dermatology intensive care unit or a burns unit. Clearly, presumptive causative drugs should be stopped as soon as possible. It should be remembered that HIV-1 infected patients with TEN are an occupational risk for health-care workers [11]. The main principles of symptomatic therapy are the same as for major burns and include analgesia, fluid replacement, anti-infectious therapy, aggressive nutritional support, warming of environmental temperature and skin care with appropriate dressings. The extent of the detachment of the epidermis should be evaluated daily as a major prognostic factor. It is expressed as a percentage of body surface area (BSA), using burn tables or the simple rule that one hand (palm and fingers) corresponds to 1% of the BSA. Hyperventilation and mild hypoxaemia on blood gas analysis indicate a high risk of progression to ARDS.

Table 76.6 Management of toxic epidermal necrolysis.

Intensive therapy or burns unit
Air-fluidized bed
Analgesia
Maintain fluid and electrolyte balance (replace up to 5 L/day)
Maintain body temperature
Maintain nutrition; oral hygiene
Frequent ophthalmological assessment
Antiseptic/antibiotic eye drops 2-hourly
Disrupt synechiae frequently
Limitation of infection
Neutropenia: reverse barrier nursing
Frequent cultures of erosions, and blood cultures
Culture tips of Foley catheters and intravenous lines
Prophylactic broad-spectrum systemic antibiotics (controversial)
Topical cleansing/antibacterial agents
0.5% silver nitrate solution on gauze *or* 10% chlorhexidine gluconate washes *or* saline washes *or* polymixin/bacitracin *or* 2% mupirocin
Avoid silver sulfadiazine
Wound care
Remove necrotic epidermis (controversial)
Paraffin gauze or hydrogel dressings
Biological dressings (xenografts, allografts, skin substitutes)

There is a significant incidence of disabling long-term complications in survivors, especially in relation to ocular and other mucous membranes. It is therefore particularly important to be aware of these and to take preventative measures. Physical contact with patients during nursing procedures may produce loss of large sheets of skin, and the use of a turning frame or a ripple or air-fluidized bed will lessen discomfort and facilitate nursing care. Trauma, as with adhesive dressings or ECG electrode attachment pads, should be minimized. Eyelids and conjunctivae should be lubricated with soft paraffin, and gently separated to prevent the formation of adhesions. Ophthalmological advice should be sought [12,13]. Use of gas-permeable scleral contact lenses resulted in improved quality of life in 90% of patients by reducing photophobia and discomfort, and also improved visual acuity and healed corneal epithelial defects in 50% of patients [14]. Amniotic membrane has been used as a dressing for eye lesions in TEN [13,15]. Autologous germinal cells taken from the limbus and grafted on a support of amniotic membrane may be beneficial in the most severe cases [16]. Skin or other infection must be treated promptly. Good mouth care is important in preventing parotitis. Vaginal examination should be repeated in women and appropriate dressings used to avoid synechiae if erosions are seen. The issue of whether necrotic tissue should be removed has been controversial; most authorities feel that this impairs healing. Eroded areas may be treated with biological [17] or synthetic [18] dressings. Use of silver nitrate impregnated dressings [19–21] has been advocated.

There is no consensus on the merits of therapy with moderately high-dose corticosteroids for TEN. Some authorities maintain that high-dose steroid therapy promotes or masks the signs of infection, delays healing, precipitates gastrointestinal bleeding, prolongs hospitalization and increases mortality [1,2,22–24]. However, others favour steroid therapy on the basis that it may reduce inflammation and keratinocyte necrosis [25]. It is generally agreed that if steroids, or any other immunosuppressive agent, are to be given, then they should be administered as early as possible in the evolution of the disease. There have been anecdotal reports on the beneficial use of plasmapheresis [26–28], but this has been questioned [29]. Both cyclophosphamide [30] and ciclosporin A [31–33] have produced improvement in anecdotal cases. Thalidomide therapy for TEN was associated with increased mortality [34,35]. *N*-acetyl cysteine was documented to be useful in a few patients [36], perhaps because it enhances drug metabolism. On the basis that potential *Fas* (CD95)-mediated keratinocyte death in TEN might be blocked by naturally occurring *Fas*-blocking antibodies included in human immunoglobulin preparations, there have been several reports, mostly favourable, on human intravenous immunoglobulin (IVIG) therapy for TEN [37–50]. In particular, early infusion of high-dose (1–2 g/kg/day for 3–4 days in adults) IVIG has been reported in a majority of studies to be beneficial in terms of improved survival and appears safe and well tolerated [47–50]; variations in the efficacy of different batches of IVIG have been recorded [41]. However, other studies failed to show any significant effect from either IVIG therapy or systemic corticosteroids on mortality in comparison with supportive care only [43,51], and there is currently no consensus on the best management for TEN [52,53]. There have been single case reports on the efficacy of treatment with anti-TNF-α antibodies [54–58]. Because of the

rarity of the condition, controlled trials assessing these different treatment approaches are very difficult to carry out. Intense pulsed light treatment had been used for persistent facial hypermelanosis following drug-induced TEN [59].

References

1 Revuz J, Roujeau J-C, Guillaume J-C *et al*. Treatment of toxic epidermal necrolysis: Créteil's experience. *Arch Dermatol* 1987; **123**: 1156–8.
2 Roujeau J-C, Revuz J. Intensive care in dermatology. In: Champion RH, Pye RJ, eds. *Recent Advances in Dermatology*, Vol. 8. Edinburgh: Churchill Livingstone, 1990: 85–99.
3 Smoot EC III. Treatment issues in the care of patients with toxic epidermal necrolysis. *Burns* 1999; **25**: 439–42.
4 Eisen ER, Fish J, Shear NH. Management of drug-induced toxic epidermal necrolysis. *J Cutan Med Surg* 2000; **4**: 96–102.
5 Fritsch PO, Sidoroff A. Drug-induced Stevens–Johnson syndrome/toxic epidermal necrolysis. *Am J Clin Dermatol* 2000; **1**: 349–60.
6 Craven NM. Management of toxic epidermal necrolysis. *Hosp Med* 2000; **61**: 778–81.
7 Hansbrough JF, Muller P, Noordenbos J, Dore C. A 10-year experience with toxic epidermal necrolysis. *J Burn Care Rehabil* 2001; **22**: 97–8.
8 Spies M, Sanford AP, Aili Low JF *et al*. Treatment of extensive toxic epidermal necrolysis in children. *Pediatrics* 2001; **108**: 1162–8.
9 Palmieri TL, Greenhalgh DG, Saffle JR *et al*. A multicenter review of toxic epidermal necrolysis treated in US burn centers at the end of the twentieth century. *J Burn Care Rehabil* 2002; **23**: 87–96.
10 Ghislain PD, Roujeau JC. Treatment of severe drug reactions: Stevens–Johnson syndrome, toxic epidermal necrolysis and hypersensitivity syndrome. *Dermatol Online J* 2002; **8**: 5.
11 Descamps V, Tattevin P, Descamps DI. HIV-1 infected patients with toxic epidermal necrolysis: an occupational risk for healthcare workers. *Lancet* 1999; **353**: 1855–6.
12 Chang YS, Huang FC, Tseng SH *et al*. Erythema multiforme, Stevens–Johnson syndrome, and toxic epidermal necrolysis: acute ocular manifestations, causes, and management. *Cornea* 2007; **26**: 123–9.
13 Gregory DG. The ophthalmologic management of acute Stevens–Johnson syndrome. *Ocul Surf* 2008; **6**: 87–95.
14 Romero-Rangel T, Stavrou P, Cotter J *et al*. Gas-permeable scleral contact lens therapy in ocular surface disease. *Am J Ophthalmol* 2000; **130**: 25–32.
15 John T, Foulks GN, John ME *et al*. Amniotic membrane in the surgical management of acute toxic epidermal necrolysis. *Ophthalmology* 2002; **109**: 351–60.
16 Tsai RJ, Li LM, Chen JK. Reconstruction of damaged corneas by transplantation of autologous limbal epithelial cells. *N Engl J Med* 2000; **343**: 86–93.
17 Pianigiani E, Ierardi F, Taddeucci P *et al*. Skin allograft in the treatment of toxic epidermal necrolysis (TEN). *Dermatol Surg* 2002; **28**: 1173–6.
18 Boorboor P, Vogt PM, Bechara FG *et al*. Toxic epidermal necrolysis: use of Biobrane or skin coverage reduces pain, improves mobilisation and decreases infection in elderly patients. *Burns* 2008; **34**: 487–92.
19 Lehrer-Bell KA, Kirsner RS, Tallman PG, Kerdel FA. Treatment of the cutaneous involvement in Stevens–Johnson syndrome and toxic epidermal necrolysis with silver nitrate-impregnated dressings. *Arch Dermatol* 1998; **134**: 877–9.
20 Dalli RL, Kumar R, Kennedy P *et al*. Toxic epidermal necrolysis/Stevens–Johnson syndrome: current trends in management. *ANZ J Surg* 2007; **77**: 671–6.
21 Huang SH, Wu SH, Sun IF *et al*. AQUACEL Ag in the treatment of toxic epidermal necrolysis (TEN). *Burns* 2008; **34**: 63–6.
22 Halebian PH, Corder VJ, Madden MR *et al*. Improved burn center survival of patients with toxic epidermal necrolysis managed without corticosteroids. *Ann Surg* 1986; **204**: 503–12.
23 Heimbach DM, Engrav LH, Marvin JA. Toxic epidermal necrolysis: a step forward in treatment. *JAMA* 1987; **257**: 2171–5.
24 Rzany B, Schmitt H, Schöpf E. Toxic epidermal necrolysis in patients receiving glucocorticosteroids. *Acta Derm Venereol (Stockh)* 1991; **71**: 171–2.
25 van der Meer JB, Schuttelaar ML, Toth GG *et al*. Successful dexamethasone pulse therapy in a toxic epidermal necrolysis (TEN) patient featuring recurrent TEN to oxazepam. *Clin Exp Dermatol* 2001; **26**: 654–6.
26 Kamanabroo D, Schmitz-Landgraf W, Czartnetski BM. Plasmapheresis in severe drug-induced toxic epidermal necrolysis. *Arch Dermatol* 1985; **121**: 1548–9.
27 Egan CA, Grant WJ, Morris SE *et al*. Plasmapheresis as an adjunct treatment in toxic epidermal necrolysis. *J Am Acad Dermatol* 1999; **40**: 458–61.
28 Bamichas G, Natse T, Christidou F *et al*. Plasma exchange in patients with toxic epidermal necrolysis. *Ther Apher* 2002; **6**: 225–8.
29 Furubacke A, Berlin G, Anderson C, Sjoberg F. Lack of significant treatment effect of plasma exchange in the treatment of drug-induced toxic epidermal necrolysis? *Intensive Care Med* 1999; **25**: 1307–10.
30 Heng MC, Allen SG. Efficacy of cyclophosphamide in toxic epidermal necrolysis: clinical and pathophysiologic aspects. *J Am Acad Dermatol* 1991; **25**: 778–86.
31 Renfro L, Grant-Kels JM, Daman LA. Drug-induced toxic epidermal necrolysis treated with cyclosporin. *Int J Dermatol* 1989; **28**: 441–4.
32 Arevalo JM, Lorente JA, Gonzalez-Herrada C, Jimenez-Reyes J. Treatment of toxic epidermal necrolysis with cyclosporin A. *J Trauma* 2000; **48**: 473–8.
33 Jarrett P, Rademaker M, Havill J, Pullon H. Toxic epidermal necrolysis treated with cyclosporin and granulocyte colony stimulating factor. *Clin Exp Dermatol* 1997; **22**: 146–7.
34 Wolkenstein P, Latarjet J, Roujeau JC *et al*. Randomised comparison of thalidomide versus placebo in toxic epidermal necrolysis. *Lancet* 1998; **352**: 1586–9.
35 Namazi MR. Increased mortality in toxic epidermal necrolysis with thalidomide: corroborating or exonerating the pathogenetic role of TNF-alpha? *Br J Dermatol* 2006; **155**: 842–3.
36 Velez A, Moreno JC. Toxic epidermal necrolysis treated with N-acetylcysteine. *J Am Acad Dermatol* 2002; **46**: 469–70.
37 Viard I, Wehril P, Bullani R *et al*. Inhibition of toxic epidermal necrolysis by blockade of CD95 with human intravenous immunoglobulin. *Science* 1998; **282**: 490–3.
38 Stella M, Cassano P, Bollero D *et al*. Toxic epidermal necrolysis treated with intravenous high-dose immunoglobulins: our experience. *Dermatology* 2001; **203**: 45–9.
39 Paquet P, Jacob E, Damas P, Pierard GE. Treatment of drug-induced toxic epidermal necrolysis (Lyell's syndrome) with intravenous human immunoglobulins. *Burns* 2001; **27**: 652–5.
40 Tristani-Firouzi P, Petersen MJ, Saffle JR *et al*. Treatment of toxic epidermal necrolysis with intravenous immunoglobulin in children. *J Am Acad Dermatol* 2002; **47**: 548–52.
41 Prins C, Kerdel FA, Padilla RS *et al*. Toxic epidermal necrolysis–intravenous immunoglobulin: treatment of toxic epidermal necrolysis with high-dose intravenous immunoglobulins—multicenter retrospective analysis of 48 consecutive cases. *Arch Dermatol* 2003; **139**: 26–32.
42 Trent JT, Kirsner RS, Romanelli P, Kerdel FA. Analysis of intravenous immunoglobulin for the treatment of toxic epidermal necrolysis using SCORTEN: the University of Miami Experience. *Arch Dermatol* 2003; **139**: 39–43.
43 Bachot N, Revuz J, Roujeau JC. Intravenous immunoglobulin treatment for Stevens–Johnson syndrome and toxic epidermal necrolysis: a prospective noncomparative study showing no benefit on mortality or progression. *Arch Dermatol* 2003; **139**: 33–6.
44 Wolff K, Tappeiner G. Treatment of toxic epidermal necrolysis: the uncertainty persists but the fog is dispersing. *Arch Dermatol* 2003; **139**: 85–6.
45 Hebert AA, Bogle MA. Intravenous immunoglobulin prophylaxis for recurrent Stevens–Johnson syndrome. *J Am Acad Dermatol* 2004; **50**: 286–8.
46 Lissia M, Figus A, Rubino C. Intravenous immunoglobulins and plasmapheresis combined treatment in patients with severe toxic epidermal necrolysis: preliminary report. *Br J Plast Surg* 2005; **58**: 504–10.
47 Mittmann N, Chan B, Knowles S *et al*. Intravenous immunoglobulin use in patients with toxic epidermal necrolysis and Stevens–Johnson syndrome. *Am J Clin Dermatol* 2006; **7**: 359–68.
48 French LE, Trent JT, Kerdel FA. Use of intravenous immunoglobulin in toxic epidermal necrolysis and Stevens–Johnson syndrome: our current understanding. *Int Immunopharmacol* 2006; **6**: 543–9.
49 Stella M, Clemente A, Bollero D *et al*. Toxic epidermal necrolysis (TEN) and Stevens–Johnson syndrome (SJS): experience with high-dose intravenous immunoglobulins and topical conservative approach. A retrospective analysis. *Burns* 2007; **33**: 452–9.
50 French LE. Toxic epidermal necrolysis and Stevens Johnson syndrome: our current understanding. *Allergol Int* 2006; **55**: 9–16.
51 Schneck J, Fagot JP, Sekula P *et al*. Effects of treatments on the mortality of Stevens–Johnson syndrome and toxic epidermal necrolysis: A retrospective study on patients included in the prospective EuroSCAR Study. *J Am Acad Dermatol* 2008; **58**: 33–40.

52 Majumdar S, Mockenhaupt M, Roujeau J, Townshend A. Interventions for toxic epidermal necrolysis. *Cochrane Database Syst Rev* 2002; **4**: CD001435.
53 Abood GJ, Nickoloff BJ, Gamelli RL. Treatment strategies in toxic epidermal necrolysis syndrome: where are we at? *J Burn Care Res* 2008; **29**: 269–76.
54 Fischer M, Fiedler E, Marsch WC, Wohlrab J. Antitumour necrosis factor-α antibodies (infliximab) in the treatment of a patient with toxic epidermal necrolysis. *Br J Dermatol* 2002; **146**: 707–9.
55 Al-Shouli S, Abouchala N, Bogusz MJ *et al*. Toxic epidermal necrolysis associated with high intake of sildenafil and its response to infliximab. *Acta Derm Venereol* 2005; **85**: 534–5.
56 Hunger RE, Hunziker T, Buettiker U. Rapid resolution of toxic epidermal necrolysis with anti-TNF-alpha treatment. *J Allergy Clin Immunol* 2005; **116**: 923–4.
57 Meiss F, Helmbold P, Meykadeh N *et al*. Overlap of acute generalized exanthematous pustulosis and toxic epidermal necrolysis: response to antitumour necrosis factor-alpha antibody infliximab: report of three cases. *J Eur Acad Dermatol Venereol* 2007; **21**: 717–9.
58 Famularo G, Di Dona B, Canzona F *et al*. Etanercept for toxic epidermal necrolysis. *Ann Pharmacother* 2007; **41**: 1083–4
59 Paquet P, Piérard GE. Intense pulsed light treatment of persistent facial hypermelanosis following drug-induced toxic epidermal necrolysis. *Dermatol Surg* 2004; **30**: 1522–5.

Prevention and future use of drugs

Cases should be notified to regulatory agencies. Patients should be advised to avoid re-exposure to the suspect drug(s). Published cases of recurrences have all been attributed to the same generic drug or to compounds chemically closely related (e.g. aromatic anticonvulsants). Therefore, there is no rationale for restricting the use of all classes of 'high-risk drugs'. Because familial cases have been reported, first-degree relatives should be alerted to their elevated risk of reaction to the same drug(s). Following realization of the importance of pharmacogenetics in the aetiology of SJS/TEN, it is recommended that genotyping be undertaken as a screening measure for the HLA allele B*1502 in all Asians prior to prescription of carbamazepine [1], and for the HLA-B*5701 allele in the case of prospective recipients of abacavir [2–5]. In predominantly Caucasian populations, 94% of patients do not carry the HLA-B*5701 allele and are at low risk for hypersensitivity reaction to abacavir [5].

References

1 Ferrell PB Jr, McLeod HL. Carbamazepine, HLA-B*1502 and risk of Stevens–Johnson syndrome and toxic epidermal necrolysis: US FDA recommendations. *Pharmacogenomics* 2008; **9**: 1543–6.
2 Rauch A, Nolan D, Martin A *et al*. Prospective genetic screening decreases the incidence of abacavir hypersensitivity reactions in the Western Australian HIV cohort study. *Clin Infect Dis* 2006; **43**: 99–102.
3 Waters LJ, Mandalia S, Gazzard B, Nelson M. Prospective HLA-B*5701 screening and abacavir hypersensitivity: a single centre experience. *AIDS* 2007; **21**: 2533–4.
4 Chui CK, Brumme ZL, Brumme CJ *et al*. A simple screening approach to reduce B*5701-associated abacavir hypersensitivity on the basis of sequence variation in HIV reverse transcriptase. *Clin Infect Dis* 2007; **44**: 1503–8.
5 Mallal S, Phillips E, Carosi G *et al*. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med* 2008; **358**: 568–79.

CHAPTER 77
Dermatological Surgery

C.M. Lawrence[1] *& N.R. Telfer*[2]

[1]Department of Dermatology, Royal Victoria Infirmary, Newcastle upon Tyne, UK
[2]Department of Dermatology, Salford Royal Hospital, Salford, UK

Critical anatomical areas, 77.1
Skin tension lines and the orientation of scars, 77.2
Head and neck, 77.2
Limbs, 77.5
Equipment and sterilization, 77.5
Safety aspects, 77.7
Complications, 77.8
Local anaesthetics, 77.10
Principles and types, 77.10
Toxic reactions, 77.10
Methods, 77.10
Biopsy techniques, 77.11
Incisional and excisional elliptical biopsy, 77.11
Punch biopsy, 77.11
Shave, 77.12
Simple excision, suture technique and wound closure, 77.13
Excision, 77.13
Sutures, 77.14
Suture technique, 77.14
Particular forms of excision, 77.15
Wound closure, 77.16
Dressings, 77.17
Basic dressing, 77.17
Pressure dressings, 77.17
Suggested dressing for wound types, 77.17
Secondary intention healing, 77.18
Skin grafts, 77.20
Full-thickness grafts, 77.20
Composite grafts, 77.20
Split-skin graft, 77.20
Pinch grafts, 77.20
Grafting techniques used for vitiligo, 77.21
Acne scar punch grafts, 77.22
Flaps, 77.23
Mohs micrographic surgery, 77.29
Miscellaneous surgical procedures, 77.34
Techniques, 77.34
Specific diseases, 77.36
Cryosurgery, 77.39
Curettage, 77.40
Electrosurgery, 77.44
Infrared coagulation, 77.47
Caustics, 77.47
Intralesional therapy, 77.48
Miscellaneous physical procedures, 77.49
Keloid therapy, 77.49
Minor surgical procedures, 77.50
Haemostasis, 77.50

Introduction

The acquisition of basic dermatological surgery skills is an important component of dermatological training. This chapter covers simple excisional surgery and provides an introduction to more advanced techniques. In addition, there are descriptions of Mohs micrographic surgery and several other surgical procedures. The reader is also referred to the specialist journal *Dermatologic Surgery*, and introductory [1–3] and intermediate textbooks [4–6]. Other books deal more specifically with cosmetic dermatological surgery [7,8] or general aspects of plastic surgery [9–11].

References

1 Bennett RG. *Fundamentals of Cutaneous Surgery*. St Louis: Mosby, 1988.
2 Burge S, Colver GB, Rayment R. *Simple Skin Surgery*, 2nd edn. Oxford: Blackwell Science, 1996.
3 Lawrence CM. *An Introduction to Dermatological Surgery*, 2nd edn. St Louis: Mosby, 2002.
4 Roenigk RK, Roenigk HH, eds. *Dermatologic Surgery*, 2nd edn. New York: Marcel Dekker, 1996.
5 Robinson JK, Hanke CW, Senglemann RD *et al. Surgery of the Skin: Procedural Dermatology*. Philadelphia: Elsevier Mosby, 2005.
6 Zachary CB. *Basic Cutaneous Surgery: a Primer in Technique*. New York: Churchill Livingstone, 1991.
7 Parish LC, Lask GP. *Aesthetic Dermatology*. New York: McGraw-Hill, 1991.
8 Stegman SJ, Tromovitch TA. *Cosmetic Dermatologic Surgery*, 2nd edn. Chicago: Year Book Medical, 1990.
9 Grabbe WC, Smith JW. *Plastic Surgery*, 3rd edn. Boston: Little, Brown, 1979.
10 McGregor IA. *Fundamental Techniques of Plastic Surgery and Their Surgical Applications*. New York: Churchill Livingstone, 1975.
11 Sisson GA, Tardy MJ. *Plastic and Reconstructive Surgery of the Face and Neck*. New York: Grune & Stratton, 1977.

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

Critical anatomical areas

It is essential to have a working knowledge of the important clinical anatomy of each operation site. The following is only a brief introduction to some of the critical anatomical details with which the operator must be familiar. Excisions down to superficial fat will rarely result in exposure of or potential damage to functionally important structures, except in a very thin subject. Incisions to deep fat or fascia and the removal of large cysts or lipomas may result in exposure of important structures. On the head and neck, division of larger arteries and veins will not cause vascular complications because of the extensive collateral circulation. However, it is important to be aware of the position of large arteries and veins in order to be prepared to deal with bleeding from these

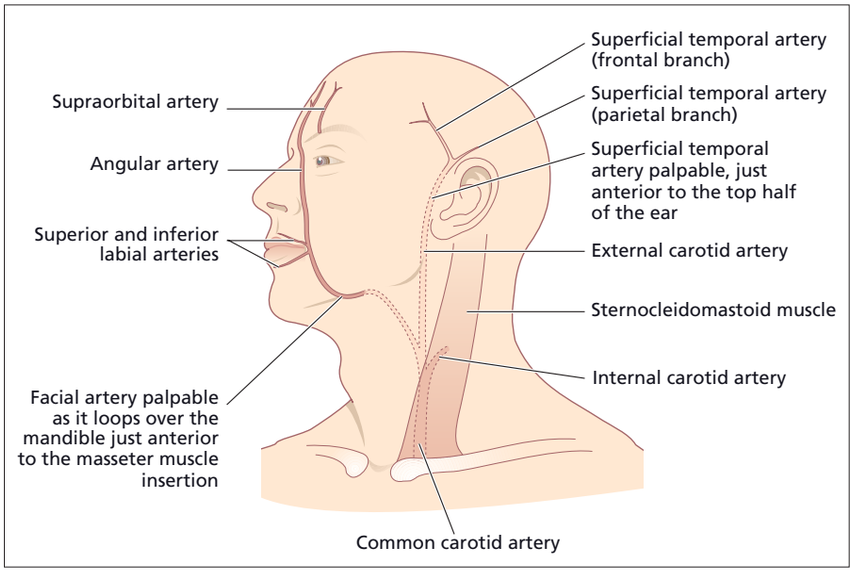


Fig. 77.1 Arteries of the head and neck encountered in skin surgery. The labial artery lies on the inside (mucosal) surface of the lip approximately 5 mm from the visible vermilion border. (---) Arteries rarely encountered; (—) arteries frequently identified during superficial skin surgery on the face.

vessels. Division of sensory nerves may produce annoying sensory loss, but this will have little functional impact on the head and neck. Knowledge of the anatomy of the supraorbital, infraorbital and mental sensory nerves is important, as these are commonly used in peripheral nerve blocks. Division of motor nerves is potentially disabling and thus it is essential to know the anatomy of the vulnerable superficial cranial and peripheral motor nerves.

Skin tension lines and the orientation of scars

Incisions should be designed to follow the wrinkles or relaxed skin tension lines (synonym stress lines; favourable skin tension lines; maximal skin tension lines) as the resulting scars will be stronger and less likely to stretch [1]. Relaxed skin tension lines run perpendicular to the direction of contraction of the underlying muscles and parallel to the dermal collagen bundles [2]; cutting transversely across these weakens the skin much more than a cut running parallel to the collagen bundles [3]. In the absence of wrinkles, relaxed skin tension lines can be identified by asking the patient to grimace or by skin manipulation. Langer's lines [4] (synonym resting stress lines) were mapped on cadaver skin, and differ from relaxed skin tension lines on the limbs and trunk [3]; they should not be used for identifying the elective direction of excision.

Head and neck

Cosmetic units

Cosmetic results of surgery are better if all the incisions remain within a cosmetic unit [5]. These are areas of skin that share similar characteristics (e.g. the nose, cheek and periorbital skin). The junction lines separating these areas are also important because scars placed in junction lines are usually unobtrusive whereas scars that cross a junction line (bridge two cosmetic units) are very obvious. It is thus important to try to design a repair so that the scars follow relaxed skin tension lines and remain within the same cosmetic unit, or run in the junction lines between two adjacent cosmetic units.

Blood vessels and lymphatic supply of face

Larger vessels, particularly the temporal artery, can be avoided by hydrodissection (see p. 77.34). The facial artery (Fig. 77.1) at the nasolabial fold, and its continuation into the angular artery at the medial canthus, are frequently divided when excising tumours at these sites. The external jugular vein runs under the platysma muscle but on top of the sternocleidomastoid muscle, and may be easily damaged during superficial incisions on the neck at this site (Fig. 77.2a). Emissary veins, connecting the intracranial and extracranial venous circulation, run across the subgaleal space towards the back of the scalp (parietal emissary vein) and just above the forehead (frontal emissary vein) [6]. These veins may be damaged when undermining the subgaleal space at these sites. Lymphatic drainage sites should be examined for metastases during follow-up of patients treated for squamous cell carcinoma or melanoma [7]. Division of skin lymphatics during incisions under the eye may result in temporary but unavoidable lower eyelid lymphoedema. Postoperative lymphatic leakage sometimes occurs after lower limb or axillary excision. This resolves spontaneously with conservative management.

Sensory nerves of face

Nerve blocks. Sensation to the face is supplied by the trigeminal (Vth) cranial nerve. The three branches readily blocked in skin surgical procedures on the head and neck include the supraorbital, infraorbital and mental nerves (Fig. 77.3). These emerge from the skull via palpable foramina, which all lie in the same plane, just medial to a vertical line running through the pupil [8]. Block-

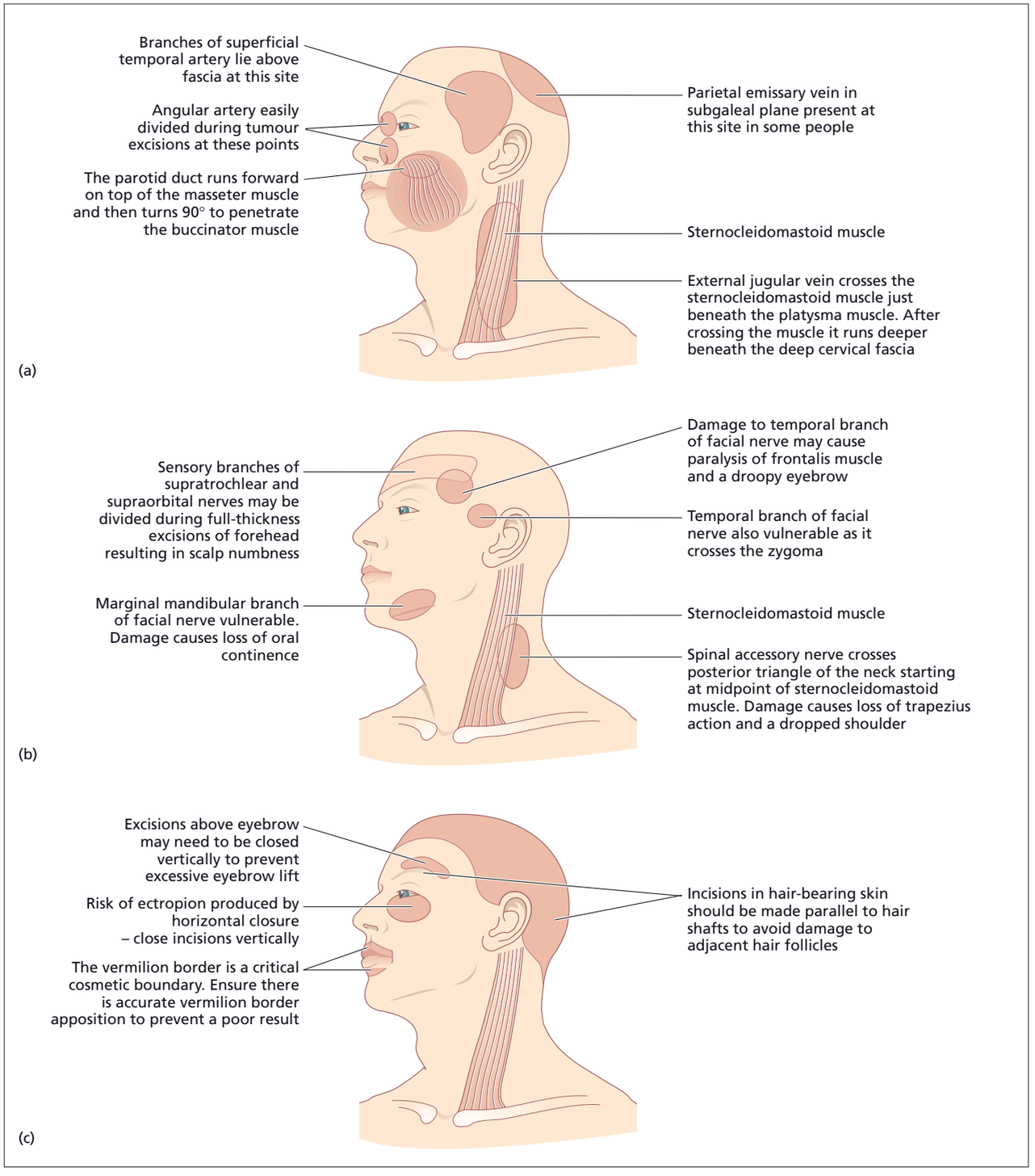


Fig. 77.2 Potential surgical hazard sites during skin surgery on the head. (a) Potential blood vessel and duct, (b) nerve and (c) cosmetic hazards on the head and neck. (From Lawrence [9].)

ing the great auricular, transverse cervical and lesser occipital nerves as they emerge, approximately 10–20 mm above and below Erb's point, from the posterior border of the middle third of the sternocleidomastoid muscle [10] produces anaesthesia of a large portion of the scalp, neck and ear. Erb's point is identified by dropping a plumb line from the mid-point of a line drawn between the mastoid process and the angle of the jaw. Where this line meets the posterior border of the sternocleidomastoid muscle is Erb's point. At this site, the spinal accessory (XIth) cranial nerve also emerges from behind the sternocleidomastoid muscle. This motor

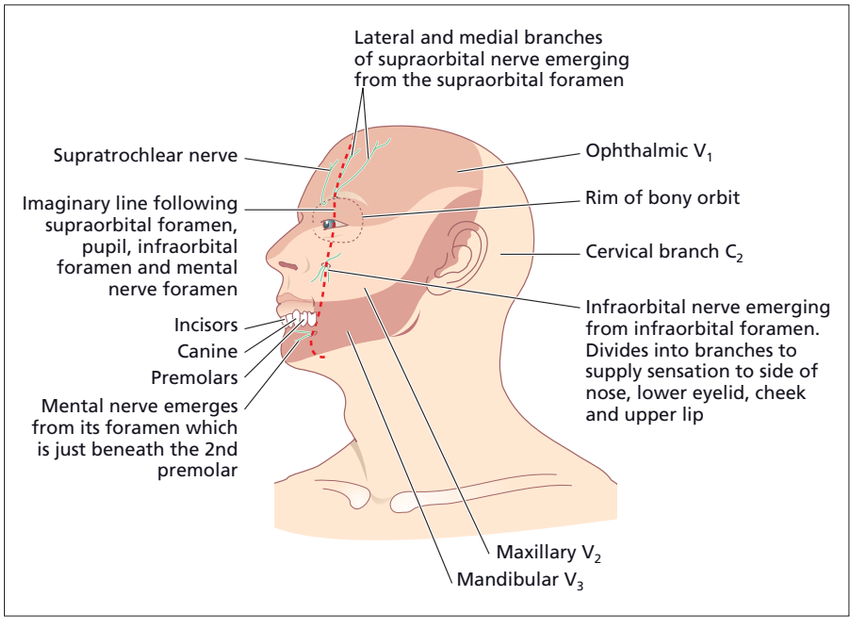


Fig. 77.3 Sensory nerves on the face used in nerve-block anaesthesia. Sensation on the face is served by the three main divisions of the trigeminal nerve: the ophthalmic, maxillary and mandibular divisions. Three important branches of these nerves—the supraorbital, infraorbital and mental nerves—emerge in the same plane along a vertical line running through the pupil.

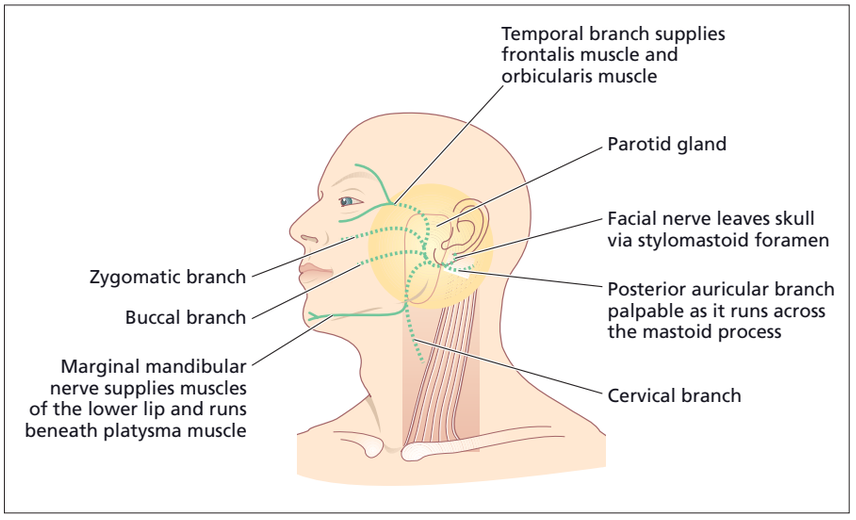


Fig. 77.4 Motor branches of the facial nerve vulnerable in skin surgery. (---) Nerves rarely encountered; (—) nerves at risk during superficial skin surgery on the face.

nerve is rarely affected by the local anaesthesia, as it lies deeper, on the floor of the posterior triangle, whereas the three named sensory branches of the cervical plexus curl round to lie on top of the sternocleidomastoid muscle [11].

Division of small sensory nerves. This is of little consequence, with the possible exception of scalp numbness following incisions on the forehead. Improvement in sensory loss can be expected for up to 1 year.

Motor nerves

Two branches of the facial (VIIth) cranial nerve, the marginal mandibular branch and the temporal branch, are vulnerable during skin surgery (Fig. 77.4). The temporal branch of the facial nerve supplies the frontalis and orbicularis muscles. Damage to the nerve supplying frontalis muscle results in difficulty raising the eyebrow, and the forehead furrows disappear. This can easily occur during excision of large tumours on the temple, lateral to the frontalis muscle, and as the nerve crosses the zygomatic arch.

Table 77.1 Undermining levels.

Site	Undermining level
Face	Mid-fat
Nose	Just above the periosteum and perichondrium
Forehead	Beneath the deep frontalis fascia (equivalent to the subgaleal plane)
Scalp	Subgaleal plane
Trunk and limb	
Small excisions	Deep fat
Large excisions	Just above the deep fascia

At both sites there is little tissue between the skin and periosteum (Fig. 77.2b). The marginal mandibular branch innervates muscles that move the lower lip. Damage can be devastating because it results in weakness of the lips, with dribbling when eating and drinking. The nerve is superficial and vulnerable as it emerges from under the parotid gland at the angle of the jaw, behind the point where the facial artery can be palpated as it crosses the mandible. More anteriorly, the nerve runs beneath the platysma muscle [12]. Variations in nerve position with age and neck position must also be considered. The remaining branches of the facial nerve are less vulnerable because they share several cross-connections and lie deeper. The other important motor cranial nerve is the accessory (XIth) nerve, which supplies the trapezius and sternocleidomastoid muscles. This may be damaged during dissection in the posterior triangle of the neck, causing weakness of the trapezius muscle and producing a dropped shoulder.

Undermining levels

When undermining to increase skin mobility, different levels are appropriate at different sites (Table 77.1).

Specific facial sites

If an incision runs across the vermilion of the *lip*, the vermilion border must be carefully marked before anaesthetic injection to avoid a poor cosmetic result (Fig. 77.2c). In older patients with poor lid elasticity, operations around the *lower eyelid* may result in ectropion if any downwards tension is applied to the lower eyelid. In a patient with poor lid elasticity, the procedure should be designed to increase rather than reduce eyelid tension; this usually means closing the wound vertically rather than horizontally. If an incision goes across the *hair line*, ensure that the scalp margin is reconstructed so that a smooth contour remains. Because hairs grow obliquely through the skin, any incision through *hair-bearing skin* should be made parallel to the hair shafts rather than vertically through the scalp so that fewer follicles are damaged.

Limbs

The only superficial motor nerve on the limbs is on the lateral aspect of the knee, where the common peroneal nerve (lateral popliteal) can be palpated against the bone as it winds round the neck of the fibula. Injury to the nerve at this site will produce a foot drop resulting from paralysis of foot dorsiflexors and elevators.

References

1 Salasche SJ, Bernstein G, Senkarik M. *Surgical Anatomy of the Skin*. Norwalk: Appleton & Lange, 1988.
2 Borges AF, Alexander JE. Relaxed skin tension lines, Z-plasty on scars and fusiform excision of lesions. *Br J Plast Surg* 1962; **15**: 242–54.
3 Kraissl CJ. The selection of appropriate lines for elective surgical incision. *Plast Reconstr Surg* 1951; **8**: 1–28.
4 Langer K. On the anatomy and physiology of the skin. I. The cleavability of the cutis. Translated and republished in *Br J Plast Surg* 1978; **31**: 3–8, with covering editorial 1–2.
5 Summers BK, Siegle RJ. Facial cutaneous reconstructive surgery: general aesthetic principles. *J Am Acad Dermatol* 1993; **29**: 669–81.
6 Sobotta J. Head, neck upper limbs and skin. In: Staubesand J, ed. *Atlas of Human Anatomy*. Munich: Urban & Schwarzenberg, 1989.
7 Romanes GJ. *Cunningham's Manual of Practical Anatomy*, 15th edn, Vol. 3. *Head and Neck and Brain*. Oxford: Oxford University Press, 1986.
8 Scott DB. *Techniques of Regional Anaesthesia*. Norwalk: Appleton & Lange/Mediglobe, 1989.
9 Lawrence CM. *An Introduction to Dermatological Surgery*, 2nd edn. St Louis: Mosby, 2002.
10 Lumley JSP. *Surface Anatomy, the Anatomical Basis of Clinical Examination*. Edinburgh: Churchill Livingstone, 1990.
11 Williams PL, Bannister LH, Berry M *et al*., eds. *Gray's Anatomy*, 38th edn. New York: Churchill Livingstone, 1995.
12 Summers BK, Siegle RJ. Facial cutaneous reconstructive surgery: facial flaps. *J Am Acad Dermatol* 1993; **29**: 917–41.

Equipment and sterilization [1–5]

Although most dermatological surgical procedures can be safely performed in well-lit, dedicated outpatient units using relatively simple equipment and surgical instruments [1–3], the absence of a need for either expensive equipment or a completely sterile environment does not justify the use of inadequate facilities or inappropriate equipment.

As dermatological surgery ranges from superficial tissue destruction and removal to surgical excision and complex wound repair, a range of basic surgical instruments should be available to the dermatological surgeon depending upon the procedure to be performed. The basic equipment, with optional items that should be available for more specialized procedures, is shown in Table 77.2. Advanced skin surgery (e.g. the excision and complex repair of difficult tumours and Mohs micrographic surgery) requires both dedicated facilities and specialized surgical instruments to achieve the best results.

Wound infection, an uncommon complication of dermatological surgery, is more commonly related to surgical technique than poor operator cleanliness or instrument sterilization. However, correct hand washing techniques are vital to the prevention of cross-infection [4]. The tradition of protracted 'scrubbing up' is not essential prior to most dermatological surgical procedures—two washes in warm running water using 4% chlorhexidine or 10% povidine–iodine solution are sufficient.

Hand hygiene in UK NHS hospitals has been the subject of much publicity and concern. The routine use of alcohol-based hand rubs [5] has been recommended to help prevent the spread of hospital acquired infections, particularly MRSA (methicillin

Table 77.2 Essential and optional equipment. (From Burge *et al*. [1].)

Essential	Optional
The room	
An examination couch with adjustable backrest	Theatre table
A stool for the surgeon	
Good lighting: Anglepoise lights	Overhead theatre lights
Equipment—preoperative preparation	
Autoclave for steam sterilization or electric oven for dry heat sterilization	
Skin preparation	
Chlorhexidine solution	
Chlorhexidine detergent (Hibiscrub®)	
Surgical gloves	
Sterile paper towels	Re-usable drapes
A window can be cut in the centre and the towel placed over the lesion	
Skin markers	Sterile pen and Indian ink
Gentian violet and pointed orange stick	
Skin marker pen	
Indelible felt-tip pen	
Anaesthetic	
Disposable syringes 2 mL, 5 mL fine needles	Dental syringe and fine needles
	Dental syringe vials
Lidocaine (lignocaine)	
1% and 2% plain and with epinephrine (adrenaline) 1 : 100 000 or 1 : 200 000	
Instruments	
Scalpel blades	
No. 15 for excision	
No. 22 for shave biopsy	
Scalpel handle	
Forceps	
Fine-toothed (e.g. Adson–Brown)	
Non-toothed	
Skin hook	
Can easily be constructed by pushing a sterile needle onto a sterile moistened cotton wool bud on an orange stick. Bend the needle into a curve	
Scissors	
Curved pointed iris scissors	
Blunt straight scissors	
Needle holders	
Small artery clamps	
Various sizes of absorbable and non-absorbable sutures attached to needles	Skin punch for biopsies, 3 mm and 4 mm
	Sharp ring curettes in various sizes
Haemostasis	
Gauze swabs	Hyfrecator
30–50% aluminium chloride in alcohol or Monsel's solution (67.5% basic ferric sulphate)	Electrocautery
	Diathermy
	Bipolar electrocoagulation
	Cryosurgery gun
	Supply of liquid nitrogen
	Silver nitrate sticks
Dressings	
Steri-strips	Opsite
Compound Benzoin tincture BP (Friar's balsam) for sticking plaster to skin	
Elastoplast	
Micropore	
Gauze	
Jelonet®	
Histopathology	
Specimen pots	
Fixative	
10% buffered formalin	EM fixative 4% glutaraldehyde
	Fixative or liquid nitrogen to store specimens for immunohistology

resistant *Staphylococcus aureus*). Hand disinfection using such alcohol-based hand rubs is associated with less skin irritation [6] and less skin barrier disruption [7] than hand washing using soap or detergent-based products.

During surgery the use of either clean, non-sterile or sterile surgical gloves is mandatory, and the wearing of eye protection is strongly recommended.

The sterilization of non-disposable medical and surgical instruments is an important factor in reducing the risk of infection. Three levels of importance have been described in this area [8]; firstly, non-critical items (e.g. dermatoscopes, which normally only come into contact with intact skin) require only low-level disinfection between patients; secondly, semi-critical items (e.g. endoscopes, which contact mucous membranes) require high-level disinfection between patients; and, finally, critical items (e.g. surgical instruments, which come into contact with sterile tissues) require sterilization between patients. Both high-level disinfection and sterilization should be preceded by manual or ultrasonic cleaning in order to remove any dried tissue, pus or blood [8–10]. Older methods of sterilization, for example boiling in water at atmospheric pressure and the use of various chemical agents (e.g. glutaraldehyde, phenolic agents), are no longer recommended [3]. The new variant Creutzfeldt–Jakob disease (vCJD) prion cannot be destroyed by sterilization, and equipment suspected of being contaminated must be quarantined. If contact is confirmed the equipment must be destroyed.

References

1 Burge S, Colver GB, Rayment R. *Simple Skin Surgery*, 2nd edn. Oxford: Blackwell Science, 1996: 5–9.
2 Grande DJ, Neuberg M. Instrumentation for the dermatologic surgeon. *J Dermatol Surg Oncol* 1989; **15**: 288–97.
3 Diwan R. Instruments for dermatologic surgery. In: Lask GP, Moy RL, eds. *Principles and Techniques of Cutaneous Surgery*. New York: McGraw-Hill, 1996: 85–100.
4 Horton R. Hand washing: the fundamental infection control principle. *Br J Nursing* 1995; **16**: 928–33.
5 Parienti JJ, Thibon P, Heller R *et al*. Hand-rubbing with an aqueous alcoholic solution vs traditional surgical hand-scrubbing and 30-day surgical site infection rates: a randomized equivalence study. *JAMA* 2002; **288**: 722–7.
6 Loffler H, Kampf G, Schmermund D, Maibach HI. How irritant is alcohol? *Br J Dermatol* 2007; **157**: 74–81.
7 Pedersen LK, Held E, Johansen JD, Agner T. Less skin irritation from alcohol-based disinfectant than from detergent used for hand disinfection. *Br J Dermatol* 2005; **153**: 1142–6.
8 Rutala WA, Weber DJ. Disinfection and sterilization in health care facilities: what clinicians need to know. *Clin Infect Dis* 2004; **39**: 702–9.
9 Sebben JE. Survey of sterile technique in dermatological surgeons. *J Am Acad Dermatol* 1988; **18**: 1107–14.
10 Sebben JE, Fazio MJ. Sterilization of equipment for dermatologic surgery. In: Lask GP, Moy RL, eds. *Principles and Techniques of Cutaneous Surgery*. New York: McGraw-Hill, 1996: 47–56.

Safety aspects

Certain basic safety measures and protocols are essential within a dermatological surgery unit in order to minimize the risks of infection and accidental injury to both patients and staff [1].

The routine use of aseptic technique minimizes the risk of bacterial colonization at the operation site, and prevents contamination from adjacent sites. Antisepsis and sterilization are discussed elsewhere (see p. 77.5). Control of blood-borne infections, especially human immunodeficiency virus (HIV) and hepatitis viruses, has two main components: prevention of transmission from patient to patient, and protection of the surgical team [2]. It is now mandatory for all British medical and nursing staff to be adequately vaccinated against hepatitis B, and for hospitals to have both dedicated infection control staff and protocols to ensure instrument sterility. One approach suggested by the US Centers for Disease Control and Prevention (CDC) is to treat *all* patients as if they were infected with HIV, hepatitis B or other blood-borne pathogens and to adopt 'universal precautions' [3].

Needle-stick injuries and other sharp instrument cuts are particularly important, and all members of the surgical team should take extreme care with the use and disposal of 'sharps'. It is extremely dangerous to either leave uncapped needles on the instrument tray or to attempt needle recapping by the two-handed method. Ideally, the surgeon should make a habit of both disposing of used needles and syringes *immediately* after use and removing all sharp disposable instruments (e.g. needles, scalpel blades) from the tray after the operation, placing these directly into 'sharps disposal' boxes. All relatives and those theatre personnel not directly concerned with the procedure should be excluded from the operating room. Clothing should be specific for surgery—apart from potentially introducing a variety of organisms to the procedure room, clothes may become contaminated.

At the preoperative consultation, a careful history may identify certain potential problems (e.g. diabetes, epilepsy) and the presence of cardiac pacemakers [4]. A full drug history is important—aspirin and anticoagulants promote bleeding and non-selective β-blockers (e.g. propranolol) may rarely interact with epinephrine (adrenaline) in local anaesthetics, resulting in malignant hypertension. On direct questioning, some people may admit to a tendency to faint very easily, and some patients with epilepsy may have a history of fits triggered by surgery or dental procedures. As there is always a risk of patient collapse in operating rooms, there must be adequate space available for an emergency resuscitation to be performed. Resuscitation drugs and equipment, together with both suction and an oxygen supply, should be readily available [5]. All theatre personnel should be trained in advanced resuscitation techniques, including emergency electrocardiography and cardiac defibrillation [6].

References

1 Jackson M, Lynch P. An attempt to make an issue less murky: a comparison of four systems for infection prevention. *Infect Control Hosp Epidemiol* 1991; **12**: 48–9.
2 Maloney ME. Infection control. In: Lask GP, Moy RL, eds. *Principles and Techniques of Cutaneous Surgery*. New York: McGraw-Hill, 1996: 57–62.
3 CDC Update. Universal precautions for prevention of human immunodeficiency virus, hepatitis B virus, and other blood-borne pathogens in health-care settings. *Morb Mortal Wkly Rep* 1988; **37**: 377–82, 387–8.
4 Sebben JE. The hazards of electrosurgery. *J Am Acad Dermatol* 1987; **16**: 869–71.
5 Nagi C, Greenway HT. Emergency airway assessment and management: guide for office practice. *J Assoc Milit Dermatol* 1985; **9**: 66–8.
6 Cummins RO, Thesis W. Encouraging early defibrillation: the AHA and automatic defibrillators. *Ann Emerg Med* 1990; **19**: 1245–7.

Table 77.3 Complications in wound healing.

Complications	Predisposing factors	Prevention
Infection	Infected lesions Poor sterility Steroids Adjacent infectious source Occlusive dressings Poor blood supply Fat, haematoma and foreign material Sutures Poor technique Excessive devitalized tissue from careless handling or electrocoagulation	Careful preoperative and operative techniques Sutureless closure Antibiotic sprays Prophylactic antibiotics for infected or potentially infected wounds
Delay in closure	Poor blood supply Excess movement Infection Tension Steroids Debilitated patient Poor nutritional status	Layered closure Gentle tissue handling Minimize devitalization of tissues Care in decision to operate Warmth Careful postoperative dressings
'Gaping scar'	Inadequate apposition Dermal instability Excess movement Infection Tension	Careful apposition Subcutaneous or subcuticular sutures Adequate postoperative support (e.g. antitension dressings)
Painful scars	Feet and fingers especially	Avoid pressure sites if possible Dressings to reduce subsequent pressure and/or movement Careful apposition
Hypertrophic scars	Site Tension Reaction to embedded material Trauma Individual susceptibility	Avoid 'cape' area if possible Good surgical technique including undermining of edges where necessary
Keloids	Previous history Black skin Upper half of body Tension	Avoid surgery where possible Antitension measures for 3 weeks Watch and prepare to treat
'Railroad tracks'	Skin sutures under too much tension	Good suture technique Use of 'non-reactive' suture material
Stitch marks 'abscess'	Sutures left in too long	Early suture removal
Wound edge inversion	Poor technique	Good surgical technique Occlusive or semi-occlusive dressings
Bleeding and/or haematoma formation	Bleeding tendency Aspirin Clopidogrel Ticlopidine Eptifibatide Tirofiban	Preoperative screening Good haemostasis Use of epinephrine (adrenaline) in local anaesthetic

Complications [1]

All dermatological surgical procedures may result in complications [1], most commonly bleeding, infection and poor wound healing (Table 77.3). Although complications will always occur, most can be prevented by a combination of thorough preoperative preparation and good surgical technique.

The incidence of complications following both general dermatological surgery and Mohs micrographic surgery is generally low. In a prospective, multi-centre study published in 2005, 84 French

dermatologists performed 3788 outpatient dermatological surgical procedures under local anaesthesia. These included excision of benign and malignant tumours (excluding 'sebaceous' cysts and pyodermas) [2]. There were 236 recorded complications occurring in 213 (6%) procedures. Excessive bleeding (3%), vasovagal syncope (1.4%) and wound infection (2%) were the main complications. Infection was superficial in 92% of cases, with one case of systemic infection. Antibiotic therapy or further surgery was required in 1%, and haemorrhagic complications appeared to be independently associated with the risk of wound infection. In 2007, the same authors reported an almost identical study (73 dermatologists performed 3491 procedures) [3]. Overall, 67 (1.9%) patients developed wound infections, with a higher rate (4.3%) of infection following complex wound repair. Once again, haemorrhagic complications were independently associated with the risk of development of wound infection.

Mohs micrographic surgery is also a safe procedure associated with a low risk of complications. An overall infection rate of 2.3% was reported following 530 Mohs procedures and 517 non-Mohs excisions performed on outpatients [4]. One US Mohs unit reported its complication rate to be equal to or lower than the published complication rates from specialists in other surgical disciplines [5]. The common practice of using clean but non-sterile gloves during Mohs tumour excision stages appears to be both safe and cost-effective. A retrospective case note review of 1239 Mohs patients (1400 Mohs procedures) revealed 25 cases of wound infection, with no significant difference in infection rates seen between those treated with either sterile or non-sterile gloves in the Mohs excision stages [6].

Warfarin and other anticoagulants pose a significant risk of postoperative complications. In a prospective study of 102 patients undergoing minor plastic surgery (37 regularly taking aspirin, 21 taking warfarin and 44 on neither drug), 57% of the patients taking warfarin developed complications, significantly more than the control and aspirin-taking groups [7].

Similarly, antiplatelet drugs (e.g. aspirin, clopidogrel, ticlopidine) potentially increase the risks of bleeding complications. In one study of patients undergoing minor plastic surgery, no significant difference in bleeding complication rates was seen between aspirin-taking and control groups [7]. However, other reports have found a link between aspirin therapy and a small but significant increased risk of postoperative bleeding following excision of cutaneous head and neck lesions [8], the risk being particularly pronounced in patients undergoing local flap wound reconstruction. Consequently, opinion differs on whether or not to discontinue aspirin or anticoagulants prior to dermatological surgery, particularly in patients at high risk of potential cerebral and cardiovascular complications if therapy is temporarily interrupted. Some authors believe this is not routinely necessary [9,10], particularly for straightforward procedures, and others recommend caution in patients taking aspirin [8], and especially in patients receiving warfarin therapy [7].

In most instances, aspirin can be continued without resulting in a worse surgical outcome, although intraoperative bleeding may take longer to control. However, at some sites (e.g. around the eye) or in procedures involving extensive undermining or complex wound reconstruction, it may be appropriate to temporarily discontinue aspirin therapy. If aspirin is stopped this must be done at least 10 days before surgery to allow a sufficient number of new platelets with normal clotting responses to be produced. Non-steroidal anti-inflammatory drugs (NSAIDs) seem to present no significant problem and can probably be continued in all circumstances [11].

The use of epinephrine-containing local anaesthetics results in vasoconstriction and prolongs the duration of anaesthesia. Intraoperatively, bleeding can be controlled by a combination of electrosurgery, pressure and ligation. Postoperatively, the use of appropriate wound dressings is important—ranging from simple Band Aid dressings for superficial wounds to layered dressings with pressure pads for larger wounds where there is a significant risk of haematoma formation (e.g. following cyst or lipoma excision; widely undermined wounds). All patients should be given verbal and written information regarding wound care and how to contact the dermatology unit if problems arise. Haematoma formation may occur at various times after surgery and usually results in acute pain and swelling. The clinical appearances, together with the age and size of the haematoma, will dictate whether to open the wound, evacuate the haematoma and obtain haemostasis, or to manage the complication conservatively.

Wound infection is a major concern, but is fortunately relatively uncommon following skin surgery of all types [2–4]. If the risk of infection is higher than normal (e.g. following excision of an ulcerated tumour from a flexural site), prophylactic antibiotic therapy may be appropriate. Postoperative infection usually presents as erythema, pain and swelling in and around the wound, 4–8 days after the procedure. Depending upon the clinical appearances, management will range from wound care, topical and systemic antibiotics, through to incision and drainage of a frank wound abscess.

Other significant problems relate to both the cosmetic and functional results of surgery. The risks of scarring must be carefully explained prior to surgery, with special attention to the possibility of distortion of facial 'free margins' (e.g. vermilion, lower eyelid) and unsightly hypertrophic scars in high-risk body sites (e.g. upper arm, shoulders, chest). Altered pigmentation in and around the wound is an additional cosmetic risk in Asian and black patients. Nerve damage is a significant concern, as both sensory and motor nerves may be damaged during dermatological surgery, particularly at certain 'high-risk' anatomical sites (see pp. 77.3–77.5).

References

1 Stasko T. Complications of cutaneous procedures. In: Roenigk RK, Roenigk HH, eds. *Dermatologic Surgery*, 2nd edn. New York: Marcel Dekker, 1996: 149–75.

2 Amici JM, Rogues AM, Lasheras A *et al.* A prospective study of the incidence of complications associated with dermatological surgery. *Br J Dermatol* 2005; **153**: 967–71.

3 Rogues AM, Lasheras A, Amici JM *et al*. Infection control practices and infectious complications in dermatological surgery. *J Hosp Infect* 2007; **65**: 258–63.

4 Futoyan T, Grande D. Postoperative wound infection rates in dermatologic surgery. *Dermatol Surg* 1995; **21**: 509–14.

5 Cook JL, Perone JB. A prospective evaluation of the incidence of complications associated with Mohs micrographic surgery. *Arch Dermatol* 2003; **139**: 143–52.

6 Rhinehart MB, Murphy MM, Farley MF, Albertini JG. Sterile versus nonsterile gloves during Mohs micrographic surgery: infection rate is not affected. *Dermatol Surg* 2006; **32**: 170–6.

7 Kargi E, Babuccu O, Hosnuter M *et al*. Complications in minor cutaneous surgery in patients under anticoagulant treatment. *Aesthetic Plast Surg* 2002; **26**: 483–5.

8 Dhiwakar MA, Khan NA, McClymont LG. Surgical resection of cutaneous head and neck lesions: does aspirin use increase hemorrhagic risk? *Arch Otolaryngol Head Neck Surg* 2006; **132**: 1237–41.
9 Billingsley EM, Maloney ME. Intraoperative and postoperative bleeding problems in patients taking warfarin, aspirin and nonsteroidal anti-inflammatory agents: a prospective study. *Dermatol Surg* 1997; **23**: 381–3.
10 Alcalay J, Alkalay R. Controversies in postoperative management of blood thinners in dermatologic surgery: continue or discontinue? *Dermatol Surg* 2004; **30**: 1091–4.
11 Stables G, Lawrence CM. Management of patients taking anti-coagulant, aspirin, non-steroidal anti-inflammatory and other antiplatelet drugs undergoing dermatological surgery. *Clin Exp Dermatol* 2002; **27**: 432–5.

Local anaesthetics [1]

Principles and types

An ideal local anaesthetic agent would be non-toxic, painless on injection, rapid in onset, highly effective and carry a low risk of sensitization. The best compromise is found in 0.5–2% lignocaine hydrochloride (lidocaine), an amide-type local anaesthetic, which is the agent of choice for most dermatological surgery. Other amide-type local anaesthetic agents include mepivacaine, bupivacaine and ropivacaine, which have a slower onset but more sustained duration than lidocaine (lignocaine) [1]. Local anaesthetics in 'multiuse' bottles generally contain parabens preservative, but those supplied in glass ampoules are often preservative-free.

Ester-type local anaesthetics, for example procaine (ester of *p*-aminobenzoic acid), are seldom used by dermatologists.

Epinephrine 1:80 000 to 1:200 000, when added to local anaesthetic solutions, prolongs the duration of anaesthesia and produces local vasoconstriction. By reducing absorption, it may reduce the risk of systemic lidocaine toxicity.

Toxic reactions [1,2]

Toxic reactions to lidocaine are rare, and more likely to occur with the use of high volumes of high-concentration solutions or if accidental intravascular injection occurs. Lidocaine toxicity usually presents as a sensation of numbness or tingling. Systemic reactions include vasodilatation, cardiac or respiratory depression, or central nervous system manifestations such as dizziness, drowsiness, tinnitus, slurring of speech, muscle twitching and seizures. These side effects are, to some extent, reversible with diazepam (Valium) but full resuscitation measures may be required.

Ester-type local anaesthetics should be used with caution in patients with renal impairment. They also cross-react with a number of drugs of the *p*-aminobenzoic acid ester type (e.g. sulphonamides, paraphenylenediamine) [3,4]. Amide-type anaesthetics should be used with care in patients with hepatic impairment.

The maximum recommended dosage for lidocaine with epinephrine is 7 mg/kg or approximately 50 mL of a 1% lidocaine solution for an average adult. In practice, most dermatological procedures require substantially lower anaesthetic doses. In order to minimize the risk of accidental intravascular injection, it is a wise precaution to either aspirate prior to infiltration or, if using very fine (e.g. 30 gauge) needles, which will not aspirate blood, to keep moving the needle about in the skin while slowly infiltrating small volumes.

Systemic absorption of epinephrine may be associated with mild tachycardia and an excited state. More serious reactions are rare but, as with lidocaine toxicity, are more likely to occur with the use of high volume, high-concentration solutions or following accidental intravascular injection. The use of epinephrine in local anaesthetics should be avoided, or it should be used with caution, during pregnancy, in combination with inhalation anaesthesia or in patients suffering from severe glaucoma [5]. Interaction with non-selective β-blockers (e.g. propranolol) may rarely cause malignant hypertension [2], but this is not a risk with 'cardioselective' β-blockers (e.g. atenolol).

Patients should always be asked if they have had any untoward reactions to local anaesthetics (e.g. in dental procedures). These may have been nothing more than fainting, as vasovagal attacks are commonly associated with local anaesthesia, and should not be confused with serious toxic reactions. In cases of serious doubt, alternative methods of anaesthesia are necessary.

Methods

Local anaesthesia may be achieved *topically* using either tetracaine (amethocaine) cream (Ametop®) or a eutectic lidocaine–prilocaine cream (EMLA®) [4], or by *local infiltration*. Both EMLA® and Ametop® are applied under occlusion, 1–2 h before the procedure. Conjunctival anaesthesia is best achieved using proxymetacaine eye drops, which sting much less than tetracaine.

Other methods of anaesthesia include *field block* and *nerve block anaesthesia* [3,5], which produce temporary blockade of sensory nerve function in a given area. Field block involves infiltration of local anaesthetic at several points around surgical sites such as the nose and ear [2], and nerve block anaesthesia involves blockade of one or more major sensory nerves. The most useful facial nerve blocks in dermatological surgery involve branches of the trigeminal (Vth) cranial nerve (Fig. 77.3)—the supraorbital (forehead), supratrochlear (glabella), infraorbital (lower eyelid, nasal sidewall, upper lip) and mental (lower lip) nerves [4,5]. The choice of local anaesthetic method depends upon a number of factors, including the procedure itself, anatomical site and expected duration of the operation.

Controversy surrounds the use of epinephrine in digital nerve block ('ring block') anaesthesia because of a real or theoretical risk of digital ischaemia. Some believe it is absolutely contraindicated [6], whereas others describe routine use without incident [7,8].

In order to minimize discomfort when administering a local anaesthetic injection, consideration should be given to using a relatively fine needle, injecting slowly, and using both verbal and tactile distraction techniques. Injecting into the subcutaneous fat is less painful than intradermal infiltration, although it does take longer for the skin surface to become anaesthetic. Whenever possible, anaesthetic solutions should be at room temperature, and epinephrine avoided if not considered useful for the particular procedure. Pain on injection is less when lidocaine solutions are buffered with sodium bicarbonate immediately prior to use [9].

Other anaesthetic agents include the following:

1 *Ethyl chloride* and *liquid nitrogen* spray give short-lived periods of anaesthesia by skin refrigeration. This may be sufficient for quick superficial procedures such as the incision of small cysts and milia, abscesses or the curettage of multiple small warts.

2 The anaesthetic effect of *antihistamines* (e.g. 1% diphenhydramine hydrochloride solution) can be used when hypersensitivity to other agents is present or strongly suspected.
3 The intradermal injection of *normal saline* produces a brief anaesthetic effect [2].
4 *Hypnosis* and *acupuncture* may be useful when performed by an experienced practitioner and in a suitable subject.
5 *General anaesthesia* is rarely used in dermatological surgery. Patients requiring a general anaesthetic (e.g. children requiring treatment of large facial birthmarks) are best admitted to hospital either as a day case or overnight.

References

1 Auletta MJ, Grekin RC. *Local Anesthesia for Dermatologic Surgery*. New York: Churchill-Livingstone, 1991.
2 Skidmore RA, Patterson JD, Tomsick RS. Local anaesthetics. *Dermatol Surg* 1996; **22**: 511–22.
3 Auletta MJ. Local anaesthesia for dermatologic surgery. *Semin Dermatol* 1994; **13**: 35–42.
4 Buckley MM, Benfield P. Eutectic lidocaine/prilocaine cream: a review of the topical anaesthetic/analgesic efficacy of EMLA. *Drugs* 1993; **46**: 126–51.
5 Adriani J. *Regional Anaesthesia: Techniques in Clinical Practice*. Springfield: Thomas, 1970.
6 Bennett RG. Anesthesia. In: Bennett RG, ed. *Fundamentals of Cutaneous Surgery*. St Louis: Mosby, 1988: 194–239.
7 Sylaidis P, Logan A. Digital block with adrenaline: an old dogma refuted. *J Hand Surg* 1998; **23**: 17–9.
8 Millard TP, James MP. Avoidance of adrenaline in peripheral local anaesthesia: a perpetuated medical myth? *Clin Exp Dermatol* 2001; **26**: 731–2.
9 Matarasso SL, Glogau RS. Local anaesthesia. In: Lask GP, Moy RL, eds. *Principles and Techniques of Cutaneous Surgery*. New York: McGraw-Hill, 1996: 63–75.

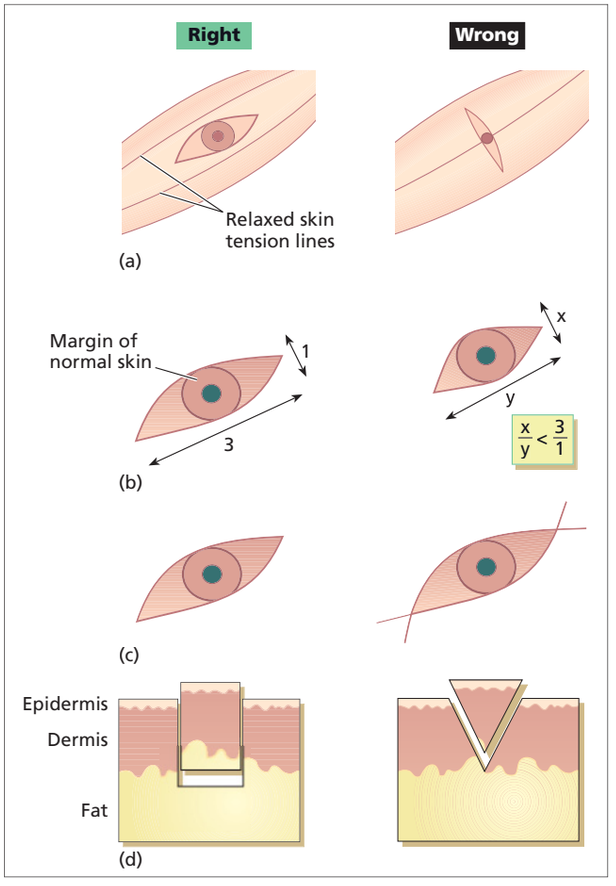


Fig. 77.5 Principles of elliptical excision. The ellipse is designed to follow skin-crease lines (a), and should be approximately three times as long as it is wide (b). Ensure that an appropriate margin of normal skin is also excised (b). At the ends of the ellipse, hold the blade vertically so that the incision lines do not cross over (c). The blade should be held at 90° to the skin when cutting the ellipse so that the wound has vertical sides down to fat. Do not bevel the blade towards the specimen as this makes the wound more difficult to close and may cut into the dermal component of the lesion (d). (From Lawrence [3].)

Biopsy techniques

Incisional and excisional elliptical biopsy

Elliptical excision biopsy is used for tumour or suspect mole removal. Incisional biopsy is used to take diagnostic biopsies of rashes and tumours before treatment is started. The technique has the advantage that the entire thickness of skin down to fat is excised. An appropriate margin can be selected if required and the incision line placed in the optimum direction [1].

For lesions on the face, orientate the ellipse so that the scar runs parallel to or within an existing skin crease (wrinkle line), or follows a boundary line between two adjacent cosmetic units. Excision direction is best assessed with the patient seated rather than lying flat, to allow for the effect of gravity on the skin crease lines. Wrinkle or smile lines can be exaggerated by asking the patient to grimace or smile, or by manipulating the skin [2]. In an excisional biopsy, measure the margin to be excised and mark the optimal line of closure before injecting the anaesthetic. When drawing on the skin, use a skin marker or Bonney's blue ink (a mixture of crystal violet and brilliant green), as other inks may tattoo the skin.

The ellipse length should be approximately three times the width, to produce an ellipse angle of approximately 30°, so that buckling does not occur when the wound is sutured (Fig. 77.5) [3]. A larger angle may suffice at some sites or in older people [4]. Make the incision as a single continuous sweep rather than a series of small nicks, and hold the blade at 90° to the skin, not angled inwards, so that the ellipse sides are vertical [5]. Ensure that the incision lines meet neatly without crossing over at the tip by starting and finishing each sweep with the blade held vertically. Incise down to fat. When the ellipse sides and tips are completely separate from the surrounding skin the ellipse should be sitting on a bed of fat. The fat under the ellipse should be cut through using scissors, while the ellipse is gently pulled away from the skin using a skin hook [6]. Undermine the edge at the appropriate level if there is any tension. Close the wound using both subcutaneous and surface sutures if necessary, using the correct suture technique.

Punch biopsy

Punch biopsy produces a core of skin down to fat. It is quick and easy to perform, and leaves only a small wound. The disadvantages

include the potential for sampling error and the difficulty in stopping bleeding if a small arteriole is punctured at the base of the wound. Punch biopsies can also be used to excise naevi on the back. At this site, wounds can be allowed to heal by second intention, with better cosmetic results than primary closure produces [7]. Subcutaneous tissue lesions can be sampled using a punch biopsy by pinching up a fold of skin to include the subcutaneous tissue before the biopsy is taken [8].

Disposable and reusable 2–8 mm diameter punches are available. When the skin is numb, drill the blade down to fat with gentle downward pressure [5]. To minimize the scar size, stretch the skin at right angles to the wrinkle lines while taking the biopsy so that, when the tension is relaxed, an oval rather than a round wound is produced, with its long axis parallel to the wrinkle lines [6]. The skin core may pop up when the surrounding skin is pressed down, or it can be hooked out using a needle. Cut through the fat at the base with scissors and remove carefully to avoid crushing the specimen. The wound can be sutured or allowed to granulate; the latter produces an acceptable small round or oval scar. If the wound is to be allowed to heal by second intention, stopping bleeding using a collagen matrix dressing results in a better cosmetic result than using Monsel's solution [9].

Shave

Shave excision is a simple, rapid and effective method of removing benign papular naevi. It can also be used to obtain a tissue diagnosis in protuberant nodular skin tumours. Shave biopsy of dermatoses affecting the epidermis or high dermis results in adequate tissue for diagnosis, and the subsequent re-epithelialization from follicular epithelium produces a good cosmetic result.

Naevi

Inject the local anaesthetic directly into the naevus, as this stiffens the tissue and makes it easier to slice off. Holding a No. 15 blade horizontally, shave off the naevus flush with the skin. Stop bleeding using cautery, electrodesiccation or a chemical haemostatic agent. Any remaining wound edge tissue fragments can be destroyed using cautery or electrodesiccation. The wound will take 2–3 weeks to heal. In approximately 45% of head and neck and 30% of trunk naevi, no visible scar remains (Fig. 77.6). In the remainder, the scar is smaller than the original naevus on head, neck and limb sites and a little larger than the naevus on trunk sites. Pigmentation at the scar edge or centre remains in approximately 25% of initially pigmented naevi after shave excision; non-pigmented naevi rarely, if ever, leave a pigmented scar [10]. Persistent pigmentation is even more common when aluminium chloride haemostasis is used rather than cautery [11]. Recurrent or retained pigment does not need to be excised. If a further specimen is sent, the pathologist must be given the full history in order to interpret the changes correctly. Hairs remain in 25% of initially hairy naevi; these can be destroyed by electrolysis if necessary. Shave excision using a safety razor or commercial equivalent (Dermablade) is also widely used [12].

Skin tumours

Shave biopsy of a solid tumour is faster and easier than an incisional biopsy, which needs to be sutured. A fragment can be



(a)



(b)



(c)

Fig. 77.6 Shave biopsy of benign papular naevi. (a) This patient had a benign tan-coloured naevus on the face (b) removed by shave excision followed by cautery, (c) resulting in a good cosmetic result 6 months later.

shaved off to confirm the diagnosis prior to definitive treatment. This type of biopsy will not help to distinguish a keratoacanthoma from a squamous cell carcinoma, and is unsuitable if histological examination of the deep margin or edge of a tumour is required to confirm the diagnosis. Bleeding can be stopped using silver nitrate stick coagulation, as the cosmetic outcome will be determined by the subsequent treatment. The fragile specimen should be mounted on paper before being placed in formalin.

References

1 Borges AF, Alexander JE. Relaxed skin tension lines, Z-plasty in scars and fusiform excisions of lesions. *Br J Plast Surg* 1962; **15**: 242–54.
2 Summers BK, Siegle RJ. Facial cutaneous reconstructive surgery: general aesthetic principles. *J Am Acad Dermatol* 1993; **29**: 669–81.
3 Lawrence CM. *An Introduction to Dermatological Surgery*, 2nd edn. St Louis: Mosby, 2002.
4 Hudson-Peacock MJ, Lawrence CM. Comparison of wound closure by means of dog ear repair and elliptical excision. *J Am Acad Dermatol* 1995; **32**: 627–30.
5 Zachary CB. *Basic Cutaneous Surgery: a Primer in Technique*. New York: Churchill Livingstone, 1991.
6 Fewkes JL, Cheney ML, Pollack SV. *Illustrated Atlas of Cutaneous Surgery*. Philadelphia: Lippincott, 1992.
7 Barnett R, Stranc M. A method of producing improved scars following excision of small lesions of the back. *Ann Plast Surg* 1979; **5**: 391–4, 435.
8 Crollick JS, Klein LE. Punch biopsy diagnostic technique. *J Dermatol Surg Oncol* 1987; **13**: 839.
9 Armstrong RB, Nichols J, Pachance J. Punch biopsy wounds treated with Monsel's solution or a collagen matrix. *Arch Dermatol* 1986; **122**: 546–9.
10 Hudson-Peacock MJ, Bishop J, Lawrence CM. Shave excision of benign papular naevocytic naevi. *Br J Plast Surg* 1995; **48**: 318–22.
11 Hudson-Peacock MJ, Lawrence CM. Cosmetic outcome following shave excision of benign papular naevi using either electrocautery or aluminium chloride for haemostasis. *Br J Dermatol* 1995; **133** (Suppl. 45): 47.
12 Gambichler T, Senger E, Rapp S *et al*. Deep shave excision of macular melanocytic nevi with the razor blade biopsy technique. *Dermatol Surg* 2000; **26**: 662–6.

Simple excision, suture technique and wound closure

Excision [1–3]

Skin biopsy specimens and cutaneous lesions can be removed using techniques other than elliptical excision, many of which (e.g. curettage, shave biopsy) do not result in a linear scar. Consequently, the decision to use formal surgical excision should balance the possible cosmetic advantages of other techniques (e.g. epidermal lesions and benign facial naevi) against the need to provide a full-thickness tissue specimen for histological examination (e.g. possible malignant melanoma).

Surgeon preparation

Dermatologists should be confident that they are competent to perform the proposed procedure and to manage any possible complications. If not, they should ask for a second opinion. The surgeon must be fully immunized against hepatitis B, and should observe safe practices with regard to handling sharps and tissue specimens. Surgical gloves should always be worn [4] and eye protection is strongly recommended.

Patient preparation

Patients should be fully aware of the significant risks, benefits and possible complications associated with the planned procedure. Informed consent [5] should be obtained, both verbally and in writing, for all invasive procedures. Usually, consent should be obtained from the parent or guardian in the case of minors, although some adolescents may be fully capable of both giving and withholding consent. Most patients about to undergo surgery are anxious and usually respond positively to appropriate reassurance as well as a calm and professional manner displayed by all members of the surgical team.

Examination and palpation of skin lesions will help to estimate their extent, depth and proximity to large blood vessels, nerves or other important structures. Langer's lines of skin tension [6] were previously used as a guide to incision, but the best cosmetic results are usually obtained by following the relaxed skin tension lines (RSTLs) [1,7], which tend to lie perpendicular to the major underlying muscles. Langer's lines and RSTLs often coincide, as on the neck. When they do not, as on the limbs, the choice depends on other factors. Excisions on the lower leg, for instance, close more easily along the long axis of the limb, rather than transversely. Testing for skin laxity by manipulating the skin usually clarifies the best direction in which to plan an excision. The size and type of excision made will also depend upon many factors, including the site and nature of the lesion to be excised and the nature of the planned skin closure.

The skin surface should be cleaned prior to operation with a detergent–antibacterial combination, most commonly containing either chlorhexidine [8] or povidone–iodine. This helps to reduce the risk of wound infection by removing pathogens and reducing the resident cutaneous bacterial flora [9].

Elliptical excision—general technique [2,3]

It can often be helpful to mark the planned lines of excision prior to cleaning the skin surface and infiltrating local anaesthetic. A reasonable period of time should be allowed for the anaesthetic to take full effect.

The small, round-ended Gillette No. 15 blade is most commonly used to make two hemi-elliptical incisions perpendicularly through the skin into the subcutaneous tissues. The length of the wound should be at least three times its breadth (the angles at the ends of the ellipse should not exceed 30°), taking care not to allow the incisions to cross each other ('fishtailing') at either end (Fig. 77.5). The skin ellipse is held firmly but gently with either fine-toothed forceps or a skin hook, and separated from its base. For both histological purposes and to facilitate wound closure, the excised specimen should contain subcutaneous fat.

For standard histological processing the specimen should be placed in a formaldehyde–saline specimen bottle, clearly labelled with the patient's details. To prevent curling of small biopsy or excision samples, these may be placed on small squares of filter paper and floated into the formalin solution. When histological confirmation of tumour clearance is required, it can sometimes be helpful to 'colour code' or place a suture at the '12 o'clock' position of the surgical specimen to facilitate orientation and examination in the pathology department. For immunofluorescence or frozen

section studies, specimens are placed on aluminium foil and immersed in liquid nitrogen.

Intraoperative bleeding is controlled by a combination of pressure, electrosurgery, clamping and ligation of vessels.

Depending upon the size of the defect and the body site, a variable degree of undermining of the wound edges will be necessary to facilitate the placing of subcutaneous absorbable sutures and to reduce wound tension. Finally, non-absorbable sutures are used to neatly appose and evert the wound edges [2,3].

The timing of suture removal depends upon the site and the amount of tension across the wound. With additional supporting surface tapes and buried sutures where appropriate, 4–5 days is usually sufficient for skin sutures on the face, 5–7 days for the scalp and neck and 10–14 days elsewhere.

References

1 Baer RL, Kopf AW. Dermatologic office surgery. In: *Year Book of Dermatology 1963–64*. Chicago: Year Book Medical, 1964: 7–47.
2 Epstein E, Epstein E Jr, eds. *Skin Surgery*, 5th edn. Springfield: Thomas, 1982.
3 Stegman SJ. *Basics of Dermatologic Surgery*. Chicago: Year Book Medical, 1982.
4 Smith JG, Chalker DK. A glove upon that hand. *South Med J* 1982; **75**: 129–31.
5 Redden EM, Baker DC. Coping with the complexities of informed consent in dermatologic surgery. *J Dermatol Surg Oncol* 1984; **10**: 111–6.
6 Ridge MD, Wright V. The directional effects of skin: a bioengineering study of skin with particular reference to Langer's lines. *J Invest Dermatol* 1966; **46**: 341–6.
7 Kraissl CJ. The selection of appropriate lines for elective surgical excision. *Plast Reconstr Surg* 1951; **8**: 1–28.
8 Kaul AF, Jewitt JF. Agents and techniques for disinfection of the skin. *Surg Gynecol Obstet* 1981; **152**: 677–85.
9 Selwyn S, Ellis H. Skin bacteria and skin disinfection reconsidered. *BMJ* 1972; **i**: 136–40.

Sutures [1–4]

An ideal suture would have high tensile strength, handle easily, provide good knot security and cause no tissue reaction. Skin sutures are of two main types: *absorbable* and *non-absorbable*.

Now that catgut is rarely used, popular synthetic *absorbable sutures* include Vicryl™ (polyglactin-910), Dexon™ (polyglycolic acid), PDS (polydioxane sulphate), Maxon™ (polyglyconate) and Monocryl™ (poliglecaprone), all of which cause very little tissue reaction and dissolve completely in 90–120 days. Absorbable sutures are usually placed either subcutaneously in the subcutaneous fat to close off potential dead space or as subcuticular intradermal sutures to close and evert wound edges.

Non-absorbable sutures include braided silk and synthetic monofilament sutures such as nylon (Ethilon™) and polypropylene (Prolene™). Most dermatological surgeons prefer the better tensile strength and low tissue reactivity of the synthetic monofilament sutures. Braided sutures such as silk and Dacron™ have better knot-tying properties but tend to drag through tissue, and their braided nature may increase the risk of wound infection. For wounds that are likely to remain under constant tension, such as those on the back or shoulders, a non-absorbable suture such as nylon can be used to close the deep subcutaneous layer. Alternatively, a running subcuticular Prolene suture can be left in place for long periods, leaving only two suture marks.

In general, skin suture needles are of the reverse cutting type (the sharp edge of the needle lies on the trailing rather than the leading edge). Suture sizes usually vary from 3/0 to 6/0, with suture selection depending on the wound size, anatomical site and surgeon preference.

Suture technique [2,3,5]

The ability to perform several different suture techniques is one of the skills needed in order to become proficient in dermatological surgery. The *simple interrupted suture* is the mainstay of final skin closure, although alternatives include a *running suture*, placed either as loops through the skin (*simple running suture*) or placed entirely within the dermis (*running subcuticular suture*). They are normally 4/0–6/0 gauge, and are placed close to the skin edge for fine approximation. If the wound tends to invert, then the deeper component of the suture can be placed more laterally to help evert the edges.

If there is tension across the wound, or a significant tendency to inversion, one or two *vertical mattress* sutures can be placed initially. A modification of this suture, the *half-buried mattress*, is also useful as a corner stitch when insetting the tips of skin flaps. The *horizontal mattress* suture (with or without bolsters) [6] can also be used to approximate long wounds or wounds under tension. Any wound tension must be managed by undermining and the use of buried sutures before the insertion of skin sutures. Failure to do this will increase the risks of infection and wound dehiscence, and often leaves permanent unsightly, papular or linear suture marks.

There are various forms of *buried suture*, which are used to close off 'dead space' in a deep wound. Normally, this is obliterated by the use of interrupted *deep subcutaneous* or buried absorbable dermal sutures [7], or by using a '*purse-string*' variant of the horizontal mattress suture. Running sutures, both cutaneous and subcutaneous, can be used to save time, but may be less secure than interrupted sutures and can be tricky to remove. The running subcuticular suture, although difficult to learn, is an elegant suture technique, and it can be left in place for long periods, leaving only two suture marks.

Tape closures (e.g. Steri-Strips™) may be used in conjunction with interrupted sutures or on their own if there is good approximation and adequate subcutaneous or subcuticular support. They provide additional wound support both while skin sutures are in place and for the immediate period following suture removal. Cyanoacrylate tissue glues may also be useful, especially in children [8], and for securing skin grafts [9].

Stainless steel staples are a rapid and effective way to close longer skin incisions. They are strong, incite very little tissue reaction, and can be useful for closing scalp wounds and skin graft donor sites [10].

References

1 Aston SJ. The choice of suture material for skin closure. *J Dermatol Surg Oncol* 1976; **2**: 57–61.
2 Dingman RO, Watanabe MJ, Izenberg PH. General principles of skin surgery. In: Epstein E, Epstein E Jr, eds. *Skin Surgery*, 5th edn. Springfield: Thomas, 1982: 74–107.
3 Stegman SJ. Suturing techniques for dermatologic surgery. *J Dermatol Surg Oncol* 1978; **4**: 63–8.
4 Swanson NA, Tromovitch TA. Suture materials, 1980s: properties, uses, and abuses. *Int J Dermatol* 1982; **21**: 373–8.

5 Stegman SJ, Tromovitch TA, Glogau RG. *Basics of Dermatologic Surgery*. Chicago: Year Book Medical, 1982.
6 Simmonds WL. Surgical gems: uses of bolsters in dermatologic surgery. *J Dermatol Surg Oncol* 1977; **3**: 281–2.
7 Albom MJ. Surgical gems: dermo-subdermal sutures for long, deep surgical wounds. *J Dermatol Surg Oncol* 1977; **3**: 504–5.
8 Ellis DAF, Shaikh A. The ideal tissue adhesive in facial plastic and reconstructive surgery. *J Otolaryngol* 1990; **19**: 68–72.
9 Craven NM, Telfer NR. An open study of tissue adhesive in full-thickness skin grafting. *J Am Acad Dermatol* 1999; **40**: 607–11.
10 Stegmaier OC. Use of skin stapler in dermatologic surgery. *J Am Acad Dermatol* 1982; **6**: 305–9.

Particular forms of excision

Variations in detail and technique apply to particular lesions and areas of the body.

Lesions on the shoulder and upper back

Surgical excision on the shoulders, upper back and deltoid areas frequently produces poor cosmetic results, with the formation of stretched and frequently hypertrophic scars. Although meticulous surgical technique, appropriate undermining and careful suture technique may minimize these problems, patients should be carefully counselled and only offered surgical excision in these areas when it is absolutely necessary. One suggested alternative to excision and repair in these areas is to excise the lesion with a narrow margin of normal skin and allow healing by secondary intention [1].

Benign naevi

Surgical excision, even by experts, leaves scars and consequently benign naevi are best either left alone or removed by shave excision when possible.

Non-melanoma skin cancer: basal cell and squamous cell carcinomas

Many different surgical and non-surgical techniques may be used to treat non-melanoma skin cancer [2,3]. The choice of treatment is based upon various factors relating to both the tumour [4] and the patient [5].

Small, primary well-defined lesions in areas of skin laxity are often best excised. An adequate margin should always be obtained, and prior skin marking following careful examination in good lighting is advisable [4]. Cure rates following surgical excision of such lesions can be excellent [6–8]. Some sites, such as the lips, ear, scalp and periocular and nasolabial areas, have a higher rate of recurrence, and (for squamous cell carcinoma) metastasis. Management of lesions in these sites, particularly if recurrent, poorly defined or showing infiltrative growth patterns, is best performed by a specialist dermatological surgeon [4,9].

Mucous membranes

Excision of lesions in the mouth and on the tongue, lips and genitalia can be difficult, with restricted access and often profuse bleeding. Consequently, only simple procedures should be attempted by non-specialists, and more complex cases referred to colleagues in oral surgery, urology and gynaecology as appropriate.

Keratoacanthoma

This is often difficult to differentiate, both clinically and histologically, from squamous cell carcinoma. Small lesions are often suitable for surgical excision, and larger lesions should be subjected to a transverse incisional biopsy passing from normal adjacent skin through the centre of the lesion and extending through the subcutaneous fat [10].

Pigmented lesions (see Chapter 54)

The diagnosis and management of pigmented lesions is a key component of clinical dermatology and forms an important part of the multidisciplinary treatment of malignant melanoma, also involving pathology, plastic surgery and clinical oncology.

Blue naevi, pigmented basal cell carcinomas, seborrhoeic keratoses and dermatofibromas are usually easily recognizable to the trained eye, although diagnostic difficulties occasionally occur. When diagnostic doubt exists, and especially when malignancy is suspected, the lesion should be excised and submitted for histopathological examination. When the lesion is too large to excise and repair directly, an incisional biopsy may be indicated (e.g. possible malignant change in a large congenital naevus or facial lentigo). In these cases, if malignant melanoma is proven on biopsy, a second procedure, possibly involving complex wound reconstruction, will often be necessary. In such cases, an initial incisional biopsy does not appear to influence the overall prognosis [11], although determination of key prognostic features (e.g. growth phase, depth of invasion, presence of vascular invasion) can only be made accurately from examination of the full excision specimen.

Hypertrophic scars

Although these may occur at any site, they are especially common in certain anatomical sites such as the upper back, shoulders and deltoid areas. Most will slowly resolve with time and regular gentle wound massage. Intralesional steroid injections can be helpful, but may cause skin and fat atrophy and should be used with caution. Hypertrophic scars may also be treated (and possibly prevented) by the use of Z-plasty techniques [12], with pressure dressings or devices [13], and silicone gel sheet dressings [14] and gel are claimed to be effective, although evidence is minimal [15].

References

1 Barnett R, Stranc M. A method of producing improved scars following excision of small lesions of the back. *Ann Plast Surg* 1979; **3**: 391–4.
2 Dzubow L, Grossman D. Squamous cell carcinoma and verrucous carcinoma. In: Friedman RJ, Rigel DS, Kopf AW, Harris MN, Baker D, eds. *Cancer of the Skin*. Philadelphia: Saunders, 1991: 74–84.
3 Telfer NR, Colver GB, Bowers PW. Guidelines for the management of basal cell carcinoma. *Br J Dermatol* 1999; **141**: 415–23.
4 Breuninger H, Dietz K. Prediction of subclinical tumour infiltration in basal cell carcinoma. *J Dermatol Surg Oncol* 1991; **17**: 574–8.
5 Randle HW. Basal cell carcinoma: identification and treatment of the high-risk patient. *Dermatol Surg* 1996; **22**: 255–61.
6 Chernosky ME. Squamous cell and basal cell carcinomas: preliminary study of 3817 primary skin cancers. *South Med J* 1978; **71**: 802–3.
7 Marchac D, Papadopoulos O, Duport G. Curative and aesthetic results of surgical treatment of 138 basal-cell carcinomas. *J Dermatol Surg Oncol* 1982; **8**: 379–87.
8 Porte A, Molle B, Zumer L *et al*. Résultat du traitement de 250 épithéliomas cutanés. *Ann Chirurg Plast* 1979; **24**: 253–6 (Abstract).

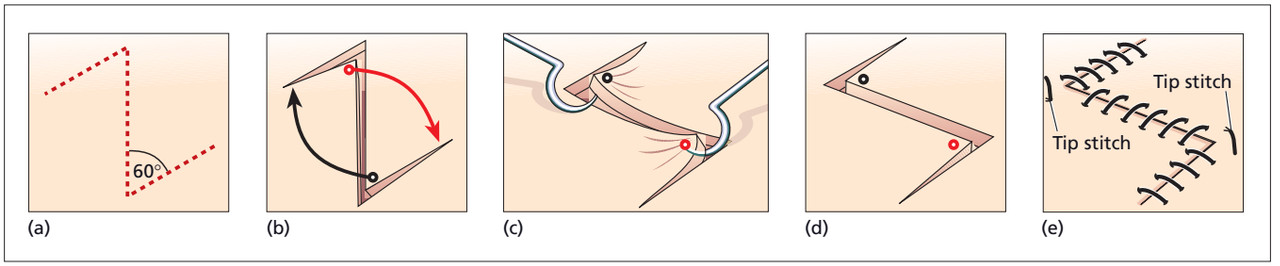


Fig. 77.7 Technique of Z-plasty. (From Eedy *et al.* [7].)

9 Bart RS, Schrager D, Kopf AW *et al*. Scalpel excision of basal cell carcinomas. *Arch Dermatol* 1978; **114**: 739–42.

10 Owen C, Telfer N. Keratoacanthoma. In: Lebwohl M, Heymann WR, Berth-Jones J, Coulson I, eds. *Treatment of Skin Disease: Comprehensive Therapeutic Strategies*. London: Mosby, 2002: 315–8.

11 Epstein E, Bragg K, Linden G. Biopsy and prognosis of malignant melanoma. *JAMA* 1969; **208**: 1369–71.

12 Longacre JJ. *Scar Tissue: Its Use and Abuse*. Springfield: Thomas, 1972.

13 Carr JA. Pressure technique. In: Harahap M, ed. *Surgical Techniques for Cutaneous Scar Revision*. New York: Marcel Dekker, 2000: 447–60.

14 O'Brien L, Pandit A. Silicon gel sheeting for preventing and treating hypertrophic and keloid scars. *Cochrane Database Syst Rev* 2006: 1; CD003826. DOI: 10.1002/14651858.CD003826.pub2.

15 Murison M, James W. Preliminary evaluation of the efficacy of dermatix silicone gel in the reduction of scar elevation and pigmentation. *J Plast Reconstr Aesthet Surg* 2006; **59**: 437–9.

Wound closure [1–3]

A significant part of dermatological surgical practice involves the repair of surgical defects. Wounds can be allowed to heal by secondary intention healing, closed primarily, or repaired using skin grafts or skin flaps. Experience and careful consideration of the various wound closure options are necessary in order to offer patients the best possible cosmetic and functional results.

The M-plasty [4]

This is occasionally useful if one end of an elliptical excision will cross an important anatomical or cosmetic line. In this situation, an M-plasty will help to reduce the overall length of excision required by bringing the apex of the excision back within the original area to be excised.

'Dog-ear' (synonym tricone) repairs [5]

'Dog-ears' (folds or humps of skin) tend to occur when the length to width ratio of an excision is insufficient to prevent the skin at the poles from bulging outwards when the opposing skin edges are brought together. They tend to occur more commonly when there is limited laxity or movement in the surrounding tissues. Excisions where the angle at the apex exceeds 30° are also liable to produce 'dog-ears'. 'Pseudo-dog-ears' occur if too much fat is left at the poles of an excision.

There are several ways in which this problem can be surmounted [3].

1 The excision can be extended and the redundant overlapping skin excised.
2 One side of the pucker can be cut back flush with the skin and the excess skin from the other side identified by drawing it across the wound; this can then be cut off.
3 The excess skin of the 'dog-ear' can be removed by converting it into a T-plasty or an M-plasty. This is a useful technique when the length of the wound cannot be extended [6].

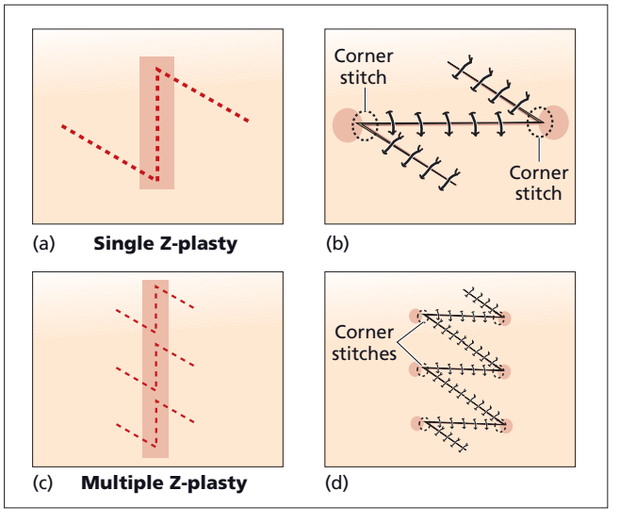


Fig. 77.8 Single and multiple Z-plasty. (a,b) Single Z-plasty. (c,d) Multiple Z-plasty. Note breaking up of zone of lateral tension (shaded areas) with multiple Z-plasty. (From Eedy *et al.* [7].)

Wound edges of unequal lengths

This problem can often be resolved by using a halving technique: a suture is placed across the centre of the wound and subsequent sutures used to divide the two resultant defects into ever smaller compartments. Because of local skin elasticity, the shorter side tends to stretch to match the longer. For more disproportionate edges, a wedge may have to be removed from the longer side in order to make the sides of the resultant ellipse more equal, or the wound can be sutured in the normal way and a 'dog-ear' repair performed to remove the excess skin from one side.

Z-plasty

This is a technique that is used to treat scar contractures, skin 'webbing' and to break up or alter the direction of linear scars to try to improve the cosmetic or functional result. The size of the angle used determines the increase in the length of the scar that will result (Figs 77.7 & 77.8).

References

1 Chernosky ME. Scalpel and scissor surgery as seen by the dermatologist. In: Epstein E, Epstein E Jr, eds. *Skin Surgery*, 5th edn. Springfield: Thomas, 1982: 189–229.
2 Stegman SJ. Planning closure of a surgical wound. *J Dermatol Surg Oncol* 1978; **4**: 390–3.
3 Stegman SJ. *Basics of Dermatologic Surgery*. Chicago: Year Book Medical, 1982.
4 Webster RC, Davidson TM, Smith RC *et al*. M-plasty techniques. *J Dermatol Surg Oncol* 1976; **2**: 393–6.
5 Gormley DE. The dog-ear: causes, prevention and correction. *J Dermatol Surg Oncol* 1977; **3**: 194–8.
6 Salasche SJ, Roberts LC. Dog-ear correction by M-plasty. *J Dermatol Surg Oncol* 1984; **10**: 478–82.
7 Eedy DJ, Breathnach SM, Walker NPJ. *Surgical Dermatology*. Oxford: Blackwell Science, 1996.

Dressings

Wound dressings are not essential [1], although optimizing wound care by using an appropriate dressing probably produces a predictably better result. An ideal dressing should meet the following criteria:

1 Soaks up excess exudate from the wound surface, thereby reducing the risk of bacterial penetration.
2 Maintains a moist wound–dressing interface to encourage migration of epidermal cells over the granulating tissue. Covered split-thickness wounds heal faster than dry wounds [2]. A scab is a poor barrier against loss of moisture from the dermal surface because it allows the surface to dry out, thus forcing the epidermis to grow under the dry wound surface. As the epidermal cells migrate, they secrete a proteolytic enzyme which dissolves the base of the scab; migration ceases when cell–cell contact occurs [3].
3 Does not contain organisms or fibres that may contaminate the wound. Cellulose-derived dressings may shed fibre fragments into the wound [4], causing a foreign-body reaction and leading to increased risk of infection.
4 Is impermeable to bacteria.
5 Causes minimal injury to healing tissue when removed.

It is often claimed that a dressing that permits increased oxygen permeability aids wound healing. Such dressings do aid healing in split-thickness wounds [5]. However, in full-thickness wounds the same synthetic wound dressings create hypoxic conditions at the healing surface [6]. Paradoxically, tissue hypoxia in full-thickness wounds appears to stimulate rather than retard granulation tissue formation [7].

Basic dressing [8]

This includes contact, absorbent and outer layers [9]. The layer in contact with the wound is non-adherent, either because it contains a greasy ointment (e.g. tulle dressing) or because it is made from a specially designed, low-adherence material (e.g. polyethylene) [10]. The absorbent layer (e.g. cotton-wool, gauze) soaks up the excess wound exudate and cushions the wound. The outer layer (e.g. tubular bandage, elasticated tape) holds the other two layers in place and applies slight pressure. The basic dressing is left in place until suture removal, but needs to be changed if it becomes wet or is saturated with exudate [11], as this greatly increases bacterial penetration. Many proprietary dressings combine two or all three components (e.g. Melolin® contains a polyethylene non-adherent layer attached to an absorbent cellulose component). The hydrogel (e.g. Vigilon®), hydrocolloid (e.g. Granuflex®), xerogel (e.g. dextranomer starch polymer), alginate (e.g. Kaltostat®) and synthetic foam dressings are designed to provide all three components, and these can also be used on pressure sores [12,13], leg ulcers [14] and full-thickness surgical wounds [15].

Pressure dressings

These are placed over the basic dressing. Most commonly, and on suitable sites, a piece of compressible padded dressing (e.g. cotton-wool, sponge, eye pad) is pressed down onto the wound with an elasticated or *crepe bandage* for 48 h. Where bandage application is difficult, a *multitape dressing* can be used. Dental rolls are placed over and pressed down onto the dressing by using adhesive tape strips, and additional adhesive (e.g. collodion or tinct. benz. co.) is used to increase the tape adhesion. A *tie-over pressure dressing* is commonly applied over skin grafts, but can be used on any wound. Paired sutures are placed around the wound and tied together to hold down a three-layered contact, absorbent and compression dressing, so that the graft is held down onto the recipient site to prevent a haematoma forming beneath it. Aquaplast, a conforming thermoplastic material, is also used to tie over skin grafts [16].

Suggested dressing for wound types

Small full- or *partial-thickness wounds* (shave and curettage sites) require a simple low-adherent dressing or paraffin tulle held in place with a conforming adhesive tape. Unsutured punch biopsy sites do not appear to benefit from occlusive dressings, but heal better with a collagen matrix dressing than they do after simply applying Monsel's solution to stop bleeding [17]. *Sutured wounds* (side-to-side closures and flaps) require a greasy antiseptic ointment application and an absorbent-backed, low-adherent dressing held in place with a conforming adhesive tape. A pressure dressing may also be required. After suture removal, apply adhesive tape strips for 5 days. On a *full-thickness graft*, apply a simple contact dressing (e.g. greasy antiseptic ointment and paraffin tulle) and then a tie-over pressure dressing which includes a sponge or cotton-wool compressible pad. On *full-thickness wounds*, a variety of wound management methods are used. If acceptable to the patient, the wound can be left without a dressing and simply cleaned two or three times daily, and a sterile, white soft paraffin or Vaseline-based antiseptic ointment applied. Alternatively, the wound can be cleaned less frequently if a combination contact/absorbent dressing is applied. During the initial exudative stage (the first 4 days) the dressing will need to be changed at least once a day. Thereafter, the dressing should be changed if the wound surface starts to dry out or the dressing becomes saturated, wet or otherwise dirty. The wound should be cleaned with a simple antiseptic (e.g. aqueous chlorhexidine, 10 vol. hydrogen peroxide) before being re-dressed using a Vaseline-based antiseptic ointment (Polyfax®), and simple contact dressing (e.g. polyethylene/cellulose dressing; Melolin®) held in place with adhesive tape.

Alternatively, a semi-permeable adhesive polyurethane [18] or gel, or colloid dressing can be used and changed as necessary. *Split-skin graft donor sites* heal faster with a dressing that maintains a moist wound–dressing interface; for example, a calcium alginate [19] or semi-permeable adhesive polyurethane film [20]. A pressure bandage applied over the wound is also required, but bleeding will still occur. The exudate can either be allowed to drain through puncture wounds made in the lower portion of the polyurethane film, or can be removed by changing the dressing more frequently, although this may introduce infection and is painful.

Wound healing is delayed by topical steroid application [21], tobacco smoking [22] and possibly age [23] via a decrease in skin blood flow with increasing arteriosclerosis [24].

References

1 Mengert WF, Hermes RL. Simplified gynecologic care. *Am J Obstet Gynecol* 1949; **58**: 1109–16.
2 Hinman CD, Maibach H. Effect of air exposure and occlusion on experimental human skin wounds. *Nature* 1963; **200**: 377–8.
3 Harris DR. Healing of the surgical wound. I. Basic considerations. *J Am Acad Dermatol* 1979; **1**: 197–207.
4 Wood RAB. Disintegration of cellulose dressings in open granulating wounds. *BMJ* 1976; **1**: 1444–5.
5 Silver IA. Oxygen tension and epithelialization. In: Maibach HI, Rovee DT, eds. *Epidermal Wound Healing*. Chicago: Year Book, 1972.
6 Varghese MC, Balin AK, Carer M, Caldwell D. Local environment of chronic wounds under synthetic dressings. *Arch Dermatol* 1986; **122**: 52–7.
7 Knighton DR, Silver IA, Hunt TK. Regulation of wound healing angiogenesis: effect of oxygen gradients and inspired oxygen concentration. *Surgery* 1981; **90**: 262–70.
8 Bennett RG. *Fundamentals of Cutaneous Surgery*. St Louis: Mosby, 1988: 310–51.
9 Telfer NR, Moy RL. Wound care after office procedures. *J Dermatol Surg Oncol* 1993; **19**: 722–31.
10 Anonymous. Local applications to wounds. II. Dressings for wounds and ulcers. *Drug Ther Bull* 1991; **29**: 97–100.
11 Colebrook L, Hood AM. Infection through soaked dressings. *Lancet* 1948; **ii**: 682–3.
12 Engdahl E. Clinical evaluation of Debrisan on pressure sores. *Curr Ther Res* 1980; **28**: 377–80.
13 Gorse GJ, Messner RL. Improved pressure sore healing with hydrocolloid dressings. *Arch Dermatol* 1987; **123**: 766–71.
14 Handfield-Jones SE, Grattan CEH, Simpson RA, Kennedy CTC. Comparison of a hydrocolloid dressing and paraffin gauze in the treatment of venous ulcers. *Br J Dermatol* 1988; **118**: 425–7.
15 Eaglstein WH. Occlusive dressings. *J Dermatol Surg Oncol* 1993; **19**: 716–20.
16 Fish FS, Hilger PA. Aquaplast thermoplastic (Opti-Mold). A unique moldable tie-down dressing for full-thickness skin grafts. *J Dermatol Surg Oncol* 1994; **20**: 239–44.
17 Armstrong RB, Nichols J, Pachance J. Punch biopsy wounds treated with Monsel's solution or a collagen matrix. *Arch Dermatol* 1986; **122**: 546–9.
18 Hien NT, Prawer SE, Katz HI. Facilitated wound healing using transparent film dressing following Mohs micrographic surgery. *Arch Dermatol* 1988; **124**: 903–6.
19 Attwood AI. Calcium alginate dressing accelerates split skin graft donor site healing. *Br J Plast Surg* 1989; **42**: 373–9.
20 James JH, Watson ACH. The use of Op-site, a vapour permeable dressing on skin graft donor sites. *Br J Plast Surg* 1975; **28**: 107–10.
21 Eaglstein WH, Mertz PM. New method for assessing epidermal wound healing: the effects of triamcinolone acetonide and polyethylene film occlusion. *J Invest Dermatol* 1978; **71**: 382–4.
22 Silverstein P. Smoking and wound healing. *Am J Med* 1992; **93** (1A): 22S–4S.
23 Ashcroft GS, Horan MA, Ferguson MW. The effect of ageing on cutaneous wound healing in mammals. *J Anat* 1995; **187**: 1–26.
24 Tsuchida Y. The effect of ageing and arteriosclerosis on human skin blood flow. *J Dermatol Sci* 1995; **5**: 175–81.

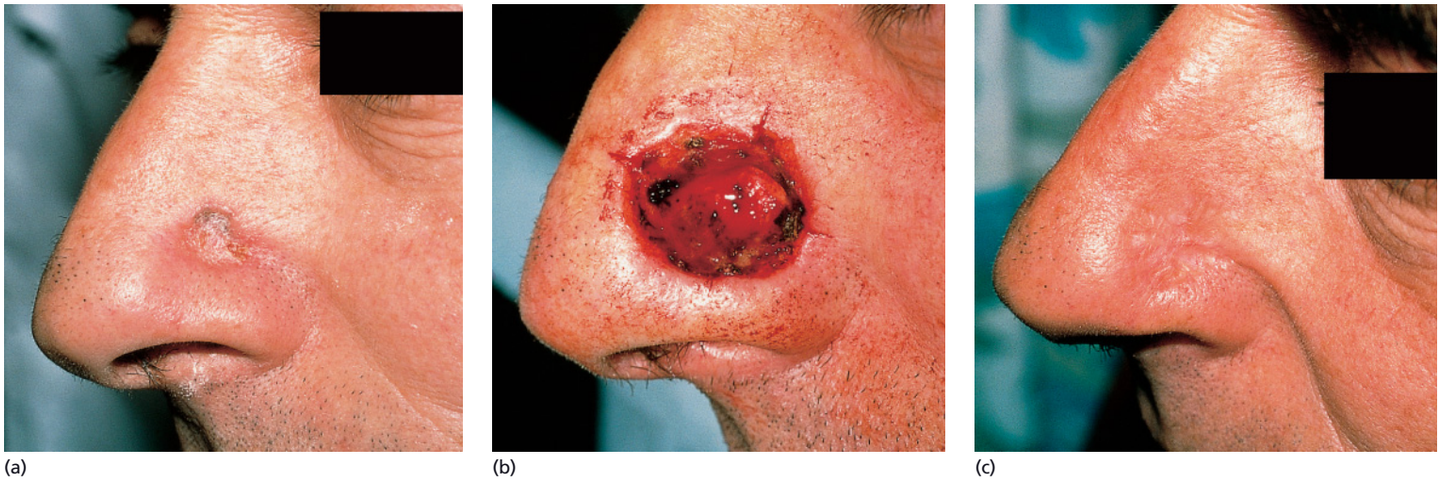
Secondary intention healing

Full-thickness wounds remaining after malignant [1,2] or benign [3] tumour excision can be left to heal by secondary intention. The cosmetic result depends on the wound site and the patient's age. The nasolabial fold, medial canthus, scalp and pre- and post-auricular skin produce particularly good results, although the technique can be used in many sites, including the fingers [4]. Almost half of the reduction in wound size occurs because of scar contraction [5] and subsequent stretching of surrounding tissues [6]. Therefore, if the wound is next to a mucocutaneous junction, such as the lip, ala nasa or eyelid, scar contraction may distort this free margin, producing poor cosmesis and function. Most other head and neck sites heal well, although in general the cosmetic results are best on concave rather than convex skin surfaces [7]. The older the patient the better the result, probably because wound contraction is aided by the availability of loose adjacent skin and because hypertrophic scarring is less common in older patients. The method can be used if there is doubt about the adequacy of excision, or closure of the defect requires a larger or more complex procedure, which the patient will not tolerate. In some situations, such as excision of naevi on the back [3] or the treatment of acne keloidalis nuchae [8] and hidradenitis [9], secondary intention healing is the preferred method as it results in a superior cosmetic result.

When a tumour is being excised, the specimen is orientated with a marking suture before complete removal, so that if further excision is required the affected margin can be identified. When bleeding is controlled, a contact dressing is applied, and this is covered by a pressure dressing for 24–48 h. Thereafter, the dressing can be changed at 2–4-day intervals, depending on the amount of exudate. At each dressing change, the wound is cleaned to remove crust or debris and a greasy antiseptic ointment (e.g. Polyfax®, Flamazine® or Betadine® ointment) and non-adherent dressing are applied. On average, a 25-mm diameter head and neck wound takes approximately 35 days to heal [10]. These wounds are surprisingly pain-free. Bacterial contamination may occur, but tissue infection is rare; when present the wound edge is tender, red and swollen. A yellow exudate is common in the first few days. Before granulation tissue appears, a yellowish fibrin clot covers the wound. Exposed periosteum and perichondrium must be kept moist and viable by using a saline-dampened alginate dressing. This encourages granulation tissue to migrate over the exposed area and also reduces the risk of bone or cartilage desiccation and necrosis [11]. If the periosteum has been stripped off, the exposed bone can be fenestrated or abraded to encourage the formation of granulation tissue and hence enhance re-epithelialization [12]. When the wound first heals, the scar often contains large looped vessels, which slowly disappear as the scar thickens. A slightly elevated, red, hypertrophic scar is then present, and the cosmetic result is not optimum until approximately 1 year (Figs 77.9 & 77.10).

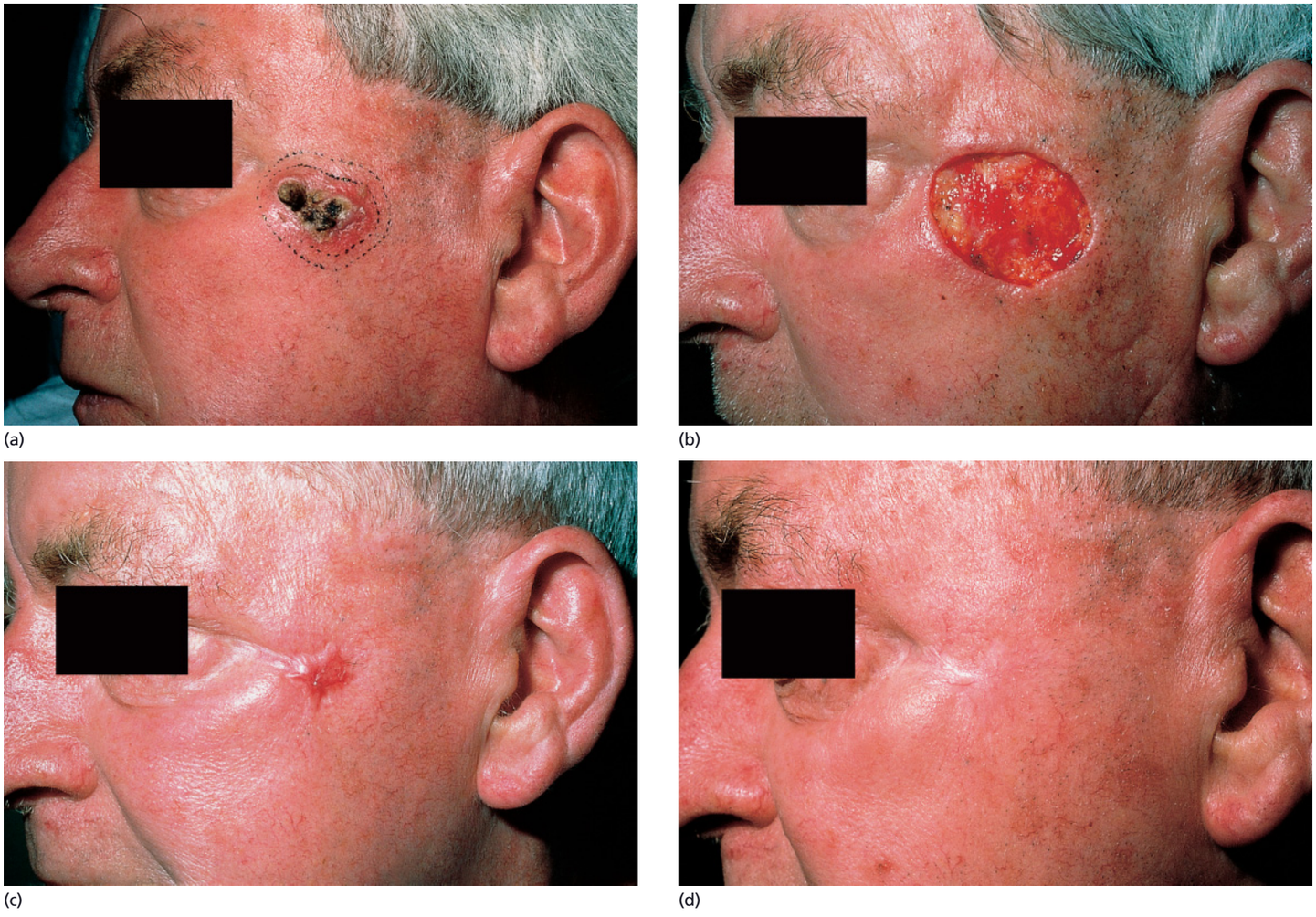
References

1 Mohs FE. *Chemosurgery: Microscopically Controlled Surgery for Skin Cancer*. Springfield: Thomas, 1978.
2 Goldwyn RM, Rueckert F. The value of healing by secondary intention for sizeable defects of the face. *Arch Surg* 1977; **112**: 285–92.



(a) (b) (c)

Fig. 77.9 (a) This man had a basal cell carcinoma on the side of the nose; (b) this was excised and the wound was allowed to heal by second intention. (c) The cosmetic result 4 months later was good.



(a) (b)

(c) (d)

Fig. 77.10 (a) This man had a basal cell carcinoma on the temple (b) excised. (c) Three months later the wound had healed but the scar was thick and red; (d) 15 months later this scar had become considerably less conspicuous.

3 Barnett R, Stranc M. A method of producing improved scars following excision of small lesions of the back. *Ann Plast Surg* 1979; **3**: 391–4, 435.
4 de Berker DAR, Dahl MGC, Malcolm AJ, Lawrence CM. Micrographic surgery for subungual squamous cell carcinoma. *Br J Plast Surg* 1996; **49**: 414–9.
5 Catty RHC. Healing and contraction of experimental full thickness wounds in the human. *Br J Surg* 1965; **52**: 542–8.
6 Lawrence CM, Comaish JS, Dahl MGC. Excision of skin malignancies without wound closure. *Br J Dermatol* 1986; **115**: 563–71.
7 Zitelli JA. Wound healing by secondary intention. *J Am Acad Dermatol* 1983; **9**: 407–15.
8 Glenn MJ, Bennett RG, Kelly AP. Acne keloidalis nuchae: treatment with excision and secondary intention healing. *J Am Acad Dermatol* 1995; **33**: 243–6.
9 Silverberg B, Smoot CE, Landa SJF, Parsons RW. Hidradenitis suppurativa: patients' satisfaction with wound healing by second intention. *Plast Reconstr Surg* 1987; **79**: 555–9.
10 Lawrence CM, Matthews JNS, Cox NH. The effect of ketanserin on healing of fresh surgical wounds. *Br J Dermatol* 1995; **132**: 580–6.
11 Snow SN, Stiff MA, Bullen R *et al*. Second intention healing of exposed facial-scalp bone after Mohs surgery for skin cancer: a review of 91 cases. *J Am Acad Dermatol* 1994; **31**: 450–4.
12 Latenser J, Snow SNP, Mohs FE *et al*. Power drills to fenestrate exposed bone to stimulate wound healing. *J Dermatol Surg Oncol* 1991; **17**: 265–70.

Skin grafts

Skin of varying thickness can be used for skin grafting. A split-skin graft is not limited in size, because the donor site regenerates. Full-thickness and composite skin grafts potentially produce better cosmetic results than split skin grafts, but are limited in size by the amount of skin that can be harvested. Compared with flaps, grafts are technically easier to perform, but generally produce inferior cosmetic results because of the differences between the donor skin and recipient site.

Full-thickness grafts

A full-thickness graft is used, in preference to a split-skin graft, when the cosmetic result and strength of the repair are important. Any site with matching and spare skin is a potential donor site [1]. Common donor sites include the skin behind and in front of the ear, nasolabial fold [2], upper eyelid, inner aspect of the upper arm, lower abdomen and supraclavicular fossa. The donor and graft sites should match for skin thickness, adnexal structures, surface markings, weathering and texture. After carefully assessing the amount and shape of skin required, the donor skin is excised down to fat [3]. The fat is then trimmed off the under surface of the graft to aid new blood-vessel penetration. Edge sutures are used to prevent shearing forces dislodging the graft, and a pressure dressing, usually held in place using tie-over sutures, is employed to prevent a haematoma lifting the graft off the recipient site (Fig. 77.11). In most instances, the donor site is chosen because there are redundant folds of skin present and the skin edges can be sutured easily after donor skin excision. At some sites (e.g. behind the ear), the donor defect can be allowed to heal by second intention. Grafts take best on dermis and granulation tissue, perichondrium and periosteum, but will perish on exposed bone or cartilage and often fail on fat. Grafts fail because of infection or poor blood supply. The latter occurs because of faulty technique (e.g. incorrect haemostasis, suturing or wound care) or because the recipient site has an inadequate blood supply (e.g. previous radiotherapy or lower leg sites in people with compromised venous and/or arterial supply). All grafts contract, and near the lower eyelid this may lead to ectropion. Hence, at this and other critical sites, grafts should be 10–25% larger than the defect to compensate for this. Depressed graft scars may be elevated by injection of autograft fat under the graft [4]. Delayed grafting to allow the recipient site to produce granulation tissue increases the chance of graft survival and enables deeper defects to fill up prior to grafting, thus producing an improved contour [5].

Composite grafts

Composite grafts are defined as those comprising two or more germ layers. In dermatology, these are grafts containing skin and cartilage components. When used to repair full-thickness ala rim defects using skin taken from the helix rim, graft survival is unpredictable [6]. In contrast, composite grafts containing skin and perichondrium, or perichondrial cutaneous grafts, are claimed to be better than full-thickness grafts for nose, ear and periocular defects, as they contract less, induce new cartilage formation, and maintain their thickness and epidermal appendages [7].

Split-skin graft

Except in extreme circumstances (e.g. extensive burns) split-skin graft size is not limited by the amount of donor skin that can be harvested, because the donor skin site will re-epithelialize by regeneration from retained adnexal remnants. Split-skin grafts can therefore be used to cover very large wounds. Because the skin is thin and relatively transparent, split grafts are also sometimes used to cover tumour excision sites where the adequacy of excision is dubious, because recurrence is more easily identified through the thinner graft than it would be after full thickness or flap closure. The disadvantages of split-skin grafts compared with full-thickness grafts are the relatively poor cosmetic result and greater graft shrinkage [1]. When a split graft is taken, skin is sliced off through the dermis, leaving behind parts of the adnexal and follicular structures from which epidermis migrates to cover the donor site. Split-skin grafts can be taken using a hand-held knife or a mechanical dermatome (Fig. 77.12a). The latter is easier to use and produces a predictably good graft. *Meshing*, or cutting multiple parallel slits in the graft, allows it to expand rather like a fishnet stocking when stretched (Fig. 77.12b). The gaps are covered by epithelium migrating from the adjacent strips of the graft (Fig. 77.12c). A meshed graft will therefore cover a wider area, allow exudate to drain through the gaps (e.g. on the leg), and will conform to an uneven contour (e.g. ear). The common donor sites include the upper arm, upper thigh and abdominal wall. The donor site is best anaesthetized using EMLA® cream [8], and heals faster and painlessly with a dressing that maintains a moist wound–dressing interface (e.g. calcium alginate [9] and semi-permeable adhesive polyurethane film; Opsite®) [10].

Pinch grafts

Pinch grafts are occasionally useful for wounds of the lower leg, although the donor site heals leaving unsightly scars. The technique is simple [11], but without careful aseptic technique success rates are low [12]. The skin is elevated on a needle tip, the apex sliced off, and when multiple skin shaves have been harvested the



(a)



(b)



(c)



(d)

Fig. 77.11 Full-thickness graft on the nose. This basal cell carcinoma on the tip of the nose (a) was excised (b). The defect size and shape was recorded using a sterile paper template (c); the template was placed on the donor skin site (d) and the appropriate-sized piece of skin excised. The fat was trimmed off the undersurface of the donor skin, and this was sutured into place on the wound (e). A tie-over dressing was applied (f). Seven days later the dressing was removed and the graft was pink and had clearly taken (g). The subsequent cosmetic result at 3 months was excellent (h).

grafts are placed at regular intervals on the clean granulating ulcer. As with all leg-ulcer skin grafting, if the causative factors are not eradicated before grafting, the ulcer will recur even if the graft is initially successful.

Grafting techniques used for vitiligo

Epidermal grafts containing viable melanocytes can be harvested using suction blisters [13], or very thin split-skin grafts [14]. Before grafting, the epidermis is removed from the hypopigmented skin by freezing to create a blister [13], or by dermabrasion [14]. Alternatively, *mini-grafts*, or tiny (1.2-mm diameter) full-thickness punch grafts of normally pigmented skin are grafted, at 2-mm intervals, into similar-sized punch wounds sited in the depigmented skin [15]. Because melanocytes migrate approximately 2 mm away from the graft site, there is no need to graft the whole area, and because the punch grafts are so small there is minimal cobblestone effect at the recipient site. In both techniques, a hidden donor site, such as the upper inner thigh or lower back, is used.



(e)



(f)



(g)



(h)

Fig. 77.11 *Continued*

Grafts of cultured, autologous melanocytes have also been tried [16].

Acne scar punch grafts

Ice-pick acne scars can be excised using a punch biopsy blade, and the wound filled with a slightly bigger punch biopsy-shaped piece of donor skin taken from a matching but unobtrusive site (e.g. behind the ear). Dermabrasion is usually subsequently required to reduce the cobblestone effect [17].

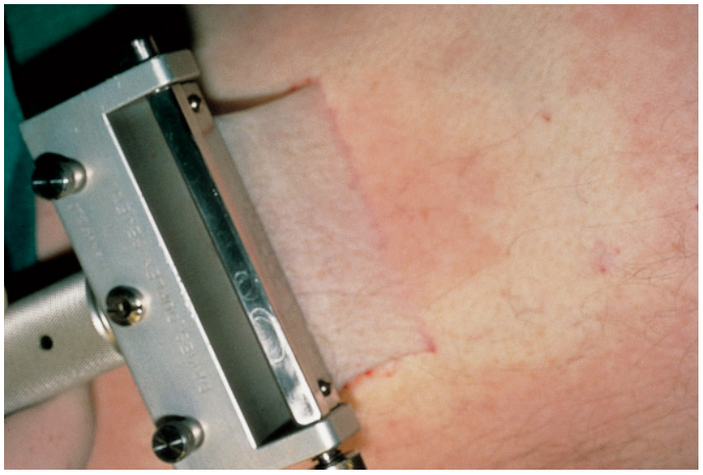
References

1 Skouge JW. *Skin Grafting: Practical Manuals in Dermatologic Surgery*. New York: Churchill Livingstone, 1991.

2 Booth SA, Zalla MJ, Roenigk RK, Phillips PK. The naso-labial fold donor site for full thickness skin grafts of nasal tip defects. *J Dermatol Surg Oncol* 1993; **19**: 553–9.

3 Roenigk RK, Zalla MJ. Full-thickness grafts. In: Robinson JK, Arndt KA, LeBoit PE, Wintroub BU, eds. *Atlas of Cutaneous Surgery*. Philadelphia: Saunders, 1996.

4 Hambley RM, Carruthers JA. Microlipoinjection for the elevation of depressed full-thickness grafts on the nose. *J Dermatol Surg Oncol* 1992; **18**: 963–8.



(a)



(b)



(c)

Fig. 77.12 Meshed split-skin graft. (a) A split-skin graft was harvested from the thigh skin using a power dermatome. (b) The skin was meshed on a mesher, and the meshed graft applied to the defect. (c) This was the appearance of the graft 11 months later.

5 Lewis R, Lang PG Jr. Delayed full-thickness skin grafts revisited. *Dermatol Surg* 2003; **29**: 1113–7.
6 Lipman SH, Roth RJ. Composite grafts from earlobes for reconstruction of defects in noses. *J Dermatol Surg Oncol* 1982; **8**: 135–7.
7 Rohrer TE, Dzubow LM. Conchal bowl skin grafting in nasal tip reconstruction: clinical and histologic evaluation. *J Am Acad Dermatol* 1995; **33**: 476–81.
8 Goodacre TEE, Sanders R, Watts DA, Stoker M. Split skin grafting using topical local anaesthesia (EMLA): a comparison with infiltrative anaesthesia. *Br J Plast Surg* 1988; **41**: 533–8.
9 Attwood AI. Calcium alginate dressing accelerates split skin graft donor site healing. *Br J Plast Surg* 1989; **42**: 373–9.
10 James JH, Watson ACH. The use of Opsite, a vapour permeable dressing on skin graft donor sites. *Br J Plast Surg* 1975; **28**: 107–10.
11 Ceilley RI, Rinek MA, Zuehlke RL. Pinch grafting for chronic ulcers on the lower extremities. *J Dermatol Surg Oncol* 1977; **3**: 303–9.
12 Kirsner RS, Falanga V. Techniques of split skin grafting for lower extremity ulcerations. *J Dermatol Surg Oncol* 1993; **19**: 779–83.
13 Falabella R. Surgical techniques for repigmentation. In: Robinson JK, Arndt KA, LeBoit PE, Wintroub BU, eds. *Atlas of Cutaneous Surgery*. Philadelphia: Saunders, 1996.
14 Kahn AM, Cohen MJ. Vitiligo: treatment by dermabrasion and epithelial sheet grafting. *J Am Acad Dermatol* 1995; **33**: 646–8.
15 Boersma BR, Westerhof W, Bos JD. Repigmentation in vitiligo vulgaris by autologous minigrafting: results in 19 patients. *J Am Acad Dermatol* 1995; **33**: 990–5.
16 Olsson MJ, Juhlin L. Transplantation of melanocytes in vitiligo. *Br J Dermatol* 1995; **132**: 587–91.
17 Johnson WC. Treatment of pitted scars: punch transplant technique. *J Dermatol Surg Oncol* 1986; **12**: 260–5.

Flaps (Figs 77.13–77.17)

A flap is a full-thickness piece of skin moved to cover a defect where the proximal portion, or pedicle, remains attached to the original site while the distal portion is moved to cover the defect [1]. The blood supply of any flap is therefore, initially, provided by its pedicle. The pedicle is sometimes based on a portion of skin which remains attached to the origin and sometimes, as in an island pedicle flap, the skin is entirely detached and the blood supply comes from the underlying subcutaneous tissue or muscle.

Dermatologists almost exclusively use *local flaps* and have no use for *distant flaps* or *free flaps*. *Distant flaps* are tunnelled subcutaneously, with a long muscle pedicle attached over long distances; for example, from the anterior chest wall skin to the head and neck. *Free flaps* involve the harvesting of, for example, a piece of forearm skin with an attached artery and vein; these vessels must then be anastomosed onto named vessels at the recipient site before the skin can be used to repair the defect.

Similarly, dermatologists mostly use *random pattern flaps* where the blood supply is inherent in the skin being moved, as opposed to *axial pattern flaps* which obtain their blood supply from one named artery; a possible exception being the midline forehead flap [4], which is based on the supratrochlear artery.

Random pattern flaps are also sometimes subdivided into *reticular*, where the blood comes from the dermal blood supply (e.g. a bilobe flap), and *segmental*, where the blood supply comes from perforating vessels in the subdermal plexus (e.g. island pedicle flaps).

The more closely a flap resembles a graft (thin, defatted skin) the greater is the contribution to its blood supply from the

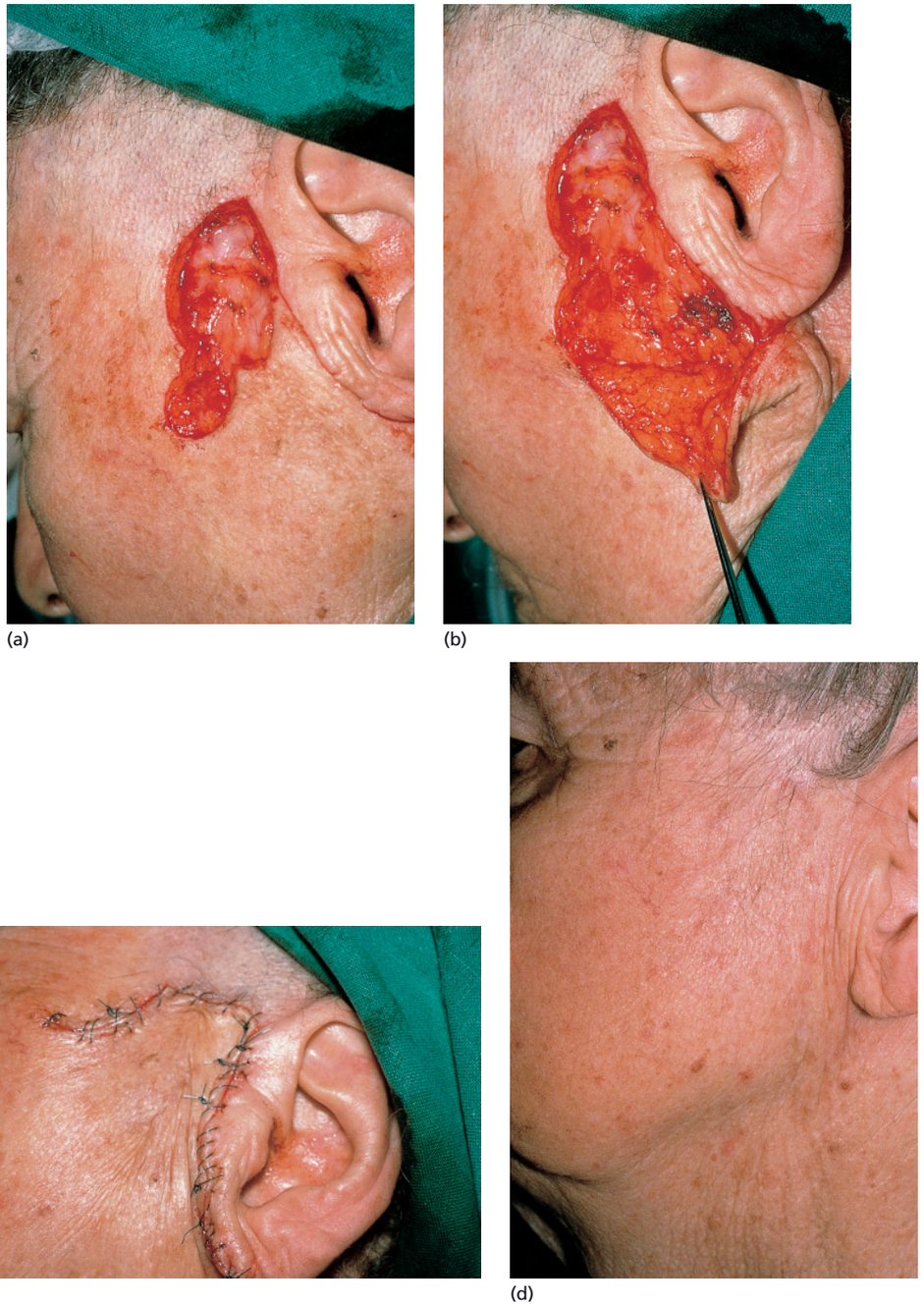


Fig. 77.13 Rotation flap on the pre-auricular skin. (a) This oddly shaped defect was closed (b) by rotating and advancing the loose skin under the chin up to cover the defect. (c) The incision line was placed in the skin crease at the anatomical boundary between the ear and the cheek, (d) and hence is inconspicuous 4 months later. The back cut was enhanced by Z-plasty under the ear (not shown).

recipient site rather than the flap pedicle. The thinner the flap, however, the greater the contraction, and this is particularly important when using thin skin around the eye. Different techniques can be used for many repairs [2], although some techniques [3] are inherently suited to the nose [4,5], chin [6], eyelid [7,8], ear [9,10], forehead [11], scalp [12], cheeks [13] and lip [14,15].

Flaps are variously categorized by the direction of movement, the name of the surgeon who first described the flap, the blood supply or the type of tissue moved. The most useful method relates to how the skin was moved to cover the defect—hence the description of advancement, rotation, transposition or pedicle flaps (Table 77.4). It is this classification that will be used here. As skin is moved to close the primary or original defect, a secondary defect is created which in turn also has to be covered. The essence of flap repair is to design the flap so that this secondary defect is created at a site where there is sufficient spare or loose skin to permit closure. On the face, loose skin is usually present in the middle of the forehead, the glabella region and bridge of the nose, the nasolabial fold, the front of the ear and the cheek. Hence, these areas of laxity will be exploited for most flaps.

Advancement flaps are used where skin must move in one direction from an area of laxity to cover the defect. Although simple to

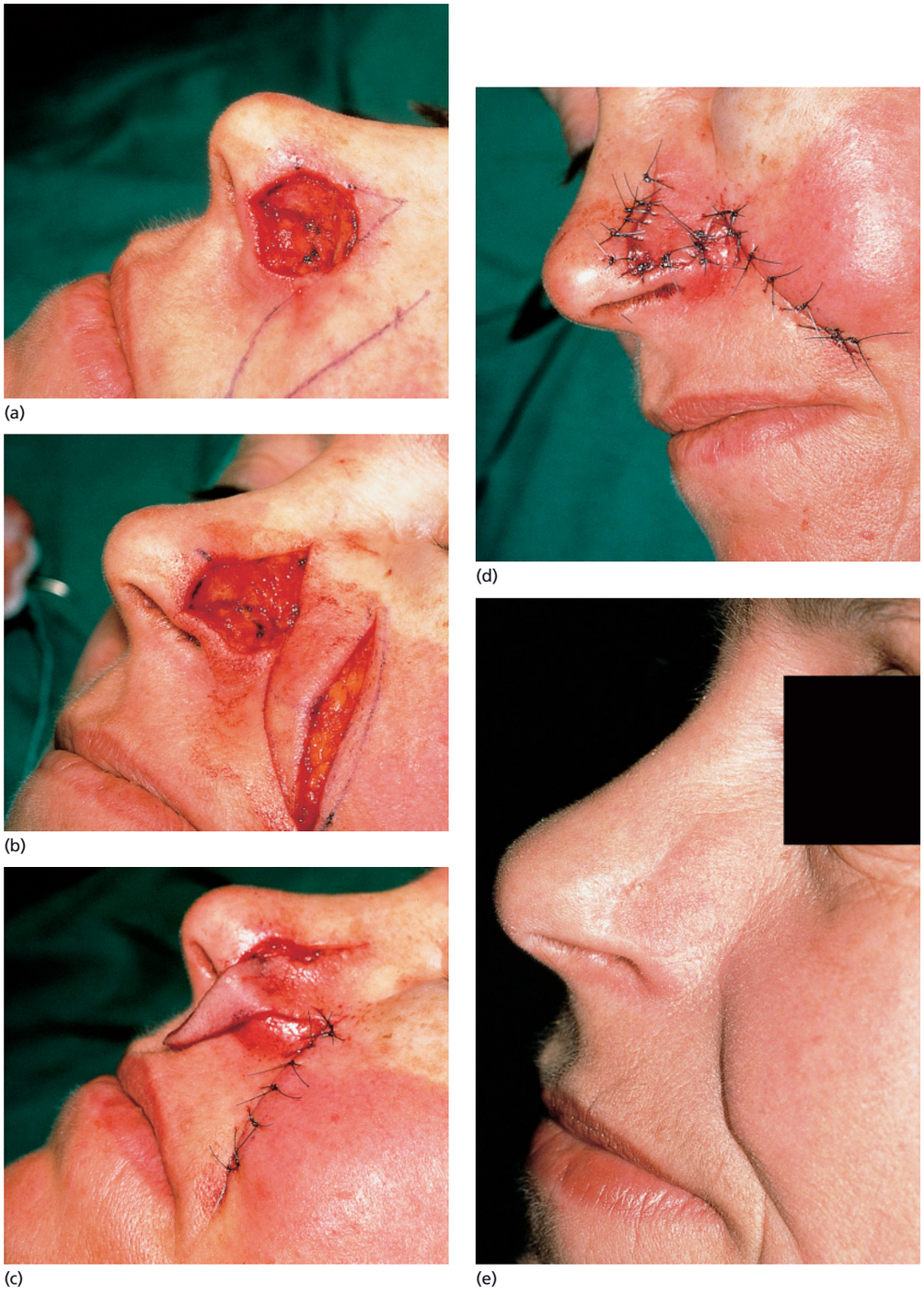


Fig. 77.14 Nasolabial fold flap. (a) This defect on the ala wall was covered by transposing a flap taken from the cheek skin (b). (c) The defect on the cheek was closed directly along the nasolabial fold, thus disguising the scar, and the flap of skin was then laid over the defect. (d) The flap was trimmed to shape and sutured into place. (e) The result 12 months later was good.

conceptualize they have limited use. The secondary defect is closed last, and the flaps have limited mobility. In many instances, defect coverage is only achieved by stretching the flap rather than transferring the tension to an area of lax skin. *Rotation flaps* usually require both advancement and rotation about a pivotal point on a broad pedicle (Fig. 77.13). Mobility is frequently limited, and long incisions and extensive undermining may be required to mobilize sufficient tissue; the secondary defect is closed last. *Transposition flaps* provide the greatest mobility, and the secondary defect is closed first (Fig. 77.14). As a result, the flap is pushed rather than dragged into the defect, so that if a transposition flap is designed properly virtually all the tension can be placed on the secondary defect rather than the flap, thus reducing the risk of ischaemic necrosis. These advantages make transposition flaps the most widely used (Fig. 77.15). A wide variety of flaps based on these three simple designs have been described, each with careful refinements for different sites (Table 77.4).

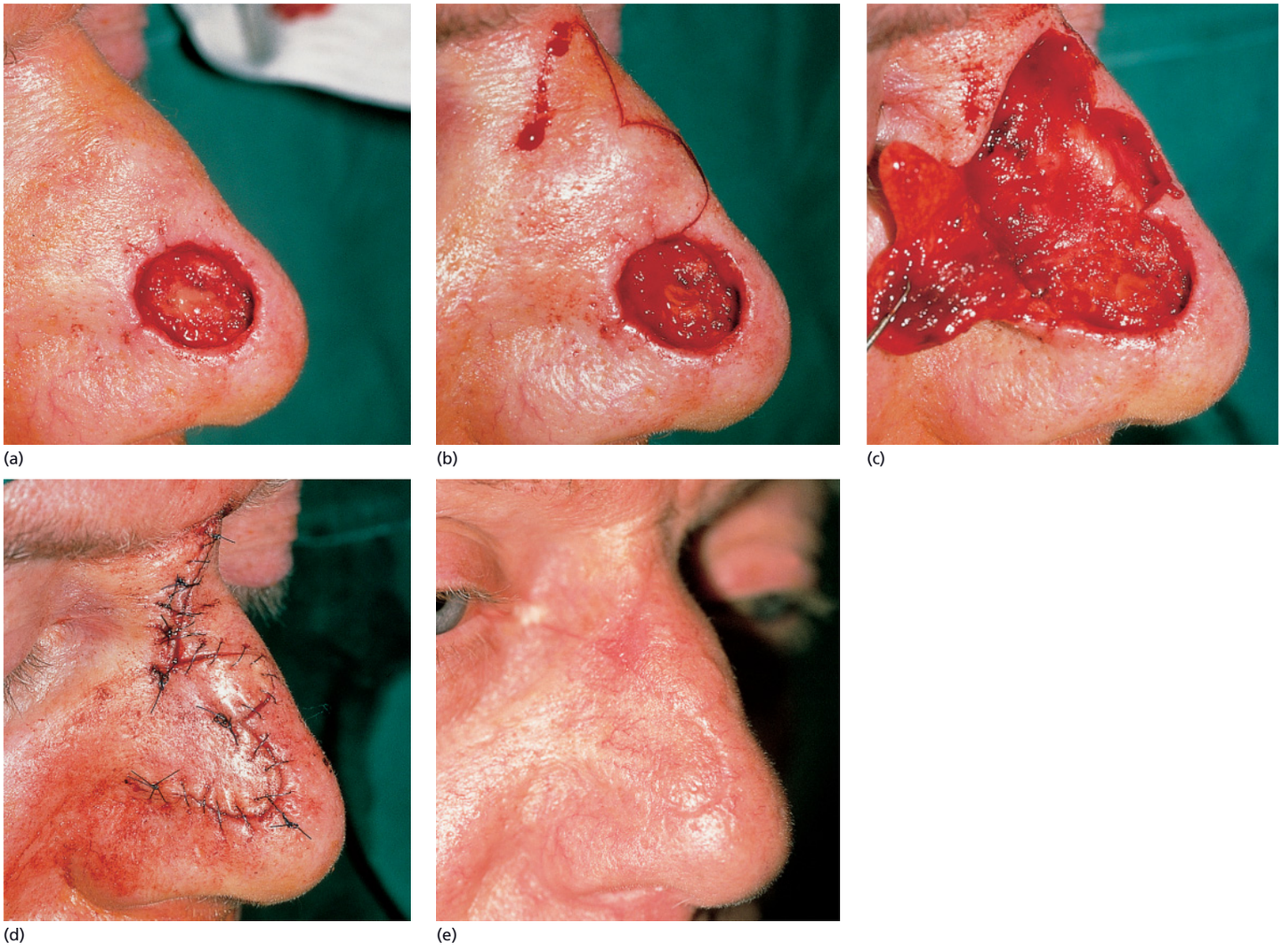
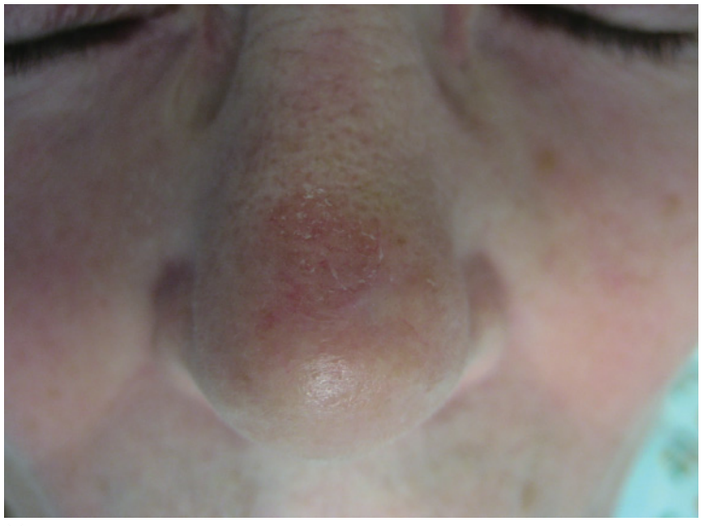


Fig. 77.15 Bilobed flap on the nose. (a) This defect near the tip of the nose was covered using a bilobed flap designed to cover the defect by exploiting the looser skin higher up on the side of the nose (b). (c) Both parts of the flap were raised together, and were transposed into the defect and the secondary defect; (d) the tertiary defect was closed directly. (e) The cosmetic result at 6 months was good.

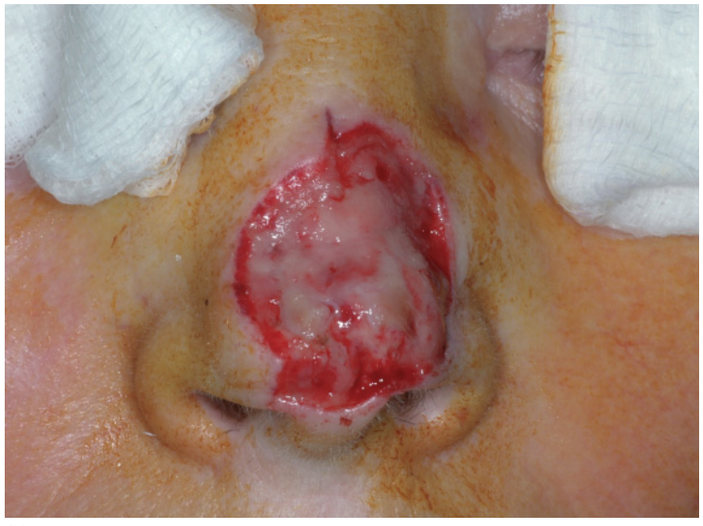
Pedicle flaps include island pedicle flaps and interpolation flaps. The island pedicle flap derives its nutritional support from the attached subcutaneous and muscle tissue, whereas the interpolation pedicle flap derives its vascular supply from a skin and subcutaneous tissue pedicle. The island pedicle flap is a one-stage procedure whereas the interpolation flap involves the creation of a bridge-like skin pedicle; this remains attached for 2–3 weeks at both the donor and defect site whilst the donor skin establishes another blood supply at the defect site. Interpolation flaps therefore always involve a second surgical stage when the pedicle has to be divided. Interpolation flaps are used when the nature, position or depth of the defect means that a simpler local flap or skin graft could not be used. Pedicle flaps still have to be moved into position by rotation, advancement or transposition, as described above, although the presence of the pedicle permits greater flexibility and less reliance on matching donor and recipient site.

Complications

Ischaemic necrosis of the flap usually occurs because of excessive tension resulting from poor design or mobility. Secondary infection is also more common if the flap has a poor blood supply [29]. On the head and neck, blood supply is excellent at all sites, but on the trunk, and especially on the lower limb, attempts at flap repair frequently result in failure because of relatively poor blood supply. Cigarette smokers are more likely to suffer from flap or graft necrosis than non-smokers (Fig. 77.17), although this can be reversed if smokers significantly reduce cigarette consumption 2 days before and 7 days after surgery [30]. If the flap scar is obtrusive, particularly on the nose, it can be revised by dermabrasion, which is best performed 6 weeks after surgery [31]. Manual dermabrasion [32] or scalpel sculpturing [33] may be less hazardous to the operator and equally effective.



(a)



(b)



(c)



(d)

Fig. 77.16 Interpolation flap. Midline forehead flap to cover a nasal tip defect. Excision of the ill-defined nasal tip BCC (a) resulted in a large and deep defect (b). Closure with a skin graft would have left a pronounced contour defect. The midline forehead flap was designed and sutured into place (c). Three weeks later the pedicle was divided. The final cosmetic result is good (d). The superior portion of the forehead donor skin was left to heal by second intention.



Fig. 77.17 Complications—flap necrosis in a cigarette smoker. Despite warnings, this patient continued to smoke before and after surgery. Possibly because of this, the rotation flap on her temple necrosed at 7 days.

Table 77.4 Flap types and uses.

Flap type	Random pattern flaps (synonym/s)	Uses	Comments
Advancement	Crescentic advancement flap [16]	Cheek/nose, cheek/upper lip closures	In effect side-to-side closure with special attention to cosmetic boundaries; a useful technique
	Single advancement (U-plasty)	Cheek, temple, forehead [6], upper lip [15]	If designed with a broad base can be very effective on the cheek
	Double advancement (H-plasty)	Forehead defects, eyebrow repairs	Little mobility, multiple scars, numb scalp; conceptually easy but difficult to get right
	O–T-plasty (A–T-plasty, V–T-plasty, Dieffenbach's winged V-plasty [17])	Lower eyelid, upper lip [15], forehead [6]	A bilateral advancement flap useful around the eye, lip, nose [3] and hair margin
	Single advancement (unilateral Burow's wedge flap) [3]	Upper lip, temple, cheek, forehead	A useful flap which is both advanced and rotated into position and the redundant skin removed using a Burow's triangle
Rotation	Single rotation with back-cut (hatchet flap)	Cheek, temple, medial canthus	A useful technique [1] (Fig. 77.13)
	Sliding glabella rotation flap (V–Y advancement)	Medial canthus, dorsal nose [18]	Exploits the redundant skin in the glabella area. Skin movement includes both advancement and rotation as do many rotation or advancement flaps
	Double rotation (O–Z-plasty)	Forehead, scalp, chin [6]	Large area of undermining required; only works on lax scalp
	Multiple rotation flaps (pinwheel design)	Scalp	Variant of O–Z-plasty
Transposition	Nasolabial flap [19]	Ala rim or side wall of the nose	Good results with careful attention to detail; pincushioning can be a problem (Fig. 77.14)
	Basic transposition/rhombic flap	Cheek, nose, chin, medial canthus, upper lip	Rarely if ever used as the true geometric rhomboid. Basic transposition flaps are very useful and generally exploit the natural elasticity of the skin so that the flap shape adapts to fit the defect [20]. A Z-plasty adaptation [21] may enhance flap mobility [22]. The glabella transposition flap (banner flap) [23] is a named variant.
	30° angle transposition flap [4] (Webster flap)	Dorsum of the nose	Not difficult; bilateral and single flaps can be used
	Bilobed [24]	Nose tip/side wall; medial canthus	Correct design important (Fig. 77.15)
Pedicle	*Interpolation flaps*		
	Median forehead pedicle flap (Fig. 77.16)	Full thickness ala wall defects; nose tip or lower third of nose	Variously described as an axial pattern flap and a random pattern flap. Two-stage procedure; the flap knuckle or pedicle has to be separated 2–3 weeks later
	Cheek interpolation flap	Nose tip or lower third of nose	In men the beard hair may be a problem at the recipient site
	Island pedicle flaps		
	Island pedicle flap [25] (kite flap of Dufourmentel)	Upper lip [14], trunk and limb	The blood supply comes from the subcutaneous tissue attached to the underside of the skin. A similar design is used in an axial flap employed for defects on the nose tip and ala. The pedicle is based on the branch of the angular artery that supplies the nasalis muscle [26]
	Bipedical advancement [27]	Forehead, nasal side wall, chin	
	Midline forehead island flap [28]	Medial canthus	The skin flap is tunnelled under the skin into the defect

References

1 Tromovitch TA, Stegman SJ, Glogau RG. *Flaps and Grafts in Dermatologic Surgery*. Chicago: Year Book, 1989.

2 Field LM. Combining flaps: medial canthal/lateral nasal root reconstruction utilising glabella 'fan' and cheek rotation flaps—an O–Z variation. *J Dermatol Surg Oncol* 1994; **20**: 205–8.

3 Summers BK, Siegle RJ. Facial cutaneous reconstructive surgery: facial flaps. *J Am Acad Dermatol* 1993; **29**: 917–41.

4 Salasche SJ, Grabski WJ. *Flaps for the Central Face*. New York: Churchill Livingstone, 1990.

5 Zitelli JA, Fazio MJ. Reconstruction of the nose with local flaps. *J Dermatol Surg Oncol* 1991; **17**: 184–9.

6 Wheeland RG. Reconstruction of the lower lip and chin using local and random pattern flaps. *J Dermatol Surg Oncol* 1991; **17**: 605–15.

7 Moy RL, Ashjian AA. Periorbital reconstruction. *J Dermatol Surg Oncol* 1991; **17**: 153–9.

8 Ross JJ, Pham R. Closure of eyelid defects. *J Dermatol Surg Oncol* 1992; **18**: 1061–4.

9 Cavanaugh EB. Management of lesions of the helical rim using a chondrocutaneous advancement flap. *J Dermatol Surg Oncol* 1982; **8**: 691–6.

10 Mellette JR. Ear reconstruction with local flaps. *J Dermatol Surg Oncol* 1991; **17**: 176–82.

11 Siegel RJ. Forehead reconstruction. *J Dermatol Surg Oncol* 1991; **17**: 200–4.

12 Field LM. Scalp flaps. *J Dermatol Surg Oncol* 1991; **17**: 190–9.

13 Bennett RG. Local skin flaps on the cheeks. *J Dermatol Surg Oncol* 1991; **17**: 161–5.

14 Zitelli JA, Brodland DG. A regional approach to reconstruction of the upper lip. *J Dermatol Surg Oncol* 1991; **17**: 143–8.

15 Spinowitz AL, Stegman SJ. Partial-thickness wedge and advancement flap for upper lip repair. *J Dermatol Surg Oncol* 1991; **17**: 581–6.
16 Mellette JR, Harrington AC. Applications of the crescentic advancement flap. *J Dermatol Surg Oncol* 1991; **17**: 447–54.
17 Field LM. The forehead V to T plasty (Dieffenbach's winged V-plasty). *J Dermatol Surg Oncol* 1986; **12**: 560–2.
18 Marchac D, Toth B. The axial frontonasal flap revisited. *Plast Reconstr Surg* 1985; **76**: 686–94.
19 Zitelli JA. The nasolabial flap as a single stage procedure. *Arch Dermatol* 1990; **126**: 1445–8.
20 Holt PJA, Motley RJ. A modified rhombic transposition flap and its application in dermatology. *J Dermatol Surg Oncol* 1991; **17**: 287–92.
21 Zachary CB. *Basic Cutaneous Surgery: a Primer in Technique*. New York: Churchill Livingstone, 1991: 87.
22 Johnson SC, Bennett RG. Double Z-plasty to enhance rhombic flap mobility. *J Dermatol Surg Oncol* 1994; **20**: 128–32.
23 Field LM. The glabella transposition 'banner' flap. *J Dermatol Surg Oncol* 1988; **14**: 376–8.
24 Zitelli JA. The bilobed flap for nasal reconstruction. *Arch Dermatol* 1989; **125**: 957–9.
25 Braun M, Cook J. The island pedicle flap. *Dermatol Surg* 2005; **31**: 995–1005.
26 Papadopoulos DJ, Pharis DB, Munavalli GS *et al*. Nasalis myocutaneous island pedicle flap with bilevel undermining for repair of lateral nasal defects. *Dermatol Surg* 2002; **28**: 190–4.
27 Flint ID, Siegle RJ. The bipedical flap revisited. *J Dermatol Surg Oncol* 1994; **20**: 394–400.
28 Field LM. Midline forehead island flap. *J Dermatol Surg Oncol* 1987; **13**: 243–6.
29 Salasche SJ, Grabski WJ. Complications of flaps. *J Dermatol Surg Oncol* 1991; **17**: 132–40.
30 Goldminz D, Bennett RG. Cigarette smoking and flap and full-thickness graft necrosis. *Arch Dermatol* 1991; **127**: 1012–5.
31 Yarborough JM. Ablation of facial scars by programmed dermabrasion. *J Dermatol Surg Oncol* 1988; **14**: 292–4.
32 Zisser M, Kaplan B, Moy RL. Surgical pearl: manual dermabrasion. *J Am Acad Dermatol* 1995; **33**: 105–6.
33 Snow SNP, Stiff MA, Lambert DR. Scalpel sculpturing techniques for graft revision and dermatologic surgery. *J Dermatol Surg Oncol* 1994; **20**: 120–6.

Mohs micrographic surgery

Definition

Mohs micrographic surgery (MMS) is a specialized treatment for skin cancer which offers both extremely high cure rates and maximal preservation of healthy tissues. Repeated cycles of surgery and intraoperative microscopic examination of the entire surgical margin of the excised tissues allows accurate and dependable identification and removal of all residual invasive tumour. Mohs micrographic surgery is most often used to treat the most challenging forms of facial basal and cutaneous squamous carcinoma and can be used to treat less common forms of skin cancer.

History

The technique evolved from the pioneering work performed by Frederic E. Mohs while working as a cancer research assistant at the University of Wisconsin in the early 1930s. Initially called chemosurgery, the original technique involved the overnight application of a noxious zinc chloride paste, with subsequent excision of the devitalized, preserved tissues, and microscopic examination of histological tissue sections. Consequently, the wounds created had to be allowed to heal by secondary intention. Mohs introduced three features which remain fundamental to the success of the modern technique:

- the tissues were sectioned and examined in the *horizontal* plane
- a unique technique for marking and colour-coding excised specimens
- a mapping process to accurately identify the location of residual tumour which could then be excised with further cycles of treatment.

As experience of the technique grew, the combination of consistently high cure rates for large and extremely destructive tumours and the surprisingly acceptable results of wound healing by secondary intention [1], resulted in a gradual acceptance of the technique by the medical community.

Mohs, who was a formally trained general surgeon, first published his results in the general surgical literature [2], but as the main interest in his work was amongst dermatologists he subsequently began to publish in the dermatological literature [3]. Practical use of chemosurgery spread slowly amongst dermatologists, and nearly 30 years passed before there were enough 'chemosurgeons' to form a society; the original 23 members of the American College of Chemosurgery (ACC) first met in 1967 [4].

The evolution of chemosurgery into the technique that is now practised worldwide began at the 1970 meeting of the ACC when Tromovitch reported no recurrences in 99 (97%) of 102 patients following excision of basal cell carcinomas (BCC) using the Mohs technique but omitting the use of zinc chloride paste and simply excising living tissue under a local anaesthetic [5,6]. This 'fresh tissue' form of the technique had been first used by Mohs himself in 1953 and had become his preferred technique for the removal of periorbital tumours, a site where the use of zinc chloride paste led to particularly severe inflammation, swelling and morbidity [7].

As confidence in chemosurgery grew, it became increasingly clear that the success of the procedure was fundamentally linked to the comprehensive microscopic control of resection, rather than *in situ* tissue fixation. Consequently, there began a gradual move away from the use of chemosurgery and an increased adoption of the fresh tissue technique of Mohs surgery, most commonly using rapidly prepared frozen tissue sections. As a result, a painful, prolonged technique, producing sloughy, granulating wounds, was replaced by a procedure which could be performed comfortably under local anaesthesia, lasting hours rather than days, and resulting in defects which could be immediately reconstructed when necessary [8].

Treatment of skin cancer

Skin cancer can be treated with a variety of techniques including topical therapy, destructive procedures and radiation therapy. However, only surgical excision and MMS provide tissue suitable for histological examination of the surgical margins. The following are the fundamental differences between traditional surgical excision and MMS:

- Traditional surgical excision relies upon removing a predetermined margin of clinically normal skin from around and underneath the cancer, and generally wider and deeper margins are recommended for more advanced, difficult and recurrent tumours. Mohs micrographic surgery does not rely upon clinical estimation as the true extent of the cancer is revealed as the technique proceeds (Fig. 77.18a–f).



(a)



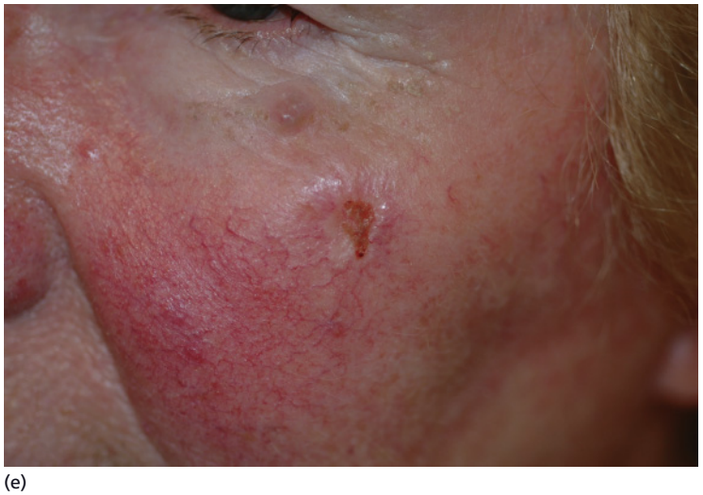
(b)



(c)



(d)



(e)



(f)

Fig. 77.18 Defects following MMS for 'high risk' facial BCC illustrating significant tumour extension beyond the apparent clinical margins. (a) Morphoeic eyebrow BCC, and defect (b) following MMS, showing extensive spread medially into the eyebrow; (c) poorly-defined BCC on the ear, and defect (d) following MMS, showing extensive spread and involvement of underlying cartilage; (e) morphoeic BBC left upper cheek, and Mohs defect (f).

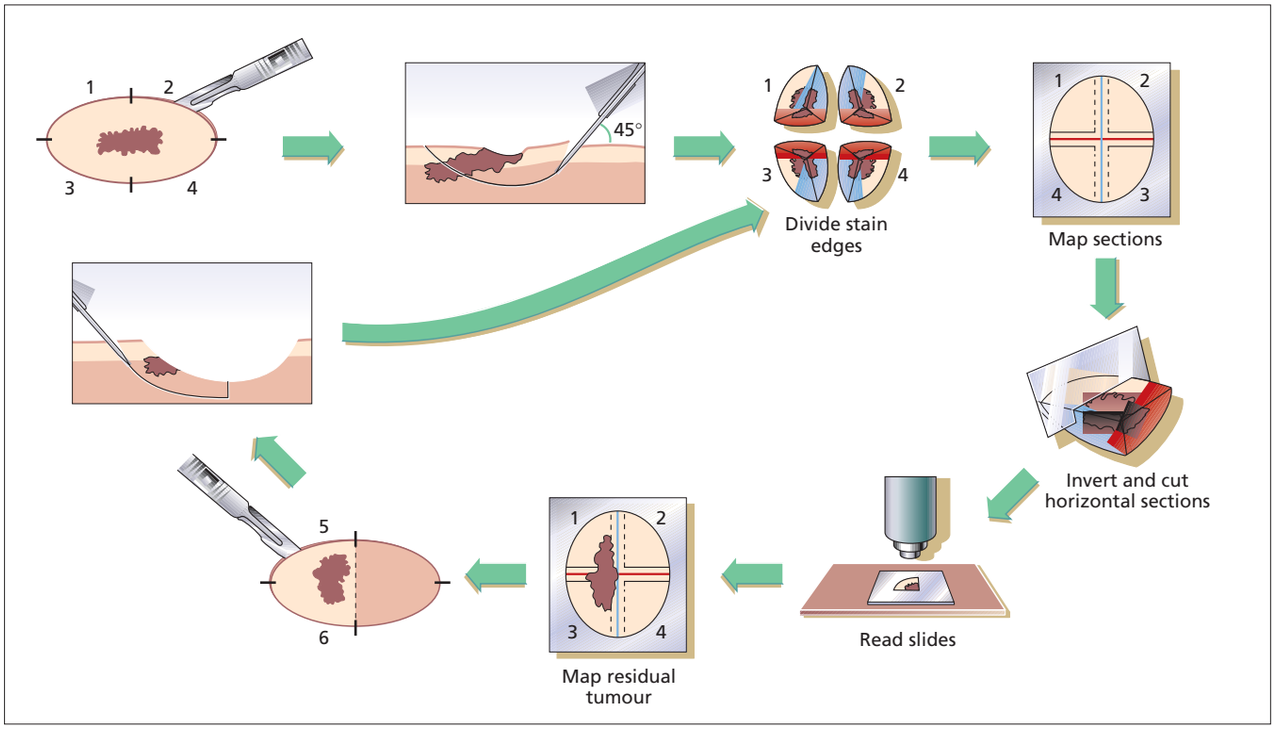


Fig. 77.19 The stages of Mohs micrographic surgery.

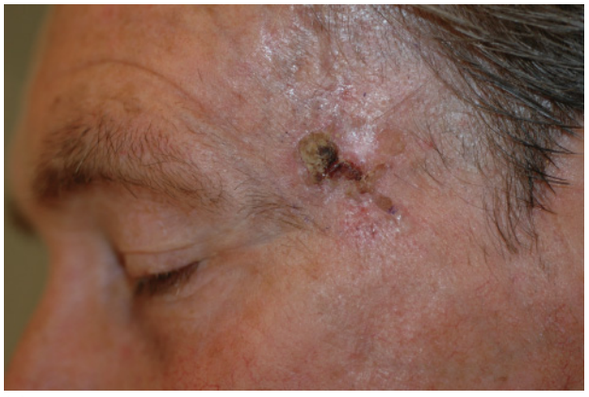
- Traditional surgical excision is generally followed by immediate reconstruction of the wound, with histological examination of the surgical margins occurring some days later. Mohs micrographic surgery uses intraoperative histological examination to establish complete tumour removal on the day of surgery. Consequently, traditional surgery may result in incomplete excision of the cancer, and difficult management decisions as the wound has already been repaired. In contrast, MMS confirms complete tumour resection *prior* to wound reconstruction.
- Traditional surgical excision generally relies upon histological evaluation of the surgical margins using vertically orientated tissue sections ('breadloafing') which has been estimated to have a sensitivity no greater than 44% [9]. In contrast, the horizontally-orientated tissue sections used in MMS are designed to allow microscopic examination of 100% of the surgical margin.
- Traditional surgical excision involves the surgeon, pathologist and possibly an anaesthetist. Mohs micrographic surgery is performed by the Mohs surgeon who also acts as anaesthetist, pathologist and reconstructive surgeon.

Procedure

The practical aspects of modern fresh-tissue MMS have been well described [8,10]. Essentially, the technique involves repeated cycles of local anaesthetic surgery and pathological investigation. Tissue is excised as a thin, flat layer with bevelled edges, which is accurately orientated, colour-coded, mapped, horizontally sectioned and examined microscopically (Fig. 77.19).

Any residual tumour identified at any part of the surgical margin is marked on the Mohs map, which accurately guides the Mohs surgeon in the re-excision of all residual tumour-involved areas (Fig. 77.20a,b). This methodical use of highly accurate, staged excisions underlies the high cure rates associated with the technique. In contrast, those areas of the wound that do not contain tumour are not excised further, which underlies the maximal tissue preservation associated with the technique. Each tissue layer is examined microscopically and, if there is still residual cancer, the process continues, layer by layer, until the cancer has been completely removed. Frozen-section histology is the preferred option for most experienced Mohs surgeons excising basal and squamous carcinoma [11], but permanent-section histology is used by some, and this means that the wounds cannot be repaired on the same day [12]. Mohs surgeons who routinely use frozen-section histology may occasionally use permanent-section histology when treating highly infiltrative or uncommon tumours [13].

In a feature unique to MMS, the final decision on the exact mode of wound repair is made only after the cancer has been completely removed, although likely wound repair options in a particular anatomical area can be discussed in advance. All wounds resulting from the old chemosurgical technique had to heal by secondary intention, but wounds following MMS are suitable for immediate reconstruction or secondary intention healing, whichever is most likely to result in the best cosmetic and functional outcome. In selected cases, other surgical specialists may perform reconstruction of the Mohs defect as part of a multidisciplinary approach to the management of aggressive facial skin cancer. In many major Mohs units, Mohs surgery is frequently performed in collaboration with plastic [14], maxillo-facial, otorhinolaryngeal (ENT) [15] and oculoplastic [16] colleagues.



(a)



(b)

Fig. 77.20 Intra-operative picture during MMS illustrating the role of the Mohs map in identifying location of residual tumour. (a) Poorly defined BCC left temple, recurrent following excision. (b) Intra-operative picture showing correlation between residual tumour (blue areas on Mohs map) and the Mohs defect.

Results

The results of MMS are impressive, with a 98–99% 5-year cure rate for BCC and a 94.4% 5-year cure rate for squamous cell carcinomas reported by Mohs himself [17]. There is considerable evidence supporting the use of MMS to treat the most difficult cases of BCC. A review of studies published since the mid-1940s suggested an overall 5-year cure rate of 99% following MMS for primary BCC [18] and 94.4% for recurrent disease [19]. Two prospective studies have been reported from Australia; in one, 5-year cure rates of 100% and 92.2% for primary and recurrent tumours were reported in 819 patients with periocular BCC [20], and in another study of 3370 BCCs on the head and neck treated with MMS there were 5-year cure rates of 98.6% for primary BCC and 96% for recurrent disease [21]. A retrospective review of 620 patients with 720 lesions gave estimated 5-year cure rates of 98.8% for primary BCC and 93.3% for recurrent disease [22].

Cutaneous squamous cell carcinoma (SCC) can also be successfully treated by MMS [17,23]. In an Australian multicentre study of 1263 cases (38.9% were recurrent lesions) treated over a 10-year period, there was an overall 5-year cure rate of 96.1% (97.4% for primary and 94.1% for recurrent disease) [24].

The comparative cost of MMS has been studied [25–27]. The procedure (to produce tumour-free margins) has a similar cost to traditional excision [25] but is less expensive than excision using intraoperative frozen-section control [26]. A study from the Netherlands found MMS was more expensive than traditional surgery [27], but as MMS is likely to produce much higher cure rates than standard excision it remains cost effective. The only study to date which tried to compare cure rates following standard excision and MMS [28] appeared to show little difference between the two treatment modalities. However, a failure to adhere to the study design (with 24 of 301 patients randomized to have standard surgical excision being moved into the MMS treatment group) raises concerns about the conclusions of this study [29].

Practical aspects and indications

Mohs micrographic surgery is a remarkably safe procedure when performed under local anaesthesia on a day-case basis [30,31].

The complete surgical margin control achieved by MMS lends itself ideally to the excision of tumours that grow in a contiguous (all parts of the tumour are directly connected to all other parts) fashion, and whereas the two most common tumours treated by MMS are BCC and SCC, many less common cutaneous tumours can be excised by experienced clinicians working in a multidisciplinary fashion and using either standard or modified forms of MMS. Such tumours include dermatofibrosarcoma protuberans (DFSP) [23,32], lentigo maligna [33], microcystic adnexal carcinoma [23,34], cutaneous sebaceous carcinoma [23], and extramammary Paget's disease [23]. The success of MMS has led to the development of other surgical/pathological techniques offering more comprehensive surgical margin control than is available using standard histology techniques. Techniques such as 'peripheral in-continuity tissue examination' [35] and 'three-dimensional histology' [36] all have their merits, but none has gained widespread popularity.

Many BCC and SCC lesions can often be adequately managed without the use of MMS, and the technique is generally reserved for 'high-risk lesions' [37,38], which can be defined by various criteria, including:

- Size (especially larger lesions) (Fig. 77.21a)
- Site (especially the perioral, periorbital, perinasal and periauricular areas where a combination of a high cure rate and maximal preservation of normal tissues and structures is vital) (Fig. 77.21b)
- Lesions with very poorly defined clinical borders (where it is difficult to accurately identify appropriate surgical resection margins)
- Clinically invasive tumours
- Failure of previous treatment (recurrent disease) (Fig. 77.21c)

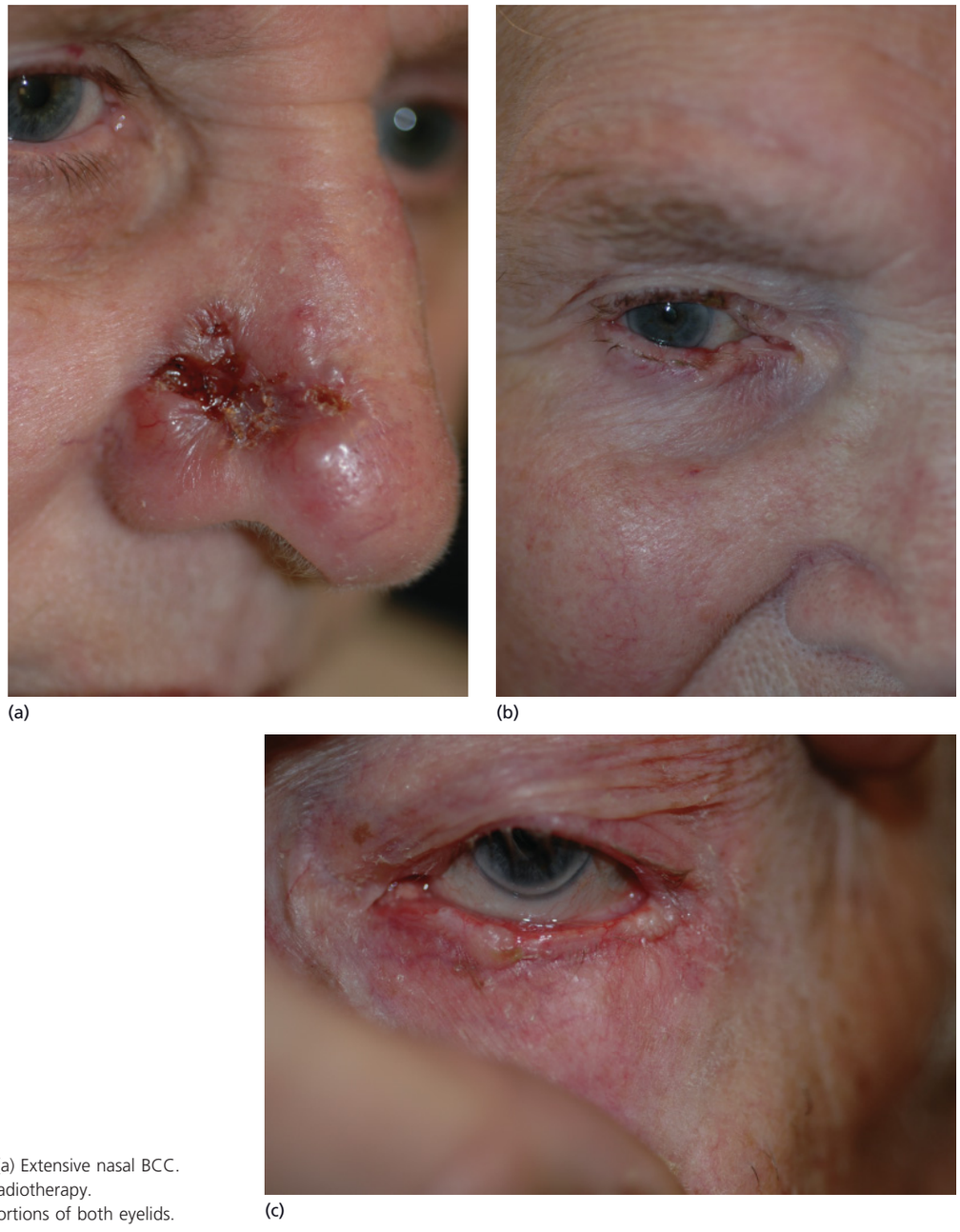


Fig. 77.21 'High risk' facial BCC suitable for MMS. (a) Extensive nasal BCC. (b) Extensive lower eyelid BCC, recurrent following radiotherapy. (c) Infiltrative medial canthal BCC involving medial portions of both eyelids.

- Histologically incompletely excised lesions
- Histological features (aggressive growth patterns, perineural spread).

Historically, the growth in popularity of the technique was due in part to its excellent success rate, highly practical nature, and the challenge posed by the reconstructive surgery required following many procedures. As the use of MMS became widespread the ACC first changed its name to the American College of Mohs Micrographic Surgery and Cutaneous Oncology (ACMMSCO), and is now the American College of Mohs Surgery (ACMS), with over 850 members. For many years the College and its members have undertaken a long-term policy of improvement of the specialty, through scientific and technical development and through the formalization of training for new Mohs surgeons through minimum 12-month, College-approved fellowships. Successful graduates from fellowship training, and others trained outside the College training schemes, should not only be proficient in the technique, but also be experts in cutaneous oncology, and highly competent reconstructive surgeons. The continuing success and development of MMS as a recognized specialty is dependent upon a consistent demonstration of high cure rates, maximal tissue conservation and good aesthetic outcomes of the technique, which can only result from appropriate training and experience.

References

1 Zitelli JA. Wound healing by secondary intention. *J Am Acad Dermatol* 1983; **9**: 407–15.
2 Mohs FE. Chemosurgery: a microscopically controlled method of cancer excision. *Arch Surg* 1941; **42**: 279–95.
3 Mohs FE. Chemosurgical treatment of cancer of the face: a microscopically controlled method of excision. *Arch Dermatol Syphilol* 1947; **56**: 143.
4 Brodland DG, Amonette R, Hanke CW, Robins P. The history and evolution of Mohs micrographic surgery. *Dermatol Surg* 2000; **26**: 303–7.
5 Tromovitch TA, Stegman SJ. Microscopic-controlled excision of cutaneous tumours. Chemosurgery, fresh tissue technique. *Cancer* 1978; **41**: 653–8.
6 Swanson NA, Taylor WB, Tromovitch TA. The evolution of Mohs surgery. *J Dermatol Surg Oncol* 1982; **8**: 650–4.
7 Mohs FE. Chemosurgery for skin cancer: fixed tissue and fresh tissue techniques. *Arch Dermatol* 1976; **112**: 211–5.
8 Cottel WI, Bailin PL, Alborn MJ *et al*. Essentials of Mohs micrographic surgery. *J Dermatol Surg Oncol* 1988; **14**: 11–3.
9 Kimyai-Asadi A, Goldberg LH, Jih MH. Accuracy of serial transverse cross-sections in detecting residual basal cell carcinoma at the surgical margins of an elliptical excision specimen. *J Am Acad Dermatol* 2005; **53**: 469–74.
10 Telfer NR. Mohs micrographic surgery for nonmelanoma skin cancer. *Clin Dermatol* 1995; **13**: 593–600.
11 Breuninger H. Micrographic surgery of malignant skin tumors: a comparison of the frozen technique with paraffin sectioning. *Facial Plast Surg* 1997; **13**: 79–82.
12 der Plessis PJ, Dahl MG, Malcolm AJ *et al*. Mohs' surgery of periocular basal cell carcinoma using formalin-fixed sections and delayed closure. *Br J Dermatol* 1998; **138**: 1003–8.
13 Barlow RJ, Ramnarain N, Smith N *et al*. Excision of selected skin tumours using Mohs' micrographic surgery with horizontal paraffin-embedded sections. *Br J Dermatol* 1996; **135**: 911–7.
14 Dobke MK, Miller SH. Tissue repair after Mohs surgery. A plastic surgeon's view. *Dermatol Surg* 1997; **23**: 1061–6.
15 Stein JM, Hrabovsky S, Schuller DE, Siegle RJ. Mohs micrographic surgery and the otolaryngologist. *Am J Otolaryngol* 2004; **25**: 385–93.
16 Sciscio A, Stewart K, Grewal J *et al*. Periocular Mohs micrographic surgery: Results of a dual-site day-surgery service. *Orbit* 2001; **20**: 209–15.
17 Mohs FE. Chemosurgery: microscopically controlled surgery for skin cancer—past, present and future. *J Dermatol Surg Oncol* 1978; **4**: 41–54.
18 Rowe DE, Carroll RJ, Day CL Jr *et al*. Long-term recurrence rates in previously untreated (primary) basal cell carcinoma: implications for patient follow-up. *J Dermatol Surg Oncol* 1989; **15**: 315–28.
19 Rowe DE, Carroll RJ, Day CL. Mohs surgery is the treatment of choice for recurrent (previously treated) basal cell carcinoma. *J Dermatol Surg Oncol* 1989; **15**: 424–31.
20 Malhotra R, Huilgol SC, Huynh NT, Selva D. The Australian Mohs database, part II: periocular basal cell carcinoma outcome at 5-year follow-up. *Ophthalmology* 2004; **111**: 631–6.
21 Leibovitch I, Huilgol SC, Selva D *et al*. Basal cell carcinoma treated with Mohs surgery in Australia II. Outcome at 5-year follow-up. *J Am Acad Dermatol* 2005; **53**: 452–7.
22 Smeets NW, Kuijpers DI, Nelemans P *et al*. Mohs' micrographic surgery for treatment of basal cell carcinoma of the face – results of a retrospective study and review of the literature. *Br J Dermatol* 2004; **151**: 141–7.
23 Thomas CJ, Wood GC, Marks VJ. Mohs micrographic surgery in the treatment of rare aggressive cutaneous tumors: the Geisinger experience. *Dermatol Surg* 2007; **33**: 333–9.
24 Leibovitch I, Huilgol S, Selva D *et al*. Cutaneous squamous cell carcinoma treated with Mohs micrographic surgery in Australia I. Experience over 10 years. *J Am Acad Dermatol* 2005; **53**: 253–60.
25 Bialy TL, Whalen J, Veledar E *et al*. Mohs micrographic surgery vs traditional surgical excision: a cost comparison analysis. *Arch Dermatol* 2004; **140**: 736–42.
26 Cook J, Zitelli JA. Mohs micrographic surgery: a cost analysis. *J Am Acad Dermatol* 1998; **39**: 698–703.
27 Essers BA, Dirksen CD, Nieman FH *et al*. Cost-effectiveness of Mohs micrographic surgery vs surgical excision for basal cell carcinoma of the face. *Arch Dermatol* 2006; **142**: 187–94.
28 Smeets NW, Krekels GA, Ostertag JU *et al*. Surgical excision vs Mohs' micrographic surgery for basal-cell carcinoma of the face: randomised controlled trial. *Lancet* 2004; **364**: 1766–72.
29 Otley CC. Mohs' micrographic surgery for basal-cell carcinoma of the face. *Lancet* 2005; **365**: 1226–7.
30 Cook JL, Perone JB. A prospective evaluation of the incidence of complications associated with Mohs micrographic surgery. *Arch Dermatol* 2003; **139**: 143–52.
31 Kimyai-Asadi A, Goldberg LH, Peterson SR *et al*. The incidence of major complications from Mohs micrographic surgery performed in office-based and hospital-based settings. *J Am Acad Dermatol* 2005; **53**: 628–34.
32 Snow SN, Gordon EM, Larson PO *et al*. Dermatofibrosarcoma protuberans: a report on 29 patients treated by Mohs micrographic surgery with long-term follow-up and review of the literature. *Cancer* 2004; **101**: 28–38.
33 Cohen LM, McCall MW, Zax RH. Mohs micrographic surgery for lentigo maligna and lentigo maligna melanoma. A follow-up study. *Dermatol Surg* 1998; **24**: 373–7.
34 Snow S, Madjar DD, Hardy S *et al*. Microcystic adnexal carcinoma: report of 13 cases and review of the literature. *Dermatol Surg* 2001; **27**: 401–8.
35 Strong JW, Worsham GF, Hagerty RC. Peripheral in-continuity tissue examination: a modification of Mohs' micrographic surgery. *Clin Plast Surg* 2004; **31**: 1–4.
36 Moehrle M, Dietz K, Garbe C, Breuninger H. Conventional histology vs. three-dimensional histology in lentigo maligna melanoma. *Br J Dermatol* 2006; **154**: 453–9.
37 Telfer NR, Colver GB, Bowers PW. Guidelines for the management of basal cell carcinoma. *Br J Dermatol* 1999; **141**: 415–23.
38 Williford PM, Feldman SR. Surgery for basal-cell carcinoma of the face. *Lancet* 2004; **364**: 1732–3.

Miscellaneous surgical procedures

Techniques

Hydrodissection

The skin can be lifted away from underlying critical arteries and veins by hydrodissection. Approximately 20 mL of saline is injected into loose tissue beneath the lesion, thereby lifting the area to be excised off any underlying vital structures. The injection must be given after local anaesthesia, just before excision. The technique works best where there is a boundary that will delay the spread of the saline, for example on the temple and the ear [1].

Snip excision

Small tags can be snipped off with a pair of sharp scissors without the need for local anaesthetic [2]. The tag should be pulled away from the skin and snipped off at its base; bleeding usually stops spontaneously. Haemostasis may be a problem with larger polyps with a well-developed blood supply; hence, an anaesthetic will be required. The wounds can be left to heal by second intention, with excellent cosmetic results [3].

Relaxing incisions

Relaxing incisions are one of several techniques used to increase skin mobility. Multiple, small, full-thickness incisions are made parallel to the skin edge at the site of greatest wound tension [4]. These allow the skin to stretch like a meshed graft, resulting in small elliptical defects, which heal by second intention. The technique is particularly useful for excisions on the lower leg, where it produces surprisingly good cosmetic results with less morbidity than split- or full-thickness grafts. The technique can be used with

other ways of improving skin mobility [5]. Other types of relaxing incision include the V–Y-plasty [6], which should not be confused with the V–Y island pedicle advancement flap (Table 77.4).

Wedge excision—lip, eyelid and ear

On the eyelid, lip and ear, a tumour can be excised and the defect readily closed by removing a full-thickness wedge with an appropriate margin of uninvolved skin. The different layers at the defect edges are then sutured, and thus the technique varies with the site. The inherent tissue elasticity of the eyelid and lip allows considerable defects to be repaired by direct closure without distorting the free margins of these structures. On the lip, defects smaller than one-third of the lip length can be closed directly following a wedge excision [7], if necessary using a W-plasty correction on the lower lip to avoid excessive distortion [8]. On the eyelid, defects of up to 50% can be closed directly, provided the correct technique is used [9]. However, a wedge excision on the ear reduces its size considerably, and buckling of the ear may occur unless the technique is modified to avoid this [10]. In most instances this type of defect is not a problem, as spectacles can still be supported by the ear and differences in ear size are rarely noticed.

Lipoma removal

Simple skin incision and lipoma excision ensures complete removal but produces a large scar. Scar size can be minimized by breaking up the lipoma into smaller fragments using blunt-ended forceps or a needle-holder inserted via a 4–6-mm punch biopsy wound made over the centre of the lipoma. The fragmented contents can then be squeezed out through the small wound. The fat can also be removed using liposuction [11]. A further development of this technique involves emulsification of the lipoma using an ultrasonic suction scalpel and removal of the fragments under endoscopic control [12]. A subfrontalis lipoma (Fig. 77.22) must be distinguished from a forehead epidermoid cyst. This can be particularly difficult to remove because of its site beneath the frontalis muscle of the forehead [13].

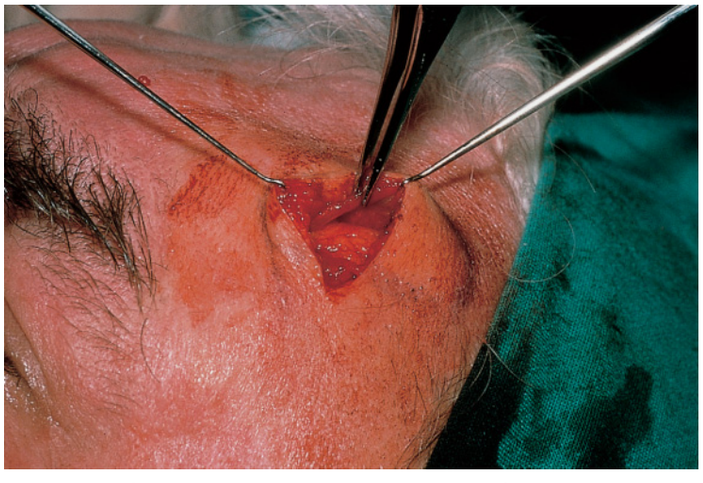


Fig. 77.22 Subfrontalis lipoma. This lipoma lies beneath the frontalis muscle. The muscle has been split vertically and is held back with forceps to reveal the lipoma.

Tissue expansion

Tissue expansion may be helpful if there is insufficient local skin laxity to allow immediate closure and a graft would produce a relatively poor cosmetic result. The skin needed to fill the defect can be stretched to the required size by steadily expanding saline-filled plastic bags placed under the skin adjacent to the proposed defect. For 8–12 weeks after insertion the bags are filled at intervals to produce a mound that stretches the overlying skin. When the defect is excised, the adjacent distended skin is then available to cover the resulting defect [14]. Because the skin used is almost identical to the piece excised, the cosmetic result is potentially excellent. Expansion does not simply stretch existing skin but actually appears to induce basal layer mitotic activity, an increase in dermal collagen, and development of an enhanced blood supply from the fibrous capsule around the implant. Atrophy of adjacent fat and muscle also occurs. In contrast, immediate tissue expansion or stretching the skin at the time of operation using skin hooks, Foley catheters [15] or sutures [16] increases available skin in the short term but appears to result in greater shrinkage and hence scar stretching.

Circumcision

This simple surgical procedure [17] may be indicated in the management of lichen sclerosus et atrophicus.

References

1 Salasche SJ, Giancola JM, Trookman NS. Surgical pearl: hydroexpansion with local anaesthetic. *J Am Acad Dermatol* 1995; **33**: 510–2.
2 Lawrence CM. *An Introduction to Dermatological Surgery*, 2nd edn. St Louis: Mosby, 2002: 75–8.
3 Fewkes JL, Cheney ML, Pollack SV. *Illustrated Atlas of Cutaneous Surgery*. Philadelphia: Lippincott, 1992.
4 Motley RJ, Holt PJA. The use of meshed advancement flaps in the treatment of lesions of the lower leg. *J Dermatol Surg Oncol* 1990; **16**: 346–8.
5 Kolbusz RV, Bielinski KB. The combined use of immediate intraoperative tissue expansion and meshing technique. *Arch Dermatol* 1993; **129**: 152–3.
6 Comaish JS. Dermatological surgery. In: Verbov JL, ed. *Dermatological Surgery*. Lancaster: MTP Press, 1986: 18.
7 Wheeland RG. Reconstruction of the lower lip and chin using local and random pattern flaps. *J Dermatol Surg Oncol* 1991; **17**: 605–15.
8 Jemec BIE. A short review of some methods of excisions from and reconstructions of lower lips. *J Dermatol Surg Oncol* 1981; **7**: 576–9.
9 Ross JJ, Pham R. Closure of eyelid defects. *J Dermatol Surg Oncol* 1992; **18**: 1061–4.
10 Tebbetts JB. Auricular reconstruction: selected single stage techniques. *J Dermatol Surg Oncol* 1982; **8**: 557–66.
11 Kaneko T, Tokushige H, Kimura N *et al*. The treatment of multiple angiolipomas by liposuction surgery. *J Dermatol Surg Oncol* 1994; **20**: 690–2.
12 Sawaizumi M, Maruyama Y, Onishi K *et al*. Endoscopic extraction of lipomas using an ultrasonic suction scalpel. *Ann Plast Surg* 1996; **36**: 124–8.
13 Salasche SJ, McCollough ML, Angeloni VL, Grabski WJ. Frontalis associated lipoma of the forehead. *J Am Acad Dermatol* 1989; **20**: 462–8.
14 Baker SR, Swanson NA. Reconstruction of midfacial defects following surgical management of skin cancer. *J Dermatol Surg Oncol* 1994; **20**: 133–40.
15 Auletta MJ, Matarasso SL, Glogau RG, Tromovitch TA. Comparison of skin hooks and Foley catheters for immediate tissue expansion. *J Dermatol Surg Oncol* 1993; **19**: 1084–8.
16 Liang MD, Briggs P, Heckler FR, Futrell JW. Pre-suturing: a new technique for closing large skin defects—clinical and experimental studies. *Plast Reconstr Surg* 1988; **81**: 694–702.
17 Harahap ML, Siregar AS. Circumcision: a review and a new technique. *J Dermatol Surg Oncol* 1986; **14**: 383–6.

Specific diseases

Epidermoid cysts

Epidermoid cysts (sometimes incorrectly called sebaceous cysts) are lined by a keratinizing epithelium, which produces the cheesy, keratinous contents. They require excision if they are disfiguring or repeatedly infected. The inflamed tissue around an infected epidermoid cyst is friable, making it difficult to excise without fragmenting the cyst wall. An infected cyst should therefore be drained, and the patient treated with an appropriate antibiotic. When the inflammation settles the cyst can be excised. Cysts inflamed as a result of a foreign-body giant cell reaction to released keratin are best treated by triamcinolone injection followed by subsequent removal. Freely mobile cysts can be easily shelled out through the smooth tissue plane that separates the very thin cyst wall from the surrounding tissue, although at this plane the cyst wall is easily punctured and must be handled gently. In all cases the entire cyst wall and punctum should be removed, the latter at the centre of a small skin ellipse, which can also be used to manipulate the cyst during removal. If the cyst ruptures during extraction, every effort should be made to remove residual wall fragments to prevent recurrence. Irrigation of the wound prior to closure will help remove residual cyst contents which might otherwise cause a granulomatous tissue reaction. To avoid long scars, very large cysts can be decompressed via a 4-mm punch biopsy before excision [1]. The wound is either left to heal for 4–6 weeks before definitive removal of the shrunken cyst or an attempt can be made to pull the cyst inside out through the circular wound using artery forceps [2]. Immobile cysts are surrounded by extensive scar tissue and usually have to be excised with the surrounding fibrotic tissue and overlying skin. Excision of large skin cysts leaves subcutaneous dead space, which must be obliterated with deep sutures to minimize the risks of haematoma formation, infection and wound dehiscence.

Hidradenitis

If medical treatment of hidradenitis suppurativa has failed, involved areas can be excised and the defects covered with skin grafts or flaps. However, cure rates of less than 20% are reported [3] and secondary infection is a frequent problem [4]. Alternatives such as excision followed by healing by second intention are well tolerated by the patient and produce good results [5]. An even simpler procedure involves deroofing the fistula, leaving the floor of the track to re-epithelialize the wounded area. Excised tissue or suspect areas should be sent for histology because of the recognized complication of malignant change [6].

Vermilionectomy

This is sometimes called a mucosal advancement [7,8]. The vermilion, usually of the lower lip, is excised, principally because of actinic damage, and replaced by lip mucosa pulled forward and sutured at the vermilion–skin border.

Split ear lobe

Split ear lobes may be congenital, or occur as a result of trauma or wearing heavy earrings. Simply de-epithelializing the sides of the cleft and suturing the exposed edges usually results in a notch appearing at the lobe edge. A full thickness or single-sided Z-plasty correction of the cut edges, depending on lobe thickness [9], is advocated as the best way to ensure good cosmesis, although many other methods are described [10].

Partial or incomplete clefts can be repaired by excising and suturing the enlarged hole. However, if there is only a narrow band of skin separating the hole from the lower pole of the lobe, it is probably best to create a complete defect by cutting the small bridge of skin and closing the defect accordingly. Earrings can be worn again only in patients with thick lobes. Some repairs incorporate reconstruction of a new earring hole at the same time as repair of the defect [11].

Chondrodermatitis nodularis

Chondrodermatitis is a benign condition; the only indication for treatment is pain causing sleep disturbance. Conservative therapy includes a soft pillow, intralesional and topical steroids, and a pressure-relieving cushion is a good first choice alternative to surgery for antihelix lesions. Lesions on the helix are easier to treat surgically than antihelix lesions and give better cure results. Surgical excision of the affected cartilage without removal of skin (Fig. 77.23) will result in cure in over 90% of helix lesions and 70% of those on the antihelix [12]. Recurrences will occur if rough or protuberant edges of cartilage are left at operation, but can be treated using the same technique [13]. A novel 'punch and graft' technique has also been described [14].

Myxoid cysts

Myxoid cysts are ganglia arising as a result of joint fluid leakage from the distal interphalangeal joint into the surrounding tissues. The principle of treatment is that the connection between the cyst and the adjacent joint must be disrupted to prevent the cyst refilling. This is presumably what happens after successful cryotherapy [15], intralesional steroid therapy or curettage, although the cure rate of these procedures is relatively poor. The connection between the joint and the cyst can be identified by injection of dye into the joint [16]. Dye injection, however, is difficult and not essential. The joint fluid leakage site can be assumed to lie between the proximal portion of the cyst and the joint. A proximally based flap can be raised, to include the cyst and skin between the cyst and joint. The cyst is incised and drained. The flap is then resited (Fig. 77.24). The resulting scar presumably seals off the leak from the joint capsule [17].

Axillary hyperhidrosis

Axilla. If medical treatments fail (see Chapter 44), botulinum toxin can be used, and this blocks sweating for 4–6 months [18]. Axillary hyperhidrosis can also be treated by excision of the sweat-gland-bearing axillary skin [19]. The operation is not difficult, but wide excision scars invariably stretch, and infections are common. Shelley described the use of a transverse excision in the centre of the hair-bearing dome of the axilla approximately 4.5 × 1.5 cm wide [20]. The sweat glands can be visualized on the undersurface of the adjacent skin and many of these can be snipped off or destroyed by electrodesiccation when the skin edges are undermined and everted [21]. Methods that attempt removal of the



Fig. 77.23 Excision of chondrodermatitis nodularis helicis. (a) This helix nodule was treated by cartilage excision. An incision was made along the helix rim and the skin reflected to expose the cartilage. (b) A sliver of cartilage was taken to include the 3-mm punch biopsy of the skin nodule. Care was taken to ensure that the cartilage edges were smooth and gently shelving up to the uninvolved cartilage. (c) The skin edges were then sutured. (d) The result at 6 months was good.

sweat glands using subcutaneous curettage or liposuction [22], leaving the skin intact, are also described.

Palmar hyperhidrosis is difficult to treat. Endoscopic transthoracic sympathectomy [23] involves division of the sympathetic trunk running over the posterior wall of the chest cavity. However, side effects are significant, and over 80% of individuals develop compensatory sweating [24]. There is also a risk of Horner's syndrome and pneumothorax. In approximately 10% of cases [25], some recurrence of sweating occurs 1–2 years after surgery. The technique can also be useful in Raynaud's disease [26]. A similar approach can be used to reduce axillary sweating, when the second to sixth thoracic ganglia have to be destroyed. Access below the third thoracic ganglion is difficult, and this is believed to account for the poorer cure rate for axillary sweating [27]. Patients can also be successfully managed by repeated botulinum toxin injections into the palm. The effects last about 6 months. Injections are painful. Transient weakness of the small hand muscles occurs in 40% [28].

References

1 O'Keeffe PJ. Trephining sebaceous cysts. *Br J Plast Surg* 1972; **25**: 411–5.
2 Patton HS. An alternative method for removing sebaceous cysts. *Surg Gynecol Obstet* 1963; **117**: 645–6.

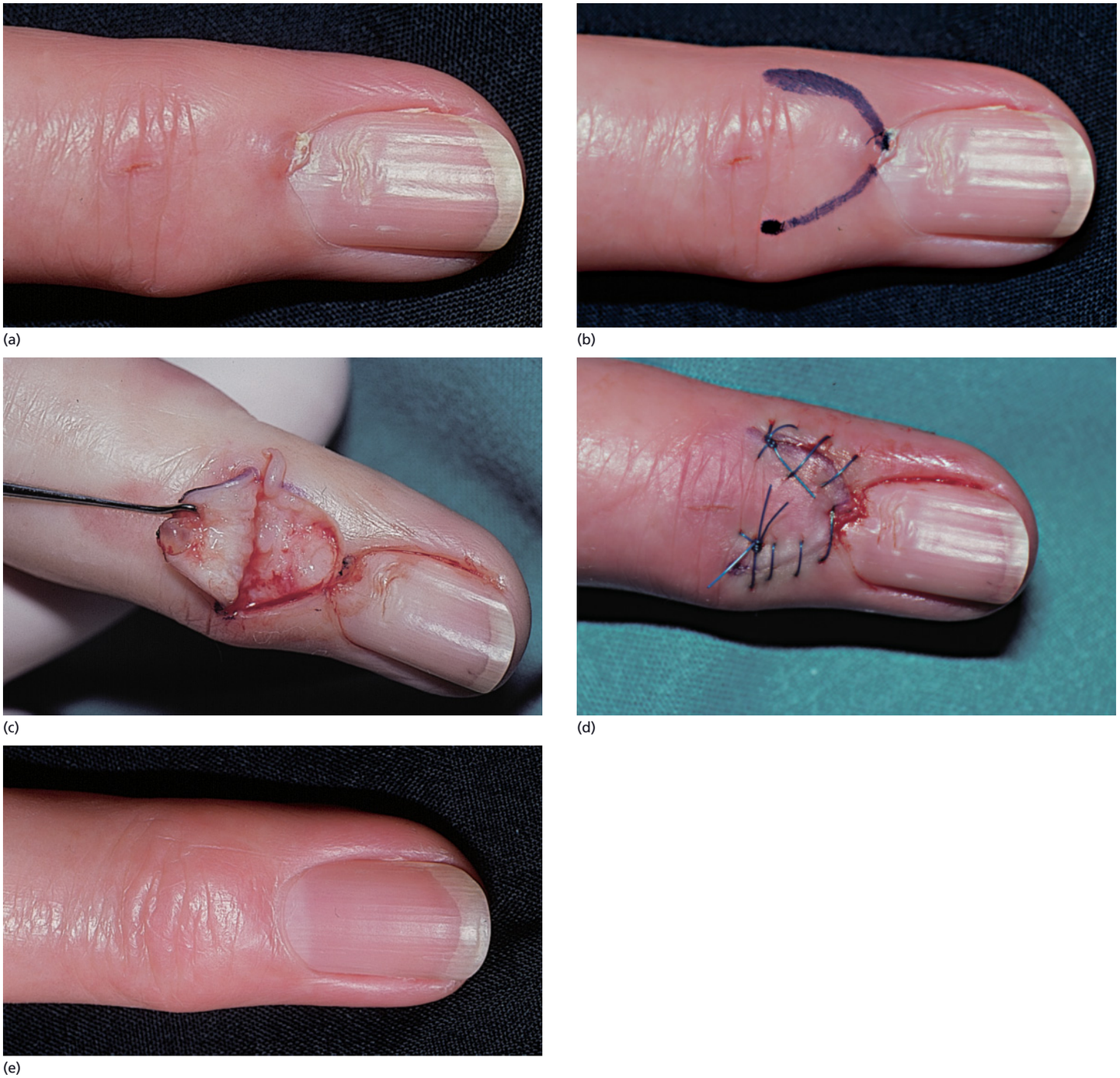


Fig. 77.24 Myxoid cyst surgical therapy. (a) The cyst is just under the proximal nail fold and producing a nail dystrophy. (b) A proximally based flap is designed to include the cyst and extend back to the distal interphalangeal joint. The flap is raised and the skin mobilized back to the DIP joint. (c) The cyst is incised and drained. No skin is excised. (d) The flap is resited and sutured. (e) The result 15 months later shows complete resolution and a normal nail plate.

3 Jemec GBE. Effect of localised surgical excisions in hidradenitis suppurativa. *J Am Acad Dermatol* 1988; **18**: 1103–7.

4 Banerjee AK. Surgical treatment of hidradenitis suppurativa. *Br J Surg* 1992; **79**: 863–6.

5 Silverberg B, Smoot CE, Landa SJF, Parsons RW. Hidradenitis suppurativa: patients' satisfaction with wound healing by second intention. *Plast Reconstr Surg* 1987; **79**: 555–9.

6 Brown SCW, Kazzazi N, Lord PH. Surgical treatment of perineal hidradenitis suppurativa with special reference to recognition of the perianal form. *Br J Surg* 1986; **73**: 978–80.

7 Wheeland RG. Reconstruction of the lower lip and chin using local and random pattern flaps. *J Dermatol Surg Oncol* 1991; **17**: 605–15.

8 Field LM. An improved design for vermilionectomy with a mucous membrane advancement flap. *J Dermatol Surg Oncol* 1991; **17**: 833–4.

9 Reiter D, Alford EL. Torn earlobe: a new approach to management with a review of 68 cases. *Ann Otol Rhinol Laryngol* 1994; **103**: 879–84.
10 Blanco-Dávila F, Vásconez HC. The cleft earlobe: a review of methods of treatment. *Ann Plast Surg* 1994; **33**: 677–80.
11 Fayman MS. Split earlobe repair. *Br J Plast Surg* 1994; **47**: 293.
12 Lawrence CM. The treatment of chondrodermatitis nodularis with cartilage removal alone. *Arch Dermatol* 1991; **127**: 530–5.
13 Lawrence CM. Surgical treatment of chondrodermatitis nodularis. In: Robinson JK, Arndt KA, LeBoit PE, Wintroub BU, eds. *Atlas of Cutaneous Surgery*. Philadelphia: Saunders 1996: 201–6.
14 Rajan N, Langtry JA. The punch and graft technique: a novel method of surgical treatment for chondrodermatitis nodularis helicis. *Br J Dermatol* 2007; **157**: 744–7.
15 Dawber RPR, Sonnex T, Leonard J, Ralfs I. Myxoid cysts of the finger: treatment by liquid nitrogen spray cryosurgery. *Clin Exp Dermatol* 1983; **8**: 153–7.
16 de Berker D, Lawrence C. Ganglion of the distal interphalangeal joint (myxoid cyst): therapy by identification and repair of the leak of joint fluid. *Arch Dermatol* 2001; **137**: 607–10.
17 Lawrence CM. Skin excision is not required in the surgical treatment of digital myxoid cysts. *Br J Dermatol* 2002; **147** (Suppl. 62): 30.
18 Wollina U, Karamfilov T, Konrad H. High-dose botulinum toxin type A therapy for axillary hyperhidrosis markedly prolongs the relapse-free interval. *J Am Acad Dermatol* 2002; **46**: 536–40.
19 Wen-Horng Wu, Sheih Ma, Jin-Teh Lin *et al*. Surgical treatment of axillary osmidrosis: analysis of 343 cases. *Plast Reconstr Surg* 1994; **94**: 288–94.
20 Hurley HJ, Shelley WB. Axillary hyperhidrosis: clinical features and local surgical management. *Br J Dermatol* 1966; **78**: 127–40.
21 Lawrence CM, Lonsdale Eccles AA. Selective sweat gland removal with minimal skin excision in the treatment of axillary hyperhidrosis: a retrospective clinical and histological review of 15 patients. *Br J Dermatol* 2006; **155**: 115–8.
22 Bechara FG, Sand M, Tomi NS *et al*. Repeat liposuction-curettage treatment of axillary hyperhidrosis is safe and effective. *Br J Dermatol* 2007; **157**: 739–43.
23 Drott C, Göthberg G, Claes G. Endoscopic transthoracic sympathectomy: an efficient and safe method for the treatment of hyperhidrosis. *J Am Acad Dermatol* 1995; **33**: 78–81.
24 Lin TS, Fang HY. Transthoracic endoscopic sympathectomy in the treatment of palmar hyperhidrosis: with emphasis on perioperative management (1360 case analyses). *Surg Neurol* 1999; **52**: 453–7.
25 Byrne J, Walsh TN, Hederman WP. Endoscopic transthoracic electrocautery of the sympathetic chain for palmar and axillary hyperhidrosis. *Br J Surg* 1990; **77**: 1046–9.
26 Nicholson ML, Hopkinson BR, Dennis MJS. Endoscopic transthoracic sympathectomy: successful in hyperhidrosis but can the indications be extended? *Ann R Coll Surg Engl* 1994; **76**: 311–4.
27 Gordon A, Colin J. Treating hyperhidrosis. *BMJ* 1993; **306**: 1752.
28 Schnider P, Moraru E, Kittler H *et al*. Treatment of focal hyperhidrosis with botulinum toxin type A: long-term follow-up in 61 patients. *Br J Dermatol* 2001; **145**: 289–93.

Cryosurgery

Various methods for freezing skin lesions have been described [1]. These achieve the following minimum temperatures: salt–ice mixture (–20°C), carbon dioxide snow (–79°C), dimethyl ether and propane (Histofreezer) (–50°C), nitrous oxide (–70°C) and liquid nitrogen (–196°C). Because of its very low temperature, liquid nitrogen works faster than other methods. It is also easy to use, inexpensive and readily available. Liquid nitrogen is therefore the most widely used cryotherapy agent. All significant studies of cryotherapy technique have used liquid nitrogen and it is the only agent discussed in this chapter. The effectiveness and freeze times of other cryogens have not been established.

Cryotherapy is believed to cause cell death in four ways.

1 Ice crystals formed in the cell damage cellular components [2]
2 Uneven intracellular ice formation during freezing leads to osmotic differences arising during thawing, which in turn causes cell disruption
3 Cold injury to small blood vessels results in ischaemic damage
4 Immunological stimulation produced by the release of antigenic components results in cell damage

The extent of injury is determined by the rate of freezing, the coldest temperature reached, the freeze time and the rate of thawing. Maximum damage is produced by rapid freezing and slow thawing. Repeating the freeze–thaw cycle produces much greater tissue damage than a single freeze because the greater conductivity of the previously frozen skin and the already impaired circulation both allow a greater and faster depth of cold penetration.

It is suggested that a temperature of –30°C is required to produce cell death. In practice tissue temperatures achieved during cryotherapy do not need to be measured because clinical studies have determined the duration of liquid nitrogen spray freeze times for common skin conditions.

Clinical methods

Liquid nitrogen is best stored in a pressurized container to reduce evaporative loss and the canister kept in a secure, ventilated, outside area. One litre of liquid nitrogen held in an unsealed vacuum flask will last approximately 6 hours. Liquid nitrogen can be applied using cotton-wool swabs dipped into the liquid. However, a liquid nitrogen spray can is easier to direct accurately, faster and more convenient.

Clinical uses

Liquid nitrogen cryotherapy has been used to treat a wide range of skin lesions (Table 77.5) [3]. The simplicity and speed of cryosurgery treatment is both a strength and a weakness. Cryotherapy can easily be done incorrectly and ineffectively. The correct technique and freeze times are required to produce results similar to those described in published studies [4].

Cryosurgical treatment of basal cell epitheliomas gives cure rates that compare favourably with other modes of therapy [5–7] provided the correct technique is used and the treatment limited to small (<20 mm), well-defined, previously untreated tumours, avoiding BCCs on the inner canthus of the eye, nasolabial and retro-auricular folds and the hair-bearing scalp. The temperature reached and the number of freeze–thaw cycles are also critical. Debulking the tumour using curettage or electrosurgery prior to cryotherapy is advocated by some authors [8,9]. However, lower leg Bowen's disease is best treated by curettage, which is superior to cryotherapy [10], which in turn is superior to radiotherapy [11].

Side effects [1]

Cryotherapy pain is significant but usually transient, and tissue swelling is common. Inflammation can be reduced with potent topical steroid applications [12]. Haemorrhagic blisters may occur but blister formation is not necessary for the cure of lesions such as viral warts. Sun-damaged and senile atrophic skin, and areas previously treated with topical steroids or X-irradiation, are more

Table 77.5 Skin conditions responsive to cryosurgery [3,13].

Naevi	Pigmented
	Epidermal
Lentigo	Benign
Vascular lesions	Telangiectasia
	Spider naevus
	Pyogenic granuloma
	Pseudopyogenic granuloma
	Kaposi's sarcoma
	Haemangioma
	Lymphangioma
Keratotic and preneoplastic	Viral warts
	Molluscum contagiosum
	Seborrhoeic keratosis
	Solar keratosis
	Cutaneous horn
	Keratoacanthoma
	Bowen's disease
Carcinoma [5–7]	Basal cell epithelioma
	Squamous cell epithelioma
	Lentigo maligna
Cysts	Epidermal
	Synovial
	Acne
	Mucous cyst
Leukoplakia	
Axillary hyperhidrosis	
Scarring	Keloid
	Acne (carbon dioxide snow, acetone 'slush')
Sebaceous hyperplasia	
Rhinophyma	

likely to blister or become necrotic after freezing. Skin necrosis is a desirable part of the treatment of neoplastic and many preneoplastic lesions, and several weeks may elapse before healing is complete. Hypopigmentation is common after liquid nitrogen cryosurgery, is particularly noticeable in dark-skinned patients and may be permanent [2,13]. Temporary post-inflammatory hyperpigmentation is to be expected following less severe freezing. Nerve damage resulting in paraesthesiae, distal anaesthesia and motor paralysis occasionally occurs [14]. Similarly, deep freezing over the lacrimal ducts may, very rarely, lead to permanent ductal obstruction [1].

References

1 Dawber R, Colver G, Jackson A, Pringle F. *Cutaneous Cryosurgery. Principles and Clinical Practice*. London: Martin Dunitz; 1997.
2 Dawber RPR. Cold kills! *Clin Exp Dermatol* 1988; **13**: 137–50.
3 Kuflik EG. Cryosurgery updated. *J Am Acad Dermatol* 1994; **31**: 925–44.
4 McKenna DB, Cooper EJ, Kavanagh GM *et al*. Amelanotic malignant melanoma following cryosurgery for atypical lentigo maligna. *Clin Exp Dermatol* 2000; **25**: 600–4.
5 Kuflik EG, Gage AA. The 5 year cure rate achieved by cryosurgery for skin cancer. *J Am Acad Dermatol* 1991; **24**: 1002–4.
6 Torre D. Cryosurgery of basal cell carcinoma. *J Am Acad Dermatol* 1986; **5**: 917–29.
7 Holt PJA. Cryotherapy for skin cancer: results over a 5 year period using liquid nitrogen spray cryosurgery. *Br J Dermatol* 1988; **119**: 231–40.
8 Conclaves JC, Martins C. Debulking of skin cancers with radio frequency before cryosurgery. *Dermatol Surg* 1997; **23**: 253–6.
9 Nordic P. Curettage-cryosurgery for non-melanoma skin cancer of the external ear: excellent 5-year results. *Br J Dermatol* 1999; **140**: 291–3.
10 Ahmed I, Berth-Jones J, Charles-Holmes S *et al*. Comparison of cryotherapy with curettage in the treatment of Bowen's disease: a prospective study. *Br J Dermatol* 2000; **143**: 759–66.
11 Cox NH, Dyson P. Wound healing on the lower leg after radiotherapy or cryotherapy of Bowen's disease and other malignant skin lesions. *Br J Dermatol* 1995; **133**: 60–5.
12 Hinds TC, Spire J, Scott LV. Clobetasol propionate ointment reduces inflammation after cryotherapy. *Br J Dermatol* 1985; **112**: 599–602.
13 Graham GF, Deltas RL, Garrett AB *et al*. Guidelines of care for cryosurgery. *J Am Acad Dermatol* 1994; **31**: 648–53.
14 Faber WR, Naafs B, Sillevis Smitt JH. Sensory loss following cryosurgery of skin lesions. *Br J Dermatol* 1987; **117**: 343–7.

Curettage

Curettage is only possible when the curetted material is more fragile than normal skin (e.g. BCC), or there is a natural cleavage plane (e.g. seborrhoeic wart) between the lesion and the surrounding skin. On mobile or fragile skin areas, a starting point for curettage can be made by fulgurizing the rim using an electrosurgery machine. Stop bleeding using either a chemical haemostatic agent (e.g. aluminium chloride 30% in isopropyl alcohol), cautery or electrodesiccation. Do not use alcohol-based skin-cleansing solutions for the latter because of the fire risk. The resulting partial-thickness wound heals by re-epithelialization from the retained adnexal epithelium.

Benign lesions

Curettage of viral warts is sometimes effective. Treatment is painful and there is a risk of scarring and recurrence. Solitary warts on the face of adults can usually be removed by curettage, otherwise viral warts should only be curetted off when other methods have failed. Curettage is probably justifiable in painful plantar warts that have not responded to other therapies. Nerve block anaesthesia may be required [1] and there is a risk of painful scar formation. Peri- and subungual warts are difficult to curette off; the nail may have to be partially removed to allow adequate curettage. Genital or perianal warts that have not responded to cryotherapy, podophyllin or imiquimod can be curetted off. Seborrhoeic warts can be treated by cryotherapy or curetted off. In contrast, pyogenic granulomas (Fig. 77.25) and hypertrophic or solitary actinic keratoses (Fig. 77.26) are best treated using curettage, as this permits histological confirmation.

Non-melanoma skin cancers

The technique is the same for both BCC and SCC (Fig. 77.27). Tense the anaesthetized skin around the lesion and scrape off the bulk of the tumour using a small, sharp curette [2]. Beware of differences in technique required when using a disposable sharp curette rather than a reusable curette. The sharp side of a disposable curette is sharp enough to slice through the underlying dermis. A fragmented specimen should be mounted on a small piece of paper, where it is allowed to congeal, before being dropped



(a)



(b)



(c)

Fig. 77.25 (a–c) Curettage and electrodesiccation of a large pyogenic granuloma on the palmar aspect of the middle finger.

into formalin. In this way the pathologist receives a single sample rather than multiple small floating fragments. Cauterize, using a hot wire with a beaded tip, or electrodesiccate the wound surface. Repeat the curettage using a smaller curette to search for residual pockets of tumour. At this stage the curette will be scraping against the normal dermis and less material will be removed. Repeat the cautery or electrodesiccation. A third cycle of curettage and cautery is required if a large amount of material is removed at the second stage. The histological specimen only confirms the diagnosis; it provides no indication about the adequacy of treatment. Do not curette recurrent tumours because of the high recurrence rates [3]. If the curette penetrates the dermis and enters fat, curettage should be abandoned as it is impossible to distinguish between soft tumour tissue and the underlying fat; if this happens the curette site will need to be excised down to and including fat. Perforation of the dermis is particularly likely to occur if an incisional biopsy has been taken prior to treatment.

Basal cell carcinoma (BCC)

Curettage of BCCs depends on the tumour being easier to scrape off than the surrounding normal tissue. Thus, if strands of fibrous tissue separate clumps of tumour (as occurs in morphoeic, infiltrative, recurrent or invasive BCCs) or the adjacent skin tears easily, cannot be tensed or hair roots impede curettage, the results will be poor and curettage should be avoided. High recurrence rates occur after curettage of recurrent [3], morphoeic [4] or large tumours [4,5], or treatment by inexperienced operators [6] (Table 77.6). When small [4–8] (less than 20 mm diameter), non-recurrent tumours [3,9,10] on suitable sites (Table 77.7) are curetted by experts [6,11], the 5-year cure rate is 95% or better (Table 77.8). Cautery and electrodesiccation can be used interchangeably and their use improves cure rates [12]. Paradoxically, despite these high cure rates, histological examination after curettage and electrodesiccation shows that some residual tumour is present in almost 30% of cases [13,14]. Thus, cure must also depend on other factors, such as residual tumour cell mass, inflammatory reaction and healing responses.

Squamous cell carcinoma (SCC)

Experience shows [8,10,15] that well-differentiated, primary, slow-growing SCCs arising on sun-exposed sites can be cured by curettage and cautery (Table 77.9). However, SCCs with a higher risk of recurrence or metastasis should not be treated by curettage. These high-risk SCCs include lesions arising on scars, ears, lips, areas of radiation or thermal injury, chronic ulcers or sinuses, Bowen's disease and non-sun-exposed sites; and large (>20 mm), thick (>4 mm), poorly differentiated and recurrent SCCs or those arising in an immune compromised patient [16,17].

Intraepidermal carcinoma (Bowen's disease)

Intraepidermal carcinoma, especially on the lower leg, heals better after curettage than cryotherapy [18], presumably because the depth of tissue destruction is more easily determined by the operator. Radiotherapy, excision, topical 5-fluorouracil and imiquimod [19] are all alternatives.



Fig. 77.26 Curettage and cautery of an actinic keratosis. (a) After local anaesthetic injection, this hyperkeratotic actinic keratosis was (b) curetted off and (c) the wound cauterized. (d) At 4 months the wound had healed leaving a barely visible scar.

References

1 Eriksson E. *Illustrated Handbook in Local Anaesthesia*, 2nd edn. Philadelphia: WB Saunders, 1980: 112–4.

2 Bennett RG. *Fundamentals of Cutaneous Surgery*. St Louis: Mosby, 1988: 536–43.

3 Menn H, Robins P, Knopf AW, Bart RS. The recurrent basal cell epithelioma: a study of 100 cases of recurrent retreated basal cell epithelioma. *Arch Dermatol* 1971; **103**: 628–31.

4 Sweet RD. The treatment of basal cell carcinoma by curettage. *Br J Dermatol* 1963; **75**: 137–48.

5 Dubin N, Kopf AW. Multivariate risk score for recurrence of cutaneous basal cell carcinomas. *Arch Dermatol* 1983; **119**: 373–7.

6 Kopf AW, Bart RS, Schrager D *et al*. Curettage-electrodesiccation treatment of basal cell carcinoma. *Arch Dermatol* 1977; **113**: 439–43.

7 Spiller WF, Spiller RF. Treatment of basal cell carcinoma by curettage and electrodesiccation. *J Am Acad Dermatol* 1984; **11**: 808–14.

8 Knox JM, Freeman RG, Duncan WC, Heaton CL. Treatment of skin cancer. *South Med J* 1967; **60**: 241–6.

9 Simpson JR. The management of rodent ulcers by curettage and cauterisation. *Br J Dermatol* 1966; **78**: 147–8.

10 Tromovitch TA. Skin cancer. Treatment by curettage and desiccation. *Calif Med* 1965; **103**: 107–8.

11 Williamson GS, Jackson R. Treatment of basal cell carcinoma by electrodesiccation and curettage. *Can Med Assoc J* 1962; **86**: 855–62.

12 Reymann F. Treatment of basal cell carcinoma of the skin with curettage. II. A follow-up study. *Arch Dermatol* 1973; **108**: 528–31.

13 Salasche SJ. Curettage and electrodesiccation in the treatment of mid-facial basal cell epithelioma. *J Am Acad Dermatol* 1983; **8**: 496–503.

14 Edens BL, Bartlow GA, Haghigi P *et al*. Effectiveness of curettage and electrodesiccation in the removal of basal cell carcinoma. *J Am Acad Dermatol* 1983; **9**: 383–8.

15 Freeman RG, Knox JM, Heaton CL. The treatment of skin cancer. A statistical study of 1,341 skin tumours comparing results obtained with irradiation, surgery and curettage followed by electrodesiccation. *Cancer* 1964; **17**: 535–8.

16 Rowe DE, Carroll RJ, Day CL. Prognostic factors for local recurrence, metastasis, and survival rates in squamous cell carcinoma of the skin, ear and lip. *J Am Acad Dermatol* 1992; **26**: 976–90.

17 Motley R, Kersey P, Lawrence C. Multiprofessional guidelines for the management of the patient with primary cutaneous squamous cell carcinoma. *Br J Dermatol* 2002; **146**: 18–25.

18 Ahmed I, Berth-Jones J, Charles-Holmes S *et al*. Comparison of cryotherapy with curettage in the treatment of Bowen's disease: a prospective study. *Br J Dermatol* 2000: **143**; 759–66.

19 Rosen T, Harting M, Gibson M. Treatment of Bowen's disease with topical 5% imiquimod cream: retrospective study. *Dermatol Surg* 2007; **33**: 427–31.

20 Lawrence CM. *An Introduction to Dermatological Surgery*, 2nd edn. St Louis: Mosby, 2002: 67–74.

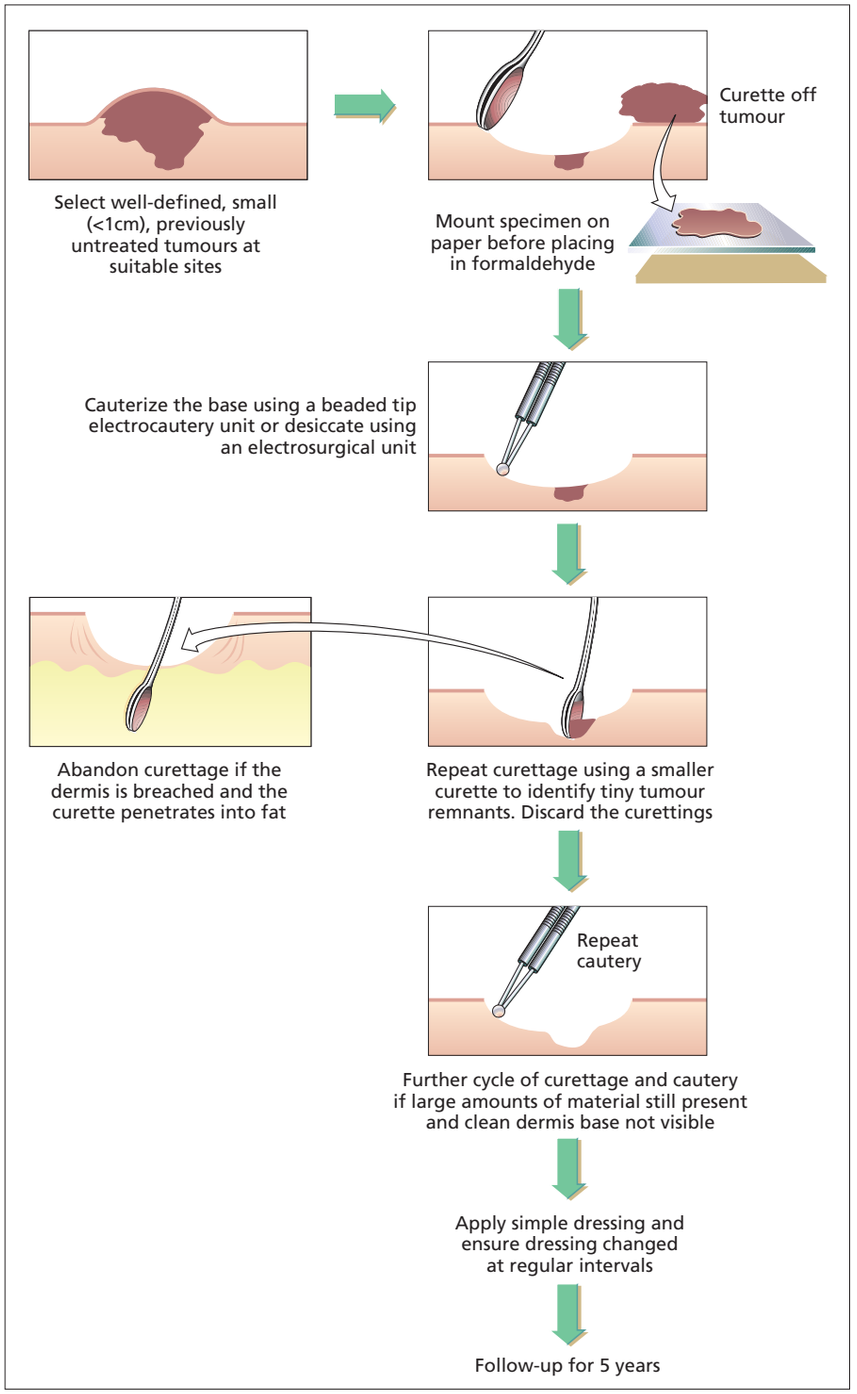


Fig. 77.27 Schematic diagram of the stages of curettage and cautery of a basal cell carcinoma. (From Lawrence [20].)

Table 77.6 Types of basal cell carcinoma (BCC) that should not be treated by curettage.

Large tumours (≥2 cm diameter)
Tumours at sites where curettage produces a poor cosmetic result, is technically difficult or is associated with a high risk of recurrence
Morphoeic, infiltrating or basisquamous BCCs
Recurrent tumours
Ill-defined tumours
Tumours penetrating muscle, fat, bone, etc.
Tumours where an incisional biopsy has been performed (risk of perforation of the dermal sling)

Table 77.7 Sites to avoid curettage and cautery of basal cell carcinomas.

Sites with a high recurrence rate after all treatment modalities	Sites where curettage is technically difficult	Sites associated with poor cosmesis after curettage
Nose	Lips	Vermilion border
Nasolabial fold	Eyelid	Ala rim
Around the eye	Hair-bearing scalp	Nose tip
Around the ear		Chin
Scalp		

Table 77.8 Cure rates following curettage and cautery and/or electrodesiccation of primary basal cell carcinoma.

Author, year of publication	Number of tumours	Duration of follow-up (years)	Number of recurrences (%)	Tumour size
Simpson [9] 1966	495	2–5	35 (7)	ns
Williamson and Jackson [11] 1962	287	3	22 (7.6)	ns
Knox *et al*. [8] 1967	282	5	4 (1.4)	<20 mm
Sweet [4] 1963	268	≥3	19 (7.1)	<20 mm
Spiller and Spiller [7] 1984	208	5	3 (1.4)	<20 mm
Tromovitch [10] 1965	75	≥5	(4)	ns

ns, not stated.

Table 77.9 Cure rates following curettage and cautery of primary squamous cell carcinoma (SCC).

Author, year of publication	Number of tumours	Duration of follow-up (years)	Percentage cure rate	Metastasis?	Tumour size (number greater and smaller than 2 cm)
Knox *et al*. [8] 1967	213	5	99	No record	185 < 2 cm 28 > 2 cm
Knox *et al*. [8] 1967	545	>1	99	1	495 < 2 cm 50 > 2 cm
Tromovitch [10] 1965	29	5	96.6	Nil	No record
Freeman *et al*. [15] 1964	407	1–5	96–100	Nil	355 < 2 cm 52 > 2 cm

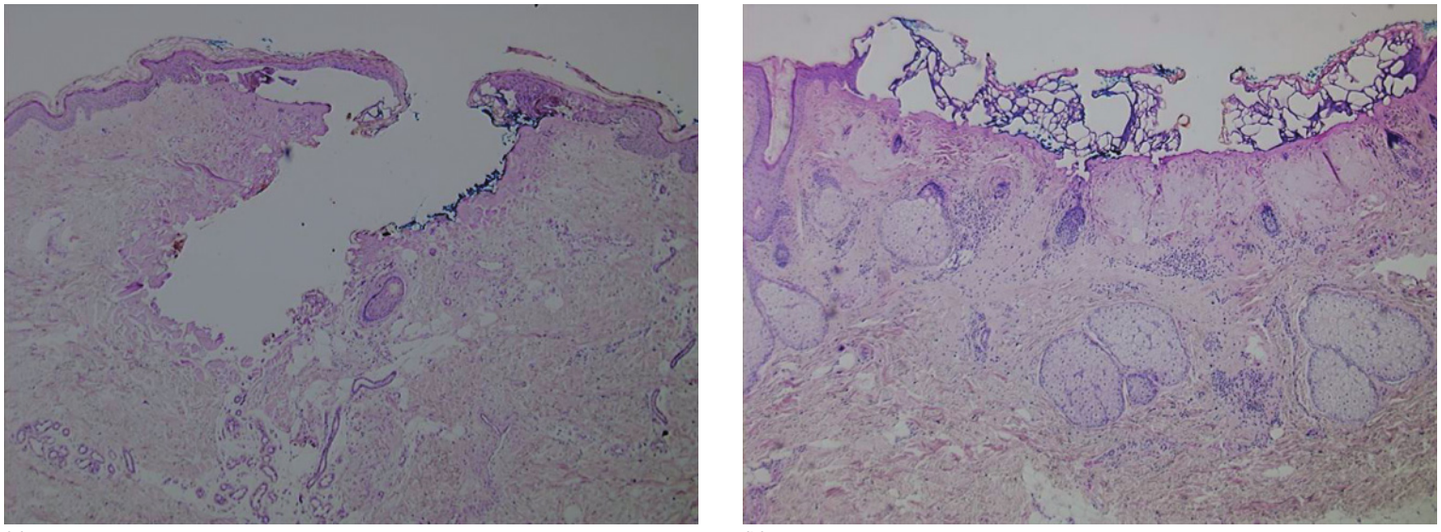
Electrosurgery

Electrosurgery includes electrodesiccation, electrofulguration, cutting diathermy (synonym electrosection, electroresection) and electrolysis [1,2]. Coagulation or tissue destruction is produced by the heat created as the electrical current passes through the tissue. Although not strictly an electrosurgical technique, electrocautery is usually also included because of its development from the age-old method of using heat in the form of hot oils, cautery irons, etc. to control bleeding.

Electrocautery

Synonyms
- Cautery
- Heat cautery
- Hot-wire cautery

The cautery machine power output should be controllable so that the tip temperature can be adjusted rather than being dependent on the battery power. A variety of tips are available. The beaded



(a) (b)

Fig. 77.28 (a) Electrodesiccation. Electrodesiccation occurs when the needle remains in contact with the skin and no spark occurs. The resulting tissue damage is deeper than that produced by electrofulgaration. (b) Electrofulguration. The needle tip is not in contact with the skin. As the spark jumps between the skin and the needle its energy is spread over a greater area, resulting in more superficial tissue damage.

tip is best for haemostasis after curettage and shave biopsy; this should be just hot enough to char a cotton swab, but not red hot as the platinum tip may melt. If the beaded tip drags on the tissue as it is drawn across the wound, the tip temperature is too low. After use, any remaining debris should be burnt off by briefly allowing the tip to glow red hot. The needle-like end of the cold point cautery tip is heated, by conduction, via a wire coil, and, before the advent of lasers, was used to treat spider naevi. The flat blade can be used for pedunculated lesions or shave excisions, but has to be glowing red hot to cut through tissue, producing a heating artefact on the excised material. Furthermore, the red-hot blade has to be quickly passed through the skin to avoid excessive heat damage at the wound site, so the direction and depth of the cut cannot be adjusted easily and the blade may accidentally cut or burn deeper into the tissue than required.

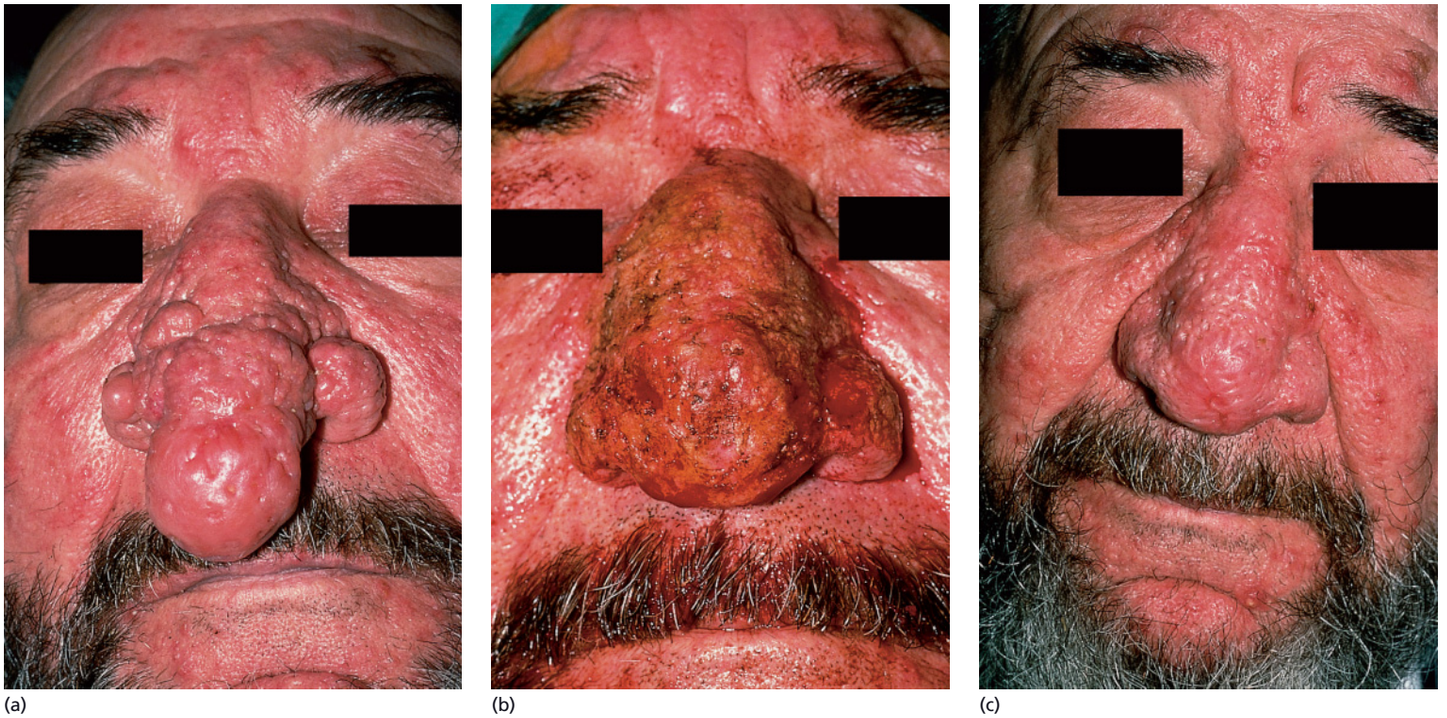
Electrosurgery

Synonyms
- Surgical diathermy
- Cold electrocautery

Waveform. Electrosurgical equipment converts domestic alternating current into high-frequency alternating current. When this passes through a high-resistance medium, such as the skin, heat is produced, resulting in tissue coagulation, desiccation or cutting, depending on the electrical waveform. A highly damped waveform (i.e. intermittent pulses of electrical discharge separated by intervals of zero voltage) results in electrodesiccation/fulguration. In contrast, a continuous waveform produces a cutting effect and a moderately damped or blended waveform (i.e. a mixture of continuous and highly damped waveforms) chiefly produces coagulation [3].

Unipolar/monoterminal/bipolar diathermy. Apart from the waveform produced, electrosurgery equipment also varies in the way the current is discharged and collected. Unipolar (monopolar) current is delivered via an active electrode, usually a needle or ball tip, resulting in a high concentration of current at the electrode tip. The current disperses through the patient's body and is collected via a dispersive (synonym indifferent, passive, return, earthing, ground) electrode with a large surface area. The current density falls with increasing distance from the active electrode and there is minimal risk of tissue damage as the current is collected over the large area of the dispersive electrode. If, due to faulty application or equipment, there is only a small area of skin/electrode contact, a burn may occur at the dispersive electrode. Also, if the current is channelled at narrow points along its path, for example the finger, an area of high-current density leading to tissue damage can occur. Bipolar electrodes avoid these hazards by producing and collecting the current using forceps so that current only travels in the tissue held between the tips. Monoterminal electrosurgical equipment (e.g. Birtcher Hyfrecator) produces a high-voltage, low-amperage current, and is designed to be used without a dispersive electrode. There is, however, a risk of a small but painful discharge occurring between the patient and the operator or other earthed point, for example the metal edge of an electrically insulated couch [4]. This can be prevented by maintaining a large area of skin contact between the operator and patient during use, or using a dispersive electrode.

Electrodesiccation/electrofulguration. These effects are produced using a monoterminal or unipolar electrode. Electrodesiccation (Fig. 77.28a) occurs when the needle remains in contact with the skin and no spark occurs. Because the current concentration is greater at the point of contact, the tissue damage is deeper compared with electrofulguration (Fig. 77.28b). During the latter,



(a) (b) (c)

Fig. 77.29 Shave excision and electrosurgery of a rhinophyma. (a) This disfiguring rhinophyma was reduced in size and (b) the nose shape recreated by shave excision and electrodesiccation of the bleeding surface under local anaesthetic, (c) resulting in an acceptable cosmetic result at 4 months.

the needle tip is not in contact with the skin and a spark jumps between the skin and the needle, but its energy is spread over a greater area. The resulting heat causes superficial damage to the tissues and is an effective way of stopping bleeding. Various needle tips have been developed for specific circumstances [5]. Because of the risk of virus transmission, a different, clean needle must be used for each patient [6].

Pacemakers and electrosurgery

There are reports of electrosurgery interfering with pacemaker function and causing temporary asystole if there is no underlying cardiac rhythm, or a demand pacemaker to switch to a fixed-rate mode [7]. The effect lasts only as long as the unit is being operated. When diathermy finishes, the pacemaker reverts to normal function. There are also anecdotal reports of the pacemaker failing shortly after electrosurgery [8]. Only pre-1990 pacemakers seem to be vulnerable, and modern pacemakers are considered to be resistant to these problems. All types of electrosurgical equipment, except cautery, can in theory cause problems, although bipolar diathermy is the least hazardous. When treating a patient with a pacemaker, short treatment bursts (less than 5 s) should be used, and diathermy should not be performed within 15 cm of the heart, the pacemaker or its leads. If considered necessary, the patient's heart rate can be monitored, and resuscitation equipment should be available. If monopolar diathermy has to be used, the path from the active electrode (diathermy tip) to the dispersive electrode should be at least 15 cm from the heart, the pacemaker and its leads.

Spider naevi

Spider naevi are probably best treated using a pulsed dye laser. They can also be destroyed using cold point cautery or electrodesiccation, but with greater risk of scarring.

Xanthelasma

Electrodesiccation and curettage of xanthelasma is relatively simple. The anaesthetized skin overlying the xanthelasma is fulgurized and disrupted. The underlying fatty deposits can be electrodesiccated, scraped off using a sharp curette, and left to heal by second intention. Trichloroacetic acid and ablative laser therapy can also be used.

Small seborrhoeic and plane warts

Eyelid seborrhoeic warts can be softened and removed by electrodesiccation provided the anaesthetized eyelid margin is pulled away to prevent conjunctival damage.

Surgical paring and electrofulguration of rhinophyma

Cutting diathermy (synonym electrosection) using a unipolar diathermy and dispersive plate is particularly useful for treatment of rhinophyma, where bleeding can be a problem [9]. Re-epithelialization takes place, with surprisingly little scarring, from the abundant pilosebaceous follicles which remain in the dermis (Fig. 77.29). Carbon dioxide laser resection is also effective.

References

1 Jackson R. Basic principles of electrosurgery. A review. *Can J Surg* 1970; **13**: 354–61.

2 Elliott JA. Electrosurgery. Its use in dermatology with a review of its development and technologic aspects. *Arch Dermatol* 1966; **94**: 340–9.
3 Boughton RS, Spencer SK. Electrosurgical fundamentals. *J Am Acad Dermatol* 1987; **16**: 862–7.
4 Sebben JE. Patient 'grounding'. *J Dermatol Surg Oncol* 1988; **14**: 926–31.
5 Sebben JE. Modifications of electrosurgery electrodes. *J Dermatol Surg Oncol* 1992; **18**: 908–12.
6 Sheretz EF, Davis GL, Rice RW *et al*. Transfer of hepatitis B virus by contaminated reusable needle electrodes after electrodesiccation in simulated use. *J Am Acad Dermatol* 1986; **15**: 1242–6.
7 Sebben JE. Electrosurgery and cardiac pacemakers. *J Am Acad Dermatol* 1983; **9**: 457–63.
8 Wajszczuk WJ, Mowry FM, Dugan NL. Deactivation of a dermal pacemaker by transurethral electrocautery. *N Engl J Med* 1969; **280**: 34–5.
9 Greenbaum SS, Krull EA, Watnick K. Comparison of CO_2 laser and electrosurgery in the treatment of rhinophyma. *J Am Acad Dermatol* 1988; **18**: 363–8.

Infrared coagulation [1–3]

The infrared coagulator produces non-coherent wavelengths in the visible and infrared spectrum of 400–2700 nm from a tungsten halogen bulb. The energy is transmitted along a quartz glass light guide, at the tip of which is a sapphire cap, which is placed in contact with the skin. The heat imparted causes thermal injury to a depth dependent on the duration of exposure, which can be set on an automatic timer and varied from 0 to 1.5 s, for example a 1-s exposure will remove tissue to a depth of approximately 0.75 mm.

The major characteristics are:

1 Non-laser radiation of maximum output 960 nm (near infrared)
2 Tungsten halogen bulb power source—15 V, 150 W
3 Pulsed energy
4 Solid quartz glass light guide
5 Diameter of treated area 2–10 mm, the larger diameters enabling more rapid treatment
6 Sapphire cap to light guide—sapphire is transparent to near infrared but rapidly conducts away heat generated in the upper dermis
7 Minimum optical hazard—the appearance of bright visible radiation causes aversion of the eyes if it is pointing in their direction, thus preventing infrared damage
8 It is portable, and relatively cheap.

It has been used mainly for tattoos [1], a variety of superficial vascular lesions [2], warts and myxoid cysts of the digit. Tattoos [1] can be treated with remarkably little morbidity. The area to be treated is mapped into overlapping circles similar in diameter to the sapphire tip, and each circle is treated with a pulsed exposure of approximately 1.25 s. An ice cube applied to the skin for 5 s before and after treatment is used to minimize conducted heat damage to surrounding skin. The immediate appearance of the coagulated tissue is white and slightly contracted; the eschar that develops over several days drops off in 2–3 weeks. Serous exudate, pain and swelling during the healing phase are generally insignificant.

Telangiectasia, port-wine stains and angioma serpiginosum have been treated using short exposure times, for example 0.75–0.875 s (also with ice). It is evidently less specific and probably less effective, with a greater risk of scarring, than an appropriate laser.

References

1 Colver GB, Cherry GW, Dawber RPR, Ryan TJ. Tattoo removal using infra-red coagulation. *Br J Dermatol* 1985; **112**: 481–5.
2 Colver GB, Cherry GW, Dawber RPR, Ryan TJ. Infra-red coagulation for removing tattoos and vascular naevi. *Br J Dermatol* 1984; **111** (Suppl. 26): 27.
3 Burge S, Colver GB, Rayment R. *Simple Skin Surgery*, 2nd edn. Oxford: Blackwell Science, 1996: 69–70.

Caustics

In experienced hands, caustics provide a simple and readily available means of destroying many superficial skin lesions. The operator should be well acquainted with the action and degree of penetration of individual caustics, and the toxic effects that may result from absorption, especially if they are to be used on large areas, and particularly when applied to the face [1,2]. In treating individual lesions, caustics are usually applied by means of a cotton-bud applicator or a wool-tipped orange stick, pointed if necessary.

Aluminium chloride hexahydrate

A 20% solution (Drichlor; Anhydrol Forte), usually applied on a cotton-bud, is a very useful styptic for superficial wounds such as those following shave excision. Ferric subsulphate (Monsel's solution) is widely used, but may leave a pigmented scar.

Silver nitrate [3]

This is used in the form of a pencil or as a strong solution to suppress exuberant granulation. It is haemostatic and may be used to arrest bleeding after curettage. Repeated use tends to lead to unsightly staining of the skin.

Phenol (liquefied phenol)

This is a valuable superficial caustic, which should, however, be used cautiously. It should not be diluted as this increases its absorption and potency [4,5], and thus also its nephrotoxicity. Ochronosis may occur from prolonged absorption. It is not a haemostatic, and bleeding limits its effectiveness. When used as a treatment for ingrown toenails it is important that the phenol is applied to a 'dry' nailbed and that sufficient time is allowed for it to take effect [6].

Potential toxicity and cardiac arrhythmias remain a major concern, especially with more extensive use, and it should not be used during pregnancy. Phenol is also used in a soap/croton oil/water mix for chemical face peels (Chapter 80). A glycol-spirit solution can be used for neutralization if required.

Trichloroacetic acid

This is an effective haemostatic caustic, which has many uses. The 30–50% concentration can be used as a styptic, and is frequently employed in conjunction with superficial curettage in the treatment of solar keratoses, seborrhoeic warts, etc. The supersaturated solution can also be used on its own to treat many benign and

dysplastic skin lesions. Trichloroacetic acid 50% is similar to phenol in its destructive effect on the epidermis.

Trichloroacetic acid may be a useful treatment for xanthelasmata and solar lentigos. It must be applied with great care, however, especially around the eyes. Its action is rapid, and a white 'frosting' occurs within a few seconds of application. The caustic action can be partially neutralized by applying alcohol, water or sodium bicarbonate-soaked gauze, but this is unlikely to have any effect once the acid has penetrated the skin.

Excess sebum should first be removed using detergent, ether or acetone. Trichloroacetic acid should then be applied with an 'almost dry' cotton applicator. The concentration to be used will vary according to site, the condition to be treated and whether the trichloroacetic acid is being used as a styptic or a superficial skin caustic. Weaker solutions of trichloroacetic acid are sometimes used for treating wider areas of skin (Chapter 80). Because of deliquescence, trichloroacetic acid should be kept in a closed, coloured and corrosion-resistant bottle.

Dichloroacetic acid

This is also a powerful caustic and skin styptic.

Monochloroacetic acid

This should not be considered as a superficial caustic. It penetrates rapidly and may remove the whole epidermis by blister formation. It may be used for mosaic warts, and can also be used for resistant periungual warts.

References

1 Brody HJ. *Chemical Peeling*. St Louis: Mosby Year Book, 1992.
2 Rubin MG. *Manual of Chemical Peels, Superficial and Medium Depth*. Philadelphia: JB Lippincott, 1995.
3 Jarson PO. Topical hemostatic agents for dermatologic surgery. *J Dermatol Surg Oncol* 1988; **14**: 623–32.
4 Conning DM, Hayes MJ. The dermal toxicity of phenol. *Br J Ind Med* 1970; **27**: 155–9.
5 Truppmann ES, Ellenberg JD. Major ECG changes during chemical facial peeling. *Plast Reconstr Surg* 1979; **63**: 44–8.
6 Frumkin A. Phenol cauterisation of nail matrix remnants. *J Dermatol Surg Oncol* 1987; **13**: 1324–5.

Intralesional therapy

Intralesional triamcinolone [1]

Aqueous suspensions of triamcinolone acetonide (10 mg/mL [Adcortyl] and 40 mg/mL [Kenalog]) and the less soluble, potentially more therapeutically potent [2], hexacetonide salt (5 and 20 mg/mL [Lederspan]) are available. Both salts can be diluted with saline or lidocaine/lignocaine. Intralesional hydrocortisone acetate (25 mg/mL) can also be used. Triamcinolone acetonide 10 mg/mL is sufficient for all conditions except keloids. The amount injected ranges from 0.1 to 0.5 mL of 10 mg/mL solution, depending on the size and nature of the lesion. The injection should be given using a 27–30-gauge needle deep in the dermis when possible, to minimize the risk of collagen atrophy. The manufacturers recommend that no more than 30 mg of triamcinolone acetonide should be given in one session, with a maximum of 5 mg at any one site. (Steroid equivalence: 5 mg prednisolone = 4 mg triamcinolone = 20 mg hydrocortisone.) Plasma cortisol levels are suppressed for a few days by 20 mg of intralesional triamcinolone acetonide given into various sites; higher doses suppress cortisol levels for longer [3]. Cushing's syndrome has occurred 2–3 weeks after a single treatment with 40 mg triamcinolone acetonide injected into keloids [4]. Local side effects include collagen atrophy [5], hypopigmentation [6], skin necrosis [6], perilymphatic linear depigmented and atrophic streaks [7,8], and telangiectasia [9].

Needleless injection of steroids

Intralesional triamcinolone is also given using a needleless injector (Dermojet or Portojet). The injection is slightly less painful than using a needle, but is principally employed because the injections can be delegated and given quickly [10]. Beware of the risk of intraocular injection if this technique is used around the eye [11]. Dose-for-dose, needleless injection of steroid appears to be less effective than needle injection, probably because some steroid solution spills onto the skin.

Uses

Intralesional triamcinolone therapy is used for inflammatory acne cysts, lichen planus, lichen simplex, lupus erythematosus [12], chondrodermatitis [13], orofacial granulomatosis [14], granuloma annulare, psoriasis and nail psoriasis [15], alopecia areata and many other steroid-responsive conditions [16].

References

1 Callen JP. Intralesional corticosteroids. *J Am Acad Dermatol* 1981; **4**: 149–51.
2 Porter D, Burton JL. A comparison of intralesional triamcinolone hexacetonide and triamcinolone acetonide in alopecia areata. *Br J Dermatol* 1971: **85**: 272–3.
3 Potter RA. Intralesional triamcinolone and adrenal suppression in acne vulgaris. *J Invest Dermatol* 1971; **57**: 364–70.
4 Teelucksingh S, Balkaran B, Ganeshmoorthi A, Arthur P. Prolonged childhood Cushing's syndrome secondary to intralesional triamcinolone acetonide. *Ann Trop Paediatr* 2002; **22**: 89–91.
5 Krusche T, Worret WI. Mechanical properties of keloids in vivo during treatment with intralesional triamcinolone acetonide. *Arch Dermatol Res* 1995; **287**: 289–93.
6 Jarratt MT, Spark RF, Arndt KA. The effects of intradermal steroids on the pituitary-adrenal axis and the skin. *J Invest Dermatol* 1974; **62**: 463–6.
7 Kikuchi I, Horikawa S. Perilymphatic atrophy of the skin: a side effect of topical corticosteroid injection therapy. *Arch Dermatol* 1974; **109**: 558–9.
8 Gupta AK, Rasmussen JE. Peri-lesional linear atrophic streaks associated with intralesional corticosteroid injections in a psoriatic plaque. *Pediatr Dermatol* 1987; **4**: 259–60.
9 Schetman D, Hambrick GW, Wilson CE. Cutaneous changes following local injection of triamcinolone. *Arch Dermatol* 1963; **88**: 820–8.
10 Abell E, Munro DD. Intralesional treatment of alopecia areata with triamcinolone acetonide by jet injector. *Br J Dermatol* 1973; **88**: 55–9.
11 Perry HT, Cohn BT, Nauheim JS. Accidental intra-ocular injection with Dermojet syringe. *Arch Dermatol* 1977; **113**: 1131.
12 Callen JP. Chronic cutaneous lupus erythematosus. Clinical, laboratory, therapeutic and prognostic examination of 62 patients. *Arch Dermatol* 1982; **118**: 412–6.
13 Lawrence CM. The treatment of chondrodermatitis nodularis with cartilage removal alone. *Arch Dermatol* 1991; **127**: 530–5.
14 Sakuntabhai A, MacLeod RI, Lawrence CM. Intralesional steroid injection after nerve block anaesthesia in the treatment of orofacial granulomatosis. *Arch Dermatol* 1993; **129**: 477–80.
15 de Berker D, Lawrence CM. A simplified protocol of steroid injection for psoriatic nail dystrophy. *Br J Dermatol* 1995; **133** (Suppl. 45): 15.

16 Lebwohl M, Heymann WR, Berth-Jones J, Coulson I, eds. *Treatment of Skin Disease—Comprehensive Therapeutic Strategies*. London: Mosby, 2002.

Intralesional therapies for skin malignancies

Intralesional methotrexate is reported to be a painless and effective method of treating keratoacanthoma, with faster than spontaneous resolution [1,2]. Intralesional 5-fluorouracil injections are very painful, but when used for 4–6 weeks destroy small, nodular BCCs [3] and some SCCs [4]. Intralesional interferon-α2b has been used to treat Bowenoid papulosis [5], melanoma [6], BCC [7,8] and SCC [9]. Up to 80% of small, solid or superficial BCCs injected using high-dose therapy appear to resolve, although adverse effects occur in 80% of patients at this dose. In contrast, only a minority of aggressive pattern, invasive BCCs respond [10]. Intralesional interleukin-2 in 1–4 weekly doses produced complete response in 8 of 12 BCC patients treated [11]. Intralesional bleomycin followed by electrical stimulation (electrochemotherapy) has been used for a range of skin tumours, including SCC [12].

References

1 Melton JL, Nelson BR, Stough DB *et al*. Treatment of keratoacanthomas with intralesional methotrexate. *J Am Acad Dermatol* 1991; **25**: 1017–23.
2 Hurst LN, Gan BS. Intralesional methotrexate in keratoacanthoma of the nose. *Br J Plast Surg* 1995; **48**: 243–6.
3 Miller BH, Shavin JS, Cognetta A *et al*. Non-surgical treatment of basal cell carcinomas with intralesional 5-fluorouracil/epinephrine injectable gel. *J Am Acad Dermatol* 1997; **36**: 72–7.
4 Kraus S, Miller BH, Swineheart JM *et al*. Intratumoral chemotherapy with fluorouracil/epinephrine injectable gel: a non-surgical treatment of cutaneous squamous cell carcinoma. *J Am Acad Dermatol* 1998; **38**: 438–42.
5 Gross G, Roussaki A, Schöpf E *et al*. Successful treatment of condylomata acuminata and Bowenoid papulosis with subcutaneous injections of low-dose recombinant interferon alpha. *Arch Dermatol* 1986; **122**: 749–50.
6 Ishihara K, Hayasaka K, Yamazaki N. Current status of melanoma treatment with interferon, cytokines and other biologic response modifiers in Japan. *J Invest Dermatol* 1989; **92**: 326s–8s.
7 Edwards I, Tucker SB, Perednia D *et al*. The effect of an intralesional sustained-release formulation of interferon alpha-2b on basal cell carcinomas. *Arch Dermatol* 1990; **126**: 1029–32.
8 Cornell RC, Greenway HT, Tucker SB *et al*. Intralesional interferon therapy for basal cell carcinoma. *J Am Acad Dermatol* 1990; **23**: 694–700.
9 Edwards L, Berman B, Rapini RB *et al*. Treatment of cutaneous squamous cell carcinoma by intralesional interferon alpha-2b therapy. *Arch Dermatol* 1992; **128**: 1486–9.
10 Stenquist B, Wennberg AM, Gisslén H, Larkö O. Treatment of aggressive basal cell carcinoma with intralesional interferon: evaluation of efficacy by Mohs surgery. *J Am Acad Dermatol* 1992; **27**: 65–9.
11 Kaplan B, Moy RL. Effect of perilesional injections of PEG-interleukin 2 on basal cell carcinoma. *Dermatol Surg* 2000; **26**: 1037–40.
12 Mir LM, Glass LF, Sersa G *et al*. Effective treatment of cutaneous and subcutaneous tumours by electrochemotherapy. *Br J Cancer* 1998; **77**: 2336–42.

Miscellaneous physical procedures

Keloid therapy

Keloids spread beyond the original wound and remain elevated, whereas hypertrophic scars are localized to the injured area and flatten spontaneously with time [1]. Both are commoner in young individuals, African-Caribbeans and at particular sites, especially the central chest, back and posterior neck, followed by the ears, deltoid areas, anterior chest, beard area and the rest of the neck [2,3]. Patients with one keloid, except those on the earlobe [4], are believed to be at risk of further keloids. Many treatments have been suggested, including excision, superficial X-ray therapy (although this may provoke malignant tumours [5]), cryotherapy [6,7], pressure [8,9], ultrasound, laser excision [10], intralesional steroids, interferon-α2b [11] and verapamil [12]. Most reports have claimed partial benefit, few have admitted failure. Despite systemic or local side effects [13], intralesional steroid, in the form of triamcinolone 10–40 mg/mL, injected into the scar every 2–3 weeks, is probably the most effective therapy, particularly for presternal and small keloids. High pressure is required to inject steroids into hard keloids, and a Luer-lock glass or hubless disposable syringe is advised [14].

Pedunculated or easily excised keloids, for example on the earlobe, are best treated by intramarginal excision and pre- and postoperative steroid injection [15]. On the earlobe, part of the skin covering the keloid can be salvaged to cover the defect created by removal of the latter [16]. Most authorities recommend a combination of surgery and triamcinolone injections. Some suggest that triamcinolone should be given before, during and after surgery [4], others use steroids during and after surgery [17], whereas others only use steroids postoperatively, to avoid the risk of wound dehiscence [18]. These authors excise and allow the wound to granulate after injecting the margins with triamcinolone. All agree that triamcinolone 40 mg/mL is usually required. On balance, it seems best to give steroids both intra- and postoperatively—approximately four times at 2- to 3-week intervals, starting 2–3 weeks after suture removal (which should be delayed for 10–14 days because of the risk of steroid-induced wound dehiscence). Freezing the keloid with liquid nitrogen before injection is also said to make triamcinolone injection easier [19]. This, however, may increase the risk of hypopigmentation. With repeated injections it becomes possible to inject more triamcinolone into the keloid, which can be felt to expand slightly as the steroid is injected. Remember that both cryotherapy and triamcinolone injections may produce skin depigmentation [4]. Alternative therapies include topical clobetasol propionate cream or flurandrenolone tape. The latter carries less risk of steroid atrophy of the adjacent skin because only the keloid is covered. Intralesional interferon-α2b appears to reduce keloid size and inhibit collagen production [11]. Intralesional verapamil is said to reduce keloid size [12] by inhibiting proline incorporation into collagen [20]. Silicone gel sheeting is advocated for larger keloids but the evidence that it is effective is not conclusive [21,22].

References

1 Berman B, Bieley HC. Keloids. *J Am Acad Dermatol* 1995; **33**: 117–23.
2 Nemeth AJ. Keloids and hypertrophic scars. *J Dermatol Surg Oncol* 1993; **19**: 738–46.
3 Datubo-Brown DD. Keloids: a review of the literature. *Br J Plast Surg* 1990; **43**: 70–7.
4 Kelly AP. Keloid surgery. In: Robinson JK, Arndt KA, LeBoit PE, Wintroub BU, eds. *Atlas of Cutaneous Surgery*. Philadelphia: WB Saunders, 1996: 241–6.
5 Hoffman S. Radiotherapy for keloids? *Ann Plast Surg* 1982; **9**: 265.
6 Rusciani L, Rossi G, Bono R. Use of cryotherapy in the treatment of keloids. *J Dermatol Surg Oncol* 1993; **19**: 529–34.
7 Shepherd JP, Dawber RP. The response of keloid scars to cryosurgery. *Plast Reconstr Surg* 1982; **70**: 677–9.

8 Nicolai JPA, Bos MY, Bronkhorst FB *et al*. A protocol for the treatment of hypertrophic scars and keloids. *Aesthetic Plast Surg* 1987; **11**: 29–32.
9 Mercer DM, Studd DM. 'Oyster splints' a new compression device for the treatment of keloid scars of the ear. *Br J Plast Surg* 1983; **36**: 75–6.
10 Kantor GR, Wheeland RG, Bailin PL *et al*. Treatment of earlobe keloid with carbon dioxide laser excision: a report of 16 cases. *J Dermatol Surg Oncol* 1985; **11**: 1063–5.
11 Granstein RD, Rook A, Flotte TJ *et al*. A controlled trial of intralesional recombinant interferon gamma in the treatment of keloidal scarring, clinical and histological findings. *Arch Dermatol* 1990; **126**: 1295–302.
12 Lawrence WT. Treatment of earlobe keloids with surgery plus adjuvant intralesional verapamil and pressure earring. *Ann Plast Surg* 1996; **37**: 167–9.
13 Krusche T, Worret WI. Mechanical properties of keloids in vivo during treatment with intralesional triamcinolone acetonide. *Arch Dermatol Res* 1995; **287**: 289–93.
14 Lawrence CM. *An Introduction to Dermatological Surgery*, 2nd edn. Edinburgh: Churchill-Livingstone, 2002.
15 Sharma BC. Keloids: a prospective study of 57 cases. *Med J Zambia* 1980; **14**: 66–9.
16 Salasche SJ, Grabski WJ. Keloids of the earlobes: a surgical technique. *J Dermatol Surg Oncol* 1983; **9**: 552–6.
17 Fewkes JL, Cheney L, Pollack SV. *Illustrated Atlas of Cutaneous Surgery*. Philadelphia: JB Lippincott, 1992: 22.5.
18 Bennett RG. *Fundamentals of Cutaneous Surgery*. St Louis: Mosby, 1988: 716–7.
19 Ceilley RI, Babin RW. The combined use of cryosurgery and intralesional injections of suspensions of fluorinated adrenocorticosteroids for reducing keloids and hypertrophic scars. *J Dermatol Surg Oncol* 1979; **5**: 54–6.
20 Lee RC, Ping J. Calcium antagonists retard extracellular matrix production in connective tissue equivalent. *J Surg Res* 1990; **49**: 463–6.
21 Phillips TJ, Gerstein AD, Lordan V. A randomised controlled trial of hydrocolloid dressing in the treatment of hypertrophic scars and keloids. *Dermatol Surg* 1996; **22**: 775–8.
22 Wittenberg GP, Fabian BG, Bogomilsky JL *et al*. Prospective, single-blind, randomised, controlled study to assess the efficacy of the 585-nm flashlamp-pumped pulsed-dye laser and silicone gel sheeting in hypertrophic scar treatment. *Arch Dermatol* 1999; **135**: 1049–55.

Minor surgical procedures

Using an orange stick, small quantities of caustic agents can be precisely applied. When 90% liquid phenol is used to treat molluscum contagiosum or small cysts, the orange stick tip may need to be sharpened so that it just fits the cavity being treated. Remember that phenol melts some plastics.

Mollusca can be squeezed to express the cellular debris from the centre of the lesion before phenol application. The tip of the orange stick is dipped into the phenol, any excess wiped off, and the stick is then placed in the centre of the lesion and gently twisted. The solution does not need to be neutralized. After initial whitening, the molluscum becomes inflamed and then resolves 7–10 days later. Treatment is painful and not usually tolerated by small children.

Xanthelasma can be treated using the blunt end of an orange stick, dampened with trichloroacetic acid, dabbed onto the affected area. Multiple small facial epidermoid or acne cysts can be treated in a similar way. The cyst is incised, the contents expressed and phenol carefully applied to the cyst lining using an orange stick. No dressing is required, but a local anaesthetic is necessary.

Milia are tiny, keratin-filled, epithelial-lined cysts with no connection to the overlying skin. They can be removed via a small skin incision made with a sterile #21 or #19 venesection needle. No anaesthetic is required. Prick the needle tip into the skin and, by pulling the cutting edge upwards, incise the skin overlying the milium. Hook or squeeze out the cyst through the skin incision.

Comedones may be emptied using a comedone expressor—a small metal instrument with a cup-shaped end, which has a central hole.

Haemostasis

Bleeding from open wounds can be stopped readily using an absorbable haemostatic dressing such as Surgicel (glucosic copolymer), Kaltostat (calcium alginate), Oxycel (oxidized cellulose) or Gelfoam (porous gelatin matrix), although the mechanism of action of these agents is poorly understood. These materials may behave like a foreign body whilst dissolving in the wound, and increase the risk of infection; large pieces should be removed before wound closure.

Chemical haemostatic agents [1] are effective on oozing skin wounds, for example after curettage and shave excision, but are ineffective in the presence of arterial bleeding, and should not be used in sutured wounds as they cause cell death, which predisposes to infection. Application should be followed by pressure on the wound for 2–3 min to allow haemostasis to occur without the chemical being washed away. Ferric subsulphate (Monsel's) solution carries the risk of iron tattooing [2]. Silver nitrate sticks are effective but caustic, and may leave scars. Aluminium chloride, either 35% in isopropyl alcohol or 20% in ethyl alcohol, is effective; occasionally, it causes histiocytic reactions in treated skin [3].

References

1 Larson PO. Topical haemostatic agents for dermatologic surgery. *J Dermatol Surg Oncol* 1988; **14**: 623–32.
2 Olmstead PM, Lund HZ, Leonard DD. Monsel's solution: a histologic nuisance. *J Am Acad Dermatol* 1980; **3**: 492–8.
3 Barr RJ, Alpern KS, Jay S. Histiocytic reaction associated with topical aluminium chloride (Drysol reaction). *J Dermatol Surg Oncol* 1993; **19**: 1017–21.

CHAPTER 78

Lasers and Flashlamps in the Treatment of Skin Disorders

R.J. Barlow

St John's Institute of Dermatology, St Thomas' Hospital, London, UK

Light and laser light, 78.1
Lasers and laser beams, 78.2
Tissue optics, 78.3
Light–tissue interaction, 78.4
Tissue cooling, 78.5
Lasers and flashlamps for vascular lesions, 78.5
Lasers and flashlamps for treatment of tattoos and pigmentary disorders, 78.9
Lasers and flashlamps for removal of hair, 78.12
Photothermal ablation in the treatment of skin disorders, 78.13
Low-power lasers, 78.15
Photodynamic therapy, 78.15

Introduction

In the years preceding 1900, light had been postulated to consist of either particles or waves. Faraday had also demonstrated that it was related to electromagnetism. In 1901, Planck resolved what had been an experimental contradiction with the prevailing wave theory by postulating that electromagnetic radiation (including light) consisted of discrete packets of energy or quanta. Einstein's [1] subsequent study of the photoelectric effect ultimately formed the basis of the modern theory of light as a wave–particle duality and, indeed, for much of quantum mechanics.

The term 'laser', which is an acronym, seems to have been first used by Gould in 1959 in a lecture entitled 'The LASER, Light Amplification by Stimulated Emission of Radiation'. The first functional laser (ruby, 694 nm) was developed by Maiman [2] in 1960. Its clinical applications were described 3 years later by Goldman [3] in the first dermatological paper on the subject. The theory of selective photothermolysis was postulated by Anderson and Parrish in 1983 [4], since when there has been an explosion of new technology and its application to skin disorders and cosmetic surgery.

This chapter will focus largely on the treatment of skin disorders, whereas the cosmetic applications of light and related technologies will be described in Chapter 80.

Light and laser light

Atoms consist of a nucleus surrounded by electrons. In their resting state, electrons are usually at a low energy level and close to the nucleus. By absorbing energy in the form of a photon (i.e. a quantum of electromagnetic radiation or light), an electron will move to a higher energy orbit (Fig. 78.1). The probability of absorption is proportional to the radiation intensity of the light, and also to the number of atoms in the resting state. In its excited and unstable state, the tendency of the electron is to drop back to the ground state. During this process, termed *spontaneous emission* of radiation, a photon of energy is released.

Emission can also be stimulated, as in a laser. As stated above, 'laser' is an acronym for 'Light Amplification by Stimulated Emission of Radiation.' *Stimulated emission* occurs after an already excited atom is perturbed by a photon with a frequency (wavelength) corresponding to the energy gap between the excited and ground states. If this happens, the excited atom reverts to the resting state, releasing energy as a second photon of the same frequency as the incident photon. Because the incident photon is not absorbed, the atom emits two photons. Importantly, each of these has the same wavelength and phase, that is they are coherent. It is this property that allows *light amplification* and the production of a laser system. During the operation of a laser, all three of these light–matter interactions take place simultaneously (namely, the energizing of atoms as well as spontaneous and stimulated emission). The energy that is required to excite the atoms is provided to the laser by an external power source in a process called *pumping*. When most of the atoms are in an excited rather than in a lower energy state, they are described as having undergone *population inversion* (a condition in which stimulated emission is more likely).

Laser light differs from light emitted by a conventional light source in that it has the following characteristics:

1 **Monochromaticity**. The identity of the excited atom determines the wavelength of the radiation produced. In a laser, this is more precisely a narrow band in a Gaussian distribution around a characteristic wavelength. The argon laser is unusual in that it emits light of two wavelengths (488 and 514 nm), a consequence of there being intermediate orbits between the excited and resting states.

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

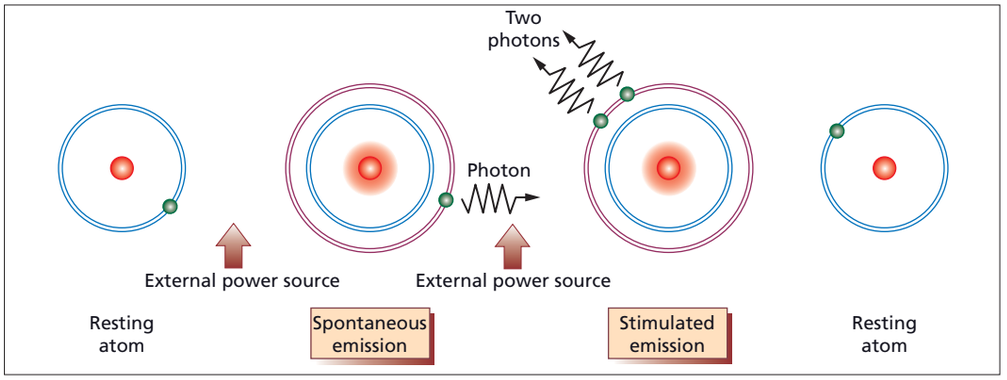


Fig. 78.1 Schematic representation of excitation of an atom with spontaneous and stimulated emission of radiation.

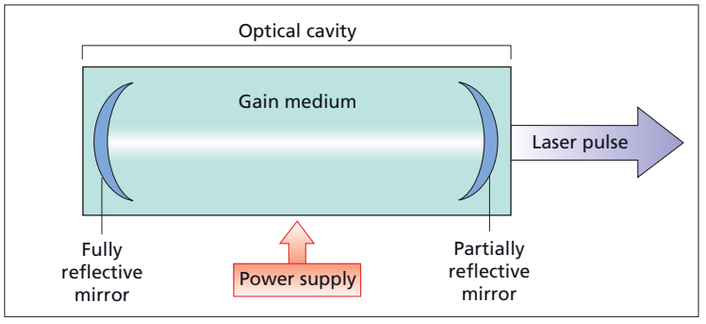


Fig. 78.2 Diagram of a laser showing the external power source, the active medium within the optical cavity and a system of fully and partially reflective mirrors.

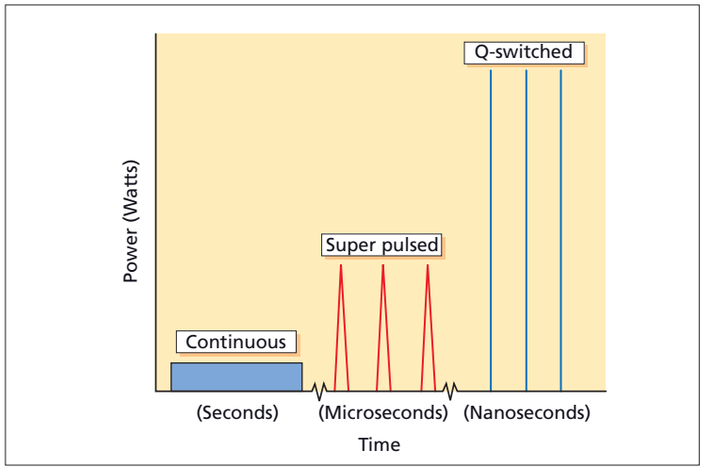


Fig. 78.3 Simplified representation of pulse types.

2 **Coherence**. Light can be likened to a sine wave. Laser light is both temporally and spatially coherent, that is the waves are in phase in time and space.
3 **Collimation**. This is a consequence of coherence and refers to its non-divergent and energy conserving properties. It means that the diameter of the beam changes only minimally over distance, unless it is focused by a lens. Both forms may be useful, such as in CO_2 laser surgery where a focused beam can be used for excision or where a collimated beam can be scanned for resurfacing.

Lasers and laser beams

Lasers are usually named after the constituents of the *gain medium*, which may be a gas, a liquid or a solid. The gain medium is contained within an *optical cavity* (Fig. 78.2). In its simplest form the optical cavity consists of two opposing mirrors, one of which is fully reflective and the other of which, the *output coupler*, is partly transparent. Photons moving parallel to the axis of the optical cavity are reflected between the two mirrors, in turn eliciting stimulated emission in the same axis. The energy required for the process of light amplification is supplied by an external source such as an electric current or light source (flashlamp or other laser). This supply of energy (pumping) amplifies the light until such time as it is emitted through the output coupler. It then enters a delivery system which transmits it to the operator handpiece. Delivery systems may take the form of fibreoptic cables or articulated arms through which light is reflected by mirrors. Fibreoptic cables are lighter and easier to operate and maintain, but they are also delicate and can break when bent or twisted beyond their tolerance. They are not sufficiently robust to transmit light emissions from systems such as CO_2, Er:YAG or the very short pulse Q-switched lasers, where articulated arms are required. Each delivery system ends in an operator handpiece through which light can be focused by a lens or transmitted as a collimated beam. Either beam type can be scanned to limit exposure time. Lasers are sometimes classified according to the pulse characteristics of the beam, which may be continuous, pulsed or quality switched (Q-switched) (Fig. 78.3). Continuous wave light consists of an uninterrupted beam of relatively low power, such as is emitted by the CO_2 laser. Light produced by lasers of this sort can be shuttered mechanically to interrupt the beam and may reduce accumulation of unwanted heat. Another modification, superpulsing, was developed so that the laser emits a rapid train of higher peak-power pulses of energy. One disadvantage of these so-called 'quasi-continuous' lasers is that the pulses are so close together that there is insufficient time for cooling. The tissue effect of this may therefore be very similar to a continuous wave laser beam.

It was only with the development of high peak-power lasers that clinically significant tissue effects could be achieved with

single pulses. Examples include the pulsed-dye laser, normal mode alexandrite and diode lasers, as well as CO_2 lasers with pulse durations in the millisecond or high microsecond range. *Q-switching* is a means of creating a very short pulse (5–100 nanoseconds) together with an extremely high peak power. This is achieved by means of an *electro-optical switch* which consists of two polarizers. Depending on their alignment, these will either transmit or block light. The pulse width is varied so that it approximates the thermal relaxation time (see below) of the target chromophore.

The beam diameter is identical to the so-called spot size and is usually Gaussian in profile. This necessitates a degree of spot size overlap during treatment in order to irradiate tissue more uniformly.

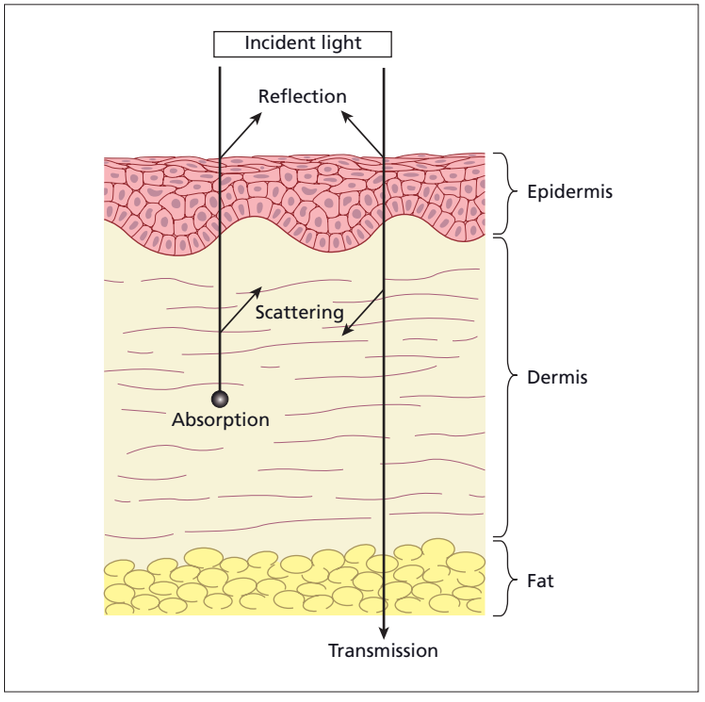


Fig. 78.4 Fate of incident light on skin.

Tissue optics

The fate of incident light on skin is as follows (Fig. 78.4):

1 **Reflection**. About 4–6% of light is reflected at the skin surface. Reflection increases with increased angle of incidence, that is it is lowest when the beam is perpendicular.

2 **Absorption**. This is governed by Beer's law, which relates the absorption of light to the properties of the substance through which the light is travelling. In essence, the law states that there is a logarithmic dependence between the transmission of light through a substance and the concentration of that substance, and also between transmission of light and its path length through the substance. Without absorption of light, there can be no effect on tissue. When a photon is absorbed by a target molecule or chromophore, all of its energy is transferred to that molecule. The basis for selective skin laser surgery is that light can be manipulated in terms of its wavelength, energy content and pulse duration so that a particular target chromophore absorbs light and is damaged or destroyed, whereas other chromophores are not.

   The endogenous chromophores of importance are melanin, haemoglobin, water and collagen (Fig. 78.5). Melanin is present in normal epidermis and hair follicles. Its principal function is to protect against sunlight and its absorption includes ultraviolet (UV) and visible light, with decreasing absorption into the near infrared spectrum. Haemoglobin has absorption peaks in the UVA, blue (400 nm), green (541 nm) and yellow (577 nm) wavelengths. Collagen absorbs in the visible and near infra-red spectra and water in the mid and far infrared regions. There are also a number of exogenous chromophores, such as tattoo ink.

3 **Scattering**. This refers to the deviation of light by non-uniformities in the medium through which it passes. In skin, this is largely due to collagen in the dermis. Because the collagen molecule is similar in size to the wavelength of visible and near

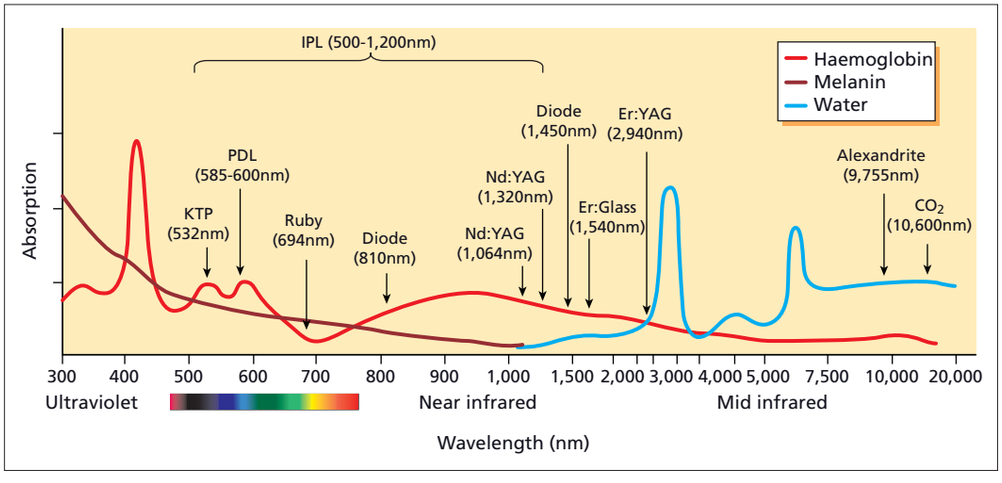


Fig. 78.5 Absorption spectra of principal tissue chromophores.

Table 78.1 Laser wavelengths and their clinical applications.

	Wavelength (nm)											
	532		585–600	694		755–810		1064		500–1200	1320 1450 1540	2094 10600
	QS	NM		QS	NM	QS	NM	QS	NM			
Epidermis:												
Pigment	++	+/–	–	++	–	+	–	–	–	+	–	+/–
Dermis:												
Pigment	+/–	–	+/–	+	–	++	–	+	–	+/–	+/–	+/–
Vessels	–	+	++	–	–	–	+	–	+	+	–	+/–
Hair	–	–	–	–	+	–	++	–	+	+/–	–	–
Appendigeal tumours	–	–	+/–	–	–	–	–	–	–	–	+	+
Resurfacing:												
Non-ablative	–	–	+/–	–	–	–	–	–	+/–	+/–	+/–	–
Ablative	–	–	–	–	–	–	–	–	–	–	–	+

QS, Q switched; NM, normal mode.

–, not used; +/–, reported indications, possibly effective; +, effective; ++, effective, may be wavelength of choice.

infrared light, scatter is mainly forward in direction. In certain situations, however, back scatter can be high enough to increase the energy density in the upper dermis to beyond that of the incident light. In relation to laser light, so-called coherent backscattering can be more than twice as much as if the incident light was incoherent.

Scattering is important in that it reduces the light energy available for absorption by the target chromophore and thereby decreases the clinical effect in tissue. Scattering in skin diminishes with longer wavelengths, allowing these to reach deep dermal structures such as hair follicles. Light between 600 and 1200 nm has been described as an optical window into the skin because it is subject to low scattering in addition to being well absorbed by endogenous chromophores. Longer wavelength light is absorbed by water and does not penetrate deeply.

4 **Transmission**. Light that is not reflected, absorbed or scattered passes to deeper tissue. This is dependent on wavelength, shorter wavelengths (300–400 nm) being scattered and penetrating less than 0.1 mm. Wavelengths in the 600–1200 nm range penetrate deeper because they are scattered less.

Light–tissue interaction (Table 78.1)

The wavelength of light determines its absorption by a tissue target or *chromophore.* In addition to being absorbed, light must have sufficient energy if it is to alter the target's structure. Energy is measured in Joules (J), although it is usually more useful to consider its *fluence* or energy density (J/cm^2). *Power* is the rate at which energy is delivered, and is measured in Watts (i.e. W or J/s). The term *irradiance* refers to the power density—the rate at which energy is delivered per unit area—and is measured in W/cm^2. Fluence and irradiance are therefore directly proportional and are inversely proportional to the square of the radius of the spot size. This means that doubling the spot size decreases the fluence and the irradiance by a factor of 4. On the other hand, increasing the spot size (up to a maximum of about 12 mm) reduces scatter.

Depending on these qualities, light may affect tissue as follows:

1 **Photostimulation**. There is equivocal evidence to suggest that low energy lasers expedite wound healing. The mechanism of this is unclear.

2 **Photodynamic change**. This forms the basis of photodynamic therapy (PDT) and usually involves the topical or systemic administration of a photosensitizer or precursor thereof. Subsequent irradiation with an appropriate light source elicits two types of photo-oxidative reaction and an immediate cytotoxic effect. PDT can also target endogenous chromophores (such as produced by *Propionibacterium acnes* and used in blue light treatment of acne vulgaris.)

3 **Photothermolytic and photomechanical reactions**. The theory of selective photothermolysis [4] has been used to target structures containing haemoglobin, melanin and collagen. It postulates that light can be used to selectively damage or destroy a chromophore if a wavelength is selected that offers as big a difference as possible between the absorption coefficient of the target and the surrounding tissue, if its energy is high enough to damage the target and if its pulse duration is less than or equal to the *thermal relaxation time* (TRT). The TRT is the time taken for the target to dissipate about 63% of the incident thermal energy. These are considered in more detail below:

i **Wavelength.** The absorption spectra of important tissue chromophores are shown in Fig. 78.5 in relation to the wavelengths of the lasers widely used in dermatology [5]. Haemoglobin has a number of different absorption peaks whereas absorption by melanin gradually diminishes with longer wavelengths of incident light. The depth of the target structure must also be considered because scattering of light in

the dermis is strongly influenced by wavelength. For this reason, long wavelength light which penetrates well but is poorly absorbed by a deep chromophore, may be more damaging to it than a shorter wavelength with the opposite characteristics. In some situations, particularly in relation to melanin, a single wavelength may not be necessary and it may even be preferable to use flashlamps because of their broad emission spectrum (500–1200 nm). These are cheaper to manufacture than lasers and can be used with light filters to allow a potentially wide range of applications. It is possible to vary their pulse durations from 0.5 to 88.5 ms and to introduce intervals between pulses of 1300 ms. At present they cannot substitute for lasers where focused, high energy beams are required.

ii **Energy fluence.** The energy contained within light is expressed in Joules (J) and its fluence or energy density per unit area in J/cm^2.

iii **Thermal relaxation time (TRT).** The TRT is related to the size of the target chromophore and varies from a few nanoseconds (tattoo particles) to several hundred milliseconds or more (leg venules).

Some tissue targets, notably the hair follicle, are not uniform in their absorption of light, and it is possible that light-assisted hair removal is better explained by an 'extended theory of selective photothermolysis' [6]. This distinguishes between an 'absorber' chromophore (in which heat is generated) and a distant 'target', to which heat is transmitted and which is damaged as a result. This may also apply to hair removal, melanin in the hair shaft and matrix cells acting as the absorber whereas the stem cells of the isthmus (and possibly the blood vessels in the papilla) represent the distant target. The time to achieve selective damage of the target is the *thermal damage time* (TDT). This is the time for the entire target, including the primary chromophore (e.g. melanin) and the surrounding target (e.g. hair follicle) to cool by about 63% and includes cooling of the primary chromophore as well as the entire target. The TDT is longer than the TRT as it allows for heat diffusion from the chromophore throughout the entire target.

A practical outcome of this theory has been termed 'thermokinetic selectivity' [7]. Because large structures cool slower than small structures, it is proposed that they reach higher and potentially damaging temperatures if the light source is manipulated appropriately. An example of this is light-assisted hair removal, where a pulse is used that is longer than the thermal damage time of the melanin-containing epidermis (1 ms) compared with the melanin-containing hair follicle (30–100 ms). Lasers or light sources with pulse durations of 5–50 ms can therefore allow energy to accumulate in, and thermally coagulate, the hair follicle. Even while the energy is being delivered, the epidermis is protected as it cools and its temperature is therefore kept below its thermal coagulation threshold.

Tissue cooling

Light in the 500–1200 nm spectrum is preferentially, but not specifically, absorbed by either haemoglobin or melanin, depending on the wavelengths employed. Epidermal melanin will therefore absorb both direct and back-scattered light from all such devices, whether or not it is the intended chromophore. Heat damage to the epidermis may result in blistering, dyspigmentation or scarring and is particularly likely in pigmented skin. To reduce this risk, the wavelength should be optimized with respect to the absorption characteristics and depth of the target chromophore. The use of long pulses [8] and cooling of the epidermis further enhances safety in these patients. The latter may be done before, during or after the light pulse or all three.

Cooling may take three forms:

1 **Cold air convection**. Air, chilled to temperatures as low as –30°C, is directed onto the area to be treated.
2 **Contact cooling**. This can involve simple application of ice-packs or more sophisticated systems in which cold water flows between colourless and transparent plates (usually sapphire as it is a more efficient conductor than glass). Although a good method of cooling, condensate which develops on the plates can obscure the skin and may require frequent removal.
3 **Cryogen spray (dynamic) cooling**. A frozen gas is sprayed onto the skin immediately before the laser pulse. Evaporative cooling has a high heat transfer coefficient and this is therefore the most efficient way of pre-cooling. With timed, automated control this method is also relatively predictable and reproducible.

One important benefit of epidermal cooling has been to allow treatments at higher energy fluences than would otherwise be considered safe, and in this way to reduce the number of treatments required. Cooling has also made it possible to safely treat patients with all except the most heavily pigmented skin types. Furthermore, cooling decreases the pain associated with treatment, thus reducing the need for topical or local anaesthetic. Cooling can cause cryogen injury if used inappropriately.

References

1 Einstein A. Zur quantentheorie der Strahlung. *Physikalische Gesellschaft Zurich Miteilungen* 1916; **18**: 47–62.
2 Maiman T. Stimulated optical radiation in ruby. *Nature* 1960; **187**: 493–4.
3 Goldman L. Pathology of the effect of the laser beam on the skin. *Nature* 1963; **197**: 912–4.
4 Anderson RR, Parrish JA. Selective photothermolysis: precise microsurgery by selective absorption of pulsed radiation. *Science* 1983; **220**: 524–7.
5 Waner M, Suen JY. Lasers in head and neck cancer. In: Myers E, Suen JY, eds. *Cancer of the Head and Neck*, 4th edn. New York: WB Saunders, 2003: 679–92.
6 Altshuler GB, Anderson RR, Manstein D *et al*. Extended theory of selective photothermolysis. *Lasers Surg Med* 2001; **29**: 416–32.
7 Dierickx C, Alora MB, Dover JS. A clinical overview of hair removal using lasers and light sources. *Dermatol Clin* 1999; **17**: 357–66.
8 Battle EF, Suthamjariya K, Alora M *et al*. Very long-pulsed (20–2000 ms) diode laser for hair removal on all skin types. *Lasers Surg Med* 2000; **12** (Suppl.): 21 (Abstract).

Lasers and flashlamps for vascular lesions

Light–tissue interaction

Oxyhaemoglobin has its main absorption peaks at 418, 542 and 577 nm. As an initial practical application of their theory of selective photothermolysis, Anderson and Parrish selected a flashlamp-pumped dye laser with a wavelength of 577 nm, a pulse duration of 0.3 ms and a fluence of $2\,J/cm^2$ [1]. In subsequent treatment of port-wine stains, this wavelength was replaced

with 585–600 nm light, which has the advantage of deeper dermal penetration (although with reduced oxyhaemoglobin absorption at the longer wavelengths [2]). A slightly longer pulse duration (0.45 ms) was used in the first generation of pulsed-dye lasers on the basis of a calculated TRT of <1 ms for vessel diameters of 10–50 μm. This may have been an underestimate, and the TRT was measured in a subsequent *in vivo* study as 1–10 ms for vessel diameters of 30–150 μm [3]. Pulsed-dye lasers are now manufactured with pulse durations of up to 40 ms although the short-pulse PDL is optimal for paediatric port-wine stains (PWS) because vessel diameters are relatively small [4]. Another laser useful for vascular anomalies (especially facial telangiectases) is the potassium titanyl phosphate (KTP) laser (532 nm), light from which does not penetrate beyond superficial vessels but which is well absorbed. The alexandrite (755 nm) and neodymium:yttrium–aluminium–garnet or Nd:YAG (1064 nm) lasers emit light with longer wavelengths and therefore relatively deep penetration. This is targeted at a low absorption peak at 900–1000 nm.

Devices in common use

The frequency doubled Nd:YAG or potassium titanyl phosphate (KTP) (532 nm) laser. Nd:YAG laser emissions can be passed through a KTP crystal to double the frequency to 532 nm. They may be flashlamp or diode pumped and are characterized by trains of short pulses which summate to give a wide pulse-like or 'quasi-continuous' effect that is not associated with purpura. Light produced by KTP lasers is highly absorbed by haemoglobin (and melanin) but its wavelength penetrates only superficially. They are widely used, with or without cooling devices, to treat small facial vessels.

Pulsed-dye lasers (585–600 nm) 4.5 and 1.5–40 ms. These contain a rhodamine dye which is excited by a xenon flashlamp to produce light at 585–600 nm in pulses of 0.45 ms (short-pulse PDL) or 1.5–40 ms (long-pulse PDL) through spot sizes of up to 12 mm diameter. Light penetrates the dermis to a depth of 1.2 mm [5] and photocoagulates vessels of up to 100 μm in diameter.

The alexandrite (755 nm) and neodymium:yttrium-aluminium-garnet (Nd:YAG) (1064 nm) lasers. These emit light with longer wavelengths and therefore relatively deep dermal penetration. The wavelengths are absorbed by a small haemoglobin absorption peak at 900–1000 nm. Used with long pulses (up to several hundred ms) and epidermal cooling systems, the Nd:YAG laser may have a role to play in treating relatively deep and large vessels, including those on the legs.

Intense pulsed light source (500–1200 nm). This device emits non-coherent light over a broad spectrum. Filters are used to eliminate wavelengths shorter than selected thresholds. There is contact cooling and its potential advantages are the large spot size and the reduced likelihood of patterning or over-correction when treating fine facial telangiectasiae.

Superficial vascular abnormalities

Anaesthesia

Topical anaesthesia is usually satisfactory for treating facial lesions in adults but local or regional anaesthesia may be required. Treatment at other anatomical sites can usually be tolerated with topical or no anaesthesia. Depending on the size and site of the lesion, children under 12 years of age may need treatment under general anaesthetic. Emollients and analgesics relieve postoperative pain, swelling and erythema. Some patients develop crusting of the treated area.

Haemangiomas

Haemangiomas appear at birth and are the commonest, benign tumours of infancy. They are characterized by endothelial hyperplasia and may proliferate for months. It is possible that they originate in maternal placenta, with which they share distinct tissue-specific markers [6]. Most regress, sometimes leaving redundant, atrophic skin. Intervention may be indicated if the site and/or size of the haemangioma are likely to cause functional impairment or abnormal psychological development. Haemangiomas have been reported to show improved colour and size when treated with the pulsed-dye [7] or Nd:YAG lasers [8]. Laser treatment may be particularly helpful in ulcerated, involuting haemangiomas [9] (Fig. 78.6), although ulceration is itself a rare complication of treatment [10]. In one uncontrolled study [11] of 548 children with 692 haemangiomas treated with a short-pulse PDL, further proliferation was halted in 96% of lesions. On the other hand, a randomized controlled study of 121 infants with early, uncomplicated haemangiomas showed no advantage of pulsed-dye laser treatment over observation at 1 year [12]. Patients with five or more separate lesions should be scanned for systemic involvement. Large haemangiomas may be life-threatening if there is organ infiltration, high-output cardiac failure or Kasabach–Merritt syndrome. In these patients, treatment should be attempted with systemic corticosteroids, and failing this with interferon-α, cyclophosphamide or vincristine [13].

Port-wine stains (PWS), or capillary malformations

Vascular malformations may be arterial, venous, capillary or lymphatic and may include elements of more than one type. 'Port-wine stains' (PWS) are capillary malformations in which the vessels are characterized by flat endothelium with normal turnover. Sturge–Weber syndrome features a PWS involving skin in the distribution of the ophthalmic branch of the trigeminal nerve, together with involvement of the ocular choroid and leptomeninges. Patients with periorbital PWS should also be tested for glaucoma.

The PDL is the intervention of choice for uncomplicated lesions, and six to eight treatments will achieve 'good results' in as many as 60% [14] (Fig. 78.7). In recent years, PDLs have been manufactured with longer wavelengths, bigger spot sizes and longer pulses, as well as with cooling devices which allow use of higher fluences. The 585-nm short-pulse PDL is probably optimal for treating paediatric PWS because vessel diameters are relatively small. More recently manufactured PDLs emit light with a wavelength of 595 nm, absorption of which by haemoglobin is lower by a factor of five than at 585 nm. However, used in conjunction with a longer pulse, this may be most suitable for the deeper, bigger vessels in resistant or adult PWS [15]. The use of spray cooling and higher fluences with both short [16] and long [17] pulse (1.5–4.0 ms) PDLs has considerably expedited treatment of

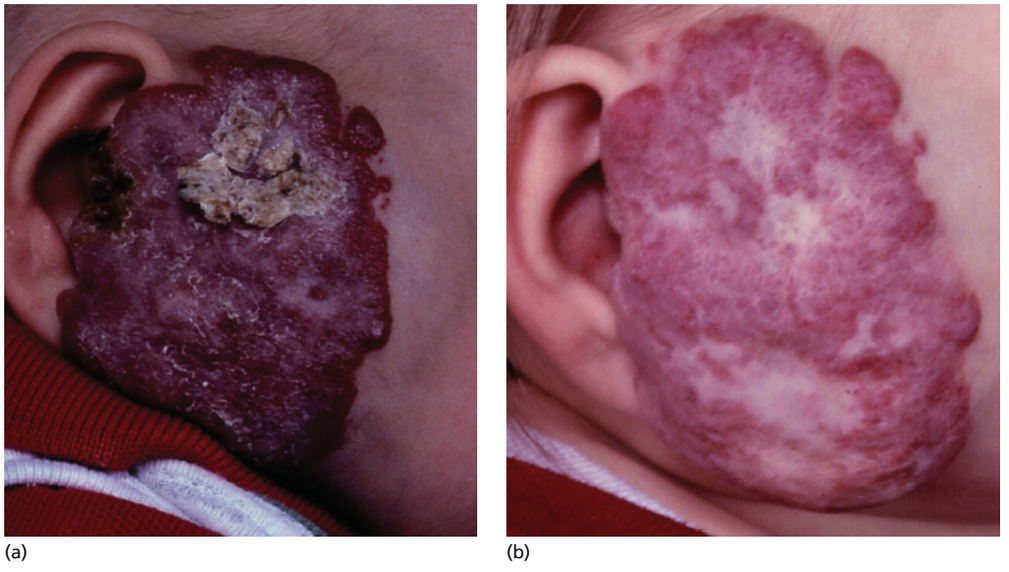


Fig. 78.6 Ulcerated haemangioma, (a) before and (b) after two pulsed-dye laser treatments.

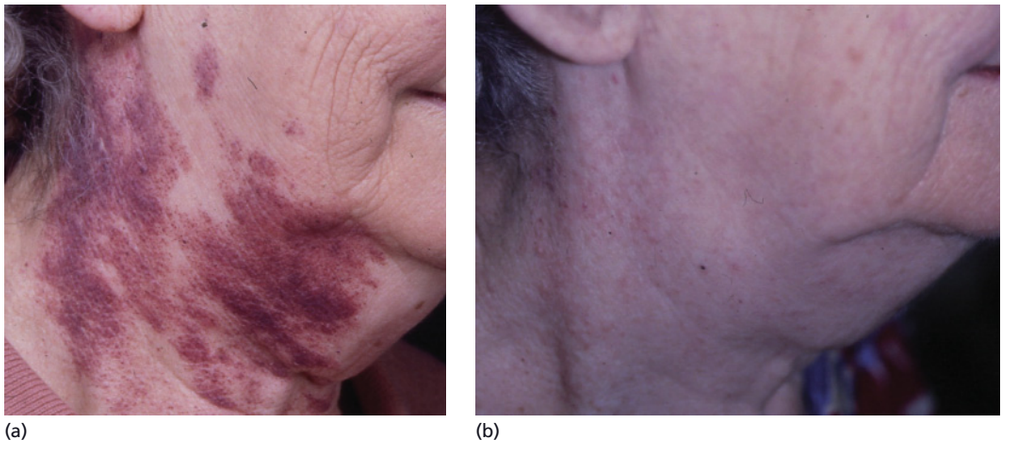


Fig. 78.7 Flat and superficial port-wine stain, (a) before and (b) after four pulsed-dye laser treatments (590 nm), showing an unusually good response.

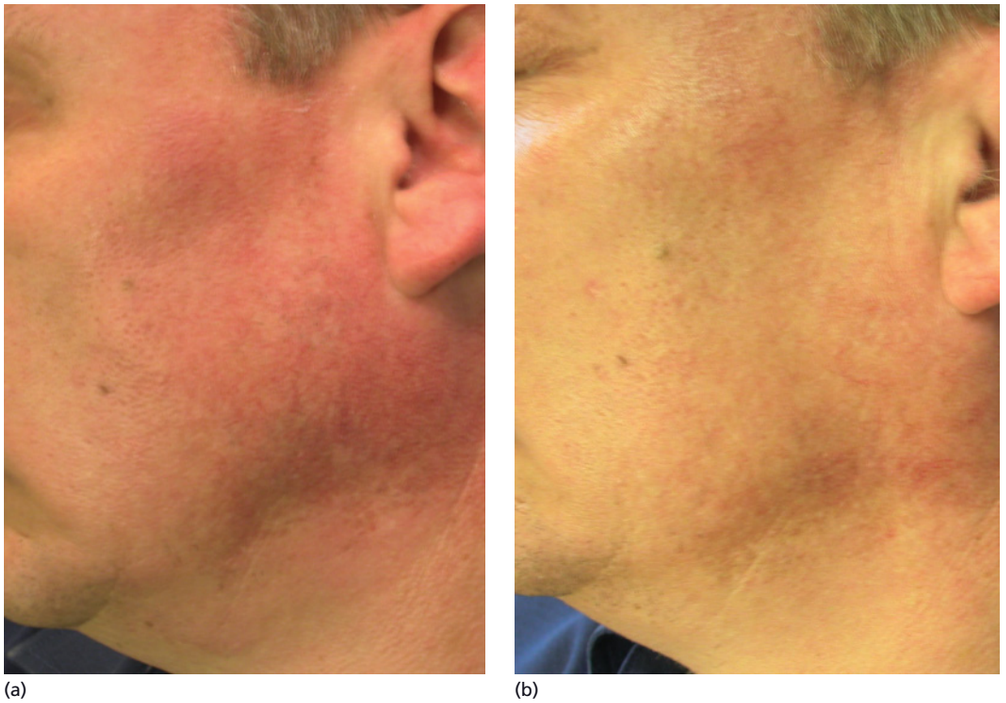
PWS. Lesions become purpuric if treated with both high fluences and pulse durations of 6 ms or less. Although reduced by both cooling and long pulsing, a degree of post-treatment purpura formation is thought to be necessary for effective treatment of lesions [18]. Factors favouring a good response to PDL treatment are youth, as well as flat and scarlet (as opposed to purple) PWS on the head and neck (excluding the cheeks or midline) [19]. Partial re-emergence (in up to 40% after 4 years) may occur after successful treatment [20].

Hypertrophic and PDL-resistant PWS have sometimes been treated with near-infrared lasers such as the alexandrite (755 nm) and Nd:YAG (1064 nm). Resistant lesions have also been treated with pulse-stacking using either short and long wavelength PDL (to treat superficial and deep vessels respectively) or combined pulsed-dye and Nd:YAG lasers [21]. Other possibilities under investigation include electro-optical synergy technology and vacuum-assisted laser treatment [22]. The mechanism of the former is supposedly that light technology can be used to preheat a tissue chromophore, the electrical resistance or impedance of which drops as a consequence and so renders it more sensitive to subsequent electrical damage. Adult patients in whom progressive vascular ectasia has resulted in very exophytic lesions are probably best treated with the CO_2 laser [23].

Flashlamps (500–900 nm) have larger spot sizes and have also been used to treat PWS, supposedly with good effect [24].

Telangiectases

These are acquired capillary malformations and usually occur as so-called spider angiomas or more diffusely as manifestations of either photodamage (including poikiloderma of Civatte) or rosacea. Spider angiomas consist of a central arteriole with a high filling pressure, and these lesions are probably best treated with the PDL. The superficial telangiectases which are commonly found in a mid-face distribution in middle-aged and elderly, fair-skinned patients respond safely and well to KTP lasers [25]. More diffuse, finer telangiectases or erythema will respond to short-pulse PDL treatment



(a) (b)

Fig. 78.8 Facial erythema, (a) before and (b) after one treatment with a flashlamp, showing minimal patterning and a near disappearance.

[26], not necessarily with associated purpura but with a risk of subsequent honeycomb patterning. The flashlamp is usually a non-bruising and probably better treatment modality [27] because it reduces erythema more gradually and is less likely to cause patterning (Fig. 78.8). However, this may be more painful than laser treatment, and several treatments may be required [28].

Leg veins

These vary in terms of size, depth and flow characteristics. In the absence of deep venous insufficiency, superficial dilated venules are best treated by sclerotherapy [27]. If this is contraindicated, these vessels should respond best to laser treatment with large spot sizes (3–4 mm), high fluences and long pulse durations, combined with effective cooling devices. Wavelength should be chosen according to the depth of the target vessel. Accordingly, long pulse (1.5–4.0 ms) PDLs were developed with wavelengths in the 585–600 nm range and, used with fluences of 7–9 J/cm², are sometimes useful for superficial vessels less than about 0.5 mm in diameter [29]. Longer wavelengths are used to target a different absorption peak of haemoglobin and achieve deeper penetration. The 3 ms alexandrite (755 nm) laser has been used with fluences of up to 80 J/cm² in treating leg vessels of up to 2 mm in diameter [30], and the Nd:YAG (1064 nm) laser [31] with fluences higher than 100 J/cm² and pulse durations of up to 1 s in treating even deeper and larger vessels. Complications are relatively common and include ulceration, dyspigmentation and scarring [27]. There are few data on the flashlamp in this context, but its emission spectrum and large applicator head would suggest a role in treating widespread, fine telangiectases.

Other cutaneous vascular lesions that respond to laser treatment, optimally with pulsed-dye laser, include angiomas and venous lakes [27]. Small, red angiofibromas may do well in young patients with tuberous sclerosus in whom ablative treatments are inappropriate. Angiokeratomas are likely to recur unless treatment elicits fibrosis. Pyogenic granulomas should probably be curetted.

Other applications of vascular lasers

Viral warts. PDLs have been used to treat viral warts [32], often at high fluences and without cooling. The rationale for this was originally that photocoagulation of the underlying dermal vessels compromised the viability of the abnormal epidermis. It seems more likely that it represents a non-specific injury to the infected epidermis. Treatment of cryotherapy-resistant warts on the nail folds and the soles of the feet is often only partly successful [33]. Here, CO_2 laser ablation may be more effective, despite the greater likelihood of pain, infection and scarring [34].

Hypertrophic scars. PDLs have been reported to improve the colour and contour of erythematous and hypertrophic (but not keloid) scars in studies which have sometimes been supported with objective measurements such as reflectance spectrometry and silicone profilometry [35]. The mechanism of action is unknown, although it is also possible that destruction of small vessels plays a part. In more raised scars, lasers may be most useful after lesions have first been substantially reduced in bulk by intralesional corticosteroids.

Psoriasis. Localized and resistant plaque psoriasis has been reported to respond to treatment with either the short- or long-pulse 585 nm PDL [36]. Although non-toxic, treatment is often painful, and can cause dyspigmentation and scarring.

Granuloma faciale. This condition is poorly understood, and it is not clear why the reddish-brown facial plaques should respond to pulsed-dye laser treatment, as has been reported [37]. Their colour is likely to be due to the inflammatory infiltrate rather than vascular dilatation.

Complications

These include dyspigmentation and both atrophic and hypertrophic scarring. They appear to be more common in pigmented skin and when treating leg vessels.

References

1 Anderson RR, Parrish JA. Microvasculature can be selectively damaged using dye lasers: a basic theory and experimental evidence in human skin. *Lasers Surg Med* 1981; **1**: 263–76.
2 Tan OT, Murray S, Kurban AK. Action spectrum of vascular specific injury using pulsed irradiation. *J Invest Dermatol* 1989; **92**: 868–71.
3 Dierickx CC, Casparian JM, Venugopalan V *et al*. Thermal relaxation of portwine stain vessels probed in vivo: the need for 1–10 millisecond laser pulse treatment. *J Invest Dermatol* 1995; **105**: 709–14.
4 Garden JM, Bakus AD. Laser treatment of portwine stains and haemangiomas. *Dermatol Clin* 1997; **15**: 373–83.
5 Spicer MS, Goldberg DJ. Lasers in dermatology. *J Am Acad Dermatol* 1996; **34**: 1–25.
6 North PE, Waner M, Mizeracki A *et al*. A unique microvascular phenotype shared by juvenile hemangiomas and human placenta. *Arch Dermatol* 2001; **137**: 559–70.
7 Ashinoff R, Geronemus RG. Capillary hemangiomas and treatment with the flashlamp-pumped pulsed dye laser. *Arch Dermatol* 1991; **127**: 202–5.
8 Landthaler M, Hohenleutner U, Abd El-Raheem T. Laser therapy of childhood haemangiomas. *Br J Dermatol* 1995; **133**: 275–81.
9 Morelli JG, Tan OT, Weston WL. Treatment of ulcerated hemangiomas with the pulsed tunable dye laser. *Am J Dis Child* 1991; **145**: 1062–4.
10 Witman PM, Wagner AM, Scherer K *et al*. Complications following pulsed dye laser treatment of superficial hemangiomas. *Lasers Surg Med* 2006; **38**: 116–23.
11 Hohenleutner S, Badur-Ganter E, Landthaler M, Hohenleutner U. Long-term results in the treatment of childhood hemangioma with the flashlamp-pumped pulsed dye laser: an evaluation of 617 cases. *Lasers Surg Med* 2001; **28**: 273–7.
12 Batta K, Goodyear HM, Moss C *et al*. Randomised controlled study of early pulsed dye laser treatment of uncomplicated childhood haemangiomas: results of a 1-year analysis. *Lancet* 2002; **360**: 502–3.
13 Perez J, Pardo J, Gomez C. Vincristine—an effective treatment of corticoid-resistant life threatening infantile hemangiomas. *Acta Oncol* 2002; **41**: 197–9.
14 Landthaler M, Hohenleutner U. Laser therapy of vascular lesions. *Photodermatol Photoimmunol Photomed* 2006; **22**: 324–32.
15 Chang C-J, Kelly K, van Gemert MJC, Nelson JS. Comparing the effectiveness of 585 vs 595 nm wavelength pulsed dye laser treatment of port wine stains with cryogen spray cooling. *Lasers Surg Med* 2002; **31**: 352–8.
16 Chang C-J, Nelson JS. Cryogen spray cooling and higher fluence pulsed dye laser treatment improve port-wine stain clearance while minimizing epidermal damage. *Dermatol Surg* 1999; **25**: 767–72.
17 Geronemus RG, Quintana AT, Lou WW, Kauvar AN. High-fluence modified pulsed dye laser photocoagulation with dynamic cooling of port-wine stains in infancy. *Arch Dermatol* 2000; **136**: 942–3.
18 Geronemus RG, Lou WW. Treatment of port-wine stains by variable pulse width pulsed dye laser: a preliminary study. *Dermatol Surg* 2001; **27**: 903–5.
19 Renfro L, Geronemus RG. Anatomical differences of portwine stains in response to treatment with the pulsed dye laser. *Arch Dermatol* 1993; **129**: 182–8.
20 Orten SS, Waner M, Flock S *et al*. Port wine stains. An assessment of 5 years of treatment. *Arch Laryngol Head Neck Surg* 1996; **122**: 1174–9.
21 Jasim ZF, Handley JM. Treatment of pulsed dye laser-resistant port wine stain birthmarks. *J Am Acad Dermatol* 2007; **57**: 677–82.
22 Childers MA, Franco W, Nelson JS, Aguilar G. Laser surgery of port wine stains using local vacuum pressure: changes in skin morphology and optical properties. *Lasers Surg Med* 2007; **39**: 108–17.
23 Ratz JL, Bailin PL, Levine HL. CO_2 laser treatment of portwine stains: a preliminary report. *J Dermatol Surg Oncol* 1982; **8**: 1039–44.
24 Raulin C, Goldman MP, Weiss M, Weiss RA. Treatment of adult port-wine stains using intense pulsed light therapy (Photoderm VL): brief initial clinical report. *Dermatol Surg* 1997; **23**: 594–601.
25 Goldberg DJ, Meine JG. Treatment of facial telangiectases with the diode pumped frequency doubled Q-switched Nd:YAG laser. *Dermatol Surg* 1998; **24**: 828–32.
26 Polla LL, Tan OT, Garden JM, Parrish JA. Tunable pulsed dye laser for the treatment of benign cutaneous vascular ectasia. *Dermatologica* 1987; **174**: 11–17.
27 Astner S, Anderson R. Treating vascular lesions. *Dermatol Ther* 2005; **18**: 267–81.
28 Raulin D, Weiss RA, Schonermark MP. Treatment of essential telangiectasias with an intense pulsed light source (PhotoDerm VL). *Dermatol Surg* 1997; **23**: 941–6.
29 Hsia J, Lowery JA, Zelickson B. Treatment of leg telangiectasia using a long pulse dye laser at 595 nm. *Lasers Surg Med* 1997; **20**: 1–5.
30 Kauvar ANB, Lou WW. Pulsed alexandrite laser for the treatment of leg telangiectasia and reticular veins. *Arch Dermatol* 2000; **136**: 1371–5.
31 Weiss RA, Weiss MA. Early clinical results with a multiple synchronized pulse 1064 nm laser for leg telangiectasias and reticular veins. *Dermatol Surg* 1999; **25**: 399–402.
32 Tan OT, Hurwitz RM, Stafford TJ. Pulsed dye laser treatment of recalcitrant verrucae: a preliminary report. *Lasers Surg Med* 1993; **13**: 127–37.
33 Huilgol SC, Barlow RJ, Markey AC. Failure of pulsed dye laser therapy for resistant verrucae. *Clin Exp Dermatol* 1996; **21**: 93–5.
34 Logan RA, Zachary CB. Outcome of carbon dioxide laser therapy for persistent cutaneous viral warts. *Br J Dermatol* 1989; **121**: 99–105.
35 Alster TS, Williams CM. Treatment of keloid sternotomy scars with the 585 nm flashlamp pumped pulsed dye laser. *Lancet* 1995; **345**: 198–200.
36 Zelickson BD, Mehregan DA, Wendelschfer-Crabb G *et al*. Clinical and histologic evaluation of psoriatic plaques treated with a flashlamp pulsed dye laser. *J Am Acad Dermatol* 1996; **35**: 64–8.
37 Ammirati CT, Hruza GJ. Treatment of granuloma faciale with the 585 nm pulsed dye laser. *Arch Dermatol* 1999; **135**: 903–5.

Lasers and flashlamps for treatment of tattoos and pigmentary disorders

Light–tissue interaction

Melanin absorbs light in the ultraviolet–1200 nm range (Fig. 78.5). At the shorter wavelengths, absorption is higher but penetration less deep than at the longer wavelengths.

The Q-switch is an electro-optical device that is used to produce pulses of only a few nanoseconds. These are designed to be within the estimated TRT of melanosomes (0.5–1 μs) [1] but longer than that of tattoo particles, which is in the low nanosecond domain. Flashlamps can pulse within the millisecond range, which is relatively long in this context. Pulses in the nanosecond range may fragment and disperse melanin and tattoo ink, thereby altering their optical properties. Most tattoo lightening is probably due to uptake and removal of the fragmented particles by activated macrophages through the lymphatic system. Some may also be removed by transepidermal elimination [2].

Devices in common use

Q-switched neodymium:yttrium-aluminium-garnet (1064 nm) and frequency-doubled (532 nm) Nd:YAG lasers. The Q-switched Nd:YAG laser emits light that penetrates 2–3 mm into the dermis and is therefore suitable for the removal of deeper dermal pigmentation [3]. By passing the beam through a KTP crystal the frequency is doubled and the wavelength halved



(a) (b)

Fig. 78.9 Freckles on sun-exposed skin, (a) before and (b) much improved after one treatment with a Q-switched ruby (694 nm) laser.

(532 nm). The shorter wavelength penetrates less deeply and is therefore more useful for the removal of epidermal pigment.

Q-switched alexandrite (755 nm) and diode (810 nm) lasers. These also emit red light at intermediate wavelengths, allowing somewhat deeper dermal penetration, although with some loss of absorption.

Intense pulsed light source (500–1200 nm). These emit non-coherent light over a broad spectrum, with potential advantages in terms of penetration and absorption. The relatively long pulse duration (0.5–88.5 ms) appears not to constitute a practical problem in treating pigment with TRT in the nanosecond domain.

Tattoos

Q-switched treatment of tattoos is cosmetically superior to older destructive modalities [4]. Black or blue tattoo pigments absorb across a broad range of wavelengths in the visible and near infrared spectrum. Green inks respond optimally to the Q-switched ruby (694 nm) [5] and Q-switched alexandrite (755 nm) lasers but often persist [6]. Conversely, red pigments respond best to the green light emitted by the frequency-doubled Nd:YAG (532 nm) [7]. The Nd:YAG laser is effective for blue/black tattoos but is relatively poorly absorbed by green pigments [8]. It has been used successfully to treat tattoos in pigmented skin [9]. Red, brown or flesh-toned inks may contain ferric oxide (Fe_2O_3) which can be reduced by laser treatment to ferrous oxide (FeO), which is black. Although test treatments are therefore important, this reaction is rare and usually responds to subsequent treatment with the appropriate wavelength. Yellow and pastel colours are difficult to treat and complete resolution is unusual. Amateur tattoos usually require fewer treatments than professional tattoos [10].

Benign pigmented lesions

Epidermal pigmentation. Ephelides and solar lentigines respond well to treatment with the Q-switched KTP (532 nm) and Q-switched ruby (694 nm) lasers (Fig. 78.9), although the former may bruise [11]. Each lesion has to be lasered individually, a sometimes tedious and hazardous task on the faces and chests of photodamaged patients in whom there is a mottled appearance of hyperpigmented lesions on a background of chronic 'bronzing' and guttate hypopigmentation. There are limited published data on the use of the flashlamp in this context and its pulse width is relatively long [12]. However, its large beam diameter allows treatment of the entire affected area and not just the pigmented lesions themselves.

Café-au-lait patches show a variable response to laser treatment [13], and repigmentation occurs in 50% [14]. Becker's melanosis consists of dermal melanophages as well as epidermal hyperpigmentation. Its response to Q-switched lasers or to flashlamps is unpredictable, particularly if there is hypertrichosis, and repigmentation may occur from the hair follicles. This has led some authors to suggest that ablative treatment with an Er:YAG laser may be preferable [15].

Seborrhoeic keratoses that resemble solar lentigines, in being flat and brown, will respond well to laser treatment. However, lesions that are warty or poorly pigmented are likely to respond better to destructive treatment modalities.

Lentigo maligna should not be treated with lasers [16].

Dermal pigmentation. Speckled and lentiginous naevus (naevus spilus) consists of a lentiginous patch speckled with compound naevi. A small, early study with both Q-switched ruby and Q-switched Nd:YAG (532 nm or 1064 nm) lasers suggested that the former was more effective. One out of six patients developed dyspigmentation and another showed focal recurrence [17]. In a larger, recent study of Japanese children, naevus spilus was noted to respond poorly to Q-switched alexandrite laser treatment [13]. The conclusions of this second study seem more plausible in view of generally disappointing experience with Q-switched laser treatment of both café-au-lait macules and compound naevi.

Naevus of Ota has been treated with the Q-switched ruby [18], alexandrite [19] and Nd:YAG lasers [20] (Fig. 78.10). The relatively deep dermal pigmentation responds optimally and with fewer complications to treatment with the Q-switched Nd:YAG laser [21]. Some patients repigment after treatment [22].

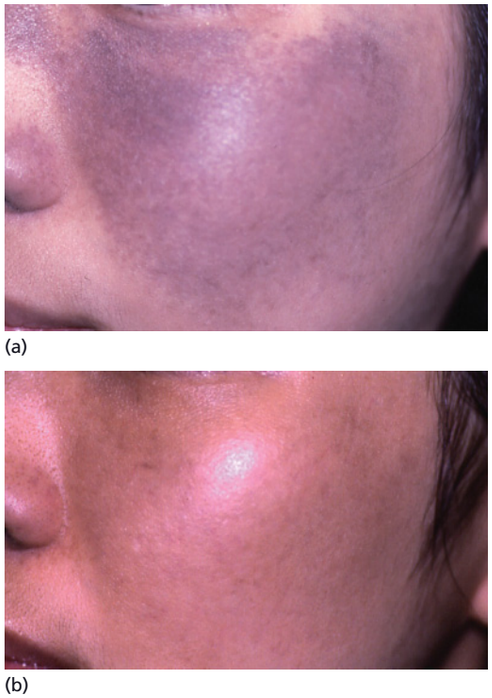


Fig. 78.10 Naevus of Ota, (a) before and (b) after two treatments with a Q-switched Nd:YAG (1064 nm) laser, showing reduction of abnormal pigment and minimal patterning.

Both congenital and acquired melanocytic naevi have been treated with Q-switched lasers [23], although this remains controversial. One reason is that the long-term effects of non-lethal laser irradiation of melanocytes are unknown. With the possible exception of flat, junctional naevi, moles tend to respond incompletely and many lesions repigment. In a study in which 31 congenital and acquired (including atypical) melanocytic naevi were treated with the Q-switched ruby laser, normal mode ruby laser or both, only 16 were visibly lighter 4 weeks after treatment [24].

Melasma can be epidermal, dermal or mixed in type, and usually responds unsatisfactorily to Q-switched laser therapy [25]. More recently, fractional photocoagulation, the 'microthermal treatment zones' of which have been claimed to function as a 'pigment escalator', has been reported to be effective in treating this condition [26]. Laser treatment of post-inflammatory hyperpigmentation, as with melasma, frequently aggravates the situation [27]. Haemosiderin seen in association with venous stasis will only occasionally respond to laser treatment. Hyperpigmentation secondary to administration of minocycline [28] and amiodarone [29] responds readily to treatment with the Q-switched ruby, alexandrite and Nd:YAG lasers.

Complications

These are most commonly dyspigmentation or scarring. They are more frequent in pigmented skin.

References

1 Chang C-J, Nelson JS, Achauer BM. Q-switched ruby laser treatment of oculodermal melanosis (nevus of Ota). *Plast Reconstr Surg* 1996; **98**: 784–90.

2 Ara G, Anderson RR, Mandel KG *et al*. Irradiation of pigmented melanoma cells with high intensity pulsed radiation generates acoustic waves and kills cells. *Lasers Surg Med* 1990; **10**: 52–9.

3 Tse Y, Levine VJ, McClain SA, Ashinoff R. The removal of cutaneous pigmentary lesions with the Q-switched ruby laser and the Q-switched neodymium:yttrium-aluminium-garnet laser: a comparative study. *J Dermatol Surg Oncol* 1994; **20**: 795–800.

4 Goldstein N, Penoff J, Price N *et al*. Techniques of removal of tattoos. *J Dermatol Surg Oncol* 1979; **5**: 901–10.

5 Kilmer SL, Anderson RR. Clinical use of the Q-switched ruby and the Q-switched Nd:YAG (1064 and 532 nm) lasers for treatment of tattoos. *J Dermatol Surg Oncol* 1993; **19**: 330–8.

6 Stafford TJ, Tan OT. 510 nm pulsed dye laser and alexandrite crystal laser for the treatment of pigmented lesions and tattoos. *Clin Dermatol* 1995; **13**: 69–73.

7 Goyal S, Arndt KA, Stern RS *et al*. Laser treatment of tattoos; a prospective, paired comparison study of the Q-switched Nd:YAG (1064 nm), frequency doubled Nd:YAG (532 nm) and Q-switched ruby lasers. *J Am Acad Dermatol* 1997; **36**: 122–5.

8 Kilmer SL, Lee MS, Grevelink JM *et al*. The Q-switched Nd:YAG laser effectively treats tattoos: a controlled dose–response study. *Arch Dermatol* 1993; **129**: 971–8.

9 Jones A, Roddey P, Orengo I, Rosen T. The Q-switched Nd:YAG laser effectively treats tattoos in darkly pigmented skin. *Dermatol Surg* 1996; **22**: 999–1001.

10 Kilmer SL. Laser treatment of tattoos. *Dermatol Clin* 1997; **15**: 409–17.

11 Taylor CR, Anderson RR. Treatment of benign pigmented epidermal lesions by Q-switched ruby laser. *Int J Dermatol* 1993; **32**: 908–12.

12 Raulin R, Greve B, Grema H. IPL technology: a review. *Lasers Surg Med* 2003; **32**: 78–87.

13 Kagami S, Asahina A, Watanabe R *et al*. Treatment of 153 Japanese patients with Q-switched alexandrite laser. *Lasers-Med-Sci* 2007; **22**: 159–63.

14 Shimbashi T, Kamide R, Hashimoto T. Long-term follow-up in treatment of solar lentigo and café-au-lait macules with Q-switched ruby laser. *Aesthetic Plast Surg* 1997; **21**: 445–8.

15 Trelles MA, Moreno-Arias GA. Beckers's nevus: erbium:YAG versus Q-switched neodimium:YAG. *Lasers Surg Med* 2004; **34**: 295–7.

16 Lee PK, Rosenberg CN, Tsao H, Sober AJ. Failure of Q-switched ruby laser to eradicate atypical appearing solar lentigo: report of two cases. *J Am Acad Dermatol* 1998; **38**: 314–7.

17 Grevelink JM, Gonzalez S, Bonoan R *et al*. Treatment of nevus spilus with the Q-switched ruby laser. *J Dermatol Surg* 1997; **23**: 365–70.

18 Goldberg DJ, Nychay SG. Q-switched ruby laser therapy of nevus of Ota. *J Dermatol Surg Oncol* 1992; **18**: 817–21.

19 Alster TS, Williams CM. Treatment of nevus of Ota by the Q-switched alexandrite laser. *Dermatol Surg* 1995; **21**: 592–6.

20 Apfelberg DB. Argon and Q-switched neodymium: yttrium-aluminium-garnet laser treatment of nevus of Ota. *Ann Plast Surg* 1995; **35**: 150–3.

21 Chan HH, Ying SY, Ho WS *et al*. An in vivo trial comparing the clinical efficacy and complications of Q-switched alexandrite (QS alex) and Q-switched 1064 nm neodymium:yttrium-aluminum-garnet (QS 1064 Nd;YAG) lasers in the treatment of nevus of Ota. *Dermatol Surg* 2000; **26**: 919–22.

22 Chan HH, Leung RS, Ying SY *et al*. Recurrence of nevus of Ota after successful treatment with Q-switched lasers. *Arch Dermatol* 2000; **136**: 1175–6.

23 Waldorf HA, Kauvar AN, Geronemus RG. Treatment of small and medium congenital nevi with the Q-switched ruby laser. *Arch Dermatol* 1996; **132**: 301–4.

24 Duke D, Byers R, Sober AJ *et al*. Treatment of benign and atypical naevi with the normal mode ruby laser and the Q-switched ruby laser. *Arch Dermatol* 1999; **135**: 290–6.

25 Taylor CR, Anderson RR. Ineffective treatment of refractory melasma and post-inflammatory hyperpigmentation by Q-switched ruby laser. *J Dermatol Surg Oncol* 1994; **20**: 592–7.

26 Tannous ZS, Astner S. Utilizing fractional resurfacing in the treatment of therapy-resistant melasma. *J Cosmet Laser Ther* 2005; **7**: 39–43.

27 Grekin RC, Shelton RM, Geisse JK, Frieden I. 510 nm pigmented lesion dye laser: its characteristics and clinical uses. *J Dermatol Surg Oncol* 1993; **18**: 341–7.

28 Tsao H, Busam K, Barnhill RN, Dover JS. Treatment of minocycline-induced hyperpigmentation with the Q-switched ruby laser. *Arch Dermatol* 1996; **132**: 1250–1.

29 Karrer S, Hohenleutner U, Szeimies RM, Landthaler M. Amiodarone-induced pigmentation resolves after treatment with the Q-switched ruby laser. *Arch Dermatol* 1999; **135**: 251–3.

Lasers and flashlamps for removal of hair

Light–tissue interaction and devices in common use

The mechanism for light-assisted hair reduction remains incompletely understood. Light is probably absorbed by melanin in the hair shaft and matrix, but it is likely that heat is then transferred to the true target structures—stem cells (mainly in the bulge area of the outer root sheath) and possibly blood vessels in the papilla [1]. Follicles in early anagen are thought to be most susceptible to laser treatment because they are more superficial than in other phases. Follicular disruption is an immediate effect and is followed by conversion from the anagen to the telogen phase, with subsequent miniaturization of the hair follicle.

The normal mode ruby (694 nm), alexandrite (755 nm), diode (800 nm) [2] and Nd:YAG (1064 nm) [3] lasers have all been used for photoepilation. Cooling is required to protect the epidermis. The TRT of a 200–300 μm follicle is about 25–50 ms but much shorter pulse durations also seem to be effective. It has also been shown that considerably longer pulses (30–400 ms) are effective in damaging the stem cells and papillary vessels, neither of which contains melanin nor is in direct contact with the melanin-rich components of the follicle. This observation has been explained in terms of an 'extended theory of selective photothermolysis' [1]. By using long pulses and by limiting the power of the light source, the heat generated by an 'absorber' (here, melanin in the hair shaft) can be kept below levels that would alter its structural and optical properties and thus interfere with further absorption of light. On the other hand the heat generated may be high enough to diffuse to and denature a distant 'target' (here, the stem cells and papillary vessels). The delay between heating of the absorber chromophore and the distant target is referred to as the thermal damage time (TDT) and is significantly longer than the TRT.

Laser-assisted hair removal

A clinical end-point of mild peri-follicular erythema and oedema is often recommended by manufacturers. Multiple treatments (three to six) performed at 6- to 8-week intervals are necessary to achieve what has been defined as 'permanent' reduction of hair growth. In an early study of 13 individuals, follicular damage was demonstrated using a ruby laser with a pulse duration of only 270 μs. Six months later only four had <50% regrowth and five showed complete regrowth of hair [4]. These results were maintained at 2 years follow-up, suggesting that long-term loss of terminal hair is possible after one treatment with the normal-mode ruby laser, albeit in a minority of patients [5].

Lasers with longer wavelengths are likely to be safer and more effective. A study of patients treated at least three times at 4- to 6-week intervals with the 3-ms alexandrite laser showed a mean long-term hair reduction of 74% [6]. This was even higher in those patients with non-pigmented skin in whom higher fluences were used. Optimal results are obtained in patients with non-pigmented skin and with pigmented hair. Fair or white hair lacks melanin and is largely resistant to treatment.

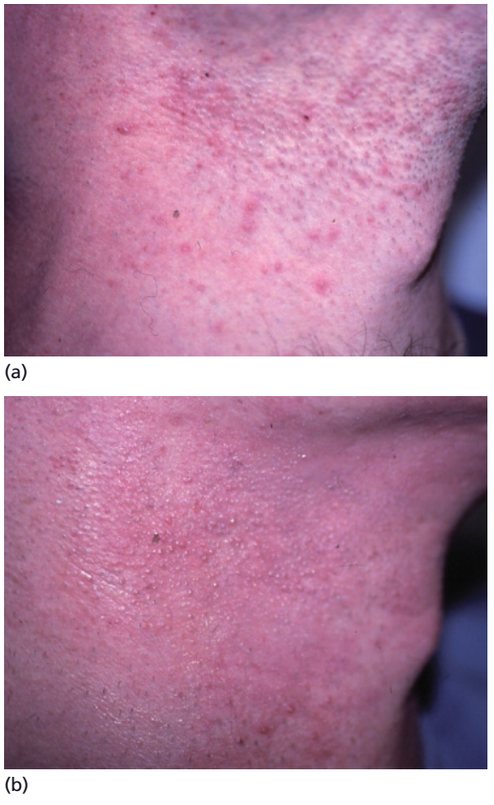


Fig. 78.11 Pseudofolliculitis barbae, (a) before and (b) after a treatment with a normal mode alexandrite (755 nm) laser. Residual hair is sparse and fine and there are no inflammatory lesions.

Flashlamps have been used to treat hypertrichosis [7] but it seems likely that subsequent blistering and dyspigmentation is more common than after laser treatment.

Skin and hair disorders in which laser-assisted hair removal may be beneficial include cosmetically poor hair grafts, pseudofolliculitis barbae (Fig. 78.11) and pilonidal sinuses [8].

Complications

There is a low incidence of usually self-limiting side effects (blistering, crusting, dyspigmentation and scarring) which depend on the laser used and on skin type [9]. The risk is highest with the ruby laser and drops with longer wavelengths. Similarly, risk is higher in patients with pigmented skin, in whom it can be reduced by two-thirds by use of the Nd:YAG laser (1064 nm). A paradoxical increase in hair growth occurs rarely [10].

References

1 Altshuler GB, Anderson RR, Manstein D *et al*. Extended theory of selective photothermolysis. *Lasers Surg Med* 2001; **29**: 416–32.
2 Campos VB, Dierickx CC, Farinelli WA *et al*. Hair removal with an 800 nm pulsed diode laser. *J Am Acad Dermatol* 2000; **43**: 442–7.
3 Bencini PL, Luci A, Galimberti M, Ferranti G. Long term epilation with long-pulsed neodymium:YAG laser. *Dermatol Surg* 1999; **25**: 175–8.
4 Grossman MC, Dierickx CC, Farinelli WA *et al*. Damage to hair follicles by normal-mode ruby laser pulses. *J Am Acad Dermatol* 1996; **35**: 889–94.

5 Dierickx CC, Grossman MC, Farinelli WA, Anderson RR. Permanent hair removal by normal-mode ruby laser. *Arch Dermatol* 1998; **134**: 837–42.
6 Eremia S, Li CY, Umar SH, Newman N. Laser hair removal: long term results with a 755 nm alexandrite laser. *Dermatol Surg* 2001; **27**: 920–4.
7 Gold MH, Bell MW, Foster TD, Street S. Long-term epilation using the EpiLight broad band, intense pulsed light hair removal system. *Dermatol Surg* 1997; **23**: 909–13.
8 Lewis AT, Benedetto AV. Lasers in dermatology: Unapproved treatments. *Clin in Dermatol* 2002; **20**: 700–14.
9 Lanigan SW. Incidence of side effects after hair removal. *J Am Acad Dermatol* 2003; **49**: 882–6.
10 Hirsch RJ, Farinelli WA, Laughlin SA *et al*. Hair growth induced by laser hair removal. *Lasers Surg Med* 2003; **32**: 63.

Photothermal ablation in the treatment of skin disorders

Light–tissue interaction

Incisional with haemostasis. The carbon dioxide (CO_2) laser (10 600 nm) can be used as an incisional or resurfacing instrument. Tissue can be incised by using a high-power, focused beam which vaporizes the tissue in its immediate path. The power, diameter and pulse characteristics of the beam determine the thickness of a surrounding cuff of thermal damage which forms due to scatter and temperature diffusion. The main advantage of thermal damage, in this context, is haemostasis.

Ablative laser resurfacing. This was performed initially with pulsed or scanned CO_2 lasers, the immediate effect of which is ablation (or vaporization) of the epidermis and sometimes the superficial papillary dermis. There is also thermal damage to a band of underlying dermis, together with collagen denaturation and contraction. In the healing period, re-epithelialization occurs from surrounding epidermis and from adnexal structures. This is followed by the formation of a band of upper dermal fibrosis, often referred to in the cosmetic literature as 'collagen remodelling'.

The CO_2 laser emits light which is relatively poorly absorbed by water and which therefore has a relatively high penetration (30 μm). Unless the irradiance is high, this elicits relatively little ablation compared with thermal damage (up to 300 μm), or less than was initially thought desirable. Furthermore, with each subsequent pass there is less and less ablation and more and more thermal damage as the water content drops in the underlying dermis. These considerations led to the development of the erbium:yttrium-aluminium-garnet (Er:YAG) laser (2094 nm) which emits a wavelength that is highly absorbed by water and therefore has a low penetration (3 μm). This in turn is associated with more ablation (2–4 μm per J/cm^2) and less thermal damage (10–15 μm). It soon became apparent, however, that a degree of thermal damage was necessary for haemostasis. In addition, the thermal damage that underlies CO_2 laser-treated sites may influence the thickness of subsequent fibrosis [1]. As a result, Er:YAG lasers were adapted to cause more rather than less thermal damage, in other words to make a wound more like that produced by a CO_2 laser. Attention eventually switched from ablative to non-ablative injury, the former having become undesirable on account of the morbidity of the burn wound.

Non-ablative photocoagulation. This has largely been applied to the effacement of wrinkles and acne scars and as such will be explored in detail in Chapter 80.

The aim of treatment is to selectively wound the upper dermis in order to induce dermal fibrosis (or collagen remodelling). The epidermis is protected and retained to avoid the problems of the open wounds caused by ablative modalities. Prerequisites for this are therefore epidermal cooling systems and wavelengths that are sufficiently long to penetrate and injure the dermis. A variety of lasers and flashlamps have been studied, including some originally developed for other purposes.

Radiofrequency and infrared devices designed to cause deep, volumetric heating and subsequent skin tightening have only been used for cosmetic purposes and will be discussed in the relevant chapter.

Fractional photocoagulation. An erbium glass laser (1540 nm) emits light through a fibre with an optical deflection and focusing system. This causes microscopic treatment zones (MTZs) of non-ablative coagulative damage to the epidermis and upper dermis. The diameter of MTZs is about 100 μm, and their depth and density determine the clinical response. These heal with micro-epidermal necrotic debris (MENDs), which supposedly remove pigment, and with subsequent fibrosis [2].

This technology improves fine wrinkles and possibly melasma and is described in more detail in Chapter 80.

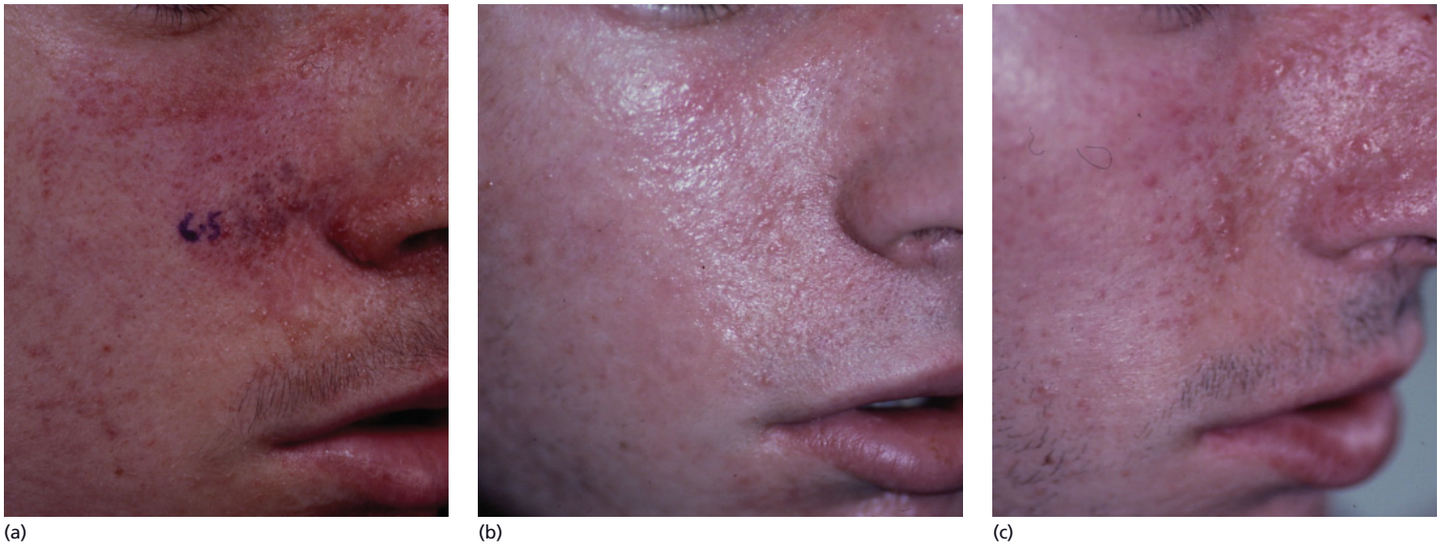
Fractional ablative resurfacing. At the time of writing, this is a clinical prototype, the development of which may be consequent upon the subtle clinical effects of fractional and other non-ablative photocoagulation. A CO_2 laser (10 600 nm) with a scanned 120 μm spot is used to create MTZs of ablative injury [3]. It is likely to occupy a place between fractional photocoagulation and ablative resurfacing in terms of increased efficacy (and increased morbidity) in cosmetic applications.

Devices in common use

Ablative

Carbon dioxide (CO_2) (10 600 nm) laser. The CO_2 laser produces light (10 600 nm) that is relatively poorly absorbed by the chromophore, water, and which therefore penetrates relatively deeply (30 μm). The beam can be operated in continuous wave or can be pulsed or Q-switched using a rotating mirror or electro-optical switch. Incisional surgery is achieved using a focused beam, whereas ablative resurfacing is effected by the scanning of either focused or high-power, wide-diameter beams. For ablation, the fluence should exceed the vaporization threshold of skin (5 J/cm^2) [4] and the pulse duration (or its laser equivalent, the 'dwell time') should be shorter than the TRT of 700–950 μs [5]. These lasers have recently been modified to perform fractional ablative resurfacing.

Erbium:yttrium aluminium garnet (ER:YAG) (2940 nm) laser. This laser emits light with a higher absorption coefficient for water and a lower optical penetration depth than the CO_2 laser. These lasers are used for ablative resurfacing and more recently have been modified for fractional procedures.



(a) (b) (c)

Fig. 78.12 Angiofibromas, (a) before, (b) 6 months after and (c) 24 months after CO_2 laser resurfacing, showing gradual recurrence of lesions over time.

Non-ablative

Neodymium:yttrium-aluminium-garnet (Nd:YAG) (1064 and 1320 nm), diode (1450 nm) and erbium:glass (1540 nm) lasers. These all produce infrared light which is absorbed by melanin or by water in collagen.

Skin disorders treated with photothermal excision and ablation

CO_2 laser incisional surgery may confer an advantage over conventional scalpel incisions because of associated haemostasis due to thermal damage around the beam. A potential disadvantage is that thermal damage of the apposed wound edges may result in slower healing and a more obvious scar. This technique may be most useful in making surgical wounds that are to heal by second intention. One example is the dissection of head and neck keloids below the hair follicles through the subcutaneous fat. Results have varied [6] but are probably better on the head than at other sites, particularly if augmented with intralesional corticosteroids before and after re-epithelialization. A difficulty in performing or assessing studies on keloids is defining what is meant by cure.

Ablative modalities remain the most effective means of resurfacing wrinkles and some acne scars, although with increased morbidity. This is explored in more detail in Chapter 80.

Epidermal dysplasia and neoplasia

CO_2 laser ablation is a useful option in treating actinic cheilitis as well as Bowen's disease on periungual folds and on the glans penis. Superficial basal cell carcinomas have also been managed with laser ablation, although this is unlikely to be the treatment of choice.

Appendigeal tumours and hyperplasia

Familial trichoepitheliomas and angiofibromas can be flattened with lasers, but lesions recur over time in some patients. It is possible that this can be prevented by making a deeper wound and preventing recurrence by eliciting more fibrosis [7].

Peri-orbital syringomas and xanthelasmas can be managed with any of a number of destructive modalities, including CO_2 laser ablation. In peri-orbital skin, the dermis is thin and it may be difficult to ablate to a depth where the procedure is not followed by either recurrence of the lesions (Fig. 78.12) or by colour and texture change. Newer, non-ablative modalities may be preferable for these conditions and for sebaceous hyperplasia. Rhinophyma can be recontoured for cosmetic purposes and in order to relieve nasal obstruction, when present.

Dermal inflammatory infiltrates

Granuloma faciale and cutaneous facial sarcoid usually present with flat, violaceous lesions which have been reported to respond to pulsed-dye laser treatment, although it seems likely that their colour owes more to the infiltrate than ectatic vessels. Plaques of granuloma faciale can be flattened with a CO_2 laser and will reform slowly, if at all. Likewise, plaques and nodules of facial sarcoid can be usefully and often indefinitely debulked if the disease is stable [8].

Miscellaneous

A number of other, unrelated conditions have been treated with CO_2 laser ablation, including periungual and plantar warts, axillary Hailey–Hailey disease and vulval lymphangiectasia/lymphangioma [9].

Skin disorders treated with non-ablative photocoagulation

These modalities are widely used for cosmetic purposes and are described elsewhere. They may have a role in treating xanthelasmas and sebaceous hyperplasia.

Complications of photothermal ablation

The risk is dependent on the depth of photothermal ablation. Before re-epithelialization, the major complication is infection and this occurs in about 4% of patients after full-face resurfacing. It is

usually due to staphylococci, although infections with *Candida* species and herpes simplex have also been implicated, and all may cause scarring. Complications after the third week include acneiform folliculitis and milia formation, contact reactions, dyspigmentation and scarring. Post-operative erythema occurs in all patients and its duration is mainly a reflection of wound depth [10]. Hypopigmentation is not usually apparent until 6 months postoperatively and may be caused by loss of epidermal melanin or by underlying fibrosis. This is now quoted as one of the reasons for the swing from ablative to non-ablative resurfacing.

References

1 Ross EV, McKinlay JR, Anderson RR. Why does carbon dioxide resurfacing work? *Arch Dermatol* 1999; **135**: 444–54.
2 Manstein D, Herron GS, Sink RK *et al*. Fractional photothermolysis: a new concept for cutaneous remodelling using microscopic patterns of thermal injury. *Lasers Surg Med* 2004; **34**: 426–38.
3 Hantash BM, Bedi VP, Kapadia B *et al*. In vivo histological evaluation of a novel ablative fractional resurfacing device. *Lasers Surg Med* 2007; **39**: 96–107.
4 Walsh JJ, Deutsch TF. Pulsed CO_2 laser tissue ablation: measurement of the ablation rate. *Lasers Surg Med* 1988; **8**: 264–75.
5 Fitzpatrick RE, Goldman MP. Advances in carbon dioxide laser surgery. *Clin Dermatol* 1995; **13**: 35–47.
6 Apfelberg DB, Maser MR, Lash H *et al*. Preliminary results of argon and carbon dioxide laser treatment of keloid scars. *Lasers Surg Med* 1984; **4**: 283–90.
7 Bittencourt RCA, Huilgol SC, Seed PT *et al*. Treatment of angiofibromas with a scanning carbon dioxide laser: a clinicopathologic study with long-term follow-up. *J Am Acad Dermatol* 2001; **45**: 731–5.
8 O'Donoghue NB, Barlow RJ. Laser remodelling of nodular nasal lupus pernio. *Clin Exp Dermatol* 2005; **31**: 27–9.
9 Huilgol SC, Neill S, Barlow RJ. CO_2 laser therapy of vulval lymphangiectasia and lymphangioma circumscriptum. *Dermatol Surg* 2002; **28**: 575–7.
10 Ratner D, Tse Y, Marchell N *et al*. Cutaneous laser resurfacing. *J Am Acad Dermatol* 1999; **41**: 367–89.

Low-power lasers

There is anecdotal and conflicting evidence relating to the use of low-power lasers and light emitting diodes for expediting wound healing [1] and for treating aphthous ulcers [2]. Increases in collagen synthesis and stimulation of immune pathways have been proposed as mechanisms of action [3].

References

1 Abergel RP, Lyons RF, Castel JC *et al*. Biostimulation of wound healing by laser: experimental approaches in animal models and in fibroblast cultures. *J Surg Oncol* 1987; **13**: 127–33.
2 Howell RM, Cohen DM, Powell GL, Green JG. The use of low energy laser energy to treat aphthous ulcers. *Ann Dent* 1988; **47**: 16–18.
3 Babapour R, Glassberg E, Lask GP. Low-energy laser systems. *Clin Dermatol* 1995; **13**: 87–90.

Photodynamic therapy

Photodynamic therapy (PDT) using a topical photosensitizer has become a popular treatment for some forms of epidermal dysplasia and superficial neoplasia, as well as for some benign skin disorders.

The photodynamic reaction requires a sensitizer, light and oxygen. The main groups of exogenous photosensitizers are the porphyrin and chlorin derivatives and the phthalocyanines. Alternatively, the haem biosynthetic pathway can be used to generate the endogenous photosensitizer protoporphyrin IX (PpIX) from 5-aminolaevulinic acid (5-ALA) or its derivatives. It is possible to achieve preferential accumulation of PpIX in target tissue, which is then irradiated with a laser or non-coherent light source. This excites the PpIX molecule, which is necessary for the formation of free radicals and singlet oxygen, which in turn damage intracellular organelles [1].

Challenges in the development of this treatment modality are the optimal formulation, delivery and duration of application of the photosensitizer as well as the irradiance, wavelength and total dose of light [2].

Light–tissue interaction

5-aminolaevulinic acid (ALA)

PDT with topical 5-ALA has become popular in dermatology since its introduction by Kennedy *et al*. in 1990 [3]. Exogenous administration of 5-ALA bypasses the feedback control mechanism and causes increased intracellular concentrations of PpIX. This in turn is metabolized within 48 h, avoiding prolonged photosensitivity. ALA is hydrophilic and most studies [2] have used a 20% concentration as an oil-in-water emulsion which is applied for 3–6 h under a light-occlusive dressing. Penetration is improved if the epidermis overlying a lesion is abnormal, and can be enhanced through use of lipophilic methyl and other esters of ALA (e.g. methyl aminolaevulinate). Of more questionable benefit are iontopheresis and the penetration enhancer, dimethylsulphoxide. Preferential accumulation within tumours may be influenced by differences in haem synthesis and iron availability [4].

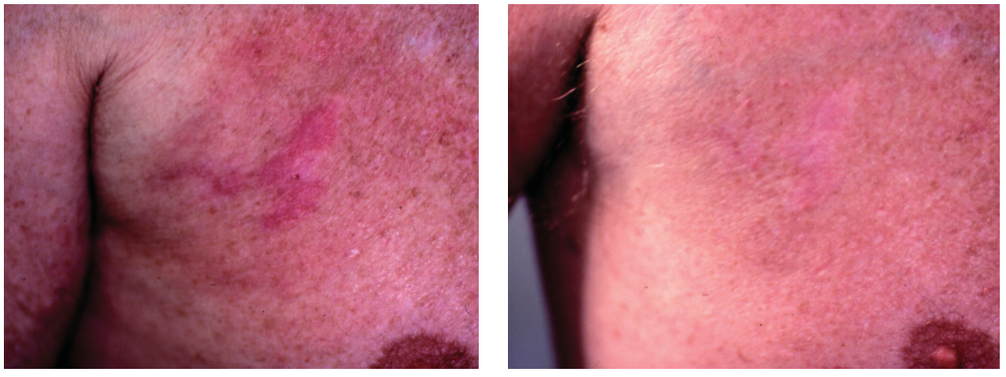
Other topical photosensitizers have also been used but data concerning these are still limited.

Light sources and doses

The absorption spectrum of porphyrins is maximal in the Soret band (centred around 410 nm), with smaller peaks between 500 and 635 nm (Q bands) [5]. In practice, lesions are irradiated with light at 630–635 nm. This corresponds to the lowest absorption peak but has better tissue penetration. Light of 630–670 nm may activate photoproducts of PpIX but probably has little clinical relevance [6]. Polychromatic light sources are as effective as lasers [7] but are cheaper and can irradiate larger skin areas with sufficiently high fluence rates (i.e. irradiance, W/cm^2) to keep treatment times within practical limits. In clinical studies, light dosage is usually estimated from the fluence (J/cm^2) alone. The limitation of this is that it does not account for variables relating to ALA, its pharmacodynamics, the wavelength or irradiance of the light or, indeed, to the tissue optics. Fluence rates higher than 50 W/cm^2 may affect oxygen availability, and if higher than 150 W/cm^2 may result in thermal injury [8].

Mechanism of action

The absorption of light excites the photosensitizer, which fluoresces as it reverts to the resting state. The excited molecule initiates two types of photo-oxidative reaction, one of which results in generation of singlet oxygen. Subsequent cell death is probably



(a) (b)

Fig. 78.13 A large superficial basal cell carcinoma on the chest, (a) before and (b) after one episode of photodynamic therapy.

mediated by apoptosis [9] and an inflammatory response secondary to direct cytotoxicity [10].

Topical PDT and skin disorders

As noted previously, clinical studies of PDT differ widely with respect to the formulation, delivery and duration of the photosensitizer (or its precursor). There is also variation in terms of the irradiance, wavelength and dose of the light and also in the light sources used. Furthermore, there are few controlled studies. It is therefore difficult to compare studies, and many reviews have had to resort to individual summaries of each and every one of them.

It is possible, however, to make the following broad observations [11]:

Actinic keratoses

Most studies have used a 20% formulation of ALA applied for 3–6 h. It seems likely that methyl 5-ALA shows preferential accumulation in actinic keratoses. Green, blue or red light seem equally efficacious. Lesions that are not hyperkeratotic show an improvement of about 70% if on the face and about half of this if on the limbs. PDT is similar in efficacy to 5-fluorouracil (5-FU) or to cryotherapy, and may be better cosmetically.

Bowen's disease/SCC in situ

Methodology has been similar to that used for actinic keratoses. Clinical cure rates are about 80%, although a proportion relapse. The consensus seems to be that PDT is more effective than 5-FU or cryotherapy and associated with fewer adverse events.

Basal cell carcinoma (BCC)

Long-term, complete clearance rates of superficial (<2 mm thick) BCCs are 80–90% if treated once or twice (Fig. 78.13). This falls to about 50% in nodular BCCs, unless they are first curetted. Cure rates are even lower with infiltrative tumours.

Other indications

PDT has been applied to a wide range of unrelated, benign skin disorders. It may be effective in treating warts, although probably only if the warts are pared and if treatment is repeated. Low-dose single treatment of patients with acne has been attempted using red or blue light, sometimes using endogenous porphyrins, and reportedly to the benefit of some patients. Claims have been made for a role in photorejuvenation.

Associated morbidity

Topical PDT is painful, the degree of discomfort sometimes seeming to be disproportionate to the superficial nature of the lesions treated. Treatment is usually followed by erythema, oedema and crusting, often responsive to emollients or topical steroids. Local photosensitivity can occur, but is short-lived. Topical PDT is usually followed by a good cosmetic result, but may be complicated by dyspigmentation.

References

1 Fisher AMR, Murphee AL, Gomer CJ. Clinical and preclinical photodynamic therapy. *Lasers Surg Med* 1995; **17**: 2–31.

2 Morton CA, Brown SB, Collins S *et al*. Guidelines for topical photodynamic therapy: report of a workshop of the British Photodermatology group. *Br J Dermatol* 2002; **146**: 552–67.

3 Kennedy JC, Pottier RH, Pross DC. Photodynamic therapy with endogenous protoporphyrin IX: basic principles and present clinical experience. *J Photochem Photobiol B Biol* 1990; **6**: 143–8.

4 Uehlinger P, Zellweger M, Wagnieres G *et al*. 5-Aminolaevulinic acid and its derivatives: physical chemical properties and protoporphyrin IX accumulation in cultured cells. *J Photochem Photobiol B Biol* 2000; **54**: 72–80.

5 Soret JL. Recherches sur l'absortion des rayons ultra violets par diverses substances. *Arch Sci Phys Nat* 1883; **10**: 430–85.

6 Gudgin Dickson EF, Pottier RH. On the role of protoporphyrin IX photoproducts in photodynamic therapy. *J Photochem Photobiol B Biol* 1995; **29**: 91–3.

7 De Jode ML, Megilligan JA, Dilkes MG *et al*. A comparison of novel light sources for photodynamic therapy. *Lasers Med Sci* 1997; **12**: 260–8.

8 Peng Q, Warloe T, Berg K *et al*. 5 amino-levulinic acid-based photodynamic therapy. Clinical research and future challenges. *Cancer* 1997; **79**: 2282–308.

9 Agarwal ML, Clay ME, Harvey EJ *et al*. Photodynamic therapy induces rapid cell death by apoptosis in L5178Y mouse lymphoma cells. *Cancer Res* 1991; **51**: 5993–6.

10 Dougherty TJ, Gomer CJ, Henderson BW *et al*. Photodynamic therapy. *J Natl Cancer Inst* 1998; **90**: 889–905.

11 Kormeili T, Yamauchi PS, Lowe NJ. Topical photodynamic therapy in clinical dermatology. *Br J Dermatol* 2004; **150**: 1061–9.

CHAPTER 79

Radiotherapy and Reactions to Ionizing Radiation

C.G. Kelly[1] *& I. Peat*[2]

[1]Northern Centre for Cancer Treatment, Newcastle General Hospital, Newcastle upon Tyne, UK
[2]Oncology Unit, Leicester Royal Infirmary, Leicester, UK

Ionizing radiation in the treatment of skin cancer, 79.1
X-ray photon beams: megavoltage and kilovoltage X-ray therapy, 79.1
Electron beams, 79.1
Moulds and implants, 79.2
Radiotherapy treatment technique, 79.3
Radiosensitivity, 79.3
Indications for radiotherapy: benign skin disease, 79.4
Keloids, 79.4
Indications for radiotherapy: malignant skin disease, 79.5
Choice of treatment, 79.5
Postoperative radiotherapy treatment, 79.7
Radiotherapy dose fractionation and treatment regimens, 79.7
Dose and radiotherapy prescription, 79.7
Dose and fractionation, 79.8
Radiotherapy for particular skin sites: basal cell carcinoma and squamous cell carcinoma, 79.8
Radiotherapy for particular skin tumours, 79.12
Acute radiation reaction (acute radiodermatitis), 79.14
Late radiation reaction (chronic radiodermatitis), 79.16
Tumour recurrence after radiotherapy, 79.17
Radiation-induced tumours, 79.18
Rare tumours associated with previous irradiation, 79.18

Introduction

The clinical effects of ionizing radiation on the skin have been known since the discovery of X-rays in 1895 [1,2]. Initially both benign and malignant skin conditions were irradiated, and dose and clinical indications were chosen empirically with little knowledge of the late effects of radiation on skin and subcutaneous tissue. Indications for treating benign disease by irradiation have declined since the advent of topical steroids.

It is in the best interest of patients suffering from skin tumours to be seen in a clinic where the expertise of specialists in radiotherapy and oncology, plastic surgery and micrographic surgery as well as dermatology are present, and this is being achieved with the mandatory development of multidisciplinary team meetings and clinics in the UK, as described in the *Improving Outcomes* guidance [3].

References

1 Goldschmidt H, Sherwin WK. Reactions to ionizing radiation. *J Am Acad Dermatol* 1980; **3**: 551–79.
2 Halpern JN. Radiation therapy in skin cancer. A historical perspective and current applications. *Dermatol Surg* 1997; **23**: 1089–93.
3 National Institute for Health and Clinical Excellence. *Guidance on Cancer Services: Improving Outcomes for People with Skin Tumours Including Melanoma: The Manual,* February 2006. http://www.nice.org.uk/nicemedia/pdf/CSG_Skin_Manual.pdf

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.

Ionizing radiation in the treatment of skin cancer

X-ray photon beams: megavoltage and kilovoltage X-ray therapy

X-rays are part of the electromagnetic spectrum, of shorter wavelength and more energetic than UV light. The most commonly used form of therapeutic radiation is now megavoltage radiotherapy, using energies of greater than one million electron volts (>1 MeV) delivered by linear accelerators, in the treatment of deep-seated tumours. However, these beams are usually not suitable for the treatment of skin cancers because of their greater penetration and skin sparing properties. X-rays in the kilovoltage range (50–140 kV) are very suitable for treating skin cancer as their maximum energy is deposited on the surface. Fall off subsequently is exponential (Fig. 79.1), and some radiation dose reaches underlying subcutaneous structures. Higher voltage beams can be used for thicker tumours.

Electron beams

Beta rays are electrons and can be derived from radioactive isotopes, such as ^{90}Strontium, or produced by a linear accelerator. An electron beam differs from a superficial X-ray beam or other photon beams as the energy does not fall off exponentially as the beam goes through tissue but builds up to a peak and then falls off rapidly (Fig. 79.2). The depth of penetration is proportional to the energy of the beam. A useful treatment depth in centimetres is approximately one-third of the energy of the beam, so a 4.5-MeV

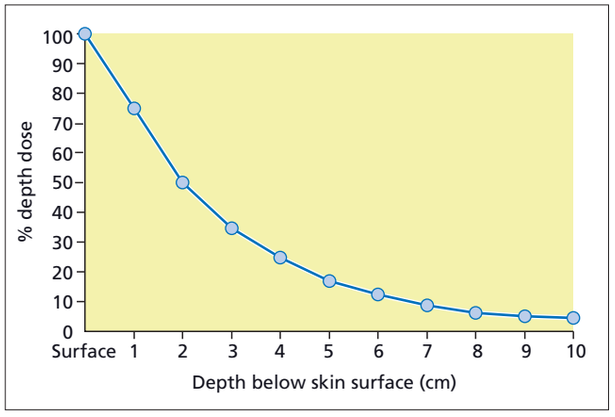


Fig. 79.1 Approximate per cent depth dose values for 90 kV superficial X-ray beam.

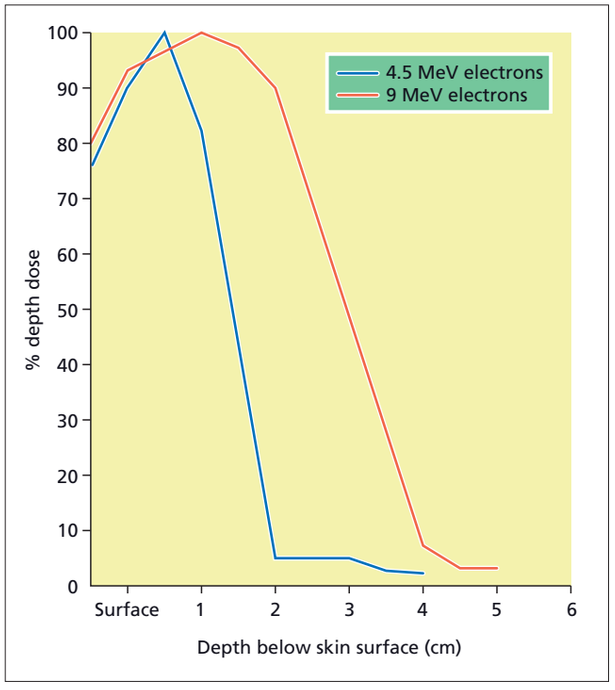


Fig. 79.2 Approximate per cent depth dose curves for 4.5 and 9 MeV electron beams.

electron beam will be useful for treating to a depth of 1.5 cm, and a 12-MeV beam to 4 cm. The width at the peak of the beam also increases with electron energy, giving more of the plateau at the peak at higher energies, as shown by the representation of the 9-MeV beam shape in Fig. 79.2. This can be useful when trying to enclose all of a thick tumour within the highest energy part of the beam. To avoid skin sparing, tissue equivalent material such as wax or paraffin gauze is applied over the tumour so that energy is deposited in this 'build-up' material, moving the beam peak left towards the skin surface in Fig. 79.2.

Superficial X-ray therapy is indicated for the majority of skin cancer treatments. However, there is a slightly higher risk of late bone and cartilage necrosis with this modality, as X-rays are absorbed proportionally more in high-molecular-weight tissues than in soft tissue. Electrons are absorbed similarly in all tissues, and have the advantage of sparing sensitive underlying tissues. This may be the modality of choice for tumours on the pinna, scalp, dorsum of the hand and tibia. Superficial X-rays have been used successfully in the past in these sites [1], but electrons are preferred nowadays [2].

Unfortunately, in practice, electrons have limited use in the treatment of common skin cancers. As an electron beam is produced by a linear accelerator, which is much larger than a superficial X-ray machine, the treatment applicator is unwieldy and the minimum applicator size on the skin is 4 cm^2 for a reliable dose calculation. Air cavities can give unacceptable dose non-homogeneity with electrons, and eye shielding is not possible for the treatment of periorbital tumours. Setting up electron treatment fields is often more time-consuming than with superficial X-ray therapy.

It is possible to irradiate the whole skin area with an electron beam [3–8]. The minimal depth–dose characteristics that may be achieved avoid the irradiation of subcutaneous structures, which would occur if X-ray therapy was used as it is absorbed exponentially. This technique is used in the treatment of mycosis fungoides [4]. Multiple radiation fields are combined to give a homogeneous dose to the whole skin down to a depth of approximately 1 cm.

References

1 Caccialanza M, Piccinno R, Kolesnikova L. Radiotherapy of skin carcinomas of the pinna: a study of 115 lesions in 108 patients. *Int J Dermatol* 2005; **44**: 513–7.
2 Miller RA, Spittle MF. Electron beam therapy for difficult cutaneous basal and squamous cell carcinoma. *Br J Dermatol* 1982; **106**: 429–36.
3 Spittle MF. Mycosis fungoides. Electron beam therapy in England. *Cancer Treat Rep* 1979; **63**: 639–41.
4 Freiman A, Sasseville D. Treatment of mycosis fungoides: overview. *J Cutan Med Surg* 2006; **10**: 228–33.
5 Floyd SR, Pantanowitz L, McDermott DF *et al*. Plasma cell problems: Case 1. Disseminated cutaneous plasmacytomas treated with total skin electron radiotherapy. *J Clin Oncol* 2005; **23**: 3138–40.
6 Knobler E. Current management strategies for cutaneous T-cell lymphoma. *Clin Dermatol* 2004; **22**: 197–208.
7 Lundin J, Osterborg A. Therapy for mycosis fungoides. *Curr Treat Options Oncol* 2004; **5**: 203–14.
8 Fuks A, Bagshaw MA. Total-skin electron treatment of mycosis fungoides. *Radiology* 1971; **100**: 145–50.

Moulds and implants [1,2]

Other treatment modalities available for the irradiation of skin cancer, but in much less common use nowadays, are a 'mould', which is a cast loaded with radioactive material applied to the surface of the tumour and secured in place for the required treatment time, or interstitial brachytherapy (described below), as in the treatment of keloid. Use of these techniques has declined in recent years, because although cosmetic results are good there is a need for hospital admission for radiation protection reasons, and the results depend on local expertise.

References

1 Guix B, Finestres F, Tello J *et al*. Treatment of skin carcinomas of the face by high-dose-rate brachytherapy and custom-made surface molds. *Int J Radiat Oncol Biol Phys* 2000; **47**: 95–102.
2 Berridge JK, Morgan DAL. A comparison of late cosmetic results following two different radiotherapy techniques for treating basal cell carcinoma. *Clin Oncol (R Coll Radiol)* 1997; **9**: 400–2.

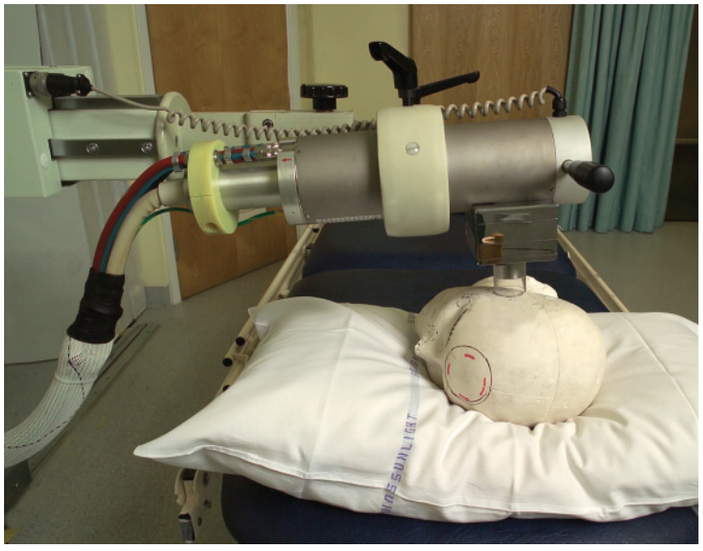
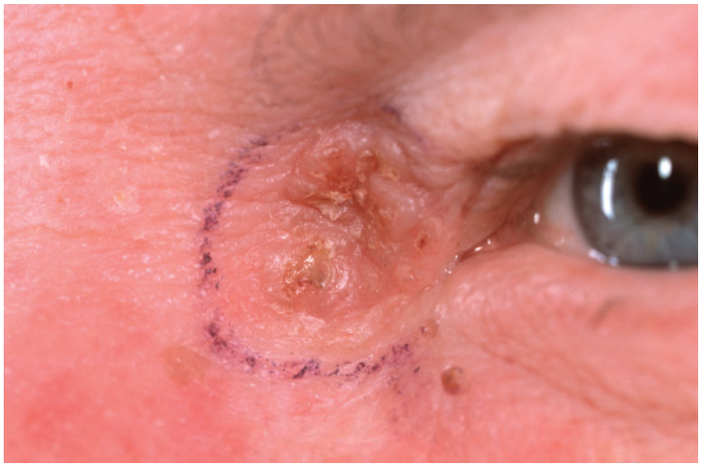


Fig. 79.3 Superficial X-ray machine.



(a)



(b)

Fig. 79.4 (a) Lead mask with area for treatment 'cut-out'. (b) BCC to be treated in this manner.

Radiotherapy treatment technique

The superficial X-ray tube is manoeuvrable and the patient can be made comfortable on a treatment couch with an applicator resting on the skin to be treated (Fig. 79.3). The tumour and a margin of normal tissue is treated with a standard applicator. If the tumour is an irregular shape in two dimensions, a piece of lead shielding 1.5 mm thick can be 'cut out' in the shape of the skin to be treated, and the applicator placed on this (Fig. 79.4). The individual surface area for treatment is measured and the treatment time adjusted by calculation, giving the number of machine units which have to be delivered for each treatment.

Once the applicator is in position, the radiographer leaves the treatment room. Treatments last for a few minutes on each occasion, and the patient is watched throughout using a remote camera system or special glass window.

Radiosensitivity

All radiation is destructive. The basis of radiotherapy is that abnormal cells repair radiation damage less well than normal cells. This inability to repair is reflected in death at mitosis. Anaplastic cells and those with a high mitotic index are more radioresponsive than differentiated cells. Radio-responsiveness and radio-curability are dissimilar and are functions of differences in cell population kinetics, so a rapidly resolving cancer may recur and a slowly resolving tumour may be completely cured. Radiotherapy is usually given as a fractionated course, as the intervals between doses allow for the recovery of normal cells. The effect of a dose of radiation is reduced by increasing the number of fractions in which it is given or by lengthening the total overall treatment time. The effect of irradiation can be modified by anoxia, infection, oedema, trauma and any inborn genetic susceptibility. The face tolerates irradiation well and radical dosages may be accompanied by good cosmetic results [1].

When irradiating benign conditions, the minimum dose and the lowest voltage appropriate to achieve the desired effect should be chosen. The threat of radiation carcinogenesis must clearly be seen in the context of the clinical indication for treatment. There is a threshold for somatic radiation changes which need not be breached in the treatment of benign conditions. The late radiation sequelae of treatment given many years ago are inexcusable with modern standards of dosimetry and equipment, and should not be seen in the treatment of benign diseases [2].

References

1 Fitzpatrick PJ, Thompson GA, Easterbrook WM *et al*. Basal and squamous cell carcinoma of the eyelids and their treatment by radiotherapy. *Int J Radiat Oncol Biol Phys* 1984; **10**: 449–54.

2 Traenkle HL. X-ray induced skin cancer in man. *Natl Cancer Inst Monogr* 1963; **10**: 423–32.



Fig. 79.5 Late sequelae after radiation treatment for ringworm—atrophy, pigmentation change, alopecia, telangiectasia and multiple BCCs.

Indications for radiotherapy: benign skin disease

Some of the misconceptions about the role of radiotherapy have arisen because of its widespread use in the past for the treatment of benign conditions. X-ray production was discovered in 1895, and soon afterwards it was noted that the antiproliferative effect of low energy X-rays was advantageous in the short term in a variety of visible tumours and benign dermatoses, and sometimes multiple retreatments were offered. There was, however, no dose measurement apart from the biological effect of 'skin erythema', no radiation protection for workers or patients, and no appreciation of the late effects of radiodermatitis, leukaemia and other malignancies, and of skin cancer induction after a very long latent period.

Radiation epilation for tinea capitis, a treatment offered widely in Europe, well demonstrates radiation carcinogenesis. In a series of 2200 who received X-ray epilation treatment for scalp ringworm during the 1940s and 50s, and who were subsequently followed by mail questionnaire for an average of 26 years, 41 had one or more BCCs of scalp or face (80 lesions in 41 cases), whereas there were only three BCCs in a comparable group of 1400 treated without X-ray [1]. Skin cancers induced by this treatment have a very long latent period, often over 30 years, and cases treated in the 1930s and 40s have been seen until recently in cancer treatment centres in the UK (Fig. 79.5). For a fascinating and well illustrated discussion of these early treatments and their consequences, see [2].

Radiotherapy is used much less now in the management of benign skin conditions than formerly and then usually only after other treatment modalities have failed or are contraindicated. In some conditions, such as psoriasis and eczema, there is a response to radiotherapy, but often only temporary [3–7]. This, coupled with the risk of late radiation-induced malignancy, has led to the decline in its use in all but the most refractory of cases. It is also still used occasionally in the management of keratoacanthoma where the differentiation from squamous cell carcinoma cannot be made with complete confidence [8–9]. Other rare uses are in Darier's disease, familial benign chronic pemphigus and acrodermatitis of Hallopeau [5–7].

Recent UK National Institute for Health and Clinical Excellence (NICE) guidance on the use of Grenz rays, which are very low kV X-rays absorbed chiefly in the epidermis, advises that the evidence for their safety and efficiency is very limited, and that their use in inflammatory skin conditions be limited to carefully selected patients, who are refractory to other treatments, and preferably under trial conditions, or at least with national data collections [3,7,10].

References

1 Shore RE, Albert RE, Reed M *et al*. Skin cancer incidence among children irradiated for ringworm of the scalp. *Radiat Res* 1984; **100**: 192–204.

2 Mould R. *A Century of X-rays and Radioactivity in Medicine, with Emphasis on Photographic Records of the Early Years*. Bristol: Institute of Physics Publishing, 1993.

3 Mortensen AC, Kjeldsen H. Carcinomas following Grenz ray treatment of benign dermatoses. *Acta Derm Venereol (Stockh)* 1987; **67**: 523–5.

4 Bleehen NM. Insights from radiation treatment for benign disease. *BMJ* 1987; **295**: 512–3.

5 Rowell NR. A follow-up study of superficial radiotherapy for benign dermatoses: recommendations for the use of X-rays in dermatology. *Br J Dermatol* 1973; **88**: 583–90.

6 Rowell NR. Ionizing radiation in benign dermatoses. In: Rook AJ, ed. *Recent Advances in Dermatology*, Vol. 4. Edinburgh: Churchill Livingstone, 1977: 329–50.

7 Fairris GM, Jones DH, Mack DP *et al*. Conventional superficial X-ray versus Grenz ray therapy in the treatment of constitutional eczema of the hands. *Br J Dermatol* 1985; **112**: 339–41.

8 Caccialanza M, Sopelana N. Radiation therapy of keratoacanthomas: results in 55 patients. *Int J Radiat Oncol Biol Phys* 1988; **16**: 475–7.

9 Donahue B, Cooper JS, Rush S. Treatment of aggressive keratoacanthomas by radiotherapy. *J Am Acad Dermatol* 1990; **23**: 489–93.

10 National Institute for Health and Clinical Excellence. *Interventional Procedure Overview of Grenz Rays Therapy for Inflammatory Skin Conditions.* March 2007. www.nice.org.uk/IPG236

Keloids

This is the most common benign condition now treated with radiotherapy. Intractable keloids resistant to intralesional steroids or other conventional treatment may respond well to radiation. Excision of the keloid with early irradiation of the scar and stitch marks is more successful, but in some sites, for example tip of shoulder and upper middle chest, where surgery is inadvisable, good response of pain, itch and redness can be achieved with some regression of the keloid itself. Relatively high doses are necessary; these will cause temporary pigmentation, which will remain for many months in pigmented skin. Doornbos *et al*. [1] noted that 17 of 18 unexcised keloids that were less than a year old regressed with 1500 cGy given in three treatments over 6 days at 120 kV. Older keloids respond less well to irradiation. The most satisfactory management of keloids is postexcision irradiation, where a dose–response relationship can be seen. Total doses less than 900 cGy, irrespective of fractionation and postsurgical interval, did not prevent recurrence. Three doses of 400 cGy were reported by Kovalic and Perez [2], to give a 73% success rate. Using the commonly employed dose of 900 cGy, Lo *et al*. [3]

described an 85% success rate and Borok *et al*. [4] a 96% response rate. No late sequelae or carcinogenesis was described by any of the previously quoted authors, with follow-up in excess of 30 years.

As well as using superficial X-rays, or electron beam radiotherapy [5], treatment can be given using a radioactive iridium wire implant. With the latter technique, at the time of excision, a small plastic tube is inserted below the incision, with both ends of the tube exposed. The patient is then transferred to the radiotherapy department within 24 h, and the tube is loaded with iridium wire, and the scar irradiated to a dose of 20 Gy at 2 mm from the wire over 2 days [6]. Escarmant *et al.* [7] describe the results of treating 783 keloid scars in 544 patients with interstitial iridium implants.

References

1 Doornbos JF, Stoffel SJ, Hass AC *et al*. The role of kilovoltage irradiation in the treatment of keloids. *Int J Radiat Oncol Biol Phys* 1990; **18**: 833–9.

2 Kovalic JJ, Perez C. Radiation therapy following keloidectomy: a 20-year experience. *Int J Radiat Oncol Biol Phys* 1989; **17**: 77–80.

3 Lo TCM, Seckel BR, Salzman FA *et al*. Single-dose electron beam irradiation in treatment and prevention of keloids and hypertrophic scars. *Radiother Oncol* 1990; **19**: 267–72.

4 Borok TL, Bray M, Sinclair I *et al*. Role of ionizing irradiation for 393 keloids. *Int J Radiat Oncol Biol Phys* 1988; **15**: 865–70.

5 Bischof M, Krempien R, Debus J, Treiber M. Postoperative electron beam radiotherapy for keloids: objective findings and patient satisfaction in self-assessment. *Int J Dermatol* 2007; **46**: 971–5.

6 Rio E, Bardet E, Ferron C. Interstitial brachytherapy of perioralfacial skin carcinomas of the face: a retrospective study of 97 cases. *Int J Radiat Oncol Biol Phys* 2005; **63**: 753–7.

7 Escarmant P, Zimmernann S, Amar A *et al*. The treatment of 783 keloid scars by iridium 192 interstitial irradiation after surgical excision. *Int J Radiat Oncol Biol Phys* 1993; **26**: 245–51.

Indications for radiotherapy: malignant skin disease

For most small basal cell carcinomas (BCCs) or squamous cell carcinomas (SCCs) without nodal involvement, surgical excision or radiotherapy will give excellent cure rates [1–4]. Superficial radiotherapy has a long history in the successful treatment of BCCs and SCCs of the skin—1695 such patients received treatment in 1945 at the Queensland Radium Institute [5]. A number of series have been reported, from 1947 onwards [6], showing cure rates of 90% or greater.

Choice of treatment

If cure is the intention, then surgery or radiotherapy are the treatment options, although a variety of other modalities, including cryotherapy, curettage and topical therapies, may provide temporary control [7,8].

The decision as to which is the most appropriate modality will depend on several factors. These include the size and location of the tumour, any involvement of underlying tissues and the likely functional and cosmetic outcome of either treatment. For small BCCs, simple excision with clear margins is ideal; it is within the remit of suitably trained practitioners and leads to good cosmesis with low recurrence rates. For larger BCCs and SCCs in critical sites, particularly around the eyes, ears and nose, plastic surgery and radiotherapy should be considered as treatment options.

The patient's overall condition is important, as is the complexity of any surgery required; even the distance from the patient's home to the radiotherapy centre may play a role in determining the choice of treatment. Social factors such as working patterns, transport availability and patient preference, where there may be a wish to avoid either surgery or multiple hospital visits for radiotherapy, have also to be taken into consideration. The decision as to which treatment modality is used should not be made solely on the basis of the patient's age. The advantages and disadvantages of each treatment modality should be explained to the patient in order to enable an informed, shared decision to be made.

If the lesion cannot be cured, again a compromise is reached. Some patients with multiple tumours elect to have treated only those that are causing symptoms. Some very large tumours will not be cured by any modality but might respond for a worthwhile period to palliative radiotherapy (Fig. 79.6).

Radiotherapy has a role to play in the treatment of almost all malignant skin conditions. Its use has been variable for several reasons. In some areas, traditional referral patterns have curtailed its use, and the siting of radiotherapy departments in the larger conurbations has not enabled universal access for all patients. Specialists have not always been aware of what various treatment modalities can offer [7]. Radiation damage, with skin atrophy, telangiectasia and necrosis and ulceration, occurred in the past, but this is now rare as a result of better dosimetry, a wider range of radiotherapy modalities [9] and more careful fractionation. Multidisciplinary team working will be strengthened in future, and with appropriate cooperation and communication between colleagues it is likely that all modalities will find their proper place, and the patient will receive optimal advice. This is in contrast with previous practice where only 2% of patients with BCC were referred to joint clinics [10], or a radiotherapeutic option was needlessly dismissed [11]. New UK national guidance [12] recommends that all health professionals treating skin cancer should be members of either a local hospital or a specialist skin cancer multidisciplinary team, and should work to locally approved protocols based upon nationally accepted guidelines, such as those of the British Association of Dermatologists [13]. The implementation of this guidance by the Cancer Networks, and the peer review process in prospect, can only improve the likelihood that the patient will receive optimum advice for their particular situation. A similar approach has been recommended in American guidelines [14].

It is not disputed that surgery offers a better cosmetic result, with the passage of time, nor that radiotherapy is able to preserve existing structure and function, although it is not of course able to replace tissue destroyed by tumour.

Few trials have been reported that compared surgery directly with radiotherapy. Avril *et al.* [15] showed that in 347 patients with facial tumours less than 4 cm in diameter, the recurrence rate within 3 to 5 years was 1/174 in the surgery group compared with 11/173 for radiotherapy. The cosmetic results were better with surgery. However, the radiotherapy regimens were heterogeneous, and the surgical results exceptionally good, better even than for Mohs surgery, where one large series had a 30-month recurrence



(a)



(b)

Fig. 79.6 (a) SCC too large to expect long-term cure. (b) Satisfactory control at 6 months.

of 3/160 tumours, compared with 5/171 for conventional surgery [16].

Published studies of radiotherapy for skin cancer do, however, report consistently high long-term control rates. Olschewski *et al.* [17] reviewed five studies treating over 5000 BCCs between 1984 and 2002, with a cure rate of over 93%, and similar results in 1267 cases treated in 1988–1992 were reported by Schulte *et al.* [18]. It is important in practice for the oncologist and plastic surgeon to be cooperative colleagues rather than rivals, each knowing what the other can offer.



(a)



(b)

Fig. 79.7 (a) SCC unsuitable for radiotherapy on the back. (b) SCC unsuitable for radiotherapy on the buttock.

Surgery preferred as primary treatment

Surgery is usually preferred to radiotherapy in a younger patient, where the cosmetic appearance of excision with or without grafting can be expected to become superior with the passage of time. Multiple lesions may also be conveniently treated at the same 'sitting'. There is evidence that radiotherapy is contraindicated in Gorlin's syndrome [12]. Bulky tumours and those requiring a field size of over 6 cm are best excised, as they are unlikely to be cured with radiotherapy. If the tumour has eroded bone or cartilage, both cure and re-epithelialization are unlikely with radiotherapy, and surgical reconstruction is preferred.

Certain anatomical sites also tolerate radiotherapy treatment less well, with more painful acute reactions and proneness to infection and slow healing; the trunk and perineum fall into this category (Fig. 79.7). Carcinomas below the knee are also better excised, as radiotherapy tends to be associated with slower healing and a risk of persistent ulceration [19].

Radiotherapy preferred as primary treatment

Radiotherapy is particularly suitable as a treatment modality for tumours of the face, especially the nose, lips, ears and around the orbit, where surgical removal may result in a poor cosmetic result or loss of function [20], or where complex surgical reconstruction would otherwise be required. Elderly patients on warfarin or with significant co-morbidity can usually tolerate treatment well, and are spared an invasive procedure and an anaesthetic. Treatment is delivered as an outpatient, and can often be accessed without a waiting list. Although the capital cost of the equipment is quite high, once installed it is a relatively cheap modality to run, and radiographer staffing can be provided efficiently from the radiographer pool if the machine is operating on certain limited days or times during the week.

There is little difference in outcome between external beam radiotherapy with either superficial X-rays or an electron beam [21]. Locally placed moulds or applicators have also been used for malignant skin tumours, placing a radioactive source over the tumour and leaving this in position for a predetermined period [9,10], or implanting radioactive wire into the tumour-bearing tissue.

The areas that have traditionally been considered as not suitable for radiotherapy, such as pinna, dorsum of the hand or anterior lower leg, can be treated if careful consideration is given to the volume treated, the total dose and the fractionation. It is also important to consider the general fitness of the patient and the condition of the skin in the site to be treated [22–25].

There are some patients who, for practical reasons, cannot have radiotherapy; for example, if they are unable to lie still because of confusion or neurological disease it can be impossible to deliver radiotherapy effectively and safely.

Postoperative radiotherapy treatment

Although ideally the patient should receive a single curative modality of treatment, sometimes in individuals who have had a macroscopic excision of a SCC or a BCC histology indicates extension beyond the excision margins. For squamous carcinoma, because of the consequences of recurrence and nodal spread, it is sensible to offer 'postoperative' radiotherapy to the scar and tumour bed, using the normal dose and fractionation regimens. With a well-healed scar or skin graft, the radiation reaction is often very mild. Adjuvant radiotherapy has been advocated by some authors [26–28] where there has been inadequate excision and further surgery is either not possible or not recommended, or if the tumour shows prognostic indicators of poor outcome such as positive lymph nodes, especially with extra-capsular spread, a large primary SCC or in higher-risk primary tumours of the head and neck. Adjuvant radiotherapy may improve outcome even after Mohs surgery [28], and there is some evidence that delaying radiotherapy may result in early tumour recurrence [29].

The situation is different for BCC. Liu *et al*. [30] reported a series of 187 incompletely excised BCCs; 119 had immediate postoperative radiotherapy, one was excised and 67 were managed expectantly. The 5-year probability of remaining relapse-free in the group immediately treated was 91% versus 61% if managed expectantly. Once relapse occurred in the group of lesions treated expectantly, 85% of the relapses were salvaged by radiation or surgery. The 10-year actuarial probability of local control for the lesions immediately treated and observed were similar—92% and 90%, respectively. Not all patients therefore require radiotherapy, and it can be reasonable to wait and see, particularly in the elderly where a 'lifetime' cure may be anticipated. To wait for recurrence also allows an appropriate treatment field to be determined. The patient will often have a preference for one particular course of action.

Table 79.1 Commonly used superficial radiotherapy dosage regimens for skin BCC and SCC.

Total dose	No. of fractions	Fractionation interval
18 Gy	1	—
28 Gy	2	7 weeks apart
35 Gy	5	Daily (for tumours less than 4 cm in diameter)
45 Gy	10	Daily (for tumours more than 4 cm in diameter)

These fractionation regimens are only examples. Many centres will have other similar but locally derived dose fraction regimens.

Radiotherapy dose fractionation and treatment regimens

Radiotherapy doses have evolved empirically over a long period of time and there is a wide range in use. As a rule, the greater the fractionation employed, that is the more the total dose is broken down into smaller fractions, the better the cosmetic effect. This is obviously very important to some patients, but others are content to accept a poorer cosmetic effect if it allows fewer visits to hospital (Table 79.1).

Dose and radiotherapy prescription

The SI unit of absorbed dose is called the Gray (Gy), and is 1 Joule/kilogram. This unit has replaced the rad. Note that 100 rad = 1 J/kg = 1 Gy; 1 rad = 1 cGy (centiGray). The dose prescription is defined by the total dose given, the energy of the beam, the number of fractions given, the total number of days over which treatment is given and the volume or area treated. For example, a typical prescription for the treatment of a small basal cell carcinoma might be '35 Gy using 90 kV superficial X-ray beam given in five fractions over 5 days to a 3-cm diameter circular area'. This time–dose relationship is crucial to understanding the biological effect.

It is often possible to see the patient as a new case and start treatment on the same day. A clinically obvious BCC is commonly treated without a tissue biopsy but it is prudent to obtain biopsy confirmation if the lesion could be a SCC, as wider treatment margins are usually advisable, and the follow-up for recurrence and lymph node metastasis differs.

The field size must be adequate to cover the extent of the tumour, with a margin of at least 5 mm, and the correct energy chosen for clearance at depth. Stretching the skin and use of a bright light will often show the extent of subepidermal infiltration of tumour. The morphoeic BCC has the reputation of a high 'recurrence rate', but regrowth of tumour is often because of a 'geographical miss'

at the edge of the field, and a failure to apply adequate margins. The oncologist marks the field to be treated directly on the patient's skin with a felt-tipped pen. The radiographer is responsible for the necessary calculations, and for delivering the dose as prescribed to this exact area of skin. For a thin BCC, 80 Kv X-rays are perfectly adequate, but if deeper penetration is suspected, or there is possibility of spread through underlying tissue planes, as for example in the nasolabial fold, a higher Kv energy can be chosen, and the radiographer instructed to apply the applicator very firmly to flatten the tissues.

Dose and fractionation

Dose and fractionation regimens are similar for BCC and SCC. There is a small therapeutic ratio between tumour cure and normal tissue necrosis, and even a slight alteration of dose or fractionation can be critical; in a retrospective study of 1005 BCCs and SCCs treated by superficial X-rays in 1976 at the Christie Hospital, Manchester, Chan *et al*. [31] found that for a field size of 3 cm^2 or less, a single fraction of 20 Gy gave a 10-year disease free rate of over 90%, with a late necrosis rate of 6%. An increase of dose to 22.5 Gy did not improve tumour control rates, but did significantly increase late necrosis, although of 60 patients with necrosis, spontaneous healing was common, and only 10 proceeded to surgical excision.

Fractionated radiotherapy is usually offered for larger tumours, as it is more likely to produce tumour control and a better long-term cosmetic result [6,32,33]. In addition, the brisker the primary treatment, the more painful the acute reaction, as there is less repair of sublethal damage in normal tissue between treatment fractions.

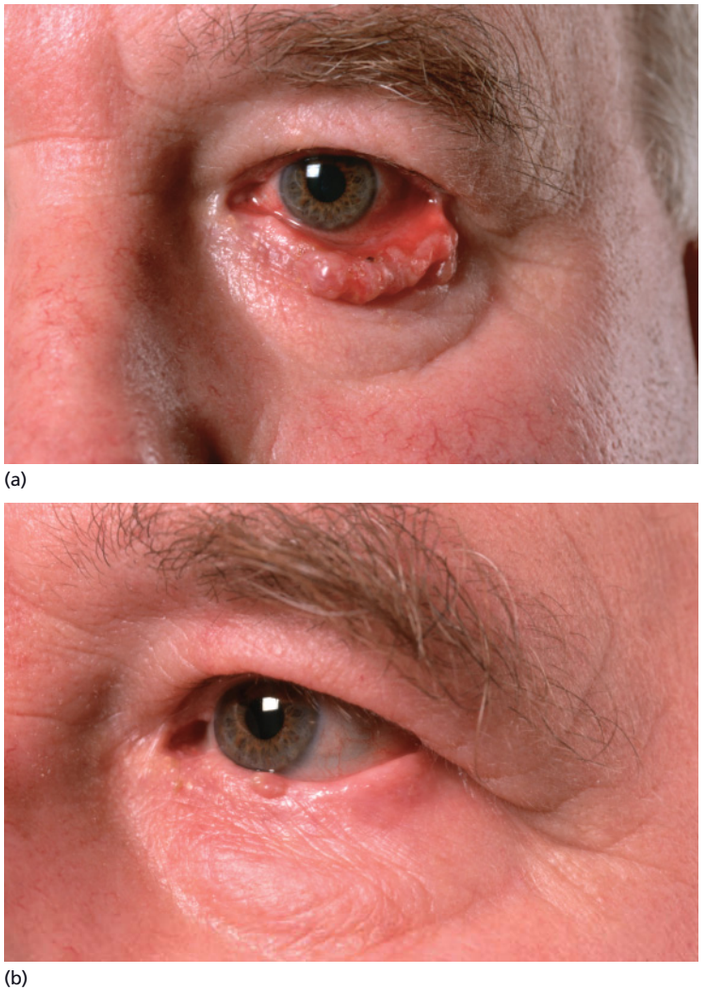
References

1 Locke J, Karimpour S, Young G *et al*. Radiotherapy for epithelial skin cancer. *Int J Radiat Oncol Biol Phys* 2001; **51**: 748–55.
2 Morrison WH, Garden AS, Ang KK. Radiation therapy for nonmelanoma skin carcinomas. *Clin Plast Surg* 1997; **24**: 719–29.
3 Goldschmidt H, Breneman JC, Breneman DL. Ionizing radiation therapy in dermatology. *J Am Acad Dermatol* 1994; **30**: 157–82.
4 Ashby MA, McEwan L. Treatment of non-melanoma skin cancer: a review of recent trends with special reference to the Australian scene. *Clin Oncol (R Coll Radiol)* 1990; **2**: 284–94.
5 Kearsley H, Harris TJ, Bourne RG. Radiotherapy for superficial skin cancer at the Queensland Radium Institute: famine in the land of plenty. *Int J Radiat Oncol Biol Phys* 1988; **15**: 995–9.
6 Rowe DE, Carroll RJ, Day CL Jr. Long-term recurrence rates in previously untreated (primary) basal cell carcinoma: implications for patient follow-up. *J Dermatol Surg Oncol* 1989; **15**: 315–28.
7 Bath-Hextall FJ, Perkins W, Bong J *et al*. *Interventions for Basal Cell Carcinoma of the Skin*. 2007, The Cochrane Collaboration.
8 Dubin N, Kopf AW. Multivariate risk score for the recurrence of cutaneous basal cell carcinomas. *Arch Dermatol* 1983; **119**: 373–7.
9 Guix B, Finestres F, Tello J *et al*. Treatment of skin carcinomas of the face by high-dose-rate brachytherapy and custom-made surface molds. *Int J Radiat Oncol Biol Phys* 2000; **47**: 95–102.
10 Motley RJ, Gould DJ, Douglas WS, Simpson NB. Treatment of basal cell carcinoma by dermatologists in the United Kingdom. British Association of Dermatologists Audit Subcommittee and the British Society for Dermatological Surgery. *Br J Dermatol* 1995; **132**: 437–40.
11 Kuijpers DI, Thissen MR, Neumann MH. Basal cell carcinoma: treatment options and prognosis, a scientific approach to a common malignancy. *Am J Clin Dermatol* 2002; **3**: 247–59.
12 National Institute for Health and Clinical Excellence. *Guidance on Cancer Services: Improving Outcomes for People with Skin Tumours Including Melanoma: The Manual*, February 2006. http://www.nice.org.uk/nicemedia/pdf/CSG_Skin_Manual.pdf
13 British Association of Dermatologists Clinical Guidelines. http://www.bad.org.uk/healthcare/guidelines/
14 National Comprehensive Cancer Network. *Basal Cell and Squamous Cell Skin Cancer Clinical Practice Guidelines*. www.nccn.org/professionals/physician_gls/PDF/nmsc.pdf
15 Avril MF, Auperin A, Margulis A *et al*. Basal cell carcinoma of the face: surgery or radiotherapy? Results of a randomised study. *Br J Cancer* 1997; **76**: 100–6.
16 Smeets NWJ, Krekels GAM, Ostertag JU *et al*. Surgical excision vs Mohs' micrographic surgery for basal cell carcinoma of the face: randomised controlled trial. *Lancet* 2004; **364**: 1766–72.
17 Olschewski T, Bajor K, Lang B *et al*. Radiotherapy of basal cell carcinoma of the face and head: importance of low dose per fraction on long-term outcome. *J Deutschen Dermatologischen Gesellschaft* 2006; **4**: 124–30 (German: English Abstr.).
18 Schulte KW, Lippold A, Auras C *et al*. Soft X-ray therapy for cutaneous basal cell and squamous cell carcinomas. *J Am Acad Dermatol* 2005; **53**: 993–1001.
19 Podd TJ. Treatment of lower limb basal cell and squamous cell carcinomas with radiotherapy. *Clin Oncol* 1992; **4**: 44–5.
20 Petrovich Z, Kuisk H, Langholz B *et al*. Results and patterns of failure in 646 patients with carcinoma of the eyelids, pinna, and nose. *Am J Surg* 1987; **154**: 147–50.
21 Griep C, Davelaar J, Scholten AN *et al*. Electron beam therapy is not inferior to superficial X-ray therapy in the treatment of skin carcinoma. *Int J Radiat Oncol Biol Phys* 1995; **32**: 1347–50.
22 Silva JJ, Tsang RW, Panzarella T *et al*. Results of radiotherapy for epithelial skin cancer of the pinna: the Princess Margaret Hospital experience, 1982–1993. *Int J Radiat Oncol Biol Phys* 2000; **47**: 451–9.
23 Avila J, Bosch A, Aristizabal S *et al*. Carcinoma of the pinna. *Cancer* 1977; **40**: 2891–5.
24 Lim JT. Irradiation of the pinna with superficial kilovoltage radiotherapy. *Clin Oncol (R Coll Radiol)* 1992; **4**: 236–9.
25 Bertelsen K, Gadeberg C. Carcinoma of the eyelid. *Acta Radiol Oncol Radiat Phys Biol* 1978; **17**: 58–64.
26 Geohas J, Roholt NS, Robinson JK. Adjuvant radiotherapy after excision of cutaneous squamous cell carcinoma. *J Am Acad Dermatol* 1994; **30**: 633–6.
27 Han A, Ratner D. What is the role of adjuvant radiotherapy in the treatment of cutaneous squamous cell carcinoma with perineural neural invasion? *Cancer* 2007; **109**: 1053–9.
28 Garcia-Serra A, Hinerman, RW, Mendenhall WM. Carcinoma of the skin with perineural invasion. *Head Neck* 2003; **25**: 1027–33.
29 Fogarty GB, Burt J, Ainslie J. Delay of postoperative radiotherapy in high risk skin cancer can be associated with recurrence. *J Plast Reconstr Aesthet Surg* 2006; **59**: 203–5.
30 Liu FF, Maki R, Warde P *et al*. A management approach to incompletely excised basal cell carcinomas of skin. *Int J Radiat Oncol Biol Phys* 1991; **20**: 423–8.
31 Chan S, Dhadda AS, Swindell R. Single fraction radiotherapy for small superficial carcinoma of the skin. *Clin Oncol* 2007; **19**: 256–9.
32 Hliniak A, Maciejewski B, Trott K. The influence of the number of fractions, overall treatment time and field size on the local control of cancer of the skin. *Br J Radiol* 1983; **56**: 596–8.
33 Berridge JK, Morgan DA. A comparison of late cosmetic results following two different radiotherapy techniques for treating basal cell carcinoma. *Clin Oncol (R Coll Radiol)* 1997; **9**: 400–2.

Radiotherapy for particular skin sites: basal cell carcinoma and squamous cell carcinoma

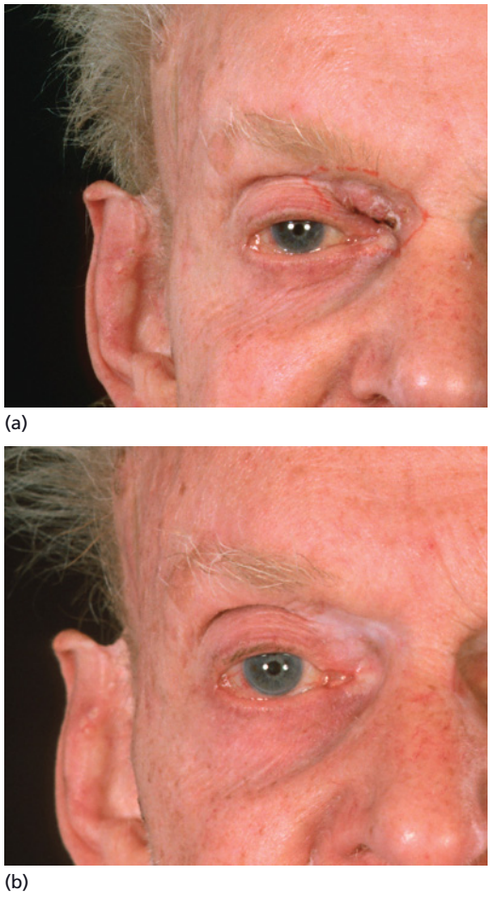
Eyelid (Fig. 79.8)

The upper eyelid, a rare site for skin cancer, is best treated surgically, as keratinization of the conjunctiva of the inner upper lid leads to traumatic damage subsequently. Tumours of the lower eyelid, however, are often suitable for superficial X-rays.



(a) (b)

Fig. 79.8 (a) BCC lower eyelid. (b) The same patient, 6 months after superficial X-ray treatment.



(a) (b)

Fig. 79.9 (a) BCC upper inner canthus. (b) The same patient, 5 years after superficial X-ray treatment.

A protective metal internal eyeshield is placed like a large contact lens over the globe of the eye, after the insertion of local anaesthetic eye drops, with an applicator resting on this and on the lower lid tumour (including an appropriate margin). Even the whole lower eyelid can be successfully treated in this manner.

Inner canthus (Fig. 79.9)

These tumours, close to the orbit, have a high cure rate if there is meticulous attention to dose calculation. An individual, thin lead mask is made for the patient by the 'mould room' technicians, with the treatment area cut out. This provides a seating for the applicator, avoids the possibility of trauma on the treated side, and protects the contralateral eye from the exit beam. If the nasolacrimal duct has been damaged by tumour and the patient has epiphora for this reason, then radiotherapy is not likely to reverse this symptom. However, it is uncommon for radiation *per se* to cause a new stenosis of the ductal system. Different authors advocate either radiotherapy or Mohs micrographic surgery depending on the size of tumour, potential for disfigurement or loss of function [1,2].

Ear (Figs 79.10 & 79.11)

Because tumours of the pinna and outer ear canal have close proximity to cartilage, electrons are preferred for treatment (see above), although in a study of 62 patients treated by kilovoltage techniques [3] of six apparent necroses, five healed spontaneously and only one required resection, with 97% local tumour control. A large Canadian study [4] showed that a persistent ulceration rate of 3% did not relate to beam energy, but to dose and fractionation, with control of cancer at 10 years of 93%. However, electron treatment does give very good results for tumours covered by a 4- or 5-cm diameter applicator [5] and most departments nowadays will offer electrons, unless for any reason the patient is unable to tolerate the linear accelerator procedures. The visible tumour is delineated, with a margin of up to 1 cm to account for the depth–dose characteristics of the electron beam, and the fact that the smallest reliable treatment applicator size is 4 cm diameter. The patient lies on the treatment couch with the ear for treatment uppermost, and wax or paraffin gauze is applied to make a level treatment surface. A lead shield protects the scalp. Once this 'sandwich' is in place, the applicator is brought down firmly on the surface, and treatment is delivered using 5 or 6 Mev electrons.



(a)



(b)

Fig. 79.10 (a) BCC upper pinna. (b) The same patient, 6 weeks after electron beam therapy.



(a)



(b)

Fig. 79.11 (a) BCC posterior aspect of the ear. (b) The same patient, 6 months after electron beam treatment.

Nose

Although skin cancers are here very closely applied to cartilage, in practice superficial X-rays give excellent control rates, and often a better cosmetic result than tumours irradiated at other sites. A lead plug is inserted inside the nostril to protect the nasal mucosa from the exit beam. At the nasolabial fold, the depth to be treated needs careful consideration.

Lip (Fig. 79.12)

Squamous cell carcinoma of the lip has a high local cure rate with radiotherapy using either electrons or kilovoltage X-rays [6]. Treatment margins should be generous, because of the tendency to spread mucosally (usually at least 1 cm of apparently normal tissue). The whole thickness of the lip is treated, choosing appropriate electron energy and build-up wax, or higher energy kilovoltage X-rays (300 Kv). A wax-coated lead gum shield protects the inner mouth from the exit beam, but a patch of sore mucositis inside the lip is inevitable, and will interfere with normal eating and drinking for a few days after treatment.

The patient is usually able to tolerate treatment to most of the upper or lower lip at a time, but not both areas simultaneously. The final cosmetic result is usually excellent.

Other areas of the face (Fig. 79.13)

Even large BCCs can do well with radiotherapy.

Parotid and cervical lymph node involvement from cutaneous squamous cell carcinoma

A subset of patients who develop cutaneous squamous cell carcinoma of the skin of the head and neck risk developing regional disease within parotid or cervical nodes, with worse outcomes [7]. Several studies have now shown that adjuvant radiotherapy gives higher rates of local control in this patient group than if they were treated with surgery alone [7–10], for both parotid and cervical node involvement [11].



(a)



(b)

Fig. 79.12 (a) SCC lip. (b) The same patient, 8 years after higher energy kilovoltage treatment.



(a)



(b)

Fig. 79.13 (a) Large BCC pre-auricular skin. (b) The same patient, 6 months after superficial X-ray treatment.

Parotid node involvement, if considered separately from cervical nodal disease, has been shown to act as an independent prognostic factor for survival, and patients with both parotid and neck node involvement do worse than those with either parotid or neck node involvement alone [12].

References

1 Leshin B, Yeatts P, Anscher M *et al*. Management of periocular basal cell carcinoma: Mohs' micrographic surgery versus radiotherapy. *Surv Ophthalmol* 1993; **38**: 193–212.

2 Malhotra R, Huilgol SC, Huynh NT *et al*. The Australian Mohs' database, part ii: periocular basal cell carcinoma outcome at 5-year follow-up. *Ophthalmology* 2004; **111**: 631–6.

3 Lim JTW. Irradiation of the pinna with superficial kilovoltage radiotherapy. *Clin Oncol (R Coll Radiol)* 1992; **4**: 236–9.

4 Hayter CRR, Lee KHY, Groome PA *et al*. Necrosis following radiotherapy for carcinoma of the pinna. *Int J Radiat Oncol Biol Phys* 1996; **36**: 1033–7.

5 Hunter RD, Pereira DTM, Pointon RCS. Megavoltage electron beam therapy in the treatment of basal and squamous cell carcinomata of the pinna. *Clin Radiol* 1982; **33**: 341–5.

6 Sykes AJ, Allan E, Irwin C. Squamous cell carcinoma of the lip: the role of electron treatment. *Clin Oncol (R Coll Radiol)* 1996; **8**: 384–6.

7 Veness MJ, Porceddu S, Palme CE. Cutaneous head and neck squamous cell carcinoma metastatic to parotid and cervical lymph nodes. *Head Neck* 2007; **29**: 621–31.

8 Jol JA, Van Velthuysen ML, Hilgers FJ *et al*. Treatment results of regional metastasis from cutaneous head and neck squamous cell carcinoma. *Eur J Surg Oncol* 2003; **29**: 81–6.

9 Audet N, Palme CE, Gullane PJ. Cutaneous metastatic squamous cell carcinoma to the parotid gland: analysis and outcome. *Head Neck* 2004; **26**: 727–32.

10 Hong TS, Kriesel KJ, Hartig GK. Parotid area lymph node metastases from cutaneous squamous cell carcinoma: implications from diagnosis, treatment, and prognosis. *Head Neck* 2005; **27**: 851–6.

11 Ch'ng S, Maitra A, Lea R. Parotid metastasis—an independent prognostic factor for head and neck cutaneous squamous cell carcinoma. *J Plast Reconstr Aesthet Surg* 2006; **59**: 1288–93.

12 Veness MJ, Morgan GJ, Palme CE. Surgery and adjuvant radiotherapy in patients with cutaneous head and neck squamous cell carcinoma metastatic to lymph nodes: combined treatment should be considered best practice. *Laryngoscope* 2005; **115**: 870–5.

Radiotherapy for particular skin tumours

Basal cell carcinoma. Radiotherapy is useful for the primary treatment of small basal cell carcinomas or larger lesions where surgery will leave a poor functional or cosmetic result. Radiotherapy also has a role to play after primary surgery if the margins are ambiguous and further surgery is thought not to be appropriate for the patient. It should not be used for re-treating BCCs which have recurred after previous radiotherapy. The morphoeic BCC subtype or the presence of underlying bone or cartilage involvement are relative contraindications for the use of radiation treatment, but even in the latter situation, radiotherapy can be given safely and effectively [1].

Squamous cell carcinoma of the skin. As with BCC, radiotherapy can be used as either the primary modality of treatment or as adjuvant treatment after surgery if there is a narrow surgical margin of clearance, the margin often being determined by the particular anatomical site of the tumour. The technique and dose are the same as for treating a basal cell cancer, but a wider margin is taken around the tumour and the patient is subjected to a more frequent and longer follow-up, as suggested in the British Association of Dermatology guidelines [2]. If the SCC has developed on the face, it is mandatory to check for cervical lymphadenopathy. Radiotherapy may be especially useful for squamous cell carcinoma on or around the nose, where resection may be incomplete or the potential for reconstruction suboptimal [3]. Adjuvant radiotherapy may reduce the development of nodal disease in higher risk cutaneous squamous cell carcinoma, as described by Veness [4].

Radiotherapy can also be useful in palliation of advanced skin tumours, and in some patients gives long-term survival [5].

Bowen's disease. Radiotherapy can be effective for Bowen's disease [3], but it is not a commonly used treatment for this condition. Lesions on the leg have to be treated with more caution [6,7] as there is a danger of ulceration and very slow healing if large areas are treated. A recent retrospective review of 44 cases by VanderSpek *et al.* [8], where radiotherapy was used as a primary treatment or for managing residual disease, showed a crude local control rate of 93%. This condition can also be treated with a local mould, although this would be a relatively uncommon treatment modality nowadays.

Malignant melanoma. Malignant melanoma cells are not insensitive to radiotherapy as is sometimes stated (Fig. 79.14), but they do require higher dose per fraction regimens to overcome their ability to sustain more sublethal damage than other cell lines. Treatments may be hypofractionated, with patients receiving larger single doses in fewer fractions—for example treatment being given three times rather than five times per week—although this may lead to a greater risk of postradiotherapy morbidity [9]. Radiotherapy is also useful for palliation of both cutaneous and visceral metastases from melanoma [10].

There have not been any published prospective, randomized, controlled trials comparing surgery in melanoma with surgery and adjuvant radiotherapy, but there have been studies suggesting improved local control if postoperative radiotherapy is given



(a)

(b)

Fig. 79.14 (a) Malignant melanoma, pre-radiotherapy. (b) Malignant melanoma, post-radiotherapy.

[11,12]. Burmeister *et al*. [13] have reported the Trans Tasman Radiation Oncology Group (TROG) trials, where adjuvant radiotherapy was given to nodal drainage areas in the neck, axilla and groin. Grade 3 lymphoedema developed in 40% of the patients having radiotherapy to the groin, in 8% of those patients having axillary radiation, and in none of those given neck irradiation. The increasing use of sentinel node biopsy may allow better patient selection and targeting of patient subgroups who may benefit from adjuvant radiotherapy. The impact of adjuvant radiotherapy on survival is unknown, but may be minimal, even if local control is improved [14].

Lentigo maligna and lentigo maligna melanoma. Radiotherapy has been used very successfully in both of these conditions. In one German study, there was no recurrence in any of 42 patients with lentigo maligna, with a mean follow-up of 15 months, and only

two patients with lentigo maligna melanoma out of 22 showed local recurrence. Cosmetic results were also reported as good or excellent in the majority of patients [15]. Similar complete responses for lentigo maligna were seen in studies from Australia [16] and Canada [17], again with good cosmetic results.

Merkel cell carcinoma. These tumours of neuroendocrine origin are most common on the head and neck, but can occur elsewhere on the skin. They have a tendency to recur locally after surgical removal and improved local control has now been shown, in a large number of studies, with a combination of wide excision and adjuvant postoperative radiotherapy to the primary tumour site and local nodal drainage [18–28], with some studies also showing improved survival. Mojica *et al.* [22] in a recent, large, retrospective study looking at 1665 cases from the NCI SEER survey data, have shown a survival benefit from the use of adjuvant radiotherapy. Adjuvant radiotherapy may not add any benefit in terms of improved local control or survival after Mohs surgery if complete excision has been achieved [29]. These are radiosensitive tumours and radiotherapy has been used as a primary treatment [30,31].

Chemotherapy using regimens for small cell lung cancer, to which these tumours are related, is used for metastatic disease. It is not known what role chemotherapy has to play in improving survival when added to adjuvant radiotherapy. The prospective Australian study by Poulsen *et al.*, using historical controls, found no effect on survival but was not powered to detect a small increase in survival [32].

Cutaneous T-cell lymphoma. Radiotherapy can be used as both a localized treatment for isolated patches or plaques and for treating all of the skin by whole-body electron beam therapy [33–35]. With the latter, the patient takes up standard predetermined poses for a number of fields, allowing maximum cutaneous exposure to the beam. If treated early in the course of the disease, the patient can remain well and disease-free for a considerable period of time, but there is still doubt as to whether patients can be cured with this technique [36]. The eyes are shielded and the patient is made aware that they will lose their nails with this technique. Despite its drawbacks, radiotherapy is the most effective modality in achieving a complete response to treatment in cutaneous lymphomas. The UK National Institute for Health and Clinical Excellence has given guidance on treatment of these uncommon tumours [37].

Cutaneous Kaposi's sarcoma. It is well known that these tumours are sensitive to low-dose radiotherapy. Either superficial X-rays or electron beams can be used depending on the thickness of the lesion(s) and consequently the depth of treatment required. Treatment is used cautiously as patients are prone to develop severe local reactions and mucositis. Radiotherapy is also used to palliate systemic disease, such as pulmonary masses [38,39].

Dermatofibrosarcoma protuberans. This low-grade sarcomatous tumour has a propensity to recur after surgery alone, and local control is improved by giving adjuvant radiotherapy [40,41].

Carcinoma metastatic to the skin from other primaries. Skin metastases tend to originate from the most common parenchymal tumours such as breast, colon and lung but, occasionally, isolated skin metastasis occurs from tumours originating in the thyroid or urinary system. The latter two sites should be borne in mind if a patient presents with a single bizarre metastasis with no obvious evidence of previous primary tumour.

Squamous cell and basal cell carcinoma in transplant patients. Skin tumours developing after organ transplant are known to have more aggressive characteristics and carry a poorer prognosis [42]. These patients develop more SCCs than BCCs, reversing the normal ratio, and can develop multiple skin cancers and at an earlier age than the non-transplant population. There is no contraindication to using radiotherapy in this group, but most patients will undergo surgery as their primary treatment, especially if they have multiple primary skin tumours. Radiotherapy may play a greater adjuvant role in this group of patients with more aggressive tumours [43]. The guidance on *Improving Outcomes for People with Skin Tumours* [37] recommends that cancer networks make special provision for surveillance for cancer in these patients.

References

1 Petrovich Z, Kuisk H, Langholz B *et al*. Treatment of carcinoma of the skin with bone and/or cartilage involvement. *Am J Clin Oncol* 1988; **11**: 110–3.

2 Motley R, Kersey P, Lawrence C. Multiprofessional guidelines for the management of the patient with primary cutaneous squamous cell carcinoma. *Br J Dermatol* 2002; **146**: 18–25.

3 Tsao MN, Tsang RW, Liu FF. Radiotherapy management for squamous cell carcinoma of the nasal skin: the Princess Margaret Hospital experience. *Int J Radiat Onc Biol Phys* 2002; **52**: 973–9.

4 Veness MJ. Treatment recommendations in patients diagnosed with high-risk cutaneous squamous cell carcinoma. *Australas Radiol* 2005; **49**: 365–76.

5 Lee WR, Mendenhall WM, Parsons JT, Million RR. Radical radiotherapy for T4 carcinoma of the skin of the head and neck: a multivariate analysis. *Head Neck* 1993; **15**: 320–4.

6 Dupree ML, Kiteley RA, Weismantle K *et al*. Radiation therapy for Bowen's disease: lessons for lesions of the lower extremity. *J Am Acad Dermatol* 2001; **45**: 401–4.

7 Cox NH, Dyson P. Wound healing on the lower leg after radiotherapy or cryotherapy of Bowen's disease and other malignant skin lesions. *Br J Dermatol* 1995; **133**: 60–5.

8 VanderSpek LA, Pond GR, Wells W. Radiation therapy for Bowen's disease of the skin. *Int J Radiat Onc Biol Phys* 2005; **63**: 505–10.

9 Chang DT, Amdur RJ, Morris CG. Adjuvant radiotherapy for cutaneous melanoma: comparing hypofractionation to conventional fractionation. *Int J Radiat Oncol Biol Phys* 2006; **66**: 1051–5.

10 Seegenschmiedt MH, Keilholz L, Altendorf-Hofmann A *et al*. Palliative radiotherapy for recurrent and metastatic malignant melanoma: prognostic factors for tumor response and long-term outcome: a 20-year experience. *Int J Radiat Oncol Biol Phys* 1999; **44**: 607–18.

11 Burmeister BH, Smithers BM, Davis S. Radiation therapy following nodal surgery for melanoma: an analysis of late toxicity. *ANZ J Surg* 2002; **72**: 344–8.

12 O'Brien CJ, Petersen-Schafer K, Papadopoulos T, Malka V. Evaluation of 107 therapeutic and elective parotidectomies for cutaneous melanoma. *Am J Surg* 1994; **168**: 400–3.

13 Burmeister BH, Mark SB, Burmeister E *et al*. A prospective phase II study of adjuvant postoperative radiation therapy following nodal surgery in malignant melanoma Trans Tasman Radiation Oncology Group (TROG) study 96.06. *Radiother Oncol* 2006; **8**: 136–42.

14 Mendenhall WM, Amdur RJ, Grobmeyer SR. Adjuvant radiotherapy for cutaneous melanoma. *Cancer* 2008; **112**: 1189–96.

15 Schmid-Wendtner MH, Brunner B, Konz B *et al*. Fractionated radiotherapy of lentigo maligna and lentigo maligna melanoma in 64 patients. *J Am Acad Dermatol* 2000; **43**: 477–82.

16 Harwood AR. Conventional radiotherapy in treatment of lentigo maligna and lentigo maligna melanoma. *J Am Acad Dermatol* 1982; **6**: 310–6.
17 Tsang RW, Liu FF, Wells W, Payne DG. Lentigo maligna of the head and neck. Results of treatment by radiotherapy. *Arch Dermatol* 1994; **130**: 1008–12.
18 Jabbour J, Cumming R, Scolyer RA. Merkel cell carcinoma: assessing the effect of wide local excision, lymph node dissection, and radiotherapy on recurrence and survival in the early stage disease – results from a review of 82 consecutive cases diagnosed between 1992 and 2004. *Ann Surg Oncol* 2007; **14**: 1943–52.
19 Veness MJ. Merkel cell carcinoma (primary cutaneous neuroendocrine carcinoma): an overview on management. *Australas J Dermatol* 2006; **47**: 160–5.
20 Veness MJ, Perera L, McCourt J. Merkel cell carcinoma: improved outcome with adjuvant radiotherapy *ANZ J Surg* 2005; **75**: 275–81.
21 Clark JR, Veness MJ, Gilbert R. Merkel cell carcinoma of the head and neck: is adjuvant radiotherapy necessary? *Head Neck* 2007; **29**: 249–57.
22 Mojica P, Smith D, Ellenhorn JD. Adjuvant radiation therapy is associated with improved survival in Merkel cell carcinoma of the skin. *J Clin Oncol* 2007: **25**: 1043–7.
23 Eich HT, Eich D, Staar S *et al*. Role of postoperative radiotherapy in the management of Merkel cell carcinoma. *Am J Clin Oncol* 2002; **25**: 50–6.
24 Medina-Franco H, Urist MM, Fiveash J *et al*. Multimodality treatment of Merkel cell carcinoma: case series and literature review of 1024 cases. *Ann Surg Oncol* 2001; **8**: 204–8.
25 Fenig E, Brenner B, Katz A *et al*. The role of radiation therapy and chemotherapy in the treatment of Merkel cell carcinoma. *Cancer* 1997; **80**: 881–5.
26 Kokoska ER, Kokoska MS, Collins BT *et al*. Early aggressive treatment for Merkel cell carcinoma improves outcome. *Am J Surg* 1997; **174**: 688–93.
27 al-Ghazal SK, Hong A. Merkel cell carcinoma of the skin treated by primary radiotherapy. *Br J Dermatol* 1997; **136**: 640–1.
28 Suntharalingam M, Rudoltz MS, Mendenhall WM. Radiotherapy for Merkel cell carcinoma of the skin of the head and neck. *Head Neck* 1995; **17**: 96–101.
29 Boyer JD, Zitelli JA, Brodland DG *et al*. Local control of primary Merkel cell carcinoma: review of 45 cases treated with Mohs micrographic surgery with and without adjuvant radiation. *J Am Acad Dermatol* 2002; **47**: 885–91.
30 Morrison WH, Peters LJ, Silva EG. The essential role of radiation therapy in securing loco-regional control of Merkel cell carcinoma. *Int J Radiat Oncol Biol Phys* 1990; **19**: 583–91.
31 Mortier L, Mirabel X, Fournier C. Radiotherapy alone for primary Merkel cell carcinoma. *Arch Dermatol* 2003; **139**: 1587–90.
32 Poulsen MG, Rischin D, Porter I. Does chemotherapy improve survival in high-risk stage I and II Merkel cell carcinoma of the skin? *Int J Radiat Oncol Biol Phys* 2006; **64**: 114–9.
33 Kirova YM, Piedbois Y, Haddad E. Radiotherapy in the management of mycosis fungoides: indications, results, prognosis. Twenty years experience. *Radiother Oncol* 1999; **51**: 147–51.
34 Kirova YM, Piedbois Y, Le Bourgeois JP. Radiotherapy in the management of cutaneous B-cell lymphoma. Our experience in 25 cases. *Radiother Oncol* 1999; **52**: 15–8.
35 Micaily B, Miyamoto C, Kantor G. Radiotherapy for unilesional mycosis fungoides. *Int J Radiat Oncol Biol Phys* 1998; **42**: 361–4.
36 Stallmeister T, Dieckmann K, Rehberger A, Jurecka W. Longterm remission of tumor-stage mycosis fungoides following total-skin electron-beam radiotherapy. *Eur J Dermatol* 1998; **8**: 240–2.
37 National Institute for Health and Clinical Excellence. *Guidance on Cancer Services: Improving Outcomes for People with Skin Tumours Including Melanoma: The Manual*, February 2006. http://www.nice.org.uk/nicemedia/pdf/CSG_Skin_Manual.pdf
38 Kirova YM, Belembaogo E, Frikha H. Radiotherapy in the management of epidemic Kaposi's sarcoma: a retrospective study of 643 cases. *Radiother Oncol* 1998; **46**: 19–22.
39 Harrison M, Harrington KJ, Tomlinson DR, Stewart JS. Response and cosmetic outcome of two fractionation regimens for AIDS-related Kaposi's sarcoma. *Radiother Oncol* 1998; **46**: 23–8.
40 Ballo MT, Zagars GK, Pisters P, Pollack A. The role of radiation therapy in the management of dermatofibrosarcoma protuberans. *Int J Radiat Oncol Biol Phys* 1998; **40**: 823–7.
41 Haas RL, Keus RB, Loftus BM. The role of radiotherapy in the local management of dermatofibrosarcoma protuberans. Soft Tissue Tumours Working Group. *Eur J Cancer* 1997; **33**: 1055–60.
42 Veness MJ, Quinn DI, Ong CS. Aggressive cutaneous malignancies following cardiothoracic transplantation, the Australian experience. *Cancer* 1999; **85**: 1758–64.
43 Veness MJ, Harris D. Role of radiotherapy in the management of organ transplant recipients diagnosed with non-melanoma skin cancers. *Australas Radiol* 2007; **51**: 12–20.

Acute radiation reaction (acute radiodermatitis) (Figs 79.15 & 79.16)

Radiation works by damaging clonogenic cells, both benign and malignant, and the damage is expressed at the next cell division, when the cell either dies or repairs sublethal damage. Tissues with a rapid turnover, such as the epidermis and mucosal endothelium, therefore show radiation damage soon after treatment, and this is the 'acute reaction'. For the treatment to result in cure, the basal or squamous carcinoma must be unable to repair this damage [1,2].

In acute radiodermatitis, histopathology shows oedema and sparseness of connective tissue beneath the epidermis. There may be flattening and loss of epidermal rete ridges with separation of the elastic tissue from the basal layer. Capillary endothelium may be hypertrophic and congested capillaries a feature. Haemorrhage and thrombosis are often observed. Special stains may show subtle changes in the DNA–RNA structure of epithelial cells as early as the third day [1,2]. During the healing phase, the patchiness of the pathology is a striking feature. Atrophy may be bordered by epidermal hyperplasia, pigmentation is very irregular, and blood vessels are of variable size and shape; deeper vessels may be fibrosed.

Normal tissue repair occurs when normal clonogenic cells on the basement membrane, which have either not received damage or have repaired sublethal damage, repopulate the basement membrane, and re-cover the epithelium [3].

In a commonly used regimen, where the patient attends at daily intervals for five doses of treatment, the irradiated skin starts to redden 5–7 days after the first treatment, because of increased vascularity and inflammation associated with cell damage. Subsequent doses add to the reaction, which proceeds through dry and sometimes moist desquamation and scabbing, usually reaching a height of discomfort at 3–4 weeks after treatment finishes, and settling over the next 2–3 weeks with re-epithelialization, which begins in the perifollicular areas, and proceeds as cell colonies coalesce to cover the denuded surface.

The acute reaction is more painful if there is ulceration and scabbing before treatment commences. The larger the surface area of the tumour and therefore the treatment field, the longer the healing takes, but even so, commonly at 6 weeks after the end of the course healing is virtually complete. The brisker the treatment, that is the larger the dose given in the shorter the time, the more marked the acute reaction is likely to be, as there is less opportunity for normal tissue repair between treatments.

However, if the skin is previously unbroken, or the tumour nodular, treatment may be followed by a very mild erythematous reaction only, with little discomfort for the patient.

Individual skin reactions vary, and those who burn in the sun tend to have a brisker reaction to X-ray treatment. Occasionally,

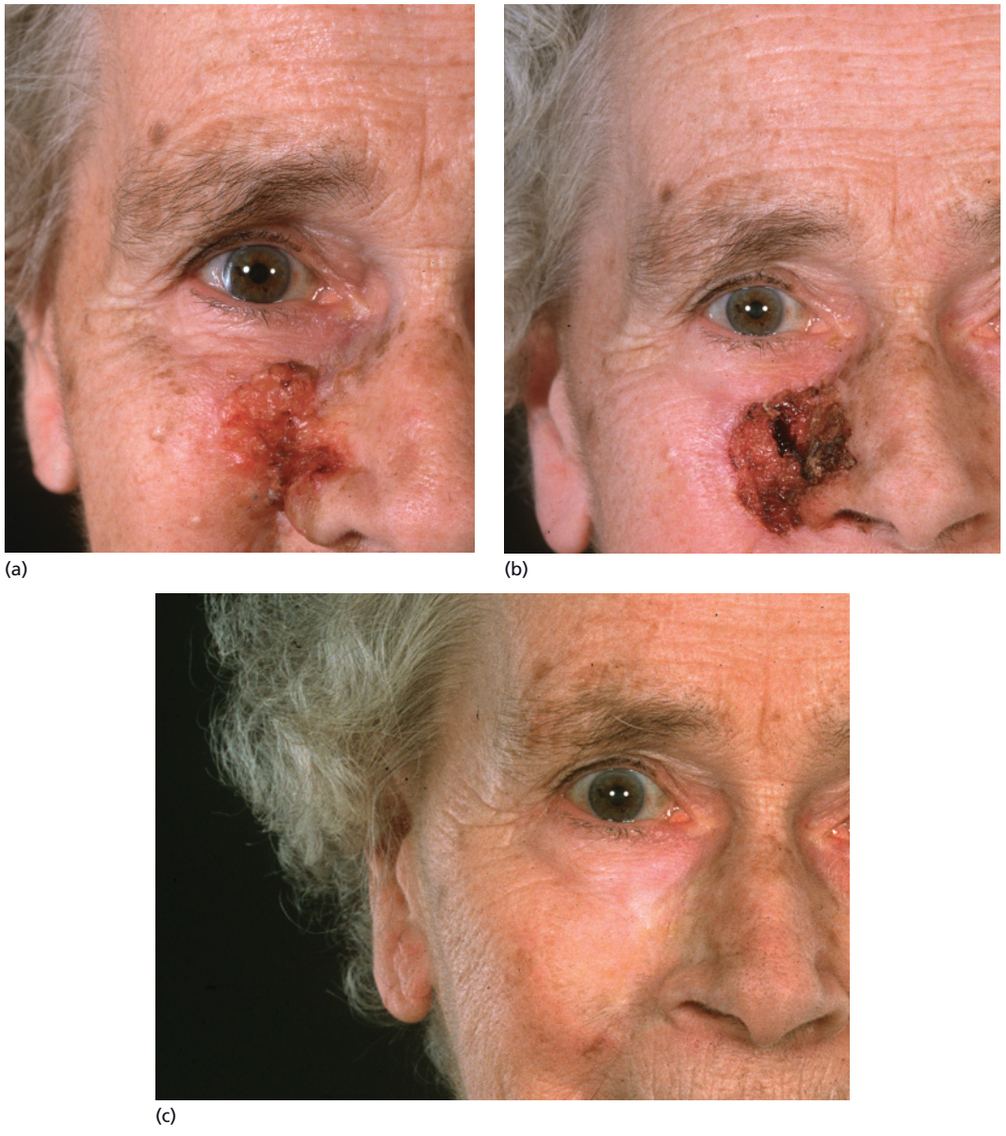


Fig. 79.15 (a) Large BCC cheek. (b) The same patient, showing acute radiation reaction 6 weeks after superficial X-ray treatment. (c) The same patient, showing settled reaction 6 months after superficial X-ray treatment.

especially on the face, infection occurs, usually with *Staphylococcus aureus,* and antibiotics are indicated.

If the exit beam passes through mucosa, a patch of mucositis will develop, of similar size to the treatment field. This reaction usually occurs earlier, and is of much shorter duration than the skin reaction, and heals completely without long-term sequelae. The nasal mucosa may swell and occasionally bleed, with the feeling of a blocked nose; in the mouth a sore patch may make eating uncomfortable for a few days. Although lead can be used to protect structures beyond the inner mucosa, such as the gums and the nasal septum, the mucosa just beneath the cancer cannot be protected.

Management of acute radiation reaction

The natural history of the acute reaction cannot be modified, but the patient can avoid making the reaction worse. They are advised to leave the area open to the air as far as possible, and to avoid trauma, extremes of heat or cold, irritation with chemical ointments and physical rubbing, which displaces regenerating clonogenic cells. Steroid creams are also best avoided. Patients are warned to report to the doctor if there is redness and soreness spreading outside the treated area, or a purulent discharge. Friction and infection may cause ulceration, as such skin cannot readily repair damage. Vigorous and repeated washing should be avoided in the acute stage. Once the treated area is dry and scabbed, normal washing can resume. It can be emphasized that only the area of skin that has been treated needs to be managed with caution—the remainder of the hair and face can be washed normally. The mucosal reaction must be endured, although application of Vaseline is sometimes soothing to the nasal mucosa, and some patients find a simple mouthwash helpful.



(a) (b) (c)

Fig. 79.16 (a) Large BCC jaw. (b) The same patient, showing acute radiation reaction 4 weeks after superficial X-ray treatment. (c) The same patient, showing settled radiation reaction 6 months after superficial X-ray treatment.

Although the reaction is described as 'like a sunburn effect' it is wrong to refer to the normal radiation reaction as a 'radiation burn', with the implication of 'overdose' or 'something going wrong'. The reaction can be predicted and explained in advance, and the patient who is well warned can usually take this in their stride, and be pleasantly surprised if the reaction is less troublesome than expected.

Late radiation reaction (chronic radiodermatitis) (Figs 79.17 & 79.18)

Tissues with a slow rate of cell division, such as subcutaneous fat, fibrous tissue and small blood vessels, will show radiation effects months or years after treatment, and this is the late reaction. At the 6-month review, the treated skin often looks slightly paler or pinker than the adjacent untreated skin; with the passage of time sequelae usually appear, with late appearances established at 5–10 years. The irradiated skin may show pallor or increased pigmentation, with lack of adnexae, and a degree of atrophy. Telangiectasiae are the main cosmetic nuisance. In time, the vascularity of the centre of the previous tumour-bearing area may show compromise and ulceration may develop, either spontaneously or after trauma; such ulcers often heal spontaneously [4].

The fundamental histopathology of chronic radiodermatitis is fibrosis of the vessels, with occlusion and varying degrees of homogenization of the connective tissue. Residual vessels may be enormously dilated. Bizarre, large, stellate fibroblasts may be seen in the dermal connective tissue in some cases. Fibrosis of the deep dermis and subcutaneous tissue may occasionally occur after megavoltage radiotherapy [5].

The changes in the epidermis vary from simple atrophy to acanthosis and extreme dyskeratosis. There is usually loss of adnexae such as hair follicles.

The late cosmetic result varies with the individual, and may reflect the underlying damage caused initially by the tumour, as well as the patient's skin type. In one study of 339 patients, occurrence of telangiectasiae, pigmentation and fibrosis were directly related to increasing size of field needed for treatment rather than the treatment regimen used [6]. The late cosmetic result is also less good if the patient has had multiple treatments with cryotherapy to the area beforehand (personal observation) or a biopsy which has left a scar. However, as radiotherapy is usually offered to the older population, often with sundamaged skin, and certainly not unblemished, patients are usually satisfied with the cosmetic result, even though imperfect, and even when warned of this in advance are quite prepared to go ahead with treatment.

Tissues which do not divide, such as neurones, may accumulate damage, but not express it; treatment will not cause numbness or pain, although persistent erosive tumour may do so.

Chronic radiation change may be confused with a recurrence of a malignant lesion. The effects of normal ageing and sun exposure may combine with the effects of ionizing radiation, and produce accelerated changes. This may also be seen when psoralens and UVA (PUVA) is used on irradiated skin.

Late radiation changes leading to ischaemic necrosis should rarely be seen when modern techniques of fractionation to a radical dose for skin malignancies are used. Radionecrosis



Fig. 79.17 (a) Extensive erosive BCC of the ear. (b) The same patient, 2 years after superficial X-ray treatment.



Fig. 79.18 Telangiectasiae after treatment for a small BCC of the nose.

typically occurs approximately 1 year following complete healing of the skin after radiotherapy, and is often precipitated by trauma or infection. Excision and grafting may provide the only satisfactory treatment of extensive radionecrosis, although small areas may slowly heal with conservative management [4].

Many thousands of patients have been treated with curative radiotherapy for BCC and SCC both in reported series and in busy radiotherapy departments. Second malignancy within the irradiated fields is very rare indeed, as would be expected from the high average age of the patient receiving radiotherapy for skin cancers.

References

1 Kurban AK, Farah FS. Effects of X-irradiation of the skin. *Acta Derm Venereol (Stockh)* 1969; **49**: 64–71.
2 Panizzon RG, Cooper JS, eds. *Radiation Treatment and Radiation Reactions in Dermatology*. Berlin: Springer, 2004.
3 Harrington K, Jankowska P, Hingorani M. Overview: molecular biology for the radiation oncologist: the 5Rs of radiobiology meet the hallmarks of cancer. *Clin Oncol* 2007; **19**: 561–71.
4 Chan S, Dhadda AS, Swindell R. Single fraction radiotherapy for small superficial carcinoma of the skin. *Clin Oncol* 2007; **19**: 256–9.
5 James WD, Odom RB. Late subcutaneous fibrosis following megavoltage radiotherapy. *J Am Acad Dermatol* 1980; **3**: 616–8.
6 Lovett RD, Perez CA, Shapiro SJ *et al*. External irradiation of epithelial skin cancer. *Int J Rad Onc Biol Phys* 1990; **19**: 235–42.

Tumour recurrence after radiotherapy

BCC and SCC can reoccur after radiotherapy [1–3] and especially if the patient has undergone multiple treatment modalities [2]. Tumour healing has invariably occurred at 6 months, and persistent ulceration usually means persistent tumour. Some authors suggest that one reason for avoiding primary radiotherapy is that surgical salvage is more difficult after treatment failure, but if the patient is referred on at an early stage, excision of the irradiated skin and grafting is usually possible. Mohs surgery may give the best results in these cases but there can even be recurrence after

this meticulous form of treatment [2]. As with surgical treatment, radiotherapy for recurrent BCC has a higher relapse rate [4], and recurrence after radiotherapy may be related to a decreased HLA G expression [5].

Retreatment with radiation is not usually offered, because the primary is by definition relatively radioresistant and the normal tissues may have already received a 'tolerance dose', thus to repeat treatment might produce radionecrosis. However, in practice, radiotherapy has been given successfully in these circumstances with acceptable cosmetic results, especially if there has been sufficient time interval between the two radiotherapy treatments [6]. Occasionally, it is reasonable to offer treatment to persistent tumour at the edge of a previous radiotherapy field, when a small degree of overlap may be acceptable; although the risk of a small area of necrosis will be higher, this strategy is often acceptable to the patient, and successful.

References

1 Shore RE. Radiation-induced skin cancer in humans. *Med Pediatr Oncol* 2001; **36**: 549–54.
2 Smith SP, Grande DJ. Basal cell carcinoma recurring after radiotherapy: a unique, difficult treatment subclass of recurrent basal cell carcinoma. *J Dermatol Surg Oncol* 1991; **17**: 26–30.
3 Lovett RD, Perez CA, Shapiro SJ, Garcia DM. External irradiation of epithelial skin cancer. *Inter J Rad Oncol Biol Physics* 1990; **19**: 235–42.
4 Bogelund FS, Philipsen PA, Gniadecki R. Factors affecting the recurrence rate of basal cell carcinoma. *Acta Derm Venereol* 2007; **87**: 330–4.
5 Urosevic M, Kempf W, Zagrodnik B *et al*. HLA-G expression in basal cell carcinomas of the skin recurring after radiotherapy. *Clin Exp Dermatol* 2005; **30**: 422–5.
6 Chao KS, Gerber RM, Perez CA. Re-radiation of recurrent skin cancer of the face. *Cancer* 1995; **75**: 2351–5.

Radiation-induced tumours

Both BCCs and SCCs can occur in areas of skin previously irradiated for other conditions, such as Hodgkin's disease or post-mastectomy, with some evidence that radiation-induced BCCs are more common [1], but this is very rarely seen in modern radiotherapy practice.

The type of tumour induced by radiation depends on both the cellular structure and the anatomical location of the damaged tissues. Basal cell epitheliomas occur following radiation to the face, scalp and trunk, whereas on the hands squamous cell tumours may occur. These are much more rarely seen since the development of more sophisticated radiotherapy machinery and a greater knowledge of radiobiology. It has not been possible to demonstrate any precise quantitative relationship between the development of cutaneous epitheliomas and the amount of radiation received on the skin surface, nor is it known what total dose or fractionation regimen would be most carcinogenic. It has long been known that carcinomas occur more profusely in areas subjected to many small doses administered at intervals over a long period. Multiple basal cell epitheliomas on the skin over the spine following radiotherapy to the lumbar spine for ankylosing spondylitis have been reported [2]. Some may show the histological appearances of the pre-malignant fibroepithelioma of Pinkus. Radiation-induced basal cell epitheliomas of the scalp may be seen 20–50 years following X-ray epilation for ringworm infection. Late radiation changes are not always visible on the scalps of these patients, and hair growth may be relatively normal.

The doses of radiation used to treat benign dermatological conditions should never produce late radiation damage of even mild type [3]. In general, radiation-induced cancers have occurred after inappropriate doses, often of many thousands of centiGray, given over a long period, frequently by lay therapists for conditions such as hirsutism or greasy skin and large pores [4], which are not indications for treatment by radiotherapy today. Shielding of structures especially sensitive to irradiation, for example the adolescent thyroid [5], was not routinely carried out. Although a greater knowledge of the limitations and effectiveness of radiation should prevent the occurrence of late radiation damage including carcinogenicity, the long latent period often demonstrated in those cases warns against early complacency [4,6].

As the numbers of childhood cancer survivors increase there is some evidence of an increased incidence of basal cell carcinoma developing within irradiated skin sites [7], but this is not confirmed by all studies [8]. As most of these children will also have had treatment with chemotherapy, the aetiological factors causing their second malignancy are not all known.

Treatment. Most radiation-induced tumours should be excised. However, where there is no radiation damage evident on the skin, a subsequent radical dose of radiotherapy can be tolerated, if planned carefully [9].

Rare tumours associated with previous irradiation

Atypical fibroxanthoma

Synonym
- Pseudosarcoma of the skin

This tumour, seen particularly in fair-skinned males who have suffered actinic damage, may also follow radiation damage [10–12]. It usually occurs on the face, but occasionally on the trunk or limbs. The clinical course is benign, despite the highly anaplastic histological appearance. Twenty-one tumours initially labelled as spindle-cell squamous carcinomas were found by Hudson and Winkelmann [10] to be atypical fibroxanthoma.

Fibrosarcoma

Sarcoma appears to arise in irradiated skin much less frequently than carcinoma, and many of the tumours are low grade, showing no tendency to produce distant metastases [13]. At least some of the reported sarcomas are in reality spindle-cell carcinomas [14]; this may be shown by the attachment of the tumour to the epidermis or by the presence of horny pearls. Radiation fibromatosis [15] is a diffuse proliferation in which bizarre and sometimes monstrous fibroblasts appear in the dermal connective tissue; the appearance can easily be mistaken for fibrosarcoma. Only exceptionally does fibromatosis undergo malignant change. It does appear that irradiation of an already chronically inflamed skin is more likely to be followed by a fibrosarcoma than irradiation of normal skin.

The fibrosarcomas, like the carcinomas following radiation, appear usually after repeated exposures to kilovoltage X-rays, and rarely from megavoltage radiation. The latent period in one series [16] averaged 26 years.

References

1 Karagas MR, McDonald JA, Greenberg ER. Risk of basal cell and squamous cell skin cancers after ionising radiation therapy. *J Natl Cancer Inst* 1996; **88**: 1848–52.

2 Meara RH. Superficial basal-cell epitheliomata following radiotherapy. *Br J Dermatol* 1964; **76**: 294–6.

3 Lukacs S, Goldschmidt H. Radiotherapy of benign dermatoses: indications, practice and results. *J Dermatol Surg Oncol* 1978; **4**: 620–5.

4 Martin H, Strong E, Spiro RH. Radiation induced skin cancer of the head and neck. *Cancer* 1970; **25**: 61–71.

5 Goldschmidt H. Dermatologic radiotherapy and thyroid cancer. *Arch Dermatol* 1977; **113**: 362–4.

6 Fuks A, Bagshaw MA. Total-skin electron treatment of mycosis fungoides. *Radiology* 1971; **100**: 145–50.

7 Levi F, Moeckli R, Randimbison L. Skin cancer in survivors of childhood and adolescent cancer. *Eur J Cancer* 2006; **42**: 656–9.

8 Paulino AC, Fowler BZ. Secondary neoplasms after radiotherapy for a childhood solid tumour. *Pediatr Hematol Oncol* 2005; **22**: 89–101.

9 Short KA, Calman FM, Ross DA. Can radiotherapy cure radiation induced skin cancer? *Clin Exp Dermatol* 2006; **32**: 109–11.

10 Hudson AW, Winkelmann RK. Atypical fibroxanthoma of the skin: a reappraisal of 19 cases in which the original diagnosis was spindle-cell squamous carcinoma. *Cancer* 1972; **29**: 413–22.

11 Kemmett D, Gawkrodger DJ, McLaren KM *et al*. Two atypical fibroxanthomas arising separately in X-irradiated skin. *Clin Exp Dermatol* 1988; **13**: 382–4.

12 Kempson RL, McGavran MH. Atypical fibroxanthomas of the skin. *Cancer* 1964; **17**: 1463–71.

13 Stout AP. Fibrosarcoma: the malignant tumor of fibroblasts. *Cancer* 1948; **1**: 30–63.

14 Traenkle HL. X-ray induced skin cancer in man. *Natl Cancer Inst Monogr* 1963; **10**: 423–32.

15 Stout AP. Juvenile fibromatosis. *Cancer* 1954; **7**: 953–78.

16 Russell B. Fibrosarcomata of the skin and subcutaneous tissues. *Trans St John's Hosp Dermatol Soc* 1959; **42**: 15–8.

CHAPTER 80

Minimally Invasive Treatments and Procedures for Ageing Skin

N.J. Lowe

Cranley Clinic, London, UK and UCLA School of Medicine, Los Angeles, CA, USA

Types of skin ageing, 80.1
Intrinsic ageing, 80.1
Extrinsic ageing, 80.2
Prevention of skin and facial ageing, 80.3
Skin rejuvenation procedures, 80.4
Volume replacement by fillers, 80.4
Botulinum toxins—their use in controlling facial lines, 80.7
Chemical peels for improvement of facial ageing, 80.9
Intense pulsed light and laser treatment—selection for cosmetic indications, 80.10
Radiofrequency, 80.13
Combination minimally invasive treatment, 80.14

Introduction

Over the last century there has been a dramatic increase in the ageing population in most developed countries. For example, it is expected that one in five Americans will be aged 65 years or older by the year 2030 (source 2000 USA census), a trend similar to that in most developed countries. Increased social pressure to look younger has led to great demand for effective cosmetic treatments for skin and facial rejuvenation. In particular, there has been an increase in what have been termed non-invasive and minimally-invasive cosmetic treatments, that is treatments that avoid surgery and involve surface skin treatment such as lasers or peels, or a variety of injections [1].

Currently, most of those seeking these treatments are women, but an increasing number of men are considering rejuvenation treatments, and it is important for the practising dermatologist to be aware of the treatment options.

Types of skin ageing

Skin ageing has historically been divided into intrinsic ageing [2], which will occur in all skin, whether or not exposed to external ageing factors, and extrinsic ageing, which is accelerated skin ageing due to external influences such as smoking and sun exposure [3].

Intrinsic ageing

There are numerous factors that contribute to intrinsic ageing, including oxidative phosphorylation that generates destructive 'superoxides', which are thought to damage mitochondrial DNA and lead to progressive cell and tissue senescence [2]. Other factors that can prematurely age skin intrinsically are inflammatory skin diseases, for example inflammatory acne which can lead to dermal injury and subsequent scarring.

Collagen comprises up to 80% of the dry weight of ageing skin, and it is type 1 collagen, which comprises 70% of the total collagen content, whose larger diameter fibres provide the mechanical and stretch integrity of the skin. Type 3 collagen, which has narrow fibres, is also important. The quality and functionality of collagen substantially decreases with time [4].

The dermis is a connective tissue matrix of collagen housed in an elastin network. As part of the intrinsic ageing process there is a reduction of fibroblast activity in the dermis, and a decline in the ability of these cells to synthesize collagen and elastin contributes to loss of elasticity and wrinkles. In combination with the decline in collagen synthesis there is altered expression of matrix metalloproteinases (MMP), which mediate collagen breakdown. As a result, intrinsic ageing and dermal thinning occurs; dermal collagen, elastin and glycosaminoglycans are all altered during the ageing process [5].

Skin collagen fibres do not appear to shrink with age, but the balance of their intermolecular cross-links changes, with an increase in cross-linking resulting in a stiffening of the skin. Ageing is also associated with a decrease in proteoglycan content, resulting in a reduction of the tensile strength of the skin. The elastic fibres show a progressive change, and there is evidence that elastin gene expression declines with age [5].

Accompanying these changes is a reduction of skin microvasculature, a reduction in activity but not in numbers of sebaceous glands, and a reduction of subdermal fat leading to skin laxity and change of facial profile (Fig. 80.1).

Hyaluronic acid and other glycosaminoglycans decline during the intrinsic ageing process; a 50-year-old is estimated to have half the hyaluronic acid level of a youth. As an accompaniment to the dermal changes of intrinsic ageing, the epidermis becomes thinner, with a reduction in thickness of 10 to 50% between the ages of 30

Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffiths. © 2010 Blackwell Publishing Ltd.



Fig. 80.1 Signs of intrinsic ageing—the patient shows brow ptosis, loss of cheek volume and malar ptosis, hollowness in the lower face, atrophic lips and marionette lines.

and 80. Mitotic activity of keratinocytes is reduced, and the epidermal transit time is increased. The orderly maturation of the epidermis becomes irregular. The corneocytes become less adherent and this produces a clinical appearance of roughness and scale. There is a flattening of the dermal–epidermal interface by as much as 35%, with increased skin fragility [4].

Table 80.1 summarizes some of the changes of intrinsic ageing.

Extrinsic ageing

Extrinsic ageing, whose principal cause is ultraviolet radiation, results in changes in areas exposed to the environment such as the face, neck and dorsal hands. UVB (290–320 nm) penetrates to the lower epidermis, whereas UVA (320–400 nm) penetrates into the dermis and may be more responsible for some of the clinical changes associated with photoageing. Other factors that contribute to facial and skin ageing include repetitive facial expressions, leading to dynamic lines and rhytides. Gravity accelerates facial skin ageing, and this factor becomes more evident in the 30s when skin elasticity starts to decline [1].

Cigarette smoking also contributes to some of the characteristic changes of skin 'coarseness' and colour, or sallowness, which can be recognized in many who smoke 10 cigarettes or more daily for 10 years [6].

Signs of extrinsically aged skin include fine and coarse rhytides, macular and diffuse pigmentation, solar lentigines, increase in surface roughness, telangiectasiae, sallowness, loss of skin tone

Table 80.1 Some features of intrinsic skin ageing.

Component	Function	Change with age
Fibroblasts	Synthesis and degradation of extracellular matrix (ECM)	Decrease in number Decline in growth factor response
Collagen	ECM component Dermal support	Reduced synthesis of 'new' and decreased degradation of existing collagen
Elastin	ECM component Elasticity of skin	Reduced microfibril content Elastin fragmentation
Keratinocytes	UV protection—barrier and mechanical protection Cell signalling Melanin carrier	Less proliferation and differentiation Reduced barrier function
Melanocytes	Melanogenesis for UV radiation protection Endogenous free radical 'quencher'	Decline in melanocyte number and life span
Langerhans' cells	Antigen presentation	Reduction in number and morphological abnormalities

and solar keratoses, basal and squamous cell carcinomas, and melanoma—particularly superficial variants such as lentigo maligna.

Structural changes that occur during extrinsic ageing include deficiency of collagen types 1, 3 and 7, which include the anchoring fibres and fibrillin in the papillary dermis. Fibrillin is thought to be one of the key structural support components. There is usually a decline in connective tissue support for dermal blood vessels, leading to vascular dilatation and the clinical appearance of telangiectasia [6].

A primary cause of UVA skin damage is oxidative damage mediated by a variety of reactive oxygen species [7]. It has been estimated that 50% of UV-induced damage results from the generation of these reactive oxygen species. Unlike intrinsic skin ageing, where collagen production declines, collagen synthesis is increased during UV radiation. There is a decrease in pro-collagen, which is absent 24 hours after exposure to sunlight. Increased production of matrix metalloproteinases, such as collagenase and gelatinase, results in collagen and dermal extracellular matrix degradation. The total collagen content of chronically sun-damaged skin is reported to be 20% less than non-solar exposed skin.

Ultraviolet exposure also leads to changes in the structural organization and function of elastic tissues. Photodamage results in abnormally thickened, tangled and disintegrated elastic fibres, which form an amorphous mass [6].

It has been shown that small fluences of repetitive UVA radiation can produce abnormal pigment and vascular damage after 12 weeks of twice-weekly radiation [8]. UV radiation creates a favourable environment for angiogenesis and dermal blood vessel fragility. UVA radiation also damages DNA, cell membranes and proteins, leading to cell ageing and an increased risk of skin cancer.

The changes of facial ageing are summarized in Table 80.2 and shown in Figs 80.1 & 80.2.

Table 80.2 Some clinical effects of intrinsic and extrinsic facial ageing (see also Figs 80.1 and 80.2).

Greater visibility of bony landmarks
Increased rhytides
Hollowing of the cheek and perioral area
Deepening nasolabial folds
Descent of facial fat pads
Brow ptosis
Upper eyelid laxity
Infraorbital laxity and fat herniation
Atrophy of lips
Descent of the corners of the mouth
Ptosis of the nasal tip
Lower face and neck sagging and laxity
Surface photodamage—lentigo, telangiectasia, solar comedones, rhytides
Solar keratoses and skin cancers

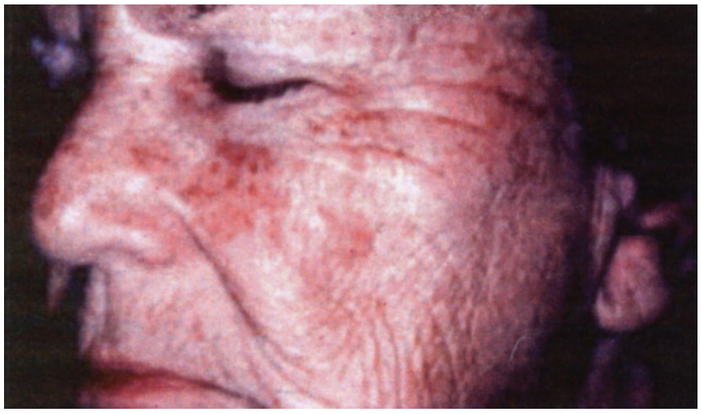


Fig. 80.2 Signs of extrinsic ageing—surface photodamage, loss of volume, lentigo, sagging, dynamic rhytid, atrophy of lips and solar elastosis.

References

1 Lowe NJ. Introduction. In: Lowe NJ, Carruthers A, Carruthers J *et al.*, eds. *Textbook of Facial Rejuvenation*. London: Informa Health Care, 2002: 1–2.

2 Gilchrest BA. Overview of skin aging. *J Cutan Ageing Cosmet Dermatol* 1988; **1**: 1–3.

3 Kligman AM, Kligman LH. Photoaging. In: Fitzpatrick TB, Eisen AZ, Wolff K *et al.*, eds. *Dermatology in General Medicine*. New York: McGraw-Hill, 1993: 2972–9.

4 Koehler MJ, Konig K, Elsner P *et al.* In vivo assessment of human skin aging by multiphoton laser scanning tomography. *Opt Lett* 2006; **31**: 2879–81.

5 Tzaphlidou M. The role of collagen and elastin in aged skin. An image processing approach. *Micron* 2004; **35**: 173–7.

6 McCullough JL, Kelly KM. Prevention and treatment of skin aging. *Ann NY Acad Sci* 2006; **1067**: 323–31.

7 Runger TM, Kappes UP. Mechanisms of mutation formation with long wave ultraviolet light (UVA). *Photodermatol Photomed* 2008; **24**: 2–10.

8 Lowe NJ, Meyers DP, Wieder JM *et al*. Low doses of repetitive ultraviolet A induce morphologic changes in human skin. *J Invest Dermatol* 1995; **105**: 739–43.

Prevention of skin and facial ageing

Topical protection is the primary means of prevention of photodamage and should be a part of routine skin care. The first sunscreen was developed in 1928, and combined benzylsalicylate and benzylcinnamate [1]. Details of sunscreens and photoprotection are discussed in Chapter 29. In order to be effective a sunscreen must be both a UVB and UVA filter or reflector. The concept of sun protection factor (SPF) as an assay for protection is well established [2,3].

The methods of evaluating protection by sunscreens against UVA continue to be debated, but guidelines have been established in the UK using an *in vitro* UVA assay [4].

Topical treatments

Photoprotection and topical treatments should be a key part of any antiageing programme. Tretinoin has been shown to be effective for improvement of both photodamaged and intrinsically aged skin [5]. It is a non-selective retinoic acid that increases epidermal thickness, promotes dermal collagen production and reduces its degradation, and inhibits UV-induced matrix metalloproteinases [6]. Other retinoids shown to produce objective clinical and histological changes include retinal, retinaldehyde and retinyl esters [7]. An important part of any topical retinoid treatment protocol is to control retinoid-induced skin irritancy while maintaining retinoid-induced skin rejuvenation. Choice of frequency of treatment and adequate skin moisturization are key variables. A range of non-prescription topical products have been claimed to possess some activity against skin ageing changes. These agents have been called cosmeceuticals, as they are not regulated as medicines by the Food and Drug Administration (FDA) in the USA, or the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK. Accurate assessment of their efficacy is often difficult because of limited available data.

A recent study of the effects of retinol on intrinsically aged forearm skin has been presented as further evidence of the rejuvenation potential of topical retinoids for ageing skin, increased dermal matrix protein synthesis and glycosaminoglycan induction being noted in this study [8].

A variety of antioxidants have been incorporated in the formulation of some topical products. There is evidence that they are capable of reducing some photodamage, with a reduction of erythema and other markers of UV damage such as sunburn cell accumulation. Some topical vitamin C analogues have been shown to regulate collagen and tissue inhibitors of matrix metalloproteinase [9]. Other antioxidants employed include botanical agents, such as extracts of grape seed, pomegranate, green tea and raspberry [10]. It appears that polyphenol and isoflavone are also ingredients that may be effective for photoprotection. Coenzyme Q-10, which is a component of a mitochondrial electron transport chain acting as an antioxidant in the skin, has also been used as a protective antioxidant in cosmeceutical topical products [11].

A variety of synthetic plant derivatives such as *N*6-furfuryladenine, and ferulic acid have also been employed in some cosmetic preparations because of their *in vitro* cell protective properties [12]. Further research is required to confirm the degree of *in vivo* human activity of these agents in different formulations for photoprotection and repair of ageing skin.

Oestrogen

Oral oestrogen use in females is associated with a statistically significant decline in the risk of skin wrinkling, but interestingly

not in atrophy [13]. These clinical changes are due to an increase in skin collagen content. Topical progesterone is associated with increased skin elasticity in pre- and postmenopausal women, suggesting a possible value for improving some aspects of ageing skin in women [14].

References

1 Shaath NA. Evolution of modern sunscreen chemicals. In: Lowe NJ, Shaath N, Pattack M, eds. *Sunscreens, Development, Evaluation and Regulatory Aspects*, 2nd edn. New York: Marcel Dekker, 1997: 3–33.
2 Food and Drug Agency. Sunscreen products for over the counter use: tentative final monograph. *Federal Register (USA)* 1993; **58**: 28194–302.
3 European Cosmetic Toiletry and Perfumery Association. Colipa sun protection factor test method. *Official Journal of the European Union* L 151, 23/06/1993.
4 Diffey BL, Robson JA. A new substrate to measure sunscreen protection factors throughout the ultraviolet spectrum. *J Soc Cosmet Chem* 1989; **40**: 127–33.
5 Kligman AM, Grove GL, Hirose R *et al*. Topical tretinoin for photoaged skin. *J Am Acad Dermatol* 1986; **15**: 836–59.
6 Griffiths CEM, Finkel J, Tranfalgia MC *et al*. An in vitro experimental model for effects of topical retinoic acid in human skin. *Br J Dermatol* 1988; **129**: 389–94.
7 Connor MJ, Ashton RE, Lowe NJ. A comparative study of the induction of epidermal hyperplasia by natural and synthetic retinoids. *J Pharmacol Exp Ther* 1986; **237**: 31–5.
8 Kafi R, Kwak S, Shumacher WE *et al*. Improvement of naturally aged skin with vitamin A (retinol). *Arch Dermatol* 2007; **143**: 606–12.
9 Pinnell SR, Murad S, Darr D. Induction of collagen synthesis by ascorbic acid. A possible mechanism. *Arch Dermatol* 1987; **123**: 1684–6.
10 Katiyar SK, Ahmad N, Mukhtar H. Green tea and skin. *Arch Dermatol* 2000; **136**: 989–94.
11 Hoppe Y, Bergemann J, Diembeck W *et al*. Coenzyme Q10, a cutaneous antioxidant and energizer. *Biofactors* 1999; **9**: 371–8.
12 Lin FH, Lin JY, Gupta JD *et al*. Ferulic acid stabilizes a solution of vitamins C and E and doubles its photoprotection of skin. *Invest Dermatol* 2005; **125**: 826–32.
13 Sator PG, Sator MO, Schmidt JB *et al*. A prospective, randomized, double blind, placebo controlled study on the influence of hormone replacement therapy on skin ageing in post menopausal women. *Climacteric* 2007; **10**: 320–34.
14 Holzer G, Riegler E, Honigsmann H *et al*. Effects and side-effects of 2% progesterone cream on the skin of peri-and post-menopausal women: results from a double-blind, vehicle-controlled, randomized study. *Br J Dermatol* 2005; **153**: 626–34.

Skin rejuvenation procedures

There are now many non-invasive or minimally invasive treatments for skin rejuvenation. The remainder of this chapter will discuss some of the more commonly accepted options (Table 80.3).

Table 80.3 Some treatment options for facial rejuvenation.

Objective	Treatment options
Superficial rejuvenation	Topical antiageing creams
	Superficial peels
	Microdermabrasion
	Intense pulsed light
Dermal remodelling	Non-ablative facial rejuvenation (lasers)
	Laser and fractional resurfacing
Muscle relaxation	Botulinum toxin type A injections
Soft tissue augmentation	Fillers
Volume replacement	
Deeper rejuvenation	Fractional resurfacing—carbon dioxide Fraxel
	Carbon dioxide lasers
	Medium peels
	Deep peels

Volume replacement by fillers

Volume replacement using a variety of dermal fillers is designed to address the subcutaneous atrophy and facial hollows that often accompany ageing. A number of soft-tissue fillers are now employed, ranging from non-biodegradable, which may be permanent, to more transient, biodegradable fillers [1]. It is important to know that these fillers have different risks of adverse events [2], which are related to the skill of the injector and the intrinsic properties of the filler [2–4].

Categories of dermal fillers

Fillers can be categorized according to their source:

- Autogeneic, e.g. fat, autologous plasma, autologous collagen
- Allogeneic, e.g. human cadaver tissue, human fibroblast cell culture
- Xenogeneic, e.g. collagen, usually derived from bovine or porcine sources; hyaluronic acid products derived from animal sources or the results of bacterial fermentation
- Synthetic products, e.g. silicone, polymethyl methacrylate, hydroxyapatite, carboxy cellulose, poly-L-lactic acid, polyacrylamide.

Specific dermal fillers

Xenogeneic bovine collagen has been used for over 20 years, and results can last from 3 to 12 months, depending on the choice of bovine collagen [5]. The duration depends on the site and type of injection selected. Because of a risk of delayed cutaneous allergic reactions with bovine collagen it is advised that double skin testing is carried out, as it has been estimated that approximately 3% of injected patients will develop delayed nodular reactions [2,6], including necrotic reactions [7].

Products developed over the last 10 years include a variety of hyaluronic acid derivatives. In some parts of the world there is little regulatory requirement for testing of these new fillers before they are used on patients. The original hyaluronic acid filler was derived from rooster combs [7], but this has now been largely superseded by materials produced by bacterial fermentation and stabilization using proprietary processes [8].

The duration of benefits from hyaluronic acids fillers for correction of nasolabial folds is usually between 6 and 12 months, but it is less when used for lip augmentation [9] (Figs 80.3 & 80.4). The duration of benefit in an individual will depend on several factors, including formulation of the hyaluronic acid filler, depth of injection and laxity of skin injected.

Side effects include immediate oedema, haematoma, delayed allergic reactions, nodules, vascular occlusion and infections, including, rarely, atypical mycobacteria [2,3].

There are still occasional delayed reactions to these fillers, leading to inflammatory nodule formation, although their frequency has declined significantly over the past 5 years [2,10]. Other volume replacements that give immediate filling include calcium hydroxyapatite, which is useful as deep injections for



Fig. 80.3 Lip augmentation: before (a) and (b) after 1 cc of hyaluronic acid filler.

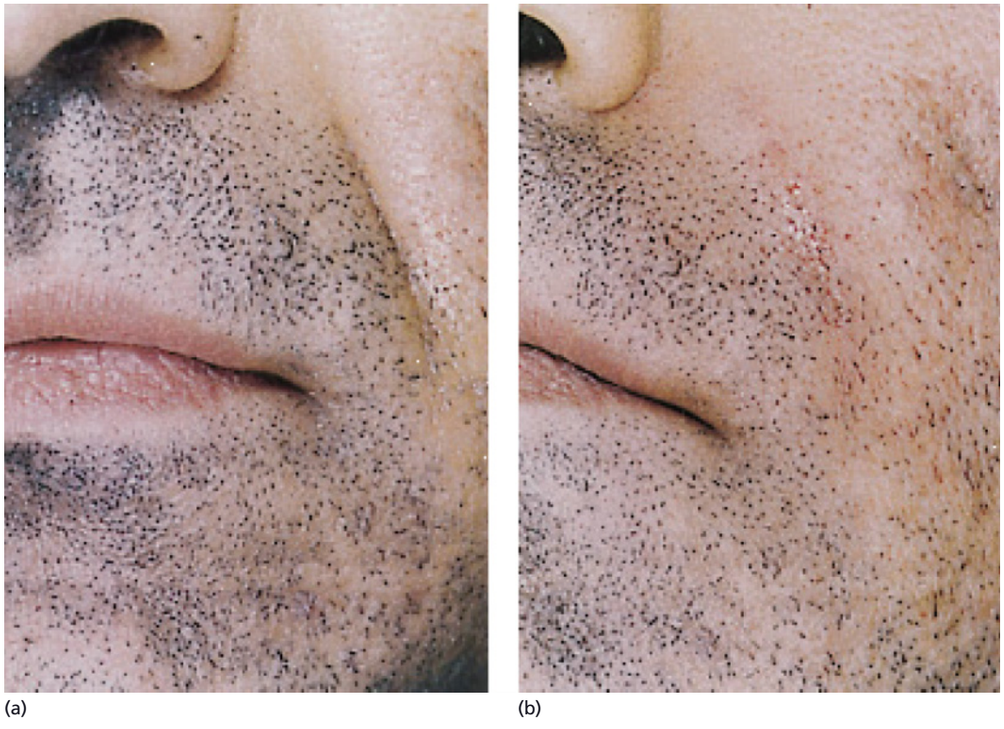


Fig. 80.4 Before (a) and (b) following 0.75 cc of hyaluronic acid filler to the nasolabial folds.

volume replacement of cheeks and deep nasolabial folds [11]. Another group of injectables that increase the collagen matrix, ground substance and dermal elastic formation by stimulating dermal fibroblast activity include poly-L-lactic acid (PLLA). This is injected as a dilute suspension which dissolves within the dermis and subcutaneous levels, inducing fibroplasia and increasing dermal and subcutaneous thickness. Originally, PLLA was used to improve the facial lipodystrophy often associated with earlier types of antiretroviral therapy [12]. It was subsequently shown to be effective for correcting facial volume loss in the ageing face and for atrophic scars. The main side effect is nodule formation, most commonly in perioral and periorbital areas, and these are therefore areas which should be avoided with PLLA [12]. It is most useful for nasolabial folds and mid-cheek sites [13]. PLLA has also been used for atrophic scar improvement [14].

Another recent approach has been to use allogeneic human-derived fibroblasts from a single source of neonatal tissue; this procedure is in the early stages of research and development [15]. Safety phase studies have shown increased dermal and epidermal thickness, and no toxicity. Further studies are proceeding.

An autologous filler that has been used for many years is fat, harvested from the patient and processed with filtration plus cleansing, or simply reinjected. A debate as to the efficacy of these different methods of fat replacement injections continues. One problem is variable duration of benefit, and it has been suggested that this is site specific, with the cheek area having the best retention of injectable fat [16]. Post-injection oedema and bruising is temporary but can last several weeks [16]. One study suggested that fresh autologous fat transfer has good viability compared with refrigerated or frozen fat storage and later injection [17].

Table 80.4 Adverse reactions to dermal fillers.

Early adverse events (occurring up to several days post-treatment)	Delayed adverse events (occurring from weeks to years post-treatment)
Injection site reactions:	Infection (e.g. atypical mycobacterial):
erythema	erythema
oedema	oedema
pain/tenderness	pain/tenderness
bruising	nodules
pruritus	systemic responses to infection
Infection:	Granulomatous inflammation:
erythema	varying from subclinical histological changes to disfiguring nodules
oedema	Migration of filler
pain/tenderness	Hypersensitivity:
pustules	aseptic abscess
nodules	Persistent hyperpigmentation
abscesses	Persistent scarring
Hypersensitivity:	
erythema	
oedema	
pain/tenderness	
Lumps caused by maldistribution	
Discoloration:	
erythema	
hypochromia	
hyperpigmentation	
Local tissue necrosis caused by vascular occlusion	

Fat is best used for deeper volume replacement of the face or localized areas of fat atrophy [16].

Adverse reactions (Table 80.4)

Adverse reactions to fillers can be described in terms of:

- Clinical seriousness
- Aesthetic relevance
- Immediate versus delayed onset
- Causality: expected procedure related events; events related to improper technique; reactions to the product.

Reactions can be attributed to the procedure itself, procedural technique and the agent injected. Some of these reactions are preventable, whereas others are inevitable; most are mild and transient. Improving product formulations, altering the concentration of product injected or changing injection technique can dramatically reduce the incidence of adverse reactions. Since its reformulation in mid-1999, the biologically engineered hyaluronic acid filler, Restylane, elicits less than one allergic reaction in 1600 treatments. There are over 85 different hyaluronic acid fillers currently available in Europe. Skin reactions with PLLA (New Fill/Sculptra) are considerably less likely if a greater dilution and deeper injection technique are employed.

References

1 Murray CA, Zloty D, Warshawski L. The evolution of soft tissue fillers in clinical practice. *Dermatol Clin* 2005; **23**: 343–53.

2 Lowe NJ, Maxwell CA, Patnaike R. Adverse reactions to dermal fillers: review. *Dermatol Surg* 2005; **31**: 1616–25.

3 Andre P, Lowe NJ, Parc A *et al*. Adverse reactions to dermal fillers: a review of European Experiences. *J Cosmet Laser Ther* 2005; **7**: 171–6.

4 Christensen L, Breiting V, Janssen M *et al*. Adverse reactions to injectable soft tissue permanent fillers. *Aesthetic Plast Surg* 2005; **29**: 34–48.

5 Cooperman LS, Mackinnon V, Bechler G, Pharriss BB. Injectable collagen: a six year investigation. *Aesthetic Plast Surg* 1985; **9**: 145–51.

6 DeLustro F, Smith ST, Sundsmo J *et al*. Reaction to injectable collagen: results in animal models and clinical use. *Plast Reconstr Surg* 1987; **79**: 581–92.

7 Hanke CW, Higley HH, Jolivette DJ *et al*. Abscess formation and necrosis after treatment with Zyderm and Zyplast collagen implant. *J Am Acad Dermatol* 1991; **25**: 319–26.

8 Duranti F, Salti G, Bovani B. Injectable hyaluronic acid gel for soft tissue augmentation. A clinical and histological study. *Dermatol Surg* 1998; **24**: 1317–25.

9 Manna F, Dentini M, Desideri P *et al*. Comparative chemical evaluation of two commercially available derivatives of hyaluronic acid (hylaform from rooster combs and restylane from streptococcus) used for soft tissue augmentation. *J Eur Acad Dermatol Venereol* 1999; **13**: 183–92.

10 Lowe NJ, Maxwell CA, Lowe P *et al*. Hyaluronic acid skin fillers: adverse reactions and skin testing. *J Am Acad Dermatol* 2001; **45**: 930–3.

11 Alam M, Yoo SS. Technique for calcium hydroxylapatite injection for correction of nasolabial fold depressions. *J Am Acad Dermatol* 2007; **56**: 285–9.

12 Valantin MA, Aubron-Olivier C, Ghosn J *et al*. Polylactic acid (New-Fill) to correct facial lipatrophy in HIV-infected patients: results of the open-label study VEGA. *AIDS* 2003; **17**: 2471–7.

13 Lowe NJ. Appropriate use of poly-L-lactic acid and clinical considerations. *J Eur Acad Dermatol Venereol* 2006; **20**: 2–6.

14 Beer K. A single center, open-label study on the use of injectable poly-L-lactic acid for the treatment of moderate to severe scarring from acne or varicella. *Dermatol Surg* 2007; **33** (Suppl. 2): S159–67.

15 Lowe NJ, Lowe PL, Patuaik R, St Clair Roberts J. A phase 1 study of 1CX-Rhy, a suspension of allogeneic human dermal fibroblasts. *J Invest Dermatol* 2007; **127**: Abstract. 254.

16 Donofrio LM. Panfacial volume restoration with fat. *Dermatol Surg* 2005; **31**: 1496–505.

17 Lidagoster MI, Cinelli PB, Levee EM, Sian CS. Comparison of autologous fat transfer in fresh, refrigerated, and frozen specimens: an animal model. *Ann Plast Surg* 2000; **44**: 512–5.

Table 80.5 Available botulinum neurotoxins.

Product	Toxin type	Toxin mol wt (kDa)	pH	Approved in Europe and USA for cosmetic use	Approved for hyperhidrosis in UK, Europe, USA	Approved for medical indications (dystonia, blepharospasm etc.) in Europe
Botox	A	900	~7	Yes	Yes	Yes
Dysport	A	500–900	~7	No	No	Yes
Xeomin	A	150	~7	No	No	Yes
Neuronox	A	Unknown	6.8	No	No	No
Myobloc/Neurobloc	B	300–500	~5.6	No	No	Yes

Botulinum toxins—their use in controlling facial lines

The first medical use of botulinum neurotoxin was described by Dr Alan Scott during the 1970s when he used a botulinum toxin type A (BTX-A) for reducing over-activity of selected periocular muscles in patients with strabismus [1–3]. Following this observation botulinum neurotoxins have been increasingly studied for a wide variety of therapeutic and aesthetic uses. Double-blind controlled studies of BTX-A for reduction of upper facial lines in the USA have shown benefit of approximately 4 months' duration [4,5]. These initial observations were followed by double-blind, placebo-controlled studies of several hundred patients performed in the USA, which demonstrated that BTX-A was safe and effective for reducing the severity of glabellar lines (lower forehead vertical frown lines) [6,7]. Significant improvement was observed as early as a few days after treatment, and the mean duration of improvement was in excess of 4 months using appropriate doses of BTX-A, which were initially 20 units for lower forehead frown lines. Several other studies confirm that BTX-A is also effective for lateral periorbital lines, often known as 'crow's feet' [8] and also rhytides of the infraorbital area [9].

There are two main serotypes of botulinum toxins used clinically—the most commonly used being botulinum toxin type A (BTX-A) (Table 80.5). Type B botulinum toxin (BTX-B) has a much shorter duration of effect than BTX-A, but is occasionally used if therapeutic resistance is observed to BTX-A.

Other clinical studies have confirmed that both type A and type B botulinum toxins are effective at reducing facial lines [10], as well as excessive sweating in areas such as the axillae [11,12]. BTX-A treatment for axillary hyperhidrosis has been approved by the MHRA in the UK, and regulatory agencies in numerous other countries including the FDA in the USA.

The mode of action of BTX-A is by rapid inhibition of acetylcholine release at the neuromuscular junction. As a result, BTX-A causes localized, reversible muscle relaxation [1], and because some facial lines result from repetitive contraction of underlying muscles this produces a reduction of facial lines [4,5,7,8]. The mode of action against hyperhidrosis (which is covered in more detail in Chapter 44) is again the result of inhibition of release of acetylcholine, which is one of the neurotransmitters for emotional, non-thermoregulatory sweating [11,12].

The sites of injection used to improve facial lines, and therefore some signs of facial ageing, are most commonly: upper face—horizontal forehead lines, vertical forehead lines, supraorbital lines, periorbital (crow's feet) lines, infraorbital lines, paranasal lines; lower face—perioral lines, vertical rhytides above the upper lip and turning down of the angles of the mouth (melomental folds) [13]. Vertical neck bands produced by platysmal muscle activity can also be reduced by the use of BTX-A [14].

Two different commercial types of BTX-A have been available in Europe since the 1990s. They are produced by different bacteria, with differing fermentation and purification processes, and have different potency and diffusion. Dilution and dosing have been investigated, and estimated conversion ratios of one type of BTX-A to the other have been proposed [15,16].

Side effects from BTX-A are local at doses used for aesthetic indications, for example bruising and brow and/or eyelid ptosis. They are usually the result of inexpert injection of BTX-A—for example, injection of too high a dose of BTX-A into the lower lateral forehead may result in both brow and upper eyelid ptosis. Injection too low in the infraorbital area may result in upper lip and lower facial weakness. Facial asymmetry may occur. These side effects are usually temporary, but can be of understandable concern to patients [17]. The physician injecting BTX-A should be trained to try to avoid these problems.

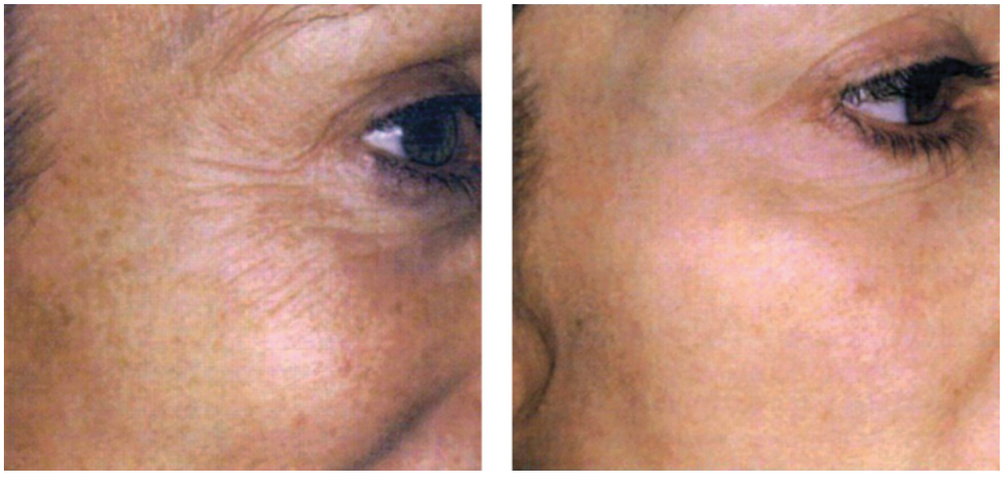
Other side effects are extremely uncommon. A rare problem is that of resistance to BTX-A, the mechanism of which is unknown, but may involve antibodies blocking the uptake or action of BTX-A.

Combination treatments with BTX-A

Combination treatments are selected for appropriate patients to rejuvenate the ageing face [17]. An example of a combination treatment is administration of BTX-A prior to use of either resurfacing lasers [18] (Fig. 80.5) or fractionated rejuvenation lasers (p. 80.11). The BTX-A is ideally delivered at least 1 week prior to the laser; this enables the hyperactive muscle action to be diminished thereby reducing the facial lines. In addition, as one theory of skin rejuvenation with these laser systems is the stimulation of neocollagenesis, it is likely that a less folded skin following BTX-A leads to more uniform neocollagenesis.

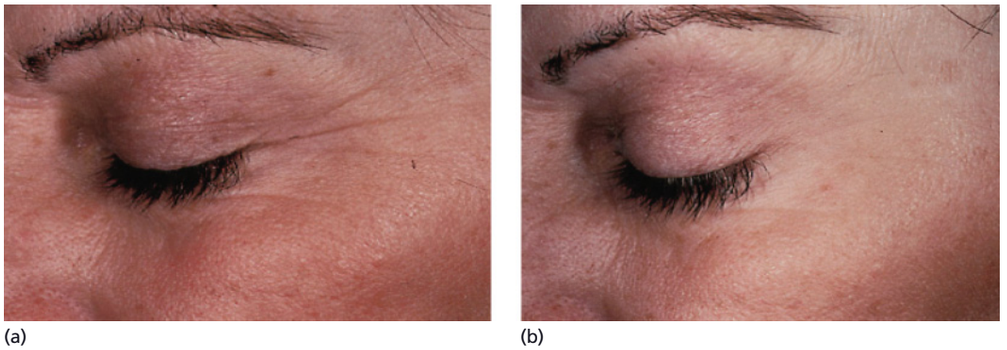
The effects of combined BTX-A injections and lasers have been confirmed as being superior to placebo injections and laser alone [18].

Another situation where combination treatments are useful is the use of BTX-A and dermal fillers in problems such as deep vertical lower forehead lines. Here, BTX-A alone will improve, but not clear, the deep furrows that are present in some patients. The



(a) (b)

Fig. 80.5 (a) Pre-treatment shows photodamage, with solar lentigo and dynamic rhytides (crow's feet). (b) Post-treatment with botulinum toxin A to crow's feet, plus ultrapulsed carbon dioxide laser resurfacing full face.



(a) (b)

Fig. 80.6 Reduction of lateral periorbital lines (crow's feet) after injection of BTX-A into the lateral orbicularis oculi muscle; (a) pre-treatment; (b) post-injection.

use of BTX-A plus temporary filler can give a more prolonged effect than using the filler alone [19]. In a similar mechanism, the use of BTX-A to the upper lip area together with filler in the upper lip can provide adjunctive benefit in the correction of upper lip lines. Dermal fillers and BTX-A can also be combined in lower facial areas, where the BTX-A is injected into areas such as depressor angulae oris and mentalis muscles and the filler is injected into melomental folds.

Figure 80.6 shows the effect of BTX-A injected in the periorbital area, thereby reducing the intensity of the periorbital rhytides.

References

1 Scott AB. Development of botulinum toxin therapy. *Dermatol Clin* 2004; **22**: 131–3.

2 Scott AB, Rosenbaum A, Collins CC. Pharmacologic weakening of extraocular muscles. *Invest Ophthalmol* 1973; **12**: 924–7.

3 Scott AB. Botulinum toxin injection into extraocular muscles as an alternative to strabismus surgery. *Ophthalmology* 1980; **87**: 1044–9.

4 Keen M, Blitzer A, Aviv J *et al*. Botulinum toxin A for hyperkinetic facial lines: results of a double-blind, placebo-controlled study. *Plast Reconstr Surg* 1994; **94**: 94–9.

5 Lowe NJ, Maxwell A, Harper H. Botulinum A exotoxin for glabellar folds: a double-blind, placebo-controlled study with an electromyographic injection technique. *J Am Acad Dermatol* 1996; **35**: 569–72.

6 Carruthers JA, Lowe NJ, Menter MA *et al*. for the BOTOX Glabellar Lines I Study Group. A multicenter, double-blind, randomized, placebo-controlled study of the efficacy and safety of botulinum toxin type A in the treatment of glabellar lines. *J Am Acad Dermatol* 2002; **46**: 840–9.

7 Carruthers JD, Lowe NJ, Menter MA *et al*. for the BOTOX Glabellar Lines II Study Group. Double-blind, placebo-controlled study of the safety and efficacy of Botulinum toxin type A for patients with glabellar lines. *Plast Reconstr Surg* 2003; **112**: 1089–98.

8 Lowe NJ, Ascher B, Heckmann M *et al*. for the Botox Facial Aesthetics Study Team. Double-blind, randomized, placebo-controlled, dose-response study of the safety and efficacy of botulinum toxin type A in subjects with crow's feet. *Dermatol Surg* 2005; **31**: 257–62.

9 Flynn TC, Carruthers JA, Carruthers JA, Clark RE II. Botulinum A toxin (BOTOX) in the lower eyelid: dose-finding study. *Dermatol Surg* 2003; **29**: 943–50.

10 Lowe NJ, Yamauchi PS, Lask GP *et al*. Botulinum toxin types A and B for brow furrows: preliminary experiences with type B toxin dosing. *J Cosmet Laser Ther* 2002; **4**: 15–8.

11 Lowe NJ, Campanati A, Bodokh J *et al*. The place of botulinum toxin type A in the treatment of focal hyperhidrosis. *Br J Dermatol* 2004; **151**: 1115–22.

12 Heckmann M, Plewig H, for the Hyperhidrosis Study Group. Low-dose efficacy of botulinum toxin A for axillary hyperhidrosis: a randomized, side-by-side, open-label study. *Arch Dermatol* 2005; **141**: 1255–9.

13 Lowe NJ. Introduction. In: Lowe NJ, Carruthers A, Carruthers J *et al*., eds. *Textbook of Facial Rejuvenation*. London: Informa Health Care, 2002: 1–2.

14 Matarasso A, Matarasso SL, Brandt FS, Bellman B. Botulinum A exotoxin for the management of platysma bands. *Plast Reconstr Surg* 1999; **103**: 645–52.

15 Ascher B, Zakine B, Kestemont P *et al*. A multicenter, randomized, double-blind, placebo-controlled study of efficacy and safety of 3 doses of botulinum toxin A in the treatment of glabellar lines. *J Am Acad Dermatol* 2004; **51**: 223–33.

16 Lowe P, Patnaik R, Lowe N. Comparison of two formulations of botulinum toxin type A for the treatment of glabellar lines: a double-blind randomized study. *J Am Acad Dermatol* 2006; **55**: 975–80.

17 Lowe NJ. When and how to combine treatments. In: Lowe NJ, Carruthers A, Carruthers J *et al*., eds. *Textbook of Facial Rejuvenation*. London: Informa Health Care, 2002: 322–5.

18 Yamauchi P, Lask GL, Lowe NJ. Botulinum toxin type A gives adjunctive benefit to periorbital laser resurfacing. *J Cosmet Laser Ther* 2004; **6**: 145–8.
19 Carruthers J, Carruthers A, Maberley D. Deep resting glabellar rhytides respond to BTX-A and hylan B. *Dermatol Surg* 2003; **29**: 539–44.

Chemical peels for improvement of facial ageing

Chemical peels have been used for many years for skin surface rejuvenation, and treating irregular pigmentation and superficial scars [1].

A limiting factor is the depth of penetration of the different chemicals used for skin peeling. Another important factor is the toxicity of the chemical, for example phenol or 50% trichloroacetic acid are considerably more toxic to the skin than 50% buffered glycolic acid peels [2,3]. Even in expert hands there are some patients who will have undesirable results from chemical peels. These may include changes in pigmentation, for example hypopigmentation, which can be permanent, and hyperpigmentation, which can be long-lasting, and may be permanent and scarring.

More superficial peels, for example glycolic acid, lactic acid [3] and Jessner's peels, will accelerate epidermal shedding, but other more aggressive peels can chemically destroy epidermis and progressive layers of the dermis by protein coagulation and cell lysis. The main classification of peels is usually based on the expected depth and severity of the peel—a commonly used classification being superficial peels, medium-depth peels and deep peels [2–4]. Examples of the peeling agents leading to different severities of peel are listed in Table 80.6.

The nature of the chemical influences the depth of peel; for example, lactic acid is usually a very superficial peeling agent and 50% trichloroacetic acid (TCA) is a much deeper peeling agent [2,3]. Another factor that affects the peel is skin preparation with topical retinoids, which is felt to increase the uniformity of the peel. It alters the stratum corneum barrier, and enhances the penetration of some peeling agents by altering epidermal and stratum corneum morphology. It is possible to change a superficial-depth glycolic acid peel into a medium-depth peel by altering the percutaneous penetration characteristics of the skin with agents such as tretinoin and other peeling agents applied prior to the final peel [5,6].

Superficial peels include a combination of resorcinol, lactic acid and salicylic acid, known as Jessner's peel. This is useful for abnormal superficial pigment, fine rhytides and very superficial scars. It can be reapplied numerous times over the treatment session [7].

Every practitioner using peels in their practice should become trained and familiar with the particular peel they will be using.

Site dependence

The density of appendigeal structures, such as pilosebaceous glands, will also govern the safety and healing of the skin following deeper chemical peels. An area such as the face, which has a much higher density of pilosebaceous structures, generally responds in a more predictable way to chemical peels than the neck, chest and limbs. Superficial peels should only be used in areas where there are minimal sebaceous appendages, that is most areas other than the face. Medium-depth peels can be used on the face, but care should be exercised in using them on other parts of the body. Because of the relatively low density of skin appendigeal structures, impaired healing can occur in these non-facial areas, resulting in an increased risk of scarring and pigmentary changes.

Skin phototype and chemical peels

Skin phototype (Table 80.7) is of key importance in chemical peel selection. Because of the risks of facial pigmentation disorders following the peels it is important that skin phototypes III and above are treated with peels that are not likely to result in hypopigmentation [7]. Patients with skin phototype III and above will always have some hyperpigmentation following peels. This is usually transient, but often requires pre- and post-treatment therapy with tretinoin 0.25% or 0.5% creams for 6 weeks prior to the peel, often together with skin lightening preparations such as hydroquinone. Post-peel treatment with these agents is usually begun after complete re-epithelialization and stabilized erythema, several weeks after the peel. This post-peel treatment may reduce the degree of hyperpigmentation [4] (Fig. 80.7).

The superficial chemical peels remain valuable for treating milder skin ageing problems and as adjunctive treatments in diseases such as acne. The medium-depth and deeper chemical peels have now largely been replaced by laser skin rejuvenation, as described below in this chapter. There is some agreement that lasers lead to a more controlled impact on the skin and are not dependent on the vagaries of chemical peeling, for example variations of percutaneous penetration and toxicity that can lead to variable results. These problems are much less with modern lasers such as fractionated lasers (Lowe, N.J. personal observations).

Table 80.6 Different depths of chemical peels.

Level	Histology	Peel
Superficial	Destruction of epidermis alone	10–25% TCA Glycolic acid 50–70% Jessner's solution
Medium	Destruction of epidermis plus papillary dermis	TCA 35% Jessner's solution Glycolic acid + 35% TCA
Deep	Destruction of reticular dermis	Baker's phenol/TCA 50%

TCA, trichloroacetic acid.

Table 80.7 Fitzpatrick's classification of skin phototypes.

Skin type	Colour	Reaction to sun
I	Very white or freckled	Always burns
II	White	Usually burns
III	White to olive	Sometimes burns
IV	Brown	Rarely burns
V	Dark brown	Very rarely burns
VI	Black	Never burns



(a) (b)

Fig. 80.7 (a) Pre-treatment and (b) post-treatment with a combined tretinoin, hydroquinone and hydrocortisone skin 'lightening cream', four glycolic peels and broad-spectrum daily sunscreen.

References

1 Stegman SJ. A comparative histologic study of the effects of three peeling agents and dermabrasion on normal and sundamaged skin. *Aesthetic Plastic Surg* 1982; **6**: 123–35.
2 Brody HJ. Variations and comparisons in medium-depth chemical peeling. *J Dermatol Surg* 1989; **15**: 953–63.
3 Van Scott EJ, Yu RJ. Alpha hydroxyl acids: procedures for use in clinical practice. *Cutis* 1989; **43**: 222–8.
4 Brody HJ. Trichloroacetic acid application in chemical peeling. Operative techniques. *Plast Reconstr Surg* 1995; **2**: 127–8.
5 Bhawan J, Palto MJ, Lee L *et al*. Reversible histologic effects of tretinoin on photodamaged skin. *J Geriat Dermatol* 1995; **3**: 62–7.
6 Coleman WP 3rd, Futrell JM. The glycolic acid trichloroacetic acid peel. *J Dermatol Surg Oncol* 1994; **20**: 76–80.
7 Lawrence NL, Cox SE, Brody HJ. Treatment of melasma with Jessner's solution versus glycolic acid: a comparison of clinical efficacy and evaluation of the predictive ability of Wood's light examination. *J Am Acad Dermatol* 1997; **36**: 589–93.

Intense pulsed light and laser treatment—selection for cosmetic indications

Selection of intense pulsed light (IPL) and lasers will depend on the nature of the clinical lesion to be treated. Table 80.8 summarizes some of the more frequent clinical lesions to be treated and the selection of the type of laser and light source to be used. The reader is also referred to Chapter 78 for further information on lasers and light sources.

Intense pulsed light system

Intense pulsed light (IPL) sources give a non-coherent emission rather than the coherent specific single wavelength of a laser [1]. Most IPL systems emit a spectrum between 500 and 1200 nm, with a variety of cut-off filters designed to reduce selectively lower visible wavelengths, for example below 515 nm or below 560 nm. This lower wavelength selectivity allows for selection of different treatment indications. For vascular problems, for example telangiectasia and haemangiomas [1], wavelengths down to 500 nm are used, whereas skin pigmentary problems such as lentigo will best respond to wavelengths down to 560 nm. Poikiloderma of Civatte has also been treated with IPL. Care has to be taken to obtain a uniform improvement [2].

Table 80.8 IPL and laser treatment of clinical problems.

Clinical problem	Type of laser
Vascular lesions	Pulsed-dye usually 585–595 nm
Telangiectasia	Copper bromide
Haemangiomas/port-wine stains	KTP
Cambell de Morgan angiomas	IPL
Benign pigmented lesions	Q-switched, ruby, alexandrite, neodynium:YAG,
Lentigo, melanosis, melasma	IPL
Tattoos	Q-switched
	Ruby, alexandrite
	Neodynium:YAG
Ageing skin, rhytides, laxity	Carbon dioxide lasers
Seborrhoeic keratoses	Erbium YAG lasers
	Fractional lasers
Hirsutes (pigmented hair)	Long pulsed ruby, alexandrite, neodynium:YAG, IPL

Skin surface cooling for cosmetic IPL and laser procedures

Surface skin cooling has provided significant safety advantages for some laser and IPL systems. The concept is that by cooling the skin surface it is possible to reduce undesirable thermal injury to the epidermis by the IPL or laser, thus diminishing the risk of hypopigmentation and scarring (see Chapter 78).

There are three main types of tissue cooling:

1 Cold air convection, which is directed on to the area prior to and during treatment
2 Contact cooling, where the laser or light tip itself is cooled and thereby cools the skin surface
3 Cryogen spray cooling, where a frozen gas is sprayed on to the skin just prior to, and with some lasers during, the delivery of the laser light [3].

Another benefit of the use of cooling is that higher laser and IPL fluences can be used, enabling otherwise more resistant lesions, for example high blood-flow telangiectasia or vascular haemangiomas, to respond. Cooling also has another important effect of reducing the discomfort associated with treatment. It is important, however, to avoid cold injury from the cooling device. Cryogen freeze injury has been seen (Lowe, N.J. personal observations), particularly in skin phototypes III and darker from cryogen-cooled hair removal lasers.

Lasers for skin ageing problems

These may be grouped into treatment of vascular, pigmented or skin surface irregularities, that is superficial rhytides, and deeper problems of skin laxity, deeper rhytides and scars.

Vascular changes associated with skin ageing

Telangiectasiae on the cheeks, nose and other light-exposed areas are vascular abnormalities commonly associated with skin ageing. In addition, poikiloderma of Civatte, particularly affecting the lateral face and neck, is a superficial abnormality that is probably the result of repetitive ultraviolet injury together with, in some patients, phototoxic or photoallergic reactions to fragrances.

Choice of lasers for these vascular problems includes vascular pulsed dye lasers (usually between 585 and 595 nm), alexandrite (755 nm), Nd:YAG lasers (1064 nm), copper bromide lasers and potassium titanyl phosphate (KTP) lasers. The initial development of these lasers resulted from knowledge of the action spectrum responsible for laser vascular injury [4].

Electrocautery is sometimes used for solitary telangiectasia. One of the problems with electrocautery is a higher risk of recurrence of the lesion and/or atrophic scarring compared with pulsed-dye lasers. However, electrocautery does not give the transient purpura associated with pulsed-dye lasers.

Intense pulsed light (IPL) sources with selective wavelength cut-offs down to 500 nm and 550 nm are also used with benefit in these vascular conditions [1,2].

An important guideline when treating a large area with any of these laser or light systems is to perform a test treatment on a small, preferably non-visible part of the skin, to ensure the correct choice of laser and laser parameters. This is particularly important before treating large areas of skin, for example poikiloderma on the neck or extensive telangiectasiae on the cheek. It is possible to get irregular 'patchy' improvement that requires numerous further treatment sessions to become more uniform and acceptable.

Some darker skin phototypes, for example phototype III and darker, may elicit long-term and occasionally permanent hyperpigmentation following light and laser therapy. If too aggressive an IPL or laser treatment is selected, skin blistering with subsequent scarring and hypopigmentation is possible [5].

Benign pigmented skin lesions associated with ageing

The most common type of benign pigmented skin lesion associated with photoageing is the solar lentigo. These usually respond well to a variety of lasers and pulsed light sources. The original observations on laser treatment by Goldman used a ruby laser for tattoos and pigmented lesions [6].

Naevus of Ota persists into old age and responds well to a variety of Q-switched pigment lasers [7].

Melasma shows an extremely variable response to all lights and laser treatments—indeed to most treatment intervention [7]. The reasons remain to be determined, but possibly involve continued endogenous or exogenous hormonal stimulation of melanogenesis [8].

Lasers for benign pigmented lesions include Q-switched ruby (605 nm), alexandrite (755 nm), Nd:YAG (532 and 1064 nm) and Q-switched KTP (532 nm) [7–9].

Frequently, patients with photodamage will exhibit a combination of facial telangiectasia, plus lentigo and diffuse facial melanosis which can be treated with IPL sources. One advantage of an IPL system is that because of its broad spectrum of visible wavelengths both these types of photodamage may respond to the IPL [5,10].

Pigmented and non-pigmented seborrhoeic keratoses will respond well to laser ablation with either carbon dioxide or Er:YAG lasers. These can give a more accurate lesion vaporization than cryotherapy, and in some patients may be less likely to result in hypopigmented areas.

Lasers for surface skin changes

The first laser to be used successfully for photodamage treatment by 'skin resurfacing' was a pulsed carbon dioxide laser [11]. The carbon dioxide laser emits a wavelength of 10 600 nm and is absorbed by tissue water content. It penetrates up to 30 μm into previously non-treated skin; once absorbed, further penetration is limited by the reduced tissue water content.

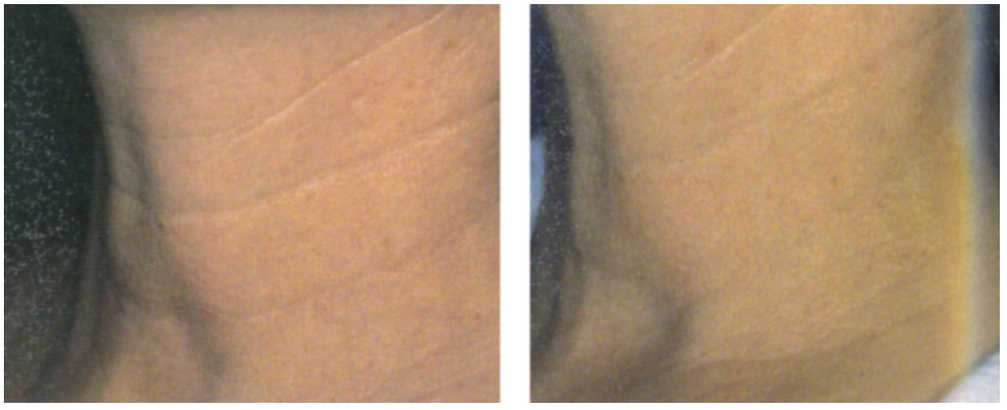
Various other types of carbon dioxide laser have been developed, including scanned devices. The concept of ultrapulsing [12,13] is to give a uniform treatment area from the laser that produces skin surface vaporization but rapid re-epithelialization from undamaged hair follicles and other adnexal structures. There is a rejuvenation of the damaged skin surface. In addition, it has been shown that with ultrapulse carbon dioxide lasers there is a degree of dermal tightening which may continue for up to 1 year after treatment [14]. This tissue tightening may be the result of either a delayed wound healing response following the laser or neocollagenesis resulting from release of cytokines and other dermal growth factor stimuli [15–17]. Other carbon dioxide devices have used scanning systems rather than ultrapulsed systems to control skin injury [18].

Another skin resurfacing laser, which has greater affinity for water absorption compared with the carbon dioxide device, is the Er:YAG laser, emitting a wavelength of 2940 nm [19,20]. It is highly absorbed by skin water, but has a relatively low penetrance of 3 to 5 μm. Ultrapulse carbon dioxide lasers are more effective than conventional Er:YAG lasers [21]. In addition, because they do not produce as much haemostasis as the carbon dioxide laser there tends to be a greater degree of bleeding during treatment [21].

Some newer Er:YAG lasers have variable pulse duration so that they act in a manner similar to the carbon dioxide laser (Lowe, N.J. unpublished observations).

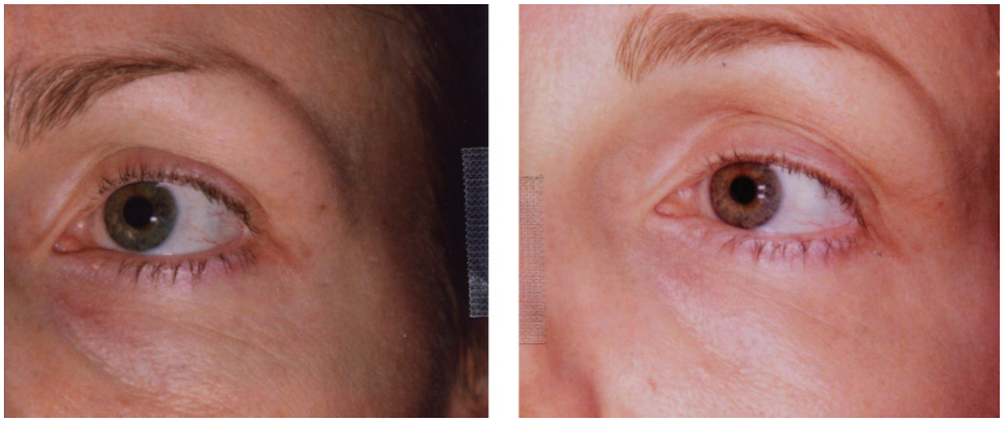
Fractional laser skin rejuvenation

Newer developments in skin rejuvenation by lasers have been the use of the fractional laser delivery systems [22]. Fractional



(a) (b)

Fig. 80.8 (a) Pre-treatment, showing mild ageing neck changes with horizontal lines and skin folding; (b) after three fractional laser treatments.



(a) (b)

Fig. 80.9 Periorbital ageing and skin laxity (a) before and (b) after five Fraxel laser treatments.

photothermolysis (FP) is a relatively new technology that creates microscopic zones or columns of thermal damage surrounded by healthy tissue, in contrast with layers of thermal vaporization from the ultrapulse carbon dioxide and Erbium:YAG lasers. The first FP laser device was introduced in 2003, as an erbium-doped fibre laser emitting at 1550 nm [22,23].

The microscopic thermal treatment zones vary in depth depending on the energy settings of the laser. As they are surrounded by an area of untreated skin this acts as a reservoir of keratinocytes for rapid repair of the treated areas of skin. Success has been reported with facial rhytides, photodamaged skin and scarring [23–25].

Initially, this system used a surface-applied blue dye to act as an optical activator of the laser [23]. The latest Fraxel laser system employs a motion detector whereby the laser is triggered by motion across the skin. This can be described as a 'rolling' FP laser system. The efficacy of FP with the 1550 nm laser, mentioned above, has been reported in a number of studies [23–25]. Results are encouraging for the improvement of surface photodamage, solar lentigo, diffuse facial melanosis, fine rhytides and atrophic facial scars (Figs 80.8–80.10). Another advantage of this laser is that it can be used (at appropriate settings) on areas other than the face, for example the neck, chest and limbs (Fig. 80.11). This is because with fractionated laser delivery, there are remaining areas of non-treated skin which lead to rapid re-epithelialization and reduced scar risk [22]. With previous lasers, for example ultrapulse carbon dioxide and Erbium:YAG, there was complete epidermal and dermal photothermolysis and a significant risk in non-facial areas of compromised, delayed healing with scarring risk due to the relative paucity of adnexal structures. A very recent development is a fractionated delivery carbon dioxide laser.

A variety of other 'pseudo-fractionated' and 'stamp' fractionated systems have been developed including systems using several wavelengths between 532 and 10 600 nm. These all have their own proponents, but as yet there is a lack of data to enable comparison with the rolling FP system.

Skin preparation and post-treatment care for laser rejuvenation

Pre-treatment preparation and post-treatment care of the skin are important, particularly in the management of pigmented and photodamaged skin. Pre-treatment with topical retinoids and, where pigmentation is a problem, additional depigmenting agents such as hydroquinone or combinations thereof, may help to enhance healing and reduce post-laser hyperpigmentation [14]. In addition, it is important to enquire about the occurrence of herpes simplex on the area to be treated, and prophylactic oral aciclovir 400 mg b.d. 1 day prior to and 7 days following laser treatment may be employed [26]. Post-laser care involves the use of topical emollients, as well as treatment of any possible post-laser acne relapses and folliculitis.



(a) (b)

Fig. 80.10 Forehead melasma, (a) before and (b) after four Fraxel laser treatments.

After initial healing—usually 1–2 weeks—the patient should be encouraged to use daily photoprotection with a sunscreen, topical antioxidants and, if necessary, depigmenting agents. Maintenance treatment can include topical retinoids, for example tretinoin 0.025% cream may be used nightly as tolerated.

Non-laser skin surface rejuvenation

A recent development is a 'plasma' skin rejuvenation system, using high surface energy generated with nitrogen gas released at high velocity. This 'plasma' system is currently being evaluated as an alternative to laser skin rejuvenation [27].

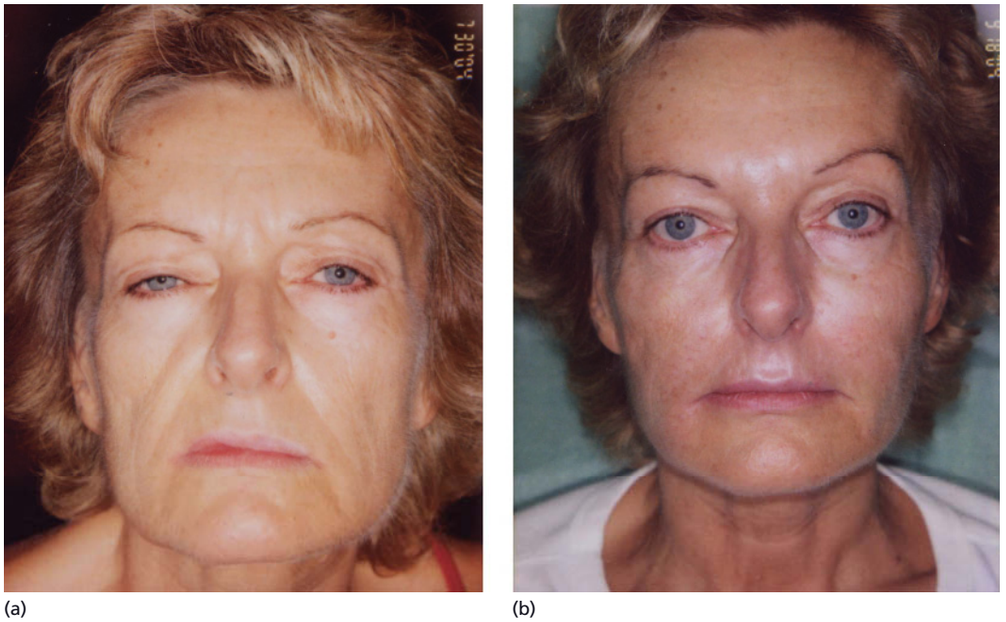
References

1 Shroeter CA, Newmann HA. An intense light source. The photoderm VL-flashlamp as a new treatment possibility for vascular skin lesions. *Dermatol Surg* 1998; **24**: 743–8.
2 Weiss RA, Goldman MP, Weiss MA. Treatment of poikiloderma of Civatte with an intense pulsed light source. *Dermatol Surg* 2000; **26**: 823–8.
3 Chang CJ, Nelson JS. Cryogen spray cooling and higher fluence pulsed dye laser treatment improve port wine stain clearance while minimizing epidermal damage. *Dermatol Surg* 1999; **25**: 767–72.
4 Tan OT, Murray S, Kurban AK. Action spectrum of vascular specific injury using pulsed irradiation. *J Invest Dermatol* 1989; **92**: 868–71.
5 Ross EV, Smirnov M, Pankratov M, Altshuler G. Intense pulsed light and laser treatment of facial telangiectasias and dyspigmentation: some theoretical and practical comparisons. *Dermatol Surg* 2005; **31**: 1188–98.
6 Goldman L, Blaney DJ, Kindel DJ Jr *et al*. Pathology of the effect of the laser beam on the skin. *Nature* 1963; **197**: 912–4.
7 Lowe NJ, Wieder JM, Sawcer D *et al*. Naevus of Ota: treatment with high energy fluences of the Q-switched ruby laser. *J Am Acad Dermatol* 1993; **29**: 997–1101.
8 Nelson JS, Applebaum J. Treatment of superficial cutaneous pigmented lesions by melanin-specific selective photothermolyis using a Q-switched ruby laser. *Ann Plast Surg* 1992; **29**: 231–7.
9 Anderson RR, Margolis RJ, Watanabe S *et al*. Selective photothermolysis of cutaneous pigmentation by Q-switched Nd:YAG laser pulses at 1064, 532 and 535 nm. *J Invest Dermatol* 1989; **93**: 28–32.
10 Goldman MP, Weiss RA, Weiss MA. Intense pulsed light as a nonablative approach to photoaging. *J Dermatol Surg* 2005; **31**: 1179–87.
11 David LM, Lask GP, Glassberg E *et al*. Laser abrasion for cosmetic and therapeutic treatment of facial actinic damage. *Cutis* 1989; **43**: 583–7.
12 Fitzpatrick RE, Ruiz-Esparza J, Goldman MP. The depth of thermal necrosis using the CO_2 laser: a comparison of the superpulsed mode and the conventional mode. *J Dermatol Surg Oncol* 1991; **17**: 340–4.
13 Fitzpatrick RE, Goldman MP. Advances in carbon dioxide laser surgery. *Clin Dermatol* 1995; **13**: 35–47.
14 Lowe NJ, Lask G, Griffin ME *et al*. Skin resurfacing with the Ultrapulse carbon dioxide laser. Observations on 100 patients. *Dermatol Surg* 1995; **21**: 1025–9.
15 Fitzpatrick RE, Tope WD, Goldman MP, Satur NM. Pulsed carbon dioxide laser, trichloroacetic acid, Baker-Gordon phenol, and dermabrasion: a comparative clinical and histologic study in a porcine model. *Arch Dermatol* 1996; **132**; 469–71.
16 Hruza G. Skin resurfacing with lasers. *Clin Dermatol* 1995; **3**: 38–41.
17 Waldorf HA, Kauvar A, Geronemus RG. Skin resurfacing of fine to deep rhytides using a char-free carbon dioxide laser in 47 patients. *Dermatol Surg* 1995; **21**: 940–6.
18 Lask G, Keller G, Lowe N, Gormley D. Laser skin resurfacing with the SilkTouch flashscanner for facial rhytides. *Dermatol Surg* 1995; **21**: 1021–4.
19 Kaufmann R, Hibst R. Pulsed erbium:YAG laser ablation in cutaneous surgery. *Lasers Surg Med* 1996; **19**: 324–30.
20 Hibst R, Stock K, Kaufmann R. Ablation and controlled heating of skin with the Er:YAG laser. *Lasers Surg Med* 1997; **9** (Suppl.): 40 (Abstract).
21 Khatri K, Russ V, Grevelink I *et al*. Comparison of erbium:YAG and CO_2 lasers in wrinkle removal. *Lasers Surg Med* 1997; **9** (Suppl.): 37 (Abstract).
22 Mannstein D, Herron GS, Sink RF *et al*. Fractional photothermolysis: a new concept for cutaneous remodelling using microscopic patterns of thermal injury. *Lasers Surg Med* 2004; **34**: 426–38.
23 Laubach HJ, Tannous Z, Anderson RR, Manstein D. Skin responses to fractional photothermolysis. *Lasers Surg Med* 2006; **38**: 142–9.
24 Geronemus RG. Fractional photothermolysis; current and future applications. *Lasers Surg Med* 2006; **38**: 169–76.
25 Glaich AS, Rahman Z, Goldberg LH, Friedman PM. Fractional resurfacing for the treatment of hypopigmented scars: a pilot study. *J Dermatol Surg* 2007; **33**: 289–94.
26 Lowe NJ, Lowe PL, Yamauchi P, Lask GL. Laser skin resurfacing. In: Lowe NJ, Carruthers A, Carruthers J *et al*. *Textbook of Facial Rejuvenation*. London: Informa Health Care, 2002: 123–38.
27 Bogle MA, Arndt KA, Dover JS. Evaluation of plasma skin regeneration technology in low-energy full-facial rejuvenation. *Arch Dermatol* 2007; **143**: 168–74.

Radiofrequency

Radiofrequency has been developed as a treatment to promote skin and facial tightening. The results to date are mixed. Appropriate patient selection is critical, with early facial laxity subjects more likely to respond than older patients.

Monopolar radiofrequency skin tightening was first approved by the US FDA in 2002 as a facial treatment. More recently, it has gained approval for treatment of selected body areas [1,2]. The concept is that a controlled radiofrequency pulse selectively heats



(a) (b)

Fig. 80.11 Before (a) and after (b) combining Botulinum toxin A (upper face), deep volume filler (upper cheeks), hyaluronic acid filler (lips) and Fraxel CO_2 repair laser (whole face).

zones of the dermis and deeper tissue, while a proprietary cooling surface system protects against injury to the epidermis and upper dermis.

Initial investigations showed some degree of improvement in selected patients, but in general the first treatment algorithms were unpredictable. Subsequently, this monopolar radiofrequency system has become more consistent and the algorithm is now to use multiple passes over the same area, with moderate energy settings, to give greater consistency.

A recent retrospective study showed that 54% of patients observed skin tightening 6 months after treatment, and 26% showed an immediate tightening. This was with the original treatment algorithm. However, with the multiple pass moderate energy treatment algorithm 87% were reported as observing immediate tightening and 92% noted skin tightening 6 months after treatment [2].

In the author's opinion one of the most important factors in the use of monopolar radiofrequency is patient selection. Patients who are candidates for facelift surgery are clearly not candidates for radiofrequency facial skin tightening. Conversely, patients who have early laxity of forehead, as well as lower facial and neck skin, may be improved using these treatments.

Other forms of radiofrequency treatment include bipolar radiofrequency, which is sometimes combined in some instruments with intense pulsed light. One of the problems with these other systems is that there has been little consistent research.

Combination minimally invasive treatment

The idea of combining several different non- or minimally invasive treatments is a relatively recent concept for facial rejuvenation. See Figure 80.11 for an example of a combination of minimally invasive treatments. Examples of such combinations include:

1 Topical agents, e.g. sunscreens, tretinoin cream, glycolic acid peels and BTX-A
2 BTX-A to forehead and crow's feet; filler to mid and lower face; Fraxel laser to face and neck
3 Fraxel laser to neck plus BTX-A to platysmal band.

These combinations are selected for appropriate indications and patterns of ageing [3,4].

References

1 Fitzpatrick R, Geronemus R, Goldberg D *et al*. Multicentre study of non-invasive radiofrequency for periorbital tissue tightening. *Lasers Surg Med* 2003; **33**: 232–42.
2 Dover JS, Zelickson B. Results of a survey of 5700 patient monopolar radiofrequency skin tightening treatments: assessment of a low-energy multiple-pass technique leading to a clinical endpoint algorithm. *Dermatol Surg* 2007; **33**: 900–7.
3 Lowe NJ. Introduction. In: Lowe NJ, Carruthers A, Carruthers J *et al.*, eds. *Textbook of Facial Rejuventation*. Informa Health Care, 2002: 1–2.
4 Lowe P, Patnaik R, Lowe N. Comparison of two formulations of botulinum toxin type A for the treatment of glabellar lines: a double-blind randomized study. *J Am Acad Dermatol* 2006; **55**: 975–80.

Index

Note: References are to pages within chapters, thus 51.10 is page 10 of Chapter 51. Tables and/or Figures removed from the main text are in *italic*. Main entries are in **bold.** Alphabetical order is word-by-word, in which hyphens are given the filing role of a space.

A
1A4 antibodies (alpha-smooth muscle actin antibodies) 10.22
AA *see* alopecia areata (AA)
Aagenaes syndrome 48.10
abacavir 75.67
  hypersensitivity 35.7, 35.21, 72.30
abatacept 74.9
ABC method (avidin–biotin–peroxidase complex method) 10.17
ABCA12 gene 11.13
ABCB1 *(MDR-1)* gene 72.29
ABCD dermatoscopy score 5.20
ABCD mnenomic, melanoma 54.37
abciximab 49.11, 49.13
abdominal aortic aneurysm 47.2
abdominal pain, in carcinoid syndrome 43.18
abdominal wall, localized atrophy 45.12–13
ablepharon–macrostomia syndrome 70.3
abnormal sensitivity to cold 28.65–71
abortion, spontaneous, in pseudoxanthoma elasticum 45.23
abrasions
  accidental tattoo due to 58.57
  child abuse 28.34
  friction 28.9, 28.31
  infection following 4.5
Abrikossoff's tumour *see* granular cell tumour
abscess(es) 10.41
  in animals 2.12
  aseptic neutrophilic 50.82
  of Bartholin's gland 71.68
  breast *see* breast, abscess
  dental 69.109
  in HIV infection 35.24
  inguinal, chancroid 34.34
  intraoral 69.109
  metastatic tuberculous 31.10, 31.19–20
  oral cavity 69.109
  perianal/perineal 71.92
  periurethral 34.26
  pilonidal sinuses 28.50
  subareolar 70.13
  sweat glands 17.43
  tubo-ovarian 34.26
absence of skin *see* aplasia cutis congenita
Absidia 36.91
  vessel-invasive infection 49.35
absorption, percutaneous 4.4–5
  in neonates 17.2
absorption spectrum 29.3
ABT-874, psoriasis 74.10
Acacia melanoxylon 26.80
Acanthamoeba 37.27
acantholysis 10.36–7
  in complement-deficient mice 40.6
  defined 40.3
  in Hailey–Hailey disease 39.33
  mechanism 40.6
  in neonatal mouse model 40.5
  plasminogen activator 40.14
    urokinase block 40.14
acantholytic dermatoses *see* Grover's disease (transient and persistent acantholytic dermatoses)
acantholytic dyskeratotic epidermal naevi 19.83
acanthoma
  clear cell 52.41
  Degos' 52.41
  pilar sheath 53.3
  spectacle-frame (acanthoma fissuratum) 28.29–30, 68.9
acanthoma fissuratum 28.29–30, 68.9
acanthome a 'cellules claires' 52.41
acanthosis 10.37
  in eczema 23.4
  epidermal, Spitz naevus 54.22
  in viral warts 33.41, 33.42
acanthosis nigricans 19.119–21
  acquired, pigmentation changes 58.25
  in animals 2.17
  congenital generalized lipodystrophy 46.37
  dermatomyositis and 58.27
  female genital region 71.80
  genitocrural dermatology 71.7
  hirsutism and 66.82
  HIV infection 35.12
  insulin resistance and 59.78, 66.82
    acne and 42.73
  male genital region 71.36
  oral involvement 69.34
  paraneoplastic 62.31, 69.34
  race and 9.15
  seborrhoeic keratosis association 52.38
  subtypes 69.34
  umbilical dermatology 71.101
acanthosis palmaris (tripe palms) 19.120, 62.31–2
Acari 38.33–54
acariasis
  canine sarcoptic 2.10
  otodectic 2.10
Acaridae 38.46–7
acarodermatitis urticarioides 38.48
Acarus siro 38.47
accessory auricle 68.4
accessory cells 4.8
accessory digit 18.92
accessory nerve 77.5
accessory tragus (auricle) 18.84–5, 68.4
ACE *see* angiotensin-converting enzyme (ACE)
ACE inhibitors, adverse effects **75.92–4**
  angio-oedema 22.20, 22.21
  flushing 43.15–16
  pemphigus 75.38
  urticaria 22.10, 75.26
acebutolol 75.91
acetaldehyde, alcohol metabolism 43.16
acetaminophen 75.72–3
acetazolamide 75.97
acetic acid 25.20
acetone 25.20, 65.56
N-acetyl-4-*S*-cysteaminylphenol 73.27
alpha-*N*-acetyl-galactosaminidase deficiency 59.34–5
acetylacetone test 26.50, 26.99
acetylated lanolin alcohol 27.13
acetylcholine (ACh) 38.1, 44.3, 63.3, 80.7
  in atopic dermatitis 24.18
  peripheral nerves 4.10
  pruritus and *21.3,* 21.4
  sweat gland control 3.12
acetylcholinesterase 3.12
N-acetylcysteine *26.46,* 47.11
  in microscopic polyangiitis 50.36
ACh *see* acetylcholine (ACh)
Achenbach's syndrome 28.27, 45.4, *45.5,* 49.16
Achillea 25.21
achondroplasia–hypochondroplasia, prenatal diagnosis *16.3*
achrocordon *see* skin tags
achromic naevus (naevus depigmentosus) 58.42, 58.44–5
achromotrichia 66.94
aciclovir
  action 74.49
  adverse effects *26.46,* **75.66**
  in eczema herpeticum 33.36
  in erythema multiforme 76.7
  in herpes B virus infection 33.34, 33.35
  in herpes simplex 33.20, 33.21
    ocular involvement 67.26
    resistance 33.21
  in herpes zoster 33.27, 35.29, 63.6–7, 67.26
    corticosteroids with 33.28
    prophylactic 33.27
  in herpetic keratitis 67.16, 67.26
  mechanism of action 33.20
  in pityriasis rosea 33.81
  topical 73.15
    herpetic keratitis 33.21
  varicella prophylaxis 33.27
  varicella treatment 33.27, 35.29
acid beta-glucosidase deficiency 59.39
α_1-acid glycoprotein 13.19
acid mucopolysaccharides, in scleroedema 51.119
acid orcein–Giemsa stain 10.8
acid phosphatase 3.52, 12.49, 38.14
acids
  burns 25.11, 27.12
  as irritants 25.20
Acinetobacter 30.46
  axilla 30.4
  in cellulitis 30.18
  differential diagnosis 36.31
  in normal skin flora 30.2, 68.2
  perineum and groin 30.4
  toe clefts 30.4
acini, sebaceous gland 42.1
acipimox 75.156
acitretin 74.35
  adverse effects **75.109**
    hair loss 66.29
    ocular 67.31
  in chloracne 27.14
  clinical indications 74.35
  in hidradenitis suppurativa 30.81
  in pemphigus 40.12
  in psoriasis 20.37, 74.35
  in psoriatic nail involvement 65.26
  in squamous cell carcinoma 52.28
  teratogenicity 72.28
Ackerman syndrome 15.29
acne
  adolescent *see* acne vulgaris
  childhood 42.75–6
  cosmetic 42.73
  drug-induced 9.5, 42.31, 42.71–3, 75.34
  ear 68.14
  endocrine 42.73
  external chemical origin (halogen acne) 27.12–15
  externally induced 42.73–4
  following spinal cord injury 63.17
  granulomatous/lymphoedematous 42.74, *42.75*
  immobility 42.76
  infantile and juvenile 42.75–6
  irritant *25.2*
  light-exacerbated 29.22
  'Mallorca' 42.79
  mechanical 42.76–7
  naevi 18.11–13, 42.78
  Norwegian 42.79
  occupational 27.12–15, **42.77**
  oil and tar 27.6, 42.77
  penile 71.27
  pitch *27.14*
  pomade 9.5, 42.31, 42.73–4
  post-acne osteoma cutis 59.70
  tropical/hydration *27.14,* 42.79
  vasculitic/pyoderma gangrenosum 42.85
  virally induced 42.79
  see also acne vulgaris
acne aestivalis 42.79, *42.80*
acne agminata 5.*14,* 31.25, **43.12–13**
  clinical features 43.13
  differential diagnosis 42.37, 61.10
    perioral dermatitis vs 43.11
acne conglobata 42.32, 42.33, *42.*71, **42.82–3**
  associated disorders 42.82–3
  isotretinoin treatment 42.62, 42.83
  treatment 42.83
    choice *42.40*
acne de jeune filles *see* acne excoriée
Acne Disability Index 72.20
acne excoriée 42.35, **42.70,** 64.29
  treatment 42.70
acne fulminans 42.83–4
  bone and joint involvement 62.*101*
  erythema nodosum and 50.83
  inflammatory bowel disease and 62.52
  treatment 42.84
    isotretinoin 42.62
acne mechanica 28.30, 28.31, 42.76–7
acne necrotica miliaris 30.26
acne necrotica varioliformis 30.26–7
  acne vulgaris vs 42.37
acne nuchae keloidalis (acne keloid) 9.9, **30.26**
Acne Quality of Life Scale (Acne-QOL; AQOL) 42.35, 72.20

acne rosacea *see* rosacea
acne venenata 27.12–15
acne vermiculata (atrophoderma vermiculata) 45.8, 66.51
acne vulgaris **42.17–70,** 42.73–4
  adolescence 8.6
  aetiology/pathogenesis 42.17, 42.20–30
    cell-mediated immunity and scarring 42.26–7
    comedogenesis 42.22–4
    growth hormone and IGFs role 42.11
    hyperinsulinaemia 42.20–1, 42.34
    inflammation role 42.25–6
    innate immune reaction 42.25, 42.26
    P. acnes role 42.24–6
    seborrhoea 42.20–2
    topical drug effects on *42.40*
  Apert's syndrome and 42.61, 42.70–1
  associated conditions **42.70–82**
  associated features 42.33
  atopic dermatitis incidence and 42.18
  biological/evolutionary significance 42.27
  body dysmorphic disorder and 42.60, 42.71
  bone and joint involvement 62.99, 62.102
  calcification after (osteoma cutis) 42.78
  candidate genes 42.19
  childhood 42.75–6
  clinical features **42.30–8**
  comedonal 42.18, 42.75
    treatment 73.35
    treatment choice *42.40*
  cysts *42.18*, 42.31
  Darier's disease and 42.71
  definition 42.17
  detergent 42.74
  diet and 42.33–4
  differential diagnosis *27.13*, 42.36–8
    perioral dermatitis vs 42.36, 43.11
    rosacea 42.36, 43.5
    secondary syphilis vs 34.12
  drug-induced 9.5, 42.31, 42.71–3, 75.34
  ear 68.14
  endocrine 42.73
  endocrine investigations *42.22*
    indications *42.21*
  epidemiology and burden 42.19
  excess sebum production and 42.20
  females 42.18, 42.21–2
  genetic factors 42.18–19
  Global Alliance algorithm for outcome improvement 42.39, *42.40*
  glycaemic index and 42.34
  grading scale 42.38, *42.38*, *42.39*
  haemorrhagic lesions 42.31, *42.32*
  hidradenitis suppurativa and 42.74–5
  hirsutism and 42.20, 42.21
  hormonal control of sebaceous activity 42.9–14
    see also sebaceous glands
  hormonal treatments 42.52–4
    adrenal androgen production inhibitors 42.53
    androgen receptor blockers 42.53–4
    indication 42.52
    oral contraceptives 42.53
    ovarian androgen production inhibitors 42.53
  hyperprolactinaemia and 42.12
  inflammatory lesions *42.17*, 42.30–1
    P. acnes role 42.24–5, 42.25–6
    scarring mechanisms 42.26–7
    steroids and isotretinoin 42.63
    topical antibiotics effect 42.43
    topical retinoids effect 42.40, 42.43
    treatment failure 42.57
  isotretinoin flare 42.62–3, 42.64
    predisposing risk factors 42.64
  isotretinoin treatment 42.14, 42.54, 42.57–66
    acne variants 42.62
    antibiotics with 42.63
    children under 12 years of age 42.60–1, 42.76
    clinical benefits 42.58–61
    cost-effectiveness 42.65
    dose schedules *42.61*, 42.62
    drug interactions 42.64, 42.65
    duration of use 42.58, 42.62
    European Directive 42.59, 42.60
    initiation of therapy 42.59–60
    long-term treatment 42.58–9
    mechanism of action 42.57–8
    poor response 42.60
    resistance 42.62–3
    side effects 42.63–5
    in significant systemic disease 42.61
    slow response, reasons 42.62–3
    treatment recommendations 42.60
    US programme (iPLEDGE) 42.60
  itching 42.32
  keratins 42.23
  late-onset 42.18. 42.19
  lesion counts 42.38
  males 42.17–18
  mature 42.18. 42.19
  mild *42.38*, 42.39
  mild to moderate *42.38*
  moderate *42.39*
  natural history 42.17–18
  nodular 42.71
    treatment choice *42.40*
  nodules 42.31, *42.37*
  non-inflammatory lesions *42.17*, 42.30
  occupation and 42.34
  oral antibiotic treatment 42.46–9, 42.54
    adverse effects *42.47*, 42.50–1, 67.31–2
    duration and dose 42.47–8
    mechanism of action 42.48
    topical agents with 42.48
  papular/pustular, treatment choice *42.40*
  penile 71.27
  persistent 42.18
    isotretinoin use 42.61, 42.63
  physiological 42.18
  physiological/environmental factors affecting 42.33–5
  polycystic ovary syndrome and 42.20, 42.21–2, 42.73
  pomade 9.5, 42.31, 42.73–4
  premenstrual flare 42.24, 42.34
  prepubertal 42.18
  prevalence 42.17–18
  prognostic factors, poor *42.39*
  psychosocial effects 42.35
  pyogenic granuloma 42.32, 42.79
  quality of life and 42.35, 64.10, 72.20
  race and 9.4–5, 42.19, 42.24
  resolution 42.18, 42.38
    mechanisms 42.27
  sandpaper 42.30
    treatment failure 42.56
  scarring 42.31–2, 42.32–3
    differential diagnosis 42.37
    mechanisms 42.26–7
    treatment 42.68–70
    types of scars 42.32–3
  scars 45.54
    keloid-like 45.54
    punch grafts 77.22
  sebaceous gland activity 42.15
    reduction/inhibition 42.14, 42.15
  seborrhoeic dermatitis and 23.29
  sebum excess 42.20–2
  sebum lipids and 42.22, 42.23
  secondary syphilis vs 34.12
  severe *42.39*, 42.82–6
  severity assessment 72.10
  sinus formation 42.31, *42.32*
  smoking and 42.34–5
  solar comedones with 42.79
  steroid 42.72
  stigma 64.6
  stress and depression 42.35
  sweating and 42.34
  topical treatment 42.39–46
    adapalene 42.39–40, 42.41, 73.36
    adverse effects 42.49–50
    antibiotics 42.39, 42.41–3, 73.9, 73.10
    azelaic acid 42.39, 42.43, 73.28
    benzoyl peroxide 42.39, 42.40, 42.41, 42.48, 42.67
    childhood acne 42.76
    complementary therapy 42.43
    dapsone 42.43
    nicotinamide 42.43, 73.51
    retinoic acid 73.34, 73.35
    retinoids 42.39–41, 42.48, 42.54
    salicylic acid 42.43
    selection 42.43–4
    tazarotene 73.37
  treatment 42.15–16, **42.38–70**
    adverse effects 42.49–52
    antibiotics *see* acne vulgaris, oral antibiotic treatment
    choice 42.38–9, 42.43–4
    concordance with 72.6
    education of patients/doctors 42.55
    general principles 42.38
    hormonal *see* acne vulgaris, hormonal treatments
    isotretinoin *see* acne vulgaris, isotretinoin treatment
    oral 42.46–9, 42.66–7
    outcome measures 42.38
    P. acnes resistance 42.41–2, 42.43, 42.47, 42.55–6
    physical 42.67–8
    poor compliance 42.55
    retinoids 64.49
    slow response or failure 42.55–6, 42.56–7, 42.60
    topical *see* acne vulgaris, topical treatment
  UV radiation and 42.34
  variants, severe 42.82–6
  see also acne
acneiform eruptions, drug-induced 42.71–3
acnitis *see* acne agminata
acquired digital fibrokeratoma 56.4, 65.31–2
acquired epidermolysis bullosa *see* epidermolysis bullosa acquisita
acquired generalized lipodystrophy (AGL) 46.37–9
acquired idiopathic livedo reticularis 28.68, *49.49*
acquired immune deficiency syndrome *see* AIDS; HIV infection
acquired perforating dermatosis 19.88–9
acral arteriovenous tumour (cirsoid aneurysm) 56.26–7, 65.35–6
acral dermatitis, chronic 23.15
acral dermatosis, acute, viral infections associated 33.76
acral lentiginous melanoma 15.11, 54.35, 54.44, *54.45*, *54.46*, 65.40
acral lick dermatitis 2.9
acral peeling skin syndromes 19.66
acral purpura 49.4, 49.32
acral vascular syndrome, paraneoplastic 62.41
Acremonium 36.8, 36.55, *36.73*, 36.92
acridinyl anisidide (AMSA) 75.133
acrivastine *22.29*
  in urticaria 22.28
acro-dermato-ungual-lacrimal-tooth syndrome 15.29, 15.64
acro-mammo-renal syndromes 70.2
acro-osteolysis
  with keratoderma 19.115
  vinyl chloride-induced 45.52
acroangiodermatitis of Mali 47.22, 49.17–18
acrocephalosyndactyly *see* Apert's syndrome
acrochordons *see* skin tags
acrocyanosis **28.66–7**
  cold-induced 49.33
  genetics 15.10
  neonatal 17.4
  reversible 49.34
acrodermatitis chronica atrophicans 30.65, 45.9–11, 45.18
acrodermatitis continua (of Hallopeau) 20.46, 65.25, 65.26, 79.4
  calcipotriol treatment 73.45
acrodermatitis enteropathica 59.59, 59.72
  in animals 2.17
  Crohn's disease and 62.49
  genitocrural 71.5
  hair loss in 66.28–9
  oral involvement 69.31
  perianal/perineal 71.91
  in pregnancy 8.12
acrodynia 69.83–4, 75.101–2
acroerythrokeratoderma (Mal de Meleda) 19.3, *19.94*, 19.100–1
acrogeria *45.58*, 45.59–60, 51.79, 51.106
acrokeratoderma, aquagenic syringeal 19.115
acrokeratoelastoidosis of Costa 9.10
acrokeratosis paraneoplastica *see* Bazex syndrome
acrokeratosis verruciformis, Darier's disease vs and features in 19.82, 19.83, 19.88
acrokeratosis verruciformis of Hopf **19.88,** 65.18
  epidermodysplasia verruciformis vs 33.58
  plane warts vs 33.44
acrokeratotic poikiloderma of Weary **15.82**
acrolein 25.21
acromegaly 8.2, 62.2, *62.101*
  ear involvement 68.18
  pigmentation 58.24
  sebum excretion rate 42.22
acromelanosis 58.21
acropachy **15.87–8**
acroparesthesiae 59.37
acropigmentation, reticulate 58.21–2
acropustulosis 65.25
  infantile 17.9–10, 50.62
acropustulosis of Hallopeau, acitretin 74.35
acrorenal field defect, ectodermal dysplasia, lipoatrophic diabetes 15.29
acrosclerosis 51.87
  vinyl chloride-related 62.47
acrospiroma 53.22, 53.27–8
  malignant 53.34
acrosyringium 53.23
  purpura around 49.21
acryl ceramides, in sebum in acne 42.23
acrylates *26.14*, 26.72–3, 65.55–6
acrylic fibres, sarcoidal reaction to 61.22–3
ACTH
  administration, pigmentation changes 58.25
  adverse effects 69.97, **75.114–15**
  in congenital adrenal hyperplasia 62.6
  in Cushing's syndrome/disease 58.24, 62.3–4
  ectopic secretion, pigmentation 58.25
  in lichen planus 41.18
  in place of systemic steroids 74.3–4
  at puberty 8.4
  sebaceous gland hypertrophy 42.11
  stimulation test 74.3
  see also ectopic ACTH syndrome
actin 10.22
  Kindler syndrome 12.17
  polymerization, melanocyte dendrite formation 58.4
actinic cheilitis *see* cheilitis, actinic
actinic dermatitis, chronic *see* chronic actinic dermatitis (CAD)
actinic elastosis 8.22
actinic keratosis 52.2, 52.12, **52.30–2**
  aetiology 52.30

ageing and 80.2
biological compensation in 52.31
Bowenoid 52.31
chromosome losses 52.29
clinical features 52.30
definition 52.30
diagnosis 52.31
epidermodysplasia verruciformis and 33.57
eyelids 67.33
flat type 52.31
following chemotherapy 75.124
hands 52.30
in HIV infection 35.39
incidence 52.2, 52.30
lichenoid 52.31
lip 52.30
see also cheilitis, actinic
malignant melanoma risk 54.33
new lesion development rate 52.31
nodular 52.36
pathology 52.30–1
pigmented 52.31, 52.38
pinna 68.30
prevention by sunscreens 29.9
progression to invasive SCC 52.29, 52.30, 52.31
relapsing and/or remitting lesions 52.30
skin biopsy 10.42
treatment 52.31–2, 77.40, *77.42*, 78.16
topical 5-FU 73.23
topical diclofenac 73.25
topical imiquimod 73.24
actinic lentigines *see under* lentigines
actinic prurigo (AP) *29.10*, **29.13–15,** 69.124
aetiology 29.13–14
clinical features *29.10*, 29.14
definition 29.13
diagnosis and differential diagnosis *29.10*, 29.14
pathology 29.14
polymorphic light eruption association 29.14
race and 9.19
treatment *29.10*, 29.14–15
actinic reticuloid (pseudolymphomatous chronic actinic dermatitis) 29.16, 29.17, 57.58
α-actinin 40.2
Actinobacillus actinomycetem-comitans 30.59
Actinomadura 36.73
Actinomyces bovis 30.75, 30.76
Actinomyces gerencseriae, female genital infection 71.68
Actinomyces israelii 30.74–5, 30.76
female genital infection 71.68
Actinomyces keratolytica 30.39
Actinomyces naeslundii 30.75
Actinomyces pyogenes 30.37
actinomycete infections **30.74–6,** 68.25, 68.27
mycetoma due to 36.72–5
actinomycetoma 36.72–5
actinomycin D, adverse effects 75.127
actinomycosis **30.74–6**
abdominal 30.75
cervicofacial 30.75
pelvic 30.75
primary cutaneous 30.75
thoracic 30.75
actinonin 12.50
actinophytosis 30.67–8
activated leukocyte cell adhesion molecule (ALCAM) 12.73
activated partial thromboplastin time (aPTT) 49.9
activated protein C (APC) 49.38
concentrates, in sepsis 49.40
resistance 14.13, 47.28, 47.42, 49.38–9
activation-induced cytidine deaminase 13.10
activator protein 1 (AP-1) 8.21, 8.22
activin A, in lichen planus 41.1–2
activin receptor-like kinase 1 (ACVRL) 47.17
acupuncture 68.7, *72.32*
blue macules at site of needles 58.54
in brachioradial pruritus 63.24
in post-herpetic neuralgia 63.7
for surgical procedures *77.11*
acute disseminated epidermal necrosis 76.1
acute febrile neutrophilic dermatosis *see* Sweet's syndrome
acute generalized exanthematous pustulosis 75.34–5
differential diagnosis 76.19
acute genital ulceration 71.65–6
acute haemorrhagic oedema of childhood/infancy 17.33–4, 49.18–19, 50.30
acute leukaemia 55.31
genetics 15.14
acute panniculitis, mechanical injury 28.27
acute papular onchodermatitis 37.5
acute-phase proteins 12.34, 13.19
C-reactive protein 12.28, 12.32, 13.4, 13.19
acute retinal necrosis syndrome 33.26
acute scrotum 71.28
ACVRL1 gene mutations 47.17
acyclovir *see* aciclovir
acyl coenzyme A compounds 46.2
AD *see* atopic dermatitis
AD (autosomal dominant) inheritance *15.2*, 15.5
adalimumab 12.42, 13.25, 72.29, 74.5–7, 75.145
clinical indications 74.6
dose range and evidence level 74.6
and methotrexate, ADEPT study 74.7
origin 74.5
in psoriasis 20.41, 74.5
Adam complex syndrome *see* amniotic bands/adhesions
Adamantiades–Behçet's disease *see* Behçet's disease
Adams–Oliver syndrome (scalp aplasia cutis congenita with limb reduction abnormalities) **15.96,** 18.68, 18.99–100
ADAMTS 3.41
ADAMTS-1 gene 3.41
ADAMTS-2 3.41
ADAMTS13, deficiency 49.12, 49.31
adapalene 73.35, **73.36**
topical
acne treatment 42.39–40, 42.41
chloracne treatment 42.77
Addison's disease **62.5–6**
in autoimmune polyglandular syndrome 62.13
candidiasis and 36.58
ear involvement 68.18
genetics 15.81
hyperpigmentation 58.24
pigmentation 58.7
sarcoidosis and 61.17
sweat in 44.6
white 62.6
Adema disease 59.72, *59.73*
ADEN (acute disseminated epidermal necrosis) 76.1
adenine 11.2
adenocarcinoma
aggressive digital papillary 53.33
female genitalia 71.77
perianal/perineal 71.91
sweat glands 53.40
adenocarcinomatosis, perianal/perineal 71.91
adenocystic carcinoma, primary cutaneous 53.37
adenoid cystic carcinoma 53.37
adenoma
apocrine tubular 53.21
ceruminous glands 68.29
papillary eccrine 53.26–7
sebaceous **42.87,** 53.15–17, 68.28, 69.23
tubular apocrine 53.26
adenosine arabinoside 74.48
adenosine deaminase deficiency 17.60
adenosine triphosphate (ATP) 46.2
adenoviruses *33.2*
ADEPT study, adalimumab and methotrexate 74.7
ADFN gene 58.44
adherence to therapy *see* concordance with therapy
adherens junctions 3.23–4, 40.2
cadherins 40.2, 40.3
functions 3.23
gene mutations 3.23–4
see also desmosomes
adhesion complex 40.1–2, 40.25
basement-membrane zone 40.1–2, 40.25
epidermis, desmosomes role 3.21–2
IgA antibodies 40.46
adhesion molecules 12.68–75
on activated keratinocytes 12.75
in allergic contact dermatitis 26.6
in Behçet's disease 50.56
cell–cell adhesion, cadherins 40.5
CX3CR1, cell–cell adhesion and leukocyte trafficking 12.48
on desmosomes 40.2
ICAM-1 12.10, 12.16, 12.73
ICAM-2 12.73
leukocyte cell adhesion molecule (LEUCAM) subfamily 12.70
on neutrophils 12.21
platelet–endothelial cell adhesion molecule (PECAM-1 or CD31) 12.73
regulating leukocyte emigration 12.74
in vasculitis 50.4
vitamin D action 73.43
adhesions
fibrinous 'violin-string' 34.30
heparan sulphate role 3.46
see also amniotic bands/adhesions
adhesive plaster, salicylic acid in, wart treatment 33.48
adhesives, in shoes 26.63, 26.68
adipocytes 3.52
brown 46.1
hibernoma 46.45
development 46.3
differentiation inhibition by antiretrovirals 46.42
histology and cell structure 46.1–2
hyperplasia 46.6, 46.9
hypertrophy 46.6, 46.9
rimming 46.26
visceral adipose tissue (VAT) 46.4
dysfunction, in obesity *46.6*, 46.6–7
white 46.1
see also lipocytes
adipogenesis 46.3
adipokines 46.2, 46.3
adiponecrosis e frigore (cold panniculitis) 17.35, 46.21
adiponectin 46.4
anti-inflammatory effects 46.4
low levels, inflammatory effects 46.4
receptors 46.4
adipose tissue 46.2
atrophy *see* lipoatrophy
brown 8.16
hypertrophy 46.34, 46.41, 70.3, 70.4
intrathoracic, increased 46.41
loss 46.34, 46.36
generalized lipodystrophy 46.37, 46.38
partial lipodystrophy 46.39–40
see also lipoatrophy; lipodystrophy
necrosis 46.44
see also subcutaneous fat, necrosis
omental, HIV lipodystrophy 46.42
pathology **46.10–12**
see also panniculitis
perivascular 46.2
physiological function 8.16–17
visceral 46.4, 46.5
white 8.16–17
see also subcutaneous fat
adiposis dolorosa (Dercum's disease) 8.17, 46.46, 46.47–9, 48.20
adiposopathy 46.7
adnexal polyp of neonatal skin 17.15, 70.8
adnexal tumours **53.1–44**
benign to malignant change 53.32
carcinoma
adenoid cystic 53.37
microcystic 53.35–6
mucinous 53.36
classification 53.2, 53.27
ductal differentiation 53.2
metastases 53.2
see also specific tumours, anatomical structures
adolescence **8.4–8**
career choice and skin disease 8.6, 8.7–8
dermatoses 8.6–8
difficulties and emotional problems 8.6
melanoma 54.48–9
normal bacterial skin flora 30.4
obesity 8.4
psychocutaneous disorders 64.30
quality of life assessment 72.23
striae 45.5, 45.6
see also puberty; *individual conditions*
adrenal glands
androgen production, inhibition 42.53
carcinoma 66.83
adrenal hyperplasia, late-onset, acne and 42.21
adrenal insufficiency *see* Addison's disease
adrenaline
in anaphylaxis 22.29, 38.15
in angio-oedema 22.29
in local anaesthetics 77.9, 77.10
in nail biopsy 65.42
skin biopsy and 10.2
adrenalitis, autoimmune 62.5
adrenarche 8.4
α-adrenoceptor blockers
in carcinoid syndrome 43.19
vibration injury 28.58
adrenocortical disease, in Carney syndrome 58.14
adrenocortical hormones, sebaceous gland activity and 42.11
adrenocorticotrophic hormone *see* ACTH
adrenoleukodystrophy 44.18
adrenomedullin 4.5
adriamycin *see* doxorubicin
ADRs *see* drug reactions
adult premature ageing syndrome *see* Werner's syndrome
adult progeria *see* Werner's syndrome
adult respiratory distress syndrome (ARDS), in toxic epidermal necrolysis 76.17
ADULT syndrome 15.29, 15.64
adult T-cell leukaemia–lymphoma (ATLL) 33.64–6, 57.37–9
clinical features 33.64–5
HTLV-1-association 57.37–9
race and 9.13
adverse drug reactions *see* drug reactions
AEC (ankyloblepharon-ectodermal dysplasia–clefting) syndrome 15.30, **15.61–3**
AECA *see* antiendothelial cell antibodies
Aeromonas 30.59, 38.55
infections of reptiles/amphibia 2.12
Aeromonas hydrophila 30.18, 30.59
aerospace industry, occupational hazards 27.18
AESOP syndrome 62.94
aesthetic surgery, body dysmorphic disorder 64.19
AF-6 (afadin) 3.23
afadin 3.23

affective disorder, in Hailey–Hailey disease 39.35
afferent nerves 12.64
African black walnut *26.81*
African blackwood *26.81*
African ebony *26.80*
African eye worm (loiasis) **37.11–12,** 38.6
African mahogany *26.81*
African teak *26.81*
African tick bite fever 38.35
African tick typhus 30.73
African trypanosomiasis 37.2, **37.29–31**
Afro–Caribbean children, circumscribed keratotic disorders 19.93
agammaglobulinaemia
  autosomal recessive 17.71–2
  X-linked 13.9, *13.13,* 17.70–1, *69.117*
agammaglobulinaemia–dwarfism–ectodermal dysplasia 15.29
age
  drug pharmacokinetics and pharmacodynamics 72.28–9
  effect on normal bacterial skin flora 30.3–4
  mechanical injury effects and 28.7, 28.18
age spots 8.23
  see also lentigo
ageing **8.21–9**
  allergic contact dermatitis and 26.8
  bacterial skin flora and 30.3–4
  biology of 8.21–2
  dermis 8.22–3
  Down's syndrome and 45.61
  drug pharmacokinetics and pharmacodynamics 72.28–9
  ear changes associated 68.5–6
  eccrine sweat glands 8.24
  epidermis 8.23
  extrinsic 80.2, *80.3*
  hair colour changes 8.23
  hair follicles 8.23–4
  immune function and 8.24, 13.15
  intrinsic 80.1–2
  irritant contact dermatitis and 25.6–7
  Langerhans' cells and 8.24
  nail growth 8.24
  nerves and sensation 8.24
  occupational dermatoses and 27.2
  pigmentation of skin 8.23
  premature 45.15, **45.56–63**
    with short stature and pigmented naevi 45.60
  prevention 80.3–4
  pruritus and 21.12, 21.17
  purpura 49.15
  risk factor for skin disease 6.12
  sebaceous and apocrine glands 8.24
  skin
    control of 8.21
    photoageing 8.21–2
    signs of 8.21
    structural changes 8.22–5
  stratum corneum 4.11
  telangiectases due to 47.13
  transepidermal water loss and 4.11
  UVR effect (photoageing) 29.7
  vascular changes associated 80.11
  wound healing and 14.2, 14.9, 14.17–18
  wrinkles and 45.2–3
agglutinins, cold-induced injury 28.71
aggrecan *3.48*
aggressive epidermotropic CD8+ (provisional) T-cell lymphomas 57.35–6
aggressive house spider 38.32
Agouti gene 2.5, 2.6
AGPAT enzymes 46.37
agranulocytosis, oral involvement 69.56
agriculture
  Bowen's disease associated 52.32
  occupational hazards 5.6, 27.18
AHEC (acute haemorrhagic oedema of childhood/infancy) 17.33–4, 49.18–19, 50.30
Aicardi–Goutières syndrome 11.15
AID (activation-induced cytidine deaminase) 13.10
AIDS
  case definition 35.4–5
  in pregnancy 8.13
  rank order of diagnoses *35.4*
  see also HIV infection
AIN *see* anal intraepithelial neoplasia
ainhum 45.69
  race and 9.12–13
air flow, role in irritant contact dermatitis 25.8
air-fluidized mattresses 28.20, 28.22
air sampling, bacterial skin flora 30.2
airbag dermatitis 28.14
Aircast Walkers® foam boot 63.10
aircrew, occupational hazards 27.18
AIRE gene 62.13
  defects 13.15
AJCC staging system, melanoma, malignant 54.49, *54.50*
AL Test system 26.85
Alagille's syndrome 62.62, 62.77
alantolactone 26.75, 26.77
alarmins 3.16
Alatina moseri 38.56
albendazole 74.50–1
  in cutaneous larva migrans 37.17
  in echinococcosis 37.25
  in gnathostomiasis 37.18
  in strongyloidiasis 37.16
  in toxocariasis 37.18
  in trichinosis 37.20
albinism 58.39–41, 66.93–4
  classification 58.39
  clinical features 58.40, *66.94*
  electron microscopy 10.29
  genetics *66.94*
  incidence 58.40
  ocular 58.39
  oculocutaneous (OCA) 58.39
    prenatal diagnosis *16.3,* 16.6
    race and 9.16
    types 58.39
  partial *see* piebaldism
  prognosis and treatment 58.40–1
  tyrosinase-negative 58.39, 58.40
  tyrosinase-positive 58.40, 58.41
  X-linked ocular 58.39
  yellow mutant 58.40
albinism–deafness syndrome (ADFN) 58.44
albino 58.1
albinoidism 58.41
Albright's hereditary osteodystrophy 56.61–2, 62.12
  genetics 15.6
Albright's sign 62.12
Albright's syndrome *see* McCune–Albright syndrome
albumin 13.19, 66.81
albuterol 75.98
Alcian blue reaction 10.8
alcohol
  avoidance in carcinoid syndrome 43.19
  flushing associated 43.16
  intolerance 22.32
  as irritant 25.19, 25.20
  metabolism 43.16
  misuse *see* alcohol abuse
  multiple symmetrical lipomatosis associated 46.46
  porphyria cutanea tarda and 45.52
  sweating and 44.7
  urticaria induced by 22.8
  use in pregnancy *see* fetal alcohol syndrome
alcohol abuse **64.46–7**
  methotrexate 74.22
  in psoriasis 20.4, 20.18
alcohols
  antiseptics 73.14
  in topical treatment 73.7
alcuronium 75.153
Alcyonidium diaphanum 38.58
aldehyde dehydrogenase 43.16
aldehydes 25.21
  as antiperspirants 73.9
  as antiseptics 73.14
alefacept 13.25
  in lupus pernio 61.21
  origin 74.8–9
  in psoriasis 20.41, 74.6, 74.8–9
alendronate 75.99
Aleppo boil (Old World cutaneous leishmaniasis) **37.34–9**
aleuroconidia 36.4
Alezzandrini's syndrome 58.46, *66.93*
alfalfa, antinuclear and anti-dsDNA antibodies 51.30
alginate dressings 14.23–4
alitretinoin (9-cis-retinoic acid) 73.36–7, 74.36
  clinical indications 74.36
  topical 73.36–7
ALK (anaplastic lymphoma kinase) 10.25
ALK-1, and ALK-5 47.17
alkali(s)
  burns 27.12
  as irritants 25.9, 25.20
alkali tests 27.11
Alkaligenes, toe clefts 30.4
alkaline phosphatase 10.16
  in sarcoidosis 61.8
alkaptonuria 44.21, 58.54, 59.98
  ear involvement 68.18
  ochronosis in 44.21
  see also ochronosis
alkyl bromides 25.21
alkyl chlorides 25.21
alkyl sulphonates 75.124
alkyl tin compounds 25.21
alkylating agents 75.124–5
  in necrobiotic xanthogranuloma 55.28
all-*trans*-retinoic acid (ATRA) 42.14
  collagen gene expression control 3.39
  male genital conditions 71.27
  in melasma 73.27
  photoageing reduction 29.7
  receptors 73.35
  sebocyte proliferation and lipids suppressed 42.14, 42.15
  see also retinoic acid (tretinoin; vitamin A acid)
alleles, definition 15.3
allergens 26.11, **26.30–84**
  additional series, tests 26.92
  airborne 22.9, 26.16–17, 26.20
  assessment of sensitization potential 26.11–12
  atopic dermatitis and 24.10–12, 24.30–1
  avoidance 26.101
    during pregnancy 24.34
  binding to skin components 26.5
  containment 26.99
  eczema and 23.5
  hand eczema and 23.13–14
  injection by arthropods 38.1–2
  leg ulcer *47.45*
  in lipsalves and lipsticks *69.119*
  in photoallergic contact dermatitis 26.23–4
  pigmented purpuric dermatoses due to 49.23
  replacement 26.99, 27.9
  responses to 13.13
  sources 26.14
  standard series 26.2, 26.91–2
  storage 26.86
  systemic reactions to 26.22–3
  urticaria due to 22.7–8
  volatile 26.16–17
  see also individual allergens
allergic contact dermatitis **26.1–106**
  after arthropod bites/stings 38.2
  age and 26.8
  in animals 2.10
  anogenital 26.18–19, 26.29
  to antimicrobial agents 26.49–58
  to applied medicaments *26.13,* 26.18, 26.22, 26.43–7
  arms 26.15–16, 26.29
  atopic dermatitis and 24.22, 26.7, 26.13–14
  axillae 26.18
  to Bryozoa 26.10, 38.58
  chronic *26.15*
  chronic venous insufficiency 47.34
  clinical examination 26.14–22
  clinical features 26.13–22
  to clothing 26.18, 26.65–8
  co-existence with other disorders 26.9
  corticosteroids associated 73.17
  to cosmetic vehicles 26.58–60
  to cosmetics 26.14, 26.16, 26.17, 26.47–9
  delayed (late) reaction time 26.6
  differential diagnosis 26.28–30
  differentiation from irritant contact dermatitis 25.6, 26.87–8
  drug influences on 26.9
  duration and behaviour 26.13
  ear 26.17, 68.14
  in elderly people 8.28
  elicitation 26.6
  environmental factors 26.10–11
  epidemiology 26.2–5
  exposed sites 26.20, 26.30
  eyelids 23.11, 26.17, 26.22, 26.31, 67.5
  facial 26.16–17, 26.29
  feet 26.19, 26.29
  female genitalia 71.58
  to footwear 26.68–9
  gender and 26.7–8
  generalized 26.19, 26.30
  gentamicin causing 73.10
  in Hailey–Hailey disease 39.34–5
  to hair dyes 26.10, 26.17, 26.60–2
  hands 26.15–16, 26.29
  history of 26.1–2
  history-taking 26.13–14
  hormones and 26.8
  in infancy and childhood 26.8–9
  Langerhans' cells regulating 55.4
  legs 23.35, *23.36,* 26.19, 26.29
  lips 26.17
  male genitalia 71.17–18
  management 26.101–3
  mechanical injury 28.22, 28.25, 28.52, 28.54
  mucosal 26.20–1
  nail involvement 65.28–9
  to nail lacquer/polish 65.54–5
  neck 26.18
  neonatal 17.22
  nipple 70.10
  non-eczematous responses 26.25–8
  occupational 26.4–5, 26.14, 26.20, 27.4, *27.5,* 27.7
  pathogenesis 26.5–6
  pathology 26.13
  perioral 26.17
  periorbital oedema 67.5
  persistent 29.17
  pimecrolimus therapy 73.32
  plant-induced 26.10, 26.15–16, 26.74–9
  population studies 26.4–5
  predisposing factors 26.6–13
  to preservatives 26.49–58
  prevalence 26.3–5
  prevention 26.99–101
  primary patterns 26.15–20
  primary site 26.13
  prognosis 26.103–4
  race and 9.13, 26.8
  to resins and plastics *26.16,* 26.20, 26.69–74
  to rubber 26.63–5
  scalp 26.17–18
  seasonal variation 26.13
  secondary patterns 26.21–2
  sensitization 26.1, 26.5–6, 26.6–7, 26.9–10

sensitizing agents 73.39
sources of allergy 26.14
susceptibility to 26.6–7
systemic non-eczematous 26.27
systemically reactivated 26.22–3
topical acne agents causing 42.49
topical therapy causing 73.4
truncal 26.18, 26.29–30
to UV filters 26.62–3
to woods, colophony and turpentine 26.79, *26.80–1*, 26.82–4
wound healing and 14.17
allergic contact urticaria *see* urticaria
allergic granulomatosis *see* Churg–Strauss syndrome
allergic reactions
canine 2.7
to HRT 8.20
to tattoo pigments 58.58
to topical antibiotics 73.10
allergy **13.12–14**
to abacavir 72.30
to aluminium 26.39–40, *26.46*
to antiperspirants 26.18
to antiseptics *26.46*
to arthropod bites and stings 38.1
to balsam of Peru 26.18, 26.22, 26.40, 26.41
to chromium 26.15, 26.18, **26.34–6**
compound 26.89
contact urticaria and 22.19
to cow's milk 22.6
to detergents 26.18
drug-induced 75.15–21
to food additives 26.17, 26.22
to gold 26.26, 26.**38–9**
history of 26.1–2
to nail polish/lacquer 26.16, 26.17, 26.18, 26.47, 26.48, 68.24
to nickel *see* nickel
to penicillin *26.46*, 34.23
to poison ivy 26.16, 26.17, 26.75
to pollen *see* pollen allergy
to retinol *26.46*
tests 13.16
to tetracyclines *26.46*, 75.53
therapy 13.25–6
to vitamin E *26.46*
to vitamin K *26.46*
Allgrove's syndrome 62.13
Allium 25.21, 26.77
Allodermanyssus sanguineus 30.74
allodynia 33.26, 63.6
allokinesis 21.1, 21.3, 21.13
allopurinol 59.103
adverse effects 75.78
Stevens–Johnson syndrome *76.4*, 76.11
in American trypanosomiasis 37.32
in palmar fibromatosis 45.46
in sarcoidosis 61.21
alloys, prosthetic implants 26.37
allyl alcohol 25.21
allylamines, topical 73.12
allysines 3.43
alopecia 66.13–14, **66.16–61**
aetiology and 66.16–18
age of onset and 66.16–17
androgenetic 8.23
in adolescence 8.6
caffeine (topical) retarding 73.49
female pattern 66.16, 66.17–18, 66.20, 66.22, 66.24, 66.25–6
Hamilton–Norwood grading scale 66.16, *66.17*
inheritance 66.18–19
limited frontoparietal 66.16
nomenclature 66.16
pathogenesis 66.19–21
pathology 66.22–3
role of androgens 66.13–14, 66.14–15, 66.16, 66.19–20
treatment 66.23–7
treatment, minoxidil 73.49–50
in animals 2.18–19
artefactual 66.53–6
caused by irritants *25.2*
central centrifugal (follicular degeneration syndrome) 9.7, **66.46,** 66.68
cicatricial
acquired 66.38–9
classification 66.39, *66.40*
non-specific 66.39
primary *66.40*
secondary *66.40*
clinical features and 66.21–2
congenital 66.59–60
cosmetic 66.53
Cronkhite–Canada syndrome 58.13
definition 5.7
in discoid lupus erythematosus 66.43–5
in dogs and other animals 2.10
drug-induced 66.29–30, 75.45
due to medical trauma 66.53
eating disorders 64.22
in follicular lichen planus 41.11
frontal fibrosing 41.11, 66.41, 66.42
generalized non-Herlitz junctional EB 39.13
in HIV infection 66.2
in Hodgkin's disease 57.63
hot comb (follicular degeneration syndrome) 9.7, **66.46,** 66.68
in hypothyroidism 62.10, 66.28, *66.29*
in incontinentia pigmenti 66.51
in lichen planus 41.11, 41.14, 41.17, 66.39, 66.41–3
lipedematous 66.58–9
neonatal occipital 17.4
paraneoplastic, in cats 2.19
pathological pulling/plucking 64.30–1
post-inflammatory cicatricial, eyebrows 67.4
in radiodermatitis 66.53–4
sarcoidosis and 61.9, 61.14
scarring *66.65*
differential diagnosis 66.36
in dystrophic EB 39.18
frontotemporal 9.7
in SLE 66.29
sulphur depletion 59.72
in syphilis 66.29, 66.52
syphilitic 34.11
telogen, postpartum 8.10
total (congenital) 66.59–60
traction 9.7, 66.53
treatment
antiandrogens 74.2–3
minoxidil 73.49–50
Vogt–Koyanagi-Harada syndrome 58.45
see also baldness
alopecia areata (AA) 64.5, 66.16, **66.31–8**
aetiology 66.31–3
animal models 2.18
in animals 2.18
atopic dermatitis and 24.23
atopy and 66.31
as autoimmune disease 66.31–2
in autoimmune polyglandular syndromes 62.13
clinical features 66.34–5, *66.36*
diabetes mellitus and 66.32
differential diagnosis 36.27, 66.35–6
eyebrow hypoplasia 67.3
genetics 15.10, 66.31
genitocrural 71.8
greying of hair and 66.92, 66.93
in HIV infection *35.42*, 66.2
infection and 66.32
management 66.36
nail involvement 66.35, *66.36*
in other species 66.33
pathology 66.33, *66.34*
prognosis 66.36
skin biopsy 10.43
stress and 66.32
tacrolimus use and 73.32
treatment 66.36–8
minoxidil 73.50
sensitizing agents 73.39
topical mechlorethamine 73.24
alopecia mucinosa 57.14, 59.26
alopecia neoplastica 70.14
alopecia totalis 66.35, 66.36, 66.37–8
topical mechlorethamine treatment 73.24
alopecia unguium 65.10
alopecia universalis 66.36, 66.38
in animals 2.18
alopecia universalis–onychodystrophy–total vitiligo 15.30
alopecia–anosmia–deafness–hypogonadism 15.30
alopecia–onychodysplasia-hypohidrosis 15.30
alopecia–onychodysplasia-hypohidrosis–deafness 15.30
alpha-actinin 40.2
alpha-hydroxy acids, in actinic elastosis 45.27
α-antitrypsin deficiency *see* α-antitrypsin deficiency *(under antitrypsin)*
α-defensins 4.5, 13.4
α-fetoprotein 47.19, 63.16
α-keratin intermediate filaments (α-KIF) 66.6
α_2-macroglobulin 13.4
α-tocopherol *see* vitamin E
Alpine sunlamp 29.1
Alpinia galanga 76.5
Alport syndrome 3.27, 3.35
alprazolam 75.81
ALPS (autoimmune lymphoproliferative syndrome) 17.65–6
Alstroemeria 26.26, 26.76
Alstrom syndrome 69.12
alteplase 75.23, 75.107
altered self hypothesis, in vasculitis 50.6
Alternaria alternata 36.77
alternating pressure mattresses 28.20, 28.22
alternative therapies *see* complementary and alternative therapy
altitude injury, ear 68.11
aluminium, allergy to 26.39–40, *26.46*
aluminium acetate 73.15–16
in otitis externa 68.25
aluminium chlorhydrate 44.11, 73.9
aluminium chloride *25.19*, 77.50
in hyperhidrosis 44.10, 44.11
in tinea pedis 36.49
aluminium chloride hexahydrate 63.22–3, **73.9,** 77.47
in epidermolysis bullosa simplex 39.31
aluminium chlorohydrates 44.11, 73.9
aluminium oxide, for calcinosis in a child 51.129
alveolar fibrosis, systemic sclerosis 51.93
alveolar ridges, bone loss in dystrophic EB 39.19
amalgam *see* dental amalgam
amantadine *26.46*, 75.88
amastia 70.2, 70.3
amaurosis fugax 50.43
amaurotic idiocy 44.18
ambiguous external genitalia 71.56
ambiphilic creams 73.7
Amblyomma 30.58, 38.34, 38.35
Ambras syndrome 66.76
Ambrosia (ragweed) 26.10, 26.20, 26.75
amelanosis 58.9
amelo-cerebrohypohidrotic syndrome 15.30
amelo-onychohypohidrotic dysplasia 15.30
amelogenesis imperfecta 69.8
amenorrhoea–galactorrhoea syndrome 66.83
American trypanosomiasis (Chagas' disease) *see* trypanosomiasis, American/South-American
amethocaine (tetracaine) 75.153, 77.10
amfebutamone 75.88–9
amicrobial pustulosis associated with autoimmune diseases 50.90
amidopyrine 75.77
amikacin 74.42
amiloride, adverse effects *70.5*
amineptine 75.78
acneiform eruptions due to 42.72
bis(4-amino-3-methylcyclohexyl) methane *27.17*
3-amino-9-ethylcarbazole 10.16
amino acid metabolism disorders 59.94–104
with hypotrichosis 66.61
amino penicillins, cutaneous adverse drug reactions 74.40
amino-plastics 26.73, 26.74
p-aminobenzoic acid 26.23, 26.62
aminocaproic acid 75.107
aminocyclitol antibiotic 74.42
aminoglutethimide 75.128
aminoglycoside antibiotics 74.42, 74.44
in Hailey–Hailey disease 39.36
topical 73.10
5-aminolaevulinic acid (ALA)
in non-melanoma skin cancer 52.16
in photodynamic therapy 78.15
topical, acne vulgaris 42.68
aminopenicillins 74.40
aminopeptidase N (APN) 12.50
aminophenazone 75.77
aminophylline 75.99
aminopterin 20.33
amiodarone *70.5*, 75.31, 75.33, 75.89
photosensitivity 29.23, 58.56
pigmentation due to 58.56, *58.57*
amisulpiride *64.52*
amitriptyline *64.51*
adverse effects 75.78
in dystrophic EB 39.30
in erythromelalgia 47.10
in hyperhidrosis 44.12
in post-herpetic neuralgia 63.7
ammonia, napkin dermatitis and 17.23
ammonium chloride, in alkali burns 27.12
ammonium persulphate 22.20, 26.17
amniocentesis 16.2, 17.11
amniotic bands/adhesions 17.15, **18.106–7,** 45.69
lymphoedema 48.11
amocarzine 75.71
amoebiasis **37.27–8**
HIV infection 35.35
perianal/perineal involvement 71.95
amoeboma 37.27
amorolfine *26.46*, 36.48–9, 36.50, 36.55
in onychomycosis 73.12
in superficial white onychomycosis 36.55
amoxicillin 75.50
amoxicillin–clavulanate, adverse effect in HIV infection 35.21
AMP-protein kinase A (AMP-PKA) pathway 46.3, 46.4
amphetamines 44.18
abuse 64.13, *64.14*
adverse effects 69.21, *70.5*, **75.86–8**
amphibia
glands 2.4
pigment cells 2.6
skin 2.2
skin infections 2.12
amphotericin B 74.46
adverse effects 75.64
in blastomycosis 36.85
in candidiasis 36.68, 36.69
in chromoblastomycosis 36.76
in coccidioidomycosis 36.86
in cryptococcosis 36.90–1
in histoplasmosis 36.83
lipid-associated 74.46
in penicilliosis 36.88

ampicillin
  adverse effects *75.22,* **75.49–50**
    fixed eruption 75.28
  in infectious mononucleosis 33.30, 75.15, 75.49
  in rosacea 43.6
AMPs *see* antimicrobial peptides
amputation
  amputation stump neuroma 56.45
  intrauterine *see* amniotic bands/adhesions
  in peripheral arterial disease 47.6, 47.8
  stump pemphigoid 28.29
  in thromboangiitis obliterans 47.8
amputees, mechanical injury 28.27–9
AMSA 75.133
Amsler grid 45.23
AMSTAR (Assessment of Multiple Systematic Reviews) 7.16
Amsterdam dwarf *see* de Lange syndrome
amyldimethyl-*p*-aminobenzoate *25.19*
amyloid proteins
  non-fibrillar 59.42
  in notalgia paraesthetica 63.23
  staining 10.10, 59.43
amyloidosis **59.42–57,** *62.45*
  anosacral 59.48
  biochemical nature of fibril proteins 59.43
  bone and joint involvement 62.105
  cardiac involvement 62.78
  clinical classification 59.46
  cutaneous
    anosacral 9.17
    race and 9.17
  cutis dyschromica 59.48
  cutis laxa and 45.14
  dialysis-related 59.57
  differential diagnosis 50.54
  ear involvement 68.15
  electron microscopy 10.30
  with familial Mediterranean fever 62.104
  gelsolin amyloidosis (AGel) 59.57
  inherited systemic 59.57
  lichen amyloidosis 9.17, 59.46
  macular amyloidosis 9.17, 58.28, 59.46
  myeloma-associated **59.50–5,** 62.70, 62.93
    treatment 59.55
  oral involvement 69.114–15, *69.116, 69.117*
  pigmentation changes 58.28
  primary **59.50–5,** 62.70
    scleroderma-like lesions 51.79
    treatment 59.55
  primary localized cutaneous **59.44–9**
    nodular PLCA 59.49
    treatment 59.49
  psoriasis and 20.19
  purpura due to 49.15, 49.18
  respiratory tract involvement 62.83
  secondary localized cutaneous (PLCA) 59.50
  secondary systemic 59.56
  serum amyloid P component (SAP) 59.42–3
  skin biopsy 10.42
  systemic 59.50
    in dystrophic EB 39.19–20
    inherited 59.57
anabolic steroids 74.32
  acneiform eruptions due to 42.72
  adverse effects *70.5,* 75.119
  keloids and 45.54
Anacardiaceae 26.2, 26.75
anaemia 62.85
  aplastic *69.116*
  chronic, persistent parvovirus B19 infection 33.63
  in dystrophic EB 39.29
  Fanconi's *see* Fanconi's anaemia/syndrome
  haemolytic *see* haemolytic anaemia
  hypoplastic, Fanconi's anaemia 58.17
  iron deficiency 62.85
    see also iron, deficiency
  megaloblastic 62.85
    pigmentation changes 58.27
  pernicious 62.85, *69.116*
  pigmentation changes 58.17, 58.27, 62.85
  sickle cell *see* sickle cell disease
  sinus histiocytosis with massive lymphadenopathy (SHML) 55.29
anaerobic organisms
  in normal skin flora 30.2
  venous leg ulcers 47.44
anaesthesia dolorosa 63.6
anaesthetic, topical
  in zoster and post-herpetic neuralgia 33.28
  see also local anaesthesia
anaesthetic blockade, regional 47.11
anagen 3.7, 3.13, 3.21, 66.7, 66.10
  in androgenetic alopecia 66.20
  duration 66.9
  premature termination 66.16
  short 66.60
anagen effluvium 66.16
anagrelide 49.29
anakinra 22.24, 75.146
  cryopyrin-associated autoinflammatory syndromes 74.11
  recombinant IL-1 receptor antagonist 74.11
anal fissures 71.87, 71.89
anal fistulae 71.87, 71.89
anal intraepithelial neoplasia (AIN) 71.97
  HPV and 33.54–5
anal leakage 71.85
anal lesions, syphilis 34.7
analgesia
  burns 28.79
  venous leg ulcers 47.49
analgesics, skin testing for reactions to 75.173
analytical studies 6.19
anamorph 36.2
anaphylactoid reactions
  drug reactions 75.12, 75.25–6
  non-allergic 22.1, 22.8, 75.12, 75.25–6, 75.153
anaphylatoxin C5a 12.24–5
anaphylatoxins 13.2, 13.4
anaphylaxis
  to arthropod bites/stings 38.1, 38.3, 38.6, 38.14–15
  definition 22.1
  drug-induced 75.5, 75.8, 75.16–17, 75.17, 75.25–6, 75.48–9
    atopic dermatitis and 24.23
    topically applied drugs 26.44
  in dystrophic EB 39.29
  exercise-induced 22.15
  food-dependent exercise-induced 22.8
  in general anaesthesia 75.153
  to latex 26.105
  in mastocytosis 22.35
  non-allergic 22.1, 22.8, 75.12, 75.25–6, 75.153
  prick testing and 22.26
  prodromal symptoms 22.8
  treatment 22.8, 22.29, 22.35, *75.176*
    antihistamines 74.31
anaplasia 10.37
Anaplasma phagocytophilum 30.58, 30.59, 50.76
anaplastic large cell lymphoma 57.31–3
anaplastic lymphoma kinase 10.25
anatomy, of skin **3.1–53**
Anatrichosoma cutaneum 37.16
ANCA *see* antineutrophil cytoplasmic antibodies
ANCA-related glomerulonephritis 51.111
anchoring fibrils 3.26, 3.30, 3.32–3, *3.33*
  collagen type VII 3.32, 3.35–6
  reduction, dystrophic EB 39.15–16, *39.16,* 39.25
anchoring filaments 3.26, 3.30
  hemidesmosome complexes 3.32
Ancylostoma brasiliense, perianal/perineal infections 71.96
ancylostomiasis 22.10, 37.2, **37.14–15,** 37.16
Anderson–Fabry disease (angiokeratoma corporis diffusum) 59.34–8, 62.68–9, 62.77, 63.11
  aetiology 59.35
  bone and joint involvement *62.100*
  sweat gland cellular inclusions in 44.18
Androctonus 38.33
androgen(s) 74.32
  acne aetiology and 42.20–2
  acneiform eruptions due to 42.72
  adrenal production, inhibition, in acne 42.53
  adverse effects *70.5,* **75.119–20**
  in androgenetic alopecia (baldness) 66.13–14, 66.14–15, 66.16, 66.19–20
  circulating, mechanisms for reducing 42.15, *42.16*
  comedogenesis, role in 42.23
  excess, acne aetiology and 42.20, 42.22, 42.76
  in gynaecomastia 70.4
  hair growth and 66.13–16
  hirsutism and 66.81–2, 66.83
  mechanism of action on hair follicles 66.14–15
  ovarian production, inhibition, in acne 42.53
  prophylactic, in hereditary angio-oedema 22.22
  sebaceous gland activity control 42.9–11, 42.12
    activity inhibition 42.15, 42.16
  sweating and 44.5
  synthesis and metabolism 66.14
    acne and 42.20, 42.21
    in skin 42.10, 42.12, 42.21
    in women 66.81
  transport proteins 66.81
androgen insensitivity syndrome 66.14, 66.16
androgen receptor(s) 42.21
  in acne 42.21, 42.23
  androgenetic alopecia and 66.14
  blockers (antiandrogens), acne vulgaris treatment 42.53–4
  gene *(Stu1)* 8.23, 66.18–19
  hair growth and 66.14
  in sebaceous glands 42.4, 42.10
androstenedione 8.8, 8.19, 42.10
  hirsutism and 66.81
5α-androsterol 44.2
5α-androsterone 44.2
Anemone 25.21
anethole 26.17
anetoderma 45.17–19, 57.43
  with granuloma annulare 60.7
  of prematurity 17.11
  primary 45.17
  secondary 45.17
aneuploidy 15.2
aneurin 59.62
aneurysm
  abdominal aortic 47.2
  cirsoid 56.26–7, 65.35–6
  tertiary syphilis 34.14
Angelman's syndrome, hypopigmentation 58.42
angel's kiss (salmon patch) 18.62–3
angina bullosa haemorrhagica 69.22, 69.84, 69.100
  oral involvement *69.65*
angioblastoma 46.36
  giant cell 56.32
angiocentric lymphoma, EBV-positive 57.40–1
angiodermatitis, disseminated pruriginous 49.24–5
angiodyskinesia 47.11
angioendothelioma, papillary intralymphatic (endovascular lymphatic) 56.32–3
angioendotheliomatosis
  malignant 50.46–7
  reactive 56.24
angiofibroma 15.22
  cellular 56.8
  laser therapy 78.14
angiogenesis 47.1
  therapeutic, using gene therapy 47.6
  VEGF increase and 8.21
  in wound healing 14.6–7
angiography 47.4
  peripheral arterial disease 47.4
angioimmunoblastic lymphadenopathy (AILD) 57.51–3
angioimmunoblastic T-cell lymphoma 57.51
angiokeratoma **18.58–60,** 47.15
  of Fabry 47.13
  female genitalia 18.60, 71.55
  of Fordyce 18.59, 47.13
  genitocrural 71.7–8
  lysosomal storage disorders and 59.35
  male genitalia 18.59, 71.11, 71.12, 71.35
  of Mibelli 18.58–9
  solitary papular 18.59
  of the vulva 18.60
angiokeratoma circumscriptum 18.58
angiokeratoma corporis diffusum *see* Anderson–Fabry disease
angioleiomyoma 56.54–5
angiolipoma 46.44–5
  infiltrating and non-infiltrating types 46.45
angiolymphoid hyperplasia with eosinophilia
  epithelioid haemangioma 56.27–8, 68.15–16
  foreign bodies 28.45–6
angioma 49.2
  cherry (Campbell de Morgan) 47.13, 47.15
  eruptive 62.44
  genetics 15.27
  genitocrural 71.7–8
  glomeruloid 62.44
  hereditary neurocutaneous 18.79
  sclerosing *see* fibrous histiocytoma
  spider *see* spider angioma
  sudoriparous 18.16, 44.9
  tufted 18.54–5, *18.56*
angioma serpiginosum 47.16–17
angiomatoid fibrous histiocytoma 56.19–20
angiomatosis
  bacillary *see* bacillary angiomatosis
  diffuse dermal 5.*10,* 70.17
angiomyofibroblastoma 56.7–8
angiomyxoma
  aggressive 56.60
  superficial 56.59
angioneurotic oedema *see* angio-oedema
angio-oedema
  acquired 13.18–19
  cholinergic 22.15
  deficiency of C1 esterase inhibitor (C1INH). 12.49
  definition 22.1
  differential diagnosis 26.29
  drug-induced 75.26
  episodic with eosinophilia 22.23
  in hepatitis B virus infection 62.59
  hereditary 22.21–2
    erythema preceding 62.107
    LE-like disease 51.17
    oral involvement 69.33, *69.117*
    screening for 13.18, 22.26
  idiopathic 22.20–1
  kinin cascade and 13.4
  in loiasis 37.11
  management 22.29
    antihistamines 74.31
  oral involvement 69.107–8

in ordinary urticaria 22.5
in parvovirus B19 infection 33.63
pathophysiology 22.5
periorbital oedema 67.5
ulcerative colitis and 62.50
in urticarial vasculitis 22.19
vibratory *22.13*, 22.15, 28.58
without weals 22.2, 22.20–1
angioplasty
claudication management 47.5
rest pain and gangrene 47.6
angiopoietin-2 48.2
angiosarcoma **56.37–40**
epithelioid 56.40–1
pinna 68.34
angiotensin 12.25
angiotensin-converting enzyme (ACE) 3.52, 13.4, 63.2
inhibitors *see* ACE inhibitors, adverse effects
in sarcoidosis 61.20
angiotensin II receptor antagonists
adverse effects 75.94
in angio-oedema 22.21
in Marfan's syndrome 45.31
angry back syndrome 23.6, 26.88, 26.95
angular artery *77.2*, *77.3*
anhidrosis **44.13–15**
in Horner's syndrome 63.22
anidulomycin 74.48
animal(s)
acrodermatitis enteropathica 2.17
alopecia 2.18–19
chromatophores and melanocytes 2.5–6
colours and pigments 2.5–7
cutaneous features of systemic disease 2.17–18
disease relationship to human disease 2.7–8
differences from human diseases 2.9, **2.20–3,** *2.22*
similarities with human diseases 2.9, *2.9*
without similar human disease **2.20–3,** *2.21*
epidermis and dermis 2.3
glands 2.4
metabolism and reactions to therapeutics 2.9
pigment cells 2.5–7
skin diseases 2.8–19
atopic dermatitis 2.13–14
bacterial infection 2.11–12
bullous disorders 2.14–15
cicatricial pemphigoid 2.15
dermatitis 2.13–14
dermatomyositis 2.15–16
drug eruptions 2.17
epidermolysis bullosa acquisita 2.15
erythema multiforme 2.16
fungal infections 2.12–13
immune-mediated 2.14–16
lupus erythematosus 2.16
mast cell tumour 2.22–3
mechanobullous 2.17
neoplastic 2.19–20
parasitic diseases 2.9–11
pemphigus 2.15
pruritic diseases 2.9, 2.10, 2.11, 2.13
psoriasis 2.14
therapeutics, differences from humans 2.9
toxic epidermal necrolysis 2.16
vasculitis and panniculitis 2.16
see also animal models; *individual types of animals*
animal colours 2.5, 2.6–7
animal models
alopecia areata 2.18
comedogenesis 42.23
human disease relationship 2.7–8
interleukin-8 (IL-8) synthesis 2.8
psoriasis 2.8
pyoderma gangrenosum-like disease 2.8
skin grafts 2.7–8
topical corticosteroid efficacy assessment 73.16
see also animal(s)
animal testing 25.9, 26.12
anisakiasis 22.8
anistreplase 75.107
ankle flare, venous 47.14, 47.33
ankle–brachial Doppler pressure index 47.3
in neuropathic ulcers 63.9
ankle–brachial index 47.3, 47.47
ankle–brachial systolic gradient 47.3
ankyloblepharon–ectodermal dysplasia–clefting (AEC) syndrome 15.30, **15.61–3**
ankyloglossia 69.36–7
ankylosing spondylitis
genetics 15.9
radiotherapy and non-melanoma skin cancer due to 52.5
ankylosymblepharon 76.18
annelid worms, chaetae 2.2
annellides *36.3*, 36.4
annexins II and IV, antibodies 49.6
annular epidermolytic ichthyosis 19.31
annular erythema 62.106–13
associated with extractable nuclear antigens 62.109
drug-induced 75.23–4
of infancy 62.108–9
neutrophilic and vascular 62.112–13
recurrent with purpura 62.112
in Sjögren's syndrome 62.109
Sweet's disease-like 51.135
annular lichenoid dermatitis of youth 41.13
annular purpura, mechanical injury 28.31
annular scaling 5.7
annulus migrans 69.94
anodontia 69.6, 69.7
anogenital intraepithelial neoplasia 33.46
anogenital pilonidal sinus 28.49–50
anogenital region
allergic contact dermatitis 26.18–19, 26.29
hidradenoma papilliferum 53.20–1
hyperpigmentation 71.2–3
hypopigmentation 71.2–3
intertrigo 71.2–3
itching 71.1–2
lesions 71.65
leukoplakia 71.3
mammary-like glands, tumours 53.37–8
Paget's disease 53.40–1
pruritus 71.1–2
trauma 28.37–8
ulcers 71.3–4
warts *see* wart(s), anogenital
zoster 33.25
anonychia 65.9
with bizarre flexural pigmentation 15.31
congenital 65.18–19
with ectrodactylia 65.18
following lichen planus 65.29
anonychia–onychodystrophy with brachydactyly type b and ectrodactyly 15.31
Anopheles see mosquitoes
anophthalmia *67.4*
anorexia nervosa 21.16, **64.21–2,** *66.65*
acne and 42.34
hypertrichosis in 66.78
pellagra 59.64
ANOTHER syndrome 62.13
anoxia 47.26
ANP (atrial natriuretic peptide) 63.3
anterior lid margin disease (ALMD) *67.12*
anthelmintics
adverse effects 75.71
see also specific agents
Anthemis 25.21
Anthocoridae 38.25
Anthocoris 38.25
anthothecol 26.79
Anthozoa 38.56
anthralin *see* dithranol
anthrax 30.25, **30.40–1**
Anthrenus 38.27
anthropometry, HIV lipodystrophy 46.42
anthroquinone dyes 26.65–6
anti-C1q antibodies 13.22, 22.81
anti-CD3 antibodies 13.23
anti-CTLA-4 antibodies, melanoma management 54.54
anti-desmoglein antibodies 69.64–5
anti-DNase 30.13
anti-double-stranded DNA antibodies 13.19
anti-EGF receptor inhibitors, acneiform eruptions due to 42.72
anti-EGFR therapy 75.132–3
anti-Hu antibodies 13.20
anti-irritants 25.25
anti-La/SSB antibodies 49.19
in neonatal lupus erythematosus 10.18, 17.16
in Sjögren's syndrome 51.137
anti-Lag antibodies 55.4
anti-Müllerian duct hormone (AMH) 8.2
anti-myeloperoxidase antibodies 50.9
anti-NADase 30.13
anti-PR3 antibodies 50.9
anti-Ri antibodies 13.20
anti-RNP antibodies, prognosis in mixed connective tissue diseases 51.111
anti-Ro/SSA antibodies 49.19, 51.49, 51.54, 51.105
annular erythema and 62.109
epitope 51.137
in neonatal lupus erythematosus 17.16
in pregnancy 51.50
in Sjögren's syndrome 51.22, 51.136
in subacute cutaneous lupus erythematosus 10.18
in vasculitis 51.136
anti-SSA (Ro) antibodies *see* anti-Ro/SSA antibodies
anti-SSB (La) antibodies *see* anti-La/SSB antibodies
anti-TGF-β1 antibodies 66.20
anti-TNF-α 46.20
adverse effects 75.145
in toxic epidermal necrolysis 76.20–1
anti-TNF agents
adverse effects 31.30, 50.49
genetic factors in response to 11.16
anti-U1RNP antibodies 62.109
anti-Yo antibodies 13.20
antiandrogens 42.53, 74.32–3
acne vulgaris treatment 42.53–4
adverse effects 42.53, 75.120
allergy *26.46*
gynaecomastia 70.4, *70.5*
photosensitivity 75.31
in androgenetic alopecia 66.24, 66.25–6
comedogenesis reduction 42.23–4
in hirsutism 66.87–8
antiapoptotic proteins 33.11
antibiotics
in acrodermatitis chronica atrophicans 45.10
in actinomycosis 30.76
adverse effects **75.47–61**
acute generalized exanthematous pustulosis 75.34
allergic contact dermatitis 26.45, *26.46*
anaphylaxis 75.5, 75.25
epidermolysis bullosa acquisita 75.40
erythema multiforme 76.3, *76.4*
oral antibiotics *42.47*
pemphigus 75.38
photosensitivity 75.31
Stevens–Johnson syndrome *76.4*, 76.11
toxic epidermal necrolysis 76.13
urticaria 22.8, 22.10, 75.26
vasculitis 50.17, *50.18*
in anthrax 30.41
in atopic dermatitis 21.13, 24.29
in botryomycosis 30.68
in brucellosis 30.56
in candidiasis 36.68, 36.69
in cellulitis 30.19–20
in chancroid 30.47, 34.35
contraceptive pill interactions 42.51–2
cytotoxic 75.126–8
in diphtheria 30.37
in ecthyma 30.17
in erysipelas 30.19–20
in erythrasma 30.83
in furunculosis 30.24
in gas gangrene 30.44
in gonococcal infection 30.46
in gonorrhoea 34.28
in granuloma inguinale 30.62, 34.37
in Hailey–Hailey disease 39.35–6
'happenstance' therapy, in syphilis 34.12
in hidradenitis suppurativa 30.81
in impetigo 30.16
inadvertent, syphilis decline due to 34.12
in invasive otitis externa 68.26
in leptospirosis 30.66
in Lyme disease 30.65–6, 62.106
in lymphoedema 48.24
in lymphogranuloma venereum 30.71, 34.33
mechanism of action, in acne 42.48
in melioidosis 30.50–1
in meningococcal infection 30.44
napkin dermatitis and 17.24
in nocardiosis 30.77
oral
acne vulgaris treatment 42.46–9, 42.54, 42.63
adverse effects *42.47*
topical vs, in acne 42.41
in otitis externa 68.25
P. acnes resistance 42.41–2, 42.43
prophylactic, in human bites 38.61
in psittacosis 30.72
in relapsing fever 30.64
resistance 30.9
P. acnes 42.41–2, 42.43
in rhinoscleroma 30.53
in rickettsial infections 30.74
in rosacea 43.2, 43.6, 43.7
in *Salmonella* infection 30.48
in sycosis 30.25
in syphilis 34.22
topical **73.9–12**
acne treatment 42.39, 42.41–3, 73.9, 73.10
adverse effects 75.61
benzoyl peroxide with, in acne 42.41
epidermolysis bullosa management 39.28
sebum production, effect 42.16
sensitization by 73.9
staphylococcal infections 73.9, 73.10, 73.11
wound healing and 14.21
in tularaemia 30.54
venous leg ulcers and 47.49
in wound infection 14.16
antibodies
adverse drug reactions mediated by 75.17
autoimmune *see* autoantibodies
defects of production 17.70–3
deficiencies *17.70*, 17.84
idiotypic 13.10
in vivo measurement of responses 17.56
maternal 13.15
monoclonal *see* monoclonal antibodies
tests for 13.18
see also specific antibodies/antigens

anticardiolipin antibodies 49.29, 49.40, 51.63
  in deep-vein thrombosis 47.28
  detection 49.40
  lupus anticoagulant and 51.63
  in Sneddon's syndrome 49.43
  transplacental transfer 49.51
anticholinergics
  adverse effects 26.17
  topical 73.9
    in hyperhidrosis 44.11, 73.9
anticoagulant pathways 49.38
  antithrombin III–heparin/heparan 49.38
  lupus anticoagulant 49.39
  thrombomodulin–protein C/S 49.38–9
anticoagulants
  adverse effects **75.104–7**
  in deep-vein thrombosis 47.29, 47.30
  in Klippel–Trenaunay syndrome 47.24
  see also specific drugs
anticonvulsant hypersensitivity syndrome *see* DRESS syndrome
anticonvulsants
  adverse effects **75.83–6**
    acneiform eruptions 42.72
    DRESS syndrome 23.47, 75.18–19, 75.26–7, 75.83, 76.10
    erythema multiforme 76.3, *76.4*
    hyperpigmentation 69.97
    pseudolymphoma 75.44
    Stevens–Johnson syndrome *76.4*, 76.11
    toxic epidermal necrolysis 76.12–13
    vasculitis 50.17, *50.18*
  in post-herpetic neuralgia 63.7
antidepressants **64.50–1**
  adverse effects 75.78–9
  in post-herpetic neuralgia 63.7
  psychocutaneous disorders
    body dysmorphic disorder 64.20
    lichen simplex 64.27
    pruritus 64.23–4
    skin picking 64.28
  SSRIs *see* selective serotonin reuptake inhibitors (SSRIs)
  starting therapy 64.50
  switching drugs 64.51
  tricyclic *see* tricyclic antidepressants
  see also amitriptyline
antidiuretic hormone (ADH) (vasopressin) 75.98
  sweat production and 44.6
antiendothelial cell antibodies 51.104, 51.111
  in polyarteritis nodosa 50.33
  in thromboangiitis obliterans 47.7
  in vasculitis 50.7–8
antiepileptic drugs *see* anticonvulsants
antiepiligrin mucous membrane pemphigoid 40.39
antifilarial drugs, filarial lymphoedema 48.24
antifungal agents
  adverse effects *26.46*, **75.64–6,** *76.4*
  azelaic acid as 73.28
  in candidiasis 36.67–8
  in chromoblastomycosis 36.76
  in dermatophytoses 36.47–9
  in Hailey–Hailey disease 39.35
  in lymphoedema 48.22
  in otitis externa 68.25
  in pityriasis versicolor 36.12
  resistance to 36.50
  systemic 74.46–8
  topical **73.12–13**
antigen(s)
  acne pathogenesis 42.26, 42.27
  in arthropod venom 38.1–2
  complete/conjugated 26.5–6, 26.11
  endogenous 4.8
  exogenous 4.8
  immunoenzyme methods 10.15–16
  immunofluorescence techniques 10.12, 10.13
  nuclear 13.19–20
  presentation 13.9–10, 17.50–1
    abnormal, UVR effect 29.5
  role in vasculitis 50.4–5
  T-dependent 13.10
  T-independent (TI) 13.10
antigen 5 38.14
antigen-presenting cells (APCs) 4.8, 13.6–7, 17.50, **55.4–5**
  in atopic dermatitis 24.13–15
  B cells as 13.7
  dermal dendritic cells as 3.19, 55.4
  effect of antimalarials 74.25
  effects of UV radiation on 13.28, *13.29*
  function 13.9–10
  Langerhans' cells as 3.17, *3.18*, 13.9, 55.4–5
  in lymph nodes 13.8–9
  macrophages as 3.19, 13.5, 55.4
  see also dendritic cells; histiocytes
antigen–antibody reaction 49.18
antihistamines 21.4, 21.17, *21.18*, 74.31, 75.149–50, H_1, H_2
  adverse effects 22.29, 26.17, *26.46*, **75.148–50**
  in atopic dermatitis 21.13, 24.29
  in carcinoid syndrome 43.19
  in delayed pressure urticaria 22.14
  in dermographism 22.14
  dose range and evidence level 74.31
  H_1
    adverse effects 75.148–9
    second-generation 22.28, *22.29*
  in Hymenoptera stings 38.14
  in lichen planus 41.18
  as local anaesthetics 77.11
  in mastocytosis 22.35
  non-sedating (second-generation) 74.32
  in pregnancy 22.29
  in pruritus 21.17, *21.18*
  in psychogenic pruritus 64.23
  in scombroid fish poisoning 43.16
  in solar urticaria 29.19
  topical 73.13
    atopic eye disease treatment 67.15
  in urticaria 22.28–9
antihistone antibodies 51.54
  minocycline-induced lupus-like reaction 42.51
antihypertensives 75.92–7
anti-inflammatory agents, systemic agents 74.2–3
antilipoprotein antibodies 55.22
antimalarials 74.25–6
  adverse effects 51.20, **75.69–71**
    hypermelanosis 58.30
    hyperpigmentation 69.97, 75.33
    nail colour changes 65.16
    ocular 67.31
  antiphospholipid syndrome therapy 49.42
  discoid lupus erythematosus treatment 51.20–1
  dose range and evidence level 74.26
  in polymorphic light eruption 29.12
antimetabolites 75.128–31
  in cicatrizing conjunctivitis 67.23
antimicrobial agents
  as allergens 26.49–58
  systemic agents **74.38–50**
  see also antibiotics; antifungal agents; antiviral agents
antimicrobial dressings 14.24
antimicrobial peptides (AMPs) 4.1, 4.5–6, *4.6*, 12.5–7
  cathelicidins 12.5
  defensins 12.4–5
  secreted by skin 3.16
antimitochondrial antibodies 62.62
antimony, pentavalent 74.51
antineoplastic drugs, topical **73.23–6**
antineutrophil cytoplasmic antibodies (ANCA) 51.104
  atypical (X-/snowdrift-/a-ANCA) 13.20, 50.8
  C-ANCA 13.20, 50.8, 50.9
  detection 13.20
  G-ANCA 50.8
  lactoferrin-ANCA 50.9
  in microscopic polyangiitis 50.36, 62.83
  P-ANCA 13.20, 50.8, 50.9
  in pyoderma gangrenosum 50.66
  in Sweet's syndrome 50.76
  in vasculitis 50.2, 50.3, 50.6, 50.7, 50.8–10
  in Wegener's granulomatosis 50.39
antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis 74.8, 74.18
antinuclear antibodies
  detection 13.19–20, *13.21*, 51.53
  in lupus panniculitis 46.25
  minocycline-induced lupus-like reaction 42.51
  in Sneddon's syndrome 49.43
  in systemic sclerosis 51.89
  in Waldenström's macroglobulinaemia 49.19
antinuclear antibody-negative SLE 51.56
antinuclear factor, on Hep-2 cells 51.53
antioestrogens 74.33, 75.119
antioxidants 26.59, 26.63
  in prevention of ageing 80.3
  reduced levels, rosacea 43.2
  in vegetable oils for topical therapy 73.6
antiparasitic agents 74.50–1
  topical 73.13–14
antiparietal cell antibodies 62.85
antiperspirants **73.9**
  allergy to 26.18
  types and indications 73.9
antiphospholipid antibodies 49.40–2
  in APLS/ lupus anticoagulant syndrome 49.40–2
  in Degos' disease 49.45
  detection 49.40
  lupus anticoagulant 51.63
  primary anetoderma and 45.17
  in Sneddon's syndrome 49.43
  in vasculitis 50.4
antiphospholipid antibody syndrome (APLS) 49.39, **49.40–2,** 51.63
  autoantigen 49.41
  cardiac involvement 62.78
  catastrophic 49.40, 49.41, 49.51
  children 49.51
  clinical features 49.41
  coagulation mechanisms 49.40
  cutaneous findings 49.41
  diagnostic criteria 49.41
  fibromuscular dysplasia with 49.48
  idiopathic thrombocytopenic purpura and 49.9
  primary, secondary 49.40
  respiratory tract involvement 62.82
  therapy 49.41–2
antiplatelet agents
  antiphospholipid syndrome therapy 49.41–2
  claudication management 47.5
  in dermatomyositis 51.129
  in erythromelalgia 47.10
  purpura due to 49.4
antiplatelet antibodies 49.6
antipolysaccharide antibody 13.15
antiprothombin antibodies, Sneddon's syndrome 49.43
antipsychotic drugs **64.51–2,** 75.82
  atypical 64.16, 64.52
antiretroviral agents
  action 74.49
  adverse effects 35.6–7, *35.21*, **35.21–2,** 70.4, **75.67–9,** 76.3, *76.4*, 76.11, 76.13
    oral *35.44*
    toxic neuropathy 63.12
  HIV-associated lipodystrophy 35.22, 46.42
  in HIV infection 35.5–8
    initiation 35.6
  immune reconstitution (inflammatory) syndrome 35.46
  novel, in HIV infection 35.6
  see also highly-active antiretroviral therapy
antirheumatic drugs (DMARDs) 20.59
anti-SRP (signal recognition particle) 51.128
antiseptics **73.14–15**
  allergy to *26.46*
  effect on normal bacterial flora 30.4
  efficacy 73.14
  in epidermolysis bullosa 39.28
  in Hailey–Hailey disease 39.35
  in impetigo 30.16
  use before topical antibiotics 73.9
  wound healing and 14.21
antistreptolysin-O 30.13
antisynthetase antibodies, `mechanic's hands' 51.125
antisynthetase syndrome 62.82
antithrombin III 49.38
  disorders 49.38
antithymocyte globulin, familial haemophagocytic lymphohistiocytosis 55.26
antithyroid antibodies 62.11
α_1-antitrypsin, urticaria and 22.4
α1-antitrypsin deficiency
  MZ phenotype 46.20
  panniculitis 46.20–1
  respiratory tract involvement 62.80
  vasculitis and 50.11, 50.53
  ZZ phenotype 46.20
antituberculous drugs 74.44–5
antitumour agents, hypermelanosis due to 58.30
antiviral agents
  adverse effects *26.46*, **75.66–9**
  antiretrovirals *see* antiretroviral agents
  systemic 74.48–50
  topical 73.15
  wart treatment 33.50
  see also specific agents
antlers 2.3
Antoni A areas 56.46
Antoni B areas 56.46
ants 38.14
anus
  anomalous papillae 18.95
  see also entries beginning anal, anogenital
anxiety
  acne and 42.35
  lichen planus association 41.3
anxiolytic drugs 64.52, 75.80–2
aortic aneurysm 45.30
aortic arch syndrome (Takayasu's arteritis) **50.44–5**
aortic incompetence 45.30
aortitis
  due to *Salmonella* 50.55
  syphilis 34.14
aortitis syndrome (Takayasu's arteritis) **50.44–5**
aortofemoral bypass 47.5–6
APAD (amicrobial pustulosis associated with autoimmune diseases) 50.90
APCs *see* antigen-presenting cells
APECED syndrome *13.13*, 15.31, 36.64, 62.13
Apert's syndrome **15.90,** 42.70–1, 68.4
  acne and 42.61, 42.70–1
  comedo naevus and 18.11
  cutaneous changes 42.71
aphthae 69.14
  benign, female genitalia 71.65–6
  definition 5.7
  recurrent aphthous stomatitis **69.44–6,** 69.48
  secondary syphilis vs 34.12

see also oral cavity, ulcers; recurrent aphthous stomatitis
aphthoviruses 33.71
Apidae *see* bees
apigenin 66.97
Apis see bees
Apium graveolens 75.162
aplasia cutis congenita **18.98–106**
differential diagnosis 18.106
with epidermolysis bullosa 18.101
see also Bart's syndrome
with fetus papyraceus 18.100–1
following intrauterine infection 18.102
isolated localized to the extremities 18.101–2
in malformation syndromes 18.102–6
overlying developmental malformation 18.100
scalp
with epidermal naevi 18.100
with limb reduction abnormalities 18.68, 18.99–100
non-syndromic 18.98–9
teratogen-induced 18.102
treatment 18.106
Apligraf
use in dystrophic EB 39.30
see also skin equivalents
APLS *see* antiphospholipid antibody syndrome
apocrine sweat glands **3.12–13,** 44.1, *44.2*
ageing and 8.24
anatomy and physiology 44.18–19
axillary 44.19
carcinoma 53.21–2, **53.33–7**
control of 44.2
cylindroma 53.28–9
ectopic 44.18
excretory duct 3.12, 53.1
carcinoma **53.32**
functions 3.3, 44.2
hidradenoma papilliferum 53.20–1
hidrocystoma (cystadenoma) 53.18–19
mixed tumour of skin 53.30–2
of Moll 67.2
in pregnancy 8.10
secretory coil 3.12, 44.19
cystic dilatation 53.18
spiradenoma *see* spiradenoma
structure 3.12
syringocystadenoma papilliferum 53.19–20
tubular adenoma 53.21
tumours **53.18–22,** 53.27
apocrinitis *see* hidradenitis suppurativa
Apocynaceae 26.79, *26.80*
APOD (acute papular onchodermatitis) 37.5
apoeccrine sweat glands 3.12, 44.1, 44.3
Apoidea *see* bees
apolipoprotein H (β_2-GPI) 49.40, 49.41
apolipoproteins 59.82
isoforms of apo E 59.89
apomorphine 75.88
apomucin, extramammary Paget's disease 53.40
apopilosebaceous unit 3.13
apoptosis 10.37
in catagen 66.11
defects 17.50
and inflammation 12.11–12
keratinocytes 12.12
lymphocyte activation and 13.11
necrosis vs 12.12
sebocytes 42.15
apoptotic cells (sunburn cells) 29.5
appetite stimulants 75.89
appetite suppressants 46.8, 75.89
scleroderma-like lesions 51.81
apraclonidine *26.46*
apronalide 75.17, 75.23
APUDoma 43.17
aquagenic syringeal acrokeratoderma 19.115
aquaplast 77.17
Aqueous Cream BP 73.2, 73.7, 73.31, 73.48
in eczema 23.38
aqueous creams 73.7
Araçatuba virus 33.8
Araceae *25.21*
arachidonic acid
metabolism, excessive, diclofenac action 73.25
pathway 13.4
synthesis 73.17
arachis oil 73.6
Arachnia propionica 30.75
Arachnida 37.2, **38.30–54**
arachnidism 38.30–2
arachnodactyly
congenital contractural 45.30–1
in Marfan's syndrome 45.30
Araneae (spiders) 38.30–3
Arao–Perkins bodies 66.21
arbor vitae *26.80*
Arcanobacterium haemolyticum 30.37
Archaeopsylla erinacei 2.3
Archives of Dermatology, Evidence-based Dermatology 7.6
area of burn assessment 28.77–9
areca nut chewing 69.106–7
AREDYLD syndrome 15.29, 70.3
arenaviruses, and *Arenaviridae 33.3,* 33.66, *33.67,* 33.68, **33.69**
areola 70.1
atopic dermatitis 70.9–10
basal cell carcinoma 70.15
biopsy 10.32
blue 70.13
hyperkeratosis 70.8–9
melanoma 70.15
mucinosis 70.17
neurofibromatosis 70.17
in pregnancy 70.1
sebaceous hyperplasia 70.13
seborrhoeic warts 70.15
supernumerary 18.92–3
telangiectasia 70.13
variations in 70.1
Argasidae 38.33–5
argentaffinoma 43.17
Argentinian haemorrhagic fever 33.69
arginine 66.6
argininosuccinic aciduria 66.67
Argonaute-2 protein 11.7
Argyll Robertson pupils 33.26, 63.15
argyria 58.54, 75.33, **75.102**
earlobe 68.8
nail colour in 65.16
pigmentation due to 58.54
skin biopsy 10.42
ariboflavinosis 59.62
aripiprazole *64.52*
aristolochic acid 75.160
armadillo proteins 3.22
'armchair legs' 48.14, 48.21
armed forces, skin disease and 8.8
arms
allergic contact dermatitis 26.15–16, 26.29
lymphoedema 48.12, 48.13
occupational dermatoses 27.3
Arndt–Gottron syndrome *see* scleromyxoedema
Arnold–Chiari malformation 18.95
aromatherapy 26.40, *72.32,* 75.160, 75.162
arrector pili 3.1, 66.2, 66.3
arsenic **75.99–100**
basal cell carcinoma due to 52.20
Bowen's disease and 52.32, 52.33, 52.35
hypermelanosis due to 58.29, 58.30
as irritant 25.21
non-melanoma skin cancers 52.4, 52.20
pigmentation induced by 65.16
arsenical keratosis 52.29, **52.34–5,** 62.47
arsenicalism, chronic 52.33
arterial disease, peripheral **47.1–12**
aetiology 47.1–2, 47.5
clinical features 47.2–3
differential diagnosis 47.4–5
investigations 47.3–4
prognosis 47.5
risk factors 47.2
treatment 47.5–6
arterial dissections, lentiginosis with 58.14
arterial priapism 71.51
arterial ulceration **47.52–4**
arterial vessels 3.51
venous vessels vs 3.52
arteries
calcification 47.8–9
calibre-persistent 69.129
occlusion, Degos' disease 49.45
in pseudoxanthoma elasticum 45.21, 45.22
thickening of walls 47.2
venous vessels vs 3.52
arteriogenesis 47.1
arteriography, peripheral arterial disorders 47.4
arteriolar disorders 47.1–12
arterioles 3.51
spider telangiectases 47.15
arteriosclerosis 47.2
arteriovenous abnormalities
malformation *see* arteriovenous malformations (AVMs)
periungual/subungual 65.35–6
arteriovenous fistulae 47.3, **47.21**
acquired 47.21
congenital 47.21
iatrogenic 47.21
pulmonary 47.17, 47.18
signs and effects 47.21
traumatic 47.21
arteriovenous malformations (AVMs) 18.61–2, 18.79, **47.21–3**
hepatic 47.18
hereditary haemorrhagic telangiectasia 47.17
arteriovenous shunts **47.21**
arteritic ulcers 51.132
arteritis
cranial *see* giant cell arteritis
lymphocytic thrombophilic 50.51–2
macular 50.51
in rheumatoid arthritis 51.132
Takayasu's **50.44–5**
arthralgia
in connective tissue disorders 62.103
in disseminated gonococcal infection 34.27
in Henoch–Schönlein purpura 50.20
in Lyme disease 62.105
in palisading neutrophilic and granulomatous dermatitis 62.103
in Reiter's syndrome 62.105
in Sweet's syndrome 62.103
in urticarial vasculitis 22.19
vasculitis and 62.102
in Whipple's disease 62.105
arthritis
in connective tissue disorders 62.103
in Lyme disease 30.64, 30.65
in multicentric reticulohistiocytosis 62.104
nail dystrophy and 65.25
psoriatic 62.103
HIV infection 35.17
rheumatoid *see* rheumatoid arthritis
suppurative, gonococci causing 34.27–8
in varicella 33.25
vasculitis and 62.102
arthritis mutilans 20.56, 62.104
arthrochalasis multiplex congenita *45.32,* 45.35
arthroconidia *36.3,* 36.4, 36.15, 36.16, 36.20, 36.37, 36.85
Arthroderma 36.18
Arthroderma benhamiae 36.2
arthrogryposis and ectodermal dysplasia 15.31
arthropods 37.2, **38.1–55**
bites/stings 38.1–5
as disease vectors 38.2
exoskeleton 2.2
in the external auditory canal 68.11
mechanism of skin injury 38.1–2
pool feeders 38.1
retained mouthparts 38.2
susceptibility to infestation/attack 38.2
vessel feeders 38.1
see also specific classes and animals
Arthus phenomenon/reaction 75.17
artificial hair implantation 28.50
artificial tears, in rosacea 43.7
artists, occupational hazards 27.18
aryl sulphatase deficiency 19.13
asbestos, acnegenicity 27.13, 42.77
Ascaris 37.1, 37.2–3
Ascher's syndrome 45.21, 69.38
ascoma 36.3
ascomycin *see* pimecrolimus
Ascomycota 36.2, 36.3, 36.18
ascorbic acid *see* vitamin C
ascospores 36.3
ascus 36.3
ash-leaf-shaped macules 15.22
ashy dermatosis 30.63
ashy dermatosis of Ramirez 58.33–4
L-asparaginase 75.132
aspartame sweetener 75.159
lobular panniculitis associated 46.14
aspartate 22.11
aspartylglucosaminuria 59.34
aspergillosis, primary cutaneous 49.35
Aspergillus
cutaneous lesions 36.92, 49.35
identification *36.8*
oral infection 69.79–80, *69.118*
otitis externa 68.21
invasive otitis externa 68.25
otomycosis 36.17, 68.27
sarcoidosis and 61.17
Aspergillus fumigatus 49.35
Aspergillus penicilloides 38.47
Aspergillus terreus 36.55
asphyxia, purpura due to 49.14
asphyxia reticularis multiplex *see* livedo reticularis
aspirin
adverse effects **75.72**
urticaria 22.8, 22.10, 75.26
challenge test 22.26
claudication management 47.5
in Kawasaki disease 50.46
low-dose 49.29
in male genital conditions 71.27
in mastocytosis 22.35
in platelet function disorders 49.13
surgical complications and 77.9
in venous leg ulceration 47.49
assassin bugs 37.31, 38.25–6
Assessment of Multiple Systematic Reviews 7.16
Assessment of the Psychosocial Effects of Acne (APSEA) 42.35
Assessments of the Psychological and Social Effects of Acne questionnaire 72.20
associations, skin disease 6.11, 6.18
ASST (autologous serum skin test) 22.9
asteatotic eczema (eczema craquelé) 8.27, **23.6–7,** 47.34
ear 68.14
generalized 23.7
hands 23.20
old age and 8.27
astemizole 22.29, 75.148–9
Asteraceae *see* Compositae
asteroid bodies 36.70, *36.71,* 61.4
asthma
in carcinoid syndrome 43.18
in Churg–Strauss syndrome 50.41
astichiasis *67.4*
astringents 73.15–16
astrocytosis, malignant 55.32–3

AT *see* ataxia telangiectasia (AT; Louis-Bar syndrome)
atabrine *see* mepacrine
ataxia, in tabes dorsalis 63.15
ataxia telangiectasia (AT; Louis–Bar syndrome) *13.13*, 18.80, 47.18–19, 62.28, *69.117*
  genetics 13.11
  immunodeficiency and 17.67–8
  necrobiosis lipoidica and 60.15
  respiratory tract involvement 62.80
atazanavir, HIV infection 35.6
atenolol 46.45, 75.91
Atherix 38.6
atherogenesis 46.6
atheroma, abdominal/limb vessels 47.52
atheromatous plaques 47.1
atherosclerosis 49.36
  arterial ulceration 47.52
  inhibition, β_2-GPI role 49.41
  lipoproteins and 59.83
  lower limb vessels 47.2
  pathogenesis 47.1–2
atherosclerotic plaques 49.36
athlete's foot *see* tinea pedis
athlete's nodules 28.31
ATLL *see* adult T-cell leukaemia–lymphoma (ATLL)
ATM gene mutations 47.18
atopic blepharoconjunctivitis (ABC), clinical features *67.13*
atopic dermatitis (AD) **24.1–34**
  acne incidence and 42.18
  acquired melanocytic naevi number 54.15
  in adolescence 8.7
  β-adrenergic blockade theory 24.15
  adult phase 24.21
  aetiology 24.3–10, 24.19
  allergic contact dermatitis and 24.22, 26.7, 26.13–14
  allergy and 24.10–12, 24.30–1
  alopecia areata and 24.23
  in animals 2.12, 2.13–14
  antimicrobial peptide expression reduced 3.16
  associated disorders 24.22–3
  atopic eye disease management and 67.16
  atopy and 24.1, 24.22
  barrier function of skin 4.2, 24.4
  canine 2.7
  childhood 8.3
    concordance with therapy 72.6
    quality of life assessment 72.23
  childhood phase 24.20–1
  clinical features 24.19–22
  clinical trials and generalization of results *6.4*
  complications 24.23–5
  costs (UK and USA) 6.5
  definition 24.1–2
  diagnosis 24.2, 24.26
  differential diagnosis 17.30, 24.26–7, 26.29
    actinic prurigo vs 29.14
    non-atopic dermatitis vs 24.1
  dry skin and 24.22
  ear 68.14, 68.23
  elderly people 8.28
  environmental factors 24.5–6
  eyelids 23.11
  female genitalia 71.58
  filaggrin in 4.2
  food allergy and 24.23
  genetics 15.1, 15.2, 15.10, 24.3–4
  growth delay and 24.24
  hands 23.14, 24.21–2
  herpes simplex and 33.35–6
    see also eczema herpeticum
  HIV infection 35.16, 35.45
  house-dust mites and 38.47
  hygiene hypothesis 24.5–6, 24.7
  IgE in 24.3, 24.4, 24.5, 24.8–9
  IL-18 gene variations 33.35
  immune function and 24.6–10, 24.13–15
  immunodeficiency and 17.53
  infantile phase 24.19–20
  infantile seborrhoeic dermatitis and 24.22
  infection and 24.12–13, 24.24
  interleukins and 21.5
  intrauterine factors 24.5
  investigations 24.27–8
  light-exacerbated, differential diagnosis 29.12
  Malassezia and 24.11, 36.13
  male genitalia 71.18
  mast cell role 3.20
  maternal factors 24.4
  mechanical injury 28.14
  menstrual cycle and 24.19
  migration and 24.2–3
  molluscum contagiosum with 33.11, 33.12
  mouse model 2.8, 2.14
  nail involvement 65.28–9
  natural history and prognosis 24.25–6
  neurogenic inflammation 12.63
  neuropeptides in 24.17
  nipple and areola 70.9–10
  occupation and 24.33–4
  ocular abnormalities in 24.24–5
  pathogenesis 24.10–19
  photosensitivity and 24.21
  pregnancy and 8.12, 24.19
  prevalence 23.3, 24.2–3
  prevention 24.33–4
  pruritus in 21.13–14, 24.17–18
  psychological factors associated 64.4, 64.9
  psychological factors in aetiology 24.19
  psychological morbidity 24.23–4
  quality of life assessment 64.10, 72.20, 72.23–4
  race and 9.13
  severity assessment 64.10, 72.9–10
  short stature and 8.3
  soap avoidance/use 73.31
  Staphylococcus aureus and 24.8, 24.10, 24.12, 30.7, 30.8–9
  stress 12.63
  support groups 72.23
  sweat in 44.6
  sweating and 24.18–19
  terminology 24.1–2
  treatment 21.13, 24.28–33
    caffeine cream 73.49
    ciclosporin 74.16
    holistic, in adolescence 8.7
    immunomodulators 73.31, 73.32
    methotrexate 74.18–19
    tacrolimus 73.31
    topical sodium cromoglycate 73.51
  trigger factors and their reduction 24.28–9
  unresponsive 24.30
  urticaria and 24.23
  vascular abnormalities 24.15–17
atopic eczema *see* atopic dermatitis (AD)
atopic eye disease 67.13–16
  description and epidemiology 67.13, 67.15
  diagnosis 67.15
  immunopathogenesis 67.15
  management 67.15–16
    atopic dermatitis and 67.16
atopic keratoconjunctivitis (AKC) *67.13*, *67.14*, 67.15, 67.16
  clinical features *67.13*
  ocular mucous membrane pemphigoid vs 67.20
atopy
  allergic contact dermatitis and 26.7
  alopecia areata and 66.31
  atopic dermatitis and 24.1, 24.22
  dermatophytosis and 36.21
  genetics 15.6
  hygiene hypothesis 24.5–6, 24.7
  irritant contact dermatitis and 25.7
  occupation and 27.2
  patch test 23.37
  perioral dermatitis and 43.11
  sarcoidosis and 61.6
atorvastatin 75.157
ATP2A2 gene, mutations in Darier's disease 39.32, 39.33
ATP2C1 gene
  expression 39.33
  mutations in Hailey–Hailey disease 39.1, 39.32, 39.33
    segmental Hailey–Hailey disease 39.37
atranol 26.77
Atrax 38.31
atrial myxoma 49.37
  cutaneous lentiginosis with 58.14
  see also myxoma, cardiac
atrial natriuretic peptide 63.3
atrichia congenita 66.59–60
atrichial sweat glands *see* eccrine sweat glands
atrophic parapsoriasis 57.58
atrophic polychondritis *see* relapsing polychondritis
atrophic vulvovaginitis 8.20
atrophie blanche 15.13, 23.35, 47.34, 49.44
atrophoderma
  follicular **15.83,** 45.7–8, 52.8–9, 62.29
  linear of Moulin 18.26
  skin biopsy 10.42–3
  vermiculate 45.8, 66.51
atrophoderma of Pasini and Pierini 45.8–9, 51.64, 51.69, 58.26
  morphoea and 51.78
  progression to systemic sclerosis 51.106
atrophoderma reticulatum 45.8, 66.51
atrophoderma vermiculata 45.8, 66.51
atrophy
  corticosteroid-induced 73.17–18, 73.31
  tacrolimus and pimecrolimus safety 73.31
atrophy, cutaneous **45.2–14**
  corticosteroid-induced 45.3–4
  definition 5.7, 45.2
  generalized 45.2–6
  honeycomb (atrophoderma vermiculata) 45.8, 66.51
  localized 45.6–13
  macular *see* anetoderma
  in onchocerciasis 37.5, *37.6*
  with rheumatoid disease 45.3
  varioliform 45.7
atropine, in hyperhidrosis 3.12, 44.12
attributable risk 6.18
atypical decubitus fibroplasia 56.5–6
atypical facial dysmorphism 16.7
atypical fibroxanthoma **56.20–2,** 68.34, 79.18
atypical lipomatous tumour 56.58
atypical mole syndrome 54.28, 54.31–2
  melanoma risk 54.34, 54.47
atypical spitzoid tumour of unknown malignant potential (STUMPs) 54.21, 54.24, 54.39
Auchmeromyia 38.8
auramine–rhodamine stain 10.10
auranofin 74.29–30
auricle *see* pinna
auriculotemporal syndrome 44.10, 44.11, 63.22
Auspitz's sign 5.18
  psoriasis 20.11
Australian blackwood *26.80*
Australian silky oak *26.81*
Austroconops 38.6
autoantibodies
  BP230 and BP180 40.42
  in bullous pemphigoid 40.30
  desmocollins 40.6
  detection 13.19–22
  in epidermolysis bullosa acquisita 40.52
  IgG 40.26, 40.30, 40.42, 40.47, 40.52
  in leprosy 32.7
  in lichen planus pemphigoides 41.21
  in mucous membrane pemphigoid 40.36
  organ-specific 13.21
  in pemphigus 40.8
  in SLE 51.29
  in thromboangiitis obliterans 47.7
  transplacental transfer 17.15–19
  type IV collagen (α3 chain) 3.27
  in urticaria 13.21–2, 22.9
  see also specific autoantibodies
autoantigen complementarity hypothesis, in vasculitis 50.6
autoantigens, desmosomes as 3.22
autoeczematization 23.5, 26.21
autoerythrocyte sensitization syndrome 49.16, 50.54, 64.33–4
autofluorescence 10.14
autoimmune acanthosis nigricans 19.120
autoimmune adrenalitis 62.5
autoimmune blistering disorders
  type VII collagen as autoantigen 3.36
  see also pemphigus
autoimmune conditions, adrenalitis 62.5
autoimmune disease-associated reactive haemophagocytic lymphohistiocytosis 49.6
autoimmune disorders 13.14–15
  acquired generalized lipodystrophy (AGL) with 46.38
  adiponectin elevation 46.4
  alopecia areata as 66.31–2
  hepatitis C virus infection and 62.60
  leg ulceration 47.55
  lichen sclerosus and 51.113
  lipoatrophic panniculitis and 46.15
  lipomembranous fat necrosis and 46.22
  lobular panniculitis and 46.14
  in pregnancy *8.11*, 8.12
  urticaria and 22.2, 22.9
  vitiligo as 58.46
autoimmune lymphoproliferative syndrome 17.65–6
autoimmune panniculitis 46.15
autoimmune polyendocrinopathy syndrome, type I 15.31
autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy syndrome 15.31
autoimmune polyglandular (polyendocrine) syndrome (APECED syndrome) *13.13*, 15.31, 36.64, 62.12–14
autoimmune progesterone dermatitis 8.9, 8.15, 8.19, 75.119
autoimmune thrombocytopenic purpura *see* idiopathic thrombocytopenic purpura (ITP)
autoimmunity, Degos' disease 49.45
autologous serum skin test 22.9
automobile industry, occupational hazards 5.6, 27.18
autonomic dysreflexia, following spinal cord injury 63.17
autonomic functions of skin 4.9–10
autonomic nervous system 4.9–10, 63.1, 63.3–4
  role in flushing 43.14
autonomic neuropathy 44.7
autoreactivity, urticaria and 22.2
autosensitization 23.5
autosomal dominant dyskeratosis congenita 15.36, **15.78–80**
autosomal dominant hypohidrotic ectodermal dysplasia 15.43, **15.58–60**
autosomal dominant ichthyosis (ichthyosis vulgaris) *see* ichthyosis vulgaris
autosomal dominant (AD) inheritance *15.2*, 15.5
autosomal dominant lamellar ichthyosis 19.23–4
autosomal dominant xeroderma pigmentosum 15.73

autosomal genes
  chromosomal abnormalities 15.10–12
  definition 15.4
autosomal recessive dyskeratosis congenita 15.37, **15.78–80**
autosomal recessive hypohidrotic ectodermal dysplasia 15.43, **15.58–60**
autosomal recessive (AR) inheritance *15.3*
avascular bone necrosis 51.47
avidin 10.17
avidin–biotin method 10.17
avidin–biotin–peroxidase complex method 10.17
AVPR (atypical vascular proliferation after radiotherapy) 56.41–2
axilla
  allergic contact dermatitis 26.18
  bacterial flora 30.4
  hidradenitis suppurativa 30.80, 30.81
  hyperhidrosis 44.7–8, 44.12, 77.36–7
  odour 44.8, 44.19, 44.20
  Paget's disease 53.40–1
  seborrhoeic dermatitis 23.31, *23.32*
  skin biopsy 10.32
  sweat glands 44.1
    apocrine 44.19
axillary freckles **15.16,** 15.17, 15.21
axillary shave 44.20
axillary web syndrome (AWS) 47.31–2, 48.29
axon reflex 63.5
axon reflex response 12.64
ayan *26.80*
azapropazone 75.77
azathioprine 13.24, 72.29, 74.14–16
  adverse effects/reactions 13.24, 20.42, *26.46*, 72.29, **75.128–9**
  in allergic contact dermatitis 26.102
  in atopic dermatitis 24.31
  clinical indications 74.15
  complications of treatment 74.15
  contraindications 74.15
  in cytophagic histiocytic panniculitis 46.24
  in dermatomyositis 51.129
  in leprosy reactions 32.18
  in linear IgA disease 40.51
  long-term risk of malignancy 51.62
  Merkel cell carcinoma association 53.42
  in pemphigus 40.12, 40.16, 74.15
  plus prednisolone, SLE 51.61
  in polymorphic light eruption 29.12
  in sarcoidosis 61.21
  in systemic lupus erythematosus 74.15
  in systemic sclerosis 51.108
azelaic acid 73.13, **73.28**
  adverse effects 42.49
  melasma treatment 73.28
  topical, acne treatment 42.39, 42.43
azidothymidine (AZT) *see* zidovudine
azithromycin *26.46*, 74.42, 75.58
  acne vulgaris treatment 42.47
  in atopic eye disease 67.16
  in genital chlamydial infections 34.31
  in granuloma inguinale 34.37
  in lymphogranuloma venereum 34.33
  in rosacea 43.6
  syphilis management 34.22, 34.24
azo dyes 26.26, 75.158
azoles 74.47
azone 73.7
AZT *see* zidovudine
aztreonam 75.51
azul (pinta) 30.63–4
azurocidin 13.4

B
B-cell directed biological therapies 74.9–10
B-cell lymphomas **57.41–51**
  actinic prurigo and 29.14
  EBV association 33.30–1
  in HIV infection 35.41
  primary 57.41–50
    cytogenetic abnormalities, PCMZL/PCFCL/PCLBCL 57.42
    diffuse large B-cell (LBCL) lymphoma 57.47–9
    follicle centre (FCL) lymphoma 57.45–6
    marginal zone (MZL) lymphoma 57.43–5
    staging classification 57.42
    WHO–EORTC classification 57.41
  secondary 57.50–1
    intravascular large B-cell lymphoma 57.50–1
    lymphomatoid granulomatosis 57.51
  WHO–EORTC classification 57.2
  see also lymphoma(s)
B-cell receptors 13.6–7, 17.49
B-cell tumours, EBV association 33.30–1
B lymphocytes 13.6–7, 17.49
  activation 17.50
    polyclonal 35.17
    regulation of 13.10
  affinity maturation 13.10
  ageing effect 8.24
  antigen presentation to 13.9–10, 17.50–1
  as antigen-presenting cells 13.7
  atopic eye disease 67.15
  B1 13.7
  B1a ($CD5^+$) 13.6, 13.7
  B1b ($CD5^-$) 13.7
  B2 13.7
  β_2-GPI antibody production stimulation 49.41
  class switching 13.10
  deficiency 13.9
  development 13.7–8, 17.49
  EBV infection 33.30
  immunogenotyping 10.30
  in lymph nodes 13.8–9
  memory 13.10
  microscopy 10.34
  mucous membrane pemphigoid 67.20
  naïve 13.10
  polyclonal activation, psoriasis in HIV infection 35.17
  in spleen 13.8
  trafficking 13.9
  in Waldeyer's ring 13.9
  in wound healing 14.3
B syndrome 69.37
B19 parvovirus *see* parvovirus B19
Baa bra 70.15
baboon syndrome 26.22, 26.44, 75.36, 75.162
bacillary angiomatosis **30.57,** 38.11, 71.32–3
  ear involvement 68.28
  in HIV infection 35.25, 68.28
  oral involvement 69.79
bacillary peliosis 30.57
Bacillus, in normal skin flora 68.2
Bacillus anthracis 30.40–1
bacillus Calmette–Guérin (BCG) immunization *see* BCG vaccination
Bacillus cereus 30.41
Bacillus oleronius, association with *Demodex* 43.3
Bacillus pyocyaneus see Pseudomonas aeruginosa
Bacillus subtilis 30.41
bacitracin *26.46*
  adverse effects 75.61
  allergic reactions to 73.10
  in impetigo 30.16
  topical, indications 73.10
back, upper, surgical excision in area 77.15
BACTEC system 31.6
bacteria
  adherence 30.5
  aerobic, normal skin flora 30.2, 30.3
  aeromonads 30.59
  anaerobic **30.59–62**
    normal skin flora 30.2, 30.3
  axilla 30.4
  barrier function of skin and 4.5–6, 30.5
  colonization of skin 30.1, 30.2
    hair follicles 42.24
  comedogenesis, role in 42.24
  coryneform (diphtheroid) 30.3, **30.35–40**
  defences against 30.5
  dysgonic fermenters (DF) 30.59
  eugonic fermenters (EF) 30.59
  external auditory meatus 6.2, 30.4
  factors modifying populations 30.3
  flora (normal skin) 30.1, **30.2–6,** 30.35–6, 68.2
    acne aetiology and 42.24
    factors affecting 30.2, 30.3–4
    genera/species 30.2–3
    in HIV infection 35.24
    hydration/dessication affecting 30.3, 30.5
    quantitative studies 30.3
    role 30.4, 30.5
    sampling methods 30.2
    semi- and quantitative data 30.2
    by site 30.4–5
    temporary residents 30.1, 30.2
    transients 30.1
  Gram-negative **30.44–59**
  Gram-positive **30.6–44**
  groin 30.4
  growth inhibition by honey 73.48
  interference 30.5, 30.7
  isolation media 30.2
  nasal vestibule 30.4
  perineum 30.4
  quantitative studies 30.3
  removal, lymphatic vessels 48.5, 48.6
  role 30.4
  sampling 30.2
  spiral **30.62–6**
  strains 30.1
  temporary residents 30.1, 30.2
  toe clefts 30.4
  transients 30.1
  umbilicus 30.4–5, 30.6
  vulva 30.4
bacterial infection **30.1–82**
  in animals 2.11–12, *2.22*
  in atopic dermatitis 24.8, 24.10, 24.12–13, 24.24, 30.7, 30.8–9
  of ears 68.19–20, 68.21
  of eyes 67.26–7
  female genitalia 71.68
  following arthropod bites/stings 38.2, 38.3
  following ear piercing 68.7
  HIV infection and 35.24–8, 35.45
  Kawasaki disease and 50.45
  of lips 69.121
  lymphoedema and 48.12, 48.15
  napkin dermatitis and 17.23
  necrotizing subcutaneous 30.68–9
  neonatal 17.42–6
  of oral cavity 69.77–9
  otitis externa 68.21
  purpura associated 49.20–1
  sarcoidal reaction in 61.22
  secondary, in varicella 33.25
  skin barrier function and 4.5, 30.5
  swimming and diving 28.53–4
  vasculitis and *50.55*
  venous leg ulcers 47.44
  vessel-invasive 49.34–5
  wounds 14.16–17
bacterial overgrowth, malabsorption 51.100
bacterial pseudomycosis (botryomycosis) 30.67–8
bacterid, panniculitic 46.32
bacteriology reports 30.1
Bacteroides 30.60
  in hidradenitis suppurativa 30.80
Bacteroides fragilis 30.59, 30.60
Bactrian camel *66.8*
bad news consultation 72.4–5
BADAS (bowel-associated dermatosis–arthritis syndrome) 50.87–8, 62.51, **62.53**
Bafverstedt's lymphadenosis benigna cutis 57.59
'bag of worms' appearance 56.48
Bailey® nylon monofilament 63.9
Baird–Parker classification system 30.2
Baisch syndrome 15.31
baking, occupational hazards 27.18
balanitis 71.8–9, 71.13, 71.18, **71.19–20,** 71.37–8, 71.40
  Candida 36.62, 36.68
  circinate 34.30, *34.31*, 71.18
  lichen sclerosus and 51.113, 51.116
  Zoon's 71.13, 71.18, **71.19–20**
balanitis xerotica obliterans 51.113, 51.116
  corticosteroids 51.118
balanitis xerotica obliterans (BXO) 71.21
balanoposthitis
  male genitalia 71.9, 71.21, 71.28, 71.34
  non-specific 71.24
  non-syphilitic spirochaetal ulcerative 71.31
baldness
  female pattern 66.16, 66.17–18, 66.20, 66.22, 66.24, 66.25–6
  male pattern *see* alopecia, androgenetic
  premature *see* alopecia, androgenetic
  reversal 66.14–15
  see also alopecia
Baller–Gerold syndrome (BGS) 15.80
ballistometry 4.11
balloon dilatation *see* angioplasty
ballooning degeneration 10.38
  herpes simplex 33.16
balm of Gilead 14.21
balsam of Peru
  allergy to 26.18, 26.22, 26.40, 26.41
  contact urticaria and 22.20
  oral provocation tests 5.25
  as scabicide 38.41
balsam of spruce 26.40
balsam of Tolu 26.40
bandaging
  compression 14.20–1, 38.31, 38.60
  four-layer technique 14.20
  'wet wrap' 73.4
Bannayan–Riley–Ruvalcaba syndrome (Bannayan-Zonana syndrome) 18.60, 62.26, 62.57, 69.38
barbers, occupational hazards 27.19
barber's hair sinuses 28.49
Barber–Say syndrome 70.3
barbiturates, adverse effects 75.80–1
bare lymphocyte syndrome 17.60–1
barium sulphide 73.29
barley, as irritant 25.21
barley itch 38.48
Barmah Forest virus *33.67*, 33.67–8
Barraquer–Simons disease 46.39–40
barrier creams 23.21, 25.25, 27.9
barrier function of skin 3.2–3, **3.10–12,** 4.1, **4.2–4,** *4.3*
  in atopic dermatitis 4.2, 24.4
  bacterial infection and 4.5, 30.5
  fungal infection and 4.5
  irritant contact dermatitis and 25.2–3
  measurement 72.11
  microorganisms and 4.5
  neonatal 17.1–2
  percutaneous absorption and 4.4–5
  sebaceous lipids and 42.6–7
  temperature regulation and 4.7
  ultraviolet radiation and 4.6–7
bartenders, occupational hazards 27.18
Bartholin's duct, tumours 71.73
Bartholin's gland, abscesses 71.68
Bartonella **30.56–8**
  vectors 38.5, 38.11
Bartonella bacilliformis 30.58
  in HIV infection 35.25
Bartonella elizabethae 30.56

Bartonella henselae 38.11, 61.5
in bacillary angiomatosis 30.57
in cat scratch disease 30.56–7
in HIV infection 35.25
staining 10.10
Bartonella quintana 30.56, 30.57
Bart–Pumphrey syndrome 19.108–9
Bart's syndrome 18.101, 39.17, 39.18, **39.22**
basal cell(s)
in basal cell carcinoma 52.20
follicular atrophoderma and 52.8–9
basal cell carcinoma (BCC) 52.2, **52.18–22**
advanced, features 52.19
aetiology 52.18–19
after chemotherapy 75.124
aggressive, in naevoid basal cell carcinoma syndrome 52.7
in animals 2.20
arsenic-induced 52.20
atypical 52.19
basisquamous 52.22–3
burns 28.91
chemical carcinogens 52.4–5
clinical course and natural history 52.20, 52.21
clinical features 52.19–20
as colostomy complication 62.54
cytodiagnosis 10.29
definition 52.18
development in BCG scar 31.29
diagnosis 52.21
differential diagnosis 52.21
Bowen's disease vs 52.33–4
desmoplastic trichoepithelioma vs 53.9
microcystic adnexal carcinoma vs 53.35
sebaceous carcinoma vs 53.19
dissemination/metastases 52.20
early
features 52.19
pathology 52.20–1
ears 68.32–3, 79.9, *79.10, 79.17*
with eccrine differentiation 53.36
elderly people *8.28*
ethnic factors associated 52.18–19
eyelids *67.10*, 67.34–5, *79.9*
face 79.10, *79.11*
familial syndromes 52.6–9
gene deletion 53.8
see also naevoid basal cell carcinoma syndrome
female genitalia 71.66, 71.77
genetics 11.18, 52.19
growth 52.20, 52.21
head and neck 52.20
histogenesis 52.19
HIV infection and 35.39
HPV infection and 52.6, 52.14
incidence 52.2, 52.18–19
infiltrative, microcystic adnexal carcinoma vs 53.35
inflammatory reaction 52.21
inner canthus *79.9*
invasive 52.19, 52.20, 52.21
loss of heterogeneity events 52.12
lupus vulgaris and 31.18, *31.19*, 31.21
male genitalia 71.48
management principles 52.17
mechanical injury 28.62
melanocyte proliferation in 52.21
metatypical 52.22–3
mitotic figures 52.20
morphoeic/sclerodermiform 52.19–20, 69.54
diagnosis 52.21
treatment 52.22
mortality 52.2
in naevoid basal cell carcinoma syndrome 52.6, 52.7, 52.8
see also naevoid basal cell carcinoma syndrome
nipple/areola 70.15
nodular 69.54
treatment 52.22, 73.24
nose 79.10
over histiocytoma 52.20
p53 gene mutations 52.12
pathology 52.20–1
perianal/perineal 71.98
perioral/lips 69.53–4
prognosis and prognostic factors 52.21–2
PUVA associated 52.4
race and 9.18
radiation-induced 52.5, 79.18
recurrence 52.20, 79.17–18
risk factors 52.18–19
sclerosing
desmoplastic trichoepithelioma vs 53.9
eyelids 67.35
skin damage and 52.19
sporadic, gene deletion 53.8
spread 52.19
squamous cell carcinoma ratio 52.2, 52.26
sun exposure patterns 52.3
sunscreen use and 73.41
superficial 52.20, 52.21, 52.33, 69.54
treatment 73.24
telangiectasia with 52.19
in transplant recipients 62.74–5, 79.13
treatment 52.8, 52.21–2, 78.14, 78.16
aim 52.21
curettage 77.40–1, *77.43*, *77.44*
destructive therapies 52.22
Mohs micrographic surgery *77.30*, 77.32, *77.33*
principles 52.17
radiotherapy 79.5–7, 79.8–12, 79.13
surgery 52.22, 77.15, *77.19*, 79.5
topical 5-FU 73.23
topical imiquimod 73.24
ulcerated 52.19, 52.20, 52.21
UVB phototherapy associated 52.4
UVR exposure and 29.7, 52.3
venous leg ulcers and 47.45–6
see also non-melanoma skin cancer (NMSC)
basal cell naevus syndrome *see* naevoid basal cell carcinoma syndrome
basal cell papilloma *see* seborrhoeic keratosis
basal lamina *see* basement membrane
basalioma *see* basal cell carcinoma (BCC)
basaloid cells
in basaloid follicular hamartoma 53.11–12
in trichoblastoma 53.10
in trichoepithelioma 53.8
Basan syndrome 15.29
basement membrane 3.6, 10.37
components 3.25–6
mechanical injury 28.7
sebaceous cells 42.3
staining 10.8, *10.9*
vascular 3.52
in wound healing 14.5
basement membrane zone (BMZ) **3.25–3.33,** 10.37
adhesion complex 40.1–2, 40.25
antibodies 40.27
collagen type IV 3.25, 3.27
components 3.25–6, *3.32*
structure and domain organization *3.31*
gene/protein systems involved in epidermolysis bullosa 3.26, *3.27*
heparan sulphate proteoglycans 3.29
IgA, IgG, C3 deposits, mucous membrane pemphigoid 67.17
laminins 3.27–9, 3.28
see also laminin-5 (laminin-332)
neutrophils 40.46
subepidermal immunobullous diseases 40.27
ultrastructure 3.25, *3.26*
basic fibroblast growth factor (bFGF)
mechanism of action 58.7
melanocyte mitogen 58.5
pigmentation regulation 58.7
scleroderma-like lesions, and cancer 51.79
basic fuchsin *see* magenta paint
basidiobolomycosis (subcutaneous zygomycosis) 36.78–9
Basidiobolus ranarum 36.78, 36.79
Basidiomycota 36.2, 36.3–4
basidiospores 36.3, 36.89
basidium 36.3
basiliximab 75.146
basisquamous basal cell carcinoma 52.22–3
basophil(s) 12.20, 13.5–6
in urticaria 22.5
basophil degranulation test 75.174
bastanido 28.32–3
batbug 38.24
Bateman syndrome 62.80
bath itch 21.10
bath oils 73.31
bathing, in atopic dermatitis 24.29
bathing attendants, occupational hazards 27.18
bathing suit ichthyosis 19.24
Bazex syndrome 45.8, 62.36, 62.48, *66.65*
ear involvement 68.18
in Hodgkin's disease 62.89
nail involvement 65.25
Bazex–Dupré–Christol syndrome (atrophoderma follicular) **15.83,** 45.7–8, 52.8–9, 62.29
Bazin's disease *see* erythema induratum of Bazin
BCG vaccination 31.28
adverse effects 75.139, 75.141
complications 31.6, 31.10, 31.28–9
disseminated 17.58
leprosy and 32.19
mechanical injury 28.62
therapeutic use 31.29
bcl-2 10.25
hair growth and 66.11
bcl-6 10.25
BCNS *see* naevoid basal cell carcinoma syndrome
BCNU *see* carmustine
BDC *see* Bazex–Dupré–Christol syndrome
BDP (Bowen's disease of the penis) 71.38–9
'bean-bag' appearance, histiocytes 46.23–4
Bean's syndrome *see* blue rubber-bleb naevus syndrome
beard
alopecia areata 66.35
ringworm 36.28–9, 36.49
weight, ageing effect 8.23–4
bearded ghoul 38.59
Beare type pili torti 15.50
Beare–Stevenson cutis gyrata syndrome **15.91**
Beare–Stevenson syndrome 18.40
beating injuries 28.32–3
Beau's lines 59.75, 65.10, **65.12–13**
in childhood 65.7
thumbnail 59.75
becaplermin 14.27, 63.10
Beck Depression Inventory 64.23
Becker's naevus **18.17–19,** *62.101*, 66.77, 78.10
with hypomastia 70.3
Becker's naevus syndrome 18.27
Becker's syndrome 58.21
Beckwith–Wiedemann syndrome 18.69–70, 68.5, 68.6
macroglossia in 69.113
bedbugs 38.24
bedsores *see* pressure ulcers
Beer's law 78.3
bees **38.13**
Africanized/'killer' 38.13
hypersensitivity to 22.8, 38.1, 38.3, 38.14–15
pheromones 38.2
venom 38.14
beeswax 26.82, 73.7
beetles 38.26–8
behavioural therapy 64.24, 64.28, 64.32
obesity 46.8
see also cognitive behavioural therapy
Behçet's disease **50.56–62,** 69.46–9
acneiform eruption, acne vs 42.37
aetiology and pathogenesis 50.56–7, 69.47
bone and joint involvement 62.102
clinical features *69.46*, 69.47
definition 50.56
diagnosis *50.58*, 50.60–1, 69.47–448
differential diagnosis 42.37, 69.47
genital involvement 50.58–9
histopathology 50.57–8
Koebner response 28.3–4
male genitalia
female genitalia 71.65
male genitalia 71.24–5, 71.25
neutrophilic eccrine hidradenitis and 44.17
ocular involvement 50.59–60, *67.25*
oral involvement 50.58, *50.59*, 69.44, *69.118*
overlap with other disorders 50.62
perianal/perineal involvement 71.90
renal involvement 62.71
respiratory tract involvement 62.82
skin lesions 50.59
thrombophlebitis migrans in 47.30
TNF antagonists 74.8
treatment 50.61–2, 69.48
vasculitis and 50.3, 50.49, 69.47
Beighton score 45.34
bejel (endemic syphilis) 30.63
beliefs
disorders of 64.12–17
skin and skin disease 64.1–2, 64.6
belimumab 74.10
Bell's palsy 33.19
Bence Jones protein 13.17, 49.32
Beneckea chitinivora 2.12
benign aphthae, female genitalia 71.65–6
benign calcifying epithelioma of Malherbe 53.12–13
benign epidermal tumours **52.38–45**
benign joint hypermobility syndrome 45.34
benign lichenoid keratoses (BLKs) 41.6
benign summer light eruption 29.12
benign tumours 52.1
female genitalia 71.72–4
male genitalia 71.35–7
perianal/perineal 71.83, 71.96
see also specific tumours
bentonite 73.8
benzaldehyde 75.162
benzalkonium chloride 26.17, 26.58, 67.22, 73.14
Benzamycin®, acne vulgaris treatment 42.41
benzathine penicillin G
in non-venereal treponematoses 30.64
syphilis management 34.22, 34.24
benzene *25.19*, 25.20
benzimidazoles 74.50–1
adverse effects 75.71
in dracunculiasis 37.13
in trichomoniasis 37.29
1,2-benzisothiazolin-3-one 26.15, *26.15*, 26.53–4
benznidazole 37.32
benzoates 5.25
benzocaine 26.45
benzodiazepines 75.81
benzoic acid 25.18, *36.47*, 36.48, 36.49
benzophenones 26.23, 26.24, 26.62
photoallergic dermatitis due to 73.40

benzo*(a)*pyrene 27.16
benzopyrone drugs, in lymphoedema 48.25
benzothiazinylalanine *58.6*
benzoyl peroxide (BPO)
  adverse effects 42.49
  antibiotics combined with 42.41, 42.48
  formulations 42.41
  indications 73.13
  as irritant *25.19*, 25.21
  mechanism of action 42.40, 42.41
  topical, acne treatment 42.39–41, 42.41, 42.48, 42.67
benzydamine *26.46*, 75.78
benzyl alcohol 26.58
benzyl benzoate 38.41, 73.14
  in *Demodex* infection in rosacea 43.3
benzyl penicillin *see* penicillin G
Ber-H2 10.25
Berardinella–Seip syndrome 46.37
Berardinelli's syndrome 66.76
BerEP4 53.35
Berloque dermatitis 26.18, 58.32
beryllium reactions 61.22
Besnier's prurigo *see* atopic dermatitis (AD)
bestatin 12.50
Bet v.1 22.20
β-blockers 64.52
  adverse effects 26.17, *26.46*, **75.90–2**
  flushing management 43.6, 43.15
  non-cardioselective 43.6
β-catenin 66.10
β-glucans 36.1
β-haemolytic streptococci *see Streptococcus*
betamethasone dipropionate 73.16
  calcipotriol with 73.45
betamethasone valerate, glaucoma association 73.19
β_2-microglobulin, in sarcoidosis 61.20
beta-rays 79.1–2
bété *26.81*
betel chewing 69.50, 69.96–7
Bethyloidea 38.14
Betta splendens 31.31
bevacizumab, melanoma management 54.54
bexarotene 57.23, 73.35, **73.36–7,** 74.37
bezafibrate 75.31
bezoar 64.31
bezoar by proxy 64.32
bFGF *see* basic fibroblast growth factor (bFGF)
BFS (burning feet syndrome) 63.25
BGS (Baller–Gerold syndrome) 15.80
bias 6.11, 6.18
  information 6.18
  language 7.7
  publication 7.7
  selection 6.18
Bid (BH3-interacting death domain protein) 12.12
bidi 69.90
BIE *see* bullous ichthyosiform erythroderma (BIE)
Bifidobacterium eriksonii 30.75
bifonazole 73.12
  in dermatophytoses 36.50
  in otomycosis 36.17
big foot disease *see* podoconiosis
big leaf mahogany *26.81*
biglycan 45.33
biguanides 75.156
bile acid sequestrants 59.93
bilharziasis *see* schistosomiasis
biliary tract disorders 62.62
bilirubin
  in sarcoidosis 61.8
  skin pigmentation 58.53
bimatoprost *26.46*, *66.79*
bindi 26.10
bio-psycho-social approach 64.49
biocides 27.5, 27.6
  as allergens 26.49–58
bioengineering 4.10–11
bioinformatics 11.8, *11.9*
biological compensation, in actinic keratosis 52.31
biological false-positive reactions (BFP) in syphilis 34.20–1
biological terrorism 33.5, 33.6
biological therapies 74.4–13
  B-cell directed 74.9–10
  cytokine-directed 74.10–11
  interactions 72.29
  in melanoma 54.53–4
  naming conventions 74.5
  psoriasis 20.41–2, 72.14, 74.10
  in psoriatic arthritis 20.59
  recombinant proteins 74.4–5
  targeting tumour necrosis factor 74.5–6
biomarkers
  lymphatic vessels 48.4–5, 48.19
  melanoma 54.51
biostatistics 6.20
biotin 10.17, 59.64
biotinidase deficiency 59.64–5
Bipolaris 36.77
Birbeck granules 3.18, 55.3–4, *55.7*
  electron microscopy 10.30
  lacking from indeterminate cells 55.3
  in Langerhans' cell histiocytosis cells 55.6, 55.7, *55.7*
  staining for 55.9
  structure and antigens 55.3–4
birch 26.105
birds
  aquatic, white colour 2.6
  glands 2.4
  mites 38.51–2
  pigment cells 2.6
  skin 2.3
birth weight 17.1
birthmarks
  simulation 64.42–3
  see also individual birthmark types
Birt–Hogg–Dubé syndrome 53.14, 53.15, 62.57, 62.69
bis(4-amino-3-methylcyclohexyl) methane *27.17*
bismuth subsalicylate 75.157
bismuthia, pigmentation in 58.55
bisphosphonates 75.99
BIT (1,2-benzisothiazolin-3-one) 26.15, *26.15*, 26.53–4
bite marks, child abuse 28.34, 28.35
bitemporal aplasia cutis 15.40, **15.83–4**
bitemporal forceps marks syndrome 15.40
bites
  arthropod 38.1–5
  cat 38.60–1
  dog 38.60–1
  human 38.61
    child abuse 28.34, 28.35
  rodent 38.61
  seal 38.61
  snake 38.60
bithionol 26.24
Bittner's syndrome 33.59
Björnstad's syndrome 66.64, *66.65*
BK mole syndrome 54.28, *62.20*, 62.21–2
BKH-S surveillance system 27.2
black blowflies 38.8
black death 30.55
black dermographism **28.92–3**
  mechanical injury 28.26
black heel 28.16, 28.31, 49.16
black palm 28.16, 28.31
black people, sarcoidosis 61.15–16
black-widow spider 38.31
blackflies 37.4, 38.5–6, 38.7
blackheads 42.22, 42.24, 42.30, *42.77*
bladder, carcinoma 31.29
BLAISE (Blaschkitis, adult) 18.26–7
Blandford fly 38.5–6, 38.7
Blaps 38.27
Blaschkitis, adult 18.26–7
Blaschko's lines 15.6, *15.7*, 18.2, **18.4**
blastic NK-cell lymphoma 57.39
blastoconidia 36.16
Blastomyces dermatitidis 36.83–5
Blastomycetes 36.4
blastomycosis **36.83–5**
  aetiology 36.83
  bone and joint involvement *62.100*
  clinical features 36.84
  definition 36.83
  differential diagnosis 31.10, 36.84
  disseminated 36.84
  histology 36.83–4
  keloidal (lobomycosis) **36.77–8**
  laboratory diagnosis 36.84–5
  male genital dermatology 71.32
  oral involvement 69.80, *69.118*, 69.121
  perianal/perineal 71.96
  primary cutaneous 36.84
  pulmonary 36.84
  South American *see* paracoccidioidomycosis
  treatment 36.85
Blatella 38.28
Blatta 38.28
Blau syndrome 45.46, 60.4, 61.16, 62.104
  mutations in NOD2 12.12
bleaches
  burns *25.11*
  as irritants 25.21
  skin 9.8
bleaching, of skin 73.27
bleeding
  causes/abnormalities causing 49.6
  in Hermansky–Pudlak syndrome 58.41
  in idiopathic thrombocytopenic purpura 49.10
  intraoperative/postoperative *77.8*, 77.9, 77.50
  neonates 49.49
    see also neonatal purpura
  occult, tests 49.5
  in thrombocytosis 49.5, 49.14
bleeding time 49.5–6
Blegvad–Haxthausen syndrome 45.17
bleomycin
  adverse effects 75.126–7
    purpura 75.23
    scleroderma *27.17*, 45.52
  intralesional
    administration method 33.50
    adverse effects 33.50
    wart treatment 33.50
  scleroderma-like changes 51.81
  topical 73.23
blepharitis *67.4*
  acute 67.6, *67.11*
  associated conditions *67.7*
  chronic 67.6–12
    causes *67.10*
    epidemiology 67.6
    immunopathogenesis 67.6, 67.11
    treatment 67.11, *67.12*
  classification 67.6, *67.7*
  follicle mite infection and 38.53
  management 67.22
  Phthirus pubis causing *67.10*
  seborrhoeic *67.7*
  in seborrhoeic dermatitis 23.31
  staphylococcal 30.32, 67.6, *67.7*, *67.8*, 67.11
    atopic eye disease with 67.16
    clinical features *67.7*
    treatment 67.11, 67.16
  streptococcal 30.32
  terminology problems 67.6
  ulcerative *67.8*
blepharochalasis **45.20–1,** 45.33, 48.23–4, *67.4*, 67.5
blepharocheilodontic syndrome 15.31
blepharoconjunctivitis
  atopic *67.13*
  HSV 67.26
blepharophyma 43.9
blind loop syndrome 44.20, 50.87–8, 62.51, **62.53**
blinded trials 7.7
blindness, mucous membrane pemphigoid 67.17, *67.18*
blinking 67.3
blister beetles 38.2, 38.26
blistering, acute drug-induced phototoxicity 29.21
blistering agents, response in ageing skin 8.23
blistering disorders, genetic *see* hereditary blistering disorders
blisters
  after cryotherapy for warts 33.49
  cold-induced injury 28.64
  formation 39.1, *39.3*, 40.29
  friction 28.2, 28.9, **28.12–13,** 28.28, 28.30–1
  gingival 69.14
  during intensive care 28.39
  oral mucosa 69.22
  sucking 17.4
  suction 28.23–4
  transillumination 17.14
  see also bullae
BLM (Bloom's syndrome) **15.76–7,** 62.27
Bloch–Siemens syndrome *see* incontinentia pigmenti (IP)
Bloch–Sulzberger syndrome *see* incontinentia pigmenti (IP)
blood
  extravasated 49.2
  fetal sampling 17.12
  increased intravascular, in skin 49.2
blood flow
  control, in capillaries 3.51
  in obesity 8.17
blood pressure, claudication management 47.5
blood samples, viral infection diagnosis 33.4–5
  two samples, timing 33.5
blood supply, skin 3.2, 3.3, **3.50–2**
blood transfusion
  adverse effects 75.154–5
  CMV transmission 33.29
  in dystrophic EB 39.29
  intrauterine 17.12
  syphilis transmission 34.5
blood urea nitrogen monitoring, burns 28.84
blood vessels **3.50–2**
  abnormal, purpura due to 49.14–15
  classification *47.13*
  decreased support of, purpura due to 49.14–15
  remodelling 47.1
  thermoregulatory role 3.50–1
Bloom–Richardson method 53.22
Bloom's syndrome (BLM) **15.76–7,** 62.27
  genetics **15.76–7**
blowflies 38.8
blue-ringed octopus 38.59
blue rubber-bleb naevus syndrome 18.72–3
  hyperhidrosis and 44.9
  iron deficiency anaemia in 62.85
  oral involvement 69.30
blue scrotum sign 62.65
blue toe syndrome 49.36
blueberry muffin baby 17.32–3, 49.20, 49.51
'blueberry muffin' lesions 33.29
bluebottle 38.8
blushing *see* flushing
BMP-2 49.47
BMP-4, in lichen planus 41.2
Bockenheimer's syndrome 47.24
body asymmetry 63.14
body composition 3.52
body dysmorphic disorder 42.60, **64.17–20,** 64.48
  acne and 42.60, 42.71
  male genitalia 71.51–2
  perianal/perineal dermatology 71.99
body image 1.1

body mass index (BMI) 8.16, 46.5
  criticisms over and advantages 46.5
body odour 44.19
  abnormal 44.19–20
  in adolescence 8.6, 8.7
  axillary 30.4, 44.8, 44.19, 44.20
  false beliefs 64.16
  production 44.2
body piercing 58.57
  allergic contact dermatitis and 26.10
  ear 68.7–9
    complications 26.17, 61.23, 68.7–8
  nipple 70.11
  oral tissue 69.96
  ornamental 28.51–2
body site, effect on mechanical injury 28.8
body surface area, percentages 76.20
body temperature
  limb, erythromelalgia 47.9
  monitoring, burns 28.83
  regulation *see* thermoregulation
boil (furuncle) **30.23–4**
Bolivian haemorrhagic fever 33.69
Bombay blackwood *26.80*
bombesin 4.10
Bombidae *see* bees
Bombus see bees
bone
  disorders **62.99–106**
  fracture 62.99
  mineralization, inhibitors 49.48
  overgrowth, McCune–Albright syndrome 58.18
bone involvement (in)
  congenital syphilis 34.16
  dystrophic EB 39.29
  Erdheim–Chester disease 55.18
  Langerhans' cell histiocytosis (LCH) 55.12
  malignant histiocytosis 55.32
  McCune–Albright syndrome 58.18
  multicentric reticulohistiocytosis 55.23
  sarcoidosis 61.6–7, *61.11*, 62.104
  systemic sclerosis 51.97
  venous leg ulcers 47.46
  xanthoma disseminatum 55.21
bone marrow
  B cell development 13.7–8
  failure, Fanconi's anaemia 58.17
  in Langerhans' cell histiocytosis (LCH) 55.11
  in mastocytosis 22.30, 22.31, 22.32, 22.33, 22.34
  transplantation
    familial haemophagocytic lymphohistiocytosis 55.26
    oral complications 69.82–3
    see also haematopoietic stem cell(s), transplantation
bone marrow aplasia, chloramphenicol 74.43
bone marrow diseases, secondary thrombocytopenia due to 49.11–12
bone morphogenetic proteins 3.3, 3.4, 3.7, 66.10
  BMP-2 49.47
  BMP-4, in lichen planus 41.2
Bonnet–Dechaume–Blanc syndrome 18.62
book dysplasia 15.31
bookbinders, occupational hazards 27.18
Böök's syndrome 66.93
boot, inflatable 48.23
BOR syndrome (branchio-oto-renal syndrome) 18.83, 18.85, 18.90, 68.3
Boraginaceae *26.80*
borax 75.163
boric acid 75.163
Bork syndrome 15.56
Borrelia 30.64
  male genital dermatology 71.22
  morphoea and 45.10
Borrelia afzelii 45.9–10, 62.106
Borrelia balanitidis 34.4
Borrelia burgdorferi 30.64–6, 45.9, 62.106
  antibodies in morphoea 51.65
  female genital dermatology 71.62
  nodular panniculitis 46.14
Borrelia duttoni 30.64
Borrelia garinii 62.106
Borrelia gracilis 34.4
Borrelia hermsi 30.64
Borrelia lonestari 38.35
Borrelia persica 38.35
Borrelia recurrentis 30.64
Borrelia refringens 34.4
Borrelia vincentii 26.46
Borst–Jadassohn phenomenon 53.23
  appearance in Bowen's disease 52.33
bortezomib 50.17, 50.49, 75.133
bosentan, cold-induced injury 28.70
Boston eruption 33.73
botryomycosis 30.67–8
botulinum toxin
  adverse effects 80.7
    ocular *67.32*
  in chromhidrosis 44.21
  cosmetic use 80.7–9
    combination treatments 80.7–8
  in genital osmidrosis 44.20
  in gustatory sweating 44.10, 44.11, 63.23
  in Hailey–Hailey disease 39.36
  in hyperhidrosis 44.11, 77.36, 77.37
  mode of action 80.7
  in notalgia paraesthetica 63.23
  products available *80.7*
  in thelalgia 70.11
  type A (BTX-A) 80.7
  type B (BTX-B) 80.7
bouba *see* yaws
Bouchard's nodes 45.70
Bourneville's disease *see* tuberous sclerosis complex
bouton d'orient (Old World cutaneous leishmaniasis) **37.34–9**
boutonneuse fever (tick typhus) 38.35
bovine papillomaviruses (BPV) 2.21
Bowdichia nitida 26.80
bowel-associated dermatosis–arthritis syndrome 44.20, 50.87–8, 62.51, **62.53**
bowel bypass syndrome 44.20, 50.87–8, 62.51, **62.53**
Bowenoid actinic keratosis 52.31
Bowenoid papulosis 71.38–9, 71.74
  of genitalia 52.37
    male genitalia 71.38–9
  HPV and 33.54–5
  treatment 73.23
Bowen's disease 52.2, 52.12, **52.32–4**
  aetiology 52.32
  arsenic exposure and 52.32, 52.33, 52.35
  clinical features 52.32–3
  definition and incidence 52.32
  diagnosis 52.33–4
  differential diagnosis
    extramammary Paget's disease vs 53.41
    HPV infection vs 33.55
  epidermodysplasia verruciformis and 33.57
  HPV-2 infection 33.55
  internal malignancy and 62.47
  invasive carcinoma in 52.33
  palmoplantar 52.5
  pathology 52.33
  of penis 52.36
  progression to invasive SCC 52.29
  recurrences 52.34
  squamous cell carcinoma arising in 52.27
  treatment 52.34, 78.14, 78.16
    curettage 77.41
    radiotherapy 79.12
    topical 5-FU 73.23
    topical imiquimod 73.24
  vulval 71.74
Bowen's disease of the penis (BDP) 71.38–9
box jellyfish 38.56, 38.57
BP180 NC16a 8.14
BP230 and BP180 *see* bullous pemphigoid antigens
BPAG1 (bullous pemphigoid antigens, BP230) *see* bullous pemphigoid antigens, BP230 (BPAG1)
BPAG2 *see* bullous pemphigoid antigens, BP180 (BPAG2; type XVII collagen); collagen, type XVII
BPAG2 gene mutations 3.31
brachial valve transplant 47.51
Brachycera 38.6–8
brachymetapody–anodontiahypotrichosis–albinoidism 15.31
Brachypelma smithi 38.30
brachytherapy, interstitial 79.2, 79.5
Braden system of risk assessment 28.20, *28.21*
bradykinin 13.4
  in angio-oedema 22.5, 22.21
  pruritus and 21.5
brain
  lesions, hyperhidrosis associated 44.7
  melanoma metastases 54.54, 54.55
  thermosensitive receptors 44.5
  tumour, pruritus associated 62.34
branchial arches, complex defects of first and second 18.80–7
branchial (cleft) cyst 18.85–6
branchio-oto-costal syndrome 18.85
branchio-oto-renal syndrome 18.83, 18.85, 18.90, 68.3
Branham's sign 47.21
Brassica 25.21
Brauer syndrome 15.40
Brauer–Buschke–Fischer keratoderma 19.95, 19.112–13
Brazil, prevalence of skin disease *6.9*
Brazilian pemphigus foliaceus 40.17–18
Brazilian rosewood *26.81*
breast **70.1–17**
  abscess 8.13, 70.10, 70.13, 70.15
    neonatal 17.43
  aplasia/hypoplasia 70.2, 70.3, 70.6, *70.7*
  artefactual disease 70.11
  cancer *see* breast cancer
  Carney complex 70.17
  Cowden's syndrome 70.17
  cutaneous larva migrans 70.17
  development 8.4, 70.1
  diffuse dermal angiomatosis 70.17
  duct ectasia/periductal mastitis complex 70.8
  enlargement, in pregnancy 8.9
  in Fox–Fordyce disease 70.17
  granular parakeratosis 70.17
  hair sinus 70.15
  hidradenitis suppurativa 70.17
  hypertrophy 70.3
  isolated enlargement 8.5
  lichen sclerosus et atrophicus 70.17
  lupus panniculitis 70.12
  lymphoedema 48.8, 48.17, 48.20
    management 48.23
  mammary duct fistula 70.13
  in menopause 8.19
  neurofibromatosis 70.17
  pityriasis rosea 70.17
  in pregnancy 70.1
  psoriasis 70.17
  pyoderma gangrenosum 50.70, 70.11
  roustabout's 70.15
  sarcoidosis 70.12, 70.14
  scabies 70.17
  seborrhoeic warts 70.15, *70.16*
  silicone implants 51.82, 51.90, 51.111
    autoimmune disease and 70.7–8
  supernumerary (accessory) 70.2–3
  telangiectasia 70.13
  vasculitis 70.11
  vitiligo 70.17
breast bud 8.4
breast cancer 62.15, 62.16, 70.13–14
  apocrine, apocrine carcinoma vs 53.21
  basal cell carcinoma 70.15
  carcinoma erysipeloides 48.31
  grading, Bloom–Richardson method 53.22
  inflammatory 48.31
  in Klinefelter's syndrome 70.4
  lymphoedema associated 48.8, 48.17, 48.20
  male 70.14, *70.15*
  melanoma 70.14, 70.15
  metastases from 70.14
  minoxidil use in 73.50
  Mondor's disease and 70.16
  mucinous, mucinous adnexal carcinoma vs 53.36
  Paget's disease of nipple and 53.38, 53.39
  in Peutz–Jeghers syndrome 58.13
  radiotherapy, syringoma association 53.25
breastfed infants, zinc deficiency 59.73–4
breastfeeding
  atopic dermatitis and 8.12, 24.34
  cracked nipples 70.10
  gonorrhoea management *34.28*
  immunity and 13.15
  prednisolone and 40.45
  scabicides and 38.42
  transfer of toxic substances 17.19
breathing exercises, lymphoedema management 48.23
Breslow thickness, melanoma 54.49, 54.52
Brevibacterium 30.3, 30.35, 30.36
  in normal skin flora 30.2, 30.3, 30.36, 68.2
  toe clefts 30.4
Brevibacterium epidermis 30.3
Brevibacterium mcbrellneri 30.3, 36.16
brilliant green dye, topical therapy 73.48
brilliantine 27.13, 27.14
Brill–Zinsser disease 30.73
brimonidine *26.46*
Brindle coat colour *2.5*, 2.7
British Association of Dermatologists 72.14
British National Formulary (BNF), topical corticosteroids 73.16
British Photodermatology Group (BPG) 29.2
British Red Cross, cosmetic camouflage 43.6
broad thumb–hallux syndrome **15.92–3**
Brocq, pigmented peribuccal pigmentation of 58.35–6
Broders' classification 52.26
bromhidrosis 8.7, **44.19–20**
bromides, acneiform eruption due to 42.73
bromism 75.152
2-bromo-2-nitropropane-1,3-diol *26.50*, 26.52
1-bromo-3-chlor-5,5-dimethylhydantoin 75.163
bromocriptine
  adverse effects 75.88
  in gigantomastia 70.3
bromodeoxyuridine 75.133
bromoderma 75.21, 75.152
bromoderma tuberosum 75.152
bromofluorene 76.5
bromophenol blue 44.4
bronchial carcinoid tumours 43.18
bronchiolitis, respiratory syncytial virus (RSV) 33.76
bronchogenic (presternal ciliated) cyst 18.87–8
bronze baby syndrome 17.12–13, 58.53
bronze diabetes *see* haemochromatosis
bronzed pigmentation *see* pigmentation
bronzing of skin 58.53
Brooke's tumour *see* trichoepithelioma

Brooke–Spiegler syndrome 53.9, 53.28, 53.29
brown adipocytes 46.1
brown adipose tissue 8.16
  see also brown fat
brown dog tick 38.35
brown fat 3.52, 8.16, 46.1
  hibernoma 46.45
  thermogenic 46.1
brown recluse spider 38.32
brown snakes 38.60
brown-tail moth 38.28, *38.29*
brown-widow spider 38.31
brucella, antigen 5.24
Brucella abortus 30.55
Brucella melitensis 30.55
Brucella suis 30.55, 30.56
brucellosis **30.55–6**
  nodular panniculitis 46.14
  sarcoidal reaction in 61.22
  sweating in 44.7
Bruch's membrane *67.4*
Brugia malayi 37.9–10
Brugia timori 37.9–10
bruises
  child abuse 28.34–6
  differential diagnosis 28.36
bruising *see* ecchymoses/bruising
Brunauer–Fuhs–Siemens syndrome 19.105–6
Brunsting Perry pemphigoid 40.35, 40.39
Brunzell syndrome 46.37
Bruton tyrosine kinase 17.71
Bruton's disease (X-linked agammaglobulinaemia) 13.9, *13.13*, 17.70–1, *69.117*
Brya ebenus *26.80*
Bryant's sign 62.65
Bryozoa (sea mats) 26.10, 38.58
BSCL2 gene 46.37
buba *see* yaws
bubo
  in chancroid 30.47, 34.34, *34.35*
  climatic *see* lymphogranuloma venereum (inguinale)
  in lymphogranuloma venereum 34.33
  in plague 30.55
Bubostomum phlebotomum 37.16
buccal fat-pad herniation 69.110
buccal mucosa
  lichen planus 41.8, 41.9
  pigmentation, Laugier–Hunziker syndrome 58.14
Buckley's syndrome *see* hyper-IgE syndrome
Budd–Chiari syndrome 49.29, 49.30
budesonide 26.45
Buehler test 26.11
Buerger's disease *see* thromboangiitis obliterans
Buerger's sign 47.2, *47.3*
buffalo gnats 38.7
buffalo hump lipohypertrophy 46.41, 46.42
buffalopox 33.8
buffered phosphate solution 27.11–12
bugs (Hemiptera) **38.23–6**
building-related illness 64.26
building trades, occupational hazards 5.*6*, 27.2, 27.3, 27.18
bulbar palsy *69.119*
bulimia nervosa **64.21–2**
  oral manifestations *69.115*
bullae
  arthropod bites inducing 38.3, 38.6
  in bullous impetigo 30.15
  in carbon monoxide poisoning 28.93–4
  in congenital syphilis 34.16
  definition 5.8
  drug-induced 75.37–40
  in drug overdose 75.37
  in epidermolysis bullosa 39.6, 39.7, 39.8, 39.13, 39.14, 39.18
    see also epidermolysis bullosa (EB)
  in Hailey–Hailey disease 39.33
  histopathology 10.37–8
  in incontinentia pigmenti (IP) 58.16
  intraepidermal 10.38
  in otitis externa 68.22
  subepidermal 10.38
  in urticaria 22.5
  see also blisters
bullous dermolysis of the newborn 39.23–4, 39.25
bullous disorders **40.1–62**
  in animals 2.14–15
  childhood *see* linear IgA disease
  in elderly people 8.28
  electron microscopy 10.29
  female genitalia 71.65–7
  herpes simplex in 33.15
  immunopathology 10.18–19
  intraepidermal 40.3–24
  neutrophilic 50.95
  ocular involvement *67.29*
  subepidermal 40.25–62
bullous eruption, measles 33.75
bullous eruptions, fixed drug eruptions, female genitalia 71.66
bullous ichthyosiform erythroderma (BIE) 15.6, 19.3, 19.29–34
  epidermolytic verrucous epidermal naevus and 18.5, 18.7–8
  genetics 15.6
  histopathology 10.39, *10.40*
  naevoid 19.31
  prenatal diagnosis *16.3*, 16.5
  see also ichthyosis bullosa of Siemens; ichthyosis hystrix
bullous impetigo, differential diagnosis 40.50
bullous myringitis 68.24
bullous pemphigoid **40.26–35,** 71.28
  aetiology 40.28
    IgG autoantibodies 40.30
  agents inducing 40.32–3
  amputees 28.29
  in animals 2.14–15
  associated diseases 40.32–3
  autoantibodies 35.19
  BP230 and BP180 40.28, 40.30, 40.36
  carcinoma and 40.32–3
  children, differential diagnosis 40.50
  clinical features 40.31–2
  defined 40.26
  differential diagnosis 40.34
  drug-induced 40.32, 75.38
  elderly people 8.27
  immunizations and 40.32
  immunopathology *10.18*, 10.19
  induced (various agents) 40.32
  ocular features 67.20
  oral involvement *69.65*
  paraneoplastic 62.45
  pathogenesis 40.28
  pathology 40.30
  prognosis 40.34
  renal involvement 62.71
  treatment 40.35
    methotrexate 74.18–19
  UV and PUVA inducing 40.32
bullous pemphigoid antigens 3.30, *3.31*
  antibodies to 39.25
  BP180 (BPAG2; type XVII collagen) 3.36, 3.37, 40.28, 40.30, 40.36
    and ectodomain 40.46
    in junctional EB 39.10, 39.25
    monoclonal antibodies to 39.25
    see also collagen, type XVII
  BP230 (BPAG1) 40.28, 40.30, 40.36
    antibodies to 39.25, 40.42
    desmoplakin and 40.30
bullous pemphigoid-like eruption, orf 33.9
bullous porphyria 59.5–6
  see also porphyria, cutaneous disease
bullous systemic lupus erythematosus 40.56–8
  associated disease 40.57
  clinical features 51.41
  differential diagnosis 40.57
bumblebees *see* bees
bumetanide 75.97
bungarotoxin 38.60
Bungarus candidus 38.60
bunyaviruses, and *Bunyaviridae* *33.3*, 33.66, *33.67*, 33.68, **33.70**
buphthalmos 18.66
bupivacaine 75.153, *77.10*
  in nail biopsy 65.41–2
buprenorphine 75.87
burden of skin disease 6.1, 6.5
  data used in 6.5–6
  developed countries 6.8, *6.9*
  developing countries 6.8, *6.9–10*
  estimating 72.14
Bureau–Barrière syndrome (acro-osteolysis with keratoderma) 19.115
Burkholderia cepacia 30.48
Burkholderia mallei 30.51
Burkholderia pseudomallei 30.50–1
Burkitt's lymphoma 33.30
burn scar carcinomas 28.91
burning feet syndrome 63.25
burning mouth syndrome 26.20, 26.39, 62.85, 69.86–7
burns **28.74–92**
  abuse of the elderly 28.91–2
  applied utensils *28.35*
  area of burn assessment 28.77–9
  assessment in hospital accident department 28.76–7
  chemical 14.1, 25.1, 27.11–12
    clinical features 25.10–11
    management 25.22–3
    neonatal 17.14
  child abuse 28.34, *28.35*, *28.90*, 28.91–2
  cigarette 28.33, 28.34, 28.92
  clinical aspects 28.75–88
  cutaneous sequelae 28.88
  decompression 28.79–80, *28.81–2*
  depth 14.10, 25.10–11
    burn classification 28.75, *28.76–7*, 28.84–5
  differential diagnosis 28.36
  documentation 28.80
  electrical *see* electrical burns
  epidemiology 25.2
  fourth-degree 25.11
  full-thickness 14.10, 14.11, 25.11
  gastrointestinal tract decompression 28.78
  healing 14.10–11
  hypertrophic scarring 28.84, *28.88–9*
  laser 28.90
    Erbium:YAG 53.7
  Lund and Bowder charts 28.77, *28.79*
  malignant neoplasms 28.90–1
  management
    dressings 14.1
    early management 14.11
    first aid and prehospital management 28.75–6
    fluid resuscitation 28.77–8, 28.80–4
    general care 28.86
    immediate wound care 28.78
    pain relief 28.79
    referral/transfer of the patient 28.80, *28.82*
    surgical interventions 28.84–6
    triage 28.80
    wound management 28.84–6
  microwave radiation 28.90
  monitoring response to resuscitation 28.83–4
  oral cavity 69.43, 69.88
  partial-thickness 14.10
    deep 14.10, 25.11
    superficial 14.10, 25.10–11
  pathophysiology 28.74–5
  prevention and epidemiology 28.74
  primary survey 28.75–6
  Pseudomonas aeruginosa infection 30.49, 30.50
  Rule of Nines 28.77, *28.78*
  rule of nines 14.10
  secondary assessment 28.76
  specialized burns units 28.80, *28.82*
  stem cell strategies 28.86–7
  torture injuries 28.33
  triage 28.80
  urine output 28.78
Burow's solution 73.15–16
  in eczema 23.37–8
burrow, definition 5.7
bursa of Fabricius 13.7
bursitis 24.25
Buruli ulcer
  in HIV infection 35.26
  Mycobacterium ulcerans 12.9, 31.6, 31.33–5
Buschke–Löwenstein tumour 33.46, **33.55,** *33.55*, 52.26
  female genitalia 71.76–7
  male genitalia 71.44–6
  perianal/perineal 71.95
  treatment 33.55
Buschke–Ollendorf syndrome 45.50, 45.68
  bone and joint involvement 62.99, *62.100*, *62.102*
  juvenile elastoma and 18.32–3
Buschke's scleroedema 51.79
buserelin 75.117
  in acne vulgaris 42.53
bush dermatitis 26.75
bush tea essential oil, in scabies 38.41
buspirone 64.52
busulfan (busulphan) 69.97, *70.5*, 75.124
  hypermelanosis due to 58.30
butchers
  occupational hazards 25.21, 27.18
  warts 33.47
butenafine 73.12
Buthidae 38.33
buthionine sulphoxime 73.27
Buthus 38.33
buttercup 25.21
butterflies 38.28–30
butterfly itch 38.29
N-butyl-4-chlorsalicylamide 26.24
butyl methoxydibenzoylmethane 26.62, 73.40
butylated hydroxyanisole 22.11, 75.159
butylated hydroxytoluene (BHT) 22.11, 73.6, 75.159
butylhydroxyanisole (BHA) 73.8
butylhydroxytoluene (BHT) 73.8
Bwamba virus *33.67*
BXO (balanitis xerotica obliterans) 71.21
bypass procedures, in lymphoedema 48.25
bystander activation hypothesis, in vasculitis 50.6

C
C1 esterase inhibitor (C1INH) 12.49, 13.3, 13.4
  deficiency *13.13*, 22.1, 22.2, 22.20, 69.107
    acquired 22.22–3
    hereditary angio-oedema and 22.21–2
    kinins and 22.4, 22.5
    screening 13.18, 22.26
C1 inhibitor, decreased, in necrobiotic xanthogranuloma 55.28
C1q, C1r, C1s *see* complement
C2 *see* complement
C3 *see* complement
C3H/HeJ mouse 2.18
C4-binding protein 13.3
  deficiency *13.13*
C5a peptidase 30.11
C8-binding protein 13.4
C-fibres *see* nerves, C fibres
c-Kit 3.21
c-kit mutation 54.4
c-Myc 3.5
  in wound healing 14.4

C-PAN (cutaneous polyarteritis nodosa) **50.37–9**
C-reactive protein (CRP) 12.28, 12.32, 13.4, 13.19
C-type lectins 12.10
C-reactive protein 13.4, 13.19
cabergoline, in restless legs syndrome 63.25
cabinet makers, occupational hazards 26.20, 26.79, 27.18–19
cachectin *see* tumour necrosis factor
cacosmia 64.26
CADASIL 50.47
cadexomer–iodine, in wound cleansing 14.21
cadherins 40.1–2
  adherens junctions 3.23, 40.2
  desmosomal 3.22
  maintaining cell–cell adhesion 40.5
  paraneoplastic pemphigus 40.23
  transmembranous 3.22
Caenorhabditis elegans, genetics 15.1
caeruloplasmin
  elevated levels 49.9
  in occipital horn syndrome 45.39
Caesalpiniaceae *26.80*
café-au-lait macules (CALMs) 15.16–18
café-au-lait spots 62.23, 62.33
  differential diagnosis 54.9
  laser therapy 78.10
  McCune–Albright syndrome 58.18
  neurofibromatosis 58.23
  skin biopsy 10.42
caffeine, topical therapy 73.49
CAGE questionnaire 64.47
CAH *see* congenital adrenal hyperplasia
CAHMR syndrome 15.33
caine mix 68.24
Calabar swelling 37.11
calamine *21.17*, 73.2, 73.8
  in miliaria 44.16
Calammatobacterium granulomatis 34.36
calcaneal petechiae 28.16, 28.31
calcific uraemic arteriolopathy *see* calciphylaxis
calcification
  after acne 42.78
  dystrophic *62.45*
  iatrogenic dystrophic neonatal 17.14
  metastatic *62.45*
    calcifying panniculitis with renal failure 46.16
  osteoma cutis 42.78
  pinnal 59.69, 62.5
  of skin 59.68–70
  small vessel 47.8–9
  subcutaneous 49.47
    venous leg ulcers 47.46
calcifying chondrodysplasia 45.8
calcifying fibrous tumour/pseudotumour 56.6–7
calcineurin inhibitors **73.31–4,** 74.16–17
  in dermatomyositis 51.129
  female genital dermatology 71.64
  in psoriasis 20.25
  treatment, psoriasis 20.25, 20.42
calcineurin pathway 13.6
calcinosis
  calcifying panniculitis vs 46.16
  penile 71.36
  post-phlebitis subcutaneous 47.46
  scrotal 71.35–6
  in systemic sclerosis 51.95
calcinosis cutis 62.44, 62.72
calciphylaxis 50.54
calciphylaxis (calcific uraemic arteriolopathy) *46.17*, **47.8–9, 49.47–8,** 62.12, 62.70–1
  calcifying panniculitis with renal failure 46.16
  differential diagnosis *47.9*
  hyperparathyroidism and 49.47
  male genital dermatology 71.25
  perianal/perineal dermatology 71.90
  risk factors 49.47
calcipotriol (calcipotriene) 73.43, **73.45–6**
  adverse effects *26.46*, 73.45, 75.163
  combination therapies 73.45
  indications 73.45–6
  in lichen sclerosus 51.118
  maximum recommended rate of use 73.45
  metabolism 73.45
  occlusion with 73.45
  in psoriasis 20.26, 73.45
    combined with PUVA 20.30
  in psoriatic nail involvement 65.26
  structure *73.44*
  topical, in lichen planus 41.18
calcitonin, in complex regional pain syndrome 63.21
calcitonin gene-related peptide (CGRP) 4.10, 12.25, 12.63, 12.64, 63.2, 63.3
  in atopic dermatitis 24.17
  immune function and 63.4
  pruritus and *21.3*, 21.4
  in Raynaud's phenomenon 63.4
  triple response of Lewis and 63.5
  in wound healing 63.4
calcitriol 29.6, 73.43, **73.45**
  doses and efficacy 73.45
  morphoea, localized 51.75
  in psoriasis 73.45
  structure 73.43, *73.44*
calcium
  abnormal oscillations, in Hailey–Hailey disease 39.33
  absorption increased by vitamin D 73.43
  deposition in external ear 68.18
  Hailey–Hailey disease pathogenesis 39.32–3
  metabolism changes 46.16
  in nail plate 65.3
calcium channel blockers
  adverse effects 69.21, **75.94–5**
  in hyperhidrosis 44.12
  oedema associated 48.6
  platelet function abnormalities 49.13
  telangiectasia with 47.15–16
  in vibration injury 28.58
  in wound healing 14.24
calcium hydroxyapatite 80.4–5
calcium pyrophosphate deposition disease 59.102
calculus, cutaneous 56.2
calf muscle pump 47.25
calf vein, thrombosis 47.29
caliciviruses *33.2*
Calliphora 38.8
Calliphoridae 38.8
callosities
  mechanical injury 28.10–12, 28.25, 28.26
  painful hereditary 19.102
calluses
  definition 5.7
  mechanical injury 28.2, 28.10–12, 28.31
  plantar warts vs 33.44
CALMs (café-au-lait macules) 15.16–18
Calocedrus decurrens 26.80
calomel 75.160
caloric restriction, obesity management 46.8
calponin 10.22
Calymmatobacterium granulomatis 30.61–2
  female genital infection 71.71
CAM 5.2 *10.12*, 10.20–1
Cam 5.2 *10.12*, 53.39, 53.40, 53.43
Camarena syndrome 15.32
Camisa's syndrome (loricrin keratoderma) 19.3, 19.19, *19.94*, 19.98
camouflage
  in androgenetic alopecia 66.24
  animals 2.5, 2.6
cAMP *see* cyclic AMP (cAMP)
Campath 13.25
Campbell de Morgan spots (cherry angioma) 47.13, 47.15
camphor 73.48
  hair regrowth and 73.39
camptodactyly 45.46–7
Campylobacter jejuni 22.8
  in erysipelas/cellulitis 30.18
CAMs *see* adhesion molecules
Canale–Smith syndrome 13.11, 13.23
canalete *26.80*
cancer
  familial syndromes 52.6
  as genetic disease 52.12
  recurrent, lymphoedema 48.14
  risk, communicating 72.2
  see also carcinogenesis; malignant disease; *specific cancers*
cancer surveillance programme, in Peutz–Jeghers syndrome 58.13
cancer susceptibility modifying genes 52.10–11
cancerphobia 64.24–5
cancrum oris 69.14
candersartan 75.94
Candida
  folliculitis 42.36
  identification *36.8*
  immunodeficiency and 17.53
  intralesional use, wart treatment 33.50
  in otitis externa 68.21
  in otomycosis 36.17
  septicaemia 36.68
  see also candidiasis
Candida africanus 69.105
Candida albicans 36.56
  adherence 36.57
  allergy to 36.63–4
  anogenital infections 71.2
  cutaneous carriage 36.56
  in denture-related stomatitis 6.103
  drug resistance 36.68
  ecology 36.56–7
  ectodermal dysplasias 15.70
  female genital infections 71.68
  gastrointestinal tract carriage 36.56, 36.58
  genitocrural infections 71.6–7
  in HIV infection 69.105
  identification 36.9, 36.66–7
  in infantile gluteal granuloma 17.27
  intravenous drug abuse 28.53
  male genital infections 71.9, 71.17, 71.18, 71.24, 71.32
  napkin dermatitis and 17.23–4
  in onycholysis 65.10
  oral carriage 36.56, 36.58, 69.88
  in otomycosis 68.27
  persorption 36.56
  polymorphisms 36.56, 36.57
  strains 36.57
  vaginal carriage 36.56
  virulence 36.57
  see also candidiasis
candida antigen test 5.24
Candida dubliniensis 36.56, 36.67, 36.68, 69.105
Candida glabrata 36.56, 36.67, 36.68, 68.25
  in HIV infection 69.105
Candida inconspicua 69.105
Candida krusei
  drug resistance 36.67, 36.68
  fungaemia, in HIV/AIDS 35.32
  in HIV infection 35.32, 69.105
  identification 36.9, 36.66
Candida lusitaniae 36.56, 36.68
Candida parapsilosis 36.56
  in HIV infection 69.105
Candida tropicalis 36.56
  in HIV infection 69.105
  identification 36.9, 36.66
Candida zeylanoides 36.56
candidiasis **36.56–69**
  acute erythematous (atrophic oral) 36.60, *69.8*, *69.88*, 69.89, 69.104–5
  acute pseudomembranous 36.60, 36.64, 36.68, 69.88–9
  aetiology 36.56–7
  angular cheilitis and 26.21, 69.122
  balanitis due to 36.62, 36.68
  chronic erythematous/atrophic 36.60, *69.88*, 69.102–4
  chronic hyperplastic *69.88*, 69.89
  chronic mucocutaneous *13.13*, **36.64–6,** 69.26, *69.88*
    autosomal dominant 36.65
    autosomal recessive 36.65
    clinical features 36.64–5
    diagnosis 36.66
    with endocrinopathy 36.65
    hypoparathyroidism and 62.12
    idiopathic 36.65
    immunodeficiency and 17.66–7
    immunology 36.65–6
    late onset 36.65
    treatment 36.69
  chronic nodular 36.61
  chronic oral multifocal (glossitis) 36.61, *69.88*, 69.105–6
  chronic plaque-like/hyperplastic (leukoplakia) 36.60–1, 69.89, 69.90, 69.91
  chronic pseudomembranous 36.60
  congenital 17.47, 36.63, 36.69
  corticosteroids and 36.59, 36.61
  Cushing's syndrome and 36.58
  cutaneous 36.61–3, 36.64
  definition 36.56
  in diabetes mellitus 36.58
  diabetic dermopathy 59.78
  differential diagnosis 36.33, 50.55
  flexural (intertriginous) 36.61, 36.64, 36.68
  genitocrural 71.5, 71.6
  histology 36.60
  in HIV infection 35.32, 35.45, 36.59–60, 69.105
  host factors 36.58–9
  hypothyroidism and 36.58, 36.65
  immunodeficiency and 36.59
  interdigital 36.61
  laboratory diagnosis *36.8*, 36.66–7
  male genital 71.32
  napkin (diaper) 36.62, 36.68–9
  neonatal 17.25, 17.46–7
  nodular/granulomatous of napkin area 36.63
  oesophageal, in HIV infection 35.32
  onychomycosis due to 36.63, 36.64, *36.65*, 36.69
  oral 36.60–1, 36.64, 69.13, 69.22, 69.88–889
    in HIV infection 35.32, 35.43
    treatment 36.68
  paronychia due to 9.18, 36.63, 36.64, 36.69, 65.21
  pathogenesis 36.57–60
  perianal/perineal 36.62, 71.92
  scrotal 36.62
  systemic 36.91
  treatment 36.67–9
  urticaria and 22.10
  vulvovaginal 36.61–2, 36.68
  see also Candida
candidide 23.9, 36.63–4
canicola fever 30.66
canine oral papillomavirus 33.42
canities *see* hair, greying
canker sores (recurrent aphthous stomatitis) **69.44–6,** 69.48
cannabinoid receptors 21.2
cannabis
  adverse effects *70.5*
  mechanical injury 28.53
canning industry, occupational hazards 27.18
Cannon's disease (white-sponge naevus) 35.43, 69.23–4
Cantagalo virus 33.8
cantharides, hair regrowth and 73.39
cantharidin 25.4, 38.26
  molluscum contagiosum 33.12
  wart treatment 33.49

canthaxanthin 75.162
Cantú's syndrome 58.20
Canvaxin whole-cell vaccine 54.54
CAP fluoroimmunoassay 5.24, 13.16, 22.19, 22.26
  acute urticaria 22.26
  occupational dermatoses 27.7
CAP syndrome 45.46
capacitance images 72.11
capecitabine 75.129
capillaries 3.50–1
  in angioma serpiginosum 47.16–17
  chronically dilated 47.12
  formation 47.1
  fragility, testing 49.5
  leakage from 49.5
  malformations 18.62–70, 18.79
  pressure 49.5
  raised pressure, venous disorders 47.26, 47.27, 47.42
  stasis, venous microcirculatory disturbance 47.26, 49.15
  thrombosis, venous leg ulceration and 47.42
capillaritis 49.4, **49.22,** 75.23
  classification *49.3*
capillaroscopy, in rosacea 43.1
capillary malformation–arteriovenous malformation syndrome 18.79
capillary malformations 47.23, 47.25
capillary microscopy 47.26, 49.2
  purpura 49.6
Capnocytophaga canimorsus 38.60
CAPS (cryopyrin-associated periodic syndrome) 22.24–5, 50.53, 62.69
capsaicin 12.65–6, 73.49
  action at vanilloid receptors 21.2, 63.2
  in atopic dermatitis 24.18
  in chromhidrosis 44.21
  dermatitis due to 9.13
  in notalgia paraesthetica 63.23
  in post-herpetic neuralgia 63.7
  in pruritus 21.17
  topical, in zoster and post-herpetic neuralgia 33.28
capsaicin-sensitive C-fibres 12.64
capsule endoscopy 48.27
captan 26.58
captopril 75.93
car assemblers, risk of occupational dermatoses *27.2*
carate (pinta) 30.63–4
carba mix 26.64
carbamazepine 64.52
  adverse effects **75.84**
    erythroderma 23.47
  in complex regional pain syndrome 63.21
  eccrine gland secretion 44.18
  isotretinoin interaction 42.65
carbapenems 74.40, 75.51–2
carbaryl (carbaril) 38.19, 38.20, 73.14
  lice infestations 73.14
carbidopa 75.88
carbimazole 18.102
carbohydrate recognition domains (CRDs) 12.10
Carbomer BP 73.2
carbon, in tattoo pigments, allergic reactions 58.58
carbon dioxide laser 78.13
  in juvenile xanthogranuloma 55.16
  in lichen planus 41.18
  pulsed, eruptive vellus cyst 53.7
  in steatocystoma multiplex 42.88
  in vulval lichen sclerosus 51.118
  wart treatment 33.49
  in xanthoma disseminatum 55.21
  see also laser therapy
carbon disulphide 25.20
carbon monoxide poisoning **28.93–4**
  nails in 65.15
carboplatin 75.133–4
carboxypeptidase 12.25
carboxypeptidase N 13.4
carboxypolymethylene (Carbomer BP) 73.2
carbromal 75.81
  non-thrombocytopenic purpura due to 49.21
carbuncle **30.24–5**
  ear 68.19
carcinoembryonic antigen (CEA) 10.21, 62.16
  extramammary Paget's disease 53.40
  malignant eccrine poroma 53.32
  Paget's disease of nipple 53.39
carcinogenesis
  initiation phase 52.12–13
  multistage 52.29
    murine model 52.12–13, 52.15, 52.29
  photoproduct formation and 52.14
  progression phase 52.12, 52.13
  promotion phase 52.12, 52.13
  thermal injury 28.72
carcinogens
  chemical 52.4–5
    multistage carcinogenesis in murine model 52.12
  exposure to 62.46–7
carcinoid crisis, acute 43.19
carcinoid syndrome **43.17–20,** 62.40, 62.43
  clinical features 43.17–18
  diagnosis 43.19
  flushing 43.14, 43.17–18
    foods associated 43.18, 43.19, *43.19*
  morphoea and 51.78
  pigmentation 58.25
  prognosis 43.19
  rosacea vs 43.5
  treatment 43.19
  tumours associated 43.17, 43.18
carcinoid tumours 43.17
  surgical excision 43.19
carcinoma
  adenocystic, primary cutaneous 53.37
  adenoid cystic 53.37
  basal cell *see* basal cell carcinoma (BCC)
  basisquamous basal cell 52.22–3
  breast *see* breast cancer
  burn scar 28.91
  cervical, HPV association 33.39, 33.54
  dyskeratosis congenita 15.79
  eccrine, eyelids 67.36
  genetics 15.27
  lymphoepithelioma-like 53.41–2
  Merkel cell *see* Merkel cell carcinoma
  microcystic adnexal 53.35–6
  mucinous 53.36–7
  mucoepidermoid, external auditory canal 68.33
  multicentric, male genitalia 71.42
  nasopharyngeal, EBV association 33.30
  oat cell, of bronchus, pigmentation changes 58.25
  penile 71.40–3
  primary neuroendocrine of skin *see* Merkel cell carcinoma
  pruritus, in old age and 8.27
  scrotal 27.15–16, 52.4, 52.25, 71.43–4
  sebaceous 42.87–8, *67.10*
    eyelids 67.35–6
  spindle-cell 97.18
  squamous cell *see* squamous cell carcinoma (SCC)
  superficial spreading, male genitalia 71.41–2
  syringoid eccrine 53.36
  trichilemmal 53.6, 68.34
  verrucous *see* verrucous carcinoma
  vertical growth, male genitalia 71.42
  see also malignant disease
carcinoma cuniculatum 33.55
carcinoma en cuirasse 62.15–16
carcinoma erysipeloides (telangiectatica) 48.31, 62.15, 62.16, 70.14
  genitocrural dermatology 71.8
carcinoma *in situ*
  female genitalia 71.74
  male genitalia 71.37–9, 71.46
  perianal/perineal 71.90, 71.97
carcinoma simplex 71.74
carcinoma telangiectoides 62.15
carcinosarcoma, ear 68.34
CARD15 gene 62.48
  in Blau syndrome 61.16
cardiac arrhythmias
  pimozide therapy 64.16
  in sarcoidosis 61.7
cardiac disease **62.75–80**
  keratoderma and woolly hair and *19.94,* 19.107
  see also specific diseases
cardiac failure, venous leg ulcers and 47.47
cardiac monitoring, burns 28.83
cardiac myxoma 49.37, 50.54
cardiac pacemakers 62.79
cardiac rhabdomyomas 15.23
Cardiff Acne Disability Index (CADI) 42.35, 72.20
Cardiff Human Mutation Database 15.1, 15.5
cardiofaciocutaneous syndrome 15.32, 18.70, 62.77
cardiolipin 51.63
cardiovascular disease
  Degos' disease 49.46
  Erdheim–Chester disease 55.18
  oral manifestations *69.117*
  venous leg ulcers and 47.43
cardiovascular system
  drugs acting on 75.89–98
  in Kawasaki disease 50.46
  in Marfan's syndrome 45.30
  in pseudoxanthoma elasticum 45.21, 45.22
  in SLE 51.43, 62.78
  in syphilis 34.14
care pathways 72.26
careers, skin disease in adolescence and 8.6, 8.7–8
Carey syndrome 15.32
Caripito itch 38.29
carmustine (BCNU) 57.23
  adverse effects *26.46,* 75.126
Carney complex (Carney's syndrome) 54.3–4, 58.14, 62.25, 62.33, 62.78–9, 69.28
  breast involvement 70.17
  with endocrine autoimmune conditions 62.13
carotenaemia 59.60, 62.64
  pigmentation 58.53
carotene 75.33
  excess 58.53
β-carotene, oral supplements 58.53
carotenoids 2.5, 5.15, 58.2
carpal tunnel syndrome 63.11, 63.14
  due to tuberculous gumma 31.20
carpenters, occupational hazards 26.20, 26.79, 27.18–19
Carpenter's syndrome 62.13
carpet beetles 25.21
Carpoglyphidae 38.47
Carpoglyphus passularum (lactis) 38.47
carprofen 75.74
carrion's disease (Oroya fever) 30.57–8, 35.25
cartilage–hair hypoplasia syndrome *13.13,* 15.32, **15.93**
Carukia barnesi 38.56
caruncles, urethral 71.73
Carvajal disease/syndrome *19.94,* 19.107, 66.70
L-carvone 26.17
Carybdea rastoni 38.56
Casal's necklace 59.63
case definition 26.3
case reports *7.3,* 7.4
case series *7.3*
case–control studies 6.3, 6.19, *7.3,* 7.4, 26.2
  appraisal 7.14–15, *7.15*
cashew nut oil 26.18, 26.75
cashew nuts 26.22
caspases
  activation 12.12
  deficiency 13.15
caspofungin 36.68, 74.48
Castellani's paint 36.48, 36.49, 73.48
Castleman's disease
  HHV-8 and 33.34
  in HIV infection 35.41
  multicentric 56.24
Castleman's tumour
  lichen planus and 41.16
  paraneoplastic pemphigus 40.23
  pemphigus 40.4
castor oil 73.6
castration and hair loss 66.13–14, 66.14–15
cat(s)
  alopecia 2.18, 2.19
  atopic dermatitis 2.13–14
  bites from 38.60–1
  bullous pemphigoid 2.14–15
  cowpox infection association 33.7
  Demodex infestation 2.10
  fungal infections 2.12–13
  lice 2.10
  lupus erythematosus 2.16
  Malassezia dermatitis 2.14
  mast cell tumours 2.22
  melanomas 2.20–1
  neoplastic skin disease 2.19–20, 2.20–1
  sarcoids 2.22
  scabies 2.10
  staphylococcal skin infections 2.12
  superficial necrolytic dermatitis 2.17
  vitiligo 2.23
  white, SCC in 2.19, 2.20
cat bites 38.60–1
cat scratch disease **30.56–7,** 38.11, 38.60, 61.5
cat scratch fever antigen 5.24
cat-scratch fever antigen 5.24
catagen 3.7, 3.13, 66.7–8, 66.11
cataract
  in atopic dermatitis 24.24–5
  corticosteroid-induced 67.15, 67.16, 67.31, 74.3
  in NF2 62.23
cataract, hypertrichosis, mental retardation syndrome 15.33
cataract–alopecia–sclerodactyly syndrome 15.33
catecholamines 12.65, 63.3
  biosynthesis, defect in vitiligo 58.47
  menopausal flushing and 8.20
β-catenin 3.4, 3.23, 66.10
  hair-follicle tumours 53.2
  pilomatricarcinoma 53.14
  pilomatricoma 53.13
catenins 40.1–2, 66.10
catering industry, occupational hazards 27.19
caterpillars 25.21, 38.28–30
catfish 38.59
cathelicidin peptides 12.5, 12.6, 12.12
cathelicidins 3.2–3, 3.16, 3.17, 4.5, 30.4, 30.5, 36.21, 43.2
  increased expression in rosacea 3.16, 43.2
  see also LL-37
cathepsins 13.4
cathepsins B, C and D 12.49
cattle
  fungal infections 2.12
  photosensitivity 2.23
  Trichophyton verrucosum 2.9, 2.12
cauda equina 63.16
causalgia *see* complex regional pain syndrome
causation of skin disease 6.11, 6.13, 6.17–18, 6.18
caustics 77.47–8
  wart treatment 33.49

cautery
  actinic keratosis 52.31
  Bowen's disease 52.34
  non-melanoma skin cancer 52.16
  see also electrocautery
cave tick 38.35
caviuna vermelha *26.81*
cayenne pepper spots 49.24
CBT *see* cognitive behavioural therapy (CBT)
CC1–CC27 12.45–6
  see also chemokines
CCAAT-enhancer-binding proteins (C/EBPs) 46.3
CCL5/RANTES mRNA 12.11
CCL18 12.46
CCL21 48.4, *48.5*, 48.6
CCL27 12.46
CCR1–CCR11, chemokine receptors 12.47–8
CCR5 55.3
  inhibition, HIV infection treatment 35.6
CCR6 55.1, 55.3
CCR7 48.6, 55.3
CD nomenclature 10.25
CD1 13.10
CD1 complex 55.1, 55.3
CD1a 10.24, 55.3
  antibodies 55.9
  Langerhans' cell histiocytosis (LCH) cells 55.7
  sinus histiocytosis with massive lymphadenopathy 55.29
CD1b, CD1c 55.3
CD2 10.25
CD3 10.25, 13.8
CD4 13.7, 13.8
  HIV receptor 35.3
CD4+/CD56+ haematodermic neoplasm (blastic NK-cell lymphoma) 57.39–40
CD4+ small/medium sized pleomorphic T-cell lymphomas 57.36–7
CD4 T-cells *see* T lymphocytes, helper (Th/CD4$^+$)
CD5 10.25
CD7 10.25
CD8 13.7, 13.8
CD8+ aggressive epidermotropic T-cell lymphomas (provisional) 57.35–6
CD8+ class I pathway, T cells 12.13
CD8 T-cells *see* T lymphocytes, cytotoxic (Tc/CD8$^+$)
CD10 10.26
CD13 55.31
CD14 13.5, 55.31
CD16 13.6
CD18 *see* complement receptors, CR3
CD19 13.3, 13.8
CD20 10.25
CD21 *see* complement receptors, CR2 (CD21)
CD23 13.3
CD25 13.8
CD27 13.10
CD28 13.10–11
CD28 agonist, 'cytokine storm' 74.4
CD30 10.25
CD30+ lymphoproliferative disorders 57.29–34
  lymphomatoid papulosis 57.29–30
  primary cutaneous (anaplastic) CD30+ large cell lymphoma 57.31–3
  T-cell lymphomas 57.29–30
CD31 10.23
  platelet–endothelial cell adhesion molecule (PECAM-1) 12.73
CD33 55.31
CD34 10.22, *10.23*, 13.7
CD34 cells 55.1, 55.3
CD35 13.3
CD40 13.10, 13.11
  deficiency 13.10
  ligand *see* CD154
  in vasculitis 50.4
CD44 13.8
CD45 10.25
CD45RA 13.10
CD45RO 13.10
CD46 13.3
  measles virus receptor 33.75
CD54, expressed by dermal dendrocytes 55.4
CD55 13.3
CD56 10.21, 10.25, 13.6, 53.43
CD59 14.4
CD68 10.24, 55.18
  histiocytes 55.15, 55.20, 55.22
CD70 13.10
CD79a 10.25
CD80 13.11, 55.3, 55.4
CD81 13.3
CD86 13.11, 55.3, 55.4
CD88
  receptor for anaphylatoxin C5a 12.24–5
  see also complement, C5a
CD95 13.11
CD117 (Kit) 3.19–20
  see also KIT gene mutations
CD150, measles virus receptor 33.75
CD154 (CD40 ligand) 13.8, 13.10, 13.11
  deficiency (X-linked hyper-IgM syndrome) 13.10, 13.12, 13.23, 17.50, 17.63–4
  idiopathic thrombocytopenic purpura 49.9
CD207 10.24
CDAGS syndrome **15.91**
CDH3 gene mutations 3.24
CDKN2A gene 54.33, 54.48, 62.21
CEA *see* carcinoembryonic antigen (CEA)
CEAP classification, chronic venous insufficiency *47.32*
cefaclor 74.41
cefalexin 74.41
celecoxib 75.77
cell adhesion 12.68–75
  cell–cell adhesion, CX3CR1 12.48
  see also adhesion molecules
cell apoptosis
  and inflammation 12.11–12
  see also apoptosis
cell markers
  analysis 13.22–3
  panels *10.12*
cell-mediated immunity (CMI)
  acne scarring 42.26–7
  in HIV infection 35.3–4
  to HPV 33.42
  in measles 33.75
  in pregnancy 8.11
  in varicella and zoster 33.23
cell wall antagonists (antifungals) 74.48
cellist's chest 28.25–6
cellular adhesion molecules *see* adhesion molecules
cellular components of inflammation 12.14
cellular retinoic acid binding proteins (CRABP-1 and -II) 73.34–5, 73.35
cellular retinol binding proteins (CRBP-I and -II) 73.34–5, 73.35
cellulite **46.9–10**
  classification and stages 46.9
  hard vs flaccid types 46.9
  management 46.10
  oedematous 46.9
cellulitis 4.5, **30.17–21**
  acute 48.24
    see also erysipelas
  after arthropod bites/stings 38.2
  bacteriology 30.17–18
  clinical features 30.18, *30.19*, *30.20*
  clostridial 30.68
  complications 30.18
  definition 5.7, 30.17
  diagnosis 30.18–19
  differential diagnosis 26.29, 30.19
  dissecting 9.9–10
  ear 68.19
  eosinophilic (Well's syndrome) 46.12, **46.33–4,** 62.87
  facial 30.18
  gangrenous 30.68
  HIV infection 35.24
  in lymphatic filariasis 37.9
  lymphoedema and 48.12, 48.15, 48.17
    management 48.24
  male genital dermatology 71.29–30
  necrotizing 30.68
  neuropathic ulcer and 63.9
  orbital 30.18
    neonatal 17.44
  perianal/perineal 30.32–3, 71.91–2
  periorbital 30.18
  preorbital, neonatal 17.44
  preseptal *67.4*
  racial influences 9.18
  recurrent 30.18, 30.20, 48.29
    lymphoedema 48.12, 48.24
  scalp *see* perifolliculitis capitis abscedens et suffodiens
  tongue 30.18
  treatment 30.19–20
    isotretinoin 74.34
  venous leg ulcers 47.50
cement
  allergic contact dermatitis to 26.15
  burns *25.11*, 25.12, 27.12
  as irritant 25.20, 27.6
centipedes 38.54
central nervous system (CNS)
  in Erdheim–Chester disease 55.18
  in juvenile xanthogranuloma 55.16
  in Langerhans' cell histiocytosis 55.11–12
  lesions, hyperhidrosis and 44.9, 44.10
  in primary angiitis 50.47
  in sarcoidosis 61.7
  in secondary syphilis 34.11
  in sinus histiocytosis with massive lymphadenopathy (SHML) 55.29
  in xanthoma disseminatum 55.21
Centre of Evidence-Based Dermatology 6.14
centrofacial lentiginosis syndrome 69.28
Centruroides 38.33
CEP *see* congenital erythropoietic porphyria (CEP)
Cephalonomia gallicola 38.14
cephalosporins 74.40–1
  adverse effects **75.50–1**
    urticaria 22.8
  gonorrhoea management 34.28
ceramides 3.10, 4.2, *4.3*, 12.14–15
  accumulation 59.36
  in atopic dermatitis 24.22
Cerapterus concolor 38.27
Ceratophyllidae 38.11
Ceratopogonidae 38.6, 38.7
cercariae 37.20–1, 37.23
cercarial dermatitis 28.55, 37.20, **37.22–3,** 38.56, 38.57
cercopithecine herpesvirus 1 (CeHV-1) **33.34–5**
cerebellar syndrome, Langerhans' cell histiocytosis (LCH) 55.12
cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) 50.47
cerebral cavernous malformation 18.74
cerebral palsy *69.119*
cerebrospinal fluid (CSF)
  in sarcoidosis 61.7
  in secondary syphilis 34.11
  syphilis diagnosis 34.21
  viral infection diagnosis 33.4
cerebrotendinous xanthomatosis 59.91
cernunnos deficiency 17.58
certolizumab, psoriasis 74.5
ceruloderma 58.36
cerumen 68.2–3
  in alkaptonuria 68.18
  dry/wet 68.2
  impacted 68.11, 68.21, 68.25
  lack of 68.21
  removal 68.2–3
cerumenolytics 68.3, 68.25
ceruminous glands 68.2
  tumours 68.28–9, 68.29–30
cervical auricle/tab 18.84, 18.85
cervical carcinoma, HPV association 33.39, 33.54
cervical examinations 71.53
cervical infection, gonococcal 34.25
cervical intraepithelial neoplasia (CIN)
  HPV and 33.54
  treatment 73.24
cervical rib 63.14, 63.24
cervical spinal involvement, psoriatic arthritis 20.57
cervicitis
  anterior, chlamydial 34.29, *34.30*
  gonococcal *34.26*
cervix, syphilitic chancre 34.7, 34.18
cestodes 37.2, 37.3, **37.24–7**
cetamolol 75.91
cetearyl (cetostearyl) alcohol 26.58–9
cetirizine *22.29*, 74.31
  adverse effects 75.149
  in urticaria 22.28
cetomacrogols 73.7
cetostearyl alcohol 73.2, *73.7*
cetrimide 73.14
cetuximab 75.132
Ceylon ebony *26.80*
CFS (cutaneous field stimulation) 62.23
CGD *see* chronic granulomatous disease
CGRP *see* calcitonin gene-related peptide
CH3/HeJ mouse 66.33
chaetae, annelid worms 2.2
Chagas' (Chagas–Mazza) disease *see* trypanosomiasis, American/South-American
chagoma, inoculation 37.32
chalazion 67.11, 67.34
chalk, as irritant 25.20
chalone hypothesis 66.9
chamomile 66.97
Chanarin–Dorfman syndrome (neutral lipid storage disease with ichthyosis) 19.52–4
chancre
  lymphogranulomatous 30.70
  soft *see* chancroid
  syphilitic 34.6–7, 69.78
    lips 69.121
  trypanosomal 37.30
  tuberculous 31.8, 31.10, 31.11–12
Chancre redux 34.7
chancroid 30.47, **34.34–5,** 71.71, 71.93
  HIV co-infection 34.34–5
  syphilitic chancre vs 34.7
CHANDS 15.35, 15.63, 15.65
Channa striata 31.31
charcoal, in fish odour syndrome 44.20
Charcot neuroarthropathy 47.58
Charcot–Leyden crystal protein 13.5
Charcot's joints 63.15
CHARGE syndrome 68.3
Charle's operation 37.10
Charles' procedure 48.25
Chediak–Higashi syndrome 12.23, 13.6, *13.13*, 17.79–80, 58.41–2, 62.28, 62.95
  bacterial infection and 30.8
  neutrophils in 17.78–9
  oral involvement 69.33, *69.117*
cheeks
  biting 69.87–8
  sebaceous glands 42.1
  spontaneous atrophic scarring 45.7
cheilitis **69.119–28**
  actinic 52.37, **69.123–4,** 78.14
    treatment 73.23, 73.24
  aetiology *69.119*

allergic 26.17, 26.41, 26.48
angular 26.17, 26.21, 36.61, 36.68, 64.22, **69.122–3**
in Down's syndrome 69.38–9
contact 69.119–20
drug-induced 69.121
eczematous 69.119
exfoliative (factitious) 69.127–8
factitious 64.39–40
glandular 69.124–5
granulomatous (Miescher's) 48.16, 61.23, 69.60, **69.125–7**
infective 69.121
irritant dermatitis and 25.16
lip-lick 23.3, 24.22, *24.23*
plasma-cell 69.128
retinoid 42.63
Volkmann's 69.124
cheiloplasty 69.126
cheilosis 69.122
solar *see* cheilitis, actinic
cheiroarthropathy 45.62
cheiropompholyx 23.16
chemical carcinogens 52.4–5
multistage carcinogenesis in murine model 52.12
see also chemicals
chemical damage, self inflicted 64.37–8
chemical depigmentation 58.50–1
chemical/gas/petroleum plant operatives, risk of occupational dermatoses *27.2*
chemical industry, occupational hazards 27.19
chemical peels 80.9–10
in acne vulgaris 42.68, 42.69
in actinic keratosis 52.32
chemical pigmentation, eyelids 67.5
chemicals
acne induced by 27.12–15
assessment of dermatitic potential 27.10–11
burns due to 27.11–12
contact purpura due to 49.21
definition 75.1
exposure to 75.162–3
leukoderma due to *27.15*
photosensitivity in animals and 2.23
pigmentation due to 58.54, 58.56–7
pigmented purpuric dermatoses due to 49.23
scleroderma due to 45.52, 75.43
skin tumours, retinoic acid therapy 73.36
see also chemical carcinogens
chemokines **12.44–8**
in atopic dermatitis 24.7
CC1–CC27 12.45–6
classic role 12.44
CXCL chemokine/receptor family (CXCL1–15) 12.45, 12.46–7
Langerhans' cells migration 55.3, 55.4
leukocyte–endothelial interactions 12.44
in lichen planus 41.1
modulation of angiogenesis during tumour growth 12.48
nomenclature, systematic names and ligands 12.45
receptors **12.47–8**
subfamilies 12.44
chemosurgery 77.29
tattoo removal 58.59
see also Mohs' micrographic surgery
chemotherapy
adverse effects **75.121–36**
acral erythema 75.122–3
alopecia 75.45
extravasation 75.122
hyperpigmentation 75.33
internal malignant disease 75.124
mucositis 69.82
neutrophilic eccrine hidradenitis 44.16–17, 75.123
skin cancer 75.124
syringosquamous metaplasia 75.123
carcinoid tumours 43.19
combination, male genital dermatology 71.44
juvenile xanthogranuloma 55.16–17
malignant histiocytosis 55.33
melanoma induction 54.48
sinus histiocytosis with massive lymphadenopathy 55.30
squamous cell carcinoma 52.28
topical, nitrogen mustard and carmustine (BCNU) 57.23
see also cytotoxic drugs; *specific chemotherapeutic drugs*
chest X-ray, burns 28.84
chest–abdomen sign 62.80
cheveux incoiffables 66.71–2
Cheyletiella 38.4, **38.49–50**
animal infestation 2.10
chi-square test 7.20
Chiari's syndrome 63.14
'chicken skin' appearance 45.21, *45.22*
chickenpox *see* varicella
Chiclero's ulcer *37.35*, 37.39–41
chigger 38.50, 38.51
chigoe 38.12–13
Chikungunya virus 33.66, *33.67*
male genital infection 71.33
chilblain lupus 51.11–12
chilblains *see* perniosis
child abuse
anogenital signs 71.15
bites 38.61
burns 28.34, *28.35*, *28.90*, 28.91–2
clinical features 28.34–5
differential diagnosis 28.36
emotional abuse 28.34, 28.38–9
female genital dermatology 71.57
mechanical injury 28.34–9
mouth ulcers and 69.43
neglect 28.34, 28.38–9
perianal/perineal dermatology 71.84
physical abuse 28.34–7
sexual 8.3, 28.34, 28.37–8, 71.57, 71.84
anogenital warts 33.40, 33.41
differential diagnosis 8.3
molluscum contagiosum 33.11
CHILD syndrome 18.27, 19.3, 19.57–8
childbirth **8.9–16**
childhood
definition 8.2
see also children; infancy and childhood
childhood cancer, melanoma risk 54.15
children
acne 42.75–6
AIDS case definition 35.5
anogenital warts 33.46
transmission 33.40–1
antiphospholipid antibody syndrome 49.51
atopic dermatitis
concordance with therapy 72.6
quality of life assessment 64.10, 72.23
drug responses and metabolism 72.28
frictional dermatitis 28.14
granulomatous perioral dermatitis 43.12, **43.13**
herpes simplex 33.15, 33.20
HIV infection 35.44–5
medication errors 72.26
melanomas 54.15, 54.48–9
molluscum contagiosum 33.12
obesity and BMI 46.5–7
prevalence studies of skin disease 6.7–8
psoriasis, treatment 73.45
psychocutaneous disorders
factitious 64.38, *64.39*
skin picking 64.28
trichotillomania 64.30–1
purpura fulminans 49.51
quality of life assessment 64.10, 72.23–4
rubella 33.70
skin 8.3
stigmatization 64.6–7
suction purpura 28.24
topical therapy, quantities *73.3*, *73.4*
UVR exposure and standard erythema dose 29.4
see also infancy and childhood
Children's Dermatology Life Quality Index 72.23
Children's Life Quality Index 72.23
Chilopoda (centipedes) 38.54
CHIME syndrome 19.60
chimera (human), with pigment anomalies 58.23
chimeric animals 2.8
chimerism 18.1
chimney sweeps, scrotal carcinoma 27.15–16, 52.25
chin, swelling (gnathophyma) 43.9, *43.10*
chin crease, in pseudoxanthoma elasticum 45.22
Chinese folk medicine, coin-rubbing 28.25
Chinese herbal medicine
adverse effects 26.45, *26.46*, **75.160–1**
carcinogens in 52.5
systemic agents 74.52
'Chinese letter pattern,' pigmentation in incontinentia pigmenti 58.16
Chinese restaurant syndrome 43.16
Chinese traditional medicine 72.31, *72.32*
Chiracanthium 38.32
Chironex fleckeri 38.56, 38.57
Chironomidae 38.7
chiropractic *72.32*
chitin 36.1
Chlamydia **30.70–2**
Chlamydia psittaci 30.71–2
Chlamydia trachomatis **30.70–1**
A-C strains 34.29
abscesses of Bartholin's gland 71.68
D-K strains 34.29
developmental cycle 34.29
direct fluorescent antibody test 34.30, 34.31
elementary bodies 34.29
genital infections **34.29–32**
perianal/perineal infections 71.93, 71.97
persistence 34.31
reticulate bodies 34.29
serovars L1, L2, L3 34.32, 34.33
vaginal discharge 71.53
chlamydial infections, genital **34.29–32**
clinical features and complications 34.29–30
diagnosis 34.30–1
epidemiology *34.2*, 34.29
management 34.31
chlamydoconidia *36.3*, 36.4, 36.74
chloasma 58.25, 58.34–5, 75.33
differential diagnosis 36.11
pigmentation in pregnancy 8.10
chloracetamide 26.58
chloracne 27.12–15, 42.31, 42.34, **42.77**
chemicals causing 42.77
ophthalmic 42.77
treatment 42.77
chloral hydrate 75.81
chlorambucil
adverse effects 75.124–5
in necrobiotic xanthogranuloma 55.28
in systemic sclerosis 51.108
chloramphenicol 26.17, *26.46*, 74.43
adverse effects 75.5, **75.59,** 75.61
bone marrow aplasia 74.43
chlordane 75.163
chlordiazepoxide 75.81
chlorhexidine 14.21, 26.58, 30.7, **73.14**
adverse effects 75.164
in impetigo 30.16
use in neonates 17.2, 17.44
chloride, in sweat 44.5
chlorinated aromatic hydrocarbons, acne associated *see* chloracne
chlorinated salicylanilides 26.23
4-chloro-3,5-dimethylphenol (chloroxylenol) 26.56, 73.14
17α-chloro steroids 42.16
chloroacetate esterase reaction 10.9
chloroatranol 26.77
chlorobenzene 25.20
chlorobiphenyl oxides 27.12
chlorobiphenyls 27.12
chlorocresol 26.56–7, *73.8*
2-chlorodeoxyadenosine
juvenile xanthogranuloma 55.16
Langerhans' cell histiocytosis (LCH) 55.13
chloroform 25.3, 25.19
chloronaphthalenes 27.12
chlorophenols 27.12
Chlorophora excelsa *26.81*
Chloropidae 38.6
chloroquine 74.25–6
adverse effects **75.69–70**
hair colour changes 66.94
hypermelanosis 58.30
nail colour changes 65.16
ocular 67.31
pruritus 37.27
in discoid lupus erythematosus 51.20
in sarcoidosis 61.21
in Sjögren's syndrome 51.138
chloroxylenol 26.56, 73.14
chlorphenamine 74.31
chlorphenesin 26.58
chlorpheniramine 22.29
chlorpromazine 64.52, 75.82
adverse effects, hyperpigmentation 58.29, 75.33
chlorpropamide, adverse effects 75.156
chlorpropamide–alcohol flushing 43.16
chlortalidone (chlorthalidone) 75.98
chlortetracycline 74.41
chocolate, acne and 42.33–4
cholecalciferol *see* vitamin D
cholera 6.11
cholestasis
pruritus in 21.9–10
recurrent in pregnancy 8.13
cholestasis–lymphoedema syndrome 48.10
cholesteatoma, external auditory canal 68.28, 68.35
cholesterol
biosynthesis, inhibition, in sebocytes 42.5
embolism 50.54
in epidermis 3.11
LDL of standard lipid profile, Friedewald formula 59.84
metabolism 66.83
reverse transport 59.82–3
in sebum 42.5
cholesterol clefts 52.45
in necrobiotic xanthogranuloma 55.28
cholesterol crystals 46.16
cholesterol embolization syndrome (CES) 49.37
cholesterol ester transfer protein (CETP) 59.83
cholesterol esters
in sebum 42.5
in Tangier disease 59.91
cholesterol sulphatase, deficiency 19.9, 19.11–12
cholesterol sulphate, in epidermis 4.2
cholesterolosis, extracellular 50.26
cholinesterase inhibitor, organophosphorus 73.14
chondritis, ear 45.42, *45.43*, 68.7, **68.19–20**
chondrocytes, origin 12.30
chondrodermatitis nodularis **68.12–13,** 77.36, *77.37*
chondrodermatitis nodularis helicis 51.95, 62.99, *62.102*
chondrodysplasia
calcifying 45.8
metaphyseal, of McKusick **15.93**

chondrodysplasia punctata (variant CDPX2) 19.50, 19.51
chondroectodermal dysplasia 69.10, 69.37, *69.118*
chondroectodermal dysplasia, mesoectodermal dysplasia (Ellis–van Creveld syndrome) 15.39, 15.65
chondroid syringoma 53.2, 53.30–2
  malignant 53.31
chondroitin 4-sulphate, structure *3.47*
chondroitin 6-sulphate, structure *3.47*
chondroitin sulphate 3.46
  in wound healing 14.3
chondroma, pinna 68.28
chondromalacia
  idiopathic cystic (ear/endochondral pseudocyst) 24.25, 68.13–14
  systemic *see* relapsing polychondritis
chondylomata acuminata 71.94
chondylomata lata, perianal/perineal dermatology 71.93, *71.94*
chordoma cutis, perianal/perineal dermatology 71.84
choreoathetosis *69.119*
chorionic gonadotrophin 8.9
  adverse effects *70.5*
chorionic villus sampling 16.1–2
Chorioptes 38.46
Chorioptes bovis 2.10
choristia, periumbilical 71.100
choristoma 18.88
  cartilaginous 68.29
  osseous (osteoma mucosae) 69.108–9
Christianson–Fourie type hidrotic ectodermal dysplasia 15.42
Christmas tree pattern, lesions 33.79
Christ–Siemens–Touraine (CST) syndrome 15.28, 15.43
chromate *see* chromium
chromatin modification 11.16
chromatophores 2.5–6
chrome, in tattoo pigments, allergic reactions 58.58
chrome ulcers 25.11
chromhidrosis **44.20–1**
chromic acid
  burns 25.23, 27.12
  as irritant 25.20
Chromista 36.1
chromium
  allergy to 26.15, 26.18, **26.34–6**
  in alloys 26.37
  avoidance of 26.35–6
  diphenylcarbazide test 27.8
  EU directive 26.35, 26.100, 27.3
  occupational exposure to 27.3
  occurrence 26.35
  oral provocation tests 5.25
  patch tests 26.36
  in shoes 26.68
chromoblastomycosis 31.10, **36.75–6**
chromogranin A 10.21
chromomycosis (chromoblastomycosis) 31.10, **36.75–6**
chromophores 29.3, 78.3, 78.4
  absorption spectra 29.3
  DNA as 29.4, 29.5
  in epidermis 29.4
chromophytosis *see* pityriasis versicolor
chromosomal instability 52.12
chromosomal translocation
  malignant histiocytosis 55.32
  monocytic leukaemia 55.31
chromosome 4, short-arm deletion syndrome 15.12, 18.2, 18.103
chromosome 5, short-arm deletion syndrome 15.12
chromosome 12, long-arm deletion syndrome 15.12
chromosomes
  abnormalities 15.2, **15.9–14**
  drug-induced damage 75.15
chronic, infantile, neurological, cutaneous, articular syndrome **15.95–6**
chronic actinic dermatitis (CAD) 26.24, *29.10*, **29.16–19**
  aetiology 29.16–17
  clinical features *29.10*, 29.17–18
  contact dermatitis association 29.16, 29.17
  definition 29.16
  diagnosis 19.17, 29.23
  differential diagnosis *29.10*, 29.17
  erythrodermic 29.18
  pathology 29.17
  pseudolymphomatous form 29.16, 29.17, 57.58
  treatment *29.10*, 29.18
    tacrolimus 73.32
chronic bullous dermatosis of childhood *5.12–13*
  oral involvement 69.69
  see also linear IgA disease
chronic genetic ulceration 71.66
chronic granulomatous disease *13.13*, 17.48–9, 17.73–5
  with DLE-like lesions 51.16
  oral involvement 69.33, *69.117*
  Sweet's syndrome and 50.76
chronic illness, psychological impact 64.4
chronic lymphocytic leukaemia, perianal/perineal dermatology 71.99
chronic mucocutaneous candidiasis *see* candidiasis
'chronic obesity lymphoedematous mucinosis' 8.17
chronic pain syndromes
  male genital dermatology 71.51–2
  perianal/perineal dermatology 71.99
chronic papular onchodermatitis 37.5
chronic penile oedema 71.30
chronic renal failure
  gynaecomastia and 70.4
  hypopigmentation 58.27
  oral involvement *69.116*
  pigmentation changes 58.27
  pruritus in 21.7–9
chronic superficial scaly dermatitis 57.57
chronic ulcerative stomatitis with epithelial antinuclear antibodies 69.64
chronic venous insufficiency (CVI) 47.12, 47.26, **47.32–6**
  classification 47.32, *47.33*
  clinical features 47.33–5
  investigations 47.35–6
chronic vulval purpura 71.61–2
chronicity 6.11
chrysalis babies 19.27
chrysarobin 66.94
chrysiasis 58.54–5, 67.5, 75.33, 75.100
chrysoderma 58.54–5
Chrysomya 38.8
Chrysops 37.11
Churg–Strauss syndrome 50.9, **50.41–3,** 50.52, 71.29
  cardiac involvement 62.78
  differential diagnosis 50.40
  eosinophilia in 62.86–7
  respiratory tract involvement 62.83
chyle 48.27
chylomicrons 59.82
  clearance 59.90
  restriction of production 59.90
chylous reflux 48.27
chymase 3.20, 12.25, 12.49
  in urticaria 22.4
chymotrypsin, pruritus and 21.5
chymotryptase, in atopic dermatitis 24.18
cicatricial pemphigoid 71.28, 71.91
  scalp 66.49
  vegetating 69.68
  see also mucous membrane pemphigoid
cicatrizing palmoplantar keratodermas *19.94*, 19.95, 19.101–2, 19.108–9
ciclopirox olamine
  in seborrhoeic dermatitis 23.33
  topical, indications 73.12
ciclosporin 13.24, 73.31, 74.16
  in actinic prurigo 29.15
  adverse effects 69.21, **75.136–8**
    hypertrichosis *66.79*
  in allergic contact dermatitis 26.102
  in atopic dermatitis 24.31
  in atopic eye disease 67.16
  in chronic actinic dermatitis 29.18
  clinical indications 74.16
  in cytophagic histiocytic panniculitis 46.24
  in dermatomyositis 51.129
  in dyslipidaemias 59.93
  female genital dermatology 71.64
  in granuloma annulare 60.10
  in Hailey-Hailey disease 39.36
  in hand eczema 23.22
  interactions 72.28–9
  in leprosy reactions 32.18
  in lichen sclerosus 51.118
  in linear IgA disease 40.51
  in pemphigus 40.12
  in pigmented purpuric dermatosis 49.26
  in polymorphic light eruption 29.12
  in psoriasis 20.38–9, 74.16
    in HIV infection 35.17
  in psoriatic arthritis 20.59
  in sarcoidosis 61.21
  in SLE 51.62
  in solar urticaria 29.20
  in subcutaneous panniculitis–like T-cell lymphoma 57.33
  in systemic sclerosis 51.108
  topical 73.32–3
    adverse effects 67.16
    in atopic eye disease 67.16
    in cicatrizing conjunctivitis 67.22
    in lichen planus 41.18
  in urticaria 22.30
cidofovir
  in herpes simplex 33.21
  in molluscum contagiosum 33.13
  in monkeypox 33.7
  in orf 33.9
  wart treatment 33.50
cigarette burns
  child abuse 28.34, 28.92
  torture injuries 28.33
'cigarette face' 45.2
cigarette smoking *see* smoking
cilazapril 75.93
cilia *see* eyelashes
cimetidine
  adverse effects 75.149–50
    erythroderma 23.47
    gynaecomastia 70.4, *70.5*
  sebaceous gland activity inhibition 42.16
  wart treatment 33.50
Cimex 38.24
Cimicidae 38.23–5
cinacalcet hydrochloride 49.48
CINCA syndrome **15.95–6,** 50.53
cinnabar 26.39, 75.160, 75.162
cinnamates 25.18, 26.17, 26.23, 26.62
cinnamic aldehyde 22.20, 25.18, 25.21
cinnarizine 75.88
CIPA (congenital insensitivity to pain with anhidrosis) 15.34
ciprofloxacin, eccrine gland secretion 44.18
circinate balanitis 34.30, *34.31*, 71.18
circinate ulcerative vulvitis 71.59
circulatory disorders
  mechanical injury 28.28–9
  palmoplantar keratodermas 19.118
circumcision 77.35
  chancroid risk reduction 34.35
  female 28.38, 71.57
  lichen sclerosus and 51.113, 51.118
  male 71.13, 71.20, 71.24, 71.39
circumscribed keratotic disorders 19.93
  hypokeratosis of palms and soles 19.116
cirrhosis
  alcoholic *69.115*
  hepatic 62.60–2, 70.4
  see also primary biliary cirrhosis
cirsoid aneurysm 56.26–7, 65.35–6
13-*cis*-RA *see* isotretinoin
cisplatin *26.46*, 75.134
citalopram 64.20, 64.24, 64.28, *64.50*
Citrobacter freundii 2.12
citronella 38.5, 38.20
citrulline 66.6
  in basal cell carcinoma 52.21
Citrus 25.21
Citrus hystrix 75.162
Civatte bodies *see* colloid bodies
CK7 10.21
CK15 53.35
CK20 *see under* cytokeratins
CLA (cutaneous leukocyte antigen) 13.4, 55.1, 76.9
Cladophialophora bantiana 36.77
Cladophialophora carrionii 36.75, 36.76
cladribine 13.24
clam digger's itch 37.22, 38.56
clamp connection 36.4
clarinettist's cheilitis 28.26
clarithromycin 32.17, 74.42, 75.58
Clark levels, melanoma 54.38
Clarkson's syndrome (systemic capillary leak syndrome) 22.23
claudication 47.2
  intermittent 47.2, 47.7
  pain, differential diagnosis 47.5
  spinal 47.5
  treatment 47.5–6
  venous 47.5
claudin 1, gene mutation 3.25
claudin 16 (paracellin-1), gene mutations 3.25
claudins 3.24, 25.2, 56.49
cleaning work, occupational hazards 5.*6*, 27.19
clear cell acanthoma 52.41
clear-cell hidradenoma 53.27–8
clear cell papulosis, genitocrural 71.6
clear cell sarcoma 54.48, 56.53–4
clearance rates, real vs apparent 6.13
cleft lip/palate 18.91, 69.37–8
  with mucous cysts of the lower lip **15.93–4**
  with syndactyly and ectodermal dysplasia 66.52
cleft lip/palate–ectodermal dysplasia syndrome 15.33
clefting, ectropion and conical teeth syndrome 15.31
clefts, needle-shaped 46.16
clegs 38.6
cleidocranial dysostosis 66.73
Clematis 25.21
CLEPD1 syndrome 15.46
climacteric 8.19
climate/climatic factors
  in allergic contact dermatitis 26.10
  risk factor for skin disease 6.12
'climatic bubo' 30.70
clindamycin *26.46*, 74.42–3, 75.58–9
  acne vulgaris treatment 42.47
  in folliculitis decalvans 42.74
  in Fox–Fordyce disease 44.22
  Propionibacterium acnes resistance 42.56
  topical
    in acne vulgaris 42.41, 73.10
    in rosacea 43.6, 73.10
cling film, for occlusion 73.4
clinical deception 64.35
clinical decisions
  factors influencing 72.4
  quality of life measures and 72.2, 72.14, 72.24
  risk–benefit analysis 72.3–4
  shared 72.1
Clinical Evidence 7.6
Clinical Pathology Accreditation 13.15
clinical questions, well-built 7.2–3

clinical trials
  drug reactions 75.2
  generalizing results for treatments *6.4*
clioquinol 26.32, 26.45
  topical corticosteroids with 73.20
clitoridectomy 71.57
clitoris
  benign tumours 71.72
  congenital and developmental abnormalities 71.56
  lichen sclerosus 71.62–3
  structure and function 71.54–5
  trauma and artefact 71.57
cloacal membrane 71.83, 71.98
clobazam 75.81
clobetasol propionate
  female genital dermatology 71.63
  lupus erythematosus profundus 51.15
  pyogenic granuloma in acne 42.79
clofazimine 74.26, 74.45
  acne vulgaris treatment 42.66
  adverse effects 75.33, **75.62–3**
    pigmentation due to 58.55
  clinical indications 74.26
  in leprosy 32.16–17, 32.18
clofibrate 75.156
clomiphene (clomifene) 75.119
  in gynaecomastia 70.5
clomipramine 64.28, 64.32, *64.51*, 75.78
clonazepam, in hyperhidrosis 44.12
clonidine *26.46*, 75.95–6
  flushing management 43.15
    in rosacea 43.6
cloning 11.4, 11.9–10
  positional 11.1, 11.12
Clonorchis sinensis 37.3
clopidogrel 75.108
  claudication management 47.5
  in erythromelalgia 47.10
  platelet function abnormalities 49.13
Cloquet's node 54.53
Clostridium
  cellulitis due to 30.68
  in gas gangrene 30.43–4
Clostridium difficile colitis 74.42–3
Clostridium histolyticum 30.43
Clostridium oedematicus 30.43
Clostridium perfringens (*C. welchii*) 30.43
  perianal/perineal dermatology 71.93
Clostridium septicum 30.43
Clostridium sordellii 30.43
Clostridium tetani, intravenous drug abuse 28.52
clothing
  allergens in 26.18, 26.65–8
  protective *25.24*, 25.25, 27.9
    against jellyfish stings 38.57
  rubber in 26.64
  sun protection 73.41
  UVR exposure minimisation 29.8
clotrimazole
  in candidiasis 36.68
  in dermatophytosis *36.47*, 36.48
  in otomycosis 36.17
  topical 73.12
  in trichomoniasis 37.29
Clouston's syndrome (hidrotic ectodermal dysplasia) 15.42, 15.67, **15.68–9,** *19.94*, 19.106, 53.23
  alopecia 66.59
  oral mucosa and lips 69.23
  teeth 69.11
cloxacillin 75.49
clozapine 64.52, 75.82
CLSM (confocal laser scanning microscopy) 5.20
clubbing of fingers *see* finger(s), clubbing
clubbing of toes **15.87–8**
clumping factor 36.58
clusterin 14.4
Clutton's joints 34.16
CMV infection *see* cytomegalovirus (CMV) infections
CNC (Carney complex) 58.14
Cnidaria 28.55, 38.55–8
co-cyprindiol
  acne vulgaris treatment 42.53
  effect on sebum composition 42.6
  sebaceous activity inhibition 42.15–16
  in sebaceous gland hyperplasia 42.87
co-morbidity, factitious skin disease 64.41
co-occurrence of diseases 6.13
co-polymers 26.74
co-trimoxazole 74.38, 74.39
  adverse effects **75.57**
    fixed eruption 75.28, 75.29
    in HIV infection 35.22
  in head louse infection 38.20
  male genital dermatology 71.27
  non-thrombocytopenic purpura due to 49.21
  photosensitive drug eruption 57.53
  in Wegener's granulomatosis 50.41
coagulation
  in antiphospholipid syndrome 49.40
  cascade 49.38
  changes, in deep-vein thrombosis 47.28
coagulation defects/disorders 49.2, 49.7
  cytophagic histiocytic panniculitis 46.24
  in Degos' disease 49.45
  ecchymoses due to 49.4
  see also coagulopathy
coagulation screen
  burns 28.84
  purpura 49.6
coagulopathy
  HIV infection 35.12–13
  systemic, cutaneous features 49.38–42
  vascular 49.42–7
  see also coagulation defects/disorders
coal mining
  accidental tattoos in miners 58.57
  occupational hazards 27.19
coal tar 20.22, **73.42**
  adverse effects 25.21, *26.46*, 75.31, 75.164
  carcinogenicity 27.16, 73.42
  content and types 73.42
  cytostatic effect 73.42
  distillates, acnegenicity 27.13
  in eczema 23.38
  in hand eczema 23.22
  high-temperature 73.42
  low-temperature 73.42
  mechanism of action and effects 73.42
  in pityriasis amiantacea 66.57
  in pityriasis capitis 66.56–7
  UV light with 73.42
coalminers, accidental tattoos 58.57
cobalt
  allergy to 26.33–4
  in alloys 26.37
  as irritant 25.21
  patch tests 26.34
  in tattoo pigments, allergic reactions 58.58
Cobb syndrome 18.62, 18.96
cobblestone skin appearance 45.21, *45.22*
cocaine, eccrine gland secretion 44.18
cocamidopropylbetaine 26.18
Coccidioides immitis 36.2, 36.85, 36.86
Coccidioides posadasii 36.85, 36.86
coccidioidin 36.85
coccidioidin test 5.24, 36.86
coccidioidomycosis **36.85–7,** *69.118*
  in HIV infection 35.34
coccygeal dimples 63.15
Cochliomyia 38.8
Cochrane, Archie 7.1
Cochrane Collaboration 6.16, 7.1, 7.5, 7.8
Cochrane Database of Systematic Reviews 7.5
Cochrane Library 7.5
Cochrane Skin Group 6.16
Cockayne's syndrome **15.75–6,** 45.61
  childhood melanoma 54.48
Cockett's operation 47.39
Cockett's syndrome 47.32
cockroaches 38.2, 38.28
cocoa butter 73.6
coconut beetles 38.27
coconut oil, in scabies 38.41
cocus *26.80*
codeine, adverse effects 75.26, 75.87
codeine phosphate, in carcinoid syndrome 43.19
coeliac disease 62.55
  dermatitis herpetiformis and 40.58
  erythema nodosum and 50.83
  oral involvement *69.116*
  psoriasis and 62.55
  transglutaminases 40.59
  urticaria and 22.2
Coelomycetes 36.4
coenzyme Q-10 80.3
Coffin–Siris syndrome 15.33
cognitive behavioural therapy (CBT) **64.53**
  body dysmorphic disorder 64.20
  in dystrophic EB 39.30
  pathological skin picking 64.28
  theory of 64.53
  trichobezoar 64.32
cohort studies 6.19, 7.3–4
  appraisal 7.14–15, *7.15*
coin-rubbing 9.8
  injuries 28.25
COL1A1 gene 45.35, 45.40
COL1A2 gene 45.35, 45.40
COL3A1 gene 45.34
COL5A1 gene 45.33
COL7A1 gene 3.32, 3.35
  mutations 39.1
    Bart's syndrome 39.22
    bullous dermolysis of newborn 39.24
    dystrophic EB 39.15–17, 39.22, 39.24, 39.27
    EB simplex superficialis 39.5
    molecular diagnosis of EB 39.27
COL17A1 gene mutations 3.36–7
  in junctional EB 39.10
colchicine
  action 74.27
  adverse effects 75.134
  clinical indications 74.27
  in cutaneous small vessel vasculitis 50.16
  dose range and evidence level 74.27
  in pyoderma gangrenosum 50.72
  in relapsing polychondritis 45.43
  in systemic sclerosis 51.108
  in urticarial vasculitis 50.23
cold (cold temperature) 28.63–5
  ear injury 62.99, *62.102*, 68.5, 68.8, 68.10
  effect on peripheral nerves 63.14
  hyperhidrosis induced by 44.7, 44.8
  occlusion syndromes due to 49.32
  vasoconstriction induced by 63.4
  vasodilatation induced by 63.4–5
  see also cold-induced injury
cold agglutinins 13.18, 28.71, 49.34
  cutaneous occlusion due to 49.34
  in infectious mononucleosis 33.30
  monoclonal and polyclonal types 49.34
cold creams 73.7
cold flexed fingers 51.112
cold-induced injury **28.63–71**
  abnormal sensitivity to cold 28.65–71
  acrocyanosis 28.66–7
  cold agglutinins 28.71
  cold exposure 28.63–5
  cryoglobulinaemia 28.71
  ear injury 62.99, *62.102*, 68.5, 68.8, 68.10
  erythrocyanosis 28.67
  frostbite 28.63–4
  hyperhidrosis and 44.8
  livedo reticularis *28.66*, 28.67–8
  neonatal 17.35–6
  perniosis 28.65–6
  physiological reactions 28.63
  trench foot 28.64
  see also cold (cold temperature); Raynaud's phenomenon
cold-induced sweating syndrome 44.7, 44.8
cold nociceptors 4.9
cold panniculitis 17.35, 46.21
cold receptors 4.9
cold sores (reactivated herpes simplex) 33.3
Coleoptera 38.26–8
colistin 74.43
colitis
  Clostridium difficile 74.42–3
  collagenous 62.53
  ulcerative *see* ulcerative colitis
collagen 3.2, 3.33, **3.34–42**
  ageing and 8.22, 80.1, 80.2
  α-chains 3.34, 3.37
  in anchoring fibrils 3.32, 3.35–6
  bovine dermal, acne scar treatment 42.69
  as chromophore 78.3
  cross-linking 3.39
  defects in Ehlers–Danlos syndrome *3.35*, 3.36
  degradation 3.40–2, 47.27, 47.54
    ageing and 8.22
    regulation 3.41
  dermal fillers 80.4
  dermis, ageing and 8.22
  disorders **45.31–44**
    see also connective tissue disorders/disease
  dissection pattern 56.38, *56.39*
  dressings 14.24
  effects of corticosteroids on 45.4, 73.17
  FACIT (fibril-associated) 3.34
  fibrillar 3.34
    synthesis 3.37
  formation in scleroderma 12.31
  gene expression regulation 3.39
    trans-/*cis*-acting 3.39
  genetic heterogeneity *3.34*
  hydroxylation reactions 3.37–8
  hydroxyproline and hydroxylysine residues 3.37
  implants, foreign body reactions 28.46–7
  in irritant contact dermatitis 25.5
  in keloids 45.54
  lysine residues 3.37, 3.38
  mechanical properties of skin and 4.8
  mRNA formation, control 3.39
  number of types 3.34
  oxidative deamination reaction 3.39
  periodicity in fibres 3.27, *3.28*
  pro-α-chains 3.37
  procollagen type III (PIIINP) 20.33, 20.35
  prolyl hydroxylation reaction 3.37
  remodelling 78.13
  resistance to proteolytic degradation 3.40
  in scars 14.7–8
  in striae 45.5
  structural organization 3.34
  subunit polypeptide 3.34
  synthesis 3.37–8
    by fibroblasts 3.49
    increased by retinoic acid 73.35
    increased in photodamaged dermis 3.39
    inhibition by corticosteroids 45.4, 73.17
    in scleroderma 12.31
    uncontrolled 3.39
  transepithelial elimination 45.64, 45.65
  triple-helical conformation 3.34, 3.37–8, 3.40
  type I 3.2, 3.35, 14.7, 80.1
    biosynthesis 3.37
    cross-linking 3.39
    decorin binding 3.46
    degradation 3.40–1
    mutations in Ehlers–Danlos syndrome 3.35

type III 3.2, 3.35, 14.7, 80.1
biosynthesis 3.37, 3.49
in Ehlers–Danlos syndrome 3.35, 45.34
in systemic sclerosis 51.92
type IV 3.2, 3.27, 3.34
α-chains 3.27, 3.35
antibodies 39.25
assembly 3.27, *3.28*
autoantibodies 3.27
basement membrane zone 3.25, 3.27
degradation 3.41
inclusions in multicentric reticulohistiocytosis 55.23
lymphatic vessels 48.4
mutations in renal diseases 3.27, 3.35
structure 3.35
vascular basement membrane 3.52
type V 3.35
biosynthesis 3.37
in Ehlers-Danlos syndrome 3.35, 45.33
type VI 3.35
type VII *3.31*, 3.34, 3.35–6, 39.16
absence, dystrophic epidermolysis bullosa 3.32
in anchoring fibrils 3.32, 3.35–6
assembly 3.27, *3.28*
biosynthesis 3.37
in bullous dermolysis of newborn 39.23
in dystrophic epidermolysis bullosa 39.15, 39.25
in epidermolysis bullosa acquisita 3.36, 40.51
gene encoding *(COL7A1) see COL7A1* gene
Gly-X-Y repeats 39.16
monoclonal antibodies to 39.25
mutations in epidermolysis bullosa *3.36*
structure 39.16
type XII 14.7
type XIV 14.7
type XVI, expressed by dermal dendrocytes 55.4
type XVII 3.36–7
biosynthesis 3.37
BPAG2 gene mutations 3.31
ectodomain and 40.46
in junctional epidermolysis bullosa 3.36–7
see also bullous pemphigoid antigens, BP180 (BPAG2; type XVII collagen)
type XXIX 3.37
types in skin 3.34–7
in wound healing 14.1, 14.7
xenogeneic bovine 80.4
'collagen disease' 51.1
collagen (vascular) disease *see* connective tissue disorders/disease
collagen (vascular) diseases *see* connective tissue disorders/disease
collagen dressings 14.24
collagenases 12.52, 14.11
abnormalities, dystrophic EB 39.16
ageing and 80.2
interstitial (MMP1) 3.40
neutrophil 3.41
in sarcoidosis 61.20
in wound debridement 14.22
collagenoma 18.31–2, 45.50
eruptive 18.31, 45.50
familial cutaneous 18.31, 45.50
plantar cerebriform 18.31
storiform 56.3
verrucous perforating 45.65
collagenosis
perforating (folliculitis) 59.80
reactive perforating 19.89
collagenous colitis 62.53
collagenous fibroma 56.10–11
collarette scale 5.7
'collarettes,' fibrinous, staphylococcal blepharitis *67.8*
collateral vessels/circulation
claudication management 47.5
'corkscrew' 47.5, 47.7
Colles' fracture 63.20, 63.21
collier's stripes 58.57
collodion (vehicle for topical therapy) 73.2
composition 33.48
wart treatment 33.48
collodion baby **17.19–21,** 19.13–17, 59.39
colloid bodies 10.38
in lichen planus 41.4, 41.5
Russell bodies 30.52
colloid degeneration *see* colloid milium (pseudomilium)
colloid milium (pseudomilium) 10.38, 45.66–7, 73.27
electron microscopy 10.30
colloid–amyloid bodies
Naegeli's syndrome 58.19
vitiligo 58.47
Vogt–Koyanagi–Harada syndrome 58.45
coloboma *67.4*
colony-stimulating factors 5.1
adverse effects 75.141–2
cells secreting 5.1
colophony (Colophonium) 26.20, 26.79, 26.82–3, 33.48
Colorado tick fever 38.34, 38.35
colostomy *see* stoma
colostrum 8.9
colour
in animals 2.5, 2.6–7
disorders *2.22*
hair *see* hair
hair coat, in animals 2.6
skin *see* pigmentation
colour developing agents, lichen planus-like contact dermatitis 41.23
coma, eccrine sweat gland necrosis induced by 44.18
combination chemotherapy, male genital dermatology 71.44
combined oral contraceptives (COCs)
acne treatment 42.53
failure rate, antibiotics affecting 42.54
melanoma and 54.57
melasma and 58.34
oral antibiotic interactions 42.51–2
comedo, definition 5.7
comedo naevus 42.78, 53.4
comedo naevus syndrome 18.27
comedogenesis
in acne 42.22–4
animal models 42.23
mechanical causes 42.76
reduced by antiandrogens 42.23–4
reduced by isotretinoin 42.58
topical drugs affecting *42.40*
comedones
in acne 42.18
in chloracne 27.13, *27.14*, 42.77
closed (whiteheads) 42.22, 42.30, 42.36
corticosteroids associated 73.19
cyclical growth 42.24
familial 42.78
familial diffuse 18.11
familial dyskeratotic 18.11, 19.76
formation *see* comedogenesis
in hidradenitis suppurativa 30.81
midfacial 42.30
open (blackheads) 42.22, 42.24, 42.30, *42.77*
pathogenesis 42.22–3
removal and extraction 42.67
rupture, reduction by topical retinoids 42.40
sandpaper 42.30, 42.56
secondary 42.31
solar/senile 42.79
retinoic acid therapy 73.36
submarine 42.31
treatment 78.14
Commission Internationale de l'Eclairage L*a*b* system 25.22
commissural pits 69.40–1
Committee on Safety of Medicines 75.4
common peroneal nerve 77.5
common variable immunodeficiency *13.13*, *17.72–3*, *69.117*
communication 72.1–5
amongst clinicians 72.26
bad news 72.4–5
risks of therapy 72.3–4
training in 72.2
community diagnosis 6.2
comparative dermatology **2.8–19**
see also animal(s)
comparative genomic hybridization (CGH) 54.24, 57.20
compartment syndrome, following arthropod bites/stings 38.2
compensation, in occupational dermatoses 27.1–2
complement 13.1, 17.48
abnormalities associated with DLE 51.17
absence from dermal–epidermal junction, systemic sclerosis 51.92
activation 13.2, *13.3*
assays 13.18–19, 17.55
C1q 13.2, 22.81
deficiency 17.83
C1r, deficiency 17.83
C1s, deficiency 17.83
C2
in angio-oedema 13.19
deficiency *13.13*, 13.18, 17.84
C3 13.2, 13.3
deficiency 13.22, 17.84
increased, oedematous scarring vasculitis panniculitis 46.32
measurement 13.18
C3 nephritic factor, partial lipoatrophy and 46.39–40
C3a 13.2, 13.4
in vasculitis 50.4
C3b 13.3
C3d 13.18
C4 13.3
deficiency 13.18, 13.22, 17.83–4, 22.22
measurement 13.18
C4a 13.2
C4b 13.3
C5 deficiency 17.84
C5a 13.2, 13.4
in vascultiis 50.4
C6 deficiency 17.84
C7 deficiency 17.84
C8 deficiency 17.84
C9 deficiency 13.18, 17.84
deficiency 13.4, 13.15, 13.18–19, 17.53, 17.82–4, 51.54
interaction with antibody deficiencies 17.84
management 17.85
in mice, acantholysis 40.6
panniculitis with 46.27
formation of blisters 40.28
lysis, sensitivity 49.30
patterns of abnormalities *13.18*
role in vasculitis 50.4–5, 50.5
Treponema pallidum movement inhibition 34.20
complement-deficient mice, acantholysis 40.6
complement receptors 13.3
CD88 13.2
CR1 (CD35) 13.3
CR2 (CD21) 13.3, 13.8
EBV infection 33.30
CR3 12.10, 13.3
deficiency 17.84
CR4 13.3
complementary and alternative therapy 64.2, **72.31–3**
acne vulgaris treatment 42.43
adverse effects 75.160–2
forms of *72.32*
potential risks 72.31, 72.32–3
in psychocutaneous disorders 64.54
rates of use 72.2, 72.31
reasons for use 72.32
complex of myxomas, spotty pigmentation and endocrine overactivity *see* Carney complex (Carney's syndrome)
complex rearrangements 15.2
complex regional pain syndrome (CRPS) 44.8, **47.10–11,** *62.101*, **63.20–2**
differential diagnosis 47.9
complex traits 11.14–16
complexion, concept of 64.1–2
compliance *see* concordance with therapy
Compositae *25.21*, 26.10, 26.18, 26.20, 26.24, 26.75–6, 26.77
Compound A (Cmpd A) 12.62
compound F 73.16
compression bandaging 14.20–1, 38.31, 38.60
complex regional pain syndrome 47.11
infantile haemangioma 18.52
long-stretch and short-stretch 47.48
multilayer 47.48
lymphoedema management 48.22
short-stretch bandaging 47.48, 48.22
venous leg ulcers 47.47, 47.48
compression of skin 4.8
compression stockings
deep-vein thrombosis 47.29
graduated elastic 47.38
lymphoedema management 48.22
post-thrombotic syndrome 47.40
varicose veins 47.38
see also elastic stockings; medical elastic compression stockings (MECS)
compression therapy
lymphoedema management 48.22–3
pneumatic, lymphoedema management 48.22–3
varicose veins 47.38
venous leg ulcers 47.47–8, 47.51
compression ultrasound (CUS), deep-vein thrombosis 47.29
computed tomography (CT)
foreign bodies 28.42
invasive otitis externa 68.26
lymphoedema 48.17
melanoma relapse 54.50
Sturge–Weber syndrome 18.66
venous malformations 18.71
computer palms 28.27
computers, disorders related to use 25.16–17
concanavalin A 13.23
conception, and drug therapies 72.28
conchoid bodies 61.4
concordance with therapy **72.5–7,** 72.25–6
influences on 72.6–7, 72.13
monitoring 72.5
strategies to improve 72.7, 72.26
conditioned hyperirritability 23.6
conditioners 66.96
condom chancre 34.7
condoms
allergic contact dermatitis due to 26.19
male genital dermatology 71.17
conductive deafness with ptosis and skeletal anomalies 15.33
condyloma
giant *see* Buschke–Löwenstein tumour
malignant, anogenital warts vs 33.42
condylomata acuminata 33.44
giant 52.26
in pregnancy 8.11
see also wart(s), anogenital
condylomata lata *34.10*, 34.11, 69.121
cone-nose bug *38.25*
cone shells 38.59

confidence intervals 6.18, 7.9, 7.17–18, 7.20–2
confluent and reticulate papillomatosis 19.121–2
confocal laser scanning microscopy 5.20
confounding 6.18
confounding factors 6.11
congenital abnormalities 18.1
  definition 15.2
  female genital dermatology 71.56
  male genital dermatology 71.13–14
  perianal/perineal dermatology 71.83–4
  umbilical dermatology 71.100
  see also developmental abnormalities; *specific abnormalities/conditions*
congenital absence of skin *see* aplasia cutis congenita
congenital adrenal hyperplasia **62.6–7,** 66.83
  children, acne and 42.76
  late-onset
    acne and 42.21–2, 42.73
    acne fulminans and 42.83
congenital adrenogenital syndrome, acne and 42.73
congenital autonomic dysfunction with universal pain loss 44.7
congenital CMV infection 33.29
congenital dermal melanocytosis *see* Mongolian spot
congenital erosive and vesicular dermatosis healing with reticulated supple scarring 17.11, 18.104, 50.62
congenital erythropoietic porphyria (CEP) 59.10
  hypertrichosis in 66.79
  prenatal diagnosis *16.3*
congenital fascial dystrophy 45.50–1
congenital generalized lipodystrophy (CGL) 46.37
congenital haemolytic anaemia, pigmentation in 58.53
congenital heart block (CHB), neonatal lupus erythematosus 51.49
congenital hypertrichosis, perianal/perineal 71.84
congenital hypertrophic lip of the hallux 65.7
congenital hypotrichosis with juvenile macular dystrophy (HJMD) 15.33
congenital ichthyosiform erythroderma (CIE) 19.17, 19.18
  see also lamellar ichthyosis
congenital ichthyosis with fine/focal scaling (CIFS; ichthyosis prematurity syndrome) 19.18–19
congenital insensitivity to pain with anhidrosis (CIPA) 15.34
congenital livedo reticularis 28.68
congenital localized absence of skin (Bart's syndrome) 18.101, 39.17, 39.18, **39.22**
congenital nodular calcification of Winer 68.18
congenital palmoplantar and perioral keratoderma *19.94,* 19.101–2
congenital palmoplantar and periorificial keratoderma with corneal epithelial dysplasia 69.25
congenital reticular ichthyosiform erythroderma 19.18
congenital ring constrictions *see* amniotic bands/adhesions
congenital rubella 17.41–2, 18.2, 33.71
congenital scalp defects with distal limb anomalies **15.96**
congenital syphilis *see* syphilis, congenital
congenital telangiectatic erythema and stunted growth (Bloom's syndrome) **15.76–7,** 62.27
congestive heart failure, in sarcoidosis 61.7
Congo floor maggot 38.8
Congo red 10.10
conical teeth, ectodermal dysplasias 15.58–9
conidia *36.2, 36.3,* 36.4, 36.9, 36.18
conidiobolomycosis 36.78–9
Conidiobolus coronatus 36.78–9
conjunctiva
  in atopic dermatitis 24.24
  biopsy 61.19
    ocular mucous membrane pemphigoid 67.19
  bulbar 67.2
  lentigo maligna 54.40–1
  naevus 54.18
  normal *67.14*
  ocular rosacea *67.7*
  palpebral 67.2
    bulbar, fusion in mucous membrane pemphigoid *67.18*
  papilloma 33.47
  scarring 67.20
    ocular mucous membrane pemphigoid vs 67.20
    Stevens–Johnson syndrome 67.21
  shortening 67.21
  ulceration, mucous membrane pemphigoid *67.18*
conjunctivitis
  acute follicular (chlamydial) 34.29, *34.31*
  adverse effects of treatment *26.46*
  chronic blepharitis with, treatment *67.12*
  cicatrizing 67.16–24
    autoimmune 67.17–20
    diseases causing 67.19, *67.20*
    epidemiology and description 67.16–17
    non-autoimmune 67.19, *67.20*
    in Stevens–Johnson syndrome 67.21
    treatment 67.22–3
    see also mucous membrane pemphigoid (MMP)
  due to Lepidoptera 38.29
  follicular *67.8,* 67.25
  gonococcal 34.25
  in graft-*versus*-host disease 67.22
  iatrogenic, ocular mucous membrane pemphigoid vs 67.20
  infective 67.19, *67.20*
  in mucous membrane pemphigoid *67.18*
  perennial allergic *67.13,* 67.15
  in psoriasis 67.5
  in rosacea 43.4, 43.5
  in sarcoidosis 61.7
  seasonal allergic *67.13,* 67.15
  in Stevens–Johnson syndrome 67.21, 76.16
  subepithelial immunobullous diseases and 67.20
  in toxic epidermal necrolysis 67.21
  vectors 38.6
connective tissue, loss, topical corticosteroids causing 73.17
connective tissue disorders/disease **45.1–70, 51.1–139**
  age of onset 51.27
  bone and joint involvement 62.103
  cardiac involvement 62.78
  classification 45.1
  cryoglobinulinaemia with 49.32
  deposition disorders 51.79
  dermatomyositis **51.120–9**
  discoid lupus erythematosus **51.4–22**
  ear involvement 68.17
  eosinophilic fasciitis 51.86
  erythromelalgia with 47.9
  genetic disorders 51.79
  graft-*versus*-host disease 51.83–6
  lupus erythematosus **51.1–62**
  metabolic disorders 51.79
  mixed 51.110–12
  morphoea 51.64–78
  occupational causes 51.80
  ocular involvement *67.29*
  oral involvement *69.117*
  overlap syndromes 51.110–12, 51.126
  panniculitis in 46.31–2
  pigmented purpuric dermatoses and 49.23
  in pregnancy *8.11,* 8.12
  respiratory tract involvement 62.80, 62.82
  rheumatoid disease **51.130–9**
  sarcoidosis and 61.17
  scleroderma 51.64
  scleroedema 51.118–20
  secondary mucinosis 59.29
  silicone breast implants and 70.7–8
  skin biopsy 10.42–3
  subacute cutaneous lupus erythematosus 51.2, 51.22–7
  systemic lupus erythematosus **51.27–63**
  systemic sclerosis **51.87–110**
  see also specific disorders and diseases
connective tissue growth factor (CTGF) 14.3
  gene expression 51.65
connective tissue panniculitis 46.15, 51.14–15, 51.87
connexins 3.24
  ectodermal dysplasias 15.67–8
  gap junctions 3.24
  homotypic and heterotypic 3.24
  mutations in fish 2.6
  scar formation and 14.8
connexons 3.24
connubial/consort allergy 26.41, 26.48
connubial dermatitis 26.18
conotruncal anomaly face syndrome 13.8
Conradi–Hünermann syndrome *62.100*
Conradi–Hünermann–Happle syndrome 19.3, 19.49–52
  prenatal diagnosis *16.3*
Conradi's syndrome (calcifying chondrodysplasia) 45.8
consent
  to skin biopsy 10.2
  to surgery 77.13
Consolidated Standards of Reporting Trials 7.16
CONSORT (Consolidated Standards of Reporting Trials) 7.16
CONSORT guidelines 6.16
constipation, in dystrophic EB 39.19, 39.28
constitutive skin colour 58.1, 58.7, **58.9–10**
constricting bands of the extremities *see* ainhum; pseudo-ainhum
consultation *see* dermatology consultation
contact dermatitis
  allergic *see* allergic contact dermatitis
  amputees 28.29
  chronic actinic dermatitis association 29.16, 29.17
  ear 68.23
  in elderly people 8.28
  eyelids 67.5
  female genitalia 71.58
  genitocrural 71.5
  insult (cumulative irritant contact dermatitis) 25.1, 25.5, 25.12–13, *25.14,* 25.15
  irritant *see* irritant contact dermatitis
  lanolin causing 73.6–7
  lichen planus-like 41.23
  male genitalia 71.17–18
  mechanical injury 28.13–14, 28.22, 28.25, 28.29, 28.52, 28.54
  occupational 27.2
  in palmoplantar hyperhidrosis 44.8
  perianal/perineal 71.84
  perioral dermatitis vs 43.11
  photoallergic 26.23–5
  pigmented 26.26
  protein 27.5
  race and 9.13, 26.8
  venous leg ulcers 47.44–5
contact hypersensitivity response (CHS) 13.27, *13.28*
  UVR effect 29.5
contact immunotherapy, alopecia areata 66.37
contact irritants, pigmented purpuric dermatoses due to 49.23
contact lens, corticosteroid contraindication 67.31
contact sensitization
  corticosteroids causing 73.17
  lanolin causing 73.6–7
  by sunscreens 29.9
  by topical antibiotics 73.10
  wart treatment 33.49
  see also contact dermatitis
contact urticaria *see* urticaria, contact
contagion, beliefs 64.6
contamination, measurement of 27.11
contiguous gene syndromes 15.6
contingency tables 7.20
contraceptive pill *see* combined oral contraceptives (COCs)
contractures, in dystrophic EB 39.29
Control of Substances Hazardous to Health legislation 26.100
contusion, ear 68.6–7
Conus (cone shells) 38.59
conversion disorder 64.25–6
converting enzymes 12.49
convulsions, febrile, in roseola infantum 33.32
cooks, occupational hazards 5.6, 27.19
Cook's syndrome 15.34
coolants, synthetic 27.5
cooling, skin surface 80.10–11
cooling pastes 73.2
Copenhagen Psoriasis Severity Index 72.9
coping strategies 64.4
copper
  as allergen 26.40
  deficiency 3.44, 66.94
  green hair induced by 66.95
  metabolism 59.76
  in occipital horn syndrome 45.39
copper chlorophyllin, in fish odour syndrome 44.20
copra itch 38.47
coproporphyria, hereditary 59.19
coproporphyrin III 30.38
coral bead sign 62.41
corals 38.55–8
Cordia 26.80
Cordylobia 38.8, 38.9, 38.10
corium *see* dermis
cornea
  in atopic eye disease 67.16
  drug-induced pigmentation 58.29, 58.30
  in dystrophic EB 39.19
  epithelial defects, in toxic epidermal necrolysis 67.21
  ocular rosacea *67.7*
  perforation, management 67.22
  persistent epithelial defect
    management 67.22
    mucous membrane pemphigoid 67.17, *67.18*
    Stevens–Johnson syndrome 67.21
  in psoriasis 67.5
  statue eye 40.39
  transplant *67.9*
  ulceration, management 67.23
corneal arcus 59.86
Cornelia de Lange syndrome *see* de Lange syndrome
corneocytes 3.1, 3.8, 4.2, 12.14
  changes with ageing 4.11, 8.23, 80.2
corneodermatoosseous syndrome 15.34
corneodesmosin 66.60
corneodesmosomes 12.14
cornifin 3.10
corns
  mechanical injury 28.10–12, 28.31
  plantar warts vs 33.44

coromandel *26.80*
corona phlebectatica paraplantaris 47.14, 47.33
corona seborrhoeica 23.30
corona veneris 34.11
coronary artery disease 47.5, 62.78
  Frank's sign 68.6
coronaviruses *33.2*
corpus luteum 8.8, 8.9
corrosion, tests for 25.9
Corrositex™ 25.9
corticosteroids 57.23, **74.2–3**
  in acne vulgaris 42.53
  acneiform eruptions due to 42.72
  adverse effects 28.46, 74.3
    cataracts 67.15–16, 67.31
    delays in wound healing 14.19
    in elderly people 8.28
    glaucoma 67.15–16, 67.31
    hypertrichosis *66.79*
    ocular 67.31
    purpura 49.15
    rosacea **43.10**
    topical use 26.18, 26.45, 45.3–4, 45.5, **73.17–20, 75.116–17**
  anti-inflammatory effects 13.23–4, 73.16–17
  antimitotic actions 73.16
  in balanitis xerotica obliterans 51.118
  candidiasis and 36.59, 36.61
  in carcinoid syndrome 43.19
  in chronic actinic dermatitis 29.18
  collagen gene expression control 3.39
  in congenital syphilis 34.16
  in dermatomyositis 51.129
  development 73.16
  fluorinated 73.23
  imidazoles with 73.12
  immunosuppressive effects 13.23–4
  induction of TLR-2 activation on keratinocytes 12.9
  inhaled, perioral dermatitis and 43.11
  intralesional 73.20, 77.48
    adverse effects 45.3–4
    in alopecia areata 66.36–7
    in discoid lupus erythematosus 51.20
    in Fox–Fordyce disease 44.22
    in granuloma annulare 60.10
    in infantile haemangioma 18.50
    in keloids/hypertrophic scars 14.15
    in Langerhans' cell histiocytosis 55.13
    in lichen planus 41.18
    needleless injection 77.48
    in psoriasis 20.25
    in pyoderma gangrenosum 50.72
  mechanical injury 28.53
  mechanism of action 73.16–17, 74.2
  mode of action 74.2
  in pemphigus 40.11–12, 74.2–3
  perianal/perineal dermatology 71.99
  in pregnancy 74.3
  purpura due to 49.15
  in pyoderma faciale 43.14
  rosacea due to **43.10**
  route of administration 74.2
  sebaceous gland activity and 42.11
  in SLE 51.61
  structure 73.16
  systemic 74.2–3
    aciclovir with in zoster 33.28
    in acne vulgaris 42.63, 42.66
    in actinic prurigo 29.14
    adverse effects 45.3–4, **75.115–16**
    in alopecia areata 66.37
    in atopic dermatitis 24.31
    in atopic eye disease 67.16
    in Churg–Strauss syndrome 50.42
    in cutaneous small vessel vasculitis 50.15
    in cytophagic histiocytic panniculitis 46.24
    in dermatophytoses 36.49
    in dystrophic EB 39.29
    in eczema 23.38
    in erythema multiforme 69.70, 76.7
    in erythroderma 23.49
    in giant cell arteritis 50.44
    in Hailey–Hailey disease 39.35
    in Henoch–Schönlein purpura 50.21
    in herpes zoster 63.6
    in hidradenitis suppurativa 30.81
    in hirsutism 66.88
    in idiopathic thrombocytopenic purpura 49.10
    indications 74.2
    in infantile haemangioma 18.49–50
    in Kasabach–Merritt syndrome/phenomenon 18.56–7
    in leprosy reactions 32.18
    in lichen planus 41.18
    in mastocytosis 22.36
    in morphoea, localized 51.74–5
    in multicentric reticulohistiocytosis 55.24
    in necrobiosis lipoidica 60.16
    in osteoporosis 74.3
    in polyarteritis nodosa 50.35
    in pyoderma gangrenosum 50.72
    in relapsing polychondritis 45.43
    route of administration 74.2–3
    in sarcoidosis 61.21
    in Sweet's syndrome 50.79
    in toxic epidermal necrolysis 76.20
    toxicity 74.3
    in urticaria 22.29
    in urticarial vasculitis 22.29, 50.22
    in Wegener's granulomatosis 50.40–1
tinea incognito and *25.15*, 36.35–6, 36.50, 73.18
topical 57.23, 64.25, 72.6, 72.7, **73.16–23**
  abuse for skin lightening 73.26
  acne vulgaris treatment 42.43
  acnegenicity 27.13
  adverse effects 26.18, 26.45, 45.3–4, 45.5, **73.17–20, 75.116–17**
  in allergic contact dermatitis 26.101
  in alopecia areata 66.36
  in atopic dermatitis 21.13, 24.29, 24.30
  in atopic eye disease 67.15–16
  calcipotriol with 73.45
  in cicatrizing conjunctivitis 67.22
  classification by potency 73.16, *73.18*
  clinical efficacy measurement 73.16
  combination therapies 73.20
  diffusion through stratum corneum 73.16
  in eczema 23.38
  effect on patch test reactions 26.9
  in erythroderma 23.49
  fear of (steroid phobia) 64.25, 72.6, 73.17
  formulations 73.20
  in Fox–Fordyce disease 44.22
  frequency of application 73.3
  glaucoma/cataract due to 67.15–16, 67.31
  in Hailey–Hailey disease 39.35
  in hand eczema 23.22
  in HSV infection of eye 67.26
  indications 73.20–1, *73.21*
  in infantile haemangioma 18.50
  infection exacerbation 73.18
  in irritant contact dermatitis 25.23
  labelling 72.7
  in lichen planus 41.17–18, 41.18
  local adverse effects 73.17–20
  in mastocytosis 22.36
  mechanism of action 73.16–17
  monitoring use 24.29
  in napkin dermatitis 17.26
  in necrobiosis lipoidica 60.16
  occlusion 73.20
  in otitis externa 68.25
  perianal/perineal conditions 71.99
  perioral dermatitis and 43.11
  potencies 73.16, *73.18*
  in pruritus 21.17
  in psoriatic nail involvement 65.26
  in pyoderma faciale 42.84
  rebound phenomena 73.19
  receptor and binding affinity 73.16–17
  rosacea induced by *73.19*
  in sarcoidosis 61.21
  in seborrhoeic dermatitis 23.33
  side effects 73.17–20
  stability 73.20
  systemic adverse effects 73.20
  unlicensed 73.20
  vascular effects 73.19–20
  vasoconstrictor assay 73.16
  vehicles 73.20
  vitiligo 58.48–9
  weekly dosage 73.20
  withdrawal 73.19
withdrawal
  in perioral dermatitis 43.12
  in steroid-induced rosacea 43.10
corticotrophin-releasing hormone (CRH) 64.9
cortisol 73.16
  in atopic dermatitis 24.19
  in Cushing's disease/syndrome 62.4
  hirsutism and 66.83
  see also hydrocortisone
Corynebacterium
  female genital infections 71.67
  male genital infections 71.31
  in normal skin flora 30.2, 30.3, 30.36, 68.2
  in pitted keratolysis 30.39
  taxonomy/classification 30.3
  in trichomycosis axillaris 30.39
Corynebacterium acnes see Propionibacterium acnes
Corynebacterium bovis 30.3
Corynebacterium diphtheriae 30.35, 30.36
  diphtheria **30.36–7**
  female genital dermatology 71.67
Corynebacterium haemolyticum 30.37
Corynebacterium hofmani 30.3
Corynebacterium minutissimum 30.3, 30.36, 30.37–8
  genitocrural infections 71.6
  in HIV infection 35.26
  Wood's light examination 5.19
Corynebacterium pyogenes 30.37
Corynebacterium tenuis 30.36
Corynebacterium xerosus 30.3
coryneforms, in normal skin flora 30.3
COSHH legislation 26.100
cosmeceuticals 80.3
cosmetic advertising 64.1–2
cosmetic camouflage 72.31
  acne scars 42.69
  in hypermelanosis 58.38
  in rosacea 43.6
  in sarcoidosis 61.10, 61.21
cosmetic fillers, sarcoidal reaction to 61.22
cosmetic industry, ageing and 8.25
cosmetic surgery/treatment
  congenital naevi 54.14
  varicose veins 47.37
cosmetic units, head and neck 77.2
cosmetics
  acnegenicity 27.13, 42.73
  advertising 64.1–2
  allergic contact dermatitis to 26.14, 26.16, 26.17, **26.47–9**
  avoidance 26.48
  comedogenic and acne due to 42.73
  EU directive 26.100
  eyelid contact dermatitis due to 67.5
  eyelid pigmentation due to 67.5
  facial melanosis due to 58.34
  hair **66.95–100**
  ingredient labelling 26.100
  irritant contact dermatitis due to 25.15
  nail 65.54–7
  patch testing 26.48–9
  perioral dermatitis and 43.11
  photodynamic substance in 58.35
  vehicles 26.58–60, 73.2–3
'costal fringe' 47.14
Costello syndrome *45.15*, 45.16
costunolide 26.75, 26.77
cotton-seed dermatitis 38.48
coumadin *see* coumarins; warfarin
coumadin necrosis 49.39
coumarins
  adverse effects 62.92, **75.105**
  in lymphoedema 48.25
  necrosis 49.39
  in secondary thrombocytopenia 49.11
  therapeutic effects 49.39
counselling
  genetic *see* genetic counselling
  interpersonal 64.53
counterstaining
  in immunoenzyme methods 10.17
  in immunofluorescence methods 10.14
cowage 21.4
Cowden's syndrome 62.25–6, 62.57
  breast involvement 70.17
  genetics **15.26–7**
  oral involvement 69.38
  palmoplantar punctate keratoses and 62.21
  PTEN gene mutations 53.5
  renal involvement 62.69
  trichilemmoma 53.5–6
cowpox 30.41, 33.7–8
cow's milk allergy 22.6
COX-1, and COX-2 *see* cyclooxygenases
coxsackieviruses **33.71–3**
  atopic dermatitis and 24.24
  A and B strains, and diseases 33.71–2, 33.73
  congenital infections 33.72
  Gianotti–Crosti syndrome 33.77
  oral infection 69.76, *69.118*
  purpura 49.20
  rashes/exanthems 33.72, 33.73
CP (cicatricial pemphigoid) *see* mucous membrane pemphigoid
CPA (Clinical Pathology Accreditation) 13.15
CPA (cyproterone acetate) *see* cyproterone acetate
CpG oligodeoxynucleotides (ODN) 12.9
CPOD (chronic papular onchodermatitis) 37.5
crabs (pubic lice) *see under* lice
cradle cap 17.11, 17.30
Crandall's syndrome *66.65*
cranial arteritis *see* giant cell arteritis
cranial nerves
  ear innervation 68.1
  palsy 61.7, *69.118*
    herpes simplex recurrence 33.18
cranio-ectodermal dysplasia **15.91–2,** 69.10
cranio-ectodermal syndrome 15.34
cranio-osteoarthropathy 15.88
craniofacial dysostosis **15.90–1**
craniofacial features, ectodermal dysplasias 15.59, 15.62, 15.64–6, 15.69
craniomandibular dermatodysostosis (familial mandibulo-acral dysplasia) 45.61–2
craniosynostoses **15.90–2**
craniosynostosis and porokeratosis (CDAGS syndrome) **15.91**
cranium bifidum 18.95
Cre/*lox* recombination 11.11
creams 73.2
  quantity applied 73.3–4
creatine, urinary 24-h 51.127
creatinine monitoring, burns 28.84
creeping eruption, cutaneous *see* larva migrans
creeping hair 28.49
Creole dyschromia 9.16
creosote 27.13
Creseis acicula 38.59

cresol 25.21
CREST/CRST syndrome 47.14, 51.104, 62.48, 62.99
  bone and joint involvement 62.99
  pigmentation changes 58.26
  respiratory tract involvement 62.82
cretinism 62.10, 62.11
Creutzfeldt–Jakob disease, new variant, sterilization of surgical equipment and 77.7
crevicular fluid 69.3
CRH (corticotrophin-releasing hormone) 64.9
cri du chat syndrome 15.12, 66.93
Crimean Congo haemorrhagic fever *33.67*, 33.70
crinkles 45.2
crisantaspase 75.132
Crisponi syndrome 45.46
crocodiles 2.3
Crohn's disease **62.48–50**
  acrodermatitis enteropathica and 62.49
  cutaneous 62.48, 62.49
  differential diagnosis 61.5
  direct skin and mucosal involvement 62.48–9
  epidermolysis bullosa acquisita and 62.49
  erythema multiforme and 62.50
  erythema nodosum and 62.50
  female genitalis involvement 71.65
  lichen nitidus association 41.22
  lymphoedema 48.13, 48.16
  male genitalia involvement 71.28, 71.30
  metastatic 62.49, 68.17
  necrobiosis lipoidica and 60.15
  oral 62.49, *69.116*
  oral intraepidermal IgA pustulosis and 62.49
  perianal/perineal involvement 71.82, 71.87, **71.89–90,** 71.91, 71.95
  polyarteritis nodosa and 62.49
  porokeratosis and 62.49
  psoriasis and 62.49
  purpura and 62.51
  pyoderma faciale and 42.84
  pyoderma gangrenosum and 50.65, 62.50–1
  reactive dermatoses associated 62.49
  reactive lesions 62.50
  sarcoidosis and 61.23
  sexual abuse 28.38
  subcorneal pustular dermatosis and 62.49
  Sweet's syndrome and *50.75,* 62.51
  vasculitis and 62.51
cromones, atopic eye disease treatment 67.15
Cronkhite–Canada syndrome 15.50, **58.13–14,** 62.57–8
cross-sectional studies 6.19, 26.2
cross-sensitization 26.44–5, 26.96
Cross' syndrome 58.42
crossing-over 15.7–8
Crosti's lymphoma 57.45
crotamiton
  in *Demodex* infection in rosacea 43.3
  in head louse infection 38.20
  in pruritus 21.17
  in scabies 38.41, 73.14
croton oil 25.3
crotonaldehyde 25.21
Crouzon's syndrome **15.90–1,** 68.4
Crow–Fukase syndrome 51.80, 58.29
  see also POEMS syndrome
Crow–Fukase–Takatsuki syndrome *see* POEMS syndrome
'crow's feet' 45.2
  botulinum toxin therapy 80.7, *80.8*
CRP (C-reactive protein) 12.28, 12.32, 13.4, 13.19
CRPS *see* complex regional pain syndrome
Cruciferae *25.21*
crust 10.38
  see also scab
cryofibrinogen 13.17–18, 22.16, 49.33
cryofibrinogenaemia 49.33–4
cryogelling, microvascular occlusion due to 49.32–4
cryoglobulin(s) **49.32–4**
  classification 49.32
  composition and associations *13.17*
  detection/investigations 49.32, 49.33
  in HCV infection 33.61, 49.32, 49.33, 50.24, 50.25, 62.59
  measurement 13.17–18
  type I (single molecule) 49.32, 49.33
  type II and III (mixed) 49.32
cryoglobulinaemia **28.71,** 49.32–3, 51.54
  cold urticaria and 22.16
  diagnosis 49.32, 49.33
  in hepatitis B virus infection 62.59
  in hepatitis C virus infection 33.61, 49.32, 49.33, 50.24, 50.25, 62.59
  lymphoproliferative disease with 49.32
  mixed 49.32, 50.24
  purpura in 49.4, 49.5, 49.19
  treatment 49.33
  type I 49.32, 50.23–4, 62.93–4
  type II 49.32, 50.24, 62.94
  type III 49.32, 50.24, 62.94
  vasculitis and 49.33, 50.23–5
cryopyrin-associated autoinflammatory syndrome (Muckle–Wells syndrome) **15.95–6,** 22.3, 59.57, 74.11
cryopyrin-associated periodic syndrome 22.24–5, 50.53, 62.69
cryosurgery **77.39–40**
  adverse effects 77.39–40
  clinical methods 77.39
  clinical uses 77.39, *77.40*
  epidermolytic/non-epidermolytic epidermal naevi 18.7
  granuloma annulare 60.10
  infantile haemangioma 18.52
  nail unit 65.48
  non-melanoma skin cancer 52.16
  sarcoidosis 61.21
  see also cryotherapy
cryotherapy
  acne vulgaris 42.68
  actinic keratosis 52.31
  Bowen's disease 52.34
  molluscum contagiosum 33.12
  warts 33.49–50
    disadvantages and sequelae 33.49
  see also cryosurgery
cryptococcosis **36.89–91**
  aetiology 36.89–90
  bone and joint involvement *62.100*
  definition 36.89
  external ear 68.28
  female genitalia involvement 71.69
  in HIV infection 35.24, 35.33, 36.89, 68.28
  meningitis 35.33
  oral involvement 69.80, *69.118*
  sarcoidosis and 61.17
Cryptococcus neoformans 36.89–91, 69.80
  female genitalia infections 71.69
  in HIV infection 35.33
cryptosporidiosis, HIV infection 35.35
crystal deposition, panniculitis with 46.16–17
crystal globulin vasculopathy 49.38
crystal-storing histiocytosis 46.17
crystal violet 10.10
  see also gentian violet
crystalline folliculitis, necrotizing crystalline 19.89
crystals, lipid-containing 46.16
CS *see* Cockayne's syndrome
CSS *see* Churg–Strauss syndrome
CST syndrome 15.28, 15.43
CSVV (cutaneous small vessel/leukocytoclastic vasculitis) *50.4,* **50.13–17**
CT *see* computed tomography
CTACK, in atopic dermatitis 24.7
CTCL (cutaneous T-cell lymphoma) *see under* lymphoma
Ctenocephalides canis 38.4, 38.11–12
Ctenocephalides felis 38.11–12
Ctenodactylus gondii 37.44
CTGF (connective tissue growth factor) 14.3
CTLA4 13.11
Cuban laurel thrips 38.26
Cubozoa 38.56
Culicidae *see* mosquitoes
Culicoides 38.6
  skin disease in animals 2.11
Cullen's sign 62.65
cultural factors 64.1–2, 64.6, 64.18
  in allergic contact dermatitis 26.10
  communication 72.2
cultural remedies, bruising/purpura due to 49.16
culture, history-taking 5.5
Cunninghamella berthollettiae 36.91
cupping 9.8
  therapeutic 28.24
Cupressaceae *26.80*
x *Cupressocyparis leylandii 26.80*
curettage **77.40–4**
  actinic keratosis 52.31, 77.40, *77.42*
  benign lesions 77.40
  Bowen's disease 52.34
  keratoacanthoma 52.43
  molluscum contagiosum 33.12
  non-melanoma skin cancer 52.16, 77.40–1, *77.43, 77.44*
  pyogenic granuloma 77.40, *77.41*
  skin biopsy 10.4
  wart treatment 33.49, 77.40
curlicue pattern 10.38
curly hair–ankyloblepharon–nail dysplasia (CHANDS) 15.35, 15.63, 15.65
Curry–Hall syndrome 69.11
Curry–Jones syndrome **15.91**
Curth–Macklin ichthyosis hystrix 19.99
Curth's angle/modified profile sign 65.7, *65.8*
Curvularia 36.55, *36.73*
Cushing's syndrome/disease 8.18, **62.3–4**
  acne and 42.73
  candidiasis and 36.58
  dermatophytosis and 36.22
  hair in 66.83
  hair loss in, in animals 2.18
  hyperpigmentation 58.24
  pityriasis versicolor and 36.10
  purpura 49.15
  sarcoidosis and 61.17
  sebaceous gland activity and 42.11
  striae in 45.5
cutaneomucosal venous malformation 18.74
cutaneous adenopathy complex 37.32
cutaneous afferent nerves 12.64
cutaneous field stimulation, in notalgia paraesthetica 63.23
cutaneous gaseous exchange 4.11
cutaneous Hodgkin's disease 57.63
cutaneous horn **52.36,** 53.13
cutaneous larva migrans *see* larva migrans, cutaneous
cutaneous leukocyte antigen (CLA) 13.4, 55.1, 76.9
cutaneous lupus erythematosus *see* discoid lupus erythematosus; lupus erythematosus (LE); subacute cutaneous lupus erythematosus
Cutaneous Lupus Erythematosus Disease Area and Severity Index 72.10
cutaneous lymphomas **57.1–64**
  see also lymphoma(s); *specific lymphomas*
cutaneous microvascular occlusion *see* microvascular occlusion
cutaneous necrosis *see* necrosis
cutaneous neurofibromas 15.17
cutaneous porphyrias *see under* porphyria
Cutaneous Reactions Database 75.3
cutaneous sarcoidosis *see* sarcoidosis, cutaneous
cutaneous T-cell lymphoma (CTCL) *see under* lymphoma
'cutaneous' vessel network 3.50
cutaneous–intestinal syndrome with oropharyngeal ulceration 49.46
cute (pinta) 30.63–4
Cuterebra 38.9
cuticle 3.14, 65.2
  insects 2.2
  marine worms 2.2
  removers 65.56
cutis *see* dermis
cutis gyrata 18.40
cutis hyperelastica *see* Ehlers–Danlos syndrome
cutis laxa 8.21, 8.22
  acquired 45.14, 45.16, 45.18
  autosomal dominant 45.15
  autosomal recessive 45.15
  congenital 45.16
  ear 68.18
  elastin gene mutations 3.44
  generalized 45.14–17
  hereditary 45.15
  localized abdominal wall 45.12–13
  post-inflammatory elastolysis and 45.19–20
  syndromes *45.15*
  X-linked (occipital horn syndrome) 3.44, 45.14, *45.15,* 45.36, **45.39**
cutis marmorata 17.4, 28.68, 62.11
  in infancy 49.48
cutis marmorata telangiectatica congenita 17.4, 18.67–8, 28.68, 49.48
  with macrocephaly 18.68
cutis rhomboidalis nuchae 45.26
cutis verticis gyrata (CVG) **15.89,** 62.39, **66.58**
  with mental deficiency 15.89
  prenatal diagnosis 16.7
  retinitis pigmentosa and sensorineural deafness 15.89
CVID (common variable immunodeficiency) *13.13, 17.72–3, 69.117*
CVS (chorionic villus sampling) 16.1–2
CX3CR1, cell–cell adhesion and leukocyte trafficking 12.48
CXCL chemokine/receptor family (CXCL1–15) 12.45, 12.46–7
CXCR2 14.3
CXCR4, inhibition, HIV infection treatment 35.6
cyanamide 75.88
cyanoacrylates 26.72, 65.28
cyanocobalamin *see* vitamin B_{12}
cyanosis
  nails in 65.15
  neonatal peripheral 17.4
cyclamates 75.159
cyclic AMP (cAMP) 67.31
  in atopic dermatitis 24.15–16
cyclic citrullinated peptide, antibodies to 13.21
cyclic GMP (cGMP)
  in malakoplakia 55.27
  in psoriasis, dithranol action 73.29
cyclist's nipple 70.10–11
cyclizine 75.149
cyclobutane pyrimidine dimers (CPD) 29.4, 29.5, 58.7
cyclocysdopaquinonimine *58.6*
cyclodopa *58.6*
cyclohexanone peroxide 25.21
cyclohexylthiophthalimide 26.65
cyclooxygenases 12.60
  COX-1 12.60
    inhibition 49.13
  COX-2 12.60
    inhibition 49.13
    lichen planus 41.15

cyclophosphamide 13.24, 74.17–18
  adverse effects 75.125
    hypermelanosis 58.30
  in cicatrizing conjunctivitis 67.23
  in dermatomyositis 51.129
  dose range and evidence level 74.17–18
  in microscopic polyangiitis 50.36
  in mucous membrane pemphigoid 40.40
  in multicentric reticulohistiocytosis 55.24
  in pemphigus 40.12
  in polyarteritis nodosa 50.35
  in Wegener's granulomatosis 50.40–1
Cyclops 37.12, 37.13, 37.18, 37.26
cycloserine 75.61
cyclosporin *see* ciclosporin
cycobemine *see* vitamin B_{12}
CYLD gene mutations 53.9, 53.28
cylindroma 53.2, 53.28–9
  benign eccrine 68.30
  malignant 53.33–4
  spiradenoma overlap 53.29
Cylindrothorax melanocephala 38.26
cyproheptadine 74.31
cyproterone acetate (CPA) 74.32
  acne vulgaris treatment 42.53
  adverse effects 66.88, *70.5*, 75.120
  in androgenetic alopecia 66.25–6
  hair growth and 66.13
  in hirsutism 66.87–8
  sebaceous activity inhibition 42.15–16
'Cyrano nose' 18.46
cysdopaquinone *58.6*
cyst(s) **52.45–8**
  acne vulgaris *42.18*, 42.31
  branchial (cleft) 18.85–6
  bronchogenic (presternal ciliated) 18.87–8
  cervical 18.85–6
  definition 5.7
  dental, in naevoid basal cell carcinoma syndrome 52.7
  dermoid
    congenital 18.88–9
    oral cavity 69.34–5
  epidermal, vulval 71.72
  epidermoid ('sebaceous') *see* epidermoid ('sebaceous') cysts
  epidermoid plantar 33.47
  epithelial (epidermoid) 52.45–6
  eruptive vellus 53.7
  eyelids 67.33
  female genital 71.72, 71.73
  in Gardner's syndrome 52.45
  genitoperineal raphe 18.94–5
  glands of Zeis 67.33
  hair germ **53.6–12**
  horn 53.35
  hydatid 37.24–5
  keratinous 52.45
  lateral cervical 18.85–6
  male genital 71.35
  marsupialized 52.46
  median raphe 71.35
  of Moll 67.33
  mucinous 71.73
  mucoid, male genitalia 71.35
  mucous/mucous retention (mucocele) 69.22, *69.65*, 69.84, **69.110**
  myxoid
    nail 65.17, 65.36–7
    surgery *77.36*, *77.38*
  'onion-skin' 46.29
  oral *69.107*
  parameatal 18.94–5
  perianal/perineal 71.83, 71.87
  phaeomycotic subcutaneous **36.77**
  pilonidal 71.87
  preauricular **18.83–4**
  sebaceous 52.45
    see also epidermoid ('sebaceous') cysts; steatocystoma multiplex
  subepidermal keratin *see* milia
  thyroglossal 18.86–7, 62.11
  traumatic inclusion 52.45
  trichilemmal *see* trichilemmal cyst
  vulval epidermal 71.72
cystadenoma, apocrine 53.18–19, 68.30
cystamine 73.27
cystatin 4.5
5-cystdopa *58.6*
cysteinyldopa 58.5, *58.6*
cystic eyelids–palmoplantar keratosis–hypodontia–hypotrichosis 15.52
cystic fibrosis *69.116*
  of pancreas 59.59
  skin wrinkling 28.93
  sweat in 44.6
  vasculitis and 50.53
cystic hygroma 48.26–7
  fetal 48.27
cysticercosis 37.3, 37.24, **37.25**
cysticercosis cellulosae cutis 37.25
Cysticercus cellulosae 37.25
cystine 66.5
cytarabine 75.129
cytochrome P450 enzymes 72.27, 72.28–9
  CYP2S1 and CYP26 73.35
  CYP26A1, in sebaceous glands 42.15
  retinoid metabolism 73.35
cytodiagnosis 10.28–9
cytokeratins
  antibodies to 10.19–21
  CK-7 10.21
  CK-15 53.35
  CK-20 10.20–1
    extramammary Paget's disease 53.40
    Merkel cells 53.31, 53.43
cytokine antagonists 12.35, 12.43
cytokine-directed biological therapies 74.9–11
'cytokine storm' 74.4
  virus-associated haemophagocytic syndrome 55.30
cytokines 12.34–5, 17.49, 64.9
  in acute wounds *14.5*
  antagonists 12.35, 12.43
  assays 13.23
  in atopic dermatitis 24.18
  ATP2C1 gene expression down-regulation 39.33
  brain 64.8
  collagen gene expression control 3.39
  ductal keratinocytes, in acne 42.24
  inflammatory, lichen planus 41.1
  in irritant contact dermatitis 25.5, 25.6
  Langerhans' cell development *55.2*, 55.1, 55.3
  NF-AT mediated transcription 74.18
  in polymorphic light eruption 29.11
  proinflammatory
    acne pathogenesis 42.25, 42.26
    activation by UV radiation 8.21, 8.22
    keratinocytes 12.15–17
  proteoglycan binding 12.31
  pruritus and *21.3*, 21.5
  recombinant 12.35
  role in inflammation 12.34–5
  sebocytes expressing 42.4–5
  stress and 64.9
  suppressor of cytokine signalling (Socs) protein pathway 12.35
  suppressors and inhibitors 12.43
  synthesized by cells of the dermis 12.76–7
  T helper cells, acne pathogenesis 42.26
  therapeutic 13.25
    adverse effects 75.141–6
  UV-induced 4.7
  UVR-induced damage and 29.5
  in vasculitis 50.4, 50.5, 50.6, 50.10–11
  in wound healing *14.5*
  see also interleukin(s)
cytomegalovirus (CMV) infections 33.29, **33.29–30**
  alopecia areata and 66.32
  clinical features 33.29
  conditions associated 33.29
  congenital 33.29
  diagnosis 33.29
  disseminated 33.29
  female genitalia 71.70
  in HIV infection 35.28, 35.29
    immune restoration and 35.29, 35.46, *35.47*
  HSV co-infection 35.28, 35.29
  in immunosuppressed patients 33.29
  intrauterine 18.2
  isolation and detection 33.29
  juvenile xanthogranuloma 55.15
  mononucleosis 33.29
  neurological complications 33.29
  neuropathy associated 63.12
  oral 69.75–6
  perianal/perineal 71.95
  perinatal and neonatal 33.29
  reactivation
    in GVHD 62.97
    in HIV infection 35.29
  retinitis 33.29
  TORCH syndrome 33.76–7
  transmission 33.29
  treatment 33.29
  vasculitis and 50.55
cytophagocytosis 55.25
cytosine 11.2
cytosine arabinoside 75.129
cytosine-phosphate-guanine (CpG) DNA sensor 12.9
cytoskeleton of cells 3.9
cytostatic drugs, hypermelanosis due to 58.30
cytotoxic drugs
  adverse effects *26.46*, *70.5*
  cytophagic histiocytic panniculitis 46.24
  isolated limb perfusion in recurrent melanoma 54.54
  Langerhans' cell histiocytosis 55.13
  topical **73.23–6**
    see also 5-fluorouracil
  see also chemotherapy
cytotoxic T cells *see* T lymphocytes, cytotoxic

D

D2-40 *see* podoplanin
Dabska's tumour 56.32–3
dacarbazine (DTIC) 75.126
  melanoma management 54.54
daclizumab (anti-CD25 IL2 receptor), psoriasis in HIV infection 35.17
dactinomycin, adverse effects 75.127
dactylitis
  blistering distal 30.33
  syphilitic 34.16
DAF (CD55) 13.3
daffodil 25.21
Daflon® 48.25
Daivobet® 73.45
Dalbergia 26.80–1
DALYs (disability adjusted life years), leprosy 32.2
danaparoid 49.28
danazol 74.32
  adverse effects **75.119**
    erythema multiforme *76.3*, *76.4*
  in angio-oedema due to C1 esterase inhibitor deficiency 22.22
  in gigantomastia 70.3
  in gynaecomastia 70.5
  prophylactic, in hereditary angio-oedema 22.22
  in SLE 51.62
  in urticaria 22.29
dandruff
  pityriasis capitis **66.56–7**
  seborrhoeic dermatitis and 23.29, 23.30
  treatment 23.32–3
  'walking'/'mobile' 38.49
Dandy–Walker syndrome 69.29
Dane particle 33.60
Danoff syndrome 62.79
danthron (dantron) 75.158
danthron erythema 71.87
dapsone 74.28, 74.45
  adverse effects **75.63**
  in bullous systemic lupus erythematosus 40.56
  in cicatrizing conjunctivitis 67.23
  in cutaneous small vessel vasculitis 50.16
  in dermatitis herpetiformis 40.62
  in dermatomyositis 51.129
  dose range and evidence level 74.28
  in erythema elevatum diutinum 50.27
  in Henoch–Schönlein purpura 50.21
  in leprosy 32.16, 32.17
  in linear IgA disease 40.50
  in mucous membrane pemphigoid 40.40
  oral, acne vulgaris treatment 42.66
  in pemphigus foliaceus 40.16
  in pyoderma gangrenosum 50.72
  resistance to 32.16
  in subcorneal pustular dermatosis 40.22
  topical, acne vulgaris 42.43
  in urticaria 22.29
  in urticarial vasculitis 50.22, 50.23
dapsone syndrome (lymphadenopathy and hepatitis) 40.62
DARE (Database of Abstracts of Reviews of Effectiveness) 7.5
Darier's disease 19.3, 19.81–6, 39.32, 39.33, 64.48
  acne and 42.71
  differential diagnosis 23.32, 40.11
    Hailey–Hailey disease vs 39.35
  ear 68.14
  female genital involvement 71.66, 71.81
  genitocrural involvement 71.5–6
  in HIV infection 35.28
  linear 18.24
  male genital involvement 71.28
  nail involvement 65.17–18, 65.27–8
  oral involvement 69.25–6
  related disorders 19.86–8
  respiratory tract involvement 62.80
  treatment 73.23, 79.4
    retinoic acid 73.36
Darier's sign 5.18, 21.10, 22.14
  in urticaria pigmentosa 22.14, 22.31–2
Darier–White disease *see* Darier's disease
darkling beetles 38.27
Darling's disease *see* histoplasmosis
dart hairs 38.28
dartoic myoma 56.54–5
Darwin's tubercle 68.4
Database of Abstracts of Reviews of Effectiveness 7.5
Datura metel 75.160
daunorubicin 75.127
D-dimer 47.29
de Barsey syndrome 45.15
de Lange syndrome (Cornelia de Lange) **15.92,** 69.38
  hypertrichosis in 66.76
De-Nol 75.157
de Sanctis–Cacchione syndrome 15.73
deafness
  ear pits and 18.83
  eighth-nerve, congenital syphilis 34.16
  erythrokeratoderma with 19.71–2
  keratodermas with *19.94*, 19.98, 19.108–10
  KID/HID syndrome 19.54–7, 19.60
  with onychodystrophy 15.35
death fever (visceral leishmaniasis) **37.41–3**
débridement, venous leg ulcers 47.48
DEC *see* diethylcarbamazine
decay-accelerating factor (CD55) 13.3
decision making *see* clinical decisions
deCODE 11.15
decompression, burns 28.79–80, *28.81–2*
decongestive lymphatic therapy 48.21–4
decorin 3.46, 14.7, 45.33

decubitus ulcer 47.57
decubitus ulcers *see* pressure ulcers
deep-sea diving 28.55
deep-vein bypass 47.51
deep vein incompetence 47.41
deep-vein insufficiency 47.33
deep-vein obstruction 47.32
deep-vein thrombosis (DVT) 47.7, 47.26, **47.28–30**
  aetiology and pathogenesis 47.28
  antiphospholipid syndrome 49.41
  clinical features 47.28–9
  cyproterone acetate causing 42.53
  diagnosis 47.29
  differential diagnosis 30.19
  epidemiology 47.28
  paraneoplastic 62.43
  post-thrombotic syndrome 47.40
  in pregnancy 8.11
  treatment 47.29–30
  venous ulceration and 47.42
  see also venous thrombosis
deer flies 37.11, 38.6
DEET 38.5
defence mechanisms *see* host defence
defensins 3.2–3, 3.16, 3.17, 4.5, 12.5–7, 13.4, 14.5, 30.5
α-defensins 4.5, 13.4
deferoxamine 75.102
deficiency diseases 6.13
deformations 18.1
Degos' acanthoma 52.41
Degos' disease (malignant atrophic papulosis) **49.45–7,** 50.54, 71.25
  benign cutaneous (skin-limited) variant 49.45, 49.46
  male genital involvement 71.25
Degos' syndrome 51.105
Degos–Touraine syndrome 45.13
7-dehydrocholesterol 29.6, 73.43
dehydrocostus lactone 26.75, 26.77
dehydroepiandrosterone
  acne aetiology and 42.21, 42.35
  in pregnancy 8.9
dehydroepiandrosterone sulphate (DHEAS) 42.10, 42.21
  acne aetiology and 42.21, 42.22
  comedogenesis and 42.23
  hirsutism and 66.81
dehydrotestosterone, acne aetiology and 42.20
delavirdine 74.50, 75.68
delayed blanch phenomenon 24.15
delayed-type bacterial antigen tests 5.24
delayed-type hypersensitivity (DTH) *see* hypersensitivity, type IV (delayed-type)
Delhi boil (Old World cutaneous leishmaniasis) **37.34–9**
deliberate self-harm, adolescents 8.7
Delleman's (Delleman–Oorthuys) syndrome (oculocerebrocutaneous syndrome) 18.37, 18.104
deltanoids 73.43–8
delusions 64.12
  olfactory 64.16–17
  of parasitosis 21.12, 64.13–16, 65.50, 68.16
demeclocycline, lichenoid eruptions due to 41.24
Demodex **38.52–4**
  dog infestations 2.9, 2.10
  folliculitis
    acne vs 42.36–7
    rosacea vs 43.5
  in HIV infection 35.36
Demodex brevis
  eradication/treatment 43.3
  rosacea pathogenesis 43.2–.3
Demodex cati 2.10
Demodex folliculorum
  eradication/treatment 43.3, 43.6
  rosacea pathogenesis 43.2, 43.3, 43.5, 43.6
Demodex gatoi 2.10
demodicosis 2.10
demography, skin disease in old age 8.25–7
denaturing gradient gel electrophoresis (DGGE) 57.12
dendrite surveillance extension and retraction cycling habitude (dSEARCH) 3.17
dendrites, melanocyte, formation of 58.4
dendritic cells 5.1
  antigen presentation 55.4
  in atopic dermatitis 24.13–15
  defensins 12.7
  dermal 3.19, 48.6
  epidermal modulation of function 24.14
  follicular 13.9
  HIV infection 35.8
  in lymph nodes 13.9
  lymphoid 4.8
  migration 48.6
  role in immune system 13.5, 13.9
  subtypes 24.13
  see also histiocytes; Langerhans' cells
dendrocytes
  dermal *see* dermal dendrocytes
  fat-storing hamartoma of **46.45**
dengue *33.67*, **33.68**
  virus serotypes 33.68
dengue fever (DF) 33.68, 38.5, 49.20
dengue haemorrhagic fever (DHF) 33.68, 49.20
dengue shock syndrome (DSS) 33.68, 49.20
denileukin diftitox 13.25
  subcutaneous panniculitis–like T-cell lymphoma 57.33–4
Dennie–Morgan fold 24.24
dense bodies 3.51
dental amalgam 75.101
  allergic contact dermatitis and 26.21, 26.39
  lichen planus pathogenesis 41.3
  tattoos 69.95–6
  urticaria associated 22.11
dental aplasia 69.6, 69.7
dental care, in severe generalized dystrophic EB 39.28
dental caries, in dystrophic EB 39.19
dental cysts, in naevoid basal cell carcinoma syndrome 52.7
dental follicle 69.2
dental papilla 69.2
dental preparations 69.120
dental sinus *42.37*
dental technicians, occupational hazards 27.19
dentifrice 69.119–20
dentine 69.2
dentinogenesis imperfecta 45.40, 45.41, 69.8
dentists, occupational hazards 27.19
dentition 69.2, *69.3*
  deciduous/milk 69.2, *69.3*
  examination 69.6
  permanent/adult 69.2, *69.3*
  see also teeth
dentogingival junction 69.3
dentooculocutaneous syndrome 15.29
denture sore mouth (chronic erythematous/atrophic candidiasis) 36.60, *69.88*, 69.102–4
dentures
  allergic contact dermatitis and 26.21
  hyperplasia induced by 69.109–10
  mouth ulcers due to 69.43
  oral changes related to 69.102–3
  stomatitis 36.60, *69.88*, 69.102–4
DEPA 38.5
dependency syndrome 48.14
depigmentation 58.9
  chemical 27.15, 58.50–1
  halo, halo naevus 54.19
  hypermelanosis treatment 58.39
  occupational 27.15
  in onchocerciasis 37.5–6
  post-inflammatory 5.16–17
  see also hypopigmentation; leukoderma
depigmenting agents
  cosmetic use 73.26, 73.27
  topical 73.26–9
depilation 73.29
  in hirsutism 66.85, 66.87
depilatories 73.29
depilatory creams 73.29
deposition disorders 51.79
  paraneoplastic 62.44, *62.45*
depression 64.3, 64.7, **64.47–8**
  acne and 42.35
    isotretinoin treatment and 42.63
  concordance with therapy and 72.6
  isotretinoin therapy and 42.63, 64.49
  lichen planus association 41.3
  major 64.47–8
  in psoriasis 64.4
  in psychocutaneous disorders 64.15, 64.18, 64.28, 64.30
  screening instruments 64.48
depressive ruminations 64.12
depth of burn classification 28.75, *28.76–7*, 28.84–5
dequalinium, male genital dermatology 71.27
dequalinium chloride 25.12, 75.164
Der f1 38.47
Der p1 38.47
Dercum's disease 8.17, 46.46, 46.47–9, 48.20
dermabrasion
  acne scars 42.69
  actinic keratosis 52.32
  congenital naevi treatment 54.14
  post-inflammatory hypermelanosis after 58.31
  skin flap scars 77.26
  tattoo removal 58.59
Dermacentor 30.53, 30.58, 30.73, 38.34, 38.35
dermal-associated linear IgA disease 40.49
dermal collagen, hyalinization 51.114
dermal dendrocytes 55.3
  fat-storing hamartoma 55.19
  fate 55.4
  histiocytoses involving 55.6, **55.14–22**
  juvenile xanthogranuloma 55.15–16
  origin and development 55.3
  phenotype 55.4
  subepidermal 55.3
  surface markers 55.3, 55.4
dermal erythropoiesis (blueberry muffin baby) 17.32–3, 49.20, 49.51
dermal fillers 80.4–6
  in combination with botulinum toxin 80.7–8
  foreign body reactions 28.46–7
dermal leishmanoid 37.41–2
dermal melanocytosis 58.36–8
dermal papilla 3.13, 66.3, 66.4, 66.7, 66.15
dermal sheath 66.4
dermal–epidermal basement membrane zone (BMZ) **3.25–33**
  see also basement membrane zone (BMZ); dermal–epidermal junction (DEJ)
dermal–epidermal junction
  deposition of IgG, IgM and C3 in scleroedema 51.119
  systemic sclerosis 51.92
dermal–epidermal junction (DEJ) 3.6, **3.25–33, 40.24–5**
  ageing and 80.2
  biopsy in epidermolysis bullosa 39.24
  ear 68.1
  hemisdesmosomes 3.30–2
  keratinocyte proliferation, signalling 3.6
  in lichen planus 41.4
  mechanical function 4.8
  melanocytes 54.1, 54.2, 54.4, 54.15, 54.18
  molecular components 3.25–6
    see also anchoring fibrils; collagen, type IV; hemidesmosome(s); laminin(s)
  regional variations in 3.3
  structure 3.1–2, 3.25–6
  in wound healing 14.5
Dermanyssidae 38.51
Dermanyssus 38.51
dermatan sulphate 3.46, 4.8
  structure *3.47*
  in wound healing 14.3
dermatitic potential 27.10–11
dermatitis
  acral lick 2.9
  airbag 28.14
  allergic contact *see* allergic contact dermatitis
  in animals 2.13–14
  annular lichenoid, of youth 41.13
  asteatotic 47.34
  atopic *see* atopic dermatitis (AD)
  atopic vs non-atopic 24.1
  autoimmune progesterone 8.9, 8.15, 8.19, 75.119
  berloque 26.18, 58.32
  bush 26.75
  canine metabolic necrolytic 2.17
  cercarial 37.20, **37.22–3,** 38.56, 38.57
  chronic acral 23.15
  chronic actinic *see* chronic actinic dermatitis (CAD)
  chronic superficial (persistent) scaly 23.7–8, 57.57
  connubial 26.18, *29.10*
  contact *see* contact dermatitis
  contagious pustular *see* orf
  cotton-seed 38.48
  definition 23.1
  discoid 64.47
  eczematous, impetiginization 47.34
  erosive pustular *see* erosive pustular dermatitis
  exfoliative *see* erythroderma
  factitial 71.56
  fibreglass 25.17, 27.6, 28.47–8
  flea bite, in animals 2.10
  flee allergy 2.10
  food-mite 38.46–7
  frictional, of children 28.14
  frictional sweat 28.14
  genitocrural 71.5
  granulomatous perioral, in children 43.12, **43.13**
  granulomatous periorificial 43.12, **43.13**
  halo 23.12–13
  hand *see under* hand(s)
  hearing-aid 26.17, 68.23–4
  housewives 23.20–3, 26.15, 27.2, 27.3
  Indian sandal 26.68
  infantile eczematoid 68.19
  infective 23.23–5, 47.34, 68.19
    of (Jamaican) children associated with HTLV-1 infection 23.25
    eczematoid 68.19
  infra-auricular 24.23
  interstitial granulomatous 50.52
  intrinsic 24.1
  irritant
    topical acne agents causing 42.49
    see also irritant contact dermatitis
  Jacquet's 17.24
  juvenile plantar 28.14
  khaki 26.26, 26.66
  lichenoid 41.5–6
  lipstick 26.17
  meadow 58.32
  meadow/strimmer/weedwacker *5.15*, 58.32
  moth 38.29
  napkin (diaper) **17.22–7,** 17.30, 25.16, 71.5
    congenital syphilis vs 34.16
    psoriasiform 17.31
  nipple, mechanical injury 28.14

nummular, mechanical injury 28.14
pachydermatous eosinophilic 24.27
palisaded neutrophilic and granulomatous 50.52
papular 23.44
of pregnancy 8.15
perianal 25.16
periocular 43.11
corticosteroids associated 73.19
perioral **43.11–12**
peristomal 25.16
persistent postirritant (postoccupational) 25.26
photoallergic, sunscreens causing 73.40
photocontact 75.32
photosensitivity 29.17
pigmented contact 26.26
pigmented cosmetic 58.35
pityrosporal *see* seborrhoeic dermatitis
pretibial pruritic papular 28.15
progesterone-induced, tamoxifen 74.33
protein contact 26.105–6, 27.5
recurrent granulomatous with eosinophilia *see* Well's syndrome
retinoid 73.27
rubber, male genitalia 71.17
sarcoid-like granulomatous 43.12, **43.13**
schistosomal 37.21
seborrhoeic *see* seborrhoeic dermatitis
soluble oil *27.4*, 27.5, 27.6
spectacle-frame 26.16, 26.17
stasis 47.34, 49.23
strimmer's 29.21, 58.32
sunscreens causing 73.40
superficial necrolytic (SND) 2.17, 2.20
systemic contact-type 75.36
tidemark 17.24
treatment, tacrolimus 73.32
uncinarial 37.14
verrucous 31.10, **36.75–6**
wear and tear 23.20
cumulative irritant contact dermatitis 25.1, 25.5, 25.12–13, *25.14*, 25.15
woodcutters' 26.77
see also atopic dermatitis (AD); contact dermatitis; eczema
dermatitis artefacta 5.*11*, 46.29
acne excoriée and 42.70
ear 68.7, 68.16
male genital dermatology 71.15
dermatitis artefacta (dermatitis factitia) 64.35–42, 71.56
see also factitious skin disease
Dermatitis Family Impact questionnaire 72.23
dermatitis gangrenosa infantum 30.78
dermatitis herpetiformis *5.14*, 40.58–62, 59.59
aetiology 40.58
associated autoimmune diseases 40.61
cicatricial conjunctivitis 67.20
clinical features 40.61
coeliac disease and 40.58
defined 40.58
differential diagnosis 40.62
acne vs 42.37
ear 68.16
elderly people 8.28
gastrointestinal investigations. 40.60
immunopathology and immunogenetics *10.18*, 10.19
iron deficiency anaemia in 62.85
linear IgA disease 40.45–9
lymphoma and 40.61
oral involvement *69.65*, 69.68–9
paraneoplastic 62.46
pathogenesis 40.59
prognosis 40.61–2
treatment, gluten-free diet 40.61–2
dermatitis medicamentosa 23.11, 75.35–7
dermatitis palmaris sicca 23.20
dermatitis passivata 64.43
dermatitis plantaris sicca 23.26
dermatitis simulata 64.42–3
dermatitis vegetans **30.77–8,** 50.89
dermatitis veineuse 47.34
dermatitis–arthritis syndrome, gonococci causing 34.27
dermatoarthritis, lipoid *see* multicentric reticulohistiocytosis
Dermatobia hominis 38.9, 38.10
dermatochalasis *67.4*
generalized 45.14–17
dermatoepidemiology 6.1
information resources 6.19
dermatofibroma *see* fibrous histiocytoma (FH)
dermatofibrosarcoma protuberans (DFSP) **56.12–14**
diagnosis *10.23*, 56.13
treatment 56.13, 79.13
dermatofibrosis, nodular, in dogs 2.17–18
dermatofibrosis lenticularis disseminata 18.32
dermatogenic enteropathy 23.27
dermatoglyphics 3.3
dermatoheliosis 45.27
dermatological care
maldistribution globally 6.16
need, supply and demand for 6.15–16
see also health services
dermatological non-disease
male genital dermatology 71.51–2
perianal/perineal dermatology 71.99
see also body dysmorphic disorder
dermatological pathomimicry 64.42
dermatology
comparative clinical **2.8–19**
see also animal(s)
definition 1.1
evolution of 1.1–5
historical bibliography 1.8–10
scope and patterns of work 1.5–8
services 1.6
training in 1.4
dermatology consultation **72.1–5**
prognosis/bad news 72.4–5
psychocutaneous disorders 64.15, 64.19, 64.34–5
Dermatology Index of Disease Severity (DIDS) 72.8–9
Dermatology Life Quality Index (DLQI) 1.1, 20.41, 42.35, 64.10, 72.9, 72.14, 72.17, *72.18*
use in adolescents 72.23
dermatology nurse specialist 72.26
dermatology research, animals, role 2.7–8
dermatome 63.1
dermatomycosis furfuracea *see* pityriasis versicolor
dermatomyofibroma 56.7
dermatomyositis **51.120–9**
aetiology 51.120–1
autoantibodies 51.121
cytokines 51.121
drug-associated 51.120–1
immunological abnormalities 51.121
infections associated 51.121
penicillamine 51.121
relationship with malignancy 51.121
in animals 2.15–16, 2.20
association with other disorders 51.127
childhood 62.99
in childhood 51.126
clinical features 51.123–5
calcification 51.125
in Chinese 51.121, 51.124
'mechanic's hands' 51.125, 51.127
muscle symptoms 51.125
oesophageal diverticula 51.125
panniculitis 51.124
differential diagnosis 26.29, 26.30, 51.120, 51.127, 51.128
drug-induced 75.42
hair loss in 66.29
hypertrichosis and 66.78
incidence 51.120
investigation of associated malignancy 51.128
juvenile, acquired generalized lipodystrophy with 46.38
oral involvement 69.71
panniculitis with 46.31
paraneoplastic 62.36–8
pathology 51.122
muscle involvement 51.122
pigmentation changes 58.27
in pregnancy 8.12, 51.127
prognosis 51.128
respiratory tract involvement 62.82
treatment 51.129
azathioprine 74.15
methotrexate 74.18–19
protein therapeutics 74.12
vasculitis and 50.48
vs systemic sclerosis 51.128
dermatomyositis-like syndrome, echovirus infections 33.73
dermatopathia pigmentosa reticularis *see* livedo reticularis
dermatopathology 10.1
dermatopathy, in dogs 2.15
Dermatophagoides see house-dust mite (HDM)
dermatophilosis, in horses 2.12
Dermatophilus congolensis 2.12, 30.39
dermatophytes 36.18–20
adherence 36.20
anthrophilic 36.18–19
classification and nomenclature 36.18, 36.37
factors affecting infection 36.21–2
female genital infections 71.68–9
geophilic 36.18, 36.19
host resistance and immunology 36.21
identification 36.5, *36.8*, 36.37, *36.38*, 36.39–42, *36.43*, 36.44–6
pathogenesis of infection 36.20–1
penetration 36.20–1
zoophilic 36.18–19
see also dermatophytosis; *specific dermatophytes*
dermatophytide reactions 23.8–9, 23.17, 36.36–7
dermatophytosis 36.**18–51**
in animals 2.12–13
atopy and 36.21
Cushing's syndrome and 36.22
diabetes mellitus and 36.22
erythroderma and 23.48
factors affecting incidence 36.21–2
female genital infections 71.68–9
histopathology 36.22–3
in HIV infection 35.32–3, 35.45
homosexual men 35.32
laboratory diagnosis 36.5, *36.8*, 36.37, *36.38*, 36.39–42, *36.43*, 36.44–6
malnutrition and 36.22
molecular diagnosis 36.9
pathogenesis 36.20–1
prevention 36.46–7
reinfection 36.50
secondary infection 36.50
tinea barbae 36.28–9, 36.49
tinea capitis (tinea tonsurans) 9.8, **36.25–8,** 36.47, 36.49, 66.16, 66.35, 66.53–4, 79.4
tinea corporis (tinea circinata) 5.*12–13*, **36.23–5,** 36.49
tinea cruris **36.33–4,** 36.49–50
tinea faciei (tinea faciale) 36.28, **36.29–30,** 36.49
tinea imbricata 36.24, *36.25*, 36.29
tinea incognito *25.15*, 36.35–6, 36.50
topical corticosteroids causing 73.18
tinea manuum 26.29, 36.32–3, 36.50
tinea pedis *see* tinea pedis
tinea unguium 36.34–5, 36.50
treatment and management 36.46–51, 73.28
treatment failure 36.50–1
see also dermatophytes
dermatoscopy *see* dermoscopy
dermatoses
acantholytic, transient and persistent 19.86–8
digitate 57.57
inflammatory, acitretin 74.36
intercellular IgA 40.19–22
methotrexate 74.20
neutrophilic, TNF antagonists 74.7
occupational *see* occupational dermatoses
pruritic, fleas on animals causing 2.9–10
subcorneal pustular 40.19–22
treatment, acitretin 74.36
see also specific dermatoses
dermatosis papulosa nigra 9.11, 52.40
dermatosis pustulosa cruris et atrophicans 9.13
dermatosparaxis *45.32*, 45.35–6
Dermestes 38.27
Dermestidae 38.27
dermicidin 4.5
dermicin 36.21
dermis 2.2, 4.4
absorption through 4.4–5
ageing 8.22–3, 45.2, 80.1
anatomy 3.2
blood supply 4.7
collagen 8.22
corticosteroid-induced atrophy 73.17
degenerations 10.38
ear 68.1
embryology 3.3–5, 3.5
evolution 2.1–4
extracellular matrix **3.33–50**
immune surveillance 3.18–19
macrophage 3.19
mechanical injury 28.5, 28.7, *28.8*
mechanical properties 4.8
'pseudoherniation' of fat into 46.10
structure *3.34*
synthesis of cytokines 12.21–2, 12.76–7
T cells 3.18–19
upper, hypermelanosis 58.31
vertebrate evolution 2.2–3
dermite ocre of Favre 49.17–18
dermo-chondro-corneal dystrophy **15.96**
dermo-odonto-dysplasia 15.35
dermoepidermal junction *see* dermal–epidermal junction (DEJ)
Dermograft® 63.10
dermographism 5.*11*, 21.6, 22.5
black 22.14
challenge test *22.13*
cholinergic 22.13
cold urticaria and 22.16
delayed 22.13
immediate symptomatic 22.12–13, *22.14*
male genital dermatology 71.16
red 22.13
treatment 22.14
white 22.14
dermographometer 22.13, 22.14
dermoid cysts
congenital 18.88–9
oral cavity 69.34–5
dermolytic pemphigoid *see* epidermolysis bullosa acquisita
dermoscopy 5.20, 49.2
melanoma vs acquired melanocytic naevi 54.19, 54.38
scabies 38.41
Spitz naevus 54.24
subungual haematoma 65.49
dermotrichic syndrome 15.35
Dermovate®, pyogenic granuloma in acne 42.79
des-arg-bradykinin 13.4
descriptive studies 6.19
desensitization 13.26
in atopic dermatitis 24.31
to drug reactions 75.176–7
in urticaria 22.9
desert rheumatism (coccidioidomycosis) 35.34

desert sore 47.56
desferrioxamine 75.102
desimipramine 75.33
  in post-herpetic neuralgia 63.7
desloratadine *22.29*
desmin 10.22
desmocollins 3.22, 40.2
  autoantibodies 40.6
desmogleins 3.22, 40.2, *40.4*
  antibodies 40.5, 40.23
  antidesmoglein 1 ELISA assays 40.8
  desmoglein-3 40.5
    gene 40.3
  Dsg1 disruption, disorders 3.22
  in pemphigus vulgaris 69.64
  recombinant (DG1 and DG3) 40.8
desmoid tumours, genetics 15.26
Desmon's syndrome 19.62
desmoplakin 3.11
  and BP230 40.30
desmoplakins-1 and 2 40.2, 40.4
desmoplasia 10.38
desmoplastic fibroblastoma 56.10–11
desmosines 3.43
desmosome junctions, splitting 40.8
desmosomes 3.21–2
  adhesion components 40.2
  antibodies to 3.22
  as autoantigens 3.22
  components 3.22, *3.23*
  electron microscopy *3.22*, 10.30
  gene mutations 3.22, *3.23*
  in Hailey–Hailey disease 39.33
  hemidesmosomes, dermoepidermal junction 40.25
  immunobullous diseases 3.22, *3.23*
  intercellular adhesion 3.21–2
  loss in pemphigus 40.15
  ultrastructure 3.21–2
desogestrel, acne treatment 42.53
desquamation 3.9
desquamation en aires 23.19
detergent acne 42.74
detergents
  allergy to 26.18
  as irritants 25.8–9, 25.20
  in shampoos 66.96
  skin barrier function and 25.3
Dettol 26.56
Deuteromycota 36.2, *36.3*, 36.4
developing countries
  burden of skin disease 6.8, *6.9–10*
  dermatological care availability 6.16
  World Bank report on skin diseases 6.16
development of skin 3.3–5
  see also embryology
developmental abnormalities **18.1–107**
  ears 68.3–5
  female genital dermatology 71.56
  male genital dermatology 71.13–14
  perianal/perineal dermatology 71.83–4
  umbilical dermatology 71.100
  see also congenital abnormalities
devil's pinches 49.16
dew itch 37.14
Dewar classification, sentinel node biopsy 54.52
Dewar photoproducts 29.4
dexamethasone, in acne vulgaris 42.53
dexpanthenol *26.46*
dextran, IV l.m.w. 51.108
DFNB29 3.25
DFSP *see* dermatofibrosarcoma protuberans
Dhobie itch *see* tinea cruris
DHT *see* 5α-dihydrotestosterone (DHT)
Di-HETE 12.32
diabetes insipidus
  infective otitis externa and 68.26
  in Langerhans' cell histiocytosis 55.11, 55.12
  sarcoidosis and 61.7, 61.17
diabetes mellitus 59.77–81
  alopecia areata and 66.32
  bullae 59.80–1
  candidiasis in 36.58, 59.78
  dermatophytosis and 36.22
  ear involvement 68.18
  foot care 47.58
  foot ulcers 47.57–8, 63.8–9
  furunculosis and 30.23
  granuloma annulare and 60.9
  gustatory hyperhidrosis in 44.10
  large vessel disease 59.77–8
  lichen planus and 41.9, 41.16
  lipoatrophic 46.37
  mastopathy 50.49
  maternal 18.2
  necrobiosis lipoidica and 60.12, 60.13, 60.15
  neuroischaemic foot 47.57
  neuropathic foot/ulcers 47.57, 47.58, 63.8–9
  neuropathy 44.7, 59.78
  non-insulin-dependent *see* diabetes mellitus, type 2
  obesity associated 46.5, 46.7
  oral lichen planus and 41.9
  perforating dermatoses and 45.63
  periodontitis and 69.18
  peripheral arterial disease 47.2, 47.4, 47.5
    investigations 47.3
  polycystic ovary syndrome and 66.82
  pruritus 21.11
  secondary dyslipidaemias 59.92
  shin spots 59.77
  thick skin 45.62
  type 1
    insulin antibodies and lipodystrophy 46.35
    partial lipodystrophy 46.40
  type 2
    flushing associated with chlorpropamide–alcohol 43.16
    insulin resistance 46.4
    obesity and 8.17
  ulcers 14.1, 14.13, 47.57–8
  venous leg ulcers 47.43
diabetic dermopathy 59.77–8
diabetic embryopathy syndrome 68.3
diabetic neuropathy 44.7, 59.78
diabetico-dermatogenic syndrome 62.67
diagnosis **5.1–26**
diagnosis-related groups 5.2
Diagnostic and Statistical Manual of Mental disorders (DSM) 64.11
  body dysmorphic disorder 64.17–18
  factitious skin disorders 64.35
diagnostic criteria 5.2
  importance in epidemiology 6.4–5
diagnostic tests
  evaluation *7.13*, 7.13–14
  immunological and allergic disease 13.15–26
dialectical behaviour therapy 64.46
diallyl disulphide 26.77
diallylglycol carbonate monomer 25.21
diallylphthalate 25.21
dialysis and related therapies
  calcifying panniculitis with renal failure 46.16
  dialysis-related amyloidosis 59.57
  treatment of psoriasis 20.44
  see also haemodialysis
Diamond's triad 62.8, 62.9
diamorphine
  in dystrophic EB 39.30
  eccrine gland secretion 44.18
Dianette® 42.15–16, 42.53
diapers *see* napkin(s)
Diaptomus 37.26
diarrhoea
  in carcinoid syndrome 43.18, 43.19
  in Langerhans' cell histiocytosis 55.11
  management 43.19
  napkin dermatitis and 17.24
diascopy 5.19
diastematomyelia 18.96
diathermy
  artefact due to 10.31
  cutting 77.44
  HPV-associated dysplasia/neoplasia 33.55
  surgical *see* electrosurgery
  unipolar/monoterminal/bipolar 77.45
  see also electrosurgery
diazacholesterol 75.157
diazepam, adverse effects *70.5*, 75.81
diazolidinyl urea *26.50*, 26.51
diazoxide, adverse effects 75.96
  hypertrichosis *66.79*
dibenzoylmethanes 26.23
Dicer 11.7
dichloroacetic acid 77.48
2,6-dichlorobenzonitrile 27.13
dichlorodiphenyltrichloroethane (DDT), acne associated 42.77
dichlorophene 26.58
2,4-dichlorophenoxyacetic acid 27.13
diclofenac
  actinic keratosis 52.31
  adverse effects 73.25, 75.75
  male genital dermatology 71.27
  topical 73.25
dictyoconidia 36.4
Dictyoptera (cockroaches) 38.2, 38.28
didanosine, adverse effects 35.22
dideoxycytidine 75.67
DIDMOHS *see* DRESS syndrome
Dieffenbachia *25.21*, 26.16
diesel oil 27.13
diet
  acne vulgaris and 42.33–4
  in allergic contact dermatitis 26.22, 26.32, 26.102
  in atopic dermatitis 24.30–1
  in dystrophic EB 39.28
  elimination/exclusion/challenge 5.25
  history-taking 5.5
  risk factor for skin disease 6.13
dietary fatty acids, ichthyoses 19.5–6
  neutral lipid storage disease with 19.54
  Refsum's disease 19.46
  Sjögren–Larsson syndrome 19.44
diethyl-β-chloroethylamine *26.46*
diethyl toluamide *25.19*
diethylcarbamazine (DEC) 74.51
  in loiasis 37.11–12
  in lymphatic filariasis 37.10
  in onchocerciasis 37.7
diethylpropion, adverse effects *70.5*
dieting, lipoedema and 48.19
differentiated vulval intraepithelial neoplasia 71.75
diffraction of light, colours in animals and 2.5
diffuse and macular atrophic dermatosis 45.13
diffuse large B-cell lymphoma (PCLBCL) 57.47–9
diffuse neurofibroma 15.21
diffuse palmoplantar keratodermas 19.3, *19.94*, 19.95–7
diflunisal 75.72
DiGeorge's syndrome 13.8, 17.50, 17.61–2, 62.12, *69.117*
digital arteries 65.4
digital nerve block 65.42, 77.10
digital papillary adenocarcinoma, aggressive 53.33
digital subtraction angiography 47.4
digitalis, adverse effects *70.5*
digitate dermatosis *see* dermatitis, chronic superficial (persistent) scaly
digitate dermatosis (chronic superficial scaly dermatitis) 23.7–8, 57.57
DigiTrac 72.10
digoxin 75.89–90
dihydopteridine reductase (DHPR), deficiencies 59.96
5α-dihydrotestosterone (DHT) 42.10, 42.16, 66.14
  synthesis 8.2
dihydroxyacetone (DHA), false tanning 73.49
dihydroxyanthranol *see* dithranol
1,3-dihydroxybenzene *see* resorcinol
1,4-dihydroxybenzene *see* hydroquinone
1,24-dihydroxycholecalciferol *see* tacalcitol
1,25-dihydroxycholecalciferol *see* calcitriol
1α-25 dihydroxycholecalciferol 73.43
5-6-dihydroxyindole (DHI) 58.5, *58.6*
5-6-dihydroxyindole carboxylic acid (DHICA) 58.5, *58.6*
diiodohydroxyquin 37.28
Dikaryomycota 36.4
Dilantin *see* phenytoin
dilated pore 53.3
diloxanide furoate 37.28
diltiazem
  adverse effects 45.52, **75.94–5**
  in hyperhidrosis 44.12
dilute Russell's viper venom time (dRVVT) 49.40
D-dimer 47.29
dimethyl acetamide *25.19*
dimethyl formamide *25.19*
dimethyl phthalate *25.19*
dimethylbenzanthracene (DMBA) 52.13
dimethylfumarate 74.29
dimethylglyoxime test 26.99, 27.8
dimethylsulphoxide 25.3, 25.7, 25.10, *25.19*, 47.11, 75.164
  histamine release 73.7
  as penetration enhancers 73.7
dimethylthiazoldiphenyl tetrazolium bromide assay 25.9
dimeticone 38.20, 73.14
dimples 69.40
  coccygeal 63.15
  lumbosacral 63.15
dinitrochlorobenzene (DNCB) 66.37
  contact sensitization, susceptibility in polymorphic light eruption 29.11
  mutagenicity 73.39
  sensitization by 73.39
  wart treatment 33.49
dinitrophenol, pigmentation due to 58.56–7
Diogenes syndrome 64.43
Diospyros *26.80*
dioxins 75.162
  chlorinated 27.12
dipeptidyl peptidase IV (DP IV) 12.50
diphencyprone (diphenylcyclopropenone) 66.37, 75.147
  sensitization by 73.39
diphenhydramine, adverse effects 22.29
diphenylcarbazide test 27.8
diphenylcyclopropenone 76.5
diphenylhydantoin *see* phenytoin
diphenylthiourea 26.26
diphtheria **30.36–7**
  see also Corynebacterium diphtheriae
diphtheroid organisms *see Corynebacterium*
Diphyllobothrium latum 37.24
dipivefrine *26.46*
Diplopoda (millipedes) 38.54–5
Diptera 38.5–11
  see also specific insects
direct fluorescent antibody test, *Chlamydia* 34.30, 34.31
direct immunofluorescence (IMF)
  lichen planus 41.5
  mucous membrane pemphigoid 67.17, 67.19
Directives on Dangerous Substances and Dangerous Preparations 26.100
directly observed therapy in tuberculosis 31.27
Dirofilaria 37.16, 37.19
dirofilariasis 37.19
dirt phobias 64.24
disability 6.5
  magnitude in skin disease 6.5

disability adjusted life years, leprosy and 32.2
disappearing bone disease 48.27
discoid eczema 23.7, **23.9–11,** 64.47
  dry 23.10
  in elderly people 8.28, 23.10
  hands 23.10
  isotretinoin causing *42.64*
  prevalence 23.3
discoid lupus erythematosus **51.4–22**
  aetiology 51.4
  Blaschko's lines 51.11
  childhood 51.14
  complement abnormalities 51.17
  differential diagnosis 51.7
  disseminated DLE (DDLE) 51.10–11
  immunocytochemistry 51.7
  immunopathology 51.5–6
  incidence and clinical features 51.8–14
  laboratory abnormalities 51.17
  neoplastic change 51.18
  pathology 51.5–7
  treatment 51.18–20
    antimalarials 51.20–1
    oral agents 51.20
    topical therapy 51.19–20
discoid lupus erythematosus (DLE) 5.*12–13,* 51.4–22
  alopecia in 66.43–5
  anetoderma in 45.17
  differential diagnosis 36.29
    systemic lupus erythematosus vs 51.2
  ear involvement 68.14–15, 68.17
  eyelids *67.10*
  facial, rosacea vs 43.5
  lichen planus with 41.20
  lip involvement 69.128
  oral involvement *69.65,* 69.71
  race and 9.15
  see also lupus erythematosus (LE)
disease associations, measures of 6.18
disease co-occurrence 6.13
disease definition 5.1–3, 6.4–5
disease-modifying antirheumatic drugs (DMARDs) 20.59
disfigurement, psychological impact 64.2
disinfectants, antiseptics vs 73.14
disodium cromoglycate 13.26
disomy, uniparental 15.7
disruptions 18.1
disseminate and recurrent infundibulofolliculitis 9.4, 19.76, 30.28
disseminate lenticular leukoderma 58.52
disseminated DLE (DDLE) 51.10–11
disseminated intravascular coagulation (DIC)
  haemorrhage 49.39
  sepsis-related purpura fulminans with 49.39–40
disseminated lipogranulomatosis *62.100*
disseminated porokeratoses 19.90–1
distal sensory polyneuropathy 63.12
distal 'wing' block 65.42
Distemonanthus benthamianus 26.80
distichiasis *67.4*
disulfiram 26.32, 75.88
dithiodimorpholine 26.65
dithranol 73.29–31
  adverse effects 25.21, *26.46,* 66.94, 75.163
  in alopecia areata 66.37
  burns 27.11
  calcipotriol with 73.45
  in clobetasol propionate 20.24
  indications 73.29
  in Lassar's paste 20.23
  mechanism of action 73.29
  pastes/creams and formulations 73.30
  in psoriasis 20.22, 20.23–4
  PUVA and 20.30
  safety 73.29
  structure *73.29*
diuretics
  adverse effects **75.97–8**
    erythema multiforme 76.3, *76.4*
    lichenoid tissue reaction 41.24, *41.25*
    vasculitis 50.17, *50.18*
  lymphoedema management 48.24–5
diving, mechanical injury 28.53–6
Divry–van Bogaert syndrome 18.79
DKC *see* dyskeratosis congenita
DKC1 gene 58.21
DLE *see* discoid lupus erythematosus (DLE)
DLQI *see* Dermatology Life Quality Index
DMDM hydantoin *26.50,* 26.52
DMSO *see* dimethylsulphoxide
DNA
  amplification, normal bacterial skin flora 30.2
  as chromophore 29.4, 29.5
  complementary (cDNA) 11.4, 11.5, 11.10
  damage *see* DNA damage
  extraction 11.3–4
  free fetal 16.9–10
  homologous replication 2.8
  instability 15.70–7
  interaction with UVR 29.4
  LE cell factor 51.52
  lesions induced by UV radiation 13.32
  library 11.4, 11.5
  manipulation 11.3–5
  methylation 11.16
  microsatellite 11.11–12
  mitochondrial 11.3
  mutations 8.21
  non-coding (junk) 11.1, 11.2
  nuclear *11.3*
  photoproducts 29.4
  prenatal diagnosis based on 16.1–3, *16.4,* 16.9–10
  repair 52.14
    UV-induced damage 52.13–14
  repair defects 47.18, 52.12, 52.13–14
    immunodeficiency and 17.67–70
    in xeroderma pigmentosum 52.10
  replication, repair of photoproducts 52.14
  sensitivity to, painful bruising syndrome 49.16
  sequencing 11.6–7, *11.8*
  structure 11.2–3
  synthesis, reduced by tar plus UV light 73.42
DNA antibodies 51.54
DNA damage
  'molecular fingerprint' 52.13
  repair 52.14
    UV-induced damage 52.13–14
  repair defects 47.18, 52.12
    immunodeficiency and 17.67–70
    in xeroderma pigmentosum 52.10
  tanning and 58.31
  UV-induced 8.21, 29.4, 29.5, 52.13–14, 58.7
    melanin protection from 58.8, 58.10
DNA hydration products 29.4
DNA photoproducts 29.4
DNA polymerases 11.6, 52.14
DNA viruses *see* virus(es), DNA
DNCB *see* dinitrochlorobenzene
dobutamine 75.98
docetaxel 75.135
dock workers, occupational hazards 38.2
'doctor shoppers' 64.19
doctor–patient relationship 72.1–2, 72.25
  psychocutaneous disorders 64.36, 64.41, 64.52–3
documentation, burns 28.80
dog(s)
  acanthosis nigricans 2.17
  acrodermatitis enteropathica 2.17
  allergic reactions 2.7
  alopecia 2.18
  atopic dermatitis 2.7, 2.13
  bacterial skin diseases 2.11–12
  bites from 38.60–1
  bullous pemphigoid 2.14–15
  coat colour and mutations affecting 2.6–7
  colour blindness 2.6
  Demodex mite infestation 2.9, 2.10
  demodicosis 2.10
  dermatomyositis 2.15, 2.20
  erythema multiforme 2.16
  flea allergy dermatitis (FAD) 2.10
  fungal infections 2.12–13
  lice 2.10
  lupus erythematosus 2.16
  mast cell tumours 2.22
  mechanobullous diseases 2.17
  melanomas 2.20–1
  merle pattern ('blue merle') 2.7
  neoplastic skin disease 2.19–20, 2.20–1
  nodular dermatofibrosis 2.17–18
  parasitic infections 2.9, 2.10, 2.11
  pemphigus foliaceus 2.15
  psoriasis 2.14
  sarcoptic acariasis 2.10
  skin diseases 2.9
  staphylococcal infections 2.11–12
  superficial necrolytic dermatitis 2.17
  sweating and temperature control 2.20
  vitiligo 2.23
dog bites 38.60–1
Dogger Bank itch 26.10, 38.58
Dohi (keratosis follicularis squamosa) 19.76
Dokumentationszentrum schwerer Hautreaktionen 6.6
dolichocephaly 45.30
domestic pets
  arthropod infestation 38.2, 38.4, 38.11–12
  bites from 38.60–1
  Cheyletiella mites 38.4, 38.49–50
  scabies 38.46
  see also cat(s); dog(s)
dominant alleles *15.2,* 15.3–4
domperidone, adverse effects *70.5*
Dong Ling Hou Tong Pian 76.3
Donohue's syndrome (leprechaunism) 45.62–3, 46.37
Donovan bodies 30.61–2, 34.37
Donovania granulomatis see Calymmatobacterium granulomatis
donovanosis *see* granuloma inguinale
DOOR syndrome 15.35
dopachrome 58.5, *58.6*
dopachrome tautomerase 58.5, *58.6*
dopamine
  adverse effects 75.98
  restless legs syndrome and 63.24
  transport 64.13
dopaminergic neurotransmission 47.12
dopaquinone 58.5, *58.6*
Doppler duplex ultrasound
  arterial 47.47
  chronic venous insufficiency 47.35
  venous leg ulceration 47.47
dorsal perforation of the prepuce 71.9
dorsal root ganglion 63.2
dorzalamide *26.46*
dose rate, UVR 29.1
DOT in tuberculosis 31.27
double-bind strategy 64.41
Dovobet® 73.45
Dowling–Degos disease **15.94–5,** 58.21, 58.22
  female genital dermatology 71.80
  genitocrural dermatology 71.7
Dowling–Meara EB simplex 39.3, 39.6–8
Down's syndrome 18.2, *53.25*
  ageing and 45.61
  angular cheilitis and 69.38–9
  crusted scabies and 38.43
  ear defects 68.3, 68.4
  genetics **15.10–11**
  macroglossia in 69.113
  oral involvement *69.119*
  periodontitis 69.17, 69.18
  scrotal tongue and 69.37
doxepin 64.23, 64.27, 64.28, 73.13, 74.32
  adverse effects *26.46,* 75.164
  in mastocytosis 22.35
  in pruritus 21.17, *21.18*
  in urticaria 22.29
doxorubicin 57.26, 65.16, 75.127–8
  hypermelanosis due to 58.30
doxycycline 74.41
  acne vulgaris treatment 42.46–7, 42.48
  adverse effects *42.50*
    ocular 67.31–2
  in genital chlamydial infections 34.31
  in lymphogranuloma venereum 34.33
  in rosacea 43.6, 43.7
  in sarcoidosis 61.21
DPCE (digital papular calcific elastosis) 45.28
DPCP *see* diphencyprone (diphenylcyclopropenone)
dracunculiasis (dracontiasis) **37.12–13**
Dracunculus medinensis 37.1–2, 37.3, 37.12–13
dragon worm **37.12–13**
Draize test 25.9, 26.12
DRESS syndrome (drug hypersensitivity) 23.47, 46.34, 75.18–19, **75.26–7,** 75.83, 76.10
  in HIV infection 35.20, 35.21
  minocycline causing 42.51
dressings 14.22–4
  alginates 14.23–4, 77.17
  antimicrobial 14.24
  burns 14.1
  collagen 14.24
  compression bandaging 14.20–1, 38.31, 38.60
  debriding 14.24
  epidermolysis bullosa management 39.28
  foams 14.24, 77.17
  following nail biopsy 65.42–3
  following surgery 7.17–18
  haemostatic 77.50
  hyaluronic acid 14.24
  hydrocolloids 14.23, 77.17
  hydrofibre 14.23
  hydrogels 14.23, 77.17
  low adherence 14.23
  multitape 77.17
  occlusive 73.4
  odour-absorbing 14.24
  pressure 77.17
  pressure ulcers 28.22–3
  saline 14.21
  selection *14.23*
  self-adhesive hydrocolloid 73.4
  semipermeable films 14.23
  skin grafts 77.17, 77.20
  venous leg ulcers 47.48
  wet-to-dry 14.22
  xerogel 77.17
drilling fluid, perforating dermatosis due to 45.64
drinking, flushing associated 43.15
'drip-sign' 64.37–8
Drosophila melanogaster, genetics 15.1
drosperinone, acne treatment 42.53, 42.54
drug(s)
  acetylation 75.14
  acneiform eruptions due to 42.71–3
  chronic ulcerative panniculitis due to 46.28
  concentrations, conventions defining 73.1–2
  conditions induced by *see* drug reactions (ADRs) (and drug-induced conditions)
  costs of unused/unwanted 72.25
  definition 75.1
  distribution 72.27, 72.28
  eruptions due to *see* drug reactions (ADRs) (and drug-induced conditions)

excretion 72.27
5-HIAA excretion changes due to 43.19
hydrolysis 75.14
to improve peripheral circulation, systemic agents 74.51
interactions **72.28–9**
with herbal remedies 72.33
labelling 7.27, 72.7
lobular panniculitis with crystals after 46.17, *46.18*
metabolism 72.27, 72.28–9
genetic factors 72.29–30
naming 75.2
overdosage 75.37
oxidation 75.13–14
pharmacodynamics 72.27–8
pharmacogenetics 72.29–30
photosensitizing 29.20, *29.21*
in pregnancy 72.28
prescription errors 72.26–7
reactions due to *see* drug reactions (ADRs) (and drug-induced conditions)
risk–benefits 72.3–4
routes of administration 72.27
special manufacture 72.26
targets, genetic polymorphism 72.29
teratogenic 72.28, 75.11
topical *see* topical therapy
see also specific drug groups
drug abuse
HIV infection and 35.45–6
lymphoedema association 48.13
mechanical injury 28.45, 28.52–3
venous leg ulcers and 47.47
see also specific drugs of abuse
drug eruptions with eosinophilia and systemic symptoms (DRESS) *see* DRESS syndrome
drug history 75.168
drug hypersensitivity syndrome *see* DRESS syndrome
drug-induced conditions *see* drug reactions (ADRs) (and drug-induced conditions)
drug rash with eosinophilia and systemic symptoms syndrome *see* DRESS syndrome
drug reactions (ADRs) (and drug-induced conditions) 6.13, **75.1–177,** 75.10
acanthosis nigricans 19.120
acne/acneiform eruptions 9.5, 42.71–3, 75.34
acute generalized exanthematous pustulosis 75.34–5
affecting eyes 67.31–2
allergic contact dermatitis *26.13,* 26.18, 26.22, 26.43–7
anaphylactoid 75.12, 75.25–6
anaphylaxis 24.23, 75.5, 75.8, 75.16–17, 75.17, 75.25–6, 75.48–9
angio-oedema 75.26
in animals 2.17
annular erythema 75.23–4
antibody-mediated (type II) 75.17
aquagenic pruritus 21.11
assessment criteria 75.2
in atopic dermatitis 24.23
bullous 75.37–40
bullous pemphigoid 40.32–3, 75.38
and associated diseases 40.32–3
cell-mediated (type IV) 75.17–21
challenge tests 75.175
cheilitis 69.121
chromosomal damage 75.15
chronic ulcerative panniculitis due to 46.28
in cicatrizing conjunctivitis treatment 67.22
classification 75.9
clinical trials and 75.2
costs of 75.2
co-trimoxazole, photosensitive eruption 57.53
cutaneous 75.7–9, 75.17–18
amino penicillins 74.40
definition 75.1–2
dermatomyositis 75.42
diagnosis 75.167–75
differential diagnosis 26.29
disease exacerbation 75.12
DRESS syndrome 23.47, 75.18–19, 75.26–7, 76.10
drug elimination 75.168
drug history 75.168
due to human error 75.2
ear involvement 68.18
eczematous 23.11, 75.35–7
effects on spermatogenesis 75.11
elderly patients 75.6
eosinophilia–myalgia syndrome 75.43
epidermolysis bullosa acquisita 75.40
eruptions
pityriasis rosea vs 33.80
secondary syphilis vs 34.11, 34.12
erythema multiforme 76.3, *76.4*
erythema nodosum 50.83–4, 75.43–4
erythroderma 23.47, 75.24–5
erythromelalgia 75.44–5
exanthematic (maculopapular) 75.22–3
facultative 75.10
female genital involvement 71.66
fixed eruptions 75.20, 75.**28–30**
in animals 2.17
female genital region 71.66
histopathology 75.21
HIV infection 35.21, 35.22
hyperpigmentation 58.30, 58.31
incidence 75.8
perianal/perineal region 71.91
flushing 43.15–16
genetic mechanisms 76.10–11
hair discoloration 66.94, 75.45
hair loss 66.29–30, 75.45
hirsutism 75.45
histopathology 75.21–2
in HIV infection 35.20–4, 75.6–7
in children 35.45
HLA associations 75.14–15
hypermelanosis 58.29–30
hyperpigmentation 75.28, 75.32–3, 75.52–3
hypertrichosis 66.79, 75.45
hypopigmentation 75.33
ichthyosis 19.63–4
idiopathic thrombocytopenic purpura (ITP) 49.9
idiosyncratic 75.12–13
IgE-dependent (type I) 75.16–17
immune complex-mediated (type III) 75.17
immunological 75.15–21
in immunosuppression 75.6–7
incidence 75.3–9
in infancy and childhood 75.6
interactions 75.10–11
intolerance 75.12–13
lichenoid eruptions 41.23–5, 75.19–20, 75.30
histopathology 75.21
linear IgA disease 40.49, 75.39–40, 76.7
lipodystrophy 35.22
see also lipodystrophy
livedo 49.21
localized lipoatrophy 46.34–5
lupus erythematosus-like syndrome 75.20, 75.41–2
male genital dermatology 71.27–8
mechanisms 35.22, 75.9–21
metabolic 75.11
mortality due to 75.2, 75.5
mycophenolate mofetil causing 20.42, 74.24
nail changes 65.16, 65.38–9, 75.46
non-immunological 75.10–15
ocular complications 67.31–2
ocular drugs 67.15, 67.16
oral 69.83, 69.97, *69.116,* 75.46–7
in HIV infection *35.44*
overdosage manifestations 75.10
pemphigoid 67.20
pemphigus 40.18–19, 75.20, 75.38–9
perianal/perineal 71.91
photosensitivity 29.20–2, 75.30–2, 75.52
pigmentation 58.55–7
pigmented purpuric dermatoses 49.23
pityriasis rosea 33.79, 33.80, 75.24
platelet function disorders 49.12–13
pseudolymphoma 57.53–4, 75.27, 75.44
psoriasiform eruptions *75.24*
purpura 49.9, 49.11, 49.21, 75.23
pustular 50.62, 75.34
reporting 5.2–3, 75.2, 75.3–4
risk of 75.6–7
scleroderma/scleroderma-like 45.52, 75.42–3
serum sickness-like syndrome 22.18
skin testing 75.168–73
sources of data 7.7, *7.8*
Stevens–Johnson syndrome *76.4,* 76.11–12
sulphonamides 74.38–9
Sweet's syndrome 50.74, *50.75*
teratogenesis 72.28, 75.11
thrombocytopenia 49.9, 49.11
toxic epidermal necrolysis 76.12–15
toxicity
cumulative 75.10
delayed 75.10
treatment 75.175–7
urticaria 22.8, 22.10, 75.16–17, 75.17, *75.25,* 75.26
vasculitis 49.21, 50.17–19, 50.49, 75.17, 75.40–1
drug transporters 72.29
drusen 45.22
dry cleaning solvents, scleroderma-like lesions 51.80
dry eyes *see* eye(s), dry
dry skin
in atopic dermatitis 24.22
in the elderly 4.11
in old age 8.27
dry zone mahogany *26.81*
drying pastes 73.2
DSAP1 gene 52.35
DSAP2 gene 52.35
dSEARCH 3.17
DTIC *see* dacarbazine
Duane's retraction syndrome 68.4
Dubovitz syndrome 15.36
duck-hunter's itch *see* larva migrans, cutaneous
Ducrey's disease *see* chancroid
duct ectasia/periductal mastitis complex 70.8
'Dudley nose' 2.23
Dufouriellus ater 38.25
Duhring–Brocq disease *see* dermatitis herpetiformis
duloxetine *64.51*
dum-dum fever (visceral leishmaniasis) **37.41–3**
Dundee Experimental Bald Rat (DEBR) 2.18, 66.33, 73.32
Duplex ultrasound scanning 47.4
Dupuytren's disease/contracture (palmar fibromatosis) 45.45–6, **56.11**
dusting powders 73.2
dutasteride, in androgenetic alopecia 66.24, 66.25
DVT *see* deep-vein thrombosis
dwarfism *see* short stature
DX-88 22.22
Dyera costulata (jelutong) 26.79, *26.80*
dyers, occupational hazards 27.19
dyes
anthroquinone 26.65–6
azo 26.60, 26.61, 26.65–6
disperse 26.65–6, 26.67
eyebrows and eyelashes 26.60
hair 66.96–8
allergic contact dermatitis and 26.10, 26.17, 26.60–2
depigmentation and 26.26
open patch testing 26.97
topical therapeutic 73.48
dynamic psychotherapies 64.53–4
dynein, melanosome transfer along melanocyte dendrites 58.4
dynorphins 21.4
dysaesthesia
in HIV infection 63.12
male genitalia 71.51–2
in peripheral neuropathy 63.11
scalp 63.23
dysaesthetic vulvodynia 71.82
dyschondroplasia with haemangioma *see* Maffucci's syndrome
dyschromatosis symmetrica hereditaria **15.95,** 58.21–2
dyschromatosis universalis hereditaria **15.95**
dysecdysis 2.9
dysencephalic syndrome of François (Hallermann–Streiff syndrome) 15.41, **18.81–2,** 45.8
dysfibrinogenaemia, acquired 49.33
dyshidrosis in syringomyelia 63.14
dyskeratoma, warty, subungual 65.18
dyskeratosis 10.39
genital papular acantholytic, female genitalia 71.81
pagetoid, male genitalia 71.46
dyskeratosis congenita (DKC) **15.78–80,** 59.48, 62.28–9, 62.95
genetics 15.36–7
immunodeficiency *13.13*
oral involvement 69.24
pigmentation 58.20–1
dyslipidaemias 59.83–94
cerebrotendinous xanthomatosis 59.91
combined 59.84, 59.88–90
drug-associated 59.92
familial hypercholesterolaemia 59.86–8
insulin resistance 59.92
lipodystrophy-associated 59.92
primary 59.86–92
secondary 59.92–3
sitosterolaemia 59.91
Tangier disease 59.91
treatment 59.93–4
working classification 59.84
see also hyperlipoproteinaemias
dysmorphophobia *see* body dysmorphic disorder
dysostosis multiplex 59.31
dysplasia 10.39
dysplastic naevi *see* naevus, atypical/dysplastic
dysplastic naevus syndrome (familial melanoma syndrome) 54.28, *62.20,* 62.21–2
dysproteinaemia 49.7
purpura in 49.19–20
dysthymia 64.48
dystrophia bullosa hereditaria 58.20
dystrophic epidermolysis bullosa *see* epidermolysis bullosa (EB), dystrophic

E

E-selectin, deficiency 13.9
EAC *see* erythema annulare centrifugum
ear(s) **68.1–35**
acne 68.14
in acromegaly 68.18
in Addison's disease 68.18
ageing changes 68.5–6
in alkaptonuria 68.18
allergic contact dermatitis 26.17, 68.14
altitude injury 68.11
in amyloidosis 68.15
anatomy and physiology 68.1–2
angiolymphoid hyperplasia with eosinophilia 68.15–16
asteatotic eczema 68.14
atopic dermatitis 68.14, 68.23

avulsion 68.7
bacillary angiomatosis 68.28
bacterial flora 6.2, 30.4
basal cell carcinoma 68.32–3, 79.9, *79.10*, *79.17*
bat 68.4
in Bazex syndrome 68.18
benign tumours 68.28–30
bullous diseases 68.16
calcium deposition 68.18
cauliflower 68.6
cold injury 62.99, *62.102*, 68.5, 68.8, 68.10
collagen vascular diseases 68.17
contact dermatitis 68.23
contusion 68.6–7
cryptococcosis 68.28
cutis laxa 68.18
Darier's disease 68.14
delusions of parasitosis and 68.16
dermatitis artefacta 68.7, 68.16
developmental defects 68.3–5
in diabetes mellitus 68.18
drug-related disorders 68.18
elastotic nodules 45.28
elephantiasis 68.16, 68.24
examination 68.3
foreign bodies 68.11
fungal infection 36.7–8, 36.17, 68.20, 68.21, 68.27–8
investigation 36.6
furunculosis 68.19, 68.27
gouty tophi 68.17
granuloma annulare 60.7, 68.15
granuloma faciale 68.16
granulomatous disorders 68.17, 68.20
haematoma 68.6–7
hairy 66.13, 68.1, *68.2*, 68.5, 68.18, 68.21
genetics 15.4
herpes simplex 68.20, 68.28
herpes zoster 68.20, 68.28
in HIV infection 68.28
hot-weather 68.2, 68.21
hypertrophy of retro-auricular folds 68.18
infection 68.18–28
irritant contact dermatitis 68.14
Jessner's benign lymphocytic infiltration 68.15
laceration 68.7
Langerhans' cell histiocytosis (LCH) 55.11
large 68.4
length 68.6
leprosy 68.17, 68.20
lichen planus 68.15
lichen simplex 68.23
lop 6.2
low-set 68.4
in lupus erythematosus 68.14–15, 68.17
in lupus vulgaris 68.17, 68.20
in lymphocytoma cutis 68.15
lymphoedema 48.12, 48.16
malignant tumours 68.18, 68.28, 68.30–4
molluscum contagiosum 68.28
Mozart's 68.4
mudi-chood 68.16
Mycobacterium marinum infection 68.17, 68.20
Paget's disease 68.30
peri-auricular anomalies 68.4
petrified 68.18, 68.35
piercing 68.7–9
complications 26.17, 61.23, 68.7–8
pityriasis versicolor 68.20
porphyria cutanea tarda 68.17–18
premalignant lesions 68.30
pseudocyst 68.13–14
psoriasis 68.14, 68.23
purpura 49.4, 68.18
pyoderma gangrenosum 68.17
radiation injury 68.11
radiotherapy 79.9, *79.10*
railroad track abnormality 68.4–5
referred pain 68.35
in relapsing polychondritis 45.42, *45.43*
sarcoidosis 61.9, 68.17
scrofuloderma 68.20
seborrhoeic dermatitis 68.14, 68.23, 68.28
self-healing epitheliomas 52.9
in SLE 51.46–7, 68.17
small 68.4
solar damage 68.10–11
swelling (otophyma) 43.9
swimmer's 68.21
syphilis 68.20
transepithelial elimination disorders 68.14
trauma 68.6–14
turkey 61.9
verruciform xanthoma 68.16
wedge excision 77.35
Wildemuth's 68.4
xanthogranuloma 68.16
xanthoma 68.17
see also external auditory canal/meatus; pinna
ear pits **18.83–4,** 68.4
ear tag (accessory tragus) 18.84–5, 68.4
earlobe
pendulous 68.18
skin crease 68.6
split 77.36
earplugs, allergic contact dermatitis due to 26.17
earrings
allergic contact dermatitis due to 26.17
embedded 68.7, 68.8
sensitization to 68.7–8
East Indian ebony *26.80*
East Indian rosewood *26.80*
Eastern equine encephalitis virus 33.66, *33.67*
easy bruising syndrome 49.15–16
eating disorders 21.16, **64.21–2**
hypertrichosis in 66.78
obesity and 46.6
oral manifestations *69.115*
see also anorexia nervosa
EB *see* epidermolysis bullosa (EB)
EBA *see* epidermolysis bullosa acquisita (EBA)
Ebenaceae *26.80*
EBM *see* evidence-based medicine
Ebola virus/disease *33.67*, 33.69–70
EBV *see* Epstein–Barr virus
EBV-associated post-transplant lymphoproliferative disorder (PTLD) 57.51
EBV-positive angiocentric lymphoma 57.40–1
EBV receptor *see* complement receptors, CR2 (CD21)
ecchymoses/bruising 49.1, 62.90
aetiology *49.3*
definition 5.7, 49.2
easy bruising syndrome 49.15–16
factitious 64.38
large, causes 49.7
non-thrombocytopenic vascular causes **49.14–21**
pigments and colour changes 49.2
size of lesions 49.4
syndrome of painful 64.33–4
trauma causing 49.14, 49.16
see also purpura
eccrine carcinoma, eyelids 67.36
eccrine hidradenitis, neutrophilic *see* neutrophilic eccrine hidradenitis
eccrine sweat glands 3.1, **3.12–13,** 44.1, *44.2*, 53.1
in adolescence 8.7
ageing and 8.24
anatomy and physiology 44.3–4, *44.5*
assessment of functioning 44.4, *44.5*
carcinoma 53.32, **53.32–3, 53.33–7**
syringoid 53.36
coma-induced necrosis 44.18
control of activity 44.5–7
dermal duct tumour 53.22, 53.24
development 3.5
disorders 44.7–16
with abnormal histology 44.16–17
with cellular inclusions 44.18
drug concentration and secretion 44.17–18
duct (excretory) 3.12, 44.4, 53.1
dilatation 53.22
tumours 53.23
duct-blocking agents 44.11
epithelioma 53.36
hidradenoma 53.22
malignant 53.34
hidroacanthoma simplex 53.22–3
hidrocystoma 53.22
innervation 44.5–6
intraepidermal sweat unit 44.4
isolation of 44.4
neonatal 17.2
papillary adenoma 53.26–7
poroid hidradenoma 53.24
poroma 53.22, 53.23–4
intradermal 53.22–3
malignant 53.32–3
in pregnancy 8.10
radiation-induced damage 44.18
secretory coil 3.12, 44.3, *44.4*
sites and number 3.12
spiradenoma 53.29–30
malignant 53.30, 53.34
structure *3.2*, 3.12
syringofibroadenoma 53.22, 53.24–5
syringofibroadenomatous hyperplasia 53.24
thermoregulation 3.3
tumours 53.2, **53.22–7**
apocrine differentiation and 53.27
malignant 53.22
see also eccrine sweat glands, carcinoma
ECG *see* electrocardiogram (ECG)
Echelle de Cotation des Lesions d'Acne 72.10
Echelle d'Evaluation Cliniques des Cicatrices d'Acne 72.10
Echiichthys vipera 38.59
Echinacea 75.162
echinocandins 74.48
echinococcosis 37.1, 37.3, **37.24–5**
Echinoidea (sea urchins) 61.22
echoviruses **33.73,** *69.118*
eclabion 17.20
ECM (erythema chronicum migrans) *see* erythema migrans
econazole
in candidiasis 36.68
in dermatophytosis *36.47*, 36.48
in *Scopulariopsis brevicaulis* infection 36.54
in tinea nigra 36.15
topical 73.12
economic burden of disease 72.14
ECP (eosinophil cationic protein) 13.5, 13.16
ecstasy pimples 28.53
ectasizing endocapillaritis 49.22
ecthyma **30.17**
ecthyma contagiosum *see* orf
ecthyma gangrenosum 30.49, **49.34–5**
in HIV infection 35.25
male genital involvement 71.30
neonatal 17.45
perianal/perineal involvement 71.92
ectoderm 2.2
ectodermal defect with skeletal abnormalities 15.37
ectodermal dysplasia
adrenal cyst with 15.38
anhidrotic (X-linked hypohidrotic) *13.13*, 17.81–2, 44.13
autosomal recessive 69.10
classification 15.27–8, 15.57
dental involvement 69.10–12
with distinctive facies and preaxial polydactyly 15.38
with ectrodactyly and macular dystrophy 15.38
gap junction protein defects 15.67–70
genetics **15.27–70**
hidrotic *see* Clouston's syndrome (hidrotic ectodermal dysplasia)
hypermelanosis 58.19
with hypodontia and taurodontism 69.10
hypohidrotic 66.60
prenatal diagnosis 16.7
with mental retardation and syndactyly 15.37
mutations in TNF-like/NF-kB signalling pathways 15.57–61
with natal teeth 15.37
and neurosensory deafness 15.47
with palatal paralysis 15.37
pure hair and nail type 15.38
with severe mental retardation 15.37
and skin fragility syndrome 15.46
with syndactyly 15.38
with syndactyly and cleft lip/palate 66.52
syndrome with tetramelic deficiencies 15.38
TP63-related phenotypes 15.61–5
X-linked hypohidrotic 69.10
ectodermal dysplasia–ectrodactyly–macular dystrophy (EEM) 3.24
ectodermal dysplasia–skin fragility syndrome, preimplantation diagnosis 16.7
ectodysplasin signalling pathway 66.11
ectoparasite infections
animal infestations 2.9–11
treatment 2.9
elderly people 8.29
ectoparasites 37.1
ectopic ACTH syndrome 62.3, 62.33
pigmentation 58.25
ectopic CRH syndrome 62.3
ectrodactylia, with anonychia 65.18
ectrodactyly, ectodermal dysplasia, clefting (EEC) syndrome 15.28, 15.38, **15.63–4**
ectrodactyly–ectodermal dysplasia 15.39
ectropion *67.4*
collodion baby 17.20
following skin grafting 77.20
following surgery *77.3*, 77.5
eculizumab 49.30
eczema **23.1–39**
acute 23.2, 23.3–4, 23.37–8
apron 23.15
asteatotic *see* asteatotic eczema (eczema craquelé)
atopic *see* atopic dermatitis (AD)
autosensitization 47.34
chronic 23.2, 23.4, 23.38
chronic infective, adult T-cell leukaemia–lymphoma 33.64
in chronic venous insufficiency 47.34
classification 23.1–2
definition 23.1
diagnostic tests 23.36–7
discoid *see* discoid eczema
drug-induced 23.11, 75.35–7
dry palmar *see* wear and tear dermatitis
dyshidrotic *see* pompholyx
in elderly people 8.28, 23.10
endogenic contact 75.36
endogenous 23.1, *23.2*, 23.3
erythroderma and 23.47
exogenous 23.1, *23.2*
eyelid 23.11
fat 23.16
female genital involvement 71.52, 71.58, 71.68
fingertip 23.15–16
forefoot 23.26
genetics 15.12
genitocrural 71.5

gravitational *see* eczema, venous
gut 23.16
hand *see under* hand(s)
histopathology 23.3–5
hyper-IgE syndrome and 23.27
hyperkeratotic palmar 23.16, 26.29
hypogammaglobulinaemia and 23.27
hypopigmentation after 58.51
hypostatic (venous) 47.34
infected 23.23, *23.24*, 23.25
infective *see* dermatitis, infective
malabsorption and 23.27
male genital involvement 71.16
management 23.36–9
microbial *see* dermatitis, infective
neonatal 17.22–31
nummular *see* discoid eczema
patchy vesiculosquamous 23.16
pathogenesis 23.5
pellagra and 23.27
perianal/perineal involvement 71.86
perioral/lick 23.3, 24.22, *24.23*
phenylketonuria and 23.27
photosensitive 29.17
post-traumatic 23.28–9
prevalence 23.3
ring 23.19–20
seborrhoeic *see* seborrhoeic dermatitis
secondary dissemination 23.5–6
slaughterhouse 23.16
stasis *see* eczema, venous
subacute 23.4, 23.38
terminology 24.1–2
treatment
corticosteroids and antimicrobial agents 73.20
wood tars 73.42
tylotic 23.16, 26.29
umbilical 71.101
unclassified 23.2
varicose 26.19
differential diagnosis 26.29
venous (gravitational) 23.35–6, 26.21, 26.44
in elderly people 8.28
venous disturbances causing 47.34
venous leg ulcers 47.45
vesicular of palms and soles 26.32
occupational 27.4, *27.5*
winter 8.27
see also asteatotic eczema (eczema craquelé)
see also dermatitis
Eczema Area and Severity Index 72.10
eczema craquelé *see* asteatotic eczema (eczema craquelé)
eczema herpeticum 24.24, **33.35–7,** 69.72–3
aetiology 33.35
clinical features 33.35
cowpox infection vs 33.7
diagnosis and treatment 33.35–6
herpes simplex recurrence 33.18
recurrence 33.35
eczema marginé/marginatum of Hebra *see* tinea cruris
Eczema Severity Score 72.14
eczema vaccinatum 33.6, 33.35
eczematide-like purpura of Doucas and Kapetanakis 49.22, 49.24–5
EDA gene 15.58
edicol ponceau 44.4
EDS *see* Ehlers–Danlos syndrome
EDTA 26.17, 26.58
Edwards' syndrome (trisomy 18) **15.11**
Edwardsiella lineata 38.56
EDXA (electron dispersive X-ray analysis) 28.42
EEC syndrome
ear defects 68.3
prenatal diagnosis *16.3*, 16.7
EEC syndrome (ectrodactyly, ectodermal dysplasia, clefting) 15.28, 15.38, **15.63–4**
EED (erythema elevatum diutinum) **50.25–7,** 50.62, 62.51
EELS (electron energy loss spectroscopy) 28.42
efalizumab 13.25, 72.14, 74.9, 75.146
in granuloma annulare 60.11
efavirenz 74.50, 75.68
photosensitivity due to 35.22
eflornithine 66.89
eflornithine hydrochloride 73.29
Ehlers–Danlos syndrome 3.27, 3.35, **45.31–9**
aetiology 45.32
associated syndromes 45.37
autosomal dominant, collagen type V mutations 3.35
bone and joint involvement *62.100*, 62.104
capillary fragility 49.5
clinical and molecular subtypes *45.32*
clinical features *45.32*
definition 45.32
diagnosis 45.37
differential diagnosis 45.16
genetics 15.5
mechanical injury 28.2, 28.8, 28.38
molecular defects *3.35*
pathology 45.32–3
pregnancy in 8.12, 45.34
prenatal diagnosis *16.3*
progeroid *45.32*, 45.36
purpura due to 49.14, 49.15
tenascin-X-deficient *45.32*, 45.37
treatment 45.37
type I (gravis/classical) *45.32*, 45.33–4
type II (mitis/classical) *45.32*, 45.33–4
type III (hypermobility) *45.32*, 45.34
type IV (vascular) 45.32, 45.34–5, 45.37
type V (X-linked) *45.32*, 45.35
type VI (kyphoscoliosis/ocular-scoliotic) *45.32*, 45.35
type VIIA (arthrochalasia) *45.32*, 45.35
type VIIB (dermatosparaxis) *45.32*, 45.35–6
type VIII (periodontitis) *45.32*, 45.36, 69.17, 69.18
type IX (occipital horn syndrome) 3.44, 45.14, *45.15*, 45.36, **45.39**
type X (fibronectin-deficiency)) *45.32*, 45.36
vascular type, collagen type III mutations 3.35
ehrlichiosis **30.58–9,** 38.35
eighth-nerve deafness, congenital syphilis 34.16
Eikenella corrodens 30.59
male genital infection 71.34
Ekbom's syndrome 64.52
ELAM-1 49.22
elastases 3.44, 13.4, 50.10
elastic fibres 3.2, 3.33, **3.42–5**
ageing effects 8.22–3, 45.2, 80.1, 80.2
biosynthesis in fibroblasts 3.49
components 3.42
see also elastin; elastin-associated microfibrils
disorders 45.14–31
effects of corticosteroids on 45.4
in Ehlers–Danlos syndrome 45.32
functions 45.14
mechanical properties of skin and 4.8
in striae 45.5
elastic microfibrils 3.2
see also elastin-associated microfibrils
elastic stockings
sclerosing panniculitis (lipodermatosclerosis) 46.30–1
venous leg ulcers 47.47–8, 47.51
see also compression stockings
elastic wave propagation, mechanical injury 28.5
elasticity of skin 45.14
elastin 3.2, 3.42, 3.43–4
ageing and 8.22, 45.2, 80.1, *80.2*
cross-linking 3.43–4
in cutis laxa 45.14, 45.15
in elastosis perforans serpiginosa 45.65
facial skin 45.2
formation 3.43–4
gene 3.44
metabolic turnover and degradation 3.44
mRNA and alternative splicing 3.44
in wound healing 14.8
elastin-associated microfibrils 3.2, 3.42, 3.44–5
formation 3.45
function and as scaffold 3.42
proteins 3.44–5
elastoderma 45.29–30
elastofibroma 45.29, 56.8–9
elastolysis
generalized *see* cutis laxa
idiopathic mid-dermal 45.19
with granuloma annulare 60.7
localized 45.17–20
perifollicular 45.20
post-inflammatory 45.16, 45.19–20
upper dermal 45.19
elastoma 18.33
juvenile 18.32–3
perforating *see* elastosis perforans serpiginosa
elastorrhexis
generalized (generalized cutis laxa) 45.14–17
papular 18.33, 45.68
elastosis 8.27
actinic/solar 8.22, 45.26–8
ear 68.10
digital papular calcific 45.28
late onset focal dermal 45.26
linear focal 45.25–6
perforating calcific 45.24–5
elastosis colloidalis conglomerata *see* colloid milium (pseudomilium)
elastosis perforans serpiginosa 19.89, 45.63, **45.65–6**
ear involvement 68.14
in Ehlers–Danlos syndrome 45.35
genetics 15.10
elastotic degeneration 10.38
elaunin fibres 3.42
elderly people **8.21–8.29**
abuse 28.91–2
acne with solar comedones 42.79
adverse drug reactions 75.6
basal cell carcinoma *8.28*
bullous disorders 8.28
clothing lice 8.29
cutaneous atrophy 45.2
Diogenes syndrome 64.43
discoid eczema 23.10
drug responses 72.28
dry skin 4.11
eccrine glands 8.24
ectoparasite infections 8.29
eczema 8.28
greying of hair 8.23
hair follicles 8.23–4
immune system 13.15
leg ulcers 8.28
malignant melanoma 8.28–9
nails 61.7
normal bacterial skin flora 30.4
pigmentation changes 8.23
post-herpetic neuralgia 8.28
pruritus 8.27, 21.12, 21.17
psoriasis 8.28
purpura of lower leg 49.17
scabies 8.29, 38.40
sebaceous and apocrine glands 8.24
skin cancer 8.28–9
skin disease 8.25–7
causes/risk factors 8.26
epidemiology 8.25, 8.26
skin senescence 8.21
topical therapy, absorption 73.4
wound healing 14.2, 14.9, 14.17–18
zoster 8.28, 33.25, *33.26*, 33.28
see also ageing; *specific conditions*
elective lymph node dissection (ELND), melanoma 54.51
Electra pilosa 38.58
electrical burns 28.33, 28.75, **28.88–90**
child abuse *28.90*
first aid 28.75
torture injuries 28.33
electricians, occupational hazards 27.19
electrocardiogram (ECG)
abnormalities, pimozide therapy 64.16
complications following neonatal monitoring 17.14
sarcoidosis 61.7, 61.20
electrocautery 77.44–5
see also electrosurgery
electrochemotherapy 77.49
electrocoagulation, wart treatment 33.49
electrodesiccation 77.44, 77.45–6
electrofulguration 77.44, 77.45–6
electrolysis 77.44
in hirsutism 66.87
electrolyte monitoring, burns 28.84
electromagnetic radiation
skin ageing and 8.21
spectrum 29.1, *29.2*
electron beam therapy 57.24–5
electron dispersive X-ray analysis (EDXA), foreign bodies 28.42
electron energy loss spectroscopy (EELS), foreign bodies 28.42
electron microscopy 10.29–30
epidermolysis bullosa 39.24–5
electronic compliance monitoring 72.5
electronic prescribing 72.26
electronics industry, occupational hazards 27.19
electrophoresis, DGGE 57.12–13
electroplating (electroforming), occupational hazards 27.20
electroresection 77.44
electrosection 77.44
electrosurgery **77.44–7**
pacemakers and 77.46
rhinophyma 77.46
spider naevi 77.46
warts 77.46
xanthelasma 77.46
see also diathermy
elementary bodies, *Chlamydia* 34.29
elephantiasis 48.15, 48.17
ear 68.16, 68.24
infection prevention 48.22
in lymphogranuloma venereum 34.33
non-filarial 9.8, 48.13
perianal/perineal involvement 71.83
tropical **37.8–10,** 48.12
vulval 30.71
elephantiasis neurofibromatosa 48.21
elephantiasis verrucosis nostras 48.14
elephants 2.3
ELISA *see* enzyme-linked immunosorbent assay
ELIspot 31.6
elkonyxis 65.13
Ellis–van Creveld (EvC) syndrome 15.39, 15.65
EMA *see* epithelial membrane antigen (EMA)
EMBASE 7.5, 7.6
embolectomy, balloon-catheter 47.6
emboli
cardiac sources 49.37–8
cholesterol **49.36–7,** 50.54
fat 49.38
microvascular occlusion due to 49.36–8
oxalate crystal 49.37
see also embolism
embolia cutis medicamentosa 75.155
embolism
acute limb ischaemia vs 47.5
cardiac myxoma 49.37, 50.54
platelet, in ischaemic disease 47.2
see also emboli

embolization
  arterial 18.61
  arteriovenous fistulae 47.21
  infantile haemangioma 18.51
embryo, wounds 14.2, 14.9
embryology
  lymphatic system 48.1–2
  sebaceous glands 42.3
  of skin 3.3–5
    melanoblasts and melanocyte development 58.3–4
    miRNA role 3.50
    vasculogenesis 47.1
    see also individual skin structures
emedastine 67.15
eMelanoBase 54.33
EMILIN1 48.4
emilins 3.45
emissary veins 77.2, *77.3*
EMLA® cream 77.10
  adverse effects 75.153–4
  in notalgia paraesthetica 63.23
  in skin biopsy 10.2
emollients 73.5, **73.31**
  in atopic dermatitis 24.29
  in bullous ichthyosiform erythroderma 19.33
  in CHILD syndrome 19.58
  in collodion babies 19.14–16
  in Darier's disease 19.85
  in eczema 23.38
  in erythroderma 23.49
  formulations 73.31
  frequency of application 73.3
  frostbite and 68.10
  in hand eczema 23.22
  in harlequin ichthyosis 19.29
  in IBIDS/PIBIDS syndrome 19.49
  in ichthyosis hystrix 19.37
  in ichthyosis vulgaris 19.7–8
  in irritant contact dermatitis 25.23, 25.25
  in lamellar ichthyosis 19.25
  in lymphoedema 48.22
  napkins impregnated with 17.26
  in Netherton's syndrome 19.41
  in non-bullous ichthyosiform erythroderma 19.19
  in pachyonychia congenita 19.104
  in pityriasis rubra pilaris 19.79
  in pruritus of senescence 21.12, 21.17
  quantity applied 73.3–4
  in senile xerosis 8.27
  in Sjögren–Larsson syndrome 19.44
  use in neonates 17.2
  in X-linked recessive ichthyosis 19.12
emotional abuse, mechanical injury 28.34, 28.38–9
emotions, influence on skin disease 64.2–3
emperipolesis, in sinus histiocytosis with massive lymphadenopathy 55.29
emulsification tendency 73.7
emulsifiers 25.20, 73.7
  in ointments 73.2
Emulsifying Ointment BP 73.31
emulsions 73.2
  definition 73.2, 73.7
  determination of nature of 73.7
  oil-in-water (O/W) 73.7
  stable 73.7
  water-in-oil (W/O) 73.7
EN *see* erythema nodosum (EN)
en cocarde (cockade) 5.7
enalapril 75.93
enamel 69.2
enamel organs 69.2
enamel workers, occupational hazards 27.19
encephalitis *33.67*
  eastern equine *33.67*
  herpes B virus infection 33.34
  herpes simplex 33.17, 33.19
  HHV-6 associated 33.32
  Japanese *33.67*
  in loiasis 37.11, 37.12
  measles 33.75
  postvaccinial, cowpox 33.7
  roseola infantum 33.32
  tick-borne *33.67*, 38.34, 38.35
  varicella 33.24
  Venezuelan equine *33.67*
  western equine *33.67*
  zoster 33.26
encephalocoele 18.95
encephalomyelitis, vaccinia vaccination 33.6
enchondroma 65.34
endarterectomy, surgical 47.5
endarteritis obliterans, syphilis 34.5
endocannabinoids 21.2
endocardial fibrosis 43.18
endocarditis
  foreign bodies 28.51
  infective 49.37–8
  marantic 49.37
  subacute bacterial 44.7, 62.78
    vasculitis and 50.55
endocrine acne 42.73
endocrine disorders **62.2–14**
  genetics 15.23
  hypermelanosis in 58.24–5
  purpura in 49.18
  see also individual diseases
endocrine system, Langerhans' cell histiocytosis (LCH) 55.11, 55.12
endoglin, gene mutations 47.17
endometriosis, female genital dermatology 71.81
endoparasites 37.1
β-endorphin, UVR exposure associated 29.7
endorphins 21.4, 64.23
endothelial cells
  in infantile haemangioma 18.41
  lymphatic 48.2
  migration, in angiogenesis 47.1
  in sclerosing panniculitis 46.30
  in vasculitis 50.8
endothelin(s), pigmentation regulation 58.8
endothelin 1 (ET1) 12.75
  keratinocyte production 58.26
  melanocyte growth and 58.5
  pigmentation regulation 58.8
endothelin 3 (ET3), pigmentation regulation 58.8
endothelin 3 gene, in mice 2.7
endothelin-B receptor gene, mutation 2.7
endothelium 3.51
  antigens 3.52
  initial lymphatics 48.2, 48.3–4
  injury, arterial disease pathogenesis 47.1
  microscopy 10.35
  structure 3.51
endothelium derived relaxing factor (EDRF) *see* nitric oxide (NO)
endotoxins, atopy and 24.5–6, 24.7
endovascular treatment, varicose veins 47.39
endovasculitis, lymphocytic 50.48
energy
  excess, lipogenesis *46.3*
  homeostasis 46.2–3, *46.3*
  need, lipolysis *46.3*
  negative balance, weight loss 46.7
  positive balance, in obesity 46.6
  reduced intake, obesity management 46.8
  storage in adipose tissue 46.2
enfuvirtide (T20), HIV infection 35.6, 35.22
ENG gene mutations 47.17
enhanced green fluorescent protein (EGFP) 3.17
enkephalins 21.4, 64.23
enophthalmos, in Horner's syndrome 63.22
entactin (nidogen) 3.28–9, *3.31*
Entamoeba, perianal/perineal infections 71.95
Entamoeba histolytica 37.2, 37.27–8
  female genital infections 71.69
enterobiasis **37.13–14**
Enterobius vermicularis 37.3, 37.13–14
  perianal/perineal infection 71.92
  vaginal discharge 71.53
enterochromaffinoma 43.17
enterococci 30.13, 30.69
enteroviruses **33.71–3**
  oral infection 69.76–7
entropion *67.4*, 67.21
environmental factors 6.12
  in allergic contact dermatitis 26.10–11
envoplakin 3.11
envoplakin BP230 40.4
enzyme immunoassays, *Treponema pallidum* 34.20
enzyme-linked immunosorbent assay (ELISA) 5.24, 13.19
  serodiagnosis of pemphigus 40.8
enzyme replacement therapy (ERT) 59.38, 59.39–40
enzymic panniculitis 46.18–20
eosin 26.17, 26.24
  topical therapy 73.48
eosinophil(s) 12.20, 13.5
  in atopic eye disease 67.15
  in Churg–Strauss syndrome 50.42
  in incontinentia pigmenti 58.15
  infiltration in panniculitis 46.12
  in Langerhans' cell histiocytosis 55.8
  in mast cell tumours, in dogs 2.22
  microscopy 10.34
  receptors 13.5
  in urticaria 22.3, 22.5
  in vasculitis 50.6–7
eosinophil cationic protein (ECP) 13.5, 13.16
eosinophil-derived neurotoxin 13.5
eosinophil peroxidase 13.5
eosinophilia 62.86–8
  aetiology 5.*21*, *62.87*
  in cholesterol embolization syndrome (CES) 49.37
  with episodic angio-oedema 22.23
  in loiasis 37.11
  recurrent granulomatous dermatitis with (Well's syndrome) 46.12, **46.33–4,** 62.87
eosinophilia–myalgia syndrome 45.52, 62.87, 75.43
  secondary mucinosis 59.29
eosinophilic cellulitis (Well's syndrome) 46.12, **46.33–4,** 62.87
eosinophilic fasciitis 51.64, 51.86, 62.87
  lipodermatosclerosis overlap 46.30, 46.31
  paraneoplastic 62.40
eosinophilic folliculitis, HIV infection 35.18–19
eosinophilic globules (Kamino bodies) 10.40, 54.22, 54.24, *54.24*
eosinophilic granules, fragmented *see* flame figures
eosinophilic granuloma *see under* granuloma(s); Langerhans' cell histiocytosis (LCH)
eosinophilic inclusions, epidermal cells in warts 33.41
eosinophilic panniculitis 46.12
eosinophilic pustulosis 17.10, 30.29
eosinophilic (idiopathic) sclerosing lipogranuloma 46.29, 46.30
eosinophilic spongiosis 40.11, 40.15
eotaxin 12.46, 13.5, 35.18
  in atopic dermatitis 24.7
ephelides *see* freckles
EphrinB2 48.2
epicanthal fold *67.4*
epicanthus inversus *67.4*
Epicauta 38.26
Epicheck 26.85
epichlorohydrin 25.21, 27.11
epicuticle 66.5
epidemic hysteria syndrome 64.25–6
epidemiological study 6.3
  disease definition needed 6.4–5
  reading checklist 6.19
  types 6.19
epidemiology **6.1–21**
  allergic contact dermatitis 26.2–5
  analytical 6.3, 6.19
  case definition 26.3
  clinical 6.1
  comparisons and inferences from 6.2–3
  computer software, information resources 6.20
  data collection 26.2–3
  definition 6.1–2
  diagnostic criteria importance 6.4–5
  historical aspects 6.1–2
  information resources 6.19, 6.20–1
  methodologies 26.2–3
  occupational dermatoses 26.3, 27.1–4
  pellagra 6.1
  populations vs individuals 6.2–4
  sarcoidosis 61.2
  scabies 6.2, 38.37–8
  scurvy 6.1
  skin disease in old age 8.25, 8.26
  skin diseases as 'entities' in population 6.2
  standardization 26.3
  terminology and glossary 6.18–19
  see also other specific diseases
EPIDERM surveillance system 6.6, 26.3, 26.4, 27.2
epidermal attachment complexes **3.21–5**
  adherens junctions 3.23–4
  desmosomes 3.21–2
  gap junctions 3.24
  tight junctions 3.24–5
epidermal barrier, formation by keratinocytes 12.14
epidermal basement membrane *see* basement membrane
epidermal cells, lipids *42.5*
epidermal cysts, vulval 71.72
epidermal development, fetal 12.15
epidermal growth factor (EGF)
  keratinocytes 12.16
  response to 12.31
  sebaceous cell activity control 42.12
  in wound healing 14.3, 14.4, 14.27
epidermal growth factor receptor (EGFR) 3.4, 3.6
  inhibitors, acneiform eruptions due to 42.72
  ligands 12.11
epidermal hyperplasia 52.44
  mechanical injury 28.11
  persistent and excessive 52.44
  wound healing response 52.44
epidermal melanin unit 58.2
epidermal naevus syndrome 18.27–30, 54.11
epidermal necrosis, acute disseminated 76.1
epidermal proliferation units 3.6
epidermal sheets 4.4
epidermal tumours, benign **52.38–45**
epidermis **3.7–16,** 4.4, 12.14
  absorption through 4.4–5
  adhesion complex, desmosomes role 3.21–2
  ageing 8.23, 45.2, 80.1–2
  anatomy 3.1, 3.2
  atrophy, retinoic acid therapy 73.35
  barrier function 4.2, 4.3
  cell turnover, ageing and 8.23
  cells, lipids in *42.5*
  composition 3.1
  corticosteroid-induced atrophy 73.17
  degenerations 10.38
  differentiation *3.6*, *3.8*, 3.11
  ear 68.1
  embryology 3.3–5
  evolution 2.1–4

function 3.2–3
hyperplasia *see* epidermal hyperplasia
hyperproliferation, keratins expressed 3.10
hypertrophy, in actinic keratosis 52.30
immunological function 4.8–9
interfollicular
development 3.4, 3.5
signalling in 3.4
stem cells and proliferation 3.6–7
invertebrate derivatives 2.1–2
as 'itch receptor' 21.2
lipids 3.9, 3.11
mechanical function 4.1, 4.8
melanocyte distribution 58.2–3
in porokeratosis 52.36
post-inflammatory hypermelanosis 58.31
proliferation of cells 3.6
racial variations 9.2
spongiotic, incontinentia pigmenti 58.15
stem cell proliferation 3.6
structure and ultrastructure **3.7–9**
see also individual layers
thickness
ageing and 8.23
increased by retinol 73.35
vertebrate evolution 2.2–3
vertebrates 2.2–3
water content, ageing and 8.22, 8.27
epidermis–dermal junction *see* dermal–epidermal junction
epidermodysplasia verruciformis (EV) **33.57–8**
aetiology and gene mutations 33.57
clinical features 33.57–8
diagnosis and treatment 33.58
in HIV infection 35.30
pathology 33.57
in transplant recipients 33.59
viral warts and non-melanoma skin cancer with 52.5
epidermodysplasia verruciformis (EV)-like syndromes 33.58, 33.59
epidermoid ('sebaceous') cysts 42.88, 52.45–6
acne vs 42.37
excision 77.36
following ear piercing 68.8
genetics 15.26
implantation 65.34
lipoma vs 46.44
mechanical injury 28.28
plantar 33.47
sites 52.45
trichilemmal cysts vs 52.46
see also steatocystoma multiplex
epidermolysis 39.1
epidermolysis bullosa (EB) 39.1, **39.1–32**
albopapuloid (Pasini) 39.21–2, 45.50
with aplasia cutis congenita 18.101
classification 39.1–2
definition 39.1
dermolytic cleavage *39.2*
diagnosis and investigations 39.1–2, 39.24–7
antigen mapping 39.25
electron microscopy 39.24–5
molecular 39.26–7
skin biopsy 39.21, 39.24
specific antibody probes 39.25–6
differential diagnosis 15.82, 39.27
dystrophic *39.2*, **39.15–24**
albopapuloid (Pasini) variant 39.21–2, 45.50
in animals 2.17
autosomal dominant 39.15, 39.16, 39.17, 39.21–4
autosomal recessive 39.15, 39.18–20
Bart's syndrome 39.17, 39.18, **39.22**
bullous dermolysis of newborn 39.23–4, 39.25
classification *39.2*
clinical subtypes 39.18–24
crusted scabies and 38.43
diagnosis 39.24, 39.25
dominant *39.2*, 39.27
ear 68.16
electron microscopy 10.29
generalized dominant 39.21–2
generalized recessive (non-Hallopeau–Siemens) 3.32, 39.20, *39.21*
hyperplastic (Cockayne–Touraine) 39.21–2
inverse recessive 39.16, 39.20, *39.21*
localized, recessive 39.15–16
management 39.28–30
molecular pathology 39.15–18
oral involvement 39.18–19, *69.32*
pretibial 39.17, **39.22**
recessive *39.2*, 39.16, 39.27
recessive, centripetalis 39.24
scalp involvement 39.19
severe generalized recessive (Hallopeau–Siemens) 39.16, 39.18–20, 39.28–30, 39.30
sporadic dominant, diagnosis 39.27
squamous cell carcinoma in 39.17, 39.19, 39.30
squamous cell carcinoma prevention 39.31
epidermal basement membrane zone role 3.26
epidermolytic cleavage *39.2*
see also epidermolysis bullosa (EB) simplex
female genital involvement 71.66
gastrointestinal involvement 62.48
generalized atrophic benign (GABEB) 3.36–7, 39.13, 66.52
genetics 15.5, 15.82
genes/proteins involved in *3.27*
hypertrichosis associated 66.78
junctional *39.2*, **39.9–15**
in animals 2.17
autosomal recessive 39.9
cicatricial 39.13, 39.15
clinical subtypes 39.11–15
diagnosis 39.24, 39.25
electron microscopy 10.29
generalized non-Herlitz 39.13
genetics 3.28, 3.31, 3.36, 39.9–11
Herlitz 39.9, 39.10, **39.11–13**
indeterminate 39.9
laminin 332 gene mutations 3.28, 39.10
late-onset 39.15
localized (non-Herlitz) 39.14
molecular pathology 39.9–11
non-Herlitz type 3.36–7, 39.4, 39.9, 39.10, **39.13,** 39.31, 66.52
non-Herlitz type, *BPAG2* gene mutations 3.31, 3.36, 39.10
oral involvement *69.32*
progressive 39.15
pyloric stenosis with 39.9–10, 39.11, 39.14
lamina lucidolytic cleavage *39.2*, 39.9
see also epidermolysis bullosa (EB), junctional
oral involvement 39.13, 39.18–19, 69.31–2
preimplantation diagnosis 16.7–8, 39.31
prenatal diagnosis 16.2–3, *16.4*, 16.5, 16.7, 16.10, 39.27, 39.31
prevalence and incidence 39.3
pseudojunctional 39.4
renal involvement 39.20, 62.71
screening 39.27
treatment 39.27–32
gene therapy 39.31
neonates and infants 39.27–8
severe generalized recessive dystrophic EB 39.28–30
epidermolysis bullosa acquisita (EBA) 40.51–6
aetiology 40.52
in animals 2.15
associated diseases 40.55
autoantigen (collagen type VII) 3.36
cicatricial conjunctivitis 67.20
clinical features 40.54
collagen type VII in 3.36, 40.51
Crohn's disease and 62.49
defined 40.51
differential diagnosis 40.55
drug-induced 40.55, 75.40
ear 68.16
EBA mucous membrane pemphigoid 40.54
electron microscopy 10.29
IgA EBA 40.55
immunopathology and immunogenetics *10.18*, 10.19
oral 69.68
paraneoplastic 62.46
pathogenesis/pathology 40.52–3
prognosis 40.55
treatment 40.55–6
epidermolysis bullosa (EB) atrophicans 39.9
epidermolysis bullosa (EB) atrophicans generalisata gravis (Herlitz junction EB) 39.9, 39.10, **39.11–13**
epidermolysis bullosa (EB) atrophicans generalisata mitis 39.13
epidermolysis bullosa (EB) dystrophica–neurotrophica 39.15
epidermolysis bullosa herpetiformis *see* epidermolysis bullosa (EB) simplex, Dowling–Meara form
epidermolysis bullosa (EB) letalis 39.9, 39.11–13
epidermolysis bullosa (EB) progressiva 39.15
epidermolysis bullosa (EB) pruriginosa 39.17, **39.22–3**
epidermolysis bullosa (EB) simplex **39.3–9**
autosomal dominant, Ogna form 39.4, 39.8
autosomal recessive 39.4
diagnosis 39.25
lethal 39.8
muscular dystrophy with 39.4, 39.8
neuromuscular disease with 39.8
basal type *39.2*, 39.6–9
classification *39.2*
clinical subtypes 39.5–9
diagnosis 39.24, 39.25
Dowling–Meara form 39.3, 39.6–8, 39.30–1
diagnosis 39.25
electron microscopy 10.29, 39.4
generalized 39.6
of hands and feet (Weber–Cockayne) 39.4, 39.6, 39.30–1
friction blisters in 28.13
keratin gene mutation 3.10
Koebner 39.4, 39.6
lethal acantholytic 39.4, 39.5–6
lethal autosomal recessive 39.8
localized (Weber–Cockayne) 39.4, 39.6, 39.30–1
mechanical injury 28.13
migratory circinate 39.9
molecular pathology 39.3–5
mottled pigmentation with 39.4, 39.8
non-Dowling–Meara generalized variant 39.4, 39.6
pyloric stenosis with 39.4, 39.8
suprabasal subtypes *39.2*, 39.5–6
treatment 39.30–1
epidermolysis bullosa (EB) simplex superficialis 39.5
epidermolytic ichthyosis, annular 19.31
epidermolytic palmoplantar keratoderma 19.3, *19.94*, 19.95–7
epidermolytic toxins 30.7
Epidermophyton floccosum 36.18, 36.21
female genital infection 71.68–9
identification *36.8*, 36.46
in tinea corporis 36.23, 36.24
in tinea cruris 36.33
in tinea incognito 36.36
in tinea manuum 36.32
in tinea pedis 36.30, 36.31
in tinea unguium 36.34
epidermotropic CD8+ (provisional) T-cell lymphomas 57.35–6
EpiDerm™ 25.9
epididymitis, in lymphatic filariasis 37.9
epididymo-orchitis, chlamydial infections 34.29
epigenetics 11.16–17
epilation 73.29
X-ray 66.53–4
epilepsy
genetics 15.23, 15.24
Lafora's myoclonic 44.18
oral involvement *69.119*
in Sturge–Weber syndrome 18.66
epiloia *see* tuberous sclerosis complex
epinephrine *see* adrenaline
epiphora *67.4*
epipodophyllin, Langerhans' cell histiocytosis (LCH) 55.13
episcleritis *67.4*
EpiSkin™ 25.9
epistasis, hereditary haemorrhagic telangiectasia (HHT) 47.17
epithelial membrane antigen (EMA) 10.21
malignant eccrine poroma 53.32
epithelial neutrophil activating peptide 78 (CXCL5, ENA-78) 12.46–7
epithelioid angiomatosis *see* bacillary angiomatosis
epithelioma
eccrine 53.36
eyelid 67.35–6
radiation-induced 79.18
sebaceous (old terminology) 53.15
self-healing 52.9–10
squamous, venous leg ulcers vs 47.45
superficial with sebaceous differentiation 53.17
epithelioma adenoides cysticum *see* trichoepithelioma
epithelioma cuniculatum 52.26, 65.38
epithelium, oral cavity 69.1
epitope, anti-Ro antibodies 51.137
epitope spreading 40.5
epitrichial sweat glands *see* apocrine sweat glands
epitrichium 17.20
eponychium *see* cuticle
epoxy resins *see* resins, epoxy
Eppendorf Itch Questionnaire 21.16
epratuzumab 74.10
epsilon aminocaproic acid, in hereditary angio-oedema 22.22
Epstein–Barr virus (EBV) **33.30–2**
acne fulminans and 42.83–4
antibodies to 33.30
dermatoses associated 33.31
diagnosis 33.30
epidemiology 33.30
female genital dermatology 71.65, 71.69
Gianotti–Crosti syndrome 33.31
haemophagocytic syndrome 33.31
hairy leukoplakia 33.31, 69.90, 69.91, 69.93
Hodgkin's disease and 35.41
hydroa vacciniforme association 29.15
infectious mononucleosis 33.30
Kikuchi's histiocytic necrotizing lymphadenitis 33.31, 33.77
latency and persistence 33.30
lymphomas and lymphoproliferative disorders 33.30–1
oral infection 33.30, 69.75, *69.118*
perianal/perineal dermatology 71.94
primary infection 33.30
reactivation in GVHD 62.97
recessive dystrophic, non-melanoma skin cancer and 52.11
shedding 33.30

sinus histiocytosis with massive lymphadenopathy (SHML) 55.29
urticaria following infection 22.8
vasculitis and 50.49
Epstein's pearls 17.5, 69.17
eptifibatide 49.13
EPUAP scheme 14.13, *14.14*
epulis
congenital 69.17
giant cell 69.20
pregnancy 8.11, 69.20–1
epulis fissuratum 69.109–10
Epyris californicus 38.14
EQ *see* erythroplasia of Queyrat
equina (glanders) 30.51
Erbium:YAG laser *see under* laser therapy
Erb's point 77.3
Erdheim–Chester disease 55.18–19
ergosterol 36.2, 73.12
erisipela de la costa 37.5
ERK1 and ERK2 mitogen-activated protein kinases 12.11
erlotinib 75.132
erosiointerdigitalis blastomycetica 36.61
erosion
definition 5.7
mulberrry-like 36.87
erosive adenomatosis of the nipple 70.12–13
erosive pustular dermatitis
legs 50.89–90
treatment 73.32
erosive pustular dermatosis
legs 47.44
scalp 66.49–50
erucism 38.28
eruptive vellus hair cyst (EVHC) 42.88
ERX1/2 51.65
erysipelas **30.17–21**
bacteriology 30.17–18
clinical features 30.18, 30.*19*
coastal *see* onchocerciasis
complications 30.18
definition 30.17
diagnosis 30.18–19
differential diagnosis 26.29
ear 68.19
in HIV infection 35.24–5
lymphoedema and 48.12, 48.15, 48.24
management 48.24
ocular involvement 67.27
recurrent 30.18, 48.29
treatment 30.19–20
erysipelas-like erythema 59.77
erysipeloid **30.42–3**
Erysipelothrix rusiopathiae (insidiosa) 30.35, 30.42–3
erythema
acral 75.122–3
acute drug-induced phototoxicity 29.21
annular *see* annular erythema
carbon monoxide poisoning 28.93
cold-induced injury 28.64
danthron 71.87
definition 5.7
erysipelas-like 59.77
gingival 69.13
granulomatous slack-skin disease 57.15
gyrate 62.110
in hepatitis B virus infection 62.59
in irritant contact dermatitis 25.22
measurement 72.11
mechanical injury 28.27, 28.39
morbilliform toxic, drug reaction in HIV infection 35.20
necrolytic migratory *see* necrolytic migratory erythema
oral cavity 69.22
palmar
paraneoplastic 62.41
in pregnancy 8.10
palmar crease 62.85
papular 51.135
perianal/perineal 71.86, 71.87
peripheral ischaemic disorders 47.2
persistent cholinergic 22.15
post-inflammatory, in acne 42.33
pressure 47.33
quantification 25.22
radiation spectrum for induction *29.5*, 29.9
recurrent scarlatiniform 30.34
recurrent toxin-mediated perineal 30.32
in rosacea 43.3, *43.4*, 43.6
SCLE-like marginally scaled 51.135
skin colour and 5.16
Sweet's disease-like annular erythema 51.135
in sympathetic nerve injury 63.20
thermal injury 28.72–3
in triple response 22.12
see also erythema annulare centrifugum
erythema ab igne **28.72–3,** *52.24*
erythema annulare centrifugum 5.*12*, 26.26, 62.38, 62.106, **62.110–12,** 75.23–4
molluscum contagiosum with 33.12
erythema annulare rheumaticum 62.107
erythema chronicum migrans *see* erythema migrans
erythema circinatum 69.94
erythema dyschromicum perstans 30.63, 58.33–4
lichen planus vs 41.17
race and 9.16–17
erythema elevatum diutinum **50.25–7,** 50.62, 62.51
erythema gyratum repens 62.107–8
paraneoplastic 62.38
tuberculosis and 31.21
erythema induratum of Bazin and of Whitfield 31.10, **31.24,** 47.57, 50.31
see also vasculitis, nodular
erythema infectiosum (fifth disease) 5.*10*, 33.62, 33.63
see also parvovirus B19 infection
erythema marginatum (rheumaticum) 62.107
rheumatic fever 51.138
erythema migrans **30.64–6,** 62.106–7
acrodermatitis chronica atrophicans and 45.10
lingual *see* tongue, geographical
erythema multiforme (EM) **76.2–8**
aetiology 69.69, 76.2–5
allergic contact dermatitis resembling 26.25–6, 26.76
in animals 2.16
atypical 76.7
clinical features 69.69, 76.6–7
in coccidioidomycosis 36.86
coxsackievirus infections and 33.72
Crohn's disease and 62.50
definition 76.1
diagnosis 69.69
differential diagnosis 40.11, 76.7
drug-induced 76.3, *76.4*
HIV infection 35.20
female genital involvement 71.66
following streptococcal infection 30.16
genitocrural 71.6
in hepatitis B virus infection 62.59
herpes-associated (HAEM) 33.18–19
in herpes simplex 33.18–19, 33.76
histopathology *76.6*
immunology 76.2
localized vesiculobullous 76.7
in lymphogranuloma venereum 30.71
major 69.69, 76.7
male genital involvement 71.25, 71.27
minor/papular/simplex form 69.69, 76.6–7
molluscum contagiosum with 33.12
oral involvement *69.65*, 69.69–70
orf association 33.9
paraneoplastic 62.46
pathology 76.5–6
persistent 76.7
post-herpetic 33.19
predisposing factors 69.69
pregnancy and 8.12
in psittacosis 30.72
reactions resembling 26.25, 76.5
terminology 76.1
treatment 69.69–70, 76.7
triggering factors 76.2, *76.3*
ulcerative colitis and 62.50
in varicella 33.25
in viral infections 33.76, 76.2
erythema multiforme-like syndrome 51.14
erythema multiforme major 67.20–1
ocular complications 67.20–1
ocular mucous membrane pemphigoid vs 67.19
see also Stevens–Johnson syndrome (SJS)
erythema necroticans (Lucio reaction/phenomenon) 32.13, 49.35
erythema neonatorum 17.4
erythema nodosum (EN) 31.24, 46.12, **50.82–7**
aetiology and pathogenesis 50.83–5
childhood 61.16
chronic 50.86
clinical features 50.86
in coccidioidomycosis 36.86
Crohn's disease and 62.50
definition 50.82–3
diagnosis 50.86
drug-induced 50.83–4, 75.43–4
enzymic (pancreatic) panniculitis mimicking *46.19*
following jellyfish stings 38.56
following streptococcal infection 30.12
histopathology 50.85–6
history and nomenclature 50.83
in lymphogranuloma venereum 30.70
pregnancy and 50.83
in psittacosis 30.72
in sarcoidosis 50.83, 61.2, 61.6, 61.8, 61.9
septal panniculitis 46.12
treatment 50.86–7
tuberculous 31.8
ulcerative colitis and 62.50
as vasculitis 61.17
in viral infections 33.76
erythema nodosum leprosum *see* lepra reactions, type 2
erythema nodosum migrans *see* erythema nodosum
erythema toxicum neonatorum 17.6–7
erythemal response 58.10
erythermalgia *see* erythromelalgia
erythralgia *see* erythromelalgia
erythrasma **30.37–9**
differential diagnosis 26.29, 36.11
genitocrural dermatology 71.6
perianal/perineal dermatology 71.95
treatment 73.10
Wood's light examination 5.19
erythrocyanosis
cold-induced injury **28.67**
with nodules 50.32
vibration injury 28.58
erythrocyte sedimentation rate (ESR) 13.19
chronic urticaria 22.26
sarcoidosis 61.20
in thromboangiitis obliterans 47.7
erythrocytes
agglutination (cold-related) 49.34
P antigen 33.63
erythroderma 23.32, **23.46–51**
adult T-cell leukaemia–lymphoma 33.64
aetiology 23.46
bullous ichthyosiform *see* bullous ichthyosiform erythroderma (BIE)
clinical features 23.46–9
complications 23.49–50
congenital ichthyosiform (CIE) 19.17–21
see also lamellar ichthyosis
crusted scabies and 23.48
definition 23.46
dermatophytosis and 23.48
diagnosis 23.49
differential diagnosis 26.30
drug-induced 23.47, 75.24–5
eczema and 23.47
gynaecomastia and 70.4
histopathology 23.46
HIV infection and 35.13, 35.16
Hodgkin's disease and 23.48
ichthyosiform 23.48
incidence 23.46
leukaemia and 23.48
lichen planus and 23.48
lymphoma and 23.48
metabolic complications 20.13
naevoid bullous ichthyosiform 19.31
paraneoplastic 62.38
pemphigus foliaceus and 23.48
pityriasis rubra pilaris and 23.48
postoperative 75.154
prognosis 23.49–50
psoriasis and 23.47
secondary haemodynamic and metabolic disturbances 23.49
Sézary syndrome and 23.48, 57.17–22
treatment 23.49, 75.176
of unknown origin 23.48–9
erythrogenic toxins 30.11, 30.34
erythrokeratoderma 19.3, 19.69–72
progressive symmetrical (Gottron's syndrome) 19.70–1, *45.58*, 45.59–60
with sensorineural deafness *69.12*
see also Mal de Meleda
erythrokeratoderma variabilis 19.3, 19.69–70, 39.27
pregnancy and 8.12
treatment 73.36
erythrokeratolysis hiemalis (Oudtshoorn disease) 19.66, 19.68–9
erythromelalgia **47.9–10,** 62.3, 62.41, 75.44–5
in myeloproliferative disorders 49.29
erythromelanosis follicularis faciei et colli 19.73
erythromelanosis follicularis of the face and neck 58.36
erythromycin 74.42, 75.58
acne vulgaris treatment 42.47, 42.48
adverse effects, ocular 67.32
chancroid treatment 34.35
in linear IgA disease 40.50
pityriasis rosea treatment 33.81
in pregnancy 42.51
Propionibacterium acnes resistance *42.42*, 42.56
in rosacea 43.6
syphilis management 34.22
topical 73.10
acne vulgaris 42.41, 73.10
zinc acetate with 42.16
erythronychia, longitudinal 65.17–18
erythrophagocytosis, virus-induced histiocytosis with 55.30–1
erythroplasia (erythroplakia), oral cavity 69.50, 69.102
erythroplasia of Queyrat (EQ) 52.36, 71.38–9
HPV infection vs 33.55
treatment 73.23
erythropoietic protoporphyria (EPP) 59.3–4, 59.16–18
clinical features 29.23
differential diagnosis 29.12, 29.14
perioral involvement 69.39
erythropoietin, adverse effects 75.147
eschar 14.1, 14.14
dry 14.17
escharotomy 14.11
burns 28.79–80, *28.81–2*
Escherichia coli
in external auditory meatus 30.4

female genital infection 71.68, 71.70
genitocrural infection 71.5
in HIV infection 35.24
in malakoplakia 55.27
in paronychia 65.21
pyoderma gangrenosum and 50.65
Escherichia coli O157:H7 49.31
escitalopram *64.50*
esomeprazole 75.157
espundia 37.39
ESR *see* erythrocyte sedimentation rate (ESR)
essential fatty acid deficiency 3.11
hair loss and 66.29
Estelle 35® 42.15–16, 42.53
esthiomene 30.70
estrone 42.12
etanercept 13.25, 72.14
adverse effects 75.145
clinical indications 74.6
dose range and evidence level 74.6
in granuloma annulare 60.11
in hidradenitis suppurativa 74.7
origin, genetically engineered fusion protein 74.5
in pemphigus 40.12
in psoriasis 20.41, 74.5
in HIV infection 35.17
in sarcoidosis 61.21
ethacrynic acid 75.97
ethambutol 74.44
adverse effects 31.27, 75.61
in tuberculosis 31.27
ethanol
as antiseptic 73.14
see also alcohol
ethchlorvynol 75.81
ethics, prenatal diagnosis and 16.10–11
ethinyloestradiol 74.33
acne treatment 42.53, 42.54
ethionamide 74.45, 75.61
Ethiopia, prevalence of skin disease *6.10*
ethnic groups and ethnicity 6.12
allergic contact dermatitis and 26.8
atopic dermatitis and 24.2–3, 24.21
hair growth and 66.80
head louse infection and 38.19
history-taking 5.5
irritant contact dermatitis and 25.6
pigmentation 58.1
pigmentation significance 58.9
risk factor for skin disease 6.12
sarcoidosis and 61.2, 61.3, 61.15–16
tuberculosis and 31.2
see also race
2-ethoxyethyl-*p*-methoxycinnamate *25.19*
ethyl acetate 25.20
ethyl chloride 77.10
2-ethyl,1,3-hexanediol *25.19*
ethylene diaminetetraacetate 73.8
ethylene glycol monomethylether 25.20
ethylene oxide 25.21, 27.11
ethylenediamine
adverse effects 26.18, 26.44
as allergen 26.59
ethylenediamine tetracetate (EDTA) 26.17, 26.58
etoposide 75.131–2
familial haemophagocytic lymphohistiocytosis 55.26
etretinate
adverse effects **75.109–10**
hair loss 66.29
in granuloma annulare 60.10
in hidradenitis suppurativa 30.81
in lichen sclerosus 51.118
in non-melanoma skin cancer 52.18
squamous cell carcinoma 52.28
in psoriasis 20.37
in psoriatic nail involvement 65.26
Eucerin 73.7
eumelanins 3.20, 66.90
in animals 2.5, 2.6
formation 58.5, *58.6*
synthesis 3.21, *3.21*
eumelanosomes 66.91
eumycetoma 36.72, 36.73, 36.74
eunuchs 66.13–14, 66.16
sebum secretion 42.10
Euphorbiaceae *25.21*
Euphyllia picteti 38.56
Euproctis 38.28, 38.29
Euroglyphus 38.47
European Pressure Ulcer Advisory Panel classification scheme 14.13, *14.14*
EuroQol EQ-5D 72.17
Eurysolen gracilis 75.160
Eutrombicula 38.50
EV *see* epidermodysplasia verruciformis (EV)
Evans' syndrome 49.9
evaporimeter 4.11
EvC (Ellis–van Creveld syndrome) 15.39, 15.65
evening primrose oil, in atopic dermatitis 24.31
Evernia prunastri 26.77
evidence-based dermatology, information resources 6.20
evidence-based medicine 6.18, **7.1–23**
evidence
appraisal and evaluation 7.7–23
finding 7.5–6
hierarchy of 7.3–4
need for 7.1–2
practice of 7.2
question formulation 7.2–3
evolution
epidermis and dermis 2.1–4
glands 2.4–5
pigmentation role 73.40
significance of melanin and pigmentation 58.8–9
skin components **2.1**
Ewing's sarcoma, extraosseous 56.54
examination of skin 5.6–22
exanthem subitum (roseola infantum) 33.32
exanthems
viral infection 33.3–4, *33.4*
see also rash(es)
excisions *see* surgery
excited skin syndrome 26.88, 26.95
excoriations
definition 5.7
neurotic 23.46
self inflicted 64.14, 64.19, 64.27–9, 64.37
exercise
anaphylaxis and 22.15
lymphoedema management 48.22
purpura due to 49.18
urticaria and 22.8
vasculitis induced by 49.18, 50.23
exfoliation, definition 5.7
exfoliative dermatitis *see* erythroderma
exfoliative toxins 30.14, 30.30
exocytosis 10.39
exogen 66.8, 66.11, 66.20
exomphalos–macroglossia–gigantism syndrome *see* Beckwith–Wiedemann syndrome
Exophiala dermatitidis 36.77, 36.92
Exophiala jeanselmei 36.77
Exophiala werneckii 36.8, 36.14
exoskeleton 2.2
exostosis
external auditory canal 68.28, 68.29
subungual *62.101*, 65.33–4
expert opinion 7.3, 7.4
exposure dose 29.1
external auditory canal/meatus
altitude injury 68.11
anatomy and physiology 68.1–2
bacterial flora 6.2, 30.4
basal cell carcinoma 68.32–3, 79.9
benign tumours 68.28–9
cholesteatoma 68.28, 68.35
eosinophilic granuloma 68.28
examination 68.3
exostosis 68.28, 68.29
foreign bodies 68.11
hypertrichosis 68.18, 68.21
infantile haemangioma 18.46
infection 68.20–8
keratosis obturans 68.28, 68.35
lichen planus 68.15
mucoepidermoid carcinoma 68.33
normal bacterial flora 30.4
osteoma 68.28, 68.29
papillomatosis 68.29
squamous cell carcinoma 68.32–3
verrucous carcinoma 68.33
see also ear(s)
external jugular vein 77.2, *77.3*
external otitis *see* otitis externa
extracellular matrix (ECM) **3.33–3.50**
components 3.33–4
see also collagen; elastic fibres; proteoglycan(s)
function and cell types 3.49
lymphatic capillaries 48.4
PDGF upregulating in mucous membrane pemphigoid 67.20
see also dermis
extracellular matrix protein 1 gene *(ECM1)* 3.50
extracorporeal photopheresis (ECP) 57.27
in pemphigus 40.12
in systemic lupus erythematosus (SLE) 51.62
in systemic sclerosis 51.108
extramammary Paget's disease (EMPD) *see* Paget's disease
extranodal NK/T-cell lymphoma (nasal type) 57.40–1
extravasation, in chemotherapy 75.122
exudative discoid and lichenoid chronic dermatosis 23.11–12
eye(s) **67.1–37**
anatomy and physiology 67.1–3
apocrine hidrocystoma 53.18
appendages 67.1–3
in atopic dermatitis 24.24–5
autoinoculation with gonococci 34.25
in Behçet's disease 50.59–60
bullous disorders *67.29*
caterpillar setae in 38.29
in congenital syphilis 34.16
in connective tissue disorders *67.29*
in Degos' disease 49.46
drug-induced disorders 67.15, 67.16, 67.31–2
dry 67.21
management 67.22
in dystrophic EB 39.19, 39.29
in Ehlers–Danlos syndrome 45.35
in herpes simplex 67.25–6
hypopigmentation, in Chédiak–Higashi syndrome 58.41
infections 67.24–8
inherited disorders 67.28–31
in juvenile xanthogranuloma 55.16
in keratinization disorders *67.29–30*
in leprosy 32.13–14
in loiasis 37.11
in Marfan's syndrome 45.30
in molluscum contagiosum 67.24–5
in necrobiotic xanthogranuloma 55.28
in onchocerciasis 37.4
parasitic diseases involving 67.27
in pseudoxanthoma elasticum 45.21, 45.22
in pyoderma gangrenosum 50.70
in relapsing polychondritis 45.43
in rosacea 43.4, 43.5, 43.7
in sarcoidosis 61.7
in SLE 51.46–7, *67.25*
in Stevens–Johnson syndrome 76.16
in Sturge–Weber syndrome 18.66
in systemic diseases 67.24, *67.25*
in systemic sclerosis 51.103
topical corticosteroid exposure, effects 73.19
in toxic epidermal necrolysis 76.18
in trypanosomiasis 37.32
tumours affecting 67.33–4
viral infection 67.25–6
in xeroderma pigmentosum 15.73
in zoster 33.25–6, *33.26*, 67.26
see also entries beginning ocular
eye flies 38.6
eye sign 37.32
eyebrows 67.1
ageing and 8.24
alopecia areata 66.35
bushy 67.3
disorders 67.3–4
dyes 26.60
fusion 67.3
hypoplasia 67.3–4
inflammatory disorders 67.4
inherited disorders *67.29*
loss and scarring 67.4
plucking 67.4
trichotillomania 67.4
eyelashes 67.2
alopecia areata 66.35
disorders 67.4
dyes 26.60
inherited disorders *67.29*
loss 67.4, *67.8*
louse infection *38.22*, 38.23
phthiriasis 67.27
trichomegaly, in HIV infection 35.41
eyelids
abnormalities 67.5–6
actinic keratosis 67.33
allergic contact dermatitis 23.11, 26.17, 26.22, 26.31, 67.5
anatomy and physiology 67.1–2
atopic dermatitis 23.11
basal cell carcinoma *67.10*, 67.34–5, *79.9*
benign cysts 67.33
benign tumours 67.33–4
blepharochalasis *see* blepharochalasis
blood supply 67.2
chalazion 67.34
chronic oedema 48.16
contact dermatitis 67.5
cysts, keratoderma with 19.95, 19.111
dermatitis, tacrolimus therapy 73.32
discoid lupus *67.10*
eccrine carcinoma 67.36
eczema 23.11
epithelioma 67.35–6
impetigo 67.26
inflammation of margin 67.6–12
see also blepharitis
irritant contact dermatitis 25.13, 25.15
juvenile xanthogranuloma 67.33
Kaposi's sarcoma 67.36
keratoacanthoma 67.34
louse infestation 67.27
lymphoedema 77.2
malignant tumours 67.34–6
margin
intraepidermal carcinoma 52.37
ulcers 67.6, *67.8, 67.9*
melanoacanthoma 67.34
melanoma 67.35, *67.36*
Merkel cell carcinoma 67.36
metastatic carcinoma 70.14
milia 67.33
millet-seed nodules 61.7
occupational dermatoses 27.4
ocular rosacea *67.7*
oedema, in rosacea 43.6
periorbital oedema 67.5
pigmentation 67.5
pigmented naevi 67.34
port-wine stain 67.34
psoriasis 67.5
purpura diagnosis 49.4
radiotherapy 79.8–9
in sarcoidosis 61.7
sebaceous carcinoma 42.87–8, 53.17, *67.10*, 67.35–6
sebaceous glands 67.2
seborrhoeic dermatitis 23.11
seborrhoeic keratosis 52.39, 67.33

shortening 67.21
skin diseases 67.5–6
squamous cell carcinoma 67.35, *67.36*
surgery *77.3*, 77.5
sweat glands 67.2
swelling (blepharophyma) 43.9
syringomas 67.33
tarsal plate 67.2
topical corticosteroid use, effects 73.19
trichoepithelioma 67.33
tricholemmoma 67.33
vascular naevi 67.34
warts 67.24
wedge excision 77.35
xanthelasma 67.33
ezetimibe 59.93

F
F granules 3.10
fabric conditioners/softeners 25.25, 26.18
fabricated and induced illness **64.44–5**
Fabry's disease *see* Anderson–Fabry disease (angiokeratoma corporis diffusum)
face
allergic contact dermatitis 26.16–17, 26.47, *26.48*
basal cell carcinoma 79.10, *79.11*
cellulitis 30.18
Demodex folliculorum in rosacea 43.2
differential diagnosis of dermatoses 26.29
embryonic development 18.80, 18.85
erythromelanosis follicularis of 58.36
fibrous papule 56.2–3
flushing *see* flushing
focal facial dermal dysplasia 45.6, 45.8
hemiatrophy 45.11–12, 51.70
Herlitz junctional EB 39.12
intradermal elastic tissue 45.2
necrobiosis 68.17
piercings 69.96
purpura 49.4
radiotherapy 79.10, *79.11*
rejuvenation techniques **80.4–14**
rosacea features 43.3
sebaceous carcinoma 53.17
seborrhoeic dermatitis 23.31
skin biopsy 10.33
spontaneous atrophic scarring of the cheeks 45.7
telangiectases 47.14
vascular tone 43.14
warts 33.41
facial Afro-Caribbean childhood eruption (FACE) 9.12, 43.12, **43.13**
facial artery 77.2
facial ectodermal dysplasia 15.40
facial hemiatrophy 46.39
facial hyperpigmentation 58.12, 58.34–8
management 73.28
facial idiopathic granulomas with regressive evolution *see* acne agminata
facial lipoatrophy 46.39–40
HAART-induced 35.22
HIV-associated 46.42
facial lymphoedema 48.12, 48.13, 48.16, 48.23
management 48.23
facial nerve 77.4–5, 77.10
facial oedema, solid 42.74, 48.13, 48.16, 48.23
facial palsy, zoster 33.25, 33.26
facial skin, ageing 8.21–2
facies, in naevoid basal cell carcinoma syndrome 52.7
facioauriculovertebral spectrum **18.82–3,** 68.4
factitious skin disease *64.11*, **64.34–46**
co-morbidity 64.41
dermatitis artefacta (dermatitis factitia) 64.35–42, 71.56
dermatology consultation 64.34–5
diagnostic criteria 64.35
investigations 64.40–1
management 64.41–2
medicolegal issues 64.45
factor V Leiden mutation 14.13, 49.38, 49.39, 49.44
factor VIII-related antigen 10.23
factor XIa 13.4
factor XIIIa 10.23
expressed by dermal dendrocytes 55.4, 55.15, 55.18
histiocytosis (class IIa) 55.15, 55.18, 55.20, 55.22
sinus histiocytosis with massive lymphadenopathy 55.29
factor B 13.18
factor H 13.3
deficiency 13.3
factor I 13.3
factory visits 27.8–9
FAE *see* fumaric acid esters
faecal contamination 71.85
faecal impaction 39.28–9
faeces, napkin dermatitis and 17.23
falanga 28.32–3
famciclovir
action 74.49
therapy
herpes simplex 33.20, 33.21
herpes zoster 33.27, 33.28, 63.6, 67.26
familial atypical multiple mole and melanoma *62.20*, 62.21–2
familial cancer syndromes 52.6
familial cold autoinflammatory syndrome **15.95–6**
familial cold urticaria 74.11
familial disorders
analysis 15.7
definition 15.2
see also specific familial disorders
familial dysautonomia 44.7, 62.80, 63.18
type II 15.34
familial dyskeratotic comedones 19.76
familial glomus tumour, genetics 15.6
familial haemophagocytic lymphohistiocytosis (FHL) 55.25–6
familial Hibernian fever 22.25, 50.53, 62.69, 62.104
familial histiocytic dermoarthritis 62.104
familial hypercholanaemia 3.25
familial hypercholesterolaemia 59.86–8
pseudo familial hypercholesterolaemia 59.92
familial hypomagnesaemia 3.25
familial male-lethal type incontinentia pigmenti 15.45
familial mandibulo-acral dysplasia 45.61–2
familial Mediterranean fever 22.25
with amyloidosis 62.104
bone and joint involvement 62.104
with urticaria 62.69
vasculitis and 50.53–4
familial melanoma syndrome 54.28, *62.20*, 62.21–2
familial multiple tumour syndromes **15.15–27**
familial partial lipodystrophy (FPLD) 46.40–1
familial peeling skin syndromes 19.66–8
familial polyendocrinopathy syndrome 36.58, 36.65
familial polymorphous light eruption 29.13
family(ies)
bad news communication 72.5
clinical decisions and *72.4*
history-taking regarding 5.5
quality of life assessment 64.10, 72.23–4
Family Dermatology Life Quality Index 72.23
FAMMM syndrome (familial atypical multiple mole melanoma syndrome) 54.28
famotidine 75.150
Fanconi's anaemia/syndrome **58.17–18,** 62.29, 62.95
anaemia in 58.17
immunodeficiency and 17.68–70
Fannia canicularis 38.6, 38.8
fansidar, adverse effects 37.27
Farber's disease 59.41
farcy 30.51
farmer's lung 61.23
Faroe Islands, prevalence of skin disease *6.9*
Fas (CD95), deficiency 13.15
Fas ligand (FasL)
in apoptosis 12.11, 40.6
toxic epidermal necrolysis and 74.11
fascial hernias, legs 45.68–9
'fascial' network 3.50
fasciitis, eosinophilic *see* eosinophilic fasciitis
fasciitis–panniculitis syndrome 46.31
fascin 55.9
Fasciola hepatica 37.3
fat
accumulation, buffalo hump 46.42
autologous transfer 46.39, 46.43, 80.5–6
loss *see* lipoatrophy
metabolism, regulation 46.2–3
subcutaneous *see* subcutaneous fat
fat cells *see* adipocytes
fat embolism 49.38, 62.99, *62.101*
fat granuloma 61.22
fat necrosis *see* subcutaneous fat, necrosis
fat tissue 46.2
as organ 46.2
see also subcutaneous fat
fatty acid(s) 46.2
energy source 46.3
free *see* free fatty acids
in ichthyoses 19.5–6
neutral lipid storage disease with 19.52, 19.54
Refsum's disease 19.45–6
Sjögren–Larsson syndrome 19.42–3, 19.44
non-esterified (NEFA) 46.3
in sebum 42.5, 42.6
in topical treatment 73.7
fatty acid esters 73.35
acnegenicity 27.13
fatty alcohol oxidation (FAO), Sjögren–Larsson syndrome 19.42, 19.44
fatty aldehyde dehydrogenase (FALDH), Sjögren–Larsson syndrome 19.42, 19.43, 19.44
faun tail 18.96, 53.6, 63.15
favourable skin tension lines, scar orientation and 77.2, 77.11, 77.13
Favre–Chaix's purpura 49.22
Favre–Racouchot syndrome 42.79, 45.27
favus 36.26, 36.27
FDH *see* focal dermal hypoplasia (FDH)
FDS (follicular degeneration syndrome) 9.7, **66.46,** 66.68
feathers 2.3
febrile convulsions, in roseola infantum 33.32
febrile ulceronecrotic Mucha–Habermann disease (FUMHD) 50.50–1
feet
aggressive digital papillary adenocarcinoma 53.33
allergic contact dermatitis 26.19, 26.29
atopic dermatitis 8.7
atopic winter *see* juvenile plantar dermatosis
burning feet syndrome 63.25
care in diabetes 47.58
diabetic ulcers 47.57–8, 63.8–9
in dystrophic EB 39.18
erythromelalgia 47.9
hair as foreign body 28.49
hyperhidrosis 44.8
localized EB simplex (Weber–Cockayne EBS) 39.6
hyperkeratosis
Dowling–Meara EB simplex 39.7
localized junctional EB 39.14
hyperpigmentation, acromelanosis 58.21
ischaemic disease 47.2
localized EB simplex (Weber–Cockayne EBS) 39.6
localized junctional EB 39.14
mechanical injury 28.10–12, 28.14, 28.16, 28.31, 28.61
microbial eczema 23.25
moccasin 36.31
neuropathic ulcers 47.57
in obesity 8.17
occupational dermatoses 27.3
pitted keratolysis 44.8
psoriasis of soles 20.15
rocker-bottom 63.8
soles of *see* soles
symmetrical lividity 44.8
tropical immersion 30.49
wrinkling 28.93
Felty's syndrome
leg ulceration associated 47.55
oral involvement 69.32–3
pyoderma gangrenosum of perianal area 51.132
female(s)
acne vulgaris 42.18
sexual development 8.2
female genital dermatology **71.52–82**
benign tumours and tumour-like lesions 71.72–4
congenital and developmental abnormalities 71.56
general approaches 71.1–4, 71.52
inflammatory dermatoses 71.58–65, 71.66
lichen planus 41.9
lichen simplex and lichenification 71.52–3
malignant neoplasms 71.76–9
miscellaneous conditions 71.79–82
non-sexually transmitted infections 71.67–70
normal flora and variants 71.55
precancerous dermatoses 71.74–6
sexually transmitted diseases 71.70–2
trauma and artefact 28.38, 71.56–7, 71.66
ulcerative and bullous disorders 71.65–7
vaginal discharge 71.52, 71.53–4, 71.69
see also individual conditions
female genital mutilation (FGM) 71.56–7
female genitalia, structure and function 71.54–6
femoropopliteal vein bypass 47.6
fenbufen 75.74
fenestrations 3.52
fenofibrate 46.47, 75.31
fenoprofen 75.74
fentanyl *26.46*
fentichlor 26.24
fenticonazole, topical 73.12
Ferguson–Smith syndrome 69.54
fermitin, Kindler syndrome 12.17
Fernandez reaction 32.15
ferric chloride, tattoos 58.57
ferric sulphate, tattoos 58.57
ferritin 49.6, 59.70
ferrous sulphate, in restless legs syndrome 63.25
ferulic acid 80.3
fetal alcohol syndrome
ear anomalies 68.3, 68.4–5
haemangioma in 18.2
hypertrichosis in 66.77
fetal development, drug exposure 72.28
fetal hydantoin syndrome, ear anomalies 68.3
fetal hydrops 33.63
fetal varicella syndrome 17.40–1, 18.2, 18.102

α-fetoprotein 47.19, 63.16
fetoscopy 16.5–7
fetuin A 49.48
fetus
  brown fat 46.1
  free DNA 16.9–10
  influence of environment 6.12
  medical procedures 17.11–12
  melanoma metastases 54.57
  rhabdomyoma 18.37
  RNA 16.9–10
  sebaceous glands 42.3
  skin biopsy 16.5–7
  testis and testosterone secretion 8.2
  ultrasound 16.7
  wound healing 14.2, 14.9
fetus papyraceus, with aplasia cutis congenita 18.100–1
Feuerstein–Mims syndrome 18.27–30, 54.11
fever
  eczema herpeticum 33.35
  hyperhidrosis and 44.7
fexofenadine *22.29*, 74.31
  in urticaria 22.28
FFDD (focal facial dermal dysplasia) 15.40, **15.83–4,** 18.103, 45.6, 45.8
FG syndrome-1 **15.96**
FGF2 *see* basic fibroblast growth factor (bFGF)
FGFR2 gene mutations 42.78
FGFR3 gene 18.6
  mutations in seborrhoeic keratosis 52.38
FGM (female genital mutilation) 71.56–7
FH *see* fibrous histiocytoma
FHL (familial haemophagocytic lymphohistiocytosis) 55.25–6
fibrates 59.93
fibreglass dermatitis 25.17, 27.6, 28.47–8
fibrillin(s) 3.2, 3.45
  ageing and 80.2
  lymphatic capillaries 48.4
  in Marfan's syndrome 45.30
fibrillin 1 (FBN1) 3.45
fibrillin 2 (FBN2) 3.45
fibrin 49.38
  cuff 47.26–7, 47.27
  in venous eczema 23.35
fibrin cuff theory 47.26–7, 47.27
fibrinogen 49.38
  in wound healing 14.3
fibrinoid necrosis/degeneration 10.38, 51.1
fibrinolysin/desoxyribonuclease 14.22
fibrinolysis 47.28
  inhibition 49.45
fibrinolytic agents, platelet function disorders 49.13
fibro-osseous pseudotumour of the digits 56.5
fibroblast(s) **3.49–50,** 12.30–2
  age-related changes 8.22
  ageing 45.60, 80.1, *80.2*
  allogeneic human-derived 80.5
  in chemical-induced scleroderma 45.52
  collagen synthesis 3.49
  cultured
    gene expression patterns 3.49–50
    transduction by transcription factors 3.50
  dermal sheath 66.4
  dermal subsets 3.7
  elastin synthesis 3.44, 3.49
  in embryonic dermis 3.3
  functions 3.49
  keloid 3.50, 14.15, 45.54
  lipoid proteinosis 3.50
  microscopy 10.35
  MMPs synthesis/secretion 3.41
  in palmar fibromatosis 45.45
  pluripotent stem cell induction 3.50
  proteoglycan synthesis 3.46
  in wound healing 14.1, 14.7–8
fibroblast-derived matrix molecules 12.30
fibroblast growth factor (FGF) 3.3, 12.31
  hair growth and 66.11
  mucous membrane pemphigoid pathogenesis 67.20
  receptors, *FGFR-2* mutation 42.71
  wound healing and 14.3, 14.5, 14.27
fibroblastic rheumatism 51.133, 62.103
  interphalangeal joints 51.133
fibroblastoma
  desmoplastic 56.10–11
  giant cell 56.14–15
fibrocystic disease, of pancreas 59.59
fibroepithelial polyp
  oral 69.20
  see also skin tags
fibroepithelioma of Pinkus 52.48
  as trichoblastoma variant 53.10
fibrofolliculoma 53.14–15
fibrohistiocytic tumours 56.15–23
  diagnosis 10.22–3
fibrokeratoma, acquired digital (periungual) 56.4, 65.31–2
fibrolipoma, neural 18.40
fibroma(s)
  calcifying aponeurotic 56.7
  collagenous 56.10–11
  female genital dermatology 71.72
  Gardner-associated 56.11
  garlic clove 65.31–2
  genetics 15.26
  nuchal 56.11
  oral cavity 69.20
  perifollicular 53.14
  periungual 65.32
  pinna 68.28
  pleomorphic 56.3–4
  sclerotic 56.3
  storiform perineural 56.49
  tendon sheath 56.10
  trichoblastic 53.10–11
  trichogenic 53.10–11
fibroma molluscum 62.2
fibromatosis **45.44–50**
  bone and joint involvement *62.101*
  congenital generalized 56.9
  deep (non-metastasizing) 45.44
  dermal plaque-like 56.7
  hereditary gingival 69.14–15
  inclusion body (digital/infantile digital) 56.9–10, 65.32
  juvenile hyaline 45.49–50, 69.15
  palmar 45.45–6, **56.11**
  penis 45.47–8, 56.11–12
  plantar 45.47, **56.11**
  radiation 97.18
  subcutaneous pseudosarcomatous 45.50, **56.4–5,** 69.112
  superficial
    fascial 45.44–8
    palmar and plantar 45.45–6, 45.47, **56.11**
fibromodulin 45.33
fibromuscular dysplasia, peripheral arteries 49.48
fibronectin 3.2, 49.33
  in Ehlers–Danlos syndrome 45.32, 45.36
  in sarcoidosis 61.20
  in wound healing 14.1, 14.3, 14.4, 14.7
fibronectin-binding proteins 30.7
fibropapillomas, in cats 2.22
fibrosarcoma 79.18–19
fibrosis
  in chronic radiodermatitis 79.16
  definition 5.7
  oral submucous 69.106–7
  subcutaneous fat injury leading to 46.11
fibrous dysplasia, McCune–Albright syndrome 58.18
fibrous histiocytoma (FH) **56.16–18**
  aneurysmal 56.16–17, 56.17, *56.18*
  angiomatoid 56.19–20
  atrophic 56.16
  atypical 56.16, 56.17
  cellular 56.16, 56.17
  epithelioid 56.16, 56.17–18
  malignant 56.22
  myxoid malignant 56.22
  nail involvement 65.32
  plexiform 56.20
fibrous lump 69.20
fibrous papule of the face/nose 56.2–3
fibrous tumours 56.2–14
  see also specific types
fibroxanthoma, atypical **56.20–2,** 68.34, 79.18
fibulin(s) 3.2, 3.45, 45.14
fibulin-4 3.45
  mutations 3.44
fibulin-5 3.45
  mutations 3.44
fiddleback spider 38.32
'fiddler's neck' 28.25, 42.76
'field effect'
  lentigo maligna 54.41
  melanoma 54.36
fievre boutonneuse 30.73
fifth disease (erythema infectiosum) *5.10*, 33.62, 33.63
  see also parvovirus B19 infection
FIGURE (facial idiopathic granulomas with regressive evolution) 43.13
filaggrin 3.1, 3.8, 3.10, 12.15, 12.50
  in atopic dermatitis 24.4
  defect, knockout mice 2.8
  gene mutations 3.8
  in stratum corneum 4.2
filariasis
  blinding *see* onchocerciasis
  Loa loa **37.11–12,** 38.6
  lymphatic **37.8–10,** 48.12
  lymphoedema 48.12, 48.24
  ocular involvement 67.27
  vectors 38.5
filiform keratodermas 19.114
filiform keratoses 19.92–3
filling materials, acne scars 42.69
Filobasidiella 36.89
filopedia, melanosome transfer to keratinocytes 58.4
filoviruses *33.3*, 33.66, *33.67*, 33.68, **33.69–70**
filter-paper test 27.8
finasteride 74.32
  adverse effects 66.25, 70.5, 75.120
  in androgenetic alopecia 66.24–5
  in hirsutism 66.88
fine-needle aspiration cytology, melanoma 54.53
fine-needle aspiration of lymph nodes 5.21
fine-tooth comb 38.20
finger(s)
  clubbing **15.87–8,** 62.35, **65.7–8**
    with acanthosis palmaris 62.32
    in inflammatory bowel disease 62.52
  cold flexed 51.112
  congenital onychodysplasia of index fingers 65.20
  digital nerve block 65.42, 77.10
  fibro-osseous pseudotumour 56.5
  myxoma 56.59
  nails *see* nail(s)
  nicotine staining 62.46
  paroxysmal haematoma 28.27, 45.4, *45.5*, 49.16
  tulip 26.16
  wrinkling **28.93**
finger pebbles 59.79
finger tip unit 73.3, *73.4*
fingernails
  lichen planus 41.14, *41.15*
  torture injuries 28.33
fingerprints 3.3
Finkelstein's disease 17.33–4, 49.18–19, 50.30
Finlay–Marks syndrome 15.52
Finn chamber 26.85, 26.86
fir *26.81*
fire ants 38.14
fire jelly 38.56
fire sponge 38.59
firjal (endemic syphilis) 30.63
first aid, burns 28.75–6
Fischer syndrome 15.39
Fischer–Volavsek syndrome 15.39
fish
  colour, patterns and genetics 2.6
  as irritants 25.21
  pigment cells 2.5–6
    mutations affecting 2.6
  scales 2.2
  skin infections 2.12
  venomous 38.59–60
fish odour syndrome 44.20
fish scale collagen (FSC) 2.2
fishing, occupational hazards 27.19
fissure, definition 5.7
fissures of Santorini 68.1
fistula
  branchial (cervical) 18.85–6
  congenital auricular **18.83–4,** 68.4
  definition 5.7
  mammary duct 70.13
  parastomal 62.54
  perianal/perineal 71.83, 71.87, 71.89
  umbilical 71.100
fistulectomy 70.13
fistulotomy 70.13
Fitz–Hugh Curtis syndrome 34.26, 34.30
fixatives
  in perfumes 26.40
  in skin biopsy 10.4–5
fixed drug eruptions *see* drug reactions (ADRs) (and drug-induced conditions), fixed eruptions
fixed effects models 7.9
FK-506 *see* tacrolimus (FK506)
flag sign 66.94
flagellation 28.33
flame figures 46.33
  conditions with 46.33
  in eosinophilic cellulitis (Well's syndrome) 46.12, **46.33–4**
  in eosinophilic panniculitis 46.12
flare, in triple response 22.12
flash burns 28.90
flashlamps 78.5
  in hypertrichosis 78.12–13
  in port-wine stains 78.7
  in telangiectases 78.8
flat flies 38.6
'flat seborrhoeic keratosis' 54.3
flatworms 37.2, 37.3, **37.20–3**
flautist's chin 28.26
flaviviruses *33.2*, 33.61, 33.66, *33.67*, **33.68**
flavonoid drugs, venous leg ulcers 47.49
FLCN gene mutations 53.14
flea(s) **38.11–13**
  animal 2.9–10, 38.4
  control agents 2.10
  diagnosis of infestation 38.4, 38.11–12
  hedgehog 2.3
  human *(Pulex irritans)* 2.10
  survival 38.4
flea allergy dermatitis (FAD) 2.10
Flegel's disease (hyperkeratosis lenticularis perstans) 10.39, 19.89–90
Fleisher syndrome 70.2
flesh flies 38.8
Flexible Collodion BP 73.2
Fli-1 10.23, 10.24
floor layers, occupational hazards 27.19
flora, skin *see* bacteria, flora (normal skin)
florid cutaneous papillomatosis 19.93
Florida horse leech 36.92
florists, occupational hazards 27.19
flour
  as irritant 25.21
  mites in 38.46–7
flow cytometry 13.16, 13.19, 13.22, 13.23, 17.56
flower cells 33.64, *33.65*

flucloxacillin 30.19–20, 75.49
fluconazole 74.47
  adverse effects 75.64
  in candidiasis 36.68, 36.69
  in coccidioidomycosis 36.86
  in dermatophytoses 36.48, 36.49
  eccrine gland secretion 44.18
  in ectodermal dysplasias 15.70
  failure to respond to 36.50–1
  in histoplasmosis 36.83
flucytosine
  adverse effects 75.64
  in candidiasis 36.68
  in chromoblastomycosis 36.76
  in cryptococcosis 36.90–1
fludarabine 13.24
  in paraneoplastic pemphigus 40.23
fludroxycortide (flurandrenolone) 73.20
fluence (energy) 29.1
fluid balance monitoring, burns 28.83–4
fluid resuscitation, burns 28.77–8, 28.80–4
flukes 37.2, 37.3, **37.20–3**
fluocinonide 73.37
fluorescein 10.12, 47.26, 75.155
fluorescence micro-lymphangiography 48.19
fluorescent treponemal antibody absorption (FTA-ABS) test 34.20, 51.52
fluoride
  tooth discoloration and 69.8
  toxicity 75.162
fluorochrome dyes 10.12
fluoroquinolones 32.17, 74.41
5-fluorouracil (5-FU)
  in actinic keratosis 52.31
  adverse effects *26.46*, 75.**129**
    pellagra 59.63
  in Bowen's disease 52.34
  intralesional 77.49
    wart treatment 33.49
  in non-melanoma skin cancer 52.17–18
    squamous cell carcinoma 52.28
  in systemic sclerosis 51.108
  topical 73.23
    photocarcinogenesis control 29.7
    wart treatment 33.49
  in xeroderma pigmentosum 15.74
fluoxetine 64.20, 64.28, *64.50*, 74.52, 75.79
  adverse effects, hyperhidrosis 44.7
flupentixol 64.52
flushing 8.20, **43.14–17**
  alcohol intake associated 43.16
  carcinoid syndrome 43.14, 43.17–18, 43.19
  causes *43.15*, 43.16
  chlorpropamide–alcohol 43.16
  drug-induced 43.15–16
  dry (without sweating) 43.14
  emotionally triggered 43.15
  food associated 43.16
    in carcinoid syndrome 43.18, *43.19*
  gustatory 43.16
  management 43.6
    nicotinic acid 73.51
  in mastocytosis 22.32, 22.35
  mediators and pathogenesis 43.2
  menopausal 8.20, 43.15
  neurally activated 43.14
  paraneoplastic 62.43–4
  persistent 43.16
  physiological 43.15
  premenstrual 8.8
  pyoderma faciale 42.84
  in rosacea 43.1, 43.2, 43.3
  scombroid fish poisoning 43.16
  unilateral gustatory 43.16
  wet (with sweating) 43.14
fluspirilene 75.82
flutamide 74.32
  in acne 42.16, 42.54
  adverse effects 42.54, 75.31, 75.134
  in androgenetic alopecia 66.26
  in hirsutism 66.89
fluticasone 73.16
fluvoxamine 64.20, 64.23–4, 64.28, *64.50*
foam cells 46.11
foam dressings 14.24
foam sclerosant 47.39
focal acantholytic dyskeratosis 69.26
focal acral hyperkeratosis, race and 9.10
focal dermal hypoplasia (FDH) 15.39, **15.84–6**
  bone and joint involvement *62.100*
  oral involvement 69.33–4
focal epithelial hyperplasia 33.47, 69.111–12
focal facial dermal dysplasia (FFDD) 15.40, **15.83–4,** 18.103, 45.6, 45.8
focal keratoderma with oral leukokeratosis 19.103
focal palmoplantar and oral hyperkeratosis syndrome 69.25
focal palmoplantar keratodermas 19.3, *19.94*, 19.95, 19.102–5
fogo selvagem (wild fire) 40.13, 40.17–18
  see also pemphigus foliaceus
folate *see* folic acid
foliate papillitis 69.107
folic acid 59.63
  deficiency 62.85, 69.56, 69.85–6, *69.116*, *69.117*
    pigmentation changes 58.27
  supplementation in methotrexate therapy 74.22–3
folie à deux 64.15, 64.36
follicle centre primary B-cell lymphoma 57.45–6
follicle mites *see Demodex*
follicle-stimulating hormone (FSH) 8.4
  in adolescence 8.4
  in menopause 8.19
  in menstrual cycle 8.8
  in polycystic ovary syndrome 66.82
follicle unit 12.63
follicles, hair *see* hair follicle(s)
follicular atrophoderma, basal cell carcinoma and 52.8–9
follicular carcinoma **53.32**
follicular casts 42.22
follicular degeneration syndrome 9.7, **66.46,** 66.68
follicular dendritic cell(s) 13.9
follicular dendritic cell sarcoma 55.31
follicular ichthyosis 19.73
  ichthyosis follicularis with alopecia and photophobia 19.58–9, 19.60
follicular infundibulum
  comedo naevus 53.4
  expanded, dilated pore 53.3
  trichoadenoma 53.3–4
  tumour 53.3
follicular keratosis
  inverted 53.2–3
  scarring 66.50–1
follicular mucinosis 57.14, 59.26
  immunophenotype 57.14
  T-cell lymphomas 57.14
  urticaria-like 59.28
follicular occlusion triad/tetrad 30.79, 42.33, 42.74
follicular units 66.3
folliculitis **30.21–30,** 59.80
  acneiform oil 42.34
  actinic 30.27–8
  agminate 36.27
  Candida 42.36
  causes *25.2*
  chronic, of legs 30.22
  chronic verrucous, in VZV infection 35.28
  Demodex
    acne vs 42.36–7
    rosacea vs 43.5
  in dermatophytosis 36.22
  differential diagnosis, acne vs 42.36–7
  dissecting
    acne and 42.33
    scalp *see* perifolliculitis capitis abscedens et suffodiens
  eosinophilic, in HIV infection 35.18–19
  eosinophilic pustular 17.10, 30.28–9
  Gram-negative 30.49, **42.84**
    acne and 42.74
    isotretinoin treatment 42.62
    Propionibacterium acnes antibiotic resistance 42.56
  in HIV infection 35.24
  isotretinoin 42.62, 42.84, 74.34
  Malassezia (seborrhoeic/pityrosporal) 23.34, 36.13
  mechanical injury 28.29
  necrotizing crystalline infundibular 19.89
  oil *27.14*, 27.16
  perforating *see* perforating collagenosis (folliculitis)
  perianal/perineal 71.91
  Pityrosporum, acne vs 42.37
  pruritic of pregnancy 8.15
  in scabies 38.39
  scalp 42.74
  staphylococcal 67.6, 67.11
  Staphylococcus epidermidis 42.36
  superficial 30.21–2
  trunk 30.27
  tufted 42.74, **66.46–7**
folliculitis decalvans 30.25, 42.74, **66.46–7**
  acne conglobata with 42.82
  treatment 42.74
folliculitis keloidalis 9.9, **30.26**
folliculitis ulerythematosa reticulata 66.51
folliculocentric keratotic disorders 19.72–6, 19.84
folliculosebaceous-apocrine tumours 53.30–2
Folling's disease *see* phenylketonuria (PKU)
follow-up studies 26.2
fondaparinux 49.27
Fong syndrome 15.8, **15.86–7**
Fonsecaea 36.75
Fonsecaea compacta 36.75
Fonsecaea pedrosoi 36.75, 36.76
food
  consumption, obesity and 46.6
  contact cheilitis due to 69.120
  flushing associated 43.16
    in carcinoid syndrome 43.19
  histamine/histamine-releasing substances in 22.8
  urticarial reactions to 22.8, 22.10–11, 26.105
food additives
  adverse effects **75.158–60**
  allergy to 26.17, 26.22
  challenge testing 22.26
  chronic urticaria due to 22.10–11
  contact urticaria due to 22.20
  oral provocation tests 5.25
  pigmented purpuric dermatoses due to 49.23
  pseudoallergic reactions to 22.10
  St John's challenge test *22.11*
food allergy
  atopic dermatitis and 24.23, 24.30–1
  tests for 5.25
food diary, in urticaria 22.26
food industry, occupational hazards 27.19
food mites 38.46–7
food preservatives 75.159
foot *see* feet
foot and mouth disease **33.74**
footwear
  allergens in 26.63, 26.68–9
  nail trauma from 65.51, *65.52*, 65.53–4
  'vegetarian' 26.69
Forcipomyia 38.6
Fordyce spots 42.1, **42.86,** 45.21, 69.2, 69.5, **69.22–3**
Fordyce's condition 71.11
  isotretinoin treatment 42.62
foregut carcinoid tumours 43.18
forehead
  sebaceous glands 42.1
  swelling (metophyma) 43.9
foreign bodies **28.39–52**
  aetiology 28.40, *28.41*
  clinical features 28.42
  definition 28.39–40
  diagnostic tools 28.42
  ear 68.11
  male genital dermatology 71.14
  penetration injury 28.40, 28.49–52
  reactions and complications 28.43–52
  sarcoidal reactions to 61.22
  in sarcoidosis 61.3–4
  treatment 28.42–3
  in wounds 14.17
foreign-body granulomas, localization to tattoos 58.58
foreign-body reaction 61.5
  to lipids 61.22
forelock, white 66.93
foreskin 71.9, 71.12–13
  circumcision 71.13, 71.20, 71.24, 71.39
Forest Plot 7.9
forestry, occupational hazards 38.2
formaldehyde
  acetylacetone test 26.50, 26.99
  adverse effects *26.46*, 75.164
  as allergen 26.49–51
  as antiseptic 73.14
  avoidance 26.50
  chromotropic acid test 26.50
  in clothes 26.65, 26.67
  in hyperhidrosis 73.9
  as irritant 25.21
  in leather tanning 26.68
  lutidine test 27.8
  nail hardeners 65.56
  onycholysis due to 65.28
  patch testing 26.50
  releasers 26.49, 26.50, 26.51–3
  resins 26.49, 26.65, 26.68, 26.69, 26.73–4
  sources *26.50*
formaldehyde solution BP 73.9
formalin 26.49
  as fixative 10.4, 10.6
  pigment artefact 10.31
  soaks 44.11
  wart treatment 33.49
  see also formaldehyde
Formicidae (ants) 38.14
Forschheimer's sign 33.70
foscarnet 74.50, 75.67
  genital ulceration in HIV-infected patients and 71.27
  for herpes simplex 33.21
foundry work, occupational hazards 27.19
four-hoof disease 26.21
4p-syndrome 18.2, 18.103
Fournier's gangrene 71.30–1, 71.95
  foreign bodies 28.51
  in HIV infection 35.25
foveal hypoplasia 58.40
Fowler's solution 52.4
Fox–Fordyce disease **44.21–2,** 70.17
  in adolescence 8.7
  in pregnancy 8.10
  treatment 73.36
FOXC2 48.2
FOXC2 gene 47.37, 47.41, 62.77
  mutation 48.9, 48.10
Fox–Fordyce disease 71.72
FOXP-1 10.26
Fox's sign 62.65
fractalkine 13.9
fractional photothermolysis 80.11–12
  striae 45.6
fraena 69.6
fragile X syndrome 68.4
  genetics 15.14
fragility disorders, skin *see* epidermolysis bullosa (EB)

fragrance(s)
  as allergens 26.40–3, 27.2
  in cosmetics 26.47
  see also perfumes
Fragrance mix I 26.42
Fragrance mix II 26.42
framboesia *see* yaws
framycetin 26.17, 26.45, *26.46*, 68.24
  topical 73.10
Franceschetti–Klein syndrome **18.80–1,** 68.4
Francisella tularensis 30.53–4
François dyscephalic syndrome 15.41
François' syndrome **15.96**
Franklin's disease 69.114
Frank's sign 68.6
freckles 54.1–2, *54.10*, 58.1, **58.10–11**
  axillary **15.16,** 15.17, 15.21
    in neurofibromatosis 58.23
  comparison with related disorders 54.2, 54.4
  flexural 62.23
  inherited and acquired disorders with 58.11
  laser therapy 78.10
  in Peutz–Jeghers syndrome 58.13
  skin biopsy 10.42
free fatty acids
  production by skin flora 30.4, 30.5
  in sebum 42.5, 42.7, 42.22
    in acne 42.22, 42.23
free radical(s)
  scavengers 47.11
  UV-induced damage and 8.21
freeze-induced injury 28.64
freezing, of tissue *see* cryotherapy
Frei intradermal test 34.33
frei jorge *26.80*
Frei test 5.24
freijo *26.80*
French paradox 47.2
frequency of skin disease 6.11–13, 6.18
Freund's complete adjuvant test 26.12
Frey's syndrome 44.10, 44.11, 63.22
friction
  dermatitis and 25.17
  napkin dermatitis and 17.23
  purpura and 49.5
  reaction to 27.6
friction injury **28.9–16**
  amputees 28.28
  black heel and palm 28.16, 28.31
  blisters 28.2, 28.9, **28.12–13,** 28.28, 28.30–1
  callosities, corns and calluses 28.2, 28.10–12
  dermatitis 28.13–14
  miscellaneous dermatoses 28.15–16
  pressure ulcers 28.17, 28.21
frictional dermatitis of children 28.14
frictional melanosis 28.15
frictional sweat dermatitis 28.14
frictional ulcers 33.18
fried tooth and nail syndrome 15.40
Friedewald formula, standard lipid profile, LDL cholesterol 59.84
frit flies 38.6
Frizzled5 3.21
frontal emissary vein 77.2
frontalis muscle 77.4
frontonasal dysplasia and dilated Virchow–Robin spaces 15.52
frostbite **28.63–4**
  ear 68.8, 68.10
fruit acids, in actinic elastosis 45.27
Frullania 26.77
frusemide (furosemide) 17.12, 75.31, 75.97
FSH *see* follicle-stimulating hormone (FSH)
FTA-ABS DS test 34.20
FTA-ABS test 34.20, 34.21
fucosidosis 59.33–4
  sweat gland cellular inclusions in 44.18
fugitive swellings **37.11–12,** 38.6
fumarate hydratase (FH) gene 2.17
fumaric acid, in psoriasis 20.40, 74.29
fumaric acid esters
  dose range and evidence level 74.29
  flushing associated 43.15
  in psoriasis 74.29
  in sarcoidosis 61.21
fumarylacetoacetic hydroxylase (FAH), deficiencies 59.97
FUMHD (febrile ulceronecrotic Mucha–Habermann disease) 50.50–1
functional mosaicism 15.6
functions of skin 3.2–3, **4.1–11**
fungal infections **36.1–93**
  in animals 2.12–13
  collection of material 36.5–7
  ear 36.7–8, 36.17, 68.20, 68.21, 68.27–8
    investigation 36.6
  endemic 36.80
  female genital dermatology 71.68–9
  glossary 36.93
  in HIV infection 35.32–5, 35.45
  laboratory investigation 36.5–10, 36.69–70, 36.80
  lips 69.121
  lymphoedema and 48.15, 48.22
  male genitalia 71.32, 71.48
  nails *see* onychomycosis
  neonatal 17.46–8
  nomenclature 36.5
  opportunistic 36.80
  oral cavity 69.79–80, *69.118*
  otitis externa 68.21
  perianal/perineal 71.92
  race and 9.12
  sarcoidal reaction in 61.22
  sarcoidosis and 61.3, 61.17
  skin barrier function and 4.5
  skin biopsy 10.42
  subcutaneous 36.69–79
  superficial and cutaneous **36.5–69**
  systemic 36.79–92, 62.80
  vasculitis and *50.55*
  venous leg ulcers and 47.44
  vessel-invasive 49.35–6
  see also specific fungal infections
fungi **36.1–5**
  classification 36.2–4
  culture 36.7–9
  dematiaceous 36.4, 36.70
  dikaryotic 36.3–4
  dimorphic 36.2, 36.80
  direct examination 36.7
  glossary 36.93
  heterothallic 36.2
  homothallic 36.2
  keratinophilic 36.18, 36.19
  moniliaceous 36.4
  nomenclature 36.4–5
  normal skin flora 36.10, 36.13, 36.56
  polymorphism 36.4, 36.56
  reproduction 36.2
  sampling 36.5–7
  staining 10.8, *10.9*, 10.10, 36.7, 36.70
  see also moulds; *specific fungi*
funisitis, congenital syphilis 34.15
funnel anus 71.85
funnel-web spiders 38.31
furaltadone *26.46*
furfuraceous scale 5.7
*N*6-furfuryladenine 80.3
furocoumarins, phytophotodermatitis 58.32
furosemide 17.12, 75.31, 75.97
furuncle **30.23–4**
furuncular myiasis 38.8, 38.9
furunculosis 30.23–4
  ear 68.19, 68.27
  perianal/perineal dermatology 71.91
Fusarium
  cutaneous lesions 36.92, 49.35, 49.36
  differential diagnosis 36.31
  identification *36.8*
  in mycetoma *36.73*
  superficial white onychomycosis and 36.55
fusidic acid *26.46*, 74.43
  adverse effects 73.10, 75.59
  in impetigo 30.16
  ophthalmic, in rosacea 43.7
  resistance to 30.9
  topical, indications 73.10
Fusidium coccineum, fusidic acid from 73.10
fusiform cells, in basal cell carcinoma 52.21
fusion inhibitors (HIV), side-effects *35.21*
Fusobacterium 30.60, 69.77
  in tropical ulcer 30.60
Futcher's lines 5.17, 9.2, *9.3*
FVS (fetal varicella syndrome) 17.40–1, 18.2, 18.102

G
G-CSF *see* granulocyte colony-stimulating factor (G-CSF)
G-proteins 62.99
  α-subunit, McCune–Albright syndrome 58.18
G syndrome 69.37
gabapentin
  adverse effects 75.86
  in brachioradial pruritus 63.24
  in complex regional pain syndrome 63.21
  in erythromelalgia 47.10
  in post-herpetic neuralgia 63.7
  in pruritus 21.8, 21.17, *21.18*
  in restless legs syndrome 63.25
  in zoster and post-herpetic neuralgia 33.28
GABEB (generalized atrophic benign epidermolysis bullosa) 3.36–7, 39.13, 66.52
gadolinium 75.151
gadolinium-based contrast agents, nephrogenic systemic fibrosis (NSF) 51.82
GAGs *see* glycosaminoglycans (GAGs)
galactorrhoea, black 70.6
galactosidase A, deficiencies 59.36
galactosyltransferase 3.38
galanin 63.3
gallamine 75.153
gallates 73.8
GALT (gut-associated lymphoid tissue) 69.3
gamma benzene hexachloride *see* lindane
gamma/delta (provisional entity) T-cell lymphomas 57.36
gammopathy, benign monoclonal 49.13
ganciclovir
  action 74.49
  herpes B virus infection 33.35
gangrene
  bacterial synergistic 47.57
  causes 47.5
  clostridial 30.68
  cold-induced injury 28.64
  cutaneous, varicella complication 33.25
  definition 5.7
  female genital region 71.67
  foreign bodies 28.51
  Fournier's 30.68, 30.69
  gas **30.43–4**
    non-clostridial 59.78
  ischaemic foot *47.2*
  male genital region 71.15, 71.30–1
  management 47.6
  in mixed connective tissue diseases 51.111
  perianal/perineal region 71.93, 71.95
  in peripheral arterial disease 47.2, 47.5
  progressive bacterial synergistic 30.68–9
  spontaneous 71.100
  ulcerative colitis and 62.51
  umbilical dermatology 71.100
  venous limb 49.28
gap junction protein defects, ectodermal dysplasias 15.67–70
gap junctions 3.24
  functions 3.24
  gene mutations 3.24
  structure 3.24
GAPO syndrome 15.41, *69.12*
gardeners, occupational hazards *5.6*, 27.19
Gardner–Diamond syndrome 49.16, 50.54, 64.33–4
Gardnerella vaginalis, vaginal discharge 71.53
Gardner's syndrome 46.44, 62.57
  bone and joint involvement *62.100*
  cysts in 52.45
  epidermoid cysts in 52.45
  fibroma in 56.11
  genetics **15.25–6**
  oral involvement 69.39
garlic
  allergic contact dermatitis due to 26.16, 26.22, *26.77*
  as irritant 25.21
  as photoallergen 26.24
garlic clove fibroma 65.31–2
gas exchange, neonatal 17.2
gas gangrene **30.43–4**
  non-clostridial 59.78
Gasterophilus 37.16, 38.9, 38.10
gastric banding, vertical 46.8
gastric carcinoid tumours 43.18
gastrinoma 62.67–8
gastrointestinal tract (GIT)
  bleeding 62.55–6
  Candida albicans carriage 36.56, 36.58
  cutaneous markers of disorders 62.47–58
  decompression due to burns injury 28.78
  in Degos' disease 49.46
  disorders **62.47–58**
    see also specific disorders and anatomical structures
  drug interactions in 75.10
  in hereditary angio-oedema 22.21
  Langerhans' cell histiocytosis (LCH) 55.11
  malignancies
    carcinoid syndrome associated 43.18
    Muir–Torre syndrome and 53.15
  malignant histiocytosis 55.32
  oral manifestations of disease *69.116*
  polyps 62.56–8
  in rosacea 43.2
  in SLE 51.44–5
  Staphylococcus aureus carriage 30.7
  tumours
    genetics 15.23
    see also specific types
  in urticarial vasculitis 22.19
gastrostomy, in severe generalized dystrophic EB 39.29
gastrula 3.3
Gaucher cells 59.39
Gaucher's disease 19.60, 59.39
  acute infantile 58.24
  bone and joint involvement *62.100*, 62.105
  pigmentation 58.24
gel electrophoresis 57.12–13
gelatinase(s) 3.41, 12.52, 14.11
  ageing and 80.2
  granules 13.4
gelatine matrix implant, acne scar treatment 42.69
gels, topical therapy 73.2
gelsolin amyloidosis (AGel) 59.57
gemcitabine 75.129
gemfibrozil 75.156
GEMSS syndrome 45.53, 51.79
gender
  allergic contact dermatitis and 26.7–8
  bacterial skin flora and 30.3–4

body dysmorphic disorder and 64.18, 64.19
effect on normal bacterial skin flora 30.3–4
irritant contact dermatitis and 25.7
mechanical skin properties and 28.7
psychocutaneous skin disease and 64.25, 64.29, 64.35
risk factor for skin disease 6.12
gene(s) 11.1
cancer 'modified' 52.13
cancer susceptibility modifying 52.10–11
candidate 11.11–14
acne vulgaris 42.19
disease-causing, identification 11.11–14
expression 11.2–3
mapping 11.12
microarrays 11.7–8, *11.9*
mismatch repair 11.18
mutation, transfection 11.10
mutator 52.12
oncogenes 11.17–18
positional cloning 11.1, 11.12
promoter region 11.3
reporter 11.10
sexual development 8.2
stable transfection 11.10
studies of expression and function 11.9–11
transcription 11.2–3
transient transfection 11.9–10
translation 11.3
tumour-suppressor 11.17–18
gene therapy 11.20–2
angiogenesis using 47.6
in epidermolysis bullosa 39.31
gene tracking 15.7
general anaesthesia 75.153, *77.11*
general anaesthetic agents 75.153
skin testing for reactions to 75.172
General Health Questionnaire (GHQ) 42.35
General Household Survey, UK 6.5
general practitioners (GPs) 6.14–15
with special interest in dermatology 72.2
generalized atrophic benign epidermolysis bullosa (GABEB) 3.36–7, 39.13, 66.52
generalized eruptive keratoacanthoma 52.44
generalized folded skin 18.36, 18.40, 18.107
generalized idiopathic ischaemic dermatopathy (GIID), in dogs 2.15
generalized pustular psoriasis (GPP) 20.48–50
acute (von Zumbusch) 20.49–50
calcipotriol treatment 73.45
localized forms 20.52
in pregnancy 20.50–1
genetic counselling **15.9,** 15.18, 15.24, 16.1
congenital naevi 54.13
Ehlers–Danlos syndrome 45.37
familial melanoma 54.34
Peutz–Jeghers syndrome 58.13
genetic diseases
blistering disorders **39.1–37**
see also epidermolysis bullosa (EB); Hailey–Hailey disease
cancer as 52.12
connective tissue diseases 51.79
obesity in, cutaneous features 8.18
see also specific genetic diseases
genetic factors 6.12
acne vulgaris 42.18–19
adverse drug reactions 75.12–13
albinism *66.94*
alopecia areata 66.31
androgenetic alopecia 66.18–19
atopic dermatitis 24.3–4
basal cell carcinoma 11.18
developmental defects 18.2–3
drug reactions 76.10–11
harlequin ichthyosis 11.13
Henoch–Schönlein purpura 50.11
immunodeficiency disorders 17.51
irritant contact dermatitis 25.6
Kawasaki disease 50.11
leprosy 32.2
lichen planus 41.2
malignant disease 11.17–19
malignant melanoma 11.18
mastocytosis 22.30, 22.31
pigmentation variations 58.9–10
pseudoxanthoma elasticum 45.21
sarcoidosis 61.3
squamous cell carcinoma 11.18
urticaria 22.3
vasculitis 50.11–12
Wegener's granulomatosis 50.11
see also genetics
genetic imprinting 24.5
genetic instability 52.12
genetic linkage 11.11–14
genetic mosaicism *see* mosaicism
genetic stability, genetic factors affecting 52.12
genetics **15.1–97**
acrokeratotic poikiloderma of Weary **15.82**
analysis of inherited disorders 15.7
autosomal genes 15.4, 15.10–12
Bazex–Dupré–Christol syndrome **15.83**
Bloom's syndrome **15.76–7**
cartilage–hair hypoplasia syndrome 15.32, **15.93**
chromosomal abnormalities 15.2, 15.9–14
CINCA syndrome **15.95–6**
clubbing of fingers and toes **15.87–8**
Cockayne's syndrome **15.75–6**
congenital scalp defects with distal limb anomalies **15.96**
contiguous gene syndromes 15.6
Cornelia de Lange syndrome **15.92**
Cowden's disease **15.26–7**
craniosynostoses 15.90–2
cutis verticis gyrata **15.89**
dermo-chondro-corneal dystrophy **15.96**
DNA instability 15.70–7
Dowling–Degos disease **15.94–5**
drug responses 72.29–30
dyschromatosis symmetrica hereditaria **15.95**
dyschromatosis universalis hereditaria **15.95**
dyskeratosis congenita 15.36–7, **15.78–80**
ectodermal dysplasias 15.27–70
familial cold autoinflammatory syndrome **15.95–6**
familial multiple tumour syndromes 15.15–27
FG syndrome-1 **15.96**
focal dermal hypoplasia syndrome 15.39, **15.84–6**
focal facial dermal dysplasia 15.40, **15.83–4**
Gardner's syndrome **15.25–6**
genetic counselling *see* genetic counselling
genodermatoses 15.1, 15.2, *15.3–4*
genomic imprinting 15.6
heterogeneity 15.5
high-throughput analysis 15.6
histocompatibility antigens 15.8–9
human genome organization *15.4*
inheritance patterns 15.2, *15.3–4*
Kindler's syndrome **15.82–3**
lines of Blaschko 15.6, *15.7*
linkage disequilibrium 15.7–8
lyonization 15.6
mosaicism 15.6, 15.11
Muckle–Wells syndrome **15.95–6**
mutations and disease 15.5, 15.6
nail–patella syndrome 15.8, **15.86–7**
neurofibromatosis 15.2, 15.6, 15.14, **15.15–21**
Noonan's syndrome **15.14–15,** 15.20–1
nosology in skin disease 15.2, *15.3–4*
nucleotide excision repair 15.71–2, 15.75–6
online databases 15.1
pachydermoperiostosis 15.87, **15.88–9**
poikilodermatous syndromes 15.78–83
polymorphisms 15.6, 15.7
principles of medical genetics 15.2–8
Rothmund–Thomson syndrome 15.51, **15.80–2**
Rubinstein–Taybi syndrome **15.92–3**
sex-linked genes 15.4, 15.12–14
tuberous sclerosis complex 15.6, **15.21–5**
twin spotting 15.7
two-hit progression to tumour formation 15.5–6
uniparental disomy 15.7
van der Woude syndrome **15.93–4**
Werner's syndrome **15.77**
xeroderma pigmentosum 15.5, **15.70–5**
see also genetic factors
genital chancre 34.6–7
genital dermatology
female *see* female genital dermatology
male *see* male genital dermatology
genital herpes *see* herpes simplex, genital infections
genital lentiginosis 54.6–7
genital lymphangiectasia 48.28
genital lymphoedema 30.70, 48.12, 48.16
management 48.23
genital mucosa, verrucous carcinoma 52.26
genital mutilation 71.15
female 71.56–7
genital papular acantholytic dyskeratosis 71.81
genital warts *see* wart(s), anogenital
genitalia
acute ulceration 71.65–6
in Behçet's disease 50.58–9
Bowenoid papulosis of 52.37
female
atrophy, in menopause 8.19
structure and function 71.54–6
see also female genital dermatology
male *see* male genital dermatology
melanoma 54.47
pyoderma gangrenosum 50.70
scabies 38.39
sebaceous glands 42.1
warts *see* wart(s), anogenital
genitocrural dermatology **71.4–8**
candidosis 71.5, 71.6
dermatitis 71.5
erythrasma 71.6
general approaches 71.1–4
infections 71.6–7
inflammatory dermatoses 71.4–6
intertrigo **71.4–5,** 71.7
tinea cruris 71.6–7
genitogingival syndrome 71.23
genitoperineal raphe, congenital sinuses and cysts 18.94–5
genitourinary tract, in dystrophic EB 39.29
genodermatoses 15.1
associated with internal malignancy **62.19–29**
bony changes in 62.99
inheritance patterns 15.2, *15.3–4*
prenatal diagnosis **16.1–11**
synophrys 67.3
genome-wide screens, high-throughput genetic analysis 15.6
GenoMEL 54.33, 54.34
genomic hybridization, comparative (CGH) 57.20
genomic imprinting 15.6
genomics 11.7–8, *11.9*
genophotodermatoses, investigations 29.24
gentamicin 26.17, 26.45, *26.46*, 30.9, 68.24, 74.42, 75.58
topical therapy 73.10
gentian violet 10.10, 25.12, 25.21
accidental tattoos 58.57
topical therapy 73.48
geographic factors 6.12
in diagnosis 5.5
geographical tongue *see* tongue, geographical
geotrichosis 69.80
gerbils 2.9
gerodermia (geroderma) osteodysplastica *45.15*, 45.60–1
gestational pemphigoid *see* pemphigoid gestationis
gestrinone 75.119
GF *see* granuloma faciale
GH *see* growth hormone (GH)
Ghon focus 31.8
Gianotti-type perioral dermatitis (granulomatous perioral dermatitis) 43.12, **43.13**
Gianotti–Crosti-like syndrome **33.77–8**
coxsackievirus infections and 33.72
diagnosis and treatment 33.78
hepatitis A and 33.74
non-viral causes 33.77
pathology and clinical features 33.77–8
viral causes 33.77
Gianotti–Crosti syndrome
EBV infection and 33.31, 33.77
HBV infection and 33.61, 33.77, 62.59, 62.64
giant cell(s)
foreign-body, in rosacea 43.4
herpes simplex 33.16
in juvenile xanthogranuloma 55.15
microscopy 10.34–5
multinucleate *see* multinucleate giant cells
in necrobiotic xanthogranuloma 55.28
septal panniculitis 46.12
giant cell angioblastoma 56.32
giant cell arteritis **50.43–4,** 61.17
granuloma annulare and 60.9
oral involvement 69.81–2, *69.117*
giant cell tumour, tendon sheath 56.15–16, 65.36
giant condyloma
female genital dermatology 71.76–7
male genital dermatology 71.44–6
perianal/perineal dermatology 71.95
giant condyloma acuminatum 52.26
giant hogweed 26.16
giant porokeratoses 19.91
giant rhinophyma, with symmetrical lipomatosis 46.46
giant trichoblastoma 53.10
gigantism 62.2
Gigantobilharzia 37.22
gigantomastia 70.3
Gilchrist's disease *see* blastomycosis
gingivae 69.2
bleeding 69.12
blisters 69.14
erythema 69.13
examination 69.6
haemangioma 69.13
hyperplasia 69.12–13
drug-induced 69.21, 75.47
in hypoplasminogenaemia 69.15
inflammation *see* gingivitis
in juvenile hyaline fibromatosis 69.15
in Noonan's syndrome 15.14
pigmentation 69.13
in scurvy 69.21
telangiectases 69.13
ulcers 69.14
white patches 69.13
gingival crevice 69.2, 69.3
gingival cysts of the newborn 17.5, 69.17
gingival fibromatosis 15.27
hereditary 69.14–15
hypertrichosis and 15.40

gingival fibromatosis–sparse hair–malposition of teeth 15.40
gingivitis 69.12
  acute ulcerative (necrotizing) 69.14, 69.77–8
  allergic 26.21, 26.41
  chronic 69.17
  desquamative 69.13, 69.19, 69.67, 69.106
  plasma cell 69.13
  in pregnancy 8.11, 69.20–1
gingivostomatitis
  allergic (atypical/plasma-cell) 69.19
  herpetic 33.16
  white folded 35.43, 69.23–4
Ginkgo biloba 26.22, 26.75, 75.162
GIT *see* gastrointestinal tract (GIT)
glabrous skin 3.3
  Merkel cells 3.16
glanders 30.51
glands
  apocrine 44.1, *44.2*
    in mammals 2.4
  atricial 2.4
  eccrine 44.1, *44.2*
    evolution 2.4
    in mammals 2.4
  epitrichial 2.4
  evolution 2.1, 2.4–5
  'generation' 2.4
  holocrine 44.1
  merocrine 2.4, 44.1
  sebaceous, in mammals 2.4
  specialized 44.1–2
  uropygial (preen), in birds 2.4
  see also specific types
glands of Montgomery 70.1
glandular fever *see* infectious mononucleosis
Glasgow seven-point check-list, melanoma 54.37
glassy membrane 66.7
glatiramer acetate 50.83–4, 75.155
  lobular panniculitis at injection site 46.14
glaucoma
  adverse effects of treatment *26.46*
  corticosteroid-induced 67.15, 67.16, 67.31, 73.19
  earlobe creases and 68.6
  in Sturge–Weber syndrome 18.66
glaziers, occupational hazards 27.19
Gleich syndrome *see* hypereosinophilic syndrome
Gli-1, overexpression 53.2
glial filament acidic protein (GFAP) 3.9
glibenclamide 75.156
glioma, nasal 18.89–90, 56.52
glipizide 75.156
Global Alliance algorithm, for acne outcome improvement 42.39, *42.40*
Global Alliance for the Elimination of Lymphatic Filariasis 37.10
global warming 26.10
globoside 33.63
glomangioma/glomangiomyoma *see* glomus tumour
glomerulonephritis
  in dystrophic EB 39.20
  ear involvement 68.17
  following streptococcal infection 30.12, 30.15–16
  in loiasis 37.11
  mesangiocapillary, partial lipoatrophy and 46.39–40
glomus bodies 65.4
glomus cells 56.43
glomus tumour **56.43–4,** 65.15, 65.17, 65.34–5
  diagnosis *10.23,* 56.43
  familial 15.6
  female genital dermatology 71.73
  hyperhidrosis and 44.9
  jugulare 68.29
  multiple 18.73–4
  solitary plaque-like telangiectatic glomangioma 47.20
glomuvenous malformation 18.73–4
Glossinidae (tsetse flies) 37.2, 37.29, 38.6
glossitis 69.22
  benign migratory *see* tongue, geographical
  deficiency 69.85–6
  median rhomboid 36.61, *69.88,* 69.105–6
  tertiary syphilis 34.14
glossodynia/glossopyrosis 26.20, 26.39, 62.85, 69.86–7
gloves
  in hand eczema 23.21–2
  latex 26.105
  protective 5.3, *5.4,* 25.25, 26.72–3
  recommended materials *25.24*
  rubber 26.63
glucagonoma syndrome *see* necrolytic migratory erythema
glucan, adverse effect in HIV infection 35.21
β-glucans 36.1
glucocorticoid receptor alpha (GRα) 73.16–17
glucocorticoid receptor beta (GRβ) 73.17
glucocorticoid response elements (GREs) 73.17
glucocorticoids *see* corticosteroids
glucose
  intolerance 8.28
  in sweat 44.6
glucose-6-phosphate dehydrogenase 73.30
glucose-6-phosphate dehydrogenase deficiency 74.39
  treatment for linear IgA disease 40.50
glucose transporter receptor 4 (GLUT-4) 46.2
glue, application to skin 64.38, *64.39*
glutaraldehyde
  as allergen 26.58
  as antiseptics 73.14
  in epidermolysis bullosa simplex 39.31
  in hyperhidrosis 44.11, 73.9
  wart treatment 33.48–9
glutathione S-transferase (GST), π isoform 2.20
gluten-free diet 40.61–2
  treatment of psoriasis 20.43
glutethimide 75.81
glyburide 75.156
glycaemic index, acne and 42.34
glycerol, anti-irritant effect 25.25
glycerol suppositories 39.28
glyceryl monoabietate 26.79, 26.82
glyceryl monothioglycolate 26.17–18
glyceryl trinitrate 75.97
  cold-induced injury 28.70
glycine, in elastin 3.43
glycine-X-Y sequence 3.32, 3.34
glycolic acid 80.9
glycolic aciduria 49.37
glycolipids, stratum corneum 3.11
glycopeptide antibiotics 74.43
glycoprotein 11b–111a (GP11b–111a), platelet-specific integrin 12.32
β_2-glycoprotein I (β_2-GPI) 49.40, 49.41
  antibodies 49.40, 49.41
glycoproteinoses 59.33
  acroparesthesiae 59.37
  degradation disorders 59.33–5
  storage disorders, classification 59.33
glycoproteins, non-collagenous 3.34
glycopyrrolate cream 73.9
glycopyrronium bromide 44.10, 44.11, 63.23, 73.9
glycosaminoglycans (GAGs) 3.2, 3.34, 3.45–9, 59.21, 59.30
  ageing and 80.1
  degradation enzyme deficiencies 59.30–1
  functions 3.46–7
  postassembly modification 3.45–6
  structure and synthesis 3.45–6
glycosylation
  blood vessels, ageing and 8.21
  collagen 3.38
glycosylphosphatidylinositol (GPI) anchor 49.30
Glycyphagidae 38.47
Glycyphagus 38.47
glycyrrhetinic acid 73.49
glyoxal 26.58
glypican family of proteoglycans 3.45
GM-CSF *see* granulocyte–macrophage colony-stimulating factor
Gnaphosidae 38.32
gnathophyma 43.9, *43.10*
Gnathostoma 37.16, 37.18–19
gnathostomiasis **37.18–19**
goblet cells
  eyelids 67.2
  loss, Stevens–Johnson syndrome 67.21
Goeckerman regimen 73.42
gold, metallic, contact allergy 26.26, **26.38–9,** 68.7–8
gold therapy 74.29–30
  adverse effects **75.100–1**
    chrysiasis 58.54–5, 75.33, 75.100
    erythroderma 23.47
    eyelid pigmentation 67.5
    flushing 43.15
    lichenoid eruptions 41.24
    oral pigmentation 69.97
    pityriasis rosea 75.24
  dose range and evidence level 74.30
Goldenhar syndrome **18.82–3,** 68.4
Golgi zones, sebaceous cells 42.3
golimumab 74.5
  psoriasis 74.5
Goltz syndrome *see* focal dermal hypoplasia (FDH)
Goltz–Gorlin syndrome *see* focal dermal hypoplasia (FDH)
Golubatz fly 38.5
Gomm–Button disease *see* Sweet's syndrome
Gomori's silver impregnation technique 10.9
gonadal mosaicism 15.6
gonadotrophin(s) 8.4
  adverse effects 75.117
    acneiform eruptions 42.72
  sebaceous gland activity and 42.11, 42.12
gonadotrophin-releasing hormone (GnRH) 8.4
  agonists
    in acne vulgaris 42.53
    in hirsutism 66.89
  pulsatile output, menstrual cycle 8.8
  receptor 8.4
  release, neurokinin B role 8.20
Gongylonema pulchrum 37.18
gonococcal infection **30.45–6**
  arthritis and 62.105
  disseminated (DGI) 34.26–8
  vasculitis and 50.55
  see also gonorrhoea
gonococci *see Neisseria gonorrhoeae*
gonorrhoea 30.45–6, **34.24–9**
  clinical features 34.25
  complications 34.26–8
  diagnosis 34.28
  epidemiology 34.25, 34.28
  management 34.28
  oropharyngeal 69.78–9, *69.118*
  in pregnancy and breastfeeding *34.28*
  prevalence *34.2*
  trichomoniasis and 37.29
  see also gonococcal infection; *Neisseria gonorrhoeae*
Goodpasture's syndrome 3.27, 3.35
Gorham's (Gorham–Stout) disease 18.76, 48.27
  bone and joint involvement 62.99, *62.100*
gorilla, lice 38.15
Gorlin–Chaudhry–Moss syndrome 15.40
Gorlin's syndrome *see* naevoid basal cell carcinoma syndrome
Gottron's papules, dermatomyositis 51.123–4
Gottron's syndrome (progressive symmetrical erythrokeratoderma) 19.70–1, *45.58,* 45.59–60
Gougerot–Carteaud syndrome 19.121–2
Gougerot–Houwer–Sjögren syndrome 51.134
  see also Sjögren's syndrome
gout 59.101, *62.101,* 62.105
  lobular panniculitis 46.17
  sarcoidosis and 61.18
  sweating and 44.7
  see also tophi, gouty
GPP (generalized pustular psoriasis), calcipotriol treatment 73.45
GPR54 receptor 8.4
GPs (general practitioners) 6.14–15
  with special interest in dermatology 72.2
graft-versus-host disease (GVHD) 17.53, 51.83–6, **62.96–9**
  acute 51.83–6, 62.96–7, 67.22
  autoantibodies to Merkel cells 3.16
  chronic 51.83–6, 62.97, *62.98,* 67.22
    hypermelanosis after 58.31
  clinical features 51.84–5
  cutaneous histological changes grading 51.83
  following blood transfusion 75.154
  hyperacute 62.96
  incidence and aetiology 51.83
  localized morphoea and 51.65
  materno-fetal 17.59
  ocular involvement 67.22
  oral involvement 69.83
  pathology 51.83–4
  prognosis 51.85
  treatment 62.97–8
graft-versus-leukaemia reaction 62.96
grafts, tattoo removal 58.59
Graham–Little–Piccardi–Lassueur syndrome 41.11, 66.42–3
grain/grain-shoveller's itch 38.48
Gram-negative bacteria
  normal skin flora 30.2
  overgrowth, folliculitis 42.84
Gram-positive cocci, normal skin flora 30.2
Gram-positive rods, normal skin flora 30.2
Gram stain 10.10
granisetron 75.79
granular cell tumour **56.50–1,** 71.73
  congenital epulis 69.17
  dermal non-neural (primitive polypoid/primitive non-neural) 56.59
  oral 69.55
  pinna 68.28
granular degeneration 10.39–40, 42.78
granular parakeratosis 70.17
granule defects, in Chédiak–Higashi syndrome 58.41
granule deficiencies 12.23
granulocyte colony-stimulating factor (G-CSF) 46.32
  adverse effects 50.74, 50.76, 75.141–2
  localized reaction to 50.90
granulocyte–macrophage colony-stimulating factor (GM-CSF) 12.16
  adverse effects 75.142
  histiocyte ontogeny 55.3
  polymorphonuclear granulocytes 12.20
  skin barrier function and 25.3
granulocytes, polymorphonuclear 12.20–4
granuloma(s) 52.44
  actinic/Miescher's/O'Brien's 45.28–9, 50.85, 60.1, 60.13–14

actinic/O'Brien's 45.28–9
in allergic contact dermatitis 26.26–7
annular elastolytic giant cell 60.13–14
Candida 36.65
Churg–Strauss 50.42, 50.52
cutaneous extravascular necrotizing 50.52
denture 69.109–10
eosinophilic
external auditory canal 68.28
pregnancy and 8.12
traumatic 69.43
see also Langerhans' cell histiocytosis (LCH)
facial idiopathic
aseptic 43.14
with regressive evolution *see* acne agminata
fat 61.22
fibrin ring 50.24
fish-tank *see Mycobacterium marinum*
foreign-body 36.75
localization to tattoos 58.58
histopathology 10.39
in HIV infection 35.26
immunization 28.45
infantile gluteal 17.27–8, 71.91, 73.18
insulin, zinc-induced 28.46
juvenile giant-cell *see* juvenile xanthogranuloma
lethal midline 69.57
lick 2.9
lipophagic 46.13
mineral oil 46.29
necrobiotic 60.3–4
oil 46.29–30
perifollicular, in lichen nitidus 41.22
pseudopyogenic 56.27–8, 68.15–16
pulse 69.109
pyogenic *see* pyogenic granuloma
radial (Miescher) 46.12
reticulohistiocytic *see* multicentric reticulohistiocytosis
sarcoid 61.3, 61.4–5
localization to tattoos 58.58
in schistosomiasis 37.21
sea urchin 38.58
silica 61.22
swimming-/diving-associated 28.55
swimming pool *see Mycobacterium marinum*
telangiectaticum *see* pyogenic granuloma
tuberculoid 31.8–10, 32.4, *32.5*
ulcerating of the pudenda *see* granuloma inguinale
umbilical 18.93, 71.100
xanthomatous, with necrobiosis 55.27–9
zirconium 61.22
see also specific types
granuloma annulare *5.12*, 59.79, **60.1–12**
aetiology 60.1–3
associations 60.9–10
autoimmune thyroiditis and 60.9
bone and joint involvement *62.101*
clinical features 60.5, *60.6*, 60.7–9
diabetes mellitus and 60.9
differential diagnosis 60.9
ear 60.7, 68.15
follicular pustulous 60.7
generalized/disseminated 60.5, *60.6*, 60.7
giant cell arteritis and 60.9
histopathology 60.3–5
in HIV infection 35.19–20, 60.1, 60.7
linear 60.7
localized 60.5, *60.6*
malignant disease and 60.9
Mauriac's syndrome and 60.9
morphoea and 60.9
necrobiosis lipoidica and 60.9, 60.15
papular umbilicated 60.7
paraneoplastic 62.38–9
'patch' 60.7
perforating 60.4, 60.7, 60.9
pustular generalized perforating 60.7
sarcoidosis and 60.9, 61.17
scalp 66.5
seasonal recurrence 60.1
skin biopsy 10.43
subcutaneous 60.7, 60.9
treatment 60.10–12
tuberculosis and 60.1
uveitis and 60.9
viral infection and 60.1
granuloma faciale **50.28–30**
in dermatophytosis 36.22
ear 68.16
treatment 50.29, 78.9, 78.14
granuloma gluteale infantum 36.63
granuloma gravidarum 8.11, 56.25
granuloma inguinale **30.61–2,** 34.36, **34.36–7,** 71.93
female genital dermatology 71.71
see also Calymmatobacterium granulomatis
granuloma multiforme 60.14, **60.17**
granuloma multiplex haemorrhagicum *see* Kaposi's sarcoma
granuloma telangiectaticum *see* pyogenic granuloma
granuloma venerum *see* granuloma inguinale
granulomatosis
Langerhans' cell *see* Langerhans' cell histiocytosis (LCH)
lipoid, Erdheim–Chester disease 55.18–19
orofacial 48.16
Wegener's *see* Wegener's granulomatosis
granulomatosis disciformis 61.5, 61.17
granulomatous cheilitis, Miescher's 48.16, 61.23, 69.60, **69.125–7**
granulomatous dermatitis 51.131
granulomatous disease(s)
chronic *see* chronic granulomatous disease
disseminated lipogranulomatosis 59.41
leg ulcers in 47.57
lethal midline granuloma 57.40
lymphoedema in 48.13, 48.23
secondary B-cell lymphomas 57.51
slack-skin disease 45.20, 57.15–16
see also specific diseases
granulomatous perioral dermatitis in children 43.12, **43.13**
granulomatous reactions
to foreign bodies 28.47, 28.48
to injected oils 46.29–30
TNF antagonists 74.8
granulomatous slack skin 45.20, 57.15–16
granulosis rubra nasi 44.18
granzyme 10.26, 13.11
grasshoppers 38.28
Graves' disease 53.22, 62.7–8
gravity, pigmented purpuric dermatoses and 49.22
gravity stasis, purpura due to 49.14
grease-gun injury 46.29–30
greases, in topical treatment 73.6
great auricular nerve 77.3
'the greater patient' concept 72.23
green shield bug 38.25
green tea extract, wart treatment 33.50
greenbottle fly 14.22, 38.8
Greither's syndrome *19.94*, 19.98–9
grenadil *26.81*
grenadilla *26.81*
Grenz rays
in allergic contact dermatitis 26.102
guidance on use 79.4
non-melanoma skin cancer associated 52.5
Grenz zone 10.39, 50.29
Grevillea 26.75, *26.81*
grey syndrome 75.64
Grey Turner sign 62.65
Griscelli syndrome *13.13*, 17.78–9, 17.80–1, 58.42, 62.95
griseofulvin 74.47–8
adverse effects 75.64–5
in dermatophytoses 36.48, 36.49, 36.50
eccrine gland secretion 44.18
pigmented purpuric dermatosis 49.26
GRO-alpha (CXCL1) 12.46
Grocott's silver staining technique 10.10
groin, bacterial flora 30.4
Grönblad–Strandberg syndrome *see* pseudoxanthoma elasticum (PXE)
gross cystic disease fluid protein-15 (GCDFP-15) 53.22
extramammary Paget's disease 53.40
ground itch 37.2, 37.14–15
strongyloidal *see* strongyloidiasis
group/mass populations reactions **64.25–6**
group therapy 64.53
Grover's disease (transient and persistent acantholytic dermatoses) 19.86–8
differential diagnosis 40.11
treatment 73.44
growth
abnormal or delayed 8.3
delay in atopic dermatitis 24.24
intrauterine retardation 17.1
postnatal 8.1–2
somatic 8.1–2
spurts 8.4
growth factors
from cells other than keratinocytes 12.76
collagen gene expression control 3.39
exogenous, in wound healing 14.27
for melanocytes 58.5
mucous membrane pemphigoid pathogenesis 67.20
pressure ulcers 28.23
trapped, venous ulcers and 47.27
see also specific factors
growth hormone (GH) 8.1
in breast development 70.1
concentration in plasma 8.2
deficiency 8.2, 8.4, 62.3
Langerhans' cell histiocytosis (LCH) 55.12
excess secretion 8.2, 62.2
gene expression 8.1
hair growth and 66.13
in hypopituitarism 62.3
recombinant, in erythromelalgia 47.10
replacement, localized lipohypertrophy 46.35
sebaceous gland activity and 42.11
growth hormone-releasing hormone 8.2
growth-regulated gene/melanoma growth stimulating activity (GRO/MGSA) 12.74
growth retardation–alopecia–pseudoanodontia–optic atrophy (GAPO) 15.41
Guanarito virus *33.67*, 33.69
guanethidine 75.96
systemic sclerosis 51.108
Guanieri bodies 33.5
guanine 11.2
Guillain–Barré syndrome, zoster 33.26
guinea pig maximization test 26.11, 27.10
guinea pig model 73.32
Guinea worm **37.12–13**
guitar nipple 28.25, 70.11
gum benzoin 26.40
gum rosin 26.79
gumma
syphilitic 34.5, 34.13–14, 66.52, 69.78
tuberculous 31.10, 31.19–20
gummatous neurosyphilis 34.14
gums *see* gingivae
Günther's disease *see* congenital erythropoietic porphyria (CEP)
gut-associated lymphoid tissue 69.3
Guthrie test 59.95
guttate morphoea *see* lichen sclerosus
GVHD *see* graft-versus-host disease
gynaecomastia **70.3–6**
aetiology *70.4*
drug-induced 70.4–5
in endocrine disorders 70.4
haemodialysis and 62.72, 70.4
management 70.5–6
physiological 70.4

H
H-caldesmon 10.22
H-*ras* proto-oncogene 52.13
Haarscheibe 53.14
hamartomatous proliferation of mesodermal component 53.14
HAART *see* highly-active antiretroviral therapy (HAART)
Haber's syndrome 52.41
habit disorders **64.26–34**
A-B-C model 64.28
Hadronyche 38.31
haem 59.2–5
biosynthesis 59.3
six key structural changes 59.4
enzyme deficiencies 59.5
see also porphyria
haemangioendothelioma
epithelioid 56.40
kaposiform (Kaposi-like infantile) 18.55–6, 56.31–2
malignant *see* angiosarcoma
retiform (hobnail) 56.32
spindle cell 56.30–1
haemangioma
acquired elastotic 56.28–9
capillary, eyelids 67.34
congenital 18.54
cutaneous arteriovenous 56.26–7, 65.35–6
epithelioid (histiocytoid) 56.27–8, 68.15–16
gingivae 69.13
glomeruloid 56.24–5
haemosiderotic 49.17
hepatic 18.52–3
hobnail (targetoid haemosiderotic) 56.29
infantile/capillary 18.40–52, 18.96
associated anomalies 18.47–8
clinical features 18.42–3
definition and classification 18.40–1
diagnosis and complications 18.44–7
management 18.48–52
pathogenesis and pathology 18.41–2
see also naevus, strawberry
laser therapy 78.6
lobular capillary *see* pyogenic granuloma
lumbosacral 18.47
microvenular 56.29–30
oral cavity 69.13, 69.22, 69.29, *69.30*
pinna 68.28
in pregnancy 8.10
sinusoidal 56.30
spinal dysraphism and 63.15
spindle cell 56.30–1
symplastic 56.31
thrombocytopenia 49.12
verrucous 18.74–5
haemangioma–haemorrhage syndrome *see* Kasabach–Merritt syndrome/phenomenon
haemangiomatosis
multifocal/benign neonatal 18.53
multifocal/diffuse (miliary) neonatal 18.53–4
haemangiopericytoma 18.58
adult 56.42
infantile 56.9, 56.42
haemangiosarcoma *see* angiosarcoma
Haemaphysalis 38.34, 38.35
Haematobia 38.6
haematocrit monitoring, burns 28.84
haematodermic neoplasms, blastic NK-cell lymphoma 57.39–40

haematological disorders **62.85–96**
in dyskeratosis congenita 15.79
eye and skin involvement *67.30*
leg ulcers and 47.56
pigmented purpuric dermatoses and 49.23
see also specific disorders
haematological tests, purpura 49.6
haematology *69.116*
haematoma
definition 5.7
ear 68.6–7
paroxysmal finger 49.16
penile 71.14
post-surgical *77.8*, 77.9
subungual 65.49–50
wound healing and 14.17
haematopoietic stem cell(s) 55.1
transplantation 13.26, 62.96–8, 76.7
in familial haemophagocytic lymphohistiocytosis 55.26
herpes-associated erythema multiforme and 33.19
oral complications 69.82–3
see also stem cell(s)
Haematopota 38.6
Haematosiphon 38.24
haematosiphoniasis 38.24
haematoxylin and eosin 10.8, *10.9, 10.10*
haematoxylin bodies, heart valves, SLE 51.34
haemochromatosis 59.71, 62.61–2
arthropathy associated 62.105
pigmentation changes 58.28
skin biopsy 10.42
haemodialysis
bacterial infection and 30.7
complications 62.72–3, 75.155
gynaecomastia and 62.72, 70.4
nephrogenic systemic fibrosis and 45.53
perforating dermatoses and 45.63
pruritus and 21.7–8, 62.72
restless legs syndrome and 63.24
see also dialysis and related therapies
haemoglobin
as chromophore 78.3
skin colour and 2.5, 5.15
haemoglobin monitoring, burns 28.84
haemoglobinuria
paroxysmal nocturnal 49.30
sleep-associated 49.30
haemolymphangiomatosis, diffuse 48.31
see also Maffucci's syndrome
haemolysis, intravascular, paroxysmal nocturnal haemoglobinuria 49.30
haemolytic anaemia
congenital, pigmentation in 58.53
Coombs-positive, ITP with 49.9
haemolytic disease of newborn *69.116*
haemolytic–uraemic syndrome (HUS) 13.3, 49.12, **49.31**
atypical 49.31
haemophagocytic lymphohistiocytosis (haemophagocytic syndrome) 17.78–9, 46.23–5, 49.12
cutaneous manifestation 46.23–5
virus-associated 55.30–1
EBV 33.31
haemophilia 49.2
bleeding time 49.6
haemophiliacs, HIV infection 35.45
Haemophilus ducreyi 30.47, 34.7, 34.34
female genital dermatology 71.71
see also chancroid
Haemophilus influenzae 15.60
Haemophilus influenzae type b 13.15
in cellulitis 30.18
haemopoietic stem cells *see* haematopoietic stem cell(s)
haemorrhage
abnormal platelet function and 49.12–14
disseminated intravascular coagulation 49.39
inflammatory 49.18–19
purpura due to 49.2, *49.3*, 49.4
Lassa fever 33.69
macular 62.90
simple, purpura due to 49.2, *49.3*, 49.4–7
splinter, nails 49.7
venous leg ulcers 47.45
haemorrhagic disease of the newborn 49.51
haemorrhagic effects, sporting activities 28.31
haemorrhagic fever
diagnosis 33.5
tick-borne 38.35
viral **33.66–70**
diagnosis 33.68
haemorrhagic fever with renal syndrome (HFRS) 33.70
haemorrhagic oedema of childhood *see* acute haemorrhagic oedema of childhood/infancy
haemorrhoids 71.96
anal fissure 71.87
syphilis vs 34.8, 34.12
haemosiderosis 62.85
hypostatic 58.53
skin pigmentation 58.53
haemosiderotic fibrohistiocytic lipomatous lesion (haemosiderotic fibrolipomatous tumour) 56.19
haemostasis, in surgery 77.50
Hageman factor 13.4
Hailey–Hailey disease 39.1, **39.32–7**
aetiology 39.32
clinical features 39.34
complications 39.34–5
cytodiagnosis 10.29
differential diagnosis 39.35, 40.11
female genital dermatology 71.66, 71.81
genitocrural 71.5–6
histopathology 39.33, 39.35
investigations 39.35
linear 18.25
male genital dermatology 71.25
prognosis 39.35
segmental 39.37
squamous cell carcinoma and 39.35
treatment 39.35–6, 79.4
Haim–Munk syndrome 19.3, 19.110, 69.16
hair
African 9.2
anatomy and physiology **66.1–16**
artificial 28.50
Asian 9.2
aural *see* ear(s), hairy
axillary 66.13
ageing and 8.24
bamboo (trichorrhexis invaginata) 19.37, 19.38, 19.39–40, 66.65–7
bayonet *66.62*
bleaches 66.85, 66.98
body, grading schemes 66.80
braiding 66.74
brush end *66.62*
bubble *66.62*
bulb *see* hair bulb
casts *66.62*
Caucasian 9.2
chest, ageing and 8.24
circle *66.62*
colour, in animals 2.6–7
conditioners 66.96
congenital abnormalities, in animals 2.18
cortex 3.13, 66.2, 66.6
cosmetics **66.95–100**
curly, curvature 3.14
cuticle 3.13, 66.2, 66.5–6
cycle *see* hair cycle
defects
folliculocentric keratotic disorders 19.72–3, 19.74–5
IBIDS/PIBIDS syndrome 19.47–9
ichthyosis follicularis with alopecia and photophobia 19.58–9, 19.60
keratoderma and cardiac disease and *19.94*, 19.107
Netherton's syndrome 19.37, 19.38, 19.39–40
differentiation 3.13–14
discs 3.16
disorders 3.14
in animals, comparison with humans *2.21*
ocular involvement *67.29*
see also specific disorders
drug-induced discoloration 66.94, 75.45
dyes 66.96–8
allergic contact dermatitis and 26.10, 26.17, 26.60–2
depigmentation and 26.26
open patch testing 26.97
ectodermal dysplasias 15.58, 15.64–6, 15.68–9
embryology 3.3
evolution 2.6, 66.1
examination in fungal infection 36.5–6
exclamation mark 66.34, *66.35*
external root sheath *see* hair, outer root sheath (ORS)
facial 8.4, 66.13
management 73.29
follicles *see* hair follicle(s)
as foreign body 28.49–51
functions 4.1
greasy, menstrual cycle and 8.8
greying 3.21, 8.23, 66.92–3
alopecia areata and 66.92
Notch signalling 3.21
pernicious anaemia and 62.85
premature 66.92–3
premature, in vitiligo 58.48
growth
androgens and 66.13–16
congenital naevi 54.11
ethnic factors 66.80
excessive 66.75–89
increased by minoxidil 73.50
normal 3.13–14
in pregnancy 8.10
rate 66.11
rate increased by caffeine 73.49
synchronous 66.27
see also hair cycle
guard 66.2
heterochromia 66.91–2
in HIV infection 35.41–2, *35.42*
inner root sheath (IRS) 3.13, 66.3, 66.4–5, 66.7
keratins 3.13–14
knotting 66.74
lanugo 66.91
laser-assisted removal 78.12–13
length, in animals 2.6–7
lichen planus 41.14
in liver disease 62.64
loss *see* hair loss
mammals 2.3
matrix
hamartoma 53.12–13
'mummified ghost' cells 53.12
tumours **53.12–14**
mechanoreceptor function in animals 2.6
medulla 3.13, 66.2, 66.6
moult waves 66.8
multiple 66.73
oral 69.37
outer root sheath (ORS) 3.13, 66.3, 66.4, 66.5
tumours **53.4–6**
permanent waving 66.98–9
pigmentation **66.89–95**
effects of physical phenomena 66.91
variations 66.91–5
plucking 66.9, 66.85
Pohl–Pinkus constriction *66.62*
in pregnancy 8.10, 66.9, 66.27
proteins 3.13–14
pubic 8.4, 66.13
ageing and 8.24
louse infection 38.22
waxing 38.22
race and 9.2, 66.13
red 3.21, 66.91
regrowth, sensitizing agent action 73.39
retinoid *66.65*
ringed 66.69–70, 66.91
scalp, ageing effect 8.23
seasonal growth 66.8–9
animals 2.3
setting 66.100
sexual, secondary 8.6
shaft
abnormalities 66.61–75
fracture 66.16
shampoos *see* shampoos
shaving 66.11, 66.85
silvery 58.42
in SLE 51.38, 66.29, *66.30*
spun-glass 66.71–2
sternal 66.13
straightening/relaxing 66.99
structure *3.2*, 3.13, 66.6
styling practices, race and 9.7
styling products 26.18
swallowing 64.31–2
tapered *66.62*
terminal 66.2, 66.13
in congenital naevi 54.11
minoxidil effect 73.50
terminal differentiation of cortical cells 3.13
terminal-to-vellus ratio, ageing and 8.23
tiger tail *66.62*
transplantation 66.23–4
in trichofolliculoma 53.7–8
types 66.2
variants 3.14
vellus 3.13, 66.2, 66.13, 66.91
ageing and 8.23
occlusion/cystic dilatation 53.7
waxing 66.87
weathering 66.74–5, 66.91
white 8.23, 66.35, 66.91, 66.92–3
forelock, in piebaldism 58.42
woolly 66.70–1
hair-bearing skin 3.3
surgical incisions 77.5
HAIR-AN syndrome 19.120, 42.73, 66.82
hair artefact 64.40
hair bulb 66.2–3, 66.3–4
in albinism 58.39, 58.40
matrix 66.4
hair collar sign 18.95, 18.98
hair cycle 3.7, 3.13–14, 66.7–13
in alopecia areata 66.33
disturbances 66.27–31
dynamics 66.20
melanogenesis and 66.90
hair follicle(s)
abnormalities in follicular atrophoderma 52.8–9
ageing/elderly people 8.23–4
in alopecia areata 66.33, *66.34*
in anagen 66.7, 66.8
anatomy 3.1, *3.2*, 66.2–67
areola periphery 70.1
bacterial flora 30.2, 30.3
bulge stem cells 3.6
carcinoma **53.32, 53.33–7**
in catagen 66.7–8
degeneration/regeneration cycle 3.7
density 66.2
distribution 66.2
embryonic development 3.3, 3.4, *3.5*, 42.3, 66.2
defective, in comedo naevus 42.78
follicular infundibulum tumour 53.3
immune privilege and 66.32
inflammatory diseases **30.21–30**
see also folliculitis

infundibulum 66.3
innervation 66.6
isthmus 66.3
loss 66.16
mechanism of androgen action 66.14–15
mechanoreceptor *(Haarscheibe)* 53.14
melanocytes 3.21, 58.3
melanogenesis 3.20, 66.90–1
mesenchymal lesions **53.14–15**
miniaturization 66.18, 66.20–1
mites *see Demodex*
naevus 53.6
prominent 9.4
regional variations in density 3.3
scars and 14.8
stem cells 3.7
suprabulbar region 66.3, *66.4*, 66.6
transplantation 66.15
tumours **53.2–4,** 53.27
hair follicle unit 12.63
hair germ 3.5
hamartoma 53.8–9
tumours and cysts **53.6–12**
hair loss
eating disorders 64.22
pathological pulling/plucking 64.30–1
see also alopecia
hair muffs 38.60
hair peg *3.5*
hair pull test 66.28, 66.30
hair sinus, breast 70.15
hair-thread tourniquet syndrome 28.50
hairdressers, occupational hazards *5.6*, 22.20, 26.47, 27.2, 27.3, 27.19
hand dermatitis 8.8
hairless mouse 66.11
hairline 66.16, *66.17*
surgery across 77.5
hairy leukoplakia 69.90, 69.91, **69.93–4**
EBV association 33.31, 35.43
in HIV infection 35.43
hairy pinnae *see* ear(s), hairy
HAL DRB1*04 (DR4), actinic prurigo and 29.14
half-moon lunule *see* lunula
halides 75.152–3
Hallermann–Streiff syndrome 15.41, **18.81–2,** 45.8
Hallopeau, acrodermatitis continua of *see* acrodermatitis continua (of Hallopeau)
Hallopeau–Siemens dystrophic epidermolysis bullosa (EB) 39.16, 39.18–20
hallux valgus, mechanical injury 28.10–11
halo, formation, venous microcirculatory disorders 47.27
halo naevus 58.49–50
halogen acne 27.12–15
halogenated acetophenones 25.21
halogenated aromatic hydrocarbons, acnegenicity 27.12–13
halogenated salicylanilides 26.24
haloperidol 64.52, 75.83
HAM56 55.15
hamartoma 47.12, 52.1, **53.6–12**
apocrine gland 18.14
basaloid follicular 53.11–12
congenital midline/rhabdomyomatous mesenchymal 18.37
congenital smooth-muscle (arrector pili) 18.35–6
congenital vellus 18.10–11
cutaneous *see* naevus
diffuse smooth-muscle 18.36–7
eccrine angiomatous 18.16
fat-storing of dermal dendrocytes **46.45,** 55.19
fibrolipomatous of nerve (neurolipomatosis) 18.40
fibrous of infancy **18.34–5,** 56.6
folliculosebaceous cystic 53.7–8
generalized follicular 66.51–2
hair germ 53.8–9
hair matrix 53.12–13
linear basaloid follicular 18.13
medallion-like dermal dendrocytic 17.15, 56.18–19
meningothelial 18.95
neuromuscular 18.37, 56.44
nodular proliferative neurocristic 54.13
pilosebaceous follicle 53.7–8
sclerosing epithelial 53.9–10
striated-muscle 18.37
sudoriferous 18.15–16
HAMP gene 62.61
Han Chinese patients 72.30
hand(s)
actinic keratosis 52.30
aggressive digital papillary adenocarcinoma 53.33
annular lesions of discoid LE 51.14
cold flexed fingers 51.112
collagenous and elastotic marginal plaques 45.28
dermatitis 72.10
career choice and 8.8
dermatitis/eczema **23.13–23,** 42.10
alitretinoin 74.36
allergic contact dermatitis 26.15–16, 26.29
asteatotic 23.20
atopic dermatitis 8.7, 23.14, 24.21–2
career choice and 8.8
chronic, lymphoedema after 48.13
classification 23.13–14
constitutional 24.22
diagnosis 27.4
differential diagnosis 23.20, *23.21*, 25.15, *25.16*
discoid 23.10
irritant contact dermatitis 25.2, 25.13, *25.14*, 25.15, *25.24*
nail involvement 65.28–9
nickel allergy and 26.31–2
as occupational dermatosis 27.2
plant-induced 26.76
prevalence 23.3
prognosis 23.21
severity assessment 72.10
tacrolimus therapy 73.32
treatment 23.21–3
disinfection 77.5, *77.7*
in dystrophic EB 39.18
eating disorder manifestations 64.22
erythromelalgia 47.9
factitious disorders 64.40
finger pebbles 59.79
hyperpigmentation, acromelanosis 58.21
lichen planus 23.20, *23.21*
mechanical injury 28.10–12, 28.14, 28.16, 28.27, 28.31
mechanic's 62.82
milia 25.15, *25.16*
neutrophilic dermatosis of the (dorsal) hands 50.80–1
occupational dermatoses 27.2, 27.3
pityriasis rubra pilaris 23.20
psoriasis 23.20, 25.15, *25.16*
of palms 20.15
scabies 25.15, *25.16*
tinea incognito *25.15*
Trichophyton infection 23.20, *23.21*, *25.15*
tripe palms 19.120
varices 47.16
wrinkling 28.93
see also palms
hand, foot and mouth disease **33.71,** 69.76–7
electron microscopy 10.30
hand cooling test 63.4–5
Hand Eczema Severity Index 72.10
hand–foot syndrome 38.14
hand washing, compulsive 64.24
hand–arm vibration syndrome (HAVS) 27.17, 28.26, 28.56, **28.57–8**
handicap, in skin disease 6.5
magnitude 6.5
Hand–Schüller–Christian syndrome *see* Langerhans' cell histiocytosis (LCH)
handymen, occupational hazards 27.20
HANES-1 study 6.7, 6.15
hang nails 65.51
hanging groin 37.5
Hanovia sunlamp 29.1
Hansemann cells 55.27
Hansen's disease *see* leprosy
hantavirus pulmonary syndrome 33.70, 49.20
hantaviruses *33.67*, 33.70, 49.20
Hapalochlaena maculosa 38.59
haplotype 11.7
Happle's syndrome (Conradi–Hünermann–Happle syndrome) 19.3, 19.49–52
prenatal diagnosis *16.3*
haptens 26.11, 26.23, 75.16
harara 38.5, 38.7
hard palate 69.2, 69.6
hardness tests, mechanical injury 28.5
harlequin colour change 17.4
harlequin ichthyosis 19.25–9
harm, critical appraisal of paper about *7.15*
Hartnup disease 59.100–1
harvest mites 30.74, 38.2, **38.50–1**
harvester ants 38.14
Hashimoto–Pritzker syndrome *see* Langerhans' cell histiocytosis (LCH)
Hashimoto's thyroiditis 62.10
sarcoidosis and 61.17
Haverhill fever 30.67
HAVS (hand–arm vibration syndrome) 27.17, 28.26, 28.56, **28.57–8**
Hawaiian box jellyfish 38.56
Haxthausen's disease (keratoderma climactericum) 19.117–18, 46.21
Hayden syndrome 15.42
Hay–Wells syndrome 15.28, **15.61–3**
hazard ratio 6.18
HBV *see* hepatitis B virus (HBV)
hCAP18 *see* LL-37
HCV *see* hepatitis C virus (HCV)
HD1 39.25
HDAC (histone deacetylase inhibitors) 57.28
HDM *see* house-dust mite
H&E (haematoxylin and eosin) 10.8, *10.9*, *10.10*
head, basal cell carcinoma 52.20
head and neck
blood vessels 77.2, *77.3*
cosmetic units 77.2
local anaesthesia 77.2–4, 77.10
lymphatic system 69.4, 77.2, *77.3*
lymphoedema 48.12, 48.13, **48.16,** 48.23
motor nerves 77.4–5
oedema 48.12
sensory nerves 77.2–4
surgery 77.2–5
see also neck; *specific areas*
head injury, hypertrichosis following 66.78
head lice *see under* lice
head load, in tropics, pigmentation effect 58.9
headache
in giant cell arteritis 50.43
herpes simplex 33.17
in traction alopecia 66.53
headsets, dermatitis due to 26.17
Heaf test 5.24, 13.22
health-related groups 5.2
health-related quality of life *see* quality of life (QOL)
health services
audit 72.13
boundaries between primary/secondary care 6.15
need, supply and demand relationship 6.15–16
needs assessment 6.14
primary care 6.14–15
referral rates 6.15
research **6.14–17,** 72.13
secondary care 6.15
uptake and number of patients using 6.14
Health Technology Assessment Database 7.5
health workers, occupational hazards 5.*6*
hearing-aids, dermatitis due to 26.17, 68.23–4
hearing impairment *see* deafness
heart
in carcinoid syndrome 43.18
disorders **62.75–80**
keratoderma and woolly hair and *19.94*, 19.107
see also specific disorders
in infantile haemangioma 18.45
in sarcoidosis 61.7
in systemic sclerosis 51.101, 62.78
in trypanosomiasis 37.32
see also entries beginning cardiac
heart failure, venous leg ulcers and 47.47
heart valves, haematoxylin bodies in SLE 51.34
heat
sensitivity, rosacea 43.2
wart treatment 33.50
heat-associated carcinomas 28.73
heat cautery 77.44–5
heat injury *see* thermal injury
heat nociceptors 4.9
heat pain threshold 4.9
heat shock proteins 51.54
hsp90 73.17
polymorphic light eruption and 29.11
in vasculitis 50.5
in wound healing 14.5
heavy-chain disease 69.114
heavy water distillate, acne associated 42.77
Heberden's nodes 45.70
Heck's disease 33.47, 69.111–12
HED *see* hypohidrotic ectodermal dysplasia (HED)
Hedgehog signalling
in follicular atrophoderma 52.9
importance during development 52.6
in naevoid basal cell carcinoma syndrome 52.6, 52.7
Heerfordt's syndrome 61.7
Heidenhain's Susa 10.31
Heimler syndrome 15.52
Helicobacter pylori 62.48
eradication, effect on rosacea 43.2, 43.6, 43.7
rosacea pathogenesis and 43.2
urticaria and 22.2, 22.10
Helleborus 25.21
HELLP syndrome 49.12, 49.31
helminth infection, eosinophilia in 62.86
heloma *see* corns
hemi-hypertrophy 63.14
hemiatrophy, facial 46.39
hemidesmosome(s) 3.26, 3.30–2
components (HD1-HD5) 3.30
gene mutations 3.31
in junctional epidermolysis bullosa 39.9, 39.25
ultrastructure 3.30
hemidesmosome-anchoring filament-anchoring fibril adhesion complex 3.3, 3.30–2
hemidesmosome-anchoring filament complexes 3.3
hemifacial atrophy 51.70
hemifacial microsomia **18.82–3,** 68.4
hemilipodystrophy 46.39
Hemiptera (bugs) **38.23–6**
hemizygous genes, definition 15.3
hemojuvulin gene 62.61
henna 66.97, 75.162
tattoos 26.60

Hennekam lymphangiectasia–lymphoedema syndrome 48.10, 48.27
Henoch–Schönlein purpura 49.18–19, **50.19–21**
  aetiology and pathogenesis 50.4, 50.5, 50.7, 50.20
  bone and joint involvement 62.102
  classification 50.2
  clinical features 50.20
  genetic factors 50.11
  male genital dermatology 71.28–9
  renal involvement 62.71
Hep-2 cells 13.19, 13.20
  anticentromere antibodies 51.103
  Sci-70 antibodies 51.104
hepadnaviruses *33.2*
heparan, structure *3.47*
heparan sulphate 3.46
  in wound healing 14.3
heparan sulphate proteoglycans (HSPGs) 3.29
heparin
  adverse effects 45.52, 62.92, **75.105–7**
    haemorrhage 49.28
    necrosis **49.27–9**
    purpura 75.23
    thrombocytopenia 49.11, **49.27–9**
  LMWH *see* low-molecular-weight heparin (LMWH)
  skin testing for reactions to 75.173
  structure *3.47*
heparin-reactive antibodies 49.27
hepatic artery ligation/embolization, in carcinoid tumours 43.19
hepatic vein thrombosis (Budd–Chiari syndrome) 49.29, 49.30
hepatitis 62.58
  chronic active, lichen planus and 41.16
  following ear piercing 68.7
  herpes simplex virus and 33.17
  prevention of spread during surgery *77.7*
  viruses **33.60–2**
    see also specific viruses
hepatitis A 33.74
  nodular panniculitis and 46.14
hepatitis A virus (HAV) 33.74, 62.59
hepatitis B virus (HBV) **33.60–1**
  aetiology and epidemiology 33.60
  angio-oedema and 62.59
  cryoglobulinaemic vasculitis and 62.59
  cutaneous manifestations of infection 33.60, 62.59
  erythema and 62.59
  erythema multiforme and 62.59
  Gianotti–Crosti syndrome and 33.61, 33.77, 62.59, 62.64
  HbcAg (core antigen) 33.60
  HBeAg (e antigen) 33.60
  HbsAg (Australia antigen) 33.60
  immune response 33.60
  lichen planus and 41.16, 62.59
  polyarteritis nodosa and 33.60–1, 50.33, 50.34, 50.35, 62.59
  prophylaxis 33.61
  pyoderma gangrenosum and 62.59
  replication 33.60
  serum sickness and 33.60, 62.59
  transmission 38.24
    by human bites 38.61
  urticaria and 22.8, 62.59
  vaccination 33.61, 62.59, 75.139
    conditions after 33.61
    lupus panniculitis and 46.25
  vectors 38.24
hepatitis C virus (HCV) **33.61–2**
  antibodies 49.32
  autoimmune disorders and 62.60
  cold-induced injury 28.71
  conditions associated with 33.62
  cryoglobulins and 33.61, 49.32, 49.33, 50.24, 50.25, 62.59
  cutaneous features of infection 33.61, 62.59–60
  lichen planus pathogenesis 41.2–3, 41.16
  necrolytic acral erythema and 62.59
  oral manifestations of infection *69.115*
  pigmented purpuric dermatoses and 49.23
  polyarteritis nodosa and 50.33, 62.59
  porphyria cutanea tarda and 33.61–2, 62.59–60
  pruritus and 21.9
  red fingers syndrome and 62.59
  replication 33.61
  tattoos 28.48
  transmission 38.24
  treatment 33.62
  vasculitis and 33.61
hepatitis D virus 62.60
hepatitis E virus 62.60
hepatitis F virus 62.60
hepatitis G virus 62.60
  HIV infection with 35.5
hepatocutaneous syndrome, in dogs 2.17
hepatocyte growth factor (HGF) 3.21
  hair growth and 66.10
  melanocyte mitogen 58.5
hepatocyte growth factor activator inhibitor-1 (HAI-1) 12.50
hepatoerythropoietic porphyria 59.13–15
hepatolenticular degeneration syndrome 59.76
hepatosplenomegaly
  in sarcoidosis 61.10
  in trypanosomiasis 37.32
hepatovirus 33.71, 33.74
heptachlor 75.163
herald patch
  differential diagnosis 33.80, 33.81
  pityriasis rosea 33.79, *33.80*
herbal remedies 64.54, *72.32*, 72.33
  acne vulgaris 42.43
  platelet function disorders 49.13
  potential risks 72.29, 72.33
herd immunity and scabies 38.37
hereditary angio-oedema *see* angio-oedema, hereditary
hereditary benign intraepithelial dyskeratosis 69.25
hereditary benign telangiectasia 47.19
hereditary blistering disorders **39.1–37**
  see also epidermolysis bullosa (EB); Hailey–Hailey disease
hereditary coproporphyria 59.19
hereditary epidermal polycystic disease *see* steatocystoma multiplex
hereditary haemorrhagic telangiectasia (HHT) 18.79–80, 47.13, **47.17–18,** 49.5
  aetiology and pathogenesis 47.17–18
  iron deficiency anaemia in 62.85
  mutations in HHTI and HHT II 49.7
  oral cavity 69.29, *69.117*
  portal hypertension and 62.63
  purpura and bleeding 49.15
hereditary leiomyomatosis and renal cell carcinoma syndrome 2.17, 62.29, 62.69
hereditary mucoepithelial dysplasia 15.42, 69.31
hereditary non-polyposis colorectal cancer (HNPCC) 52.10
  sebaceous adenoma association 42.87
hereditary onycho-osteodysplasia (Hood) syndrome 15.8, **15.86–7**
hereditary osteo-onychodysplasia 15.8, **15.86–7**
hereditary polymorphous light eruption 29.13
hereditary progressive mucinous histiocytosis 59.25
hereditary sclerosing poikiloderma **15.82**
hereditary sensory autonomic neuropathy (HSAN)
  type I 63.18
  type II 63.18
  type III 44.7, 62.80, 63.18
  type IV 63.18–19
  type V 63.19
heregulin-a 62.16
Herellea see Acinetobacter
Hermansky–Pudlak syndrome 9.16, 17.78–9, 17.81, 49.12, 58.41, 62.52, 62.95
hernias
  fascial, legs 45.68–9
  muscular 28.61–2
heroin 75.28, 75.87
herpangina **33.71,** 69.76
herpes-associated erythema multiforme (HAEM) 33.18–19
herpes B virus (B virus; CeHV-1) 33.34–5
herpes gestationis *see* pemphigoid gestationis
herpes gladiatorum 33.17
herpes iris of Bateman 76.7
herpes labialis 69.72–3
herpes simplex *5.14, 33.14,* **33.14–22,** *69.118*
  aetiology 33.14–15
  antibodies 33.19, 33.35
  atopic eczema and 33.35–6
  autoinoculation/inoculation 33.15, 33.17
  children 33.15, 33.20, 35.45
  clinical features *5.4,* 33.16–20
  cytodiagnosis *10.28,* 10.29
  diagnosis 33.19
  differential diagnosis 26.29
  ear involvement 68.20, 68.28
  electron microscopy 10.30
  erythema multiforme and 33.18–19, 76.2
  genital infections 33.15, 33.17, 33.18
    females 71.57, 71.70
    in HIV infection 35.28
    males 71.33
    maternal primary 33.15, 33.21
    prevalence *34.2*
    primary 33.16, *33.17*
    recurrent 33.17, 33.18
    treatment 33.20, 33.21
  gingivostomatitis 33.16
  Hailey–Hailey disease vs 39.35
  in HIV infection 33.15, 35.28, 35.45, 68.28
    immune restoration and 35.28, 35.46, *35.47*
  immune response 33.15, 33.21
  immune restoration disease 35.28, 35.46, *35.47*
  in immunodeficiency 33.15, 33.17, 33.18, 33.20
  intrauterine infection 17.39, 18.2, 33.15, 33.21
  keratoconjunctivitis 33.17, 33.18
  latent infections 33.14
  in malaria 37.27
  neonatal infection 17.39–40, 33.15, 33.17, 33.20
  non-primary first-episode 33.15
  ocular 67.16, 67.25–6
  oral 33.16, 69.13, 69.72–4
    in HIV infection 35.43
    primary 33.15, 33.16
    prophylaxis 33.21
    recurrent 33.17–18, 33.20, 33.21
  paronychia due to 65.22–3
  pathology 33.16
  perianal/perineal disease 71.95
    in HIV infection 35.28
  primary infection 33.16–17
    complications 33.17
    HSV-1 33.14–15, 33.16
    HSV-2 33.15, 33.16
    recurrence comparison 33.18
    treatment 33.20
  prophylaxis 33.20, 33.21
  recurrent infection 33.15, 33.17–19
    complications 33.18–19
    intraoral 69.73
    labial 69.72–3
    treatment 33.20–1
  stomatitis 33.16, 69.13, 69.72–4
  TORCH syndrome 33.76–7
  trauma facilitating 33.15, 33.18
  treatment 33.20–1
    topical agents 73.15
  vesicles 33.16, 33.18
  whitlow 33.17
herpes simplex virus (HSV) *33.14,* **33.14–22**
  blepharoconjunctivitis 67.26
  DNA detection 33.19
  HSV-1 33.14, 33.16, 33.17, 33.18
    eczema herpeticum 33.35
  HSV-2 33.14, 33.16, 33.17, 33.18
    Well's syndrome and 46.33
  mutants, drug resistance 35.28
  reactivated 67.25
    oral 33.3
    prevention 33.20, 33.21
  shedding 33.14, 33.17
    subclinical 33.18
  transmission 33.14, 33.15
  vaccines 33.21
herpes zoster *see* zoster
herpes zoster oticus 33.25, 33.26
  management 33.28
herpes zoster sine eruptione 33.25, 67.26
Herpesvirus hominis 33.24
  see also herpes simplex virus (HSV)
Herpesvirus varicellae 33.22, 33.24
  see also varicella zoster virus (VZV)
herpesviruses *33.2,* **33.14–37**
  classification *33.14*
  electron microscopy 10.30
  oral infection 69.76
  transmission by human bites 38.61
  see also specific viruses
herring brine 25.21
Hertog's sign 62.10
HES *see* hydroxyethyl starch (HES)
Hess test 49.5
hetastarch *see* hydroxyethyl starch (HES)
heterochromia 66.91–2
heterogeneity, genetic 15.5
heterophile antibodies, EBV infection 33.30
heterozygosity, loss of 11.18
heterozygous genes, definitions 15.3–4
Heubner's arteritis 34.5
HEV (high endothelial venule) 13.9, 13.10
hexachlorophene (hexachlorophane) 14.21, 25.21, 26.24, 73.15, 75.164
2,4-hexadienoic acid 25.18, 26.58, 73.8
Hexathelidae 38.31
HF *see* hydrofluoric acid
HFE gene 62.61
HFEA (Human Fertilization and Embryology Authority) 16.8–9
HGU (Human Genetics Unit) 15.1
HHF35 10.22
HHV-1 *see* herpes simplex virus (HSV), HSV-1
HHV-2 *see* herpes simplex virus (HSV), HSV-2
HHV-3 *see* varicella zoster virus (VZV)
HHV-4 *see* Epstein–Barr virus (EBV)
HHV-5 *see* cytomegalovirus (CMV) infections
HHV-7 *see* human herpesvirus 7 (HHV-7)
HHV-8 *see* human herpesvirus 8 (HHV-8)
Hibernian fever 22.25, 50.53, 62.69, 62.104
hibernoma **46.45**
HID (hystrix ichthyosis and deafness) syndrome 15.46, 19.36, 19.37, 19.54–7
hidradenitis
  in adolescence 8.7
  idiopathic recurrent palmoplantar 44.17
  neutrophilic eccrine *see* neutrophilic eccrine hidradenitis
hidradenitis suppurativa **30.79–82,** 42.74–5, 64.7
  acne and 42.33
  acne conglobata and 42.82
  aetiology 30.79–80

bone and joint involvement 62.102
breast 70.17
clinical features 30.80–1
complications 30.81
diagnosis 30.81
genitocrural dermatology 71.5
isotretinoin treatment 42.62
pathology 30.80
perianal/perineal dermatology 71.88–9
TNF antagonists 74.7
treatment 30.81–2, 77.36
hidradenocarcinoma 53.34
hidradenoma 53.27–8
clear-cell 53.27–8
eccrine 53.22
malignant 53.34
nodulocystic 53.27–8
papillary 71.72
poroid 53.24
hidradenoma papilliferum 53.20–1, 68.30
hidradenomes eruptifs *see* syringoma
hidroacanthoma simplex 53.22–3
hidrocystoma
apocrine 53.18–19
eccrine 53.22, 67.33
eyelid 67.33
hidrotic ectodermal dysplasia 15.42, 15.67, **15.68–9,** *19.94,* 19.106
see also Clouston's syndrome (hidrotic ectodermal dysplasia)
HIES *see* hyper-IgE syndrome
high-density lipoprotein (HDL) cholesterol, retinoids 74.37
high endothelial venule 13.9, 13.10
high-resolution comparative genomic hybridization 11.13
high-throughput genetic analysis 15.6
higher bacterial infections, female genital dermatology 71.68
highly-active antiretroviral therapy (HAART) 35.1, 35.5
adverse effects 35.21, 75.67
in children 35.45
gynaecomastia 70.4, *70.5*
lipoatrophy 35.22
sarcoidosis 61.6
anogenital wart regression 35.30
CD4 T-cell reconstitution 35.4
immune reconstitution (inflammatory) syndrome 35.46
indications 35.17, 35.18, 35.32
in Kaposi's sarcoma 35.37
lipodystrophy association 46.41, 46.42
skin cancer warning 35.40
success and survival improvement 35.6
hip circumference 46.5
Hippelates 30.14, 38.6
Hippoboscidae 38.6, 38.7
Hippocrates 72.5, 72.25
Hippocratic fingers **15.87–8**
Hippomane manchinella 25.21
hippopotamus 2.3, 2.4
hirsutism **66.80–9**
acne association 42.20, 42.21
in acromegaly 62.2
antiandrogens 74.32
definition 66.75, 66.80
diagnostic approach 66.84–5
drug-induced 75.45
endocrine factors 66.80–4
grading 66.80
idiopathic 66.83
investigations *66.85*
perianal/perineal 71.85
in pregnancy 8.10, 66.82
treatment 66.85, *66.86,* 66.87–9
see also hypertrichosis
Hirudinea 38.55
histamine **12.57–9**
in arthropod saliva/venom 38.1
atopic eye disease 67.15
in cholinergic urticaria 22.15
cold urticaria and 21.4
electromagnetic radiation inducing release 8.21
in flushing 43.14, 43.16
food and 22.8
in Hymenoptera venom 38.14
intradermal injection 22.5
liberators 22.8
mast cell release 67.15
pruritus and 21.3–4
release by DMSO 73.7
triple response of Lewis and 63.5
urticaria and 22.4, 22.8, 22.9
histamine receptors 74.31
cloning 12.26
H_1 21.3, 22.4
H_2 21.3, 22.4
H_3 21.3, 22.4
H_4 21.3, 22.4
pruritus and 21.3
histamine-release test 75.174
histatins 12.6–7
histiocytes
in benign cephalic histiocytosis 55.15
cytophagic 46.23–5
differentiation/development 5.1–3
in familial haemophagocytic lymphohistiocytosis 55.25
foamy 55.21
juvenile xanthogranuloma 55.15
function *55.2,* 55.4–5
in granuloma annulare 60.4
microscopy 10.34
in multicentric reticulohistiocytosis 55.23
ontogeny 55.1–3
phagocytosis by 55.4, 55.26
proliferation
cytophagic histiocytic panniculitis 46.23–4
haemophagocytic syndrome 46.23
malignant 55.32, 55.33
in sinus histiocytosis with massive lymphadenopathy 55.29
in solitary giant xanthogranuloma 55.15
see also histiocytosis
histiocytic markers 10.24
histiocytic sarcoma 55.31
histiocytoma
aneurysmal fibrous 49.17
basal cell carcinoma over 52.20
fibrous *see* fibrous histiocytoma
generalized eruptive 55.15, 55.19
giant-cell *see* multicentric reticulohistiocytosis
progressive nodular 55.20
solitary (solitary epithelioid) 55.23, 55.24
histiocytoma cutis *see* fibrous histiocytoma (FH)
histiocytosis **55.1–34**
benign cephalic (papular of the head) 55.15, **55.17–18**
bone and joint involvement 55.12, 55.21, 55.23, 55.32, *62.101*
class I (Langerhans' cell involvement) 55.6, **55.6–14**
see also Langerhans' cell histiocytosis (LCH)
class IIa (dermal dendrocyte involvement) 55.6, **55.14–22**
histopathology/diagnosis 55.15
see also juvenile xanthogranuloma
class IIb (non-Langerhans' cell, non-dermal dendrocytes) 55.6, **55.23–31**
class III (malignant) 38.7, 55.6, **55.31–4**
immunohistochemistry 55.31, 55.32, 55.33
of LCH type 55.7, 55.32
malignant reticulohistiocytosis 55.32–3
monocytic leukaemia 55.31–2
true histiocytic lymphoma 55.33–4
virus-associated haemophagocytic syndrome vs 55.30
classification 55.5–6
crystal-storing 46.17
familial sea-blue 55.26
generalized eruptive 55.15, 55.19
hereditary progressive mucinous 55.27
histiocyte function changes causing symptoms *55.2*
intravascular (intralymphatic) associated with rheumatoid arthritis 62.103
oral involvement 69.58–9
papular, of head 55.15, **55.17–18**
progressive nodular 55.20
pure cutaneous *see* Langerhans' cell histiocytosis (LCH)
regional, cytophagic histiocytic panniculitis 46.23
sea-blue 55.26
self-healing *see* Langerhans' cell histiocytosis (LCH)
self-limiting types 55.17
virus-induced, with erythrophagocytosis 55.30–1
histiocytosis X *see* Langerhans' cell histiocytosis (LCH)
histology technicians, occupational hazards 27.19
histone deacetylase inhibitors 57.28
histone modification 11.16
histopathological techniques, foreign bodies 28.42
histopathology **10.1–43**
Histoplasma capsulatum 36.2, 36.80–3
in HIV infection 35.34
histoplasmin test 5.24, 36.86
histoplasmosis **36.80–3**
acute disseminated 36.82
acute pulmonary 36.82
aetiology 36.81
chronic disseminated 36.82
chronic pulmonary 36.82
clinical features 36.81–2
definition 36.80–1
diagnosis 36.82–3
disseminated 35.33
histology 36.81
in HIV infection 35.33–4
large-form (African) 36.81, 36.83
male genital dermatology 71.32
oral involvement 69.80, *69.118*
perianal/perineal 71.96
primary cutaneous 36.82
small-form 36.81
treatment 36.83
history-taking 5.3–6
HIV (human immunodeficiency virus) 35.1
attachment and infection process 35.3
circulating recombinant forms (CRFs) 35.2
genetic variability and error rate 35.2, 35.5
gp41 protein 35.3, 35.6
group M 35.2
groups, subtypes (clades) and sub-subtypes 35.2–3
immunosuppressive effects 35.4
receptors and co-receptors 35.3, 35.6
recombination 35.2
rev, tat, nef, vpr, vpu genes 35.3
reverse transcription 35.3, 35.6
structure 35.3
types 35.2
viral load 35.5
HIV-1 35.2
HIV-2 35.2
HIV-associated adipose redistribution syndrome (HARS) 46.41–2
HIV infection **35.1–47**
abscesses 35.24
acanthosis nigricans 35.12
actinic keratosis 35.39
acute primary/seroconversion 35.10–11
differential diagnosis *35.11*
alopecia areata 66.2
American trypanosomiasis (Chagas' disease) 35.35
amoebiasis 35.35
anal cancer 35.30, 35.39
angiolipoma 46.45
anogenital warts 35.29–30
antibody response 35.3
arthropod bites/stings 38.2, 38.7
atopic dermatitis 24.24, 35.16, 35.45
atypical mycobacterial infections 35.25–6
bacillary angiomatosis 35.25, 68.28
bacterial infection 35.24–8, 35.45
basal cell carcinoma 35.39
breast hypertrophy and 70.3
candidiasis 35.32, 35.43, 35.45, 36.59–60, 69.105
cell count monitoring 13.22
cellulitis 35.24
chancroid co-infection 34.34–5
in children 35.44–5
chronic actinic dermatitis and 29.16
clinical features *35.10*
co-infections 35.5
coagulopathies 35.12–13
coccidioidomycosis 35.34, 36.86
Corynebacterium minutissimum 35.26
cryoglobulinaemia and 28.71
cryptococcosis 35.24, 35.33, 36.89, 36.90–1, 68.28
cryptosporidiosis 35.35
cutaneous larva migrans 35.36
cytomegalovirus (CMV) infection 35.28, 35.29
Demodex infection 35.36
dermatological manifestations **35.8–47**
see also specific manifestations
dermatophytosis 35.32–3, 35.45
diagnosis 35.8, *35.11*
early, benefits 35.6, 35.8–9
differential diagnosis *35.11*
drug reactions 35.20–4
non-antiretroviral drugs *35.20*
oral *35.44*
duct ectasia/periductal mastitis complex and 70.8
ear involvement 68.28
eosinophilic folliculitis 35.18–19
epidemiology 35.1–2
erythema elevatum diutinum and 50.25
erythroderma 35.13, 35.16
eyelash disorders (trichomegaly) 67.4
fungal infections 35.32–5, 35.45
furunculosis and 30.23
global trends *35.2*
granuloma annulare and 35.19–20, 60.1, 60.7
granuloma inguinale (donovanosis) and 34.37
gynaecomastia and 70.4
haemophagocytic syndrome and 46.23
haemophiliacs 35.45
hair changes 35.41–2, *35.42,* 66.2
hairy ears and 68.5
hairy leukoplakia and 35.43, 69.93–4
hepatitis G and 35.5
herpes simplex 33.15, 35.28, 35.45, 68.28
oral 35.43
histoplasmosis 35.33–4, 36.81
HLA associations 35.3, 35.4, 35.5
homosexual men 35.2, 35.5, 35.13, 35.15, 35.30, 35.32
HPV infections and 33.59, 35.29–30
hyperpigmentation 35.12
ichthyosis 35.11–12
immune evasion 35.6
immune restoration disease 35.28, 35.29, 35.46, *35.47*
immunology 35.3–4
incidence *34.2*
indicator conditions 35.1, *35.4,* 35.8
infections **35.24–36**
see also specific infections
infective otitis externa and 68.26
inflammatory dermatoses 35.13–15
intravenous drug users 35.45–6

investigations 35.9
Kaposi's sarcoma and 56.34
leishmaniasis 35.35, 37.43
leprosy and 32.2, 35.26
lichen planus and 41.12
lipodystrophy syndrome 46.41–3
long-term non-progressors 35.3, 35.5
long-term survivors 35.5
lymphoma 35.41
malakoplakia 35.36
male genital dermatology 71.34, 71.39, 71.40–1, 71.48
melanoma 35.39–40
microsporidiosis 35.35
molecular epidemiology 35.2–3
molluscum contagiosum 33.11, 35.30–1, 35.45, 68.28
  of eyelids 67.24–5
mortality *34.2*, 35.2
MRSA infections 35.24
mucocutaneous involvement 35.1, 35.8
Mycobacterium avium complex infection and 31.7, 35.25–6
Mycobacterium chelonae infection and 31.7
Mycobacterium fortuitum infection and 31.7
Mycobacterium gordonae infection and 31.7
Mycobacterium kansasii infection and 31.7
Mycobacterium scrofulaceum infection and 31.7
Mycobacterium terrae infection and 31.7
Mycobacterium tuberculosis infection and 31.2, 31.7, 35.25
Mycobacterium xenopi infection and 31.7
nail involvement 35.41–2, *35.42*, 65.16, 65.23
natural history 35.5
neonatal 17.42
neoplasms **35.36–41,** *35.40*
  see also Kaposi's sarcoma
neuropathy associated 63.12
neutrophilic eccrine hidradenitis and 44.17
non-AIDS defining cancers 35.39
oncocerciasis 35.36
onychomycosis 35.33, 35.41
oral manifestations 35.42–4, 69.19, 69.56, 69.81, 69.97–8, *69.118*
  ulceration 35.42
oropharynx in 35.42–4
parvovirus B19 35.31
pathogenesis 35.4, 35.6
penicilliosis 35.34, 36.88
perianal/perineal dermatology 71.83, 71.94, 71.95, 71.97–9
periodontal disease 35.43
pigmentary disorders 35.12
Pneumocystic carinii pneumonia 35.4–5, 35.21, 35.35
porphyria cutanea tarda in 35.20
prevention of spread during surgery *77.7*
prognostic indicators *35.11*
progression rates 35.5
protozoal infections 35.35–6
pruritic papular eruption 35.19, 35.45
pruritus 21.14, 35.11–12
psoriasis 20.4, 35.17–18
rapid progressors 35.5
Reiter's syndrome 35.17
resistance to infection 35.3
risk of adverse drug reactions 75.6–7
rosacea 43.3
sarcoidosis and 61.6
scabies and 35.36
  crusted (Norwegian) 38.44
seborrhoeic dermatitis and 23.29, 23.30, 23.32, 35.15–16, 35.45, 36.13, 68.28
seroconversion 35.3, 35.8, 35.10
  dermatological manifestations *35.10*
sexual transmission 35.2
soft-tissue infections 35.24
sporotrichosis 35.26
squamous cell carcinoma 35.39
Staphylococcus aureus and 30.7, 30.8, 35.24, 35.45
survival improvements 35.5, 35.6
syphilis co-infection 34.3, 34.14, 34.23, 35.25
testing, 'normalization' 35.9
time to AIDS development 35.5
tinea corporis/faciei *35.32*
toxic epidermal necrolysis and 76.8–9
transmission 35.5
  resistance 35.6
  sexually transmitted infections and 34.1
  side-effects 35.6–7
  vertical 35.44
treatment **35.5–8**
  failure, causes 35.5
  guidelines 35.6
  initiation 35.6
  see also antiretroviral agents
tuberculosis and 31.2, 31.7, 31.8, 31.20, 31.27
varicella zoster virus (VZV) infection 35.28–39
vasculitis and 50.55
vectors 38.24
viral infections 35.28–32
vitiligo 35.12
warts 33.59
in women 35.44
  genital involvement 71.57, 71.67, 71.71
xerosis 35.11–12
yaws in 35.25
zoster 33.25, 68.28
see also AIDS
HIV-wasting syndrome 46.42
hives *see* urticaria
HJMD (congenital hypotrichosis with juvenile macular dystrophy) 15.33
HLA-3, in lichen planus 41.2
HLA-5, in lichen planus 41.2
HLA associations 12.13–14, 15.8–9
  adverse drug reactions 72.30, 75.14–15, 75.100
  alopecia areata 66.31
  Behçet's disease 50.56, 69.47
  chemical-induced scleroderma 45.52
  erythema multiforme 69.69, 76.2
  geographical tongue 69.100
  giant cell arteritis 50.43
  granuloma annulare 60.1
  hidradenitis suppurativa 30.80
  HIV infection 35.3, 35.4, 35.5
    psoriasis 35.17
  idiopathic thrombocytopenic purpura 49.10
  lichen planus 41.2
  pityriasis rosea 33.78
  sarcoidosis 61.3, 61.18
  scabies 38.38
  Stevens–Johnson syndrome 76.10–11
  toxic epidermal necrolysis 76.10–11
  urticaria 22.3
HLA-B8 40.45
HLA-CW7 40.45
HLA-Cw0602, psoriasis in HIV infection 35.17
HLA-DQB1*0301 40.36
HLA-DQB1*0503 40.3
HLA-DR, expressed by dermal dendrocytes 55.4
HLA-DR typing
  HLA-B8 51.2
  HLA-B8 and -DRw3 51.54
  systemic sclerosis 51.90
HLA-DR2 40.41
HLA-DR3 40.45
HLA-DRB1*0102 40.17
HLA-DRB1*0402 40.3
HLA-DRB1*1401 40.3
HLRCC syndrome 2.17, 62.29, 62.69
HMB45 10.21, 58.3
HNPs (human neutrophil peptides) 4.5
hoarseness, as a sign of systemic disease 62.84
hobbies
  allergic contact dermatitis and 26.14
  disorders associated with *5.6*
  history-taking 5.5
hobnail cells 56.29, 56.32, 56.33
hobo spider 38.32
Hodgkin's disease 57.63, 62.89–90
  allergic contact dermatitis and 26.9
  cutaneous 57.63
  dyskeratosis congenita 15.79
  EBV association 35.41
  erythroderma and 23.48
  exfoliative dermatitis 57.63
  hair loss in 66.29
  in HIV infection 35.41
  HPV infections 33.59
  ichthyosis with 19.63
  pigmentation changes 58.26
  pruritus in 21.11, 62.89
  Reed–Sternberg cells 57.29
  sarcoidal reaction in 61.23
Hoigne reaction 34.23
Holmes–Adie syndrome 44.14
holocarboxylase synthetase deficiency 59.64
holocrine glands 42.1
holoderma *see* knuckle pads
holomorph 36.2
Homans' procedure 48.25
homeopathy *72.32*, 75.162
homeostasis, of skin **3.5–7**
homocysteinurias (homocystinurias) 45.30, 59.99
  hair colour in 66.95
homogentisic acid 73.27
  accumulation in ochronosis 58.54
homogentisic acid oxidase 73.27
homologous recombination 11.10–11
homologous restriction factor protein 13.4
homosexual men *see* men who have sex with men (MSM)
homozygous genes, definitions 15.3–4
honey, in wound treatment 14.21, 73.48
honeybees *see* bees
HOOD syndrome 15.8, **15.86–7**
hookworm disease 22.10, 37.2, **37.14–15,** 37.16
hordeolum (stye) 67.6, 67.26–7
hormonal therapy, acne *see under* acne vulgaris
hormone replacement therapy (HRT) 8.19
  complications 8.20
  female genital dermatology and 71.52
  flushing management 8.20
  melasma rarity 58.34
hormone-sensitive lipase (HSL) 46.3
hormones
  acne aetiology and 42.20–2
  allergic contact dermatitis and 26.8
  collagen gene expression control 3.39
  fat and energy metabolism control 46.2
  in menopause 8.19
  menstrual cycle 8.8
  pregnancy 8.9–10
  at puberty 8.4–5
  sebaceous gland activity and *see* sebaceous glands
horn, cutaneous **52.36,** 53.13
horn cysts 53.35
horn flies 38.6
Horner's syndrome **63.22**
hornets 38.14
horns (rhino) 2.3
Hornstein–Knickenberg syndrome 53.14, 53.15, 62.57, 62.69
horse botfly 38.9, 38.10
horse flies 37.11, 38.6, 38.7
horseradish peroxidase 10.15, 10.16
horses
  alopecia 2.18
  bullous pemphigoid 2.14–15
  fungal infections 2.12
  hypertrichosis 2.18, *2.19*
  melanoma 2.20
  photosensitivity 2.23
  pruritic skin disease 2.11
  sarcoids 2.21–2
  skin infections 2.12
Hortaea werneckii *36.8*, 36.14
Horton's disease *see* giant cell arteritis
hosiery, support/compression 14.20
hosiery workers, occupational hazards 27.6
hospital workers, occupational hazards 27.19–20
host defence
  bacterial infections 30.1–2
  innate 12.5
    see also immunity, innate
  role of normal skin flora 30.4, 30.5
  see also immune system; immunity
host–parasite relationships 30.2
hot combing 9.7, 66.46, 66.99
hot flushes/flashes *see* flushing
hot-tubs 28.54–5
house-dust mite (HDM) **38.47–8**
  atopic dermatitis and 24.10, 24.31
house flies 38.6, 38.8
house mouse mite 38.51
housewives' dermatitis 23.20–3, 26.15, 27.2, 27.3
housework, occupational hazards 26.14, 26.15, 27.2, 27.3, 27.20
Howel-Evans syndrome *19.94*, 19.106, 19.107, 62.20–1, 62.48
HOX gene expression, fibroblasts 3.50
Hoyeraal–Hreidarrson syndrome 17.70
HPS *see* haemophagocytic lymphohistiocytosis (haemophagocytic syndrome)
HPV *see* human papillomavirus (HPV)
HRF 13.4
HRT *see* hormone replacement therapy
HSAN *see* hereditary sensory autonomic neuropathy
HSCT (haematopoietic stem cell transplantation) *see under* haematopoietic stem cell(s)
HSP *see* Henoch–Schönlein purpura
HSV *see* herpes simplex virus (HSV)
5-HT *see* serotonin (5-HT)
HTA (Health Technology Assessment Database) 7.5
HTLV *see* human T-lymphotropic virus(es) (HTLV)
HTLV-1 *see* human T-lymphotropic virus type 1 (HTLV-1)
HTLV-2 33.64
HTLV-3 33.64
HTLV-4 33.64
human adjuvant disease, induced by silicone or paraffin implants 51.82
human androgen receptor *(HUMARA)* gene *see HUMARA* gene
human β-defensins (hBDs) 3.17, 4.5, 13.4, 14.5, 36.21
  in acne pathogenesis 42.25
human bites 38.61
human bocavirus infections 33.62
human botfly 38.9, 38.10
human chorionic thyrotrophin (hCT) 8.9
Human Fertilization and Embryology Authority 16.8–9
Human Genetics Unit (HGU) 15.1
human genome organization *15.4*
Human Genome Project 11.1, 15.1
human granulocytic anaplasmosis 30.58
  Sweet's syndrome and 50.76
human herpesvirus 1 (HHV-1) *see* herpes simplex virus (HSV), HSV-1
human herpesvirus 2 (HHV-2) *see* herpes simplex virus (HSV), HSV-2

human herpesvirus 3 (HHV-3) *see* varicella zoster virus (VZV)
human herpesvirus 4 (HHV-4) *see* Epstein–Barr virus (EBV)
human herpesvirus 5 (HHV-5) *see* cytomegalovirus (CMV) infections
human herpesvirus 6 (HHV-6) **33.32–3,** 62.97
  antibodies 33.32, 33.33
  clinical features 33.32–3
  diagnosis and treatment 33.33
  pityriasis rosea and 33.79, 33.81
  reactivation 33.33
human herpesvirus 7 (HHV-7) **33.33,** 62.97
  pityriasis rosea and 33.79, 33.81
human herpesvirus 8 (HHV-8) **33.33–4,** 35.36, 56.33
  latent infection 33.34
  latent nuclear antigen-1 (LNA-1) 56.36
  pityriasis rosea and 33.79
  primary infection 33.34
  tumour development and 33.34
human immunodeficiency virus *see* HIV (human immunodeficiency virus)
human immunoglobulin *see* immunoglobulin(s)
human leukocyte antigens, disease associations *see* HLA associations
human neutrophil peptides 4.5
human papillomavirus (HPV) **33.37–60**
  anal carcinoma and 35.30, 35.39
  anogenital intraepithelial neoplasia and 33.54–5, 33.59, 35.30
  antibodies 33.54
  Bowenoid papulosis and 33.54–5
  Buschke–Löwenstein tumour and 33.46, **33.55**
  cervical carcinoma and 33.39, 33.54, 35.30
  cervical infection 33.39
  cervical intraepithelial neoplasia and 33.54
  clinical conditions by HPV type *33.38*
  diagnosis 33.39
  DNA 33.37
    integration into host chromosome 33.39, 33.54
    in skin cancers 33.55, 52.6
  E6 and E7 proteins 33.39, 33.42, 52.14
  electron microscopy 33.39
  in epidermal dysplasia and neoplasia 33.37, 33.39, **33.54–7**
    treatment 33.55
  epidermodysplasia verruciformis and *see* epidermodysplasia verruciformis (EV)
  expression of signals in keratinocytes 12.16
  genital infection 33.39
    in females 71.55, 71.69, 71.70–1, 71.76
    in males 71.9, 71.20, 71.34, 71.36, 71.38–46
    see also wart(s), anogenital
  genotypes 33.37, *33.38*
    in epidermodysplasia verruciformis 33.57
  in Hailey–Hailey disease 39.35
  high-risk HPVs 33.54, 33.55, 52.5
  in HIV/AIDS 33.59, 35.29–30
  HPV-1 33.37, 33.40, 33.41, 33.43
  HPV-2 33.40, 33.42, 33.47, 33.59
  HPV-3 33.44
  HPV-4 33.59
  HPV-6 33.44, 33.47, 33.55, 35.30
  HPV-7 33.47
  HPV-10 33.44
  HPV-11 33.37, 33.44, 33.47, 33.55, 35.30
  HPV-13 33.47
  HPV-16 33.37, 33.42, 33.54
  HPV-18 33.54
  HPV-32 33.47
  HPV-57 33.47
  HPV-116 35.30
  immunity to 33.42
  in immunodeficiency 17.52, 33.58–9
  in immunosuppression **33.58–60**
  infection sites 33.38, 33.39
  inverted follicular keratosis and 53.2
  latent infection 33.39, 33.47
  in lichen sclerosus 51.116
  low-risk HPVs 52.5
  non-melanoma skin cancer and 52.5–6, 52.14
  occupational infections 33.47
  oncogenesis 33.39
  oral cavity *69.118*
    malignant disease 69.50
    papilloma 69.110–11
  papillomas and 33.37–8
  penile cancer and 35.30
  penile intraepithelial neoplasia and 33.54–5
  perianal intraepithelial neoplasia 33.54–5
  perianal/perineal dermatology and 71.83, 71.94, 71.95, 71.97
  persistent infections 33.57
  in pregnancy 8.11
  prevalence, non-melanoma skin cancers and 52.14
  reactivation, with lichen planus treatment 41.18
  replication in keratinocytes 33.37
  squamous cell carcinoma and 33.55, 52.5, 65.37
  subclinical infection 33.39
  tissue culture difficulties 33.37
  in transplant recipients 33.59
  trichilemmoma and 53.5
  tropism for stratified squamous epithelium 33.37
  tumours associated with 33.37, 33.39, **33.54–7**
    see also specific tumour types
  typing 33.37, 33.41, 52.5–6
  vaccination 33.42
  vulvar intraepithelial neoplasia and 33.54–5
  warts 33.39–54, 65.31
    see also warts
human parvovirus B19 *see* parvovirus B19
human placental lactogen (hPL) 8.9
human secretory-pathway Ca^{2+}/Mn^{2+}-ATPase isoform 1 (hSPCA1) 39.32
human T-lymphotropic virus(es) (HTLV) **33.64–6**
  HTLV-1 *see* human T-lymphotropic virus type 1 (HTLV-1)
  HTLV-2 33.64
  HTLV-3 33.64
  HTLV-4 33.64
human T-lymphotropic virus type 1 (HTLV-1) 33.64–6
  adult T-cell leukaemia–lymphoma (ATLL) and 33.64–6, 57.37–9
  atopic dermatitis and 24.24
  clinical features of infections 33.64–5
  crusted scabies and 38.44
  diagnosis and treatment of infection 33.65
  infective dermatitis of children associated 9.12, 23.25
  myelopathy/tropical spastic paraparesis (HAM/TSP) and 33.64–6
  transmission and replication 33.64
HUMARA gene
  Erdheim–Chester disease 55.18
  Langerhans' cell histiocytosis 55.7
humblebees *see* bees
humectants 26.59, 73.7
humidity, role in irritant contact dermatitis 25.8
humoral response, HIV infection 35.3
Hunter's syndrome *see* mucopolysaccharidoses
huntsmen spiders 38.32
Huriez syndrome (keratoderma with scleroatrophy) *19.94,* 19.99–100
Hurler's syndrome *see* mucopolysaccharidoses
Hutchinson–Gilford syndrome *see* progeria
Hutchinsonian incisors 69.8, 69.78
Hutchinson's lupus 28.65
Hutchinson's melanotic freckle *see* lentigo maligna
Hutchinson's sign 33.26, 54.45, 65.39, 65.40, 67.26
Hutchinson's teeth 34.17
Hutchinson's triad 34.17
HUVS (hypocomplementaemic urticarial vasculitis syndrome) 13.22, 22.19, 50.22
HV *see* hydroa vacciniforme (HV)
hyaline bodies 33.11
hyaline degeneration 10.38
hyalinization, dermal collagen 51.114
hyalinizing spindle cell low-grade fibromyxoid tumour with giant rosettes *see* sarcoma
hyalinosis, systemic
  infantile 45.50
  juvenile hyaline fibromatosis 45.49–50, 69.15
Hyalomma 38.34
hyaluronic acid 3.2, 3.46
  ageing and 80.1
  dermal fillers 80.4, *80.5,* 80.6
  dressings 14.24, 63.10
  functions 3.46, 3.49
  structure 3.45–6, *3.47*
  synthesis 3.45–6
  in wound healing 3.49
hyaluronic acid derivatives, foreign body reactions 28.47
hyaluronidase 38.1, 38.14
hydantoin, hypermelanosis due to 58.29–30
hydatid disease 37.1, 37.3, **37.24–5**
hydralazine, adverse effects 75.96
  vasculitis 50.17, 50.18
hydration, measurement 25.22
hydrazines 25.21
hydroa vacciniforme (HV) *29.10,* **29.15–16,** 29.23, 46.32–3
  diagnosis 29.23
hydrochloric acid
  as irritant *25.19,* 25.20
  neutralization 25.23
hydrocoele, in lymphatic filariasis 37.9–10
hydrocolloid dressings 14.23, 47.48
hydrocortisone 73.16
  contact sensitivity due to 73.17
  development 73.16
  in lichen planus 41.18
  relative absorption levels *73.4*
  sebaceous gland activity and 42.11
  see also cortisol
hydrodissection 77.2, 77.34
hydrofibre dressings 14.23
hydrofluoric acid
  burns 25.11, 25.23, 27.11, 27.12
  as irritant 25.20
hydrogel dressings 14.23
hydrogen peroxide
  as antiseptic 73.14–15
  bleaching hair 66.85, 66.98
  in hair dyes 66.97
  in otitis externa 68.25
  in wound cleansing 14.21
15-hydroperoxyabietic acid 26.79
hydrophilic lipophilic balance (HLB) 73.7
hydropic degeneration 10.38, *10.39*
hydroquinone 27.15, **73.26–7**
  abuse for skin lightening 73.26, 73.27
  adverse effects 75.33, 75.164–5
  exogenous ochronosis and 73.27
  for freckles 58.11
  hypermelanosis treatment 58.38–9
  monobenzylether of 73.27
Hydrous Ointment BP 73.7
hydroxyprolinuria, in sarcoidosis 61.20
4-hydroxyanisole 73.27
hydroxybenzoates 22.26, 73.8
  see also parabens
hydroxycarbamide (hydroxyurea) therapy 47.54–5, 62.86, 74.18
  adverse effects 75.134–5
    lichenoid tissue reaction 41.25
    nail colour changes 65.16, 65.38
    pigmentation 58.55
    ulcer development in sickle cell anaemia 49.47
  dose range and evidence level 74.18
  in myeloproliferative disorders 49.29
  in psoriasis 20.36, 74.18
hydroxychloroquine 13.24, 74.25–6
  adverse effects **75.69–70**
    hypermelanosis 58.30
    ocular 67.31
  in discoid lupus erythematosus 51.20
  in pemphigus foliaceus 40.16
  in SLE 51.61
  in urticarial vasculitis 50.23
25-hydroxycholecalciferol 73.43
hydroxyethyl starch (HES) 21.15, 75.155
  pruritus 28.44
5-hydroxyindole acetic acid (5-HIAA), carcinoid syndrome diagnosis 43.19
11-hydroxylase deficiency 62.7
21-hydroxylase deficiency 62.6–7, 66.83
  partial 42.21
hydroxylysine 3.37, 3.38
hydroxyproline, excretion, collagen degradation 3.40
hydroxyquinolones 26.18
3β-hydroxysteroid dehydrogenase 42.10, 42.12, 66.14
17β-hydroxysteroid dehydrogenase 42.10, 42.12, 66.14
hydroxysteroid dehydrogenases 42.3
5-hydroxytryptamine *see* serotonin (5-HT)
hydroxyurea therapy *see* hydroxycarbamide (hydroxyurea) therapy
hydroxyzine 64.23
  adverse effects 22.29, 75.149
  in urticaria 22.28
Hydrozoa 38.55, 38.56–7
hyfrecation, macrocomedones 42.63, 42.67
hygiene hypothesis 6.17–18, 24.5–6, 24.7
Hylesia 38.29
hymen 71.55, 71.56
Hymenoptera **38.13–15**
  hypersensitivity to 22.8, 38.1, 38.3, 38.14–15
  pheromones 38.2
  venom 38.14
hyper-IgD syndrome 13.7, 22.25
  vasculitis and 50.53
hyper-IgE syndrome *13.13,* 17.76–7
  bacterial infection and 30.8
  bone and joint involvement *62.100,* 62.104
  differential diagnosis 24.26–7
  eczema and 23.27
  in HIV infection 35.16
  oral involvement 69.33, *69.117*
hyper-IgM syndrome, X-linked 13.10, 13.12, 13.23, 17.50, 17.63–4
hyperaemia, management 67.22–3
hyperandrogenism 66.20
hyperbaric oxygen therapy *see* oxygen, hyperbaric therapy
hyperbilirubinaemia 62.64
  phototherapy 58.53
  pigmentation in 58.53
hypercalcaemia 59.68–9
  in HTLV-1 infection 33.65
  in pseudoxanthoma elasticum 45.23
  in sarcoidosis 61.8, 62.71

subcutaneous fat necrosis of the newborn and 17.36
vitamin D causing 73.43
hypercalciuria, in sarcoidosis 61.8
hypercholanaemia, familial 3.25
hypercholesterolaemia 59.84, 59.86–8
hypercoagulation, thrombophlebitis migrans and 47.31
hypercorticism *see* Cushing's syndrome/disease
hypercytokinaemia 55.26
hyperelasticity 4.8
hypereosinophilic syndrome 62.41, 62.87–8
differential diagnosis 24.27
eosinophilic vasculitis and 50.27
oral involvement 69.59
vasculitis and 50.53
hyperferritinaemia 49.6
hypergammaglobulinaemia 49.19
hyperglucagonaemia 62.66–7
hyperglycaemia, in congenital generalized lipodystrophy 46.37
hypergranulosis 10.39
hyperhidrosis **44.7–13**
in adolescence 8.7
asymmetrical 44.8–9
axillary 44.7–8, 44.12, 77.36–7
compensatory 44.9, 44.12, 44.13–14
craniofacial 44.7–8, *44.9*, 44.11
emotional 44.7–8, *44.9*
flushing and 43.15
following spinal cord injury 63.17
generalized 44.7
gustatory 44.10–11, 63.22–3
idiopathic circumscribed 44.9, 44.11
inguinal 71.6
localized 44.8–9
mechanical injury 28.30
nail–patella syndrome and 44.8
olfactory 44.10
palmoplantar 44.7–8, 77.37
palmoplantar keratoderma and 19.95, 44.8
paraneoplastic 62.35–6
in syringomyelia 63.14
treatment 44.10, 44.11–13, 73.9, 77.36–7
hyperhomocysteinaemia 50.54
Hypericum perforatum 72.29, 75.160, 75.162
hyperimmunoglobulin D and periodic fever syndrome 62.104
hyperinsulinaemia 46.7
acne aetiology and 42.20–1, 42.34
hyperirritable skin 27.11
hyperkeratosis
actinic keratosis 52.30
in dermatophytosis 36.22
disseminated superficial 'actinic' porokeratosis 52.35
in eczema 23.4
epidermolytic 10.39–40, 42.78
follicular 10.40, 42.74
histopathology 10.39–40
mechanical injury 28.11, 28.14, 28.15, 28.24, 28.28
nipple and areola 19.93, 70.8–9
oil 27.16
palmar 26.29
palmoplantar, in dermatopathia pigmentosa reticularis 58.20
subungual 51.12, 65.12, 65.15, 65.24
in syphilis 34.11
in viral warts 33.41, 33.42
hyperkeratosis follicularis et parafollicularis in cutem penetrans *see* perforating collagenosis (folliculitis)
hyperkeratosis lenticularis perstans (Flegel's disease) 10.39, 19.89–90
hyperkeratotic psoriasis 15.11
hyperlipoproteinaemias
Fredrickson classification 59.83
HIV lipodystrophy 46.42
type I 59.90
type III 59.88–9
type IV 59.91
type V 59.90
WHO classification 59.83
hypermelanosis *see* hyperpigmentation
hyperoxaluria 49.37, 50.54
absorptive 49.37
primary 49.37
secondary 49.37
hyperparakeratosis 69.93, 69.94
hyperparathyroidism **62.12**
calciphylaxis (calcific uraemic arteriolopathy) 47.8
pruritus and 21.8
secondary/tertiary, in calciphylaxis 49.47
hyperphenylalaninaemia syndromes 59.94–6
non-PKU 59.96
see also phenylketonuria (PKU)
hyperpigmentation 58.9, **58.10–39**
acquired *58.38*
in acromegaly 62.2
in acromelanosis 58.21
ACTH administration and 58.25
in actinic lichen planus 41.12–13
in Addison's disease 58.7, 58.24, 62.5–6
aetiology *9.4*, *25.2*
in amyloidosis 58.28
in anaemia 58.27
anogenital 71.2–3
in Becker's syndrome 58.21
in Cantú's syndrome 58.20
in carcinoid syndrome 58.25
in Carney complex 69.28
in chronic venous insufficiency 47.33
in contact dermatitis 26.26
in Cronkhite–Canada syndrome 58.13
in Cushing's syndrome 58.24
cutaneous lesion associated 58.38
in dermatomyositis 58.27
in dermatopathia pigmentosa reticularis 58.20
differential diagnosis 58.38
diffuse progressive, in mycosis fungoides 58.26
in disseminated superficial 'actinic' porokeratosis 52.35
drug-induced 58.29–30, 75.28, 75.32–3, 75.52–3
in dyskeratosis congenita 58.21
in endocrine diseases 58.24–5
ephelides *see* freckles
facial 58.12, 58.25, 58.34–8
management 73.28
see also melasma
familial progressive 58.19
in Fanconi's anaemia 58.17
female genital dermatology 71.79–80
following chemical peel 80.9
following cryosurgery 77.40
in Gaucher's disease 58.24
generalized, in HIV infection 35.12
genetic causes 58.9, *58.38*
gingival 69.13
in haemochromatosis 58.28
hands and feet, acromelanosis 58.21
hereditary disorders with 58.19
in HIV infection 35.12
in hyperthyroidism 58.24, 62.8
hypomelanosis occurring with 58.31, 58.33
incontinentia pigmenti *see* incontinentia pigmenti (IP)
interscapular skin 58.31
lentigines *see* lentiginosis
lichen planus 41.13
in liver disease 62.64
in lymphomas 58.26
in malabsorption syndromes 58.28
in McCune–Albright syndrome 58.18
mechanical injury 28.15, 28.28, 28.31
in megaloblastic anaemia 62.85
melasma-like 58.34
in Mendes da Costa–van der Valk syndrome 58.20
menstruation and 58.25
in morphoea 58.26
mucocutaneous 58.12
in multiple organ failure 58.27
in Naegeli's syndrome 58.19
in Nelson's syndrome 62.4
in neoplastic diseases 58.25
in nervous system diseases 58.26
in neurofibromatosis 58.23
in Niemann–Pick disease 58.24
oral cavity 9.3, 58.12, 69.21–2, 75.47
oral contraceptives and 58.25, 75.33
palms and soles 9.2, *9.3*
paraneoplastic 62.33, *62.34*
in pellagra 58.28
periorbital 58.19
persistent post-inflammatory, in acne 42.33
in Peutz–Jeghers syndrome 58.12
in phaeochromocytoma 58.25
photodynamic and phototoxic reactions 58.32
in pityriasis versicolor 36.11
post-inflammatory 5.16–17, *9.4*, 9.5, 26.26, 58.7, 58.29, 58.30–1, 58.35, 71.2–3
treatment 73.26, 73.27
in pregnancy 58.25
in primary biliary cirrhosis 58.28
progressive cribriform and zosteriform 18.18
in prurigo pigmentosa 23.44–5
in renal failure 58.27, 62.72
reticulate
acropigmentation 58.21–2
poikiloderma of Civatte 58.35
zosteriform 58.22–3
in rheumatoid arthritis 58.26
in sarcoidosis 61.14
in scleroderma 58.26
in SLE 58.27
in Still's disease 58.26
in systemic disorders 58.25–9
in systemic sclerosis 58.26
tanning *see* tanning
treatment 58.38–9
acquired hypomelanosis due to 58.50
retinoic acid 73.36
urticaria pigmentosa with 58.38
in Vagabond's disease 58.28–9
in vitamin A deficiency 58.28
in Werner's syndrome 58.23
in xeroderma pigmentosum 58.24
see also melanosis; pigmentation
hyperpituitarism 62.2
sweating in 44.7
hyperplasia
intravascular papillary endothelial 69.102
mechanical injury 28.11
sebaceous gland, female genital dermatology 71.55
squamous, male genital dermatology 71.37
UVR-induced 29.5
verrucous, mechanical injury 28.28
hyperprolactinaemia 66.83
acne 42.12
hyperpyrexia
in anhidrosis 44.13
in HSAN V 63.19
hypersensitivity angiitis *50.4*, **50.13–17**
hypersensitivity reactions
in animals, comparison with humans *2.21*
classification 13.12, *13.14*
tattoos 28.48
type I (immediate)
in atopic eye disease 67.15
see also allergy
type II *13.14*
type III (immune complex) *13.14*
urticaria as 22.18
urticarial vasculitis as 50.22
in viral infections 33.3
type IV (delayed-type) *13.14*, 26.25
acne pathogenesis 42.25, 42.27
actinic prurigo 29.14
chronic, acne scarring and 42.27
induction phase 29.11
polymorphic light eruption 29.9, 29.11
Propionibacterium acnes role/effect 42.7
reduced in obesity 8.17
role of macrophages 13.5
tests 13.22
types 26.5
types 26.5
hypersplenism, in sarcoidosis 61.7
hypertelorism *67.4*
hypertension
raised leptin levels and 46.7
in SLE 51.43
in Takayasu's arteritis 50.45
venous 23.35–6
venous leg ulcers and 47.43
hypertensive ulcers 47.52–4
hyperthyroidism **62.7–10**
flushing associated 43.16
hair in 66.28, 66.78
hyperpigmentation in 58.24–5
pruritus in 21.11
sarcoidosis and 61.17
sweating in 44.7
hypertrichosis **66.75–80**
acquired generalized 66.77–9
acquired localized 66.79–80
in Berardinelli's syndrome 66.76
congenital 71.84
congenital generalized 66.75–7
lipodystrophy 46.37
congenital localized 66.77
congenital macrogingivae and 66.76
in Cornelia de Lange syndrome 66.76
definition 66.75
dermatomyositis and 66.78
drug-induced 66.79, 75.45
minoxidil 73.49, 73.50
in eating disorders 66.78
with epidermolysis bullosa 66.78
equine 2.18, *2.19*
external auditory canal/meatus 68.18, 68.21
in fetal alcohol syndrome 66.77
in hyperthyroidism 66.78
in hypothyroidism 66.78
iatrogenic 66.79
laser therapy 78.12–13
lumbosacral 66.77
in malnutrition 66.78
in mucopolysaccharidoses 66.76
naevoid 66.77
pinna 68.1, *68.2*, 68.5
see also ear(s), hairy
in porphyria 66.79
in pregnancy 8.10
in spinal dysraphism 63.15
in trisomy 18 66.77
universal 66.76
in Winchester syndrome 66.76
see also hirsutism
hypertrichosis and dental defects 15.42
hypertrichosis lanuginosa 66.75–6
acquired 66.77–8
paraneoplastic 62.35
hypertriglyceridaemia(s) 59.84
in congenital generalized lipodystrophy 46.37
see also hyperlipoproteinaemias
hypertrophic osteoarthropathy 15.87, **15.88–9**
hypertrophic scarring, burns 28.84, *28.88–9*
hyperviscosity disorders, purpura in 49.4, 49.5
hyphae 36.2, *36.3*
aerial 36.9
extrapilary 36.20
Hyphomycetes 36.4

hypnosis 64.54
  for surgical procedures 77.11
  wart treatment 33.50
hypnotics 75.80–2
hypoadrenalism *see* Addison's disease
hypoalbuminaemia, in erythroderma 23.49
hypocalcaemia 62.12
hypochlorous acid 13.4
hypochondriasis 64.12
hypocomplementaemia
  partial lipoatrophy and 46.39
  in urticarial vasculitis 22.18, 22.19, 50.22
hypocomplementaemic urticarial vasculitis syndrome (HUVS) 13.22, 22.19, 50.22
hypocorticism *see* Addison's disease
Hypoderma 38.9, 38.10
hypodermatitis sclerodermaformis 46.30–1
hypodontia 69.6, 69.7
  nail dysgenesis with 69.6
  taurodontism and sparse hair with 69.10
hypogammaglobulinaemia
  echovirus infections and 33.73
  eczema and 23.27
hypoglossal palsy 69.6
hypoglycaemia, sweating in 44.7
hypogonadism 8.5
  delayed puberty 8.6
  genetics 15.81
hypohidrosis **44.13–15**
hypohidrotic ectodermal dysplasia (HED) 15.28, 15.43
  deafness and 15.44
  differential diagnosis 15.81
  in dogs 2.18, 2.20
  hypothyroidism and agenesis of the corpus callosum and 15.44
  hypothyroidism and ciliary dyskinesia and 15.44
  immune deficiency, osteopetrosis and lymphoedema with 15.44, **15.60**
  immune deficiency and 15.43, **15.60**
  mutations in TNF-like/NF-kB signalling pathways **15.58–60**
  papillomas and acanthosis nigricans with 15.44
hypomagnesaemia, familial 3.25
hypomastia 70.2, 70.3
hypomelanosis *see* hypopigmentation
hypomelanosis of Ito 58.45, *62.100*
hypomelanotic macules of tuberous sclerosis 58.44
hypomelia–hypotrichosis–facial haemangioma syndrome 18.70, 66.61
hyponychium 3.15, 65.2, 65.46
hypoparathyroidism **62.12**
  candidiasis and 36.58
hypophosphatasia *69.117*
hypopigmentation 58.9, **58.39–53**
  acquired 58.50–3
    causes *58.51*
    chemical depigmentation 58.50–1
  in actinic lichen planus 41.12–13
  aetiology 9.4, *25.2*
  along Blaschko's lines 58.45
  anogenital 71.2–3
  in Chédiak–Higashi syndrome 58.41
  in contact dermatitis 26.26, *26.27*
  corticosteroid-induced 73.17
  in disseminated superficial 'actinic' porokeratosis 52.35
  drug-induced 75.33
  eyelids 67.5
  female genital dermatology 71.79
  following chemical peel 80.9
  following cryosurgery 77.40
  following patch/photopatch testing 26.94, *26.95*
  genetic and naevoid disorders 58.39–50
  halo, in halo naevus 58.49–50
  hypermelanosis occurring with 58.31, 58.33
  idiopathic guttate 9.11, 58.52
  in inflammatory disorders 58.52
  of Ito 58.45, *62.100*
  in liver disease 62.64
  male genital dermatology 71.49
  in mycosis fungoides 9.7
  in napkin dermatitis 17.25
  occupational 27.1, 27.15
  in onchocerciasis 37.5–6
  paraneoplastic *62.34*
  in pityriasis versicolor 36.11
  post-inflammatory 9.5–6, 26.26, 58.51–2, 71.2–3
  in sarcoidosis 61.14
hypopituitarism 62.2–3
  in sarcoidosis 61.7
hypoplasminogenaemia 69.15, 69.59
hypoproteinaemia 66.29
  venous leg ulcers 47.43
hypopyon *67.4*
hypopyon ulcers *67.9*
hyposensitization
  adverse effects 75.140–1
  in allergic contact dermatitis 26.102
hyposteatosis 23.6
hypotension, pressure ulcers 28.18
hypothalamic–pituitary–adrenal (HPA) axis 64.8, 64.9
hypothalamo–pituitary–gonadal axis
  normal 8.4
  premature puberty 8.5
hypothenar hammer syndrome **28.26,** 28.56, 50.54
hypothermia, erythroderma and 23.49
hypothyreosis erythema migrans 62.106
hypothyroidism **62.10–12**
  candidiasis and 36.58, 36.65
  hair loss in 62.10, 66.28, *66.29*
    in animals 2.18
  hypertrichosis in 66.78
  palmoplantar keratoderma with myxoedema 19.118
  pruritus in 21.11
  sarcoidosis and 61.17
  thermal injury 28.72–3
hypotrichosis
  congenital 66.60–1
  disorders of amino acid metabolism and 66.61
  eyelid cysts and hypodontia with 66.61
  hypomelia–hypotrichosis–facial haemangioma syndrome 66.61
  keratosis pilaris with 66.60
    lentiginosis and 66.60–1
  localized autosomal recessive 66.67
  Marie–Unna hereditary 66.60
  resulting from short anagen 66.60
hypotrichosis-osteolysis-periodontitis-palmoplantar keratoderma syndrome 15.45
hypotrichosis simplex 66.60
hypotrichosis–lymphoedema–telangiectasia syndrome 48.10
hypovolaemic shock, burns 28.77
hypoxanthine guanine phosphoribosyl transferase (HGPRT) 59.102, 74.14
hypoxia-inducible factor-1a 14.6
hysteria 64.25–6
hystrix-like ichthyosis with deafness (HID) syndrome 15.46

I

I cell disease 59.32
iatrogenic swelling, male genital dermatology 71.49–50
iatrogenic vaginal discharge 71.53
IBIDS/PIBIDS syndrome 19.47–9
ibuprofen *26.46,* 75.74
ibuproxam *26.46*
ICAM-1 *see* intercellular adhesion molecule-1
icatibant 22.21, 22.22
ICDRG (International Contact Dermatitis Research Group) 26.2
ICE (IL-1alpha converting enzyme) 12.43, 12.49
'ice-pick' marks 52.8
ice provocation test 27.17
ICE syndrome 19.61
ICF syndrome 17.65
ichthammol (Ichthyol) 73.42
  in eczema 23.38
ichthyoses, congenital **19.3–63**
  bullous ichthyosiform erythroderma 19.3, 19.29–34
    see also bullous ichthyosiform erythroderma (BIE)
  CHILD syndrome 18.27, 19.3, 19.57–8
  CHIME syndrome 19.60
  collodion babies **17.19–21,** 19.13–17, 59.39
  Conradi–Hünermann–Happle syndrome *16.3,* 19.3, 19.49–52
  harlequin 19.25–9
  HID syndrome 19.36, 19.37, 19.54–7
  IBIDS/PIBIDS syndrome 19.47–9
  ichthyosis bullosa of Siemens 19.3, 19.34–5
  ichthyosis follicularis with alopecia and photophobia 19.58–9, 19.60
  ichthyosis hystrix 19.3, 19.35–7, 19.99
  ichthyosis vulgaris 19.6–9
  KID syndrome 19.54–7, 19.60
  lamellar 19.3, 19.21–5
  multiple sulphatase deficiency 19.13
  Netherton's syndrome 19.3, 19.37–42
    see also Netherton's syndrome (NS)
  Neu–Laxova syndrome 19.59–60
  neutral lipid storage disease with 19.52–4
  non-bullous ichthyosiform erythroderma 19.17–21
  Refsum's disease 19.3, 19.45–7
  Sjögren–Larsson syndrome *16.3,* 19.3, 19.42–5
  sporadic genetic syndromes with 19.60–3
  X-linked recessive 19.3, 19.9–13
ichthyosis
  acquired (late-onset) 19.63–5, 62.32
  anhidrosis and 44.13
  autosomal dominant, genetics 15.5
  congenital *see* ichthyoses, congenital *(above)*
  harlequin 11.13, 17.20
    prenatal diagnosis *16.3,* 16.6, 16.7
  in HIV infection 35.11–12
  ichthyosiform atrophy 57.63
  lamellar *see* lamellar ichthyosis (LI)
  malabsorption 59.58
  X-linked *see* X-linked ichthyosis
ichthyosis bullosa of Siemens 19.3, 19.34–5
ichthyosis follicularis, atrichia and photophobia (IFAP) syndrome 15.45
ichthyosis follicularis with alopecia and photophobia (IFAP) 19.58–9, 19.60
ichthyosis hystrix 19.3, 19.35–7, 19.99
  HID (hystrix ichthyosis and deafness) syndrome 19.36, 19.37, 19.54–7
  of Rheydt 19.37
ichthyosis linearis circumflexa (ILC) 19.37, 19.39, 19.40, 19.41
  see also Netherton's syndrome (NS)
ichthyosis prematurity syndrome 19.18–19
ichthyosis vulgaris 3.8, 4.2, 19.6–9, 24.22
  genetics 15.5
  skin biopsy 10.42
ichthyotic scale 5.7
icodextrin 75.99
ICOS (inducible co-stimulator) 13.11
icterus *see* jaundice
'id' eruption 47.34
idiopathic acquired anhidrosis 44.13
idiopathic facial aseptic granuloma 43.14
idiopathic guttate hypomelanosis 58.52
idiopathic lipogranuloma, male genital dermatology 71.50
idiopathic midline destructive disease 69.58
idiopathic multiple pigmented sarcoma *see* Kaposi's sarcoma
idiopathic nodular panniculitis 46.13–14
idiopathic sclerosing lipogranuloma 46.29, 46.30
idiopathic thrombocytopenic purpura (ITP) 49.1, **49.9–11**
  drug-induced 49.9
  in pregnancy 49.12
  remission and treatment 49.10
  viral infection associated 49.9, 49.10
idoxuridine 73.15
  action 74.49
  adverse effects *26.46,* 75.66
  orf 33.9
  topical, herpes simplex 33.21
IFAP syndrome 15.45
Ig *see* immunoglobulin(s)
IGF-1 *see* insulin-like growth factor-1 (IGF-1)
IGF-2, sebaceous gland activity and 42.11
Iggo discs 3.16
ileostomy *see* stoma
ileoumbilical fistula 71.100
iliac compression syndrome 47.32
iliac thrombosis 47.28
iloprost 14.24, 47.6
ILVEN (inflammatory linear verrucous epidermal naevus) 18.19–21, 20.17
imatinib 66.94, 75.132
imidazoles
  adverse effects *26.46*
  in candidiasis 36.68, 36.69
  corticosteroids with 73.12
  in dermatophytosis *36.47,* 36.48, 36.49
  in otitis externa 68.25
  topical 73.12
imidazolidinyl urea *26.50,* 26.51–2
iminodipeptiduria 47.54
imipenem 74.40
imipramine *64.51,* 75.33, 75.79
imiquimod
  adverse effects 75.147–8
    lip ulceration 54.43
  in basal cell carcinoma in HIV infection 35.39–40
  in Bowen's disease 52.34
  in granuloma annulare 60.10
  in infantile haemangioma 18.52
  in lentigo maligna 54.43
  topical therapy 73.24
  wart treatment 33.49–50
immediate pigment darkening (IPD) 58.31
immersion foot **28.64**
immigrants, latent syphilis diagnosis 34.12
immobility acne 42.76
immobilization
  lymphoedema and 48.14
  pressure ulcers and 28.18, 28.21
immune complex(es) 26.25
  adverse drug reactions mediated by 75.17
  circulating, viral infections 33.3
  in cutaneous small vessel vasculitis 50.13
  in hepatitis B virus infection 62.59
  hypersensitivity *see* hypersensitivity reactions, type III (immune complex)
  in leprosy 32.7
  pigmented purpuric dermatoses and 49.22
  in polyarteritis nodosa 50.33
  role in purpura 49.18
  role in vasculitis 22.18, 22.19, 49.18, 50.4–5, 50.5

type II/III cryoglobulins 49.32
vasculitis *see* vasculitis
immune-mediated disease
in animals 2.14–16
see also specific diseases
immune privilege, alopecia areata and 66.32
immune reconstitution (inflammatory) syndrome/immune restoration disease (IRIS/IRD) 35.46
immune response
adaptive
suppression by UVR 29.6
see also immunity, acquired
ageing and 8.24
in HIV infection 35.3–4
innate
stimulation by UVR 29.6, 29.7
see also immunity, innate
modifiers, topical, non-melanoma skin cancer 52.17
primary 13.6
secondary 13.6
stimulation, molluscum contagiosum therapy 33.13
wound healing and 14.2–4
immune surveillance 3.18–19
altered, malignancy after lymphoedema 48.15
immune system 17.48–51
adaptive
activation *3.18*
see also immunity, acquired
ageing and 13.15
in atopic dermatitis 24.6–10, 24.13–15
defects
ichthyosis 19.61
pityriasis rubra pilaris 19.79
deficiency *see* immunodeficiency
dynamic nature of 13.6
hair cycle and 66.11
hygiene hypothesis 24.5–6, 24.7
immune surveillance 3.18–19
in infancy and childhood 13.15
innate (non-adaptive) *see* immunity, innate
integration of parts *13.2*
interaction with nervous system 63.4
Langerhans' cells 3.17–18
lichen planus pathogenesis 41.1–2
lymphatic system function 48.6, 48.29
malignant disease and 13.15
mast cell functions 3.20
microbial recognition 12.8–9
oral cavity 69.3
psychological effects 64.8–9
skin 2.8, **3.16–19**
structure and function **13.1–11**
suppression *see* immunosuppression
UVR-induced changes 29.5–6, 52.14
see also immunity
immune thrombocytopenic purpura *see* idiopathic thrombocytopenic purpura (ITP)
immunity
acquired **13.6–11,** 17.49–51
adverse drug reactions and 75.17–21
in candidiasis 36.58
components 13.6–7
disorders 17.57–70
in leprosy 32.3, 32.7
in sarcoidosis 61.5–6
tests of 17.56–7
to arthropod bites/stings 38.1
innate 3.16–17, 12.5, **13.1–6,** 17.48–9
in acne pathogenesis 42.25, 42.26
in atopic dermatitis 24.13–14
cellular components 13.4–6
defects 17.73–82
non-specific defence mechanisms 13.1–2
soluble factors 13.2–4
tests of 17.55–6
in pregnancy 8.11
immunization granulomas 28.45
immunoadsorption 13.25
pemphigus 40.12
immunoblotting 10.18
immunobullous diseases **40.1–62**
desmosomes as autoantigens 3.22, *3.23*
intraepidermal 40.3–24
intraepithelial *67.17*
mixed 40.49
ocular complications *67.17*
treatment 67.22–3
subepidermal *see* subepidermal immunobullous diseases
subepithelial *67.17*
conjunctivitis 67.20
immunochemistry 13.16–19
immunocytochemistry, sebaceous glands 42.3–5
immunocytoma 57.43
immunodeficiency **13.11–12**
candidiasis and 17.66–7, 36.59
cellulitis/erysipelas and 30.18
classification of disorders 17.51
CMV infection in 33.29
diagnosis 17.51–7
DNA repair defects and 17.67–70
due to abnormal B-cell development 13.8
examination 17.54
genetics 17.51
herpes simplex in 33.15, 33.17, 33.18, 33.20
history-taking 17.51–3
HPV infections in 17.52, 33.58–9
infection and 17.54–5
see also specific infections
laboratory investigation 17.54–5
mice 2.7–8
non-infectious non-specific manifestations 17.53–4
oral manifestations *69.117*
primary 13.11, 13.12, *13.13*
cutaneous features *17.54*
neonatal disorders 17.48–85
warts and HPV infections in 33.59
secondary 13.11, 13.12, *13.14*
short-limbed dwarfism and 17.64–5
varicella and zoster in 33.23, 33.24, 33.25, 33.27
warning signs *17.55*
warts in 17.52, 33.58–9
see also specific immunodeficiency disorders
immunoelectron microscopy 10.18
immunoenzyme (immunoperoxidase) methods
applications 10.18–28
techniques 10.15–18
immunofluorescence mapping, epidermolysis bullosa (EB) 39.1–2
immunofluorescence methods 13.19
applications 10.18–28
techniques 10.12–15
immunofluorescence microscopy
EB simplex 39.4
junctional EB 39.10
immunogenotyping 10.30
immunoglobulin(s) 13.7
absence from dermal–epidermal junction 51.92
assay 17.56
C domains 17.49
D (diversity) segment 17.49
heavy (H) chains 17.49
intravenous *see* intravenous immunoglobulin (IVIg)
joining (J) segment 17.49
light (L) chains 17.49
measurement 13.16–17
monoclonal 13.17
patterns *13.17*
receptors
FceR1, in atopic dermatitis 24.14
FceRIa 22.4
FceRIb, in atopic dermatitis 24.3
in sarcoidosis 61.5, 61.6
structure 17.49
superfamily 12.73–5
V domains 17.49
immunoglobulin A (IgA) 13.7
adhesion complex 40.46
in atopic dermatitis 24.9–10, 24.12
deficiency 13.7, 17.73, 69.3
selective *69.117*
in dermatitis herpetiformis 40.59
dermatosis 40.19–22
clinical features 40.4, 40.20
pathogenesis 40.19–20
pathology 40.19
treatment 40.20
see also linear IgA disease
in Henoch–Schönlein purpura 50.20
IgA1 13.7
IgA2 13.7
immune complexes 49.18
myeloma 49.13
immunoglobulin A (IgA)-mediated epidermolysis bullosa acquisita 40.55
immunoglobulin D (IgD) 13.7
immunoglobulin E (IgE) 13.7
allergen-specific 13.16
anti-IgE antibodies 51.104
in atopic dermatitis 24.3, 24.4, 24.5, 24.8–9
in atopic eye disease 67.15
in contact urticaria 27.5
detection of antibodies 5.23–4
mast cell activation 3.20
measurement 13.16
receptors 13.5
in sweat 44.6
synthesis, dysregulation in HIV infection 35.16
tests for drug-specific antibody 75.173–4
total level 13.16
urticaria and 22.7–8
immunoglobulin G (IgG) 13.7
anticardiolipin antibody, SLE 51.63
in atopic dermatitis 24.9
autoantibodies 40.26, 40.47, 40.52
in bullous pemphigoid 40.30
in epidermolysis bullosa acquisita 40.52
in mucous membrane pemphigoid 40.36
in heparin-induced thrombocytopenia 49.27
receptors, IgG–antigen complexes 12.32
in Sjögren's syndrome 13.7
subclasses 13.7
immunoglobulin M (IgM) 13.7
cold agglutinin-related cutaneous occlusion 49.34
immunohistochemistry, melanoma 54.49
immunological functions of skin 4.1, 4.8–9
immunological tolerance 13.29–30, 26.12
immunomodulators **73.31–4,** 74.25–30, 75.136–8
topical, wart treatment 33.49–50
immunopathology 10.11–28
immunophilins 73.17, 74.18
immunorestoration, in HIV infection 35.46
immunosuppression
adverse drug reactions and 75.6–7
in atopic dermatitis 21.13
in atopic eye disease 67.16
cicatrizing conjunctivitis 67.22–3
cold-induced injury 28.71
crusted scabies and 38.43–4
cutaneous manifestations 75.123–4
eczema herpeticum and 33.35
for eyelid diseases 67.5
female genital dermatology and 71.64, 71.69
follicle mite infection and 38.53
for idiopathic thrombocytopenic purpura 49.10
internal malignancy and 62.47
male genital dermatology and 71.39, 71.41
Merkel cell carcinoma association 53.42
molluscum contagiosum and 33.11
mucous membrane pemphigoid and 67.20
non-melanoma skin cancer association 52.11, 52.14
in ocular features of immunobullous disorders 67.22–3
reaction to arthropod bites/stings and 38.2
in sarcoidosis 61.21
seborrhoeic dermatitis and 23.29
squamous cell carcinoma and 52.26–7
systemic 13.27–8, *13.29*
UV-induced 8.22, **13.26–34,** 26.10
reduced by sunscreens 73.41
immunosuppressive therapy
Darier's disease 19.85
Netherton's syndrome 19.41
non-bullous ichthyosiform erythroderma 19.19
non-specific 74.14–24
pityriasis rubra pilaris 19.79
SLE 51.61
immunotherapy **13.23–6**
adverse effects *26.46,* **75.138–41**
alopecia areata 66.37
in hand eczema 23.22
Hymenoptera venom 38.15
in latex sensitivity 26.106
melanoma metastatic to brain 54.55–6
urticaria 22.29–30
Impact of Psoriasis Questionnaire (IPSO) 72.20
impairment 6.5
imperforate hymen 71.56
impetiginization, eczematous dermatitis 47.34
impetigo 4.5, **30.14–17**
bacteriology 30.14
bullous 30.14
bacteriology 30.14
clinical features 30.15
desmoglein 1 (Desg1) disruption 3.22
epidemiology 30.14
neonatal 17.42, 30.14
pathology 30.14–15
canine 2.11–12
clinical features 30.15
complications 30.15–16
definition 30.14
differential diagnosis 36.27
epidemiology 30.14
eyelids 67.26
follicular of Bockhart 30.22
herpes labialis and 69.72, *69.73*
non-bullous (impetigo contagiosa of Tilbury Fox) 30.14, 30.15
pathology 30.14–15
renal involvement 62.71
in scabies 38.39
treatment 30.16, 73.10
impetigo herpetiformis 8.12
genitocrural dermatology 71.5
implantable defibrillators 62.79
implantation, foreign body reactions 28.46–7, 28.50, 28.52
imprinting, genomic 15.6
in situ hybridization 11.9
incense cedar *26.80*
INCI (International Nomenclature of Cosmetic Ingredients) 26.24, 26.41, 26.48
incidence 6.11, 6.18
definition 26.2
incisional biopsy, panniculitis 46.11
inclusion bodies
eosinophilic 10.29
sarcoidosis 61.4

incontinentia pigmenti (IP) 15.45, 17.81–2, 48.10, 58.15, **58.15–17,** 58.16
  aetiology and genetics 58.15
  alopecia in 66.51
  bone and joint involvement *62.100*
  clinical stages and features 58.15–16
  dental involvement 69.6
  extra-cutaneous features 58.16, *58.17*
  familial male-lethal type 15.45
  gene 58.15
  genetics 15.6, 15.13
  histopathology 10.41
  oral involvement 69.95
  pathology 58.15
  subungual keratotic tumours 65.38
  treatment 58.16
incontinentia pigmenti achromians of Ito 58.45
indandiones 75.105
indentation tests, mechanical injury 28.5
indentometry 4.11
indeterminate cells 55.3
Indian sandal dermatitis 26.68
Indian tick typhus 30.73
indinavir 75.68–9
  adverse effects 45.5
    photosensitivity 35.22
indirect immunofluorescence, ocular mucous membrane pemphigoid 67.19
indium 26.40
indometacin (indomethacin) 75.76
  dermatomyositis 51.129
  isotretinoin interaction 42.65
inducible co-stimulator 13.11
infancy and childhood
  acute haemorrhagic oedema of childhood/infancy 17.33–4, 50.30
  adverse drug reactions 75.6
  allergic contact dermatitis 26.8–9
  atopic dermatitis 24.19–21
  bacterial skin flora 30.4
  dermatomyositis 62.99
  fibrous hamartoma 56.6
  immune system 13.15
  longitudinal melanonychia 65.39
  myofibromatosis 56.9
  nails 65.6–7
    ingrowing 65.6–7, 65.53
  nomenclature 17.1
  periodontitis 69.18
  psoriasis 17.31–2
  sarcoidosis 61.16
  scabies 38.39–40, 38.42
  seborrhoeic dermatitis **17.28–31,** 23.29, 23.34, 24.22, 24.26
  subcutaneous fat necrosis following hypothermic cardiac surgery 17.37–8
  Sweet's syndrome 50.63
  urticaria 22.6–7
  wound healing 14.2
  see also children; infant(s)
infant(s)
  epidermolysis bullosa (EB)
    Herlitz junctional 39.12
    management 39.27–8
  epidermolysis bullosa (EB) simplex
    Dowling–Meara form 39.7
    generalized 39.6
  normal bacterial skin flora 30.4
  skin and skin disease **8.1–4**
  topical therapy
    corticosteroid adverse effects 73.20
    quantities *73.3, 73.4*
  see also infancy and childhood
infantile acne 42.75–6
infantile gluteal granuloma 17.27–8, 71.91, 73.18
infantile neuronal ceroid lipofuscinosis, prenatal diagnosis *16.3*
infantile Refsum's disease 19.46
infantilism 8.3
Infant's Dermatitis Quality of Life Index (IDQOL) 72.23
infection(s)
  in animals 2.9–13, *2.21*
  atopic dermatitis and 24.12–13, 24.24
  Behçet's disease and 50.56
  bone and joint involvement *62.100,* 62.105
  children 8.3
  cryoglobinulinaemia with 49.32
  diabetic foot ulcers 47.57–8
  ear 68.18–28
  exacerbation, corticosteroids associated 73.18
  eyes 67.24–8
  Henoch–Schönlein purpura and 50.20
  in HIV infection **35.24–36**
    see also individual infections
  immunodeficiency and 17.54–5
  intrauterine 18.2, 18.102
  leg ulcers due to 47.56–7
  in lymphoedema 48.12, 48.15, 48.24
    prevention 48.22, 48.24
  microvascular occlusion due to 49.34–6
  neonatal 17.39–48
  panniculitis 46.27–8
  pigmented purpuric dermatoses due to 49.23
  in pregnancy 8.11
  purpura associated 49.20–1
  respiratory tract 62.80
  risk factors 6.12–13
  secondary thrombocytopenia due to 49.11
  Sweet's syndrome and *50.75*
  tattoos and 58.58
  in transplantation recipients 62.74
  urticaria and 22.2, 22.8, 22.10, 22.11
  vasculitis and 50.5–6, 50.49, 50.55–6
  venous leg ulcers 47.44, 47.49
  see also bacterial infection; fungal infections; viral infection; *specific infections*
infection phobias 64.24
infectious mononucleosis
  acne after 42.79
  ampicillin reaction 75.15, 75.49
  CMV causing 33.29
  EBV causing 33.30
  HHV-6 associated 33.32
infective eczematoid dermatitis 68.19
infective vaginal discharge 71.53
infertility, sexually transmitted diseases causing 34.1
inflammasome NALP-3 12.4
inflammation **12.1–77**
  acne pathogenesis 42.24, 42.25–6
    topical drugs affecting *42.40*
  adiponectin action 46.4
  cell apoptosis and 12.11–12
  cellular components 12.14–15
  clinical features 12.2–5
  cryopyrin-associated autoinflammatory syndromes 74.11
  drug absorption increase 73.4
  histopathological features 12.3
  hypermelanosis after 58.29, 58.30–1
  hypomelanosis and 58.51–2
  lipoatrophia semicircularis and 46.36
  lymphoedema and 48.8, 48.12–13
  major histocompatibility complex and 12.13
  mechanical injury 28.31
  mediators of 12.33–67
    acute-phase proteins 12.34
    keratinocytes 12.15–17
    lysosomal 12.53
    in pigmentation regulation 58.7
    tumour necrosis factor 74.5
    UVR-induced damage and 29.5
    see also specific mediators
  neurogenic 63.2
    atopic dermatitis 12.63
    non-specific post-inflammatory pigmentation 58.29
  phases 12.1–4
  platelets in 12.33
  recurrent episodes (recurrent cellulitis) 48.29
  of subcutaneous fat 46.10–11
    see also panniculitis
  UVR exposure as cause 29.5
  vasculature and 12.68
  wound healing and 14.2–4
  see also inflammatory dermatoses; inflammatory response; *specific inflammatory disorders*
inflammatory bowel disease
  ocular involvement *67.25*
  TNF antagonists 74.7
inflammatory bubo 34.7
inflammatory dermatoses
  acitretin therapy 74.36
  female genitalia 71.58–65, 71.66
  genitocrural 71.4–6
  in HIV infection 35.13–15
  male genitalia 71.16–29
  perianal/perineal 71.84–91
  in pregnancy 8.13–15
  umbilical 71.101
  see also specific inflammatory dermatoses
inflammatory linear verrucous epidermal naevus (ILVEN) 18.19–21, 20.17
inflammatory myxohyaline tumour of the distal extremities with virocyte or Reed–Sternberg-like cells 56.15
inflammatory response 12.1–2
  acute phase (first 6 h) 12.2–3
  in basal cell carcinoma 52.21
  chronic phase 12.4
  exaggerated, complex regional pain syndrome 47.10, 47.11
  in premalignant epithelial lesions 52.29
  in squamous cell carcinoma 52.25, 52.26
  to *Treponema pallidum* 34.4, 34.7
  vasodilatation 12.4
  see also inflammation
inflammatory vaginal discharge 71.53–4
infliximab 13.25, 74.5
  adverse effects 75.145
  chimeric human–murine monoclonal antibody 12.42, 74.5
  clinical indications 74.6
  in cutaneous small vessel vasculitis 50.16
  dose range and evidence level 74.6
  in granuloma annulare 60.11
  in pemphigus 40.6, 40.12
  in psoriasis 20.41, 72.14, 74.5
    in HIV infection 35.17
  in pyoderma gangrenosum 50.72
  in sarcoidosis 61.21
influenza viruses 33.75
information technology, prescribing pathway 72.26
infraorbital nerve 77.2, *77.4,* 77.10
infrared coagulation 77.47
  nail unit 65.48
  wart treatment 33.49
infrared radiation
  erythema ab igne 28.72–3
  experimental effects 28.72
  heat-associated carcinomas 28.73
  thermal injury 28.71–4
infundibular crystalline folliculitis, necrotizing 19.89
infundibulofolliculitis, disseminate and recurrent 9.4, 19.76, 30.28
infundibuloma (dilated pore) 53.3
ingrowing nails *see* nail(s), ingrowing
inguinal hyperhidrosis 71.6
inguinal lymph node dissection (ILND) 48.8
inguinal syndrome, lymphogranuloma venereum 30.71, 34.33
inhaled drugs 72.27
inherited disorders
  analysis 15.7
  definition 15.2
  see also specific inherited disorders
injury
  mechanical *see* mechanical injury
  thermal *see* thermal injury
  see also trauma
ink-spot lentigo *54.2,* 54.5
innate immunity *see* immunity, innate
inner canthus, radiotherapy 79.9
inner root sheath (IRS) 3.13, 66.3, 66.4–5, 66.7
innervation
  autonomic 63.3–4
  blood vessels 63.3
  immune system and 63.4
  motor 77.2
    head and neck 77.4–5
  neurophysiological testing 63.4–5
  sensory 63.1–3
    head and neck 77.2–4
    surgery and 77.2
  skin 3.2, 3.12, 3.15–16, 63.1–6
  wound healing and 63.4
inocoterone 42.16
inoculation chagoma 37.32
inoculation sites, sarcoidosis 61.13
insect(s) 37.2, **38.5–30**
  cuticle 2.2
  see also arthropods; *specific insects*
insect bite reactions
  actinic prurigo vs 29.14
  hypersensitivity, in HIV infection 35.19
  purpura and bleeding 49.17
insect repellents 38.5
insecticides 38.5
insulin
  adverse effects **75.120**
  antagonism by growth hormone 8.1–2
  antibodies 46.35
    cross-reaction 46.35
  in breast development 70.1
  fat hypertrophy and 46.35
  functions 46.4
  lipodystrophy 46.34, 46.35, 59.80
  in polycystic ovary syndrome 66.82
  reactions 59.80
  resistance 8.17, 46.4, 46.6, 66.82
    acanthosis nigricans and 59.78
    acne and 42.73
    in dyslipidaemias 59.92
    in HIV lipodystrophy 46.42
  sensitivity 46.4
insulin-like growth factor-1 (IGF-1)
  growth and 8.2
  hair growth and 66.10
  in hyperpituitarism 62.2
  sebaceous gland activity and 42.11
insulin-like growth factor-2 (IGF-2), sebaceous gland activity and 42.11
insulinoma 62.67–8
  flushing association 43.16
integrins 3.2, **12.68–70,** 13.9
  α5-β5 pathways 51.65
  α6β4 3.6, 3.28, *3.30, 3.31,* 39.11
    functions *3.30*
    reduced expression in junctional EB with pyloric stenosis 39.11
  avidity 12.70
  basal cell–basement-membrane interface 12.69
  β-integrins 13.3
    β4, in junctional EB 39.10
  cell binding of laminins via 3.28, *3.30,* 3.32
  knockout mice studies 12.69
  leukocyte cell adhesion molecule (LEUCAM) subfamily 12.70
  leukocyte rolling 12.74
  platelet-specific, glycoprotein 11b–111a (GP11b–111a) 12.32
  very late antigens of activation 12.69

in wound healing 12.69, 14.3, 14.4–5, 14.6
intense pulsed light source (IPLS) therapy *see under* laser therapy
intensive care, mechanical injury 28.39
intent-to-treat design 7.7
intention-to-treat analysis 7.11
inter-quartile range 7.17, *7.18*
intercellular adhesion junctions *see* adherens junctions
intercellular adhesion molecule-1 (ICAM-1) 8.21, 49.22
ageing and 8.21
effects of UV radiation on 13.28
in lichen planus 41.2
in polymorphic light eruption 29.11
in sarcoidosis 61.20
intercellular IgA dermatosis 40.19–22
interdigital keratoderma 19.115–16
interdigitating dendritic cell sarcoma 55.31
interdigitating reticulum cells 3.17, 55.3, 55.4
interference, colours in animals and 2.5
interferon(s) **12.41**
adverse effects, allergic contact dermatitis *26.46*
interactions 72.29
receptors, in tuberculosis 31.4
therapy, warts 33.49
type I
cells producing 41.1
in lichen planus 41.1
interferon-alpha (IFN-α) therapy 13.25
adverse effects 75.142–3
sarcoidosis 61.3
carcinoid syndrome 43.19
cryoglobulinaemic vasculitis 50.25
hepatitis C 33.62
HTLV-1 infection 33.65
infantile haemangioma 18.50–1
intralesional 77.49
warts 33.49
Kasabach–Merritt syndrome/phenomenon 18.57
mastocytosis 22.36
melanoma 54.53–4
orf 33.9
squamous cell carcinoma 52.28
interferon-beta (IFN-β) therapy, intralesional, warts 33.49
interferon-gamma (IFN-γ) 17.49
defects in IL-12-dependent pathway 17.81
epitope, Langerhans' cell histiocytosis cells 55.8
in leprosy 32.7
in lichen planus 41.1
receptor 13.5
release assays 31.6
therapy 13.25
adverse effects 75.142–3
granuloma annulare 60.10
in vasculitis 50.4, 50.6
in wound healing 14.3
interferon-inducible protein 10 (CXCL10, IP-10) 12.46
interleukin(s) **12.35–40**
anti-IL12/23 74.10
IL-17 to IL-35 12.38
see also specific interleukins
interleukin-1 (IL-1) 12.35, 13.5, 64.9
adverse effects 75.144
electromagnetic radiation and 8.21
receptor activation, UV radiation 8.21
in sarcoidosis 61.5
sebocytes expressing 42.4–5
specific blocking agent 12.43
in vasculitis 50.4, 50.6
in wound healing 14.3
interleukin-1 (IL-1) receptor antagonist (IL-1RA) 12.43, 74.11
in vasculitis 50.10
interleukin-1α (IL-1α) 12.43
in acne aetiology 42.25, 42.26
comedogenesis in acne and 42.24
hair growth and 66.11
as inflammatory mediator 42.25
skin barrier function and 25.3
interleukin-1α (IL-1α) converting enzyme (ICE) 12.43, 12.49
interleukin-2 (IL-2) 12.35–6, 17.49
in idiopathic thrombocytopenic purpura 49.10
in leprosy 32.7
pruritus and 21.5
in sarcoidosis 61.5
stress and 64.9
therapy 13.25
adverse effects 75.144
intralesional 77.49
lobular panniculitis at injection site 46.14
melanoma 54.54
vitamin D action 73.43
interleukin-3 (IL-3) 12.36
adverse effects 75.144
interleukin-4 (IL-4) 12.36, 13.5–6
adverse effects 75.144
receptor 24.4
in tuberculosis 31.4–5
interleukin-5 (IL-5) 12.36
interleukin-6 (IL-6) 12.36
adverse effects 75.144
electromagnetic radiation and 8.21
in lichen planus 41.1
interleukin-7 (IL-7), thymic stromal lymphopoietin (TSLP) and 12.36
interleukin-8 (IL-8) 12.36–7, 12.46, 13.4
in acne pathogenesis 42.25
in pyoderma gangrenosum 50.65
synthesis, animal model 2.8
in vasculitis 50.10
vitamin D action 73.43
interleukin-9 (IL-9) 12.36–7
interleukin-10 (IL-10) 12.37, 12.44, 20.42
stress and 64.9
in UV-induced immunosuppression 13.31, 52.14
vitamin D action 73.43
interleukin-11 (IL-11) 12.37
interleukin-12 (IL-12) 12.37, 17.49
receptor 13.5
tuberculosis and 31.4
in UV-induced immunosuppression 13.31, 52.14
interleukin-13 (IL-13) 12.37, 13.5–6
in tuberculosis 31.4
interleukin-14 (IL-14) 12.37
interleukin-15 (IL-15) 12.37
interleukin-16 (IL-16) 12.37
interleukin-18 (IL-18), in atopic eczema and eczema herpeticum 33.35
interleukin-18 (IL-18) receptor antagonist (IL-18RA) 12.43
interleukin-31 (IL-31), in atopic dermatitis 21.5, 24.18
intermediate filaments 3.9
endothelial cells 3.51
genes and mutations 3.9
see also keratin intermediate filaments
intermediate pigment darkening (IPD) 58.10
intermittent claudication 47.2, 47.7
internal mechanical injury 28.60–2
internalin A 30.42
International Agency for Research on Cancer (IARC), vitamin D, sunlight and cancer 29.6
International Contact Dermatitis Research Group 26.2
International Foundation for Dermatology 6.16
International Nomenclature of Cosmetic Ingredients 26.24, 26.41, 26.48
international normalized ratio (INR) 47.29, 49.13
International Nosology of Heritable Disorders of Connective Tissue 45.32
International Statistical Classification of Mental and Behavioural Disorders (ICD-10) 64.11, 64.21
Internet, as resource for Münchausen patient 64.44
interpapillary ridges, actinic keratosis 52.30–1
interpersonal counselling 64.53
interpersonal psychotherapy 64.53
interphalangeal joints, fibroblastic rheumatism 51.133
interscapular skin, hypermelanosis 58.31
interstitial fluid
excess 48.7, *48.7*, 48.8
see also lymphoedema; oedema
lymphatic drainage 48.5–6
pressure 48.8
reabsorption 48.5, 48.7
interstitial granulomatous dermatitis 51.131, 62.103–4
intertrigo
acute erosive genitocrural, HIV infection 35.10
anogenital 71.2–3
Candida 36.61, 36.64, 36.68
differential diagnosis 36.33
genitocrural **71.4–5,** 71.7
sports injury 28.31
streptococcal 30.33
submammary 70.3
intervention studies 6.19
intestinal bypass arthritis–dermatitis syndrome 44.20, 50.87–8, 62.51, **62.53**
intestinal lymphangiectasia 48.27–8
intolerance reactions 22.8
intra-abdominal pressure 8.17
intracranial pressure, raised 54.11
antibiotics causing 67.31
intraepidermal bullous diseases 40.3–24
intraepidermal carcinoma, of eyelid margin 52.37
intraepidermal neutrophilic IgA dermatosis 50.62, 62.49
intralesional corticosteroids, adverse effects 28.46
intramuscular injections, complications 75.155–6
intraocular pressure, elevated 73.19
intrapartum injuries, mechanical injury 28.39
intrauterine contraceptive devices 75.118
intrauterine programming and atopic dermatitis 24.5
intravascular large B-cell lymphoma 57.50–1
intravascular papillary endothelial hyperplasia **56.23–4,** 69.102
intravascular pressure, raised, purpura due to 49.14
intravenous drug abuse, mechanical injury 28.45, 28.52–3
intravenous immunoglobulin (IVIg) 13.25, 74.11
adverse effects 75.138
in idiopathic thrombocytopenic purpura 49.10
in Kawasaki disease 30.79, 50.46
in pemphigus 40.12
rituximab and 74.9
in toxic epidermal necrolysis 76.20
in urticaria 22.30
intravenous infusion, complications 75.154
introital narrowing 71.57, 71.62
intron 11.3
inverse pattern psoriasis 71.18
invertebrates, ectoderm, exoskeleton and cuticle 2.1–2
involucrin 3.1, 3.8, 3.10, 4.2
iodides 44.18
acneiform eruption due to 42.73
iodine
adverse effects 75.152, 75.165
as antiseptic 73.15
hypersensitivity 73.15
toxicity 73.15
use in neonates 17.2
iodine releasing agents, as antiseptic 73.15
iodism 75.152
iododerma 75.21, 75.152
iodophores 73.15
iodopropynyl butyl carbamate 26.58
ionizing radiation 79.1
damage to ears 68.11
naevi due to 18.2
squamous cell carcinoma associated with HPV and 33.55
treatment modalities *see* radiotherapy
iontophoresis
in epidermolysis bullosa simplex 39.31
in hyperhidrosis 44.11
IP *see* incontinentia pigmenti (IP)
IP-10 14.3
IPD (intermediate pigment darkening) 58.10
IPEX syndrome 13.11, 13.15, 17.67, 24.7, 62.13
ipilumamab, melanoma management 54.54
iPLEDGE, isotretinoin use 42.60
iproniazid 75.79
iridiophores 2.5
iridium 26.40
iridocyclitis 61.6, 61.7
iris
hamartomas 58.23
lesions 76.1, *76.6*, 76.7
in sarcoidosis 61.7
iris (plant) 25.21
iroko *26.81*
iron
adverse effects 75.101
deficiency 59.70–1, 62.48, 62.85
chronic diffuse telogen effluvium and 66.28
differential diagnosis 40.50
hair colour change in 66.94
oral involvement 69.56, 69.85–6, *69.116*
pruritus in 21.10
restless legs syndrome and 63.24
wound healing and 14.18
disorders, restless legs syndrome 47.12
intoxication 59.71
metabolism 59.70
overload 59.71
pigment, in skin 58.53
supplements, in dystrophic EB 39.29
iron salt tattoos 58.57
irradiance 29.1
spectral 29.3
total 29.2
irradiation monochromator 29.2
irritant contact dermatitis **25.1–26**
acute 25.1, 25.11–12
after arthropod bites/stings 38.2
clinical features 25.11–19
to cosmetics 25.15
cumulative (chronic) 25.1, 25.5, 25.12–13, *25.14*, 25.15
delayed 25.12
differentiation from allergic contact dermatitis 25.6, 26.87–8
ear 68.14
epidemiology 25.1–2
eyelids 25.13, 25.15
female genitalia 71.58
friction and 25.17
hand 25.2, 25.13, *25.14*, 25.15, *25.24*
histology 25.4–5
history 25.1
immunopathology 25.5
investigations 25.21–2
male genitalia 71.17
management 25.23, *25.24*
mechanical 25.17–18, 28.13, 28.22
models 25.9–10
nail involvement 65.28–9

neonatal 17.22–8
occupational 25.13, *25.14*, 27.4, 27.5–7
pathogenesis 25.2–3
pathology 25.3–6
phototoxicity and 25.17
physical 27.6–7
predisposing factors 25.6–10
prevention 25.24–5, *25.26*
prognosis 25.26
site and vulnerability 25.7
volatile/airborne 25.15
see also burns, chemical
irritants 6.12, *25.14*, **25.19–21**
airborne 25.15
avoidance 23.21
contact responses to *25.2*, 25.10
delayed-type stinging sensation 25.19
eczema and 23.5
see also irritant contact dermatitis
identification 25.9–10
immediate-type stinging sensation 25.19
mechanical 25.17–18, 25.21
mechanism of action 25.3
occupational 27.3, 27.18–21
quantifying response to 25.22
symptomatic (subjective) responses to 25.18–19, 25.24
topical therapy agents as 73.4
volatile 25.15
see also specific irritants
irritation
acute, tests for 25.9–10
chronic, tests for 25.10
tests for 25.9
threshold 27.11
IRS (inner root sheath) 3.13, 66.3, 66.4–5, 66.7
irukandji 38.56
ischaemia
acute limb 47.5
management 47.6
causes 47.5
critical leg 47.2, 47.4
peripheral disorders **47.1–9**
pressure ulcers 28.16–18
see also arterial disease, peripheral
ischaemic fasciitis 56.5–6
isoconazole
in dermatophytosis 36.48
topical 73.12
isocyanates 26.74
isodesmosine 3.43–4
isolated limb infusion, melanoma recurrence treatment 54.55
isolated limb perfusion, melanoma recurrence treatment 54.54
isomorphic phenomenon/response *see* Koebner phenomenon/response
isoniazid 59.63, 74.44
adverse effects 31.27, *70.5*, **75.61–2**
acneiform eruptions 42.72
prophylactic, in HIV infection 31.7
resistance to 31.27
in tuberculosis 31.27
isopropanol (isopropyl alcohol) 25.20
antiseptic 73.14
isopropyl dibenzoylmethane 26.62
isopropyl linoleate 27.13
N-isopropyl-*N*′-phenyl-*p*-phenylenediamine 26.15, 26.26, 26.64
4-isopropylcatechol, hypermelanosis treatment 58.39
isosorbide, male genital dermatology 71.27
isothiazolinones 26.53–4
isotretinoin 20.37, 42.57, 74.34–5
in acne conglobata 42.62, 42.83
in acne fulminans 42.62, 42.84
in acne-related conditions *42.59*
in acne vulgaris *see* acne vulgaris, isotretinoin treatment
adverse effects 42.63–5, **75.110–13**
discoid eczema *42.64*
ocular 67.31
questionnaire on 42.63
systemic 42.64
apoptosis of sebocytes 42.15
in cellulitis 74.34
in chloracne 27.14
clinical indications 74.34
dose range and evidence level 74.35
effect on sebum composition/synthesis 42.6
effects in sebocyte culture 42.58
European Directive on use 42.59, 42.60
in folliculitis decalvans 42.74
in Fordyce's condition 42.62
in Gram-negative folliculitis 42.62, 42.84, 74.34
in granuloma annulare 60.10
in hidradenitis suppurativa 30.81
mechanism of action 42.57–8
metabolism 42.64, 42.65
in sebaceous glands 42.14, *42.15*, 42.58
metabolites 42.58
in miliaria profunda 44.16
mood changes and 64.49
in pyoderma faciale 42.84, 43.14
in rhinophyma 43.9
in rosacea 43.6, 74.34
in rosacea fulminans 42.62
in sarcoidosis 61.21
in sebaceous gland hyperplasia 42.87
in sebocyte proliferation reduction 42.14
in sebum synthesis reduction 42.14
in squamous cell carcinoma 52.28
teratogenicity 42.59, 42.63, 72.28
tetracycline contraindication 42.64, 42.65
topical 42.39–40, 42.54
benzoyl peroxide vs 42.41
topical 5-FU with 73.23
itch–scratch cycle 21.5, 21.13
itching *see* pruritus
ITGB4 and ITGA6 mutations 39.11
Ito, hypomelanosis of 58.45
Ito, naevus of 54.9
itraconazole 15.10, 74.47
adverse effects 75.64
in blastomycosis 36.85
in candidiasis 36.68, 36.69
in chromoblastomycosis 36.76
in coccidioidomycosis 36.86
in dermatophytoses 36.48, 36.49, 36.50
failure to respond to 36.50–1
in histoplasmosis 36.83
in *Malassezia* folliculitis 36.13
in otomycosis 36.17
in paracoccidioidomycosis 36.88
in penicilliosis 36.88
in pityriasis versicolor 36.12
in *Scopulariopsis brevicaulis* infection 36.54
in *Scytalidium* infection 36.52
in seborrhoeic dermatitis 23.33
in sporotrichosis 36.72
in yellow nail syndrome 65.16–17
ITRF-4 10.25
ITT (intention-to-treat)
analysis 7.11
design 7.7
ivermectin 74.51
adverse effects 75.71
in dogs 2.11
in animals 2.11
in crusted scabies 38.44
in cutaneous larva migrans 37.17
in *Demodex* infection in rosacea 43.3
in head louse infection 38.20
in loiasis 37.12
in lymphatic filariasis 37.10
in onchocerciasis 37.7
in phthiriasis palpebrarum 38.23
in scabies 38.41–2
in strongyloidiasis 37.15–16
topical 73.14
IVIg *see* intravenous immunoglobulin (IVIg)
Ixodes 30.58, 30.64, 30.73, 38.34, 38.35, 62.106
Ixodidae 38.33–5

J
jacaranda *26.81*
Jackson–Lawler syndrome (pachyonychia congenita type 2) 15.49, 19.3, 19.94, 19.103–4, 42.88, 65.20
Jacob's disease 69.40
Jadassohn–Lewandowsky syndrome (pachyonychia congenita type 1) 15.49, 19.3, 19.94, 19.103–4, 65.20
Jadassohn's naevus phakomatosis 18.27–30, 54.11
Jaffe–Lichtenstein disease 47.55
JAK-2 mutations, in myeloproliferative disorders 49.29, 62.86
JAK-3 13.11
Jak–Stat–Socs pathway 12.28, 12.35
Jamaica ebony *26.80*
Janeway lesions 62.78
Japanese encephalitis *33.67*
Japanese lacquer tree 26.75
Jarisch–Herxheimer reaction 34.23, 75.15
jaundice 62.58, 62.63–4
in malaria 37.27
pigmentation in 58.53
jejunoileal bypass surgery
adverse effects 8.17–18
BADAS and 50.87
necrobiosis lipoidica after 60.15
vasculitis-associated panniculitis after 46.32
Jellinek's sign 58.24–5, 62.8
jellyfish 38.55–8
jelutong 26.79, *26.80*
Jessner's (benign) lymphocytic infiltration 57.60
differential diagnosis 51.7
ear 68.15
Jessner's peel 80.9
jewellers, occupational hazards 27.20
Jews, Ashkenazi 44.7
jigger 38.12–13
jigsaw-puzzle appearance, cylindroma 53.28
jimble 38.56
JMML (juvenile myelomonocytic leukaemia) 15.14–15, 15.20
Job's syndrome *see* hyper-IgE syndrome
jogger's nipples 28.31, 70.10–11
Johanson–Blizzard syndrome 15.45, 18.103, *69.12*
Johnson neuroectodermal syndrome 15.30
Joint Tuberculosis Committee 31.27
joints
Charcot's 63.15
Clutton's 34.16
disorders **62.99–106**
hypermobility 45.30, 45.34, 62.104
neutrophilic dermatoses and 50.82
in sarcoidosis 61.6–7
in systemic sclerosis 51.102
jojoba oil, in scabies 38.41
Jorgenson syndrome 15.43
joules (J) 29.1
journals 7.5–6
jugular lymph sac (JLS) 48.2
jumping spiders 38.32
Jun proteins, loss, in SCID mouse model 2.14
junctional activity *54.10*
junctional adhesion molecules (JAMs) 3.24
junctional epidermolysis bullosa *see* epidermolysis bullosa (EB), junctional
junctional naevus *see* naevus, junctional
Jung's disease 23.27
Junin virus *33.67*, 33.69
juvenile acne 42.75–6
juvenile chronic myeloid leukaemia 15.20
juvenile dermatitis herpetiformis/pemphigoid *see* linear IgA disease
juvenile dermatomyositis 51.126
juvenile myelomonocytic leukaemia (JMML) 15.14–15, 15.20
juvenile onset ischaemic dermatopathy, in dogs 2.15
juvenile plantar dermatosis 23.26
mechanical injury and 28.14
juvenile rheumatoid arthritis 51.133–6
juvenile spring eruption 29.12
juvenile xanthogranuloma 15.20, 55.6, **55.15–17**
clinical features 55.16
diagnosis, prognosis and treatment 55.16–17
eyelids 67.33
Langerhans' cell histiocytosis and 55.10
neonatal 55.16
non-xanthomatous 55.15
spindle cell variant 55.15

K
K gene, in dogs 2.6
Kabuki syndrome 68.4
kala azar (visceral leishmaniasis) **37.41–3**
kallikrein 21.5
Kallin's syndrome 39.9
Kallmann's syndrome 19.11, 19.12, 70.2
kambala *26.81*
Kamino bodies 10.40, 54.22, 54.24, *54.24*
kanamycin 26.45, 75.58
Kangri cancer 52.5
Kanzaki disease 44.18, 59.34
Kaposi's sarcoma **35.36–8, 56.33–7**
aetiology 56.33–4
African type 48.30
AIDS-associated 33.33, 35.4, **35.36–8,** 48.30, 48.31, 56.34
in children 35.45
differential diagnosis 35.37
oral 35.43
staging and diagnosis 35.37
treatment 35.37, *35.38*
classic 48.30, 56.33–4
clinical features 35.37, 56.34–5
definition 56.33
differential diagnosis *35.37*, 56.36
endemic 56.34
external ear 68.28, 68.34
eyelids 67.36
iatrogenic 56.34
immunodeficiency-associated 48.30, 48.31
Koebner response 28.3
lymphangiomatous 56.35
from lymphatic endothelium 48.30
lymphatic origin of 48.30
lymphoedema and 48.14, 48.30–1
male genital dermatology 71.48
markers 49.18
Mediterranean type 48.30
oral 35.43, 69.13, 69.22, 69.55, 69.99
pathogenesis 35.36–7, 56.33–4
pathology 56.35–6
perianal/perineal dermatology 71.98–9
in pregnancy 8.13
promontory sign 56.35
race and 9.18–19
regression 56.36
staging 56.35–6
in transplant recipients 62.74–5
treatment 35.37, *35.38*, 56.36, 79.13
alitretinoin *see* isotretinoin
Kaposi's sarcoma-associated herpesvirus (KHSV) *see* human herpesvirus 8 (HHV-8)
Kaposi's varicelliform eruption 24.24, **33.35–7**
aetiology 33.35
clinical features 33.35

dermatoses associated with 33.35
diagnosis and treatment 33.35–6
Kaposi–Stemmer sign 48.15
karyorrhexis 10.40, 46.26
Kasabach–Merritt syndrome/phenomenon 18.56–7, 56.31
kaposiform haemangioendothelioma and 18.55
thrombocytopenia and 49.12
tufted angioma and *18.56*
Katayama fever 37.21
kava dermopathy 59.64, 75.161–2
Kawasaki disease **30.78–9,** 50.45–6
aetiology 30.78
cardiac involvement 62.78
differential diagnosis 76.7
genetic factors 50.11
oral involvement 69.84, *69.118*, 69.121
pathogenesis 50.5–6
keds 38.6, 38.7
keloids 14.2, 14.15, **45.54–6**
in acne 42.32
treatment 42.69
fibroblasts 3.50
following ear piercing 68.8
following surgery *77.8*
linear 45.54
male genital dermatology 71.36
race and 9.15
treatment 45.55, 73.36, 77.49–50
intralesional corticosteroids 14.15
laser therapy 78.14
radiotherapy 45.55, 79.4–5
topical imiquimod 73.24
kenogen 66.8, 66.20
Kenya tick typhus 30.73
keratan sulphate, structure *3.47*
keratin(s) 3.1, 3.9
accumulation, keratoacanthoma 52.42, 52.43
acidic (type II) 3.10, 10.20
in acne 42.23
antibodies to 10.19–21, 39.25
basic (type I) 3.10
cuticular 66.5
epidermal 3.1
expressed by sebocytes 42.12
genes 3.9–10, 3.10
hair *(HaKRT1-6* and *HbKRT1-6)* 3.14
mutations 3.10, 11.12
hair 3.13–14, 66.6
hard 65.2, 65.3
K1/K10 pair 3.10
K2e 3.10
K5/K14 pair 3.10
mutations in epidermolysis bullosa simplex 39.3–4
K8/K18 pair 3.10
K9 3.10
K15 3.10
K17 3.14
mutations in steatocystoma multiplex 42.88
nail 65.3
neutral-basic (type II) 10.20
in pachyonychia congenita 65.3
soft 65.3
in stratum corneum 4.2
structure 3.9, *3.31*
types 3.9, 3.10
keratin-associated proteins 66.6
keratin intermediate filaments 3.1, 3.9, 3.10, 3.21–2, 3.30, 40.2
desmosomes and 3.21–2, 40.1–2
detachment in pemphigus 40.15
hemidesmosomes and 3.30, 40.28
α-keratin intermediate filaments (a-KIF) 66.6
keratinization
management 67.22
in seborrhoeic keratosis 52.39
trichilemmal 66.3
keratinization disorders **19.1–122**
acanthosis nigricans 19.119–21
acitretin therapy 74.36
classification 19.1–2
confluent and reticulate papillomatosis 19.121–2
Darier's disease and related disorders 19.3, 19.81–8
erythrokeratodermas 19.69–72
filiform keratoses 19.92–3
Flegel's disease 19.89–90
folliculocentric keratotic 19.72–6, 19.84
ichthyoses 19.3, 19.4–65
isotretinoin therapy 74.34
keratolytic treatments
bullous ichthyosiform erythroderma 19.33
CHILD syndrome 19.58
ichthyosis hystrix 19.37
ichthyosis vulgaris 19.8
lamellar ichthyosis 19.25
Netherton's syndrome 19.41
non-bullous ichthyosiform erythroderma 19.19
non-epidermolytic palmoplantar keratoderma 19.97
pachyonychia congenita 19.104
Sjögren–Larsson syndrome 19.44
X-linked recessive ichthyosis 19.12
minute keratoses 19.92–3
miscellaneous circumscribed keratotic 19.93
molecular genetics 19.1–4, 19.94–5
ocular involvement *67.29–30*
palmoplantar keratodermas 19.93–119
peeling skin syndromes 19.66–9
perforating keratotic 19.88–9
pityriasis 19.65, 19.76–81, 19.84
porokeratoses 19.90–2
retinoid therapy
bullous ichthyosiform erythroderma 19.33
CHILD syndrome 19.58
Darier's disease 19.85
harlequin ichthyosis 19.29
IBIDS/PIBIDS syndrome 19.49
ichthyosis hystrix 19.37
ichthyosis vulgaris 19.8
KID/HID syndrome 19.56
lamellar ichthyosis 19.25
Netherton's syndrome 19.41
neutral lipid storage disease with ichthyosis 19.54
non-bullous ichthyosiform erythroderma 19.19
non-epidermolytic palmoplantar keratoderma 19.97
pachyonychia congenita 19.104
pityriasis rubra pilaris 19.79
Sjögren–Larsson syndrome 19.44
X-linked recessive ichthyosis 19.12
systemic treatments
bullous ichthyosiform erythroderma 19.33
CHILD syndrome 19.58
Darier's disease 19.85
harlequin ichthyosis 19.29
IBIDS/PIBIDS syndrome 19.49
ichthyosis hystrix 19.37
ichthyosis vulgaris 19.8
KID/HID syndrome 19.56
lamellar ichthyosis 19.25
Netherton's syndrome 19.41
non-bullous ichthyosiform erythroderma 19.19
pityriasis rubra pilaris 19.79
Sjögren–Larsson syndrome 19.44
X-linked recessive ichthyosis 19.12
topical treatments
bullous ichthyosiform erythroderma 19.33
CHILD syndrome 19.58
collodion babies 19.14–16
Darier's disease 19.85
harlequin ichthyosis 19.29
IBIDS/PIBIDS syndrome 19.49
ichthyosis hystrix 19.37
ichthyosis vulgaris 19.7–8
lamellar ichthyosis 19.25
Netherton's syndrome 19.41
non-bullous ichthyosiform erythroderma 19.19
non-epidermolytic palmoplantar keratoderma 19.97
pachyonychia congenita 19.104
pityriasis rubra pilaris 19.79
Sjögren–Larsson syndrome 19.44
X-linked recessive ichthyosis 19.12
see also specific disorders
keratinocyte(s) 3.1, 3.8, **3.9–10,** 12.14–17, 54.1
adhesion between 3.22
abnormal, in Hailey–Hailey disease 39.33
adhesion molecules 12.75
ageing and 80.2
androgen metabolic enzymes 42.12
apoptosis 12.12
Fas ligand (FasL) and 12.11
TNF-receptors 12.42
atypical, squamous cell carcinoma 52.25
barrier function and 4.2
basal
cleavage in epidermolysis bullosa simplex *39.2*, 39.3
epidermal proliferation units 3.6
nail matrix 3.15
stem cell activity, control 3.6
structure 3.8
in Bowen's disease 52.33
chemokines 12.16–17
in chronic wounds 14.11
cultured 14.26
use in dystrophic epidermolysis bullosa 39.29
cytokines and pro-inflammatory mediators 12.15–17
ductal
cytokines produced 42.24
proliferation abnormalities in acne 42.22–3, 42.25–6
topical retinoid effects 42.40
endothelin-1 production 58.26
epibasal 3.8
epidermal barrier formation 12.14
epidermal growth factor (EGF) 12.16
growth factor, hair growth and 66.10
human papillomaviruses (HPV) and 12.16, 33.37
hyperproliferation 3.16
in acne 42.22–3, 42.25–6
induction in acne 42.23
reduced by isotretinoin 42.58
topical retinoid effects 42.40
immature, seborrhoeic keratosis 52.39
induction of TLR-2 activation by glucocorticoids 12.9
intercellular adhesion molecule-1 (ICAM-1) 12.10, 12.16, 12.73
in irritant contact dermatitis 25.5
in junctional epidermolysis bullosa 39.9
keloid 14.15
koilocytosis, in warts 33.41
in lichen planus 41.1
mediators of inflammation 12.15–17
melanocyte contact 58.2, 58.7
melanosome transfer to 58.4–5
migration 3.2
MMPs synthesis/secretion 3.41
number served by melanocyte 58.2
proliferation, lentigo 54.3
receptor-blocking strategies 12.17
in Stevens–Johnson syndrome 76.9–10
structure 3.9–10
surrounding melanocytes 54.18
terminal differentiation 3.6, 3.10
in toxic epidermal necrolysis 76.9–10
ultraviolet radiation and 12.16, 52.13–14
vascular endothelial growth factor (VEGF), MHC and 12.16
in vitiligo 58.47
in wound healing 14.4–5
keratinocyte transglutaminase 3.10
keratitis *67.4*
bacterial *67.14*
chronic blepharitis with, treatment *67.12*
dendritic 67.26
epithelial, in molluscum contagiosum 67.25
filamentary *67.4*
geographical 67.26
herpetic 33.17, 33.18, 33.21, 67.16, 67.26
interstitial *67.4*
congenital syphilis 34.16
rosacea 43.4, 43.5, 43.7
stromal and endothelial 67.26
keratitis, ichthyosis and deafness syndrome *see* KID syndrome
keratoacanthoma 52.42–4
aetiology and incidence 52.42
clinical features 52.42–3
diagnosis 52.43
eyelids 67.34
generalized eruptive 52.44
growth and size 52.42
oral cavity 69.54–5
pathology 52.43
recurrence 52.42
sebaceous 53.15
sites 52.42
squamous cell carcinoma vs 52.26, 52.27
subungual/periungual 65.38
surgery 77.15
treatment 52.43–4
keratoconjunctivitis
atopic *see* atopic keratoconjunctivitis (AKC)
in atopic dermatitis 24.24
in herpes simplex 33.17, 33.18
treatment 67.15–16
vernal *67.13*, *67.14*, 67.15, 67.16
keratoconjunctivitis sicca *67.4*
in sarcoidosis 61.7
keratoconus 24.24, *67.4*
keratoderma
climactericum (Haxthausen's disease) 19.117–18
definition 5.7
filiform 19.114
loricrin 19.3, 19.19, 19.94, 19.98
palmoplantar *see* palmoplantar keratoderma
palmoplantaris transgrediens *see* Mal de Meleda
punctate, plantar warts vs 33.44
race and 9.10
Sybert's *19.94*, 19.99
keratoderma blenorrhagica 34.30, *34.31*
keratoderma climactericum 8.20
keratoelastoidosis marginalis 45.28
keratohyalin granules 3.8, 4.2
clumped, warts 33.41
in obesity 8.17
keratolinin/cystatin 3.10
keratolysis exfoliativa 19.66, 23.19
keratolysis plantare sulcatum **30.39–40,** 44.8
keratoma hereditarum mutilans 45.70
keratomycosis nigricans palmaris *36.8*, **36.14–15**
keratopathy *67.4*
keratoses
actinic *see* actinic keratosis
arsenical 52.29, **52.34–5,** 62.47
benign lichenoid (BLKs) 41.6
eyelids 67.33
filiform 19.92–3
inverted follicular 53.2–3
lip
leukokeratosis *see* cheilitis, actinic
treatment 73.23
oral 69.90–3
post-ionizing radiation 52.37
seed-like of the palms and soles 62.33

smoker's 69.90
snuff-dipper's 69.90
stucco 52.40
sublingual 69.91
tar 52.37
keratosis circumscripta 19.78
keratosis follicularis *see* Darier's disease
keratosis follicularis spinulosa decalvans 19.74–5, 19.84, 66.51
keratosis follicularis squamosa (Dohi) 8.17, 19.76
keratosis lichenoides chronica (Nékam's disease) **41.27–8,** 73.44
keratosis obturans 68.28, 68.35
keratosis pilaris 19.72–4, 19.84, 24.22, 45.8
acne vs 42.37
hypotrichosis with 66.60
lentiginosis and 66.60–1
treatment 73.36
keratosis pilaris atrophicans faciei 66.51
keratosis punctata 9.10
keratosis senilis *see* actinic keratosis
keratosis spinulosa 19.75, 19.76
keratosis spinulosa (lichen spinulosus) 19.75, 19.76
keratouveitis, HSV 67.26
kerion 30.25, 36.22, 36.27, 36.36, 36.49
Trichophyton verrucosum as cause 2.12
kerosene 25.20
ketanserin 74.52
in systemic sclerosis 51.108
in wound healing 14.24
ketoconazole 74.47
adverse effects *70.5,* 75.65
in blastomycosis 36.85
in candidiasis 36.68
in dermatophytoses 36.48, 36.49
eccrine gland secretion 44.18
in histoplasmosis 36.83
in *Malassezia* folliculitis 36.13
in paracoccidioidomycosis 36.88
in pityriasis capitis 66.56
in pityriasis versicolor 36.12
in seborrhoeic dermatitis 23.33
in tinea nigra 36.15
topical 73.12
ketoprofen
adverse effects *26.46,* 75.74
as photoallergen 26.24
ketotifen, in rosacea 43.6
khaki dermatitis 26.26, 26.66
khat 69.50
Khaya 26.81
khaya mahogany *26.81*
khellin 58.48
KHSV *see* human herpesvirus 8 (HHV-8)
Ki-67 53.43
keratinocyte hyperproliferation in acne 42.22–3
in mast cell tumours, in dogs 2.22
Ki-M1p 55.15
kicking injuries 28.33
KID syndrome 15.46, 15.68, **15.69–70,** 19.54–7, 19.60
oral involvement 69.26
kidneys
disorders **62.68–75**
oral manifestations *69.116*
see also chronic renal failure; renal disease; renal failure
drug elimination 72.27
in sarcoidosis 61.7, 62.71
in SLE 51.44
in systemic sclerosis 51.101
transplantation *69.116*
nephrogenic systemic fibrosis and 45.53
non-melanoma skin cancer and 52.11
skin changes in recipients 62.74–5
in Wegener's granulomatosis 50.39–40
'wire-loop' lesions 51.34
see also entries beginning renal
Kikuchi–Fujimoto disease 33.31, 33.77
Kikuchi's disease 33.31, 33.77, 51.134
SLE and 51.58
Kikuchi's histiocytic necrotizing lymphadenitis, EBV infection and 33.31, 33.77
killer-inhibitory receptors 13.6
Kimura's disease 46.34, 56.27, 68.15
Kindler's syndrome 12.17, **15.82–3,** 39.1, 39.2, *39.2,* 45.13, 69.40
diagnosis 39.24–5, 39.25
Kindlin-1 39.25
kinesin, melanosome transfer along melanocyte dendrites 58.4
kinesiotaping, lymphoedema management 48.23
kinetensin 12.25
kinin(s) 38.1
cascade 13.2, 13.4
in urticaria 22.5
kininase II *see* angiotensin-converting enzyme
Kinmonth's lymphoedema praecox 48.10
Kirghizian dermato-osteolysis 15.46
KIRs (killer-inhibitory receptors) 13.6
kissing bugs 37.2, 37.31, 38.25
Kit (CD117) 3.19–20
KIT gene mutations 3.20
in mastocytosis 22.30, 22.31
in piebaldism 58.42, 66.93
Kit ligand (mast cell growth factor/stem cell factor (M/SCF)), melanocyte mitogen 58.5
Kitamura's disease 58.21
Klebsiella oxytoca, in invasive otitis externa 68.25
Klebsiella pneumoniae rhinoscleromatis 30.51–3
KLICK syndrome 19.19
Kligman cream 73.27, **73.28**
Klinefelter's syndrome 47.42
breast cancer and 70.14
genetics **15.13–14**
gynaecomastia and 70.4
Klippel–Trenaunay syndrome (KTS) **18.76–8, 47.23–4,** 47.37
acroangiodermatitis (of Mali) and 49.17
aetiology 18.77
bone and joint involvement 62.99, *62.100*
clinical features 18.77
definition 18.76
differential diagnosis 18.77
lymphoedema and 48.10, 48.12, 48.21
nomenclature 18.76
oral involvement 69.30
treatment 18.77–8
Kloos–Schleifer classification system 30.2
knee, surgery 77.5
Knemidokoptes mutans 38.46
Knemidokoptidae 38.46
knock-out animals 2.8, 11.11
knock-out vector 2.8
knuckle pads 19.93, 19.108–9, **45.48,** 45.49
race and 9.15
Kobberling–Dunnigan syndrome 46.40–1
Köbner-like isomorphic phenomenon, common warts 33.43
Koch phenomenon 31.3–4, 31.6
Koebner epidermolysis bullosa (EB) simplex 39.4, 39.6
Koebner phenomenon/response 5.8
eczema and 23.28–9
in erythema multiforme 76.7
friction and 25.17
in Hailey–Hailey disease 39.34
in lichen planus 41.6, 41.12
in mechanical/thermal injury 28.2–3, 28.15, 28.48, 28.73
in nails 65.24
in psoriasis *5.12,* 20.8, 20.17
in reactive perforating collagenosis 45.64
in sarcoidosis 61.10
sexual abuse and 51.117
in vitiligo 26.26, *26.27,* 58.47
Koenen tumour 15.22, 65.31, 65.32
koganbyo 37.22
Kohlmeier–Degos' disease *see* Degos' disease
koilocytosis, in viral warts 33.41
koilonychia 62.85, **65.8**
in childhood 65.6
kojic acid 73.28
kokardennaevus 54.20–1
Koplik's spots 33.75, 69.95
koro syndrome 71.51
Kostmann's syndrome 17.48, 17.75
KP1 *see* CD68
krala *26.81*
KRAS gene 15.15
Kronmayer lamp 29.2
KRT1 gene 18.5
KRT5 gene mutation, epidermolysis bullosa simplex 39.3–4
KRT10 gene 18.5
KRT14 gene mutation, epidermolysis bullosa simplex 39.3–4
KS *see* Kaposi's sarcoma
KTS *see* Klippel–Trenaunay syndrome (KTS)
kua'sha 28.25
kumkum 26.10
Kunjin virus *33.67*
Kveim test 5.24, 61.1, **61.19–20**
kwashiorkor 35.41, 59.67, 66.94
Kyasanur forest disease *33.67*
kyphoscoliosis 45.30
in Ehlers–Danlos syndrome 45.34, 45.35
Kyrle's disease *see* perforating collagenosis (folliculitis)

L

L granules, sulphur-rich 3.10
L-selectin *see* selectins
La/SS-B antibodies 51.50
Laband's syndrome 68.4
labetalol 75.91
labia majora 71.54, 71.56, 71.72, 71.79
labia minora 71.54, 71.56, 71.62–3
labial melanotic macules *54.2,* 54.6, 54.7
laboratory tests 5.21–2
immunological and allergic disease 13.15–26
labour, delayed in X-linked ichthyosis 8.9
Lacazia loboi 36.77, 36.78
laceration, pinna 68.7
lacrimal apparatus *67.3*
cicatrization 67.21
lacrimal glands 67.2–3
in graft-versus-host disease 67.22
in sarcoidosis 61.7
in Stevens–Johnson syndrome 67.21
lactate
as irritant 25.19
in sweat 44.5, 44.6
lactation
drug therapy and 72.28
sebaceous gland activity 42.12
lactic acid 80.9
lactic acid stinging test 25.10
lactiferous ducts 70.1, 70.8, 70.11
lactoflavine 59.62
lactogen 8.9
lactucin 26.75
lactucopicrin 26.75
LAD *see* leukocyte adhesion deficiency (LAD)
Lag antigen, Birbeck granules 55.4
Laginel–Lavastine and Viard type, lipoatrophy 46.39
Lagochilascaris minor 37.18
lagophthalmos 32.14, *67.4,* 67.21
LAMA3 gene, mutations in junctional epidermolysis bullosa 39.10
LAMB syndrome 49.37, 54.4, 58.14, 62.25, 62.79, 69.28
LAMB3 gene, mutational hotspots and R42X and R635X 39.10
Lambdopsalis bulla 66.1
Lambeth study 6.6–7, *6.7,* 6.15
lamellar bodies/granules *see* membrane-coating granules
lamellar desquamation/exfoliation of the newborn **17.19–21,** 59.39
lamellar ichthyosis (LI) 19.3, 19.21–5
prenatal diagnosis *16.3*
treatment 73.36
see also non-bullous ichthyosiform erythroderma
lamina densa 3.25, *3.26*
cleavage below in dystrophic epidermolysis bullosa *39.2,* 39.15
lamina lucida 3.25, *3.26*
cleavage in junctional epidermolysis bullosa *39.2*
salt-split 40.47
laminin(s) 3.27–3.29
cell binding mediated by integrins 3.28, *3.30*
chain composition 3.27, *3.28*
functions 3.28
G domain 3.27, *3.29*
lymphatic vessels 48.4
subunits and structure 3.27–3.28, *3.29*
in wound healing 14.6
laminin-1, antibodies to 39.25
laminin-5 (laminin-332) 3.6, 3.25–6, 3.27, *3.30,* 40.36
α6β4 integrin binding 3.28, *3.30,* 3.32
in anchoring filaments 3.32
gene mutations 3.28
in junctional epidermolysis bullosa 3.28, *3.30,* 39.10
antibody probes for diagnosis 39.25
monoclonal antibodies to 39.25
structure 3.27, *3.29, 3.31,* 3.32
lamins, nuclear 3.9
in partial face-sparing lipodystrophy 46.41
lamivudine *26.46,* 75.67
adverse effects 35.22
lamotrigine 64.52
adverse effects 75.86
in complex regional pain syndrome 63.21
Lampona 38.32
lamprene *see* clofazimine
Lamprene, pigmentation due to 58.55
Lanette O 26.58–9
Langer–Giedion syndrome 15.55, **15.65–6**
Langerhans' cell granulomatosis *see* Langerhans' cell histiocytosis (LCH)
Langerhans' cell histiocytosis (LCH) 3.18, **55.6–14**
aetiology 55.6–7
bone involvement 55.12
bone marrow 55.11
clinical features 17.25, 55.9–12
clonality 55.7
CNS involvement 55.11–12
cutaneous features 55.9–10
definition 55.6
diagnosis 55.7, 55.12
diagnostic markers 55.8–9
differential diagnosis 17.30, 55.12, 55.23
ears 55.11
endocrine system involvement 55.11, 55.12
female genital dermatology 71.79
gastrointestinal 55.11
Hashimoto–Pritzker variant 55.8, 55.9
immunocytochemistry 55.8–9
immunoglobulins 55.6
incidence 55.9
investigation 55.12–13
juvenile xanthogranuloma and 55.10
male genital dermatology 71.48
malignant 55.7, 55.32
multisystem *55.10,* 55.11, 55.12
treatment 55.13
nails 55.11
oral involvement 55.11, *69.118*
pathology 55.7–8
perianal/perineal dermatology 71.99

pregnancy and 8.12
prognosis 55.12
pulmonary 55.7, 55.11
reduced T-cell response 55.6, 55.7
seborrhoeic dermatitis vs 55.9
treatment 55.12, 55.13
topical mechlorethamine 73.24
Langerhans' cell histiocytosis (LCH) cells 55.6, 55.7, *55.7*, *55.8*
Birbeck granules 55.3–4, 55.6
CD1a 55.7
histology/ultrastructure *55.7*, 55.7–8
surface markers 55.8–9
T cell response inhibition 55.6, 55.7
Langerhans' cell sarcoma 55.31
Langerhans' cells 3.1, **3.17–18,** 4.8, 12.16
abnormal *see* Langerhans' cell histiocytosis (LCH) cells
in acne pathogenesis 42.26, 42.27
activated, surface markers *55.3*, 55.4
ageing and 8.24, *80.2*
in allergic contact dermatitis 26.6
antigen presentation by 55.3, 55.4–5
Birbeck granules 3.18, 55.3–4
culture 55.3
cytokines released 3.17, 55.3
deficiency 3.17–18
differentiation/development 55.1–3
effects of UVR on 13.28, *13.29*, 29.5
embryology 3.5
functions 3.3, 3.17, *3.18*, 13.9, 55.4–5
hair bulb 66.4
in HIV-associated psoriasis 35.17
in HIV infection 35.8
in HPV infection and warts 33.42
hyperplasia 10.24
in irritant contact dermatitis 25.5
in lichen planus 41.4
maturation 55.3
migration 3.17, 3.18, 55.3, 55.4
factors controlling *5.2*, 5.3, 55.1
signals initiating 55.4
motion mechanism 3.17
in nail matrix 65.2
ontogeny 55.1–3
phenotype *55.3*, 55.3–4
precursors 55.1, *55.2*
structure and ultrastructure 3.17–18
surface markers 10.24–5, *55.3*, 55.3–4, 55.5
langerin 10.24
Langer's lines 77.2, 77.13
Langhans' giant cell 10.34–5
in lichen nitidus 41.21
in pancreatic panniculitis 46.18
language
barriers 72.2
skin/skin disease and 64.1, 64.6
language bias 7.7
lanolin
as allergen 26.58
comedogenicity 27.13
composition 73.6
as emollient 73.6
in topical therapy 73.6–7
lanreotide, in carcinoid syndrome 43.19
lansoprazole 75.157
lanugo 66.2
large B-cell lymphoma (PCLBCL) 57.47–9
large vessel disease 51.39
larva currens *see Strongyloides stercoralis*
larva migrans
cutaneous **37.16–17**
breast involvement 70.17
in HIV infection 35.36
oral 69.101
visceral *see* toxocariasis
larval therapy, pressure ulcers 28.22
laryngo-onycho-cutaneous (LOC) syndrome 39.15
larynx, lichen planus 41.9
laser burns **28.90**
Erbium:YAG 53.7
laser Doppler flowmetry, in erythema 25.22
laser evoked potentials 63.5
laser therapy **78.1–16**
ablative resurfacing 78.13–15
acne 42.67, 42.69
actinic cheilitis 78.14
adverse effects 33.49
angiofibroma 78.14
argon 78.1
basal cell carcinoma 78.14
Becker's naevus 18.18, 78.10
Bowen's disease 78.14
café-au-lait spots 78.10
classification 78.2
CO_2 *see* carbon dioxide laser
in combination with botulinum toxin 80.7
continuous 78.2
cosmetic/rejuvenation 80.7, 80.10–13
epidermolytic/non-epidermolytic epidermal naevi 18.7
Erbium:YAG laser 78.13
osteoma cutis 42.78
fractional ablative resurfacing 78.13
fractional photocoagulation 78.13
freckles 78.10
gain medium 78.2
granuloma faciale 50.29, 78.9, 78.14
haemangioma 78.6
hair removal 66.87, 78.12–13
history of 78.1
HPV-associated dysplasia/neoplasia 33.55
hypertrichosis 78.12–13
hypertrichosis lanuginosa 66.76
hypertrophic scars 78.8
incisional 78.13, 78.14
infantile haemangioma 18.51
intense pulsed light source (IPLS) 78.6, 78.10
acne 42.67
cosmetic use 80.10–11
hereditary haemorrhagic telangiectasia 47.18
port-wine stains 18.64
telangiectasia 47.20
keloids 78.14
KTP 78.6
leg veins/venules 78.8
lichen planus 41.18
light 78.1–2
light–tissue interactions 78.4–5, 78.5–6, 78.9, 78.12, 78.13
low-level (LLLT) 78.15
lymphoedema management 48.23
melanocytic naevus 78.11
melasma 78.11
naevoid basal cell carcinoma syndrome 52.8
naevus of Ota 78.10, *78.11*
nail unit 65.48
Nd:YAG 78.6, 78.9–10, 78.14
essential telangiectasia 47.19
lichen planus 41.18
telangiectasia 47.20
varicose veins 47.39
necrobiosis lipoidica 60.16
non-ablative photocoagulation 78.13, 78.14
non-melanoma skin cancer 52.17
optical cavity 78.2
osteoma cutis 42.78
peri-orbital syringoma 78.14
photothermal ablation 78.13–15
phymas 43.10
port-wine stain 18.64–5, 78.6–7
psoriasis 20.43, 78.8
pulsed 78.2–3
pulsed-dye (PDL) 47.20, 78.6–7
side-effects 18.64
warts 33.49
Q-switched 78.2, 78.3, 78.9–10
resurfacing 80.7, 80.11
rhinophyma 43.10, 78.14
sarcoidosis 61.21
seborrhoeic keratosis 78.10
solar lentigines 78.10
speckled and lentiginous naevus 78.10
spot size 78.3, 78.4
striae 45.6
tattoos 58.59, 78.10
telangiectases 47.19, 47.20, 78.7–8
in rosacea 43.6
tissue cooling 78.5
tissue optics 78.3–4
trichoepithelioma 78.14
varicose veins 47.39
vascular lesions 78.5–9
warts 33.49, 78.8
xanthelasma 78.14
Lasiodiploidea theobromae 36.55
Lasiohelea 38.6
Lassa fever *33.67*, 33.69
diagnosis 33.5
Lassar's paste, dithranol 20.23
latanoprost *26.46*, *66.79*, 66.94, 75.165
late-infantile neuronal ceroid lipofuscinosis, prenatal diagnosis *16.3*
late-onset (acquired) ichthyoses 19.63–5, 62.32
latent transforming growth factor-β (LTBP) 3.45
lateral pterygoid muscle, examination 69.4–5
latex 26.63
contact urticaria to 26.105, 27.5
sensitivity
immunotherapy 26.106
male genital dermatology 71.17
spina bifida and 63.16
testing for 26.106, 27.7
see also rubber
latrodectism 38.31
Latrodectus 38.31
Lattice System Global Assessment 72.9
Laugier–Hunziker(–Baran) syndrome 58.14–15, 65.38, 69.28
laurel oil 76.5
lavender oil
adverse effects *70.5*
in head louse infection 38.20
as insect repellent 38.5
lawsone 66.97
Lawsonia spp. 66.97
laxatives
adverse effects 75.158
in dystrophic epidermolysis bullosa 39.28
laxity, skin 45.14
see also cutis laxa
LBP (lipopolysaccharide-binding protein) 12.9
LCH *see* Langerhans' cell histiocytosis
LDF (laser Doppler flowmetry), in erythema 25.22
LE *see* lupus erythematosus (LE)
le tic des levres 64.39–40, 69.127–8
lead acetate hair dye 66.97
lead poisoning 75.33
lead subacetate 75.165
lectins 13.23
Ledderhose's disease 45.47, **56.11**
leeches 38.55
Leeds acne grading system 72.10
LEF1 3.4, 66.10
leflunomide 13.24, 75.138
leg(s)
allergic contact dermatitis 23.35, *23.36*, 26.19, 26.29
atherosclerosis 47.2
burning pain 47.11
chronic folliculitis 30.22
disseminated superficial actinic porokeratosis 52.35–6
erosive pustular dermatitis 50.89–90
erythromelalgia 47.9–10
fascial hernias 45.68–9
injuries, venous ulceration and 47.42
ischaemic disease 47.2
neurovascular disorders 47.9–12
occupational dermatoses 27.3
pustular dermatitis atrophicans 30.22
red streaks 48.29
surgery 77.5
telangiectases 47.13
ulcers *see* ulcer(s), leg
see also lower limb
Leg Club Foundation 14.21
legionellosis 30.*67*
Leguminosae *26.80*
Leiden mutation 54.33
leiomyoma **56.54–6**
congenital 18.37
genetics 15.26
genital 56.54–5
in females 71.73
oral 69.113
pilar 56.54–5
leiomyoma cutis 56.54–5
leiomyomatosis, multiple cutaneous and uterine 56.55
leiomyosarcoma 56.56
Leishmania 37.2, 37.27, 37.33
Leishmania aethiopica 37.34, *37.35*, 37.36, 37.37, 37.39
Leishmania brasiliensis, ocular infection 67.27
Leishmania brasiliensis brasiliensis *37.34*, *37.35*, 37.39, 37.40
Leishmania brasiliensis guyanensis *37.34*, *37.35*, 37.39–40
Leishmania brasiliensis panamensis *37.34*, *37.35*, 37.40
Leishmania brasiliensis peruviana *37.34*, *37.35*, 37.39, 37.40
Leishmania chagasi *37.34*
Leishmania donovani, ocular infection 67.27
Leishmania donovani donovani 37.41
Leishmania donovani infantum 37.34, 37.36, 37.39, 37.41
Leishmania major 37.34, 37.35, *37.36*, 37.39
Leishmania mexicana amazonensis *37.34*, *37.35*
Leishmania mexicana mexicana *37.34*, *37.35*, 37.39
Leishmania tropica 37.34, 37.35–6, 37.37, 37.39
female genital dermatology 71.69
ocular infection 67.27
leishmaniasis **37.33–44**
American (South American) cutaneous *37.34*, *37.35*, **37.39–41**
differential diagnosis 31.10
diffuse/disseminated cutaneous 37.37, *37.38*
epidemiology *37.34*
genital involvement, in males 71.33
in HIV infection 35.35, 37.43
lip involvement 69.121
lupoid (chronic) 37.37, 37.39, 61.5, 61.13
mucosal **37.39–41**
ocular involvement 67.27
Old World cutaneous **37.34–9**
oral involvement 69.81
perianal/perineal involvement 71.96
post-kala-azar dermal 37.41–2
in returned travellers 37.41
ulcers in 47.57
vectors 38.5, 44.7
visceral **37.41–3**
world distribution *37.33*
leishmaniasis cutis diffusa 37.37, *37.38*
leishmaniasis recidivans 37.37, 37.39
leishmanin test 37.34, 37.37, 37.38, 37.42
leisure activities, risk factor for skin disease 6.13
LEKTI 24.4, 66.65–6
Lelis' syndrome 15.44
Lennert's lymphoma 57.64
lentigines 8.23, **54.2–6,** *54.10*, 71.80
actinic (solar) *54.2*, 54.4
laser therapy 78.10, 80.2, 80.11
lentigo maligna development from 54.4, *54.5*, 54.41
management 58.39, 73.26, 73.27

in Carney syndrome 58.14
definition 58.11
freckles vs 54.1, 54.4
ink-spot *54.2,* 54.5
paraneoplastic 62.33
PUVA *54.2,* 54.4–5, 58.33
senile (age spots) 8.23, 54.3, 58.39
simple *54.2,* 54.3–4
lentigines neonatorum 17.8
lentiginosis 54.2–54.3, 58.11–15
arterial dissections with 58.14
centrofacial 58.12
cutaneous with atrial myxomas 58.14
eruptive 58.11
generalized 58.11
genital 54.6–7
hereditary *54.2,* 54.3
inherited patterned 58.11, 69.28–9
keratosis pilaris and hypotrichosis with 66.60–1
multiple lentigines syndrome 58.12
oral 69.28
periorificial *see* Peutz–Jeghers syndrome
segmental 54.2–54.3
unilateral (zosteriform) 58.11
lentiginous melanocytic hyperplasia 54.30
lentigo maligna 8.28–9, *54.5,* 54.40, 54.42
actinic (solar) lentigo progression to 54.4, *54.5,* 54.41
ageing and 8.23, 80.2
differential diagnosis 54.41–2
seborrhoeic keratosis vs 52.38
mucosal melanosis similarity 54.7
periocular (conjunctival) 54.40–1
treatment 54.42–3
azelaic acid 73.28
radiotherapy 79.12–13
topical imiquimod 73.24
lentigo maligna melanoma 54.35, 54.40–4, 79.12–13
development 54.41
in situ see lentigo maligna
pathology 54.42
treatment 54.43, *54.44*
leonine facies 32.11, 43.5, 43.6
leopard skin 37.6
'leopard spotting' 45.22
LEOPARD syndrome 54.3, **58.12,** 62.77, *69.12,* 69.28
features 58.12
Lepidoptera (butterflies/moths) 25.21, 38.28–30
lepidopterism 38.28
lepra reactions 32.3–4
distinction from relapse 32.17
treatment and 32.17–18
type 1 32.4, 32.6, 32.12
type 2 32.4, 32.6, *32.7,* 32.12–13, 32.18, 75.43
thalidomide and 74.30
leprechaunism (Donohue syndrome) 45.62–3, 46.37
leproma 32.5
lepromin test 32.7, 32.15
leprosy **32.1–20**
aetiology 32.1–2
anhidrosis and 44.13
bone and joint involvement *62.100*
borderline 32.3–4, 32.5–6
features *32.9,* 32.11–12
lepromatous 32.4, 32.6
tuberculoid 32.4, 32.5–6
classification 32.4
clinical features 32.8–12
definition 32.1
diagnosis 32.14–15
differential diagnosis 32.15–16, 60.17
ear involvement 68.17, 68.20
early lesions 32.8
eye involvement 32.13–14
female genital involvement 71.67
genetics 32.2
geographical distribution 32.2–3
histology 32.4–6, *32.7*
history 32.1
HIV infection and 35.26
immunology 32.6–7
indeterminate 32.6, 32.8
lepromatous 32.3, 32.5, 32.7
eyebrow hypoplasia 67.3
features 32.9–11
polar *32.8*
subpolar 32.11
Lucio reaction/phenomenon 32.13, 49.35
mechanisms of damage *32.4*
nerve involvement 32.4, 32.5, 32.6, 32.12, 32.17
complications of damage 32.18
cranial nerve palsy *69.118*
diagnosis 32.13, *32.14*
lepromatous 32.10, 32.11
tuberculoid 32.8–9
ocular involvement 67.27
pathogenesis 32.3–4
patient education 32.18
in pregnancy 8.11
prevention and control 32.19
prognosis 32.14
pure neuritic 32.12
rehabilitation 32.18
relapse 32.17
serology 32.7–8
subclinical infection 32.2–3
treatment 32.16–19
clofazimine 74.26
tuberculoid 32.4, *32.5,* 32.7
differential diagnosis 31.10, 61.5, 61.13
eyebrows 67.3–4
features 32.8–9
polar *32.8*
ulcers 47.56
vaccination 32.19
LEPs (laser evoked potentials) 63.5
leptin 46.3
in acquired generalized lipodystrophy 46.38
body mass index (BMI) and 46.6
congenital deficiency 46.3
in polycystic ovary syndrome 66.82
at puberty 8.4
resistance 46.3, 46.6–7
role in wound healing 14.1
Leptocimex 38.24
Leptoconops 38.6, 38.7
Leptosphaeria senegalensis 36.73
Leptospira 30.62, 30.66
leptospirosis **30.66**
Leptotrichia buccalis 30.60
Leptotrombidium 38.50
Lesch–Nyhan syndrome 59.102–3, 65.50, 69.43, *69.117*
Leser–Trélat sign 52.38, 53.38, 62.31, 62.32
lesions
agminate 5.9
annular 5.8, 5.9, 5.12, 32.15, 62.106–13
arcuate *5.8*
child abuse-associated 28.34–5
colour 5.15–17, *5.18*
confluent 5.9
digitate *5.8*
discoid *5.8, 23.10*
distribution 5.15, *5.16, 5.17*
in drug addicts 28.52–3
grouped/clustered 5.9, 5.14
guttate 5.7
intensive care-associated 28.39
linear 5.8, *5.9, 5.11, 5.12*
livedo *5.8, 5.10*
palpation 5.17–18
pattern 5.9, *5.14,* 5.15
petaloid *5.8*
polycyclic *5.8*
reticulate 5.8, *5.10, 5.12*
satellite 5.9, *5.15*
scattered/disseminated/exanthematous 5.9, *5.15*
serpiginous *5.8*
shape 5.8–9, *5.10, 5.11, 5.12–13*
sparing 5.9
stellate *5.8*
swimming-/diving-associated 28.55
symmetrical 5.15
target 5.8, 38.32
terminology 5.6–8
whorled *5.8*
see also specific lesions
lesser occipital nerve 77.3
lesser weever fish 38.59
lethal cutaneous and gastrointestinal arteriolar thrombosis *see* Degos' disease
lethal toxin 30.41
Letterer–Siwe disease *see* Langerhans' cell histiocytosis (LCH)
leu^5-enkephalin 12.25
leucine-rich repeat (LRR) 12.9
proteoglycans 3.46
leukaemia 62.88
acute myeloid (AML) 55.31
adult T-cell *see* adult T-cell leukaemia–lymphoma (ATLL)
chronic myeloid (granulocytic)
juvenile 62.96
neutrophilic eccrine hidradenitis and 44.17
treatment of skin lesions 73.24
erythroderma and 23.48
genetics 15.14–15, 15.20
juvenile myelomonocytic (JMML) 15.14–15, 15.20
lymphatic 57.62
pigmentation changes 58.26
mast-cell 22.31, 22.33
monocytic 55.31–2
oral involvement 69.57, *69.116*
perianal/perineal involvement 71.99
leukaemia cutis 55.31–2, 57.61–2, 62.15, 62.88
leukaemia inhibitory factor (LIF) 58.5
leukaemia–lymphoma (HTLV-1-associated) *see* adult T-cell leukaemia–lymphoma (ATLL)
leukaemoid reaction 62.88
leukocidal toxins 30.8
leukocyte adhesion deficiency (LAD) 13.9, 17.48, 17.77–8
LAD-1 12.22, 17.77–8
LAD-2 17.78
LAD-3 17.78
oral involvement 69.16
leukocyte cell adhesion molecule (LEUCAM) subfamily, integrins 12.70
leukocyte emigration, regulation by adhesion molecules 12.74
leukocyte function-associated antigens, LFA-1 13.9
leukocyte migration inhibition test 75.174
leukocyte procoagulant activity 26.98
leukocyte rolling 12.74
leukocyte trafficking, CX3CR1 12.48
leukocyte trapping, in venous disorders 47.27
leukocytoclasis, in vasculitis 50.7
leukoderma 58.9
disseminate lenticular 58.52
drug-induced 75.33
following allergic contact dermatitis 26.26
occupational 27.15, 58.50
post-inflammatory 58.48
syphilitic 58.31
leukoderma acquisitum centrifugum (halo naevus) 58.49–50
leukoderma syphiliticum 34.10, 34.12
leukoedema 17.5, 69.23
leukokeratosis
genetics 15.14
lips *see* cheilitis, actinic
oral, focal keratoderma with 19.103
leukomelanoderma 73.27
leukonychia 65.14, **65.15**
apparent 65.15
post-inflammatory 65.29
punctate 65.15
subtotal 65.15
total 65.15
transverse 65.15
leukopathy, symmetrical progressive 58.52
leukopenia, oral involvement 69.56
leukophores 2.5
leukoplakia 69.13, 69.22, 69.50, **69.89–94**
anogenital 71.3
candidal 36.60–1, 69.89, 69.90, 69.91
female genital dermatology 71.52
genetics *15.79*
hairy *see* hairy leukoplakia
heterogeneous/speckled 69.90, 69.91
homogeneous 69.90
malignant transformation 69.90–1, 69.92
oral, treatment 73.23
proliferative verrucous 69.90, 69.91
syphilitic 69.78, 69.90, 69.91
leukotriene(s) 12.60–2, 13.4
modifiers 12.61
leukotriene antagonists 74.31
dose range and evidence level 74.31
in Sjögren–Larsson syndrome 19.44
in urticaria 22.29
leukotriene B4 (LTB_4), inflammatory acne pathogenesis 42.26
leukotriene C4 (LTC_4) 12.25, 12.27, 12.32, 12.46, 12.61, 12.66, 12.74
in urticaria 22.4
leuprolide, in acne vulgaris 42.53
leuprorelin 75.117
levamisole
adverse effects 68.18, 75.71
dermatomyositis 51.129
levator palpebrae superioris 67.2
Levin syndrome I 15.34
levocabastine 67.15
levocetirizine *22.29*
adverse effects 75.149
levodopa
adverse effects 75.88
in restless legs syndrome 63.25
sebaceous gland activity 42.12
seborrhoeic dermatitis and 23.29
levomepromazine (levopromazine) 75.82
levonorgestrel 75.118
acne treatment 42.53
levuride 23.9, 36.36–64
Lewar's disease 69.109
Leyland cypress *26.80*
LH *see* luteinizing hormone
LH 7.2 monoclonal antibody 39.25
Lhermitte–Duclos disease 62.26
l'homme rouge 23.49
LI *see* lamellar ichthyosis
liarozole
dose range and evidence level 74.37
in psoriasis 20.42
Libman–Sacks endocarditis 51.33
lice **38.15–23**
clothing/body 38.2, 38.15, 38.16, **38.21–2**
elderly people 8.29
dogs and cats 2.10
head 38.15, 38.16, **38.17–21**
treatment 73.13, 73.14
pubic (crabs) 38.15, 38.16–17, *38.18,* **38.22–3,** 71.7, 71.34
blepharitis due to *67.10*
eyelash infestation 67.27
treatment 73.13, 73.14
topical therapy 73.13–14
lichen amyloidosus 59.46
lichen aureus 49.22, 49.23, **49.25**
treatment 49.26
lichen myxoedematosus 59.21–3, *62.45*
lichen nitidus **41.21–3,** 65.29
clinical features and sites 41.22
histology 41.21–2
lichen planus with 41.22

linear 41.22
male genitalia 71.24
papules 41.21, 41.22
race and 9.5
treatment 41.22–3
lichen nuchae 23.40
lichen planopilaris 41.7, 41.11–12, 41.14
female genitalia 71.60
scalp 41.11, 66.39, 66.41–3
see also lichen planus, follicular lesions
lichen planus **41.1–20,** 59.79
actinic (subtropical) 41.12–13
erythematous 41.13
acute, confluence of lesions 41.14
allergic contact dermatitis and 26.26
alopecia 41.11, 41.14, 41.17, 66.39, 66.41–3
annular *5.12–13,* 41.7, 41.13, 41.17
associated conditions 41.16–17
atrophic 41.13–14
histology 41.5
buccal *5.10,* 41.8, 41.9
bullous 41.20–1, 41.25
histology 41.5
cicatricial conjunctivitis 67.20
clinical features 41.6–9
complications 41.14–16
dental amalgam association 41.3
diabetes mellitus and 41.9, 41.16
differential diagnosis 40.40, 41.17, 51.117
discoid lupus erythematosus with 41.20
ear 68.15
epidermodysplasia verruciformis vs 33.58
epitheliomatous transformation 41.8
erosive 69.61, *69.62*
erythroderma and 23.48
follicular lesions 41.11–12
histology 41.5
genetic factors 41.2
genital 41.9
in females **71.59–61,** 71.76
in males **71.23–4**
genitocrural 71.5
guttate 41.14
hair involvement 41.14
hands 23.20, *23.21*
hepatitis B virus and 41.16, 62.59
hepatitis C virus and 41.2–3, 41.16
histology 41.4–6
HIV and 41.12
hyperpigmentation 41.12, 41.13
hypertrophic 9.5, 41.7, 41.10
histology 41.4–5
prognosis 41.17
treatment 41.18
idiopathic 41.16
immune system in 41.1–2
incidence 41.4
itching 41.9
Koebner response 28.3, 28.48, 28.73
laryngeal 41.9
lichen nitidus with 41.22
linear 18.23–4, 41.12
multiple lesions 41.12
in liver disease 62.64
localization to tattoos 58.58
macular variant 41.17
'mixed' with DLE 41.20
mucosal 41.7–8, 41.9, 41.15, 41.17, 41.18
histology 41.5
treatment 41.18
nails 41.14, *41.15,* 65.25, 65.29–30
Nékam's disease as variant 41.27
oesophageal 41.9
oral 26.26, 41.9, 69.61–3, *69.65*
complications 41.15
diabetes mellitus and 41.9, 41.16
differential diagnosis 41.9
drugs associated 41.25
histology 41.4
pathogenesis 41.1, 41.2, 41.3, 41.23
treatment 41.18, 73.37
oral erosive, ciclosporin therapy 73.33
palms and soles 26.29, 41.7, *41.8,* 41.14
papules 41.4, 41.6
paraneoplastic 62.38
pathogenesis 41.1–3
perianal/perineal *71.90*
pigmentation 41.7
plane warts vs 33.44
post-inflammatory hypermelanosis after 58.31
prognosis 41.17
pruritus in 41.9, 41.17
race and 9.5
relapses 41.17, 41.18
reticular 69.61
scalp 41.11, 66.39, 66.41–3
secondary syphilis vs 34.12
segmental 41.12
sites 41.7
'spiny' lesion variant 41.7
subacute, confluence of lesions 41.14
tongue 41.8, 41.9
treatment 41.17–20, 73.36
ulceration of feet 41.14, 41.18
variants 41.9–14
viral infections associated with 41.2–3
without itching 41.17
zosteriform 41.12
lichen planus follicularis 41.11
tumid forms 41.14
lichen planus-like contact dermatitis 41.23
lichen planus pemphigoides 40.34, 41.20–1, 69.63
drugs causing/associated with 41.25
lichen planus pigmentosus 41.13, 41.17
lichen planus subtropicus 41.12–13
lichen planus/lichen sclerosus overlap syndrome 69.63
lichen purpuricus *see* lichen aureus
lichen ruber moniliformis (Nékam's disease) **41.27–8,** 73.4
lichen ruber pemphigoides 41.20–1
lichen sclerosus 40.40, 51.64, 51.112–18, 54.6, 71.87
aetiology 51.113
anogenital lesions in women 51.115
associations 51.113
Borrelia and 30.65
breast 70.17
child sexual abuse and 28.38
in children 8.3
female 51.117
clinical features 51.114–15
differential diagnosis 51.117
in elderly people 8.27
extragenital 45.18
female genitalia 51.115, 71.57, **71.62–5,** 71.76, *71.77*
human papilloma virus in 51.116
incidence 51.113
male genitalia **71.20–3,** 71.40, *71.41*
balanitis xerotica obliterans 51.113, 51.116
malignant changes 51.116
in menopause 8.20
morphoea in 51.77
nail involvement 65.29
oral 51.115, 69.63–4
pathology 51.114
perianal/perineal 71.87
prognosis 51.117
purpura and bleeding in 49.17
scalp 66.50
treatment 51.118
urethral stenosis in males 51.116
vasculitis and 50.49
lichen scrofulosorum 31.10, **31.21–2,** 31.29
lichen nitidus vs 41.22
lichen simplex **23.39–41,** 64.27
clinical features 23.40
definition 23.39
diagnosis 23.40–1
ear 68.23
female genitalia 71.52–3
histopathology 23.39–40
male genitalia 9.14, 71.16
neck 23.32
perianal/perineal 71.84, 71.85
treatment 23.41
lichen simplex chronicus 9.13–14, 23.40, 26.17
lichen spinulosus (keratosis spinulosa) 19.75, 19.76
lichen striatus *5.11,* **23.41–2,** 65.29
race and 9.5
lichen verrucosus et reticularis (Nékam's disease) **41.27–8,** 73.44
lichenification **23.39–42,** 64.27
aetiology 23.39
in atopic dermatitis in animals 2.13
clinical features 23.39
definition 5.7, 23.39
in eczema 23.4
female genitalia 71.52–3
genetics 15.10
giant of Pautrier 23.40
histopathology 23.39
mechanical injury and 28.2, 28.28
pebbly 23.40
perianal/perineal 71.84–6
lichenified onchodermatitis 37.4, *37.5, 37.6*
lichenoid, definition 41.1
lichenoid eruptions
definition 41.1
drug-induced 41.23–5
melanoma and 41.6
post-inflammatory hypermelanosis 58.31
see also lichen planus
lichenoid melanodermatitis 41.13
lichenoid photoeruptions 41.25
lichenoid reactions, symptomatic **41.23–7**
lichenoid tattoo reaction 58.58
lichenoid tissue reaction
contact 26.26
histopathology 10.40
lichens 26.24, 26.77, 26.82
lick granuloma 2.9
lidocaine 77.10
adverse effects 77.10
dosage 77.10
in nail biopsy 65.41–2
in post-herpetic neuralgia 63.7
in tick removal 38.36
topical, in oral lichen planus 41.18
life quality index *see* Dermatology Life Quality Index (DLQI)
ligands 26.11
ligase IV deficiency 17.58
light
amplification 78.1
laser 78.1–2
nature of 78.1–2
therapy *see* phototherapy
tissue interactions 78.4–5, 78.5–6, 78.9, 78.12, 78.13
light cautery
comedones 42.67
macrocomedones 42.63
light-emitting diodes (LEDs) 29.2
light exposure
mechanical injury 28.8, 28.53
photodermatitis 28.92
light-induced reactions, tattoo pigments and 58.58
light-reflection rheography (LRR) 47.36
light therapy, acne vulgaris 42.67, 42.68
lightning burns 28.90
lightning pains 34.14
lignocaine *see* lidocaine
likelihood ratio 7.13
Liliaceae 26.76
limb(s)
disproportionate growth 47.23
lower *see* lower limb
melanoma recurrence, management 54.54–5
overgrowth (hypertrophy) 48.21
swelling
causes *48.20*
differential diagnosis **48.19–21**
investigations 48.17–19
as lymphoedema complication 48.15
see also lymphoedema
upper *see* upper limb
limbal broadening 39.19
limbitis
management 67.23
mucous membrane pemphigoid *67.18*
limb–mammary syndrome (LMS) 15.46, **15.64**
limbus *67.4*
lime burns 25.12
limonene (dipentene) 26.41, 26.42, 26.82
lincomycin 75.58–9
lincosamides, side effects 74.42–3
lindane
adverse effects 75.164
in scabies 38.41
withdrawal 73.14
linea alba 8.10, 17.5, 69.87
linear dermatitis herpetiformis *see* linear IgA disease
linear epidermal naevus syndrome *62.100*
linear furrows 45.2
linear IgA disease 40.45–51
acne vs 42.37
aetiology 40.45
cicatricial conjunctivitis and 67.20
clinical features 40.48–9
defined 40.45
dermal-associated 40.49
differential diagnosis 40.50, 76.19
drug-induced 40.49, 75.39–40, 76.7
immunoelectron microscopy 10.29
immunopathology *10.18*
oral involvement *69.65,* 69.68–9
paraneoplastic 62.46
pathogenesis/pathology 40.46–7
prognosis 40.50
treatment 40.50–1
ulcerative colitis and 62.51–2
linear IgA mucous membrane pemphigoid 40.49
linear lichenoid dermatosis *see* lichen striatus
linear naevus syndrome *see* naevus, sebaceous
linear porokeratosis 18.25–6, 19.91
linear subcutaneous bands 51.131
lines of Blaschko 15.6, *15.7*
linezolid 30.9
lingual varices 69.6
linkage disequilibrium 15.7–8
linoleate 3.11
linoleic acid 73.5
reduced in sebum in acne 42.23, 42.26
Linton's operation 47.39
Linuche unguiculata 38.56
lip(s) 69.1–2
acquired lesions 69.119–28
actinic keratosis 52.30
allergic contact dermatitis 26.17
augmentation 80.4, *80.5*
basal cell carcinoma 69.53–4
chancre 69.121
chapping 69.119
cleft *see* cleft lip/palate
in discoid lupus erythematosus 69.128
double lip 69.38
examination 69.5
fissure 69.129
staphylococcal 30.32
haemorrhagic crusting 69.121, 76.16
keratoacanthoma 69.54–5
in leishmaniasis 69.121
leukokeratosis *see* cheilitis, actinic
melanotic macule 69.27
myxoid cyst 69.22, *69.65,* 69.84, **69.110**
naevi 69.29
oedema 48.16
pigmentation, Laugier–Hunziker syndrome 58.14

pits/sinuses 18.3, **18.90–2,** 69.40–1
lip-pit syndrome **15.93–4**
pseudocleft 69.37
radiotherapy 79.10, *79.11*
in reactive perforating collagenosis 69.129
in sarcoidosis 69.129
secondary syphilis and *34.9*
senile haemangioma (venous lake) 47.16, 69.101
squamous cell carcinoma 69.42, 69.49–50, 79.10, *79.11*
surgery *77.3*, 77.5
syphilitic chancre 34.7
in systemic lupus erythematosus 69.128
tattoos 69.96
ulcers
due to calibre-persistent artery 69.129
imiquimod association 54.43
vermilion zone 69.1–2
vermilionectomy 77.36
wedge excision 77.35
lip-pit syndrome **15.93–4**
lipid(s)
antibacterial properties 4.5
epidermal cells *42.5*
foreign-body reaction to 61.22
photoprotective function 4.7
polar, stratum corneum 3.11
role in skin barrier function 3.11, 4.2, 25.2, 25.8
sebaceous cells 42.3, 42.5
sebum 42.5, *42.5*, 42.6
skin surface, abnormalities in HIV infection 35.15
stratum corneum 3.10, 3.11
synthesis in epidermis 3.10–11
tear film 67.2, 67.3
in vehicles for topical therapy 73.5, *73.6*
vernix caseosa 17.4
lipid metabolism, disorders **59.81–93**
dyslipidaemias *see* dyslipidaemias
lipid pathway
ATP binding cassette A-1 (ABCA1) 59.83
endogenous/exogenous 59.82
reverse cholesterol transport 59.82–3
lipid storage disease 44.18, 59.81–93
see also specific diseases
lipid vacuolation, neutral lipid storage disease with ichthyosis 19.52–4
lipidosis, lipoedema vs 48.19
lipiodol 48.17
lipoarabinomannan 31.1, 46.41–3, 70.3, 70.4
lipoatrophia semicircularis 46.36
lipoatrophic diabetes 46.37
lipoatrophy 45.63, 46.11, 46.34
facial *see* facial lipoatrophy
generalized 46.37–9
HIV-associated 35.22, 46.41
insulin 46.34, 46.35
lipoatrophic panniculitis 46.15
localized 46.34–7
'idiopathic' 46.35–7
involutional vs inflammatory 46.35
partial 46.31–2, 46.37, 46.39–40
semicircular 28.27, 46.36
trauma-related 46.36
see also lipodystrophy
lipoblastoma 18.38–9, 56.57
lipoblastomatosis 56.57
lipocortin 73.17
lipocytes 46.2
coagulative necrosis 46.18
fat storage and metabolism 46.2–3
'ghost' 46.18
see also adipocytes
lipodermatosclerosis 46.30–1, 47.27, **47.34**
acute 46.30, *46.31*
chronic, lymphoedema with 48.13
lipodystrophia centrifugalis abdominalis infantalis 46.36
lipodystrophy **46.34–43**
acquired 46.34
generalized 46.37–9
antiretroviral drug association 46.41–3
breast 70.3, 70.4
centrifugal 46.36
congenital 46.34
generalized 46.37
cystic angiomatosis with 46.37
drugs associated with 35.22
generalized 46.34, 46.37–9
acquired 46.37–9
congenital 46.37
HIV-associated 35.22, 46.41–3, 70.3, 70.4
insulin 46.34, 46.35
lipoedema vs 48.19
metabolic abnormalities in 46.41, 46.42
partial (progressive) 46.34, 46.36, 46.39–40, 62.70
face-sparing 46.40–1
familial (FPLD) 46.40–1
treatment 35.22
see also lipoatrophy
lipodystrophy syndrome, HIV-associated 46.41–3, 70.3, 70.4
lipoedema 48.19–20
lipoedema–lymphoedema syndrome 48.19
lipofibromatosis 56.12
lipofuscins, in chromhidrosis 44.20–1
lipogenesis 46.2, *46.3*
regulation in sebaceous glands 42.12
sebaceous 42.5
lipogranuloma
idiopathic 71.50
male genitalia 71.15, 71.50
sclerosing 46.28, 46.29–30
female genitalia 71.56
foreign bodies 28.43–4
idiopathic (eosinophilic) 46.29, 46.30
see also paraffinoma
lipogranulomatosis, disseminated 59.41
lipohypertrophy, buffalo hump 46.42
lipoid dermatoarthritis *see* multicentric reticulohistiocytosis
lipoid proteinosis 59.41–2, *62.100*
abnormal fibroblasts 3.50
lipolysis 46.2–3, 46.3, *46.3*
lipoma **46.43–9**
aetiology and histopathology 46.44
clinical features 46.44
congenital 18.39
diagnosis 46.44
frontalis-associated 46.45
in Gardner's syndrome 46.44
genetics 15.26, 15.27
granular cell (hibernoma) 46.45
lumbosacral 18.39
multiple 46.44, 46.46–7
oral 69.113
pleomorphic 56.57–8
in spinal dysraphism 63.15, 63.16
spindle cell 56.57–8
tendon sheath 46.44
treatment 46.44, 77.35
variants 46.44
lipomastia 70.3, 70.4
lipomatosis **46.46–7**
congenital 18.39–40
congenital diffuse 46.47
Dercum's disease 8.17, 46.46, 46.47–9, 48.20
encephalocraniocutaneous 18.39, 46.46
mediastinal 46.46
mediastinoabdominal 46.46
multiple symmetrical 46.46–7
non-symmetrical 46.46
pelvic 46.46
physiological, racial form 46.46
renal sinus and perirenal 46.46
lipomatosis dolorosa (Dercum's disease) 8.17, 46.46, 46.47–9, 48.20
Lipometer® 42.7
lipomodulin 13.23–4
lipomyelomeningocoele 18.96
Liponyssoides 38.51
lipophagic granuloma 46.13
lipopolysaccharide(s)
in atopic dermatitis 24.7
receptor 13.5
in vasculitis 50.5
lipopolysaccharide-binding protein (LBP) 12.9
lipoprostaglandin E_1, livedoid vasculopathy 49.44
lipoprotein lipase 46.7, 59.89
enhanced activity, multiple symmetrical lipomatosis 46.46
lipoproteins 46.2
atherosclerosis and 59.83
classification 59.82
elevated levels *see* hyperlipoproteinaemias
low-density (LDL)
oxidised 49.41
of standard lipid profile, Friedewald formula 59.84
triglyceride rich (TRLs) 59.90
liposarcoma 56.58
well-differentiated 56.58
liposomes 73.2
T4 endonuclease V formulation 73.23
unilamellar 4.2
liposuction (lipectomy) 46.47
in HIV lipodystrophy 46.43
in lipoedema 48.20
in lymphoedema 48.25
lipoteichoic acid 30.7, 30.12
β-lipotrophin 58.7
lipoxins 12.61, 13.4
5-lipoxygenase (5-LO) 12.61
inhibitor, acne vulgaris treatment 42.66
lipsalves
contact cheilitis due to 69.119
possible allergens in *69.119*
Lipschütz-type ulcers, female genitalia 71.65–6
Lipschütz ulcers
CMV infection 33.29
EBV infection and 33.31
lipsticks 26.17
contact cheilitis due to 69.119
possible allergens in *69.119*
liquefaction degeneration 10.38, *10.39*
liquid nitrogen 33.49, 77.10, 77.39
in acne vulgaris 42.68
photocarcinogenesis control 29.7
skin biopsy sample in epidermolysis bullosa 39.24
see also cryotherapy
Liquid Paraffin BP 73.6, 73.31
liquiritin 73.28
liquorice 73.28, 73.49, 75.160
Lisch nodules **15.16,** 15.17, 58.18, 58.23, 62.23
lisinopril 75.93
Listeria monocytogenes 30.35, 30.42
listeriosis **30.42**
neonatal 17.45, 30.42
Listrophoridae 38.46
Listrophorus gibbus 38.46
lithium 64.52
adverse effects **75.80**
acneiform eruption 42.73
erythema multiforme 76.3, *76.4*
erythroderma 23.47
lichenoid tissue reaction 41.25
Lithraea 26.75
livedo 5.8, *5.10*, **49.48**
antiphospholipid syndrome 49.41
'broken,' in cutaneous calciphylaxis 49.47, 49.48
drug-induced 49.21
livedo annularis *see* livedo reticularis
livedo racemosa 49.48
Sneddon's syndrome 49.42, 49.48
livedo reticularis *28.66*, **28.67–8,** 49.48, 51.132, 58.20
acquired, non-physiological 28.68, *49.49*
antiphospholipid syndrome 49.41
cholesterol embolus and 49.36, 49.37
in cryoglobulinaemia 49.33
leg ulceration associated 47.55
Sneddon's syndrome 49.42, 49.48
summer ulceration with *see* livedoid vasculopathy
livedo vasculitis *see* livedoid vasculopathy
livedoid vasculopathy 47.34, 47.55, **49.44**
leg ulceration associated 47.55
liver
disorders **62.58–65**
acute yellow atrophy 27.11
alcoholic liver disease, methotrexate contraindications 20.34, 74.21
cirrhosis 62.60–2
cutaneous features of chronic disease *62.61*
oral manifestations *69.115*
pruritus in 21.9–10
schistosomiasis 37.22
skin pigment changes in 62.63–4
spider telangiectases 47.14, 47.15
viral hepatitis, methotrexate contraindications 74.21
drug metabolism 72.27, 72.28–9
drug-related phenomena 62.62–3
in echinococcosis 37.24
metastases, carcinoid syndrome 43.17, 43.19
in sarcoidosis 61.7–8
systemic disease and 62.63
in systemic sclerosis 51.101
transplantation 47.18
liver function tests, isotretinoin use and 42.64–5
liver spots 8.23, 54.3, 58.39
liverworts 26.77, 26.82
lizard skin 37.5, *37.6*
lizards 2.4, 2.12
epidermis, shedding 2.3
pigment cells 2.6
LKB1 gene 58.12, 58.13
LL-37 3.16–17, 4.5, 43.2
in eczema herpeticum 33.35
see also cathelicidins
LM *see* longitudinal melanonychia
LMNA gene mutations 46.41
LMS (limb–mammary syndrome) 15.46, **15.64**
LMX1B gene 15.86, 62.69
Loa loa 37.2, 37.3, 37.11–12, 37.16
loath (endemic syphilis) 30.63
lobomycosis **36.77–8**
Lobo's disease **36.77–8**
local anaesthesia **77.10–11**
animals 2.9
field block 77.10
in laser therapy 78.6
methods 77.10–11
in nail biopsy/surgery 65.41–2
nerve block 77.2–4, 77.10, 77.40
in pregnancy 77.10
principles 77.10
ring block 65.42, 77.10
in skin biopsy 10.2
topical 77.10
local anaesthetic agents
adverse effects 26.17, **75.153–4,** 77.10
artefacts in specimens due to 10.31
in pruritus 21.17
skin testing for reactions to 75.172–3
surgical complications associated with 77.9
types 77.10–11
local lymph node assay 26.12
locusts 38.28
LOD (lichenified onchodermatitis) 37.4, 37.5, *37.6*
lod score 11.12

l'oedème bleu 46.28
Löeffler's syndrome 37.14, 37.16
Loeys–Dietz syndrome 45.30
lofepramine *64.51*
Lofgren's syndrome 61.7
logwood hair dye 66.97
loiasis **37.11–12,** 38.6
lomustine 75.125
lone star tick 38.35
longitudinal melanonychia 58.55, 65.2, 65.14, **65.38–41**
  biopsy 65.40
  in childhood 65.39
  in HIV infection 65.16, 65.23
  in lichen planus 65.29
  race and 9.3
  in SLE 58.27
loose anagen hair syndrome 66.72–3
loperamide, in carcinoid syndrome 43.19
lopinavir–ritonavir, adverse effect 35.22
loratadine *22.29*
  adverse effects 75.149
  in urticaria 22.28
loricrin 3.1, 3.10
loricrin keratoderma 19.3, 19.19, 19.94, 19.98
lormetazepam 75.81
Lothian Atopic Dermatitis Study 6.5
lotions 73.2
  thickened (gels) 73.2
Louis, Pierre Charles Alexander 7.1
Louis–Bar syndrome *see* ataxia telangiectasia (AT; Louis-Bar syndrome)
louse flies 38.6
lovastatin 75.156
love bites 28.24
Lovibond's angle/profile sign 65.7, *65.8*
low-density lipoprotein (LDL)
  oxidised 49.41
  of standard lipid profile, Friedewald formula 59.84
low-level laser therapy (LLLT) 78.15
  lymphoedema management 48.23
low-molecular-weight heparin (LMWH)
  in deep-vein thrombosis 47.29, 47.30
  heparin-induced thrombocytopenia and 49.28
  in superficial venous thrombosis 47.30
lower limb
  bilateral whole-limb swelling 48.12
  lymphangiectasia 48.28
  lymphoedema 48.11–12, 48.20
  oedema, rapid development 49.17
  purpura 49.7, 49.17
  see also leg(s)
loxapine 75.82
LOXL1 gene 3.39
LOXL3 3.39
Loxosceles 38.32
Loxoscelidae 38.31, 38.32
loxoscelism 38.31, 38.32
LPS *see* lipopolysaccharide(s)
LPS-binding protein (LBP) 12.9
Lucilia 14.22, 38.8
Lucilia sericata, larval therapy 28.22
Lucio reaction/phenomenon 32.13, 49.35
lues maligna 34.11, 34.14
lumbar sympathectomy, in systemic sclerosis 51.108
lumbosacral dimples 63.15
lumican 45.33
lumpy scalp syndrome 18.104, 68.5
Lund and Bowder charts 28.77, *28.79*
lungs
  Erdheim–Chester disease 55.18
  Langerhans' cell histiocytosis (LCH) 55.7, 55.11
  in SLE 51.43, 62.82
  in systemic sclerosis 51.98
  see also entries beginning pulmonary, respiratory
lunula 3.14, 65.1
  in nail–patella syndrome 65.19
  red 65.17, 65.36
lupoid grains 61.10
lupoid sycosis 30.25
lupus anticoagulant 49.39, 49.40
lupus anticoagulant syndrome 49.40–2, 51.52, 51.63
  clinical features 51.63
lupus band test 10.18
lupus erythematosus (LE) **51.1–62**
  aetiology, sunlight 12.12
  in animals 2.16
  antimalarials in 74.25
  assessment 72.10
  cell factor, deoxyribonucleoprotein 51.52
  cell phenomenon 51.52
  cell test 51.52
  cold-induced injury 28.65
  cutaneous 74.19
  cutaneous atrophy 45.6
  differential diagnosis 29.12, 61.10
  discoid *see* discoid lupus erythematosus (DLE)
  drug-induced 29.21
  drug-induced syndrome resembling 75.20, 75.41–2
  ear involvement 68.14–15, 68.17
  erythema multiforme-like syndrome and 51.14
  exfoliative cutaneous, in dogs 2.16
  gyratus repens 51.11
  hypomelanosis in 58.52
  idiopathic thrombocytopenic purpura and 49.9
  immunopathology 10.18
  keratoderma produced by 19.117, 19.118
  leg ulceration and 47.55
  localization to tattoos 58.58
  matrix metalloproteinases (MMPs) and 12.52
  methotrexate in 74.19
  neonatal **17.16–18,** 51.49–51, 62.78, 62.109
    telangiectases in 47.14
  neutrophilic dermatoses and 50.63
  pigmentation changes 58.27
  post-inflammatory hypermelanosis after 58.31
  subacute cutaneous 51.22–7
  subcutaneous nodules 51.14–15
  systemic *see* systemic lupus erythematosus (SLE)
  treatment
    antimalarials 74.25
    methotrexate 74.19
lupus erythematosus gyratum repens 62.39
lupus erythematosus profundus 46.25–7, 51.14–16
  associated features 51.16
  breast involvement 46.25–6, 70.12
  clinical features 51.15
  histopathology 51.15
  hypertrophicus et profundus 51.14–15
  telangiectases 51.16
  treatment 51.15–16
lupus-like reaction, minocycline-induced 42.51
lupus mastitis 46.25–6, 70.12
lupus miliaris disseminatus faciei *see* acne agminata
lupus nephritis 51.35
lupus panniculitis *see* lupus erythematosus profundus
lupus pernio 61.1, 61.7, 61.9–10, *61.11*
  rosacea vs 43.5
  treatment 61.21
lupus vulgaris 31.10, **31.16–19**
  clinical features 31.16–17
  complications 31.17–18, *31.19*
  cutaneous atrophy 45.6
  definition 31.16
  diagnosis 31.18–19
  differential diagnosis 61.5, 61.13
  ear involvement 68.17, 68.20
  following BCG vaccination 31.29
  histopathology 31.9–10, 31.16
  incidence 31.16
  miliary 31.17
  papular and nodular forms 31.17
  pathogenesis 31.16
  plaque form 31.16, *31.17*
  prognosis 31.17–18
  treatment 31.19, 31.28
  tumour-like forms 31.17, *31.18*
  ulcerative and mutilating forms 31.16, *31.18*
  vegetating form 31.16–17, *31.18*
luteinizing hormone (LH) 8.4
  in adolescence 8.4
  LH:FSH ratio, acne aetiology and 42.22
  menopausal flushing and 8.20
  in menstrual cycle 8.8
  in polycystic ovary syndrome 66.82
lutidine test 27.8
Lutzomyia 37.33, 38.5
Lycopodium serratum 75.160
Lycosa 38.30
Lycosidae 38.32
Lyctocoris campestris 38.25
Lyell's syndrome *see* toxic epidermal necrolysis (TEN)
Lyme disease **30.64–6,** *69.118*
  arthralgia in 62.105
  erythema migrans 62.106–7
  late-phase 30.65, 45.9–11, 45.18
  ocular involvement 67.27
  race and 9.18
  syphilis serological cross-reactivity 34.21
  vectors 38.35
lymecycline
  in acne vulgaris 42.46, 42.47, 42.48
  in rosacea 43.6
lymph 13.8–9
  drainage 48.3
  drainage failure 48.7, 48.8
    causes *48.8*
  flow 48.6
  increased load (capillary filtration) *48.7*, 48.13
  stasis 48.15
  thrombosis 48.29
  transport 48.5–6
lymph blisters 48.26, 48.28
lymph node-to-venous shunts 48.25
lymph nodes
  fine-needle aspiration 5.21
  head and neck 69.4, 77.2, *77.3*
  involvement in squamous cell carcinoma 79.10–11
  lymph drainage to 48.5
  in melanoma *see under* melanoma, malignant
  radiotherapy, lymphoedema after 48.13
  structure and function 13.8–9
lymph sacs, primitive 48.1
lymphadenectomy, melanoma 54.53
lymphadenitis
  histiocytic necrotizing 33.77
  in HIV infection 35.24–5
  inguinal, chancroid 34.34
  Kikuchi's histiocytic necrotizing, EBV infection and 33.31
  lower limb 48.29
  tuberculous 35.25, 35.45
lymphadenoma, cutaneous 53.11
lymphadenopathy
  in cat scratch disease 30.57
  generalized, secondary syphilis 34.11
  in Gianotti–Crosti-like syndrome 33.77
  in granuloma inguinale (donovanosis) 34.36
  in lymphogranuloma venereum 34.33
  in rubella 33.70
  in sarcoidosis 61.1, 61.7, 61.9, 61.13
  sinus histiocytosis with massive lymphadenopathy (SHML) 55.29
  in SLE 51.48
lymphadenosis benigna cutis (of Bafverstedt) 30.65, 57.59
lymphangiectasia 48.15, 48.25
  cutaneous 48.28–9
  genital 48.28
  intestinal 48.27–8
  vulval 71.81
lymphangioblasts 48.1, 48.2
lymphangioendothelioma, benign (acquired progressive lymphangioma) 48.30, 56.41
lymphangiogenesis 48.2
  post-natal 48.2
lymphangiography 48.9, 48.19
  magnetic resonance 48.19
lymphangioma 48.25, **48.25–7**
  acquired (cutaneous lymphangiectasia) 48.28–9
  acquired progressive (benign lymphangioendothelioma) 48.30, 56.41
  cavernous 48.27
  female genitalia 71.72
  genitocrural 71.7–8
  macrocystic 48.27
  oral cavity 69.34
  pinna 68.28
  progressive 48.30, 56.41
  secondary 48.28
  term usage 48.25
lymphangioma circumscriptum 48.26
lymphangiomatosis, diffuse 48.27
lymphangiomyomatosis 48.30
lymphangions 48.4
lymphangiopericytoma 48.30
lymphangiosarcoma 48.15, 48.31
  see also angiosarcoma
lymphangiothrombosis 48.29
lymphangitis 5.*12*, **48.29**
  in lymphatic filariasis 37.9
  milker's nodule 33.10
  obliterative 48.8
  in orf 33.9
  recurrent 48.29
  sclerosing 71.14
lymphatic capillaries 48.3–4
  increased filtration *48.7*, 48.13, 48.21
lymphatic cisterns 48.26
lymphatic endothelial cells (LECs) 48.2
lymphatic hyperplasia, dermal 48.2
lymphatic leukaemia 57.62
  pigmentation changes 58.26
lymphatic malformations (LMs) 18.75–6, **48.25–7**
  cervicofacial 48.27
  classification 48.26
  localized congenital 48.25–6
  macrocystic 48.26–7
  microcystic 48.26
  truncal 48.27
  see also lymphangioma
lymphatic network 3.52
lymphatic system 48.1
  acquired abnormalities **48.29–30**
  anatomy 48.3
  biomarkers 48.4–5, 48.19
  congenital abnormalities **48.25–7**
    see also lymphatic malformations (LMs)
  development 48.1–2
    failure 48.25
  disorders **48.1–31**
    see also specific disorders
  eyelids 67.2
  function 48.5–6
lymphatic tumours **48.30–1,** 56.41–2
lymphatic vessel(s)
  acquired abnormalities **48.29–30**
  anatomy 48.3
  aplasia 48.9
  biomarkers 48.4–5, 48.19
  blood vessels differentiation 48.4, 48.19
  contractile collectors 48.3, 48.4, 48.6
    malformations in 48.26
    progressive distal failure 48.12

decongestive therapy 48.21–4
dendritic cell migration 48.6
dermal backflow 48.3, 48.19
development 48.1–2
  failure 48.25
  post-natal 48.2
die-back phenomenon 48.12
dilatation *see* lymphangiectasia
disorders **48.1–31**
  see also specific disorders
distal hypoplasia 48.11
dysfunctional, lymphoedema due to 48.14
failure, oedema 48.7, 48.8
function 48.5–6
hypoplasia and hyperplasia 48.9
immune function 48.6, 48.29
initial (non-contractile, terminal) 48.3–4
  function and lymph transport 48.5–6
  imaging 48.19
insufficiency 48.7–8, 48.29
manual drainage therapy 48.23
obliteration 48.8, 48.29
obstruction 48.8, 48.11, 48.28
pressure 48.6
recurrent acute inflammatory episodes 48.29
reduced number 48.8
reflux in 48.8
remodelling 48.2
separation from blood vessels 48.2
structure 48.3–5
thrombosis 48.29
transplantation 48.25
transport in 48.5–6
valves 48.3, 48.4
lymphatic vessel endothelial hyaluronan receptor *see* LYVE-1
lymphatic vessel-to-venous shunts 48.25
lymphaticovenous anastomosis 48.25
lymphocoele 48.29–30
lymphocyst 48.29–30
lymphocyte(s) 12.14, 12.17–30
  activation, suppression by tacrolimus/pimecrolimus 73.31
  infiltrates 57.60
    band-like, in lichen planus 41.4, 41.5
  infiltration
    differential diagnosis 51.7
    in familial haemophagocytic lymphohistiocytosis 55.25
    in syphilis 34.5
  nuclear dust, karyorrhexis and 46.26
  proliferation, in cytophagic histiocytic panniculitis 46.23–4
  subpopulation measurements 13.22–3
  toxicity assay 75.174
  transformation tests 26.98, 75.174
  see also B lymphocytes; T lymphocytes
lymphocyte function antigens, LFA-1 13.9
lymphocytic lymphoma, differential diagnosis 51.7
lymphocytoma
  borrelial 62.106
  solitary, in Lyme disease 30.65
lymphocytoma cutis 57.59
  differential diagnosis 51.7, 61.13
  ear 68.15
lymphoedema 3.52, 46.7, **48.7–48.19**
  angiosarcoma and 56.38
  assessment before treatment 48.21
  breast 48.8, 48.17, 48.20
    management 48.23
  breast cancer-related 48.8, 48.17, 48.20
  cellulitis and 48.12, 48.15, 48.17
    management 48.24
  classification and causes 48.9
  clinical diagnosis/features 48.14–15
  complications 48.15
  congenital 48.9
    eyelid 48.16
  Crohn's disease and 48.13, 48.16
  definition 48.7
  dysfunctional lymphatics causing 48.14
  ear 48.12, 48.16
  epidemiology 48.7–8
  eyelids 77.2
    congenital 48.16
  facial 48.12, 48.13, 48.16
    management 48.23
  familial, after puberty 48.10
  filarial 48.12, 48.24
  genetic forms 48.10–11
  genital 30.70, 48.12, 48.16
    management 48.23
  germline forms 48.10
  in granulomatous diseases 48.13, 48.23
  head and neck 48.12, 48.13, **48.16**
    management 48.23
  hereditary type I 48.8, 48.9–10
  hereditary type II 48.10
  in herpes simplex 33.18
  infection prevention 48.22, 48.24
  infection treatment 48.24
  infections after 48.15
  infections causing 48.12
  inflammation with 48.12–13
  inherited forms 48.9–10
  investigations 48.17–19
  in Kaposi's sarcoma 48.14, 48.30–1
  Klippel–Trenaunay syndrome and 48.10, 48.12, 48.21
  localized 48.17
  lower limb 48.11–12, 48.20
  malignancy as complication 48.15
  malignancy associated 48.8, 48.14, 48.30
  management 43.6–7, **48.21–5**
    best practice 48.21
    drug therapy 48.24–5
    efficacy evidence 48.23
    of infections 48.24
    intensive and maintenance 48.23
    physical therapy 48.21–4
    surgery 48.25
    weight loss and oxygen 48.23
  massive localized 48.17
  mechanical injury and 28.1–2, 28.8, 28.31
  melanoma and 48.8
  midline 48.16
    management 48.23–4
  in Noonan's syndrome 15.14
  obesity and 48.20–1
  palmoplantar keratodermas and 19.118
  pathology 48.8
  pathophysiology 48.8–9
  pelvic malignancy 48.8
  penile 71.28, 71.49–50
  periorbital oedema 67.5
  pitting absence 48.14
  in pregnancy 8.17
  primary 48.7, **48.9–12**
    causes *48.9*
    congenital 48.8, 48.9–10
    genetic/inherited forms 48.9–11
    phenotypes 48.11–12
  proximal obstructive 48.11, 48.15
  referrals 48.21
  in rosacea 43.4, 43.6–7, 48.13, 48.16
  sarcoidosis and 48.13, 48.23
  scar 48.17
  secondary 47.35, 48.7, **48.12–14**
  soft stage and hard late-stage 48.8
  trauma-induced *48.12*, 48.13
  truncal 48.15
    management 48.23
  upper limb 48.12, 48.13
  venous disease association *48.12*, 48.13
  venous leg ulcers and 47.45
  vulval 48.16, 71.81
lymphoedema praecox 48.7, 48.9, 48.10
lymphoedema tarda 48.7, 48.8, 48.9
lymphoedema–distichiasis syndrome (LDS) 48.8, 48.9, 48.10, 62.77
lymphoepithelioma, nasopharynx 53.41–2
lymphoepithelioma-like carcinoma 53.41–2
lymphogranuloma venereum (inguinale) **30.70–1, 34.32–4,** 48.12, 71.71–2, 71.93
  clinical features 34.32–3
  syphilis vs 34.7
lymphography
  indirect 48.19
  isotope 48.17
  X-ray contrast 48.17
lymphohistiocytosis
  autoimmune disease-associated reactive haemophagocytic 49.6
  familial haemophagocytic (FHL) 55.25–6
lymphoid markers 10.25–6
lymphoid tissue
  primary 13.7–8
  secondary 13.8–9
lymphoma(s) **57.1–64,** 62.89–90
  adult T-cell leukaemia/lymphoma *see* adult T-cell leukaemia–lymphoma (ATLL)
  angiocentric, EBV-positive 57.40–1
  angiotropic (intravascular) 33.65, 46.23, 50.46–7
  B-cell *see* B-cell lymphomas
  Burkitt's 33.30
  CD30-positive large cell 33.65
  cutaneous **57.1–64**
  cutaneous B-cell 62.89
  cutaneous T-cell (CTCL) 62.89
    chronic actinic dermatitis vs 29.18
    diffuse plane xanthomatosis in 55.22
    γ/δ group (CGD-TCL) 46.23
    in HIV infection 35.41
    in hyperparathyroidism 62.12
    hypopigmentation 58.52
    ichthyotic variant 62.90
    pigmented purpuric dermatoses and 49.23
    radiotherapy 79.13
    topical mechlorethamine treatment 73.23–4
    treatment 73.36
  dermatitis herpetiformis and 40.61
  ear 68.18, 68.34
  EBV association 33.30–1
  erythroderma and 23.48
  formation, chronic actinic dermatitis and 29.17
  genital involvement
    in females 71.79
    in male 71.48
  HIV infection and 35.41
  hydroa-like 46.32–3
  Ki-1 positive 55.32
  large cell, EBV association 33.30–1
  large cell anaplastic 57.31–3
    malignant histiocytosis vs 55.32
  Lennert's lymphoma 57.64
  mucosa-associated lymphoid tissue (MALT) 57.2, 57.43
  NK-cell
    blastic 57.39
    EBV association 33.31
  oral 69.57–8, *69.116*
  perianal/perineal 71.99
  pigmentation changes 58.26
  plasmablastic 35.41
  primary cutaneous
    (anaplastic) CD30+ large cell lymphoma 57.31–3
    hepatoerythropoietic porphyria 59.13–15
    WHO–EORTC classification **57.2**
  pseudolymphomas, ADRs 57.53–4
  radiotherapy and non-melanoma skin cancer due to 52.5
  sarcoidal reaction in 61.23
  sarcoidosis and 61.17, 62.40
  subcutaneous panniculitis-like T-cell (SPTL) *see under* T-cell lymphomas
  sweating in 44.7
  T-cell *see* T-cell lymphomas
  true histiocytic 55.31, **55.33–4**
  zoster complication 33.23, 33.25
  see also B-cell lymphomas; non-Hodgkin's lymphoma; T-cell lymphomas
lymphomatoid granulomatosis *see* polymorphic reticulosis
lymphomatoid papulosis 57.29–30
lymphopenia, HIV infection 35.10
lymphophagocytosis, in sinus histiocytosis with massive lymphadenopathy 55.29
lymphoproliferative disorders
  cryoglobinulinaemia and 49.32
  EBV association 33.30–1
  primary cutaneous CD30+ 57.29–34
    lymphomatoid papulosis 57.29–30
  see also specific lymphoproliferative disorders
lymphorrhoea 48.15, 48.26
lymphosarcoma, pigmentation changes 58.26
lymphoscintigraphy 5.22, 48.17
  melanoma 54.51, 54.52
  normal *48.18*
lymphostatic vasculopathy 48.8
lymphvasculogenesis 48.2
  failure/impairment 48.8
lynx spiders 38.32
lyonization 15.6
lysine, in tropoelastin 3.43
lysine residues
  collagen 3.37, 3.38
  elastin 3.43, 3.44
lysosomal storage disorders **59.30–41**
  angiokeratoma-associated 59.35
lysosomal trafficking regulator, gene mutation, in Chédiak–Higashi syndrome 58.41
lysosomes
  mediators of inflammation 12.53
  sebaceous cell 42.3
lysozyme 10.24, 13.1, 13.4, 30.4
  in sarcoidosis 61.20
lysyl hydroxylase 45.35
lysyl oxidase (LOX) 3.39, 3.44, 45.35, 45.39
lysyl oxidase-like genes/proteins 3.39
Lytta vesicatoria 38.26
LYVE-1 10.24, 48.19
  lymphatic vessel marker 48.4, *48.5*

M

M cells 13.9
M-plasty 77.16
M proteins 30.12, 30.13
Maastricht model 47.27
Mac387 10.24
  antibodies 55.19
macassar *26.80*
Machado–Guerreiro's test 37.32
Machaerium scleroxylon 26.81
machine tool operators/setters, risk of occupational dermatoses *27.2*
Machupo virus *33.67*, 33.69
macrocephaly, with cutis marmorata telangiectatica congenita 18.68
macrocheilia *69.126*
macroclimate 6.12
macrocomedones 42.22, 42.30, *42.57*
  isotretinoin flare and 42.63
  removal 42.63, 42.67
  treatment failure 42.56–7
macroconidia *36.3*, 36.4, 36.18, 36.41
macrogingivae, congenital 66.76
α_2-macroglobulin 13.4
  venous microcirculatory disorders 47.27
macroglossia 62.2, 69.113, *69.114*
macrogols *see* polyethylene glycols
macrolide antibiotics 74.42
  acne vulgaris treatment 42.46–7
macromastia 70.3
macromelanosomes 58.23

macronychia 65.9
macrophage(s) 12.4, 12.26–30, 13.9, 17.48
  arterial disease pathogenesis 47.1
  CD11b, UVR effects 29.5
  cytokines released 46.4
  dermal 3.19
  in embryonic dermis 3.3
  foamy 46.11
  in granuloma inguinale 34.37
  immature 55.4
  intraepidermal *see* Langerhans' cells
  in leprosy 32.7
  malignancies involving **55.31–4**
  melanin in, incontinentia pigmenti 58.15
  microscopy 10.34
  phagocytosis 55.4
    failure 55.27
  receptors 55.4
  in relapsing febrile nodular panniculitis 46.13
  in subcutaneous fat 46.4, 46.6, 46.11
  surface markers 55.29
  tissue *55.2*
    phagocytic function 55.4
    see also histiocytes
  in visceral adipose tissue, in obesity 46.4
  in wound healing 14.3
  see also monocyte(s); monocyte–macrophage system
macrophage activation syndrome 49.6
macrophage inflammatory protein(s), in vasculitis 50.10
macrophage inflammatory protein-1α (MIP-1α) 12.16, 12.18, 12.25, 12.39, 12.45, 12.46, 13.4
macrophage inflammatory protein-1β (MIP-1β) 12.46
macrophage migration inhibition assay 75.174
  lichenoid eruptions due to drugs 41.23
macrophage migration inhibitory factor (MIF) 12.27
macrophage–monocytes *see* monocyte–macrophage system
Macrothele 38.31
macrotia 68.4
maculae caeruleae 38.22–3, 49.17
macular amyloidosis 9.17, 58.28, 59.46
macules
  amelanotic, vitiligo 58.47–8
  ash-leaf 15.22
  blue, in argyria 58.54
  definition 5.7
  differential diagnosis 32.15
  erythema dyschromicum perstans 58.33
  erythematous, herpes zoster 67.26
  freckles 58.10
  genetics 15.16–18, 15.22
  hypomelanotic 58.52
    vitiligo 58.47
  inflammatory, in acne 42.32
  labial melanotic *54.2*
  Laugier–Hunziker syndrome 58.14
  lentigo 54.3
  in leprosy 32.9
  melanotic *see* melanotic macules
  Peutz–Jeghers syndrome 58.12
  simple haemorrhage/purpura 49.2, *49.3*, 49.4
  tuberous sclerosis 58.44
maculopapular rash 5.7, *33.4*
madarosis 32.11, 62.10, 67.4, *67.4*
MAdCAM 13.9
Madelung's neck 46.46
Madura foot *see* mycetoma
Madurella grisea *36.73*
Madurella mycetomatis 36.72, *36.73*, 36.74
maduromycosis *see* mycetoma
madurosis *67.8*
Maffucci's syndrome 18.72, 65.34
  bone and joint involvement *62.100*
  lymphoedema 48.11, 48.31
  oral involvement 69.13, 69.29, 69.30
magenta paint 36.48, 36.49
  topical therapy 73.48
maggot therapy, venous leg ulcers 47.48
maggots 14.22, 38.8
MAGIC syndrome 45.44, 69.47
magnetic resonance angiography (MRA), peripheral arterial disease 47.4
magnetic resonance imaging (MRI) 5.22
  foreign bodies 28.42
  muscle hernias 28.62
  sarcoidosis 61.7
  Sturge–Weber syndrome 18.66
  venous malformations 18.71
magnetic resonance lymphangiography (MRL) 48.19
Magnolia officinalis 75.160
main succulente 63.14
maintenance, of skin **3.5–7**
Majocchi's disease (purpura annularis telangiectodes) 49.22, **49.25**
Majocci's granuloma, in HIV infection 35.32
major basic protein 13.5, 67.15
  in urticaria 22.3
major complement components, deficiencies 51.54
major histocompatibility complex (MHC) 13.14
  class I molecules 4.8, 13.10
    deficiency 17.61
    hair cycle and 66.11
  class II molecules 4.8, 13.9–10
    deficiency 17.60–1
    expressed by phagocytes 55.4
  dysfunction or genetic alteration of MHC alleles 12.13–14
  genetics 15.8–9
  inflammation and 12.13
  MHC class I chain-related gene B (MICB) 12.14
  peptide-binding capacity 12.13
Mal de Meleda 19.3, *19.94*, 19.100–1
mal de pinto (pinta) 30.63–4
mal morado 37.7
malabsorption 59.58–9, *69.116*
  bacterial overgrowth 51.100
  causes 59.58
  in children with HIV infection 35.45
  eczema and 23.27
  hair loss and 66.29
  pigmentation changes 58.28
  systemic sclerosis 51.99
  vitamin B12 deficiency, systemic sclerosis 51.102
malaise, systemic, in photosensitivity disorders 29.23
malakoplakia 55.27
  HIV infection 35.36
  vulval 71.70
malaria 37.27, 38.2, 38.5, 44.7
  pigmentation in black people and 58.9
Malassezia
  aberrant reaction to, HIV infection 35.15
  antibody response to 36.11
  atopic dermatitis and 24.11, 36.13
  in confluent and reticulate papillomatosis 36.13–14
  dermatitis in animals due to 2.14
  folliculitis 23.34, 36.13
    acne vs 42.37
  genetics 15.10
  identification 36.9
  in invasive otitis externa 68.25
  male genital infection 71.18, 71.33
  in neonatal pustulosis 17.47–8
  in normal skin flora 30.2, 36.10, 36.13
  in pityriasis capitis 66.56
  pityriasis versicolor and 36.10, 36.11, 36.12
  seborrhoeic dermatitis and 17.29, 23.29, 23.30, 36.13, 66.56
Malassezia furfur 42.24
  acne aetiology and 42.24
  folliculitis 42.37
Malassezia globosa 42.75
Malassezia pachydermatitis, in dogs 2.14
Malassezia sympodialis 33.35, 42.75
malathion 73.14
  in clothing/body louse infection 38.22
  in head louse infection 38.19
  resistance 38.20
  in scabies 38.41
Malayan krait 38.60
male(s)
  acne vulgaris 42.17–18
  sexual development 8.2, 8.4
  spermatogenesis 8.4
male angiomyofibroblastoma-like tumour 76.8
male genital dermatology **71.8–52**
  circumcision 71.13, 71.20, 71.24, 71.39
  congenital and developmental abnormalities 71.13–14
  drug reactions 71.27–8
  foreskin 71.9, 71.12–13
  general approaches 71.1–4, 71.8–10
  inflammatory dermatoses 71.16–29
  lichen planus 41.9
  malignant neoplasms 71.46–9
  miscellaneous conditions 71.49–52
  non-sexually transmitted infections 71.29–33
  normal genital variants 71.11–12
  pain and swelling 71.49–50, 71.51–2
  premalignant dermatoses and carcinoma *in situ* 71.37–9
  sexually transmitted diseases 71.33–5
  squamous cell carcinoma 71.22, **71.39–46**
  structure and function of male genitalia 71.10–11
  trauma and artefact 28.24, 28.39, 71.14–16
  tumours 71.35–7
  see also individual conditions
maleopimaric acid 26.79, 26.82
malformation sequence 18.1
malformation syndromes 18.1
  aplasia cutis congenita in 18.102–6
malformations 18.1, **47.21–5**
  arteriovenous *see* arteriovenous malformations (AVMs)
  capillary 47.23, 47.25
  venous *see* venous malformations
Malherbe, benign calcifying epithelioma of 53.12–13
Mali, prevalence of skin disease *6.10*
malignant atrophic papulosis *see* Degos' disease
malignant disease 52.1
  acanthosis nigricans 19.120
  in amputees 28.29
  benign tumours vs 52.2
  burns and 28.90–1
  development *see* carcinogenesis
  direct spread to skin 62.15–17
  ear 68.30–4
  female genital region 71.76–9
  following chemotherapy 75.124
  genetics 11.17–19
  genodermatoses associated 62.19–29
  granuloma annulare and 60.9
  haematological 62.88–90
  hyperpigmentation 58.25
  ichthyoses 19.39, 19.55, 19.56, 19.61, 19.63
  immune system and 13.15
  immunopathology 10.19
  internal
    acquired acanthosis nigricans 58.25
    Bowen's disease and 52.33
    cutaneous markers **62.14–29**
    Muir–Torre syndrome 52.10, 53.15
    multicentric reticulohistiocytosis 55.24
    thrombophlebitis migrans and 47.30, 47.31
  investigation 62.14
  lymphoedema associated 48.8, 48.14
  as lymphoedema complication 48.15
  male genital region 71.46–9
  mechanical injury 28.62–3
  metastatic 52.1, 62.17–19
    female genital involvement 71.79
    immunopathology 10.24
    male genital involvement 71.48
    nail involvement 65.34
    oral cavity 69.55–6
    radiotherapy 79.13
    telangiectatic 62.16
    tumour-to-tumour 62.18
    umbilical dermatology 71.101
  neoplastic vaginal discharge 71.54
  oral cavity 69.13, 69.22, 69.42, 69.49–456, 69.98–9
    metastatic 69.55–6
  palmoplantar keratodermas 19.106, 19.116–17
  pigmented purpuric dermatoses and 49.23
  pruritus and 21.11
  radiotherapy and non-melanoma skin cancer due to 52.5
  reduced by sunscreens 73.41
  sarcoidosis and 61.17
  scleroderma-like lesions and bFGF 51.79
  sweating associated 44.7
  Sweet's syndrome and 50.74, *50.75*
  TNM staging *69.51*
  transplacental transfer 17.19
  tuberculosis and 31.18, *31.19*, 31.21
  umbilical dermatology 71.101
  wound healing and 14.18
  xeroderma pigmentosum and 15.72
  see also carcinoma; tumour(s); *specific tumours*
malignant down 66.78
malignant melanoma *see* melanoma, malignant
malignant neoplasms *see* malignant disease
malignant peripheral nerve sheath tumours (MPNST) 15.18
malingering 64.43
'Mallorca' acne 42.79
malnutrition
  child abuse 28.38–9
  in children with HIV infection 35.45
  dermatophytosis and 36.22
  hair colour change in 66.94
  hair loss in 66.29
  hypertrichosis in 66.78
  pityriasis versicolor and 36.10
  pressure ulcers 28.18, 28.21–3
  purpura in 49.18
  wound healing and 14.18
malondialdehyde, increased levels, rosacea 43.2
Malpighian layer 3.8
  ballooning of cells, VZV infection 33.23–4
MALT (mucosa-associated lymphoid tissue) 57.2
MALT lymphomas 57.2, 57.43
maltase deficiency 44.18
Malvaceae *26.81*
mammalian target of rapamycin (mTOR) 74.5
mammals
  glands 2.4
  hair 66.1
  pigment cells 2.6
    mutations affecting 2.6–7
  skin 2.3
  see also animal(s); *specific mammals*
mammary glands 44.18, 70.1
  ectopic, anogenital 53.37
  see also breast
mammary-like glands, anogenital 53.37
  tumours 53.37–8
mammary ridges 70.1
mammo-renal syndromes 70.2
mammoplasty, reduction 70.3

mandible 69.2
  examination 69.5
mandibulofacial dysostosis **18.80–1,** 68.4
manganese
  in Hailey–Hailey disease 39.33
  in tattoo pigments, allergic reactions 58.58
mange
  demodectic 2.10
  dogs 2.10
  'head' (feline) 2.10
  sarcoptic 2.10
  sheep and cattle 2.10–11
mango 26.75
mangrove fly 37.11
mannan-/mannose-binding lectin/protein 13.2, 13.3, 17.48
  deficiency 13.4
  measurement 13.18
mannans 36.1, 36.58
mannose receptor, and other C-type lectins 12.10
mannosidoses 59.34
Mansonella ozzardi 37.8
Mansonella perstans 37.8
Mansonella streptocerca 37.8
Mansonia altissima *26.81*
Mantoux test 31.6
manual lymphatic drainage therapy (MLD), in lymphoedema 48.23
Manuka honey 73.48
manzanillo tree *25.21*
MAP kinase pathway 3.16–17
  stem cell signalling 3.6
maprotiline 75.79
marasmus 59.67
  hair loss in 66.29
marbling, neonatal 17.4
Marburg disease/virus *33.67*, 33.69–70
  diagnosis 33.5
Marcain *see* bupivacaine
Marfan's syndrome **45.30–1**
  aetiology 45.30
  bone and joint involvement *62.100*
  clinical features 45.30
  definition 45.30
  diagnosis 45.30–1
  FBN1 gene 3.45
  management 45.31
  mechanical injury 28.2
  pathology 45.30
  pregnancy and 45.31
Margarita Island ectodermal dysplasia 15.46
marginal papular acrokeratoderma 9.10
marginal papular keratodermas 19.95, 19.114–15
marginal zone lymphoma, primary B-cell 57.43–5
marine worms, cuticle and epidermis 2.2
Marjolin's ulcer 28.20, *28.91*
marking nut tree 26.75
Marshall's syndrome 15.46, 46.20
MART-1 *see* Melan-A
martin bug 38.24
mask of pregnancy *see* melasma
masons, occupational hazards 27.20
mass populations reactions **64.25–6**
massage, in lymphoedema 48.23
masseter muscles, examination 69.4
Masson's ammoniacal silver nitrate stain 10.8–9
Masson's naevic corpuscles 54.19
Masson's pseudoangiosarcoma (intravascular papillary endothelial hyperplasia) **56.23–4,** 69.102
Masson's trichrome stain 10.9
Masson's vegetant intravascular haemangioendothelioma (intravascular papillary endothelial hyperplasia) **56.23–4,** 69.102
mast cell(s) **3.19–20,** 12.24–6, 13.5
  activation 3.20, 22.4
    IgE-mediated 3.20
  in atopic dermatitis 3.20
  in atopic eye disease 67.15
  cathelicidins 12.7
  connective tissue type 3.19
  cytoplasmic granules 3.19
  degranulating triggers *22.35*
  dermal 3.19
  in embryonic dermis 3.3, 3.19
  functions 3.20
  increased in ageing skin 8.22
  in infantile haemangioma 18.42
  inflammatory mediator release 3.20
    sodium cromoglycate action 73.51
  in mastocytosis 22.30, 22.34
  microscopy 10.35
  mucosal type 3.19
  nerve interactions 3.20
  neutral protease content 12.24
  origin and development 3.19
  products released 3.20
  pruritus and 21.4, 21.8
  receptors 12.25
  in rosacea 43.4
  secretory granule 12.25
  staining 10.9
  tumours, in animals 2.9, 2.22–3
  in urticaria 22.3, 22.4–5
mast cell growth factor/stem cell factor (M/SCF), melanocyte mitogen 58.5
mast cell tryptase 13.16
mast cell tumours, in animals 2.9, 2.22–3
mast-cell growth factor *see* stem-cell factor
mastectomy, angiosarcoma following 56.38
mastitis 8.13
  in breastfeeding 70.10
  duct ectasia/periductal mastitis complex 70.8
  granulomatous 31.25
  lupus 46.25–6
  neonatal 17.43
mastocytoma 22.32
  in cats 2.22
  skin biopsy 10.43, 22.34
mastocytosis **22.30–6,** 62.43
  aetiopathogenesis 22.31
  aggressive 22.31, 22.33
  bone and joint involvement 62.99, *62.101*
  bullous 22.32
  classification 22.30–1
  clinical presentation 22.31
  cutaneous 22.30, *22.31*, 22.31–3
    diffuse 22.33
  emergency management 22.35
  flushing associated 43.16
  genetics 22.30, 22.31
  histopathology 22.34
  investigation 22.34–5
  management 22.35–6
  prevalence 22.31
  prevention 22.35
  prognosis 22.36
  pruritus in 21.10, 22.32, 22.35
  systemic 22.30, *22.31*, 22.33–4
mastopathy, diabetic 50.49
materia alba 69.87
Matricaria *25.21*
matrilysins 12.5, 12.52
matriptase 12.50
matrix Gla protein 49.48
matrix metalloproteinases (MMPs) 3.40–1, **12.51–3**
  ADAMs 12.51
  ageing and 80.1, 80.2
  in chronic wounds 14.11
  hair growth and 66.10
  inhibitors *see* tissue inhibitors of metalloproteinases (TIMPs)
  in Kawasaki disease 50.45
  matrilysin (MMP-7) 12.5, 12.52
  MMP1 3.40, 8.21–2, 47.27
  MMP2 47.27
  MMP3 (stromelysin-1) 3.41
  MMP8 3.41
  MMP9, in lichen planus 41.2
  MMP10 (stromelysin-2) 3.41
  synthesis and secretion 3.41
  tissue inhibitors *see* tissue inhibitors of metalloproteinases (TIMPs)
  UVR-induced 8.21, 8.22, 29.7
  in Winchester's syndrome 45.50
  in wound healing 14.4, 14.5
  wrinkles and 45.2
Mauriac's syndrome 60.9
Maurice's syndrome 33.18
mauve stinger 38.56
Max Joseph spaces, in lichen planus 41.4
maxacalcitol 73.43, 73.46
  structure *73.44*
maxilla 69.2
  examination 69.5
maximal skin tension lines 77.2, 77.11, 77.13
maximization test 26.11, 27.10
May–Thurner syndrome 47.32
Mazzotti's test 37.7
MBL *see* mannan-/mannose-binding lectin/protein
MBP *see* mannan-/mannose-binding lectin/protein
MBT (mercaptobenzothiazole) 26.64
MC1R (melanocortin 1 receptor) 3.21, 29.5, 54.2, 54.33, 58.7
MC1R gene 2.5, 2.6, 54.33, 66.90–1
MC903 *see* calcipotriol
McCune–Albright syndrome 15.18, 58.18–19, 62.13, 62.99, *62.100*
  neurofibromatosis vs 58.18
McGrath syndrome 15.46
MCP *see* CD46
MCUS (multiple cutaneous and uterine leiomyomatosis) 56.55
MDBGN (methyldibromo glutaronitrile) 26.55
MDS *see* myelodysplastic syndrome
MDT (multidrug regimen), in leprosy 32.16–17
meadow dermatitis 58.32
  phytophotodermatitis 29.21, **58.32,** 75.162
mean 7.17, *7.18*
measles **33.75–6,** 69.95, *69.118*
  aetiology and pathology 33.75
  antibodies 33.75
  atypical, in HIV infection 35.45
  clinical features 33.75
  diagnosis and prevention 33.75
  MMR vaccination 33.71
  neonatal purpura 49.20
  treatment 33.76
measurement of disease **72.8–14**
  correlation with QOL measures 72.14
  value of 72.8
mebendazole 74.50–1
  in dracunculiasis 37.13
  in enterobiasis 37.14
mechanical acne 42.76–7
mechanical injury **28.1–63**
  amputees 28.27–9
  biomechanical considerations 28.4–9, 28.11
  child abuse 28.34–9
  determinants 28.2, 28.6–7
  evaluation methods 28.5–6
  foreign bodies 28.39–52
  friction 28.2, 28.9–16, 28.28
  hypothenar hammer syndrome 28.26, 28.56
  internal 28.60–2
  Koebner response 28.2–3, 28.15, 28.48, 28.73
  malignant neoplasms 28.62–3
  miscellaneous reactions to mechanical trauma 28.25–39
  musical instruments 28.25–6
  Nikolsky sign 28.4, 76.17
  overview 28.1–4
  pathological variation 28.8
  physiological variation 28.7, 28.18
  pressure ulcers 28.16–23, 28.27–8
  sexual abuse 28.34, 28.37–8
  skin function and properties 28.5–7
  skin lesions in drug addicts 28.52–3
  sports injuries 28.30–2, 28.53–6
  suction 28.23–5, 28.39
  swimming and diving 28.31, 28.53–6
  torture injuries 28.32–4
  vibration 28.56–60
mechanical nociceptors 4.9
mechanical properties of skin 4.7–8
mechanics, occupational hazards 27.20
'mechanic's hands,' antisynthetase antibodies 51.125
mechanobullous diseases 39.1
  in animals 2.17
  see also epidermolysis bullosa (EB)
mechanoreceptors 4.9, 4.*10*, 63.2
  rapidly adapting 4.9
  slowly adapting 4.9
mechlorethamine
  and carmustine (BCNU) 57.23
  hypersensitivity to 73.23
  topical 73.23–4
  see also nitrogen mustard
Meckel's diverticulum 18.93
meclofenamate sodium 75.76
medial canthus 67.2
  basal cell carcinoma 67.35
  in mucous membrane pemphigoid *67.18*
medial pterygoid muscle, examination 69.5
median 7.17, *7.18*
median raphe cysts, male genital region 71.35
median umbilical ligament 18.94
medical elastic compression stockings (MECS)
  deep-vein thrombosis 47.29, 47.30
  Klippel–Trenaunay syndrome 47.24
  thrombophlebitis migrans 47.31
  see also compression stockings
medical literature
  appraisal and evaluation of research papers *7.10*, *7.13*, *7.15*, 7.16–23
  databases 7.5–6
  keeping up with 7.2
  language bias 7.7–8
  publication bias 7.7, 7.8
  searching 7.5–6
medical publications *see* medical literature
MedicAlert bracelet 38.15
  in latex allergy 26.106
medicolegal issues
  factitious skin disease 64.45
  occupational dermatoses 27.17–18
Medina worm **37.12–13**
Mediterranean fever 30.73
MEDLINE 7.5, 7.6
medroxyprogesterone acetate 75.119
MedWatch 75.3
Mees' lines 65.15, 65.16
mefenamic acid 75.76
mefloquine 75.70
Megalopyge 38.29
megalymphatics 48.12
megestrol 75.89, 75.119
meglumine antimoniate 37.39
Meibomian ductules
  epithelial metaplasia 67.21
  keratinization 67.11
Meibomian gland 42.1, 67.2
  dysfunction *67.7*, *67.9*
    epidemiology 67.6
    in Stevens–Johnson syndrome 67.21
  hypertrophy 27.13
  lipids, composition change in rosacea 43.7
  normal, ducts 67.11

Meibomian gland disease (MGD) 67.11
Meibomian lipids 67.11
Meibomian seborrhoea *67.7*, 67.11
meibomitis *67.7*, *67.9*
meibum, abnormal production 67.11
Meige's disease 48.9, 48.10
meiosis, definition 15.3
Meirowsky phenomenon 58.10
Meissner's corpuscles 3.15, 4.9, 4.*10*, 63.2, 63.14
Mel-5 10.21, 20.22
Melaleuca alternifolia oil see tea tree oil
Melan-A 10.21, 20.22
Melan-A mart melanoma antigen 53.39
melanin(s) 5.15, 54.1, 58.1
  absence, vitiligo 58.47
  in animals 2.5
  in basal cell carcinoma 52.21
  biological significance **58.8–9**
  as chromophores 78.3
  evolution 2.1
  forms/types 2.5
  function 3.3
  hair pigmentation and 3.20, 66.89–890, 66.90–1
  in Hodgkin's disease 57.63
  increased, Peutz–Jeghers syndrome 58.13
  mixtures of eumelanins and pheomelanins 58.5, *58.6*
  mucocutaneous, Peutz–Jeghers syndrome 58.12
  photoprotective role 4.7
  pigment types 3.20
  protective function 58.8, 58.10
  synthesis/production 3.21, 4.7, 58.2, 58.5, *58.6*
    by *C. albicans* 36.57
    delayed effect of tanning 29.5
    genetic variation 58.2–3
    inhibition by depigmenting agents 73.27
    see also melanogenesis
  types 58.5, *58.6*
melanoacanthoma 52.39–40
  eyelid 67.34
  see also melanotic macules
melanoacanthosis *see* melanotic macules
melanoblasts 3.3
  development in neural crest 58.3
  migration and differentiation 58.3–4
melanocortin
  in Addison's disease 58.7
  MC1
    Melanocortin-1 gene 2.5, 2.6
    sebocytes expressing 42.4
  MC5, sebocytes expressing 42.4
Melanocortin-1 gene 2.5, 2.6
Melanocortin-1 receptor genes 2.5, 2.6, 54.33, 66.90–1
melanocortin receptor(s)
  MC5-R, sebocytes 42.4
  melanocortin 1 receptor (MC1R) 3.21, 29.5, 54.2, 54.33, 58.7
    MC1R gene 2.5, 2.6, 54.33, 66.90–1
melanocyte(s) 3.1, **3.20–1,** 54.1, *54.10*, 54.15, 58.1, **58.2–5**
  absence
    lichen planus 41.4
    piebaldism 58.42
    vitiligo 58.47
  age-related changes *80.2*
  age-related reduction in number 58.3
  in alopecia areata 66.33
  in animals 2.5–6, 2.6
  autoantibodies, in vitiligo 58.46
  in basal layer of epidermis 58.2, *58.3*
  birds 2.6
  compound naevus, and cell types 54.18
  in culture 58.2
  culture of 58.5
    response to UV 58.7
  cytological atypia, atypical naevus 54.30
  dendrite formation 58.4
  dendritic, in dermal melanocytosis 58.36
  dermal–epidermal junction 54.1, 54.2, 54.4, 54.15, 54.18
  development 58.3–4
    signalling and transcription factors 58.3
  differentiated 3.21
  distribution 58.2–3
    regional *58.3*
  electron microscopy 10.29–30
  embryology and affinities 3.3, 3.5, 3.21
  evolution 2.5–6
  G-protein-coupled receptors 3.21
  grafts 77.22
  in greying hair 66.92
  hair bulb 66.4, 66.90
  hair follicles 58.3
  increased activity 58.31
  increased number 58.9, 58.11, 58.31
    tanning 58.31
    see also lentiginosis
  keratinocytes surrounding 54.18, 58.2, 58.7
  large, reduced, piebaldism 58.42
  lentiginous hyperplasia 54.30
  lips 69.2
  markers 3.21, 10.21–2
  melanin synthesis 4.7, 58.2
    genetic variation 58.2–3
  migration into dermis 54.18
  mitogens and growth factors 58.5
  in nail matrix 3.15, 65.2, 65.14
  number in skin 58.9
  number of keratinocytes associated 58.2
  in piebaldism 66.93
  proliferation 54.2
    atypical naevus 54.28
    basal cell carcinoma 52.21
    melanoma 54.35–6
    seborrhoeic keratosis 52.39
  race and 9.2
  reduction in number
    age-related 58.3
    disorders 3.21
  regulation 58.7–8
  response to UV 58.7
  signalling pathways 3.21
  stem cells 3.21
  UV-induced growth arrest 58.7
melanocyte lineage, development 58.3
melanocyte-specific antibody, HMB-45 58.3
melanocyte-stimulating hormone (MSH) 12.63–4
  melanocyte mitogen 58.5
  melanosome transfer to keratinocytes 58.4
  MSH-2, in Muir–Torre syndrome 53.15
  pigment cell regulation in fish 2.5–6
α-melanocyte-stimulating hormone (α-MSH) 29.5
  pigmentation and 66.90–1
  sebaceous gland activity 42.12
β-melanocyte-stimulating hormone (β-MSH)
  in Cushing's syndrome and hyperpigmentation 58.24
  hypermelanosis in systemic disorders 58.25, 58.27
melanocytic lesions, dermal 54.7–9
melanocytic naevi *see* naevus, melanocytic
melanocytoma 54.9
melanocytoma–acanthoma, in dogs 2.21
melanocytosis
  dermal 58.36–8
  disseminated dermal 58.38
  leptomeningeal 54.13–14
  oculodermal *see* naevus, of Ota
  see also hyperpigmentation
melanodermatitis, lichenoid 41.13
melanoepithelioma, non-naevoid, type 1 52.39–40
melanogenesis 58.2
  biochemistry **58.5–6**
  hair follicles 66.90–1
  increased 58.9
  oestrogen effect 58.7
  UV-stimulated 58.31, 58.32
  see also melanin(s), synthesis/production
melanogenuria, slaty-blue dermal melanosis 58.25
melanoleucoderma 15.47
melanoma, malignant **54.32–57**
  ABCD categories/mnemonic 54.37
  acquired melanocytic naevi progression 54.37, 54.38
  acral lentiginous 15.11, 54.35, 54.44, *54.45*, *54.46*, 65.40
  aetiology 29.7, 54.32–3
  AJCC staging system 54.49, *54.50*
  amelanotic 65.39
    subungual *54.46*
  animal-type 54.48
  in animals 2.20–1, *2.22*
  anorectal 54.47
  antibodies, diagnostic use 54.39
  'at risk' patients, identification 54.34
  atypical mole syndrome 54.34, 54.47
  atypical naevi progressing to 54.28, *54.29–30*, *54.31*
  biomarkers 54.51
  biopsy 54.38
  breast 70.14, 70.15
  Breslow thickness 54.49, 54.52
  carcinoma erysipeloides 48.31
  CDKN2A gene 54.33
  childhood 54.48–9
  Clark levels 54.38
  clinical diagnostic aids 54.37
  clinicopathological variants 54.35–6
  communicating prognosis 72.5
  congenital naevi progression 54.10, 54.13
  CT scan after relapse 54.50
  dermoscopy 54.19, 54.38
  desmoplastic 54.42, *54.43*
  differential diagnosis 54.6, 54.38–9
    acquired melanocytic naevi vs 54.19, 54.38–9
    atypical melanocytic naevus vs 54.28, 54.38
    basal cell carcinoma vs 52.21
    halo naevus vs 54.20
    malignant blue naevus vs 54.27
    metastasizing Spitz naevus vs 54.22
    Spitz naevus vs 54.22, 54.23–4, 54.39
  ear 68.33–4
  early, features 54.19
  elective lymph node dissection (ELND) 54.51
  equine, human melanoma comparison 2.20
  evolving from congenital naevi 54.10, 54.13
  eyelids *67.35*, *67.36*
  familial 54.33–4, 54.48
  family history 54.47–8
  female sex hormones and 54.56–7
  fine needle aspiration cytology 54.53
  follow-up after surgery 54.53
  following chemotherapy 75.124
  generalized lentiginosis and *54.3*
  genetics 6.12, 11.18
  genital 54.47
    female genital region 71.77–8
    male genital region 71.47
  Glasgow seven-point check-list 54.37
  growth phases 54.35–6
  halo naevus with 58.49
  histogenetic types/sites 54.37–49
  in HIV infection 35.39–40
  immunohistochemistry 54.49
  in situ *54.29–30*, 54.35–6, *54.39*
    early, vs atypical naevus 54.28
  incidence 54.32
    increased with sunscreen use 73.41
  intracerebral primary 54.13
  invasive
    elderly people 8.28–9
    treatment 54.39
  juvenile *see* naevus, Spitz
  lentigo maligna *see* lentigo maligna melanoma
  lichenoid tissue reaction association 41.6
  lymph node involvement 54.47, 54.50
    de novo origin 54.47
    management 54.53
  lymphoedema 48.8
  lymphoscintigraphy 54.51, 54.52
  management/treatment 54.49–56
    after excision of primary 54.50–3
    anti-CTLA-4 antibody therapy 54.54
    azelaic acid 73.28
    biological therapies 54.53–4
    of brain metastases 54.55–6
    follow-up after surgery (stage I/II) 54.53
    interferon-alpha (IFN-α) therapy 54.53–4
    metastatic to lymph glands 54.53
    palliative care 54.54, 54.55, 54.56
    radiotherapy 54.55, 54.56, 79.12
    recurrent disease in limb 54.54–5
    stage IV disease 54.54, 54.55–6
    topical imiquimod 73.24
  metastasis *5.15*
    brain 54.54, 54.55–6
    childhood melanoma 54.48
    in transit 54.54–5, *54.55*
    to lymph glands, management 54.53
    placental and fetal 54.57
    in pregnancy 54.56
    retarded in horses 2.20
    sites 54.51, 54.54
    solitary brain 54.54, 54.55
    topical imiquimod 73.24
    unknown primary site 54.47
  minimal deviation 54.48
  mortality 54.32
  mucosal 54.46–7
  multiple primary 54.47–8
  myxoid 54.42
  naevoid 54.48
  neurotropic 54.42
  nipple, Paget's disease vs 53.39
  nodular 54.35, 54.36, 54.40, *54.54*
    elderly people 8.29
  Notch signalling abnormality 3.21
  obesity and 8.17
  oral cavity 54.6, 69.98–9
  palliative management 54.54, 54.55, 54.56
  palmoplantar 54.35, 54.44, *54.45*
  phenotypic risk factors 54.33
  photography, detection by 54.31
  pre-pubertal 54.48–9
  pregnancy and 8.12, 54.56–7
  prevention 54.34
  prognosis 54.49–50, 54.52
  PUVA lentigo and 54.5
  race and 9.18
  radial growth phase 54.28, 54.36
    early, vs atypical naevus 54.28
  recurrence
    local 54.54–5
    risk factors 54.49
  relapse, staging at 54.50
  risk after childhood cancer 54.15
  risk markers, atypical melanocytic naevi 54.28
  secondary from occult primary site 54.47
  sentinel node biopsy 54.39, 54.50, 54.51–2, 54.53
  slaty-blue dermal melanosis 58.25
  small cell 54.48
  of the soft parts 54.48
  solar (actinic) keratosis and 54.33
  spitzoid 54.22, 54.23–4, 54.25
    see also naevus, Spitz

stage III disease, radiotherapy 54.56
stage IV disease 54.51
management 54.54, 54.55–6
staging 54.49, 54.50–1
subungual/periungual 54.44–6, 65.39–41
differential diagnosis 54.18
in situ 54.46
sun exposure and 6.12, 29.7, 54.32–3, 54.34
sunscreen use 54.34, 73.41
superficial spreading *54.31*, 54.35, 54.36, *54.37*, **54.37–40**
atypical naevi progression 54.28, *54.29–30*, *54.31*
congenital naevi complication 54.13
differential diagnosis 54.38
generalized lentiginosis and *54.3*
halo naevus vs 54.20
pathology 54.38–9
regression 54.37
sites, colour 54.37
verrucous variant 54.38–9
surgical treatment of primary site 54.39
survival rates 54.52
susceptibility, in lentiginosis *54.3*, 54.4, 54.5
TNM staging system 54.50, *54.50*
transplacental transfer 17.19
umbilical 71.101
vaccines 54.54
vaginal 54.47
verrucous 54.38–9
vertical growth phase 54.36
vulval 54.47
Melanoma Genetics Consortium 54.33
melanoma-inhibitory activity (MIA) 54.51
melanoma–astrocytoma syndrome *62.20*, 62.22
melanoma–nervous system tumours (NST) syndrome *62.20*, 62.22
melanonychia *see* longitudinal melanonychia
melanophages 54.26
in amyloidosis 58.28
hyperpigmentation treatment 73.26
melanophores 2.6
melanophylin 58.4
melanosis
Becker's *see* naevus, Becker's
circum-/intra-oral 69.21
frictional 28.15
genital *54.2*
mucosal 54.6–7
neurocutaneous 54.11
penile 58.15, 71.49
periorbital 67.5
post-inflammatory 47.33
primary acquired 54.40–1
smoker's 69.96
transient neonatal pustular 9.12, 17.8–9
universal acquired 58.22
vulvovaginal 58.15, 71.79–80
melanosis circumscripta precancerosa of Dubreuilh *see* lentigo maligna
melanosomes 3.20, 58.1
absence, piebaldism 58.42
compound 62.6
development 58.3
electron microscopy 10.29–30
ellipsoidal 58.10
in freckles 58.10
Laugier–Hunziker syndrome 58.14
racial differences *3.21*, 9.2, 58.10
size and number, racial differences *3.21*
transfer to keratinocytes 4.7, 58.4–5
transport to dendrite of melanocytes 58.4
variations in skin colour and 58.10
in warts 33.47
melanotic lesions, mucosal **54.6–7**
see also melanotic macules
melanotic macules 69.27, 69.98
dermal 54.7–9
labial *54.2*, 54.6, 54.7
pigmented (mucosal) *54.2*, 54.6–7
see also melanoacanthoma
melanotic progonoma 56.52–3
α-melanotrophin 58.7
β-melanotrophin 58.7
γ-melanotrophin 58.7
melasma 58.25, 58.34–5
laser therapy 78.11, 80.11
race and 9.16
rarity with HRT 58.34
topical therapy 73.26–7, 73.27, 73.28
melatonin
adverse effects *70.5*
hair growth and 66.9
receptors 3.21
Meleda, mal de 19.3, *19.94*, 19.100–1
Meleney's ulcer 47.57
Meliaceae *26.81*
melioidosis **30.50–1,** 62.80
Melkersson–Rosenthal syndrome 42.74, 48.16, 61.23, 69.37, 69.60, 69.125
Meloidae 38.2, 38.26
melorheostosis 18.33, 62.103
melphalan
adverse effects 75.125
isolated limb perfusion in recurrent melanoma 54.54
Meltzer's triad 49.33
membrane co-factor protein *see* CD46
membrane-coating granules (Odland bodies) 3.1, 3.8, 3.11, 4.2, 4.3
membrane inhibitor of reactive lysis (CD59) 14.4
MEN *see* multiple endocrine neoplasia (MEN)
men who have sex with men (MSM)
dermatophytosis 35.32
genital chlamydial infections 34.29
gonorrhoea 34.25, 34.26
herpes simplex infection 33.16
HIV infection/AIDS 35.2, 35.5, 35.13, 35.15, 35.30, 35.32
lymphogranuloma venereum 34.32, 34.33
syphilis 34.3, 34.7
MEN1 gene 62.24, 62.68
Mendes da Costa syndrome *see* erythrokeratoderma variabilis
Mendes da Costa–van der Valk syndrome 58.20
menin 62.24
meningeal neurosyphilis 34.14
meningioma 18.95
cutaneous 56.51–2
meningism, herpes simplex 33.17
meningitis
anthrax 30.41
cryptococcal 35.33
in loiasis 37.11
meningococcal 30.44–5
recurrent lymphocytic 33.19
meningococcaemia, purpuric 49.20
meningococcal infection 30.44–5, 62.105
purpura in 49.20
septicaemia 30.44, 49.20, 62.105
see also Neisseria meningitidis
meningocoele 18.95
meningoencephalitis 30.44
in sarcoidosis 61.7
zoster 33.26
meningoencephalocoele 18.95
meningothelial heterotopias 56.51–2
meningovascular syphilis 34.14
Menkes' syndrome 3.44, 45.14, 45.39
copper defect 3.44, 45.14, 59.76
hair in 66.63, 66.64, *66.65*
occipital horn syndrome and 3.44, 45.14, 45.36, 45.39
menopausal flushing 8.20, 43.15
menopause **8.19–21**
age of onset 8.19
definition 8.19
female genital changes 71.55
hormonal and physiological changes 8.19
premature 8.19
skin disorders 8.20
sweating associated 44.7
menotrophin 75.117
menstrual cycle **8.8–9**
allergic contact dermatitis and 26.8
atopic dermatitis and 24.19
cutaneous changes 8.8–9
hormonal influences 8.8
initiation 8.4
sebum production changes 42.11
urticaria and 22.11
menstrual toxic shock syndrome 71.67
menstruation, pigmentation changes 58.25
mental deficiency 15.23
mental illness, perceptions of 64.7
mental nerve *77.2*, *77.4*, 77.10
mental neuropathy 62.39
menthol
in pruritus 21.17
topical therapy 73.48
mepacrine (quinacrine) 13.24, 74.25–6
adverse effects 75.70
lichenoid eruptions 41.24
nail colour changes 65.16
pigmentation 58.55
in discoid lupus erythematosus 51.21
in subacute lupus erythematosus 51.23
mephenesin 66.94
mephenytoin, melasma-like hyperpigmentation 58.34
Mepilex 39.28
Mepitel 39.28
mepivacaine 77.10
meprobamate, adverse effects 75.81
mequinol 73.27
mercaptans, substituted 73.29
mercaptobenzothiazole 26.64
6-mercaptopurine 20.40, 59.63
mercurials 26.17
as allergens 26.39
organic 26.57–8
mercuric chloride 10.31
mercury **75.101–2**
as allergen 26.21, 26.39
exposure to during pregnancy 18.2
in homeopathic medicines 75.162
hypersensitivity to 75.34
as irritant 25.21
lichen planus pathogenesis and 41.3
lichenoid eruptions due to 41.24
pigmentation due to 58.55
poisoning 69.83–4
in tattoo pigments, allergic reactions 58.58
topical application 75.165
see also dental amalgam
mercury arc lamps 29.1
mercury compounds, abuse for skin lightening 73.26
Merkel cell(s) 3.1, **3.15–16,** 63.2
autoantibodies to 3.16
cytokeratin 20 53.31
in desmoplastic trichoepithelioma 53.9
development 3.3, 3.5, 3.16
glabrous skin 3.16
hyperplasia 3.16
immunohistochemistry 53.43
immunoreactivity 3.15
neurosecretory granules 3.15
origin 3.16
size and structure 3.15–16
trichoblastoma 53.10
Merkel cell carcinoma 3.16, 33.37, 53.42–4
eyelids 67.36
genetics 15.27
in trichilemmal cyst 53.4
see also Merkel cell tumours
Merkel cell polyomavirus 33.37, 53.42
Merkel cell tumours
diagnosis 10.20–1
ear 68.34
radiotherapy 79.13
see also Merkel cell carcinoma
Merkel cell–neurite complexes 3.15–16
Merkel's receptors 4.9, *4.10*
merthiolate 25.21, *26.46*, 73.8
mesalazine 75.56
mesenchymal cells 3.3–4, 3.49
dermis formation 3.5
signalling 3.3–4
mesenchymal markers 10.22–4
mesna 75.125
SLE 51.62
mesoderm 3.3
Mesoknemidokoptes laevus 38.46
mesomelic dwarfism–skeletal abnormalities–ectodermal dysplasia 15.47
mesperidine, lobular panniculitis with crystals after 46.17
17α-mesterolone 42.16
meta-analyses 6.16, 7.4
appraisal and evaluation 7.7–11
metabolic disorders **59.1–104**
connective tissue diseases 51.79
eye and skin involvement *67.30*
oral manifestations *69.117*
in pregnancy *8.11*, 8.12
scleroderma-like lesions 51.79
metabolic syndrome 46.7
criteria *46.7*
psoriasis and 6.13
metachromasia, scleroedema 51.119
metal halide lamps 29.2
metal piercings 28.51–2
metal workers, occupational hazards 27.20
metalloelastases 3.44
metals
as allergens 26.30–40
pigmentation due to 58.54–5
prosthetic implants 26.37
see also specific metals
metaphyseal chondrodysplasia of McKusick **15.93**
metaplasia 10.40
metastases *see* malignant disease, metastatic
metastatic calcification 59.69–70
metformin, in hirsutism 66.88–9
methacrylic acid esters, lichen planus-like contact dermatitis 41.23
methaemoglobinaemia, linear IgA disease 40.50
methandienone, dermatomyositis 51.129
methanol 25.3, 25.19, 25.20
methenamine 73.9
methicillin 75.50
methicillin-resistant *Staphylococcus aureus* (MRSA) 30.9, 38.8, 74.40
community-acquired 30.9, 30.22
foreign bodies 28.48
in HIV infection 35.24
male genital infection 71.33
in neuropathic ulcers 63.9
otitis externa and 68.21
prevention of spread 77.5, 77.7
wound infection 14.16
methimazole 18.102
methotrexate 13.24, **74.19–23**
adalimumab and, ADEPT study 74.7
adverse effects *70.5*, 72.29, 74.21, **75.130–1**
acute toxic effects 20.34, 72.29
dermatological 75.130
oral 69.56
systemic 75.130–1
toxicity in elderly people 8.28
alcohol abuse 74.21–2
in atopic dermatitis 24.31, 74.18–19
in bullous pemphigoid 74.18–19
contraindications 74.21
in cutaneous lupus erythematosus (LE) 74.19
in dermatomyositis 51.129
in dermatoses 74.20

dose range and evidence level 20.33, 74.19
absolute or relative overdose 74.22
acute toxicity and overdosage 74.23
folate supplementation 74.22–3
genetic factors in response to 11.16
interactions 72.29
intralesional 77.49
in liver disease, contraindications 20.34, 74.21
management of therapy 74.21–32
concurrent therapy 20.33
haematological abnormalities. 74.23
laboratory control 20.34
monitoring schedule 74.22
in microscopic polyangiitis 50.36
in morphoea 51.75
in non-alcoholic steatohepatitis (NASH) 74.21
in pregnancy 74.21
prescribing safety 72.26, 74.21
in psoriasis 20.33–5, 74.18–19
in HIV infection 35.17
in psoriatic arthritis 20.59
in sarcoidosis 61.21, 74.20
in SLE 51.62
topical 73.23
4-methoxyphenol 73.27
5-methoxypsoralen, Berloque dermatitis and 58.32
8-methoxypsoralen, adverse effects, ocular 67.32
methyl aminolevulinic acid (Metvix®) cream 43.6
methyl bromide 75.163
6-methyl coumarin 26.23
methyl-ethylketone 25.20
methyl methacrylate 27.9
methyl salicylate 75.165
methylamfetamine 75.87
methylation, genomic imprinting 15.6
4-methylbenzilidene camphor 26.62
methylcellulose 73.2
methylcellulose eye drops 51.138
methylchloroisothiazolinone 26.53
methyldibromo glutaronitrile 26.55
methyldopa
adverse effects *70.5*, 75.96
lichenoid tissue reaction due to 41.25
methylene blue 17.12
methylene chloride 25.20
trans-3-methyl-2-hexanoic acid 44.1
methylisothiazolinone 26.53
methylphenidate 75.83
methylprednisolone, SLE 51.62
methylprednisolone aceponate 73.16
metoclopramide, adverse effects *70.5*
metophyma 43.9
metoprolol 75.91
metronidazole 74.43
adverse effects *26.46*, 75.**59**
in amoebiasis 37.28
in *Demodex* infection in rosacea 43.3
in dracunculiasis 37.13
in fish odour syndrome 44.20
in rosacea 43.3, 43.6
in seborrhoeic dermatitis 23.33
topical 73.10
in rosacea 43.6, 73.9, 73.10
in trichomoniasis 37.29
Mexican chicken bug 38.24
Mexico
dermatological care 6.16
prevalence of skin disease *6.9*
mexiletine 75.165
Meyerson phenomenon (halo dermatitis) 23.12–13
Meyerson's naevus 54.20
MGIT 31.6
MGUS (monoclonal gammopathy of uncertain significance) 13.15
MHA-TP test 34.20
MHC *see* major histocompatibility complex (MHC)
mi mutants 58.3
mianserin *64.51*
adverse effects 75.79
erythema multiforme 76.3, *76.4*
Mibelli's porokeratosis 19.91, 66.51
disseminated superficial 'actinic' porokeratosis vs 52.36
mice *see* mouse
Michaelis–Gutmann bodies 55.27
Michelin tyre baby 18.36, 18.40, 18.107
Michel's transport medium 10.4–5, 39.24
miconazole
in candidiasis 36.68
in dermatophytosis 36.48
in napkin dermatitis 17.26
topical 73.12
miconidin 26.76
microabscess
Munro 10.41, 65.25
papillary tip 10.41
Pautrier 10.41
microaneurysms, Degos' disease 49.45
microangiopathy 47.26
thrombotic 49.12
microarrays 11.7–8, *11.9*
high-throughput genetic analysis 15.6
microbial recognition, by immune system 12.8–9
microcephaly lymphoedema–chorioretinal dysplasia 48.10
Microciona prolifera 38.59
microclimate 6.12
Micrococcus
classification 30.2
in normal skin flora 30.2, 30.3, 30.4
bacterial counts 30.3
quantitative studies 30.3
Micrococcus kristinae 30.2, 30.3
Micrococcus luteus 30.2, 30.3
Micrococcus lylae 30.2, 30.3
Micrococcus sedentarius 30.2, 30.3, 30.39
Micrococcus varians 30.2, 30.3
microcomedones 42.22, *42.23*, 42.25, 42.43
microconidia *36.3*, 36.4, 36.41
microcystic adnexal carcinoma 53.35–6
microdeletion syndromes 18.2
microdeletions 15.2
microdontia 69.7
microfibril-associated fibrillar proteins (MFAP) 3.45
microfibril-associated glycoprotein (MAGP) 3.45
microfibrils 3.2, 3.42
see also elastin-associated microfibrils
microfilaments 3.9
β_2-microglobulin, in sarcoidosis 61.20
microhaemagglutination, *Treponema pallidum* 34.20
microimmunofluorescence (MIF), lymphogranuloma venereum 34.33
micronychia 65.9
micropapular eruptions, syphilis 34.11, 34.12
microphthalmia mice 2.7
microRNA (miRNA) 3.50
microsatellite instability (MSI) 57.20
Muir–Torre syndrome 52.10, 53.15
microscopic polyangiitis (polyarteritis) **50.35–7**
respiratory tract involvement 62.83
microscopy 5.18, 5.20–1
capillary *see* capillary microscopy
dark-field, syphilis diagnosis 34.3, 34.18–19
electron *see* electron microscopy
epiluminescence *see* dermoscopy
fluorescence 36.7
indirect immunofluorescence 16.5–6
preparation for 10.32
tissue sections 10.31–6
microsponges 73.2
microsporidiosis, HIV infection 35.35
Microsporum 36.18
identification *36.8*
see also dermatophytes
Microsporum audouinii 36.19
dermatophytide due to 36.36
identification 36.37, *36.39*
investigation 36.6
in tinea capitis 36.25–6, 36.27
in tinea corporis 36.23, 36.24
in tinea faciei 36.29
Microsporum canis 36.19, 36.21
in animals 2.12
identification 36.37, *36.40*
investigation 36.6
in tinea barbae 36.28
in tinea capitis 36.26, 36.27
in tinea corporis 36.24, 36.25
in tinea faciei 36.29
Microsporum equinum
identification 36.39
in tinea capitis 36.26
Microsporum ferrugineum
identification 36.39
investigation 36.6
in tinea capitis 36.26, 36.27
Microsporum fulvum 36.26
Microsporum gypseum 36.6, 36.26, 36.39, *36.40*
in animals 2.12, 2.13
Microsporum nanum 36.6, 36.26, 36.40
Microsporum persicolor 36.19, 36.24, 36.40–1
Microsporum vanbreuseghemii 36.26
microthalmia (mi) mutants 58.3
microtia 68.4
microtubules 3.9
melanosome, for transfer 58.4
microvascular damage, pressure ulcers 28.17
microvascular occlusion 49.3, **49.26–48,** 50.54–5
calcific uraemic arteriolopathy 49.47–8
classification of disorders *49.27*
coagulopathies with cutaneous features 49.38–42
cryogelling causing 49.32–4
emboli causing 49.36–8
platelet plugs causing 49.27–31, 49.41
reticulocytes causing 49.47
vascular coagulopathies causing 49.42–7
vessel-invasive organisms causing 49.34–6
microvilli 2.2
microwave radiation burns **28.90**
MIDAS syndrome 18.103–4
genetics 15.4, 15.85
midazolam, in dystrophic EB 39.30
midges 38.7
biting 38.6, 38.7
midgut tumours, carcinoid syndrome associated 43.18
midline cervical cleft 18.86
Miescher's granulomatous cheilitis 48.16, 61.23, 69.60, **69.125–7**
Miescher's radial granulomas 46.12
MIFT-1 10.21, 20.22
migraine, rosacea association 43.1
migration
atopic dermatitis and 24.2–3
risk factor for skin disease 6.12
migration index 26.98
migration inhibition factor 26.98
migratory thrombophlebitis 47.30–1, 62.42–3, 62.66
Mikaelian syndrome 15.47
Mikulicz cell 30.52
Mikulicz syndrome 61.7, 69.57
Mikulicz's syndrome 51.49
see also Sjögren's syndrome
milfetosine 74.51
milia **52.47–8**
colloid *see* colloid milium
definition 5.7, 52.47
differential diagnosis 42.36, 52.47–8
in dystrophic EB 39.18, 39.21
eyelid 67.33
hands 25.15, *25.16*
incidence and aetiology 52.47
neonatal 17.5
treatment 52.48, 78.14
Milian's white atrophy (atrophie blanche) 15.13, 23.35, 47.34, 49.44
miliaria 44.13, **44.15–16**
aetiology and pathology 44.15
amputees 28.29
causes *25.2*
clinical features 44.15–16
natural history 44.16
neonatal 17.7–8
in pregnancy 8.10
pustular 44.16
sports injuries 28.30
treatment 44.16
miliaria crystallina (sudamina) 17.7–8, 44.15–16
miliaria profunda 44.15–16
miliaria pustulosa 17.7, 17.8
miliaria rubra 17.7–8, 44.15–16
miliary eruptions, syphilis 34.11
milium *see* milia
milk
acne and 42.34
allergy 22.6
milk lines 70.1, 70.2
milker's nodule 33.10–11
milker's sinuses 28.49
millipedes 38.54–5
milowood *26.81*
Milroy's disease 48.8, 48.9–10
Mima
in normal skin flora 30.2
see also Acinetobacter
Mimosaceae *26.80*
mineral oil
as carcinogen 52.4
injections in sclerosing lipogranuloma 46.28, 46.29–30
in topical treatment 73.6
Mineral Oil USP 73.6
minimal erythema dose (MED) 29.5, 29.8
minocycline 74.41
acne vulgaris treatment 42.47, 42.48
adverse effects *26.46*, 42.50–1, 75.54
black galactorrhoea 70.6
drug hypersensitivity syndrome 42.51
hyperpigmentation 69.97, 75.33, 75.52–3
lupus-like reaction 42.51
nail colour changes 65.38
ocular 67.31–2
pigmentation 42.50–1
pigmentation due to 58.55–6
in dissecting folliculitis of scalp 42.74
dose range and evidence level 74.30
in hidradenitis suppurativa 42.75
in leprosy 32.17
Propionibacterium acnes resistance 42.47, 42.56
in rosacea 43.6, 43.7
in sarcoidosis 61.21
topical, in acne 42.41
minoxidil 73.49–51
adverse effects 26.18, 73.50, 75.**96–7,** 75.165–6
ear canal hypertrichosis 68.18, 68.21
hypertrichosis *66.79*
in alopecia areata 66.37, 73.50
in androgenetic alopecia 66.24, 66.25, 73.49–50
indications 73.50
mechanism of action 73.50
minute keratoses 19.92–3
miosis, in Horner's syndrome 63.22
MIP-1α 12.16, 12.18, 12.25, 12.39, 12.45, 12.46, 13.4
MIP-1β 12.46
miracidia 37.20, 37.23
MIRL (CD59) 14.4
miRNA 3.50
mirror watching 64.19
mirtazapine 21.17, *21.18*, 64.51, 75.79

mites 38.**36–54**
  rosacea pathogenesis 43.2–.3
  see also Demodex
MITF gene, Waardenburg's syndrome 58.44
Mitf protein 58.3
mitochondria
  DNA damage, UVR-induced 8.21, 29.7
  radical oxygen species 12.55
  sebaceous cells 42.3
  toxicity of antiretroviral drugs 35.22
mitochondrial keratoderma with deafness 19.109
mitogen-activated protein kinases (MAPKs) 12.8–9
  ageing and 8.22
mitogens, for melanocytes 58.5
mitomycin *26.46*, 75.128
  mucous membrane pemphigoid 40.40
mitral incompetence 45.30
mitral valve prolapse 70.3
  in Marfan's syndrome 45.30
  in pseudoxanthoma elasticum 45.22
Mitsuda reaction 32.15
Mitsuda test 5.24
mixed connective tissue disease **51.110–12**
  immunology 51.111
  oral involvement 69.71
  respiratory tract involvement 62.82
  U1-RNP, specific antibody 51.110, 51.112
mixed immunobullous disease 40.49
mixed tumour of the skin 53.30–2
mizolastine *22.29*, 75.149
  adverse effects 22.29
MLH1, Muir–Torre syndrome 53.15
MLH1 gene 52.10
MLS syndrome *see* MIDAS syndrome
MMPs *see* matrix metalloproteinases (MMPs)
MMR (measles, mumps and rubella) vaccination 33.71
MMS *see* Mohs' micrographic surgery
MOAHL index 26.3
MOAHLFA index 26.3
Mobiluncus spp., vaginal discharge 71.53
Mohr's syndrome 68.4
Mohs' micrographic surgery 54.43, **77.29–34**
  adjuvant radiotherapy 79.7
  basal cell carcinoma 52.22, *77.30*, 77.32, *77.33*
    eyelids 67.35
  comparison with traditional surgery 77.29, *77.30*, 77.31
  complications 77.8, 77.9
  definition 77.29
  dermatofibrosarcoma protuberans 56.13
  history 77.29
  indications and practical aspects 77.32–3
  nail unit 65.48
  non-melanoma skin cancer 52.16, 52.17
  procedure 77.31, *77.32*
  results 77.32
  squamous cell carcinoma 52.27, 77.32
    in dystrophic EB 39.30
  tumours recurring after radiotherapy 79.17–18
moisture, pressure ulcers 28.21
moisturizing creams 27.9
molars, mulberry 34.17
Mole Max system™ 54.38
molecular biology **11.1–22**
molecular genetics, keratinizing disorders 19.1–4, *19.94–5*
  see also specific disorders
molecular immunology 13.23
molecular mimicry, vasculitis and 50.5
molephobia 64.24–5
moles (acquired melanocytic naevi) **54.15–21,** *54.16*
Moll's gland 67.2
  cyst 67.33
mollusca fibrosa 15.17
molluscipox viruses 33.5, 33.11, 35.30
molluscs 38.59
  in HIV infection 35.30–1
  pigment cells 2.5
molluscum bodies 33.11
molluscum contagiosum **33.11–14,** 71.34
  aetiology 33.11
  agminate form 33.11
  antibody formation 33.11
  atopic dermatitis with 24.24, 33.11, 33.12
  children 33.12
  clinical features 33.11–12
  cytodiagnosis 10.29
  diagnosis 33.12
  distribution of lesions 33.12
  ear 68.28
  eczema associated 23.24
  epidemiology 33.11
  eyelids 67.24–5
  follicular 33.12
  giant 33.11
  in HIV infection 33.11, 35.30–1, 35.45, 68.28
  immune response 33.12, 33.13
  immunodeficiency and 17.52, *17.53*, 33.11
  MCV-1 and MCV-2 33.11
  treatment 33.12–13, 35.30–1, 77.50
    topical imiquimod 73.24
molluscum fibrosum gravidarum 8.13
molluscum sebaceum *see* keratoacanthoma
mometasone furoate 73.16
'Mona Lisa smile' 64.36
Mondor's disease 38.56, 47.30, **47.31,** 48.29, 62.43, **70.16**
  breast carcinoma associated 62.43, 70.16
  thrombophilia *62.91*, 70.16
Mongolian spot 17.5, 54.7–8, 58.1, **58.36**
  in phakomatosis pigmentovascularis 18.69
  race and 9.11
  skin biopsy 10.43
mongolism *see* Down's syndrome
monilethrix 15.47, 66.61–3
moniliasis *see* candidiasis
monkeypox 33.7
monkeys, herpes B virus infection from 33.34
monoamine oxidase inhibitors 75.79
monobenzone 73.27
monobenzylether of hydroquinone (monobenzone) 27.15, 73.27
  hypermelanosis treatment 58.39
monochloroacetic acid 77.48
  wart treatment 33.49
monoclonal antibodies
  19-DEJ-1 39.25
  adverse effects 75.146
  epidermolysis bullosa diagnosis 39.25
  therapeutic 13.25, 13.26, 57.28
monoclonal gammopathy of uncertain significance 13.15
monoclonality/tumours, pigmented purpuric dermatoses and 49.23
monocyte(s) 12.26–9, 17.48
  chemotaxis, isotretinoin effect 42.58
  development/ontogeny 5.1, *5.2*
  emigration 12.74–5
  in granuloma inguinale 34.37
  half-life 5.1
  histiocyte ontogeny 5.1, *5.2*
  malignancies **55.31–4**
  maturation 5.1
  microscopy 10.34
  in wound healing 14.3
monocyte chemoattractant protein 1 (MCP-1) 46.7
monocyte chemotactic proteins (MCPs) 12.46
  in vasculitis 50.10
monocyte–macrophage system 12.26–9, 13.5
  major functions of monocytes/macrophages 12.27
  major products released 12.27
  major receptors expressed 12.27
  role of macrophages in immunity 12.29
  see also macrophage(s); monocyte(s)
monocytic leukaemia 55.31–2
monomethylether of hydroquinone, depigmentation due to 58.50
mononeuritis multiplex 61.7, 63.11
  in HIV infection 63.12
mononuclear cells, Sézary-like 57.18
mononuclear phagocytes 4.8
  increased in ageing skin 8.22
  Langerhans' cells 3.17
mononucleosis
  CMV causing 33.29
  HHV-6 associated 33.32
  see also infectious mononucleosis
monosodium glutamate 22.11, 43.16
monostotic fibrous dysplasia 68.28
monosulfiram 38.41
monosymptomatic delusions of malodour 44.19
mons pubis 71.54
Monsel's solution 10.4, 10.31, 77.50
montelukast 12.61, 13.4, 74.31–2
  adverse effect 75.150
  in delayed pressure urticaria 22.14
  dose range and evidence level 74.31
Montgomery's disease *see* xanthoma disseminatum
mood stabilizers 64.52
Moon's molars 69.8
Moore–Federman syndrome 51.79
Moraceae *26.81*
morado (pinta) 30.63–4
Moraxella 30.46–7
morbakka 38.56
morbidity 6.6
Morbihan's disease 43.4, 48.13, 48.16
morbilli *see* measles
Morbillivirus 33.75
morbus Dercum (Dercum's disease) 8.17, 46.46, 46.47–9, 48.20
morbus errorum 38.22
Morgellons syndrome 64.12, 64.17
Moroccan leather skin appearance 45.21, *45.22*
morphine
  adverse effects 75.87
  in burns 28.79
  pruritus and 21.3
morphoea **51.64–78**
  atrophoderma of Pasini and Pierini and 45.8
  Borrelia and 30.65, 45.10
  breast hypoplasia and 70.6, *70.7*
  children, methotrexate and systemic corticosteroids 74.20
  en coup de sabre 66.48, *66.49*
  generalized 51.76–8
    aetiology 51.77
    clinical features 51.77–8
    differential diagnosis 51.78
  granuloma annulare and 60.9
  linear 51.69–70, 66.48, *66.49*
  localized 51.64–75
    aetiology 51.64–5
    associated lesions 51.72–3
    chronic graft-vs-host disease and 51.65
    clinical features 51.68–9
    differential diagnosis 51.74
    drug-associated 51.65
    frontoparietal lesions 51.70
    immunohistochemistry 51.67
    incidence 51.68
    laboratory abnormalities 51.73–4
    linear morphoea 51.69–70
    localized scleroderma in children 51.71
    ocular lesions 51.70
    panscleroticmorphoea in children 51.71–2, 51.75
    pathology 51.67
    post BCG vaccination 51.65
    prognosis 51.74
    superficial morphoea 51.69
    treatment 51.74–5
    types 51.64
  panscleroticmorphoea, in children 51.71–2, 51.75
  pigmentation changes 58.26
  post-irradiation 62.16, 62.40
  race and 9.14
  radiotherapy site 70.6
  superficial 51.69
  synonyms 51.64
morphoea profunda (deep morphoea), panniculitis in 46.31
morpholines, topical 73.12
morsicatio buccarum 69.87–8
mortality 6.6
  due to adverse drug reactions 75.2, 75.5
Mortimer's malady 61.1
Morton Bay stinger 38.56
Morton's metatarsalgia (Morton's neuroma) 56.45
morula cells 37.31
morulae 30.58
Morvan's syndrome 63.14
mosaic acral keratosis 19.115
mosaicism 18.1, 18.3
  chromosomal abnormalities 15.11
  epidermal naevi and 18.5
  functional 15.6
  gonadal 15.6
  lichen striatus and 23.41
Moschowitz's syndrome (thrombotic thrombocytopenic purpura (TTP)) 49.12, **49.31,** 69.114
mosquito bites, hypersensitivity 33.31
mosquitoes 37.9, 37.27, 38.2, 38.5, 38.6–7
mossy foot *see* podoconiosis
moths 25.21, 38.28–30
motor innervation, skin 3.2
motor neuropathy 51.132
moulds 9.12, 36.2
  identification 36.9–10
  saprophytic 36.17–18
  see also fungi
moult waves 66.27, 66.33
moulting
  animals 2.3
  seasonal 2.3, 66.8–9
  waves 66.8
mouse
  coat colour mutants 58.4
  hypomorphic 11.11
  knockout 2.7, 11.11
  microphthalmia 2.7
  mites 38.51
  models
    assessment of dermatitic potential 27.10
    multistage carcinogenesis 52.12–13, 52.15
    neonatal, acantholysis 40.5
  pigment mutants 58.4
  strains with cancer induction susceptibility 52.13
  transgenic 2.7, 11.10–11
  triple knockout 2.8
mouse ear swelling test 26.12
mouse fingers 28.27
mouth *see* oral cavity
mouthwash 69.119–20
  pigmented melanotic macules 54.6–7
movingui *26.80*
moxibustion 9.8
Moynahan's syndrome 66.59–60
MPNST (malignant peripheral nerve sheath tumours) 56.53
MPS *see* mucopolysaccharidoses (MPS)
MRI *see* magnetic resonance imaging (MRI)

MRSA *see* methicillin-resistant *Staphylococcus aureus* (MRSA)
MSH *see* melanocyte-stimulating hormone (MSH)
MSH2 gene 52.10
MSH2 protein, Muir–Torre syndrome 53.15
MSX1 gene 15.65
mTOR signalling 48.30
MTS *see* Muir–Torre syndrome
MTT assay (dimethylthiazoldiphenyl tetrazolium bromide assay) 25.9
MUC1 53.41
MUC5AC 53.41
Mucha–Habermann disease (pityriasis lichenoides) 57.54–7
  febrile ulceronecrotic 50.50–1
  oral involvement 69.85
  pityriasis lichenoides et varioliformis acuta 50.50–1, 69.85
mucicarmine 36.90
mucin 59.21
  abnormal deposits, Degos' disease 49.45
  in basal cell carcinoma 52.21
  in granuloma annulare 60.4
  pretibial deposition 8.17
  stains 53.36
  tear film 67.3
mucinosis **59.21–9**
  areola 70.17
  chronic obesity lymphoedematous 62.8
  classification 59.21
  cutaneous focal 59.25
  focal, oral 69.39
  follicular 57.14, 59.26
  hereditary progressive mucinous histiocytosis 59.25
  lichen myxoedematosus 59.21–3
  mucinous naevus 59.25
  papular *62.45*
    acral persistent 59.24
    of infancy 59.24
    juvenile and adult 59.24
    in L-tryptophan-induced eosinophilia–myalgia syndrome 59.29
  plaque-like cutaneous 59.25
  reticular erythematous 59.25
  secondary 59.29
    collagen vascular diseases 59.29
    in L-tryptophan-induced eosinophilia–myalgia syndrome 59.29
    papulonodular mucinosis with SLE 59.29
    toxic oil syndrome 59.29
  in SLE 51.40
mucinous carcinoma 53.36–7
mucinous cysts, female genital dermatology 71.73
Muckle–Wells syndrome (cryopyrin-associated autoinflammatory syndrome) **15.95–6,** 22.13, 59.57, 74.11
mucocele 69.22, *69.65,* 69.84, **69.110**
mucocutaneous candidiasis–endocrinopathy syndrome (autoimmune polyglandular (polyendocrine) syndrome) *13.13,* 15.31, 36.64, 62.12–14
mucocutaneous lymph-node syndrome *see* Kawasaki disease
mucoepidermoid carcinoma, external auditory canal 68.33
mucoid cysts, male genital dermatology 71.35
mucolipidoses 59.32
mucopolysaccharides
  in scleroedema 51.119
  see also glycosaminoglycans (GAGs)
mucopolysaccharidoses (MPS) **59.30–2**
  classification 59.31
  clinical features 59.30
  diagnosis and treatment 59.32
  eponyms 59.31
  hypertrichosis in 66.76
  oral involvement *69.117*
  prenatal diagnosis *16.3*
  sweat gland cellular inclusions 44.18
Mucor
  otitis externa and 68.21
  vessel-invasive infection 49.35
mucormycosis *see* zygomycosis
mucosa
  in allergic contact dermatitis 26.20–1
  biopsy 10.32
    in sarcoidosis 61.19
  buccal (cheek)
    examination 69.5–6
    lichen planus-like reactions 26.26
  in erythema multiforme 76.7
  examination in fungal infection 36.6
  eyelids 67.2
  in generalized non-Herlitz junctional EB 39.13
  in hereditary haemorrhagic telangiectasia 47.17
  hyperpigmentation, Addison's disease 58.24
  labial 69.5
  in lichen nitidus 41.22
  in lichen planus *see* lichen planus
  in lupus vulgaris 31.17
  in multicentric reticulohistiocytosis 55.24
  oral cavity 69.2
    disorders 69.21–115
    hyperpigmentation 69.95
  in sarcoidosis 61.15
  in Stevens–Johnson syndrome 76.16
  surgical excision in 77.15
  in syphilis
    congenital 34.15
    primary 34.7
    secondary *34.9, 34.10,* 34.11
    tertiary 34.14
  in toxic epidermal necrolysis 76.17
mucosa-associated lymphoid tissue (MALT) 57.2
  lymphomas 57.2, 57.43
mucosal advancement 77.36
mucosal barrier injury *see* mucositis
mucosal melanotic lesions **54.6–7**
mucositis 69.82, 79.10
  plasma cell orificial 69.128
mucous membrane pemphigoid (MMP) **40.35–41,** 67.17–20, *71.66*
  aetiology 40.36
  in animals 2.15
  associated diseases. 40.39
  clinical features 40.38–9
  defined 40.35
  differential diagnosis 40.34, 40.40
  epidermolysis bullosa acquisita 40.54
  immunoelectron microscopy 10.29
  immunopathology and immunogenetics *10.18*
  linear IgA 40.49
  ocular 67.17–20
    clinical features 67.17, *67.18*
    conjunctival biopsy 67.19
    diagnostic criteria 67.19
    differential diagnosis 67.19–20
    direct immunofluorescence 67.17, 67.19
    epidemiology 67.17
    immunopathology 67.20
    indirect immunofluorescence 67.19
  oral involvement *69.65,* 69.67–8
  pathogenesis 40.36–8, 67.20
  pathology 40.36–8
  predominantly ocular
    diagnostic criteria 67.19
    diagnostic problems 67.17, 67.19
  prognosis 40.40
  treatment 40.40–1
  see also cicatricial pemphigoid
mucous membranes *see* mucosa
mucoviscidosis 59.59
Mucuna pruriens 21.4
mucunain 21.4
mudi-chood 68.16
  race and 9.7–8
Muehrcke's paired white bands 65.15
Muir–Torre syndrome (MTS) 52.10, 53.15, 53.16, 62.26, 62.35
  sebaceous adenoma association 42.87
  sebaceous carcinoma association 53.17
mulberry-like erosion 36.87
mulberry molars 34.17, 69.8
Muller technique (phlebectomy) 47.39
Müllerian ducts, atrophy 8.2
multicentric carcinoma, male genital dermatology 71.42
multicentric Castleman's disease 56.24
multicentric reticulohistiocytosis 55.23–5
  bone and joint involvement *62.101,* 62.104
  clinical features 55.23–4
  oral involvement 69.59
  paraneoplastic 62.41
  respiratory tract involvement 62.83
Multiceps 37.24
multidrug regimen, in leprosy 32.16–17
multidrug resistance 1 *(MDR-1)* gene 72.29
multifactorial disorders, genetics 15.2
multinucleate giant cells
  Langerhans' cell histiocytosis 55.8
  multicentric reticulohistiocytosis 55.23
  VZV infection 33.24
  see also giant cell(s)
multiorgan syndrome 49.38
multiple carboxylase deficiency 17.25, 17.30
multiple decarboxylase deficiency 59.65
multiple endocrine neoplasia (MEN)
  type 1 62.24, 62.68
  type 2A 59.48, 62.24
  type 2B (type 3) 62.24–5, 69.36
multiple endocrinopathy syndrome *see* autoimmune polyglandular (polyendocrine) syndrome
multiple hamartoma syndrome *see* Cowden's syndrome
multiple hamartoma (and neoplasia) syndrome *see* Cowden's syndrome
multiple lentigines (LEOPARD) syndrome *see* LEOPARD syndrome
multiple mucosal neuroma syndrome 59.48, 62.24
multiple myeloma 62.92–5
  oral 69.114, *69.116*
  sarcoidosis and 61.17
multiple neurofibromas **15.16,** 15.17
  see also neurofibroma; neurofibromatosis
multiple organ failure, pigmentation changes 58.27
multiple self-healing epithelioma of Ferguson-Smith 52.9–10
multiple sulphatase deficiency 19.13
multipotent cells, neural crest 58.3
multistage carcinogenesis *see* carcinogenesis
Mulvihill–Smith syndrome 45.60
MUM-1 10.25
mumps *69.118*
  MMR vaccination 33.71
Münchausen's syndrome **64.44**
  factitial panniculitis 46.28
Münchausen's syndrome by proxy 28.39, **64.44–5**
Munro microabscess 10.41, 65.25
mupirocin
  in impetigo 30.16
  resistance to 30.9
  topical therapy 73.10
muriform cells 36.75, 36.76
murine model
  multistage carcinogenesis 52.12–13, 52.15
  see also mouse
muromonab 13.25
Murray Valley virus *33.67*
Murray–Puretic–Drescher syndrome (juvenile hyaline fibromatosis) 45.49–50, 69.15
Musca domestica 38.6, 38.8
muscarinic receptors, sweat gland 3.12
Muscidae 38.6, 38.7, 38.8
muscle
  atrophy 47.11
  growth between birth and maturity 8.1
  in sarcoidosis 61.7
  in SLE 51.47
  in systemic sclerosis 51.101–2, 51.105
  tumours 56.54–7
  weakness, in leprosy 32.18
muscle glycogenosis, scleroderma-like lesions 51.79
muscle herniation of the limbs 28.61–2
muscular dystrophy 3.35
  with autosomal recessive EB simplex 39.8
  EB simplex with 39.4
  late-onset 3.31
musculoskeletal system, in dystrophic EB 39.29
music box spine keratodermas 19.114
musical instrument injuries 28.25–6
musk ambrette 26.23, 26.24, 26.41
mustard gas burns 27.11
mustards 25.21
mustine *see* mechlorethamine; nitrogen mustard
mutagenesis
  UV radiation causing 52.13–14
  see also DNA damage
mutator genes 52.12
mutilating keratoderma with ichthyosis (loricrin keratoderma) 19.3, 19.19, *19.94,* 19.98
myasthenia gravis, with autosomal recessive EB simplex 39.8
mycelium 36.2
mycetoma 30.75, **36.72–5**
  aetiology 36.72–3
  clinical features 36.73
  definition 36.72
  differential diagnosis 36.73–4
  histology 36.73
  laboratory diagnosis 36.74
  treatment 36.74
Mycobacterial Growth Indicator Tube (MGIT) 31.6
mycobacterial infections 74.42
  atypical, in HIV infection 35.25–6
  diagnosis 31.6–7
  epidemiology 31.2–3
  ocular involvement 67.27
Mycobacterium 31.1
  cell wall structure 31.1
  characteristics 31.1, *31.2*
  epidemiology 31.2–3
  fast growers 31.1, *31.2,* 31.38–41
  HIV infection and 31.7
  non-tuberculous 31.1, **31.30–41**
    epidemiology 31.2–3
  slow growers 31.1, *31.2,* 31.6
Mycobacterium abscessus **31.38–40**
Mycobacterium avium complex **31.36–7,** 69.79
  diagnosis of infection 31.6
  ectodermal dysplasias 15.60
  HIV infection and 31.7
  sarcoidosis and 61.2
Mycobacterium avium-intracellulare, HIV infection 35.25–6
Mycobacterium balnei see Mycobacterium marinum
Mycobacterium bovis 31.8, 31.10, 31.11, 31.28
  in malakoplakia 55.27
Mycobacterium chelonae 31.7, **31.38–40,** 69.79
Mycobacterium fortuitum complex 31.3, 31.7, **31.38–40**

Mycobacterium genavense 31.41
Mycobacterium goodii 31.38
Mycobacterium gordonae
  diagnosis of infection 31.6
  HIV infection and 31.7
Mycobacterium haemophilum 31.40–1
Mycobacterium immunogenum 31.38
Mycobacterium kansasii 31.2, **31.33**
  diagnosis of infection 31.6
  HIV infection and 31.7
Mycobacterium leprae 32.1–2, 32.2–3
  antibodies to 32.7
  female genital infections 71.67
  see also leprosy
Mycobacterium malmoense 31.41
Mycobacterium marinum **31.30–3**
  diagnosis of infection 31.6
  differential diagnosis 31.13, 60.9
  ear infection 68.17, 68.20
  sarcoidosis and 61.2
  in sea urchin granuloma 38.58
  swimming and diving 28.54
Mycobacterium mucogenicum **31.38–40**
Mycobacterium parascrofulaceum 31.35
Mycobacterium paratuberculosis, sarcoidosis and 61.2
Mycobacterium peregrinum 31.38
Mycobacterium platypoecilus see Mycobacterium marinum
Mycobacterium scrofulaceum 31.7, 31.35–6
Mycobacterium simiae 31.2
Mycobacterium smegmatis **31.38–40**
Mycobacterium szulgai 31.36
Mycobacterium terrae 31.7
Mycobacterium tuberculosis 31.1, 31.8, 32.1
  detection by PCR 31.26
  female genital infections 71.67
  in HIV infection 35.25
  protective immunity to 31.4
  re-emergence 31.2
  sarcoidosis and 61.2
  staining 10.10
  see also tuberculosis
Mycobacterium ulcerans 31.6, 31.**33–5**
  Buruli ulcer 12.9
Mycobacterium wolinskyi 31.38
Mycobacterium xenopi 31.2, 31.7, 31.41
mycolactone 31.33, 31.34
mycophenolate mofetil 13.24, 20.42, 72.27, 72.29, **74.24–5**
  adverse effects 20.42, 74.24
  in atopic dermatitis 24.31
  clinical indications 74.24
  in lichen sclerosus 51.118
  in mucous membrane pemphigoid 40.40
  in pemphigus 40.12
  in sarcoidosis 61.21
  in urticarial vasculitis 50.23
mycophenolate sodium 74.24
Mycoplasma **30.69–70**
  infection 62.80
  seal finger and 38.61
  Stevens–Johnson syndrome and 30.69, 62.80
Mycoplasma hominis, female genital infections 71.68
mycoses *see* fungal infections
mycosis fungoides **57.1–13**
  aetiology 57.3
  allergic contact dermatitis and 26.9
  classification
    ISCL EORTC revised staging classification 57.7, 57.11
    TNM classification 57.6
  clinical features 57.3–4
  differential diagnosis 26.30, 57.5
    pathological differential diagnosis. 57.10–11
  diffuse progressive hyperpigmentation 58.26
  ear 68.34
  follicular mucinosis and 57.14
  in HIV infection 35.41
  hypopigmented 9.7
  invisible 21.10
  ISCL diagnostic criteria for early MF 57.11
  molecular pathogenesis 57.19
    abnormalities of T-cell activation 57.20
    dysregulated T-cell signalling pathways 57.21
    gene expression studies 57.21
  oral involvement 69.58
  pathology 57.8
    extracutaneous disease 57.11
    immunopathology 57.10
  pigmented purpuric dermatoses and 49.23
  poikilodermatous 45.13
    hypopigmentation in 58.52
  pregnancy and 8.12
  prognosis 57.7, 57.8
  pruritus in 21.10
  race and 9.7
  skin directed therapies 57.23–5
    PUVA 57.24
    radiotherapy and electron beam therapy 57.24–5
  staging classification, revised 57.7, 57.11
  systemic therapies 57.25–9
    combination therapy 57.25–6
    doxorubicin 57.27
    extracorporeal photopheresis 57.27
    histone deacetylase inhibitors 57.28
    immunotherapy 57.25
    monoclonal antibody therapy 57.28
    randomized trials 57.22
    retinoids 57.25
  T-cell receptor gene analysis 57.12–13
  see also Sézary syndrome
myelitis, transverse, in zoster 33.26
myelocytic leukaemia 57.62
myelodysplastic syndrome 62.88–9, 69.57
  in multicentric reticulohistiocytosis 55.24
myelofibrosis, idiopathic, pigmentation changes 58.26
myeloma *see* multiple myeloma
myeloma-associated amyloidoses 59.50
myelomeningocoele 18.95
myeloperoxidase 13.4
  deficiency 13.4, *69.117*
myeloproliferative disorders **49.29–30**
  cutaneous lesions 49.29–30
  leg ulcers 47.56
MYH-associated polyposis 53.12
myiasis 38.2, **38.8–11**
Mylabris 38.26, 38.27
myoblastoma
  congenital epulis 69.17
  granular cell 71.73
myocarditis, chagasic 37.32
myoepithelioma 53.31
myofibroblastic tumours 56.2–14
myofibroblasts
  microscopy 10.35
  in palmar fibromatosis 45.45
  in wound healing 14.1, 14.7
myofibroma, adult 56.9
myofibromatosis, infantile 18.35, 56.9
myoma, pinna 68.28
myonecrosis, clostridial *see* gas gangrene
myopathy
  inflammatory, HTLV-1 infection 33.65
  partial lipodystrophy 46.40
  in sarcoidosis 61.7
myopericarditis, vaccinia vaccination 33.6
myopericytoma 56.42–3
myosin Va, melanosome transfer along melanocyte dendrites 58.4
Myroxylon pereirae see balsam of Peru
myths, skin and skin disease 64.1
myxoedema
  palmoplantar keratoderma with 19.118
  see also hypothyroidism; pretibial myxoedema
myxofibrosarcoma 56.22
myxoid cyst
  nail 65.17, 65.36–7
  surgery 77.36, *77.38*
myxoid degeneration 10.38
myxoma
  cardiac 62.78–9
    embolism 50.54
    see also atrial myxoma
  dermal nerve sheath 56.49–50
  digital 56.59
  oral cavity 69.113
myxoma syndrome 62.25
myxoviruses **33.75**

N
Na-K-ATPase 44.3, 44.4
nabumetone *75.77*
NADPH oxidase 12.54, 13.4, 13.5
Naegeli–Franceschetti–Jadassohn syndrome 15.48, 58.19–20
Naegeli's syndrome 58.19–20
naevi *see* naevus
naevoid basal cell carcinoma syndrome 52.5, **52.6–8,** *62.20*, 62.21
  aetiology and incidence 52.6–7
  basal cell carcinomas 52.6, 52.7, 52.8
    recurrence 52.8
  bone and joint involvement 52.7, *62.101*
  clinical features 52.7
  diagnosis 52.7
  genetics 52.6–7
  malignancies in 52.7
  oral involvement 52.7, 69.39–40
  pathology 52.7
  treatment 52.7–8, 73.23
naevoid bullous ichthyosiform erythroderma 19.31
naevomelanocytes 54.30
naevoxanthoendothelioma *see* juvenile xanthogranuloma
naevus **18.1–80**
  acantholytic dyskeratotic epidermal 19.83, 65.18
  achromic (naevus depigmentosus) 58.42, 58.44–5
  acne 18.11–13, 42.78
  acne-free 18.13
  aetiology 18.2–3
  apocrine 18.14–15
  atypical/dysplastic *54.16*, 54.19, **54.27–32,** 71.47
    male genitalia 71.47
    melanoma development 54.28, *54.29–30, 54.31*
    melanoma vs 54.38
  balloon cell 54.17
  basal cell with comedones 18.13–14
  bathing-trunk (giant) 54.11, *54.12*
  Becker's **18.17–19,** *62.101*, 66.77, 78.10
    with hypomastia 70.3
  benign, excision 77.15
  blue *54.16*, 54.25–7, 58.1, **58.37**
    compound 54.26
    'malignant' 54.26, 54.27
    oral mucosa 69.29
    skin biopsy 10.43
  cartilage (accessory tragus (auricle)) 18.84–5, 68.4
  cellular (acquired melanocytic) **54.15–21,** *54.16*
  cellular blue 54.25–7
  CHILD 18.21–3, 19.57
  classification 18.3, *18.4*
  cockade 18.96, 54.20–1
  collagen 18.31–2
  combined (blue/cellular blue) 54.26
  comedo/comedone 18.11–13, 71.38
  compound *54.10*, 54.15, 54.16, 69.29
    pathology 54.18
  compound blue 54.26
  congenital melanocytic *54.10*, **54.10–15**
    giant *see* naevus, giant congenital melanocytic
  conjunctival 54.18
  connective tissue 18.30–5
  deep penetrating 54.26
  definition 18.1
  dermal 18.30–40, 54.11
  dermatitic epidermal (inflammatory linear verrucous) 18.19–21, 20.17
  desmoplastic 54.22, 54.24
  dilated pore 18.14
  dysplastic *see* naevus, atypical/dysplastic
  eccrine 18.15–17
  eccrine angiomatous 18.16
  elastic 18.32–4
  epidermal 18.**4–40**
    linear 5.*11*
  epidermal syndrome 54.11
  fat 18.37–40
  faun tail 53.6, *66.77*
  female genitalia 71.72
  fibrous tissue 18.34–5
  follicular 18.10–14
  garment 54.11, *54.12*
  genetic factors 18.2–3
  giant congenital melanocytic 54.11, *54.12*, 54.13, 63.15
    childhood melanoma 54.48–9
  hair-follicle 53.6
  halo (Sutton's) **54.19–20,** 54.39, 58.49–50
  inflammatory linear verrucous epidermal (ILVEN) 18.19–21, 20.17
  intradermal *54.10*, 54.15, 54.16–17, *54.18*, 69.29
    pathology 54.18–19
  of Ito 54.9, 58.37
    race and 9.17
  junctional *54.10*, 54.15, *54.17*, 69.29
    pathology 54.18
    shape/colour variations 54.19
  linear basal cell 18.13–14
  linear connective tissue 18.31
    proteoglycan type 18.34
  male genitalia 71.11–12, 71.47
  malignant blue 54.26, 54.27
  melanocytic 15.12–13, **54.9**
    acquired **54.15–21,** *54.16*
    atypical/dysplastic **54.27–32**
    blue/blue-black 54.25–7
    common acquired *54.16*
    compound 54.11
    congenital *54.10*, **54.10–15**
    dermal 54.11
    development/evolution 54.18–19
    female genital region 71.72
    giant congenital 54.11, *54.12*, 54.13, 63.15
    giant congenital, childhood melanoma 54.48–9
    laser therapy 78.11
    male genital region 71.11–12
    melanoma differential diagnosis 54.19, 54.38–9
    numbers and melanoma risk 54.33
    pinna 68.28
    prevalence 54.9
    race and 9.17
    terminology *54.10*
    unusual sites 54.17–19
  Meyerson's 54.20
  mucinous 18.34
  muscle 18.35–7
  naevocytic (acquired melanocytic) **54.15–21,** *54.16*
  nail matrix/bed 54.18
  non-acne 42.78
  number
    melanoma risk 54.33
    sunscreen use relationship 73.41
  oral cavity 69.29
  organoid, syringocystadenoma papilliferum 53.19
  of Ota 54.8–9, 58.1, **58.36–7**
    bone and joint involvement *62.100*
    eyelid 67.34

laser therapy 78.10, *78.11*, 80.11
race and 9.17
pigmented
of eyelid 67.34
hairy *see* naevus, Becker's
with premature ageing and short stature 45.60
porokeratotic eccrine duct and hair follicle 18.17
porokeratotic eccrine ostial and dermal duct 18.11, **18.16–17**
proteoglycan 18.34
pure eccrine 18.15–16
reticulate vascular *see* cutis marmorata telangiectatica congenita
satellite 54.11, *54.12*
sebaceous **18.8–10,** 42.78, 46.46, 69.23
bone and joint involvement *62.100*
eccrine poroma in 53.23
segmental 18.2
shave biopsy 77.12
speckled and lentiginous 5.*14*, 54.14, 78.10
spider 5.19
treatment 77.46
spindle cell, of Reed 54.22, 54.23
Spitz (spindle and epithelioid cell) 54.14, *54.16*, **54.21–5**
agminate 54.22
desmoplastic 54.22, 54.24
differential diagnosis 54.23–4, 54.39
microscopy 10.35
multiple 54.22
sites and types 54.22
strawberry 18.40–52, 18.96
eyelids 67.34
see also haemangioma, infantile/capillary
subcutaneous 18.30–40
subungual 65.38, *65.39*
Sutton's *see* naevus, halo (Sutton's)
sweat glands 44.9
systematized 18.2
trichilemmal cyst 53.4
true apocrine 18.14
true hair-follicle 18.10–11
vascular 18.40–80
eyelid 67.34
race and 9.19
verrucous epidermal 18.5–8
warty, retinoic acid therapy 73.36
white-sponge 35.43, 69.23–4
woolly hair 66.71
zosteriform 18.2
naevus anaemicus 5.19, 18.65
with telangiectactic vessels 47.20
naevus anelasticus 18.33
naevus cells *see* melanocyte(s)
naevus comedonicus 18.11–13, 42.78
male genital 71.36
naevus depigmentosus 58.42, 58.44–5
naevus en cocarde 54.20–1
naevus flammeus
salmon patch 18.62–3
see also port-wine stain
naevus follicularis 42.78
naevus fusco-caeruleus zygomaticus 54.9
naevus fuscocaeruleus ophthalmomaxillaris *see* naevus, of Ota
naevus lipomatodes cutaneus superficialis 18.37–8
naevus mucinosus 18.34
naevus sebaceus of Jadassohn *see* naevus, sebaceous
naevus spilus 54.14
naevus sudoriferus (pure eccrine naevus) 18.15–16
naevus syringocystadenoma papilliferum **18.14–15,** 53.19–20, 68.30
naevus unilateralis comedonicus 42.78
nafarelin, in acne vulgaris 42.53
naftifine *26.46*, 36.47, 73.12
Nager syndrome 68.3
nail(s) **3.14–15**
acrylic 26.16, 26.27, 26.47
acrylic gel systems 65.55–6
ageing 8.24, 65.7
in alopecia areata 66.35, *66.36*
anatomy and structure 3.14–15
in arthritis 65.25
atrophy, Cronkhite–Canada syndrome 58.13
attachment abnormalities 65.9–12
avulsion, surgical 65.44
in Bazex syndrome 65.25
beading 65.14
Beau's line *see* Beau's lines
biopsy 65.41–9
biting/picking 64.33, 65.50–1
black streaks 58.14
braces 65.9
brittle 8.24
buffing 65.56
in childhood 65.6–7
childhood idiopathic atrophy 41.14
clubbing *see* finger(s), clubbing
colour changes 65.2, 65.14–18, 65.24
cosmetics 65.54–7
in crusted scabies 38.44
cuticle (eponychium) 3.14
in Darier's disease 19.82, 19.83, 65.27–8
degloving 65.10
dermatitis 65.28–9
development 3.3, 3.5, 3.14
developmental abnormalities 65.18–20
disease, measuring impact 72.20
distal ridge 3.14
drug-induced changes 65.16, 65.38–9, 75.46
pigmentation 75.33
dysgenesis with hypodontia 69.6
in dystrophic EB 39.21
ectodermal dysplasias 15.62, 15.64–6, 15.68–9
ectopic 18.92
elderly people 65.7
embryology 3.3, 3.5
exogenous pigment 65.14
factitious disorders 64.40
factors affecting rate of growth *65.5*, *65.6*
functions 3.3, 3.14, 4.1
fungal infection *see* onychomycosis
in generalized EB simplex 39.6
in generalized non-Herlitz junctional EB 39.13
grooves
longitudinal 65.12
transverse 65.12–13
growth
ageing and 8.24
linear 65.5–6
habit tic deformity 65.12, 65.24, *65.25*, 65.51
in Hailey–Hailey disease 39.34
half-and-half 65.15
hang 65.51
hardeners 65.56
in Herlitz junctional EB 39.12
in hidrotic ectodermal dysplasia 19.106
in HIV infection 35.41–2, *35.42*, 65.16, 65.23
in hyperthyroidism 62.8
hypertrophy 65.51, *65.52*, 65.53
in hypoparathyroidism 62.12
infections 65.21–3, *65.28*, 65.56–7
see also onychomycosis
ingrowing 65.53–4
in childhood 65.6–7, 65.53
in HIV infection 35.41
treatment 65.48
lamellar dystrophy *see* onychoschizia
in Langerhans' cell histiocytosis (LCH) 55.11
in lichen nitidus 41.22, 65.29
in lichen planus 41.14, *41.15*, 65.25, 65.29–30
in lichen sclerosus et atrophicus 65.29
in lichen striatus 65.29
linear growth 65.5–6
in liver disease 62.64
median canaliform dystrophy of Heller 65.12
melanoma under 54.44–6
mending kits 65.56
morphology 65.5
ageing and 8.24
multicentric reticulohistiocytosis 55.23–4
Neapolitan 65.15
in Nékam's disease 41.27
nutcracker 65.51
ostlers' 65.51
in pachyonychia congenita 19.3, *19.94*, 19.103–4, 59.48
in peripheral nerve injury 63.14
photo-onycholysis 65.11, 65.16, 75.32
pigmentation 9.3
drug-induced 75.33
pincer (involuted/trumpet) 65.8–9
pitting 65.13, 65.23–4
treatment 73.37
in pityriasis rubra pilaris 65.25
Plummer's 62.8
preformed plastic 65.26, 65.56
in pregnancy 8.10
Pseudomonas aeruginosa infection 30.49, 65.10, 65.11, 65.21, 65.22
in psoriatic arthritis 20.57
pterygium inversum unguis 51.95
quitters 65.14
racket 65.9
in Reiter's syndrome 65.25
ridges, lichen planus 41.14
ridging 8.24, 65.7, 65.14
longitudinal 3.15
in sarcoidosis *61.11*, 61.15
'sausage links' 8.24
in scabies 38.39, 38.44
in scleroatrophic syndrome of Huriez 45.12
sculptured 65.55
shedding 65.9–10
silicone rubber prostheses 65.56
in SLE 51.38
splinter haemorrhage 3.15, 49.7
spoon-shaped 65.8
squamous cell carcinoma 65.21–2, 65.37–8
subungual haematoma 65.49–50
subungual hyperkeratosis 20.16, 51.12
subungual melanoma 65.39–41
surgery 65.41–9
in syphilis 34.11
in systemic sclerosis 51.95
Terry's 65.15
thickening 65.12
trauma
acute 65.49–50
chronic repetitive 65.50–1
delayed 65.49
from footwear 65.51, *65.52*, 65.53–4
malignant melanoma and 65.39
from manicure instruments 65.51
tumours involving 65.30–41
twenty-nail dystrophy *65.13*, 65.29, 65.30
viral warts 65.30–1
washboard 65.12, 65.24
white bands 39.35
yellow nail syndrome 62.83, 65.12, **65.16–17**
see also toenails; *entries beginning subungual; specific nail structures*
nail apparatus 3.14–15
anatomy and biology 65.1–7
arteriovenous abnormalities 65.35–6
blood supply 65.4–5
development 65.1
fibrous tumours 65.31–2
function 65.1
microscopic anatomy 65.2–4
squamous cell carcinoma 65.37–8
surgery 65.41–4
nail bed 3.14, 3.15, 65.1, 65.2
adherent nature 65.5
biopsy 65.41, 65.44–5
blood supply 65.4
colour changes 65.15
development 65.5
keratinization 65.3
laceration 65.49
lichen planus 65.29
microscopic anatomy 65.2–3
naevi 54.18
pallor 65.15
pigmentation due to antimalarial drugs 58.30
role in creation of nail plate 65.5
squamous cell carcinoma 52.25
nail cream 65.56
nail fold 3.14
arteriovenous abnormalities 65.35–6
biopsy 65.46–7
biting 65.50
lateral 3.14, 65.1–2
microscopic anatomy 65.2
proximal/posterior 3.14, 65.1
telangiectases 47.14
nail fold capillaries
dermatomyositis 51.124
purpura 49.6
nail gel 65.26
nail matrix 3.14–15
biopsy 65.41, 65.43, 65.45–6
blood supply 65.4
cell kinetics 65.5
cellular structure 3.15
definition 65.2
melanoma 54.44–6
microscopic anatomy 65.2
naevi 54.18
phenolization 65.48, 65.53
nail plate 3.14, 65.1
anatomy 65.2, 65.5
biopsy 65.41, 65.47–8
colour changes 65.14–15
effects of ageing 65.7
microscopic anatomy 65.3
in psoriasis 65.24, *65.25*
staining 65.54
thickness measurement 65.3
nail polish/lacquer 65.54–5
in psoriasis 65.26
nail polish/lacquer removers 65.55
Nail Psoriasis Severity Index 65.23, 72.9
nail unit 3.14–15
see also nail apparatus
nail wall 65.2
nail whitener 65.56
nail wrapping 65.56
nail–patella syndrome 15.8, **15.86–7, 65.19**
bone and joint involvement *62.100*
hyperhidrosis and 44.8
renal involvement 62.69
Naja nigricollis 38.60
nalidixic acid 75.31, 75.60
naloxone 21.17
NALP-3 inflammasome 12.4
naltrexone 29.7
in pruritus 21.14, *21.18*
NAME syndrome 49.37, 54.4, 58.14, 62.25, 62.79, 69.28
naming conventions, biological therapies 74.5
Nance–Horan syndrome 69.11
nano-indentation tests, mechanical injury 28.5
NAP-2 (CXCL7) 12.46, 12.74
naphthalene 27.12
naphthoquinone 66.97
napkin(s)
candidiasis 36.62, 36.68–9
disposable 17.25–6
emollient impregnation 17.26
frequency of change 17.26
washable 17.25, 17.26
see also dermatitis, napkin (diaper)

napkin dermatitis *see* dermatitis, napkin (diaper)
napkin psoriasis 17.24, 17.31–2
nappy rash 71.5
  see also dermatitis, napkin (diaper)
naproxen 75.29, 75.74–5
NAPSI (Nail Psoriasis Severity Index) 65.23, 72.9
narrative therapy 64.20
Naruto Research Institute Otsuka Atrichia (NOA) mouse 2.8
nasal crease 18.90
nasal discharge, congenital syphilis 34.15
nasal planum
  lupus erythematosus in dogs 2.16
  vitiligo in dogs 2.23
nasal vestibule
  bacterial flora 30.4
  normal bacterial flora 30.4
nasolabial folds, dermal fillers 80.4, *80.5*
nasopharyngeal carcinoma, EBV association 33.30
nasopharyngeal myiasis 38.8
nasopharynx, lymphoepithelioma 53.41–2
Nasu–Hakola disease 46.22–3
National Center for Biotechnology Information (NCBI) 15.1
National EB Registry (USA) 39.3, 39.19, 39.30
National Guideline Clearinghouse 7.5, 7.6
National Institute for Health and Clinical Excellence (NICE) 7.5, 7.6
  guidance on biological therapies 72.14
  photodynamic therapy, for non-melanoma skin cancer 52.16
natural history of diseases **6.13–14**
natural killer *see* NK cells
natural killer (NK) lymphoma *see* NK-cell lymphoma
natural moisturizing factors 4.8
natural rubber latex *see* latex
naturopathy 75.162
Naucoridae 31.34
Nav 1.7 47.9
Navajo poikiloderma 15.50
Naxos disease 3.23, *19.94*, 19.107, 66.70
NBCCS *see* naevoid basal cell carcinoma syndrome
NBS-LRR (nucleotide-binding site and leucine-rich repeat) proteins 12.9
NC/Nga mouse 2.8
NCAM (CD56) 10.21, 10.25, 13.6, 53.43
NCBI (National Center for Biotechnology Information) 15.1
NCKX5 3.20
Nd:YAG laser therapy *see under* laser therapy
near-miss sudden infant death syndrome 44.6
Necator americanus 37.2, 37.14–15
neck
  allergic contact dermatitis 26.18
  atopic dirty 24.20
  basal cell carcinoma 52.20
  Casal's necklace 59.63
  congenital cartilaginous rests (cervical auricle/tab) 18.84, 18.85
  erythromelanosis follicularis of 58.36
  fiddler's 28.25, 42.76
  flushing *see* flushing
  lichen nuchae 23.40
  lichen simplex 23.32
  macrocystic lymphatic malformations 48.27
  Madelung's 46.46
  vascular tone 43.14
  white fibrous papulosis 45.67–8
  see also head and neck
necklace of Venus 34.10
necrobiosis 10.40, 60.1
  facial 68.17
  xanthomatous granulomas with 55.27–9
necrobiosis lipoidica 59.79, **60.12–17**
  aetiology 60.12
  after jejunal bypass surgery 60.15
  annular 60.13
  associations 60.15–16
  ataxia telangiectasia and 60.15
  'burnt out' 60.13, *60.14*
  clinical features 60.13–15
  Crohn's disease and 60.15
  diabetes mellitus and 60.12, 60.13, 60.15
  differential diagnosis 60.14–15
  granuloma annulare and 60.9, 60.15
  granuloma multiforme and 60.14
  histopathology 60.12–13
  leg ulcers in 47.57
  sarcoidosis and 61.17, 61.23
  scalp 66.5
  treatment 60.16–17
  ulcerated 60.13, *60.14*
  ulcerative colitis and 60.15
necrobiotic xanthogranuloma *see* xanthogranuloma, necrobiotic
necrolysis 10.40
  toxic epidermal 71.6
necrolytic acral erythema, in hepatitis C virus infection 62.59
necrolytic migratory erythema 62.38, 62.66–7, 71.6, 71.80
  in dogs 2.17
  female genital involvement 71.80
  genitocrural 71.6
  oral ulceration in 69.85
necrosis 10.40
  acute disseminated epidermal 76.1
  adipose tissue 46.44
    see also subcutaneous fat, necrosis
  apoptosis vs 12.12
  avascular bone 51.47
  burns 28.89
  carbon monoxide poisoning 28.94
  caseation 31.8, 31.9, 31.10
  coagulative, lipocytes 46.18
  cold-induced injury 28.64
  coumadin 49.39
  cutaneous **49.49**
    calciphylaxis differential diagnosis 46.16
    causes *49.50*
    localized 49.49
  geographical 56.61
  heparin causing **49.27–9**
  intravenous drug abuse 28.53
  in loxoscelism 38.32
  male genital region 71.24–6, 71.27, 71.31
  pressure ulcers 28.16, 28.18, 28.22
  subcutaneous fat *see* subcutaneous fat, necrosis
necrotizing cellulitis 30.68
necrotizing crystalline infundibular folliculitis 19.89
necrotizing fasciitis 30.68–9
  ear 68.19
  following human bites 38.61
  intravenous drug abuse 28.52
  neonatal 17.44–5
  ocular involvement 67.27
necrotizing gingivitis 69.14, 69.77–8
necrotizing infections
  perianal/perineal 71.92–3
  subcutaneous 30.68–9
necrotizing infundibular crystalline folliculitis 19.89
necrotizing sarcoid granulomatosis 50.52, 62.83
necrotizing sialometaplasia 69.84–5
necrotizing subcutaneous infections 30.68–9
necrotizing venulitis 14.18
nectin–afadin complex 3.23
nectins 3.23
nedocromil 13.26
need, for dermatological care 6.15–16
needle-stick injuries 77.7
needs assessment, in dermatology 6.14
neem oil 38.5
  in head louse infection 38.20
  in scabies 38.41
nefopam 75.87
'negative-pressure' tests, purpura 49.5
negative pressure therapy 28.23
neglect
  mechanical injury 28.34, 28.38–9
  of self care *64.12*
NEH *see* neutrophilic eccrine hidradenitis
Neisseria catarrhalis, in external auditory meatus 30.4
Neisseria flora, in external auditory meatus 30.4
Neisseria gonorrhoeae 30.45–6, 34.24–5
  child abuse and 28.37, 71.57
  detection and culture 34.28
  disseminated infections 34.26
  in paroxysmal nocturnal haemoglobulinuria 49.30
  perianal/perineal infections 71.93
  symptoms and treatment of infection 71.71
  vaginal discharge 71.53
  see also gonorrhoea
Neisseria meningitidis 13.15, 30.44–5
  in paroxysmal nocturnal haemoglobulinuria 49.30
  see also meningococcal infection
Nékam's disease **41.27–8,** 73.44
nelfinavir, adverse effects 35.22
Nelson's syndrome 62.4
  pigmentation *58.8*
Nematocera 38.5–6
nematocysts 38.55, 38.56, 38.57
nematodes 37.2–3, **37.3–20**
NEMO gene 15.58, 17.81–2
  mutation 48.10
neoangiogenesis 47.1
Neofibularia nolitangere 38.59
neomycin
  adverse effects 26.17, 26.18, 26.45, *26.46*, 68.24
  in fish odour syndrome 44.20
  in impetigo 30.16
  topical 73.10
neonatal acne 42.75
neonatal cephalic pustulosis 42.75
neonatal juvenile xanthogranuloma 55.16
neonatal lupus erythematosus **17.16–18, 51.49–51,** 62.78, 62.109
  aetiology 51.49
  clinical features 51.49–50
  prognosis 51.51
  treatment 51.50
neonatal mouse model, acantholysis 40.5
neonatal onset multisystem disease 22.24
neonatal progeroid syndrome 46.37
neonatal pseudohydrocephalic progeroid syndrome of Wiedemann–Rautenstrauch 45.60
neonatal purpura 49.20, **49.49, 49.51**
  causes 49.49, 49.51
neonatal purpura fulminans 17.33, 17.46, 49.39, 49.51
  causes 49.51
neonatal suction blisters 28.24
neonate(s) **17.1–85**
  acne 42.75
  acropustulosis 17.9–10, 50.62
  adnexal polyp 17.15, 70.8
  atrophic lesions 17.15
  bacterial infection 17.42–6
  bacterial skin flora 30.3–4, 30.4–5
  breast abscess/mastitis 17.43
  bullae and/or erosions *17.43*
  bullous dermolysis 39.23–4, 39.25
  bullous impetigo 17.42, 30.14
  candidiasis 17.25, 17.46–7
  chemical burns 17.14
  chrysalis babies 19.27
  CMV infection 33.29
  cold injury 17.35–6
  complications
    of medical procedures 17.11–14
    of phototherapy 17.12–13
    of prematurity 17.11
  congenital erosive and vesicular dermatosis healing with reticulated supple scarring 17.11
congenital syphilis evaluation 34.21
contact dermatitis 17.22–8
dysmature/small for dates 17.1, 17.6
eccrine sweat glands 17.2
ecthyma gangrenosum 17.45
eczematous eruptions 17.22–31
electrocardiographic monitoring 17.14
eosinophilic pustulosis 17.10
epidermolysis bullosa, management 39.27–8
fungal infection 17.46–8
gas exchange 17.2
hair loss and growth 17.4
harlequin colour change 17.4
herpes simplex 33.15, 33.17, 33.20
HIV infection 17.42
iatrogenic dystrophic calcification 17.14
infections 17.39–48
  bacterial 17.42–6
  candidiasis 17.25, 17.46–7
  CMV 33.29
  fungal 17.46–8
  herpes simplex 33.15, 33.17, 33.20
  HIV infection 17.42
  Staphylococcus aureus 17.42–4
  varicella (VZV) 33.23
  viral 17.39–42
intravenous medication 17.14
listeriosis 17.45, 30.42
low birth-weight 17.1
lupus erythematosus *see* neonatal lupus erythematosus
maternal pemphigus vulgaris antibodies 40.5
mechanical injury 28.39
milia 17.5
miliaria 17.7–8
miniature puberty 17.5, 17.6
multifocal/benign haemangiomatosis 18.53
multifocal/diffuse (miliary) haemangiomatosis 18.53–4
necrotizing fasciitis 17.44–5
needle marks 17.14
nomenclature 17.1
normal bacterial skin flora 30.3–4, 30.4–5
occipital alopecia 17.4
overheating 17.2
pemphigus foliaceus 40.15
pemphigus vulgaris 17.18–19
percutaneous absorption 17.2
perianal dermatitis 17.22
peripheral cyanosis 17.4
phototherapy 17.12–13
phototoxic reactions 17.12
physiological scaling 17.4
pneumothorax 17.14
postmature/post-term 17.1, 17.6
premature/preterm 17.1
  appearance 17.6
  barrier function 17.2
  complications 17.11
primary immunodeficiency disorders 17.48–85
purpura fulminans 17.33, 17.46
pustular eruptions *17.8*
pustulosis
  cephalic 17.47
  Malassezia 17.47–8
  of transient myeloproliferative disorder 17.10–11
routine skin care in napkin area 17.26
scalp trauma 66.53
scarring
  due to delivery procedures 17.12
  following intrauterine procedures 17.11–12
sclerema neonatorum 17.38–9
sebaceous glands 17.2, 17.4–5, 42.3
sebum secretion 17.2
skin **8.1–4**

appearance 17.4–6
barrier function 17.1–2
disease **8.1–4**
disorders 17.1–15
function 17.1–4
small for gestational age 17.1
staphylococcal scalded skin syndrome 17.42–3
Staphylococcus aureus
carriage 30.4–5, 30.6
infection 17.42–4
subcutaneous fat disorders 17.34–9
subcutaneous fat necrosis 17.36–7, 46.12
toxic erythema 17.6–7
transcutaneous oxygen monitoring 17.13–14
transepidermal water loss 17.2
transient neonatal pustular melanosis 9.12, 17.8–9
transient porphyrinaemia 17.13
transillumination blisters 17.14
transplacental transfer of maternal autoantibodies 17.15–19
umbilical artery catheterization 17.13
umbilical dermatology 71.100
umbilicus 30.4–5
varicella zoster virus infection 33.23
viral infection 17.39–42
VZV infection prophylaxis 33.27
neoplasms *see* malignant disease
neoplastic vaginal discharge 71.54
neoprene 26.68
neopterin, in sarcoidosis 61.20
Neotestudina rosatii 36.73
Neotrombicula 38.50
NEP (neutral endopeptidase) 12.64, 63.2
nephelometry 13.18
nephrocalcinosis 62.71
nephrogenic fibrosing dermopathy *see* nephrogenic systemic fibrosis
nephrogenic rest 18.96
nephrogenic systemic fibrosis (NSF) 45.53, 51.82–3, 62.73, 75.151–2
nephrolithiasis 62.71
nephrotic syndrome *69.116*
dyslipidaemias 59.92
NER (nucleotide excision repair) 15.71–2, 15.75–6
nerve block 77.2–4, 77.10
in curettage 77.40
head and neck 77.2–4
nerve growth factor (NGF) 12.64, 64.5
mast cell development 3.19
pruritus and 21.5
in wound healing 63.4
nerves
Aα fibres 63.1
Aβ fibres 4.9, 63.5
Aδ fibres 4.9, 63.1, 63.2, 63.5
in complex regional pain syndrome 47.10
adrenergic fibres 63.3–4
ageing effect 8.24
biopsy, in leprosy 32.15
C fibres 4.9, 63.1, 63.2
capsaicin-sensitive 12.64
in complex regional pain syndrome 47.10
mast cells and 21.4
pruritus and 21.2
sweat gland innervation 3.12
cholinergic fibres 63.3
destruction in zoster 33.24
in leprosy 32.4, 32.5, 32.6, 32.12, 32.17
complications of damage 32.13, *32.14*, 32.18
lepromatous 32.10, 32.11
tuberculoid 32.8–9
post-ganglionic fibres 63.3
supply to skin 3.12, 3.15–16
nervosism 64.3
nervous system diseases
pigmentation changes 58.26
see also central nervous system (CNS); neurological disorders
Netherton's syndrome (NS) 19.3, 19.37–42, 66.65–7
immunodeficiency and 17.70
prenatal diagnosis *16.3*
SPINK5 12.25, 12.50
tacrolimus therapy 73.32
nettle 22.2
nettle rash *see* urticaria
Neu–Laxova syndrome 17.20–1, 19.59–60
neural cell adhesion molecule (CD56) 10.21, 10.25, 13.6, 53.43
neural crest 3.3, 3.16, 18.4
abnormalities, Waardenburg's syndrome 58.43
melanoblast development 58.3
multipotent cells 58.3
neural dysfunction, pressure ulcers 28.17
neural tube defects (spinal dysraphism) 18.95–8, 63.15–17
neuralgia
post-herpetic *see* post-herpetic neuralgia
trigeminal *69.119*
neurilemmoma *see* schwannoma
neuritis, retrobulbar, in sarcoidosis 61.7
neuro-Behçet's disease 50.60, 50.82
neuro-immuno-cutaneous system 63.4
neuro-Sweet's syndrome 50.60
neurocutaneous syndromes, eye and skin involvement *67.30*
neurodermatitis 64.27
circumscribed *see* lichen simplex
disseminated *see* atopic dermatitis
neuroectoderm 3.3
neuroendocrine carcinoma, primary, of skin *see* Merkel cell carcinoma
neuroendocrine system, immune system interactions 64.8–9
neuroepithelioma, peripheral 56.54
neurofibroma
breast 70.17
cutaneous 15.17
diffuse 56.49
female genital region 71.73
multiple **15.16,** 15.17
see also neurofibromatosis
pigmented 54.26
pinna 68.28
plexiform 56.48–9
in pregnancy 8.12
solitary 56.47–8
neurofibromatosis
in adolescence 8.7
breast 70.17
female genital region 71.73
genetics 15.2, 15.6, 15.14, **15.15–21**
McCune–Albright syndrome vs 58.18
mechanical injury 28.8
pigmentation 58.23
segmental 15.20
type 1 56.48, *62.20,* 62.23
oral involvement 69.41–2
pigmentation 66.93
respiratory tract involvement 62.80
urinary tract involvement 62.69
type 2 *62.20,* 62.23
neurofibromatosis–Noonan syndrome 15.20–1
neurofibrosarcoma 56.53
neurogenic hypothesis, vitiligo 58.47
neurohormones, targeting sebocytes 42.4
neuroimmunology 63.4
neurokinin A 63.2, 63.3
immune function and 63.4
triple response of Lewis and 63.5
in wound healing 63.4
neurokinin B, menopausal flushing 8.20
neurolabyrinthitis 34.16
neuroleptics *see* antipsychotic drugs
neurolipomatosis 18.40
neurological abnormalities/involvement
in Degos' disease 49.46
genetics 15.17–18, 15.73
in secondary syphilis 34.11
in SLE 51.45–6
in Sneddon's syndrome 49.43
in systemic sclerosis 51.102
in xeroderma pigmentosum 15.73
neurological disorders
congenital ichthyoses and 19.60, 19.61
CHIME syndrome 19.60
Conradi–Hünermann–Happle syndrome 19.49–51
IBIDS/PIBIDS syndrome 19.47–9
ichthyosis follicularis with alopecia and photophobia 19.58, 19.60
KID/HID syndrome 19.54–7, 19.60
multiple sulphatase deficiency 19.13
Refsum's disease 19.45, 19.46
Sjögren–Larsson syndrome 19.44
X-linked recessive ichthyosis 19.11
erythrokeratoderma with 19.71–2
oral involvement *69.119*
see also nervous system diseases
neuroma
amputation stump (traumatic) 56.45
epithelial sheath 56.52
Morton's 56.45
multiple mucosal 56.45
solitary circumscribed (palisaded encapsulated) 56.45–6
neuromediators **12.62–8**
sources and target cells 12.63
stress 12.63
neuromedin N 12.25
neuromuscular disease, with autosomal recessive EB simplex 39.8
neurone-specific enolase 10.21, 53.43
pruritus and 21.2, 21.8
neuropathic pain 12.62, 47.9
treatment 47.10
neuropathic ulcers *see* ulcer(s), neuropathic
neuropathy
autonomic 44.7
cold-induced 63.14
diabetic 44.7, 59.78
in HIV infection 63.12
keratoderma with 19.110
painful, erythromelalgia 47.9
neuropeptide Y 4.10, 63.3
in atopic dermatitis 24.17
GnRH release inhibited by 8.4
neuropeptides 63.2–3, 64.9
in atopic dermatitis 24.17
immune function and 63.4
peripheral nerves 4.10
secretory 63.3
wound healing and 63.4
neuropilin-1 14.6
neurosecretory granules, Merkel cells 3.15
neurosyphilis 34.14, 63.15, *69.119*
asymptomatic 34.14
congenital 34.16
differential diagnosis 34.14
gummatous 34.14
meningeal 34.14
tabetic 34.14
treatment *34.22,* 34.23
see also syphilis
neurotensin 12.25
neurotheisometer 63.9
neurothekeoma
cellular 56.50
dermal nerve sheath myxoma 56.49–50
neurotic excoriation 23.46
Neurotip® 63.9
neurotransmitters 63.2
peripheral nerves 4.10
sweat glands 3.12
neurotrophin-4, pruritus and 21.5
neurotropic virus 33.1
neurovascular disorders, of extremities **47.9–12**
neutral endopeptidase (NEP) 12.64, 63.2
neutral lipid storage disease (NLSD) with ichthyosis 19.52–4
neutropenia 17.75–6
chronic benign *69.117*
cyclical/cyclic *13.13,* 17.75, 69.33, *69.117*
familial 69.33
severe congenital (Kostmann's syndrome) 17.48, 17.75
neutrophil(s) 12.21–2
abnormalities/deficiencies 12.22–3
acne pathogenesis 42.26
basement-membrane zone 40.46
collagenases 3.41
defensins 12.5–7
depression of activities 12.22
dermatitis herpetiformis and 40.59
emigration 12.22
function 13.4–5, 17.48
tests 13.23, 17.55–6
increased in ageing skin 8.22
in infective panniculitis 46.27–8
in irritant contact dermatitis 25.5
microscopy 10.34
oral health and 69.3
pattern recognition receptors 13.5
recruitment 12.21–2
rolling activated 12.74
scavenger receptors 13.5
in subcorneal pustular dermatosis 40.21
synthesis of cytokines 12.21–2
in urticaria 22.3, 22.5
in vasculitis 50.6–7
in wound healing 14.1, 14.2–3
neutrophil activating peptide-2 (NAP-2) 12.46, 12.74
neutrophil/macrophage colony-forming unit (NM-CFU) 5.1
neutrophil-specific granule deficiency 17.75–6
neutrophilia 62.86
neutrophilic bullous disorders 50.95
neutrophilic dermatosis **50.62–95**
acute febrile *see* Sweet's syndrome
bone and joint involvement *62.101,* 62.103
classification 50.62–4
of the dorsal hands 50.80–1
extracutaneous 50.81–2
inflammatory bowel disease and 62.51
oral involvement 69.15–16
pustular 50.88–90
respiratory tract involvement 62.83
rheumatoid 50.92–3
TNF antagonists 74.7
neutrophilic eccrine hidradenitis **44.16–17,** 50.62, 50.93–5
annular lesions 62.112
in chemotherapy 75.123
neutrophilic panniculitis 46.32, 50.90–1
neutrophilic pustulosis *50.89*
neutrophilic sebaceous adenitis 50.62–3
nevirapine 74.50, 75.68
nevus fuscocaeruleus ophthalmomaxillaris *see* naevus, of Ota
New World screw-worms 38.8
newborn *see* neonate(s)
NF *see* neurofibromatosis
NF-1 gene 58.23
NF-2 gene 58.23
NF-κB 12.8, 20.40, 46.16
activation
in cylindroma 53.28
by UV radiation 8.21, 8.22
ectodermal dysplasias 15.57–61
NF1 *see* neurofibromatosis, type 1
NF1 gene 62.23
NF1-like syndrome 15.21
NF2 (neurofibromatosis type 2) *62.20,* 62.23
NF2 gene 62.23
NGF *see* nerve growth factor (NGF)
niacin *see* nicotinic acid
niacinamide, in erythema elevatum diutinum 50.27
nicardipine 75.95

NICE *see* National Institute for Health and Clinical Excellence (NICE)
Nicholas Favre disease *see* lymphogranuloma venereum (inguinale)
nickel
  allergy **26.30–3**
    chemistry 26.30
    clinical features 26.31–2
    effects of earrings 68.7
    incidence and prevalence 26.30
    patch tests 26.32
    pimecrolimus therapy 73.32
    prognosis 26.32
    therapy 26.32
    urticaria and 22.11
  in alloys 26.37
  avoidance 26.32
  dietary intake 26.22, 26.31
  dimethylglyoxime test 26.99, 27.8
  EU directive *26.30*, 26.99
  exclusion from diet 26.22, 26.32, 26.102
  occurrence and sources 26.30–1
  oral provocation tests 5.25
  prevention of dermatitis due to 27.9
  in shoes 26.68
  systemic reactions to 26.22
nickel patch test reagent, sensitization by, hair regrowth and 73.39
Nicolau's syndrome 75.155
nicorandil 69.83, 75.95
  male genital dermatology 71.27
nicotinamide
  pemphigus foliaceus 40.16
  supplements in carcinoid syndrome 43.19
  tetracycline and 74.30
    dose range and evidence level 74.30
  topical therapy 73.51
    acne vulgaris 42.43
nicotine
  eccrine gland secretion 44.18
  finger staining 62.46
  replacement 47.5
nicotine acid esters 25.18
nicotine patches *26.46*
nicotinic acid 59.63
  adverse effects 75.113
  effect on lipid profile 59.93
  flushing associated 43.16
  topical therapy 73.51
nidogens 3.28–9, *3.31*
nidus 18.61
Niemann–Pick C1-like protein 59.93
Niemann–Pick cells 59.40
Niemann–Pick disease 44.18, *69.117*
  pigmentation 58.24
  types A and B 59.40
nifedipine 74.52
  adverse effects 69.21, *70.5*, **75.95**
  systemic sclerosis 51.108
  in wound healing 14.24
nifurtimox 37.32
Nigerian satinwood *26.80*
night sweats 44.7
Nijmegen breakage syndrome *13.13*, 17.68
Nikolsky sign 28.4, 40.8
  in toxic epidermal necrolysis 76.17
nimesulide 75.77
nipple 70.1
  atopic dermatitis 70.9–10
  basal cell carcinoma 70.15
  benign papillomatosis 70.12–13
  in breast cancer 70.13
  cracked 8.13, 70.10
  cyclist's 70.10–11
  dermatitis/eczema
    due to mechanical injury 28.14
    friction dermatitis 25.17
    Paget's disease vs 53.39
  discharge 53.38
  erosive adenomatosis 70.12–13
    Paget's disease vs 53.39
  florid papillomatosis 70.12–13
  guitar 70.11
  hyperkeratosis 19.93, 70.8–9
  inverted 70.8
  jogger's 70.10–11
  mechanical injury 28.14, 28.25, 28.31
  melanoma 70.15
  neurofibromatosis 70.17
  Paget's disease *see under* Paget's disease
  papillary adenoma 70.12–13
  piercing 70.11
  rudimentary 70.3
  sebaceous glands 42.1
  seborrhoeic warts 70.15
  sore, in puerperium 8.13
  supernumerary 18.92–3, 70.2–3
  tassel ornaments 70.11
  variations in 70.1
  'wide-set' 70.2
niridazole 75.71
NISCH syndrome 19.62
nitrazepam 75.81
nitric oxide (NO) 12.56, 13.4
  actions and mechanism of 73.51
  depletion, paroxysmal nocturnal haemoglobinuria 49.30
  neutralization 25.23
  pathophysiological role in skin. 12.56
  role in wound healing 14.1, 14.25
  topical therapy 73.51
nitric oxide (NO) cream, molluscum contagiosum 33.12
nitric oxide synthase (NOS) 12.54
nitrite 73.51
nitritoid reactions 43.15
nitroblue tetrazolium reduction test 13.23
nitroethane 25.20
nitrofurantoin 75.59
nitrogen mustard
  adverse effects 75.124–5, 75.136
    allergic contact dermatitis *26.46*
  carmustine (BCNU) and 57.23
  CD30+ lymphoproliferative disorder 57.30
  topical 75.136
  see also mechlorethamine
nitroglycerin patches 26.25, *26.46*
nitrosamines 27.5
nitrosoureas, adverse effects *70.5*, 75.126
nitrous oxide cryoprobe, vulval lichen sclerosus 51.118
nits 38.16, 38.19, *66.62*
NK-cell lymphoma
  CD4+/CD56+ haematodermic neoplasm 57.39–40
  EBV association 33.31
NK cells 12.18, 13.6
  deficiency 13.6
  EBV infection 33.31
  increased activity, epidermodysplasia verruciformis 33.57
  receptors 13.6
NK/T-cell lymphoma (nasal type) 57.40–1
NK T cells 13.6, 13.31
NNT (number needed to treat) 7.8–9, 7.12
NO *see* nitric oxide
no-see-ums 38.6
Nocardia 50.55
  actinomycetoma due to 36.72, *36.73*, 36.74
  infections, amikacin 74.42
Nocardia asteroides 30.76
Nocardia brasiliensis 30.76
Nocardia minutissima see Corynebacterium minutissimum
Nocardia otitidis caviarum 30.76
nocardiosis **30.76–7**
nociceptors 4.7, 4.9, 21.2
NOD-like receptor (NLR) family 12.4, 12.9, 12.12
NOD (nucleotide-binding oligomerization domain) proteins 12.4, 12.9, 12.12
  NOD receptors 12.4, 12.9
  NOD2 mutations, Blau syndrome 12.12
NOD2 gene *see CARD15* gene
nodal diffuse large B-cell lymphoma 57.47–9
nodular dermatofibrosis, in dogs 2.17–18
nodular fasciitis 45.50, **56.4–5,** 69.112
nodule(s)
  in acne vulgaris 42.31, *42.37*
  apple-jelly 5.19, 31.11, 31.16, 37.37, 61.13
  athlete's 28.31
  coppery red, in tertiary syphilis 34.12
  cutaneous epithelioid angiomatous 56.28
  in cutaneous polyarteritis nodosa 50.37–8
  in cysticercosis 37.25
  definition 5.7
  dermal tumour 54.36
  differential diagnosis 32.15
  elastotic of the ear 45.28
  fibrous digital 45.50
  glial heterotopic 18.89–90, 56.52
  in infective panniculitis 46.27
  in leprosy 32.9
  in lupus panniculitis 46.25
  in oil granuloma (sclerosing lipogranuloma) 46.29
  onchocercal 37.4, 37.6–7
  prayer 9.13–14, 9.15
  subepidermal calcified 56.2
  viral infections, milker's nodule 33.10
  weathering 68.10, *68.11*
  yellow-tinged facial 53.15, 53.16
nodulectomy, in onchocerciasis 37.7
Noggin 3.3
noma 69.14, 69.77–8
noma neonatorum 17.45–6
nomenclature 5.1
NOMID (neonatal onset multisystem disease) 22.24
non-accidental injury *see* child abuse
non-alcoholic steatohepatitis (NASH) 74.21
non-bullous ichthyosiform erythroderma (NBIE) 19.17–21
non-clostridial gas gangrene 59.78
non-epidermolytic palmoplantar keratoderma *19.94*, 19.97
non-esterified fatty acids (NEFA) 46.3
non-Hodgkin's lymphoma
  oral 69.55
  perianal/perineal involvement 71.99
  sarcoidal reaction in 61.23
non-melanoma skin cancer (NMSC) **52.1–48**
  cancer susceptibility modifying genes 52.10–11
  chemoprevention in high-risk patients 52.17–18
  chronic injury and scarring and 52.11
  definitions 52.1–2
  detection and diagnosis 52.15
  environmental risk factors 52.3–6
    chemical carcinogens 52.4–5
    HPV 52.5–6
    PUVA 52.4
    UV radiation 52.3
    UVA 52.3
    UVB phototherapy 52.4
    X-rays and thermal radiation 52.5
  epidemiology 52.2–6
  epidermodysplasia verruciformis and 52.5
  familial cancer syndromes 52.6
  high-risk, management 52.17–18
  host susceptibility factors 52.6
  immunosuppression association 52.11
  intermediate-risk, management 52.17
  low-risk, management 52.17
  management **52.15–18**
    destructive vs excisional 52.16
    high-risk patients 52.17–18
    optimal treatment by risk level 52.17
    specific treatments 52.16–17
    treatment selection 52.15–16
  molecular and cellular biology **52.12–15**
    cancer as genetic disease 52.12
    HVP role 52.14
    multistage carcinogenesis 52.12–13
    UV radiation causing mutations 52.13–14
  molecular genetic analysis 52.12
  mortality and morbidity 52.2
  multiple lesions, management 52.17–18
  premalignant lesions and 52.2, 52.11
    disorders associated **52.2–12**
    epithelial lesions **52.29–38**
    squamous cell carcinoma development 52.25
  radiation-induced, long latent period 52.5
  risk factors 52.10–11
  risk in premalignant epithelial lesions 52.29
  treatment plan 52.17
  UVR associated 29.7
  see also basal cell carcinoma (BCC); squamous cell carcinoma (SCC); *other specific cancers*
non-naevoid melanoepithelioma, type 1 52.39–40
non-nucleoside reverse transcriptase inhibitors (NNRTIs) *35.7*
  action 74.49–50
  in HIV infection 35.6, *35.7*
  side-effects *35.21*
non-perfused pig ear model 25.9
non-specific balanoposthitis 71.24
non-steroidal anti-inflammatory drugs (NSAIDs)
  adverse effects **75.72–8,** 75.166
    allergic contact dermatitis *26.46*
    anaphylactoid reactions 75.25
    erythema multiforme *76.4*
    fixed eruption 75.29
    lichenoid tissue reaction 41.24, 41.25
    photosensitivity 29.20, 29.21, 75.31
    Stevens–Johnson syndrome *76.4*, 76.11
    toxic epidermal necrolysis 76.13
    urticaria 22.8, 22.10, 75.26
    vasculitis 50.17, *50.18*
  bleeding time, effect 49.6
  in mastocytosis 22.35
  skin testing for reactions to 75.173
  topical 73.25, 75.166
    as photosensitizers 26.24
non-syphilitic spirochaetal ulcerative balanoposthitis 71.31
non-venereal (epidemic) treponematoses **30.62–4**
Noonan's syndrome (NS) 62.77
  ear defects in 68.4
  genetics **15.14–15,** 15.20–1
  lymphoedema 48.10
  oral involvement 69.41
noradrenaline (norepinephrine) 12.65, 63.3, 64.9
  peripheral nerves 4.10
norethisterone *26.46*
normal flora *see* bacteria, flora (normal skin)
normolipaemic plane xanthomatosis *62.45*
northern blotting 11.5–6
northern fowl mite 38.51
nortriptyline *64.51*
  in post-herpetic neuralgia 63.7
Norwegian acne 42.79
Norwegian scabies *see* scabies, crusted (Norwegian)
NOS (nitric oxide synthase) 12.54
nose
  'Cyrano nose' 18.46
  'Dudley nose' 2.23
  fibrous papule 56.2–3
  glioma 56.52
  radiotherapy 79.10
  saddle-nose deformity 34.14, 34.17

sarcoidosis 61.9, 61.15
self-healing epitheliomas 52.9
'snow nose' 2.23
swelling, rhinophyma *see* rhinophyma
notalgia paraesthetica 21.15, 23.42, 58.31, 63.23
Notch signalling 3.6–7
hair greying and 3.21
melanoma development 3.21
NOTCH3 protein/*NOTCH3* gene 50.47
Notoedres cati 2.10, 38.36, 38.46
Nottingham Eczema Severity Score (NESS) 64.10, 72.9
Nottingham Health Profile 72.16
novolac 26.73
NRL *see* latex
NS *see* Netherton's syndrome (NS); Noonan's syndrome (NS)
NSAIDs *see* non-steroidal anti-inflammatory drugs
nuchal stain 18.62–3
nuclear factor B essential modulator (NEMO) 58.15
nuclear factor κB (NF-κB) *see* NF-κB
nuclear factor of activated T-cells (NFAT) 73.31
nuclear lamins 3.9
in partial face-sparing lipodystrophy 46.41
nuclear matrix proteins 3.9
nucleic acid amplification tests (NAATS)
genital chlamydial infections 34.30
gonorrhoea detection 34.28
lymphogranuloma venereum 34.33
nucleoside reverse transcriptase inhibitors (NRTI) *35.7*
HIV-associated lipodystrophy 46.42
HIV infection 35.5, *35.7*
side-effects *35.21*, 35.22
nucleotide-binding oligomerization domain (NOD) proteins 12.4, 12.9, 12.12
nucleotide-binding site and leucine-rich repeat (NBS-LRR) proteins 12.9
nucleotide excision repair (NER) 15.71–2, 15.75–6
numb chin syndrome 62.39
number needed to treat 7.8–9, 7.12
nummular dermatitis, mechanical injury 28.14
nurse specialist 72.26
nursing measures, pressure ulcers 28.20
nutrition, in severe generalized dystrophic EB 39.29
nutritional disorders **59.58–76**
nutritional status
child abuse 28.38–9
pressure ulcers 28.18, 28.21–3
NV (nodular vasculitis) 31.24–5, **50.31–3**
nylon fibres, sarcoidal reaction to 61.22–3
nymphohymenal tears 71.56, *71.66*
nystatin *26.46*, 74.46
adverse effects 75.65
in candidiasis 36.68
topical 73.12

O

oak moss 26.77
oast house disease 66.95
oat cell carcinoma of bronchus, pigmentation changes 58.25
obesity **8.16–19,** 46.2, **46.5–8**
adolescent 8.4
aetiology 8.16, 46.5–7
associated diseases 46.5, 46.6
cutaneous 8.17–18
diabetes mellitus 46.5, 46.7
cellulite vs 46.9
in childhood 46.5
cutaneous pathophysiology 8.17
delayed-type hypersensitivity response in 8.17
Dercum's disease 46.48
epidemiology 46.5
foot shape changes 8.17
lymphoedema and 48.20–1
macrophages in visceral adipose tissue 46.4
measurement 8.16
melanoma and 8.17
perianal/perineal dermatology 71.85
pressure and pain sensitivity 8.17
prevention and treatment 46.7–8
risk factors 8.16
screening, BMI use 46.5
sweating and 8.17, 44.7
syndromes with cutaneous features 8.18
treatments 8.17–18
venous leg ulcers and 47.43, 47.47
visceral adipocyte dysfunction *46.6*, 46.6–7
Objective Severity Assessment of Atopic Dermatitis 72.10
observational studies 6.19
obsessive–compulsive disorder (OCD) 42.70, 64.18, 64.30
occipital horn syndrome 3.44, 45.14, *45.15*, 45.36, **45.39**
occludins 3.24
occlusion
microvascular *see* microvascular occlusion
role in irritant contact dermatitis 25.8, 25.12
occlusive dressings 73.4
occlusive thromboarteriopathy **50.44–5**
occupation
arthropod infestation/attack and 38.2
atopy and 27.2
disorders associated with *5.6*
epidemiology of occupational dermatoses and 27.2–3
exposure to depigmenting chemicals *27.15*
hazards associated with 27.18–21
history-taking 5.5
nickel allergy and 26.30, 26.32
risk of skin disease and 6.12, *27.2*
occupational acne 27.12–15, 42.34, **42.77**
occupational causes, connective tissue diseases 51.80
Occupational contact Dermatitis Disease severity Index 72.10
occupational dermatoses **27.1–23**
acne 27.12–15, 42.34, **42.77**
ageing and 27.2
argyria 58.54
atopic dermatitis 24.33–4
Bowen's disease 52.32
chemical burns 27.11–12
chemical depigmentation 58.50–1
clinical features 27.3
contact dermatitis
allergic 26.4–5, 26.14, 26.20, 26.79, 27.4, *27.5*, 27.7
irritant 25.13, *25.14*, 27.4, 27.5–7
contact urticaria 22.20, 26.105, 27.5
definition 27.1
depigmentation 27.15
diagnosis 27.4–5
eczematous 27.1–11
epidemiology 26.3, 27.1–4
fungal infections from animals 2.12
HPV infection 33.40, 33.47
incidence 27.2
investigations 27.7–9
iron salts and accidental tattoos 58.57
irritants and sensitizers 27.3, 27.18–21
leukoderma 27.1, 58.50
management 27.10
medicolegal aspects 27.17–18
milker's nodule 33.10
mite-associated 38.46–7, 38.48
non-eczematous 27.11–15
non-melanoma skin cancers 52.4
orf 33.9
paronychia 65.21
period of exposure and 27.3
prevention 27.9–10
skin protection programme *25.26*
primary 27.2
prognosis 27.9
psychogenic 64.25–6
scleroderma 27.16, *27.17*
scrotal cancer 52.4, 52.25
skin cancer 27.15–16
stress and 27.2
vibration white finger 27.17
vitiligo 27.15, *58.9*
warts 33.40, 33.47
occupational exposures, UVR and standard erythema dose 29.4
OCD (obsessive–compulsive disorder) 42.70, 64.18, 64.30
ochronosis 62.105, 75.33
endogenous 73.27
exogenous 73.27, 75.165
pigmentation 58.54
see also alkaptonuria
Ockelbo disease 33.66
octopus 38.59
Octopus apollyon 38.59
octreotide
in carcinoid syndrome 43.19
long-acting depot 43.19
2-*n*-octyl-4-isothiazolin-3-one 26.54
ocular disorders
congenital ichthyoses and 19.60
CHIME syndrome 19.60
Conradi–Hünermann–Happle syndrome 19.49–51
harlequin ichthyosis 19.26, 19.27
IBIDS/PIBIDS syndrome 19.47–9
ichthyosis follicularis with alopecia and photophobia 19.58–9, 19.60
KID/HID syndrome 19.54–7
Refsum's disease 19.45, 19.46
Sjögren–Larsson syndrome 19.44
X-linked recessive ichthyosis 19.10
keratoderma with oculocutaneous tyrosinaemia 19.95, 19.111–12
see also eye(s); visual impairment
ocular rosacea 43.4, 43.5, 67.6, *67.7*
clinical features *67.9*
epidemiology 67.6
treatment 43.7, 67.11
oculo-dentodigital (ODD) syndrome 15.48
oculo-osteocutaneous syndrome 15.31
oculoauriculovertebral spectrum **18.82–3,** 68.4
oculocerebral syndrome with hypopigmentation 58.42
oculocerebrocutaneous syndrome 18.37, 18.104
oculocutaneous albinism *see* albinism, oculocutaneous (OCA)
oculodermal melanocytosis *see* naevus, of Ota
oculoglandular complex 37.32
oculomandibulodyscephaly with hypotrichosis 15.41, **18.81–2,** 45.8
oculomucocutaneous syndromes *69.47*
see also specific syndromes
oculotrichodysplasia 15.48
ODD (oculo-dentodigital) syndrome 15.48
odds ratio 6.18, *7.8*, 7.9, 7.15
Odland bodies 3.1, 4.2, *4.3*
Odontacarus 38.50
odonto-onycho-hypohidrotic dysplasia with mid-line scalp defect 15.38
odonto-onychodermal dysplasia 15.48
odontogenic keratocysts 69.39
odontomicronychial dysplasia 15.48
odontotrichomelic syndrome 15.53
odour(s)
body *see* body odour
workplace 64.26
Oeciacus 38.24
oedema
acute haemorrhagic of childhood/infancy 17.33–4, 49.18–19, 50.30
brawny 48.14
causes *48.7*, 48.19
chronic **48.7**
chronic ankle 48.7
chronic upper facial erythematous 43.4
filtration (increased capillary function) 48.7
following ear piercing 68.7
genetics 15.14
lymphatic failure causing 48.5
penile 28.39, 71.30, 71.49
periorbital 48.23, 67.5
pitting 47.29, 47.33, 48.7, 48.14
post-cellulitis 30.20
in pregnancy 8.11
premenstrual 8.8
skin colour and 5.16
solid facial 42.74, 48.13, 48.16, 48.23
in triple response 22.12
vulval 71.81
see also lymphoedema
oedema toxin 30.41
Oedemeridae 38.27
oesophagus
aperistalsis 51.99
blistering 39.19
carcinoma, keratoderma with *19.94*, 19.106, 19.107
cutaneous markers of disorders 62.48
diverticula, in dermatomyositis 51.125
in dystrophic epidermolysis bullosa 39.19, 39.28
in lichen planus 41.9
spasm 39.28
strictures 39.19, 39.28
in systemic sclerosis, cobblestone appearance 51.92
oestradiol *26.46*, 42.12
hair growth and 66.9
secretion, menstrual cycle 8.8
Oestridae 38.9
oestriol 8.9
oestrogen(s) 74.33
in breast growth/development 8.4, 70.1
cellulite association 46.9–10
in gynaecomastia 70.4
hair growth and 66.9, 66.11
male breast cancer and 70.14
in menopause 8.19
in menstrual cycle 8.8
in oral contraceptives, acne treatment 42.53
pigmentation changes and 58.7, 58.25
postmenopausal period 8.19
at puberty 8.4
receptors 42.12
receptors in skin, in menopause 8.19
sebaceous gland activity control 42.12
secretion 8.2
skin ageing and 80.3–4
spider telangiectases and 47.14, 47.15
synthesis 8.8, 8.19
transplacental passage 70.4
oestrogen therapy
acne vulgaris 42.53
adverse effects *70.5*, **75.117–18**
hypermelanosis 58.29
Marfan's syndrome 45.31
menopausal flushing 8.20, 43.15
in prevention of ageing 80.3–4
topical, menopausal women 8.19
see also oral contraceptives
oestrone 8.19
Oestrus 38.9
OFD *see* orofaciodigital (OFD) syndrome
office workers, occupational hazards 27.20
ofloxacin 32.17
Ofuji's disease 35.18
eosinophilic pustular folliculitis 17.10, 30.28–9
oil(s)
cooking, contamination 27.13
cutting 27.13

diesel 27.13
folliculitis due to *27.14*, 27.16
grape seed 27.13
hyperkeratoses due to 27.16
as irritants 25.20
machine 27.6
soluble 25.20, *27.4*, 27.5, 27.6
sweet almond 27.13
vegetable, comedogenicity 27.13
oil acne 42.77
oil beetles 38.26
oil granuloma 46.29–30
oil-in-water emulsions (O/W) 73.7
Oil of Cade 73.42
oil of eucalyptus 38.5
oil of wintergreen 75.165
Oily Cream BP 73.2, 73.7
oily creams 73.7
Ointment of Wool Alcohols BP 73.7
ointments 73.2, 73.5
quantity applied 73.3–4
OKT3 75.146
olanzapine 64.16, *64.52*, 75.83
in acne excoriée 42.70
old age *see* elderly people
Old World screwworms 38.8
older patients *see* elderly people
oleic acid 73.5
oleogranuloma (oil granuloma) 46.29–30
oleoma (oil granuloma) 46.29–30
olfactory delusions 64.16–17
oligodontia 69.6, 69.7
oligohydramnios 18.1
oligosaccharidoses 59.33
oligosacharides, abnormal, detection 59.33
Olindias sambaquiensis 38.56
olive oil 73.6
Ollier's disease 18.72, 65.34
Olmsted's syndrome *19.94*, 19.101–2, 69.25
olsalazine 75.56
omalizumab 74.11, 75.146
Omenn's syndrome 17.59
omeprazole, adverse effects *70.5*, 75.157
OMIM (Online Mendelian Inheritance in Man) 11.2, 15.1
ommochromes 2.5
omphalith 71.100
omphalitis 17.44
omphalocele 71.100
omphalomesenteric duct anomalies 18.93–4
Omsk virus *33.67*
onchocerciasis 37.3, **37.4–8,** 38.5
genital involvement in males 71.33
in HIV infection 35.36
ocular involvement 67.27
onchodermatitis, acute papular 37.5
oncogenes 11.17–18
ondansetron 75.79
onion
allergic contact dermatitis due to 26.77
as irritant 25.21
in naturopathy 75.162
'onion-skin cysts' 46.29
Online Mendelian Inheritance in Man (OMIM) 11.2, 15.1
ONPPD (*o*-nitro-*p*-phenylenediamine) 26.60
Onychocola canadensis 36.53
onychocryptosis *see* nail(s), ingrowing
onychodermal band 3.15, 65.2
onychodysplasia, congenital of the index fingers 65.20
onychodystrophy, Naegeli's syndrome 58.19
onychogryphosis 65.5, 65.12, 65.51, *65.52*, 65.53
onycholysis **65.10–11**
in allergic contact dermatitis 26.27
dermatophyte-associated 36.35
drug-induced 75.46
in hyperthyroidism 62.8
idiopathic 65.10
manicure instrument-associated 65.51
in pregnancy 8.10
in *Pseudomonas* infection 30.49, 65.10, 65.11
in psoriasis 65.24
treatment 73.37
secondary 65.11
treatment 65.10–11
onychomadesis 65.10, 65.13
onychomatricoma 65.32–3
onychomycosis
Candida 36.63, 36.64, *36.65*, 36.69
in childhood 65.7
definition 36.53
dermatophyte-associated (tinea unguium) 36.34–5, 36.50
differential diagnosis 65.25, *65.28*
distal and lateral subungual 36.34, 36.63
in elderly people 65.7
endonyx 36.35
genetics 15.10
in HIV infection 35.33, 35.41
laboratory investigation 36.6, *36.8*
non-dermatophyte moulds as cause 36.53–6
proximal subungual 36.35
in psoriasis 65.24
Scopulariopsis brevicaulis 36.53–4
Scytalidium 36.51–2
superficial white 36.34, 36.50, 36.53, **36.55**
totally dystrophic 36.35
treatment 73.12
Trichophyton equinum 2.12
onychopapilloma 65.18
onychophagia 64.33, 65.50
onychoptosis defluvium 65.10
onychorrhexis 65.12
onychoschizia 65.13–14
in childhood 65.6
onychotillomania 64.33, 65.50
onychotrichodysplasia and neutropenia 15.49
O'Nyong-Nyong virus infection 33.66, *33.67*
open epicutaneous test 26.11–12
ophiasis 66.35
ophthalmia neonatorum 34.25, *34.27*
ophthalmia nodosa 38.29
ophthalmoganglionar complex 37.32
ophthalmomyiasis 38.8, 38.9
opilacao *see* trypanosomiasis, American/South-American
opioid peptides
flushing in rosacea and 43.2
pruritus and 21.3, 21.4, 21.8, 21.9, 24.18
opioid receptors 21.4
opioid therapy
adverse effects **75.86–8**
post-herpetic neuralgia 63.7
topical, dystrophic epidermolysis bullosa 39.30
Opitz syndrome 69.37
Opitz–Firas syndrome 69.37
Opitz–Kaveggia syndrome **15.96**
opportunistic infections 30.1
in HIV infection, in pregnancy 8.13
in HTLV-1 infection 33.65
see also specific infections; specific pathogens
opsonins 13.2, 13.4
optic nerves, in sarcoidosis 61.7
optical whiteners 26.65, 26.67
oral allergy syndrome 22.20, 26.105, 69.108
oral care, in dystrophic epidermolysis bullosa 39.28
oral cavity *69.5*
abscess 69.109
in acanthosis nigricans 69.34
in acrodermatitis enteropathica 69.31
allergic contact dermatitis 26.20–1
in amyloidosis 69.114–15, *69.116*, *69.117*
anatomical variants 69.6–7
angio-oedema 69.107–8
bacterial infections 69.77–9
in Behçet's disease 50.58, *50.59*, 69.44, *69.118*
biology 69.1–3
blisters 69.14, 69.22
in blue rubber-bleb naevus syndrome 69.30
burns 69.43, 69.88
Candida albicans carriage 36.56, 36.58, 69.88
candidiasis 36.60–1, 36.64, 69.13, 69.22, 69.88–9
treatment 36.68
in cardiovascular disease *69.117*
complications of bone marrow transplantation 69.82–3
in connective tissue disorders *69.117*
in Cowden's syndrome 69.38
in Crohn's disease 62.49, *69.116*
in Darier's disease 69.25–6
dermoid cyst 69.34–5
in discoid lupus erythematosus *69.65*, 69.71
drug reactions 69.83, 69.97, *69.116*, 75.46–7
in dystrophic epidermolysis bullosa 39.18–19
in epidermolysis bullosa 69.31–2
epithelium 69.1
erythema 69.22
erythema multiforme *69.65*, 69.69–70
erythroplasia (erythroplakia) 69.50
examination 69.5–7
fibroepithelial polyp (fibrous lump) 69.20
fibroma 69.20
focal mucinosis 69.39
fungal infections 69.79–80, *69.118*
in gastrointestinal disease *69.116*
in Goltz(–Gorlin) syndrome 69.33–4
in graft-versus-host disease 69.83
haemangioma 69.13, 69.22, 69.29, *69.30*
in haematological disease *69.116*
in hereditary angio-oedema 69.33
in hereditary haemorrhagic telangiectasia 69.29, *69.117*
in herpes zoster 69.74–5, *69.118*
in HIV infection 69.19, 69.56, 69.81, 69.97–8, *69.118*
immunity in 69.3
in immunodeficiency *69.117*
in Kawasaki disease 69.84, *69.118*, 69.121
keratoacanthoma 69.54–5
keratoses 69.90–3
in KID syndrome 69.26
in Kindler syndrome 69.40
in Klippel–Trenaunay–Weber syndrome 69.30
in Langerhans' cell histiocytosis (LCH) 55.11, *69.118*
leiomyoma 69.113
in leishmaniasis 69.81
lentiginosis 69.28
in leukocyte adhesion deficiency 69.16
lichen planus 26.26, 69.61–3, *69.65*
lichen sclerosus et atrophicus 69.63–4
lipoma 69.113
in liver disease *69.115*
in localized epidermolysis bullosa simplex (Weber–Cockayne EBS) 39.6
lumps/swellings 69.33–6, 69.109–15
lymphangioma 69.34
lymphatic system 69.4
in Maffucci's syndrome 69.13, 69.29, 69.30
malignant disease 69.13, 69.22, 69.42, 69.49–456, 69.98–9, *69.116*
metastatic 69.55–6
melanoma 54.6, 54.47
in metabolic disorders *69.117*
mucosa 69.2
disorders 69.21–115
hyperpigmentation 69.95
mucous membrane pemphigoid *69.65*, 69.67–8
multiple myeloma 69.114, *69.116*
myxoma 69.113
naevi 69.29
in neurofibromatosis type I 69.41–2
in neurological disorders *69.119*
nodular fasciitis 69.112
in Noonan's syndrome 69.41
oedema within 48.16
papilloma 69.110–11
in Papillon–Léfèvre syndrome 69.16
paracoccidioidomycosis 36.87, *69.118*, 69.121
pemphigus vulgaris 69.64–6
in Peutz–Jeghers syndrome 69.27, 69.28, *69.116*
pigmentation/pigmented lesions 9.3, 69.21–2, 69.26–9, 69.95–100, 75.47
plasmacytoma 69.114
protozoal infestations 69.81
in psoriasis 69.94
in psychiatric disease *69.115*
purpura 49.5, 69.21–2, 69.99–9100
pyoderma gangrenosum 50.70
pyogenic granuloma 69.20
red lesions 69.29–231, 69.100–6
in renal disease *69.116*
rhabdomyoma 69.112
rhabdomyosarcoma 69.112
sarcoidosis 69.109, *69.118*
sebaceous adenoma 69.23
soreness 69.85
in Sturge–Weber syndrome 69.13, 69.29, 69.30
submucous fibrosis 69.106–7
in Sweet's syndrome 69.49
in syphilis 34.18, 69.78, 69.90, 69.91, *69.118*
primary 34.7, 34.8
secondary 34.11, 34.12
tertiary 34.14
in systemic disease *69.115–19*
in systemic lupus erythematosus 69.71
tattoos 69.95–6
telangiectases 69.22, 69.101
in toxic epidermal necrolysis 69.70–1
in tuberculosis 69.79, *69.118*
in tuberous sclerosis 69.41, *69.118*
ulcers 69.22, 69.33, **69.42–9**
aetiology *69.14*, *69.42*
in Behçet's disease 50.58, *50.59*, 69.44, *69.118*
Crohn's disease and 62.50
drug-induced 69.83
eosinophilic 69.43
herpetiform 69.45
in HIV infection 35.42
local factors 69.43
major aphthous (Sutton's) *see* Sutton's disease
minor aphthous (Mikulicz) 69.44–5
in systemic disease 69.56–84
ulcerative colitis and 62.50
varicella 33.24, 69.74
vasculitides 69.81–2
verrucous carcinoma 52.26
vesiculobullous disorders 69.64–71
vesiculoerosive disorders 69.31–3
viral infections 69.72–7, *69.118*
in Waldenström's macroglobulinaemia 69.114
warts 69.111
white lesions 69.13, 69.87–95
see also leukoplakia
in Wiskott–Aldrich syndrome 69.31
in xeroderma pigmentosum 69.42
oral commissures 69.2
oral contraceptives
acne vulgaris treatment 42.53
adverse effects 69.97, **75.118**
hyperpigmentation 58.25, 75.33
allergic contact dermatitis and 26.8
female genital dermatology and 71.52
flushing management 43.15

hidradenitis suppurativa and 30.80, 30.81
interactions with antibiotics 75.55
telogen effluvium and 66.28
oral dysaesthesia 26.20, 26.39, 62.85, 69.86–7
oral hairy leukoplakia, EBV and 33.31
oral lesions, genetics 15.17
oral leukokeratosis, focal keratoderma with 19.103
oral–facial–digital syndrome, type I 62.69–70
orange peel appearance, skin 46.9
orange tawny 38.50
orbicularis oris 69.1
orbital oedema, genetics 15.14
orchitis, in lymphatic filariasis 37.9
orf **33.8–10,** 69.121
clinical features, diagnosis and treatment 33.9
organelles, defects in Chédiak–Higashi syndrome 58.41
organic solvents 25.3, 25.20, *27.17*
scleroderma-like lesions 51.80
organoid naevus syndrome 18.27–30, 54.11
'orgasm cutanée' 64.23, 64.27
oriental sore **37.34–9**
orlistat 8.18
ornamental piercings 28.51–2
Ornithobilharzia 37.22
Ornithodoros 38.35
Ornithonyssus 38.51
ornithosis **30.71–2,** 62.80, 62.107
orofacial granulomatosis 26.20–1, **69.59–61**
orofaciodigital (OFD) syndrome
type I 15.49, 69.37
type II 69.37
orokeratosis striata lichenoides (Nékam's disease) **41.27–8,** *73.44*
oropharyngeal infection, gonococcal 34.25
oropharynx, in HIV infection 35.42–4
Oropouche viruses *33.67,* 33.70
orosomucoid 13.19
Oroya fever 30.57–8, 35.25
orthomyxoviruses *33.3,* 33.75
orthopoxviruses 33.5, 33.7, 33.8
Orthoptera 38.28
Osler–Rendu–Weber disease *see* hereditary haemorrhagic telangiectasia (HHT)
Osler's nodes 62.78
osmidrosis 44.19–20
Osnabrueck Hand Eczema Severity Index 72.10
ossification, skin 59.70
osteoarthritis, venous leg ulcers and 47.46
osteochondritis, in congenital syphilis 34.16
osteochondroma, subungual 65.33
osteocytes, origin 12.30
osteodystrophy, Albright's hereditary 15.6
osteoectasia 45.23
osteogenesis imperfecta **45.40–1,** 69.8
bone and joint involvement *62.100*
collagen gene mutations 3.35
purpura in 49.15
osteoid osteoma 65.34
osteolysis, massive *see* Gorham's (Gorham–Stout) disease
osteoma
external auditory canal 68.28, 68.29
genetics 15.26
jaw 69.39
osteoid 65.34
pinna 68.28
osteoma cutis 42.78, 51.69, 56.61–2, 62.99, *62.101*
osteoma mucosae 69.108–9
osteomyelitis 62.99
chronic recurrent multifocal 62.104
diabetic foot ulcers and 47.58
in invasive otitis externa 68.26
in neuropathic ulcer 63.9
pressure ulcers and 28.19–20
in tertiary syphilis 62.105
osteomyelitis syphilitica 34.16
osteonectin 14.3
osteopathy *72.32*
osteopoikilosis 18.33, 51.98, 62.99, *62.102*
osteopontin 49.47
osteoporosis, cutaneous atrophy and 45.3
Ota, naevus of *see* naevus, of Ota
otalgia 68.1, 68.22
psychogenic 68.35
otitis externa **68.20–7**
acute diffuse 68.22
acute localized 68.27
allergic and 'ide' reactions 68.24
in animals 2.11
benign non-necrotizing 68.24
bullous 68.22
chronic 68.22–3
clinical features 68.22–3
complications 68.24
contact dermatitis and 26.17
differential diagnosis 68.23–4
environmental factors 68.21
genetic and constitutional factors 68.20–1
granular 68.22
histopathology 68.22
hypertrophic 68.24, 68.25
incidence 68.20
infective 68.20
invasive (malignant/necrotizing) 30.49, 68.25–7, 68.28
mycotic 36.7–8, 36.17, 68.27–8
necrotic 36.17
pathogenesis 68.20
Pseudomonas aeruginosa infection and 30.49, 68.21, 68.22, 68.25
reactive 68.20, 68.23
recurrent 68.24
seborrhoeic 68.23
secondary sensitization 68.24
secondary trauma 68.24
traumatic 68.21
treatment 68.24–5
Otodectes cynotis 2.11, 38.46
otodental dysplasia 69.11
otomycosis 36.7–8, 36.17, 68.27–8
otophyma 43.9
Oudtshoorn disease 19.66, 19.68–9
ovarian disorders
hirsutism and 66.82
purpura in 49.18
ovarian follicles 8.19
ovarian tumours, hirsutism and 66.82
ovary
androgen production, inhibition 42.53
atrophic 8.19
ovulation 8.8
'owl eye' intranuclear inclusions, CMV 33.29
22-oxa-calcitriol *see* maxacalcitol
oxalic acid 25.20
oxaliplatin 75.134
oxerutins 48.25
oxiconazole, topical 73.12
oxidative burst 13.4, 13.5
oxidative stress 12.55
oxidizing agents as irritants 25.21
oxprenolol 75.91
oxybenzone 26.23, 26.24
oxybutinin 44.12
oxycodone 63.7
Oxycopis vittata 38.27
oxygen
hyperbaric therapy 14.25
gas gangrene 30.44
lymphoedema 48.23
neonatal transcutaneous monitoring 17.13–14
in photosensitivity reactions 29.20
role in wound healing 14.1, 14.25
transcutaneous oxygen tension ($tcPO_2$) 4.11, 47.3, 47.26
oxygen perfusion, pressure ulcers 28.18
oxygen tension, *Propionibacterium acnes* growth and acne 42.25
oxyhaemoglobin 5.15
in erythema 25.22
oxymetazoline, flushing management in rosacea 43.6
Oxyopidae 38.32
oxypentifylline, flushing and 43.15
oxyphenbutazone 75.28, 75.77
oxytalan fibers 3.42
oxytetracycline 74.41
acne vulgaris treatment *42.47,* 42.48
adverse effects, ocular 67.31–2
oxyuriasis **37.13–14**
Oxyuris infestation, perianal/perineal inflammation 71.84

P
P antigen, erythrocyte 33.63
P-cadherin
gene mutations 3.24
in Hailey–Hailey disease 39.33
P-selectin 13.4
P value 6.18, 7.11, 7.19, 7.20–1
p16 gene mutations, cancer and 52.12
p16 protein, in melanoma pathogenesis 54.33
p38 mitogen-activated protein kinase (p38MAPK) 40.6
p53 15.61
inactivation by E6 protein of HPV 33.39
proliferating trichilemmal tumour and 53.5
UV-induced melanocyte growth arrest and 58.7
UVR-induced activation 29.5
p53 gene
ectodermal dysplasias and 15.61
mutations
cancer and 52.12, 52.32
UVR-induced 29.7
p59 protein 73.17
p63 gene 10.24
mutations in ectodermal dysplasias 15.61
p63 protein 3.6, 10.24, 15.61
p73 gene, ectodermal dysplasias and 15.61
p73 protein 15.61
PABA (*p*-aminobenzoic acid) 26.23, 26.62
PACAP (pituitary adenylate cyclase-activating peptide) 12.63–4, 63.3
pacemakers, electrosurgery and 77.46
pachyderma *37.6*
pachydermatoglyphy 62.31–2
pachydermatous eosinophilic dermatitis, differential diagnosis 24.27
pachydermia oralis 35.43, 69.23–4
pachydermodactyly 45.48–9
mechanical injury and 28.15
pachydermoperiostosis 15.87, **15.88–9,** 45.41–2, 62.2, *62.101*
pachyonychia congenita (PC) 59.48, **65.20**
genetics 15.49
Jackson-Lawler type (PC-2) *see* Jackson–Lawler syndrome (pachyonychia congenita type 2)
Jadassohn–Lewandosky type (PC-1) *see* Jadassohn–Lewandowsky syndrome (pachyonychia congenita type 1)
keratins in 65.3
mechanical injury and 28.13
oral involvement 69.24
prenatal diagnosis *16.3*
Pacinian corpuscles 4.9, *4.10,* 63.2, 63.14
paclitaxel 75.135–6
Paederus 38.26–7
PAF *see* platelet-activating factor (PAF)
Paget cells 53.38–9
pagetoid dyskeratosis 69.91
male genital dermatology 71.46
pagetoid reticulosis 57.15
pagetoid vulval intraepithelial neoplasia 71.75
Paget's disease
extramammary **53.40–1,** 62.16–17
diagnosis 10.21
external ear 68.30
female genitalia 71.78–9
male genitalia 71.46–7
perianal/perineal 71.98
pseudoxanthoma elasticum and 45.23
topical 5-FU 73.23
topical imiquimod 73.24
nipple **53.38–40,** 62.16, *70.10,* 70.14
breast cancer and 53.38, 53.39, 70.14
pagoda red 10.10
pain
abdominal, in Henoch–Schönlein purpura 50.20
arterial ulceration 47.52
chronic skin 63.23–4
complex regional pain syndrome 44.8, 63.20–2
congenital insensitivity to 63.19
in cryosurgery 77.39
deafferentation 63.6
in erythromelalgia 47.9
in furunculosis 30.24
lightning 63.11, 63.15
mediation 4.9
oral 69.85
plantar warts 33.44
in post-herpetic neuralgia 63.6
quality of 5.4
referred, to ear 68.35
sensitivity, in obesity 8.17
threshold, increased with age 8.24
zoster 33.25, 33.26
pain management
burns 28.79
in dystrophic epidermolysis bullosa 39.30
venous leg ulcers 47.49
pain syndromes
male genitalia 71.51–2
perianal/perineal 71.99
vulval 71.81–2
painful bruising syndrome 49.16, 64.33–4
painful fat syndrome 48.20
painful swelling, male genitalia 71.49
painters, occupational hazards 27.20
paints (topical therapy) 73.2
Pakistan, prevalence of skin disease *6.10*
Pal-E 48.4
palate
cleft *see* cleft lip/palate
tertiary syphilis 34.14
palisaded neutrophilic and granulomatous dermatitis 51.131, 62.103–4
palladium 26.37–8
pallor 62.85
'porcelain-white' 49.45
vasoconstrictor assay for corticosteroids 73.16
palmar arteries 65.4
palmar crease erythema 62.85
palmar dermatitis, mechanical injury and 28.14
palmar erythema, in pregnancy 8.10
palmoplantar hyperkeratosis and alopecia 15.49
palmoplantar keratoderma (PPK) 19.3, **19.93–119,** 59.48
acquired 19.116–19
cicatrizing *19.94,* 19.95, 19.101–2, 19.108–9
classification 19.93–4
congenital and perioral *19.94,* 19.101–2
deafness and 19.3, *19.94,* 19.108–10
diffuse *19.94,* 19.95–7

extracutaneous features *19.94*–5, 19.106–12
filiform 19.114
focal 19.3, *19.94,* 19.95, 19.102–5, 62.20–1
hereditary 69.16
hidrotic ectodermal dysplasia *19.94,* 19.106
hyperhidrosis and 44.8
malignancy and 19.106, 19.116–17
marginal papular 19.114–15
miscellaneous syndromes 19.115–16
in Naegeli's syndrome 58.19
Nékam's disease and 41.27
periodontitis with *see* Papillon–Lefèvre syndrome
porokeratotic 19.112–13
punctate 19.95, 19.112–13
striate 19.3, *19.94,* 19.95, 19.105–6, 19.107
transgredient *19.94,* 19.95, 19.98–101
palmoplantar keratoderma varians *see* palmoplantar keratoderma (PPK), focal
palmoplantar pits, naevoid basal cell carcinoma syndrome 52.7
palmoplantar porokeratosis (of Mantoux) 19.91
palmoplantar pustulosis (PPP)
acitretin therapy 74.35
bone and joint involvement 62.101–2, *62.103*
palmoplantar skin, structure 3.9
palms
biopsy 10.32
erythema, paraneoplastic 62.41
hairy malformation 18.14
hyperhidrosis 44.7–8, *77.37*
hyperkeratotic eczema 23.16, 26.29
hyperpigmentation 9.2
keratosis punctata 9.10
lichen nitidus 41.22
lichen planus 26.29, 41.7, *41.8,* 41.14
liver 62.64
melanocytic naevi 54.17–18
melanoma 54.44, *54.45*
recurrent focal palmar peeling 23.19
seed-like keratoses 62.33
tripe 62.31–2
vesicular eczema *see* pompholyx
see also hand(s)
Palomena prasina 38.25
palpation of skin 5.17–18
palpebral arteries 67.2
palpebral fornices, superior and inferior 67.2
PAMPs *see* pathogen-associated molecular patterns (PAMPs)
PAN *see* polyarteritis nodosa (PAN)
panatrophy
of Gower 45.11
local 45.11
sclerotic 45.11
pancornulins 3.10
pancreas
cystic fibrosis 59.59
disorders *see* pancreatic disease
pancreatic cancer 54.33, 54.34
enzymic panniculitis in 46.18
flushing and 43.16
pancreatic disease **62.65–8**
subcutaneous fat necrosis 46.18–20, 62.65–6
see also specific diseases
pancreatic enzymes, panniculitis due to 46.18–20
pancreatic panniculitis 46.18–20
pancreatitis *69.116*
acute 62.65
enzymic panniculitis after 46.18
pancuronium 75.153
pancytopenia with congenital defects *see* Fanconi's anaemia/syndrome
panda sign 49.4, 49.15
Paneth's cells 4.5
pangeria *see* Werner's syndrome
panhypopituitarism 46.35
pannexins 3.24
panniculitis **46.10–12, 46.12–34,** 51.14–15, 51.87
acute
infectious id 46.32
mechanical injury 28.27
in animals 2.16
α1-antitrypsin deficiency 46.20–1
autoimmune 46.15
calcifying, with renal failure 46.16–17
cellular proliferative disease 46.23
chronic ulcerative, drug-induced 46.28
classification 46.11
cold 17.35, 46.21
complement deficiency with 46.27
connective tissue 46.31–2, 51.87
crystal deposition association 46.16–17
cytophagic histiocytic 46.23–5
Degos' disease 49.45
in dermatomyositis 46.31–2, 51.124
drug-induced 35.22
chronic ulcerative 46.28
enzymic (pancreatic) 46.18–20
eosinophilic 46.12
factitial 46.28–9, 46.29
fasciitis–panniculitis syndrome 46.30, 46.31
granulomatous 46.14, 46.27
granulomatous lipophagic 46.32
in HIV infection 35.25
idiopathic nodular 46.13–14
infective 46.27–8
lipoatrophic (connective tissue/autoimmune) 46.15
lipophagic 46.15
lobular 46.11, **46.13–25**
plasma cell 46.14
unusual causes 46.14
vasculitis with 31.24–5, **50.31–3**
lupus 46.25–7, 50.49
lymphoedema and 48.13
migrating 37.17
mixed (septal and lobular) 46.11, **46.25–32**
neutrophilic 46.32, 50.90–1
nodular 46.13, 46.24
complement deficiency 46.27
cystic 46.22
infectious causes 46.14
oedematous scarring vasculitic 46.32–3
paraneoplastic 62.40
post-steroid 46.16
'primary' lipophagic 46.15
pustular 51.132
pustular neutrophilic 46.32
relapsing febrile nodular 46.13
sclerosing (lipodermatosclerosis) 46.30–1
self-inflicted 46.28–9
septal 46.11, **46.12,** 46.32
viral infections and 33.76
subacute nodular migratory 46.12
ulcerative 46.20
vasculitis with 46.11, **46.32–4**
panniculitis-like T-cell lymphomas, subcutaneous (SPTL) *see under* T-cell lymphomas
pannus *67.4*
panobinostat 11.16
panophthalmitis 38.29
pansclerotic morphoea of children 51.71–2, 51.75
Panstrongylus megistus 37.31
Panton–Valentine leukocidin 30.8, 30.23–4
pao ferro *26.81*
PAP (postaxial polydactyly) 18.92
PAPA syndrome 42.82, 50.53, 50.66, 62.104
papatasi fever 38.5
papaya 25.21
paper money skin 62.64
Papilionaceae *26.80*
papillary hidradenoma 71.72
papillary hyperplasia 69.112
papillary tip microabscess 10.41
papillary vessels, actinic keratosis 52.31
papilloedema, in sarcoidosis 61.7
papilloma
basal cell *see* seborrhoeic keratosis
carcinogen-induced in murine model 52.12, 52.13
conjunctiva 33.47
definition 5.7
focal dermal hypoplasia syndrome 15.84
histopathology 10.40–1
HPV causing 33.37–8
nasal inverting 33.47
oral 69.110–11
progression to cancer, murine model 52.13
papillomatosis
acanthotic chronic 62.54
confluent and reticulate *5.10,* 19.121–2, 36.13–14
in eczema 23.4
external auditory canal 68.29
florid
cutaneous 19.93
oral 69.53
histopathology 10.41
respiratory 33.47
reticulate 73.44
in seborrhoeic keratosis 52.39
in viral warts 33.41
vulval 33.46
papillomatoverrucous palmoplantar keratoderma 19.95, 19.115
papillomaviruses *33.2,* 33.37
canine oral 33.42
human *see* human papillomavirus (HPV)
β-papillomaviruses, epidermodysplasia verruciformis and 52.6
Papillon–Lefèvre syndrome *13.13,* 15.50, *19.94,* 19.110, 19.111
late-onset 69.16
oral involvement 69.16, 69.33
papovaviruses *33.2*
papular acantholytic dermatosis (transient and persistent acantholytic dermatoses) 19.86–8
papular acrodermatitis of childhood *see* Gianotti–Crosti syndrome
papular atrichia 66.59
papular keratoderma, marginal 19.95, 19.114–15
papular mucinosis *see* mucinosis, papular
papular–purpuric gloves and socks syndrome 33.63, 49.20, 69.99
viral infections associated 33.63, 33.76, 35.31
papules
in acne, early *42.25, 42.31*
in acne conglobata 42.82
benign lymphangiomatous 48.28–9
common warts 33.42
definition 5.7
fissured ('split'), in syphilis 34.11, 34.16
in Gianotti–Crosti-like syndrome 33.77
infantile pedal 17.15
in juvenile xanthogranuloma 55.16
in Langerhans' cell histiocytosis 55.9
in leprosy 32.9
lichen nitidus 41.21, 41.22
lichen planus 41.4, 41.6
milker's nodule 33.10
'moist' in syphilis *34.10*
necrotizing, cryptococcosis *35.33*
in orf 33.9
papular xanthoma 55.19–20
piezogenic pedal 28.61
psoriasiform, in syphilis *34.10,* 34.11
rheumatoid 50.52
'sago grain,' plantar warts 33.43
secondary syphilitic 34.7, *34.9, 34.10,* 34.10–11
papuloerythroderma of Ofuji 9.13, **23.50–1,** 62.38
papulosis
Bowenoid *see* Bowenoid papulosis
clear cell, genitocrural dermatology 71.6
malignant atrophic *see* Degos' disease (malignant atrophic papulosis)
papulosquamous infections, in animals *2.21*
papulovesicles, hydroa vacciniforme 29.15
papulovesicular acrolocated syndrome *see* Gianotti–Crosti syndrome
para-aminosalicylic acid 74.45
parabens 26.54–5, 73.8, *75.159*
paracellin-1 (claudin 16), gene mutations 3.25
paracetamol 75.72–3
parachlorometacresol 26.56–7, 73.8
parachlorometaxylenol 26.56, 73.14
parachlorophenylalanine 43.19
Paracoccidioides brasiliensis 36.87, 36.88
paracoccidioidomycosis **36.87–8,** *69.118,* 69.121
in HIV infection 35.34
male genitalia 71.32
'paradoxical healing,' tertiary syphilis *34.13*
paraffin, acnegenicity 27.13
paraffin implants, scleroderma 51.82
paraffinoma 28.43–4, 46.28, 46.29–30
classical 46.28, 46.29
orbital/palpebral 46.28
paragonimiasis **37.23**
Paragonimus 37.23
parahydroxybenzoic acid esters 73.8
parakeratosis
in actinic keratosis 52.30–1
Crohn's disease and 62.49
granular, in obesity 8.17
histopathology 10.41
in irritant contact dermatitis 25.4
in lichen planus 41.4
mechanical injury and 28.11
reversal in psoriasis, coal tar and 73.42
parakeratosis pustulosa 65.23, 65.25
parakeratosis variegata 57.58
paralysis
in leprosy 32.18
tick 38.35
Paramyxovirus 33.75
paramyxoviruses *33.3,* 33.75
paraneoplastic disorders 62.29–46
genodermatoses 62.19–29
paraneoplastic pemphigus 40.22–4
clinical features 40.4
immunopathology and immunogenetics 40.4
parangi *see* yaws
paranitrophenyl phosphatase 44.3
paranoia 64.17
paraphenylenediamine 26.17, 26.25, 26.26, 26.60–2, 26.64, 66.97
sensitization to 26.95
substituted, lichen planus-like contact dermatitis and 41.23
in temporal henna tattoos 58.57
paraphimosis 71.8–9, 71.20–1
parapoxviruses 33.5, 33.8–9, 33.10
paraproteinaemia 69.114
diffuse plane xanthomatosis with 55.22
paraneoplastic 62.44
purpura in 49.19
xanthomata and 59.92
paraproteins 13.17, 62.92–5
in necrobiotic xanthogranuloma 55.28
parapsoriasis 57.57
large plaque, early stage mycosis fungoides 57.13
small plaque 57.13
parapsoriasis-en-plaque, benign 23.7–8, 57.57
pararosaniline chloride *see* gentian violet

parasites **37.1–44**
  hosts 37.1
  life histories 37.1–3
  see also specific parasites
parasitic diseases
  animals 2.9–11
    comparison with humans *2.21*
  ocular involvement 67.27
  perianal/perineal involvement 71.92
  see also specific diseases
parasitosis, delusional 21.12, 64.13–16, 65.50, 68.16
parasympathetic nervous system 63.1, 63.3
parathormone, pruritus and 21.8
parathyroidectomy 49.48
parathyroidism, genetics 15.81
paratoluenediamine 66.97
paratyphoid 30.47–8
paravaccinia (milker's nodule) 33.10–11
parchment pulps 23.6
Parents' Index of Quality of Life in Atopic Dermatitis (PIQol-AD) 72.20
parietal emissary vein 77.2, *77.3*
Parinaud's oculoglandular syndrome 30.57
Parker's stain 36.7
Parkes–Weber syndrome 18.61–2, 47.24
  lymphoedema with 48.21
parkinsonism *69.119*
  seborrhoeic dermatitis and 23.29
Parkinson's disease
  restless legs syndrome and 47.12
  sweating in 44.7
paronychia
  bacterial (acute) 30.32, 65.21
  Candida 9.18, 36.63, 36.64, 36.69, 65.21
  in childhood 65.6
  chronic 36.63, 65.21–2, *65.28*
  herpetic 33.17, 65.22–3
  in HIV infection 35.41
  mechanical injury and 28.25
  in psoriasis 65.25
  Scytalidium 36.52
  syphilis differential diagnosis 34.7
  syphilitic 34.11, 34.16
  treatment 65.22
parotid duct 69.5
  operations, gustatory hyperhidrosis following 44.10
parotid gland examination 69.5
Paroven® 48.25, 75.98
paroxetine *64.50*
  adverse effects 75.79
  in pruritus 21.12, 21.17, *21.18*
paroxysmal nocturnal haemoglobinuria (PNH) 13.4, **49.30–1**
Parrot's nodes 34.17
Parrot's pseudoparalysis 34.16
Parry–Romberg syndrome 45.11–12, 51.70
PARs *see* proteinase-activated receptor(s)
Parthenium 26.10, 26.20, 26.75, 26.76
parthenolide 26.75
parvovirus B19 6.12–13, 33.62
  antibodies to 33.63
  genotypes 33.62
parvovirus B19 infection 6.12–13, **33.62–4**
  clinical features 33.63, 33.76
  diagnosis and treatment 33.63
  in HIV infection 35.31
  pathogenesis 33.63
  in pregnancy 33.63
  purpura in 49.20
parvoviruses *33.2*, **33.62–4**
  PARV4 and PARV5 33.62
PAS stain *see* periodic acid-Schiff (PAS) staining
PASI (Psoriasis Area and Severity Index) 7.11–12, 20.41, 72.9, 72.14
Pasini's syndrome 39.21–2, 45.50
passive haemagglutination test 75.174
passive transfer test 5.23
paste bandages 73.2, 73.42
  in eczema 23.38
  in lichen simplex 23.41
pastes 73.2
  drying (cooling) 73.2
  protective (fatty) 73.2
Pasteurella canis 30.54
Pasteurella dagmatis 30.54
Pasteurella multocida 30.18, **30.54,** 38.60–1
  in cats 2.12
Pasteurella stomatis 30.54
Pastia's lines 30.34
Patau's syndrome (trisomy 13) **15.11,** 18.102–3, 62.77, 68.4
patch test 5.22, 13.22, **26.84–93**
  acrylic resins 26.73
  allergen storage 26.86
  aluminium 26.40
  in atopic dermatitis 24.11
  atopy 23.37
  children 26.8–9
  chromium 26.36
  clothing 26.67
  cobalt 26.34
  colophony 26.83
  complications 25.17, 26.94–5
  compound allergy 26.89
  concentrations 26.85–6, 26.92–3
  contact dermatitis around venous leg ulcer 47.44–5
  cosmetic vehicles 26.58, 26.59
  cosmetics 26.48–9
  cross-reactions 26.96
  dose 26.86
  drugs 26.45, 75.168–9, 75.170
  ear battery 68.24
  in eczema 23.37
  epoxy resins 26.71
  exposure time 26.86–7
  false-negative reactions 26.89, 27.7
  false-positive reactions 26.87–8, 27.7
  footwear 26.69
  formaldehyde 26.50
  formaldehyde resins 26.74
  fragrances 26.40, 26.42
  gold 26.38
  hair dyes 26.61
  history 26.2
  ICDRG scoring system 26.87
  indications 26.84
  irritants 25.9–10
  late reactions 26.87, 26.95
  mercury 26.39
  methods 26.84–6
  MOAHL index 26.3
  MOAHLFA index 26.3
  multiple primary hypersensitivities 26.96
  multiple reactions 26.95–7
  nickel 26.32
  non-invasive measurement techniques 26.88
  non-specific hyperreactivity 26.95
  occupational dermatoses 27.7–8
  open 26.97
  palladium 26.38
  plant allergens 26.77–8
  predictive 26.11–12
  in pregnancy 26.85
  preservatives/biocides 26.50, 26.51, 26.52, 26.53–4, 26.55, 26.56, 26.57
  propolis 26.83
  quenching 26.89
  quick 75.169
  readings and interpretation 26.87–8
  relevance 26.88
  rubber 26.64–5
  selection of test substances 26.91–2
  sensitivity 26.12
  site 26.86
  standardized protocol 26.2
  test materials 26.85
  ultraviolet filters 26.62
  unexplained positive reactions 27.7
  vehicles 26.85, 26.92–3
  woods 26.83
patched gene 11.11, 11.17, 11.18, 52.6, 52.12, 53.2
  mutation in naevoid basal cell carcinoma syndrome 52.19, 62.21
patent urachal duct 71.100
Paterson–Brown–Kelly syndrome 62.48
pathergy
  in Behçet's disease 50.59
  in pyoderma gangrenosum 50.68
pathogen-associated molecular patterns (PAMPs) 12.4, 12.9
  acne aetiology 42.25
'patient-centred care' 72.1
patient education, in atopic dermatitis 24.28
patient expectations 72.1–3
Patient Generated Index 72.16, 72.22
Patient Health Questionnaire-9 64.48
patient information, drug therapy 72.7
Patient-Orientated Eczema Measure (POEM) 72.9, 72.10, 72.14
patient reported outcomes (PROs) 64.10
patient self-help groups 6.14, 64.7, 72.33–4
pattern-recognition receptors (PRRs) 12.9, 13.5
Paul–Bunnell test 33.30
Paussidae 38.27
Pautrier-like microabscesses, in Langerhans' cell histiocytosis 55.8
Pautrier microabscesses 10.41, 57.9, 57.38, 57.54
  in adult T-cell leukaemia-lymphoma (ATLL) 57.37–8
PAX3 gene 2.7, 58.3, 58.44
PBC *see* primary biliary cirrhosis
PC *see* pachyonychia congenita (PC)
PCBs *see* polychlorinated biphenyls
PCDFs (polychlorinated dibenzofurans) 27.12–13
PCMC (chlorocresol) 26.56–7, 73.8
PCMX (chloroxylenol) 26.56, 73.14
PCOS *see* polycystic ovary syndrome (PCOS)
PCR *see* polymerase chain reaction
PCT *see* porphyria cutanea tarda
PCV (plasma cell vulvitis) 71.61
PDE (phosphodiesterase), in atopic dermatitis 24.15–16
PDGF *see* platelet-derived growth factor
peanut agglutinin 55.9
  Langerhans' cell histiocytosis cells 55.8, 55.9
pearly penile papules *71.11*
peau d'orange 45.26, 45.53, 48.7, 62.15, 70.14
  in rosacea 43.3
PECAM-1 *see* CD31
PECL (cutis laxa and post-inflammatory elastolysis) 45.19–20
PEComa 56.60
pectus excavatum 45.30
pederin 38.26
Pediatric Symptom Checklist 72.23
pediculicides, in head louse infection 38.19–20
pediculosis capitis *see* lice, head
Pediculus, in primates 2.10
Pediculus capitis see lice, head
Pediculus humanus see lice, clothing/body
peeling skin syndromes 19.66–9
pegfilgrastim 50.76
Pelagia noctiluca 38.56
pelargonium 25.21
pellagra 59.63
  aetiology 29.21
  eczema and 23.27
  epidemiology 6.1
  pigmentation changes 58.28
pelvic inflammatory disease (PID)
  chlamydial infections causing 34.29–30
  gonococci causing 34.26
pelvic malignancy, lymphoedema 48.8
PELVIS syndrome 18.47, 18.96
Pemberton sign 62.8, 62.44
PEMKB (pseudoepitheliomatous micaceous and keratotic balanitis) 71.37–8
pemphigoid **40.26–35**
  bullous *see* bullous pemphigoid
  cicatricial *see* mucous membrane pemphigoid (MMP)
  drug-induced 67.20
  ear 68.16
  genital involvement
    in females 71.66
    in males 71.28
  genitocrural involvement 71.5
  mucous membrane *see* mucous membrane pemphigoid (MMP)
  oral cavity 69.22
  perianal/perineal involvement 71.91
  stump 28.29
pemphigoid gestationis 8.13, 8.14, 21.14, **40.41–5**
  aetiology 40.41–2
  associated diseases 40.44
  clinical features 40.43
  defined 40.41
  differential diagnosis 40.45
  immunopathology and immunogenetics *10.18*, 10.19
  pathogenesis/pathology 40.42–3
  prognosis 40.44
  transplacental 17.19
  treatment 40.45
pemphigoid nodularis 40.33–4
  pruritus in 21.15
pemphigoid vegetans 40.34
  oral involvement 69.68
pemphigus **40.3–24**
  aetiology 40.3–4
  in animals 2.15
  autoantibodies to Merkel cells 3.16
  azathioprine therapy 40.12, 40.16, 74.15
  clinical features 40.4
  defined 40.3
  diagnosis, direct immunofluorescence of IgG 40.8
  drug-induced 40.18–19, 75.20, 75.38–9
  ear 68.16
  familial benign chronic *see* Hailey–Hailey disease
  genital involvement
    in females 71.66
    in males 71.28
  genitocrural involvement 71.5
  immunopathology *10.18*, 10.19
  loss of desmosomes 40.15
  oral 69.22
  paraneoplastic 40.22–4, 62.44–5, 76.19
    in animals 2.15
    antibodies to desmosomal proteins 3.22
    B cell malignancies and 62.90
    oral 69.66–7
    overlap with lichen planus pemphigoides 41.20–1
    respiratory tract involvement 62.83–4
  pathology 40.7–8
  peristomal 62.54
  in pregnancy 40.9
  presentation as paronychia 65.21
  prognosis 40.9
  treatment 40.11–12
    corticosteroids 40.11–12
    immunosuppressive agents 40.12
    infliximab 40.6, 40.12
    prognosis 40.9
    rituximab 74.9
    topical or intralesional steroids 40.11
  see also specific types
pemphigus erythematosus (Senear–Usher syndrome) 40.4, 40.16, 51.41
  in animals 2.15
  cytodiagnosis 10.29
  differential diagnosis 40.16

pemphigus foliaceus 40.13–17
  aetiology 40.13
  in animals 2.10, 2.12, 2.15
  anti-DG1 antibodies 40.13–14
  antigen 40.13
  clinical features 40.4, 40.15–16, 40.18
  cytodiagnosis 10.29
  defined 40.13
  desmogleins 40.2
  differential diagnosis 40.15, 40.16
  endemic 40.17–18
  erythroderma and 23.48
  evolving into pemphigus vulgaris 40.13
  immunogenetics 40.4
  immunopathology 40.4
    apoptotic mechanisms in keratinocytes 12.12
  pathogenesis 40.13
  pathology 40.15
  prognosis 40.16, 40.18
  race and 9.14
  treatment 40.16, 40.18
    rituximab 74.9
pemphigus herpetiformis 40.15–16
pemphigus neonatorum 17.42
pemphigus syphiliticus 34.16
pemphigus vegetans 40.3–13
  aetiology 40.4, 40.10
  clinical features 40.4
  cytodiagnosis 10.29
  defined 40.10
  differential diagnosis 39.35, 40.11
  Hallopeau and Neumann types 40.10
  oral 69.67
pemphigus vulgaris 40.3–13
  aetiology 40.3–4
  in animals 2.15
  clinical features 40.4, 40.8–9
  cytodiagnosis 10.29
  desmoglein antibodies 40.5–6
  desmogleins 40.2
  differential diagnosis 40.11, 40.34, 40.40
  immunopathology and immunogenetics 40.4
  maternal antibodies 40.5
  neonatal 17.18–19
  non-desmoglein antibodies 40.6
  oral lesions 69.64–6
  race and 9.14
  treatment, rituximab 74.9
penciclovir
  action 74.49
  herpes simplex therapy 33.20, 33.21
  topical 73.15
penetration enhancers 73.7–8
penetration injury, foreign bodies 28.40, 28.49–52
D-penicillamine therapy
  adverse effects **75.102–4**
    copper deficiency 3.44
    dermatomyositis 51.121
    elastosis perforans serpiginosa 45.65
    gigantomastia 70.3
    gynaecomastia *70.5*
    pemphigus 75.38
    pseudopseudoxanthoma elasticum 45.25
    scleroderma 45.52
  systemic sclerosis 51.108
penicillin(s) **74.39–41**
  adverse effects **75.48–9**
    allergy *26.46*, 34.23, 74.39
    anaphylaxis 75.5, 75.25, 75.48–9
    syphilis treatment and 34.22, 34.23
    urticaria 22.8, 22.10, 75.26
  amino 74.40
  in cellulitis/erysipelas 30.20
  penicillinase-resistant 74.40
  penicillinase-sensitive 74.39
  resistance, *Staphylococcus aureus* 74.40
  skin testing for reactions to 75.170–2
  see also specific penicillins
penicillin G 74.39
  syphilis management 34.22, 34.23
penicillin V 74.40
  in recurrent cellulitis and lymphoedema 48.24
penicilliosis 36.88–9
  in HIV infection 35.34
Penicillium
  in otitis externa 68.21
  in otomycosis 68.27
Penicillium marneffei 36.88–9
penile acne 71.27
penile calcinosis 71.36
penile carcinoma 71.40–3
penile haematoma 71.14
penile horn 71.37
penile intraepithelial neoplasia (PIN) 71.38–9, 71.40
  HPV and 33.54–5
penile lymphoedema 71.28, 71.49–50
penile melanosis 58.15, 71.49
penile necrosis 71.24–6
penile oedema 28.39, 71.30, 71.49
penile rupture 71.14
penile thrombophlebitis 71.14
penile ulceration, in herpes simplex 33.16, *33.17*
penile warts 33.44, *33.45*
penis
  amoebiasis 37.28
  apocrine cystadenoma 18.94
  Bowen's disease of 52.36
  fibromatosis (plastic induration/fibrous sclerosis) 45.47–8, 56.11–12
  granuloma inguinale 34.36
  lichen nitidus 41.22
  lichen planus 41.7, 41.9
  median raphe cyst 18.94–5
  plastic surgery 71.50
  pyoderma gangrenosum 50.70
  saxophone 30.70
  syphilis 34.7
Penrose drain 65.42, *65.43*
pentachlorophenols 25.21
pentaerythrotol tetranitrate 75.97
pentamidine isethionate 37.31, 37.39, 75.72
Pentatomidae 38.25
pentazocine 75.87–8
  lobular panniculitis with crystals after 46.17, *46.18*
  scleroderma and *27.17*, 45.52
pentazocine ulcers 28.45, 28.53
pentoxifylline 14.24
  in dermatomyositis 51.129
  in systemic sclerosis 51.108
  in venous leg ulcers 47.49
pentraxins 13.4
  in vasculitis 50.7
PEODDN (porokeratotic eccrine ostial and dermal duct naevus) 18.11, **18.16–17**
PEP syndrome *see* POEMS syndrome
peppermint oil 26.17, 38.5
peptidase D deficiency **45.39–40, 47.54**
peptidases 38.1
peptide histidine methionine 63.3
peptidoglycan 30.8
PeptoBismol 75.157
per protocol analysis 7.11
perchlorethylene, scleroderma-like lesions and 51.80
perchloroethylene 25.20
perennial allergic conjunctivitis (PAC) 67.15
  clinical features *67.13*
perfloxacin 32.17, 75.33
perforating collagenosis (folliculitis) 19.84, 19.88, 19.89, 30.27, 45.63, 59.80, 68.14
  ear involvement 68.14
  reactive 19.89, 45.63, 45.64–5, 69.129
  renal involvement 62.72
perforating dermatosis **45.63–6**
  acquired reactive 45.63–4
  chemical-induced 45.64
perforating folliculitis *see* perforating collagenosis (folliculitis)
perforating keratotic disorders 19.88–9
perforins 10.26, 13.6, 13.11
performing artists, occupational hazards 27.20
perfumes
  as allergens 26.40–3
  Berloque dermatitis and 58.32
  as photoallergens 26.23, 58.32
  see also fragrance(s)
peri-auricular anomalies 68.4
periadenitis mucosa necrotica recurrens *see* Sutton's disease
perianal intraepithelial neoplasia, HPV and 33.54–5
perianal oil granuloma 46.29
perianal/perineal area **71.83–100**
  benign tumours 71.83, 71.96
  candidiasis 36.62
  cellulitis 30.32–3
  child sexual abuse and 28.37–8
  congenital and developmental abnormalities 71.83–4
  dermatitis 25.16
  in dystrophic epidermolysis bullosa 39.19, 39.21, 39.28–9
  general approaches 71.1–4, 71.82–3
  hidradenitis suppurativa 30.80
  infections 71.91–6
  inflammatory dermatoses 71.84–91
  neonatal dermatitis 17.22
  Paget's disease 53.40–1
  premalignant dermatoses and frank malignancies 71.90, 71.96–9
  pruritus *see* pruritus ani
  sexually transmitted diseases 71.83, 71.93–5
  structure and function 71.83
  syphilitic chancre 34.7
  trauma and artefact 71.84
  see also entries beginning anogenital; perineum
perianal warts *33.46*
periappendicitis, gonococci causing 34.26
periarteritis nodosa *see* polyarteritis nodosa
pericarditis, in sarcoidosis 61.7
perichondritis, ear 68.7, **68.19–20**
pericytes 3.3, 3.51, 56.42
  microscopy 10.35
periderm 3.3
peridigital dermatosis *see* juvenile plantar dermatosis
perifollicular elastolysis (PFE), in acne 42.33
perifolliculitis, in dermatophytosis 36.22
perifolliculitis capitis abscedens et suffodiens 30.29–230, 42.33, **42.74, 66.47–8**
  features and treatment 42.74
perihepatitis, acute 34.26
perilipin 46.2
perineal syndrome 71.99
perineum
  bacterial flora 30.4
  hidradenitis suppurativa and 30.80
  watering-can 62.48–9
  see also perianal/perineal area
perineurioma 56.49
periodic acid-Schiff (PAS) staining 10.8, *10.9*, 10.10, 36.7
  foreign bodies 28.42
periodic fever syndromes
  bone and joint involvement 62.104
  hereditary 22.24–5
periodontal ligament 69.2
periodontitis
  chronic 69.18
  in diabetes mellitus 69.18
  in Down's syndrome 69.17, 69.18
  early-onset 69.17, 69.18
  in Ehlers–Danlos syndrome *45.32*, 45.36, 69.17, 69.18
  keratoderma with *19.94*, 19.110, 19.111
  in neutrophil dermatoses 69.15
  in Papillon–Léfèvre syndrome 69.16, 69.18
  in Prader–Willi syndrome 69.17
  in Unna–Thost syndrome 69.16
periodontium 69.2
  disorders 69.12–21
    in HIV infection 35.43
    inflammatory *see* periodontitis
perioral dermatitis **43.11–12**
  acne vs 42.36
  Gianotti-type 43.12, **43.13**
  granulomatous, in children 43.12, **43.13**
perioral region
  allergic contact dermatitis 26.17
  examination 69.3–5
periorbital oedema 67.5
periorificial lentiginosis *see* Peutz–Jeghers syndrome
periostin 14.6
periostitis
  in congenital syphilis 34.16
  venous leg ulcers and 47.46
peripheral arterial disease *see* arterial disease, peripheral
peripheral circulation 74.51–2
  systemic agents 74.51
peripheral ischaemic disorders **47.1–9**
  see also arterial disease, peripheral
peripheral nerve sheath tumour, malignant 56.53
peripheral nerves
  injury 63.13–14
  thickening 32.9, 32.11–12, 32.15
peripheral neuroectodermal tumours 56.44–54
peripheral neuropathy **63.11–13**
  aetiology *63.11*
  in chloracne 27.13
  dysproteinaemia and skin changes with 58.29
  glove and stocking 32.11, 63.11
  in HIV infection 63.12
  hyperhidrosis and 44.7
  investigation 63.11–12
  in sarcoidosis 61.7
  silent 32.17
peripheral primitive neuroectodermal tumour 56.54
peripheral sensory neuropathy 51.132
peripheral T-cell lymphoma 57.34–40
  see also specific types
peripherin 3.9
Periplaneta 38.28
periporitis, swimming-/diving-associated 28.54–5
periporitis staphylogenes 17.7, 17.43, 30.32, 44.16
peritoneal dialysis, bacterial infection and 30.7
periumbilical choristia 71.100
periungual fibromas 15.22
periungual warts 33.43, 33.48
perivascular epithelioid cell tumour 56.60
perleche *see* cheilitis, angular
Perls' Prussian blue reaction 10.9, *10.10*
permanent waving (perm) 66.98–9
permeability constants 4.4
permeability of skin 4.4–5
  ageing and 8.23
permeability regulation, by tight junctions 3.24
permethrin
  in clothing/body louse infection 38.22
  cream 73.13
  in *Demodex* infection in rosacea 43.3
  in head louse infection 38.19
  in scabies 38.41
perniosis **28.65–6,** 74.51–2
  ear 68.5, 68.10
  lesions resembling 62.42
peroxidase–antiperoxidase complex 10.15, 10.16
peroxisome proliferator-activated receptors *see* PPARs (peroxisome proliferator-activated receptors)

perphenazine, black galactorrhoea due to 70.6
persistent acantholytic dermatosis 19.86–8
persistent avasculopathy syndrome 49.17
persistent light reaction 26.24, 29.17, 29.21
persistent pigment darkening (PPD) 58.31
persistent superficial dermatitis 57.57
persistent vitelline duct 71.100
personal experience, value of as evidence 7.3, 7.4
personality disorders 64.36, 64.42
  borderline type 64.41, 64.46
perspiration 3.12
  active sweating 3.12
  insensible 3.12
  see also sweating
pertinax bodies 65.2
Peruvian lily 26.26, 26.76
pes cavus with lymphoedema 48.10
pesticides, scleroderma-like lesions 51.80
PET scanning 5.22
petechiae 49.4, 62.90
  capillary pressure and Hess test 49.5
  causes 49.7
  definition 5.7, 49.2
  in fat embolism 49.38, 62.99
  in immunodeficiency 17.53
  in infectious mononucleosis 33.30
  oral cavity 69.21, 69.22
  raised intravascular pressure causing 49.14
  size of lesions 49.4
petechial gloves and socks syndrome 49.20
petrolatum, comedogenicity 27.13
Petrolatum USP 26.85, 73.2, 73.6
petroleum 25.20, 27.13
Peutz–Jeghers syndrome 54.3, **58.12–13,** 62.56–7
  genetics 58.12
  mucocutaneous pigmentation 58.12
  oral involvement 58.12, 69.27, 69.28, *69.116*
Peyer's patches 13.9
Peyronie's disease 45.47–8, 56.11–12, 71.27
PFA closure time 49.6
PFAPA syndrome 50.54
Pfeiffer's syndrome **15.91**
PFR (phenol formaldehyde resin) 26.73–4
PG (proteoglycan) *see* proteoglycan(s)
PG (pyoderma gangrenosum) *see* pyoderma gangrenosum (PG)
PG-M1 10.24
PGD *see* preimplantation genetic diagnosis
PGH (preimplantation genetic haplotyping) 16.1, 16.8–9
PGL (phenolic glycolipid) 32.1
PGL-1 antibodies 32.7
PGP-9.5 21.2
PHACE syndrome 18.47–8, 18.88
phacomas, retinal 15.23
Phaeoannellomyces werneckii *36.8*, 36.14
phaeochromocytoma 44.7, 62.35–6, 62.43–4
  granulosis rubra nasi and 44.18
  hyperpigmentation in 58.25
phaeohyphomycosis **36.77**
phaeomelanins 3.20, 5.15, 66.90
  in animals 2.5, 2.6
phaeomelanosomes 66.90–1
phagocytes 55.4
  antigen-presentation capacity 55.4
  dermal dendrocyte action 55.3
  receptors 55.4
phagocytosis 55.4
  Demodex folliculorum in rosacea 43.2
  Langerhans' cell role 3.17
  Treponema pallidum 34.4
phagolysosomes 55.4
phakomatosis pigmentokeratotica 18.27, 18.30
phakomatosis pigmentovascularis 18.68–9
pharmaceutical industry, occupational hazards 27.19
pharmacists 72.7, 72.26
  self-help on skin disease and 6.14
pharmacodynamics 72.27–30
pharmacoepidemiology 75.4
pharmacogenetics 11.16, 72.29–30, 76.10–11
pharmacokinetics 72.27
pharmacovigilance 75.3, 75.4
pharyngitis, herpes simplex 33.17
phenacetin 75.73
phenelzine 75.79
phenindione 75.105
pheniramine *26.46*
phenobarbital, eccrine gland secretion 44.18
phenol 75.166, 80.9
  as caustic 33.49, 77.47
  liquefied 77.47
    diluted 33.12
  wart treatment 33.49
phenol esters 25.3
phenol formaldehyde resin 26.73–4
phenolic glycolipid 32.1
  PGL-1 antibodies 32.7
phenolphthalein 75.158
  hyperpigmentation due to 58.30
phenols
  as allergens 26.79
  burns 25.11, 27.12
  depigmentation due to 27.15
  hair regrowth and 73.39
  as irritants *25.19*, 25.21
  in pruritus 21.17
  substituted
    depigmentation due to 58.50
    hypermelanosis treatment 58.39
phenoplastics 26.73–4
phenothiazines 75.82
  adverse effects *70.5*, 75.148
    allergy *26.46*
    erythema multiforme 76.3, *76.4*
    galactorrhoea 70.6
    hypermelanosis 58.29
    hyperpigmentation 69.97
    photosensitivity 75.31
  as photoallergens 26.24
phenothrin 38.19, 73.13
phenotypes, online databases 15.1
phenotypic walking 11.12
phenoxymethyl penicillin 74.40
  in recurrent cellulitis and lymphoedema 48.24
phenprocoumon 75.105
phenyl-benzimidazole sulphonic acid 26.62
phenylalanine, elevated levels *see* hyperphenylalaninaemia syndromes
phenylbutazone 49.46
  adverse effects 75.77
    erythema multiforme *26.46*
    erythroderma 23.47
p-phenylenediamine *see* paraphenylenediamine
phenylephrine *26.46*, 75.98
phenylketonuria (PKU) 59.94–5
  eczema and 23.27
  hair colour in 66.94
  maternal 18.2
phenylpyruvic oligophrenia *see* phenylketonuria (PKU)
phenytoin
  adverse effects *70.5*, **75.84–6**
    acneiform eruptions due to 42.72
    anticonvulsant hypersensitivity syndrome 76.10
    gingival swelling 69.21
    in HIV infection 35.20
    hypermelanosis 58.29–30
    hypertrichosis *66.79*
    melasma-like hyperpigmentation 58.34
    scleroderma 45.52
  eccrine gland secretion 44.18
pheomelanin, formation 58.5, *58.6*
pheromones 3.3, 44.2
  insect 38.2
phialides *36.3*, 36.4, 36.76
Phialophora *36.77*
Phialophora verrucosa 36.75, 36.76
philtrum 69.2
phimosis 34.7, 34.11, 71.8, 71.20–2, 71.40
phlebactasia 47.24
  genuine diffuse 47.24
phlebectomy 47.39
phlebography 47.36
  ascending 47.36
  descending 47.36
phlebolithiasis 18.71, 69.29
Phlebotomus 37.33, 37.35, 38.5
phlyctenule *67.4*
PHM (peptide histidine methionine) 63.3
phobias 64.12, **64.24–5**
phorbol esters 13.23
Phormia 38.8
phosphate metabolism, in chronic renal failure 46.16
phosphodiesterase, in atopic dermatitis 24.15–16
phospholipase(s) 31.34, 38.1, 38.14
phospholipase A2 8.21
phospholipid(s)
  nail plate 65.3
  stratum corneum 3.11, 4.2
phospholipid transfer protein (PLTP) 59.83
phosphonoformate (foscarnet), herpes simplex 33.21
phosphoric acid *25.19*
phosphorus burns 27.12
phosphorus sesquisulphide *26.15*
photo-onycholysis 29.6, 65.11, 65.16, 75.32
  doxycycline causing *42.50*
photoactivation 26.23
photoageing 8.21–2, 8.22, 29.7, 45.26, 80.2
  prevention and reduction 80.3–4
  treatment
    retinoids 73.35, 73.36
    tazarotene 73.37
photoallergens 29.19, *29.21*, 75.32
photoallergic reactions 26.23–5, 75.32
  drug-induced 29.20–1
photobiology **29.1–24**
  basic principles **29.1–4**
  definition 29.1
  emission spectra 29.1–2
  see also ultraviolet (UV) radiation
photobleaching 10.14–15
photocarcinogenesis 29.7
photochemotherapy 57.24
  extracorporeal *see* extracorporeal photopheresis (ECP)
  see also photodynamic therapy; PUVA therapy
photodamage
  collagen synthesis increase 3.39
  ecchymotic haemorrhage 49.4
  squamous cell carcinoma and 52.24, 52.27
  see also ultraviolet (UV) radiation
photodermatitis 28.92
  plant-induced 29.21, **58.32,** 75.162
photodermatoses **29.9–23**
  acquired, with autoimmune basis 29.9–20
    see also actinic prurigo (AP); chronic actinic dermatitis (CAD); hydroa vacciniforme (HV); polymorphic light eruption (PLE); solar urticaria (SU)
  clinical evaluation 29.23
  dermatoses exacerbated by UVR *29.22*, 29.22–3, 29.23
  differential diagnosis 29.23
  DNA repair defects *see under* DNA
  drug-/chemical-induced photosensitivity
    endogenous *see* porphyria, cutaneous
    exogenous 29.20–2
  investigations 29.23–4
  management, sunscreen use 73.41
  phototesting and provocation tests 29.23
  race and 9.19
  UVA-induced 29.9
  see also photosensitivity
photodynamic change 78.4
photodynamic reactions, hyperpigmentation 58.32
photodynamic therapy 20.43, **78.15–16**
  acne 42.67
  actinic keratosis 52.32, 78.16
  basal cell carcinoma 78.16
  Bowen's disease 52.34, 78.16
  granuloma annulare 60.10
  molluscum contagiosum 33.12
  naevoid basal cell carcinoma syndrome 52.8
  non-melanoma skin cancer 52.16
  in perioral dermatitis 43.12
  photosensitivity due to 29.21
  pro-drugs 52.16
  psoriasis 20.43
  rosacea 43.6
  sarcoidosis 61.21
  warts 33.49
photoexacerbation, of skin diseases *29.22*, 29.22–3
photography
  acne 72.10
  occupational hazards 27.20
  psoriasis 72.9
photoimmunology **13.26–34,** 26.10
photoleukomelanodermatitis 75.33
photomechanical reactions 78.4–5
photons 29.1
  absorption spectra and, excitation 29.3
photopatch testing 29.24
photoperiod and hair growth 66.9
photopheresis 13.25
  extracorporeal (ECP) 57.67
photophobia
  in albinism 58.40
  ichthyosis follicularis with alopecia and (IFAP) 19.58–9, 19.60
  in oculocutaneous tyrosinaemia 19.112
photoplethysmography (PPG) 47.36
  digital 47.36
photoproducts
  carcinogenesis and 52.14
  DNA damage and repair 52.14
photoprotection 58.38, 73.41, 80.3
  in actinic prurigo 29.14
  in chronic actinic dermatitis 29.18
  hydroa vacciniforme 29.15
  in polymorphic light eruption 29.12
  in solar urticaria 29.19
  see also sunscreens; ultraviolet (UV) radiation, exposure minimisation
photorecall reactions 75.32
photosensitivity
  in animals 2.23
  in atopic dermatitis 24.21
  in carcinoid syndrome 43.18
  causes 2.23
  clinical evaluation 29.23
  differential diagnosis 26.29, 26.30, 29.23
  drug-/chemical-induced 29.20–2, 58.56, 75.30–2, 75.52
    acne medications 42.34
    co-trimoxazole 57.53
    endogenous *29.21*
    exogenous 29.20–1, *29.21*, 29.23
    in HIV infection 35.22
  eye and skin involvement *67.30*
  IBIDS/PIBIDS syndrome 19.47–9
  investigations 29.23–4
  in lymphogranuloma venereum 30.70
  persistent 29.21
  see also photodermatoses

photosensitivity dermatitis 29.17
photosensitization 29.7
photosensitizers 26.23–4, 78.15–16
  drugs acting as 29.20, *29.21*
    see also photosensitivity, drug-/chemical-induced
  plant, in animals 2.23
photosensitizing agents, lichenoid photoeruptions and 41.25
photostimulation 78.4
phototesting procedures 29.23
phototherapy
  atopic dermatitis 21.13, 24.31
  Darier's disease 19.85
  dermographism 22.14
  eczema 23.38
  eosinophilic folliculitis in HIV infection 35.18
  granuloma annulare 60.10
  hand eczema 23.22
  mastocytosis 22.36
  neonatal, complications 17.12–13
  pityriasis rubra pilaris 19.79–80
  pruritus 21.18
  seborrhoeic dermatitis 23.33
  UVB 29.1
  UVB narrow-band
    actinic prurigo 29.14–15
    chronic actinic dermatitis 29.18
    polymorphic light eruption 29.12
    vitiligo 58.48
photothermal ablation 78.13–15
photothermolytic reactions 78.4–5
phototoxic reactions 25.17, 26.16, 26.23
  drug-induced *5.15*, 29.20, 29.21, *29.21*, 75.31
  hyperpigmentation 58.32
  tests for 25.9
  topical, dyestuffs causing 29.20–1
phototrichography 66.11
phototypes, skin *29.6*, 29.8
  chemical peels and 80.9, *80.10*
phragmoconidia 36.4
phrynoderma 19.75–6, 19.84
phthalic anhydride 25.20
Phthiraptera *see* lice
phthiriasis 67.27
phthiriasis palpebrarum *38.22*, 38.23
Phthiriasis pubis see lice, pubic (crabs)
phycomycosis
  vulval 71.69
  see also zygomycosis
phylloerythrins 2.23
phymas **43.9–10**
Physalia 38.55, 38.56, 38.57
physical exercise, pressure ulcer risk and 28.21
Physician's Global Assessment 72.9
physiological livedo reticularis 28.68
phytanic acid 19.45–6
phytohaemagglutinin A 13.23
phytomenadione 45.52
phytophotodermatitis 29.21, **58.32,** 75.162
pian *see* yaws
pian bois *37.34*, *37.35*, **37.39–41**
PIBIDS syndrome 19.47–9
PIC3CA gene 18.6
pica 62.85
picaridin 38.5
picatura de pito *37.34*, *37.35*, **37.39–41**
Picea 26.81
picking of skin, pathological 64.19, 64.27–9
PICO 7.2
picornaviruses *33.2*, **33.71–4**
picric acid, pigmentation due to 58.56–7
piebaldism 58.42–3, 66.93
  in Waardenburg's syndrome 58.43
piedra
  black 36.5, **36.15–16**
    fungal culture 36.7, *36.8*
  white 30.3, 36.5, **36.16–17**
    fungal culture 36.7, *36.8*
Piedraia hortae 36.8, 36.15
  female genital infection 71.69
piercings 64.2
  ornamental 28.51–2
piezogenic pedal papules 28.61
pigment anomalies, human chimeras with 58.23
pigment cells 2.5–7
  in animals 2.5–7
  evolution 2.1
  regulation in fish 2.5–6
'pigment type switching' 2.6–7
pigmental demarcation lines 58.1, *58.2*
pigmentary incontinence
  in lichen planus 41.4
  see also incontinentia pigmenti (IP)
pigmentation **58.1–59**
  advantages of 58.8
  ageing and 8.23
  in anaemia 58.17, 58.27, 62.85
  ashy colour 58.33
  blue 58.36
    naevi 54.25–7
  blue-black, minocycline causing 58.56
  blue-grey 58.55
    drug-induced 58.29
  bronze 58.53
    in haemochromatosis 58.28
  bronzing of skin 58.53
  brown 58.7, *58.8*
  changes, causes 58.9
  chemicals causing 58.54, 58.56–7
  in chronic radiodermatitis 79.16
  constitutive 58.1, 58.7, **58.9–10**
  disadvantages of 58.9
  disorders
    in animals 2.23
    classification 58.9
    eye and skin involvement *67.30*
    in HIV infection 35.12
    localized areas 58.9
    see also hyperpigmentation; hypopigmentation; *specific disorders*
  endogenous non-melanin **58.53–4**
  evolutionary significance 58.8–9, 73.40
  exogenous pigments **58.54–9**
  eyelids 67.5
  facial, grey-brown 58.35
  facultative/inducible 58.1
  in fixed drug eruption 75.28
  genetic causes of variations 58.9–10
  idiopathic lenticular 69.28
  of lesions 5.15–17, *5.18*
  in lichen planus 41.7
  loss *see* depigmentation
  measurement 72.11
  melanocytes *see* melanocyte(s)
  melanocytes and keratinocyte interface 58.2
  minocycline-induced changes 42.50–1
  mottled, in epidermolysis bullosa simplex 39.4, 39.8
  nails 9.3
  non-melanin **58.53–4**
  normal 5.15, **58.1–2**
  oestrogen effect 58.7
  oral cavity 9.3, 69.21–2, 69.26–9, 69.95–100, 75.47
  paraneoplastic 62.33, *62.34*
  patchy, in chloracne 27.13
  post-inflammatory 9.*4*
  post-phototoxic 29.21
  in pregnancy 8.10
  race and 9.1, 58.1, 58.10
  regulation 58.1, **58.7–8**
    endocrine factors 58.7
    paracrine/autocrine factors 58.7–8
    UV radiation response 58.7
  in response to sun exposure 58.8, 58.10
  reticulate
    dermatopathia pigmentosa reticularis 58.20
    Naegeli's syndrome 58.19
    post-inflammatory 58.31
  slate-brown, drug-induced 58.30
  slate-grey 58.36
    in incontinentia pigmenti (IP) 58.16
  subungual 54.45
  variations 58.10
pigmented cosmetic dermatitis 58.35
pigmented flexural lichen planus 71.59–60
pigmented iris hamartomas (Lisch nodules) **15.16,** 15.17, 58.18, 58.23, 62.23
pigmented neuroectodermal tumour of infancy 56.52–3
pigmented peribuccal pigmentation of Brocq 58.35–6
pigmented purpuric dermatoses **49.22–6**
  chronic, infectious 49.23
  differential diagnosis 50.54
  familial 49.25
  granulatomous 49.25
  idiopathic 49.22, 49.23
  lichenoid 49.22, 49.25
  linear and quadrantic 49.25
  morphological patterns and pathology 49.22
  progressive *see* Schamberg's disease
  secondary 49.23–4
  systemic causes 49.23–4
  treatment 49.26
  venous 49.23
pigmented purpuric lichenoid dermatosis of Gougerot and Blum 49.22, 49.25
pigments, animal 2.5
pigs
  bullous pemphigoid 2.14–15
  flea infestations 2.10
PIIINP 62.61
PIK3CA gene, mutations 52.38
pilar cyst *see* trichilemmal cyst
pilar sheath acanthoma 53.3
pilary canal 42.1
pili annulati 66.69–70, 66.91
pili incarnati 30.22–3
pili multigemini (pili bifurcati) 66.73–4
pili torti *66.62*, 66.63–4, *66.65*
  developmental delay and 15.50
  onychodysplasia and 15.50
pili trianguli et canaliculi 66.71–2
pilocarpine 3.12, *26.46*
pilodental dysplasia with refractive errors 15.50
piloerection 28.53
pilomatricarcinoma 53.14
pilomatricoma (pilomatrixoma) 53.12–13
  pinna 68.28
  superficial 53.13
pilonidal cysts 71.87
pilonidal sinus
  anogenital 28.49–50
  male genital dermatology 71.26–7
  perianal/perineal dermatology 71.87, *71.88*
  umbilical dermatology 71.101
pilosebaceous duct
  cornified plug, acne aetiology 42.24, 42.25
  junction with epithelium, basal cell carcinoma 52.21
pilosebaceous follicle, inflammation, epidermoid cyst 52.45
pilosebaceous naevoid disorders 42.78
pilosebaceous unit 3.1, **3.13–14,** 53.1
  in acne *42.17*
  androgen effects on 42.21
  classes 3.13
  development 3.13
  hamartoma 53.7–8
  hyperkeratosis 53.2
  microenvironment, acne pathogenesis 42.25
  outflow obstruction 42.24, 42.25
pimecrolimus 20.42, 51.23, 51.118, 73.31, **73.32,** 74.17
  adverse effects *26.46*, 75.146–7
  in allergic contact dermatitis 26.102
  in atopic dermatitis 24.30, 73.32
  in eczema 23.38
  in Fox–Fordyce disease 44.22
  in granuloma annulare 60.10
  in perioral dermatitis 43.12
  in seborrhoeic dermatitis 23.33, 35.16
  structure *73.32*
  systemic exposure 73.32
  topical 73.32
    in rosacea 43.6
pimozide 21.12, 64.52
  in acne excoriée 42.70
  adverse effects 64.16
  in delusional parasitosis 64.16
PIN *see* penile intraepithelial neoplasia
pinch-pulling 28.25
pinch sign, positive *5.18*
pindolol 75.91
pine processionary caterpillar 38.28–9
pineapple 25.21
pinene 26.82
Pink disease 69.83–4, 75.101–2
Pinkus tumour 52.48
  as trichoblastoma variant 53.10
pinna
  accessory 68.4
  ageing changes 68.5–6
  altitude injury 68.11
  anatomy and physiology 68.1, *68.2*
  angiosarcoma 68.34
  basal cell carcinoma 68.32, 79.9, *79.10*
  benign tumours 68.28–9
  calcification 59.69, 62.5
  chondroma 68.28
  conditions resembling benign tumours 68.29
  contusion and haematoma 68.6–7
  development 68.3
  developmental defects 68.3–5
  examination 68.3
  fibroma 68.28
  granular cell tumour 68.28
  haemangioma 68.28
  hypertrichosis 68.1, *68.2*, 68.5
    see also ear(s), hairy
  infection 68.19–20
  laceration and avulsion 68.7
  lymphangioma 68.28
  malignant melanoma 68.33–4
  melanocytic naevi 68.28
  myoma 68.28
  neurofibroma 68.28
  osseo-integrated implants 68.16
  osteoma 68.28
  piercing 68.7–9
    complications 26.17, 61.23, 68.7–8
  pilomatricoma 68.28
  premalignant epithelial neoplasms 68.30
  radiation injury 68.11
  restoration following loss 68.16
  schwannoma 68.28
  seborrhoeic keratosis 68.28
  solar damage 68.10–11
  solar keratosis 68.30
  squamous cell carcinoma 68.30–2
  squamous cell papilloma 68.28
  trauma 68.6–14
  trichoepithelioma 68.28
  trichofolliculoma 68.28
  variations in shape 68.4–5
  Winer's pore 68.28
  see also ear(s)
pinprick sensation in leprosy 5.18
pinta 30.63–4
  late, hyperpigmentation after 58.31
pintids 30.63
Pinus 26.79, *26.81*
pinworms **37.13–14**
  perianal/perineal infection 71.92
piperazine 75.71, 75.149
piperidine 75.149
piroxicam 75.75–6
Pit-1 49.47

pitch
  acnegenicity 27.13, *27.14*
  carcinogenicity 27.16, 73.42
pits
  ear **18.83–4,** 68.4
  lip *see under* lip(s)
  preauricular 68.4
pitted keratolysis **30.39–40,** 44.8
pituitary adenylate cyclase-activating peptide (PACAP) 12.63–4, 63.3
pituitary dysfunction
  Langerhans' cell histiocytosis (LCH) 55.12
  see also hyperpituitarism; hypopituitarism
pituitary hormones
  in pregnancy 8.9
  sebaceous gland activity and 42.11–12
pituitary–adrenal axis
  suppression, steroid therapy 73.20, 74.4
  tests of 74.3
pityriasiform scale 5.7
pityriasis alba 23.27–8, *58.10*
  hypopigmentation in 58.52
  pityriasis rosea vs 33.81
  vitiligo vs 58.48
pityriasis amiantacea 20.14, 20.16, 66.57
pityriasis capitis **66.56–7**
pityriasis circinata, pityriasis rosea vs 33.81
pityriasis circinata et marginata 33.80
pityriasis follicularum 38.53
pityriasis lichenoides **50.50–1,** 57.54–7
  in liver disease 62.64
  pityriasis rosea vs 33.81
  vasculitis and 50.3
pityriasis lichenoides chronica 50.50
  race and 9.5–6
pityriasis lichenoides et varioliformis acuta 50.50–1, 69.85
pityriasis nigra *36.8,* **36.14–15**
pityriasis rosea **33.78–81**
  aetiology 33.78–9
  breast 70.17
  clinical features 33.79–80
  diagnosis 33.80–1
  differential diagnosis 23.32, 33.80–1
  drug-induced 33.79, 33.80
  drug-induced reactions resembling 33.80, 75.24
  HHV-6 association 33.79, 33.81
  HHV-7 association 33.33, 33.79, 33.81
  HHV-8 association 33.79
  pathology 33.79
  race and 9.6
  second attacks/eruptions 33.79
  secondary syphilis vs 34.11
  treatment 33.81
pityriasis rotunda 9.10, 19.65, 62.32
pityriasis rubra pilaris (PRP) 19.76–81, 19.84
  erythroderma and 23.48
  hands 23.20
  nail involvement 65.25
  TNF antagonists as treatment 74.7
pityriasis versicolor **36.10–13**
  in adolescence 8.7
  aetiology 36.10–11
  clinical features 36.11
  definition 36.10
  differential diagnosis 23.32, 36.11
  ear involvement 68.20
  histology and pathogenesis 36.11
  hypopigmentation in 58.52
  laboratory diagnosis 36.7, 36.12
  race and 9.6
  treatment 36.12
  vitiligo vs 58.48
Pityrosporum see Malassezia
pizotifen, in erythromelalgia 47.10
pizzicato paronychia 28.25
PKU *see* phenylketonuria (PKU)
placenta, melanoma metastases 54.57
placental alkaline phosphatase 55.9
  Langerhans' cell histiocytosis cells 55.8, 55.9
placental hormones 8.9
plague **30.54–5**
  bubonic 30.55, 38.11
  pneumonic 30.55
plagues of Egypt 38.27
plakins 3.22, 40.4
  antibodies 40.23
    in paraneoplastic pemphigus 40.23
plakoglobin 3.23, 40.1–2
plakophilin 40.2
  deficiency 39.2, 39.4
  gene mutations 39.5–6
plakophilin-1 3.22
  deficiency, epidermolysis bullosa simplex 39.4, 39.5–6
Planck's constant 29.1
plant alkaloids, photosensitivity in animals and 2.23
plant growers, occupational hazards 27.19
plantar dermatitis, mechanical injury 28.14
plantar keratodermas *see* palmoplantar keratoderma (PPK)
plants
  allergic contact dermatitis and 26.10, 26.15–16, 26.74–9
  irritant contact dermatitis and 25.17–18, 25.21
  mites on 38.48
  patch testing 26.77–8
plaque(s)
  atheromatous 47.1
  atherosclerotic 49.36
  definition 5.7
  differential diagnosis 32.15
  in incontinentia pigmenti (IP) 58.16
  vernal *67.14*
plaque-like cutaneous mucinosis 59.25
plasma cell(s) 13.7, 13.10
  infiltration, in syphilis 34.5
  microscopy 10.34
plasma cell vulvitis (PCV) 71.61
plasma exchange *see* plasmapheresis
plasma proteins
  abnormalities, purpura and 49.19
  mutations, amyloidosis and 59.57
plasma skin rejuvenation 80.13
plasma viscosity 13.19
plasmacytoid predendritic cells, type 1 interferon-producing 3.19
plasmacytolymphoma 31.21
plasmacytoma, oral 69.114
plasmacytosis, idiopathic 69.19–20
plasmapheresis 13.25
  in cryoglobulinaemic vasculitis 50.25
  in dermatomyositis 51.129
  in hereditary angio-oedema 22.22
  in necrobiotic xanthogranuloma 55.28
  in pemphigus 40.12
  in SLE 51.62
  in solar urticaria 29.20
  in systemic sclerosis 51.108
  in urticaria 22.29–30
plasmids 11.4, 11.9–10
plasmin, in wound healing 14.4
plasminogen, in wound healing 14.4
plasminogen activation inhibitor-1 (PAI-1) 46.7
plasminogen activator
  activity 12.50, 40.6
  receptors 12.50
  urokinase, blocking acantholysis 40.14
Plasmodium 37.1, 37.27
plastic surgery
  in body dysmorphic disorder 64.19
  to penis 71.50
plastics, as allergens 26.69–74
plastics industry, occupational hazards 27.20
platelet(s) 12.32–4, 49.7–8
  adherence and activation 49.8
  aggregation 49.8
    abnormal 49.45
  in arterial disease and atherosclerosis 47.1–2
  autoantibodies 49.9, 49.11
  consumption, haemangioma 49.12
  count
    decreased *see* thrombocytopenia
    elevated 49.29
      see also thrombocytosis
    in heparin-induced thrombocytopenia 49.27
    in Hermansky–Pudlak syndrome 58.41
    in idiopathic thrombocytopenic purpura 49.9
    normal 49.5
    purpura investigation 49.5
  destruction, drug-/toxin-induced 49.11
  dysfunction
    drug-induced 49.4
    renal disease and 49.18
    simple macular haemorrhage 49.4
    see also platelet disorders
  function abnormalities *49.8,* **49.12–14**
    drug-induced 49.12–13
    due to skin diseases 49.13
    inherited *49.8*
    purpura due to 49.12–14
  hyper-activity 49.14
  in immune defence and inflammatory processes 12.33
  immune destruction 49.9
  membrane glycoproteins
    autoantibodies 49.9
    inhibitors 49.11, 49.13
  neutralization procedure 49.40
  plug formation 49.8
  plugging 49.26
    microvascular occlusion due to 49.27–31, 49.41
  shape, microspicules 12.32
  'sticky,' in deep-vein thrombosis 47.28
  in wound healing 14.1, 14.2–3
platelet-activating factor (PAF) 12.59, 13.4, 75.174
platelet-derived growth factor (PDGF) 12.31
  in giant cell arteritis 50.43
  in mucous membrane pemphigoid pathogenesis 67.20
  wound healing and 14.3, 14.27
platelet disorders 62.90–2
  purpura due to **49.7–12,** *49.8*
    elevated counts *49.8*
    functional abnormalities *49.8*
  see also thrombocytopenia; thrombocytosis
platelet factor 4 (PF4) 49.11
  antibodies 49.27
platelet function analysers (PFA) 49.6
platelet-specific integrins, glycoprotein 11b–111a (GP11b–111a) 12.32
platelet–endothelial cell adhesion molecule-1 *see* CD31
platelet–neutrophil interaction 12.32
platinum 26.40
PLC *see* pityriasis lichenoides chronica
PLE *see* polymorphic light eruption (PLE)
PLEC1 gene mutations, in epidermolysis bullosa simplex 39.4
plectin 3.30, *3.31,* 39.4
  gene mutations 3.31
  monoclonal antibodies to 39.25
pleomorphism 10.41
plethysmography 47.36, 47.47
pleuromutilins 73.10
PLEVA (pityriasis lichenoides et varioliformis acuta) 50.50–1, 69.85
plexiform fibrohistiocytic tumour 56.20
plica polonica 38.19
PLLA (poly-L-lactic acid) 80.5, 80.6
'plucked chicken' skin 62.85
plumbers, occupational hazards 27.20
plumber's itch *see* larva migrans, cutaneous
Plummer–Vinson syndrome 62.48
PMD 38.5
pneumatosis cystoides intestinalis 51.100
Pneumocystic carinii (jiroveci) 17.50, 17.52, 17.58, 36.92
  ear polyps due to 68.28
  pneumonia, in AIDS/HIV infection 35.4–5, 35.21, 35.35
pneumonia
  encapsulating 17.74
  giant-cell, in measles 33.75
  Mycoplasma 30.69
  Pneumocystic carinii (jiroveci), in AIDS/HIV infection 35.4–5, 35.21, 35.35
  in psittacosis 30.72
  respiratory syncytial virus (RSV) 33.76
pneumothorax, neonatal 17.14
Pneumovirus 33.75
PNH (paroxysmal nocturnal haemoglobinuria) 13.4, **49.30–1**
podoconiosis 48.13
  race and 9.8
podophyllin
  adverse effects 33.49, 75.166
  burns 27.11
  contraindications 33.49
    pregnancy 8.11
  mechanism of action 33.49, 73.25
  wart treatment 33.49, 73.25
podophyllotoxin 73.25
  mechanism of action 33.49
  wart treatment 33.49, 73.25
podophyllum 73.25
Podophyllum emodi 75.160
podoplanin 10.24, 48.4, *48.5*
  skin biopsy, in lymphoedema 48.19
podopompholyx 23.16
POEM (Patient-Orientated Eczema Measure) 72.9, 72.10, 72.14
POEMS syndrome 45.54, 51.80, 58.29, 62.13, 62.44, *62.45,* 62.94
  bone and joint involvement *62.101*
  cutaneous abnormalities 33.34
  flushing in 43.16
  glomeruloid haemangioma 56.24
Pogonomyrmex 38.14
Pogosta disease 33.66
POHL gene 15.72
poikiloderma
  acquired 45.13
  definition 5.7, 45.13–14
  hereditary acrokeratotic of Weary 45.13
  hereditary sclerosing of Weary 45.13
  in megaloblastic anaemia 62.85
poikiloderma congenitale 15.51, **15.80–2,** 45.13, 45.61, 62.27
  bone and joint involvement *62.100*
  greying of hair 66.92
poikiloderma of Civatte 45.13, 58.35, 80.10, 80.11
poikiloderma with neutropenia 15.50
poikilodermatous epidermolysis bullosa 51.79
poikilodermatous parapsoriasis 57.58
poikilodermatous syndromes, genetics 15.78–83
point estimate 7.9
poison bun sponge 38.59
poison ivy
  allergy to 26.16, 26.17, 26.75
  erythema multiforme-like reactions and 26.25, 76.5
poison oak 26.75
poison sumac 26.75
pokeweed mitogens 13.23
Poland syndrome 70.2, 70.3
poldine methylsulphate 44.11, 73.9
polidocanol 47.39, 75.156
poliomyelitis virus 33.71
poliosis 66.93
poliovirus 33.1
Polistes 38.14
pollen allergy
  atopic dermatitis and 24.10
  oral allergy syndrome and 22.20
  urticaria and 22.9

pollinosis *see* pollen allergy
Pollitt syndrome 15.51, 15.55
pollution, atopic dermatitis and 24.5
poly-L-lactic acid (PLLA) 80.5, 80.6
polyA tail 11.3
polyarteritis nodosa (PAN) *5.10,* **50.33–5**
  aetiology and pathogenesis 50.7, 50.33
  breast involvement 70.11
  clinical features 50.33–4
  Crohn's disease and 62.49
  cutaneous **50.37–9**
  definition 50.33
  diagnosis 50.34
  differential diagnosis 50.14, 50.32
  hepatitis B virus infection and 33.60–1, 50.33, 50.34, 50.35, 62.59
  hepatitis C virus infection and 50.33, 62.59
  histopathology 50.33, *50.34*
  leg ulcer association 47.55
  male genital dermatology 71.29
  microscopic *see* microscopic polyangiitis (polyarteritis)
  ocular involvement *67.25*
  oral involvement 69.81, *69.117*
  respiratory tract involvement 62.83
  treatment 50.35
  in viral infections 33.77
polyarthralgia/polyarthritis
  in multicentric reticulohistiocytosis 55.23
  in parvovirus B19 infection 33.63
  in Ross River virus infection 33.66
  in sarcoidosis 61.6–7
  in SLE 51.42
polybrominated biphenyls 27.13
polychlorinated biphenyls 27.12–13
  congenital poisoning 18.2
polychlorinated dibenzofurans 27.12–13
polychondritis, relapsing, panniculitis with 46.32
polycyclic hydrocarbons 27.16
polycystic ovary syndrome (PCOS) 66.80, 66.81–2
  acne association 42.20, 42.21–2, 42.73
  investigation and assessment *66.86*
  management *66.86*
polycythaemia rubra vera (PRV) 62.86
  disseminated pustular dermatosis *50.89*
  pruritus in 21.10, 62.86
polycythaemia vera 49.29
polydactyly 18.92
polyenes 74.46
  topical 73.12
polyethylene glycols (PEGs) 27.12
  cetylethers (cetomacrogols) 73.7
  in topical therapy 73.7
polyfibromatosis syndrome 45.45
polyhydric alcohols 73.2
polylactic acid 46.43
polymastia 70.2–3
polymerase chain reaction (PCR) 10.11, 11.6
  in analysis of inherited disorders 15.7
  in fungal infection diagnosis 36.9
  in granuloma inguinale diagnosis 34.37
  in HSV detection 33.19
  in lymphogranuloma venereum diagnosis 34.33
  in normal skin flora analysis 30.2
  real-time 11.6
  reverse transcription 11.6
  in syphilis diagnosis 34.19
  in tuberculosis diagnosis 31.26
  in viral infection diagnosis 33.4
  in VZV detection 33.27
polymorphic eruption of pregnancy (PUPPP) 8.13, 8.14, 21.14
polymorphic light eruption (PLE) **29.9–13,** 44.16
  actinic prurigo association 29.14
  in adolescence 8.7
  aetiology 29.11
  clinical features *29.10,* 29.11–12
  definition 29.9, 29.11
  diagnosis 29.12, 29.23
  differential diagnosis *29.10,* 29.12, 51.7
  hereditary/familial 29.13
  investigations *29.10,* 29.12
  pathology 29.11
  persistent, variant 29.14
  race and 9.19
  small papular 29.12
  treatment *29.10,* 29.12
  treatment-induced flares 29.12
polymorphic reticulosis
  oral involvement 69.58
  respiratory tract involvement 62.83
polymorphism
  definition 10.41
  fungi 36.4, 36.56
  genetic, functional impact 15.6
  single nucleotide, in analysis of inherited disorders 15.7
polymorphonuclear granulocytes 12.20–4
  see also basophil(s); eosinophil(s); neutrophil(s)
polymyalgia rheumatica, giant cell arteritis and 50.43, 50.44
polymyositis
  paraneoplastic 62.36
  in pregnancy 8.12
  in sarcoidosis 61.7
polymyxin B, topical therapy 73.10
polymyxin E (colistin) 74.43
polymyxins *26.46*
polyomaviruses 33.37, 53.42
polyostotic fibrous dysplasia 47.55, 66.52, 68.28
  in McCune–Albright syndrome 58.18
polypharmacy 72.28
polyposis
  genetics 15.25–6
  MYH-associated 53.12
polyposis, skin pigmentation, alopecia and fingernail changes (Cronkhite–Canada syndrome) 15.50, **58.13–14,** 62.57–8
polyps
  adnexal polyp of neonatal skin 70.8
  fibroepitheliomatous *see* skin tags
  gastrointestinal 62.56–8
  oral 69.20
  in Peutz–Jeghers syndrome 58.12–13
    see also Peutz–Jeghers syndrome
  umbilical 18.93–4, 71.100
polythelia (supernumerary nipple) 18.92–3, 70.2–3
polythene gloves 73.4
  corticosteroid therapy and 73.20
polyvinyl chloride 45.51–2, 62.47
  disease 51.80
polyvinyl pyrrolidone (PVP) 28.44
  foreign-body reaction to 61.22
pomade 27.13, 27.14, 42.73, 66.99
pomade acne 42.31, 42.73–4
pompholyx **23.16–19,** 26.32
  definition 23.1
  differential diagnosis 26.29
  occupational 27.4, *27.5*
  in palmoplantar hyperhidrosis 44.8
  prevalence 23.3
Pontiac fever 30.67
pool palms 28.14
popliteal pterygium syndrome 15.94, 18.91
popliteal vessel occlusion 47.5
population studies 6.2
PORCN gene 15.84
pore-forming proteins 13.2
porfimer sodium, photosensitivity due to 29.21
Porifera (sponges) 38.59
porocarcinoma 53.32–3
porokeratosis **15.91,** 19.90–2
  Crohn's disease and 62.49
  in HIV infection 35.39
  linear 18.25–6
  male genital dermatology 71.37
  of Mibelli 19.91, 66.51
  disseminated superficial 'actinic' porokeratosis vs 52.36
  pathology 52.36
  perianal/perineal dermatology 71.97
  punctate 18.17
  scaling in *5.7, 5.12–13*
  skin biopsy 10.42
  superficial actinic disseminated 52.35–6
  treatment 73.23
poroma, eccrine 53.22, 53.23–4
  intradermal 53.22–3
  malignant 48.14, 53.32–3
porphyria **59.1–20**
  acute attacks 59.7–9, 59.19–21
  clinical features 59.3–8
  treatment 59.8
  aetiology 59.7
  laboratory testing 59.8–10
  congenital erythropoietic *see* congenital erythropoietic porphyria (CEP)
  cutaneous disease
  with acute attacks 59.19–21
  bullous porphyria 59.5–6
  congenital erythropoietic porphyria 59.10–12
    see also congenital erythropoietic porphyria (CEP)
  erythropoietic protoporphyria *see* erythropoietic protoporphyria (EPP)
  hepatoerythropoietic protoporphyria 59.13–15
  hereditary coproporphyria 59.19
  major biochemical findings 59.9
  pathogenesis 59.3–6
  porphyria cutanea tarda (PCT) *see* porphyria cutanea tarda (PCT)
  variegate porphyria 59.19–20, 62.46, 66.79
  without acute attacks 59.10–18
  diagnosis, spectrofluorimetry 59.9
  drug-induced 75.32, 75.37
  erythropoietic *69.117*
  haem enzyme deficiencies 59.5
  hepatoerythropoietic 66.79
  hypertrichosis in 66.79
  long-term management 59.8
  ocular involvement *67.25*
  uroporphyrinogen decarboxylase (UROD) in 59.5
  see also specific types
porphyria cutanea tarda (PCT) 59.12–15, 62.64
  alcohol and 45.52
  differential diagnosis 26.29
  drug-induced 75.32, *75.37*
  ear 68.17–18
  fibrin cuff-theory and 47.27
  haemochromatosis and 62.61
  hair colour in 66.95
  hepatitis C virus infection and 33.61–2, 62.59–60
  in HIV infection 35.20
  hypertrichosis in 66.79
  paraneoplastic 62.46
  pigmentation changes 58.26
  in pregnancy 8.12
  sarcoidosis and 61.18
porphyria variegata 59.19–20, 62.46, 66.79
porphyrinaemia, transient neonatal 17.13
porphyrins, phototoxicity 59.2
Porphyromonas 30.60
port-wine stain 18.63–5
  clinical features 18.63–4
  eyelids 67.34
  in Klippel–Trenaunay syndrome 47.23
  pathology and pathogenesis 18.63
  race and 9.19
  spinal dysraphism and 63.15
  in Sturge–Weber syndrome 18.65–7
  treatment 18.64–5, 78.6–7
Portuguese man-of-war *(Physalia)* 38.55, 38.56, 38.57
posaconazole 36.68, 36.83, 36.86, 74.47
positron emission tomography 5.22
post-herpetic neuralgia 33.24, 33.26, **63.6–8,** 67.26
  elderly people 8.28
  management 33.28, 73.49
  prevention 63.6–7
post-inflammatory elastolysis and cutis laxa (PECL) 45.19–20
post-inflammatory hyperpigmentation 58.29, 58.30–1
  anogenital 71.2–3
post-inflammatory hypopigmentation 58.51–2
  anogenital 71.2–3
post-ionizing radiation keratosis 52.37
post-marketing surveillance studies 7.4
post-phlebitic syndrome *see* post-thrombotic syndrome (PTS)
post-phlebitis subcutaneous calcinosis 47.46
post-radiation vascular proliferation, atypical 48.31
post-steroid panniculitis 46.16
post-thrombotic limb 47.33
post-thrombotic syndrome (PTS) 47.23, 47.26, 47.35, **47.40–1**
  deep-vein thrombosis and 47.29, 47.40
  venous ulceration 47.42
post-transplant lymphoproliferative disease (PTLD) 57.51
  EBV association 33.31
postaxial polydactyly 18.92
posterior lid margin disease (PLMD) *67.12*
posthitis 71.8–9
postmenopausal syndrome 21.13
postnatal growth 8.1
postural exercises, lymphoedema management 48.23
postvaccinial encephalitis, cowpox 33.7
potassium, in sweat 44.5
potassium arsenite 52.4
potassium hydroxide 25.20, 27.12
  in molluscum contagiosum 33.12
potassium iodide 74.48
  in granuloma annulare 60.10
  in sporotrichosis 36.72
potassium *p*-aminobenzoate, in lichen sclerosus 51.118
potassium permanganate 73.15
  in allergic contact dermatitis 26.101
  in eczema 23.37–8
  in flexural candidiasis 36.68
  as irritant 25.21
  in tinea pedis 36.49
  treatment of burns 25.23
Potter's syndrome 18.1
Potts, Sir Percival 52.4
povidine, panniculitis due to 46.28
povidone–iodine 30.7, 75.165
  in impetigo 30.16
  in wound cleansing 14.21
powders 73.2
  inorganic and organic types 73.8
  topical therapy 73.8
power 7.22
poxvirus officinalis (vaccinia virus) 33.6
poxviruses *33.2,* **33.5–14**
  genera 33.5
  spread 33.5
  see also specific poxviruses
PPARs (peroxisome proliferator-activated receptors) 12.10, 12.28
  ligands (endogenous) 42.4
  PPAR-γ 12.60, 46.3
    mutations in partial face-sparing lipodystrophy 46.41
    in sebaceous gland development 3.5
  sebaceous glands 42.4
  subtypes, in sebaceous glands 42.4
PPD (*p*-phenylenediamine) *see* paraphenylenediamine
PPD (purified protein derivative) 31.6
PPP *see* palmoplantar pustulosis (PPP)

practolol 75.91
Prader–Willi syndrome 46.5, 58.42
  hypopigmentation in 58.42
  periodontitis in 69.17, 69.18
pramipexole 63.25
pravastatin 75.156–7, 75.157
prayer nodules 9.13–14, 9.15, 28.11
prayer sign 45.62
praziquantel
  in cysticercosis 37.25
  in paragonimiasis 37.23
  in schistosomiasis 37.22
prazosin, in systemic sclerosis 51.108
pRb protein, inactivation by E7 protein of HPV 33.39
pre-adipocyte 46.1, 46.3
preaxial polydactyly 18.92
prebiotic supplements, in atopic dermatitis 24.31, 24.34
precocious puberty, in McCune–Albright syndrome 58.18
predendritic cells, type 1 interferon-producing plasmacytoid 3.19
predictive value 6.19
PrediSkin™ 25.9
prednisolone
  in acne fulminans 42.84
  in acne vulgaris 42.53, 42.66
  in atopic eye disease 67.16
  breastfeeding and 40.45
  in bullous pemphigoid 40.35
  in cicatrizing conjunctivitis 67.23
  in dermatomyositis 51.129
  in discoid lupus erythematosus (DLE) 51.20
  interactions 72.29
  in Langerhans' cell histiocytosis (LCH) 55.13
  in polymorphic light eruption 29.12
  prednisone vs 74.2
  pulsed steroid therapy 74.3
  in pyoderma faciale 43.14
  in systemic lupus erythematosus (SLE) 51.61, 51.62
  see also corticosteroids
prednisone, prednisolone vs 74.2
pregabalin, in zoster and post-herpetic neuralgia 33.28
pregangrene *47.2*
pregnancy **8.9–16**
  acrodermatitis enteropathica and 8.12
  AIDS and 8.13
  alcohol use in *see* fetal alcohol syndrome
  allergen avoidance in 24.34
  allergic contact dermatitis and 26.8
  atopic dermatitis and 8.12, 24.19
  autoimmune disorders and *8.11*, 8.12
  autoimmune progesterone dermatitis in 8.15, 8.19, 75.119
  breast changes 70.1
  condylomata acuminata and 8.11
  connective tissue disorders and *8.11*, 8.12
  dermatomyositis and 8.12
  dermatoses associated with 8.13
  dermatoses modified by 8.11–12
  drug therapy in 18.2, 72.28
    antihistamines 22.29
    co-trimoxazole 74.39
    corticosteroids 74.3
    erythromycin 42.51
    methotrexate contraindications 74.21
    retinoids 74.38, 75.113
    thalidomide 51.21
  eccrine, apocrine and sebaceous gland activity 8.10
  Ehlers–Danlos syndrome and 8.12, 45.34
  eosinophilic granuloma and 8.12
  epulis 8.11, 69.20–1
  erythema multiforme in 8.12
  erythema nodosum and 50.83
  erythrokeratoderma variabilis and 8.12
  Fox–Fordyce disease and 8.10
  generalized pustular psoriasis of pregnancy 20.50–1
  gigantomastia in 70.3
  gingivitis in 8.11, 69.20–1
  gonorrhoea management *34.28*
  haemolytic–uraemic syndrome and 49.31
  hair in 8.10, 66.9, 66.27
  hirsutism in 66.82
  hormonal changes 8.9–10
  HPV infection and 8.11
  infections and immunity 8.11
  inflammatory dermatoses specific to 8.13–15
  Langerhans' cell histiocytosis and 8.12
  Lassa fever in 33.69
  leprosy and 8.11
  local anaesthesia in *77.10*
  Lyme disease in 30.65
  Marfan's syndrome and 45.31
  mask of *see* melasma
  maternal drug exposure 72.28
  melanoma 8.12, 54.56–7
  metabolic disorders in *8.11*, 8.12
  mosquito bites during 38.2
  mycosis fungoides and 8.12
  nails in 8.10
  neurofibromata and 8.12
  papular dermatitis of 8.15
  partial lipoatrophy and 46.39
  parvovirus B19 infection and 33.63
  patch testing in 26.85
  pemphigoid gestationis **40.41–5**
  pemphigus 40.9
  pigmentation in 8.10, 58.25
  pityriasis rosea in 33.80
  polymyositis and 8.12
  porphyria cutanea tarda and 8.12
  prevention, isotretinoin use *42.59*, 42.59–60
  prurigo of pregnancy 8.14–15, 23.45
  pruritic urticated papules and plaques of pregnancy 8.13, 8.14, 21.14
  pruritus gravidarum 8.13
  pruritus in 21.14–15
  pseudoxanthoma elasticum and 8.12, 45.23
  psoriasis and 8.12
  pyoderma faciale in 43.14
  restless legs syndrome in 47.12
  rubella in 33.71
  sarcoidosis and 61.8
  scabicide use 38.42
  scleroderma and 8.12
  sebaceous gland activity 42.12
  sexually transmitted diseases and outcomes 34.1
  skin changes 8.10–11
  skin tags 8.13
  SLE and 8.12
  spider telangiectases in 8.10, 47.14, 47.15
  Stevens–Johnson syndrome and 8.12
  striae distensae (striae gravidarum) 8.13
  syphilis and 34.11
  syphilis management in 34.22–3
  thalidomide and 51.21
  thrombocytopenia in 49.12
  thrombotic thrombocytopenic purpura and 49.31
  toxic erythema (toxaemic rash; PUPPP) 8.13, 8.14, 21.14
  trace element excess/deficiency 18.2
  tumours and *8.11*, 8.12
  urticaria and 22.11
  vascular changes 8.10–11
  warts and 8.11
pregnenolone 8.9
prehospital management, burns 28.75–6
preimplantation genetic diagnosis 16.1, 16.7–9
  epidermolysis bullosa (EB) 39.31
preimplantation genetic haplotyping 16.1, 16.8–9
prelymph 48.5
prelymphomatous eruption *23.8*
premalignant dermatoses
  male genital dermatology 71.37–9
  perianal/perineal dermatology 71.96–9
premalignant epithelial lesions 52.2, **52.29–38**
  cancer risk 52.29
  HPV infection and 52.6
  inflammatory reaction in 52.29
  risk factors and aetiology 52.29
  see also actinic keratosis; Bowen's disease
premalignant fibroepithelial tumour (of Pinkus) 52.48
  as trichoblastoma variant 53.10
prematurity, ichthyosis prematurity syndrome 19.18–19
premelanosomes 66.93
premenstrual flushing 8.8
premenstrual syndrome 8.8–9, 42.34
prenatal diagnosis **16.1–11**
  DNA-based 16.1–3, *16.4*
  epidermolysis bullosa (EB) 39.27, 39.31
  ethical aspects 16.10–11
  fetal ultrasound 16.7
  fetoscopy and fetal skin biopsy 16.5–7
  non-invasive 16.9–10
  preimplantation 16.7–9
prescribing
  electronic 72.26
  errors 72.26
  topical therapy **73.1–5**
presenting complaint, history-taking 5.4–5
preseptal cellulitis *67.4*
preservatives
  as allergens 26.49–58
  food 75.159
  as irritants 25.20
  in topical therapy 73.8
pressure
  in palpation 5.17
  sensitivity, in obesity 8.17
pressure erythema 47.33
pressure ulcers 14.13–15, **28.16–23,** 47.57
  in amputees 28.27–8
  classification 28.18–19
  clinical features 28.18–19
  complications 28.19–20
  epidemiology 28.16–17
  following spinal cord injury 63.17
  management 28.22–3
  pathogenesis and pathophysiology 28.17
  pathology 28.18
  perianal/perineal 71.84
  prevention 28.20–2
  risk factors *14.14*, 28.17–18, 28.20, *28.21*
  sites 14.13–14
  treatment 73.10
pretibial myxoedema 8.17, 48.13, **62.8–9**
pretibial pruritic papular dermatitis, mechanical injury 28.15
prevalence 6.18
  definition 26.2
  period 6.18
  point 6.18
  skin disease 6.11
    see also specific diseases
prevalence studies of skin disease 6.6–8
  examined skin disease 6.6–8
  self-reported disease 6.6
prevention of skin diseases 6.3
  see also specific diseases
prevention paradox 6.3, *6.4*
Prevotella 30.60
priapism 71.51
prick test *see under* skin testing
prickly heat 17.7–8, 44.15–16
primary acquired melanosis (PAM) 54.40–1
primary biliary cirrhosis (PBC) 62.62
  lichen planus and 41.16
  oral involvement *69.115*
  pigmentation changes 58.28
  sarcoidosis and 61.18
primary care 6.14–15
primary cutaneous lymphomas *see under* lymphoma(s)
primary idiopathic hypertrophic pulmonary osteoarthropathy *see* pachydermoperiostosis
primary irritant napkin dermatitis *see* dermatitis, napkin
primates
  alopecia in 2.19
  flea infestations 2.10
primin 26.18, 26.76, 26.77
Primula 26.1
  erythema multiforme-like reactions and 26.25, 76.5
  sensitization by, hair regrowth and 73.39
Primula obconica
  allergenicity 26.10, 26.16, 26.17, 26.76
  depigmentation and 26.26, *26.27*
  eyelid oedema due to 26.17
  lichen planus-like eruption due to 26.26
  secondary involvement patterns 26.21
printers
  occupational hazards 27.20
  risk of occupational dermatoses *27.2*
pro-drugs, photodynamic therapy 52.16
pro-haptens 26.11
pro-opiomelanocortin (POMC) 12.65, 58.7
  UVR-induced production 29.5, 29.7
probability
  post-test 7.14
  pre-test 7.13
  of skin disease 6.11
probenecid, adverse effects in HIV infection 35.20
probiotic supplements, in atopic dermatitis 24.31, 24.34
procainamide 75.90
procaine 77.10
procaine penicillin, syphilis management 34.22, 34.23
procarbazine 75.126
procoagulant tendency 49.38
procollagen 80.2
  type III (PIIINP) 20.33, 20.35
proctitis, gonococcal 34.25, *34.26*
proctocolitis, ulcerative, in lymphogranuloma venereum 34.33
profilaggrin 3.10
  in epidermis 4.2
profilins 22.20
progeria 8.21, 45.58–9, 51.79, 66.59
  bone and joint involvement *62.100*
  greying of hair 66.92–3
progesterone
  autoimmune progesterone dermatitis 8.9, 75.119
  in breast development 70.1
  menstrual cycle 8.8
  pigmentation changes associated with 58.25
  in pregnancy 8.9
  receptors 42.11
  sebaceous gland activity 42.11
  topical
    in acne 42.16
    in prevention of ageing 80.4
progesterone-induced dermatitis, tamoxifen therapy 74.33
progestins, in oral contraceptives, acne treatment 42.53
proglottids 37.24
prognosis, communication to patient 72.4–5
programmed cell death *see* apoptosis
progressive macular hypomelanosis 9.16
progressive multifocal leukoencephalopathy 50.47
progressive osseous heteroplasia 45.68

progressive symmetrical erythrokeratoderma (PSEK) 19.70–1
prolactin
  in breast development 70.1
  hair growth and 66.9
  hirsutism and 66.83
  in hyperpituitarism 62.2
  in hypopituitarism 62.3
  in pregnancy/after birth 8.10
prolapse, urethral 71.73
prolidase deficiency **45.39–40, 47.54**
proline therapy, in prolidase deficiency 45.40
prolyl hydroxylation reaction, collagen synthesis 3.37
promethazine 26.44, 74.31
prominent auricular (Darwin's) tubercle 68.4
prominent sebaceous glands *71.11*
promonocytes 5.1
promontory sign 56.35
Pronematus davisi 38.48
propane sultone 27.11
n-propanol, as antiseptic 73.14
propantheline 44.12
proparacaine *26.46*
properdin 51.6
Propionibacterium 30.3, 30.35, **30.40,** 30.59
  erythromycin-resistant 73.10
  growth inhibition by azelaic acid 73.28
  in normal skin flora 30.2, 30.3, 30.4
  subgroups 42.24
Propionibacterium acnes 30.3, 30.40, 42.7
  acne aetiology and 42.24–6
    as initiating factor 42.26
    topical drugs affecting *42.40*
  in acne fulminans 42.83
  in acne necrotica varioliformis 30.26, 30.27
  antibiotic resistance 42.41–2, 42.43, 42.47, 42.55–6
    causes and MIC levels 42.56
    mutations 42.56
    prevalence 42.56
    specific antibiotics 42.56
    strategies to prevent *42.42*
  in axilla 30.4
  biological significance 42.27
  free fatty acid production 30.4, 30.5
  genome 42.24
  lipase action on sebaceous triglycerides 42.6
  in normal skin flora 30.4
  number, acne pathogenesis and 42.24, 42.25
  oxygen tension and 42.25
  progressive macular hypomelanosis and 9.16
  in pyoderma faciale 43.14
  reduced counts, isotretinoin effect 42.58
  in SAPHO syndrome 42.85
  sarcoidosis and 61.2
  skin colonization, immunomodulatory role 42.6
  skin flora 30.4
  substances released by 42.25
  topical therapy 73.10
  Wood's light examination 5.19
Propionibacterium avidum 30.3, 30.4, 30.40
Propionibacterium granulosum 30.3, 30.40
propolis 26.82–3, 75.160
propranolol 75.91
  flushing management 43.15
  lichenoid tissue reaction due to 41.25
proptosis, in sarcoidosis 61.7
propylene carbonate *25.19*
propylene glycol *25.19*, 25.20, 73.7
  as preservative in topical therapy 73.8
  in scabies 73.14
propylene glycol diacetate *25.19*
17α-propyltestosterone 42.16
Prosimulium 38.5
prostacyclin (PGI_2) 12.60, 13.4
  formation, platelet aggregation inhibition 49.8
  in systemic sclerosis 51.108
prostacyclin analogues, in Raynaud's phenomenon 51.108
prostaglandin(s) **12.60–2,** 13.4
  in irritant contact dermatitis 25.5
  pruritus and *21.3,* 21.5
  in wound healing 14.3, 14.24
prostaglandin D_2 (PGD_2), urticaria and 22.4
prostaglandin D_2 receptor 1 (DP1) 73.51
prostaglandin E 21.5
prostaglandin E_1 (PGE_1), rest pain and gangrene therapy 47.6
prostaglandin E_2 (PGE_2) 21.5
  pigmentation regulation 58.7
prostate cancer
  androgenetic alopecia and 66.19
  flushing in 43.15
  lymphoedema in 48.8
prostatitis, gonococci causing 34.26
prosthetic implants
  metallic 26.37
  osseo-integrated 68.16
  urticaria and 22.11
prosthetic limbs 25.16
Protaceae *26.81*
protamine 75.107
protease(s) **12.49–51,** 38.1
  in atopic dermatitis 24.18
  pruritus and *21.3,* 21.4–5, 24.18
protease-activated receptors (PARs) 12.50
  in atopic dermatitis 24.18
  PAR-1, -3 and -4 12.33, 12.49, 12.66
protease inhibitors 12.50, *35.7,* 74.50
  adverse effects *35.21,* 35.22, 75.68–9
  in HIV-associated lipodystrophy 46.42
  in HIV infection 35.6, *35.7*
  mechanical and thermal injury 28.2
protectin 14.4
protein A 30.8
protein C 49.38
  activated *see* activated protein C (APC)
  activation, dysfunction, in purpura 49.20, 49.39
  calciphylaxis (calcific uraemic arteriolopathy) 47.8
  concentrates 49.39, 49.40
  deficiency 17.33, 47.28, 49.38, 49.44, 62.91
    acquired severe 49.39–40
    homozygous 49.39
  disease associated with 49.39–40
  resistance 17.33
  severe acquired dysfunction 49.39
protein contact dermatitis 26.105–6, 27.5
protein kinase C inhibitor, in psoriasis 20.42
protein p59 73.17
protein S 49.38
  acquired severe dysfunction 49.40
  calciphylaxis (calcific uraemic arteriolopathy) 47.8
  deficiency 17.33, 47.28, 49.39, 49.44, 62.91, *62.91*
  disease associated with 49.39–40
protein synthesis 11.3
protein therapeutics **74.4–13**
protein tyrosine phosphatase receptor type D (PTPRD) locus 52.12
proteinase 3 13.4, 50.39
proteinase-activated receptor(s) 63.2–3
  pruritus and *21.3,* 21.4, 21.5
proteinase-activated receptor-2 (PAR-2) 3.20, 12.25
proteoglycan(s) 3.2, 3.34, 3.45–9
  ageing and 80.1
  cell-surface 3.46
  core proteins 3.46
  deposition, changes in 3.49
  functions 3.46–7
  molecular characteristics and distribution *3.48*
  structure and synthesis 3.45–6, *3.48*
    see also glycosaminoglycans (GAGs)
  synthesis in fibroblasts 3.49
  in wound healing 14.1, 14.3, 14.7
proteoglycan binding, cytokines 12.31
proteomics 11.8
Proteus
  in external auditory meatus 30.4
  genitocrural infection 71.5
  in paronychia 65.21
  wound infection 14.16
Proteus mirabilis 42.56
Proteus syndrome 18.27, **18.78–9,** 48.11, 62.26
  aetiology 18.78
  bone and joint involvement *62.100*
  clinical features 18.78
  definition 18.78
  diagnosis 18.78–9
  differential diagnosis 18.77
  encephalocraniocutaneous lipomatosis as variant 46.46
  pathology 18.78
  treatment 18.79
prothrombin 49.38
  G20210A mutation 49.44
proto-oncogenes 11.17, 52.12
proton pump inhibitors 75.157
protoporphyria, erythropoietic *see* erythropoietic protoporphyria (EPP)
Prototheca infection, swimming-/diving-associated 28.54
protothecosis 36.92
protozoa 36.1, 37.2
protozoal infections 37.2, **37.27–44**
  female genitalia 71.69
  in HIV infection 35.35–6
  ocular involvement 67.27
  oral involvement 69.81
  urticaria and 22.2, 22.10
  see also specific infections
provocation tests 5.25
Prox-1 10.24, 48.2, 48.4, *48.5,* 48.19
prozone phenomenon 34.19
PRP *see* pityriasis rubra pilaris (PRP)
prurigo 21.1, **23.42–6**
  actinic *see* actinic prurigo (AP)
  actinic (Hutchinson's summer) 23.45
  chronic of adults (subacute) 23.44
  definition 23.42
  dermographic 23.45
  early onset of pregnancy 8.14–15
  late-onset of pregnancy (PUPPP) 8.13, 8.14
  nodular (Hyde's) 23.42–4
  of pregnancy 8.14–15, 23.45
  scratch *see* dermographism
prurigo annularis 8.15
prurigo diathesique *see* atopic dermatitis
prurigo gestationis of Besnier 8.14–15
prurigo nodularis (of Hyde) 21.1, 21.2, 64.27
  differential diagnosis 29.14
prurigo pigmentosa 23.44–5, 58.31
pruritic papular eruption, in HIV infection 35.19, 35.45
pruritic urticarial papules and plaques of pregnancy (PUPPP) 8.13, 8.14, 21.14
pruritus **21.1–18**
  in acne vulgaris 42.32
  in animals 2.9, 2.10, 2.13
  anogenital 71.1–2
  aquagenic 21.10, 21.11–12, 62.86
  assessment 72.10–11
  in atopic dermatitis 8.7, 21.13–14, 24.17–18
  atopic eye disease 67.15
  brachioradial 21.15–16, 62.34, 63.23–4
  central itch 21.3
  in cholestasis 21.9–10
  chronic 21.1
  in chronic renal failure 21.7–9
  classification 21.1
  in clothing/body louse infection 38.22
  in cold-induced injury 28.65
  degree of 5.4
  in diabetes mellitus 21.11
  in eating disorders 21.16
  in elderly people 8.27, 21.12, 21.17
  epidemiology 21.1–2
  female genital dermatology 71.52
  genetics 15.18
  genitocrural dermatology 71.7
  haemodialysis and 21.7–8, 62.72
  in head louse infection 38.19
  in hepatitis C virus infection 62.60
  in HIV infection 21.14, 35.11–12
  in Hodgkin's disease 21.11, 62.89
  hydroxyethyl starch 21.15, 28.44
  in hyperparathyroidism 62.12
  in hyperthyroidism 21.11
  in hypothyroidism 21.11
  in intravenous drug abuse 28.53
  investigation 21.16
  in iron deficiency 21.10
  in lichen planus 41.9, 41.17
  in lichen simplex 23.40
  liver disease and 62.62, 62.63
  male genital dermatology 71.16, 71.34, 71.51
  malignant disease and 21.11
  management 21.16–18
  in mastocytosis 21.10, 22.32, 22.35
  measurement 21.2, 21.16
  in mycosis fungoides 21.10
  neurogenic 21.1, *21.7*
  neuropathic 21.1
  in nodular prurigo 23.43
  non-inflamed skin 21.5–7
  in notalgia paraesthetica 21.15
  in onchocerciasis 37.5
  opioids and 21.3, 21.4, 21.8, 21.9, 24.18
  paraneoplastic 62.33–5
  pathophysiology 21.2
  in pemphigoid nodularis 21.15
  perianal/perineal 71.85
  peripheral mediators in skin disease 21.3–5
  in polycythaemia rubra vera 21.10, 62.86
  in polymorphic light eruption (PLE) 29.11
  postmenopausal 21.13
  in pregnancy 21.14–15
  as presenting complaint 5.4
  in primary biliary cirrhosis 62.62
  proteases and *21.3,* 21.4–5, 24.18
  pruriceptive 21.1, 21.7
  psychogenic 21.1, 21.12–13, 64.23–4
  in renal failure 62.72
  in scabies 38.38
  scalp 38.19
  of senescence 21.12, 21.17
  in Sézary syndrome 21.10, 21.11
  solar 21.16
  stigma of 64.2
  swimming-/diving-associated 28.55
pruritus ani 21.12, **21.15,** 37.14, 64.27, 71.83, **71.85–7,** 71.92
  allergic contact dermatitis and 26.18, 26.44
pruritus gravidarum 8.13
pruritus vulvae 21.12, 21.13, **21.15**
PRV *see* polycythaemia rubra vera (PRV)
Psalydolytta 38.26
Pseudeurotium ovalis 36.55
pseudo-ainhum 45.69–70
pseudo-autosomal regions 15.4
pseudo-Cushing's syndrome 62.4
pseudo-Darier sign 18.35
pseudo-elephantiasis 34.36–7
pseudo-Kaposi's sarcoma 47.22, 49.17–18
pseudoacne, nasal crease 18.90
pseudoallergic reactions 22.8, 22.10
pseudochancre redux 34.7
pseudochromhidrosis 44.21
pseudocowpox (milker's nodule) 33.10–11

pseudocyst
  ear/endochondral 24.25, 68.13–14
  myxoid/mucoid *see* cyst(s), myxoid
pseudoephedrine 75.99
pseudoepitheliomatous hyperplasia 47.45, 52.25, **52.44–5**
  incontinentia pigmenti vs 58.15
pseudoepitheliomatous micaceous and keratotic balanitis (PEMKB) 71.37–8
pseudofolliculitis 30.22–3
pseudofolliculitis barbae 9.9, 28.50, 78.12
  acne vs 42.37
pseudoglucagonoma syndrome 62.64
pseudogynaecomastia 70.4
pseudohermaphroditism 66.14, 66.16
pseudohyphae 36.2
pseudohypoaldosteronism 17.8, 44.15
pseudohypoparathyroidism 62.12
pseudologica fantastica 64.35, 64.44
pseudolymphoma 69.58
  B-cell/T-cell 57.53–4
  induced by arthropod bites 38.3
pseudolymphomatous drug hypersensitivity syndrome 75.27, 75.44
pseudomelanoma 54.19
pseudomembranous colitis 42.47, 42.51
Pseudomonas
  anogenital ulcers *71.4*
  in botryomycosis 30.67
  burn wound infection 28.86
  genital infection, in females 71.70
  in HIV infection 35.24
  perianal/perineal infection 71.93
  swimming-/diving-associated infections 28.55
  umbilical infection 71.101
Pseudomonas aeruginosa **30.48–50**
  amikacin therapy 74.42
  in cellulitis 30.18
  ear piercing-associated infection 28.51, 68.7
  ecthyma gangrenosum 49.35
  ectodermal dysplasias 15.60
  in erysipelas 30.18
  female genital infection 71.67
  genitocrural infection 71.5, 71.7
  in HIV infection 35.24–5
  nail infection 30.49, 65.10, 65.11, 65.21, 65.22
  neonatal infection 17.45–6
  in normal skin flora 30.3, 68.2
  in otitis externa 30.49, 68.21, 68.22, 68.25
  perianal/perineal infection 71.92
  in perichondritis 68.19
  septicaemia 30.49, 30.50
  swimming-/diving-associated infection 28.54–5
  topical antibiotic therapy 73.10
  venous leg ulcer infection 47.44
  wound infection 14.16, 30.49, 30.50
Pseudomonas cepacia 30.48
Pseudomonas fluorescens, mupirocin from 73.10
Pseudomonas folliculitis, swimming-/diving-associated infection 28.54–5
Pseudomonas pseudomallei 30.50–1
Pseudomonas pyocyanea see Pseudomonas aeruginosa
pseudomonilethrix *66.65*
Pseudonaja 38.60
pseudonits 38.19
pseudopelade 66.39
  lichen planus 41.14
pseudopelade of Brocq 66.38, **66.45–6**
pseudopemphigoid 67.20
pseudophotodermatitis 26.75
pseudoporphyria 29.7
  drug-induced 29.21, 75.32, 75.37–8
pseudopseudohypoparathyroidism 62.12
pseudopseudoxanthoma elasticum 45.25
pseudopyogenic reaction 46.13
pseudorhagades 69.39
pseudosarcoma **56.20–2,** 68.34, 79.18
pseudoscars 45.6
  brown 45.6, *45.7*
  discoid 45.6
  stellate 45.6, *45.7*
pseudoscleroderma 48.22, 51.79, 51.120
pseudosyndactyly
  in dystrophic epidermolysis bullosa 39.18
  in generalized non-Herlitz junctional epidermolysis bullosa 39.13
pseudothalidomide syndrome 18.70, 66.61
pseudotumours, in Ehlers–Danlos syndrome 45.32, 45.33
pseudovaginal perineoscrotal hypospadias 66.14
pseudoverrucous lesions 62.54
pseudoxanthoma elasticum (PXE) **45.21–4**
  aetiology 45.21
  bone and joint involvement *62.100*
  definition 45.21
  diagnosis 45.23
  differential diagnosis 45.16
  disorders resembling 62.85
  iron deficiency anaemia in 62.85
  pathology 45.21–3
  perforating 45.24–5
  pregnancy and 8.12, 45.23
  purpura due to 49.14
  treatment 45.23
psittacosis **30.71–2,** 62.80, 62.107
PSOR6 gene 2.14
Psoralea corylifolia 75.162
psoralen(s) 29.21
  adverse effects
    hypertrichosis *66.79*
    ocular 67.32
    photosensitivity 75.31
  photochemotherapy *see* PUVA therapy
  photomutagenic 29.21
  topically applied, adverse effects 58.48
  vitiligo treatment 58.48
'psoriasiform dermatitis of the pawpads' 2.14
psoriasiform-lichenoid dermatosis, in dogs 2.14
psoriasis **20.1–60**
  acute pustular 8.12, 76.19
  in adolescence 8.7, 8.8
  aetiology 20.2–9
    nuclear factor-kappa B (NF-kappaB) 12.10
    peroxisome proliferator-activated receptors (PPARs) 12.10
  alcohol abuse and 64.47
  in amputees 28.29
  amyloidoses and 20.19
  animal models 2.8
  biomarkers 20.19
  breast 70.17
  career choice and 8.8
  in children 17.31–2, 20.13, 20.16
    infantile and juvenile pustular psoriasis 20.51
  clinical features 20.9–19, *73.44*
    atypical forms 20.16–19
    common chronic stable plaque 20.10
    complications 20.18
    disease associations 20.17–18
    modification by site 20.14–16
    onset 20.1, 20.9–10
    seborrhoeic dermatitis 20.17
  clinical variants 20.11–14
    bullous pemphigoid and 40.35
    erythrodermic 20.12–13, 20.16
    guttate 20.11
    pityriasis amiantacea 20.14, 20.16
    rupioid, elephantine and ostraceous psoriasis 20.12
    unstable phases 20.12
  coeliac disease and 62.55
  course and prognosis 20.20
  Crohn's disease and 62.49
  differential diagnosis 20.19, 26.29
  in dogs 2.14
  drug-induced/exacerbated *75.24*
  ear 68.14, 68.23
  in elderly people 8.28
  epidemiological aspects 20.1–2
    environmental risk factors 20.3–4
    psychogenic factors 20.4
    sunlight 20.3
  erythroderma and 23.47
  erythrodermic, calcipotriol treatment 73.45
  eyelids 67.5
  female genital dermatology 71.52, 71.58–9, 71.68
  flexural (inverse) 8.28
  following streptococcal infection 30.12
  friction and 27.6, 28.15
  generalized pustular *see* generalized pustular psoriasis (GPP)
  genetics 15.1, 15.2, 15.6, 15.11, 20.3–4
    replicated genetic loci 20.3–4
  genitocrural dermatology 71.5
  guttate, pityriasis rosea vs 33.81
  hands 23.20, 25.15, *25.16*
    palms 20.15
  histopathology 20.9
    Auspitz's sign 20.11
  in HIV infection 35.17–18
  HPV association 33.47
  hypopigmentation after 58.51
  Koebner phenomenon/response *5.12*, 28.2–3, 28.48
  localization to tattoos 58.58
  male genital dermatology 71.18
  metabolic syndrome association 6.13
  naevoid 18.24
  nails 20.15–16, 36.35, 65.10, 65.13, **65.23–7, 65.23–7,** *65.28*
    acitretin therapy 74.35
    calcipotriol therapy 73.45
  napkin 17.24, 17.31–2
  ocular involvement 67.5
  onycholysis in 65.10
  oral involvement 69.94
  Paget's disease of nipple vs 53.39
  pathogenesis 20.2–9
  pathogenetic mechanisms 20.5–9
    immunology and inflammation 20.7
    Koebner phenomenon 20.8
  perianal/perineal involvement 71.84
  peristomal 62.54
  pityriasis rubra differentiated 19.77
  plaque, chronic, topical corticosteroid use 73.19
  pregnancy and 8.12
  psoriasis area severity index (PASI) score 7.11–12, 20.41
  psoriatic arthritis *see* psoriatic arthritis
  psychological factors 64.4, 64.9
  pustular 20.44–54, 50.62, 62.12
    acrodermatitis continua 20.46–8
    acute 8.12, 76.19
    acute generalized exanthematous psoriasis 20.52
    acute generalized pustular psoriasis (von Zumbusch) 20.49–50
    circinate, annular and linear pustular psoriasis 20.52
    generalized *see* generalized pustular psoriasis (GPP)
    infantile and juvenile pustular psoriasis 20.51
    palmoplantar pustulosis 20.44–6
    subcorneal pustular dermatosis of Sneddon and Wilkinson 20.52–4
  quality of life assessment 64.10, 72.14, 72.19–20, 72.24
  race and 9.14
  remissions 20.20
  Salford Psoriasis Index 20.21
  sarcoidosis and 61.18
  scalp 23.32
  seborrhoeic dermatitis and 23.32
  severity assessment 72.9, 72.14
  skin-directed therapies 20.21–8
    calcipotriol 73.45
    calcitriol 73.45
    coal tar and UV 73.42
    corticosteroids
      intralesional 20.25
      topical 20.25
    dithranol 73.29
    lasers 20.43, 78.8
    occlusive dressings alone 20.28
    penetration enhancers 73.7
    photodynamic therapy 20.43
    pimecrolimus 73.32
    psoralen photochemotherapy *see under* PUVA therapy
    retinoic acid 73.36
    tacalcitol 73.44–5
    tacrolimus 73.32
    tar 20.21–2
    tazarotene 73.37
    topical calcineurin inhibitors 20.25, 20.42
    topical mechlorethamine 73.24
    topical methotrexate 73.23
    UV phototherapy 20.28–33
    vitamin D analogues 73.43
    wood tars 73.42
  sweat retention in 44.13
  systemic therapies 20.33–41
    ABT-874 74.10
    acitretin 20.37, 74.35
    adalimumab 20.41, 74.5
    alefacept 20.41, 74.6, 74.8–9
    anti-IL12/23 74.10
    azidothymidine 20.42
    biological 72.14
    biological therapies directed against cytokines 20.41–2, 74.10
    certolizumab 74.5
    ciclosporin 20.38–9, 74.16
    Dead Sea Clinic 20.29
    dialysis and related therapies 20.44
    etanercept 20.41, 74.5
    etretinate 20.37
    fumaric acid 20.40, 74.29
    gluten-free diet 20.43
    golimumab 74.5
    hydroxycarbamide 20.36, 74.18
    infliximab 20.41, 74.5
    liarozole 20.42
    methotrexate 20.33–5, 74.18–19
    mycophenolate mofetil 20.42, 74.24–5
    retinoic acid metabolism blockers 20.42–3, 74.37
    somatostatin 20.42
    sulfasalazine 20.42
    T-cell inhibitors 74.6
    ustekinumab 74.10
    vitamin A analogues 20.27–8 *see also* retinoids
    vitamin D analogues 20.26
  treatment
    concordance with 72.5, 72.6, 72.7
    risk–benefit analysis 72.3
    skin-directed *see* psoriasis, skin-directed therapies
    systemic *see* psoriasis, systemic therapies
  umbilical involvement 71.101
  Zumbusch-type 20.49, 20.51
Psoriasis Area and Severity Index (PASI) 7.11–12, 20.41, 72.9, 72.14
Psoriasis Disability Index (PDI) 72.19–20
Psoriasis Family Impact questionnaire 72.24
psoriasis susceptibility loci (PSORS) 12.14
psoriasis vulgaris 20.10
  treatment, tacrolimus 73.32
psoriatic arthritis 20.54–9
  aetiology and pathogenesis. 20.54
  clinical features 20.54–5
  differential diagnosis 20.58
  histopathology 20.58
  lymphoedema in 48.13
  MMPs and 12.53

Moll and Wright classification 20.54–5
nail involvement 20.57
pathogenetic mechanisms. 20.55
prognosis 20.59
radiological changes 20.58
treatment 20.58–60
disease-modifying antirheumatic drugs (DMARDs) 20.59
methotrexate 20.59
surgery and infection 20.59–60
psoriatic nail dystrophy, acitretin therapy 74.35
psoriatic onycho-pachydermo-periostitis 65.25, 65.26
PSORIQoL 72.20
Psoroptes 38.46
Psoroptes cuniculi 2.11
Psoroptes ovis 2.10
Psoroptidae 38.46
psychiatric disorders 64.46, 64.54
classification 64.11–12
oral manifestations *69.115*
psychiatric liaison 64.3–4, 64.15
psychiatric treatments **64.49–54**
alternative therapies 64.54
drug therapy 64.50–2
see also psychotherapies
psychocutaneous disorders
body awareness 64.17–22
dermatological beliefs 64.12–17
factitious 64.34–45
group/mass reactions 64.25–6
harmful habits 64.26–34
organic diseases associated with 64.13, 64.17
phobias 64.24–5
pruritus 64.23–4
psychodermatology 64.2–4
Psychodidae (sandflies) 37.33, 37.39, 38.2, 38.5, 38.7
Psychodopygus 37.33
psychological factors
congenital naevi 54.14
in diagnosis 5.5
psychological importance of skin 64.1–2
psychological methods, wart treatment 33.50
psychoneuroimmunology 64.3, 64.8–9
psychosocial factors, acne and 42.35
psychosocial questionnaires, acne impact 42.35
Psychosomatic Scale for Atopic Dermatitis (PSS-AD) 72.20
psychosomatics 64.3, **64.4–5**
psychotherapies 64.8, **64.52–4**
body dysmorphic disorder 64.20
cognitive behavioural therapy 64.53
dynamic 64.53–4
psychocutaneous disorder 64.28
self-mutilation 64.46
therapeutic relationship 64.52–3
psychotropic agents 75.78
PTBPFR (*p*-tertiary butylphenol formaldehyde resin) 26.68, 26.69, 26.73–4
PTCH1 gene mutation, in naevoid basal cell carcinoma syndrome 52.19, 62.21
PTD (toluene-2,5-diamine) 26.60, 26.61
PTEN gene 18.6, 62.25, 62.26
mutations
in Cowden's syndrome 53.5
induced by UVR, melanoma and 29.7
PTEN hamartoma tumour syndrome 62.25–6
pterins 2.5
Pterocarpus soyauxii 26.81
pterygium 65.11
in lichen planus 65.29
ventral 51.95, 65.11–12
pterygium inversum unguis 51.95, 65.11–12
pterygoid sign 69.4–5
Pthirus gorillae 2.10, 38.15
Pthirus pubis see lice, pubic (crabs)
ptosis 67.5
in Horner's syndrome 63.22
PTPN11 gene 15.15, 15.20–1
PTSAgs (pyrogenic toxin superantigens) 30.31
pubarche 8.5
puberty 8.2, **8.4–8**
age for 8.4
nutrition affecting 42.34
delayed 8.6
dermatoses of 8.6–8
gynaecomastia in boys 70.4
hair growth 8.4, 66.13
hormonal events and cutaneous changes 8.4–5
initiation, hormonal changes 8.4
leptin 'gate' for 8.4
miniature 17.5, 17.6
partial/incomplete 8.5
precocious 8.5
classification *8.5*
in McCune–Albright syndrome 58.18
sebum composition changes 42.5
skin changes during 8.6, 8.7
pubic hair
genitocrural dermatology 71.8
patterns and distribution 71.10, *71.11*
pubic lice *see under* lice
public health, skin disease problem 6.4–8
publication bias 7.7, 7.8
PubMed Clinical Queries 7.6
puerperium **8.9–16**
Pulex irritans 2.10, 38.11
Pulicidae 38.11
pulmonary fibrosis, psoriasis and 20.18
pulmonary stenosis, genetics 15.20
pulmonary symptoms, genetics 15.23, 15.24
pulsed-dye laser (PDL) therapy *see under* laser therapy
pulseless disease **50.44–5**
pulses, peripheral ischaemic disease 47.2
punch biopsy, panniculitis 46.11
punctate keratoderma 19.95, 19.112–13
punkies 38.6
pupils
Argyll Robertson 33.26, 63.15
in Ross's syndrome 44.14
PUPPP (pruritic urticarial papules and plaques of pregnancy) 8.13, 8.14, 21.14
puretic syndrome 45.49–50, 69.15
purified protein derivative 31.6
purine nucleoside phosphorylase deficiency 17.60
purpura **49.1–51,** 62.90
abnormal blood vessels causing 49.14–15
acral 49.4, 49.32
actinic (Bateman's/senile) 49.15
aetiology 49.2–4, *49.3*
see also specific causes
ageing association 49.15
allergic contact dermatitis and 26.26
in amyloidosis 49.15, 49.18
anaphylactoid *see* Henoch–Schönlein purpura
annular, mechanical injury 28.31
autoimmune thrombocytopenic *see* idiopathic thrombocytopenic purpura (ITP)
bland retiform 49.39–40
chronic, partial lipodystrophy 46.40
classification 49.1, **49.2–4**
clinical patterns 49.4
cocarde 49.19
contact 49.21
corticosteroid-induced 49.15
Crohn's disease and 62.51
in cryoglobulinaemia 49.33
in cutaneous small vessel vasculitis 50.14, *50.15*
decreased blood vessel support causing 49.14–15
definition 49.1, **49.2**
diagnosis 49.4–5
distribution/body sites 49.4–5
drug-induced 75.23
non-thrombocytopenic 49.21
thrombocytopenic 49.11
dysproteinaemic 49.19–20
ear 68.18
in endocrine disorders 49.18
exercise-induced 49.18, 50.23
Favre-Chaix's 49.22
generalizations about 49.7
genetic tests 49.6–7
genital/'bathing trunk' 49.20
gravitational 49.17–18
in Henoch–Schönlein purpura 50.20
histological testing 49.5
idiopathic thrombocytopenic *see* idiopathic thrombocytopenic purpura (ITP)
immune thrombocytopenic *see* idiopathic thrombocytopenic purpura (ITP)
infection-associated 49.20–1
inflammatory 49.2, *49.3,* 49.4, 49.7, 49.16
drug-/toxin-induced 49.21
infections causing 49.20
see also Henoch–Schönlein purpura
inflammatory retiform 49.3, 49.32
investigations 49.5–7
indications/factors suggesting 49.4
laboratory tests 49.5–7
itching (eczematide-like) 49.22, 49.24–5
lower legs 49.7, 49.17
in malignant disease 62.14–15
in malnutrition 49.18
multifactorial, systemic diseases 49.18
nail fold capillaries 49.6
neonatal *see* neonatal purpura
non-inflammatory 49.3–4, 49.26
non-inflammatory retiform 49.3–4
non-palpable 49.4–7
non-thrombocytopenic
systemic diseases causing 49.18
toxin-/drug-induced 49.21
vascular causes *49.3,* **49.14–21**
occlusion/ischaemia causing *49.3*
see also microvascular occlusion
oral cavity 69.21–2, 69.99–9100
in ovarian disorders 49.18
palpable 49.2, 49.4, 49.32, 62.91
pathogenic mechanisms 49.2–4
pathophysiology 49.4–5
perifollicular 49.15
periorbital 49.4, 49.15
physical and artefactual causes 49.16
pigmented dermatoses *see* pigmented purpuric dermatoses
platelet defects causing **49.7–12,** *49.8*
functional abnormalities *49.8,* 49.12–14
thrombocytopenia *see* thrombocytopenia
thrombocytosis *49.8,* 49.14
post-infectious cockade 17.33–4, 49.18–19, 50.30
post-transfusion 49.11
psychogenic/factitious *64.12,* 64.33–4, 64.38
raised intravascular pressure causing 49.14
in renal failure 62.72
reticulate 62.91
retiform 49.44, 49.48
bland (sepsis-related purpura fulminans) 49.39–40
retiform pattern 49.2, 49.7, 49.39
rubella 33.71
senile 49.15
simple macular haemorrhage 49.2, *49.3,* 49.4–7
diagnosis 49.4–5
lesion size *49.3,* 49.4
size of lesions *49.3,* 49.4
in skin diseases 49.17
solar 49.17
sport injury 28.31, 28.54
suction injury 28.24
thrombotic thrombocytopenic (TTP) 49.12, **49.31,** 69.114
toxin-induced 49.11, 49.21
trauma association 49.14, 49.16
ulcerative colitis and 62.51
in urticaria 22.25
vulval, chronic 71.61–2
Waldenström's macroglobulinaemia 49.13, 49.19
in Wegener's granulomatosis 50.40
see also ecchymoses/bruising
purpura annularis telangiectodes (Majocchi's disease) 49.22, **49.25**
purpura en cocarde avec oedeme 17.33–4, 49.18–19, 50.30
purpura fulminans 49.51
in children 49.51
neonatal 17.33, 17.46, 49.39, 49.51
causes 49.51
post-infectious 49.39–40, 49.40
sepsis-related 49.39–40
purpura progressiva pigmentosa *see* pigmented purpuric dermatoses
purpura pulicosa 49.17
purpura rheumatoide *see* Henoch–Schönlein purpura
purpura simplex 49.15–16, 49.22
purpura telangiectatica arciformis 49.25
pustular dermatitis atrophicans, legs 30.22
pustular dermatosis 40.19–22
pustule(s) 10.41
definition 5.7
drug-induced 50.62, 75.34
Kogoj's spongiform 10.41
malignant 30.41
in pyoderma faciale 43.13–14
subcorneal 10.41
in viral infections 33.4, 33.7
pustulosis
acitretin therapy 74.35
acute generalized exanthematous *see* acute generalized exanthematous pustulosis
neonatal cephalic 42.75
neutrophilic *50.89*
PUVA lentigo *54.2,* 54.4–5, 58.33
PUVA therapy 20.29–31
acne induction 42.34
actinic prurigo 29.15
adverse effects
acne 27.13
lentigines *54.2,* 54.4–5, 58.33
ocular 67.32
seborrhoeic dermatitis 23.30
alopecia areata 66.37
atopic dermatitis 24.31
carcinogenic hazard 20.31
chronic actinic dermatitis 29.18
clinical indications 20.30–1
cohort study (US) 6.6
combined therapy 20.30
dermographism 22.14
eczema 23.38
effect on contact allergic reactions 26.9
effect on skin properties 28.8
extracorporeal photophoresis and, in pemphigus 40.12
granuloma annulare 60.10
Hailey-Hailey disease 39.36
hand eczema 23.22
Langerhans' cell histiocytosis (LCH) 55.13
livedoid vasculopathy 49.44
male genital dermatology 71.40, 71.49
mastocytosis 22.35–6
necrobiosis lipoidica 60.16
non-melanoma skin cancer and 52.4
patient selection 20.30
pemphigus 40.12
pigmented purpuric dermatoses 49.26
polymorphic light eruption 29.12

psoriasis 20.29–31
in HIV infection 35.17
of nails 65.26
responses to 64.4
sarcoidosis 61.21
solar urticaria 29.20
with topically applied psoralens 20.32
trimethylpsoralen (TMP) bath PUVA 20.32
using other psoralens 20.32
vitiligo 58.48
see also psoralen(s)
PVP *see* polyvinyl pyrrolidone (PVP)
PWS *see* port-wine stain
PXE *see* pseudoxanthoma elasticum (PXE)
Pyemotes 38.48
pyknosis 10.41
pyloric atresia, congenital 3.31
pyloric stenosis
epidermolysis bullosa simplex with 39.4, 39.8
junctional epidermolysis bullosa with 39.9–10, 39.11, 39.14
pyoderma
in animals 2.10
chancriform 30.77
definition 5.7
erythromycin therapy 74.42
folliculitis and atopy with 23.27
malignant 50.69
secondary, in dogs 2.13
staphylococcal
in dogs 2.11
erythromycin 74.42
streptococcal 30.14, *30.15*, 30.16, 30.33
pyoderma faciale (rosacea fulminans) 42.84–5, **43.13–14**
isotretinoin treatment 42.62
scarring 43.14
pyoderma gangrenosum (PG) **50.64–74,** 51.132
aetiology and pathogenesis 50.65–7
atypical 50.68–9
see also neutrophilic dermatosis, of the dorsal hands
bone and joint involvement 62.102
breast 50.70, 70.11
bullous 46.32, 50.68–9
classic/ulcerative 50.68
clinical features 50.68–70
Crohn's disease and 50.65, 62.50–1
definition 50.64
diagnosis 50.70
differential diagnosis *50.71*
diseases associated *50.65*
ear involvement 68.17
factitial panniculitis vs 46.28
genital involvement 50.70
in males 71.25
hepatitis B virus infection and 62.59
histopathology 50.67–8
history 50.64
leg ulcers in 47.57
in liver disease 62.64
nomenclature 50.64
ocular involvement 50.70
oral involvement 50.70
paraneoplastic 62.41
perianal/perineal involvement 71.95
peristomal 50.69, 50.72
pustular 50.68
pyoderma vegetans vs 30.77, 30.78
respiratory tract involvement 50.70
sarcoidosis and 61.18
superficial/vegetative 50.69
treatment 50.72–4, 73.24
ciclosporin 74.17
TNF antagonists 74.7
ulcerative colitis and 50.65, 62.50–1
upper limbs/trunk/face 50.69–70
variants *50.64*
vasculitis and 50.49, 50.67
pyoderma gangrenosum acne 42.85
pyoderma gangrenosum-like disease, in animal models 2.8
pyoderma vegetans **30.77–8,** 50.89
pyodermatitis–pyostomatitis vegetans 50.70, 62.51
pyodermite vegetante of Hallopeau 30.77
pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) syndrome 42.82, 50.53, 50.66, 62.104
pyogenic granuloma **56.25–6,** 71.100
in acne 42.32, 42.79
curettage 77.40, *77.41*
eccrine poroma vs *53.23*
nail involvement 65.35
oral cavity 69.20, 69.102
pyorrhoea 69.18
pyostomatitis vegetans 50.70, 62.50, 69.59
pyrantel pamoate 37.14, 37.15
pyrazinamide 74.45
adverse effects 31.27, 75.62
in tuberculosis 31.27
Pyrenochaeta unguius hominis 36.55
pyrethroids 38.19, 38.20, 73.13–14
pyridostigmine *26.46*
pyridoxine 59.62, 75.113
pyrimethamine
adverse effects 75.70
Stevens–Johnson syndrome 76.11
in toxoplasmosis 37.44
pyrin domain (PYD) 12.9
pyritinol 75.89
pyrogallol 66.97
pyrogenic toxin superantigens 30.31
pyrrolizidine alkaloids, photosensitivity in animals and 2.23
Pythium insidiosum 36.92

Q

Q-switched ruby laser, congenital naevi treatment 54.14
QFT (Quantiferon-TB Gold) 31.6
Quality Adjusted Life Year (QALY) 72.22
quality of life (QOL) **72.13–24**
acne and 42.35
clinical decisions and 72.2, 72.14, 72.24
definitions 64.10, 72.13
disability and 64.10
measurement 64.10, **72.13–24**
children and families 64.10, 72.20, 72.23–4
clinical use 72.24
correlation with clinical indices 72.14
dermatology-specific 72.17–19
disease-specific 72.19–21
general health 72.16–17
patient-specific 72.22
practical clinical use 72.24
value of 72.13–14, 72.16
Quality of Reporting of Meta-Analyses 7.7, 7.16
Quantiferon-TB Gold 31.6
quartz *27.17*
quaternary ammonium compounds 25.20, 73.14
quaternium-15 *26.50*, 26.51
Questionnaire on Experience with Skin complaints (QES) 72.20
quetiapine *64.52*, 75.83
quills 2.3
quinacrine *see* mepacrine
Quincke's oedema *see* angio-oedema
quinidine, adverse effects 75.90
hypermelanosis 58.30
quinine
adverse effects 75.71, 75.159
hypermelanosis 58.30
lichenoid tissue reaction 41.24
rash 37.27
as food additive 75.159
as photoallergen 26.24
quinizarin 44.4
quinoline mix 68.24
quinolone antibiotics 74.41, 75.59–60
quinones 26.25
QUOROM (Quality of Reporting of Meta-Analyses) 7.7, 7.16

R

R-spondin family 3.5, 3.14
13-*cis*-RA *see* isotretinoin
Rab protein, Rab27A, melanosome transfer 58.4
Rab3a, melanosome transfer to keratinocytes 58.4
rabbit botfly 38.9
rabbit-ear model 42.23, 42.73
rabbitfish 38.59
rabies 38.61
vaccination
alopecia after in dogs 2.18
dermatomyositis after, in dogs 2.15
Rabson–Mendenhall syndrome 45.63
Rac, melanocyte dendrite formation 58.4
race **9.1–19**
acanthosis nigricans and 9.15
acne and 9.4–5, 42.19, 42.24
acne nuchae keloidalis and 9.9
actinic prurigo and 9.19
adult T-cell leukaemia/lymphoma and 9.13
ainhum and 9.12–13
allergic contact dermatitis and 9.13, 26.8
atopic dermatitis and 9.13
bacterial skin flora and 30.3–4
basal cell carcinoma and 9.18
Candida paronychia and 9.18
capsaicin dermatitis and 9.13
cellulitis and 9.18
cerumen and 68.2
classification 9.1, 9.2
contact dermatitis and 9.13
definitions 9.1
dermatosis papulosa nigra and 9.11
dermatosis pustulosa cruris et atrophicans and 9.13
discoid lupus erythematosus and 9.15
dissecting cellulitis and 9.9–10
effect on normal bacterial skin flora 30.3–4
epidermal structure and function and 9.2
erythema dyschromicum perstans and 9.16–17
facial Afro-Caribbean childhood eruption and 9.12
focal acral hyperkeratosis and 9.10
fungal infection and 9.12
hair and 9.2, 66.13
hair styling practices and 9.7
HTLV-1 associated infective dermatitis and 9.12
idiopathic guttate hypopigmentation and 9.11
Kaposi's sarcoma and 9.18–19
keloids and 9.15
keratoderma and 9.10
keratosis punctata and 9.10
knuckle pads and 9.15
lichen nitidus and 9.5
lichen planus and 9.5
lichen simplex chronicus and 9.13–14
lichen striatus and 9.5
Lyme disease and 9.18
malignant melanoma and 9.18
melanocytic naevi and 9.17
melanosomes differences *3.21*, 9.2, 58.10
melasma and 9.16
Mongolian spot and 9.11
morphoea and 9.14
mudi-chood and 9.7–8
mycosis fungoides and 9.7
naevus of Ito and 9.17
naevus of Ota and 9.17
nail pigmentation and 65.39
oculocutaneous albinism and 9.16
otitis externa and 68.20–1
papuloerythroderma of Ofuji and 9.13
pemphigus foliaceus and 9.14
pemphigus vulgaris and 9.14
photodermatoses and 9.19
pigmentation and 9.1, 58.1, 58.10
pigmentation significance 58.9
pityriasis lichenoides chronica and 9.5–6
pityriasis rosea and 9.6
pityriasis rotunda and 9.10
pityriasis versicolor and 9.6
podoconiosis and 9.8
polymorphic light eruption and 9.19
primary cutaneous amyloidosis and 9.17
progressive macular hypomelanosis and 9.16
pseudofolliculitis barbae and 9.9
psoriasis and 9.14
rosacea and 9.14
sarcoidosis and 9.14
seborrhoeic dermatitis and 9.6
sickle cell disease and 9.12
skin bleaching and 9.8
skin structure and function variations 9.1–4
squamous cell carcinoma and 9.18
stratum corneum variations 9.2, 9.13
syphilis and 9.6
systemic sclerosis and 9.14
tinea capitis and 9.8
transient neonatal pustular melanosis and 9.12
vascular naevi and 9.19
vitiligo and 9.6–7
vulvodynia and 9.19
warts and 9.18
radiant exposure 29.1
radiation
contaminating 29.3
electromagnetic *see* electromagnetic radiation
infrared *see* infrared radiation
ionizing *see* ionizing radiation
solar simulated (SSR) 29.5
thermal, non-melanoma skin cancer associated 52.5
ultraviolet *see* ultraviolet (UV) radiation
visible 29.1
radiation reaction *see* radiodermatitis
radical oxygen species (ROS) 12.54–6
radiculoneuropathy, herpes simplex 33.17
radio-isotope scanning 5.22
radio repair, occupational hazards 27.20
radioallergosorbent test 13.16
see also CAP fluoroimmunoassay
radiocontrast media
adverse effects 75.25, **75.150–2**
histamine liberation 22.8
radiocurability 79.3
radiodermatitis 47.52
acute 79.14–16
alopecia due to 66.53–4
chronic 66.53–4, 79.16–17
chronic, telangiectases in 79.16
loss of eccrine function in 44.18
male genital dermatology 71.18
perianal/perineal 71.90
radiofrequency 80.14
radiofrequency ablation (RFA), varicose veins 47.39
radiofrequency devices, cellulite management 46.10
radiography
foreign bodies 28.42
sarcoidosis 61.20
see also X-ray(s)
radioimmunoassay 13.19
radionecrosis 79.16–17, 79.18
radiopharmaceuticals 75.152
radioresponsiveness 79.3
radiosensitivity 79.3, *79.4*

radiotherapy
  acrodermatitis continua (of Hallopeau) 79.4
  adjuvant 79.7
  adverse effects 44.18, 62.47
    angiosarcoma 56.37, 56.38
    carcinogenesis 79.4, 79.18–19
    mucositis 69.82, 79.10
    non-melanoma skin cancer 52.5
  angiosarcoma following 56.37, 56.38
  atypical vascular proliferation following 56.41–2
  basal cell carcinoma 79.5–7, 79.8–12, 79.13
  benign disease 79.4–5, 79.18
  Bowen's disease 79.12
  choice of 79.5–7
  comparison with surgery 79.5–7
  contraindication, in naevoid basal cell carcinoma syndrome 52.7
  cutaneous T-cell lymphoma 79.13
  Darier's disease 79.4
  dermatofibrosarcoma protuberans 56.13, 79.13
  dose 79.7–8
  electron beams 79.1–2, 79.9
  eyelid 79.8–9
  face 79.10, *79.11*
  fractionation 79.3, 79.8
  Hailey–Hailey disease 79.4
  hand eczema 23.22
  immunosuppressive effects 13.25
  implants 79.2, 79.5
  infantile haemangioma 18.51–2
  inner canthus 79.9
  juvenile xanthogranuloma 55.16
  Kaposi's sarcoma 56.36, 79.13
  Kasabach–Merritt syndrome/phenomenon 18.57
  keloids 45.55, 79.4–5
  kilovoltage 79.1, *79.2*
  Langerhans' cell histiocytosis 55.13
  late sequelae 79.4
  lentigo maligna 79.12–13
  lentigo maligna melanoma 79.12–13
  lichen planus association 41.3
  lips 79.10, *79.11*
  lymph nodes, lymphoedema after 48.13
  male genital region 71.44
  malignant melanoma 54.55, 54.56, 79.12
  megavoltage 79.1
  Merkel cell carcinoma 79.13
  metastatic carcinoma 79.13
  moulds 79.2
  mycosis fungoides 57.24
  in necrobiotic xanthogranuloma 55.28
  non-melanoma skin cancer 52.5, 52.16
  palliative 79.5, *79.6*
  photon beams 79.1, *79.2*
  postoperative 79.7
  sarcoidosis 61.21
  squamous cell carcinoma 52.27, 68.31, 79.5–7, 79.8–12, 79.13
  technique 79.3
  tinea capitis 79.4
  treatment modalities 79.1–2
  treatment regimens 79.7–8
  tumour recurrence following 79.17–18
  wart treatment 33.50
  whole-brain, melanoma metastatic to brain 54.55
Raeder's syndrome 63.22
RAG-1 gene/enzyme 13.6, 13.8
RAG-2 gene/enzyme 13.6, 13.8
ragweed 26.10, 26.20, 26.75
ragwort, photosensitivity in animals and 2.23
'rain scald' (dermatophilosis), in horses 2.12
raised limb bands *see* amniotic bands/adhesions
ramipril 75.93
Ramsay–Hunt syndrome 33.26, 68.20, 69.74
  management 33.28
  zoster and 33.26
random effects models 7.9
randomization, RCTs 7.10–11
randomized controlled trials (RCT) 7.1
  applicability 7.13
  appraisal and evaluation 7.11–15
    importance of results 7.12–13
    individual trials 7.10–13
    results applied to patients 7.13
  masking 7.11
  outcome variables 7.12
  randomization 7.10–11
  surrogate endpoints 7.12
  validity 7.10–13
  value of 7.3, 7.4
  see also systematic reviews
ranitidine
  adverse effect 75.150
  in hand eczema 23.22
  sebaceous gland activity inhibition 42.16
  in urticaria 22.28
RANTES 13.4
  in atopic dermatitis 24.4
  in HIV infection 35.4, 35.18
  in lichen planus 41.1
  thymus and activation-regulated chemokine (TARC/CCL17) 12.33, 12.44, 12.46
  in vasculitis 50.10
  vitamin D action 73.43
ranula (mucocele) 69.22, *69.65*, 69.84, **69.110**
Ranunculus 25.21
RAPADALINO syndrome 15.80
rapamycin (sirolimus) 13.25, 74.25, 75.138
  mammalian target of rapamycin (mTOR) 74.5
rapeseed oil, toxic oil epidemic syndrome (Spain) 51.82
raphe cysts, male genital region 71.35
rapid plasma reagin (RPR) test 34.19
Rapp–Hodgkin syndrome 15.51
Rapunzel syndrome 64.32
RAR-selective retinoids 20.27
RARs *see* retinoic acid receptors (RARs)
RAS (recurrent aphthous stomatitis) **69.44–6,** 69.48
RASA1 gene mutation 47.21
rash(es)
  in actinic prurigo 29.14
  in adult T-cell leukaemia–lymphoma 33.64
  in chronic actinic dermatitis 29.17
  in congenital syphilis 34.16
  in coxsackievirus infections 33.71–2
  in echovirus infections 33.73
  in erythema infectiosum (fifth disease) 33.62, 33.63
  factitious 64.42–3
  in HIV infection 35.10
  in infectious mononucleosis 33.30
  in Lassa fever 33.69
  macular *33.4*
  maculopapular 5.7, *33.4*
  maculopapular–petechial *33.4*
  maculopapular–vesicular *33.4*
  in Marburg and Ebola diseases 33.70
  in measles 33.75
  papular *33.4*
  papulovesicular *33.4*
  papulovesiculopustular *33.4*
  in pityriasis rosea 33.79
  in polymorphic light eruption (PLE) 29.11, 29.23
  roseolar (macular syphilide) 34.8–10
  in rubella 33.70
  in scarlet fever 30.34
  in secondary syphilis 34.8, 34.10, 34.11
  urticarial, viral infections *33.4*
  in varicella 33.23, 33.24
  vesicular, viral infections *33.4*
  vesiculopapular *33.4*
  in viral infections 33.3–4, *33.4*
RAST 13.16
  see also CAP fluoroimmunoassay
rat-bite fevers 30.67
rat skin transcutaneous electrical resistance test 25.9
Raynaud's phenomenon 63.4, 74.51–2
  aetiology and pathology 28.68–9
  anticentromere antibodies 51.103
  clinical features 28.69–70
  cold-induced injury **28.68–71**
  development of SLE 51.36
  diagnosis 28.70
  differential diagnosis 28.57–8, 28.66, 51.106
  following fish stings 38.59
  hyperhidrosis and 44.8
  occupational, vibration white finger 27.17
  onset of systemic sclerosis 51.94
  paraneoplastic 62.41
  telangiectases in 47.14
  treatment 28.70
    prostacyclin analogue iloprost 51.108
  vascular lesions 51.132
Raynaud's syndrome, oesophageal aperistalsis 51.99
RCTs *see* randomized controlled trials (RCT)
reactive oxygen species (ROS)
  dithranol mechanism of action 73.29
  skin ageing and 80.2
  UVA-1 forming 29.1
reactive perforating collagenosis 19.89, 45.63, 45.64–5, 69.129
reboxetine *64.51*
recessive alleles 15.3–4
RecQ helicase 58.23–4
RECQL4 gene 15.80–1
rectal carcinoid tumours 43.18
rectum, syphilitic lesions 34.7, 34.8
recurrent aphthous stomatitis **69.44–6,** 69.48
recurrent focal palmar peeling 23.19
recurrent scarlatiniform erythema 30.34
red, white and blue sign 38.32
red-back spider 38.31
red bug 38.50
red-cell aplasia 33.63
Red Cross 72.31
red fingers syndrome 62.59
red-man syndrome 23.48–9, 75.60
red poultry mite 38.51
red sponge 38.59
Redd African padauk *26.81*
redox status, rosacea 43.2
reducing agents as irritants 25.21
5α-reductase 42.3, 42.10, 44.18, 66.14, 66.15
  acne aetiology and 42.21, 42.23
  deficiency 66.14
  isoforms 42.10, 42.21, 42.23
  in sebocytes 42.10
5α-reductase inhibitors
  in hirsutism 66.88
  isotretinoin as 42.16
  progesterone as 42.11, 42.16
Reduviidae 37.31, 38.25–6
Reed syndrome (hereditary leiomyomatosis and renal cell carcinoma syndrome) 2.17, 62.29, 62.69
Reed–Sternberg cells, in Hodgkin's disease 57.29
Reed–Sternberg-like cells 57.30
referrals
  psychiatry 64.15
  rates, for specialist care 6.15
reflex sympathetic dystrophy *see* complex regional pain syndrome (CRPS)
reflux 47.25, 47.35
  venous *see* venous reflux
refractory errors, in albinism 58.40
Refsum's disease 19.3, 19.45–7
regional diversity of skin 3.3
regional ileitis *see* Crohn's disease
registers of skin disease 6.6
regulated upon activation normal T cell expressed and secreted *see* RANTES
Reiter's syndrome 34.30, *34.31*, 50.62
  bone and joint involvement *62.101*, 62.105
  female genital involvement 71.59
  HIV infection 35.17
  male genital involvement 71.18
  nail involvement 65.25
  ocular involvement *67.25*
  oral involvement 69.71, *69.118*
rejuvenation techniques **80.4–14**
relapsing fever **30.64**
relapsing linear acantholytic linear dermatosis *see* Hailey–Hailey disease
relapsing polychondritis **45.42–4**
  bone and joint involvement 62.104
  following ear piercing 68.8
  neutrophilic dermatoses associated 50.91–2
  panniculitis with 46.32
  paraneoplastic 62.40
  respiratory tract involvement 62.82
  vasculitis and 50.48–9, 50.54, 50.91–2
relative risk 6.18
relaxin 3.41
relaxin family peptide receptor-1 (RFPR1) 3.41
REM syndrome 59.25
renal disease **62.68–75**
  ichthyosis and 19.61
  purpura due to 49.18
  in SLE 51.44
  in systemic sclerosis 51.101
  'wire-loop' lesions 51.34
  see also kidneys, disorders; *specific diseases*
renal failure 27.11
  calcifying panniculitis with 46.16–17
  chronic *see* chronic renal failure
  cutaneous signs 62.72–3
  end-stage, restless legs syndrome 47.12
  pigmentation changes 58.27
renal transplantation *see* kidneys, transplantation
renal tumours, genetics 15.23
reoviruses *33.3*
repeatability 6.19
repifermin 14.27
reports, histopathology 10.36
reptiles
  glands 2.4
  pigment cells 2.6
  scales and skin 2.3
  skin infections 2.12
research, health services **6.14–17**
research papers, appraisal and evaluation *7.10*, *7.13*, *7.15*, 7.16–23
reserpine, systemic sclerosis 51.108
  contraindications 51.108
resins
  acrylic 26.72–3
  as allergens 26.69–74
  epoxy
    allergic contact dermatitis and *26.16*, 26.20, 26.70–2
    depigmentation due to 26.26
    filter-paper test 27.8
    scleroderma-like lesions 51.80
  formaldehyde 26.49, 26.65, 26.68, 26.69, 26.73–4
resol 26.73
resorcin, acne vulgaris treatment 42.43
resorcinol *25.19*, 73.13, 75.166
  shampoo 73.13
resource allocation 72.13
respiratory papillomatosis 33.47
respiratory syncytial virus (RSV) 17.58, 33.75, **33.76**

respiratory tract
  blastomycosis 36.84
  coccidioidomycosis 36.85
  cryptococcosis 36.89, 36.90
  disorders **62.80–5**
    see also specific disorders
  drugs acting on 75.98–9
  histoplasmosis 36.82
  in infantile haemangioma 18.46
  infections 62.80
    herpes simplex virus 33.17
  lymphoid structure 13.9
  neutrophilic dermatoses 50.81, *50.82*
  paracoccidioidomycosis 36.87
  pyoderma gangrenosum 50.70
  sarcoidosis 61.6, 61.7
  in SLE 51.43, 62.82
  in Wegener's granulomatosis 50.39–40
  xanthoma disseminatum 55.21
  see also lungs
rest pain 47.2, 47.7
  management 47.6
restaurant personnel, occupational hazards 27.20
resting stress lines (Langer's lines) 77.2, 77.13
restless legs syndrome **47.11–12, 63.24–5**
restriction enzymes 11.4
restriction fragment length polymorphism (RFLP) 15.7, 32.1
restrictive dermopathy 17.20, 45.51
Restylane 80.6
RET gene 62.24
retapamulin 73.10
rete ridges 3.16
  ageing and 8.23
  glucocorticoid-induced atrophy 45.4
  lichen nitidus 41.22
  saw-tooth appearance in lichen planus 41.4
  warts (common/plantar) 33.41
reticular degeneration 10.38
reticular erythematous mucinoses 59.25
reticular pigmented anomaly of the flexures **15.94–5,** 58.22
reticulate acropigmentation 58.21–2
reticulate acropigmentation of Dohi **15.95,** 58.21–2
reticulate acropigmentation of Kitamura 58.21
reticulate body, *Chlamydia* 34.29
reticulin, in sarcoidosis 61.3, *61.4*
reticulocytes, occlusion due to 49.47
reticulocytoma/reticulohistiocytoma cutis *see* multicentric reticulohistiocytosis
reticuloendothelial system 12.26
  sarcoidosis 61.7
reticuloendotheliosis, non-lipid *see* Langerhans' cell histiocytosis (LCH)
reticulohistiocytoma (solitary epithelioid histiocytoma) 55.23, 55.24
reticulohistiocytoma cutis *see* multicentric reticulohistiocytosis
reticulohistiocytosis
  diffuse cutaneous 55.24
  malignant 55.32–3
  multicentric giant-cell *see* multicentric reticulohistiocytosis
reticulosis
  aleukaemic 55.32–3
  histiocytic (malignant) 55.32–3
  histiocytic medullary 55.32–3
    virus-induced 55.30–1
retiform parapsoriasis 57.58
retina
  acute retinal necrosis syndrome 33.26
  angioid streaks 45.21, 45.22
  anlage tumour *56.52–3*
  detachment 24.25
  phacomas 15.23
retinacula cutis 45.2
retinal necrosis syndrome, acute 33.26
retinitis, CMV 33.29
retinoblastoma, familial 54.48
retinochoroiditis 61.7
retinoic acid (tretinoin; vitamin A acid) 73.35, **73.35–6**
  in acne 42.39–40, 42.40
  in actinic elastosis 45.27
  adverse effects 42.49, 75.113, 75.166
    retinoid dermatitis due to 73.27
  depigmenting action 73.27
  in dystrophic EB 39.29
  formulations 42.39
  hair regrowth and 73.39
  hypermelanosis treatment 58.39
  isomers 73.35
  metabolism blocking agents 20.42–3, 74.37
  in molluscum contagiosum 33.12
  photocarcinogenesis control 29.7
  in prevention of ageing 80.3
  receptors 73.35
  for solar lentiginosis 73.26
  in systemic sclerosis 51.108
  topical 57.23, 73.34, **73.35–6,** 75.166
    in acne vulgaris 73.34
    in chemically-induced skin tumours 73.36
    indications 73.35–6
    in keloids 45.55
    in osteoma cutis 42.78
  wart treatment 33.49
9-*cis*-retinoic acid (13cRA) *see* alitretinoin (9-cis-retinoic acid)
13-*cis*-retinoic acid (13cRA), squamous cell carcinoma 52.28
retinoic acid metabolism blocking agents 20.42–3, 74.37
retinoic acid nuclear receptors (RAR, RXR) 3.39
retinoic acid receptor (RAR)-selective retinoids 20.27
retinoic acid receptors (RARs) 42.14, 73.35, 73.36, 73.37
  acne treatment and 42.40, 42.58
  RAR-α and RAR-β 42.40, 42.58
retinoic acid-responsive elements (RARE) 3.39
retinoid acid-binding protein (RAR) 42.40
retinoid dermatitis 73.27
retinoid X receptors (RXRs) 73.35, 73.36
  hair growth and 66.11
retinoids 20.27, 20.37–8, **73.34–9, 74.33–8**
  adverse effects 74.37, **75.108–13**
    on cancer suppression 74.33
    on cell differentiation 74.33
    effects on mood 64.49, 75.112–13
    hair loss 66.29–30
    on neutrophil migration 74.33
    photosensitivity 42.50
    systemic 75.111–12
    teratogenicity 42.50, 72.28, 74.38
  binding proteins and regulation 73.34–5
  chemical peels and 80.9
  collagen gene expression control 3.39
  endogenous 73.34–5
    naturally occurring 73.35
    see also retinol
  in epidermodysplasia verruciformis 33.58
  in hand eczema 23.22
  in hidradenitis suppurativa 30.81
  in HPV-associated dysplasia/neoplasia 33.55
  immunostimulation 74.33
  mechanism of action 73.34–5
  metabolism 73.35
  in naevoid basal cell carcinoma syndrome 52.8
  in ocular rosacea 43.7
  oral
    non-melanoma skin cancer 52.18
    ocular side effects 67.31
    wart treatment 33.50
  photosensitivity with 42.50
  in pregnancy 74.38, 75.113
  in psoriatic nail involvement 65.26
  RAR-selective 20.27
  receptors and binding to 73.35
  safety precautions 74.37
  sebaceous gland activity control 42.14–15
  synthetic 73.34, 73.35
  systemic
    epidermolytic/non-epidermolytic epidermal naevi 18.7
    teratogenicity 73.35
    see also retinoids, oral
  teratogenicity 42.50, 72.28, 73.35, 74.38
  topical 57.23
    in acne 42.39–41, 42.48, 73.34, 73.35, 73.36
    in chloracne 42.77
    indications 73.34
    mechanism of action 42.40
retinol **73.34, 73.35**
  allergy to *26.46*
  cosmetic uses 73.35
  deficiency, wound healing and 14.18
  excess 66.29
  intoxication 75.108
  metabolism 73.35
  in prevention of ageing 80.3
  topical application 73.35
  see also vitamin A
retinopathy, antimalarials causing 67.31
retrobulbar neuritis, in sarcoidosis 61.7
retroviral entry inhibitors 74.50
retroviruses *33.2*, **33.64–6**
  HTLV-1-associated adult T-cell leukaemia–lymphoma 57.37–8
  replication 33.64
  Tax protein 33.64
  see also HIV infection
revascularization
  claudication 47.5–6
  rest pain and gangrene 47.6
reverse genetics 11.1
reverse transcriptase 11.6, 33.1, 33.64
reverse transcription, HIV 35.3, 35.6
reverse transcription polymerase chain reaction 11.6
reversible posterior leukoencephalopathy syndrome 50.47
rexinoids 73.36
Reye's syndrome, in varicella 33.25
Reynold's syndrome 62.62
RFLP (restriction fragment length polymorphism) 15.7, 32.1
rhabdomyocytes, microscopy 10.35
rhabdomyolysis, in varicella 33.25
rhabdomyoma 56.57
  cardiac 15.23
  fetal 18.37
  oral 69.112
rhabdomyosarcoma
  cutaneous 56.57
  ear 68.34
  oral 69.112
rhabdoviruses *33.3*
rhagades 34.15, 69.122
  in Hailey-Hailey disease 39.34
Rhagionidae 38.6
rheography, light-reflection 47.36
rheumatic fever 51.138, 62.78
  erythema marginatum in 51.138, 62.107
  streptococcal infection and 30.12
rheumatism, fibroblastic 62.103
rheumatoid arthritis 62.103
  cutaneous atrophy and 45.3
  dermatological manifestations 51.130–3
  leg ulceration associated 47.55
  lymphoedema in 48.13
  pigmentation changes 58.26
  pustular neutrophilic panniculitis 46.32
  treatment
    flushing associated 43.15
    TNF antagonists 74.7
  vascular lesions 51.132
  vasculitis and 50.48
rheumatoid disease, dermatological manifestations 51.130–3
  fibroblastic rheumatism 51.133
  pseudoscleroderma tous changes 51.130
rheumatoid factor 13.10
  activity of type II/III cryoglobulins 49.32
  detection 13.20–1
  in syphilis 34.21
rheumatoid neutrophilic dermatosis 51.131
rheumatoid nodules 51.130–2
rheumatoid ulcers 47.55
rhinitis, congenital syphilis 34.15
rhino mouse model 42.23
rhinoceros 2.3
Rhinocladiella aquaspersa 36.75
rhinoentomophthoromycosis 36.78–9
Rhinoestrus 38.9
rhinophyma **43.9–10**
  electrosurgery 77.46
  giant, symmetrical lipomatosis with 46.46
  laser therapy 78.14
  malignancy association 43.9
  treatment 43.6
rhinoscleroma **30.51–3,** 69.121
rhinosporidiosis **36.78**
Rhinosporidium 36.78
Rhipicephalus 38.34, 38.35
Rhizoglyphus 38.47
Rhizomucor 36.91
Rhizopus 36.91, 68.27
  vessel-invasive infection 49.35
Rho, melanocyte dendrite formation 58.4
rhodamine RB200 10.12
rhodium 26.40
Rhodnius prolixus 37.31
rhodopsin, formation reduction 67.31
Rhodotorula 69.105
Rhus 26.1
rhytides 80.2
ribavirin
  adverse effects 75.67
  in cryoglobulinaemic vasculitis 50.25
  Lassa fever 33.69
  measles 33.76
riboflavinaemia, pigmentation 58.53
riboflavine 59.62
RICE therapy 38.32
Richner–Hanhart oculocutaneous syndrome 19.95, 19.111–12, 59.97
rickets *69.116, 69.117*
  vitamin D-resistant 66.11
Rickettisa akari 30.74
Rickettisa conori 30.73
Rickettisa rickettsii 30.73
Rickettisa tsutsugamushi 30.74
rickettsial infections **30.72–4,** 38.35, 38.51
  vasculitis and 50.55
rickettsialpox 30.74
Riehl's melanosis 58.35
rifampicin 74.44, 74.45
  adverse effects 31.27, **75.62**
  in leprosy 32.16, 32.17
  resistance to 31.27, 32.1–2
  in tuberculosis 31.27
rifamycins 74.44
Rift Valley fever *33.67*, 33.70
Riga–Fede disease 69.43
rilanocept, cryopyrin-associated autoinflammatory syndromes 74.11
Riley–Day syndrome (type III hereditary sensory autonomic neuropathy) 44.7, 62.80, 63.18
Riley–Smith syndrome (Bannayan–Riley–Ruvalcaba syndrome) 18.60, 62.26, 62.57, 69.38
ring block 77.10
  for nail biopsy 65.42
ringworm
  beard 36.28–9, 36.49
  body *see* tinea corporis (tinea circinata)
  face *see* tinea faciei (tinea faciale)

foot *see* tinea pedis
groin *see* tinea cruris
hand (tinea manuum) 26.29, 36.32–3, 36.50
nails (tinea unguium) 36.34–5, 36.50
scalp *see* tinea capitis (tinea tonsurans)
steroid-modified *see* tinea incognito
treatment and management 36.46–51
rio-palisander *26.81*
RISC (RNA-induced silencing complex) 11.8, *11.9*
risk
attributable 6.18
relative 6.18
risk factors, for skin disease **6.11–13,** 6.18
causative 6.11
see also individual risk factors
risk–benefit analysis 72.3–4
risperidone 64.16, *64.52*
ritonavir, adverse effects 35.22
rituximab 13.25
adverse effects 75.146
in angio-oedema 22.22
in cryoglobulinaemic vasculitis 50.25
in cutaneous small vessel vasculitis 50.16
in dermatomyositis 74.10
dosing schedule 74.9
indications 74.10
in pemphigus 40.12, 74.9
in vasculitides 74.10
in Wegener's granulomatosis 50.41
river blindness *see* onchocerciasis
RLS (restless legs syndrome) **47.11–12, 63.24–5**
RNA
amplification, syphilis diagnosis 34.19
double-stranded (dsRNA) 11.7
fetal 16.9–10
interference (RNAi) 11.7, *11.9*
manipulation 11.4–5
microRNA (miRNA) 11.7
short hairpin (shRNA) 11.10
small interfering (siRNA) 11.7, *11.9*, 11.10
structure and function 11.2–3
RNA-induced silencing complex 11.7, *11.9*
RNA interference (RNAi) 11.7, *11.9*
RNA polymerases 11.3, 11.6
RNA viruses *see* virus(es), RNA
Ro antigen 13.19
road workers, occupational hazards 27.20
Roberts syndrome 18.70, 66.61
Robi comb 38.20
Robinson syndrome 15.35
Rochalimea see Bartonella
Rochalimea henselae see Bartonella henselae
Rocky Mountain spotted fever 30.73, 38.34, 38.35
purpura 49.20
rocuronium 75.153
rodent bites 38.61
rodent botfly 38.9
rodent ulcer *see* basal cell carcinoma (BCC)
Romaña's sign 37.32
Rombo syndrome 52.9
rope sign 62.103–4
ropinirole 63.25
ropivacaine 77.10
in nail biopsy 65.42
roquinimex 75.148
ROS *see* reactive oxygen species (ROS)
rosacea **43.1–9**
antimicrobial peptide expression increased 3.16
cathelicidin peptides, pathogenic role 12.5
clinical features 43.1, 43.3
complications 43.3–4
corticosteroid-induced **43.10,** *73.19*
definition 43.1
Demodex and 38.53, 43.2–3, 43.5, 43.6
differential diagnosis 43.5, 51.9, 61.5
acne vs 42.36, 43.5
perioral dermatitis vs 43.11
epidemiology 43.1
erythema 43.3, *43.4*, 43.6
erythematotelangiectatic 43.1, 43.2, 43.6
eye involvement 43.4, 43.5, 43.7
flushing 43.1, 43.2, 43.3
aggravating factors 43.3
management 43.6
gastrointestinal symptoms with 43.2
granulomatous 43.2, *43.5*
acne agminata as variant 43.13
acne vs 42.37
Helicobacter pylori role in 43.2
eradication effect 43.2, 43.6, 43.7
histopathology 43.4–5
in HIV infection 43.3
inflammatory lesions 43.1, 43.3, 43.4, *43.5*
inflammatory papulopustular *43.4*
lymphoedema and 43.4, 48.13, 48.16
management 43.6–7
migraine association 43.1
nomenclature 43.1
ocular *see* ocular rosacea
papulopustular 43.2, *43.4*, 43.5, **43.6**
pathogenesis 43.1–3
peau d'orange 43.3
prognosis 43.5
progression 43.3
race and 9.14
salivary gland involvement 43.4
sarcoidal reaction in 61.23
seborrhoeic dermatitis and 23.29
severity assessment 72.10
solid facial oedema 42.74
steroid **43.10,** *73.19*
telangiectasia 43.4, 43.6
treatment 43.5–6
antibiotics 43.2, 43.6, 43.7
isotretinoin 43.6, 74.34
metronidazole 43.3, 43.6
topical antibiotics 73.9, 73.10
rosacea fulminans *see* pyoderma faciale (rosacea fulminans)
Rosai–Dorfman disease *see* sinus histiocytosis with massive lymphadenopathy (SHML; Rosai–Dorfman disease)
rose spots 30.48
Roselli–Gulienetti syndrome 15.33
Rosenberg Self-esteem Scale 64.7
Rosenthal–Kloepfer syndrome 15.89
roseola infantum 33.32
roseolar rash (macular syphilide) 34.8–10
Ross River virus 33.66–7, *33.67*
Ross's syndrome 44.11, 44.13–14
rotenone 38.41
Roth spots 62.78
Rothman–Makai syndrome 46.15
Rothmund–Thomson syndrome *see* poikiloderma congenitale
rotigotine 63.25
roustabout's breast 70.15
rove beetles 38.26–7
Rowell's syndrome 51.14, 76.7
RSPO4 gene 11.9, *11.10*
RT-PCR 11.6
RTS (Rothmund–Thomson syndrome) *see* poikiloderma congenitale
rubber
as allergen 26.63–5
dermatitis due to 71.17
in footwear 26.63, 26.68–9
sensitizers in *26.64*
sources of exposure 26.63
synthetic 26.65
vulcanization 26.63
see also latex
rubber dermatitis, male genital dermatology 71.17
rubber workers, occupational hazards 27.20
rubbing (the skin) 5.18, 64.27
in response to pruritus 21.5
rubella **33.70–1**
aetiology and clinical features 33.70–1
congenital 17.41–2, 18.2, 33.71
diagnosis, prophylaxis 33.71
MMR vaccination 33.71
in pregnancy 33.71
TORCH syndrome 33.76–7
rubeosis 59.77
Rubinstein–Taybi syndrome **15.92–3,** 18.70
Rud's syndrome 19.11
rue 26.16
Ruffini corpuscles 4.9, *4.10*
Ruffini organs 3.15
rule of hand, quantity of topical therapy 73.3
Rule of Nines 14.10, 28.77, *28.78*
Rule of Tens 72.14
ruminations, depressive 64.12
Rumpel–Leede sign 49.5
rupatadine 74.31–2
Russell bodies 30.52
Russell's sign 64.22
rust-red flour beetle 38.27
rusters 28.93
Rutaceae, phytophotodermatitis due to 29.21
rutosides 47.39–40, 75.98
Ruvalcaba–Myhre–Smith syndrome (Bannayan–Riley–Ruvalcaba syndrome) 18.60, 62.26, 62.57, 69.38
RXRs *see* retinoid X receptors (RXRs)

S
S100 protein 10.21–2, 10.24
juvenile xanthogranuloma 55.15–16
Langerhans' cell histiocytosis cells 55.9
melanoma vs Paget's disease of nipple 53.39
sinus histiocytosis with massive lymphadenopathy 55.29
S100A6, expressed by dermal dendrocytes 55.4
S100beta protein, melanoma 54.51
SAA (serum amyloid A) 13.4, 13.19
Sabinas brittle hair and mental deficiency syndrome 15.51
Saccharomyces 69.105
sacculus rotundus 13.7
sacral herpes zoster *see* zoster
SACRAL syndrome 18.47, 18.96
SADBE *see* squaric acid dibutylester
saddle-nose deformity 34.14, 34.17
Saethre–Chotzen syndrome **15.91**
SAHA syndrome 42.73, 66.82
St John's wort 72.29, 75.160, 75.162
Saksenaea vasiformis 36.91
salabrasion of tattoos 58.59
Salamon syndrome 15.56
salbutamol 75.98
Salford Psoriasis Index 64.10, 72.9, 72.20
salicylamide 75.73
salicylic acid
in acne vulgaris 42.43, 42.68
adverse effects 75.166
as allergen 26.62
application and cautions 33.48
dithranol with 73.30
in hand eczema 23.22
as irritant *25.19*
isotretinoin interaction 42.65
in molluscum contagiosum 33.12
as penetration enhancer 73.7
in pityriasis amiantacea 66.57
in pityriasis capitis 66.57
topical 5-FU with 73.23
topical corticosteroids with 73.20
wart treatment 33.48
salicylic acid peel, in acne vulgaris 42.68
salicylism 19.8, 75.166
saline, as local anaesthetic 77.11
saliva 69.3
salivary gland examination 69.5
salivary gland involvement, rosacea 43.4
salivary gland swelling, HIV infection 35.42
salmeterol 75.98
salmon patch 18.62–3
Salmonella 30.47–8
aortitis due to 50.55
salt-split, lamina lucida 40.47
Salticidae 38.32
saltpetre disease 45.25
sampling error 6.18
San Joaquin valley fever *see* coccidioidomycosis
sand-worm eruption *see* larva migrans, cutaneous
sandflies 37.33, 37.39, 38.2, 38.5, 38.7
sandfly fever 38.5
Sandhoff disease 44.18
Sanfilippo's syndrome *see* mucopolysaccharidoses
santos palisander *26.81*
SAP (SLAM-associated protein) 13.6
SAP (serum amyloid P) component 59.42–3
saphenofemoral junction (SFJ) 47.25
saphenous nerve, damage 47.38
saphenous vein
greater (GSV) 47.25, 47.30, 47.38
ligation and stripping 47.38
short (SSV) 47.25, 47.30, 47.39
SAPHO syndrome 20.17, 42.85, 62.101
saquinavir 75.68
photosensitivity due to 35.22
sarcoid
equine 2.21–2
micropapular of face, acne vs 42.37
sarcoid-like granulomatous dermatitis (granulomatous perioral dermatitis) 43.12, **43.13**
'sarcoid of Darier–Roussy' 61.13
sarcoidal reactions 61.13, 61.21–3
sarcoidosis **61.1–23**
Addison's disease and 61.17
aetiology 61.2–3
alopecia and 61.9, 61.14
associated diseases 61.17–18
bone and joint involvement 61.6–7, *61.11*, *62.101*, 62.104
breast 70.12, 70.14
cardiac involvement 61.7, 62.78
childhood 61.16
chronic urticaria and 61.17
connective tissue disorders/disease and 61.17
course and prognosis 61.18–19
Crohn's disease and 61.23
Cushing's syndrome/disease and 61.17
cutaneous **61.8–17**
angiolupoid 61.9
annular 61.9
atrophic 61.14
classification 61.8
clinical features 61.8–9
erythrodermic 61.14
hyperpigmentation in 61.14
hypopigmentation in 61.14
ichthyosiform 61.14
lichenoid 61.14, *61.15*
lupoid 61.14
lupus erythematosus-like 61.14
maculopapular and erythematous 61.10, *61.11*
nodular 61.10, *61.12*
papular (small nodular) 61.10, *61.12*
plaque 61.10, *61.12*, *61.13*
pruriginous 61.14
pseudotumoral 61.14
psoriasiform 61.14
ulcerated 61.16
verrucose 61.16
definition 61.1
diabetes insipidus and 61.7, 61.17
differential diagnosis 61.5
ear involvement 61.9, 68.17
early/intermediate/late 61.6

with endocrine autoimmune conditions 62.13
epidemiology 61.2
erythema nodosum and 50.83
extrapulmonary manifestations 61.6
general symptoms 61.6
genetic and familial factors 61.3
gout and 61.18
granuloma annulare and 60.9, 61.17
Hashimoto's thyroiditis and 61.17
hepatic involvement 61.7–8
histological features *61.5*
histopathology 61.3–4
history 61.1–2
HIV infection and 61.6
hypercalciuria and hypercalcaemia in 61.8
hyperthyroidism and 61.17
hypomelanosis in 58.52
hypothyroidism and 61.17
immunology 61.5–6
inclusion bodies 61.4
infection and 61.17
investigations 61.19–20
leg ulceration 47.55
lip involvement 69.129
localization to tattoos 58.58
main features 61.1
malignant disease and 61.17
mortality 61.19
mucosal involvement 61.15
muscle involvement 61.7
myxoedema and 61.17
nail involvement *61.11*, 61.15
nasal
rosacea vs 43.5
see also lupus pernio
necrobiosis lipoidica and 61.17, 61.23
nervous system involvement 61.7
ocular involvement 61.7, *67.25*
mucous membrane pemphigoid vs 67.20
oral involvement 69.109, *69.119*
paraneoplastic 62.40
porphyria cutanea tarda and 61.18
pregnancy and 61.8
primary biliary cirrhosis and 61.18
psoriasis and 61.18
pulmonary 61.6, 61.7
pyoderma gangrenosum and 61.18
race and 9.14
renal involvement 61.7, 62.71
respiratory tract involvement 62.83
reticuloendothelial involvement 61.7
scalp 66.5
scar 61.10, 61.12–13
staging 61.6
subcutaneous 61.13–14
syphilis and 61.18
treatment 61.20–1
methotrexate 74.20
TNF antagonists 74.7
vasculitis and 61.17
sarcoidosis–lymphoma syndrome 61.17, 62.40
sarcoids, feline 2.22
sarcoma
(acral) myxoinflammatory fibroblastic 56.15
clear cell 56.53–4
epithelioid 56.60–1
Ewing's, extraosseous 56.54
follicular dendritic cell 55.31
granulocytic 69.57
histiocytic 55.31
interdigitating dendritic cell 55.31
Kaposi *see* Kaposi's sarcoma
Langerhans' cell 55.31
low-grade fibromyxoid 56.22–3
proximal-type epithelioid 56.61
see also specific forms of sarcoma
Sarcophaga 38.8
Sarcophagidae 38.8
Sarcoptes scabiei 37.1, 38.36–7, 38.43, 38.46
see also scabies
Sarcoptes scabiei var. *canis* 2.10
sarcoptic mange 2.10, 38.36, 38.46
Sarcoptidae 38.36–46
see also scabies
sartans *see* angiotensin II receptor antagonists
Satchmo's syndrome 28.26
saw-toothing 10.41
sawah itch 37.22
SC phocomelia (Roberts syndrome) 18.70
scab 14.10, 77.17
definition 5.7
scabicides 38.41–2, 38.44
scabies **38.36–46**
animal 38.46
breast 70.17
canine 38.4
clinical features 38.38–40
crusted (Norwegian) 38.2, 38.37, 38.39, **38.43–6**
erythroderma and 23.48
keratoderma caused by 19.117
diagnosis 38.40–1
differential diagnosis 24.26, 26.29, 26.30
elderly people 8.29, 38.40
epidemiology 6.2, 38.37–8
feline 2.10
hands 25.15, *25.16*
HIV infection and 35.36
identification of mites 5.20
immunology 38.38
in infancy and childhood 38.39–40, 38.42
institutional outbreaks 38.44–5
keratoderma caused by 19.117
male genital region 71.34
morphology and biology of mite 38.36–7
Panama 6.2, 6.3
persistent nodules 38.42
prevention 6.3
syphilis vs 34.7
treatment 38.41–3, 73.13–14
scabies incognito 38.39
scalded skin syndrome *see* toxic epidermal necrolysis (TEN)
scalds
wound management 28.84–5
see also burns
scale, definition 5.7
scales
bird 2.3
elasmoid 2.2
fish 2.2
placoid 2.2
reptile 2.3
scalp
allergic contact dermatitis 26.17–18
aplasia cutis congenita
with epidermal naevi 18.100
with limb reduction abnormalities 18.68, 18.99–100
non-syndromic 18.98–9
apocrine tubular adenoma 53.21
biopsy 10.32, 10.43
in androgenetic alopecia 66.23
in chronic telogen effluvium 66.31
in cicatricial alopecia 66.39
in folliculitis decalvans 66.47
in trichobezoar 64.32
cellulitis
isotretinoin 74.34
see also perifolliculitis capitis abscedens et suffodiens
cicatricial pemphigoid 66.49
congenital melanocytic naevus *54.12*
crusted scabies 38.44
cylindroma 53.28
discoid lupus erythematosus 66.43–5
dissecting cellulitis 42.74
isotretinoin treatment 42.62
see also perifolliculitis capitis abscedens et suffodiens
dissecting folliculitis 42.33, 42.74
dysaesthesia 63.23
dystrophic EB 39.18
erosive pustular dermatosis 66.49–50
follicular lichen planus 41.11
folliculitis 42.74
folliculitis decalvans 30.25, 66.46–7
granuloma annulare 66.5
hair
density 66.2
see also hair
hypotrichosis simplex 66.60
Langerhans' cell histiocytosis 55.9
lichen planopilaris 41.11, 66.39, 66.41–3
lichen planus 41.11, 66.39, 66.41–3
lichen sclerosus 66.50
lichen sclerosus et atrophicus 66.50
linear morphoea 66.48, *66.49*
medical trauma 66.53
metastases to 62.18
necrobiosis lipoidica 66.5
porokeratosis of Mibelli 66.51
post-irradiation tumours 52.20
pressure ischaemia 66.53
pruritus 38.19
psoriasis 20.14, 20.28, 23.32
ringworm *see* tinea capitis (tinea tonsurans)
sarcoidosis 66.5
scabies 38.39, 38.44
scaling disorders 66.56–7
scarring follicular keratosis 66.50–1
scleroderma 66.48
sebaceous carcinoma 53.17
sebaceous glands 42.1
seborrhoeic dermatitis 23.30, 66.56–7
syringocystadenoma papilliferum 53.19–20
thickened 66.58–9
trichilemmal cysts 52.46
scalp–ear–nipple syndrome 15.52
Scanpor tape 26.85
scar lymphoedema 48.17
scar sarcoid, in zoster 33.26
scar tissue
amputees 28.27
differential diagnosis 28.36
pressure ulcers 28.18
torture injuries 28.33
see also scar(s) and scarring
scar(s) and scarring 14.1
in acne *see* acne vulgaris
adverse/excessive 14.2
after cryotherapy for warts 33.49
assessment of severity 14.8
atrophic 45.6
dystrophic EB 39.18
generalized non-Herlitz junctional EB 39.13
treatment in acne 42.68–9
atrophic macular, in acne 42.32
cigarette paper 45.33
in syphilis 34.12, 34.13
congenital reticulate 45.6
definition 5.8, 14.7
dermabrasion 42.69
excision 42.68
features 14.7–8
hypertrophic 14.2, 14.15, **45.54–6**
acne 42.32
following surgery *77.8*, 77.15
laser therapy 78.8
treatment 73.36
treatment in acne 42.69
ice-pick, in acne 42.33
keloid *see* keloids
lymphoedema 48.17
mature 14.7
non-melanoma skin cancer after 52.11
prevention/reduction 14.8
pyoderma faciale 43.14
remodelling 14.7
sarcoidosis 61.10, 61.12–13
self-healing epitheliomas 52.9
surgical
complications *77.8*, 77.9
orientation 77.2, 77.11, 77.13
vaccinia vaccination 33.6
see also scar tissue
SCARF syndrome *45.15*
scarlet fever (scarlatina) 30.16, **30.33–5**
staphylococcal 30.7–8, 65.21
scarring *see* scar(s) and scarring
scatter factor (SF), melanocyte mitogen 58.5
scattering of light, colours in animals and 2.5
scavenger receptors (SR) 12.10
macrophage–monocyte 13.5
neutrophil 13.5
SCART1 and SCART2 12.10
SCC *see* squamous cell carcinoma (SCC)
Scedosporium apiospermum 68.25
in mycetoma *36.73*, 36.74
in otomycosis 36.17
scent glands, mammals 42.2
SCF (stem-cell factor) 3.19, 12.24, 12.31
Schamberg's disease 49.22, 49.24, 49.25
pigmentation in 58.53
treatment 49.26
Schamroth's window 65.7
Schaumann bodies 61.4
Scheie's syndrome *see* mucopolysaccharidoses (MPS)
Schilder's disease, pigmentation changes 58.26
Schimke immuno-osseous dysplasia 58.23
Schimmelpenning's syndrome 18.27
Schindler disease 59.34
Schinzel syndrome 15.55
Schinzel–Giedion midface-retraction syndrome 15.52
schistocytes 49.12
Schistosoma haematobium, female genital dermatology 71.69
schistosomiasis 37.3, **37.20–2**
perianal/perineal involvement 71.95–6
schizophrenia 64.17, 64.18
diagnostic test 43.16
schizotripanides 37.32
schizotrypanosomiasis *see* trypanosomiasis, American/South-American
Schizotrypanum cruzi (Trypanosoma cruzi) 37.31–2
Schmidt's syndrome 62.13
Schnitzler's syndrome 22.23–4, 50.53, 62.94
Schnyder's syndrome 19.71–2
Schoengastia 38.50
schoolchildren, infections (skin) 8.3
schools, epidemic hysteria 64.25–6
Schöpf–Schulz–Passarge syndrome 15.52, 19.111, 53.18
Schwann cells, microscopy 10.35
schwannoma **56.46–7**
ancient 56.46
cellular 56.47
epithelioid 56.47
glandular 56.47
malignant 56.53
melanotic 56.47
neuroblastoma-like 56.47
pacinian 56.47
pinna 68.28
plexiform 56.47
Sci-70 antibodies 51.104
SCID *see* severe combined immunodeficiency (SCID)
Scl-70 (topoisomerase 1), localized scleroderma 51.74
SCLE *see* subacute cutaneous lupus erythematosus (SCLE)
SCLE-like marginally scaled erythema 51.135
sclerae, blue 45.34, 45.40, 45.41
scleredema *see* scleroedema
scleredema diabeticorum 59.79
sclerema neonatorum 17.38–9, 46.16
scleroatrophic syndrome of Huriez 45.12
scleroatrophy, keratoderma with *19.94*, 19.99–100

scleroderma 51.64
  aetiology 51.64–5
  bone and joint involvement *62.101,* 62.103
  chemical-induced 45.51–3, 75.43
  in children 51.71
  collagen formation 12.31
  drug-induced 45.52, 75.42–3
  exogenous/iatrogenic 51.81–3
    drug-associated 51.81
  induced by silicone or paraffin implants 51.82
  occupational 27.16, *27.17*
  paraneoplastic 62.40
  pigmentation changes 58.26
  in pregnancy 8.12
  pseudoscleroderma 51.79, 51.120
  respiratory tract involvement 62.80, 62.82
  scalp 66.48
  silicone breast implants and 51.82, 70.7
  silicosis and 51.80
  skin biopsy 10.42
  systemic *see* systemic sclerosis
  Thibierge–Weissenbach type 47.14
  vasculitis and 50.48
  see also morphoea
Scleroderma domesticum 38.14
scleroderma-like lesions
  resulting from epoxy resin 51.80
  resulting from organic solvents 51.80
  resulting from pesticides 51.80
sclerodermatomyositis, in childhood 51.126
sclerodermiform reactions, vitamin K/B_{12} 28.44–5
scleroedema 51.118–20
  aetiology 51.118
  associated conditions 51.119
  of Buschke 51.79
  clinical features 51.119
  differential diagnosis 51.120
  histology 51.118
  metachromasia 51.119
  treatment 51.120
scleroedema (of Buschke) 30.12, *62.45*
scleroma (rhinoscleroma) **30.51–3,** 69.121
scleromalacia perforans 51.131
scleromyxoedema 51.79, 59.21–3, *62.45*
  bone and joint involvement *62.101,* 62.105
  respiratory tract involvement 62.83
scleromyxoedema-like illness of renal disease *see* nephrogenic systemic fibrosis
sclerosants 47.38
sclerosing lipogranuloma *see* lipogranuloma, sclerosing
sclerosing lymphangitis, male genital dermatology 71.14
sclerosis, definition 5.8
sclerotherapy
  varicose veins 47.24, 47.38
  venous malformations 18.71
sclerotic cells 36.75, 36.76
sclerotic fibroma 56.3
SCN9A gene mutations 47.9
SCOFF questionnaire 64.22
Scoggins type dyskeratosis congenita 15.36
scolex 37.24
Scolioidea 38.14
scombroid fish poisoning, flushing 43.16
scopolamine *26.46*
Scopulariopsis brevicaulis
  identification 36.8
  onychomycosis due to 36.53–4
SCORAD (scoring atopic dermatitis) 64.10
scorbutus, deficiency *see* vitamin C
Scorpiones (scorpions) 38.33
scorpionfish 38.59
SCORTEN prognosis score 76.18–19
Scotchcast boot 47.57
scratch prurigo *see* dermographism
scratching 21.1, 21.2, 21.5
  arthropod bites/stings 38.3
  measurement 21.2
  in palpation of lesions 5.18
  see also pruritus
screening 6.19
scrofuloderma 31.8, 31.10, **31.14–15,** 31.28
  ear involvement 68.20
  following BCG vaccination 31.29
  histopathology 31.9
  perianal/perineal dermatology 71.95
scrotal angiokeratomas 71.12
scrotal cancers 71.43–4
  squamous cell carcinoma 52.25
scrotal carcinoma 27.15–16, 52.4
scrotal tongue *see* tongue
scrotum
  acute 71.28
  angiokeratoma of Fordyce 18.59
  biopsy 10.32
  blue scrotum sign 62.65
  calcinosis 59.69, 71.35–6
  candidiasis 36.62
  'dirty' brown spots 35.33
  gangrene 71.15
  lichen simplex 9.14, 71.16
scrub itch 38.50–1
scrub typhus 38.50
scrumpox 33.17
scurvy *see* vitamin C, deficiency
scutula 36.27
Scyphozoa 38.56
Scytalidium
  diagnosis 36.8
  differential diagnosis 36.31
  infection caused by 9.12, 36.51–3
SD (standard deviation) 7.17
SDZ ASM 981 *see* pimecrolimus
SE (standard error) 7.18–19
sea anemones 38.55–8
sea bathing 28.55
sea chervil 38.58
sea mats 26.10, 38.58
sea urchins 38.58–9, 61.22
seabather's eruption 37.22, 38.56
seal bites 38.61
seal finger 38.61
seasonal allergic conjunctivitis (SAC) 67.15
  clinical features *67.13*
seatworm **37.13–14**
  see also Enterobius vermicularis
sebaceoma 53.15–17
sebaceous activity, in late childhood and puberty 8.2
sebaceous adenitis, neutrophilic 50.62–3
sebaceous cells *see* sebocytes (sebaceous cells)
sebaceous cyst 52.45
  see also epidermoid ('sebaceous') cysts
sebaceous duct 42.1
  development 42.3
  hypercornification, in acne 42.22, 42.23, 42.24
sebaceous glands 3.1, **42.1–89,** *44.2,* 66.2, 66.3
  acini 42.1
  acne *see* acne vulgaris
  activity
    excess, in acne 42.20
    inhibition 42.15–17
    isotretinoin reducing 42.58
    measurement 42.7–9
  adenoma **42.87,** 53.15–17, 68.28, 69.23
  ageing and 8.24, 80.1
  androgen metabolism and enzymes for 42.10
  carcinoma 42.87–8, 53.15, 53.17–18, *67.10*
    ear 68.34
    eyelids 67.35–6
  cell culture 42.12
  cell dynamics 42.1, 42.3
    see also sebocytes
  development 3.5, 42.3
  distribution 42.1–2
  ear 68.1
  ectopic (Fordyce spots) 42.1, **42.86,** 45.21, 69.2, 69.5, **69.22–3**
  embryology 3.3
  endocrine control of activity 42.9–14, 42.76
    acne aetiology and 42.20–2
    adrenocortical hormones 42.11
    androgens 42.9–11, 42.12
    in cell culture 42.12
    oestrogens 42.12
    pituitary hormones 42.11–12
    in pregnancy and lactation 42.12
    progesterone 42.11
  eyelids 67.2
  free/unrelated to hair follicles 42.1
  functions 42.6–7
  histochemistry 42.3–5
  homogeneous/heterogeneous outflow *42.21*
  hyperplasia 42.86–7
    female genital region 71.55
  hypertrophy, ACTH causing 42.11
  immunocytochemistry 42.3–5
  inhibition of activity 42.15–17
  isolation methods 42.8
  mammals 42.2
  mitotic activity 42.8
  neonatal 17.2, 17.4–5
  nipple 70.1
  in pregnancy 8.10
  prepubertal period 42.5, 42.9
  proliferative regions 42.1
  prominent *71.11*
  regulation 42.3
  retinoid control of activity 42.14–15
  secretion, measurements 42.7–9
  size
    decreased by oestrogens 42.12
    estimation 42.8
    isotretinoin reducing 42.14, 42.58
    testosterone administration effect 42.10
  species-to-species variations 42.8
  structure 42.1–3
  tumours 42.87, **53.15–18**
    multiple benign 53.15
    see also sebaceous glands, carcinoma
  ultrastructure 42.3–5
  vitamin E secretion 42.7
sebaceous glands of Zeis 67.2
sebaceous keratoacanthoma 53.15
sebaceous naevus of Jadassohn *see* naevus, sebaceous
sebaceous naevus syndrome (epidermal naevus syndrome) 18.27–30, 54.11
sebaceous pilosebaceous unit 3.13
sebocystomatosis *see* steatocystoma multiplex
sebocytes (sebaceous cells)
  activity, inhibitors 42.15–17
  apoptosis 42.15
  cell culture, isotretinoin effects 42.58
  dynamics 42.1, 42.3
  hormonal actions 42.10–12
    in cell culture 42.12
  immortalized 42.12, 42.14
  isolation methods 42.8
  keratin expression 42.12
  lipids 42.3, 42.5
    surface, changes between birth and puberty 42.5–6
  lipogenesis 42.5
    hormonal control of 42.10, 42.11, 42.12
  maturation prolonged by isotretinoin 42.14
  neurohormones targeting 42.4
  prepubertal 42.3–4
  proliferation 42.1
    glucocorticoids stimulating 42.11
    reduced by retinoids 42.14
  5α-reductase isoform 42.10
  terminal differentiation 42.3, 42.15
  testosterone synthesis 42.12
  ultrastructure 42.3–5
sebometer 42.7
sebopsoriasis 23.32, 36.14
seborrhoea 42.79
  acne vulgaris aetiology 42.20–2, 42.30
  following spinal cord injury 63.17
  isotretinoin 74.34
  Meibomian *67.7,* 67.11
  see also sebum, excess production
seborrhoeic dermatitis **23.29–34,** 64.47
  in adolescence 8.7
  aetiology 23.29–30
  in candidiasis 36.64
  clinical features 23.30–2
  dandruff and 23.29, 23.30
  definition 23.29
  diagnosis 23.32
  differential diagnosis 26.29
    perioral dermatitis vs 43.11
    rosacea vs 43.5
    secondary syphilis vs 34.12
  in dogs 2.14
  ear 68.14, 68.23, 68.28
  elderly people 8.28
  eyelids 23.11
  face 23.31
  female genitalia 71.52, 71.58
  flexures 23.31–2
  following spinal cord injury 63.17
  histopathology 23.30
  in HIV infection 23.29, 23.30, 23.32, **35.15–16,** 68.28
    haemophilias and drug abusers 35.45
    Malassezia and 36.13
  incidence 23.29
  infantile **17.28–31,** 23.29, 23.34, 24.22, 24.26
  Langerhans' cell histiocytosis vs 55.9
  light-exacerbated 29.22
    differential diagnosis 29.12
  Malassezia and 17.29, 23.29, 23.30, 36.13, 66.56
  male genital region 71.18
  morphological variants 23.30
  parkinsonism and 23.29
  perianal/perineal dermatology 71.84
  petaloid 23.31
  pityriasiform 23.31
  pityriasis rosea vs 33.80
  psoriasiform 17.31, 23.31
  psoriasis and 23.32
  race and 9.6
  refractory, HIV infection 35.16
  scalp 23.30, 66.56–7
  treatment 23.32–3
    pimecrolimus 73.32
    tacrolimus and Kaposi's sarcoma 35.36–7
  trunk 23.31
seborrhoeic keratosis **52.38–9**
  aetiology and incidence 52.38
  breast 70.15, *70.16*
  clinical features 52.38–9
  compound melanocytic naevi vs 54.19
  cystic 52.39
  differential diagnosis 52.38, 52.39
  early SCC vs 52.39
  eruptive 62.32
  eyelids 52.39, 67.33
  laser therapy 78.10, 80.11
  malignancies associated 52.38
  melanoma vs 54.38
  number and size, age-related increase 52.38
  pathology 52.39
  pinna 68.28
  solid variant 52.39
  treatment 52.39
seborrhoeic warts *see* seborrhoeic keratosis
sebotrophic factor 8.10
sebum
  in adolescence 8.6, 8.7
  ageing effects 8.24

analysis difficulties 42.5
biological significance 42.27
biosynthesis 42.5–6
see also sebum, production
cholesterol 42.5
composition 42.5–6
in acne 42.22
changed by diet/hormones/drugs 42.6
excess production
in acne 42.20, 42.79
mechanisms *42.20*
see also seborrhoea
excretion rate (SER) 42.7, 42.8, 42.22
acne aetiology and 42.21, 42.22
acromegaly 42.22
oral drugs effect on *42.50*
formation 3.5
functions 42.3, 42.6–7
fungistatic action 42.7
linoleic acid reduction, in acne 42.23, 42.26
lipids 42.5, *42.5*, 42.6
in acne 42.22, 42.23
synthesis regulation 42.12
neonatal secretion 8.2, 17.2
outflow obstruction, acne pathogenesis 42.24, 42.25
in pregnancy 8.10
production 42.5–6, *42.11*
age-related changes 42.9–10
androgens controlling 42.9–11, 42.12, 42.20, 42.53, 42.79
eunuchs 42.10
interfollicular variation 42.21
measurement 42.7–9
men 42.10
menstrual cycle effect 42.11
in rats vs humans, rates 42.8
reduced by all-*trans*-RA 42.14, 42.15
reduced by antiandrogens 42.53
reduced by isotretinoin 42.14
topical drugs affecting *42.40*
women 42.10
in seborrhoeic dermatitis 23.29
triglycerides 42.5, 42.6, 42.22
vacuoles 42.3
volume, at birth and adults 42.9
sebum-absorbent tape (Sebutape®) 42.8
sebum excretion rate (SER) *see* sebum
Sebutape® 42.8
secondary care 6.15
secosteroids 73.43–8
Secretan's syndrome 64.37
Secrétan's syndrome 48.13
secretory granules 13.4
secretory leukocyte protease inhibitor 14.3
secretory protease inhibitor 4.5
SED (standard erythema dose) 29.4
sedatives 75.80–2
sedentary lifestyle, cellulite and 46.10
sedge pool itch 37.22
seed ticks 38.35
SEER programme 54.32
segmental Hailey–Hailey disease 39.37
segmental neurofibromatosis 15.20
Seidlmayer's syndrome (acute haemorrhagic oedema of childhood/infancy) 17.33–4, 49.18–19, 50.30
Seldinger-type retrograde aortography 47.4
selectin family 12.70–2
selectins
E-selectin, deficiency 13.9
L-selectin 13.4, 13.9, 58.26
neutrophils 12.22
P-selectin 13.4
in wound healing 14.3
selective serotonin reuptake inhibitors (SSRIs) 64.20, **64.50**
adverse effects 64.50, 75.79–80
doses and indications *64.50*
in erythromelalgia 47.10
psychocutaneous disorders
body dysmorphic disorder 64.20
pruritus 64.23–4
skin picking 64.28
trichobezoar 64.32
see also antidepressants
selenium disulphide 73.13
selenium metabolism 59.76
selenium sulphide
in dermatophytoses 36.49
indications 73.13
in pityriasis capitis 66.56–7
in pityriasis versicolor 36.12
selenium sulphide shampoo 73.13
self-adhesive hydrocolloid dressings 73.4
Self Administered PASI (SAPASI) 72.9
self-destruct theory of Lerner, vitiligo 58.47
self-efficacy 64.5
self-esteem 64.5–6, 64.7
self-flagellation 28.33
self-harm *64.12*, **64.45–6**
in eating disorders 64.21
mouth ulcers and 69.43
repetitive 64.46
skin injury/disease in adolescents 8.7
substance P 12.66
suicidal ideation and 64.45–6
self-healing epitheliomas 52.9–10
self-help 6.14
self-help groups 6.14, 64.7, 72.33–4
self-inflicted skin injury/disease, adolescents 8.7
self-mutilation
mouth ulcers and 69.43
see also self-harm
self-reported skin disease 6.6
semen, delayed hypersensitivity to 26.19
semicircular lipoatrophy, mechanical injury 28.27
semilunar valves 47.25
Senear–Usher syndrome *see* pemphigus erythematosus (Senear–Usher syndrome)
Sener syndrome 15.52
senescence
of skin 8.21
see also ageing
senile comedones *see* comedones
senile haemangioma (venous lake) 47.16, 69.101
senile lentigines (age spots) 8.23, 54.3, 58.39
senile orbital fat prolapse 67.5
senile purpura 49.15
senile warts *see* seborrhoeic keratosis
senile xerosis *see* asteatotic eczema (eczema craquelé)
Sensenbrenner syndrome 15.34, **15.91–2**
sensitive skin 25.2, 25.18–19
formulating products for 25.10
sensitivity
analysis 7.9
clinical 26.12
to cold 28.65–71
latent 26.12
patch-test 26.12
threshold of 26.12
in xeroderma pigmentosum 15.72
sensitivity factor attachment protein receptor (SNARE) 58.4
sensitization
allergic contact dermatitis and 26.1, 26.5–6, 26.6–7, 26.9–10
assessment of potential 26.11–12
to earrings 68.7–8
following patch/photopatch testing 26.94–5
risk 26.12
sensitizers/sensitizing agents
children 8.3
occupational 27.3, 27.18–21
in old age 8.28
topical 73.39–40
universal 73.39
sensorineural hearing loss, enamel hypoplasia and nail defects 15.52
sensory evoked potentials 63.5
sensory functions of skin 4.1, 4.9–10
ageing effect 8.24
sensory nerve endings, skin 3.2
sensory perception, pressure ulcers 28.21
sentinel node biopsy 54.51–2
atypical spitzoid tumours 54.25
breast cancer 48.8
malignant melanoma 54.39, 54.50, 54.51–2, 54.53
Merkel cell carcinoma 53.43
micrometastases, detection 53.43
squamous cell carcinoma in dystrophic EB 39.30
separation artefact 10.30
SEPs (sensory evoked potentials) 63.5
sepsis, purpura fulminans 49.39–40
septa 36.2, 36.3
septal panniculitis *see under* panniculitis
Septi-Check 31.6
septicaemia
Candida 36.68
following ear piercing 68.7
meningococcal 30.44, 49.20, 62.105
Pseudomonas 30.49, 30.50
in toxic epidermal necrolysis 76.17–18
SERCA2, in Darier's disease 39.32, 39.33
serglycin 3.46
serine–threonine kinase gene *(STK11/LKB1)* 58.12, 58.13
serological tests, viral infections 33.4, 33.5
seroma 48.29–30
serotonin (5-HT) 38.1
carcinoid tumours 43.18
metabolic pathway *43.18*
release during vascular injury 12.32
serotonin antagonists, diarrhoea management in carcinoid syndrome 43.18, 43.19
Serratia marcescens, neutrophilic eccrine hidradenitis and 44.17
sertaconazole, topical 73.12
sertindole *64.52*
sertraline *64.50*
serum amyloid A (SAA) 13.4, 13.19
serum amyloid P component (SAP) 59.42–3
serum opacity factor 30.12
serum sickness 22.7, 22.18, 75.17, 75.27–8
in hepatitis B virus infection 33.60, 62.59
serum sickness-like syndrome 22.18
Servelle–Martorell syndrome 47.24
sesquiterpene lactones 26.25, 26.75, 26.77
Sessinia 38.27
setae 38.28, 38.29
Setleis' syndrome 15.40, 18.103, 45.6
severe combined immunodeficiency (SCID) *13.13*, 17.49–50, **17.57–60,** *69.117*
mouse model 2.14
mutations 13.8, 13.11
RAG-1/RAG-2 defects 13.8
Severity Scoring in Atopic Dermatitis (SCORAD) 72.6, 72.9–10, 72.11, 72.14, 72.22
Seveso 27.13, 75.162
sex determination 8.2
sex hormone(s) 74.32
female, melanoma and 54.56–7
therapeutic 74.32
sex hormone-binding globulin (SHBG) 42.53, 66.14, 66.81
sex hormone-related conditions, hair loss in, in animals 2.18
sex-linked genes
chromosomal abnormalities 15.12–14
definition 15.4
sexual abuse
differential diagnosis 51.117
female genital dermatology 71.57
Koebner phenomenon 51.117
mechanical injury 28.34, 28.37–8
perianal/perineal dermatology 71.84
see also child abuse
sexual contacts
management in gonorrhoea 34.28
management in syphilis 34.23
sexual development 8.2–3, 8.3
delayed 8.3
sexual dysfunction, following spinal cord injury 63.17
sexually transmitted infections (STIs) **34.1–37**
adverse pregnancy outcomes 34.1
chancroid **34.34–5**
child sexual abuse 28.37–8
chlamydial *see* chlamydial infections, genital
donovanosis **34.36–7**
female genital dermatology 71.70–2
global burden 34.1
gonorrhoea *see* gonorrhoea
herpes simplex 33.15, 33.16, *33.17*
incidence 34.1
lymphogranuloma venereum **34.23–34**
male genital dermatology 71.33–5
perianal/perineal dermatology 71.83, 71.93–5
screening, in syphilis management 34.22
syphilis *see* syphilis
treatment and prevention 34.1, 34.2
see also individual infections
Sézary cells, in erythrodermic chronic actinic dermatitis 29.18
Sézary syndrome 57.17–22
atopic dermatitis and 24.25
clinical features 57.17
defined 57.17
dysregulated T-cell signalling pathways 57.21
electron microscopy 10.30
erythroderma and 23.48
in HIV infection 35.41
immunopathology 57.10, 57.17–18
molecular pathogenesis 57.19
abnormalities of T-cell activation 57.20
pruritus in 21.10, 21.11
specific chromosomal abnormalities 57.20
treatment 57.22–9
see also mycosis fungoides
Shabbir's syndrome 39.15
shagreen patches 15.22, 18.31
shake lotions 73.2
shale tars 73.42
shammah 69.50
shampoos 66.96
antieczema 29.22
formulations 66.96
medicated 26.18
in pityriasis capitis 66.56–7
safety 66.96
in seborrhoeic dermatitis 23.32–3
sharks 2.2
shave therapy, venous leg ulcers 47.51
shaving, wart transmission 33.40
SHBG (sex hormone-binding globulin) 42.53, 66.14, 66.81
Shea butter 73.6
shear force, pressure ulcers 28.17, 28.21
sheep nostril fly 38.9
sheep shearing, breast disorders associated 70.15
sheep tick *38.34*, 38.35
sheet metal workers, occupational hazards 27.20
shell nail syndrome 65.8
SHFM (split-hand split-foot syndrome) 15.61, 15.65
Shimpo's syndrome *see* POEMS syndrome
shingles *see* zoster
shoemakers, occupational hazards 27.21
shoes *see* footwear

shop assistants, occupational hazards 27.21
short anagen syndrome 66.27
short-arm deletion syndromes 15.12
short bowel syndrome
  biotin deficiencies 59.64
  genitocrural dermatology 71.7
short stature 8.3
  disorders associated *8.3*
  Langerhans' cell histiocytosis 55.12
  pituitary 62.3
  with premature ageing and pigmented naevi 45.60
  short-limbed dwarfism with immunodeficiency 17.64–5
  syndromes of 8.3
SHORT syndrome 46.37
shoulder, surgical excision in area 77.15
shrinking lungs syndrome 62.82
Shulman's syndrome 51.86
Shwachman(-Diamond) syndrome 17.75
  ichthyosiform erythroderma in 19.61
sialidosis 59.32, 59.34
  prenatal diagnosis *16.3*
Siamese fighting fish 13.31
SIAoscopy (spectrophotometric image analysis of pigmented lesions) 5.20
Siascope 54.38
Siberian tick typhus 38.34, 38.35
sibutramine 75.89
Sicariidae 38.31, 38.32
sick building syndrome 64.26
sick-cell syndrome 45.23
sickle cell disease 62.85–6
  leg ulceration 47.56, 49.47
  oral involvement *69.116*
  pigmentation in 58.53
  race and 9.12
  treatment 49.47
  venous leg ulcers 47.43
sickness behaviour 64.8
Sickness Impact Profile (SIP) 72.16
sickness role 64.35–6
SIFT (skin integrity function test) 25.9
'sign of the groove' 34.33
signal recognition particle (SRP) 51.128
signalling
  imiquimod and Toll-like receptors 73.24
  innate immunity and antimicrobial peptides *3.16*, 3.17
  Langerhans' cells migration 55.4
  melanocyte development 58.3
  melanocytes 3.21
  skin development 3.3–5
  stem cells 3.6–7
'signature' mutations 52.13
signe de la bandera 66.94
sildenafil 75.99
  flushing associated 43.15
silicates, sarcoidal reaction to 61.22
silicon dioxide *27.17*
silicone
  foreign body reactions to 28.46
  organic 25.21
  panniculitis due to 46.28
silicone breast implants 51.82, 51.90, 51.111, 70.7–8
  foreign body reactions 28.46
  scleroderma 51.82
silicone gels and dressing 73.51
silicosis, associated with scleroderma 51.80
silver
  pigmentation due to 58.54
  see also argyria
silver acetate 58.54
silver nitrate 73.16, 77.47, 77.50
  hair dye 66.97
  wart treatment 33.49
silver sulfadiazine 14.11, 14.21, 73.11, 74.39, 75.166
  burns 28.85–6
  epidermolysis bullosa management 39.28
'silvery hair' syndrome 58.42
Simonart's bands 69.37
simple lymphatic drainage (SLD) 48.23
simulation of skin disease 64.42–3
Simuliidae (blackflies) 37.4, 38.5–6, 38.7
Simulium 38.5–6, 38.7
  skin disease in animals 2.11
simvastatin 75.156–7
Sindbis virus 33.66, *33.67*
single-gene disorders *see* genodermatoses
single nucleotide polymorphism 11.7, 11.13, 11.15
sinus(es)
  acne vulgaris 42.31, *42.32*
  anogenital pilonidal 28.49–50
  barber's hair 28.49
  branchial (cervical) 18.85–6
  cloacal 71.83
  definition 5.8
  dental *42.37*
  dermal
    congenital 63.16
    dorsal 18.95–6
  dermoid, congenital 18.88–9
  dorsal dermal 18.95–6
  genitoperineal raphe 18.94–5
  hair, of breast 70.15
  hair as a foreign body 28.49–50
  lips 18.3, **18.90–2,** 69.40–1
  milker's 28.49
  pilonidal 71.87, *71.88*, 71.101, 78.12
  preauricular **18.83–4,** 68.4
  pressure ulcers 28.20
  umbilical–urachal 18.94
sinus histiocytosis with massive lymphadenopathy (SHML; Rosai–Dorfman disease) 55.29–30
  extranodal 55.29
  with neutrophilic predominance 50.62
  pure cutaneous 55.29
sinusoidal haematolymphoid malignancy 55.32–3
Siphonaptera *see* flea(s)
Siphonophora 38.55
Siphunculina 38.6
Sipple syndrome (MEN type 2A) 62.24
Sipple's syndrome (multiple mucosal neuroma) 56.45
sirolimus (rapamycin) 13.25, 74.25, 75.138
sissoo *26.80*
Sister Mary Joseph's nodule 62.18, 62.66
Sistrunk procedure 48.25
sitosterolaemia 59.91
Six Area Six Sign Atopic Dermatitis (SASSAD) score 72.10
Sjögren–Larsson syndrome (SLS) 19.3, 19.42–5
  prenatal diagnosis *16.3*
Sjögren's syndrome 51.134
  aetiology 51.134–5
  annular erythema in 62.109
  associated with SLE 51.138
  in childhood 51.136
  classification criteria 51.134
  clinical features and pathology 51.135–6
  diagnosis 51.137
  with endocrine autoimmune conditions 62.13
  hyperglobulinaemic purpura 51.136
  immunity and 13.2
  immunoglobulins in 13.7, 51.105
  laboratory abnormalities 51.136–7
  ocular involvement *67.25*
  ocular mucous membrane pemphigoid vs 67.20
  primary biliary cirrhosis and 62.62
  respiratory tract involvement 62.82
  sarcoidosis and 61.7
  in systemic sclerosis 51.105
  treatment 51.137–8
    chloroquine 51.138
  vasculitis and 50.49, 50.52–3
SJS *see* Stevens–Johnson syndrome (SJS)
SKALP/elafin 3.10
skeletal abnormalities
  genetics 15.17
  ichthyosis and 19.61
skeletal anomalies–ectodermal dysplasia–growth and mental retardation 15.53
skeletonization, arteriovenous fistulae 47.21
skin
  anatomy/organization **3.1–53**
    ageing effects 8.22–5
  barrier function *see* barrier function of skin
  blood supply 3.2, 3.3, **3.50–2**
  congenital localized absence (Bart's syndrome) 18.101, 39.17, 39.18, **39.22**
  corticosteroid-induced thinning 73.17
  development *see* embryology, of skin
  dimensions 3.1
  functions 2.8, 3.2–3, **4.1–11**
  as immune system 2.8, **3.16–19**
  from infancy to old age **8.1–29**
  maintenance **3.5–7**
  objective assessment 72.11
  psychological significance 64.1–2
  regional variation **3.3**
  surface area, between birth and maturity 8.1
  water content, changes with ageing 8.22, 8.27
skin-ache syndrome 63.24
skin appendage tumours **53.1–44**
  see also adnexal tumours
skin-associated lymphoid tissue (SALT) 57.2
skin bioequivalents, use in dystrophic EB 39.29–30
skin biopsy 10.1–2
  actinic granuloma 45.29
  actinic keratosis 10.42
  amyloidosis 10.42
  argyria 10.42
  artefacts 10.7, *10.8*, 10.30–1
  atrophoderma 10.42–3
  blue naevus 10.43
  café-au-lait spots 10.42
  connective tissue disease 10.42–3
  consent to 10.2
  contraindications 10.2, *10.3*
  curettage 10.4
  dermal deposits 10.42
  dermatitis artefacta 64.40
  diagnostic 10.2
  elliptical incisional/excisional 10.3, 77.11
  epidermolysis bullosa 39.21, 39.24
  fetal 16.5–7
  freckles 10.42
  frozen sections 10.6
  fungal infection 10.42
  granuloma annulare 10.43
  haemochromatosis 10.42
  ichthyosis vulgaris 10.42
  indications 10.1–2
  instruments *10.3*
  laboratory methods 10.6–11
  leprosy 32.15
  local anaesthesia 10.2
  lymphoedema 48.19
  mastocytoma 10.43, 22.34
  mastocytosis 22.34
  Mongolian spot 10.43
  multiple 10.2
  needle 10.4
  peripheral neuropathy 63.11–12
  pigmentary disorders 10.42
  porokeratosis 10.42
  punch biopsy 10.3–4, 50.12, 77.11–12
  sarcoidosis 61.19
  scalp 10.32, 10.43
  scleroderma 10.42
  sections revealing little/no abnormality 10.42–3
  shave biopsy 10.4, 77.12–13
    epidermolysis bullosa 39.24
  site of 10.32–3
  specimens *see* tissue specimens
  techniques 10.3–4, 77.11–13
  telangiectasia macularis eruptiva perstans 10.43
  urticaria 10.43, 22.3, 22.26
  urticaria pigmentosa 10.43
  urticarial vasculitis 22.26, 50.22
  vasculitis 50.12
  vitiligo 10.42
skin bleaching 58.38, 73.27
  vitiligo management (hyperpigmented areas) 58.49
skin-bleaching preparations 9.8
skin cancer
  acitretin chemoprophylaxis 74.36
  in animals 2.19–20
    comparison with humans *2.21*
  in elderly people 8.28–9
  following chemotherapy 75.124
  melanoma *see* melanoma, malignant
  non-melanoma *see* non-melanoma skin cancer (NMSC)
  occupational 27.15–16
  registration data 6.6
  see also specific cancers
skin cleansers, as irritants 25.20
skin colour
  measurement 72.11
  melanin *see* melanin(s)
  non-melanin pigmentation **58.53–4**
  see also pigmentation
skin-derived precursors (SKPs) 3.7
Skin Disorders Specialist Library 7.6
skin equivalents 14.26
  in burns 14.11
skin failure 4.1, 4.7
skin flaps **77.23–8**
  advancement 77.24–5, *77.28*
  axial pattern 77.23
  bilobed *77.25*
  complications 77.26, *77.27*
  distant 77.23
  free 77.23
  interpolation 77.26, *77.27*, *77.28*
  island pedicle 77.26, *77.28*
  local 77.23
  nasolabial fold *77.25*, *77.28*
  pedicle 77.26, *77.27*, *77.28*
  random pattern 77.23
  reticular 77.23
  rotation *77.24*, 77.25, *77.28*
  segmental 77.23
  transposition 77.25, *77.26*, *77.28*
skin flora *see* bacteria, flora (normal skin)
skin fragility disorders *see* epidermolysis bullosa (EB)
skin grafts **77.20–3**
  acne scars 77.22
  allografts 14.26
  animal models 2.7–8
  autografts 14.26
  autologous split-thickness, in dystrophic EB 39.29
  composite 77.20
  dressings 77.17, 77.20
  in dystrophic EB 39.29–30
  epidermal 77.21
  full-thickness 77.20, *77.21–2*
  hair 66.23–4
  in vitro culture *see* skin equivalents
  lymphatic vessel role after 48.6
  meshed 47.51, 77.20, *77.23*
  mini-grafts 77.21
  pinch 14.25, 47.51, 77.20–1
  punch 77.21, 77.22
  split-skin 10.19, 14.25, 77.20, *77.23*
  venous leg ulcers 47.49, 47.51–2
  in vitiligo 58.49, 77.21–2
skin injury *see* mechanical injury; thermal injury
skin integrity function test 25.9
skin lightening agents 73.26, 73.27

skin phototypes *29.6*, 29.8
skin sensitivity *see* sensitivity
skin snips, in onchocerciasis 37.7
skin surface cooling 80.10–11
skin tags 52.40–1, 59.79, 62.58
  female genitalia 71.72
  peri-auricular 68.4
  pregnancy 8.13
skin tension lines, scar orientation and 77.2, 77.11, 77.13
skin testing **5.22–4**
  delayed tests 5.24
  drugs 75.168–73
  in vitro 26.98, 75.173–5
  intradermal/intracutaneous tests 5.22–4, 26.97
    drugs 75.168–9
  leukocyte procoagulant activity 26.98
  lymphocyte transformation tests 26.98
  migration inhibition test 26.98
  modified prick test 5.23
  patch testing *see* patch test
  photopatch test 26.84, **26.93–4,** 29.24
    complications 26.94–5
    cosmetics 26.49
    indications 26.93
    protocols 26.93
    readings 26.94
    test materials 26.94
  pre-employment 27.8
  prick test 5.23, 13.16
    anaphylaxis and 22.26
    in atopic dermatitis 24.10–11
    drugs 75.168–9
    to food 26.106
    occupational dermatoses 27.7
    oral allergy syndrome 22.20
    urticaria 22.19, 22.26
  repeat open application tests (ROAT) 26.49, 26.97
  scratch test 5.23
    to food 26.106
  skin window technique 5.23
  spot tests 26.99
  in urticaria 75.173
  usage tests 26.97
skin thickening
  lymphoedema 48.8, 48.14, 48.17
  mechanical injury 28.28
skin thickness
  in irritant contact dermatitis 25.22
  measurement 72.11
Skindex 72.17, 72.18
Skindex-29 64.10
skinfold thickness 46.5
skin–psyche interactions 64.3–4
SLAM (CD150), measles virus receptor 33.75
SLAM-associated protein 13.6
'slapped cheek' appearance (fifth disease) *5.10*, 33.62, 33.63
  see also parvovirus B19 infection
SLC24A5 gene 3.20
SLD (simple lymphatic drainage) 48.23
SLE *see* systemic lupus erythematosus (SLE)
sleeping sickness (African trypanosomiasis) 37.2, **37.29–31**
slit-skin smear
  in leishmaniasis 37.38
  in leprosy 32.15
  in post-kala-azar dermal leishmaniasis 37.42
SLP-76 deficiency 48.2
SLS *see* Sjögren–Larsson syndrome (SLS)
Smad-4 3.4
Smad-7 3.4
Smad protein family 14.3, 14.7, 14.8, 51.65
small proline-rich proteins (SPR1) 3.10
small vessel vasculitis 12.32, 62.82
smallpox (variola) 33.5, *33.6*
  diagnosis 33.5
smear tests, vaginal discharge 71.53
Smith–Lemli–Opitz syndrome, prenatal diagnosis *16.3*
smoker's keratoses 69.90
smoker's melanosis 69.96
'smoker's patches' 41.9
smoking 20.4
  acne and 42.34–5
  actinic elastosis and 45.27
  cessation, claudication treatment 47.5
  cigars 69.90
  cold-induced injury 28.64
  hair colour and 66.95
  male genital dermatology 71.40
  mechanical injury 28.8
  oral keratoses and 69.90
  oral melanosis and 69.96
  pigmented melanotic macules 54.6
  pipes 69.90
  reverse 69.90, 69.96
  skin ageing and 80.2
  skin flap necrosis and 77.26, *77.27*
  telangiectases due to 47.13
  ulcerative colitis and 50.66
  wound healing and 14.19
  wrinkles and 45.2
smooth muscle
  hyperplasia 47.52
  origin 12.30
smooth muscle cells
  arteriole walls 3.51
  microscopy 10.35
snake(s) 2.9
  epidermis 2.3
  glands 2.4
  mites 38.51
  skin infections 2.12
snake bites 38.60
snake envenomation 48.5
snakehead 31.31
SNARE 58.4
Sneddon's syndrome 49.42–4, 50.54
  clinical features 49.43
Sneddon–Wilkinson disease *see* subcorneal pustular dermatosis
snip excision 77.34
snipe flies 38.6
'snow nose' 2.23
snowflake sign 16.7
SNP (single nucleotide polymorphism) 11.7, 11.13, 11.15
snuff-dipper's keratoses 69.90
'snuffles,' congenital syphilis 34.15
soap
  avoidance in atopic dermatitis 73.31
  as irritant 25.20
soap substitutes 23.21, 25.25, 73.31
Social Exclusion Theory 64.7
social factors
  in diagnosis 5.5
  venous leg ulcers 47.43–4
socio-economic status
  allergic contact dermatitis and 26.10
  risk factor for skin disease 6.12
  syphilis and 34.2
sociocultural factors 64.1–2, 64.6, 64.7, 64.18
sociosexual communication 4.11
soda ash 25.20
sodium, in sweat 44.5–6
sodium aurothiomalate 74.29–30
  flushing associated 43.15
  see also gold therapy
sodium benzoate 22.26, 25.18, 75.159
sodium bicarbonate, in acid burns 27.12
sodium carbonate *25.19*
sodium cromoglycate
  adverse effects *26.46*, **75.99**
  in atopic eye disease 67.15
  in mastocytosis 22.35
  mechanism of action 73.51
  topical therapy 73.51–2
sodium hydroxide
  burns due to 27.12
  as irritant *25.19*, 25.20
sodium hypochlorite 25.21
sodium lauryl sulphate 25.3, 25.4–5
  preservatives with 26.50
  skin irritation thresholds 25.25
sodium silicate 25.20
sodium stibogluconate 37.39
sodium tetrachlorophenate 27.13
sodium tetradecyl sulphate (STD) 47.39
sodium thiosulphate 49.48
sodium valproate 64.52
  adverse effects **75.86**
    scleroderma 45.52
  in zoster and post-herpetic neuralgia 33.28
sodoku 30.67
soframycin, topical 73.10
soft palate 69.2
soft sore *see* chancroid
soft-tissue fillers 75.156
soft-tissue infections, HIV infection 35.24
soft-tissue tumours **56.1–62**
soft warts *see* skin tags
solar comedones, acne with 42.79
solar elastosis, in rosacea 43.4
solar keratosis *see* actinic keratosis
solar lentigo *see under* lentigines
solar purpura 49.17
solar simulated radiation (SSR) 29.5
solar urticaria (SU) *22.13*, 22.16–17, *29.10*, **29.19–20**
  clinical features *29.10*, 29.19, 29.23
  definition and aetiology 29.19
  diagnosis *29.10*, 29.23
  differential diagnosis *29.10*, 29.12, 29.23
  fixed 29.19
  idiopathic 29.19
Solenopsis (fire ant) 38.14
soles
  biopsy 10.32
  hairy malformation 18.14
  hyperpigmentation 9.2, *9.3*
  juvenile plantar dermatosis 23.26
  lichen nitidus 41.22
  lichen planus 26.29, 41.7, *41.8*, 41.14
  melanocytic naevi 54.17–18
  melanoma 54.44, *54.45*
  psoriasis 20.15
  seed-like keratoses 62.33
  vesicular eczema *see* pompholyx
  warts *see* wart(s), plantar
solid phase assays 13.19
solitary epithelioid histiocytoma 55.23, 55.24
solitary plaque-like telangiectatic glomangioma 47.20
soluble *N*-ethylmaleimide-sensitivity factor attachment protein receptor (SNARE) 58.4
soluble oil dermatitis *27.4*, 27.5, 27.6
somatic mutation theory 52.10
somatic mutations 15.5
somatostatin 4.10
  in atopic dermatitis 24.17
  effects 12.64–5
  growth and 8.2
  in psoriasis 20.42
somatotrophin *see* growth hormone
sonic hedgehog (Shh) 3.4, 53.2
  hair growth and 66.10
soot, carcinogenicity 27.15–16
sorafenib 75.132
sorbic acid 25.18, 26.58, 73.8
sores, pressure *see* pressure ulcers
sortography, Seldinger-type retrograde 47.4
SOS1 gene 15.15
Southern blotting 11.5–6
Southern tick-associated rash illness 38.35
sowda 37.5
Sox10/SOX10 gene 58.3
  mutation 2.7
  Waardenburg's syndrome 58.44
SOX18 mutations 48.10
soybean oil 38.5
Sp1 14.6
Spaniopsis 38.6
Spanish fly *see* cantharidin
Sparassidae 38.32
spargana 37.26
sparganosis **37.26–7**
sparganum proliferum 37.26
SPCA1 39.32, 39.35
spearmint oil 26.17
specialized burns units 28.80, *28.82*
specialized support systems 28.20, 28.22
specific granules 13.4
  deficiency 12.23
SPECT, invasive otitis externa 68.26
spectacle-frame acanthoma 28.29–30, 68.9
spectacle frames, dermatitis 26.16, 26.17
spectinomycin 74.42
spectral irradiance 29.3
spectrophotometric image analysis of pigmented lesions 5.20
spectroradiometer 29.3
spermatogenesis 8.4
  drug effects on 75.11
SPF *see* sun protection factor (SPF)
spheroids 45.33
spherules 36.85
spherulin 36.86
sphingolipidoses, classification 59.33
sphingolipids 4.2
spices, as irritants 25.21
spicules 38.28
spider angioma 47.14–15, 47.20, 62.64, 78.7
  in pregnancy 8.10, 47.14, 47.15
spider mites 38.48
spiders 38.30–3
Spiegler–Fendt sarcoid 57.59
  differential diagnosis 51.7
Spiegler's tumour 53.28–9
spina bifida 18.95, 18.96, 63.15–16
spinal accessory nerve 77.3–4
spinal cord
  development 63.15
  implantable stimulator 47.8
  injury 44.9, 63.17
    pressure ulcers 28.17
  tethering 63.15
spinal dysraphism 18.95–8, 63.15–17
spinal muscular atrophy, with autosomal recessive EB simplex 39.8
spindle and epithelioid cell naevus *see* naevus, Spitz
spindle cell carcinoma 97.18
spindle cell naevus of Reed 54.22, 54.23
spindle cell tumours, Kaposi's sarcoma 35.36
spines
  animals 2.3
  caterpillar 38.29
  sea urchin 38.58
SPINK5 gene 12.25, 24.4, 66.65
  Netherton's syndrome 12.25, 12.50
spinous layer 3.1
spiny dogfish 38.59
spiradenocarcinoma 53.34
spiradenoma 53.2, 53.29–30
  cylindroma overlap 53.29
  eccrine 53.29–30
  malignant 53.30, 53.34
spiramycin 75.58
Spirillium minor 30.62, 30.67
spirochaetes **30.62–6**
  Treponema pallidum see Treponema pallidum
  Treponema pallidum differentiation 34.4
Spirometra 37.16, 37.24, 37.26–7
spironolactone 74.32
  in acne vulgaris 42.53
  adverse effects *26.46*, 42.53, 70.4, *70.5*, **75.97**
  in androgenetic alopecia 66.25
  in hirsutism 66.88
  sebaceous gland activity inhibition 42.16
spitting cobra 38.60
Spitz naevus *see* naevus, Spitz
Spitz tumour *see* naevus, Spitz
spitzoid tumour, atypical 54.21, 54.25, *54.25*
spleen, role in immunity 13.8

splenectomy, idiopathic thrombocytopenic purpura 49.10
splenomegaly
  in myeloproliferative disorders 49.29
  thrombocytopenia due to 49.11–12
splinter haemorrhage 65.15, **65.18**
  nails 3.15
  in psoriasis 65.24–5
split-hand split-foot (SHFM) syndrome 15.61, 15.65
split-skin technique 10.19, 14.25, 77.20, *77.23*
spondylitis, ankylosing *see* ankylosing spondylitis
sponges 38.59
spongiosis 10.41, 23.1
  in eczema 23.3–4
  eosinophilic 40.11, 40.15
  in irritant contact dermatitis 25.4
  neutrophilic 50.63, *50.89*, 50.90
  in seborrhoeic dermatitis 23.30
spontaneous gangrene 71.100
spooning 49.16, 62.85
sporangiophore 36.3
Sporothrix schenckii 36.70, 36.71–2
sporotrichosis **36.70–2**
  aetiology 36.70
  clinical features 36.70–1
  cutaneous 36.70–1
  definition 36.70
  differential diagnosis 36.71
  fixed 36.71
  histology 36.70, *36.71*
  in HIV infection 35.26, 35.34
  laboratory diagnosis 36.71–2
  lymphangitic 36.71
  systemic 36.70, 36.71
  treatment 36.72
sports injuries, mechanical injury 28.30–2, 28.53–6
spotted fevers 30.73–4
Spred/Sprouty family, proteins 48.2
spruce *26.81*
spurge *25.21*, 26.16
'spy in the tube' 72.5
squalene
  in sebum 42.5, 42.22
    in acne 42.22, 42.23
  toxicity 73.12
squalene epoxidase 73.12
Squalus acanthias 38.59
squamous cell carcinoma (SCC) 52.2, **52.24–9**
  actinic keratosis progression 52.29, 52.30, 52.31
  aetiology 52.24
  after chemotherapy 75.124
  aggressive cutaneous, management 52.27, 52.28
  allelotype analysis 52.12
  anaplastic 52.26
  basal cell carcinoma ratio 52.2, 52.26
  Bowen's disease progression 52.27, 52.29
  burns 28.91
  canine 2.19
  chemical carcinogens 52.4–5
  clinical course 52.25
  clinical features 52.24–5
  de novo 52.26
  definition 52.24
  diagnosis 52.27
  differential diagnosis, keratoacanthoma vs 52.26, 52.27, 52.43
  diseases associated 52.24
  in dystrophic epidermolysis bullosa 39.17, 39.19, 39.30
  early 52.31
    seborrhoeic keratosis vs 52.39
  in epidermodysplasia verruciformis 33.57–8
  in epidermolysis bullosa
    dystrophic 39.17, 39.19, 39.30
    Herlitz junctional EB 39.12
  erythema ab igne and 52.24
  extension 52.26
  external auditory canal 68.32–3
  eyelids 67.35, *67.36*
  feline 2.19
  female genital region 51.116, 71.63, 71.66, **71.76**
  genetics 11.18, 52.12
  in Hailey–Hailey disease 39.35
  HIV infection and 35.39
  HPV infection and 33.55, 52.5–6, 52.6, 52.14
  immunosuppression for organ transplants and 52.26–7
  in situ, Bowenoid papulosis of genitalia as 52.37
  incidence 52.2, 52.24
  inflammatory reaction 52.25, 52.26
  intermediate stages not always found 52.29
  invasive 52.25
  lichen planus complication 41.15
  lips 69.42, 69.49–50, 79.10, *79.11*
  loss of heterogeneity events 52.12
  lupus vulgaris and 31.18, 31.21
  lymph node involvement 79.10–11
  lymphangioma circumscriptum and 48.26
  male genital region 71.22, **71.39–46**
  management principles 52.17
  mechanical injury 28.62
  metastases 52.26, 52.27
    in dystrophic EB 39.19, 39.30
    prediction of 52.26
    risk factors 52.27
  mitotic figures 52.26
  mortality 52.2
  nail apparatus 65.37–8
  oral 69.49–53
  p53 gene mutations 52.12
  papillomatous 52.25
  pathology 52.25–6
  perianal/perineal 71.97
  photodamage associated 52.24
  pilonidal sinus 28.50
  pinna 68.30–2
  precancerous conditions 52.25, 52.28
  presentation as paronychia 65.21–2
  pressure ulcers 28.20
  prevention 52.28
    in dystrophic EB 39.31
    by sunscreens 29.9
  prolidase deficiency and 47.54
  PUVA associated 52.4
  race and 9.18
  radiation-induced 79.18
  recessive dystrophic EBV and 52.11
  recurrence/recurrent 52.27, 79.17–18
  risk factors 52.24
  scrotal 27.15–16, 52.25
  sites 52.25
  sun exposure patterns 52.3
  sunscreen use and 73.41
  in transplant recipients 62.74–5, 79.13
  treatment 52.27–8
    adjuvant chemotherapy 52.28
    curettage 77.41, *77.44*
    destructive therapies 52.27
    Mohs micrographic surgery 52.27, 77.32
    radiotherapy 52.27, 68.31, 79.5–7, 79.8–12, 79.13
    surgery 77.15, 79.5, *79.6*
  ulceration 52.25
  ultraviolet radiation and 29.7, 52.3, 52.24, 52.27
  UVB phototherapy associated 52.4
  verrucous 52.26
  vulva 51.116
  well-differentiated 52.25–6
  see also non-melanoma skin cancer (NMSC)
squamous cell papilloma, pinna 68.28
'squamous eddies' 53.2
squamous hyperplasia, male genital dermatology 71.37
squaric acid dibutylester (SADE) 66.37
  sensitization by 73.39
squirting papilla 23.30
SSR (sympathetic skin response) 63.4
SSRIs *see* selective serotonin reuptake inhibitors (SSRIs)
SSSS *see* staphylococcal scalded skin syndrome (SSSS)
St John's wort 72.29, 75.160, 75.162
stab wounds, torture injuries 28.33
stable fly 38.6, 38.7
staining
  antigen non-specific 10.14
  artefacts due to 10.31
  fungi 10.8, *10.9*, 10.10, 36.7, 36.70
  immunoenzyme methods 10.16–17
  immunofluorescence methods 10.13–14
  tissue specimens 10.8–11
standard deviation 7.17
standard error 7.18–19
standard erythema dose (SED) 29.4
stanozolol 49.34
  acneiform eruptions due to 42.72
  prophylactic, in hereditary angio-oedema 22.22
  in sclerosing panniculitis (lipodermatosclerosis) 46.30–1
  in venous leg ulcers 47.49
Staphylinidae 38.26–7
staphylococcal blepharitis *see* blepharitis, staphylococcal
staphylococcal erythrogenic toxin 30.8
staphylococcal pyoderma *see* pyoderma, staphylococcal
staphylococcal ring 2.11
staphylococcal scalded skin syndrome (SSSS) 28.92, 30.14, **30.30**
  desmoglein 1 (Desg1) disruption 3.22
  differential diagnosis 76.15, 76.19
  in HIV infection *35.24*
  neonatal 17.42–3
Staphylococcus
  burns, infections 28.85, 28.92
  classification 30.2–3
  coagulase-negative 30.4, 30.10–11
    normal skin flora 30.3
  coagulase-positive *see Staphylococcus aureus*
  in ecthyma 30.17
  erythrogenic toxin 30.8
  exotoxins 24.8
    damage to desmogleins 40.2
  infections
    animals 2.11–12
    of eyes 67.26–7
    in HIV infection 35.24
    male genital 71.29–30
    perianal/perineal 71.85, 71.91–2
    topical antibiotic therapy 73.9, 73.10, 73.11
  neutrophilic eccrine hidradenitis and 44.17
  in normal skin flora 30.2, 30.3, 68.2
  pyoderma *see* pyoderma, staphylococcal
Staphylococcus albus, paronychia due to 65.21
Staphylococcus aureus **30.6–10**
  in acne necrotica varioliformis 30.26, 30.27
  animal infections 2.11, 2.12
  antibiotic resistance 30.9
  antibodies to 30.8
  atopic dermatitis and 24.8, 24.10, 24.12, 30.7, 30.8–9
  bacterial interference 30.7
  blepharitis 30.32, 67.6, 67.11
  in botryomycosis 30.67
  breast abscess and 70.13
  in carbuncle 30.24
  carriage/carriers 30.6–7
    gastrointestinal 30.7
    nasal 30.4, 30.6–7
    neonatal 30.4–5, 30.6
    suppression 30.7
  in cellulitis 30.17–18
  in chancriform pyoderma 30.77
  colonization of diseased skin 30.7
    reduced by corticosteroids 73.18
  cutaneous infection 30.8–9
  in dermatitis vegetans 30.77
  dissemination 30.4
  ear infection 68.19, 68.21, 68.22
  in ectodermal dysplasias 15.60
  in erysipelas 30.17–18
  exotoxins 24.8
  female genital infection 71.67, 71.70
  fissure of lower lip 30.32
  folliculitis 30.22, 42.74, 67.11
  foreign bodies 28.52
  in furunculosis 30.23
  gastrointestinal carriage 30.7
  genitocrural dermatology 71.5, 71.17
  in hidradenitis suppurativa 30.79–80
  HIV infection and 30.7, 30.8, 35.24, 35.45
  in impetigo 30.14, *30.15*
  intravenous drug abuse and 28.52
  in invasive otitis externa 68.25
  Kawasaki disease and 50.45
  in malakoplakia 55.27
  methicillin-resistant (MRSA) *see* methicillin-resistant *Staphylococcus aureus* (MRSA)
  mupirocin-resistant 39.28
  nasal carriage 30.4, 30.6–7
  neonatal carriage 30.4–5, 30.6
  neonatal infection 17.42–4
  in neuropathic ulcers 63.9
  normal skin flora 30.1, 30.4
    elderly men 30.4
  in normal skin flora 30.3, 30.4
  in otitis externa 68.21, 68.22
  paronychia due to 30.32, 65.21
  perianal/perineal infections 71.92
  in periporitis staphylogenes 30.32
  production of biologically active substances 30.7–8
  resistance to infection 30.8
  scalp folliculitis 42.74
  in scarlet fever 30.7–8, 65.21
  skin free fatty acid effect on 42.7
  in staphylococcal scalded skin syndrome 30.30
  strain 502A 30.7
  in subacute bacterial endocarditis 62.78
  in superficial folliculitis 30.22
  surface components 30.7
  in sycosis 30.25
  therapy, topical antibiotics 73.9, 73.10
  in toxic shock syndrome 30.31
  in tropical ulcer 30.60
  umbilical infections 30.4–5, 30.6
  venous leg ulcer infections 47.44
  in Wegener's granulomatosis 50.39, 50.55
  wound infection 14.16
  see also methicillin-resistant *Staphylococcus aureus* (MRSA)
Staphylococcus capitis 30.3
Staphylococcus cohnii 30.3
Staphylococcus epidermidis 30.3, 30.11, 42.24
  acne aetiology and 42.24
  blepharitis 67.6, 67.11
  cellulitis 30.18
  folliculitis 42.36, 42.84
  growth inhibition by azelaic acid 73.28
  in invasive otitis externa 68.25
  in miliaria rubra 44.15
  in normal skin flora 30.3, 68.2
  in pyoderma faciale 43.14
Staphylococcus haemolyticus 30.3
Staphylococcus hominis 30.3
Staphylococcus hyicus 2.11, 2.12
Staphylococcus intermedius, animal infections 2.12
Staphylococcus pseudintermedius 2.11, 2.12
Staphylococcus saccharolyticus 30.2
Staphylococcus saprophyticus 30.3, 30.11

Staphylococcus simulans 30.3
Staphylococcus warneri 30.3
Staphylococcus xylosus 30.3
starch pastes 73.2
starch powders 73.2, 73.8
starch/iodine test 44.4, *44.5*
stargazers 38.59
STARI (Southern tick-associated rash illness) 38.35
starvation
  acne and 42.34
  gynaecomastia and 70.4
  sebum synthesis rate 42.6
STAT kinase 13.11
STAT3 66.10
statins 59.93
  adverse effects 75.156–7
  claudication management 47.5
statistical methods 7.19–22
statue eye 40.39
stavudine, photosensitivity due to 35.22
stearyl alcohols 73.7
stearyl amine 25.20
steatocystoma multiplex 42.88, **52.47**
  familial 42.88
  histogenesis 52.45
  isotretinoin treatment 42.62
steatopyga 46.46
Steel factor (mast cell growth factor/stem cell factor (M/SCF)) *see* stem-cell factor (SCF)
stele 66.7
stellae 66.21, 66.38
stellate bodies 61.4
  bullous dermolysis of the newborn 39.23, 39.25
stellate cells 3.3
stem cell(s) 3.5–6, 13.7
  bulge 3.6
  $CD34^+$ pluripotent 3.19
  embryonic (pluripotent) 3.7
  epithelial 3.5–6
    asymmetrical division 3.6, *3.7*
  haematopoietic *see* haematopoietic stem cell(s)
  hair follicle 3.6, 3.7, 66.3, 66.9
  markers 3.6
  melanocyte 3.21
  multipotent, in fat 3.52–3
  pluripotent, fibroblasts induced to be 3.50
  proliferation 3.6, *3.7*
  sebocyte *3.6*
  signalling 3.6–7
  strategies for burns 28.86–7
  transplantation 13.26, 76.7
    see also haematopoietic stem cell(s)
  wound healing and 14.26
stem-cell factor (SCF) 3.19, 12.24, 12.31
  adverse effects 75.144
Stenella araguata 36.14
Stenotrophomonas maltophilia 30.51
Stensen's duct *see* parotid duct
stenting
  claudication management 47.5
  varicose veins 47.39
Stephania tetrandra 75.160
Sterculiaceae *26.81*
stereotactic radiosurgery (SRS), melanoma metastatic to brain 54.55
steric hindrance 40.6
sternal clefts 18.88
sternocleidomastoid muscle 77.2, *77.3*
sternocostoclavicular hyperostosis 62.101
steroid nasal spray, rosacea associated in children 43.10
steroid phobia 73.17
steroid receptor(s) 73.16, 73.17
steroid receptor superfamily 73.43
steroid rosacea **43.10,** *73.19*
steroid sulphatase deficiency 19.9, 19.11–12
steroid therapy *see* corticosteroids
steroid ulcers 47.56
sterol, synthesis in epidermis 3.11
Stevens–Johnson syndrome (SJS) 69.69, **76.8–22**
  aetiology 76.9–15
  in animals 2.17
  cheilitis in 69.121
  clinical features 76.16–17
  conjunctival damage 67.20
  definition 76.1
  diagnosis 76.19–20
  drug-induced 42.51, *76.4,* 76.11–12
    antiretroviral drugs causing 35.7
  genetic markers 72.30
  HIV infection 35.7, 35.20
  immunology 76.9–10
  incidence 76.8–9
  male genital involvement 71.25
  Mycoplasma and 30.69, 62.80
  ocular complications 67.20, *67.21,* 76.16
    management 67.22–3
  pathology 76.15
  perianal/perineal involvement 71.91
  pharmacogenetics 76.10–11
  post-measles vaccination 33.75
  pregnancy and 8.12
  prevention 76.22
  prognosis 76.18–19
  terminology 76.1
  treatment 76.20–2
  in varicella 33.25
Stewart–Bluefarb syndrome 47.22
Stewart–Treves syndrome 48.15, 48.31, 56.37, 56.38
Stickler syndrome 15.46
stiff baby syndrome 19.14
stiff skin syndromes, infantile 45.50–1
stigma 64.2, **64.6–8**
  leprosy and 32.1
  skin disease in old age 8.25
Stigma Scale of mental illness 64.7–8
stigmata 49.16
stilbenes 26.79
stilboestrol, adverse effects *70.5*
stillbirths, congenital syphilis 34.15
Still's disease
  adult-onset 51.134, 62.104
  bone and joint involvement 62.104
  erythema marginatum in 62.107
  hyperferritinaemia and purpura 49.6
  juvenile 51.133
  leg ulceration associated 47.55
  pigmentation changes 58.26
stinger suits 38.57
stinging sensation
  delayed-type 25.19
  immediate-type 25.19
stingrays 38.59
stings
  arthropod 38.1–5, 38.13–15
  Cnidaria 38.55–8
  fish 38.59–60
  Hymenoptera 38.13–15
  Mollusca 38.59
  swimming and diving 28.55
  see also insect bite reactions
stinking mayweed 25.21
STK11 gene 58.12, 58.13
stoma
  cutaneous complications 62.53–4
  peristomal pyoderma gangrenosum 50.69, 50.72
stomach, cutaneous markers of disorders 62.48
stomatitis
  angular *see* cheilitis, angular
  blackberry 30.53
  chronic ulcerative with epithelial antinuclear antibodies 69.64
  denture-related (candidiasis) 36.60, *69.88,* 69.102–4
  drug-induced 75.47
  herpes simplex 69.13, 69.72–4
  monoclonal plasmacytic ulcerative 69.84
  necrotizing ulcerative, in HIV infection 35.43
  recurrent aphthous **69.44–6,** 69.48
  vesicular **33.74**
    coxsackievirus infections 33.71, 33.72
    hand, foot and mouth disease 33.71
stomatitis nicotina 69.90
Stomoxys calcitrans (stable fly) 38.6, 38.7
stonefish 38.59
storax 26.40
storiform patterning 10.38, 10.41–2
stork bite/mark (salmon patch) 18.62–3
Stormorken's syndrome 19.62
strangulation of the penis 28.38, 71.14
stratum basale 3.8
  structure 3.8
stratum compactum 4.2
stratum corneum 3.1, 3.8, 3.10, 4.4
  absorption through 4.4–5
  ageing 4.11
  assembly/formation 3.10–11
  bacterial flora 30.2
  barrier function 3.2–3, 4.2, *4.3*
  composition 3.10–11
  corticosteroid diffusion 73.16
  ear 68.1
  effects of wetness 17.23
  glabrous skin 3.3
  in irritant contact dermatitis 25.2, 25.8–9
  mechanical function and properties 4.8
  mechanical injury 28.5, 28.6–7
  neonatal 17.1–2
  precursors and formation 3.10
  racial variations 9.2, 9.13
  structure 3.1, 3.8, 3.10
  two-compartment model 4.2
stratum corneum tryptic enzyme (SCTE) 12.5, 43.2
stratum dysjunctum 4.2
stratum germinativum (basale) 3.8
stratum granulosum 3.8, 3.10
  ear 68.1
stratum intermedium 42.3
stratum lucidum 3.9
stratum spinosum 3.8, 4.2
  structure 3.8
straw itch 38.48
strawberry naevus *see* naevus, strawberry
streblodactyly 45.47
Strengthening the Reporting of Observational Studies in Epidemiology 7.17
Streptobacillus moniliformis 30.67
streptocerciasis **37.8**
streptococcal pyodermas, erythromycin 74.42
streptococcal toxic shock-like syndrome 30.12, 30.35
Streptococcus (streptococci) **30.11–14**
  α-haemolytic 30.11, 30.13
  β-haemolytic 30.11, 30.67
    ear infection 68.19
    erythema nodosum and 50.83
    eye infection 67.27
    normal skin flora 30.1
  in cellulitis 30.17, 30.18
  in cutaneous disease *30.11*
  in erysipelas 30.17
  erythema elevatum diutinum and 50.25
  eye infections 67.27
  female genital infection 71.67
  γ-haemolytic 30.11
  genitocrural infection 71.5
  group A
    in HIV infection 35.24–5
    see also Streptococcus pyogenes
  group B 30.13, 30.17, 30.33, 30.69
    vulva 30.4
  group C 30.12–13, 30.17, 30.69
  group D 30.13, 30.69
  group F 30.13, 30.80
  group G 30.12–13, 30.17
  group L 30.13
  in Henoch–Schönlein purpura 50.20
  in impetigo 30.14, 30.15–16
  intertrigo due to 30.33
  in normal skin flora 30.2
  perianal/perineal infection 71.92
  pyoderma due to 30.14, *30.15,* 30.16, 30.33
    erythromycin 74.42
  serology 30.13
  urticaria following infection 22.8
Streptococcus faecalis, female genital infection 71.68
Streptococcus milleri 30.80
  female genital infection 71.67
  perianal/perineal infection 71.88
Streptococcus pneumoniae
  in ectodermal dysplasias 15.60
  in erysipelas 30.18
  in orbital cellulitis 30.18
Streptococcus pyogenes 30.4, **30.11–12**
  in blepharitis 30.32
  burns 28.85
  carriage 30.11–12
    management 30.12
  complications of infection 30.12
  control of epidemics 30.12
  in dermatitis vegetans *30.77*
  in ecthyma 30.17
  exotoxins 30.11
  growth inhibition by free fatty acids on skin 30.4
  in HIV infection 35.24
  initiation of infection 30.12
  Kawasaki disease and 50.45
  M proteins 30.11
  male genital infection 71.30
  in nasal vestibule 30.4
  perianal infection 30.32–3
  scarlet fever and 30.16, 30.34
  skin strain 30.12
  superinfection of chromic acid burns 27.12
  T proteins 30.11
  throat strain 30.12
  topical therapy 73.10
  toxic shock syndrome and 30.31
  umbilicus 30.5
  vulvovaginitis 30.32
Streptococcus viridans 30.13
  in subacute bacterial endocarditis 62.78
streptodornase, in wound debridement 14.22
streptokinase 75.107
  in wound debridement 14.22
Streptomyces 30.39
Streptomyces somaliensis 36.72, *36.73*
Streptomyces tsukubaensis 73.31
streptomycin 74.42, 74.44
  adverse effects *26.46,* 31.27, **75.58**
  in tuberculosis 31.27
stress 64.4, 64.5
  acne and 42.35
  alopecia areata and 66.32
  atopic dermatitis and 24.19
  herpes simplex recurrence 33.18
  immune response and 64.8–9
  lichen planus association 41.3
  neuromediators 12.63
  nodular prurigo and 23.42
  occupational dermatoses and 27.2
  oxidative stress 12.55
  role in pompholyx 23.17
  urticaria and 22.11–12
  workplace 64.26
  wound healing and 14.1
stress lines (skin tension lines) 77.2, 77.11, 77.13
stretch marks *see* striae
stretching of skin 4.8, 5.18
striae 4.8, 5.*11,* **45.4–6**
  aetiology 45.5
  clinical features 45.5
  corticosteroid-induced 45.3, 45.5, *73.18*
  definition 45.5
  diagnosis 45.5
  elastotic 45.25–6
  in liver disease 62.64
  pathology 45.5
  treatment 45.6

striae distensae (striae gravidarum) 8.13
  sports injury 28.31
striate keratoderma 19.3, *19.94*, 19.95, 19.105–6, 19.107
strimmer's dermatitis 29.21, 58.32
  see also phytophotodermatitis
string test 37.15
STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) 7.17
stromelysins 12.52, 14.11
Strongyloides stercoralis 37.2, 37.14, 37.15–16
  disseminated infection 49.36
  perianal/perineal infection 71.96
strongyloidiasis 22.10, **37.15–16**
  disseminated 49.36
  purpura 49.20
strontium sulphide 73.29
structure of skin **3.1–3.53**
stucco keratosis 52.40
  treatment 73.24
students, medical 72.2
stump pemphigoid 28.29
STUMPs (atypical spitzoid tumours of unknown malignant potential) 54.24, 54.39
Sturge–Weber syndrome **18.65–7**
  bone and joint involvement *62.100*
  ocular involvement 18.66
  oral involvement 69.13, 69.29, 69.30
styes 67.6, 67.26–7
styrene 25.21
subacute cutaneous lupus erythematosus (SCLE) 51.2, 51.22–7
  aetiology 51.22
  autoantibody status 51.22
  clinical features 51.23–4
    urticarial lesions and vasculitis 51.38–9
  drug associations 51.24
  histopathology 51.22–3
  Ro/SS-A antibodies 51.49
  treatment 51.23–4
subareolar duct papillomatosis *see* nipple, erosive adenomatosis
subclavian artery, occlusion 47.2
subcorneal pustular dermatosis 40.19–22, 50.62, 50.95, 62.49
  differential diagnosis 40.21
subcutaneous fat **3.52–3, 46.1–49**
  absence 54.11
  atrophy *see* lipoatrophy
  blood supply 46.2, 46.11
    compromised, encapsulated fat necrosis 46.22
  brown 3.52, 46.1
  central accumulation, HIV lipodystrophy 46.42
  cold injury, panniculitis 46.21
  composition 46.2
  deeper (lamellar) layer 46.2
  drug/oil-induced injury 46.28
  embryology 46.1
  fibrosis after injury 46.11
  functions 3.3, 3.52, 46.1, 46.2
  gynoid vs android distribution 46.2
  histology 46.1–2
  hyaline necrosis 46.26
  hypertrophy 46.34, 46.41, 70.3, 70.4
  increased deposition 46.41
  inflammation, macrophage associated 46.4, 46.6, 46.11
  inflammatory disorders 46.10–11
    see also panniculitis
  lobules 46.2
    encapsulated fat necrosis 46.22
  loss *see* lipoatrophy; lipodystrophy
  lymph drainage 46.2
  macrophages in 46.4, 46.6, 46.11
  measurement methods 46.5
  mechanical injury 28.27
  necrosis 46.11, 46.13, 46.21–3, 46.44
    following hypothermic cardiac surgery in infancy 17.37–8
    lipomembranous (membranocystic) 46.22–3
    of newborn 17.36–7, 46.12
    nodular cystic (encapsulated) 46.22
    obesity 8.17
    in pancreatic disease 46.18–20, 62.65–6
  neonatal disorders 17.34–9
  physiology 46.2–4
  'pseudoherniation' 46.10
  superficial (areolar) layer 46.2
  traumatic injury
    blunt trauma 46.28–9
    cellular events after 46.11
  see also panniculitis
subcutaneous nodules
  lipoma 46.44
  panniculitis 46.11
subcutaneous panniculitis-like T-cell lymphoma (SPTL) 57.33
subcutaneous panniculitis-like T-cell lymphoma of α/β T-cell phenotype (SPTL-AB) 46.23, 46.24, 46.25
subcutaneous panniculitis-like T-cell lymphoma of γ/δ T-cell phenotype (SPTL-GD) 46.23, 46.24, 46.25
subcutis *see* subcutaneous fat
subepidermal calcified nodules 56.2
subepidermal immunobullous diseases 40.25–62
  clinical features 40.26
  immunopathology and immunogenetics 40.27
  variants 40.26
  see also bullous pemphigoid; *specific diseases*
subepidermal nodular fibrosis *see* fibrous histiocytoma (FH)
subfascial endoscopic perforator surgery 47.39
submandibular duct 69.5
submandibular gland examination 69.5
submucous fibrosis 69.106–7
substance abuse 64.13, *64.14*, 64.18
  see also alcohol abuse
substance P 4.10, 12.64, 12.66, 63.2, 63.3, 64.5, 64.9
  in atopic dermatitis 24.17
  capsaicin stimulating release 73.49
  flushing in rosacea 43.2
  immune function and 63.4
  pruritus and *21.3*, 21.4
  triple response of Lewis and 63.5
  in urticaria 22.5
  in wound healing 63.4
subungual exostosis *62.101*, 65.33–4
subungual haematoma 65.49–50
subungual hyperkeratosis 20.16, 51.12, 65.12, 65.15, 65.24
subungual keratoacanthoma 65.38
subungual keratotic tumours 65.38
subungual melanoma *see* melanoma, malignant
subungual onychomycosis
  distal and lateral 36.34, 36.63
  proximal 36.35
subungual osteochondroma 65.33
subungual pigmentation 54.45
subungual warty dyskeratoma 65.18
succinylcholine 75.153
sucker-daddy syndrome 28.24
sucking blister 17.4
suckling pads 17.5
sucralfate 17.26
suction injury **28.23–5,** 28.39
suction pads 28.24
suction tests, mechanical injury 28.5
sucupira *26.80*
Sudeck's atrophy 47.11, 63.21
  see also complex regional pain syndrome
sudorific nervous system 3.12
sugar, in wound treatment 14.21
Sugio–Kajii syndrome **15.65–6**
suicide **64.48–9**
  acne and 42.35, 42.63
  assessment of risk 64.48–9
  body dysmorphic disorder 64.19, 64.48
  rate of in UK 64.48
  with self-harm 64.45–6
Suidasia nesbitti 38.47
SUKA (subungual keratoacanthoma) 65.38
sulconazole
  in dermatophytosis *36.47*, 36.48
  topical 73.12
sulcus terminalis 69.2
sulfadiazine 44.17–18
sulfadoxine, adverse effects 75.56–7
  Stevens–Johnson syndrome 76.11
sulfaguanidine 44.17–18
sulfamethoxypyridazine 74.28, 75.56
  linear IgA disease 40.51
sulfapyridine 74.28
sulfasalazine
  adverse effects 75.33, 75.56
  in cicatrizing conjunctivitis 67.22–3
  in lichen sclerosus 51.118
  in psoriasis 20.42
  in psoriatic arthritis 20.59
  in urticaria 22.29
sulfones 74.28, 74.45
sulindac 75.76
sulphapyridine, in cicatrizing conjunctivitis 67.22–3
sulphasalazine *see* sulfasalazine
sulphatases 3.45–6
17β-sulphinyl steroids 42.16
sulphites 22.11, 75.159
sulphonamides 74.38–9
  adverse effects 26.17, 74.38–9, **75.55–8,** 75.61
    mechanisms 76.10
  in cicatrizing conjunctivitis 67.23
  as photoallergens 26.24
  in toxoplasmosis 37.44
sulphonated oils 25.20
sulphonylureas 75.156
sulphur
  acne vulgaris treatment 42.43
  depletion 59.72
  granules 30.75
  metabolism 59.72–4
  in scabies 38.41
sulphur-deficient brittle hair, IBIDS/PIBIDS syndrome 19.47–9
sulphur granules 30.75
sulphur-rich L granules 3.10
sulphuric acid, burns 27.12
sulpiride 64.52
sultones 26.27
Sulzberger–Garbe disease 23.11–12
Sumatra, prevalence of skin disease *6.10*
summer penile syndrome 38.51
sun exposure
  avoidance
    epidermodysplasia verruciformis 33.58
    naevoid basal cell carcinoma syndrome 52.7
    see also photoprotection; sunscreens; ultraviolet (UV) radiation, exposure minimisation
  cancers in HIV infection and 35.39, 35.40
  malignant melanoma 6.12, 29.7, 54.32–3, 54.34, 73.41
  Merkel cell number change 3.15
  minimization 29.8–9
  non-melanoma skin cancers 29.7
  simple lentigo 54.3
  telangiectases due to 47.13
  see also sunlight; ultraviolet (UV) radiation
sun protection factor (SPF) 29.8, 58.31, 73.40–1, 80.3
  calculation 73.40
  high-SPF sunscreens 29.9
  see also sunscreens
sun tan 73.40
  false 73.49
  see also tanning
sunbathing, non-melanoma skin cancers and 52.3
sunbeds/sunlamps 29.4
  DNA damage 58.31
  usage, malignant melanoma risk 54.33
  see also tanning
sunburn 4.7, 29.4, 58.7
  avoidance/prevention 29.8
  exaggerated, drugs associated 29.20, *29.21*
  malignant melanoma risk 54.33
  sensitivity to 29.5
  treatment 29.8
sunburn cells 29.5
sunlight 29.4
  acne improvement and cautions 42.34
  actinic lichen planus 41.13
  feel-good and health factors 29.6–7
  UVR source 29.1
  vitamin D synthesis 29.6
  see also sun exposure; ultraviolet (UV) radiation
sunscreens 29.8–9, 52.3, **73.40–1**
  actinic keratosis reduction 52.32
  in ageing prevention 80.3
  allergic contact dermatitis to 26.62–3
  chemical 73.40
  classification 73.40–1
  contact sensitization by 29.9
  dermatitis due to 73.40
  dihydroxyacetone in 73.49
  efficacy and mechanism of action 29.8
  endogenous 73.40
  exogenous 73.40
  high-SPF 29.9
  ideal, characteristics 73.40
  in lipsticks and lipsalves 69.119
  melanoma prevention 54.34, 73.41
  mineral oxide micropigments 29.8
  misuse/abuse 73.40
  naevi number and 73.41
  organic micropigments 29.8, 29.9
  photoallergic reactions to 29.20
  photodermatoses management 73.41
  physical 73.40
  polymorphic light eruption treatment 29.12
  prescribable 29.9
  resistance to water (substantivity) 29.8, 73.40
  SPF rating *see* sun protection factor (SPF)
  UVR interaction with 73.40
  vehicles for 73.2
sunset yellow 22.11, 75.158
superantigens 17.50–1
  in Kawasaki disease 30.78
  staphylococcal 73.20
    corticosteroid mechanism of action and 73.17
    S. aureus 24.8, 24.12, 30.8
  streptococcal 30.11
  in vasculitis 50.4, 50.5–6
superficial acral fibromyxoma 56.6
superficial necrolytic dermatitis (SND), dogs 2.17, 2.20
superficial papillary adenomatosis *see* nipple, erosive adenomatosis
superficial spreading carcinoma (squamous cell) 71.41–2
superficial spreading carcinoma, male genital 71.41–2
superficial spreading melanoma *see* melanoma, malignant
superficial white onychomycosis (SWO) 36.34, 36.50, 36.53, **36.55**
superglue (cyanoacrylates) 26.72, 65.28
superior vena cava obstruction 62.44
supernumerary digit 18.92
supernumerary nipple 18.92–3, 70.2–3
superoxide anion 13.4

superoxide dismutase, reduced levels, rosacea 43.2
support groups 64.7, 72.33–4
  atopic dermatitis 72.23
suppressor of cytokine signalling (Socs) protein pathway 12.35
suprabasal cleavage
  in EB *39.2*
  in Hailey–Hailey disease 39.33
supraorbital nerve 77.2, *77.4*, 77.10
supratrochlear nerve 77.10
suramin
  adverse effects 75.135
  in African trypanosomiasis 37.31
  in onchocerciasis 37.7
surface-active agents 25.20
surfactants 26.59, 66.96
surgery **77.1–50**
  adjuvant radiotherapy 79.7
  in burns 28.84–6
  comparison with Mohs micrographic surgery 77.29, 77.31
  comparison with radiotherapy 79.5–7
  complications 77.8–10
  critical anatomical areas 77.1–5
  dressings 7.17–18
  equipment and sterilization 77.5, *77.6*, *77.7*
  excision 77.13–14, 77.15–16
    elliptical 77.13–14
    snip 77.34
    wedge 77.35
  haemostasis 77.50
  head and neck 77.2–5
  hydrodissection 77.2, 77.34
  incision and scar orientation 77.2
  in infantile haemangioma 18.51
  Kasabach–Merritt syndrome/phenomenon 18.57
  legs 77.5
  minor procedures 77.50
  nail apparatus 65.41–9
  in non-melanoma skin cancer 52.17
  in pressure ulcers 28.23
  relaxing incisions 77.34–5
  safety measures and protocols *77.7*
  snip excision 77.34
  sutures 77.14–15
  tissue expansion 77.35
  undermining levels 77.5
  wedge excision 77.35
  wound closure 77.16–17
  see also skin biopsy
Sutton's disease 69.45
  female genitalia 71.65
Sutton's naevus (halo naevus) **54.19–20,** 58.49–50
Sutton's ulcer, female genital dermatology 71.65
sutures 77.14–15
suxamethonium 75.153
swallow bug 38.24
swamp cancer 36.92
sweat
  apocrine 44.19
    odour 30.4
  assessment of production 44.4, *44.5*
  chloride in 44.5
  coloured 44.20–1
  composition 3.12, 44.5–6
  in cystic fibrosis 44.6
  glucose in 44.6
  immunoglobulin E (IgE) in 44.6
  lactate in 44.5, 44.6
  mammals 2.4
  odour 30.4
  production 3.12
  retention
    apocrine 44.21–2
    eccrine 44.13
    in psoriasis 44.13
  sodium in 44.5–6
  urea in 44.5, 44.6
sweat dermatitis, frictional 28.14
sweat ducts
  carcinoma, sclerosing/syringomatous 53.35–6
  intraepidermal, development 3.5
sweat glands **3.12–13**
  abscess 17.43
  adenocarcinoma 53.40
  apocrine (epitrichial) *see* apocrine sweat glands
  apoeccrine 3.12, 44.1, 44.3
  axillary 44.1
  carcinoma **53.32**
    apocrine/follicular **53.33–7**
    eccrine **53.32–3, 53.33–7**
  comparative anatomy and physiology 44.1–3
  ear 68.1
  eccrine (atrichial) *see* eccrine sweat glands
  ectodermal dysplasias 15.59, 15.62, 15.64–6, 15.69
  embryology 3.3
  intermediate (apoeccrine) 3.12
  naevi 44.9
  odour production 44.2, 44.8, 44.19–20
  secretion inhibition 73.9
  tumours **53.18–37**
    apocrine **53.18–22**
    eccrine **53.22–7**
    eccrine or apocrine/follicular **53.27–32**
    miscellaneous **53.37–42**
sweating 3.12
  acne and 42.34
  ageing effect 8.24
  atopic dermatitis and 24.18–19
  cholinergic, ageing effect 8.24
  control of 3.12, 44.2, 44.5–7
  flushing with (wet flushing) 43.14
  following spinal cord injury 63.17
  gustatory, treatment 73.9
  innervation and control 3.12
  mental/emotional 3.12
  mental stimuli 44.5
  obesity and 8.17
  thermal 3.12
  thermoregulatory 4.7, 44.2, 44.4, 44.5
  see also hyperhidrosis
'sweating sickness' 44.7
Sweden, prevalence of skin disease *6.9*
'sweet itch' 2.11
Sweet's disease-like annular erythema 51.135
Sweet's syndrome 46.34, **50.74–80**
  acral, of dorsal hands 50.80–1
  aetiology and pathogenesis 50.74, *50.75*, 50.76–7
  annular lesions 62.112
  atypical 46.32
  bone and joint involvement 62.103
  childhood 50.63
  classic/idiopathic 50.74
  clinical features 50.78–9
  conditions associated 50.74, *50.75*
  Crohn's disease and *50.75*, 62.51
  definition 50.74
  diagnosis 50.79
  differential diagnosis 50.70
  drug-induced 50.74, *50.75*
  histopathology 50.77–8
  history and nomenclature 50.74
  infection and *50.75*
  neutrophilia in 62.86
  oral involvement 69.49
  paraneoplastic 50.74, *50.75*, 62.41
  photoaggravated/photoinduced 50.78
  pustulosis in *50.89*
  scrofuloderma and 31.14
  subcutaneous 50.90–1
  treatment 50.79–80
  ulcerative colitis and *50.75*, 62.51
  vasculitis and 50.3, 50.77–8
swelling, male genital 71.49–50
swimmer's itch (cercarial dermatitis) 28.55, 37.20, **37.22–3,** 38.56, 38.57
swimmer's shoulder 28.31
swimming
  mechanical injury 28.31, 28.53–6
  skin hazards 30.49
Swiss-cheese-like pseudocystic spaces 46.28, *46.28*, 46.29
Swiss type ectodermal dysplasia 15.29
SWO (superficial white onychomycosis) 36.34, 36.50, 36.53, **36.55**
Sybert's keratoderma *19.94*, 19.99
sycosis **30.25–6**
  in HIV infection 35.28
  mycotic 30.25
Sydney funnel-web spider 38.31
Syk protein 48.2
symblepharon *67.4*, *67.18*
  in dystrophic EB 39.19
symmetrical dyschromatosis of the extremities 58.21–2
symmetrical interdigital keratoderma 19.115–16
symmetrical lividity of the feet 44.8
symmetrical progressive leukopathy 58.52
sympathectomy
  in complex regional pain syndrome 63.21
  gustatory hyperhidrosis following 63.22
  Horner's syndrome following 63.22
  in hyperhidrosis 44.12, 77.37
  in thromboangiitis obliterans 47.8
  transthoracic endoscopic 43.15
sympathetic nervous system 63.1
  injury 63.20
  lesions, hyperhidrosis and 44.9, 44.10
  sweating and 3.12
sympathetic skin response 63.4
sympathomimetics, adverse effects 26.17
Symphoromyia 38.6
symptoms, history-taking 5.4
Symtrack itch rating system 21.2
synaptophysin 10.21
synbiotic supplements, in atopic dermatitis 24.31, 24.34
syndactyly, with ectodermal dysplasia and cleft lip/palate 66.52
syndecan-1 3.16, 3.45
syndecan-4 3.16, 3.45
syndecans 3.45
syndromes
  definition 5.2
  overlap 5.2
synergistic bacterial gangrene 71.67
synergistins 75.60
synophrys 67.3
syphilide
  corymbose 34.11
  lichenoid 34.11
  macular (roseolar rash) 34.8–10
  nodular (tubercular) 34.12–13
  nodulocutaneous *34.13*
  papular *34.9*, *34.10*, 34.10–11
  papulosquamous 34.11
  pustular ulcerative 34.11
  serpiginous nodulo-squamous 66.52
syphilis **34.1–24**
  acquired **34.6–15**
  alopecia 34.11, 66.29, 66.52
  anetoderma in 45.17
  antibodies 34.20, 34.21
    detection 34.19–21
  atypical, in HIV infection 35.25
  biopsy specimens 34.18, 34.19
  bone and joint involvement 34.16, *62.100*, 62.105
  cardiovascular 34.14, 34.16
    treatment *34.22*
  causative organism 34.3–4
  congenital 17.25, 17.46, **34.15–18**
    diagnosis 34.21
    early 34.15–16, *34.18*
    late 34.16, *34.18*
    prevention 34.24
    stigmata 34.16–17
    transmission 34.5, 34.12
    treatment 34.16, 34.23, *34.23*
  control 34.24
  dactylitis in 34.16
  definition 34.1
  diagnosis **34.18–21**
    biological false-positive tests 34.20–1
    CSF examination 34.21
    dark-field microscopy 34.3, 34.18–19
    latent syphilis 34.12
    molecular amplification tests 34.19
    rapid point-of-care tests 34.20
    serological screening 34.20–1, 34.24
    serological tests (STS) 34.16, 34.19–21
    specimens 34.18
  differential diagnosis 34.7–8, 34.11–12, 61.5, 61.10
  ear involvement 68.20
  endemic 30.63
  female genital involvement 71.71
  follow-up 34.23
  histopathology 34.5
  HIV co-infection 34.3, 34.14
    treatment 34.23
  incidence *34.2*, 34.2–3, 34.15
  incubation period 34.5
  latency 34.5, 34.11
  latent 34.12, 34.23
    diagnosis, CSF examination 34.21
  leukoderma in 58.31
  male genital involvement 71.33–4
  management 34.22–4
    failure 34.23
    in pregnancy 34.22–3
    of sexual contacts 34.23
  medico-social background 34.2
  in men who have sex with men (MSM) 34.3, 34.7
  meningovascular 34.14
  natural history 34.5
  neurosyphilis *see* neurosyphilis
  ocular involvement 67.27
  oral involvement 69.78, 69.90, 69.91, *69.118*
  parenchymatous 34.14
  pathogenesis 34.4
  perianal/perineal involvement 71.93
  in pregnancy 34.15, 34.24
  primary **34.6–8**
    diagnosis 34.18
    differential diagnosis 34.7–8
    sites 34.7
    treatment *34.22*
  prognosis 34.23–4
  race and 9.6
  reinfections 34.23
  risk factors 34.24
  sarcoidal reaction in 61.22
  screening 34.24
  secondary 34.8–12
    diagnosis 34.18
    differential diagnosis 34.11–12, 61.10
    hair loss in 34.11, 66.29, 66.52
    papules 34.7, *34.9*, 34.10–11
    pityriasis rosea vs 33.80
    post-inflammatory hypermelanosis after 58.31
    renal involvement 62.71
    sarcoidosis and 61.18
  secondary prevention 34.24
  stages 34.5
  stigmata 34.16
  tattoo localization and 58.58
  tertiary (late) 34.12–14
    diagnosis 34.18, 34.19
    differential diagnosis 31.10, 34.14
    follow-up 34.23
    gumma 34.13–14
    leg ulcers 47.56
    management 34.22
    mucous membrane lesions 34.14
    osteomyelitis in 62.105
    scalp involvement 66.52
    scars 45.6

tests for **34.18–21**
see also syphilis, diagnosis
transmission 34.5, 34.12
treatment 34.2
see also syphilis, management
untreated, course of 34.5
vaccine development problem 34.24
syringobulbia 63.14
syringocystadenoma *see* syringoma
syringocystadenoma papilliferum **18.14–15,** 53.19–20, 68.30
syringocystoma *see* syringoma
syringofibroadenoma, eccrine 53.22, 53.24–5
syringoid eccrine carcinoma 53.36
syringoma 53.25–6, 71.72
chondroid 53.2, 53.30–2
malignant 53.31
eruptive 53.25
eyelid 67.33, 78.14
female genitalia 71.72
genetics 15.10
male genitalia 71.36
malignant 53.35–6
syringomyelia **63.14–15**
post-traumatic 63.17
syringosquamous metaplasia 44.17, 75.123
systematic reviews 6.16, 7.4
appraisal and evaluation 7.7–11
Cochrane Database of Systematic Reviews 7.5
information resources 6.20
systemic agents **74.1–54**
anti-inflammatory agents 74.2–3
antiallergic agents 74.31
antifungal drugs 74.46–8
antimicrobials 74.38–50
antiparasitic agents 74.50–1
antiviral drugs 74.48–50
biological therapies 74.4–13
Chinese herbal medicine 74.52
drugs to improve peripheral circulation 74.51
immunomodulating agents 74.25–30
immunosuppressive agents 74.14–24
levels of evidence of efficacy 74.1
protein therapeutics 74.4–13
retinoids 74.33–8
sex hormones and related compounds 74.32
see also specific agents for further references
systemic capillary leak syndrome 22.23
systemic disease and the skin **62.1–113**
in animals 2.17–18
bone and joint disorders **62.99–106**
cardiac disease **62.75–80**
endocrine disorders **62.2–14**
eye involvement 67.24, *67.25*
gastrointestinal disorders **62.47–58**
haematological disorders **62.85–96**
liver disorders **62.58–65**
pancreatic disorders **62.65–8**
renal disorders **62.68–75**
respiratory disorders **62.80–5**
see also individual diseases and disease groups (e.g. liver, disorders)
systemic lupus erythematosus (SLE) **51.27–63**
aetiology 51.28
abnormal cell-mediated immunity 51.30
autoantibodies 51.29, 51.32
environmental factors 51.30
genetic/environmental factors 51.32
infections, stress and hormonal factors 51.31
viral involvement 51.31
age of onset 51.27
alopecia 66.29
anetoderma in 45.17
in animals 2.16
annular erythema in 62.109
antinuclear antibody-negative SLE 51.56
ARA criteria for diagnosis 51.27
association with other diseases 51.56–7
autoantibodies 51.29, 51.32, 51.63
bone and joint involvement 62.102
bullous *see* bullous systemic lupus erythematosus
cardiac involvement 51.43, 62.78
in childhood 51.48
clinical features 51.35–48
avascular bone necrosis 51.47
bullous SLE 51.41
calcification 51.47
cardiac involvement 51.43
cutaneous features 51.36
eyes/ears 51.46–7, 68.17
gastrointestinal tract 51.44–5
hair changes 51.38, 66.29, *66.30*
hepatic lesions 51.45
hypertension 51.43
IgG anticardiolipin antibody 51.63
lupus anticoagulant 51.63
lymphadenopathy 51.48
mucinosis 51.40
muscle changes 51.47
neurological and psychiatric disease 51.45–6
other cutaneous changes 51.40
polyarthritis with inflammation 51.42
pulmonary infiltration 51.43
renal changes 51.44
rheumatoid-like deformity 51.42
thyroid disease 51.45
vasculitis 51.39
cryoglobinulinaemia with 49.32
diagnosis 51.27
differential diagnosis 51.59
discoid lupus erythematosus vs 51.2
rosacea vs 43.5
drug-associated 51.31–2, 51.63
ear involvement 51.46–7, 68.17
in the elderly 51.48
genetic counselling 51.61
genetics 15.13
hair changes 51.38, 66.29, *66.30*
HPV infections 33.59
idiopathic thrombocytopenic purpura and 49.9
idiotypes and anti-idiotypes 51.29
immunohistology 51.34
incidence 51.27
laboratory investigations 51.52
lip involvement 69.128
lupus panniculitis 46.25
ocular involvement 51.46–7, *67.25*
oral involvement 69.71
paraneoplastic 62.39–40
pathological features 51.33
pathology
DLE and 51.34
Libman–Sacks endocarditis 51.33
pemphigus foliaceus and 40.16
pigmentation changes 58.27
in pregnancy 8.12, 51.48
prognosis 51.59–60
respiratory tract involvement 51.43, 62.82
treatment 51.61–3
azathioprine 74.15
ciclosporin 51.62
corticosteroids 51.61
danazol 51.62
dietary measures 51.62
extracorporeal photochemotherapy 51.62
hydroxychloroquine 51.61
immunosuppressive drugs 51.61
methotrexate 51.62
plasmapheresis 51.62
prednisolone 51.61, 51.62
specific treatment as for DLE 51.62
TNF antagonists 74.8
vasculitis and 50.48, 51.39
systemic scleroderma *see* systemic sclerosis
systemic sclerosis **51.87–110**
aetiology 51.88
HLA-DR typing 51.90
microchimerism 51.90
other factors 51.90
associations 51.105–6
autoimmunity 51.89, 51.105
in childhood 51.105
classification 51.91
clinical features 51.94–105
bone changes 51.97
calcinosis 51.97
cardiac involvement 51.101, 62.78
central nervous system 51.102
cutaneous changes 51.94–5
dental changes 51.102
eye changes 51.103
hepatic involvement 51.101
involvement of the gastrointestinal tract 51.99
joint involvement 51.102
morphoeic patches 51.106
muscle involvement 51.101–2, 51.105
osteopoikilosis 51.98
pulmonary involvement 51.98
renal involvement 51.101
tendon involvement 51.102
terminal absorption of the phalanges 51.97
without skin involvement 51.97
diagnosis 51.91
differential diagnosis 51.106
dermatomyositis vs 51.128
ocular mucous membrane pemphigoid vs 67.20
genetic factors 51.90
immunoglobulin/complement absence from dermal–epidermal junction 51.92
incidence 51.87
laboratory abnormalities 51.103–4
anticentromere antibodies 51.103
methotrexate 74.20
natural history 51.94
paraneoplastic 62.40
pathology 51.91
pigmentation changes 58.26
in pregnancy 51.105
prognosis 51.107
progressive 62.99
bone and joint involvement 62.103
race and 9.14
Sjögren's syndrome in 51.105
treatment 51.107–9
variations 51.104–5

T
T4 endonuclease V 15.74
liposomal formulation 73.23
T-cell inhibitors, psoriasis 74.6
T-cell leukaemia–lymphoma *see* adult T-cell leukaemia–lymphoma (ATLL)
T-cell lymphomas **57.3–40**
adult T-cell leukaemia–lymphoma (HTLV-1-associated) 57.37–9
see also adult T-cell leukaemia–lymphoma (ATLL)
aggressive epidermotropic CD8+ (provisional) 57.35–6
bexarotene 57.23, 74.37
CD4+/CD56+ haematodermic neoplasm (blastic NK-cell lymphoma) 57.39–40
CD4+ small/medium sized pleomorphic 57.36–7
CD30+ lymphoproliferative disorders 57.29–34
anaplastic large cell lymphoma 57.31–3
lymphomatoid papulosis 57.29–30
EBV association 33.31
extranodal NK/T-cell lymphoma (nasal type) 57.40–1
follicular mucinosis 57.14
gamma/delta (provisional entity) 57.36
granulomatous slack-skin disease 57.15–16
hydroa vacciniforme and 29.15
mycosis fungoides 57.3–13, 57.22–9
pagetoid reticulosis 57.15
peripheral T-cell lymphoma 57.34–40
primary cutaneous CD30+ lymphoproliferative disorders 57.29–34
secondary 57.51–3
angioimmunoblastic T-cell lymphoma 57.51–2
post-transplant lymphoproliferative disorder (PTLD) 57.51–2
Sézary syndrome 57.17–29
subcutaneous, panniculitis in 46.23
subcutaneous panniculitis-like (SPTL) 46.26, 57.33
of α/β T-cell phenotype (SPTL-AB) 46.23, 46.24, 46.25
of γ/δ T-cell phenotype (SPTL-GD) 46.23, 46.24, 46.25
WHO–EORTC classification 57.2
see also lymphoma(s)
T-cell receptors 4.8, 13.6–7
development 13.7, 13.8, 17.49
gd 13.6
gene analysis 57.12–13
T lymphocytes 13.6–7, 13.7, 17.49, 64.9
activation 4.8, 13.10–11, 17.50, *24.13*
Langerhans' cell role 3.17, *3.18*
adverse drug reactions and 75.18–19
ageing effect 8.24
in allergic contact dermatitis 26.6
anergy 17.50
antigen presentation to 13.9–10, 17.50–1, 55.4
in atopic dermatitis 24.6–8, 24.11
blister formation 40.26
CD8+ class I pathway 12.13
clonal proliferation, cytophagic histiocytic panniculitis 46.23
cytokines released 35.4, 35.18, 35.22, 42.26
acne pathogenesis 42.26
cytotoxic (Tc/$CD8^+$) 12.13, 13.7
activation 4.8
commercially available antibodies to 10.25
development 13.8
in HIV infection 35.3–4
increased in pruritic papular eruption in HIV 35.19
increased in psoriasis in HIV infection 35.17
in lichen planus 41.1
reduced in Langerhans' cell histiocytosis 55.6
subtypes 13.11
Tc1 13.11
Tc2 13.11
in delayed-type hypersensitivity reactions 26.5
depression/anergy
in Langerhans' cell histiocytosis (LCH) 55.6, 55.7
in measles 33.75
in dermis 3.18–19
development 13.7, 13.8, 17.49–50
differentiation 35.4
EBV infection 33.31
in eczema 23.5
extrathymic generation 13.8
γδ 13.6
in Behçet's disease 50.56
in Langerhans' cell histiocytosis 55.8
in vasculitis 50.6
in granuloma annulare 60.4
helper (Th/$CD4^+$) 13.7, 64.9
acne scarring and 42.27
activation 4.8

in atopic dermatitis 24.6–7
autoreactive, antiphospholipid syndrome 49.41
commercially available antibodies to 10.25
defective in psoriasis in HIV infection 35.17
destruction in HIV infection 35.4, 35.5, 35.10
development 13.8
differentiation 24.13–14, 35.4
in HIV infection 35.4
in lichen planus 41.1
polymorphic light eruption 29.11
reconstitution by HAART 35.4
subtypes 13.11
in urticaria 22.3
in vasculitis 50.6
see also Th1 cells, Th2 cells, Th3 cells (below)
helper (Th/CD4$^+$) count
AIDS-defining complication 35.5
eosinophilic folliculitis in HIV infection 35.18
in HIV infection 35.5
immunogenotyping 10.30
in vitro function tests 13.23
intraepidermal 4.8
in leprosy 32.7
in lymph nodes 13.8–9
microscopy 10.34
natural killer (NK) 13.6
induction by UV radiation 13.31
in pyoderma gangrenosum 50.65
quantification 17.56–7
receptors *see* T-cell receptors
reduction
in familial haemophagocytic lymphohistiocytosis 55.25–6
in HIV infection 35.4, 35.5
in HPV infection 33.42
regulatory (Treg) 13.11, 31.4
in atopic dermatitis 24.7
deficiency 13.11
induction by UV radiation 13.30–1
role in skin immunological function 4.8
in sarcoidosis 61.4, 61.5
in sensitization 26.12
in spleen 13.8
in Stevens–Johnson syndrome 76.9
suppressor 13.30
Th1 cells 13.11, 17.50
in acne pathogenesis 42.25, 42.26
in atopic eye disease 67.15
cytokines 35.4, 42.26
in HIV infection 35.4
mucous membrane pemphigoid 67.20
NFAT regulation of, immunomodulators and 73.31
Th2 cells 13.11, 17.50
in atopic eye disease 67.15
cytokines 35.4, 35.18, 35.22
in HIV infection 35.4, 35.22
NFAT regulation of, immunomodulators and 73.31
response, Langerhans' cells 3.17
Th3 cells 13.11
in toxic epidermal necrolysis 76.9
trafficking 13.9
in tuberculosis 31.4
UV radiation effects on 13.30–1
in vasculitis 50.6–7
in vitiligo 58.46
in wound healing 14.3
t-PA (tissue plasminogen activator) 47.6
t-test 7.19–20
Tabanid, skin disease in animals 2.11
Tabanidae 38.6, 38.7
Tabanus (horse flies) 37.11, 38.6, 38.7
tabes dorsalis 34.16, 63.11, **63.15**
tabetic neurosyphilis 34.14
tacalcitol 73.43, 73.44–5
adverse effects *26.46*
doses 73.44
indications 73.44–5
in psoriasis 20.26, 73.44
in seborrhoeic dermatitis 23.33
structure *73.44*
Tacaribe complex viruses 33.69
tâche noire 38.35
tachykinins 63.2
substance P 12.64
tachyphylaxis, corticosteroid-induced 73.19
tacrolimus (FK506) 13.25, 20.42, 51.23, 51.118, **73.31–2,** 74.17
adverse effects *26.46,* 73.31, 75.146–7
in allergic contact dermatitis 26.102
in atopic dermatitis 24.30, 73.31
in children 73.31
in chronic actinic dermatitis 29.18
in eczema 23.38
in granuloma annulare 60.10
in granuloma faciale 50.29
indications 73.31, 73.32
Kaposi's sarcoma association 35.36–7
in pyoderma gangrenosum 50.72
in sarcoidosis 61.21
in seborrhoeic dermatitis 23.33
structure *73.32*
systemic exposure 73.31–2
topical 73.31–2
indications 73.31, 73.32
in lichen planus 41.18
in rosacea 43.6, 43.10
tacrolimus-binding proteins 74.18
Taenia saginata 37.24
Taenia solium 37.1, 37.3, 37.24, 37.25
taeniasis 37.24
larval (cysticercosis) 37.3, 37.24, **37.25**
tags *see* skin tags
Takayasu's arteritis **50.44–5**
talarozole 74.37
talc 73.2, 73.8
granuloma 71.100
sarcoidal reaction to 61.22
talking therapies 64.4
tall oil rosin 26.79
talon noir (black heel) 28.16, 28.31, 49.16
tamoxifen
adverse effects 75.119
dermatomyositis and 51.121
in gynaecomastia 70.5
in progesterone-induced dermatitis 74.33
tanapox 33.14
tanapox virus 33.5
Tangier disease 59.91
tanners, occupational hazards 27.21
tanning 58.1, 58.10, 58.31–3
delayed 4.7, 58.31
delayed effects 29.5
DNA damage 58.31
immediate effects 29.5
immediate pigment darkening (IPD) 58.31
persistent pigment darkening (PPD) 58.31
phases 58.31
UV light 58.31–3
see also sun tan
tanning devices, UVR exposure 29.4
tanning salon exposure 58.31
see also sunbeds/sunlamps
Tanzania, prevalence of skin disease *6.10*
TAP proteins 13.10
tapeworms (cestodes) 37.2, 37.3, **37.24–7**
tar 73.41–3
as carcinogen 52.4
carcinogenicity mechanism 73.42
coal *see* coal tar
dithranol with 73.30
shale 73.42
sources 73.41–2
topical corticosteroids with 73.20
wood 73.42
tar acne 42.77
tar keratoses 52.37
TAR syndrome (thrombocytopenia–absent radii syndrome) 18.70
tarantula 38.30
target lesions 76.1, 76.6, 76.7
tartrazine 5.25, 22.11, 22.26, 75.26, 75.158
tattoos **58.57–9,** 64.2
accidental/traumatic 58.57
allergic contact dermatitis and 26.10
allergic reactions 58.58
amalgam 69.95–6
complications 28.48–9, 58.58
decorative 58.57–9
history and prevalence 58.57
granulomatous reactions to 26.27, 26.39
henna 26.60, 58.57
infections associated 58.58
lichenoid reaction 58.58
lips 69.96
oral cavity 69.95–6
pigments 26.27
reactions 28.48–9
lichen planus and 41.16
sarcoidal 61.13, 61.22
removal 58.59, 78.10
infrared coagulation 77.47
skin disease localization 58.58
techniques and materials 58.58
temporary 26.25, 26.26, 58.57
treatment (reactions) 58.59
taurodontia, absent teeth and sparse hair 15.53
taurodontism 69.8, 69.9–10
taxanes 75.135–6
Tay's syndrome (IBIDS/PIBIDS syndrome) 19.47–9
tazarotene 20.27, 73.35, **73.37,** 75.113
adverse effects 73.37
tazarotenic acid 73.37
TCDD 27.12, 27.13
TCOF1 gene 18.80–1
TDO (trichodentoosseus) syndrome 15.54, **15.65,** 69.11
TDT (thermal damage time) 78.5, 78.12
tea tree oil (TTO)
acne vulgaris treatment 42.43
adverse effects 26.45, 26.47, *70.5,* 75.160, 75.162
in head louse infection 38.20
as insect repellent 38.5
in scabies 38.41
teak *26.81*
tear film 67.11
lipid 67.2, 67.11
precorneal 67.2, 67.3
functions 67.3
lipids 67.2, 67.3
mucin 67.3
removal, lacrimal pump 67.3
tear substitutes 67.31
Tectona grandis 26.81
Tedania ignis 38.59
TEE (transepithelial elimination) 45.63, 45.64, 45.65, 68.14
teeth 69.2
abnormal enamel
generalized non-Herlitz junctional EB 39.13
Herlitz junctional EB 39.12
junctional EB with pyloric stenosis 39.14
late-onset junctional EB 39.15
abnormalities in dogs 2.18
care, in severe generalized dystrophic EB 39.28
caries, in dystrophic EB 39.19
in congenital syphilis 34.16–17, 69.8
discoloration 69.8, *69.9,* 75.55
early loss 69.7–8
in ectodermal dysplasia 15.58–9, 15.62, 15.64–6, 15.68, 69.10–12
eruption 69.2, *69.3*
delayed 69.7
premature 69.7
examination 69.6
Hutchinsonian incisors 69.8, 69.78
Hutchinson's 34.17
hypoplasia 69.8, *69.9*
impaction 69.7
in incontinentia pigmenti 69.6
in Langerhans' cell histiocytosis 55.11
loosening 69.7–8
loss 69.6
malformation 69.8, *69.9*
missing 69.7
mulberry (Moon's) molars 69.8
natal 69.7
neonatal 69.7
notation *69.3*
peg-shaped 69.8
premature eruption 55.11
screwdriver 34.17
supernumerary (supplemental) 69.6, 69.7
taurodont 69.8, 69.9–10
Turner's 69.8
wisdom 69.7
see also dentition
teething 69.7
Tegenaria agrestis 38.32
teichoic acid 30.7, 30.8
teicoplanin 30.9, 74.43
telangiectases/telangiectasia 47.12, **47.12–21**
aetiology *47.13*
in ageing skin 8.21, 80.2, 80.11
ankles 47.14
in basal cell carcinoma 52.19
breast 70.13
calcium channel blockers with 47.15–16
capillary 47.37
in chronic radiodermatitis 79.16
cold-induced injury 28.68, 28.70
development 47.12–13
essential 47.19, *47.20*
facial 47.14
generalized essential 47.19
gingival 69.13
in granulosis rubra nasi 44.18
hereditary acrolabial 70.13
hereditary benign 47.20
hereditary haemorrhagic *see* hereditary haemorrhagic telangiectasia (HHT)
lupus erythematosus profundus 51.16
macular 47.12
male genital region 71.51
nail-fold 47.14
in necrobiosis lipoidica 60.13, *60.14*
oral cavity 69.22, 69.101
paraneoplastic 62.44
post-radiotherapy 70.14
primary *47.13,* 47.16–20
ribs, lower border 47.14
in rosacea 43.4, 43.6
secondary *47.13,* 47.13–16
spider *see* spider angioma
systemic sclerosis 51.95, 51.96
thermal injury 28.72
treatment 47.20–1
laser therapy 78.7–8
nicotinic acid 73.51
venous 47.39
vessel classification *47.13*
telangiectasia macularis eruptiva perstans 22.32–3, 47.13, 47.14
skin biopsy 10.43
telangiectatic erythema and stunted growth, congenital **15.76–7**
telecanthus *67.4*
teledermatology 72.2
telemedicine 5.25–6
teleomorph 36.2
television repair, occupational hazards 27.20
telogen 3.7, 3.13, 66.8, 66.9, 66.10
in androgenetic alopecia 66.20
telogen effluvium 66.16, 66.20, **66.27–31**
acute 66.27–8
chronic 66.22, 66.30–1
chronic diffuse 66.28–30
definition 66.27
delayed anagen release 66.27–8

diagnosis 66.28
in HIV infection 66.2
immediate anagen release 66.27
pathogenesis 66.27
postpartum (telogen gravidarum) 66.9, 66.27–8
short anagen syndrome 66.27
skin biopsy 10.43
telogen gravidarum 66.9, 66.27–8
telomerase 58.21
temazepam 75.81
temoporfin, photosensitivity due to 29.21
temozolomide, melanoma management 54.54
brain metastases 54.54, 54.56
temperature
cold *see* cold (cold temperature)
hair growth and 66.9
limb, erythromelalgia 47.9
role in irritant contact dermatitis 25.8
sensitivity to 4.7, 4.9
see also body temperature; thermoregulation
temperature set point 44.5
temporal arteritis *see* giant cell arteritis
temporalis muscle, examination 69.4
temporomandibular joint
examination 69.4–5
herniation 68.29
in multicentric reticulohistiocytosis 69.59
in psoriatic arthritis 20.57
TEN *see* toxic epidermal necrolysis (TEN)
tenascin 14.3, 14.4
tenascin-X 45.32
deficiency *45.32*, 45.33, 45.34, 45.37
tendon(s)
in systemic sclerosis 51.102
xanthomata 59.84
tendon sheath
fibroma 56.10
giant cell tumour 56.15–16, 65.36
Tenebrionidae 38.27
teniposide, familial haemophagocytic lymphohistiocytosis 55.26
tenofovir 75.67
tenosynovitis, gonococci causing 34.27
tensile strength of skin 45.14
tensile tests, mechanical injury 28.5
teratogens 18.1, 75.11
aplasia cutis congenita due to 18.102
drugs 72.28, 75.11
acitretin 72.28
isotretinoin 42.59, 42.63, 72.28
retinoids 42.50, 72.28, 73.35, 74.38
systemic retinoids 73.35
teratoma 18.88
terbinafine 73.12, 74.47
adverse effects 75.64, 75.65–6
in chromoblastomycosis 36.76
in dermatophytoses 36.47–8, 36.49, 36.50
failure to respond to 36.50–1
in pityriasis versicolor 36.12
in *Scytalidium* infection 36.52
in sporotrichosis 36.72
TERC gene 15.78–9, 58.21
terconazole, topical 73.12
terephthalydiene dicamphor sulphonic acid 73.40
terfenadine 22.29, 75.148–9
terminal pilosebaceous unit 3.13
terminology, diagnosis and 5.1
terpenes 26.41, 26.79
TERT gene 15.78–9
4-tertiary butylcatechol, depigmentation due to 58.50
p-tertiary butylcatechol 27.15
p-tertiary butylphenol 27.15
depigmentation due to 58.50
p-tertiary butylphenol formaldehyde resin 26.68, 26.69, 26.73–4
testes
fetal 8.2
at puberty 8.4
tumours 70.4
testosterone
absorption, reduced with age 8.23
acne aetiology and 42.20, 42.21, 42.22
acneiform eruptions due to 42.72
activity in skin 42.10
administration, effect on sebaceous glands 42.10, 42.20
adverse effects 75.119
in androgenetic alopecia 66.13–14, 66.19
effect on sebum composition 42.6
in females, acne aetiology and 42.20
hair growth and 66.9, 66.13
hirsutism and 66.81, 66.83
metabolism 8.2, 42.10, 42.21
inhibition 42.16
oestrogen synthesis 8.8
at puberty 8.4
reduced, by oral contraceptives in acne 42.53
synthesis 8.2, 8.8, 66.14
at puberty 8.4
sebocytes 42.12
transdermal delivery *26.46*
testosterone 5α-reductase 44.18
see also 5α-reductase
tetanus
prophylaxis in burns 28.79
tungiasis and 38.13
tetanus toxoid, grease-gun injuries and 46.29
tetracaine 75.153, 77.10
tetrachlorethylene 75.71
tetrachloroazobenzene 27.13
2,3,7,8-tetrachlorodibenzo-*p*-dioxin 27.12, 27.13
tetrachlorophenols 25.21
tetrachlorsalicylanilide 26.24
tetracosactide (tetracosactrin)
in lichen planus 41.18
in lieu of systemic steroids 74.3–4
tetracyclines 74.41–2
acne vulgaris treatment 42.46–7, 42.48
adverse effects 42.50, 74.41, **75.52–5**
allergy *26.46*, 75.53
fixed eruption 75.28
hyperpigmentation 75.52–3
lichenoid eruptions 41.24
nail colour changes 65.16
photosensitivity 75.31, 75.52
systemic 75.54
tooth discoloration 69.8, *69.9*, 75.55
dose range and evidence level 74.30
drug interactions 75.54, 75.55
gastrointestinal absorption 75.54
isotretinoin contraindication 42.64, 42.65
nicotinamide and 74.30
in pemphigus 40.12
in perioral dermatitis 43.12
in pregnancy 75.55
Propionibacterium acnes resistance 42.56
resistance 45.26, 74.41
rosacea treatment 43.6, 43.7
topical 73.11
in acne 42.41
P. acnes resistance 42.42
toxicity 74.41
tetrahydrobiopterin, defective metabolism, vitiligo pathogenesis 58.47
tetramelic deficiencies, ectodermal dysplasia, deformed ears and other abnormalities 15.53
Tetranychidae 38.48
tetraphocomelia–thrombocytopenia syndrome 18.70
TEWL *see* transepidermal water loss (TEWL)
textile workers, occupational hazards 5.*6*, 27.21
textiles *see* clothing
TG1 (keratinocyte transgluraminase) 3.10
thalassaemia 62.85–6
pseudoxanthoma elasticum and 45.23
thalidomide 13.24, 64.27, 72.28, 74.30–1
actinic prurigo therapy 29.15
adverse effects 68.4, **75.64**
in aphthous ulceration in HIV infection 35.42–3
in complex regional pain syndrome 63.21
in discoid lupus erythematosus 51.21
dose range and evidence level 74.31
in erythema multiforme 76.7
irreversible peripheral neuropathy 74.30
in Langerhans' cell histiocytosis 55.13
in leprosy reactions 32.18
pregnancy and 51.21
in sarcoidosis 61.21
thallium poisoning 75.160
thallus 36.2
thanatophoric dwarfism/dysplasia, prenatal diagnosis *16.3*
Thaumetopoea 38.28–9
thaumetopoein 38.29
thelalgia 70.11
thelarche 8.4, 8.5
Thelazia callipaeda 37.18
Thelyphassa 38.27
theobroma oil 73.6
theque 10.42, *54.10*
therapeutic cupping 28.24
therapeutic outcome, factors influencing 72.25–8
Theraphosidae 38.30
therapy *see* treatment
Theridiidae 38.31
thermal damage time 78.5, 78.12
thermal injury **28.63–94**
burns 28.74–94
cold-induced 28.63–71
heat and infrared radiation 28.71–4
Koebner response 28.2–3, 28.73
Nikolsky sign 28.4
overview 28.1–4
response determinants 28.2
thermal radiation, non-melanoma skin cancer associated 52.5
thermal relaxation time 78.4, 78.5, 78.12
thermokinetic selectivity 78.5
thermoreceptors 4.7, 4.9
thermoregulation 4.1, 4.7, 63.3
in anhidrosis 44.13
role of blood vessels 3.50–1
role of skin 3.3, 4.1, 4.7
role of sweat glands 4.7, 44.2, 44.4, 44.5
variations in 44.7
thesaurosis 61.22
Thespesia populnea 26.81
thiabendazole 74.51
in cutaneous larva migrans 37.17
in dracunculiasis 37.13
in scabies 38.41
in tinea nigra 36.15
thiambutosine 74.46
thiazide diuretics *see* diuretics
thiazolidinediones, HIV lipodystrophy 46.42
Thibierge–Weissenbach type, scleroderma 47.14
Thiersch grafts, localized morphoea 51.65
thimble jellyfish 38.56
thimerosal 25.21, *26.46*, 73.8
thinners 25.20
thinning of skin, corticosteroid-induced 73.17
thioacetazone 75.62
thioalcohols 73.29
thioflavine T method 10.10
thioglycollates 25.21, 73.29
6-thioguanine 20.40
thiomersal 25.21, *26.46*, 73.8
thiopurine methyltransferase (TPMT) 11.16, 13.24, 72.29, 74.14–15
deficiency 74.15
thioridazine 75.82
thiotepa
adverse effects 75.33, 75.125–6
eccrine gland secretion 44.18
thiothixene 75.82
thiouracils, adverse effects **75.121**
vasculitis 50.17, 50.18
thiourea, as photoallergen 26.24
Thompson buried dermis flap operation 48.25
thonzylamine 75.149
thoracic duct 13.8, 48.5
Thost–Unna keratoderma 19.97
threadworm **37.13–14**
see also Enterobius vermicularis
Three Item Severity Score 72.10
3T3 NRU PT test 25.9
thrips 38.26
thrombin 49.38
inhibitors 49.28
receptors, PAR-1, -3 and -4 12.49
thromboangiitis obliterans (Buerger's disease) 47.4, **47.6–8,** 50.54
male genital dermatology 71.28
thrombophlebitis migrans in 47.30
thrombocytes *see* platelet(s)
thrombocythaemia 49.14, 49.29–30
in erythromelalgia 47.9, 47.10
thrombocytopenia 49.2, 49.7
antiphospholipid syndrome 49.41
in bone marrow diseases 49.11–12
in congenital syphilis 34.16
drug-/toxin-induced 49.11, 75.23
gestational/incidental 49.12
in haemangioma 49.12
heparin-induced 49.11, **49.27–9**
in HIV infection 35.10
infection-associated 49.11
platelet counts 49.5, 49.8
in pregnancy 49.12
purpura due to *see* thrombocytopenic purpura
secondary 49.11–12
simple macular haemorrhage 49.4
symptomatic 49.11–12
thrombocytopenia–absent radii syndrome 18.70
thrombocytopenic purpura **49.7–12**
autoimmune/immune *see* idiopathic thrombocytopenic purpura (ITP)
idiopathic *see* idiopathic thrombocytopenic purpura (ITP)
in infectious mononucleosis 33.30
secondary/symptomatic 49.11–12
thrombotic 49.12, **49.31,** 69.114
in varicella 33.25
thrombocytosis
bleeding and purpura 49.5, 49.14
essential 49.29
myeloproliferative 49.29–30
purpura due to *49.8*
thrombolysis 47.6
thrombomodulin 49.38
thrombomodulin–protein C/S anticoagulant pathway 49.38–9
thrombophilias 47.42, 49.7, 62.91–2
venous pigmented purpuric dermatoses 49.23
thrombophlebitis
penile 71.14
superficial 47.30
breast and chest wall (Mondor's disease) 48.29
thrombophlebitis migrans 47.30–1, 62.42–3, 62.66
thrombopoietin receptor, mutation 49.29
thrombosis 47.28
antiphospholipid antibodies causing 49.41
calf vein 47.29
capillary, venous leg ulceration and 47.42
deep vein *see* deep-vein thrombosis (DVT)
in heparin-induced thrombocytopenia 49.27

iliac 47.28
lethal cutaneous and gastrointestinal arteriolar *see* Degos' disease
non-inflammatory hyaline 49.33
in paroxysmal nocturnal haemoglobinuria 49.30
pathogenic mechanism 49.38
prevention, in myeloproliferative disorders 49.29
thrombotic thrombocytopenic purpura 49.31
venous *see* deep-vein thrombosis (DVT); venous thrombosis
thrombospondin 1 (TSP-1) 12.33
thrombospondins 14.3
in Ehlers–Danlos syndrome 45.33
thrombotic microangiopathy 49.12
thrombotic thrombocytopenic purpura (TTP) 49.12, **49.31,** 69.114
thromboxanes (TX) 12.60, 13.4
in wound healing 14.3
thrush
oral (acute pseudomembranous candidiasis) 36.60, 36.64, 36.68, 69.88–9
vulvovaginal 36.61–2, 36.68
Thuja plicata 26.80
thumb
deformity and alopecia 15.53
racket 65.9
thumb sign 45.30
thumbnail, Beau's line 59.75
thunder flies (thrips) 38.26
Thy-1 12.69
thymic stromal lymphopoietin (TSLP) 12.36, 24.14
thymidine kinase 73.15
virus drug resistance 33.21
thymidylate synthase 11.16
thymine 11.2
thymol, topical therapy 73.48–9
thymoma, candidiasis and 36.65
thymus
ageing and 13.15
developmental failure 13.8
T cell development 13.7, 13.8
thymus and activation-regulated chemokine (TARC/CCL17) *see* RANTES
thyroglossal cysts 62.11
thyroglossal duct 18.86–7
thyroid
cancer 62.11
function, urticaria and 22.2, 22.26
lingual 69.35–6
medullary carcinoma 62.44
flushing associated 43.16
in pregnancy 8.9
in SLE 51.45
thyroid acropachy 62.9–10, *62.101*
thyroid transcription factor-1 10.24
thyroiditis, autoimmune, granuloma annulare and 60.9
thyrotoxicosis *see* hyperthyroidism
thyrotrophin, human chorionic 8.9
thyroxine
adverse effects 75.120–1
hair growth and 66.9, 66.11
in urticaria 22.29
Thysanoptera 38.26
TIA-1 10.26
tiabendazole, adverse effects 75.71
tiaprofenic acid *26.46,* 75.75
tibia, sabre 34.16
tibial–peroneal vessel occlusion 47.5
tic de lèvres 69.127–8
ticilumumab, melanoma management 54.54
tick-borne encephalitis *33.67*
tickle sensation 21.1
ticks 30.73, 37.1, **38.33–6**
ehrlichiosis and 30.58
Lyme disease and 30.64, 62.106
paralysis due to 38.35
relapsing fever and 30.62–3
removal 38.35–6
ticlopidine 75.108
Tietz's syndrome 58.43
tight junctions 3.24–5
tight skin contracture syndrome (restrictive dermopathy) 17.20, 45.51
TIME system 14.19
time trade off (TTO) 72.22
TIMPs *see* tissue inhibitors of metalloproteinases (TIMPs)
tin ear syndrome 68.6
tincture of benzoin 26.41
tinctures 73.2
tinea, male genitalia 71.32
tinea amiantacea 36.27
tinea barbae 36.28–9, 36.49
tinea capitis (tinea tonsurans) **36.25–8,** 36.47, 36.49
alopecia and 66.16
alopecia areata vs 66.35
race influences on 9.8
radiation epilation 79.4
scalp scaling 66.56
tinea corporis (tinea circinata) 5.*12–13,* **36.23–5,** 36.49
in HIV infection *35.32*
tinea cruris **36.33–4,** 36.49–50, 71.6–7
tinea faciei (tinea faciale) 36.28, **36.29–30,** 36.49
in HIV infection *35.32*
tinea flavea *see* pityriasis versicolor
tinea imbricata 36.24, *36.25,* 36.29
tinea incognito *25.15,* 36.35–6, 36.50
in HIV infection 35.32
topical corticosteroids causing 73.18
tinea manuum 26.29, 36.32–3, 36.50
tinea nigra *36.8,* 36.**14–15**
tinea nodosa *see* piedra, black
tinea pedis 26.29, **36.30–2**
eczematous 23.25
lymphoedema and 48.22
prevention 36.46–7
swimming and diving 28.54
treatment 36.49
tinea tonsurans *see* tinea capitis (tinea tonsurans)
tinea unguium 36.34–5, 36.50
tinea versicolor *see* pityriasis versicolor
tinidazole 75.59
tioconazole
in dermatophytosis 36.48, 36.50
topical 73.12
tiopronin 75.104
TIRAP/Mal 12.8
see also Toll-like receptors
tirofiban 49.13
tissue engineering 14.26
tissue expansion 28.60–1, 77.35
in androgenetic alopecia 66.24
in congenital naevi 54.14
tissue inhibitors of metalloproteinases (TIMPs) 3.41
hair growth and 66.10
TIMP-1–4 12.51
tissue macrophages *see* histiocytes
tissue plasminogen activator 47.6
in vasculitis 50.4
tissue specimens
artefacts 10.7, *10.8,* 10.30–1
blocking and sectioning 10.6, 10.7, 10.31
care of 10.4–5
fixatives and transport media 10.4–5, 10.6, 10.31
information provided with 10.4
microscopy 10.31–6
preparation 10.6–7
for immunoenzyme methods 10.16–17
for immunofluorescence methods 10.12–13
routine processing 10.7, *10.8*
staining 10.8–11, 10.31
tissue-engineered skin equivalents *see* skin equivalents
titanium, implants 26.37, 28.52
titanium dioxide 73.8
as sunscreen 73.40
Tityus 38.33
tixocortol pivalate 26.45, 73.18
TMEP *see* telangiectasia macularis eruptiva perstans
TNF *see* tumour necrosis factor (TNF)
TNF-receptor-associated periodic syndrome 22.25, 50.53, 62.69, 62.104
TNM classification of tumours *69.51*
toadfish 38.59
tobacco
chewing 69.50, 69.90
melanosis and 69.96
oral keratoses and 69.90
see also smoking
tobramycin 26.17, 26.45, 75.58
tocopherol 59.61
toe(s)
clubbing of **15.87–8**
congenital malalignment of the great toe 65.7
fibro-osseous pseudotumour 56.5
toe clefts
bacterial flora 30.4
erythrasma 30.37, 30.38
normal bacterial flora 30.4
toenails
ingrown, in HIV infection 35.41
lichen planus 41.14
torture injuries 28.33
see also nail(s)
togaviruses, and *Togaviridae 33.2,* 33.66, **33.66–8,** *33.67,* 33.70
detection, blood samples 33.4–5
Toker's cells 53.40
Toll/IL-1 receptor (TIR) domain 12.8
Toll-like receptors 12.8–9, 13.5, 17.48, 32.6–7
acne aetiology 42.25
pathway deficiencies 17.82
potential uses 12.8
TLR-7 73.24
Toll signalling, non-melanoma skin cancer treatments and 52.17
tolmetin 75.77
tolnaftate *26.46,* 36.49
topical, indications 73.12
toluene 25.20
toluene-2,5-diamine 26.60, 26.61
toluidine blue 10.9
toluidine blue unheated serum test (TRUST) 34.19
tongue 69.2
antibiotic sore (acute erythematous (atrophic oral) candidiasis) 36.60, *69.88,* 69.102–4
black hairy 69.95
brown hairy 69.95
cellulitis 30.18
central papillary atrophy (median rhomboid glossitis) 36.61, *69.88,* 69.105–6
circumvallate papillae 69.2
depapillation 69.22
examination 69.6
filiform papillae 69.2
foliate papillae 69.2
fungiform papillae 69.2
furred 69.95
geographical 69.22, 69.37, **69.100–1**
treatment 73.36
in hereditary haemorrhagic telangiectasia 47.17
in lichen planus 41.8, 41.9
in lymphangioma 69.34
red starberry 30.34
scrotal (fissured/plicated) 48.16, 69.6, 69.37, 69.100, 69.125
tertiary syphilis vs 34.14
strawberry 30.78–9, 69.101
in syphilitic chancre 34.7
in tertiary syphilis 34.14
tie (ankyloglossia) 69.36–7
white strawberry 30.34
tonofilaments 10.19
in Dowling–Meara EB simplex 39.25
tonsillitis
bilateral syphilitic 34.11
lingual 69.35
tonsils
atrophy 13.9
lingual 69.2, 69.6, 69.35
syphilitic chancre 34.7
tonus of skin 4.8
toombak 69.50
tooth and nail syndrome 15.56
toothpaste 69.119–20
allergy to 26.17, 26.21
tophi, gouty 62.105
ear 68.17
see also gout
topical anaesthetic
in zoster and post-herpetic neuralgia 33.28
see also local anaesthesia
topical immune response modifiers, non-melanoma skin cancer 52.17
topical negative pressure therapy 28.23
topical therapy 72.27, **73.1–52**
absorption 73.4, *73.4*
adverse effects 25.21, **75.163–7**
advice for patients 73.4
chemotherapy, nitrogen mustard (mechlorethamine) and carmustine (BCNU) 57.23
concordance with 72.6
corticosteroids *see* corticosteroids
drug concentration 73.1–2
efficacy 73.2
formulation **73.5–9**
frequency of application 73.3
hazards and adverse effects 73.4
odour 73.5
penetration enhancement 73.7–8
prescribing **73.1–5**
preservatives 73.8
quantity applied 73.3–4
retinoids *see* retinoids
self-treatment failures 73.4
for skin diseases 73.9–52
traditional remedies 73.48–9
vehicles for 26.59, 73.2–3
choice 73.2–3
constituents *73.6*
corticosteroid therapy 73.20
formulation 73.5–9
role 73.5
types 73.2
see also individual drugs and drug groups
topoisomerase 1 (Scl-70), localized scleroderma 51.74
TORCH syndrome 33.76–7, 49.20, 49.51
Torre syndrome *see* Muir–Torre syndrome
torsional tests, mechanical injury 28.5
tortoises, skin disease 2.12
Tortoiseshell gene 2.6–7
torture injuries 28.32–4
Torulopsis, female genital infections 71.68
Torulopsis glabrata see Candida glabrata
torus mandibularis 69.6
torus palatinus 69.6
total skin irradiation 57.24–5
touch
light touch sensation 5.18
psychological importance of 64.2
sense of 4.9
touch corpuscles 3.16
touch domes 3.16
touch pads 3.3
Touraine-Solente-Golé syndrome *see* pachydermoperiostosis
tourniquet
fingers 65.42, *65.43*

self-inflicted injury, lymphoedema after 48.13
tourniquet syndrome 71.14
hair-thread 28.50
Touton giant cell
Erdheim–Chester disease 55.18
juvenile xanthogranuloma 55.15
xanthoma disseminatum 55.21
Townes–Brocks syndrome 18.82, 68.3
toxaemic rash of pregnancy (PUPPP) 8.13, 8.14
toxic epidermal necrolysis (TEN) 74.11, **76.8–22**
aetiology 76.9–15
in animals 2.16
antiretroviral drug causing 35.7, 35.20
clinical features 69.70, 76.17
Nikolsky sign 40.8
complications 76.17–18
definition 76.1
diagnosis 69.70–1, 76.19–120
drug-induced 42.51, 76.12–15
genetic risk 72.30
genitocrural involvement 71.6
GVHD 51.83
immunology 76.9–10
incidence 76.8–9
investigation 76.17
ocular complications 67.20–1, *67.21*
ocular involvement 76.18
oral involvement 69.70–1
pathology 76.15, *76.16*
pharmacogenetics 76.10–11
prevention 76.22
prognosis 76.18–19
renal involvement 62.71
staphylococcal 30.30
terminology 76.1
treatment 69.71, 76.20–2
toxic erythema of the newborn 17.6–7
toxic oil syndrome *27.17*, 45.52, 75.43, 75.159
epidemic syndrome, of Spain 51.82
secondary mucinosis 59.29
toxic pustuloderma *see* acute generalized exanthematous pustulosis
toxic shock syndrome **30.31**
differential diagnosis 76.19
streptococcal 30.12, 30.35
toxic shock syndrome toxin 1 24.8, 30.7, 30.31
Kawasaki disease and 50.45
Toxicodendron 26.10, 26.22, 26.75, 26.77
see also poison ivy
toxins
thrombocytopenia due to 49.11
see also individual microbial genera
Toxocara 37.17–18
toxocariasis 22.10, **37.17–18**
Well's syndrome vs 46.33
Toxoplasma gondii 33.76, 37.27, 37.44
toxoplasmin test 5.24
toxoplasmosis 18.2, **37.44**
TP63-related phenotypes, ectodermal dysplasias 15.61–5
TPA, carcinogenesis in murine model 52.13
TPHA test 34.20
TPI test 34.20
TPMT *see* thiopurine methyltransferase (TPMT)
TPPA test 34.20
trabecular cell carcinoma of skin *see* Merkel cell carcinoma
trace elements, excess/deficiency in pregnancy 18.2
trachyonychia 65.13, 65.25, 66.35
traditional Chinese herbal medicine, systemic agents 74.52
traditional Indian medicines, carcinogens in 52.5
traditional remedies, topical 73.48–9
tragi 68.1–2
TRAIL/TRAIL receptors 50.42
tramadol 63.7
tranexamic acid, in hereditary angio-oedema 22.22, 22.29
trans-3-methyl-2-hexanoic acid 44.1
transcription factors 11.3
melanocyte development 58.3
transcription-mediated amplification assay (TMA), gonorrhoea detection 34.28
transdermal drug delivery systems *26.46*, 72.27, 75.167
transepidermal water loss (TEWL) 27.11, 44.5, 72.11
ageing and 4.11
in atopic dermatitis 24.22
definition 4.11
irritant contact dermatitis and 25.2, 25.6, 25.7
measurement 4.10–11, 25.22
neonatal 17.2
race and 9.2
transepithelial elimination 45.63, 45.64, 45.65, 68.14
transferrin 13.19, 36.21, 36.58
transforming growth factor-α (TGF-α)
sebaceous cell activity control 42.12
in wound healing 14.4
transforming growth factor-β (TGF-β) 12.29, 12.31–2, 12.35–6, 12.42–3
ageing skin and 8.22
collagen gene expression control 3.39
elastin-associated microfibrils 3.45
hair growth and 66.11, 66.15
mucous membrane pemphigoid pathogenesis 67.20
in telangiectasia 47.13
in wound healing 14.3, 14.4, 14.8
transgenic animals 2.7, 2.8, 11.10–11
transglutaminases 3.10, 4.2
coeliac disease 40.59
transgredient palmoplantar keratodermas *19.94*, 19.95, 19.98–101
transient acantholytic dermatosis 19.86–8, 62.33
transient amplifying cells 66.3
transient bullous dermolysis of the newborn 39.23–4
transient myeloproliferative disorder, neonatal pustulosis and 17.10–11
transient neonatal porphyrinaemia 17.13
transient receptor potential ion channels 21.2
transillumination blisters 17.14
transitional cells 3.9
translators 72.3
translocation abnormalities 15.2
transplantation recipients 62.98
bone marrow *see* bone marrow, transplantation
immunosuppression
non-melanoma skin cancers after 52.11, 52.26–7, 79.13
squamous cell carcinoma after 52.11, 52.26–7
immunosuppressive therapy 57.51
Kaposi's sarcoma 56.34
kidney *see* kidneys, transplantation
liver 47.18
post-transplant lymphoproliferative disorder 33.31, 57.51–2
skin cancer in 79.13
skin changes in 62.74–5
solid organ, warts and HPV infections 33.59
transverse cervical nerve 77.3
transverse myelitis, in zoster 33.26
transverse nasal groove 18.90
Trantas' dots 67.15
TRAP (TNF-receptor-associated periodic syndrome) 22.25, 50.53, 62.69, 62.104
trauma
chronic, non-melanoma skin cancer after 52.11
eczema following 23.28–9
lymphoedema after 48.13
mechanical *see* mechanical injury
post-inflammatory hypermelanosis after 58.31
purpura due to 49.14, 49.16
thermal *see* thermal injury
traumatic ulcerative granulomatous disease 69.43
traumiterative dermatitis (cumulative irritant contact dermatitis) 25.1, 25.5, 25.12–13, *25.14*, 25.15
travel, hazards associated 5.6
trazodone *64.51*
adverse effects 75.79
erythema multiforme 76.3, *76.4*
Treacher Collins syndrome (mandibulofacial dysostosis) **18.80–1,** 68.4
treatment
concordance with **72.5–7,** 72.25–6
determination of efficacy 7.1–2
determination of outcomes 7.12
general principles 72.25
risk–benefit analysis 72.3–4
topical *see* topical therapy
transdermal drug delivery *26.46*
trematodes 37.2, 37.3, **37.20–3**
trench fever 30.56
trench foot **28.64**
trench mouth 69.77
trephine punches, panniculitis 46.11
Treponema 30.59, 30.60, 30.62, 34.3–4
Treponema pallidum 34.1
antigen tests 34.20, 34.21
enzyme immunoassays 34.20
female genital infection 71.71
identification, dark-field microscopy 34.3, 34.18–19
immune response evasion 34.4
immunogens 34.4
microbiology 34.4
morphology 34.3–4, 34.18
movement 34.3–4
inhibition 34.20
Nichol's strain 34.3, 34.20
pathogenesis 34.4
Reiter strain 34.3, 34.21
repeat protein genes (TPR) 34.4
serological tests 34.16, 34.19–21
see also syphilis
Treponema pallidum haemagglutination test (TPHA) 34.20
Treponema pallidum immobilization (TPI) test 34.20
Treponema pallidum microhaemagglutination (MHA-TP) 34.20
Treponema pallidum particle agglutination (TPPA) test 34.20
Treponema pallidum ssp. *carateum* 30.63
Treponema pallidum ssp. *endemicum* 30.63
Treponema pallidum ssp. *pertenue* 30.63
Treponema phagedenis (Reiter's strain) 34.3, 34.21
treponematoses
non-venereal (epidemic) **30.62–4**
ocular involvement 67.27
see also specific diseases
treponemicides 34.22
tretinoin *see* retinoic acid (tretinoin; vitamin A acid)
TREX1 gene 11.15
triage, burns 28.80
triamcinolone, intralesional 73.20, 77.48
adverse effects 45.3–4
in hand eczema 23.22
in keloids 45.55
in necrobiosis lipoidica 60.16
in psoriatic nails 65.26
in sarcoidosis 61.21
triamcinolone acetonide 73.16
intralesional, childhood acne 42.76
triamcinolone hexacetonide, psoriasis, intralesional therapy 20.25
Triatoma infestans 37.31
Triatoma sanguisuga 38.25
Triatomidae 37.31
Triatominae 38.25–6
triazinate 75.136
triazoles 74.47
tribal scarification marks, sarcoidosis 61.13
tribavirin *see* ribavirin
Tribolium 38.27
tribromosalicylanilide 26.23, 26.24
trichiasis *67.4*, 67.21
management 67.22
trichilemmal carcinoma 53.6
ear 68.34
trichilemmal cyst 52.45, 52.46, 53.4
cylindroma vs 53.29
naevus 53.4
proliferating 53.4–5
trichilemmal tumour, proliferating 53.4–5
trichilemmoma 53.5–6
desmoplastic 53.5
eyelid 67.33
Trichinella spiralis 37.3
trichinosis/trichiniasis/trichinelliasis **37.19–20**
trichloracetic acid 77.47–8, 80.9
wart treatment 33.49
trichlorethylene, scleroderma-like lesions 51.80
resulting from perchlorethylene 51.80
trichloroacetic acid, molluscum contagiosum 33.12
trichloroethylene 25.4, 25.20, 75.162
trichlorophenols 25.21
2,4,5-trichlorophenoxyacetic acid 27.13
tricho-dento-osseous syndrome 69.11
tricho-odonto-onychial dysplasia 15.54
tricho-odonto-onycho-dermal syndrome 15.54
tricho-onycho-dental (TOD) dysplasia 15.54, 69.11
trichoadenoma 53.3–4
trichobezoar 64.31–2
Trichobilharzia 37.22
trichoblastic fibroma 53.10–11
trichoblastoma 53.8, 53.10–11
adamantinoid 53.11
giant 53.10
trichochrome B 58.7
trichochromes 58.5, *58.6*
synthesis 58.5, *58.6*
trichoclasis *66.62*
'trichocyte,' secondary pathway, differentiation 3.13
trichodental dysplasia 15.53
trichodental syndrome 69.11
trichodentoosseus (TDO) syndrome 15.54, **15.65**
trichodiscoma 53.14
trichoepithelioma 53.8–9
desmoplastic 53.9–10, 53.35
eyelid 67.33
laser therapy 78.14
pinna 68.28
solitary giant 53.10
syringoma vs 53.26
trichofolliculoma 53.7–8
pinna 68.28
trichography, telogen effluvium 66.27, 66.28
trichohyalin granules 3.13
tricholemmoma, eyelid 67.33
trichomalacia *66.62*
trichomegaly 67.4
Trichomonas 37.27, 37.29
male genital infections 71.35
Trichomonas vaginalis, vaginal discharge 71.53, 71.69
trichomoniasis **37.29**
trichomycosis
female genital dermatology 71.67
genitocrural dermatology 71.7
trichomycosis axillaris (trichomycosis nodosa) 30.39
trichomycosis nodularis *see* piedra, black

trichomycosis pubis 71.31
trichonodosis *66.62*
trichonychodental (TOD) syndrome 15.54, 69.11
trichooculodermovertebral syndrome 15.31
trichophytin test 5.24
Trichophyton 36.18
  hand infection 23.20, *23.21*, *25.15*
  identification *36.8*
Trichophyton concentricum 36.22
  identification 36.41
  in tinea corporis 36.49
  in tinea faciei 36.29
  in tinea imbricata 36.24
Trichophyton equinum 2.12, 36.41
Trichophyton erinacei 2.12
Trichophyton gourvilii 36.26, 36.27
Trichophyton megninii
  identification 36.41
  in tinea barbae 36.28
  in tinea capitis 36.26
  in tinea corporis 36.22
  in tinea unguium 36.35
Trichophyton mentagrophytes 2.12, 36.19, 36.20, 36.21
  in animals 2.12
  dermatophytide reaction 23.9
  identification 36.41–2
  nomenclature 36.2
  in tinea barbae 36.28
  in tinea capitis 36.26, 36.27
  in tinea corporis 36.24
  in tinea cruris 36.33
  in tinea faciei 36.29
  in tinea manuum 36.32
  in tinea pedis 36.30, 36.31
  in tinea unguium 36.34
Trichophyton rubrum 36.20–1, 36.21, 36.22
  female genital infections 71.68–9
  genitocrural infections 71.6–7
  hand infection *25.15*
  in HIV infection 35.32, 35.33, 35.41
  identification 36.42, *36.43*
  investigation 36.5
  perianal/perineal infections 71.92
  in tinea barbae 36.28
  in tinea capitis 36.26
  in tinea corporis 36.23, 36.24, 36.25
  in tinea cruris 36.33
  in tinea faciei 36.29
  in tinea manuum 36.32
  in tinea pedis 36.30, 36.31, 36.49
  in tinea unguium 36.34, 36.35
  topical therapy 73.12
Trichophyton schoenleinii 36.19, 36.20
  identification 36.42, *36.44*
  investigation 36.6
  in tinea barbae 36.28
  in tinea capitis 36.25–6, 36.27, 36.49
Trichophyton simii 36.19, 36.44
Trichophyton soudanense 36.19
  identification 36.44
  in tinea capitis 36.26, 36.27
  in tinea unguium 36.34, 36.35
Trichophyton tonsurans 36.19, 36.20
  dermatophytide due to 36.36
  identification 36.44, *36.45*
  in tinea barbae 36.28
  in tinea capitis 36, 36.26, 36.27, 49
  in tinea faciei 36.29
  in tinea unguium 36.34
Trichophyton verrucosum 36.20, 36.22
  in cattle 2.9, 2.12
  dermatophytide due to 36.36
  identification 36.45
  investigation 36.5
  in tinea barbae 36.28
  in tinea capitis 36.26, 36.27
  in tinea corporis 36.24
  vaccine 36.29
Trichophyton violaceum 36.20, 36.21
  identification 36.45–6
  in tinea barbae 36.28
  in tinea capitis 36.26, 36.27, 36.49
  in tinea incognito 36.36
  in tinea manuum 36.32
  in tinea pedis 36.30
  in tinea unguium 36.34
Trichophyton yaoundei 36.26, 36.27, 36.46
trichoptilosis *66.62*
trichorhinophalangeal syndromes (TRPS) 15.55, **15.65–6**
trichorrhexis invaginata (TI; bamboo hair) 19.37, 19.38, 19.39–40, 66.65–7
trichorrhexis nodosa 15.55, *66.62*, **66.67–8,** 66.75, 66.91
  proximal 66.68
trichoschisis *66.62*, 66.68
Trichosporon
  cutaneous lesions 36.92
  genitocrural infections 71.5
  identification *36.8*
  in white piedra 36.16
Trichosporon beigelii, female genital dermatology 71.69
trichosporosis
  female genitalia 71.69
  genitocrural 71.7
  perianal/perineal 71.95
trichostasis spinulosa 66.73
trichothiodystrophy (TTD) 59.72, *66.65*, 66.68–9
  aetiology and pathogenesis 19.47–8
  collodion membrane 19.14
  differential diagnosis 19.24
  TTD-E, TTD-F, TTD-A syndromes **19.47–9**
  xeroderma pigmentosa pathogenesis studies 52.10
trichotillomania 64.30–1, **66.54–6**
  aetiology 66.54–5
  clinical features 66.55
  differential diagnosis 66.35–6, 66.55
  eyebrows 67.4
  pathology 66.54
  psychopathology 66.54–5
  treatment 66.55
trichrome stains 10.9
triclocarban 73.15
triclosan 26.58, 73.15
tricone repair 77.16
tricyclic antidepressants 64.28, 64.32, 64.50–1
  adverse effects *70.5*, 75.78–9
  in zoster and post-herpetic neuralgia 33.28
  see also antidepressants
trifluoperazine 75.82
  acne excoriée 42.70
trifluorothymidine, herpes simplex 33.21
trifluridine *26.46*
trigeminal nerve
  block 77.2–4
  maxillary division, zoster 33.26
  zoster 33.25–6, 33.28
trigeminal trophic syndrome 63.13
triggering receptors expressed by myeloid cells (TREMs) 12.28
triglyceride rich lipoproteins (TRLs) 59.90
triglycerides 46.2
  hydrolysis 46.3
  medium chain (MCTs) 48.27
  in sebum 42.5, 42.22
  storage in fat cells 46.2, 46.6
trimethadione 75.86
trimethoprim 74.39, 75.57–8
  acne vulgaris treatment 42.47, 42.48
  adverse effects 42.51
    ocular 67.32
  hidradenitis suppurativa 42.75
  Propionibacterium acnes resistance 42.56
trimethoprim–sulfamethoxazole *see* co-trimoxazole
trimethylaminuria 44.20
trimipramine *64.51*
trinitrotoluene 66.95
triparanol 75.157
tripe palms (acanthosis palmaris) 19.120, 62.31–2
triple A syndrome 62.13
triple H syndrome 62.13
triple response of Lewis 22.12, 63.5
tripotassium dicitratobismuthate 75.157
trisodium phosphate *25.19*, 25.20
trisomy 13 **15.11,** 18.102–3, 62.77, 68.4
trisomy 18 **15.11,** 62.77, *66.77*
trisomy 21 *see* Down's syndrome
Triton tumour (neuromuscular hamartoma) 18.37, 56.44
tromantadine *26.46*
Trombiculidae (harvest mites) 30.74, 38.2, **38.50–1**
trombidiosis 38.50–1
tropical acne *27.14*, 42.79
tropical bedbug 38.24
tropical countries, pigmentation significance 58.9
tropical elephantiasis **37.8–10,** 48.12
tropical fowl mite 38.51
tropical immersion foot 30.49
tropical phagedena *see* ulcer(s), tropical (phagedenic)
tropical sore 47.57
tropical ulcer *see* ulcer(s), tropical
tropicamide *26.46*
tropisetron *75.79*
tropoelastin 3.43
Trousseau's sign (migratory thrombophlebitis) 47.30–1, 62.42–3, 62.66
TRP (transient receptor potential) ion channels 21.2
TRPS (trichorhinophalangeal syndromes) 15.55, **15.65–6**
TRT (thermal relaxation time) 78.4, 78.5, 78.12
TRUE test 26.85
Tryp1 (DHICA oxidase) 58.5, *58.6*
Trypanosoma 37.2, 37.27, 37.29
Trypanosoma cruzi 37.31–2
Trypanosoma gambiense 37.29–31
Trypanosoma rhodesiense 37.29–31
trypanosomiasis
  African 37.2, **37.29–31**
  American/South-American 37.2, **37.31–3**
    in HIV infection 35.35
  ocular involvement 37.32
  vectors 38.6, 38.25
tryptase 12.25, 12.49
  in atopic dermatitis 24.18
  in mastocytosis 22.33, 22.34
  release from mast cells 63.3
  in urticaria 22.4
tryptophan *27.17*, 45.52, 59.63
  eosinophilia–myalgia syndrome and 59.29, 75.43
  hair colour and 66.91
  metabolism 43.18
L-tryptophan-induced eosinophilia–myalgia syndrome 59.29, 75.43
TSC *see* tuberous sclerosis complex (TSC)
TSC1 gene 62.23
TSC2 gene 62.23
tsetse flies 37.2, 37.29, 38.6
TSLP (thymic stromal lymphopoietin) 12.36, 24.14
TSLS (streptococcal toxic shock-like syndrome) 30.12, 30.35
TSST-1 *see* toxic shock syndrome toxin 1
TST (tuberculin skin test) 5.24, 31.6, 31.8, 31.21
tsutsugamushi disease (scrub typhus) 38.50
TTD *see* trichothiodystrophy (TTD)
TTF-1 (thyroid transcription factor-1) 10.24
tubercle 31.8–10, 32.4, *32.5*
  naked 61.3
tubercles of Montgomery 70.1
tuberculids 31.10, **31.21–6**
  aetiology 31.21
  definitions 31.21
  nodular 31.10, 31.24–5
  papulonecrotic 31.10, 31.22–4
tuberculin skin test 5.24, 31.6, 31.8, 31.21
tuberculosis 31.1, **31.7–30,** 62.80
  congenital 17.46, 31.20
  cutaneous 31.10–30
    classification 31.10, *31.11*
    malignant disease and 31.18, *31.19*, 31.21
  diagnosis 31.6, 31.26
  differential diagnosis 31.10, *61.5*
  epidemiology 31.2, 31.7–8
  extremely/extensively drug-resistant (XDR) 31.1, 31.2, 31.27–8
  female genital region 71.67
  fish 31.31
  gangrenous 31.20
  granuloma annulare and 60.1
  histopathology 31.8–10, *61.5*
  HIV infection and 31.2, 31.7, 31.8, 31.20, 31.27
  immunology 31.3–6
  latent 31.6
  leg ulcers 47.57
  lymph node infection 48.12
  lymphadenitis 35.25, 35.45
  male genital region 71.31
  miliary 31.9, 31.10, 31.15–16
  multidrug-resistant (MDR) 31.1, 31.2, 31.27
  natural history 31.8
  nodular vasculitis and 50.31, 50.32
  notification 31.26
  ocular involvement 67.27
  oral involvement 69.79, *69.118*
  orificial 31.9, 31.10, 31.15
  perianal/perineal 31.10, 71.95
  perioral 31.10
  primary 31.8
  primary complex 31.8
  primary inoculation 31.8, 31.10, 31.11–12
  prognosis 31.26
  re-emergence 31.2
  re-infection 31.8
  reactivation 31.30
    with TNF-antagonist therapy for psoriasis 74.4, 74.7
  secondary 31.8
  sweating in 44.7
  Takayasu's arteritis and 50.44
  treatment 31.26–8
  vegetating 31.20
  warty 31.9, 31.10, 31.12–13, 31.28
  see also Mycobacterium tuberculosis
tuberculosis colliquativa cutis *see* scrofuloderma
tuberculosis cutis orificialis 31.9, 31.10, 31.15
tuberculosis verrucosa cutis (warty tuberculosis) 31.9, 31.10, 31.12–13, 31.28
tuberous sclerosis complex (TSC) 62.23–4, *66.65*
  in adolescence 8.7
  bone and joint involvement *62.100*
  genetics 15.6, **15.21–5**
  hypomelanotic macules of 58.44
  lesions, acne lesions vs 42.37
  non-symmetrical lipomatosis with 46.46
  oral involvement 69.41, *69.118*
  poliosis in 66.93
  renal involvement 62.69
  respiratory tract involvement 62.80
tubo-ovarian abscess 34.26
tubocurarine 75.153
tubulin 3.9
tularaemia **30.53–4,** 38.6, 38.35
tulipalins 26.16, 26.76
tuliposides 26.76
tulips 26.16, 26.76
Tulle dressings 47.48
tumbu fly 38.8, 38.9, 38.10
tumoral calcinosis 59.69

tumour(s)
  benign vs malignant 52.2
  definition 5.8, 52.1
  formation, genetics 15.5–6
  metastases 52.1
  obesity and 8.17
  in pregnancy *8.11*, 8.12
  soft-tissue **56.1–62**
  vascular 18.40–60
  see also malignant disease; *specific tumours*
tumour-like lesions, female genital 71.72–4
tumour necrosis factor (TNF) **12.42–3**
  adverse effects 75.144
  anti-TNF monoclonal antibodies 74.5
  biological therapies 74.5–10
  in ectodermal dysplasias 15.57–61
  in linear IgA disease 40.45
  pathogenesis of chronic inflammatory disease states 74.5
  recurrent melanoma management 54.54
  TNF-α 12.42–3, 13.5, 17.49, 64.9
    hair growth and 66.11
    in lichen planus 41.1
    receptor activation, UV radiation 8.21
    in SAPHO syndrome 42.85
    sebocytes expressing 42.4–5
    in SJS/TEN lesions 76.9
    skin barrier function and 25.3
    in tuberculosis 31.4
    in vasculitis 50.4, 50.6, 50.10
    in wound healing 14.3
  TNF-β 12.42
  TNF-γ 42.26
  TNF-receptor-associated periodic syndrome (TRAPS) 12.42
  TNF receptors
    keratinocyte apoptosis 12.42
    soluble 74.5
    types 12.42
tumour necrosis factor (TNF) antagonists 20.41, 74.5–10
  in Behçet disease 74.8
  clinical indications 74.6
  in hidradenitis suppurativa 74.7
  in inflammatory bowel disease 74.7
  in pityriasis rubra pilaris 74.7
  in psoriasis 74.5
    and reactivation of tuberculosis 74.4
  in pyoderma gangrenosum 74.7
  in rheumatoid arthritis 74.7
  in sarcoidosis 74.7
  side effects 74.6
  see also tumour necrosis factor
tumour-suppressor genes 15.2, 52.12
  two-hit progression to tumour formation 15.5
tungiasis **38.12–13**
Tungidae 38.11, 38.12–13
Tuomaala syndrome 15.31
turban tumour 53.28–9
turbimetry 13.18
Turcot's syndrome, genetics 15.25
turf toe 28.31
Turicella otidis 68.2
turmeric 38.41
Turner phenotype 70.2
Turner sign (Grey Turner sign) 62.65
Turner's syndrome 62.77
  acquired melanocytic naevi number 54.15
  ear defects in 68.4
  genetics **15.12–13**
  lymphoedema 48.10
  macrocystic lymphatic malformations 48.27
Turnpenny type ectodermal dysplasia 15.37
turpentine 25.20, 26.79, 26.82–3, 75.163
turtles 2.3
  skin disease 2.12
twenty-nail dystrophy *65.13*, 65.29, 65.30
twin spotting 15.7
twin studies
  acne aetiology 42.18
  atopic dermatitis 24.3
twistometry 4.11
two-hit hypothesis 11.17, 52.6–7
Tydeidae 38.48
tylosis 62.20–1, 69.24–5, *69.116*
  with oesophageal cancer 19.106
tympanic membrane 68.1, 68.2
Tyndall effect 54.26
typhoid 30.47–8
typhus
  arthropod vectors 44.7
  epidemic 30.72–3
  murine (endemic) 30.73
  purpura 49.20
  scrub 30.74
  sporadic 30.73
  tick 30.73
typus amstelodamensis **15.92**
  see also de Lange syndrome (Cornelia de Lange)
typus maculatus 58.20
Tyrophagus 38.47
tyrosinaemia 59.97
  oculocutaneous (type II) 59.97
    keratoderma with 19.95, 19.111–12
    prenatal diagnosis *16.3*
tyrosinase 73.28
  gene, albinism 58.39
  inhibition 73.27
  melanin synthesis 58.5, *58.6*, 58.7
tyrosine, melanin synthesis 58.5, *58.6*
tyrosine kinase pathway, stem cell signalling 3.6
tyrosine kinase receptors 63.18, 63.19
  in piebaldism 58.42
Tyson's glands of prepuce 42.1
Tzanck smear 5.21, 10.28–9, 35.28
Tzank preparation 40.8

U
U1-RNP, specific antibody 51.110, 51.112
Uber lipoidgranulomatose 55.18–19
UCA (urocanic acid) 4.7, 13.32, 29.6
UK, prevalence of skin disease *6.9*
UK National Patient Safety Agency 72.26
UK Sickness Impact Profile 72.17
ulcer(s)
  acute genital 71.65–6
  acute tuberculous (orificial tuberculosis) 31.9, 31.10, 31.15
  anogenital 71.3–4
  arteritic 51.132
  burns 28.91
  Chiclero's *37.35*, 37.39–41
  decubitus/pressure *see* pressure ulcers
  definition 5.8
  diabetic 14.1, 14.13
    foot 47.57–8, 63.8–9
    see also ulcer(s), neuropathic
  in dystrophic EB 39.18
  female genital 71.65–7
  foot
    diabetes 47.57–8, 63.8–9
    lichen planus 41.14
  genetics 15.13
  gingival 69.14
  hypertensive 47.52–4
  hypopyon *67.9*
  in immunodeficiency 17.52
  in infantile haemangioma 18.45, 18.49
  intravenous drug abuse 28.45, 28.53
  ischaemic 47.2, *47.3*
  'kissing' 34.7
  leg 14.12–13, **47.41–58,** 51.132
    aetiology *14.12*, 47.54–7
    allergens *47.45*
    allergic contact dermatitis and 26.19, 26.43–4
    arterial 14.13, **47.52–4**
    in autoimmune disease 47.55
    chronic 8.28, 47.41
    decubitus 47.57
    definition and epidemiology 47.41
    elderly people 8.28
    in granulomatous diseases 47.57
    in haematological disease 47.56
    in haemoglobinopathies 62.85
    in hydroxyurea deficiency 47.54–5
    hyperhidrosis and 44.9
    hypertensive (Martorell's) 47.53–4
    infections associated 47.56–7
    in livedoid vasculopathy (vasculitis) 47.55
    in prolidase deficiency 47.54
    in pyoderma gangrenosum 47.57
    recurrent 47.50–1
    in rheumatoid arthritis 47.55
    in sickle cell anaemia 47.56, 49.47
    silver sulfadiazine therapy 73.11
    in SLE 47.55
    vasculitic/vasculopathy 47.55
    venous *see* venous ulceration
  leprosy 47.56
  lip, due to calibre-persistent artery 69.129
  Lipschutz *see* Lipschütz ulcers
  male genital 71.24–6
  Meleney's 47.57
  neuropathic (neurotrophic/perforating) 47.57, 62.99, **63.8–11,** 63.15, 63.20
    diabetes 47.57
    see also ulcer(s), diabetic
  oral cavity *see under* oral cavity
  parastomal 62.54
  penetrating (ulcus terebrans) 52.19
  pentazocine 28.45, 28.53
  perianal/perineal 71.94
  in prolidase deficiency 47.54
  rheumatoid 47.55
  rodent *see* basal cell carcinoma (BCC)
  'snail-track' 34.11
  steroid 47.56
  streptococcal 30.33
  syphilitic chancre 34.6–7
  treatment
    hydroxycarbamide (hydroxyurea) 47.54–5
    topical 73.10
  in trigeminal trophic syndrome 63.13
  tropical (phagedenic) 30.60–1, 47.57
    Staphylococcus aureus in 30.60
  tuberculous 47.57
  tumours associated 47.45
  venous stasis (gravitational) 14.1
  in Wegener's granulomatosis 50.40
  see also pressure ulcers
ulcerative colitis **62.50–3**
  angio-oedema and 62.50
  erythema multiforme and 62.50
  erythema nodosum and 62.50
  gangrene and 62.51
  linear IgA disease and 62.51–2
  lobular panniculitis and 46.14
  necrobiosis lipoidica and 60.15
  purpura and 62.51
  pustular neutrophilic dermatoses in *50.89*
  pyoderma gangrenosum and 50.65, 62.50–1
  reactive lesions 62.50
  smoking and 50.66
  Sweet's syndrome and *50.75*, 62.51
  urticaria and 62.50
  vasculitis and 62.51
ulcus cruris 47.35
  see also venous ulceration
ulcus molle *see* chancroid
ulcus terebrans 52.19
ulerythema oophryogenes 66.51
ulerythema sycosiforme (lupoid sycosis) 30.25
Ullrich–Turner syndrome *see* Noonan's syndrome (NS)
ulnar mammary syndrome 15.55
ultrasound 5.22
  colour Doppler duplex
    chronic venous insufficiency 47.35
    venous leg ulceration 47.47
  compression (CUS), deep-vein thrombosis 47.29
  fetal 16.7
  foreign bodies 28.42
  HIV lipodystrophy 46.42
  in mastocytosis 22.34
  in muscle hernias 28.62
  skin thickness measurement 72.11
  spinal 63.15
ultraviolet filters, as allergens/photoallergens 26.23, 26.24, 26.62–3
ultraviolet (UV) phototherapy
  carcinogenic hazard 20.31
  psoriasis 20.28–33
    broad-band vs narrow-band 20.28
  TL-01 lamps 20.28
  UVB, non-melanoma skin cancer and 52.4
ultraviolet protection factor (UPF) 29.8
ultraviolet (UV) radiation **29.1–3**
  abnormal cutaneous effects *see* photodermatoses
  acne and 42.34, 42.67
  ageing due to *see* photoageing
  antigen induced by 29.11, 29.17, 29.19
  barrier function of skin and 4.6–7
  basal cell carcinoma and 29.7, 52.3
  carcinogenicity 27.16
  cutaneous effects of exposure **29.5–7,** 45.2
    acute systemic effects 29.6–7
    early effects 29.5–6
    late effects 29.7
  definitions and units 29.1
  dermatoses exacerbated by *29.22*, 29.22–3, 29.23
  direct/indirect effects on skin 8.21
  diseases associated with exposure *see* photodermatoses
  DNA damage *see* DNA damage
  DNA photoproducts 29.4
  DNA repair defects and 52.13–14
    see also DNA damage, repair defects
  dosimetry (radiometry) 29.2–3
    calibration 29.3
  environmental exposure to 29.4
  exposure minimisation 29.8–9
    clothing 29.8
    squamous cell carcinoma 52.28
    sunscreens *see* sunscreens
    see also photoprotection; sun exposure, avoidance
  exposure quantification 29.4
  feel-good and health factors 29.6–7
  filters, as allergens/photoallergens 26.23, 26.24, 26.62–3
  genetic changes due to 52.13
  immunological effects **13.26–34,** 26.10, 52.14
  immunomodulatory effects 29.6
  immunosuppression due to 8.22, 52.14
    non-melanoma skin cancers 52.14
    reduced by sunscreens 73.41
  intensity increased by reflection 29.8
  interactions with atmosphere 29.3
  interactions with matter 29.3–4
  interactions with skin 29.4
  lentigines 54.2
  malignant melanoma and 6.12, 29.7, 54.32–3, 54.34
  matrix metalloproteinase activation 8.21, 8.22
  mechanical injury 28.8, 28.53
  melanocyte growth arrest due to 58.7
  melanocyte response 58.7
  melanosome transfer to keratinocytes 58.4
  modification, optical components 29.2
  mutagenic effects 52.13–14
  nature of 29.1
  non-melanoma skin cancers 52.3, **52.13–14,** 52.19
  photodermatitis 28.92
    plant-induced 29.21, **58.23,** 75.162

pigmentation 58.7
solar elevation affecting 29.8
sources 29.1–2
spectrum 29.1, *29.2*
squamous cell carcinoma and 29.7, 52.3, 52.24, 52.27
tanning with 58.31–3
see also tanning
thermal injury 28.72
transmission to dermis 29.4
UVA 8.21, 29.1, 52.3, 52.13
absorbers 29.9
actinic prurigo 29.14
adverse effects 73.40
carcinogenic potential 52.3
chronic actinic dermatitis 29.16–17, 29.18
discoid lupus erythematosus 51.5
hydroa vacciniforme 29.15
hyperpigmentation associated 58.10
immunosuppressive effects 13.26, 13.33
interactions with atmosphere 29.3
long-wave, sunscreens and 73.40
mutations induced by 52.13–14
penetration of skin 4.7
photoageing 29.7
polymorphic light eruption 29.11
pseudoporphyria 29.7
skin penetration 80.2
solar urticaria 29.19
sources 29.1
sunscreen protection from 29.8, 29.9, 73.40
UVA-1 (340–400 mm) low-dose broadband 29.1
lichen sclerosus 51.118
morphoea 51.75
SLE 51.62
UVA-II 29.1
UVB 8.21, 29.1, 52.3, 52.13
actinic prurigo 29.14
chronic actinic dermatitis 29.18
coal tar with 73.42
Hailey–Hailey disease aggravation 39.33
immunosuppressive effects 13.26–34
interactions with atmosphere 29.3
melanocyte response 58.7
mutations induced by 52.13
penetration of skin 4.6–7
photoageing 29.7
polymorphic light eruption 29.11
repair of damage 52.13, 52.14
skin penetration 80.2
solar urticaria 29.19
sources 29.1
suberythemal, in Hailey-Hailey disease 39.36
sunscreen protection from 73.40
UVB phototherapy, non-melanoma skin cancer and 52.4
UVC 29.1, 52.3, 52.13
sources 29.1
vitamin D synthesis 29.6
wavelengths 29.1, *29.2*, 29.5
see also sun exposure; sunlight
Umbelliferae, phytophotodermatitis due to 29.21
umbilical artery catheterization 17.13, 71.84
umbilical cord, inflammation 34.15
umbilical dermatology **71.100–2**
congenital and developmental abnormalities 18.93, 71.100
general approaches 71.1–4, 71.100
inflammatory dermatoses 71.101
trauma and artefact 71.100–1
tumours and implantations 71.101
umbilicus
bacterial flora 30.4–5, 30.6
developmental anomalies 18.93, 71.100
granuloma 18.93
polyp 18.93–4, 71.100
structure and function 71.100
uncein, monoclonal antibodies to 39.25
Uncinaria stenocephala 37.16
uncircumcised males 71.13
uncombable hair, retinal pigmentary dystrophy, dental abnormalities and brachydactyly 15.56
uncombable hair syndrome 66.71–2
uncoupling protein-1 (UCP-1) 46.1
undecylenic acid *26.46*, *73.13*
undifferentiated vulval intraepithelial neoplasia 71.74
unheated serum reagin (USR) test 34.19
unilateral naevoid telangiectasia syndrome 47.19
uniparental disomy 11.18, 15.7, 16.2, 52.12
universal acquired melanosis 58.22
Unna–Thost syndrome 69.16
Ununo Enyi (granuloma multiforme) 60.14, **60.17**
upper eyelid dermatosis syndrome 67.5
upper limb
lymphoedema 48.12, 48.13
see also arms
urachal duct 71.100
urachus, anomalies 18.94
uraemia 44.20
calciphylaxis (calcific uraemic arteriolopathy) 47.8
urate crystals, lobular panniculitis 46.17
urea
as penetration enhancer 73.7
in sweat 44.5, 44.6
urea frosting 62.72
Ureaplasma urealyticum 30.69
female genital infection 71.68
urethra
caruncles *71.73*
prolapse 71.73
stenosis in males, lichen sclerosus 51.116
urethritis
anterior, chlamydial 34.29, *34.30*
gonococcal 34.25, *34.26*
urinary tract
anomalies associated with supernumerary nipples 70.2
developmental anomalies 17.24
in menopause 8.19
urine
napkin dermatitis and 17.23
output in burns 28.78
urocanic acid (UCA) 4.7, 13.32, 29.6
UROD (uroporphyrinogen decarboxylase) 59.5
urokinase 75.107
blocking acantholysis 40.14
uroporphyrinogen decarboxylase (UROD) 59.5
urostomy *see* stoma
Urtica dioica 22.2
urticants 25.18
urticaria **22.1–30**
acute 22.2, **22.7–9**
allergic 22.7–8
idiopathic 22.7
in infectious mononucleosis 33.30
intermittent 22.2
investigation 22.26
non-allergic (intolerance reactions) 22.8
pityriasis rosea vs 33.80
pseudoallergic 22.8
after streptococcal infection 30.16
alcohol-induced 22.8
allergic 22.7–8
allergic contact 22.19–120, 26.104–6
female genitalia 71.58
aquagenic *22.13*, 22.17
associated with dental amalgam 22.11
associated with prosthetic implants 22.11
associations 22.2–3
atopic dermatitis and 24.23
autoantibodies in 13.21–2, 22.9
candidiasis and 22.10
childhood 22.6–7
cholinergic *22.13*, 22.15, 22.16
chronic 22.2, **22.9–12**
aggravating factors 22.10–12
autoimmune 22.9
autoimmune, ciclosporin therapy 74.16
idiopathic 22.9
infection and 22.10
intermittent 22.2
investigation 22.26–7
papular 23.44
pseudoallergic 22.10
psychological factors 64.4–5
sarcoidosis and 61.17
classification 22.2
coeliac disease and 22.2
cold 22.4, 22.5, 22.16
acquired 22.16
challenge test *22.13*
familial 22.16, 22.24
following jellyfish stings 38.56
histamine and 21.4
idiopathic 22.16
secondary to serum cryoproteins 22.16
systemic 22.16
contact 22.2, **22.19–20,** 26.25
allergic/immune 22.19–120, 26.104–6
allergic/immune, of female genitalia 71.58
causes *22.20*
non-allergic/non-immune 22.20, 25.1, 25.18, 25.24
occupational 27.5
definitions 22.1–2
delayed pressure 22.3, *22.13*, 22.14–15
diagnosis 22.25
differential diagnosis 22.25
drug-induced 22.8, 22.10, 75.16–17, 75.17, *75.25*, 75.26
factitious 2 2.12–13, *22.14*
familial cold 22.16, 22.24
with familial Mediterranean fever 62.69
female genital region 71.58
food/food additive-associated 22.8, 22.10–11, 26.105
genetics 22.3
heat 22.15–16
Helicobacter pylori and 22.2, 22.10
in hepatitis B virus infection 22.8, 62.59
histology 22.3–4
historical background 22.2
history taking 22.25
idiopathic 22.2
infection and 22.2, 22.8, 22.10, 22.11
lesions in SLE 51.38
localized heat *22.13*, 22.15–16
male genital region 71.16
mechanical injury 28.53
menstrual cycle and 22.11
natural history 22.27
nickel allergy and 22.11
ordinary 22.2, **22.5–12**
aetiology 22.7–12
childhood 22.6–7
clinical features 22.5–6
papular 22.23, 38.2, 38.3
due to fleas *38.3*, 38.11
paraneoplastic 62.38
parasite infection and 22.2, 22.10
in parvovirus B19 infection 33.63
pathophysiology 22.4–5
physical **22.12–18**
challenge tests *22.13*
classification *22.12*
pregnancy and 22.11
prevalence 22.3
in schistosomiasis 37.21
skin biopsy 10.43, 22.3
skin testing 75.173
solar *see* solar urticaria (SU)
stress and 22.11–12
thyroid disorders and 22.2, 22.26
treatment 22.27–30
antihistamines 74.31
doxepin 74.32
ulcerative colitis and 62.50
vibratory *22.13*, 22.15
weal-less 21.6
urticaria-like follicular mucinosis 59.28
'urticaria-like' plaques 51.131
urticaria multiformis endemica (harara) 38.5, 38.7
urticaria pigmentosa 22.30, **22.31–2**
Darier's sign in 22.14, 22.31–2
in dogs 2.22
histopathology 22.34
hypermelanosis with 58.38
KIT gene mutations 3.20
skin biopsy 10.43
urticarial fever 37.21
urticarial papular and plaque eruption 26.25–6
USA, prevalence of skin disease *6.9*
ustekinumab 20.42, 74.10
uta 37.40
UV radiation *see* ultraviolet (UV) radiation
uveitis *67.4*
anterior 61.6, 61.7, *67.4*
in Behçet's disease 50.59–60
granuloma annulare and 60.9
hypopyon 50.60
intermediate *67.4*
posterior 50.59–60, 61.7, *67.4*
in sarcoidosis 61.6, 61.7

V

VAC (vacuum-assisted closure) 28.23
vaccination/vaccines
adverse effects 75.138–40, 76.3, *76.4*, 76.12, 76.13
anthrax 30.41
BCG *see* BCG vaccination
Canvaxin whole-cell vaccine 54.54
hepatitis B *see under* hepatitis B virus (HBV)
HPV infection 33.42
HSV infection 33.21
leprosy 32.19
Lyme disease 62.106
malignant melanoma 54.54
measles 33.75
MMR 33.71
rabies *see under* rabies
rubella 33.71
Trichophyton verrucosum 36.29
vaccinia 33.6, 33.7
vasculitis and 50.5, *50.18*, 50.55
VZV infections (varicella/zoster) 33.27, 63.7
vaccinia **33.6–7,** 69.121
accidental (autoinoculation) 33.6
generalized 33.6
progressive 33.6
vaccination 33.6, 33.7
vacuoles, sebum 42.3
vacuum-assisted closure (VAC) 28.23
vagabond's disease 38.22
pigmentation changes 58.28–9
vagina
Candida albicans carriage 36.56
lichen planus 41.9
in menopause 8.19
vaginal discharge 71.52, 71.53–4, 71.69
vaginal intraepithelial neoplasia, treatment 73.24
vaginal stenosis 8.12
vaginitis, in trichomoniasis 37.29
valaciclovir
action 74.49
in herpes B virus infection 33.34
in herpes simplex 33.20, 33.21
in herpes zoster 63.6, 67.26
in zoster 33.27, 33.28
valdecoxib 75.77

valganciclovir
  in CMV infection 33.29
  in HHV-8 infection 33.34
validity 6.18–19
  external 6.19
  internal 6.18–19
valley fever *see* coccidioidomycosis
valproate *see* sodium valproate
Valsalva manoeuvre 49.4
valves, semilunar, of veins 47.25
valvuloplasty 47.51
Van der Bend chamber 26.85
van der Woude syndrome **15.93–4,** 18.3, 18.90, 18.91, 69.40, 69.41
van Gieson stain 10.9
van Lohuizen's syndrome *see* cutis marmorata telangiectatica congenita
vancomycin *26.46,* 74.43, 75.60–1
  in drug-induced linear IgA disease 40.49, 76.7
  in MRSA infection 30.9
vanilloid receptors 21.2, 63.2, 73.49
vanishing bone disease *see* Gorham's (Gorham–Stout) disease
vanishing creams 73.7
vanishing penis syndrome 71.13
variant Creutzfeldt–Jakob disease, sterilization of surgical equipment and 77.7
varicella **33.22–8**
  aetiology and epidemiology 33.22–3
  antibodies 33.23
  chronic 33.25
  clinical features 33.24–5
  complications 33.24–5
  cytodiagnosis 10.29, 33.27
  diagnosis 33.27
  encephalitis 33.24
  fetal damage 33.23, 33.24
  fetal varicella syndrome 17.40–1, 18.2, 18.102
  fever in 33.24
  haemorrhagic 33.24
  immune response 33.23, 33.27
  in immunocompromised patients 33.23, 33.24, 33.25, 33.27
  incubation period 33.24
  maternal 33.23
  mortality 33.24, 33.25
  oral involvement 33.24, 69.74
  pathology 33.23–4
  persistent verrucous 35.45
  prevention 33.27
  scars 45.6
  subclinical 33.23
  treatment 33.27–8
  vaccination 33.27
  vesicles 33.24
varicella gangrenosa 33.25
varicella zoster virus (VZV) **33.22–8**
  detection (antigen, DNA, proteins) 33.27
  in HIV infection 35.28–39
  infection
    disseminated, in HIV infection 35.29
    female genitalia 71.69
    see also varicella; zoster
  Oka strain 33.27
  reactivation 33.22, 33.23
    in HIV infection 35.28–39
    see also zoster
  replication 33.23–4
  transmission 33.23
  vaccine 8.28, 33.27, 63.7
  viraemia 33.22, 33.23
varices, hands 47.16
varicography 47.36
varicose eczema 26.19
  differential diagnosis 26.29
varicose veins 47.13, **47.37–40**
  arteriovenous shunting 47.21
  clinical features and diagnosis 47.37
  in pregnancy 8.10–11
  prevalence and classification 47.37
  primary 47.37
  recurrent 47.1, 47.38
  reticular 47.37
  secondary 47.37
  surgery 47.38–9, 47.51
    lymphoedema after 48.13
  treatment 47.37–40
    complications *47.38*
    sclerotherapy 47.24
  truncal 47.37
varicosity 47.23, 47.35
  female genital dermatology 71.55
  venous 47.35, 47.37
    see also varicose veins
variegate porphyria (VP) 59.19–20, 62.46, 66.79
variola (smallpox) 33.5, *33.6*
vasa vasorum, occlusion 34.5
vascular cell adhesion molecule-1 (VCAM-1) 13.9
  in polymorphic light eruption 29.11
  in vasculitis 50.7, 50.8
vascular changes, in pregnancy 8.10–11
vascular coagulopathies 49.42–7
vascular diseases
  eye and skin involvement *67.30*
  pigmented purpuric dermatoses and 49.23
  see also specific diseases
vascular endothelial growth factor (VEGF) 48.2
  in giant cell arteritis 50.43
  hair growth and 66.10
  increased, UV radiation associated 8.21
  in infantile haemangioma 18.41
  keratinocytes 12.16
  MHC and 12.16
  over-expression in psoriasis 20.5
  in rosacea 43.1–2
  VEGF-A 48.2
  VEGF-C 48.2
  VEGF-D 48.2
  in wound healing 14.2, 14.6
vascular endothelial growth factor receptor-1 (VEGFR-1) 14.6, 48.2
vascular endothelial growth factor receptor-2 (VEGFR-2) 14.6
vascular endothelial growth factor receptor-3 (VEGFR-3) 10.24, 48.2
  gene mutation 48.10
  lymphatic vessel marker 48.4, *48.5,* 48.19
vascular malformations *18.41,* 18.60–75
  arteriovenous 18.61–2, 18.79
  capillary 18.62–70, 18.79
  venous 18.70–4
vascular permeability
  dengue haemorrhagic fever 33.68
  mast cell activation effect 3.20
vascular permeability factor *see* vascular endothelial growth factor (VEGF)
vascular proliferation, atypical post-radiation 48.31
vascular reactivity, abnormal, rosacea pathogenesis 43.1–2
vascular spider *see* spider angioma
vascular system
  in Behçet's disease 50.60
  in Ehlers–Danlos syndrome 45.32, 45.34–5
  head and neck 77.2, *77.3*
  skin 3.2, 3.3
vascular tone, face and neck 43.14
vascular tumours **18.40–52**
  benign 56.25–31
  indeterminate malignancy 56.31–7
  malignant 56.37–41
  reactive 56.23–5
  see also haemangioma
vasculature, inflammation and 12.68
vasculitic acne 42.85
vasculitis **50.1–56,** 51.1
  α_1-antitrypsin deficiency and 50.11, 50.53
  ANCA-associated 74.8
    TNF antagonists in 74.8
  in animals 2.16
  annular lesions 62.112–13
  arterial ulceration 47.52
  Behçet's disease and 50.3, 50.49, 69.47
  bone and joint involvement 62.102
  breast 70.11
  cerebral 50.46–7
  of Churg and Strauss *see* Churg–Strauss syndrome
  classification 50.1–3
  Crohn's disease and 62.51
  cryoglobulinaemic 50.23–5, 50.54
  cutaneous
    in scabies 38.39
    small vessel/leukocytoclastic *50.4,* **50.13–17**
  cystic fibrosis and 50.53
  definition 50.1
  differential diagnosis 50.54–5
  drug-induced 49.21, 50.17–19, 50.49, 75.17, 75.40–1
  effector cells 50.6–7
  eosinophilic (recurrent cutaneous eosinophilic necrotizing) 50.27–8, 62.112
  evaluation 50.12–13
  exercise-induced 49.18, 50.23
  familial Mediterranean fever and 50.53–4
  genetic factors 50.11–12
  hepatitis C and 33.61
  hyper-IgD syndrome and 50.53
  hypereosinophilic syndrome and 50.53
  hypocomplementaemic *see* vasculitis, urticarial
  immune complex 49.18, 49.19, 49.32
    cryoglobulins causing 49.32, 49.33
    IgA *see* Henoch–Schönlein purpura
  in immunodeficiency 17.53
  infection and 50.5–6, 50.49, 50.55–6
  laboratory 50.2
  leg ulceration associated 47.55
  leukocytoclastic 46.32, 49.18, 50.48
  livedo *see* livedoid vasculopathy
  lymphocytic 50.47–50
  mimics 50.49
  nodular 31.24–5, **50.31–3**
  nomenclature 50.1–3
  panniculitis with 46.11, **46.32–4**
  paraneoplastic 50.4, 50.49, 50.54, 62.41–2
  in parvovirus B19 infection 33.63
  pathogenesis 50.3–12
  pustular *50.89*
  pyoderma gangrenosum and 50.49, 50.67
  relapsing polychondritis and 50.48–9, 50.54
  renal involvement 62.71
  respiratory tract 62.82–3
  in rheumatoid arthritis 51.132
  sarcoidosis and 61.17
  segmental hyalinizing *see* livedoid vasculopathy
  Sjögren's syndrome and 50.49, 50.52–3
  in SLE 50.48, 51.39
  small vessel 12.32, 62.82
  Sweet's syndrome and 50.3, 50.77–8
  in systemic disease 50.52–4
  ulcerative colitis and 62.51
  urticarial 22.18–19, 50.21–3, 50.48
    histopathology 22.3, 50.22
    hypocomplementaemic 13.22, 22.19, 50.22
    with monoclonal gammopathy (Schnitzler's syndrome) 22.23–4, 50.53, 62.94
    normocomplementaemic 50.22
  vaccination and 50.5, *50.18,* 50.55
  Wiskott–Aldrich syndrome and 50.54
vasculogenesis 47.1
vasculopathy
  crystal globulin 49.38
  leg ulceration associated 47.55
  livedoid *see* livedoid vasculopathy
  progressive, Degos' disease 49.45
  sickle cell 49.47
Vaseline 73.6
vasoactive intestinal peptide (VIP) 3.12, 4.10, 63.3, 64.9
  in atopic dermatitis 24.17
  immune function and 63.4
  production by tumours 62.68
  in urticaria 22.5
  in wound healing 63.4
vasoactive intestinal peptide (VIP)–secretin-peptide family, PACAP 12.64
vasoconstriction
  cold-induced 28.63, 28.65, 63.4
  corticosteroid-induced 73.19–20
  responses in atopic dermatitis 24.15
vasoconstrictor assay, topical corticosteroids 73.16
vasodilatation
  antidromic 63.5
  cold-induced 63.4–5
  in eczema 23.4
  inflammatory response 12.4
  minoxidil action 73.49
  nicotinamide inducing 73.51
  prolonged, telangiectases 47.13
  rebound, corticosteroid-induced 73.19–20
vasodilators, in flushing pathogenesis 43.14
vasopressin 75.98
Vater–Pacini corpuscles 3.15
VCAM-1 *see* vascular cell adhesion molecule-1
VCSS classification, chronic venous insufficiency *47.33*
VDRL test 34.19, 34.21
vecuronium 75.153
vegetable oils, in topical treatment 73.5–6, *73.6,* 73.8
vegetation, definition 5.8
VEGF *see* vascular endothelial growth factor (VEGF)
VEGFR-1 (vascular endothelial growth factor receptor-1) 14.6, 48.2
VEGFR-2 (vascular endothelial growth factor receptor-2) 14.6
VEGFR-3 *see* vascular endothelial growth factor receptor-3
vehicles
  cosmetics 26.58–60
  for topical therapy *see under* topical therapy
veil cells 3.51
veiled cells 55.3, 55.4
veins
  anatomy 47.25
  deep 47.25
    incompetence 47.41
    insufficiency 47.33
  disorders *see* venous disorders
  pathophysiology 47.25–8
  perforating (perforators) 47.25
    eczema and 47.34
    insufficiency 47.33, 47.34, 47.39
  physiology 47.25
  'sunburst' 47.39, *47.40*
  superficial 47.25
    insufficiency 47.32–3, 47.42
  valve incompetence 47.25
  varicose *see* varicose veins
veldt sore 47.56
vellus cyst, eruptive 53.7
vellus hair 3.13
velocardiofacial syndrome 13.8
Venereal Disease Research Laboratory (VDRL) antigen test 34.19, 34.21
venesection, in polycythaemia rubra vera 62.86
Venezualan haemorrhagic fever 33.66, *33.67,* 33.69
venlafaxine 64.20, *64.51*

veno-occlusive priapism 71.51
Venofer 39.29
venom
  Cnidaria 38.55
  fish 38.59–60
  Hymenoptera 22.8, 38.14
  Mollusca 38.59
  scorpion 38.33
  sea urchin 38.58
  snake 38.60
  spider 38.31, 38.32
venous ankle flare 47.14, 47.33
venous disorders **47.25–41**
  chronic 47.13
  chronic insufficiency *see* chronic venous insufficiency (CVI)
  deep vein incompetence 47.41
  lymphoedema association *48.12*, 48.13
  physiology/pathophysiology 47.25–8
    mechanisms 47.26–8
  post-thrombotic syndrome *see* post-thrombotic syndrome (PTS)
  varicose veins *see* varicose veins
  see also venous thrombosis; *specific disorders*
venous hypertension 47.25, 47.26, 47.37
  chronic, lipodermatosclerosis 46.30–1
  elderly people 8.28
  in livedoid vasculopathy 49.44
  post-thrombotic syndrome 47.40
  venous leg ulceration and 47.42
  see also venous pressure, elevated
venous insufficiency
  acroangiodermatitis (of Mali) and 49.17
  in arteriovenous fistulae 47.21
  chronic *see* chronic venous insufficiency (CVI)
  deep veins 47.33
  lymphoedema association *48.12*, 48.13
  perforating (perforators) veins 47.33, 47.34, 47.39
  superficial 47.32–3, 47.42
venous lake (venous varix) 47.16, 69.101
venous macrocirculation 47.25
venous malformations 18.70–4, **47.23–5**
  disorders associated 47.23–5
  solitary 47.23
venous microcirculation 47.26–8
venous outflow obstruction 47.26
  deep-vein 47.32
venous pressure 47.25
  ambulatory, normal lowering 47.25
  elevated 47.25, 47.26, 47.27, 47.41
    pigmented purpuric dermatoses and 49.22
    see also venous hypertension
  measurement 47.36
venous reflux 47.25–6, 47.32–3
  investigations 47.35
  superficial 47.37
venous return 47.25
venous stasis
  lipomembranous fat necrosis and 46.22–3
  purpura due to 49.14
venous surgery, for varicose veins 47.38
venous thrombosis 47.25, **47.28–32**
  Mondor's disease *see* Mondor's disease
  in paroxysmal nocturnal haemoglobinuria 49.30
  recurrent 47.7
  superficial 47.30
  see also deep-vein thrombosis (DVT)
venous tone 47.25
venous ulceration 47.35
  fibrin cuff-theory 47.26–7, 47.27
  leg **47.41–52**
    arterial disease coexistence 47.42
    associated conditions 47.43–6
    clinical features 47.42–3
    complications 47.43–6
    diagnosis 47.47
    epidemiology 47.41–2
    failure to heal 47.42
    haemorrhage 47.45
    healing, pathology 47.42
    infections 47.44, 47.49
    malignant changes 47.45–6, 47.50
    management 47.47–50
    measurement 47.49
    pathogenesis 47.42
    recurrent 47.50–1, 47.51
    social factors 47.43–4
    surgery 47.51–2
    see also ulcer(s), leg
  lipodermatosclerosis 47.34
  pathogenic theories 47.26–7
venous varicosity 47.35, 47.37
  see also varicose veins
venous vessels 3.51
venules 3.51
  chronically dilated 47.12
  dilatation, telangiectasia 47.12, 47.13
  leg, laser therapy 78.8
venulitis
  cutaneous necrotizing *50.4*, **50.13–17**
  in urticarial vasculitis 22.18
verapamil 75.95
Verbenaceae *26.81*
vermilionectomy 77.36
vernal keratoconjunctivitis (VKC) *67.14*, 67.15, 67.16
  clinical features *67.13*
vernal plaque *67.14*
vernix caseosa 17.2, 17.4, 17.6, 17.11, 30.3–4, 42.3
Verocay bodies 56.46
verruca necrogenica 31.12
'verruca socks' 33.48
verrucae 28.54
verruciform xanthoma
  female genital dermatology 71.73
  male genital dermatology 71.36
verrucous carcinoma 33.55, 52.26
  external auditory canal 68.33
  female genital dermatology 71.76–7
  male genital dermatology 71.22, 71.42, 71.44–6
  oral cavity 69.53
  see also Buschke–Löwenstein tumour
verrucous hyperplasia, mechanical injury and 28.28
verrucous perforating collagenoma 45.65
verruga peruana 30.57–8
versican 3.46
  gene *3.48*
vertebral collapse, in Langerhans' cell histiocytosis (LCH) 55.12
vertebrates
  epidermis and dermis 2.2–3
  pigment cells 2.5
vertical growth carcinoma, male genital dermatology 71.42
vertical traction, in evaluation of mechanical properties of skin 28.5
very late antigen-1 13.9
vesicles 10.37
  in carbon monoxide poisoning 28.93–4
  in CMV infection 33.29
  definition 5.8
  fluid, viral infection diagnosis 33.4
  in foot and mouth disease 33.74
  in hand, foot and mouth disease 33.71
  in herpangina (coxsackievirus infection) 33.71
  in herpes simplex 33.16, 33.18
  intradermal, incontinentia pigmenti 58.15
  in Kaposi's varicelliform eruption 33.35
  in varicella 33.24
  in viral infections 33.4
  in zoster 33.25
vesico–urachal diverticulum 18.94
vesicular bodies 4.2
vesicular stomatitis virus **33.74**
vesiculobullous systemic lupus erythematosus 40.56–8
Vespa 38.14
Vespidae/Vespoidea 38.14
Vespula 38.14
vestibular papillae, female genital dermatology 71.55
vestibular papillomatosis, female genital dermatology 71.55
vestibulodynia 71.82
veterinarians, occupational hazards 27.3, 27.5, 27.21
veterinary dermatology 2.8–19
Viagra *see* sildenafil
vibration injury **28.56–60**
vibration tests, mechanical injury 28.5
vibration white finger 27.17, 28.26, 28.56, **28.57–8**
vibratory angio-oedema 28.58
Vibrio alginolyticus 30.18
Vibrio cholerae 6.11
Vibrio vulnificus 30.59
vibrissae 66.2, 66.6
vidarabine 35.28, 74.48
vigabatrin 75.86
villi 10.42
vimentin 3.9, 3.51, 10.22, 69.39
VIN *see* vulval intraepithelial neoplasia (VIN)
vinblastine 75.132
vincristine
  adverse effects *70.5*, 75.132
  in infantile haemangioma 18.51
  in Kasabach–Merritt syndrome/phenomenon 18.57
vinegar
  in alkali burns 27.12
  in jellyfish stings 38.57
vinyl chloride *27.17*, 45.51–2
vinyl chloride disease 51.80
violin spider 38.32
VIP *see* vasoactive intestinal peptide (VIP)
VIP–secretin-peptide family, PACAP 12.64
viral infection **33.1–81**
  acne association 42.79
  in animals *2.22*
  antibody production 33.4
  in atopic dermatitis 24.12–13, 24.24
  bystander activation hypothesis and 50.6
  cutaneous problems 33.76–81
  cytodiagnosis 10.29
  Degos' disease aetiology 49.45
  ear 68.20
  electron microscopy 10.30
  erythema multiforme and 33.76, 76.2
  erythema nodosum and 33.76
  exanthems 33.3–4, *33.4*
  eyes 67.24–5
  female genital dermatology 71.69–70
  Gianotti–Crosti syndrome in *see* Gianotti–Crosti syndrome
  granuloma annulare and 60.1
  haemorrhagic fevers **33.66–70**
    diagnosis 33.68
  idiopathic thrombocytopenic purpura association 49.9, 49.10
  insect-borne **33.66–70**
  laboratory diagnosis 33.4–5
    specimens 33.4
  latent 33.3
  lips 69.121
  lytic 33.3
  neonatal 17.39–42
  oral cavity 69.72–7, *69.118*
  papular–purpuric gloves and socks syndrome 33.76
  pathogenesis 33.1–3
  pathology **33.1–5**
  permissive cells 33.1
  persistent 33.3
  polyarteritis nodosa in 33.77
  purpura associated 49.20–1
  reactivation 33.3
  sarcoidal reaction in 61.22
  sarcoidosis and 61.17
  serological tests 33.4, 33.5
  TORCH syndrome 33.76–7
  vasculitis and 50.49, 50.55
  see also individual viral infections
viral warts *see* human papillomavirus (HPV)
Virchow's triad 47.28
virus(es)
  assembly and release 33.3
  attachment 33.1
  classification *33.2–3*
  culture 33.4
  detection methods 33.4
  DNA 33.1, *33.2*, 33.4, 33.14
    double-stranded DNA 33.1, *33.2*, 33.5
    single-stranded DNA *33.2*
  in lichen planus pathogenesis 41.2–3
  neurotropic 33.1
  proteins 33.3
  replication 33.1, 33.3, 33.4
  RNA 33.1, *33.2*, 33.3–4
    diseases/infections 33.75
    negative-sense 33.1, *33.3*
    positive-sense (mRNA) 33.1, *33.2–3*
  RNA tumour 33.1
  see also specific viruses
virus-associated haemophagocytic syndrome 55.30–1
virus-induced histiocytic medullary reticulosis 55.30–1
virus-induced histiocytosis with erythrophagocytosis 55.30–1
visceral leishmaniasis **37.41–3**
viscous extension/slip 4.8
vision, colour, in animals 2.6
visual impairment
  in giant cell arteritis 50.43, 50.44
  in infantile haemangioma 18.45–6
  in leprosy 32.13–14
  in onchocerciasis 37.4, 37.5, 37.7
vitallium 26.37
vitamin(s) **59.60–7**
vitamin A 64.49
  analogues *see* retinoids
  deficiency 59.60, 67.31
    pigmentation changes 58.28
  derivatives, in sebaceous gland activity reduction 42.16
  intoxication 59.60
  isotretinoin interaction 42.65
  measles treatment 33.76
  oral, acne vulgaris treatment 42.66
  see also retinol
vitamin A acid *see* retinoic acid (tretinoin; vitamin A acid)
vitamin B complex 59.62
vitamin B supplements, high-dose, pyoderma faciale and 42.84
vitamin B_1 75.113
vitamin B_3 *see* nicotinic acid
vitamin B_6 59.62, 75.113
vitamin B_{12} 59.62–3
  deficiency 62.85
    hair colour changes in 66.94
    oral involvement 69.56, 69.85–6, *69.116*, *69.117*
    pigmentation changes in 58.27
    in systemic sclerosis 51.102
  sclerodermiform reaction 28.44–5
vitamin C 59.65–6
  adverse effects 75.114
  analogues 80.3
  deficiency 59.65–6, 59.66
    bone and joint involvement *62.101*, 62.105
    differential diagnosis 50.54
    epidemiology 6.1
    gingival involvement 69.21, *69.117*
    purpura in 49.4, 49.15
    wound healing and 14.18
  dithranol with 73.30
  supplements
    in miliaria 44.16
    in wound healing 14.24

vitamin D 59.61
  analogues **73.43–8**
    in psoriasis 20.26, 73.43
    sensitization by 73.43
  calciotropic activity 73.43
  cutaneous calciphylaxis and 49.48
  cytokine release 73.43
  deficiency 29.6, 29.9, 54.34
  in psoriasis 73.43
  receptor 73.43
    hair growth and 66.11
  response elements 73.43
  synthesis 4.1, 29.6, 54.34, 73.43
    pigmentation hindering 58.9
  therapeutic actions, mechanisms 73.43
  Williams–Beuren syndrome and 45.25
vitamin D_3 29.6
vitamin E 59.61
  adverse effects 75.114, 75.167
  allergy to *26.46*
  secretion by sebaceous glands 42.7
  topical 75.167
vitamin K
  adverse effects 45.52, 75.114
  allergy to *26.46*
  antagonists 47.29
  deficiency, wound healing and 14.18
  prophylaxis 49.51
  sclerodermiform reaction to 28.44–5
vitamin K-dependent coagulant factors 49.39
Vitamin K epoxide reductase (VKORC1) 72.29
vitelline duct 71.100
  anomalies 18.93–4
vitiligo 58.46–9, 59.79
  in Addison's disease 62.5
  aetiology 58.46–7
  with alopecia areata 66.35
  in animals 2.23
  assessment 72.11
  autoantibodies 58.46
  breast 70.17
  clinical features 58.47–8
  complete 58.48
  diagnosis 58.48
  diascopy 5.19
  differential diagnosis 36.11
  disorders associated *58.46*, 58.48
  electron microscopy 10.29–30
  with endocrine autoimmune conditions 62.13
  female genital dermatology 71.63
  hair colour and 58.48, 66.93
  in HIV infection 35.12
  incidence 58.46
  koebnerization 26.26, *26.27*, 28.3
  male genital dermatology 71.49
  neurogenic hypothesis 58.47
  occupational 27.15, *58.9*
  pathology 58.47
  piebaldism vs 58.42
  quality of life 64.10
  race and 9.6–7
  segmental 58.48
  self-destruct theory of Lerner 58.47
  skin biopsy 10.42
  skin grafts 77.21–2
  spontaneous repigmentation 58.48
  treatment 58.48–9, 73.26, 73.27
  trichrome 58.48
  in Vogt–Koyanagi-Harada syndrome 58.46
  Wood's light examination 5.19
vitronectin 13.4, 14.3, 14.4
VLA-1 (very late antigen-1) 13.9
Vogt–Koyanagi–Harada syndrome (VKHS) 58.45–6, 66.93
  premature greying of hair 58.48
Vohwinkel's syndrome 19.3, 19.19, *19.94*, 19.98, 19.108, 45.70
Voight's lines 5.17, 9.2, *9.3*
volcano lesion 37.38
volume expanders, platelet function disorders 49.12–13
vomiting
  self-induced 64.22
  sweating following 44.7
  urticaria and 22.5
von Frey's syndrome 44.10, 44.11
von Hippel–Lindau syndrome *62.20*, 62.22, 62.69
von Kossa method 10.10
von Recklinghausen's disease *see* neurofibromatosis, type 1
von Willebrand factor 49.12, 49.29
  receptor, GP1bα, expressed by dermal dendrocytes 55.4
  in wound healing 14.3
von Willebrand's disease, bleeding time 49.6
voriconazole 36.68, 36.69, 36.86, 74.47, 75.66
vorinostat 57.28
Vörner's keratoderma (epidermolytic palmoplantar keratoderma) *19.94*, 19.95–7
VP (variegate porphyria) 59.19–20, 62.46, 66.79
VP-16 *see* etoposide
vulva
  allergic contact dermatitis 26.18–19
  amoebiasis 37.28
  angiokeratoma 18.60
  bacterial flora 30.4
  cancer, lymphoedema 48.8
  cicatricial pemphigoid, differential diagnosis 51.117
  elephantiasis 30.70
  hidradenoma papilliferum 53.20–1
  lichen planus 41.9
  lichen sclerosus 51.113–18
  lymphangiectasia 48.28
  lymphoedema 48.16
  normal bacterial flora 30.4
  Paget's disease 53.40–1
  pruritus 21.12, 21.13, **21.15**
  pyoderma gangrenosum 50.70
  squamous cell carcinoma 51.116
  syphilitic chancre 34.7
vulval epithelium 71.52, 71.53
vulval intraepithelial neoplasia (VIN) **71.74–6**
  differentiated 71.75
vulval lentigines 71.80
vulval lymphangiectasia 71.81
vulval lymphoedema 71.81
vulval melanosis 71.79–80
vulval oedema 71.81
vulval pain syndromes 71.81–2
vulval papillomatosis 33.46
vulval phycomycosis 71.69
vulval purpura, chronic 71.61–2
vulvar intraepithelial neoplasia (VIN)
  HPV and 33.54–5
  treatment 73.24
vulvar pemphigoid 40.34
vulvitis 71.59, 71.61
  in trichomoniasis 37.29
vulvodynia 71.81–2
  contact allergy and 26.19
  race and 9.19
vulvovaginal melanosis 58.15
vulvovaginal–gingival lichen planus (VVG-LP) 41.9, *41.10*, 71.60
vulvovaginitis
  atrophic 8.20
  Candida 36.61–2, 36.68
  streptococcal 30.32
VWF (vibration white finger) 27.17, 28.26, 28.56, **28.57–8**
V–Y plasty 77.35

W
W-plasty 77.35
Waardenburg's syndrome 58.43–4, *69.12*
  clinical features and variants 58.43
  genes, dog coat colour and 2.7
  genetics 2.7, 58.44
  piebaldism in 66.93
  piebaldism vs 58.42
Wachters' keratoderma (focal palmoplantar keratodermas) 19.3, *19.94*, 19.95, 19.102–5
Wade–Fite stain 10.10
waist circumference 46.5
Walbaum–Dehane–Schlemmer syndrome 15.56
Waldenström's macroglobulinaemia 22.24, 49.13
  oral involvement 69.114
  purpura in 49.19
Waldeyer's oropharyngeal ring 13.9, 69.2
Wallace's line 5.15, *5.16*
walnut hair dye 66.97
warble fly 38.9
warfarin
  adverse effects **75.105,** 75.167
  cutaneous calciphylaxis associated 49.48
  platelet function abnormalities and 49.13
  surgical complications and 77.9
warfarin necrosis 49.39
  male genital dermatology 71.27
warmth receptors 4.9
wart(s) **33.39–54**
  acne vs 42.37
  affecting eyelids 67.24
  anatomist's/prosector's 31.10, 31.12
  anogenital 33.39
    'acuminate' 33.44
    in children 33.40–1, 33.46
    clinical features 33.44–6
    epidemiology 33.39–40, *34.2*
    flat warts 33.46
    genital lymphangiectasia vs 48.28
    in HIV infection 33.59, 35.29–30
    immunity impairment 33.42
    incubation period 33.40, 33.41
    infectivity and transmission 33.40
    malignant condylomas vs 33.42
    maternal, infectivity 33.40
    non-sexual transmission 33.40–1
    pathology 33.42
    prevalence *34.2*
    recurrence 33.46
    sexual transmission 33.40, 33.41
    sites 33.44
    terminology 33.44
    transmission in adults 33.40
    transmission in children 33.40–1
    treatment 33.49, 33.50, 33.51, 73.25
    see also condylomata acuminata
  in atopic dermatitis 24.24
  butchers' 33.47
  clinical features 33.42–6
  common 33.40
    around genitalia 33.43
    clinical features 33.42–3
    malignant change 33.43
    pathology 33.41
    transmission 33.40
  cryotherapy 33.49–50
  curettage 33.49, 77.40
  deep palmoplantar 33.41
  digitate 33.44
  duration 33.44, 33.46
  electrosurgery 33.49, 77.46
  epidemiology 33.39–40
  in epidermodysplasia verruciformis 33.57
  filiform 33.44, *33.45*
  genital, imiquimod therapy 73.24
  hands 33.48
  in HIV infection and AIDS 33.59
  in immunodeficiency 17.52, 33.58–9
  incubation period 33.40, 33.41
  laser therapy 33.50, 78.8
  mosaic plantar *5.14*, 33.44, 33.48
  Murray Williams' 23.39
  nail involvement 33.43, 33.48, 65.30–1
  non-melanoma skin cancer and 52.11
  non-melanoma skin cancer associations in EV 52.5
  occlusion 33.48
  oral cavity 33.47, 33.48, 69.111
  pathology 33.41–2
  perianal *33.46*, 33.59, 35.45
    treatment 73.25
  periungual 33.43, 33.48
  phobias 64.24
  pigmented 33.47
  plane (flat) 33.42, 33.59
    clinical features 33.44, *33.45*
    imiquimod therapy 73.24
  plantar 33.40
    clinical features 33.43–4
    pathology 33.41
    transmission 33.40
    in transplant recipients 33.59
    treatment 33.48, 33.49, 33.50
  race and 9.18
  regression 33.42, 33.43, 33.44, 33.48
  sarcoidosis and 61.17
  satellite 33.44
  seborrhoeic *see* seborrhoeic keratosis
  senile *see* seborrhoeic keratosis
  soft *see* skin tags
  surgery 33.49
  tar 27.16
  transmission 33.40
    iatrogenic 33.40, 33.50
  in transplant recipients 33.59, 62.74
  treatment 33.48–54
    bleomycin 73.23
    imiquimod 73.24
    sensitizing agents 73.39
    topical 5-FU 73.23
  vaccination 33.50
  see also human papillomavirus (HPV)
'wart paint' 33.48
Warthin–Starry technique 10.10, 34.19, 35.25
warts, hypogammaglobulinaemia, infection, myelokathexis syndrome 17.81, 33.59
warty dyskeratoma 69.26
WAS *see* Wiskott–Aldrich syndrome
washing, compulsive 64.24
washing powders 25.20
WASP (Wiskott–Aldrich syndrome protein) 17.62
wasps
  hypersensitivity to 22.8, 38.1, 38.3, 38.14–15
  social 38.14
  solitary 38.14
  venom 38.14
Wassermann reaction 51.2
water
  evaporation from skin surface 3.12
  as irritant 25.19
water-in-oil (W/O) emulsions 73.7
Waterhouse–Friderichsen syndrome 62.5
waterless cleansers 25.20
Watson's syndrome 15.20
wattle 18.84
wax(es)
  ear *see* cerumen
  emulsifying 73.7
  in topical therapy 73.7
wax esters, in sebum 42.5, 42.22
waxy keratoses of childhood 19.93
weal and flare reaction, in solar urticaria 29.19
weals
  amplification and prolongation 22.4
  caused by physical stimuli 22.12
  definition 5.8, 22.1
  in delayed pressure urticaria 22.14
  immediate weal skin tests 5.22, 5.23–4
  intradermal injection skin testing 5.22–3
  measurement 5.23
  resolution 22.4
  urticarial 22.5, *22.6*, 22.25
wear and tear, in telangiectases 47.13

wear and tear dermatitis 23.20
  cumulative irritant contact dermatitis 25.1, 25.5, 25.12–13, *25.14*, 25.15
Weber–Christian syndrome 46.13, 46.15, 46.24
Weber–Cockayne syndrome 39.4, 39.6, 39.30–1
  friction blisters in 28.13
weed-wacker dermatitis 58.32
  see also phytophotodermatitis
weeverfish 38.59
Wegener's autoantigen 13.4, 50.39
Wegener's granulomatosis (WG) 45.42, **50.39–41**
  aetiology and pathogenesis 50.5–6, 50.7, 50.39, 50.55
  breast involvement 70.11
  cardiac involvement 62.78
  clinical features 50.39–40
  cutaneous small vessel vasculitis in 50.13
  differential diagnosis 50.69–70
  ear involvement 68.17
  genetic factors 50.11
  ocular involvement *67.25*
  oral involvement 69.58, *69.118*
  in parvovirus B19 infection 33.63
  relapse 30.7
  respiratory tract involvement 62.83
  treatment
    cyclophosphamide 74.17
    TNF antagonists 74.5, 74.8
Weibel–Palade bodies 3.51–2
  electron microscopy 10.30
  P-selectin 12.71
weight loss
  cellulite management 46.10
  lymphoedema management 48.23
  in obesity 46.7–8
Weil's disease 30.66
Weir Mitchell's disease 47.9
Weir–Mitchell type, partial lipoatrophy 46.39–40
welders, occupational hazards 27.21
well being, concept of 64.4
Wells' syndrome (eosinophilic cellulitis) 46.12, **46.33–4,** 62.87
Werlhof's disease *see* idiopathic thrombocytopenic purpura (ITP)
Wermer syndrome 62.24, 62.68
Werner's syndrome **15.77,** 15.81, 45.57–8, 51.79, 58.23–4, 62.27–8
  atrophy of acral parts 51.79
  bone and joint involvement *62.100*
  greying of hair 66.92
West Nile fever/virus *33.67*, 38.5
western blotting 11.5
  Treponema pallidum 34.20
Western equine encephalitis virus 33.66, *33.67*
western red cedar *26.80*
wet-wrap technique
  in atopic dermatitis 24.30
  in eczema 23.38
wetting agents 25.20
Weyer acrofacial dysostosis 15.56
WG *see* Wegener's granulomatosis (WG)
whales 2.3
Wharton's duct 69.5
Whiff test 71.53
WHIM syndrome 17.81, 33.59
whiplash rove beetles 38.27
whipping injuries 28.32
Whipple's disease 59.59, 61.23, 62.55
  arthralgia in 62.105
whirlpools 28.54–5
Whitaker's syndrome *13.13*, 15.31, 36.64, 62.12–14
white atrophy 15.13, 23.35, 47.34, 49.44
white blood cells
  trapping, in venous disorders 47.27
  see also entries beginning leukocyte
'white clots' 49.28
white finger 27.17, 28.26, 28.56, **28.57–8**
white folded gingivostomatosis 35.43, 69.23–4
white ovoid macules 15.22
White Soft Paraffin BP 73.2
  in eyelash louse infection 38.23
white-spot disease *see* lichen sclerosus
'white spotting' 58.42
white-tailed spiders 38.32
whiteheads 42.22, 42.30, 42.36
Whitfield's ointment 25.18, *36.47*, 36.48, 36.49
  composition and indications 73.13
whitlow
  herpetic 33.17, 65.22–3
  syphilis differential diagnosis 34.7
WHO, Adverse Reactions Database 75.3, 75.4
whole-body occlusion, corticosteroid therapy 73.20
Wickham's striae, lichen planus 41.6
Widmer classification, chronic venous insufficiency *47.32*
widow spiders 38.31
Wiener's pore (dilated pore) 53.3
wigs 26.18, 66.24
Wilkinson's triangle 26.24
Williams syndrome 3.44, 45.25
willingness to pay (WTP) 72.22
Wilson's disease 59.76
Wimberger's sign 34.15
Winchester syndrome 45.50, 66.76
Winer's pore, pinna 68.28
'wire-loop' lesions, kidneys 51.34
Wiskott–Aldrich syndrome *13.13*, 62.28, 62.95–6, *69.117*
  bacterial infection and 30.8
  genetics 13.11
  immunodeficiency and 17.62–3
  oral involvement 69.31
  vasculitis and 50.54
Wiskott–Aldrich syndrome protein (WASP) 17.62
witchcraft syndrome 64.40
witch's milk 17.5
Witkop syndrome 15.56, 15.65
Witkop–von Sallmann syndrome 69.25
Wnt 66.10
  signaling 3.3, 3.4, 3.7
    adherens junctions action 3.23
Wnt/β-catenin pathway, melanocyte development 58.3
Wohlfahrtia 38.8, 38.9
Wolbachia 37.7, 37.9
wolf spiders 38.32
Wolffian ducts 8.2
Wolf–Hirschhorn syndrome 15.12, 18.2, 18.103
women
  HIV infection 35.44
  risk of adverse drug reactions 75.6
  sebum production 42.10
  see also entries beginning female
wood, allergic contact dermatitis to 26.79, *26.80–1*, 26.82–4
Wood Alcohols BP 73.7
wood dust 25.21, 26.20
wood rosin 26.79
wood tars 73.42
woodcutters' dermatitis 26.77
Wood's lamp 29.2
  pigmentation examination 58.9
Wood's light 5.19–20, 36.6
  in erythrasma 30.38
  in pityriasis versicolor 36.11
woodworkers, occupational hazards 27.21
wool 2.3
  fibres as irritant 25.19
wool fat *see* lanolin
wool wax alcohols 26.58
woolly hair, hypotrichosis, everted lower lip and outstanding ears 15.56
woolly hair, keratoderma and cardiac disease and *19.94*, 19.107
Woringer–Kolopp disease 57.15
World Bank, skin diseases report 6.16
World Health Organization (WHO), Adverse Reactions Database 75.3, 75.4
Woronin bodies 36.3
wound(s)
  activated fibroblasts 12.31
  acute 14.9
  assessment 14.19–20
  chronic 14.1–2, 14.11–12
  cleansing 14.21–2
  closure 14.10
  compression bandaging 14.20–1, 38.31, 38.60
  debridement 14.22
  desiccation 14.17
  dressings *see* dressings
  embryonic 14.2, 14.9
  fetal 14.2, 14.9
  foreign bodies 14.17
  full thickness 14.10
  granulation tissue (provisional matrix) 14.1, 14.3, 14.6, 14.7
  haematoma formation 14.17
  healing *see* wound healing
  infection 14.16–17
  maggot debridement 14.22, 38.8
  measurement 14.19
  myiasis 38.8, 38.9, 38.10
  non-healing 64.38, 64.43
  open 14.10
  partial thickness 14.10
  Pseudomonas aeruginosa infection 14.16, 30.49, 30.50
  surgical
    closure 77.16–17
    complications 77.5, 77.8–9
    dog-ear/pseudo-dog-ear repairs 77.16
    dressings 7.17–18, 77.9
    infection 77.5, *77.8*, 77.9
    secondary intention healing 77.12, 77.15, 77.16, 77.18, *77.19*
    unequal length edges 77.16
  treatment
    honey role 73.48
    principles 14.19–27
wound care
  burns 28.78, 28.84–6
  pressure ulcers 28.22–3
  see also dressings
wound-care services 14.21
wound healing **14.1–27**
  angiogenesis 14.6–7
  biological aspects 14.1–9
  clinical aspects 14.9–15
  complications 14.15–19
  defensins 12.7
  effects of age 14.2, 14.9, 14.17–18, 45.2
  in elderly people 14.2, 14.9, 14.17–18
  fibroblast recruitment and matrix synthesis 14.7–8
  hyaluronic acid 3.49
  impaired, corticosteroid-induced 73.19
  improvement, retinoic acid 73.36
  in infancy and childhood 14.2
  inflammation and immune response 14.2–4
  inflammatory cells 14.1, *14.2*
  integrins 12.69
  by primary intention 14.9–10
  re-epithelialization 14.4–6, 14.10, 14.17
  by secondary intention 14.10
    following Mohs micrographic surgery 77.29
    surgical wounds 77.12, 77.15, 77.16, 77.18, *77.19*
  skin innervation and 63.4
  stress and 14.1
  systemic factors affecting 14.18–19
  tertiary 14.10
wrinkles 8.19, 8.22–3, 8.27
  ageing and 45.2–3
  definition 45.2
  glyphic 45.2
  treatment 8.25, 8.27
wrinkling, abnormal 28.93
wrinkly skin syndrome 45.15, 45.61
wrist sign 45.30
WRN gene 15.77
Wuchereria bancrofti 37.3, 37.9–10
Wyburn–Mason syndrome 18.62

X
X-linked chronic granulomatous disease 13.4
X-linked dominant ichthyosis (XLDI; Conradi–Hünermann–Happle syndrome) 19.3, 19.49–52, *62.100*
X-linked dominant (XLD) inheritance *15.4*, 15.5
X-linked dyskeratosis congenita 15.36
X-linked hypohidrotic ectodermal dysplasia 15.43, **15.58–60**
X-linked ichthyosis
  genetics 15.5, 15.6
  pregnancy/labour in 8.9
  recessive 3.11, 19.3, 19.9–13
X-linked lymphoproliferative syndrome 13.6, 13.11, 17.64
  vasculitis and 50.49
X-linked recessive dyskeratosis congenita **15.78–80**
X-linked recessive ichthyosis 3.11, 19.3, 19.9–13
X-linked recessive (XLR) inheritance *15.3*
X-ray(s) 79.1, *79.2*
  in allergic contact dermatitis 26.102
  burns 28.84
  contrast lymphography 48.17
  epilation by 66.53–4
  non-melanoma skin cancer association 52.5
  in Sturge–Weber syndrome 18.66
  venous malformations 18.71
  see also radiography
xanthelasma 59.84
  eyelids 67.33
  treatment 77.46, 77.50, 78.14
xanthoerythroderma perstans 23.7–8, 57.57
xanthogranuloma
  adult-onset 68.16
  ear 68.16
  generalized lichenoid variant 55.16
  juvenile 15.20, 67.33
  necrobiotic 55.27–9, 60.14, *62.45*
    eyelids 67.33
  solitary giant 55.15
  spindle cell 55.20
xanthogranulomatous reaction 55.6, 55.15
xanthoma 59.81–93
  in acquired generalized lipodystrophy (AGL) 46.38
  bone and joint involvement 62.105
  ear 68.17
  eruptive 59.79, 59.85
  eyes 59.84–5
  juvenile *see* juvenile xanthogranuloma
  multiple eruptive in infancy *see* juvenile xanthogranuloma
  in necrobiotic xanthogranuloma 55.27
  palmar 59.85
  papular 55.19–20
  tendons 59.84
  tuberous 59.85
  verruciform 68.16, 69.112–13
    psoriasis in HIV infection vs 35.17
xanthoma disseminatum 55.15, **55.20–2**
  atypical 55.22
  variant 55.21
xanthoma multiplex/naeviforme *see* juvenile xanthogranuloma
xanthoma tuberosum, congenital *see* juvenile xanthogranuloma

xanthomatosis
  cerebrotendinous 59.91
  diffuse normolipaemic plane 55.22
  diffuse plane 55.22
xanthosiderohistiocytosis 55.21
  disseminated *see* xanthoma disseminatum
xenon arc lamp 29.2
Xenopsylla cheopis 30.73, 38.11
xeroderma, pruritus, in old age and 8.27
xeroderma pigmentosum (XP) *13.13*, **52.10,** *62.20*, 62.22
  aetiology 15.70–1
  autosomal dominant 15.73
  clinical diversity 15.72
  clinical features 15.72–3
  diagnosis 15.73, 29.23
  differential diagnosis 15.81
  DNA repair defects 52.10
  genetics 15.5, **15.70–5**
  melanoma association 54.48
  neoplasia and 15.72
  neurological complications 15.73
  nucleotide excision repair 15.71–2
  ocular lesions 15.73
  oral involvement 69.42
  pathology 15.72
  pigmentation in 58.24
  prenatal diagnosis *16.3*
  skin sensitivity 15.72
  squamous cell carcinoma in 52.28
  treatment 15.73–4, 73.23
  trichothiodystrophy and 66.68
  XP variant 15.71–2
xeroderma–talipes–enamel defect (XTE) syndrome 15.56
xerosis
  eating disorders and 64.22
  in HIV infection 35.11–12
  pruritus and 21.12
  senile *see* asteatotic eczema (eczema craquelé)
xerostomia 69.3
  drug-induced 75.46
  in HIV infection 35.42
  oral candidosis and 69.88
XLD *see* X-linked dominant
XLD (X-linked dominant) inheritance *15.4*, 15.5
XLR (X-linked recessive) inheritance *15.3*
XP *see* xeroderma pigmentosum (XP)
XTE (xeroderma–talipes–enamel) defect 15.56
XXXXY syndrome 15.14, 68.4
XXYY syndrome 15.14
XYY syndrome 15.14, 42.18

Y
Y-linked genes 15.4
Yasmin®, acne treatment 42.53
yatapox 33.5
yaws 30.36, **30.63,** 38.6, 71.31–2, 71.95
  bush *37.34*, *37.35*, **37.39–41**
  'daughter yaws' 30.63
  in HIV infection 35.25
  latent syphilis vs 34.12
  'mother yaw' 30.63
yeasts 36.2
  black 36.77
  identification 36.9
  lipophilic, overgrowth 42.75
  normal skin flora 35.13, 36.10
  see also fungi
Yellow and White Soft Paraffin BP 73.6
yellow card scheme 75.3
yellow fever *33.67*, **33.68,** 38.5
yellow-jackets 38.14
yellow nail syndrome 48.10, 48.21, 62.83, 65.12, **65.16–17**
  in HIV infection 35.41
Yersinia enterocolitica 30.55
  in cellulitis 30.18
Yersinia pestis 30.54–5
Yersinia pseudotuberculosis 30.34, 50.45
'yesterday use' question 72.6–7
yohimbine 75.119
Yucatan pig model 73.27

Z
Z-plasty 77.16
zafirlukast 12.61, 13.4
Zanier–Roubicek syndrome 15.56
ZAP-70 kinase 13.8
ZB (Zoon's balanitis) 71.13, 71.18, **71.19–20**
Zeis gland 67.2
  cysts 67.33
Zemaphyte 75.161
Zenker's fluid 10.31
zidovudine
  action 74.49
  adverse effects 75.67–8
    hypermelanosis 58.29
    nail colour changes 65.38
  in HIV infection 35.5, 35.17
  in HTLV-1 infection 33.65
  in psoriasis 20.42
Ziehl–Neelsen stain 10.10
zileuton (Zyflo) 12.61, 13.4
zinc
  deficiency *see* zinc deficiency
  metabolism 59.75
  oral, acne vulgaris treatment 42.66
  supplements, effects on wound healing 14.24–5
  topical 14.24
  wart treatment 33.50
zinc acetate, topical erythromycin with 42.16, 42.41
zinc chloride 25.21
zinc deficiency 59.60, **59.72–4**
  acne lesions vs 42.37
  acquired 62.65
  in acrodermatitis enteropathica 69.31
  in animals 2.17
  in breastfed infants 59.73–4
  hair loss in 66.28–9
  napkin dermatitis and 17.25
  necrolytic acral erythema and 62.59
  during pregnancy 18.2
  treatment, oral zinc sulphate 59.75
  venous leg ulcers and 47.44
  wound healing and 14.18
zinc metalloenzymes 3.41
zinc oxide 73.8
  dithranol with 73.30
  paste(s) 73.2
    bandaging 47.48
  as sunscreen 73.40
zinc paste bandaging 47.48
zinc pyrithione 66.56, 73.13
zinc pyrithione shampoo 73.13
zinc-responsive dermatosis 2.17
zinc–insulin granulomas 28.46
Zineryt® 42.16
Zinsser–Engman–Cole syndrome *see* dyskeratosis congenita (DKC)
zirconium granuloma 61.22
zirconium hydroxychloride *25.19*
Zlotogora–Ogur syndrome 15.33
Zollinger–Ellison syndrome 62.24, 62.67–8
zonisamide 75.86
zonula occludens proteins 3.24–5
Zoon's balanitis (ZB) 71.13, 71.18, **71.19–20**
Zoon's vulvitis 71.61
zoster 33.3, **33.22–8**
  acne and 42.79
  aetiology and epidemiology 33.23
  anogenital region 33.25
  antibodies 33.23
  clinical features 33.25–6
  complications 33.26
  cytodiagnosis 10.29
  diagnosis 33.27
    electron microscopy 10.30
  disseminated 33.25
  ear involvement 68.20, 68.28
    see also herpes zoster oticus
  in elderly people 8.28, 33.25, *33.26*, 33.28
  gustatory hyperhidrosis following 44.10
  in HIV infection 33.25, 68.28
  immune response 33.23
  in immunocompromised patients 33.23
  in infancy 33.23
  in malaria 37.27
  male genital region 71.33
  motor involvement 33.25
  ophthalmic 33.25–6, *33.26*, 33.28, 67.26
    in HIV infection 35.28
  oral involvement 69.74–5, *69.118*
  orofacial 33.26
  pain 33.25, 33.26
    see also post-herpetic neuralgia
  pathology 33.24
  perianal/perineal 71.95
  prevention 33.27
  renal involvement 62.71
  sacral
    male genital region 71.33
    perianal/perineal 71.95
  sensory nerve 33.25, 33.26
  thoracic disease 33.25
  treatment 33.27–8
  trigeminal nerve 33.25–6
    management 33.28
  vaccine 63.7
  see also varicella zoster virus (VZV)
zoster immune globulin 33.27
zoster sine eruptione 33.25, 67.26
zosteriform reticulate hyperpigmentation 58.22–3
zotepine *64.52*
Zumbusch-type psoriasis 20.49, 20.51
Zyflo 12.61, 13.4
Zygomycetes 36.2–3
  vessel-invasive infection 49.35
zygomycosis 36.91–2
  blood vessel invasion 50.55
  male genital dermatology 71.32
  oral involvement *69.118*
  rhinocerebral 69.80
  subcutaneous 36.78–9
zymodemes 37.27